Introduction to Mathematical Physiology III: The Dynamics of Excitability

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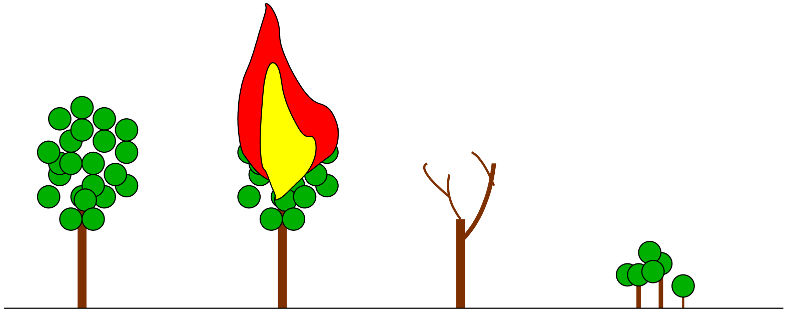
Examples of Excitable Media

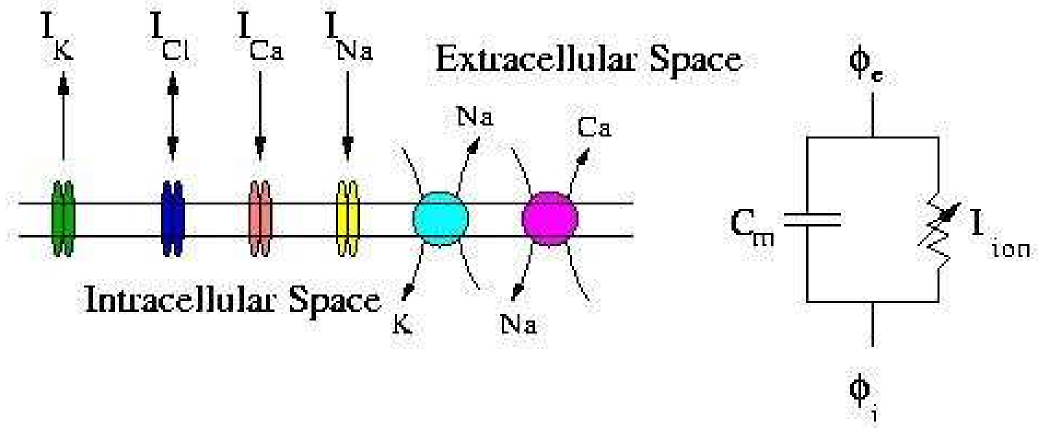
- B-Z reagent
- Nerve cells
- cardiac cells, muscle cells
- Slime mold (*dictystelium discoideum*)
- CICR (Calcium Induced Calcium Release)
- Forest Fires

Features of Excitability

- Threshold Behavior
- Refractoriness
- Recovery

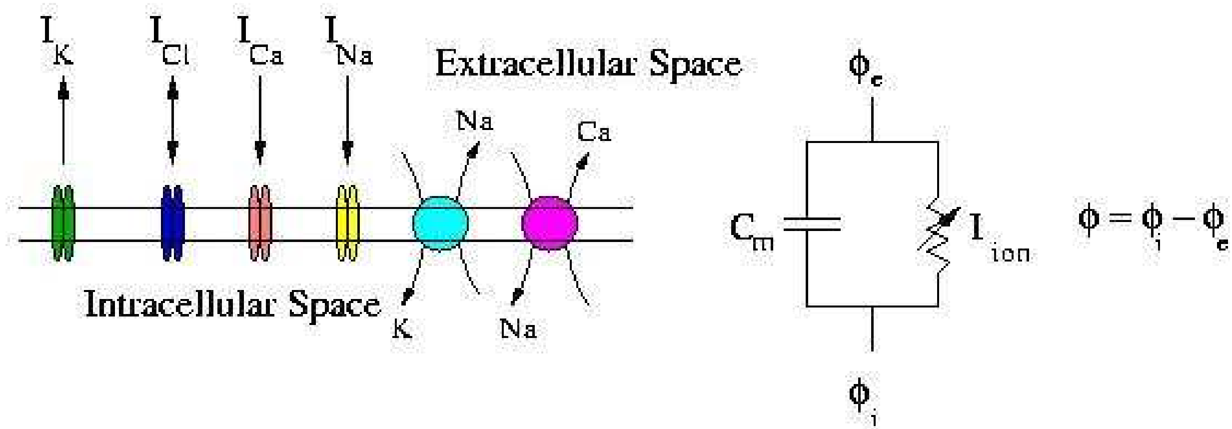


Modeling Membrane Electrical Activity



$\phi = \phi_i - \phi_e$

Modeling Membrane Electrical Activity



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

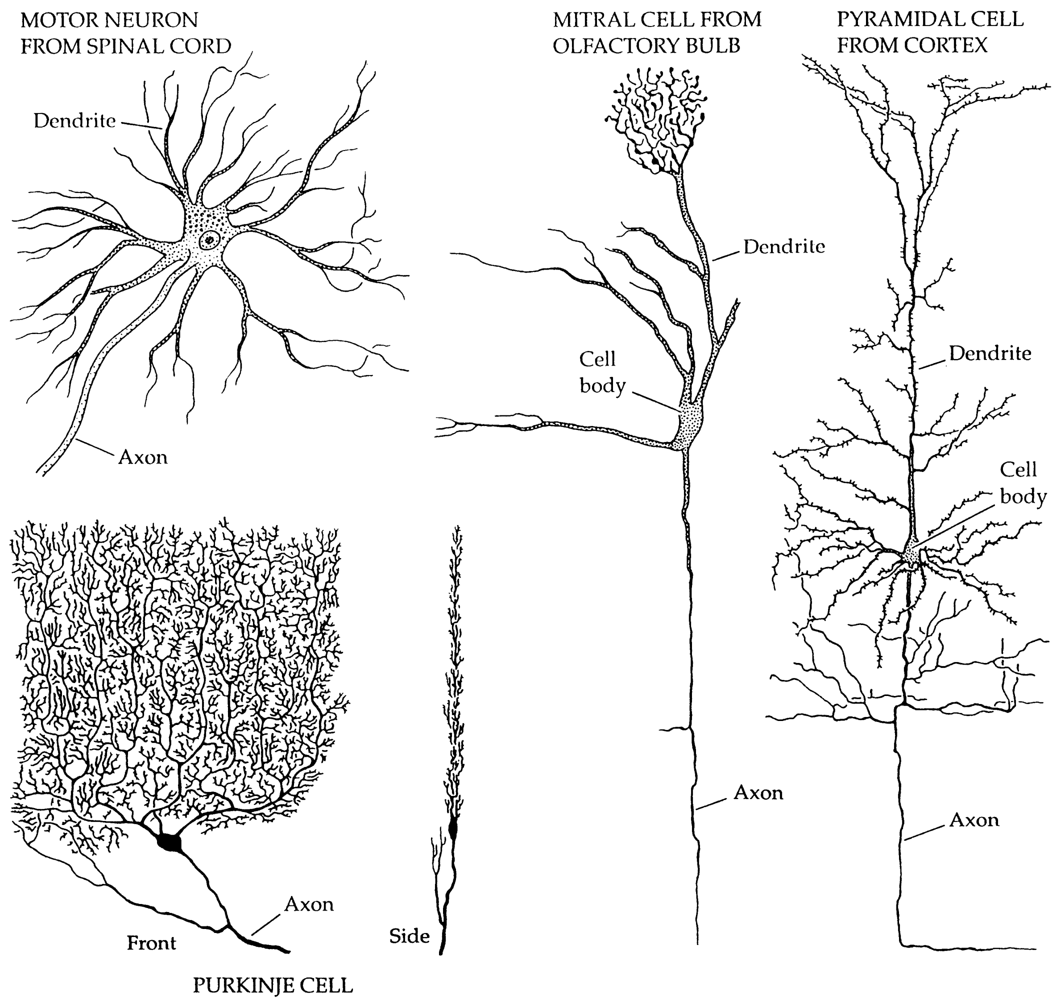
$$C_m \frac{d\phi}{dt} + I_{ion}(\phi, w) = I_{in} \quad \text{where} \ \frac{dw}{dt} = g(\phi, w), \qquad w \in R^n$$

