States of Conductance(g_K, g_{Na})

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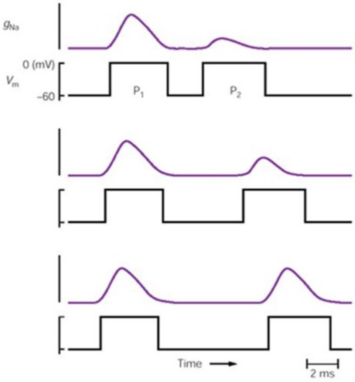
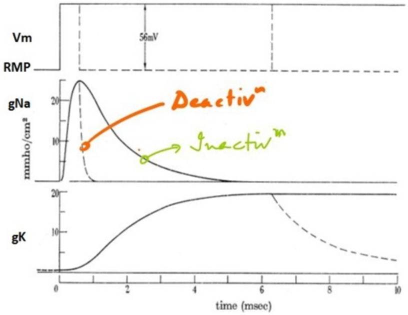
February 11th, 2014

Outline

- Activation, Deactivation and Inactivation
- States of Conductances
- Dependence of g_{Na} & g_{Na} on V_m and t

Activation, Deactivation and Inactivation



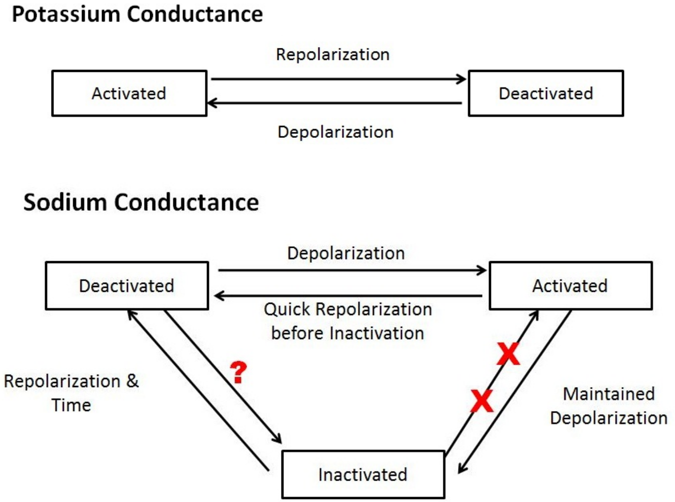


BB 636 Course Material, IIT Bombay

Some Terminology

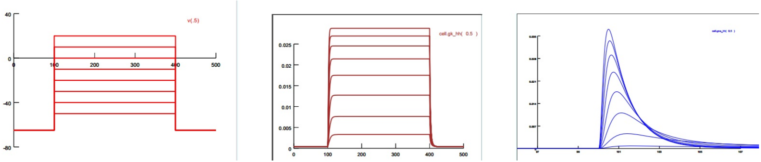
- **Gating**: Conformational changes in an ion channel induced by an extrinsic source (i.e., voltage, ligands, stretch, etc.). Such conformational changes are responsible for functional properties like activation and inactivation.
- **Activation**: Opening of a channel due to the presence of a gating signal.
- **Deactivation**: Closing of a channel due to removal of the gating signal (i.e. the opposite of activation).
- **Inactivation**: Closing of a channel in the continued presence of the gating signal. The term "inactivation" is usually only applied to voltage-gated channels, whereas "desensitization" describes the analogous process for ligand-gated channels.

State of Conductances



Dependence of g_{Na} and g_K on V_m & Time

- Variation of g_{Na} and g_K at different values of V_m
- Both Magnitude & Rate of Change of g_{Na} and g_K vary with the extent of depolarization
- g_{Na} and g_K to be evaluated as functions of voltage & time

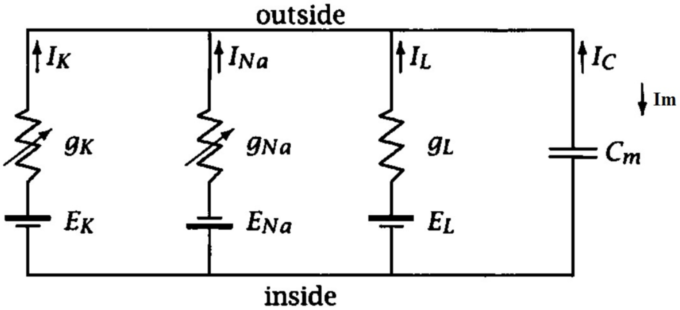


Hodgkin-Huxley Model

Points to be covered

- Parallel Conductance Model for Active Membrane
- Gating Variables
- Modelling $g_K(V_m, t)$ and $g_{Na}(V_m, t)$
- Results from Hodgkin Huxley Model-Fit with Experimental Data
- Summary
- Current Equations for I_{Na}, I_K, I_L and I_C

