Rate constants as probabilities

Consider again the following model:

$$C \underset{\beta(v)}{\overset{\alpha(v)}{\rightleftarrows}} O$$

Probabilistic interpretation of α and β:

$$\alpha : P(C \to O \text{ in } dt) = \alpha dt$$

$$\beta : P(O \to C \text{ in } dt) = \beta dt$$

Probability that the channel is open at time $t + dt$:

$$\begin{aligned} P(O, t+dt) &= P(C,t) \cdot P(C \to O \text{ in } dt) \\ &+ P(O,t) \cdot P(\text{not } \ O \to C \text{ in } dt) \\ &= P(C,t) \cdot (\alpha dt) + P(O,t) \cdot (1 - \beta dt) \end{aligned}$$

$$\begin{aligned} P(O, t+dt) &= P(C,t) \cdot (\alpha dt) + P(O,t) \cdot (1 - \beta dt) \\ &= (1 - P(O,t)) \cdot (\alpha dt) + P(O,t) \cdot (1 - \beta dt) \end{aligned}$$

since $P(C,t) + P(O,t) = 1$.
Divides by dt and rearranges:

$$\frac{P(O, t+dt) - P(O,t)}{dt} = \alpha \cdot (1 - P(O,t)) - \beta \cdot P(O,t)$$

Going to the limit:

$$\frac{dP(O,t)}{dt} = \alpha \cdot (1 - P(O,t)) - \beta \cdot P(O,t)$$

Which we recognise this as the usual gating equation.

The general case with n different states

We write $S(t) = j$ if the system is in state j at time t, and define

$$\phi_j(t) = P(S(t) = j).$$

k_{ij} is the probability rate going from $S = i$ to $S = j$:

$$k_{ij} dt = P(S(t+dt) = j | S(t) = i)$$

Probability of staying $S = i$:

$$P(S(t+dt) = i | S(t) = i) = 1 - \sum_{j \neq i} k_{ij} dt = 1 - K_i dt$$

where $K_i = \sum_{i \neq j} k_{ij}$

Time evolution of $\phi_j(t)$

$$\begin{aligned} \phi_j(t+dt) &= \phi_j(t) \cdot P(\text{staying in } j \text{ for } dt) \\ &+ \sum_{i \neq j} \phi_i(t) P(\text{enter } j \text{ from } i \text{ in } dt) \\ &= \phi_j(t) \cdot (1 - K_j dt) + \sum_{i \neq j} \phi_i(t) k_{ij} dt \end{aligned}$$

Divide by dt and rearrange:

$$\frac{\phi_j(t+dt) - \phi_j(t)}{dt} = -K_j \phi_j(t) + \sum_{i \neq j} \phi_i(t) k_{ij}$$

And in the limit:

$$\frac{d\phi_j(t)}{dt} = \sum_{i=1}^{n} k_{ij} \phi_j(t), \quad k_{ii} = -K_i$$

Waiting time

How long time (T_i) does the system spend in a state S_i before leaving? We define $P_i(t) := P(T_i < t)$.
Note $K_i dt = P(\text{leaving } S_i \text{ during } dt)$

$$\begin{aligned} P_i(t+dt) &= P(\text{transition has already occurred at } t) \\ &\quad + P(\text{not occurred yet}) \cdot P(\text{it takes place in this interval}) \\ &= P_i(t) + (1 - P_i(t)) \cdot K_i dt \end{aligned}$$

Divides, and goes to the limit:

$$\frac{dP_i(t)}{dt} = K_i(1 - P_i(t))$$

Which has the solution:

$$P_i(t) = 1 - e^{-K_i t}$$

Waiting time

$P_i(t)$ is the cumulative distribution. The probability density function is easily found:

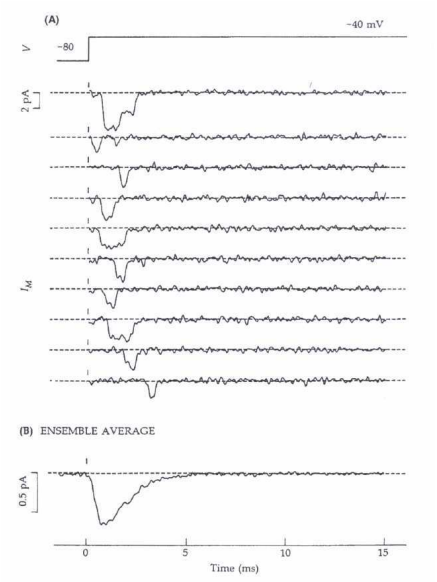
$$p_i(t) = \frac{dP_i(t)}{dt} = K_i e^{-K_i t}$$

