Dynamical Systems for Biology - Excitability

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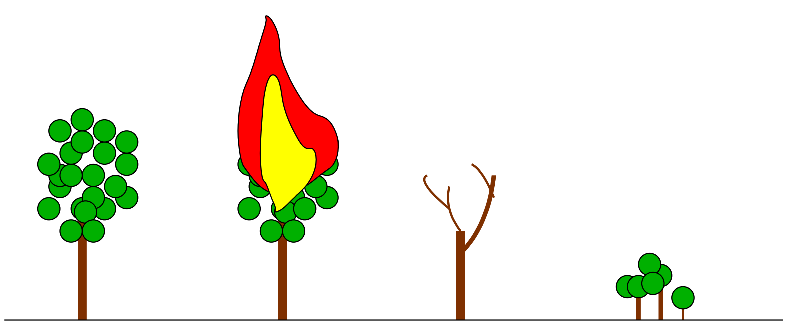
Examples of Excitable Media

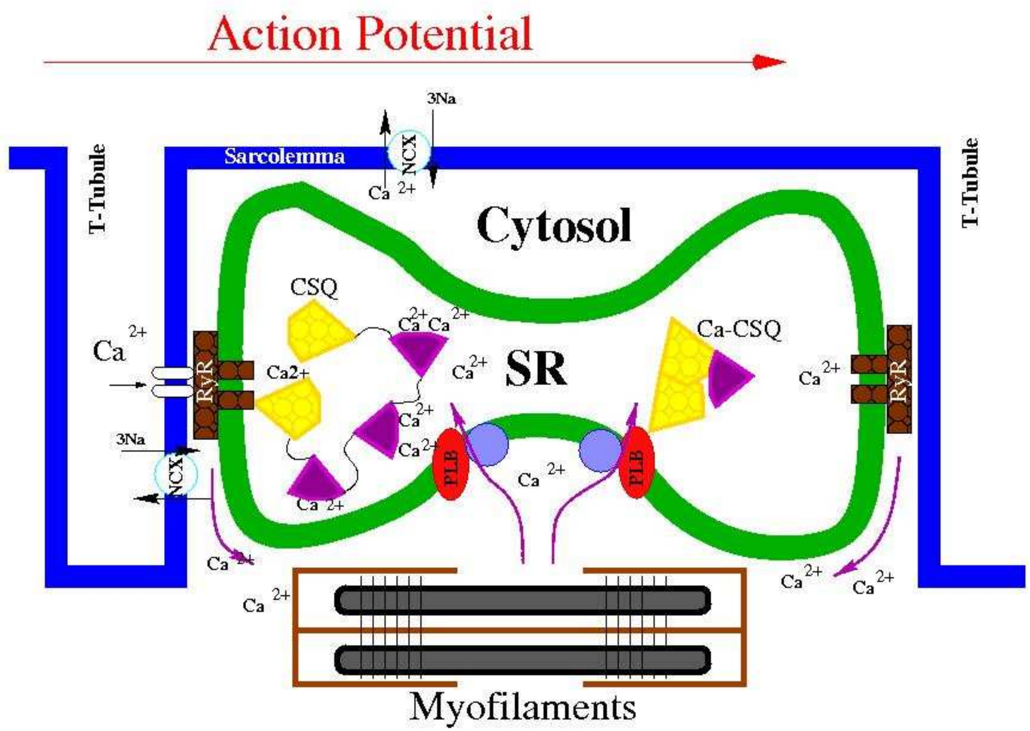
- B-Z reagent
- CICR (Calcium Induced Calcium Release)
- Nerve cells
- cardiac cells, muscle cells
- Slime mold (*dictystelium discoideum*)
- Forest Fires

Features of Excitability

- Threshold Behavior
- Refractoriness
- Recovery

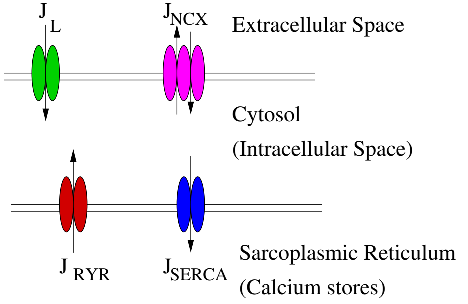


Intracellular Calcium



Calcium Handling

$$v\frac{dc}{dt} = J_{RYR} - J_{SERCA} + J_L - J_{NCX}$$



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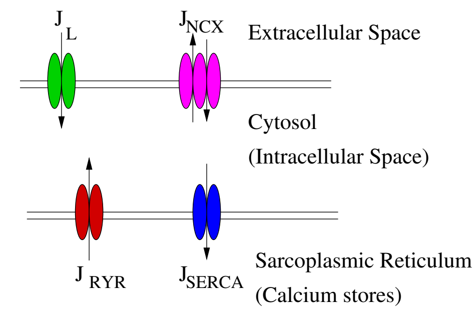

with

J_{RYR} **Ry**anodine **R**eceptor - calcium regulated calcium channel,

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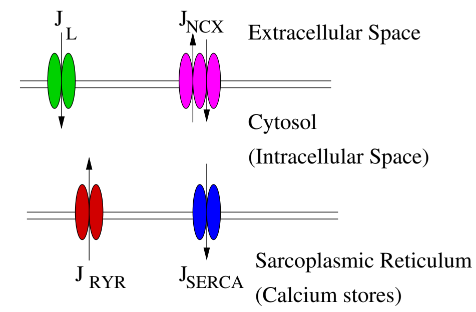

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J_{SERCA} Sarco- and Endoplasmic Reticulum Calcium ATPase,

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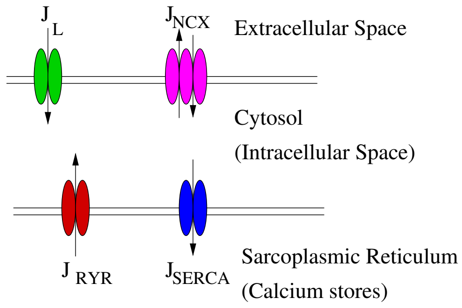

