3 Action potentials: Insight following brutal approximations

The Hodgkin-Huxley equations for the behavior of the action potential in squid, and similar equations for action potentials in other cells, are impossibly complicated even with the approximations of Ohmic currents, etc. We now consider the use of rather brutal approximations, and phase plane techniques to illustrate the dynamics, as a means to get insight into regenerative neuronal events. The Hodgkin-Huxley equations were functions of four variables.

- \( V(x,t) \) ← transmembrane potential
- \( m(V,t) \) ← activation parameter for \( Na^+ \) current
- \( h(V,t) \) ← inactivation parameter for \( Na^+ \) current
- \( n(V,t) \) ← activation parameter for \( K^+ \) current

The goal is to reduce the Hodgkin Huxley equations from a dependence on 4 variables to a dependence on at most two variables. We first consider the case of an isopotential cell, and then address pulse propagation.

3.1 Fitzhugh’s Dimensional Reduction of the Hodgkin-Huxley Model

We return to the Hodgkin Huxley equations and focus on the generation of action potentials. We thus ignore space so that we have as the voltage equation

\[
\tau \frac{\partial V(x,t)}{\partial t} = -\frac{r_m g_{Na^+}}{2\pi a} m^3(V,t) h(V,t) (V - V_{Na^+}) \\
- \frac{r_m g_{K^+}}{2\pi a} n^4(V,t) (V - V_{K^+}) - \frac{r_m g_{leak}}{2\pi a} (V - V_l) + \frac{r_m I_o}{2\pi a}
\]

which has nine independent biophysical parameters, i.e., \( a, \tau, r_m, g_{Na^+}, g_{K^+}, g_{leak}, V_{Na^+}, V_{K^+}, \) and \( V_{leak} \) as well as three (or more in principle) fitting parameters as exponents on the activation and inactivation functions. The activation and inactivation functions are further described by the three activation equations

\[
\frac{dh(V,t)}{dt} = \frac{h_\infty(V) - h(V,t)}{\tau_h(V)} \quad (3.4)
\]

\[
\frac{dm(V,t)}{dt} = \frac{m_\infty(V) - m(V,t)}{\tau_m(V)} \quad (3.5)
\]
\[
\frac{dn(V,t)}{dt} = \frac{n_\infty(V) - n(V,t)}{\tau_n(V)}
\]  
(3.6)

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 nine additional parameters.

Four equations and 18 parameters is too much! We methodically brutalize them as follows:

1. The response time for the activation of the sodium current is fast time. We approximate this as infinitely fast and replace \(m(V,t)\) by its steady state, This leaves us with a single “fast” variable, that we continue to denote \(V(x,t)\).

2. The equation for \(V(t)\) will contain an essential nonlinearity to allow regenerative behavior. This is found by looking at the I-V relation for the squid axon at short times, when the \(Na^+\) current is fully activated. Roughly, it follows a cubic dependence.

3. Both the inactivation of the \(Na^+\) current and the activation of the \(K^+\) current are slow. It was noted that an increase in \(n(V,t)\) corresponds to a decrease in \(h(V,t)\). In fact, Fitzhugh noted that both activation functions \(n(V,t)\) and \(1 - h(V,t)\) linearly covary. This leaves us with a single “slow” variable, that we denote \(W(t)\). Rinzel showed that this can take the form

\[
W(V,t) = \frac{S_o}{1 + S_o^2} \{ S_o [1 - h(V,t)] + n(V,t) \}
\]  
(3.7)

where \(S_o\) is defined at rest, i.e.,

\[
S_o \equiv \frac{1 - h(V_o, t_o)}{n(V_o, t_o)}.
\]  
(3.8)

We will go further (without real justification), and linearize the equation for \(W(V,t)\).

4. The membrane time-constant can be ignored, that is, taken as infinity. The relaxation of the neuronal dynamic thus occurs on the time-scale of the slow recovery variable \(W(t)\).

