1 Biophysics of action potentials in "point" neurons

We now step back and detail the biophysical basis of spike generation by neurons.

1.1 Review of the Nernst potential

Consider a cell. It consists of two compartments, labeled "inside" and "outside", each filled with Na^+ and Cl^- ions and separated by a lipid membrane. On the inside of the cell, the concentration of ions is denoted $[Na^+]_{in}$ and $[Cl^-]_{in}$ and on the outside they are denoted $[Na^+]_{out}$ and $[Cl^-]_{out}$. To get a feel for the scale of $moles/liter$, let's put it into terms relevant for the size of a cell, i.e., ions per cubic micrometer. In a biological cell, the ion concentration is about 0.15 M, so we have about $10^8 ions/\mu m^3$ in a cell.

We set the cell so that, initially, $[Na^+]_{in} = [Cl^-]_{in}$ and $[Na^+]_{out} = [Cl^-]_{out}$ and the two sides are electrically neutral. Further, we impose $[Na^+]_{out} > [Na^+]_{in}$. Suppose we put a sub-nanometer pore that allows only one kind of ion to pass. To be concrete, we open up a hole that allows $[Na^+]$ ions, but not $[Cl^-]$ ions, to pass. This is a Na^+ selective channel. What follows is:

- Initially, the $[Na^+]$ moves down its concentration gradient, driven by diffusion.
- As Na^+ ions move across the wall, the solutions in the two compartments are no longer electrically neutral. Positive charge (from the Na^+) leaves the outside and builds up on the inside. This leads to an electric field across the wall.
- The electric fields points from the inside to the outside and opposes motion of additional Na^+ ions.
- In time, the electric field caused by the initial movement of ions points from the inside to the outside. This field is the direction that opposes motion of additional Na^+ ions and will prevent any more Na^+ ions from moving. As this point the system is in equilibrium.

The result is that the concentration difference in Na^+ ions between the inside and outside of the cell leads a difference in electrical potential across the cell.

The value of the potential is found by equating the chemical potential to move an ion across the membrane, μ, with the electrical potential by $eV = \mu$, i.e.,

$$\begin{aligned} \mu &= \left(\frac{\partial F}{\partial N}\right)_{T,V} \\ &= -k_B T \frac{\partial ln Z}{\partial N} \\ &= -k_B T \frac{\partial ln \frac{\xi^N}{N!}}{\partial N} \end{aligned} \tag{1.1}$$

$$
\begin{aligned}
&= -k_B T \frac{\partial \left(N ln\xi - N ln N \right)}{\partial N} \\
&= k_B T \, ln N \; + \; \text{constant}
\end{aligned}
$$

where Z is the partition function, ζ is the partition function per ion, the denominator of $N!$ accounts for the ways to arrange N identical ions, and we approximated $N! \rightarrow N^N$ (Sterling's formula). Thus

$$
V = \frac{k_B T}{e} ln \frac{[Na^+]_{out}}{[Na^+]_{in}} \tag{1.2}
$$

We see immediately that V is on the order of $\frac{k_B T}{e} \approx 25$ mV.

Review of Goldman-Katz (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

$$
\begin{aligned}
\vec{v}_D(x,t) &= \mu \vec{E}(x,t) \\
&= -\mu \frac{\partial V(x,t)}{\partial x} \hat{x}
\end{aligned} \tag{1.3}
$$

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

$$
\begin{aligned}
\vec{J}_D(x,t) &= [Ion](x,t) \; \vec{v}_D(x,t) \\
&= \mu [Ion](x,t) \; \vec{E} \\
&= -\mu [Ion](x,t) \frac{\partial \, V(x,t)}{\partial x} \hat{x}.
\end{aligned} \tag{1.4}
$$

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

$$
J(x,t) = -D \frac{\partial [Ion](x,t)}{\partial x} - \mu [Ion](x,t) \; \frac{\partial V(x,t)}{\partial x}. \tag{1.5}
$$

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

$$
\int_{V(x')}^{V(x)} dV = -\frac{D}{\mu} \int_{x'}^{x} \frac{d[Ion](x)}{[Ion](x)} \tag{1.6}
$$

and thus

$$
\begin{aligned}
\Delta V &= V(x) - V(x') \\
&= \frac{D}{\mu} ln \left(\frac{[Ion](x)}{[Ion](x')} \right).
\end{aligned} \tag{1.7}
$$

