Chapter 3

The Classical Hodgkin-Huxley ODEs

3.1 The Hodgkin-Huxley Model

In the 1940s, Alan Hodgkin and Andrew Huxley clarified the fundamental physical mechanism by which electrical impulses are generated by nerve cells, and travel along axons, in animals and humans. They experimented with isolated pieces of the giant axon of the squid. They summarized their conclusions in a series of publications in 1952; the last of these papers [76] is arguably the single most influential paper ever written in neuroscience, and forms the foundation of the field of mathematical and computational neuroscience. This chapter is an introduction to the Hodgkin-Huxley model.

Hodgkin and Huxley threaded a silver wire lengthwise through the axon, thereby eliminating spatial variations in the membrane potential v. This is called the *space clamp* technique, originally developed by George Marmont [113]. They conducted a series of experiments to clarify the mechanism underlying the action potentials in the space-clamped squid axon, and summarized the mechanism in the form of a system of ordinary differential equations[4] (ODEs).

The equation describing how v evolves with time is based on the assumption that a nerve cell membrane acts like a *capacitor*, separating two charge layers of opposite signs. This *dipole layer* gives rise to a jump in the electrical potential; this jump is the membrane potential v. According to the fundamental equation of a capacitor,

$$Cv = Q, \tag{3.1}$$

Electronic supplementary material: The online version of this chapter (doi: 10.1007/978-3-319-51171-9_3) contains supplementary material, which is available to authorized users.

[4] An "ordinary differential equation" (ODE) involves derivatives of functions of one variable only. By contrast, a "partial differential equation" (PDE) involves partial derivatives of functions of several variables.

C. Börgers, *An Introduction to Modeling Neuronal Dynamics*,
Texts in Applied Mathematics 66, DOI 10.1007/978-3-319-51171-9_3

where Q is the separated charge (the charge carried by the two layers is $\pm Q$), and the constant of proportionality, C, is called the *capacitance*. If Q and v depend on time, t, we can differentiate both sides of (3.1) to obtain

$$C\frac{dv}{dt} = I_{\text{total}}, \tag{3.2}$$

where $I_{\text{total}} = dQ/dt$ is the total electrical current from one side of the capacitor to the other; this equation is the starting point for the Hodgkin-Huxley ODEs.

Based on experiments, Hodgkin and Huxley hypothesized that I_{total} was made up of four components: A sodium current I_{Na}, a potassium current I_{K}, a small additional current which they called the *leak current* and denoted by I_{L}, carried by chloride and other ions, and the current I that they themselves injected, using electrodes, in the course of their experiments. Thus

$$C\frac{dv}{dt} = I_{\text{Na}} + I_{\text{K}} + I_{\text{L}} + I. \tag{3.3}$$

The currents I_{Na}, I_{K}, and I_{L} are assumed to obey Ohm's law (see (2.6)):

$$I_{\text{Na}} = g_{\text{Na}}(v_{\text{Na}} - v), \quad I_{\text{K}} = g_{\text{K}}(v_{\text{K}} - v), \quad I_{\text{L}} = g_{\text{L}}(v_{\text{L}} - v).$$

Here v_{Na} and v_{K} are the Nernst potentials of sodium and potassium, respectively. If the leak current were exclusively carried by chloride, v_{L} would be the Nernst potential of chloride, but since it is carried by a mixture of ion species, v_{L} is a weighted average of the Nernst potentials of those ion species. Since I_{Na}, I_{K}, and I_{L} change sign when v passes v_{Na}, v_{K}, and v_{L}, one also refers to v_{Na}, v_{K}, and v_{L} as *reversal potentials*.

Hodgkin and Huxley derived from their experiments that, and how, the conductances g_{Na} and g_{K} track changes in v. Their descriptions of g_{Na} and g_{K} take the following forms:

$$g_{\text{Na}} = \overline{g}_{\text{Na}} m^3 h, \qquad g_{\text{K}} = \overline{g}_{\text{K}} n^4, \tag{3.4}$$

where $\overline{g}_{\text{Na}}$ and $\overline{g}_{\text{K}}$ are constant conductances, and m, h, and n are time-dependent dimensionless quantities varying between 0 and 1. Hodgkin and Huxley proposed the following physical interpretation of eqs. (3.4). Suppose that each sodium channel is guarded by four *gates* in series, that these gates open and close independently of each other, and that all four gates must be open for the channel to be open. Suppose further that there are three gates of one type, let us call them the m-gates, and one gate of another type, let us call it the h-gate. If m and h denote the fractions of open m- and h-gates, respectively, then the fraction of open sodium channels is $m^3 h$. Similarly, if a potassium channel has four identical independent gates in series, with the channel open only if all four gates are open, and if n denotes the fraction of open potassium gates, then the fraction of open potassium channels is n^4. This physical interpretation is not to be taken literally.[5] The observation is simply that if it were true, the sodium and potassium conductances would in fact

