Hodgkin-Huxley Model

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What makes the electrical properties of a neuron so interesting, including the ability to generate and propagate action potentials, arise from nonlinearity associated with active (voltage-dependent) membrane conductances, as denoted by g_i in the following equation

$$C_m \frac{dV}{dt} = -\sum_i g_i(V - E_i) - \bar{g}_L(V - E_L) + I_e. \tag{1}$$

The fact that we can experimentally observe currents entering single channels is truly amazing. The technology that allows an accurate measures of the amplitude of single-channel currents is called *patch clamp recording*, developed by Erwin Neher and Bert Sakmann. Neher and Sakmann won the Nobel prize in 1991 for their seminar contribution to patch clamp method. In patch clamp recording, the tip of a small glass pipette (with a diameter of 1 μm) is sealed to the membrane of a cell. Under ideal condition, with slight suction on the pipette, a seal resistance can be as high as a few GΩ (10^9 ohms). With a state-of-the-art amplifier, small currents across the patch of membrane inside the pipette tip can be recorded. The high resistance seal ensures that such currents flow through the amplifier rather than escaping through the rim of the patch. When recording, an online feedback control system holds the membrane potential of the cell almost instantaneously. This is done by (1) calculate the difference between the current membrane potential with the desired membrane potential. (2) Apply a feedback current to exactly compensate the membrane current flowing across the cell, so that the membrane potential is always hold at a constant value.

Patch clamp recordings of the current flowing through single channels indicate that channels fluctuate rapidly between open and closed states in a stochastic manner. However, the neuronal dynamics model we discuss so far is deterministic. This is justified because the conductance of a given ion channel type arises from a large number of channels. If these channels fluctuate independently of each other, the fraction of channel open at any given time is approximately equal to the probability P that any single channel is open. Let's denote $\bar{g}_i$ as the

maximum conductance for a given type of ion channel, the actual conductance $g_i = \bar{g}_i P_i$. Understanding active conductance now reduces to understanding how the channel open probability depends on voltage, neurotransmitter concentration, etc.

This is the structure of a delay-rectifier K^+ channel (show the 3D movie), which is comprised of four identical subunits. The opening of the channel appears to require all four units to undertake a structural change. In reality, the gating mechanisms underlying the conformational change of the subunit as well as the ion selectivity is complex and delicate. However, if our goal is to understand the current-carrying ability of a channel, it suffices to introduce a swinging gate picture: all four gates need to be opened simultaneously for a channel to open. if the movement of each gate is independent from each other, then we have

$$P_{\mathrm{K}} = n^k, \tag{2}$$

where n is the probability that any one of the gate opens, and we choose $k = 4$. Hodgekin and Huxley chose this formation of equation and use $k = 4$ to fit their experimental data, 40 years before the membrane protein structure of the potassium channel was determined. Indeed, Roderick MacKinnon, who solved the structure of the voltage-activated potassium channel, won the Nobel Prize in Chemistry in 2003.

Now let's describe the transition of each subunit gate from close to open using a simple kinematic model. The transition from closed $\rightarrow$ open occurs at a forward voltage-dependent rate $\alpha_n(V)$, and open $\rightarrow$ close occurs at the voltage-dependent rate $\beta_n(V)$. The probability to find a subunit gate open over short period time is $\alpha_n(1-n)\Delta t$; the probability to find a subunit gate close over short period time is $\beta_n n \Delta t$. The change of open probability over time $n\Delta t$ is given by the difference of the above two terms. Putting things together, we have

$$\frac{dn}{dt} = \alpha_n(V)(1-n) - \beta_n(V)n. \tag{3}$$

By introducing a steady-state probability

$$n_\infty(V) = \frac{\alpha_n}{\alpha_n + \beta_n},$$

and

$$\tau_n = \frac{1}{\alpha_n + \beta_n},$$

Equation 3 can be rewritten as

$$\tau_n \frac{dn}{dt} = n_\infty - n. \tag{4}$$

What can we say about the voltage-dependence of n_∞ and τ_n ? In the simplest model, the opening of a gate can be viewed as moving an effective charge qe across the membrane, and the free-energy difference between open and close gates will be $\Delta F = F_0 - qeV$. Thus, from statistical physics, we have

$$\frac{n_\infty}{1-n_\infty} = \exp(-\Delta F/k_B T).$$

Solving for n_∞, we have

$$n_\infty = \frac{1}{1+\exp[(F_0 - qeV)/k_B T]}. \tag{5}$$

Note that we do not know the exact value of F_0 and q. They are chosen to best-fit the experimental data. I will leave students as a homework to determine the functional form of τ_n based on the experimental data.

