Electro-physiology

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I. Channel current

1. Diffusion primer

* Conventional diffusion

Conservation law: $\underbrace{\frac{\partial}{\partial t} c(x,t)}_{\text{concentration}} = -\frac{\partial}{\partial x} \underbrace{J(x,t)}_{\text{flux}} + \underbrace{f(x,t)}_{\text{production}}$

Fick's law: $J(x,t) = -D\frac{\partial}{\partial x} c(x,t)$

Reaction-diffusion equation: $\frac{\partial}{\partial t} c(x,t) = D\frac{\partial^2}{\partial x^2} c(x,t) + f(x,t)$

* Electrochemical diffusion

Fluxes: $J(x,t) = J_{chemical}(x,t) + J_{electric}(x,t)$

Fick's law: $J_{chemical}(x,t) = -D\frac{\partial}{\partial x} c(x,t)$

lectro valency, electric potential

Planck's equation: $J_{electric}(x,t) = -u \underbrace{\frac{z}{|z|}}_{\text{get sign}} c(x,t) \underbrace{\boxed{\frac{\partial}{\partial x}\phi(x,t)}}_{\text{electric field}}$

Mobility - diffusion coefficient: $u = D\frac{|z|F}{RT}$

F → Faraday constant; T → absolute temperature; R → universal gas constant

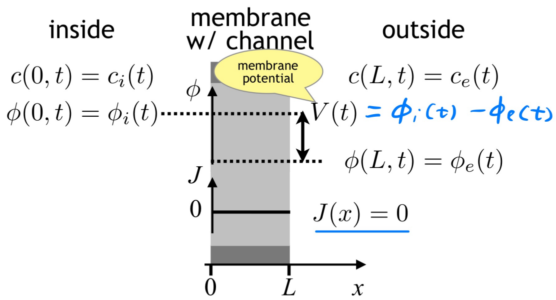
Nernst - Planck equation:

$$\boxed{J(x,t) = -D\left(\frac{\partial}{\partial x} c(x,t) + \frac{zF}{RT} c(x,t)\frac{\partial}{\partial x}\phi(x,t)\right)}$$

"any-time equation" — always true

2. Electrochemical diffusion through the membrane

* Case 1 : No flux



☆ flux = 0 → membrane potential = Nernst potential

BUT

membrane pot. = Nernst pot. $\not\rightarrow$ flux = 0

$$J(x,t) = -D\left(\frac{d}{dx}c(x,t) + \frac{zF}{RT}c(x,t)\frac{d}{dx}\phi(x,t)\right) = 0$$

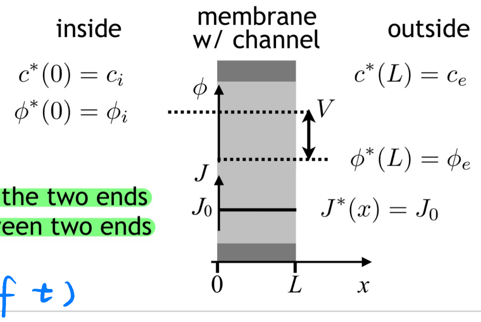
Nernst potential:

$$\boxed{V = \phi_i(t) - \phi_e(t) = \frac{RT}{zF}\ln\left(\frac{c_e(t)}{c_i(t)}\right)}$$

→ dependent on concentrations

* Case 2: Steady state → Constant flux + membrane potential = Nernst pot.

⇒ no change in concentration anywhere over time



boundary condition:
- concentration at the two ends and voltage between two ends is kept fixed

(independent of t)

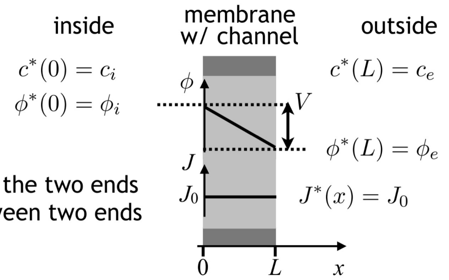
$$J^*(x) = -D\left(\frac{d}{dx}c^*(x) + \frac{zF}{RT}c^*(x)\frac{d}{dx}\phi^*(x)\right) = J_0$$

Only possible $J_0 = 0$

$$\boxed{V = \frac{RT}{zF}\ln\frac{c_e}{c_i} \iff J^* = 0}$$

Steady-state form of Nernst equation

* Case 3: Steady state → constant flux + linear potential (constant field)



boundary condition:
- concentration at the two ends and voltage between two ends is kept fixed

$$J^*(x) = -D\left(\frac{d}{dx}c^*(x) + \frac{zF}{RT}c^*(x)\frac{d}{dx}\phi^*(x)\right) = J_0$$

Solution: $$J^* = \frac{D}{L}\frac{zFV}{RT}\frac{c_i - c_e e^{-\frac{zVF}{RT}}}{1 - e^{-\frac{zVF}{RT}}}$$

$I = zFJ$

$P = \frac{D}{L}$ → channel permeability

$$\boxed{\text{Goldman-Hodgkin-Katz equation: } \quad I^* = P\frac{z^2F^2}{RT}\cdot V \cdot \frac{c_i - c_e e^{-\frac{zVF}{RT}}}{1 - e^{-\frac{zVF}{RT}}}}$$

Without assumption on electric field:

Use Poisson equation $\frac{d^2}{dx^2}\phi(x,t) = -\frac{F}{\epsilon} z c(x,t)$

ϵ → dielectric constant

→ No general analytical solution

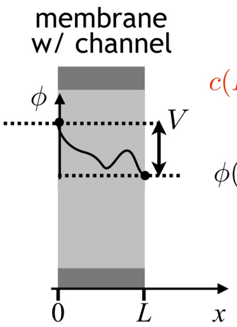
* Opponent charges within the channel

$z_1 = +1$
$z_2 = -1$
$P_1 \gg P_2$

inside

$c_1(0,t) = c_2(0,t) = c_i$

$\phi(0,t) = \phi_i$



outside

$c(L,t) = c(L,t) = c_e$

$\phi(L,t) = \phi_e$

$$\frac{\partial}{\partial t} c_1(x,t) = -\frac{\partial}{\partial x} J_1(x,t)$$

✰ Assumptions:

