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LECTURE NOTES FOR NEUROPROTHETICS

TUM-MÜNCHEN, ELECTRICAL ENGINEERING

Contents

1 The Neuron

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Neurons are a specialized class of cells found in nearly every living animal apart from some very simple organisms. They share most of the typical properties of other cells like a nucleus, which contains the genetic material, and other organells, like mitochondria. What sets them apart from other cells is that they are electrically excitable, which enables them to transmit rapid signals, so called action potentials (AP), through the body. Neurons create connections with each other via synapses and build up a large and complex neuronal network. This network, which efficently processes and transmits information within the organism, is called the nervous system.

Neurons come in a huge variety of shapes and sizes. Many of them were discoverd when their specific function was still unknown so that they are often named after their shape (see Fig. 1.1). Despite this big variety, there are some elements which are common to most higher neurons (see also Fig. 1.2).

- Soma: This is the cell body of the neuron. It houses the nucleus as well as most of the machinery needed to keep the cell alive. The soma is also sometimes contacted by synapses of other neurons (axosomatic synapse).
- Dendrite: The dendrite is the input branch of the neuron. It is often devided into multiple branches (see the Purkinje cell in Fig. 1.1 as an extreme example). This is where the neuron is classically contacted by synapses (axodendtritic synapse).
- Axon: The output branch of the neuron. These long projections are the main transmission line of the nervous system. A bundle of axons is called a nerve and can extend for up to one meter. Depending on the type of neuron, the axon can be wrapped by Schwann cells creating a multi layer cover called myelin sheath. The gap between two successive segments of the myelin sheath is called node of Ranvier. In some cases, axons are also connected by synapses (axoaxonic synapse).

Neurons are not only mere transmission lines. A specialized class of them, the sensory receptors, have evolved to sophisticated sensors for physical stimuli like heat, smell, light or sound. The information collected by these sensory cells is transmitted via nerve fibres in the

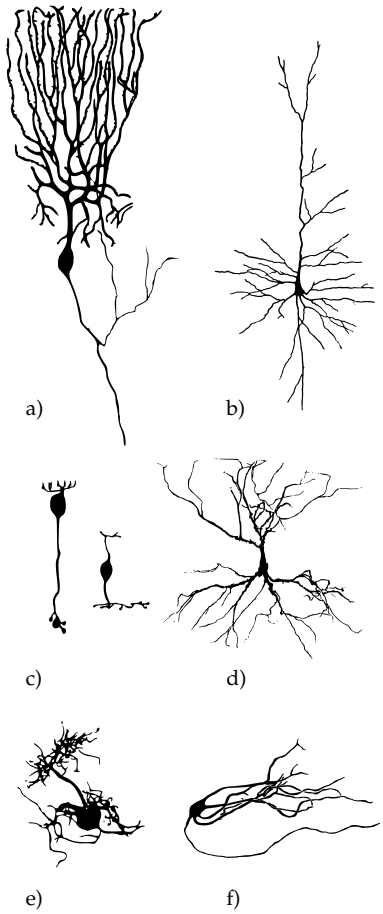

Figure 1.1: Some examples of neuronal shapes (graphics are unscaled): *a)* Purkinje cell of the cerabellum *b)*, cortical pyramidal cell, *c)* retinal bipolar cells, *d)* hippocampal pyramidal cell, *e)* globular bushy cell of the cochlear nucleus *f)*, octopus cell of the cochlear nucleus.

direction of the brain. These ascending pathways are called *afferent* fibres while those transmitting information back in the direction of the periphery are called *efferent* fibres.

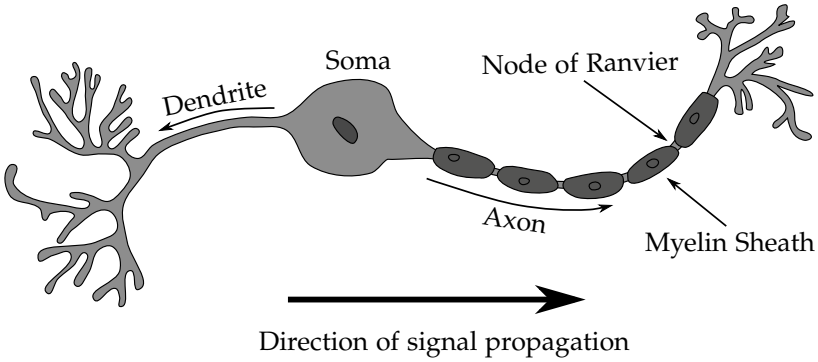

Figure 1.2: A basic neuron with its most important components. The *soma* houses the cell's nucleus, the *dendrite* is the cell's main input and the *axon* transmits action potentials to the target neurons.

