Chapter 2

Cellular electrophysiology: modeling and simulation

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2.1 Introduction

All cells have a difference in voltage across the cell membrane. This is the so-called *membrane potential*. Some cells, such as neurons and muscle cells, use the membrane potential as a signal. In that case, a cell may be stimulated by application of a small current during a short time period. If the current is sufficiently strong, the membrane potential goes through a large excursion, which is called an *action potential*, before returning to its resting value. Action potentials are used as signaling mechanism in the brain and to initiate muscular contraction. Cells that are able to generate an action potential are *excitable*. Examples of excitable cells are neurons, cardiac cells, and smooth and skeletal muscle cells. By establishing electrical connections between the cells, action potentials can propagate through a network of connected cells. Electrical connections between neurons are usually established via *synapses*, while cardiac muscle cells are electrically connected through so-called *gap junctions* [5].

Over the past 100 years, physiologists have studied the generation and propagation of action potentials. The first quantitative mathematical model of a propagating action potential was developed by Alan Hodgkin and Andrew Huxley [11]. In 1952, Hodgkin and Huxley published a series of articles describing their experiments and model of the squid giant action potential [10, 7, 6, 8, 9] for which they won the Nobel Prize in Physiology and Medicine in 1963 (shared with J.C. Eccles). Since the Hodgkin-Huxley model is a beautiful example of a physiological model, we discuss the model in these lecture notes.

2.2 Cell membrane models

The cell membrane can be modeled as a capacitor in parallel with a number of ionic currents (Figure 2.1). The voltage difference across the membrane is the *membrane potential* V_{mem} and is defined

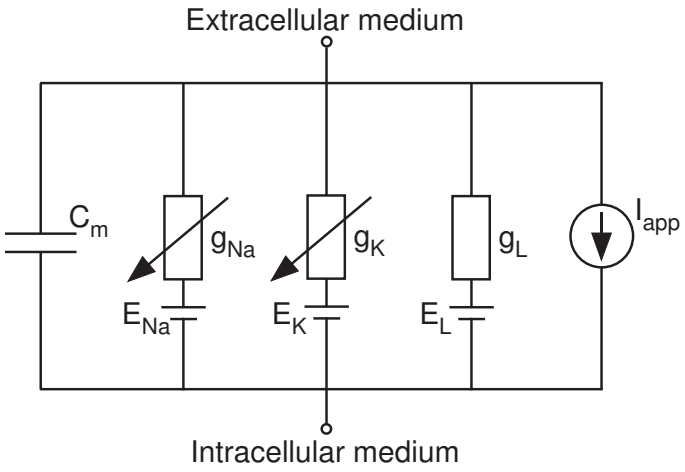

Figure 2.1: Basic components of the Hodgkin–Huxley model. The cell membrane is represented as a capacitance C_{m}. Voltage-gated Na^+ and K^+ channels are represented by nonlinear conductances g_{Na} and g_{K}. Leak ion channels are represented by a linear conductance g_{L}. The electrochemical gradients driving the flow of ions are represented by batteries E_{Na}, E_{K}, and E_{L}. The applied stimulus current is represented by a current source I_{app}.

by

$$V_{\mathrm{mem}} = V_{\mathrm{int}} - V_{\mathrm{ext}}, \tag{2.1}$$

where V_{int} is the intracellular potential and V_{ext} the extracellular potential. The main ionic currents are the sodium (Na^+) and potassium (K^+) currents, denoted by I_{Na} and I_{K}, respectively. Although there are other currents such as chloride (Cl^-) and calcium (Ca^{2+}) currents, in the Hodgkin-Huxley model they are lumped together into one *leakage current* denoted by I_{L}. From Figure 2.1, we derive the following differential equation for V_{mem}

$$C_{\mathrm{m}} \frac{\mathrm{d}V_{\mathrm{mem}}}{\mathrm{d}t} + I_{\mathrm{Na}} + I_{\mathrm{K}} + I_{\mathrm{L}} = I_{\mathrm{app}}, \tag{2.2}$$

where C_{m} is the membrane capacitance expressed in μF per cm^2 membrane surface and I_{app} is the applied current to generate an action potential. All ionic currents and the applied current are expressed in μA per cm^2 membrane surface.

