Single Neuron Modeling: Conductance-Based Models

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CONTENTS

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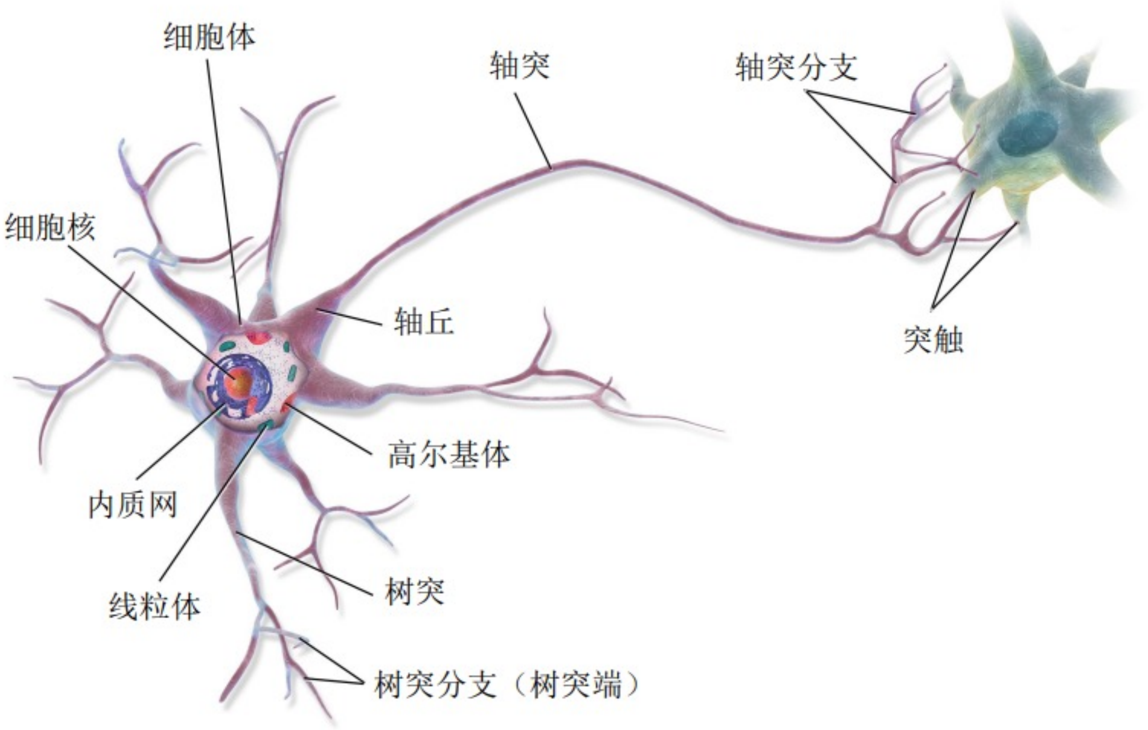
01

Neuronal structure, resting potential, and equivalent circuits

Neuronal structure

Components of a neuron:

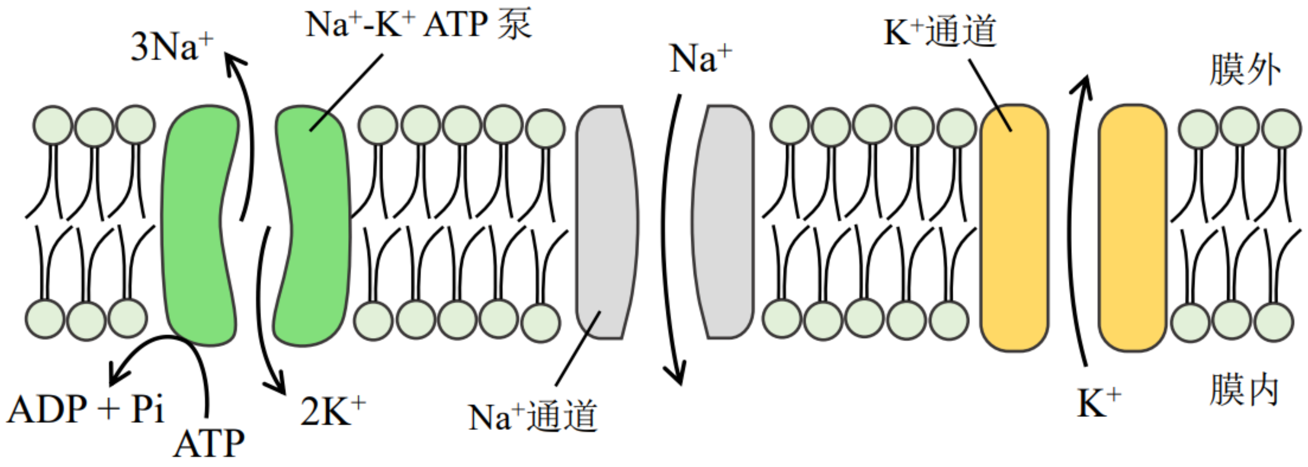
- Cell body/soma
- Axon
- Dendrites
- Synapses



Resting potential

Transport proteins for ions in neuron cell membranes:

- Ion channels: Na^+ channels, K^+ channels, … (gated/non-gated)
- Ion pumps: the Na^+-K^+ pump



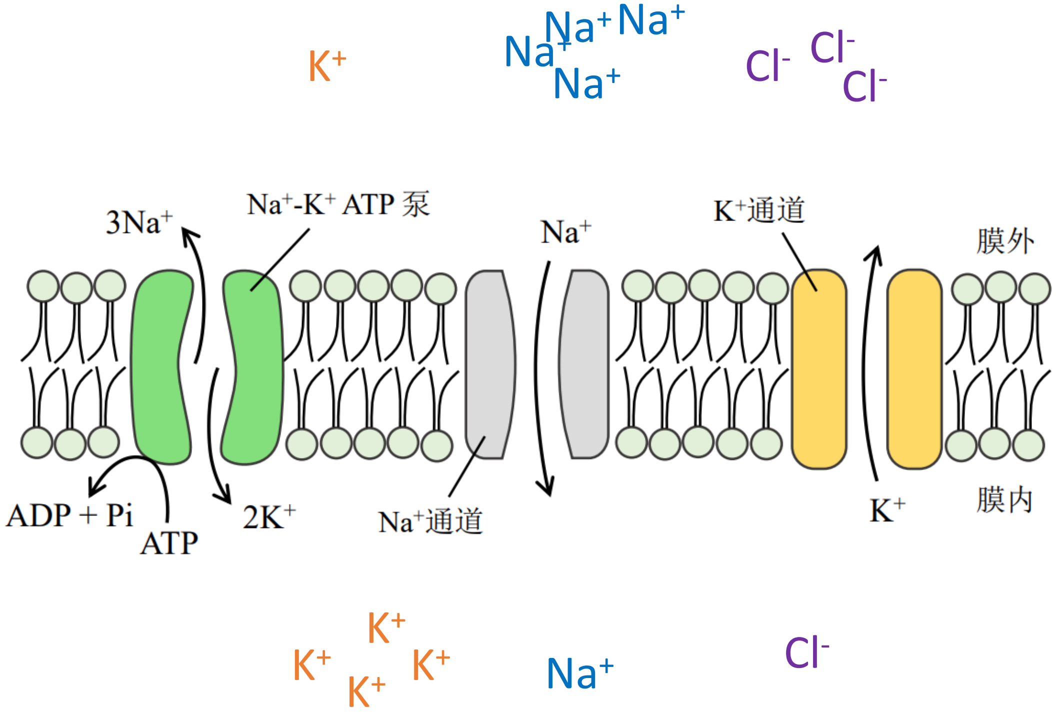
Resting potential

- Ion concentration difference → chemical gradient → electrical gradient
- Nernst Equation:

$$E = \frac{RT}{zF} \ln \frac{[\text{ion}]_{\text{out}}}{[\text{ion}]_{\text{in}}}$$

- Goldman-Hodgkin-Katz (GHK) Equation:

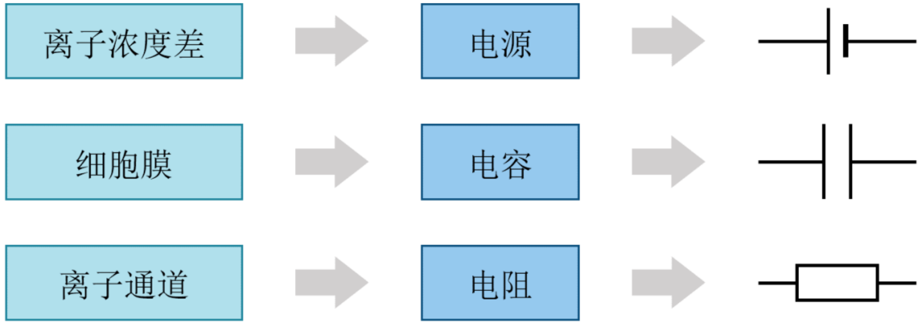
$$V_m = \frac{RT}{F} \ln \left(\frac{P_{\text{Na}}[\text{Na}^+]_{\text{out}} + P_{\text{K}}[\text{K}^+]_{\text{out}} + P_{\text{Cl}}[\text{Cl}^-]_{\text{in}}}{P_{\text{Na}}[\text{Na}^+]_{\text{in}} + P_{\text{K}}[\text{K}^+]_{\text{in}} + P_{\text{Cl}}[\text{Cl}^-]_{\text{out}}} \right)$$



Equivalent circuits

Components of an equivalent circuit:

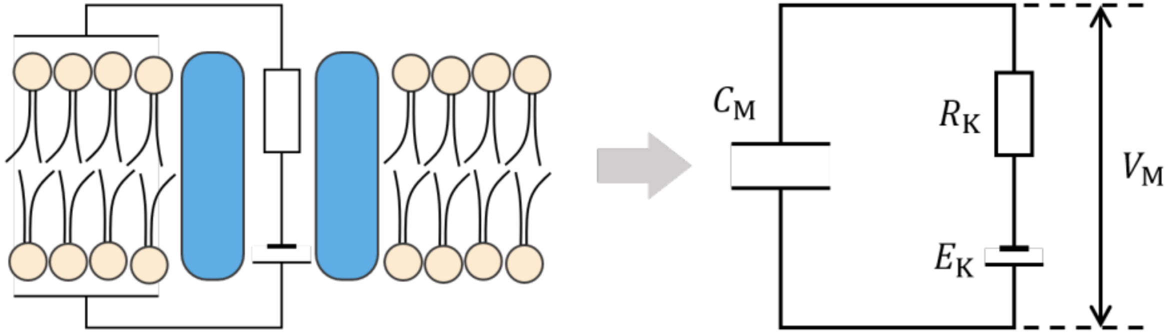
- Battery
- Capacitor
- Resistor



Considering the potassium channel **ONLY**:

$$0 = I_{\text{cap}} + I_K = c_{\text{M}}\frac{\mathrm{d}V_{\text{M}}}{\mathrm{d}t} + \frac{V_{\text{M}} - E_{\text{K}}}{R_{\text{K}}},$$

$$c_{\text{M}}\frac{\mathrm{d}V_{\text{M}}}{\mathrm{d}t} = -\frac{V_{\text{M}} - E_{\text{K}}}{R_{\text{K}}} = -g_{\text{K}}(V_{\text{M}} - E_{\text{K}}).$$

