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Foundations of Neurophysics

AUTHOR-DR K.SOWMIYA CO-AUTHOR-DR.CICILIGNATIUS & S.MANIMARAN

Summary
This chapter presents an introductory course to the biophysics of neurons, comprising a discussion of ion channels, active and passive membranes, action potentials and postsynaptic potentials. It reviews several conductance-based and reduced neuron models, neural networks and neural field theories. Finally, the basic principles of the neuroelectrodynamics of mass potentials, i.e. dendritic fields, local field potentials, and the electroencephalogram are elucidated and their putative functional role as a mean field is medium portions only discussed.

1 Introduction

Metaphorically, the brain is often compared with a digital computer [1, 2] that runs software algorithms in order to perform cognitive computations. In spite of its usefulness as a working hypothesis in the cognitive [3–6] and computational [7–18] neurosciences, this metaphor does obviously not apply to the hardware level. Digital computers consist of circuit boards equipped with chips, transistors, resistors, capacitances, power supplies, and other electronic components wired together. Digital computation is essentially based on controlled switching processes in semiconductors which are nonlinear physical systems. On the other hand, brains consist to 80% of water contained in cells and also surrounding cells.

How can this physical wet-ware substrate support

computational dynamics?

This question should be addressed in the present chapter. Starting from the physiological facts about neurons, their cell membranes, electrolytes, and ions [19–21], I shall outline the biophysical principles of neural computation [12, 13, 15, 18, 22–25] in parallel to those of computation in electronic circuits. Thus, the interesting physiological properties will be described by electric "equivalent circuits" providing a construction kit of building blocks that allow the modeling of membranes, single neurons, and eventually neural networks. This field of research is broadly covered by computational neuroscience. However, since this discipline also deals with more abstract approximations of real neurons (see Sect. 1.4.3) and with artificial

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Lectures in Supercomputational Neuroscience:

Dynamics in Complex Brain Networks. Berlin: Springer, 2008.

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neural networks, I prefer to speak about neurophysics, i.e. the biophysics of real neurons.

The chapter is organized as a journey along a characteristic neuron where the stages are Sects. 1.2–1.4. Looking at Fig. 8.1 in Chap. 8, the reader recognizes the cell bodies, o r somata, of three cortical neurons as the triangular knobs.
Here, our journey will start by describing the microscopically observable membrane potentials. Membranes separating electrolytes with different ion concentrations exhibit a characteristic resting potential. In a corresponding equivalent circuit, this voltage can be thought of being supplied by a battery. Moreover, passive membranes act as a capacitance while their semipermeability with respect to particular kinds of ions leads to an approximately ohmic resistance.
This property is due to the existence of leaky ion channels embedded in the cell membrane. At the neuron's axon hillock (trigger zone), situated at the base of the soma, the composition of the cell membrane changes. Here and along the axon, voltage-gated sodium and potassium channels appear in addition to the leakage channels, both making the membrane active and excitable. As we shall see, the equivalent circuit of the membrane allows for the derivation of the famous Hodgkin-Huxley equations of the action potentials which are the basic of neural conductance models. Traveling along the axon, we reach the presynaptic terminals, where the Hodgkin-Huxley equations have to be supplemented by additional terms describing the dynamics of voltage-gated calcium channels. Calcium flowing into the terminal causes the release of transmitter vesicles that pour their content of neurotransmitter into the synaptic cleft of a chemical synapse. Then, at the postsynapse, transmitter molecules dock onto receptor molecules, which indirectly open other ion channels.
The kinetics of these reactions give rise to the impulse response functions of the postsynaptic membranes. Because these membranes behave almost passively, a linear differential equation describes the emergence by the convolution product of the postsynaptic pulse response with the spike train, i.e. the sequence of action potentials. Postsynaptic potentials propagate along the dendrites and the soma of the neuron and superimpose linearly to a resulting signal that eventually arrives at the axon hillock, where our journey ends.
In Sect. 1.5, we shall change our perspective from the microscopic to the macroscopic. Here, the emergence of mass potentials such as the local field potential (LFP) and the electroencephalogram (EEG) will be discussed.

1.2 Passive Membranes

Neurons are cells specialized for the purpose of fast transfer and computation of information in an organism. Like almost every other cell, they posses a

cell body containing a nucleus and other organelles and they are surrounded by a membrane separating their interior from the extracellular space.

