Subthreshold Voltage-Gated Channels

In this module we will examine voltage-gated channels that are active in the voltage range around −80 to −50mV. We will not consider spike-generating currents, but only the subthreshold effects voltage-gated channels can have on steady states and stability.

Theoretical Neuroscience, Dayan and Abbott. Chapter 5 p166-173. MIT Press
Spiking Neuron Models, Gerstner and Kistler. Chapter 2 p41-45. Cambridge Univeristy Press

• Ionic Current with a Single Activation Variable

We consider a species of ionic channel that has two states: open and closed with energy $E_o(V)$ and $E_c(V)$ respectively. The rate that a closed channel opens is $\alpha(V)$ and the rate an open channel closes is $\beta(V)$ - the rates are voltage dependent. Let n be the fraction of open channels. The rate of increase of n is equal to the difference between the total opening and closing rates

$$\frac{dn}{dt} = \alpha(V)(1-n) - \beta(V)n. \tag{1}$$

This equation may be rewritten in a more convenient form

$$\tau_n \frac{dn}{dt} = n_\infty - n \quad \text{where} \quad n_\infty = \frac{\alpha(V)}{\alpha(V)+\beta(V)}. \tag{2}$$

The time constant $\tau_n = 1/(\alpha+\beta)$ is voltage dependent, however, in much of the later analysis it will be considered constant. The quantity $n_\infty(V)$ gives the fraction of channels open in the steady state. The time constant τ_n measures how quickly n tracks the voltage-dependent target n_∞ as the voltage changes.

Thermodynamics tells us that in the steady state the probability of being in a state with energy E is proportional to e^{-E/k_BT} where k_B is the Boltzmann factor. We assume that the energy depends linearly on voltage: $E = a + bV$. The ratio of closed to open states must follow

$$\frac{1-n_\infty}{n_\infty} = \exp\left(-\frac{E_c - E_o}{k_BT}\right) = \exp\left(-\frac{V - V_{1/2}}{\Delta_V}\right) \tag{3}$$

where in the second identity the energy difference has been expanded as a function of voltage up to linear order. On rearragning for n_∞ we get

$$n_\infty = \frac{1}{1 + e^{-(V-V_{1/2})/\Delta_V}}. \tag{4}$$

This is a sigmoidal activation function with $V_{1/2}$ being the voltage where half the channels are open and with Δ_V being the width of the activation curve. The sign of Δ_V determines whether the channel is: for Δ_V positive, a *depolarisation* activated channel (it opens when the voltage increases towards 0mV); or for Δ_V negative, a *hyperpolarisation* activated channel (opening when the voltage decreases away from 0mV). The ionic current flowing out of the cell through this gated channel is therefore

$$I_n = g_n n(V - E_n) \tag{5}$$

where g_n is the total conductance per unit area of membrane through these channels when they are all open. The reversal potential E_n of the channel depends upon which species of ion it carries.

• A Two-Variable Model and the Steady States

The dynamics of the membrane voltage are now governed by two equations; a voltage equation for the charging of the membrane due to the ionic currents and the dynamics of the activation variable n

$$C\frac{dV}{dt} = g_L(E_L - V) + g_n n(E_n - V) + I_{app} \quad (6)$$

$$\tau_n\frac{dn}{dt} = n_\infty(V) - n. \quad (7)$$

In the steady state the activation variable is given by $n^* = n_\infty(V^*)$ where, for $I_{app} = 0$, the steady-state voltage V^* satisfies

$$V^* - E_L = \frac{(E_n - E_L)g_n n_\infty}{g_L + g_n n_\infty}. \quad (8)$$

The resting potential V^* is higher or lower than the leak reversal depending on the sign of $(E_n - E_L)$. If $(E_n - E_L) > 0$ it is a *depolarising* current because it increases the voltage from its leak value. If $(E_n - E_L) < 0$ it is a *hyperpolarising* current because it decreases the voltage from the leak value.

