

Chapter 2

Modeling the Activation of Neural Cells

Abstract This chapter treats a short review regarding the working principles and modeling of neurons. These concepts form the theoretical basis of neural stimulation and are therefore used throughout the book. In the first section the physiological principles of neurons are discussed and an electrical model of the neural membrane will be derived. In the second section the stimulation of neural tissue will be discussed. It will be seen how the passage of current through electrodes will ultimately lead to physiological change in the neural tissue.

2.1 Physiological Principles of Neural Cells

2.1.1 *Neurons*

Almost all neural cells, or neurons, share four common functions: reception, triggering, signaling, and secretion [1]. In Fig. 2.1 an illustration of these components is given. At the input of the neuron the incoming signals are *received* at the *dendrites* of the neuron. The number and nature of these signals depend on the type of neuron: neurons can have anywhere from a few up to hundreds of thousands of inputs. Input signals are always graded (analog) signals. For the neuron in Fig. 2.1 the input is formed by synaptic potentials, resulting from the neurotransmitter release of other cells.

All the local signals will come together at a point where a *trigger* can be generated if a certain threshold is reached. The trigger is an all-or-none spike shaped signal called an action potential. In the neuron in Fig. 2.1 the trigger point is at the *soma* of the neuron (more specifically the axon hillock). The soma also contains the nucleus of the neuron and synthesizes most neuronal proteins that are essential for operation of the cell.

The action potentials generated at the trigger point will propagate over the *axon* of the neuron. Action potentials propagate over the axon in a regenerative manner without loss of amplitude and therefore the signal can cover large distances. Because the shape and amplitude of the action potential remain constant, the information is contained in the number of spikes and the time between them. The axon therefore has a *signaling* function. An axon may be *myelinated*, which means it is surrounded by myelin sheath, an insulating layer. The myelin is discontinuous and the points

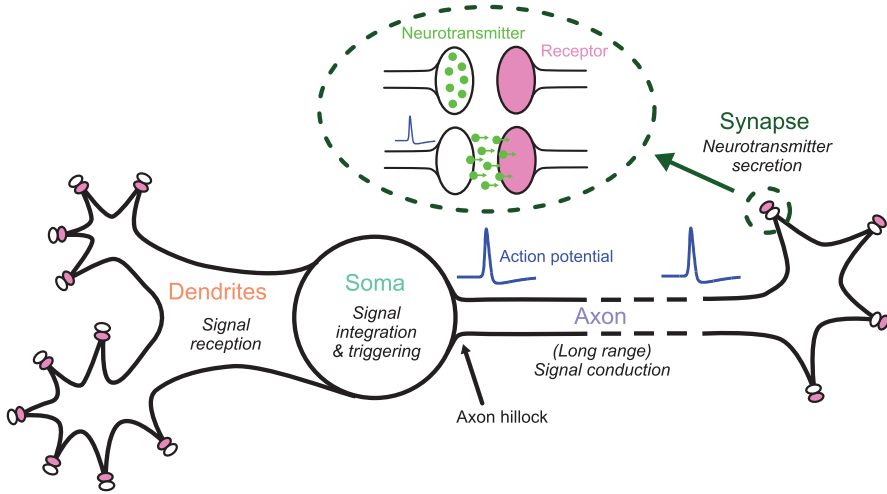


Fig. 2.1 Schematic representation of the basic organization common to all nerve cells: signal reception (dendrites), signal integration and triggering (soma), signal conduction (axon), and neurotransmitter secretion (synapse)

where it is absent are called the *nodes of Ranvier*. Myelin greatly increases the propagation velocity of the axon potentials.

The end of the axon connects to other cells by means of a *synapse*. The action potential causes the *secretion* of a neurotransmitter, which is subsequently received by the receptor, thereby forming a unidirectional connection. The release of a neurotransmitter can be considered the output of the neuron. The neurotransmitter signal is again graded: its amplitude depends on the number and frequency of action potentials that are generated. Whether a synapse has an excitatory or inhibitory effect (increasing or decreasing the chance for an action potential, respectively) depends on the receptor only: one single neurotransmitter can cause both excitatory and inhibitory responses, depending on the receptor.

2.1.2 Modeling of the Cell Membrane

The graded signals at the dendrites as well as the action potentials manifest themselves as changes in the voltage over the cell membrane of the neuron. The membrane consists of two layers of phospholipids that form a seal between the inside of the cell (cytoplasm) and the outside (extracellular fluid). The membrane voltage $V_m = V_{in} - V_{out}$ is defined as the difference between the potentials of the cytoplasm and extracellular fluid. The cytoplasm is characterized by a high concentration of potassium (K^+) and large organic anions (denoted as A^-). The extracellular space has a surplus of sodium (Na^+) and chloride (Cl^-).

