

The Hodgkin-Huxley Theory of Excitability

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What is (cell) excitability?

Excitable cells do the following:

1. small applied current \implies fast adjustments of membrane potential to steady level.
2. large enough applied current \implies membrane potential undergoes a large excursion before reverting to steady level.

Non-excitable cells exhibit fast adjustments of membrane potential regardless of the applied current.

Background: Nernst Equilibrium Potential

- Two reservoirs of the ion S , of different concentrations, separated by a membrane.
- Total charge of the reservoirs is 0. Hence S is balanced by another ion S' , of opposite charge.
- Membrane is permeable to S only, not to S' .
- Osmotic pressure drives S from high concentration to low, creating a charge imbalance (voltage, electrical potential difference) across membrane.
- Equilibrium is reached when this membrane potential is balanced by osmotic pressure. This potential at equilibrium is called the *Nernst equilibrium potential* for the ion S and it is given by

$$V_S = \frac{RT}{zF} \ln \left(\frac{[S]_e}{[S]_i} \right),$$

where k = Boltzmann's, F = Faraday's, R = universal gas, T = common temperature of reservoirs in K, $[S]_e$ = external concentration, $[S]_i$ = internal concentration.

- **Observation** Let $V = V_i - V_e$ be the actual membrane potential (with external taken as reference). Then whenever $V \neq V_S$, there will be an induced current carried by S so as to reduce $V - V_S$

Why need a model?

Non-excitable cells obey the *capacitor* model (but excitable ones do not):

$$C_m \frac{dV}{dt} + I_{\text{ion}}(V, t) = 0,$$

- C_m = capacitance of cell membrane
- $V = V_i - V_e$ = membrane potential
- $I_{\text{ion}} = I_{\text{Na}} + I_{\text{K}} + I_{\text{L}} - I_{\text{app}}$

Assumptions of the Capacitance Model

- C_m is constant.
- The following hold *instantaneously*:
 - $I_{\text{Na}} = g_{\text{Na}}(V - V_{\text{Na}})$,
 - $I_{\text{K}} = g_{\text{K}}(V - V_{\text{K}})$,
 - $I_{\text{L}} = g_{\text{L}}(V - V_{\text{L}})$.
- The ionic conductances g_{Na} , g_{K} and g_{L} are constant.

Capacitor Model for Non-excitable Cells

$$C_m \frac{dV}{dt} = -g_{\text{eff}}(V - V_{\text{eq}}) + I_{\text{app}},$$

where

- $g_{\text{eff}} = g_{\text{Na}} + g_{\text{K}} + g_{\text{L}}$ and,
- $V_{\text{eq}} = \frac{g_{\text{Na}}V_{\text{Na}} + g_{\text{K}}V_{\text{K}} + g_{\text{L}}V_{\text{L}}}{g_{\text{eff}}}.$

Thus,

$$V(t) = \left(V_{\text{eq}} + \frac{I_{\text{app}}}{g_{\text{eff}}} \right) \left(1 - \frac{1}{\exp\left(\frac{g_{\text{eff}}t}{C_m}\right)} \right) + \frac{V(0)}{\exp\left(\frac{g_{\text{eff}}t}{C_m}\right)}$$

The time constant C_m/g_{eff} in this model is on the order of 1000 msec.

But this doesn't work for excitable cells. In come Hodgkin & Huxley (HH)! They were awarded the 1963 Nobel Prize in physiology and medicine for their work in modelling the excitability of the squid giant axon.

Hodgkin-Huxley Conjecture

General Assumptions: V_{Na} , V_{K} and V_{L} are constants.

HH retained the following assumptions from the capacitor model:

- $C_m \frac{dV}{dt} + g_{\text{Na}}(V - V_{\text{Na}}) + g_{\text{K}}(V - V_{\text{K}}) + g_{\text{L}}(V - V_{\text{L}}) - I_{\text{app}} = 0.$
- C_m , g_{L} are constant. (Why?)
- The following hold *instantaneously*:
 - $I_{\text{Na}} = g_{\text{Na}}(V - V_{\text{Na}}),$
 - $I_{\text{K}} = g_{\text{K}}(V - V_{\text{K}}),$
 - $I_{\text{L}} = g_{\text{L}}(V - V_{\text{L}}).$

HH therefore conjectured that:

g_{Na} **and** g_{K} **vary with the transmembrane potential.**

The Hodgkin-Huxley theory essentially boils down to modelling the g_{Na} and g_{K} dependences on the transmembrane potential in order to explain the “excursion” behavior exhibited by the squid axon.

