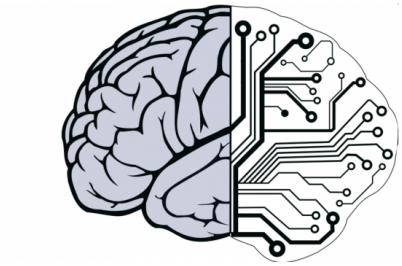
"*Though this be madness, yet there is method in't.*"
Shakespeare: Hamlet: Act 2 Scene 2

Abstract Neuron Dynamics

The true physics, computing, and information handling behind neuronal operation



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In 2012, the Human Brain Project summarised its goal:
"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."

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" [4]

In this research, we arrived at the boundaries of classic science fields and are moving now through terra incognita. However, the "great journey into the unknown" [4] begins earlier and at a much lower level: at revisiting the fundamental phenomena, laws, interactions, abstractions and omissions of science. There is no independent 'life science', only science; with the same 'first principles' but with different abstractions and approximations on its top for living and non-living matter. We need the "discovery" that for describing biological processes *we need different abstractions and approximations*. Without aligning them along the first principles, "integration between data and knowledge from different disciplines" actually lacks "integration". "More Is Different" [5]; 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". [4] Really, "a new understanding of the brain" is needed.

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. Science fields, including neuroscience, must use different approximations and abstractions to describe nature's infinite variety. We need a consistent model that comprises all relevant interactions (and only those!) and aligns with the notions of the related other science fields. Neuroscience is not an exception. Unfortunately, nature does not care that science divided its description into disciplines. We must care that the disciplines are aligned along different approximations and abstractions and a cross-disciplinary science 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 still manageable.

We agree that "No single researcher or discovery will solve the brain's mysteries". However, usually a single researcher used to call attention to that, with the development of science and in light of new discoveries, a new paradigm must be introduced. Their slowness and complexity requires explicitly considering the *time-dependent handling*

of biological processes. *No presently available theoretical description and simulator are capable to perform that task*. The worst inheritances of neuroscience are the static view from anatomy; omitting revisiting periodically the basic hypotheses in the light of new research results; the abstractions of the classic science (single speed, isolated, pair-wise, instant interactions in a homogeneous and isotrop infinite medium) applied to biological materials without revisiting them; and the tradition of applying ad-hoc mathematical formulas without correct physical processes in the backgound (actually creating an alternative nature) instead of understanding the basics of the underlying processes.

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' [6]. 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" [7]. 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'[6]. 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***' [8]. We base our discussion on those general basic principles and create an 'abstract physical neuron' skipping the 'implementation details' nature uses. Given that in many cases wrong physical principles, notions and measuring 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 [9]. We agree that "The basic structural units of the nervous system are individual neurons" [6], 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" [10], [9] so we also model multiple neurons. To start with, we introduce a *science-based abstract dynamic*, as opposed with the *static empirical cell-biology specific*, description of neuronal operation.

"The brain computes! This is accepted as a truism by the majority of neuroscientists." [11] Despite the impressive results of grandious projects [4, 12], '*we so far* ***lack principles to understand rigorously how computation is done*** in living, or active, matter'[13]. To understand how "computation is done", we generalize computing [14] in close cooperation with communication [15]. The "Brain initiative", after ten years, must admit [4] that "we still do not understand the brain's underlying computational logic". The Human Brain Project believes that it is sufficient to build a computing system with theoretical ability for simulating 1 billion neurons, and do not want to admit that itcan be used [16] 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 [17]. Despite that lack of knowledge, the half-understood principles of neuromorphic computing are extensively used [18, 19], although it is seen that brain-inspired computing needs a master plan [20]. We attempt to synthesize the available knowledge with a fresh eye, and intend to make a leap in understanding neu-

ral computing, scrutinizing our knowledge pieces one-by-one, for credibility, relation to other pieces, to other sciences, finding contradictions and its resolutions, *defying fallacies*.

Although we experience that the brain processes an enormous amount of information, furthermore, we know impressive details 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 the neuronal networks represent, process and store the information they use. What makes the case worse, due to the lack of knowing the abstract way of neuron's operation, the so called "neural information science" uses a wrong mathematical background. Applying Shannon's information theory [21] 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 [22]). Although Shannon warned [23] 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 [24, 25]. We introduce the appropriate interpretation of information for biology. We show how computing must be generalized to include biological computing.[14]

The site is not exclusively about theory: we give also a programmed implementation of the ideas we describe. Our simulator has 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 assumptions and limited variability formulas. Our methods enable discussing the major aspects from the phenomena of natural operation of neurons to analyzing the effects of invasive electricity-related investigation methods on neuroscience. Presently we offer some demos, class implementations, test cases to demonstrate simulating capabilities. Our intention is to develop a full-value educational, demonstration and research tool.

Warning: Please consider that this development is a one-man undertaking, and it shall develop theory, evaluation of published experiments, software implementation, its testing and their documentation. There exist pre-developed code fragments, science publications and docs, so it develops relatively quickly, but it needs time to put them together in a consistent state. Please come back later and see if there is something new (see the date and version).

Chapter 1

Abstract single neurons

In this section – in the spirit of Johnston and Wu [6] – we review how the relevant major components of a single neuron follow the basic principles. We use the physiological notions and terms in a general sense, going into details only to the absolutely necessary depth. However, we cite the corresponding research papers describing the details. 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 (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, which physical components cooperate. We discuss the physical, electrical, and physiological details in the subsections. Furthermore, we summarize how the components are put together to form, conceptually, the action potential we experience.

In our abstract model, we consider that neurotransmitters, receptors and specialized membrane proteins (for their detailed discussion see https://neuronaldynamics.epfl.ch/online/Ch1.S1.htmlthe textbook on Neuronal Dynamics) *only implement a kind of (time and energy consuming) chemical/enzimatic decoupling of the electric signal transmission*. 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.

1.1 Abstract modeling

Textbooks, such as Neuronal dynamics and [11], 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 ad-

mit 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*" [3]. 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*." [26]. That mathematics is beautiful but describes some alternative nature instead of the real one. 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.

As Figure .1.1 (Fig. 1.2 from [6]) summarizes: "Electrical signals travel from the cell body of a neuron (left) to its axon terminal in the form of action potentials. Action potentials trigger the secretion of neurotransmitters from synaptic terminals (upper insert). Neurotransmitters bind to postsynaptic receptors and cause electric signals (synaptic potential) in the postsynaptic neuron (right). Synaptic potentials trigger action potentials, which propagate to the axon terminal and trigger secretion of neurotransmitters to the next neuron." 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. This bad consequence comes from the fact that HH omitted the fact that, according to Coulomb's Law, ions in the currents repulse each other, and that is the reason why slow current flow, without applying an external potential.

1.1.1 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' [7].

