9 The Biophysics of Action Potentials in "Point" Neurons 2

9.1 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 thin lipid wall. 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 $moles/liter$, lets 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^+ 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 this potential is found by equating the chemical potential to move an ion across the membrane, ν, with the electrcal potential by $eV = \nu$, i.e.,

$$\nu = \left(\frac{\partial F}{\partial N}\right)_{T,V} = -k_B T \frac{\partial lnZ}{\partial N} = -k_B T \frac{\partial ln\frac{\xi^N}{N!}}{\partial N} = k_B T\, lnN + \text{constant} \qquad (9.9)$$

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

$$V = \frac{k_B T}{e} ln \frac{[Na^+]_{out}}{[Na^+]_{in}} \tag{9.10}$$

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

9.2 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

$$\begin{aligned} \vec{v}_D(x,t) &= \mu \vec{E}(x,t) \tag{9.11} \\ &= -\mu \frac{\partial V(x,t)}{\partial x} \hat{x} \end{aligned}$$

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

$$\begin{aligned} \vec{J}_D(x,t) &= [Ion](x,t)\, \vec{v}_D(x,t) \tag{9.12} \\ &= \mu[Ion](x,t)\, \vec{E} \\ &= -\mu[Ion](x,t) \frac{\partial V(x,t)}{\partial x} \hat{x}. \end{aligned}$$

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

$$J(x,t) = -D \frac{\partial [Ion](x,t)}{\partial x} - \mu[Ion](x,t) \frac{\partial V(x,t)}{\partial x}. \tag{9.13}$$

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

$$\int_{V(x')}^{V(x)} dV = -\frac{D}{\mu} \int_{x'}^{x} \frac{d[Ion](x)}{[Ion](x)} \tag{9.14}$$

and thus

$$\Delta V = V(x) - V(x') = -\frac{D}{\mu} ln\left(\frac{[Ion](x)}{[Ion](x')}\right). \tag{9.15}$$

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

$$\Delta V = V_{Nernst} = -\frac{k_B T}{ze} ln\left(\frac{[Ion](x)}{[Ion](x')}\right) \tag{9.16}$$

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

$$\mu = D\frac{ze}{k_B T}. \tag{9.17}$$

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,

$$J(x,t) = -D\left(\frac{\partial [Ion](x,t)}{\partial x} + \frac{ze}{k_B T}[Ion](x,t)\frac{\partial V(x,t)}{\partial x}\right). \tag{9.18}$$

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.,

$$
\begin{aligned}
I &= -zeJ(x)A \tag{9.19}\\
&= zeDA\left(\frac{d[Ion](x)}{dx} + \frac{ze}{k_B T}[Ion](x)\frac{\Delta V}{L}\right).
\end{aligned}
$$

or
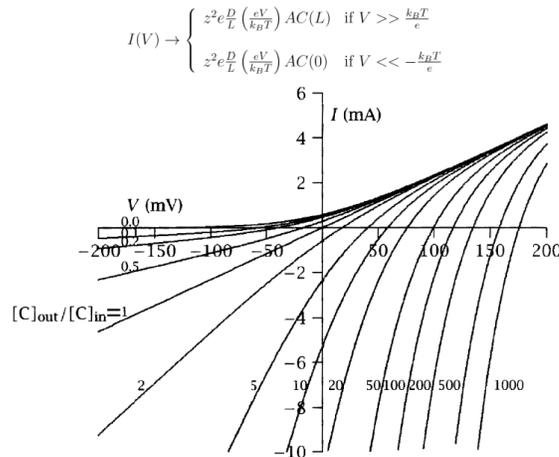
$$L\frac{d[Ion](x)}{dx} + \frac{ze\Delta V}{k_B T}[Ion](x) = \frac{IL}{zeDA} \tag{9.20}$$

Which we can solve directly to obtain

$$I = ze\frac{DA}{L}\frac{zeV}{k_B T}\frac{[ion]_{in} - [ion]_{out}e^{-\frac{zeV}{k_B T}}}{1 - e^{-\frac{zeV}{k_B T}}} \tag{9.21}$$

where we took the voltage to be $V = 0$ on the outside on the cell and this replace $\Delta V \leftarrow V$.

