Chapter 6

The Classical Hodgkin-Huxley PDEs

The model proposed by Hodgkin and Huxley in 1952 is not a set of ODEs, but a set of PDEs — the dependent variables are not only functions of time, but also of space. This dependence will be neglected everywhere in this book, except in the present chapter. You can therefore safely skip this chapter, unless you are curious what the PDE-version of the Hodgkin-Huxley model looks like, and how it arises.

When there is no piece of silver wire threaded through the axon, that is, when there is no space clamp, the membrane potential v, as well as the gating variables m, h, and n, become dependent on the position on the neuronal membrane. It turns out that this adds one ingredient to the mechanism: diffusion of v along the neuronal membrane. In this chapter we explain what this means, and why it is true, for the simplest case, a cylindrical axon.

We consider a cylindrical piece of axon, and denote by "z" the coordinate along the axis of the cylinder. We still make a simplification: We allow the dependent variables to depend on z, but not on the angular variable. For symmetry reasons, this is sensible if the axon is a circular cylinder. We will develop a partial differential equation (PDE) describing the time evolution of v.

Suppose that $\Delta z > 0$ is small, and let us focus on the small piece of axon between $z - \Delta z/2$ and $z + \Delta z/2$; see Fig. 6.1. The current entering this piece through the cell membrane is approximately

$$I_m = 2\pi a \Delta z \, \left[\overline{g}_{\mathrm{Na}} m(z,t)^3 h(z,t) \, (v_{\mathrm{Na}} - v(z,t)) + \overline{g}_{\mathrm{K}} n(z,t)^4 \, (v_{\mathrm{K}} - v(z,t)) + \right.$$

$$\left. \overline{g}_{\mathrm{L}} \, (v_{\mathrm{L}} - v(z,t)) + I(z,t) \right], \tag{6.1}$$

where a denotes the radius of the cylinder, the constants $\overline{g}_{\mathrm{Na}}$, $\overline{g}_{\mathrm{K}}$, and $\overline{g}_{\mathrm{L}}$ are conductance densities, and I denotes the applied current density. The factor $2\pi a \Delta z$ is the surface area of the small cylindrical piece. The subscript m in I_m stands for "membrane."

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The voltage difference between locations z and $z - \Delta z$ gives rise to a current. The value of this current at location $z - \Delta z/2$ is assumed to be given by Ohm's

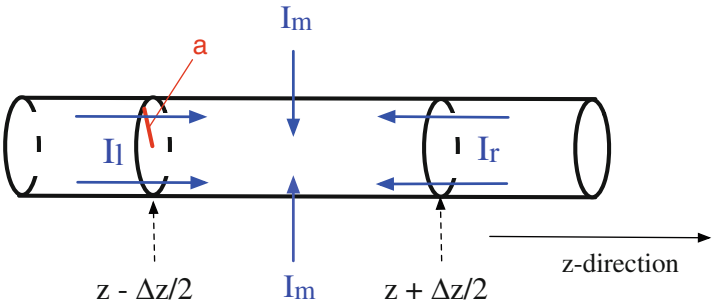

Figure 6.1. *A cylindrical piece of axon of radius a with the transmembrane ionic current I_m and the currents entering from the left and the right, I_l and I_r.*

law:

$$I_l = \frac{v(z - \Delta z, t) - v(z, t)}{r_i \Delta z}, \tag{6.2}$$

where r_i is the *longitudinal resistance of the cell interior* per unit length. (By convention, a current carried by charge entering the piece of axon between $z - \Delta z/2$ and $z + \Delta z/2$ is positive.) The subscript l stands for "left." Similarly, the voltage difference between locations z and $z + \Delta z$ gives rise to a current into the piece of axon between $z - \Delta z/2$ and $z + \Delta z/2$ that is approximately equal to

$$I_r = \frac{v(z + \Delta z, t) - v(z, t)}{r_i \Delta z}. \tag{6.3}$$

The equation governing $v(z, t)$ is

$$2\pi a \Delta z C \frac{\partial v}{\partial t}(z, t) = I_m + I_l + I_r, \tag{6.4}$$