The Cell Membrane

A cell is separated from its surrounding by a thin, semipermeable membrane, which is critical for its survival and function. The cell membrane is made up by fatty acids, so called phospholipids (see Fig. 1.3). The lipids arrange themselves to minimize the free energy by turning their hydrophilic heads towards the aqueous medium on both sides of the membrane, leaving the hydrophobic tails on the inside of a double layer. This structure form a stable and tight membrane in water, although it is not fixed but behaves more like a two dimensional liquid with a thickness of about 7 nm.

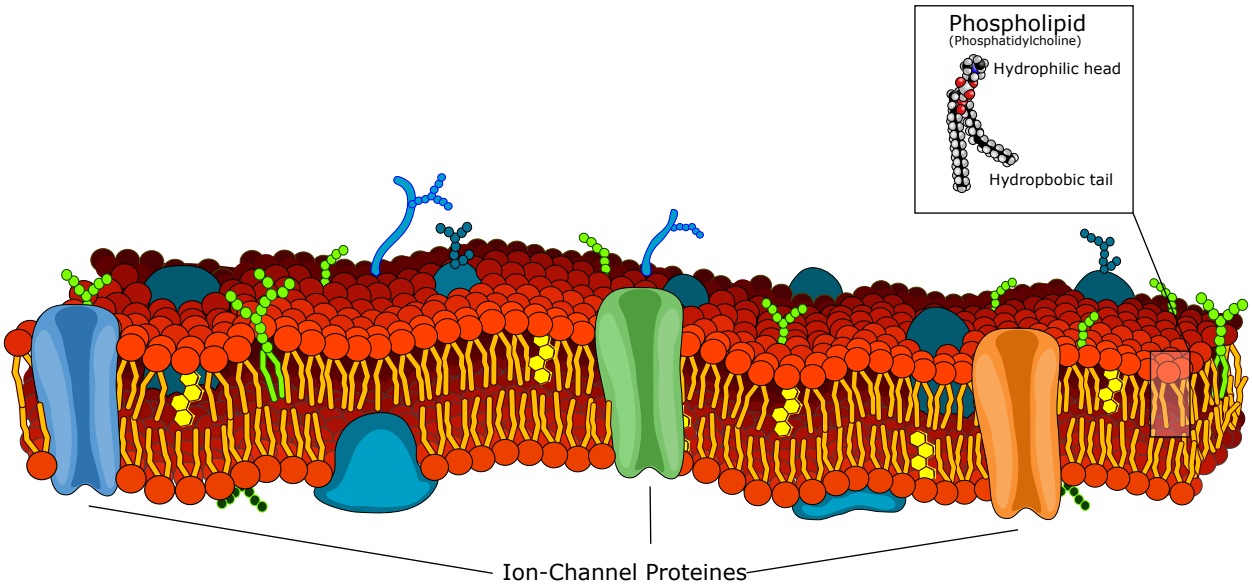

Figure 1.3: The cell membrane consists of a phospholipid bilayer which self-assembles due to the interaction of the phospholipids' hydrophilic and hydrophobic sections with the surrounding aqueous medium.

Several functional protein structures are embedded in the membrane. Most important in our context are the ion-channel proteins

and we will discuss their function in detail in the following sections.

The membrane separates the intracellular fluid from the extracellular fluid. These two fluids fundamentally differ in the concentration of water solvable ions, which, as we will see, is the basis for the electric signalling in neurons. The extracellular fluid contains a relative high concentration of sodium (Na^+), chloride (Cl^-) and calcium (Ca^{2+}) while the intracellular fluid is rich in potassium (K^+). The extracellular solution is a reminiscence of the ocean, where the first cells developed from complex chemistry in salty seawater (table salt = NaCl).

