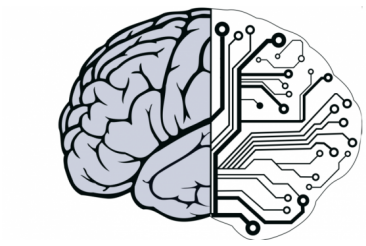
"Though this be madness, yet there is method in't."
Shakespeare: Hamlet: Act 2 Scene 2

Dynamic Abstract Neural Computing with Electronic Simulation (DANCES)

The true physics, physiology, computing & information science behind neuronal operation



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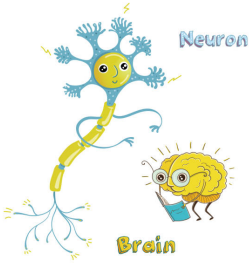

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Foreword

"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*, new treatments for brain disease and *new brain-like computing technologies*."

— the Human Brain Project, summarised its goal @2012

" *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" [9] @2015

Many-disciplinarity In this research, we arrived at the boundaries of classic science fields and are moving now through terra incognita. The "great journey into the unknown" [9] must begin earlier and at a much lower level: revisiting the fundamental phenomena, disciplines, laws, interactions, abstractions, and omissions of science. During that journey, we must also show which approximations are oversimplifications and which phenomena are misunderstood, measured, or interpreted in the wrong approach. There is no independent 'life science', only science, with the same 'first principles' but different abstractions and approximations for living and non-living matter and proper relations between them.

Different science disciplines consider different details relevant; see Fig. .0.1. Despite the efforts of the project leader, no picture can be derived about the *elephant*, although *the details of the elephant* are accurate. Without aligning the knowledge elements along the first principles, "integration between data and knowledge from different disciplines" actually lacks "integration". "More Is Different" [10]; at least it should be. Without recognizing that, 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". [9] We need the "discovery" that we need *different abstractions and approximations* for describing biological processes. However, an abstraction is usable in practice only when paired with a

Figure .0.1: The difficulty of many-disciplinary research on the example of describing the elephant. (a 2,500 years-old Chineese silk painting)

generalization: the more abstract the assumption, the more general and widely applicable the concept or conclusion, especially when interfacing different scientific disciplines. *By abstractions, we can reduce the unbelievably detailed world into manageable pieces, and by abstraction, we can learn anything general.* Abstraction is, in fact, everywhere, including inside each of us. It is a core element of cognition.

The dynamic operation of individual neurons, their connections, higher-level organizations and 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*, and at which point *a living matter becomes intelligent* and conscious; whether and how all this stuff can be handled by science. We need a consistent model that comprises all relevant interactions (and only those!) and aligns with the notions of the related other scientific fields. Neuroscience is not an exception. Unfortunately, nature does not care that science divides its description into disciplines. We must ensure that the disciplines are aligned along different approximations and abstractions, and that cross-disciplinary research must combine them. However, the process is not trivial and not automatic. We cannot derive an "equation for everything". In the interest of being able to describe nature, one has to pass between 'Scylla' and 'Charybdis': being still sufficiently accurate and detailed in describing phenomena while keeping the mathematical complexity (and computational need) of description remains still manageable.

Interdependence of disciplines When describing principles of neural computing, for the same reasons, we follow von Neumann's method when describing principles of technical computing [11]. "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."

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 instead of using them side by side in physiology; why 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). In our case, this zigzag way of reading is made more accessible by using hyperlinks in the document.

Abstract discussion We attempt to *see the forest for the trees.* Nature uses an infinite variety of implementing neurons. However, in the CNS they can cooperate with each other. 'Despite the extraordinary diversity and complexity of neuronal morphology and synaptic connectivity, *the nervous systems adopts* ***a number of basic principles*** for all neurons and synapses' [3]. We understand that that "*the fundamental task of the nervous system is to* ***communicate and process information***". Furthermore, the "**neurons convey neural information** by virtue of electrical and chemical signals"[3]. 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***' [12]. We base our discussion on those general basic principles and create an 'abstract physical neuron', skipping the 'implementation details' nature uses. We want to rely on general principles and avoid implementing obsolete details for a holistic understanding. We also want to avoid hypothesizing biologically non-plausible methods and principles, creating some alternative nature.

Physiology *The mentioned signals are electrochemical ones with temporal behavior* instead of purely electrical and purely chemical ones happening in a timeless world, with numerous significant consequences. Our point of view is new and unusual; it conflicts, on many points, with the commonly accepted opinions of the respective science. Physiology, which serves as the "implementation base" for neural computing, needs a revolution and replacing the "classic physiology" with "modern physiology" by introducing a new paradigm, as the partial failure

(concerning discovering secrets of neural computing) of the grandiose projects cited above has shown. Biology stayed at a static description level, typically appropriate for describing static states; using biology's *static entities* is insufficient. However, *neural processes* happen at well-observable speeds which *need a dynamic description instead of an ad-hoc description of state jumps*. For describing the observed phenomena case-by-case explanations are provided (in some cases lacking scientific reality), and ad hoc laws and understanding are provided. *We introduce for life sciences the laws of motion (in the sense of Newton, Hamilton, and Schrödinger), (based on time derivatives of the static entities)*, furthermore, *the needed dynamically created component which can implement the needed dynamic processes*. Considering them solves the mystery of how a biological neural network can react at a speed about two orders of magnitude higher than it could be expected based on its static behavior (the time difference between adjacent spikes) and, in general, how life science builds on top of science. Even though it is stated "the emergence of life cannot be predicted by the laws of physics" [13], furthermore, that the existence of life is against the laws of thermodynamics. Describing physiological processes and understanding neural information processing need a revolution.

Physics 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 2.6 towards 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?" [14] (notice the need *using events and describing the spatiotemporal behavior (in other words: implementing them by slow currents)* implied in the question; two items which our system targets) *No presently available theoretical description and simulator can perform that task.*

Given that, in many cases, wrong physical principles, notions, and methods are used in measuring and modeling neurons, we need to discuss the true physics behind biological phenomena. To do so, we need to understand how neurons represent and process information [15]. We agree that "The basic structural units of the nervous system are individual neurons" [3], 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" [16, 15] so we also model multiple neurons. 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.

Neuroscience The worst inheritances of neuroscience are the static view from anatomy and classic physiology; omitting revisiting periodically the primary hypotheses in light of new research results; the abstractions of the classic science (single speed, isolated, pair-wise, instant interactions in a homogeneous and isotropic infinite medium) applied 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. We show that when considering the correct physics, the finite size of neuronal membranes and the finite speed of ion currents solve the mystery that the combination of non-living materials shows signs of life at an appropriate combination of their values.

Mathematics We can only admire von Neumann's genial prediction that "the language of the brain, not the language of mathematics" [17], given that most of the cited experimental evidence was unavailable at his age. Similarly, one can also agree with von Neumann [11] and Sejnowski [18] 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: [19] "an *effective procedure* is a set of rules telling you, moment 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 [20, 21]. We formulate problems, provide their numerical solutions, and open the way for mathematics to provide analytical solutions.

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 identical propagation speeds of diffusion and electromagnetic waves to using equivalent circuits. Those wrong parallels hide the need for introducing electrodiffusion instead of net 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, that in biology, concentration changes evoke potential changes, and create large potential gradiens. Those interanl gradients may start dynamical electrical currents in biological tissues.

Computing "The brain computes! This is accepted as a truism by the majority of neuroscientists." [8] To understand how "computation is done", we generalize computing [22] in close cooperation with communication [23]. "A piecemeal approach will not yield the major jumps in understanding for which the BRAIN Initiative was designed" [24]. We attempt to 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, to other sciences, finding contradictions and their resolutions, *defying fallacies*. We show how elementary neuronal operation is carried out, why biological computing is by orders of magnitude more effective the technical one, how the biological implementation enables learning, how and why the features of the two computing differ.

Information Although we experience that the brain processes an enormous amount of information, 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 neuron operation, the so-called "neural information science" uses a wrong mathematical background. We introduce the appropriate interpretation of information for biology.

Intelligence Scrutinizing time awareness of biological computing and learning discovers 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'" [25]. 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" [25, 19].

Simulator The site is not exclusively about theory: we also give a programmed implementation of the ideas we describe. Our simulator has a direct science base instead of ad-hoc mathematical formulas; and the only one which is able to reproduce the true biological time course of neurons, from first principles of science, without arbitrary ad-hoc assumptions and limited variability formulas. Our methods enable discussing the major aspects of the 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 a full-value educational, demonstration, and research tools.

Believers in science Hodgkin and Huxley in 1952 [7] 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. Their work became the "Holy Bible" of physiology. The editors 'do not believe' (see Fig. .0.2) if science advanced in the past seven decades and they censor publishing new ideas in scientific journals.

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

Figure .0.2: "Believing" in science (in the age of Galillei).

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."

Warning: Please consider that this development is a one-man 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 need time to be consistently put together. Please come back later and see if something is new (see the date and version).

Chapter 1

Abstract single neurons

-"Despite the extraordinary diversity and complexity of neuronal morphology and synaptic connectivity, the nervous systems adopts a number of basic principles" [3]

E. Scrödinger: What is life?[14] @1992

In this chapter – in the spirit of Johnston and Wu [3] – we review how the relevant major components of a single neuron follow the basic principles when processing neuronal information and how they cooperate, conceptually. We discuss the physical (mainly electrical and electrodiffusional), computational, information theoretical and physiological details in different chapters. In those discussions we return to the same notions repeatedly, in von Neumann's 'zigzag' way, from a different point of view (at a different abstraction level).

In chapter 3 we go to a less abstract level ("abstract physiology"). We must discuss some important misconceptions, provide the right conceptions, and explain why the wong concept misguides research. Our discussion is closely related to physics, discussed in chapter 2. When discussing the underlying physical laws, we assume a knowledge of classic physics above the college-level and go back to the very basic physical notions and principles instead of taking over the approximations and abstractions (in this context: ordinary laws of physics) used in the *classic physics for non-biological matter* and less complex (strictly pair-wise, single type, finite interaction speed in homogenous isotropic medium) interactions. We attempt to 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 in section 2.6.3 (in this context 'extraordinary laws of physics'), and introduce a component which implements them. 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; futhermore, 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 abstact notions when attempt to go one step closer to the mystery how information is represented, encoded and decoded, transmitted and processed, in chapter 5.

1.1 Introduction

Here we discuss neurons in an absolutely abstract way, in the sense that we attempt to explain what are the princliples 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 when formulating neuron's functionality and features in an abstract way, similar to the one cited in connection with communication and information. However, we keep an eye on the discussion in other chapters and we name also the biological component, without discussing its details.

We introduce (and, in this aspect, correct the current common understanding) that not purely electrical, instead, *electrodiffusional* processes govern the operation of neurons and derive the correct their correct mathematical and physical handling. Furthermore, we complete the theory of electrodiffusion with introducing the time derivatives of the processes, in this way enabling the quantitative description of (a mathematical description of the abstract operation) neurons, that serves as a basis for discussing quantitatively the neural computing processes and the information handling. However, these corrections must be carried out in disciplinarily separated chapters. In the present chapter, we consider only the holistic picture, without those details.

Our abstract model is focused on the signal processing function of the neuron. However, our goal cannot be reached without the correct physiological understanding of its mechanisms. In this chapter we consider that neurotransmitters, receptors and specialized membrane proteins *only implement a kind of (time and energy consuming) chemical/enzimatic decoupling of the signal transmission mechanism.* The idea resembles opto-coupling in electronics: makes *the signal transmission independent from the local potential value.* If neurons would use galvanic coupling, when the resting potential of one of the neurons gets equal to that of the extracellular space, the resting potential of all connected neurons gets equal to that of the extracellular space. That is, without this decoupling, the death of one neuron would lead immediately to the death of the entire neural network. Furthermore, the neurons could not make independent signal processing.

1.2 Abstract modeling

The 'abstract physical neuron', as we call our model, attempts to follow the line which Hodgkin and Huxley [7] pointed to. 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 changes their conclusions. Our discussion follows essentially the same principles, but reinterprets the used basic terms for the concrete biological case study. The 'abstract' means here that we omit the physiological details and focus on the abstracted operating principle, *what* the function or component wants to implement. The 'physical' means that we put a physical mechanism behind the different stages of operation. Our intention is to find the appropriate stages, or, *the series of dynamic stages*, with corresponding transitions between. 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 some cases, the stage (or its interfaces) has a dominant interaction and a correcting interaction; so we need to invent new procedures. Such multiple simultanous interaction cases are rarely discussed in science. When discussed, the interaction speeds are considered as they are the same.

1.2.1 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."[26]. The only neuron model [7] 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 'brain-storming' or 'call for a collective effort' nature of the paper legitimates nearly all possible classifications.

We discuss that model in a separate section 3.4; with their genial observations and conclusions, and with 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 perform minor corrections to fix the scientific direction. As we discussed above, we admire HHs activity. However, in the interest of advancing the science, we must include the new discoveries into their picture; furthermore, we must fix their (admittedly wrong) physical picture. In this chapter, we provide only a birds' perspective, more details on the underlying physics and physiology are described in chapters 2 and 3.

1.2.2 Existing models

Textbooks, such as Neuronal dynamics and [8], usually skip the question *how* the neuron, a piece of living material, is modeled. Instead, they put behind their formulas, without validating it for biology, the picture taken from the classic

physics, which were validated for different circumstances (for non-living material): for describing electric circuits. Hodgkin and Huxley 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*" [7]. Their followers introduced further ad-hoc assumptions, that were needed to provide satisfactory agreement with the experimental evidence, into their admittedly wrong physical picture. The 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 Hodgkin-Huxley model and a host of simplified equations derived from them have inspired the development of *new and beautiful mathematics*." [27]. That mathematics is really new and beautiful but, unfortunately, *describes some alternative nature instead of the real one*.

Even, in the collection of topics "Single Neuron Computation" [28], 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". Finally, instead of finding out the correct equivalent circuit, a better agreement can be achieved between the "realistic" neurons built from discrete electronic components with well established mathematics. 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 opening chapter of the book and a basis for the discussion of the adjacent chapters, the many controversial models evidently lead to their conclusion that "this raises the possibility that the neuron is itself a network". The validity of the approach is at least questionalized [29]: "Is realistic neuronal modeling realistic?" This approach, explicitly, suggests that nature should build its neurons from discrete electronic components, on in other words, nature must adat to the mathematical equations. It is much easier to study such neurons.

1.2.3 Disciplinary approach

Electrodiffusion, the fundamental interaction for our discussion, is a very special case for the classical science; its discussion see in section 2.6. By discipline, it belongs to thermodynamics and electricity. Both disciplines have terms 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 speed 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 electrodiffusional processes.

Our abstract physical neuron shows different faces towards different 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, the new discoveries that vitiates the old picture and introduce the new one. Unlike in the old view, we check the consistency of the different views between each other.

In the old picture, the neuron is static and a hidden (empirical) mechanism controls its operation. It provides an overdetailed biological description that includes *static* currents and assumes fake (physically unrealistic) operating details. The new picture bases on a correct physics background.

For physiology, a neuron is a piece of semipermeable membrane surrounded by electrolytes having enormously different concentrations on its two sides; which receives and sends different current pulses. For physics, it is a system with variable and mixed speed interaction, which needs concerting microscopic and macroscopic features; checking validity of statistics per stage and per time; handling the operations with entities distributed in time and space; reinterpreting many approximations and laws from the classical physics to biology. For electronics, it is a *serial RC* circuit 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 working out handling of bio-electric processes, where the "charge production" by the biological objects combine with delays due to the finite speed and finite size. One must take special care when applying laws, that for example, conservation has a form which differs from the one used in classical physics. For mathematics, it is a set of differential equations (per-stage differing boundary conditions); time-aware and biology-aware algorithms; 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 object with its *local time*, which is independent from the wall-clock time and 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.

1.2.4 Electric operation

In this section – in the spirit of Johnston and Wu [3] – we review how the relevant significant components 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 classic physics, which was validated for different circumstances (non-living material). 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***' [7]. 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 that power may again change. All of them are connected by conducting (metallic) ideal wires, and their interaction speed is infinitely high (the Newtonian 'instant interaction'). 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.

We have the physical picture in mind about neurons that a neuron is implemented as a serial (i.e., differentiator-type) electric oscillator, which has gated current inputs and provides a timed output. We explicitly add that the charge carrier the neuron works with are *ions* (instead of electrons) and that the signal propagation mechanism is *electrodiffusion* (instead of electromagnetic field propagation). These distinctions involve numerous special features as follows.

We explicitly introduce the notion of 'slow current', in the sense discussed in section 2.3.4. We omit non-significant interactions, and restrict our discussion to interaction speed pairs, where we use the idea of classical physics approximation that the higher interaction speed is 'instant' and we work out the mathematics for accouting 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 directly between the membrane and the extracellular space or on the surface electrolyte layer on 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) or they move in an electrically homogeous medium without external driving force, respectively. Cardiac *slow currents* (current pulses of duration in several msecs range) [30] have been discovered, and their speed [31] was found in the range $0.02 - 5\ m/sec$. In neurophysiology, ion current speeds ranging from a few mm/s to dozens of m/s has been observed. The size relations in neuronal systems are discussed in section 3.1.1.

1.2.5 Classic vs modern approach

The spatiotemporal neuronal operation is too complex and quick 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 by Hodgkin and Huxley 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 an electrodiffusional process.

