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5 Brutal approximations to estimate the spike rate versus input (I/O) curve

The Hodgkin-Huxley equations for the behavior of the action potential in squid, and similar equations for action potentials in other cells, exhibit some rather simple behaviors, including repetitive spiking in response to a sustained input current, a discontinuity in the rate of spiking with increasing levels of input current, and a linear speed of propagation of action potentials along axons. Of course, there are neurons with other dynamics, as occurs for motoneurons in which the firing rate is a piece-wise near-linear function of the input so that the spike rate can be arbitrarily low (Figure 1).

Figure 1: The f-I relation for two different neurons, one with only HH current and one with an additional potassium current, I_Z , that activates during the recovery phase of the action potential and only slowly inactivates.



Despite the simple behavior, the underlying equations 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.

5.1 The Hodgkin-Huxley model

If only as a reminder, the HH model comprises a set of self-consistent equations that describe the voltage across the membrane in terms of the opening and closing of ion channels as a function of voltage and time. The four state variables are:

- $V(x,t) \leftarrow$ 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 full circuit equation for an axon, rather than a point neuron, where we now include space since we will later calculate the AP speed, is

$$\tau \frac{\partial V(x,t)}{\partial t} - \lambda^2 \frac{\partial^2 V(x,t)}{\partial x^2} = -\frac{r_m \overline{G}_{leak}}{2\pi a} \left(V - V_{leak}^{Nernst} \right)$$

$$- \frac{r_m \overline{G}_{Na^+}}{2\pi a} m^3(V,t) h(V,t) \left(V - V_{Na^+}^{Nernst} \right)$$

$$- \frac{r_m \overline{G}_{K^+}}{2\pi a} n^4(V,t) \left(V - V_{K^+}^{Nernst} \right) + \frac{r_m}{2\pi a} I^{ext}$$
(5.1)

which has ten independent biophysical parameters, i.e., the axon diameter, a, the membrane time-constant at rest, τ , the membrane specific resistance at rest, r_m , the space constant, λ (λ is the distance over which a subthreshold response decays; more on this later), the maximal conductances \overline{G}_{Na^+} , \overline{G}_{K^+} , \overline{G}_{leak} , $V_{Na^+}^{Nernst}$, $V_{K^+}^{Nernst}$, and V_{leak}^{Nernst} . The activation and inactivation functions are further described by the three activation equations

$$\frac{dh(V,t)}{dt} = \frac{h_{\infty}(V) - h(V,t)}{\tau_h(V)}$$
(5.2)

$$\frac{dm(V,t)}{dt} = \frac{m_{\infty}(V) - m(V,t)}{\tau_m(V)}$$
(5.3)

$$\frac{dn(V,t)}{dt} = \frac{n_{\infty}(V) - n(V,t)}{\tau_n(V)}$$
(5.4)

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 nine additional parameters, or more. These equations, with phenomenological parameterizations guided by physical chemistry, provide a remarkable understanding of many properties of the action potential. But they cannot be solved in analytical form. We thus seek an approximate formulation to gain insight to the transition from quiescence to spiking.

5.2 Dimensional reduction for a point neuron

We methodically brutalize the HH equations for a point neuron as follows:

• The response time for the activation of the sodium current is fast. We approximate this as infinitely fast and replace m(V, t) by its steady-steady value, which is bound to track to V(t). This leaves us with a single "fast" variable that we continue to denote V(t).

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

$$W(V,t) = \frac{S_o}{1+S_o^2} \left\{ S_o \left[1 - h(V,t) \right] + n(V,t) \right\}$$
(5.5)

where S_o is defined at rest, i.e.,

$$S_o \equiv \frac{1 - h(V_o, t_o)}{n(V_o, t_o)}.$$
(5.6)

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

• 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 (Figure 2). Roughly, it follows a cubic dependence. Recalling the previous brutal model for pulse initiation, this functional form can allow for two stable equilibria is a useful starting point.

Figure 2: The fast onset and slower recovery phase of an action potential. Note the initial "N"-like shape. The Na^+ -current begins to turn-off and a K^+ current turns on and the membrane potential returns to the rest level.



$$f(V) = \frac{1}{v_o^2} \left(V - V_{rest} \right) \left(V - V_{thresh} \right) \left(V - V_{peak} \right)$$
(5.7)

where v_o is a scaling constant of $O(k_B T/e)$.

• The membrane time-constant is ignored. The relaxation of the neuronal dynamic thus occurs on the time-scale of the recovery variable W(t).

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(t)" obeys

$$\tau \frac{dV}{dt} = -f(V) - W + I^{ext}$$
(5.8)

where τ is the fast time-scale and f(V) (Equation 5.7) is a cubic polynomial similar in form to the instantaneous Hodgkin-Huxley Na^+ current (Figure 2).