- two different species move inside the channel
- opposite charges & uneven permeabilities
- boundary conditions:
  - electroneutrality in/out side the cell
  - Concentration & potential at the two ends kept fixed

$$\frac{\partial}{\partial t} C_1(x,t) = -\frac{\partial}{\partial x} J_1(x,t)$$

$$J(x,t) = -D_1\left(\frac{\partial}{\partial x} C_1(x,t) \overset{z=+1}{\oplus} \frac{F}{RT} C_1(x,t) \frac{\partial}{\partial x}\phi(x,t)\right)$$

$$\frac{\partial}{\partial t} C_2(x,t) = -\frac{\partial}{\partial x} J_2(x,t)$$

$$J(x,t) = -D_2\left(\frac{\partial}{\partial x} C_2(x,t) \overset{z=-1}{\ominus} \frac{F}{RT} C_2(x,t) \frac{\partial}{\partial x}\phi(x,t)\right)$$

$$\frac{\partial^2}{\partial x^2}\phi(x,t) = -\frac{F}{\epsilon}\left(C_1(x,t) - C_2(x,t)\right)$$

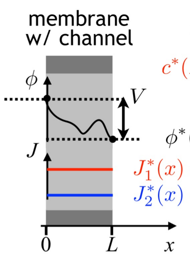
At Steady state → Constant flux

$z_1 = +1$
$z_2 = -1$
$P_1 \gg P_2$

inside

$c_1^*(0) = c_2^*(0) = c_i$

$\phi^*(0) = \phi_i$



outside

$c^*(L) = c^*(L) = c_e$

$\phi^*(L) = \phi_e$

$J_1^*(x) = J_1^*$

$J_2^*(x) = J_2^*$

$$-\bar{J}_1^* = \frac{d}{d\bar{x}} \bar{c}_1^*(\bar{x}) + \bar{c}_1^*(x) \frac{d}{d\bar{x}} \bar{\phi}^*(x)$$

$$-\bar{J}_2^* = \frac{d}{d\bar{x}} \bar{c}_2^*(\bar{x}) - \bar{c}_2^*(x) \frac{d}{d\bar{x}} \bar{\phi}^*(x)$$

$$\frac{d^2}{d\bar{x}^2}\bar{\phi}^*(x) = -\lambda^2\left(\bar{c}_1^*(x) - \bar{c}_2^*(x)\right)$$

✰ Dimensionless variables:

$\bar{x} = x/L$

$\bar{\phi} = (\phi - \phi_e) F/RT$

$\bar{V} = VF/RT$

$\bar{C}_n = C_n / (C_i + C_e)$

$\bar{J}_n = (L/D_n) J_n / (C_i + C_e)$

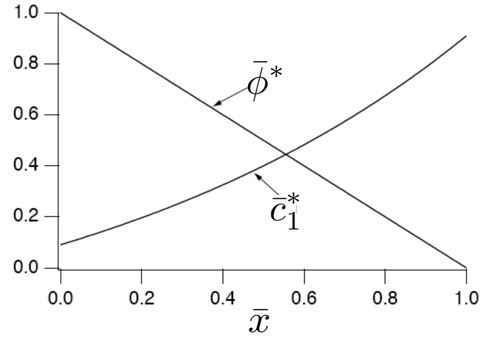
$\lambda^2 = L^2 F^2 (C_i + C_e) / (\epsilon R T)$

3. Channel current

* Short channel limit

$$\lambda^2 = L^2 F^2 (c_i + c_e) / (\epsilon RT) \to 0$$

$(L \to 0$ and / or $c_i + c_e \to 0)$



$$\Downarrow$$

$$\frac{d^2}{d\bar{x}^2} \bar{\phi}^*(\bar{x}) = 0$$

$$\Downarrow$$

$$\bar{\phi}^*(\bar{x}) = (1-\bar{x})\bar{V} \longrightarrow \text{linear}$$

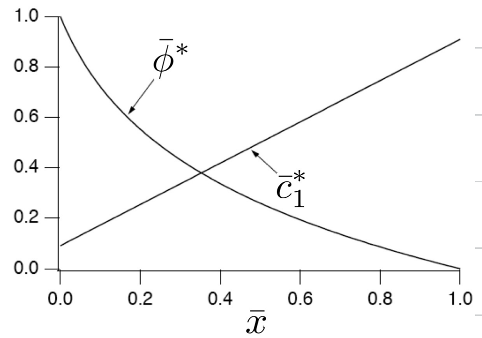
$$\bar{J}_1^* = \bar{V} \cdot \frac{\bar{c}_i - \bar{c}_e e^{-\bar{V}}}{1 - e^{-\bar{V}}}$$

$$\bar{c}_1^*(\bar{x}) = \frac{\bar{J}_1^*}{\bar{V}} + \left(\bar{c}_i - \frac{\bar{J}_1^*}{\bar{V}}\right) e^{\bar{V}\bar{x}}$$

> Goldman – Hodgkin – Katz current equation:
>
> $$I_1^*(V) = P_1 \frac{F^2}{RT} \cdot V \cdot \frac{c_i - c_e e^{-\frac{VF}{RT}}}{1 - e^{-\frac{VF}{RT}}}$$