where C denotes capacitance density as before. Using eqs. (6.1), (6.2), and (6.3), and dividing (6.4) by $2\pi a \Delta z$, we find:

$$C \frac{\partial v}{\partial t}(z, t) = \frac{1}{2\pi a r_i} \frac{v(z + \Delta z, t) - 2v(z, t) + v(z - \Delta z, t)}{\Delta z^2} +$$
$$\overline{g}_{\mathrm{Na}} m(z, t)^3 h(z, t) \, (v_{\mathrm{Na}} - v(z, t)) + \overline{g}_{\mathrm{K}} n(z, t)^4 \, (v_{\mathrm{K}} - v(z, t)) +$$
$$\overline{g}_{\mathrm{L}} \, (v_{\mathrm{L}} - v(z, t)) + I(z, t). \tag{6.5}$$

We pass to the limit as $\Delta z \to 0$, and find, omitting the arguments z and t, and indicating partial derivatives with subscripts (see exercise 1):

$$C v_t = \frac{1}{2\pi a r_i} v_{zz} + \overline{g}_{\mathrm{Na}} m^3 h \, (v_{\mathrm{Na}} - v) + \overline{g}_{\mathrm{K}} n^4 \, (v_{\mathrm{K}} - v) + \overline{g}_{\mathrm{L}} \, (v_{\mathrm{L}} - v) + I. \tag{6.6}$$

The resistance of the cell interior per unit length, r_i, is usually assumed to be inversely proportional to the cross-sectional area of the axon [88, eq. (8.5)]:

$$r_i = \frac{R_i}{\pi a^2}, \tag{6.7}$$

where R_i is called the *resistivity* of the cell interior, independent of a. Using this relation in (6.6), we obtain the equation as written by Hodgkin and Huxley [76]:

$$Cv_t = \frac{a}{2R_i}\, v_{zz} + \overline{g}_{\mathrm{Na}} m^3 h\ (v_{\mathrm{Na}} - v) + \overline{g}_{\mathrm{K}} n^4\ (v_{\mathrm{K}} - v) + \overline{g}_{\mathrm{L}}\ (v_{\mathrm{L}} - v) + I. \tag{6.8}$$

Even though the gating variables now depend on z, (3.9) remains unchanged.

Equation (6.8) is related to diffusion. To explain the connection, imagine a long thin rod filled with a water-ink mixture. The ink diffuses in the water. Let $\rho = \rho(z,t)$ denote the ink concentration (amount of ink per unit length) at position z at time t. It can then be shown that

$$\rho_t = \epsilon \rho_{zz}, \tag{6.9}$$

for some number $\epsilon > 0$; see exercise 2. Thus (6.8) can be stated as follows. The membrane potential obeys the Hodgkin-Huxley equations, but diffuses in space at the same time. The *diffusion coefficient*, $a/(2R)$, is a conductance (not a conductance density); see exercise 3. Hodgkin and Huxley measured $a = 0.0238\,\mathrm{cm}$, and $R = 35.4\,\Omega\mathrm{cm}$ (Ω stands for ohm, the unit of resistance, Ω =V/A=1/S), implying $a/(2R) \approx 0.34\,\mathrm{mS}$.

To solve eqs. (6.8) and (3.9) numerically, one *discretizes* the z-axis, i.e., one computes the functions v, m, h, and n at a finite number of points z only, in effect returning to (6.5). Time can be s, for example, using the midpoint method described in Chapter 4. We omit the details here.

The model predicts the existence of sharp voltage *pulses* traveling along the axon. Qualitatively, the mechanism is as follows. When the voltage v is raised in one location, it *diffuses* into neighboring locations because of the diffusion term $(a/(2R))v_{zz}$ on the right-hand side of (6.8). This triggers the spike-generating mechanism — sodium channels opening up — in those neighboring locations, while the spike is ended in the original location by the opening of the potassium channels and the closing of the sodium channels. Thus the pulse travels. However, this discussion does not explain why the pulse typically travels uni-directionally. Action potentials typically originate in the axon near the cell body. Because the cell body is much larger in diameter than the axon, back-propagation into the cell body is more difficult than propagation away from it. Once uni-directional pulse propagation begins, it is easy to understand how it can be maintained: The tissue in the wake of the pulse is refractory; this is why the diffusion of v, which has no directional preference, causes the pulse to propagate forward, but not backward.