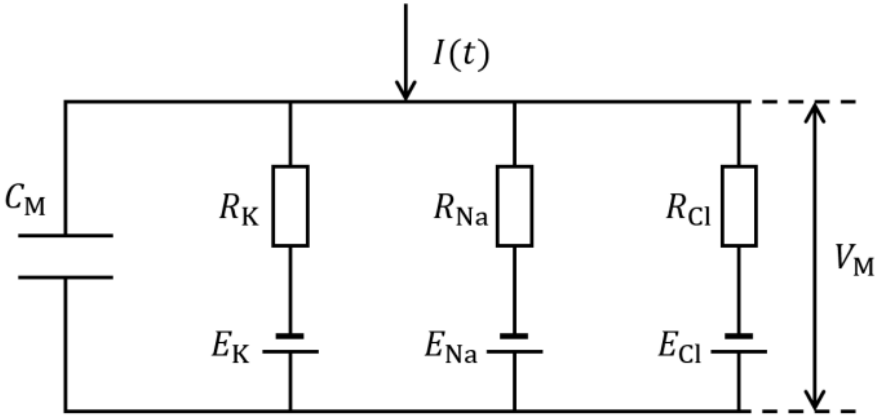


Equivalent circuits

Considering the Na⁺, K⁺, and Cl⁻ channels and the external current $I(t)$:

$$\frac{I(t)}{A} = c_{\mathrm{M}} \frac{\mathrm{d}V_{\mathrm{M}}}{\mathrm{d}t} + i_{\mathrm{ion}}$$

$$\Rightarrow \boxed{c_{\mathrm{M}} \frac{\mathrm{d}V_{\mathrm{M}}}{\mathrm{d}t} = -g_{\mathrm{Cl}}(V_{\mathrm{M}} - E_{\mathrm{Cl}}) - g_{\mathrm{K}}(V_{\mathrm{M}} - E_{\mathrm{K}}) - g_{\mathrm{Na}}(V_{\mathrm{M}} - E_{\mathrm{Na}}) + \frac{I(t)}{A}}$$



Steady-state membrane potential given a constant current input I:

$$\Rightarrow \quad c_{\mathrm{M}} \frac{\mathrm{d}V_{\mathrm{M}}}{\mathrm{d}t} = -(g_{\mathrm{Cl}} + g_{\mathrm{K}} + g_{\mathrm{Na}})V_{\mathrm{M}} + g_{\mathrm{Cl}}E_{\mathrm{Cl}} + g_{\mathrm{K}}E_{\mathrm{K}} + g_{\mathrm{Na}}E_{\mathrm{Na}} + \frac{I(t)}{A}$$

$$V_{ss} = \frac{g_{\mathrm{Cl}}E_{\mathrm{Cl}} + g_{\mathrm{K}}E_{\mathrm{K}} + g_{\mathrm{Na}}E_{\mathrm{Na}} + I/A}{g_{\mathrm{Cl}} + g_{\mathrm{K}} + g_{\mathrm{Na}}} \xrightarrow{I=0} V_{ss,I=0} = E_R = \frac{g_{\mathrm{Cl}}E_{\mathrm{Cl}} + g_{\mathrm{K}}E_{\mathrm{K}} + g_{\mathrm{Na}}E_{\mathrm{Na}}}{g_{\mathrm{Cl}} + g_{\mathrm{K}} + g_{\mathrm{Na}}}$$

02

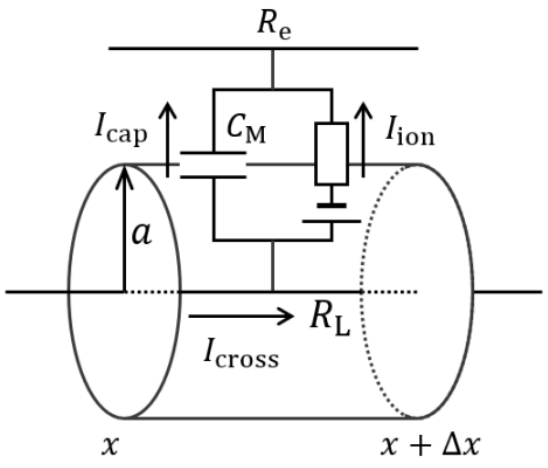
Cable Theory & passive conduction

Cable Theory

How electrical signals are transmitted along a single neuron (an axon)?

Considering the axon as a long cylindrical cable:

$$\boxed{I_{\text{cross}}(x,t)} = \boxed{I_{\text{cross}}(x+\Delta x,t)} + \boxed{I_{\text{ion}}(x,t)} + \boxed{I_{\text{cap}}(x,t)}$$



$$V(x+\Delta x,t) - V(x,t) = -I_{\text{cross}}(x,t)R_L = -I_{\text{cross}}(x,t)\frac{\Delta x}{\pi a^2}\rho_L$$

$$\boxed{I_{\text{cross}}(x,t)} = -\frac{\pi a^2}{\rho_L}\frac{\partial V(x,t)}{\partial x}$$

$$\boxed{I_{\text{ion}}} = (2\pi a\Delta x)i_{\text{ion}}$$

$$\boxed{I_{\text{cap}}(x,t)} = (2\pi a\Delta x)c_M\frac{\partial V(x,t)}{\partial t}$$

$$(2\pi a\Delta x)c_M\frac{\partial V(x,t)}{\partial t} + (2\pi a\Delta x)i_{\text{ion}} = \frac{\pi a^2}{\rho_L}\frac{\partial V(x+\Delta x,t)}{\partial x} - \frac{\pi a^2}{\rho_L}\frac{\partial V(x,t)}{\partial x}$$

$$c_M\frac{\partial V(x,t)}{\partial t} = \frac{a}{2\rho_L}\frac{\partial^2 V(x,t)}{\partial x^2} - i_{\text{ion}}$$

Cable Equation

Cable Theory

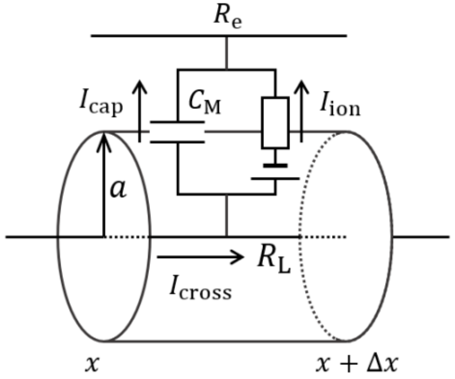
$$c_M \frac{\partial V(x,t)}{\partial t} = \frac{a}{2\rho_L}\frac{\partial^2 V(x,t)}{\partial x^2} - i_{ion}$$

Cable Equation

Passive conduction: ion currents are caused by leaky channels exclusively

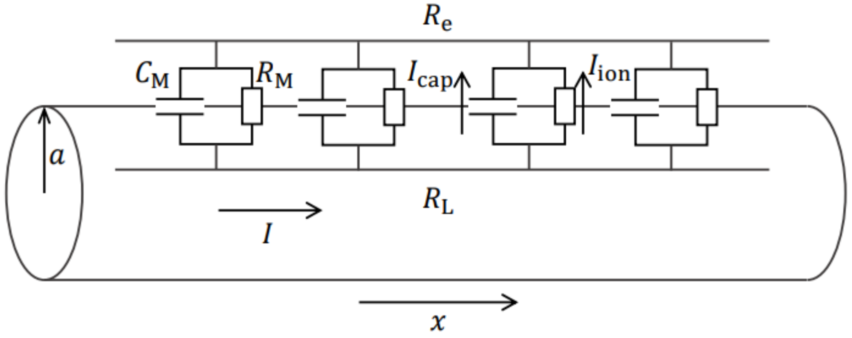
$$i_{ion} = V(x,t)/r_M \Rightarrow c_M \frac{\partial V(x,t)}{\partial t} = \frac{a}{2\rho_L}\frac{\partial^2 V(x,t)}{\partial x^2} - \frac{V(x,t)}{r_M}$$

$$\tau \frac{\partial V(x,t)}{\partial t} = \lambda^2 \frac{\partial^2 V(x,t)}{\partial x^2} - V(x,t) \qquad \lambda = \sqrt{0.5 a r_M/\rho_L}$$



If a constant external current is applied to $x = 0$
the steady-state membrane potential $V_{ss}(x)$ is

$$\lambda^2 \frac{d^2 V_{ss}(x)}{dx^2} - V_{ss}(x) = 0 \xrightarrow{I_{cross}(0,t) = I_0} V_{ss}(x) = \frac{\lambda \rho_L}{\pi a^2} I_0 e^{-x/\lambda}$$



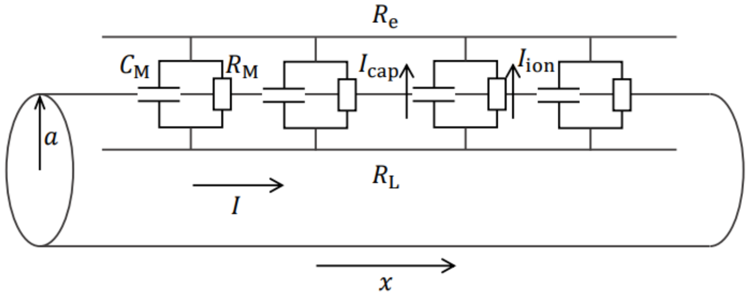
Cable Theory

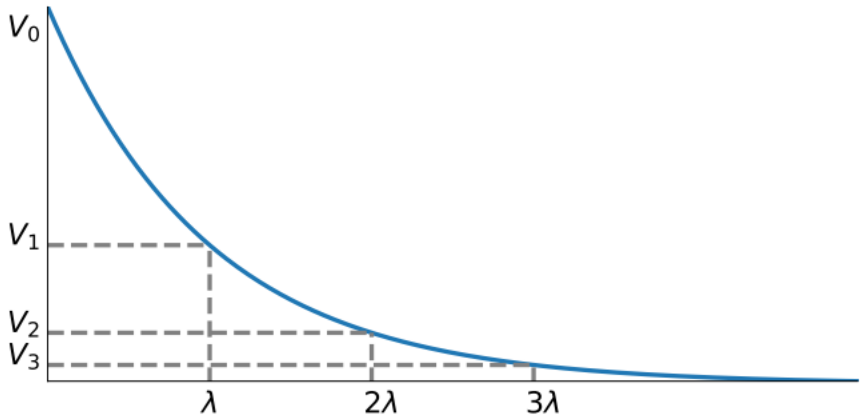
$$c_M \frac{\partial V(x,t)}{\partial t} = \frac{a}{2\rho_L} \frac{\partial^2 V(x,t)}{\partial x^2} - i_{ion}$$

Cable Equation

Passive conduction: ion currents are caused by leaky channels exclusively

$$V_{ss}(x) = \frac{\lambda \rho_L}{\pi a^2} I_0 e^{-x/\lambda}$$





03

Action potential & active transport

Action potential

How to transmit electrical signals with less or no decay?

