Parallel conductance model

So far we have modelled neuronal membranes by just one resistance (conductance) variable. We now split this into several conductances (see Fig. 1). We will treat the K and Na channels as having a variable resistance that depends on voltage.

Previously we considered a membrane equation of the form:

\[ I = C \frac{dV}{dt} + g(V - V_{rest}) \]

We now replace this with:

\[ I = C \frac{dV}{dt} + g_K(V, t)(V - E_K) + g_{Na}(V, t)(V - E_{Na}) + g_L(V - E_L) \]

where \( g_L \) is the “leak” conductance, including all other conductances apart from K and Na.

The form of the \( g(V, t) \) functions

In a seminal mathematical model Hodgkin and Huxley (Nobel Prize in Physiology or Medicine, 1963) proposed that the K and \( Na^+ \) conductances could be written as products of gating variables and maximum conductances:

\[ g_K(V, t) = Y_K(V, t) \overline{g}_K \]
\[ g_{Na}(V, t) = Y_{Na}(V, t) \overline{g}_{Na} \]

where \( Y_K \) and \( Y_{Na} \) are gating variables between 0 and 1 and \( \overline{g}_K \) and \( \overline{g}_{Na} \) are maximum conductances. Comparing their experimental data with a model of an ion channel as a voltage-dependent gate (Fig. 2; mathematical details beyond the scope of this course), Hodgkin and Huxley proposed that in particular:

\[ g_K(V, t) = n^4 \overline{g}_K \]
\[ g_{Na}(V, t) = m^3 h \overline{g}_{Na} \]

where \( n, m \) and \( h \) are the gating variables in the gate model. Each has first-order kinetics, i.e. follows an equation of the form

\[ \frac{dn}{dt} = \alpha_n (1 - n) - \beta_n n \]

where \( \alpha_n \) and \( \beta_n \) are functions of voltage:

\[ \alpha_n(V) = \alpha_0 e^{\gamma z F V / RT} \]
\[ \beta_n(V) = \beta_0 e^{-(1 - \gamma) z F V / RT} \]

and similarly for \( m, h \).

Since the \( \alpha \)'s and \( \beta \) functions are independent of time, the equations for \( n(t), m(t), h(t) \) can be easily solved to give

\[ n(t) = n_0 - \left[ (n_0 - n_\infty) \left( 1 - e^{-t/\tau_n} \right) \right] \]

where

\[ n_\infty = \frac{\alpha_n}{\alpha_n + \beta_n}, \quad \tau_n = \frac{1}{\alpha_n + \beta_n} \]

and similarly for \( m, h \).
The Hodgkin-Huxley equations

Thus finally we have

\[ I = C \frac{dV}{dt} + g_K n^4 (V - E_K) + g_{Na} m^3 h (V - E_{Na}) + g_L (V - E_L) \]

or equivalently

\[ I = C \frac{dV}{dt} + g_K \left( (n_0 - n_\infty) \left( 1 - e^{-t/\tau_n} \right) \right)^4 (V - E_K) + g_{Na} m_\infty^3 h_0 \left( 1 - e^{-t/\tau_m} \right)^3 e^{-t/\tau_n} (V - E_{Na}) + g_L (V - E_L) \]

(note that \( m_0 \) and \( h_\infty \) are negligibly small).

While these equations cannot be solved analytically they can be easily simulated numerically. They match remarkably well with data from the squid giant axon (Fig. 3). How each of the variables changes during an action potential is shown in Fig. 4. The basic mechanism of spike generation is summarized in Fig. 5.

Spike propagation

It is possible to calculate the speed at which spikes propagate along axons. We must now treat voltage a function of space as well as time (Fig. 6). Using cable theory (not covered in this course) we can derive the equation:

\[ \frac{a}{2R_i} \frac{\partial^2 V}{\partial x^2} = C_m \frac{\partial V}{\partial t} + I_K + I_{Na} + I_L \]

where \( R_i \) is the longitudinal resistance of the axon. This is a partial differential equation that is in general hard to solve. However, since we know that spikes propagate with approximately constant speed we can use wave equation:

\[ \frac{\partial^2 V}{\partial x^2} = \frac{1}{\theta^2} \frac{\partial^2 V}{\partial t^2} \]

where \( \theta \) is the conduction velocity. This allows us to replace the \( \frac{\partial^2 V}{\partial x^2} \) term with a \( \frac{\partial^2 V}{\partial t^2} \) term, giving us an ordinary differential equation:

\[ \frac{a}{2R_i \theta^2} \frac{d^2 V}{dt^2} = C_m \frac{dV}{dt} + I_K + I_{Na} + I_L \]

This is relatively easy to solve, giving us

\[ \theta = \sqrt{Kn / 2R_i C_m} \]

where \( K \) is an experimentally measurable constant. For the squid giant axon one obtains \( \theta \approx 20 \) m/sec, which is in good agreement with experimental measurements.