[5] However, when a potassium channel was imaged in detail for the first time [39], decades after the work of Hodgkin and Huxley, the channel turned out to have four identical subunits.

be described by eqs. (3.4), with $\overline{g}_{\mathrm{Na}}$ and $\overline{g}_{\mathrm{K}}$ equal to the largest possible sodium and potassium conductances, realized when all channels are open. The variables m, h, and n are therefore called *gating variables*.

In the Hodgkin-Huxley model, m, h, and n obey simple first-order ODEs of the form

$$\frac{dm}{dt} = \frac{m_\infty(v) - m}{\tau_m(v)}, \qquad \frac{dh}{dt} = \frac{h_\infty(v) - h}{\tau_h(v)}, \qquad \frac{dn}{dt} = \frac{n_\infty(v) - n}{\tau_n(v)}, \tag{3.5}$$

where m_∞, τ_m, h_∞, τ_h, n_∞, and τ_n are functions of v yet to be discussed. Instead of explicitly spelling out the three equations for m, h, and n, we will from now on briefly write

$$\frac{dx}{dt} = \frac{x_\infty(v) - x}{\tau_x(v)} \qquad \text{for } x = m, h, n. \tag{3.6}$$

If x_∞ and τ_x were constants, independent of v, (3.6) would be equivalent to

$$x(t) = x(0)e^{-t/\tau_x} + x_\infty(1 - e^{-t/\tau_x}). \tag{3.7}$$

We always assume τ_x to be positive. The right-hand side of (3.7) is then a weighted average of $x(0)$ and x_∞. The weight multiplying $x(0)$ starts out, at $t = 0$, at 1, and decays to 0 exponentially fast. The weight multiplying x_∞ starts out at 0, and converges to 1 exponentially fast. Thus $x(t)$ moves from $x(0)$ to x_∞ (its limit as $t \to \infty$) exponentially fast. The time it takes for $x(t)$ to make "substantial progress" towards x_∞, namely, the time it takes for the weight in front of $x(0)$ to decay by a factor of $1/e$, is τ_x. We say that $x(t)$ converges to x_∞ *exponentially with time constant* τ_x. Thus eqs. (3.5) express that m, h, and n move towards m_∞, h_∞, and n_∞, exponentially with time constants τ_m, τ_h, and τ_n. Note, however, that m_∞, h_∞, and n_∞ are "moving targets" — they change as v changes. How quickly m, h, and n respond to changes in v, and therefore in m_∞, h_∞, and n_∞, is measured by τ_m, τ_h, and τ_n.

The functions $x_\infty(v)$ and $\tau_x(v)$, $x = m, h, n$, were defined by Hodgkin and Huxley so that the resulting ODEs would match their experimental data. Figure 3.1 shows the graphs of these functions. The formulas given by Hodgkin and Huxley will be listed at the end of this chapter. First we will make a few observations based on the graphs.

1. τ_m is approximately 10 times smaller than τ_h and τ_n. Thus m responds to changes in v much faster than h and n. The Hodgkin-Huxley equations are a *slow-fast system*, that is, there are two significantly different time scales, a slow one and a fast one.

2. m_∞ and n_∞ are increasing functions of v. One therefore calls m and n *activation variables*. In the language of the hypothesized physical interpretation discussed earlier, as v rises, m-gates open, and so do n-gates, although on a ten times slower time scale. One also says that the m- and n-gates are *activation gates*.

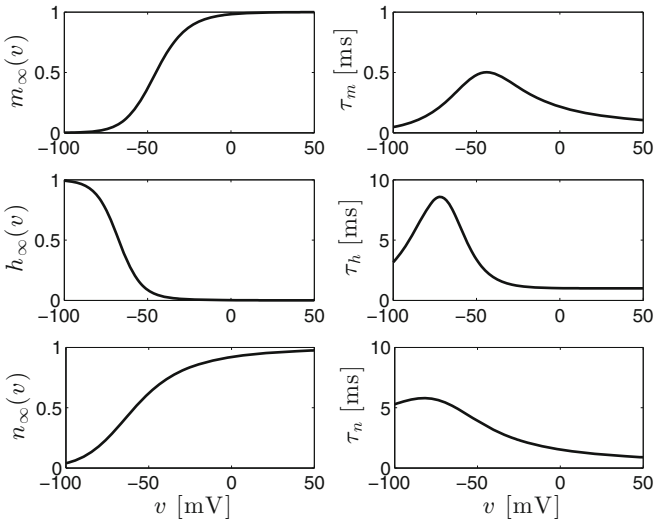

Figure 3.1. *The functions $x_\infty(v)$ and $\tau_x(v)$, $x = m, h,$ and n, in the Hodgkin-Huxley model.* [HH_GATING_VARIABLES]