In or-der to collect information from their environment, the soma of a characteristic
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neuron branches out into a dendritic tree while another thin process, the axon, provides an output connection to other neurons [19–21]. The cell plasma in the interior as well as the liquid in the extracellular space are electrolytes, i.e. solutions of different kinds of ions such as sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), chloride (Cl^-), and large organic ions. However, the concentrations of these ions (denoted by $[Na^+]$, $[K^+]$, $[Ca^{2+}]$, etc.)

one side of the cell membrane to the other (see Fig. 2.1 of can differ drastically from
Therefore,the membrane is subjected to two competing forces: the osmotic force aiming at a compensation of these concentration gradients on the one hand, and the Coulomb force aiming at a compensation of the electric potential gradient. Biochemically, cell membranes are lipid bi-layers swimming like fat blobs in the plasma soup [19,20], which makes them perfect electric isolators. Putting such a dielectric between two opposite electric charges yields a capacitance of capacity

$$C_m = \frac{Q}{U}, \qquad (1.1)$$

where Q is the total charge stored in the capacitance and U is the voltage needed for that storage. Hence, a membrane patch of a fixed area A that separates different ion concentrations can be represented by a single capacitance $C_m = 1\ \mu F\ cm^{-1} \times A$ in an equivalent “circuit” shown in Fig. 1.1 [19, 20].
Generally, we interpret such equivalent circuits in the following way: The upper clamp refers to the extracellular space whereas the clamp at the bottom measures the potential within the cell. Due to its higher conductance, the extracellular space is usually assumed to be equipotential, which can be designated as $U = 0$ mV without loss of generality.

Ion Channels

If neuron membranes were simply lipid bi-layers, there would be nothing more to say. Of course, they are not. All the dynamical richness and computational complexity of neurons is due to the presence of particular proteins, called ion channels, embedded in the cell membranes. These molecules form tubes

traversing the membrane that are permeable to certain kinds of ions [19–25]. The "zoo" of ion channels is comparable with that of elementary particles. There are channels whose pores are always open (leakage channels) but permeable only for sodium or potassium or chloride. Others possess gates situated in their pores which are controlled by the membrane potential, or the presence of certain substances or even both.
We shall refer to the first kind of channels as to voltage-gated channels, and to the second kind as to ligand-gated

C_m
Fig. 1.1. Equivalent "circuit" for the capacitance C_m of a membrane patch

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channels. Furthermore, the permeability of a channel can depend on the direction of the ionic current such that it behaves as a rectifier whose equivalent "circuit" would be a diode [19, 20]. Eventually, the permeability could be a function of the concentration of particular reagents either in the cell plasma or in the extracellular space, which holds not only for ligand-gated channels. Such substances are used for classifying ion channels. Generally, there are two types of substances. Those from the first class facilitate the functioning of a channel and are therefore called agonists. The members of the second class are named antagonists as they impede channel function.

Omitting these complications for a while, we assume that a single ion channel of kind k behaves as an ohmic resistor with conductance

$$\gamma_k = \frac{1}{\rho}$$

where ρ_k is the resistivity of the channel. A typical value (for the gramicidin-A channel) is $\gamma_{GRAMA} \approx$ 12 pS. Figure 1.2 displays the corresponding equivalent "circuit".

In the remainder of this chapter, we will always consider membrane patches of a fixed area A. In such a patch, many ion channels are embedded, forming the parallel circuit shown in Fig. 1.3(a).
According to Kirchhoff's First Law, the total conductance of the parallel circuit is

$$g_k = N_k \gamma_k \quad (1.3)$$

when N_k channels are embedded in the patch, or, equivalently, expressed by the channel concentration $[k] = N_k/A$,

$$g_k = [k] A \gamma_k .$$

1.2.2 Resting Potentials

By embedding leakage channels into the cell membrane, it becomes semipermeable, i.e. permeable for certain kinds of ions while impenetrable for others. If there is a concentration gradient of a permeable ion across a semipermeable membrane, a diffusion current I_{diff} through the membrane patch A is created, whose density obeys Fick's Law

$$j_{diff} = -D\,q\,\frac{d[I]}{dx}, \qquad (1.4)$$

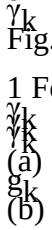

Fig. 1.2. Equivalent "circuit" for a single ohmic ion channel with conductance γ_k

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Fig. 1.3. Equivalent circuits (a) for ion channels of one kind k connected in parallel; (b) Substituted by a single resistor of conductance $g_k = 3\ \gamma_k$

where d[I]/dx denotes the concentration gradient for ion I, q its charge, and $D = k_B T / \mu$ is the diffusion constant given by Einstein's relation [26] (k_B is Boltzmann's constant, T is the temperature and μ is the viscosity of the electrolyte) [22–25]. This diffusion current can be described by an equivalent "circuit" given by a current source I_{diff} (Fig. 1.4).