The mean waiting time is the expected value of T_i:

$$E(T_i) = \int_0^\infty t p_i(t) dt = \frac{1}{K_i}$$

(If K_i does not depend on t)

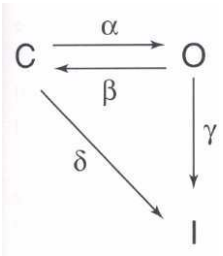
Single channel recordings



Single channel analysis

Single channel recordings contain statistical information that can be used to estimate transition rate:

- Ratio of experiments where channel directly inactivates
- Distribution of the number of times the channel re-opens before finally inactivating
- Mean open time
- Mean close time



1: If first (and final) transition is $C \to I$

The channel is initially in the closed state.
As the transmembrane potential is elevated two things can happen:

$$P(C \to O) = A = \alpha/(\alpha + \delta)$$

$$P(C \to I) = \delta/(\alpha + \delta) = (\delta - \alpha + \alpha)/(\alpha + \delta) = 1 - A$$

Estimation of $1 - A$: The ratio of experiments where the channel fail to open.

2 & 3: Time spent in C and O

In the experiments where channels do open, record the time spent in C.
The distribution is described by: $P(t) = 1 - \exp(-\alpha)$
The average waiting time will be $E(T) = 1/\alpha$.

Record the duration the channel is open. The distribution is described by: $P(t) = 1 - \exp(-\beta - \gamma)$
The average waiting time will be $E(T) = 1/(\beta + \gamma)$.

4: Number of re-openings

Probability that the channels opens k times before inactivating:

$$\begin{aligned} P[N = k] &= P[N = k \text{ and finally } O \to I] + P[N = k \text{ and finally } C \to I] \\ &= A^k B^{k-1}(1 - B) + A^k B^k (1 - A) \\ &= (AB)^k \left(\frac{1 - AB}{B} \right) \end{aligned}$$

Where $A = \alpha/(\alpha + \delta)$ and $B = \beta/(\beta + \gamma)$
B can be estimated by fitting to the observed data.

Excitability

Excitable Cells 5.1

Unlike other cells, excitable cells can be triggered to set off an action potential.

During the action potential the transmembrane potential departs from its resting potential, reaches a peak potential and returns to the resting potential after some time.

Nerve cells and cardiac cells uses the action potential as a signal to neighboring cells.

The trigger must be of a certain size, if below the threshold the cell will not “fire”.

The Hodgkin-Huxley Model

Developed to study the action potential of the squid nerve cells.

Assumed three different current I_{Na}, I_{K} and I_{L}
Assumed also linear current-voltage relationship:

$$-C_m\frac{dv}{dt} = I_{\text{ion}} = g_{\text{Na}}(v - v_{\text{Na}}) + g_{\text{K}}(v - v_{\text{K}}) + g_{\text{L}}(v - v_{\text{L}})$$

Can collect the current terms due to linearity:

$$C_m\frac{dv}{dt} = -g_{\text{eff}}(v - v_{\text{eq}})$$

where

$$g_{\text{eff}} = g_{\text{Na}} + g_{\text{K}} + g_{\text{L}}$$

and

$$v_{\text{eq}} = \frac{g_{\text{Na}}v_{\text{Na}} + g_{\text{K}}v_{\text{K}} + g_{\text{L}}v_{\text{L}}}{g_{\text{eff}}}$$

v_{eq} is a weighted average of the individual equilibrium potentials.
The weighing factors are time and voltage dependent.

A steady applied current I_{app} moves the membrane potential to different equilibrium.

$$C_m\frac{dv}{dt} = -g_{\text{eff}}(v - v_{\text{eq}}) + I_{\text{app}} = 0$$

Implies

$$v = v_{\text{eq}} + \frac{1}{C_m\, g_{\text{eff}}}I_{\text{app}}$$

The applied current will be compensated by an ionic current going the opposite way, thus the net current will be zero.

