Chapter 3

Detailed neural models

3.1 Neuron physiology

3.1.1 Neural components and signals

The human brain is able to perform complicated mental tasks including feeling, acting, learning and memorizing. It is possible thanks to its complex structure that is formed of the individual building blocks, the neural cells or neurons.

There are different types of neurons that are distinguished by their functions. The different functional properties are accompanied by different morphological properties. Although neurons have different forms and perform different functions, all of them typically consist of three well-defined regions: the cell body, the dendrites, and the axon illustrated in Fig. 3.1. Each of these parts plays a special role in the processing and transmission of information in the form of electrical signals. The cell body, called soma, is the metabolic center of the cell. Here proteins, necessary for the continuous functioning of the cell, are synthesized.

The two other cell regions, the axon and the dendrites, extend from the cell body. They provide connections through which the neuron receives electrical signals and produces responses. The dendrites perform the function of information processing. They are the largest components of the neuron and have a complicated branched structure. The morphological structure of the dendritic tree plays an important role in the communication between neurons. It affects the way in which the neuron process information, since the integration of the input signals depends on the structure of the dendritic tree.

The contact points between two neurons are called synapses, whereas the channels in the dendritic trees, by which the signals are processed, are referred to as synaptic channels.

The axon, which transfers the information to the next neuron, can vary in length and is often a thin tube. The signals are usually generated in the axon hillock, a place near the soma, and are delivered along the axon to the other neuron. Each neuron has only one axon. Thus, the axon can be characterized

as the transmitting element of the neuron [17, 36, 28, 9].

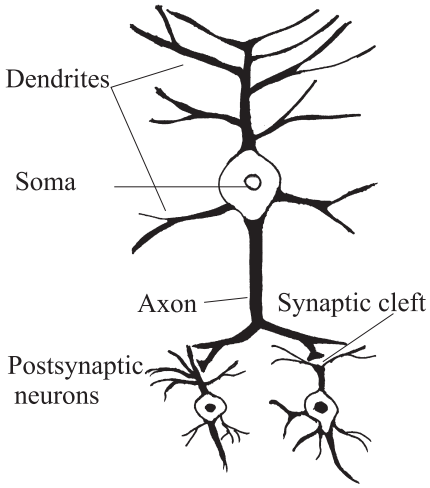

Figure 3.1: Schematic structure of a biological neuron.

3.1.2 Synaptic connections

The information that is transmitted from one cell to another is contained in the electrical signals that are propagated between the cells. Ionic currents across the membrane underlie the generation of action potentials. If the membrane voltage exceeds a certain threshold value the cell is excited in the form of a short electrical pulse (spike or action potential). The action potential is then propagated along the axon to the contact point with the other cell. Ionic currents across the membrane underlie the generation of action potentials.

Synapses are the structures providing the transfer of signals from one cell to another. Cells generating and receiving a signal are called presynaptic and postsynaptic cells, correspondingly. There are two types of synapses: electrical and chemical. In the electrical synaptic connection, the membranes of two cells are in direct contact. A signal from the presynaptic cell is transmitted to the postsynaptic cell by an ion flow through the gap-junction channels in the membranes of the neighboring cells.

In contrast to the electrical synapses, a small space, the synaptic cleft, separates two cells in the case of the chemical synaptic connection (see Fig. 3.2). Initiated in the axon hillock, the signal is delivered through the axon of the presynaptic cell to the so-called axon terminal (or terminal button). The depolarization of the cell during the action potential leads to the opening of the Ca^{2+} channels that releases the neurotransmitters in the synaptic cleft (see Fig. 3.3). The neurotransmitter causes the opening of the special receptor channels in the

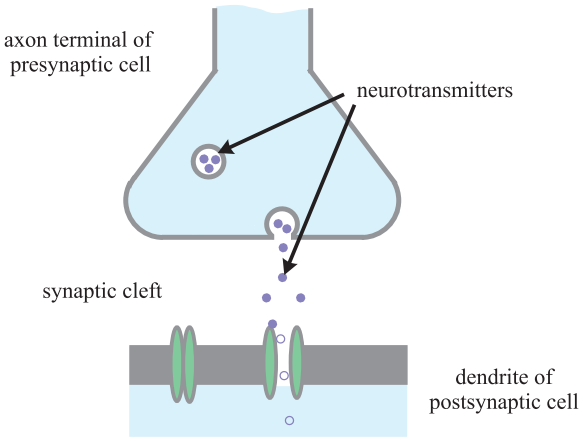

Figure 3.2: The main elements of chemical synapses.

postsynaptic cell. The opening of these channels leads to a Na^+ ions flow into the postsynaptic cell. This process causes a change in the membrane potential of the postsynaptic cell.