2.3 Ionic membrane currents

When the cell is at rest, the membrane potential V_{mem} typically has a value between -80 and -90 mV. Consider ionic membrane current I_{ion} describing the current flow of ion species *ion* over the membrane. In case the charge of *ion* is positive (e.g., Na^+, K^+, or Ca^{2+}), $I_{ion} < 0$ means positive charge is flowing into the cell and the membrane depolarizes, i.e., the membrane potential V_{mem} becomes less negative. In case $I_{ion} > 0$, positive charge moves out of the cell and the membrane is repolarizing, i.e., V_{mem} returns to its resting value.

The current size of I_{ion} flowing into or out of the cell is related to the intracellular and extracellular concentrations of *ion* and, since *ion* is charged, on the membrane potential. The net force acting on

the ion thus depends on the electrical and chemical gradients and is referred to as the *electrochemical gradient* or *driving force* [2]. The driving force is defined as $(V_{\text{mem}} - E_{ion})$, where E_{ion} is the equilibrium potential, or *Nernst potential*, of *ion*. E_{ion} is given by the *Nernst equation*

$$E_{ion} = \frac{RT}{z_{ion}F} \ln\left(\frac{[ion]_{\text{e}}}{[ion]_{\text{i}}}\right), \tag{2.3}$$

where R is the universal gas constant (8.3143 $\text{J}\cdot\text{K}^{-1}\cdot\text{mol}^{-1}$), T is the absolute temperature (310 K), z_{ion} is the valence of *ion* (1 for Na^+ and K^+, and 2 for Ca^{2+}), F is Faraday's constant (96.4867 C/mmol), and $[ion]_{\text{e}}$ and $[ion]_{\text{i}}$ are the extracellular and intracellular concentrations of *ion*.

The direction of I_{ion} across the membrane is determined by the sign of $(V_{\text{mem}} - E_{ion})$. The current size depends on the driving force as well as the conductance g_{ion} of the membrane to *ion*, i.e.,

$$I_{ion} = g_{ion}(V_{\text{mem}} - E_{ion}), \tag{2.4}$$

which is equivalent to Ohm's law. g_{ion} depends on the number and states of the ion channels. Let γ denote the conductance of a single channel, N the number of channels, and p the probability of a channel being in the open state, then

$$g_{ion} = \gamma N p. \tag{2.5}$$

The product of γ and N determines the maximum conductance $G_{ion} = \gamma N$ and equation (2.4) is usually written as

$$I_{ion} = G_{ion}\, p\, (V_{\text{mem}} - E_{ion}). \tag{2.6}$$

The probability p of a channel being in the open state corresponds to the fraction of channels in the open state in the cell. It is assumed that the channel is controlled by a gate that can be either open or closed. Let α_p denote the opening rate constant and β_p the closing rate constant. Since p is the fraction of channels in the open state, the rate of opening is equal to $\alpha_p(1 - p)$ and the rate of closing is equal to $\beta_p\, p$. The dynamics of p are determined by the difference between the rates of opening and closing, i.e.,

$$\frac{\text{d}p}{\text{d}t} = \alpha_p(1 - p) - \beta_p\, p. \tag{2.7}$$

At steady-state, the rates of opening and closing are equal, i.e.,

$$\alpha_p(1 - p) = \beta_p\, p, \tag{2.8}$$

from which follows

$$p = p_\infty = \frac{\alpha_p}{\alpha_p + \beta_p}. \tag{2.9}$$

Let $p(t)$ denote the value of p at time t and p_0 the value of p at time t_0, then the solution of differential equation (2.7) is

$$p(t) = p_\infty - (p_\infty - p_0) \exp\left(-\frac{t - t_0}{\tau_p}\right), \tag{2.10}$$