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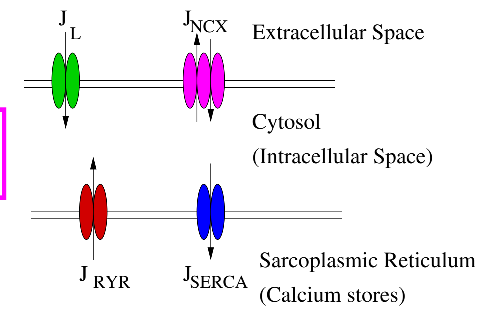

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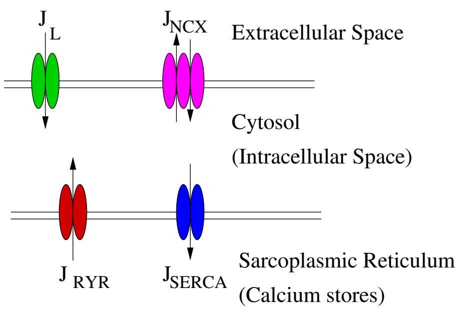

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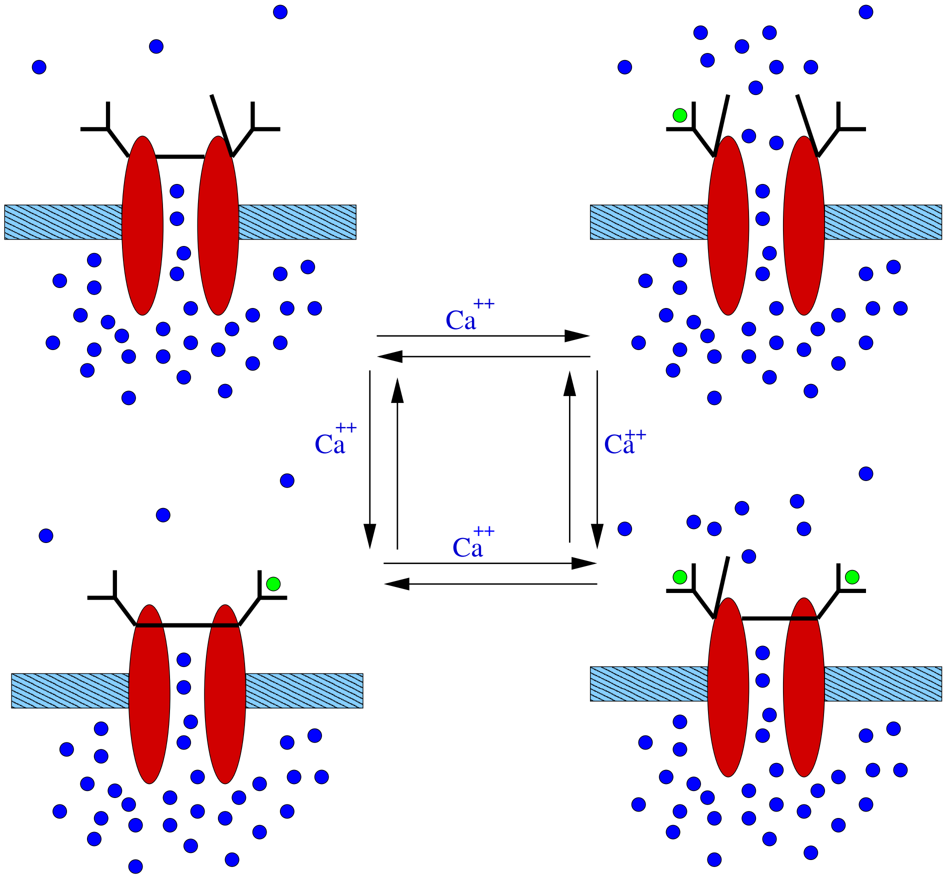
Challenge: Determine the flux terms.

Ryanodine Receptors



Ryanodine Receptors

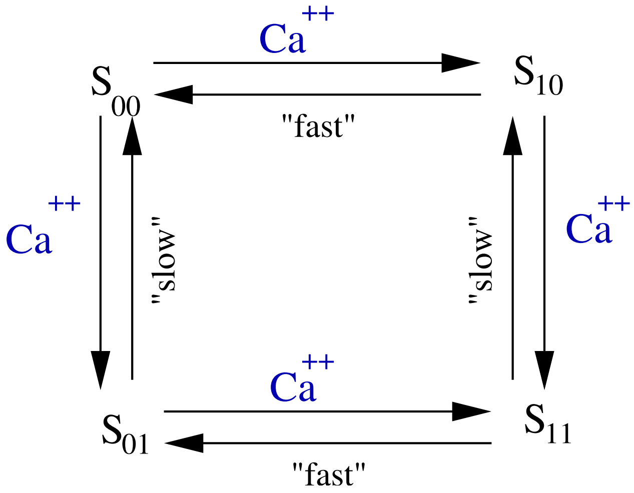
Flux through ryanodine receptor is diffusive,

$$J_{RYR} = g_{max} P_o (c - c_{sr})$$

where $P_o = S_{10}^3$ is the open probability. To determine P_o, we must find S_{10}:

$$\frac{dS_{10}}{dt} = k_1 c S_{00} + k_{-2} S_{11} - k_{-1} S_{10} - k_2 c S_{10}$$

and so on.



Observation

If the binding sites are independent (no cooperativity), then

$S_{10} = mh$, $S_{00} = (1-m)h$, $S_{11} = m(1-h)$, $S_{01} = (1-m)(1-h)$,

where

$\frac{dm}{dt} = \phi_m(c)(1-m) - \psi_m(c)m, \qquad \frac{dh}{dt} = \phi_h(c)(1-h) - \psi(c)h$.

Furthermore, m is a fast variable, so can be taken to be in qss, $m = m_\infty(c)$.

Consequently,....

