Mathematical Derivation of the Hodgkin–Huxley PDE Model

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Abstract

We derive the Hodgkin–Huxley model from a membrane–circuit analogy and extend it to the one-dimensional cable equation. The membrane is treated as a parallel plate capacitor with conductances for Na^+, K^+, and leak. The Na^+ and K^+ pathways use m, h, n gating. The leak term is ungated with a fixed reversal potential. The aim is a concise, consistent derivation that explicitly links the biophysics to the equations.

Contents

1 Background

Some evolutionary advantages of squids are their physical speed and quick reflexes. They swim at around 15 mph, twice that of what a human runs, and extend their tentacles in about 20-40 milliseconds, nearly 10 times as fast as a human blink. At first glance, squids are unremarkable, but these agile traits are a product of something extraordinary, a peculiar characteristic that sets them apart from all other species. Squids have the largest nerve cell found in the animal kingdom, the giant squid axon. Sharpen a pencil and take a look at its point. That point is a good estimate of the maximal diameter of a giant squid axon. Reduce that pencil point by a factor of 1000, this is a good estimate of the diameter of a human nerve cell. As for the giant squid axon's length, that has a maximum of approximately 1 meter, or about 3.28 feet. The takeaway: they have big neurons, making the neuron easy for scientists to work with.

This unique feat caught the research interest of physiologists/biophysicists Alan Hodgkin and Andrew Huxley. In 1952, Hodgkin and Huxley published a series of papers in *The Journal of Physiology* that revolutionized our understanding of computational neuroscience, and earned them the Nobel Prize in Physiology or Medicine, in 1963. Part of their findings is the primary subject of this paper, the Hodgkin-Huxley Model, a system of partial differential equations used to model neuronal signal propagations.

1.1 Neuronal Anatomy and Action Potentials

Before we delve into the intricacies of the Hodgkin-Huxley Model, an introductory understanding of neuronal anatomy and physiology is crucial for context. Neuron's look quite different from other cells. They have a large center, called a *soma*, where we could find the cell nucleus and other organelles. Then there is the *axon*, a large arm-like structure (in spirit at least) reaching away from a neuron and to another. The axon is responsible for propagating signals down to its *axon terminal*. This signal is how neurons communicate with each other. In this context, the signal propagation is referred to as *axonal propagation*.

Neurons communicate communicate via signal propagation like school students whisper a message down a line. The first student wants to get a message to the front the line, so they tell the student in front of them. The second student now has a choice: to relay or not relay the message to the next student, an all or nothing response. The process continues until either someone decides not to share the message with the next student, or the message reaches its destination.

Signals stop propagating at the axon terminal. This is where a neuron releases a neurotransmitter into the *synaptic gap*, an area between the axon of a sending neuron and the *dendrites* of a receiving neuron. Dendrites are also arm-like structures, and their purpose is to—let's say—catch the signal from the axon of another neuron, though they're generally much smaller than axons. The *synapse* is the junction between two neurons, consisting of the presynaptic terminal, the synaptic cleft, and the postsynaptic membrane. Non-neuronal cells in multicellular organisms communicate by secreting signaling molecules. These molecules may diffuse through an interstitial medium before being received and interpreted by neighboring cells. Neurons operate somewhat differently in that their secretions take the form of neurotransmitters, which are released at specialized junctions such as *axodendritic synapses*.

Before a neuron releases neurotransmitters into the synaptic cleft, an electrical impulse moves through the *presynaptic neuron* (the first or sending neuron). The *postsynaptic neuron* (the second or receiving neuron) then takes the data (i.e., neurotransmitter), interprets it and, in some way, responds. The neuron may respond by sending the signal along to other neurons, ultimately repeating the process, or it can do absolutely nothing. This phenomenon is called an *action potential*—a fast electrical signal that travels down the neuron's axon as an all or nothing response to some stimuli.