The membrane itself is a very good isolator, but diffusion of ions through the membrane is possible through ion channels (proteins that span the membrane). Due to the movement of charge, an electric field forms across the membrane, which will lead to a conduction current opposing the diffusion current. The voltage at which the conduction and diffusion current are in equilibrium for one type of ion is called the Nernst voltage and is given by Malmivuo and Plonsey [2]:

$$V_x = \frac{RT}{z_x F} \ln \frac{c_{i,x}}{c_{o,x}} \quad (2.1)$$

Here R is the gas constant [$8.314 \text{ J}/(\text{mol K})$], V_x is the Nernst potential for one specific ion type x , T is the temperature [K], F is Faraday's constant [$9.6 \cdot 10^4 \text{ C/mol}$], z_x is the valence of the ion, and $c_{i,x}$ and $c_{o,x}$ are the intracellular and extracellular ionic concentrations [mol/cm^3], respectively. Each type of ion channel can now be modeled with a voltage source that is equal to the Nernst potential in series with a conductance $g_{m,x}$ that represents the conductivity of the ion channel. This is depicted in Fig. 2.3 for the sodium, potassium, and chloride channels. Due to the fact that the Nernst potentials of the individual species are unequal, the total membrane is in a dynamic equilibrium: there is a constant flux of ions flowing through the membrane.

The concentration gradients of the sodium and potassium ions are maintained by means of an $\text{Na}^+ - \text{K}^+$ -pump, as also depicted in Fig. 2.2. This is another membrane spanning protein that pumps out 3 Na^+ ions for every 2 K^+ ions that it pumps in the cell. This electrogenic behavior causes V_m to be slightly more negative and can be modeled by two current sources as depicted in Fig. 2.3. The influence of the pump is usually very small and is therefore often neglected in the model.

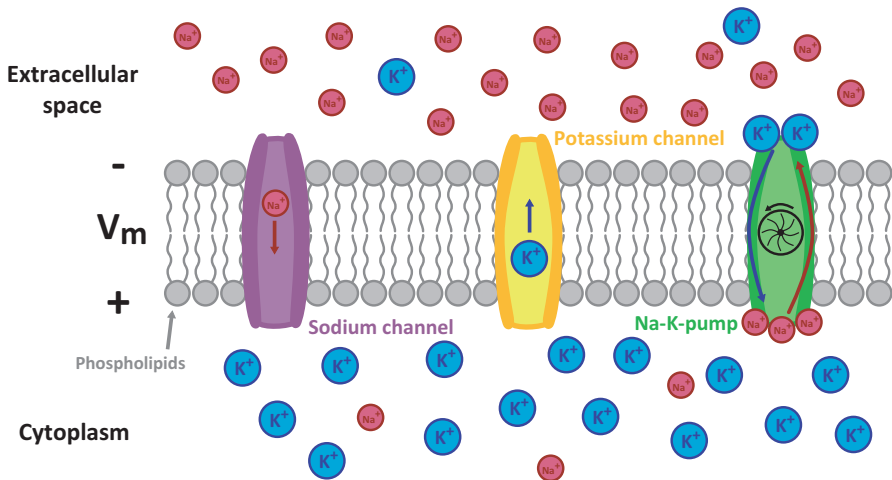


Fig. 2.2 Schematic representation of the cell membrane with ion channels for the most important cations (Na^+ and K^+). The membrane voltage $V_m = V_{in} - V_{out}$ is also depicted. The anions (Cl^- and A^-) are omitted for clarity

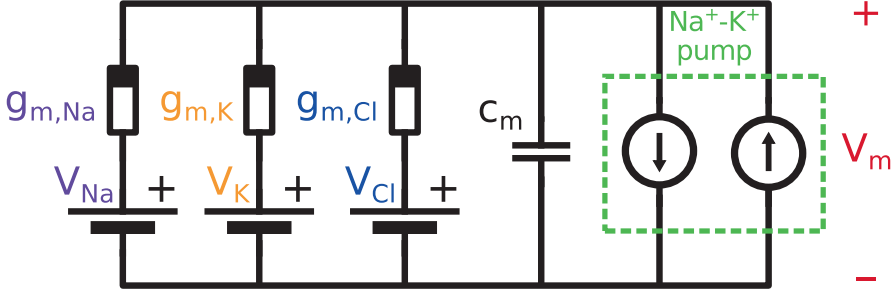


Fig. 2.3 Electrical model of a cell membrane. The voltage sources represent the Nernst potentials of the specific ion species, while g_m are the respective ion channel conductances. The current sources represent the Na⁺-K⁺-pump and are often neglected due to their very small influence on the cell's resting potential. Finally the membrane has a capacitance C_m

Neurons may also have an active mechanism to control the concentration gradient of the chloride ions. If this is not the case the chloride ions redistribute passively only, which means that V_{Cl} is equal to the resting potential of the membrane. There are also large organic anions in the cytoplasm of the cell, denoted as A^- . There are no ion channels for these species, which means they do not contribute to V_m . Finally the membrane is characterized by a membrane capacitance C_m , as depicted in Fig. 2.3.