The difference in concentration between the two sides of the membrane is sustained by a specialized trans-membrane protein, the so called Na^+/K^+ATPase or sodium-potassium pump (Fig. 1.4). This protein mechanically moves sodium out and potassium into the cell. The concentration difference gives rise to an electric potential accross the membrane. Depending on the cell type, the *intracellular potential* (V_i) is at about -50 mV to -100 mV when compared to the *extracellular potential* (V_e). This potential difference is also called the cell's *resting potential*.

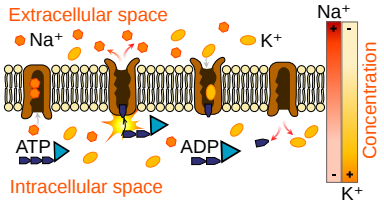

Figure 1.4: The sodium-potassium pump helps to keep up the ion gradient by moving ions against the diffusion gradient. Per cycle, the energy gained by transforming one molecule of Adenosine triphosphate (ATP) into Adenosindiphosphate (ADP) is used to transport three Na^+ ions out of the cell and two K^+ ions back in.

The Cell's Resting Potential

The cell's resting potential is the result of an interaction between diffusion and electric forces. Different ion concentrations inside and outside the cell cause a diffusion gradient. On the other hand, ions diffusing through pores in the cell membrane generate an electric potential difference inside the cell compared to the extracellular medium. This causes an electric field accross the cell membrane, which in turn excerts electric forces on ions (see Fig. 1.5).

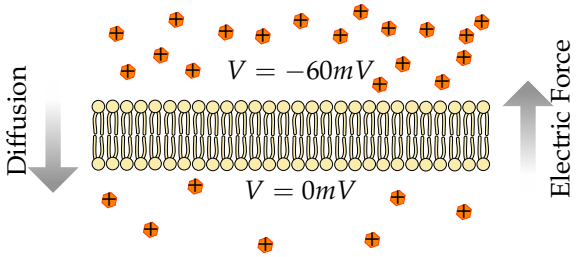

Figure 1.5: Two forces act on ions. A concentration gradient causes a diffusion force and an electric voltage gradient excerts an electric force on charged particles like ions.

To get an idea how these two forces interact and finally result in a resting potential, we analyse the equations describing these two effects.

The ion flux caused by diffusion is described by Fick's first law:

$$j_{diff,k} = -D_k \nabla C_k \tag{1.1}$$

where $j_{diff,k}$ is the ion flux of the ion species k in $\mathrm{mol}/m^2 s$, D_k is the diffusion constant in m^2/s and C_k the concentration in mol/m^3. The diffusion runs always from high concentration to low concentration,

which means in the opposite direction of the concentration gradient ($-\nabla C_k$).

The flux of ions in an electric field ($-\nabla\Phi$), called migration, is proportional to the mobility μ_k of the ion (in m^2/Vs) in the medium and the number of available ions, given by C_k:

$$-j_{elec,k} = \pm\mu_k C_k \nabla\Phi \tag{1.2}$$

where the sign is choosen depending on the ion's charge (positive for cations, negative for anions).

The mobillity is directly related to the diffusion constant by the Einstein equation:

$$D_k = \frac{RT}{|z_k|F}\mu_k \tag{1.3}$$

where T is the absolute temperature in Kelvin, $R = 8.3143\,\mathrm{J/molK}$ the gas constant, z the unitless ion valence and $F = 9.64867 \cdot 10^4\,\mathrm{C/mol}$ the Faraday constant.

When we add the ion flux from diffusion and migration to yield the net ion flux ($j_k = j_{diff,k} + j_{elec,k}$), we arrive at the Nernst-Planck equation:

$$j_k = -D_k\left(\nabla C_k + \frac{Fz_kC_k}{RT}\nabla\Phi\right), \quad \text{for } k = 1\ldots N \tag{1.4}$$

When the membrane is thin, the change of both concentration and potential is small in all directions but normal to the membrane (x direction). Then we can simplify the gradients to single differentials ($\nabla C_k \to \frac{dC_k}{dx}$ $\nabla\Phi \to \frac{d\Phi}{dx}$) and simplify the equation:

$$\frac{d\Phi}{dx} = \frac{RT}{Fz_kC_k}\left(\frac{-j_k}{D_k} - \frac{dC_k}{dx}\right) \tag{1.5}$$

Walther Nernst:

Walther Hermann Nernst, (25 June 1864 – 18 November 1941) was a German physicist who is known for his work which finally lead to the formulation fo the third law of thermodynamics, for which he won the 1920 Nobel Prize in chemistry.