* Long channel limit

$$\lambda^2 = L^2 F^2 (c_i + c_e) / (\epsilon RT) \to \infty$$



$$\Downarrow$$

$$\bar{c}_1^*(x) - \bar{c}_2^*(x) = 0 \quad \text{Constant conc. difference}$$

$$\Downarrow$$

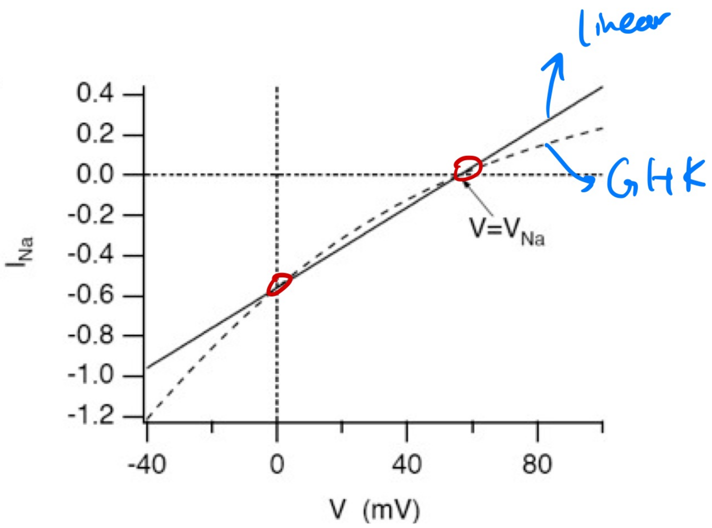
$$\bar{c}_1^*(\bar{x}) = \bar{c}_i + (\bar{c}_e - \bar{c}_i)\bar{x}$$

$$\bar{\phi}^*(\bar{x}) = -\frac{\bar{V}}{\bar{V}_1} \ln\left[\frac{\bar{c}_i}{\bar{c}_e} + \left(1 - \frac{\bar{c}_i}{\bar{c}_e}\right)\bar{x}\right] \qquad \bar{V}_1 = \ln\left(\frac{\bar{c}_e}{\bar{c}_i}\right)$$

$$\bar{J}_1 = \frac{\bar{c}_e - \bar{c}_i}{\bar{V}_1}(\bar{V} - \bar{V}_1) \longrightarrow \text{linear} \qquad V_1 = \frac{RT}{F}\ln\left(\frac{c_e}{c_i}\right) \to \text{Nernst potential}$$

> Linear I–V curve:
>
> $$I_1^*(V) = \underbrace{P_1 \frac{F^2}{RT} \frac{c_e - c_i}{\ln c_e/c_i}}_{g_1 \text{ conductance}} \cdot (V - V_1)$$

* GHK vs linear I-V relationship



GHK and linear model gives the same current at

- $V = V_0 \longrightarrow$ Nernst potential
  No current
- $V = 0 \longrightarrow \frac{d\phi}{dx} = 0$
  No electrical potential difference, only diffusion

☆ Key assumption: separation of time scale

— each subsystem can be described by its <u>steady state</u> (variables are constant) as long as its time scale is much faster than the time scale of interaction between the subsystems

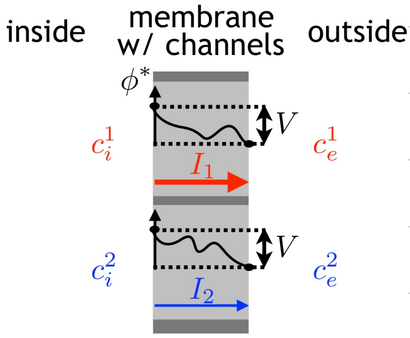
☆ Summary

short channel → GHK: $I^*(V) = P\,\frac{F^2}{RT} \cdot V \cdot \frac{c_i - c_e\, e^{-\frac{VF}{RT}}}{1 - e^{-\frac{VF}{RT}}}$

long channel → linear: $I^*(V) = \underbrace{P\,\frac{F^2}{RT}\,\frac{c_e - c_i}{\ln c_e/c_i}}_{g} \cdot \left[V - \underbrace{\frac{RT}{F}\ln\left(\frac{c_e}{c_i}\right)}_{V_0}\right]$

I. Resting membrane potential

1. Channel current cancels out



Channels are in parallel:

$$I_m(V) = \sum_i I_i(V)$$

$$I_m(V_{rest}) = 0$$

GHK: $$V_{rest} = -\frac{RT}{F}\ln\left(\frac{\sum_{j|z_j=-1} P_j c_e^j + \sum_{j|z_j=+1} P_j c_i^j}{\sum_{j|z_j=-1} P_j c_i^j + \sum_{j|z_j=+1} P_j c_e^j}\right)$$

$$= -\frac{RT}{F}\ln\left(\frac{P_{Na^+}[Na^+]_i + P_{K^+}[K^+]_i + P_{Cl^-}[Cl^-]_e}{P_{Na^+}[Na^+]_e + P_{K^+}[K^+]_e + P_{Cl^-}[Cl^-]_i}\right)$$

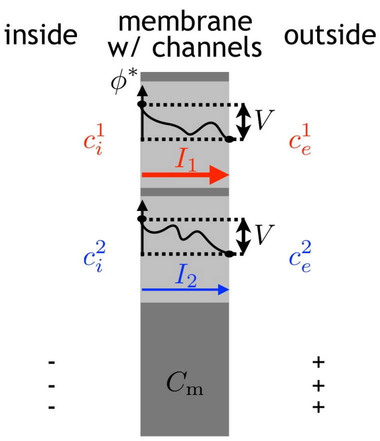
Linear: $$V_{rest} = \frac{\sum_j g_j V_j}{\sum_j g_j}$$

$\sum_j g_j V_j$ → total current

$\sum_j g_j$ → total conductance

$$= \frac{g_{Na^+}V_{Na^+} + g_{K^+}V_{K^+} + g_{Cl^-}V_{Cl^-}}{g_{Na^+} + g_{K^+} + g_{Cl^-}}$$