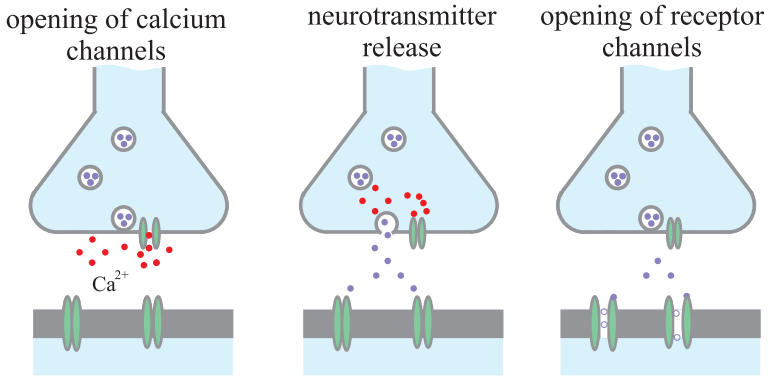

Figure 3.3: Synaptic transmission at a chemical synapse.

The synapse's properties define the connections between cells [17, 36] and the change of signal form from the presynaptic to the postsynaptic cell is determined by the properties of the synaptic channels. The instantaneous transmission of the signals at electrical synapses can be contrasted with the time delayed signal transfer in the case of chemical synapses.

3.1.3 Cell membrane

The cell membrane is a lipid bilayer that is essentially impermeable to most charged ions. As a result of this insulating property, a difference in the electrical potential between the inside and the outside of the cell is maintained at the resting potential. The membrane acts as a capacitor accumulating the charges along the inner and outer sides of the cell. Thus, the resulting membrane potential V_m is the difference between the potentials inside (V_{in}) and outside (V_{out}) of the cell:

$$V_m = V_{in} - V_{out}, \tag{3.1}$$

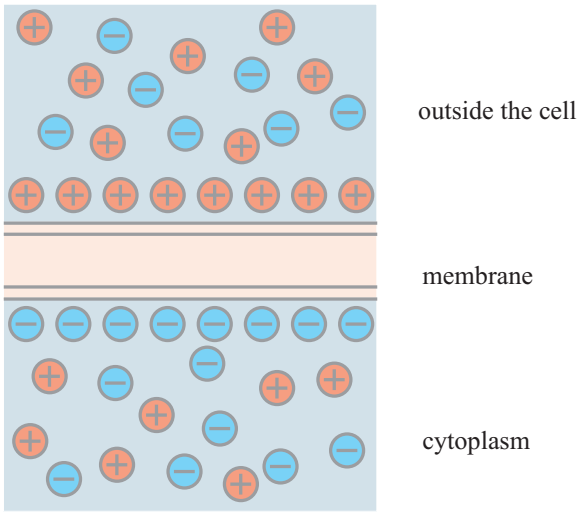

Figure 3.4: An accumulation of positive and negative charges along the membrane and outside of the cell results in the membrane potential.

The membrane potential of a cell at rest (i.e. when there is no signal activity) is referred to as the resting potential and varies typically from $-60\ mV$ to $-75\ mV$ (the inside of the cell is usually negatively charged). The resting membrane potential originates from the unequal concentration of charged ions inside and outside of the cell. For example, glial cells have a high Na^+ and Cl^- concentration outside of the cell and a high concentration of K^+ inside. The inside of the cell is neutral, since there is also negative ions that compensate the positively charged K^+ ions. The chemical driving force causes the diffusion of K^+ ions from the inner area of the cell into the surrounding fluid, since the membrane of glial cells is permeable to K^+ ions. Because of accumulating of the negative charge in the inside of the cell, the appearing electrical driving force tends to move K^+ in the opposite direction. The equilibrium value will be achieved when the two forces are mutually compensated.