Second, it enables experimenting with "snapshots" of the operation (the feedback fixes neurons voltage to a particular value), hiding that the operation is dynamic and needs a dynamic description by laws of motion. The method has enabled them to get an understanding of what was happening in the neuron at each stage in the action potential. Correspondingly, they have set up the classic description, comprising 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] The method resembles to adapting the "perfect" circles to the real-world planetal orbits by perturbations until one discovers their laws of motion and understands they are ellipses. "Central to the BRAIN Initiative is the discovery, development and dissemination of new theories" [24], but there is no project to validate the principles used in the so called theoretical descriptions. Neuroscience theory stayed at their static theory; which forms a fundemental obstacle in front of understanding the dynamic operation of neural systems.

1.3 Components

As [3] summarizes: "Electrical signals travel from the cell body of a neuron to its axon terminal in the form of action potentials. Action potentials trigger the secretion of neurotransmitters from synaptic terminals. Neurotransmitters bind to postsynaptic receptors and cause electric signals (synaptic potential) in the postsynaptic neuron. *Synaptic potentials trigger action potentials, which propagate to the axon terminal* and trigger secretion of neurotransmitters to the next neuron." We must admit that *those signals are transmitted by electrodiffusion processes instead of net electric phenomena.* We move a towards a more abstract and more detailed view of considering neuronal opearation: "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." [32] Note that those "ceaseless variations" can be correctly handled by our dynamic methods.

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." [33] 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).

Nature is overly complex: science fields must use different approximations and abstractions. To set up a holistic model, we attempt to *see the forest for the trees.* Nature uses an infinite variety of implementing neurons. However, '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*' [3] so they can cooperate. We base our discussion on those basic principles 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).We use physiological notions and terms only in a general sense, going into details only at the necessary depth. However, we do cover the details in chapter 3 and cite the corresponding research papers.

We agree that 'The basic structural units of the nervous system are individual neurons' [3]. However, we also know that neurons "are linked together by dynamically changing constellations of synaptic weights" and "cell assemblies are best understood in light of their output product" [16]. We agree that '*the fundamental task of the nervous system is to* ***communicate and process information***'. Furthermore, the '***neurons convey neural information*** *by virtue of electrical and chemical signals*' [3]. 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***' [12]. We generalized the notions of computing [22] and information[15] for biology and use the notions introduced there throughout the paper. To understand, among others, the role of synaptic weights, the formation of APs, and neuronal information processing, we must understand, on that abstract level, which general rules govern the neuronal electrical (more precisely: electrodiffusional) processes.

1.3.1 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')*" [34].

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) [34]. They are either closed or open without a noticeable transition state, but as discussed in [35, 36], 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.

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 [34]. The presence of the two layers on the opposite sides of the membrane actually implements the control square-ware 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.

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 axon and neuronal membrane. When they 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} m/s) but they experience each other's electric repulsion that can speed up their speed to the range 1 m/s. (BTW: this effect can be misinterpreted as a sudden ion adsorption [37] on the surface of the membrane.) The final effect resembles an electric condenser: for a short time, ion-rich and ion-poor layers are formed on the two sides of the semipermeable isolator membrane.

Although the individual ion channels open and close 'randomly', the repulsion force on the two surfaces of the membrane acts as an additional valve. As [34] 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.

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.

This behavior explains why ion currents start up with a sharp exponential rise [38] (fitting polynomial lines [7] 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.

[39]

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. 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" [34], 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"[31]. 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" [34]. 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 [35, 36]. 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" [34].

1.3.2 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, 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 current 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 [34] 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 [40] 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. (II.2.28).

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 2.8.2) 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' [34]. The depolarization happens in an avalanche-like way [41] over the entire membrane surface. This process creates an ion-rich layer in the proximity of the membrane on the intracellular side and leaves behind an ion-poor layer on the opposite side. 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. (II.2.28)), 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, β 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 α 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 [38] (one of the big mistakes was fitting polynomial lines [7] to those critical regions, comprising both exponential and no-current regions: it hides the sudden change of membrane's current [38] 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 2.7.3, it is easy to make a systematic error, given that the measurement method can affect the result.

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} m/s), but they experience each other's electric repulsion, which can speed up their speed to the range 1 m/s. (BTW: this effect can be misinterpreted as sudden ion adsorption [37] on the surface of the membrane.) The final effect resembles an electric condenser: for a short time, ion-rich and ion-poor 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.

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.

1.3.3 Axons

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. 3.17.) 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).

1.3.4 Neuronal membrane

At the dawn of finding methods for describing neuronal operation, HH published high-precision measurements [7] 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.*" [7] 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 mystic 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 (irrealistic 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 [37]. 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 [7]: "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 [7] (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 2.7.3; 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" [13] (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 [42]) 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 [43, 44] 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 1.3.1. The ion channels open and close themself 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 3.15 and III.3.10), but they need time to reach the AIS later (see Figure 1.3) when in the meantime the membrane' voltage proceeded toward its hyperpolarized state; so they seem to appear dozens of microseconds later at the AIS, explaining the relative refractory period.

The inflow charge generates a "potential wave" (a solid current outflow) through the AIS; see the discussion in section 3.3. 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 2.7, 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 [1]); see section 3.3.

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.(I.1.3)

$$\frac{dV_m}{dt} = -\frac{1}{C_m} I_{axon};\ V_m(t) = \frac{I_{wall} * (1 - e^{-\alpha * t})}{C_m} \tag{I.1.1}$$

that generates a change in the membrane current

$$\frac{dI_m}{dt} = \frac{1}{R_m}\frac{dV_m}{dt};\ I_m^{on}(t) = g_m(V)V_m(t) \tag{I.1.2}$$

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 [7]* 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 [45]. 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 [7]). 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*" [7]. The potential is equalized by the AIS current, producing a net exponential decay:

$$I_m^{off} = I_{Wall} * e^{(-\frac{\alpha}{R_m C_m} * t)} \tag{I.1.3}$$

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 oon 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 [46], 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 1.4.2. Notice that the

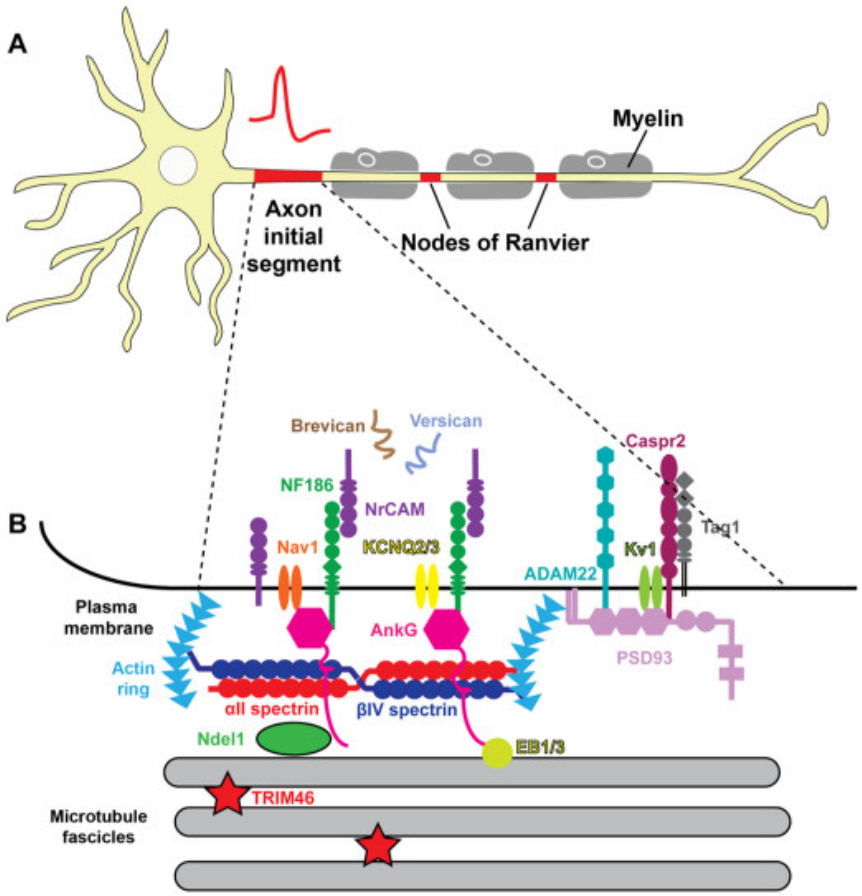


Figure I.1.1: The structure of the Axon Initial Segment. [1] Ann. N.Y. Acad. Sci. 1420 (2018) 46–61, Figure 1 ©2018 New York Academy of Sciences.

content of that memory may depend on the neuronal environment.

1.3.5 Axon Initial Segment

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' [2].

"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

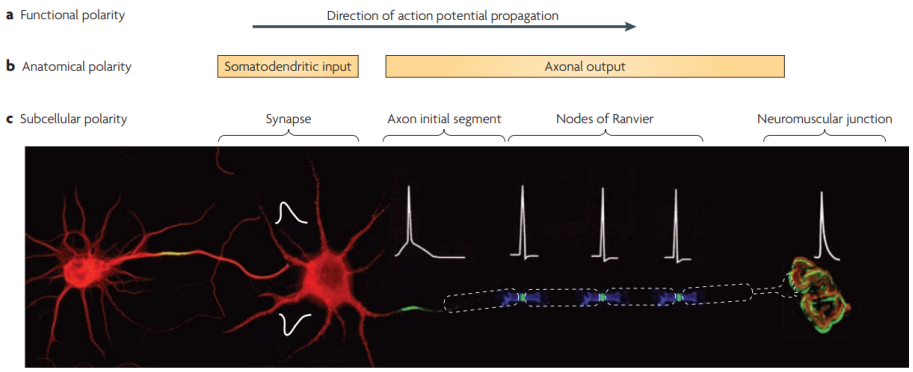


Figure I.1.2: Neurons are highly polarized cells [2], Figure 1 ©2010 Macmillan Publishers Limited.

potentials at the axon initial segment (AIS), a 20–60 μm long domain located at the proximal axon/soma interface that has a high density of voltage-gated ion channels." As discussed in [47], see also their Figure 1, reproduced here as Figure I.1.1, the structure of the Axon Initial Segment is known to the smallest details. As the illuminating investigations in 2008 [1] 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" [2]; providing a direct evidence that (unlike in HH's model) the input and output currents (and voltage time derivatives) are independent, see also Fig. I.1.2. 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 of the neuronal oscillator. Inventing AIS changed the viewpoint of neuroscience [33].

At the time when HH published [7] their electrical model for the neuron, the structure of the neuron, the AIS and its role in the electric operation was not yet known. Despite the early warning that '*it was not possible to separate the change into resistance and capacity components*' [4], a commonly accepted truism was that neurons, in some sense, behave as electric oscillators. 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 ([3] Figure 3.1 or [8] Figure 1.1), and it is a commonly accepted fallacy even today [48]. 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 2.8. 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".

1.3.6 Neuronal oscillator

1.4 Operations

In this section, we attempt to provide a "birds' eye view" of our model's operation. We must refer to the need of the zigzag discussion. The central notion of neuronal operation is the 'Action Potential'. We introduce the fundamental terms in a way that we assume that the audience has at least a fundamental knowledge of the subject. We name the terms, and refer to the corresponding sections discussing physics that bases them and the sections which in terms of "abstract physiology" (without biological details) provided more details. We explicitly consider that "slow" currents implement the functionality and we also name which activity why does need time. We discuss the (still abstract) operation details in section 3.3. Fig. 1.3 shows a schematic AP, with connected characteristic points, and nearly realistic figures on the axis, and the ordinates, and abscissas of the characteristic points. The figure shows the result of a numeric simulation, see Chapter 7. See also Fig. III.3.4 (notic that the time scale is logarithmic), where results of using physical models are depicted.

1.4.1 Conceptual operation

In our view, the physical neuron operates with currents, uses 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 received through its synapses or artificial current gradients. 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 thresholds.

Stage 'Computing'

With reference to Fig. 1.3, we subdivide neuron's operation to three stages (green, red, and blue sections of the broken diagram line). We start in stage 'Relaxing' (is 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), since all component have the same potential

The neuron receives inputs as 'Axonal inputs'. For the first input in stage 'Relaxing', the neuron enters stage 'Computing'. The physical implementation is a step-like current gradient which evokes a voltage gradient dV/dt on the membrane in its intracellular segment, see section 1.4.4. The membrane is connected to the extracelular segment through a resistor (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 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' arrives before the neuron returns to stage 'Relaxing', the voltage increases, and it might reach a threshold voltage. In such a case, the neuron enters the 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 calculation is finished. The result of the computation is the time passed between receiving the first 'Axonal input' and the neuron closes its input sources (and simultaneously, opens the ion channels in its wall, see below). No more input shall be received, so the neuron disables its synaptic inputs, and prepares for delivering the result of its 'computing' (nothing shall be stored: the delivery is a fixed-length process, will follow immediately). Notice that the result is a cooperation between the neuron and its upstream neurons. One of the upstream neurons opens the computing, and the receiving neuron terminates it.

In this stage, the role of the slow speed is not evident. The current arrives through an axon, passes the terminal and arrives to the AIS; the time

components cannot be separated.

Stage 'Delivering'

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 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. The amount of the rushed-in ions is several times more than those received during the stage 'Computing'.

The ion channels on all 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 differentitor 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.

Stage 'Relaxing'

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 compu-

tation: the previous result is under delivering (parallelly, independently), the axonal inputs are open again. However, the membrane's potential at this point is my 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 though the AIS). A new computation begins 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. 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 $\zeta = 0.35$.

Classic stages

We can maps our 'modern' stages to those 'classic stages' and enables defining the length of the AP.. The effect of slow current affects only the boundary between our "Delivering" stage and "Relaxing" stages. Classic physiology sees the difference and distinguishes 'absolute' and 'relative' refractory periods with a smeared boundary between, furthermore, 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 hyperpolarization. Our derivation of the stages draws a clear-cut line between them, and shows that only one refractory period exists, plus the effect of the slow current.

The front side delivers the information when the rush-in happened, the back side is mainly needed for restoring the resting potential.

Implications for computing

Fig. 1.3 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" [49]
- "information stored directly at a synapse can be retrieved directly" [49]
- part of the information (in 'volatile' memory) is stored only for the period when it might be needed (a real cache)
- "Computing" is much shorter than "Delivering"
- asynchronous; the operation time varies (no pipelining)

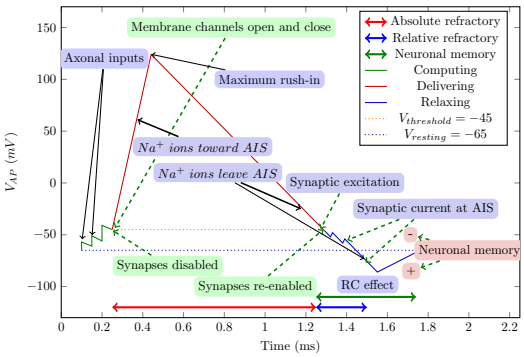


Figure 1.3: The conceptual graph of the action potential

- "Send only information that is needed, and send it as slowly as possible" [49]
- using derivative enables transferring more information and functionality; for example, synchronization [40]
- for simulation: there is no need to send and integrate spike shapes, only *the time of sending*

1.4.2 Action Potential (AP)

1.4.3 Synaptic control

1.4.4 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) [5] 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 [50] 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.(II.2.25). 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 1.4.3 and Figure 3.15. 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 inflexion when it is repolarized' [7].

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* [51]: 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" [44]: 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 3.3.7. The shape of PSP also plays a vital role in in synchronizing neurassemblies [16, 40].

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 3.5.

Chapter 2

Physics for biology

-"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 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."

-"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. Scrödinger: What is life?[14] @1992

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'. Scrödinger 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 form of physical laws describing the 'extraordinary' (in our reading: non-disciplinary) behavior of living matter. No doubt, the basic notions and terms need to 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 analyzis to do so. We need to 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, maily electricity, which was worked out for homogenous, 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.

In his very accurately formulated question, Schrödinger focussed to (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 it in the labs. Those laws are extraordinary '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 by processes which have material carriers, which change their positions with finite speed, so (unlike in classical mechanics) the events have also the characteristics 'time' in addition to their 'position'. 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).

- '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.

- 'accounted for by physics'[by extraordinary laws] We are used to abstract and test a static attribute, and we derive the 'ordinary' laws of motions for the 'net' interactions. In the case of physiology, nature prevents us to test 'net' interactions. We need to 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. To describe the dynamic behavior of living matter, we must introduce a dynamic description.

- 'yet tested in the physical laboratory'[including physiological ones] simply means that we need to test those 'constructions' in laboratories, in their true environment and in 'working state'. As we did it also 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'.

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 *classic physics for non-biological matter* and less complex interactions. We attempt to provide a holistic picture, from a physical point of view, which physical components cooperate. 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. Here we scrutinize the basic notions and discover some differences between physics and biology as consequences of the required different abstractions and approximations.

In this chapter we derive the needed 'extraordinary laws', which are derived by 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 interations 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 using the appropriate approximations for the biological cases we can derive those 'extraordinary' laws of physics. Which laws are more complex to derive and we need to 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; that is all.

2.1 Introduction

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 that contradict each other if 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 at the same time, different science fields, and their interplay. "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".[52] 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 of the language, and even that humans already discovered the needed piece. For example, mathe-

matical calculus (integral and differential) was invented mainly for the practical needs of analyzing spatial motion of bodies. Similarly, Minkowski's mathematics theory proliferated widely [53] only after inventing the special theory of relativity. Although the mathematical description was developed earlier, there was no practical need to apply it. The classic 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.

Math 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 classic 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 of 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 are described by them 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.

Science, unfortunately, is separated into classic 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 [54] (using the speed of light as the value for its external parameter). Still, the Minkowski-mathematics [55] 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.

