

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

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

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 $\text{G}\Omega$ (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

$$P_K = n^k, \quad (2)$$

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

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

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

$$\tau_n \frac{dn}{dt} = n_\infty - n. \quad (4)$$

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

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

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

$$P_{\text{Na}} = m^k h. \quad (6)$$

Here m is similar to n for the potassium channel. Hodgkin and Huxley 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

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

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

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

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

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.

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

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

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