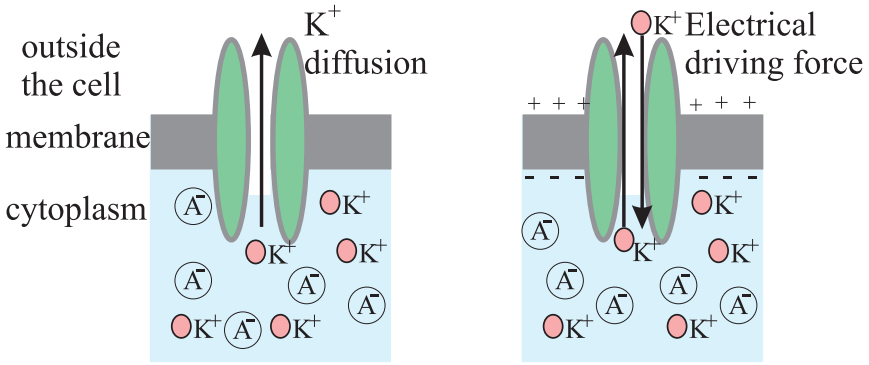

Figure 3.5: Diffusion and electrical forces underlie the process of driving K^+ ions through an ionic channel.

When these forces have equal strength, the equilibrium potential is established. It can be calculated based on the termodynamical principles from the Nernst formula:

$$E_{eq} = \frac{RT}{zF} \ln \frac{[c]_o}{[c]_i}, \tag{3.2}$$

where R is the gas constant, T is the temperature, z is the valence of the ion ($+1$ for K^+), F is the Faraday constant, and $[c]_o$ and $[c]_i$ are the concentrations of ions outside and inside the cell.

The equilibrium potential of potassium is $E_K = -80\ mV$. The same process takes place for the Na^+ ions whose concentration is higher inside the cell than outside. The membrane potential established as the result of these two processes is the resting membrane potential and is usually about $-69\ mV$.

3.1.4 Ionic channels

A number of ionic channels are embedded in the membrane. A typical neuron may have about a dozen or even more different types of channels. Only a single type of ion can pass through a certain type of channel. The leakage ionic channels are responsible for maintaining the resting membrane potential and are usually open all the time.

The voltage-gated channels are responsible for the process of information transmission within a cell. These channels are opened and closed as a function of the membrane voltage. The ion transfer across the cell membrane is regulated by the opening and closing of the voltage-gated channels. The generation of the stereotyped electrical signals, the action potentials, is regulated by the dynamics of the opening and closing of the voltage-gated channels.

The British scientists A.Hodgkin and A.Huxley performed experiments on the giant axon of the squid and described mathematically the dynamics of the action potential initiation [1]. They were able to demonstrate that the current

flowing across the membrane of the squid axon is composed of two ionic currents, potassium and sodium. The form of an action potential is shown in Fig. 3.6.

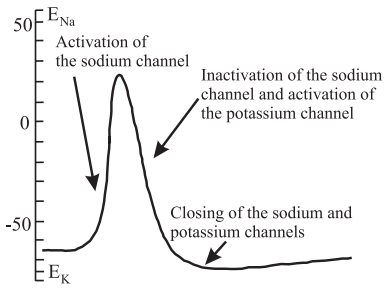

Figure 3.6: The stages of spike initiation.

From a biological point of view, the following sequence of events results in the generation of an action potential. First, a depolarization of the membrane (caused by an injected current or a current from the synaptic channels) leads to the opening of the sodium channels, which generates an increase in the inward sodium current. The mechanism of opening the sodium channels, which is shown in Fig. 3.7a) and Fig. 3.7b), is regulated by the activation gate. It changes the membrane potential towards the sodium equilibrium potential $V_m = +65\ mV$. This stage characterizes the rising phase of the action potential (see Fig. 3.6).