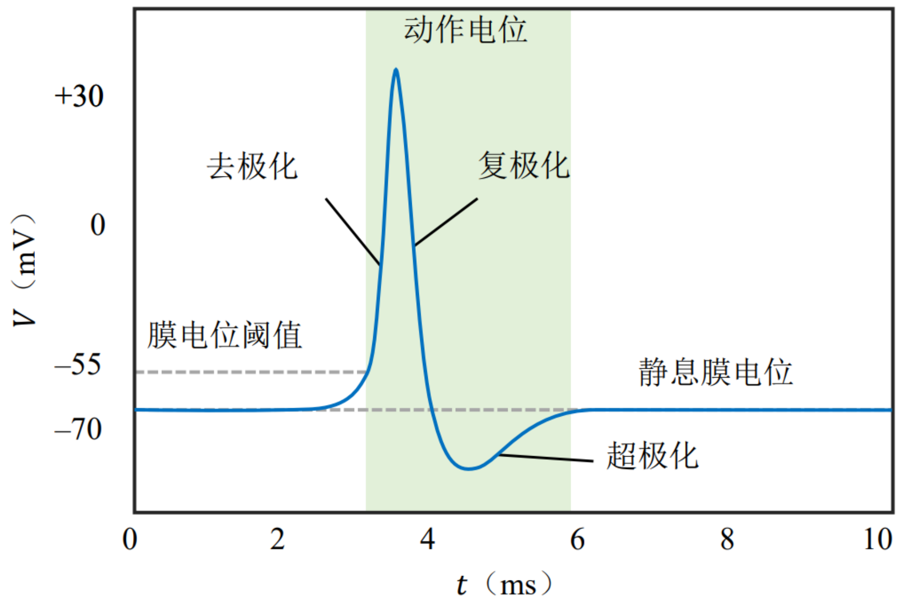
Steps of an action potential:

- Depolarization
- Repolarization
- Hyperpolarization
- Resting

Characteristics:

- All-or-none
- Fixed shape
- Active electrical property

ACTION POTENTIAL

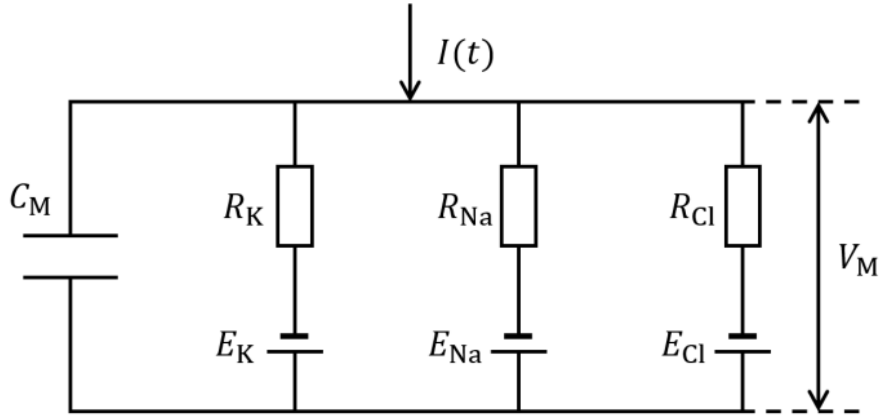


Action potential

How to simulate an action potential?

$$\frac{I(t)}{A} = c_{\mathrm{M}} \frac{\mathrm{d}V_{\mathrm{M}}}{\mathrm{d}t} + i_{\mathrm{ion}}$$

$$\Rightarrow \quad c_{\mathrm{M}} \frac{\mathrm{d}V_{\mathrm{M}}}{\mathrm{d}t} = -g_{\mathrm{Cl}}(V_{\mathrm{M}} - E_{\mathrm{Cl}}) - g_{\mathrm{K}}(V_{\mathrm{M}} - E_{\mathrm{K}}) - g_{\mathrm{Na}}(V_{\mathrm{M}} - E_{\mathrm{Na}}) + \frac{I(t)}{A}$$



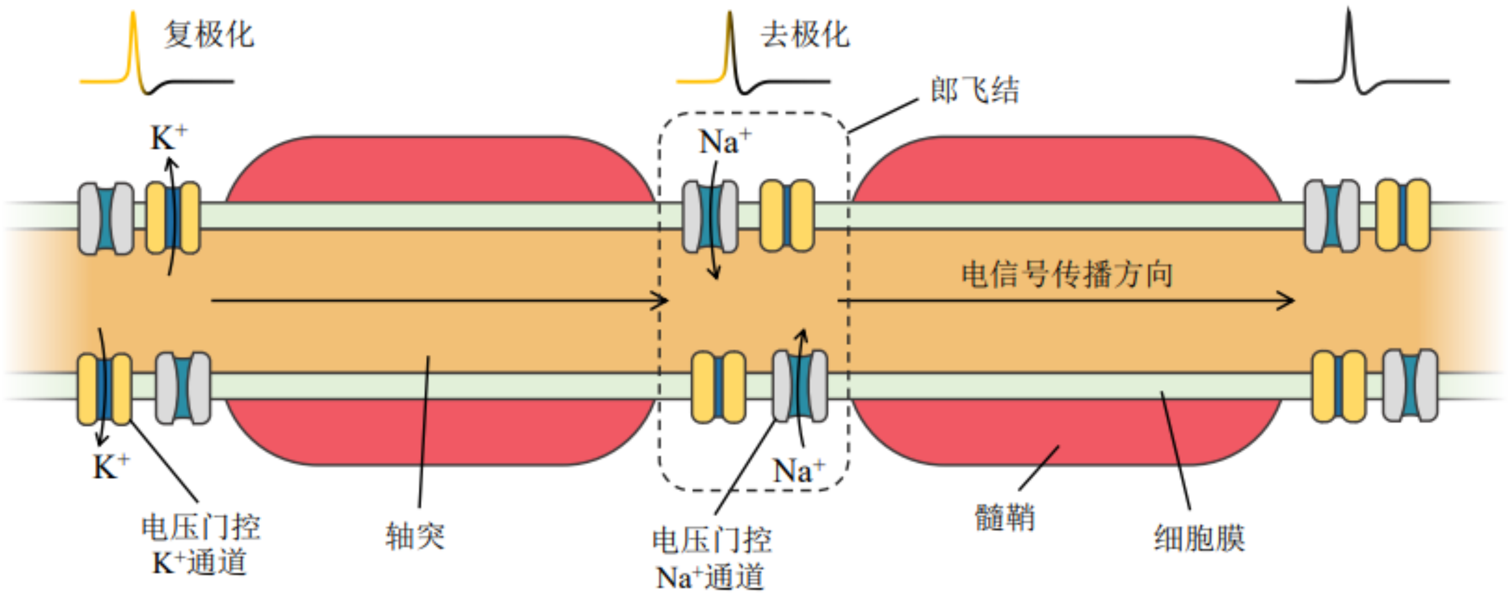
Mechanism: **voltage-gated ion channels**

$g_{\mathrm{Na}} \Rightarrow g_{\mathrm{Na}}(V)$ $\quad$ $g_{\mathrm{K}} \Rightarrow g_{\mathrm{K}}(V)$ $\quad$ $g_{\mathrm{Cl}} \Rightarrow g_{\mathrm{Cl}}(V)$

How would the conductance change with voltage?

Nodes of Ranvier

Saltatory conduction with a much higher speed and less energy consumption



04

The Hodgkin-Huxley (HH) Model

Modeling of ion channels

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Modeling of each ion channel: $g_m = \bar{g}_m \, m^x$

Modeling of each ion gate:

$$\mathrm{C} \underset{\beta(\mathrm{V})}{\overset{\alpha(\mathrm{V})}{\rightleftharpoons}} \mathrm{O}$$

(closed) (open)

$1 - m$ m

Gating variable

$$\frac{\mathrm{d}m}{\mathrm{d}t} = \alpha(V)(1-m) - \beta(V)m = \frac{m_\infty(V) - m}{\tau_m(V)}$$

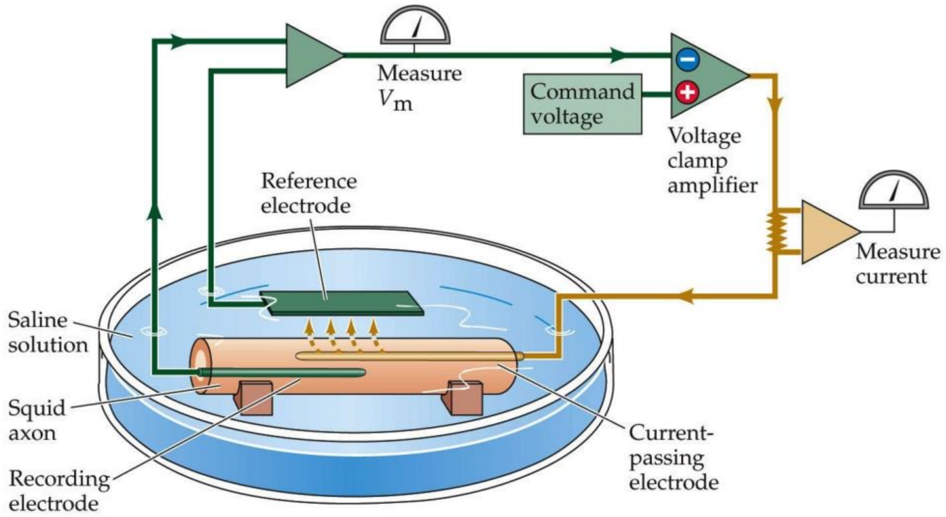
$$m_\infty(V) = \frac{\alpha(V)}{\alpha(V)+\beta(V)}$$

$$\tau_m(V) = \frac{1}{\alpha(V)+\beta(V)}$$

If V is constant: $m(t) = m_\infty(V) + (m_0 - m_\infty(V))\mathrm{e}^{-t/\tau_m(V)}$

How to measure $m_\infty(V)$ and $\tau_m(V)$?