The action potential is the phenomenon that neurons use to conduct electrical impulses. The impulses are conducted using ion channels which move positively charged ions across the neuronal membrane. Neurons like to be in a *resting state*, typically around -70 millivolts (mV), which is called the resting membrane potential. However, signals can displace a neuron from its resting membrane potential. When a signal displaces a neuron from its resting membrane potential enough so that it reaches what is called the *voltage threshold*, typically around -50 mV to -55 mV, the neuron fires an action potential.

For example, if a neuron is at a resting membrane potential of -70 mV with a voltage threshold of -50 mV and you inject a current that depolarizes the membrane by 30 mV, bringing it's membrane potential to -40 mV, then it would have surpassed its voltage threshold—causing the neuron to fire an action potential.

An action potential is fired in the effort of returning a neuron to its resting state and to communicate a signal with other neurons.

2 The Hodgkin Huxley System of ODEs

From here, we seek to derive the Hodgkin-Huxley system of ODEs, which I will refer to as the HHO for short. Cells move ions through the cell membrane using channels and pumps which are embedded in the cell membrane. The channels to be discussed throughout this derivation are channels for sodium and potassium as well as a general 'leak' channel.

The sodium channels include two important structural components, the m-gate and the h-gate. The m-gate opens or closes the sodium channel—like a door. However, the h-gate plugs the sodium channel—like a cork. Thus, the h-gate renders the sodium channel inactive at which point the m-gate may not open or close the channel. The potassium channels have only one of these gates, the n-gate. The n-gate opens or closes the potassium channel. We'll discuss these gates more later.

The structure of the cell membrane is where our derivation begins. The cell membrane is a *phospholipid bilayer*. Each phospholipid is composed of a phosphate group (the head) and two fatty-acid chains (the tails), creating the lipid component. The tails are non-polar, and thus hydrophobic. The heads are polar, and thus hydrophilic. Cytoplasm and the interstitial space consist largely of water. Thus, the phospholipids arrange themselves in such a way that the heads face the intracellular and extracellular space, but the tails face each other in a region free of water (see top of Fig. 1).

The channels allow polar ions to pass through the membrane without disrupting the cell's structural integrity. Most importantly, the membrane has a non-polar region enclosed by two polar regions with channels that maintain a concentration gradient between the intracellular and extracellular space. This makes our cell membrane analogous to a *capacitor* and our channels analogous to *resistors*, making the membrane's organization analogous to a circuit model, which is where our derivation truly begins.

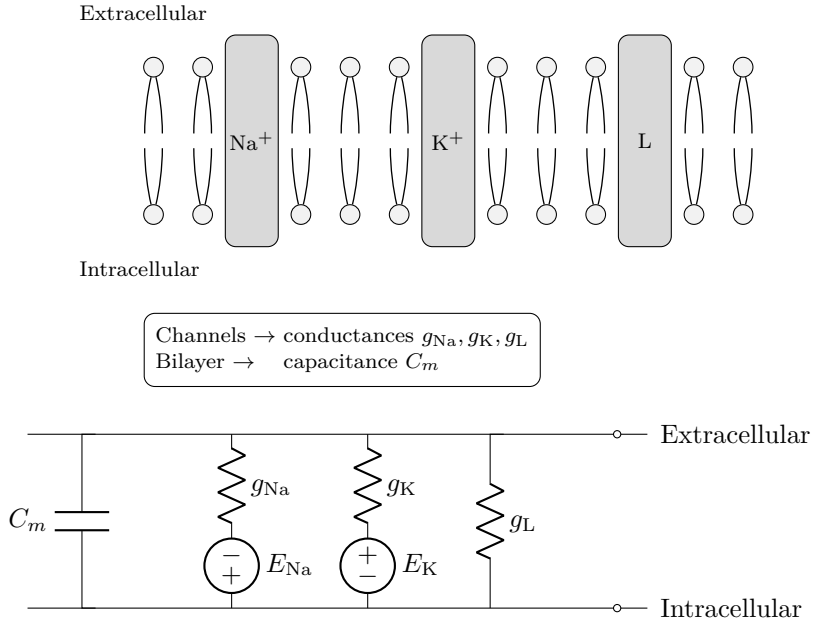

Figure 1: Membrane–circuit correspondence for the Hodgkin–Huxley model.

