Introduction to Mathematical Physiology III: The Dynamics of Excitability

J. P. Keener

Mathematics Department
University of Utah
Examples of Excitable Media

- B-Z reagent
- Nerve cells
- cardiac cells, muscle cells
- Slime mold (*dictyostelium discoideum*)
- CICR (Calcium Induced Calcium Release)
- Forest Fires

Features of Excitability

- Threshold Behavior
- Refractoriness
- Recovery
Modeling Membrane Electrical Activity

Transmembrane potential is regulated by transmembrane ionic currents and capacitive currents:

\[ C_m \frac{d\phi}{dt} + I_{\text{ion}}(\phi; w) = I_{\text{in}} \]

where \( \frac{dw}{dt} = g(\phi; w) - w^2 R_n \)

\[ \phi = \phi_i - \phi_e \]
Transmembrane potential $\phi$ is regulated by transmembrane ionic currents and capacitive currents:

$$C_m \frac{d\phi}{dt} + I_{ion}(\phi, w) = I_{in} \quad \text{where} \quad \frac{dw}{dt} = g(\phi, w), \quad w \in R^n$$
Examples include:

- **Neuron** - [Hodgkin-Huxley model](#)
- **Purkinje fiber** - Noble
- **Cardiac cells** - Beeler-Reuter, Luo-Rudy, Winslow-Jafri, Bers
- **Two Variable Models** - reduced HH, FitzHugh-Nagumo, Mitchell-Schaeffer, Morris-Lecar, McKean, Puschino, etc.)
The Squid Giant Axon...
is not the Giant Squid Axon
The Hodgkin-Huxley Equations

\[ C_m \frac{dV}{dt} + I_{Na} + I_K + I_l = 0, \]

where \( I_{Na} \) is the sodium current, \( I_K \) is the potassium current, and \( I_l \) is the leak current.
The Hodgkin-Huxley Equations

\[ C_m \frac{dV}{dt} + \left[ I_{\text{Na}} \right] + I_K + I_I = 0, \]

with sodium current \( I_{\text{Na}} \).
The Hodgkin-Huxley Equations

\[ C_m \frac{dV}{dt} + [I_{Na}] + [I_K] + I_l = 0, \]

with sodium current \( I_{Na} \), potassium current \( I_K \),
The Hodgkin-Huxley Equations

\[ C_m \frac{dV}{dt} + [I_{Na}] + [I_K] + [I_l] = 0, \]

with sodium current \( I_{Na} \), potassium current \( I_K \), and leak current \( I_l \).
Ionic currents are typically of the form

\[ I = g(\phi, t) \Phi(\phi) \]
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where \( g(\phi, t) \) is the total number of open channels, and \( \Phi(\phi) \) is the \( I-\phi \) relationship for a single channel.
**Voltage Dependent Conductance**

Example: Sodium and Potassium channels - Voltage clamp experiments
Four independent subunits:

\[ C \xleftrightarrow{\alpha(V)} O. \]

\[ \xleftrightarrow{\beta(V)} \]

so that

\[ S_0 \xleftrightarrow{\beta(V)} S_1 \xleftrightarrow{2\beta(V)} S_2 \xleftrightarrow{3\beta(V)} S_3 \xleftrightarrow{4\beta(V)} S_4 \]

One can show that \( x_4 = n^4 \) where

\[ \frac{dn}{dt} = \alpha(V)(1 - n) - \beta(V)n \]
Two types of subunits

Conducting state is $S_{12}$. Then $X_{12} = m^2 h$, where

$$\frac{dm}{dt} = \alpha (1 - m) - \beta m$$

$$\frac{dh}{dt} = \gamma (1 - h) - \delta h$$
Hodgkin and Huxley found that

\[ I_k = g_k n^4 (\phi - \phi_K), \quad I_{Na} = g_{Na} m^3 h (\phi - \phi_{Na}), \]

where

\[ \tau_u(\phi) \frac{du}{dt} = u_\infty(\phi) - u, \quad u = m, n, h \]
Hodgkin-Huxley Equations

\[ C_m \frac{dV}{dt} = -\bar{g}_N a m^3 h (V - V_{Na}) - \bar{g}_K n^4 (V - V_K) - g_L (V - V_L) + I_{app}, \]

where

\[ \frac{du}{dt} = \alpha_u (1 - u) - \beta_u u, \quad u = m, n, h. \]