2.1.3 Ion Channel Gating

The membrane is characterized by a resting potential $V_m = V_{rest} \approx -70$ mV that is determined by the values of V_x and $g_{m,x}$ of the model in Fig. 2.3. In this situation $g_{m,x}$ is determined by so-called *rested channels*, which are always open and have a fixed conductance. When V_m becomes more negative (hyperpolarizing) or slightly more positive (depolarizing), the values of $g_{m,x}$ remain approximately constant and the membrane is said to respond in a passive (electrotonic) way.

However, when the membrane potential is depolarized up to a certain threshold, so-called *gated channels* for sodium and potassium that exist in the axon will open; the conductance of these channels depends on the value of V_m . When the membrane voltage is increased to about -50 mV (by depolarization), the conductivity of the membrane for sodium ions increases very rapidly. Simultaneously, the potassium ion permeability starts to increase as well, but the process is much slower. This means the sodium ions start to flow from the outside to the inside first, making the inside more positive. When the membrane voltage is increased up to about 20 mV the potassium conductivity is increased as well and potassium ions begin to flow from the inside to the outside, decreasing the membrane voltage. Finally, the membrane reaches its equilibrium voltage again.

These gated channels are responsible for the regenerative manner in which the action potentials propagate along an axon. If an action potential is generated at some point of the axon, it depolarizes the membrane further down the axon, which will generate a new action potential at that point.

The most widely used model to describe the channel conductance and its rich dynamic properties as a function of the membrane voltage is given by the Hodgkin–Huxley model [3]. Neglecting the $\text{Na}^+ \text{-} \text{K}^+$ -pump in Fig. 2.3, the total membrane current i_m is described by:

$$i_m = c_m \frac{dV_m}{dt} + (V_m - V_{Na})g_{m,Na} + (V_m - V_K)g_{m,K} + (V_m - V_{Cl})g_{m,Cl} \quad (2.2)$$

The conductances are given by the following equations:

$$g_K = G_K n^4 \quad (2.3a)$$

$$g_{Na} = G_{Na} m^3 h \quad (2.3b)$$

$$g_{Cl} = G_L \quad (2.3c)$$

The conductances G_{Na} , G_K , and G_L are constants, while the factors n , m , and h are described by the following differential equations:

$$\frac{dm}{dt} = \alpha_m(1 - m) - \beta_m m \quad (2.4a)$$

$$\frac{dh}{dt} = \alpha_h(1 - h) - \beta_h h \quad (2.4b)$$

$$\frac{dn}{dt} = \alpha_n(1 - n) - \beta_n n \quad (2.4c)$$

Here the factors α_x and β_x depend on the membrane overpotential $V' = V_m - V_{rest}$ via:

$$\alpha_m = \frac{0.1 \cdot (25 - V')}{\exp \frac{25 - V'}{10} - 1} \quad \beta_m = \frac{4}{\exp \frac{V'}{18}} \quad (2.5a)$$

$$\alpha_h = \frac{0.07}{\exp \frac{V'}{20}} \quad \beta_h = \frac{1}{\exp \frac{30 - V'}{10} + 1} \quad (2.5b)$$

$$\alpha_n = \frac{0.01(10 - V')}{\exp \frac{10 - V'}{10} - 1} \quad \beta_n = \frac{0.125}{\exp \frac{V'}{80}} \quad (2.5c)$$

These equations model the electrical response of a membrane containing gated ion channels. The equations will be used to obtain the response of the membrane during electrical stimulation, described in the next section.

2.2 Stimulation of Neural Tissue

As shown in the previous section, neurons are electrochemical systems. Drugs have long been used to alter the chemical component of this system for therapeutic purposes. Drawback of this approach is that drugs generally affect the whole nervous system and are therefore easy to induce unwanted side effects.

Neural stimulation uses the electric component of the nervous system by locally altering the membrane voltage of the neurons. Neural stimulation has been applied using electrical, magnetic, and more recently, optical and acoustic stimuli.

Electrical stimulation of neural tissue uses an electric field to artificially recruit neurons in order to tap into the neural system on a functional level. Using stimulation neurons can be forced to generate action potentials (activation) or prevented from generating them (inhibition). This section reviews the stimulation process from the stimulator up to the membrane voltage.