The commonly used physical picture (see, for example, [11], page 9) is only half

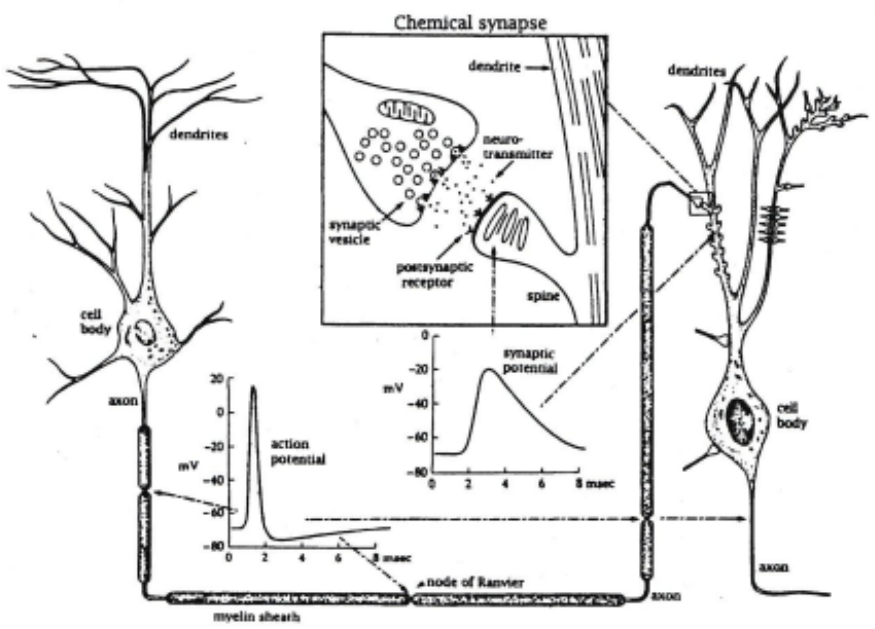


Figure .1.1: Summary of conveying information by electric and chemical signals

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 [27] (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 [28] 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

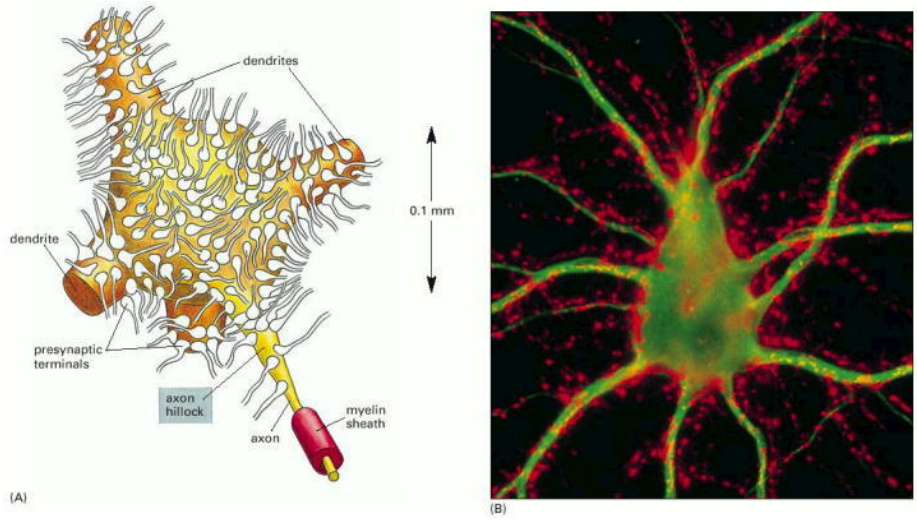


Figure .1.2: The size of presynaptic terminals. ©Original

observed.

The size of presynaptic terminals https://www.ncbi.nlm.nih.gov/books/NBK26910/bin/ch11f38.jpg(reproduce here as Fig. .1.2) is about two orders of magnitude smaller than the cell body and its dendrites [29], chapter 11. In other words, the "dendritic trees can be quite large, containing up to 98% of the entire neuronal surface area" [7]. "Because the cell body is small compared with the dendritic tree, its membrane potential is roughly uniform" [29]. 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 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." [29]. 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.

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 $1\ cm/s$ [2] measured within a cell body and the axonal speed $20\ m/s$ [3].

action potential layer ion channels

Chapter 2

Neurophysiology (abstract)

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. 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.

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.

Without having charge, the particles in a solution follow the laws of thermodynamics. Having charge affects their mass distribution and leads to measurable effects in the solution's local electric distribution: the change of one gradient generates the change of the other. However, the corresponding "laws of motion" are still missing. We must introduce (at least) two interaction speeds (at least 'fast' and 'slow' currents) and derive physics-based mathematical approximation to describe the experiences. We generally show a way of handling interactions with speeds differing by orders of magnitude. It is a pre-requisite of attempting to describe life by laws of science: life is based on electrodiffusion processes in biological matters. We derive a method and the mathematical form of calculating the Nernst-Planck equation's time derivatives, showing how that time course can describe processes with the participation of the (neuronal) membrane. *The derived equations are the Maxwell equations for electrodiffusion and*

also the laws of motion for biology. We show that a semipermeable membrane introduces a new interface (a layer of atomic width) between the electrolyte and the membrane that can be described only using microscopic and macroscopic terms simultaneously. We also discuss the operation of gated ion channels in semipermeable membrane, furthermore, that ions change their speed from *drift* speed to *potential-assisted* speed or even *potential-accelerated* speed. The case studies also include how and why action potential is evoked due to finite size of the neurons and finite speed of their charge processing. The time-aware computing procedure (considering the finite speed of charge carriers) naturally describes the biophysically plausible abstract model of electric charge processing in biological neurons.

Biology uses the idea of ”instant interaction” borrowed from classic physics and describes its ”slow” currents using equations developed for instant interaction; i.e., as if they were ”fast” currents. The lack of idea about slow currents leads to the introduction of fake currents (which have no source, change the ion type, introduce non-physical delays between the two secondary electric entities voltage and current, and so on). *Experimental biology sees the time, but its theory does not want to admit it.* Instead of introducing that biological processes need time, biology suggts that physics has a wrong notion about speed, space, time, and electricity. Unfortunately, biophysics participates in this business: in some cases simply translates notions, terms and equations from classic physics (mainly theory of electricity), without validating that the original abstraction remains valid in the case of biology.

Nature is infinitely complex, and science must make abstractions for a particular assembly of phenomena to describe them with reasonable accuracy using a piece of that language. We create a dialect of that universal language and validate its usage for our assembly of phenomena. Different science fields may use different abstractions and dialects, developing new ones or attempting to inherit them from other science fields. However, in the latter case, *we must not borrow their validation without scrutinizing whether in the case of our abstractions they remain valid*. To describe its electric operations, biology borrowed laws and equations from physics, where it was assumed that the speed of interaction is the speed of EM interaction, the interactions have the same speed and they are strictly pair-wise. Although technical electricity knows and describes that macroscopic currents are a million times slower and different laws describe them, biology did not borrow the idea or where it did (the telegrapher’s equation); it did it incorrectly.