The separation of charges by the diffusion current leads to an increasing potential gradient dU/dx across the membrane. Therefore, a compensating ohmic current

$$j_{ohm} = -\sigma\frac{dU}{dx}$$

flows back through the leakage channels ($\sigma = q^2[I]/\mu$ is the conductance of the electrolyte expressed by the ion concentration and its charge). Then the total current $j = j_{diff} + j_{ohm}$ (visualized by the circuit in Fig. 1.5) is described by the Nernst-Planck equation

$$j = -D\,q\,\frac{d[I]}{dx} - \frac{q^2}{\mu}[I]\frac{dU}{dx}$$

The Nernst Equation

The general quasi-stationary solution of (1.6), the Goldman-Hodgkin-Katz

equation ((2.4) in Chap. 2), clearly exhibits a nonlinear dependence of the ionic current on the membrane voltage [22–25]. However, for only small deviations from the stationary solution — given by the Nernst equation

$$E_I = \frac{k_B T}{q} \ln \frac{[I]_{out}}{[I]_{in}}$$

Fig. 1.4. Equivalent "circuit" either for the diffusion currents through the cell membrane or for the active ion pumps

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I_{diff}
Equivalent circuit for the derivation of the Nernst-Planck equation (1.6)

where $[I]_{out}$ is the ion concentration in the extracellular space and $[I]_{int}$ within the cell — the current can be regarded as being ohmic.

For room temperature, the factor $k_B T / q \approx 25$ mV. With the concentrations from Fig. 2.1, Chap. 2, this leads to the characteristic resting potentials; e.g. $U_{K^+} = -101$ mV, and $U_{Na^+} = +56$ mV.

Each sort of ion possesses its own Nernst equilibrium potential. We express this fact by a battery in an equivalent "circuit".

Now, we are able to combine different ion channels k all selective for one sort of ions I with their corresponding power supplies. This is achieved by a serial circuit as shown in. This equivalent circuit will be our basic building block for all other subsequent membrane models.

If the clamp voltage of this circuit has the value U , we have to distribute this voltage according to Kirchhoff's Second Law as

$$U = \frac{I}{g_k} + E_I ,$$

leading to the fundamental equation

$$I_k = g_k(U - E_I)$$

The Goldman Equation

As an example, we assume that three types of ion channels are embedded in the membrane patch, one pervious for sodium with the conductance g_{Na^+}, another pervious for potassium with the conductance g_{K^+}, and the third pervious for chloride with the conductance g_{Cl^-}, respectively. displays the corresponding equivalent circuit.

Interpreting the top of the circuit as the extracellular space and the bottom as the interior of the neuron, we see that the resting potential for potassium

E_I

Fig. 1.6. Equivalent circuit for the Nernst equilibrium potential

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g_k

E_I

Equivalent circuit for a population of ion channels of kind k selective for the ion sort I embedded in a membrane with resting potential E_I

and chloride is negative (denoted by the short tongue of the battery symbol) while the sodium equilibrium potential is positive in comparison to the extracellular space.

According to Kirchhoff's First Law, the total current through the circuit is

$$I = I_{Na^+} + I_{K^+} + I_C$$

To obtain the stationary equilibrium, we have to set $I = 0$. Using the fundamental equation (1.8), we get the equation

$$0 = g_{Na^+}(U - E_{Na^+}) + g_{K^+}(U - E_{K^+}) + g_{Cl^-}(U - E_{Cl^-}),$$

whose resolution entails the equilibrium potential

$$U = \frac{g_{Na^+} E_{Na^+} + g_{K^+} E_{K^+} + g_{Cl^-} E_{Cl^-}}{g_{Na^+} + g_{K^+} + g_{Cl^-}}$$

Equation (1.10) is closely related to the Goldman equation that can be derived from the Goldman-Hodgkin-Katz equation [24]. It describes the net effect of all leakage channels. Therefore, the circuit in Fig. 1.8 can be replaced by the simplification found in Fig. 1.9.

Accordingly, the leakage current is again given by (1.8)

$$I_l = g_l(U - E_l)$$

g_{Cl^-}

E_{Cl^-}

g_{K^+}

E_{K^+}

g_{Na^+}

E_{Na^+}

sodium, potassium and chloride with their respective Nernst potentials

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g_l

E_l

Fig. 1.9. Equivalent circuit for the total leakage current and its corresponding leakage potential E_l

Characteristic values are $g_l = 1\ 3\ \mu S$ for the leakage conductance and $E_l =$ -69 mV for the leakage potential as the solution of (1.10) [19, 20].

