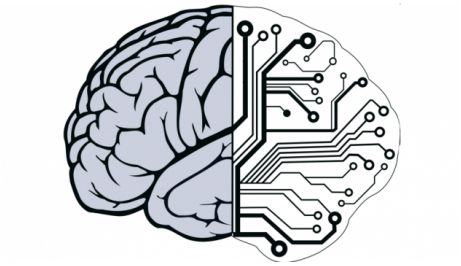
"*Though this be madness, yet there is method in't.*"
Shakespeare: Hamlet: Act 2 Scene 2

Abstract Neuron Dynamics

The true physics, computing, and information handling behind physiology



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Overview

Why another neuron(al) theory and simulator

The dynamic operation of individual neurons, their connections, higher-level organizations and connections, and finally the brain and the mind, 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. 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 (the single speed, isolated pair-wise instant interactions) applied to biological materials without revisiting them; and applying ad-hoc mathematical formulas without correct physical processes in the backgound (actually creating an alternative nature).

Nature is overly complex: science fields must use different approximations and abstractions 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. *No presently available theoretical description and simulator are capable to perform that task*.

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' [1]. 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'[1]. The goal was set decades ago: '*The ultimate aim of computational neuroscience is to explain* ***how electrical and chemical signals are used*** *in the brain to* ***represent and process information***' [2]. We base our discussion on those general basic principles and create an @link NeuronPhysical 'abstract physical neuron'@endlink, 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 @link PHYSICS the true physics@endlink behind biological phenomena. To do so, we need to understand ¡i¿how neurons information@endlink¡/i¿ [3]. We agree that 'The basic structural units of the nervous system are individual neurons' [1], but we are also aware

of that neurons 'are linked together by dynamically changing constellations of synaptic weights' and 'cell assemblies are best understood in light of their output product' @cite BuzsakiCellAssemblies:2010, so we also

'The brain computes! This is accepted as a truism by the majority of neuroscientists.' @cite KochBiophysics:1999 However, '¡i¿we so far ¡b¿lack principles to understand rigorously how computation is done¡/b¿¡/i¿ in living, or active, matter' @cite NaturalComputation:2018. To understand how "computation is done", we in close cooperation with @cite RoleOfInformationTransferSpeed:2022. We attempt to synthetise the available knowledge with a fresh eye, and intend to make a leap in understanding neural computing, scrutinizing our knowledge pieces one-by-one, for credibility, relation to other pieces, to other sciences, finding contradictions and its resolutions, ¡i¿defying fallacies¡/i¿. Sometimes you may need our or the search engine (see the right side of the title line).

The site is not exclusively about theory: we give also a programmed implementation of the ideas we describe. has direct science base, instead of ad-hoc mathematical formulas; and the only one which is able to reproduce 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.

¡b¿Warning: ¡/b¿Please consider that this development is a one-man undertaking, and it shall develop theory, evaluation of published experiment, 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

Modeling single neurons

Single neurons

Chapter 2

Physiology (abstract)

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.

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" [4].

2.2 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.

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 'instant' in the sense that one interaction is much faster than the process under study; we use the notion in that sense and consider the faster interaction as instant. 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.*

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 macroscopicwhere more than one abstractions must be used. Still, they show behavior of both worlds, furthermore, they change their behavior during the course of the studied process.

2.3 Electrodiffusion

In our research, the key point is that life 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.

2.3.1 Nernst-Planck equation

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, 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, they are 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, density, 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.

Steady state

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 spaces on each other) using the *Nernst-Planck electrodiffusion equation*

$$\frac{d}{dx}V_m(x) = -\frac{RT}{\zeta_k F}\frac{1}{C_k(x)}\frac{d}{dx}C_k(x) \tag{2.1}$$

It is discussed in good textbooks (see, for example, [5], 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 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 [6]). 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 [5] 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 (*space 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.(2.1) describes a stationary state with no ionic movement. Deriving a time course (time derivatives) from the space 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 [7]. As expected, selecting the speed (aka calculating the appropriate value of the macroscopic speed) plays a key role, especially since we are at the boundaries of physics abstractions; furthermore, we are mixing microscopic and macroscopic notions. The actual speed model depends on the concrete case; see section 2.4.