2. Membrane as a capacitor



opposite charges accumulated on opposing side of the lipid bilayer (insulator)

↓

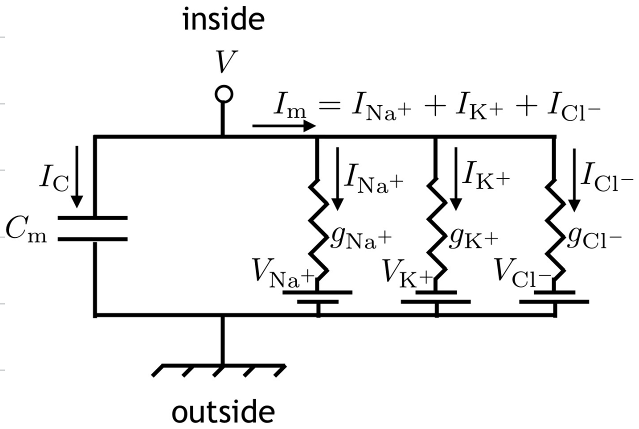
membrane act as a capacitor

$$C_m V = Q$$

$$C_m \frac{d}{dt}V(t) = \frac{d}{dt}Q(t) = I_c(t)$$

	V_X (mV)	g_X $\left(\frac{\text{mS}}{\text{cm}^2}\right)$
Na^+	+55	0.01
K^+	-75	0.20
Cl^-	-69	0.05
C_m $\left(\frac{\mu\text{F}}{\text{cm}^2}\right)$	1.0	

3. The cell as an RC circuit



Unit: $\frac{\mu A}{cm^2}$ $\frac{mS}{cm^2}$ mV

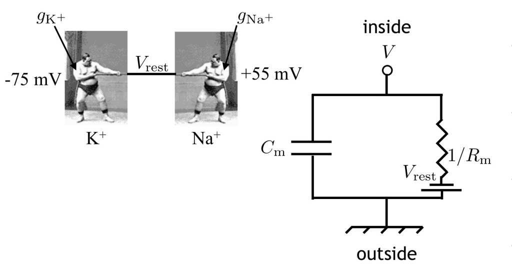
$$-I_{Na^+}(t) = g_{Na^+} \cdot (V_{Na^+} - V(t))$$

$$-I_{K^+}(t) = g_{K^+} \cdot (V_{K^+} - V(t))$$

$$-I_{Cl^-}(t) = g_{Cl^-} \cdot (V_{Cl^-} - V(t))$$

Current balance equation:

$$\left[\frac{\mu F}{cm^2}\frac{1}{ms}mV\right] \rightarrow C_m \frac{d}{dt}V(t) = -I_{Na^+}(t) - I_{K^+}(t) - I_{Cl^-}(t) \leftarrow \left[\frac{\mu A}{cm^2}\right]$$

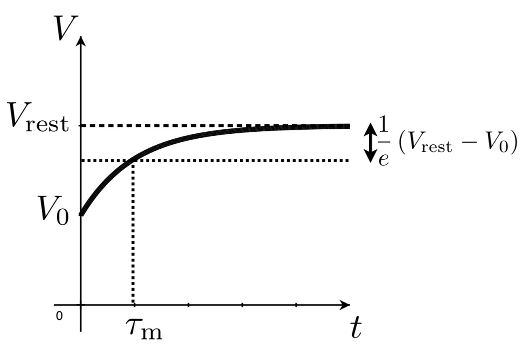


$$= g_{Na^+}(V_{Na^+} - V(t)) + g_{K^+}(V_{K^+} - V(t)) + g_{Cl^-}(V_{Cl} - V(t))$$

$$= \frac{1}{R_m}(V_{rest} - V(t))$$

$$\boxed{V_{rest} = \frac{g_{Na^+}V_{Na^+} + g_{K^+}V_{K^+} + g_{Cl^-}V_{Cl^-}}{g_{Na^+} + g_{K^+} + g_{Cl^-}}}$$ resting potential

$$\boxed{R_m = \frac{1}{g_{Na^+} + g_{K^+} + g_{Cl^-}}}$$ membrane resistance



$$\frac{d}{dt}V(t) = \frac{V_{rest} - V(t)}{\tau_m}$$

$\tau_m = C_m R_m$ membrane time constant

$$V(t) = V_{rest} - (V_{rest} - V_0)e^{-\frac{t}{\tau_m}}$$

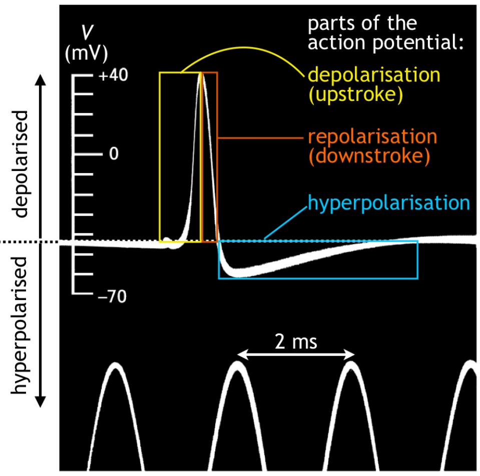
$$V(0) = 0$$

Note:
- Na^+ and K^+ conductances set the resting membrane potential
- Speed of convergence depends on the overall membrane conductance

