

Revised 14 Jan 2020 09:58

2 Action Potentials - Hodgkin and Huxley build on Boltzman, Kirchoff, Nernst and Planck

The experiments of Hill, Katz, Hodgkin, and Huxley laid out the ionic basis of spike generation. We have already considered some of the fundamental physics that goes into this:

- Lipid membranes are the means to form cellular compartments. This, by definition, provides a means to develop and maintain concentration differences. The voltage drop is confined to the membrane.
- Electrochemistry, via ionic concentration gradients, is the basis for potentials across a cell membrane. The alternative - the movement of charge that is confined to a transmembrane protein - is not observed.
- Pumps for Na^+ and K^+ , with Cl^- as the dominant counter ion, are the basis for the concentration gradient. The dominant pump is Na- K-ATPase, aka the Na^+/K^+ exchanger. Suffice it to say that the pump is sufficiently slow so that it, and other pumps, do not compete with the spike generation. On the other hand, the pump rate is sufficiently high so that the ion concentration gradients are maintained for reasonable spike rates.
- Conservation of current, via Kirchoff's Law, as a means to describe cables is used as the basis for a description of the transmembrane voltages.
- Ion permeabilities that can switch with voltage according to a Boltzman relation. We considered an extreme version of this relation in week 1.

At the time of the pioneering experiments, the field of electrical circuits and electrochemistry were mature, so there was a theoretical framework in place for the planning of experiments and interpretations. Yet our presentation will have more structure built into it than is suggested by the historical record.

2.1 Review of Nernst-Planck I-V Relation

In the presence of a weak electric field the motion of ions is limited by the collisions so that the velocity, as opposed to acceleration, is proportional to the force. We have

$$\begin{aligned}\vec{v}_D(x, t) &= \mu \vec{E}(x, t) \\ &= -\mu \frac{\partial V(x, t)}{\partial x} \hat{x}\end{aligned}\tag{2.2}$$

where $\vec{v}_D(x, t)$ is known as the drift velocity, albeit we take the one-dimensional case at present, and μ is the mobility. We can now calculate the flux due to the electric field as

$$\begin{aligned}\vec{J}_D(x, t) &= [Ion](x, t) \vec{v}_D(x, t) \\ &= \mu [Ion](x, t) \vec{E} \\ &= -\mu [Ion](x, t) \frac{\partial V(x, t)}{\partial x} \hat{x}.\end{aligned}\tag{2.3}$$

The total flux includes diffusion down a concentration gradient as well as the electric force. For simplicity, we drop vector notation as all movement is along the \hat{x} -axis. Then

$$J(x, t) = -D \frac{\partial [Ion](x, t)}{\partial x} - \mu [Ion](x, t) \frac{\partial V(x, t)}{\partial x}.\tag{2.4}$$

At equilibrium, $J(x, t) = 0$. Then

$$\int_{V(x')}^{V(x)} dV = -\frac{D}{\mu} \int_{x'}^x \frac{d[Ion](x)}{[Ion](x)}\tag{2.5}$$

and thus

$$\Delta V = V(x) - V(x') = -\frac{D}{\mu} \ln \left(\frac{[Ion](x)}{[Ion](x')} \right).\tag{2.6}$$

We previously showed that this equilibrium potential is just given by the Nernst formula, i.e.,

$$\Delta V = V_{Nernst} = -\frac{k_B T}{ze} \ln \left(\frac{[Ion](x)}{[Ion](x')} \right)\tag{2.7}$$

where we include the possibility of a polyvalent ion and write ze for the charge. Thus

$$\mu = D \frac{ze}{k_B T}.\tag{2.8}$$

We can now put all of the formalism together to get a final equation for the flux in terms of a single transport coefficient, D , i.e.,

$$J(x, t) = -D \left(\frac{\partial [Ion](x, t)}{\partial x} + \frac{ze}{k_B T} [Ion](x, t) \frac{\partial V(x, t)}{\partial x} \right).\tag{2.9}$$