3. h_∞ is a decreasing function of v. One therefore calls h an *inactivation variable*. As v rises, h-gates close, but ten times slower than m-gates open. One also says that the h-gate is an *inactivation gate*.

By contrast with the sodium and potassium conductances, the *leak conductance* g_{L} is constant. For aesthetic reasons, we write

$$g_{\mathrm{L}} = \overline{g}_{\mathrm{L}}.$$

We summarize the Hodgkin-Huxley model of the space-clamped squid axon:

$$C\frac{dv}{dt} = \overline{g}_{\mathrm{Na}} m^3 h(v_{\mathrm{Na}} - v) + \overline{g}_{\mathrm{K}} n^4 (v_{\mathrm{K}} - v) + \overline{g}_{\mathrm{L}}(v_{\mathrm{L}} - v) + I, \tag{3.8}$$

$$\frac{dx}{dt} = \frac{x_\infty(v) - x}{\tau_x(v)}, \qquad x = m, h, n. \tag{3.9}$$

This is a system of four ODEs for the four unknown functions v, m, h, and n. Up to now, we have thought of C as capacitance, $\overline{g}_{\mathrm{Na}}$, $\overline{g}_{\mathrm{K}}$, and $\overline{g}_{\mathrm{L}}$ as conductances, and I as a current. However, dividing both sides of (3.8), by the total membrane area, we see that the precisely same equation holds if we think of C, $\overline{g}_{\mathrm{Na}}$, $\overline{g}_{\mathrm{K}}$, $\overline{g}_{\mathrm{L}}$, and I as capacitance, conductance, and current *per unit membrane area*, i.e., as capacitance, conductance, and current *densities*. Following Hodgkin and Huxley, this is how we will interpret these quantities from here on.

All that is left to do to specify the model completely is to specify the constants C, v_{Na}, v_{K}, v_{L}, $\overline{g}_{\mathrm{Na}}$, $\overline{g}_{\mathrm{K}}$, and $\overline{g}_{\mathrm{L}}$, and the formulas for $x_\infty(v)$ and $\tau_x(v)$, $x = m, h, n$. The constants are

$$C = 1\,\mu\text{F/cm}^2, \quad v_{\text{Na}} = 45\,\text{mV}, \quad v_{\text{K}} = -82\,\text{mV}, \quad v_{\text{L}} = -59\,\text{mV},$$

$$\overline{g}_{\text{Na}} = 120\,\text{mS/cm}^2, \quad \overline{g}_{\text{K}} = 36\,\text{mS/cm}^2, \quad \overline{g}_{\text{L}} = 0.3\,\text{mS/cm}^2,$$

See Section 1.3 for a discussion of the units used here and throughout this book.

Note that $\overline{g}_{\text{L}}$ is very much smaller than $\overline{g}_{\text{Na}}$ and $\overline{g}_{\text{K}}$. Nonetheless the leak conductance is crucial for the behavior of the model. The reason is that between voltage spikes, $\overline{g}_{\text{L}}$ is *not* very small in comparison with $\overline{g}_{\text{Na}} m^3 h$ and $\overline{g}_{\text{K}} n^4$; see exercise 3. Sodium and potassium channels are largely closed between voltage spikes, while the leak channels remain open.

We now specify $x_\infty(v)$ and $\tau_x(v)$, $x = m, h, n$. First, we observe that (3.6) can be re-written in the form

$$\frac{dx}{dt} = \alpha_x(v)(1 - x) - \beta_x(v)x. \tag{3.10}$$

The relation between the parameters x_∞ and τ_x in (3.6), and the parameters α_x and β_x in (3.10), is

$$x_\infty = \frac{\alpha_x}{\alpha_x + \beta_x}, \qquad \tau_x = \frac{1}{\alpha_x + \beta_x}, \tag{3.11}$$

or, equivalently,

$$\alpha_x = \frac{x_\infty}{\tau_x}, \qquad \beta_x = \frac{1 - x_\infty}{\tau_x}. \tag{3.12}$$

Thinking of gates guarding channels as before, and assuming that open gates close and closed gates open at random times, with time rates dependent on v, one can interpret α_x as the time rate at which closed gates open, and β_x as the time rate at which open gates close. That is, in a short time Δt, the probability that a closed gate opens is approximately $\alpha_x \Delta t$, and the probability that an open gate closes is approximately $\beta_x \Delta t$. The differential equation governing x can be described either by specifying x_∞ and τ_x, or equivalently by specifying α_x and β_x.