2.1 ODE System Derivation

2.1.1 Main ODE

Let our cell membrane be a *parallel plate capacitor* and our ion channels be resistors. Then, our total current, I, is the sum of the *capacitive* current (i.e., $I_C = C_m \frac{\mathrm{d}V}{\mathrm{d}t}$) and the ionic currents through sodium, potassium, and leak pathways, denoted I_{Na}, I_{K}, I_{L} (i.e., $I = I_{\mathrm{Na}} + I_K + I_L$). Voltage here is the membrane potential (the potential difference between the intracellular and extracellular space). Capacitance, in our case denoted C_m for membrane capacitance, is the amount of charge held by a capacitor. By Kirchhoff's current law, we arrive at:

$$I \;=\; C_m \frac{dV}{dt} \;+\; I_{\mathrm{Na}} \;+\; I_K \;+\; I_L. \tag{1}$$

We rewrite this to be

$$C_m \frac{dV}{dt} \;=\; -\, I_{\mathrm{Na}} \;-\; I_K \;-\; I_L \;+\; I. \tag{2}$$

2.1.2 Ionic Currents

By Ohm's Law, each current may be defined as the net change between membrane potential (or voltage), V, and *reversal potential*, V_j, all multiplied by the *conductance*, g_j, where $j \in \{\mathrm{Na}, \mathrm{K}, \mathrm{L}\}$ indexes the current. Reversal potential is the membrane potential at which the net current of ion j is zero (here flow of j across the membrane will cease or *reverse* its direction). Conductance is a measure of how easily a particular ionic current can flow. Hence, our currents take the following general form:

$$I_j = g_j(V - V_j) \tag{3}$$

We'll revisit conductance momentarily.

2.1.3 Gating Variables

The state of an ion channel—open, closed, or inactivated—is set by voltage-dependent gating. There are two gate types: *activation gates*—which are open or closed— and *inactivation gates*—which are blocking (no ion flow) or non-blocking (ion flow). A channel is **open** if all activation gates are open and the inactivation gate (if present) is unblocked, **closed** if at least one activation gate is closed and the inactivation gate (if present) is unblocked, and **inactivated** if the inactivation gate is blocked, in which case the state of the activation gates is irrelevant.

The currents we're considering for this derivation are from sodium, potassium, and leak. Sodium channels have an activation gate (the m-gate) and an inactivation gate (the h-gate). Potassium channels have only an activation gate (the n-gate). The leak pathway has no gates.

Depending on the phase of an action potential, we can guess the likelihood of specific channels being in specific states. For example, when a neuron is at rest, sodium and potassium channels are mostly closed (not inactivated). During depolarization, sodium channels are mostly open and potassium channels are only starting to open. During repolarization, sodium channels are largely inactivated and potassium channels are open. Hence, we could make probabilistic inferences about the state of each gate.

Let m be the probability that the m-gate is open, n be the probability that the n-gate is open, and h be the probability that the h-gate is unblocked. Because gating is voltage-dependent and V varies over time, gate states change over time through their dependence on V. Accordingly, we treat n, m, and h as time-dependent probabilities, denoted $n(t)$, $m(t)$, and $h(t)$. Information about $n(t)$, $m(t)$, and $h(t)$ in specific scenarios may be found experimentally, but that isn't our goal. Instead, we aim to derive expressions for $\frac{\mathrm{d}n}{\mathrm{d}t}$, $\frac{\mathrm{d}m}{\mathrm{d}t}$, and $\frac{\mathrm{d}h}{\mathrm{d}t}$.

Gates switch between states—**closed** $\leftrightarrow$ **open** (activation) or **unblocked** $\leftrightarrow$ **blocked** (inactivation). Let $\alpha_i(V)$ be the voltage-dependent transition rate into the state represented by i (open for m and n; unblocked for h), and $\beta_i(V)$ as the rate out of that state, where $i \in \{m, n, h\}$.