While the Nernst potential for one kind of ions denotes a stationary state, the Goldman equilibrium potential results from a continuous in- and outflow of ions that would cease when all concentration gradients had been balanced. To stabilize the leakage potential the cell exploits active ion pumps modeled by a current source as displayed in Fig. 1.4. These ion pumps are proteins embedded in the cell membrane that transfer ions against their diffusion gradients by consuming energy. Maintaining resting potentials is one of the energetically most expensive processes in the nervous system [27]. This consumption of

energy is, though rather indirectly, measurable by neuroimaging techniques such as positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) [19, 20, 28, 29].

Active Membranes

The resting potentials we have discussed so far are very sensitive to changes in the conductances of the ion channels. While these are almost constant for the leakage channels, there are other types of channels whose conductances are functions of certain parameters such as the membrane potential or the occurrence of particular reagents. These channels make membranes active and dynamic. The former are called voltage-gated whereas the latter are referred to as ligand-gated. Basically, these channels occur in two dynamical states: their pore may be open (O) or closed (C).

The conductance of closed channels is zero, while that of an open channel assumes a particular value γ_k. Therefore, a single gated channel can be represented by a serial circuit of a resistor with conductance γ_k and a switch S, as depicted in Fig. 1.10.

Let N_k be the number of gated channels of brand k embedded in our membrane patch of area A, and let O_k and C_k the number of momentarily open and closed channels of this kind, respectively. As argued in Sect. 1.2.1, the total conductance of all open channels is given by Kirchhoff's First Law as

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γ_k

Equivalent circuit for a single gated channel with open-conductance γ_k

$$g_k = O_k \gamma_k ,$$

while

$$\bar{g}_k = N_k \gamma$$

is now the maximal conductance of these channels.

Action Potentials

Signals propagate mainly passively along the dendritic and somatic membranes until they reach the axon hillock, or trigger zone of the neuron. Here, the composition of the membrane changes significantly and voltage-gated sodium and potassium channels supplement the all-pervasive leakage channels. Above, we have modeled these channels by switches connected serially with ohmic resistors. Now, the crucial question arises: Who opens the switches? Here, for the first time, a stochastic account is required. Ion channels are macro-molecules and hence quantum objects. Furthermore, these objects are weakly interacting with their environments. Therefore the cell membrane and the electrolytes surrounding it provide a heat bath making a thermodynamical treatment necessary. From a statistical point of view, an individual channel has a probability of being open, p_k, such that the number of open channels is the expectation value

$$O_k = p_k$$

Inserting (1.14) into (1.12) yields the conductance
$g_k = p_k N_k \gamma_k = p_k \bar{g}_k$
.
The problem of determining the probability p_k is usually tackled by modeling Markov chains [24, 25]. The simplest approach is a two-state Markov process shown in Fig. 1.11, where C and O denote the closed and the open state, respectively, while α, β are transition rates.
The state probabilities of the Markov chain

Fig. 1.11. Two-state Markov model of a voltage-gated ion channel

whose transition rates are given by the thermodynamic Boltzmann weights
$\alpha_k = e$
$k_B T$
where W (C, → O) is the necessary amount of energy that has to be supplied (1.17)
by the heat bath to open the channel pore.
Channel proteins consist of amino acids that are to some extent electrically polarized [19–21]. The gate blocking the pore is assumed to be a subunit with charge Q. Call $W_0(C \rightarrow O)$ the work that is necessary to move Q through
the electric field generated by the other amino acids to open the channel pore. Superimposing this field with the membrane potential U yields the total transition energy
$W(C \rightarrow O) = W_0(C \rightarrow O) + QU$. (1.18)
If QU <0, W (C → O) is diminished and the transition C → O is facilitated [12], thereby increasing the rate α_k according to
$\alpha_k(U) = e$

The equations (1.15, 1.16, 1.19) describe the functioning of voltage-gated ion channels [12,13,15, 23–25]. Yet, voltage-gated resistors are also well-known in electric engineering: transistors are transient resistors. Though not usual in the literature, I would like to use the transistor symbol to denote voltage-gated ion channels here (Fig. 1.12). In contrast to batteries, resistors and capacitors, which are passive building blocks of electronic engineering, transistors are active components thus justifying our choice for active membranes.
$\bar{g}_k$
Fig. 1.12. Equivalent circuit for a population of voltage-gated ion channels. The maximal conductance $\bar{g}_k$ is reached when the transistor is in saturation

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E_I g_k
Fig. 1.13. Equivalent circuit for a population of voltage-gated ion channels of kind k selective for the ion sort I embedded in a membrane with resting potential E_I

Corresponding to Fig. 1.7, the equivalent circuit for a population of voltage-gated channels of kind k permeable for ions I supplied by their respective resting potential E_I is provided in Fig. 1.13.

