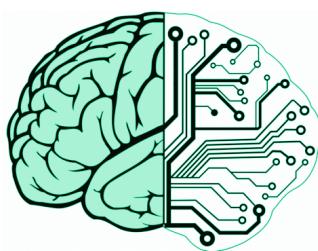


*”Though this be madness, yet there is method in’t.”*

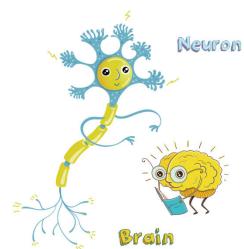
Shakespeare: Hamlet: Act 2 Scene 2

Dynamic Abstract Neural Computing  
with Electronic Simulation  
(DANCES) Version *0.1.12*



János Végh

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# Foreword

”The Human Brain Project should lay the technical foundation for a new model of ICT-based brain research, driving *integration between data and knowledge from different disciplines*, and catalysing a community effort to achieve a *new understanding of the brain... and new brain-like computing technologies.*”  
the Human Brain Project, summarised its goal @2012

**Understanding the dynamic brain** The ***dynamic*** operation of individual neurons, their connections, higher-level organizations, connections, the brain with its information processing capability, and finally, the mind with its conscience and behavior, are still among the big mysteries of science: *at which point the non-living matter becomes a living one, at which point the living matter becomes intelligent* and conscious; whether and how science can handle all this stuff. We really need a new understanding. The hype in the newly launched projects is excessive and seems to lose the hope to build brain research on a firm science base. For example, the newly (at the end of 2025) launched “Brain/MINDS 2.0” program in Japan was launched ”with the goal of developing a marmoset model for neuroscience”, using only mathematical models, without targeting the understanding of the underlying physical processes. The case is much similar to the ‘Theory of Everything’ in physics, which is developed since science exists and is a never-ending project. Likely, the length of the time needed for neuroscience will not be much shorter, although the project period is limited to years.

**Abstract discussion** Nature uses an infinite variety of implementing neurons. Our goal is not to discuss all infinitely complex molecular, biochemical and physiological details of neuronal operation; it is not necessary, since in the Central Nervous System (CNS) they can cooperate with each other. ‘Despite the extraordinary diversity and complexity of neuronal morphology and synaptic connectivity, *the nervous systems adopt a number of basic principles* for all neurons and synapses’. [1] We base our holistic discussion on those general basic principles and create an ‘abstract physical neuron’, skipping the ‘implementation details’ nature uses. We need different abstractions and approximations for describing biological processes. However, an abstraction is usable in practice

only when paired with a generalization: the more abstract the assumption, the more general and widely applicable the concept or conclusion. *By abstractions, we can reduce the unbelievably detailed world into manageable pieces, and by abstraction, we can learn anything general.* We must show which approximations are oversimplifications and which phenomena are misunderstood; measured, or interpreted in the wrong approach. Abstraction is, in fact, everywhere, including inside each of us. It is a core element of cognition.

**Zigzag reading** For the same reasons, we follow von Neumann's method when described principles of technical computing [2]. "The ideal procedure would be, to take up the specific parts in some definite order, to treat each one of them exhaustively, and go on to the next one only after the predecessor is completely disposed of. However, this seems hardly feasible. The desirable features of the various parts, and the decisions based on them, emerge only after a somewhat zigzagging discussion. It is, therefore, necessary to take up one part first, pass after an incomplete discussion to a second part, return after an equally incomplete discussion of the latter with the combined results to the first part, extend the discussion of the first part without yet concluding it, then possibly go on to a third part, etc. Furthermore, these discussions of specific parts will be mixed with discussions of general principles, of the elements to be used, etc." For example, basic concepts such as the membrane potential and its regulation in resting and transients states, belong to chapter Physics, and their detailed scientific, physics-based, discussion is given there, but their corresponding aspects must be discussed in chapters 'Abstract neuron' and less abstract 'Physiology' as well. We make this zigzag reading more accessible by using hyperlinks and cross-references throughout the document.

**Simulator** The site is not exclusively about theory: we also give a programmed implementation of the ideas we describe. Our simulator has a direct scientific base instead of ad-hoc mathematical formulas; and the only one which can reproduce the true biological time course of neurons, from the first science principles, without arbitrary ad-hoc assumptions and limited variability formulas. Our methods enable discussing the major aspects of phenomena of the natural operation of neurons to analyze the effects of invasive electricity-related investigation methods on neuroscience. We offer demos, class implementations, performance benchmarks, and test cases to demonstrate simulating capabilities. We intend to develop full-value educational, demonstration, and research tools.

**Warning** Please consider that this development is a one-person undertaking. Moreover, it shall develop theory, evaluate published experiments, implement software, test it, and document it. Pre-developed code fragments, science publications, and docs exist, so they develop relatively quickly, but we need time to put them together consistently. Please return later and see if something is new (see the date and the version).

# State-of-the-art

*”We stand on the verge of a great journey into the unknown—the interior terrain of thinking, feeling, perceiving, learning, deciding, and acting to achieve our goals—that is the special province of the human brain . . . No single researcher or discovery will solve the brain’s mysteries.”* — from the preamble to “BRAIN 2025: A Scientific Vision” [3] @2015

**Many-disciplinarity** Brain research is one of the fields where *”nature is not interested in our separations, and many of the interesting phenomena bridge the gaps between fields.”* [4] We need a consistent model that comprises all relevant interactions and components (and only those!) and aligns with the notions of the related scientific fields. Different science disciplines consider different details relevant; see Fig. 1. Despite the efforts of the project leader, no picture can be derived about the *elephant*, although *the details of the elephant* are accurate. This problem is mentioned in the China Brain Project when evaluating the similar past and present programs over the world that *”a systematic understanding of the brain is still lacking, possibly due to the fragmentation of research strategies”*

**Modeling concepts** To model something, means to reduce a system with unknown behavior to another system with already well-known behavior. The two systems will never be identical, only similar in certain aspects; furthermore, their similarity is subject of the environment, so the models have their range of applicability. To model a living structure with a non-living one, ab ovo, has its dangers. One possible approach is to describe a system’s response to the environment, typically using parametrized mathematical formulas, without the aim of predicting a non-observed response. It is usually a good starting point for understanding the system’s operation, but without a deeper understanding of the details, it remains a ‘looks like’ description. Science typically reduces the observations to an abstract level, such as how an ideal charge or mass behaves (meaning that it provides mathematically calculable predictions). Science of living matter attempted to follow for its subject the principles developed for non-living matter. However, because of the *”different construction”*, it experienced discrepancies. Unfortunately, instead of developing the appropriate test



Figure 1: The difficulty of many-disciplinary research on the example of describing the elephant. (a 2,500 years-old Chinese silk painting)

methods, which could derive the appropriate laws describing living matter, biology stopped at the point that "laws of science cannot describe life". Since, to some measure, the known laws can describe the phenomena, and they describe known (well-tested) scientific mechanisms, life science has created the missing mechanisms based on mathematical formulas, without abstracting them as science did; in this way it has lost the predictive power of the laws describing the new (hypothesized) mechanisms and the expectation that the formulas must be based on some mechanism.

Neuronal modeling is a good (or bad) example of that modeling style. Hodgkin and Huxley [5] genially noticed that their high-precision and meticulous observations can be described mathematically (the title of their paper was "A quantitative description"). Unfortunately, with the best intention, they attempted to put a physical picture behind their formulas, although they warned that their "equations are not anything more than an empirical description", "the interpretation given is unlikely to provide a correct picture of the membrane" and "the success of the equations is no evidence in favour of the mechanism ... we tentatively had in mind when formulating them". Despite their prophetic thoughts, that hypothesized incorrect mechanism defined the development path of neuroscience for decades, and led to the present crisis and the need of "new understanding". We discuss their "physical model" (created by their successors) and compare it to our physical model.

We agree with the unfortunate distinction "a biological model is often understood to be simply a diagram depicting the interrelationships of various (sub)systems in a process, whereas a physical model is expected to be a theoretical description of a process involving a number of equations of motion stemming from the first principles (if possible), testable against a range of tunable experimental conditions. It must lead to a quantitative prediction and not simply

reproduce already known results” [6] cited and expressed in [7]. ”Riddled with some major misunderstandings and suffering from a lack of familiarity with the physics involved, this debate has been ongoing for some while without being picked up in mainstream neuroscientific literature.”

**Omitting time** All present projects work only in three dimensions, forgetting that, unlike the instant interactions in non-living science, the interaction speed in living tissues is million times slower, so the time has a fundamental role in neural operation. The time dimension of the dynamic operation should be included in the maybe structurally accurate brain maps to produce a functionally useful digital twin of the brain. Neither the fundamentally parallel operation of the brain can be simulated by a fundamentally sequential computer, nor the unbelievably dense wiring can be technically achieved; not mentioning numerous differences of the operating characteristics.

Due to the lack of an adequate level of interpretation of the concepts of operation (both in the case of biological and technical calculations), the basis of efforts is the hope of ”what if it works”. In order to obtain further funding, various projects consistently and purposefully replace the successful digital implementation of the connectivity that can be created (based on different and presumably correct brain maps) with the unsuccessful implementation of their communication. The digital implementation adds a quasi-random technical time contribution to the operating times, which is not noticeable in digital systems created without real timing conditions and implemented with random timings. Moreover, in systems consisting of a large number of neurons, communication simply collapses, or the connectivity has to be significantly reduced. In such demonstration systems, a small number of ”neurons” compared to the brain actually produce an operation that remotely resembles the operation of a biological part of the brain, but does not show useful functionality. The situation is aggravated by the fact that researchers try to force a similarity to Artificial Intelligence onto the brain. This is justified only by the fact that, in addition to the current technical implementation, developers no longer understand the operation of Artificial Intelligence (AI), as well as neuroscientists the exact principles of how the brain works.

**Physics** ”The construction [of living matter] is different from anything we have yet tested in the physical laboratory.” ”It is working in a manner that cannot be reduced to the *ordinary* laws of physics” [8]. We attempted to test and describe living matter, including the brain, with methods based on the ordinary laws of science, which we concluded for non-living matter. Also, we must understand that the fundamental differences need an accurate understanding of the biological currents and their measuring processes. Those *static* methods did not consider its ”special construction”; furthermore, they do not need (and, as a consequence, do not have) *dynamic* ”laws of motion” in the sense as science does.

Their slowness and complexity require explicitly considering the *time-aware*

*handling* of processes, including the ones of biological and technical computing. Essentially, we make the first steps in section 2.3 toward answering E. Schrödinger’s question: ”How can *the events in space and time* which take place within *the spatial boundary* of a living organism be accounted for by physics and chemistry?” [8] Notice the need of *using events and describing the spatiotemporal behavior (in other words: implementing them by slow currents in a finite volume)* implied in the question; three items which our text targets. *No presently available theoretical description and simulator can perform that task.* We show that when considering the correct physics, *the finite size of neuronal membranes, the finite speed of ion currents,* and the correct description of *discrete to continuous transition*, we can solve the mystery that the combination of non-living materials shows signs of life at an appropriate combination of their parameter values. We derive the required ’non-ordinary’ (non-disciplinary) laws for describing life by physics. We emphasize again that the first principles are the same, but the different ”construction” of the living matter needs different – ’non-ordinary’ – approximations and laws.

**Electricity** Electronics and brain research were born at the same time, developed together and fertilized each other. Sometimes, the too-tight parallels led to discrepancies, from assuming the same charge carrier and transfer mechanism for conductors and biological structures to using equivalent circuits, or misunderstanding the essence of spiking for electronically implemented circuits. Those wrong parallels hide the need for introducing thermoelectricity with its mixing speeds instead of separated electrical and diffusion processes, that life is governed by finite-speed (”slow”) currents and that finite-size (distributed) biological objects cannot be directly and accurately mapped to point-like (ideal) electrical components. We need to connect the atomic electricity to the macroscopic one; furthermore, in biology, concentration changes evoke potential changes and create large potential gradients (and vice versa). Those internal gradients start dynamical electrical *ion* currents in biological tissues.

**Thermodynamics** One of the most exciting aspects of our discussion is providing the way as thermodynamics can be used to describe neuronal operation. As we discuss, our physics-based model, which considers ions’ charge and mass inseparable, naturally answers the long-standing question how thermodynamics can describe life. We show how the dual nature of ions connects electrical and thermodynamic features of neurons. A Carnot-type process can be interpreted for the neuronal process, and energy consumption and energetic efficiency can be quantitatively interpreted.

**Physiology** Physiology, which serves as the ”implementation base” for neural computing, needs a revolution and replacing ”classical physiology” with ”modern physiology” by introducing a new paradigm. Our point of view is new and unusual; it conflicts, on many points, with the commonly accepted opinions of the respective science disciplines. The facts and observations are the

same, but their interpretation may differ due to the underlying 'non-ordinary' laws of physics. Biology stayed at a static description level, typically appropriate for describing static states. *Neural processes* happen at well-observable speeds, which *need a dynamic description instead of an ad-hoc description of state jumps*. We introduce for life sciences their *dynamic laws of motion* (in the sense of Newton, Hamilton, and Schrödinger), (based on the time derivatives of the static entities). Furthermore, we explain why and how a fraction of the charges constitute living matter change obeying their laws of motion, creating the *needed dynamic component which can implement the needed dynamic processes*. Considering them solves the mystery of how life science builds on top of science. We defy that "the emergence of life cannot be predicted by the laws of physics" [9], furthermore, that "the existence of life is against the laws of thermodynamics".

**Neuroscience** We understood early that "*the fundamental task of the nervous system is to communicate and process information*". The goal was set decades ago: '*The ultimate aim of computational neuroscience is to explain how electrical and chemical signals are used in the brain to represent and process information*' [10]. Today, computational neuroscience turned into introducing mathematical models, slightly or not related to reality, implementing them using a "technomorph biology" [11], while it keeps wondering why nature behaves differently. The worst inheritances of neuroscience are the static view from anatomy and classical physiology; omitting to revisit periodically the primary hypotheses in light of new research results; applying the abstractions of classical science (single speed, isolated, pair-wise, instant interactions in a homogeneous and isotropic infinite medium) to biological materials without revisiting their validity. Moreover, the tradition of applying ad-hoc mathematical formulas without correct physical processes in the background (actually creating an alternative nature) instead of understanding the basics of the underlying processes. To start with, we introduce *science-based abstract dynamics* (by introducing the needed laws of motion), as opposed to the *empirical cell-biology's static* description of neuronal operation. We agree that "the basic structural units of the nervous system are individual neurons" [1], but we are also aware of that neurons "are linked together by dynamically changing constellations of synaptic weights" and "cell assemblies are best understood in light of their output product" [12, 13] so we also model multiple neurons.

**Mathematics** We can only admire von Neumann's genial prediction that "the language of the brain, not the language of mathematics" [14], given that most of the cited experimental evidence was unavailable at his age. Similarly, one can also agree with von Neumann [2] and Sejnowski [15] that "whatever the system [of the brain] is, it cannot fail to differ from what we consciously and explicitly consider mathematics"; adding that *maybe the appropriate mathematical methods are not yet invented*. Our procedure still meets the requirement given by Feynman: [16] "an effective procedure is a set of rules telling you, mo-

ment by moment, what to do to achieve a particular end; it is an algorithm.” Furthermore, it considers that “timing of spike matters” giving way to interpreting Hebb’s learning rule [17, 18], which usually remains outside of the scope of mathematics. We formulate problems, provide their numerical solutions, and open the way for mathematics to provide analytical solutions. Not surprisingly, the need for applying new approximations for the non-ordinary laws [19] for describing living matter needs slightly different (in this sense, non-ordinary) mathematical formulation describing them. Furthermore, new algorithms [20] are to be developed for simulation.

**Computing** ”The brain computes! This is accepted as a truism by the majority of neuroscientists.” [21] However, even after many years and grandiose projects, ”Yet for the most part, we still do not understand the brain’s underlying computational logic” [3]. To understand how ”computation is done”, we generalized computing [22], in close cooperation with communication [23], for biology. We understand that ”a piecemeal approach will not yield the major jumps in understanding for which the BRAIN Initiative was designed” [24]. We synthesize the available knowledge with a fresh eye and intend to make a leap in understanding neural computing, scrutinizing our knowledge pieces one by one for credibility, relation to other pieces, other disciplines, finding contradictions and their resolutions, *defying fallacies*. We show how an elementary neuronal operation carries out computing, why biological computing is by orders of magnitude more effective than the technical one, how the biological implementation enables learning, how and why do the features of the two computing systems differ.

**Information** Although we experience that the brain processes an enormous amount of information; furthermore, we know impressive details about how the brain uses it to react appropriately to stimuli from its environment, we still do not know the details and the underlying general principles how neuronal networks represent, process, and store the information they use. What makes the case worse, is, that, due to the lack of knowledge of the abstract way of neuronal operation, the so-called ”neural information science” uses a wrong mathematical background. We understand how neurons represent and process information [13]. We introduce the appropriate interpretation of information for biology.

**Intelligence** Scrutinizing time awareness of biological computing, learning, and intelligence discovers [25] that they have practically only their name in common with the technical ones. As a consequence, ”biological brains are more efficient learners than modern ML algorithms due to extra ‘prior structure’” [26]. We must not forget ”There is no reason whatever for believing that our brain is the supreme *ne plus ultra* of an organ of thought in which the world is reflected.” [8] Furthermore, ”it is also possible that non-biological hardware and computational paradigms may permit yet other varieties of machine intelligence

we have not yet conceived” [26, 16]. We start to conceive them by analyzing the fundamental processes which can be ”directly associated with consciousness” [8].

## How do we proceed

All what we derive here, needs zigzag reading. As emphasized many times, we confine our discussion to some abstract disciplinary level, with pointers to special topics. We interpret known physiological evidence on top of the correct ’non-ordinary’ laws of physics and derive the needed mathematical handling separately but in parallel with that physics. The physiological conclusions should be understood even if you do not understand the underlying physical and mathematical details. For this reason, we repeat differently detailed explanations in different chapters. If you understand *why* the non-ordinary physical laws for living matter are more or less different from the ordinary ones for non-living matter, you may leave the details for your expert colleagues (physicists and mathematicians). Mathematical handling also involves the fundamental principles of using the abstractions and approximations of constructing laws for physics and needs a thorough knowledge of both fields. Anyhow, you will need to be aware of that college-level physics is usually not sufficient to understand the deepness of the material and you will need to re-read the concepts; the more you know it (and especially the more false biophysics you learned) the more carefully. A half-understanding of the physical base hinders your learning and the development of brain science.

Nature is overly complex: science fields must use different approximations and abstractions. When setting up a holistic model, we attempt to *see the forest for the trees*. We must pass between ’Scylla’ and ’Charybdis’: being still sufficiently accurate and detailed in describing phenomena while keeping the mathematical complexity (and computational need) of description still manageable. Without understanding that living matter needs different approaches and testing methods from science, really, ”no single researcher or discovery [and we add: even no ’vibrant ecosystem for rigorous and ethical research with human research participants as partners’ or ’a community effort’] will solve the brain’s mysteries” [3]. We must express the same fundamental principles in the form of laws differing from the laws valid for the classical physics for non-living material, and validate them. To do so, we must revisit whether we did the appropriate simplifications and approximations, furthermore, if we mapped those correct phenomena to the appropriate mathematical descriptions. We must defy some important misconceptions, provide the right conceptions, and explain why the wrong concept misguides research.

We aim to proceed along the lines (but fixing its conceptual mistakes, mainly the rigid disciplinarity) that was formulated @2012 as “The Human Brain Project (HBP) should lay the technical foundation for a new model of Info-Communication Technology (ICT)-based brain research, driving integration between data and knowledge from different disciplines, and to achieve a new understanding of the brain...and new brain-like computing technologies.” [27].

Moreover, in the Brain Initiative (BI), "There is a clear need for a tighter and more carefully managed integration and realignment of the work" [3]. However, "HBP is not developing with the expected level of integration and the project controls in place are not adequate to achieve this aim." [27]. The "great journey into the unknown" [3] must begin at a much lower level: revisiting the fundamental phenomena, disciplines, laws, interactions, abstractions, omissions, and testing methods of science.

You may have arrived with different backgrounds and goals. Consequently, you may have different spots of interest and paths through this material. The site is about neuron-based computing, which, for today, may mean very different topics. Of course, one must first understand the physical operations. The primary goal is to deal with biologically implemented neurons' operation (they are created 'as is'; maybe not entirely understood, but attempting to discover it) and also artificially manufactured neurons which attempt to imitate the biological ones, grasping one or more of their features; furthermore, their networks, operations, features and fallacies. A further goal is to understand the features of their larger assemblies, and how they implement advanced computations.

## The old understanding

Recently, experimental and theoretical neurophysiology have diverged; this is the fundamental reason why the brain's elementary operation is not understood. Experimental research uncovers new facts and additional details. At the same time, instead of realizing and admitting that some initial hypotheses were incorrect, theory creates more ad hoc hypotheses and generates new (experimentally untested) theories. Given that biology claims that laws of nature are not valid for living matter, those newly created (and self-contradicting) theories have only a slight relation to nature. Bad examples include that

- experimentalists measure the ion current's speed in the range of m/s, but theory uses equations that assume a million times higher speed
- experimental research has shown that the Axon Initial Segment (AIS) concentrates the majority of ion channels; however, theory suggests that all ion channels are distributed throughout the membrane
- the current producing the Action Potential (AP) travels through AIS (that is, the resistor represented by the AIS is connected in series to the neuronal condenser); theory insists that the resistor represented by the AIS is connected in parallel to the neuronal condenser
- the parallel  $RC$  circuit cannot produce the experimentally observed neuronal behavior, another ad hoc assumption was introduced: a  $K^+$  current flows against the  $Na^+$  current in the opposite direction, with a precisely coordinated (although unexplained) temporal behavior of ion channels, despite experimental evidence

- the ions have ‘mobility’, but do not need a driving force, and the electric field does not influence their movement
- a ‘leakage current’ must flow, even in the resting state, despite the metabolic efficiency of biology; again, despite experimental evidence
- the leakage current consists of ’leakage ions’, which move independently of the strong potential across the membrane
- the current has the magic feature that it can both emit and absorb heat; this is the only discipline where a dissipative process is reversible.

Anything is possible, given that the laws of nature cannot describe life (or, maybe, life scientists do not know those laws).

The miserable fact is that several aspects of the ”old understanding” are wrong. Among others

- The charge carriers are ions (with a mass nearly 100,000 times bigger and a propagation speed a million times slower than that of electrons). The Coulomb forces between ions is neglected, that excludes understanding that the current comprises ions and that the current transmission mechanism is drastically different
- The biological matter’s current conduction mechanism differs from the one in metals (leading to assuming the conduction speed of free electrons in ionic solutions for ions; the laws of electricity created for light and fast electrons are not valid in the same form for heavy and slow ions a wrong interpretation of conductance; wrong discussion of the electric operation of cells based on false analogies with classic electric circuits)
- In the slow ion currents, the electric repulsion, along with the biological ‘construction’ (constraints, and components with limited capacity), leads to ’skin’ effects that fundamentally alter the physical behavior. The ions create a thin ( $<1\text{ nm}$  thick) ion-rich layer in the electrolyte near the membrane. These skins are responsible for conducting phenomena rather than lipid-based mechanical changes. Classical theory handles the membrane-separated segments (bulk electrolyte) as homogeneous (misses the layer where the dynamic processes of operating the neuron happen) ”the crucial system in biology isn’t a molecule or a molecular class whatsoever, but the interface created by biomolecules in water” [28]
- Ions have simultaneously features charge and mass; changing one of them, changes the other
- The repelling of the slow charged particles naturally causes mechanical and other changes; the signals propagate in the absence of external electrical voltage (concentration gradient and mechanical pressure)
- The slow ion currents and the finite sizes are responsible for the timing relations of the cells

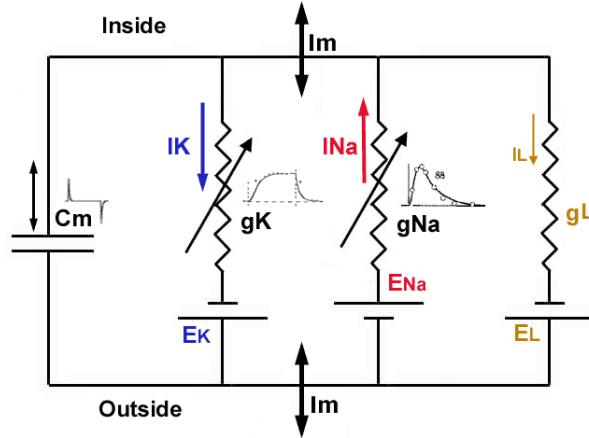


Figure 2: The equivalent circuit for the Hodgkin-Huxley model

- neurons' potential changes are the result of electrochemical (electrodiffusional) processes instead of net electrical ones

Physiology introduced the extremely harmful concept of equivalent electrical circuit, see Fig. 2 that excludes understanding that

- The ions in electrolites move under the simultaneous effect of dual electrical/thermodynamic forces. Bioelectrical (thermodynamic) processes generate control voltages in biology, and they change continuously, i.e., it obscures the need of considering the cooperation and interference between electrical and thermodynamic disciplines; furthermore, it excludes understanding the associated mechanical, optical, and other changes.
- The voltage is location- and time-dependent during AP creation;
- The clamping methods introduce a feedback that contributes an electron current (converted to ion current) to the native ion current; the assumed ‘conduction change’ mechanisms contradict the first principles of charge and mass conservation.
- The communication network has a heavily time-dependent operation
- The neuronal signal processing and computation works with temporal arguments and results
- In the neuronal oscillator, a wrong oscillator type is in use; the vital component AIS, discovered a half century ago and understood two decades ago, is not yet integrated into the theory of neuronal operation (leading to the ad-hoc introduction of a non-existent rectifying current)

- A potential controlled mechanism, instead of fake lipid ion forwarding mechanism, forwards the charge carriers; disabled understanding *why* the neuron remains stable and *how* its power supply works

Biology has a statical view. It neglects that the underlying laws of classical physics developed for infinite, homogeneous, structureless medium, where the interactions have the same speed, are applied to finite, inhomogeneous, structured living matter, where *the interactions have enormously different speeds*; furthermore, that the phenomena happen on the boundary of the continuous and particle views. The static view does not need (furthermore, does not enable to find) the laws of motion (in the sense of laws of Newton, Schrödinger, Hamilton)

- It relies on biophysics, which applies the existing ('ordinary') laws of classical physics in an inadequate way. Classical physics derived its laws for 'another construction'; that is, biological matter also needs different approximations, laws and mathematical formalism. Consequently, what followed, was wrong, including the computational principles, just because of the wrong model.
- Experimentally, clamping and patching (using feedback) introduce foreign currents into the cell, stop its native operation and enable deriving conclusions from that artificial, statical operating mode for the native, dynamical operating mode.
- Theoretically, statical *states* are assumed, and the experienced dynamicity (*processes*) is accounted for as perturbation.
- The *voltage gradient*, instead of currents, controls the neuronal oscillator's operation, which is known from the well-established theory of electricity but neglected in physiology.

Similar is the case with neuronal computing and communication [29].

- Biology applies von Neumann's principles of computing [2], although von Neumann said that applying the idea to biology was 'unsound'.
- It refers to *Shannon's communication theory* [30], although *Shannon explicitly protested* [31] against doing so.
- It attempts to compare the so-called 'spiking neural networks', different mathematical learning algorithms, and even the functionality of artificial intelligence, without being aware that they have only the name in common with their biological counterparts [13].
- The opposite direction faces also similar issues: borrowing only one aspect of biological computing cannot make an approach successful [11], neither in building supercomputers nor in biomorph architectures, large neural networks, brain simulation, or artificial intelligence systems.

Current physiology is based on some tragic misunderstandings (due to the lack of physical knowledge)

- The static worldview, inherited from anatomy and confirmed by the incorrect interpretation of clamping, resulted in treating neuronal operation as perturbations to a static state, without considering causality. The case is similar to the incorrect hypothesis in physics that the orbits of the planets “must be” perfect circles; therefore, the observed deviations “must be” the result of perturbations. Assuming perturbations hides the need for laws of motion in both cases. Relying on incorrect hypotheses excluded the introduction of the correct laws of motion (and, in general, understanding that there are laws underlying the observations). It required working out an elaborate system of perturbations (the work of generations of scientists using a wrong hypothesis).
- The disciplinary approach (combined with overestimating the wrong hypothesis about lipid mechanisms) obscures the fact that the resting potential originates from combined electrical/thermodynamic effects; among others, that the reason for the transient voltage increase is a drastic concentration increase, and that during an AP, drastic transient concentration changes produce the observed voltage changes. The exact mechanism is responsible for the axonal signal transfer (instead of a magic action of cooperating lipids).
- A spectacular example of the schizophrenic perspective in physiology is [32], which, theoretically, starts from the Hodgkin-Huxley model. Experimentally, they measure that there is no time delay between  $K^+$  and  $Na^+$  current; the same subthreshold and suprathreshold voltage gradients generate an AP with the same way but different magnitude (the AP is generated without exceeding some threshold, because a gradient of any size generates such a voltage on the AIS; and the current  $K^+$  itself also shows symptoms of hyperpolarization); the leakage current has the same (negligible) magnitude in resting and transient states (showing that two different ‘leakage’ mechanisms are present in the two states; furthermore, this current cannot be responsible for the membrane’s resting potential); they work with ‘ion counting’ but do not attempt to find out the identity of the ‘leakage’ ions; the leakage ions are neither  $K^+$  nor  $Na^+$ , nor they generate Nernst voltage. Theoretically, they assume that the neuron “pumps 3  $Na^+$  ions out of the cell and two potassium ions in”; experimentally, they show in their Fig. 6 that the ratio changes between 0.01 and 7.5
- The non-scientific approach, which posits that science’s first principles do not apply to life, excludes attempts to introduce physical explanations for processes in living matter and opens pathways for creating an alternative worldview where science creates nature instead of merely describing it.

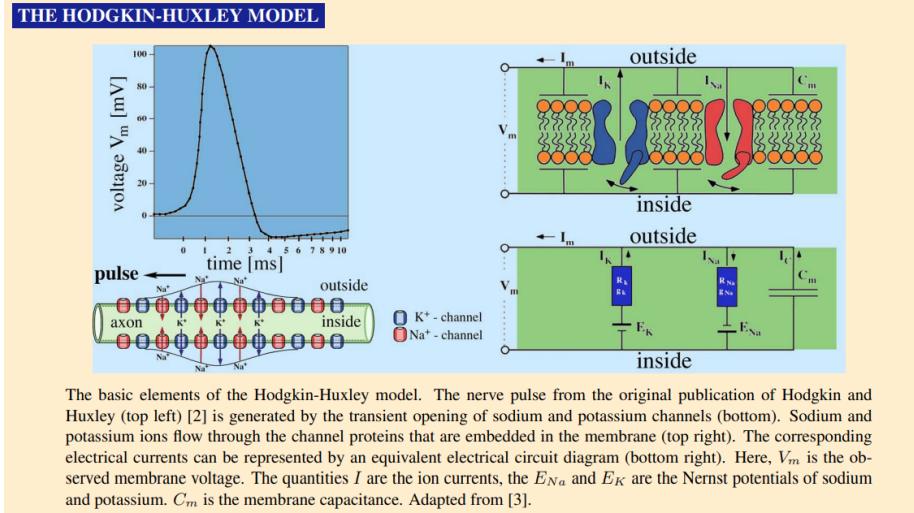


Figure 3: The Hodgkin-Huxley model as reproduced by [33]

**The "model" behind the "old understanding"** A concise summary of the "model" is shown in Fig. 3. Fig. 2 shows the equivalent circuit, which exactly corresponds to the "model" introduced by Hodgkin and Huxley (HH) and their followers and which is used, in different variations, almost exclusively even today. Given that the model is described by equations describing electric circuits, it assumes that electrons constitute the currents. The figure is great in showing that some magic power changes the conductances/resistance without any reason one could perceive. For two of the resistances (annotated as  $g_K$  and  $g_{Na}$ ) the (misidentified) conductance (actually, current) are displayed (compare those conductances to their Fig. 2 and Fig. 6), the third one is due to leakage (with an unknown time course and ionic composition). The condenser is annotated with the output voltage of the differentiator  $RC$  circuit (compare to Fig. 2.1), although the circuit is surely a parallel  $RC$  circuit. This conglomerate very effectively prevents any understanding. Despite of its aim to be an electric circuit, it cannot explain any mechanical, thermodynamic, etc. observations. As an electric model, it cannot reply to fundamental questions, such as *why* an AP begins, *why* the conductance changes, *how* the environment affects its parameters. It simply attempts to illustrate how a hypothetic electrical circuit, with a series of ad hoc (unnatural) assumptions, could produce a behavior in some aspects similar to the electric behavior of a simple  $RC$  electric oscillator, consisting of ideal discrete components.

## The new understanding

Hodgkin and Huxley in 1952 [5] advanced neurophysiology by contributing a long series of *observations* on neuronal operation. However, as they warned, many of the *mechanisms* must be fixed or replaced: "must emphasize that the interpretation given is unlikely to provide a correct picture of the membrane". We honor their outstanding work and want to supplement and enhance their interpretations and hypotheses instead of defying them. However, their work became the "Holy Bible" of physiology and a major obstacle of development in neuroscience. Attempts to present a more complete picture of neuronal physiology, have met with fierce opposition from mainstream neuroscience and, as a consequence, currently remain underdeveloped and insufficiently tested. Commonly misunderstood as to their basic premises and the physical principles they are built on, and mistakenly perceived as a threat to the generally acknowledged explanatory power of the 'classical' HH framework" [34]. The editors 'do not believe' (see Fig. 4) if science advanced in the past seven decades and they censor publishing new ideas in scientific journals. Likely, they did not know that science must "have no respect whatsoever for authority; forget who said it and instead look what he starts with, where he ends up, and ask yourself, 'Is it reasonable?' ... If we suppress all discussion, all criticism, proclaiming 'This is the answer, my friends; man is saved!' we will doom humanity for a long time to the chains of authority, confined to the limits of our present imagination." (Richard P. Feynman) Editors of neuroscience-related journals do not agree with Feynman. They do not want a "new understanding".

The editors' comments on the manuscript "The Physics Behind the Hodgkin-Huxley Empirical Description of the Neuron", submitted to "Physics of Life Reviews". Oct 11, 2024. Rejected without reading. PLREV-D-24-00173  
 "The physics behind the Hodgkin-Huxley model of the neuron is certainly within the scope of PLRev. This model has been extensively studied since it was proposed in 1952 and its proponents won the Nobel Prize in 1963. So it is a challenge to say something original and relevant about this model in 2024. Since the author has no previous publications on the topic, *the Editorial Board does not believe that the review will have any impact on this very well-established research topic.*"

Similary, the manuscript EBJO-D-25-00228 "The unified cross-disciplinary model of the operation of neurons" was believed (after two months of hesitation) was not sent to reviewers, Dec 21, 2025. "We regret to inform you that European Biophysics Journal is unable to accept your manuscript for publication. We have considered it with care but believe it would be better suited to a more theoretical and/or neuroscience-focused journal."

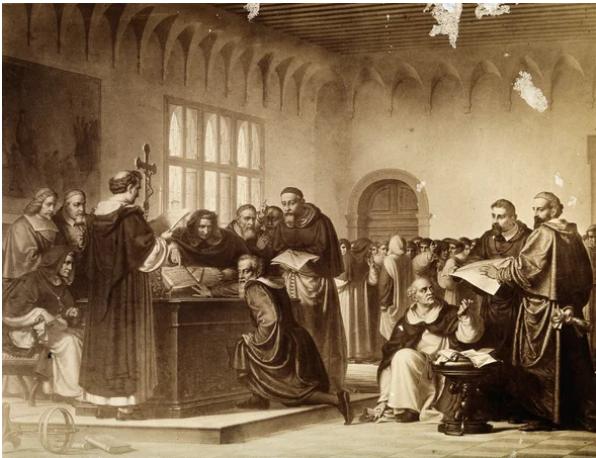


Figure 4: "Believing" in science (in the age of Galilei).

As the Human Brain Project formulated, to enter a new level, "a new understanding of the brain" is needed. It is also correct that "integration between data and knowledge from different disciplines, and catalysing a community effort" is requested. To form a holistic and coherent picture, one really needs several disciplines, openness, and deep knowledge of the related disciplines from the researchers, furthermore also *some knowledge about the bridges to the other disciplines*, as Feynman expressed. Furthermore, *finding the non-ordinary laws of the underlying physics*, including *developing the needed mathematical handling*, as Schrödinger expected. Moreover, after that, *a community effort along the principles of the new theoretical understanding* is needed for validating and revisiting the interpretation of the results of former observations in light of the "new understanding". The present content was written in the spirit of Feynman that we must "have no respect whatsoever for authority; forget who said it and instead look what he starts with, where he ends up, and ask yourself, 'Is it reasonable?'". Reading it, needs the same attitude. It needs much patience; the more patience and effort, the more the reader knows about the subject in the spirit of "old understanding". The "new understanding", the "non-ordinary laws" of physics, spiced with newly developed mathematics, is not easy, not quick, and not effortless. Furthermore, it requires a well-controlled thinking, much above the level "this way we used to interpret the things and reply to this question for decades". Our discussion is a much more faithful description of neurons' operation than the old one.

The "great journey into the unknown" [3] must begin at a much lower level: revisiting the fundamental phenomena, disciplines, laws, interactions, abstractions, omissions, and testing methods of science. Research must build on top of classical science, but be reinterpreted for living matter. There is no independent 'life science', only science. It is based on the same 'first principles' but using different abstractions and approximations for living and non-living mat-

ter and having the appropriate relations between them. "There is a clear need for a tighter and more carefully managed integration and realignment of the work" [35]. Without aligning the knowledge elements along the first principles, the "integration between data and knowledge from different disciplines", lacks "integration". However, even the review of the targeted HBP project summarized that "HBP is not developing with the expected level of integration and the project controls in place are not adequate to achieve this aim." [35]. "More Is Different" [36].

We provide (at least, part of) "a new understanding of the brain". We 'integrate and realign' seemingly distant scientific fields by applying the abstractions and approximations required for living matter. We have reached the boundaries of classical science disciplines, as we have done many times during the past century. We are now moving through terra incognita, where we cannot navigate using the classical disciplinary science. Putting different disciplines side by side, separated according to phenomena in inanimate science, is undoubtedly not perfect and sufficient for describing living matter because of its "different construction" as Schrödinger formulated [8] decades ago. We make a fresh start by rethinking some fundamental ideas of science concepts [37] that seem divergent across these major scientific fields. Research must build upon classical science, but be reinterpreted in light of living matter.

*Biology represents a complex case where phenomena cannot be reasonably reduced to a single discipline*, as classic inanimate science does. Cell biochemistry sufficiently well describes the lipid bilayers that constitute the membrane [38], but does not explain that the negative and positive ends of lipids in an electrolytic solution attract and absorb ions, forming a charged layer on both surfaces of the membrane. This way, the membrane represents a condenser. Cell science does not establish its electrical phenomena; instead, it attempts to elucidate complex lipid activities that explain charge transfer, resting and transient potential, and the entire biological operation using mathematical formulas without a realistic physical background. Electrophysiology combines currents of electrons and ions, and uses Ohm's Law for its admittedly non-Ohmic systems. It introduces foreign (clamping) currents into biological systems; attributing their effect to a changed conductance of the membrane without explaining how the voltage and current can be independent of charge carriers. By introducing current feedback (which, by definition, compensates for any gradient in the system), it applies an opposite-phase control unit against the neuron's native control unit and concludes that, after compensation, there is no gradient in the system; in other words, that *life exists without needing a driving force*. It is not aware that inside the neuron, there is a condenser with a voltage difference between its plates; instead, it believes that a 'leakage current' flows through resistors distributed over the membrane. That current is special in that, among other things, it has neither a chemical composition nor charge carriers; furthermore, it can not only emit but also absorb heat. Neuroscience observes the thermodynamic and mechanical changes but cannot connect them with the electrical phenomena. Lacking the required physical background, *biology claims that physical laws cannot describe processes in living matter*; without providing

a plausible and self-consistent theoretical model. We show that, at a closer look, the concepts with the same name have different interpretations. We must understand that physical laws are about 'net' cases, while biology is about mixed cases, on the boundary of the classical disciplines, or even on the 'nobody's land. We must build a bridge (or maybe a new sub-discipline), concepts and measurement methods for that 'different construction', instead of abusing concepts and test methods of inanimate science to the living matter.

We proceed in a zigzag way when discussing different levels of understanding. Our discussion is closely related to physics, discussed in chapter 2. When discussing the underlying physical laws, we assume a knowledge of classical physics above college-level and go back to the fundamental physical concepts and principles instead of taking over the approximations and abstractions (in this context: ordinary laws of physics) used in the *classical physics for non-biological matter* and less complex (strictly pair-wise, single type, finite interaction speed in homogenous isotropic medium) interactions. We provide a holistic picture, from a physical point of view, by explaining which physical/physiological components cooperate. We derive the laws of motion for thermodynamical/physiological processes of biology in section 2.3.5 (in this context, 'non-ordinary laws of physics'), and introduce a component which implements them. In chapter 3 we go to a less abstract level ("abstract physiology"). We summarize how the components are put together to form, conceptually, the dynamic operation of neural systems, including that *why* the action potential is evoked; furthermore, in general, *how* the processes happen. This abstract discussion serves as a basis for explaining what computing for biology means, see chapter 4; how the idea of computing can be generalized to include the biological implementation; furthermore, how biology implements those general computing principles. Similarly, we use these abstract concepts when we go one step closer to the mystery how biological information is represented, encoded and decoded, transmitted and processed, in chapter 5. After reviewing the operation of individual neurons, we study their cooperation of their "constellations" in chapter 6. We separate the operation of single neurons from the cooperation of neurons, a vital point for understanding the brain's elementary operation. We show how those elementary operations confine the functionality of vast populations of neurons, belonging to the notion of intelligence in chapter 7. We also provide hints how those operations affect intelligence.

**The "model" behind the "new understanding"** In our view, we consider that neuron is a semipermeable elastic spherical lipid membrane (i.e., low transmission capacity ion channels are present in the wall), which has a membrane tube (axon) connected. Through that membrane tube, the neuron connects to its "downstream" neurons. Between the membrane and the axon, a high transmission capacity component (AIS) is located. We explicitly consider that the neuronal current consists of ions i.e., the current is slow and the ions repel each other. The biological structures can become statically charged, and they can accelerate/decelerate the ions to different speeds. Those different speeds

can be responsible for different phenomena, from forming a resting potential to producing enormous electric gradients, including creating charged electrolyte layers temporarily near to the membrane's surface needed for the dynamic operation. A Proportional-Integral-Derivative (PID) controller controls the neuronal operation, which also defines its experienced electrical behavior (describes the features of currents in the resting and the transient stages). The repulsion between the ions represents an electrical force, which, in the closed volume of the neuron, provokes a mechanical force (a mechanical pressure). Our view naturally connects the features seen by thermodynamics and electricity, showing that those disciplinary views see the two sides of the same coin. The forces due to electricity and thermodynamics are proportional to each other, so, at the price of using a "falsified" force (increased with the force from the another discipline), one can perform calculations using both (the correct) electrical or the thermodynamic theory. For discussing the creation of an AP, the electrical theory provides more comfortable tools, while for discussing its transportation through the axon, using the thermodynamic theory is more comfortable. The model resolves the many contradictions between theory and experiments, and enables deriving the correct concepts for the energetic operation of neurons, as well as interpreting its information processing.

# Chapter 1

## Single (abstract) neurons

"Despite the extraordinary diversity and complexity of neuronal morphology and synaptic connectivity, *the nervous systems adopts a number of basic principles*" [1]. In this chapter, we derive those principles in an explicit form from the first principles of science and we prepare that discussion in an abstract level. We prepare the concepts and principles which enable us to answer E. Schrödinger's question concerning physics. In the spirit of Johnston and Wu [1], we introduce the relevant major components of a single abstract neuron that still follow the basic principles when processing neuronal information, moreover, the abstract principles of how they cooperate, conceptually. Our motto is similar to the frequently cited saying 'Cherchez la femme': *Look for the charge*, meaning "no matter what the problem, some charge is often the root cause" (however, we consider also effects of the thermodynamics on charge, given that the charges are ions instead of electrons. Furthermore, we shortly consider the mechanical, optical, etc. consequences.). The expression comes from the novel *The Moths of Paris* by Alexandre Dumas and is frequently used in detective novels in the sense that there are always complications and unusual situations, but "no matter what the problem, a woman is often the root cause". Although, in most cases, the cause is seemingly different. However, the primary entity when speaking about neural operations, is the charge. Exactly as formulated: "Transient electrical signals are particularly important for carrying *time-sensitive information* rapidly and over long distances. These transient electrical signals—receptor potentials, synaptic potentials, and action potentials—are all produced by *temporary changes* in the electric current into and out of the cell, changes that drive the electrical potential across the cell membrane away from its resting value." "we consider how transient electrical signals are generated in the neuron." [39], page 126. We note, however, that the electric phenomena are closely related to other disciplines, mainly thermodynamics.

## 1.1 Introduction

Nature uses an infinite variety of implementing neurons. However, they can cooperate. "We must be prepared to find it working in a manner that cannot be reduced to the **ordinary** laws of physics". [8] We base our discussion on those (sometimes 'non-ordinary') laws, see section 2.3.2, and create an 'abstract physical neuron' model, skipping the 'implementation details' nature uses. Notice that at that time, it was not yet recognized that the electric signals propagate with a finite speed also in the dendrites (or, more precisely, its handling in mathematics and physics was not solved), not only on the axons; furthermore, that AIS is a separated (and, for forming an AP: vital) component of the neuron. We develop the needed 'non-ordinary' laws in chapter 2.

"Neurons are specially endowed with the ability to communicate precisely and rapidly with other cells at distant sites in the body." "Neurons have receptive dendrites at one end and a transmitting axon at the other. This arrangement is the structural basis for unidirectional neuronal signaling." "The cell membrane of neurons contains specialized proteins—ion channels and receptors—that facilitate the flow of specific inorganic ions, thereby *redistributing charge and creating electrical currents* that alter the voltage across the membrane." [39], page 71. We follow this line and explain how processes, that traditionally belong to different science disciplines, redistribute charges and create electrical currents, them discuss how the cell handles the electrical charge. The details are described in Chapter 2, where the fundamental differences caused by the charge carrier are discussed.

We agree that "The basic structural units of the nervous system are individual neurons" [1]. However, we also know that multiple neurons "are linked together by **dynamically** changing constellations of synaptic weights" and "cell assemblies are best understood in light of their output product" [12]. However, the classic understanding replaces the dynamic description with a perturbation-level correction to a mostly wrong (and century-old) **static** description; furthermore, it lacks the laws of motion, and the modern understanding of the operation of the **dynamic** components the detailed operation requires. The final reason is the wrong understanding of living matter's non-disciplinary scientific operation, so we must go back to the first principles of science. Here, we give a holistic picture of neuronal operation and provide details in the subsequent chapters.

We agree that '*the fundamental task of the nervous system is to communicate and process information*'; furthermore, that '**neurons convey neural information** by virtue of electrical and chemical signals' [1]. The goal was set decades ago: '*The ultimate aim of computational neuroscience is to explain how electrical and chemical signals are used in the brain to represent and process information*' [10]. It was also confirmed two decades later: "Information is carried within neurons and from neurons to their target cells by electrical and chemical signals. **Transient electrical signals** are particularly important for carrying **time-sensitive information** rapidly and over long distances" [39], page 126. Our goal is to describe the role of neuroscience signals in an abstract level, provide their mathematical description based on established

physical processes, to understand their interdependence, to explain the physics they use, to find out in the later chapter how at physical level the information is represented and processed.

First of all, we introduce (and, in this aspect, correct the current common understanding) that neurons' "output product" [12] *is created and transmitted by thermoelectric processes instead of net electric phenomena or net thermodynamic*. Feynman was right, also in this point: "*nature is not interested in our separations, and many of the interesting phenomena bridge the gaps between fields.*" [4] We derive the correct mathematical and physical handling processes, not considering the disciplinary boundaries, pointing to where the disciplinary omissions and approximations are not valid, deriving the required correct handling of the physical processes together with the mathematics required to handle them. We use the theory developed in section 2.3, where (among others) the time derivatives of the processes are introduced, in this way enabling the quantitative mathematical description of the neurons' abstract operation, that serves as a basis for discussing quantitatively the neural computing processes (as we discuss in section 2.3.5, these derivatives are the laws of motion of ions) and their information handling. However, these corrections must be carried out in disciplinarily separated chapters.

In the present chapter, we consider only the holistic picture, without details (in an abstract way) in the sense that we attempt to explain what are the principles that neurons' functionality implement. Our point might be felt as a technical one, although it is not so. We only attempt to stay at an abstraction level, similar to the one cited in connection with communication and information, when formulating neuron's functionality and features. We keep an eye on the discussion in other chapters and we present *a purely physical model with purely physical interactions, in the spirit of the limited interaction speed*. We borrow the names of components and their operations from biology. We use physical principles and laws behind them (the details are discussed in separate chapters). We build an artificial (abstract) neuron, using the 'ordinary' and 'non-ordinary' laws of physics. We use explicitly the finite speed of ions in electrolytes and derive the 'extraordinary' laws from the mixing of the interaction speeds. We demonstrate that our abstract model passes the duck test "If it looks like a duck, swims like a duck, and quacks like a duck, then it probably *is* a duck".

## 1.2 Abstract modeling

Our abstract model focuses on the neuron's signal processing function. However, we cannot reach our goal without the correct physiological understanding of its mechanisms. In the next chapter, we show that nature and its observable phenomena are complex; it is pointless to dispute which of the scientific disciplines describes neuronal behavior. The non-disciplinary approach shows that the firm and fast electric interaction sufficiently well describes neuronal operation after introducing the equivalent "thermodynamic electrical potential".

In this chapter we consider that neurotransmitters, receptors and specialized membrane proteins *only implement a kind of (time and energy-consuming) chemical/enzymatic decoupling of the signal transmission mechanism*. The idea resembles opto-coupling in electronics: makes *the signal transmission independent from the local potential value*. Suppose neurons use galvanic coupling when the resting potential of one of the neurons equals the extracellular space. In that case, all connected neurons' resting potential is equal to that of the extracellular space. Without this decoupling, the death of one neuron would immediately lead to the death of the entire neural network. Furthermore, the neurons could not make independent signal processing.

### 1.2.1 Modeling approaches

The spatiotemporal neuronal operation is too complex and fast to enable a sufficiently detailed and accurate observation of neuronal operation. Given that the action potential involves rapid changes in membrane potential, the genial idea (originally introduced by Cole and Curtis [40]) applied by Hodgkin and Huxley [5] was to slow down (actually to "freeze") its dynamics by the "voltage clamp" device, which can set the membrane's potential at a particular voltage and keep it there, using electrical stimulation and feedback. *This advantage of the method is its disadvantage at the same time*. First, since it uses purely electric stimulation and feedback, it suggests that the stimulated operation is also purely electrical, hiding that it is a thermoelectric process (and it is accompanied by mechanical changes). Second, it enables experimenting with "snapshots" of the operation (the feedback fixes the neuron's voltage, in a frozen state, to a particular value), hiding that *the operation is dynamic and needs a dynamic description by laws of motion*. Third, the feedback the method uses means introducing 'foreign' (external), time-dependent current into the cell, is not in their equations.

The method has enabled them to gain an initial understanding of what was happening in the neuron at each stage of the action potential. Correspondingly, they have set up a classic *predictive description* (a very precise set of observations, in the form of mathematical equations), describing *purely electrical static processes*. Although they correctly determined that an influx of sodium ions through voltage-gated sodium ion channels causes a rapid shift in membrane potential, which causes the initiation of the electrical signal that is known as the action potential, their picture (which, in their opinion, "the interpretation given is unlikely to provide a correct picture of the membrane") could not accurately describe the observations, especially their timing relations.

The main goal of the BRAIN initiative was "observing their [the neural system's] *dynamic* patterns of activity as the circuit functions *in vivo* during behavior, and *perturbing* these patterns to test their significance". [24] This method is exactly equivalent with the predictive Ptolemaic system for describing planetary motion, that lacked the (Newtonian) laws of motion. The "natural" expectation for the paths of celestial bodies was that they must travel in uniform motion along the most "perfect" path possible. It presumed "perfect" circles (without

reasoning) for planetary orbits and adapted them to the real-world planetary orbits by *perturbing* them (without reasoning why that perturbation occurs), instead of discovering their laws of motion and understanding that they are ellipses. Ptolemy's model explained the observed "imperfection" by postulating that irregular movements were due to a combination of several regular circular motions ("perturbation") and introducing ad hoc spheres. The idea of the "perfect path" had to be replaced with "Newton's law of universal gravitation". At first glance, that universal law, without solving its differential equation, has no relation to the ideal path.

"Central to the BRAIN Initiative is the discovery, development, and dissemination of new theories". [24] However, there is no project to validate the principles used in the so-called theoretical descriptions. Neuroscience theory remained static, forming a fundamental obstacle to understanding the dynamic operation of neural systems. This is precisely why a new perspective must be introduced. The static view means that by measuring technologies such as clamping or freezing means that *we forcefully prevent the gradients from changing, which change is the life itself*. That view enables us to study fine details of samples taken from living materials that themselves do not live (in the sense of activity they do in their native state), and *hides that they have internal forces which move them according to their laws of motion; furthermore, that such laws exist*. Measuring electrical activity in a living system affects its electrical (and, through this, chemical) behavior.

We must also defy existing ideas and notions, shortly discuss why they show some initial successes and why they lead to wrong conclusions; furthermore, introduce new ideas (why we must combine electricity and thermodynamics (as well as mechanical changes) instead of using them side by side in physiology; why do we need to revisit physical principles to handle interactions with different speeds; which rules are valid when combining phenomena of the boundary of microscopic and macroscopic worlds; what is the true abstract operating principle of neurons; why information has a different meaning and needs different handling in technical and biological implementations).

### 1.2.2 Model types

"There is a widely accepted distinction between merely modeling a mechanism's behavior and explaining it. ... Some models are data summaries. Some models sketch explanations but leave crucial details unspecified or hidden behind filler terms. Some models are used to conjecture a how-possibly explanation without regard to whether it is a how-actually explanation." [41]. The only neuron model [5] which attempted to equip fellow researchers with scientific background based on the authors' experiences and their conclusions drawn by using mathematical equations from experimental observation, is evaluated extremely differently. The scientifically unusual brainstorming or 'call for a collective effort' nature of the paper legitimates nearly all possible classifications.

We discuss that model in a separate section 3.6; with their genial observations and conclusions, and the minor mistakes they made when making that

huge first step into the unknown. As always, the second step must include more discoveries and new perspectives (in our case, of more than seven decades), and minor corrections must be performed to fix the scientific direction. As we discussed, we admire HH's activity. However, in the interest of advancing science, we must include the discoveries into their picture.

HH considered their work (in the classification above) as a data summary with clear signs of using empirically measured conductance and fitted polynomials for their measured data. Unfortunately, their followers accepted their ad-hoc assumptions even though the model "sketches explanations but leaves crucial details unspecified or hidden behind filler terms". They even introduced further ad-hoc assumptions needed to provide satisfactory agreement with the experimental evidence into HH's admittedly wrong physical picture, and they forgot the doubts and question marks HH described and took their unproven hypotheses as facts. "These equations and the methods that arose from this combination of modeling and experiments have since formed the basis for every subsequent model for active cells. The Hodgkin-Huxley model and a host of simplified equations derived from them have inspired the development of *new and beautiful mathematics*." [42]. That mathematics is new and beautiful, but, unfortunately, *describes some pseudo-nature instead of the genuine one*. Unfortunately, their (wrong) oscillator model is used by neurophysiology textbooks [1, 21, 43] and also neurophysiology research, including grandiose projects [24] or Human Brain Project. From a wrong starting point, with the wrong ideas in mind, only more fake spheres are added to the model, but no good research results are achieved.

Even in the collection of topics "Single Neuron Computation" [44], their chapter 1 "introduces the topics of electrotonic (electronic circuit equivalent) modeling of realistic neurons and the interaction of dendritic morphology and voltage-dependent membrane properties on the processing of neuronal synaptic input". This approach suggests that nature should build its neurons from discrete electronic components. In other words, nature must adapt to mathematical equations. *Studying such neurons built from discrete electronic components with well-established mathematics is much easier than finding the correct physical background*. The book chapters attempt to compose a neuron from (models of) different sub-components, interactions, etc. The approach is sufficiently good to serve as the book's opening chapter and as a basis for discussion in the adjacent chapters. However, the many controversial models lead them to conclude that "this raises the possibility that the neuron is itself a network". Yes, the Prolemaian model can describe nature using an infinite (perhaps recursive) set of spheres. The validity of the approach is at least questioned [45] (given that the model is called "realistic"): "Is realistic neuronal modeling realistic?"

### 1.3 Modeling and disciplinarity

As of today (2025), the understanding of neuronal operation remains divergent. As [46] formulated, "bio-electric and a thermodynamic perspectives" are fighting, mostly in the spirit of "if the only tool you have is a hammer, you tend to

see every problem as a nail”, and discusses ”answerable what-if questions that have been overlooked or purposefully neglected thus far”, without attempting to integrate those disciplinary perspectives. (BTW: that effort would be hopeless: as we discuss, the life-related phenomena happen in the ”nobody’s land”: the ”construction of the living matter” requires dividing processes into pieces and describe them with different physical processes that are interfaced to each other.) By neglecting that ions are ”material points” that also have charge, the cellular phenomena cannot be described in either approach alone, given that they are simultaneously governed by the laws of the two mentioned fields, with many specialties. Furthermore, molecular and enzymatic effects also shape the operation, in most cases adding color to it. Our discussion combines appropriately the two disciplines (not the two perspectives!) in an almost abstract approach, emphasizing also their cooperation, furthermore, at some places mentioning also biochemistry. First, we give an overview (with the intention of providing sufficiently solid background for the audience having not too deep knowledge in physics, thermodynamics, and electricity), and we expand the quantitative details in later chapters with a complete disciplinary underpinning.

As we mentioned, other, more physical (sometimes extreme, sometimes called multi-physics) approaches ”have met with fierce opposition from mainstream neuroscience” [34]. The thermodynamic effects seemingly mask the true causes of neuronal function and lead to a misunderstanding of physiological evidence. We discuss the operation of neurons mainly in electrical terms after deriving an ”equivalent thermodynamical electric field”, we can, by considering the electric repulsion of ions, associate the observed mechanical effects and explain the thermodynamical effects of neuronal operation. We discuss the thermoelectrical, computational, information theoretical, and physiological details in different chapters. In those discussions, we return to the same concepts repeatedly, in von Neumann’s ’zigzag’ way, from different points of view (at different abstraction levels and disciplinary depths).

Again, another approach: over the decades, computational and/or mathematical neuroscience implemented ad hoc mathematical formulas only slightly related to neuronal operation because theoretical neuroscience did not provide the correct scientific background. They forgot the warning that ”the success of the equations is no evidence in favour of the mechanism” [5]; biophysics attempts to find out unestablished mechanisms for the equations. It is not possible to understand even correct experimental observations and to design thoughtful experiments; furthermore, among others, to understand the role of synaptic weights, the formation of APs, and neuronal information processing, without fixing the scientific background (or providing a wrong background), the misunderstood electric operation and misinterpreted physiological observations; furthermore, the abused concepts of technical computing and information that result in ”technomorph biology”[11]. Moreover, we must introduce non-disciplinary physical laws, maybe a more appropriate name for the idea that E. Schrödinger coined [8].

The ’abstract’ means that we omit the physiological details and focus on the abstracted operating principle, *what* the function or component wants to

implement, *why* neededs. The 'physical' means that we put a *non-disciplinary* physical mechanism behind the different stages of operation. We intend to find the appropriate stages, or *the series of dynamic stages*, with corresponding transitions. Our method is to omit, per stage, the less important interactions and processes. In some (but not all!) cases, we can reduce the actual stage to a single (dominant ) interaction, described by a single scientific discipline. In other cases, the stages (or their interfaces) have a dominant interaction and a correcting interaction, so we need to invent new procedures. Such multiple simultaneous interaction cases are rarely discussed in science. When discussed in science disciplines, the interaction speeds are considered to be the same, and the related laws are used in their simplified form. This is the only place where our description is 'non-ordinary': we check whether the omissions leading to the 'ordinary' laws are legal, and derive our 'non-ordinary' laws where needed. Those laws are non-ordinary only in the sense that, instead of the 'ordinary' ones we used to in classical science, we use the correct approximation and abstractions needed "because the construction is different from anything we have yet tested in the physical laboratory" [8]. Furthermore, they may be "non-ordinary" also in a mathematical sense.

### 1.3.1 Non-disciplinary approach

Our abstract physical neuron shows different faces toward the different classical scientific disciplines. Those faces are more or less different in the classical and our "modern" view. We mean we discuss the latter but mention the former, evaluating the wrong hypotheses and the discoveries that vitiate the old picture and introducing the new one. Unlike in the old view, we check the consistency of the different views with each other. In the old picture, the neuron is static, and a hidden (only empirical) mechanism controls its operation. It provides an over-detailed biological description that includes *static* currents and assumes fake (narrative and physically unrealistic) operating details. The new picture is based on a sound physical background and a quantitative description.

Thermoelectricity, the fundamental interaction for our discussion, is a very special case for classical science. By discipline, it belongs to thermodynamics and electricity. Both disciplines have concepts interpreted in microscopic and macroscopic terms. What makes the case similar to the well-understood electromagnetism is that two kinds of force fields act simultaneously on the object under study. What makes the case fundamentally different is that *the force fields' propagation speeds differ by several orders of magnitude*. We must derive new mathematical methods for handling different interaction speeds. We succeeded in providing the driving forces and the laws of motion (the time course) of thermoelectric processes, see section 2.3.

For physiology, a neuron is a semipermeable membrane surrounded by electrolytes having enormously different concentrations on its two sides; which receives and generates different current pulses. For physics, it is a system with variable and mixed speed interaction, which needs to be considered in terms of microscopic and macroscopic features; checking the validity of statistics per

stage and per time; handling the operations with entities distributed in time and space; handling the operations with entities distributed in time and space; reinterpreting many approximations and laws from classical physics to biology. For electronics, it is a *serial RC* circuit (instead of parallel one) which operates with *slow* ion currents and has finite sizes. Its condenser is equipped with several gated inputs (the neural condenser gates its inputs depending on its voltage), and an ungated output. It needs to work out the handling of bio-electric processes, where the "charge production" by the biological objects combined with delays due to the finite speed and finite size. One must take special care when applying laws from the science of non-living matter. The first principles are the same, but the laws have forms that differ from the ones used in classical physics and resemble those used in theories of relativity. Usually, as we mentioned, only the *differential* form of those equations is valid, as opposed to the simplifying *integral* form. For mathematics, it is a set of differential equations (per-stage differing boundary conditions); time-aware and biology-aware algorithms [20, 11]; unusual mathematical methods such as result-depending integration limits; handling the one-way synchronized cooperation of neurons; biologically faithfully reproducing neural learning; among others. For programming and simulation, a neuron is an event-controlled object with its *simulated local time*, which is independent of the wall-clock time; interacting with the structure of the neurons in the computation and the computing architecture. It needs faithfully reproduced timing relations, and because of the steep derivative functions, adaptive numerical solving algorithms; handling neuron-local and neurassembly-local simulated times to keep the system synchronized; among others. Of course, separating the disciplines cannot be perfect; the disciplinary laws mutually and permanently interact, allowing only differential descriptions. Some repetitions and intensive zigzagging are inevitable.

### 1.3.2 Creating the brain

Let us play with the idea that we are assisting God (or evolution) in creating the World. We are a subcontractor, and our task is to design the brain. We must consider several constraints. The brain we design, to mention a few major items, must

- be governed by the available laws of nature
- use the available (living and non-living) matter
- be compatible with the objects to be controlled
- control biological objects
- be as powerful and energy efficient as possible
- be inexpensive (both its creation and operation)
- elaborate protocols to work with unreliable components

- apply tricks to overcome the inherently slow operation of its components
- process (encode, transmit, decode, store) information
- cope with harsh environmental conditions
- adapt to changes in the environment and in its own components

Two other subcontractors were already working on creating the World. They have conducted a "feasibility study" and elaborated the necessary laws (including their mathematical formalism) for their field. They have the right and freedom to simplify and elaborate on the implementation details, provided that the principles of cooperation among the parts are not violated. They are self-consistent within their field and do not conflict with the first principles of nature. Given that the task was challenging and the general laws complex, the group subcontracted to deal with non-living matter, made simplifications (approximations and abstractions) and worked out their own laws (today we know that work as laws of non-living nature); sometimes only implicitly adding that their laws are simplified ones and are consistently valid only to the field of that group's activity. With those simplifications, they achieved success in their field, though they sometimes had to revisit them. In those cases, new science disciplines were born, such as discovering the non-independence of space, time, and mass, which led to the theories of relativity, or discovering the relations between the continuous and discrete descriptions of nature in thermodynamics and quantum theory.

When, somewhat later, the second group subcontracted for creating laws of living matter, they were allowed (and obliged) to use the product of the first group. They wanted to take a flying start, and they took over those simplifications (the simplified laws describing non-living matter), saying that those simplifications were proven successful for the other group; instead of deriving their specific simplifications for their specific field, the living matter. Initially, they were successful; the minor discrepancies were attributed to their inexperience. As the discrepancies started to grow, the second subcontractor started to claim that the laws describing non-living matter are not valid for living matter, *without discovering which other laws describe living matter*. Our approach to that problem is that we scrutinize the interactions and describe their effects in a non-disciplinary way.

The third working group started to work when the second group already had some significant achievements, and aimed to organize the cooperation of units based on the principles of living matter, in two stages. Of course, they were allowed (and obliged) to use the products of the second group when creating resources and operating principles of the network of living matter organized into biological units. Although the original goal was only to concentrate the work of specific goal-oriented groups of units for survival, the method (called neural computing) developed by the group was so successful that a higher-level unit coordinating the lower-level coordinating units has been created. Of course, it inherited the laws developed for the former levels. As the operating complexity of that latter unit (called the brain) grew, again higher-level functionality

appeared (called the mind) that is again based on the inherited lower-level laws. That means, to understand the high-level functionalities, one needs a very accurate understanding of the elementary neuronal operations, which has the precondition of understanding life itself. (We just mentioned a fourth working group of increasing importance. After that the performance of technical computing, due to physical and technological reasons, to enhance the energy and computing efficiency of technical computing systems, a growing interest appeared toward borrowing concepts of biological computing.)

The best approach to the problem of describing life by science was given by E. Schrödinger [8], by saying that the fundamental principles must be the same, but the 'ordinary' laws of science we derived for non-living matter might differ from the 'non-ordinary' laws of science describing living matter. He expressed his firm scientific conviction and commitment that (by using different approximations) we can derive those laws based on science, despite that the "construction" of living matter needs different approaches. In other words, the general laws of nature ("the first principles") behind the simplified laws derived as approximations describing "non-living matter" and the ones describing "living matter" differ only in the approximations they use. This way, the 'ordinary' and 'non-ordinary' laws, together, describe nature; among others, they describe life.

We point out that when we map the formal laws of non-living matter onto living matter, we do so outside their range of validity. Instead, in some cases, we must derive special approximations valid for living matter, and derive the appropriate laws for those abstractions. We derive the correct laws (valid for living matter), which –according to Schrödinger's expectation– are 'non-ordinary' in the sense that their form and range of validity differ from the 'ordinary' ones we use in classic science. The general laws of nature are universal; their simplified ones can be disciplinary. However, "*nature is not interested in our separations, and many of the interesting phenomena bridge the gaps between fields.*" (Richard P. Feynman) We know that nature is infinitely complex, all science disciplines apply approximations, and use mathematics to describe that simplified nature. To "design" neuronal operation, we must consider and coordinate all related disciplines. They are not contradicting each other, but some of their fundamental considerations may prove to be oversimplifications when the respective discipline must cooperate. It also brings to light that we need to invent new pieces of mathematics.

In this section, we assume that, in addition to the well-known 'ordinary laws, those 'non-ordinary' laws exist (we will derive them in Chapter 2 given that they may belong to different scientific disciplines), and we derive the abstract rules that enable neuronal cooperation. We describe the known (and more or less understood) static components, the recently discovered (but not yet integrated) ones, furthermore the dynamic components and processes needed for the observed operation, but remained hidden by the testing methods.

### 1.3.3 Existing models

Textbooks, such as Neuronal dynamics and [21], usually skip the question *how* the neuron, a piece of living material, is modeled. Instead, they put behind their formulas, without validating them for biology, the picture taken from classical physics, which was validated for different circumstances (non-living material), for describing electrical circuits. This way, they shoot themselves in the foot. At the time of setting up their model, it was not known that the overwhelming majority of ion channels were concentrated in the AIS, and only a small fraction is distributed over the membrane's surface. HH hypothesized that the (at that time, only hypothesized) ion channels are distributed over the membrane, so that the neuron can be modeled as a distributed *RC* oscillator circuit, corresponding to a parallelly connected oscillator comprising discrete elements *R* and *C*. Their model was the best possible one in their time, but we know for decades [47, 48, 49, 50, 51], that those ion channels that they hypothesized serve only for maintaining the resting state, and the transient state needs a different mechanism.

HH seem to be one of the rare exceptions, but as they admit, the "*interpretation given is unlikely to provide a correct picture of the membrane*", furthermore, that "*a physical theory of this kind does not lead to satisfactory functions ... without further ad hoc assumptions*" [5].

## 1.4 Concepts of the play

"Breaking down topics into digestible chunks and explaining them helps you identify gaps in your knowledge. This creates new neural pathways in your brain, which makes connecting ideas and concepts easier." R.P.Feynman

In this section – in the spirit of Johnston and Wu [1] – we review how the relevant significant components, actors and actions of a single neuron follow the 'basic principles'. Textbooks usually skip *how* the neuron, a piece of living material, is modeled. Instead, they put behind their formulas (unfortunately, referring to HH), without validating them for biology, the picture taken from classical physics, which was validated for different circumstances (non-living matter) in a classical disciplinary concept. HH seem to be one of the rare exceptions, also in the context that they admit that the '*interpretation given is unlikely to provide a correct picture of the membrane*', furthermore that '*physical theory of this kind does not lead to satisfactory functions ... without further ad hoc assumptions*' [5]. Their followers introduced further ad-hoc assumptions, needed to provide satisfactory agreement with the experimental evidence, into their admittedly wrong physical picture. Those models assume that the circuits comprise point-like ideal *discrete elements* such as condensers and resistors, and some mystic power changes their parameters; furthermore, ideal batteries with a voltage that, again, may change their voltage. All of them are connected by conducting (metallic) ideal wires, and their interaction speed is infinitely high

(the Newtonian 'instant interaction'). That approach leads to the 'electrotonic model' [52], which is half-century old. It was question marked whether they can be realistic [45] at all. That abstract model enables them to use the well-known classic equations named after Ohm, Kirchoff, Coulomb, Maxwell, and others. However, those abstractions have severe limitations when applied to living material; moreover, they mislead research in some aspects. It could be useful in its time of discovery, at a very elementary level, but it surely cannot describe the details discovered during the past half century.

We provide a "birds' eye view" of our model's operation. We must refer back to the need of the zigzag discussion. We introduce our fundamental terms and notions in a way that we assume the audience has at least a fundamental knowledge of the subject. We refer to the corresponding sections, discussing the physics that establishes them, and the sections which, in terms of "abstract physiology" (without biological details), provide more details.

When describing neuronal operation, we start with the point: "neurons are sites where *information is handled in analog rather than digital form*. There may be hundreds of excitatory nerve endings on the surface of one postsynaptic cell. Each terminal is capable of secreting the excitatory (or inhibitory) chemical. The rate of secretion is governed by the rate of arrival of presynaptic impulses. True, each impulse in one terminal liberates a definite amount of transmitter, but there may be many impulses in many such terminals. The postsynaptic depolarization that ensues is essentially a continuously gradeable process. The membrane potential of a neuron waxes and wanes with the ceaseless variations of excitatory and inhibitory input, and with it varies the stream of impulses issued in its axon. *The digital pulse code of presynaptic fibers is thus converted into an analog process at the junction, only to be reconverted into a digital pulse code again in the axon of the postsynaptic cell. The logical operations are all performed in the analog mode at the synapses.*" [53] We emphasize that all processes are slow (in the sense that they have well-observable time course as opposed with sudden changes and 'non-ordinary' laws of science describe them), furthermore, that neurons exist only in their dynamic way; their static discussion is misleading. Note that those "ceaseless variations" can be correctly handled by our dynamic methods.

Following the path to understanding neural functionality (mainly: the brain and life in general) involves creating the necessary microbiological components, their elementary functions (physical function, stimulus processing, cooperation, and reproduction), and their higher-level cooperation (networks). The overview of the entire operation requires not only a multitude of scientific disciplines but also their cooperation and periodic coordination (reconciliation) of their approaches. A fundamental aspect is the precise description of the temporal behavior [23] of the participating processes (very slow compared to the interaction speeds usual in physics), for which the laws derived from generally used physical approaches are not suitable (their use produces misleading results) - almost the same holds also for technical computing. Computing science is still based on the principles laid down by von Neumann [2]. However, the technology in the meantime has reversed the ratio of transfer and processing times, so

the theory is used far outside its range of validity. Since approximately 2000, the theoretical description has become increasingly inadequate for actual computing technology [11], particularly for computing accelerators and networked solutions, as it overlooks Feynman's warning [16] that computers belong to the engineering field rather than mathematics. The finite speed of interaction (data transmission) becomes increasingly important as the operating speed increases. It enforces technical limitations [22, 11] on the performance of supercomputers [54] and neural networks [55] (whether biology-imitating or technical ones); their performance strongly decays as the system's size increases. The technical solutions inherited from the single-processor age, combined with the non-time-aware viewpoint of their theories in both computing and biology [11], prevent the correct discussion, and even more, combining them, whether attempting to imitate one with the other (biomimetic architectures, brain simulation, or artificial intelligence) or combining them (brain-computer interfaces). We aim to continue researching ways to improve cooperation between these disciplines by analyzing their features theoretically and simulating them.

### 1.4.1 Operation in a nutshell

We have Scrödinger's comments in mind when constructing the physical picture about neurons, that we must be very careful. *We must not use the 'ordinary' laws of physics derived for non-living material without revisiting them because "the construction is different from anything we have yet tested in the physical laboratory"* [8]. The fundamental principles are the same, but we must use different approximations and abstractions for living material. For this reason, maybe it is more correct to call those laws 'non-disciplinary' instead of 'non-ordinary' laws. We must also include the discoveries from the past seven decades, among others that a neuron shall be modeled as a serial (i.e., differentiator-type) electric oscillator, which has gated current inputs (instead of a parallel oscillator without gating inputs) and provides a timed output. We explicitly add that the charge carriers, the neuron works with, are *ions* (instead of electrons) and that the signal propagation mechanism is *thermoelectric* (instead of electric field propagation or thermodynamic diffusion), in many cases even without having free carriers in the respective volume. (We do not consider the ideas that the associated mechanical, optical, etc. changes cause electric phenomena. They reverse the true causality: they do not have a triggering cause; the view inherited from the narrative biology.) Electrochemical operation, especially that of semipermeable membranes, requires special attention: charge carriers are "created" inside the biological matter. Omitting purposefully the clear physical background results in performing wrong measurements and introducing wrong concepts into biology. These distinctions involve numerous special features as follows. The play is divided into scenes and acts, where actors play roles in front of sets. Here we will only give a "guide" summary. Some parts of the plot are discussed in detail, others only in outline. Fundamentally, in this chapter we provide a mostly narrative discussion, the detailed explanation (assuming a deeper knowledge in physics and mathematics) is left for other chapters.

In the non-disciplinary physical model (the 'abstract physical neuron', as we call it), a neuron (highly simplified) is a sphere with two lipid layers (membrane), a similarly insulating output tube (axon), and an incompressible, partially ionized electrolyte fluid with different composition and concentration inside and outside. They contain ions, simple chemical molecules, and complex biological formations. These components may have gradients and move at continuously changing speeds that can vary by several orders of magnitude during operation. The lipid layer is partially permeable (controlled or uncontrolled) for the components above (channels, mainly ion channels).

Between the membrane and the axon, there is a large amount of uncontrolled ion channels (AIS). The membrane represents a confined space in which ions behave differently from in an infinite space; furthermore, it significantly alters the properties of the few-nanometer-thick layer near the membrane. The elastic wall of the membrane is covered with ion layers, and therefore, a potential difference is created there (the resting potential). In this layer, the concentration and potential change significantly with distance from the membrane due to interactions between the membrane's ion layers and the electrolyte. Ions sent by other neurons can enter the internal volume through controlled inputs (synapse).

The membrane functions as a PID control circuit. Under a small external influence, neuron remains in its resting state and regulates itself through non-controlled ion channels in its membrane. If the external influence exceeds a threshold, the controlled channels suddenly release a large amount of ions into the internal space, putting the neuron into a transient state. The membrane potential changes suddenly (within a few dozen nanoseconds), and, due to the mutual repulsion of ions, the pressure acting on the membrane wall and the ion concentration in the layer near the membrane also increase significantly.

Since the same physical action generates the voltage gradient and the concentration gradient (and, consequently, the pressure), they are inseparable and proportional to each other. Generating a voltage change (clamping, direct current, magnetic pulse), or a pressure change (ultrasound, mechanical) on the membrane mutually cause the other to change. Introducing ions (synaptic input) generates both changes. The control circuit tries to restore the resting state, during which the mentioned changes decrease proportionally together. The transient state of the neuron can, in principle, be described by any of the mentioned entities, but, as a practical matter, *the effects of changes in the other entities must also be taken into account*: no single discipline can describe the changes. The elastic membrane implements an almost critically damped vibration, but the "vibrating mass" and the "spring force" are constantly changing. In an electric resonant circuit, the capacitor's voltage and capacitance change due to the finite amount of charge. *The pressure wave caused by a force shock and the voltage wave caused by a voltage shock describe the same effect*. In both cases, the other effect must be taken into account to some measure: an infinitesimal movement of the ion also involves a change in both pressure and voltage. Changes in pressure and charge alter the membrane's thickness (and therefore its capacity), and both voltage and pressure can cause a structural change (phase change, "melting") of the lipid chains that make up the membrane. In the case

of the pressure wave, the speed is naturally finite (mass must be moved). For the electric wave, there are laws regarding only instantaneous interaction; so, they must be adapted to slow ion currents based on physical assumptions. It is simpler to describe the generation of the action potential as an electrical oscillator circuit, and its propagation as a pressure wave (although this only represents the wave front well: the AP lasts as long as there is a non-equilibrium charge in the neuron: the repulsion between the ions pushes the ions out of the closed space, so the intensity of the wave continuously decreases). Hyperpolarization is described in the electrical view as a capacitive current in the sequential oscillator circuit, in the thermodynamic view as a suction effect occurring in the opposite phase of the membrane. In both cases, however, it must be taken into account that charge and mass are inseparable in ions, and that their cross-disciplinary effects significantly reduce the applicability of the disciplinary laws.

Today, two major branches of disciplinary theories compete for being applied to describe the neuronal operation [56, 7, 46, 57, 58]. The electric view essentially roots in the Nobel prize winner idea by Hodgkin and Huxley [5]. They could not make a perfect job, mainly due to the lack of discoveries made several decades later; including ours, about handling the finite speed of the biological ionic currents (and, due to that, the dynamic features), which drastically change their conclusions. In contrast with their *empirical description*, which derived mathematically formulated measured observations, our discussion, although follows essentially the same principles, reinterprets and pinpoints the used basic terms, sets up a physical model and *explains* the physically underpinned processes. "However, the theory could not explain the physical phenomena such as reversible heat changes, density changes and geometrical changes observed in the experiments" [57]. The thermodynamic view roots in the (possibly Nobel-prize winner) idea of Heimburg and Jackson [59]. They proposed that the action potential is essentially a sound wave (a soliton). "However, there are several other questions that this has to answer like ion flow involvement in nerve signal propagation as stated by HH model and also the faster propagation in myelinated nerves than in unmyelinated." [57] Given that our model natively connects charge and mass of ions, it has good chances to succeed in explaining the missing phenomena.

### 1.4.2 The scene

Although we attempt to be as much abstract as possible, we must stick to the necessary measure to the biological background. The scene where the events we discuss happen are mainly the surface of the neuronal membrane (see Figure 1.1) and the different kinds of permeable points (ion channels, see Figure 1.2). The membrane separates two electrolyte segments of solved salts with different composition and concentration; our abstract view is shown in Fig. 2.12. The salt molecules, individually, are entirely separated charges or dipoles with fractional charges, and they appear in many roles in the show. As shown, the membrane is not a plain thick surface and simple holes embedded into it, but in our first approximation we describe the phenomena by considering them in such a simple

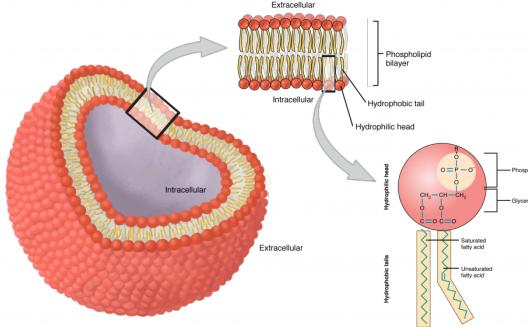


Figure 1.1: A simulated picture of the neuron membrane. We can consider the membrane as a closed surface (in our idealist view, a sphere), being slightly opened at an attached tube, the axon. For certain processes, we can also consider just a tiny section as a planar piece, see also Figure 1.2

way. We refine the description and describe the modification due to being at the boundary of discrete and continuous electricities in section 2.5.5 and leave discussing the biological details for the cited references.

We do not discuss the features of the lipid bilayer, just note that the lipid chains have a polar structure: the negative end is oriented to the center of the cell while the positive end extends out to the periphery [39] page 74. This feature establishes the electric behaviour of the membrane in electrolytes, as we describe in section 2.5. The freely moving ions are attracted to the surfaces and the layers they form represent a condenser. Given the elasticity of the membrane, furthermore, the repulsion between the charge carriers, both the electrical and the wave-like mechanical changes during AP generation follow.

The membranes can form (in our picture) an almost flat surface (which actually is the surface of a sphere-like object or a cylinder). When we discuss a membrane, we consider it to be a perfect isolator and discuss the ion channels in its wall (which enable electric connection between the two segments on its two sides). The membrane's processes can so far only be described in an incomplete manner. [33]

Notice that the ion absorption on the surfaces generates an inhomogeneity in the electrolytes in proximity to the surface. These dynamic electrolyte layers represent a new color on the palette. Those ions (due to electric and thermodynamic forces) are fixed on the surfaces (as entirely separated charges) in resting state and (in polarized state) are present in the electrolytes on its two sides. In the resting state, we consider that dynamically balanced state at one level as a kind of PID controller. We describe also the transient state of the controller when an intense inward current pulse triggers an outward current pulse.

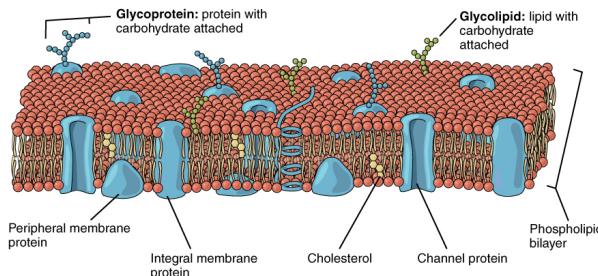


Figure 1.2: The cell membrane is a phospholipid bilayer containing many different molecular components, including proteins and cholesterol, some with carbohydrate groups attached. Lipids are amphiphilic molecules that like water on one side and repel water on the other side due to the hydrocarbon chains. In contact to water lipids spontaneously form double layers (see Figure 1.2) that are the basic building blocks of biomembranes.

### 1.4.3 The actors

One must distinguish static actors that are permanently on the scene and dynamic ones that appear only for a period.