Examples

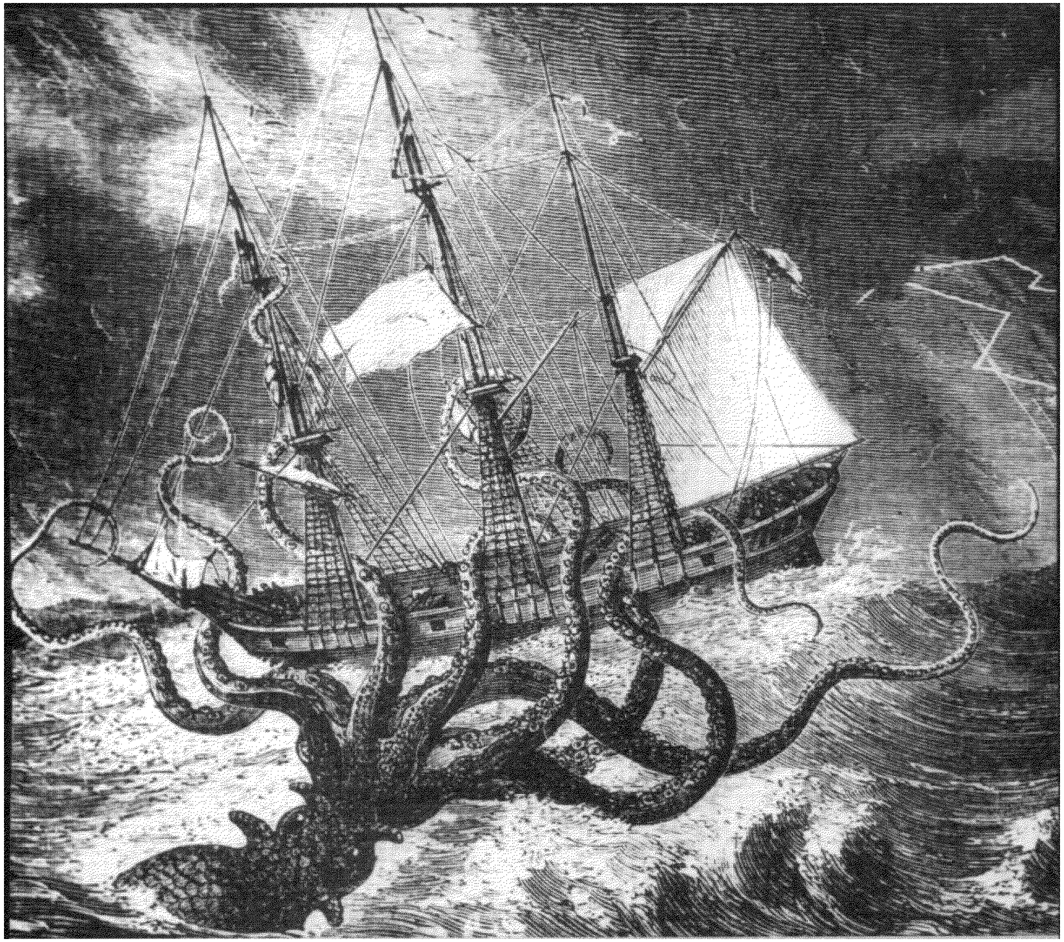
Examples include:

- 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, Puschino, etc.)

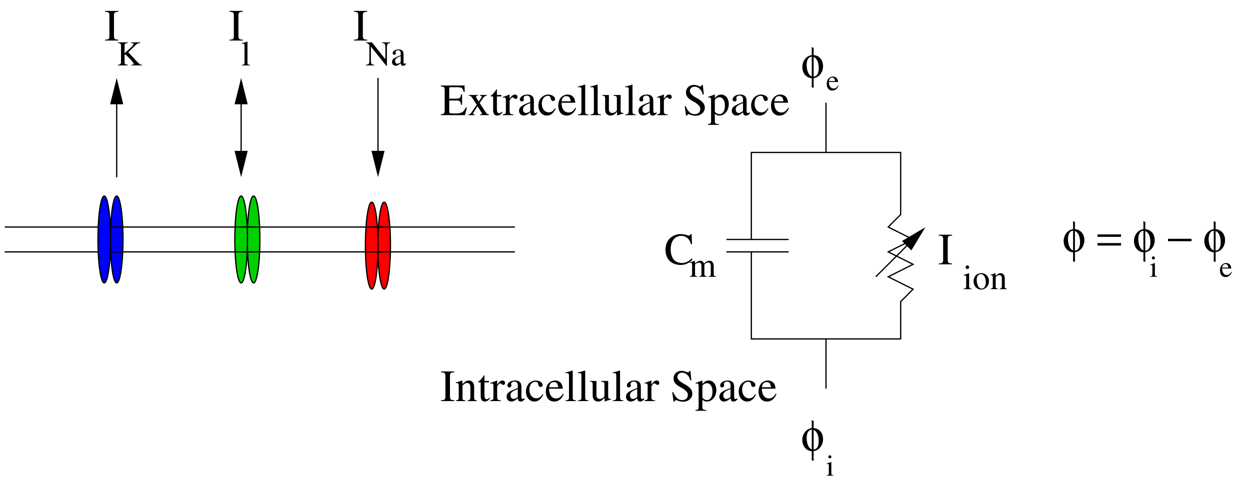
The Squid Giant Axon...