Parallel Conductance Model for Active Membrane



The equation for membrane current is

$$I_m = I_C + I_K + I_{Na} + I_L \text{ or}$$

$$I_m = C_m \frac{dVm}{dt} + g_K(V_m, t)(V_m - E_K) + g_{Na}(V_m - E_{Na}) + g_L(V_m - E_L)$$

Image from Johnston and Wu, 1994

Modelling $g_K(V_m, t)$ and $g_{Na}(V_m, t)$

$$g_K(V_m, t) = Y_K(V_m, t)\bar{g}_K \qquad g_{Na}(V_m, t) = Y_{Na}(V_m, t)\bar{g}_{Na}$$

where $Y_K(V_m, t)$, $Y_{Na}(V_m, t) =$ function of gating variables between 0 and 1
$\bar{g}_k$, $\bar{g}_{Na}$ = maximum K^+ & Na^+conductances.

- The K^+ channels have an activation variable,n and
- Na^+ channels have an activation variable, m and an inactivation variable,h.

The gating variables

For **Potassium Channels**, there is one gating variable

n (activation gating variable)

For **Sodium Channels**, there is two gating variable

m (activation gating variable)

h (inactivation gating variable)

The gating variables

For **Potassium Channels**, there is one gating variable **n** (activation gating variable)

$$n \underset{\alpha_n}{\overset{\beta_n}{\rightleftharpoons}} (1 - n)$$

$$Activated(Open) \underset{\alpha_n}{\overset{\beta_n}{\rightleftharpoons}} Deactivated(Closed)$$

α_n and β_n are the rate constants (functions of V_m)

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

Solve the differential equation!

Initial condition: At $t = 0, n = n_0$

Potassium Conductance, g_K

$$n(t) = \frac{\alpha_n}{\alpha_n + \beta_n} - \left(\frac{\alpha_n}{\alpha_n + \beta_n} - n_0 \right) \exp\left(-t(\alpha_n + \beta_n)\right)$$

At $t = \infty$, $n_\infty = \dfrac{\alpha_n}{\alpha_n + \beta_n}$, $\tau_n = \dfrac{1}{\alpha_n + \beta_n}$

n_∞ and τ_n = are the steady state value and time constants of 'n' at a particular V_m, respectively.

The equation now becomes

$$n(t) = n_\infty - (n_\infty - n_0) \exp\left(\frac{-t}{\tau_n}\right)$$

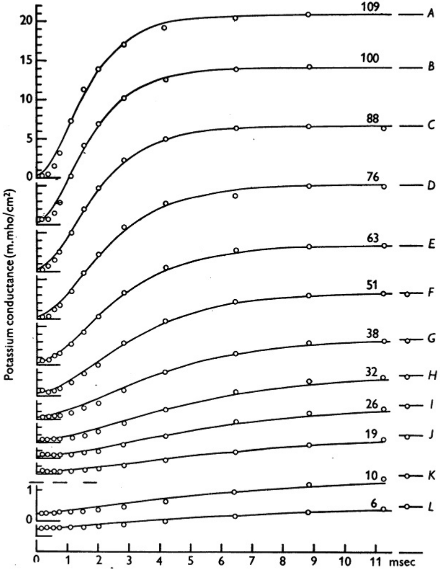
$$g_K(V_m, t) = \left[n_\infty - (n_\infty - n_0) \exp\left(\frac{-t}{\tau_n}\right) \right] \bar{g}_k$$

or $g_K(V_m, t) = [n(V_m, t)] \, \bar{g}_k$

It was found that when $[n(V_m, t)]^4$, the fit with experimental data was very good. Thus, the final equation is

$$g_K(V_m, t) = [n(V_m, t)]^4 \, \bar{g}_k$$

Results from Hodgkin Huxley Model



Sodium Conductance, g_{Na}

There are 2 gating variables: **m**(activation) and **h**(inactivation)

$$m \underset{\alpha_m}{\overset{\beta_m}{\rightleftharpoons}} (1 - m)$$

$$\text{Activated(Open)} \underset{\alpha_m}{\overset{\beta_m}{\rightleftharpoons}} \text{Deactivated(Closed)}$$

$$h \underset{\alpha_h}{\overset{\beta_h}{\rightleftharpoons}} (1 - h)$$

$$\text{Non-inactivated} \underset{\alpha_h}{\overset{\beta_h}{\rightleftharpoons}} \text{Inactivated}$$

α_m, α_h, β_m and β_h are the rate constants (functions of V_m)

Sodium Conductance, g_{Na}

$$\frac{dm}{dt} = \alpha_m(1-m) - \beta_m m,\ m_\infty = \frac{\alpha_m}{\alpha_m + \beta_m},\ \tau_m = \frac{1}{\alpha_m + \beta_m}$$
$$\frac{dh}{dt} = \alpha_h(1-h) - \beta_h h,\ h_\infty = \frac{\alpha_h}{\alpha_h + \beta_h},\ \tau_h = \frac{1}{\alpha_h + \beta_h}$$

The equations for m and h

$$m(t) = m_\infty - (m_\infty - m_0)\exp\left(\frac{-t}{\tau_m}\right)$$
$$h(t) = h_\infty - (h_\infty - h_0)\exp\left(\frac{-t}{\tau_h}\right)$$

But at $t = \infty$, $h_\infty = 0$ as all the channels are in the inactivated state.

