1 Action potentials: Brutal approximations to the HH-model to assess threshold behavior

The Hodgkin-Huxley equations for the behavior of the action potential in squid, and similar equations for action potentials in other cells, are "exact" but impossibly complicated. We now consider the use of phase plane techniques a means to get insight into regenerative neuronal events, such as those exhibited by the Hodgkin Huxley equations.

1.1 Dimensional Reduction of the Hodgkin-Huxley Model

The Hodgkin-Huxley equations are functions of 4 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 2 variables. We thus ignore space so that we have as the voltage equation

\[
\frac{\tau}{2\pi a} \frac{\partial V(x,t)}{\partial t} = -\frac{r_m g_{Na^+}}{2\pi a} m^3(V,t) h(V,t) (V - V_{Na^+}) - \frac{r_m g_{Ka^+}}{2\pi a} n^4(V,t) (V - V_{K^+}) - \frac{r_m g_{leak}}{2\pi a} (V - V_l) + \frac{r_m I_o}{2\pi a} \tag{1.1}
\]

which has 9 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 3 (or more in principle) fitting parameters as exponents on the activation and inactivation functions. The activation and inactivation functions are further described by the equations

\[
\frac{dh(V,t)}{dt} = \frac{h_\infty(V) - h(V,t)}{\tau_h(V)} \tag{1.2}
\]

\[
\frac{dm(V,t)}{dt} = \frac{m_\infty(V) - m(V,t)}{\tau_m(V)} \tag{1.3}
\]

\[
\frac{dn(V,t)}{dt} = \frac{n_\infty(V) - n(V,t)}{\tau_n(V)} \tag{1.4}
\]
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 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 value, i.e., \( m_\infty(V) \).

   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

   \[
   W(V, t) = \frac{S_o}{1 + S_o^2} \left\{ S_o (1 - h(V, t)) + n(V, t) \right\} \tag{1.5}
   \]

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

   \[
   S_o \equiv \frac{1 - h(V_0, t_0)}{n(V_0, t_0)}. \tag{1.6}
   \]

   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

   \[
   \frac{dV}{dt} = f(V) - W + I \quad (1.7)
   \]

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

   \[
   \frac{dW}{dt} = \phi (V + a - bW). \quad (1.8)
   \]

   Note that \( \phi \) sets the time scale for the slow variable and thus is a big number and 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.

1.2 A Quick Review of the Phase Plane

Before we get knee deep in the phase plane, let’s back up and recall what is meant by graphical analysis.

Consider \( \frac{dx}{dt} = f(x) \)

- When \( \frac{dx}{dt} > 0 \), \( x \) is increasing and the flow is the right along \( x \), i.e., \( \to \)
- When \( \frac{dx}{dt} < 0 \), \( x \) is decreasing and the flow is the left along \( x \), i.e., \( \leftarrow \)

This is illustrated in the attached figure for the case of \( \frac{dx}{dt} = \sin x \)

Another way to look at this is to consider a potential, \( U(x) \), where \( f(x) = -\frac{\partial U(x)}{\partial x} \) so that \( U(x) = \cos x \).

The power of this method comes with sets of equations with 2 dependent variables, i.e., of the form

\[
\begin{align*}
\frac{dV}{dt} &= function(V, W, I, \text{constants}) \equiv F(V, W, I, \text{constants}) \quad (1.9) \\
\frac{dW}{dt} &= function(V, W, \text{constants}) \equiv G(V, W, \text{constants})
\end{align*}
\]

Then we can observe the possible trajectories of the system graphically, and get insight into certain perturbations.

1.3 The Fitzhugh-Nagumo Model

1.3.1 Formulation

For concreteness, I will use a form of \( f(V) \) that is cubic and potentially antisymmetric and will thus serve to yield a qualitative understanding of spiking. We start with

\[
f(V) = \left(1 - \frac{V}{V_{\text{rest}}} \right) \left(1 - \frac{V}{V_{\text{thresh}}} \right) \left(1 - \frac{V}{V_{\text{peak}}} \right) \quad (1.10)
\]

For simplicity, it is often easiest to take all voltage levels relative to the threshold, for which \( V_{\text{threshold}} = 0 \) and \( V_{\text{rest}} < 0 < V_{\text{peak}} \). We then have an equation that is roughly valid on the time-scale of the leading edge of the spike - or the first 0.1 ms of the action potential, i.e.,

\[
f(V) = -V \left(1 - \frac{V}{V_{\text{rest}}} \right) \left(1 - \frac{V}{V_{\text{peak}}} \right) \quad (1.11)
\]
The fast variable, $V(t)$, captures the features of the instantaneous I-V relation at the height of the action potential. It obeys

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

(1.12)

The slow variable, $W(t)$, obeys

$$\frac{dW}{dt} = \phi (V + a - bW)$$

(1.13)

where, by construction, $\phi$ has a value $\phi << 1$.

### 1.3.2 Analysis

1. In steady state these must satisfy

$$W = f(V) + I$$

(1.14)

which, for the case $I = 0$, has a local minimum at

$$V_{\min} = \frac{1}{3} \left( V_{\text{peak}} + V_{\text{rest}} - \sqrt{V_{\text{peak}}^2 + V_{\text{rest}}^2 - V_{\text{peak}}V_{\text{rest}}} \right)$$

(1.15)

and a local maximum at

$$V_{\max} = \frac{1}{3} \left( V_{\text{peak}} + V_{\text{rest}} + \sqrt{V_{\text{peak}}^2 + V_{\text{rest}}^2 - V_{\text{peak}}V_{\text{rest}}} \right)$$

(1.16)

as well as

$$W = \frac{V}{b} + \frac{a}{b}$$

(1.17)

The parameter $b$ sets the scale of growth versus decay. The idea is that a train of pulses will be produced when $\frac{dW}{dt} \approx 0$ when $V$ is near rest and $\frac{dW}{dt} > 0$ when $V$ is near it’s peak value.