Without a loss of generality, consider only the m-gate. Over time, some m-gates open while other m-gates close. Closed m-gates open at a voltage-dependent rate of α_m. Since the probability that a randomly chosen m-gate is closed is $1 - m(t)$, opening m-gates (i.e., newly opened m-gates) contribute $+\alpha_m \cdot (1 - m)$ to the change in probability of a randomly chosen m-gate being open. Open m-gates close at a voltage-dependent rate of β_m. Since the probability that a randomly chosen m-gate is open is $m(t)$, closing m-gates contribute

$-\beta_m \cdot m(t)$ to the change in probability of a randomly chosen m-gate being open. There are no other scenarios to consider. Hence,

$$\frac{\mathrm{d}m}{\mathrm{d}t} = \alpha_m(1 - m(t)) - \beta_m m(t). \tag{4}$$

It follows that

$$\frac{\mathrm{d}n}{\mathrm{d}t} = \alpha_n(1 - n(t)) - \beta_n n(t), \tag{5}$$

$$\frac{\mathrm{d}h}{\mathrm{d}t} = \alpha_h(1 - h(t)) - \beta_h h(t). \tag{6}$$

2.1.4 Conductances

Potassium channels have four activation gates (n-gates). Sodium channels have three activation gates (m-gates) and one inactivation gate (h-gate). Recall that leaks has none. Let $\bar{g_j}$ be the maximum conductivity for a j ion. Then conductance is the product of the maximum conductivity and the probability that each gate is open or active respectively. We thus obtain

$$g_{\mathrm{K}} = \bar{g}_{\mathrm{K}} \left(n(t)\right)^4, \tag{7}$$

$$g_{\mathrm{Na}} = \bar{g}_{\mathrm{Na}} \left(m(t)\right)^3 h(t), \tag{8}$$

$$g_{\mathrm{L}} = \bar{g}_{\mathrm{L}}. \tag{9}$$

2.1.5 Full ODE System

We've now derived every necessary part of the ODE system. The model is system is expressed in its most common form.

$$C_m \frac{\mathrm{d}V}{\mathrm{d}t} = (V_{\mathrm{K}} - V)\bar{g}_{\mathrm{K}}(n(t))^4 + (V_{\mathrm{Na}} - V)\bar{g}_{\mathrm{Na}}(m(t))^3 h(t) + (V_{\mathrm{L}} - V)\bar{g}_{\mathrm{L}} + I \tag{10}$$

$$\frac{\mathrm{d}m}{\mathrm{d}t} = \alpha_m(1 - m(t)) - \beta_m m(t) \tag{11}$$

$$\frac{\mathrm{d}n}{\mathrm{d}t} = \alpha_n(1 - n(t)) - \beta_n n(t) \tag{12}$$

$$\frac{\mathrm{d}h}{\mathrm{d}t} = \alpha_h(1 - h(t)) - \beta_h h(t) \tag{13}$$

This system of ODEs can be used to model the voltage of a point neuron. Neurons are three dimensional and thus our derivation is, at this point, incomplete.

3 The Hodgkin Huxley Model

The full Hodgkin-Huxley model includes a rather interesting spatial component. The meaning of this spatial component is most digestible through its derivation. Neurons receive signals from surrounding neurons at the dendrites and, if they decide[1] to, propagate the signal down the axon. We can represent the axon as an object made up of several cylinders with different heights and different radii. However, if we take the height to be infinitesimal (i.e., the axon is made of infinitely many cylinders of infinitesimal height), our representation becomes precise. This is conceptually similar to the Riemann Sum, but we seek to model voltage, not area or volume.

[1]This is an intentional oversimplification to avoid discussing derivations of the α and β functions, which are experimentally derived, but include voltage threshold, the parameter that determines if a signal is propagated.

