8 Action Potentials - Hodgkin, Huxley, Kirchoff and Boltzman

FIGURE - chapt-8-hh-currents.eps

The experiments of Hill, Katz, Hogkin, 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 generations. 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.
- Permeabilities that can switch with voltage according to a Boltzman relation. We considered an extreme version of this relation in the past.

FIGURE - chapt-8-nak-pumps.eps

At the time of the original experiments the field of electrical circuits and electrochemistry were pretty mature, so there was a theoretical framework in place for the planning of experiments and interpretations. But our discussion certainly has more structure built into it than is suggested by the historical record.

8.1 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.

$$\tau \frac{\partial V(x,t)}{\partial t} - \lambda^2 \frac{\partial^2 V(x,t)}{\partial x^2} = -\frac{r_m}{2\pi a} I_m(x,t) \tag{8.1}$$

where $I_m(x,t)$ now includes all membrane currents, including the $V\frac{2\pi a}{r_m}$ current due to passive flow. The sign convention is that current flows out.

The value of the currents $I_m(x,t)$ are given by the Nernst-Plank relation, so that for the Na^+ current

$$I_{Na^+}(x,t) = eA\left(\frac{D(V,x,t)}{L}\right)_{Na^+}\frac{eV}{k_BT}\frac{[Na^+]_{in} - [Na^+]_{out}e^{-\frac{eV}{k_BT}}}{1-e^{-\frac{eV}{k_BT}}} \tag{8.2}$$

where the spatial dependence of the current is determined by the density of pores, reflected through the functional dependence of D on x, the possible transient properties of the current are set by the temporal dependence of D, and the possible switching of the current with voltage is set by the voltage dependence of D, so that $D = D(V,x,t)$.

FIGURE - chapt-8-i-v.eps

For changes in potential that are $|V| < \frac{k_BT}{e}$, the current can be *approximated* by a linear relation (at least it often *is* approximated by a linear relation; it depends on the definition of *is*)

$$I_{Na^+}(x,t) \approx g_{Na^+}(V,x,t)(V(x) - V_{Na^+}) \tag{8.3}$$

where $g_{Na^+}(V,x,t) \equiv eA\left(\frac{D(V,x,t)}{L}\right)_{Na^+}\frac{e}{k_BT}[Na^+]_{out}$ is the conductance for the sodium current. The essential nonlinearities of the membrane incorporated into $g_{Na^+}(x) \rightarrow g_{Na^+}(x,V)$, are detailed below.

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 $g_{Leak}(x)$. To jump to the chase, we write

$$\begin{aligned}\tau\frac{\partial V(x,t)}{\partial t} &= \lambda^2\frac{\partial^2 V(x,t)}{\partial x^2} - \frac{r_m}{2\pi a}I_o(x,t) - \frac{r_m g_{Na^+}(V,x,t)}{2\pi a}(V(x,t) - V_{Na^+}) \\ &- \frac{r_m g_{K^+}(V,x,t)}{2\pi a}(V(x,t) - V_{K^+}) - \frac{r_m g_{leak}(x)}{2\pi a}(V(x,t) - V_{leak})\end{aligned} \tag{8.4}$$

Looking back, the above expression is really quite general since all the ugly 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.

The first thing we do is get rid of spatial variation - life is hard enough. Hodgkin and Huxley did this by placing a conductor down the center of the axon, a clever and essential idea at the time.

8.2 Functional Form of the Conductances

The business end is the form of the conductances $g_{ion}(V,t)$, although in the laboratory one measures the current, which is proportional to the product $g_{ion}(V,t)(V - V_{ion})$. The expectation is that the conductance is in the form of a scale factor times a voltage (and time) dependent term for the opening of channels, denoted $P_{open}(V,t)$. This probability is itself the product of any number of voltage and time dependent terms that sense the membrane voltage and either activate the or inactivate the current, denoted $P_{act}(V,t)$ and $P_{inact}(V,t) = 1 - P_{act}(V,t)$, respectively.