Stimulation is considered at three different levels:

- The electrode level: the electrodes and the tissue are modeled using an equivalent electrical circuit and form the load of a stimulator.
- The tissue level: the tissue itself is modeled as a volume conductor and the electrical stimulation leads to an electric field inside this volume conductor.
- At the neuronal level: the electric field will influence the local extracellular membrane potential of a neuron, which will ultimately trigger or suppress an action potential.

2.2.1 *The Electrode Level: Electrode–Tissue Model*

The electrical energy that is used to recruit neurons is injected into the target area by means of electrodes. These electrodes form the load of the stimulator circuit and in order to design an efficient and safe system it is essential to have an electrical model of this load.

In the electrode electrons are the charge carrying particles, while in tissue charge is carried by ions. This means that the system needs to be considered as an electrochemical system. The equivalent circuit is typically divided into two parts: the electrode–tissue interface Z_{if} and the tissue impedance Z_{tis} as is shown in Fig. 2.4.

2.2.1.1 Electrode–Tissue Interface

Processes at the Electrode–Tissue Interface

At the interface of the electrode and the tissue some interaction must take place between the electrons in the electrodes and the ions in the tissue. There are two types of interactions possible: charge accumulation and electrochemical reactions.

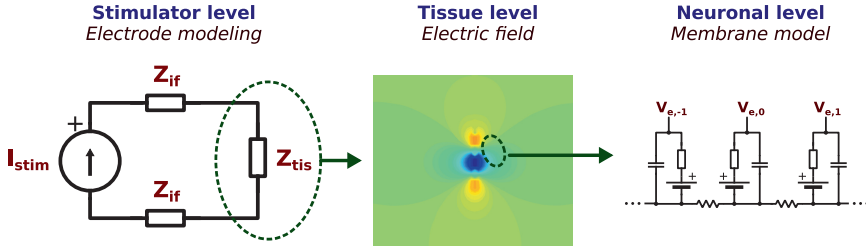


Fig. 2.4 Three levels of hierarchy at which neural stimulation is considered. The stimulator level considers the electrical equivalent circuit that is connected to the stimulator circuit. The tissue level zooms in on the tissue impedance by considering it as a volume conductor. The neuronal levels zoom further in on the neuron itself and how the membrane voltage develops during stimulation

Charge accumulation is simply the accumulation of charge carriers (double layer charging) near the interface. In this mechanism no charge is transferred between the electrode and the tissue. In case of *electrochemical reactions* charge is transferred at the interface by means of redox reactions. One electrode acts as the anode: an oxidation half-reaction describes how the electrode loses electrons. The other electrode acts as the cathode: a reduction half-reaction shows how the electrode accepts electrons.

Each half-reaction is first of all described by an electrode potential V_n that resembles the built-in potential of the electrode in equilibrium that results from the difference in electrochemical potential between the electrode and the tissue. Like Eq. (2.1) for the cell membrane, this potential is described using the Nernst equation:

$$V_n = V_0 - \frac{RT}{zF} \ln \frac{a_{red}}{a_{ox}} \quad (2.6)$$

Here V_0 is the half-cell potential under standard conditions, while the second term corrects for deviations from these conditions. The factors a_{red} and a_{ox} are the activity of the reduction and oxidation species in the half cell, which are closely related to the concentrations of the gaseous and aqueous species and z is the valence of the reaction.

When an overpotential $\eta_a = V_{if} - V_n$ is established over the interface, the kinetics of the reactions are described using the electrochemical current density i_{net} in the Butler–Volmer equation [4]:

$$i_{net} = i_0 \left\{ \frac{[O]_{0,t}}{[O]_{\infty}} \exp(-\alpha_c z f \eta_a) - \frac{[R]_{0,t}}{[R]_{\infty}} \exp((1 - \alpha_c) z f \eta_a) \right\} \quad (2.7)$$

Here i_0 is the exchange current density, α_c is the cathodic transfer coefficient, $f \equiv F/RT$, and $[O]_{0,t}/[O]_{\infty}$ and $[R]_{0,t}/[R]_{\infty}$ are the ratios between concentrations of the oxidized and reduced species at the electrode and in the rest of the tissue,

respectively. For high overpotentials the ratios $[O]_{0,t}/[O]_{\infty}$ and $[R]_{0,t}/[R]_{\infty}$ will decrease, causing the reaction to become mass limited at the limiting current $i_{L,a}$ or $i_{L,c}$ for the anodic and cathodic reactions, respectively.