Believing that the mathematical equations developed for the abstraction of ”instant interaction” of classic physics are valid for biology, leads to describing a surrealistic virtual nature, where charges are not present but creating potential the conductance depends on the applied voltage [30], and that conductance governs biological operation; the mystic reason of creating AP is ”based on an indirect inference, that excitatory inputs interact sublinearly when located somewhere in the distal dendritic tree” (for a review see section 5.2 in [11]); signals propagate with delays without assuming that it happens due to the finite speed of current that delivers the signal; applying telegrapher’s equations, which assume that current flows out of the cable, to the case of axons where the current remains the same while it travels; modeling and showing dependencies of infinite-speed electric circuits for finite-speed biological circuits; applying Kirchoff’s Conservation Law to space segments where ions are created inside (diffuse into

the segment); that the temporal operation due to many-synaptic inputs is governed by some cross-correlation of independent inputs; that the information processing of time-dependent analog signals is described by a formalism developed for time-independent digital signals.

Since Euclid, we know ”there is no royal road to geometry”. We add that there is no biologist's road to nature. The true nature is different from the one they assume when they apply the mathematical formalism developed for the approximations and abstraction of classic science. One must derive the proper approximations relevant to the studied phenomena, usually comprising several interactions with speeds differing by orders of magnitude, develop the appropriate abstractions and approximations, then develop the corresponding mathematics. This is also valid for the case of electricity in metals, from the speed of EM interaction down to the drift speed of electrons. Even we know that the speed of a macroscopic current is between those two extreme values. Extrapolating our notions about the macroscopic world to the microscopic one and assuming the classic interaction speed (the ”instant interaction”), abstracted from the vast interaction speed of EM waves to at least ten orders of magnitude lower interaction speed, is misleading.

2.1 Membrane

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" [31].

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.

2.1.1 Consequences

The discussed feature have important consequences for biology.

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

We consider three operating regimes for neuronal membranes. Eq. (.3.9) 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

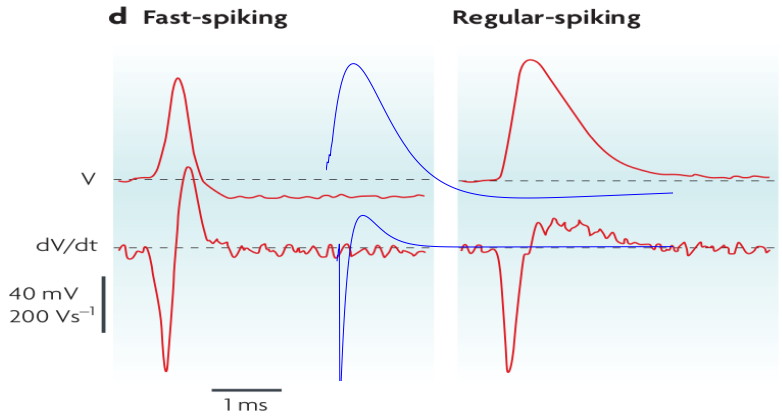


Figure .2.1: The simultaneously measured AP and oAPTD. Our theoretically derived AP and iAPTD are overlayed to Fig. 2d in [1]."©2007 Nature Publishing Group. Bean, B. P. (2007): The action potential in mammalian central neurons. Nature Reviews Neuroscience, 8(6), 451–465. doi:10.1038/nrn2148"

membrane-width-dependent term. However, otherwise, the state can be described by Eq. (.3.9).

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.(.3.9) 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 in the order of at least dozens of seconds.

Connecting science to life

The two layers, plus the demon, also naturally explain why that difference comes into existence. As we discuss in section 3.5, 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." [33] 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*.

2.2 Action Potential

As we also discussed [15], 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 3.5.1). The other is that, conceptually, *the neuron is considered to be a purely electric system that connects to thermodynamics only through the time-independent Nernst-Planck equation*. The third is that even the description of the purely electric operation is wrong: biology separated the primary abstraction of electric 'charge' from its secondary manifestations of abstractions 'potential' and 'current'; furthermore, it assumes that a 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 [9], 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 [3] 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

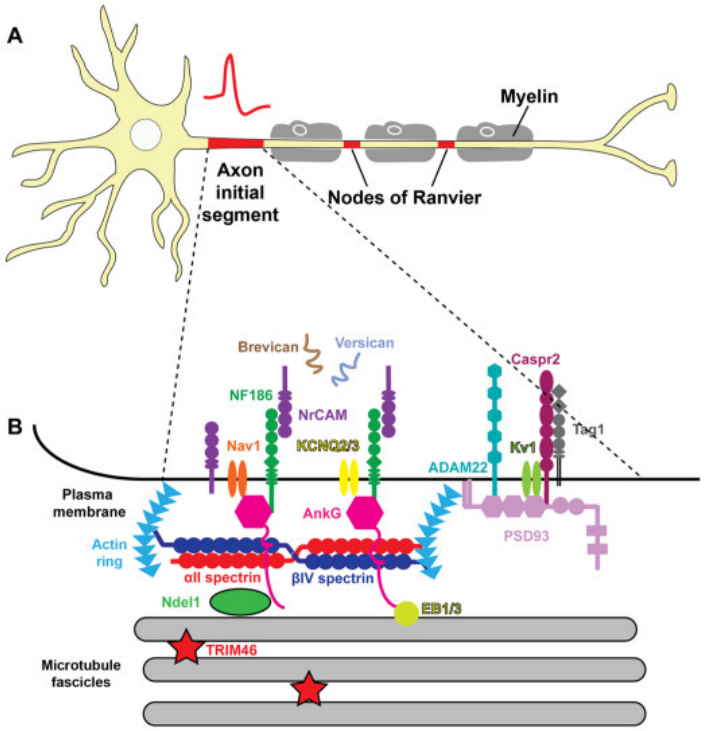


Figure .2.2: The structure of the Axon Initial Segment. [2] Ann. N.Y. Acad. Sci. 1420 (2018) 46--61, Figure 1 ©2018 New York Academy of Sciences.

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 [34]) 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*."[26]. However, there was no model, and the beautiful mathematics describes a fictitious neuron.

One of the most influencing bad ideas was expressed by their Eq.(1). In their time, at that limited microscope resolution, they did not see any structure within the neuron's membrane, so logically, they assumed that the measured capacitance and resistance were distributed. Correspondingly, they introduced an electric equivalent circuit assuming that the neuronal RC circuit comprised parallelly connected discrete R and C elements. They described the neuronal operation as based on an integrator-type equivalent electric circuit with the corresponding equations.