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

$$
\begin{aligned}
\Delta V &= V_{Nernst} \\
&= -\frac{k_B T}{ze} ln \left(\frac{[Ion](x)}{[Ion](x')} \right)
\end{aligned} \tag{1.8}
$$

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

$$\mu = D\frac{ze}{k_BT}. \tag{1.9}$$

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,

$$J(x,t) = -D\left(\frac{\partial[Ion](x,t)}{\partial x} + \frac{ze}{k_BT}[Ion](x,t)\frac{\partial V(x,t)}{\partial x}\right). \tag{1.10}$$

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 $V(x) = \Delta V \cdot x/L$. We have an equation for the electrical current, I, *i.e.*,

$$\begin{aligned} I &= -zeJ(x)A \\ &= zeDA\left(\frac{d[Ion](x)}{dx} + \frac{ze}{k_BT}[Ion](x)\frac{\Delta V}{L}\right). \end{aligned} \tag{1.11}$$

or

$$L\frac{d[Ion](x)}{dx} + \frac{ze\Delta V}{k_BT}[Ion](x) = \frac{IL}{zeDA} \tag{1.12}$$

which we can solve directly to obtain

$$I = ze\frac{DA}{L}\,\frac{zeV}{k_BT}\,\frac{[ion]_{in} - [ion]_{out}e^{-\frac{zeV}{k_BT}}}{1 - e^{-\frac{zeV}{k_BT}}} \tag{1.13}$$

where we took the voltage to be $V = 0$ on the outside on the cell and thus replace $\Delta V \leftarrow V$ (Figure 1). The essential feature is that the $I - V$ curve is nonlinear for voltage changes on the order of $\frac{k_BT}{ze} \approx \frac{25}{z}\ mV$ away from the reversal potential.

In the limit that $V >> 0$ we see that $I \to (ze)^2[ion]_{in}\frac{DA}{L}\ \frac{1}{k_BT}V$ and in the limit In the limit that $V << 0$ we see that $I \to (ze)^2[ion]_{out}\frac{DA}{L}\ \frac{1}{k_BT}V$. 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.,

$$\begin{aligned} I &= ze\frac{DA}{L}\,[ion]_{in}\,\frac{zeV}{k_BT}\,\frac{1 - \frac{[ion]_{out}}{[ion]_{in}}e^{-\frac{zeV}{k_BT}}}{1 - e^{-\frac{zeV}{k_BT}}} \\ &= ze\frac{DA}{L}\,[ion]_{in}\,\frac{zeV}{k_BT}\,\frac{1 - e^{-\frac{ze(V - V_{Nernst})}{k_BT}}}{1 - e^{-\frac{zeV}{k_BT}}} \end{aligned} \tag{1.14}$$