is not the Giant Squid Axon

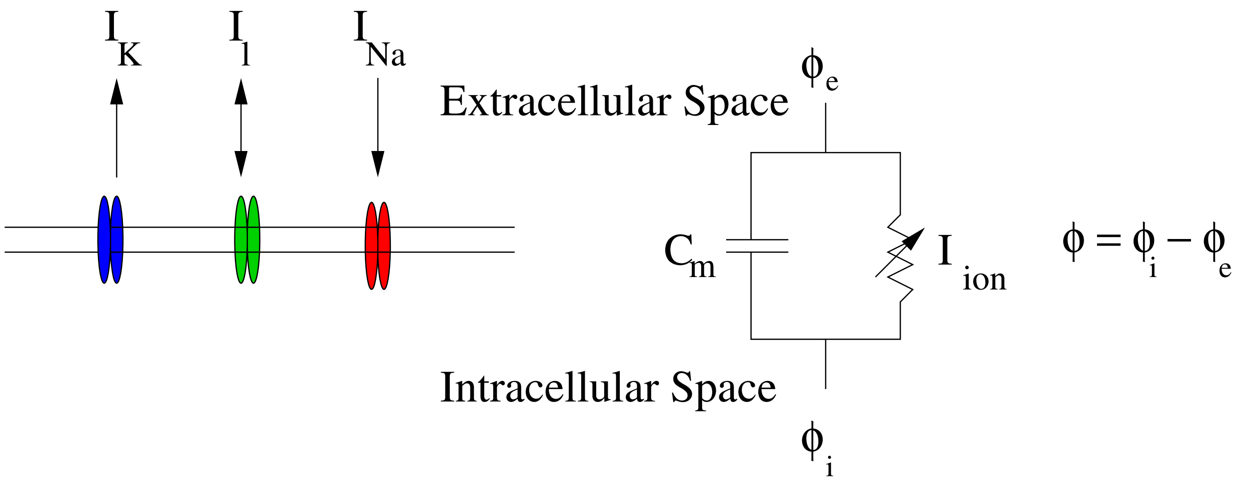


The Hodgkin-Huxley Equations



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

The Hodgkin-Huxley Equations



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

with sodium current I_{Na},

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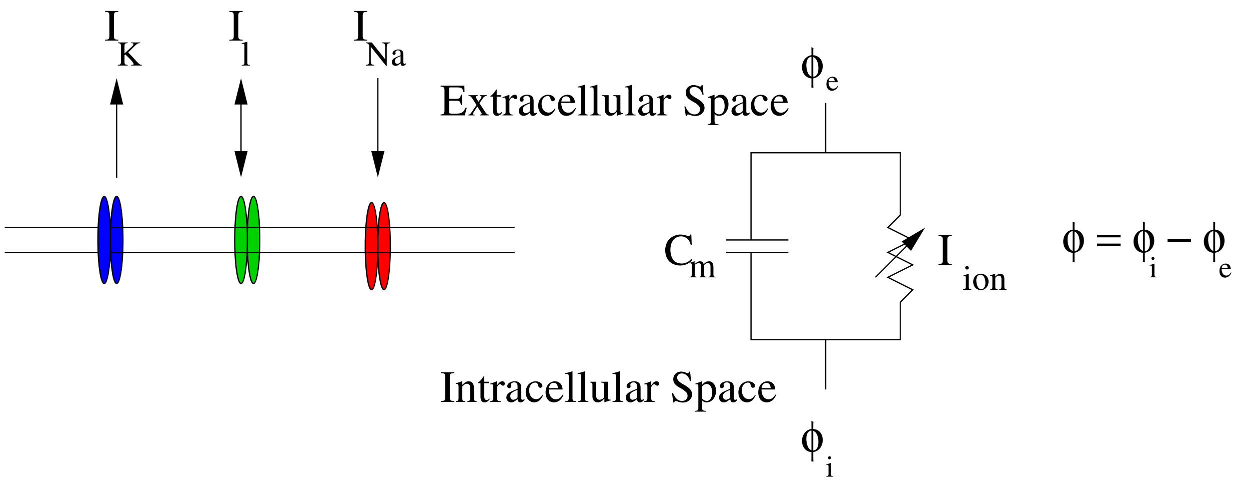
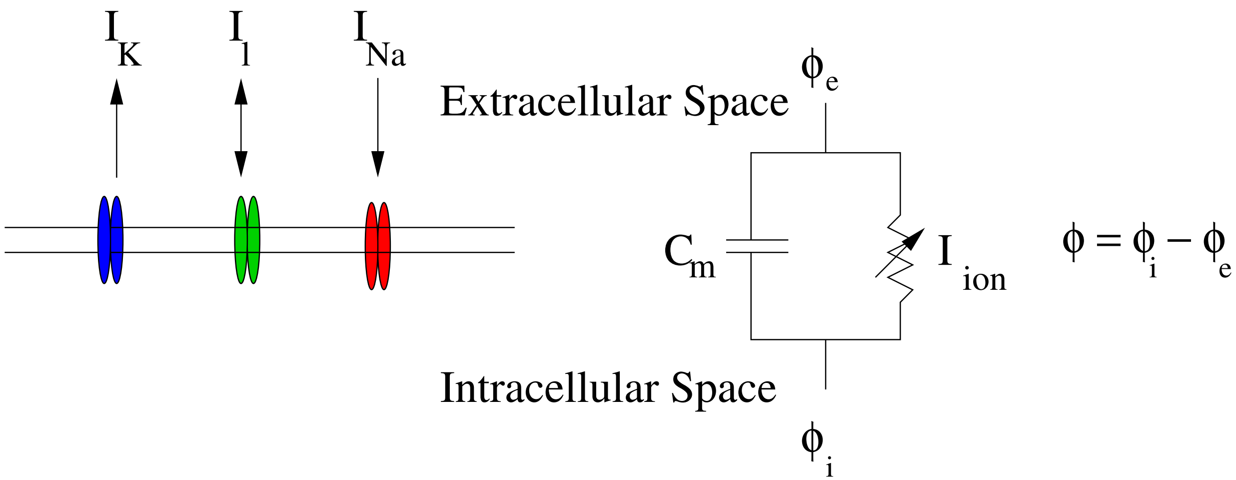
The Hodgkin-Huxley Equations



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

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

The Hodgkin-Huxley Equations



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

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

Ionic Currents

Ionic currents are typically of the form

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

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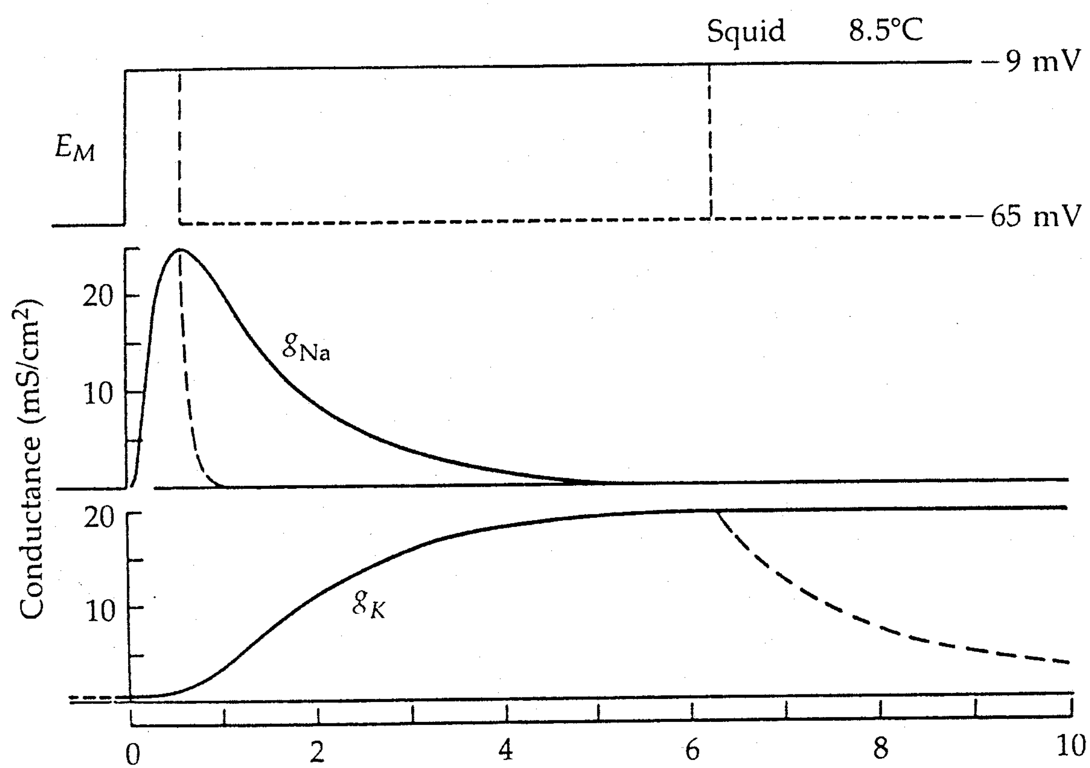
$$I = \boxed{g(\phi, t)}\,\boxed{\Phi(\phi)}$$