5. All of the above motivates the simplified form credited to Fitzhugh and Nagumo, which contains two equations to describe fast and slow (recovery) variables. The “fast” variable “\(V\)” obeys

\[
\frac{dV}{dt} = f(V) - W + I
\]  
(3.9)

where time is in units of \(\tau\) and \(f(V)\) is a cubic polynomial similar in form to the instantaneous Hodgkin-Huxley \(Na^+\) current. The simplest example is

\[
f(V) = V \left( 1 - \frac{V}{V_{thresh}} \right) \left( 1 - \frac{V}{V_{peak}} \right).
\]  
(3.10)

The “slow” variable “\(W\)” obeys

\[
\frac{dW}{dt} = \phi \left( V - bW \right)
\]  
(3.11)
Note that $\frac{1}{\phi}$ sets the time scale for the slow variable and thus $\phi$ is a small number. The parameter $b$ sets the scale of growth versus decay. Further, that there are no product terms, i.e., terms of the form "$WV$", to cause intractable mathematics. Our goal is to use this brutalized form to derive the properties of the spike by viewing the action potential as a limit cycle, etc.

### 3.2 Stability analysis

In equilibrium the variables must satisfy

\[ W = f(V) + I \quad (3.12) \]

and

\[ W = \frac{V}{b} \quad (3.13) \]

The idea is that a train of pulses will be produced when $\frac{dW}{dt} \approx 0$ for $V$ near rest and $\frac{dW}{dt} > 0$ when $V$ is near its peak value. This implies that $b > 0$, so that the slow parameter turns on at high potentials.

We address the issue of spiking by considering the stability of the system. We expand around an equilibrium point $(V_o, W_o)$. Then we can expand the original equations to obtain an expression for $(V(t), W(t))$ in the vicinity of $(V_o, W_o)$. We write

\[ F(V, W) \approx F(V_o, W_o) + \left. \frac{\partial F}{\partial V} \right|_{(V_o, W_o)} \delta V + \left. \frac{\partial F}{\partial W} \right|_{(V_o, W_o)} \delta W \quad (3.14) \]

eq etc., so that with $F_1(V, W) = f(V) - W + I$ and $F_2(V, W) = \phi (V - bW)$ we have

\[ \frac{d\delta V}{dt} = f'(V_o)\delta V - \delta W \quad (3.15) \]

and

\[ \frac{d\delta W}{dt} = \phi \delta V - b\phi \delta W. \quad (3.16) \]

We do the usual thing of assuming that the solutions are of the form $\delta V(t) \approx A_1e^{\alpha_1 t} + A_2e^{\alpha_2 t}$, etc., with the constraints that the real parts of both $\alpha$’s must be negative for a solution to be stable, and the $\alpha$’s must be purely imaginary for a stable limit cycle, i.e., oscillatory solution. Thus, we evaluate

\[ \begin{vmatrix} f''(V_o) - \alpha & -1 \\ \phi & -b\phi - \alpha \end{vmatrix} = 0 \quad (3.17) \]

and

\[ \alpha_{1,2} = \frac{(f'(V_o) - b\phi) \pm \sqrt{(f'(V_o) + b\phi)^2 - 4\phi}}{2} \quad (3.18) \]

The first term on the RHS is always negative only for $b\phi > f'(V_o)$. This is the statement of stability. For the cell to fire repetitively, we must have instability, or satisfy

\[ f'(V_o) > b\phi \quad (3.19) \]
Since both $b$ and $\phi$ are positive, this means that the slope of $f(V_0)$ must be positive. This only happens only between the minimum and maximum values of $f(V)$. The details of $f(V)$ outside of the region are seen to be unimportant.

As a means to look at the onset of firing, we expand just about the point of stability/instability. We let

$$1 + \epsilon \equiv \frac{f'(V_0)}{b\phi}$$

(3.20)

so that

$$\alpha_{1,2} = \epsilon \frac{b\phi}{2} \pm i \sqrt{\phi - b^2 \phi^2}.$$  

(3.21)

As $\epsilon$ goes from negative to positive the system goes from stable to unstable, yet the value of the imaginary past, which sets the frequency, is unchanged. This is why the frequency jumps from zero (stable solution, with no oscillation) to a finite value of

$$f \approx \frac{1}{2\pi} \sqrt{\phi} \sqrt{1 - b^2 \phi}$$

(3.22)

$$\approx \frac{1}{2\pi} \sqrt{\phi}$$

where the final step holds if $b^2 \phi \ll 1$ consistent with $b$ of order 1 and $\phi \ll 1$. It is remarkable that the frequency depends only on $\phi$, which is the ratio of time scales between the fast and slow variables. Thus, as the system changes from stability to unstable, the frequency remains the same, i.e., the oscillations start from a nonzero value.