The delay-rectified potassium channel has persistent conductances: the channel are slowly activated upon depolarization and are slowly closed upon hyperpolarization. Some other channels, such as voltage-gated sodium channels, only open transiently when the membrane potential is depolarized because they are gated by two processes with opposite voltage dependence. For such channel, the probability to open the ion channel is given by

$$P_{\mathrm{Na}} = m^k h. \tag{6}$$

Here m is similar to n for the potassium channel. Hodgkin and Huxely used $k = 3$ to fit their model. Upon depolarization, m will increase towards one. However, h has the opposite dependence on voltage. Depolarization causes h to decrease and hyperpolarization causes h to increase. Thus to turn on a transient conductance maximally, it may first be necessary to hyperpolarize the neuron below its resting potential, this would open the gate for h. In the second step, upon depolarization, m will increase. Only when m and h are both nonzero, the channel will be opened.

The Hodgkin-Huxley model for generation of an action potential is constructed by a summation of leaky current, a delayed-rectified K^+ current, and a transient Na^+ current, and Equation 1 becomes

$$C_m \frac{dV}{dt} = -\bar{g}_{\mathrm{K}} n^4 (V - E_{\mathrm{K}}) - \bar{g}_{\mathrm{Na}} m^3 h (V - E_{\mathrm{Na}}) - \bar{g}_L (V - E_L) + I_e. \tag{7}$$

$$\frac{dn}{dt} = \alpha_n(V)(1-n) - \beta_n(V) n \tag{8}$$

$$\frac{dm}{dt} = \alpha_m(V)(1-m) - \beta_m(V) m \tag{9}$$

$$\frac{dh}{dt} = \alpha_h(V)(1-h) - \beta_h(V) h. \tag{10}$$

Below I will provide detailed parameter values used in Hodgkin and Huxley model. It is your homework to simulate the dynamic equations and check whether it could generate action potentials.

$$\alpha_n = \frac{0.01(V+55)}{1-\exp(-0.1(V+55))},\ \beta_n = 0.125\exp(-0.0125(V+65)),$$

$$\alpha_m = \frac{0.1(V+40)}{1-\exp(-0.1(V+40))},\ \beta_m = 4\exp(-0.0556(V+65)),$$

$$\alpha_h = 0.07exp(-0.05(V+65)),\ \beta_h = \frac{1}{1+\exp(-0.1(V+35))}.$$

Two-Dimensional Nonlinear Systems

The HH model is difficult to be understood analytically. We thus consider a simplified model

$$C_m\frac{dV}{dt} = -\bar{g}_{\rm K}n(V-E_{\rm K}) - \bar{g}_{\rm Na}m_\infty(V)(V-E_{\rm Na}) - \bar{g}_L(V-E_L) + I_e. \quad (11)$$

$$\tau_n\frac{dn}{dt} = n_\infty(V) - n. \quad (12)$$

Note that there are several simplifications we have made. First, we assume that the sodium current is persistent by eliminating the h variable. Second, we drop the exponent in the gating variable of the potassium channel. Third, we shall assume that for a given voltage, the sodium current reaches the steady state instantaneously. In what condition can we make such an assumption?

Before we discuss how to analyze the above two-dimensional system, I would like to briefly introduce some mathematical methods that we will use. This is the minimum requirement you need to understand the lecture.

Nonlinear differential equation

The neural dynamics we deal with are generally nonlinear. The most general differential equation we consider takes the form

$$\frac{d\mathbf{x}}{dt} = \mathbf{f}(x) \quad (13)$$

where $\mathbf{x}$ is an N component vector and $\mathbf{f}$ is vector of functions. Unless it is unstable, the behaviors of the dynamics fall into three classes. For one class, called stable fixed points or point attractors, $\mathbf{x}(t)$ approaches a time-independent vector $\mathbf{x}(\infty)$, when $t \to \infty$. In another class, called the limit cycle, $x(t)$ becomes

periodic at large times and repeats itself indefinitely. For the third class of solutions, the chaotic ones, $x(t)$ never repeats itself but the trajectory of the system lies in a limited subspace of the total space of allowed configurations called a strange attractor. Chaotic solutions are extremely sensitive to initial conditions.