III. Action potential

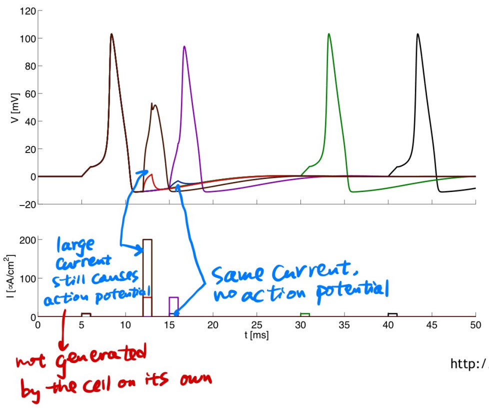
membrane potential regimes:

resting membrane potential



Hodgkin & Huxley, 1939

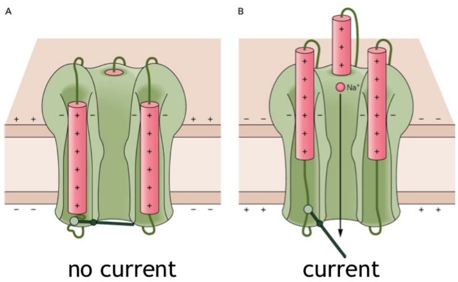
synonyms:
- action potential
- spike
- firing



http://www.eng.cam.ac.uk/~m.lengyel

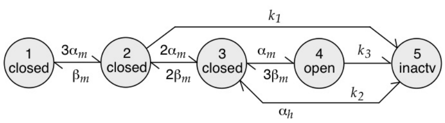
refractory period
- relative → Completely unresponsive to any stimulus
- absolute → Can fire action potential with a much larger stimulus

1. Voltage gated ion channels



- each channel is composed of gates
- a channel is fully open if ALL of its gates are open
- gates open independently

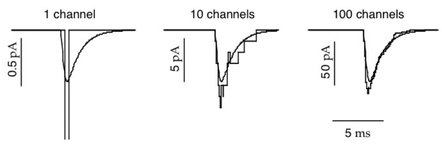
reaction scheme for channel



occupancy probs p_1 p_2 p_3 p_4 p_5

channel conductance depends on state $g_1{=}0$ $g_2{=}0$ $g_3{=}0$ $g_4{=}1$ $g_5{=}0$

rate constants depend on membrane potential $\alpha_{\mathrm{m}}(V)$ $\beta_{\mathrm{m}}(V)$ $\alpha_{\mathrm{h}}(V)$

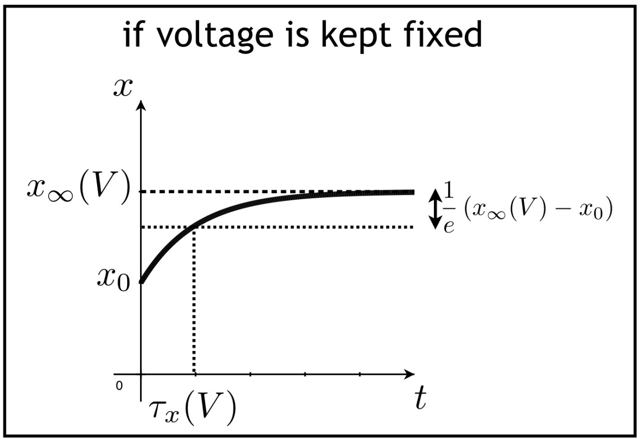


Reaction scheme for a single gate:

$$\underset{\text{closed}}{C} \underset{\beta_x(V)}{\overset{\alpha_x(V)}{\rightleftharpoons}} \underset{\text{open}}{O}$$

$$\frac{d}{dt}x(t) = \underbrace{\alpha(V(t))(1-x(t))}_{C \to O} - \underbrace{\beta_x(V(t))\,x(t)}_{O \to C} \qquad x \in \{0, 1\}$$

$$\frac{d}{dx}x(t) = \frac{x_\infty(V(t)) - x(t)}{\tau_x(V(t))}$$



Steady-state value:

$$x_\infty(V) = \frac{\alpha_x(V)}{\alpha_x(V) + \beta_x(V)}$$

Time constant:

$$\tau_x(V) = \frac{1}{\alpha_x(V) + \beta_x(V)}$$

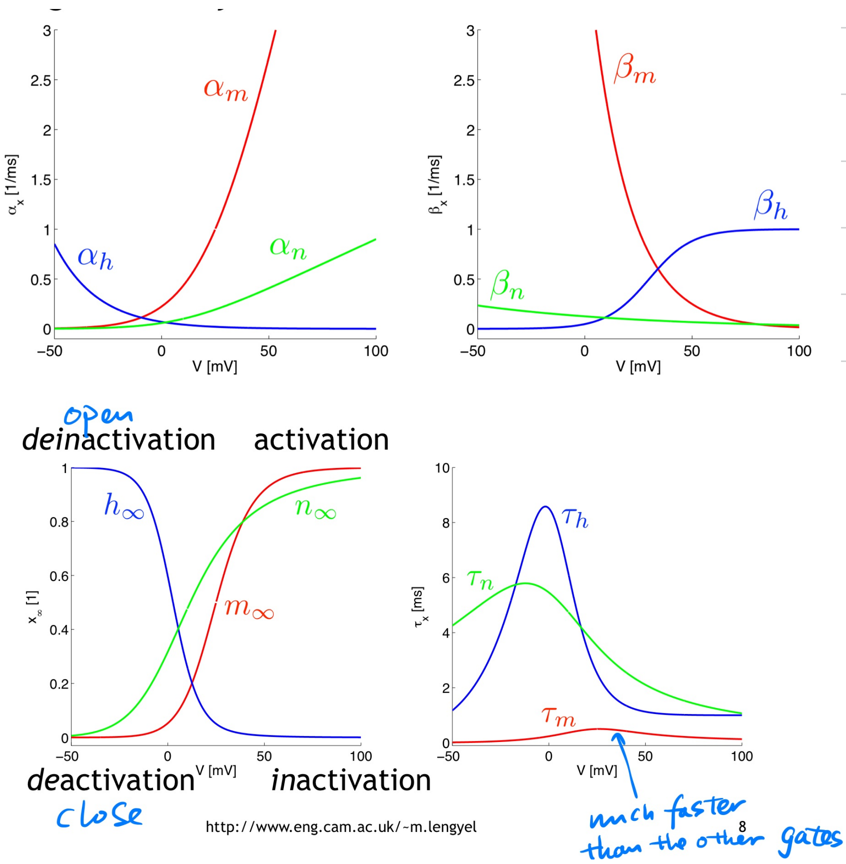
$$\boxed{\begin{aligned} g_{Na^+}(t) &= \bar{g}_{Na^+}\, m^3(t)\, h(t) \\ g_{K^+}(t) &= \bar{g}_{K^+}\, n^4(t) \end{aligned}}$$