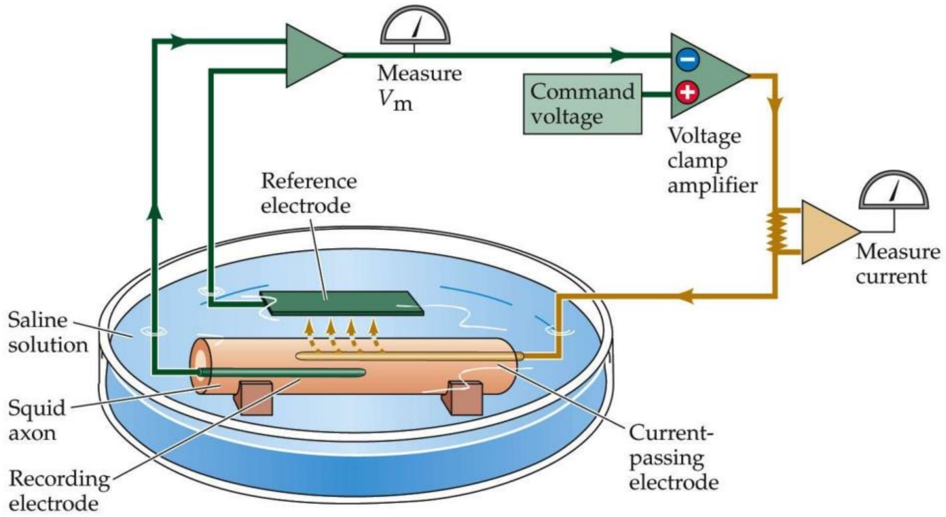
Voltage clamp



Voltage clamp

$$\frac{I(t)}{A} = c_M \frac{dV_M}{dt} + i_{ion}$$

$$\Rightarrow \quad c_M \frac{dV_M}{dt} = -g_{Cl}(V_M - E_{Cl}) - g_K(V_M - E_K) - g_{Na}(V_M - E_{Na}) + \frac{I(t)}{A}$$



- The membrane potential is kept constant
- The current from capacitors is excluded
- Currents must come from leaky/voltage-gated ion channels

$$I_{cap} = c\frac{dV}{dt} = 0$$

$$I_{fb} = \quad i_{ion} = g_{Na}(V - E_{Na}) + g_K(V - E_K) + g_L(V - E_L)$$

[The Voltage Clamp Method - YouTube]

1. Leaky channels

Hyperpolarization → the sodium and potassium channels are closed

$$I_{\mathrm{fb}} = g_{\mathrm{Na}}(V - E_{\mathrm{Na}}) + g_{\mathrm{K}}(V - E_{\mathrm{K}}) + g_{\mathrm{L}}(V - E_{\mathrm{L}})$$

$$\Downarrow$$

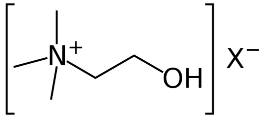
$$I_{\mathrm{fb}} = g_L(V - E_L)$$

$$g_{\mathrm{L}} = 0.3\,\mathrm{mS/cm^2},\ E_{\mathrm{L}} = -54.4\,\mathrm{mV}$$

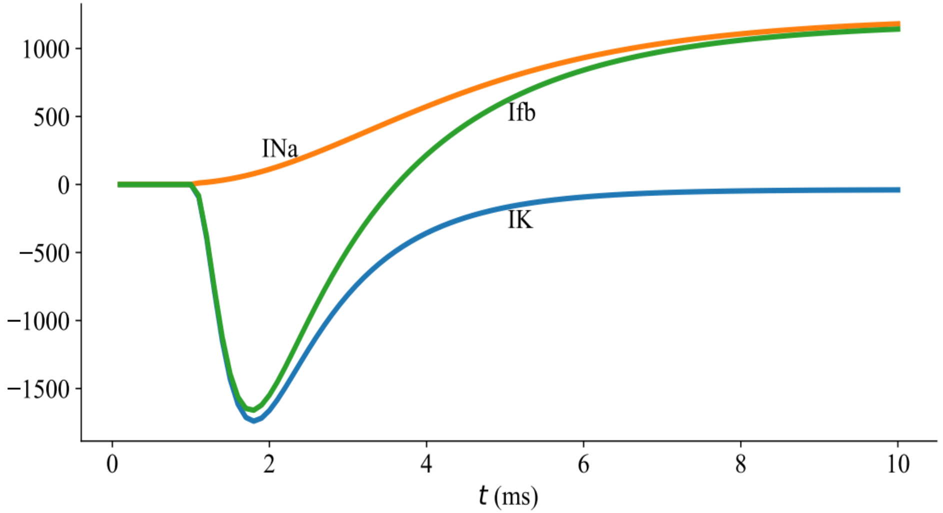
2. Potassium and sodium channels

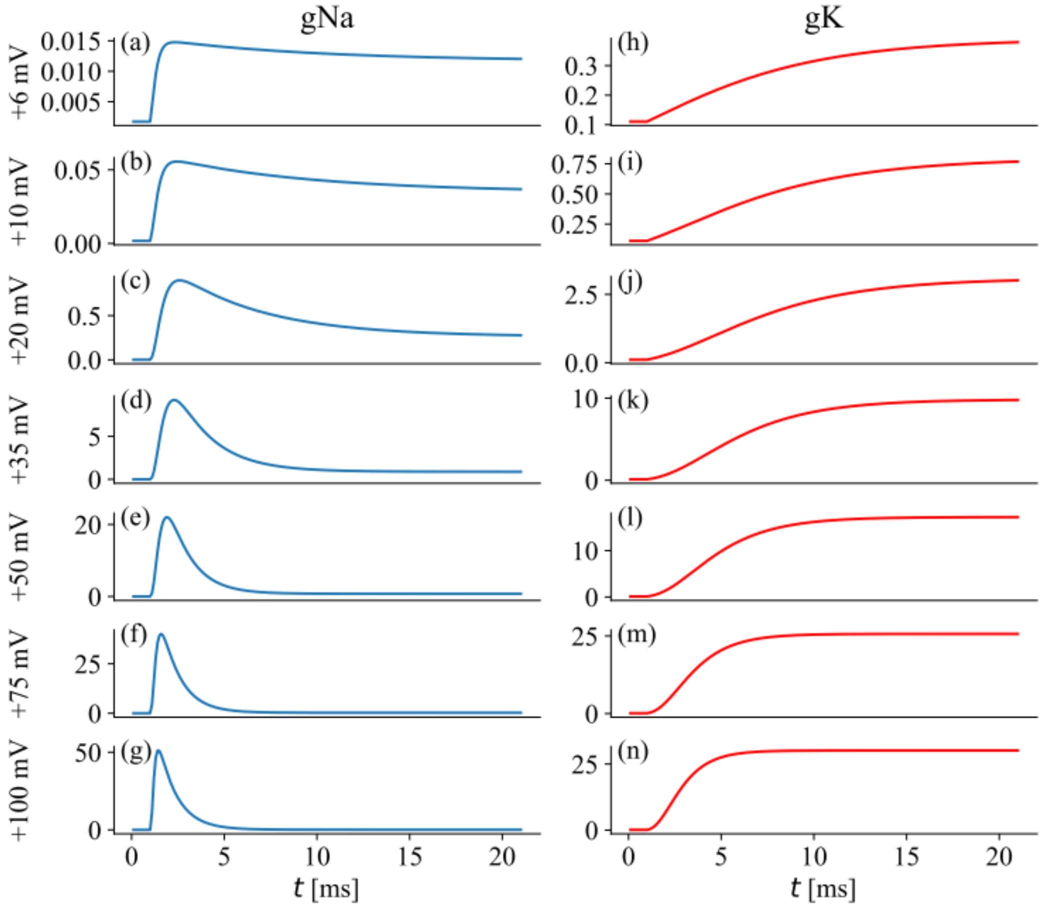
Potassium channels: Use choline to eliminate the inward current of Na^+

Na^+ current: $I_{\mathrm{fb}} - I_{\mathrm{K}}$



choline





2. Potassium and sodium channels

Potassium channels

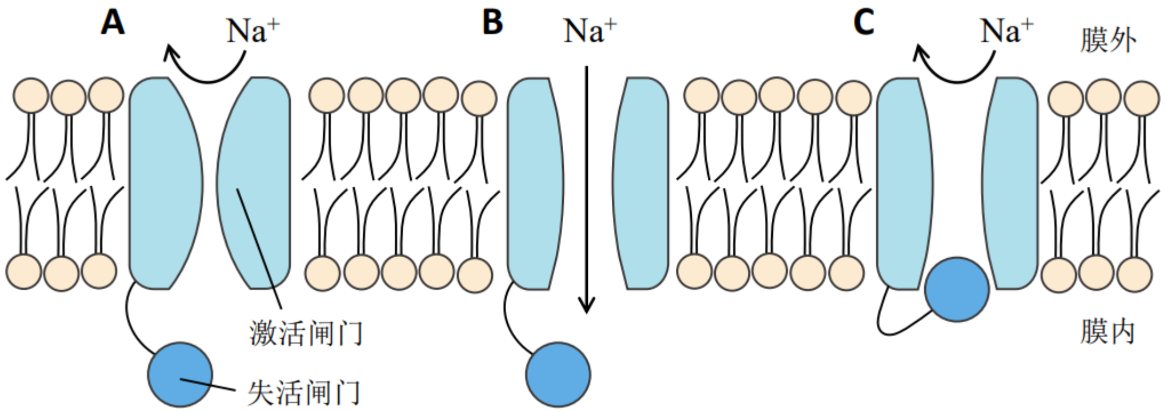
- Resting state (gate closed)
- Activated state (gate open)

Activation gate: $g_K = \bar{g}_K n^x$

Sodium channels

- Resting state (gate closed)
- Activated state (gate open)
- Inactivated state (gate blocked)