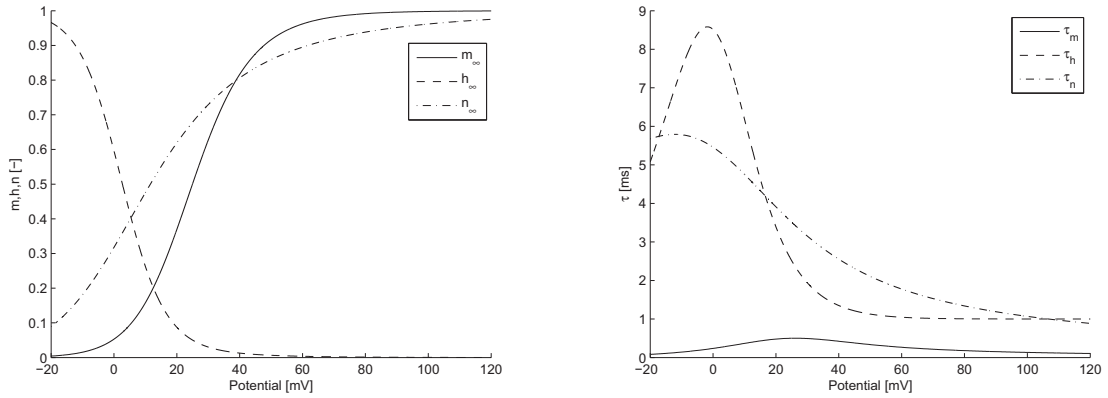

Figure 2.2: Steady-state values (left) and time constants (right) of gating variables m, h, and n as function of potential V.

where time constant τ_p is defined by

$$\tau_p = \frac{1}{\alpha_p + \beta_p}. \tag{2.11}$$

Opening rate constant α_p and closing rate constant β_p depend on V_{mem} and are usually fitted to experimental data using a Boltzmann-type equation [2]. All ionic membrane currents of the Hodgkin-Huxley model as well as models describing cardiac electrophysiology are described in this way using one or more gating variables. Examples of these models are the Di Francesco-Noble model of the Purkinje fiber [4], the Beeler-Reuter model of the mammalian ventricular action potential [1], the Priebe-Beuckelmann model [12] and the model by Ten Tusscher *et al.* [13, 14] describing the human ventricular action potential, and the Courtemanche-Ramirez-Nattel model [3] describing the human atrial action potential. There are many more models available that are based on the principles introduced by Hodgkin and Huxley.

Extracellular and intracellular concentrations of Na^+, K^+, Cl^-, and Ca^{2+} are influenced by the ionic membrane currents. In most modern models, the extracellular concentrations are assumed to be constant, while the intracellular concentrations are kept up-to-date (e.g. [3, 14]). In the Hodgkin-Huxley model, also the intracellular ionic concentrations are assumed to be constant, since the amount of ions crossing the membrane is relatively small [11]. Under the assumption that ionic concentrations are constant and not affected by the action potential, also the Nernst potentials remain constant.

2.4 The Hodgkin-Huxley equations

In 1952, Hodgkin and Huxley published their model describing the action potential of the squid giant axon (”giant” because of the size of the axon, *not* the size of the squid) [9]. In the Hodgkin-Huxley model it is assumed that the potential V represents the deviation from the resting membrane potential V_{rest}. Thus, for the membrane potential V_{mem}, it holds

$$V_{\text{mem}} = V_{\text{rest}} + V. \tag{2.12}$$

The Hodgkin-Huxley model is defined by the following system of differential equations

$$C_{\mathrm{m}}\frac{\mathrm{d}V}{\mathrm{d}t} = -G_{\mathrm{Na}}\,m^3\,h\,(V-V_{\mathrm{Na}}) - G_{\mathrm{K}}\,n^4\,(V-V_{\mathrm{K}}) - G_{\mathrm{L}}\,(V-V_{\mathrm{L}}) + I_{\mathrm{app}}, \tag{2.13}$$

$$\frac{\mathrm{d}m}{\mathrm{d}t} = \alpha_m(1-m) - \beta_m\,m, \tag{2.14}$$

$$\frac{\mathrm{d}h}{\mathrm{d}t} = \alpha_h(1-h) - \beta_h\,h, \tag{2.15}$$

$$\frac{\mathrm{d}n}{\mathrm{d}t} = \alpha_n(1-n) - \beta_n\,n. \tag{2.16}$$

$C_{\mathrm{m}} = 1.0\,\mu\mathrm{F/cm}^2$ is the membrane capacitance and G_{Na}, G_{K}, and G_{L} are *conductances* expressed in mS (milli Siemens) per cm^2 membrane surface (unit Siemens is defined by $\mathrm{S} = \Omega^{-1}$). V_{Na}, V_{K}, and V_{L} are adjusted equilibrium potentials for I_{Na}, I_{K}, and I_{L}, respectively, and m, h, and n are gating variables.