#### Slow current

We explicitly introduce the notion of 'slow current', in the sense discussed in sections 2.3 and 2.4.4. We omit non-significant interactions, and restrict our discussion to interaction speed pairs, where we use the idea of classical physics's approximation that the higher interaction speed is 'instant' and we work out the mathematics for accounting the lower interaction's speed. In our approximation, we work with speed pairs such as diffusion vs voltage-assisted speeds, or voltage-assisted vs voltage-accelerated speeds. This classification usually coincides with the one that the ionic current flows under the effect of fellow charges in the same media or another object (external or charged-up due to electrodifusional reasons). The physical difference is whether the movement of ions is assisted by an enormous potential gradient connected to some object (they move in an electrically homogeneous medium without external driving force, for example, between the extra- and intracellular regions when passing the ion channels; a ('fast' macroscopic current) or they move under the local potential in the electrolyte (for example, in the layer proximal to the isolating membrane) assisted by the electrostatic repulsion of ions in the same layer ('slow' macroscopic current). Cardiac *slow currents* (current pulses of duration in several msec range) [60] have been discovered, and their speed [61] was found in the range  $0.02 - 5 \text{ m/sec}$ . In neurophysiology, similarly, ion current speeds ranging from a few  $\text{mm/s}$  to dozens of  $\text{m/s}$  has been observed. The size relations in neuronal systems are discussed in section 3.1.1.

We explicitly consider that "slow" currents implement the functionality and

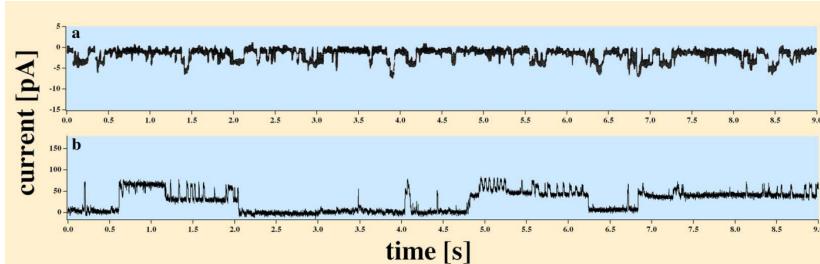


Figure 1.3: (a) Currents through membranes of a frog muscle cell containing the acetylcholine receptor are quantized. (b) This is also true for currents through a synthetic lipid membrane close to the transition maximum. In spite of slightly different experimental conditions, amplitude and typical time scale are similar. Multiple steps in the data indicate that several pores might open simultaneously. Figure 3 in [33].

we also name which activity why does need time. When describing neuronal processes, we use neuron's "local time" that begins when in the computing cycle the first synaptic input arrives or when the network synchronizes it as described in section 1.5.2. We discuss the (still abstract) operation details in section 3.5. Fig. 1.6 shows a schematic AP, with connected characteristic points, and nearly realistic figures of the "local time" values on the axis, and the ordinates, and abscissas of the characteristic points. The figure shows the result of a numeric simulation using our current Post-Synaptic Potential (PSP) model, see Chapter 8. See also Fig. 3.9 (notice that the time scale is logarithmic), where results of using our physical model are depicted.

### **Ion channels**

The ion channels are very important players, in most processes. Their operation (their current delivering capacity, operating principles, ion selectivity, etc.) is a source of misunderstandings. They heavily cooperate with the membrane and the proximal layers on its two surfaces.

### **Charged layers**

The membrane is considered as a condenser, where charges with opposite signs on the two sides of the membrane are located. The charges are located in a very thin ( $< 1 \text{ nm}$ ) layer where most of the discussed electric phenomena happen. The attraction between the ions on the opposite sides acts in a way that a 'virtual charged sheet' is created: the electric field keeps the ions in place in the direction perpendicular to the surface while in parallel with the surface the ions can move as the thermodynamic gradient dictates. The operation of charged layers is underpinned by Fig. 1.3: whether natural or synthetic, the actual voltage gradient defines the opening/closing of the channels.

### Driving forces

A crucial point of our description is that the ions move under the effect of combined thermodynamic and electrical gradients. *These two cannot be separated and the ions will move if any of the two gradients are present, given that they generate the other gradient.* After deriving the "equivalent thermodynamic electrical gradient", we refer to the sum of the two gradients as "thermoelectric gradient".

#### 1.4.4 Life cycle

Living organisms change from moment to moment along their internal laws and we can study them at different abstraction levels. "Despite the extraordinary diversity and complexity of neuronal morphology and synaptic connectivity, *the nervous systems adopts a number of basic principles*". [1] Although we will discuss their internal operation in terms of particular processes (the actual level depends on the process), here we classify the obvious results of observations according to the principles the foreword to this chapter mentions: how nature implements those "basic rules" by more simple *processes* and *states* (which we can describe by using ordinary or extraordinary laws) and which *events* it provides for the observer (which we can use for staging those very complex "signs of life").

Fig. 1.4 illustrates our abstract view of a neuron, in this case as a "stage machine". Notice that the double circles are *stages* (*states* with event-defined periods) connected by bent arrows representing *instant stage transitions*, while at some other abstraction level we consider them as *processes* having a temporal course with their own *event* handling. Fundamentally, the system is circulating along the blue pathway, and maintains its state by using the black loops, but sometimes it takes the less common red pathways. It receives its inputs cooperatively (controls the accepted amount of its external inputs from the upstream neurons by gating them by regulating a stage variable), furthermore it actively communicates *the time of its state change* (that is: *not its state* as assumed in the so called neural information theory) toward the downstream neurons in a process parallel with its mentioned activity.

#### 1.4.5 Stages of operation

Initially, a neuron is in stage "Relaxing" which is the ground state of its operation. (We also introduce a "Sleeping" or "Standby" helper stage, which can be imagined as a low-power mode in electronical or state maintenance mode of biological computing; or "creating the neuron" in biology; a "no payload activity" stage.) The stage transition from "Sleeping" also *resets the internal stage variable* membrane potential (to the value of the resting potential). In biology, a "leakage" background activity takes place: it changes (among others) the stage variable towards the system's "no activity" value.

An event (in form of a pulse of slow ions) arriving from the environment

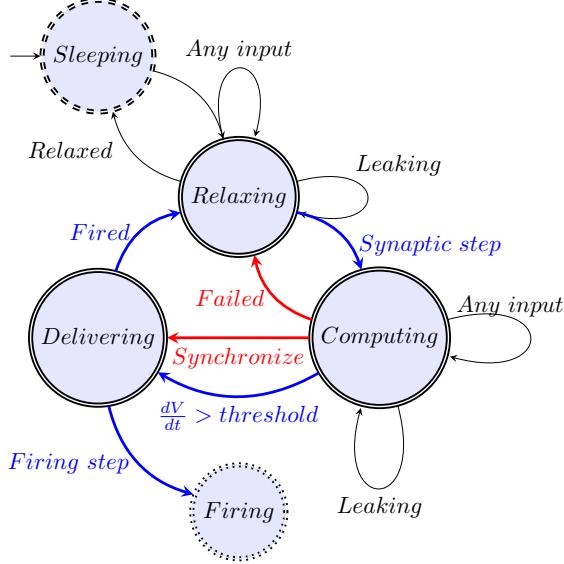


Figure 1.4: The model of neuron as an abstract state machine

acts as a "look at me" signal and the system passes to "Computing" stage: an excitation begins. The external signal acts as triggering a stage change and, simultaneously, contributes to the value of the internal stage variable (membrane voltage). During normal operation, when the stage variable reaches the critical value (the threshold potential), the system generates an event: passes to stage "Delivering" and "flushes" the collected charge. In that stage, it starts to deliver a signal toward the environment (to the other neurons connected to its axon) and after a fixed period, passes to stage "Relaxing", without resetting the stage variable. From this event on, it is again in stage "Relaxing", where the "leakage" and the input pulses from the upstream neurons contribute to its stage variable. Process "Delivering" operates an independent subsystem ("Firing"): happens simultaneously with process of "Relaxing" which, after some time, usually passes to the next "Computing".

*The stages "Computing" and "Delivering" mutually block each other and the I/O operations happen in parallel with them.* They have temporal lengths, and they must follow in the well-defined order (a "proper sequencing" [2, 22]) "Computing"  $\Rightarrow$  "Delivering"  $\Rightarrow$  "Relaxing". Theoretically, a three-state system is needed to define the direction of time [62]; a fundamental issue for quantum-based computing is the lack of a third state. In electronical computing we can introduce this as "up" edge and "down" edge, with a "hold" stage between. A charge-up process must always happen before discharging. Stage "Delivering" has a fixed period, stage "Computing" has a variable period (depends mainly on the upstream neurons), and the total length of the computing period equals their sum. The (physiologically defined) length of the "Delivering" period limits

neuron's firing rate; the length of "Computing" is usually much shorter.

In any stage, a "leak current" (through ion channels, but mainly the AIS instead of the membrane) changing the stage variable is present; *the continuous change (the presence of a voltage gradient) has a fundamental importance for a biological computing system* This current is proportional to the stage variable (membrane current); it is *not* identical with the fixed-size "leak current" assumed in the Hodgkin-Huxley model [5]. The event which is issued when stage "Computing" ends and "Delivering" begins, separates two physically different operating modes: inputting payload signals for computing and inputting "servo" ions for transmitting (signal transmission to fellow neurons begins and happens in parallel with further computation(s)). Given that stages "Computing" and "Delivering" take time, and the next "Computing" can only start through the stage "Relaxing", furthermore "Delivering" can only begin after "Computing" finished, *these stages mutually block each other* (and the length of the "Delivering" period limits neuron's firing rate).

There are two more possible stage transitions from the stage "Computing". First, the stage variable (due to "leaking") may approach its initial value (the resting potential) without firing and the system passes to stage "Relaxing"; in this case we consider that the excitation "Failed". This happens when leaking is more intense than the input current pulses (the input firing rate is too low or a random firing event started the computing). Second, an external pulse may have the effect to force the system (independently from the value of the stage variable) to pass instantly to stage "Delivering", and after that, to "Relaxing". (When several neurons share that input signal, they will go to "Relaxing" at the same time: they get synchronized; a simple way of synchronizing low-precision asynchronous oscillators.)

Anyhow: a neuron operates in cooperation with in its environment (the fellow neurons, with outputs distributed in space and time). It receives multiple inputs at different times (at different offset times from the different upstream neurons) and in different stages. In stage "Computing", the synaptic inputs are open, while in stage "Delivering", the synaptic inputs are closed (the input is ineffective). It produces multiple outputs (in the sense that the signal may branch along its path), in form of a signal with temporal course.

### Stage 'Computing'

The neuron receives its inputs as 'Axonal inputs'. For the first input in stage 'Relaxing', the neuron enters stage 'Computing'. The time of this event is the base time used for calculating the neuron's "local time" (in describing the operation and in the simulator). Notice that producing the result is a cooperation between the neuron and its upstream neurons (the neuron gates its input currents). One of the upstream neurons opens computing, and the receiving neuron terminates it.

The physical implementation is a steep current gradient which evokes a steep voltage gradient  $dV/dt$  on the condenser 'membrane' in its intracellular segment, see section 1.8.1. The membrane is connected to the axon through a resistor

'AIS' (these components, switched in serial, constitute the neuronal oscillator). Given that the current creates a potential gradient on the membrane, the increased potential starts a current ("Leaking") proportional to the voltage difference between the membrane and the axon (across the AIS). This current decreases the membrane's potential (discharges the condenser). In lack of further excitation, the membrane's potential decreases back to its resting value and the neuron returns to stage 'Relaxing'.

However, for repeated excitation, when the next 'Axonal input' arrive(s) before the neuron returns to stage 'Relaxing', the voltage increases further, and it might reach a threshold voltage. In such a case, the neuron enters stage 'Delivering' (the red section of the broken diagram line). The time at which point this happens depends on the arrival of spikes and the discharge of the membrane (when the difference of the received charge and the loss due to discharge evokes a sufficiently large voltage on the condenser's capacity). At that point, the computation is finished. *The result of the computation is the time* passed between receiving the first 'Axonal input' and the time when the neuron closes its input sources (and simultaneously, opens the ion channels in its wall, see below, to enter stage "Delivering"). No more input shall be received, so the neuron disables its synaptic inputs, and prepares for delivering the result of its 'computation' (nothing shall be stored: the result is the time of sending the message, but the delivery period takes time; is a fixed-length process, will follow immediately). In this stage, the role of the slow speed is not evident. The current arrives through an axon, passes the terminal and arrives at the AIS; the time components cannot be separated.

### Stage 'Delivering'

In this stage, the result is ready: the time between the arrival of the first synaptic input and reaching the membrane's threshold voltage is measured. No more input is desirable, so the neuron's input synapses remain closed. Simultaneously, the neuron starts its "servo" mechanism: it opens its ion channels and an intense ion current starts to charge the membrane. It is an 'instant' current. The voltage on the membrane quickly rises, but it takes a short time until its peak voltage is reached. Given that the charge-up current is instant and the increased membrane voltage drives an outward current, the membrane voltage gradually decays. When the voltage drops below the threshold voltage, the neuron re-opens its synaptic inputs and passes to stage "Relaxing": it is ready for the next operation. The signal transmission to downstream neurons happens in parallel with the recent "Delivering" stage and the next "Relaxing" and maybe "Computing" stages.

Delivering the result needs huge power because of the noisy environment and the huge distances, so at the beginning of the 'Delivery' phase, the neuron switches in a 'servo' mechanism. Exceeding the threshold voltage (either as a consequence of the 'spatiotemporal' summing several spikes or a single spike with sufficiently large voltage gradient [63]) opens the voltage-gated ion channels in the membrane's wall. Due to the vast voltage gradient across the two segments of

the membrane, an enormous amount of ions rush-in into the intracellular space and the intense current increases the membrane's potential; for the details see section 2.4. The amount of the rushed-in ions is several times more than those received during the stage 'Computing'.

The ion channels over the surface of the neuron open at the same time, and they are open only for a very short period (actually, they implement a sudden "step current"). However, this current on the surface is created at different distances from the AIS and (due to the final speed of the ions) and the time until the ions arrive at the AIS depends on the distance to AIS. Due to this effect, the current quickly increases; until it reaches a maximum. The time when the AP reaches maximum value (due to the event that the current from the most distant places of the membrane could reach AIS), and from this point it starts to decrease. (there is no other special threshold voltage value: the charge from the rush-in current distributes on the surface; the current injection can charge the fixed capacity membrane to that voltage). At this point the neuronal condenser is maximally depolarized.

The neuronal condenser is loaded to its maximum, and the resistor (the AIS) enables a current to flow out, so the condenser (the membrane) discharges (repolarizes). Here enters into the picture that the neuron is resemblant to a serial oscillator. The condenser stores the charge for some period, and releases it to the AIS at a later time. As a result, the direction of the current on the neuron's membrane reverses, see the shape of the output voltage in table 2.1. The essential difference between the serial and parallel  $RC$  oscillators is that the differentiator circuit can produce opposite voltage on its output without assuming any additional mechanism, such as an outward current, given that *a current pulse has rising and falling edges which can natively produce positive and negative voltage derivatives*. As the result of the process, the potential reaching the AIS goes to negative; a phenomenon called hyperpolarization.

Notice that the current in the red section (plus also in the blue section) of the diagram line still originates from the rushed-in charge. The observer sees the sum of the resistive and capacitive currents; maybe new axonal inputs superimposed. The ion current's finite speed plays again. When the axonal arbors re-open, the ion flows into the membrane at some distant point, so its effect will be observed some time later; apparently when the neuron membrane is about its hyperpolarized state.

### Stage 'Relaxing'

In this stage, the neuron re-opens its synaptic gates. Recall that the ion channels used for generating an intense membrane current are already closed. The neuron passes to stage 'Relaxing' and is ready for a new computation: the previous result is under delivering (parallelly, independently), the axonal inputs are open again. However, the membrane's potential at this point may differ from the resting potential. A new computation begins (the neuron passes to the stage "Computing") when a new axonal input arrives. Given that the computation is analog, a current flows through the AIS, and the result is the length of the

period to reach the threshold value, the membrane voltage plays the role of an accumulator (with a time-dependent content): a non-zero initial value acts as a short-time memory in the next computing cycle. The local time is reset when a new computing cycle begins, but not when eventually the resting potential reached.

As the membrane's voltage drops below the threshold voltage, the neuron re-opens its synaptic gates (the ion channels in the membrane's wall are already closed). The neuron passes to stage 'Relaxing' and is ready for a new computation: the previous result is under delivering (parallelly, independently), the axonal inputs are open again. However, the membrane's potential at this point may differ from the resting potential. Given that the computation is analog, the membrane voltage plays the role of an accumulator (with a time-dependent content, given that the current flows through the AIS). A new computation begins (the neuron passes to the stage "Computing") when a new axonal input arrives. Given that the result is the time to reach the threshold value, the non-zero initial value acts as a short-time memory.

The ion current's finite speed plays again. When the axonal arbors re-open, the ion flows into the membrane at some distant point, so its effect will be observed some time later; apparently when the neuron membrane is about its hyperpolarized state.

### Classic stages

We can map our 'modern' stages to those 'classic' stages and we can see why defining the length of the Action Potential is problematic. The effect of slow current affects the apparent boundary between our "Delivering" stage and "Relaxing" stages. Classical physiology sees the difference and distinguishes 'absolute' and 'relative' refractory periods with a smeared boundary between. Furthermore, it defines the length of the spike with some characteristic point, such as reaching the resting value for the first or second time, or reaching the maximum polarization/hyperpolarization. Our derivation of the stages (see Fig. 1.6) defines clear-cut breakpoints between them.

We can define the length of the spike as the sum of the variable-size length of period "Computing" and fixed-size period "Delivering". The "absolute refractory" period is defined as the period while the neuron membrane's voltage keeps the gates of the synaptic inputs closed (the value of membrane voltage is above their threshold). That period is apparently extended (and interpreted as a "relative refractory" period, which sensitively depends on the conduction velocity [64]) by the period when although the gating is re-enabled, but the slow current did not yet arrive to the AIS where it contributes to the measured AP, see Fig. 1.6. *Only one refractory period exists, plus the effect of the slow current.*

## 1.5 Processes of operation

In the neuron autonomous processes happen.

### 1.5.1 Synaptic control

As discussed, controlling the operation of its synapses is a fundamental part of neuronal operation. It is a kind of gating and implements an 'autonomous cooperation' with the upstream neurons. The neuron's gating uses a 'downhill method' for gating: while the membrane's potential is above of that of the axonal arbor, the charges cannot enter the membrane. As soon as the membrane's voltage exceeds the threshold voltage, the synaptic inputs stop, and restart only when the voltage drops below of that threshold. The synaptic gating makes interpreting neural information and entropy, as we discuss it in [13] and chapter 5, at least hard.

### 1.5.2 Synchronization

For the cooperation of neurons, it is of fundamental importance to synchronize their operation. The neurons have low accuracy, while their concerted actions need precisely synchronized pulses (about two orders of magnitude shorter time resolution than the inter-spike intervals!).

Given that the voltage gradient is the pace of temporal change, a faster rush-in current in the upstream neuron (seen as a steeper slope [63]) can evoke firing, independently from the membrane's voltage. This observation, alone, underpins that exceeding a *voltage threshold* leads to firing. Receiving a synchrony signal forces an instant firing. After firing, the first synaptic input sets the time base as we have discussed it above.

It is interesting to note that, according to Shannon, a single spike does not carry information, given that the shape of the spikes are identical, only its time can deliver information. And, yet, a single spike can carry the information that a new collective operation (of neuron assemblies) begins and the participating neuron's operation must synchronize their "local time" to a remote basetime. In the sense of time-space, the signal resets the time base of all receiver neurons to zero. That is, all their synchronized upstream neurons will reset their timebase to that synchrony signal. Consequently, the neuron will receive its input spikes on a relatively well-defined scale, despite that the sender neurons send their spikes at different absolute times; by automatically "calculating" and applying the needed offset time. The neuron's frequency stability is low, so the synchrony signal (the base frequencies) must be repeated relatively frequently for the system's stable operation. Of course, the neuron does not know the absolute time.

The local time's starting time  $t_o$  is the time when the first synaptic input arrives and its range of interpretation ends when a new computation starts or when the membrane's potential goes back to its resting value.

### 1.5.3 Learning

It might also happen that (also depending on the residual membrane voltage) the outgoing spike's delivering begins immediately after last spike arrives. Given that the rising edge delivers the important timing information, and the voltage gradients contributions received before the last spike somewhat faded in the meantime, one can understand Hebb's observation in terms of learning: the last spike (before firing) contribute more than the ones received earlier.

## 1.6 Neuron as control circuit

The neuron as a system aims to collect inputs from its upstream neurons and to provide an intense output that informs the downstream neurons. A large number of voltage-gated ion channels, distributed in the neuron's wall, implements the input charge of this overshoot and the overshoot output current flows through a similarly large number of persistently open ion channels concentrated in AIS. The intense slow current produces a condenser-like behavior (capacitive current); the phenomena called polarization and hyperpolarization (not polarization, instead a complete charge separation) of the membrane provide the necessary positive and negative error signals for the controller in the transient state.

We considered that the neuron has a stable base state. On the one side, this resting state must be dynamically stabilized for little perturbations (and to provide a mechanism when the cell grows, divides, or ages). On the other side, it must be able to restore the state after rough perturbations, causing short-time transients (when restoring the membrane's potential after issuing a spike). The two states need different physical mechanisms: a set of ungated low-current ion channels for the resting state, and a set of high-intensity ion channels for the transient state. Of course, for starting a spike, the input channels must be gated while the output ion channels can work without gating.

From control theory, it is known that the goal of the system is to govern the application of system inputs to drive the system to a desired state while minimizing any delay, overshoot, or steady-state error and ensuring control stability. The neuron implements a controller that monitors the controlled process variable (membrane voltage) and compares it with the reference or setpoint (the resting potential). The difference between the process variable's actual and desired values called the error signal, is the actual offset potential. It is applied as feedback to generate a control action to bring the controlled process variable to the same value as the set point.

Biology uses such a simple controller. The gradients are used to adjust the process variable by their positive and negative contributions, and the different speeds of the thermodynamical and electrical interactions minimize the delay (i.e., provide the maximum speed of operations, vital for survival). The difference between the process variable's actual and desired values called the error signal, is the actual offset potential. It is applied as feedback to generate a

control action to bring the controlled process variable to the same value as the set point. The steady-state error is minimized by setting the process variable to the reference point using long-term stable parameters (geometry and overall concentration). The low-intensity current through the always-open resting ion channels provides dynamic stability in the steady state. The permanently zero error signal indicates a lack of operations. In contrast, the permanently nonzero error signal is a sign of abnormal operation and is likely a symptom of a neurological disease. See also section 1.6.2.

The system aims to provide an intense output that informs the downstream neurons. This overshoot is implemented by a large number of voltage-gated ion channels distributed in the neuron's wall. The overshoot current flows through a similarly large number of persistently open ion channels concentrated in AIS. The intense slow current produces a condenser-like behavior (capacitive current); the phenomena called polarization and hyperpolarization (not polarization, which is a complete charge separation instead) of the membrane provide the necessary positive and negative error signals for the controller in the transient state.

### 1.6.1 Electricity builds and thermodynamics corrects

From a control theoretical point of view, the condenser geometry sets the 'always the same' value and the currents serve to keep or restore that value. Forming membrane's potential is an excellent example of the principle that nature uses "one process to build and the other to correct" [65].

After introducing a finite-width membrane into an electrolyte, a potential difference between the two membrane surfaces is created; see Eq.(2.69). When adjusting the membrane's potential, we must consider its ground and excited states separately, given that the perturbations in these two cases are vastly different. Nature employs various mechanisms to maintain the ground state and recover it after generating a spike. Although nature's tools are remarkably similar (channels and pumps; here, we discuss only the 'downhill' channels), the significant difference in current intensity needs a different discussion.

The potential's and the electric field's magnitudes depend on the concentration and the geometry (the finite width of the membrane). The ions' chemical nature comes into play only if the polarizability can differ for different molecules. The thickness of the charged layer  $\Delta z$  has a significant impact on the resulting electric field (i.e., the neuron's 'setpoint'). If biological fragments are formed and settle down on the membrane's intracellular side, due to the increased  $\Delta z$ , the resting potential (and the threshold potential) may change, leading to neurological diseases.

Given that the same number of charged ions must be present on the two sides of the membrane, their surface density  $\sigma_A$  must be the same. Notice that the effect is purely electrostatic, resulting in an asymmetric ion distribution; no permeability is needed. If the membrane is (slightly) permeable, ions will move across the membrane until equilibrium is reached. The resulting potential difference is directly proportional to the concentration difference.

The classical condenser has an electric field, as the blue dashed diagram line shows in Fig. 2.12. No field is outside or inside the condenser plates (see Fig. 2.11). There is a sudden jump in the field on the conductor's surface (the armatures) and a constant field between the plates. (The charged layer can be ideally thin if electrons are sitting on the surface but is of finite thickness on the opposite side where ions are on the surface. This latter effect is not discussed in classical electricity.)

The biological condenser behaves differently; see the red diagram line. The electrolyte (instead of an insulator) outside the condenser drastically changes the structure of the field. The electric field on the surface and between the plates changes by a factor of 3 to 4. Outside the plates, the polarization creates a field that changes logarithmically. An ion layer with finite thickness is built near the membrane's surface. It is uniformly charged, so the field is linear. At the internal surface of the condenser, it takes the value of the field calculated for the gap; on the other side of the layer, it takes the value of the logarithmic field at that position. The dashed line represents the gap field, the continuous line represents the charged layer field, and the dotted line represents the electrolyte field. We can observe the "correspondence principle": the particle-continuous fields join seamlessly; furthermore, if the polarizability of the electrolyte decreases toward zero, the field value approaches the classical value.

As Eq.(2.49) shows, the "thermodynamic electric field" increases as temperature increases, and raises the setpoint. As Eq.(2.33) shows, the current decreases as temperature increases, in line with the experimental evidence. The amplitude of action potential is decreased given that the setpoint increased and its duration is reduced given that the current decreases.

The thickness of the charged layer has a significant impact on the resulting electric field (i.e., the neuron's 'setpoint'). If biological fragments are formed and settle down on the membrane's intracellular side, due to the increased  $\Delta z$ , the resting potential (and the threshold potential) may change, leading to neurological diseases.

### 1.6.2 Robustness of the control circle

An exciting thought experiment is discussed in [66]. "First, we consider a hypothetical membrane that is permeable only to  $Na^+$  ions. Suppose that  $[Na^+]_o$ , the outside or extracellular sodium concentration, is 145 mM, and  $[Na^+]_i$  is 12 mM. And suppose that initially, there is no membrane potential. The diffusion gradient for  $Na^+$  favors  $Na^+$  entry into the cell, and the initial  $Na^+$  influx carries a charge that builds up on the inside of the cell. This produces a potential (recall that separation of charge produces a potential) across the membrane that impedes further  $Na^+$  ion movement because the positive charges repel the positively charged  $Na^+$  ion."

The paper correctly explains that in the case of  $Na^+$  only, the potential sets up to 66.6 mV. (We quietly add that plus a layer of the corresponding  $Cl^-$  ions on the other segment, in a similar concentration ratio, builds up; so also, the attraction between positive and negative charges contributes to the

effect.) In lack of our argumentation, it cannot explain why that potential builds up; only why that concentration ratio establishes: the Nernst law, alone, does not explain the effect. Furthermore, the statement is valid only for a well-defined semipermeable membrane. We can add that the same concentrations develop if initially identical concentrations are present on both sides. The finite width of the membrane creates its electric potential, which is a consequence of charge separation, as stated. If there are no ions initially inside, then no charge separation occurs, and therefore, no ion transport begins due to the membrane's electric potential. However, the thermal driving force exists, and the started ion transport quickly builds the electric layer, which effectively helps to establish the resting potential.

This robustness also explains why, during replication (cell division), cells also inherit their operating ability and resting potential; the existing membrane cell continues to grow in the same way. Its voltage remains the same, and the voltage defined in this way adjusts the concentrations appropriately. Moreover, it explains why, during evolution, cells first formed: a couple of lipids came together to form a membrane, establishing cellular electricity. As Fig. 1.5 depicts, the concentrations may adapt to the living conditions (whether living in see-water), but the general operating principles remained the same. The see-water environment enables using thinner membrane and lower membrane voltage; however, the same electric field is used in all cases.

Given that neurons share the external (global) concentrations (defined by the vast amount of ions in bulk), they provide a firmly fixed offset value to the always-the-same electric potential. This way, the operations of the individual neurons do not interfere. Furthermore, the internal (local) concentrations can adjust themselves even following a very rough charge perturbation while issuing an AP; moreover, when the living organism is growing.

### 1.6.3 Controller

We consider the neuron as a simple automated voltage controller with a pre-defined structure (a biological oscillator with a constant capacity (membrane) and resistance (AIS)), unidirectional input (synapses) and output (axon) connections with the environment, some *dynamic components* (ionic currents in the temporarily formed electrolyte layers), and a single temporary "stage variable" (the membrane's potential). The circuit essentially collects charge (while it is leaking, furthermore, gates its inputs) in its ground state, and when the stage variable (the membrane's potential) – under external impact(s) – reaches a well-defined constant critical value (the threshold potential), it flushes the collected charge. By regulating the single stage variable, the system can pass from stage to stage, in a well-defined way. The neuron transmits the collected information to its downstream neurons: the "Delivering" process transmits the charge carriers from the surface layer of the membrane to the AIS and the ion channels 'instantly' deliver the ions to the beginning of the axon where they pass along as the laws of motion of electrodiffusion dictate; see also section 1.8.

In our (somewhat simplified) view, a neuron is an autonomous system that

has a well-defined equilibrium state. We do not mention here the details needed to maintain the equilibrium state, furthermore, we subdivide the charge processing into subprocesses by their physical nature. In reply to the environment (mainly upstream neurons) the neuron lets a given amount of positive charges from the electrolyte layer (handled as a "charged infinite sheet") formed on the high-concentration side of its membrane to enter the low-concentration side where it forms temporarily a similar layer. This process is instant. The ions produce a voltage increase on the well-defined capacity of the neuron. That voltage serves as a driving force for removing the rushed-in ions through its axon, through the AIS with as well-defined resistance. The ions arrive through ion channels at different places of the membrane, so they need different times to reach their outflow point. The travel time can be interpreted as "storing the charge for some time", which can be modeled by a classic condenser (which is a discrete element and uses instant current). The resistance of the AIS limits the current on the surface to a value which is much less than the inflow through the membrane. We assume that the repulsion between charged particles in the electrolyte layer is remarkable that tends to make the charged layer equipotential. However, the different speeds for the mass and charge transport processes limits the propagation speed of ions and it leads to the phenomena similar to the ones discussed in section 3.5.6. Equations (2.11) and (2.14) describe the processes, although they must be combined with the geometry of the neuronal membrane. The result of the interference of those processes is known as Action Potential. Important to notice that the charge transfer from the layer on the high-concentration side to the layer on the low concentration side is accompanied with considerable voltage and concentration changes in both layers during generating the AP, see also section 2.2.7. These changes manifest in considerable current (and voltage) gradients.

A physical neuron operates with current gradients that enables it using very precise timings, and cooperates with the fellow individual neurons and their assemblies. Its goal is implementing a computing unit, which receives input information in form of native current gradients or artificial current gradients through its synapses. In any case, the received current evokes a potential gradient, and *the voltage gradient operates the neuron*. In this abstract interpretation, the neuron is represented as a *serial* electric *RC* oscillator circuit, which implements some voltage gradient (or maybe current density) threshold. [63] provided evidence that a spike with sufficiently large slope of current density (in other words, potential gradient) is capable alone to evoke the critical voltage gradient needed to evoke an action potential.

#### 1.6.4 Goldman-Hodgkin-Katz potential

It has already been stated, based on experimental evidence, that "the membrane permeability to the ions has nothing to do with the potential generation and the ions' adsorption on the membrane surface generates the membrane potential"; for a review, see [67]. The idea itself is nonsense: in a balanced state, no ion transport happens, so even without permeability, the balanced

state persists; the resting potential has nothing to do with either ions' mobility or permeability or with ion absorption [68]. Furthermore, there is no idea in Goldman-Hodgkin-Katz (GHK) about whether the 'setpoint' (why that specific concentration or potential difference) is present and why the same potential is reset after rough perturbations such as issuing an AP or replicating a cell. The causality is reversed: the potential is a static concept and is set electrically, and the two gradients form the experienced concentrations from the available solvent molecules. For the time course of gradient formation, mobility and permeability play a role, but not in determining concentrations or the resting potential.

In our clear physical picture, the thermodynamic forces on one side and on the other side of the membrane are summed. They counterbalance each other; furthermore, jointly the effect of the neuronal condenser, see Fig. 1.5. As we emphasized, the concentration gradients are ion-specific. Furthermore, as discussed in connection with Eq.(2.18), the Nernst equation comprises a per-ion indefinite constant (a potential difference). To calculate a linear combination of terms comprising an arbitrary constant is nonsense, and so is adding absolute concentrations on the different sides of the membrane, or changing the base of the logarithm used in a calculation to match the experimental value. It is not more than number magic. The potential is described by coupled equations as discussed in connection with Eq. (1.2).

The  $Ca^{2+}$  ions do not fit into the GHK picture. One of the reasons why GHK cannot be good is that  $[Ca^{2+}]$  is omitted. Biologically, it is hard to believe that  $Ca^{2+}$  does not participate in the game of life (especially since biology sees the need for  $Ca^{2+}$  pumps). Physically, a single concentration on one side of the membrane cannot maintain balance; as the different ion-exchange processes shown in Table 3.1 and Fig. 1.5 demonstrate. When adding a new ion to the solution, the sum concentration increases, and so the electrical force increases, forcing the previous elements to find new concentrations on both sides. The appearance of a new chemical element indirectly changes the concentrations of the others (a good example is the role of the negligible amount of  $Ca^{2+}$ ).

## 1.7 Resting potential

The excellent textbook [39] separates the neuron membrane's states into resting and transient states. Concerning the resting state, the statement that "the resting membrane potential results from the separation of charge across the cell membrane" is only half the truth; here we tell the second half. We refine their statement "by discussing how resting ion channels establish and maintain the resting potential" [39], page 126. In the resting state, two effects are considered. On the one side, the potential is created by a static charge-up: "the cell membrane potential results from the separation of net positive and net negative charges on either side of the membrane". Furthermore, as we discussed, it is only a small part of the potential: the polarization of the electrolyte's dipoles contributes to the rest. On the other hand, it was claimed that "the resting membrane potential is the result of the [low intensity] passive flux of individual

ion species through several classes of resting channels” [39], although it was question marked whether the membrane permeability is a primary property for the membrane potential generation, for a review, see [67]. The claim is rooted in the measurements by Hodgkin and Huxley [69], as we discuss in section 1.10.1. Its numeric figure was correct, but it was mistakenly interpreted as being produced by a “leaking current” on the membrane’s parallel resistance. Paper [66] stated correctly “that separation of charges produces a potential” and derived the thermodynamic part in two different ways but did not account for the electric potential. We derive how that electric potential is produced by separating charges and how its value can be calculated from the first principles.

More precisely, inseparable thermodynamic and electrical processes keep the potential set by the inseparable electric and thermodynamic backbone defined by the lipid structure of the cell. It is one of the frequent cases when one effect implements a functionality (the backbone closely defines the frames of the operation), and the other (in this case, combined thermodynamics and electricity) corrects it when it implements a complex operational (dynamical) functionality: “stimulated phase transitions enable the phase-dependent processes to replace each other … one process to build and the other to correct” [65].

The book asks the central questions, “How do ionic gradients contribute to the resting membrane potential? What prevents the ionic gradients from dissipating by diffusion of ions across the membrane through the resting channels?” However, it leaves them essentially open by giving only a qualitative answer, as it discusses only membrane permeability without explaining how the resting potential is created and regulated through charging and polarization.

We demonstrate in section 2.5 that classical electric methods can calculate the membrane’s potential resulting from charge separation and polarization. However, some physically plausible assumptions must be made to provide numerical figures. The electric processes are inseparable from the corresponding thermodynamical processes [19], which we discuss by deriving a “thermodynamical electrical field”. The other minor effect is a low-intensity “passive flux” (material transport) produced by the “resting channels”. They are ion channels not necessarily only across the membrane; they also include the ion channels in the AIS [48, 47, 49, 51, 70]. The “resting current” is about two orders of magnitude lower [71], see also section 1.10.1 than it was assumed at the time of writing the book; correspondingly, its role is much smaller in the transient state, producing an AP which we discuss elsewhere [72].

The membrane’s electric potential defines the resting potential, and the “electric” and “thermodynamic” potentials work together to control neuronal operation. The anatomically defined “electric” membrane potential plus the (compared to the internal amount) vast amount of ions in the extracellular segment and so the stable concentration provides a solid reference point. In the resting state, the membrane potential is balanced the presence of always-open “resting ion channels”. When ions flow into the membrane, the “resting ion channels” can keep the balance: the internal  $K^+$  and  $Na^+$  concentrations are adjusted as the  $Na^+$  flows in.

The importance of the subject was correctly estimated decades ago [73]:

"For the past forty years our understanding and our methods of studying the biophysics of excitable membranes have been significantly influenced by the landmark work of Hodgkin and Huxley. Their work has had far reaching impact on many different life science subdisciplines where concepts of cell biology have come to be important. These include not only neurophysiology but also endocrinology, muscle and cardiac physiology, and developmental biology. The ionic currents and electrical signals generated by neuronal membranes are of obvious importance in the nervous system. But ionic fluxes also play important roles in affecting cellular functions such as secretion, contraction, migration, etc."

In this state, the goal is to provide stability by using slow and less intense currents. As [39] discusses, there are 'holes' (non-controlled ion channels) in the membrane where the counterforce is missing. The difference in the electric and thermodynamic forces could accelerate ions until the Stokes-Einstein speed (see Eq.(2.33)) is reached. Given that the deviation from the set-point is slight, the intensity and speed of the current are low. The slow ion transport delivers both charge and mass, so the gradients permanently direct the process control variable toward the reference point. Given that the 'resting channels' are scattered on the surface of the membrane and it takes time for the gradients delivered by slow ions to reach the entrance of an ion channel (see also section 2.5.7), some slight variations in the actual value of the membrane's potential necessarily exist. Given that the AIS comprises non-gated ion channels with much higher density than those in the membrane, the variations and the control ("leaking") are marginal, and for mainly through the ion channels in the membrane's walls, as observed in experimental physiology.

The electric voltage contribution is unidirectional, the two-component thermodynamic contributions, depending on the concentrations, can be positive or negative. If choosing the zero potential at the middle of the electric potential, we can interpret that the concentration combinations maintain their ionic concentrations (and so also thermodynamic voltage contributions) independently on both sides starting from a zero potential level. They generate potentials autonomously in the segments proximal to the opposite surfaces of the membrane. The electric charge on the membrane creates another voltage independently. However, that voltage must fit between the two thermodynamic voltages. Any deviation in the potentials starts a current directing the concentrations and voltages toward a balanced state. The process is complex: the sum of surface concentration of ions must be the same on both sides for the condenser and the ratios on the intracellular and extracellular sides must be adjusted to satisfy the conditions

In a balanced state, the left sides are zero: at the contact point between the electrolyte and the membrane there are no potential differences, while in perturbed state they are non-zero and so they represent the driving forces for restoring the balance. (Recall that the ions are slow and that the local electric and concentration gradients control the local potentials.) From the derivation, follows that

Legend to Figures 1.5 and 1.8:

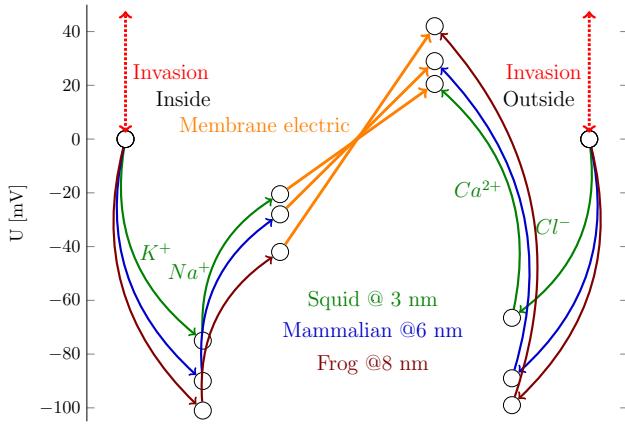


Figure 1.5: The mechanism for controlling neuronal operation is the same in all cases shown in Table 3.1. It appears that the thicker membrane produces a higher membrane electric potential and requires a higher thermal potential to compensate for it. However, it can solve the task using a lower salt concentration. Given that the electric membrane potential accelerates the ions across the ion channels in the membrane, and the operation is faster. The electric field has a similar value, as shown in Fig. 2.8. Furthermore, the total concentration decreases as the membrane thickness and potential increase.

We arbitrarily choose the zero potential in the solution, on both sides of the membrane. The membrane maintains its potential difference across its surfaces (practically unchanged). The electrolytes on its two sides are galvanically connected to the plate, so they must adjust their concentrations to produce the thermodynamic potential to adjust the electrolyte's potential to zero, otherwise the potential difference drives a current through the electrolyte (ion transport). The two segments must cooperate in balancing the system. They have the same ions in different concentrations. Until the potential gets balanced (or invasion happens), ions will move from one segment to the other. Notice that the *difference* of the thermodynamic potentials is balanced for the system. The *per ion* thermodynamic forces are different for the different ions

Figure 1.5 also shows that in its native state, the neuron is electrically balanced: in the internal and external segments, the resulting thermodynamical and electrical forces are equal (see also Fig. 2.6: the internal and external reference points are galvanically connected.) Any foreign invasion into the neuron's life (chemical or electrical, including clamping) changes the left-side reference value to an externally set value. The neuron must adjust its  $Na^+$  and  $K^+$  concentrations to reach a new balance while the invasion persists. That is, any

invasion ("testing in the physical laboratory") changes the concentrations and voltages inside the cell. In addition, the internal biological processes can trigger internal processes that contribute (from the measurement's point of view) foreign currents or processes, see also section 1.8. The feedback the clamping methods apply introduces a compensating current. Even a simple conductance measurement device is active: it applies a test voltage that generates a test current, which sensitively affects the ionic composition of the neuron (recall that the concentrations may differ by up to six orders of magnitude). Although modern electronic devices attempt to conceal this effect, they subtly influence biological operation.

From our result, it follows that for more chemical elements, a per-element coupled set of equations exists plus the sum concentration agreed electric fields that are valid simultaneously and define the process variable (aka membrane potential) of the neural regulatory circuit. In a more symmetrical form

$$0_{in/out} = \frac{U_{electric}^{Total}(c, \Delta z, d)}{2} + \sum_{k;in/out} U_{thermal}^{C_k}(d) + \sum_{k;in/out} U_{invasion} \quad (1.1)$$

$$c = \sum_k C_k^{ext} = \sum_k C_k^{int} \quad (1.2)$$

That is, we have an unidirectional electric potential difference and oppositely directed thermal voltages. In the balanced state, the two potentials must be equal. When changing say one concentration, it changes the other concentration on the same side, and the surface charge density of the condenser. The changed electric voltage re-adjusts the thermodynamic voltage, and as a consequence, the concentrations, in the other segment. There is no simple way to express, say,  $[Na^+]$  in the function of  $[K^+]$  or vice versa, and similarly for the other ions. Everything moves. The size matters: the amount of ions in the external segment is many orders of magnitude higher, and the gradients are reciprocally proportional to the amount of ions.

## 1.8 Generating action potential

### 1.8.1 The conceptual operation

A commonly accepted truth that "*transient electrical signals are particularly important for carrying time-sensitive information rapidly and over long distances. These transient electrical signals—receptor potentials, synaptic potentials, and action potentials—are all produced by temporary changes in the electric current into and out of the cell, changes that drive the electrical potential across the cell membrane away from its resting value.*"[39]" "Most voltage-gated channels, in contrast, are closed when the membrane is at rest and require membrane depolarization to open."

By putting together the operating stages (as we have mentioned: in a well-defined order), one receives the characteristic process of neuronal operation

(an operating cycle): the stage variable changes in a well-defined pace in the function of the local time. As depicted in Fig. 1.6, the stage variable can be well observed inside the cell, furthermore, it has a well-measurable effect outside the cell. The notion of neuronal operation is the current pulse (called 'Action Potential') has a central role in neural operation. Here we discuss concepts of its production, while its sending and receiving in the next sections. The stages we have discussed previously are color-coded in the diagram line. The stage variable in the "Computing" stage is observable only inside the cell. After the beginning of stage "Delivering", the characteristics of the emitted charge pulse are well observable also outside the cell. The figures on the axes are approximately correct: the measurable voltage change is up to several dozens of millivolts, and the time scale is up to several milliseconds.

As we discussed in section 1.8.1, at the beginning of an operating cycle, synapses are open and some input pulses (gradient steps) increase the membrane's potential [74, 75] (the green section of the broken line). After exceeding the membrane's threshold voltage (the dotted orange line), the synapses' gating mechanism closes the current inputs and the membrane's rush-in mechanism begins to work due to opening voltage-controlled ion channels in the membrane's wall. The effect extends over the surface in an avalanche-like way [76]. The voltage increases until all ion channels get opened. The ion channels close after a very short period and the neuronal  $RC$  circuit continues its operation with discharging the condenser (the red section of the broken line). Given that the condenser stores part of the received charge, the capacitive current decreases and later reverses and reverts also the resulting current (and, consequently, the measurable voltage; this effect is observed as the membrane gets hyperpolarized). In this period (the blue section of the broken line) the synapses are open again and the received synaptic input gradients contribute again to the membrane's voltage. That is, a new cycle (this time starting with a potential differing from the resting value) can start and that residual potential acts as a memory (the details of the electrical processes are discussed in section 2.4.8). Notice that all mentioned events are spatiotemporal; most noticeably, the arrival of the synaptic inputs to the synaptic terminal following the absolute refractory period is much earlier than they are observable as an increase in the potential value (measured at the AIS). Also notice that there is no direct connection between the input and output voltages: the  $RC$  circuit fundamentally changes the neuronal output.

With reference to Fig. 1.6, we subdivide neuron's operation to three stages (green, red, and blue sections of the broken diagram line), in line with the state machine in Fig. 1.4. We start in stage 'Relaxing' (it is a steady-state, with the membrane's voltage at its resting value). Everything is balanced, the synaptic inputs are enabled. No currents flow (neither input nor output; at this point we do not consider the dynamic balancing current discussed in section 2.8), since all component have the same potential, there is no significant driving force for an output current.

As the figure suggests, an external invasion, typically, an electric voltage on the intracellular side, changes the balanced state and due to the parameters are

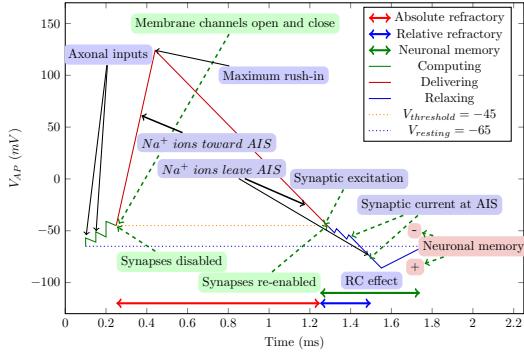


Figure 1.6: The conceptual graph of the action potential

linked, changes all concentrations. When moving the system out of its balanced state, in any way, a driving force appears that moves the system towards finding a new balanced state. However, recall that the ions are slow, so *the changes are not instant*.

The neuron has a stage variable (the membrane potential) and a regulatory threshold value. There exists a threshold for *voltage gradient* instead of the *membrane's voltage* itself (the voltage gradient provides a 'driving force'). As we detail in section 2.7.3, the voltage sensing is based on voltage gradient sensing, which phenomenon correlates with the value of membrane's voltage. Given that physiological measurements (such as clamping) suppress the gradient, and only the voltage is measured in a 'freezed' state, this difference has remained hidden. Crossing the membrane's voltage threshold value upward and downward causes a stage transition from "Computing" to "Delivering" and from "Delivering" to "Relaxing", respectively. Another role of that regulatory value is to open/close the input synapses. Furthermore, when the value exceeds the threshold, an intense current starts to charge up the condenser, that later discharges. We show that, although the change correlates with the value of membrane's voltage, the neuron's membrane actually senses the voltage gradient.

Given that the neuron's operation resembles an *RC* oscillator, the capacitive current of the condenser changes its direction, leading to changing the potential relative to the charge-up potential value to a value of opposite sign. The time constant of the *RC* oscillator is set so that the rushed-in current generates a nearly critically damped oscillation (with a damping parameter about  $\zeta = 0.35$ ).

Notice that all these processes happen with well-defined speeds, i.e., the different stages have well-defined temporal lengths. The length of period "Delivering" is fixed (defined by physiological parameters), the length of "Computing" depends on the activity of the upstream neurons (furthermore, on the gating due to the membrane's voltage). Due to the finite speed, we discuss all operations in neuron's own "local time".

When the membrane's voltage decreases below the threshold value, the axonal inputs are re-opened, that may mean an instant passing to stage "Computing" again. The current stops only when the charge on the membrane disappears (the driving force terminates), so the current may change continuously, changing the voltage on the circuit's output. The time of the end of operation is ill-defined, and so is the value of the membrane's voltage at the time when the next axonal input arrives. *The residual potential acts as a (time-dependent) memory*, with about a msec lifetime; see Fig. 1.6.

With putting together the operating stages (as we have mentioned: in a well-defined order), one receives the characteristic process of neuronal operation (an operating cycle): the stage variable changes in a well-defined pace in the function of the local time. As depicted in Fig. 1.6, the stage variable can be well observed inside the cell, furthermore, it has a well-measurable effect outside the cell. The notion of neuronal operation is the current pulse (called 'Action Potential') has a central role in neural operation. Here we discuss concepts of its production, while its sending and receiving in the next sections. The stages we have discussed previously are color-coded in the diagram line. The stage variable in the "Computing" stage is observable only inside the cell. After the beginning of stage "Delivering", the characteristics of the emitted charge pulse are well observable also outside the cell. The figures on the axes are approximately correct: the measurable voltage change is up to several dozens of millivolts, and the time scale is up to several milliseconds.

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### Sending AP

Sending AP begins when the membrane's potential exceeds the threshold and terminates when it drops below the threshold. The time of the stage "Delivering" is entirely determined by the parameters  $C$  and  $R$  of the neuronal oscillator, so all outgoing spikes have the same shape. However, depending of the time of the previous spike (or, more precisely, the value of the membrane's potential at the moment of the start of "Delivering"), the shape may be apparently different. The measurable potential is the sum of the "tail" of the previous spike plus the front of "this" spike; and both of them have their temporal course (the currents that evoke those voltages are slow). The effect of gating can be observed with a time delay at the AIS (the slow current entering through the synaptic terminals needs time to reach the AIS), and the value of that delay depends on the geometry of the neuron, mainly on the position of the synaptic terminal. On its "local time" scale, the AP starts when the first exciting synaptic pulse arrives, usually (due to exceeding the threshold for the voltage gradient) leading to starting the neuron's rush-in current.

### Receiving AP

The native input arrives through the synaptic terminals, at the time determined by the upstream neuron (in the sense that at what absolute time it sends the spike and how long the spike travels). The time window of the "Computing" period opens when the first input arrives and so the further inputs arrive at a later time. The time window ends when the membrane's voltage exceeds its threshold. Given that the computing time is in the order of  $0.1\text{ ms}$  and the total length of an AP is in the order of up to  $10\text{ ms}$ , only the first temporal part of the received spike can be processed and can contribute to the result: as the membrane's potential increases, the neuron closes its synapses. That means that the neurons coöperate with their upstream neurons: the contributions to their membrane's charge through their synapses change even between the adjacent spikes. Even, the composition of the sum may change, depending on in which order the input spikes arrive.

### Post-synaptic potentials (PSP)

During regular neuronal operation, spikes arrive through synapses, and their effect can also be measured as a PSP. When a spike (evoked by a single AP, elicited by current injection in presynaptic cells) [77] arrives at a synapse, it can be represented that a (short pulse of) "slow" current arrives through the axon. However, the inflow of the axonal current is "slow", and a "critical mass" of ions is needed to start a well-defined current inflow into the membrane, so neuronal arborization [78] takes place, forming an "ion buffer". If a current  $I$  arrives through the axon, when entering the arbor, the cross section  $A$  suddenly increases, so  $v$  suddenly decreases; see Eq.(2.23). The arbor buffers the charge received in the spike. The mechanism that the ion current 'takes away' the ions

does not work in the arbor. The ions can move under the voltage gradient resulting from the mutual repulsion and the current drain towards the membrane. *The drain current (into the membrane) is proportional to the voltage gradient between the arbor and the membrane, giving a natural explanation how the membrane's potential controls synaptic contributions, furthermore why the potential increase in the "relative refractory" period changes with the membrane's potential.* For details, see section 1.5.1 and Figure 3.22. Whether the buffer is filled or empty explains that ‘both sodium and potassium conductances increase with a delay when the axon is depolarized but fall with no appreciable inflection when it is repolarized’ [5].

The arbor essentially (and anatomically) belongs to the axon, but its functionality is also similar to that of the membrane. It *plays a vital role in the information processing in the brain* [79]: defines the crucial input parameter “time of arrival of a spike”, makes the intensity of synaptic inputs nearly independent from the shape of the spike (less depending on the presynaptic neuron; important for the cooperation); furthermore, links adjacent spikes, providing a neuronal memory. The buffering effect may be seen as “making a hole in the membrane” [75]: exceeding a critical mass (charge in the arbor) may start an intensive current into the membrane and manifest in a sudden  $\frac{d}{dt}V$  change, see section 3.5.6. The shape of PSP also plays a vital role in synchronizing neurassembles [12, 63].

The buffering changes the shape of the received AP: it integrates the input axonal current and distorts the received AP’s shape toward a PSP: there is no AIS in the axon (no oscillator). Most schematic figures showing signal transmission from a presynaptic neuron to a postsynaptic neuron miss the point that at the synapse, the AP appears as having a different shape. Furthermore, they misidentify the temporal length of AP essentially to a period between the beginning of the charge-up to the end of reaching the hyperpolarization peak voltage (comprising the ‘Delivering’ stage and some part of ‘Relaxing’). Our discussion shows that the stage ‘Computing’ (reaching the threshold potential) and ‘Relaxing’ (*the long tail after hyperpolarization*) are a vital part of AP. The former is the result of the neuronal computation and the latter (among others) provides short-term neuronal memory for neuronal cooperation.

The intense current from this buffer starts to charge the membrane and discharge the arbor. We arrive back at the case we saw in the case of a clamping where a “slow” axonal input current from the arbor arrived at the membrane at its junction. It flows with its finite speed on the membrane’s surface, while, at the same time, the newly created potential decays exponentially. Initially, while the buffer is charging, the current increases exponentially as the spike arrives, manifesting in the observable PSP. We can validate our model-based hypothesis by fitting experimental data; see section 3.7.

### 1.8.2 The implementation of the ActionPotential

As we discussed in connection with Fig. 1.5, fundamentally the neuron is electrically balanced and for small perturbations, its control mechanisms return its

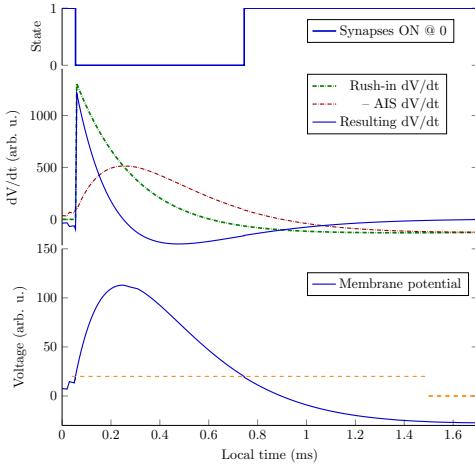


Figure 1.7: The summary of AP generation. The voltage time derivatives (the middle subfigure), resulting by summing the  $\frac{d}{dt}V_{AIS}$ ,  $\frac{d}{dt}V_M$  and a constant corresponding to the clamping current, that define the membrane's output voltage (the AP, the bottom subfigure), that control synaptic contributions (top sub-figure).

state to the dynamically balanced resting state. To produce an AP, the neuron uses a voltage-dependent "ion-production" mechanism (its "structure differs from anything we tested in physical laboratories"). As physiology observed, a large amount of  $Na^+$  ions rush into the intracellular segment. They cause a sudden increase in the local potential of the proximal layer of the membrane. The potential creates a considerable combined gradient across the AIS, and an intensive current starts to flow. Due to the ions' low speed, the current needs time to reach the AIS. Actually, a discharge process takes place. Given that the charges are created over the finite-size surface of the membrane, charges from different positions arrive at different times (although they were created at the same time): a smeared double-exponential current appears on the AIS. However, the membrane with its capacitance  $C$  and the AIS with its resistance  $R$  forms a ***serial RC*** oscillator (one of the catastrophic fallacies in nerophysiology is to hypothesize the circuit is ***parallel*** distorts the shape to what can be measured by physiology).

In a special type of invasion, when suddenly a large amount of  $Na^+$  rushes in (i.e., the trigger is external, but the ions derive from a biological process), the current throughput of the "resting ion channels" is not sufficient anymore: the instant increase of  $Na^+$  concentration drastically increases, and so does the membrane's potential. At that point, the neuron is out of balance: although most of the  $Na^+$  ions can flow out through the AIS, the system also changes its  $K^+$  concentration through the limited capacity "resting ion channels" until the

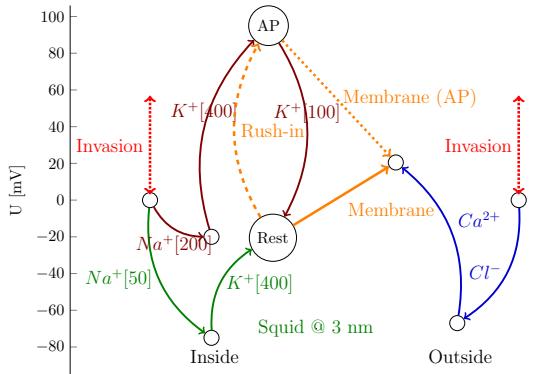


Figure 1.8: The mechanism of producing AP (using numbers referring to the case of squid shown in Table 3.1. In the resting state, the inside thermal potentials follow the green path. When the rush-in of  $Na^+$  ions increases the internal concentration to [200], the potential on the internal side of the membrane increases to  $+90\text{ mV}$ , and the neuron must decrease its  $K^+$  concentration to restore the resting potential, or release an action potential through the AIS.

balanced state regained. This latter effect must not be mismatched with the capacitive current, which (due to its changed direction) causes the phenomenon known as "hyperpolarization".

Figure 1.8 shows the schematic course of potentials and concentrations during issuing an AP. Follow the green path: the concentration ratio of  $Na^+$  and  $K^+$  ions define a thermodynamic contribution in the intracellular segment. Follow the blue path: the  $Cl^-$  and  $Ca^{2+}$  ions define a thermodynamic contribution in the extracellular segment.

Notice the two-sided negative feedback effect: a change in the value of the "command potential" or "command concentration" changed the other value. In the case of voltage invasion, the ratio of the ion concentrations also changes. In this case, the feedback amplifier is the delicate balance of the electric and thermodynamic force fields. In the case of clamping, another (electric) feedback amplifier is introduced into the system and they work against each other. The neuron attempts to restore its balance without external potential (it cannot distinguish the foreign potential from its membrane potential), and changes its concentrations accordingly. A vital difference is the *speed* of the feedback amplifier. The electrical one works with electric speed, while the thermodynamic one with the several orders lower thermodynamic speed. When switching (or changing) the external ("command") voltage, the neuron must first get into its "steady state". It takes time. "The command potential, which is selected by the experimenter and can be of any desired amplitude and waveform" [39]. However,

if the measured data readings are not from a steady state, the measurement is wrong: the different amplifier speeds (different current speeds) surely distort the measured value. Compare the figure to Fig. 2.6

On the left side, two positive ions are in the solution, and the membrane potential (due to charge separation) rises toward the outside segment; the ions cannot go "uphill". Similarly, the  $Cl^-$  ions cannot go uphill (due to their negative charge, the same potential is also rising for them). This single membrane potential keeps all ions in their segments. However, the  $Ca^{2+}$  ions can travel "downhill". Calcium pumps needed: although in minimal concentration,  $Ca^{2+}$  ions flow into the intracellular segment, and they must be pumped out. (BTW: this is also the reason why measuring  $Ca^{2+}$  concentration is inaccurate.)

As we discussed above, the concentrations and voltages in the extracellular segment, with its vast amount of ions, remain unchanged in resting and transient states. Follow the red path: when  $Na^+$  ions rush into the intracellular segment; they increase the concentration from 50 mM to (say) 200 mM. This sudden change decreases the thermal contribution of  $Na^+$  potential to [20 mV], but because the total charge on the membrane significantly increases, the resulting voltage on the intracellular side of the membrane increases to 90 mV. The neuron could decrease its potential to the resting value if it could decrease  $K^+$  concentration to 100 mM. However, the ion delivering capacity of the "resting ion channels" is not sufficient: they are sized to maintain the resting state. (Furthermore, the electric contribution appears instantly, while the thermodynamic one, due to the finite speed of ions, only with some delay [19].) Follow the dashed orange path: the large amount of rush-in  $Na^+$  ions drastically increases the surface concentration on the membrane, so the potential suddenly changes to 90 mV. Follow the dotted orange path: the electric field of the membrane suddenly changes its direction from positive slope to negative so that the excess positive ions can move "downhill" out of the intracellular space through the high-capacity ion channel array (AIS) at the end of the neuron. Its internal end is at the high membrane potential, while the external end is at the low potential of the extracellular segment.

Given that the outer concentrations are unchanged, so is the membrane potential. The system must preserve its balanced state under the constraints that the inside sum of concentrations of the positive ions remains the same while the outside concentrations of all ions remains unchanged change according to Eq.(1.2). That is, we have a sum concentration and the dependence of  $[K^+]_i$  on  $[Na^+]_i$

$$[C]_i = [K]_i + [Na]_i \quad (1.3)$$

$$-\frac{U_{electric}}{2 * 58} = \log_{10} \left( \frac{[K^+]_o}{[C]_i - [Na^+]_i} \right) + \log_{10} \left( \frac{[Na^+]_o}{[Na^+]_i} \right) \quad (1.4)$$

that enables us to derive  $[K^+]_i$  in function of  $[Na^+]_i$  (i.e., what  $[K^+]_i$  concen-

tration can keep the balance with the given  $[Na^+]_i$  concentration):

$$10^{\left(-\frac{U_{electric}}{2*58} - \log_{10}\left(\frac{[Na^+]_o}{[Na^+]_i}\right)\right)} = \frac{[K^+]_o}{[K^+]_i}$$

$$[K^+]_i = [K^+]_o * 10^{\left(\frac{U_{electric}}{2*58} + \log_{10}\left(\frac{[Na^+]_o}{[Na^+]_i}\right)\right)}$$

The other way round is that by knowing all concentration values, we can calculate the voltage on the membrane:

$$U_M = U_{electric} + 58 * \left( \log_{10} \frac{[Na^+]_o}{[Na^+]_i} + \log_{10} \frac{[K^+]_o}{[K^+]_i} \right)$$

This enables us to draw the membrane's voltage at different concentrations, as shown in Fig.

The set-point on the extracellular side remains fixed. On the intracellular side, initially, the actual voltage is above the set-point on the extracellular side, so at the two ends of the AIS, a positive driving force moves the ions toward the downstream neuron. However, the charge on the membrane continuously decreases and consequently, the voltage slope increases and the current through the membrane decreases. At some point, the voltage drops below the set-point of the extracellular side. The neuron continues restoring its set-point on the intracellular side, but now the resulting potential across the membrane is reversed. The resulting potential continues having a larger positive slope, so the direction of the reversed current grows. At this stage, most of the rushed-in charge has flown out, so the driving force decreases and a low-intensity current restores the balanced state, to the previous set-point. When measuring at the AIS, one observes that the potential rises suddenly, then decreases below the set-point (hyperpolarizes the membrane), than a decreasing current (flowing in the opposite direction due to the changed slope of the resulting potential, but comprising the originally rushed-in  $Na^+$  ions) slowly restores the resting potential. Here comes to light the finite speed of ions again. The ions can follow the potential changes with a delay due to their finite speed, causing an apparent delay in the time course of the AP's current.

## 1.9 Transmitting action potential

## 1.10 Consequences of the resting potential

Our single abstract neuron differs from the classic neurons in several points.

### 1.10.1 Resting current

Although through the thickness of the ion layer  $\Delta z$ , the ion's water-related behavior can influence the surface charge density, one can draw the conclusion that when only one type of ion is solved in the liquid, approximately the

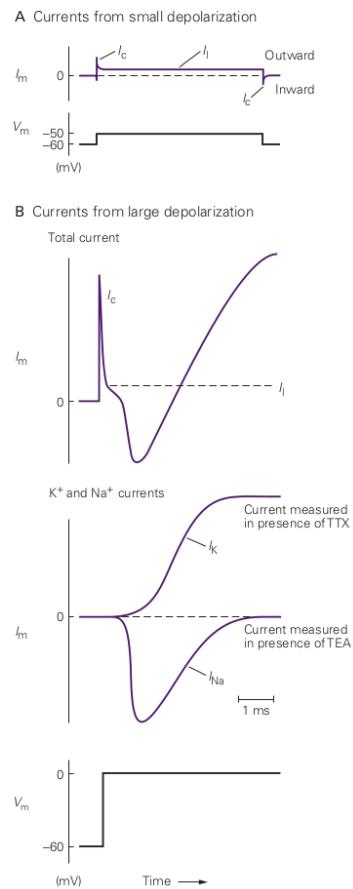


Figure 1.9: **Errata in blue.** A voltage-clamp experiment demonstrates the sequential activation of two types of voltage-gated channels. A. A small depolarization (10 mV) elicits capacitive and leakage currents ( $I_c$  and  $I_l$ , respectively), the components of the total membrane current ( $I_m$ ). There is no leakage current, see section 1.10.1 and the capacitive current is something different. The two small and opposite sharp changes are due to switching a *current* instead of voltage to the membrane (nothing is activated), see the signal shapes of the differentiator circle in Fig. 2.1. B. A larger depolarization (60 mV) results in larger capacitive and leakage currents, plus a time-dependent inward ionic current followed by a time-dependent outward ionic current. The larger current induces larger voltage gradient that opens voltage-controlled ion channels in the membrane's wall, and the slow current – distorted by the *RC* circuit as discussed – appears with a time delay on the the always-open channels in the AIS. Top: Total (net) current in response to the depolarization. Middle: Individual  $Na^+$  and  $K^+$  currents. Bottom: Voltage step and also current step. This is why  $I_c$  must be subtracted.  $I_K$  and  $I_{Na}$  are both capacitive currents, flowing in opposite directions, as discussed in section 2.4.8 (Fig. 7-3 in [39].)

same concentration difference between the segments produces approximately the same "thermodynamic electric field" that can counterbalance the electric field of the biological condenser. One can notice that in the classic measurement by Hodgkin-Huxley, the sum of the concentrations of  $K^+$  and  $Na^+$  in the cytoplasm and extracellular fluid (in mM) are 380 and 390, respectively, while the sum concentrations of  $Cl^-$  and  $Ca^{2+}$  are 450 and 460; practically all equal, as our analysis derived it must be. The deviations are well within the uncertainty of the measured values.

HH did a complete measurement, and derived *precise* measured data. However, their measurement was not *accurate* because their model was wrong. In a balanced state, no current flows, so no voltage is generated. For this reason, they assumed that a permanent leaking current  $I_L$  was flowing on the membrane, and on its resistance, it generated a 42.5 mV voltage [69]. In Hodgkin and Huxley's picture, the question *what ion constitutes the current* remains open. It was claimed that the only permeability pathways open at rest are  $g_{leak}$  and  $g_K$ . It follows that at the resting membrane potential, the leak current equals the potassium current. That is, at rest, two currents flow (without driving force in a balanced state), one consisting of  $K^+$  ions and another of one  $leak^{+/-}$  ions (??) (depending on the direction, it could be positive or negative), and neither of them changes the concentration neither on the departure nor on the arrival segment, neither the concentration of the other ions; defying also Nernst's law.

The idea of leakage current was wrong: the voltage Hodgkin and Huxley measured [69] is correct, but – as our model correctly explains – it was generated by charge separation instead of a current through a distributed resistor. It is permanently present while ionic segments are on its sides, even when no current flows. Measuring the energy consumption of neuronal operation [71] confirms that no resting current, in the sense as HH used the notion, exists.

### 1.10.2 Heat emission/absorption

As explained in section 2.4.3, there are alternative methods of producing a voltage difference across the membrane's surface; with and without current. Hodgkin and Huxley took the wrong choice. The lack of resting current also solves the long-standing mystery of "reversible heat release during the action potential", which is inconsistent with the Hodgkin–Huxley model. In the framework of that theory, Ohmic currents flow through resistors that dissipate heat due to friction, no matter in which direction ( $W = I^2 * R$ ) the ion currents flow. As Hodgkin wrote [80]: "Hill and his colleagues found [81] that an initial phase of heat liberation [of the action potential] was followed by one of heat absorption. [...] a net cooling on open-circuit was totally unexpected and has so far received no satisfactory explanation."

The issue here is that the dissipation was attributed to the "leakage current." (Although, due to the different conduction mechanisms, it is not dissipated in the way electron energy is dissipated in solids.) However, as our explanation shows, the voltage generated across the membrane is due to charging instead of a permanently flowing current, so no dissipation was present given that no

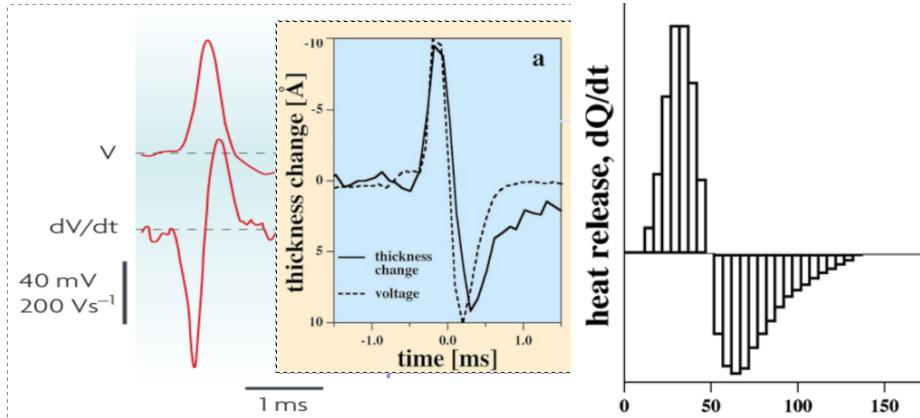


Figure 1.10: The red diagram lines show the membrane voltage and its gradient during producing an action potential [82], Fig. 4. The black diagram lines show the size-related and heat-related changes during producing an action potential [33], Fig. 1. and [83], Fig. 18.5. The voltage gradient has, by convention, opposite polarity.

resting current was present. Although the energy to build a potential on the membrane and to maintain it needs biological energy consumption, the process of generating an action potential is, in principle, reversible: ions flow into the layer on the membrane and flow out through the AIS.

According to that, the "temperature of individual particles" with the mean kinetic energy  $E$  is  $T = \frac{2*E}{3*k_B}$  (where  $k_B$  is the Boltzmann constant and  $T$  is the thermodynamic temperature of the bulk quantity of the substance); that is the temperature is directly proportional to the kinetic energy. The ions on the two sides of the membrane are in the state with temperature  $T$  before and after the AP. When the  $Na^+$  ions rush into the intracellular space, they gain energy through electrostatic acceleration by the membrane's electric potential, so the same ions appear on the intracellular side as having more energy, i.e., slightly higher temperature. In the second phase of the AP, those more energetic ions that provide excess voltage above the resting potential leave the membrane through the AIS, so the temperature decreases in the second phase. The heat liberation and absorption is a direct experimental evidence of the "slow current" and the mechanisms described above.

### 1.10.3 GHK potential

In the light of our findings, we must reconsider a few key conceptions. We derived (see Eq.(2.69)) that the gap voltage depends on the thickness of the membrane and the overall concentration. Furthermore, we demonstrated that the gap voltage is equivalent to the resting potential (correctly: potential difference) and is independent of ion mobility or ion composition in the solution. Derived

values, such as the Goldman-Hodgkin-Katz potential, should be rethought. The idea is nonsense: in a balanced state, no ion transport happens, so even without permeability, the balanced state persists; as experiments proved, the resting potential has nothing to do with either ions' mobility or permeability nor with ion absorption [68]. The causality is reversed: the potential is a static notion and is set electrically, and the two gradients form the experienced concentrations from the available solvent molecules. For the time course of forming the gradients and maintaining the balance, mobility and permeability play a role but not in determining the concentrations or the resting potential.

The  $Ca^{2+}$  ions do not fit into the GHK picture. However (see our Table 3.1), it provides a thermodynamic contribution in the same order of magnitude as the charge separation by the membrane. If we add the potential due to  $Ca^{2+}$ , we arrive at the correct result that the total balance of the thermodynamic contributions equals zero, that is, the resting potential is zero. The electric potential contribution is an additional term, resulting in the resting potential.

When adding a new ion to the solution, the sum concentration increases, and so the electric force increases, forcing the previous elements to find new concentrations on both sides. The appearance of a new chemical element indirectly changes the concentrations of the others (a good example is the role of the negligible amount of  $Ca^{2+}$ ). No linear summing or similar assumptions can be made. The potential is described by coupled equations as discussed in connection with Eq.(1.2). As we discussed in connection with Eq.(2.18), the integral form of the Nernst equation implies an undetermined additive constant. To calculate a linear combination of terms comprising an arbitrary constant is nonsense, and so is changing the base of the logarithm used in a calculation to match the experimental value.

#### 1.10.4 Reversal potential

From our picture, it is clear that the reversal potential is reached when the potential on the inner segment is lowered or lifted in such a way that the orange sloping potential in Fig. 1.8 turns horizontal. To reach it (provided that the potential on the other side is kept fixed), the concentrations on the invasion site must be changed. The invasions resulting in the exact (but opposite) change of potentials from the two sides leads to different concentrations. The invasion acts as changing the potential at the corresponding surface side of the membrane. Given that the difference between the two potentials on the two surfaces defines the driving forces, the concentration on the other side is also affected. That is, the reversal potential exists, but its value depends on the context, see the discussion about invasions.

### 1.10.5 Pressure wave

By using the value of the force acting on a unit charge in the field across the membrane is

$$F_{Na^+} = 10^7 * 1.60217663 * 10^{-19} = 1.6 * 10^{-12} [N] \quad (1.5)$$

we can estimate how the pressure of the neural cell increases due to the rush-in charges at the beginning of the AP. As evidence shows, the local potential at the internal surface of the membrane increases by  $\Delta U = 100$  [mV]. This increase means a change in the force acting on an ion (see Eq. (1.5)) by  $1.6 * 10^{-12}$  [N]. When we assume  $10^7$  rush-in ions and unchanged cell size, the total force acting on the membrane increases by  $1.6 * 10^{-5}$  [N]. This change in force means on the neuron's  $8 * 10^{-9}$  [ $m^2$ ] surface (see [1], page 12) a pressure change

$$\Delta P = \frac{1.6 * 10^{-5} [N]}{8 * 10^{-9} [m^2]} = 2 * 10^3 \left[ \frac{N}{m^2} \right] \quad (1.6)$$

This change is large enough to explain why pressure wave and other mechanical changes [84] also start at the beginning of the AP, and other (such as optical, density) changes are accompanied with it. Nature invests energy also in the conventional way, a term  $P\Delta V$ , into the thermodynamics of neural operation; not only in the form of storing energy in the changed electric field. Thermodynamics and electricity must not be separated also from the point of view of the appearance of energy investment.

Given that [85] measured  $5 \frac{dyn}{cm^2} = 0.5 \frac{N}{m^2}$ , we have good reason to presume that this changed pressure increases the neuron's size and the neuron's elasticity.

The peak of swelling was shown to coincide fairly accurately with the peak of the action potential (i.e. when the . [86]

Notice an important difference. The acceleration of an ion is unbelievably large. It is sufficiently large to keep the potential at the same value, provided that the ions must follow a small change, such as due to the "leaking" current through the AIS. Similarly, the ions can 'instantly' follow quick changes such as a square wave gradient. However, if many similar ions are ahead, their repulsion decreases the acceleration, and the ion travels only at a few m/s speed. The huge forces and accelerations means that a potential change acts immediately. However, the force decays quickly. The ions start to move 'instantly', but the charge carriers can move only with a limited speed, much below the interaction speed of electromagnetic (EM) interactions. The effect can propagate only with that lower speed.

See the case of axon: there exist a mechanical constraint that the ions cannot spread through the wall (they must keep the direction), and the ion package propagates as Equs.2.11 and 2.14 describe it.

#### Membrane's charge

[21], page 7 provides a numeric estimation that "a spherical cell of  $5 - \mu m$  radius with a resting potential of  $-70$  mV stores about  $0.22 * 10^{-12}$  coulomb of charge

just below the membrane and an equal but opposite amount of charge outside". As we estimated above, a charge in the same order of magnitude (or above it) is involved in forming an action potential, so the assumption that the membrane is a kind of electric circuit with a fixed potential and the moving ion current does not change membrane's potential, is far from reality. That amount of charge represents  $10^7$  ions. From this we can estimate that the ions are at a  $0.5\text{ nm}$  distance from each other.

As the caption of Fig. 11.22 in [87] formulated: "A small flow of ions carries sufficient charge to cause a large change in the membrane potential."

### 1.10.6 Role of proteins

"When measuring currents through small membrane segments, the conductance events appear in a quantized steps, i.e. one observes a switching between current-on and current-off events. In biological membranes one normally assumes that this phenomenon is caused by the opening and closing of ion channel proteins (Fig. 3a). The two conduction states are called open and closed channels. As already described above, these channel proteins play an important role in the Hodgkin-Huxley model of nerve pulse conduction. Interestingly, one finds very similar events in synthetic membranes that are free of proteins (e.g., [10, 11]), in particular if one is close to the melting transition (Fig. 3b). Both current amplitude and the typical opening time scales are practically indistinguishable from those of protein-containing membranes. Obviously, the finding of quantized current events is not a proof for the activity of proteins even though this is what is generally assumed since membranes close to transition display the same characteristics. Whether the events in protein-containing membranes and those in pure lipid membranes have the same origin is yet an open question." [33]

## 1.11 Implications for computing, communication, information

### 1.11.1 Delivering information

As follows from our interpretation, the appearance of a huge voltage gradient (evoked by the sudden rush-in current) represents the output information the neuron delivers, and also the input information it receives from its upstream neurons through its synapses. Given that the input currents delivered by the spikes are gated by the neuron, the information that can be accounted in the computation must be in the front side of spikes. (The back side is mainly needed for restoring the resting potential.)

The front side (in the form of a sudden step in the value of the voltage gradient) delivers an extremely precise timing information about at what time the rush-in event in the sender happened, explaining the half-understood experience [88] why "the timing of spikes is important with a precision roughly two orders of magnitude greater than the temporal dynamics of the stimulus". If

exceeding the threshold is the consequence of the charge arriving from a single upstream neuron, the neuron simply transmits the timing information it received. If several smaller gradients are summed (and recall that the component gradients decay with time after their arrival) for reaching the gradient, then their information content is weighted.

### 1.11.2 Implications for computing

Fig. 1.6 also reveals some secrets of the effective biological computing.

- biology makes the "weighted summing" of neuron's synaptic inputs simultaneously, in one single operation making multiplication and integration, furthermore selecting the time window and its effective synaptic inputs
- the heavily used neuronal information "is stored, as it should be, in every circuit" [89]
- "information stored directly at a synapse can be retrieved directly" [89]
- part of the information (in 'volatile' memory) is stored only for the period when it might be needed (a real temporary cache)
- "Computing" is much shorter than "Delivering"
- asynchronous; the operation time varies (no pipelining)
- "Send only information that is needed, and send it as slowly as possible" [89]
- using voltage temporal gradients enables transferring more information and functionality; for example, synchronization [63]
- for simulation: there is no need to send and integrate spike shapes, only *the time of arrival/sending*

### 1.11.3 Implications for communication

# Chapter 2

## Physics for neurons

- "Is life based on the laws of physics?"..."*New laws to be expected in the organism*"

"From all we have learnt about the structure of living matter, we must be prepared to find it working in a manner that cannot be reduced to the **ordinary laws of physics**. And *that not on the ground that there is any 'new force' or what not*, directing the behavior of the single atoms within a living organism, *but because the construction is different from anything we have yet tested in the physical laboratory.*"

"How can the *events in space and time* which take place *within the spatial boundary* of a *living organism* be accounted for by *physics* and *chemistry*?" – E. Schrödinger: What is life?[8] @1992

In his very accurately formulated question, Schrödinger focused on (at least) these significant points

- '*events*' Unlike non-living matter, *living matter is dynamic, changing autonomously by its internal laws*; we must think differently about it, including making hypotheses and testing them in the labs. Those laws are non-ordinary 'because the construction is different', but its principles must not differ from the ones we already know. Processes happen inside it, and we can observe some characteristic points.
- '*space and time*' Those characteristic points are significant changes resulting from processes that have material carriers, which change their positions with finite speed, so (unlike in classical mechanics) the events also have the characteristics 'time' in addition to their 'position'. In biology, the spatiotemporal behavior is implemented by *slow ion currents*. The meticulous observations must describe the events by using special 'space-time' coordinates (to distinguish it from the one used in theories of relativity, we call it 'time-space' coordinate). In other words, instead of 'moments' we must consider 'periods'.

- '*within the spatial boundary*' Laws of physics are usually derived for stand-alone systems, in the sense that the considered system is infinitely far from the rest of the world; also, in the sense that the changes we observe do not significantly change the external world, so its idealized disturbing effect will not change it. In biology, we must consider changing resources
- '*accounted for by physics*'[by extraordinary laws] We are accustomed to abstracting and testing a static attribute, and we derive the 'ordinary' laws of motion for the 'net' interactions. In the case of physiology, nature prevents us from testing 'net' interactions. We must understand that some interactions are non-separable, and we must derive 'extraordinary' laws. The forces are not unknown, but the known 'ordinary' laws of motion of physics are about single-speed interactions.
- '*living matter*' To describe its dynamic behavior, we must introduce a dynamic description.
- '*yet tested in the physical laboratory*'[including physiological ones] We need to test those 'constructions' in laboratories, in their actual environment, and in 'working state'. As we did with non-living matter, we need to develop and gradually refine the testing methods as well as the hypotheses. Moreover, we must not forget that our methods refer to 'states', and this time, we test 'processes'. Not only in measuring them but also in handling them computationally, we need slightly different algorithms.

Science created abstract concepts such as space and time, mass and charge. It based its concepts and laws on abstractions that were calculated by approximations and contained *only one* of these concepts. The recognition of the discreteness of energy led to quantum mechanics. The recognition of the non-independence of space and time led to the creation of the theory of relativity. Both realizations had far-reaching consequences. In addition, we understood that under certain circumstances we must treat particles as a kind of continuous wave, and continuous waves as particles. These micro-objects interact with their environment, including our measuring instruments; with a measurement method suitable for particle detection, we see them as particles, and with an instrument suitable for wave measurement, we see them as waves. (How one micro-object sees the other remained cryptic.) This kind of micro-level behavior is inherent in nature; our methods of description and measurement must be adapted to nature and not the other way around. We have understood that the Newtonian approach has its limitations; finite-velocity interactions can only be described with a different kind of mathematics, the introduction of the concept of space-time. In another approach, mass is also related to space and time; taking this into account, we can describe nature with curved space-time. We can also say that according to classical physics, we can describe phenomena with sufficient accuracy using only the aforementioned concepts (the zeroth derivatives). According to modern physics, however, for a more accurate description, we must take into account the first derivative with respect to time, and even the second derivative with respect to time for a general description.

The so-called modern physics was born when experiments began to contradict the idea that all phenomena of nature could be described in such a simple way. Neuroscience has similarly accumulated a number of experiences that contradict theory, although mainstream neuroscience has either ignored them or explained them with ad-hoc flawed and unfounded hypotheses. It happens despite Hodgkin's opinion "*in thinking about the physical basis of the action potential perhaps the most important thing to do at the present moment is to consider whether there are any unexplained observations which have been neglected in an attempt to make the experiments fit into a tidy pattern*" [80], page 70. In this field (and in the physical foundation of biology in general), a similar modern approach is needed, which first requires a review of the fundamental assumptions of the underlying physics. Classical physics classified phenomena into disciplines that largely described nature well. Modern physics has revealed new relationships, but they have also organically integrated into the fabric of science as a whole. To understand the living organism, in the spirit of R.P. Feynman, we must make "excursions" between disciplines: "We make no apologies for making these excursions into other fields, because the separation of fields, as we have emphasised, is merely a human convenience, and an unnatural thing. Nature is not interested in our separations, and *many of the interesting phenomena bridge the gaps between fields.*" [4] E. Schrödinger expressed his conviction that no new force or unknown interaction is emerging; only a previously unknown regularity concept must be found, then the non-ordinary laws organically integrate into the fabric of science, together with the already known laws. In this chapter we make an attempt to find such a concept in the hope that scrutinizing the features of ions leads to a solution.

