10 Action Potentials - 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 "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.

The Hodgkin-Huxley equations were functions of 4 variables.

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

FIGURE - chapt-8-hh-currents.eps

As a warm-up exercise, we start with an important but simplier problem, the speed of an action potential

10.1 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.,

$$u \approx \frac{\lambda(AP)}{2\tau(AP)} = \frac{\sqrt{\frac{r_m}{2\rho_c}a}}{2r_m c_m} \tag{10.1}$$

with r_m dominated by $\overline{G}_{Na^+}$, so that

$$u \approx \frac{1}{2c_m}\sqrt{\frac{\overline{G}_{Na^+}}{2\rho_c}a} = \frac{\lambda}{2\tau}\sqrt{r_m\overline{G}_{Na^+}} \tag{10.2}$$

To get a better approximation, we first recall that the Hodgkin-Huxley neuron in the absence of external input is given by

$$\begin{aligned}\tau\frac{\partial V(x,t)}{\partial t} &= \lambda^2\frac{\partial^2 V(x,t)}{\partial x^2} - r_m\overline{G}_{Na^+}m^3(V,t)h(V,t)\left(V - V_{Na^+}\right) \\ &- r_m\overline{G}_{Ka^+}n^4(V,t)\left(V - V_{K^+}\right) - r_m\overline{G}_{leak}\left(V - V_l\right)\end{aligned} \tag{10.3}$$

along with equations (three of them) for the activation parameters $n(V,t)$, $m(V,t)$, and $h(V,t)$, where the conductanes 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.

The equation for Na^+ current 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.

FIGURE - chapt-10-volt-clamp-summary.eps

We take

$$f(V) = -\left(1 - \frac{V}{V_{rest}}\right)\left(1 - \frac{V}{V_{thresh}}\right)\left(1 - \frac{V}{V_{peak}}\right) \tag{10.4}$$

or, with $V \rightarrow V - V_{rest}$,

$$f(V) = V\left(1 - \frac{V}{V_t}\right)\left(1 - \frac{V}{V_p}\right) \tag{10.5}$$

with $0 < V_t < V_p$. Thus all potentials are with respect to the resting level.

FIGURE - chapt-10-F(V).eps

We then 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.,

$$\tau\frac{\partial V}{\partial t} = \lambda^2\frac{\partial^2 V}{\partial x^2} - r_m\overline{G}_{Na^+}V\left(1 - \frac{V}{V_t}\right)\left(1 - \frac{V}{V_p}\right) \tag{10.6}$$

This equation ignores the recovery term and provides an interesting lesson about a neuron with only noninactivating Na^+ currents (perhaps this can be built with the right molecular tools someday). Recall that the rest level is $V_{rest} = 0mV$ so that the voltage in the above equation represents the change away from rest.

We then perform a series of tricks and approximations (Hunter, McNaughton and Noble).

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

$$-\tau u\frac{dV}{dz} = \lambda^2\frac{d^2V}{dz^2} - r_m\overline{G}_{Na^+}V\left(1 - \frac{V}{V_t}\right)\left(1 - \frac{V}{V_p}\right) \tag{10.7}$$

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

$$\dot{V} \equiv \frac{dV}{dz} = -\frac{V}{\Lambda}\left(1 - \frac{V}{V_p}\right) \tag{10.8}$$

- Take $V(z \to \pm\infty) = 0$
- The trick is to rewrite the equation with

  $$\frac{d^2V}{dz^2} = \frac{d\dot{V}}{dV}\dot{V} \tag{10.9}$$

  so that

  $$\frac{d\dot{V}}{dV} = -\frac{1}{\Lambda}\left(1 - 2\frac{V}{V_p}\right) \tag{10.10}$$

- Then

  $$-\tau u \dot{V} = \lambda^2 \frac{d\dot{V}}{dV}\dot{V} + \Lambda r_m \overline{G}_{Na^+}\left(1 - \frac{V}{V_t}\right)\dot{V} \tag{10.11}$$

  or

  $$-u\frac{\tau}{\Lambda} + \frac{\lambda^2}{\Lambda^2} - r_m\overline{G}_{Na^+} = \left(\frac{2\lambda^2}{\Lambda^2 V_p} - \frac{r_m\overline{G}_{Na^+}}{V_t}\right)V \tag{10.12}$$