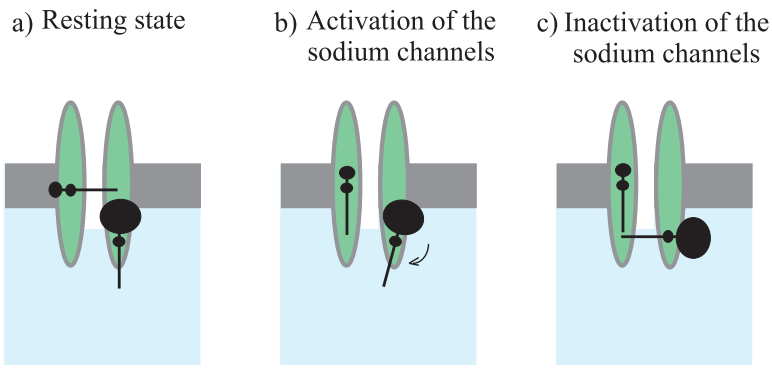

Figure 3.7: Response of the sodium channel activation and inactivation gates to a depolarization of the membrane.

After that, two different processes cause the falling phase of the action potential (see Fig. 3.6). First, the sodium channels begin to close, that corresponds to the closing of the inactivation gate of the sodium channels. The inactivation mechanism of a sodium channel is shown in Fig. 3.7c). Second, the potassium channels open, with the same delay as the sodium channels, since their

opening rate is smaller than that of the sodium channels. This changes the membrane potential towards the value of the potassium equilibrium potential $V_m = -80\ mV$. In contrast to the sodium channels, the potassium channels are not time dependent and remain open as long as the membrane is depolarized. As the membrane potential approaches the resting value both the sodium and the potassium channels close (the sodium channels deactivate and the potassium activation gates close).

3.2 Computational aspects

In this section, I present the computational methods based on the electrical equivalent scheme of the neuron cell. I start with the Hodgkin-Huxley model that describes the process of action potential generation in the frame of the single-cell models. Then, I introduce the methods of studying the influence of the cell morphology on the cell's electrical properties. I start with an analytical approach known as the cable theory, which is based on the assumption that the cell membrane is electrically passive (voltage independent). Then, the compartmental modelling approach is presented. It is derived from the cable theory by replacing the continuous cable equation with differential equations for each isopotential compartment, which forms a system of ordinary differential equations. The resulting system permits a detailed simulation of complex neural structures.

3.2.1 The Hodgkin-Huxley model

Hodgkin and Huxley showed that the process of spike generation can be presented as a quantitative model consisting of four differential equations.

In the Hodgkin-Huxley model of the giant squid axon, the general ionic current is composed of three components: the sodium and potassium currents from the corresponding voltage-gated channels and a leakage current from a passive chlorine channel:

$$I_{ion} = I_{Na} + I_K + I_L \tag{3.3}$$

Each of these currents is proportional to the conductance G of the corresponding channels and the driving force $E_{eq} - V_m$:

$$I_{ion} = G_{Na}(E_{Na} - V_m) + G_K(E_K - V_m) + G_L(E_L - V_m) \tag{3.4}$$

Hodgkin and Huxley have postulated that the conductance of the sodium and potassium currents is changed dynamically as a function of the membrane voltage. They assumed that the voltage dependence can be described with three dynamic variables, n, m, and h. The variable n represents the activation gating variable of the potassium channels, while m and h represent the activation and inactivation gating variables of the sodium channels. It was shown that the

conductance of the sodium and potassium channels can be described according to the following formulas:

$$\begin{aligned} G_{Na} &= g_{Na} m^3 h \\ G_K &= g_K n^4, \end{aligned} \tag{3.5}$$

where g_{Na} and g_K are the maximum conductance of the Na^+ and K^+ channels.