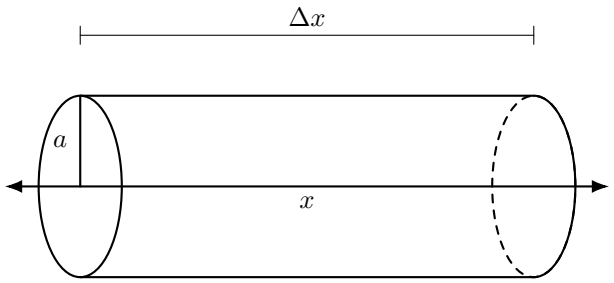

Figure 2: Cylindrical segment with longitudinal axis x, radius a, and length Δx.

Now that we are considering a neuron in three dimensions, we must consider the objects within a neuron that impede the flow of an incoming current. The results is a *longitudinal resistance*, R_l (the resistance at some cross section). This resistance depends on *intracellular resistivity*, r_l, which is the resistivity of the medium—the cytoplasm, along with any other internal structures—within that cross section.

Consider one of these cylinders. Let there be a longitudinal axis along the center of the cylinder—call it the x-axis. Since it's a cylinder, the radius, a, and the height, Δx, are fixed. Our longitudinal resistance becomes:

$$R_l = \frac{r_l \Delta x}{\pi a^2} \tag{14}$$

where πa^2 is the cross sectional area[2] and Δx is the height of the cylinder.

Suppose a current is traveling through the axon and begins to enter this specific cylinder at some initial point[3], x_0, at some time, t. Again by Kirchhoff's current law, all current flow into the cylinder must leave the cylinder. Define movement across the axis in the direction of $x_0 + \Delta x$ from x_0 to be movement in the positive direction. The change in voltage[4] at time t is given by

$$\Delta V = V(t, x_0 + \Delta x) - V(t, x_0). \tag{15}$$

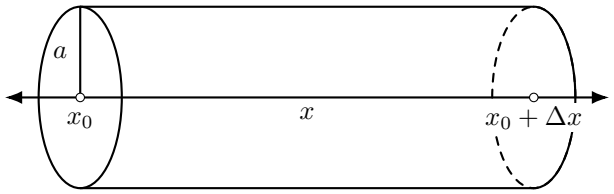

Figure 3: Cylindrical segment from x_0 to $x_0 + \Delta x$ with radius a.

By Ohm's law ($V = IR$), ΔV is the product of the incoming current, denote this as I_{in} and the axial resistance over Δx, which is R_l (14). Denoting the incoming current as I_{in} we obtain

$$\Delta V = \frac{r_l \, \Delta x}{\pi a^2} \, I_{\text{in}}. \tag{16}$$

By isolating the I_{in} current:

$$I_{\text{in}} = \frac{\pi a^2}{r_l} \frac{\Delta V}{\Delta x}. \tag{17}$$

Finally, we take the height of the cylinder to be infinitesimal. As $\Delta x \to 0$, we obtain the limit definition of a derivative:

$$\lim_{\Delta x \to 0} \left[I_{\text{in}} = \frac{\pi a^2}{r_l} \frac{\Delta V}{\Delta x} \right]$$

[2]The cross sections are circles, evidently.

[3]While the current does enter the cylinder from a point on its base, we **not** assume this base is at the origin of the longitudinal axis. I.e., $x_0 \neq 0$, at least not necessarily or by the assumptions made here.

[4]In case you missed it, voltage now has a spatial component—the longitudinal position along the axon.

$$I_{\text{in}} = \frac{\pi a^2}{r_l}\frac{\partial V}{\partial x}. \tag{18}$$

In order to include this current in our model, we distribute the other currents over the area of a short cylindrical segment. This area is the product of the circumference of the circular cross-section, $2\pi a$, and the segment height, Δx. That is, we distribute the factor $2\pi a\Delta x$ across each term on both sides of the ODE (10).