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

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

.

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In the limit that $V >> 0$ 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 $V << 0$ 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.,

$$
\begin{aligned}
I &= ze \frac{DA}{L} [ion]_{in} \frac{zeV}{k_B T} \frac{1 - \frac{[ion]_{out}}{[ion]_{in}} e^{-\frac{zeV}{k_B T}}}{1 - e^{-\frac{zeV}{k_B T}}} \\
&= ze \frac{DA}{L} [ion]_{in} \frac{zeV}{k_B T} \frac{1 - e^{-\frac{ze(V - V_{Nerst})}{k_B T}}}{1 - e^{-\frac{zeV}{k_B T}}}
\end{aligned}
\tag{9.22}
$$

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 $\frac{k_B T}{ze} \approx 25/z \; mV$ 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

$$
I = g_{ion}(V, t) \left[V \frac{1 - e^{-\frac{ze(V - V_{Nerst})}{k_B T}}}{1 - e^{-\frac{zeV}{k_B T}}} \right].
\tag{9.23}
$$

9.3 A Cell Circuit with Active Currents

Let's 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,

$$
\tau \frac{dV(t)}{dt} - V(t) = -R_m g_{Na+}(V, t) V \frac{1 - e^{-\frac{e(V - V_{Na+})}{k_B T}}}{1 - e^{-\frac{zeV}{k_B T}}}
\tag{9.24}
$$

$$
- R_m g_{K+}(V, t) V \frac{1 - e^{-\frac{e(V - V_{K+})}{k_B T}}}{1 - e^{-\frac{zeV}{k_B T}}} - R_m g_{Cl-}(V, t) V \frac{1 - e^{-\frac{e(V - V_{Cl-})}{k_B T}}}{1 - e^{-\frac{zeV}{k_B T}}} + I^{ext}(t)
$$

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.

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

$$
I_{ion}(t) \approx g_{ion}(V, t) \left[V(t) - V_{ion} \right].
\tag{9.25}
$$

This approximation is on the one hand unwarranted, but simplifies the equations into a circuit formulation.

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$$\tau \frac{V(t)}{dt} - V(t) \quad = \quad R_m g_{Na^+}(V,t)\left[V(t) - V_{Na^+}\right] \tag{9.26}$$

$$- \quad R_m g_{K^+}(V,t)\left[V(t) - V_{K^+}\right] - R_m g_{leak}\left[V(t) - V_{leak}\right] + R_m I^{ext}(t).$$

Figure 2: A circuit model for the conductance-based equations of Hodgkin-Huxley equations
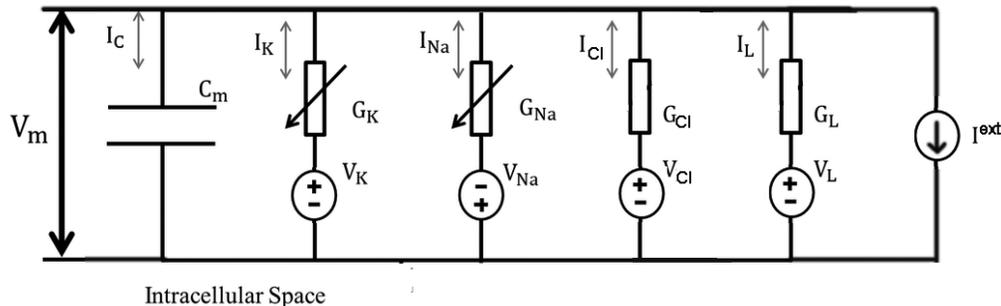
9.4 Functional Form of the Conductances