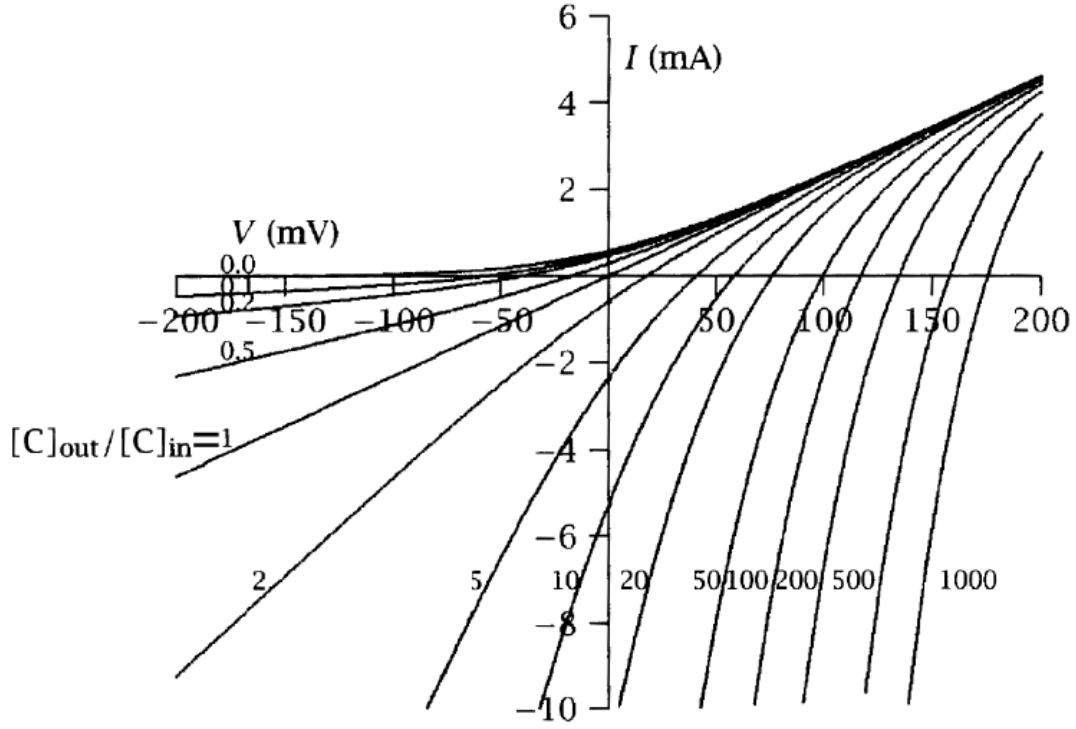
and is known as the Goldman-Katz relation. The essential feature is that the $I - V$ curve is nonlinear for voltage changes on the order of $\frac{k_BT}{ze} \approx 25/z\ mV$ away from the reversal potential.

We can pack all of the prefactors together as a single conductance, $g_{ion}(V)$ where we include the possibility that the pores, or conductances, can be modulated by the transmembrane voltage through $D = D(V,t)$. We write

$$I = g_{ion}(V,t)\,\left[V\,\frac{1 - e^{-\frac{ze(V - V_{Nernst})}{k_BT}}}{1 - e^{-\frac{zeV}{k_BT}}}\right]. \tag{1.15}$$

Figure 1: The I-V relation for ions is nonlinear. Convention is to ignore this nonlinearity and take I = g $(V - V_{Nernst})$

$$I(V) \rightarrow \begin{cases} z^2 e \frac{D}{L} \left(\frac{eV}{k_B T}\right) AC(L) & \text{if } V >> \frac{k_B T}{e} \\ \\ z^2 e \frac{D}{L} \left(\frac{eV}{k_B T}\right) AC(0) & \text{if } V << -\frac{k_B T}{e} \end{cases}$$



.

1.2 Cell circuit with active currents

Lets develop the framework for the physics and electrochemistry of the action potential $V(t)$ for a cell with no spatial extent. We start in the most general manner by adding active currents to the equation for a leaky capacitor,

$$\begin{aligned} \tau \frac{dV(t)}{dt} - V(t) &= -R_m g_{Na^+}(V,t)\, V\, \frac{1 - e^{-\frac{e(V - V_{Na^+})}{k_B T}}}{1 - e^{-\frac{zeV}{k_B T}}} \\ &- R_m g_{K^+}(V,t)\, V\, \frac{1 - e^{-\frac{e(V - V_{K^+})}{k_B T}}}{1 - e^{-\frac{zeV}{k_B T}}} \\ &- R_m g_{Cl^-}(V,t)\, V\, \frac{1 - e^{-\frac{e(V - V_{Cl^-})}{k_B T}}}{1 - e^{-\frac{zeV}{k_B T}}} + I^{ext}(t) \end{aligned} \tag{1.16}$$

where τ is the time constant of the passive membrane, R_m is the resistance of the membrane, and $I^{ext}(t)$ includes all external inputs. The sign convention is that positive current flows out.