Modeling of the Electrode–Tissue Interface

The two different processes mentioned in the previous paragraph now need to be translated to equivalent electrical models. The interface is characterized by two types of mechanisms: reversible and irreversible processes [5].

Reversible currents are characterized by the fact that they store charge at the interface. This can be due to charge accumulation (capacitive currents), but also due to reversible electrochemical reactions (pseudo-capacitive currents). In the case of, for example, hydrogen plating, hydrogen atoms are bound to the electrode surface, effectively storing charge at the interface. Both processes are characterized by their reversibility: the stored charge can be recovered by reversing the electrical current. The reversible currents are modeled with a capacitor C_{dl} .

Irreversible currents, also often labeled as the faradaic currents, are due to irreversible processes such as electrochemical processes in which the reaction products cannot be reversed, such as oxygen evolution. They are modeled with a charge transfer resistor R_{CT} . Furthermore it is often chosen to model the equivalent built-in potential V_{eq} (combining the relative contribution of V_n for each electrochemical reaction) as a voltage source in series with R_{CT} .

The values of C_{dl} and R_{CT} highly depend on the size, geometry, and materials used for the electrodes. Furthermore, the complex kinetics of the electrochemical reactions according to Eq. (2.7) make both components highly non-linear. In many applications the model is linearized.

Note that the naming of C_{dl} (dual layer capacitor) and R_{CT} (charge transfer resistor) can be confusing. A dual layer capacitor suggests that it only models charge accumulation, while it can also model the charge transfer of pseudo-capacitive current (which is *not* modeled in the charge transfer resistance!).

Electrodes with almost exclusively reversible currents (e.g., platinum electrodes) are called polarizable electrodes: by injecting current through these electrodes, the interface will be polarized. Electrodes with predominantly faradaic currents are non-polarizable electrodes (e.g., Ag/AgCl electrodes).

2.2.1.2 Tissue Impedance

The tissue impedance is the electrical equivalent circuit of the tissue itself. The voltage over this component is directly related to the strength of the electric field, as will be seen in the next subsection. The second order spatial difference of this electric field is subsequently important for recruiting the neurons. Current based stimulation is often preferred to make the voltage over the tissue (and hence the electric field strength) independent of the interface impedance Z_{if} : $V_{tis} = I_{stim}Z_{tis}$.

The impedance of the tissue first of all heavily depends on the electrode geometry: if the electrodes are big (i.e., have a large effective area), the impedance will be low. Because of their low impedance, big electrodes need a higher current than small electrodes to create the same voltage and thus electric field strength. However these big electrodes create a much larger electric field, therefore affecting a large population of neurons. Small electrodes create a much smaller electric field, affecting much less neurons while using only a little bit of current.

It depends on the application whether small or big electrodes are used. That is why such a wide range of currents and impedances is encountered in literature: from a few μA for micro-electrodes with Z_{tis} in the order of $100\text{ k}\Omega$ to tens of mA for big electrodes with R_{tis} in the order of $10\text{ }\Omega$.

Besides electrode size the impedance also depends on the tissue properties: it can incorporate as many of the tissue properties as desired: non-linearity, anisotropy, inhomogeneous, time-variant, and dynamic properties. However many of these properties make it hard to handle the model in standard circuit simulators. In many cases the tissue is simply modeled using a resistor R_{tis} only. If the dynamic properties are important a capacitor C_{tis} can be placed in parallel as a first approximation.

In literature or in electrode specifications one often finds a single value for the “electrode impedance.” Usually this value corresponds to the impedance measured at 1 kHz with very low excitation levels. This value represents the equivalent impedance of the whole system depicted in Fig. 2.5.

2.2.2 Tissue Level: Electric Field Distribution

In the previous subsection the tissue was considered as a discrete impedance Z_{tis} as part of the load of the stimulator. In this section we zoom in on the tissue itself by considering it as a volume conductor. Neural tissue has non-linear, inhomogeneous, anisotropic, and time-variant electrical properties.

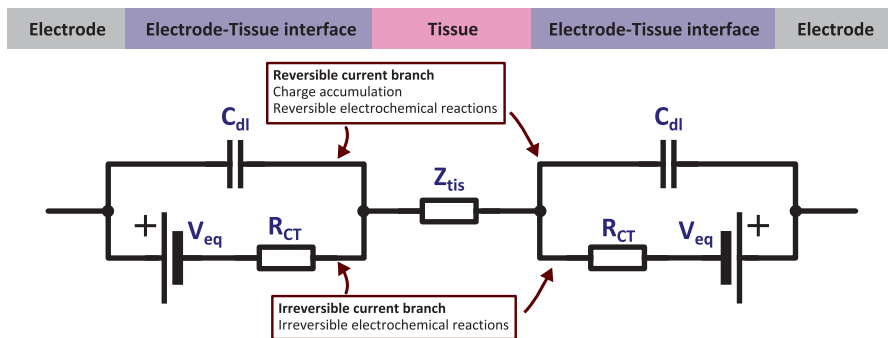


Fig. 2.5 Equivalent electrical model of the electrode system. The interface model consists of a capacitive branch (C_{dl}) and a faradaic branch (R_{CT} and V_{eq}). The tissue itself is modeled with impedance Z_{tis} . Note that all components have non-linear properties