Classic physics is based on the Newtonian idea that everything happens simultaneously; space and time are absolute. Consequently, if its objects interact, their interaction must be instantaneous; in other words, their interaction speed is infinitely large. Furthermore, electromagnetic waves with the same high (but finite) 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. Fur-

thermore, 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.

Still, we need a different abstraction (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 to be able to explain some details; which are naturally explained by assuming finite interaction speeds and their combinations.

2.2 Abstractions& approximations

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. For example, 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.

Biology, and especially neuronal operations, produces examples where wrong omissions in the complex processes results in absolutely wrong results. In those cases some initial resemblance between our theoretical predictions and our phenomena exist, 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" [7]. 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 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 excercised. We give a short review of history and kinds of interaction speeds.

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. Given the vital role of charge and current in neuronal operation, we give their precise interpretation. Special emphasis is given to the true interpretation of conductance, one of the central terms in biology.

2.3 Speeds

Considering the role of the time, space and matter is the subject of endless debates in science. Considering finite interaction speeds is against using a "nice and classic 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.

2.3.1 Speed of light

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.

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 [56]. Although Newton surely knew that the observation speed was finite, in his "Philosophiae Naturalis Principiai Mathematica" [57], 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 [58] 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 [55] 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* [59] 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.

2.3.2 Speed in neuroscience

Helmholtz, in 1850, sent a short report off to the Academy [60] "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" [61].

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 [62] 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' [34].

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

[27]. (Notice that it is a consequence of the wrong oscillator model hypothesized by Hodgkin an 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".

2.3.3 Finite-speed interactions

When speaking about speed, especially the speed of charged objects inside neurons, 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 [1]) 10^{-2}; diffusion speed of electrons in a wire 10^{-4}, current 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 [63]) 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.

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.

Considering the finite field propagation speed requires revisiting the fundamental physical laws. The famous Coulomb's Law (in a Lorentz-transformed form) should be written as

$$\frac{F(t)}{Q_1} = k\frac{Q_2}{r^2}(t-\frac{r}{c}) \tag{II.2.1}$$

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. 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 2.7.1, using a wrong definition of current means assuming 'instant interaction', that is, that neural signals propagete 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

$$I_{out}(t) = -I_{in}(t-\Delta t) \tag{II.2.2}$$

We can calculate the delay time Δt (in a slightly simplified form) classically, from distance r along the path of the current and the macroscopic speed v of the current. Let us consider a 30 cm current path (a wire). The time delay is in the *nsec* range for EM propagation speed, but it is in the 10 *msec* range for the speed calculated from the telegraph equation and measured in metallic wires; furthermore, in the case of axonal current [7], on a 0.3 *cm* distance, it is in the 0.1 *msec* region. Inside a neuron, the current is so slow that the peak-to-peak temporal distance of an AP at different places inside the neuron is several times more than the temporal length of the AP, see Fig. 3f in [1]. *We must not describe the axon or the membrane with the usual 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.* For its exact interpretation see sections on axonal charge delivery

and on the true membrane current, Fig. 3.16, 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).

Using the cable equation, as Hodgkin and Huxley attempted [7], 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).

2.3.4 Mixed speeds

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 classic 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 electric 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.

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 [64]. Telegrapher's

equations (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 [65, 22].

Science uses 'instant' in the sense that one interaction is much faster than the process under study; we use the notion in that sense and consider the faster interaction as instant. The approach of classic 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, we put together a *series of stages* to describe the observed complex phenomena observed, 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.*

2.4 Spatiotemporal

Will be based on [23, 67, 68]

2.5 Resources

Co-existing processes my affect each other by changing resources: change in one quantity changes the other. Methematics descibes such processes by linked differential equations. A known mathematical example is the "predator-prey" equations.

2.6 Electrodiffusion

It has been a long-standing mystery in electrodiffusion 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 use the Laws about strictly pair-wise interactions.* They have no choice: there is no formalism to handle non-equal speeds.

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* 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 [66] 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, is 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.

To describe the interrelation of these two effects, we need to conduct case studies and apply casual approximations. We are at the boundary of microscopic and macroscopic worlds, and we must consider different interactions with different speeds to describe the phenomena, which are neither purely microscopic nor macroscopic and where more than one abstraction must be used. Still, they show the behavior of both worlds; furthermore, they change their behavior during the studied process. It is important to remember that we are dealing with a mix of macroscopic and microscopic descriptions, and this understanding is a crucial aspect of our research.

2.6.1 Thermodynamics

We are at the boundary 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 'extraordinary' behavior and one can conclude 'extraordinary' laws when does not use the appropriate approximation(s). We need more careful handling (and more 'extraordinary' laws) if we consider the interactions in a finite volume, with strongly different conditions on its boundaries.

As we discussed we can handle atomicity in different abstractions, as chargeless or massless points, and can derive laws for a single interaction, see Newton's Law and Coulomb's Law. The 'physical points' (having charge and mass) can be abstracted as the behavior that there are *two* underlying interactions; correspondingly it has less simple laws of forces and motions. The macroscopic

features (such as pressure, temperature, potential and concentration) of systems of physical points are interpreted as statistical quantities and their laws are discussed by the scientific discipline thermodynamics. Its notions drastically differ from the ones of classical fields. Here the 'temperature' is a generalization: a homogenouous distribution means that the physical quantities (such as momentum and energy) have a well established distribution instead of uniform values of those 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 "speed", 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 homogenity is a dynamical one: particles movement changes it continuously and it is constant only as a statistical average.

The distribution, however, can be calculated for chargeless 'mass point's only. The interference of those forces and that they affect two different features of the atomic particles leads 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 provided mathematical equations of the fourth law of motion in thermodynamics. The experimental verification [69] of that law mentions "the well-known difficulty of carrying out these experiments". Using our mathematical relations between the electrical and chemical diffusion, we can overcome that experimental difficulty. The significance of our Our Eq.(II.2.17) is, that one can derive the speed of electrodiffusion in electrolytes, which are otherwise not measurable ("hopping in a breeze": 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).

According to Wikipedia, "the Onsager reciprocal relations express the equality of certain ratios between flows and forces in thermodynamic 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) [70] 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. Our approach results in a more realistic approach to the ion transport problems, in many areas; in addition to biological systems, also for semiconductor devices and nanofluidic systems.

In our research, the key point is that life (including neural processes) is based (mainly) on electrodiffusion 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 three 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 in the stage, and we can work out a physics-based approximation that a mathematical formalism can describe.

2.6.2 Electrolytes

In biology, the electrolyte solutions do not surely satisfy the conditions we use notions of electricity in physics, see section 2.7. The number of charged objects (the ion concentration) may change in time, and a chemical driving force may also move the objects independently from the electric field. When measuring only the macroscopic electric parameters voltage and current (measuring current believing we measure directly conductance; in addition, measuring it in a wrong way), *we attribute the injected charge carriers' low propagation speed to the medium* when describing the phenomenon that "the conductance changes" in the function of the voltage [45]. (BTW: conductance is a "steady-state" notion; see its definition in section 2.7.3 and in section A.3.12 in [3]: "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" [8]. *Using quickly changing (alternating) currents, either sinusoidal or random for measuring conductance, measures some ill-defined current.*) The measurement must be fixed: the tacit assumptions above must be fulfilled.

Biologists are "resetting the clock", instead of admitting that the current speed is finite. 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: we abstracted the notion of conductance for conductors. Physics describes biological operations perfectly. 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. *Using the Newtonian 'instant interaction' as the drift 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). In biological systems, it is not necessarily the case: the drift speed of ions or the

macroscopic speed of ionic current conveying electrostatic interaction is very low, and so they may follow the electric field propagation apparently with a time shift (if they are improperly distributed, as was explicitly noticed [7]). However, as Fig. 3.17 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. One should *measure* the voltage instead of *assuming* the potential appears immediately, even without charge carriers. Furthermore, one should not introduce a foreign voltage into a system (by measuring its conductance) when studying the electric features of that system.

Another major 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 [7]: "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. (II.2.28)), 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 III.3.14, this effect may lead to conclusions opposite to the real ones.

2.6.3 Laws of motion

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 electromagnetic and gravitational interactions are finite, we can use the 'instant interaction' approximation in classic 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. 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 actually 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. It's important to remember that we are dealing with a mix of macroscopic and microscopic descriptions, and this understanding is a key aspect of our research.

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, 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. In both abstractions, they attempt to distribute as equally as possible in a given volume. 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.

When an electrolyte is contained in a closed volume, the ions exist in a state of thermal and electric equilibrium. In the absence of external influences or a separating membrane, both gradients are balanced and at zero. In this scenario, the 'carrier' - the ions - can be influenced by two different types of interactions, each represented by a distinct abstraction in these processes.

One can parallelize describing how objects change their position in physiology with how Newton's laws of motion relate an object's motion to the forces acting on it. The first and third law are *static* ones, the second one is *dynamic*. We can translate the first law to electrolytes that without external invasion, a solution at rest will remain at rest. The third law, for electrolytes, essentially states that in a solution at rest the electric and thermodynamic forces are equal; this is expressed by the Nernst-Planck electrodiffusion equation. 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.

For electrolytic solutions, 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 subfields. 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, physiology cannot describe the electrochemical processes: *the second law of motion for electrodiffusion is missing*. As a consequence of the instant interaction, classic 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 subfields) translate the force into acceleration.

2.6.4 Steady state

In electrolytes, 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. The 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 an electrolyte (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. Two driving forces act on the ions: thermodynamically and electrodynamically. In a steady state, at every spatial point of the segment, the two driving forces are equal, and the ions will not move. We can describe the equilibrium state (the mutual dependence of the *spatial gradients* of the electric and thermodynamic fields on each other) using the *Nernst-Planck electrodiffusion equation*

$$\frac{d}{dx}V_m(x) = -\frac{RT}{q*F}\frac{1}{C_k(x)}\frac{d}{dx}C_k(x) \tag{II.2.3}$$

It is discussed in good textbooks (see, for example, [8], Eq (11.28), where its derivation is exhaustively detailed). In the equation, x 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, $V_m(x)$ the potential, and $C_k(x)$ 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 the field's propagation speed. Where the notion of propagation speed was introduced, the speed is identical for all interactions.

Eq.(II.2.3) 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 a semi-quantitative handling using physical principles. We consider the electric ion current represented by viscous charged fluids [71]. As expected, selecting the speed (aka calculating the appropriate value of the macroscopic speed, see Eq.(II.2.30)) plays a key role, especially since we are at the boundaries of physics abstractions; furthermore, we are mixing microscopic and macroscopic notions. The actual speed model depends on the concrete case; see section 2.7.1.

2.6.5 Time derivatives

There exist attempts to interpret the task of transporting ions under the effect of several interactions with different speeds (for a review, see [70]). 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 [8] 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.*

When describing processes (i.e., dynamical systems), we must have one or more equations of motions (aka changing speeds). In classic science, the (Newtonian) laws of motion do not include a time-gradient. In the Einsteinian world, velocity explicitly appears when describing the interrelation of basic entities mass, position, and time. In classic 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 electrodiffusion interactions. In the classic ('instant interaction') science, the time derivatives are either not interpreted or can be derived through the externally derived joint interaction speed. 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 classic 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 carrier of the force fields are continuous, so one can calculate and make infinitesimal changes in the driving forces; they do not change system's energy. If one gradient changes, the other automatically changes in the opposite direction. In another words: the driving forces are permanently balanced, the magnetic and electric 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 electrodiffusion process, we essentialy start with the same point of view. We assume that the thermodynamic and electric 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 macroscopic potential. On the other side, we use another macroscopic parameter, the macroscopic concentration. The equation bridges those macroscopic parameters by using universal constants from the microscopic world. However, unlike in the case of electromagnetism, we cannot make infinitesimally small changes in the gradient since the carrier of the force fields is "atomic". Furthermore, moving it infinitesimally (changing only its position coordinates), the changes in the electric and

thermodynamic gradients do not result in a new balanced state: the effect of ion's *charge* has an immediate effect in 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 and we did not consider that the time changes. In the newtonian world, everything happens at the same time so we cannot handle instant and finite interaction speeds simultaneously. The infinitesimally small change disappears only when the slower interaction reaches the other carriers in the volume. *When the interaction speeds are different, the energy conservation is valid only if we use space-time.*

Fortunately, we can derive the infinitely small change in a way 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 negigible. 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 one that moves together with the ion. In the second frame, no ionic movement takes place along the direction of movement. In line with that the speed of the light is independent from 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), in the second one it is dynamically balanced (the gradients change to keep the ion in rest). *The gradients the moving ion experiences are the ones that the standing ion experiences at another time (depending on its speed). In this way, we can provide the needed time course of the process.*

Compared with the electromagnetic case, we see three crucial differences. One, the mass' propagation speed is millions of times slower than the charge's propagation speed. Two, the moving ion represents mass transport and moving charge (electric current) simultaneously. Three, 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 electric and magnetic driving forces are equal, whatever time is needed to reach that balanced state. In contrast, in electrodiffusion, the velocity changes concentration gradient, and, simultaneously potential gradient.

We assume that equation II.2.3 is valid for a given time t. At time $t + dt$, in another steady state, the two interactions manifest at different times: we have

$$\frac{d}{dx}V_m(x + v(x) * dt) = -\frac{RT}{q * F}\frac{1}{C_k(x)}\frac{d}{dx}C_k(x) \tag{II.2.4}$$

or, equivalently, it can be expressed as

$$\frac{d}{dx}C_k(x - v(x) * dt) = -\frac{q * F}{RT}C_k(x)\frac{d}{dx}V_m(x) \tag{II.2.5}$$

The concentration at position x determines the potential (apart from an inte-

gration constant) at position:

$$dV_m(x) = dx * \frac{d}{dx}V_m(x) = -dx\frac{RT}{q*F}\frac{1}{C_k(x)}\frac{d}{dx}C_k(x) \tag{II.2.6}$$

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

$$\frac{d}{dt}V_m(x) = v(x) * \frac{d}{dx}V_m(x) = -v(x) * \frac{RT}{q*F}\frac{1}{C_k(x)}\frac{d}{dx}C_k(x) \tag{II.2.7}$$

or

$$\frac{d}{dt}V(x) = \frac{D*R}{F} * C(x) * \frac{dC}{dx} * \frac{RT}{q*F}\frac{1}{C(x)}\frac{d}{dx}C_k(x) \tag{II.2.8}$$

Since

$$v = -\frac{D*R}{F} * C(x) * \frac{dC}{dx} \tag{II.2.9}$$

$$\frac{dV(x)}{dt} = \frac{D*R*R*T}{q*F*F} * C(x) * \frac{dC(x)}{dx} \tag{II.2.10}$$

$$\frac{dV}{dt} = \left(C * \frac{T*R^2}{q*F^2}\right) * D * \frac{d^2C}{dx^2} \tag{II.2.11}$$

Given that

$$\frac{dV}{dt} = D * \frac{d^2C}{dx^2} \tag{II.2.12}$$

expresses Fick's Second Law of Diffusion, we can derive the ratio between the electric and thermodynamic temporal gradients.

As section 2.8 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, see equations II.2.38 and III.3.6, which directly consider the current production mechanism. Similarly, at time $t - dt$, in another steady state, we have

$$dC_k(x - v(x) * dt) = dx * \frac{d}{dx}C_k(x) = -dx\frac{q*F}{RT}V_m(x)\frac{d}{dx}V_m(x) \tag{II.2.13}$$

$$\frac{d}{dt}C_k(x) = v(x) * \frac{d}{dx}C_k(x) = -v(x)\frac{q*F}{RT}V_m(x)\frac{d}{dx}V_m(x) \tag{II.2.14}$$

2.6.6 Fick's Law

By expressing the speed through the Stokes-Einstein relation, see Eq.(II.2.33)

$$\frac{dV}{dt} = \frac{D*R*R*T}{q*F*F} * \frac{d^2C}{dx^2} = \left(\frac{T*R^2}{q*F^2}\right) * D * \frac{d^2C}{dx^2} \tag{II.2.15}$$

Or, alternatively,

$$\frac{dV}{dt} = \left(\frac{T*R}{F}\right)^2 \frac{k}{6*q*\pi*\eta*a} * \frac{d^2C}{dx^2} \tag{II.2.16}$$

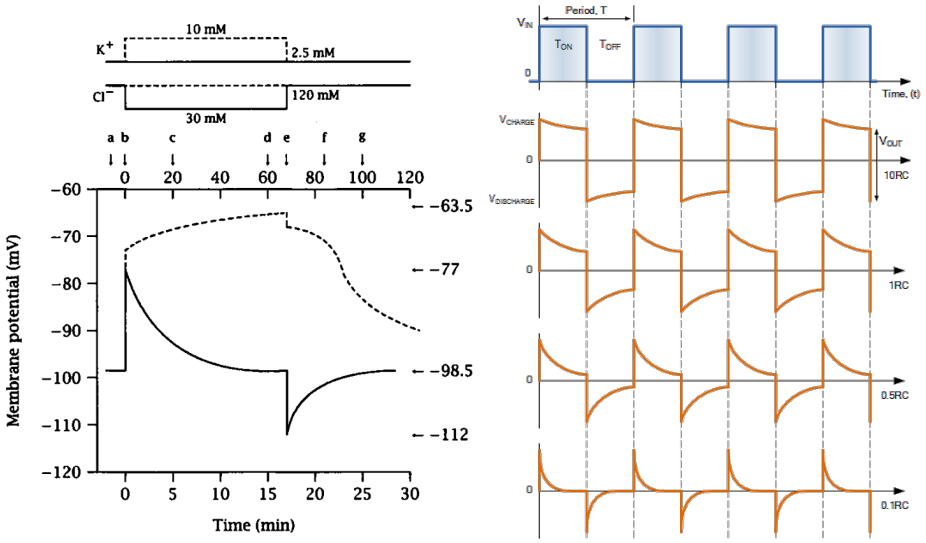


Figure 2.1: Left: The effect of applying *a square-wave-like concentration change* to membrane; Figure 2.2 from [3] Right: the effect of applying *a square-wave like voltage change* to an electric differentiator-type *RC* oscillator.