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

Voltage Dependent Conductance

Example: Sodium and Potassium channels - Voltage clamp experiments



K^+ Channel Gating

Four independent subunits:

$$C \underset{\beta(V)}{\overset{\alpha(V)}{\rightleftharpoons}} O.$$

so that

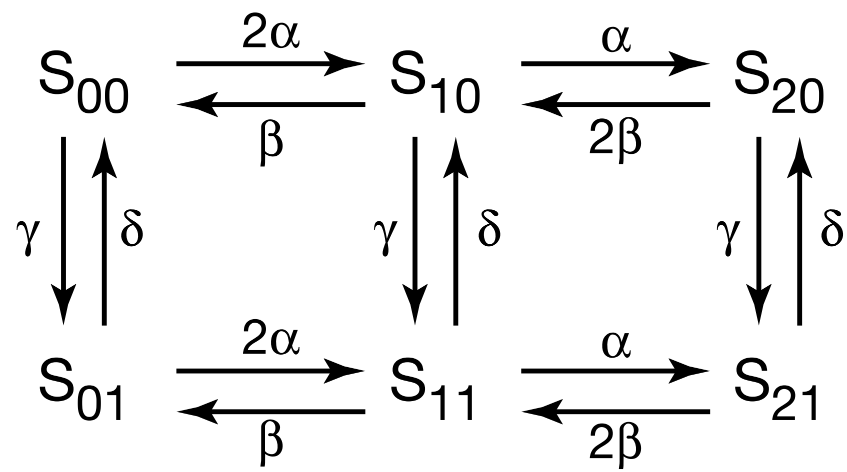
$$S_0 \underset{\beta(V)}{\overset{4\alpha(V)}{\rightleftharpoons}} S_1 \underset{2\beta(V)}{\overset{3\alpha(V)}{\rightleftharpoons}} S_2 \underset{3\beta(V)}{\overset{2\alpha(V)}{\rightleftharpoons}} S_3 \underset{4\beta(V)}{\overset{\alpha(V)}{\rightleftharpoons}} S_4$$

One can show that $x_4 = n^4$ where

$$\frac{dn}{dt} = \alpha(V)(1-n) - \beta(V)n$$

Na^+ Channel Gating

Two types of subunits



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

$$\frac{dm}{dt} = \alpha(1-m) - \beta m$$
$$\frac{dh}{dt} = \gamma(1-h) - \delta h$$

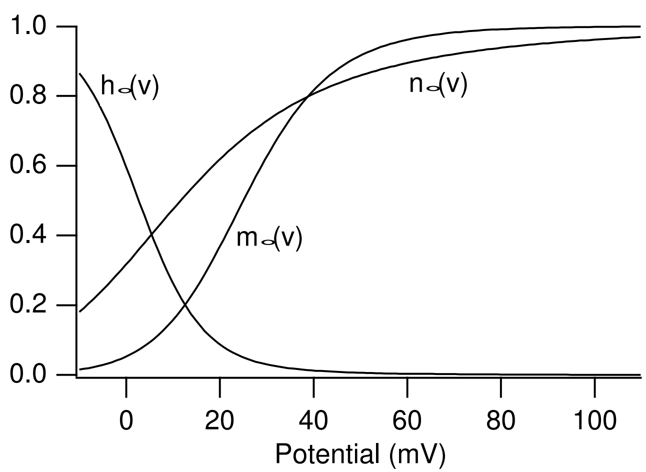
Currents

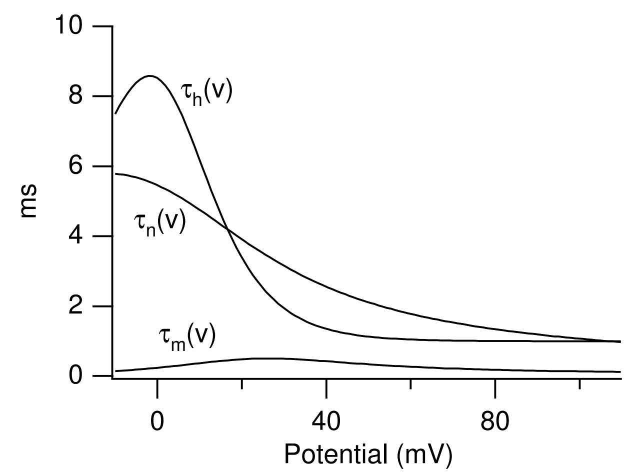
Hodgkin and Huxley found that

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

where

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





Hodgkin-Huxley Equations

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

where

$$\frac{du}{dt} = \alpha_u (1 - u) - \beta_u u, \qquad u = m, n, h.$$

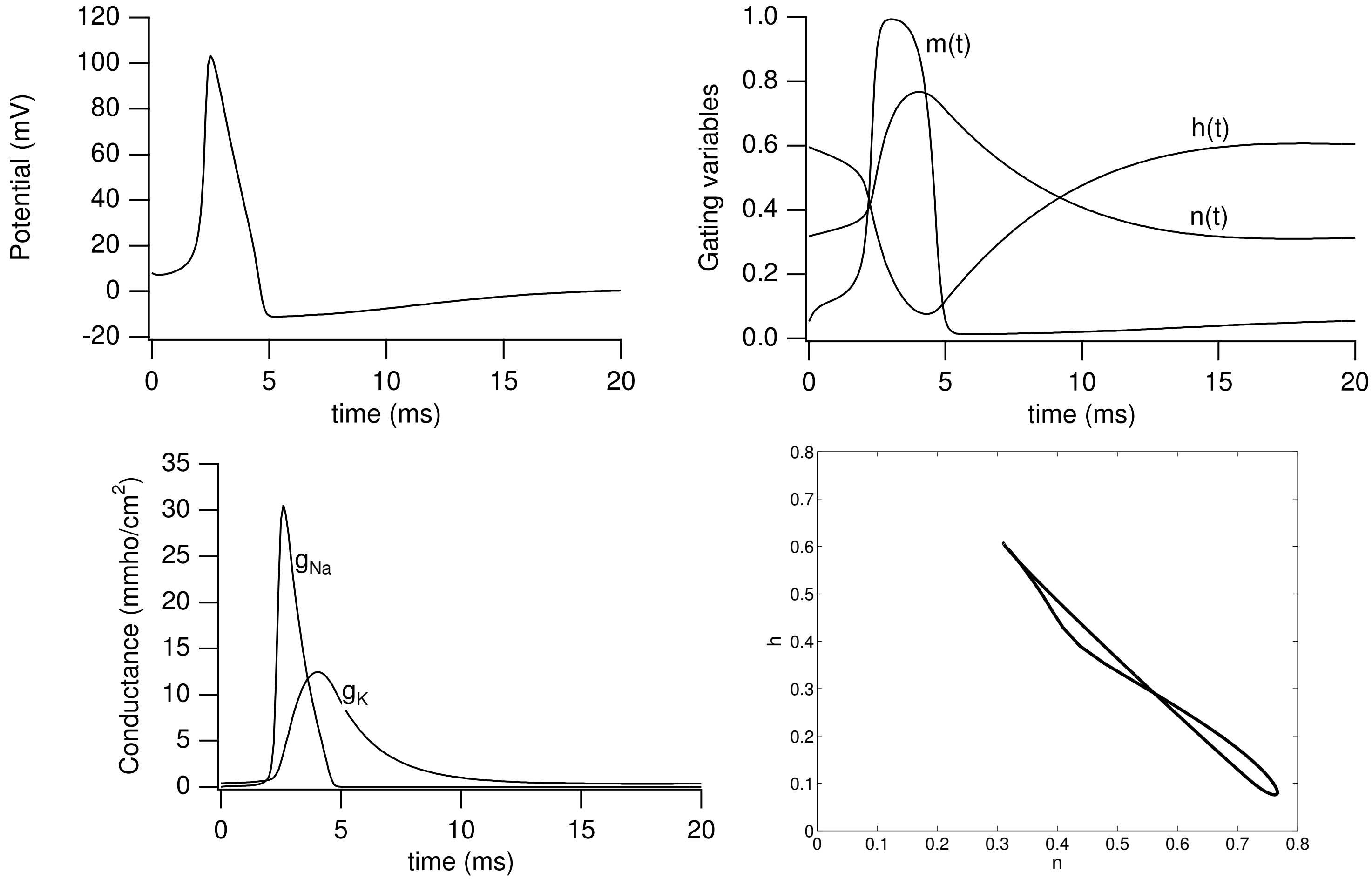
The specific functions α and β proposed by Hodgkin and Huxley were (in units of ms^{-1})