AAA

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 space 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; 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 coordinates are connected; in the same way as in the special theory of relativity. Let us assume that the gradients acts 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. 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, is that the moving ion represents mass transport and moving charge (electric current) simultaneously. When deriving space 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, electrodiffusion changes concentration gradient, and, simultaneously potential gradient.

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We assume that equation 2.1 is valid for a given time t. At time $t + dt$, in another steady state, the two interactions manifest at different times: we have

$$\frac{d}{dx}V_m(x + v(x) * dt) = -\frac{RT}{\zeta_k F}\frac{1}{C_k(x)}\frac{d}{dx}C_k(x) \tag{2.2}$$

or, equivalently, it can be expressed as

$$\frac{d}{dx}C_k(x - v(x) * dt) = -\frac{\zeta_k F}{RT}C_k(x)\frac{d}{dx}V_m(x) \tag{2.3}$$

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

$$dV_m(x) = dx * \frac{d}{dx}V_m(x) = -dx\frac{RT}{\zeta_k F}\frac{1}{C_k(x)}\frac{d}{dx}C_k(x) \tag{2.4}$$

so (and here the constant disappears)

$$\frac{d}{dt}V_m(x) = v(x) * \frac{d}{dx}V_m(x) = -v(x) * \frac{RT}{\zeta_k F}\frac{1}{C_k(x)}\frac{d}{dx}C_k(x) \tag{2.5}$$

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

$$dC_k(x - v(x) * dt) = dx * \frac{d}{dx}C_k(x) = -dx\frac{\zeta_k F}{RT}V_m(x)\frac{d}{dx}V_m(x) \tag{2.6}$$

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

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 assume that the ions are tiny charged 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.

2.3.2 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. (2.1) provides only space derivatives.

Electric invasion

By introducing time derivatives by Eqs. (2.5) and (2.7), we can derive further terms that describe the relation between concentration and potential for the case when the first time derivative of the space coordinate is not zero. (Here, we explicitly parallel 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 quantitatively 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.

2.3.3 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 separating 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.,

$$\int_0^{+\infty} z\frac{dV}{dx}(x) \tag{2.8}$$

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 2.1. 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

$$F_m \propto \int_0^{+\infty} \big(\frac{dV}{dx}(x) - \frac{dV}{dx}(x+1)\big) \tag{2.9}$$

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

$$F_m \propto \big(\int_0^{-\infty} \frac{V}{x}dx - \int_0^{+\infty} \frac{V}{x+1}dx\big) = -ln(x)\big]_0^{\infty} + ln(x+1)\big]_0^{\infty} \tag{2.10}$$

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

$$F_m(x) \propto ln(\frac{x}{x+1}) \tag{2.11}$$

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

$$\frac{dV}{dx}(x) \propto F_{bulk}\big(ln(\frac{x}{x+d})\big) \tag{2.12}$$

Although from thermodynamical point of view the segments are isolated, the extra potential gradient invokes an extra concentration gradient change according to Eq.(2.1). Integrating by parts (using that $\int udv = uv - \int vdu$) we arrive at that the potential is

$$V(x) = ln\big(\frac{x}{x+d}\big)x - ln(|x+d|) + C \tag{2.13}$$

or in a different form

$$V(x) = V_o * ln\big(\frac{x}{|x+d| * (x+d)}\big) + C \tag{2.14}$$

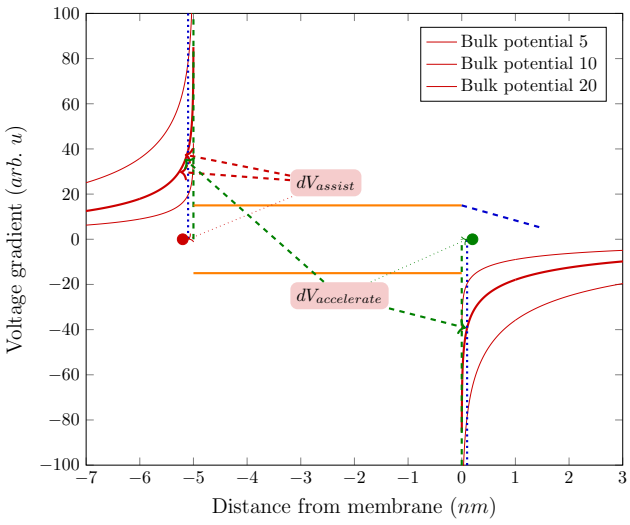

Figure 2.1: The neuronal membrane's extra *potential gradient* in the function of the distance from the membrane's surface and the bulk potential. The thickness of the atomic layers proximal to membrane's surfaces are also shown.