Gating equations:

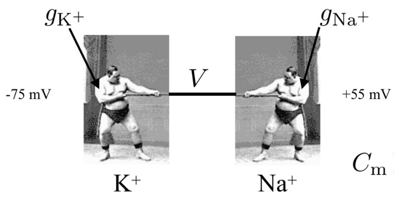
$$\frac{d}{dt}m(t) = \frac{m_\infty(V(t)) - m(t)}{\tau_m(V(t))}$$

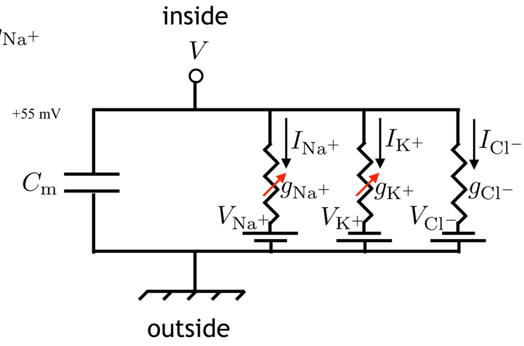
$$\frac{d}{dt}h(t) = \frac{h_\infty(V(t)) - h(t)}{\tau_h(V(t))}$$

$$\frac{d}{dt}n(t) = \frac{n_\infty(V(t)) - n(t)}{\tau_n(V(t))}$$



2. The Hodgkin – Huxley model



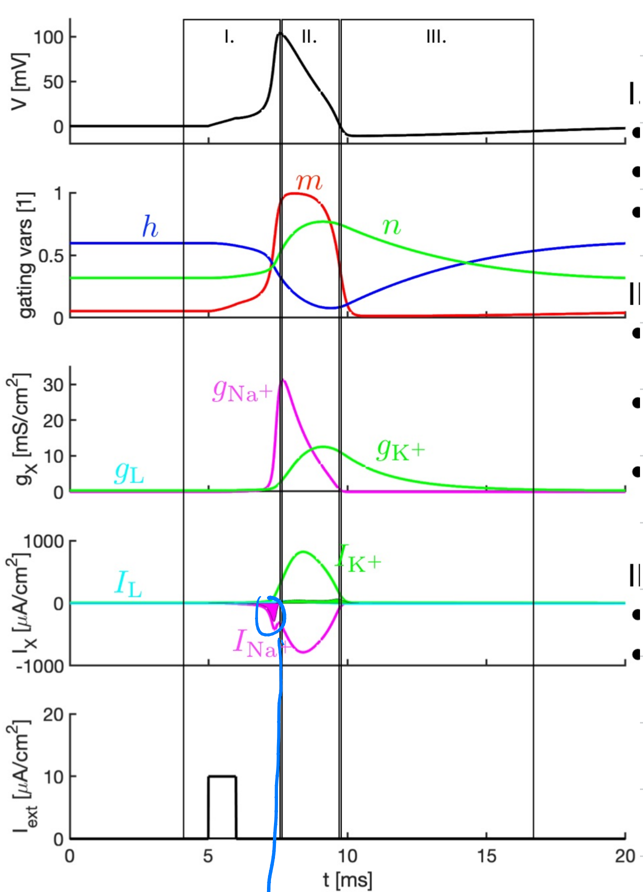


Current balancing equation:

$$C_m \frac{d}{dt} V(t) = \bar{g}_{Na^+} m^3(t)\, h(t)\, (V_{Na^+} - V(t)) +$$

$$\bar{g}_{K^+} n^4(t)\, h(t)\, (V_{K^+} - V(t)) +$$

$$\underbrace{\bar{g}_L (V_L - V(t))}_{\text{leak current}} + I_{ext}(t)$$



'useful' current that actually leads to the action potential — other currents get cancelled

In action:

I. ① Depolarisation (fast +ve feedback)

- injected current depolarises V
- depolarised V activates m → Na^+ channel opens
- activated m further depolarise V

II. ② Repolarisation (slow –ve feed back)

- depolarised V activates n and inactivates h
- activated n and inactivated h repolarises V → K^+ channel opens
- replorising V deactivates m → Na^+ ch. closes

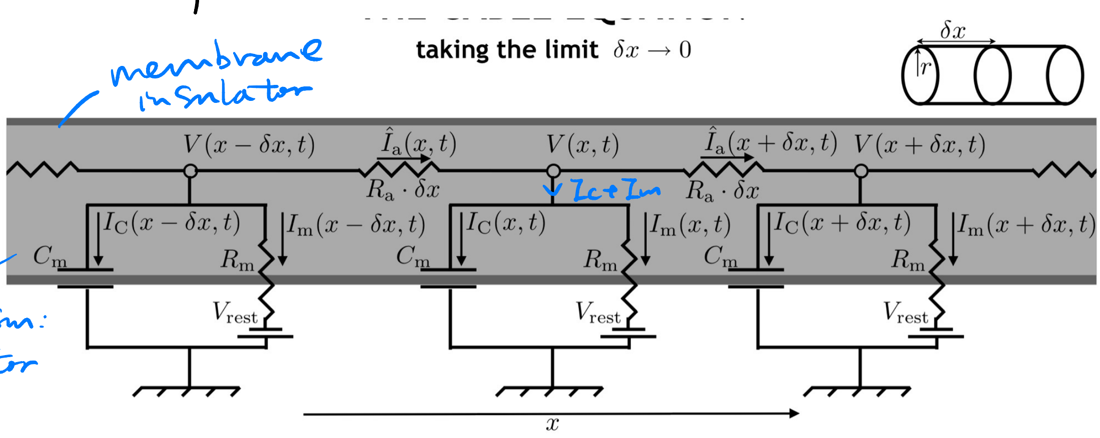
III. ③ Hyperpolarisation

- n deactivates and h deinactivates — determines the refractory period
- V returns to resting membrane potential