Sodium current I_{Na}

The sodium conductance is described by two gating variables m and h. Since m is close to zero at rest and increases at the beginning of the action potential, m is called the *sodium activation* gating variable. On the other hand, h is close to one during rest and decreases during the action potential. Therefore, h is called the *sodium inactivation* gating variable. The best fit to experimental data was found by describing sodium activation to the third power, i.e.,

$$I_{\mathrm{Na}} = G_{\mathrm{Na}}\,m^3\,h\,(V-V_{\mathrm{Na}}), \tag{2.17}$$

where G_{Na} is the maximum I_{Na} conductance ($G_{\mathrm{Na}} = 120\ \mathrm{mS/cm}^2$) and V_{Na} is the adjusted equilibrium potential for Na^+ ($V_{\mathrm{Na}} = 115$ mV). Opening rate constants α_m and α_h and closing rate constants β_m and β_h (unit $(\mathrm{ms})^{-1}$) depend on V and are defined by

$$\alpha_m = 0.1\frac{25-V}{\exp\left(\frac{25-V}{10}\right)-1} \tag{2.18}$$

$$\beta_m = 4\exp\left(\frac{-V}{18}\right) \tag{2.19}$$

$$\alpha_h = 0.07\exp\left(\frac{-V}{20}\right) \tag{2.20}$$

$$\beta_h = \frac{1}{\exp\left(\frac{30-V}{10}\right)+1} \tag{2.21}$$

In Figure 2.2, the steady-state values $m_\infty = \frac{\alpha_m}{\alpha_m+\beta_m}$ and $h_\infty = \frac{\alpha_h}{\alpha_h+\beta_h}$ and the time constants $\tau_{\mathrm{m}} = \frac{1}{\alpha_m+\beta_m}$ and $\tau_{\mathrm{h}} = \frac{1}{\alpha_m+\beta_m}$ are shown as function of V.

Potassium current I_{K}

The potassium conductance is described by a single gating variable n which is called the *potassium activation* gating variable. The best fit to experimental data was found by describing potassium acti-

vation to the fourth power, i.e.,

$$I_{\mathrm{K}} = G_{\mathrm{K}}\, n^4\, (V - V_{\mathrm{K}}), \tag{2.22}$$

where G_{K} is the maximum I_{K} conductance ($G_{\mathrm{K}} = 36$ mS/cm^2) and V_{K} is the adjusted equilibrium potential for K^+ ($V_{\mathrm{K}} = -12$ mV). Opening rate constant α_n and closing rate constant β_n (unit (ms)$^{-1}$) depend on V and are defined by

$$\alpha_n = 0.01 \frac{10 - V}{\exp\left(\frac{10-V}{10}\right) - 1} \tag{2.23}$$

$$\beta_n = 0.125 \exp\left(\frac{-V}{80}\right) \tag{2.24}$$

In Figure 2.2, the steady-state value $n_\infty = \frac{\alpha_n}{\alpha_n+\beta_n}$ and the time constant $\tau_{\mathrm{n}} = \frac{1}{\alpha_n+\beta_n}$ are shown as function of V.

Leak current I_{L}

In contrast with the sodium and the potassium current, the leak current is not described by a gating variable. The conductance of the leak current is assumed to be constant, i.e.,

$$I_{\mathrm{L}} = G_{\mathrm{L}}\, (V - V_{\mathrm{L}}), \tag{2.25}$$

where G_{L} is the I_{K} conductance ($G_{\mathrm{L}} = 0.3$ mS/cm^2) and V_{L} is the adjusted equilibrium potential ($V_{\mathrm{L}} = 10.6$ mV).