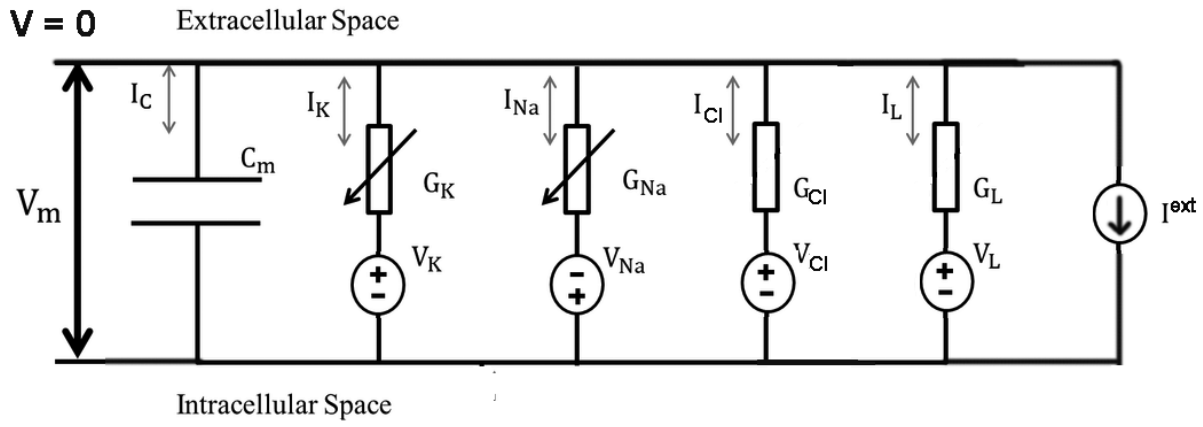
All of the interesting physics is in the form of the conductances $g_{ion}(V,t)$ so the apparently complicated form of Goldman-Katz is irrelevant. But Hodgkin and Huxley ignored Goldman-Katz for unclear historical reasons and chose to approximate the I-V relation in terms of a voltage and time dependent conductance and a term where the voltage relative to a battery at the Nernst potential. Thus yields a circuit equation (Figure 2). Of course, one can expand Goldman-Katz near $V = V_{Nernst}$, which gives

$$I = \left[g_{ion}(V,t) \, \frac{zeV_{Nernst}/k_BT}{1 - e^{-zeV_{Nernst}/k_BT}} \right] (V - V_{Nernst}) \, . \tag{1.17}$$

where the terms in the square brackets are just a rescaled conductance. The rectifying form of Goldman-Katz is only important if one swings on both sides of the reversal potential; this only occurs for Cl^-1. All told, this dubious approximation reduces the equations into a circuit formulation (Figure 2).

$$\begin{aligned} \tau \frac{dV(t)}{dt} \; - \; V(t) \quad &= \quad R_m g_{Na^+}(V,t) \, [V(t) - V_{Na^+}] \\ &- \quad R_m g_{K^+}(V,t) \, [V(t) - V_{K^+}] \\ &- \quad R_m g_{leak} \, [V(t) - V_{leak}] \; + \; R_m I^{ext}(t). \end{aligned} \tag{1.18}$$

Figure 2: A circuit model for the conductance-based equations of Hodgkin-Huxley equations



1.3 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 $g_{ion}(V,t)[(V,t) - V_{ion}]$. 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, i.e., the opening of channels designated by $P_{activate}(V,t)$, and the inactivations, i.e., the closing of channels designated by $P_{inactivate}(V,t)$. This allows for transient behavior by the sequential flow and stoppage of currents. Recall that all probabilities vary between 0 and 1. Thus

$$g_{Ion}(V,t) \equiv \bar{g}_{Ion} \times P_{activate}(V,t) \times P_{inactivate}(V,t). \tag{1.19}$$

1.3.1 A differential equation for $P_{activate}(V,t)$

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

$$P_{act}^{open}(V,t) + P_{act}^{closed}(V,t) = 1 \tag{1.20}$$

and

$$\begin{aligned} \frac{dP_{act}^{open}(V,t)}{dt} &= k_{open}(V)P_{act}^{closed}(V,t) - k_{closed}(V)P_{act}^{open}(V,t) \\ &= -\left[k_{open}(V) + k_{closed}(V)\right] P_{act}^{open}(V,t) + k_{open}(V) \\ &= -\left[k_{open}(V) + k_{closed}(V)\right] \times \left[P_{act}^{open}(V,t) - P_{act}^{open}(V,\infty)\right] \end{aligned} \tag{1.21}$$

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

$$\frac{dP_{act}(V,t)}{dt} = -k_{obs}\left(P_{act}(V,t) - P_{act}(V,\infty)\right). \tag{1.22}$$

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.