For a sufficiently large I_{app}, v will pass the threshold potential and an action potential is triggered. The conductivities will vary greatly.

Voltage Clamp measurements

The transmembrane potential is forced by an applied current to a fixed value.

Since $I_{\text{ion}} = -I_{\text{app}}$ for a fixed v, we can measure I_{ion} as a function of time for a given level of v.

Since v is fixed the observed variations must be due to temporal variation in the conductivities.

Total membrane current for different steps, 5.1

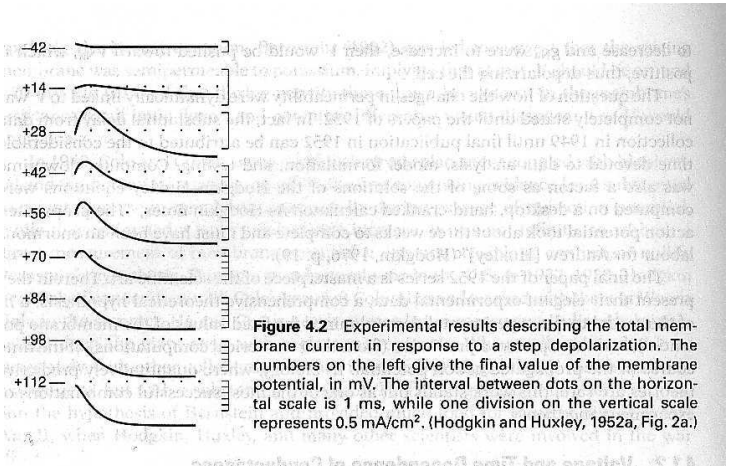


Figure 4.2 Experimental results describing the total membrane current in response to a step depolarization. The numbers on the left give the final value of the membrane potential, in mV. The interval between dots on the horizontal scale is 1 ms, while one division on the vertical scale represents 0.5 mA/cm². (Hodgkin and Huxley, 1952a, Fig. 2a.)

From measurements to models

Initially, Hodgkin and Huxley assumed $I_{\text{ion}} = I_{\text{Na}} + I_{\text{K}}$. Two kind of experiments conducted:

- 1: Normal concentrations
- 2: $[\text{Na}]_e$ replaced by cohline $\Rightarrow$ affects I_{Na} but not I_{K}.

Assumed further:

- Initially $I_{\text{K}} = 0$
- $I^1_{\text{Na}}/I^2_{\text{Na}}$ = C, constant
- $I^1_{\text{K}} = I^2_{\text{K}}$

Once I^1_{ion} and I^2_{ion} is recorded we can determine C from the first and the second assumptions.

Expressions for the currents in terms of measurable quantities can now be obtained:

$$I^1_{\text{Na}} = \frac{C}{C-1}(I^1_{\text{ion}} - I^2_{\text{ion}})$$

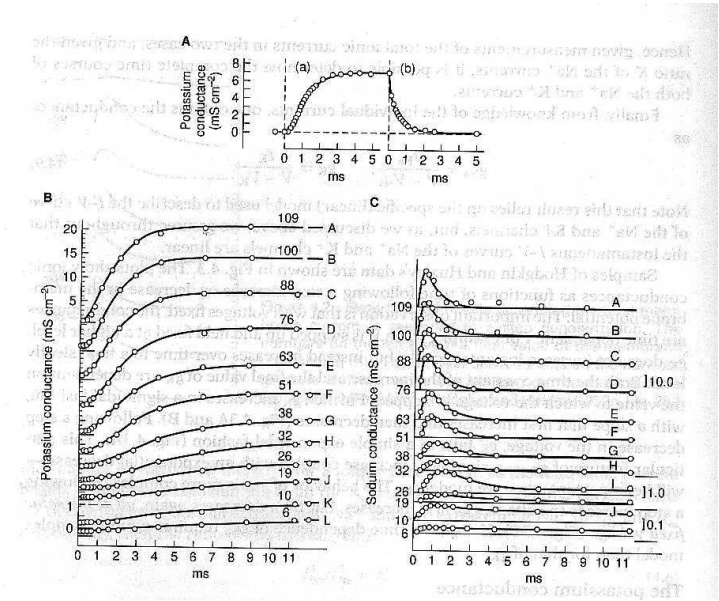
$$I_{\text{K}} = \frac{1}{1-C}(I^1_{\text{ion}} - CI^2_{\text{ion}})$$

Assuming linear current-voltage relationships we get expressions for the conductivities:

$$g_{\text{Na}} = \frac{I_{\text{Na}}}{V - V_{\text{Na}}}, \quad g_{\text{K}} = \frac{I_{\text{K}}}{V - V_{\text{K}}}$$

For each pair of voltage clamp experiment (with a given voltage step), we now have a time course for g_{Na} and g_{K}.