Thus for each channel we can write

$$\begin{aligned} g_{ion}(V,t) &= \bar{g} P_{open}(V,t) \\ &= \bar{g}\left(P_{act}(V,t)P'_{act}(V,t)\cdots(1-P''_{act}(V,t))\left(1-P'''_{act}(V,t)\right)\cdots\right) \\ &= \bar{g}\left(P_{act}(V,t)P'_{act}(V,t)\cdots P''_{inact}(V,t)P'''_{inact}(V,t)\cdots\right) \end{aligned} \tag{8.5}$$

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

$$g_{Na^+}(V,t) = \bar{g}_{Na^+} P^3_{act}(V,t) P'_{inact}(V,t) \tag{8.6}$$

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

$$P_{act}(V,t) + P_{inact}(V,t) = 1 \tag{8.7}$$

and

$$\begin{aligned} \frac{dP_{act}(V,t)}{dt} &= \frac{1}{\tau_{act}(V)} P_{inact}(V,t) - \frac{1}{\tau_{inact}(V)} P_{act}(V,t) \\ &= -\left(\frac{1}{\tau_{act}(V)} + \frac{1}{\tau_{inact}(V)}\right) P_{act}(V,t) + \frac{1}{\tau_{inact}(V)} \\ &= -\left(\frac{1}{\tau_{act}(V)} + \frac{1}{\tau_{inact}(V)}\right) P_{act}(V,t) + \left(\frac{1}{\tau_{act}(V)} + \frac{1}{\tau_{inact}(V)}\right) P_{act}(V,\infty) \\ &= -\left(\frac{1}{\tau_{act}(V)} + \frac{1}{\tau_{inact}(V)}\right)\left(P_{act}(V,t) - P_{act}(V,\infty)\right) \end{aligned} \tag{8.8}$$

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

$$\frac{dP_{act}(V,t)}{dt} = -\frac{P_{act}(V,t) - P_{act}(V,\infty)}{\tau_{obs}(V)} \tag{8.9}$$

In total, there are two inherently voltage dependent terms, the previous steady state value and the observed time constant. We consider the steady-state behavior and kinetics of a two-state system as a means of understanding and parameterizing

the basic physics of these terms in the current. 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.

FIGURE - chapt-8-channel-summary.eps

For sake of argument, lets say that the activation sensor works by having a dipole interact with the transmembrane potential. This interaction is

$$\begin{aligned} Energy &= -\vec{\mu}\cdot\vec{E} = zed\frac{\partial V}{\partial x} \approx \left(z\frac{d}{L}\right)eV \\ &\equiv z'eV \end{aligned} \tag{8.10}$$

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

$$\frac{P_{act}(V,\infty)}{P_{inact}(V,\infty)} = e^{\frac{z'e(V-V_b)}{k_BT}} \tag{8.11}$$

where V_b is the internal potential drop across the activation sensor. Thus

$$P_{act}(V,\infty) = \frac{1}{1+e^{-\frac{z'e(V-V_b)}{k_BT}}} \tag{8.12}$$

$$P_{inact}(V,\infty) = \frac{e^{\frac{z'e(V-V_b)}{k_BT}}}{1+e^{-\frac{z'e(V-V_b)}{k_BT}}} \tag{8.13}$$

SKETCH - BOLTZMAN FACTORS

We now come to the issue of the observed time constant, or equilibration time for the channel. In general, from a classical view point, the rate is determined by the time it take for the sensors to rearrange themselves in the activated versus inactivated state.

SKETCH - ACTIVATION BARRIERS

The time-constants $\tau_{act}(V)$ and $\tau_{inact}(V)$, in the absence of an applied electric field, i.e., $V = 0$, are of the form

$$\frac{1}{\tau_{act}(0)} = \nu e^{\frac{-\Delta G_o}{k_BT}} \tag{8.14}$$

and thus

$$\begin{aligned} \frac{1}{\tau_{inact}(0)} &= \nu e^{\frac{-\Delta G_o - z'eV_b}{k_BT}} \\ &= \frac{1}{\tau_{act}(0)} e^{\frac{-z'eV_b}{k_BT}} \end{aligned} \tag{8.15}$$

whet ν is a molecular attempt frequency and ΔG_o is a barrier height. With the addition of an electric field, the activation barrier is modified. The simplest assumption is that $\tau_{act}(V)$ is raised as much as $\tau_{inact}(V)$ is lowered. Thus

$$\frac{1}{\tau_{act}(V)} = \frac{1}{\tau_{act}(0)} e^{\frac{-z'eV}{2k_BT}} \tag{8.16}$$

and

$$\frac{1}{\tau_{inact}(V)} = \frac{1}{\tau_{act}(0)} e^{\frac{-z'eV_b}{k_BT}} e^{\frac{z'eV}{2k_BT}} \tag{8.17}$$