Mammalian neurons

Mammalian neurons have additional types of ion channels. For instance more than 10 channels can be involved in spike generation in human neocortical neurons. One can write down generalizations of the Hodgkin-Huxley equations to describe these situations. But the behaviour of high-dimensional nonlinear differential equations is difficult to visualize, and even more difficult to analyse.
**Simplification of the Hodgkin-Huxley equations**

The Hodgkin-Huxley equations:

\[ I = C \frac{dV}{dt} + g_K n^4 (V - E_K) + g_Na m^3 h (V - E_{Na}) + g_L (V - E_L) \]

are 4-dimensional, that is \( m, n, h \) and \( V \) all change with time. However, since the dynamics of \( m \) is much faster than \( n, h \) or \( V \), and the time constants for \( n \) and \( h \) are roughly the same, it is possible to reduce the system to only two important variables. This can be done in several different ways. This allows much easier visualization, and much more mathematical analysis.

**Example: The Wilson model**

This simplification of the Hodgkin-Huxley equations can be written as

\[ C \frac{dV}{dt} = I - w g_K (V - E_K) - g_Na (V - E_{Na}) \]

\[ \frac{dw}{dt} = \frac{1}{\tau_w} [b(V) - w] \]

where \( w \) is a “recovery variable”. Although these equations are much simpler, they still produce interesting spiking behaviour. This is illustrated in Fig. 7. Also shown is a phase-plane analysis of the model.

**Summary**

- The Hodgkin-Huxley equations were the first quantitative description of action potentials, and are still highly relevant today.
- They can be simplified in various ways to two-dimensional systems of equations, which are much easier to analyse.

**Recommended reading**


Figure 1: The circuit representing a neuron can be broken up into different conductances representing different channels. Here the Na and K channel are voltage-dependent, and all other conductances are collected together as the “leak” conductance $g_L$.

Figure 2: Gating of membrane channels. In both figures, the interior of the neuron is to the right of the membrane, and the extracellular medium is to the left. A A cartoon of gating of a persistent conductance. The gate is opened and closed by a sensor that responds to the membrane potential. The channel also has a region that selectively allows ions of a particular type to pass through the channel. B A cartoon of the gating of a transient conductance. The activation gate is coupled to a voltage sensor (circled $+$) and acts like the gate in A. A second gate, denoted by the ball, can block that channel once it is open. The top figure shows the channel in a deactivated (and deinactivated) state. The middle panel shows an activated channel, and the bottom panel shows an inactivated channel. Only the middle panel corresponds to an open, ion-conducting state.
Figure 3: The upper trace shows the shape of the action potential theoretically predicted by Hodgkin and Huxley. The lower trace shows the shape of an action potential they actually recorded from a squid giant axon.

Figure 4: The dynamics of some of the key variables in the Hodgkin-Huxley model. The bottom trace shows the currents injected. The first current injection is too small to cause a spike.
Figure 5: Schematic illustration of the minimal mechanisms necessary for the generation of a spike. A voltage-gated Na channel allows the influx of Na$^+$ ions and thereby the depolarization of the cell. After a short time the Na channel is blocked and a voltage-gated K channel opens. This results in a hyperpolarization of the cell. Finally, the hyperpolarization causes the inactivation of the voltage-gated channels and a return to the resting potential.

Figure 6: Schematic illustrations of spike propagation along an axon.
Figure 7: Behaviour of the Wilson model. A Simulated spike trains. The upper graph simulates fast spiking typical of inhibitory neurons in the mammalian neocortex. The middle graph shows neurons with longer spikes. The lower graph shows that even more complex behaviour, typical of mammalian neocortical neurons, can be modelled. ADP stands for after-depolarizing potential. B Principles of phase plane analysis. C Phase plane of the Wilson model.