We focus on the case of current through a pore of cross sectional area A that spans a membrane of thickness L . We further assume that the electric field is uniform (not true, but it allows us to make some uncluttered progress) and that we are in steady state, so that $V(x) = \Delta V \frac{x}{L}$. We have an equation for the electrical current, I , i.e.,

$$\begin{aligned}I &= -zeJ(x)A \\ &= zeDA \left(\frac{d[Ion](x)}{dx} + \frac{ze}{k_B T} [Ion](x) \frac{\Delta V}{L} \right).\end{aligned}\tag{2.10}$$

This equation is in the form of $\frac{d[Ion](x)}{dx} + \text{constant} \times [Ion](x) = \text{another constant}$, which we can solve directly to obtain

$$I = ze \frac{DA}{L} \frac{zeV}{k_B T} \frac{[ion]_{in} - [ion]_{out} e^{-\frac{zeV}{k_B T}}}{1 - e^{-\frac{zeV}{k_B T}}}. \quad (2.11)$$

In the limit that $V \gg 0$ we see that $I \rightarrow (ze)^2 [ion]_{in} \frac{DA}{L} \frac{1}{k_B T} V$ and in the limit In the limit that $V \ll 0$ we see that $I \rightarrow (ze)^2 [ion]_{out} \frac{DA}{L} \frac{1}{k_B T} V$. Thus in the limits of large and small voltages Ohm's Law, i.e., $I = GV$, is obeyed and the conductance is greater when the current flows from high concentration of ions to low concentrations of ions. The $I - V$ relation is often expressed in terms of the Nernst potential, i.e.,

$$\begin{aligned} I &= ze \frac{DA}{L} [ion]_{in} \frac{zeV}{k_B T} \frac{1 - \frac{[ion]_{out}}{[ion]_{in}} e^{-\frac{zeV}{k_B T}}}{1 - e^{-\frac{zeV}{k_B T}}} \\ &= ze \frac{DA}{L} [ion]_{in} \frac{zeV}{k_B T} \frac{1 - e^{-\frac{e(V - V_{Nerst})}{k_B T}}}{1 - e^{-\frac{zeV}{k_B T}}} \end{aligned} \quad (2.12)$$

and is known as the Nernst-Planck relation. The essential feature is that the $I - V$ curve is nonlinear for voltage changes on the order of $\frac{k_B T}{ze} \approx 25/z \text{ mV}$ away from the reversal potential.

2.2 Cable Equation with Active Currents

Let's develop the framework for the physics and electrochemistry of the action potential. This allows one to form a plan, and thus put the experiments in a context. We start in the most general manner by adding active currents to the cable equation, i.e.,

$$\tau \frac{\partial V(x, t)}{\partial t} - \lambda^2 \frac{\partial^2 V(x, t)}{\partial x^2} = -\frac{r_m}{2\pi a} I_m(x, t) \quad (2.13)$$

where τ is the time constant of the passive membrane, λ is the electrotonic length of the passive membrane, a is the radius of the axon, and r_m is the specific resistance of the membrane, and $I_m(x, t)$ includes all membrane currents, i.e., active and passive.. The sign convention is that positive current flows out.

The expression for each of the currents $I_m(x, t)$ is given by the Nernst-Planck relation, which properly accounts for the difference in conductance moving from region of high charge density to that of low charge density, and *vice versa*. The possible transient properties of the current are set by adding a temporal dependence to D for each of the ions, and the possible switching of the current with voltage is set by adding a voltage dependence to D for each of the ions, so that $D_{Na^+} = D_{Na^+}(V, x, t)$, etc.

For changes in potential that are on the order of $\frac{k_B T}{ze}$ away from the reversal potential, the current is typically *approximated* by a linear relation using the high concentration. For sodium, this relation is

$$I_{Ion}(x, t) \approx g_{Ion}(V, x, t) [V(x, t) - V_{Nerst}] \quad (2.14)$$

with

$$g_{Ion}(V, x, t) = zeA \left(\frac{D(V, x, t)}{t} \right)_{Ion} \frac{ze}{k_B T} [Ion]_{out}. \quad (2.15)$$

The current through the conductance is then

$$I_{ion}(V, x, t) = g_{ion}(V, x, t) \times [V(x, t) - V_{Nernst}]. \quad (2.16)$$