This immediately implies that $b > 0$, so that the slow parameter turns on at high potentials.

2. We want only a single fixed point in the solution at large values of $V$. Rather than try to solve a cubic, we note that slopes are equal when the curves just touch in the upper right-hand plane and two solutions just form, i.e., $\frac{dW}{dV} = f'(V)$ must equal $\frac{dW}{dV} = \frac{1}{b}$. Further, since the intersection occurs with $V > b$, $b$ is bounded by

$$0 < b < \frac{1}{f(V = V_{\max})}$$

(1.18)

This is a statement that the relative density of the slow current cannot exceed an upper limit that depends on the maximum voltage (e.g., height of the action potential).

The constant $a$ shifts the equilibrium point, found through the equilibrium equations for $V$ and $W$, i.e.
\[ f(V) - \frac{V}{b} = \frac{a}{b} - I \]  

so that \( a \) can be subsumed within \( I \).

3. Additional constraints appear 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

\[
F(V, W) \approx F(V_o, W_o) + \frac{\partial F}{\partial V} \bigg|_{V_o, W_o} \delta V + \frac{\partial F}{\partial W} \bigg|_{V_o, W_o} \delta W 
\]

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

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

\[
\frac{d\delta W}{dt} = \phi \delta V - b\phi \delta W
\]

We do the usual thing of assuming that the solutions are of the form \( \delta V(t) \approx A_1 e^{\alpha_1 t} + A_2 e^{\alpha_2 t} \), 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

\[
| \begin{array}{cc}
  f'(V_o) - \alpha & -1 \\
   \phi & -b\phi - \alpha
\end{array} | = 0
\]

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

The first term on the RHS is always negative only for \( b\phi > f'(V_o) \). If we then expand as \( b\phi = (1 + \epsilon)f'(V_o) \) or \( (1 - \epsilon)b\phi = f'(V_o) \), we have

\[
\alpha_{1,2} = \frac{(1 - \epsilon)b\phi - b\phi \pm \sqrt{[(1 - \epsilon)b\phi + b\phi]^2 - 4\phi}}{2}
\approx \frac{-\epsilon b\phi \pm 2\sqrt{b^2 \phi^2 - \phi}}{2}
\approx \frac{-\epsilon b\phi}{2} \pm i \sqrt{\phi \sqrt{1 - b^2 \phi}}
\]

Thus the real part of the roots are negative only for \( \epsilon > \epsilon_0 \), which are always satisfied near the value \( V_{min} \). Thus with \( \epsilon > 0 \) the solution decays as a damped oscillation with a time constant of

\[
\tau \approx \frac{1}{\alpha} \approx \frac{2}{\epsilon b\phi}
\]
and a frequency, as $\epsilon \to 0$, of

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

(1.27)

~

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

where the final step holds if $b^2 \phi << 1$ consistent with $b \sim 1$ and $\phi << 1$. In fact, for the system to oscillate, we must have $b < 1/\sqrt{\phi}$, which does not contradict the earlier constraint of $0 < b < 1/f(V_{\text{max}})$.

Since $\phi$ is small, the system decays only slowly near the equilibrium point. It is remarkable that the frequency depends, to first order, on a single parameter in the model.

One critical issue, is that the frequency depends only on $\phi$, which is the scale of the difference in time scales between the fast and slow variables, and not on $\epsilon$. 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. The presence of a small value of $\phi$ implies that the trajectories are simple. In particular, the slope of the trajectory is

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

(1.28)

so that $\frac{dW}{dV} \approx 0$, 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.

1.3.3 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, and with reference to the attached figure:

- 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 the equilibrium point on the left hand side is no longer stable or $\epsilon = 0$ in the above analysis, and the $\alpha$’s are imaginary with value

$$\alpha_{1,2} \approx \pm i\sqrt{\phi}.$$  

(1.29)

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

1.3.4 Saddle Node versus Hoft Bifurcations

Our final point concerns the onset of oscillations from zero frequency. Unlike the case of digital logic, when strongly nonlinear circuitry is the order of the day, sensory systems and motor plants tend to require the use of graded system (although one can build this from an ensemble of binary systems with a spectrum of thresholds).

Oscillations can start at zero frequency for the case $b > 1$ (strong inhibition), so that $4b^2\phi \sim 1$. This is accompanied by three rather than a single crossing of the $\frac{dV}{dt} = 0$ and $\frac{dW}{dt} = 0$ nullclines. The initial frequency can obtain any value as the real part of $\alpha$ becomes positive (unstable), i.e.,

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

(1.30)

The intermediate crossing serves as a saddle point, that is, paths along a particular trajectory lead to the point while all other paths lead away. As the current $I$ increases, the stable resting point and the unstable threshold point begin to merge and oscillations start. An example of this occurs with A-type $K^+$ currents.
Command Voltage

-9 mV

-65 mV

axon in low-sodium seawater - 10% of NaCl

axon in seawater

algebraic difference between curves

SQUID 8.5°C

1 mA/cm²

0 2 4

Time (msec)
Outward current

\[ |i_K| > |i_{Na}| \]

Inward current

\[ |i_{Na}| > |i_K| \]