Given that as Fick's Second Law of Diffusion is expressed by Eq.(II.2.12), we can derive the ratio between the electric and thermodynamic temporal gradients, using values $T = 300\ K$, $q = 1$, $F = \ 96495\ A{*}s/mol$, $R = 8.31446261815324\ J{*}K^{-1}{*}mol^{-1}$

$$\frac{dV}{dt} = 2.23 * 10^{-6} * D * \frac{d^2C}{dx^2} = \mathbf{2.23 * 10^{-6}} \frac{dC}{dt} \tag{II.2.17}$$

2.6.7 Invasions

Concentration derivative

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. 2.1. According to Eq. (II.2.3), a negative square wave of the concentration change must provoke a drastic positive potential change, with a time course described by Eq. (II.2.7). The step-like change results in a step in the voltage, and according to the Stokes formula (see Eq. (II.2.30)) 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 [3], 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-ware 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 τ can be around 0.3 RC.

From the figure we can estimate that the "half width" of the *concentration-provoked* potential change is about 200 *sec*. (The experiment is not dedicated, we just read back data from a textbook figure.) In Fig. III.3.9, we see that the *electrically-provoked* potential gradient's half width is about 0.1 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. (II.2.17).0 If we assume that the propagation speed in the electrolite is $2 * 10^8$ m/s, we can conclude 10^2 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 derivative

2.6.8 Segmented electrolytes

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.

When thermal or electrical invasion happens, ion's distribution changes. 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. We must also discuss another fallacy that the structured biological objects behave as the metals do under the effect of electric 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 electric 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 symmetric due to 'Maxwell-demon'-like transmit gates (semipermeable membrane); and when a physical effect concerts the operation of the demons.

One segment

The electrodiffusion experience shows that reaching a steady state is a temporal *process*, and even the spatial and temporal development of the voltage/concentration gradient can be measured as individual processes. It is also evident from experiments that diffusion is a fast *process* and that the propagation of the electrostatic field is unimaginably fast (but must be process, too). In other words, we have two enormously different interaction speeds. Eq. (II.2.3) provides only position derivatives.

Electric invasion By introducing time derivatives by Eqs. (II.2.7) and (II.2.14), we can derive further terms that describe the relation between concentration and potential for the case when the first time derivative of the position coordinate is not zero. (Here, we explicitly parallel with the Lorentz transformation in the special theory of relativity: the presence of a speed-dependent term changed the essential behavior of the basic notions of mass, time, force, and so on.) In principle, we could introduce a $\frac{d}{dt}$ term as $\frac{d}{dx}\frac{dx}{dt}$ where $\frac{dx}{dt} = v$ (v is the interaction speed of the respective interaction). The practical difficulty is that the diffusion speed is smaller by several orders of magnitude than that of the EM interaction. However, what truly sets electrodiffusion apart is the absence of a direct equivalent of the Maxwell-equations. In this unique field, the chemical concentration and the electric field generate each other at different pace, presenting a fascinating departure from traditional physics.

In classic 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 'classic 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.*

Chemical invasion One of the worst consequences of using 'equivalent circuits' to describe the electric operation of neurons is believing that the currents in the biological circuit do not change the concentration, and through the concentration, also the potential. 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). 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 describe theoretically the physical background of the correctly measured 'transversal current' observed on the axons; 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 the neurophysical electric

processes, including their time course.

Another wrong consequence is that the two secondary abstractions 'potential', and 'current', became independent from the primary abstraction 'charge' and each other. 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 electric data pairs and the misconception that biological structures and materials must behave like metals.

Two segments

We can separate the volume into two segments by a thin isolating membrane. The membrane is thin; we assume the separating membrane is transparent for the electric interaction (the electric field affects the ions in the other segment on the other side of the membrane) but not for their masses (mechanically separates the segments).

Infinitely thin membrane When we separate the volume by an *infinitely thin* membrane, we actually do not affect the electric and thermal distributions in the now separated segments. Given that the electric potential of the ions can have its effect through the separating membrane and the thermodynamic collisions with the membrane are elastic, nothing changes. Although the exchange of ions between the segments will not be possible any more, no change is induced and the equation remains the same.

For the discussion below, we assume that a two-dimensional surface separates the volume and we discuss the gradient along a line, perpendicular to that plane surface. Actually, we discuss a one-dimensional distribution. Due to the presence of fellow charges, an ion at distance x from one of the surfaces experiences the sum of the forces of all charges, i.e.,

$$\int_0^{+\infty} z\frac{dV}{dx}(x) \tag{II.2.18}$$

force from one direction, which is counterbalanced by a similar force from the neighbors on the other side.

Membrane with a finite width Now let us separate the volume into two segments by a membrane with a finite thickness d, see Figure II.2.2. The membrane is a perfect isolator, i.e., no charge carriers exist between its two surfaces. In this way we separate the two segments by distance 1 (we measure distance in units of the thickness d when deriving the mathematical dependence, but use physical units in the figure), the first force is unchanged while second force reduces. In this way the net force at position x becomes

$$F_m \propto \int_0^{+\infty} \big(\frac{dV}{dx}(x) - \frac{dV}{dx}(x+1)\big) \tag{II.2.19}$$

Given that the potential is composed from those of the neighboring individual ions of form $\frac{1}{x^2}$, we assume that

$$F_m \propto (\int_0^{-\infty} \frac{V}{x}dx - \int_0^{+\infty} \frac{V}{x+1}dx) = -ln(x)\big|_0^{\infty} + ln(x+1)\big|_0^{\infty} \quad \text{(II.2.20)}$$

We use the approximation that $\ln(\infty) \approx \ln(1+\infty)$ and we arrive at that the

$$F_m(x) \propto ln(\frac{x}{x+1}) \quad \text{(II.2.21)}$$

As it is well known from the theory of electricity, separating charges creates an extra potential gradient and potential which are proportional with the potential and the concentration. That is, we need to assume that the extra potential along our line is described by a function of form

$$\frac{dV}{dx}(x) \propto F_{bulk}\big(ln(\frac{x}{x+d})\big) \quad \text{(II.2.22)}$$

Although from thermodynamical point of view the segments are isolated, the extra potential gradient invokes an extra concentration gradient change according to Eq.(II.2.3). Integrating by parts (using that $\int udv = uv - \int vdu$) we arrive at that the potential is

$$V(x) = ln\big(\frac{x}{x+d}\big)x - ln(|x+d|) + C \quad \text{(II.2.23)}$$

or in a different form

$$V(x) = V_o * ln\big(\frac{x}{|x+d| * (x+d)}\big) + C \quad \text{(II.2.24)}$$

Figure II.2.2 shows the membrane's extra potential gradient in function of the distance from the membrane's surface for three different bulk potentials (i.e., different concentrations). Here, we use physical length units (instead of the abstract distances used during the derivation) and an arbitrary voltage gradient scale. Suppose we assume the estimation given in [34] 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 microscopic worlds. We derived our integrand from the picture of discrete charges but integrated it into the picture of continuous charge distribution, so we have an empirical factor between them. 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.)

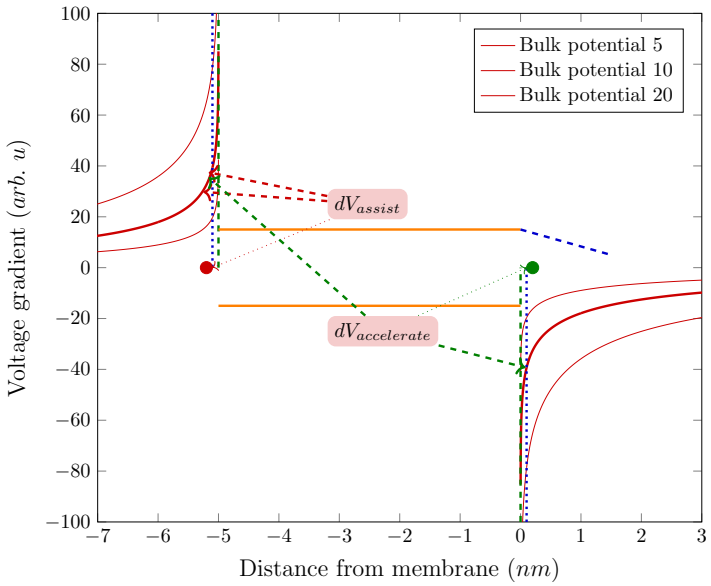


Figure II.2.2: The neuronal membrane's extra *potential gradient* in the function of the distance from the membrane's surface and the bulk potential. The thickness of the atomic layers proximal to membrane's surfaces are also shown.

We assumed that the membrane's width is 5 nm. An ion channel is depicted in the middle of the figure with a diameter of about 1.5 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 nm. For comparison, recall that the size of the tip of the clamp pipette is in the range of $1,000$ nm and the size of the soma in the range of $10,000$ nm.

The figure shows three different bulk concentrations, so one can estimate (using non-matching diagram lines) what happens if the concentrations change between the two segments (although their interaction slightly complicates the process). The bulk concentration naturally changes the potential, so a difference in the potentials can be measured. However, this may be the voltage between the bulks, one bulk and one layer, or two layers. When measuring potential in the segments using such a pipette and touching the membrane one actually may measure some average potential which contains only a tiny proportion from the layer, so the mentioned extra potential gradient cannot be measured by that method. Anyhow, the ion currents flow between the two layers under the potential, which can drastically differ from the bulk potential. Derived values,

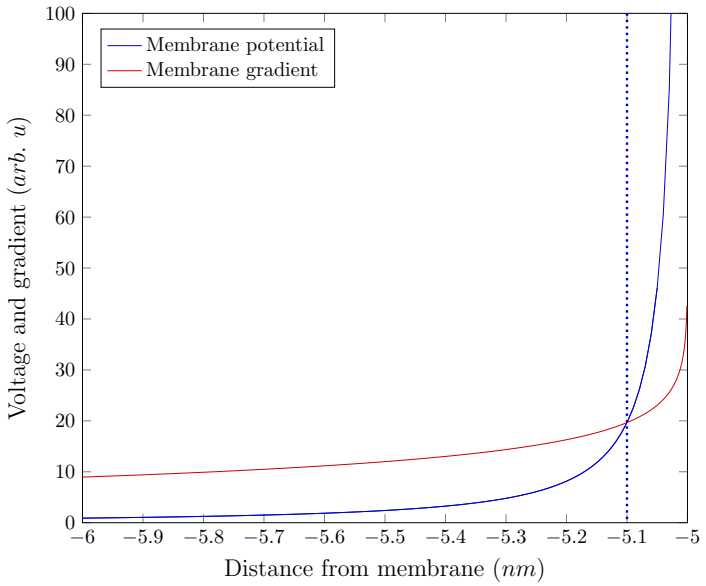


Figure II.2.3: The extra membrane potential gradient see Eq.(II.2.22) and extra potential Eq.(II.2.23) in the function of the distance from the membrane's surface. Also shown the assumed thickness of the 'atomic ion layer' . For illustration, a simple capped ion channel in the membrane's wall is also displayed, but its effect on the potential is not accounted for.

such as the GHK potential, should be rethought.

Simple invasion Separating a volume into two segments has no initial effects: the *bulk* concentration and potential remain the same on the two sides of the membrane. However, the finite thickness will result in a lack of balance near the surfaces of the membrane. Changing the bulk concentration or potential in one of the segments creates a corresponding gradient across the separating membrane (and also evokes new bulk parameters in the resting state). In the layers proximal to the membrane, the ions will experience an extra force. 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 in physical features the membrane represents, as we discussed above. (Notice, however, that while increasing the concentration in one segment means having an unlimited possibility of increasing bulk potential, decreasing it may be limited by the reduced number of charge carriers.)

The electric repulsion/attraction across the membrane will form two layers on the two surfaces: an ion-rich layer on the high-concentration side and an ion-poor layer on the low-concentration side. Here, refer to Fig.(II.2.2). We do not clone the figure, although the bulk parameters differ. The ions in the other segment do not counterbalance the repulsion force at the membrane, so the values of the local potential in the proximal layer near the membrane in the segment with the higher concentration will be above the one in the bulk of the segment and of course, the potential will also be higher. Similarly, the repulsion of the ions in the opposite layer will create an ion-poor layer on the low-concentration segment in the proximal layer near the membrane, with a changed thickness in the skin. However, the values of the local concentration and potential remain the same in the bulk of the respective layer.

The result is a condenser-plate effect: two layers are formed on the isolator's two sides where the charges' repulsion does not counterbalance the repulsion in the bulk of the corresponding segment. Fig. II.2.3 displays how the function shapes of the potential and its gradient change in the function of the distance from the membrane. 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). However, the smaller repulsion acts as a kind of attraction: it prevents 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. (II.2.3). The gradients change gradually within the segments and step-like across the membrane. Recall our remark above on the limitations of the thickness of the layers in proximity to the membrane, which also enforces limitations on the potential in the layer. No current can flow through the membrane; there is no leaking current.

We also need to notice the difference in the local gradients in the function of distance from the membrane's surface. If something changes, a dV_{assist} gradient appears between the layers and will rearrange concentration and voltage in the segment. Notice that this gradient is by orders of magnitudes smaller than the gradient $dV_{accelerate}$ which accelerates the ions in the proximity of the channel entrance (see the red ball in front of the entrance of the ion channel). According to the Stokes formula (see Eq. (II.2.30)), the corresponding speeds also differ by orders of magnitudes, enabling us to distinguish *potential-assisted* and *potential-accelerated* speeds, and correspondingly, speak about *'slow' and 'fast' currents* that the ions represent at a macroscopic level. 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 [1]), 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.

Membranes & layers

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 electrodiffusion 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 homogeneous. Gravity keeps it in place, and it is at rest. However, sometimes, for some periods, also other (thermodynamic and electric) 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. 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 membranes 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. As experienced, at some combination of their parameters, qualitatively

different phenomena happen, which, in the abstraction biology uses, are 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*. 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*. Using our approach, we may defy that "the emergence of life cannot be predicted by the laws of physics" [13].

Demon in the membrane

We can build 'Maxwell-demon'-like objects into the separating membrane: a gated ion channel, see Fig. (II.2.2). Under certain conditions, it can be opened in only one direction and only for a limited period, and 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 can go somewhat closer to the other segment (the local concentration and potential may get somewhat higher on the high-concentration side, with the corresponding changes on the other side of the cap), but they 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. It only keeps one way closed for part of the time, and the voltage performs selecting the ions.

Voltage sensing "Voltage sensing by ion channels is the key event enabling the generation and propagation of electrical activity in excitable cells."[72] 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" [73]. Usually, a "sliding helix" (structural) model is assumed. Using our model, we can easily interpret why the voltage-controlled ion channel gets opened due to purely electrostatic reasons. The cap and the membrane are isolators and the adhesion sticks them firmly to each other. They work as the two plates of a 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).

When ions appear in the layer, the mutual repulsion between the membrane and the cap opens the cap, which is connected to the membrane only at one point. The fluctuation of the voltage gradient due to 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 on the cap and the membrane regulates), as observed.

Given that the membrane and the cap are isolators in a resting state, no electric repulsion is evoked between them. However, when a current flows into the surface layer, they both get covered by a very thin electric skin. As described above, the ions keep a distance due to their mutual repulsion. Given that the cap and the membrane are joined only at one point and the cap is slightly elevated, the repulsion force may have a component in the direction of lifting the cap. The gate remains open as long as the local charge distribution enables it.

Passing through the ion channel 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 $100,000\ V/cm$" [34]. That enormous gradient, comparable to that of electrostratic particle accelerators, "snorts" the ions from the high-concentration side into the low-concentration side and causes a process "like a flee hopping in a breeze" . Recall that, in physics, the *drift speed*, the *electric repulsion-assisted speed,* and the *electric potential-accelerated speed* of ions differ by several orders of magnitude (for visibility, the ratio of the gradients in Fig. II.2.2 is not proportional). Consequently, "transport efficiency of ion channels is 10^5 times greater than the fastest rate of transport mediated by any known carrier protein" [34].

The accelerating potential gradually (but quickly) disappears when the particle exits the ion channel (see the green ion in the figure), and the ion returns to 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, 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" [34].

The snorked ions "hop" into the layer. In the beginning, with their *voltage-accelerated* speed, it could take less than $\frac{5*10^{-9}m}{10^3 m/s}\ s$ to pass the channel (simulation [74] 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 $\frac{5*10^{-9}m}{10^{-1}m/s}\ s$), 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. On the low concentration side, 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 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 side's potential due to the accelerated current's 'ram pressure' (or 'impact pressure'). Due to their electric repulsion, the ions induce a similar change on the opposite segment.

Delivering current between layers The passage is too quick to affect the bulk (see also the discussion in section 3.2.1), 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. 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 ions saturate the layer 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 (we assumed 10 nm 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 [6], see Fig. III.3.9, which time is prolonged up to 10 ms by the neuronal RC circuit; the ions are slow when the voltage on the is low, see Eq. (II.2.30). Assuming those distances and speeds, including the *potential-assisted* speed of the slow current, we are on a time scale matching the available observations.