The Nernst Equation

In the special case where we consider only one ion type at steady state, we can further simplify Eqn. 1.5 as the total ion flow j_k must be zero. We also introduce a different nomenclature for concentration where the concentration C_k of an ion K is written as $[K]$:

$$\frac{d\Phi}{dx} = -\frac{RT}{Fz_k}\frac{1}{[K]}\frac{d[K]}{dx} \tag{1.6}$$

when [1]integrated over the membrane we gain:

$$E_{Nernst,k} = \frac{RT}{z_kF} ln\frac{[K]_e}{[K]_i} \tag{1.7}$$

This equation is also known as the Nernst equation. It can be used to calculate the transmembrane potential at which electric and diffusion forces for a single ion species are in equilibrium. This is also called the ion's *Nernst* or *equilibrium* or *diffusion potential*. Table 1.1 lists examples of typical ion concentrations found in a neuron and the corresponding Nernst potential.

[1]

$$E_{Nernst,k} = \int_{\Phi_i}^{\Phi_e} d\Phi = \frac{RT}{z_kF}\int_{[K]_i}^{[K]_e}\frac{1}{[K]}dC_k$$
$$= \Phi_i - \Phi_e = \frac{RT}{z_kF} ln\frac{[K]_e}{[K]_i}$$

The Goldmann equation

As discussed before, there are always multiple ions involved in generating the cell's resting potential. In our case, where we consider N types of ions, we gain a system of N differential equations coupled by the common potential Φ. If we would postulate a net ion flow of zero for all ions and keep in mind that there can only be one transmembrane potential, we would end up with the following relation:

$$\frac{[Na_e^+]}{[Na_i^+]} = \frac{[K_e^+]}{[K_i^+]} = \frac{[Cl_e^-]}{[Cl_i^-]}$$

Looking at Table 1.1 we quickly see that this relation, which is also called the Donnan equilibrium, is not fulfilled in the living cell. This is due to the previously mentiond sodium-potassium pump and other minor pumps present in the cell membrane. As these pumps constantly move ions across the membrane, the assumption of zero flux $j_k = 0$ is invalid. A better approximation of the cell's resting potential under non equilibrium is given by the Goldmann equation which, with other assumptions, also results fom equation 1.5:

$$V_{m,rest} = -\frac{RT}{F} ln \frac{P_K[K^+]_e + P_{Na^+}[Na^+]_e + P_{Cl^-}[Cl^-]_i}{P_K[K^+]_i + P_{Na^+}[Na^+]_i + P_{Cl^-}[Cl^-]_e} \tag{1.8}$$

Here P_K, P_{Na}, P_{Cl} are the membrane permeabillities for the different ions.

Ion	$[ion]_i$	$[ion]_e$	E_{nernst}
	mM	mM	mV
Na^+	12	145	+67
K^-	155	4	-98
Cl^-	4	123	-90
Ca^{2+}	10^{-4}	1.5	+129

Table 1.1: Examples for typical ion concentrations and the resulting nernst potentials.

An Equivalent Circuit of the Cell Membrane

A more intuitive way to look at this is to draw an equivalent circuit of the problem. In this circuit, the membrane can be implemented as an electric capacity C_m and each ion species as a battery in series to a resistor. The battery represents the Nernst potential of the single ion species while the resistance depends on the premeability of the membrane for this kind of ion. The ion pumps can now be added as current sources parallel to the membrane capacity.