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 stopage of currents. Recall that all probabilities vary between 0 and 1 Thus

$$g_{Ion}(V,t) \equiv \bar{g}_{Ion} \times P_{activate}(V,t) \times P_{inactivate}(V,t). \tag{9.27}$$

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

$$P_{act}^{open}(V,t) + P_{act}^{closed}(V,t) = 1 \tag{9.28}$$

and

$$\frac{dP_{act}^{open}(V,t)}{dt} \quad = \quad k_{open}(V)P_{act}^{closed}(V,t) - k_{closed}(V)P_{act}^{open}(V,t) \tag{9.29}$$

$$= \quad -\left[k_{open}(V) + k_{closed}(V)\right]P_{act}^{open}(V,t) + k_{open}(V) \tag{9.30}$$

$$= \quad -\left[k_{open}(V) + k_{closed}(V)\right] \times \left[P_{act}^{open}(V,t) - P_{act}^{open}(V,\infty)\right]$$

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

$$\frac{dP_{act}(V,t)}{dt} = -k_{obs}\left(P_{act}(V,t) - P_{act}(V,\infty)\right). \tag{9.31}$$

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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

$$
\begin{aligned}
Energy & = -\vec{p} \cdot \vec{E} = qd\,\cos\theta\,\frac{\partial V}{\partial x} \approx \left(q\frac{d\cos\theta}{L}\right)V \qquad (9.32) \\
& \equiv z'e\,V
\end{aligned}
$$

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

$$
\frac{P_{act}^{open}(V,\infty)}{P_{act}^{closed}(V,\infty)} = e^{\frac{z'e(V-V_{bias})}{k_BT}} \qquad (9.33)
$$

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

$$
P_{act}^{open}(V,\infty) = \frac{1}{1 + e^{-\frac{z'e(V-V_{bias})}{k_BT}}} \qquad (9.34)
$$

and

$$
P_{act}^{closed}(V,\infty) = \frac{e^{\frac{z'e(V-V_{bias})}{k_BT}}}{1 + e^{-\frac{z'e(V-V_{bias})}{k_BT}}} \qquad (9.35)
$$

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

$$
k_{open}(0) = \nu e^{\frac{-\Delta G_o}{k_BT}} \qquad (9.36)
$$

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

$$
\begin{aligned}
k_{closed}(0) & = \nu e^{\frac{-\Delta G_o - z'eV_{bias}}{k_BT}} \qquad (9.37) \\
& = k_{open}(0)e^{\frac{-z'eV_{bias}}{k_BT}}
\end{aligned}
$$

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

$$k_{open}(V) = k_{open}(0)e^{\frac{-z'eV}{2k_BT}} \tag{9.38}$$

and

$$k_{closed}(V) = k_{open}(0)e^{\frac{-z'eV_{bias}}{k_BT}}e^{\frac{z'eV}{2k_BT}}. \tag{9.39}$$

Thus

$$
\begin{aligned}
k_{obs}(V) &= k_{open}(V) + k_{closed}(V) \\
&= k_{open}(0)\left(e^{\frac{-z'eV}{2k_BT}} + e^{\frac{-z'eV_{bias}}{k_BT}}e^{\frac{z'eV}{2k_BT}}\right) \\
&= k_{open}(0)e^{\frac{-z'eV_{bias}}{2k_BT}}\left(e^{\frac{-z'e(V-V_{bias})}{2k_BT}} + e^{\frac{z'e(V-V_{bias})}{2k_BT}}\right) \\
&= k'_{open}(0)\ cosh\left(\frac{z'e(V-V_{bias})}{2k_BT}\right).
\end{aligned} \tag{9.40}
$$

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.

An Aside: Multiple Voltage Sensors. Real channels often have multiple voltage seniors 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 pluging this value back into the equation for the slope.