Figure 2.1 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 [8] that in the case of resting potential, the scale of the gradient that accelerates the ions across the ion channel is calibrated approximately as kV/cm. Recall that we are still speaking about the resting state and only about the extra gradient evoked by the finite-width membrane. We are at the boundaries of the macroscopic and microscopic worlds. We derived our integrand from the picture of discrete charges but integrated it into the picture of continuous charge distribution, so we have an empirical factor between them. We assume an atomic layer (a skin) on the surface. However, the layer itself can also be modeled as having just a few ions under their mutual repulsion on the surface or a few atomic layers on top of each other, depending on the concentration and voltage in the bulk on the two sides. (The diagram line is valid in the plane crossing the membrane and the ion channel.)

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.(2.1). 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. **??** 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. (2.1). The gradients change gradually within the segments and step-like across the membrane. Recall our remark above on the limitations of the thickness of the layers in proximity to the membrane, which also enforces limitations on the potential in the layer. No current can flow through the membrane; there is no leaking current.

We also need to notice the difference in the local gradients in the function of distance from the membrane's surface. If something changes, a dV_{assist} gradient appears between the layers and will rearrange concentration and voltage in the segment. Notice that this gradient is by orders of magnitudes smaller than the gradient $dV_{accelerate}$ which accelerates the ions in the proximity of the channel entrance (see the red ball in front of the entrance of the ion channel). According to the Stokes formula (see Eq. (2.23)), 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 [9]), 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.

2.3.4 Demon in the membrane

We can build 'Maxwell-demon'-like objects into the separating membrane: a gated ion channel, see Fig. (2.1). 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 by ion channels is the key event enabling the generation and propagation of electrical activity in excitable cells."[10] How voltage gating of channels works is still a mystery. 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" [11]. 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 work as 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.

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 $100,000\ V/cm$" [8]. 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. 2.1 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" [8].

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" [8].

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 [12] 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.

The passage is too quick to affect the bulk (see also the discussion in section 2.3.6), 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 [13], see Fig. **??**, 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. (2.23). Assuming those distances and speeds, including the *potential-assisted* speed of the slow current, we are on a time scale matching the available observations.

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 [14]) 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 [15].

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^+ [8]". The two ions have the same charge, but K^+ is nearly 70% heavier than Na^+, a definite disadvantage when accelerated by a vast electric gradient. When the layer on the arrival side gets saturated, its potential reaches the potential of the bulk on the high concentration side (this is necessary to decelerate the accelerated ions), and so the channel gets closed (the accelerating potential disappears for a short period until the ions from the layer flow away toward the drain or they diffuse toward the bulk). We assume that the ions continuously accelerate, then decelerate, due to the potential gradient (which we assume to be constant for a moment). When Na^+ ions stopped after passing the channel and built up a repulsive layer proximal to the channel's exit, the K^+ ions pass only about 60% of the channel's length. The Na^+ ions, which started from the departure layer with a handicap of $2\ to\ 3\ nm$, will arrive earlier than the K^+ ions from the $0.1\ nm$ thick charged layer proximal to the channel's entrance. That is, this handicap results in a strong enrichment of Na^+ ions.

Given the potential reverses, the late ions are decelerated and then accelerated in the reverse direction (recall that the layer they started from is still empty and attractive), and they simply go back due to the departure side. The ions also repulse each other while being accelerated (the accelerating gradient acts on a distance of $5\ nm$ while the ions may approach each other to a distance of $0.1\ nm$, so the mutual repulsion can be significant). In this way, the heavier ions help their competitors and vice versa. (The different ions can also connect to different, heavy-weight components of the solution, drastically changing the picture.) The result is that only the lighter ions can pass the channel from an ion mixture when the cup is suddenly removed. The passage is super-fast; it is in the $psec$ region (with a *voltage-accelerated* speed compared to

the *voltage-assisted* speed of after-loading ions from the next layer), and the created potential quickly decays.