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

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

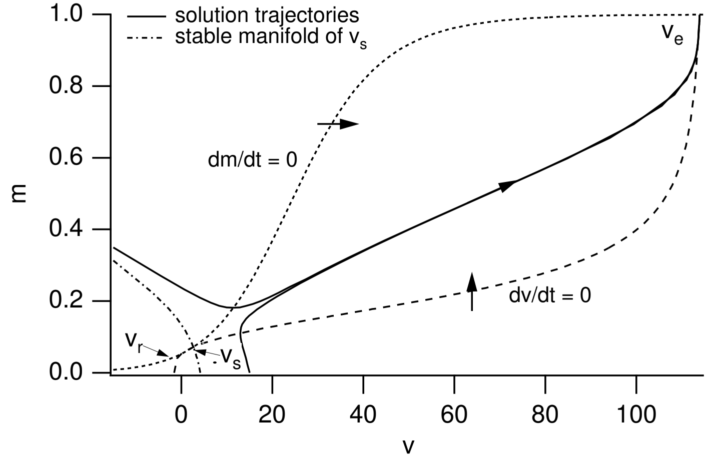
$$\alpha_n = 0.01 \frac{10 - v}{\exp(\frac{10-v}{10}) - 1}, \qquad \beta_n = 0.125 \exp\left(\frac{-v}{80}\right).$$

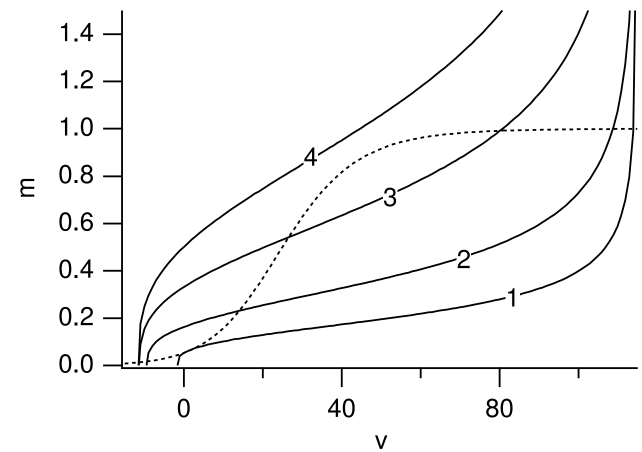
Action Potential Dynamics



Fast-Slow Subsystem Dynamics

Observe that $\tau_m << \tau_n, \tau_h$





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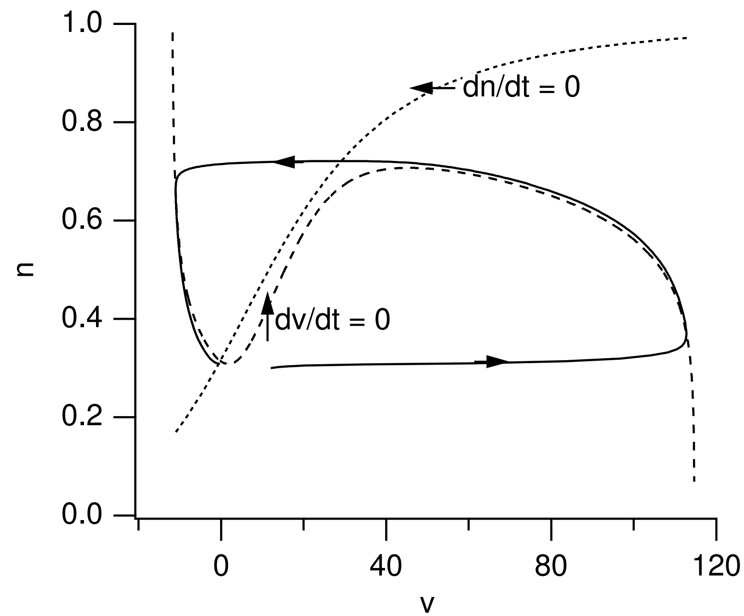
Two Variable Reduction of HH Eqns

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

$$C\frac{d\phi}{dt} = \bar{g}_K n^4(\phi - \phi_K) + \bar{g}_{Na} m_\infty^3(\phi)(N - n)(\phi - \phi_{Na}) + \bar{g}_l(\phi - \phi_L),$$

$$\tau_n(\phi)\frac{dn}{dt} = n_\infty(\phi) - n.$$



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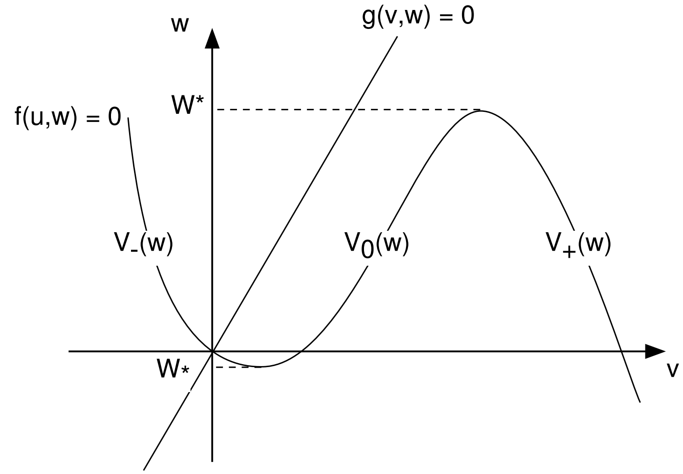
Two Variable Models

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.