Role of ion channels The channels operate as demons (from the point of view of the segments). Some power opens them and the two layers autonomously transfer ions in a *potential-accelerated* operating mode, and then the power puts the cap back on the top of the channel. Even the channels can recognize the ions' chemical nature and transmit only a selected ion type. During a continuous current transfer by a population of ions, the channels can stochastically open, close, and re-open. Notice that the channels are passive during those processes, although the enormous voltage gradient can rearrange their structure and change their behavior through that. 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.*

The demons also concert their actions using the layer containing charges as a communication medium. 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 [44]) in 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 [41].

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^+ [34]". The two ions have the same charge, but K^+ is nearly 70% heavier than Na^+, a definite disadvantage when accelerated by a vast electric 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 pass 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.

Given 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), and they simply go back due 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.

2.7 Electricity in biology

The phenomenon that the body operates with electric signals was discovered about one and a half century ago [61], 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" [4] 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" [4]. However, at that time physiologically defined fine details were not known. 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" [3]. In this section, we proceed along the line pointed by those latter authors in Chapter 2 of their book. However, we must recall that *this charge is delivered chemically, i.e., it is the result of an electrodiffusion process.* We will not repeat that chapter but will cite their sentences (without giving the source) where we supplement their approach.

Although it is basically 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", furthermore, the electric gradient becomes more role than presumed. 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' current 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.*" [3], Appendix A. We do not want to repeat the content of that appendix, except some points where we add notes, correction or pinpointing.

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." [3]

2.7.1 Current

The correct definition of current is a differential one: $i = dq/dt$, as given by A.3.4 in [3]. A.3.5 in [3] correctly defines that "Ohm's law states that the ratio of voltage to current is a constant: $R = V/i$". By measuring the two charge-related entities one can derive the *"resistance", the opposion of material to current; an attribute of the medium* where the measurement is caried out. *As was observed in science, charge conserves, also in biology.* The law expresses *charge conservation at any point, in a differential form. However, it is not valid as an integral.*

The other way round, as given by Eq. (1.4) in [8], 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*)." [8] *It is straightforward, but, unfortunately, it is not true.* It 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 such as on the membrane or axon or exit to a non-measured segment in the system) or "created" (enter from a non-measured segment such as through ion channels) or be distributed within the "wire" such as on the surface of the dendritic surface. We measure current or voltage (show temporal behavior) but the experience shows that the charge (the current integrated for time and space in the appropriately chosen measured system) instead of the current itself which conserves. As was discussed early also in biology, "the amount of the substance" is what conserves, instead of its derivate as assumed in that wording. *Mismatching current and its derivative misguides understanding neurophysical phenomena.*

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 exists 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 values 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.

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, the incoming charge equals outgoing charge. The non-differential definition contradicts charge conservation and also, contradicts itself. Actually, *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 on the charge itself.* Kirchoff's law expresses charge conservation and it can be interpreted as current conservation only if the electric interaction is instant and the the measured system is closed (or complete).

On a microscopic scale, a charge creates a potential field and that field acts on another charge. In a conducting wire, 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 $dQ = q*n*A*dx$. If the charges move with a macroscopic speed $v = \frac{dx}{dt}$, at macroscopic level, we define the current I as the charge moved per unit of time as

$$I = \frac{dQ}{dt} = q * n * A * v \tag{II.2.25}$$

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 needs an external or internal force field. However, notice that the fellow charge carriers in the current also affect the speed, see also section 2.7.5. 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, in the biological half, ions. We must convert the charge carrier there and back, furthermore, consider its possible side effect. 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. 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 simultanously. 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" [3]. So are

some definitions, too. Definitions and measurements, which are not accurate, conclude in wrong results. They may be precise, but they are not accurate.

Current's speed

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

$$F_d = 6 * \pi * \eta * a * v \tag{II.2.26}$$

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

$$F_e = k\frac{dV}{dx}q \tag{II.2.27}$$

with a constant speed v. It is not the *drift* speed: because of the electric repulsion, it is a *potential-assisted* 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_e, that is :

$$I = \frac{k * q^2 * A}{6 * \pi * \eta * a} * n * \frac{dV}{dx} \tag{II.2.28}$$

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*. However, 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.

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

$$I = \frac{C(x) * A * dx * q}{dt} = C(x) * A * q * v \tag{II.2.29}$$

Combining equations II.2.28 and II.2.29:

$$v = \frac{k * q}{C(x) * \eta * 6 * \pi * a} * \frac{dV}{dx} \tag{II.2.30}$$

The higher the potential's space derivative and the fewer ions that can share the task, the higher the speed. We hypothesize (it needs a detailed simulation) that in the case of this charged fluid, the electric repulsion plays the role of 'viscosity'.

The higher the charge density, the stronger the force equalizing the potential; so η 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 voltage. 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:

$$D = \frac{k * T}{6 * \pi * \eta * a} \tag{II.2.31}$$

so we can express the speed with diffusion coefficient

$$v = \frac{D}{T} * \frac{q}{C(x)} * \frac{dV}{dx} \tag{II.2.32}$$

or alternatively

$$v = -\frac{D * R}{F} * C(x) * \frac{dC}{dx} \tag{II.2.33}$$

In the equation, x 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, $V(x)$ the potential, and $C(x)$ the concentration of the chemical ion.

Models in neuroscience (as reviewed in [42]) 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" [7] 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 2.3, 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 range of validity. 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 2.3.4 discusses, when force fields having different propagation speeds are mixing, special calculation methods must be used.

As we discuss below, in electrolytes, two forces may act on the ions, and their balance may drastically the phenomena we can observe. When the two forces are balanced (either globally: not 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 electrodiffusion gradient change: a current inflow changes both concentration and potential gradient), the ions accelerate to their Stokes-Einstein speed (see Eqs. (II.2.32) and (II.2.33). 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 speed differing by several ordes or 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 d the limited speed

2.7.2 Time relations

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 [43, 44] in the membrane's voltage. We know that the charges on its surface can flow out only through the ion channels [1] 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 [1]. *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 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 glsAP in this approach.*

The "point representation" model results in a wrong parallel with the *"integrator-type" RC* electric circuits: by assuming distributed 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" 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 [1]. 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 to 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) 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 2.7.1), 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. (III.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 3.3.3 and Figure 3.5. We can also derive

$$v_{AIS} = \frac{V_{AIS} - V_{rest}}{R * A * n * q} \tag{II.2.34}$$

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:

$$\frac{dV}{dt} = \frac{A * n * q * v}{C}; \; \frac{dV}{dx} = \frac{dV}{dt}\frac{dt}{dx} = \frac{A * n * q}{C} \tag{II.2.35}$$

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 Law. 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. (II.2.34). 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 [44] 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' [46]).
- 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. 3.15); 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. 3.17), and they are filled in their steady state (at beginning discharging), producing entirely different temporal behavior ("changing conductance").

2.7.3 Conductance&impedance

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." [4] 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 (see also the beginning of this section). 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

Charge is the primary abstraction in connection with electrical terms. Charge generates a potential field, and its movement generates current (furthermore, electromagnetic waves). When those secondary entities interact with some macroscopic material, their relation to that material defines some 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).

To measure conductance, we must generate charge: we must apply some voltage to the medium and measure the current with which the medium responds. The fact is known in neurophysiology (but either forgotten or not understood), see [3], 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 [75]. 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 field 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, 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, and measuring conductivity actually means measuring current, see section 2.7.1. Somehow, researchers forgot this warning and attibuted 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 ion inflow, moves the ions it produces, and measures the resulting output current.* Recall Eq.(II.2.28): 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 [7] 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). 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.

2.7.4 Currents in layers

As we detailed, the ions change their location during the observed potential changes.

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.(II.2.3) 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 [8]. 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)

$$I_{Drain} = I_o * \exp(-\frac{1}{\beta} * t) \tag{II.2.36}$$

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 [50, 51] in the case of axons (later on the membrane), or on a resistor, see the AIS [76]. 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 3.3.3, 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, 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 [77].

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

$$I_{source} = I_o * (1 - \exp(-\frac{1}{\alpha} * t)) \tag{II.2.37}$$

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)

$$I_{out} = I_o * (1 - \exp(-\frac{1}{\alpha} * t)) * exp(-\frac{1}{\beta} * t) \tag{II.2.38}$$

The voltage's time derivative describing the current in a system with source and current, needed for the biological law of motion (see section 2.6.5), is given by Eq. (III.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. III.3.9). 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 [6] is reproduced in our Fig. III.3.9. 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.

2.7.5 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 the 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. 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. The mutual repulsion is unbalanced at the edge of the spike (and recall that

the rising edge of the current is exponential). However, so the ions can move toward the end of the axon (the membrane) and the ions notice (with the speed of the electric interaction) the potential gradient created by the lack of those ions. Given that the potential-assisted speed is by orders of magnitude lower than the speed of the electric interaction, *the axonal current propagate in the tube at the potential-assisted speed*. The charges can be observed as the potential they generate propagates along the axon.

Notice that it is *not* a classic longitudinal current under the effect of some external potential. Here the the proceeding charge gradient generates a voltage gradient and since they are opposite. it simply generated (The classic modell 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 accomodate to the spike's current intensity at the places of the channels; given that the total charge delivered by the spike remains the same during the axonal delivery.)

2.7.6 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 V/m gradient [34]. The value of the force acting on a unit charge is

$$F_{Na^+} = 10^7 * 1.60217663 * 10^{-19} = 1.6 * 10^{-12}\ N \tag{II.2.39}$$

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

$$a = \frac{F_{Na^+}}{m_{Na^+}} = 0.42 * 10^{14}\ \frac{m}{s^2} \tag{II.2.40}$$

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

$$t_{traverse} = \sqrt{\frac{2 * 5 * 10^{-9}}{0.42 * 10^{14}}} = 1.54 * 10^{-11}\ s \tag{II.2.41}$$

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

$$v_{Na^+} = 0.42 * 10^{14}\ *\ 1.54 * 10^{-11} = 600\ m/s \tag{II.2.42}$$

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

$$I_{channel} = \frac{10^3 * 1.60217663 * 10^{-19}}{1.54 * 10^{-11}} = 10^{-5} A \tag{II.2.43}$$

(The thermal speed is about an order of magnitude higher. It is in the range of several μAs, for a short period. It is distributed in the spatiotemporal surface of a neuron, and contributes to a current of dozen of pAs.)

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 the molecular transitions. It is highly unprobable, that it can happen 10^3 times reconfiguration of long molecule chains can happen in such short periods.

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

$$a = \frac{F_{K^+}}{m_{K^+}} = 0.246 * 10^{14} \frac{m}{s^2} \tag{II.2.44}$$

With this acceleration, the K^+ ions traverse in the 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 uncomparably 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 2.7.6.

The huge forces and accelerations means that change 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 speed.

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 10^3 ions per channel. For all channels, in the order of 10^4 channels on the membrane, the number of ions appearing (suddenly, in *psec* time per channel (see section 2.7.6) 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 Nernsnt-Planck equation could explain that the concentration gradient causes a potential gradient, i.e., explain why 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 ha ving 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 [8]: we assume 100 pF capacitance and 100 $M\Omega$ resistance (i.e., $\tau = 10^{-2}$ s). If we assume that the charge flows out in a period of 10 ms, we should measure a 160 pA current on the axon, furthermore, that current causes a 160 mV voltage drop (aka Action Potential) on the resistance. 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 (II.2.3), 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} mm^2 and thickness say up to $10 * 10^{-9}$ m. With those numbers we arrive at that in that layer the ion density during generating an action potential is 10^{23} 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 describing why an AP evokes in a neuron.

Rush-in concentration

As we described in section 2.6.6, this sudden concentration change provokes a voltage gradient as described by Eq. (II.2.17). From that point on, gradients $\frac{dV}{dt}$ and $\frac{dC}{dt}$ excite each other, as described by Eqs. (II.2.4) and (II.2.5). 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 at the AIS. Here the ion channels represent a resistance (also limits the current), so a current starts, see section 3.3.4, 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. (II.2.9) 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 approprite parameters behaves as a damped RC circuit.

Layer speed

We assume that two Na^+ ions are at a distance of 10 nm. The force between them is

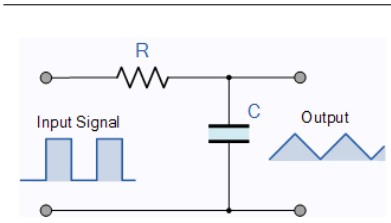
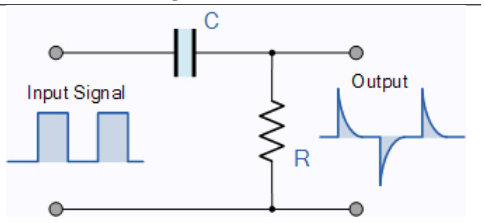
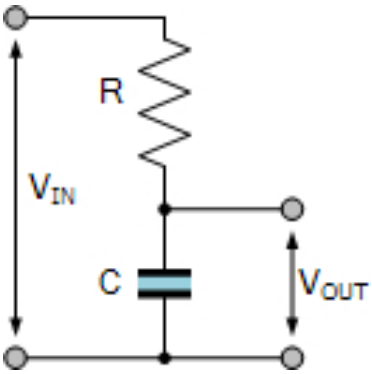
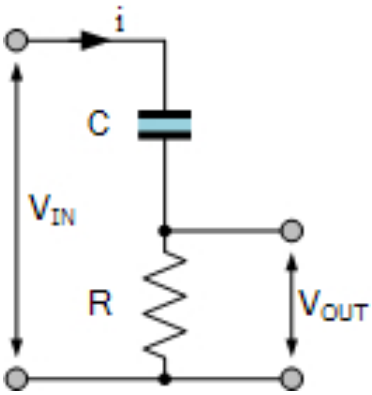
$$F_{Na^+} = \frac{1}{4 * \pi * \epsilon_o} \frac{q_1 * q_2}{r^2} = 9 * 10^9 \left(\frac{1.60217663 * 10^{-19}}{10^{-8}} \right)^2 = 2.311027 * 10^{-14}\ N \tag{II.2.45}$$

2.8 Oscillator

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.

The simplest oscillators comprise only a resistor and a capacitor. Beause 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 ot their ends, leaving only two options how to connect the input an output signals to them. Correspondingly, we can produce a parallel or a serial connection.

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
	
	

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. In the case of an *integrator*, (connecting the elements serially) "the input is connected to a resistance while the output voltage is taken from across a capacitor"; in the case of a *differentiator*, "the input signal is applied to one side of the capacitor with the output taken across the resistor". Correspondingly, their output voltages are

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 mismatched 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) that their output is defined by the *time integral* of the input voltage (or current) or by its *time derivative*. 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 integrator and differentiator are entirely different assemblies from the same components (based on the abstraction that R and C are discrete elements and the wiring is an ideal conductor), as their differential equations and waveforms show; see table from the electric tutorial. Although they 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 most vital difference between those circuits (see also the figures in `https://www.electronics-tutorials.ws/rc`) is that their output is defined by the *time integral* of the input voltage or by its *time derivative. 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 3.3.3). 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 [27, 78], 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 2.6.5): the differentiator is the circuit, which can be described by the biological laws of motion, namely by Eq.(II.2.7).

As discused in section 1.4.2, we divide neuronal operation (generating an Action Potential) into stages. We have different physical models in the different stages of operation. We have changed the fake *integrator*-type *RC* circuit (see section 3.4.6) 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.

2.8.1 Integrator-type oscillator

As discussed in section 3.1.3, although the notion of AIS was already known at the time when HH [7] published their Nobel-prize winner suggestions, but its role was not known. The *RC* circuits were well-known electric elements with established theory. As detailed in section 3.4, 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

$$I = C_M \frac{dV}{dt} + I_i \tag{II.2.46}$$

In their picture, those *currents* control the operation of the neuronal membrane. The basic issue with their idea 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 [7] 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.

2.8.2 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. (BTW: this behavior explains why a large slope of the arriving spike [40] can trigger an instant spike: the large slope (much higher than a normal one) of the current induces a much higher voltage contribution around the point of arrival on the membrane, and so it alone can raise the local potential above the threshold voltage near to the junction, triggering the known mechanism.) The input voltage V_{IN} comprises different contributors, and the differentiation is linear; i.e., we shall sum up the different contributing terms linearly (compare our equation to Eq.(II.2.49))

$$\frac{d}{dt}V_{OUT} = \sum \frac{d}{dt}V_{IN} \tag{II.2.47}$$

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 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 derivate can be well approximated by a steep exponential function, see Eq. (II.2.38) (see the middle inset in Fig. III.3.4).

HH's original Eq.(1)

$$I = C_M\frac{dV}{dt} + I_i \tag{II.2.48}$$

explicitly says that the total current is the total membrane current divides 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.(II.2.47)),

$$\frac{d}{dt}V_{OUT} = \frac{I}{C_M} - \frac{I_i}{C_M} \tag{II.2.49}$$

The equation is true only if the consenser's current and the ion current are both constant. However, it is valid only in the clamping condition's steady state, i.e., in the "freezed" state of the neuron. 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.*

The basic issue with their idea 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.

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.

Chapter 3

Abstract neurophysiology

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 [7]
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 electrodiffusion, 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. Scrödinger: What is life?[14] @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.

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" [52]. Classic 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.

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".

It is hazardous to introduce technically (and incorrectly) derived and misinterpreted macroscopic features and interpret them as fundamental electric notions. 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. 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.