Activation gate + inactivation gate: $g_{Na} = \bar{g}_{Na} m^3 h$



The gates of sodium channels

2. Potassium and sodium channels

Modeling of each ion gate:

$$g_K = \bar{g}_K n^x$$

$$g_{Na} = \bar{g}_{Na} m^3 h$$

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

$$\frac{dm}{dt} = \alpha_m(V)(1-m) - \beta_m(V)m$$

$$\frac{dh}{dt} = \alpha_h(V)(1-h) - \beta_h(V)h$$

$$\frac{dm}{dt} = \alpha(V)(1-m) - \beta(V)m = \frac{m_\infty(V) - m}{\tau_m(V)}$$

$$m_\infty(V) = \frac{\alpha(V)}{\alpha(V)+\beta(V)}$$

$$\tau_m(V) = \frac{1}{\alpha(V)+\beta(V)}$$

$$m(t) = m_\infty(V) + (m_0 - m_\infty(V))e^{-t/\tau_m(V)}$$

The Hodgkin-Huxley (HH) Model

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$$c_{\mathrm{M}} \frac{\mathrm{d}V_{\mathrm{M}}}{\mathrm{d}t} = -g_{\mathrm{Cl}}(V_{\mathrm{M}} - E_{\mathrm{Cl}}) - g_{\mathrm{K}}(V_{\mathrm{M}} - E_{\mathrm{K}}) - g_{\mathrm{Na}}(V_{\mathrm{M}} - E_{\mathrm{Na}}) + \frac{I(t)}{A}$$

$$\begin{cases} c\dfrac{\mathrm{d}V}{\mathrm{d}t} = -\bar{g}_{\mathrm{Na}} m^3 h\,(V - E_{\mathrm{Na}}) - \bar{g}_{\mathrm{K}} n^4\,(V - E_{\mathrm{K}}) - \bar{g}_{\mathrm{L}}\,(V - E_{\mathrm{L}}) + I_{\mathrm{ext}}, \\ \dfrac{\mathrm{d}n}{\mathrm{d}t} = \phi\,[\alpha_n(V)(1-n) - \beta_n(V)n] \\ \dfrac{\mathrm{d}m}{\mathrm{d}t} = \phi\,[\alpha_m(V)(1-m) - \beta_m(V)m]\,, \\ \dfrac{\mathrm{d}h}{\mathrm{d}t} = \phi\,[\alpha_h(V)(1-h) - \beta_h(V)h]\,, \end{cases}$$

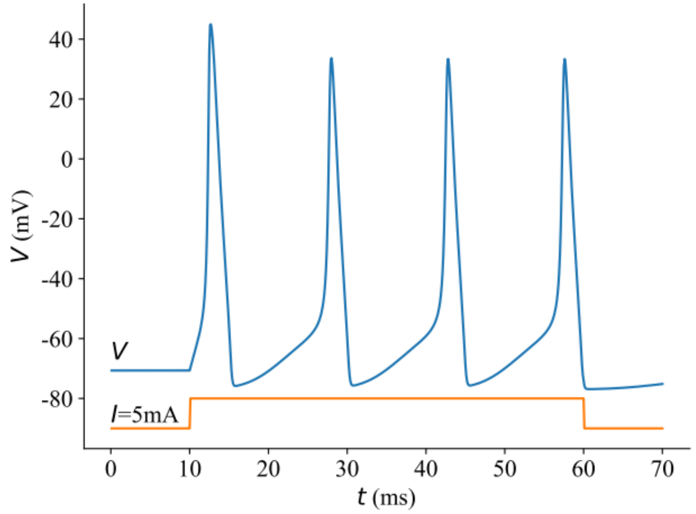
$$\alpha_n(V) = \frac{0.01(V+55)}{1-\exp\left(-\frac{V+55}{10}\right)}, \quad \beta_n(V) = 0.125\exp\left(-\frac{V+65}{80}\right),$$

$$\alpha_h(V) = 0.07\exp\left(-\frac{V+65}{20}\right), \quad \beta_h(V) = \frac{1}{\left(\exp\left(-\frac{V+35}{10}\right)+1\right)},$$

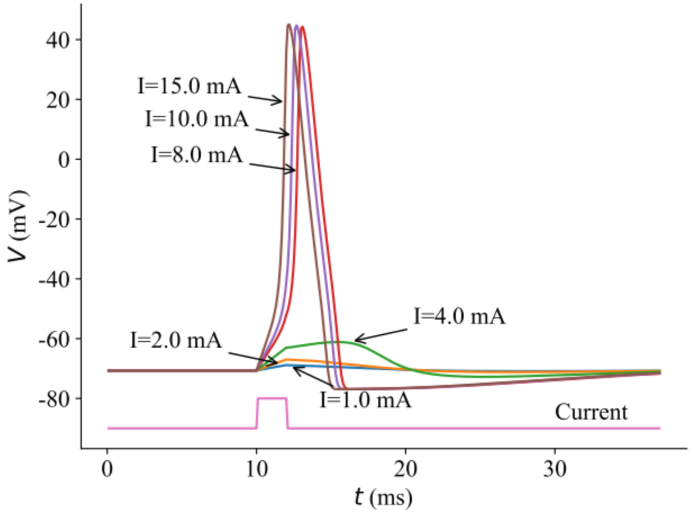
$$\alpha_m(V) = \frac{0.1\,(V+40)}{1-\exp\left(-(V+40)/10\right)}, \quad \beta_m(V) = 4\exp\left(-(V+65)/18\right).$$

$$\phi = Q_{10}^{(T-T_{\mathrm{base}})/10}$$

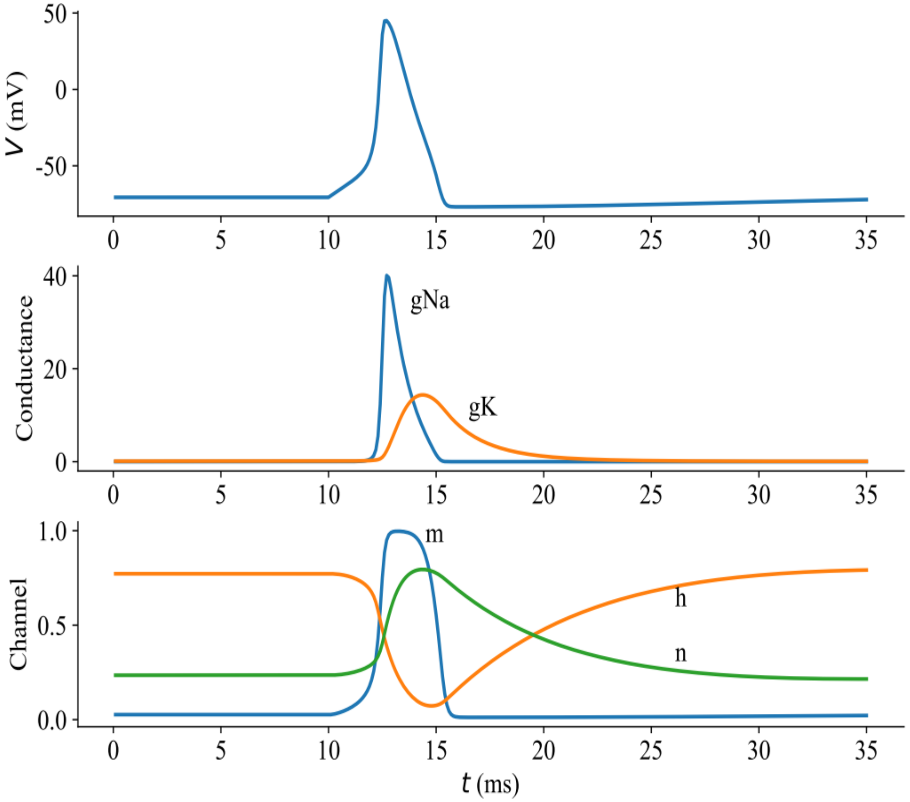
The Hodgkin-Huxley (HH) Model



Response to a constant input



All-or-none characteristics



Change of ion channel conductance and gating variables

How to fit each gating variable?

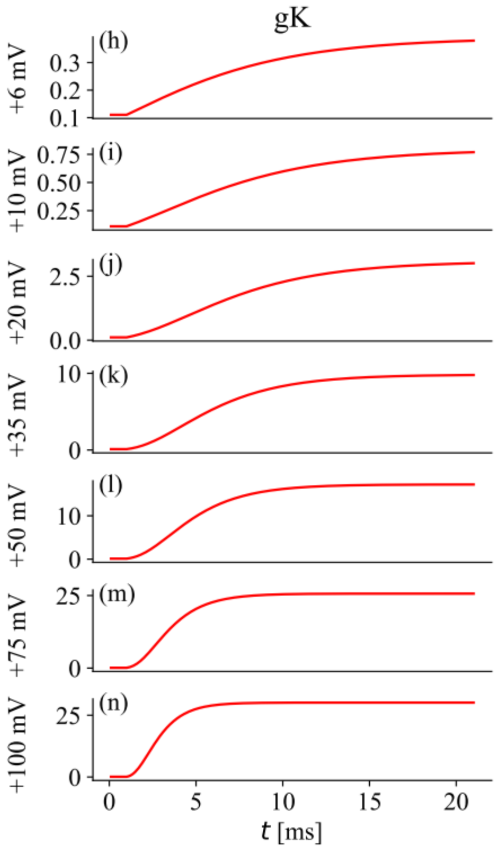
Fitting n:

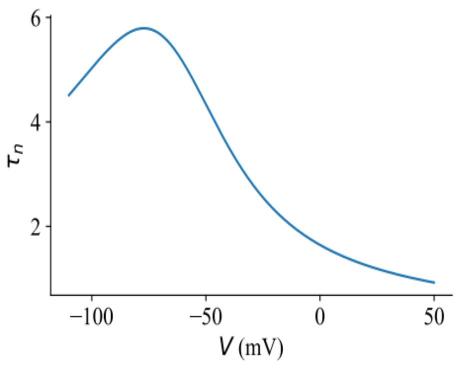
$$g_K = \bar{g}_K n^x \qquad m(t) = m_\infty(V) + (m_0 - \boxed{m_\infty(V)})e^{-t/\boxed{\tau_m(V)}}$$

$$g_K(V,t) = \bar{g}_K \left[n_\infty(V) - (n_\infty(V) - n_0(V))e^{-\frac{t}{\tau_n(V)}} \right]^x$$