IV. Propagation

1. The Cable equation

membrane insulator



cytoplasm: conductor

☆ Assumptions:

- No radial or angular voltage variations
- Equipotentiality outside the cell

$$\underbrace{\left[\overset{[\mu A/cm^2]}{I_c(x,t) + I_m(x,t)}\right]}_{\text{current / unit area}} \underbrace{\overset{[cm^2]}{2r\pi\,\delta x}}_{\text{surface}} = \overset{[\mu A]}{\hat{I}_a(x,t) - \hat{I}_a(x+\delta x,t)}$$

$$\hat{I}_a(x,t) = \frac{V(x-\delta x,t) - V(x,t)}{\underset{[k\Omega\, cm]}{R_a} \cdot \frac{\delta x}{r^2\pi} \frac{[cm]}{[cm^2]}}$$

$$C_m \frac{\partial}{\partial t} V(x,t) = \underbrace{\frac{V_{rest} - V(x,t)}{R_m\, [k\Omega cm^2]}}_{-I_m(x,t)} + \underset{\text{external current}}{I_{ext}(x,t)} + \frac{r}{2R_a} \frac{\partial^2}{\partial x^2} V(x,t)$$

$$\boxed{\tau_m \frac{\partial}{\partial t} V(x,t) = \lambda^2 \frac{\partial^2}{\partial x^2} V(x,t) - V(x,t) + R_m I_{ext}(x,t)}$$

Time constant: $\tau_m = C_m R_m$ [ms]	$V_{rest} = 0$ mV
Space constant: $\lambda = \sqrt{\frac{R_m r}{2R_a}}$ [cm]	

2. Solutions of the linear cable equation

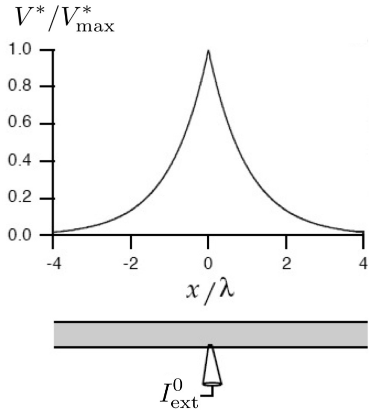
* Constant point current injection — steady-state solution

(1) Infinite cable

$$I_{ext}(x,t) = I^0_{ext}\,\delta(x)$$

$$\hat{I}_{total} = 2\pi r \int_{-\infty}^{+\infty} I_{ext}(x)\,dx = I^0_{ext}\,2\pi r$$

$$\boxed{V^*(x) = \underbrace{\hat{I}_{total}\,\hat{R}_{in}}_{V^*_{max}}\, e^{-\frac{|x|}{\lambda}}}$$



input resistance

$$\hat{R}_{in} = \frac{V^*_{max}}{\hat{I}_{total}} = \frac{\hat{R}_\lambda}{2}$$

two branches in parallel

$[k\Omega]$

unit resistance

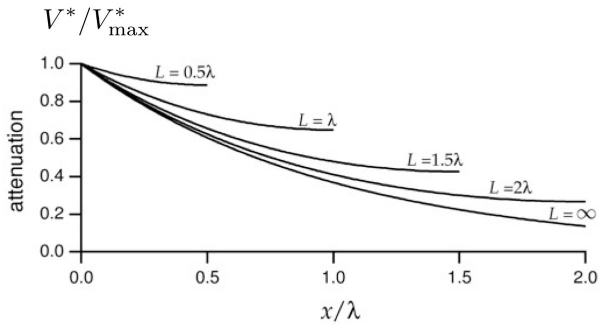
$$\hat{R}_\lambda = \frac{R_m}{2\pi r\lambda} = \frac{R_a\lambda}{\pi r^2} = \frac{\sqrt{R_m R_a}}{\sqrt{2}\,\pi}\, r^{-3/2}$$

membrane resistance — axial resistance → of segment of length λ and radius r

(for semi-infinite cable $\hat{R}_{in} = \hat{R}_\lambda$)

(2) Finite cable

$$\boxed{\frac{V^*(x)}{V^*_{max}} = \frac{\cosh\frac{L-x}{\lambda}}{\cosh\frac{L}{\lambda}}}$$