The total current, $I_m(x, t)$, incorporates both voltage dependent, i.e., $g_{Na^+}(V, x, t)$ and $g_{K^+}(V, x, t)$ and voltage independent, i.e., $g_{Cl^-}(x)$, terms. In fact, by tradition all the voltage independent terms are lumped and called $g_{Leak}(x)$. We write

$$\begin{aligned} \tau \frac{\partial V(x, t)}{\partial t} &= \lambda^2 \frac{\partial^2 V(x, t)}{\partial x^2} - \frac{r_m g_{Na^+}(V, x, t)}{2\pi a} (V(x, t) - V_{Na^+}) \\ &- \frac{r_m g_{K^+}(V, x, t)}{2\pi a} (V(x, t) - V_{K^+}) - \frac{r_m g_{leak}(x)}{2\pi a} (V(x, t) - V_{leak}) \\ &- \frac{r_m}{2\pi a} I_o(x, t). \end{aligned} \quad (2.17)$$

where I_o is externally inject current, including synaptic currents. The above expression is really quite general since all the voltage dependencies can be stuffed into the voltage dependent conductances. Further, as we shall see, in many relevant cases the channels conduct only over a narrow range of physiological voltages, so a linear approximation is often not too unreasonable. Lastly, if addition ions become relevant - did I hear Ca^{2+} ? - one can simply add the relevant terms to the cable equation.

2.3 Functional Form of the Conductances

The business end is the form of the conductances $g_{ion}(V, x, t)$, although in the laboratory one measures the current which is proportional to the product $g_{ion}(V, t)[(V, x, t) - V_{Nernst}]$. The expectation is that the conductance is in the form of a a maximum conductance, \bar{g} , times voltage and time dependent terms for the activation and inactivation of channels, denoted by $P_{activate}(V, x, t)$ and $P_{inactivate}(V, x, t)$, respectively. Recall that all probabilities vary between 0 and 1 Thus

$$g_{Ion}(V, x, t) \equiv \bar{g}_{Ion} \times P_{activate}(V, x, t) \times P_{inactivate}(V, x, t). \quad (2.18)$$

More generally, there may be multiple voltage sensors so the form can be generalized to

$$\begin{aligned} g_{Ion}(V, x, t) &\equiv \bar{g}_{Ion} \times [P_{activate}(V, x, t) \cdots P'_{activate}(V, x, t)] \\ &\times [P_{inactivate}(V, x, t) \cdots P'_{inactivate}(V, x, t)]. \end{aligned} \quad (2.19)$$

Inactivation is just a term that tries to close rather than open a channel. In practice, channels that have been identified to date have identical activating and identical inactivating terms. For example, we will see that the sodium current is of the form $g_{Na^+}(V, x, t) = \bar{g}_{Na^+} \times P_{act}^3(V, t) P_{inact}(V, x, t)$.

It is time for us to ignore, for now spatial variation. Hodgkin and Huxley did this by placing a conductor down the center of the axon, a clever and essential idea at the time. This means we ignore the λ^2 term in the cable equation and for each channel we can write

$$g_{Ion}(V, t) \equiv \bar{g}_{Ion} \times [P_{act}(V, t) \cdots P'_{act}(V, t)] \times [P_{inact}(V, t) \cdots P'_{inact}(V, t)]. \quad (2.20)$$

In general, the activation and inactivation terms are governed by a first order equation that describes their dynamic. We have

$$P_{act}^{open}(V, t) + P_{act}^{closed}(V, t) = 1 \quad (2.21)$$

and

$$\frac{dP_{act}^{open}(V, t)}{dt} = k_{open}(V)P_{act}^{closed}(V, t) - k_{closed}(V)P_{act}^{open}(V, t) \quad (2.22)$$

$$\begin{aligned} &= -[k_{open}(V) + k_{closed}(V)]P_{act}^{open}(V, t) + k_{open}(V) \\ &= -[k_{open}(V) + k_{closed}(V)] \times [P_{act}^{open}(V, t) - P_{act}^{open}(V, \infty)] \end{aligned} \quad (2.23)$$