Potassium and Sodium conductance



Model for the Potassium conductance

Assumed $\frac{dg_{\mathsf{K}}}{dt} = f(v,t)$.

Ended up with introducing a second variable:

$$g_{\mathsf{K}} = \overline{g}_{\mathsf{K}} n^4, \text{ with } \frac{dn}{dt} = \alpha(v)(1-n) - \beta(v)n$$

and $\overline{g}$ is the maximum conductance. Forth power was chosen to get the correct shape of the solution.

The solution of

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

with constant coefficients is

$$n(t) = n_\infty + (n(0) - n_\infty)e^{-t/\tau_n}$$

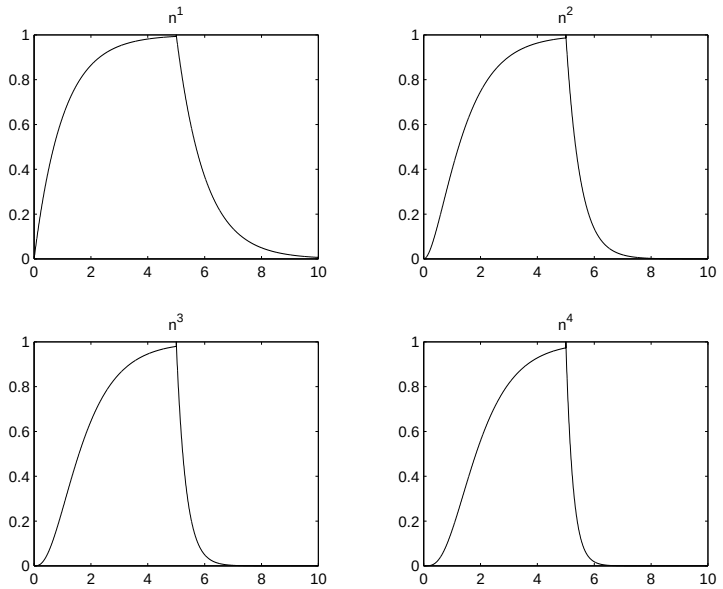
If we assume that $n_\infty(0) = 0$ a step from from 0 to v yields:

$$\begin{aligned} n(t) &= n_\infty(v) + (n_\infty(0) - n_\infty(v))e^{-t/\tau_n(v)} \\ &= n_\infty(v)(1 - e^{-t/\tau_n(v)}) \end{aligned}$$

A step in the other direction gives:

$$\begin{aligned} n(t) &= n_\infty(0) + (n_\infty(v) - n_\infty(0))e^{-t/\tau_n(0)} \\ &= n_\infty(v)e^{-t/\tau_n(0)} \end{aligned}$$

Gating variable raised to different powers



Sodium conductance model

H&H realized that two different sub units were at work. Ended up with

$$\frac{dg_{\text{Na}}}{dt} = \overline{g}_{\text{Na}} m^3 h$$

Values for m_τ, m_∞, h_τ and h_∞ obtained by fitting the solution to plots of g_{Na}.

The Hodgkin-Huxley model

Introduces a third current, not time dependent:

$$C_m \frac{dv}{dt} = -\overline{g}_{\text{K}} n^4 (v - v_{\text{K}}) - \overline{g}_{\text{Na}} m^3 h (v - v_{\text{Na}}) - \overline{g}_{\text{L}} (v - v_{\text{L}})$$

with

$$\frac{dg}{dt} = \alpha_g(v)(1 - g) - \beta_g(v) g, \quad g = m, h, n$$

Model based on voltage clamp measurement. How will it behave under normal conditions?

The model will predict the action potential.

Analysis of the Hodgkin-Huxley model

Qualitative analysis, 5.1.3

Would like to reduce the number of state variables to simplify analysis.