Hodgkin and Huxley measured the quantities x_∞ and τ_x and computed from them the time rates α_x and β_x (measured in ms^{-1}) as functions of v (measured in mV). It is easier to fit α_x and β_x with simple formulas than to fit x_∞ and τ_x directly, because all α_x and β_x are monotonic functions of v, while the τ_x are not. Up to notation[6], Hodgkin and Huxley's formulas are

$$\alpha_m(v) = \frac{(v + 45)/10}{1 - \exp(-(v + 45)/10)}, \qquad \beta_m(v) = 4\exp(-(v + 70)/18),$$

$$\alpha_h(v) = 0.07\,\exp(-(v + 70)/20), \qquad \beta_h(v) = \frac{1}{\exp(-(v + 40)/10) + 1},$$

$$\alpha_n(v) = \frac{1}{100}\,\frac{v + 60}{1 - \exp(-(v + 60)/10))}, \qquad \beta_n(v) = \frac{1}{8}\,\exp(-(v + 70)/80).$$

(See Section 1.3 for a discussion of the physical units that are implied here.) Note that in the formulas for α_m and α_n, the denominators become zero for special values

[6] Denoting by v_{HH} the "v" of Hodgkin and Huxley, our "v" is $-v_{HH} - 70\,\text{mV}$, in line with the notation that is now common.

of v: $v = -45$ for α_m, and $v = -60$ for α_n. L'Hospital's rule needs to be used to evaluate α_m and α_n for those values of v (exercise 4).

We already discussed *action potentials* or *voltage spikes* in Section 1.1; they are illustrated in Figs. 1.3 and 1.4, for instance. In the Hodgkin-Huxley model, action potentials are generated when the m-gates open up in response to an initial depolarization, causing a sodium current into the cell. This sodium current raises v further, and a sort of chain reaction ensues. The rise in v is terminated when the h-gates close, thereby ending the inflow of sodium, and the n-gates open, leading to an outflow of potassium. It is crucial here that τ_m is much smaller than τ_h and τ_n; see Fig. 3.1. If the time constants were all equal, the closing of the h-gates and the opening of the n-gates could cancel the opening of the m-gates immediately, thereby preventing the voltage spike.

3.2 Activation, Inactivation, De-activation, and De-inactivation

The purpose of this brief section is to clarify some potentially confusing, but common and occasionally convenient terminology.

In Hodgkin-Huxley-like models, a gating variable x is generally called an *activation variable* if x_∞ is an increasing function of v, and an *inactivation variable* if x_∞ is a decreasing function of v. As mentioned earlier, in the classical Hodgkin-Huxley model, m and n are activation variables, and h is an inactivation variable.

An increase in an activation variable as a result of depolarization causes *activation* of the current. A decrease in an activation variable as a result of hyperpolarization causes *de-activation* of the current. A decrease in an inactivation variable as a result of depolarization causes *inactivation*, and an increase in an inactivation variable as a result of hyperpolarization causes *de-inactivation* of the current. Note in particular that de-activation is not the same as inactivation, and de-inactivation is not the same as activation.

We also sometimes use the word "induced." For instance, a current with an inactivation gate that is de-inactivated in response to hyperpolarization might be called "hyperpolarization-induced." A current with an activation gate that is activated in response to firing might be called "firing-induced."

Exercises

3.1. Using separation of variables, derive (3.7) from (3.6).

3.2. Suppose that

$$\frac{dx}{dt} = \frac{2-x}{4}, \qquad x(0) = 1.$$

What is $x(3)$?

3.3. Suppose that $v = -75$ mV is held fixed until the values of m, h, and n reach equilibrium. What are the sodium, potassium, and leak conductance densities now?

3.4. Using l'Hospital's rule, compute $\lim_{v\to -45} \alpha_m(v)$ and $\lim_{v\to -60} \alpha_n(v)$.

3.5. $(*)$ Using a computer, plot α_x and β_x, $x = m$, h, and n. You can use the code that generates Fig. 3.1 as a starting point, if you like.

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An Introduction to Modeling Neuronal Dynamics

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2017, XIII, 457 p. 356 illus., 186 illus. in color. With online files/update., Hardcover
ISBN: 978-3-319-51170-2