The specific functions \( \alpha \) and \( \beta \) proposed by Hodgkin and Huxley were (in units of ms\(^{-1}\))

\[ \alpha_m = 0.1 \frac{25 - v}{\exp\left(\frac{25-v}{10}\right) - 1}, \quad \beta_m = 4 \exp\left(\frac{-v}{18}\right), \]

\[ \alpha_h = 0.07 \exp\left(\frac{-v}{20}\right), \quad \beta_h = \frac{1}{\exp\left(\frac{30-v}{10}\right) + 1}, \]

\[ \alpha_n = 0.01 \frac{10 - v}{\exp\left(\frac{10-v}{10}\right) - 1}, \quad \beta_n = 0.125 \exp\left(\frac{-v}{80}\right). \]
Action Potential Dynamics

Potential (mV)

Gating variables

Conductance (mmho/cm²)

Excitable Cells – p.14/33
Observe that $\tau_m << \tau_n, \tau_h$
Set \( m = m_\infty(\phi) \), and set \( h + n \approx N = 0.85 \).
This reduces to a two variable system

\[
\begin{align*}
C \frac{d\phi}{dt} &= g_K n^4 (\phi - \phi_K) + g_{Na} m_\infty^3 (\phi) (N - n)(\phi - \phi_{Na}) + g_l (\phi - \phi_L), \\
\tau_n (\phi) \frac{dn}{dt} &= n_\infty (\phi) - n.
\end{align*}
\]
Following is a summary of two variable models of excitable media. The models described here are all of the form

\[
\frac{dv}{dt} = f(v, w) + I
\]
\[
\frac{dw}{dt} = g(v, w)
\]

Typically, \( v \) is a “fast” variable, while \( w \) is a “slow” variable.
The model that started the whole business uses a cubic polynomial (a variant of the van der Pol equation).

\[ F(v, w) = Av(v - \alpha)(1 - v) - w, \]
\[ G(v, w) = \epsilon(v - \gamma w). \]

with \( 0 < \alpha < \frac{1}{2} \), and \( \epsilon \) “small”.
FitzHugh-Nagumo Equations

\[
dw/dt = 0 \\
dv/dt = 0
\]
Mitchell-Schaeffer two-variable model (also in a slightly different but equivalent form by Karma)

\[ F(v, w) = \frac{1}{\tau_{in}} w v^2 (1 - v) - \frac{v}{\tau_{out}}, \]

\[ G(v, w) = \begin{cases} 
\frac{1}{\tau_{open}} (1 - w) & v < v_{gate} \\
-\frac{w}{\tau_{close}} & v > v_{gate}
\end{cases} \]

Notice that \( F(v, w) \) is cubic in \( v \), and \( w \) is an inactivation variable (like \( h \) in HH).
To make the Mitchell-Schaeffer look like an ionic model, take

\[
C_m \frac{dv}{dt} = g_{Na} h m^2 (V_{Na} - v) + g_K (V_K - v),
\]

\[
\tau_h \frac{dh}{dt} = h_\infty(v) - h
\]

where

\[
m(v) = \begin{cases} 
0, & v < 0 \\
v, & 0 < v < 1 \\
1, & v > 1 
\end{cases}
\]

\[
h_\infty = 1 - f(v),
\]

\[
\tau_h = \tau_{open} + (\tau_{close} - \tau_{open}) f(v)
\]

\[
f(v) = \frac{1}{2} (1 + \tanh(\kappa(v - v_{gate}))),
\]
Excitable Cells – p.22/33
This model was devised for barnacle muscle fiber.

\[ F(v, w) = -g_{ca}m_\infty(v)(v - v_{ca}) - g_k w(v - v_k) - g_l(v - v_l) + I_{app} \]
\[ G(v, w) = \phi \cosh\left(\frac{1}{2} \frac{v - v_3}{v_4}\right)(w_\infty(v) - w), \]

\[ m_\infty(v) = \frac{1}{2} + \frac{1}{2} \tanh\left(\frac{v - v_1}{v_2}\right), \quad w_\infty(v) = (1 + \tanh\left(\frac{v - v_3}{2v_4}\right)). \]
McKean suggested two piecewise linear models with $F(v, w) = f(v) - w$ and $G(v, w) = \epsilon(v - \gamma w)$. For the first,

$$f(v) = \begin{cases} 
-v & v < \frac{\alpha}{2} \\
 v - \alpha & \frac{\alpha}{2} < v < \frac{1+\alpha}{2} \\
 1 - v & v > \frac{1+\alpha}{2}
\end{cases}$$

where $0 < \alpha < \frac{1}{2}$.