1.3.2 The form of $P_{activate}(V,\infty)$

For sake of argument, let's 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

$$\begin{aligned} Energy &= -\vec{p}\cdot\vec{E} = qd\ cos\phi\ \frac{\partial V}{\partial x} \approx \left(q\frac{dcos\theta}{L}\right)V \\ &\equiv z'e\ V \end{aligned} \tag{1.23}$$

where ϕ 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

$$\frac{P_{act}^{open}(V,\infty)}{P_{act}^{closed}(V,\infty)} = e^{\frac{z'e(V-V_{bias})}{k_BT}} \tag{1.24}$$

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

$$P_{act}^{open}(V,\infty) = \frac{1}{1 + e^{-\frac{z'e(V-V_{bias})}{k_BT}}} \tag{1.25}$$

and

$$P_{act}^{closed}(V,\infty) = \frac{e^{\frac{z'e(V-V_{bias})}{k_BT}}}{1 + e^{-\frac{z'e(V-V_{bias})}{k_BT}}} \tag{1.26}$$

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

1.3.3 The form of $k_{open}(V)$

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

$$k_{open}(0) = \nu e^{\frac{-\Delta G_o}{k_B T}} \tag{1.27}$$

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

$$\begin{aligned} k_{closed}(0) &= \nu e^{\frac{-\Delta G_o - z' e V_{bias}}{k_B T}} \\ &= k_{open}(0) e^{\frac{-z' e V_{bias}}{k_B T}} \end{aligned} \tag{1.28}$$

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 raise as much as that of the open state is lowered. Thus

$$k_{open}(V) = k_{open}(0) e^{\frac{-z' e V}{2 k_B T}} \tag{1.29}$$

and

$$k_{closed}(V) = k_{open}(0) e^{\frac{-z' e V_{bias}}{k_B T}} e^{\frac{z' e V}{2 k_B T}}. \tag{1.30}$$

Thus

$$\begin{aligned} k_{obs}(V) &= k_{open}(V) + k_{closed}(V) \\ &= k_{open}(0) \left(e^{\frac{-z' e V}{2 k_B T}} + e^{\frac{-z' e V_{bias}}{k_B T}} e^{\frac{z' e V}{2 k_B T}} \right) \\ &= k_{open}(0) e^{\frac{-z' e V_{bias}}{2 k_B T}} \left(e^{\frac{-z' e (V - V_{bias})}{2 k_B T}} + e^{\frac{z' e (V - V_{bias})}{2 k_B T}} \right) \\ &= k'_{open}(0)\ cosh \left(\frac{z' e (V - V_{bias})}{2 k_B T} \right). \end{aligned} \tag{1.31}$$

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.

1.3.4 Synopsis

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. The measured currents for one voltage sensor is

$$I^{\text{active}} = \bar{g}_{Ion} \times P_{activate}(V, t) \times \left[V - V^{\text{Nernst}} \right] \tag{1.32}$$

from which one extracts $P_{activate}(V, t)$ by measuring the current as a function of voltage. This is a nontrivial procedure, as all currents but one must be blocked while $P_{activate}(V, t)$

as well as a potential $P_{inactivate}(V,t)$ must be measured. Currently, the measurements are best done by measuring "tail" currents to avoid the contributions of leakage currents. This is now a standard art and we urge you to look in a Neurobiology text. Our focus is on where the Physics takes hold.

1.4 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.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. This framework includes the observation that the peak of the time constants and the midpoint of the activation functions occur at nominally the same potential. The dynamic equations are

$$\begin{aligned} \tau \frac{dV(x,t)}{dt} &= -r_m \overline{g}_{Na^+} m^3(V) h(V) \left(V - V_{Na^+}\right) \\ &- r_m \overline{g}_{Ka^+} n^4(V) \left(V - V_{K^+}\right) \\ &- -r_m \overline{g}_{leak} \left(V - V_l\right) + r_m I^{ext}(t). \end{aligned} \tag{1.33}$$

which has 7 independent biophysical parameters, i.e., τ, r_m, $\overline{g}_{Na^+}$, $\overline{g}_{K^+}$, $\overline{g}_{leak}$, V_{Na^+}, V_{K^+}, and V_{leak} as well as 12 (or more in principle) fitting parameters as exponents on the activation and inactivation functions.

