Cellular Electrodynamics

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Reference/Acknowledgement:
- TF Weiss (Cellular Biophysics)
- D Freeman
Some key observations...

Interrelationships between:

- Na⁺ flux
- ‘active’ transport
- action potentials

Active transport not a priori required for AP generation

DNP reduces ATP production
Some key observations...

Na\(^+\) flux affects APs (*early on*)

K\(^+\) flux affects APs (*later on*)

Figure 4.2

Figure 4.5

→ Na\(^+\) flux affects APs (*early on*)

→ K\(^+\) flux affects APs (*later on*)
Idea 1 – Multiple permeant ions with different conductance (e.g., $G_k >> G_{Na}$)

Idea 2 – $K^+$ and $Na^+$ conductances can vary over time
What are $G_K(V_m,t)$ and $G_{Na}(V_m,t)$?

→ Not easy to empirically distinguish, so new electrophysiological techniques were required
Space-Clamp

Eliminates spatial dependence
(i.e., make an electrically large cell a small one)

Conduction velocity
(Core-Conductor model)

\[ r_i = \frac{\rho_i}{\pi a^2} \]

\[ v = \sqrt{\frac{\kappa m a}{2\rho_i}} \]

Figure 4.10

Kenneth Cole & George Marmont (1940s)

Figure 2.15
Electrically ‘small’ cell can still fire action potentials
Voltage-Clamp

Space clamp
\[ \frac{\partial V_m}{\partial z} = 0 \]

Step voltage clamp
\[ \frac{\partial V_m}{\partial z} = \frac{\partial V_m}{\partial t} = 0 \]

Separation of ionic currents
Separating Ionic Currents

$V_m(t)$

$t$

Depolarizing step

$V_m^f$

Hyperpolarizing step

$V_m^i$

$J_m(t)$

Brief surge of outward current

Persistent, late outward current

Transient, early, inward current

$K^+?$

$Na^+?$

Figure 4.12

Figure 4.6

$J_C$ $J_K$ $J_{Na}$ $J_L$

$G_K(V_m,t)$ $G_{Na}(V_m,t)$ $G_L$

$V_K^+$ $V_{Na}^+$ $V_L^+$

Intracellular

Membrane

Extracellular
Capacitive Current

\[
V_m(t) \quad t
\]

Depolarizing step \( V_m^f \)

Hyperpolarizing step

\[
J_m(t)
\]

Brief surge of outward current

Persistent, late outward current

Transient, early, inward current

Figure 4.12

\[
K_m(z,t) \Delta z
\]

\[
c_m \Delta z
\]

\[
V_m(z,t)
\]

\[
V_m^0 +
\]

\[
V_m -
\]

\[
i_e(t) = A J_m = A C_m \frac{dV_m}{dt} + A G_m (V_m - V_m^0)
\]

\[
\frac{A C_m}{A G_m} \frac{dV_m}{dt} + V_m = V_m^0 + \frac{i_e(t)}{A G_m}
\]

Figure 4.13
But what of the other ionic currents?

\[
\frac{1}{2\pi a(r_o + r_i)} \frac{\partial^2 V_m}{\partial z^2} - \frac{1}{a(r_o + r_i)} \frac{\partial V_m}{\partial t} + G_K(V_m, t) (V_m - V_K) + G_Na(V_m, t) (V_m - V_{Na}) + G_L(V_m - V_L)
\]

- What are \( G_K(V_m, t) \) and \( G_Na(V_m, t) \)?

\[ V_{Na} = \frac{RT}{F} \log \frac{c_{Na}^0}{c_{Na}^i} \]

- Separating ionic currents by subtraction (assumes \( J_K \) unaffected by changes in [Na\(^+\)])
Reversal Potential?

Close to Na\(^+\) Nernst potential!
Figure 4.16
NOTE: Other methods besides subtraction (e.g., TTX to block Na\(^+\) current, replace K\(^+\) w/ Cs\(^+\), etc...)

\[ K^+ \text{ simply turns on (with a bit of a slow start)} \]

\[ Na^+ \text{ more complex (early ‘activation’, followed by ‘inactivation’)} \]

Figure 4.20
What are $G_K(V_m,t)$ and $G_{Na}(V_m,t)$?

→ Physiological data suggests Na$^+$ *activates* and then *inactivates* while K$^+$ simply *activates* (based upon $V_m$)
Model for $G_K(V_m,t)$ and $G_{Na}(V_m,t)$?

1. Use voltage-clamp to obtain suitable data

$$G_K(V_m,t) = \frac{J_K(V_m,t)}{V_m - V_K}$$

$$G_{Na}(V_m,t) = \frac{J_{Na}(V_m,t)}{V_m - V_{Na}}$$

2. Devise sufficient model to describe

→ First-order kinetics variables

$$\frac{dx}{dt} = \alpha x (1 - x) - \beta x x$$
Review: First-Order Chemical Kinetics

First-order, reversible reaction

\[ R \xrightleftharpoons[\beta]{\alpha} P \]

\[ \frac{d c_R(t)}{dt} = \beta c_P(t) - \alpha c_R(t) \quad \text{AND} \quad \frac{d c_P(t)}{dt} = \alpha c_R(t) - \beta c_P(t) \]