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

$$\Lambda = \frac{\lambda}{\sqrt{r_m\overline{G}_{Na^+}}}\sqrt{\frac{2V_t}{V_p}} \tag{10.13}$$

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

$$u = \frac{\lambda}{2\tau}\sqrt{r_m\overline{G}_{Na^+}}\,\sqrt{\frac{2(V_p - 2V_t)^2}{V_p V_t}} \tag{10.14}$$

and we see that the speed depends on the threshold (roughly a constant) and on the ratio $\frac{r_m\overline{G}_{Na^+}V_{Na^+}}{1+r_m\overline{G}_{Na^+}} \approx V_{Na^+}$. We pick up 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

$$\sqrt{\frac{2(V_p - 2V_t)^2}{V_p V_t}} \to \sqrt{\frac{2(V_p - 2V_t + V_r)^2}{(V_p - V_r)(V_t - V_r)}} \approx 4 \tag{10.15}$$

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.

FIGURE - chapt-10-myelin.eps

10.2 Threshold Phenomenon

The above analysis does not address the threshold phenomena of the action potential. A means to see where the threshold for active propagation originates, we now include recovery through a potassium current that provides negative feedback by acting as the integral of V. Thus we write

$$\begin{aligned} \tau \frac{\partial V(x,t)}{\partial t} &= \lambda^2 \frac{\partial^2 V(x,t)}{\partial x^2} - r_m \overline{G}_{Na^+} f[V(x,t)] \\ &\quad + r_m \overline{G}_{K^+} \int_{-\infty}^{t} dt' V(x,t') \end{aligned} \tag{10.16}$$

With $\int_0^1 dV f(V) > 0$, so that excitation exceeds inhibition, theorems by Aronson and Weinberger define the initial spatial distribution of $V(x,t)$ that can lead to an action potential, i.e., analytical justification of threshold potential. This is a minimalist description f threshold phenomena (although their proof is not very intuitive).

FIGURE - chapt-10-propagation.eps

10.3 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

$$\begin{aligned} \tau \frac{\partial V(x,t)}{\partial t} &= -\frac{r_m \overline{g}_{Na^+}}{2\pi a} m^3(V,t) h(V,t) \left(V - V_{Na^+}\right) \\ &- \frac{r_m \overline{g}_{Ka^+}}{2\pi a} n^4(V,t) \left(V - V_{K^+}\right) - \frac{r_m \overline{g}_{leak}}{2\pi a} \left(V - V_l\right) + \frac{r_m}{2\pi a} I_o \end{aligned} \tag{10.17}$$

which has 9 independent biophysical parameters, i.e., a, τ, 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. The activation and inactivation functions are further described by the equations

$$\frac{dh(V,t)}{dt} = \frac{h_\infty(V) - h(V,t)}{\tau_h(V)} \tag{10.18}$$

$$\frac{dm(V,t)}{dt} = \frac{m_\infty(V) - m(V,t)}{\tau_m(V)} \tag{10.19}$$

$$\frac{dn(V,t)}{dt} = \frac{n_\infty(V) - n(V,t)}{\tau_n(V)} \tag{10.20}$$

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., by $m_\infty(V)$

FIGURE - chapt-10-mhn.eps

This leaves us with a single "fast" variable, that we contimue 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.

FIGURE - chapt-10-volt-clamp-summary.eps

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.

SKETCH - "n" VERSUS "1-h"

This leaves us with a single "slow" variable, that we denote $W(t)$.

Rinzel showed that this can take the form

$$W(V,t) = \frac{S_o}{1+S_o^2}\left\{S_o\left[1-h(V,t)\right]+n(V,t)\right\} \tag{10.21}$$

wherw S_o is defined at rest, i.e.

$$S_o \equiv \frac{1-h(V_o,t_o)}{n(V_o,t_o)}. \tag{10.22}$$

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

$$\frac{dV}{dt} = f(V) - W \ + I \tag{10.23}$$

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

$$\frac{dW}{dt} = \phi\left(V + a - bW\right). \tag{10.24}$$

Note that ϕ sets the time scale for the slow variable snd thus is a big number and that there are no prouct terms, i.e., terms of the form "WV", to cause intractable mathematics.