First, a preliminary.

$$
\begin{aligned}
\frac{dP_{act}^{open}(V,\infty)}{dV} &= \frac{d\left(\frac{1}{1+e^{-\frac{z'e(V-V_{bias})}{k_BT}}}\right)}{dV} \\
&= \frac{z'e}{k_BT}\frac{e^{-\frac{z'e}{k_BT}}}{\left(1+e^{-\frac{z'e(V-V_{bias})}{k_BT}}\right)^2} \\
&= \frac{z'e}{k_BT}P_{act}^{open}(V,\infty)\left(1 - P_{act}^{open}(V,\infty)\right).
\end{aligned} \tag{9.41}
$$

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

$$\frac{d[P_{act}^{open}(V, \infty)]^N}{dV} = N[P_{act}^{open}(V, \infty)]^{N-1} \frac{dP_{act}^{open}(V, \infty)}{dV} \qquad (9.42)$$

$$= N\frac{z'e}{k_B T}[P_{act}(V, \infty)]^N [1 - P_{act}^{open}(V, \infty)]$$

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

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

$$(9.43)$$

which has a zero at the finite voltage of

$$V = V_{bias} + \frac{k_B T}{z'e} \log N. \qquad (9.44)$$

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

$$\frac{d[P_{act}^{open}(V, \infty)]^N}{dV} = \left(\frac{N}{1+N}\right)^{N+1} \frac{z'e}{k_B T} \qquad (9.45)$$

which increases from

$$\frac{d[P_{act}^{open}(V, \infty)]^N}{dV}\bigg|_{N=1} = \frac{1}{4}\frac{z'e}{k_B T} \qquad (9.46)$$

to the $4/\mathrm{e} = 1.47$-times larger asymptotic value of

$$\frac{d[P_{act}^{open}(V, \infty)]^N}{dV}\bigg|_{N\to\infty} = \frac{1}{\mathrm{e}}\frac{z'e}{k_B T}. \qquad (9.47)$$

Essentially, the transition from closed to open takes place over the range $\frac{k_B T/z'e}{4}$ to $\frac{k_B T/z'e}{\mathrm{e}}$, 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 $z' \to \infty$, 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 $k_{obs}t$.

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9.5 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

$$\tau \frac{dV(x,t)}{dt} = -r_m \bar{g}_{Na^+} m^3(V) h(V) \left(V - V_{Na^+}\right) \tag{9.48}$$
$$- \; r_m \bar{g}_{Ka^+} n^4(V) \left(V - V_{K^+}\right) - r_m \bar{g}_{leak} \left(V - V_l\right) + r_m I^{ext}(t).$$

which has 7 independent biophysical parameters, i.e., τ, r_m, $\bar{g}_{Na^+}$, $\bar{g}_{K^+}$, $\bar{g}_{leak}$, 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.

$$\frac{dh(V,t)}{dt} = \frac{h_\infty(V) - h(V,t)}{\tau_h(V)} \tag{9.49}$$

$$\frac{dm(V,t)}{dt} = \frac{m_\infty(V) - m(V,t)}{\tau_m(V)} \tag{9.50}$$

$$\frac{dn(V,t)}{dt} = \frac{n_\infty(V) - n(V,t)}{\tau_n(V)} \tag{9.51}$$

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

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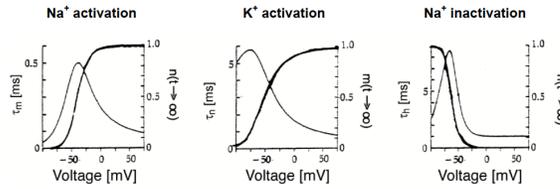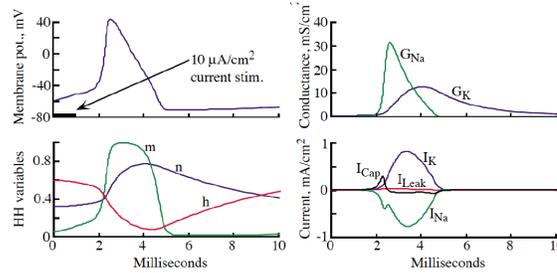

Figure 4: Computtation shows the form of the currents throuhtout the action potential.

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.