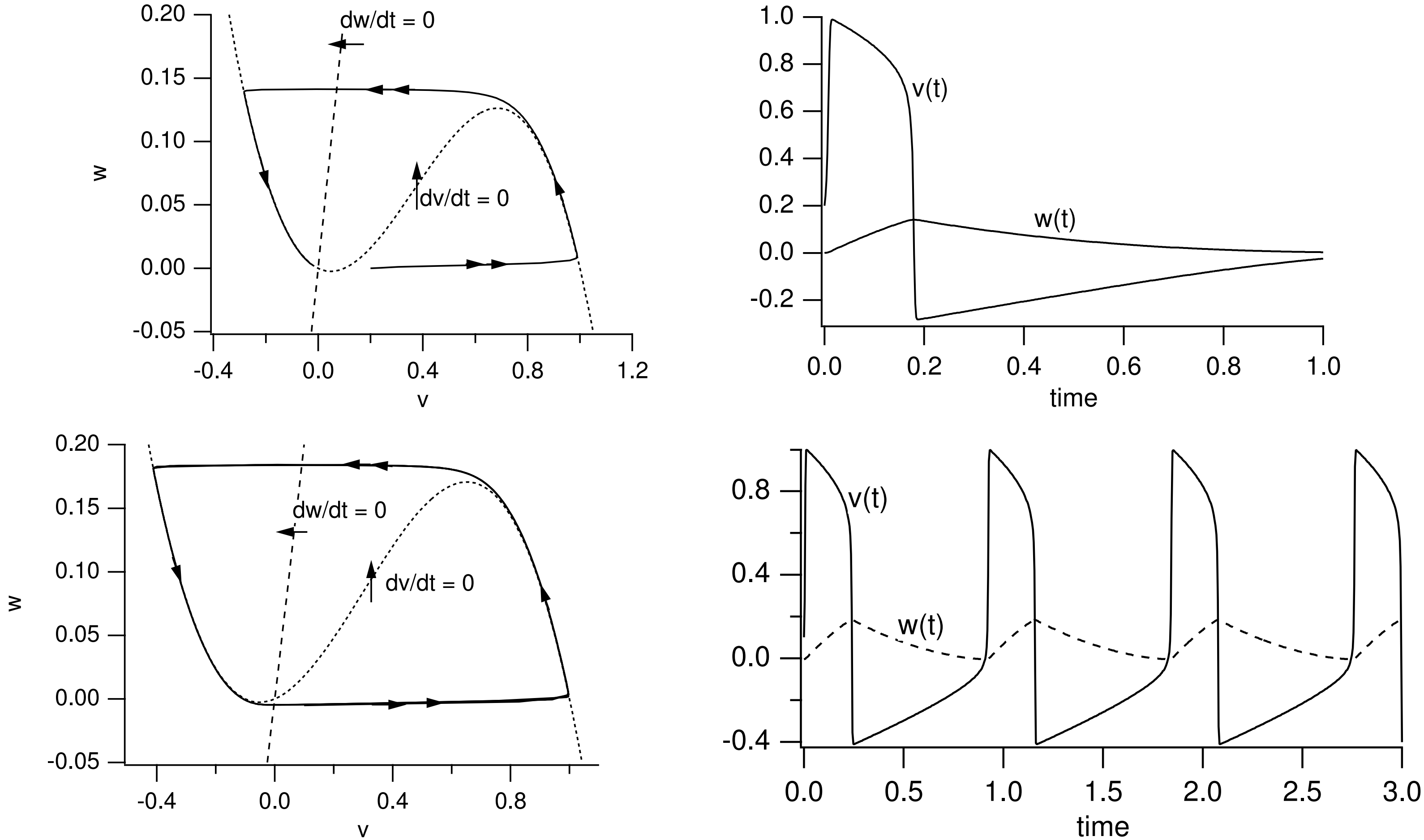
Cubic FitzHugh-Nagumo

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”.

FitzHugh-Nagumo Equations



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Mitchell-Schaeffer

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).

Mitchell-Schaeffer Revised

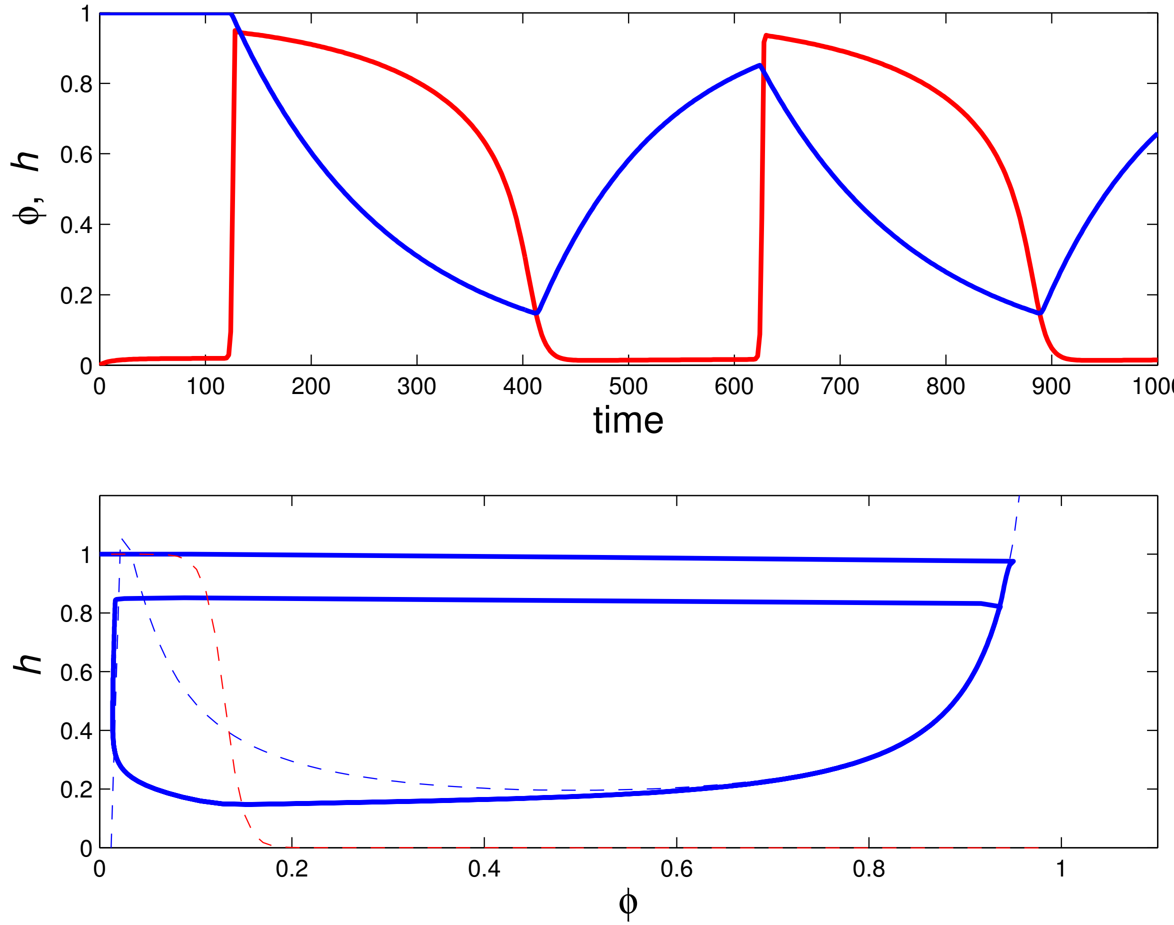
To make the Mitchell-Schaeffer look like an ionic model, take