The Hodgkin-Huxley Equations
Now we are prepared to derive the Nobel-prize-winning Hodgkin-Huxley equations for the action potential [32] (see also [12–15, 23–25]). Looking again at

Fig. 1.8, one easily recognizes that an increase of the sodium conductance leads to a more positive membrane potential, or, to a depolarization, while an increasing conductance either of potassium or of chloride entails a further negativity, or hyperpolarization of the membrane potential. These effects are in fact achieved by voltage-gated sodium and potassium channels which we refer here to as AN and AK, respectively. Embedding these into the cell membrane yields the equivalent circuit shown in Fig. 1.14.[3]

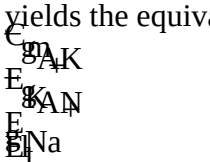

Fig. 1.14. Equivalent circuit for the Hodgkin-Huxley equations (1.25, 1.27–1.29)

[3] I apologize to all electrical engineers for taking their notation rather symbolically. Certainly, this circuit has neither protection resistors nor voltage stabilizers and should not be reproduced. Sorry for that!

The first and second branches represent the voltage-gated potassium and sodium channels, respectively. The third is taken from the stationary descriptions of the leakage potential (Sect. 1.2.2) while the capacitance is now necessary to account for the dynamics of the membrane potential. According to Kirchhoff's First Law, the total current through the circuit adds up to an injected current I_m,

$$I_m = I_{AK} + I_{AN} + I_l + I_C \,.$$

The partial currents are

$$I_{AK} = p_{AK}\,\bar{g}_{AK}\,(U - E_{K^+}) \quad (1.21)$$

$$I_{AN} = p_{AN}\,\bar{g}_{AN}\,(U - E_{Na^+}) \quad (1.22)$$

$$I_l = g_l\,(U - E_l) \quad (1.23)$$

$$I_C = C_m \frac{dU}{dt} \,,$$

where (1.21, 1.22) are produced from (1.15) and (1.8), (1.23) is actually (1.11) and (1.24) is the temporal derivative of (1.1). Taken together, the membrane potential U (t) obeys the differential equation

$$C_m \frac{dU}{dt} + p_{AK}\,\bar{g}_{AK}\,(U - E_{K^+}) + p_{AN}\,\bar{g}_{AN}\,(U - E_{Na^+}) + g_l\,(U - E_l) = I_m \,.$$

Equation (1.25) has to be supplemented by two master equations: (1.16) for the open probabilities p_{AK}, p_{AN} and the rate equations (1.19) for α_{AK}, α_{AN}.

Unfortunately, this approach is inconsistent with the experimental findings

of Hodgkin and Huxley [32]. They reported two other relations

$$p_{AK} = n^4; \qquad p_{AN} = m^3 h, \quad (1.26)$$

where n, m and h now obey three master equations

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

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

$$\frac{dh}{dt} = \alpha_h (1 - h) - \beta_h .$$

The equations (1.25, 1.27–1.29) are called Hodgkin-Huxley equations [12–15, 23–25, 32]. They constitute a four-dimensional nonlinear dynamical system controlled by the parameter I_m. Figure 1.15 displays numerical solutions for three different values of I_m.

Figure 1.15 illustrates only two of a multitude of dynamical patters of the Hodgkin-Huxley system. Firstly, it exhibits a threshold behavior that is due to a Hopf bifurcation [18]. For subthreshold currents (solid line: $I_m = 7.09$ μA), one observes a damped oscillation corresponding to a stable fixed point in

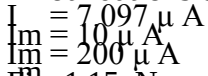

Fig. 1.15. Numeric solutions of the Hodgkin-Huxley equations (1.25, 1.27–1.29) according to the Rinzel-Wilson model (Sect. 1.4.3) for three different values of the control parameter I_m. Solid: subthreshold current $I_m = 7.09$ μA; dashed: super-threshold current $I_m = 10$ μA; dashed-dotted: even higher current $I_m = 200$ μA

the phase space. If the control parameter I_m exceeds a certain threshold θ, this fixed point destabilizes and a limit cycle emerges (dashed line: $I_m = 10$ μA). Secondly, further heightening of I_m leads to limit cycles of increased frequencies (dashed-dotted line: $I_m = 200$ μA). This regular spiking dynamics explains the law of all-or-nothing as well as the encoding principle by frequency modulation in the nervous system [19–21].