The choice of the parameter $b$ such that the system is unstable will lead to a limit cycle ($\epsilon > 0$). This corresponds to a neuron that oscillates in the absence of external input.

### 3.3 State-space trajectories

The presence of a small value of $\phi$ implies that the trajectories are simple. In particular, the slope of the trajectory is

$$\frac{dW}{dV} = \frac{\frac{dW}{dt}}{\frac{dV}{dt}} = \phi \frac{V - bW + I}{f(V) - W + I}$$

(3.23)

so that $\frac{dW}{dV} \approx \phi \approx 0$, i.e., the trajectories are nearly horizontal, unless we are close to the nullcline for $\frac{dV}{dt}$. Further, the speed along the horizontal nullcline is small compared to that on the vertical nullclines.

#### 3.3.1 Examples

It is now useful to examine the behavior to perturbed values of $V$ and $W$. We see that the response is stable so long as we are on the left side of the cubic curve, otherwise a spike is initiated. Interesting cases occur when the value of $b$ is chosen to insure stability in the absence of input, but transient current injection leads to a shift in $V$. In particular (see graphics of phase plane):
• Spike initiation by a depolarizing current pulses (point C).
• Absolute refractory period in response to a depolarizing current pulse (point A).
• Relative refractory period in response to a depolarizing current pulse (point B).
• Abolition of a spike by a hyperpolarizing pulse (point D).

Our final and perhaps most important example is to consider the effect of injecting steady current, $I$, which causes the nullcline for $\frac{dV}{dt}$ to shift up or down. This leads to a current threshold. As mentioned above, the firing rate jumps discontinuously from 0 to a nonzero value. This happens when $I$ is increased so that $b\phi = f'(V_o)$ or $\epsilon = 0$ in the above analysis, and the $\alpha$’s are imaginary with value
\[\alpha_{1,2} \approx \pm i \sqrt{\phi}.\] (3.24)

Thus the frequency at the onset of oscillations starts away from zero.

3.4 Speed of the Action Potential

A naive approach is to take the speed to be that from the cable equation with parameters for the cell during an action potential, i.e.,
\[u \approx \frac{\lambda_{AP}}{2\tau_{AP}} = \frac{\sqrt{\frac{r_m}{2\rho_c}a}}{2r_m c_m}\] (3.25)
with $r_m$ dominated by $(\overline{G}_{Na^+})^{-1}$, so that
\[u \approx \frac{1}{2c_m} \sqrt{\frac{G_{Na^+}}{2\rho_c}a} = \frac{\lambda}{2\tau} \sqrt{r_m G_{Na^+}}\] (3.26)

To get a better approximation, we first recall that the Hodgkin-Huxley neuron in the absence of external input is given by
\[
\frac{\tau}{\partial_t} \frac{\partial V(x,t)}{\partial x} = \lambda^2 \frac{\partial^2 V(x,t)}{\partial x^2} - r_m \overline{G}_{Na^+} m^3(V,t) h(V,t) (V - V_{Na^+})
- r_m \overline{G}_{Ka^+} n^4(V,t) (V - V_{K^+}) - r_m \overline{G}_{leak} (V - V_{leak})\] (3.27)
along with equations (three of them) for the activation parameters $n(V,t)$, $m(V,t)$, and $h(V,t)$, where the conductances have units of $(\Omega cm^2)^{-1}$, i.e., conductance per unit area, so we don’t have to chase factors of $2\pi a$. We need consider only the leading edge or front of the action potential so that we can ignore the potassium currents. In this limit the I-V relation for the $Na^+$ current can be assumed to follow a cubic dependence, as above. Thus we again take
\[f(V) = V \left(1 - \frac{V}{V_{thresh}}\right) \left(1 - \frac{V}{V_{peak}}\right)\] (3.28)
with \(0 < V < V_p\) where the resting potential is set to zero in the model so that all potentials are with respect to the resting level.