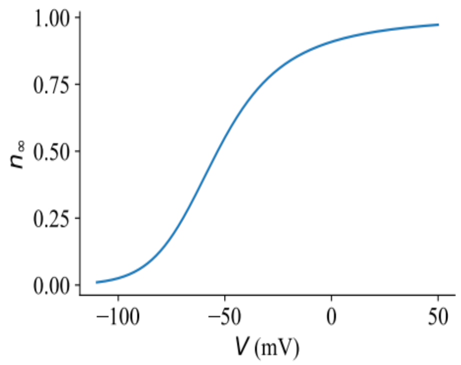
$$g_{K\infty} = \bar{g}_K n_\infty^x, g_{K0} = \bar{g}_K n_0^x$$

$$g_K(V,t) = \left[g_{K\infty}^{1/x} - (g_{K\infty}^{1/x} - g_{K0}^{1/x})e^{-\frac{t}{\tau_n(V)}} \right]^x$$

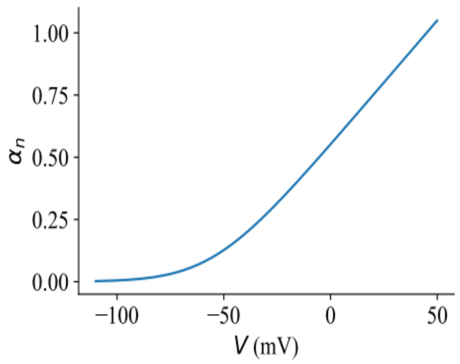




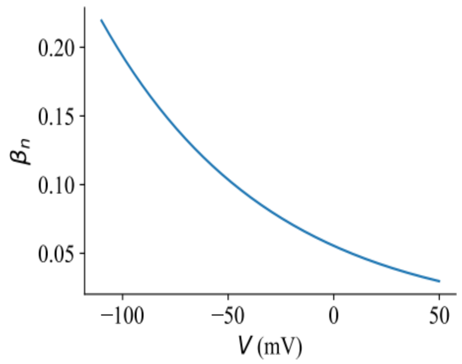
(a) $\tau_n(V)$ 随电压 V 的变化曲线



(b) $n_\infty(V)$ 随电压 V 的变化曲线



(c) $\alpha_n(V)$ 随电压 V 的变化曲线



(d) $\beta_n(V)$ 随电压 V 的变化曲线

How to fit each gating variable?

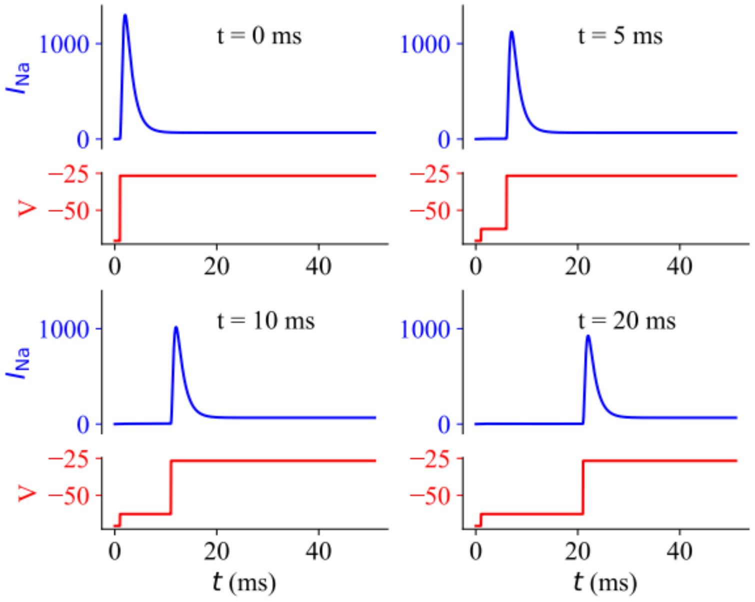
Fitting h:

$$m(t) = m_\infty(V) - (m_\infty(V) - m_0)\exp(-t/\tau_m(V))$$

$$h(t) = h_\infty(V) - (h_\infty(V) - h_0)\exp(-t/\tau_h(V))$$

$$g_{\mathrm{Na}}(t) = \bar{g}_{\mathrm{Na}} m(t)^3 h(t)$$

$$= \bar{g}_{\mathrm{Na}}\left[m_\infty(V) - (m_\infty(V) - m_0)\,\mathrm{e}^{-\frac{t}{\tau_m(V)}}\right]^3\left[h_\infty(V) - (h_\infty(V) - h_0)\,\mathrm{e}^{-\frac{t}{\tau_h(V)}}\right]$$



$$\frac{I_{\mathrm{Na}}(\Delta V, t)}{I_{\mathrm{Na}}(\Delta V, 0)} = \frac{h^{\mathrm{cond}}(V_r + \Delta V, t)}{h^{\mathrm{cond}}(V_r + \Delta V, 0)}$$

$$= \frac{h_\infty(V_r + \Delta V) - (h_\infty(V_r + \Delta V) - h_0)\exp(-t/\tau_h(V_r + \Delta V))}{h_\infty(V_r + \Delta V) - (h_\infty(V_r + \Delta V) - h_0)\exp(-0/\tau_h(V_r + \Delta V))}$$

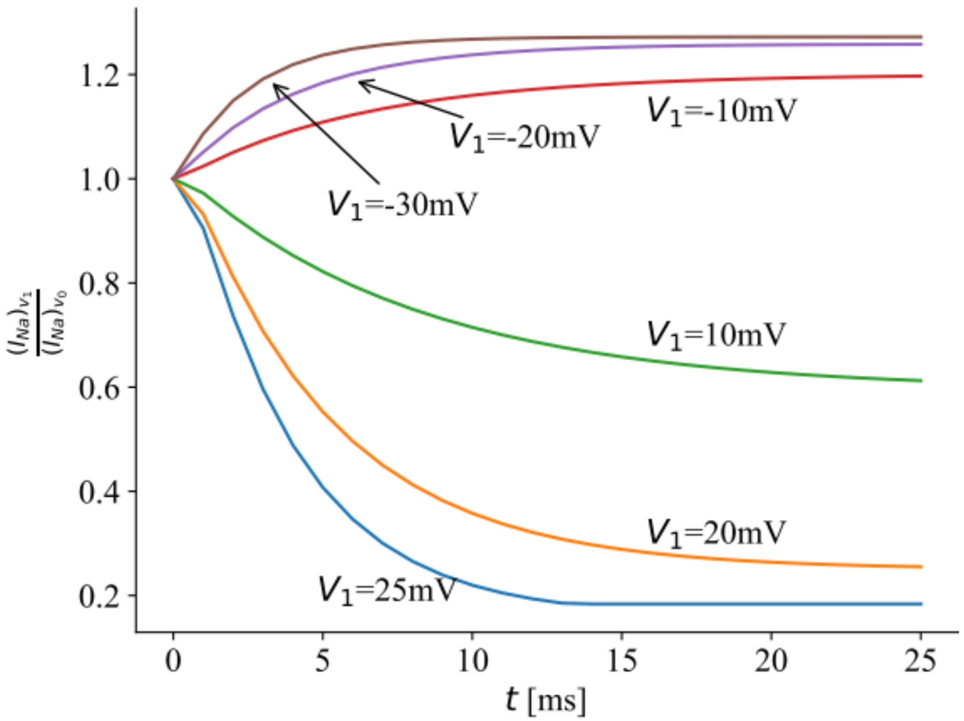
$$= y - (y - 1)\exp(-t/\tau_h(V_r + \Delta V))$$

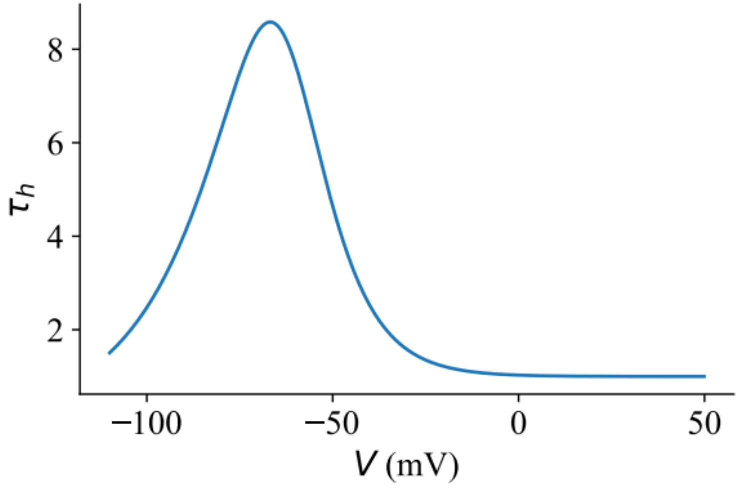
$$y = \frac{h_\infty(V_r + \Delta V)}{h_0}$$

How to fit each gating variable?

Fitting h:

$$\frac{I_{\mathrm{Na}}(\Delta V, t)}{I_{\mathrm{Na}}(\Delta V, 0)} = y - (y-1)\exp(-t/\tau_h(V_r + \Delta V)). \quad \rightarrow \quad \tau_h$$





(a) $\tau_h(V)$ 随电压 V 的变化曲线

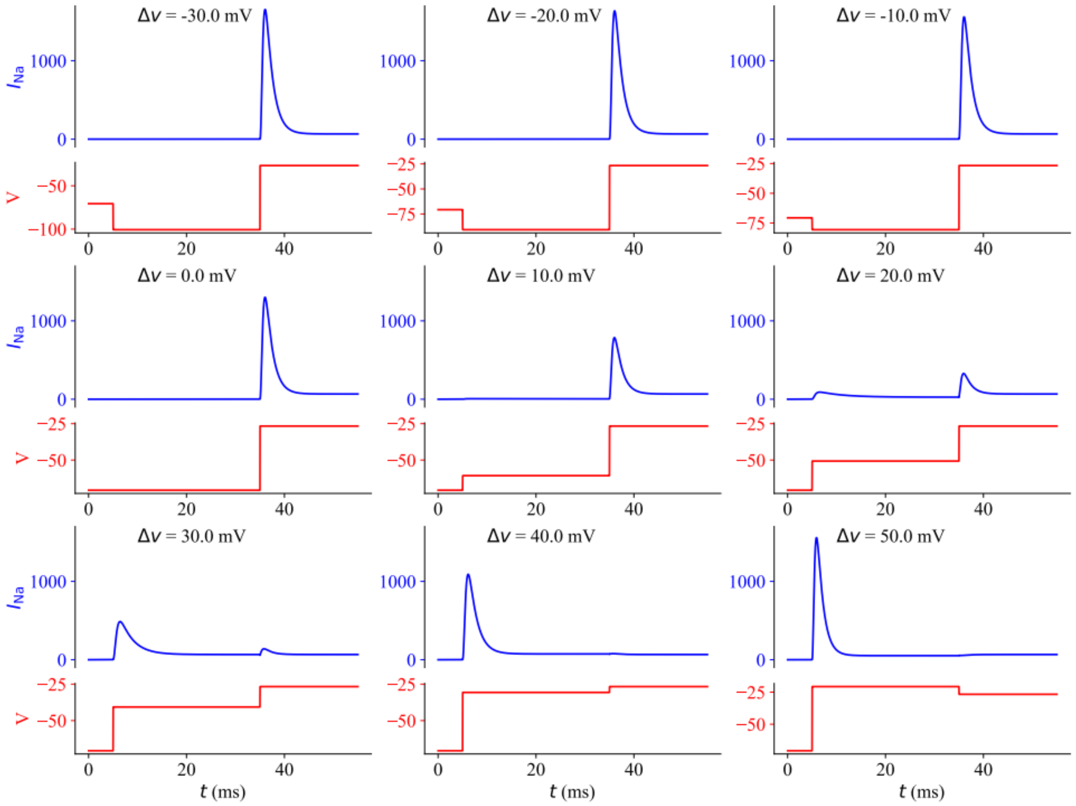
How to fit each gating variable?