In order to interpret the Hodgkin-Huxley equations (1.25, 1.27–1.29) biologically, we have to consider (1.26)first. It tells that our simple two-state Markov chain (Fig. 1.11) is not appropriate. Instead, the description of the active potassium channel requires a four-state Markov chain comprising three distinct closed and one open state [24, 25]. However, (1.26) allows for another instructive interpretation: According to a fundamental theorem of probability theory, the joint probability of disjunct events equals the product of the individual probabilities upon their stochastic independence. Since $p_{AK} = n^4$, we can assume the existence of four independently moving gating charges within the channel molecule. Correspondingly, for the sodium channel we expect three

independent gating charges and one inhibiting subunit since $p_{AN} = m^3 h$.
is supported by patch clamp measurements where the channel's pores were blocked by the Fugu's fish tetradotoxin [19–21]. Although the blocked channel could not pass any ions, about three brief currents were observed. We can imagine these charges as key cylinders that have to be brought into the right positions to unlock a cylinder lock (thus opening the channel).
The emergence of an action potential results from different kinetics of the ion channels. If the cell membrane is slightly depolarized by the current I_m,

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the opening rate α_n for the sodium channels increases, thus entailing a further depolarization of the membrane. The positive feed-back loop started in this way leads to a torrent of inflowing sodium until the peak of the action potential is reached. Then, the membrane potential is positive in comparison to the extracellular space, causing voltage-gated potassium channels to open. Due to its negative equilibrium potential, potassium leaves the cell thereby hyperpolarizing the interior. Contrastingly, the hyperpolarization of the membrane reduces the open probability of the sodium channels, which become increasingly closed. Another positive feed-back loop enhances the hyperpolarization thereby overshooting the resting potential. While the potassium channels change very slowly back to their closed state, the sodium channels become additionally inactivated by a stopper subunit of the channel molecule whose kinetics is governed by the h term. This inhibition process is responsible for the refractory time prohibiting the occurrence of another action potential within this period.

1.3.2 Presynaptic Potentials

A spike train, generated in the way described by the Hodgkin-Huxley equations, travels along the axon and, after several branches, reaches the presynaptic terminals. Here, the composition of the membrane changes again. Voltage-gated calcium channels are present in addition to the voltage-gated potassium and sodium channels, and can be described by another branch in Fig. 1.14. The class of voltage-gated calcium channels is quite extensive and they operate generally far from the linear (ohmic) domain of the Goldman-Hodgkin-Katz equation [13, 15, 24, 25]. However, according to Johnston & Wu [24], an ohmic treatment of presynaptic Ca^{2+} channels is feasible such that their current is given by

$$I_{AC} = l^5 \bar{g}_{AC} (U - E_{Ca^{2+}}) ,$$

where l obeys another master equation

$$\frac{dl}{dt} = \alpha_l (1 - l) - \beta_l l . \quad (1.31)$$

In the absence of an injected current ($I_m = 0$), the presynaptic potential $U(t)$ is then governed by the differential equation

$$C_m \frac{dU}{}$$

$$+ I_{AK} + I_{AN} + I_{AC} + I_l = 0 \quad .$$

dt

Neglecting calcium leakage, the current (1.30) leads to an enhancement of the intracellular concentration $[Ca^{2+}]_{int}$ that is described by a continuity equation [12]

$$\frac{d[Ca^{2+}]_{int}}{dt} = -\frac{I_{AC}}{Qn_a} \quad (1.33)$$

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Here, $q = 2e$ is the charge of the calcium ion (e denoting the elementary charge). Avogadro's constant N_A scales the ion concentration to moles contained in the volume V. The accumulation of calcium in the cell plasma gives rise to a cascade of metabolic reactions. Calcium does not only serve as an electric signal; it also acts as an important messenger and chemical reagent, enabling or disenabling the functioning of enzymes.

The movement of neurotransmitter into the synaptic cleft comprises two sub-processes taking place in the presynaptic terminal: Firstly, transmitter must be allocated, and secondly, it must be released. The allocation of transmitter depends on the intracellular calcium concentration (1.33), while it is stochastically released by increased calcium currents (1.30) as a consequence of an arriving action potential with a probability p.