• Phase-Plane Analysis

A convenient way to analyse equation (8) is to rewrite the equations in the form

$$\tau_v\frac{dV}{dt} = V_\infty(n) - V + RI_{app} \quad (9)$$

$$\tau_n\frac{dn}{dt} = n_\infty(V) - n. \quad (10)$$

where $\tau_v = CR$ and $R = (g_L + ng_n)^{-1}$ has units of resistance and $V_\infty(n)$ is found from (8) to be

$$V_\infty(n) = \frac{E_L g_L + E_n g_n n}{g_L + g_n n}. \quad (11)$$

We continue with the $I_{app} = 0$ case. When $n = n_\infty$ the rate of change of n is zero. When $V = V_\infty$ the rate of change of voltage is zero. These lines in the V, n plane are called *nullclines* and the fixed points are found at their interactions. The nullclines are better written as functions of V by inverting the function $V = V_\infty(n)$ so that $n_1 = V_\infty^{-1}(V)$ and $n_2 = n_\infty(V)$

$$n_1 = \frac{g_L}{g_n}\left(\frac{V - E_L}{E_n - V}\right) \qquad n_2 = \frac{1}{1 + e^{-(V - V_{1/2})/\Delta_V}}. \quad (12)$$

On plotting these two equations on a graph of V (x-axis) versus n (y-axis) it is straightforward to see that there are two cases: (i) if the gradients of n_1 and n_2 have the same sign (a hyperpolarisation-activated hyperpolarising current or a depolarisation-activated depolarising current) it is possible to have one or three fixed points; (ii) if the gradients have different sign (a hyperpolarisation-activated depolarising current or a depolarisation-activated hyperpolarising current) it is only possible to have one fixed point. Case (i) for which the gradients have the same sign corresponds to positive feedback - when the voltage moves away from rest the voltage-gated currents amplify the change. Case (ii) for which the gradients have different signs corresponds to negative feedback - when the voltage moves away from rest the voltage-gated currents act to counter the change.

• Linearisation of the Two-Variable Model

Equations (9) and (10) are non-linear and hard to study analytically. One method is to linearise the equations near a fixed point. The forms of the eigenfunctions of the two-variable system then give information on the fixed-point stability. On writing $V = V^* + \delta V$ and $n = n^* + \delta n$ we get

$$\tau_v \frac{d\delta V}{dt} = \left.\frac{dV_\infty(n)}{dn}\right|_{n*} \delta n - \delta V \tag{13}$$

$$\tau_n \frac{d\delta n}{dt} = \left.\frac{n_\infty(V)}{dV}\right|_{V*} \delta V - \delta n \tag{14}$$

where τ_n and τ_v are constants:

$$\tau_v = \frac{C}{g_L + g_n n^*}. \tag{15}$$

It proves convenient to convert δn to a voltage-like variable $y = \delta n/(dn_\infty/dV|_{V^*})$ and also to rescale time by $t = s\tau_n$. Writing δV as v we get

$$\frac{dv}{ds} = -Pv + Qy \tag{16}$$

$$\frac{dy}{ds} = v - y \tag{17}$$

where

$$P = \frac{\tau_n}{\tau_v} \quad \text{and} \quad Q = \frac{\tau_n}{\tau_v} \left.\frac{dV_\infty(n)}{dn}\right|_{n^*} \left.\frac{dn_\infty(V)}{dV}\right|_{V^*}. \tag{18}$$

It can be noted that the sign of Q signifies whether the feedback is positive or negative (see the previous section) and that the gradients can be related to the tangents of the phase-plane analysis via

$$\left.\frac{dV_\infty(n)}{dn}\right|_{n^*} = \left(\left.\frac{dn_1(V)}{dV}\right|_{V^*}\right)^{-1}. \tag{19}$$

The eigenfunctions $\lambda_\pm$ of this equation set satisfy

$$\lambda^2 + (P+1)\lambda + P - Q = 0 \quad \text{so that} \quad \lambda = \frac{1}{2}\left(-(P+1) \pm \sqrt{(P+1)^2 + 4(Q-P)}\right) \tag{20}$$

from which the stability of the equations may be analysed. If λ is real then an instability can occur when $\lambda_+ > 0$ which happens when $Q > P$. Complex roots (damped oscillations in the voltage) appear when

$$(P-1)^2 + 4Q < 0 \quad \text{so that} \quad Q < -\frac{1}{4}(P-1)^2. \tag{21}$$

If $P + 1 < 0$ the complex roots are unstable and spontaneous oscillations are possible. For the cases considered so far $P > 0$ (see Eq 18). However, there are circumstances where the effective conductance can become negative (see Questions). It can be noted that $Q < 0$, the case of negative feedback, is required for damped oscillatory solutions, though this is not sufficient.