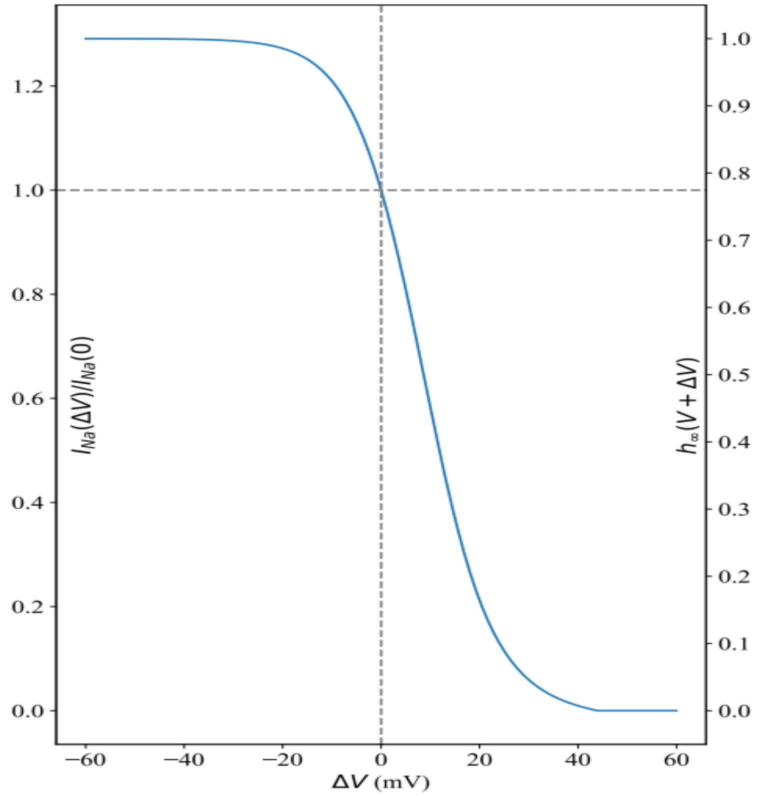
Fitting h: $h_\infty(V)$?

Let t to be large enough so that variable h has reached its steady state

$$\frac{I_{\text{Na}}(\Delta V,t)}{I_{\text{Na}}(\Delta V,0)}=\frac{h^{\text{cond}}(V_r+\Delta V,t)}{h^{\text{cond}}(V_r+\Delta V,0)}=\frac{h_\infty(V_r+\Delta V)}{h_0}=\frac{h_\infty(V_r+\Delta V)}{h_\infty(V_r)}$$

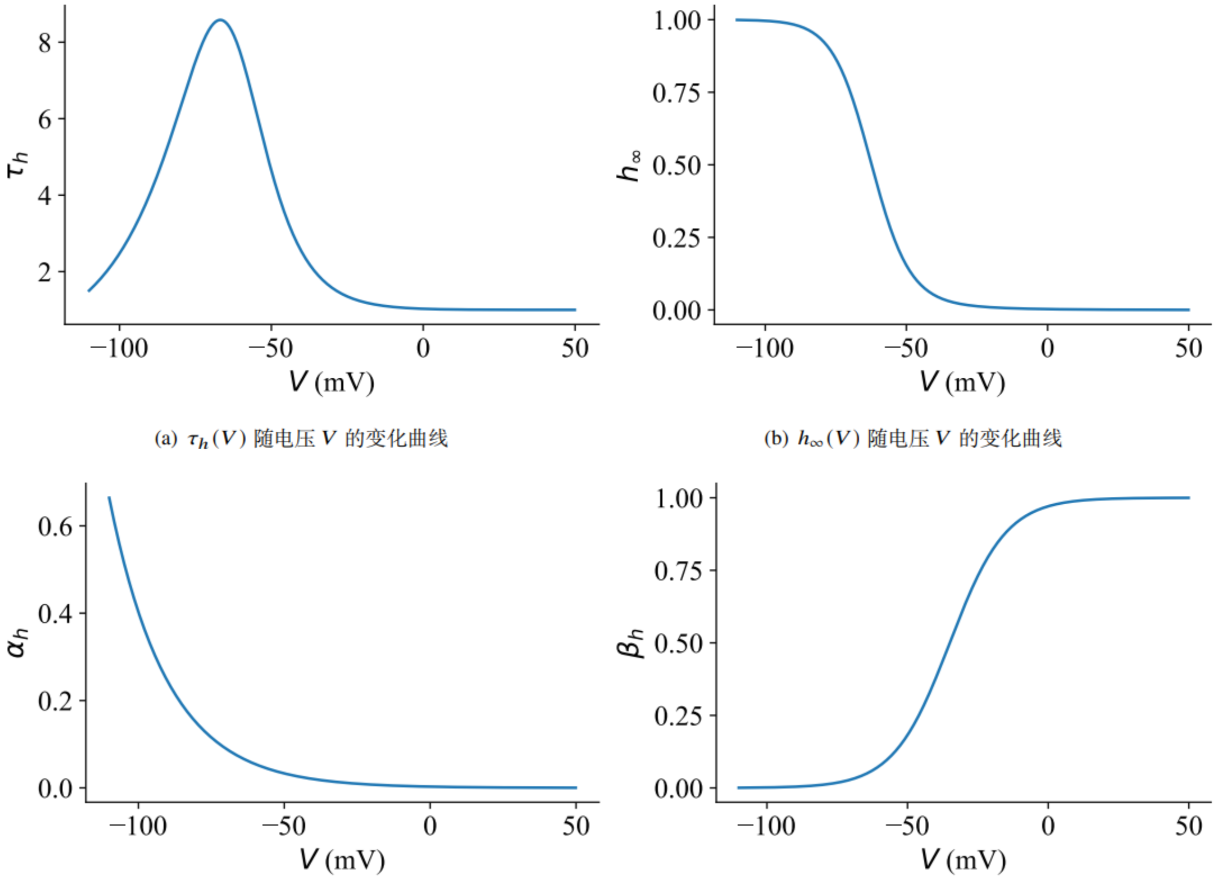
$h_\infty(V)$ ✓





How to fit each gating variable?

Fitting h:



(a) $\tau_h(V)$ 随电压 V 的变化曲线

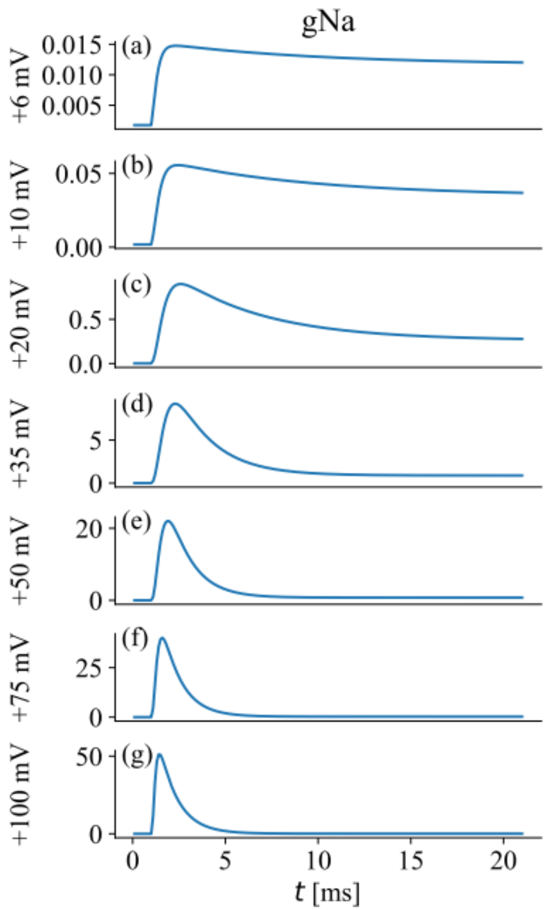
(b) $h_\infty(V)$ 随电压 V 的变化曲线

(c) $\alpha_h(V)$ 随电压 V 的变化曲线

(d) $\beta_h(V)$ 随电压 V 的变化曲线

How to fit each gating variable?