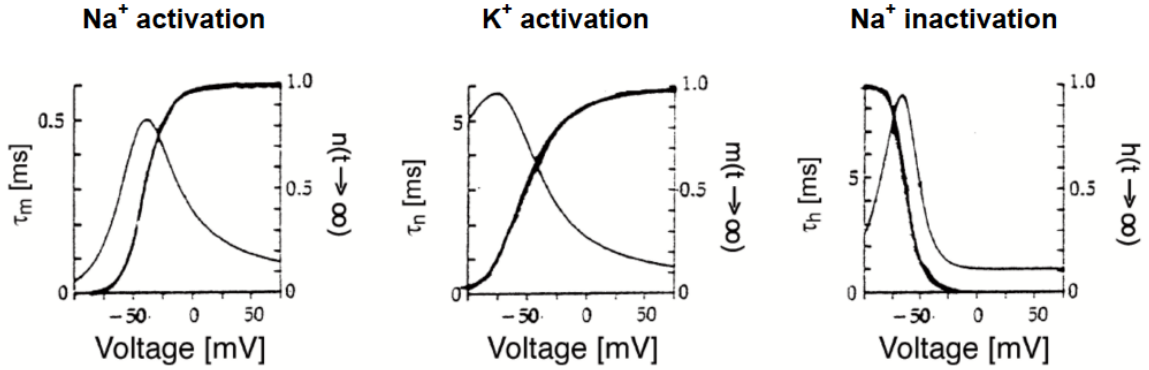
$$\frac{dh(V,t)}{dt} = \frac{h_\infty(V) - h(V,t)}{\tau_h(V)} \tag{1.34}$$

$$\frac{dm(V,t)}{dt} = \frac{m_\infty(V) - m(V,t)}{\tau_m(V)} \tag{1.35}$$

$$\frac{dn(V,t)}{dt} = \frac{n_\infty(V) - n(V,t)}{\tau_n(V)} \tag{1.36}$$

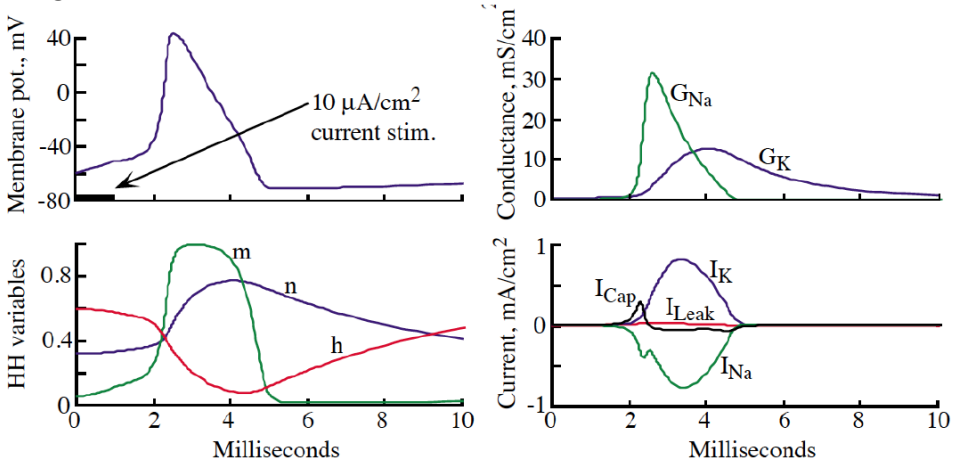
where $n_\infty(V) \equiv n(V, t \to \infty)$ and the parameterization for each rate expression has three fitting parameters, i.e., z', V_b, $\tau_{obs}(0)$, for a total of 9 parameters (Figure 3).

Figure 3: The parameters experimentally derived for the Hodgkin Huxley equation, from data. From Hodgkin and Huxley1952.



These circuit equations, derived from current clamp data (Figure 4), were used to predict the shape of the action potential in both the space clamped and, as we will discuss later, in the non-space clamped propagating place. The results showed self consistency about the ionic currents and the voltage changes (Figure 5).

Figure 4: Computation shows the form of the currents throughout the action potential.



To recap, the action potential results from an instability in the conductance such that the direction of the membrane current transiently reverses 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.

Figure 5: Logic of the onset activation parameter derived for the Hodgkin Huxley K^+ and Na^+ currents from data. From Hodgkin and Huxley1952 as summarized by Fee class notes.