3.1 The physical model

As Figure III.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 poten-

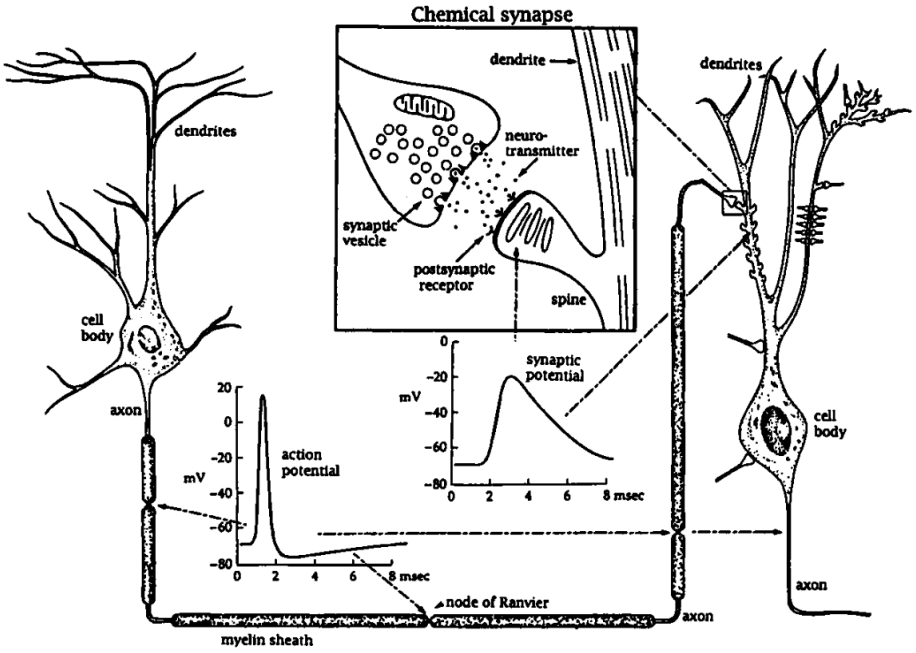


Figure III.3.1: Summary of conveying information by electric and chemical signals. (Fig. 1.2 from [3]

tials 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." These sentences should read that ions carry the observed potential changes. 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.

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.

???The two conditions imply that we must use slow currents. As we discuss in sections 2.7.1 and 2.7.1

3.1.1 Size of neuronal components

The 'dendritic trees can be quite large, containing up to 98 % of the entire neuronal surface area' [52]. 'Because the cell body is small compared with the dendritic tree, its membrane potential is roughly uniform' [34]; 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' [34]; see our mathematical discussion of this physiological evidence in section 3.3.4. 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.

The size of presynaptic terminals is about two orders of magnitude smaller than the cell body and its dendrites [34], chapter 11. 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' [52].

The size of presynaptic terminals https://www.ncbi.nlm.nih.gov/books/NBK26910/bin/ch11f38.jpg(r here as Fig. III.3.2) is about two orders of magnitude smaller than the cell body and its dendrites [34], chapter 11. In other words, the "dendritic trees can be quite large, containing up to e98% of the entire neuronal surface area" [52]. "Because the cell body is small compared with the dendritic tree, its membrane potential is roughly uniform" [34]. 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". "Each incoming

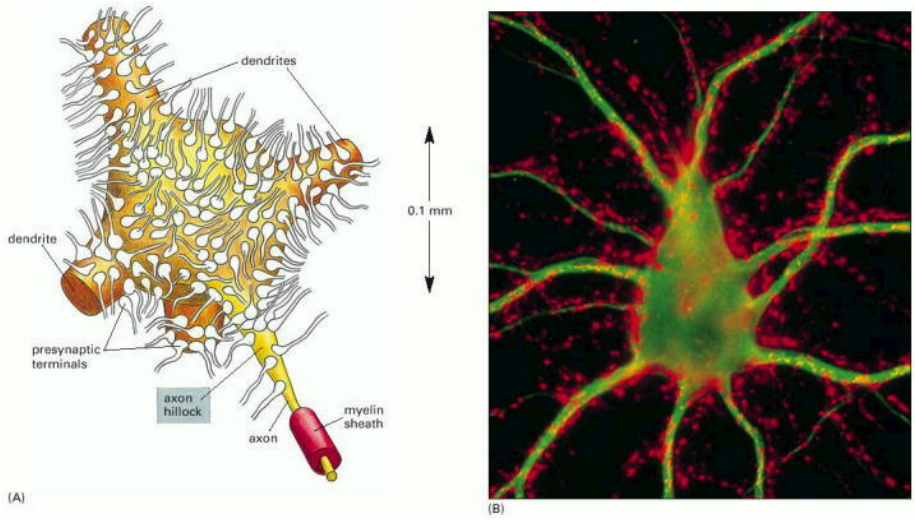


Figure III.3.2: The size of presynaptic terminals. ©Original

signal is reflected in a local PSP of graded magnitude, which decreases with distance from the site of the synapse." "Temporal and spatial summation together provide the means by which ... many presynaptic neurons jointly control the membrane potential." [34]. This former sentence should read that *its measurable effect (their 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 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 mebrane 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' [52].

The commonly used physical picture (see, for example, [8], 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 'leaking 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). Cardiatic slow currents have been discovered [30] (actually, current pulses of duration in several msecs 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 [31] was found in the range of $0.02 - 5$ m/sec. In neurophysiology, ion current speeds ranging from a few mm/s to dozens of 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 mm and the synaptic signals appear at the AIS 0.2 ms after their arrival to their presynaptic terminals, we can estimate the speed of 'slow current' as 0.5 m/s (see our discussion on the signals appearing in the 'relative refractory' period). This result is in line with our result derived the speed value 1 cm/s [1] measured within a cell body and the axonal speed 20 m/s [7].

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 unique compartment called the axon initial segment (AIS)"[33]. 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.

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' [35, 36, 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" (see also section 2.7.1). 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' [8]. 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 1.3.1. 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 [8], "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. (II.2.25). 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" [8]; 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. (II.2.28)). 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. (II.2.1)). 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 Galillei-transform is sufficient), transforms the distance to time and vice versa. Under the effect of clamping, the current is decreased by the stream proportionally:

$$\frac{dI_{axon}}{dt} = -\alpha * I_{axon};\ I_{axon}(t) \approx I_{wall} * (1 - \exp(-\alpha * t)) \qquad \text{(III.3.1)}$$

(α is a timing constant of dimension $(1/time)$).

3.1.5 Membrane

Even at writing this text at the end of 2024, 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 electrodiffusion processes.

We might imagine the importance and operation of this thin layer in line with the Earth athmosphere. 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, furthermore, its volume is far from being homogenous. Basically, the gravity keeps it in place, but for some periods, also other (thermodynamic and electric) forces evoke inside it and lead to transient changes. Basically, it is in rest, but sometimes high-speed huge masses may move transiently inside it. Its thickness is negligible compared to the size of the bulks on their two sides, and we can describe the bulks without considering its density, mass, size, etc. Still, this thin layer is responsible for the wheather, its transient processes define the visibility from both sides (define propagation of electromagnetic fields), and it can protect us from electromagnetic radiations and even from some meteorits. It can temporarily absorb products of slow processes (water evaporation), 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. Small changes (natural ones, such as a slight difference of 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 distributing the injected material.

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 athmosphere 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 descibe the neuron's dynamic behaviour, we need to derive the corresponding laws of motion. We need a meticulous and unusual analyzis 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" [13].

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.

3.2 Electrodiffusion

As we discuss in section 2.6.6,

Biological cells comprise components such as electrolytes, semipermeable membranes, solutions with expremely different concentration. Surprisingly, they show spontaneous electrical activity. As Eq.(II.2.17) shows, the electrical interaction speed is million times higher than the chemical one. In section 2.6 we discussed the

3.2.1 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 [77] provide indirect evidence for the effect's existence.

We consider three operating regimes for neuronal membranes. Eq. (II.2.3) 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. (II.2.3).

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.(II.2.3) 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 that 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.

3.2.2 Connecting science to life

The two layers, plus the demon, 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." [79] 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*.

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 cooperate in the nature, even if we need to elaborate new mathematical methods for that goal, see section 2.3.4.

3.3 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 [7], *the AP can be described from the first principles of physics* when using the right physical approximations and abstractions.

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 measurements [7] 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*." [27]. *That mathematics is beautiful but describes some alternative nature instead of the real one*, see also section 3.6.

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' [1] and "we should not seek a special organ for 'information storage' – it is stored, as it should be, in every circuit" [49]. This latter source points to the important point 'Communication consumes 35 times more energy than computation'. [80] One more point why *computation and communication must not be handled separately* [11]. 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.

3.3.1 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) [7]

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, az 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" [44]), 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 "whyänd "how" open. "*Why* action potentials are initiated in the axon is still unclear" [1].

3.3.2 The modern picture

We know that ion current flows in through the axons, and the delivered charge produces local transient voltages [43, 44] 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 [1]. *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 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" [77], 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 [81] that attempts to describe non-ideal membranes, considering also mechanical deformations, uses only "fast" waves. Similarly, the model in [77] 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.

3.3.3 Action Potential

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 electrodiffusion-based systems, are described by electrodiffusional time-dependent equations. However, it is not so.

One of the fundamental reasons is that the way of *providing time derivatives of the electrodiffusion process was not known* (see our section 2.6.5). 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

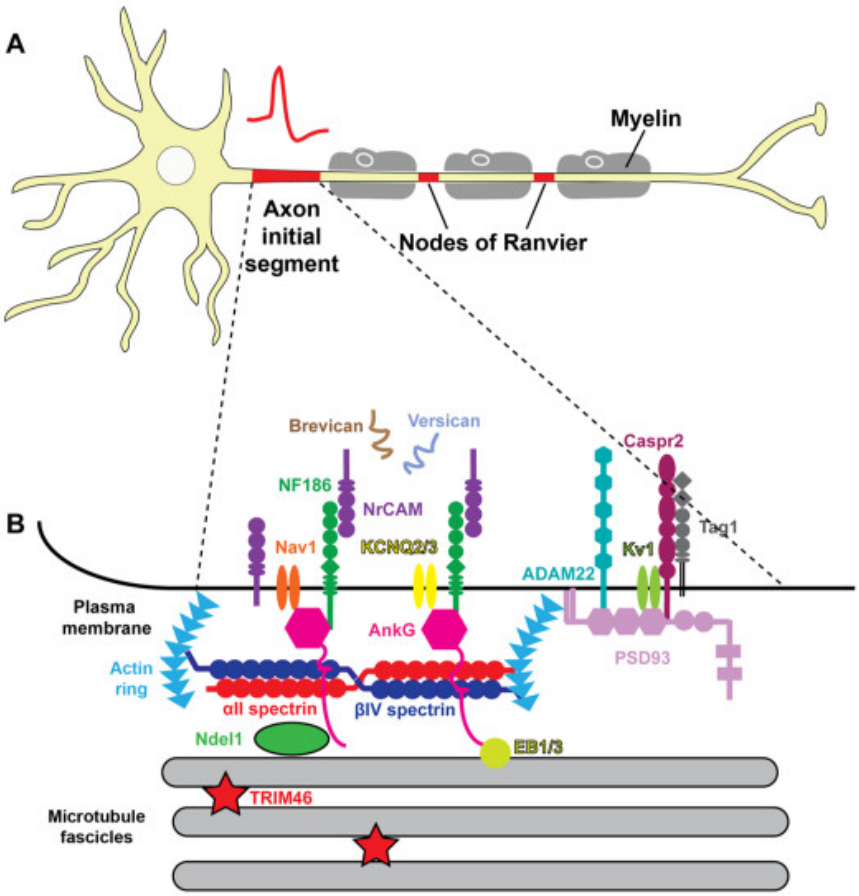


Figure III.3.3: The structure of the Axon Initial Segment. [1] Ann. N.Y. Acad. Sci. 1420 (2018) 46--61, Figure 1 ©2018 New York Academy of Sciences.

secondary manifestations of abstractions 'potential' and 'current'; furthermore, it assumes that a mysteric power changes biological 'conductance' against all physics laws (applying laws of electricity to their 'non-ohmic' systems). The 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 [15], 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 [7] 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 [82]) whether it is model at al 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*."[27]. 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. Un-

fortunately, 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 [33, 1]. 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. III.3.3, 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 [80] 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 III.3.4: 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

$$V_{out}(t) = RC \sum \frac{dV_{in}}{dt} \tag{III.3.2}$$

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

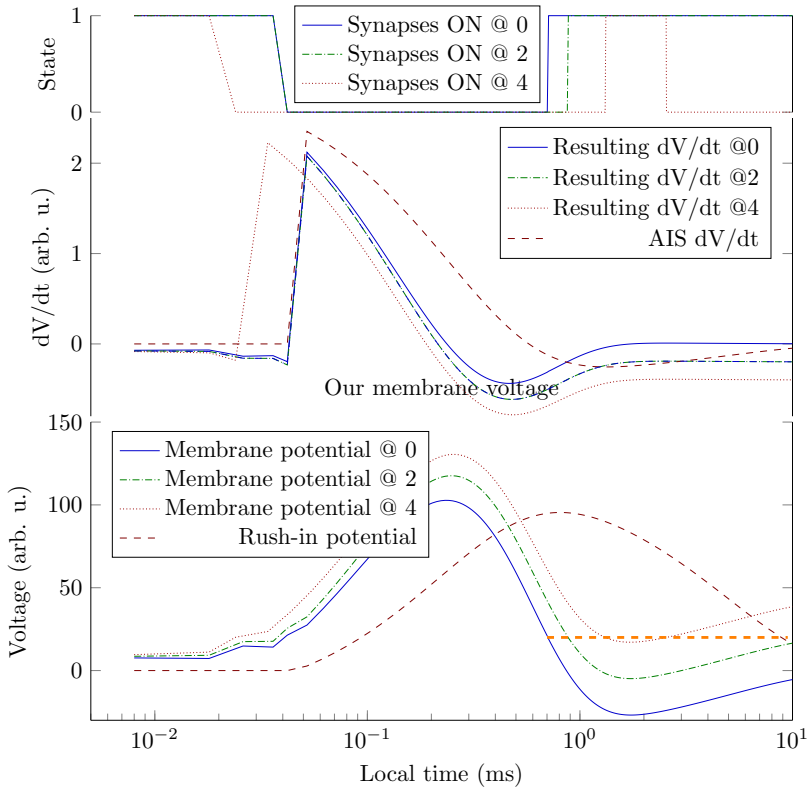


Figure III.3.4: How the physical processes describe membrane's operation

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 [4], 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 III.3.4 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 exhousted 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 *the biology uses and the dynamic one that really describes its behavior*. The 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.(III.3.2)) instead of static currents (as everyone 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 will flow, and the output and input currents must be equal.

The top inset shows how the membrane potential controls the synaptic inputs. Given the ions from the neuronal arbor [50, 51] 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. III.3.9 shows how the resulting APTD controls the output APs shape: the derivative changes its polarity by $\approx$ 500 mV/ms in ≈ 0.5 ms, which means across a 50 μm 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.

As the meticulous review [6] 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.

3.3.4 Neural currents

We can subdivide currents within the neuron based on their origin, physical path and temporal behavior.

Patching current

When clamping, 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 form a presynaptic neuron), the received input has the form of PSP, where the time derivate 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 2.6.7, 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 3.5.2 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 III.3.12. 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 3.4.6.

AIS current

The AIS represents a non-distributed resistance R_M, and the current flowing through it is

$$I_{AIS} = -\frac{V_M - V_{rest}}{R_M} \tag{III.3.3}$$

(it is an outward current, so it is negative), and its voltage time derivative is

$$\frac{d}{dt}V_{AIS}(t) = -\frac{V_M(t) - V_{rest}}{C_M R_M} \tag{III.3.4}$$

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.

$$V_a(t) = V_o * (1 - exp(-a * t)) * exp(-b * t) \tag{III.3.5}$$

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

$$\frac{dV_a}{dt} = \frac{1}{\alpha} * exp(-\frac{1}{\alpha} * t - \frac{1}{\beta} * t) - \frac{1}{\beta} * exp(-\frac{1}{\beta} * t) * exp(1 - exp(-\frac{1}{\alpha} * t)) \tag{III.3.6}$$

The same voltage derivate (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 III.3.10.

Native case

In the native case (the membrane's voltage created instantly and then no external invasion happens), the resulting voltage derivative is

$$\frac{d}{dt}V_{OUT}(t) = \frac{d}{dt}V_M(t) + \frac{d}{dt}V_{AIS}(t) \tag{III.3.7}$$

Figure III.3.7 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 3.5 and also Figure III.3.10.

Complex case

In the most complex case, the time derivative of voltage we need to work with is

$$\frac{d}{dt}V_{OUT}(t) = \frac{d}{dt}V_{AIS}(t) + \frac{d}{dt}V_M(t) + \sum_i \frac{d}{dt}V_{SYN,i}(t) + \frac{d}{dt}V_{ARTIF}(t) \tag{III.3.8}$$

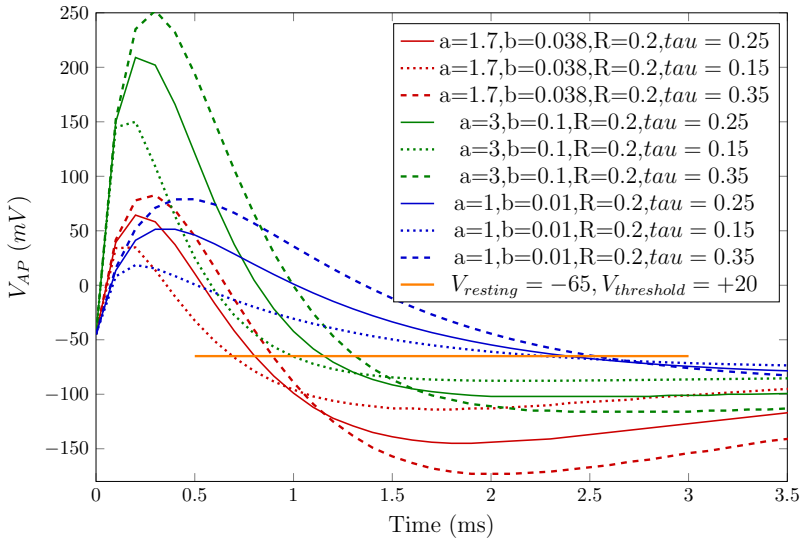


Figure 3.5: The shape of the AP as the result of integrating the differential Equation (III.3.7), at different input and output currents and timing constant

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.