Regarding ions, separately, we can handle their charge and mass well, we know the relevant laws. Their properties are analogous to the particle-wave duality: depending on the interaction (i.e. the measurement method), we see the ion as either a charge or a mass. *We see the same object, but we measure it based on the concepts of a different discipline.* Therefore, we must connect charge and mass, just like space and time in the case of relativity. They do not exist independently of each other and their combined behavior differs from what we expect based on the classical disciplinary approach. Interestingly, similar to relativity, the velocity establishes the connection between the two quantities here.

Furthermore, we must introduce a connection for the currents represented by ions, such as the one introduced by statistical mechanics when corresponding to the discrete and the continuum approach. However, in our case, the correspondence is established based on geometric considerations and, due to the connection of the two properties, we cannot apply statistical laws based on one property in an unchanged form. Moreover, in most biological cases, the quantities involved are so small that statistical interpretation is severely limited. The fundamental approximation of physics that the force field acts on the particle, but the particle's effect on the field is negligible, is not met. In some cases, closed spaces give rise to counterforces that fundamentally change the processes taking place. *Ignoring these properties of living systems has led to the erroneous*

*statement that science cannot describe living matter and its processes.* It is undoubtedly more complicated and requires a revision of several approximations, but it is possible.

## 2.1 Introduction

The roles of time, space and matter are subjects of endless debates in science. Considering finite interaction speeds is against using a "nice and classical physics" with its nice mathematical formulas, but omitting the different speeds misled and may mislead research in several fields. Biology produces situations where the complexity of phenomena and the needed carefulness meets the ones needed in cosmology. The difference is that, in biology, the consequences of phenomena are immediate and they can be studied experimentally.

To describe the related phenomena, we must scrutinize, case by case, which interactions are significant and which interaction(s) can be omitted; instead of setting up ad-hoc models for living matter that contradict each other and fundamental scientific principles when used outside their narrow range of validity. To provide their correct physics-based description, we must understand the corresponding behavior of living material, including that it works with slow ion currents, electrically active, non-isotropic, structured materials, and consequently, its temporal behavior (the speeds of interactions) matters. We must consider macroscopic and microscopic phenomena (continuous and discrete features) at the same time, different science fields, and their interplay (or mixing). "Living complex systems in particular create high-ordered functionalities by pairing up low-ordered complementary processes, e.g., one process to build and the other to correct". [65] We need to check the validity of our abstractions.

Galilei said, "Mathematics is the language in which God has written the universe". However, it is not sure that when we attempt to read a piece of the universe written in that language, we use the right piece and dialect of the language, and even that humans already invented the needed piece. For example, mathematical calculus (integral and differential) was invented mainly for the practical needs of analyzing spatial motion of celestial bodies. Similarly, Minkowski's mathematics theory proliferated widely [90] only after inventing the special theory of relativity. Although the mathematical description was developed earlier, there was no practical need to apply it. The classical laws of motion were valid only until more meticulous observations required to consider speed and acceleration (time derivatives of position) dependence in addition to position dependence. Newton's *static* laws remained valid, but for the *dynamic* description we must revisit the second law of motion.

Also, we must not forget that "mathematics is not just a language. Mathematics is a language plus reasoning. It's like a language plus logic. Mathematics is a tool for reasoning." (Richard P. Feynman) Mathematical formulas work with numbers but math theorems and statements begin with "If ... then". They have their range of validity, even when they describe nature. Using mathematics to describe the classical equations of motion, to calculate forces and

times that speed up bodies above the speed of light is possible, but in that case mathematics is applied to an inappropriate approximation to nature. When approaching the speed of light, different physical approximations (that calls for different mathematical handling) are to be used. *A mathematical formula, without naming which interactions it describes and naming under which conditions and approximations the formula can be applied, are just numbers without meaning. It surely describes something but only eventually describes what we studied.* Galilei made measurements with objects having friction, but his careful analysis extrapolated his results to the abstraction that no friction was present. *We know his name because of making meticulous abstractions and omissions (and mainly: recognizing the need to do so!)* instead of publishing a vast amount of half-understood measured data.

In this chapter we underpin that "living matter, while not eluding the 'laws of physics' as established up to date, is likely to involve 'other laws of physics' hitherto unknown, which however, once they have been revealed, will form just as integral a part of science as the former" [8]. We scrutinize the oversimplifications, wrong abstractions and derive the laws which are not unknown but need more careful formulation of the first principles when applied to living matter. Seven decades later, E. Schrödinger's question is still open "The origins of life stands among the great open scientific questions of our time [91]. We hope the analysis in this chapter takes us one step closer to the reply.

## 2.2 Abstractions& approximations

Science disciplines attempt to discover the infinitely complex nature in a disciplinary approach. To describe a *well defined* range of phenomena, we use approximations and omissions, and we create abstractions which can then be described by known laws using the universal language of mathematics. We use the abstraction "charge" and "charge carrier" for electrons, protons, ions, etc., and we can describe the electricity-related abstract features of the carriers. We must not forget, however, that *those laws have been derived for abstractions based on approximations and omissions*, and so they also *have their range of validity*. To apply laws from different fields of science, we must scrutinize whether all laws we use are applied within their range of validity.

Science, unfortunately, is separated into classical and modern science based on whether the theoretical description assumes infinitely fast interaction (the Newtonian model) or acknowledges the finite interaction speed (the Einsteinian model). However, *the finite interaction speed is erroneously associated with the speed of light and frames of reference moving relative to each other with speeds approaching the speed of light*. Assuming that the interaction speed is finite is sufficient to build up the special theory of relativity [92] (using the speed of light as the value for its external parameter). Still, the Minkowski-mathematics [93] behind the special theory of relativity works with any speed parameter  $c$ . The same mathematics describes technical [22] and biological [23] computing systems, where there are no moving reference frames, but the finite interaction

speed has noticeable effects on the operation of the system.

Another main source of confusion is that the phenomena happen in a limited region of space, and we study processes (in a period instead of a moment) where the environment is not "infinitely far" from the studied object and *the studied process interacts with its environment*. We must consider that the resources are finite.

Science has a well-established method for deriving its laws. It groups resemblant phenomena to major disciplines and they branch along even more resemblance to sub-discipline. The hierarchy is not strict, given that "nature is not interested in our separations, and many of the interesting phenomena bridge the gaps between fields." [4]. Mathematics is a discipline on its own right. It abstracted its notions from nature's concrete objects and phenomena, and its abstract methods serve as a solid base for the fellow sciences and are frequently used to describe new discoveries. It is commonly accepted that physics is the very basic tool to study nature at some elementary level. Chemistry, at another level of abstracting the nature, is based upon its laws, and constructs its laws for the phenomena it researches. The laws of physics are borrowed and respected, and the laws of chemistry cannot conflict with the laws of chemistry. Biology is the discipline studying living matter, and is considered to be an even higher level abstraction, with its own laws. These laws, as expected, cannot conflict with the laws of chemistry and physics. However, it looks like some laws, mainly the ones belonging to thermodynamics, are not perfect for describing biological phenomena. Especially, the life itself seems to contradict the second law of thermodynamics. E. Schrödinger suspected that some non-ordinary laws are to be derived to describe life.

Classical physics is simplifying the things until can attribute a single substance (such as mass or charge) to the tested object and in its laboratories derives accurately the laws and determines the attributes of the substances. As E. Schrödinger has drawn the attention to, "the construction [of living matter] is different from anything we have yet tested in the physical laboratory". Science experienced many times that the approximation do not describe some phenomena accurately. At that times, scrutinizing the fundamental assumptions (such as whether the Galilei's relativity principle remain valid when approachin the speed of light, or the matter remains continuous when decreasing extremely the tested sample) has led to establishing new scientific fields, such as theories of relativity or theory of quantum mechanics.

### 2.2.1 Time, space, and matter

Classical physics is based on the Newtonian idea that space and time are absolute so everything happens simultaneously. Moreover, all interactions (and their observation) have the same speed. Consequently, when their objects interact, it must be instantaneous; in other words, their interaction speed is infinitely large. Furthermore, electromagnetic waves with the same high (logically, infinitely high) speed inform the observer. This self-consistent abstraction enables us to provide a "nice" mathematical description of nature in various phenomena:

the classic science. In the first year of college, we learned that the idea resulted in "nice" reciprocal square dependencies, Kepler's and Coulomb's Laws. We discussed that the macroscopic phenomenon "current" is implemented at the microscopic level by transferring (in different forms) "atomic" charge, and that movement of charges has no effect on the environment. Furthermore, that *without charge (and, without atomic charge carriers), neither potential nor current exists*. In the following year, we learned that the speed of light is finite and that solids show a macroscopic behavior "resistance" against forwarding microscopic charges.

### 2.2.2 Discrete versus continuous

Science experimentally underpinned that the world around us, although for the first look it seems to be continuous, comprises small discrete components. Correspondingly, science has a somewhat schizophrenic view. We know that electric charges are quantized (they are integer multiples of some elementary charge), but Colulomb's Law has no explicit limitations for the magnitude of the charge or for the distance of the charged particles (say the size of the elementary charge) in the law. Similarly, we consider electric current as continuous (differentiable) quantity, although we know it is quantized. In some cases one must connect those two different views. The most prominent case is is thermodynamics, where we explicitly consider particles in the phase space and derive macroscopic features using statistical assumptions. The different omissions and approximations explain, why thermodynamics can be directly applied neither to ionic solutions nor to electrons in the free electron cloud in solids. In the case of biology, the case is even more critical: sometimes the distances are just a few times more than the characteristic size of ions and the number of particles if much less than the number enabling to draw statistically reliable conclusions. However, special geometrical relations and physical assumptions enable us to bridge the particle view and the continuous view.

### 2.2.3 Speeds

The role of speed and time, particularly in the context of an object's changing location over time, has long held a mystique in the realm of scientific discovery (and recently returned to be mystic again in cosmology). This intrigue can be traced back to historical debates, such as Zeno's paradoxes. The acknowledgement that an object's movement speed can influence our observations is a topic that has sparked significant scientific discourse over the years. In this section, we aim to draw parallels between the historical debate on the finite speed of light and its contemporary implications in various scientific disciplines, such as the finite speed of ionic currents in biology.

It has been a long-standing mystery that interactions with different speeds play their role *simultaneously*. The issue forces researchers to give non-scientific explanations to everyday phenomena only because *they routinely assume that*

*the interactions have the same speed, and they use the laws about strictly pairwise interactions.* They have no choice: there is no formalism to handle non-equal speeds.

We need different abstractions (finite-speed interaction in modern physics) for different phenomena that require different mathematical handling, which is not as simple and friendly. The *speeds of observation* and propagation of electric fields remain the same in biology, and it is easy to extrapolate, mistakenly, that *all* interactions have infinitely large interaction speeds. However, also *slow* interaction speeds exist, furthermore, *different interaction speeds can intermix in the same phenomenon*. Neglecting that effect introduces the need to assume *fake mechanisms and effects* for explaining some details; which are naturally explained by assuming finite interaction speeds and their combinations.

In this section, we discuss mainly currents. *To deliver a current, one needs moving charged particles that need acting of some external (electric, magnetic, or chemical) force or a mixture of forces. We have speeds of EM interaction, thermal motion of the charge carriers, macroscopic current, drift speed, and their mixing, simultaneously, in the same phenomenon.* In the theoretical description of processes, instant interaction (i.e., the abstraction of non-physical, infinitely large interaction speed) is used in most cases. In the cases when absolutely needed, the generic notion of "speed" is used without specifying which one of the mentioned speeds it means.

### Speed of light

In 1676, the Danish astronomer Ole Rømer was making meticulous observations of Jupiter's moon Io and concluded not only that the speed of light is finite, but he measured its value with sufficient accuracy. Rømer never published a formal description of his method, possibly because of the opposition of his bosses, Cassini and Picard, to his ideas. Cassini knew Rømer's idea and the measurement data. However, instead of accepting the finite value of the speed of observation, he made periodic corrections to the tables of eclipses of Io to take account of its irregular orbital motion: *periodically resetting the clock*. The speed of light must remain infinitely large.

However, the theory of finite speed quickly gained support among other natural philosophers of the period, such as Christiaan Huygens and Isaac Newton [94]. Although Newton surely knew that the observation speed was finite, in his "Philosophiae Naturalis Principia Mathematica" [95], published in 1687, he decided to refer to observations that they happen "at the same time" despite knowing that what we observe at the same times, happen at different times. Using instant interaction results in "nice" mathematical laws and enables us to describe most of nature's experiences with sufficient accuracy. Einstein, in 1905, discovered [96] that the speed of observation (in moving reference frames) may play a decisive role in interpreting scientific phenomena. The results he derived using Minkowski-coordinates [93] were counter-intuitive, with many unexpected consequences. Instead of introducing improvement(s) or correction(s) to the existing classic principles and methods, he introduced a new principle:

the finite (limiting) interaction speed. The *disciplinary analysis of the reception of Minkowski's Cologne lecture reveals an overwhelmingly positive response on the part of mathematicians, and a decidedly mixed reaction on the part of physicists* [97] has turned to the exact opposite. Today, physics generally accepts the description, that is, the existence of finite interaction speed (resulting in the birth of a series of modern science disciplines). However, other science disciplines, including biology and computing science, refute (or at least do not use) it; despite that its effects are evident.

### Speed in neuroscience

Helmholtz, in 1850, sent a short report off to the Academy [98] "I have found that a measurable time passes when the stimulus exerted by a momentary electric current on the hip plexus (Hüftgeflecht) of a frog propagates itself to the nerves of the thigh and enters the calf muscle." His teacher "had thought that the speed of nervous conduction might be in excess of the speed of light and could probably never be measured. Helmholtz's father, on hearing of the experiment and the surprisingly slow measured speed, wrote to his son that he would as soon believe this result as that one can see the light of a star that burned out a million years ago" [99].

With the development of measurement technology, it became evident that finite speed is a general feature of the "nervous connection". (Somehow, "the speed of nervous conduction" has been renamed to "conduction velocity", neglecting the clear distinction that physics makes between the two wording.) With the dawn of instrumental electronics and computing, the McCulloch-Pitts model [100] introduced the picture that the brain can be modeled by a network of simple perceptron nodes connected by wires; that is, it comprises a two-state equipotential membrane connected with perfect wires. The experimental research also quickly (re-)discovered that those wires forward signals in a particular way; the speed of the potential wave is finite. Furthermore, *the axons are not equipotential during transmission*. Although its structure is practically identical with axons, *biology assumes that, unlike an axon, the membrane remains equipotential during its operation, although the evidence shows the opposite: 'the action potential spreads as a traveling wave from the initial site of depolarization to involve the entire plasma membrane'* [87].

When seeing that assuming an equipotential membrane was wrong and a single equipotential surface (in other words, classic physics' instant interaction) cannot describe neurons adequately, multi-compartment models (typically comprising equipotential cylinders with different potentials) have been introduced [42]. (Notice that it is a consequence of the wrong oscillator model hypothesized by Hodgkin and Huxley: the membrane is modeled as a series of resistors and capacitors.) Then (forgetting that Ohm's Law is valid only for classic physics's 'instant interaction', furthermore, that no external potential is connected to either of the compartments, and no charge is present at the beginning, except at the input of the first compartment), the individually equipotential compartment pieces were connected by individual resistors. This model shows that the

more compartments, the better the agreement (accuracy) with experiments. It happens because the shorter is the size of the compartment (approaches a differential equation), the less noticeable is the deviation from the true non-equipotential surface. This conclusion means that charging the capacitance attached to the compartment takes time, resulting in a delayed distributed current. Using infinitely many compartments, we would arrive at the differential equations describing a delayed distributed current on the surface of the non-equidistant membrane. However, biology did entirely not give up its position. It admitted that membrane current exists, but only between compartments, and its speed must be infinite (or, at least, the speed of EM interaction). However, at least the compartment pieces must be equipotential. Instead of fixing the wrong hypothesis, biology is "periodically resetting the clock". Instead of accepting that the charged ions represent a "slow current" (compared to the "fast current" represented by electrons and their charge transmission method), biology introduced changing conductance, delayed current, rectifying current,

### Finite-speed interactions

When speaking about speed, especially about the speed of charged objects inside biological objects, one needs to consider microscopic and macroscopic levels of understanding. On the boundaries of the two levels, we need to make distinctions between different kinds of speeds, among others (in units of  $m/s$ ), the propagation speed  $10^8$  of the electric field (aka potential gradient), the speed  $10^5$  of thermal motion and potential-accelerated motion, the apparent speed of current (potential-assisted speed of a macroscopic stream, both in metals and electrolytes; mainly due to the repulsion of nearby ions in the stream)  $10^1$ , for ion current inside a neuron (see Fig. 1 in [47])  $10^{-2}$ ; diffusion speed of electrons in a wire  $10^{-4}$ , drift speed of the individual carriers in aqueous solutions  $10^{-7}$ ; and of ions moving in a narrow tube filled with viscous liquid  $10^{-8}$ . Fortunately, in most *but not all* cases, different mechanisms (such as the Grotthuss mechanism or free electron model; for a review, see [101]) at the level of microscopic structure help to create the illusion of a high macroscopic propagation speed (million times higher than the speed of its microscopic carriers). *The same carrier can have macroscopic speeds differing by orders of magnitude, depending on the context;* see a biological example at ion channels. When more than one of those speeds plays a role in the phenomenon we study, we must carefully consider its context and prepare for handling *fast* and *slow* effects, furthermore, their mixing.

When an object can interact with another in a way abstracted by science as more than one interaction type, we need to find the relation (the 'extraordinary' law) between them. Such a famous case is electricity and magnetism. Their interrelation is defined by the Maxwell equations: how an electrical field creates a magnetic one and vice versa (notice that the law is about their *space derivatives*, aka *space gradients* instead of the entities themselves). While we understand that the speeds of electromagnetic and gravitational interactions are finite, we can use the 'instant interaction' approximation in classical physics

because one effect of the first particle reaches the second particle simultaneously with the other effect, leading to the absence of a time-dependent term in the mathematical formulation.

An apparently similar case is found in electrodiffusion, where ions can be abstracted as mass and charge, one belonging to thermodynamics and the other to electricity. There is, however, an essential difference between those cases: the interaction speeds are the same in the first case (moreover, in the spirit of classical physics, the interactions are instant) and differ by several orders of magnitude in the second one. Of course, the Maxwell equations can be nicely solved and modeled also for biology if one introduces [102] that the axial currents have the same speed (BTW: which was measured as 20 m/s) as the electric and magnetic waves, furthermore the longitudinal current is (?)defined(?) to have no attenuation. Furthermore, it is likely also defined that current needs no driving force and this is why the positive and negative ions flow in the same direction. It is really a novel paradigm leading to ”(mis)understanding cell interactions”, but definitely describes some alternative nature.

### Speed in laws of science

Actually, the famous Coulomb's Law is expressed as

$$\frac{F(t)}{Q_1} = k \frac{Q_2}{\vec{r}^2} \quad (2.1)$$

$\vec{r}$  is a space-time distance. That is, in the Newtonian approximation, time is identical at all places, so we used to omit it. However, physics knows also the notion of *retarded time*. Considering the finite field propagation speed requires revisiting the fundamental physical laws. (in a Lorentz-transformed form) should be written as

$$\frac{F(t)}{Q_1} = k \frac{Q_2}{r^2} \left( t - \frac{r}{c} \right) \quad (2.2)$$

The electrostatic field that charge  $Q_1$  experiences due to the finite propagation speed  $c$  of the electric field (or interaction) corresponds to that  $Q_2$  at a distance  $r$  generated  $\frac{r}{c}$  time ago ( $k$  is the constant describing the electric interaction). This term has no role if the two charges do not change their position; similarly to that in the special theory of relativity, only the relative movement leads to complications. If the distance changes, its effect is so tiny that the term can usually be omitted. So, our college knowledge can serve as a good first approximation.

This speed term pops another law from classical physics into our minds: Kirchhoff's junction rule. The law is perfect in the approximation 'instant interaction' that classical physics uses, but not for biology. First, because it expresses charge conservation, *it is invalid when charges are "created" inside biological objects* (ions diffuse into the junction; see the role of ion channels in the wall of membranes). Second, it is not valid for input currents arriving with finite speeds into finite-size space regions, but it is valid for a single point

in space-time (in other words, in differential equation form). As we discuss in section 2.4.4, using a wrong definition of current means assuming 'instant interaction', that is, that neural signals propagate with the speed of light. The currents (and the voltages), measured at two different points in space-time, are different. Consequently, for extended objects (such as a line-like finite-size neuron), it is valid only with a time delay

$$I_{out}(t) = -I_{in}(t - \Delta t) \quad (2.3)$$

The time delay in biology is in the 1 msec range. *We must not describe the axon or the membrane by the differential form the non-differential form Kirchoff equation: the input and the output currents flow at different times (the charge carriers need time to reach from input to output). We must not describe the axon or the membrane with the non-differential form of the Kirchoff equation: the input and the output currents flow at different times (the charge carriers need time to reach from input to output); only the differential equation form expresses charge conservation* (furthermore, in the case of "producing" ions, even by the differential form is invalid). For its exact interpretation see sections on axonal charge delivery and on the true membrane current, Fig. 3.23, and the text around it. *Studying electric phenomena on structured media, such as biological cells, needs much care.* We must not apply laws derived from entirely different conditions (mainly metals).

#### 2.2.4 Instant interaction

Physics notoriously suffers from the lack of handling different simultaneous interactions; facing such a case leads to misunderstandings, debates and causality problems. Such a famous case is the interaction speed of entanglement. In that time, E. Schrödinger introduced his famous Law Of Motion in quantum-mechanics entirely analogously as I. Newton introduced his Laws of Motion. Similarly to the Newtonian 'absolute time', the quantum mechanical interaction is supposed to be 'instant' (this is the price for having 'nice' equations in classical and quantum mechanics), i.e., its speed is supposed to be infinitely high. However, at that time was already known that the electric interaction (propagation of electromagnetic waves) is finite, so if an object has quantum mechanical interaction (aka entanglement) and electrical interaction, the corresponding forces start at the same time, but arrive at the other object at different times. The entanglement arrives instantly, the electromagnetic effect arrives at the time we can calculate from the interaction speed and the spatial distance of the objects. This leads to causality problems: the effect of the two interactions of photons entangled earlier in an exploded supernova should be measured at two different times; meaning a "spooky remote interaction" as A. Einstein coined, and leads to contradictions such as the Einstein–Podolsky–Rosen paradox. Actually, the issue roots in the improper handling of mixing interaction speeds: the Schrödinger-equation introduces the infinitely large interaction speed, while the EM interaction has finite speed.

*The confusion and question marks in connection with describing the life by science mostly arise from the interpretation of notion 'speed' in physics.* When discussing the underlying physical laws, we go back to the very basic physical notions instead of taking over the approximations and abstractions used in the *classical physics for non-biological matter* and less complex interactions. As we emphasized many times, we construct laws and conclusions based on somewhat simplified abstractions about nature, in all fields of science. The notions and laws depend on the circle of phenomena we know and want to describe. The Newtonian and Einsteinian worlds are basically distinguished by considering *speed dependence* that actually means *explicite time dependence*. Interesting consequences are that in the Einsteinian world, the mass is not constant, the time and space are not absolute, and so on. We can be prepared to some similar counter-intuitive experiences in physiology "we must be prepared to find it working in a manner that cannot be reduced to the **ordinary** laws of physics" [8]. Here we scrutinize the basic notions and discover some differences between physics and biology as consequences of the required different abstractions and approximations.

During our college studies, we mentioned that light is an electromagnetic wave with a vast but finite propagation speed. Still, we forgot to highlight that, at the same time, it is the propagation speed of the electric (, and magnetic, and gravitational) interaction force fields as well. The effect of "Retarded-Time Potential" is also known in physics and communication engineering. Algorithms "marching-on-in time" and "Analytical Retarded-Time Potential Expressions" are derived to handle the problem; for a discussion, see [103]. Telegrapher's equations (unfortunately, also used to describe biological signal transfer) explicitly assume a finite propagation speed millions of times slower than the (implicitly assumed) EM interaction's. The issue is not confined to large distances: designers of micro-electronic devices also must consider the effect: they introduced clock time domains and clock distribution trees; see, for example [104, 22].

Science uses 'instant' in the sense that one interaction is much faster than the process under study; we consider the faster interaction as instant. The approach of classical science is based on the oversimplified approximation that the interaction speed is *always* much higher than the speed of changes it causes and that the processes can *always* be described by a single stage. In our approach, for biology, we put together a *series of stages* to describe the observed complex phenomena, where the stages provide input and output for each other, involve more than one interaction speed, and use per-stage-valid approximations. We simplify the approximations by omitting the less significant interactions and introduce ideas for accounting for the different interaction speeds. This way, we reduce the problem to a case that science can describe mathematically. *This procedure is fundamentally different from applying some mathematical equations derived for an abstracted case of science to a complex biological phenomenon without validating that we use the appropriate formalism.*

### 2.2.5 Physics and biology

A common fallacy in biology is that physics cannot underpin the operation of living matter, citing E. Schrödinger. However, the claim falsifies his opinion by omitting the most essential word 'ordinary'. Schrödinger wanted to emphasize the opposite: there is no new force (no unknown new interaction), only studying living matter needs different testing methods in the physical laboratory. He suggested to answer the question "Is life based on the laws of physics?" affirmatively, but expected to discover the appropriate forms of physical laws describing the 'non-ordinary' (in our reading: non-disciplinary) behavior of living matter. No doubt, the basic notions and terms must be interpreted precisely for living matter, much beyond the level we used to at college level. However, after that reinterpretation, we can interpret features of living matter, although we need a more careful, many-disciplinary analysis to do so. We must use the appropriate abstractions and approximations for the phenomena, depending on the level needed in the given cooperation of objects and interactions. In this section we discuss some of the relevant terms and notions of physics, differentiating which approximation is appropriate only for physics (mainly electronics) and, instead, which approximation should be used for biology. As we discuss, *biophysics simply translated the corresponding major terminus technicus words from the theory and practice of physics' major disciplines, mainly from electricity, which were worked out for homogeneous, isotropic, structureless metals, and for strictly pair-wise interactions with a single (actually, 'instant') interaction speed; to the structured, non-homogeneous, non-isotropic, material mixtures and for multiple interaction speeds.* Those notions do not always have unchanged meaning, and how much they do, depends on the actual conditions. The precise meaning needs a case-by-case analysis.

The physical models consider infinitely large volumes, surfaces, distances; furthermore, and most importantly: instant interactions. Is the cell large enough to consider it infinitely large (at least on the scale using ion's size); that is to apply laws of science derived for abstraction 'infinitely large'? When working with charge, we know that charge is quantized, while the macroscopic quantities voltage and current are continuous (derivable). Do cells contain a sufficient number of charge carriers to apply macroscopic notions? Do the thousands of times smaller ion channels transfer enough charge to speak about well-defined current? When a couple of ions are transferred through an ion channel, do they change significantly the potential that accelerates them?

Science could serve as a firm base for all its disciplines. As we discuss, *its disciplines use abstractions based on limited-validity approximations* based on the same first principles. However, *the approximations are different for biology and physics.* In physics, some processes we observe are fast enough so that we can use the abstraction that they are essentially jumps between states. In some cases, the approach can be –more or less– successful. For the slower, well-observable processes, we have the laws of motion that describe how the processes happen under the effect of some driving force. We also experienced that nature is not necessarily linear (in the sense that it depends only on space coordinates

but not on their derivatives), which we can describe by "nice" mathematical formulas. A century ago, A. Einstein invented that the approximations I. Newton introduced two centuries earlier are not sufficiently accurate for describing the movement of bodies at high speeds. In other words, a new paradigm, the constancy of the speed of light, must have been introduced that caused a revolution in physics and led to the birth of "modern physics".

*Life, including the brain's operation, is dynamic.* As Schrödinger formulated, the "construction of living matter" differs from the one science used to test in its labs. The scientific abstraction based on "states" (i.e., on instant changes) fails for the case of biology, where "processes" happen (i.e., the changes are obviously much slower). The commonly used measuring methods such as clamping, patching, and freezing, reduce the life to states (and correspondingly, the related theories describe states with perturbation [105]). On the one side, this technology fixes the cell at some well-defined static state and enables us to observe a static anatomic picture of the cell. On the other, it eliminates the dynamic processes, i.e., *hides for forever the essence of the life that the cell exists in a continuous change governed by laws of motion.* Those methods stop the processes for studying them, in this way killing their dynamicity to be measured. It was forgotten that using feedback for stabilizing an autonomously working electrical system means introducing foreign currents and this way falsifying its operation.

Furthermore, it is hazardous to introduce technically (and incorrectly) derived and misinterpreted macroscopic features and interpret them as fundamental electric notions. In general, instead of understanding and developing the correct scientific base of the operation, saying that science cannot describe it. The idea of conductance has been introduced to neurophysiology almost a century ago. It was taken from physics, where the notion was derived for metals (conductors, instead of electrolytes). Since then, its original interpretation has been forgotten, and today (in contrast with physics), it has become a primary entity for describing electric characteristics of biological cells. We explain how the right physics background enables us to discover wrong physical models and misinterpreted notions of physics in neurophysiology; furthermore, how the right interpretation opens the way to the correct interpretation of neuronal information. We set up an abstract electric model of neuronal operation.

We derive the needed 'non-ordinary laws', which are derived by using the same first principles as the 'ordinary laws', but are abstracted for the approximations valid for living matter. As we discuss, those 'ordinary' laws were derived for strictly pair-wise interactions at very high speeds. In biology, we can observe interactions at million times smaller speed, in inhomogeneous, non-isotropic, structured material. *Biology has not the conditions for which we derived the ordinary laws of physics.* We show that the ordinary laws are also the result of approximations (including omissions) and by using the appropriate approximations for the biological cases we can derive those 'non-ordinary' laws of physics. Which laws are more complex to derive and we must use several stages (with the approximations changing from stage by stage) instead of one single stage in the case of the 'ordinary' laws. However, *all laws follow the same principles.*

Biology, and especially neuronal operation, produces examples where wrong omissions in complex processes results in absolutely wrong results. In those cases some initial resemblance between our theoretical predictions and our phenomena exist, but the success in simple cases provides no guarantee that the model was appropriate: "the success of the equations is no evidence in favour of the mechanism" [5]. Finally, all laws are approximations and the accuracy of verifying their predictions is limited. Several theories can describe the same phenomenon with the required accuracy. We also show in the section about the finite interaction speeds that the mostly known laws (from Newton, Coulomb, Kirchoff, etc.) are also approximations. They have their range of validity, although it is often forgotten.

One such neuralgic point of omissions and approximations is the vastly different interaction speeds; furthermore, that where the speed is considered at all, *the same speed is assumed for all interactions*. The laws are abstract also in the sense that, say, the objects in the laws of physics have either mass or electric charge, but not both. It is the researcher's task to decide which combination of laws can be applied to the given condition. For example, one can assume in most cases that the speeds sum up linearly, except at very high speeds. Biology provides excellent case studies where different interactions shape the phenomenon and special care must be exercised. We give a short review of history and kinds of interaction speeds.

Another point is that science started with the assumption that the non-living matter is continuous, although it was early discovered that there are smallest pieces of that matter. When reached that size, we experienced that different subsets of science laws describe that matter and the atoms they contain; in is one of the hardest tasks to establish relations between those subsets. Again, we used abstractions that that the continuous matter is infinitely large and that the isolated atoms are infinitely far from each other and from the external world. We also experienced the semi-infinite cases, and studied the behavior of surfaces and interfaces; which, again is different from both that of the atoms and their large masses. Given that biological objects are between those microscopic and macroscopic sizes, and they are surrounded by surface, we must be prepared that no simple rules describe their behavior.

Neuronal operation is at the boundary where sometimes, in the same phenomenon, one interaction can be interpreted at macroscopic level, some another must already be interpreted at microscopic level. Furthermore, a series of stages (instead of a single state) and processes (instead of stages) describe the subject under study. Given the vital role of charge and current in neuronal operation, we give their precise interpretation. Furthermore, we must consider that the processes happen in a finite volume, "within the spatial boundary". Special emphasis is given to the true interpretation of conductance, one of the central terms in biology.

### 2.2.6 Spatiotemporal

In biology, it was evident that the transfer (conduction) time must be considered together with the computing (synaptic) time (in this sense, presynaptic to postsynaptic transmission time). The name "spatiotemporal" and a (separated) time dependence is commonly used [105], in the sense that Precise Firing Sequence (PFS) "tended to be correlated with the animal's behavior"; furthermore, that "*the results suggest that relevant information is carried by the fine temporal structure of cortical activity*" [106]. The "neural dynamics" was studied and "*spatiotemporal spreading of population activity was mapped*" [107] by methods used to describe the *static computing methods*: interspike intervals histograms, auto-correlation and cross-correlation. Because of the peculiarities of this information handling, *there are severe doubts whether the notions of the classic neural information theory are valid for biological computing systems* [13]. The correct method of describing biological computation is still missing, given that the significant item of the computing is missed: *the time and position are connected through the information transfer speed* (called conduction velocity).

Will be based on [23, 108, 109]

In Fig. 2.1, for visibility, two spatial and one temporal coordinate are shown. In the following figures, some illustration enable to omit one more spatial dimension, i.e., effectively to draw the events as a two-dimensional diagram.

### 2.2.7 Finite resources

"How can *the events in space and time* which take place ***within the spatial boundary*** of a living organism be accounted for by physics and chemistry?" [8]

Co-existing processes may affect each other by changing resources: changing one quantity changes the other. Mathematics describes such processes by linked differential equations, such as the Lotka-Volterra equations. A known mathematical example is the "predator-prey" equations.

#### Ion channels

We want to describe the change of voltage due to limited resources using an idea similar to the predator-prey model. We have charged sheets (represented by ions in the electrolyte) with potential  $U_H$  and  $U_L$  on the two surfaces of the membrane, plus we consider the corresponding neighboring layers on their side toward the "bulk" of the segment. We assume that the layers' capacity is constant and is of the same value, so the change of charge is linearly proportional to the change of the voltage.

We consider that a charge transfer happens from the layer with potential  $U_H$  to the layer with potential  $U_L$  (that is, the *same charge* is removed and added, respectively) with a high speed (we call it *potential-accelerated* speed), furthermore, that with a much lower speed (we call it *potential-assisted* speed)

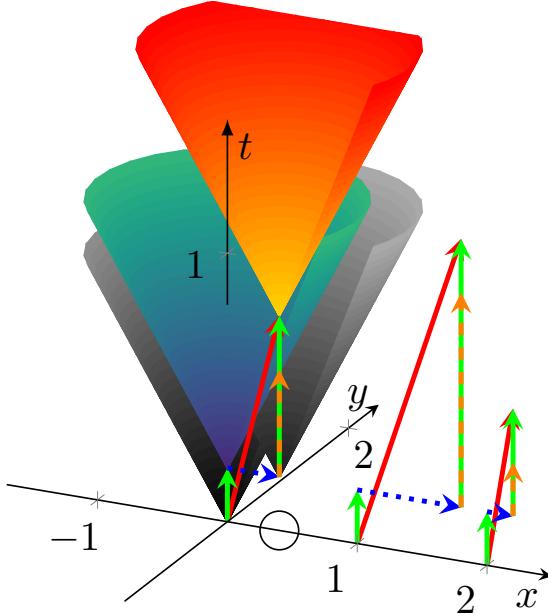


Figure 2.1: The temporal diagram, i.e., the way of calculation to combine the spatial distance (transmission time, blue arrows) and computing time (green arrows) illustrated in the time-space coordinate system. The orange-green vertical arrow shows that the second computing unit must idly wait until the transmitted result reaches its position, because of the finite transmission time. The axes  $x$  and  $y$  refer to space coordinates (transformed to time using the conduction velocity), the axis  $t$  refers to the time itself. The arrows starting from points 0, 1 and 2 on the  $x$  axis illustrate timing for three different propagation speeds. The red vector points from the beginning to the end of the process. Its length may serve as a statistical entity to describe temporal distance of the units.

the charge in the neighboring layer increases and decreases, respectively, those voltages are ( $U_{H-1}$  and  $U_{L+1}$ ).

That is, we assume four voltages and the initial conditions

$$U_{H-1} = U_H = U; \quad U_{L-1} = U_{L+1} = 0;$$

We assume a constant capacity for the layers and that the amount of transferred charge (or voltage) is proportional to the difference of voltages in the respective layers.

$$\frac{dU_H}{dt} = -\alpha * (U_H - U_L) + \beta * (U_{H-1} - U_H)$$

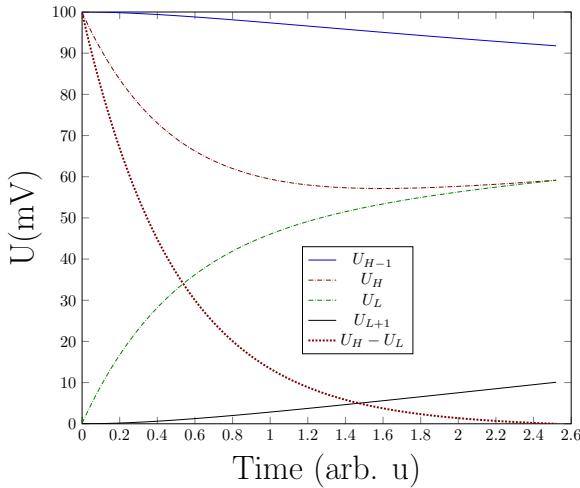


Figure 2.2: The potential values connected to the operation of ion channels. The arbitrary values of the transfer speeds (for visibility instead of approach real values) are  $\alpha = 1$ ;  $\beta = .1$ ;  $\gamma = 0.0001$ ; furthermore the time scale is also arbitrary.

$$\frac{dU_L}{dt} = +\alpha * (U_H - U_L) - \beta * (U_L - U_{L+1})$$

Furthermore, we assume that the after-diffusion from and to the layers next to the proximal layers is negligible aside from the high speed of the charge exchange between the proximal layers, that is

$$\frac{dU_{H-1}}{dt} = -\gamma * (U_{H-1} - U_H)$$

$$\frac{dU_{L+1}}{dt} = +\gamma * (U_L - U_{L+1})$$

As Fig.2.2 depicts, voltages  $U_H$  and  $U_L$  quickly approach their balanced values. When they get equal, the driving force cancels. In the meantime, the voltages  $U_{H-1}$  and  $U_{L+1}$  tend to approach  $U_H$  and  $U_L$ , respectively. The diffusional and energy producing processes, depending on the local conditions, change the voltages on the two ends of the channel, creating the illusion that the channel opens and closes. As [33] analyzed, this on/off behavior of currents can be observed for natural and synthetic lipid membranes; with and without caps. In spite of slightly different experimental conditions, amplitude and typical time scale are similar.

## 2.3 Ions' thermodynamics

Although science knows from the beginning of scientific thinking that the material world around us comprises discrete objects (particles) that cannot be divided without limitations at a given abstraction level, most of the scientific laws were devised for a continuous material, such as the laws about pressure and current. Our laws about mass and charge (and so: on energy, impulse and so on), are about discrete concepts. Furthermore, science has created abstract concepts such as space and time, mass and charge, continuous and discrete views. Classical science considered only one such concept at a time. Thermodynamics was the first discipline which connected two of those separated attributes, the discrete and continuous views.

### 2.3.1 Specialties of cellular thermodynamics

As we discussed, we can handle atomicity in different abstractions, as charge-less or mass-less points (but anyhow: 'material point' as A.Einstein coined [96]). We derived laws for a single interaction, see Newton's Law of Universal Gravitation and Coulomb's law. However, ions require different thinking [19]: *thermodynamics is about non-interacting particles*. In the frame of classic science, the interactions are instant, and so the interaction speeds are the same. Evidence shows that this is not the case for electrodiffusion; they differ by about six orders of magnitude. The assumption of classic science that everything happens at the same time evidently cannot be applied; correspondingly, the diffusion coefficient of electrodiffusion has yet to be discovered.

#### Dual substances

The ions as 'material points' (having charge and mass) can be abstracted that they have a behavior that there are *two* underlying interactions and experience two different force fields that cannot be separated further; correspondingly they have less simple laws of forces and motion. Classic science describes one type of forces using laws of electricity (the points have charge but no mass), another type using laws of mechanics (the points have mass but no charge). We must recall that thermodynamics is about non-interacting particles (except their direct collisions as hard-ball points). When speaking about ions, the volume elements in the phase space are not independent: the energy and momentum of a particle depend on the other particles.

#### Microscopic vs macroscopic

The macroscopic features (such as pressure, temperature, potential, and concentration) of systems of 'material points' are interpreted as having statistical behavior and their laws are discussed by the scientific discipline thermodynamics. Its notions drastically differ from the ones of classical fields. Here the concepts such as 'temperature' or 'pressure' are a generalization: a homogeneous distribution means that classical physical substances (such as momentum

and energy) have a well-established distribution instead of single uniform values of parameters. At the same time (in infinitely large volumes) the macroscopic parameters 'concentration' and 'potential' (notice that they are based on the single-interaction abstractions 'mass' and 'charge', respectively) are simple densities, although to interpret them, a large number of particles must be considered. For the more careful experimenter, it is evident that this homogeneity is a dynamical one: particles' movement changes it continuously and it is constant only as a statistical average.

### Limited volumes

The processes happen at the boundaries of the microscopic and macroscopic worlds, and we must consider different interactions at different speeds. To describe the phenomena, which are neither purely microscopic nor macroscopic, more than one abstraction must be used. Still, they show the behavior of both worlds. Furthermore, they change their behavior during the course of the studied process. The inappropriate handling of mixing interaction speeds lead to 'non-ordinary' behavior and one can conclude 'non-ordinary' laws when uses the appropriate approximation(s). We need a more careful handling (and more approximations) when we consider the interactions in a finite volume, with strongly different conditions on its boundaries. We need to conduct case studies and apply casual approximations to describe the phenomena, which are neither purely microscopic nor macroscopic and where more than one abstraction must be used. It is important to remember that we are dealing with a mixture of macroscopic and microscopic descriptions, and this understanding is a crucial aspect of our research.

### Reciprocal relations

The distributions, however, can be calculated for charge-less and size-less 'material points' only. The interference of those forces and that they affect two different features of the atomic particles lead to unusual disciplinary consequences. For his discovery of the reciprocal relations in thermodynamics, Lars Onsager was awarded the 1968 Nobel Prize in Chemistry. The presentation speech referred to his result that "Onsager's reciprocal relations represent a further law making a thermodynamic study of irreversible processes possible". In that sense, *we provide mathematical equations of the fourth law of thermodynamics* in section 2.3.5. The experimental verification [110] of that law mentions "the well-known difficulty of carrying out these experiments". By using our mathematical relations between the electrical and chemical diffusion, we can overcome that experimental difficulty. The significance of our Eq.(2.22) is, that one can derive the speed of electrodiffusion in electrolytes, which are otherwise not measurable ("hopping in a breeze" [21]: we would have to measure potential changes at distances of the size of the electrodes, with picosec resolution while the electrolytic electrodes cause nearly msec delays).

### Mixing speeds

What truly sets ions' thermodynamics apart in physics is the absence of a direct equivalent of the Maxwell-equations. By introducing time derivatives by Eqs. (2.11) and (2.14), we can provide their equivalent equations that describe the relation between concentration and potential for the case when the first time derivative of the position coordinate is not zero. The practical difficulty is that the diffusion speed is by several orders of magnitude smaller than that of the EM interaction. Furthermore, the applied electric field speeds up the ions to potential-assisted or -accelerated speeds, and classical physics is not prepared to handle mixing interaction speeds.

In classical physics, the EM interaction is instant, so the time derivatives of the electric and magnetic fields can change simultaneously. In the approximation we use, we consider the EM speed infinitely high – in the spirit of 'classical physics' – and we consider the finite speed of ions using physical approximations, which are simplified representations of the actual physical processes. In our mathematical model, *the electric field gradient acts instantly on the charge, but the effect of the concentration gradient reaches its position with some delay*. In this unique field, the chemical concentration and the electrical field generate each other at different pace, presenting a fascinating departure from traditional ('ordinary') physics. Another speed-related difference is that we must introduce – among others– local and global conservation laws, similar to the case of general theory of relativity.

### Electric charges

In our research, the key point is that life (including neural processes) is based (mainly) on thermo-electric processes. The contradictions and duality (mainly) arise from the enormously different interaction speeds of the electric and diffusion processes. In our approach, we divide ion movements into stages, based on the speed of the dominating electric interaction. We introduce diffusion (or *potential-less*), *potential-assisted* (based on the mutual repulsion only), and *potential-accelerated* (internal voltage on biological components accelerates the ions) speeds. In some cases, the diffusion and electric processes follow each other in separate phases, so in some phase, they can be better approximated as "net" electrical system, combining "fast" and "slow" currents. We show that the processes can be staged in such a way that in addition to the dominant interaction, only one more significant interaction remains on the stage, and we can work out a physics-based approximation that a mathematical formalism can describe.

### Constraints

Newton's laws of motion apply also to ions in the cell, given that they are independent of how the exerting forces are generated. As we discuss in section 2.3.4, the "special construction" of living matter leads to cases when "conditional counterforces" may apply. Furthermore, there are constraints arising

from the structure of the living matter, and they move the 'material point' in a viscous media instead of vacuum; furthermore, the balanced states, as well as the processes from and to those states, are described by the interplay of those forces.

### 2.3.2 Non-ordinary laws

Science laws about separate interactions of masses and charges are based on abstractions, which enable and need approximations and omissions. While we understand that the speeds of electrical and gravitational interactions are finite, we can use the 'instant interaction' approximation in classical physics. This is because one effect of the first particle reaches the second particle at the same time as the other effect, leading to the absence of a time-dependent term in the mathematical formulation (although in special cases the 'retarded interaction' shall be discussed). However, this is not the case in electrodiffusion, where the mass transfer is significantly slower than the transfer speed of the electromagnetic field. To describe the interrelation of these two effects, we need to conduct case studies and apply casual approximations. *Science uses the notion 'instant' in the sense that one interaction is much faster than the process under study;* we consider the faster interaction as instant.

From a physical point of view, ionic solutions are confined to a well-defined volume, with no interaction with the rest of the world. What makes the things more complicated, their volume has evidently finite size with bounding surface(s), so we must adapt the corresponding laws to the case of finite resources. At a microscopic level, on the one hand, we use the abstraction they consist of chargeless and sizeless simple balls with mass, have thermal (kinetic) energy, and collide with each other, as thermodynamics excellently describes it. On the other hand, we use another abstraction, which is massless and sizeless charged points with mutual repulsion. Combining those different concepts is not possible without conflicts and contradictions. At a microscopic level, in both abstractions, they attempt to distribute as equally as possible in a given volume. However, we can notice the difference that the equilibrium (*nomen est omen*) is dynamic for the thermodynamic and static for the electrostatic interaction. At a macroscopic level, we use the abstraction that the respective volume is filled with a continuous medium with uniformly distributed macroscopic parameters such as temperature, pressure, concentration, and potential.

One can parallelize describing how ions change their position with how Newton's laws of motion relate an object's motion to the forces exerting on it. The first and third laws are *static* ones, the second one is *dynamic*. We can translate the first law to ions that without external invasion, their volume at rest will remain at rest. The third law, for ions' volume, essentially states that in a resting state at every points the electrostatic and thermodynamic forces are equal; this is expressed by the Nernst-Planck electrodiffusion equation (for the case of no transport). The second law, for mechanics, expresses the time course of the object: *the position's time derivative*. Notice that in this case we make *one abstraction* that the object (the carrier) has *one attribute*, its mass. (Recall,

how important was for the special theory of relativity that the *accelerated mass* and the *gravitational mass* were identical.)

For ions, we have *two abstractions*, and two attributes '*charge*' and '*mass*', and the two forces act on the two attributes which science classified to belong to different science disciplines. We cannot express easily how the electric and thermodynamic forces will change the object's position because those forces act differently on different attributes. No time derivatives are known, only position derivatives. Due to this hiatus, physics (and consequently: physiology) cannot describe the electrochemical processes: *the second law of motion for electrodifusion is missing*. As a consequence of the instant interaction, *classical science has no mechanism for handling the case when two different force fields (gradients) having different propagation speeds act on an object and two different abstractions (charge and mass, belonging to different science disciplines)* translate the force into acceleration. Here we use Boltzmann's idea: we derive the particles' speed from the continuum mass's speed. Furthermore, our idea is to derive a pseudo-electrical field (see section 2.5.3) and potential to combine those two interactions and their respective disciplines.

When describing processes (i.e., dynamical systems), we must have one or more equations of motion (aka changing speeds): how the time gradient of the fundamental entities are changing in the function of the fundamental entities. In classical science, we have only one fundamental entity: the position and also the driving forces depend only on the position. The Newtonian laws of motion do not depend on a temporal gradient. *In 'ordinary' science, we have a single-speed, single-substance interaction abstraction*; so we have one law of motion; an analytical solution is possible. In the Einsteinian world, speed explicitly appears when describing the interrelation of fundamental concepts mass, position, and time. Actually, a tightly related second entity (position and time) appears; and the speed connects them. In all cases, the law has the form of a differential equation; i.e., we can derive the fundamental entities by integration. In the case of the dual-speed interaction of ions, only numerical solution is possible.

*In our 'non-ordinary' science, we have a double-speed, double-substance interaction abstraction*; correspondingly, we have *two* laws of motion. Furthermore, for ions we use a continuous and a particle-based approach, sometimes simultaneously. In our laws of motion (see Eq.(2.11) and Eq.(2.14)) we also have explicit speed dependence in describing the interrelation of concentration and potential. Actually, we are thinking in two entities (concentration and potential), but both of them are parametrized by position  $x$ . In line with the Einsteinian case, the time shines up, and, again, the speed connects those entities. However, the different interaction speeds act on the coordinates differently, that is, the effects of changed entities cannot be separated. This is why we need 'non-ordinary' laws. (Given that our thermodynamical speed is always by orders of magnitude lower than the electrical (limiting) speed, we neglect transforming the time.)

In all cases, the law has the form of a differential equation; i.e., we can derive the fundamental entities by integration. *In 'ordinary' science, we have a single-speed interaction abstraction*; so we have one law of motion; an analytical

solution is possible. In a non-ordinary case, we have a dual-speed interaction, and a numerical solution is likely the only option.

### 2.3.3 Statistical mechanics

Thermodynamics is a somewhat misunderstood branch of physics. As its name suggests, it deals with heat, work, and temperature, and their relationship to energy, entropy, and the physical properties of matter. However, it is based on statistical mechanics, which combines two fundamentally different concepts of nature: the continuum and the discrete. It uses probability-theoretic concepts that may not apply to the system under study. The connection between the two fields was established by Ludwig Boltzmann, who treated the number of particles in an element of phase space, calculated from a probability distribution, as a real number and then applied the laws governing those particles.

The essential points of Boltzmann's general equation are that *the force acting on the particles is instantaneous, the particles only come into contact by direct collisions, the volume is infinite, the number of particles is sufficiently large, and the system is closed*. Only with these assumptions can we assume that the volume in the phase space does not change. In the case of neutral atoms or molecules in a large, closed volume, the conditions are met, and Boltzmann's equations describe the observed behavior of the systems. Another approach can be derived (the so-called Vlasov equations) when there is a long-range interaction between particles (for example, the Coulomb interaction between ions of the same charge), which excludes direct particle collisions. The latter describes, for example, plasmas in which atoms are fully ionized and ions move through a cloud of free electrons. This model also partially describes electrons moving in the periodic force field of the ion lattice in a solid, but it is not considered a thermodynamic system in the former sense; that concept is reserved for particles that interact only by direct collisions.

When applied to ions and especially to electrolytes, the conditions for the applicability of the Boltzmann equations are largely not met. Due to the low temperature compared to plasmas, the vast majority of molecules do not dissociate, so they interact only through direct collisions. A minimal number of ions, due to their identical charge, avoids direct collisions with each other through long-range interactions; they do, however, collide with neutral molecules and also the neutral molecules collide with each other. Ions play leading roles in biological processes and can therefore interact through both direct collisions and long-range forces. For this reason, *the Boltzmann equations are certainly not applicable to the description of the processes taking place in electrolytes*, which directly explains why thermodynamics cannot describe processes of life based on electrolytes.

Further limitations are that, in biological systems, statistical concepts must be applied to a very small number of particles in a closed space of finite volume, where coercive forces also occur, and processes beyond the experimenter's control make it doubtful that we can interpret a closed system. The main problem, however, is that ion charge and mass are inseparable; furthermore, the speed of

the electrostatic interaction of the particles with each other is instantaneous, in accordance with Boltzmann's original assumption. However, the speed of the diffusional interaction, which is calculated from the change in the distribution of the particles, is orders of magnitude slower. Of course, the particle's motion simultaneously changes the strengths of both the electrical and thermodynamic interactions. The diffusional effect occurs only when the particle reaches the region where it changes the concentration, whereas the force field created by the other particles changes immediately.

Classical physics can only handle instantaneous interactions; in the Newtonian worldview, all interactions co-occur. Overall, the traditional approach to thermodynamics cannot be applied to biological systems. In essence, Erwin Schrödinger stated that *ordinary* scientific laws cannot describe living matter. At the same time, he expressed his conviction that no new force or unknown interaction is emerging; only a previously unknown regularity concept must be found, then the non-ordinary laws organically integrate into the fabric of science, together with the already known laws.

### 2.3.4 Steady state

In volumes containing ions, the ions experience two effects in those two abstractions. When an invasion in the volume happens, electric potential, pressure, temperature, or concentration changes locally; dynamic changes begin to restore its balanced steady state. When the invasion persists, the system finds another steady state. If the invasion is local and affects only one macroscopic parameter, another macroscopic parameter(s) may change at the rest of the locations. An observer experiences that changing one macroscopic parameter of the system causes an unexpected (and unexplainable) local change in another macroscopic parameter. *The microscopic world maps the changes from one abstraction to the other.* Experimentally, the microscopic world maps the change from the world of electric abstraction to the world of thermodynamic abstraction and vice versa. Theoretically, we can do the exact mapping of macroscopic electrical and thermodynamical parameters using microscopic universal constants.

The phenomenon of invasion called 'electrodiffusion' means that when a potential gradient is created in a volume with ions (while its thermodynamical parameters, such as its volume and temperature, are constant), it creates a concentration gradient. Conversely, a created concentration gradient creates a potential gradient. In a more inclusive form: in a physical system where multiple forces act on the body (specialized to an ion in electric and thermodynamic fields), dissipating energy and under constraint forces

$$F_{exerting} = F_{electric} + F_{thermodynamic} + F_{friction} + F_{external} + F_{constraint} \quad (2.4)$$

That means when describing an ionic transfer process, *we must not separate the electric current from the mass transfer:* they happen simultaneously and mutually trigger each other. Furthermore, we must take into account the external force (say clamping), internal friction (moving in viscoseous fluid) and

the possible conditional counterforces (such as open/closed ion gates). Notice that the thermodynamic term is ion-specific while the other terms are not. To be entirely balanced, the system must be balanced to all elements. In this way, changing one concentration implicitly changes all other concentrations and the electric field. Similarly, changing the electrical force by adding an external potential, changes the thermodynamic force, and so, the concentrations. In terms of our equations, the same equation sounds

$$F_{exerting} = Eq.(2.68) + Eq.(2.50) + F_{external} + Eq.(2.33) + F_{constraint} \quad (2.5)$$

The temporal gradients are usually described by partial derivatives of spatial or feature parameters. The definition of a partial derivative of a function of several variables is its derivative with respect to one of those variables, *with the others held constant*. In the case of ions, changing the concentration means simultaneously changing the electrical charge; that is, the concentration gradient and the electrical gradient depend on each other. In other words, one cannot calculate the partial derivatives of ions' concentration and the electrical potential, only their total derivative. As a consequence, equations that calculate the partial derivatives of the concentration and the electrical potential with respect to time are either incorrect or approximations. The discussions, for example, the one leading to Eq. (11.30) in [21], assume that the interaction speeds are identical and that the partial derivatives can be interpreted for ions. Both assumptions are wrong. However, the claim that "while diffusion is like a hopping flea, electrodiffusion is like a flea that is hopping in a breeze" [21] (attributed to Hodgkin) is true; see also our Eq. (2.22).

We can describe the equilibrium state (the mutual dependence of the *spatial gradients* of the electrical and thermodynamic fields on each other) using the famous Nernst-Planck transport equation

$$\frac{\partial c}{\partial t} = \nabla \cdot \left[ \underbrace{D \nabla c}_{Diffusion} - \underbrace{\mathbf{v} c}_{Advection} + \underbrace{\frac{D q z}{k_B T} \mathbf{E}}_{Electromigration} \right] \quad (2.6)$$

Unfortunately, Eq. (2.6) also comprises the issue specific for ions: it calculates the not-interpreted partial derivative without taking into account that at least the advection term modifies the local electrical gradient by changing the concentration. Assuming that the concentration is at equilibrium ( $\frac{\partial c}{\partial t} = 0$ ; even if its calculation method and its value are questionable), without an external electrical field ( $\mathbf{E} = 0$ ), the change due to diffusion (in a statistical sense) is zero, and the flow velocity is zero ( $\mathbf{v} = 0$ ), results in the *Nernst-Planck electrodiffusion equation*

$$\frac{d}{dz} V_m(z) = -\frac{RT}{q * F} \frac{1}{C_k(z)} \frac{d}{dz} C_k(z) \quad (2.7)$$

describes the equilibrium state (the mutual dependence of the *spatial gradients* of the electrical and thermodynamic fields on each other). In good textbooks (see, for example, [21], Eq (11.28)), its derivation is exhaustively detailed. In the

equation,  $z$  is the spatial variable across the direction of the changed invasion parameter,  $R$  is the gas constant,  $F$  is the Faraday's constant,  $T$  is the temperature,  $q$  the valence of the ion,  $V_m(z)$  the potential, and  $C_k(z)$  the concentration of the chemical ion. In simple words, it states that the change in concentration of ions creates a change in the electric field (and vice versa), and in a stationary state, they remain unchanged. However, in the classic science there is no way to take into account the field's propagation speed. We must call attention to a nuance: to keep balance, the concentration and the potential must change in opposite directions. However, since they are implemented by ions, moving an ion's mass changes the ion's charge in the same direction.

It is one of the rare cases when the starting point was wrong, but the conclusion was right. In Eq (2.6), an identical speed for all interactions was assumed. The equation is a rearranged flux equation, where an identical speed for all interactions was assumed. Although the equation is not really applicable for describing the transport of ions (in its practical applications, the identical speed was calculated as a "mean-field", where the "mean" stands for some average of interaction speeds differing by several orders of magnitude), in an equilibrium state, the actual value of both interaction speeds is zero, so they have the same value; furthermore, no advection takes place. This way, the wrong partial derivative is irrelevant.

It is a serious difficulty with using Eq.(2.7) that it relates entirely different quantities, so it is not easy to apply it. There exist attempts to interpret the task of transporting ions under the effect of several interactions with different speeds (for a review, see [111]). However, "a *mean-field approximation* of ion interactions and continuum descriptions of concentration and electrostatic potential" actually means *averaging gradients propagating with speeds  $10^8$  m/s (electromagnetic interaction) and  $10^1$  m/s (ionic current), respectively, which is not appropriate for either (any way of averaging)*. The computational methods need position-dependent diffusion coefficient profiles, and in addition, they are generally quite limited for most confined regions such as ion channels. For this reason, they have joint issues, limitations, and high computational complexity; furthermore, biophysics [21] explains, "while diffusion is like a hopping flee, electrodiffusion is like a flee that is hopping in a breeze". This sentence is the complete mathematical description of a state change. *The lack of notion of non-infinite interaction speed does not enable theory to say anything*. The theory considers the *process* as just a momentary "hop" between two *states*, although it admits that there are longer and much shorter moments. Classic theory has no idea what to do with non-infinite interaction speeds. *This mistake is a significant obstacle, among others, when attempting to comprehend how the electrochemical charge handling implements neuronal computation and information transfer, furthermore, the life itself*.

In 'ordinary' physics, where the charge and mass are independent, changing one side changes the other in the opposite direction. In 'non-ordinary' physics, the two differentials must change in the same direction given that ions' charge and mass cannot be separated. Correspondingly, when initiating an AP in a neuron, the rush-in of ions increases both concentration and potential simulta-

neously. Moreover, to restore equilibrium, the gradients of the two macroscopic parameters must have the same sign, since they refer to the same ion. The thermodynamic force acting on an ion is added to the electrical force. The two are inseparable; the magnitude of the force is 'falsified'.

Eq. (2.7) is the derivative of the equation 2.18 known as *Nernst equation*. In other words, Eq.(2.7) and Eq.(2.18) are the differential and integral formulations, respectively, of the same knowledge. (Eq. (2.18) results in opposite signs according to the 'ordinary' and 'non-ordinary' laws of physics. Experience shows that the 'non-ordinary' laws result in the correct sign.)

That means, of course, that the Nernst equation is valid only in a system at equilibrium with no material flow (it cannot be interpreted for transient states, such as generating AP in a cell). The limits of the integration are chosen arbitrarily (by choosing the reference concentration  $C_k^{int}$ ). Hence, the derived potential values inherently include an additive term (a potential difference), so one must not compare them directly if they use different reference potentials  $C_k^{int}$ ; see reversal potential values. Furthermore, it is nonsense to combine the quantities from the intracellular and extracellular sides additively, whether concentrations, or mobilities, or Nernst voltages, as it happens in the GHK equation, see [72]. We note one more feature, that since the potential is linearly proportional to the concentration (and so are their derivatives), the function is of form  $f(x) = -\frac{1}{x}$ , where, *as an exception, the square of the first derivative equals the second derivative:  $f''(x) = (f'(x))^2$* .

### 2.3.5 Laws of motion: time derivatives

To derive laws of motion of ions in electrolytes, one must use non-ordinary methods after scrutinizing which approximation can be used for living matter. Below, we derive an approach that enables us to handle interaction speeds that differ by orders of magnitude. Science has created abstract concepts such as space and time; mass and charge. Modern physics was born when experiments began to contradict the fact that nature could be described in such simple terms. The recognition of the non-continuity of energy led to the creation of quantum mechanics, and the recognition of the non-independence of space and time led to the creation of the theory of relativity, with far-reaching consequences. We understood that under certain circumstances, we must treat particles as kinds of continuous waves, and continuous waves as kinds of particles. We understood that the Newtonian approach has limitations, and that interactions at finite speeds can only be described by a different kind of mathematics, namely the concept of spacetime. Moreover, mass is also related to space and time; taking this into account, we can describe nature in terms of curved spacetime. According to classical physics, we can describe phenomena with sufficient accuracy using only the aforementioned concepts (the zeroth derivatives). According to modern physics, for a more accurate description, we must take into account the first derivative with respect to time. For a general description, we must consider the second derivative as well.

Regarding ions, we can handle their charge and mass separately; we know

the relevant laws. However, in the case of ions, we must connect charge and mass, just as in the case of the theory of relativity, space and time. Interestingly, here too, the velocity creates the connection between the two abstract features. Furthermore, we must introduce a relation for the currents carried by ions, similar to that introduced in statistical mechanics for the correspondence between the particle and the continuum views. However, in our case, the correspondence is established on geometric grounds.

Eq.(2.7) describes a stationary state with no ionic movement. Deriving a time course (time derivatives) from the position derivatives is not possible in a strict mathematical sense. However, we can provide it by using physical principles. We consider the electric ion current represented by viscous charged fluids [112]. As expected, selecting the speed (aka calculating the appropriate value of the macroscopic speed, see Eq.(2.15)) plays a key role, especially since we are at the boundaries of physics abstractions; among others, we are mixing microscopic and macroscopic notions. The actual speed model depends on the concrete case; see section 2.4.4.

In classical physics, because of the lack of time-dependent terms in the expressions, the changes are described by position-dependent terms (*position derivatives*), both in the case of electromagnetic and electrodiffusional interactions. In classical ('instant interaction') science, the time derivatives are either not interpreted or can be derived by scaling through the externally derived joint interaction speed as a scale factor. As explained, we can extend the idea to enormously different speeds and derive time derivatives if we consider the faster interaction to be instant.

In the timeless classical physics, there is no explicit dependence on the time: everything happens simultaneously. In a resting state, the Maxwell equations essentially follow from the conservation of energy. One form of energy transforms into another form, and the system arrives in another balanced state. The carriers of the force fields are continuous and have no masses, so one can calculate and make infinitesimal changes in the driving forces; they do not change the system's energy. If one gradient changes, the other automatically (per definitionem) changes in the opposite direction. In another words: the driving forces are permanently balanced, the magnetical and electrical forces act instantly ("at the same time") and they are always of opposite sign. A time derivative cannot be interpreted: everything happens at the same time; in other words, at the same space-time (in the classic interpretation, the time is the same at any point).

In an electrodiffusional process, we start with the same point of view. We assume that the thermodynamical and electrical driving forces are equal in an equilibrium state. That assumption results in the Nernst-Planck equation. On one side, we use a macroscopic parameter, the potential. On the other side, we use another macroscopic parameter, the concentration. The equation bridges those macroscopic parameters by using universal constants from the microscopic world.

At first glance, the case is similar to that of electrical and magnetic fields. However, we cannot make infinitesimally small changes in the gradient since the carrier of the force fields is "atomic". Furthermore, moving it infinitesi-

mally (changing only its position coordinates), the changes in the electrical and thermodynamic gradients do not result in a new balanced state. The effect of ions' *charge* has an immediate effect on the volume, but ion's *mass* has a delayed effect. The infinitesimally small change in the position results in an infinitesimally small increase in the energy of the system, given that moving a carrier changes the potential and the concentration in the same direction, since we did not consider that the time coordinate changes as well. In the Newtonian world, everything happens at the same time, so we cannot handle instant and finite interaction speeds simultaneously. Eq. (2.18) contradicts energy conservation. The infinitesimally small energy change disappears only when the effect of the slower interaction reaches the other carriers in the volume. *When the interaction speeds differ, energy conservation is valid only if one uses space-time.*

Fortunately, we can derive the infinitely small change where the time and space (position) coordinates are connected; essentially, in the same way as in the special theory of relativity. Let us assume that the gradients act on the mass and the charge, but the ion's effects on the gradients are negligible. According to the principle of relativity, *the phenomena must remain the same in a reference frame moving with a constant speed relative to the first one*, and we choose the system that moves together with the ion. In the second frame, no ionic movement occurs along the movement's direction. In line with the fact that the speed of light is independent of the reference frame, we assume that the higher interaction speed remains the same in both systems: it is instant. The observers in both reference frames must see that the system is balanced. The difference is that in the first frame, the system is *statically* balanced (no change in the gradients, but the ion is moving), and in the second one, it is *dynamically* balanced (the gradients change to keep the ion at rest). *The gradients the moving ion experiences are the ones that the standing ion experiences at another time (depending on its speed). This way, we can provide the needed time course of the process.*

Compared with the electromagnetic case, we see crucial differences. First, the mass's propagation speed (forming a new concentration gradient) is millions of times lower than the charge's. Second, the moving ion simultaneously represents mass transport and charge transport. Third, when deriving position derivatives, we conclude from the assumption that there is no movement (in other words, no explicit dependence on the time): the effect of the electrical and magnetic driving forces is equal, whatever time is needed to reach that balanced state. In contrast, in electrodiffusion, the velocity changes the concentration gradient, and simultaneously, the potential gradient.

We assume that equation (2.7) is valid for a given time  $t$ . At time  $t + dt$ , in another steady state, the two interactions manifest at different times: we have

$$\frac{d}{dz} V_m(z + v(z) * dt) = -\frac{RT}{q * F} \frac{1}{C_k(z)} \frac{d}{dz} C_k(z) \quad (2.8)$$

or, equivalently, it can be expressed as

$$\frac{d}{dz} C_k(z - v(z) * dt) = -\frac{q * F}{RT} C_k(z) \frac{d}{dz} V_m(z) \quad (2.9)$$

The concentration at position  $z$  determines the potential (apart from an integration constant) at position:

$$dV_m(z) = dz * \frac{d}{dz} V_m(z) = -dz \frac{RT}{q * F} \frac{1}{C_k(z)} \frac{d}{dz} C_k(z) \quad (2.10)$$

so (and here the constant disappears) the time derivative is

$$\frac{d}{dt} V_m(z) = v(z) * \frac{d}{dz} V_m(z) = -v(z) * \frac{RT}{q * F} \frac{1}{C_k(z)} \frac{d}{dz} C_k(z) \quad (2.11)$$

or

$$\frac{d}{dt} V(z) = \frac{D * R}{F} * C(z) * \frac{dC}{dz} * \frac{RT}{q * F} \frac{1}{C(z)} \frac{d}{dz} C_k(z) \quad (2.12)$$

Similarly, at time  $t - dt$ , in another steady state, we have

$$dC_k(z - v(z) * dt) = dz * \frac{d}{dz} C_k(z) = -dz \frac{q * F}{RT} V_m(z) \frac{d}{dz} V_m(z) \quad (2.13)$$

$$\frac{d}{dt} C_k(z) = v(z) * \frac{d}{dz} C_k(z) = -v(z) \frac{q * F}{RT} V_m(z) \frac{d}{dz} V_m(z) \quad (2.14)$$

We expressed the dependence of gradients on each other using the ion's speed  $v$  as intermediate variable, that can be expressed by the Stokes-Einstein relation as

$$v = -\frac{D * R}{F} * C(z) * \frac{dC}{dz} \quad (2.15)$$

After simplifying the expression and using the aforementioned special feature of the  $\frac{1}{x}$  type function

$$\frac{dV(z)}{dt} = \frac{D * R * R * T}{q * F * F} * \frac{dC(z)}{dz} * \frac{dC(z)}{dz} \quad (2.16)$$

$$\frac{dV}{dt} = \left( \frac{T * R^2}{q * F^2} \right) * D * \frac{d^2 C}{dz^2} \quad (2.17)$$

As section 2.4.8 discusses, in general, the electric operation of an electrolyte can be described by this law of motion. For practical calculations, the voltage time derivative can be calculated directly from the input current, thereby accounting for the current production mechanism, see equations (2.37) and (3.6), which directly consider the current production mechanism. We must not forget that we started from a quasi-equilibrium state; that is, our description is valid only for quasi-static processes.

We note here that in closed volumes, for example, see Schrödinger's points on the specific aspects of life, one must consider further effects. The electrostatic forces of the ions exerted on each other, and the wall exerts a counterforce on the ions in the microscopic view, and on the fluid in the macroscopic view, which manifests as a mechanical force and pressure. This aspect is not considered in the general transport equation (2.6); one must add one more term

when calculating mass transport. If the volume is not hermetically closed (say, the ion channels in the wall of the membrane represent a "hole" for the ions), the combined electrostatic plus mechanical pressure can provide a driving force (instead of hypothesizing a magic lipid mechanism) for producing a mass transport. If the change in concentration and potential happens suddenly (see the rush-in of  $Na^+$  ions at the beginning of an AP in neurons), that "explosion" creates an "impact force" exerting on the membrane and the conterforce starts a pressure wave and other mechanical changes, as discussed in [130]. The elastic membrane generates *The electrical and thermodynamic phenomena are just two sides of the same coin* as discussed in [72], and underpinned by some plausible numericals estimations in "speculations"

Fortunately, the overwhelming majority of the energy of the excitation is stored as elastic energy of the membrane, and the pressure is proportional to the measurable voltage, so describing the electrical behavior is sufficient to provide a sufficiently precise description of the processes in the membrane, but one has to keep in mind that the force is composed of electrical and thermodynamic components.

### 2.3.6 Nernst's law

In a segmented electrolyte, the electric charges are typically globally balanced; however, they may become unbalanced locally due to physical reasons. The two sides of Eq.(2.7) are the derivatives of the equation

$$V_{C_k} = \frac{RT}{q * F} \ln \left( \frac{C_k^{ext}}{C_k^{ref}} \right) \quad (2.18)$$

known as *Nernst equation*. In other words, *Eq.(2.7) and Eq.(2.18) are the differential and integral formulations of the same knowledge*. The limits of the integration are chosen arbitrarily (by choosing the reference concentration). Hence, the derived potential inherently comprises an additive term (a potential difference), so they are not intercomparable directly if they use a different reference  $C_k^{ref}$ . The derivatives are spatial derivatives; the temporal derivatives (needed for describing the time course) of the concentration(s) and voltage are derived above and in [19].

### 2.3.7 Fick's Law

By expressing the speed through the Stokes-Einstein relation, see Eq.(2.34)

$$\frac{dV}{dt} = \frac{D * R * R * T}{q * F * F} * \frac{d^2C}{dx^2} = \left( \frac{T * R^2}{q * F^2} \right) * D * \frac{d^2C}{dx^2} \quad (2.19)$$

Or, alternatively,

$$\frac{dV}{dt} = \left( \frac{T * R}{F} \right)^2 \frac{k}{6 * q * \pi * \eta * a} * \frac{d^2C}{dx^2} \quad (2.20)$$

Given that

$$\frac{dV}{dt} = D * \frac{d^2C}{dx^2} \quad (2.21)$$

expresses Fick's Second Law of Diffusion, we can derive the ratio between the electric and thermodynamic temporal gradients. Using values  $T = 300\text{ K}$ ,  $q = 1$ ,  $F = 96495\text{ A*s/mol}$ ,  $R = 8.31446261815324\text{ J*K}^{-1}\text{*mol}^{-1}$

$$\frac{dV}{dt} = 2.23 * 10^{-6} * D * \frac{d^2C}{dx^2} = \mathbf{2.23 * 10^{-6}} \frac{dC}{dt} \quad (2.22)$$

We can provide a rough, experimental estimation of the value. The time course of the gradient (half-width) in Figure 2.2 in [1] was produced in  $0.3 * 10^3\text{ s}$ . Reciprocally, a voltage gradient needs  $0.1 * 10^{-3}\text{ s}$  to produce the same concentration gradient, see Fig. 2d in [82]. Their ratio is  $3 * 10^{-6}$ . The other way round, when we assume that the propagation of the electric field in the solution is  $2 * 10^8\text{ m/s}$  and multiply it by the factor above, we arrive at the speed of ion's speed in the range around  $10^2\text{ m/s}$ .

Given that we can assume that the electrical interaction speed is about the respective speed of light, we arrive at that the speed of material transport (the speed of the mechanical wave) is about  $100\text{ [m/s]}$ . Given that the mechanical wave carries an electric charge, it induces an electrical charge on the other side of the axon. This way, the particles move under the combined effect of a thermodynamic force and an electrical force. The amount of induced charge depends on the specific capacity of the axon (the thickness of the myelin layer on it), so the resultant force (and, due to this, the Stokes-Einstein speed) of the axonal current depends on the thickness of the myelin layer.

## 2.4 Ions' electricity

### 2.4.1 Why ions' electricity is different

In this section, discussing electricity, to avoid "reinventing the wheel", we heavily rely on the excellent site HyperPhysics, hosted by the Department of Physics and Astronomy of University of Georgia. Their material is excellent for discussing engineering electricity, where the charge carriers are electrons. However, they extended their material with bioelectric phenomena, tacitly agreeing with some fallacies created by biophysics. They do not scrutinize the differences caused in the electric phenomena by the structure of living matter, the effects of the limited volume of a cell, using slow positive ions in electrolytic solutions instead of fast free electron clouds in solids, the interaction with thermodynamics, among others. So, we must discuss the deviations in detail, which originate from the same reasons as discussed in section 2.3.1. The fundamental concepts are the same, but we must rethink several approximations. Furthermore, sometimes we must consider the classical continuous electricity, sometimes particle-based electricity; sometimes the mixture of the two, or a transition between them. In biological cells, the usual "infinite" conditions (infinitely far, infinitely small,

etc.) of the classical electronics are not fulfilled: it depends on the context what can be omitted with respect to some other entity or size. Say, the charge in the intracellular volume is "infinitely smaller" than that in the extracellular volume, but "infinitely larger" than the charge handled in an ion-channel-related operations. The biological organization prevents discussing living matter as homogeneous and isotropic medium, the active "charge production" in some biological constructions needs a precise interpretation of the conservation laws, and the charge carriers speed needs revisiting the interpretation of the fundamental physical laws.

Electricity is one of the fundamental disciplines of classical physics. It operates with concepts such as charge, current, voltage; furthermore, their spatial or temporal change described by their gradients (spatial or temporal derivatives). Physical and biological electricity are similar, but not identical. The former was already an established discipline when the latter started to discover that biological objects also show signs of electric processes happening inside them. Of course, the already available concepts, laws, measurement devices and procedures were taken over, and based on the resemblance between those two kinds of electricities, their identity was and is assumed. The laws of physical electricity, in most cases, describe also biological electricity to some measure. However, in some cases, there are drastic differences between them. Not considering those differences leads to misunderstandings and wrong conclusions. It is a common fallacy in physiology that the applied potential  $U$  generates a current. Instead, even in invasive measurements, its gradient ( $E = U/z$ ) has the effect, where  $z$  is the distance, for example, between the clamping point and the membrane or the AIS. Inside the cells, there are no batteries. Instead, the different ion concentrations produce electric gradient ( $E = \frac{dU}{dz}$ ) that forms the driving force for moving the ions through the AIS.

Physical electricity operates with concepts of ideal (voltage or current) generators and (ideal, that is single-substance) discrete components, connected by ideal conducting wires. The wires are passive components, just connect the discrete components and the electric phenomena happen in the discrete elements, with one idealized feature. Electricity inherited the Newtonian picture that everything happens simultaneously and applies a hybrid picture. It considers that there exists no delay on the connecting wires, although charge passes in the current. The current is defined as temporal change of charge, but it is explicitly considered only in the slightly non-ordinary phenomena capacitance, inductance and impedance; it is considered as instant in the phenomenon called resistance. In biological electronics, neither of the above notions can be interpreted in unchanged form.

Fortunately, physiology inherited the ambition from physics to measure its subject, together with the measurement methodologies and devices. However, as we detail in section 2.4.10, measuring living matter (because of its "special construction") requires at least considerable care, sometimes different methodologies and appropriate interpretation; including the understanding of the special kind of electricity it applies.

The different charge transmission mechanism introduces another important

difference, the relation to thermodynamics. In physical electronics, the medium is a solid, where the electrons heavily interact with the nodes in the solid (forming a kind of 'electron cloud'). In a good approximation, they are not comprising free and independent particles, so their phenomena are not related to thermodynamics. The ions, in contrast, are nearly independent, non-interacting particles, so they would be described by thermodynamics. However, they are simultaneously charged particles, so they are governed also by the laws of electricity; that is the driving force is a net electric field. The case is somewhat similar to the case when an ion moves in simultaneously applied electric and magnetic fields, and it is considerably different in that the thermodynamic interaction also represents a mass transport, inseparably, so the driving force is the sum of the thermal and electric gradients. The real complication is that the interactions have different speeds.

### 2.4.2 Charge

Charge is one of the fundamental properties of matter, one of the fundamental abstractions in science, and the primary abstraction in connection with electrical concepts. Although charge is an abstract property, it must always have a carrier. Without a carrier, no current and voltage can happen. In contrast with the classical electricity, significance should be attached to the circles representing the ion and electron, in the sense of implying a relative size and mass. In a useful first construct, they are hard-sphere objects. The most important opening idea, electrically, is that they have a property called "charge" which is the same size, but opposite in polarity for the ion and electron and the ions can have multiple charge. The ions are about 50,000 – 100,000 times heavier and about the same factor larger than electrons, and this difference leads to crucial other differences, for example in their speed and conduction mechanism. For the sake of simplicity, we always think about positive ions, although we know also there are negative ions. An essential implication is that the ion and electron will strongly attract each other, while two positive ions or two electrons would strongly repel each other. All charges observed in nature are multiples of these fundamental charges. The charge generates an electric field, its spatial integral results in potential difference or voltage, and its movement generates a current (furthermore, electromagnetic waves that we do not discuss here). It is important, that a voltage can be generated either by driving a current through a solid or having charges in two different points in an electric field.

Ions differ from electrons we used to in physical electricity. Their conduction mechanisms are entirely different, and they are not necessarily present in the discussed medium. They may be produced by biological mechanisms, and they are slow (have a couple of  $m/s$  speed). Figure 2.3 illustrates how classical electronics and biology considers charges and their moving. Both disciplines provide an atomic level description, but unfortunately they use the same words for their concepts, although their meaning can be entirely different.

One of the fundamental symmetries of nature is the conservation of electric charge; it is valid, of course, for living matter as well. No known physical process

produces a net change in electric charge. Claims such as "the current cannot disappear, it has to go somewhere" [21], page 9, are wrong. On the one side *only charge conserves, its time derivative, the current, does not*. On the other, *charge conserves only globally, but not locally*: the charge moves from one place to another. The case is similar to the case of general relativity, and also its reason is the same: the finite speed of interaction. In the general theory of relativity, local and global energies had to be introduced; for its mathematical handling, see, also Noether's theorem. In the case of biology, the speed of interaction is the conduction velocity. It is a limiting speed in the sense as the concept is used in the theories of relativity: in biology, no effect can be faster than the (actual) conduction speed. Further complication arise from thermoelectricity and neurotransmitters. *In no case can one think that ions in living matter behave as electrons in metallic conductors.* One must be especially careful that the electric testing circuits are hybrid: in half of the circuit, the charge carriers are electrons, while in the other half, they are ions. There must be two points where the charge carriers must be converted there and back, with all potential, speed and timing issues. The media and the charge carriers in those two halves are entirely different. Using the fundamental laws of electricity without changes means assuming that the ions travel at the same speed in electrolytes as electrons in metal conductors, surely misleading researchers.

An isolated single charge can be called an "electric monopole". Equal positive and negative charges placed close to each other constitute an electric dipole; solved salts in biological liquids typically represent dipoles. From some point, they have fraction of a unit charge. From our point, it is important that the dipoles are directed. Their orientation can be affected by external fields, furthermore the nearby dipoles affect each other's field and dipole moment.

### 2.4.3 Voltage and electric field

It is worth to recall some features of voltage. Classical electricity applies a hybrid approach, again. In classical circuits, the voltage arrives instantly, but in the discrete elements, such as condensers and solenoids, have a mathematically described time course. We must extend the notion of electric field by considering the contribution of pseudo-electric field arising from thermodynamics.

For a biological interpretation, we can start from the picture used in the case of condensers: charges arrive into a discrete element and they change a macroscopic feature (called capacity) of that discrete object of the electric circuit. We assume that a driving force exists across the two ends of the condenser. In physical electricity, the ideal condenser is point-like. Given that it is sizeless and the interaction is instant, the derivative  $\frac{dU}{dx}$  cannot be interpreted within the condenser. In that abstraction, the electric field is a step-like function, see, for example, Fig. 2.11.

In biology, the objects are extended and the charge carriers are slow ions, so we can ask how the voltage gradient  $\frac{dU}{dx}$  changes across biological objects. Here, again, comes into the picture the different charge propagation mechanism. As we discuss in section 2.3.5, the electric and thermodynamic interaction speeds are

very different, and the ions have the attributes mass and charge simultaneously, the *potential of the charge can travel only with the speed of the slow ions, so the transport equations such as Eq. (2.7) have a wrong theoretical foundation; consequently they need context-dependent half-empirical coefficients.*

Electricity explains that voltage can be measured without or with electric current; having entirely different physical background. Accumulating charge on an insulator results in producing an electrostatic field. Of course, while charging, a current flows and energy is needed to produce a voltage, but it is a one-time action; the created potential difference persists. In a condenser, a counterforce counterbalances the attraction between opposite charges on the opposite plates, no charge movement takes place, and no energy is needed to keep up the voltage. Another possibility is when the charge moves (either an electron of the 'free electron cloud' moves against the friction of a solid or an ion moves with the Stokes-Einstein speed against viscosity) in a medium, see Fig. 2.3. In these latter cases, a current (charge transfer) and potential difference can be observed across the considered space region (a solid conductor or an ion channel). The important difference between producing a voltage difference by charge-up and flowing current is that charge-up is a one-time action, while keeping up a voltage difference while generating the current requires continuous energy investment.