In the resting state, transmitter vesicles are anchored at the cytoskeleton by proteins called synapsin, which act like a wheel clamp. The probability to loosen these joints increases with the concentration $[Ca^{2+}]_{int}$. Liberated vesicles wander to one of a finite number Z of active zones where vesicles can fuse with the terminal membrane thereby releasing their content into the synaptic cleft by the process of exocytosis [19–21]. Allocation means that $Y \leq Z$ active zones are provided with vesicles, where

$$Y = \kappa([Ca^{2+}]_{int})\, Z \quad (1.34)$$

is the average number of occupied active zones, and $\kappa([Ca^{2+}]_{int})$ is a monotonic function of the calcium concentration that must be determined from the reaction kinetics between calcium and synapsin mediated by kinases. The release of transmitter is then described by a Bernoulli process started by an arriving action potential. The probability that k of the Y occupied active zones release a vesicle is given by the binomial distribution

逸

Y

p(k, Y) =

灌

k

p (1 − p)Y −k . (1.35)

k

For the sake of mathematical convenience, we shall replace the binomial distribution by a normal distribution

1

ρ(k, Y) =

紊

exp (k − y)2

囍 −

2πy(1 − p)

珑

, (1.36)

2y(1 − p)

where y = Y p is the average number of transmitter releasing active zones. Assuming that a vesicle contains on average n_T = 5000 transmitter molecules [19, 20], we can estimate the mean number of transmitter molecules that are released by an action potential as

T = n_T Y p = n_T Z p

$\kappa([Ca^{2+}]_{int})$. (1.37)

Correspondingly, the expected number of transmitter molecules released by k vesicles is given by

$-g_{Ca^{2+}}$

$E_{Ca^{2+}}$

Fig. 1.16. Equivalent circuit for the calcium-controlled transmitter release (indicated by the arrows of the LED)

n_T Y

T (k) =

紊

exp (k − y)2

囍 −

2πy(1 − p)

珑

. (1.38)

2y(1 − p)

Finally, we need an equivalent circuit symbol for the transmitter release. Electronics suggests the use of the LED symbol (light-emitting diode).

Connected all together, the calcium controlled transmitter release might be represented by the branch shown ..

1.3.3 Postsynaptic Potentials

After being poured out into the synaptic cleft of a chemical synapse, transmitter molecules diffuse to the opposite postsynaptic membrane, unless they have not been decomposed by enzymic reactions. There, they dock onto receptor molecules , which fall into two classes:

ionotropic receptors are actually

transmitter-gated ion channels, whereas metabotropic receptors are proteins that, once activated by transmitter molecules, start metabolic processes from second messenger release up to gene expression. At particular pathways, they control the opening of other ion channels gated by intracellular reaction products. The directly transmitter-gated channels are fast and effective, while the intracellularly gated channels react very slowly [19–21,33]. In this section, I shall treat two distinct examples from each receptor class.

Excitatory Postsynaptic Potentials

One important transmitter-gated ion channel is (among others, such as the AMPA, $GABA_A$, and NMDA receptors) the nACh receptor that has nicotine as an antagonist. It becomes open if three or four molecules of the neurotransmitter acetylcholine (ACh) dock at its surface rising into the synaptic cleft. These molecules cause shifts of the electric polarization within the molecule which opens the gate in the pore. This process can be modeled by a Markov chain similarly to the exposition in Sect. 1.3.1. However, another treatment is also feasible, using chemical reaction networks [30, 33].

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The open nACh channel is conductive for sodium as well as for potassium ions, such that its reversal (resting) potential is provided by the Goldman equation (1.10). Yet the sodium conductance is slightly larger than that for potassium yielding a net current of inflowing sodium ions. Since this current is depolarizing, the nACh channels constitute excitatory synapses. Therefore, they generate excitatory postsynaptic potentials (EPSP). On the other hand, hyperpolarizing channels, such as the $GABA_A$ channel, constitute inhibitory synapses generating inhibitory postsynaptic potentials (IPSP).

Let us once more consider a membrane patch of area A containing N_{nACh} receptors. Again, let O_{nACh} be the number of momentarily opened and C_{nACh} the number of closed channels. According to (1.12), the conductance of all open channels connected in parallel is then $g_{nACh} = O_{nACh}\,\gamma_{nACh}$. Opening of the channels can now be described by the chemical reaction equation

C + 3 T 逸 O , (1.39)

where C denotes the closed and O the opened molecules. T stands for the

transmitter ACh. Because in each single reaction, three molecules T react with one molecule C to produce one molecule O, the corresponding kinetic equation[30, 31, 33] comprises a cubic nonlinearity,

$$\frac{dO}{dt} = \nu_1 C T^3 - \nu_2 O , \quad (1.40)$$

where ν_1 denotes the production and ν_2 the decomposition rate of open channels in (1.39). These reaction rates depend on the temperature of the heat bath and probably on metabolic circumstances such as phosphorylation. This equation has to be supplemented by a reaction-diffusion equation for the neurotransmitter reservoir in the synaptic cleft

$$\frac{dT}{dt} = \nu_2 O - \nu_3 T E - \sigma T , \quad (1.41)$$

where $\nu_2 O$ is the intake of transmitter due to decaying receptor-transmitter complexes, which is the same as the loss of open channels in (1.40), $\nu_3 T E$ is the decline due to reactions between the transmitter with enzyme E, and σT denotes the diffusion out of the synaptic cleft. Its initial condition $T(t = 0)$ is supplied by (1.38). Taken together, the equations (1.40, 1.41) describe the reaction-diffusion kinetics of the ligand-gated ion channel nACh.