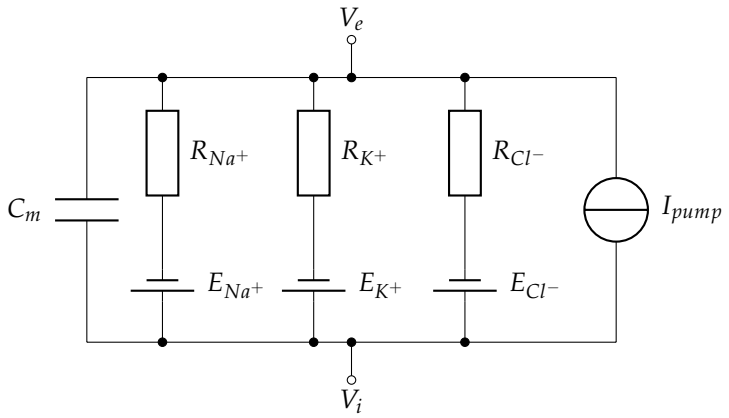

Figure 1.6: A equivalent circuit of the cell at resting potential. Each ion species is represented as a resistor and a battery. The battery represents the ions Nernst potential while the resistor defines how permeable the membrane is for this type of ion. The membrane is implemented as a capacity and the ions pumps as a simple current source.

We can now easily write down Kirchhoffs law for the cell where we define the transmembrane voltage as $V_m = V_i - V_e$:

$$0 = C_m \frac{dV_m}{dt} + I_{Na^+} + I_{K^+} + I_{Cl^-} + I_{pump} \tag{1.9}$$

$$C_m \frac{dV_m}{dt} = -\left(\frac{V_m - E_{Na^+}}{R_{Na^+}} + \frac{V_m - E_{K^+}}{R_{K^+}} + \frac{V_m - E_{Cl^-}}{R_{Cl^-}} + I_{pump} \right) \tag{1.10}$$

This equation shows that the influence of the Nernst potential for one ion species is proportional to the membrane conductiviy $g_k = 1/R_k$ for this ion. The influence of the ion pump can be neglected relative to the net conductivity of the membrane in most cases.

Signal transmission in the Neuron

In the previous sections, we have discussed the physiology of neurons and how a difference in ion concentration is used to create a stationary resting potential. The next section will show how large, short time variations in this potential, so called action potentials, are used to transmit signals along the axon of a neuron.

A short history of Electrophysiology

The earliest description of an interaction between electric potentials and nervous tissue is probable the famous frog-leg experiment by Luigi Galvani in 1780, who, by accident, stimulated the muscle fibers in a frogs leg when his steel preparation knife touched a brass hook that he used to hold the leg in place. Not yet knowing about the effect of Galvanism (obviously named after him), he interpreted what he saw as *animal electricity*, the live force within the muscle of the frog. A few years later he would find that he doesn't need two metals but that he could use one of the recently developed batteries.

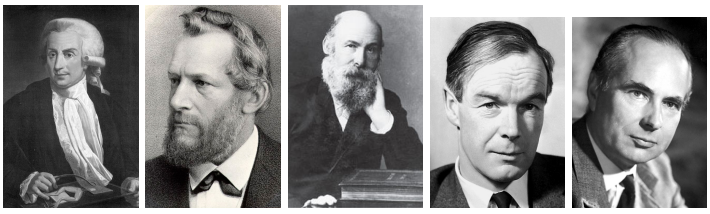

Figure 1.7: From left to right: Luigi Galvani, Julius Bernstein, Emil du Bois-Reymond, Allen Hodgkin and Andrew Huxley

It would take quite a while until we would get a deeper understanding of the effect that caused the muscle to twitch. In 1850, the German physiologist Emil Du Bois-Reymond (1818 - 1896) first described the large shift in voltage preceding muscle movement which would later be called an action potential. In 1902, another German physiologist, Julius Bernstein (1839 - 1917), introduced the *membrane theory*. He postulated that action potentials are caused by a rapid change in the cell membrane's sodium permeability. Then, in the years between 1937 and 1952, a number of papers published by the English physiologists Alan Hodgkin and Andrew Huxley would set the basis of our current understanding of how neurons function. Even

though they still mostly speculated about the underlying mechanisms, their description was surprisingly accurate and even the equations they used to model the processes where later found to be physically meaningful. In 1963, their groundbreaking work was awarded with the Nobel Price in Medicine and Physiology.

Ionic currents

In 1934 Hodgkin and Huxley started a series of experiments on the squids giant axon. This axon is one of the largest found in nature and reaches diameters up to 1 mm. Its large size enabled them to directly insert an electrode into the axon (see Fig. 1.8) and to record the currents through the membrane.