Calcium Dynamics

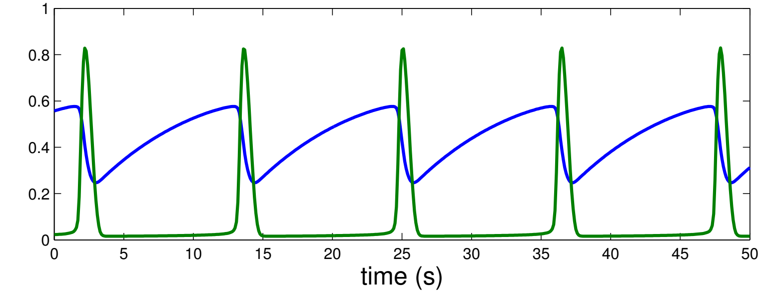
$$\frac{dc}{dt} = (g_{max} P_o + J_{er})(c_e - c) - J_{SERCA},$$

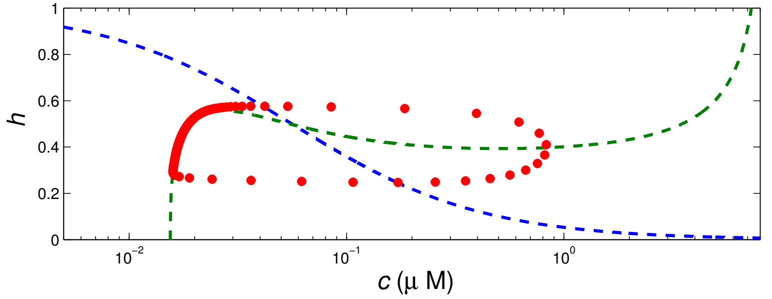
$$\frac{dh}{dt} = \phi_h(c)(1-h) - \psi_h(c)h,$$

where

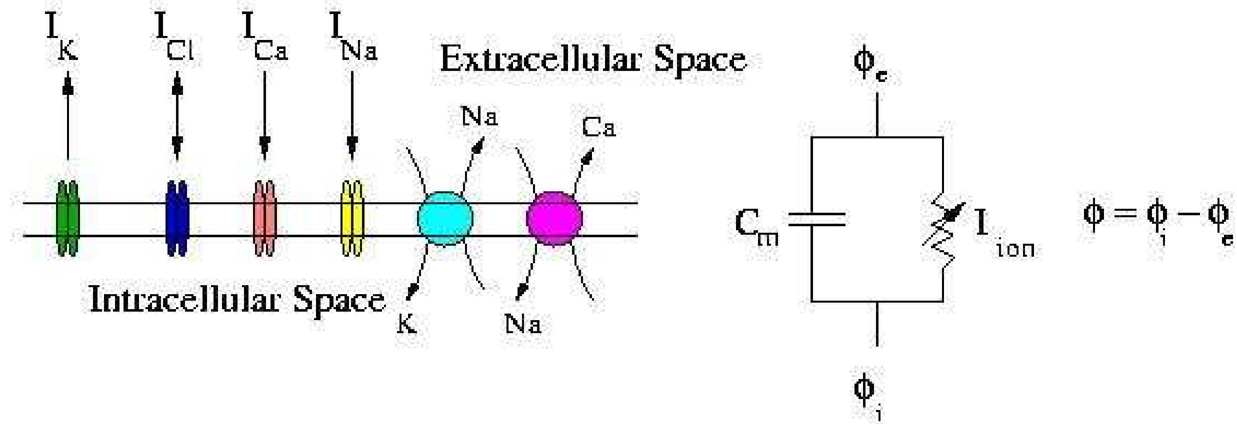
$$J_{SERCA} = V_{max} \frac{c^2}{K_s^2 + c^2},$$

$$P_o = h^3 f(c)$$





Membrane Electrical Activity



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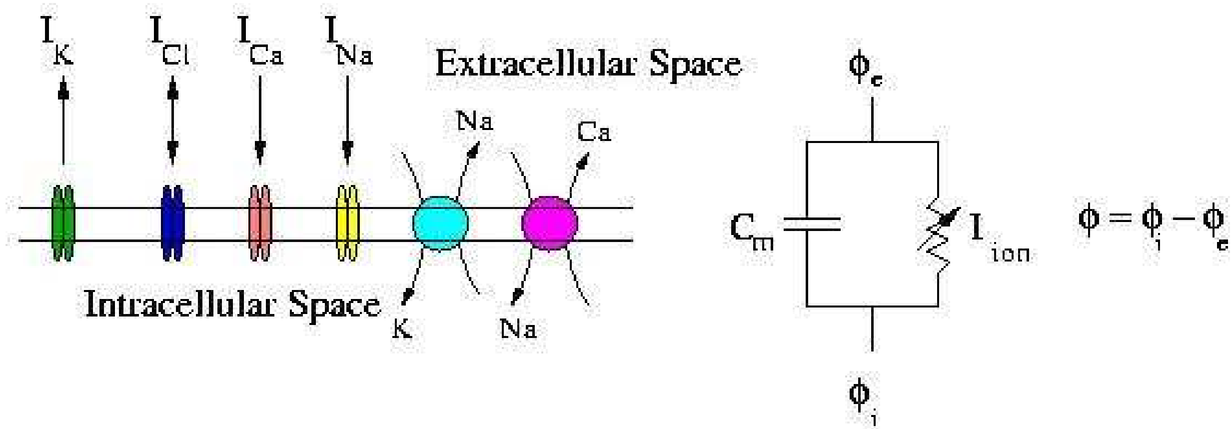


Transmembrane potential ϕ is regulated by transmembrane ionic currents and capacitive currents:

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

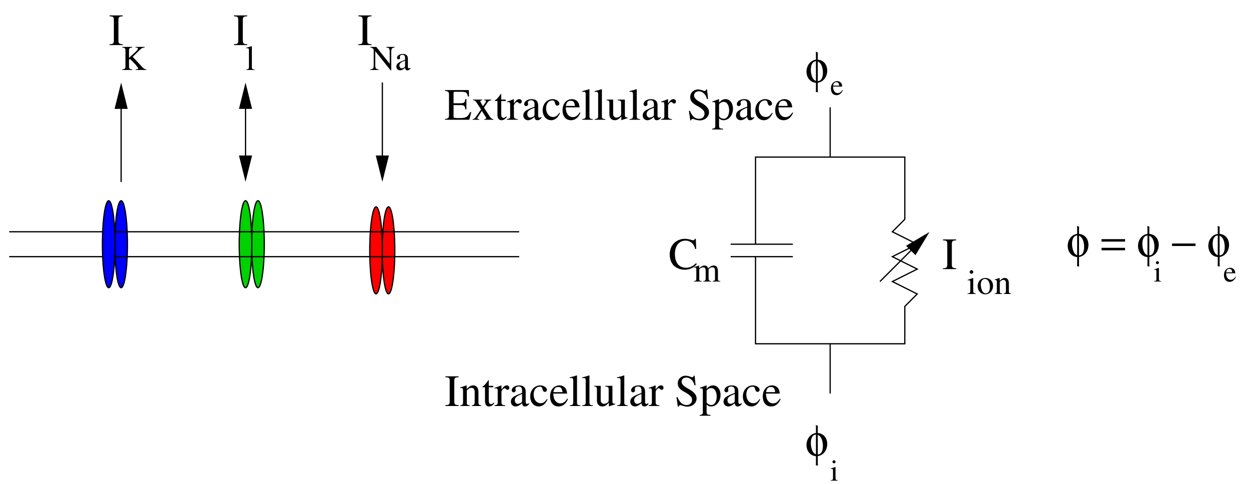
(Reminder: This is a conservation equation.)

Examples

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, etc.)

The Hodgkin-Huxley Equations



$$C_m \frac{dV}{dt} + I_{\mathrm{Na}} + I_{\mathrm{K}} + I_{\mathrm{l}} = 0,$$

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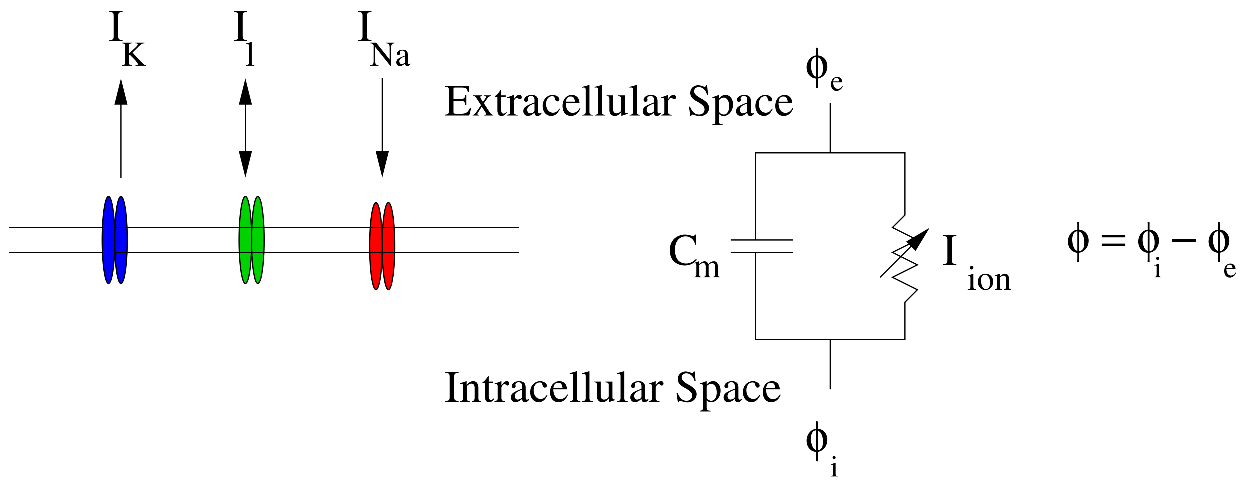

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with sodium current I_{Na},

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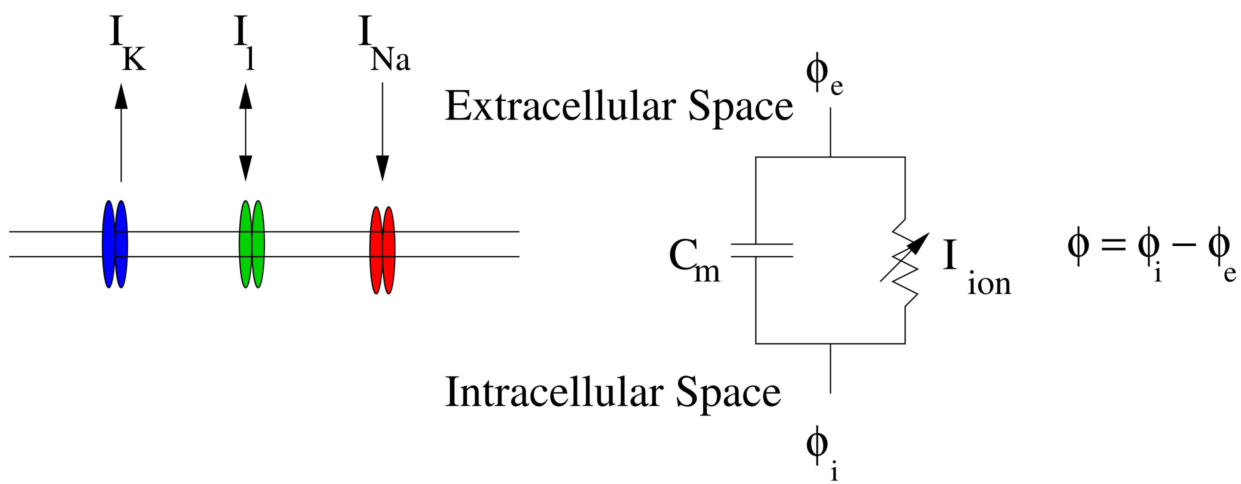

$$C_m \frac{dV}{dt} + \boxed{I_{\mathrm{Na}}} + \boxed{I_{\mathrm{K}}} + I_{\mathrm{l}} = 0,$$