Thus

$$\begin{aligned} \frac{1}{\tau_{obs}(V)} &= \frac{1}{\tau_{act}(V)} + \frac{1}{\tau_{inact}(V)} \\ &= \frac{1}{\tau_{act}(0)} \left(e^{\frac{-z'eV}{2k_BT}} + e^{\frac{-z'eV_b}{k_BT}} e^{\frac{z'eV}{2k_BT}} \right) \\ &= \frac{1}{\tau_{act}(0)} e^{\frac{-z'eV_b}{2k_BT}} \left(e^{\frac{-z'e(V-V_b)}{2k_BT}} + e^{\frac{z'e(V-V_b)}{2k_BT}} \right) \\ &= \frac{1}{\tau_{obs}(0)} \, cosh \left(\frac{z'e(V-V_b)}{2k_BT} \right) \end{aligned} \tag{8.18}$$

This functional form has the shape of a bowl (an igloo for $\tau_{obs}(V)$). Thus the larger the magnitude of the voltage change, the shorter the time or the faster the rate.

The bottom line is that the above forms for $P_{act}(V, \infty)$ and $\tau_{obs}(V)$ 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 activaton functions occur at the same potential. As we shall see this is usually - but not always - obeyed.

From a rmal point of view, the transmembrane voltage, $V(x,t)$ and the activation parameters for each current, $P_{act}(V,t)$, form the state variables for the the system. For the Hodgkin-Huxley model there are 4 state variables total, while for models of thalamic relay neurons the numer of state variables is (presently) 13.

8.3 Experimental Self-Consistency of the Hodgkin-Huxley Model

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 pharamcological 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 $P_{act}(V, \infty)$ and $\tau_{obs}(V)$ for that ion.

FIGURE - chapt-8-volt-clamp.eps

FIGURE - chapt-8-volt-clamp-set.eps

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.

FIGURE - chapt-8-mhn.eps

The dynamic equations are

$$\begin{aligned} \tau \frac{\partial V(x,t)}{\partial t} &= \lambda^2 \frac{\partial^2 V(x,t)}{\partial x^2} - \frac{r_m \overline{g}_{Na^+}}{2\pi a} m^3(V) h(V) \left(V - V_{Na^+}\right) \\ &- \frac{r_m \overline{g}_{Ka^+}}{2\pi a} n^4(V) \left(V - V_{K^+}\right) - \frac{r_m \overline{g}_{leak}}{2\pi a} \left(V - V_l\right) + \frac{r_m}{2\pi a} I_o \end{aligned} \tag{8.19}$$

which has 10 independent biophysical parameters, i.e., a, τ, λ, r_m, $\overline{g}_{Na^+}$, $\overline{g}_{K^+}$, $\overline{g}_{leak}$, 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.

$$\frac{dh(V,t)}{dt} = \frac{h_\infty(V) - h(V,t)}{\tau_h(V)} \tag{8.20}$$

$$\frac{dm(V,t)}{dt} = \frac{m_\infty(V) - m(V,t)}{\tau_m(V)} \tag{8.21}$$

$$\frac{dn(V,t)}{dt} = \frac{n_\infty(V) - n(V,t)}{\tau_n(V)} \tag{8.22}$$

where $n_\infty(V) \equiv n(V, t \to \infty)$ 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.

FIGURE - chapt-8-simulations.eps

FIGURE - chapt-8-hh-fi.eps

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 od the action potential is small, less than one millisecond. Further, the current flow is localized so that the voltage disturbance propagates as a wave.

FIGURE - chapt-8-volt-clamp-summary.eps

FIGURE - chapt-8-hh-currents.eps