where $P_{act}^{open}(V, \infty)$ is the steady value of the activation. Thus

$$\frac{dP_{act}(V, t)}{dt} = -k_{obs}(P_{act}(V, t) - P_{act}(V, \infty)). \quad (2.24)$$

where $k_{obs}(V) = k_{open}(V) + k_{closed}(V)$. There are two inherently voltage dependent terms, the steady state value and the observed time constant. We consider the steady-state behavior and kinetics of a two-state system as a means to understand and parameterize the basic physics of these terms. The idea is that a thermal average or a population of two-state systems is a reasonable portrayal of ionic currents. In fact, the decomposition of macroscopic currents in terms of channels is a justification for this view.

For sake of argument, lets say that the activation sensor works by having a dipole interact with the transmembrane potential. Dipole is of the form $\vec{p} = q\vec{d}$ and the dipole experiences a torque from the electric field in the membrane that results in an energy

$$\begin{aligned} Energy &= -\vec{p} \cdot \vec{E} = qd \cos\theta \frac{\partial V}{\partial x} \approx \left(q \frac{d \cos\theta}{L} \right) V \\ &\equiv z'e V \end{aligned} \quad (2.25)$$

where θ is the angle between the dipole and the normal to the membrane, and we have lumped all factors into the charge $z'e$.

The steady state extent of activation to inactivation is given by the usual Boltzmann relation

$$\frac{P_{act}^{open}(V, \infty)}{P_{act}^{closed}(V, \infty)} = e^{\frac{z'e(V-V_{bias})}{k_B T}} \quad (2.26)$$

where V_{bias} is the internal potential drop across the activation sensor. Thus

$$P_{act}^{open}(V, \infty) = \frac{1}{1 + e^{-\frac{z'e(V-V_{bias})}{k_B T}}} \quad (2.27)$$

and

$$P_{act}^{closed}(V, \infty) = \frac{e^{\frac{z'e(V-V_{bias})}{k_B T}}}{1 + e^{-\frac{z'e(V-V_{bias})}{k_B T}}} \quad (2.28)$$

$P_{act}^{open}(V, \infty)$ is in the form of the logistic function.

We now come to the issue of the observed rate constant or the channel. In general, from a classical view point, the rate is determined by the time it takes for the dipole sensors to rearrange themselves in the activated versus inactivated state. The rate-constants $k_{open}(V)$ and $k_{closed}(V)$, in the absence of an applied electric field, i.e., $V = 0$, are of the form

$$k_{open}(0) = \nu e^{\frac{-\Delta G_o}{k_B T}} \quad (2.29)$$

where ν is an attempt frequency to jump over the barrier and ΔG_o is a barrier height. Then

$$\begin{aligned} k_{closed}(0) &= \nu e^{\frac{-\Delta G_o - z'eV_{bias}}{k_B T}} \\ &= k_{open}(0) e^{\frac{-z'eV_{bias}}{k_B T}} \end{aligned} \quad (2.30)$$

where ν is a molecular attempt frequency and clearly $k_{inact}(0) < k_{act}(0)$. With the addition of an electric field, the activation barrier is modified. The simplest assumption is that the energy of the closed state is raised as much as that of the open state is lowered. Thus

$$k_{open}(V) = k_{open}(0) e^{\frac{-z'eV}{2k_B T}} \quad (2.31)$$

and

$$k_{closed}(V) = k_{open}(0) e^{\frac{-z'eV_{bias}}{k_B T}} e^{\frac{z'eV}{2k_B T}}. \quad (2.32)$$

Thus

$$\begin{aligned} k_{obs}(V) &= k_{open}(V) + k_{closed}(V) \\ &= k_{open}(0) \left(e^{\frac{-z'eV}{2k_B T}} + e^{\frac{-z'eV_{bias}}{k_B T}} e^{\frac{z'eV}{2k_B T}} \right) \\ &= k_{open}(0) e^{\frac{-z'eV_{bias}}{2k_B T}} \left(e^{\frac{-z'e(V-V_{bias})}{2k_B T}} + e^{\frac{z'e(V-V_{bias})}{2k_B T}} \right) \\ &= k'_{open}(0) \cosh \left(\frac{z'e(V - V_{bias})}{2k_B T} \right). \end{aligned} \quad (2.33)$$

This functional form has the shape of a bowl with a minimum at $V = V_{bias}$. Thus the larger the magnitude of the voltage change, the faster the rate of the shorter the opening time.