2.3.5 Current handling

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, so the charge current is zero. However, they induce the corresponding changes on the opposite side. As Eq.(2.1) 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 [5]. 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. 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 layer in the segment with low concentration)

$$I_{Drain} = I_o * \exp(-\frac{1}{\beta} * t) \tag{2.15}$$

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 [16, 17] in the case of axons (later on the membrane), or on a resistor, see the AIS [18]. 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 **??**, 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 [19].

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

$$I_{source} = I_o * (1 - \exp(-\frac{1}{\alpha} * t)) \tag{2.16}$$

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

$$I_{out} = I_o * (1 - \exp(-\frac{1}{\alpha} * t)) * exp(-\frac{1}{\beta} * t) \tag{2.17}$$

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. **??**). 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 [13] is reproduced in our Fig. **??**. 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.

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.

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 [20]. (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 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.)

2.3.6 Consequences

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

We consider three operating regimes for neuronal membranes. Eq. (2.1) describes the steady state. As we discussed, in the case of the finite membrane width of biological neurons, a gradient of a particular form is created in the electrolyte, also comprising a membrane-width-dependent term. However, otherwise, the state can be described by Eq. (2.1).

In single-shot mode, along the axis of the ion channel, at large distances, the concentration and potential remain essentially unchanged during the process. Using our time derivatives, we can describe the details, including the process's time course. Given that the slowest interaction defines the propagation speed and the proportion of the layer to the bulk is extremely tiny, no significant change in bulk can be measured. The interaction speed in the bulk is practically the *drift* speed (and the gradients are zero).

In the case of high-rate, repetitive measurements, the changes occurring in the proximal layers can slowly influence the parameters of the bulk. However, this effect becomes significant only in long-term observations when a large number of single actions take place in quick succession. In a continuous high-rate firing mode, the layers have parameters other than the ones required by Eq.(2.1) for the resting state for a growing fraction of the time. We can estimate the time roughly as how long the ions can diffuse to a distance of 0.1 mm (in the order of $\frac{10^{-4}m}{10^{-4}m/s}$), and how many times that distance is greater that the assumed width of the layer proximal to the membrane's surface (in the order of $\frac{10^{-4}m}{10^{-8}m}$, that causes a 100% change). We arrive at that a rate 100 Hz will deliver a charge causing a percentage increase of the bulk concentration is in the order of at least dozens of seconds.

Connecting science to life

The two layers, plus the demon, also naturally explain why that difference comes into existence. As we explained above, when a *finite-width* membrane separating the two segments appears in the volume (due to the evolution or the development of the individual biological object), two thin electrolyte layers will be formed proximal to its surfaces on the two sides, even if the concentrations are equal. As observed, "a membrane potential arises when there is a difference in the electrical charge on the two sides of a membrane, due to a *slight excess* of positive ions over negative ones on one side and a slight deficit on the other." [21] 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*.

2.4 Calculating ion's speed

2.4.1 General

In the macroscopic world, we describe the current as the statistical time course of charge carriers carrying charge ζ_k through a cross section A. In the length dx of the wire, we have charge $dQ = \zeta_k * n * A * dx$. If the charges are moving with a speed $v = \frac{dx}{dt}$, we define the current as the charge moved per unit of time as

$$I = \frac{dQ}{dt} = \zeta_k * n * A * v \tag{2.18}$$

Notice that the macroscopic current I is zero if any of the factors is zero. If no

potential difference across the spatial points in the electrolyte exists, no current flows, so the speed is zero. However, if a potential gradient $\frac{dV}{dx}$ exists, *a force*

$$F_e = k\frac{dV}{dx}\zeta_k \tag{2.19}$$

acts on the ions in the volume. According to Stokes' Law, to move a spherical object with radius R in a fluid having dynamic viscosity η, we need a force

$$F_d = 6 * \pi * \eta * R * v \tag{2.20}$$

to move the ion in the electric force field 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. Because of the equality of these two forces, by combining these three equations, we arrive at

$$I = \frac{n * k * \zeta^2 * A}{6 * \pi * \eta * R} * \frac{d}{dx}V_m(x) \tag{2.21}$$