Obtaining $g_{\text{Na}}(v)$ & $g_{\text{K}}(v)$ Experimentally - I

The Experimental Technique of the Voltage Clamp:

- induce a sudden jump in the transmembrane potential and then hold it fixed by appropriately controlling a supplied current.
- measure the supplied current = – transmembrane current.

HH found: After such a voltage step (upward), the total ionic current is initially inward, and later becomes outward.

HH further assumed (why?): The initial inward current is carried predominantly by Na^+ , whereas the later outward current predominantly by K^+ .

Obtaining $g_{\text{Na}}(v)$ & $g_{\text{K}}(v)$ Experimentally - II

HH's experimental trick (ingenuity):

- (2) – replaced 90% of extracellular Na^+ with choline
 - but only slightly changing the resting potential (or equivalently, V_{Na} , right?)
- (1) Normal extracellular Na^+ concentration.

HH measured: $K_{\text{init}} := \left(\frac{I_{\text{Na}}^1}{I_{\text{Na}}^2} \right)_{\text{init}}$

This measurement makes sense based on the assumption that the initial current is predominantly carried by Na^+ .

HH further assumed:

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$$K(t) := \left(\frac{I_{\text{Na}}^1}{I_{\text{Na}}^2} \right) (t) = K_{\text{init}}, \quad \text{i.e. constant.}$$

Essentially, they assumed the ratio K is independent of the transmembrane potential. (Right?)

- $I_{\text{K}}^1 = I_{\text{K}}^2$, i.e. K^+ channels are unaffected by the change in extracellular Na^+ concentration.

Obtaining $g_{\text{Na}}(v)$ & $g_{\text{K}}(v)$ Experimentally - III

HH then deduced (I_L dropped out? It will reappear later though.):

$$\left. \begin{aligned} I_{\text{ion}}^1 &= I_{\text{Na}}^1 + I_{\text{K}}^1 \\ I_{\text{ion}}^2 &= I_{\text{Na}}^2 + I_{\text{K}}^2 \end{aligned} \right\} \implies \begin{cases} I_{\text{Na}}^1 &= \frac{K}{K-1} (I_{\text{ion}}^1 - I_{\text{ion}}^2) \\ I_{\text{K}} &= \frac{1}{K-1} (I_{\text{ion}}^1 - K I_{\text{ion}}^2) \end{cases}$$

So finally, HH experimentally obtained

$$g_{\text{Na}}(t) = \frac{I_{\text{Na}}(t)}{V - V_{\text{Na}}}, \quad \text{and} \quad g_{\text{K}}(t) = \frac{I_{\text{K}}(t)}{V - V_{\text{K}}}.$$

Fig. 4.3

Note that V is held fixed during these voltage clamp experiments.

Now, the Hodgkin-Huxley Model

HH proposed:

$$g_K(t) = \overline{g_K} n(t)^4,$$

The function $n(t)$ is a “gating” variable for the K^+ channel which satisfies

$$0 \leq n(t) \leq 1, \quad \tau_n(v) \frac{dn}{dt} = n_\infty(v) - n,$$

where

- $\overline{g_K}$ is a constant,
- $v(t) := V(t) - V_{\text{eq}}$,
- V_{eq} is the resting potential (a constant) of the cell,
- $\tau_n(v)$ is the time “constant” for n at a fixed potential v .
- $n_\infty(v)$ is the “terminal” value of $n(t)$ at the fixed potential v .