The bottom line is that the above forms for $P_{act}^{open}(V, \infty)$ and $k_{obs}(0)$ provide a formulation of the ionic basis for the action potentials. This framework includes the observation that the peak of the time constants and the midpoint of the activation functions occur at the same potential. As we shall see this is usually - but not always - obeyed.

2.4 The Consequence of Multiple Voltage Sensors

Real channels often have multiple voltage sensors as noted earlier. Ideally, these give rise to active currents that are proportion to $P_{act}^{open}(V, t)$ to a power. What is the consequence of this?

The first question concerns the steady state value $[P_{act}^{open}(V, \infty)]^N$. We wish to find the value of V where the slope, $d[P_{act}^{open}(V, \infty)]^N/dV$ is greatest, which means calculating V for which $d^2[P_{act}(V, \infty)]^N/dV^2=0$ and plugging this value back into the equation for the slope.

First, a preliminary.

$$\begin{aligned} \frac{dP_{act}^{open}(V, \infty)}{dV} &= \frac{d\left(\frac{1}{1+e^{-\frac{z'e(V-V_{bias})}{k_B T}}}\right)}{dV} \\ &= \frac{z'e}{k_B T} \frac{e^{-\frac{z'e}{k_B T}}}{\left(1 + e^{-\frac{z'e(V-V_{bias})}{k_B T}}\right)^2} \\ &= \frac{z'e}{k_B T} P_{act}^{open}(V, \infty) (1 - P_{act}^{open}(V, \infty)). \end{aligned} \quad (2.34)$$

Then the derivative of $[P_{act}^{open}(V, \infty)]^N$ is

$$\begin{aligned} \frac{d[P_{act}^{open}(V, \infty)]^N}{dV} &= N[P_{act}^{open}(V, \infty)]^{N-1} \frac{dP_{act}^{open}(V, \infty)}{dV} \\ &= N \frac{z'e}{k_B T} [P_{act}(V, \infty)]^N [1 - P_{act}^{open}(V, \infty)] \end{aligned} \quad (2.35)$$

and the second derivative of $P_{act}^N(V, \infty)$ is

$$\frac{d^2 P_{act}^N(V, \infty)}{dV^2} = N \left(\frac{z'e}{k_B T}\right)^2 [P_{act}^{open}(V, \infty)]^N [1 - P_{act}^{open}(V, \infty)] [N - (N+1)P_{act}^{open}(V, \infty)] \quad (2.36)$$

which has a zero at the finite voltage of

$$V = V_{bias} + \frac{k_B T}{z'e} \log N. \quad (2.37)$$

Thus there is a shift in the inflection point of the opening probability as a weak function of N .

The slope at the inflection becomes

$$\frac{d[P_{act}^{open}(V, \infty)]^N}{dV} = \left(\frac{N}{1+N}\right)^{N+1} \frac{z'e}{k_B T} \quad (2.38)$$

which increases from

$$\frac{d[P_{act}^{open}(V, \infty)]^N}{dV} \Big|_{N=1} = \frac{1}{4} \frac{z'e}{k_B T} \quad (2.39)$$

to the $4/e = 1.47$ -times larger asymptotic value of

$$\frac{d[P_{act}^{open}(V, \infty)]^N}{dV} \Big|_{N \rightarrow \infty} = \frac{1}{e} \frac{z'e}{k_B T}. \quad (2.40)$$

Essentially, the transition from closed to open takes place over the range $\frac{k_B T/z'e}{4}$ to $\frac{k_B T/z'e}{e}$, or 6 mV to 9 mV for $z' = 1$. The slope becomes steeper as the dipole moment increase, *i.e.*, the slope is linear in the increase in z' . As $z' \rightarrow \infty$, the activation curve $P_{act}^{open}(V, \infty)$ tends to a step function.