Our goal is to use this brutalized from to derive the properties of the spike by viewing the action potential as a limit cycle, etc.

10.4 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., →
- When $\frac{dx}{dt} < 0$, x is decreasing and the flow is the left along x, i.e., ←

This is illustrated for the case of $\frac{dx}{dt} = \sin x$

FIGURE - chapt-10-phase-plane-sinx.eps

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

$$\begin{aligned}\frac{dV}{dt} &= function(V, W, I, constants) \equiv F(V, W, I, constants) \qquad (10.25)\\ \frac{dW}{dt} &= another\ function(V, W, constants) \equiv G(V, W, constants)\end{aligned}$$

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

10.5 The Fitzhugh-Nagumo Model

10.5.1 Formulation

For simplicity, I will use a form of $f(V)$ that is antisymmetric and thus slightly different form than that taken above. This is fine as we only seek qualitative understanding. Just to connect with the above, we start with

$$\begin{aligned}f(V) &= -\left(1 - \frac{V}{V_{rest}}\right)\left(1 - \frac{V}{V_{thresh}}\right)\left(1 - \frac{V}{V_{peak}}\right) \qquad (10.26)\\ &= \frac{V^3 - V^2(V_r + V_t + V_p) + V(V_tV_p + V_tV_r + V_rV_p) + V_rV_tV_p}{V_rV_tV_p}\end{aligned}$$

We next set the constant term to zero (delicately - note the denominator) by the choice $V_t \approx 0$ and take the quadratic term to zero, so that $V_p = -(V_t + V_r) \approx -V_r$. Then (ignoring the exploding denominator)

$$\begin{aligned} f(V) &\propto V^3 - V_p^3 V \\ &\equiv \frac{1}{3}V^3 - V \end{aligned} \tag{10.27}$$

The fast variable, $V(t)$, captures the features of the instantaneous I-V relation at the height of the action potential. It obeys

$$\frac{dV}{dt} = V - \frac{1}{3}V^3 - W + I \tag{10.28}$$

FIGURE - chapt-10-FN-nullclines.eps

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

$$\frac{dW}{dt} = \phi\,(V + a - bW) \tag{10.29}$$

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

10.5.2 Analysis

1. In steady state these must satisfy

$$W = V - \frac{1}{3}V^3 + I \tag{10.30}$$

which, for the case $I = 0$, has a local miniumum at $(V, W) = (-1, -2/3)$ and a local maximum at $(V, W) = (1, 2/3)$, and

$$W = \frac{V}{b} + \frac{a}{b} \tag{10.31}$$

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.

FIGURE - chapt-10-flow.eps

2. We want only a single fixed point in the solution. 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., $\frac{dW}{dV} = 1 - V^2$ and $\frac{dW}{dV} = \frac{1}{b}$ or $\frac{1}{b} > 1 - V^2$. Since the interseption occurs woith $0 < V < 1$, b is always finit with $b < 1/(1 - V_{max}^2)$, so that

$$0 < b < \frac{1}{1 - V_{max}^2} \tag{10.32}$$

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).

We can get a sense for the size of a by looking at the limit $I = 0$ so that $a = bW_o - V_o$. An equilibrium that is at the minimum of $f(V)$, where $(V_o, W_o) = (-1, -2/3)$, gives $a = 1 - \frac{2}{3}b$ or

$$a < 1 \tag{10.33}$$

for this special case.

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

$$F(V,W) \approx F(V_o, W_o) + \left.\frac{\partial F}{\partial V}\right|_{V_o,W_o} \delta V + \left.\frac{\partial F}{\partial W}\right|_{V_o,W_o} \delta W \tag{10.34}$$

etc., so that with $F_1(V,W) = V - \frac{1}{3}V^3 - W + I$ and $F_2(V,W) = \phi\,(V + a - bW)$ we have