Similarly,

$$\begin{aligned} g_{\text{Na}}(t) &= \overline{g_{\text{Na}}} m^3(t) h(t) \\ \tau_m(v) \frac{dm}{dt} &= m_\infty(v) - m, \\ \tau_h(v) \frac{dh}{dt} &= h_\infty(v) - h. \end{aligned}$$

The Full Hodgkin-Huxley Model

$$\begin{aligned}C_m \frac{dv}{dt} &= -\bar{g}_{\text{Na}} n^4 (V - V_{\text{Na}}) - \bar{g}_{\text{K}} m^3 h (V - V_{\text{K}}) - \bar{g}_{\text{L}} (V - V_{\text{L}}) + I_{\text{app}}, \\ \frac{dm}{dt} &= \alpha_m (1 - m) - \beta_m m, \\ \frac{dn}{dt} &= \alpha_n (1 - n) - \beta_n n, \\ \frac{dh}{dt} &= \alpha_h (1 - h) - \beta_h h,\end{aligned}$$

where $\alpha_n(v)$ and $\beta_n(v)$ are related to $n_\infty(v)$ and $\tau_n(v)$ by:

$$n_\infty(v) = \frac{\alpha_n(v)}{\alpha_n(v) + \beta_n(v)}, \quad \tau_n(v) = \frac{1}{\alpha_n(v) + \beta_n(v)},$$

and similarly for $\alpha_m(v)$ and $\beta_m(v)$, $\alpha_h(v)$ and $\beta_h(v)$.

Next, need to determine the functions $m_\infty(v)$, $n_\infty(v)$, $h_\infty(v)$, $\tau_m(v)$, $\tau_n(v)$, and $\tau_h(v)$. And in turn the α 's and β 's.

Determining the α 's and β 's - I

Voltage-clamp experiments again:

The solution to the IVP,

$$\begin{cases} \tau_n(v_0) \frac{dn}{dt} = n_\infty(v_0) - n \\ n(0) = 0 \end{cases}$$

with v_0 fixed, is

$$n(t; v_0) = n_\infty(v_0) \left[1 - \exp\left(-\frac{t}{\tau(v_0)}\right) \right].$$

And, $g_K(t; v_0) = \bar{g}_K n^4(t; v_0)$.

Recall now that HH have experimentally obtained $g_{K,\text{measured}}(t; v_0)$ for a collection of values of v_0 . Thus fitting $g_K(t; v_0)$ to $g_{K,\text{measured}}(t; v_0)$ for each such v_0 yields a discrete set of values for $n_\infty(v)$ and $\tau_n(v)$.

Finally, fitting a smooth curve through these points yields (approximations to) the functions $n_\infty(v)$ and $\tau_n(v)$.

Fig. 4.4

Determining the α 's and β 's - II

Do the same for $\tau_m(v)$, $m_\infty(v)$ and $\tau_h(v)$, $h_\infty(v)$ and get:

Fig. 4.5

Fig. 4.6

Q: Why do the n_∞ 's in Fig. 4.4 and Fig. 4.5 look different?

Dynamics Explained - I

- Initially, $V(0) = V_{\text{eq}} \approx V_K = -70\text{mV}$, and $v(0) = 0$.
- A large enough external current is applied for long enough to raise the membrane potential over a certain threshold. (Then the applied current is turned off, correct?)
- Observation:
 - $\tau_m(v)$ small $\implies m(t)$ tracks $m_\infty(v(t))$ fast.
 - $\tau_n(v) \approx \tau_v(v)$ relatively large $\implies n(t)$ and $h(t)$ track $n_\infty(v(t))$ and $h_\infty(v(t))$ slowly.

Dynamics Explained - II

Results:

- The m gates “swing” open as soon as membrane potential is stepped up. (Note that the h gates were already open at rest; see Fig. 4.5). This causes the initial inward Na^+ current.
- This causes v to rise further, and in turn m itself! This also explains the “overshooting” in the cell’s depolarization, (in contrast to the case of non-excitable cells or the constant-conductances capacitor model.)
- However, as v rises, so does n while τ_n decreases, and hence the response rate of n also increases as v rises. This explains the delayed emergence of the outward K^+ current.
- As v rises, both h and τ_h decrease. Thus inhibition of the Na^+ starts and it occurs at an increasing rate. This explains the eventual diminution of the inward Na^+ current.

Fig. 4.7, 4.8, 4.9