It is a common fallacy in physiology that the applied potential  $U$  generates a current. However, it is a kind of energy. Instead, its gradient ( $E = U/d$ ) has the effect, where  $d$  is the distance, for example, between the clamping point and the membrane or the AIS. It is important to distinguish potential and the difference of potentials in two different points. The latter, together with the distance of the points, leads to a gradient.

#### 2.4.4 Current

In the macroscopic world, we describe the current as the statistical time course of charge carriers carrying charge  $q$  through a cross section  $A$ . At any point and at any time, the incoming charge equals the outgoing charge. Kirchoff's law expresses *charge conservation at any point, in a differential form*. The correct definition of current is a differential one:  $i = dq/dt$ , as given for physiology by Appendix A.3.4 in [1]. By using this definition, A.3.5 correctly defines that "Ohm's law states that the ratio of voltage to current is a constant:  $R = V/i$ ". So is its reciprocal, the conductance. By measuring the two charge-related entities one can derive the "*resistance*", *the opposition of material to current; an attribute of the medium* where the measurement is carried out.

The other way round, as given by Eq. (1.4) in [21], is wrong. "It is straightforward to describe the dynamics of this circuit by applying Kirchhoff's current law, which states that the sum of all currents flowing into or out of any electrical node must be zero (*the current cannot disappear, it has to go somewhere*)."<sup>1</sup> [21] *It is straightforward, but, unfortunately, it is not true. The charge, instead of current, cannot disappear, it has to go somewhere. There is no conservation law for the time derivative of the charge, only for the charge itself. Mismatching charge and its derivative misguides understand-*

*ing neurophysical phenomena.* The non-differential definition contradicts charge conservation and also, contradicts itself.

The current can be interpreted in its integral form as current conservation only if the electric interaction is instant, the discrete components are point-like, and the measured system is closed (or complete). However, it is not necessarily valid in its integral form. The latter form is an approximation, (more or less) valid for classical physics, but surely not valid for biology. The current can temporarily disappear (it can be stored, delayed, say on the membrane of axon or exit to a non-measured segment in the system) or "created" (enter from a non-measured segment, say, through ion channels) or be distributed within the "wire" such as on the surface of the dendritic tree.

In biology, thermodynamical processes produce the voltage and it has a time course. Believing that an equivalent battery provides a constant voltage results in attributing changing conductance to the membrane, as we discuss in section 2.4.5.

### Ionic currents in a cell

On a microscopic scale, a charge creates a potential field and that field acts on another charge. In a conducting wire, filled with ions (the solids have a different current transfer mechanism), there are free charges, their number per unit volume is given by  $n$ , and  $q$  is the amount of charge on each carrier. If the conductor has a cross section of  $A$ , in the length  $dx$  of the wire we have charge  $dQ = q * n * A * dz$ . If the charges move with a macroscopic speed  $v = \frac{dz}{dt}$ , at macroscopic level, we define the current  $I$  as the charge moved per unit of time as

$$I = \frac{dQ}{dt} = q * n * A * v \quad (2.23)$$

Notice that if any of the factors is zero, the macroscopic current  $I$  is zero. *Microscopic carriers must be present in the volume* and have charge, the cross section must not be zero, and the charge carriers must move with a potential-assisted speed, which requires an external or internal force field. However, notice that the fellow charge carriers in the current also affect the speed, see also section 2.4.4. One of the fundamental mistakes by HH was to omit that effect (practically, neglecting the Coulomb force for ion's electric interaction) and that the electrical potential is created by diffusion processes instead of ideal electric batteries.

When describing the macroscopic phenomenon "current" in metals we apply a potential difference to a macroscopic piece of space (or measure it) and measure the statistical time course of the charge carriers which are electrons. In the abstraction we use, the external potential is constant (we use a "voltage generator") and the charge delivering has no "side effects". However, we must realize, that we have a hybrid circuit: in the electric half, electrons represent the current, while in the biological half, ions. We must convert the charge carrier there and back, furthermore, consider its possible side effects. When describing "current" in entirely biological systems, it is represented by ions, and it is either

a native current (without an external potential), or an artificial injected current (or potential generating a current). This way, the current is always producing or is accompanied by a change in concentration gradient, given that the moving ions represent mass transfer and charge transfer simultaneously. The potential and current are connected through the features of the medium (material) that hosts our measurement. One must not forget that "Unfortunately, most measuring devices in neurophysiology are precise without being accurate" [1]. So are some definitions, too. Definitions and measurements, which are not accurate, conclude in wrong results.

### Current's speed

According to Stokes' Law, to move a spherical object with radius  $a$  in a fluid having dynamic viscosity  $\eta$ , we need a force

$$F_d = 6 * \pi * \eta * a * v \quad (2.24)$$

(drag force) acting on it. A (microscopic) electric force field  $\frac{dV}{dz}$  inside the wire would accelerate the charge carriers continuously with a force

$$F_{electric} = k * E(z) * q \quad (2.25)$$

until they reach a constant speed  $v$ . It is not the *drift* speed: because of the electric repulsion, it is a *potential-assisted* or *potential-accelerated* speed that can be by orders of magnitude higher. The medium, in which the charge moves, shows a (macroscopic, speed-dependent) counterforce  $F_d$ , which in steady state equals  $F_{electric}$ , that is :

$$I = \frac{k * q^2 * A}{6 * \pi * \eta * a} * n * E(z) \quad (2.26)$$

We extend the original idea by using

$$E(z) = \frac{\delta V}{\Delta z} \quad \text{in linear potential} \quad (2.27)$$

$$= \frac{dV}{dz} \quad \text{in graded potential} \quad (2.28)$$

$$= E_{electric} + E_{(thermal)} \quad \text{in electrolytes} \quad (2.29)$$

The amount of current in a wire is not only influenced by the electric force field (specific resistance) but also by the number of charge carriers  $n$ . While the latter is commonly considered constant and part of the former, this is not necessarily the case for biological systems with electrically active structures inside. The medium's internal structure introduces significant modifications. Applying an electric field to a wire can generate varying amounts of current as the number of charge carriers changes. For axons, we use a single-degree-of-freedom system, a viscous damping model, so the *ions will move with a field-dependent constant*

*velocity in the electric space*; so it takes time while they appear on the membrane. The activity of potential-controlled ion channels in its wall may change  $n$  in various ways; furthermore, that change can result in 'delayed' currents during measurement, for example, in clamping, as physiological measurements witness.

If we have a concentration  $C(z)$ , in the volume  $A * dz$ , we have  $dQ = C(z) * A * dz * q$  charge, resulting in another expression for the current

$$I = \frac{C(z) * A * dz * q}{dt} = C(z) * A * q * v \quad (2.30)$$

Combining equations 2.26 and 2.30:

$$v(z) = \frac{k * q}{C_k(z) * \eta * 6 * \pi * a} * E(z) \quad (2.31)$$

The higher the resulting space derivative (gradient) and the fewer ions that can share the task of providing a current, the higher the speed. We hypothesized (it needs a detailed simulation) that in the case of this charged fluid, the electric repulsion plays the role of 'viscosity' [19]. The higher the charge density, the stronger the force equalizing the potential; so  $\eta$  is the lower, the higher the charge density (proportional to  $C_k$ ). For the sake of simplicity, we assume that the speed is proportional to the space gradient of the local gradient. Recall that *our equations refer to local concentrations only. The electric gradient can propagate only with the speed of the concentration gradient*, given that only the chemically moved ions can mediate the electric field. *The lower interaction speed limits the other interaction speed if the interactions generate each other.*

The dependence of the diffusion coefficient on the viscosity can be modeled by the Stokes-Einstein relation:

$$D = \frac{k * T}{6 * \pi * \eta * a} \quad (2.32)$$

so we can express the speed with diffusion coefficient

$$v(z) = \frac{D}{T} * \frac{q}{C(z)} * E(z) \quad (2.33)$$

or alternatively

$$v(z) = -\frac{D * R}{F} * C(z) * E(z) \quad (2.34)$$

In the equation,  $z$  is the spatial variable across the direction of the changed invasion parameter,  $R$  is the gas constant,  $F$  is the Faraday's constant,  $T$  is the temperature,  $q$  the valence of the ion,  $V(z)$  the resulting potential, and  $C(z)$  the concentration of the chemical ion. For the experimental evidence, see section 3.7.1.

Models in neuroscience (as reviewed in [113]) almost entirely ignore these aspects. In our physical model, we see that the measurable membrane potential and current change in the function of the ions' speed, the concentration, and its time derivative; furthermore, all mentioned quantities depend on the effective potential.

### ”Fast” and ”slow” currents

”it seems difficult to escape the conclusion that the changes in ionic permeability depend on the movement of some component of the membrane which behaves as though it had a large charge or dipole moment.”

”it is necessary to suppose that there are more carriers and that they react or move more slowly” [5]

What could be the component that has large charge and moves slowly, if we do not stick to the ’instant current’?

As discussed in section 2.2.3, the overwhelming majority of physics phenomena can be described using the approximation that their interaction is instant; in other words, the interaction speed is infinitely high. In electricity it is a commonly used abstraction that the electric field and the current are ”instant”. Although we know that the field propagates with a speed near to the speed of light, and it is only an illusion (thanks to the ”free electron cloud”) that the current propagates at such a speed, the abstraction based on the approximation that those speeds are infinitely high, works. However, that abstraction has a range of validity and the biological systems not necessarily belong to it. It means that the laws of physics are valid, but in biology another approximations must be applied. The absolute value of speeds alone would not mean a problem, but as section 2.3 discusses, when force fields having different propagation speeds are mixing, special calculation methods must be used.

In electrolytes, two forces may act on the ions, and their balance may drastically influence the phenomena we can observe. When the two forces are balanced (either globally: no gradient acts across the volume; or locally: the two gradients differ by location, but at all places balance each other) no effective force acts on the ions. The electrolyte is in rest, and the thermodynamics entirely determines the speed of the ions: it is the *diffusion speed*. When some external electric gradient or concentration gradient applies (due to some internal charge-up process, external potential, external gradient change; or internal thermoelectric gradient change: a current inflow changes both concentration and potential gradient), the ions accelerate to their Stokes-Einstein speed (see Eqs. (2.33) and (2.34)). If the gradient does not change, they will move with that speed. This speed is much higher than the diffusion speed. On their path they may experience different gradients and they modify their speed correspondingly.

As we discuss in connection with the operation of ion channels, relatively small voltage (in the order of dozens of  $mV$ ) may act on very short distances (in the order of  $nm$ ), producing vast potential gradients (in the order of several tens of  $kV\ cm/s$ ). Given that the ions travel short distances with vast speed, they may experience very different forces and they may travel with a speed differing by several orders of magnitude in a few  $nm$  distance. In addition, since the moving ion causes change in the electric and potential gradients in a short distance, moreover due to the very low speed, the active volume on the departure and arrival sides are limited to a limited thickness.

In some cases, when precisely measuring the time course of current compared to the time course of voltage, one can experience a 'phase delay' between them. Given that we are convinced that the charge conserves (does not appear/disappear) and the abstractions 'current' and 'voltage' are secondary abstractions and the manifestations of the primary abstraction 'charge', the experience inspired further research, that led to inventing 'inductive', 'capacitive' and 'resistive' currents. Science can describe how those currents combine and generate each other. In biology, similar delays are experienced, but the 'phase delays' have been attributed to the media (membrane conductivity), without providing a clear reason how the *same charge* can produce its two different manifestations (potential and current) at different times.

Biology did not give an explanation (similar to the Maxwell equations); instead, it claims that the living matter has a 'non-ohmic' behavior, and that it cannot be described by the laws of physics. Including that some hidden power, for an unknown reason, changes the conductivity (meaning that charge can disappear/reappear; defying the law of charge conservation). However, it was not the case: in the living matter further interactions and their mixing speeds must be considered.

If we trigger at the same time two effects that propagate from one point to another, and they arrive at the target at different times, the phenomenon may have different reasons. We may hypothesize that the triggering of one of them was delayed, or that their speed was different or that they took a break during their journey. Biology (without explaining or reasoning) assumes some 'delayed rectifier current' and refuses the other two reasons.

As we discuss, there is a vastly different range of interaction speeds in science and during the electric processes in biological tissues, the charges may change their speeds when they pass from one biological object to another one. When sticking to mathematical formulas derived for pair-wise single speed interactions in homogeneous isotropic media in classic science, we miss the possibility to describe the true nature. The formulas representing a good approximation for one abstraction are not necessarily valid for another approximation. The abstraction 'metals' differ sufficiently from the abstraction 'biological tissues and cells', so we cannot hope that the notions, abstractions, approximations and laws describing the first one can describe the second one, despite that some initial resemblance exists.

There may be different reasons why a current appears apparently with a delay compared to the voltage, such as: the charge carriers of the current have finite speed, they are produced inside the media during the measurement, or they are stored for some reason for some time and released only some time later (as the conditions within the circuit change). In a limited way, one can imitate one effect with the other. As discussed in connection with Eq. (2.23), the current depends linearly on the number of the charge carriers  $n$ . The physical processes changing the number of charge carriers also define the intensity of the current, providing a way to imitate a slow current by a fast current, where the number of charge carriers is modulated by the spatiotemporal time course of the physical process of producing ions in the system.

Given the lack of mathematics describing the “slow” currents, it is a common practice to imitate a neuronal circuit with a simple electric  $RC$  circuit having capacity  $C$  and resistance  $R$ . Although in biology it is common to describe an ‘electric equivalent’ of biological circuits, among others, biological oscillators one must not forget that instead of electrical processes (driven by an ideal voltage generator) electrochemical processes happen. The parallels have severe limitations.

The macroscopic equivalence is implemented at microscopic levels, among others, using ion channels huge electric gradients. The interplay of those biological objects can enormously change the speed of ions, that is the speed of ion current. Within the same phenomenon, the same charge carrier can have speeds differing by orders or magnitude.

From the structure of neuron’s membrane follows immediately that in the neuronal oscillator the capacity  $C$  and resistance  $R$  are connected serially instead of parallel. We assume a discrete equipotential membrane with capacity  $C$  that leaks through a discrete resistance  $R$ . This also means we cannot apply Kirchoff’s *Junction Law*: the capacitive and resistive currents are not equal, because the condenser stores part of the charge that flows in through the membrane and the synapses.

Different damped oscillations can be produced depending on those parameters. The imitation is limited: the “rise time” gets smeared, and the output signals differ for the neural and the electric circuits. Instead of a step function, we expect for a “slow” current, we receive a smooth peak-like current time course (called a damped oscillator function). However, we can use the formalism developed for the “fast” current. Adjusting its parameters allows the electric circuit to produce a behavior resemblant to a neuronal circuit.

Notice that in our imitated neuronal circuit, the peak of the “fast” current appears later. The “slow” current is seen, although the delay time is not explicitly present. If we use chained electric RC circuits, such as in the case of multi-compartment membrane models [42, 114], the second such circuit receives the output voltage of the first circuit at a later time, and so on. It is also described by a system of similar equations, but they are valid at different times. Handling the many equipotential compartments attempts to cover the fact that one imitates finite membrane size and slow currents.

However, in biology storing charge is implemented differently. The notion of storing charge can be used also in the sense that for the time of passing a finite-size element with finite propagation speed, the charge carriers spend the corresponding time in the element. That phenomenon resembles storing the charge, and that imitation enables us to describe a behavior resemblant to that of the biological circuit. Attempting to imitate the effects of biological “slow” currents using electric parallels hides that generating an AP is their native feature. No additional currents and sophisticated control mechanisms are needed: deriving-action-potential is a natural consequence of the interplay of the finite speed of the “slow” ionic current and the finite size of the neuronal membrane; furthermore, that slow currents may play a role also in cognitive functions.

### Currents in layers

As we detailed, the ions change their location during the observed potential changes. The currents described here flow in a thin layer on the top of the membrane

### Current drain

The ions (from any source) entering the layer with a high ion concentration in the segment with the lower bulk concentration will reside in the layer near the separating membrane; they are in thermal and electric equilibrium. They cannot diffuse inside their segment due to the attraction of the ions in the segment, so the mass current is zero. They cannot pass into another layer: the electric driving force is missing (or even, slightly opposite), so the charge current is zero. However, they induce the corresponding changes on the opposite side. As Eq.(2.7) describes, nothing changes.

The case fundamentally changes when a current drain appears in the layer. It decreases the local charge and potential, and the rest of the charge tends to be equipotentially distributed in the respective layer; a *potential-assisted* (slow) current will start. Given that the total charge in the layer decreases, its effect on the opposite side decreases, and the total amount of charge in the opposite layer also decreases, manifesting in bulk potential change. This charge "redistributes itself" on the two sides of the membrane [21]. However, the circuit is closed through the drain and the extracellular space but not directly across the capacitor. Consequently, slow currents flow inside the two adjacent layers as well as in the bulks. In the high-potential layer, parallel to the membrane's surface, and in the low-potential layer perpendicularly to the membrane, towards the bulk part of the segment. They are simple discharge-type currents (we consider only the one flowing in the layer in the segment with low concentration)

$$I_{D\text{rain}} = I_o * \exp\left(-\frac{1}{\beta} * t\right) \quad (2.35)$$

Given that the slow current, due to its finite speed, has a limited charge-delivering ability, unlike in electronics, no limiting resistance is needed in the circuit. The current generates voltage either on a capacitor, see axonal arbor [78, 79] in the case of axons (later on the membrane), or on a resistor, see the AIS [50]. If the delivered current can deliver more charge than that can flow away through the current drain, the effect of 'ram current' ('impact current') can be observed. Finally, as discussed in section 3.5.3, the AP is a direct consequence of the 'ram current' due to the rushed-in ions.

Our equations call attention to the neglected aspects that the current evoking an AP on the AIS *requires ions to be present in the electrolyte layer near the membrane*; furthermore, that the rushed-in ions must propagate from the exits of the ion channels (and similarly, from the synaptic terminals) in the layer on the surface of the membrane to the AIS, AIS, which needs time. The potential changes observed at different membrane locations manifest the slow currents

in the membrane. Recall the sizes of the measuring tip and that of the layer: the presence of the charged layer likely cannot be directly noticed. However, its effects were noticed indirectly [84].

### Current source

In the segment, external currents can also appear. Examples include synaptic inputs through the neuron's synaptic terminals (with a time course of a PSP), the current from the AIS to the beginning of the axon (with a time course of an AP, and artificial currents with various time courses). In those cases, the external current delivers ions, generating the concentration's and potential's time course. As discussed, in our approximation the current increases the charge carriers on the arrival side and decreases it on the departure side. If the source is a potential-less current, a simple discharge function describes it

$$I_{source} = I_o * (1 - \exp(-\frac{1}{\alpha} * t)) \quad (2.36)$$

As evidence shows, the current provided by a population of ion channels depends only on their number and surface density, and the ion channels are distributed evenly over the surface. The charges appear everywhere on the surface, including near the drain. That means that the drain current starts immediately (the repulsion of the appeared charge creates the driving force), and an exponentially increasing current will flow in the layer with a potential-assisted speed. Its intensity will change due to the changing intensity of the source current and the changed potential drop in the drain. The two currents flow simultaneously, and its intensity is the product of the source current and drain current (this form, with different coefficients, seems to be valid for several biological systems comprising ion channels)

$$I_{out} = I_o * (1 - \exp(-\frac{1}{\alpha} * t)) * \exp(-\frac{1}{\beta} * t) \quad (2.37)$$

The voltage's time derivative describing the current in a system with source and current, needed for the biological law of motion (see section 2.3.5), is given by Eq. (3.6)

The channels in the membrane's wall open quickly and the ions appear instantly; i.e., they produce a steep voltage gradient in the layer on the membrane (see Fig. 3.13). As discussed, because of the size of the measuring tip, this gradient is attributed to the membrane even though it has no charge carriers. As the local potential in the layer increases on one side, and decreases on the other, the driving force across the membrane in the ion channels decreases, and the rush-in current slows down; the 'ram current' quickly produces a negative gradient. (The effect can also be interpreted as the effect of storing charge in the neural  $RC$  circuit's condenser.) The effect measured in [82] is reproduced in our Fig. 3.13. Later, the effect of the sudden change consolidates, and the gradient disappears (similarly to a damped oscillation) in a discharge-like way due to the

intense current toward the drain. (The classic picture using fast currents would produce a simple discharge gradient with no AP-like form.)

As discussed, having charge carriers in the proximal layers of the membrane is a non-stationary stage, so the membrane tends to restore its steady state. In the classic model, simple equipotential surface (infinitely fast current) is assumed to provide only a static picture of the neuron. Our model uses slow current which can provide a dynamic picture: our equations can describe the time course of concentration and potential inside and outside the neuron.

### Current without potential

Notice that our interpretation and equations excellently and naturally describe also the currents propagating without an external voltage, among others the axonal current and the membrane's current. The AP arrives at the beginning of the axon in the form of a traveling wave of a slow current (an ion packet delivering ions). Recall that ions move in the "skin" layer on the membrane, and they continue their way in the axon's internal surface, creating a similar skin on the internal surface of the tube. There is really no ion current in the volume of the axon, as the classic physiology observed. However, the current is delivered in the atomic "skin" on the internal volume of the axonal tube, in full conformance with the laws of electricity, combined with the laws of thermodynamics.

The mechanism of the current transmission is the one we described above. We can subdivide the ion packet into  $n$  pieces, and we choose a  $dt$  time such that each piece travels a distance  $v * dt$ . That means that the pieces "jump" in the position of their neighbor to the end of the time slot  $dt$ . Front. Cell. Neurosci., 28 August 2023

Volume 17 - 2023 — <https://doi.org/10.3389/fncel.2023.1232020> The mutual repulsion is unbalanced at the edge of the spike (and recall that the rising edge of the current is exponential). The uneven distribution of ions in the first piece in the spike and the one immediately in front of it means a gradient. The ions are not in a stationary state and the forces due to the concentration and voltage gradients act in the direction of the spike propagation. The two gradients represent a driving force (see Eq.(2.7)) that moves the volume element to the position of the neighbor immediately in front of it. The case is described by Newton's first law: the gradient acts on the charges by the force as described by Eq. (2.31). Given that the  $(n - 1)$ -th element also moves with speed  $v$ , it leaves an empty volume element behind, so the gradient due to ions in the  $(n - 1)$ -th element "pulls" the ions after the rest of the spike. The potential-assisted speed is by orders of magnitude lower than the speed of the electric interaction, so *the axonal current propagates in the tube at the potential-assisted speed*. The charges can be observed as the potential they generate propagates along the axon and different changes [84] are accompanied to the primary change that the ions keep the maximal possible distance from each other while they are moving with a macroscopic speed  $v$  along the tube (they cannot exit the tube). The electric repulsion of ions causes the observed travelling waves.

Notice that it is *not* a classic longitudinal current under the effect of some

external potential: charge and voltage gradients represent an internal driving force. A very viscous electrostatic fluid represents the current where the ions do not lose their potential energy. (The classic model for axonal charge propagation assumes a periodically changing in- and outflow of ions in connection with propagating a 10 ms long spike at 10 m/s speed requires the ion channels at distance of 1 mm to concert the actions: at what rate to pump ions in at the beginning and the end to appropriately adjust the pumping intensity to accommodate to the spike's current intensity at the places of the channels; given that the total charge delivered by the spike and the shape of the spike remains the same during the axonal delivery.)

#### 2.4.5 Resistance/Conductance

Voltage and current, the secondary electric entities, derive directly from charge, the primary entity, and (except time) no external entity is used. In contrast, when deriving resistance or conductance, one measures how the tested object relates to electricity. At this point comes to the light the meaning of E. Schrödinger's warning about how do we test in physics laboratories. Although physics knows (based on their electric behavior) conductors, insulators and semiconductors, the *characteristics of the material* under testing is never mismatched into electrical terms. Paper [115] discusses why introducing a fundamental circuit element (the memristor) led to decades-long confusion, when attempting to introduce new laws of electricity. Introducing neuron (in the form of equivalent circuits where the "biological matter" changes electric characteristics without any causality), that changes the rules of the game in electricity, has led to similar confusion. Physics provides examples when the relation of voltage and current seems to change and deviate from the Ohmic case. However, the first principle of energy conservation provides a hint to the correct interpretation. In physics, the energy and charge conserves (instead of current as [21], page 9, claimed), so we could introduce capacitive and inductive current, capacitive and inductive energy.

When those secondary entities interact with some macroscopic material, their relation to that material defines a feature, such as dielectricity or resistance. *Those ternary entities manifest (i.e., are measurable) only when charge is present.* Experience shows that, *in the presence of electric potential*, different media show different resistance against *transferring charges*, so we define resistance/conductance *as one of the media's macroscopic features* (which is connected to microscopic features by Stokes's Law). There is a crucial difference between the current propagation's mechanisms in solids and in biological materials.

As we derive in Eq.(2.30), we can define a current for electrons and ions moving in an external force field, but the physical background in the two cases are entirely different. The technical current direction is opposite with the flow of electrons (and negative ions) but agrees with the direction of positive ions. The ions are much heavier than electrons, and even they can combine in electrolytes with water molecules, so their mass ratio can reach the order of 50,000–100,000.

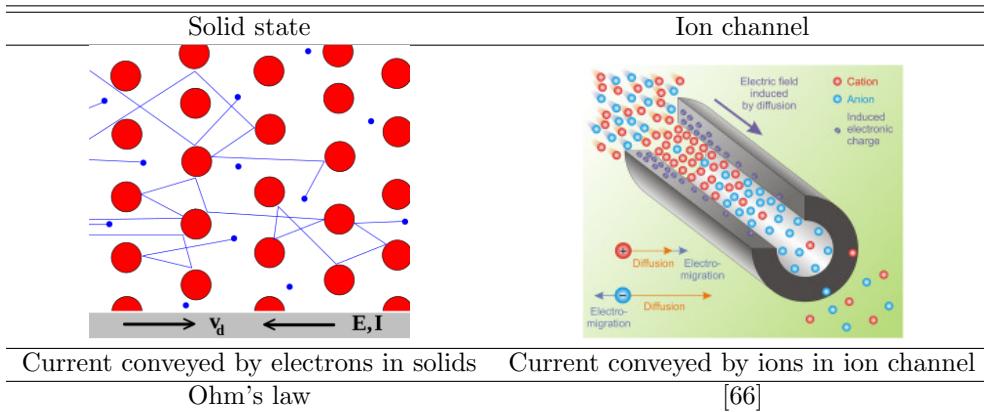


Figure 2.3: Electric resistance types

The charge propagation mechanism is entirely different (see also Fig. 2.3). As the Drude model describes, in solids, electrons (shown in the figure in blue) constantly bounce among heavier, stationary crystal ions (shown in red). The Drude model treats electrons like pinballs bouncing among the ions that make up the structure of the material. With each collision, though, the electron is deflected in a random direction with a velocity that is much larger than the velocity gained by the electric field. The net result is that electrons take a zigzag path due to the collisions, but generally drift in a direction opposing the electric field. Important, that the collisions are inelastic, so the electrons lose (most of) their energy. The energy is absorbed by the solid's gridpoints, which later is released in form of heat. The process is irreversible.

In biological matter, ions convey electricity. So called ion channels are used for the transfer. Here diffusion and electromigration takes place, by orders of magnitude different speeds. The ions traverse typically without collision, under the effect of an electric field. The process is reversible. See also section 1.10.2.

Resistance, as can be concluded from its name, means that in a medium some external (electrical, mechanical, thermodynamic, or any other) power exerts a force on an electric charge and the medium exerts a counterforce on the charge (resists moving the charge). In the case of solids (metals), the medium has free charge carriers (electrons) inside, which mediate the electric field applied to a space segment of the solid. Due to the charge transmission mechanism, the charge carriers form "instantly" a field inside the solid. However, it is known that the propagation speed is finite: it takes about 1 ns to propagate to a 30 cm distance, forcing the designers of electronic circuits to introduce "clock domains", "clock distribution tree" and so on, when the accurate timing of signals is of importance. In the case of electrolytes, the charge carriers are ions with 50,000 times higher mass and a million times lower propagation speed, so the timing requirements are even more critical. In living structures, in closed volume segments, local electrical fields (typically of biological/chemical/enzymatical ori-

gin) may be present, so no freely moving charge carriers can be present in the volume and the permanently present electric field may change the phenomena drastically. Furthermore, biologically active structures may "produce" charge carriers inside. The fundamental laws of electricity are the same, but describing electrical processes of living matter with internal processes inside need more care than in the case of non-living matterd without such processes.

When measuring resistance by dividing the measured values of voltage and current, a quantity of dimension resistance or conductance can be derived. Measuring those two charge-related characteristics requires performing two independent measurements, using two independent measuring devices; furthermore, assuring that one uses matching values (measured simultaneously) for the calculation. This is why, for comfort, resistance/conductance measuring devices have been developed and are in use (for their Of course, even that instrument cannot measure directly the ratio of those two secondary quantities, it makes (a little and forgivable) cheating. It reduces the measurement to measuring current by applying a little voltage (of known value) to the device under test, and displays the calculated result in units of resistance/conductance. The device uses the differential form of deriving the current: measures voltage and current at the same time. Here comes into the play the cheating: instead of actually measuring the voltage, the device uses voltage measured earlier and current value measured at the time of measurement. In the case of 'instant interaction', the two measurement are simultaneous. The procedure is anyhow an invasion into the circuit, but (when used with care and knowing how the device works) perfect for performing a simplified and bequem measurement. When implemented with modern technology, in most cases the unwanted offset does not have significant effect. However, in biology, the 'service current' needed for the measurement is in the range of the currents due to biological effects, and can bias measured values.

Two more kinds of issues come to the light when measuring in biological circuits. As we mentioned, although the measurement device works with electrons and in the half with 'instant interaction', the current keeps the timing of the slow current in the biological time; that is, one uses a 'delayed current' value in measuring the resistance. This is why good physiology textbooks (such as [1] emphasize that resistance/conductance is a 'steady-state' characteristics. Forgetting this fundamental feature results more or less distorted values; an extreme example is 'demonstrating' that the neuron is a low-pass filter, see section 3.8.8.

Another issue is that the device of course cannot distinguish what the experimenter wants to measure and cannot separate its own current that its required voltage produces from the current that the tested object autonomously generates. It works with 'instant' electricity: it works using Ohm's law, and divides the momentary value of the measured current with the known value of the generating voltage. In the case of technical electricity, the current instantly follows its driving force. In biology, however, the charge carriers are slow (at least in the biological half of the circuit), so it needs time until the effect of the voltage change gets observable. In the case of changing gradients, the conductance

meter uses non-matching pairs of voltage and current data: the device is designed for measuring in a 'steady-state'. The gradient and its effect are shifted by the time period that the charge carrier needs to travel from the place of its "excitation" to the place of the measurement. It is in the order of nanoseconds in technical circuits and it can be in the order of fragments of milliseconds, depending on the speed of the ions (depends on the gradient) and the distance traveled, in biological matter. So, the measured conductance is surely wrong, the question is only how much it is wrong.

Notice that the middle figure in Fig. 1.7 shows two essential potential gradient contributions. Given that for the current

$$I = \frac{U}{R}$$

or, in another form

$$\frac{I_{true} + I_{clamp}}{U} = \frac{1}{R}$$

That is, when one measures using voltage clamp (see Fig. 2.6), the price paid for fixing the voltage is adding the feedback current to the measured current, and calculate the conductance from a wrong value pair. Apparently, the conductance increases as the 'foreign' current (that is compensated by the feedback) changes, creating the illusion that "the conductance changes". The conductance does not change, it is the effect of the used current feedback, needed to keep the voltage constant against neuronal operation.

#### 2.4.6 Capacitance

In technical electricity, capacity means that charge is accumulated in a discrete circuit element. Experience shows that the voltage measurable on the element is proportional to the stored charge. The factor of proportionality is called capacity.

Actually, the *charge disappears* from the wires, so the capacity comprises a static and a dynamic component: part of the charge remains permanently in the element, part of it just is travelling on the surfaces of its plates, between the junctions of the wires to the capacitor. As we discussed, in the engineering the current is instant, so the dynamic component is missing: the charge instantly arrives from the beginning junction to the end, while it is accumulated in its two extended pieces of wire, as discussed in section 2.5.5.

The slow ions also cause deviations in charge storing. In biology, the circuit elements are extended and it takes time until they appear on its output. The biological condenser stores the charge also in the form that the charge carriers travel on its surface. Given that the rush-in mechanism means that the ions appear "instantly" on the condenser's surface through the ion channels in its wall, and they must travel from their "place of creation" to the AIS, the capacity of the condenser changes when a current flows.

### 2.4.7 Imitating ion's electricity

#### Time dependence

#### Charge storing

We have evidence that the membrane's charge is proportional to the membrane's voltage: the membrane has a fixed capacity  $C$ . We know that the arriving axonal currents (as well as the rushed-in ions after exceeding the membrane's threshold voltage) cause massive transient changes [74, 75] (in other words: gradients) in the membrane's voltage. We know that the charges on its surface can flow out only through the ion channels [47] in the neuron's AIS, which we represent with a resistance  $R$ . We have evidence that the AIS only mediates the membrane's changing voltage to the axon [47]. *So, we have good reasons to assume that the membrane is not equipotential when generating an AP.* Our hypothesis about "slow" currents' presence thoroughly explains the phenomena about the temporal behavior of neuronal processes mentioned. However, given that the classic picture also explains many phenomena, we must establish the connection between the two models and draw the borders within which the classic description can be used, and where our time-aware model must be used.

Some resemblance indeed exists in charge handling in electrical and biological circuits. However, the validity of parallels is limited. Assume an infinitesimally fast ion current on the surface will keep the membrane's potential constant all the time. We can use the formalism developed for electricity, even in biology, if we want to use the *point representation* of a neuron. The price we pay is that we do not have access to the voltage and current of our finite-size membrane: they are confined in our fictive discrete elements (point representations within our point representation of neurons) despite the evidence listed above. This abstraction is appropriate for designing electric circuits and has a suitable formalism that describes their behavior. *However, neither membrane nor AIS has the facilities to generate an AP in this approach.*

The "point representation" model results in a wrong parallel with the "*integrator-type*"  $RC$  electric circuits: by assuming discrete resistance and capacitance, we set up a fake hypothesis that the voltage drops within the resistor, and that current flows into the condenser and the charge is stored in it. A late consequence of the century-old idea of "point representation" (which immediately follows from the 'instant interaction') is that we must omit the temporal dependence of axonal signal arrival; we try finding a correlation between neuron's inputs; we do not see the role of fellow neurons in neural operation; we attempt to describe neuronal information with inappropriate representation and using inappropriate mathematical methods, etc.

The "extended point" model reveals that all currents flow into the membrane, which is a *distributed* condenser, and the AIS with a resistor  $R$  is a *discrete* output component of the circuit; see also Fig. 1 in [47]. That is, the neuron shall be modeled as a "*differentiator-type*"  $RC$  circuit, having entirely different electric behavior from that of the commonly used "point representation" model (with its implicit "*integrator-type*"  $RC$  circuit) predicted. From

biological point of view, the vital difference is that this circuit type can produce an output voltage with opposite sign, enabling to describe hyperpolarization, without needing any fake extra mechanisms, such as outflow of an intens  $K^+$  current.

In our model, the neuron membrane is simply a two-dimensional elastic isolator surface (where needed, we imagine it as a thin, long, and narrow rectangular piece) that has current sources at different positions (axonal arbors), many concerted current sources in its body (the ion channels in the membrane's wall) and a current drain (AIS) at the other. The input and output currents increase/decrease the voltage on the membrane. In our time-aware model, we assume that the ions on the membrane's surface represent a kind of "free ion cloud" (see also section 2.4.4), so we can interpret the capacitance  $C$  (at least for our differential equation) in a classic way. However, charge carriers are not necessarily present on the surface. In the case of a neuronal membrane, the stable basic state is that there are no charges on the surface. If charge carriers (from an external source) appear, the potential increase that their appearance causes leads them to be removed. A "slow" current on the surface with a speed  $v = \frac{dx}{dt}$  represents a current  $I_{slow} = A * n * q * v$ .

In its steady state, the ions (from the rushed-in ions, axonal currents, or artificial currents) create a uniform potential over the membrane. In our simplified discussion, we omit the less intense input currents (which also cause transient voltage changes, which should be summed with that from the effect of the rushed-in ions) and discuss only the one-time contribution due to the rushed-in ions. On the one hand, in its non-steady state, the neuronal  $RC$  circuit uses the time derivative of the potential due to the rushed-in ions as input, see Equ. (3.6)). On the other, the potential drops due to the current drain (the AIS at the end), where the current is

$$I_{AIS} = \frac{V_{AIS} - V_{rest}}{R}$$

According to Kirchoff's Law, the current (and consequently the voltage derivative) through the AIS must be equal to that of the membrane due to the rushed-in ions. We can solve the differential equation numerically; see section 3.5.3 and Figure 3.10. We can also derive

$$v_{AIS} = \frac{V_{AIS} - V_{rest}}{R * A * n * q} \quad (2.38)$$

that is, the speed of the "slow" current is proportional to the voltage  $V_{AIS}$ . The current  $I_{slow}$  will change the membrane's voltage:

$$\frac{dV}{dt} = \frac{A * n * q * v}{C}; \quad \frac{dV}{dx} = \frac{dV}{dt} \frac{dt}{dx} = \frac{A * n * q}{C} \quad (2.39)$$

That is, the potential in the function of the distance will drop in the same way as if the membrane had a distributed resistance  $R$ . However, the resistance is located to the AIS, as if it were a discrete element. In electronics, the capacity  $C$  is interpreted as opposite charges on the condenser's plates. In biology,

no similar stored charge exists. The *charges spend some time on the surface*, inversely proportional to the current's speed (the inward positive current due to rushed-in ions and the outward positive current of the pumped-out ions has been observed, but not the corresponding negative currents). The distributed resistance and the specific capacitance are constant in the function of position over the membrane's surface so that those values can be used in differential equations based on Kirchoff's Laws. Notice, however, that currents joining the membrane at different points may spend different times on the surface (meaning different capacitance values), so the capacity changes in the function of the time, in this way distorting the time constant  $RC$  and so the shape of AP.

The potential in the function of the time and the speed of the slow current mutually generate each other, as described by Eq. (2.38). In a steady state, no current flows. When some current arrives through the axons, or flows out through the AIS, a slow current starts to balance the potential difference created by the current. Changing the amount of charge on the surface transiently leads to a non-equipotential membrane. Notice the difference: if we assume instant interaction, we assume a constant membrane potential using discrete elements  $R$  and  $C$ . The voltage drops on the discrete element  $R$ , and the charge is stored in the discrete element  $C$ . *The voltage outside the discrete elements is constant, except for the voltage step, due to some incoming current (including the AIS, and there is no way to interpret how and why the AP is created.* On the contrary, if the current is slow, it needs time to reach another position (we can change the membrane's local "charge storing" ability), and it can either increase or decrease the local voltage. When using a voltage generator with appropriate temporal behavior, *the "slow" current explains why and how an AP in a biological neuron is evoked.*

We can hypothesize that

- "making a hole" in the membrane [75] means that "slow" ions are pressed into the membrane through the axon.
- the inflection point is the turning point where the outward current exceeds the inward current, and it can be considered to be the time of the arrival of a spike (in the case of the first spike, it can be the signal 'Begin Computing' [116]).
- the inflow and outflow happen in parallel (the slopes of the PSP voltage course differ from those of the current pulse; see also their numeric time constants in Fig. 3.22); that is, we will see the difference between a "slow" and a "fast" current, with a particular temporal behavior.

### Time delay

The time needed to move a charge to a distance comprises two contributions. To move a charged particle in a piece of material ("the wire"), first, we must produce a force to accelerate the particle inside the wire at the position of the particle (the needed time is the distance to its location divided by the *speed of*

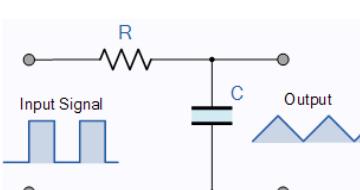
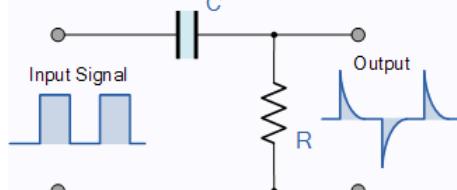
*propagation of the electric potential field*). The second contribution is that the charged particle needs time to reach the other end of the wire (the distance to the external world divided by the *particle's drift speed*). The object must be accelerated to that speed by that electric field; for the sake of simplicity, we consider the needed time negligible. To calculate the "time delay", we need to sum the field and charge propagation times. Let us suppose that the electric field's propagation speed is infinite and the charge is in the immediate vicinity of the end of the wire. Fortunately, different physical mechanisms (such as "free electron cloud") can produce the illusion of a much faster macroscopic *current speed*. In that case, the travel time of the charge is negligible. However, we can expect only in that case that the charge promptly contributes to the current, i.e., the current follows the voltage without delay.

We consider the cases of galvanic wire and electrolytic wire. There is no essential difference in the field propagation time: for our human senses (and even slower electronic tools), it is a good approximation that the electric field appears promptly along the wire, including the position of the charged particle. In galvanic wires, the electrons behave like an electron cloud: uniformly distributed in the wire. When the electric field appears (in the sense above: promptly), there are electrons in the infinitely small vicinity to the end of the wire. The field speeds them up immediately, so they exit the wire, and some other electrons enter the wire at the other end simultaneously. The charge carriers enter and exit immediately after an external potential is applied.

The phase change of voltage and current follow each other without a (noticeable) delay. Ohm's Law is valid for this case: the derived entity connecting them (resistance or conductivity) is constant. The Law expresses the charge conservation: the same number of carriers passes the cross-section at any time. Remember that *the essential conditions were that free charge carriers were present and uniformly distributed in the wire. Furthermore, they were moved by only one microscopic force* (not considering the forces implementing an average macroscopic "resistance"). Even in metallic components, the derived material characteristics depend on many factors when we apply a step-like change in the voltage or the current. The so-called on-resistance is also known outside electrolytes and is influenced by various parameters such as temperature and supply voltage.

In an electrolytic wire, the ions in the electrolyte may be uniformly distributed (they form a kind of "free ion cloud" inside the electrolyte), i.e., after the electric field is applied, the ions can immediately exit the electrolyte and produce an electric current. In summary, the ions are very slowly moving charged objects (compared to the free electrons; BTW: the electrons move only slightly faster than ions; only the cloud provides the illusion of their high speed). However, they can create a prompt ionic current, provided that they are present in the corresponding volume and their concentration is isotropic. The living cell with its semipermeable membranes can produce situations where isolated structures do not fulfill that condition, and the less careful observer identifies the situation as non-ohmic behavior. As we discussed, the axonal tubes are empty (no charge carrier) at the beginning of a clamping experiment (see the measurement results in Fig. 3.24), and they are filled in their steady state (at beginning discharging),

Table 2.1: RC circuit types

The RC Integrator	The RC differentiator
$V_{out}^{Integrator} = \frac{1}{RC} \int_0^t V_{in} dt$	$V_{out}^{Differentiator} = RC \frac{dV_{in}}{dt}$
Low Pass Filter	High Pass Filter
	

producing entirely different temporal behavior ("changing conductance").

#### 2.4.8 Oscillator

The simplest *RC* oscillator circuits comprise only a resistor and a capacitor. Because the capacitor "stores" the charges, the output signal is different from the input signal (the circuit "forms" the signal). Their behavior can be described by mathematical equations, as given in Table 2.1. Notice that the two discrete elements are connected at one of their ends, leaving only two options how to connect the input and output signals to them. Correspondingly, we can produce a parallel or a serial connection.

It may have different reasons why a current appears with a delay compared to the voltage, such as: the charge carriers of the current have finite speed, or, although they have infinitely high speed, they are stored for some reason for some time and released only some time later (as the conditions within the circuit change). In a limited way, we can imitate one effect with the other. Electronics uses the abstraction that circuits are composed of point-like discrete elements implementing abstract features such as resistance and capacitance, and they are connected with abstracted ideal wires, with no resistance. Given the lack of mathematics describing "slow" currents, it is usual to imitate a neuronal circuit with a simple electric *RC* circuit having capacity  $C$  and resistance  $R$ . In that picture, the electric behavior can be described by summing the resistance and capacitance to single discrete components, i.e., we can use the formulas taken from electronics.

These ideal discrete elements can be connected in two ways, and those combinations have drastically different behavior, as their differential equations and waveforms show; see table from the electric tutorial. The two circuits comprise the same electric components, but wired in a different way: they form a *serial* and a *parallel* circuit, respectively. The serial circuit is a passive ***RC differentiator*** circuit: "the input is connected to a capacitor while the output voltage is taken from across a resistance" and it is not to be confused with the parallel passive ***RC integrator*** circuit where "the input is connected to a resistance

*while the output voltage is taken from across a capacitor*". One of the most vital differences between those circuits (see also the figures in Table 2.1 and in <https://www.electronics-tutorials.ws/rc>) that their output is defined by the *time integral* of the input voltage (or current) or by its *time derivative*.

Although the two oscillators have the same time constant  $RC$ , they form the input signal entirely differently. From the figures showing the generated signal forms, one sees that in the case of the *differentiator*, the input signal's rising edge generates a positive output voltage, and the falling edge generates a negative voltage, in resemblance with the action potential. By replacing the input square wave current with a physically plausible input current function, we have good hopes to reproduce the AP voltage on the output of the circuit.

From a biological point of view, *the differentiator can produce output voltage that differs from the input voltage in its sign, while the integrator cannot. The differentiator can produce output voltage that differs from the input voltage in its sign, while the integrator cannot. No additional currents and sophisticated control mechanisms are needed to describe the action potential with a differentiator-type neuronal RC circuit: it is a natural consequence of the interplay of the finite speed of the "slow" ionic current and the finite size of the neuronal membrane* (see section 3.5.3). The shape of the output waveform depends on the pulse width ratio to the  $RC$  time constant. When  $RC$  is much larger than the pulse width, the output waveform resembles the input signal, even in the case of the square wave input.

If we use chained electric  $RC$  circuits, such as in multi-compartment membrane models [42, 114], the second circuit receives the output voltage of the first circuit at a later time, and so on. The system can be described by a system of equations similar to the one describing the single-compartment system, but they are valid at different times. Handling the many equipotential compartments attempts to cover the fact that one imitates finite membrane size and slow currents.

The Differentiator is a High Pass Filter type of circuit that can convert a square wave input signal into high frequency spikes at its output (For non-square wave input, the spikes get smeared). When the capacitor is fully charged the output voltage across the resistor is zero. *The arrival of the falling edge of the input waveform (whether square-wave or other type of falling edge) causes the capacitor to reverse its current giving a negative output contribution*, and the output spike changes from a positive value to a negative value, purely because it is a derivative. From the point of view of laws of motion (see section 2.3.5): the differentiator is the circuit, which can be described by the biological laws of motion, namely by Eq.(2.11).

As discussed in section 1.8.1, we divide neuronal operation (generating an AP) into stages. We have different physical models in the different stages of operation. We have changed the fake *integrator*-type  $RC$  circuit (see section 3.6.5) to the correct *differentiator*-type one; eliminated the fake  $K^+$  current; derived the neuronal AP from the first principles of science, eliminating the empirical functions. *These changes mean that we need an entirely new mathematical formalism to discuss neuronal operations.* Discussions about Green's function,

Fourier series, and similar stuff need revisiting: they target the wrong model.

### Integrator-type oscillator

As discussed in section 3.1.3, although the notion of AIS was already known at the time when HH [5] published their Nobel-prize winner suggestions, its role was not known. The *RC* circuits were well-known electric elements with established theory. As detailed in section 3.6, the misinterpretation of some experimental facts mislead them and they chose the wrong type of *RC* circuit (see Table 2.1). Their equations and conclusion are based on the *integrator* type *RC* circuit. They said, 'The first step in our analysis is to *divide the total membrane current into a capacity current and an ionic current*'. Their Eq.(1) is

$$I = C_M \frac{dV}{dt} + I_i \quad (2.40)$$

In their picture, those *currents* control the operation of the neuronal membrane. The basic issue with their idea (see our discussion at Eq. (2.42) is that the output voltage (aka AP) is

$$V_{OUT} = \frac{1}{RC} \int_0^t V_{IN} dt$$

( $V_{IN}$  can be interpreted given that the two discrete elements are switched in parallel). It implies that to produce an output voltage (see the output line shapes in Table 2.1) that first rises, after peaking, goes negative, then returns to zero,  $V_{IN}$  must contain a strongly negative time-depending term which is synchronized to the other currents. To produce such a term, HH [5] used a circuit where the resistances/conductances change according to some *empirical* function (i.e, an *ad-hoc function*, without science base). In other words, some mystic power must regulate the conductance of the elements, to make them behave as we know from another discipline, the theory of electricity. Starting form a wrong point (having a bad model in mind) it is simply not possible to arrive at a reasonable description. HH (and their followers) had to introduce false physical assumptions and several further ad-hoc assumptions.

### Differentiator-type oscillator

In the correct *differentiator-type RC* circuit we need to work with the *time derivatives of the input voltages the input currents cause in the membrane*. We need to correct HH: *the time derivatives instead of currents govern the action potential*. This behavior explains why a large slope of the arriving spike [63] can trigger an instant spike: the large slope (much higher than a normal one) of the current induces a much higher voltage gradient contribution around the point of arrival on the membrane, and so it alone can raise the local voltage gradient above the threshold voltage near to the junction, triggering the known mechanism. The input voltage  $V_{IN}$  comprises different contributors (with different temporal courses), and the differentiation is linear; i.e., we shall sum up

the different contributing terms linearly (compare our equation to Eq.(2.42))

$$\frac{d}{dt}V_{OUT}(t) = \sum \frac{d}{dt}V_{IN}(t) \quad (2.41)$$

To describe the AP, the output voltage of the  $RC$  circuit, we need to provide all contributions  $\frac{dV}{dt}$  and solve the differential equation numerically.

The different contributions are discussed in section 3.5.4. The time derivatives of the different voltages can be calculated using different physical models, corresponding to the different stages of operation. Because of the presence of slow currents, they need different travel times and the different contributions have different time courses. We assume that the membrane is equipotential, that is,  $V_M(t)$  depends only on the time, so it is identical with the voltage function to  $V_{AIS}(t)$ .

Here comes to light *the fundamental difference between the static and dynamic description: the temporal course of the charge is identical with the current only if the current is constant* such as in the case of clamping/patching. In the case of a constant current where  $I = \frac{dQ}{dt}$ , the voltage increase  $dV$  on the capacity  $C$  of the membrane is  $\frac{dQ}{C} = \frac{I*dt}{C}$ , so

$$\frac{d}{dt}V = \frac{I}{C}$$

The *constant* current input to the neuron causes a constant membrane's voltage derivative contribution. However, the currents are not necessarily constant; especially not for neuronal spikes. If the artificial current follows a math function, *the time derivative* of that function should be used. In the case of a native current (i.e., receiving a spike from a presynaptic neuron), the received input has the form of PSP, where the time derivative can be well approximated by a steep exponential function, see Eq. (2.37) (see the middle inset in Fig. 3.9).

HH's original Eq.(1) (reproduced here as Eq. 2.40) explicitly says that the total current is the total membrane current divided into capacitive current plus the ionic current. When we rearrange HH's Eq.(1) into the form (to compare it to the correct right entity in Eq.(2.42)),

$$\frac{d}{dt}V_{OUT} = \frac{1}{V_M C_M} \frac{I}{C_M} - \frac{I_i}{C_M} \quad (2.42)$$

However, it is valid only in the clamping condition's steady state, i.e., in the "freezed" state of the neuron. We see that *the equation (in the function of the time) is true only if in artificial mode the clamping (due to the feedback) adds a foreign difference current (not present in the equation) or in native mode the neural condenser and the upstream neuron agrees to produce the exact shape of the action potential*. For a working neuron, the condenser current follows the laws of the oscillator and the ionic current follows the distribution we know from the PSP. Consequently, *their gradients change in time differently, and that is the reason of forming an AP*.

Notice also the differences, that HH's ionic current *decreases* the voltage derivative, our one *increases* it, and in their case the resistive current is the difference between the total current and the ionic current, while in our case the current that flows out through the AIS equals the sum of the input currents, but they have a different time course: the neuronal condenser stores some charge for a while.

#### 2.4.9 Ions' dynamics

As a kind of consistency check, for estimating the orders of magnitude of movement's parameters of charged heavy balls.

##### Rush-in speed

If we assume that a 50 mV potential difference exists across the 5 nm thick membrane, it translates to a  $10^7 \text{ V/m}$  gradient [87]. The value of the force acting on a unit charge is

$$F_{Na^+} = 10^7 * 1.60217663 * 10^{-19} = 1.6 * 10^{-12} \text{ N} \quad (2.43)$$

Given that the mass of a  $Na^+$  ion is  $m_{Na} = 3.81915 * 10^{-26} \text{ kg}$ , it causes an acceleration

$$a = \frac{F_{Na^+}}{m_{Na^+}} = 0.42 * 10^{14} \frac{\text{m}}{\text{s}^2} \quad (2.44)$$

The distance  $d$  to travel is the thickness of the neuronal membrane  $5 * 10^{-9} \text{ nm}$  and we assume a continuously accelerating ion, and using  $d = \frac{1}{2} * a * t^2$

$$t_{traverse} = \sqrt{\frac{2 * 5 * 10^{-9}}{0.42 * 10^{14}}} = 1.54 * 10^{-11} \text{ s} \quad (2.45)$$

In this period the ion is accelerated to the speed  $v = a * t$

$$v_{Na^+} = 0.42 * 10^{14} * 1.54 * 10^{-11} = 600 \text{ m/s} \quad (2.46)$$

The current we can attribute to an ion channel, provided that  $10^3$  ions pass through an single ion channel, it means

$$I_{channel} = \frac{10^3 * 1.60217663 * 10^{-19}}{1.54 * 10^{-11}} = 10^{-5} \text{ A} \quad (2.47)$$

(The thermal speed is about an order of magnitude higher. It is in the range of several  $\mu\text{As}$ , for a short period. It is distributed in the spatiotemporal surface of a neuron, and contributes to a current of dozen of  $p\text{As}$ .)

Notice an important difference. The acceleration of an ion is unbelievably large. It is sufficiently large to keep the potential at the same value, provided that the ions must follow a small change, such as due to the "leaking" current through the AIS. Similarly, the ions can 'instantly' follow quick changes such as a square wave gradient. However, if many similar ions are ahead, their repulsion

decreases the acceleration, and the ion travels only at a few  $m/s$  speed. The huge forces and accelerations means that a potential change acts immediately. However, the force decays quickly. The ions start to move 'instantly', but the charge carriers can move only with a limited speed, much below the interaction speed of EM interactions. The effect can propagate only with that lower speed.

See the case of axon: there exist a mechanical constraint that the ions cannot spread through the wall (they must keep the direction), and the ion package propagates as Equs.2.11 and 2.14 describe it.

As shown above, the ions' passage time, is much below 1  $ns$ . To switch that very intense and very short current pulse, one needs an at least as fast switch. The mechanical handling, using mechanical caps, (see the value of acceleration) is not possible. It needs an electronic control, see the layers of the two sides of the membrane.

Furthermore, the time is only slightly higher than the magnitude of molecular transitions. It is highly unprobable, that it can happen  $10^3$  times reconfiguration of long molecule chains can happen in such short periods.

### Rush-in concentration

As we described in section 2.3.7, this sudden concentration change provokes a voltage gradient as described by Eq. (2.22). From that point on, gradients  $\frac{dV}{dt}$  and  $\frac{dC}{dt}$  excite each other, as described by Eqs. (2.8) and (2.9). In simple physical picture, the rush-in ions appearing on the neuron's membrane are confined in the volume formed in an atomic layer on its surface. They attempt to be uniformly distributed. The electric repulsion enables a hyper-viscous behavior for the electric fluid, so the surface – without invasion – would be equipotential. The membrane is an excellent isolator, except at the AIS. Here the ion channels represent a resistance (also limits the current), so a current starts, see section 3.5.4, creating a potential gradient.

Here comes into play the limiting effect of the interaction speed. Given that the electric repulsion is mediated by the concentration, the decrease of the potential can happen with the speed of the slow current in the proximity of the AIS and the ions from the distant region can increase it with their potential-assisted speed. The potential gradient creates a speed gradient in proximity of the AIS, while it remains zero at larger distances. The speed gradient propagates with the speed given by Eq. (2.15) and its delayed effect creates a "ram current" effect, which – in a good approximation – is resemblant to the effect of an  $RC$  circuit. The charge is "stored" (cannot flow out because of the limiting resistor) for some time and at appropriate parameters the neuron behaves as a damped  $RC$  circuit.

### Rush-in charge

Let us suppose we have a simple electrodiffusion, say, positive ions rush-in into the intracellular space of a neuron through the membrane's ion channels, in one packet, about  $10^5$  ions per channel. For all channels, in the order of  $10^2$  channels on the membrane, the number of ions appearing (suddenly, in  $psec$  time per channel (see section 2.4.9) and in  $nsec$  time per membrane) on the surface is only  $10^7$ . This charge appears as current at the beginning of the AIS and moves (the neuron's membrane discharges) without an external potential. The huge difference in the charge density (and concentration) on the membrane's surface and the no-charge at the beginning of the axon can explain why a current flows. (The other way round: ions escape into the volume and they repulse each other; so they will move in the direction of the drain).

The Nernst-Planck equation could explain that the concentration gradient causes a potential gradient, i.e., explain why do we see a current without voltage. However, the number of ions is not surely sufficient to apply thermodynamics. At the same time, the ions exist in a volume having thickness about tenths of nanometer, i.e., the density of the ions can be sufficient to behave as a macroscopic charged fluid in that limited volume. This case is neither "net" macroscopic nor microscopic. On the one side, the Nernst-Planck equation refers to large (on this scale) volume. On the other, evidence shows that dozens of  $pA$  current flows, and behaves in a macroscopic way.

When we assume  $10^7$  rushed-in ions for evoking a single action potential, it means  $1.6 * 10^{-12} Cb$  charge. We take the typical resistance and capacitance values from [21]: we assume  $100 \text{ pF}$  capacitance and  $100 M\Omega$  resistance (i.e.,  $\tau = 10^{-2} \text{ s}$ ). If we assume that the charge flows out in a period of  $10 \text{ ms}$ , we should measure a  $160 \text{ pA}$  current on the axon, furthermore, that current causes a  $160 \text{ mV}$  voltage drop (aka Action Potential) on the resistance. See also section 3.7.3:  $300 \text{ pA}$  flows in a  $5 \text{ ms}$  period. Similar value can be derived from [82]. All those values are in the order of the measured values.

So, the charge from the micro-world can be excellently mapped to the measured macroscopic current. On the other way round, due to the Nernst-Planck equation (2.7), it could be expressed as a consequence of the sudden increase in the concentration (a concentration gradient  $\frac{dC}{dx}$ ) of the chemical ions on the surface. Provided that thermodynamics can be applied to a volume of area of  $10^{-2} \text{ mm}^2$  and thickness say up to  $10 * 10^{-9} \text{ m}$ . With those numbers we arrive at that in that layer the ion density during generating an action potential is  $10^{23} \text{ m}^{-3}$ , which is not far from the numbers where thermodynamics can be applied; so we assume that the Nernst-Planck equation (and the ones we described as "laws of motion of electrodiffusion") can be used to describe why an AP evokes in a neuron.

### Ion selectivity

We assume that in a balanced state, a  $Na^+$  and a  $K^+$  ion are placed at the entrance of the ion channel. According to the calculations above,  $Na^+$  ions

pass the ion channel in 15  $ps$ . At the same time, since the mass of a  $K^+$  ion is  $m_K = 6.492 * 10^{-26} kg$ , and the same force accelerates it, its acceleration

$$a = \frac{F_{K^+}}{m_{K^+}} = 0.246 * 10^{14} \frac{m}{s^2} \quad (2.48)$$

With this acceleration, the  $K^+$  ions traverse in the ion channel a distance only  $d = \frac{1}{2} * 0.246 * 10^{14} * (1.54 * 10^{-11})^2 = 2.92 * 10^{-9} nm$ . That means that when the  $Na^+$  ions already arrived at the low-concentration layer, at that time the  $K^+$  ion passed only  $\frac{2}{3} * d$  distance. If the potential on the arrival side increases due to the already arrived ions, they will experience a repulsive potential, and they will not be able to arrive: they cannot pass the uphill potential barrier and they turn back, with the downhill gradient.

Given the current intensity above, that the ion channels' size is not much larger than an ion, furthermore that the time available for interaction is shorter than the chemical transition time for the molecules,

As shown above, the ions' passage time is incomparably fast compared to the neuronal processes' characteristic time. Furthermore, the time is about two orders of magnitude shorter than the atomic transitions, so it is highly unprobable, that reconfiguration of long molecule chains can be realistic. To switch that very intense and very short current, one needs an at least as *fast switch*. The mechanical handling, using mechanical caps, (see the value of acceleration) is not possible. It needs an electronic control, see the layers on the two sides of the membrane, see section 2.4.4.

An intuitive grasp of concepts of electricity and electrical circuits is helpful for understanding some of the basic theory in cellular neurophysiology.

#### 2.4.10 Measuring

The difficulties of making electric measurement on living matter were known since the beginnings: "Since it is quite generally believed that the depolarization of a nerve fiber membrane, during excitation and propagation, involves an increased permeability to ions there have been many attempts to detect and to measure this change as an increase in the electrical conductivity. ... In these cases the *measuring current was also the stimulating current* and it was not possible to analyze the changes satisfactorily." [40] It is worth to recall that *performing an electric measurement on the operation of some electric system always represents an intervention into the electric process of the system under study*; the question only is how much the measurement influences those operating processes. Measuring the conductance of an isolating membrane, with ion channels in its wall and slow ions flowing in its surface layers, is one of the

hardest measuring tasks. We discuss below some fine differences compared to measuring in metals. We interpret the notions precisely below.

When measuring electric resistance (or conductance), we need:

- Charged objects that can be moved, the charge carriers
- An electric field that moves the charge carriers
- No other field (such as concentration gradient) that moves the charge carriers
- A medium that 'resists' moving the charge carriers

If an electric potential is applied to an ionic solution, the cations of the solution are drawn to the electrode that has an abundance of electrons, while the anions are drawn to the electrode that has a deficit of electrons. The movement of anions and cations in opposite directions within the solution amounts to a current. Notice that the current inside the electrolyte is represented by ions, in the rest of the electric circuit, by electrons; the electrode must convert the charge carrier. The electrode actively participates in the process (even if it is a measurement), and its operation takes time. Recall that the current delivered by the ions means at the same time a change in concentration (transport of material). If the ions can freely change their position, after some relaxation time, the driving forces due to the electric charge and the concentration balance each other as the Nernst-Planck equation describes.

The electric measurement means an intrusion into the measured system. To measure voltage and current (we call them secondary entities), we can minimize the intervention. However, to measure conductance, we must generate charge (see Fig. 2.4): we must apply some voltage to the medium and measure the current with which the medium responds; that is, a foreign voltage falsifies the measurement result. The fact is known in neurophysiology (but either forgotten or not understood), see [1], section A.3.12: "*(input impedance) can be measured by applying a voltage and measuring the resulting current or by injecting a current and measuring the resulting voltage*". We often forget that we concluded the notion for metals and that if the number of moved charge carriers changes during the measurement, or a "foreign" (not considered) force field also affects the object, our measurement will produce fake results; see for example electromagnetic forces and the decades-long history of memristors [115]. Moreover, we assumed an isotropic medium (unlike complex biological objects). The current may delay, disappear, and re-appear in an improperly designed measurement. It is not against the laws of physics; it is due to the incomplete knowledge of physics.

A "conductance meter" device *actively applies a potential that affects the measured object*. It assumes that the tested object is passive (also in the sense that switching that field on causes no structural change in the medium) and it is in a field-less stationary electric state. *The device calculates the displayed result as if the object were metal and no foreign current or voltage was present*. For active components (the measured object actively reacts to the applied voltage,

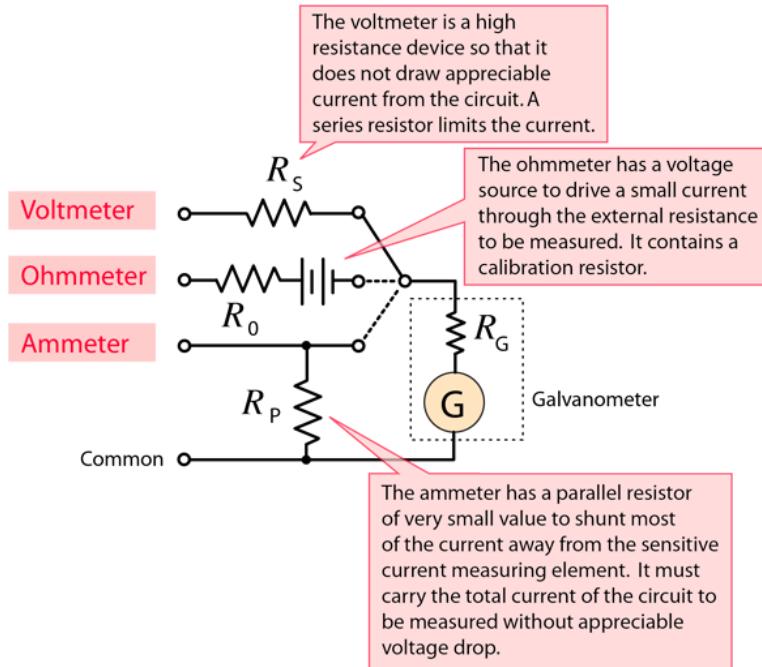


Figure 2.4: Though most modern meters have solid state digital readouts, the physics is more readily demonstrated with a moving coil current detector called a galvanometer. Since the modifications of the current sensor are compact, it is practical to have all three functions in a single instrument with multiple ranges of sensitivity. Schematically, a single range "multimeter" might be designed as illustrated.

"from Hyperphysics by Rod Nave, Georgia State University".  
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and even for resistors used in actively working electric circuits), it provides fake measurement results: it calculates resistance/conductance using Ohm's Law from its input data that contains "foreign" current contribution(s).

It is frequently forgotten that the mentioned processes "produce" electric charge in the measured system. Measuring conductivity actually means measuring current, see section 2.4.4. Somehow, researchers forgot this warning and attributed the created charge to some changed conductivity. In the case of a biological membrane, no charge carriers are present in its resting state. However, the applied voltage may open voltage-controlled ion channels, and the field may move the ions through them. *The device sees its own effect: the voltage it applies generates an ion inflow, moves the ions it produces, and measures the resulting output current.* Recall Eq.(2.26): the current grows as the number of charge carriers  $n$  increases; a real danger when measuring conductance in

the presence of ion channels. Different devices and different settings provide different conductance values for the same membrane. (Assuming some resting conduction in axons is a self-contradiction. To have conduction, charge carriers need to be present, which means the presence of ions that means potential above the resting potential. Those ions flow out to the galvanically connected membrane. *The measurement device generates the "resting conductance" attributed to axons and membrane.* It is a systematic error due to the incomplete understanding of the physics of electric measurements. See Fig. 6 in [5] at high clamp voltage, the device's voltage contribution is insignificant. However, it is at least comparable to the measured effect at low clamp voltage.)

Furthermore, *one must forget to make parallels with the single-speed electric circuits*, especially using their ready-made equations (used outside their range of validity) assuming a voltage generator: biological circuits are different. Biological interactions are governed by more complex laws, especially if interactions at enormously different speeds play a role. However, like in the case of modern versus classic physics, the first principles can provide good hints in the limiting case. If we face a controversy, we apply the wrong basic assumptions and omissions/approximations.

Ohm's Law is valid only in its *differential form*. The charge, whether injected artificially or natively through the synapses into the membrane, needs time to travel from their entry point to their exit. The two definitions are equivalent only if the current's speed is infinitely large (instant interaction) or in other words, it does not depend on the time. The non-differential definition fixes current and makes material's features variable. *The wrong definition rejects known laws of physics and introduces new laws which it does not define. It rejects the first principles of science and introduces empirical laws without understanding them.* The misunderstanding arises from using the wrong abstraction of "electrical node". In classical electricity, the abstraction 'instant interaction' means that the node is discrete and sizeless. *Kirchoff's law implies that the current enters and exits the node simultaneously*, which is not the case in biology. It is a self-contradiction: the change in the current's time course (a charge related electric entity) is transferred to the medium. Due to the wrong definition one simply divides non-matching data value pairs and attributes the effect of the wrong definition (using inappropriate abstraction of "instant interaction") to the process under study. It is the source of a series of misunderstandings and directs physiology towards a wrong direction (it did not ask: why charge conservation is not valid). In classical electricity, in the world of 'instant interaction' the Kirchoff's law is a good *approximation* (but correct books also mention that on a 30 cm piece of wire there exist a 1 ns delay). However, the case is different in physiology: the speed of current is in the range of m/s; there is a "phase delay" between the voltage and the current.

### Capacitance

In the classical theory of electricity, we use the abstraction that the propagation of electric signals is instant and some discrete elements change the electric fea-

tures of the circuits, the wires are only a passive medium. One of the discrete elements is the condenser and one can observe that the voltage on that element is proportional to the charge it stores; we call it "capacity".

When considering the finite speed of the charge carriers, one can identify two components, a resident one and a transient one. The resident capacity means that the ions sit on the surface as we can calculate from the concentration of the ionic solution, see Eq.(2.69). This capacity is estimated by [1], page 12, to be  $1 \mu F/cm^2$  and the surface area  $7.85 * 10^{-5} [cm^{-2}]$ ,  $7.85 * 10^{-11} [cm^{-2}]$ . The number of uncompensated ions  $4.7 * 10^7$ , that raises  $100 mV$  on the membrane.

The transient capacity arises from the finite speed and finite size of the neuron.

**Interfacing biology** Another problem to solve when measuring chemical electrolytes using electronic devices is their interfacing. At some point, the ionic charge must be converted to electrons (there and back), which usually happens in electrolyte electrodes. Interfacing the analyzed electrolytic wire and metallic wire in the measurement circuit introduces problems, not only the contact potentials but also a time delay. These electrodes need to carry the ions to some distance, and that process is outside of the time scale of the primary measured process. The effect is noticed but not explained [5]: "the steady state relation between sodium current and voltage could be calculated for this system and was found to agree reasonably with the observed curve at 0.2 msec after the onset of a sudden depolarization." Moreover, given that *the speed of ions depends on the depolarizing voltage (see Eq. (2.26)), this time gap also depends on the depolarizing voltage*: the higher the voltage, the shorter the time gap, demonstrated in their Fig. 3. As we demonstrate in Figure 3.21, this effect may lead to conclusions opposite to the real ones.

### Voltage/current clamping/patching

The very common measuring method reveals some fundamental differences between the electric behavior of conductors and living matter. "The reason for voltage-clamping the axon is threefold: (1) By keeping the voltage constant, **one can eliminate the capacitive current, that is**,  $I_C = C \frac{dV}{dt} = 0$ ; (2) by keeping the voltage constant, **one can measure the time-dependent characteristics of ion conductances** without the influence of voltage-dependent parameters; and (3) by inserting two silver wire electrodes into the axon, one can space-clamp it so that the **whole length of the axon is isopotential** (silver wires short-circuit the interior of the axon)." [1] That is: (1) the experimenter wants to make sure that  $\frac{dV}{dt}$  does not change. *A late consequence of choosing a wrong RC oscillator model*. In the wrong model, the *integrator*, integrating the currents can be done and the voltage gradient has no role. In the correct model, the *differentiator*, the gradient controls neuron's operation. (2) Clamping introduces extra current (not measured) to the neuronal circuit. From the known relations in Ohm's law, we use the fixed voltage and the sum

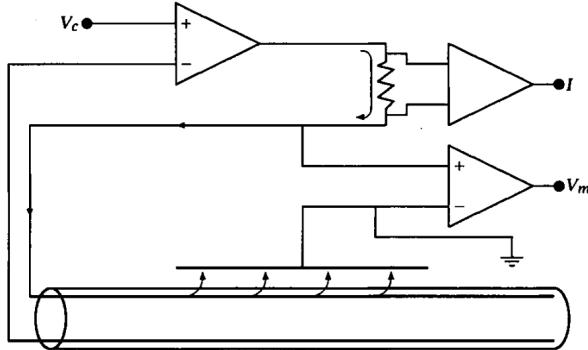


Figure 2.5: (Fig. 6.1 in [1]) "Schematic diagram of the two-wire voltage-clamp experiments on the squid axon. One wire is used for monitoring the membrane potential and the other for passing current. *The voltage clamp amplifier injects or withdraws charges from the interior of the squid axon in order to hold the membrane voltage constant (voltage is clamped at the command voltage,  $V_C$ ).*"

of the 'real' current plus the 'foreign' current, and attribute the observed deviation to that the conductance changed. Actually, the measurement device is not appropriate for that purpose. (3) As we discussed, the ion current is flowing on the thin layer on the internal surface of the axon. There are no charge carriers to deliver the potential from those electrodes to the stream of ions (the ions are pressed to the wall of the axon and the dielectric layer repulses the carriers). This effect is why Hodgkin and Huxley experienced [5] a time delay between a voltage and the current: the axon is not equipotential because it is not a conventional conductor. Again, physiology is resetting the clock: (1) they want to believe that voltage gradients have no role and so they eliminate it (2) they do not want to understand that voltage and current are not independent from the charge and the measuring device changes the measured value (3) they do not want to accept that the charge carrier and the charge transmission mechanism, and because of that, the behavior of the biological systems, are different from those in classical electronics. The low speed of ions hinders the fundamental understanding, mainly of the temporal operation.

Notice two of the common fallacies in the figure. "The highly conductive internal current electrode, which short-circuits the axoplasmic resistance, reducing axial resistance to zero". First, the current flows in the  $< 1 \text{ nm}$  thick layer on the internal surface of the membrane instead of inside the axon. The electrode keeps only the potential of the "bulk" constant, unless the internal electrode fits perfectly (with better than the mentioned size accuracy) into the tube. Furthermore, the membrane's surface can open/close ion channels in its wall, adding foreign current that causes a change in the value of the command potential. Second, there are *two* feedback amplifiers of the figure: the natural one (see Fig. 1.8) and the feedback in the clamp instrument. As we discussed,

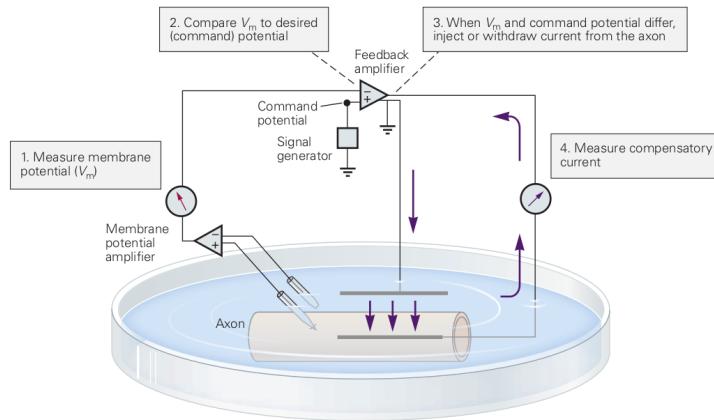


Figure 2.6: "The negative feedback mechanism of the voltage clamp. Membrane potential ( $V_m$ ) is measured by one amplifier connected to an intracellular electrode and an extracellular electrode in the bath. The membrane potential signal is displayed on an oscilloscope and is also fed into the negative terminal of the voltage-clamp feedback amplifier. The command potential, which is selected by the experimenter and can be of any desired amplitude and waveform, is fed into the positive terminal of the feedback amplifier. The feedback amplifier then subtracts the membrane potential from the command potential and amplifies any difference between these two signals. The voltage output of the amplifier is connected to the internal current electrode, a thin wire that runs the length of the axon core. The negative feedback ensures that the voltage output of the amplifier drives a current across the resistance of the current electrode that alters the membrane voltage to minimize any difference between  $V_m$  and the command potential. To accurately measure the current-voltage relationship of the cell membrane, the membrane potential must be uniform along the entire surface of the axon. This is made possible by the highly conductive internal current electrode, which short-circuits the axoplasmic resistance, reducing axial resistance to zero. This low-resistance pathway eliminates all variations in electrical potential along the axon core." (Fig. 7.2 in [39])

only the steady-state measurements can be accurate. The control voltage that is "selected by the experimenter and can be of any desired amplitude and waveform", is misleading: when using non-constant waveform, the system is not in steady state.

See Figure 1.8: "Any conductor that has a linear current-voltage (I-V) curve is said to be ohmic. Not all conductors have linear I-V curves. Most neurons, for example, have nonlinear or nonohmic I-V relations." The neuron is not a simple conductor. "Only a narrow region of the V-I or I-V curves of a neuron can usually be considered ohmic." [1], page 488. When studying its behavior using 'foreign' voltage or current, outside that narrow region, the measuring proce-

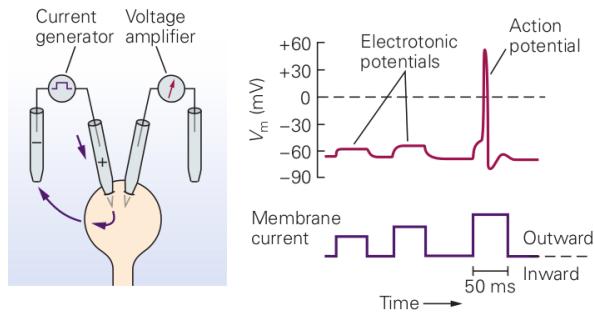


Figure 2.7: (Fig. 6.2c in [39]) Voltage recorded in presence of clamping current.

dure may trigger neuron's own electric processes, and the careless experimenter observes that – from his point of view – 'foreign' contribution as a deviation from the ohmic relations. See examples in section 3.1. "The construction is different from anything we have yet tested in the physical laboratory" [8]; we need to use different methods for that different construction.

### Interpreting cells Ohmic/non-Ohmic behavior

Figure 2.7 shows, how the measurable membrane potential drastically changes in the function of the measuring (clamping) current intensity. At the positions labeled as "Electrotonic potential" the neuron is in steady state: neither its condenser charges/discharges, nor its ion channels open. When starting from the resting potential, the membrane follows a charge-up function, a saturating exponential. We just note here that the shape of the front side may depend on where the current is introduced. If the microelectrode is inserted directly into the cell, the current causes really a charge-up current. If it is inserted to an axon from an upstream neuron, where no charge carriers are present at the resting potential, the axon must let ions in the tube. This effect also results in a saturating voltage, as experienced by Hodgkin-Huxley [5], see Fig. 3.19. In the two cases the timing constants are similar, but definitely different.

The figure enables one to explain what is misinterpreted in biology in connection with Ohm's law (and why using a conductance meter in such a case is wrong). Let us divide the membrane current (labeled as "Membrane current") with the  $V_m$  membrane potential, into regions. In the "flat" regions (in steady state) we receive the same value and the result can be interpreted as "conductance". In those regions the cell behaves 'Ohmic'. However, it is 'non-ohmic' around the rising and falling edges of the test current, furthermore, if the amplitude of the signal is higher than some threshold value. After receiving the rising edge of the measuring signal, the membrane's condenser stores part of the charge. If one knows the laws of electricity, fits a saturating exponential to the curve as the membran potential rises when the condenser charges and the physics is all right. If one believes that the condenser must take instantly

the voltage, might say that  $V_m/I_m$  changes, that is the membrane's conductance/capacitance changes and has a time constant. Similar explanation can be given, when the falling edge arrives and the condenser discharges. When the current exceeds a threshold value, the ion channels in membrane's wall open and an extra current (not from the current generator) flows into the membrane. If one believes that the correct value that must be used in deriving conductance is the one that the test generator provides (and the conductance meter does so), divides the test current (instead of the total current) with the measured membrane potential evoked by the total current, uses non-matching value pairs. Non-understanding physics results in claiming non-Ohmic behavior. Neither the conductance nor the capacitance of a cell changes under the effect of electric test signals. Only the measurement is wrong.

**Measuring electrolytes** Substances that give ions when dissolved in water are called electrolytes. Certain chemical elements can naturally hold a positive or a negative electrical charge, and they react to their micro- and macro electric environment. A molecule has internal attraction forces that keep its ions in place, and has two charge centers (dipoles). When another dipole or a macroscopic external electric field (which can be of electrical or chemical origin) appears near the molecule, its perturbing effect can affect the relation of the ions to each other. Initially, the two charge centers increase their distance (the molecule polarizes). When that disturbance is strong enough, the ions can entirely separate (the molecule ionizes). The local electric field fluctuates, so the state of the ions is dynamic: they dissociate, the free ions recombine. The ions can exist in ionized and polarized states. The state (and behavior) of ions depends on their environment.

A small part (about  $10^{-3}$ ) of the molecules dissociates (i.e. the ions leave their counterpart with opposite charge behind) and they move freely in the volume. In other words, the electrolyte liquid can then conduct electricity due to the mobility of the positive and negative ions, which are called cations and anions, respectively. The rest of molecules can be in a more or less polarized state, providing a possibility of producing internal electric field. The macroscopic state of the molecules depends on, for example, how far they are from the boundary of the segment; whether global or local external invasion is applied.

Thermoelectric experience shows that, when applying such changes, reaching a steady state is a temporal *process*, and even the spatial and temporal development of the concentration gradients can be measured as individual processes (the voltage gradient is too fast to measure it). It is also evident from experiments that diffusion is a fast *process* and that the propagation of the electrostatic field is unimaginably fast ; see our discussion around Eq. (2.22), but it must be process, too. In other words, we have two enormously different interaction speeds. Eq. (2.7) provides only position derivatives. However, Eq.(2.11) and Eq.(2.14) provide the time derivatives for describing the time course of the processes.

In physiology, electrolyte solutions do not surely satisfy the conditions we use for the notions of electricity in physics, see section 2.4. The number of charged

objects (the ion concentration) may change in time (even without the presence of biological structures), and a chemical driving force may also move the objects independently from the electrical field. When measuring only the macroscopic electric parameters voltage and current, and especially when measuring current believing we measure directly conductance; in addition, measuring it in a wrong way; (for the details see section 2.4.10) *we attribute the consequences of the injected charge carriers' low propagation speed to the medium* and we describe the phenomenon that "the conductance changes" in the function of the voltage [117]. (We know that the macroscopical speed of current changes with the clamping speed, see Eq.(2.33 and section 3.7.1), that might change the time difference between the non-matching value pairs, leading to the illusion that the conductance changes.) The measurement must be fixed: the tacit assumptions about notions of electricity must be fulfilled.

Conductance is a "steady-state" notion; see its definition in section 2.4.10 and in section A.3.12 in [1]: "the input impedance measured *after the voltage has reached a steady state* following a step change in injected current is defined as input resistance", or "the input resistance ... obtained by dividing the *steady-state* voltage change by the current using it" [21]. *Using quickly changing (alternating) currents, either sinusoidal or random for measuring conductance, measures some ill-defined current.* The experience is resemblant to studying dielectric dispersion in physics. "Because there is a lag between changes in polarisation and changes in the electric field, the permittivity of the dielectric is a complex function of the frequency of the electric field." Rearranging charges inside the tested medium needs time. Different polarization types have similar behavior, at much higher frequencies, because of the much shorter distances that rearranging the charges need. In the case of neurons, charges must be rearranged on nearly 0.1 mm distances, and "can no longer follow the oscillations of the electric field" at much lower frequencies; see section 3.8.8. Yes, "the construction is different from anything we have yet tested in the physical laboratory".

Physiologists seem to forget the definition and they measure something they think to be "conductance" in non-steady state. They are "resetting the clock", instead of explicitly admitting that the current speed is finite; despite that they measure it to be in the few  $m/s$  range. The conductance (per definitionem) does not change; only the (maybe: foreign) charge carriers may need time to deliver the current: *we calculate the conductance from non-matching value pairs* (or not-steady-state). Wording that biological systems show "non-ohmic behavior" means that they are not metals (they have a charge transfer mechanism differing from the "free electron cloud"): we abstracted the notion of conductance for metals (or at least steady-state). Physics describes biological operations perfectly; although, it may use 'non-ordinary' laws. Electric operations are also ohmic in biology, but one has to use the correct (time-aware, i.e., considering the speed of the charged carrier) interaction speed, correct definition and measurement method. *Using the Newtonian 'instant interaction' as the speed of charged ions or the macroscopic speed of their current, is a catastrophic hypothesis and contradicts all our phenomena.*

The ohmic behavior means that voltage and current relate to each other, as we learned in college, only when the electrostatic interaction speed is very high (in the mathematical/physical description, the interaction is instant); furthermore, free charge carriers are present in the volume. In biological systems, it is not necessarily the case: the macroscopic speed of ionic current conveying electrostatic interaction is very low, and so they may follow the electrical field propagation apparently with a time shift (if they are improperly distributed, as was early explicitly noticed [5]). As Fig. 3.24 displays, when measuring the secondary entities (instead of a ternary one), everything comes to the right: the voltage and current change using the same time course. Of course, as they are derived from the same primary entity 'charge'. One should *measure* the voltage instead of *assuming* the potential appears immediately, even without charge carriers (the locally present individual charges generate the potential). Furthermore, one should not introduce a foreign current into a system (by measuring its conductance or fixing its electric state by adding some feedback current by clamping/patching) when studying the electrical features of that system.