Expressing the electric conductivity (1.12) through the maximal conductivity $\bar{g}_{nACh}$,

$$g_k = \frac{O_{nACh}}{N_{nACh}} \bar{g}_{nACh}$$

suggests a new equivalent circuit symbol for ligand-gated channels. The conductance is controlled by the number of transmitter molecules, i.e. the number of particular particles in the environment. This corresponds to the phototransistor in electronic engineering which is controlled by the number of photons

Fig. 1.17. Equivalent circuit for a population of ligand-gated ion channels of kind k

collected by its base. Hence, I would like to suggest the circuit shown in Fig. 1.17 as an equivalent to the nACh receptor.

In order to compute the postsynaptic potential, the circuit in Fig. 1.17 has to be connected in parallel with the leakage conductance and the membrane capacitance as in Fig. 1.18.

The EPSP for the nACh receptor then obeys the equations

$$C_m \frac{dU}{dt} = O_{nACh} +$$

N_{nACh}
$-g_{nACh}(U - E_{nACh}) + g_l(U - E_l) = 0$ (1.43)
together with (1.40, 1.41), and initial condition (1.38).
However, instead of solving these differential equations, most postsynaptic potentials can be easily described by alpha functions as synaptic gain functions

$$U_{PSP}(t) = E_{PSP}\,\alpha\, t\, e^{2}\,\Theta(t)\,, \quad -\alpha t \qquad (1.44)$$

[12–16, 18]
where α is the characteristic time constant of the postsynaptic potential (PSP) and

$$\Theta(t) = \begin{cases} 0 & for\ t \le 0 \\ 1 & for\ t > 0 \end{cases} \qquad (1.45)$$

is Heaviside's jump function.

Fig. 1.18. Equivalent circuit for the postsynaptic potential generated by ligand-gated channels of kind k with reversal potential E_{PSP}

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10^{-3} 10^{-2} 10^{-1} 10^{0} 10^{1}

Numeric solutions of the kinetic equations (1.40, 1.41, 1.43) for the nACh receptor. Dashed-dotted: the number of ACh molecules (max = 500); dashed: the number of open nACh channels (max = 500); solid: the EPSP U (t); dotted: an alpha function .
The time axis is logarithmically scaled; the functions are rescaled and (if necessary) shifted for better visibility
displays the numerical solution of equations (1.40, 1.41, 1.43) for arbitrarily chosen parameters together with a "fitted" alpha function for comparison. Obviously, the correspondence is not that large.
Inhibitory Postsynaptic Potentials.

Synapses are excitatory if they open sodium or calcium channels with more positive reversal potentials compared to the resting state. Their neurotransmitters are generally acetylcholine (ACh) or the amino acid glutamate. Contrastingly, most inhibitory synapses employ the amino acids glycine or GABA (gamma-amino-butyric-acid) to open potassium or chloride channels with more negative reversal potentials. While the $GABA_A$ receptor is transmitter-gated such as the nACh receptor discussed in the previous section, the $GABA_B$- and mACh receptors (having the toadstool toxin muscarine as an antagonist) activate intracellular G
which subsequently open G
protein-gated potassium channels [19–21]. The activation of G protein-gated

potassium channels comprises the following chemical reactions

$R_0 + T \leftrightarrows R^*$ (1.46)

$R^* + G_0 \leftrightarrows RG^* \rightarrow R^* + G^*$

$G^* \rightarrow G_0$

$C + n\,G^* \leftrightarrows O$,

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where R_0 is the metabotropic $GABA_B$ receptor in its resting state, T the GABA, R^* the transmitter-activated receptor on the one hand, and D the same transmitter-receptor complex in its inactivated state on the other hand; furthermore, G_0 is the G protein in its resting state, $(RG)^*$ a short-lived activated receptor-G protein complex and G^* the activated G protein; finally, C is the G protein-gated potassium channel in its closed state and O in the open state. The channel possesses n docking sites for G protein molecules.

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