We now have an equation that is roughly valid on the time-scale of the leading edge of the spike - roughly the first 0.1 ms of the action potential, i.e.,

\[
\tau \frac{\partial V}{\partial t} = \lambda^2 \frac{\partial^2 V}{\partial x^2} - r_m \overline{G}_{Na^+} V \left(1 - \frac{V}{V_{thresh}}\right) \left(1 - \frac{V}{V_{peak}}\right)
\]  

(3.29)

We next perform a self-consistent analysis to determine the speed of propagation and the width of the rising edge.

- Let \(V(x,t) = V(x-ut) \equiv V(z)\), so that

\[
-\tau u \frac{dV}{dz} = \lambda^2 \frac{d^2 V}{dz^2} - r_m \overline{G}_{Na^+} V \left(1 - \frac{V}{V_{thresh}}\right) \left(1 - \frac{V}{V_{peak}}\right)
\]  

(3.30)

- Assume that \(V\) propagates as a front when \(V\) is not near \(V = 0\) or \(V = V_{peak}\), where \(\frac{dV}{dz} = 0\). We define the width of the front as \(\Lambda\), which has to be found self consistently, and take

\[
\dot{V} \equiv \frac{dV}{dz} = -\frac{V}{\Lambda} \left(1 - \frac{V}{V_{peak}}\right)
\]  

(3.31)

where the slope is negative as the propagating front moves into a region with \(V = 0\).

- Take \(V(z \to \pm \infty) = 0\)

- The trick is to rewrite the equation with

\[
\frac{d^2 V}{dz^2} = \frac{d}{dV} \left(\frac{dV}{dz}\right) \frac{dV}{dz} = \frac{d\dot{V}}{dV} \dot{V}
\]  

(3.32)

so that

\[
\frac{d\dot{V}}{dV} = -\frac{1}{\Lambda} \left(1 - 2 \frac{V}{V_{peak}}\right).
\]  

(3.33)

- Then

\[
-\tau u \dot{V} = \lambda^2 \frac{d\dot{V}}{dV} \dot{V} + \Lambda r_m \overline{G}_{Na^+} \left(1 - \frac{V}{V_{thresh}}\right) \dot{V}
\]  

(3.34)

or

\[
-\frac{u}{\Lambda} + \frac{\lambda^2}{\Lambda^2} - r_m \overline{G}_{Na^+} = \left(\frac{2 \lambda^2}{\Lambda^2 V_{peak}} - \frac{r_m \overline{G}_{Na^+}}{V_{thresh}}\right) V
\]  

(3.35)

The terms proportional to \(V\) and those independent of \(V\) must independently sum to zero. Thus

\[
\Lambda = \frac{\lambda}{\sqrt{r_m \overline{G}_{Na^+}}} \sqrt{\frac{2V_{thresh}}{V_{peak}}}
\]  

(3.36)
and we see that the space constant is shortened during an action potential. Further, 

$$u = \frac{\lambda}{2\tau} \sqrt{r_m G_{Na^+}} \sqrt{\frac{2(V_{peak} - 2V_{thresh})^2}{V_{peak} V_{thresh}}}$$  

and we see that the speed depends on the threshold (roughly a constant) and on the ratio 

$$\frac{r_m G_{Na^+} V_{Na^+}}{1 + r_m G_{Na^+}} \approx V_{Na^+}.$$ 

Our analysis leads to an "extra term" that illustrates quite clearly how the control of the action potential height and threshold will affect the speed. The size of the extra term is 

$$\sqrt{\frac{2(V_{peak} - 2V_{thresh})^2}{V_{peak} V_{thresh}}} \rightarrow \sqrt{\frac{2(V_{peak} - 2V_{thresh} + V_{rest})^2}{(V_{peak} - V_{rest})(V_{thresh} - V_{rest})}} \approx 4$$  

using reasonable values. Remember that all of the above was derived just with a phenomenological model of the nonlinear fast, $Na^+$ current. This appears legitimate since this current is an order of magnitude faster than the slow recovery dynamics. We learn that potential regulation of cell parameters provides an alternate means, compared with myelination, for a neuron to adjust the speed of propagation.