Hodgkin and Huxley showed that the gating variables can be described by the following equations:

$$\begin{aligned} \frac{dm}{dt} &= \alpha_m(V_m)(1-m) - \beta_m(V_m)m \\ \frac{dh}{dt} &= \alpha_h(V_m)(1-h) - \beta_h(V_m)h \\ \frac{dn}{dt} &= \alpha_n(V_m)(1-n) - \beta_n(V_m)n \end{aligned} \tag{3.6}$$

The functions α and β are functions of V_m. For their description, one typically uses one of three standard functions with the parameters A, B, and $V0$ [20]:

- exponential:
$$\alpha(V) = A \cdot exp((V - V0)/B), \tag{3.7}$$
- linear-exponential:
$$\alpha(V) = \begin{cases} A \cdot (V - V0)/(exp((V - V0)/B) - 1)), V \neq V0, \\ A, V = V0 \end{cases} \tag{3.8}$$
- sigmoid:
$$\alpha(V) = A/(exp((V - V0)/B) + 1) \tag{3.9}$$

For the standard Hodgkin-Huxley model, the following parameters are used:

$$\begin{aligned} \alpha_m(V_m) &= \frac{0.1(25 - V_m)}{\exp\frac{(-35-V_m)}{10} - 1} \\ \beta_m(V_m) &= 4 \exp\frac{(-V_m - 60)}{18} \\ \alpha_h(V_m) &= 0.07 \exp\frac{(-V_m - 60)}{18} \\ \beta_h(V_m) &= \frac{1}{\exp\frac{(-30-V_m)}{10} + 1} \\ \alpha_n(V_m) &= \frac{0.01(-50 - V_m)}{\exp\frac{(-50-V_m)}{10} - 1} \\ \beta_n(V_m) &= 0.125 \exp\frac{(-V_m - 60)}{80} \end{aligned} \tag{3.10}$$

The next important step in the establishment of the Hodgkin-Huxley model is to consider the differential equation based on the electrical properties of the membrane. Due to the electrical insulation properties of the membrane, it acts as a capacitor. The change in capacitance current can be influenced by the current from the ionic channels or by an injected current. According to Kirchoff's law, one can write

$$C_m \frac{dV_m}{dt} = I_{Na} + I_K + I_L + I_{inject}. \tag{3.11}$$

The equivalent electrical circuit of the Hodgkin-Huxley model is shown in Fig. 3.8. It consists of a capacitor representing the membrane in parallel with resistors characterizing ionic channels and their associated batteries with the equilibrium potentials derived from the Nernst potential.

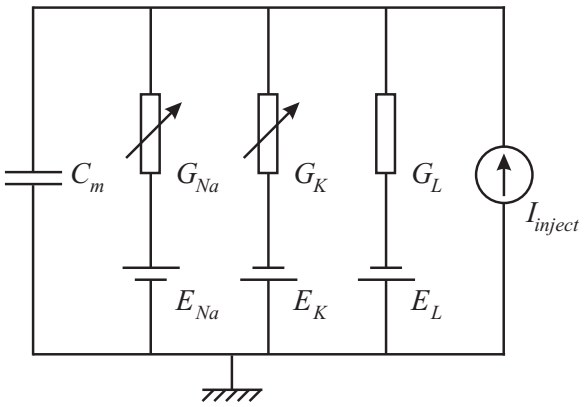

Figure 3.8: The electrical circuit equivalent circuit of a short segment of the giant squid axon from the Hodgkin-Huxley model.

To sum up, Eq. 3.11, Eq. 3.6, and Eq. 3.10 mathematically describe the action potential generation considered in the Hodgkin-Huxley model. The Hodgkin-Huxley model is a result of the functioning of the sodium, potassium and leakage channels. The system of differential equations consists of the equations describing the membrane current and the dynamics of the gating mechanisms in the ionic channels.

Hodgkin and Huxley developed the main principles used to describe the dynamics of the voltage-gated channels. Various types of voltage-gated channels are present in neural systems. However, they can be described by equations similar to Eq. 3.6 [54, 56]. Sometimes the dynamics of the channels also depends additionally on such factors as the Ca^{2+} or K^+ concentration.