As shown above, we can calculate the time derivatives from the space derivatives, provided that the speed v is known. If we have a concentration C_k, in the volume $A * dx$, we have $Q = C_k * A * dx * \zeta_k$ charge, resulting in another expression

$$I = \frac{C_k * A * dx * \zeta_k}{dt} = C_k * A * \zeta_k * v \tag{2.22}$$

Combining the two equations:

$$v = \frac{k * \zeta_k}{C_k * \eta * 6 * \pi * R} * \frac{d}{dx}V_m(x) \tag{2.23}$$

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

2.4.2 Axon

Notice that our equations also work in a reversed way. If we combine Eqs. (2.23), (2.1), and (2.7), we can express how the potential changes in the function of time. If

we know the macroscopic current speed and the current's time course (directly proportional to the concentration gradient) we can calculate how the concentration gradient, and, consequently the potential gradient generate each other. We must not forget that *we are speaking about the skin instead of the bulk of the solution in the tube*.

Artificial mode

Initially, the membrane, the clamping point on the axon, and the intracellular fluid have the resting potential (the axon is galvanically connected to the membrane). When the clamping potential suddenly appears, an electric field $\frac{dV}{dx} \propto (V_{membrane} - V_{clamp})$ appears outside and inside the axon. The extracellular space with its high ion concentration C_k^{ext} represents an "ion cloud": when the clamping voltage is switched on, a "fast" current instantly delivers the potential along the *outer* surface of the axon. However, this is not the case on the *inner* surface: there is no charge on it that could change the potential.

The commonly used physical picture behind the process is that the membrane, as if it were metal, is equipotential, and the "fast" axonal current flows directly to the membrane. The case of biology is reversed compared to the classic electricity. The unusual physical situation here is that prompt $\frac{dV}{dx}$ changes are interpreted only for the case of instant interaction. Here, V remains the same: there is no charge around to produce a potential. Given that the charge carriers' speed is low, the propagation of the field has a finite speed (other than the propagation speed of the electromagnetic waves and that of the electrostatic field). The charges increase the potential locally (see Eq. (2.1)) until the clamping potential reaches the axon's end at the membrane. At that point, the driving force disappears: the potential at the two ends of the axon becomes the same.

As experimental evidence [23, 24] shows, the current arriving at the membrane initially exponentially increases and, in a millisecond time, saturates; this is misinterpreted as "delayed rectifying current" and leads to the fake conclusion that "the membrane's conductance changes". (The macroscopic streaming of ions inside the tube only slightly complicates the process: the local internal concentration can saturate only later, given that the stream delivers part of the inflowing ions to another place within the axon.) Given that we can calculate and measure the clamping current using Eq. (2.18), we can describe the potential along the axonal tube.

Axons do not passively follow the potential's time course but mediate the changes in their internal volume by using the ion pool available in their extracellular volume. Even though they are tubes and deliver charge, *we must not describe that process using the telegrapher's equation because of fundamental differences*. The electric telegraph cable continuously loses charge (current is leaking due to the specific resistance of the cable). In contrast, the biological cable keeps the current constant by pumping ions in and out. The relevant physical entities are potential and concentration gradients, as described by the Nernst-Planck equation, instead of the electric and magnetic gradients, as described by the Maxwell equations. In a biological cable, no potential is switched to the end of the cable and no leaking current is present. The lack of leaking is because the potential and concentration gradients mutually excite each other.

The applied potential opens ion channels in the axon's wall, but pumping ions in

and out needs enormous energy. A "longitudinal current" (forwarding charged particles in the direction of the apparent current) decays exponentially, so biology uses different methods for transferring information using charged particle carriers. Using "transversal current" (perpendicular to the apparent charge transfer on the surface of a membrane or inside an axon tube) or "circular current" (repolarization inside the Ranvier cells) enables transferring charge to large distances. However, using those tricks is not for free: according to Levy's measurements [25], forwarding spikes needs about 35 times more energy than producing them. The charge moves autonomously (although the membrane uses "servo" ions when pumping). Considering transient changes in the membrane's potential and discussing the charge diffusion through the axon's wall would not result in a deeper understanding of the neuronal operation in the process considered, so we omit them.