They assumed that a fixed voltage drives a constant current through the circuit, and the discrete R and C elements share that current. Correspondingly, a leaking current must exist, and the resting brain must dissipate power (as later estimated, around $20\ W$). However, the operation of the neuronal circuit resulted in well-measurable hyperpolarization (the output voltage changes its sign), which the equivalent *parallel* electric circuit cannot produce, so they assumed that in addition to a Na^+ current, a delayed K^+ current to flow through the neuron membrane in *the opposite direction*, against the flow of Na^+ ions. In their milestone work, their goal was to derive equations for practical application, so they introduced equations describing the measured electric observations. Unfortunately, they attempted to determine which processes were going on inside the biological neuron.

In the past years, instrumental advances have enabled us to discover the "white spots" of their time. Around 2018, the AIS was discovered and understood [35, 2]. 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. .2.2, 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 con-

cluded 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 [36] 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 .2.3: 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

$$V_{out}(t) = RC \sum \frac{dV_{in}}{dt} \tag{.2.1}$$

As we derived, the (the measured AP) output voltage can be described by the equation describing the serial RC circuit. Our equations enable us to calculate the ion current's time course from the potential's time derivative. We need to sum the time derivatives of the voltages that drive the neuronal oscillator through its membrane (of course, considering that the current needs time to travel from its entry point to the membrane's body) and solve the differential equation by integrating it in time. The resulting output voltage time derivative can be measured in front of and after the AIS. Interestingly, the time derivative was measured as early as 1939 [37], 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 .2.3 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

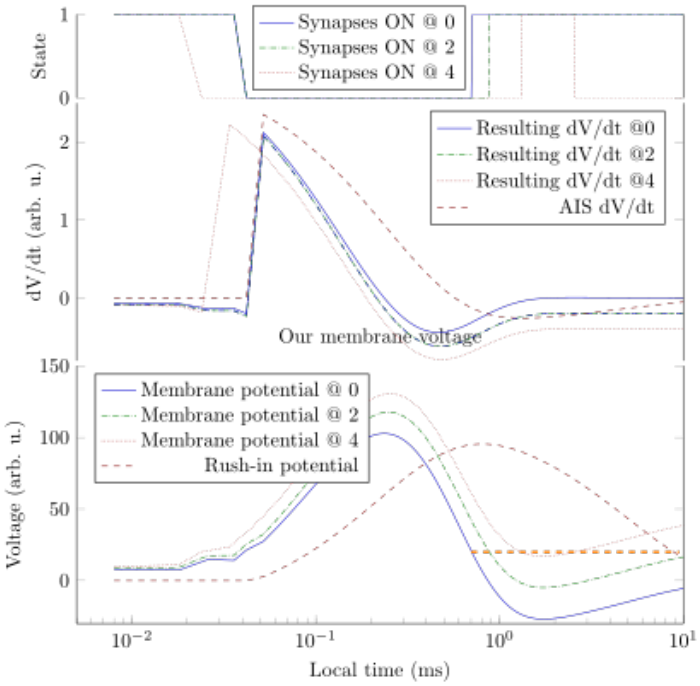


Figure .2.3: How the physical processes describe membrane's operation

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.(.2.1)) 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 [38, 39] 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. .2.1 shows how the resulting iAPTD controls the output APs shape: the derivative changes its polarity by $\approx\ 500\ mV/ms$ in $\approx 0.5\ ms$, which means across a $50\ \mu m$ AIS a $20,000\ V/m$ gradient change on the AIS. This voltage gradient is sufficient to accelerate the ions in the ion channels and decelerate them again; this is how to reverse the current direction. We see the effect of 'ram current' as AP Notice the broadening effect of the gradient measuring technology. A voltage difference is measured at a distance difference, and – due to the signal's speed – the time difference is comparable in size to the period of polarity change of the signal.

As the meticulous review [1] 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.

2.3 Experimental evidence

2.3.1 Stokes' Law

The most known and influencing axon current measurement has been published in 1952 [3]. 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 [3] 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.

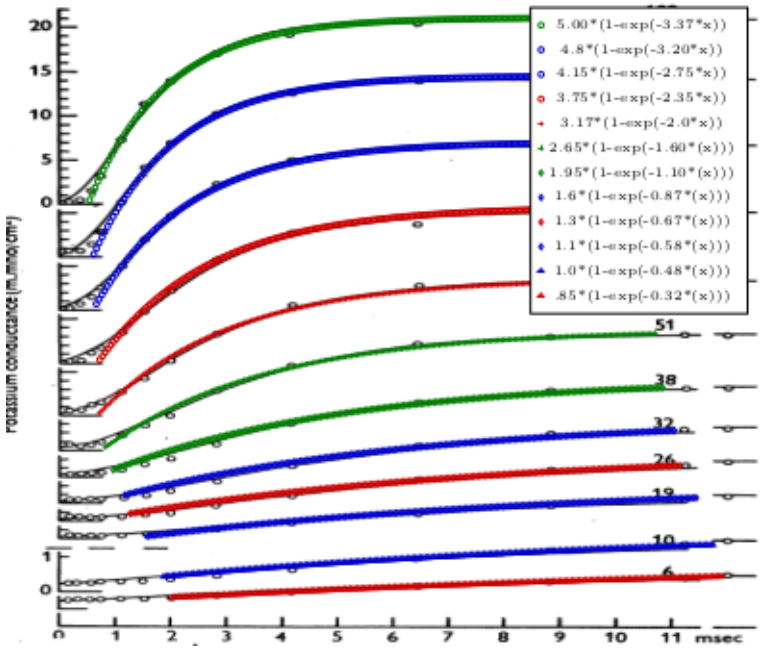


Figure 2.4: Finding time constants and membrane current by fitting data measured by HH (Fig. 3 in [3]) with our theoretically derived function (see Eq.(**??**))("Copyright [1991] Society for Neuroscience")

They measured the time course of the axonal current at different clamping voltages. Their result is reproduced in Fig. 2.4. As we discussed, ions diffuse in the axon's wall, producing a saturation-type current. Our simple model assumes that α is constant in time but (through v and $\frac{dV}{dx}$) depends on the clamping voltage).

Chapter 3

Physics for biology

A common fallacy in biology is that physics cannot precisely underpin the operation 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 analyzis to do so. We need to use the appropriate abstractions and approximations for the phenomena, depending on the level of abstraction 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 for physics (mainly electronics) and which approximation should be used instead it for biology. As we discuss, biophysics simply translated the major terminus technicus words from the corresponding words from the theory and practice of physics' major subfields, maily electricity, which was worked out for homogenous, isotropic, structureless metals; to the structured, non-homogeneous, non-isotropic, material mixtures and for a single interaction speed. 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.

As 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. Here we scrutinize the basic notions and discover similar differences between physics and biology as consequences of the required different abstractions and approximations.

3.1 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 valid-

ity. 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".[7] 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, mathematical calculus (integral and differential) was invented mainly for the practical needs of analyzing spatial motion of bodies. Similarly, Minkowski's mathematics theory proliferated widely [40] 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 are valid only until more meticulous observations require to consider speed and acceleration (time derivative of position) dependence in addition to position dependence.