3.2.2 Cable theory

The cable theory describes the propagation of electrical pulses along cables. This theory can be applied to describe the transmission of electrical pulses within the neuron cell, since the shape of the axons and the dendritic trees formed by a thin tube of nerve membrane is similar to that of a long, branching cable. The intracellular cytoplasm and extracellular fluid of the neuron cell are ionic media. The passive membrane acts as a capacitor and therefore the dendrites are usually unable to generate action potentials and can be considered as long conducting cables. The work of W. Rall [58] offers the most significant contribution to the cable theory.

The main assumption is that only the longitudinal component, i_i of the current through the cable, should be considered. In this case the membrane potential $V(x,t)$ of the cable is a function of the single coordinate x and the time, t. This can be justified by the small radius of the axon and dendrite cables compared to their length. According to Ohm's law

$$\frac{1}{r_i}\frac{\partial V}{\partial x} = -i_i, \tag{3.12}$$

where r_i is the cytoplasmic resistivity, the resistance per unit length along the x-axes.

For convenience, we consider the membrane potential V with respect to the resting membrane potential E_{rest}, i.e. we set $V = V_m(x) - E_{rest}$. Since the membrane is assumed to be passive, the change of the longitudinal current can be influenced either by the capacitance current or the current through the passive channels:

$$\frac{\partial i_i}{\partial x} = -i_m = -(\frac{V}{r_m} - c_m\frac{\partial V}{\partial t}) \tag{3.13}$$

where r_m and c_m are the membrane resistance and the capacitance per unit length. Combining Eq. 3.12 and Eq. 3.13, one gets the cable equation:

$$\frac{1}{r_i}\frac{\partial^2 V}{\partial x^2} = c_m\frac{\partial V}{\partial t} + \frac{V}{r_m} \tag{3.14}$$

Sometimes it is useful to express the electrical characteristics of the membrane in terms of *specific capacitance* C_M, *specific resistance* R_M, and *specific axial resistance* R_A, i.e. the measures per unit area:

$$\begin{aligned} C_m &= lc_m = \pi dlC_M \\ R_m &= r_m/l = \frac{R_M}{\pi dl} \\ R_a &= r_i l = \frac{4lR_A}{\pi d^2} \end{aligned} \tag{3.15}$$

Defining the space and time constants λ and τ_m:

$$\begin{aligned} \lambda &= \sqrt{r_m/r_i} = \sqrt{(d/4)R_M/R_A} \\ \tau_m &= r_m c_m = R_M C_M = R_m C_m, \end{aligned} \tag{3.16}$$

one can rewrite the cable equation 3.14 in the form

$$\lambda^2 \frac{\partial^2 V}{\partial x^2} - \tau_m \frac{\partial V}{\partial t} - V = 0, \tag{3.17}$$

Equation (3.17) can sometimes be written in terms of the dimensionless variables $X = x/\lambda$ and $T = t/\tau_m$

$$\frac{\partial^2 V}{\partial X^2} - \frac{\partial V}{\partial T} - V = 0, \tag{3.18}$$

The space constant characterizes the change of the membrane potential with the length of the cable. If we consider a solution of the cable equation for the so-called "steady state case" ($dV/dt = 0$) with the boundary conditions $V = V_0$ at $X = 0$ and $V = 0$ at $X = \infty$ the solution will take the form

$$V(X) = V_0 e^{-x/\lambda} = V_0 e^{-X} \tag{3.19}$$

The potential will decay exponentially with increasing distance along the cable (curve E, Fig. 3.9). The space constant λ defines the distance over which the e-fold voltage decreasing occurs.