• The "slow" variable "W(t)" obeys

$$\tau \frac{dW}{dt} = \phi \left(V - bW \right). \tag{5.9}$$

Note that dimensionless parameter $1/\phi$ sets the time scale for the slow variable and thus ϕ is a small number so that $\tau/\phi \gg \tau$. The dimensionless parameter b sets the scale of growth versus decay of the recovery variable.

- There are no product terms, i.e., terms of the form "WV", to cause intractable mathematics.
- The variables V, W, and I^{ext} share the same units.

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.

5.3 Stability analysis

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 (Figure 3). We expand around an equilibrium point (V_o, W_o) . In equilibrium, the variables $V \leftarrow V_o$ and $W \leftarrow W_o$ must satisfy

$$W_o = -f(V_o) + I^{ext} \tag{5.10}$$

and

$$W_o = \frac{V_o}{b}.\tag{5.11}$$

We expand the original equations to obtain an expression for (V(t), W(t)) in the vicinity of (V_o, W_o) . We write

$$F(V,W) \approx F(V_o, W_o) + \frac{\partial F}{\partial V} \Big|_{(V_o, W_o)} \delta V + \frac{\partial F}{\partial W} \Big|_{(V_o, W_o)} \delta W$$
(5.12)



and expand with $F(V, W) = -f(V) - W + I^{ext}$ and $V \leftarrow \delta V + V_o$, which leads to

$$\frac{d\delta V}{dt} = -f'(V_0)\delta V - \delta W \tag{5.13}$$

so that only the derivative of f(V) in the vicinity of V_o is important. We further expand with $F(V, W) = \phi (V - bW)$ and $W \leftarrow \delta W + W_o$ leads to

$$\frac{d\delta W}{dt} = \phi \ \delta V - b\phi \ \delta W. \tag{5.14}$$

The solutions for these linear equations 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

$$\begin{vmatrix} -f'(V_0) - \alpha & -1\\ \phi & -b\phi - \alpha \end{vmatrix} = 0$$
(5.15)

and

$$\alpha_{1,2} = \frac{\left(-f'(V_0) - b\phi\right) \pm \sqrt{\left(-f'(V_0) + b\phi\right)^2 - 4\phi}}{2}$$
(5.16)

The first term on the RHS is always negative only for $b\phi > -f'(V_0)$. This is the statement of stability. For the cell to fire repetitively, we must have instability, or satisfy

$$-f'(V_0) > b\phi \tag{5.17}$$

which can correspond to a point for V in the range between the local maximum and local minimum of -f(V) since the slope of $f(V_0)$ must be negative since both b and ϕ are positive. The details of f(V) outside of this region are unimportant.

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

$$-f'(V_0) \approx b\phi \tag{5.18}$$

where $-f'(V_0)$ is positive between the local minimum and local maximum, i.e., where the curves cross in Figure 3. Then

$$\alpha_{1,2} = \frac{-f'(V_0) - b\phi}{2} \pm \frac{\sqrt{(-f'(V_0) - b\phi + 2b\phi)^2 - 4\phi}}{2}$$

$$\approx \frac{-f'(V_0) - b\phi}{2} \pm i\sqrt{\phi - b^2\phi^2}$$
(5.19)

As $-f'(V_0) - b\phi$ 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

spike frequency
$$\sim \frac{1}{2\pi}\sqrt{\phi}$$
 (5.20)

for b of order 1 and $\phi \ll 1$. It is remarkable that the frequency depends only on ϕ , which is the ratio of time scales between the fast and slow variables. Thus, as the system changes from stable 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 in the absence of an external input corresponds to a neuron that oscillates in the absence of input.

5.4 State-space trajectories

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

$$\frac{dW}{dV} = \frac{\tau \frac{dW}{dt}}{\tau \frac{dV}{dt}}$$

$$= \phi \frac{V - bW}{-f(V) - W + I^{ext}}$$
(5.21)

so that $\frac{dW}{dV} \approx \phi \rightarrow 0$, i.e., the trajectories are nearly horizontal, unless we are close to the nullcline for $\frac{dV}{dt}$ (Figure 4). Further, the speed along the horizontal nullcline is small compared to that on the vertical nullclines. Larger values of ϕ will eventually prevent a full action potential as the recovery variable can turn activate too quickly (Figure 4).



5.4.1 Examples

It is useful to examine the behavior to perturbed values of V and W. 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 (Figure 5):

- 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).



A final issue is to consider the effect of injecting steady current, I_o^{ext} , which causes the nullcline for $\frac{dV}{dt}$ to shift up or down. This leads to a current threshold, where I^{ext} is increased until $b\phi > -f'(V_o)$ in the above analysis.