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 approximation 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 is, unfortunately, 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 [41] (using the speed of light as the value for its external parameter). Still, the Minkowski-mathematics [42] behind the special theory of relativity works with any speed parameter c. The same mathematics describes technical [14] and biological [15] 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. Furthermore, that *without charge, 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 speed 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.

3.2 Abstractions and 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. As Hodgkin and Huxlex expressed: "the success of the equations is no evidence in favour of the mechanism" [3]. 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.

3.3 Interaction speeds in nature

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.

3.3.1 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 [43]. Although Newton surely knew that the observation speed was finite, in his ”Philosophiae Naturalis Principiai Mathematica” [44], 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 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 [42] 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 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* [45] 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.

3.3.2 Speed in neuroscience

Helmholtz, in 1850, sent a short report off to the Academy [46] "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" [47].

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 [48] 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 (and that of the attached "transversal ion current") 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' [29].

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 [26]. 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 are used, the better is the agreement (accu-

racy) 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".

3.3.3 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), the speed 10^5 of thermal motion and potential-assisted motion, the apparent speed of current (as 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 [2]) 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 [49]) 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*; a biological example see 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 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

$$\frac{F(t)}{Q_1} = k\frac{Q_2}{r^2}(t-\frac{r}{c}) \tag{.3.1}$$

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, but it is valid for a single point in space-time (in other words, in differential equation form). 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

$$I_{out}(t) = -I_{in}(t - \Delta t) \tag{.3.2}$$

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 [3], on a $0.3\ cm$ distance, it is in the $0.1\ msec$. 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 [2]. *We must not describe the axon or the membrane with the usual Kirchoff equation: the input and the output currents flow at different times; 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. **??**, 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 @cite HodgkinHuxley:1952, led to numerical difficulties, and they faced the principal problem: their equations assumed infinitely fast electric interaction, and they attempted to combine them with the (unknown) finite macroscopic speed of current in neuronal telegraph cables. The validity of using cable equations for biological objects is at least doubtful: deriving a telegrapher equation assumes applying an external potential to the cable filled with charge carriers, and in the case of biological membranes neither external potential nor permanently present charge carriers exist. Furthermore, the cable equation assumes continuous current outflow (a distributed resistance), which is not true for the neuronal membrane (current flows only toward the AIS).

3.3.4 Mixing interaction speeds

It is a mystery in biology 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*.

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 field 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 [50]. Telegrapher's equations (also used to describe biological signal transfer) explicitly assume a finite propagation speed millions of times slower than the 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 [51, 14].

The theoretical model [9] 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 [3, 52], 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 operation.

3.3.5 Simultaneous interactions

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 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 quantities). 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 the classic physics – the interactions are instant) and differ by several orders of magnitude in the second. Of course, the Maxwell equations can be nicely solved and modeled if one introduces [**?**] 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. It is really a novel paradigm leading to "(mis)understanding cell interactions", but definitely describes some alternative nature.

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.

The instant interaction in the 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. We put together a series of stages to describe the complex phenomena observed in the neurons' electric processing, 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 the different interaction speeds. In this way we reduce the problem to a case that science can describe mathematically. *This procedure is different from that one applies some mathematical equations derived for an abstracted case of science to a biological phenomenon without validating that we use the appropriate formalism; than eventually attemps to find the mechanism which is described by the formalism.*

We are at the boundary of microscopic and macroscopic world, and we must consider different interactions with 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.

3.4 Electricity in biology

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' [37]. However, at that time physiologically defined fine details were not known.

In the 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; or one may believe that the system shows 'non-ohmic' behavior; that is it cannot be described by Laws of physics. The oscillators represent a case when the primary electric entities represent a case needing careful analyzis.

3.4.1 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. On 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

$$I = \frac{dQ}{dt} = q * n * A * v \tag{.3.3}$$

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 usually needs an external force field. However, notice that the fellow charge carriers in the current also affect the speed. One of the basic mistakes by HH was to omit that effect (practically, neglecting the Coulomb force for ion's electric interaction).

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 with 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.

3.4.2 Current's speed

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

$$F_d = 6 * \pi * \eta * R * v \tag{.3.4}$$

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

$$F_e = k\frac{dV}{dx}q \tag{.3.5}$$

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 :

$$I = \frac{k * q^2 * A}{6 * \pi * \eta * R} * n * \frac{dV}{dx} \tag{.3.6}$$

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

$$I = \frac{C_k(x) * A * dx * q}{dt} = C_k(x) * A * q * v \tag{.3.7}$$

Combining equations .3.6 and .3.7:

$$v = \frac{k * q}{C_k(x) * \eta * 6 * \pi * R} * \frac{d}{dx} V_m(x) \tag{.3.8}$$

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 speeds limit the other interaction speed if the interactions generate each other.*

Models in neuroscience (as reviewed in [53]) 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.

3.4.3 Conductance

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." [37] It is wort to recall that *performing an electric measurement on the operation of some electric system always represents an intervention into the electric process of the system under study*; the question only is how much the measurement influences those operating processes. Measuring 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. It is frequently forgotten that the mentioned processes "produce" electric charge in the measured system. Somehow, researchers forgot this warning and attibuted the created charge to some changed conductivity. We attempt to interpret the notions precisely below.

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

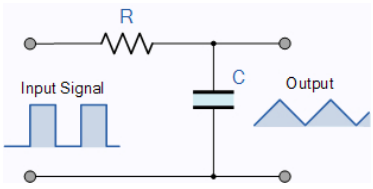
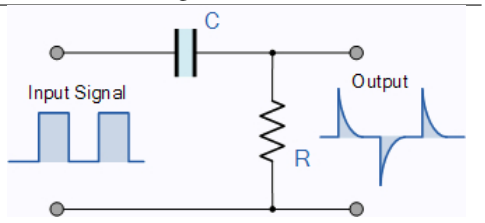
- Charged objects that can be moved, the charge carriers
- An electric field that moves the charge carriers
- No other field (such as concentration gradient) that moves the charge carriers
- A medium that 'resists' moving the charge carriers

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 [6], 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 [54]. 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 is in a fieldless stationary electric state. *The device calculates the displayed result as if the object*

Table 3.1: RC circuit types

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

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).

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.(.3.6): the current grows as the numer 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 conductance attributed to axons and membrane*, which are resting conductance. A systematic error due to the incomplete understanding of the physics of electric measurements. See Fig. 6 in [3] 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.

3.4.4 Oscillator

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 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 **??**) that their output is defined by the *time integral* of the input voltage (or current) or by its *time derivative*. From 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 rising output voltage, and the falling edge generates a voltage with opposite sign compared to the input 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.

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 3.5.1): the differentiator is the circuit, which can be described by the biological laws of motion, namely by Eq.(.3.13).