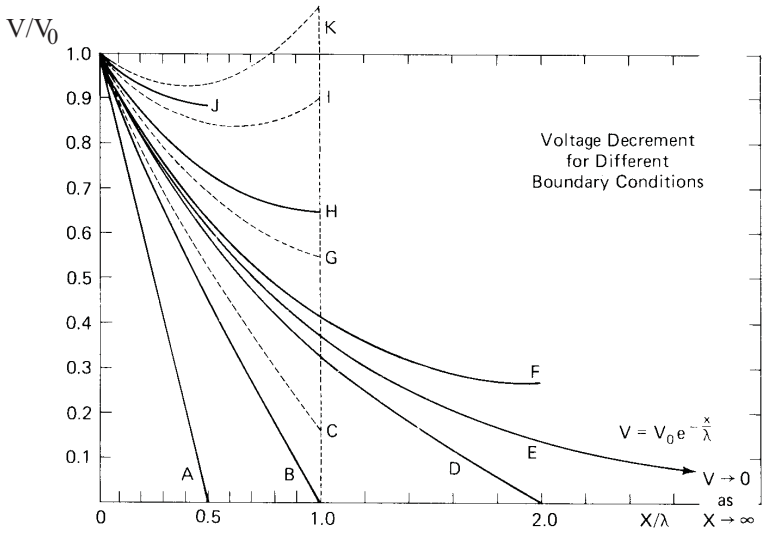

Figure 3.9: Solutions of the cable equation for different boundary conditions. Curve E presents a solution for an infinite cable length. Curves A, B, and D show a steeper decay for "clamped to rest" conditions. Curves F, H, and J, showing less slope, are for the "sealed end" conditions. From [60].

The curves F, H, and J show the solutions of the cable equation for the cable of a finite length with "sealed end" boundary conditions, so that no current flows

at the end. The curves represent the solutions for the cable lengths, $L = 0.5$, $L = 1$, $L = 2$, respectively.

In the next important case, if the point $X = L$ is clamped to the resting potential that corresponds to the condition $V = 0$, and therefore $V_m = E_{rest}$, the solution will take the form presented by curves A, B, and D, for the cable lengths, $L = 0.5$, $L = 1$, $L = 2$, respectively.

Curves I and K represent the voltage-clamped solution, i.e. $V = 0.9V_0$ and $V = 1.1V_0$ at $X = L$.

Curves C and G show solutions with the conditions when the leakage current at $X = L$ is equal to VG_L, where G_L is the leakage conductance at $X = L$. Curve C corresponds to $G_L/G_\infty = 4$, curve G to $G_L/G_\infty = 1/4$, where G_∞ is the corresponding conductance for the infinite cable (curve E).

The real dendritic trees have a branched structure, which corresponds to the solution lying between the "sealed end" and the "clamped to the rest" solutions. The space and time constants determine the form of the solution.

3.2.3 The compartmental approach

To describe a membrane with active channels (whose current is variable, e.g. synaptic or voltage-gated channels), one needs to include in the cable equation an additional elements, representing the current from the active channels: I_{act}.

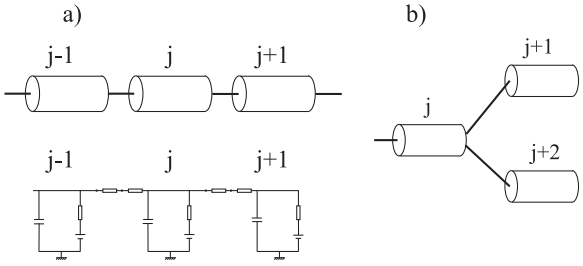

Figure 3.10: The segmentation used in the compartmental modelling approach. a) Cylindrical compartments and the equivalent electrical scheme b) A branched cable presented with cylindrical segments.

Let us consider a cable divided into a number of identical cylindrical segments, each of the length Δx (see Fig. 3.10). Such discretization provides approximately constant potential within each segment (compartment)[33, 12]. Taking into account the influence of the active channels, one can write the cable equation as

$$\frac{(\Delta x)^2}{R_a}\frac{\partial^2 V_j}{\partial x^2} = C_m\frac{\partial V_j}{\partial t} + \frac{V_j}{R_m} + I_{act}, \tag{3.20}$$

where V_j is the membrane potential of the jth compartment.