One way is to treat the slowest variables as constants. Of the three gating variables m has the fastest dynamics. (Controls the activation of the Na-current).

Reduced model:

$$C_m \frac{dv}{dt} = -\overline{g}_{\text{K}} n_0^4 (v - v_{\text{K}}) - \overline{g}_{\text{Na}} m^3 h_0 (v - v_{\text{Na}}) - \overline{g}_{\text{L}} (v - v_{\text{L}})$$

Equilibria in the reduced HH-model

The nullclines $\frac{dv}{dt} = 0$ and $\frac{dm}{dt} = 0$ form curves in the (v, m)-plane. Their intersections are the equilibria.

Initially three steady states v_r, v_s and v_e. v_r and v_e are stable and v_s unstable.

As n_0 and h_0 changes, the $\frac{dv}{dt} = 0$ line will shift. v_e will decrease, coincide with v_s and disappear.

v_r will become the only stable equilibrium.

Phase plot for the fast sub-system

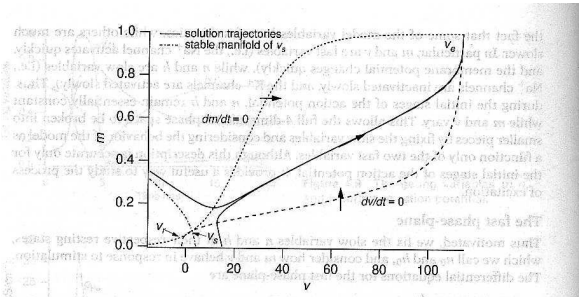


Figure 4.10 The Hodgkin–Huxley fast phase-plane, showing the nullclines $dv/dt = 0$ and $dm/dt = 0$ (with $h_0 = 0.596$, $n_0 = 0.3176$), two sample trajectories and the stable manifold of the saddle point v_s.

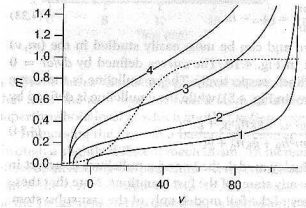


Figure 4.11 The Hodgkin–Huxley fast phase-plane as a function of the slow variables, showing the m nullcline (dashed) and the movement of the v nullcline (solid) and the disappearance of the steady states. For these curves, parameter values are (1) $h_0 = 0.596$, $n_0 = 0.3176$; (2) $h_0 = 0.4$, $n_0 = 0.5$; (3) $h_0 = 0.2$, $n_0 = 0.7$; and (4) $h_0 = 0.1$, $n_0 = 0.8$.

Alternative reduction:

- m is very fast, almost in equilibrium: $m = m_\infty(v)$
- $h + n$ almost constant: $h = 0.8 - n$

We then have

$$C_m \frac{dv}{dt} = -\overline{g}_{\mathsf{K}} n^4 (v - v_{\mathsf{K}}) - \overline{g}_{\mathsf{Na}} m_\infty^3(v) \overbrace{(0.8 - n)}^{h} (v - v_{\mathsf{Na}}) - \overline{g}_{\mathsf{L}} (v - v_{\mathsf{L}})$$

Equilibria found by looking at the crossing of the nullclines $\frac{dv}{dt} = 0$ and $\frac{dn}{dt} = 0$ in the (v, n)-plane.

Phase plot for the fast-slow reduced system

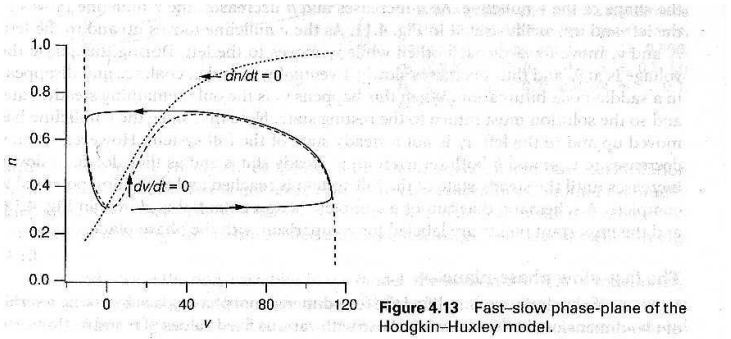


Figure 4.13 Fast–slow phase-plane of the Hodgkin–Huxley model.