L : Length of cable

* Pulse current injection —— time-dependent solution

Assumption: infinite cable

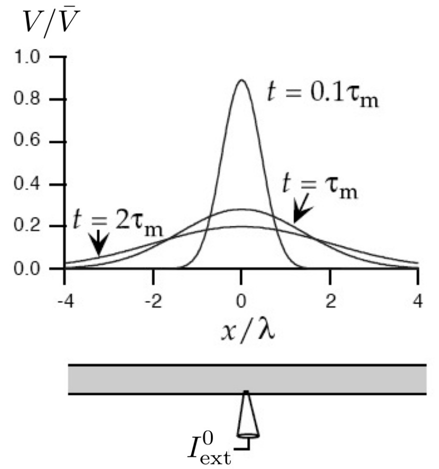
$$I_{ext}(x,t) = I^0_{ext}\,\delta(x)\,\delta(t)$$

$$\hat{Q}_{total} = \int_{-\infty}^{+\infty} 2\pi r \int_{-\infty}^{+\infty} I_{ext}(x,t)\,dx\,dt$$

$$= I^0_{ext}\; 2\pi r\; 1\,cm\; 1\,ms \quad [nC]$$

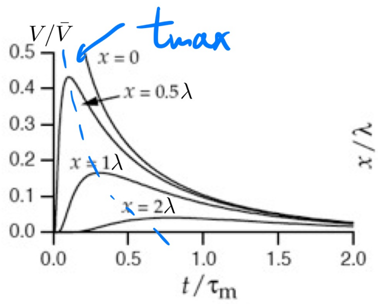
$$\boxed{V(x,t) = \frac{1}{2\pi r}\,\frac{\hat{Q}_{total}}{c_m}\,\underbrace{\frac{1}{\sqrt{4\pi\lambda^2\frac{t}{\tau_m}}}\,e^{-\frac{x^2}{4\lambda^2\frac{t}{\tau_m}}}}\; e^{-\frac{t}{\tau_m}}}$$

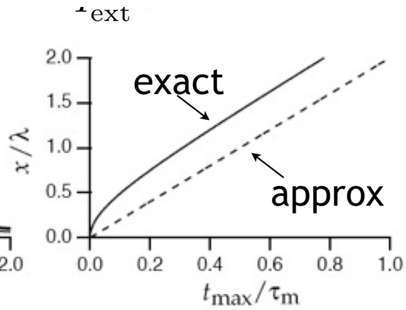
Gaussian with $\mu = 0$ and $\sigma = \sqrt{2}\lambda\sqrt{t/\tau_m}$



$$t_{max} = \frac{\tau_m}{4}\left(\sqrt{1+4(x/\lambda)^2} - 1\right) \approx x\,\frac{\tau_m}{2\lambda}$$

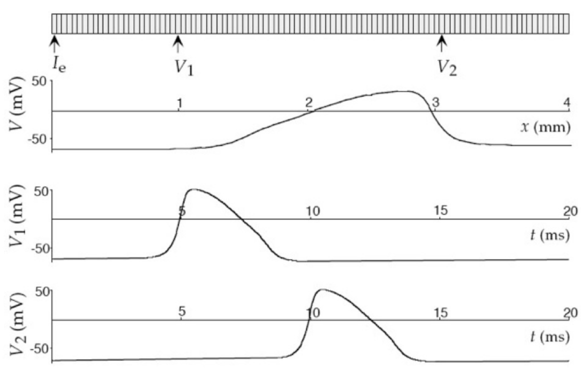
$$\boxed{\text{propagation speed: } \frac{2\lambda}{\tau_m} \propto \sqrt{r}}$$

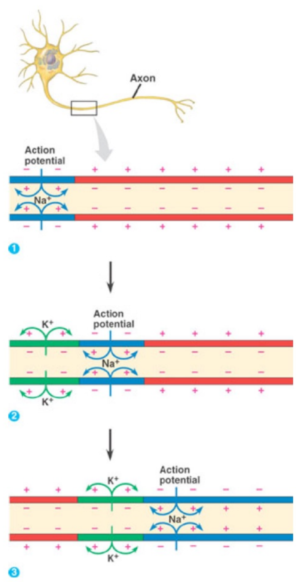




3. Active propagation

Uni-directional due to refractory period → does not propagate to where it came from





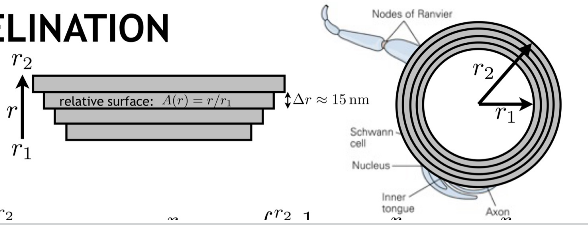
propagation speed: $\frac{2\lambda}{\tau_m} \propto \sqrt{r}$

4. Myelination

MYELINATION

$$R_m(r) = \frac{r_1}{r} R_m$$

$$C_m(r) = \frac{r}{r_1} C_m$$



$$R_m^{myelin} = \frac{1}{\Delta r}\int_{r_1}^{r_2} R_m(r)\,dr = \frac{r_1}{\Delta r} R_m \int_{r_1}^{r_2} \frac{1}{r}\,dr = \frac{r_1}{\Delta r} R_m \ln\frac{r_2}{r_1}$$

$$\frac{1}{C_m^{myelin}} = \frac{1}{\Delta r}\int_{r_1}^{r_2} \frac{1}{C_m(r)}\,dr = \frac{r_1}{\Delta r}\frac{1}{C_m}\int_{r_1}^{r_2}\frac{1}{r}\,dr = \frac{r_1}{\Delta r}\frac{1}{C_m}\ln\frac{r_2}{r_1}$$

$$\tau_m^{myelin} = C_m^{myelin} R_m^{myelin} = \tau_m$$

$$\lambda_m^{myelin} = \sqrt{\frac{R_m^{myelin} r_1}{2R_a}} = \sqrt{\frac{R_m}{2\Delta r R_a} r_1^2 \ln\frac{r_2}{r_1}}$$

Goal: optimise r_1 for fixed r_2 $\longrightarrow$ $\frac{d\lambda^{myelin}}{dr_1} = 0$

Solution:

$$\boxed{\begin{aligned} r_1 &= r_2\sqrt{\frac{1}{e}} \\ \lambda^{myelin} &= r_2\sqrt{\frac{R_m}{4\Delta r R_a e}} \quad \propto r_2 \end{aligned}}$$

propagation speed: $\frac{2\lambda^{myelin}}{\tau^{myelin}} \propto r_2$