Below we shall consider the point attractor, in which $\mathbf{x}_\infty$ is called the fixed point of the system, when $f(\mathbf{x}_\infty) = 0$. Near the fixed point, we can perform perturbation analysis by expanding f to the first order near the fixed point

$$\mathbf{f}(\mathbf{x}(t)) = \mathbf{f}(\mathbf{x}_\infty) + \mathbf{J}\epsilon(t), \tag{14}$$

where $\mathbf{J}$ is the Jacobian matrix, whose elements are given by

$$J_{ij} = \frac{\partial f_i(\mathbf{x})}{\partial x_j} \tag{15}$$

Thus the dynamics that need to be analyzed near the fixed point is given by

$$\frac{d\epsilon}{dt} = \mathbf{J}\epsilon \tag{16}$$

We know how to analyze this linear equation. The fixed point $\mathbf{x}_\infty$ is a stable fixed point only when the real part of all eigenvalues of the Jacobian matrix $\mathbf{J}$ are negative. Here, let's consider a very simple scenario, where the system we are considering is two-dimensional.

Analysis of a two-dimensional nonlinear system near the fixed point

Let's now consider a very simple case: the Jacobian matrix $\mathbf{J}$ is two-dimensional. In this case, we have

$$\mathbf{J} = \begin{bmatrix} a & b \\ c & d \end{bmatrix}$$

The characteristic equation becomes

$$\det \begin{bmatrix} a-\lambda & b \\ c & d-\lambda \end{bmatrix} = 0$$

Expanding the determinant yields

$$\lambda^2 - \tau\lambda + \Delta = 0 \tag{17}$$

where $\tau = \mathrm{Tr}\mathbf{J} = a + b$ and $\Delta = \mathrm{Det}\mathbf{J} = ad - bc$. Then we have

$$\lambda_{1,2} = \frac{\tau \pm \sqrt{\tau^2 - 4\Delta}}{2} \tag{18}$$

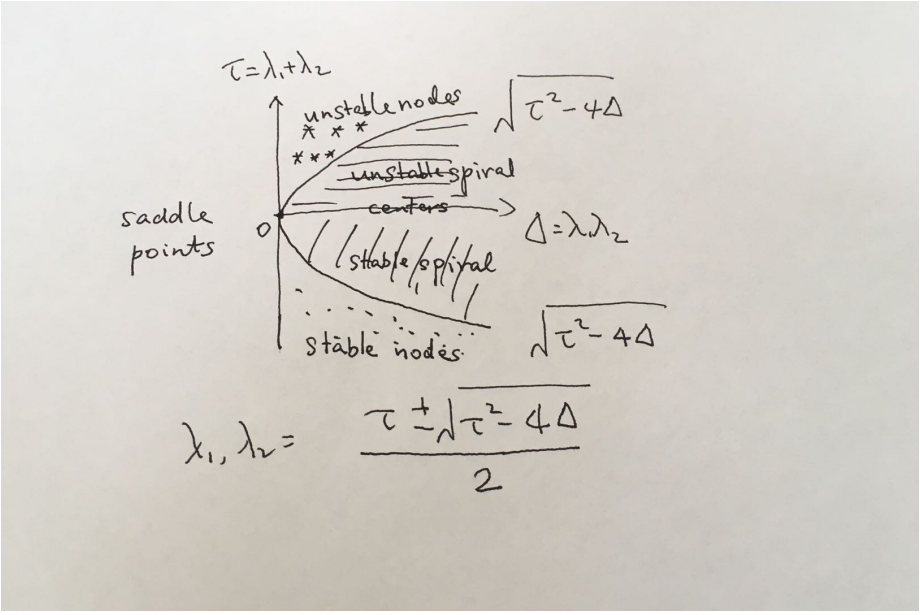

Figure 1: phase diagram of fixed point stability

Vector field and phase trajectory

A vector function $(x(t), y(t))$ is a solution of the two-dimensional system

$$\dot{x} = f(x, y), \tag{19}$$
$$\dot{y} = g(x, y), \tag{20}$$

starting with an initial condition $(x(0), y(0)) = (x_0, y_0)$. This requirement has a simple geometrical interpretation: a solution is a curve $(x(t), y(t))$ on the phase plane which is tangent to the vector field.

Poincare-Bendixson Theorem

See slides.

Now let us go back to the two-dimensional model. Let us determine the null-clines of the $I_{Na,p} + I_K$-model. The V-nullcline is given by the equation

$$I_e - \bar{g}_L(V - E_L) - \bar{g}_{\mathrm{Na}} m_\infty(V)(V - E_{\mathrm{Na}}) - \bar{g}_{\mathrm{K}} n(V - E_{\mathrm{K}}) = 0 \tag{21}$$

which has the solution

$$n = \frac{I_e - \bar{g}_L(V - E_L) - \bar{g}_{\mathrm{Na}} m_\infty(V)(V - E_{\mathrm{Na}})}{\bar{g}_{\mathrm{K}}(V - E_{\mathrm{K}})} \tag{22}$$

It typically has the form of a cubic parabola. The steady state of the gating variable n defines the n-nullcline, given by

$$n = n_\infty(V) \tag{23}$$

The $V-$ and $n-$nullclines partition the phase plane into four regions, in each of which the vector field has a different direction:

(a) Both V and n increase.