$$2\pi a\Delta x\left[C_m\frac{\mathrm{d}V}{\mathrm{d}t}\right] = 2\pi a\Delta x\left[(V_{\text{K}}-V)\bar{g}_{\text{K}}(n(t))^4 + (V_{\text{Na}}-V)\bar{g}_{\text{Na}}(m(t))^3h(t) + (V_{\text{L}}-V)\bar{g}_{\text{L}} + I\right] \tag{19}$$

Adding the new current (18):

$$2\pi a\Delta x\left[C_m\frac{\mathrm{d}V}{\mathrm{d}t}\right] = \frac{\pi a^2}{r_l}\frac{\partial V}{\partial x} + 2\pi a\Delta x\left[(V_{\text{K}}-V)\bar{g}_{\text{K}}(n(t))^4 + (V_{\text{Na}}-V)\bar{g}_{\text{Na}}(m(t))^3h(t) + (V_{\text{L}}-V)\bar{g}_{\text{L}} + I\right] \tag{20}$$

Isolating the capacitive current (I_C):

$$C_m\frac{\mathrm{d}V}{\mathrm{d}t} = \frac{1}{2\pi a\Delta x}\left[\frac{\pi a^2}{r_l}\frac{\partial V}{\partial x}\right] + (V_{\text{K}}-V)\bar{g}_{\text{K}}(n(t))^4 + (V_{\text{Na}}-V)\bar{g}_{\text{Na}}(m(t))^3h(t) + (V_{\text{L}}-V)\bar{g}_{\text{L}} + I \tag{21}$$

Taking the limit as $\Delta x \to 0$ yields a differential operator:

$$C_m\frac{\mathrm{d}V}{\mathrm{d}t} = \lim_{\Delta x\to 0}\left[\frac{1}{\Delta x}\left(\frac{a}{2r_l}\frac{\partial V}{\partial x}\right)\right] + (V_{\text{K}}-V)\bar{g}_{\text{K}}(n(t))^4 + (V_{\text{Na}}-V)\bar{g}_{\text{Na}}(m(t))^3h(t) + (V_{\text{L}}-V)\bar{g}_{\text{L}} + I \tag{22}$$

$$C_m\frac{\mathrm{d}V}{\mathrm{d}t} = \frac{\partial}{\partial x}\left[\frac{a}{2r_l}\frac{\partial V}{\partial x}\right] + (V_{\text{K}}-V)\bar{g}_{\text{K}}(n(t))^4 + (V_{\text{Na}}-V)\bar{g}_{\text{Na}}(m(t))^3h(t) + (V_{\text{L}}-V)\bar{g}_{\text{L}} + I \tag{23}$$

We'll leave the differential operator as is, in lieu of making more assumptions. If we were to assume a uniform radius, then the resistance may be scaled out of the operator—at which point $\frac{\partial}{\partial x}\left[\frac{a}{2r_l}\frac{\partial V}{\partial x}\right]$ would become $\frac{a}{2r_l}\frac{\partial^2 V}{\partial x^2}$. Without that assumption, resistance depends on the longitudinal position. In which case, the differential operator applies to a and r_l and may not be scaled out. Erring on the side of generality, a and r_l remain within the argument of the operator and the Hodgkin-Huxley Model has been derived[5].

$$\begin{aligned}
C_m\frac{\mathrm{d}V}{\mathrm{d}t} &= \frac{\partial}{\partial x}\left[\frac{a}{2r_l}\frac{\partial V}{\partial x}\right] + (V_{\text{K}}-V)\bar{g}_{\text{K}}(n(t))^4 + (V_{\text{Na}}-V)\bar{g}_{\text{Na}}(m(t))^3h(t) + (V_{\text{L}}-V)\bar{g}_{\text{L}} + I \\
\frac{\mathrm{d}m}{\mathrm{d}t} &= \alpha_m(1-m(t)) - \beta_m m(t) \\
\frac{\mathrm{d}n}{\mathrm{d}t} &= \alpha_n(1-n(t)) - \beta_n n(t) \\
\frac{\mathrm{d}h}{\mathrm{d}t} &= \alpha_h(1-h(t)) - \beta_h h(t)
\end{aligned}$$

[5] Tada!

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