The electric field \overline{E} is in general found using Gauss' law:

$$\nabla \cdot \overline{E} = \frac{\rho}{\epsilon} \quad (2.8)$$

Here ρ is the charge density and ϵ is the permittivity. Assuming quasi-static conditions, the curl of \overline{E} must be zero according to Faraday's law of induction:

$$\nabla \times \overline{E} = -\frac{d\overline{B}}{dt} = 0 \quad (2.9)$$

According to the Helmholtz decomposition theorem, each continuously differentiable vector can be decomposed in a curl-free and a divergence free component. The curl being zero (Eq. (2.9)), the potential is related to the electric field via:

$$\overline{E} = -\nabla\Phi \quad (2.10)$$

Substituting Eq. (2.10) into Eq. (2.8) gives the Poisson equation:

$$-\nabla^2\Phi = \frac{\rho}{\epsilon} \quad (2.11)$$

For tissue it holds in general that $\rho = 0$, which reduces Poisson equation into the Laplace equation: $\nabla^2\Phi = 0$. The goal is now to solve this equation for certain boundaries as set by the tissue and the stimulation electrodes.

A way to numerically solve the Laplace equation is by using finite element method analysis. A model can be constructed for the electrodes as well as for the tissue. For illustrative purposes a model is created for the electrode leads in Fig. 2.6a. These electrode leads are made of silicone rubber and can be used for spinal cord stimulation. The platinum electrodes are ring shaped with a diameter of 1.5 mm and a height of 3 mm.

A 2D model of these electrodes was constructed in the ANSYS software environment, which is depicted in Fig. 2.6a. The conductivity of the electrodes and the insulation was chosen to be $\sigma_s = 9.52 \cdot 10^6$ S/m and $\sigma_p = 2 \cdot 10^{-14}$ S/m, respectively. The tissue was modeled as an isotropic and homogeneous plane with a conductivity of $\sigma_t = 0.3$ S/m [6].

In Fig. 2.6 the simulation results of the potential distribution for various stimulation strategies are depicted. In Fig. 2.6b only one electrode is driven with a current source of 10 mA (monopolar operation), while the edges of the tissue plane were connected to 0 V to mimic a large counter electrode. In Fig. 2.6c one electrode is used as the cathode, while the other is the anode (bipolar stimulation). In Fig. 2.6d one electrode is used as a cathode and is driven with 10 mA, while the other two electrodes both act as the anode and are driven with 5 mA each.

As can be seen from Fig. 2.6, the shape and size of the electric field heavily depend on the choice of the electrodes, as well as on how they are operated.