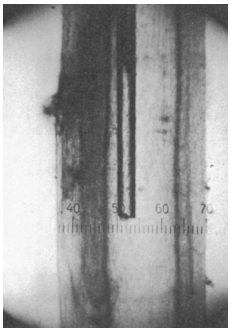

Figure 1.8: Photomicrograph of a recording electrode inside a giant axon; one division = $33\mu m$ (from Hodgkin & Huxley, 1939).

To test their setup, they first applied short current shocks to the inserted electrode to test if they could elicit action potentials. The original results from this experiment are shown in Figure 1.9. As expected from our equivalent circuit, the initial displacement of the membrane potential was proportional to the charge of the applied pulse but stronger pulses also elicited a large but delayed, voltage spike with constant amplitude – an action potential.

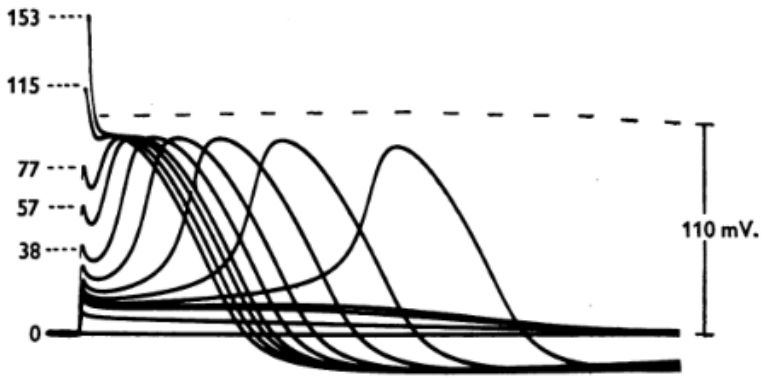

Figure 1.9: Original Data from Hodgkin & Huxley 1952: Time course of the membrane potential following a short current shock. The numbers attached to the curves give the charge of the shock per area in $\mu C/cm^2$

To get a better idea of the currents involved in the action potential, they used a *current clamp* experiment where the membrane potential was fixed by applying a voltage to the internal electrode. They used a second electrode to measure the current through the membrane. Their results from such an experiment are shown in 1.10. In these measurements we can see two different components. A fast, transient, inward (positive) current at the beginning of the stimulus overlaid a slow outward (negative) current. Hodgkin and Huxley hypothesised that these two components were the sum of two independent ionic currents, one for sodium and one for potassium. To test this hypothesis, they repeated the experiment in a solution, where they replaced sodium with cholin. In agreement with their hypothesis, this completely removed the initial inward current while keeping the slow outward current intact.

This independence of ionic currents would also be expected from the equivalent circuit we used to explain the resting potential (Fig.

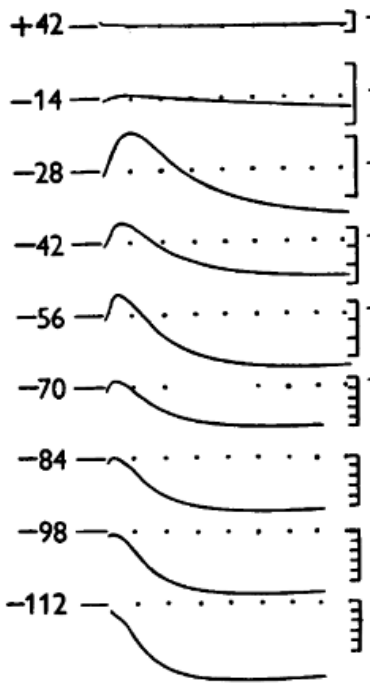

Figure 1.10: Original Data from Hodgkin & Huxley 1952: Records of membrane current during *voltage clamps*. The voltage is annotated in mV. Vertical scale: 1 division is 0.5 $^{nA}/_{cm^2}$ Horizontal scale: interval between dots is 1 [ms]. Inward currents are defined positive.

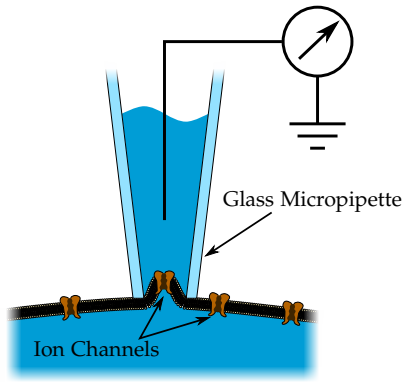

Figure 1.11: For patch clamping, a glass micropipette is used to contact a small patch of membrane containing one or few ion channels. The electrode is filled with an ionic solution so that the currents through the channels can be measured.