$$\frac{d\delta V}{dt} = (1 - V_o^2)\delta V - \delta W \tag{10.35}$$

$$\frac{d\delta W}{dt} = \phi\,\delta V - b\phi\,\delta W \tag{10.36}$$

We do the usual thing of assuming that the solutions are of the form $\delta V(t) \cong A_1 e^{\alpha_1 t} + A_2 e^{\alpha_2 t}$, etc.,with the constraints that the real parts of both α's must be negative for a solution to be stable, and the α's must be purely imaginary for a stable limit cycle , i.e., oscillatory solution. Thus, we evaluate

$$\begin{vmatrix} 1 - V_o^2 - \alpha & -1 \\ \phi & -b\phi - \alpha \end{vmatrix} = 0 \tag{10.37}$$

$$\alpha_{1,2} = \frac{(1 - V_o^2 - b\phi) \pm \sqrt{(1 - V_o^2 + b\phi)^2 - 4\phi}}{2} \tag{10.38}$$

The first term on the RHS is always negative only for $b\phi > (1 - V_o^2)$. If we then expand as $b\phi = (1+\epsilon)\,(1 - V_o^2)$ or $(1-\epsilon)b\phi = (1 - V_o^2)$, we have

$$
\begin{aligned}
\alpha_{1,2} &= \frac{(1-\epsilon)b\phi - b\phi \pm \sqrt{[(1-\epsilon)b\phi + b\phi]^2 - 4\phi}}{2} \\
&\approx \frac{-\epsilon b\phi \pm 2\sqrt{b^2\phi^2 - \phi}}{2} \\
&\approx \frac{-\epsilon b\phi}{2} \mp i\,\sqrt{\phi}\,\sqrt{1-b^2\phi}
\end{aligned}
\tag{10.39}
$$

Thus the real part of the roots are negative only for $b\phi > (1 - V_o^2)$, which are always satisfied on the left side of the dip, i.e., $V_0 < -1$. Thus with $\epsilon > 0$ the solution decays as a damped oscillation with a time constant of

$$
\tau \approx \frac{1}{\alpha} \approx \frac{2}{\epsilon b\phi}
\tag{10.40}
$$

and a frequency, as $\epsilon \to 0$, of

$$
\begin{aligned}
f &\approx \frac{1}{2\pi}\sqrt{\phi}\,\sqrt{1-b^2\phi} \\
&\sim \frac{1}{2\pi}\sqrt{\phi}
\end{aligned}
\tag{10.41}
$$

where the final step holds if $b^2\phi << 1$ consistent with $b \sim 1$ and $\phi << 1$. In fact, for the stsem to oscillate, we must have $b < 1/sqrt\phi$, which is not so terrribly different in size from the earlier constrainnt of $b < 1/(1 - V^2)$.

Since ϕ is small, the system decays only slowly near the (V_o, W_o) equilibrium point. It is remarkable that the frequency depends, to first order, on a single parameter in the model.

SHOW ANIMATION

One critical issue, that we will return to, is that the frequency depends only on ϕ, which is the scale of the difference in time scales between the fast and slow variables, and not on ϵ. Thus, as the system changes from stability to unstable, the frequency remains the same, i.e., the oscillations start from a nonzero value.

SHOW ANIMATION

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.

SHOW ANIMATION

3. The presence of a small value of ϕ implies that the trajectories are simple. In particular, the slope of the trajectory is

$$
\frac{dW}{dV} = \frac{\frac{dW}{dt}}{\frac{dV}{dt}} = \phi\frac{V + a - bW}{V - \frac{1}{3}V^3 - W + I}
\tag{10.42}
$$

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.

FIGURE - chapt-10-FN-trajectories-1.eps

10.5.3 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.

FIGURE - chapt-10-FN-trajectories-2-eps

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:

- 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).

SHOW ANIMATIONS

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 $b\phi = 1 - V_0^2$, or $V_0 = -\sqrt{1 - b\phi}$ or $\epsilon = 0$ in the above analysis, and the α's are imaginary with value

$$\alpha_{1,2} \approx \pm i\sqrt{\phi}. \tag{10.43}$$

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

FIGURE - chapt-10-f-vs-I.eps

10.5.4 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 α becomes positive (unstable), i.e.,

$$f \approx \frac{1}{2\pi}\sqrt{\phi}\,\sqrt{1 - b^2\phi} \tag{10.44}$$

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

FIGURE - chapt-10-saddle-node.eps