Equilibrium:

\[ \frac{d c_R(t)}{dt} = \frac{d c_P(t)}{dt} = 0 \rightarrow \beta c_P(\infty) = \alpha c_R(\infty) \]

\[ \frac{c_P(\infty)}{c_R(\infty)} = \frac{\alpha}{\beta} = K_a \quad \text{(association, equilibrium, affinity, stability, binding, formation constant)} \]

Kinetics: assume total amount of reactant and product is conserved

\[ c_R(t) + c_P(t) = C \]

\[ \frac{d c_R(t)}{dt} = \beta \left( C - c_R(t) \right) - \alpha c_R(t) \]

\[ \frac{d c_R(t)}{dt} + (\alpha + \beta)c_R(t) = \beta C \]
Review: First-Order Chemical Kinetics

First-order, reversible reaction

\[ R \xrightleftharpoons[\beta]{\alpha} P \]

First-order linear differential equation with constant coefficients

\[ c_R(t) = c_R(\infty) - \left( c_R(\infty) - c_R(0) \right) e^{-t/\tau}, \text{ for } t > 0 \]

\[ c_R(\infty) = \frac{\beta}{\alpha + \beta} C = \frac{1}{1 + K_a} C \quad \text{AND} \quad \tau = \frac{1}{\alpha + \beta} \]

First-order, reversible reaction

\[ R \xrightleftharpoons[\beta]{\alpha} P \]

- \[ c_R(0) \]
- \[ K_a C/(1 + K_a) \]
- \[ c_R(t) \]
- \[ c_P(t) \]
- \[ c_P(0) \]
- \[ C/(1 + K_a) \]
- \[ \tau = \frac{1}{\alpha + \beta} \]
HH: First-Order Kinetics

\[
\frac{dx}{dt} = \alpha_x (1 - x) - \beta_x x
\]

\[
\tau_x \frac{dx}{dt} + x = x_\infty
\]

\[
x_\infty = \frac{\alpha_x}{\alpha_x + \beta_x} \text{ and } \tau_x = \frac{1}{\alpha_x + \beta_x}
\]

\[
x(t) = x_\infty - (x_\infty - x_0) e^{-t/\tau_x} \quad t \geq 0
\]

- Dynamics (i.e., depend. upon \(t\)) captured by chemical kinetics

- Voltage depend. (i.e., \(V_m\)) captured by how kinetic’s parameters affected by membrane potential
\[
\begin{align*}
m(V_m, t) + \tau_n(V_m) \frac{dn(V_m, t)}{dt} &= n_\infty(V_m) \\
m(V_m, t) + \tau_m(V_m) \frac{dm(V_m, t)}{dt} &= m_\infty(V_m) \\
h(V_m, t) + \tau_h(V_m) \frac{dh(V_m, t)}{dt} &= h_\infty(V_m)
\end{align*}
\]

\[
\begin{align*}
\tau_m &= \frac{1}{\alpha_m + \beta_m}, \quad \text{and} \quad m_\infty = \frac{\alpha_m}{\alpha_m + \beta_m}, \\
\tau_h &= \frac{1}{\alpha_h + \beta_h}, \quad \text{and} \quad h_\infty = \frac{\alpha_h}{\alpha_h + \beta_h}, \\
\tau_n &= \frac{1}{\alpha_n + \beta_n}, \quad \text{and} \quad n_\infty = \frac{\alpha_n}{\alpha_n + \beta_n}.
\end{align*}
\]

\[m \quad \text{– sodium activation}\]

\[h \quad \text{– sodium inactivation}\]

\[n \quad \text{– potassium activation}\]
\[ G_K(V_m, t) = \overline{G}_K n^4(V_m, t) \]
\[ G_{Na}(V_m, t) = \overline{G}_{Na} m^3(V_m, t) h(V_m, t) \]

→ Functional form to best fit the data
(e.g., exponentiating yields sigmoids)

\[ \alpha_m = \frac{-0.1(V_m + 35)}{e^{-0.1(V_m+35)} - 1}, \]
\[ \beta_m = 4e^{-(V_m+60)/18}, \]
\[ \alpha_h = 0.07e^{-0.05(V_m+60)}, \]
\[ \beta_h = \frac{1}{1 + e^{-0.1(V_m+30)}}, \]
\[ \alpha_n = \frac{-0.01(V_m + 50)}{e^{-0.1(V_m+50)} - 1}, \]
\[ \beta_n = 0.125e^{-0.0125(V_m+60)}, \]
Fast Na$^+$ activation

Slower Na$^+$ deactivation and K$^+$ activation

$\overline{G}_{Na} = 120$, $\overline{G}_K = 36$, and $G_L = 0.3$ mS/cm$^2$; $C_m = 1$ $\mu$F/cm$^2$; $c_{Na}^0 = 491$, $c_{Na}^i = 50$, $c_K^0 = 20.11$, $c_K^i = 400$ mmol/L; $V_L = -49$ mV; temperature is 6.3°C.
Figure 4.26

Potassium kinetics

Sodium kinetics

\[ V_{ma} \text{ (mV)} \]

\[ \tau_n \text{ (ms)} \]

\[ m, m_\infty \]

\[ n, n_\infty \]

\[ h, h_\infty \]

slow K\textsuperscript{+} onset

fast Na\textsuperscript{+} onset, delayed offset

basis for AP generation