Biophysics I  (BPHS 4080)

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Website: http://www.yorku.ca/cberge/4080W2018.html
Space-Clamp

Kenneth Cole & George Marmont (1940s)

$J_m(t)$

$V_m(t)$

Figure 4.10

$V_1(t)$

$V_2(t)$

1.6 cm

Axon

Axon

Wire

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

Figure 2.15
Voltage-Clamp

Note: No action potentials ‘fire’ under voltage clamp

→ Provides a means to study ionic currents
Separating Ionic Currents

$V_m(t)$

Depolarizing step $V_m^f$

$t$

$V_m^i$

Hyperpolarizing step

$J_m(t)$

Brief surge of outward current

Persistent, late outward current

$K^+$?

Transient, early, inward current

$Na^+$?

Figure 4.12
Changing $[\text{Na}^+]$

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

→ Separating ionic currents by subtraction (assumes $J_K$ unaffected by changes in $[\text{Na}^+]$)

![Diagram showing separation of ionic currents](image-url)
Reversal Potential?

$V_m(t) \text{(mV)}$

$J_{ion}(t) \text{(mA/cm}^2\text{)}$

$V^\circ_m$

$V_m^f$

$J_{ion}(t)$

Time (ms)

Figure 4.14

→ Close to Na$^+$ Nernst potential!
Figure 4.16
Separating Ionic Currents

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

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

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

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

$\rightarrow$ Physiological data suggests Na$^+$ activates and then inactivates while K$^+$ simply activates (based upon $V_m$)
Figure 1.32

→ Electrically ‘small’ cell can still fire action potentials
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

$$\frac{dx}{dt} = \alpha x (1 - x) - \beta x x$$

Figure 4.23
First-order, reversible reaction

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

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

Equilibrium:

\[
\frac{dc_R(t)}{dt} = \frac{dc_P(t)}{dt} = 0 \quad \Rightarrow \quad \beta c_P(\infty) = \alpha c_R(\infty)
\]

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

**Kinetics:** assume total amount of reactant and product is conserved

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

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

\[
\frac{dc_R(t)}{dt} + (\alpha + \beta)c_R(t) = \beta C
\]
First-order, reversible reaction

\[ \begin{align*}
R & \xrightarrow{\alpha} P \\
\xrightarrow{\beta}
\end{align*} \]

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

\[ \begin{align*}
R & \xrightarrow{\alpha} P \\
\xrightarrow{\beta}
\end{align*} \]

Graph showing the reaction kinetics with:
- \( c_R(0) \) and \( c_R(t) \)
- \( c_P(0) \) and \( c_P(t) \)
- \( C \)
- \( K_a C/(1 + K_a) \)
- \( C/(1 + K_a) \)
- \( \tau = \frac{1}{\alpha + \beta} \)
HH: First-Order Kinetics

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

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

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

functions of \( V_m \) only

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

- 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
$n(V_m, t) + \tau_n(V_m) \frac{dn(V_m, t)}{dt} = n_\infty(V_m)$

$m(V_m, t) + \tau_m(V_m) \frac{dm(V_m, t)}{dt} = m_\infty(V_m)$

$h(V_m, t) + \tau_h(V_m) \frac{dh(V_m, t)}{dt} = h_\infty(V_m)$

$\tau_m = \frac{1}{\alpha_m + \beta_m}$, and $m_\infty = \frac{\alpha_m}{\alpha_m + \beta_m}$

$\tau_h = \frac{1}{\alpha_h + \beta_h}$, and $h_\infty = \frac{\alpha_h}{\alpha_h + \beta_h}$

$\tau_n = \frac{1}{\alpha_n + \beta_n}$, and $n_\infty = \frac{\alpha_n}{\alpha_n + \beta_n}$.

$m$ – sodium activation

$h$ – sodium inactivation

$n$ – potassium activation
Functional form to best fit the data (e.g., exponentiating yields sigmoids)

\[
G_K(V_m, t) = \overline{G}_K n^4(V_m, t)
\]

\[
G_{Na}(V_m, t) = \overline{G}_{Na} m^3(V_m, t) h(V_m, t)
\]

\[
\alpha_m = -0.1 \frac{(V_m + 35)}{e^{-0.1(V_m+35)} - 1},
\]

\[
\beta_m = 4e^{-(V_m+60)/18},
\]

\[
\alpha_h = 0.07e^{-0.05(V_m+60)},
\]

\[
\beta_h = \frac{1}{1 + e^{-0.1(V_m+30)}},
\]

\[
\alpha_n = -0.01 \frac{(V_m + 50)}{e^{-0.1(V_m+50)} - 1},
\]

\[
\beta_n = 0.125e^{-0.0125(V_m+60)},
\]

Figure 4.23
Fast Na$^+$ activation

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

$\overline{G}_{Na} = 120$, $\overline{G}_K = 36$, and $G_L = 0.3$ mS/cm$^2$; $C_m = 1$ μF/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

- $V_{Na}$ (mV)
- $\tau_n$ (ms)
- $n, n_\infty$

Slow $K^+$ onset

Sodium kinetics

- $V_{Na}$ (mV)
- $\tau_m, \tau_h$ (ms)
- $m, m_\infty$
- $h, h_\infty$

Fast $Na^+$ onset, delayed offset

Basis for AP generation