**Electrical and chemical invasions** When thermal or electrical invasion happens, the ion's distribution changes. (Above we assumed an infinitely large volume. Limiting the volume's size means an asymmetry for the ions in the volume and brings to light unexpected phenomena.) We must also discuss another fallacy that the structured biological objects behave as the metals do under the effect of electrical forces. To derive an abstraction similar to the ones as sciences derive their Laws, we assumed that the ions are tiny charged heavy balls, and they attempt to have a uniformly distributed concentration and potential in the considered space segment. We discuss the cases when an external electrical invasion happens in one segment, when an external chemical invasion happens in one segment, the case when a physical surface mechanically separates the ions in two neighboring segments with different features, when the two separated segments are not symmetrical due to 'Maxwell-demon'-like transmit gates (semipermeable membrane); and when a physical effect concerns the operation of the demons.

The cellular electrodiffusion phenomena are very complex, and it is not a simple task to choose which physical/chemical effects can be omitted so that their omission does not prevent us from explaining physiological phenomena. We discuss mainly the commonly used fundamental omission that the speed of ionic movement cannot play a role in describing neuronal operation.

See also section 2.7.4.

## 2.5 Electrolyte's electricity

It was already guessed that the membrane's resting potential is of electrostatic origin [118, 66, 68, 67, 119]. When ions are confined in a closed volume, they exist in a state of thermodynamic and electrical equilibrium. However, those equilibrium states cannot be discussed independently. We must discuss them in

a non-disciplinary way because the participating ions belong simultaneously to the disciplines of electricity and thermodynamics; furthermore, we must cross the borderline between discrete and continuous points of view of nature [19]. Furthermore, the features of living matter may change when measured in physics laboratories as usual. When measuring them, we must consider that "the construction is different from anything we have yet tested in the physical laboratory" [8].

In the absence of external influences (that includes the lack of a separating membrane), both gradients are balanced and are at zero. When something perturbs this state, the system attempts to find a new balanced state, using temporal processes. The details of how it reserves and restores its balanced state are discussed in section 2.8. In this scenario, two interactions can influence the 'carrier' (the ion). We discussed in section 2.3 and in [19] that those phenomena in living matter need deriving and applying 'non-ordinary' laws of science, and the laws of motion of biology can describe the time course of those processes. Fundamentally, due to the mixing of interaction speeds, considering only one of the interactions leads to fundamentally incorrect conclusions.

### 2.5.1 Electrolytes

Specific chemical substances can naturally hold either a positive or negative electrical charge and react to their micro-, macro-, electrical and thermodynamic environments. A molecule has internal electric forces that keep its ions in place, so it has two charge centers (dipoles). When another dipole or a macroscopic external electric field (which can be of electrical or chemical origin) appears near the molecule, its perturbing effect can affect the relation of the ions to each other. The two charge centers initially increase their distance (the molecule polarizes). When that disturbance is strong enough, the ions can entirely separate (the molecule ionizes). The local electric field fluctuates, so their state is dynamic: the molecules dissociate, and the free ions recombine. Depending on their environment, the substances can exist in base, ionized, and polarized states (and behaviors).

In biological cells, a small portion (approximately  $10^{-3}$  part) of the molecules dissociates (i.e., the ions separate from their counterparts with opposite charges), and they move freely within the volume. In other words, the electrolyte liquid can then conduct electricity due to the mobility of the positive and negative ions. Notice, however, that, unlike the electrons in solids, the ions do not form a "free electron cloud": they must move "in person", that is they deliver charge with the speed of the carrier. The rest of the molecules can be more or less polarized, allowing for the possibility of producing an internal electric field in the solution. Here comes into the picture that in the biological structures, the ions are in a closed space and counterforces may exert on them. When a mechanical counterforce does not keep back an ion, it moves out from a space where electrical or thermodynamic gradient is present. That is, near biological objects that are charged and inside them, in a balanced state, no freely moving ions can be present.

The cellular thermoelectric phenomena are very complex, and it is not a simple task to choose which physical/chemical effects can be omitted so that their omission does not prevent us from explaining physiological phenomena. When ions are contained in a closed volume, they exist in a state of thermal and electrical equilibrium. In the absence of external influences (that includes the lack of a separating membrane), both gradients are balanced and are at zero. When this state is perturbed, the system attempts to find a new balanced state, using temporal processes. In this scenario, the 'carrier' - the ion - can be influenced by two different types of interactions, each represented by a distinct abstraction in these processes. In this section we discover some conditions how electric charges in electrolytes, furthermore, electrical and thermodynamical processes (excluding biochemical details) cooperate for concerting processes commonly called 'life'. We discuss that those phenomena are not against the laws of science, only against discussing them in terms of a single grasped science discipline. Simply, the structures in living matter shall be discussed at another abstraction level, and those structures need deriving and applying 'non-ordinary' laws of science.

More precisely, we must discuss them in a non-disciplinary way, due to that the participating ions belong simultaneously to the disciplines electricity and thermodynamics. When measuring them, we must consider that "the construction is different from anything we have yet tested in the physical laboratory". Actually, ions' behavior is not different; the environment ("the construction") is different; see section 2.3.1. Fundamentally, due to mixing interaction speeds, considering only one of the interactions (the disciplinary discussion) leads to wrong conclusions.

We discover that in segmented electrolytes, the interplay of disciplines, especially if the segments have largely different concentrations, produce very thin but important layers, which, by using 'dynamic layer Maxwell's-demon'-like objects, produce self-contained phenomena known as 'signs of life' in biology. Furthermore, the features of living matter may change during measuring them (by their internal laws) in a way usual in physics laboratories. Given that, in many cases, inappropriate physical principles, notions, and methods are used in measuring and modeling neurons, we need to discuss the true physics (the correct approximations, valid in cross-disciplinary approach) behind biological phenomena.

### 2.5.2 Inhomogeneities in the solution

In a segmented electrolyte we experience different forces, furthermore, the electric fields have different sources. For a closed system, the electric charges are balanced, but locally they may be unbalanced due to physical reasons. In a steady state, some other force must counterbalance the mentioned forces. That force may be a mechanical one: the ions sitting on the surface of the membrane press the surface due to the attractive force on ions and the membrane mechanically provides the needed counterforce. In addition, due to a concentration gradient, a thermodynamic force may act on the ions.

When any inhomogeneity is present (an ion is forcefully moved, by investing

energy, to a place other than the one which is needed to be in a steady state), the ions may move due to different reasons, which, per definitionem, means current (and means potential energy). Notice the important aspect that, at a microscopic level, moving an ion simultaneously means redistributing charge and mass. At a macroscopic level, it results in simultaneous changes in the local macroscopic characteristics such as concentration and potential. These observations are expressed by Onsager's reciprocal relations [110].

That means when describing an ionic transfer process, *we must not separate the electric current from the mass transfer*: they happen simultaneously, and mutually trigger each other. Notice that *the thermodynamic term is ion specific, while the electric term is not*. To be entirely balanced, the system must be balanced to all elements. In this way, changing one concentration implicitly changes all other concentrations and the electric field.

It is a huge mistake to introduce equivalent electrical circuits with their fixed-voltage voltage generators. It forces one to assume that the conductances of the players (membrane, synapses, AIS) change without any reason, and prevents understanding how the competition of the thermodynamic and electric processes govern neuronal operation. It leads, among others to attributing conductance change to membranes which are simple isolators with no charge carriers that could implement charge transfer, see section 2.4.4. This assumption neglects the driving force the mentioned forces provide. Instead, it attributes the magic ability to the ion channels that they can change their transmission ability as the actual situation requires, without having driving force. This approach obscures that biological electricity is of thermodynamic origin, and block understanding neuronal operation, that is the brain's understanding.

### 2.5.3 Deriving "thermodynamic electrical field"

We assume that, in a balanced state, the concentrations on the two sides of the membrane are  $C_k^{ext}$  and  $C_k^{in}$ , respectively; furthermore we assume that

$$\frac{dC_k}{dz} \approx \frac{C_k^{ext} - C_k^{in}}{d}$$

To simplify the math writing, we neglect the change caused by considering the difference (maybe we should apply a near-unity factor); we use the larger concentration magnitude instead. Using the constants and  $T = 300$ , and that  $U = E * d$ , we can derive the equivalent "thermodynamic electric field" for the case of a permeable ion channel in the membrane

$$E_{thermal}^{C_k} = -\frac{RT}{q * F} \frac{1}{C_k^{ext}} \frac{C_k^{ext} - C_k^{in}}{d} \approx -\frac{RT}{q * F} \frac{1}{d} \quad (2.49)$$

It does not depend on the concentrations and depends reciprocally on the membrane thickness (given in nm); furthermore, it is valid separately for all  $C_k$

$$E_{thermal}^{C_k}(d) = -2.585 * 10^{-2} \frac{1}{d} \left[ \frac{V}{m} \right] \quad (2.50)$$

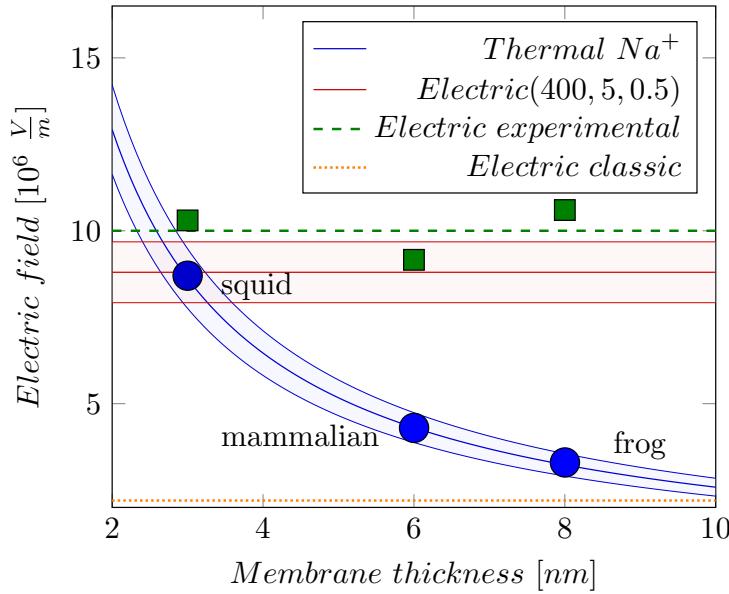


Figure 2.8: The thermodynamic "electric field" depends on the membrane's thickness, see Eq.(2.50). The electric gradient depends on the charged layer's concentration and thickness; see Eq.(2.68). The dots mark measured data shown in Table 3.1.

For a 5 nm membrane thickness, it results in  $5.17 * 10^6 \frac{V}{m}$ , which compares well to the the electrically derived value delivered by Equ.(2.68). Figure 2.8 depicts its dependence on the membrane's width and how it compares to the charge-generated electric field. Correspondingly,

$$U_{\text{thermal}}^{C_k}(5) = -25.85 \quad [\text{mV}] \quad (2.51)$$

In simple words, the Nernst-Planck equation states that the changes in concentrations of ions create changes in the electric field (and vice versa), and in a stationary state, they remain unchanged. Notice that in the case of an ion mixture, a joint charge-generated electric field exists, and they equal, per ion, the concentration-generated "electric fields", see section 3.4.

In the steady state, in contrast with the case of an ion in the infinite space, some other forces also contribute to the mentioned ones. To discuss how nature restores the steady state when a microscopic change occurs in a balanced state

of a biological solution, we write the well-known Nernst-Planck equation (see Eq.(2.7)) in a slightly extended form:

$$\underbrace{(-F_{constr}(z))}_{\text{Constraint}} = \underbrace{e_{el} * E_{Gap}^{Total}(c, \Delta z)}_{\text{Electrical}} + \underbrace{e_{el} * E_{thermal}^{\textcolor{red}{C_k}}(d)}_{\text{Thermodynamical}} \quad (2.52)$$

$$\underbrace{(+F_{Transp}(z))}_{\text{Transport}} \underbrace{(+F_{Invasion}(z))}_{\text{External}} \quad (2.53)$$

We multiplied the usual two terms by the elementary charge, so its terms are expressed as forces, plus we added an external force (its role is discussed below). Furthermore, changing one force triggers a corresponding counterforce and/or causes the ion to move in a viscous fluid. That is, the speed of the material transport gradually changes as the steady state approached; furthermore, it is by orders of magnitude smaller than the speed of the interactions. When neuroscience teaches that "pumps that maintain ion gradients ... transport ions against their electrical and chemical gradients" [39], page 101, one shall ask what kind of force acts on the ion, keeping in mind E. Schrödinger's opinion that not "any 'new force' or what not" [8] affects ions' motion.

An interesting option is when the counterforce combines two disciplines. When  $Na^+$  ions rush-in at the beginning into the membrane, they produce simultaneously a huge electrical and thermodynamic gradient. The repulsion among the ions creates a huge mechanical pressure that presses the elastic membrane. The counterforce starts a mechanical shock wave (soliton) [59], that is simultaneously an electrical potential wave [72] that is measured as AP. Only using cross-disciplinary discussion (non-ordinary laws) enables understanding neuronal operation. That means when describing an ionic transfer process, *we must not separate the electric current from the mass transfer*: they happen simultaneously and mutually trigger each other. Notice that the thermodynamic term is ion-specific while the electric term is not. To be entirely balanced, the system must be balanced to all elements. In this way, changing one concentration implicitly changes all other concentrations and the electric field.

It was a colossal mistake to introduce equivalent circuits with their fixed-value voltage generators. It forces one to assume that the conductances of the players (membrane, synapses, AIS) change without any reason and prevents understanding how the competition between thermodynamic and electric processes governs neuronal operation. It leads, among others, to attributing conductance change to membranes, which are simple isolators with no charge carriers that can implement charge transfer, see section 2.4.4; this way attributing the change of an electric entity to the biological material. This assumption neglects the driving force the mentioned forces provide. Instead, it attributes the magic ability to the ion channels that they can change their transmission ability as the actual situation requires.

When discussing balanced states, no transport occurs, so the transport force cancels, and the mobility has no role. The counterforce adapts to the situation. That force may be a mechanical one: the ions sitting on the surface of the membrane press the surface due to the attractive force of ions, and the membrane

mechanically provides the needed counterforce. If the boundary of the segments is not freely penetrable, the counterforce equals the difference between those two forces. In this way, no force acts on the ions; the two gradients persist. When the ions can move freely between the segments, they will move until they produce a concentration gradient (a thermodynamical force) for the given ionWhen neuroscience teaches that "pumps that maintain ion gradients . . . transport ions against their electrical and chemical gradients" [39], page 101, one shall ask what kind of force acts on the ion, keeping in mind E. Schrödinger's opinion that not "any 'new force' or what not" [8] affects ions' motion. that counterbalances the electrical gradient (the electrical force) and then the transport stops. A transport force is needed to reach the Stokes-Einstein speed (see Eq.(2.33)) in a viscous fluid.

We must not forget that initially, the Nernst-Planck equation described a transfer process (i.e., a dynamic equation), assuming the same speed for mass and charge transfers. We used it only to describe the balanced state (i.e., a static equation at zero speed) and added the term describing external (such as mechanical constraint) force that may be involved; it affects the process, but it does not belong to either of the respective fields. Commonly known mechanical constraints appear in a non-conducting layer called the membrane, where that counterforce prevents ions from penetrating the membrane layers. A membrane is a perfect isolator, i.e., no charge carriers exist between its two surfaces, so it is senseless to introduce the notion of its conductance. (There may be ion channels that deliver ions built into the membrane, but it is a different subject.) The separation results from *charge separation*, a mechanism distinct from *polarization*, as typically described in most biology textbooks. In the form we derived, the equation correctly describes the ion transfer, a current conveying ions with the speed controlled by the actual gradients, instead of assuming an ion current traveling with the apparent speed of electric current in solids.

We must not forget that originally the Nernst-Planck equation described a transfer process (i.e., a dynamic equation), assuming the same speed for mass and charge transfers. We used it only to describe the balanced state (i.e., a static equation, at zero speed), and added the term describing external (such as mechanical constraint) force may be involved; it affects the process, but it does not belong to either of the respective fields. Commonly known mechanical constraints are a non-conducting layer, called membrane, where that counterforce prevents ions from penetrating the membrane layers. A membrane is a perfect isolator, i.e., no charge carriers exist between its two surfaces. (There may be ion channels, that deliver ions, built into the membrane, as we discuss in section 2.7.3, but it is a different subject.) The current clearly results from charge separation; a mechanism distinct from polarization most biology textbook uses. In the form we derived, the equation correctly describes the ion transfer, a current conveying ions with the speed controlled by the actual gradients, instead of assuming an ion current traveling with the apparent speed of electric current in solids.

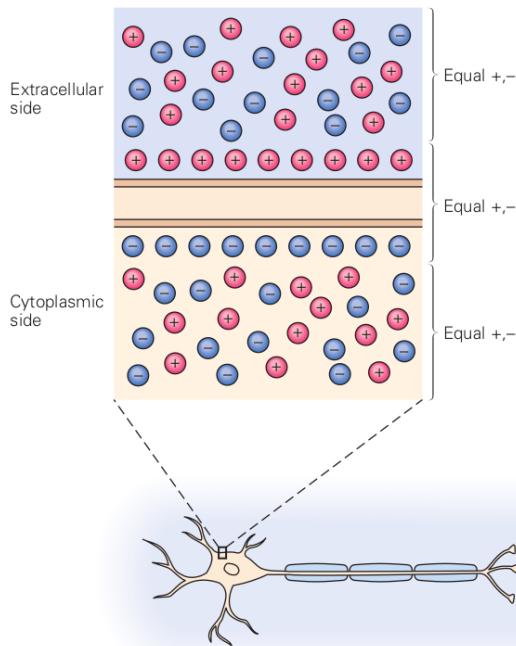


Figure 2.9: The cell membrane potential results from the separation of net positive and net negative charges on either side of the membrane. The excess of positive ions outside the membrane and negative ions inside the membrane represents a small fraction of the total number of ions inside and outside the cell at rest. (Fig. 6.1 in [39])

#### 2.5.4 One segment

We prepare a tiny electrolyte volume filled with a solution containing ions (such as  $Na^+$ ,  $K^+$  and  $Ca^{2+}$ ; furthermore, of course  $Cl^-$  or similar). The overwhelming majority of those ions is chemically bound, but a minority might exist separately from each other; especially under external macroscopic changes applied to the volume. For the discussion below, we assume that the segment has a two-dimensional surface boundary (see Fig. 2.9) and we discuss the gradients along a line, perpendicular to that plane surface. We compose the segments from such layers (sheets), ( $x, y$ ) parallel plates, and describe the gradients in direction of  $z$ . Having the membrane's shape in mind, we introduce the idea of 'thin physical layer', that is parallel with the membrane and has a finite width. We compose the segments from such layers having different potentials.

In the calculations below, we need the notion of 'surface charge density' (interpreted for an 'infinitely thin layer' in physics; given in  $C \cdot m^{-2}$ ). We know that 1 mM concentration means that  $6.023 \cdot 10^{20}$  atoms are present in  $1 \text{ m}^3$ .

We can derive (assuming singly-charged ions) the *volume charge density* (the concentration  $c$  is given in  $mM$ )

$$\sigma_V(c) = c * N_A * e_{el} = c * 6.023 * 10^{20} * 1.602 * 10^{-19} \quad (2.54)$$

$$= 96.4 * c \left[ \frac{C}{mM * m^3} \right] \quad (2.55)$$

where  $N_A$  is the number of ions in a *millimol* and  $e_{el}$  is the elementary charge. By assuming an arbitrary 'physical ion layer thickness'  $\Delta z$  we can calculate the *surface charge density*  $\sigma_A(\Delta z)$  we need for our calculations below as

$$\sigma_A(c, \Delta z) = 96.4 * c * \Delta z \left[ \frac{C}{mM * m^2} \right] \quad (2.56)$$

Below, we interpret classical physics's notions from the theory of 'continuous' electricity, interpreted for 'infinite' cases, for the finite world of biological objects ('living matter') and the atomic world of ions. We know the permittivity of free space

$$\epsilon_o = 8.854 * 10^{-12} \left[ \frac{C}{V * m} \right]$$

From the theory of electricity we know that a charged layer generates a field

$$E_z(c, \Delta z) = \frac{\sigma_A(c, \Delta z)}{2 * \epsilon_o} = 5.45 * 10^3 * c * \Delta z \left[ \frac{V}{m nm * mM} \right] \quad (2.57)$$

We assume that when ions are present in an electrolyte having concentration  $c$  in a 'conducting layer' of thickness  $\Delta z$  on an isolating surface, they produce such an electric field. Furthermore, we assume that the electric field is formed (after integrating the contributions of the rings over the surface) as shown in Fig. 2.10 (for deriving that equation, see section 2.5.5). Notice that here we run into conflict between the 'infinitely thin' layer of physics and the biologically implemented (finitely) 'thin physical layer', so we use a thickness parameter  $\Delta z$ .

### 2.5.5 Two segments

Let us separate the volume into two segments and compose the segments from 'thin physical layers' (sheets) having different concentrations (and such potentials) of ions. We assume the membrane is transparent for the electrical interaction (the electrical field affects the ions in the other segment on the other side of the membrane) but not for their masses (mechanically separates the segments). Separating a volume into two segments by a thin membrane has no initial effects: it actually does not affect the electrical and thermal distributions; the *bulk* concentration and potential remain the same on the two sides of the membrane (even the double layers are electrically neutral).

We consider the immediate environment of the neuron's membrane as adjacent parallel ( $x, y$ ) plates and find the electric field's  $z$  component of those plates

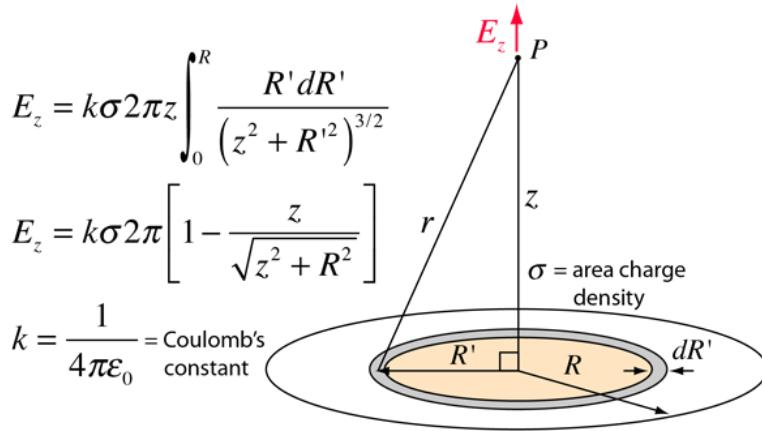


Figure 2.10: The electric field of a disc of charge can be found by superposing the point charge fields of infinitesimal charge elements. This can be facilitated by summing the fields of charged rings.

in the points as shown in Fig. 2.10. In classical electricity, the charge remains on the surface of the conducting layer and the electric field is zero inside the conducting layer; the electric field contributions cancel each other. In electrolyte segments, (a tiny fraction of) the molecules decompose into ionized state (dissociate), see Fig. 2.9, and the created ions interact with a bounding membrane using a not entirely understood mechanism [120]. Although not explicitly, we consider electric double layers to be present proximate to the membrane and ions of the dispersion medium are adsorbed on the particle's surface; depending on the chemical features of the medium.

Although it is not discussed in the classical textbooks, the rest of the dipole molecules get polarized, but do not dissociate; in this way forming virtual charges. Unlike in the conductors, the electrolyte segment next to the surface layer contains dipole molecules, that have more or less balanced charges (the polarization depends also on the external electric field), so they have much less mobility than the dissociated ions: their size and mass is by orders of magnitude bigger and their electric force is a fragment of that of the ions. Their charge is virtual: it comes to light only in the appropriate environment, but creates an electric field in the same way as real charge does. The final reason of creating virtual charges are real charges and/or external fields, so an electric field due to virtual charges can exist also inside dielectric matters such as biological cells.

### Charge layers in segment

Figure the ionic basis of a membrane potential shows and explains the case introduced by separating the cell into two segments by a finite-width membrane; although does not explain even qualitatively, *why* the ions behave apparently

against the laws of thermodynamics: the left and right sides of the figure are apparently identical. On the left side (the case of infinitely thin membrane), at an exact balance of charges on each side, the potential across the membrane is zero. We explain that the finite thickness will result in a lack of balance (introduces inhomogeneity and creates a voltage and concentration gradient) proximal to the surfaces of the membrane, even if the concentrations on the two sides are the same. Changing the bulk concentration or potential in one of the segments creates a corresponding gradient across the separating membrane that increases the inhomogeneity proximal to the membrane. The ions will experience an extra force due to the gradient, but the mechanical counterforce of the membrane will keep them back in the segment. The *concentration and potential, inseparably and having the same time course*, will change across the two sides of the membrane just because of the gap's physical features the membrane represents.

We consider that the segment is composed of electrically conducting discs (the ions are free to move on the surface) and the charged discs' contribution to the electric field at point  $P$  (see Fig. 2.10) can be calculated as known from the theory of electricity. Due to the symmetry in direction of  $z$ , in a homogenous solution, the resulting electric field in the plane perpendicular to direction  $z$  is zero: we have contributions of the same size with opposite signs.

Here we used the abstraction of an infinitely thin "charged sheet" and that there is a step-like gradient in the electric field in the gap. The physical reality is that the charge is represented by ions, which simultaneously represent a mass; furthermore, the thickness of the surface layer they form is by orders or magnitude thicker than the layer that the electrons form. In an equilibrium state, the forces due to the voltage and concentration gradients (see Eq.(2.7)) must be counterbalanced by an external force. An interference between science disciplines can also manifest here. We know at the same time that at the boundaries of electrolytes, different interfaces, including electrically neutral electric double layers, can be formed by only partly known processes [121]. The presence of those structures makes drawing quantitative conclusions hard.

### Simple conducting sheet (a classical condenser)

When discussing the internal electric operation of a neuron, first we consider a condenser that obeys laws of classical electricity and has the geometrical size of a biological neuron. We apply the physics terms to that pseudo-biological object and test whether the values we derive are consistent with physiological phenomena. A tiny (according to [1], page 12, about  $2 * 10^{-3}$ ) portion of the positive ions leave their negative counterions behind and form a thin positively charged ion layer on the surface of the membrane (of course, the same happens on the opposite side with negative ions). Experience shows, that – also in biology – two very thin (but not infinitely thin) layers of ions are formed on the two sides of the membrane, see the caption of figure (Fig. 11.22 in [87]): "The ions that give rise to the membrane potential lie in a thin ( $< 1 \text{ nm}$ ) surface layer close to the membrane". The two surfaces get covered by a sub-nanometer-thick

conducting layer, on the top of a  $5\text{ nm}$  nanometer thick insulator. So, we model the cell with two finite-width "conductive sheet" layers. These layers represent an electric condenser (so we can calculate the internal electric field between the plates) and they counterbalance each other's electric field outside the condenser. We may assume that the solid surface represents the needed counterforce to keep the charges in rest.

One cannot expect geometrically plane surfaces: there are some biological objects of up to  $1\text{ nm}$  size on the surface. So, we assume a physical 'uniformly charged sheet' with an average thickness  $\Delta z = 0.5\text{ nm}$  on the surface. For the sake of simplicity, we assume a step-like function for the electric field. It is zero in the segment outside the "conducting sheets" (the 'bulk' portions) as well as inside the sheets. Between the sheets, it jumps to the value of the electric field of a charged sheet with surface density  $\sigma_A$  (see Eq.(2.56)). (In this picture we see that there is a jump in the value of the electric field (and so: in the force acting on a charge) in the two sides of the physical layer. Here we still assume that a mechanical counterforce due to surface's roughness keeps the charges in place inside the charged layer.)

We assume that all unbalanced (dissociated) ions are in the layer, and the rest contains no dissociated ions, furthermore, that the ions' concentration is unchanged in the segment. By assuming a  $0.5\text{ nm}$  thick layer on the surfaces of the membrane, our model delivers an electric field (see Eq.(2.57))

$$E_{Classic}^{Gap}(c, \Delta z) = E_z(c, \Delta z) = 4.45 * 10^3 * c * \Delta z \left[ \frac{V}{m \text{ nm} * mM} \right] \quad (2.58)$$

In the case of a  $400\text{ mM}$  solution and a  $0.5\text{ nm}$  'thin physical layer' it evaluates to an electric field

$$E_{Classic}^{Gap}(400, 0.5) = 0.11 * 10^7 \left[ \frac{V}{m} \right]$$

and at a  $5\text{ nm}$  membrane thickness the voltage across the plates becomes

$$U_{Classic}^{Gap}(400, 0.5, 5) = 2 * E_{Classic}^{Gap}(400, 0.5) * 10^{-3} * d = 10.84 \text{ [mV]} \quad (2.59)$$

The number of uncompensated ions needed for the cell, using the method in [1], is  $0.88 * 10^7$ . Remarkably, the calculated values are about by a factor of 5 lower than the experimentally derived values. "An electrical potential difference about  $50 - 100\text{ mV}$  ... exists across a plasma membrane only about  $5\text{ nm}$  thick, so that the resulting voltage gradient is about  $100,000\text{ V/cm}$ " [87]. "The number of uncompensated ions needed for the cell is  $4.7 * 10^7$ " [1]. We are in the right order of magnitude but we arbitrarily assumed a layer thickness, a non-dielectric medium. Furthermore, given that the charges are distributed uniformly in the layer, the electric field changes linearly between the two sides of the conducting sheet. The deviation from the experienced values suggests that the dipoles' presence in the electrolyte bulk significantly changes the achievable electric field and potential across the plates. Our simple model seems to be a strong oversimplification.

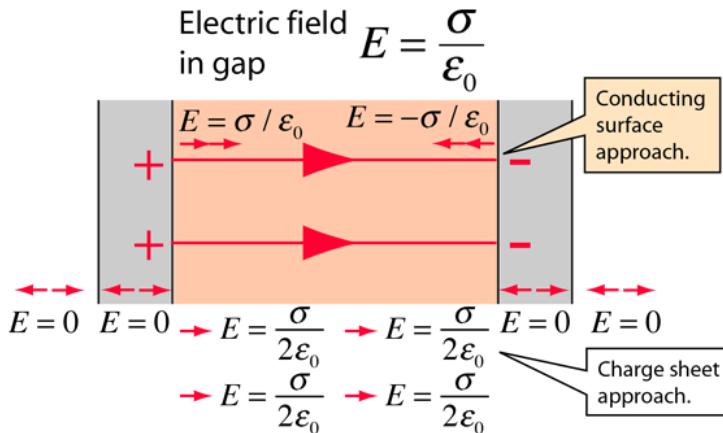


Figure 2.11: The oppositely charged parallel surfaces of the membrane are treated like conducting plates (infinite planes, neglecting fringing), then Gauss' law can be used to calculate the electric field between the plates. Presuming the plates to be at equilibrium with zero electric field inside the conductors, then the result from a charged conducting surface can be used.

If the distance between the plates is finite, the resulting electric field will differ from zero. With such a model, a usual parallel plate condenser can be derived, as shown in Fig. 2.11. We have two charged disks (infinite conducting sheets), and an insulator layer between them. In the classical picture, the opposite charges' amount on the two plates must be the same. As shown, a constant electric field is present inside the membrane (across the plates of the condenser) and zero electric field inside the parallel conducting plates, as well as outside the condenser. In this ideal picture, the charges are aligned on the border of two (infinitely thin) conducting layers and cannot move. Anyhow, the attractive force between the opposite charges on the plates keeps them fixed in direction of  $z$ . The repulsive force between the charges with the same sign keeps their surface density in the  $(x, y)$  plane uniform: the infinitely thin plates are equipotential. The strong electrostatic force can produce an enormous acceleration for the individual ions, but the thermodynamic gradient can only change with a several orders of magnitude lower speed, allowing measurable changes in the current intensity on the surface). This picture is valid for the equilibrium state of charges, infinitely small non-dissociating charge carriers and perfectly smooth surfaces.

Figure 2.12 (the blue diagram lines) show the electric field around the neuronal membrane. In this picture we see that there is a jump in the value of the electric field (and so: in the force acting on a charge) in the two sides of the physical layer and we assume that the physical layer somehow emulates the well-defined boundary on the side opposite to that proximal to the membrane.

### Condenser in dielectric material

In its integral form, Gauss's flux theorem states that the flux of the electric field out of an arbitrary closed surface is proportional to the electric charge enclosed by the surface, irrespective of how that charge is distributed. The surface layer represents a steep potential and concentration gradient. Above we assumed that the counterforce that keeps the charges in their place against their electric repulsion is a kind of mechanical force: the ions cannot pass through the membrane. However, such a counterforce does not exist on the side toward the 'bulk' part of the segment. The charges on the plates do not generate an electric field toward the bulk, but the concentration does, according to Eq.(2.7), provided that there are charge carriers in the bulk. We hypothesize that virtual electric charges exist in the electrolytes and their field provides the missing electric field. In our real picture we assume a finite-thickness charged layer, and correspondingly that inside the conducting layer the electric field changes linearly. Toward the bulk of the electrolyte, a layer of dipoles creates dielectric layer with an extra electric field. These two layers have the same electric field at the boundary and (according to Gauss's theorem, their sum appears in the gap as the resulting electric force field; see the red diagram line in Fig. 2.12.

When explaining the effect of dielectricity, we must explicitly consider the duality of ions that they obey laws of electricity and thermodynamics *simultaneously*; furthermore, the complexity of the electric structure of the solution, and that the charge carriers have finite size (see "electron size" vs "dipole size") .

According to the theory of electricity, the free charge carriers (the dissociated ions) are located on the surface where they form strongly charged thin layers (condenser's plates) in the segments separated by a membrane on the two surfaces of the membrane; two proximal charge layers on the surfaces of the membrane. We assume that those ions behave as point charges, i.e., due to the attraction from the opposite charges on the opposite plate, they do not produce an electric field toward the side of the bulk of the electrolyte layers. In the classical picture, those layers represent step-like gradients in the electric field along the  $z$  axis and the constraint that the ions must not enter the membrane provides the counterforce needed to keep the ions in place.

From thermodynamical point of view, a driving force acts as long as a concentration gradient between neighboring layers exists. From electrical point of view, the layers are simple parallel-plate condensers, that produce no electric field outside their closed volume, and they are connected serially; plus the top layer has free ions. The electric field is proportional with the bulk concentration in the layer. The changes in the local electrical gradient may also change the degree of dissociation and polarization, and they may produce a graded local electric field. These two driving forces have opposite directions and in a balanced state, the same magnitude. The external force acts in a way that it constraints the molecules to stay in their layers; it adapts (compensates also for the different interaction speeds) while the gradients are changing. It presses the proximal layer to the membrane and the neighboring layers to each other. (In other words, the internal electric force due to the forcefully changed polarization

continuously decreases the electric field and so the potential gradient and so the concentration gradient.)

Due to the finite width and the surface's roughness, the conducting layer has a finite width, the electric field is step-like with step size of the size of dipoles, furthermore, it is homogenous in the layers. Due to the rest of that electric field toward the bulk layer the dipoles proximal to the neighboring dipole layer get directed and also their polarization increases; in other words, they "produce" an electric field. The final effect is that a dipole layer is attracted to the charged layer and it forms another layer that shows a charged layer toward the bulk. The process repeats; the process results in a decaying electric field in function of the distance from the membrane's surface.

In our model we build the volume of the electrolyte from thin layers of directed dipole molecules (the thinness  $\Delta z$  is limited by the size of molecules) in the volume separated into two segments with electrolytes by a membrane with a finite thickness  $d$  (that is, a point's distance in the electrolyte from the two disks will be  $z$  and  $z + d$ , respectively). The contributing force field of an infinitesimal volume on the axis at point  $z$  due to the charged sheet

$$dE(c, \Delta z, z) = \underbrace{E_{Classic}^{Gap}(c, \Delta z) * z * \frac{1}{z^2} * dz}_{\text{Potential from sheet}} \quad (2.60)$$

$$= E_{Classic}^{Gap}(c, \Delta z) \frac{1}{z} * dz \quad (2.61)$$

and the total potential due to all elements  $dz$  from the left side is (in the mathematical formulas below we express the distance in units of  $\frac{z}{d}$ , so here  $z$  is dimensionless).

$$U_{left}(c, \Delta z, d) = E_{Classic}^{Gap}(c, \Delta z) * d * \int_{-\infty}^0 \frac{1}{z} dz \quad (2.62)$$

$$= E_{Classic}^{Gap}(c, \Delta z) * d * \left[ \ln |z| \right]_0^\infty \quad (2.63)$$

In the case of a single-segment volume, within the segment, a similar potential with opposite sign, generated by the charges on the neighboring sides of the considered charged sheet, counterbalances the potential described by Eq.(2.63). However, when a membrane with thickness  $d$  separates the segments (with no charges in the gap), the right side of the potential will be

$$U_{right}(c, \Delta z, d) = E_{Classic}^{Gap}(c, \Delta z) * d * \left[ \ln |z + 1| \right]_1^\infty \quad (2.64)$$

That is, the gap sets the potential difference across the membrane to

$$U(c, \Delta z, d) = E_{Classic}^{Gap}(c, \Delta z) * d * \left( \left[ \ln |z| \right]_{-\infty}^0 - \left[ \ln |z + 1| \right]_1^\infty \right) \quad (2.65)$$

awakes in the condenser, across the separated surfaces. We use the approximation that  $\ln(\infty) \approx \ln(1 + \infty)$  and we arrive at that

$$U(c, \Delta z, d) = E_{Classic}^{Gap}(c, \Delta z) * d * \left[ \ln\left(\frac{z}{z+1}\right) \right]_0^1 \quad (2.66)$$

describes the potential across the plates; that is, the classic potential shall be multiplied by the result of the integral.

### Bridging the micro- and macro views to electricity

We assumed that the function can be interpreted for regions  $(-\infty, 0)$  and  $(1, +\infty)$ . However, here were we arrived at the boundary of discrete electricity and continuous electricity. We use a trick similar to the one Boltzmann used in his famous equation, except that we calculate the number of charge carriers from geometrical instead of statistical assumptions. The thinness of layers is limited at least by the ion's size. Furthermore, the membrane's surface is not flat; there are structures (mainly lipids) with size of up to  $1 \text{ nm}$ , so it is probably realistic to consider a layer thickness of  $0.5 \text{ nm}$  as we did above (on our mathematical scale  $0.1 = \frac{0.5 \text{ nm}}{5 \text{ nm}}$ ), for which the multiplier is 2.4. A similar calculation using layer thickness  $0.125 \text{ nm}$  (on our mathematical scale, 0.025) results in a multiplier 3.7; so we assume a multiplier 3 (corresponding to  $0.25 \text{ nm}$ ). Correspondingly, we assume an electric field

$$E_{Gap}^{Dielectric}(c, \Delta z) = 3 * E_{Classic}^{Gap}(c, \Delta z) \left[ \frac{V}{m \text{ nm} * mM} \right] \quad (2.67)$$

due to the dielectricity in the segment. Actually, this is the contribution of the dielectricity in the segment, and is to be added to the value of the classic contribution, the field generated by the conducting plates, so the final multiplier is 4. (The experience is known in technical electricity: the electrolytic capacitors *achieve several times higher charge storage capacity by using (pseudocapacitance)*. By using "roughened anode foil", the thickness of electrolytes is increased and the roughening provides the needed mechanical support. Actually, a thicker electrolyte layer wraps the condenser plates and the dipoles in the thicker electrolyte provide an additional charge storage facility. We leave the question open how much the measured condenser capacity comprises real and pseudo capacitance.)

Correspondingly,

$$E_{Gap}^{Total}(400, 0.125) = 4 * E_{Classic}^{Gap}(400, 0.125) = 8.8 * 10^6 \left[ \frac{V}{m} \right] \quad (2.68)$$

and at  $5 \text{ nm}$  membrane thickness, the voltage across the plates becomes

$$U_{Gap}^{Total}(400, 0.125, 5) = E_{Gap}^{Total}(400, 0.125) * (5 * 10^{-9}) = 45 \text{ [mV]} \quad (2.69)$$

Hodgkin in 1964 measured molarity values in squid axons for ions  $K^+$ ,  $Na^+$  and  $Cl^-$ , (400,50,40-150) inside and (20,440,560) outside, and they provided

potential values  $55 - 75 \text{ mV}$  [1]. "The plasma membrane of all cells, including nerve cells, is approximately 6 to 8 nm thick and consists of a mosaic of lipids and proteins." [39], page 71. "The outer membrane of nerve cells is composed of a lipid bilayer  $\approx 8 - 10 \text{ nm}$  thick" [122] Using such a value for the membrane's thickness may result in a value up to 100% higher, furthermore, the usual concentration is also up to 20% higher. Given that we used a plausible but ad hoc "charged layer thickness" and gap distance, we cannot expect a better agreement.

In our model we assumed that the ions form a uniformly charged layer on the surface (so inside that layer the electric field changes linearly with coordinate  $z$ ), there is no charge between the condenser plates so the electric field is constant (it is equal with the value taken on the proximal side of the layer), and in the dielectric solution changes as described by Eq. (2.67). On the boundary of the dielectric layer and the thick charged layer the field takes the same value.

The potential's and the electric field's magnitudes are independent of the chemical nature of the ion. At a given concentration, the potential difference is caused by the finite width of the membrane plus the dissociation of the ions. Given that the same number of charged ions must be present on the two sides of the membrane, the surface density  $\sigma_A$  must be the same on the two sides. Notice that the effect is purely electrostatic, and will result in an asymmetric distribution of ions; no permeability is needed. If the membrane is permeable, ions will move across the membrane until equilibrium reached. The resulting potential difference depends linearly on the concentration difference. In the light of our derivation of the resting potential, one must revisit the derivation of the Goldman-Hodgkin-Katz potential, see 2.5.6.

### **Electric field in a two-segment electrolyte**

Fig. 2.12 displays how the function shapes of electric field change in the function of the distance from the membrane. As discussed, the physical distance between two two segments with electric charge causes a charge condensation on the surface of the separating membrane. In the case of classic condenser, this primary charge density is abstracted as an infinitely thin layer of charges (electrons) on an ideally plain layer, and the rest of the volume is abstracted that no charge carrier is included. This case is perfectly described by the classic electricity theory. In the case of electrolytes, the separating membrane's surface is not ideal, furthermore the electrostatic force can press some biological objects to the surface, so we must assume that the primary charge forms a uniformly charged layer with finite thickness on the surface. In the uniformly charged layer the electric field is a linear function of the distance from the surface. The presence of dielectric molecules in the rest of the volume creates secondary (virtual) dipole charges, that contribute to the electric field, as shown. The two fields join to each other at the boundary of the charged layer. The electric field on the surface of the membrane is the sum of those two fields. The opposite charges on the other plate generate another electric field in the opposite direction.

As shown in the figure, the field steeply rises near to the membrane. At the

membrane surface, it reaches its maximum value; on both sides of the membrane. Inside the membrane, there are no charges, so the field remains constant, for both types of condensers. Notice that the classic condenser can be considered as the abstraction of the real condenser to the case of zero dielectricity.

The electric field acts on the ions, but there may be present a mechanical counterforce, plus a thermodynamic force arising from the difference of ions' concentrations. (We just notice here that *the electric driving force does not depend on the chemical type of the ions, but the thermodynamical force does*. The mechanical counterforce is adaptive, per ion, so it can keep different types of ions in rest.) If there are 'holes' (ion channels) in the membrane, there is no mechanical counterforce, so the ions could move under the effect of the difference between the electric and thermodynamic forces. The latter depends on the chemical nature of the ions, so it natively provides selectivity: the resulting forces are different for ions of different types. The usual "downhill" method of explanation must be corrected: the *resulting potential* instead of the *electric potential* defines how the ions move.

The figure shows two ions (green and red) at the axis of the ion channel in two positions (the empty circles along the axis of the ion channel), at the beginning and end of a movement, when the ion channel is open. On the diagram lines, filled circles show the electric fields on the diagram lines at the position of the ions.

In the charged layer the ion *density* is constant, that is the thermodynamic force is zero while the electric force decreases with the distance from the membrane's surface

If the channel opened, the mechanical counterforce cancels, the ions will move under the effect of the resulting force, that comprises not only the thermodynamic and electric forces, but also the force to move the ion with the Stokes-Einstein speed. In the position at the entrance of the ion channel (see the red ions), if the channel is open, the large thermodynamic and electric forces 'push' the ions into the channel. Here the concentration gradient quickly cancels, but the huge potential gradient will accelerate it toward the other segment. After passing the membrane with a high speed, the ion faces a quickly decreasing field, and its speed quickly decreases. The leave of ions changes both concentration and charge density in the vicinity

In the position farther from the membrane's surface (see the green ions) the ions must travel 'uphill'; that is, they cannot travel instantly toward the membrane. They must wait until the gradient change caused by the ions pushed into the gap reaches their position. As the figure shows, the ions quickly move out from the region with high charge density and very slowly refill that region with ions from the region farther from the membrane. This speed difference results in a quick change in the local electric field. In the region of the other plate, the ions decrease the (opposite) local potential. As the result, there are less ions ready to travel on the one side, and the potential difference continuously decreases on the other, so the flow of ions stops: the ion channel shuts itself down (and, on both sides, starts to regenerate the potential as it was before the channel's cap was removed). That is, the ion channel is opened by a slow

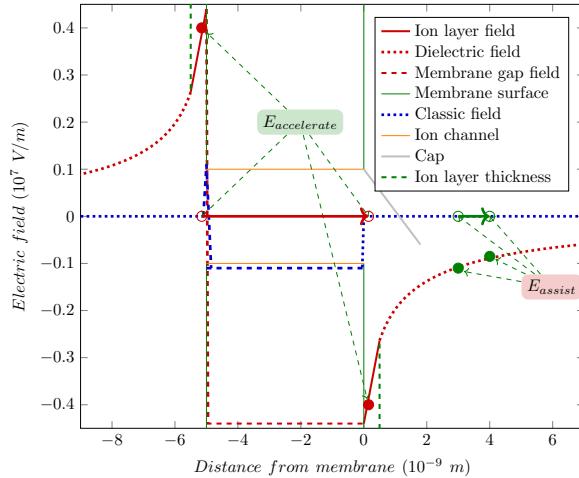


Figure 2.12: The neuronal membrane's *electric field* in the function of the distance from the membrane's surface and the bulk potential. The thickness of the atomic layers proximal to membrane's surfaces are also shown.

mechanical cap, but it is closed by a fast electric shutter. While the potential self-closes the channel, the electric fields on the two sides of the membrane have to relax: the ions and dipoles have time to change their position and even their polarization and ionization state. The local gradients will rearrange concentration and electric field in the segment.

As depicted, in the two regions, there is a significant difference in the value of the effective force acting on the ions (they are using  $E_{accelerate}$  and  $E_{assist}$ , so they produce different Stokes-Einstein speeds (see Eq. (2.31)). Based on those speeds, one can introduce "fast" and "slow" ions and correspondingly, speak about '*slow*' and '*fast*' currents that the ions represent at a macroscopic level. The corresponding speeds also differ by orders of magnitudes. For this study, we assume the diffusion, potential-assisted and potential-accelerated speeds, in  $m/s$  to be  $10^{-4}$ ,  $10^{-1}$  (also inside neurons [47]),  $10^{+3}$ , respectively (used only to estimate the order of magnitude of some respective operating times). When staging, we assume the greater of the mixing speeds as 'infinitely large' and omit the time that the process needs, while discussing how the slower process proceeds.

We are in line with the estimation given in [87] that in the case of resting potential, the scale of the gradient that accelerates the ions across the ion channel is calibrated approximately as  $kV/cm$ . Recall that we are still speaking about the resting state and only about the extra gradient evoked by the finite-width membrane. We are at the boundaries of the macroscopic and mi-

croscopic worlds. We derived our integrand from the picture of discrete charges but integrated it into the picture of continuous charge distribution. We assume an atomic layer (a skin) on the surface. However, the layer itself can also be modeled as having just a few ions under their mutual repulsion on the surface or a few atomic layers on top of each other, depending on the concentration and voltage in the bulk on the two sides. (The diagram line is valid in the plane crossing the membrane and the ion channel.)

We assumed that the membrane's width is  $5\text{ nm}$ . An ion channel is depicted in the middle of the figure with a diameter of about  $1\text{ nm}$ . Furthermore, we assume that the ion's size and, correspondingly, the thickness of the atomic layer in the electrolyte on the surface of the membrane is about  $0.1\text{ nm}$ . For comparison, recall that the size of the tip of the clamp pipette is in the range of  $1,000\text{ nm}$  and the size of the soma in the range of  $10,000\text{ nm}$ .

Our results align with the observation (see caption of 11.22 in [87]: "A small flow of ions carries sufficient charge to cause a large change in the membrane potential. The ions that give rise to the membrane potential lie in a thin ( $<1\text{ nm}$ ) surface layer close to the membrane". See the dotted line in Fig. 2.12; notice that the x-scale on the figure spans  $1\text{ nm}$  only. The amount of unbalanced ions is in the range of  $10^7$ , and so is the amount of rush-in ions. In addition, those ions on the high-concentration side rush-in to the low-concentration side and cause the large change in the membrane potential. Their absolute amount is small compared to the total number of ions in the cell, but it is significant compared to the number of unbalanced ions.

### Membranes with ions channels

The attraction between the ions in the two skin layers prevents the ions in the layers on the two sides from diffusing into/from the bulk without a current drain in the layer for an extended period. This steady state results from the interplay of the concentration and the potential described by Eq. (2.7). The gradients change gradually within the segments and drop suddenly across the membrane. No current can flow through the membrane; there is no leaking current.

Here, we assume that no ion channels are in the excellently isolating wall (ion channels would mean a current drain and, therefore, a voltage drop).

#### 2.5.6 Goldman-Hodgkin-Katz potential

It was already stated, based on experimental evidence, that "the membrane permeability to the ions has nothing to do with the potential generation and the ions adsorption on the membrane surface generates the membrane potential", for a review see [67]. The idea itself is nonsense: in a balanced state, no ion transport happens, so even without permeability, the balanced state persists; the resting potential has nothing to do with either ions' mobility or permeability nor with ion absorption [68]. Furthermore, there is no idea in GHK about whether the 'setpoint' (why that specific concentration or potential difference) is present and why the same potential is reset after rough perturbations such as issuing

an AP or replicating a cell. The causality is reversed: the potential is a static concept which is set electrically, and the two gradients form the experienced concentrations and potentials from the available solvent molecules. For the time course of forming the gradients, mobility and permeability play a role, but not in determining the concentrations or the resting potential.

In our clear physical picture, the thermodynamic forces on the one side and on the other side of the membrane are summed. They counterbalance each other; furthermore, jointly the effect of the neuronal condenser, see Fig. 1.5. As we emphasized, the concentration gradients are ion-specific. Furthermore, as we discussed in connection with Eq.(2.18), the Nernst equation comprises a per-ion indefinite constant (a potential difference). To calculate a linear combination of terms comprising an arbitrary constant is nonsense, and so is adding absolute concentrations on the different sides of the membrane, or changing the base of the logarithm used in a calculation to match the experimental value. It is not more than number magic. The potential is described by coupled equations as discussed in connection with Eq. (1.2).

The  $Ca^{2+}$  ions do not fit into the GHK picture. One of the reasons why GHK cannot be good is that  $[Ca^{2+}]$  is omitted. Biologically, it is hard to believe that  $Ca^{2+}$  does not participate in the game of life (especially since biology sees the need for  $Ca^{2+}$  pumps). Physically, one concentration alone on one side of the membrane cannot keep balance; as the different ion exchange processes, Table 3.1 and Fig. 1.5 show. When adding a new ion to the solution, the sum concentration increases, and so the electrical force increases, forcing the previous elements to find new concentrations on both sides. The appearance of a new chemical element indirectly changes the concentrations of the others (a good example is the role of the negligible amount of  $Ca^{2+}$ ).

### 2.5.7 Moving in the membrane's potential

In Fig. 2.12, an ion channel is depicted in the middle of the figure with a diameter of about  $3\text{ nm}$  for visibility. Furthermore, we assume that the ion's size and, correspondingly, the thickness of the atomic layer in the electrolyte on the surface of the membrane is about  $0.1\text{ nm}$  (although with their electric double layers, they can also reach the size of  $1\text{ nm}$ ). For comparison, recall that the size of the tip of the clamp pipette is in the range of  $1,000\text{ nm}$  and the size of the soma in the range of  $10,000\text{ nm}$ .

#### Passing through ion channels

Figure 2.12 also hints at how ions can move in the proximity of the membrane. On the left side, the electric field increases toward the membrane, so the ions cannot move in that direction without an initial force being applied. The case is the same on the right side, because the charge is the opposite. An ion must gain energy to get closer to the membrane, which means, at the same time, higher potential energy. This situation explains why the ions do not diffuse into the bulk region. At their present positions, the counterforces by the membrane (and

the dipole layer on it) balance the attraction from the opposite side. The ion channels can work in continuous mode (the "resting ion channels") and impulse mode (gated by "caps" on the channels, in transient mode).

Notice that the resulting electric field cannot accelerate an ion except when the ion is at the beginning of the open ion channel across the membrane. Here, the mechanical counterforce is missing, and the field drops to the value generated by the condenser inside the plates. Here, a vast electric field accelerates the ions to a high speed (although a force needed to move against the viscosity decreases the electrostatic acceleration). The empty red circles show an ion that traverses through the channel. The figure shows their electric fields on the two sides, at the beginning and end of the channel. (On the right side, the electric field is negative, but so is the charge of the ions.)

### Moving in the polarized electrolyte

The electric acceleration sharply decreases after leaving the ion channel (see the right side). As shown by the difference of the vertical positions of the filled red and green balls, the difference in the electric field values is huge across the membrane ( $E_{accelerate}$ ) and considerable inside the dielectric electrolyte ( $E_{assist}$ ) as shown by the difference in the electric field values of the green balls. The field still accelerates, but significantly less intensely than the one in the gap. Suppose we assume that the ion quickly accelerates to its Stokes-Einstein speed. In that case, the travel speeds in those space regions are proportional to the difference of the fields in the shown positions and the reciprocals of their travel times.

The passed ions decrease the concentration, and the electric field on the high-concentration side increases on the low-concentration side. Similarly, the gradients decrease and increase, changing locally the gradients. At the exit, the field continues to accelerate the ion. However, the increasing potential and concentration increasingly decelerate the passing ions, so they quickly brake them to the assisted speed. Then, the effect of the electric field cancels, and the ions will move with their diffusion speed ("the ion stops").

### Ion selectivity

As Eq.(2.53) states, the electrolyte separated by a permeable membrane is balanced when the electrical and thermodynamical forces are equal. The  $E_{thermal}^{C_k}(d)$  "electric field" depends on the chemical quality of the ion; the electrical field does not. That means the resulting driving forces acting on the different ions are different. While one ion experiences a resulting force and moves to the other segment, the other remains resting. Of course, the ions moving across the segments change the overall concentrations in both segments (and so the electric field contribution), indirectly affecting the balanced state of the other ions. When a mixture of ions is present in the volume, all ions feel a different driving force, and the solution as a whole will be balanced when the resulting forces for all chemical ions are balanced. The permanently open ion channels only passively participate in the process. The driving forces of the

ions are different, and they produce, depending on the actual concentrations, the selectivity of the channels.

When  $Na^+$  ions rush into the intracellular layer, they roughly increase the overall concentration and the potential. All other ions, including  $K^+$ , feel a driving force. The targeted membrane potential is set electrically, and the driving gradients may behave controversially during the transient period. The actual voltage gradient may temporarily direct the chemical gradient in opposite directions. Phenomena such as 'over-relaxation', in this sense, similar to 'hyperpolarization', may happen.

However, the layer itself can also be modeled as having just a few ions under their mutual repulsion on the surface or a few atomic layers on top of each other, depending on the concentration and voltage in the bulk on the two sides. (The voltage gradient diagram line validates the plane crossing the membrane and the ion channel.)

Our results align with the observation (see caption of 11.22 in [87]). The amount of unbalanced ions is in the range of  $10^7$ , and so is the amount of rush-in ions. In addition, those ions on the high-concentration side rush into the low-concentration side and cause a large change in the membrane potential. Their absolute amount is small compared to the total number of ions in the cell, but it is significant compared to the number of unbalanced ions.

## 2.6 Neuronal components

In this section, we discuss statical and dynamical components. We attribute a new role to the AIS, and introduce the dynamic layers on the surfaces of the membrane.

It is hard to separate the operation of the individual channels from the operation of their population in the walls of membranes (layers), see also the sections on axonal and neuronal membrane. When the ions pass the channel, they face two effects on the two sides of the membrane. On the side of departure with high concentration, they suddenly "empty" the thin layer in the immediate proximity of the membrane. On the side of arrival with low concentration, again, the arrived ions suddenly form a "filled" thin layer. The ions in both segments can move only with their corresponding diffusion speed (in the order of  $10^{-4} \text{ m/s}$ ), but they experience each other's electric repulsion, which can speed up their speed to the range  $1 \text{ m/s}$ . (BTW: this effect can be misinterpreted as a sudden ion adsorption [68] on the surface of the membrane.) The final effect resembles an electric condenser: for a short time, ion-rich layers are formed on the two sides of the semipermeable isolator membrane. The two layers attract each other, so the ions in the layers can diffuse toward their respective neighboring layers only moderately.

### 2.6.1 Ion channels

"The function of ion channels is to allow specific inorganic ions to diffuse rapidly down their electrochemical gradients across the lipid bilayer... Nerve cells (neurons), in particular, have made a specialty of using ion channels, and ... use a diversity of such channels for receiving, conducting, and transmitting signals... *Ion channels cannot be coupled to an energy source to perform active transport, so the transport that they mediate is always passive ('downhill')*" [87]. Despite this clear view, the *laws of motion* of ions in those channels are not discussed in the literature. As we discuss in section 2.7.3, they behave in a mystic way: from some point of view, they behave as 'demons'.

It is hard to separate the operation of the individual channels from the operation of their population in the walls of membranes (layers), see also sections 2.6.5 and 2.6.4 about axon and neuronal membrane. When ions pass the channel, they face two effects on the two sides of the membrane. On the side of departure with high concentration (where they of course have high electric potential), they suddenly "empty" the thin layer in the immediate proximity of the membrane (for a detailed discussion see section 2.2.7 about the effect of finite resources). On the side of arrival with low concentration, again, the arrived ions suddenly form a 'filled' thin layer. The ions in both segments can move only with their corresponding diffusion speed (in the order of  $10^{-4} \text{ m/s}$ ) but in the presence of a voltage gradient they experience each other's electric repulsion that can speed up their speed to the range  $1 \text{ m/s}$ . (BTW: this effect can be misinterpreted as a sudden ion adsorption [68] on the surface of the membrane.) The final effect resembles an electric condenser: for a short time, layers with opposite charges are formed on the two sides of the semipermeable isolator membrane, which are canceled in the frame of issuing an AP.

#### Role of speeds

Recall that, in physics, the *drift speed*, the *electric repulsion-assisted speed* and the *potential-accelerated speed* of ions differ by several orders of magnitude. As a consequence, "transport efficiency of ion channels is  $10^5$  times greater than the fastest rate of transport mediated by any known carrier protein" [87], reproduced here as Fig. 2.13. The ion channels are either closed or open without a noticeable transition state, but as discussed in [62, 123], for their adequate description three states are needed: they can also be in inactivated state. We can consider the channel operation as "infinitely fast" compared to the speed of processes in front and behind of the channel: the massive difference in speeds explains why ion channel opening and closing resembles a 'digital operating mode'. The different speeds play a significant role in the correct operation and the cooperation of different neuronal objects, including ion channels in the walls of membranes and axons.

The rapid influx of ions causes a sudden increase in the potential on the intracellular side. Conversely, the ions' removal from the layer on the extracellular side near the membrane 'empties' the layer, and the after-diffusion (despite the

large concentration difference) with the low drift speed (even if it is assisted by the repulsion of the fellow ions) takes time. Because of the slow after-diffusion, the transfer stops well before the ion channels get inactivated. See also the operation of clamped axons: removing the surface ion layer enables the membrane to prolong its 'open' state (again, in statistical sense). Basically, the diffusion speed in those layers (in a statistical sense) and the lack or presence of ions in the proximal layer, defines the 'open' and 'closed' states of the channel population. The ion channels have three states, but their population has only two. One can hardly interpret a third state of ion channels without considering the effect of the membrane's charged layers as we discuss below.

### Opening and closing

The different speeds play a significant role in the correct operation and the cooperation of different neuronal objects, including ion channels in the walls of membranes and axons. We discuss their effect also in section 2.2.7: they affect also the resource-availability of ion charges in the electrolyte segments. Given that the "transport efficiency of ion channels is  $10^5$  times greater than the fastest rate of transport mediated by any known carrier protein"<sup>1</sup>[87], we can consider that speed as 'infinitely fast' compared to the speeds of neuronal ion currents. For cardiac APs, where only a few ion channels participate, "the slow currents appear to have been caused by repeated openings of one or more channels" [61]. For neuronal APs, where many ion channels participate, "the durations of channel opening and closing vary greatly"; furthermore, "the rate at which current flows through an open channel is practically constant" [87].

Experimental evidence shows that although "the durations of channel opening and closing vary greatly, the rate at which current flows through an open channel is practically constant [87]. The presence of two layers on the opposite sides of the membrane actually implements the control square-wave signal on the figure. Those layers also explain why the ion channels (in a statistical sense) behave as digital, despite that the individual ion channels are not digital.

As Fig. 2.13 depicts, an ion channel is open roughly for  $10^{-2}$  s and the peak amplitude is  $1.6 * 10^{-12}$  A, so the maximum charge that can be transferred in a single shot is  $1.6 * 10^{-14}$  C, which assumes  $10^5$  ions per shot per channel. (If we assume that the ions pass the ion channel one by one, without pausing, the passage time of an ion is  $10^{-7}$  s. Given that the electrolyte electrodes contribute a considerable delay, the value might be not accurate.)

The entered ions cannot leave sufficiently quickly the proximity of the channel's exit, so their potential prevents the rest of ions from entering the membrane: the ion layer closes the channel. Recall that the number of the uncompensated ions is about  $5 * 10^7$ , the several (typically several hundreds) simultaneously working ion channels overcompensate the ion balance: despite the forceful external potential, no more ions can enter the membrane (the 'downhill' gradient cancels; if we use the approximation that the ions traverse the channel length instantly). In the rest of the shown period, despite that the external voltage (the square wave) is still present, the potential of the stalled ions (the internal

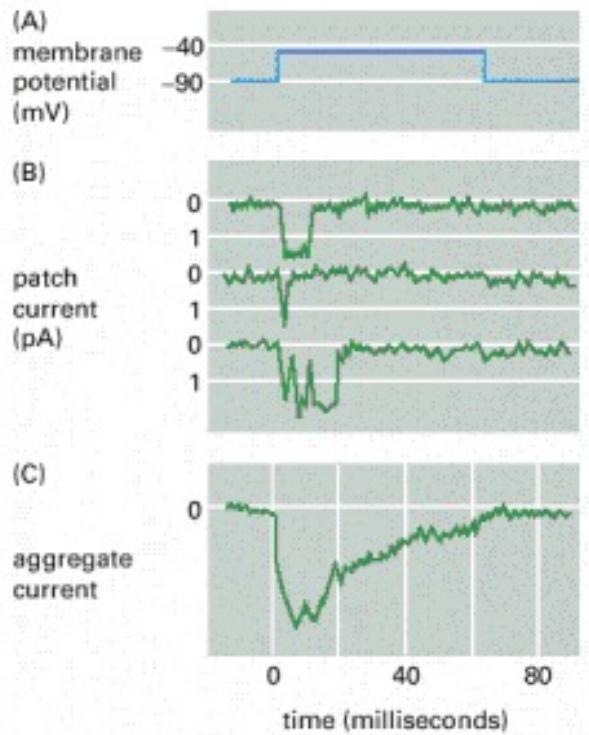


Figure 2.13: Patch-clamp measurements for a single voltage-gated  $\text{Na}^+$  channel (Fig. 11.32 in [87]). Notice that due to the low current intensity, the measurement method comprises integration that "smears" line shape. Also notice that the shape of the aggregate current comprises different time contributions due to the different distances of channels from the measurement tip.

voltage) keeps the channel closed: no new rising edge (voltage gradient) arrives. In the figure, the aggregate current enables us to estimate the total number of channels to be  $100 - 120$ . Clearly, the aggregate current shows two effects: the individual ion channels' contributions, which are measured within the channels, have steep rising and falling edges. As the figure depicts, after  $20\text{ ms}$  no more new openings happen. Following that, the currents flow toward the point where the aggregated current measured: the charge on the membrane quietly discharges. (The reason of the decay is the same as in the case of the AP a slow current flows on the surface; so their time constant is the same, although the fluctuation due to the arrival time of the contributions of the individual channels is more observable.) Again, the external voltage is stable, the internal voltage decreases, so the aggregate current decreases. The membrane's conductance does not change. However, the resulting potential that directs the current is the sum of the external and internal potentials. As the charge diffuses toward the bulk region, the internal potential decays, and so does the measurable aggregate

current.

Although the individual ion channels open and close 'randomly', the repulsion force on the two surfaces of the membrane acts as an additional valve; its discussion see in section 2.2.7. As [87] discusses, 'this potential difference ... exists across a plasma membrane only about 5 nm thick, so that the resulting voltage gradient is about 100,000 V/cm'. In a statistical sense, part of the ion channels can be open after the population members received the 'open' signal, part of the population can be closed or inactivated, but when the layer enables, the ions in the proximal layer can escape to the other side of the membrane.

It is also known that for their adequate operation, the ion channels need to implement three states: in addition to the 'on' and 'off' states, they can also be in an inactivated state [62, 123]. However, the population of the ion channels has only 'on' and 'off' states; furthermore, for some reason the population get "fatigued": "the probability, that any individual channel will be in the open state, decreases with time" [87]. It is due to the finite resources, as we quantitatively discuss it in section 2.2.7.

As Fig. 2.13 depicts, it is the gradient (the rising edge), instead of the membrane potential, which starts the individual patch currents (and, of course, the aggregate current). Depending on the environment of the channel's exit (the fluctuation of the charge density), the channel has an a maximum 'let-in' time. The representative patch currents show that the channel can definitely and quickly open,

### 2.6.2 Ion pumps

"These pumps differ from ion channels in two important details. First, whereas open ion channels have a continuous water-filled pathway through which ions flow unimpeded from one side of the membrane to the other, each time a pump moves an ion, or a group of a few ions, across the membrane, it must undergo a series of conformational changes. As a result, the rate of ion flow through pumps is 100 to 100,000 times slower than through channels. Second, pumps that maintain ion gradients use energy, often in the form of adenosine triphosphate (ATP), to transport ions against their electrical and chemical gradients. Such ion movements are termed active transport." [39], page 101.

The role of ion pumps must be revisited, too. It is not clear what a force can "transport ions against their electrical and chemical gradients" and how can they deliver in sufficiently short times the ions needed for the operation. In the resting state, instead of some magic lipid mechanism (ion pumps), the resultant potential (the sum of the electric and thermodynamical potential for the individual ions) moves the ions through the channels in the membrane. The resulting conductance on those channels is about 50 times smaller [47, 51] than that of the AIS. In a typical mammalian cell, see Table 3.1, the sum of the electric and thermodynamical potentials are  $-32 \text{ [mV]}$   $K^+$  ions and  $+4 \text{ [mV]}$   $Na^+$  ions. The same values for squids are  $-33 \text{ [mV]}$   $K^+$  and  $+13 \text{ [mV]}$   $Na^+$ . Correspondingly, the resulting force moves sodium ions out of the cell and potassium ions into the cell. The so called "Na-K pump" *is supposed* to actively transport

(using energy from Adenosine Triphosphate (ATP)) sodium ions out of the cell and potassium ions into the cell. However, in the old model no mechanism is provided how the ions gain energy from ATP and how the ions are moved by some magic mechanism by protein conformations. In our "new understanding" it is clear physics: the resulting force moves the ions in and out, simultaneously.

As Figure 6 in [32] displays, the ratio of  $K^+$  and  $Na^+$  changes sharply during the transient state. Theoretically, they assume that the neuron "pumps 3  $Na^+$  ions out of the cell and two potassium ions in"; experimentally, they show in their Fig. 6 that the ratio changes between 0.01 and 7.5. The classical theory cannot explain this behavior and leads to exciting conclusions: "Furthermore, we analyzed energy properties of each ion channel and found that, under the two circumstances, power synchronization of ion channels and energy utilization ratio have significant differences. This is particularly true of the energy utilization ratio, which can rise to above 100% during subthreshold activity." [32]

Our electric model says that both the concentration (due to  $Na^+$  rush-in) and local membrane potential drastically changes during the transient state. As long as the resulting potential is above  $\approx 33\text{ mV}$ , the driving force acting on potassium ions is positive, i.e., the pump will move both ions out of the cell. The potential gradient near the membrane explains also the energy delivery: ATP, by hydrolysis, generates ions which are moved to the "plates" of the condenser. (as we discuss in section 1.6, in transient state, the "setpoint" of the control circuit is also changed, and to restore the condenser's voltage, those ions must be collected.)

### 2.6.3 Ion layers

Semipermeable membranes, with ion channels in their walls, separating electrolyte segments with ion concentrations differing by orders of magnitude, play a unique role in neuronal electric operation. It is at least problematic to interpret the operation of the individual channels without understanding their dynamic interaction with the electrolyte and the semipermeable membrane.

We consider the external concentration constant: the extracellular space is infinitely large, and its concentration remains by orders of magnitude higher than the internal one. Our assumption is valid for the *global static* concentration (we call it 'bulk'), but not for the *local dynamic* one. The voltage-controlled ion channels open when on the lower concentration side, the local voltage exceeds some threshold value.

In the *resting state* (without a voltage offset around the ion channels), the channels keep balance between the separated segments. However, when an ion channel gets open (meaning that ions from the high-concentration side can pass through it to the low-concentration side), for a short period, the ions change the *local* concentration and potential of the electrolyte in the proximity of the entrance and exit of the channels, forming two proximal layers. The case drastically changes if an additional potential gradient appears. In that case, (part of) the ion layer, formed on the membrane's surface due to the charge arriving through the ion channels, is continuously removed by the macroscopic ion cur-

rent from the immediate proximity of the ion channels. The layer gets saturated later, and the conditions of transferring ions through the channels persist for longer, so they remain open, enabling a continuous ion inflow (a macroscopic current; see the discussion about clamping dynamic operation using AIS).

The ion channels have three states, but their population has only two. Fundamentally, the lack or presence of *unbalanced* ions in the proximal layers defines the 'open' and 'closed' states of the channel population. The individual ion channels open and close in a stochastic way. In a statistical sense, part of the ion channels can be open, and another part can be closed or inactivated. However, only when the layer's potential enables, can the ions in the proximal layer escape to the other side of the membrane, even if the channel is open. The ion channels have no reason to re-open because of the lack of offset voltage (and that layer). That is, primarily, the presence of the layers on the two sides of the membrane defines the ion inflow, and the individual ion channels can freely (re)open, close, or inactivate until the layer provides a sufficiently large potential offset. This transient state is the key to understanding the dynamic operation of neurons.

There is a strong electric field on the boundary of the segments. As [87] discusses, 'an electrical potential difference about 50–100 mV ... exists across a plasma membrane only about 5 nm thick, so the resulting voltage gradient is about 100,000 V/cm'. In their 'off' state, the voltage-controlled ion channels are mechanically closed, so the ions cannot follow that gradient. However, when (due to the collected synaptic charge or the significant slope of the arriving spike [63] or clamping) a voltage offset appears at the ion channel, so it opens. Due to the enormous gradient, ions rush in from the extracellular segment into the intracellular one. This means a high speed, that is, a 'fast' current, see Eq. (2.26).

However, upon arriving at the other side of the membrane, they experience the electric field disappearing, so the stream of ions stalls. The stalled ions increase the local potential (see section 2.4.8) around the channel's exit, and the ions will move along the parallel potential gradient toward neighboring channel exits. 'The description just given of an action potential concerns only a small patch of plasma membrane. However, the self-amplifying depolarization of the patch, is sufficient to depolarize neighboring regions of the membrane, which then go through the same cycle. In this way, the action potential spreads as a traveling wave from the initial site of depolarization to involve the entire plasma membrane' [87]. The depolarization happens in an avalanche-like way [76] over the entire membrane surface. This process creates ion-rich layers in the proximity of the membrane on both sides. At the end of the process, the potential in the layer on the intracellular side temporarily reaches the potential inside the bulk of the extracellular side. The ions in the layer experience two forces: in the direction parallel to the membrane's surface, the electric repulsion due to the fellow ions in the same layer; furthermore, in the perpendicular direction, the attraction of the ions in the opposite layer.

The first force acts in distributing the potential uniformly over the surface, and *in this way (per definitionem)*, *an ion current flows in parallel with the*

*surface.* This ion current is slow: the ions are moving in a viscous solution under the effect of a potential gradient (see Eq. (2.26)), if any. In the lack of external potential, it is of type relaxation. The presence of a current drain (such as AIS on the membrane or the axonal arbor on the axon) also means a potential difference, and an exponential discharge function of type  $\exp(-\beta * t)$  describes that current,  $\beta$  is a time constant.

The second one acts against diffusion and prevents the ions from leaving the layer. Until that current stops (due to the saturation of the layer), *an ion current will flow in the direction perpendicular to the surface.* That current is "fast" only within the ion channel until the driving force disappears, and becomes "slow" in the electrolyte layer, where the received charge saturates the layer. A current of form  $(1 - \exp(-\alpha * t))$  can describe the saturation, where  $\alpha$  is a time constant. Recall that the current's speed depends on the voltage gradient, so the intensity and the temporal behavior of the currents are different, even between the "parallel" and "perpendicular" current directions, given that two different mechanisms control the process, despite that we consider the motion of the same charged particles. As a result of the two processes, a function of type  $(1 - \exp(-\alpha * t)) * \exp(-\beta * t)$  describe the local charge distribution in the function of time. Although the timing constants change as the potential changes, we use the approximation that the layer is thin; furthermore, its concentration and potential have zero gradients in a direction perpendicular to the membrane. However, a steep potential gradient exists between the layer and the rest of the segment.

The 'caps' on the top of the ion channels act as individual regulators, and the ion channels continuously and randomly open, close, and inactivate. Their statistical population enables a macroscopic ion inflow throughout the surface and the electric repulsion distributes the charge over the surface, tending to make the local potential uniform over the surface. The repulsion and attraction forces on the two surfaces of the membrane around the channel's exit act as an additional valve on the ion transport: the population of ion channels must cooperate with them, given that the ions move 'downhill'.

This behavior explains why ion currents across the membrane start up with a sharp exponential rise [124] (one of the big mistakes was fitting polynomial lines [5] to those critical regions, comprising both exponential and no-current regions: it hides the sudden change of membrane's current [124] caused by the state change of the ion channels); why initiating an AP has precise timings (both the charge-up signal and pressing ions through the AIS; why axonal arbors can provide a precise "Begin Computing" signal. Measuring the conductance of ion channels, requires special care. As discussed in section 2.4.10, it is easy to make a systematic error, given that the measurement method can affect the result.

We posit explicitly that our parameters can be directly concluded from the measurable parameters such as membrane surface size, its ion channel density, specific membrane capacitance and absolute resistance of the AIS. Having those parameters of components of the non-living matter, plus the time course of the input currents, we can describe how and why a the living matter shows the behavior we can observe. This exact discussion provides an excellent base for

understanding neuronal assemblies' operation, furthermore revealing details of neuronal information storage and transfer.

This behavior explains why ion currents start up with a sharp exponential rise [124] (fitting polynomial lines [5] to those critical regions was a big mistake: it hides the sudden change caused by the state change (opening) of the ion channels, and that the 'rising edge' is actually described by an exponential increase); why initiating an AP has precise timings (both the charge-up signal and pressing ions through the AIS; why axonal arbors can provide a precise 'ComputingBegin' signal. For the details, see the following subsections. Measuring the conductance of ion channels, requires special care. It is easy to make a systematic error, given that the measurement device can affect the result.

Notice that the charged layers mean that a population of ion channels must cooperate. Although the individual ion channels open and close 'randomly', the repulsion force on the two surfaces of the membrane acts as an additional valve. In a statistical sense, some ion channels are open after the population members received the 'open' signal, but when they are open, only the ions in the proximal layer can escape to the other side of the membrane.

#### 2.6.4 Neuronal membrane

At the dawn of finding methods for describing neuronal operation, HH published high-precision measurements [5] enabling detailed testing of theories explaining the seen physiological behavior. *Their good physical model that "movement of any charged particle in the membrane should contribute to the total current" only lacked considering the finite speed at which the objects in their measured system react to the observer's invasion (in addition to assuming the wrong oscillator type); furthermore, they have started from the commonly used wrong assumption that conductance is a primary electric entity. This wrong physical basis forced them to make unphysical assumptions to explain their findings. Although they attempted to give a physical background, they felt that "the interpretation given is unlikely to provide a correct picture of the membrane."* [5] Using the Newtonian notion of interaction speeds is misleading and blocks understanding electrophysiological phenomena.

##### The 'delayed' membrane current

They could "find equations which describe the conductances with reasonable accuracy and are sufficiently simple for theoretical calculation of the AP and refractory period". *However, their equations cannot explain the delay experienced by a sudden change; furthermore, they explained that AP is created because of, for some secret reason, the membrane's conductance changes in time (although they noticed the presence of a "slow" current that behaves differently from the "fast" currents that their equations describe).* The primary issue with their model is that it concludes, as they admitted, a wrong description (unrealistic delay) of sudden changes, such as the arrival of a spike, of making clamping

measurements, or of interpreting the mechanism of neuronal information transfer.

Their followers modified both the form of their mathematical description (without assuming any physical model, using ad-hoc equations) to achieve minor improvement in the temporal behavior of the description. For a review of ideas, see [68]. This latter work attempted to introduce “a physiologically, physically and chemically viable model” that had to assume a physically not plausible ion-adsorption buildup mechanism to be able to explain the mentioned delay, see their Eq. (45). Those attempts, however, did not change what HH noticed [5]: “there is the difficulty that *both sodium and potassium conductances increase with a delay when the axon is depolarized but fall with no appreciable inflexion when it is repolarized*”. Without admitting a “slow” current exists, we must presume that sodium and potassium concerted their actions, and conductance is indeed misinterpreted in both cases. HH concluded [5] (presumably after many unsuccessful attempts) that ”there is little hope of calculating the time course of the sodium and potassium conductances from first principles”. It is correct: the existence of such a time course itself is against the first principles of science. However, if we make correct (physically plausible, instead of ad-hoc) assumptions, *we can derive a “time course”* (well, not of the conductance because it is a misinterpretation of the physical phenomena, see section 2.4.10; instead) *of the ionic current from first principles* although we must mix microscopic and macroscopic parameters.

It is a long-standing enigmatic phenomenon that ”the emergence of life cannot be predicted by the laws of physics” [9] (unlike the creation of technical systems). Still, we can provide a complete description of the biological phenomena from first principles if we consider the finite interaction speed instead of using the idea of “prompt interaction” taken from classic physics, which is a fake abstraction for that goal. Models in neuroscience (as reviewed in [113]) almost entirely leave the mentioned aspects out of scope. We introduce a finite interaction speed without introducing either twisted mathematical handling or obscure physical (for example, adsorption) mechanisms. In our straightforward physical model, we see the measurable membrane potential and current change in the function of the speed of ions  $v$ .

The commonly used physical picture behind the process is that the membrane, as if it were metal, is equipotential, and the “fast” axonal current flows directly to the membrane. This assumption is why we expect an instant appearance of the axon’s current in the membrane’s current (instead, we experience a “time-dependent conductance”).

### The ‘true’ membrane current

This axonal charge-up current, a phenomenon we are exploring from an abstract perspective, flows into the membrane. It causes transient changes [74, 75] in its voltage, providing *direct evidence that the membrane is not always equipotential. The ions on the membrane’s surface can propagate at a finite speed*. The membrane attempts to remain isopotential, the ions move freely on its surface.

After the membrane reaches its threshold potential, the voltage-controlled ion channels open, and many ions from the extracellular space rush into the intracellular space, as we explained in section 2.6.1. The ion channels open and close themselves autonomously and quickly. *There is no way or no need to simultaneously open other ion channels in the opposite direction. As we discussed above, the charged ions immediately in front of the membrane generate an electric gradient in the order of 100,000 V/cm.*

The sudden membrane potential change in the charge-up period acts as a valve. Given that the ions in the axonal arbor need to enter the membrane against the actual membrane potential, the potential stops the ion inflow to the membrane for the period while the membrane's voltage is above the threshold: it effectively inhibits further inflow through all axons. This behavior naturally explains the absolute refractory period. After the membrane's voltage drops below the threshold value, the ions can enter the membrane again (see Figures 3.22 and 3.17), but they need time to reach the AIS later (see Figure 1.6) when in the meantime the membrane's voltage proceeded toward its hyperpolarized state; so they seem to appear dozens of microseconds later at the AIS, explaining the relative refractory period (measured in [64]).

The inflow charge generates a "potential wave" (a solid current outflow) through the AIS; see the discussion in section 3.5. The decreasing charge causes the membrane's potential to decrease toward its resting potential, so it falls below the threshold voltage of the axonal gate at some point. If ions are still waiting on the other side, stopped when the membrane's charge-up process started (recall that they cannot exit the axon of the presynaptic neuron, and previously they could not enter the membrane), or newly arrived while the gate was closed, they can enter the membrane again. The ions travel a finite distance on the surface of the membrane with a finite speed, so there must be a delay between their entry and exit times. Furthermore, the inflow current must equal the outflow current. As discussed in section 2.4, charge conservation is not necessarily valid in *all contexts* of biological operation. If we measure the input and output currents, they may differ (see Fig. 1. in [47]); see section 3.5.

Notice that, to some measure, the case of switching a clamping voltage on is analogous to the arrival of a spike. Initially, the axon contains no ions. The front evoked by a step function is linear because of the slow current. In the classic picture, the axonal current flows into the membrane with capacity  $C_m$  and increases the membrane's voltage  $V_m$  with a time constant discussed after Eq.(2.72)

$$\frac{dV_m}{dt} = -\frac{1}{C_m} I_{axon}; \quad V_m(t) = \frac{I_{wall} * (1 - e^{-\alpha*t})}{C_m} \quad (2.70)$$

that generates a change in the membrane current

$$\frac{dI_m}{dt} = \frac{1}{R_m} \frac{dV_m}{dt}; \quad I_m^{on}(t) = g_m(V)V_m(t) \quad (2.71)$$

where  $g_m = \frac{1}{R_m}$  is the conductance of the membrane. That is, the measurable current equals the product of the conductance and the clamping voltage.

Equs.(3)-(5) in [5] express this relation. If we assume that the axonal current is “fast”, we arrive at the wrong conclusion that the conductance is voltage- or time-dependent. In contrast, if we assume that the axonal current is “slow”, we naturally conclude that Ohm’s Law is correct and valid also for biology: the conductance/resistance is constant.

*There is no voltage-dependent conductance* [117]. Instead, the finite speed of ions and the wrong assumption that conductance is a primary entity misleads physiological research. *With wording that “conductance changes”, one states that charge carriers appear/disappear/reappear; that is, the charge conservation is not fulfilled* (with nonphysical consequences listed in connection with the model in [5]). The physics background of the phenomenon is that the number of charge carriers changes (ions are “created” in the axon, and they appear on the membrane, as we detailed above).