with sodium current I_{Na}, potassium current I_{K},

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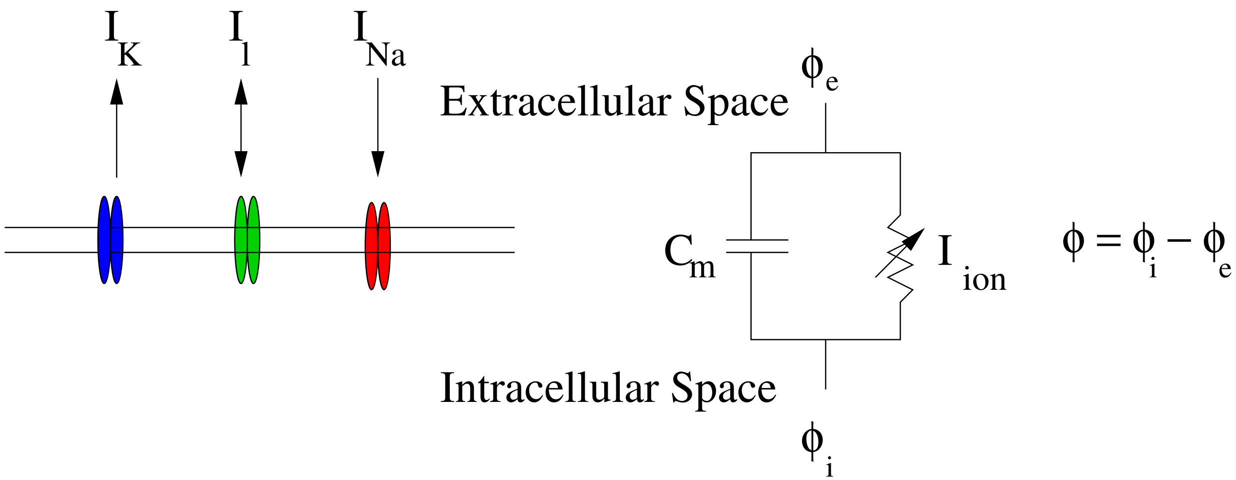

$$C_m \frac{dV}{dt} + \boxed{I_{\mathrm{Na}}} + \boxed{I_{\mathrm{K}}} + \boxed{I_{\mathrm{l}}} = 0,$$

with sodium current I_{Na}, potassium current I_{K}, and leak current I_{l}.

Ionic Currents

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$$I = \; g(\phi, t) \;\; \Phi(\phi)$$

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$$I = \boxed{g(\phi, t)}\,\boxed{\Phi(\phi)}$$

where $g(\phi, t)$ is the total number of open channels, and $\Phi(\phi)$ is the I-ϕ relationship for a single channel.