The modeling presented in this chapter, due to Hodgkin and Huxley, does not address all questions concerning the spatial propagation of action potentials in nerve cells. Real nerve cells may have approximately cylindrical pieces, but they are not overall of cylindrical shape. They are very complicated geometric objects.

A careful discussion of how to handle the complications arising from the geometry of nerve cells would go very far beyond the scope of this book. However, the principle discovered by Hodgkin and Huxley is correct even for nerve cells with realistic geometry: When the membrane potential is high at one location, it raises the membrane potential in neighboring locations via diffusion. This triggers the spike-generating mechanism based on sodium and potassium currents in the neighboring locations. Action potentials are traveling pulses generated in this way.

Often neurons of complicated shape are modeled as composed of cylindrical and spherical pieces, coupled by gap junctions, with each of the pieces satisfying a system of Hodgkin-Huxley-like ODEs. Models of this kind are called *multi-compartment models*. In this book, however, we will use single-compartment models only. That is, we will pretend that all neurons are space-clamped. This simplifying assumption is made frequently in mathematical neuroscience.

Axons are leaky cables immersed in salty water, a subject that was of interest to people even before the days of Hodgkin and Huxley. On August 15, 1858, a message was sent from Europe to North America through a transatlantic cable for the first time in history. The cable connected Valentia Harbor in Ireland with Trinity Bay in Newfoundland. It held up for only three weeks — but many new and improved transatlantic cables followed during the second half of the 19th century. In the early 1850s, the transatlantic cable project motivated the great Scottish physicist William Thomson, nowadays known as Lord Kelvin, to study the physics of leaky cables immersed in water. He showed that the voltage would diffuse along the length of the cable; thus he derived the term proportional to v_{zz} that appears in the Hodgkin–Huxley PDE.

Exercises

6.1. In deriving (6.8), we used that

$$\lim_{\Delta z \to 0} \frac{v(z+\Delta z,t) - 2v(z,t) + v(z-\Delta z,t)}{\Delta z^2} = \frac{\partial^2 v}{\partial z^2}(z,t) = v_{zz}(z,t).$$

Explain why this is true using l'Hospital's rule or, better, Taylor's theorem.

6.2. Here is a sketch of the derivation of (6.9). Fill in the details by answering the questions. Consider an interval $[a,b]$ along the z-axis, and assume that ink enters $[a,b]$ through the right boundary ($z=b$) at a rate proportional to $\rho_z(b,t)$. Denote the constant of proportionality by ϵ. So the rate at which ink enters $[a,b]$ through the right boundary is $\epsilon\rho_z(b,t)$.

(a) Explain why you would expect ϵ to be positive.

Assume also that ink enters $[a,b]$ through the left boundary ($z=a$) at rate $-\epsilon\rho_z(a,t)$.

(b) Explain what motivates the minus sign.

The total amount of ink in $[a, b]$ then changes at the rate

$$\frac{d}{dt}\int_a^b \rho(z,t)dz = \epsilon\left(\rho_z(b,t) - \rho_z(a,t)\right)$$

(c) Explain why the above equation is equivalent to

$$\int_a^b \left(\rho_t - \epsilon\rho_{zz}\right)\, dz = 0. \tag{6.10}$$

(d) Explain: If we assume that $\rho_t - \epsilon\rho_{zz}$ is a continuous function of z, and if (6.10) holds for *all* intervals $[a, b]$, then (6.9) must hold.

6.3. (a) What is the physical dimension of r_i? (b) What is the physical dimension of R_i? (c) What is the physical dimension of ϵ in eq. (6.9)?

6.4. (†) Suppose that the axon is a circular cylinder of variable radius $a = a(z) > 0$. What do the Hodgkin-Huxley PDEs become in that case? To find out, rethink the derivation given in this chapter.