In contrast, when the clamping voltage is switched off, the axon is still filled with charge carriers (but not filled after); the resting potential reaches the end at the membrane “instantly”. The driving force disappears, the ion stream stops, and no more ions enter the membrane. The lack and the presence of ions in the axon when switching clamping on and off, respectively, produce the difference that “*conductances increase with a delay when the axon is depolarized but fall with no appreciable inflexion when it is repolarized*” [5]. The potential is equalized by the AIS current, producing a net exponential decay:

$$I_m^{off} = I_{Wall} * e^{(-\frac{\alpha}{R_m C_m} * t)} \quad (2.72)$$

During the regular operation of a neuronal membrane, after opening the ion channels, a vast amount of ions flow into the intracellular space from the extracellular space, imitating the effect of switching a clamping voltage. The essential difference is that the ions arrive through the axon to the joining point in clamping. In contrast, through the membrane’s ion channels, they directly contribute on the membrane’s entire surface. The membrane’s size is finite, so with a finite current speed, it takes time until the charges on the membrane’s surface arrive at the AIS, in the same way as we discussed for the axonal current. These findings have significant implications for our understanding of the operation of neurons, including their signal processing and memory.

From a computational point of view [116], a persisting significant deviation from the resting potential (the arrival of the first spike from one of the upstream neurons) provides the signal ‘Begin Computing’, opening the ion channels in the membrane provides ‘End Computing’. After that, we will be in the ‘Signal Delivery’ phase until the end of the charge-up process. After that, ‘Signal Transmission’ follows. Our simple neuronal condenser can only perform one operation, to integrate the current it receives. Its result is the integration time itself. *It cannot distinguish its operands* (which synaptic inputs provided the current it integrates). Furthermore, *not all operands must be present at the beginning of the computation process. The membrane potential slowly returns to its resting value; furthermore, the current arriving during the ‘relative refractory period’, represent a (time-dependent) memory*, see section 1.8.1. Notice that the

content of that memory may depend on the neuronal environment.

### 2.6.5 Axon

We model the axons as electrolyte-filled semipermeable membrane tubes with ion channels in their walls. The axons do not passively follow the potential's time course, but they mediate the changes in their internal volume by using an ion pool available in their extracellular volume. The applied potential (including that of the mediated ions) opens the ion channels in the axon's wall.

In their native mode of operation, the three modes of ion channels define the 'direction of the time' [62, 123, 23] (the direction of the current that transmits the spike). The layer that the front of the spike creates on the surface (on both sides of the tube) propagates in both directions, but it cannot open the ion channels on the side where the spike arrived from, and the ion channels are still inactivated.

Clamping sets up an artificial working regime for the ion channels: the permanent electric field on the outer surface enables ions to enter the inner volume where formerly no ions (and no potential) existed. The rushed-in ions will flow away from the place of their entrance (recall that the current removes part of the ion layer on the surface), and a slow current toward the membrane can start. Under clamping conditions, the experimenter sets the voltage instead of the transmitted signal and in a static way instead of an autonomous dynamic one.

Initially, the membrane, the clamping point on the axon, and the intracellular and extracellular fluid maintain their resting potential. When an external potential is applied suddenly to some point of the axon, an electric field  $\frac{dV}{dx} \propto (V_{membrane} - V_{clamp})$  appears on the *outside surface* of the axon. The extracellular space with its high ion concentration  $C_k^{ext}$  represents an "ion cloud". When the clamping voltage is switched on, a "fast" current instantly delivers the potential along the *outer* surface of the axon. However, this is not the case (at least not in the initial moment) on the *inner* surface. *There is no charge present that could change the potential:* 'the intracellular concentration at rest is around five orders of magnitude less than that in the extracellular space' [21]. The physical picture that the clamping potential instantly appears at the end of the axon at the membrane (i.e., if (apparently) they have an infinitely large propagation speed) is valid only if charge carriers exist in the axon.

As described above, the charge gradually increases the potential along the axon (starting from the position of the clamping electrode) until the clamping potential reaches the axon's end at the membrane. (We could see the effect when measuring voltage instead of conductance on the axonal tube instead of the membrane, shown in our Fig. 3.24.) At that point, the driving force gradually disappears: the potential at the end of the axon and that on the membrane becomes the same. The macroscopic streaming of ions inside the tube only slightly complicates the process: the local internal concentration can saturate only later, given that part of the inflowing ions is delivered to another place within the axon. Notice that the current (and the voltage) on the axon

increases in the function of the time exponentially instead of linearly or step-wise, which would be expected when assuming instant interaction or no “slow” macroscopic current.

In this model, we assume that during the time  $dt$ , in the volume  $dx$ , we have a constant ion inflow  $I_{wall}$  through the axon’s wall, which increases the charge and concentration already in the volume. The charges in the tube experience the field  $\frac{dV}{dx}$ , and they move with speed  $v$  inside the tube (see Eq. (2.26)). The ionic fluid with velocity  $v$  (proportional to  $\frac{dV}{dx}$ ) transfers the ionic charge in the volume to the neighboring element at a distance  $v * dt$ , and delivers the charge and concentration from the neighboring element at a distance  $-v * dt$  into this element. At the time  $t$ , the concentration at  $x$  will result from the inflow at the place  $x - v * t$  (see also the general discussion around Eq. (2.2)).

As described above, the charge gradually increases the potential along the axon (starting from the position of the clamping electrode) until the clamping potential reaches the axon’s end at the membrane. (We could see the effect when measuring voltage instead of conductance on the axonal tube instead of the membrane, shown in our Fig. 3.24.) At that point, the driving force gradually disappears: the potential at the end of the axon and that on the membrane becomes the same. The macroscopic streaming of ions inside the tube only slightly complicates the process: the local internal concentration can saturate only later, given that part of the inflowing ions is delivered to another place within the axon. Notice that the current (and the voltage) on the axon increases in the function of the time exponentially instead of linearly or step-wise, which would be expected when assuming instant interaction or no “slow” macroscopic current.

The unusual physical situation in making electric measurements in biological systems is that, in the metallic half of the circuit, the electrode at the membrane (and, if being equipotential, the membrane itself, too) takes “instantly” the external voltage. However, in the biological half of the circuit, the voltage  $V$  at the end of the axonal tube initially remains the same: inside the tube, there is no charge around to produce a potential (actually, without charge inflow, it is a piece of insulator).

### 2.6.6 Axonal arbor

### 2.6.7 Axon Initial Segment

At the time when HH published [5] their electrical model for the neuron, the structure of the neuron, the AIS and its role in the electric operation was not yet known. HH introduced the idea explicitly that the electrically equivalent circuit of a neuron is an *RC* oscillator. They did not see any structural elements on the membrane, so logically, they assumed it was a distributed resistor and capacitor, which really has resemblance with a *parallelly switched RC oscillator*. However, they made a wrong choice of the circuit type, and their choice (probably due to inertia) was repeated in good textbooks such as ([1] Figure 3.1 or [21] Figure 1.1), and it is a commonly accepted fallacy even today [125]. This wrong choice led to

the need to assume a false (rectifying) ionic current and blocks understanding, among others, *why* AP is initiated.

From the discussion and figure above, it is clear that the right choice is a "<https://www.electronics-tutorials.ws/rc/rc-differentiator.html>" *differentiator* where 'the input signal is applied to one side of the capacitor with the output taken across the resistor'. The currents are directly created on the membrane (condenser) and the output voltage (AP) is taken across the resistor (AIS). In other words: *the neuronal membrane is a serial instead of a parallel circuit*, with far-reaching consequences.

For electrical modeling, we can use the approximation that a *distributed* condenser (the neuronal membrane) and a *discrete* resistor (the AIS form an *RC* circuit, see also the discussion in section 2.4.8. It is clear that all currents (including the synaptic currents, the membrane's rush-in current, and the artificial currents either patching them directly to the membrane or clamping them to its axons) flow into the condenser (and cause potential increases calculated using the membrane's capacitance). Furthermore, the potential drops only due to the current flowing through the AIS. It is the exact equivalent of a passive *RC differentiator* circuit: "the input is connected to a capacitor while the output voltage is taken from across a resistance" and not to be mismatched with a passive *RC integrator* circuit where "the input is connected to a resistance while the output voltage is taken from across a capacitor".

## 2.7 Neuronal operation

### 2.7.1 Animal electricity

"All animals that move have electricity in their bodies. Electricity is the only thing that's fast enough to carry the messages that make us who we are. Our thoughts, our ability to move, see, dream, all of that is fundamentally driven and organized by electrical pulses. It's almost like what happens in a computer but far more beautiful and complicated." –(neuroscientist Rodolfo Llinas quoted in "Electricity's spark of life" by Emily Sohn in Science News for Students, 29 September 2003).

The phenomenon that the body operates with electric signals was discovered about one and a half century ago [99], and the idea that "In simple cases of ionized substances both the amount of substance and the force acting may be expressed in electrical terms" [40] shined up nearly a century ago. The basic idea of biological current was correctly defined at the beginning: "The permeability of a membrane to a penetrating substance is given quantitatively by the amount of the substance which crosses a unit area of the membrane in unit time under the action of a unit force. In simple cases of ionized substances both the amount of substance and the force acting may be expressed in electrical terms. Then the permeability may be ultimately converted into coulombs per second for a square centimeter and a potential difference of 1 volt, which is the conductance,

in reciprocal ohms, for a square centimeter” [40]. However, at that time physiologically defined fine details were not known. conductance current!biological One must never forget that ”*movement of ions* across the plasma membrane *results in changes of electrical potential* across the membrane, and these potential changes are the primary signals that convey biological messages” [1] (***using “equivalent circuits” hides that the potential changes***). equivalent electrical circuit In this section, we proceed along the line pointed by those latter authors in Chapter 2 of their book.

We must recall that *this charge is delivered chemically, i.e., it is the result of an thermoelectric process*, so the concentration and the potential change simultaneously. Also, *the charge carriers are ions instead of electrons and the transfer mechanisms are entirely different*. From purely simplistic considerations concerning the many orders of magnitude in the ratio of their size and mass, we see that the charge carriers have speeds differing by orders of magnitude, that requires revisiting the classic laws such as instant interaction (behind the ideas such as Kirchoff’s laws, Ohm’s law, ’retarded potential’). Furthermore, the ions are not fixed to isolating surfaces, and some biological ”constructions” may be active elements from the point of view of electronics: the membrane may store charge (disappears) for some period and ion channels may ”produce” charge in the measured system. Also, the molecules may dissociate and polarize under the effects of local potentials, enabling to create macroscopically different parameters such as potential and concentration, see also Onsager’s reciprocal relations [110]. In the case of living matter, we must handle thermodynamical and electrical forces simultaneously. There are no ’net abstract’ cases where only electrical forces act on the ions. This feature, accompanied by the slowness and large size of the ions, requires attention and rethinking the basic notions of electricity.

We must also call attention to the dynamic behavior of charges inside living matter. Basically, they are balanced, but, and it is vital for describing the life, they can get unbalanced in a local region for shorter or longer periods. This balanced state is the basis for having a resting potential (longer), and the perturbed (unbalanced) state is the basis for creating and transferring action potential, among others. *The change of those states are described by the laws of motion, and their continuous change is the life itself.*

Although it is fundamentally correct that ”because dissociated ions carry electric charges, their movement is influenced not only by concentration gradients but also by electric fields”, these gradients are competing with each other and their complex interaction controls the biological processes. ”Based on thermodynamic principles, ions tend to flow from regions of high concentrations to regions of low concentrations” (see [1], page 9), furthermore, the electric gradient gets more role than presumed; see Onsager’s reciprocal relations [110]. We must never forget that *ions represent both charge and mass, so a current means delivering mass and vice versa*. In some cases, when precisely measuring the time course of current compared to the time course of voltage, one can experience a ’phase delay’ between them. This may inspire further research, such as inventing ’inductive’, ’capacitive’ and ’resistive’ currents in electricity; or one

may believe that the system shows 'non-ohmic' behavior in biology; that is, it cannot be described by laws of physics.

An often forgotten thought is that "The things that neurophysiologists typically want to measure are electrical signals such as action potentials and synaptic potentials, or the membrane currents responsible for these potentials. *Under ideal circumstances, the physical act of measuring a neurophysiological event would have no effect on the electrical signal of interest. Unfortunately, this is seldom the case in neurophysiology.*" [1], Appendix A. We do not want to repeat the content of that appendix, except some points where we add notes, corrections or pinpointings. We add, however, that neurophysiologists make measurements in hybrid circuits, where the charge carriers are ions in one half of the circuit and electrons in the other. The conversion introduces several issues, among others delays (resulting in measuring non-matching value pairs); introducing negatively charged high-speed particles into systems having positively charged low-speed particles; intermixing inhomogenous, non-isotropic, structured matter into the systems and applying laws derived for homogeneous, isotropic, unstructured matter; applying laws derived for the "free electron cloud" to the case of slowly moving dipole molecules.

It is worth to recall: **Accuracy:** The degree to which a measurement indicates the true magnitude of a measurable quantity. **Precision:** The resolution and reproducibility of a measurement; implies nothing about accuracy. A measurement can be precise without being accurate. The reverse, however, is usually not true." [1] We add: sometimes, we measure a quantity which differs from the one we wanted to measure. Especially, if we interpret erroneously what we wanted to measure and how do we measure it.

## 2.7.2 Membranes & layers

As described, separating electrolytes by a finite-width membrane leads to changes in the distribution of ions, in their macroscopic parameters 'concentration' and 'potential'. The actual distribution of course depends on the thickness of the membrane and the electrolyte concentration in the segments. Experience shows that although the material of the membrane is a good isolator, the membrane is permeable in some sense (see section 2.7.3), sometimes selectively and sometimes in one direction only; sometimes in a controlled way. The presence of layers on the membrane is experimentally confirmed. It is perfectly seen that the dissociated ions are mainly in the proximal  $< 1 \text{ nm}$  layer of the membrane, see the caption of figure (Fig. 11.22 in [87]). The ionic concentrations are largely different in its two segments and the ion channels have their cap on the side of segment with lower concentration. However, it is experimentally hard to measure anything in this layer; furthermore, the statical interpretation of cellular operation prevents understanding their dynamic operation, including their role in creating and transferring electric signals.

Membranes, and especially the semipermeable ones, are fundamental pieces in many places, from biological objects to industrial filters. They operate on the border of microscopic and macroscopic worlds, combine movements having

speeds differing by several orders of magnitude, separate non-living and living matters and combine electrical and thermodynamical interactions. We show that a fragile skin near the surface of biological membranes is responsible for the biological thermoelectric processes.

We might imagine this layer's importance and operation in line with the Earth's atmosphere. Its features drastically deviate from the features of the bulks on its two sides. It is separated by a sharp contour on one side and an ill-defined border on the other; its volume is far from being homogeneous. Gravity keeps it in place, and it is at rest. However, sometimes, for some periods, also other (thermodynamical and electrical) forces evoke inside it and lead to transient changes, moving huge masses with high-speeds inside it. Its thickness and mass are negligible compared to those of the bulks on their two sides, and we can describe the bulks without considering their density, mass, size, etc. Still, this thin layer is responsible for the weather; its transient processes define the visibility from both sides (define propagation of electromagnetic fields), and it can protect us from EM radiations. It can temporarily absorb products of slow processes (water evaporation) and deliver masses of high density (much above its density, such as water, sand, etc.) to continental distances, creating the illusion that it stores that matter. Minor changes (natural ones, such as a slight difference in air temperature, and artificial ones, such as injecting condensation nuclei in clouds) can result in enormous changes. Even we can imagine volcanic eruptions as semipermeable gates for material with apparently random operation and distribution of the injected material. Physics sees correctly its importance and role: "the crucial system in biology isn't a molecule or a molecular class whatsoever, but the interface created by biomolecules in water" [28].

To describe those complex and continuous phenomena at least approximately, we must separate them into stages. We can describe the stages approximately using omissions, approximations, and abstractions, usually considering only one dominant phenomenon. The described phenomena are interrelated in a very complex way and depend on different parameters. To some point, we can describe that thin layer using a static picture and provide an empirical description of its processes, even though we can give some limited-validity mathematical descriptions for those stages. However, we understand that for describing the time course of the transition (contrasting with step-like stage changes) between those well-defined stages of the atmosphere, we need a *dynamic description* to discover the *laws of motion* governing the processes.

Similar is the case with the neuronal membrane and the neuronal operation. Now, we are at the point where their decades-old static description is insufficient. We need to derive the corresponding laws of motion to describe the neuron's dynamic behavior. We need a meticulous and unusual analysis to derive them. In a neuron, in the abstraction science uses, we put together only an ionic solution, a semipermeable membrane, and currents that reach and leave them. All these belong to non-living matter. As experienced, at some combination of their parameters and gradients, qualitatively different phenomena happen, which, in the abstraction biology uses, are called signs of life; our system starts to belong

to living matter. Given that the approximations, the derived abstractions, and the mathematical formalisms describing them are different for the two cases, *it looks like we have two different, only loosely bound worlds*. We realize we have arrived at the boundary of non-living and living matters, and we must go back to the *first principles of science* to clarify where their boundary is. However, by using our approach, we may defy that "the emergence of life cannot be predicted by the laws of physics" [9]. Our artificial duck looks, quacks and swims like a duck.

### 2.7.3 Demon in the membrane

We intend to build an artificial neuron using materials and principles of non-living science. We build 'Maxwell-demon'-like objects into the separating membrane: gated ion channels, see Fig. (2.12). The ion channels operate as demons (from the point of view of the segments and the observer). Some power opens them, they autonomously transfer ions in a *potential-accelerated* operating mode, and then that power puts the cap back on the top of the channel. Let us separate our volume with a semipermeable membrane having capped ion channels inserted into its material. As long as the caps of the ion channels are closed and the ion concentration on the two sides of the membrane are the same, we do not see any change in the state of the solutions. However, our construction 'looks like a duck'.

Although the channels can stochastically open, close, and re-open, they transmit more or less well defined charge quanta. Even the channels can recognize the ions' chemical nature and transmit only a selected ion type. The channels are passive during those processes, although the enormous voltage gradient can rearrange their structure and change their behavior through that. The demons also concert their actions using the layer containing charges as a communication medium; their population maintains a well defined macroscopic current across the membrane. Our construction swims like a 'duck'.

#### Voltage sensing

"Voltage sensing by ion channels is the key event enabling the generation and propagation of electrical activity in excitable cells." [126] How voltage gating of channels works is still a mystery; one of the worst consequences that Hodgkin and Huxley separated the potential from ions and their current. It is not easy to investigate it experimentally: "the structural basis of voltage gating is uncertain because the resting state exists only at deeply negative membrane potentials" [127]. Usually, a "sliding helix" (structural) model is assumed.

Under certain conditions, an ion channel can be opened in only one direction and only for a limited period, and this way the membrane becomes semipermeable. We imagine an ion channel as a simple hole (a cylinder) between the high and low-concentration segments with a cap on its top (on the side of the low-concentration segment). Until the cap is removed/lifted (the channel gets open), practically nothing changes. At the points where the ion channels are located

the ions cannot penetrate the membrane. Unlike the original Maxwell demon, our demon does not have information in advance about which particle should be transmitted: it is passive in selecting the particle. (Passive here means that no biologically produced energy is used: the electric potential energy from the voltage difference across the membrane moves the ions to the other side of the membrane.) It only keeps one way closed for part of the time, and the voltage performs selecting the ions.

We can easily interpret why our voltage-controlled ion channel model gets opened and closed due to purely electrostatic reasons. It works as the two-plate simple nano-scale electrometer (of type quadrant, Lindermann, Hoffman, and Wulf) similar to the ones used to measure the small electrical potential between charged elements (e.g., plates or fine quartz fibers). Given that the membrane and the cap in their resting state are isolators, no electrical repulsion is evoked between them and the adhesion sticks them firmly to each other, representing a permanent force. The van der Waals force is inversely proportional to the squared distance between the dipoles in the cap and the membrane, respectively, and is linearly proportional to the perimeter of the channel.

However, when a slow ion current flows into the surface layer in the proximity of the cap, charges appear in the layer proximal to the membrane; the membrane and the cap get covered by a very thin electrical skin. The charge on the cap is proportional to the surface of the cap and similarly inversely proportional to the squared distance between the cap and the membrane. A local voltage gradient is generated by the local gradient of the slow ion current (see below), and the force acting on the cap is proportional to the product of the voltage gradient and the area of the cap. Given that the cap is slightly elevated, the repulsion force may have a component in the direction of lifting the cap. Since the van der Waals force is of fixed size, the electrical repulsion exceeds it at a critical voltage gradient value and the channel opens. The gate remains open as long as the local charge distribution enables it. The cap is connected to the membrane only at one point, so it cannot fly away and also cannot close again until the charge on the surface is present. In the absense of charge, the cap makes a random movement and the short-distance van der Waals force may eventually fix the cap again to the membrane, this way closing the channel. The voltage sensing electrometer opens the channel and the lack of charge on the surface enables to close it, but the closing is not immediate (the mass of the cap is by orders of magnitude larger than the mass of an ion that can pass the channel). The fluctuation of the voltage gradient due to the gradient of the slow current in the layer in the proximity of the membrane near the ion channel's exit opens, closes, and re-opens the channel in an apparently stochastic way (actually, as the repulsion of charges due to the fluctuating current on the cap and the membrane regulates it), as observed. Having gates (caps) is needed only for the synchronized operation of the channels: opening and closing work also in the absence of caps, as discussed.

When one cap is removed, the rushed-in ions in the proximity of the channel's exit suddenly increase the local potential (produce fast transient changes [75]) proximal to the spot centered at the exit in the layer on the membrane's surface.

The surface outside the spot remains at a lower potential, so the ions in the layer start moving toward other channel exits, delivering potential to those channel exits. Given that they are voltage-controlled, they get open, and the process continues in an avalanche-like way [76]. The avalanche, as explained, needs a sufficiently large voltage gradient; which can be triggered by several synaptic inputs if they sum up appropriately. Alternatively, a single spike with sufficiently steep front slope [63] can be sufficient; providing a simple way of synchronizing neuronal assemblies (and proving that not the voltage, but the voltage gradient, single of summed, controls the operation).

### Passing through the ion channel

The operation of the ion channel, alone, cannot explain that the channel closes after a given number of ions passed the channel; that number is not (entirely) random. Actually, the local behavior of the membrane's surface layers regulate the number of ions.

The segments are no longer mechanically separated when the cap is removed. The charged ions are enabled to rush into the lower concentration segment. They experience an enormous accelerating gradient: "an electrical potential difference about 50–100 mV ... exists across a plasma membrane only about 5 nm thick, so that the resulting voltage gradient is about 100,000 V/cm" [87]. That enormous gradient, comparable to that of electrostatic particle accelerators, "snorts" the ions from the high-concentration side into the low-concentration side and causes a process "like a flea hopping in a breeze". Consequently, "transport efficiency of ion channels is  $10^5$  times greater than the fastest rate of transport mediated by any known carrier protein" [87]. Recall that, in physics, the *drift speed*, the *electrical repulsion-assisted speed*, and the *electrical potential-accelerated speed* of ions differ by several orders of magnitude (for visibility, the ratio of the gradients in Fig. 2.12 is not proportional).

The snorted ions "hop" into the layer from the another layer. In the beginning, with their *voltage-accelerated* speed, it could take less than  $\frac{5 \cdot 10^{-9} \text{m}}{10^3 \text{m/s}}$  s to pass the channel (simulation [128] uses a psec representative time interval), in the end, they may slow down to the *voltage-assisted* level as the potential gradually decreases (which is still  $\frac{5 \cdot 10^{-9} \text{m}}{10^{-1} \text{m/s}}$  s), so we can omit that time when calculating the charged layer formation. Due to the enormous speed difference between the *accelerated* and *assisted* speeds, the passage is practically instant. The accelerating field through the hole across the layers persists, although it decreases; see Fig. 2.2. On the high-concentration segment, only the ions in the layer in the immediate proximity of the entrance can feel the accelerating potential and move with the potential-accelerated speed. The after-diffusion with the *potential-assisted* speed from the next neighboring layer in the high potential segment is by orders of magnitude slower than the passage through the hole with the *potential-accelerated* speed. Depending on the process parameters, the local potential can rise above the high-concentration segment's potential for a short period due to the accelerated current's 'ram pressure' (or 'impact pres-

sure'). Due to their electrical repulsion, the ions induce a similar change on the opposite segment.

The accelerating potential around the channel's exit gradually (but quickly) disappears when the particle exits the ion channel (see the green ion in the figure), and the ion arrives at the bulk potential. It practically stops: it can continue only with its *potential-assisted* (later with *drift*) *speed, which is several orders of magnitude lower*. However, the rest of the ions are still accelerated through the channel, and somewhat later, they also land in the formerly low-concentration layer, further increasing its potential and concentration. The passed-through ions increase the local potential in the layer in the low-concentration segment and decrease the local potential in the layer in the high-concentration segment. Given that the after-diffusion speeds in the layers are limited, "as ion concentrations are increased, the flux of ions through a channel increases proportionally but then levels off (saturates) at a maximum rate" [87].

Here the effect of the finite resources, see section 2.2.7, explicitly appears. As we discuss in sections 2.4.9 and 1.10.5, about  $10^3$  ions are transferred per channel. These ions are snorted from one layer in the high-concentration segment into another layer in the low-concentration layer. The driving force gradually decreases, see Fig. 2.2.7, because ions leave the first layer and they appear in the second mentioned layer. The potential-assisted speed to replace the leaving ions into the first segment from the bulk as well as diffusing out from the second segment without appropriate driving forces is by orders of magnitude slower, so we can approximate the process that a gradually decreasing accelerating force drives the ions. The process leads to a special reversal of concentrations and potentials. In a very short period, in the layer on the formerly low-concentration side a very thin high-potential layer is formed that prevents further ions from entering the formerly high-concentration layer: the process of transferring ions through the channel closes the door behind the needed amount of ions. Now the gradient diminished and the van der Waals force can close the channel again.

The commonly used picture about the operation of ion channels [129] is definitely wrong.

- the potential generated across the membrane is entirely neglected
- the ions have no driving force and the hypothesized protein carriers are too slow [87]
- the considered van der Waals force is too weak to be noticed by the ions (the 'cation-attractive negative ends' of the Alpha helices are too far)
- the assumed force by the 'cation-attractive negative ends' destabilize the ion path: as the deviation from the central path increases, so increases the deviating driving force
- even if the weak van der Waals force would work for a single ion, the next ion would be rejected by the strong Coulomb-force due to the first ion

### Delivering current across the membrane

The passage is too quick to affect the bulk (see also the discussion in section 3.3.1), given that the ions can only use a *potential-assisted* speed to reach distant places in both segments. Again, the charge and mass conservation works: the ions pass suddenly from the high-concentration side to the low-concentration side, only from one layer to another. The mentioned *layers on the two sides will actively initiate and terminate the ion transfer through the ion channels, but the ions can only pass through an open channel*. One layer saturates, and the other empties. After a while, *the source of ions will be exhausted. Those layers' existence suggests revisiting the idea of describing neuronal operation by two single potentials of the bulks on the two sides of the membrane.*

Following their arrival, the driving force perpendicular to the membrane's voltage disappears, and the ions form a thin "hot spot" in the layer. The electric repulsion acts in parallel with the membrane's surface and leads to distributing the ions (decreasing the gradient by distributing the charge locally) around the channel's exit. The ions saturate the layer on the membrane's surface with a time constant between ( $\frac{10^{-8}m}{10^{-1}m/s}$  s) at the beginning and ( $\frac{10^{-8}m}{10^{-4}m/s}$  s) at the end of their arrival period (we assumed 10 nm average distance between ion channel exits on the membrane). We shall take the longer time, so that we can expect a time constant for the saturation current around the ion channel's exit in the order of 0.1 ms. When charging up the membrane in an avalanche-like way, the ions must pass on average a distance of about 0.05 mm from its center to its farthest point, so we expect a 0.5 ms ( $\frac{5*10^{-5}m}{10^{-1}m/s}$  s) time until the membrane's slow current charges up the membrane to its maximum potential. The created charge must flow out from the farthest point in the neuron membrane of size 0.1 mm in time of order at or below 1 ms ( $\frac{10^{-4}m}{10^{-1}m/s}$  s); see the length of the  $\frac{dV}{dt}$  pulse measured at the beginning of the AIS [82], see Fig. 3.13, which time is prolonged up to 10 ms by the neuronal  $RC$  circuit; the ions are slow when the voltage on the AIS is low, see Eq. (2.31). Assuming those distances and speeds, including the *potential-assisted* speed of the slow current, we are on a time scale matching the available observations.

### Ion selectivity

Maybe the mechanism of channel passing can also contribute to explaining ion selectivity. "The normal selectivity cannot be explained by pore size, because  $Na^+$  is smaller than  $K^+$  [87]". The two ions have the same charge, but  $K^+$  is nearly 70% heavier than  $Na^+$ , a definite disadvantage when accelerated by a vast electrical gradient. When the layer on the arrival side gets saturated, its potential reaches the potential of the bulk on the high concentration side (this is necessary to decelerate the accelerated ions), and so the channel gets closed (the accelerating potential disappears for a short period until the ions from the layer flow away toward the drain or they diffuse toward the bulk). We assume that the ions continuously accelerate, then decelerate, due to the potential gradient (which we assume to be constant for a moment). When  $Na^+$  ions stopped after

passing the channel and built up a repulsive layer proximal to the channel's exit, the  $K^+$  ions passed only about 60% of the channel's length. The  $Na^+$  ions, which started from the departure layer with a handicap of 2 to 3 nm, will arrive earlier than the  $K^+$  ions from the 0.1 nm thick charged layer proximal to the channel's entrance. That is, this handicap results in a strong enrichment of  $Na^+$  ions. For the detailed calculations see section 2.4.9.

Given that the potential reverses, the late ions are decelerated and then accelerated in the reverse direction (recall that the layer they started from is still empty and attractive), they simply go back to the departure side. The ions also repulse each other while being accelerated (the accelerating gradient acts on a distance of 5 nm while the ions may approach each other to a distance of 0.1 nm, so the mutual repulsion can be significant). In this way, the heavier ions help their competitors and vice versa. (The different ions can also connect to different, heavy-weight components of the solution, drastically changing the picture.) The result is that only the lighter ions can pass the channel from an ion mixture when the cup is suddenly removed. The passage is super-fast; it is in the psec region (with a *voltage-accelerated* speed compared to the *voltage-assisted* speed of after-loading ions from the next layer), and the created potential quickly decays by diffusion.

The commonly used picture about the operation of selectivity filters is surely wrong. The assumed mechanical operation of the pores is simply too slow: the assumed structural change needs  $10^{-8}$  s and the ions passage time is about  $10^{-11}$  s (furthermore, it must be repeated about  $10^3$  times per passage). If a wrong ion is caught, it must be transported back to its departure side, through the right ions (against their repulsion), and the right ions must retry. Neither for moving forward nor backward an appropriate driving force is present in that picture.

#### 2.7.4 Equivalent circuits

One wrong consequence of forgetting that the charge transfer mechanism is entirely different, the charge carriers are large and heavy (and as a consequence: slow) ions instead of electron (cloud), furthermore they are not necessarily present in the volume under test and the 'construction' of biological matter enables the tested medium to produce charge carriers, using 'equivalent circuits' for neuronal operation. This fallacy entirely falsifies the conclusions from the measurements.

Another wrong consequence of using 'equivalent circuits' to describe the electrical operation of neurons is believing that the currents in the biological circuit do not change the concentration, and through the concentration, also the potential; see also section 2.2.7. The 'equivalent circuits', of course, use a constant potential (they follow the abstraction used in the theory of electricity, although the 'ideal batteries' also may produce their voltage using chemical processes), and unreasonably, some mystic process changes the resistance/conductance of components. This wrong abstraction results in numerous misunderstandings, among others, introducing ideas such as parallel oscillator equivalent of neuron, input resistance, delayed rectifier current, resting current, and time- or voltage-

dependent conductance. Furthermore, we cannot interpret, among others, *how neuronal electricity works in lack of external potential; how slow currents operate neuron's infrastructure, how and why action potential is generated*. Deriving the time course of the Nernst-Planck potential opens the way to a quantitative understanding of neurophysical electrical processes, including their time course.

Again another wrong consequence is that the two secondary abstractions 'potential', and 'current', became independent from the primary abstraction 'charge' and each other (significantly contributing to the fallacy that 'physics cannot describe life'). Our equations and the underlying discussion point to the fact that *the potential and the current cannot be separated from the charge*. No 'delayed rectifying current' and 'voltage- (or time-) dependent conductance' exist. Those notions originate from the wrong interpretation of measured data derived from mismatching measured electrical data pairs and the misconception that biological structures and materials must behave like metals.

As we discussed in section 2.5.5, the unbalanced charge in neurons and the charge injected suddenly into the intracellular segment during a rush-in action are in the same order of magnitude. We also discussed that the charge injection (the appearance and flow of charge in the proximal layer on the membrane's surface) causes well measureable mechanical, optical, etc. changes [84] on the membrane. Those changes are well observable on the low-concentration side, in the form of slow currents, and large-scale concentration and potential changes.

Those changes also mean that a large amount of charge passes from the high-concentration side to the low concentration side of the membrane, and causes a sudden drop on the high-concentration side of the membrane. As discussed, that change means simultaneously a change in the corresponding potentials across the membrane that solves the mystery why the AP stops. The potential across the membrane is defined by the difference of the potential of the two thin layers (see section 2.7.2) on the membrane's surface. As we discussed, a huge electric field exists across the plates of the neuronal condenser, while a moderate one in the proximal layers. That means that the ions can quickly leave the high concentration when the rush-in injection begins. They produce an 'empty' layer (and a potential gradient) whithin that layer and the ions in the neighboring layer start to move using the 'downhill' potential. However, they do have a much slower speed, so they 'stop' at some distance.

### 2.7.5 Operating states

The two electric fields show essentially different dependencies on the neuron's parameters. Recall that although the parameters we used are biologically plausible, they are only estimations. The qualitative conclusions, however, remain valid. As Figure 2.8 shows, in the function of the membrane's thickness, the electric field across the membrane due to electric charges (it does not depend on the thickness of the membrane), for different physically plausible assumptions; furthermore, the thermal electric field.

The balanced state is set to where the thermodynamic and electric "electric field" diagram lines cross each other; around 5 nm; the value we assumed in

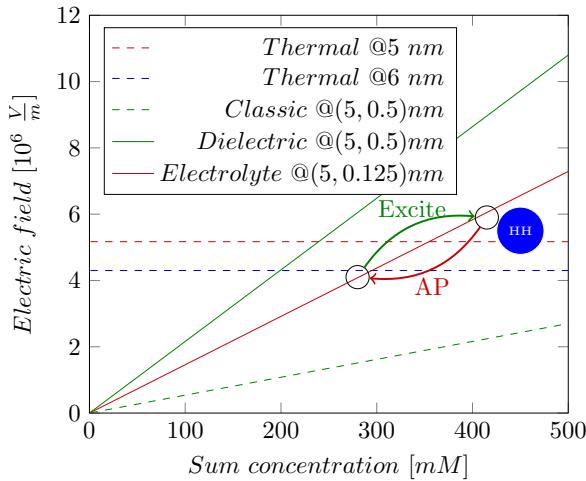


Figure 2.14: The electric and the thermal "electric fields" at different concentrations, see Eq.(2.68).The thermal electric field varies with the thickness parameter and depends on the concentration; see Eq.(2.50). Balanced states are where the sloping lines cross the horizontal ones. The dot marks where Hodgkin and Huxley provided measured data.

evaluating our equations. On the other hand, we can check the electric field's dependence on the summed-up concentration of the ions in the segment (see Fig. 2.14). Here, the thermodynamic electric field is constant but different at different width parameters. The classic condenser does not provide a reasonably balanced state (a matching line). The dielectric diagram line seems to provide a realistic estimation when using biologically reasonable parameters. One can describe the neuron as a balanced system at the intersection of the sloping and the horizontal lines. In the resting state, only minor deviations from this state exist in both the electric field and the chemical concentration.

In the transient state, if we assume that a charge transfer causes a significant potential change around  $100\text{ mV}$  in the layer of width  $100\text{ nm}$ , it means a  $0.1 * 10^6 \left[ \frac{\text{V}}{\text{m}} \right]$  jump in the electric field that corresponds to a  $100 \left[ \text{mM} \right]$  jump in the concentration (for only a short time and only in that mentioned layer not in bulk; see also Fig. 1.8). During issuing an AP, the system finds its way back to the crossing point (the path is not simple: both concentrations on both sides of the membrane and the electric field in the mentioned layer change; the process is relaxation, as it is seen in the shape of an AP).

Even we can imagine how the electric process happens in this controlled

system (for visibility, the positions of the marks are not proportional to the mentioned numbers). The system is in a balanced state at a crossing point. The two circles connected by bent arrows represent that when an excitation begins at the point with lower concentration and higher potential (the cytoplasm side and negative resting potential), ions rush into the surface layer, so the ion concentration increases, that increases the electric field; which is seen that the membrane potential suddenly increases. The increased potential starts a current, but the current is slow, and the intensity of the current through the channels in the membrane's wall is higher than the current of the drain (AIS) so the system issues an AP while returning to its starting point. The system will move along the line, with the restriction that it is a movement in the phase space (the change in concentration is not proportional with the time), and the different points on the membrane's surface may have the potential at different times (the spatiotemporal behavior). Due to the capacitive current, the local potential may temporarily drop below the set-point (as observed in physiology, this is known as hyperpolarization). The time course of the processes are described by the laws of motion of biology [19] (the time derivatives of the Nernst-Planck equation), and the simplified model works as described in section 4 of [11] and its computational details in [20].

## 2.8 Neuron as control circle

From control theory, it is known that the goal of a controlled system is to govern the application of system inputs to drive the system to a desired state while minimizing delay and overshoot, steady-state error, and ensuring control stability. The neuron implements a controller that monitors the controlled process variable (the membrane voltage) and compares it with the reference or setpoint (the resting potential). Recall that the geometry, the composition, and the concentration of electrolytes define the setpoint, as discussed in section 2.5. The difference between the process variable's actual and desired values, known as the error signal, represents the actual offset potential. It is applied as a feedback to generate a control action that brings the controlled process variable to the setpoint value.

From a control theoretical point of view, the condenser geometry and the ion concentrations set the 'always the same' value (the set-point; see also Figure 2.8) and the currents serve to keep or restore that value. After introducing a finite-width membrane into an electrolyte, a potential difference between the two membrane surfaces is created; see Eq. (2.69). When adjusting the membrane's potential, we must consider its ground and excited states separately, given that the perturbations in these two cases are vastly different. Nature employs various mechanisms to maintain the ground state and recover it after generating a spike. Although nature's tools are remarkably similar (channels and pumps; here, for discussing 'downhill' channels, we must consider the charge-up of different components), the significant difference in current intensity warrants a separate discussion.

### 2.8.1 PID's potential controlling

Biology uses a simple PID controller with proportional, integral, and derivative components. In simple words, it means that the output of the system (the output voltage measurable on the AIS) depends on the input voltage (the present: input current if the resistance is constant), the integrated input current(s) (the past: how much the biological objects changed due to electrical effects), and their derivatives (the future: how the actual gradients tend to form the action potential). (Notice that calculating the derivatives of the interdependent parameters needs care, as discussed in [130], given that the components are non-ideal biological components rather than the ideal discrete components.) The sum of those summands defines the resulting output voltage. The biological case is more complicated than the technical one because biology works with slow ions, and the components have their temporal dependence (applying the laws created for fast currents needs emulation, as discussed in section 2.4.7). Furthermore, the summands have several constituents and the neurons handle those current-related constituents autonomously. That is, unlike what is assumed in the classic physiology, the output voltage is not necessarily a simple function of the mentioned input variables; furthermore, it is not sufficient to consider the "present" of the system. The classic models all omit the derivatives' contributions (a direct consequence of using clamping that 'freezes' their state, the 'future' cannot be interpreted) except that of the capacitive current, which is the passive consequence of the input currents. Furthermore, the 'Integrate and Fire'-type models consider the integrated currents only in the 'charge-up' ('Computing') period of operation and they entirely omit that different physical processes are going on in different stages of operation. That is, *even the best classic models can not describe neuronal operation completely and correctly.*

The gradients are used to adjust the process variable through their positive and negative contributions (corresponding to rising and falling edges), and the different speeds of the thermodynamic and electrical interactions minimize the delay (i.e., provide the maximum operational speed, vital for survival). The steady-state error is minimized by setting the process variable to the reference point using long-term stable parameters (geometry and overall concentration). The low-intensity current through the always-open resting ion channels provides dynamic stability in the steady state.

We considered that neuron has a stable base state. On the one side, this resting state must be dynamically stabilized for little perturbations using as little energy as possible (and to provide a mechanism when the cell grows, divides, or ages). On the other side, it must be able to restore the state after rough perturbations as quickly as possible, causing short-time transients (when restoring the membrane's potential after issuing a spike). In both the resting and transient states, the system attempts to return to its balanced state, though the mechanisms required differ.

In its excited state, the system aims to provide an intense output that informs the downstream neurons. This overshoot is initiated by a large number of voltage-gated ion channels (distinct from the non-gated ion channels used

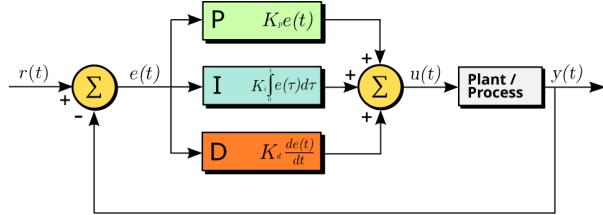


Figure 2.15: A block diagram of a PID controller in a feedback loop.  $r(t)$  is the desired process variable (PV) or setpoint (SP), and  $y(t)$  is the measured PV. (Wikipedia)

to maintain the resting potential) distributed in the neuron's membrane. The overshoot current flows through those persistently open ion channels, which are concentrated in the AIS (which has about two orders of magnitude higher channel density than the wall). The intense slow current produces a condenser-like behavior (capacitive current); the phenomena called "polarization" and "hyperpolarization" (not polarization; instead, a movement of completely separated charge in the surface layer of the electrolyte) of the membrane provide the necessary positive and negative error signals for the controller in the transient state by moving the actual potential value of the membrane above and below the resting potential value. The potentials and the electrical field's magnitudes depend on the concentration and the geometry (the finite size of the membrane). The ions' chemical nature comes into play only if the polarizability can differ for different molecules.

The time course of the overall control function  $u(t)$  of the general PID controller in function of the error variable  $e(t)$  in Fig. 2.15 is described by

$$u(t) = K_p \left( e(t) + \frac{1}{T_i} \int_0^t e(\tau) d\tau + T_d \frac{de(t)}{dt} \right) \quad (2.73)$$

where  $T_i = \frac{K_p}{K_i}$  is the time integration constant,  $T_d = \frac{K_d}{K_p}$  is the derivative time constant (notice the independent time constants). That is, in the world of a neuron, the "theory of everything" is

$$V_M^{OUT}(t) = K_p \left( \underbrace{V_M^{IN}(t)}_{clamping, synaptic} + \underbrace{\frac{1}{T_i} \int_0^t V_M^{IN}(\tau) d\tau}_{membrane's wall} + \underbrace{T_d \frac{dV_M^{IN}(t)}{dt}}_{AIS, synaptic} \right) \quad (2.74)$$

The first term represents the constant effect of the external world (including synaptic inputs, clamping, and exciting brain tissue). The second term represents the time-averaged contribution, such as charging up the membrane, including clamping current. The voltage is mainly due to current through ion channels in the membrane's wall; it represents a parallel  $RC$  circuit. The third

term represents the sum of the gradients due to all effects (the external world, the internal processes, and the outflow through the AIS); it represents a serial  $RC$  circuit. The underbraces of the equation identify which components of the neuron contribute the terms of the PID equation. The presence of some terms depends on the neuron's actual stage; furthermore, the  $R$  values in the parallel and serial  $RC$  circuit differ (resulting in different time constants).

### 2.8.2 HH's potential controlling

One can reformulate the HH's famous Eq. (1) in [5] to the form of the PID equation

$$\underbrace{I \times R_{AIS}}_{V_M^{OUT}} = \underbrace{\overbrace{I_i \times R_M}^{proportional}}_{ionic} + \underbrace{\frac{1}{C_M \times R_{AIS}} \int_0^t \cancel{(I_{bio} - I_{clamp})(\tau)} d\tau}_{T_i} + \underbrace{\frac{C_M \times R_M}{T_d} \frac{dV_M}{dt}}_{derivative, capacitive} \quad (2.75)$$

The proportional term comprises the ionic (and external) currents. At the time when Eq. (2.75) was set up, AIS was not yet known, so HH assumed that in the proportional term, the resistance is identical to the membrane's resistance implemented by the ion channels in the wall (leading to the ideas of "leakage current" and "resting potential", misleading physiological research.) The experimental conditions canceled the integral term entirely: the negative feedback from clamping precisely counterbalances the neuron's internally generated current, so the current integrates to zero. (BTW: the "integrate and fire" type models artificially revive the forgotten integral term.) The derivative term assumes that all currents are constants, so the voltage changes only due to the capacitive current. It entirely forgets that gradients are needed to operate an electrical system (leading to the ideas of constant-voltage batteries and magically operated resistors in the equivalent circuits, see Fig. 2). It was forgotten that a non-constant current contributes a gradient to the derivative term, although it was known from the beginning that the APs comprise relatively steep rising and falling edges. HH's formalism describes only the 'present' (as can be expected when freezing the state), has no predictive power nor can give account of neuronal memories.

HH considered only the proportional term, plus in the derivative term, the voltage gradient due to the condenser (but not the capacitive current itself, directly leading to the wrong ad-hoc hypothesis of the presence of  $K^+$  for explaining hyperpolarization). Given that clamping obscures the presence of gradient-like changes in the system, they missed that *the input currents also produce a voltage gradient and that the output current through the AIS also produces a gradient*. Furthermore, the equation shows that external currents (e.g., the rising and falling edges of step functions) also cause significant changes in the output voltage. Similarly, a "foreign" invasion (changing mechanically the positions of charges by pressure, ultrasound, magnetic pulse, changing the concentration in one of the segments, and so on) generates a change in the position

of charges on the neuronal membrane. This way, it generates a voltage gradient (as well as a pressure gradient and other changes), which may trigger neuronal spikes. Subthreshold excitations provide direct experimental evidence that the description of the resting state includes both serial and parallel contributions.

### 2.8.3 Comparing equations describing neuron's output voltage

When comparing Eq. (2.41) describing the operation of a simple serial  $RC$  oscillator taken from the theory of electricity, Eq. (2.75) describing HH's differential equation (having PID in mind), and the complete Eq. (2.74) describing neuron-specific PID, one can see that they describe the same process in different (experimental and mathematical) approximations. As experience shows, Eq. (2.41) describing the 'net electric' model provides a sufficiently accurate description of the AP, proving that the dominating effect comes from the derivate term and that the thermodynamic term is linearly proportional to the electric one. Furthermore, as we emphasized by discussing the physical processes and the mathematical terms, to some measure, the "parallel  $RC$  circuit" is also present in the process, although its current amplitude is by two orders of magnitude lower than that of the "serial  $RC$  circuit"; furthermore, the time constants of the two circuits are also largely different, making the effect of the parallel circuit unnoticeable. The slow current also play a role: the ion currents are 'local': given that the channels in the membrane's wall are always open, the current on its way towards the AIS may flow out through a nearby ion channel, so only a fragment of the 'resting current' reaches the AIS. Eq. (2.74) provides a high-accuracy description of the process, but for most practical applications using Eq. (2.41) provides sufficiently good results, while Eq. (2.75) is based on an incorrect 'physical model' and requires a series of incorrect ad-hoc hypotheses to describe observations. Note that the forces acting on ions have both electrical and thermodynamic components, but they are proportional to each other. That is, although the absolute values of the coefficients in the equations are not accurate; their effects are. Surely, the description of the process is complicated, but appropriate approximations give sufficiently precise and computationally reasonable results.



## Chapter 3

# Abstract neurophysiology

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In honor and spirit of the Nobel-laureates:

- "For the sake of illustration we shall try to provide a physical basis for the equations, but must emphasize that the interpretation given is unlikely to provide a correct picture of the membrane."

- "the success of the equations is no evidence in favour of the mechanism of permeability change that we tentatively had in mind when formulating them."  
— Hodgkin and Huxley, 1952 [5]

They were brave enough to admit that at some point they must stop and to publish their excellent observations "as is"; despite their feeling that they could not grasp adequately the processes. Their intention was to help their fellow researchers in using their observations in practical research. They did their best with attempting to provide a correct picture of the membrane. We interpret their much inspiring model in light of the later interpretation, theoretical and experimental results, critics and speculations. We attempt to put those constituents together into a consistent model, with a science background, with calculable details, including physical and mathematical handling of thermoelectricity, handling mixing interaction speeds and slow ion currents.

- "From all we have learnt about the structure of living matter, we must be prepared to find it working in a manner that cannot be reduced to the ordinary laws of physics. And *that not on the ground that there is any 'new force' or what not*, directing the behaviour of the single atoms within a living organism, *but because the construction is different from anything we have yet tested in the physical laboratory.*"

E. Schrödinger: What is life?[8] @1992

This is valid also for delayed rectifying current, non-ohmic behavior, ions lacking their repulsion in ionic currents, moving ions with the speed of EM interaction in electrodiffusion, separating current and voltage, voltage dependent conductance, and so on.

"And therefore when we go to investigate we shouldn't pre-decide what it is we are trying to do except to find out more about it." "The first principle is that you must not fool yourself, and you are the easiest person to fool."

"Scientific knowledge is a body of statements of varying degrees of certainty — some most unsure, some nearly sure, but none absolutely certain."

— Richard P. Feynman

Biological objects, with their semipermeable membranes, separating ionic solutions into sections with concentrations differing by orders of magnitude, furthermore containing voltage-controlled ion channels that react actively to electric fields, are more complex cases for understanding their detailed operation. In addition, they implement a complex operational (dynamic) functionality: "stimulated phase transitions enable the phase-dependent processes to replace each other ... one process to build and the other to correct" [65]. Classical theory cannot explain some details of neurophysiological phenomena, including neurons' charge processing, especially their temporal behavior, that implements its information processing capability because physiology incorrectly interprets the fundamental electric terms. Extrapolating notions derived from metals to electrolytes, especially to biological neurons with electrically active internal structures, may be misleading.

### 3.1 The physical model

As Figure 3.1 summarizes: "Electrical signals travel from the cell body of a neuron (left) to its axon terminal in the form of action potentials. Action potentials trigger the secretion of neurotransmitters from synaptic terminals (upper insert). Neurotransmitters bind to postsynaptic receptors and cause electric signals (synaptic potential) in the postsynaptic neuron (right). Synaptic potentials trigger action potentials, which propagate to the axon terminal and trigger secretion of neurotransmitters to the next neuron." Furthermore, the "**neurons convey neural information** by virtue of electrical and chemical signals" [1]. These sentences should read that ions carry the observed potential changes and that the signal propagation is low. Notice that at that time it was not yet recognized that the electric signals propagate with a finite speed also in the dendrites, not only on the axons.

Basically, we follow the Johnston&Wu's "general principles. As in general in science, we must introduce different abstractions and approximations for describing nature, see section 2.2. Making a model for neuron represents a special challenge. As one of the simplest biological entities, the neurons interface the non-living and living science, furthermore, the microscopic and macroscopic world.

We must be very cautious with modeling the electrical features. "an understanding of the electrical properties of dendrites is critical for evaluating the errors associated with the electrophysiological measurements of synaptic function".

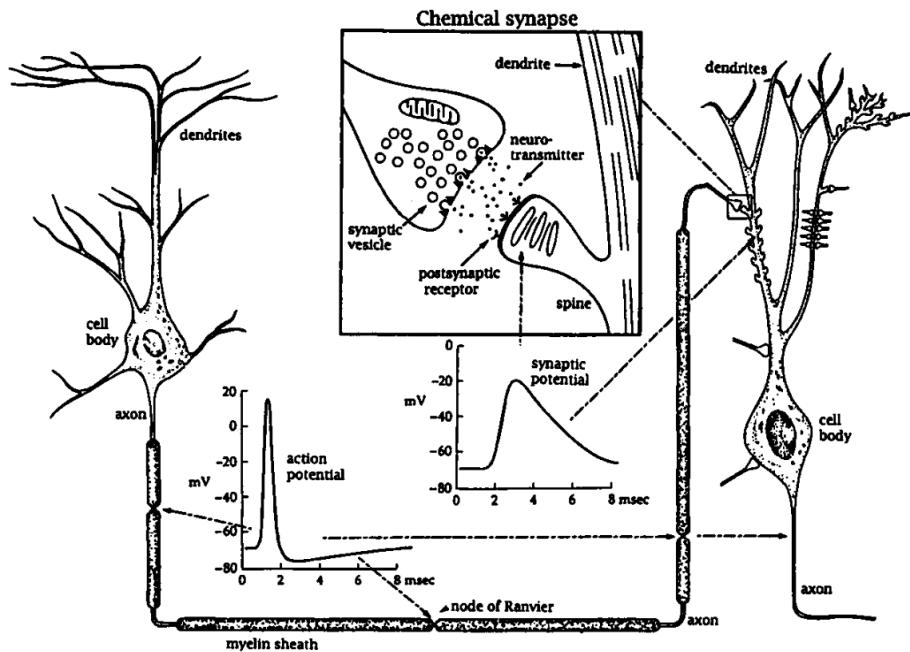


Figure 3.1: Summary of conveying information by electric and chemical signals. (Fig. 1.2 from [1])

???The two conditions imply that we must use slow currents. As we discuss in sections 2.4.4 and 2.4.4

"Electrotonic is a rather arcane term that is used to describe passive electrical signals, that is, signals (current or voltage) that are not influenced by the voltage-dependent properties of the membrane. It will become obvious that this theory is too simple to explain the complexities of dendrites, but at least it is a good starting point." [1] In other words, that model is usable only for a static description, "it is too simple", but there is no commonly used other idea. Unfortunately, in physiology, the interrelations expressed by the Onsager-relations remain entirely out of scope; presumably primarily because of the lack of laws of motions of thermodynamics. The chemical concentration and the electrical potential is only loosely connected, and only statically and for the bulks of cellular segments.

### 3.1.1 Size of neuronal components

The 'dendritic trees can be quite large, containing up to 98 % of the entire neuronal surface area' [65]. 'Because the cell body is small compared with the dendritic tree, its membrane potential is roughly uniform' [87]; we assume that *the neuron's membrane itself is equipotential*. However, *the dendrites are not equipotential while delivering signals*. Their potential is a composite of the

effects of all the signals impinging on the cell, weighted according to the distances of the synapses from the cell body'. 'Temporal and spatial summation together provide the means by which ... many presynaptic neurons jointly control the membrane potential.' 'Each incoming signal is reflected in a local PSP of graded magnitude, which decreases with distance from the site of the synapse' [87]; see our mathematical discussion of this physiological evidence in section 3.5.4. This latter sentence should read that *its measurable effect (their local potential) decreases*, compared to the one at the presynaptic terminals. As the surface, over which it propagates during its journey through the dendrites, extends, the charge density decreases, but the total charge is conserved until the cell body is reached. These statements mean (assuming that those signals travel with the same speed in the dendrites) that *experiments underpin the presence of a 'slow current' of ions in neurons*, although the notion is not introduced.

Experimental evidence shows that the electric signals have a finite speed in axons, dendrites, and cell bodies and that within the cell, the overwhelming majority of propagation time is spent in the dendrites. The mathematical handling of finite speeds is not simple, especially within a biological cell, so we separate the cell into two regions and make the approximation that within the cell body, the interaction is instant (that is, the Laws of electricity are valid). However, outside the cell body, the finite interaction speed in the dendrites leads to observable effects that significantly influence the cell's operation. *We set up a hybrid model: the cell body is equipotential (aka: can be described by a 'fast current'), but the dendrites (and they contribute the overwhelming majority of the signal path within the cell) are non-equipotential. They must be described by approximations based on a 'slow current'.* With that model, we explain the up to now not understood features of neuronal charge processing; furthermore, why is that 'the interplay between the synaptic and neuronal dynamics, when the network is near a critical point, both recurrent spontaneous and stimulated phase transitions enable the phase-dependent processes to replace each other' [65].

The size of presynaptic terminals <https://www.ncbi.nlm.nih.gov/books/NBK26910/bin/ch11f38.jpg> (reproduced here as Fig. 3.2) is about two orders of magnitude smaller than the cell body and its dendrites [87], chapter 11. In other words, the "dendritic trees can be quite large, containing up to e98% of the entire neuronal surface area" [65]. "Because the cell body is small compared with the dendritic tree, its membrane potential is roughly uniform" [87]. We pinpoint that since the ionic currents spend most of their travel time in the dendritic tree, we assume that the overwhelming portion of the travel time derives from the dendrites; so the contribution from the travel on the body is omitted. In this sense it is unimportant whether *the membrane itself is equipotential*. However, it is crucial that *the dendrites are not equipotential while delivering signals*. Their potential "is a composite of the effects of all the signals impinging on the cell, weighted according to the distances of the synapses from the cell body". "Temporal and spatial summation together provide the means by which ... many presynaptic neurons jointly control the membrane potential." [87]. This former sentence should read that *its measurable effect (their potential) decreases*, compared to the one at the

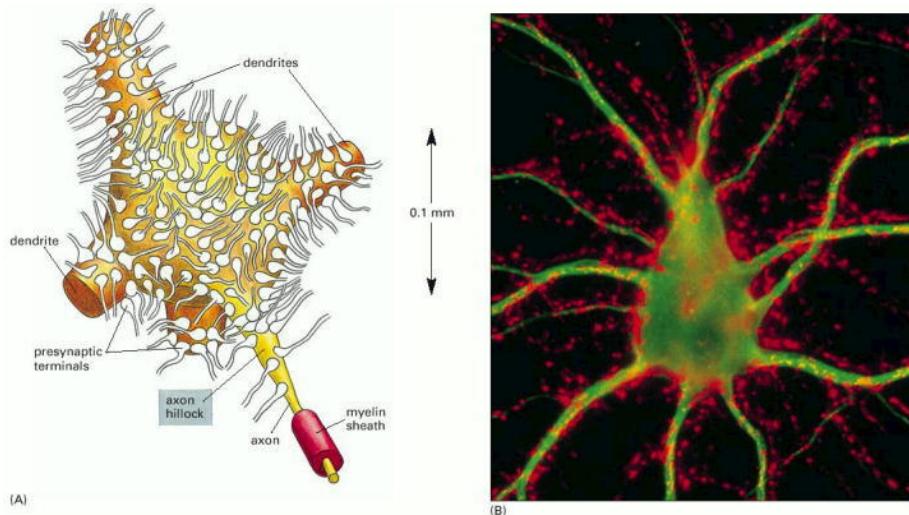


Figure 3.2: The size of presynaptic terminals. ©Original

presynaptic terminals. As the surface, over which it propagates during its journey through the dendrites, extends, the charge density decreases, but the total charge conserves until the cell body reached. The latter sentence should read that the presynaptic *terminals* and the *membrane potential* mutually control each other. Given that the ions can reach the presynaptic terminal passively by using a "downhill" potential between the axonal arbor and the membrane, once, they cannot enter the membrane until the membrane's potential is higher than that in the axonal arbor and twice, whwn they can enter, the current depends on the potential difference between the membrane and the arbor.

### 3.1.2 Neuron's potential

Experimental evidence shows that the electric signals have a finite speed in axons, dendrites and cell body; furthermore, that *within the cell, the overwhelming majority of propagation time is spent in the dendrites*. The mathematical handling of finite speeds is not simple, especially within a biological cell, so we separate the cell into two regions and make the approximation that within the cell body the interaction is instant (that is, the Laws of electricity are valid), but outside the cell, in the dendrites the finite interaction speed leads to observable effects that significantly influence cell's operation (we need different approximation; we must not apply automatically the equations borrowed from electricity). *We set up a hybrid model: the cell body is equipotential (aka: can be described by a 'fast current'), but the dendrites (and they contribute the overwhelming majority of the signal path within the cell) are non-equipotential and they must be described by approximations based on the notion of a 'slow current'.* With that model, we explain the up to now not understood features of neuronal

charge processing, furthermore, why is that 'the interplay between the synaptic and neuronal dynamics, when the network is near a critical point, both recurrent spontaneous and stimulated phase transitions enable the phase-dependent processes to replace each other' [65].

The commonly used physical picture (see, for example, [21], page 9) is only half of the truth: "there is never any actual movement of charge across the insulating membrane ... the charge merely redistributes itself across the two sides by the way of the rest of the circuit." On the one side, redistribution of charge *per definitionem* means a current, on the other, that picture contradicts also the notion of 'specific conductance': the rest of the circuit cannot participate in a 'leakage current' through a distributed resistor. The cell has a resistance (see the AIS) and an area, but still, no specific resistance can be interpreted. The charge moves in the proximal layer of the electrolytes (in the form of a 'slow current' near to dendrites), then the circuit closes though the AIS and the extracellular segment. *We explicitly introduce the notion of 'slow current', and show that we need to divide the membrane's ionic currents roughly into two categories, whether they flow directly between the intracellular and the extracellular space or within the layer on the surface of the membrane.*

The physical difference is whether the movement of ions is assisted by the enormous potential gradient between the extra- and intracellular regions when passing the ion channels ('fast' current) or they move in the electrolyte layer proximal to isolating membrane assisted by the electrostatic repulsion of ions in the same layer ('slow' speed of a macroscopic current). Cardiac slow currents have been discovered [60] (actually, current pulses of duration in several msec range). It was correctly observed that "the slow currents appear to have been caused by repeated openings of one or more channels" and their speed [61] was found in the range of  $0.02 - 5 \text{ m/sec}$ . In neurophysiology, ion current speeds ranging from a few  $\text{mm/s}$  to dozens of  $\text{m/s}$  has been observed.

These statements mean (assuming that those signals travel with the same speed in the dendrites) that the *presence of a 'slow current' of ions in neurons is experimentally underpinned*, although the notion is not introduced (mainly because its mathematical handling is not solved). Assuming that the dendrites' size is about  $0.1 \text{ mm}$  and the synaptic signals appear at the AIS  $0.2 \text{ ms}$  after their arrival to their presynaptic terminals, we can estimate the speed of 'slow current' as  $0.5 \text{ m/s}$  (see our discussion on the signals appearing in the 'relative refractory' period and [64]). This result is in line with our result derived the speed value  $1 \text{ cm/s}$  [47] measured within a cell body and the axonal speed  $20 \text{ m/s}$  [5].

### 3.1.3 Axon Initial Segment

"Neurons ensure the directional propagation of signals throughout the nervous system. The functional asymmetry of neurons is supported by cellular compartmentation: the cell body and dendrites (somatodendritic compartment) receive synaptic inputs, and the axon propagates the action potentials that trigger synaptic release toward target cells. Between the cell body and the axon sits a

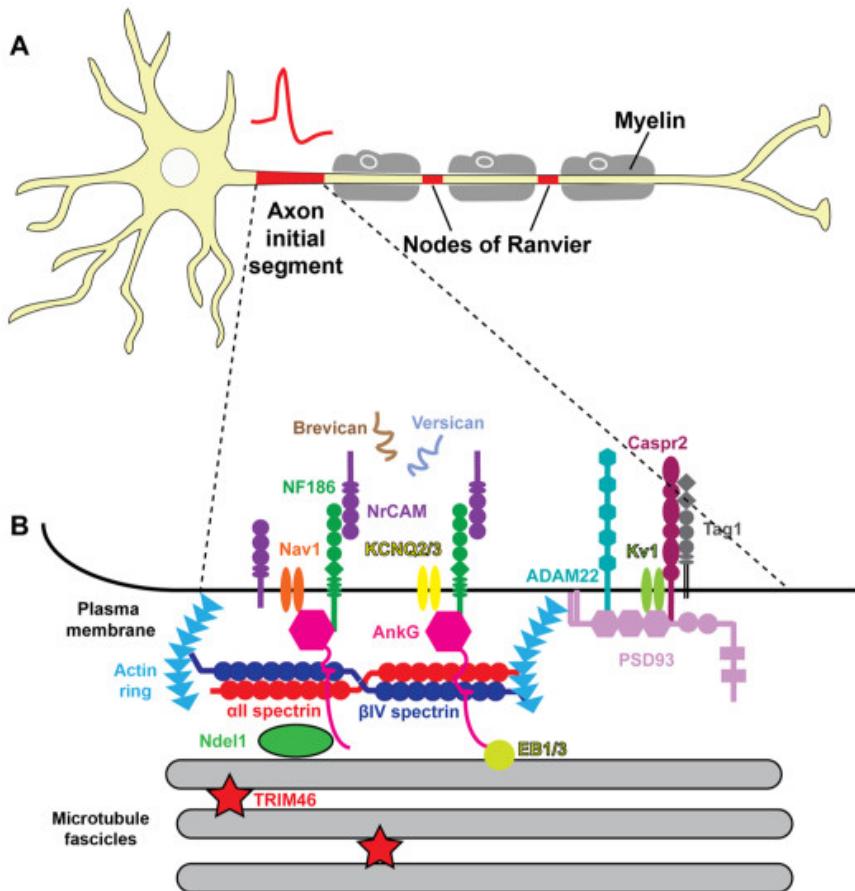


Figure 3.3: The structure of the Axon Initial Segment. [47] Ann. N.Y. Acad. Sci. 1420 (2018) 46–61, Figure 1 ©2018 New York Academy of Sciences.

unique compartment called the axon initial segment (AIS)”[51]. In the light of the new experimental and theoretical results, we need to add new components, roles and operating modes to the one assumed by the present physiology.

Also we must add the invention from about three decades later: ”Neurons ensure the directional propagation of signals throughout the nervous system. The functional asymmetry of neurons is supported by cellular compartmentation: the cell body and dendrites (somatodendritic compartment) receive synaptic inputs, and the axon propagates the action potentials that trigger synaptic release toward target cells. *Between the cell body and the axon sits a unique compartment called the axon initial segment (AIS)*. The AIS was first described 50 years ago [i.e., nearly two decades after HH published their study], and its molecular composition and organization have been progressively elucidated during the following decades. .... Recent years have also brought crucial insights

into the functions of the AIS: how ion channels at its surface generate and shape the action potential.” [51] We provide the physics and mathematics of how AIS shapes the action potential (or more precisely, we show what an important role it plays in forming AP).

In our model, the AIS gets independent from the membrane, and this separation leads to crucial changes. (BTW, the name is misleading: the AIS is part of the neuronal oscillator, and it forwards a traveling potential wave to the axon instead of belonging to it.) ‘Although by definition a neuron must have an axon to assemble an AIS, the relationship between AIS assembly and axon specification *in vivo* has not been determined yet’ [48].

”The axon initial segment (AIS) is located at the proximal axon and is the site of action potential initiation. This reflects the high density of ion channels found at the AIS. ... The summation of synaptic inputs gives rise to action potentials at the axon initial segment (AIS), a 20–60  $\mu\text{m}$  long domain located at the proximal axon/soma interface that has a high density of voltage-gated ion channels.” As discussed in [70], see also their Figure 1, reproduced here as Figure 3.3, the structure of the Axon Initial Segment is known to the smallest details. As the illuminating investigations in 2008 [47] revealed, the AIS has very dense ion channels. That is, from an electrical point of view, those parallelized channels can be abstracted as a *discrete conductance* (or resistance) between the membrane and the axon. The membrane itself can be abstracted as a *distributed condenser* with no resistance (in contrast with the viewpoint of biophysics, that the membrane plus AIS is considered a distributed element, where the capacitor and condenser cannot be separated). Notice the important point: ”Neurons are also anatomically polarized, as they can be subdivided into a somatodendritic input domain and an axonal output domain” [48]; providing a direct evidence that (unlike in HH’s model) the input and output currents (and voltage time derivatives) are independent, see also Fig. 3.4. More precisely, they form the input and output of a neuronal oscillator, as our model suggests. Notice how the AP changes its shape during its propagation in the adjacent segments, as our model explains: the broadening by axonal arbor, the voltage-gradient generated shape on the AIS, the appearance of iAPTD at the distant junction. Notice the lack of hyperpolarization at the beginning and end of the pipeline; a clear effect of the neuronal oscillator. Inventing AIS changed the viewpoint of neuroscience [51].

### 3.1.4 Axons

We model the axons as electrolyte-filled semipermeable membrane tubes with ion channels in their walls. The axons not passively follow the potential’s time course, but they mediate the changes in their internal volume by using an ion pool available in their extracellular volume. The applied potential (including that of the mediated ions) opens the ion channels in the axon’s wall.

In their native mode of operation, the three modes of ion channels define the ‘direction of the time’ [62, 123, 23] (the direction of the current that transmits the spike). The layer that the front of the spike creates on the surface (on both

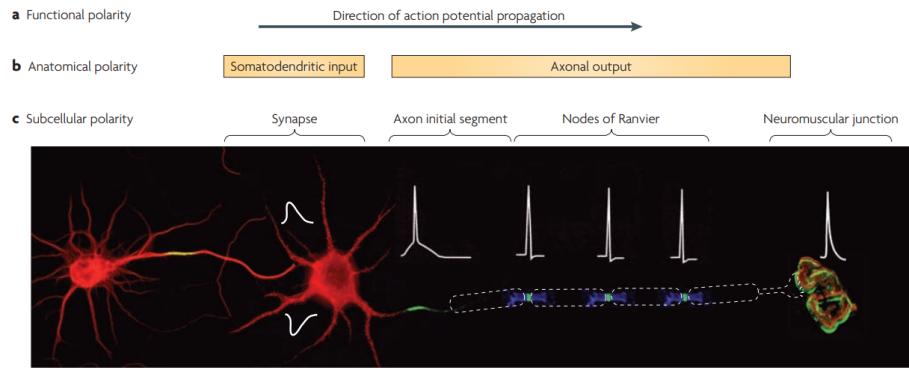


Figure 3.4: Neurons are highly polarized cells [48], Figure 1 ©2010 Macmillan Publishers Limited.

sides of the tube) propagates in both directions, but it cannot open the ion channels on the side where the spike arrived from, and the ion channels are still inactivated.

Clamping sets up an artificial working regime for the ion channels: the permanent electric field on the outer surface enables ions to enter the inner volume where formerly no ions (and no potential) existed. The rushed-in ions will flow away from the place of their entrance (recall that the current removes part of the ion layer on the surface), and a slow current toward the membrane can start. Under clamping conditions, the experimenter sets the voltage instead of the transmitted signal and in a static way instead of an autonomous dynamic one.

Initially, the membrane, the clamping point on the axon, and the intracellular and extracellular fluid maintain their resting potential. When an external potential is applied suddenly to some point of the axon, an electric field  $\frac{dV}{dx} \propto (V_{membrane} - V_{clamp})$  appears on the *outside surface* of the axon. The extracellular space with its high ion concentration  $C_k^{ext}$  represents an "ion cloud" (see also section 2.4.4). When the clamping voltage is switched on, a "fast" current instantly delivers the potential along the *outer* surface of the axon. However, this is not the case (at least not in the initial moment) on the *inner* surface. *There is no charge present that could change the potential:* 'the intracellular concentration at rest is around five orders of magnitude less than that in the extracellular space' [21]. The physical picture that the clamping potential instantly appears at the end of the axon at the membrane (i.e., if (apparently) they have an infinitely large propagation speed) is valid only if charge carriers exist in the axon.

The persisting clamping voltage gradually triggers the opening of ion channels in its wall along the axon, leading to a continuous inflow through the axon's wall from the extracellular space into the intracellular space as a "fast current"; see section 2.6.1. The ions entering the intracellular space remain inside the

axon: the cylindrical surface enables only a one-way (inward) traffic for the ions. As discussed in section 11.4 of [21], "once calcium enters the intracellular cytoplasm it is not free to diffuse". The ions start to create an ion-rich layer on the internal surface. However, a gradient parallel to the wall exists. The ions experience the electric field (which is present initially only at the clamping point but extends with the passing time) along the axis, speed up, and (after a short while) the ion's speed becomes constant in time but its value depends on the actual electric field, see Equ. (2.23). The *ions will slowly move along the axon with a field-dependent constant velocity in the electric space* in a viscous solution. The moving ions deliver charge, so the potential gradually extends along the electrolyte tube (the axon). "In axon fibers, the effective diffusion constant was estimated to be about one-tenth of the diffusion coefficient in aqueous solution" [21]; however, under the effect of the potential gradient, and the mutual repulsion, they form a "slow current" (and that macroscopic current may have a much higher propagation speed). *The current and potential are not instant, as we consider in the classic theory of electricity:* they propagate with the speed of the ion current.

In this model, we assume that during the time  $dt$ , in the volume  $dx$ , we have a constant ion inflow  $I_{wall}$  through the axon's wall, which increases the charge and concentration already in the volume. The charges in the tube experience the field  $\frac{dV}{dx}$ , and they move with speed  $v$  inside the tube (see Eq. (2.26)). The ionic fluid with velocity  $v$  (proportional to  $\frac{dV}{dx}$ ) transfers the ionic charge in the volume to the neighboring element at a distance  $v * dt$ , and delivers the charge and concentration from the neighboring element at a distance  $-v * dt$  into this element. At the time  $t$ , the concentration at  $x$  will result from the inflow at the place  $x - v * t$  (see also the general discussion around Eq. (2.2)). The higher the speed  $v$ , the more significant the difference between the "inflow" and the "present" concentration. The stream inside the axon, a la Minkowski (although in this simple case, a Galilei-transform is sufficient), transforms the distance to time and vice versa. Under the effect of clamping, the current is decreased by the stream proportionally:

$$\frac{dI_{axon}}{dt} = -\alpha * I_{axon}; \quad I_{axon}(t) \approx I_{wall} * (1 - \exp(-\alpha * t)) \quad (3.1)$$

( $\alpha$  is a timing constant of dimension (1/time)).

When the stimulation happens inside the axon, and the axon forwards the charge package in the reverse direction [49], towards the AIS . The AIS uses a "downhill" method of charge forwarding (it is a barrier in both directions), so it can forward the imitated "AP" towards the soma. It is a propagation in the reverse direction, since the stimulation arrives from the "wrong" direction, and the but not a backpropagation. The capacitance of the dendrites explains the shape of the signal.

The AP's first front already passed to the axon and is forwarded there. It is hard to imagine that the commonly used "transversal current", the ion channels, not only synchronize themselves to the length and speed of the spike, but they also sense the direction of the potential gradient.

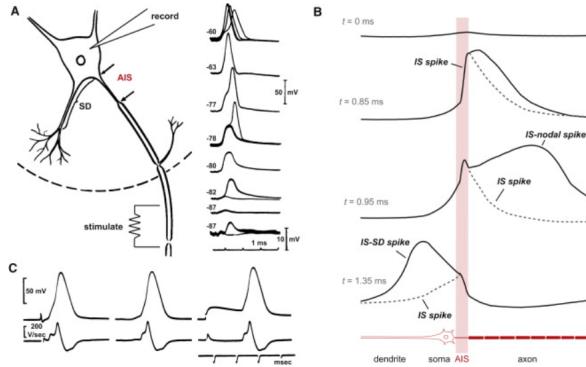


Figure 3.5: Action Potential Initiation in the Axon Initial Segment [49].

### 3.1.5 Membrane

Even at writing this text (at the middle of 202), textbooks comprise the old and bad cellular structure.

Membranes are fundamental in many places, from biological objects to industrial filters. They operate on the border of microscopic and macroscopic worlds, separating non-living and living matters, and combining electrical and thermodynamical interactions. We show that an extremely thin skin near to the surface of biological membranes is responsible for the biological thermoelectric processes.

To describe those complex and continuous phenomena at least approximately, we must separate them to stages. Using omissions, approximations and abstractions, we can describe the stages approximately, usually considering only one dominant phenomenon. The described phenomena are interrelated in a very complex way and depend on different parameters. To some point, we can describe that thin layer using a static picture and providing an empirical description of its individual processes, even we can give some limited validity mathematical descriptions for those stages. However, we understand that for describing the transition (contrasting with step-like stage changes) between those well-defined stages of the atmosphere we need a *dynamic description* and we need to find out the *laws of motion* governing the processes.

Similar is the case with the neuronal membranes and the neuronal operation. Now we are at the point where their decades-old static description is not sufficient. To describe the neuron's dynamic behaviour, we need to derive the corresponding laws of motion. We need a meticulous and unusual analysis to derive them.

In a neuron, in the abstraction science uses, we put together only ionic solution, semipermeable membrane and currents reaching them. As experienced, at some combination of their parameters, qualitatively different phenomena happen, which, in the abstraction biology uses, called signs of life. Given that the

approximations, the derived abstractions and the mathematical formalisms describing them are different for the two cases, *it looks like we have two different, only loosely bound worlds*. However, if we realize we arrived at the boundary of non-living and living matters, we must go back to the first principles of science. Using our approach, maybe we can defy that "the emergence of life cannot be predicted by the laws of physics" [9].

The layers, for their regular operation, have both source and drain. In neurons, the source is distributed over the surface of the layers and the drain is concentrated at the terminating end of the layer. The two currents are flowing simultaneously, i.e., the source of the drain current has a time course, so the product of the two currents can be measured. (actually, it is a differential equation, and in the elementary cross-section, Kirchoff's Junction Law is valid). Generally, it takes time until the source current reaches the drain's position.

Initially, biology used the abstraction that the measured resistance and capacitance are distributed along the membrane's surface. It assumed a *discrete* equipotential membrane with capacity  $C$  and that it leaks through a discrete resistance  $R$ . However, in biology, no discrete elements for storing charge exist. The notion of storing charge can be used only in the sense that for the time of passing a finite-size element with finite propagation speed, the charge carriers spend the corresponding time in the element. That phenomenon resembles storing the charge, and that imitation enables us to describe a behavior resemblant to that of the biological circuit. *Attempting to imitate the effects of biological "slow" currents using electric parallels hides that generating an AP is their native feature*; furthermore, slow currents may also play a role in cognitive functions.

## 3.2 Addendum

In this section, we add some notions, pinpointing and fixes to the chapters of book [1], needed mainly to make enhanced abstractions for biology, with the goal to derive the needed 'extraordinary' laws of physics. The quotations are from that book, without citing the book per quotation, providing only page number. Our fixes and notations are typeset in blue, and confine themselves to the most needed text, so the best way of reading is to read the two texts simultaneously.

### 3.2.1 Ion movement in excitable cells

Page 9 "In excitable cells, movement of ions across the plasma membrane results in changes of electrical potential across the membrane, and these potential changes are the primary signals that convey biological messages from one part of the cell to another part of the cell" *Given that those messages are delivered by ions, the conveyed biological messages also mean changes of concentration. After crossing the membrane, the ions (as slow currents) also physically move in the layer on the surface of the plasma membrane.* To consider the process and

the dynamically formed component is essential in understanding why and how APs form, as well as how those signals are processed and transmitted. Their effect is significant. As shown in Page 12, the total number of ions in the spherical cell is  $2 * 10^{13}$ . As we estimate in section 3.3.1, the number of ions conveyed in a single signal is about  $10^7$ , which seems to be negligible. However, the number of uncompensated ions is estimated, in line with our estimate for the order of number of ions per pulse, as  $4.7 * 10^7$ , so it is absolutely necessary to consider the finite resources, as we do it in section 2.2.7. In line with our estimate, in the order of  $10^4$  pulses in quick succession are needed to drastically change the number of ions (aka concentration or potential of the bulk) in the cell.

### 3.2.2 Physical laws that dictate ion movement

Page 10 "The first two laws concern two processes: diffusion of particles caused by concentration differences and drift of ions caused by potential differences. The third law concerns the relationship between the proportional coefficients of the first two processes, the diffusion coefficient  $D$  and the drift mobility  $\mu$ ." Unfortunately, here the reciprocal relations, which we discuss in section 2.3, between the processes is missing, as well as the role of the finite resources, which we discuss in section 2.2.7. *The worst context of this abstraction is that it hides the fact that the diffusion coefficients and speeds differ by several orders of magnitude, as it refers to the Nernst-Planck equation at zero flux, where both speeds are zero* (and they are really equal only in that case). The equation, in addition, does not consider that by moving ions, we change the potential and concentration simultaneously and inseparably; that is, handling the case with partial derivatives is not allowed.

Page 15 "The negative sign indicates that  $I$  flows in the opposite direction as  $\frac{\partial V}{\partial x}$  and in the opposite (same) direction as  $\frac{\partial [C]}{\partial x}$  if  $z$  is positive (negative). This equation describes the passive behavior of ions in biological systems." Unfortunately, there are doubts here if partial derivation can be applied at all: when changing one of the abstract entities the other changes simultaneously, given that the ion represents mass and charge simultaneously; that is, the ions represent mass- and current flow of the same sign.

### 3.2.3 The Nernst equation

Page 15 "The NPE gives the explicit expression of ionic current in terms of concentration and electric potential gradients." As we discuss in section 2.3.5, NPE is valid only in the 'mean-field' approximation, i.e., when we assume that the diffusion and electrical interactions have the same speed. That is, we can safely use it only in equilibrium state. Furthermore, although it was derived for equilibrium state, it implies that for the short time of forming an AP, the concentration also changes, given that the potential changes. According to their Table 2.1, for a short period, up to two orders of magnitude change in the concentration can take place. See also section 2.5.5.

### 3.2.4 Ion distribution and gradient maintenance

Page 17 "These ionic concentration gradients across the cell membrane constitute the driving forces (or chemical potentials) for ionic currents flowing through open channels in the membrane. In other words, the ionic concentration gradients act like DC batteries for cross-membrane currents." First, the relation is mutual; it could be considered that there are also chemical batteries. Second, the ionic currents flow not only through the membrane; they can flow also through the extracellular space. Furthermore, one must tell also *when* it flows. Third, the driving force of those DC batteries significantly changes during operation; significantly changing how an action potential is forms.

### 3.2.5 Membrane permeability

Page 24 "Within the membrane, if one assumes that  $[C]$  drops linearly with respect to  $x$ ." Since the ions are simultaneously also charges, the potential also drops linearly, as explicitly said on page 26. If so, ions must accelerate across the membrane surfaces, which is not discussed.

## 3.3 Electrodifusion

The Onsager reciprocal relations express the equality of certain ratios between flows and forces in thermodynamical systems out of equilibrium, but *where a notion of local equilibrium exists. This is exactly the case for a neuron during producing an action potential.* The closest relative to our derivation is the Poisson-Nernst-Planck (PNP) and its mathematically simplified version (Poisson-Boltzmann-Nernst-Planck) [111] model are based on a *mean-field approximation of ion interactions and continuum descriptions of concentration and electrostatic potential.* Given that the Nernst-Planck equation is essentially a flux equation for the special case of zero flux, furthermore that Planck essentially included Fick's second law in the PNP model, our approach seems to be self-consistent and a significant extension to the famous model. As we discussed, it is not reasonable to calculate a mean value for those vastly different interaction speeds. We derived a realistic approach to the ion transport problems, in many areas; in addition to biological systems, also for semiconductor devices and nanofluidic systems.

Biological cells comprise components such as electrolytes, semipermeable membranes, solutions with extremely different concentration. Surprisingly, they show spontaneous electrical activity. As Eq.(2.22) shows, the electrical interaction speed is million times higher than the chemical one.

### 3.3.1 Operating regimes

Our equations also call attention to a neglected aspect of evoking APs: the rush-in ions increase the local potential in the proximal layer to *above the potential*

*of the bulk in the intracellular segment*, typically even to slightly above the potential in the bulk of the extracellular segment. Consequently, *the concentration must also at least approach or even slightly exceed the level of the extracellular concentration* for a short period and in a very thin layer near the membrane (the timing relations were discussed above). The mechanical waves [84] provide indirect evidence for the effect's existence.

We consider three operating regimes for neuronal membranes. Eq. (2.7) describes the steady state. As we discussed, in the case of the finite membrane width of biological neurons, a gradient of a particular form is created in the electrolyte, also comprising a membrane-width-dependent term. However, otherwise, the state can be described by Eq. (2.7).

In single-shot mode, along the axis of the ion channel, at large distances, the concentration and potential remain essentially unchanged during the process. Using our time derivatives, we can describe the details, including the process's time course. Given that the slowest interaction defines the propagation speed and the proportion of the layer to the bulk is extremely tiny, no significant change in bulk can be measured. The interaction speed in the bulk is practically the *drift speed* (and the gradients are zero).