Fitting m:



1. $g_{\mathrm{Na}}(V_r) \approx 0 \;\Rightarrow m_0 \approx 0$

2. At high depolarization voltage: $h_\infty \approx 0$

$$
\begin{aligned}
g_{\mathrm{Na}}(t) &= \bar{g}_{\mathrm{Na}} m(t)^3 h(t) \\
&= \bar{g}_{\mathrm{Na}} \left[m_\infty(V) - (m_\infty(V) - m_0)\, \mathrm{e}^{-\frac{t}{\tau_m(V)}} \right]^3 \left[h_\infty(V) - (h_\infty(V) - h_0)\, \mathrm{e}^{-\frac{t}{\tau_h(V)}} \right] \\
&= g'_{\mathrm{Na}}(V)\, [1 - \exp(-t/\tau_m(V))]^3 \exp(-t/\tau_h(V))
\end{aligned}
$$

$$g'_{\mathrm{Na}}(V) = \bar{g}_{\mathrm{Na}} m_\infty(V)^3 h_0$$

$\Rightarrow$ $g'_{\mathrm{Na}}(V)$ ✓ $\tau_m(V)$ ✓

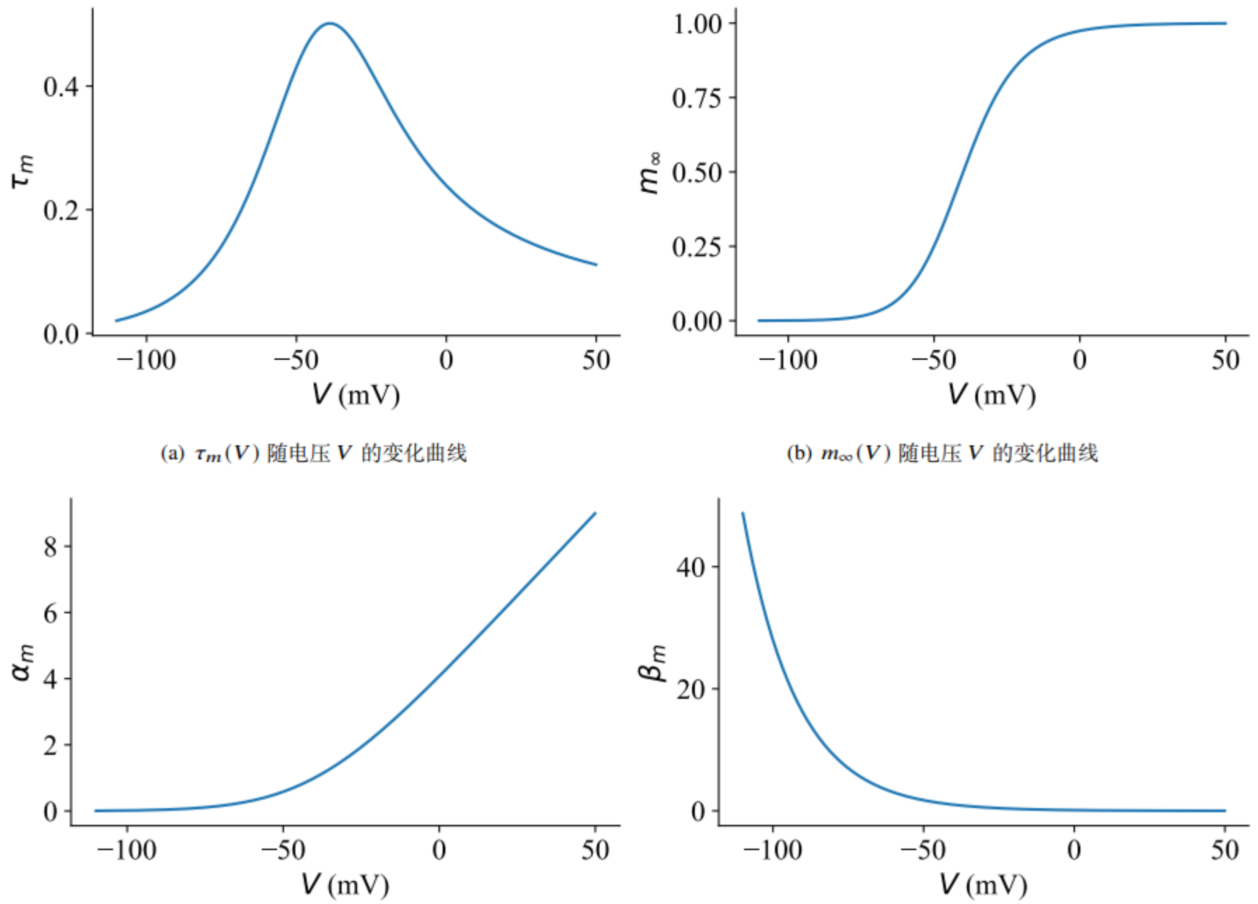
3. High depolarization voltage: $m_\infty \approx 1$

$\Rightarrow$ $\bar{g}_{\mathrm{Na}} \approx g'_{\mathrm{Na}}/h_0$

$\Rightarrow$ $m_\infty = \sqrt[3]{g_{\mathrm{Na}}/(\bar{g}_{\mathrm{Na}} h_0)}$ ✓

How to fit each gating variable?

Fitting m:



(a) $\tau_m(V)$ 随电压 V 的变化曲线

(b) $m_\infty(V)$ 随电压 V 的变化曲线

(c) $\alpha_m(V)$ 随电压 V 的变化曲线

(d) $\beta_m(V)$ 随电压 V 的变化曲线

05

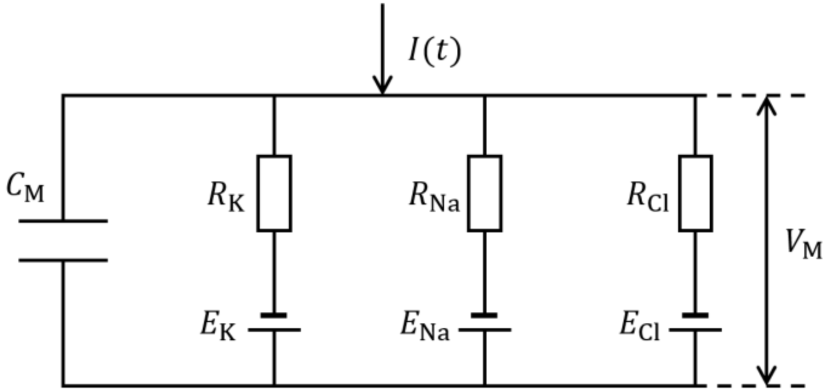
Summary

Summary

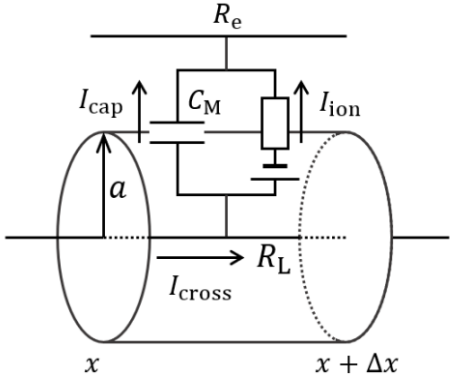
- Equivalent circuits:

$$\frac{I(t)}{A} = c_{\mathrm{M}} \frac{\mathrm{d}V_{\mathrm{M}}}{\mathrm{d}t} + i_{\mathrm{ion}}$$

$$\Rightarrow \quad c_{\mathrm{M}} \frac{\mathrm{d}V_{\mathrm{M}}}{\mathrm{d}t} = -g_{\mathrm{Cl}}(V_{\mathrm{M}} - E_{\mathrm{Cl}}) - g_{\mathrm{K}}(V_{\mathrm{M}} - E_{\mathrm{K}}) - g_{\mathrm{Na}}(V_{\mathrm{M}} - E_{\mathrm{Na}}) + \frac{I(t)}{A}$$



- Cable theory: $$c_{\mathrm{M}} \frac{\partial V(x,t)}{\partial t} = \frac{a}{2\rho_{\mathrm{L}}} \frac{\partial^2 V(x,t)}{\partial x^2} - i_{\mathrm{ion}}$$



- Passive conductance

Summary

- Action potential

Mechanism: voltage-gated ion channels $g_{\mathrm{Na}} \Rightarrow g_{\mathrm{Na}}(V)$ $\quad g_{\mathrm{K}} \Rightarrow g_{\mathrm{K}}(V)$

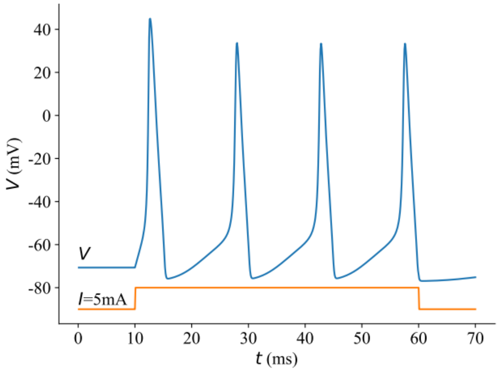
- The Hodgkin-Huxley Model
- Voltage clamp

$$c\frac{\mathrm{d}V}{\mathrm{d}t} = -\bar{g}_{\mathrm{Na}}m^3h\,(V - E_{\mathrm{Na}}) - \bar{g}_{\mathrm{K}}n^4\,(V - E_{\mathrm{K}}) - \bar{g}_{\mathrm{L}}\,(V - E_{\mathrm{L}}) + I_{\mathrm{ext}},$$

$$\frac{\mathrm{d}n}{\mathrm{d}t} = \phi\,[\alpha_n(V)(1-n) - \beta_n(V)n]$$

$$\frac{\mathrm{d}m}{\mathrm{d}t} = \phi\,[\alpha_m(V)(1-m) - \beta_m(V)m]\,,$$

$$\frac{\mathrm{d}h}{\mathrm{d}t} = \phi\,[\alpha_h(V)(1-h) - \beta_h(V)h]\,,$$

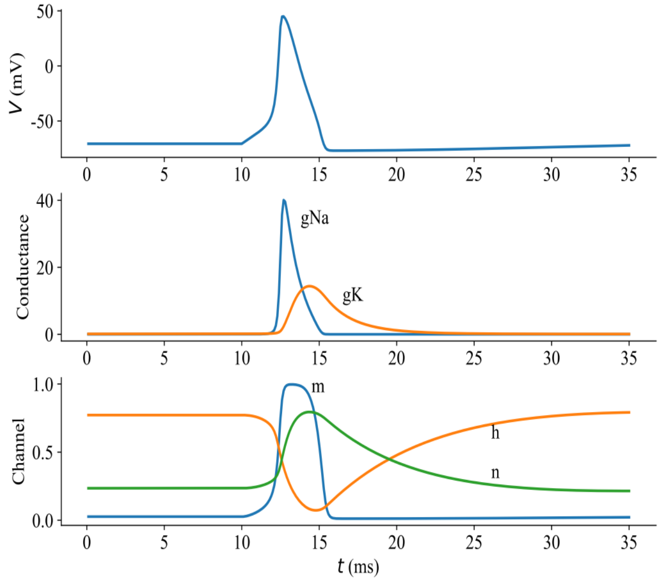


$$\alpha_n(V) = \frac{0.01(V+55)}{1-\exp\left(-\frac{V+55}{10}\right)}, \quad \beta_n(V) = 0.125\exp\left(-\frac{V+65}{80}\right),$$

$$\alpha_h(V) = 0.07\exp\left(-\frac{V+65}{20}\right), \quad \beta_h(V) = \frac{1}{\left(\exp\left(-\frac{V+35}{10}\right)+1\right)},$$

$$\alpha_m(V) = \frac{0.1\,(V+40)}{1-\exp\left(-(V+40)/10\right)}, \quad \beta_m(V) = 4\exp\left(-(V+65)/18\right).$$

$$\phi = Q_{10}^{(T-T_{\mathrm{base}})/10}$$



Summary

What are the advantages and disadvantages of the HH model?

THANK YOU

Aug. 24, 2023