3.5 Electrodiffusion

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* (external voltage accelerates the ions) speeds. In some cases, biological systems 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 work out a physics-based approximation that mathematical formalism can describe.

3.5.1 Laws of motion

From a physical point of view, ionic solutions are confined to a well-defined volume, with no interaction with the rest of the world. At a microscopic level, on the one hand, we use the abstraction they are 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, esentially 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 time derivative of its change of position*. Notice that in this case we make *one abstraction* that the object (the carrier) has *one attribute*, its mass.

For 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 hyatus, physiology cannot describe the electrochemical processes: *the second law of motion for electrodiffusion is missing*. Biophysics sees that the interaction speeds differ enormously: "while diffusion is like a hopping flee, electrodiffusion is like a flee that is hopping in a breeze" [11]. This sentence is the complete mathematical description of a state change. 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.

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*

$$\frac{d}{dx}V_m(x) = -\frac{RT}{\zeta_k F}\frac{1}{C_k(x)}\frac{d}{dx}C_k(x) \tag{.3.9}$$

It is discussed in good textbooks (see, for example, [11], 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, ζ_k 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.

Calculating 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 [55]). 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 [11] 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.

Eq.(.3.9) 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 [56]. As expected, selecting the speed (aka calculating the appropriate value of the macroscopic speed, see Eq.(.3.8)) 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 3.4.2.

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 .3.9 is valid for a given time t. At time $t + dt$, in another steady state, the two interactions manifest at different times: we have

$$\frac{d}{dx}V_m(x + v(x) * dt) = -\frac{RT}{\zeta_k F}\frac{1}{C_k(x)}\frac{d}{dx}C_k(x) \tag{.3.10}$$

or, equivalently, it can be expressed as

$$\frac{d}{dx}C_k(x - v(x) * dt) = -\frac{\zeta_k F}{RT}C_k(x)\frac{d}{dx}V_m(x) \tag{.3.11}$$

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

$$dV_m(x) = dx * \frac{d}{dx}V_m(x) = -dx\frac{RT}{\zeta_k F}\frac{1}{C_k(x)}\frac{d}{dx}C_k(x) \tag{.3.12}$$

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

$$\frac{d}{dt}V_m(x) = v(x) * \frac{d}{dx}V_m(x) = -v(x) * \frac{RT}{q * F}\frac{1}{C_k(x)}\frac{d}{dx}C_k(x) \tag{.3.13}$$

As section 3.4.4 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 .3.25 and .3.26, which directly consider the current production mechanism.
Similarly, at time $t - dt$, in another steady state, we have

$$dC_k(x - v(x) * dt) = dx * \frac{d}{dx}C_k(x) = -dx\frac{\zeta_k F}{RT}V_m(x)\frac{d}{dx}V_m(x) \qquad (.3.14)$$

$$\frac{d}{dt}C_k(x) = v(x) * \frac{d}{dx}C_k(x) = -v(x)\frac{\zeta_k F}{RT}V_m(x)\frac{d}{dx}V_m(x) \qquad (.3.15)$$

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.

3.5.2 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. (.3.9) provides only position derivatives.

Electric invasion

By introducing time derivatives by Eqs. (.3.13) and (.3.15), 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.

3.5.3 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.,

$$\int_0^{+\infty} z\frac{dV}{dx}(x) \tag{.3.16}$$

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 .3.1. 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

$$F_m \propto \int_0^{+\infty} \big(\frac{dV}{dx}(x) - \frac{dV}{dx}(x+1)\big) \tag{.3.17}$$

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

$$F_m \propto \big(\int_0^{-\infty} \frac{V}{x}dx - \int_0^{+\infty} \frac{V}{x+1}dx\big) = -ln(x)\big]_0^{\infty} + ln(x+1)\big]_0^{\infty} \tag{.3.18}$$

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

$$F_m(x) \propto ln(\frac{x}{x+1}) \tag{.3.19}$$

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

$$\frac{dV}{dx}(x) \propto F_{bulk}\big(ln(\frac{x}{x+d})\big) \tag{.3.20}$$

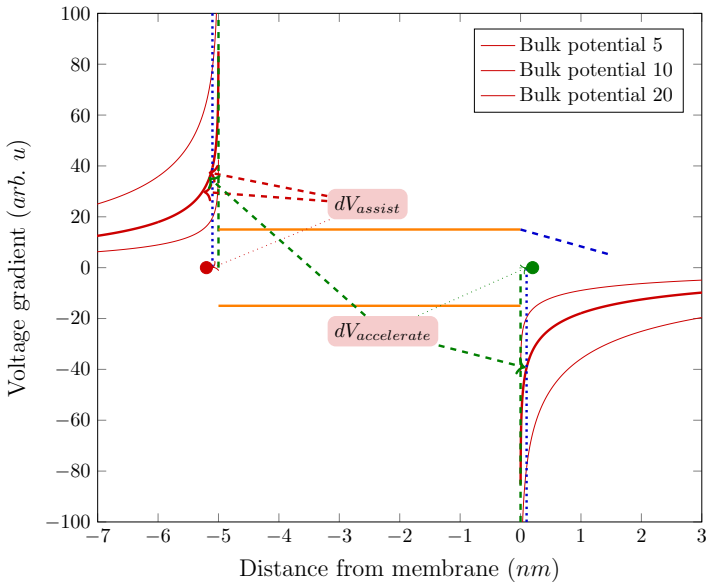


Figure .3.1: The neuronal membrane's extra *potential gradient* in the function of the distance from the membrane's surface and the bulk potential. The thickness of the atomic layers proximal to membrane's surfaces are also shown.

Although from thermodynamical point of view the segments are isolated, the extra potential gradient invokes an extra concentration gradient change according to Eq.(.3.9). Integrating by parts (using that $\int udv = uv - \int vdu$) we arrive at that the potential is

$$V(x) = ln\big(\frac{x}{x+d}\big)x - ln(|x+d|) + C \tag{.3.21}$$

or in a different form

$$V(x) = V_o * ln\big(\frac{x}{|x+d| * (x+d)}\big) + C \tag{.3.22}$$

Figure .3.1 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 [29] 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

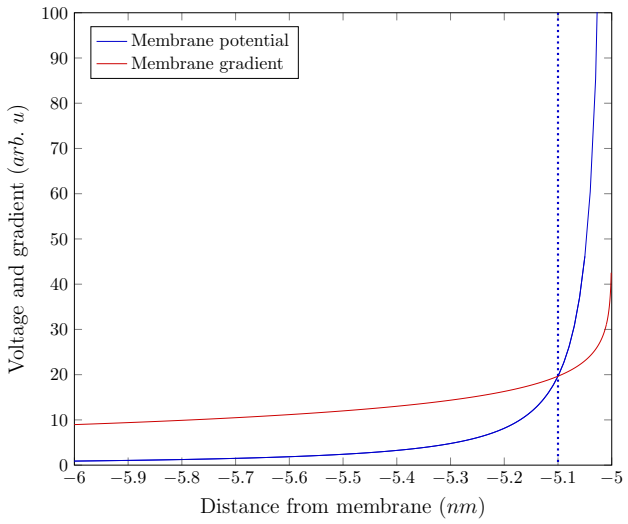


Figure .3.2: The extra membrane potential gradient see Eq.(.3.20) and extra potential Eq.(.3.21) in the function of the distance from the membrane's surface. Also shown the assumed thickness of the 'atomic ion layer' . For illustration, a simple capped ion channel in the membrane's wall is also displayed, but its effect on the potential is not accounted for.