In the case of high-rate, repetitive measurements, the changes occurring in the proximal layers can slowly influence the parameters of the bulk. However, this effect becomes significant only in long-term observations when a large number of single actions take place in quick succession. In a continuous high-rate firing mode, the layers have parameters other than the ones required by Eq.(2.7) for the resting state for a growing fraction of the time. We can estimate the time roughly as how long the ions can diffuse to a distance of 0.1 mm (in the order of  $\frac{10^{-4}m}{10^{-4}m/s}$ ), and how many times that distance is greater than the assumed width of the layer proximal to the membrane's surface (in the order of  $\frac{10^{-4}m}{10^{-8}m}$ , that causes a 100% change). We arrive at that a rate 100 Hz will deliver a charge causing a percentage increase of the bulk concentration is in the order of at least dozens of seconds.

### 3.3.2 Connecting science to life

The two layers, plus the demon, see section 2.7.3, also naturally explain why that difference comes into existence. As we explained above, when a *finite-width* membrane separating the two segments appears in the volume (due to the evolution or the development of the individual biological object), two thin electrolyte layers will be formed proximal to its surfaces on the two sides, even if the concentrations are equal. As observed, “a membrane potential arises when there is a difference in the electrical charge on the two sides of a membrane, due to a *slight excess* of positive ions over negative ones on one side and a slight deficit on the other.” [131] We add that some potential difference is created by the presence of the membrane alone, as discussed above. When a demon also appears in the membrane (initially a simple hole), the random movement of ions with *finite speed* through the *finite length* of the ion channels may also solve the

mystery of *why a cell comes into life during evolution*. Maybe we can answer E. Schrödinger's profound question: "What is life, and how did it emerge from non-life?"

Erwin Schrödinger's famous book "What Is Life? The Physical Aspect of the Living Cell" provides a nice example of disciplinary thinking. Schrödinger's lecture focused on one important question: "how can the events in space and time which take place within the spatial boundary of a living organism be accounted for by physics and chemistry?" He discussed the living cell's operation from the point of view of thermodynamics, forgetting that the ions have also charges, so the electric interaction must also be considered. The basic difficulty to consider both of them is that their interaction speed differs by a factor about a million, and physics has no proper approximation to handle them simultaneously. Considering the laws of a single discipline, either theory of thermodynamics, or theory of electricity, is not sufficient. We must elaborate the way how they co-operate in the nature, even if we need to elaborate new mathematical methods for that goal, see section 2.3.

### 3.3.3 Spatiotemporal behavior

as we discussed in section 2.2.6,

## 3.4 Resting potential

Table 3.1 shows our results for three different famous published cases. It looks like the calibration of the concentration of negative and positive ions needs scaling and the measurement of  $Ca^{2+}$  comprises issues.

When calculating the values in Table 3.1, we used  $\Delta z = 1.05$  and employed the membrane's thickness data from various publications to demonstrate that our theoretical approach is correct and that using the correct data can provide even the absolute values of the membrane potential. The higher-than-expected value of  $\Delta z$  may suggest that the ions and membrane's double layers in the electrolyte may also play a role. Dedicated, complete investigations can reveal the details.

## 3.5 Action potential

The AP is one of science's big mysteries. We put together an isolating membrane, isolating membrane tubes connected to the membrane, voltage-controlled ion channels in their walls, and an electrolyte solution around them. We apply currents/voltage levels or pulses to the tubes, and at some point (at some appropriate combination of parameters; too small or too large currents result in stopping APs, the system starts to issue APs: *the non-living matter turns into living matter*). In contrast with the expectations of HH [5], *the AP can be described from the first principles of physics* when using the right physical approximations and abstractions.

Table 3.1: The summary data table for equilibrium (Data from Table 2.1 in [1]. For the graphic representation of potential balance see Figure 1.5 )

Ion	[In] [mM]	[Out] [mM]	$U_{therm} \frac{RT}{zF} \log\left(\frac{[C_o]}{[C_i]}\right)$ [mV]	$U_{electr}^{theor}$ [mV]	$U_{electr}^{exper}$ [mV]	$U_{membr}$ [mV]
Squid [5] T=293 K° Width = 3 [nm] Field = 14.0 [MV/m]						
$K^+$	400	20	$-75.5 = 58\log\left(\frac{20}{400}\right)$	<b>41.9</b>	<b>41.4</b>	-62.0
$Na^+$	50	440	$+54.8 = 58\log\left(\frac{440}{50}\right)$			
$Cl^-$	40	560	$-66.5 = 58\log\left(\frac{560}{40}\right)$	<b>41.9</b>	<b>42.0</b>	63.0
$Ca^{2+}$	0.27*	10	$+45.5 = 29\log\left(\frac{10}{0.27}\right)$			
* used for the published value 0.4						
Frog muscle (Conway) T=293 K° W = 8 [nm] E = 9.6 [MV/m]						
$K^+$	124	2.25	$-101 = 58\log\left(\frac{2.25}{124}\right)$	<b>88.9</b>	<b>83.6</b>	-125.4
$Na^+$	10.4	109	$+59.2 = 58\log\left(\frac{109}{10.4}\right)$			
$Cl^-$	1.5	77.5	$-99.4 = -58\log\left(\frac{77.5}{1.5}\right)$	<b>88.9</b>	<b>82.7</b>	124.1
$Ca^{2+}$	0.021*	2.1	$+58.0 = 29\log\left(\frac{2.1}{0.021}\right)$			
* used for the published value 4.9						
Mammalian cell T=310 K° W= 6 [nm] E= 11.1 [MV/m]						
$K^+$	140	5	$-89.7 = 62\log\left(\frac{5}{140}\right)$	<b>57.7</b>	<b>57.3</b>	-85.8
$Na^+$	15	145	$+61.1 = 62\log\left(\frac{145}{15}\right)$			
$Cl^-$	4	110	$-89.2 = -62\log\left(\frac{110}{4}\right)$	<b>57.7</b>	<b>56.9</b>	85.9
$Ca^{2+}$	0.04*	5	$+60.8 = 31\log\left(\frac{5}{0.04}\right)$			
* used for the published value 0.0001						
$Na^+$ ions only [66] T=310 K° W= 6 [nm] E = 10.0 [MV/m]						
$Na^+$	12	145	$+66.6 = 62\log\left(\frac{145}{12}\right)$	60.7	66.6	

Neurons interface the living and the non-living components of nature. To understand the details of their respective operation, an exact interpretation of notions and laws of non-living matter is also needed. Applying the laws derived for an approximation abstracted for the conditions of classic science is misleading and prevents us from understanding that, *at different abstraction levels, neurons are living components and simultaneously, still, they can be described by the laws of non-living science*; provided that we use the right abstractions and approximations, as their case requires. They are studied by research methods and tools of fellow sciences and are described by the universal language of nature: mathematics. However, not necessarily by the mathematical procedures developed for other goals and used in classic science.

HH attempted to find a mathematical formalism for their very precise mea-

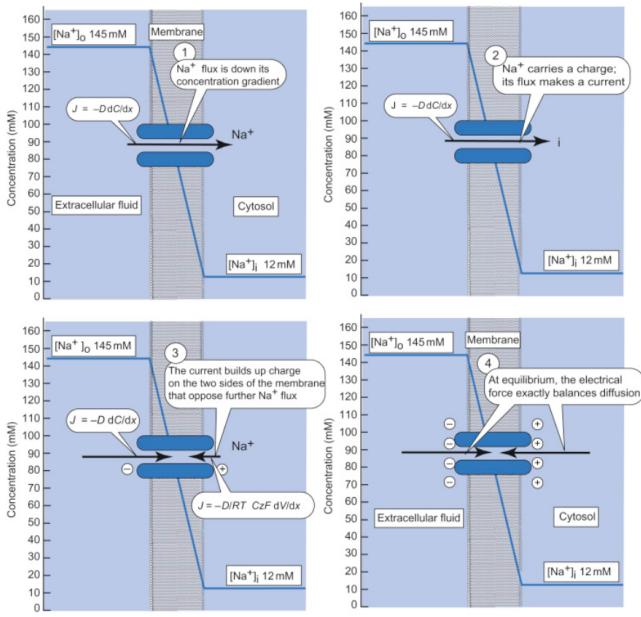


Figure 3.6: (Figure 3.1.1 in [66]) Generation of the  $Na^+$  equilibrium potential across a hypothetical membrane that is permeable only to  $Na^+$ . The  $[Na]_o$  in this case is high, about  $145\text{ mM}$ , whereas  $[Na]_i$  is  $12\text{ mM}$ . Thus the diffusion gradient favors  $Na^+$  flux from the outside to the inside of the cell. Since  $Na^+$  is electrically charged, flux of only  $Na^+$  makes a current across the membrane that separates charges and thus produces an electrical potential. The electric field exerts forces on  $Na^+$  that retards its movement. When the diffusive force exactly balances the electrical force, flux is zero and the potential is  $E_{Na}$ , the sodium equilibrium potential.

surements [5] and find out *empirically* what kind of mathematics (invented for the approximations used in classic science) can – more or less – describe their experiences, despite that “a number of points were noted on which the calculated behaviour of our model did not agree with the experimental results to provide a correct picture of the membrane.” Their followers forgot the doubts and question marks HH described and took their unproven hypotheses as facts. “These equations and the methods that arose from this combination of modeling and experiments have since formed the basis for every subsequent model for active cells. The HH model and a host of simplified equations derived from them have inspired the development of *new and beautiful mathematics*.” [42]. *That mathematics is beautiful but describes some alternative nature instead of the real one*, see also section 3.8.

Despite the impressive advances in neuroscience during the past decays, there are still ‘white spots’. ‘Why action potentials are initiated in the axon is still

unclear' [47] and "we should not seek a special organ for 'information storage' – it is stored, as it should be, in every circuit" [89]. This latter source points to the important point 'Communication consumes 35 times more energy than computation'. [71] One more point why *computation and communication must not be handled separately* [2]. It also asks the questions *what is information, how it is stored, processed and transmitted*.

We can model a neuron as an oscillator where the membrane changes its potential above a resting potential, receives (gated) synaptic currents through its axons and through its ion channels, furthermore external currents/voltages provided by the experimenter. Those currents are slow, so we must consider their speed to produce the membrane's correct behavior, either as a time delay or a time course of a current intensity.

### 3.5.1 The classic picture

"there is little hope of calculating the time course of the sodium and potassium conductances from first principles"  
(surely, if one uses empirical functions) [5]

In the classic picture, we assume that the membrane is equipotential. When the axonal input current charges it up to some threshold value, an intense charge-up process starts due to ion inflow. After the membrane's voltage exceeds some other threshold, a spike begins. After some time, and for some reason, an outward "delayed rectifying current" starts from some hidden source and hyperpolarizes the membrane. Somewhat later, both currents stop, in a concerted way, for some reason. In the classic approach, a spike is sent and received instantly (an incoming spike "makes a hole" [75]), the charge it delivers is added to the membrane in a snap, and the neuron fires in a snap somewhat later. The process details are known (although some processes are only hypothesized, and others are misunderstood). However, the control mechanism of the process is unknown or mystic: the classic model answers the question "what" but leaves the questions of type "why and "how" open. "Why action potentials are initiated in the axon is still unclear" [47].

### 3.5.2 The modern picture

We know that ion current flows in through the axons, and the delivered charge produces local transient voltages [74, 75] on the membrane around the arbor of the synaptic connection. Furthermore, the ions form "packets" when immediately before issuing an AP they arrive at the AIS [47]. *We hypothesize that for the period of generating an AP (furthermore, for the period of receiving synaptic inputs), the membrane does not remain equipotential.* The membrane is a two-dimensional, very thin, elastic, semipermeable, insulator surface (a long and narrow rectangle) with a high concentration of ions on the extracellular side. Axon tubes are connected to the intracellular side at some points of the long

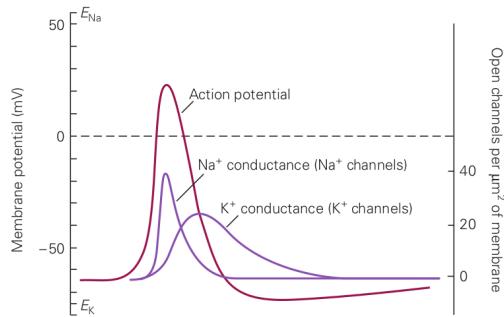


Figure 3.7: **Errata in blue.** (Fig. 7-1 in [39]). The sequential opening of voltage-gated  $Na^+$  and  $K^+$  channels generates the action potential. Wrong. The  $Na^+$  channels are voltage controlled, and they open when AP is initiated. There are no  $K^+$  channels in the game. Some resting  $K^+$  channels exist and they contribute to the total current. Some  $K^+$  flows out through the AIS, but it is by two order of magnitudes less than shown. Actually, these two currents are the condenser currents, before and after potential reversal on the condenser. The ' $Na^+$  current' is the current generated by the sharp 'switch-on' potential gradient, with a distortion caused by approximating the current's time course by a polynomial. One of Hodgkin and Huxley's great achievements was to dissect the change in conductance during an action potential into separate components attributable to the opening of  $Na^+$  and  $K^+$  channels. Mostly wrong. There is no change in conductance, it was a wrong concept. They were tight in assuming the existence of ion channels and their opening/closing, but it is not the case for  $Na^+$ . The shape of the action potential and the underlying conductance changes can be calculated from the properties of the voltage-gated  $Na^+$  and  $K^+$ . Wrong. They used empirical measured distributions, instead of properties of ion channels. (Adapted, with permission, from [5].)

rectangle and AIS at the other end. The membrane attempts to remain equipotential and forwards the charge toward regions at lower potential. This way, the ionic charge forms a “slow” current and gets distributed over the membrane’s surface along some potential gradient for about a few hundred microseconds.

Due to that charge, a new epoch begins when the membrane potential reaches its threshold value. That voltage opens the valves (ion channels) in the membrane’s wall, ions rush into the intracellular space (a positive current). The intense “slow” current quickly increases the membrane’s potential, so the axonal inflow stops. The membrane has a single flow-out point, the AIS, where a less intense “slow” current leaves the cell with a delay and arrives at the very beginning of the axon. In the first phase, the axon pumps the received current out to the extracellular space (a negative current), causing a measurable macroscopic current. Later, the pumped-in and pumped-out ions along the axon are balanced and begin transferring the spike along the axon.

"Action potentials (APs) have been measured using electrophysiological methods and understood as electrical signals generated and propagating along the axonal membrane" [84], and "the AP is accompanied by fast and temporary mechanical changes" (such as axonal radius, pressure, optical properties, the release and subsequent absorption of a small amount of heat, and shortening of the axon at its terminus).

Interestingly, even the paper [132] that attempts to describe non-ideal membranes, considering also mechanical deformations, uses only "fast" waves. Similarly, the model in [84] predicts a "traveling wave of voltage" without seeing that it also means a traveling wave of current, i.e., a finite speed ("slow") current ("we emphasize that the driven waves we consider will travel at the speed of the electrical AP that drives them"). The electrostatic repulsion leads to mechanical stress on the membrane.

An interesting parallel with science is that 'classic physics' is based on the abstraction that position-related phenomena do not depend on time (the time derivative of the position) and that the 'classic physiology' is based on the abstraction that the charge-related phenomena do not depend on time (the time derivative of the current). In 'modern physics', although mathematics, based on the Newtonian abstraction, perfectly describes a wide range of phenomena, near to the limiting speed the Einsteinian abstraction entirely different mathematics must be used to describe nature perfectly. Similarly, *in the 'modern physiology' the time derivative of charge movement must also be taken into account* when describing the dynamic physiological behavior of neurons that needs different approximations. Neglecting the time derivative of the position may result in calculating speed above the limiting speed (the speed of light), and neglecting considering the time derivative of charge movement may result in a wrong understanding of the neuronal electric operation.

### 3.5.3 Role of AIS

As we also discussed [23], more interactions are involved in the living matter, and the interactions need a spatiotemporal description. We use the notion of time dependence in the Einsteinian sense: the basic entities such as *location and time are connected through their interaction speed* and they are not independent parameters in the Newtonian sense. So, we expected that neurons, as dynamical thermoelectricity-based systems, are described by thermoelectric time-dependent equations. However, it is not so.

One of the fundamental reasons is that the way of *providing time derivatives of the thermoelectricity process was not known* (see our section 2.3.5). The other is that, conceptually, *the neuron is considered to be a purely electric system that connects to thermodynamics only through the time-independent Nernst-Planck equation*. The third is that even the description of the purely electric operation is wrong: biology separated the primary abstraction of electric 'charge' from its secondary manifestations of abstractions 'potential' and 'current'; furthermore, it assumes that a mystic power changes biological 'conductance' against all physics laws (applying laws of electricity to their 'non-ohmic' systems). The

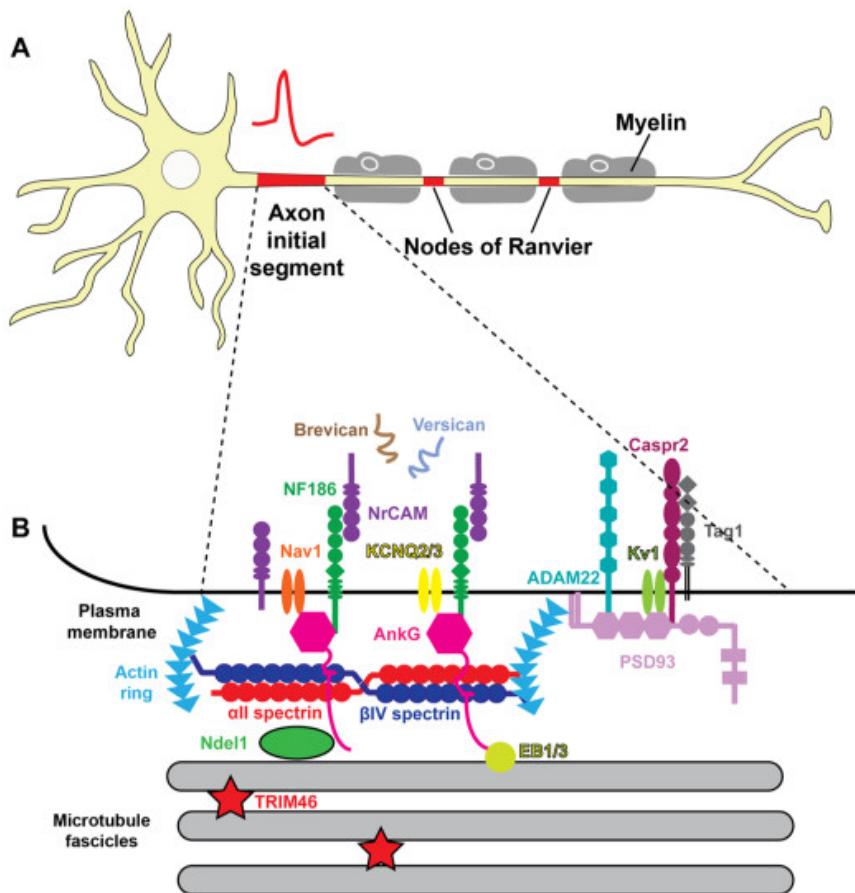


Figure 3.8: The structure of the Axon Initial Segment. [47] Ann. N.Y. Acad. Sci. 1420 (2018) 46–61, Figure 1 ©2018 New York Academy of Sciences.

fourth is modeling problems we discuss below. Theory of biology, among others, stayed at its century-old ideas about equipotential neuron surface, time-unaware information processing [13], although the experimental physiology delivers a vast amount of evidence for the opposite.

By assuming that biological operation can be described by well-known electric terms, Hodgkin and Huxley [5] advanced neuroscience enormously. However, their seven-decades-old hypotheses must be updated from several points of view. Among others, they provided a static empirical description (their differential equations rely on derivatives of an empirical function fitted to empirical measurement data, and even in a wrong way). They excluded interpreting the physical background of their empirical description using an empirical conductance function; in this way, really, there is “little hope of calculating .. from first principles”. Their suggestion about equivalent circuits introduced the idea

that the membrane's potential remains unchanged during operation despite the ion traffic, the ions in the current do not affect concentration, and the components of the circuit operate with the speed of the EM waves. By introducing the delayed current and that some mystic power controls the operation of neurons by changing their conductance, they gave way to introducing the fallacy that science and life sciences are almost exclusive fields. Furthermore, their (unintended) model provokes questions (for a review see [58]) whether it is model at all and what controversies it delivers.

They meticulously wrote that “the success of the equations is no evidence in favour of the mechanism ... that we tentatively had in mind when formulating them”. Although “certain features of our equations were capable of a physical interpretation”, “the interpretation given is unlikely to provide a correct picture of the membrane”. Despite their doubts, biophysics produced fictitious mechanisms to underpin their equations, describing an admittedly wrong physical picture instead of setting up a correct physical operation and describing the processes by deriving physically plausible approximations and using correct mathematical expressions. Although they warned that “the agreement [between our theory and experiments] must not be taken as evidence that our equations are anything more than an *empirical description*”, their followers forgot their doubts and question marks and took their unproven hypotheses as facts. ”These equations and the methods that arose from this combination of modeling and experiments have since formed the basis for every subsequent model for active cells. The model and a host of simplified equations derived from them have inspired the development of *new and beautiful mathematics*.“[42]. However, there was no model, and the beautiful mathematics describes a fictitious neuron.

One of the most influencing bad ideas was expressed by their Eq.(1). In their time, at that limited microscope resolution, they did not see any structure within the neuron's membrane, so logically, they assumed that the measured capacitance and resistance were distributed. Correspondingly, they introduced an electric equivalent circuit assuming that the neuronal  $RC$  circuit comprised parallelly connected discrete  $R$  and  $C$  elements. They described the neuronal operation as based on an integrator-type equivalent electric circuit with the corresponding equations.

They assumed that a fixed voltage drives a constant current through the circuit, and the discrete  $R$  and  $C$  elements share that current. Correspondingly, a leaking current must exist, and the resting brain must dissipate power (as later estimated, around 20 W). However, the operation of the neuronal circuit resulted in well-measurable hyperpolarization (the output voltage changes its sign), which the equivalent *parallel* electric circuit cannot produce, so they assumed that in addition to a  $Na^+$  current, a delayed  $K^+$  current to flow through the neuron membrane in *the opposite direction*, against the flow of  $Na^+$  ions. In their milestone work, their goal was to derive equations for practical application, so they introduced equations describing the measured electric observations. Unfortunately, they attempted to determine which processes were going on inside the biological neuron.

In the past years, instrumental advances have enabled us to discover the

“white spots” of their time. Around 2018, the AIS was discovered and understood [51, 47]. From an electric point of view, the AIS is an array of ion channels with well-measurable resistance; it can be abstracted as a discrete resistance. As the anatomical evidence shows, see Fig. 3.8, the currents flow into the membrane and flows out through the AIS. The currents are not shared, and even, the output current cannot directly be concluded from the sum of the input currents: the charge is temporarily stored by the membrane (as a distributed condenser). The correct equivalent circuit is one in which the condenser and resistor are switched in serial (although the resemblance has limitations), that is a differentiator-type electric circuit. This circuit is sensitive to voltage gradient, so the rising and falling edges of an input signal (such as a PSP) can natively produce an opposite voltage on its output, making the need (and the existence) of the assumed delayed  $K^+$  current at least questionable. Also, a recent measurement [71] concluded that the neuronal computation (contrasted with the resting state) needs only 0.1 W and neuronal communication needs only 3.5 W; that is, the leaking current, at least due to the parallel  $RC$  circuit, does not exist (see our Figure 3.9: a current flows only if membrane’s potential is above the resting potential).

We know from the recent discoveries and understanding of the correct model that currents flow into the condenser (the membrane) and are taken out through the resistor (the AIS). Our theoretical discussion solidly underpins that the physical picture behind the commonly accepted neuronal electric model must be fixed. As we discussed, unlike in the classic model, *the driving voltage and the membrane current have a time course. No current is shared by the resistor and condenser, there is no input resistance, resting current of the parallel oscillator, delayed  $K^+$  current, and changing conductance.*

The correct equivalent circuit is a *differentiator-type oscillator*, where the output voltage is given by the equation

$$V_{out}(t) = RC \sum \frac{dV_{in}}{dt} \quad (3.2)$$

The sum of all *input voltage gradients* generates the *output voltage*, which drives a current through the AIS. The fundamental difference between the two circuit types, that in the correct circuit there is no shared current and there is no direct correction between the input and the output currents. Instead, in the dynamic picture, the changes in the input charge (the temporal course of the current) generates a resulting voltage gradient and their sum drives the  $RC$  circuit, which (under its laws) generates the output voltage which drives a current (pulse) though the AIS. Here comes to light *the biggest mistake in deriving HH’s equations: the temporal course of the charge is identical with the current only if the current is constant* such as in the case of clamping.

As we derived, the (the measured AP) output voltage can be described by the equation describing the serial  $RC$  circuit. Our equations enable us to calculate the ion current’s time course from the potential’s time derivative. We need to sum the time derivatives of the voltages that drive the neuronal oscillator through its membrane (of course, considering that the current needs

time to travel from its entry point to the membrane's body) and solve the differential equation by integrating it in time. The resulting output voltage time derivative can be measured in front of and after the AIS. Interestingly, the time derivative was measured as early as 1939 [40], but its role has not been understood, mainly due to the wrong electric model. *The causality is reversed. The voltage gradient is the primary entity produced by the cellular circuit, and that leads to the production of an AP by the neuronal oscillator.*

Figure 3.9 shows how the described physical processes control neuron's operation. In the middle inset, when the membrane's surface potential increases above its threshold potential due to three step-like excitations opens the ion channels,  $Na^+$  ions rush in instantly and create an exponentially decreasing, step-like voltage derivative that charges up the membrane. The step-like imitated synaptic inputs are resemblant to the real ones: the incoming PSPs produce smaller, rush-in-resemblant, voltage gradient contributions. The charge creates a thin surface layer current that can flow out through the AIS. This outward current is negative, and proportional to the membrane potential above its resting potential. At the beginning, the rushed-in current (and correspondingly, its potential gradient contribution) is much higher than the current flowing out through the AIS, so for a while the membrane's potential (and so: the AIS current) grows. When they get equal, the AP reaches its top potential value. Later the rush-in current gets exhausted and its potential-generating power drops below that of the AIS current, the resulting potential gradient changes its sign and the membrane potential starts to decrease.

In the previous period, the rush-in charge was stored on the membrane. Now, when the potential gradient reverses, the driving force starts to decrease the charge in the layer on the membrane, which per definitionem means a reversed current; without foreign ionic stream and current through the AIS. This is the *basic difference between the static picture* that Hodgkin and Huxley hypothesized and *the dynamic one that really describes its behavior*. The correct equivalent electric circuit of a neuron is a serial, instead of a parallel, oscillator, and its output voltage is defined dynamically by its voltage gradients (see Eq.(3.2)) instead of static currents (as physiology erroneously assumes). In the static picture the oscillator is only an epizodist, while in the time-aware (dynamic) picture it is a star.

Notice also that *only the resulting  $\frac{dV}{dt}$  (APTD) disappears* with the passing time. Its two terms are connected through the membrane potential. As long as the membrane's potential is above the resting value, a current of variable size and sign will flow, and the output and input currents are not necessarily equal: the capacitive current changes the rules of the game.

The top inset shows how the membrane potential controls the synaptic inputs. Given the ions from the neuronal arbor [78, 79] can pass to the membrane using 'downhill' method, they cannot do so if the membrane's potential is above the threshold. The upper diagram line shows how this gating changes in the function of time.

Fig. 3.13 shows how the resulting APTD controls the output APs shape: the derivative changes its polarity by  $\approx 500 \text{ mV/ms}$  in  $\approx 0.5 \text{ ms}$ , which means

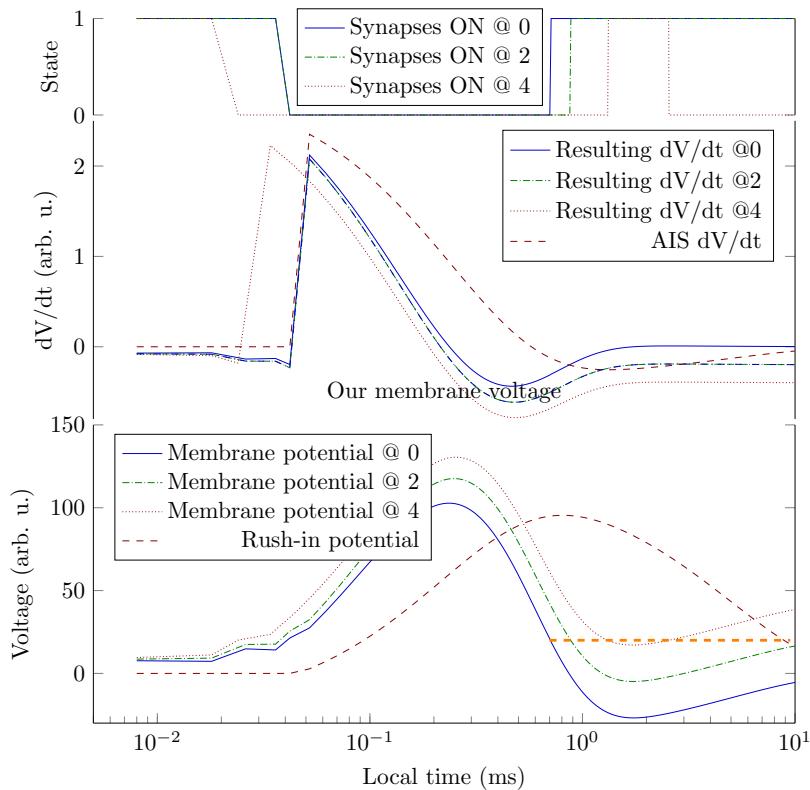


Figure 3.9: How the physical processes describe membrane's operation. The rushed-in  $Na^+$  ions instantly increase the charge on the membrane, then the membrane's capacity discharges (produces an exponentially decaying voltage derivative). The ions are created at different positions on the membrane, so they need different times to reach the AIS, where the current produces a peaking voltage derivative. The resulting voltage derivative, the sum of the two derivatives, drives the oscillator. Its integration produces the membrane potential. When the membrane potential crosses the voltage threshold value, it switches the synaptic currents off/on.

across a  $50 \mu m$  AIS a  $20,000 V/m$  gradient change on the AIS. This voltage gradient is sufficient to accelerate the ions in the ion channels and decelerate them again; this is how to reverse the current direction. We see the effect of 'ram current' as AP. Notice the broadening effect of the gradient measuring technology. A voltage difference is measured at a distance difference, and – due to the signal's speed – the time difference is comparable in size to the period of polarity change of the signal.

### 3.5.4 Neural currents

We can subdivide currents within the neuron based on their origin, physical path and temporal behavior.

#### Patching current

When patching, a current is directly introduced to the neuron's body. In the case of a constant current where  $I = \frac{dQ}{dt}$ , the voltage increase  $dV$  on the capacity  $C$  of the membrane is  $\frac{dQ}{C} = \frac{I*dt}{C}$ , so

$$\frac{d}{dt}V = \frac{I}{C}$$

The direct *constant* current input  $\frac{d}{dt}V_{PATCH}$  to the neuron cell body is a simple constant current that causes a constant membrane's voltage derivative contribution. However, the currents are not necessarily constant. If the artificial current follows a math function, *the time derivative* of that function should be used. In the case of a native current (i.e., receiving a spike from a presynaptic neuron), the received input has the form of PSP, where the time derivative can be well approximated by a steep exponential function. One must be careful that (step-like) *sudden changes may produce very steep spikes* (see the wave forms in Table 2.1 on differentiating a square wave function); furthermore, as we discuss in section 3.7.3, the step-like concentration change causes exactly the same change in the output voltage, only the time scale differs in a factor of  $10^6$ .

#### Clamping current

When clamping, the current is injected through an axon, by switching a clamping voltage to the axon. Given that the current is delivered through the axon, the mechanisms described in section 3.7.2 must be considered. The current at the switch ON/OFF events behaves as a step function; that is, it produces a saturating and a discharging current, respectively. The switch-on effect is known also in technical electricity; in biology its time constant is in the order of  $1 ms$ , that is drastically influences the measured biological processes, see Figure 3.19. Recall that in the case of clamping, the *derivative* contains an exponential function. In the case of patching, the *derivative* is the derivative of a (nearly) square-wave function. For a discussion of the measured result, see section 3.6.5.

### AIS current

The AIS represents a non-distributed resistance  $R_M$ , and the current flowing through it is

$$I_{AIS} = -\frac{V_M - V_{rest}}{R_M} \quad (3.3)$$

(it is an outward current, so it is negative), and its voltage time derivative is

$$\frac{d}{dt}V_{AIS}(t) = -\frac{V_M(t) - V_{rest}}{C_M R_M} \quad (3.4)$$

Notice that this current depends on  $C_M R_M$ , all others on  $C_M$ . (This current was mis-identified by HH as 'leaking current': if no other current/voltage derivative is present, the membrane discharges. In resting state the derivative is zero: the condenser is charged up and no leaking current flows.

$$V_a(t) = V_o * (1 - \exp(-a * t)) * \exp(-b * t) \quad (3.5)$$

### Synaptic and rushed-in current

In the case of those currents, as we discussed in the cases of membrane and axon, a saturation-type function multiplied by a decay-type function describes the current, so the voltage derivative is

$$\frac{dV_a}{dt} = \frac{1}{\alpha} * \exp(-\frac{1}{\alpha} * t - \frac{1}{\beta} * t) - \frac{1}{\beta} * \exp(-\frac{1}{\beta} * t) * \exp(1 - \exp(-\frac{1}{\alpha} * t)) \quad (3.6)$$

The same voltage derive (with different parameters  $a$  and  $b$ ) is valid for  $\frac{d}{dt}V_M(t)$  due to the membrane rush-in current (as discussed above, the voltage derivate is proportional to the current through a factor  $1/C_M$ ). See also Figure 3.17.

### Native case

In the native case (the membrane's voltage created instantly and then no external invasion happens), the resulting voltage derivative is

$$\frac{d}{dt}V_{OUT}(t) = \frac{d}{dt}V_M(t) + \frac{d}{dt}V_{AIS}(t) \quad (3.7)$$

Figure 3.11 shows the functional forms of  $V_M(t)$  and  $\frac{d}{dt}V_M(t)$  ( *PSP current* and its *voltage derivative*) at some reasonable parameter values  $a$  and  $b$ . (Notice that the front of an arriving spike, as well as at the beginning of clamping, the front is almost clearly exponential.) Notice the sudden change of the derivative after the output (spike delivery) begins: the exponential increase of  $V_M(t)$  really causes a steep change in its derivative at low time values. For different values of parameters  $a$  and  $b$ , a variety of function shapes describing APs can be created, see Figure 3.10 and also Figure 3.17.

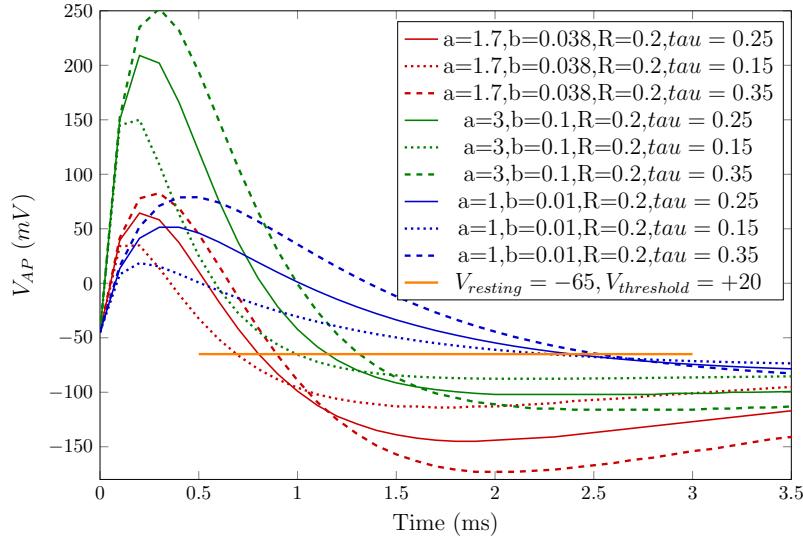


Figure 3.10: The shape of the AP as the result of integrating the differential Equation (3.7), at different input and output currents and timing constant

### Complex case

In the most complex case, the time derivative of voltage we need to work with is

$$\frac{d}{dt}V_{OUT}(t) = \frac{d}{dt}V_{AIS}(t) + \frac{d}{dt}V_M(t) + \sum_i \frac{d}{dt}V_{SYN,i}(t) + \frac{d}{dt}V_{ARTIF}(t) \quad (3.8)$$

The first term is always present. The second term only if previously exceeding the threshold value caused by membrane's charge-up (an instant effect). The third term changes during the stages of operation, as we describe below. The last term is an "artificial" contribution (and so: it depends on experimental settings), but it is frequently used in experimental research. Notice that whether voltage or current clamping is applied, it only means what the experimenter keeps constant; it acts with its *voltage derivative*. The same holds for the mathematical form of the used current/voltage.

The equation enables us to understand the experience that the shape of the AP is always the same. More precisely, the integrals of the contributing  $\frac{d}{dt}V(t)$  terms remain the same. Furthermore, if the contributors remain the same, the resulting shape also remains the same. Of course, only in steady state. It changes, if the next spike arrives before the resting potential restored,

or synaptic input arrives when synaptic inputs are enabled, or the artificial current changes.

### Currents in different stages

The neuron's electric operation comprises several stages, and the different physical phenomena produce different currents in those stages. The stages of neuronal operation, and the presence of slow and fast currents, furthermore the gating mechanisms significantly shade the picture.

As we introduced, the ion currents are 'slow' if they arrive through the axon (as [5] measured, an apparent 'delay' can be observed between the voltage and the current).

The 'artificial' contributions  $\frac{d}{dt}V_{CLAMP}$  and  $\frac{d}{dt}V_{PATCH}$ , of course, depend only on the investigators and no additional (stage-dependent) rule is followed (although the delay may apply).

The contribution  $\frac{d}{dt}V_{AIS}(t)$  is always on; the neuron all the time, independently from its history, operating stage and its inputs, attempts to restore its resting potential. The  $I_{AIS}$  is active all the time, active all the time. However, it is *not* a "leaking current". It is proportional to the difference of the *membrane's potential above the resting potential*. In resting state, its value is zero, see The mechanism in *resting state* is different.

The contribution  $\frac{d}{dt}V_M(t)$ , once 'DeliveringBegin' issued, will not be stopped (except 'Synchronize') until the membrane voltage drops below the threshold value. If the artificial currents are too high (see 3.17), the stage 'Delivering' may last forever.

The contributions  $\frac{d}{dt}V_{SYN,i}(t)$  are only enabled when the membrane's voltage is below the threshold level. The amplitude of the current/voltage derivative depends on the membrane's voltage. The synaptic inputs  $I_{SYN,i}$  are active only in the charge-up and 'relative refractory' period. Actually, when *the membrane potential is kept above the threshold value*: the ions cannot enter the intracellular space against the higher membrane potential: the 'normal' inputs can be blocked [133]. See also Figure 1.6.

### 3.5.5 Charge conservation

In our model, an intense ion current generator with step-like behavior represents the membrane, and a less intense negative current generator (drain) represents AIS. We return to the case we describe in connection with PSP, see Eq. (3.5), with a crucial difference. The flow-in and the flow-out points are at a distance and a "slow" ion current must flow between them. If the current travels to a fixed distance with a fixed speed, as we discuss in connection with Equ. (2.2), we expect that the output current appears with a delay compared to the input current. We assume that the charge conserves, i.e., the input current equals the output current. That means, for a one-dimensional membrane, *we shall write Kirchoff's Junction Law in the form*

$$I_{out}(t) = -I_{in}(t-\Delta t) \quad (3.9)$$

instead of the usual form, without delay. In Fig. 1 in [47] one can see that the current travels with speed less than 1 cm/s toward AIS, and that Kirchoff's Law is valid only in the form given by Eq. (3.9). It is, essentially, what the telegraph equation expresses for technical computing: *the macroscopic current has finite speed.*

We assume that the input current due to the rushed-in ions is similar to the one we derived in connection with PSP see Equ. (3.5). That is, we expect that the resulting (net) current is a “ghost” image shown in Fig. 3.23, which can be interpreted as a kind of interference (a difference between a positive current and shifted negative current) between the input and output currents, and expresses *Kirchoff's Junction Law for “slow” current in a neuron*. For the figure, we assumed  $\Delta t = 0.49\text{ ms}$ , and the parameters used to generate the function displayed in Fig. 3.25. The negative output current has been observed and measured by [5], see their Fig. 18, but – due to the lack of the idea of “slow current”, furthermore using the mistakenly measured empirical dependencies of “conductivity” – it has been identified as outward  $K^+$  current. A high sodium channel density is present in the AIS [47] to form AP, and imaging ions show (see their Fig. 3f in [47]) that  $Na^+$  ions arrive at it. Hypothesizing  $K^+$  in all cases leads to some discrepancy see for example, ‘It is counter- intuitive that removing a potassium conductance would decrease the excitability of a neuron’ [82], and

In our model, the membrane acts as a *voltage generator* with the time course described by Eq. (3.6), with the appropriate coefficients. This change is a drastic departure from the classic picture using a *current generator*, where a “fast” current flows through the resistor, generating a voltage that charges the capacitor. Initially, the capacitor is empty, so it will temporarily store the charge; that charge produces the ‘damping’ contribution later but cannot explain a negative contribution. To explain the experienced hyperpolarization, a  $K^+$  current in the opposite direction must be assumed, although it has no source charge in the membrane and no experimental proof underpins its existence *during evoking an AP*; see [82].

In our modern picture, the initial ion inflow saturates, and the relatively low-intensity slow current removes the charges from the membrane’s surface. The membrane attempts to remain equipotential despite the experienced current drain, but the slow current needs time to reach the AIS. The interplay of the finite-speed current flowing on the finite-size surface and the voltage-dependent exponential outflow shape the AP. *There is no need to assume the inflow or outflow of specific currents and the change of ion type. The extended size of the membrane, accompanied by slow ion propagation, entirely explains why the spikes are issued and provides its parameters. Similarly, no control mechanism is needed: biology takes advantage of the slow ion propagation speed.* (The function displayed should be convolved with a function considering the distribution of distances between the input and output points; i.e., consider an actual membrane shape).

To describe how the neuron’s membrane forms an AP, we consider that the membrane becomes highly charged (i.e., will have a considerable potential) af-

ter opening its ion channels. That potential difference will drive a macroscopic current toward the AIS, where a macroscopic current flows out, as described in [47]. The mathematical formalism is the same as in the case of PSP, see Eq. (3.5), except that the current inflow is more intense, given that the membrane's surface is much larger. Although the AIS is much smaller, its much higher ion channel density [47] enables it to forward that intense "longitudinal" current toward the axon (where it is transmitted as a "transversal current"; see good textbooks and our discussion). As we discussed, an AP can be described by three parameters: how the rush-in current rises (a function of the area and ion channel density), how the rushed-in charge can flow out (including how long the current path is), and the parameters of the neuronal  $RC$  circuit.

That current on the condenser with capacity  $C_m$ , alone, would produce a voltage change  $\frac{dV_{chargeup}}{dt}$ : it is the input side of the circuit. The membrane (in cooperation with the AIS) behaves as a differentiator  $RC$  circuit. It will significantly change the form of the voltage's time course on its output side (as discussed in section 2.4.4, one can imitate the effects of a "slow" current flowing on a system with distributed parameters using equations created for discrete parameter case). The membrane potential produces a current that discharges the condenser, decreasing the potential generated by the membrane's current.

Our model hypothesizes that the current due to the rushed-in ions maintains the time course of the *voltage derivative* in the input side, see Eq.(3.7). We shall solve the equation numerically to receive the *output voltage*, the AP. The shape of the voltage due to the slow current on the membrane, described by Eq. (3.5) and its derivative, described by Eq. (3.6), are depicted in Fig. 3.11; with the parameters concluded from Fig. 3.22. The formalism and model are the same also in the case of a membrane; only the coefficients are different.

By varying those parameters, a variety of AP shapes can be described using the same model, see Fig. 3.10. The various colors and line types demonstrate the influence of parameter values on the calculated shape of the AP. We based our calculations on a resting potential of -65 mV and a threshold offset potential of +20 mV. The red lines represent AP for current intensities similar to those used to generate the diagram line in Fig. 3.25. The green and blue lines depict the AP for higher and lower intensity currents, respectively. The continuous lines show the AP for a neuronal oscillator with capacity  $C$  we used to generate Fig. 3.25. The dotted and dashed lines represent circuits with higher and lower time constant values, respectively. Our research suggests that assuming a *differentiator-type*  $RC$  circuit for the neuronal membrane can imitate the effects of the "slow" current's temporal behavior, see Fig. 3.23. As we discussed in section 2.4.4, the time constant  $RC$  drastically influences the resemblance of the (PSP-like) input function shape and the (AP-like) output shape. Furthermore, the higher the charge-up current compared to the fixed-value output current (defined by  $R$ ), the more resemblant the output voltage shape and the empirical AP.

In the picture, we suggest here, the voltage of the membrane increases enormously (described in a physically plausible way and with a mathematically and physically correct time-dependent function), observed as large transient local

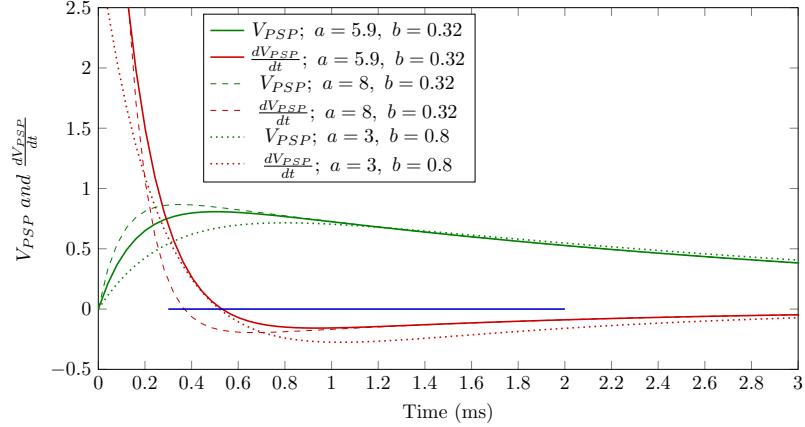


Figure 3.11: The rush-in (and post-synaptic potential) and its derivative, as provided by Eqs. (3.5) and (3.6). The PSP diagram line was fitted to data measured by [77]

voltages [74, 75]. The membrane, acting as a semipermeable insulator surface, hosts charge carriers that distribute on it, capable of reaching other areas with finite surface speed. Consequently, the AIS will experience only a marginal increase upon receiving an axonal input, and only with a delay. A temporally distributed charge packet is the sole factor that evokes the observed voltage increase, without any other assumed in- and outflow of ions. This novel approach to understanding the initiation of APs sets our model apart.

### 3.5.6 Voltage time derivative

The time derivative was measured already in 1939 [40], see Fig. 3.12. However, its role has not yet been recognized. Interestingly, Cole and Curtis derived the AP by integrating the experimentally derived  $\frac{d}{dt}V$ , essentially in the same way as we do. (they also discussed the widening/smearing effect of the measuring technology)

The shape and different parameters of AP has been the subject of numerous studies. For example, [82] measured AP, simultaneously with its time derivative of the APTD for a wealth of neuron types. Those measurements provide a direct proof for the existence of the APTD our theoretical approach introduced, see equations (3.6), (3.7), (3.5) and Figs. 3.13 and 3.11. However, notice that the causality is reversed. The current inflow through the neuron's membrane generates APTD, and its time course generates AP through the *RC* circuit. Notice that the theoretical APTD is much sharper than the experimental one.

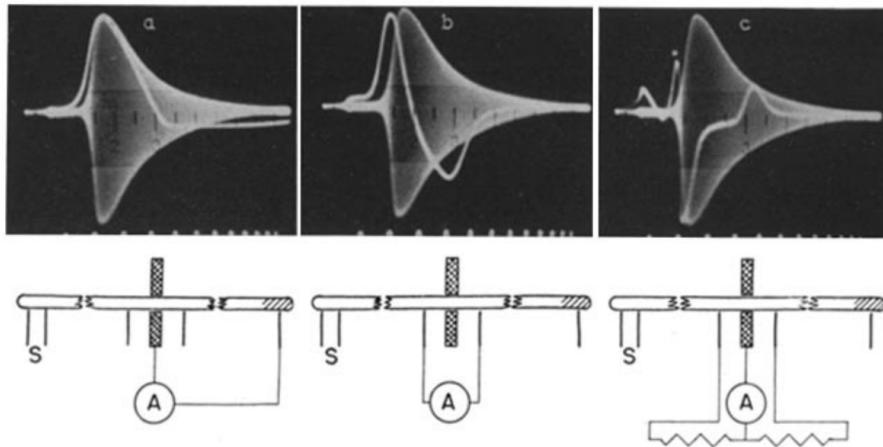


Figure 3.12: Measuring the time derivative in [40], from 1939

Actually, the latter value is a differentia ratio (instead of differential quotient) from measured values. The measuring electrodes's size defines the position (and time) difference. In the case of measuring a signal with very sharp form the two quotients differ significantly.

Fig. 3.14 shows how the rushed-in ions produce the AP. The blue diagram line describes how the AP depends on the voltage gradient. The life begins at coordinates (0,0), in the tiny orange circle, with exciting the neuron. The synaptic excitation is pulse like, so the voltage simply rises without a gradient being generated. When the membrane's voltage threshold reached, the potential does not change, but the gradient jumps due to the (instant) appearance of the runshed-in ions, see the rightmost point. From this point on, the potential increases while the gradient decreases; the diagram line proceeds from right to left. The potential increases as the ions entering the surface layer at some point farther from the AIS: to travel such a distance, needs time. The highest point reached when the ions from the largest distance could reach the AIS. (The influx was instant, the charge will continuously decrease due to the current through the AIS. The change in the layer behaves as a high-viscosity charged fluid. The electric and thermodinamic driving forces propagate with enormously different speed, and the fluid must be contiguous; so the voltage temporally increases before the AIS (ram current or impact current), and the fluid turns back which means that the ion current changes its direction (condenser effect). Due to the decreasing current, the voltage starts to decrease, although the voltage gradient is still positive (it is the contribution of the rush-in current, only). The negative current continues and turns first the gradient to negative whihc turns the potential to negative (a state known as 'hyperpolarization'), and finally the relaxed current takes but the potential and the gradient back to zero (the resting potential).

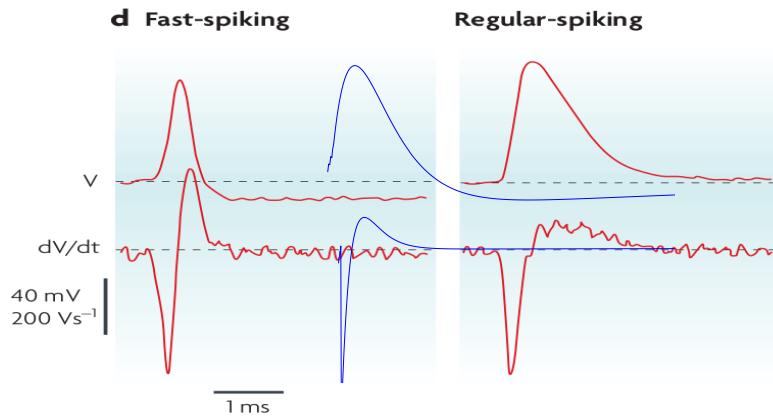


Figure 3.13: The simultaneously measured AP and APTD Our theoretically derived AP and APTD are overlayed to Fig. 2d in[82]. See also our Figure 3.17. ©2007 Nature Publishing Group. Bean, B. P. (2007): The action potential in mammalian central neurons. *Nature Reviews Neuroscience*, 8(6), 451-465. doi:10.1038/nrn2148”.

The green dashed diagram line shows the AP in the function of the voltage measurable on the AIS (the difference of the gradients of the rush-in and the outflow gradients). This diagram line also starts from the orange circle, but since the excitation increases the potential that generates current (and so potential gradient) on the AIS, the gradient goes to negative as the potential increases. When the potential reaches the threshold value, the gradient jumps to its maximal positive value and the potential increase at a decreasing pace. It reaches its maximum value when the resulting gradient reaches zero. The negative gradient turns the potential even to negative (hyperpolarization) while approaching its zero driving force. (the outflow current decreases the gradient, so, the parabola gets asymmetric). The oscillator comprises one turning point; it is perfectly damped (to provide the fastest operating speed).

### Hydraulic jump

When we consider the electrolyte layer of the ions as a ‘viscous charged fluid’ [112], we can expect phenomena similar to the hydrodynamic ones. For neurons, the gravitation is to be replaced with the attraction of the ion layer on the other side of the membrane, and the barrier with the resistor, see section 2.5.5. The so called ‘hydraulic jump’ (see Fig. 3.15) means that when the moving fluid faces a barrier (the AIS), the otherwise constant voltage in the

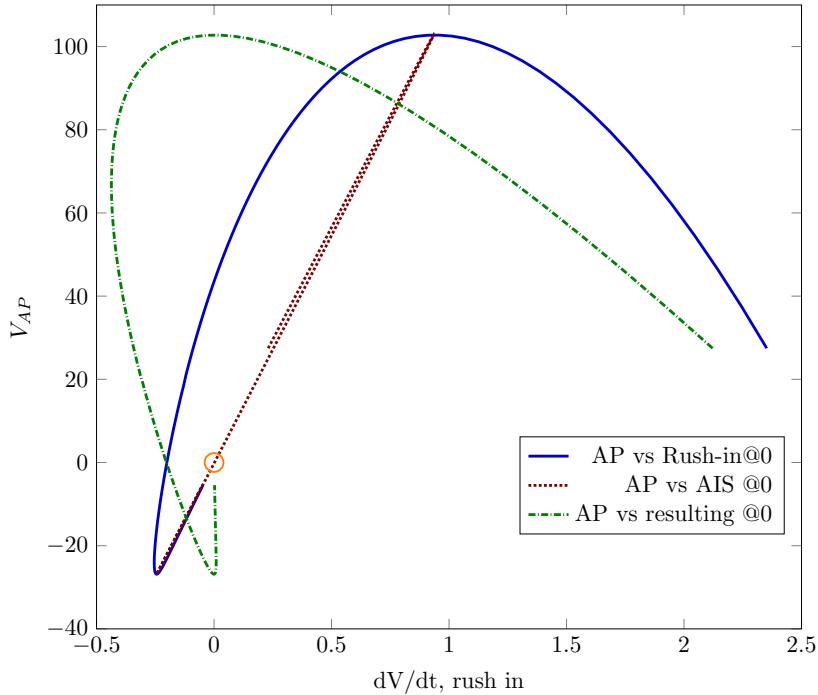


Figure 3.14: How the voltage gradient created by the rush-in current drives the Action Potential.

layer on the surface of the membrane jumps (relatively smoothly) to a much higher potential and after peaking, produces a damped oscillation, resembling to an action potential. We note that the finite distances make a difference with respect to the numeric simulation. No new fluid arrives, so there can be a flow component in the reverse direction.

The latter component can produce a turbulence and a strongly different potential when the driving force derived from the gravitational force changes, see Figure 3.16. Recall that maybe the AIS has also the role of the dissipator: reflections and back-propagation in the axon must be avoided. Based on dedicated data on the geometry of neurons, realistic numerical simulations could be carried out with the existing softwares.

In the picture above, we can understand that, "the choice of orthodromic versus antidromic stimulation can bias or even invert experimental findings", as demonstrated experimentally [135]. The stimulation injects fluid in both directions and the reflections can result in contradictory observations.

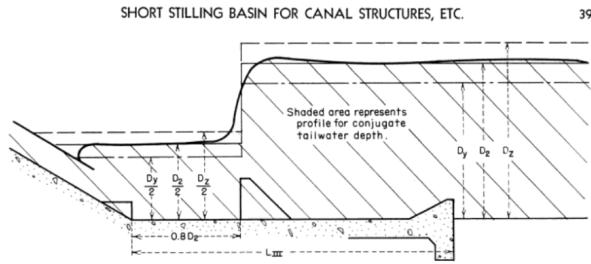


FIGURE 19.—Approximate water surface and pressure profiles (Basin III).

Figure 3.15: The phenomenon of 'Hydraulic jump' [134]

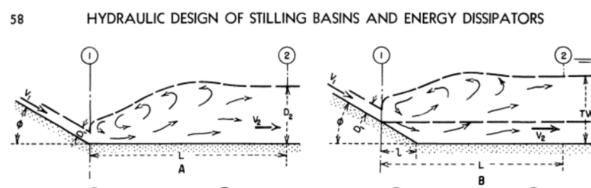


Figure 3.16: How the flow can self-dissipate its flow[134].

### 3.5.7 Synaptic control

When researching the electric operation, 'foreign' currents and voltages (as opposed to the 'native' ones) are applied. Our model can describe the effects of such artificial invasions. The synaptic control can be best understood on the example of modeling constant external current. As we discussed, a constant current (in 'steady-state', after the transients relaxed) can be modelled as adding a constant  $\frac{d}{dt}V$  term to the sum of the voltage time derivatives directing the neuron's AP. Figure 3.17 calls attention to some important consequences of applying artificial currents and shows how our model handles them. (Notice that the subfigures share the logarithmic time scale the begins at the arrival of the first synaptic input. For the sake of simplicity we use an arbitrary voltage scale, and imitate synaptic inputs with an instant membrane voltage step). For understanding the terms and notions, see also Figures 1.6 and 8.1.

The bottom subfigure displays the action potential observable on the AIS. The '0' case is a simple delivering (see section 3.5.4), when no external invasion is present. The AP is as experimentally observed: in the 'Relaxing' stage the neuron receives three synaptic inputs. When the first input arrives, the neuron passes to stage 'Computing'. For the effect of the third input, the neuron membrane exceeds the threshold voltage and the neuron passes to stage 'Delivering'. First the rushed-in ions increase the membrane's potential, then the AIS decreases it to its resting value. As we discussed, the synaptic inputs are disabled in the 'Delivering' stage. The top subfigure shows how the synaptic inputs are enabled/disabled during generating the AP when the threshold level

crossed. The synapses are OFF only during the 'Delivering' stage (conventionally considered as the 'absolute refractory' period). For the sake of simplicity, for this figure we assumed an instant re-enabling, that is, that after crossing the threshold potential value, the re-enabled synaptic inputs appear at the AIS without delay. The background also displays the voltage caused by the  $Na^+$  ions. The voltage scale is arbitrary, but the time scale is true: the neuronal condenser "stores" the ions and the stored current will reverse its direction when the rush-in current reaches its peak value; the reverse current appears as a negative current (decreases membrane's potential below the value of its resting potential).

If the external invasion is relatively small (codename '2'), the stages are reached at different 'local time' values compared to the case without external invasion. The stage 'Delivering' begins practically at the same time, but the polarization and hyperpolarization peak voltages are remarkable higher for the '2' case). Notice that the synaptic inhibition time is considerably longer: the extra charge extends the time until the membrane's potential can decrease below the threshold level. If the invasion is stronger (codename '4'), the hyperpolarization still exists, but the membrane's voltage decreases only for a short period below the threshold: the external input will increase the voltage above the threshold again. Notice that (on the top subfigure) the synaptic inputs are re-enabled at a much later time, and they remain enabled only until the membrane's current exceeds the threshold again (actually, the synaptic inputs can approach an ill-defined state). At a slightly higher invasion current, the membrane's voltage cannot decrease below the threshold: due to that 'foreign' current, the synaptic inputs get 'forever' disabled ('blocked'). The experimental evidence was published in [133]; also displaying that some protection exists in neurons against 'overloading'.

### 3.6 Hodgkin&Huxley's empirical description

As we discuss in section 2.4, the body's electric signals were discovered early, the principles, notions and technical equipments have been elaborated. Even, some meticulous measurements correctly interpreted some of its signals. The development of electronical technology enabled their systematic study in the beginning of the 50's. However, experimenters often forgot that "*Under ideal circumstances, the physical act of measuring a neurophysiological event would have no effect on the electrical signal of interest. Unfortunately, this is seldom the case in neurophysiology.*" [1].

The first systematic attempt to describe the results of observations in terms of well-known laws of electricity was published around 1952 [5]. A collection of their (modernized) papers is available [69]. They made a huge amount of meticulous measurements and wanted to help the science community with providing equations for practical applicability. To speed up reaching that goal, they introduced *empirical functions* and derived equations, which, not surprisingly, described the *empirical observations* quite accurately. The importance of their

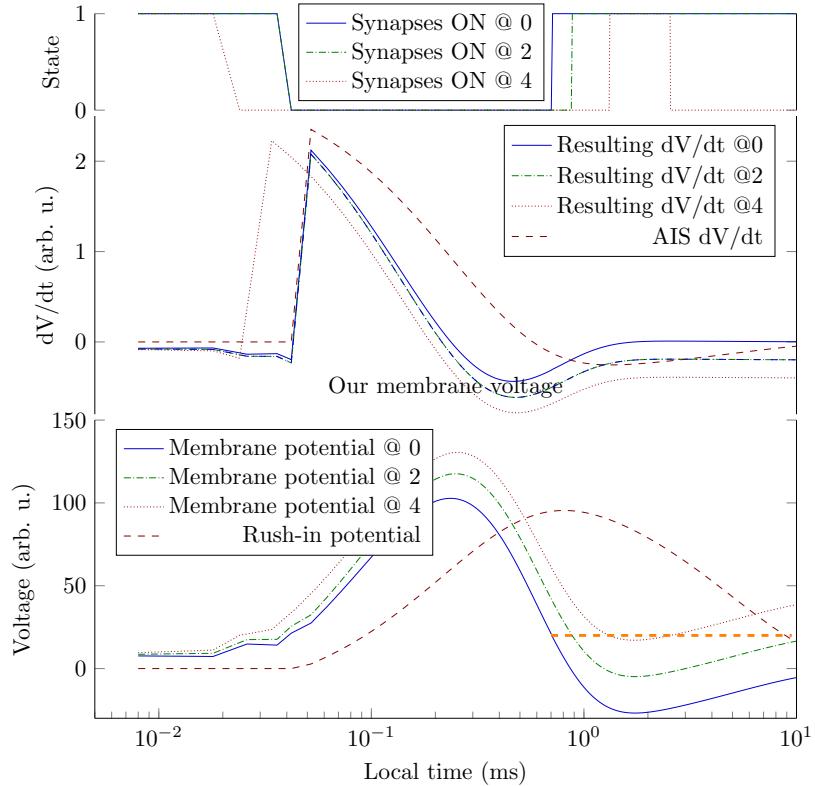


Figure 3.17: The summary of AP AP generation. The voltage time derivatives (the middle subfigure), resulting by summing the  $\frac{d}{dt} V_{AIS}$ ,  $\frac{d}{dt} V_M$  and a constant corresponding to the clamping current, that define the membrane's output voltage (the AP, the bottom subfigure), that control synaptic contributions (top subfigure). See also Fig.8.1

work is best highlighted by that it inspired different disciplines for discussion.

"although highly successful in predicting and explaining many of the electric characteristics of the action potential, the HH model, nevertheless cannot accommodate the various non-electrical physical manifestations (mechanical, thermal and optical changes) that accompany action potential propagation, and for which there is ample experimental evidence. [34]

A technical reason is described in [136]: "The fact that the whole process for calculation of a 4–5 ms interval, showing the initiation of and recovery following

an action potential, could be accomplished in 8 hours is astonishing." The must-be oversimplification does not belong to the core of the theory. When using the recent computing systems, not necessarily the old oversimplified models should be coded. One could also use modern, more compute intensive, and physically correct models.

### Self-evaluation

In their brilliant publication [5], Hodgkin and Huxley evaluated their results "that our equations [must not be taken as] anything more than an empirical description" and "the [partial] success of the equations is no evidence in favour of the mechanism". When validating their observations, they have found serious question marks: "a number of points were noted on which the calculated behaviour of our model did not agree with the experimental results. We shall now discuss the extent to which these discrepancies can be attributed to known shortcomings in our equations." "One was that the membrane capacity was assumed to behave as a '*perfect*' condenser, ... the other was that the equations governing the potassium conductance do not give as much *delay in the conductance rise* on depolarization as was observed in voltage clamps". They did have the intuition that something was wrong and they correctly guessed its reason: "it seems difficult to escape the conclusion that the changes in ionic permeability depend on *the movement of some component* of the membrane which behaves as though it had a large charge....it is necessary to suppose that *there are more carriers and that they react or move more slowly ... there is no evidence from our experiments of any current associated with the change in sodium permeability, apart from the contribution of the sodium ion itself*".

They emphasized that their work "must not be taken as evidence that their equations are anything more than an empirical description". They made the first step of "a great journey into the unknown" and were very cautious by saying that "the success of the equations is no evidence in favour of the mechanism that they tentatively had in mind when formulating them".

In his late work [136], Hodgkin evaluated the filtered experiences: "We soon realized that *the carrier model could not be made to fit certain results*, for example the nearly linear instantaneous current voltage relationship, and that it had to be replaced by some kind of voltage-dependent gate. As soon as we began to think about molecular mechanisms it became clear that *the electrical data would by themselves yield only very general information* about the class of system likely to be involved. So we settled for the more pedestrian aim of finding a simple set of mathematical equations which might plausibly represent the movement of electrically charged gating particles."

### Nobel-laudation

Unfortunately, they also attempted to understand which physical processes happen in the membrane, but they concluded with the feeling that "*the interpretation given is unlikely to provide a correct picture of the membrane*." Despite

their explicit warning, that "the success of the equations is no evidence in favour of the mechanism that we tentatively had in mind when formulating them". Despite, they received the Nobel-prize "for their discoveries concerning the **ionic mechanisms** involved in excitation and inhibition in the peripheral and central portions of the nerve". As the philosophical approach to their work discusses, "One could dismiss this curious passage as scientific modesty if it were not for the fact that Hodgkin and Huxley argue for their conclusions." [41] The science community rushed to apply the equations, instead of validating them. To compensate for the disagreements with the experimental data, further ad-hoc assumptions have been introduced, making their admittedly wrong picture even worse.

In the sense of philosophy, "there is a widely accepted distinction between *merely modeling a mechanism's behavior* and *explaining* it. The equations must be supplemented by a causal interpretation: one might, for example, agree by convention that the effect variable is represented on the left, and the cause variables are represented on the right, or one might add "these are not mere mathematical relationships among variables but descriptions of causal relationships in which this variable is a cause and this other is an effect," and not vice versa", for more details see [41, 137]. The lack of causality is one reason why HH have had the feeling they missed the correct picture of the membrane. The other reason is that some fine details of their oversimplified picture was not accurate, although the additional (and arbitrary) ad-hoc assumptions have hidden the disagreements. The followers have "fitted elephants" [26] by adding many more ad-hoc effects with too many parameters.

### 3.6.1 Measurement science

As highlighted in [41], they performed a very meticulous analysis and characterized the time-course of the action potential phenomena in terms of different features (the concise listing taken from [41])

- the form, amplitude, and threshold of an action potential;
- the form, amplitude, and velocity of a propagated action potential;
- the form and amplitude of the resistance changes during an action potential;
- the total movement of ions during an action potential;
- the threshold and response during the refractory period;
- the existence and form of subthreshold responses;
- the production of action potentials after sustained current injection (that is, anodal break);
- the subthreshold oscillations seen in the axons of cephalopods

"A measurement can be precise without being accurate." [1] *Accuracy means characterizing the true measurable quantity.* In this sense, their measurement is precise but not accurate: they measured precisely wrong quantities, which, unfortunately, can be made and thought sufficiently resemblant to the real ones.

### 3.6.2 Mathematics

"These equations and the methods that arose from this combination of modeling and experiments have since formed the basis for every subsequent model for active cells. The Hodgkin-Huxley model and a host of simplified equations derived from them have inspired the development of *new and beautiful mathematics*." [42].

### 3.6.3 Physics

"A. L. Hodgkin and A. F. Huxley published what was to become known as the model of the action potential. This model would subsequently be considered a cornerstone of electrophysiology and neuroscience, since it concerned the ionic mechanisms involved in the operation of the nerve cell membrane." [138]

#### Neglecting Coulomb's Law

### 3.6.4 Driving force

As we discuss in section 2.4.8, HH introduced by their Eq. (1) (reproduced by us as Eq. (2.40)) the basic description of *the membrane current during a voltage clamp* with that "the justification for this equation is that it is the simplest which can be used and that it gives values for the membrane capacity which are independent of the magnitude or sign of  $V$  and are *little affected by the time course of  $V$* ". (It is again a reversed approach: the capacity, per definitionem, means the ability to store charge and is one of the attributes of the medium instead of the electric characteristic of the tested circuit. For the case of clamping, it is an approximation that the temporal course of the clamping voltage is kept constant, the current remains constant. As we discuss in section 3.5.4, in the case of a constant current where  $I = \frac{dQ}{dt}$ , the voltage increase  $dV$  on the capacity  $C$  of the membrane is  $\frac{dQ}{C} = \frac{I*dt}{C}$ , so we can derive the "driving force" (compare it to Eq. (2.11)) as they interpreted it

$$\frac{d}{dt}V = \frac{I}{C}$$

The direct *constant* current input  $\frac{d}{dt}V_{PATCH}$  to the neuron cell body is a simple constant current that causes a constant membrane's voltage derivative contribution. That is, if one checks the dependence of the output voltage on  $\frac{d}{dt}V$  and  $I$ , in the presence of a constant  $C$ , one observes the same dependence. However, the currents are not necessarily constant.

### 3.6.5 Electricity

#### Equivalent circuits

The biological 'equivalent circuit' models assume that the circuits comprise point-like ideal *discrete elements* such as condensers and resistors, and some hidden power changes their parameters according to some mathematical formulas, furthermore ideal batteries with voltage that may again be changed by that power. All they are connected by conducting (metallic) ideal wires and their interaction speed is infinitely high (the Newtonian 'instant interaction'). Using that abstract model enables them to use the well-known classic equations, named after Ohm, Kirchoff, Coulomb, Maxwell and others. However, those abstractions have severe limitations. Biology applies Ohm's Law to its objects while claims that its objects are non-ohmic; understands that neural currents comprise ions while claims that the ions do not feel the Coulomb repulsion; measures ions' propagation speed but in its equations it claims that their effects are instant; hypothesizes non-existing physical mechanisms to make their nature. In general, biophysics abstracts from the world of the physics-inspired mathematical formulas a fictitious nature where biology lives and hypothesises complementary mechanisms to achieve some resemblance with the true biological word. The examples include that ions in the ion channels do not repulse each other; that charge, potential and current are independent of each other; that ion currents do not repulse each other neither when they travel from the presynaptic terminal to the AIS; that some hidden power opens the ion channels to let ions in into the intracellular space, that ions with the same charge move in opposite directions when ions rush-in into the intracellular segment of the neuron; that the ions pass ion channels without being accelerated by the potential difference across the membrane; the telegraph equations are applied to the case of axons although neither external potential nor current loss exists; and so on.

Even that unfortunate idea of equivalent circuits leads to analyzing "electrotrophic (electronic circuit equivalent) modeling of realistic neurons and the interaction of dendritic morphology and voltage-dependent membrane properties on the processing of neuronal synaptic input" [44]; that is, to study a simulated neuron built from discrete electronic components. However, the idea needs to put together many components "raises the possibility that the neuron is itself a network". On the one side, such an idea misguides the neurophysical research (since actually a fake neural system is scrutinized, the validity of the approach is questioned [45]), and on the other, since electroengineers understand the neuronal operation from the wrong model, it also misguides building neuromorphic architectures.

The equivalent circuits are a source of misinterpretations. As [1] formulates, "In other words, the ionic concentration gradients act like DC batteries for cross-membrane currents." We call the attention again, that *ions* represent the current, that is *that current changes changes the concentration, that changes the voltage of the DC battery, unlike in the case of the equivalent circuits*. This

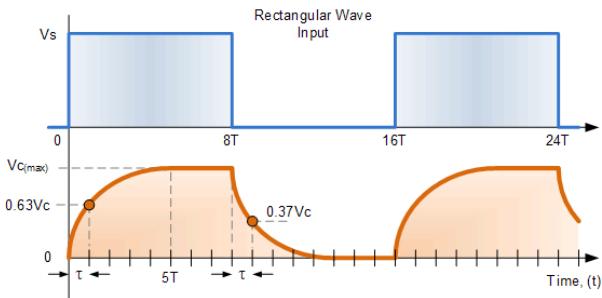


Figure 3.18: The output waveform of an integrator-type electric  $RC$  circuit at a long ( $8 * \tau$ ) pulse width square wave input (see Eq.(<https://www.electronics-tutorials.ws/>)

difference is significant in understand how the basic neuronal circuit works. Introducing equivalent circuits prevents explaining the fundamental electric phenomena.

This was how — Richard P. Feynman approached all knowledge: What can I know for sure, and how can I come to know it? It resulted in his famous quote, “*You must not fool yourself, and you are the easiest person to fool.*” Feynman believed it and practiced it in all of his intellectual work.

### Oscillator type

If we apply a continuous square wave voltage waveform to an integrator-type electric  $RC$  circuit, we receive an output wave form shown in Fig. 3.18. After switching a voltage to the circuit, a charge-up process starts, then the output voltage saturates. After switching the voltage off, the condenser discharges. *The time constant  $\tau$  for the charge and discharge processes are identical.* If the time period of the input square wave waveform is made longer (in the figure with a half-period “ $8 * \tau$ ”), the capacitor would then stay fully charged longer and also stay fully discharged longer.

HH measured [5] the time course of the neuronal membrane (i.e., a neuronal  $RC$  circuit) when switched clamping axonal voltage on and off. Their measurement result is shown in Fig. 3.19. They experienced a formal similarity with switching a voltage of an integrator-type  $RC$  circuit on and off, compare to Fig. 3.18, so *they concluded that the response of the neuronal circuit is identical to that of the integrator-type electric  $RC$  circuit* (see our discussion in sections 2.4.8 and 2.4.8). They (mistakenly) concluded that the electric equivalent circuit of a neuron is a parallelly switched electric  $RC$  oscillator. One more evidence that ”the success of the equations is no evidence in favour of the mechanism that we tentatively had in mind when formulating them”.

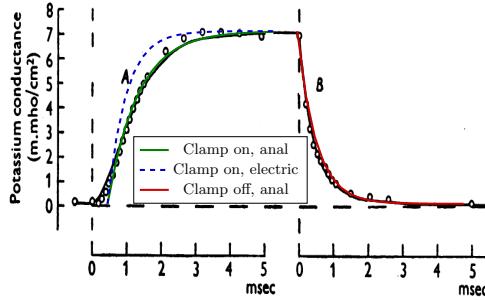


Figure 3.19: The green and red diagram lines are calculated for the clamping-on and clamping-off case. The dashed blue line models the case that the neuron is a purely electric system, as opposed to the case of clamping the axonal tube with ion channels in its wall. The black bulbs are for measured points. Moreover, the fitted polynomial line is reproduced from [5].

Figure 3.19 shows *two* switch-on diagram lines, with two different  $\tau$  time constants. The blue line ("electric") is drawn with the measured time constant of the switch-off discharge. According to the theory of electricity, the time constants of the falling and rising edge must be the same in the case of an electric integrator. The green diagram line (the one fitted to the measured data) correspond to a different  $\tau$  time constant. The effect was observed by [5], but they did not explain and also did not interpret it. Although their fitted polynomial nearly hides the effect, a little "hump" at around 3 ms can be observed. The reason is that the charge-up current is not constant, it also has a time course; despite that they stabilized the voltage.

The different time constants should have been a warning sign for HH that *the measured effect differs from the one they had in mind*. They wanted to believe and demonstrate that they have measured the output signal of a serial  $RC$  circuit. With the evaluation of their measurement, they suggested some wrong hypotheses

- They misidentified the current as *the change of conductance*. No conductance change happens, only a condenser changes and discharges. They worked with a condenser, not with a resistor.
- They meticulously observed and measured that the time constants  $\tau$  of the exponential charge-up and discharge processes are different; but did not care that they should be identical and also did not care of the "hump".
- They measured the resulting charge-up composite process. As we explain in section 2.4.4, before switching the clamping voltage, there is no charge carrier inside the axonal tube; first, the ions must diffuse into the axon.

- They fitted the rising time course with a polynomial, hiding that it comprises a saturating voltage of the condenser, that the current through the axon also saturated with a different time constant, and at the beginning the line had a zero current contribution.

On the one side, they underpinned that our equations 2.36 and 2.35 describe correctly the axonal chargeup current and discharge currents, respectively. On the other, as they noticed that the time constants of the two processes are significantly different (see the green and the dashed blue diagram lines), underpinned that the axonal charge production mechanism significantly changes the axonal source current. The green line has significantly slower rise since the axonal current only gradually increases after switching the clamping on. Without that current change, the charge-up current would follow the blue line. Unfortunately, there are three physical processes, with similar time constants. One, that they wanted to demonstrate is the steady state: the current leads to a saturated current. Two, that the clamping "creates" charge carriers in the axon, so the charging current changes. Three, the initial switch-on creates a voltage gradient on the membrane, so an action potential is also started.

Their equations more or less precisely describe the features of the wrong oscillator type and those of the non-existing  $K^+$  current introduced for compensating for the wrong oscillator selection.

### Cable equation

Selecting the wrong oscillator type (actually, assuming distributed parallel oscillator circuit) and the wrong electrotonic model leads to somewhat surprising consequences, such as using the telegrapher equations in a wrong way for describing neuronal transfer. By using the cable equation, as Hodgkin and Huxley attempted [5], led to numerical difficulties, and they faced the principal problem: their equations assumed infinitely fast electric interaction, and they attempted to combine them with the (unknown) finite macroscopic speed of current in neuronal telegraph cables. The validity of using cable equations for biological objects is at least doubtful: deriving a telegrapher equation assumes applying an external potential to the cable filled with charge carriers, and in the case of biological membranes neither external potential nor permanently present charge carriers exist. Furthermore, the cable equation assumes continuous current outflow (a distributed resistance), which is not true for the neuronal membrane (current flows only toward the AIS).

## 3.7 Experimental evidence

Using published data, we can derive direct experimental evidence for our statements.

Researchers, including Hodgkin and Huxley [5], are thinking in the Newtonian way. That is, they expect the current to appear promptly after switching on the clamping voltage. By using so, they assume that the transport speed of

electrodiffusion in an axon and the electromagnetic field propagation are the same. That fallacy is why Hodgkin and Huxley were convinced that *the slowly moving charged object that they observed could not be current*.

### 3.7.1 Stokes-Einstein relation

As we derived theoretically in section 2.4.4, in general case, the ion current generated by a potential gradient is proportional with the electric gradient (see Eq. (2.26)) and so the macroscopic current speed (see Eq. (2.33)). By using the Stokes-Einstein relation we can also express the speed in the function of the potential gradient. According to that prediction, when we interpret that the clamping voltage is uniformly distributed along the axon, we have a  $\frac{dV}{dx}$  (proportional to the clamping voltage), and the current proportional to ion speed, we can expect a linear dependence between them.

The mostly known and influencing axon current measurement has been published in 1952 [5]. They used a single-axon input and measured at different clamping voltages the neuronal membrane's current (although they called it as conductance), which in this way was identical to the axon current. Their result is reproduced in Fig. 3.20 as the black bulbs and diagram lines.

As we discussed, ions diffuse across the axon's wall, producing a saturation-type current in the axon and later on the membrane. As expected from our theoretical consideration in section 3.7.2, the experimental data are fitted with the theoretical function 3.1 to their experimental data (just reading back their graphically published measurement results). The parameters of the theoretical function are displayed in Fig. 3.21 in the function of the clamping voltage. Our simple model assumes that the  $\alpha$  time constant (through  $v$  and  $\frac{dV}{dx}$ ) depends on the clamping voltage). As expected, the potassium current, proportional to ion speed, changes linearly in function of the voltage gradient (proportional to the clamping voltage), see the blue dots. The similar dependence of the time constant on the clamping voltage (see the red circles) underpins that our theoretical discussion leading to Eq. (3.1) is correct. Even, the diffusion coefficient or viscosity can be derived. The diffused-in ions were transported towards the membrane as a "slow" macroscopic ionic current (the speed of current HH [5] measured and also theoretically derived to be about 20 m/s); it is in the order of magnitude we mentioned for the speed of macroscopic currents in metals and electrolytes.

A systematic discrepancy exists at the low time values of the time course function between the one fitted originally by [5] and the one fitted by us. The former one is a simple polynomial that is simply a wrong quasi-model; our fitting uses the correct model function. The dependence we use (a sudden and delayed exponential increase in membrane's current) has been experimentally measured by [124]. The figure suggests that the saturation current depends linearly on the speed of ions (i.e., on the clamping voltage, see Fig. 3.20 and Fig. 3.21) in the tube.

We can spot two issues in connection with their measuring and one with the evaluation method of their excellent measurement. A fundamental problem to

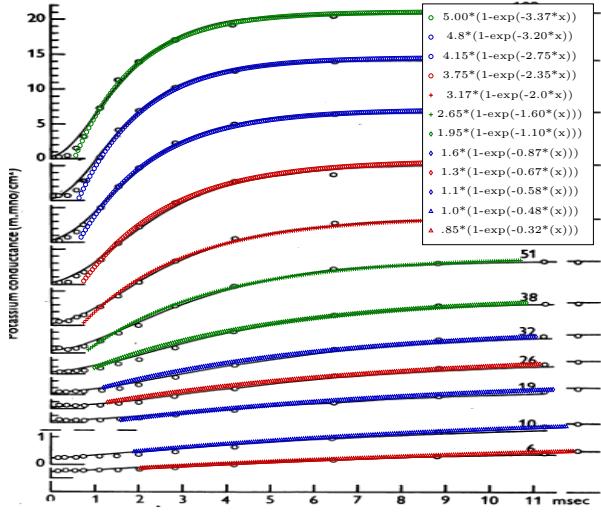


Figure 3.20: Finding time constants and membrane current by fitting data measured by HH (Fig. 3 in [5]) with our theoretically derived function (see Eq.(3.1)) ("Copyright [1991] Society for Neuroscience")

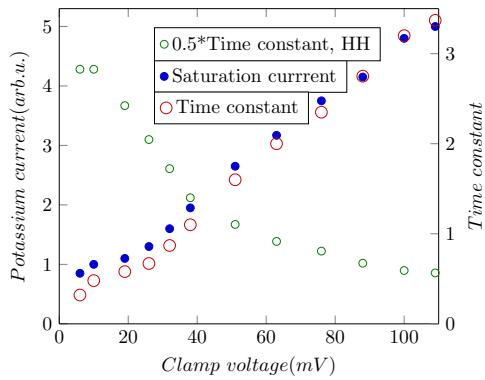


Figure 3.21: The experimental proof of the validity of the Stokes-Einstein relation to neurons. The proportionality of membrane's current (i.e., ions' speed) and time constant, respectively, with the clamping voltage (i.e., the voltage gradients). Data taken from Fig. 3.20 and Table I of [5], respectively.

solve when measuring chemical electrolytes using electronic devices is their interfacing. At some point, the ionic charge must be converted to electrons (there and back), which usually happens in electrolyte electrodes. Interfacing the analyzed electrolytic wire and metallic wire in the measurement circuit introduces problems, not only the contact potentials but also the time delay due to the using electrolyte electrodes. These electrodes need to carry the ions to some distance, and that process is outside of the time scale of the primary measured process. The effect is noticed but not explained [5]: “the steady state relation between sodium current and voltage could be calculated for this system and was found to agree reasonably with the observed curve at 0.2 msec after the onset of a sudden depolarization.” Moreover, given that *the speed of ions depends on the depolarizing voltage (see Eq. (2.26)), this time gap depends on the depolarizing voltage*: the higher the voltage, the shorter the time gap, demonstrated in their Fig. 3. Actually, their fitted polynomial chooses a wrong time scale and adds the delaying effect of the electrolyte electrodes to the measured time. Since this delay depends on the clamping voltage, the measured time constant comprises a systematic voltage-dependent contribution, so it distorts the fitting and delivers wrong time constants.

The second issue is that they measured conductance, which measurement procedure (as we discuss it in section 2.4.10) means introducing a small voltage into the measured system and generating a small current in it, which – by biological mechanisms – may produce further charge carriers inside it. The generated small current contributes to the true current in the system, and the device measures their sum, that is, the true current plus that offset. As long as the true current is large (notice that the clamping voltage spans nearly two orders of magnitude), the contribution of the device causes only a negligible distortion. At small clamping voltages, however, that contribution is comparable to the measured effect, so it significantly distorts the measurement and shows much higher current than the true one.