Several factors regulate the time course of the process. A physically plausible assumption is that when an external potential (such as clamping) is applied to some point of the axon, it immediately opens the ion channels in the wall of the axon, and ions start to enter the axon. "The intracellular concentration at rest is around five orders of magnitude less than that in the extracellular space" [5], and it continuously increases towards the extracellular concentration, thanks to the newly opened ion channels. A continuous inflow through the axon's wall from the extracellular space along the axon into the intracellular space increases their concentration inside the tube as a "fast current". The ions move towards the membrane as a "slow" current with a macroscopic speed. We consider the external concentration constant: the extracellular space is infinitely large, and its concentration is higher by orders of magnitude than the internal one.

The concentration also means charge density. The ions entering the intracellular space remain inside the axon (as discussed in section 11.4 of [5], "once calcium enters the intracellular cytoplasm it is not free to diffuse"). Experience shows that they experience the electric field, and (after a while) the ion's speed is constant in time but depends on the actual electric field. The *ions will slowly move* along the axon *with a field-dependent constant speed in the electric space* in a viscous solution. "In axon fibers the effective diffusion constant was estimated to be about one-tenth of the diffusion coefficient in aqueous solution" [5]; they form a "slow current". This is the reason why Hodgkin and Huxley hypothesized [23] that *"some* (otherwise invisible) *charged component of the membrane is slowly moving* and affects the ionic permeability" (the second half of the sentence intends to explain why membrane's conductance changes). They were thinking in the Newtonian way, assuming that the transport speed of electrodiffusion in the axon and the propagation of the electromagnetic field were the same, so the moving object could not be a current. This is why they expected the current to appear instantly as they switched the clamping voltage. The fake analogy with electricity was misleading in their case, too.

Native mode

Another particular case is when a spike travels along the axon. It is essentially 'propagation in a free space' (apart from the geometry of the axon limiting the 'free space' to the inner volume of a tube). Initially, electrical charge and chemical mass enter the

axon through the AIS. Given that the amount of current does not change during its transmission, a significant output current was HH [23] already measured. The axon, however, actively participates in transferring the charge.

Notice that the case of switching clamping voltage is somewhat analogous to the arrival of a spike. Initially, the axon contains no ions. The spikes (at least their front side) arriving at a synapse can be reasonably approximated by a step function (although actually, they are a steep exponential): the ions delivered in the rising edge are stalled (until the voltage can open the voltage-controlled ion channels), so, at the price of some delay, their front size can be approximated with a step function. Actually, their *time derivative* is what excites the neuron, i.e., their contribution is similar to that of the rush-in current, see Figure **??**. The spikes do not approach their corresponding saturation value (it would result in a slow operation), mainly because the negative voltage gradient (and, correspondingly, the current in the opposite direction) is slightly similar to a square-wave current input.

2.4.3 Membrane

We consider that the macroscopic ion flow into the membrane changes its concentration and potential, and it acts on the moving particles by producing a local change on the respective part of the membrane. Even for a numeric solution, we need to define a time-derivative form of Eq.(2.1) using additional assumptions; see our equations (2.5) and (2.7).

The ionic current flowing into the membrane initially increases linearly. *The conductance on the membrane has no reason to change; only the number of charge carriers on the membrane is increasing.* The usual biological interpretation of the fundamental physical notions is wrong. The current in the tube saturates: the inflow of ions through its wall increases, and the macroscopic flow of ionic current inside the tube decreases it: the axon has a transfer capacity. Simultaneously, the current flows into the membrane and starts a ”slow” current toward the AIS that represents a current drain and, in this way, causes a potential gradient. The saturation current depends on the speed of ions in the tube.

The internal concentration *in the proximal layer* near the membrane can increase by orders of magnitude, see Eq.(2.1). However, this change cannot significantly influence *the bulk of its segment* because the diffused-in ions are transported toward the membrane as an ionic current. The voltage difference drives the ionic current, and the ionic current that flows into the membrane (ions moving in a viscous fluid) continuously decreases that driving force. Given that the local potential, current, concentration, and the speed of the ion flow mutually influence each other, no analytical solution can be given. In our nearly ”net electric” model, ”slow” current flows through the axon into the membrane. We shall assume that the speed of ions depends on the effective field strength and the membrane condenser’s potential increases. We consider the effects that the delivered charge gradually changes the potential and, of course, the chemical concentration.