Another effect of multiple voltage sensors is on the time dependence of channel opening, whose onset is delayed and steeper for large values of N . To get a sense of this, consider the approach to steady-state for $[P_{act}^{open}(V, t)]^N$; at short times the leading term is of order $(k_{obs}t)^N$, which increase slower than $k_{obs}t$.

2.5 Experimental Self-Consistency of the Hodgkin-Huxley Model

From a formal point of view, the transmembrane voltage, $V(x, t)$ and the activation parameters for each current, $P_{act}^{open}(V, t)$, form the state variables for the the system. For the Hodgkin-Huxley model there are four state variables total, while for models of thalamic relay neurons the number of state variables is (presently) 13.

The actual decomposition of currents is done by blocking the membrane conductances to all but one channel and using a voltage clamp to measure I_m versus V . The block is done by pharmacological means or by ion substitution. Currently, the measurements are best done by measuring "tail" currents to avoid the contributions of leakage currents. In any case, one arrives at measured currents for each ion that can be used to parameterize $P_{act}^{open}(V, x, \infty)$ and $\tau_{obs}(V, x)$ for that ion.

The Hodgkin-Huxley equations are functions of 4 variables.

- $V(x, t) \leftarrow$ the transmembrane potential
- $m(V, t) \leftarrow$ the activation function ($P_{act}(V, t)$) for Na^+ current
- $h(V, t) \leftarrow$ the inactivation function (a separate function, $P'_{inact}(V, t) = 1 - P'_{act}(V, t)$) for Na^+ current
- $n(V, t) \leftarrow$ the activation function ($P''_{act}(V, t)$) for K^+ current

The exact fitting parameters are in standard texts and we will not show them. The functional dependencies on V that we expect are clearly seen.

The dynamic equations are

$$\begin{aligned} \tau \frac{\partial V(x, t)}{\partial t} &= \lambda^2 \frac{\partial^2 V(x, t)}{\partial x^2} - \frac{r_m \bar{g}_{Na^+}}{2\pi a} m^3(V) h(V) (V - V_{Na^+}) \\ &- \frac{r_m \bar{g}_{K^+}}{2\pi a} n^4(V) (V - V_{K^+}) - \frac{r_m \bar{g}_{leak}}{2\pi a} (V - V_l) + \frac{r_m}{2\pi a} I_o. \end{aligned} \quad (2.41)$$

which has 10 independent biophysical parameters, i.e., a , τ , λ , r_m , \bar{g}_{Na^+} , \bar{g}_{K^+} , \bar{g}_{leak} , V_{Na^+} , V_{K^+} , and V_{leak} as well as 3 (or more in principle) fitting parameters as exponents on the activation and inactivation functions.

$$\frac{dh(V, t)}{dt} = \frac{h_\infty(V) - h(V, t)}{\tau_h(V)} \quad (2.42)$$

$$\frac{dm(V, t)}{dt} = \frac{m_\infty(V) - m(V, t)}{\tau_m(V)} \quad (2.43)$$

$$\frac{dn(V, t)}{dt} = \frac{n_\infty(V) - n(V, t)}{\tau_n(V)} \quad (2.44)$$

where $n_\infty(V) \equiv n(V, t \rightarrow \infty)$ and the parameterization for each rate expression has three fitting parameters, i.e., z' , V_b , $\tau_{obs}(0)$, for a total of 9 parameters.

These circuit equations, derived from current clamp data, were used to predict the shape of the action potential (in both the space clamped and non-space clamped case) and later the speed of propagation. The results showed self consistency about the ionic currents and the voltage changes and the propagation speed.

To recap, the action potential results from an instability in the conductance (negative conductance), such that the direction of the membrane current transiently reverses (growth) in response to a perturbative current. Eventually, the conductance saturates and recovers to a linear response. In both cases, the cell is leaky and the effective time-constant is transiently very short, so that the width of the action potential is small, less than one millisecond. Further, the current flow is localized so that the voltage disturbance propagates as a wave.