The second model suggested by McKean had

$$f(v) = \begin{cases} 
-v & v < \alpha \\
 1 - v & v > \alpha
\end{cases}$$

and $\gamma = 0$. 
A model devised to give very fast 2D computations (the code is known as EZspiral)

\[ F(v, w) = v(1 - v)(v - \frac{w + b}{a}), \]

\[ G(v, w) = \epsilon(v - w). \]
A piecewise linear model devised to match cardiac restitution properties

\[ F(v, w) = f(v) - w \]

\[ G(v, w) \frac{1}{\tau(v)} (v - w) \]

where

\[ f(v) = \begin{cases} 
-30v, & v < v_1 \\
\gamma v - 0.12, & v_1 < v < v_2 \\
-30(v - 1), & v > v_2 
\end{cases} \]

\[ \tau(v) = \begin{cases} 
2, & v < v_1 \\
16.6, & v > v_1 
\end{cases} \]

with \( v_1 = \frac{0.12}{30 + \gamma}, \quad v_2 = \frac{30.12}{30 + \gamma} \).
For the Aliev model,

\[ F(v, w) = g_a(v - \beta)(v - \alpha)(1 - v) - vw \]
\[ G(v, w) = -\epsilon(v, w)(w + g_s(v - \beta)(v - \alpha - 1) \]

where \( \epsilon(v, w) = \epsilon_1 + \mu_1 \frac{w}{v + \mu_2}. \)

Reasonable parameter values are \( \beta = 0.0001, \alpha = 0.05, g_a = 8.0, \)
\( g_s = 8.0, \mu_1 = 0.05, \mu_2 = 0.3, \epsilon_1 = 0.03, \epsilon_2 = 0.0001. \)
These dynamics describe the oxidation-reduction of malonic acid. For this system,

\[
F(v, w) = v - v^2 - (fw + \phi_0)\frac{v - q}{v + q} \tag{13}
\]

\[
G(v, w) = \epsilon(v - w) \tag{13}
\]

with typical parameter values \(\epsilon = 0.05, q = 0.002, f = 3.5, \phi_0 = 0.01\).
**Action Potential Duration Restitution Curve**

\[ APD_n + DI_n = BCL. \]

where \( APD_n = A(DI_{n-1}) \) is the restitution curve. It follows that

\[ DI_n = BCL - A(DI_{n-1}), \]
Features of Excitable Systems

- Threshold Behavior, Refractoriness
- Alternans
- Wenckebach Patterns
All cardiac models are of the form

\[ C_m \frac{d\phi}{dt} + I_{ion}(\phi, w, [Ion]) = I_{in} \]

with currents, gating and concentrations for sodium, potassium, calcium, and chloride ions.
The Beeler-Reuter Model

\[ C_m \frac{d\phi}{dt} + I_{Na} + I_{K} + I_{x} + I_{s} = 0, \]

Excitable Cells – p.32/33
The Beeler-Reuter Model

\[ C_m \frac{d \phi}{dt} + [I_{Na}] + I_K + I_x + I_s = 0, \]

with sodium current \( I_{Na} \),
$C_m \frac{d\phi}{dt} + I_{Na} + I_{K} + I_{x} + I_{s} = 0,$

with sodium current $I_{Na}$, time independent potassium current $I_{K}$,
The Beeler-Reuter Model

\[ C_m \frac{d\phi}{dt} + I_{Na} + I_K + I_x + I_s = 0, \]

with sodium current \( I_{Na} \), time independent potassium current \( I_K \), gated potassium current \( I_x \), and (slow) calcium current \( I_s \).
The Beeler-Reuter Model

\[ C_m \frac{d\phi}{dt} + I_{Na} + I_K + I_x + I_s = 0, \]

with sodium current \( I_{Na} \), time independent potassium current \( I_K \), gated potassium current \( I_x \), and (slow) calcium current \( I_s \).
The Beeler-Reuter Model

\[ C_m \frac{d\phi}{dt} + I_{Na} + I_K + I_x + I_s = 0, \]

with sodium current \( I_{Na} \), time independent potassium current \( I_K \), gated potassium current \( I_x \), and (slow) calcium current \( I_s \).
Detailed Ionic Models- Luo-Rudy