3.3.5 Neural voltage

The time derivative was measured already in 1939 [4], see Fig. III.3.8. However, its role has not yet been recognized. Interestingly, Cole and Curtis derived the

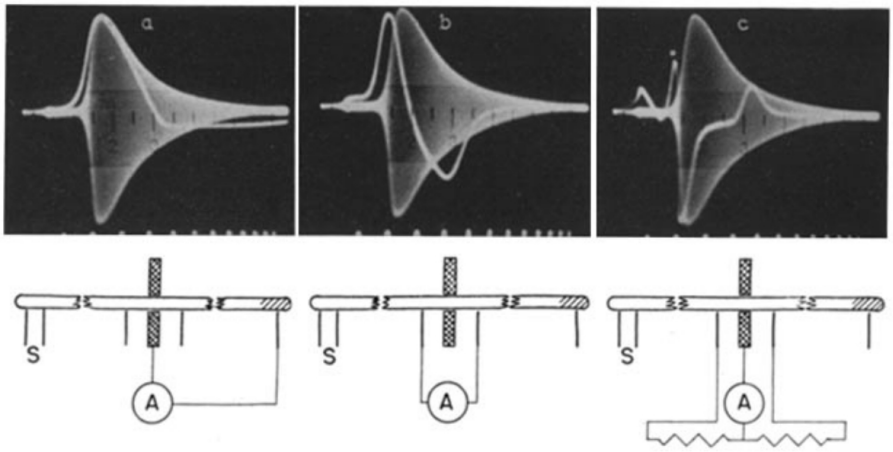


Figure III.3.6: Measuring the time derivative in [4], from 1939III.3.8

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)

3.3.6 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. (III.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. (II.2.1), 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*

$$I_{out}(t) = -I_{in}(t-\mathbf{\Delta t}) \tag{III.3.9}$$

instead of the usual form, without delay. In Fig. 1 in [1] 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. (III.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. (III.3.5). That is, we expect that the resulting (net) current is a "ghost" image shown in Fig. 3.16, 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 $\Delta t = 0.49\ ms$, and the parameters used to generate the function displayed in Fig. III.3.18. The negative output current has been observed and measured by [7], 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 [1] to form AP, and imaging ions show (see their Fig. 3f in [1]) 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' [6], and

In our model, the membrane acts as a *voltage generator* with the time course described by Eq. (III.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 [6].

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) after opening its ion channels. That potential difference will drive a macroscopic current toward the AIS, where a macroscopic current flows out, as described in [1]. The mathematical formalism is the same as in the case of PSP, see Eq. (III.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 [1] 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

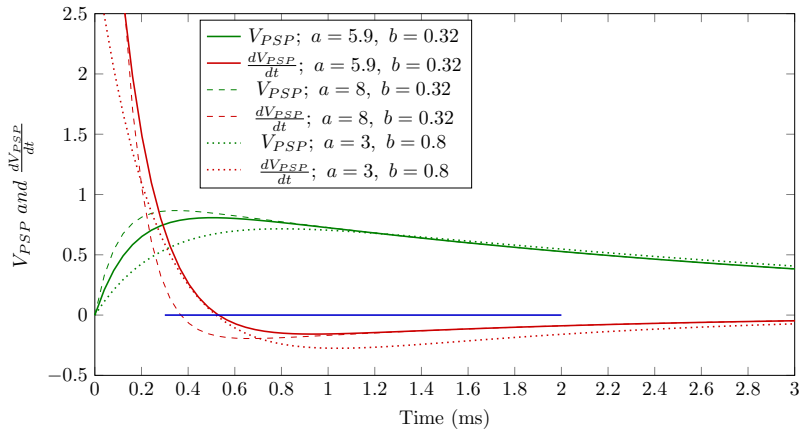


Figure III.3.7: The rush-in (and post-synaptic potential) and its derivative, as provided by Eqs. (III.3.5) and (III.3.6). The PSP diagram line was fitted to data measured by [5]

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 2.7.1, 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.(III.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. (III.3.5) and its derivative, described by Eq. (III.3.6), are depicted in Fig. III.3.7; with the parameters concluded from Fig. 3.15. 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. 3.5. 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. III.3.18. 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. III.3.18. 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. 3.16. As we discussed in section 2.7.1, 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 voltages [43, 44]. 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.

3.3.7 Voltage time derivative

The time derivative was measured already in 1939 [4], see Fig. III.3.8. 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, [6] 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 (III.3.6), (III.3.7), (III.3.5) and Figs. III.3.9 and III.3.7. 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. 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.

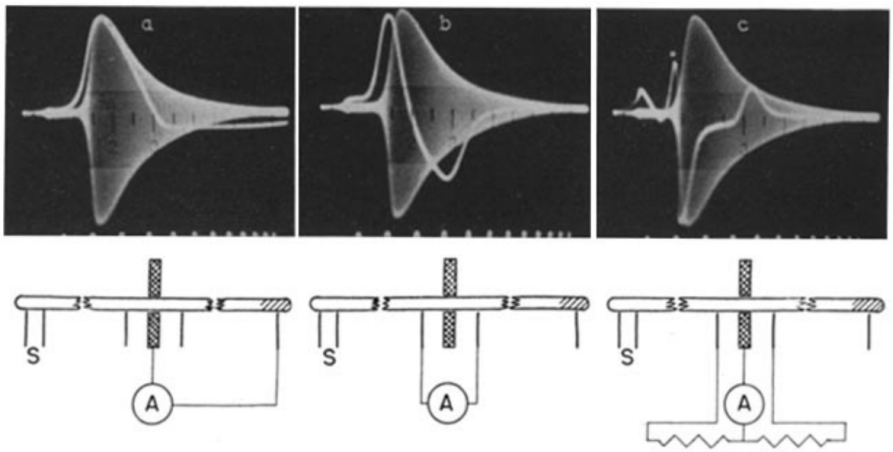


Figure III.3.8: Measuring the time derivative in [4], from 1939

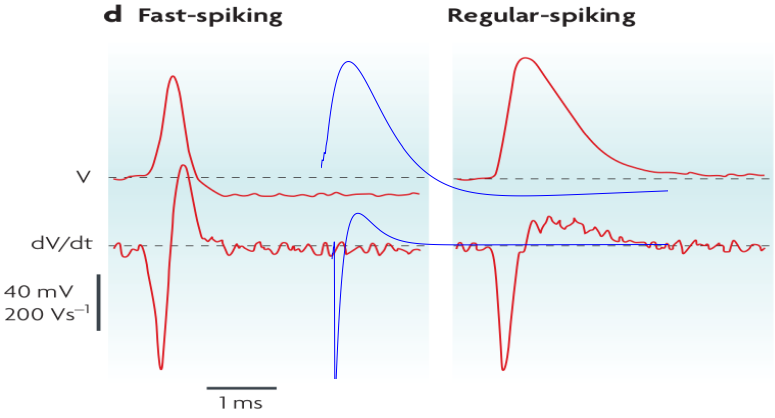


Figure III.3.9: The simultaneously measured AP and APTD Our theoretically derived AP and APTD are overlayed to Fig. 2d in[6]. See also our Figure III.3.10. "©2007 Nature Publishing Group. Bean, B. P. (2007): The action potential in mammalian central neurons. Nature Reviews Neuroscience, 8(6), 451-465. doi:10.1038/nrn2148".

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 III.3.10 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 1.3 and VII.7.1.

The bottom subfigure displays the action potential observable on the AIS. The '0' case is a simple delivering (see section 3.3.4), 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 [83]; also displaying that some protection exists in neurons against 'overloading'.

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 [7] 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 III.3.10), 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 [83]. See also Figure 1.3.

3.4 Hodgkin&Huxley's empirical description

As we discuss in section 2.7, 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 electronic technology enabled their systematic study in the beginning of the 50's.

The first systematic attempt to describe the results of observations in terms of well-known laws of electricity was published around 1952 [7]. 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 work is best highlighted by that it inspired different disciplines for discussion.

Self-evaluation

In their brilliant publication [7], 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 [84], 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 interpre-*

tation given is unlikely to provide a correct picture of the membrane." Despite their explicite 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-prise "for their discoveries concerning the **ionic mechanisms** involved in excitation and inhibition in the peripheral and central portions of the nerve". As the phylosphical 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." [85] 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 [85]. The lack of causality is one reasons 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, althought the additional (and arbitrary) ad-hoc assumptions have hidden the disagreements. The followers have "fitted elephants" [25] by adding many more ad-hoc effects with too many parameters.

3.4.1 Measurement science

As highlighted in [85], the performed a very meticulous analysis and characterized the time-course of the action potential phe nomenally terms of different features (the concise listing taken from [85])

- 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."[3] *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.

3.4.2 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*." [27].

3.4.3 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." [86]

Neglecting Coulomb's Law

3.4.4 Electrodiffusion

3.4.5 Driving force

As we discuss in section 2.8.1, HH introduced by their Eq. (1) (reproduced by us as Eq. (II.2.46)) the basic decription 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 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 3.3.4, 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. (II.2.7)) 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.

3.4.6 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; hypotesizes non-existing physical mechanisms to make their nature. In 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 ions 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 accross 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 "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" [28]; that is, to study a simulated neuron built from discrete electronic components. However, the idea needs to put together many compone "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 questionalized [29]), 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 [3] 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

difference is significant in understand how the basic neuronal circuit works. Introducing equivalent circuits prevents explaining the fundamental electric phenomena.

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. 3.11. 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 τ 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 [7] 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. III.3.12. They experienced a formal similarity with switching a voltage of an integrator-type *RC* circuit on and off, compare to Fig. 3.11, 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 2.8.1 and 2.8). 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 III.3.12 shows *two* switch-on diagram lines, with two different τ time constants. The blue line ("electric") is drawn with the measured time constant of the swith-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 τ time constant. The effect was observed by [7], but they did not explain and also did not interpret it. The reason is that the charge-up current is not constant, it also has a time course. Unfortunately, the time course of the charge-up current is also a saturation-type current, and its time constant differs from that of the condenser charge-up. Although their fitted polynomial nearly hides the effect, a little "hump" at around 3 ms can be observed. The diagram line must have the shape corresponding to the product of shape of the charge-up current and the saturation curve of the condenser. 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 contants τ of the exponential charge-up and discharge processes are different; but did not care that they should be indentical and also did not care of the "hump".
- They measured the resulting charge-up composite process. As we explain in section 2.7.1, 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 begining the line had a zero current contribution.

On the one side, they underpinned that our equations II.2.37 and II.2.36 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.

Their 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.

Cable equation

3.5 Experimental evidence

3.5.1 Stokes' Law

As we derived theoretically in section 2.7.1, in general, the ion current generated by a potential gradient is proportional with the electric gradient (see Eq. (II.2.28)) and and macroscopic current speed (see Eq. (II.2.30)

The mostly known and influencing axon current measurement has been published in 1952 [7]. They used a single-axon input and measured the neuronal membrane's current, which in this way was identical to the axon current. The diffused-in ions are transported towards the membrane as a "slow" macroscopic ionic current (the speed of current HH [7] 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.

They measured the time course of the axonal current at different clamping voltages. Their result is reproduced in Fig. 3.13. As we discussed, ions diffuse in the axon's wall, producing a saturation-type current. As expected from our theoretical consideration in section 3.5.2, the experimental data are fitted with the theoretical function III.3.1. Our simple model assumes that α is constant in time but (through v and $\frac{dV}{dx}$) depends on the clamping voltage).

A systematic discrepancy exists at the low time values of the time course function between the one fitted originally by [7] and 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 exponential increase in membrane's current) has been experimentally measured by [38]. The figure suggests that the saturation current depends on the speed of ions (i.e., on the clamping voltage, see Fig. 3.13 and Fig. III.3.14) in the tube.

A major 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 the time delay due to the use of 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 [7]: "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. (II.2.28)), this time gap depends on the depolarizing voltage*: the higher the voltage, the shorter the time gap, demonstrated in their Fig. 3.

We fitted our theoretical function (see Eq.(II.2.37) to the measured data published in [7] and derived the time constant and saturation current using the clamping voltage as parameter. In Fig. III.3.14, we compare our fitted data values with those derived by HH and displayed in their Table I. Actually, their fitted polynomial chooses a wrong time scale, and adds a period of the delayeing 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 distort the fitting and delivers wrong time constants. This effect may lead to conclusions opposite to the real ones. 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.

3.5.2 Axon

3.6 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 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"* [3]. The illusion of having an imposing knowledge base inspired undertakings such as simulating the entire human brain.

The brain must be studied "from the Inside Out" [87]. 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 [42] do not consider those differences.

3.6.1 Equivalent electrical circuit

3.6.2 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" [8]. 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" [8], 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, which is less then 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 [88].

3.6.3 Passive distributed membrane

The role of the neuronal membrane is controversial as used in physiology. As [8] 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 I.1.1. When inventing the AIS, the wrong hypothesis turned into a fallacy.

3.6.4 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.

3.6.5 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 [8] 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" [80]. 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.*

3.6.6 '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 [34]), 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' [34] 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 [34], chapter 11: 'The interior of the resting neuron or muscle cell is at an electrical potential about $50 \ldots 100\ mV$ 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." [34]. Maybe, in biology, Newton's third law in not active? We show a numeric calculation in section 2.7.6.

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, [34] 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 [34] was published, the structure of AIS [76] 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 [6] 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.

3.6.7 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" [48]. 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.

3.6.8 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 [89] (their figure is reproduced in Fig. III.3.20) 'demonstrated' experimentally the 'low-pass' behavior of their neuron. It shows an example when one proves 'experimentally' what they want to believe.

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 [69], 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 III.3.10. 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 [83] the too high current blocks spiking (more precisely, receiving the triggering signal).

From our conceptual model of generating AP (see Fig. 1.3), 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 synaptic inputs are not enabled; see also Figure III.3.10. 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'.*

3.6.9 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 [8], 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_{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 [1] 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 2.7.1, 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 [8]: "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. (III.3.9) formulates Kirchoff's Law in biology. Using *a virtual parameter "capacity C" for biological neurons misleads research: introduces a nonexisting "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.

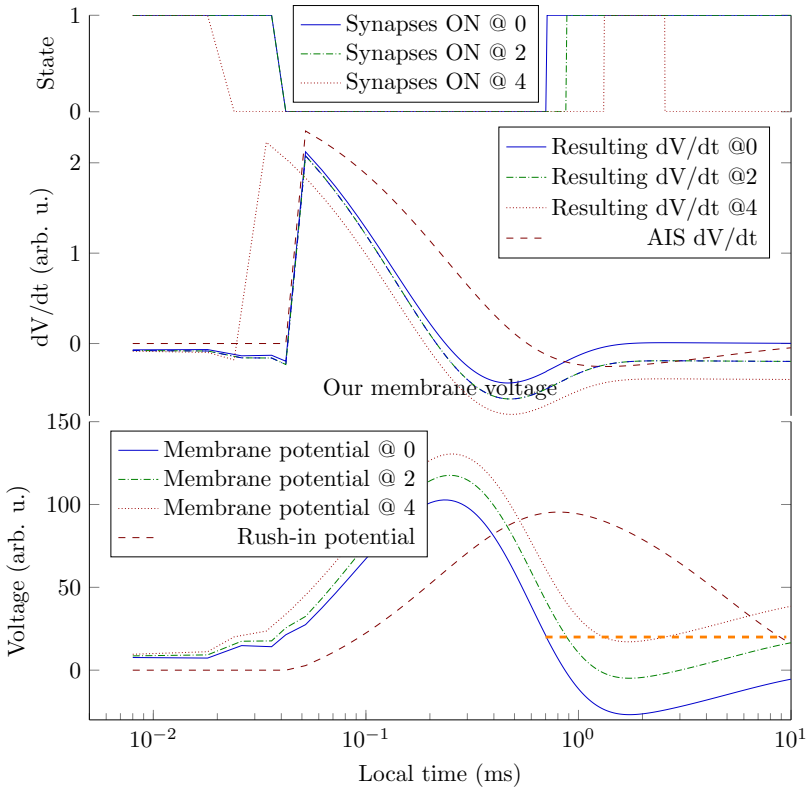


Figure III.3.10: The summary of AP generation. The voltage time derivatives (the midle subfigure), resulting by summing the $\frac{d}{dt}V_{AIS}$, $\frac{d}{dt}V_M$ and a constant corresponding to the clamping current, that define the membrane's output voltage (the AP, the bottom subfigure), that control synaptic contributions (top subfigure). See also Fig.VII.7.1

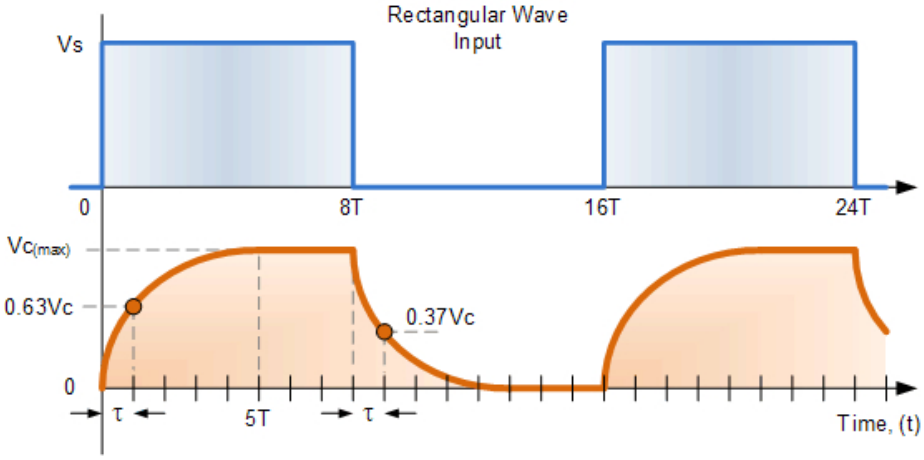


Figure 3.11: The output waveform of an integrator-type electric RC circuit at a long $(8 * \tau)$ pulse width square wave input (see Eq.(https://www.electronics-tutorials.ws/)

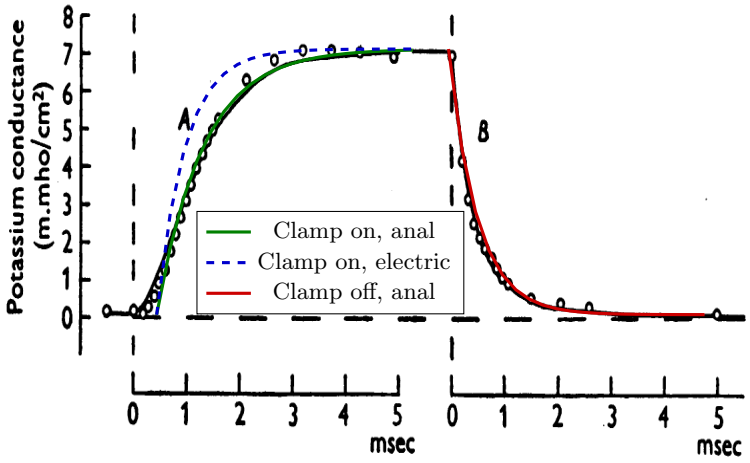


Figure III.3.12: The green and red diagram lines are calculated for the clamping-on and clamping-off case. The dashed blue line models the case that the neuron is a purely electric system, as opposed to the case of clamping the axonal tube with ion channels in its wall. The black bulbs are for measured points. Moreover, the fitted polynomial line is reproduced from [7].