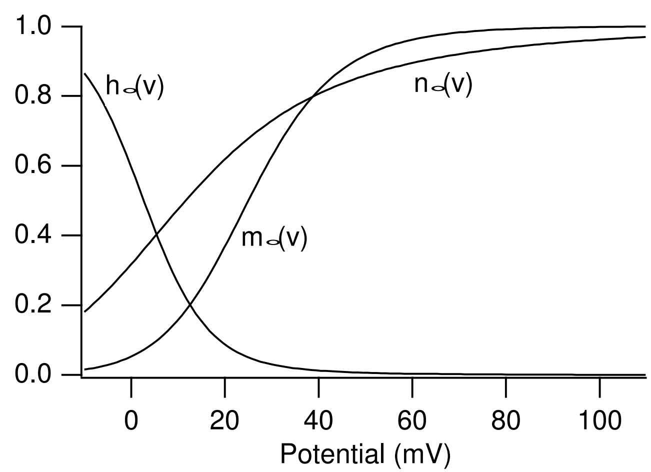
Currents

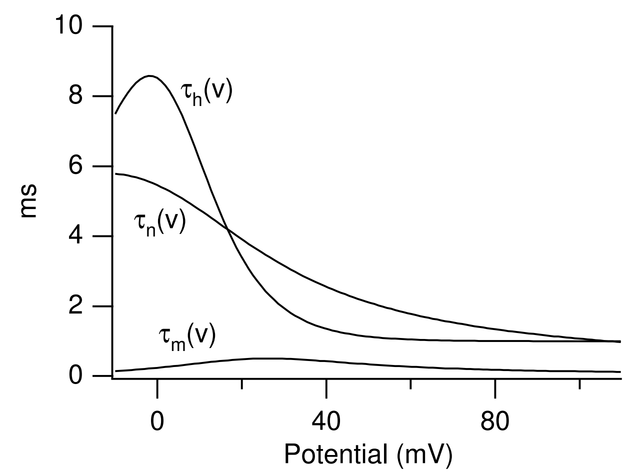
Hodgkin and Huxley found that

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

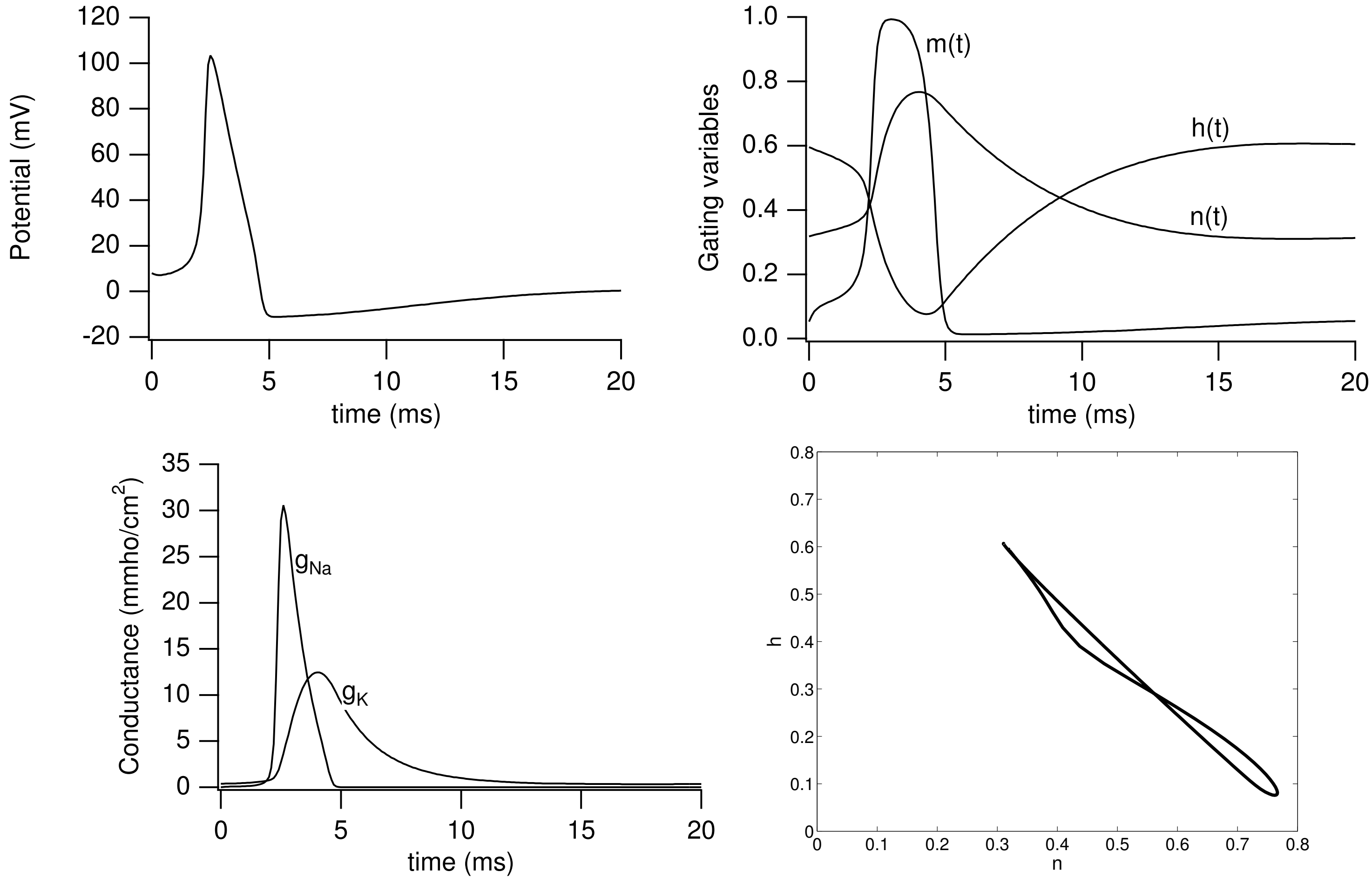
where

$$\tau_u(\phi)\frac{du}{dt} = u_\infty(\phi) - u, \qquad u = m, n, h$$





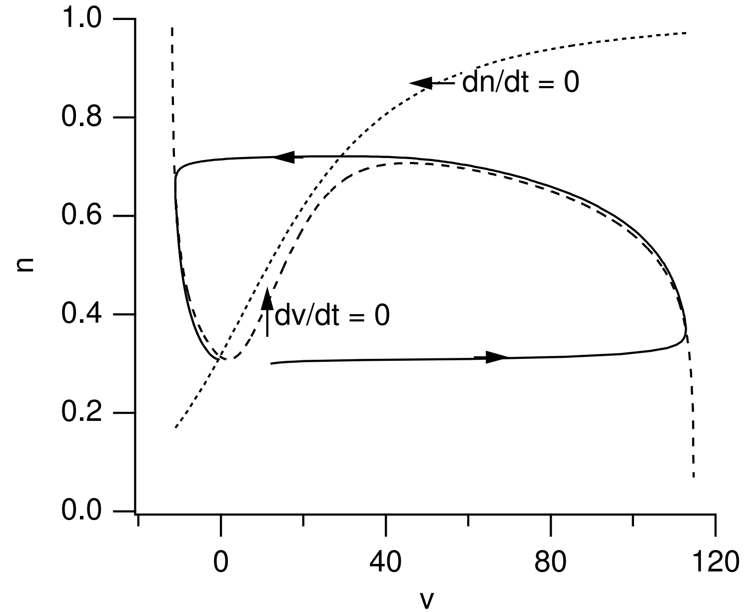
Action Potential Dynamics



Two Variable Reduction of HH Eqns

Set $m = m_\infty(\phi)$, and set $h + n \approx N = 0.85$.
This reduces to a two variable system

$$
\begin{aligned}
C\frac{d\phi}{dt} &= \bar{g}_K n^4(\phi - \phi_K) + \bar{g}_{Na} m_\infty^3(\phi)(N - n)(\phi - \phi_{Na}) + \bar{g}_l(\phi - \phi_L), \\
\tau_n(\phi)\frac{dn}{dt} &= n_\infty(\phi) - n.
\end{aligned}
$$

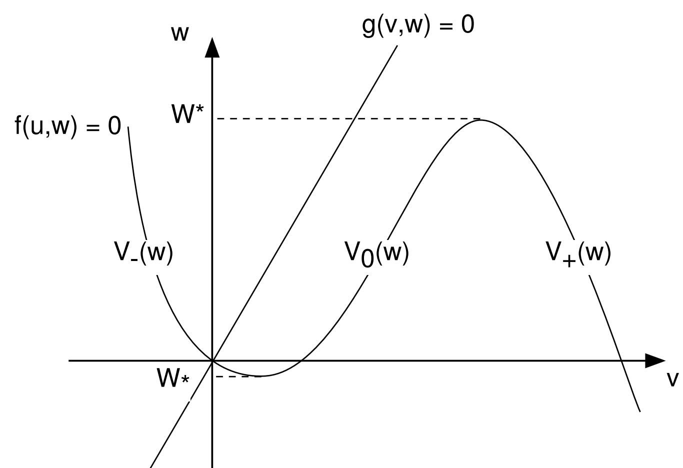


Two Variable Models

Following is a brief 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.