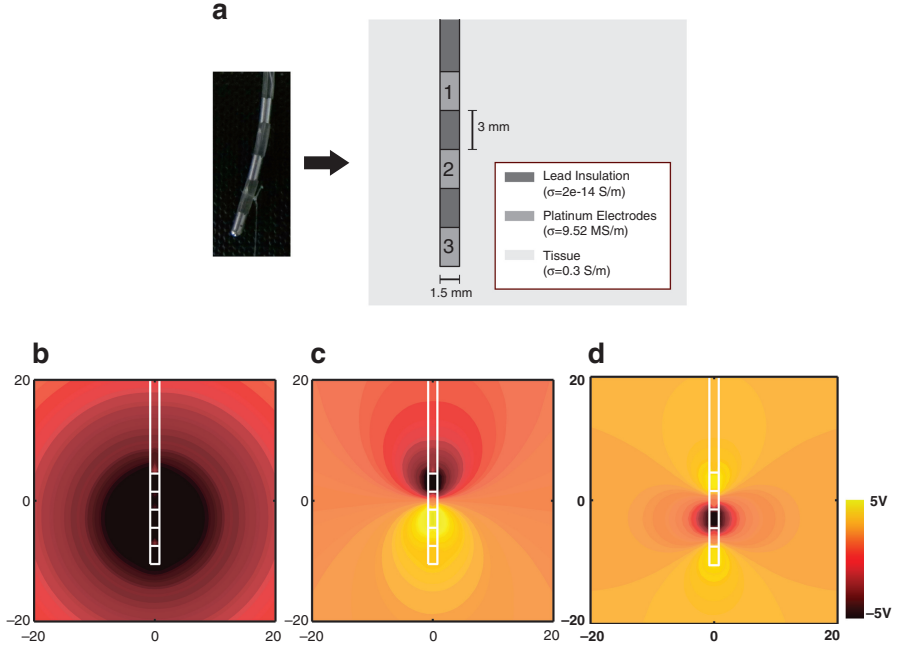


Fig. 2.6 Illustrative simulations showing the potential distribution due to a stimulation current through electrodes. In (a) the finite element model is sketched, while in (b), (c), and (d) the potential distributions of monopolar, bipolar, and tripolar stimulation configurations are shown, respectively. The dimensions on the axis are in mm

2.2.2.1 Monopole Example

For specific cases the electric field can be solved analytically. Here we will analyze the potential distribution of a point source (monopole) in an infinite homogeneous isotropic volume conductor with conductivity σ . This situation can approximate a real situation when the distance from the electrode becomes large with respect to the electrode size.

The current from the source will spread out in the volume conductor equally to all directions, hence the current density at a distance r from the source decreases proportionally with the area of a sphere:

$$\vec{J} = \frac{I_{stim}}{4\pi r^2} \vec{a}_r \quad (2.12)$$

Here I_{stim} is the stimulation current and \vec{a}_r is the unit vector in the radial direction with the point source at the origin. Using Ohm's law $\vec{J} = \sigma \vec{E}$ and realizing that the electric field only varies over the radial direction, the potential is found using Eq. (2.10) via integration of the electric field over r as:

$$\Phi = \frac{I_{stim}}{4\pi\sigma r} \quad (2.13)$$

Equation (2.13) will be used in Chap. 4 to analyze the electric field resulting from a particular type of stimulation pattern.

2.2.3 Neuronal Level: Axonal Activation

Knowing the potential distribution in the tissue, it is possible to analyze the resulting membrane potential in the neurons. Although activation or inhibition of the neurons can occur anywhere, often axonal activation is considered [7–9]. A cable model is used for which the axon is divided into segments that contain the membrane model of Fig. 2.3: the membrane capacitance C_m , the resting potential V_{rest} , and a resistance Z_{HH} modeling the membrane channels. Each membrane model is connected using an intracellular resistance R_i . This is schematically depicted in Fig. 2.7.

The cable model is now placed in the potential field that was found in the previous section, which will determine the extracellular potentials $V_{e,n}$ along the axon. Based on these potentials, the membrane voltage $V_{m,n} = V_{i,n} - V_{e,n}$ at node n can be found by solving the following equation that follows directly from Kirchhoff's laws [7]:

$$\frac{dV_{m,n}}{dt} = \frac{1}{C_m} \left[\frac{1}{R_i} (V_{m,n-1} - 2V_{m,n} + V_{m,n+1} + V_{e,n-1} - 2V_{e,n} + V_{e,n+1}) - i_{HH} \right] \quad (2.14)$$

Here i_{HH} is the current described by the Hodgkin–Huxley equations through the impedance Z_{HH} . As will be shown in Chap. 4, this equation can be used to analyze the membrane voltage during a stimulation pulse. If the membrane voltage is elevated above the threshold for a certain amount of time, the dynamics of the Hodgkin–Huxley equations predict that an action potential will be generated.

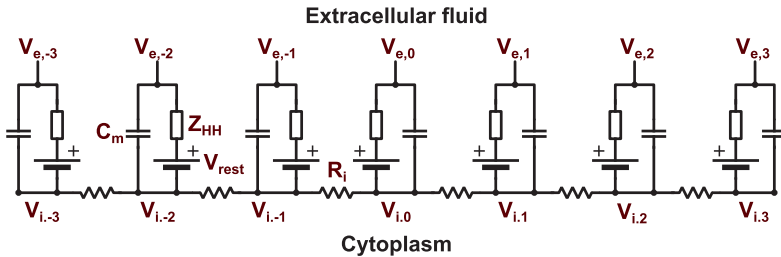


Fig. 2.7 Axon model used to evaluate the membrane voltage $V_m = V_i - V_e$ during a stimulation. The extracellular potentials $V_{e,i}$ are determined by the electric field resulting from the stimulation current

From Eq. (2.14) the source term due to the electric field can be isolated and is found as:

$$f_n = \frac{V_{e,n-1} - 2V_{e,n} + V_{e,n+1}}{\Delta x^2} \quad (2.15)$$

Here it is used that $R_i = 4\rho_i\Delta x/(\pi d^2)$ and $C_m = \pi dLc_m$ in which ρ_i is the intracellular resistivity, d is the axon diameter, L is the length of membrane segment, c_m is the membrane capacitance per unit area, and Δx is the segmentation length of the membrane. f_n is called the activation function [9] and for $\Delta x \rightarrow 0$, it becomes the second order derivative of the extracellular potential. As a first approximation it can be stated that as long as $f_n > 0$ for a certain axon segment, V_m will increase and hence it is likely that activation will occur. This assumes that the stimulation is strong enough and enabled long enough to allow V_m to rise above the threshold.