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.)

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, such as the GHK potential, should bee 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.(.3.1). 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. .3.2 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. (.3.9). 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 dis-

tance 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. (.3.8)), 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 [2]), 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.

3.5.4 Demon in the membrane

We can build 'Maxwell-demon'-like objects into the separating membrane: a gated ion channel, see Fig. (.3.1). 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."[57] 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" [58]. 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 $100,000\,V/cm$" [29]. 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. .3.1 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" [29].

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" [29].

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 [59] 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 2.1.1), 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 [1], see Fig. .2.1, 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. (.3.8). 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 [60]) 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 [61].

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^+ [29]". 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.

3.5.5 Current handling

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

Current drain in the layer

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.(.3.9) 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 [11]. 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)

$$I_{Drain} = I_o * \exp(-\frac{1}{\beta} * t) \tag{.3.23}$$

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 [38, 39] in the case of axons (later on the membrane), or on a resistor, see the AIS [62]. 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 2.2, 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 [32].

Current source in the layer

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

$$I_{source} = I_o * (1 - \exp(-\frac{1}{\alpha} * t)) \tag{.3.24}$$

As evidence shows, the current provided by a population of ion channels depends only on their number and surface density, and the ion channels are distributed evenly over the surface. The charges appear everywhere on the surface, including near the

drain. That means that the drain current starts immediately (the repulsion of the appeared charge creates the driving force), and an exponentially increasing current will flow in the layer with a potential-assisted speed. Its intensity will change due to the changing intensity of the source current and the changed potential drop in the drain. The two currents flow simultaneously, and its intensity is the product of the source current and drain current (this form, with different coefficients, seems to be valid for several biological systems comprising ion channels)

$$I_{out} = I_o * (1 - \exp(-\frac{1}{\alpha} * t)) * exp(-\frac{1}{\beta} * t) \quad (.3.25)$$

The voltage's time derivative describing the current in a system with source and current, needed for the biological law of motion (see section 3.5.1), is

$$\frac{dV_a}{dt} = \frac{1}{\alpha} * exp(-\frac{1}{\alpha} * t - \frac{1}{\beta} * t) - \frac{1}{\beta} * exp(-\frac{1}{\beta} * t) * exp(1 - exp(-\frac{1}{\alpha} * t)) \quad (.3.26)$$

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. .2.1). 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 [1] is reproduced in our Fig. .2.1. Later, the effect of the sudden change consolidates, and the gradient disappears (similarly to a damped oscillation) in a discharge-like way due to the intense current toward the drain. (The classic picture using fast currents would produce a simple discharge gradient with no AP-like form.)

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

Current without external potential

Notice that our interpretation and equations excellently and naturally describe also the axonal current propagating without an external voltage. The AP arrives at the beginning of the axon in the form of 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.

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. One can quantitatively model the transmission along the axon using the equations and a three-state ion model [63]. (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 beginning to properly 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.)

slow current electric features

Chapter 4

Neural computing

Computing

Chapter 5

Neural information

Information

Bibliography

[1] B. Bean, Nature Reviews Neuroscience **8** (2007). DOI 10.1038/nrn2148

[2] M.H.P. Kole, S.U. Ilschner, B.M. Kampa, S.R. Williams, P.C. Ruben, G.J. Stuart, Nature Neuroscience **11**, 178 (2008). DOI 10.1038/nn2040

[3] A.L. Hodgkin, A.F. Huxley, J. Physiol. **117**, 500 (1952)

[4] J. Ngai, Neuron **112** (2024). DOI 10.1016/j.neuron.2024.09.007

[5] P.W. Anderson, Science **177**, 393 (1972). DOI 10.1126/science.177.4047.393

[6] D. Johnston, S.M. sin Wu, *Foundations of Cellular Neurophysiology* (Massachusetts Institute of Technology, Cambridge, Massachusetts and London, England, 1995)

[7] B. Podobnik, M. Jusup, Z. Tiganj, W.X. Wangi, J.M. Buld, H.E. Stanley, Applied Physical Sciences **45**, 11826 (2017). DOI 10.1073/pnas.1705704114

[8] T.J. Sejnowski, C. Koch, C.P. S, Science **9**, 1299 (1988). DOI 10.1126/science.3045969

[9] J. Végh, Á.J. Berki, Entropy **24**(8), 1086 (2022). DOI 10.3390/e24081086

[10] G. Buzsáki, Neuron **68**(4), 362 (2010). DOI 10.1016/j.neuron.2010.09.023

[11] C. Koch, *Biophysics of Computation* (Oxford University Press, New York, Oxford, 1999)

[12] E. Human Brain Project. Human Brain Project. https://www.humanbrainproject.eu/en/ (2018)

[13] D. Chu, M. Prokopenko, J.C. Ray. Computation by natural systems. https://www.researchgate.net/publication/328398755_Computation_by_natural_systems (2018). DOI 10.1098/rsfs.2018.0058. Accessed: 2024-03-30

[14] J. Végh, Informatics **8**(4) (2021). DOI 10.3390/informatics8040071

[15] J. Végh, Á.J. Berki, Acta Biotheoretica **70**(4), 26 (2022). DOI 10.1007/s10441-022-09450-6

[16] S.J. van Albada, A.G. Rowley, J. Senk, M. Hopkins, M. Schmidt, A.B. Stokes, D.R. Lester, M. Diesmann, S.B. Furber, Frontiers in Neuroscience **12**, 291 (2018)

[17] J. Végh, Brain Informatics **6**, 1 (2019). DOI 10.1186/s40708-019-0097-2

[18] US DOE Office of Science. Report of a Roundtable Convened to Consider Neuromorphic Computing Basic Research Needs. https://science.osti.gov/-/media/ascr/pdf/programdocuments/docs/Neuromorphic-Computing-Report_FNLBLP.pdf (2015)

[19] D. Markovic, A. Mizrahi, D. Querlioz, J. Grollier, Nature Reviews Physics **2**, 499 (2020). DOI https://www.nature.com/articles/s42254-020-0208-2.pdf

[20] A. Mehonic, A.J. Kenyon, Nature **604**, 255 (2022). DOI 10.1038/s41586-021-04362-w

[21] C.E. Shannon, The Bell System Technical Journal **27**(3), 379 (1948). DOI 10.1002/j.1538-7305.1948.tb01338.x