2.5 Action potential simulation

By reformulating equation (2.7) using definitions (2.9) and (2.11), the dynamics of gating variable p are described by

$$\frac{\mathrm{d}p}{\mathrm{d}t} = \frac{p_\infty - p}{\tau_p}, \tag{2.26}$$

where p_∞ represents the steady-state value and τ_p the time constant. Let $p^{(k)}$ denote the solution of p at time $k\Delta t$, then $p^{(k+1)}$ can be computed by

$$p^{(k+1)} = p_\infty - (p_\infty - p^{(k)}) \exp\left(-\frac{\Delta t}{\tau_p}\right). \tag{2.27}$$

Using this integration scheme, the action potential of the squid giant axon can be simulated by integrating the Hodgkin-Huxley equations over time. In Figure 2.3, action potentials are shown for various (constant) values of stimulus current I_{app}. In addition, traces of the ionic membrane currents I_{Na}, I_{K}, and I_{L} are shown as well as traces of the gating variables m, h, and j during one action potential ($I_{\mathrm{app}} = 10\ \mu$A/cm^2).

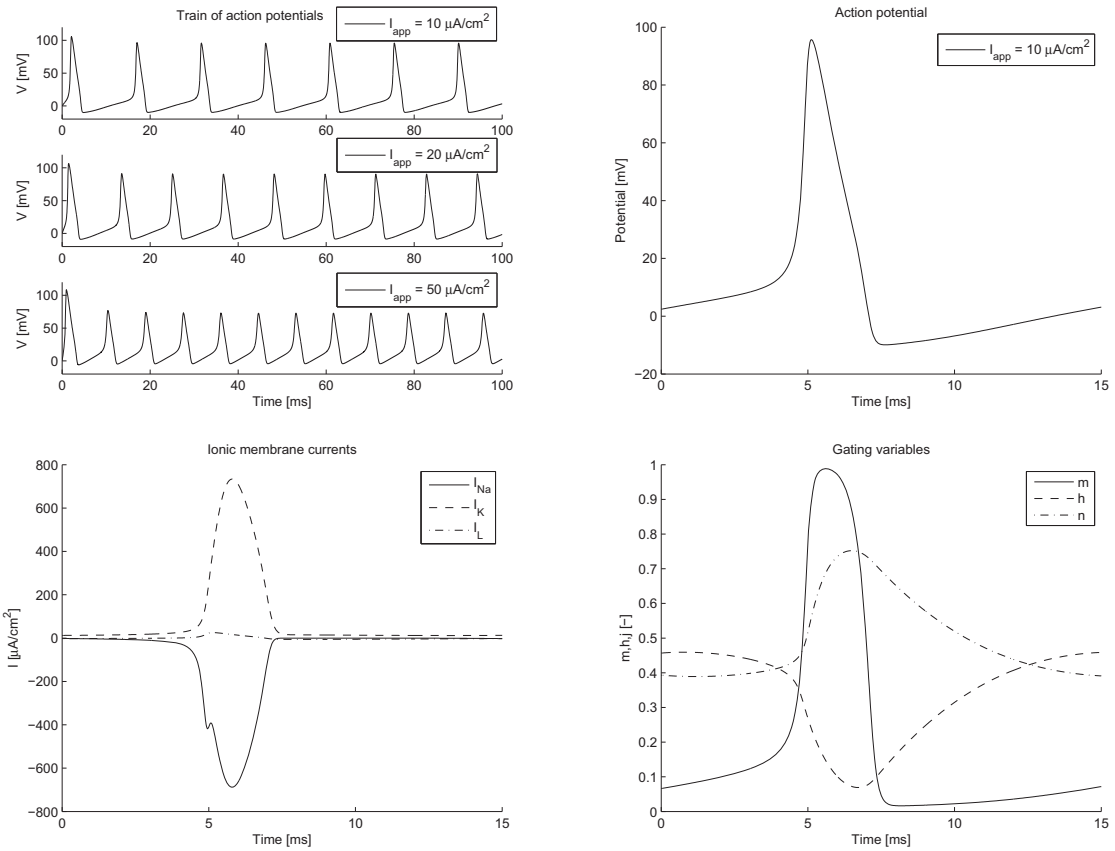

Figure 2.3: Action potentials generated with Hodgkin-Huxley equations. Top-left: Train of action potentials for $I_{\text{app}} = 10$, 20, and 50 μA/cm^2. Top-right: Action potential for $I_{\text{app}} = 10\,\mu$A/cm^2. Bottom-left: Corresponding traces of ionic membrane currents I_{Na}, I_{K}, and I_{L}. Bottom-right: Corresponding traces of gating variables m, h, and n.

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