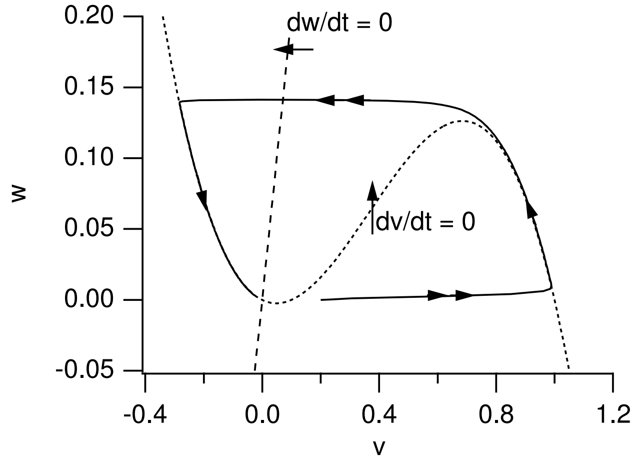
Cubic FitzHugh-Nagumo

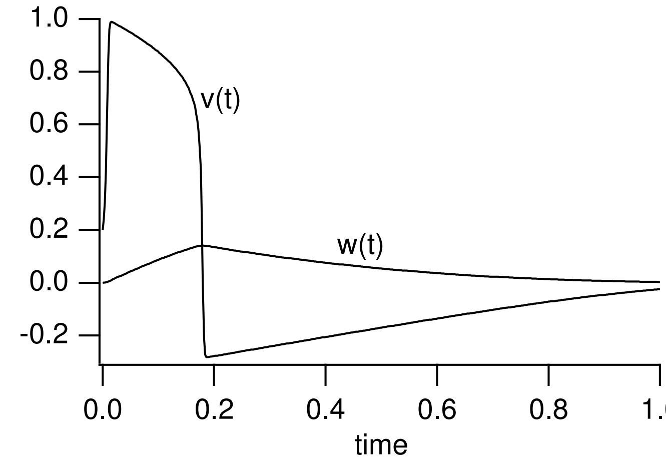
The model that started the whole business uses a cubic polynomial (a variant of the van der Pol equation).

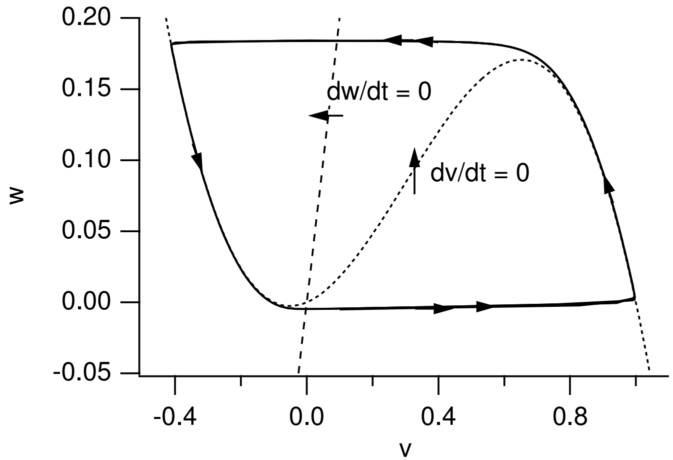
$$
\begin{aligned}
F(v,w) &= Av(v-\alpha)(1-v)-w, \\
G(v,w) &= \epsilon(v-\gamma w).
\end{aligned}
$$

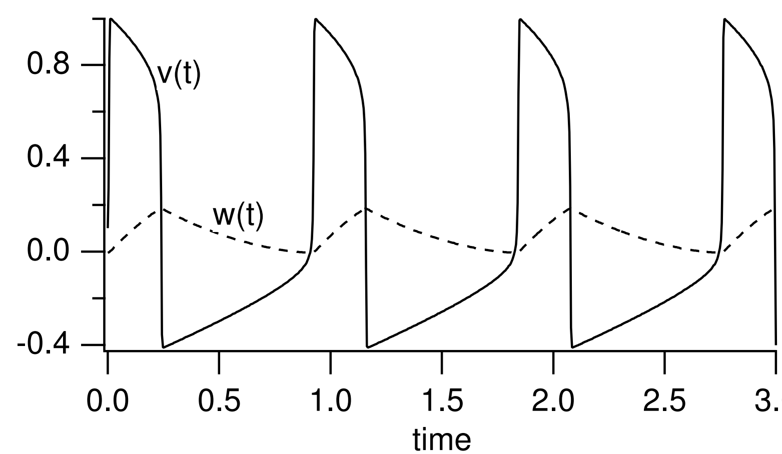
with $0 < \alpha < \frac{1}{2}$, and ϵ “small”.
(Remark: This model is used these days only by mathematicians.)