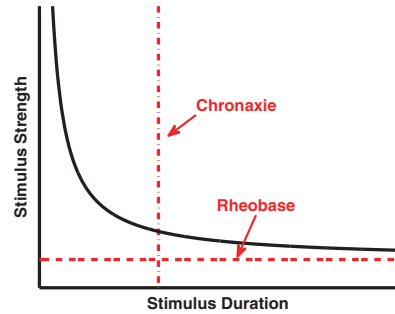
Thus, in conclusion, for a membrane to be recruited, f_n needs to be sufficiently positive for a certain amount of time. This property can be translated to a relation between the minimum required stimulation current I_{stim} and the stimulation duration t_{stim} . This property is well known and is summarized in the *charge–duration curve*, which shows the following hyperbolic relationship: $I_{stim} = a/t_{stim} + b$ [10]. This curve is sketched in Fig. 2.8. The minimum stimulation current $I_{stim} = b$ required to achieve stimulation is called the rheobase [10], while the $t_{stim} = a/b$ corresponding with twice the rheobase is called the chronaxie. The chronaxie is the point at which the energy of the stimulation pulse E_{pulse} is minimal:

$$E_{pulse} = I_{stim}^2 Z_{load} t_{stim} = \left(\frac{a^2}{t_{stim}^2} + b^2 t_{stim} \right) Z_{load} \quad (2.16)$$

Here Z_{load} is the impedance of the electrodes. The minimum energy is found to be equal to the chronaxie via:

$$\frac{dE_{pulse}}{dt_{stim}} = \left(\frac{-a^2}{t_{stim}^2} + b^2 \right) Z_{load} = 0 \rightarrow t_{stim} = \frac{a}{b} \quad (2.17)$$

Fig. 2.8 Strength–duration curve showing the required stimulation intensity as a function of the stimulus duration. The rheobase and chronaxie are depicted as well



2.3 Conclusions

In this chapter an overview has been given of the electrophysiological principles of neurons. It was shown how the electrochemical properties of the neural cell membrane are responsible for the generation of action potentials. Furthermore, it was shown how electrical stimulation influences the neural tissue: a stimulation current will generate an electric field in the tissue, which will influence the membrane voltage of the neurons by depolarizing or hyperpolarizing the membrane. The minimum required stimulation intensity is described by the strength–duration curve, showing a hyperbolic relationship between the stimulation amplitude and duration.

References

1. Kandel, E., Schwartz, J.H., Jessell, T.: Principles of Neural Science. McGraw-Hill, New York (2000)
2. Malmivuo, J., Plonsey, R.: Bioelectromagnetism – Principles and Applications of Bioelectric and Biomagnetic Fields. Oxford University Press, New York (1995)
3. Hodgkin, A.L., Huxley, A.F.: A quantitative description of membrane current and its application to conduction and excitation in nerve. *J. Physiol.* **117**(4), 500–544 (1952)
4. Zoski, C.: Handbook of Electrochemistry. Elsevier, Amsterdam (2006)
5. Merrill, D.R., Bikson, M., Jefferys, J.G.R.: Electrical stimulation of excitable tissue – design of efficacious and safe protocols. *J. Neurosci. Methods* **141**, 171–198 (2005)
6. Butson, C.R., McIntyre, C.C.: Tissue and electrode capacitance reduce neural activation volumes during deep brain stimulation. *Clin. Neurophysiol.* **116**, 2490–2500 (2005)
7. McNeal, D.R.: Analysis of a model for excitation of myelinated nerve. *IEEE Trans. Biomed. Eng.* **23**(4), 329–337 (1976)
8. Warman, E.N., Grill, W.M., Durand, D.: Modeling the effects of electric fields on nerve fibers: determination of excitation thresholds. *IEEE Trans. Biomed. Eng.* **39**(12), 1244–1254 (1992)
9. Rattay, F.: Analysis of models for extracellular fiber stimulation. *IEEE Trans. Biomed. Eng.* **36**(7), 676–682 (1989)
10. Lapicque, L.: Définition Expérimentale de l'excitabilité. *C. R. Séances Soc. Biol. Fil.* **61**, 280–283 (1909)

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