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

where

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

Mitchell-Schaeffer Revised-II



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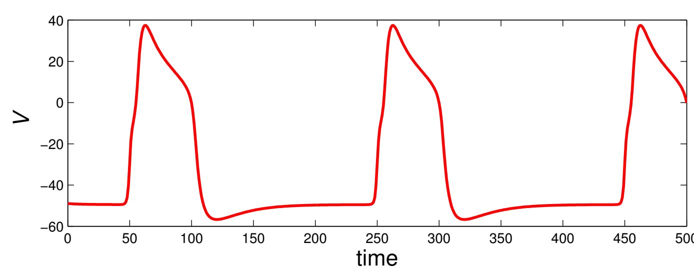
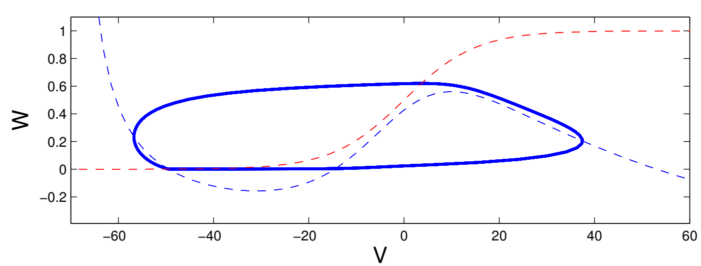
Morris-Lecar

This model was devised for barnacle muscle fiber.

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

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





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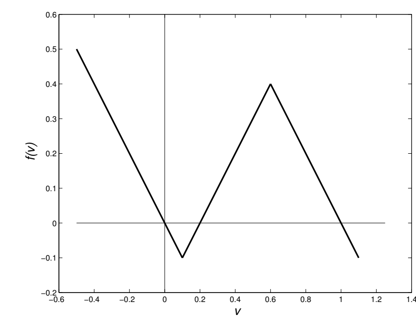
McKean

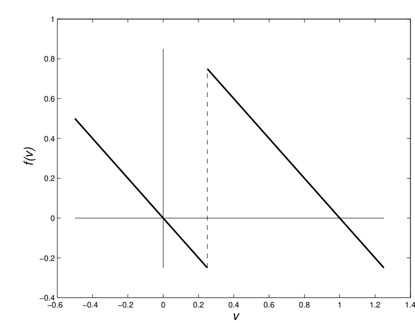
McKean suggested two piecewise linear models with $F(v,w) = f(v) - w$ and $G(v,w) = \epsilon(v - \gamma w)$. For the first,

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



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 $\gamma = 0$.

Barkley

A model devised to give very fast 2D computations (the code is known as EZspiral)

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

$$G(v,w) = \epsilon(v-w).$$

Puschino

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

$$f(v) = \begin{cases} -30v, & v < v_1 \\ \gamma v - 0.12, & v_1 < v < v_2, \\ -30(v-1), & v > v_2 \end{cases}, \qquad \tau(v) = \begin{cases} 2 & v < \\ 16.6 & v > \end{cases}$$

with $v_1 = \frac{0.12}{30+\gamma}$, $v_2 = \frac{30.12}{30+\gamma}$. (Go Back)

Aliev

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 $\beta = 0.0001$, $\alpha = 0.05$, $g_a = 8.0$, $g_s = 8.0$, $\mu_1 = 0.05$, $\mu_2 = 0.3$, $\epsilon_1 = 0.03$, $\epsilon_2 = 0.0001$.

Tyson-Fife

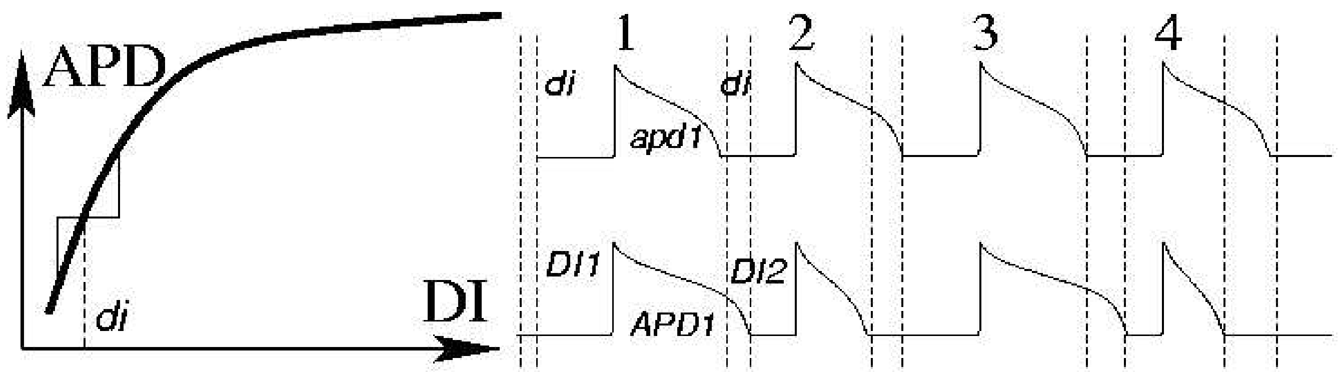
These dynamics describe the oxidation-reduction of malonic acid. For this system,

$$F(v,w) = v - v^2 - (fw + \phi_0)\frac{v-q}{v+q} \quad (-13)$$

$$G(v,w) = \epsilon(v - w) \quad (-13)$$

with typical parameter values $\epsilon = 0.05$, $q = 0.002$, $f = 3.5$, $\phi_0 = 0.01$.

APD Alternans



Action Potential Duration Restitution Curve

$$APD_n + DI_n = BCL.$$

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

$$DI_n = BCL - A(DI_{n-1}),$$

APD Map Animated

Imagine the Possibilities

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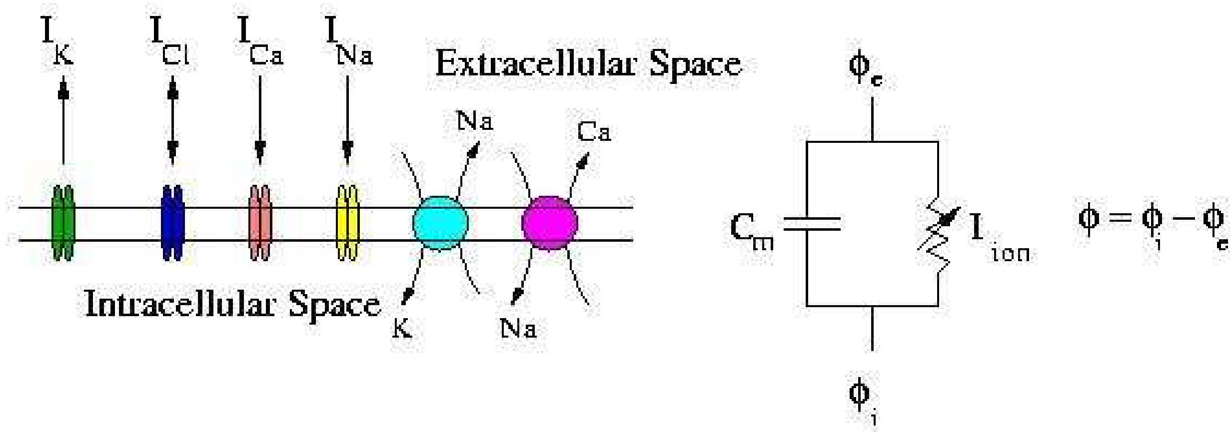
Features of Excitable Systems

- Threshold Behavior, Refractoriness
- Alternans
- Wenckebach Patterns

Cardiac Models



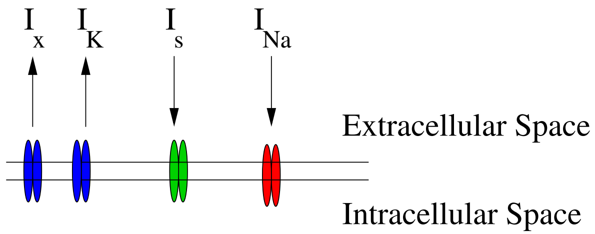
All cardiac models are of the form

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

with currents, gating and concentrations for sodium, potassium, calcium, and chloride ions.