FitzHugh-Nagumo Equations









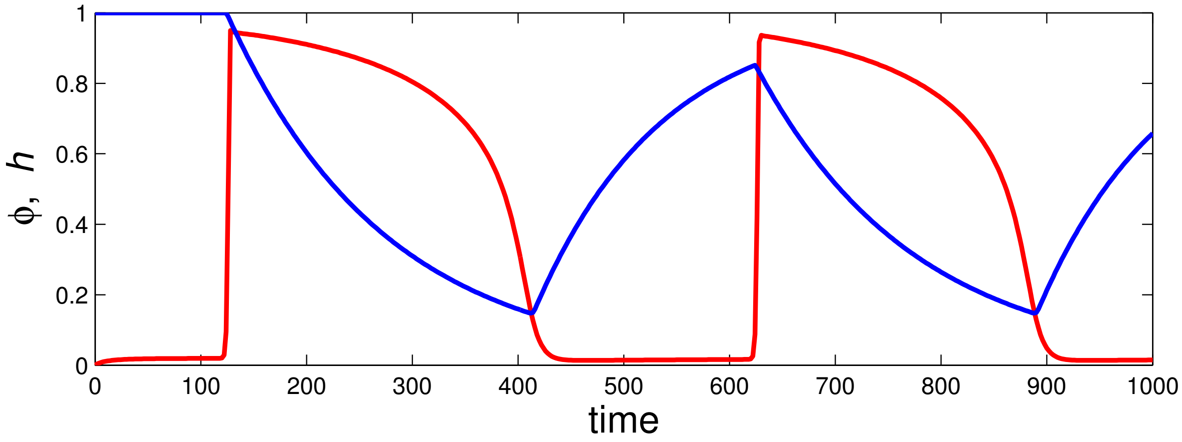
Mitchell-Schaeffer-Karma

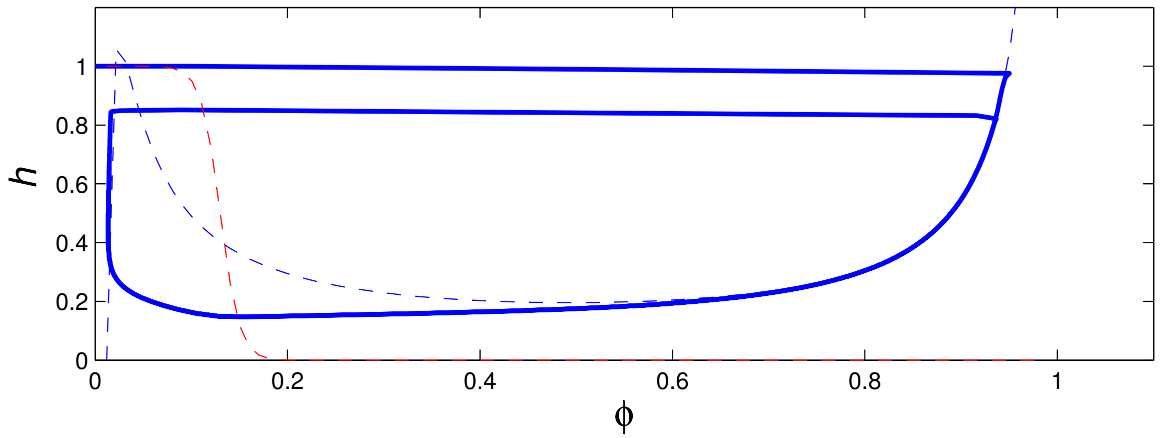
$$
\begin{aligned}
C_m \frac{dv}{dt} &= g_{Na} h m^2 (V_{Na} - v) + g_K (V_K - v), \\
\tau_h \frac{dh}{dt} &= h_\infty(v) - h
\end{aligned}
$$

where

$$
m(v) = \begin{cases} 0, & v < 0 \\ v, & 0 < v < 1 \\ 1, & v > 1 \end{cases}, \qquad
\begin{aligned}
h_\infty &= 1 - f(v), \\
\tau_h &= \tau_{open} + (\tau_{close} - \tau_{open}) f(v) \\
f(v) &= \tfrac{1}{2}(1 + \tanh(\kappa(v - v_{gate}))),
\end{aligned}
$$

MSK Phase Portrait



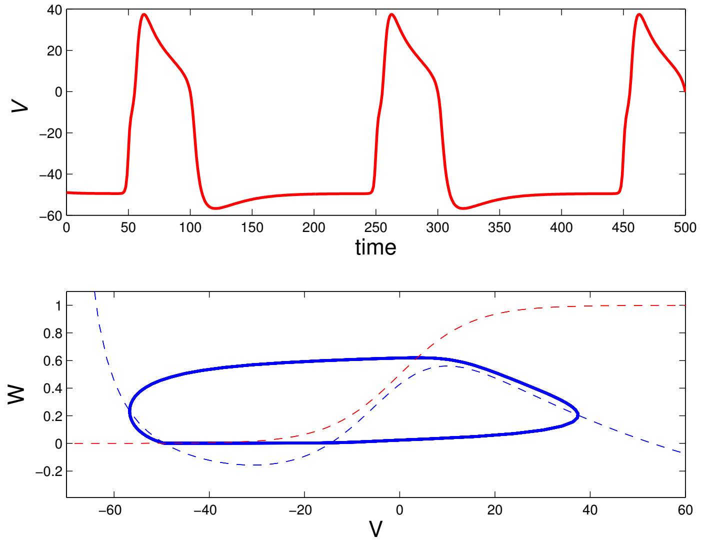


Morris-Lecar

This model was devised for barnacle muscle fiber.

$$
\begin{aligned}
F(v,w) &= -g_{ca}m_\infty(v)(v-v_{ca}) - g_k w(v-v_k) - g_l(v-v_l) + I_{app} \\
G(v,w) &= \phi\cosh(\frac{1}{2}\frac{v-v_3}{v_4})(w_\infty(v)-w),
\end{aligned}
$$

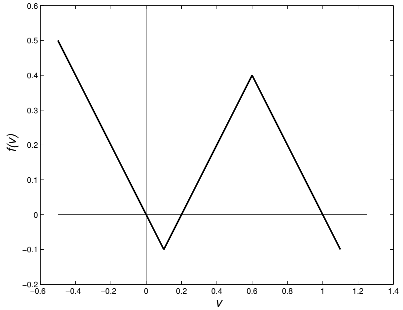
$$
m_\infty(v) = \frac{1}{2} + \frac{1}{2}\tanh(\frac{v-v_1}{v_2}), \qquad w_\infty(v) = (1+\tanh(\frac{v-v_3)}{2v_4})).
$$



McKean

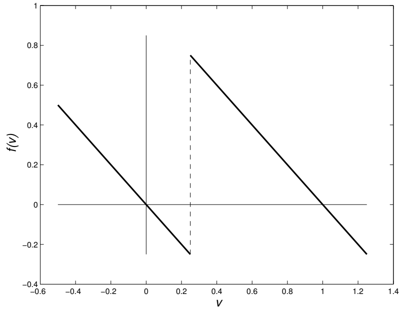
McKean suggested two piecewise linear models with $F(v,w) = f(v) - w$ and $G(v,w) = \epsilon(v - \gamma w)$. For the first,

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



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 $\gamma = 0$.

Imagine the Possibilities
Mathematical Biology
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Features of Excitable Systems

- Threshold Behavior, Refractoriness
- Alternans
- Wenckebach Patterns

Summary

From last time:

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