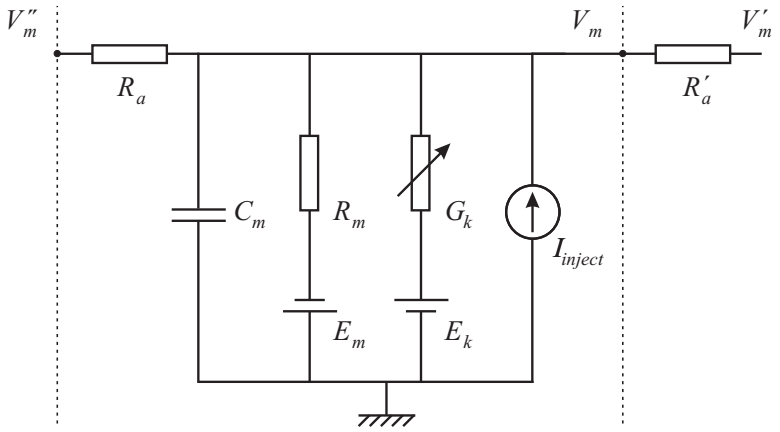

Figure 3.11: The equivalent electrical circuit for a basic neural compartment.

The finite-difference approximation of this equation will give the following expression for the first term

$$\frac{\partial^2 V}{\partial x^2} \rightarrow \frac{V_{j+1}(t) - 2V_j(t) + V_{j-1}(t)}{(\Delta x)^2} \tag{3.21}$$

Using the actual membrane potential V_m one can rewrite Eq. 3.20 in the more traditional form used in the compartmental modelling approach.

$$C_m \frac{dV_m}{dt} = \frac{E_m - V_m}{R_m} + \sum_k [(E_k - V_m)G_k] + \frac{V_m^{'} - V_m}{R_a^{'}} + \frac{V_m^{''} - V_m}{R_a} + I_{inject}, \tag{3.22}$$

where V_m is the actual membrane potential that can be associated with the variable V in the cable equation. The potentials $V_m^{'}$ and $V_m^{''}$ correspond to adjacent compartments. The current between the compartments is caused by the difference of the potentials V_m and $V_m^{'}$ across the axial resistance R_a and $R_a^{'}$. Passive (voltage independent) channels are represented by a resistance R_m and its associated equilibrium potential E_m. The conductances of the active channels, sensitive to a certain type of ion or a combination of ions, are represented by the conductance variable G_k.

All components from Eq. 3.22 are shown in Fig. 3.11 representing an electrical circuit of a neural compartment.

The same principle can be used to simulate branching cables. The additional term representing the current from the compartment in the adjacent branch should be added into Eq. 3.22. Fig. 3.10b) shows the compartmentalization of a branched cable. In the compartmental approach neurons with complex structures can be simulated using a number of compartments (see Fig. 3.12).

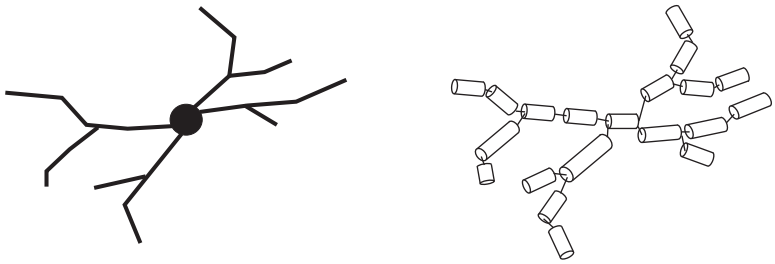

Figure 3.12: A neuron with complex structure can be represented as a set of compartments

The mathematical result of the compartmental approach is a system of ordinary differential equations, which can be solved numerically in parallel. The advantage of this approach is that there are no restrictions on the membrane properties. The shape of a cell can therefore be taken into account. The active channels (e.g. the Hodgkin-Huxley channels) are also included since the system can contain the equations describing the dynamics of the voltage-gated channels (see the previous paragraph).

3.3 Summary

This chapter gave a review of detailed modelling methods in which the anatomical and biophysical properties of neurons are included. First, the structure of a neuron and the signal processing were described from a biological point of view. The work of Hodgkin-Huxley, describing the dynamics of action potential generation, was considered as a basis for studying the functioning of neurons and their connections.

Then, descriptions of the main approaches for modelling of real networks: the cable theory, and compartmental modelling, were presented. The cable theory describes voltage changes through the length of a dendritic tree with passive membrane properties. Compartmental models can be used to treat membranes with active channels based on the neuron morphology and the channel dynamics equations. Based on these two models, one can build detailed models of neural systems to study their functioning.