The ions’ speed introduces macroscopic factors, so the description can only be semi-quantitative: the layered flow in a tube likely needs empirical data. In this way, we can derive an excellent approximation (although only numerically and also using

empirical constants) of the time course of voltage, current, and conductance from the first principles. We may assume, however, that, in general, the ionic current makes only negligible change in the concentration of the bulk of the segments on the two sides of the membrane, although the long-term high-rate firing may lead to observable changes in the bulk's concentration and potential.

2.5 Action Potential

As we also discussed [26], more interactions are involved in the living matter, and the interactions need a spatiotemporal description. We use the notion of time dependence in the Einsteinian sense: the basic entities such as *location and time are connected through their interaction speed* and they are not independent parameters in the Newtonian sense. So, we expected that neurons, as dynamical electrodiffusion-based systems, are described by electrodiffusional time-dependent equations. However, it is not so.

One of the fundamental reasons is that the way of *providing time derivatives of the electrodiffusion process was not known* (see our section 2.3.1). 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 [3], 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 [23] advanced neuroscience enormously. However, their seven-decades-old hypotheses must be updated from several points of view. Among others, they provided a static empirical description (their differential equations rely on derivatives of an empirical function fitted to empirical measurement data, and even in a wrong way). They excluded interpreting the physical background of their empirical description using an empirical conductance function; in this way, really, there is "little hope of calculating .. from first principles". Their suggestion about equivalent circuits introduced the idea that the membrane's potential remains unchanged during operation despite the ion traffic, the ions in the current do not affect concentration, and the components of the circuit operate with the speed of the EM waves. By introducing the delayed current and that some mystic power controls the operation of neurons by changing their conductance, they gave way to introducing the fallacy that science and life sciences are almost exclusive fields. Furthermore, their (unintended) model provokes questions (for a review see [27]) 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*."[28]. 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 [29, 9]. 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. **??**, the currents flow into the membrane and flows out through the AIS. The currents are not shared, and even, the output current cannot directly be concluded from the sum of the input currents: the charge is temporarily stored by the membrane (as a distributed condenser). The correct equivalent circuit is one in which the condenser and resistor are switched in serial (although the resemblance has limitations), that is a differentiator-type electric circuit. This circuit is sensitive to voltage gradient, so the rising and falling edges of an input signal (such as a PSP) can natively produce an opposite voltage on its output, making the need (and the existence) of the assumed delayed K^+ current at least questionable. Also, a recent measurement [25] 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 **??**: 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

$$V_{out}(t) = RC \sum \frac{dV_{in}}{dt} \tag{2.24}$$

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 [30], 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 **??** shows how the described physical processes control neuron's operation. In the middle inset, when the membrane's surface potential increases above its threshold potential due to three step-like excitations opens the ion channels, Na^+ ions rush in instantly and create an exponentially decreasing, step-like voltage derivative that charges up the membrane. The step-like imitated synaptic inputs are resemblant to the real ones: the incoming PSPs produce smaller, rush-in-resemblant, voltage gradient contributions. The charge creates a thin surface layer current that can flow out through the AIS. This outward current is negative, and proportional to the membrane potential above its resting potential. At the beginning, the rushed-in current (and correspondingly, its potential gradient contribution) is much higher than the current flowing out through the AIS, so for a while the membrane's potential (and so: the AIS current) grows. When they get equal, the AP reaches its top potential value. Later the rush-in current gets exhousted and its potential-generating power drops below that of the AIS current, the resulting potential gradient changes its sign and the membrane potential starts to decrease.

In the previous period, the rush-in charge was stored on the membrane. Now, when the potential gradient reverses, the driving force starts to decrease the charge in the layer on the membrane, which per definitionem means a reversed current; without foreign ionic stream and current through the AIS This is the *basic difference between the static picture* that Hodgkin and Huxley hypothesized *the biology uses and the dynamic one that really describes its behavior*. The equivalent electric circuit of a neuron is a serial,

instead of a parallel, oscillator, and its output voltage is defined dynamically by its voltage gradients (see Eq.(2.24)) 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 [16, 17] 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. **??** 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.

Chapter 3

Physics for biology

Physics

Chapter 4

Neural computing

Physics

Chapter 5

Neural information

Information

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