(b) V decreases but n still increases.

(c) Both V and n decrease.

(d) V increases but n still decreases.

Fine-tuning and Homeostasis

"With four parameters I can fit an elephant, and with five I can make him wiggle his trunk." *John von Neumann*

The Hodgkin-Huxley model has been very successful in explaining the biophysical mechanisms underlying action potential generation. The combination of different types of voltage-dependent ion channels could give rise to a variety of complex activity patterns. One prominent example is the stomatogastric ganglion neurons in the lobster or crabs. Experimentalists have been able to identify 7-8 voltage-dependent conductances in a single cell, and detailed computer models based on Equation 7 could achieve a high degree of agreement with the experimental data. However, one must systematically search the parameter space for the conductances to reproduce, for example, the triphasic rhythmic bursting pattern seen in PD/AB cells. This task turns out to be really complex. Given the large variety of protein expression in different cells and across different animals, it is not clear how the neuron itself is able to solve this problem. Clearly, it needs a robust solution, otherwise the function of the whole system will screw up.

What are possible solutions that might avoid fine-tuning the system? The expression level of membrane channel proteins depends on the mRNA expression level, and the mRNA expression level depend on transcription factor activation. Many important transcription factors in the cell are known to be Ca^{2+} dependent or dependent on other Ca^{2+} sensing enzymes. Moreover, Intracellular Ca^{2+} is a good indicator of cellular excitability. Therefore, some feedback control rules -using intracellular $[Ca^{2+}]$ as single physiological variable - may be used to specify and maintain the activity pattern of a neuron by regulating the ion channel conductance. Below, I will discuss one such model developed by O'Leary and Marder, which is inspiring and might point towards the right direction.

Let us denote m_i as the concentration of mRNA that encodes channel protein g_i. Here the lower case i denotes a specific type of ion channel. We now make an assumption that the expression rate for mRNA is down-regulated by $[Ca^{2+}]$.

$$\frac{dm_i}{dt} = \alpha_{m_i} - \beta_{m_i}[Ca^{2+}]. \tag{24}$$

Here α_m is the forward synthesis rate of mRNA, and the negative sign indicates that $[Ca^{2+}]$ will down-regulate mRNA synthesis. Now we might rewrite this equation by introducing $Ca^{2+}_{tgt} = \alpha_{m_i}/\beta_{m_i}$, and $\tau_i = 1/\beta_{m_i}$. Then we have

$$\tau_i \frac{dm}{dt} = Ca^{2+}_{tgt} - [Ca^{2+}], \tag{25}$$

Equation 25 implies that the average concentration of calcium will approach a specific "target" value Ca^{2+}_{tgt} at the steady state. The channel protein g_i expression rate is given by

$$\frac{dg_i}{dt} = \alpha_g m_i - \beta_g g_i, \tag{26}$$

where α_g and β_g are synthesis and degradation rates respectively. Now when the system approaches the steady state, each m_i as well as g_i approaches a value that is dependent on the integral error of calcium signal:

$$g_i \sim m_i = \frac{1}{\tau_i} \int (Ca^{2+}_{tgt} - [Ca^{2+}])dt$$

One interesting prediction of this model is that the steady state conductances for different ions are strongly correlated. When taking the ratios, the integral cancels so that

$$\frac{g_i}{g_j} \approx \frac{\tau_j}{\tau_i}.$$

Different mRNA expression rate constant τ_i specifies the correlation of each conductance. This is in agreement with experimental data, in which strong correlations of ion channel expression were found for different cell types. When combining the above two equations with the Hodgkin-Huxley type model, we could then describe how a single neuron might self-regulate over time (or over development) to achieve a specific activity pattern.

$$C\frac{dV}{dt} = \sum_{i=1}^{N} \bar{g}_{max} m_i^{p_i} h_i^{q_i} (V - E_i)$$

$$[Ca^{2+}] = K \exp(V/V_0)$$

The functional form of $[Ca^{2+}]$ is chosen so that it is a monotonically increasing function of membrane potential. By keeping the mean calcium concentration at some targeted value, the model could indeed self-tune itself to generate the

desired activity pattern. However, a few outstanding questions remain open. It is likely that some conductances will be down-regulated by calcium while others will be up-regulated by calcium. However, this model is completely agnostic about this. Incorporating these factors into the model remains a challenging problem.