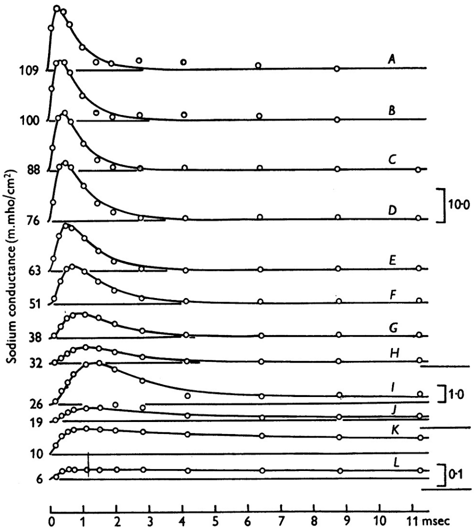
Thus, $h(t) = h_0 \exp\left(\frac{-t}{\tau_h}\right)$

Sodium Conductance, g_{Na}

Now,
$g_{Na}(V_m, t) = [m(V_m, t)h(V_m, t)]\, \bar{g}_{Na}$
But the above equation did not give a good fit with the experimental data. The equations fitted well when the m variable was raised to 3.
Thus, $g_{Na}(V_m, t) = \left[m(V_m, t)^3 h(V_m, t)\right] \bar{g}_{Na}$ or

$$g_{Na}(V_m, t) = \left(m_\infty - (m_\infty - m_0) \exp\left(\frac{-t}{\tau_m}\right)\right)^3 \left(h_0 \exp\left(\frac{-t}{\tau_h}\right)\right) \bar{g}_{Na}$$

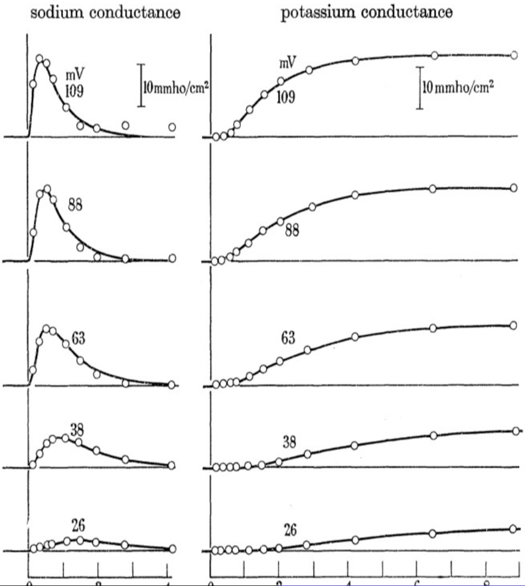
Results From Hodgkin Huxley Model



Summary: How Hodgkin and Huxley did this?

1. Voltage clamp at a different depolarizing voltages
2. Calculate steady state value (x_∞) and time constant, τ at each clamping voltage, V_m (x=n, m or h)
3. Determine α_x and β_x with the following formulae
   $x_\infty = \dfrac{\alpha_x}{\alpha_x + \beta_x}$, $\tau_x = \dfrac{1}{\alpha_x + \beta_x}$
4. Plot the points for α_x and β_x vs. V_m and derive an empirical curve fit equations
5. Use these equations for α_x and β_x to calculate the steady state value (n_∞) and time constants, τ at different V_m.
6. Determine the maximum conductances, $\bar{g}_x$ and initial values using the experimental data. Calculate g_x
7. Check if the values of conductances calculated fit with the experimental data.

Hodgkin-Huxley Results



Use these Current Equations to generate an AP

Potassium Current,I_K

$I_K(V_m,t) = [n(V_m,t)]^4\,\bar{g}_K$

Sodium Current, I_{Na}

$I_{Na}(V_m,t) = \left[m(V_m,t)^3 h(V_m,t)\right]\bar{g}_{Na}(V_m - E_{Na})$ or

Leakage Current, I_L The leakage current is the current carried mostly by Cl^- ions.

$I_L = \bar{g}_L * (V_m - E_L)$

Capacitive Current, I_C

$$I_C = C_m \frac{dv_m}{dt}$$

C_m is the membrane capacitance So we can now calculate the membrane current as

$I_m = I_C + I_K + I_{Na} + I_L$

References

- Foundations of Cellular Neurophysiology, 1st Edition, Johnston and Wu, 1994.
- Hodgkin, Alan L., and Andrew F. Huxley. "A quantitative description of membrane current and its application to conduction and excitation in nerve." The Journal of physiology 117.4 (1952): 500.