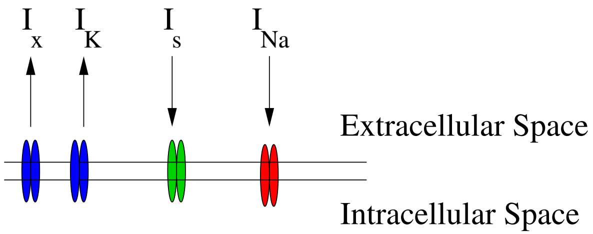
The Beeler-Reuter Model

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



The Beeler-Reuter Model

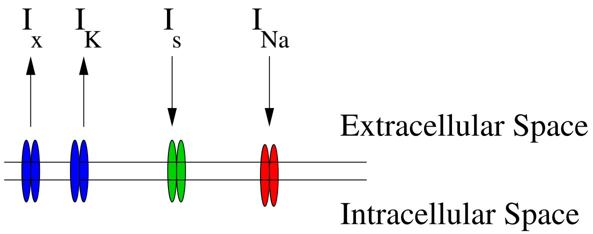
$$C_m \frac{d\phi}{dt} + \boxed{I_{\mathrm{Na}}} + I_{\mathrm{K}} + I_{\mathrm{x}} + I_{\mathrm{s}} = 0,$$



with sodium current I_{Na},

The Beeler-Reuter Model

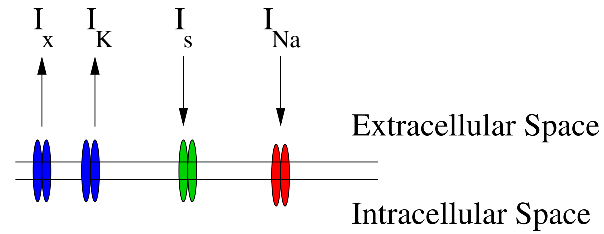
$$C_m \frac{d\phi}{dt} + \boxed{I_{\mathrm{Na}}} + \boxed{I_{\mathrm{K}}} + I_{\mathrm{x}} + I_{\mathrm{s}} = 0,$$



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

The Beeler-Reuter Model

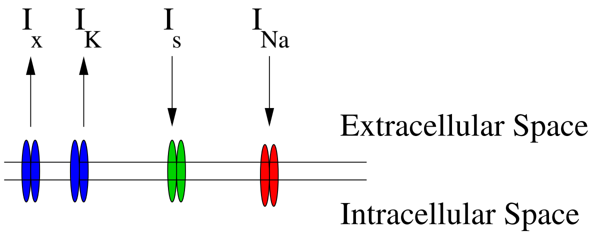
$$C_m \frac{d\phi}{dt} + \boxed{I_{\mathrm{Na}}} + \boxed{I_{\mathrm{K}}} + \boxed{I_{\mathrm{x}}} + \; I_{\mathrm{s}} \; = 0,$$



with sodium current I_{Na}, time independent potassium current I_{K}, gated potassium current I_{x},

The Beeler-Reuter Model

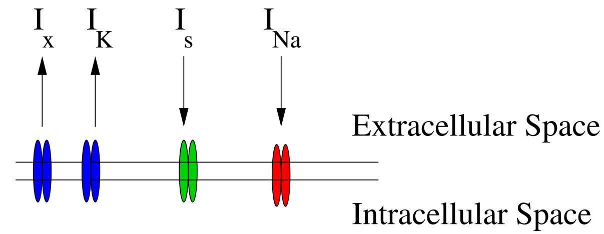
$$C_m \frac{d\phi}{dt} + \boxed{I_{\rm Na}} + \boxed{I_{\rm K}} + \boxed{I_{\rm x}} + \boxed{I_{\rm s}} = 0,$$



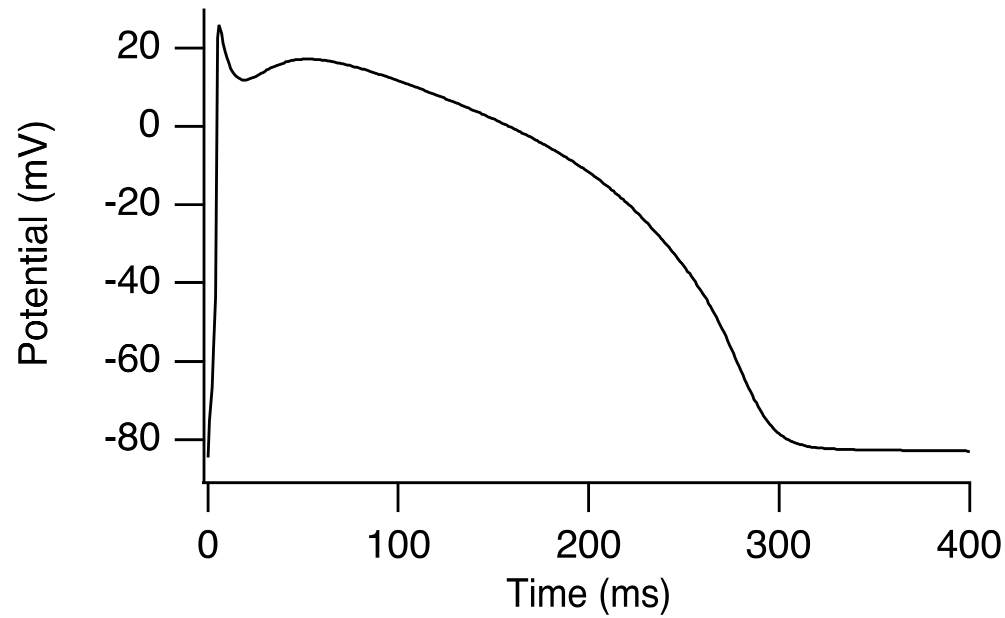
with sodium current $I_{\rm Na}$, time independent potassium current $I_{\rm K}$, gated potassium current $I_{\rm x}$, and (slow) calcium current $I_{\rm s}$.

The Beeler-Reuter Model

$$C_m \frac{d\phi}{dt} + \boxed{I_{\mathrm{Na}}} + \boxed{I_{\mathrm{K}}} + \boxed{I_{\mathrm{x}}} + \boxed{I_{\mathrm{s}}} = 0,$$



with sodium current I_{Na}, time independent potassium current I_{K}, gated potassium current I_{x}, and (slow) calcium current I_{s}.



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Detailed Ionic Models- Luo-Rudy