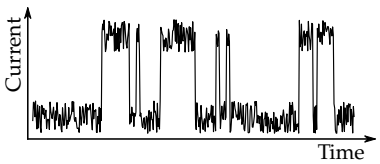

Figure 1.12: Schematic of the current through one single ion channel as it could be measured using a patch clamp setup. The measured current toggles between two distinct values, one representing the closed and the other the open channel.

1.6). The change in current could then be attributed to a change in conductivity g_k for the according ion type k. Hodgkin and Huxley arrived at exactly the same conclusion and, using a series of refined experiments and detailed analysis, where also able to arrive at a detailed description of the dynamics underlying the change in conductance. This set of equations, also called the Hodgkin Huxley equations, will be discussed in detail throughout this script.

Hodgkin and Huxley's explanation for the change in conductivity was the existence of specific channels through which ions can pass through the membrane. These channels can open and close depending on the membrane voltage, modulate the ionic current and thus create such complex responses like action potentials.

Ion Channels

A direct confirmation for the existence of specific ion channels became possible with the development of a technique called patch clamp recording, for which Erwin Neher and Bert Sakmann received the 1990 Nobel Price in Physiology or Medicine.

For patch clamping, a thin micropipette is fabricated by pulling a heated glass capillary such that a tip diameter in the micrometer range is achieved. The pipette is filled with an ionic solution and the tip is positioned close to a cells membrane by using micromanipulators. A short sucking action on the pipette creates a high-resistance connection between the tip and the cell membrane (see Fig. 1.11). By doing this, a small patch of membrane is isolated from the surrounding medium. This patch is so small that it contains few and optimally only one ion channel. An electrode in the pipette can now be used to measure the ionic current through one single ion channel.

If we look at such a measurement, we can see that the current seems to be toggling between zero and a distinct state (see Fig. 1.12). This observation can be explained by assuming that ion channels are either fully open or fully closed with no intermediate state. The proportion of time spent in the open state can be interpreted as the probability for this single channel to be open.

The density of channels in the membrane is quite high so that we always deal with a large number of channels. In such a setting, the open probability of a single channel is equivalent to the percentage of channels which are in the open state. Using this relationship we can write down the ionic current for a single ion species:

$$I_i(V) = N\gamma P_O(V)(V - V_{Nernst}) \tag{1.11}$$

Where N is the number of ion channels, P_O the voltage dependent open probability of a channel, γ the conductivity of one single channel, V the transmembrane voltage and V_{Nernst} the Nernst potential for this ion species.

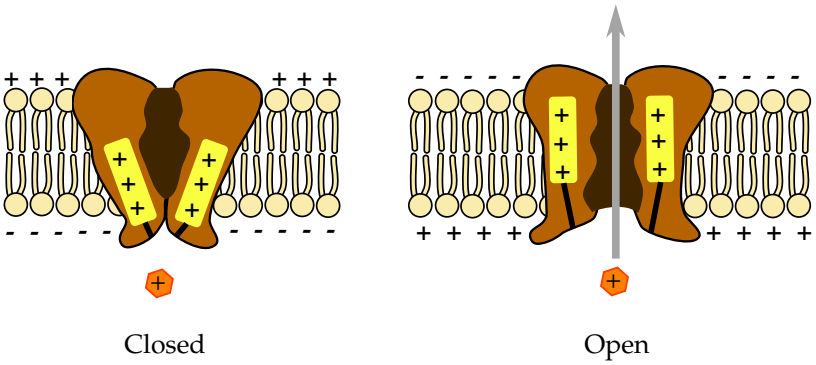

Figure 1.13: Schematic view of the gating mechanism in a voltage gated ion channel. A charged element called the voltage sensor is displaced due to a change in the external potential. This leads to a change in the conformation and switches the channel from its closed to the open state.