[22] A.G. Dimitrov, A.A. Lazar, J.D. Victor, Journal of Computational Neuroscience **30/1**, 1 (2011). DOI 10.1007/s10827-011-0314-3

[23] C.E. Shannon, IRE Transactions in Information Theory **2**, 3 (1956)

[24] D.H. Johnson, *Information theory and neuroscience: Why is the intersection so small?* (IEEE, 2008), pp. 104–108. DOI 10.1109/ITW.2008.4578631

[25] L. Nizami, Cybernetics & Human Knowing **26**(4), 47 (2019)

[26] B. Ermentrout, T.H. David, *Mathematical Foundations of Neuroscience* (Springer, New York, 2010)

[27] B.J. Patlak, M. Ortiz, J. Gen. Physiol. **86**, 89 (1985)

[28] P.F. Cranefield, F.A. Dodge, *Slow Conduction in the Heart* (Springer Netherlands, Dordrecht, 1980), pp. 149–171. DOI 10.1007/978-94-009-8890-3_7. URL https://doi.org/10.1007/978-94-009-8890-3_7

[29] B. Alberts, A. Johnson, J. Lewis, et al., *Molecular Biology of the Cell*, 4th edn. (New York: Garland Science, New York, 2002)

[30] M. Stemmler, C. Koch, Nat Neurosci **2**, 521 (1999)

[31] Y.A. Cengel, Entropy **23**(6) (2021). DOI 10.3390/e23060779. URL https://www.mdpi.com/1099-4300/23/6/779

[32] A. El Hady, B.B. Machta, Nature Communications **6**, 6697 (2019). DOI 10.1038/ncomms7697

[33] D. Purves, G.J. Augustine, D. Fitzpatrick, L.C. Katz, A.S. LaMantia, J.O. McNamara, S.M. Williams (eds.), *Neuroscience*, 2nd edn. (Sinauer Associates, 2001). URL https://www.ncbi.nlm.nih.gov/books/NBK10799/

[34] D.E. Pence, Philosophy of Science **84**(5), 1177 (2017). DOI 10.1086/694040

[35] C. Leterrier, Journal of Neuroscience **38**(9), 2135 (2018). DOI 10.1523/JNEUROSCI.1922-17.2018

[36] W.B. Levy, V.G. Calvert, Proceedings of the National Academy of Sciences **118**(18), e2008173118 (2021). DOI 10.1073/pnas.2008173118

[37] K.S. Cole, H.J. Curtis, The Journal of General Physiology (1939). DOI doi.org/10.1085/jgp.22.5.649

[38] A. Goikolea-Vives, H. Stolp, Int J Mol Sci **15** (2021). DOI 10.3390/ijms22158220

[39] K. Hasegawa, K. ichiro Kuwako, Seminars in Cell & Developmental Biology **129**, 103 (2022). DOI https://doi.org/10.1016/j.semcdb.2022.02.015. URL https://www.sciencedirect.com/science/article/pii/S1084952122000544. Special Issue: Molecular dissection of cognition, emotion and thought by Akira Sawa & Takeshi Sakurai / Special Issue: Emerging biology of cellular protrusions in 3D architecture by Mayu Inaba and Mark Terasaki

[40] L. Pyenson, Archive for History of Exact Sciences **17**, 71 (1977). DOI 10.1007/BF00348403

[41] A. Das, *The special theory of relativity: a mathematical exposition*, 1st edn. (Springer-Verlag New York, 1993)

[42] Hermann Minkowski, Nachrichten von der Königlichen Gesellschaft der Wissenschaften zu Göttingen (in German) pp. 53–111 (1908)

[43] Wikipedia. Roemer's determination of the speed of light. URL https://en.wikipedia.org/wiki/R%C3%B8mer%27s_determination_of_the_speed_of_light

[44] I. Newton. Philosophiae naturalis principia mathematica. URL https://www.britannica.com/topic/Principia

[45] S. Walter, ESI News **1**(3), 6 (2008)

[46] H. Schmidgen. Of frogs and men: the origins of psychophysiological time experiments, 1850-1865 (1850)

[47] The rise of experimental psychology (1850)

[48] W.S. McCulloch, W. Pitts, j-BULL-MATH-BIOPHYS **5**(4), 115 (1943). DOI https://doi.org/10.1007/BF02478259. URL http://link.springer.com/article/10.1007/BF02478259

[49] I. Popov, Z. Zhu, A.e.a. Young-Gonzales, Commun Chem **6** (2023). DOI 10.1038/s42004-023-00878-6

[50] H.A. Ulku, A.A. Ergin, IEEE Transactions on Antennas and Propagation **59**(11), 4123 (2011). DOI 10.1109/TAP.2011.2164180

[51] W. Luk. Imperial College London, textbook. http://www.imperial.ac.uk/~wl/teachlocal/cuscomp/notes/chapter2.pdf (Accessed on Dec 14, 2020) (2019)

[52] A. Mason, A. Nicoll, K. Stratford, The Journal of Neuroscience **11**, 79 (1991)

[53] D.S. Bassett, P. Zurn, J.I. Gold, Nature Reviews Neuroscience **19**, 566 (2018). DOI 10.1038/s41583-018-0038-8

[54] I. Abraham, Nature Scientific Reports **8**, 10972 (2018). DOI 10.1038/s41598-018-29394-7

[55] Q. Zheng, W. G.W., J Chem Phys **19** (2011). DOI 10.1063/1.3581031

[56] D. Forcella, J. Zaanen, D. Valentinis, D. van der Marel, Phys. Rev. B **90**, 035143 (2014). DOI 10.1103/PhysRevB.90.035143. URL https://link.aps.org/doi/10.1103/PhysRevB.90.035143

[57] I. Karbat, et al., Cell **178** (2019)

[58] G. Wisedchaisri, et al., Cell **178**, 993.1003.e12 (2019). DOI 10.1016/j.cell.2019.06.031

[59] C. Kutzner, D.A. Köpfer, J.P. Machtens, B.L. de Groot, C. Song, U. Zachariae, Biochimica et Biophysica Acta **1858**, 1741 (2016)

[60] C. Koch, T.A. Poggio, Proceedings of the Royal Society of London. Series B. Biological Sciences **218**, 455 (1983)

[61] J.M. Beggs, D. Plenz, Journal of Neuroscience **23**(35), 11167 (2003). DOI 10.1523/JNEUROSCI.23-35-11167.2003

[62] C.Y.M. Huang, M.N. Rasband, Ann N Y Acad Sci. **1420**, 46 (2018). DOI 10.1111/nyas.13718

[63] I. Goychuk, P. Hänggi, J.L. Vega, S. Miret-Artés, Phys. Rev. E **71**, 061906 (2005). DOI 10.1103/PhysRevE.71.061906. URL https://link.aps.org/doi/10.1103/PhysRevE.71.061906

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