The third issue is, that they fitted their data with a polynomial function, which draws a ”smooth” diagram line, at low time values contracting an initial ”no current” period with a period where the current grows exponentially. Given that the ”no current” period decreases as the clamping voltage increases, the polynomial fits a variable composition of current in those two periods.

We fitted our theoretical function (see Eq.(2.36)) to their measured data published in [5], omitting the delay period due to the electrolyte electrodes. This way we eliminated the first and third issues. We derived the timing constant and saturation current values using the clamping voltage as parameter. In Fig. 3.21, we compare our fitted data values with those derived by HH (displayed in their Table I).

In the case of using the right function for fitting the measured current value, we receive the theoretically expected conclusion, that the time constant depends linearly on the clamping voltage (that is, on the voltage gradient), while fitting the data with the wrong (polynomial) function, the time contants show an opposite dependence. The saturation current shows in both cases a linear dependence.

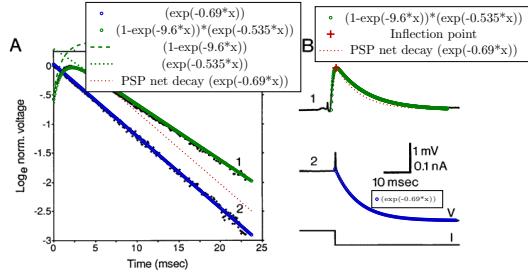


Figure 3.22: A) PSP decay (curve 1) and the decay after an injected depolarizing current pulse (curve 2) recorded in the same cell. B) Voltage traces (upper and middle) from which the curves in A were derived, together with the current record (lower) for the pulse. The colored marks and diagram lines are calculated using the model's "slow" current. Measurement data (with black) are reproduced from Fig. 4 of [77] ("©[1991] Society for Neuroscience" ).

The wrong evaluation method led Hodgkin and Huxley to conclusions opposite to the real ones, from the correct measured data. Their measurement is precise but not accurate. It has very sever consequences: covers the presence of "slow current" and disables understanding the physical process happening inside the neuron. Given that in the meantime the measurement technology developed (smaller electrolyte electrodes with much shorter delays furthermore conductance meters with higher internal impedance have been developed), and they coded those parameters (without the voltage-dependence we pointed out) into their polynomial coefficients (which are used in their differential equations), those issues significantly contributed to the difficulties their followers experienced when applying their equations.

### 3.7.2 Axon

We have a constant voltage at the end of the tube; the "slow" current "flowing out" from the tube increases and appears on the membrane, *establishing the illusion that the conductance of the tube increases. Resistance/conductance cannot be interpreted when charge carriers flow into the resistor* (and this is the case with the axon) from the environment: the "slow" current produces a different behavior (increases the number of charge carriers  $n$ ), see Eq. (2.26).

### 3.7.3 Invasions

Applying a step-like invasion (either concentration or voltage square-wave shaped change)

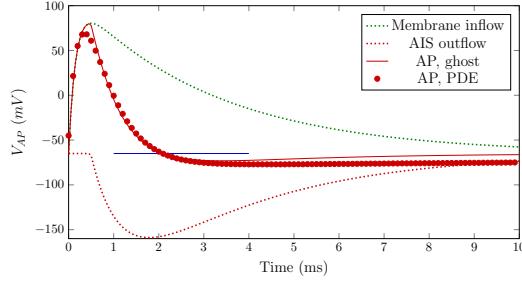


Figure 3.23: The "ghost image" formed by the delayed membrane current: the origin of the AP. The finite-speed ions transferred on the finite-size surface of the membrane: Kirchoff's Law in biology. The assumed delay time between input and output currents is 0.49 ms, the function form and its parameters are displayed in Fig. 3.25.

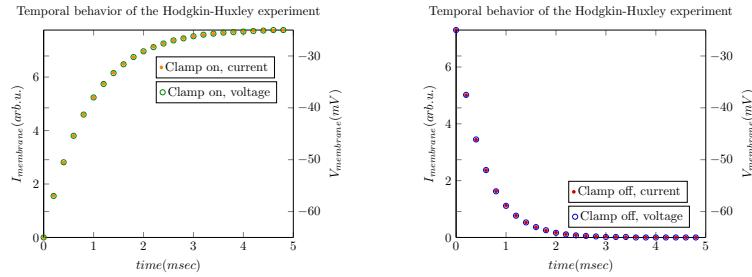


Figure 3.24: The time course of voltage and current a clamping experiment, calculated numerically for switching the clamping on and off.

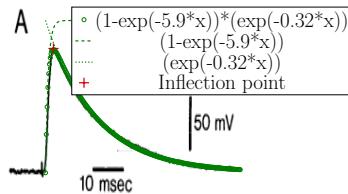


Figure 3.25: Time course of the post-synaptic potential evoked by a single AP. The colored marks and diagram lines are calculated using the model's "slow" current. Measurement data reproduced from Fig. 2 of [77] ("©[1991] Society for Neuroscience").

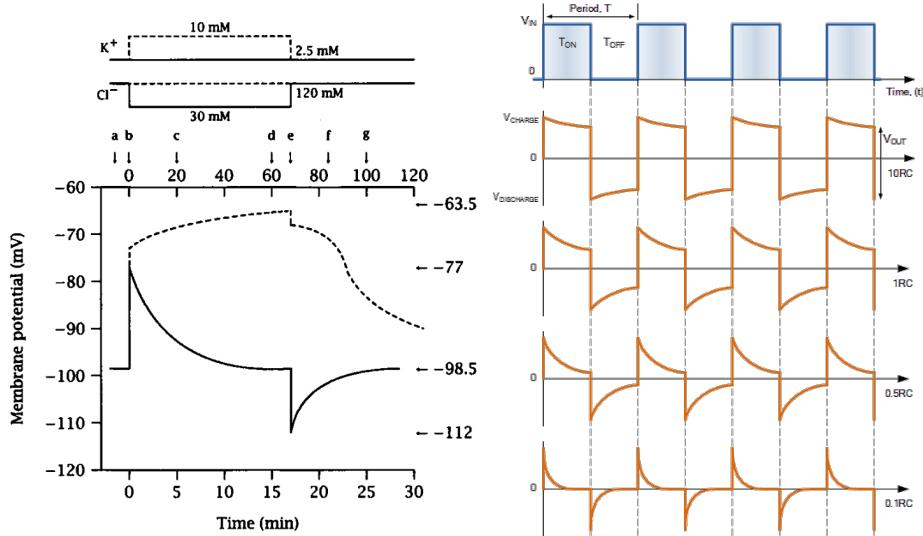


Figure 3.26: Left: The effect of applying a square-wave-like concentration change to membrane; Figure 2.2 from [1] Right: the effect of applying a square-wave like voltage change to an electric differentiator-type  $RC$  oscillator.

### Concentration square wave

It has been experimentally investigated the behavior of membrane potential in response to sudden changes of the extracellular concentration of the two permeable ions of the cell. The extracellular concentrations were abruptly changed, as depicted in the left side of Fig. 3.26. According to Eq. (2.7), a negative square wave of the concentration change must provoke a drastic positive potential change, with a time course described by Eq. (2.11). The step-like change results in a step in the voltage, and according to the Stokes formula (see Eq. (2.31)) the ions feel a huge voltage gradient, so they will move with high speed, and an intense current will start. Given that the current means also delivering chemical ions, the membrane tends to find another equilibrium state, corresponding to the newly set concentration, as explained in [1], page 22.

From an electric circuit point of view, the abruptly appearing and disappearing new thermodynamical driving force starts to remove charges and recover charges. Essentially, it indirectly discharges and charges the solution. In the right side of the figure, the effect on the output voltage of a differentiator-type electric equivalent circuit is shown under applying a sufficiently long square-wave input voltage change to its input. The negative edge of the concentration change causes indirectly a positive edge in the voltage, and vice versa, so the generated membrane potential should be compared to the reply of the electric circuit to a square-wave input voltage. We can deduce that the serially switched differentiator-type  $RC$  circuit faithfully reproduces the membrane's electric behavior. From the figure we can conclude that the corresponding time constant

$\tau$  can be around  $0.3 \text{ RC}$ .

From the figure we can estimate that the "half width" of the *concentration-provoked* potential change is about  $200 \text{ sec}$ . (The experiment is not dedicated, we just read back data from a textbook figure.) In Fig. 3.13, we see that the *electrically-provoked* potential gradient's half width is about  $0.1 \text{ ms}$  (the lower figure, a relatively short non.rectangle excitation). The experimental value of the ratio of these widths is  $2 * 10^6$  (it provides the ratio of the corresponding interaction speeds). For the theoretical value see Eq. (2.22).0 If we assume that the propagation speed in the electrolyte is  $2 * 10^8 \text{ m/s}$ , we can conclude  $10^2 \text{ m/s}$  *potential-assisted* speed for the change of concentration (actually, also the potential-assisted speed of current), in line with our other estimations and the published measurements.

### Voltage square wave

Similarly, one can apply a voltage square wave to a biological cell, see Fig. 3.27. Compare it to the bottom row of the electrical simulation. From the figure we can conclude that the corresponding time constant  $\tau$  can be around  $0.2 \text{ RC}$ .

Notice that the arrival of a square wave evokes

$$n = \frac{300 * 10^{-12} * 5 * 10^{-3}}{1.602 * 10^{-19}} = 10^7 \quad (3.10)$$

ions, in the order of we assumed in section 2.4.9.

### Action potential

As we discussed, after the membrane's potential exceeds its threshold, a membrane-evoked external invasion happens. The suddenly appearing potential change (although it is distributed over its surface) on the membrane is in resemblance with those square-wave excitation functions. Not surprisingly, the amount of charge which evokes an AP is also similar, as we discuss in section 2.4.9.

## 3.8 Fallacies

As we mentioned, when discovering new facts and more details, not only do they need to be inserted into the existing set, but the validity of *all* assumptions and approximations must be revisited. Maybe the discovery supersedes one or more of the old items, provides a new hypothesis in place of an old one, turns a hypothesis into fact, or question marks the overall validity (at least part) of the set of approximations and abstractions. Alternatively, it turns a hypothesis into a fallacy.

Neuroanatomy provided an unbelievable wealth of details about the CNS, its structure, components, their infinite variety of implementation, connection, chemical/enzymatical composition, and so on. A vast amount of data is collected and available, and uncountable attempts (mathematical models) have

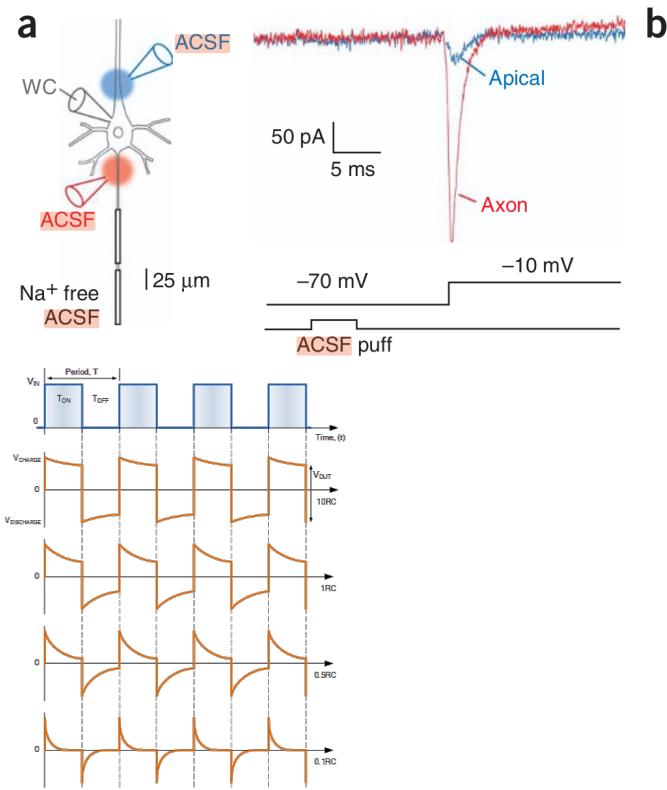


Figure 3.27: Left: The effect of applying a square-wave-like voltage change to membrane; Figure 2.a from [47]. Schematic diagram of the recording configuration in  $\text{Na}^+$ -free ACSF showing the location of the two ACSF application pipettes for applying  $\text{Na}^+$ -rich ACSF to the apical dendrite (blue) and AIS (red), and the somatic whole-cell recording pipette. Right, examples of whole-cell  $\text{Na}^+$  current evoked by voltage steps (middle), which were preceded by brief (5 ms) applications (bottom) of  $\text{Na}^+$ -rich ACSF to the AIS ('axon', red) or the proximal apical dendrite ('apical', blue). Right: the effect of applying a square-wave like voltage change to an electric differentiator-type  $RC$  oscillator.

been made to describe the actual phenomena. However, focusing on too many details prevents understanding that "the nervous systems adopts a number of basic principles" [1]. The illusion of having an imposing knowledge base inspired undertakings such as simulating the entire human brain.

The brain must be studied "from Inside Out" [139]. First of all, understanding how the known and established physical laws underpin the operation of single neurons (the interface of non-living matter and living matter) instead of hypothesizing additional laws and phenomena complementing/overwriting them, led to creating a fictive nature, which in some points resemblant to the

real one. The abstraction, the discrete components connected by ideal wires that can describe electric phenomena, is successful in electronics. However, it is not valid for neurons (see mainly the electrotonic models), although some rough resemblance indeed exists. The basic differences are that *the structure of living matter is different and that many interactions with drastically different interaction speeds are behind the phenomena*, as contrasted with the (mostly) single interaction with a single speed of electronics.

*Nature is based on the collective operation of single neurons and is prepared to consider the finite operating and transmitting times and uncertainties/failures of operation, unlike (most) technical networks.* However, the usual neural network models [113] do not consider those differences.

### 3.8.1 Equivalent electrical circuit

”These ionic concentration gradients across the cell membrane constitute the driving forces (or chemical potentials) for ionic currents flowing through open channels in the membrane. In other words, the ionic concentration gradients act like DC batteries for cross-membrane currents.” [1]

### 3.8.2 Point-like neuron

The abstraction we need to use always includes simplifications and omissions, depending on which phenomena we want to study. If we want to describe Earth’s orbit around our Sun, we can consider it point-like at an elementary level and assume pairwise interaction between them. However, for finer details, we need to consider its structure, size, and the disturbing effects of other planets and its Moon. Whether the abstraction of having point-like neurons is valid depends on the targeted phenomenon.

In the initial investigations, the *size of the cells* was seen to be much smaller than the *size of their connections*. In addition, the axons were much earlier available for experimental investigations, suggesting that the observed signals originate and terminate in the network nodes. This abstraction might be appropriate (with some limitations, mainly due to the connection speed) until we can develop technical tools to study the *internal operation* of the network nodes. ”We assume that the dimensions of the cell are small enough so that spatial variations in the membrane potential can be neglected” [21]. Its internal operations and phenomena can only have an artificial timing, its input signals are artificially correlated, and its mystic internal operation produces an action potential as an output signal in a pair-wise interaction.

When starting from ’the so-called point representation of a neuron” [21], admitting that ”such an approximation would be valid, for instance, if we were investigating a small, spherical cell without a significant dendritic tree”, we necessarily conclude that ”individual neurons convert the incoming streams of binary pulses into analog, spatially distributed variables”. This statement attempts to underpin that in the neural networks digital pulses are traveling,

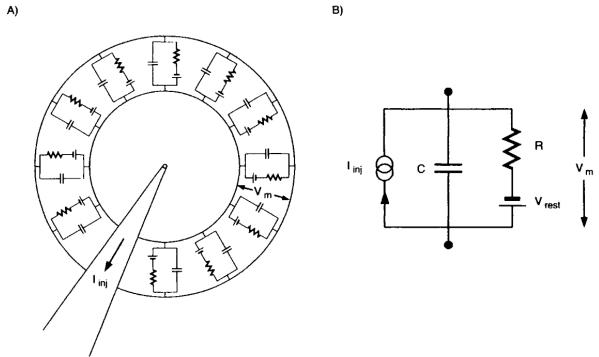


Figure 3.28: Equivalent electrical model of a spherical cell with passive membrane. [21] Fig. 1.2

which is less than the half of truth. This point of view blocks the interpretation of even the phenomena that are correctly seen and leads to the design of wrong experiments. Among others, it results in the immediate consequence of interpreting neuronal communication as streams of binary pulses, which leads to applying Shannon's mathematical theory to neural communication, despite Shannon's sharp opposition [31].

### 3.8.3 Passive distributed membrane

The role of the neuronal membrane is controversial as used in physiology. As [21] discussed, 'from an electrical point of view, the properties of the membrane can be satisfactorily described by a sole element: a capacitance.' However, on the same page, the caption of Figure 1.1 explains that 'Proteins inserted into the membrane, here ionic channels, provide a conduit through the membrane.' Also, the 'associated lumped electrical circuit for this patch, consisting of a capacitance and a resistance *in series* with a battery' (and parallel with each other). That picture is wrong; see Figure 3.3. When inventing the AIS, the wrong hypothesis turned into a fallacy.

### 3.8.4 Membrane as a wrong isolator

When assuming that the membrane's resistance and capacitance are distributed over its surface, one must also assume that it has imperfect resistance despite no known mechanisms to conduct an ionic current. The membrane is a perfect isolator connected to a resistance the neuron's AIS represents. The ionic current (although it is not a 'leaking current') can flow out through it. The right picture that the capacitor and resistor are connected serially instead of parallel, as introduced several decades ago, defies the fallacy that the membrane is a non-perfect isolator.

### 3.8.5 Energy consumption

The passive distributed membrane implies that in its resting state (without operation and communication), a permanent 'leaking current' flows out from the  $RC$  circuit through the parallel resistance  $R$ . If we assume (see, for example [21] page 11)  $R = 100 M\Omega$  and  $V_M = 0.1 V$ , we arrive at  $I_{rest} = 1pA$  and  $P_{rest} = 10^{-9} W$  power consumption per neuron. We arrive at power consumption  $100 W$  for the brain's neurons if all neurons resting without communication. For the  $10^{11}$  neurons of the brain we arrive at power consumption if all neurons are *resting* without communication. It is plausible to assume that the working neuron consumes more energy (the synaptic currents are in the  $nA$  range, although their fill-out factor is low). "The audit points out that, rather than the oft-quoted 20 W of glucose available to the human brain, *the fraction partitioned to cortical computation is only 0.1 W of ATP*" [71]. Assuming a leaking current, a must-be consequence of the parallel  $RC$  neuronal oscillator, results in more power consumption of about two orders of magnitude than the measured value. *The existence of a leaking current is against the experimental evidence and the metabolic efficiency of the biology of evolution.*

### 3.8.6 'Delayed rectifying' current

As a consequence of using, by mistake, the integrator-type instead of the differentiator-type  $RC$  circuit, the textbooks (see, for example [87]), explain that 'the membrane potential would have simply relaxed back to the resting value after the initial depolarizing stimulus if there had been no voltage-gated ion channels in the membrane'. This statement is wrong. The figure refers to an electric integrator-type circuit instead of a neuronal oscillator.

Unlike in the resting state, when generating an AP, there is no intense  $K^+$  current. The explanation that 'the efflux of  $K^+$  through  $K^+$  channels, which open in response to membrane depolarization' [87] is wrong. As we described, the  $Na^+$  ions form for a short time (a small fraction of a millisecond), a thin  $Na^+$ -rich layer on the intracellular side of the membrane (this effect is misinterpreted as ions adsorption @cite Hodgkin-HuxleyAdsorption:2021), and, correspondingly, a  $Na^+$ -poor layer on the extracellular side. The strong repulsive force would prevent  $K^+$  ions in the intracellular side from reaching their specific ion channels, even if the  $K^+$  channels would 'know' when to open. The driving force for  $K^+$  would act in the opposite direction. Furthermore, an attractive force would act on the  $Cl^-$  ions. How big the driving force could be, can be understood from [87], chapter 11: 'The interior of the resting neuron or muscle cell is at an electrical potential about  $50 \dots 100 mV$  more negative than the external medium. Although this potential difference seems small, it exists across a plasma membrane only about  $5 nm$  thick, so that the resulting voltage gradient is about  $100,000 V/cm$ .' The diameter of the ion channel is about  $0.1 nm$ , and 'two  $K^+$  ions in single file within the selectivity filter, separated by about  $8 A$ . Mutual repulsion between the two ions is thought to help move them through the pore into the extracellular fluid.' [87]. Maybe, in biology, Newton's third

law is not active? We show a numeric calculation in section 2.4.9.

Fortunately, the correct differentiator-type circuit produces the 'hyperpolarized' AP voltage time course (below the resting potential) alone, without needing to hypothesize some (unphysical) 'ghost' current.

As discussed, the rushed-in  $Na^+$  ions produce a 'traveling wave' on the membrane. However, [87] shows that potential only on the axon. The textbook skips the conclusion that a traveling wave spreads over the membrane, because it would kill the starting hypothesis that *the membrane is isopotential while generating an Action Potential*.

The effect of the ion channels alone cannot produce a traveling wave. However, as we discussed, the rushed-in ions create a huge charge density on the membrane's surface, and that charge can exit only through the AIS. That macroscopic 'slow current' on the intracellular side of the membrane, on the differentiator-type  $RC$  circuit, produces the 'traveling wave' observed about the AIS and along the axon. When the book [87] was published, the structure of AIS [50] was not known. Now it is. It is high time to fix the neuronal circuit type and explain how to create the action potential with a correct model based on the first principles of science.

HH's equations more or less accurately describe the features of the wrong oscillator type and those of the non-existing  $K^+$  current introduced for compensating for the wrong oscillator selection. As the meticulous review [82] made clear, "typically only a fraction of the various voltage-dependent potassium currents present in a neuron is significantly activated *during normal action potentials*". That is, they might be significant in other periods, but not during generating normal APs.

### 3.8.7 Membrane refractoriness

After introducing the notion of "slow current" notion, *no relative and absolute refractoriness exists*, only refractoriness. The period, called "relative refractoriness" in the time-independent discussion, is an illusion. The slow currents, received through the synapses, need time to reach AIS, so they appear dozens of microseconds later at the AIS. In that period, the output voltage on AIS is already below the resting potential, which is the extension of the absolute refractory period. Given that the AP is already in its hyperpolarized state in that period, its exciting contribution is much harder to observe than at the beginning of an AP, starting from the resting potential. However, the physical background is the same.

The causality is reversed: not "the minimal distance between two spikes defines the absolute refractory period of the neuron" [125]. Instead, as we discuss, until the membrane's potential is above the threshold (which period is defined by physiological parameters), the synaptic inputs are closed, so if another spike arrives until the synapses are re-opened, it is neglected.

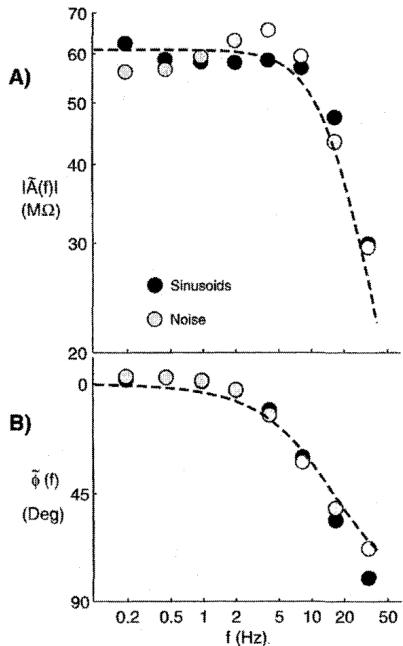
### 3.8.8 Membrane as low-pass filter

The fallacy that in the neuronal  $RC$  circuit the elements are switched in parallel, implies the commonly used fallacy that a biological neuron is a low-pass filter. A neuron can be represented as a *differentiator*-type  $RC$  oscillator belonging to high-pass filters in the world of instant interaction of electronics. However, neurophysiology sticks to assuming that 'the cell membrane composed of a resistance and a capacitance in parallel ( $RC$  circuit)' and it should show the signs of a Low-Pass Filter. The experimental work [140] (their figure is reproduced in Fig. 3.29) 'demonstrated' experimentally the 'low-pass' behavior of their neuron. It shows an example when one proves 'experimentally' what they want to believe. Likely Feynman's warning was forgotten: "The first principle is that you must not fool yourself – and you are the easiest person to fool."

The fundamental issue with evaluating their data is misunderstanding of the neuron's function. *A neuron does not pass signals: it receives ones and produces new signals.* Furthermore, the physiological notions are interpreted for a 'steady state', i.e., using alternating current invalidates their basic assumptions. It is senseless to check its signal-passing feature: it is a wrong question to nature. The statement is valid for other measurements using alternating currents, too. According to [110], page 22, "Also included are  $L_{ij}$  determined using sinusoidally varying voltage and pressure. This kind of experiment gives values of  $L_{ij}$  which are frequency dependent. However, the values approach a constant value at sufficiently low frequency."

Any foreign input current into the membrane, whether it is noise or a sine signal, increases the momentary and the average resting potential of the membrane, that is, decreases the probability that the synaptic trigger arrives at a moment when the synaptic input is enabled. For how synaptic inputs are enable in function of artificial currents, see our Figure 3.17. The arrival time of the spike from the presynaptic neuron is independent from the operation of the postsynaptic neuron, so the signals arrive at a 'random time' in the neuron's local time system. With increasing the frequency of that foreign signal, more input charge increases the membrane's voltage. The longer the membrane voltage is above its threshold potential, the less is the chance to re-open the neuron's synaptic inputs, i.e., to receive inputs from the 'regularly firing cell': the triggers arrive with a high probability in the absolute refractory period. In the case of varying frequencies, this effect, combined with the finite ion current speed, makes the measured firing rate unpredictable. In a later research, it was noticed that [133] the too high current blocks spiking (more precisely, receiving the triggering signal).

From our conceptual model of generating AP (see Fig. 1.6), it is immediately clear that although in the 'native mode' of operation, the falling edge of the AP would result in the membrane's voltage falling below the threshold, in this way re-enabling synaptic inputs. However, in 'artificial' mode, the foreign current can keep the voltage above the threshold (for shorter or longer periods, additionally), so the synaptic signal cannot enter the membrane, given that in periods when the membrane has potential value above the threshold, the



**Fig. 1.4 CORTICAL CELLS BEHAVE LIKE AN RC CIRCUIT** When either noise or sinusoidal currents are injected into the cell body of regularly firing cells in guinea pig visual cortex, the membrane potential can be adequately modeled as resulting from convolving the current input by a low-pass **filter** of the sort described in Eqs. 1.14 and 1.15 (dashed lines; here with  $R = 58.3 \text{ M}\Omega$  and  $\tau = 9.3 \text{ msec}$ ;  $V_{\text{rest}} = -70.7 \text{ mV}$ ; Carandini et al., 1996). (A) The amplitude of the **filter** and (B) its phase. The noise current curve reveals a shallow peak at around 8 Hz. We conclude that from the point of view of somatic input-output, these cells can be reasonably well described by a single **RC** compartment. The responses were obtained by computing the first harmonic of the membrane potential response and dividing by the current. The power of the first harmonic was between 9 and 141 times the power of the higher harmonics. Reprinted by permission from Carandini et al., (1996).

Figure 3.29: Illustrating the fallacy that neurons represent a low-pass filter. [21]  
 Fig. 1.4

synaptic inputs are not enabled; see also Figure 3.17. The synaptic inputs are re-enabled only later when the membrane's potential is under the threshold potential when a new synaptic trigger arrives. That is, the triggering effect of the "regularly firing cells" is suppressed by the artificially increased neuronal membrane voltage. *The effect has nothing to do with the effect 'Low-Pass Filter'.* See also section 2.5.

### 3.8.9 Thresholds of initiating AP

As discussed above, ion channels have a voltage threshold that opens them. We can successfully interpret how the microscopic threshold of the ion channels forms the macroscopic phenomenon that a voltage threshold exists for the membrane. Section 17.3 in [21], introduces further (current and charge) thresholds. After introducing the "slow current" notion, we can understand that the same voltage threshold manifests in apparently different thresholds.

As discussed, introducing a sustained current  $I_{\text{clamp}}$  implies the introduction of a sustained slow current on the membrane's surface. The sustained current means a sustained presence of ions on the surface, resulting in a continuous increase of potential offset over the resting potential value. As observed, "the somatic membrane potential responds with a slight overshoot". Given that the charge collection for initiating an AP starts at a voltage above the resting

potential, the voltage threshold is reached earlier. The introduced external current  $I_A$  is added to the sustained clamping current. The charge delivered by the newly added slow current appears delayed (after the onset). Depending on the point of the membrane the current is added, the delay may be up to 1 msec. (As [47] demonstrated, the propagation speed inside a neuron is in the order of less than 1 cm/s; furthermore, as we discussed, the need to use electrolyte electrodes can prolong the measured delay time considerably.) *The current threshold is another manifestation of the voltage threshold.*

As we discussed in section 2.4.4, the virtue of a capacitive current is used only to imitate the effect of a slow current: biology has no discrete capacitance. The capacitive current exists only as a virtual notion in the electric circuit comprising discrete elements that are considered parallel with the biology-imitating circuit comprising distributed elements. In the lack of notion of a “slow” current, for “rapid events”, one may attempt to replace the “delayed rectifying current” with an instantaneous current. As formulated in section 17.3.5 in [21]: “Because we are considering rapid events, the steady-state I-V in Eq. 17.4 must be replaced by the instantaneous I-V curve”. However, the rapid events are not rapid enough to make such a replacement in a differential equation. This replacement results in their Eq. (17.7) non-matching values are used. As we explained, Eq. (3.9) formulates Kirchoff’s Law in biology. Using a virtual parameter “capacity  $C$ ” for biological neurons misleads research: introduces a nonexistent “charge threshold”, which exists only due to mismatching notions of finite-speed biological circuits with notions of the infinite-speed abstract electric circuits, used to imitate a finite-speed current in terms of a virtual infinite-speed current.

# Chapter 4

# Neural computing

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Pinpointing the interpretation of computing Coming soon!

For now, see [22, 55, 54]

The theory of generalized computing, technical and biological

*"each neuron is a compact, efficient, nonlinear, analog summing device, ... the rules of which are not quite understood as of yet."* [53] @1972

*"the dynamic interaction of inputs in dendrites containing voltage-sensitive ion channels is capable of realizing logical operations, nonlinear interactions, and local domains of computation. This raises the possibility that a neuron is itself a network."* [44] @2014

Leads to the question: "Is realistic neuronal modeling realistic?" [45] @2016

*"We so far lack principles to understand rigorously how computation is done in living, or active, matter"* [141] @2018

*"we still do not understand the brain's underlying computational logic"* [3]. @2024

Despite the impressive results of grandiose projects [3, 142], and the sometimes triumphal communications, there has been no significant advance in understanding neuronal computing in four decades. Unfortunately, they attempt to merge the decades-old, outdated theory [143] with the modern technical hardware and software facilities. Furthermore, even the true advances are miscommunicated [27]. The true advances are mismatched with unrealist designs and plans. The Human Brain Project believes that it is sufficient to build a computing system with theoretically sufficient resources for simulating 1 billion neurons, and do not want to admit that it can be used [144] to simulate only by orders of magnitude less, below 100 thousand, simply because of the presently available serial systems do not enable to reach such a performance [145]. Despite that even the system with 1-million-core proved to be non-useable, building a 10-million-core system received the green light. Despite that lack of knowledge, the half-understood principles of neuromorphic computing are extensively used [146, 147], although it is seen that brain-inspired computing needs a master plan [148]. Maybe, really, *"a new understanding of the brain" [and the cooperation of scientific disciplines] is needed.*

"Indeed, the operation of our brain differs vastly from that of human-made computing systems, both in terms of topology and in the way it processes information, which explains its different aptitudes" [147]

Our "present-day digital computers are optimized for high-precision calculations but consume an inordinate amount of energy when they run the type of cognitive tasks that the brain excels at" [147].

Today we have the "golden age" of neuromorphic (brain-inspired, artificial intelligence) architectures and computing. However, the meaning of the word has changed considerably since Carver Mead [149] coined the wording. Today practically every single solution that borrows at least one single operating principle from the biology, and mimics some of its functionality in a more or less successful way, deserves this name. As always, to grasp out some single aspect and implement it in an environment and from components based on entirely different principles, is dangerous. Historically, 'neuromorphic' architectures were suggested to be based on different principles and components, such as mechanics, pneumatics, telephones, analog and digital electronics, computing. Some initial resemblance surely exists, and even some straightforward systems can demonstrate more or less successfully functionality in some aspects similar to that of the nervous system. There is a noteworthy analogy between the deep learning of neuronal nodes and the long-term potentiation found in synapses.

However, when scrutinizing the scalability (i.e., how those systems shall work when used under real-life conditions in which a vast number of similar subsys-

tems shall work and cooperate), the picture is not favorable at all. "*Successfully addressing these challenges [of neuromorphic computing] will lead to a new class of computers and systems architectures*" [146] has been targeted. However, as noticed by the judges of the Gordon Bell Prize, "*surprisingly, [among the winners,] there have been no brain-inspired massively parallel specialized computers*" [150]. Despite the vast need and investments, furthermore the concentrated and coordinated efforts, just because of mimicking the biological systems with computing inadequately.

Given "*that the quest to build an electronic computer based on the operational principles of biological brains has attracted attention over many years*" [151], modeling the neuronal operation became a well-known field in both electronics and computing. At the same time, more and more details come to light about the computational operations of the brain. However, it would appear, that the 'wet' neuroscience is miles ahead of the 'silicon' neuroscience. There are projects and exaggerated claims about extremely large computing systems, even about targeting the simulation of the brain of some animals and eventually even the human brain. Often these claims are followed by a long silence, or some rather slim or no results. As that the operating principles of the large computer systems tend to deviate from the operating principles of a single processor, it is worth reopening the discussion on a decade-old question "*Do computer engineers have something to contribute. . . to the understanding of brain and mind?*" [151]. Maybe, and they surely have something to contribute to the understanding of computing itself. *There is no doubt that the brain does computing, the key question is how?*

## 4.1 Introduction

Here *computing* is handled in a broader sense: information processing *in any implementation*. It covers conventional computing, biomorphic computing, biological (neural) computing, and computing relating, among others, (the technology of) artificial intelligence. The computing objects use both their inputs and their internal state to calculate their output. The time-aware computing means to consider that *computing means both processing the available data and delivering data to and from the computing object*. Furthermore, that those operations must be synchronized (and in this way they block each other); and that not only that those processes need time, but *the inputs, the output and the internal states all have their temporal behavior*. We show that taking into account that temporal dependence explicitly, leads to considerable differences in their behavior as opposed with the behavior expected based on the time-unaware description. Please take care when reading. The text is, of course, computing-oriented, so it uses words processor, core, thread, hardware thread, memory, etc. However, it uses them in a slightly different way, in a different meaning. So, please read the corresponding manual, or skim it at least, before going into details. The approach we take seems to be overly complicated, but it is needed to build a more effective and capable computing. It majorly simplifies

modern many-thread computing, but its real advantage manifest in large-scale computing.

Technical sciences (mainly electronics and computing science) have developed to the level where elementary electronic components in number comparable to the elementary components of the CNS can be assembled. Those large systems attempt to resemble each other. On the one side, biology inspires huge electronical systems (from HPC to ANN). On the other side, electronic systems (mainly large-scale computers, but also special-purpose electronic simulators) attempt to imitate brain-like biological systems, with goals ranging from simulating the dynamics of molecular processes to creating artificial intelligence. Furthermore, there are attempts to combine and interface them.

The false parallels with electric circuits (i.e., neglecting the fundamental differences between the *digital* and *neuro-logical* operating modes), moreover the preconception that nature-made biological computing must follow notions and conceptions of manufactured computing systems hinders understanding genuine biological computing.

## 4.2 Computing and communication

## 4.3 Computing and information

## 4.4 Computing and biology

As discussed in [62, 123], for the adequate description of the operation of ion channels, the major components of neuronal computing, three-state systems must be used. In the present two-state digital electronic logic systems, discharging the internal capacitances can be considered a "refractory" period, i.e., a third state, which defines time's direction. However, it is not known if such a third state can be available among the quantum states at all. Because of these reasons, in the foreseeable future, quantum computers will not represent an alternative general-purpose architecture. "Building such machines are decades away" [152]. However, biological neurons are three-state systems @endlink.

## 4.5 Computational modeling of neuronal membrane

## 4.6 Timing relations

## 4.7 Action Potential

In this section we discuss the *concept* of action potential in an abstract sense that enables to define its notions, features and stages. Our approach here is hybrid: we know that the events are connected to ion movements and that

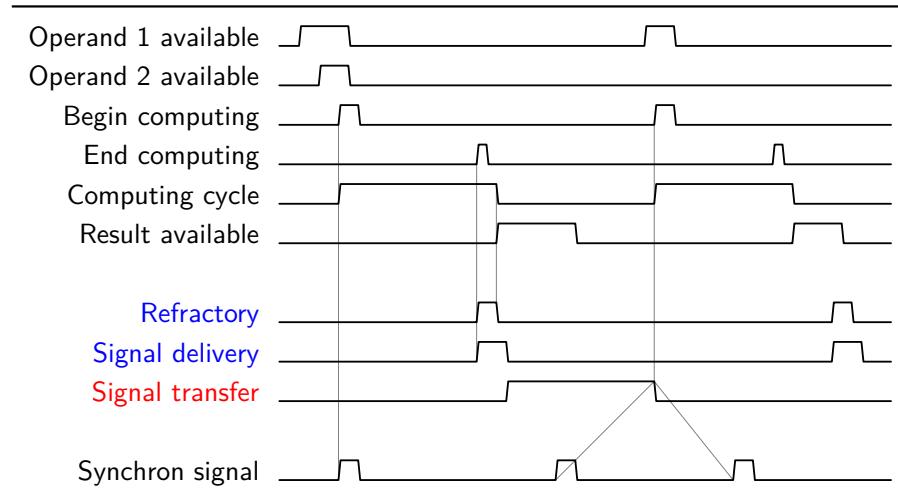


Figure 4.1: Timing relations of von Neumann's complete timing model, with data transfer time in chained operations; synchronization becomes an issue as the physical size of the computing system grows. Notice that synchrony signals must be bypassed or neglected. Timing relations of von Neumann's timing model: the data *transfer* time neglected apart from data *processing* time; synchronization can have small dispersion. Notice that the central synchronization signal appears at different places in the processor at different times.

the components' cooperation forms the action potential. The physiological and physical details are discussed in the respective chapters 3 and 2, where we provide citations describing the physiological details. We consider the neuron as an *abstract computing element* and show how a neuron implements the generalized computing we discuss in chapter4.

We assume that the neuron is in state "Relaxing", so the membrane's voltage is at the resting value. The membrane and the AIS are at the same potential, so no current is present (no "leaking current" exists). When input charge (through the synapses or directly through the membrane) arrives to the membrane, its potential increases. The increased membrane potential means a potential difference between the membrane and the axon, so it drives a current through the AIS. The current (not identical with the leaking current) decreases the membrane's potential between adjacent synaptic inputs. For simplicity, we assume that the axonal inputs cause a step-like change in the membrane's voltage. Between the inputs the current through the AIS decreases the membrane's potential. As we discuss, the neuronal computation actually measures the time between the arrival of the first synaptic input and exceeding the threshold; it is in the order of tenths of a millisecond.

When the resulting potential exceeds a threshold value, for a very short time (in the order of tenth of picoseconds) the ion channels in the membrane's

wall open and a large amount of ions suddenly (in a step-like way) increase the membrane's potential in its surface layer; see section 2.5.5. The current due to the rushed-in ions creates a local potential gradient and the ions (with a potential-assisted speed) saturate the layer (the mechanism is described in section 3.3), open all ion channels. The rushed-in ions feel the potential gradient toward the AIS, but they can move in the layer on the surface with a finite speed, so the current from the different points of the membrane need different times to reach the AIS. Correspondingly, the current (due to the current "created" by the nearby ion channels) reaches the AIS instantly, while the current from the farthest point needs tenths of a millisecond to get to the AIS. After that, given that the current cannot flow out "instantly", the current produces a kind of "damped oscillation": drops below the resting potential and then asymptotically approaches it, without exceeding it. It is the effect of the neuronal oscillator, marked as "RC-effect". In some sense, the ionic current "disappears": it gets stored in the neuronal condenser while it travels on the surface of the membrane.

During this process, the membrane's voltage controls the synaptic inputs. Given that the ions can reach the membrane using a "downhill" method, the current stops when the membrane's potential rises above that of the axonal arbor, and will not flow until the membrane's potential drops again below the threshold: the synapses will be disabled and re-enabled.

Biology observed the "absolute refractory" period, which is interpreted that the synapses are disabled for a period, and it is a correct observation. Different is the case for the "relative refractory" period. Actually, the synaptic inputs arrive at the junction of the axon, and the current must travel to the AIS, that needs time (in the order of tenth of a millisecond). Given that the AP is measured at the AIS the main contributor' current in the meantime proceeds toward the "hyperpolarized" state, and so the synaptic inputs apparently contribute outside of the "absolute refractory" period, so this extension is called "relative refractory". Actually, the origin of both periods is the same, only the effect's time scale is shifted by the ionic current's travel time.

As discussed, after that the membrane's voltage drops below the threshold potential, the neuron can start a new computing. The signal "ComputingBegin" is defined as the signal arriving first after then the neuron membrane's potential crossed the threshold value from the higher voltage direction. At that point, the membrane's voltage can be above or below the resting potential, and, correspondingly, the charge integration starts from a value higher or lower than the resting potential. Effectively, the value of the potential (more precisely, *when* the first synaptic input arrives at the AIS) represents a memory with initially a negative, later positive, time-dependent content.

Our stages slightly deviate from the ones commonly used in physiology. We define the stage "Computing" as the period between the arrival from the first synaptic input to exceeding the threshold. The stage "Delivering" is defined as the period while the membrane's voltage stays above the threshold. The stage "Relaxing" begins when the "Delivering" ends, and may be interrupted by a synaptic input. Notice that because of the spatiotemporal nature, the time values have a definite meaning only if the place of the measurement is also

provided: it is one coordinate of a space-time point.

The computer representation (actually a state machine) is shown in Figure 1.4.

Will be based on [116] [22]

# Chapter 5

# Neural information

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Applying Shannon's information theory [30] to neuroscience started immediately after the significance of Shannon's seminal paper was recognized, and different research directions began to use it (for a review, see [153]). Although Shannon warned [31] against the indiscriminate use of the theory and called attention to its valid scope: "The hard core of information theory is, essentially, a branch of mathematics", and it "is not a trivial matter of translating words to a new domain". The improper application of the information theory to neural communication is going on [154, 155].

"In the terminology of communication theory and information theory, [a neuron] is a multiaccess, partially degraded broadcast channel that performs computations on data received at thousands of input terminals and transmits information to thousands of output terminals by means of a time-continuous version of pulse position. Moreover, [a neuron] engages in an extreme form of network coding; *it does not store or forward the information it receives but rather fastidiously computes a certain functional of the union of all its input spike trains* which it then conveys to a multiplicity of select recipients" [156]. Will be based on [13] [23] [29]

The theoretical model [13] described how the slow operation of biological objects explains biological phenomena, but due to the lack of dedicated measurements it could only indirectly underpin the theory's correctness. Now, we give an exact quantitative explanation of the precise measurements [5, 77], which have not been correctly understood in the past decades due to the lack of understanding of the role of the finite interaction speed (conduction velocity) in neuronal operations.

Issuing the same signal carries no information (represents zero entropy)

# Chapter 6

## Multiple neurons

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Will be based on [13] [23] [29]

When we discuss the operation of neurons, we must not forget that “what makes the brain a remarkable information processing organ is not the complexity of its neurons but the fact that it has many elements interconnected in a variety of complex ways” [39]. At this level of abstraction, one does not need to consider biological details, since ”Despite the extraordinary diversity and complexity of neuronal morphology and synaptic connectivity, the nervous systems adopts a number of basic principles” [1]. A neuron operates in cooperation with in its environment (the multiple fellow neurons, with outputs distributed in space and time). It receives multiple inputs at different times (at different offset times from the different upstream neurons) and in different stages. Neurorassemblies

We learned that the neuron’s behavior can hardly be described mathematically and be modeled electronically. Furthermore, the length of the axons between the neurons and the conduction velocity of the neural signals entirely define the time of the data transfer (in the msec range); all connections are direct. The transferred signal starts the next computation as well (asynchronous mode). ”A preconfigured, strongly connected minority of fast-firing neurons form the backbone of brain connectivity and serve as an ever-ready, fast-acting system. However, full performance of the brain also depends on the activity of very large numbers of weakly connected and slow-firing majority of neurons.” [157]

One must be careful when extrapolating results derived for a single “neuronal link” to a set of neurons. If we consider that the number of input spikes carries the information, it is typical that several spikes arrive at a neuron, and only one spike is produced: “A single neuron may receive inputs from up to 15,000–20,000 neurons and may transmit a signal to 40,000–60,000 other neurons” [158]. “In the terminology of communication theory and information theory, [a neuron] is a multiaccess, partially degraded broadcast channel that performs computations on data received at thousands of input terminals and transmits information to thousands of output terminals by means of a time-continuous version of pulse position. Moreover, [a neuron] engages in an extreme form of network coding; it does not store or forward the information it receives but rather fastidiously computes a certain functional of the union of all its input spike trains which it then conveys to a multiplicity of select recipients” [156]. In this way, some “information loss” surely takes place. If we consider that the ISI carries information and a neuron takes into consideration in its “computing” only the spikes which arrive within an appropriate time window, some information is lost again. Even the result of the computation, a single output spike, may be issued before either of the input spikes was entirely delivered. One more reason why the notion of information should be revisited.

## Chapter 7

# Intelligence

will be based mainly on [25]

It is at least hard, if possible at all, to define the meaning of the word "intelligence" and really dozens of meanings are used around [159]. The fundamental questions to reply are "Whether it is implemented by molecules, cells, liquid crystals, silicon or digital code, the essential operations of understanding are the same. Can the system acquire information external to itself? Can it generate an internal model of the external world by encoding information about it such that it can make predictions and inferences?" [160].

The confusion starts at a much lower level. "At one extreme, the 'cognitive' in *cognitive neurosciences* has replaced the older term information processing. At the other extreme the term 'cognition' refers to those higher level processes fundamental to the formation of conscious experience. In common parlance, the term 'cognition' means thinking and reasoning." [39]. At the lowest level, both implementations do information processing. However, even at their lowest level, they process differently interpreted information on different structures using different methods. The notion of 'cognition' (similarly to 'conscience', and other notions) are not transferable between those implementations.

The major operating difference is the sequential operation of technical systems that directly affects imitating biological operations. One of the primary motivations for using neural networks was the demand for processing actions on the correct biological time scale: "Many theoretical neurobiologists have turned to different types of models that include parallel processing, which they call neural networks." [39], page 37. "The branch of computer science known as artificial intelligence originally used serial processing to simulate the brain's cognitive processes—pattern recognition, learning, memory, and motor performance. These serial models performed many tasks rather well, including playing chess. However, they performed poorly with other computations that the brain does almost instantaneously" [39], page 37. More differences, stemming from their different 'technology', are discussed in [25].

## 7.1 Information vs intelligence vs cognition

"At one extreme the 'cognitive' in cognitive neuroscience has replaced the older term *information processing*.

At the other extreme the term 'cognition' refers to those higher level processes fundamental to the formation of conscious experience.

In common parlance the term 'cognition' means thinking and reasoning." [39]  
When we must use those words, we use it exclusively in the first meaning:  
the collective activity of neurons for processing information at the 'technically'  
lowest level.

Although it is challenging both to list the crucial differences between technological components attempting to mimic a biological component and to separate the HW and SW issues, some of the most important ones are mentioned below.

The confusion starts at a much lower level. "At one extreme the 'cognitive' in cognitive neuroscience has replaced the older term 'information processing'. At the other extreme the term 'cognition' refers to those higher level processes fundamental to the formation of conscious experience. In common parlance the term 'cognition' means thinking and reasoning." [39]. At the lowest level, both implementations do information processing. However, even at their lowest level, they process differently interpreted information on different structures using different methods. The notion of 'cognition' (similarly to 'conscience', and other notions) are not transferable between those implementations.

Fundamentally, we are in line with the standpoint of E. Schrödinger [8] (The physical basis of consciousness): "What kind of material process is directly associated with consciousness? . . . consciousness is linked up with certain kinds of events in organized, living matter, namely, with certain nervous functions . . . It is still more gratuitous to indulge in thoughts about whether perhaps other events as well, events in inorganic matter, let alone all material events, are in some way or other associated with consciousness."

# Chapter 8

## Neural simulator

"I don't understand the things that I cannot create" R.P.Feynman

The many enormous differences between technical and biological computing make simulation of neural operation a real challenge. A fundamental issue is that the biological time of the events is not directly proportional to the computer processing time. Given that the processing time comprises computing time plus transfer time, time-stamping cannot provide a solution for time handling. The time stamp records when an event happens in the computing process instead of its biological time. Given that several neurons share the computing resources and the computer's execution is sequential, the events happening at a biologically identical time will generate time stamps at technically different times. Furthermore, from the same reason, the generated event will be considered again at different times with a (technically random) delay compared to the time of generating those events and to each other. Furthermore, the propagation time through the axons cannot be included. These effects are late consequences of omitting the transfer time in computing science.

The goal is to "create" neurons and their systems; in spirit of Feynman. In some sense, it is a "duck test". We simulate a duck and test it it looks like, swims and quacks. We demonstrate that our abstract model passes the duck test "If it looks like a duck, swims like a duck, and quacks like a duck, then it probably *is* a duck". See also Feynman's opinion on understanding.

### 8.1 Simulation principles and technology

The central idea of simulation is the notion of "event". We use events almost in the everyday sense; that something happens at some given time. In technical computing, an event is an electric signal, that means the beginning or end of an elementary operation, or signals transferring control to another place in the program. In biology, "A signal is a physical event that, to the receiver, was not

bound to happen at the time or in the way it did.” [161] Similarly, we ”define an elementary operation of the brain as a single synaptic event” [162].

The basic issue with simulating biology with technology is that *two* time scales exist and they are connected by *events* only. The length of the computing and the biological operation are not proportional at all. Furthermore, neuronal operations happen simultaneously, while technical operations work in a sequential way (or maybe in parallelized sequential way) that breaks happening events simultaneously.

The way as we perform simulation that we define events (such as beginning or end of computing, receiving an input, etc) and we perform the actions that happen at the same (biological) time. The ”same time” in this context means that the simulated times are within a so called ”time resolution”. The biological actions are implemented as a kind of callback function that is called when the corresponding (simulated) time arrives. Choosing smaller time resolution results in slightly more accurate results at the price of much more computing time.

The software we use is a special C++ based library SystemC with a user-level scheduler [163, 164]. The primary purpose of the software is to prepare electronic designs, so a lot of formal elements are to be considered. Those elements are typically confined in low-level modules, and the user-accessible modules resemble normal c++ modules, although their name and description max reflect specialties.

### 8.1.1 Event and timing

As always, we need to uses approximations and mix physical processes with the terms of simulation

#### Types of time

The notion of time is vital for biological and electronic computing [23, 108]. However, when simulating biological objects by electronic computers, the they are not identical, and, what is worse, they are even not proportional. The way as computers work [165], destroys even their sequence. For this reason, a pseudo-time is used, which we call ’simulated time’. The biological processes are cut into segments of variable size. At the beginning the period for the biological process is set and its length is transferred to the scheduler of the engine (important: this scheduler sits on top of the scheduler of the operating system and works independently from it). The information comprises a callback function, at what simulated time what activity is to be executed. Many biological processes run simultanously and they individually communicate with the scheduler. This way, the scheduler has the information which biological process wants to use the processor, in a chronological order. The scheduler maintains the simulated time as multiples of a ’time resolution’. In this way the continuous simulated time is mapped to discrete time steps. The time between those discrete steps is considered they are the same.

When the next element of the queue follows, the scheduler increases the simulated time to the value of the requested time of action of the actual item. If more than one action is scheduled to the same time, all those actions are performed, in an arbitrary order. At the end of the period, the callback function notifies the biological process that the requested timing period is over (meaning that the requested computing activity was performed) and the scheduler takes the next item in the queue. If the time of that item is different, the system advances to that time value.

This way the biological objects work on the same time scale. Through the elapsed time and/or notifying each other, they can cooperate. Although the periods of the simulated time and the period while the computer works out the simulated task are greatly disproportional, the simulation is perfectly timed. The simulated process asks to schedule its phases to the biologically correct time, and they are executed at a processor time when the processor has free activity time.

## 8.2 SystemC, the background language and engine

In the SystemC engine there exists a time resolution, a small period in which all events 'happen at the same time'. (for biological neurons, a  $2\mu s$  time resolution seems to be sufficient.) for describing all its features a complete Reference Guide [163] for developing the code, but using the well-written core of the package it is sufficient to study the textbook [164].

## 8.3 Ripes Simulator

The final goal is use the technology developed in the RIPES simulator, to visualize and manipulate variable of the neurons and their groups at different levels. Presently, program classes, demos and tests, furthermore, first of all: theoretical background is provided and shared on the site.

## 8.4 GTKWave simulator

Although it remains almost entirely hidden for the average user, the simulator is essentially an electronic design software. It produces an 'ObjectName.vcd' file that, correspondingly, can be analyzed using the tools of electronic design. One of the popular tools is GTKWave. The contents of the .vcd file can be displayed as shown in 8.1. (To reproduce the figure, one has to switch the signal forms to 'analog stepwise' and 'analog interpolated', respectively, and increase the 'insert analog height extension' to the single-text line annotation.)

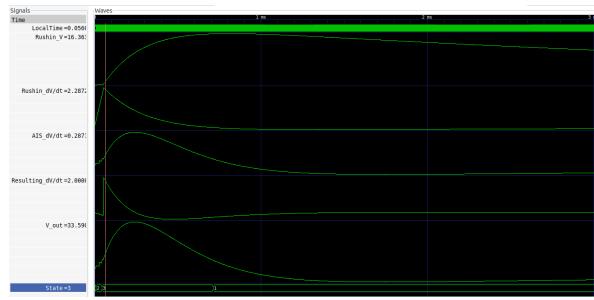


Figure 8.1: The summary of AP generation as seen in the simulator. The information is essentially the same that in Figure 3.17 (for codename '0', i.e., 'Simple delivery'). The rush-in current produces its voltage time derivative, the resulting voltage time derivative generates the neuron's output voltage, the AP. The neuron passes (due to the excitation) from stage 'Relaxing' (codename '1') to 'Computing' (codename '2') and 'Delivering' (codename '2') as described above.

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# Glossary

**AIS** Axon Initial Segment. 8, 9, 11, 20, 30, 38, 42, 44, 46, 47, 53, 56, 58, 59, 63, 96, 99, 112, 122, 137, 155, 167, 180, 183, 206, 210, 212, 213, 222, 223, 232, 251, 252, 268

**AP** Action Potential. 8, 11, 20, 26, 34, 35, 42, 46, 53, 54, 56, 58, 63, 105, 182, 183, 202, 206, 210, 212, 223, 224, 252, 268, 273

**BI** Brain Initiative. 12

**EM** electromagnetic. 78, 87, 170, 187

**HBP** Human Brain Project. 12

**HH** Hodgkin and Huxley. 24, 30, 60, 204

**ICT** Info-Communication Technology. 12

**local time** The biological time the individual neuron's operation that begins when their first synaptic input arrives. 27, 53

**PID controller** A proportional–integral–derivative controller is a feedback-based control loop mechanism commonly used to manage machines and processes that require continuous control and automatic adjustment.. 34

**PSP** Post-Synaptic Potential. 53, 210



# Bibliography

- [1] D. Johnston, S.M.S. Wu, *Foundations of Cellular Neurophysiology* (Massachusetts Institute of Technology, Cambridge, Massachusetts and London, England, 1995)
- [2] J. von Neumann, IEEE Annals of the History of Computing **15**(4), 27 (1993). DOI 10.1109/85.238389
- [3] J. Ngai, Neuron **112** (2024). DOI 10.1016/j.neuron.2024.09.007
- [4] R.P. Feynman. Principles of scientific thinking. <https://blog.hptbydts.com/richard-feynmans-principles-of-scientific-thinking>
- [5] A.L. Hodgkin, A.F. Huxley, J. Physiol. **117**, 500 (1952)
- [6] J. Tuszyński, M. Kurzynski, *Introduction to molecular biophysics* (CRC Press, Boca Raton, London, New York, Washington D.C., 2003)
- [7] B. Drukarch, M.M.M. Wilhelmus, S. Shrivastava, Reviews in the Neurosciences **33**(3), 285 (2022). DOI doi:10.1515/revneuro-2021-0094. URL <https://doi.org/10.1515/revneuro-2021-0094>
- [8] E. Schrödinger, *Is life based on the laws of physics?* (Cambridge University Press, Canto, 1992), p. 76–85. URL <https://archive.org/details/WhatIsLife-EdwardSchrodinger/>
- [9] Y.A. Cengel, Entropy **23**(6) (2021). DOI 10.3390/e23060779. URL <https://www.mdpi.com/1099-4300/23/6/779>
- [10] T.J. Sejnowski, C. Koch, C.P. S, Science **9**, 1299 (1988). DOI 10.1126/science.3045969
- [11] J. Végh, Applied Sciences **15**(11) (2025). DOI 10.3390/app15115805. URL <https://www.mdpi.com/2076-3417/15/11/5805>
- [12] G. Buzsáki, Neuron **68**(4), 362 (2010). DOI 10.1016/j.neuron.2010.09.023
- [13] J. Végh, Á.J. Berki, Entropy **24**(8), 1086 (2022). DOI 10.3390/e24081086

- [14] von Neumann, John, *The Computer and the Brain* (New Haven, Yale University Press, 1958). URL [https://complexityexplorer.s3.amazonaws.com/supplemental\\_materials/5.6+Artificial+Life/The+Computer+and+The+Brain\\_text.pdf](https://complexityexplorer.s3.amazonaws.com/supplemental_materials/5.6+Artificial+Life/The+Computer+and+The+Brain_text.pdf)
- [15] L. Abbott, T.J. Sejnowski, *Neural Codes and Distributed Representations* (Cambridge, MA: MIT Press, 1999)
- [16] R.P. Feynman, *Feynman Lectures on Computation* (CRC Press, 2018)
- [17] D. Hebb, *The Organization of Behavior* (New York: Wiley and Sons, 1949)
- [18] N. Caporale, Y. Dan, Annual Review of Neuroscience **31**(1), 25 (2008). DOI 10.1146/annurev.neuro.31.060407.125639. URL <https://doi.org/10.1146/annurev.neuro.31.060407.125639>. PMID: 18275283
- [19] J. Végh, arXiv, in review in Continuum Mechanics and Thermodynamics **1** (2025)
- [20] J. Végh, Algorithms **1** (2025). DOI 10.3390/a19010006
- [21] C. Koch, *Biophysics of Computation* (Oxford University Press, New York, Oxford, 1999)
- [22] J. Végh, Informatics **8**(4) (2021). DOI 10.3390/informatics8040071
- [23] J. Végh, Á.J. Berki, Acta Biotheoretica **70**(4), 26 (2022). DOI 10.1007/s10441-022-09450-6. URL <https://link.springer.com/article/10.1007/s10441-022-09450-6>
- [24] N.S. Hsu, H.Y. Fang, K.K. David, J.W.G. Gnadt, C. Peng, E.M. Talley, J.M. Ward, J. Ngai, W.J. Koroshetz, Current Opinion in Neurobiology **65** (2020)
- [25] J. Végh, A.J. Berki, Advances in Artificial Intelligence and Machine Learning **1**, 131 (2021). DOI 10.54364/AAIML.2021.1109
- [26] P. Mitra, Nature Machine Intelligence **3** (2021). DOI 10.1038/s42256-021-00345-8
- [27] Human Brain Project. A closer look at scientific advances (2023). URL [https://sos-ch-dk-2.exo.io/public-website-production-2022/filer\\_public/6f/70/6f706305-a2e3-45b8-a42b-dfb476222a6a/230413\\_hpb22\\_digital.pdf](https://sos-ch-dk-2.exo.io/public-website-production-2022/filer_public/6f/70/6f706305-a2e3-45b8-a42b-dfb476222a6a/230413_hpb22_digital.pdf)
- [28] M.F. Schneider, Progress in Biophysics and Molecular Biology **162**, 2 (2021). DOI <https://doi.org/10.1016/j.pbiomolbio.2020.10.001>. URL <https://www.sciencedirect.com/science/article/pii/S0079610720301000>. On the Physics of Excitable Media. Waves in Soft and Living Matter, their Transmission at the Synapse and their Cooperation in the Brain

- [29] J. Végh, A.J. Berki, Mathematical Biology and Engineering **20**, 12380 (2023). DOI 10.3934/mbe.2023551
- [30] C.E. Shannon, The Bell System Technical Journal **27**(3), 379 (1948). DOI 10.1002/j.1538-7305.1948.tb01338.x
- [31] C.E. Shannon, IRE Transactions in Information Theory **2**, 3 (1956). URL <http://csc.ucdavis.edu/~cmg/papers/Shannon.IRETransInfoTh1956b.pdf>
- [32] Y. Wang, R. Wang, X. Xu, Neural Plast. p. 6207141 (2017). DOI <https://doi.org/10.1155/2017/6207141>. URL <https://pmc.ncbi.nlm.nih.gov/articles/PMC5337805/>
- [33] T. Heimburg, Physik Journal **8**(3), 33 (2009)
- [34] B. Drukarch, M. Wilhelmus, Frontiers in Cellular Neuroscience **17** (2023). DOI 10.3389/fncel.2023.1232020
- [35] (2015)
- [36] P.W. Anderson, Science **177**, 393 (1972). DOI 10.1126/science.177.4047.393
- [37] J. Végh, Entropy (2025). DOI <http://dx.doi.org/10.2139/ssrn.5217729>
- [38] A. Kahana, D. Lancet, Nature Reviews Chemistry **5**, 870–878 (2021). DOI <https://doi.org/10.1038/s41570021003297>
- [39] E.R. Kandel, J.H. Schwartz, T.M. Jessell, S.A. Siegelbaum, A.J. Hudspeth, *Principles of Neural Science*, 5th edn. (The McGraw-Hill Medical, New York Chicago etc., 2013)
- [40] K.S. Cole, H.J. Curtis, The Journal of General Physiology (1939). DOI <http://doi.org/10.1085/jgp.22.5.649>
- [41] C.F. Craver, Synthese **153**(3), 355 (2006). DOI 10.1007/s11229-006-9097-x
- [42] B. Ermentrout, T.H. David, *Mathematical Foundations of Neuroscience* (Springer, New York, 2010)
- [43] Gerstner, Kistler, *Spiking Neuron Models. Single Neurons, Populations, Plasticity* (Cambridge University Press, 2002)
- [44] T. McKenna, J. Davis, S. Zornetzer, *Single Neuron Computation. Neural Networks: Foundations to Applications* (Academic Press, 2014). URL <https://books.google.hu/books?id=n7CjBQAAQBAJ>
- [45] M. Almog, A. Korngreen, J Neurophysiol. **5**, 2180 (2016). DOI doi:10.1152/jn.00360.2016

- [46] Holland, L. and de Regt, H.W. and Drukarch, B., History and Philosophy of the Life Sciences **46** (2024). DOI 10.1007/s40656-024-00644-4
- [47] M.H.P. Kole, S.U. Ilschner, B.M. Kampa, S.R. Williams, P.C. Ruben, G.J. Stuart, Nature Neuroscience **11**, 178 (2008). DOI 10.1038/nn2040. URL <https://www.nature.com/articles/nn2040>
- [48] M. Rasband, Nat Rev Neurosci **11**, 552 (2010). DOI 10.1038/nrn2852
- [49] M. Kole, G. Stuart, Neuron **73**(2), 235 (2012). DOI <https://doi.org/10.1016/j.neuron.2012.01.007>. URL <https://www.sciencedirect.com/science/article/pii/S0896627312000505>
- [50] C.Y.M. Huang, M.N. Rasband, Ann N Y Acad Sci. **1420**, 46 (2018). DOI 10.1111/nyas.13718
- [51] C. Leterrier, Journal of Neuroscience **38**(9), 2135 (2018). DOI 10.1523/JNEUROSCI.1922-17.2018
- [52] D. Perkel, M. B., J Neurophysiol. **41**, 621 (1978). DOI 10.1152/jn.1978.41.3.621
- [53] G. Somjen, *SENSORY CODING in the mammalian nervous system* (New York, MEREDITH CORPORATION, 1972). DOI 10.1007/978-1-4684-1707-4
- [54] J. Végh, The Journal of Supercomputing **76**(12), 9430 (2020). URL <http://link.springer.com/article/10.1007/s11227-020-03210-4>
- [55] J. Végh, Neural Computing and Applications **33**(1), 16847 (2021). DOI 10.1007/s00521-021-06456-y. URL <http://link.springer.com/article/10.1007/s00521-021-06456-y>
- [56] B. Drukarch, M. Wilhelmus, Progress in Neurobiology **169**, 172 (2018). DOI 10.1016/j.pneurobio.2018.06.009
- [57] R. Appali, S. Petersen, U. van Rienen, Advances in Radio Science **8**, 75 (2010). DOI 10.5194/ars-8-75-2010
- [58] D.E. Pence, Philosophy of Science **84**(5), 1177 (2017). DOI 10.1086/694040
- [59] T. Heimburg, A.D. Jackson, Proceedings of the National Academy of Sciences pp. 9790–9795 (2005). DOI 10.1073/pnas.0503823102
- [60] B.J. Patlak, M. Ortiz, J. Gen. Physiol. **86**, 89 (1985)
- [61] P.F. Cranefield, F.A. Dodge, *Slow Conduction in the Heart* (Springer Netherlands, Dordrecht, 1980), pp. 149–171
- [62] B. Linder, J. Garcia-Ojalvo, A. Neiman, L. Schimansky-Geier, Physics reports **392**(6), 321 (2004)

- [63] A. Losonczy, J. Magee, *Neuron* **50**, 291 (2006). DOI 10.1016/j.neuron.2006.03.016
- [64] M.C. Kiernan, K. Cikurel, H. Bostock, *Brain* **124**(4), 816 (2001). DOI 10.1093/brain/124.4.816. URL <https://doi.org/10.1093/brain/124.4.816>
- [65] B. Podobnik, M. Jusup, Z. Tiganj, W.X. Wangi, J.M. Buld, H.E. Stanley, *Applied Physical Sciences* **45**, 11826 (2017). DOI 10.1073/pnas.1705704114
- [66] I.I. Ryzhkov, D.V. Lebedev, V.S. Solodovnichenko, A.V. Minakov, M.M. Simunin, *Journal of Membrane Science* **549**, 616 (2018). DOI <https://doi.org/10.1016/j.memsci.2017.11.073>. URL <https://www.sciencedirect.com/science/article/pii/S0376738817327060>
- [67] H. Tamagawa, M. Sasaki, W. Lin, B. Delalande, *Mod Concept Material Sci.* **6** (2024)
- [68] Hirohisa Tamagawa and Titus Mulembo and Vera Maura Fernandes de Lima and Wolfgang Hanke, *Progress in Biophysics and Molecular Biology* **167**, 3 (2021). DOI <https://doi.org/10.1016/j.pbiomolbio.2021.10.004>. URL <https://www.sciencedirect.com/science/article/pii/S0079610721001279>
- [69] A.M. Brown, *A companion guide to the Hodgkin-Huxley papers* (The Physiological Society, Seattle, WA 98195, USA, 2022)
- [70] C.Y.M. Huang, M.N. Rasband, *Annals of the New York Academy of Sciences* **1420** (2018). DOI 10.1111/nyas.13718
- [71] W.B. Levy, V.G. Calvert, *Proceedings of the National Academy of Sciences* **118**(18), e2008173118 (2021). DOI 10.1073/pnas.2008173118
- [72] J. Végh, arXiv, in review in *Journal of Biological Physics* pp. 1–76 (2025). DOI <https://doi.org/10.48550/arXiv.2507.11448>
- [73] J. Rinzel, *Bulletin of Mathematical Biology* **52**(1), 5 (1990). URL <https://www.sciencedirect.com/science/article/pii/S0092824005800035>
- [74] Khorsand P and Chance F , *PLoS ONE* **3**(11), e3786 (2008). DOI doi.org/10.1371/journal.pone.0003786
- [75] C. Koch, T.A. Poggio, *Proceedings of the Royal Society of London. Series B. Biological Sciences* **218**, 455 (1983)
- [76] J.M. Beggs, D. Plenz, *Journal of Neuroscience* **23**(35), 11167 (2003). DOI 10.1523/JNEUROSCI.23-35-11167.2003

- [77] A. Mason, A. Nicoll, K. Stratford, *The Journal of Neuroscience* **11**, 79 (1991)
- [78] A. Goikolea-Vives, H. Stolp, *Int J Mol Sci* **15** (2021). DOI 10.3390/ijms22158220
- [79] K. Hasegawa, K.i. Kuwako, *Seminars in Cell & Developmental Biology* **129**, 103 (2022). DOI <https://doi.org/10.1016/j.semcd.2022.02.015>. URL <https://www.sciencedirect.com/science/article/pii/S1084952122000544>. Special Issue: Emerging biology of cellular protrusions in 3D architecture by Mayu Inaba and Mark Terasaki
- [80] A.L. Hodgkin, *The conduction of the nervous impulse* (Liverpool University Press, Liverpool, UK, 1964, 1964)
- [81] B.C. Abbott, A.V. Hill, J.V. Howarth, *Proc. R. Soc. London. B.* **148**, 149–187 (1958)
- [82] B. Bean, *Nature Reviews Neuroscience* **8** (2007). DOI 10.1038/nrn2148
- [83] T. Heimburg, *Thermal Biophysics of Membranes*, 1st edn. (2007 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim, 2007)
- [84] A. El Hady, B.B. Machta, *Nature Communications* **6**, 6697 (2019). DOI 10.1038/ncomms7697
- [85] Iwasa, K and Tasaki, I. and Gibbons, RC., *Science* **17**(4467), 338 (1980). DOI 10.1126/science.7423196
- [86] I. Tasaki, K. Iwasa, *J Physiol (Paris)* **77**, 1055 (1981)
- [87] B. Alberts, A. Johnson, J. Lewis, et al. *Molecular biology of the cell* (2002). URL <https://www.ncbi.nlm.nih.gov/books/NBK26910/>
- [88] I. Nemenman, G.D. Lewen, W. Bialek, R.R. de Ruyter van Steveninck, *PLOS Computational Biology* **4**(3), 1 (2008). DOI 10.1371/journal.pcbi.1000025
- [89] P. Sterling, S. Laughlin, *Principles of Neural Design*, 1st edn. (The MIT Press, Cambridge, Massachusetts and London, England, 2017)
- [90] L. Pyenson, *Archive for History of Exact Sciences* **17**, 71 (1977). DOI 10.1007/BF00348403
- [91] S.I. Walker, *Reports on Progress in Physics* **80**(9), 092601 (2017). DOI 10.1088/1361-6633/aa7804. URL <https://doi.org/10.1088/1361-6633/aa7804>
- [92] A. Das, *The special theory of relativity: a mathematical exposition*, 1st edn. (Springer-Verlag New York, 1993)

- [93] Hermann Minkowski, Nachrichten von der Königlichen Gesellschaft der Wissenschaften zu Göttingen (in German) pp. 53–111 (1908)
- [94] Wikipedia. Roemer's determination of the speed of light. [https://en.wikipedia.org/wiki/R%C3%BCmer%27s\\_determination\\_of\\_the\\_speed\\_of\\_light](https://en.wikipedia.org/wiki/R%C3%BCmer%27s_determination_of_the_speed_of_light) (2024)
- [95] I. Newton. Philosophiae naturalis principia mathematica. URL <https://www.britannica.com/topic/Principia>
- [96] A. Einstein, Annalen der Physik (in German) **10**(17), 891 (1905). DOI 10.1002/andp.19053221004
- [97] S. Walter, ESI News **1**(3), 6 (2008)
- [98] H. Schmidgen. Of frogs and men: the origins of psychophysiological time experiments, 1850-1865 (1850). URL <https://epub.uni-regensburg.de/27126/1/schmidgen.pdf>
- [99] E. Phsychology. The rise of experimental psychology (1850). URL <https://ebrary.net/269412/psychology/helmholtz>
- [100] W.S. McCulloch, W. Pitts, j-BULL-MATH-BIOPHYS **5**(4), 115 (1943). DOI <https://doi.org/10.1007/BF02478259>. URL <http://link.springer.com/article/10.1007/BF02478259>
- [101] I. Popov, Z. Zhu, A.e.a. Young-Gonzales, Commun Chem **6** (2023). DOI 10.1038/s42004-023-00878-6
- [102] J. Isakovic, I. Dobbs-Dixon, D. Chaudhury, et al., Sci Rep **8** (2018). DOI 10.1038/s41598-018-31054-9
- [103] H.A. Ulku, A.A. Ergin, IEEE Transactions on Antennas and Propagation **59**(11), 4123 (2011). DOI 10.1109/TAP.2011.2164180
- [104] R. Ho, M. Horowitz. More about wires and wire models. [https://web.stanford.edu/class/archive/ee/ee371/ee371.1066/lectures/lect\\_09\\_1up.pdf](https://web.stanford.edu/class/archive/ee/ee371/ee371.1066/lectures/lect_09_1up.pdf) (accessed on 29 April 2025) (2007)
- [105] W. Maass, T. Natschläger, H. Markram, Neural Computation **14**(11), 2531 (2002). DOI 10.1162/089976602760407955
- [106] Y. Prut, E. Vaadia, H. Bergman, I. Haalman, H. Slovin, M. Abeles, J. Neurophysiol **79** (1998)
- [107] D. Plenz, A. Aertsen, Neuroscience **70/4**, 893 (1996)
- [108] J. Végh, Global Journal of Computer Science and Technology: Hardware & Computation **20/1**, 13 (2020). URL <https://doi.org/10.34257/GJCSTAVOL20IS1PG13>

- [109] G. Buzsáki, J. Végh, *Space, time and memory*, 1st edn. (Oxford University Press, 2025). URL <https://global.oup.com/academic/product/space-time-and-memory-9780192882547>
- [110] D.G. Miller, THERMODYNAMICS OF IRREVERSIBLE PROCESSES THE EXPERIMENTAL VERIFICATION OF THE ONSAGER RECIPROCAL RELATIONS . Tech. Rep. Contract No. W-7405-eng-48, UNIVERSITY OF CALIFORNIA, Lawrence Radiation Laboratory, Livermore, California (1959). DOI 10.1021/cr60203a003
- [111] Q. Zheng, W. G.W., J Chem Phys **19** (2011). DOI 10.1063/1.3581031
- [112] D. Forcella, J. Zaanen, D. Valentini, D. van der Marel, Phys. Rev. B **90**, 035143 (2014). DOI 10.1103/PhysRevB.90.035143. URL <https://link.aps.org/doi/10.1103/PhysRevB.90.035143>
- [113] D.S. Bassett, P. Zurn, J.I. Gold, Nature Reviews Neuroscience **19**, 566 (2018). DOI 10.1038/s41583-018-0038-8
- [114] R. Stock, J. Kaiser, E. Müller, et al., Open Res Europe **3** (2023). DOI 10.12688/openreseurope.15775.1
- [115] I. Abraham, Nature Scientific Reports **8**, 10972 (2018). DOI 10.1038/s41598-018-29394-7
- [116] J. Végh, in *2021 international conference on computational science and computational intelligence; foundations of computer science*, vol. 21 (IEEE Las Vegas, USA; July 26-29, IEEE, 2021), vol. 21, p. FCS4404
- [117] M. Stemmler, C. Koch, Nat Neurosci **2**, 521 (1999)
- [118] H. Tamagawa, S. Morita, Membranes **4**(2), 257 (2014). DOI 10.3390/membranes4020257. URL <https://www.mdpi.com/2077-0375/4/2/257>
- [119] H. Tamagawa, T. Nakahata, R. Sugimori, B. Delalande, M. T, Acta Biophysicae **71**(15) (2023). DOI 10.1007/s10441-023-09467-5
- [120] A. Baumgart, J.R. Clarke, G.C. Cranfield, R. Zerlotti, F.T. Buoninsegni, Biophysical Journal **124** (2025). DOI 10.1016/j.bpj.2024.11.557
- [121] K. Dobhoff-Dier, M.T. Koper, Current Opinion in Electrochemistry **39**, 101258 (2023). DOI <https://doi.org/10.1016/j.coelec.2023.101258>. URL <https://www.sciencedirect.com/science/article/pii/S2451910323000510>
- [122] L.J. Gentet, G.J. Stuart, J.D. Clements, Biophysical Journal **79**(1), 314 (2000). DOI [https://doi.org/10.1016/S0006-3495\(00\)76293-X](https://doi.org/10.1016/S0006-3495(00)76293-X). URL <https://www.sciencedirect.com/science/article/pii/S000634950076293X>

- [123] I. Goychuk, P. Hänggi, J.L. Vega, S. Miret-Artés, Phys. Rev. E **71**, 061906 (2005). DOI 10.1103/PhysRevE.71.061906. URL <https://link.aps.org/doi/10.1103/PhysRevE.71.061906>
- [124] G. Baranauskas, M. Martina, The Journal of Neuroscience **26**, 671 (2006)
- [125] W. Gerstner, W.M. Kistler, R. Naud, L. Paninski, *Neuronal Dynamics*: (Cambridge University Press, Cambridge, UK, 2014)
- [126] I. Karbat, et al., Cell **178** (2019)
- [127] G. Wisedchaisri, et al., Cell **178**, 993.1003.e12 (2019). DOI 10.1016/j.cell.2019.06.031
- [128] C. Kutzner, D.A. Köpfer, J.P. Machtens, B.L. de Groot, C. Song, U. Zachariae, Biochimica et Biophysica Acta **1858**, 1741 (2016)
- [129] B. Hille, A.C. M, R. McKinnon, Nature Medicine **5**(10), 1105 (1999)
- [130] T. Heimborg, Chemistry and Physics of Lipids **267**, 105461 (2025). DOI <https://doi.org/10.1016/j.chemphyslip.2024.105461>. URL <https://www.sciencedirect.com/science/article/pii/S0009308424000860>
- [131] D. Purves, G.J. Augustine, D. Fitzpatrick, L.C. Katz, A.S. LaMantia, J.O. McNamara, S.M. Williams (eds.), *Neuroscience*, 2nd edn. (Sinauer Associates, 2001). URL <https://www.ncbi.nlm.nih.gov/books/NBK10799/>
- [132] A. Boldini, M. Porfiri, npj Comput Mater (2022). DOI 10.1038/s41524-022-00827-2
- [133] D. Bianchi, A. Marasco, A. Limongiello, et al., J Comput Neurosci **33**, 207–225 (2012). DOI 10.1007/s10827-012-0383-y
- [134] A.J. Peterka, *Hydraulic Design of Stilling Basins and Energy Dissipators* (United States Department of the Interior, 1958)
- [135] B. Barlow, A. Longtin, B. Joós, PLoS Comput Biol. **20** (2024). DOI 10.1371/journal.pcbi.1011846
- [136] T. Tansey, *Alan Hodgkin, Chance and design: reminiscences of science in peace and war*, vol. 37 (Cambridge University Press, 1992, 2012). DOI 10.1017/S0025727300058555
- [137] C.F. Craver, Philosophy of Science **75**(5), 1022 (2008). DOI 10.1086/594543
- [138] M. Oleksowicz, in *Proceedings of the SISFA 43rd Annual Conference, Padova, 5-8, sept 2023; at Padova, Italy* (2024). DOI 10.6093/978-88-6887-297-7
- [139] G. Buzsáki, *The Brain from Inside Out*, 1st edn. (Oxford University Press, 2019)

- [140] M. Carandini, F. Mechler, C. Leonard, J. Movshon, *J Neurophysiol.* pp. 3425–41 (1996). DOI 10.1152/jn.1996.76.5.3425
- [141] D. Chu, M. Prokopenko, J.C. Ray, *Interface Focus* **8** (2018). DOI 10.1098/rsfs.2018.0058. Accessed: 2025-03-20
- [142] E. Human Brain Project. Human Brain Project. <https://www.humanbrainproject.eu/en/> (2018)
- [143] Human Brain Project. Hodgkin-Huxley Neuron Builder. <https://hhnb.ebrains-italy.eu/hh-neuron-builder/> (2023)
- [144] S.J. van Albada, A.G. Rowley, J. Senk, M. Hopkins, M. Schmidt, A.B. Stokes, D.R. Lester, M. Diesmann, S.B. Furber, *Frontiers in Neuroscience* **12**, 291 (2018). URL <https://www.frontiersin.org/journals/neuroscience/articles/10.3389/fnins.2018.00291/full>
- [145] J. Végh, *Brain Informatics* **6**, 1 (2019). DOI 10.1186/s40708-019-0097-2. URL <https://braininformatics.springeropen.com/articles/10.1186/s40708-019-0097-2>
- [146] US DOE Office of Science. Report of a Roundtable Convened to Consider Neuromorphic Computing Basic Research Needs (2015). URL [https://science.osti.gov/-/media/ascr/pdf/programdocuments/docs/Neuromorphic-Computing-Report\\_FNBLP.pdf](https://science.osti.gov/-/media/ascr/pdf/programdocuments/docs/Neuromorphic-Computing-Report_FNBLP.pdf)
- [147] D. Markovic, A. Mizrahi, D. Querlioz, J. Grollier, *Nature Reviews Physics* **2**, 499 (2020). DOI <https://www.nature.com/articles/s42254-020-0208-2.pdf>
- [148] A. Mehonic, A.J. Kenyon, *Nature* **604**, 255 (2022). DOI 10.1038/s41586-021-04362-w
- [149] C. Mead, *Proc. IEEE* **78**, 1629 (1990)
- [150] G. Bell, D.H. Bailey, J. Dongarra, A.H. Karp, K. Walsh, *The International Journal of High Performance Computing Applications* **31**(6), 469 (2017). URL <https://doi.org/10.1177/1094342017738610>
- [151] S. Furber and S. Temple, *J. R. Soc. Interface* **4**, 193 (2007). DOI 10.1098/rsif.2006.0177
- [152] A. Cho, *Science* **364**(6447), 1218 (2018). DOI 10.1126/science.364.6447.1218
- [153] A.G. Dimitrov, A.A. Lazar, J.D. Victor, *Journal of Computational Neuroscience* **30**/**1**, 1 (2011). DOI 10.1007/s10827-011-0314-3
- [154] D.H. Johnson, *Information theory and neuroscience: Why is the intersection so small?* (IEEE, 2008), pp. 104–108. DOI 10.1109/ITW.2008.4578631

- [155] L. Nizami, *Cybernetics & Human Knowing* **26**(4), 47 (2019). URL <https://core.ac.uk/download/pdf/333651513.pdf>
- [156] T. Berger, W.B. Levy, *IEEE Transactions on Information Theory* **56**(2), 852 (2010). DOI 10.1109/TIT.2009.2037089
- [157] G. Buzsáki, K. Mizuseki, *Nature Reviews Neuroscience* **15**, 264 (2014). DOI 10.1038/nrn3687
- [158] S. Gordon (ed.), *The Synaptic Organization of the Brain*, 5th edn. (Oxford Academic, New York, 2005). DOI 10.1093/acprof:oso/9780195159560.001.1
- [159] N. Rouleau, M. Levin, *Nat Mach Intell* **6**, 1424 (2024). DOI 10.1038/s42256-024-00955-y. URL <https://doi.org/10.1038/s42256-024-00955-y>
- [160] Editorial, *Nat Mach Intell* **6** (2024). DOI 10.1038/s42256-024-00968-7
- [161] D.M. MacKay, W.S. McCulloch, *The bulletin of mathematical biophysics* **14**(2), 127 (1952)
- [162] T.J. Sejnowski, *IEEE Annals of the History of Computing* **11**(03), 197 (1989). DOI 10.1109/MAHC.1989.10028
- [163] IEEE/Accellera. Systems initiative. <http://www.accellera.org/downloads/standards/systemc> (2017)
- [164] C.D. Black, J. Donovan, B. Bunton, A. Keist, *SystemC: From the Ground Up*, 2nd edn. (Springer, New York, 2010)
- [165] J. Végh, in *Proceedings of the 2020 International Conference on Computational Science and Computational Intelligence (CSCI'20: December 16-18, 2020, Las Vegas, Nevada, USA* (IEEE Computer Society, 2020), pp. 1260–1264. DOI 10.1109/CSCI51800.2020.00235