Channel Gating

For an ion channel to open or close, the channel protein has to undergo a change in conformation. This means that its three-dimensional structure changes. In Equation 1.11, the opening probability and with that the probability for a change in conformation depends on the transmembrane voltage. We call such a channel a voltage gated channel. There exists a multitude of differently gated channels like ligand gated (secondary chemicals), temperature gated or pressure gated channels. For our discussion, we are only interested in voltage gated channels. In this kind of channels, the gating process is mediated by a charged domain of the proteine. This domain is called the voltage-sensor (see Figure 1.13). The different potentials on both sides of the membrane apply a force on the voltage sensor. The greater the force, the higher the probability for the channel to open.

Changes in biological systems are never instantaneous but rather continuous processes. If we think of a simplest model for such a system, we would come up with a transition between two states where the probability to be in one or the other state changes with voltage dependent rate constants α und β (see Fig. 1.14). Even if this description is strongly simplified, as a real channel would normally have to undergo several structural changes to open or close, it is accurate enough to describe what is happening. Equation 1.17 describes the underlying differential equation for this process. Here, the probability for the channel to be open is denoted as P, therefore the probability for the channel to be closed is $(1 - P)$

$$\text{closed} \underset{\beta(V_m)}{\overset{\alpha(V_m)}{\rightleftharpoons}} \text{open}$$

Figure 1.14: A simplified description of the transition between two channel states open and closed.

$$\frac{dP}{dt} = \alpha(V)(1 - P) - \beta(V)P \tag{1.12}$$

To get a better notion of the behaviour of this differencial equation, we can rewrite it

$$\frac{dP}{dt} = (\alpha(V) + \beta(V)) \left(\frac{\alpha(V)}{\alpha(V) + \beta(V)} - P \right) \tag{1.13}$$

and simplify it to:

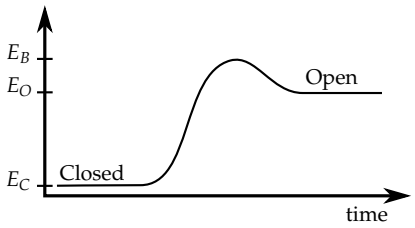

Figure 1.15: Energy diagram for the conformation change of an ion channel. The channel has a low energy closed state and a high energy open state with an energy barrier inbetween.

$$\frac{dP}{dt} = \frac{1}{\tau_P(V)}(P_\infty(V) - P) \tag{1.14}$$

$$\tag{1.15}$$

with:

$$\tau_P(V) = \frac{1}{\alpha(V) + \beta(V)} \tag{1.16}$$

$$P_\infty(V) = \frac{\alpha(V)}{\alpha(V) + \beta(V)} \tag{1.17}$$

These equations can be interpreted as an exponential growth or decay towards the steady-state value $P_\infty \in [0, 1]$ with the time constant τ_P in seconds, where both of these depend on the membrane voltage V.

We now have to find the functions $\alpha(V)$ and $\beta(V)$. Each conformation of the protein is equivalent to an energy level. For the transition from one state to the next, an energy barrier E_B has to be overcome. Figure 1.15 shows the resulting energy diagram. The probability and therefore the rate of change between two energy levels is described by Bolzmann functions. In our case, the two equations are:

$$\alpha = A_\alpha e^{\frac{E_C - E_B}{kT}} \tag{1.18}$$

$$\beta = A_\beta e^{\frac{E_O - E_B}{kT}} \tag{1.19}$$

Where $k = 1.38 \cdot 10^{-23}\text{J/K}$ is the Bolzmann constant, T the temperature in Kelvin and E the energy in Joule. The energy needed to change the conformation can be described as the movement of a gating charge qB in the electrical field created by the transmembrane potential V. The constant B stands for both the amount of charge and the distance over which it has to travel. Using this we can write correspondinglytants as:

$$\alpha = A_\alpha e^{\frac{qB_\alpha V}{kT}} = A_\alpha e^{\frac{B_\alpha V}{V_T}} \tag{1.20}$$

$$\beta = A_\beta e^{\frac{qB_\beta V}{kT}} = A_\beta e^{\frac{B_\beta V}{V_T}} \tag{1.21}$$

And in fact, when Hodgkin and Huxley fitted the voltage dependence of the rate constants gained from their measurements, they arrived at very similar equations which will be discussed in the corresponding chapter.