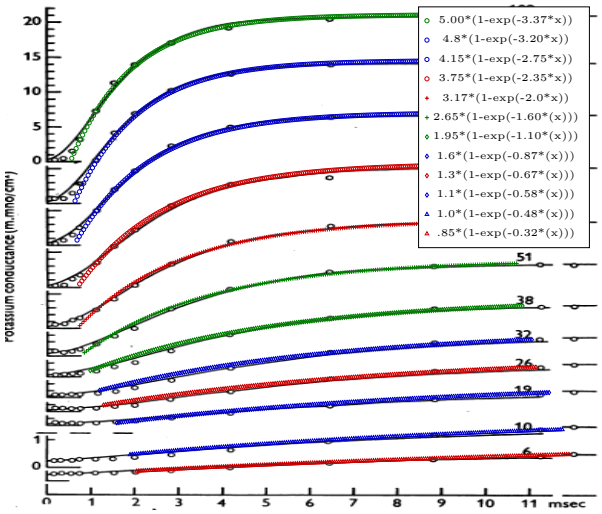


Figure 3.13: Finding time constants and membrane current by fitting data measured by HH (Fig. 3 in [7]) with our theoretically derived function (see Eq.(III.3.1))("Copyright [1991] Society for Neuroscience")

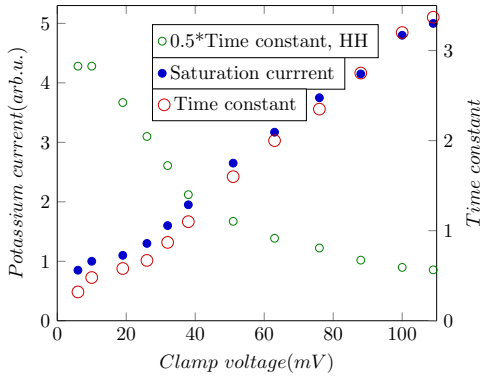


Figure III.3.14: The proportionality of membrane's current and time constant, respectively, with the clamping voltage. Data taken from Fig. 3.13 and Table 1 of [7].

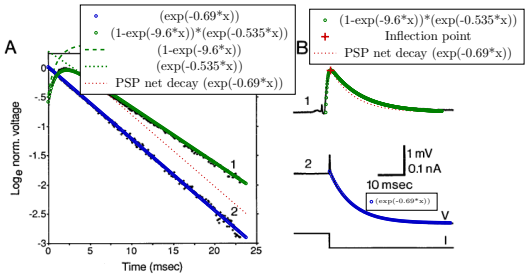


Figure 3.15: A) PSP decay (curve 1) and the decay after an injected depolarizing current pulse (curve 2) recorded in the same cell. B) Voltage traces (upper and middle) from which the curves in A were derived, together with the current record (lower) for the pulse. The colored marks and diagram lines are calculated using the model's "slow" current. Measurement data (with black) are reproduced from Fig. 4 of [5] ("©[1991] Society for Neuroscience").

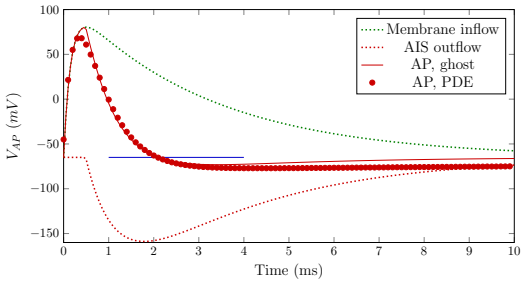


Figure 3.16: The "ghost image" formed by the delayed membrane current: the origin of the AP. The finite-speed ions transferred on the finite-size surface of the membrane: Kirchoff's Law in biology. The assumed delay time between input and output currents is 0.49 ms, the function form and its parameters are displayed in Fig. III.3.18.

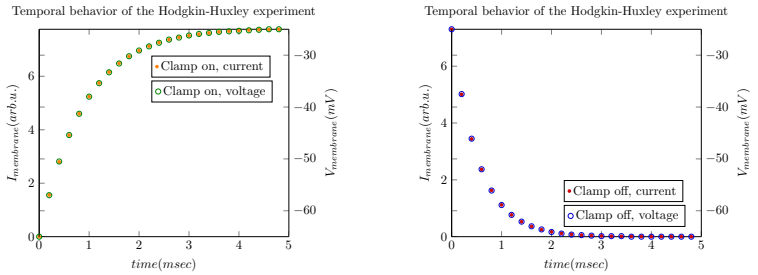


Figure 3.17: The time course of voltage and current a clamping experiment, calculated numerically for switching the clamping on and off.

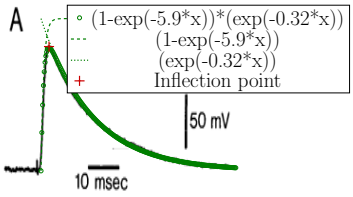


Figure III.3.18: Time course of the post-synaptic potential evoked by a single AP. The colored marks and diagram lines are calculated using the model's "slow" current. Measurement data reproduced from Fig. 2 of [5] ("©[1991] Society for Neuroscience").

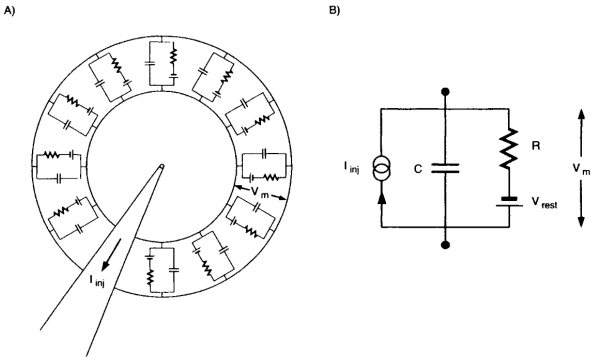


Figure III.3.19: Equivalent electrical model of a spherical cell with passive membrane. [8] Fig. 1.2

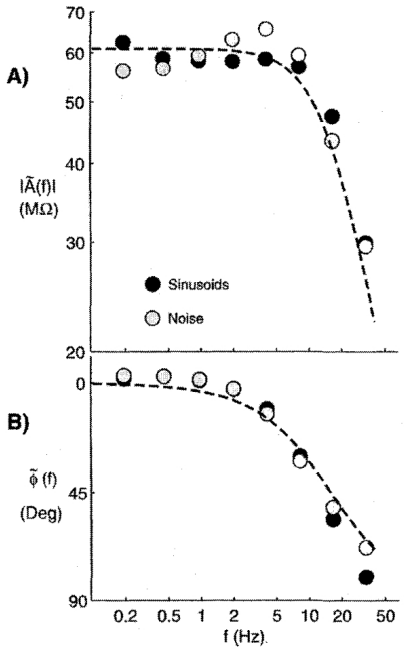


Fig. 1.4 CORTICAL CELLS BEHAVE LIKE AN *RC* CIRCUIT When either noise or sinusoidal currents are injected into the cell body of regularly firing cells in guinea pig visual cortex, the membrane potential can be adequately modeled as resulting from convolving the current input by a low-pass filter of the sort described in Eqs. 1.14 and 1.15 (dashed lines; here with $R = 58.3$ MΩ and $\tau = 9.3$ msec; $V_{\text{rest}} = -70.7$ 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 III.3.20: Illustrating the fallacy that neurons represent a low-pass filter. [8] Fig. 1.4

Chapter 4

Neural computing

Pinpointing the interpretation of computing Coming soon!

For now, see [22, 90, 91]

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.*" [32] @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.*" [28] @2014

Leads to the question: "Is realistic neuronal modeling realistic?" [29] @2016

"We so far *lack principles to understand rigorously how computation is done* in living, or active, matter" [92] @2018

"*we still do not understand the brain's underlying computational logic*" [9]. @2024

Despite the impressive results of grandiose projects [9, 93], and the sometimes triumphal communications, there has been no significant advance in understanding neuronal computing in four decades. 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 [94] 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 [95]. Despite that lack of knowledge, the half-understood principles of neuromorphic computing are extensively used [96, 97], although it is seen that brain-inspired computing needs a master plan [98]. 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" [97]

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" [97].

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 [99] 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 subsystems 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*" [96] 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*" [100]. 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*" [101], 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?*" [101]. 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) attemp to imitate brain-like biological systems, with goals ranging from simulating the dynamics of molecular processes to creating artificial intelligence. Furthermore, there are attemps 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 [35, 36], 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" [102]. 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 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' 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

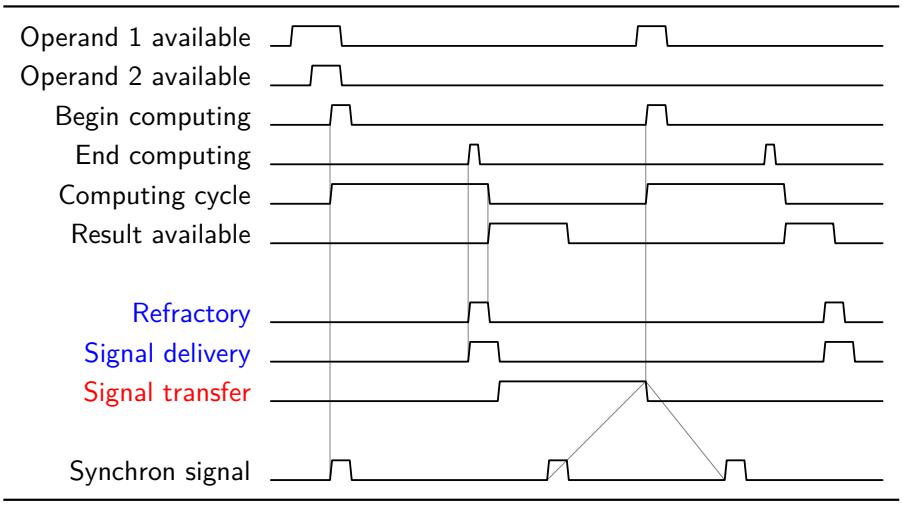


Figure 4.1: Timing relations of von Neumann's complete timing model, with data transfer time in chained operations; synchronization becomes an issue as the physical size of the computing system grows. Notice that synchrony signals must be bypassed or neglected. Timing relations of von Neumann's timing 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.

of tenths of a millissecond.

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 2.6.8. 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 3.2), 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 get 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 measurent is also provided: it is one coordinate of a space-time point.

The computer representation (actually a state machine) is shown in Figure 4.2.

Will be based on [46] [22]

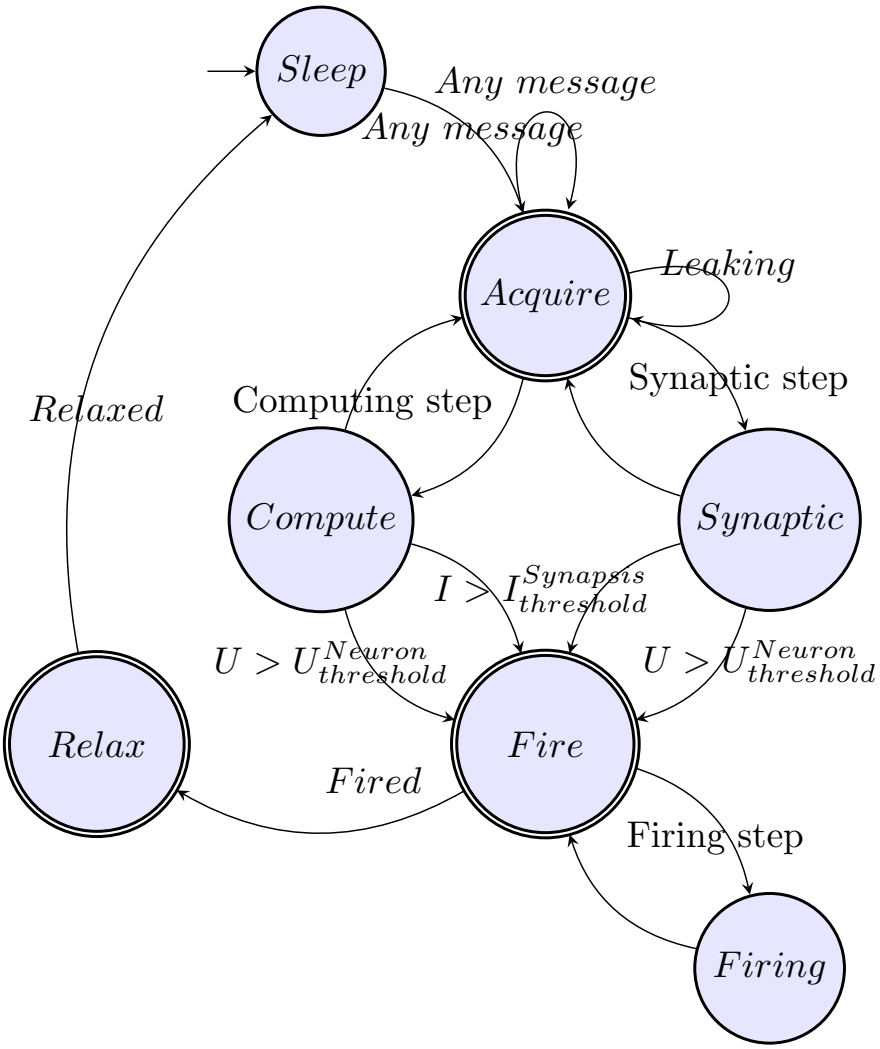


Figure 4.2: The neuronal state machine for event-driven simulation

Chapter 5

Neural information

Applying Shannon's information theory [103] 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 [104]). Although Shannon warned [88] 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 [105, 106].

"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" [107].

Will be based on [15] [23] [108]

The theoretical model [15] 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 [7, 5], 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.

Chapter 6

Intelligence

will be based mainly on [109]

Chapter 7

Neural simulator

Simulation

The many enormous differences make simulation of neural operation a real challenge.

7.1 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 and 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." [110] Similarly, we "define an elementary operation of the brain as a single synaptic event" [111].

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 [112, 113]. 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.

7.2 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 Refererence Guide [112] for developing the code, but using the well-written core of the package it is suffient to study the textbook [113].

7.3 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 backround is provided and shared on the site.

7.4 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 VII.7.1. (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.)

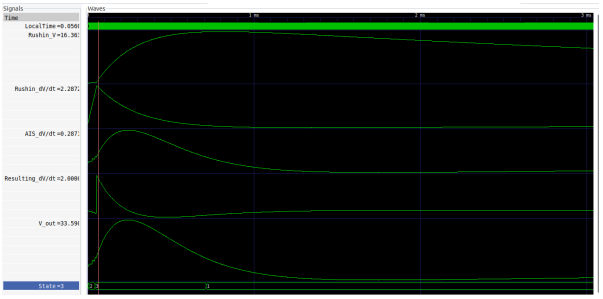


Figure VII.7.1: The summary of AP generation as seen in the simulator. The information is essentially the same that in Figure III.3.10 (for codename '0', i.e., 'Simple delivery'). The rush-in current produces its voltage time derivative, the resulting voltage time derivative generates the neuron's output 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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