Imagine the Possibilities

Mathematical Biology
University of Utah

Introduction to Physiology III - Excitability

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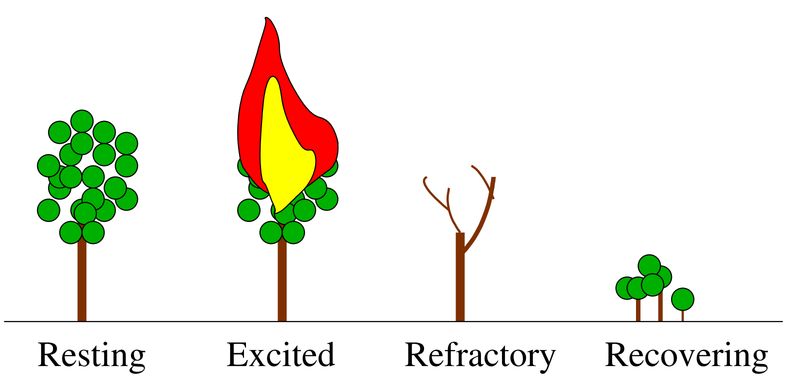
Examples of Excitable Media

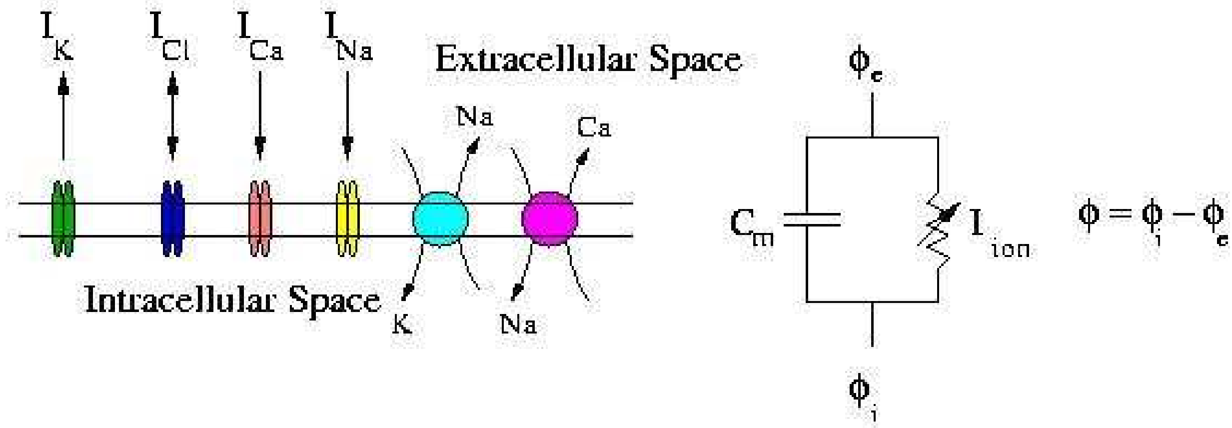
- CICR (Calcium Induced Calcium Release)
- Nerve cells
- cardiac cells, muscle cells
- Slime mold (*dictystelium discoideum*)
- B-Z reagent
- Forest Fires

Features of Excitability

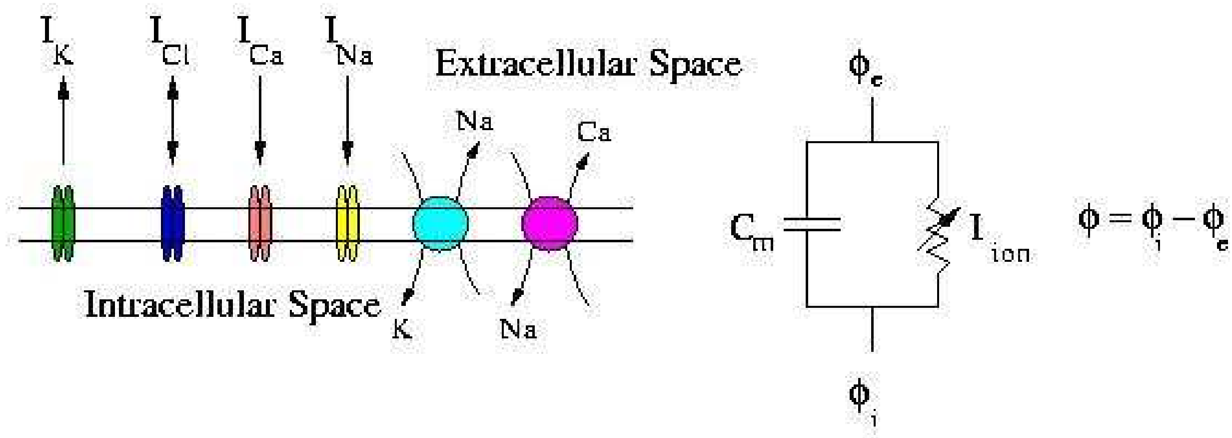
- Threshold Behavior
- Refractoriness
- Recovery



Modeling Membrane Electrical Activity



Modeling Membrane Electrical Activity



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

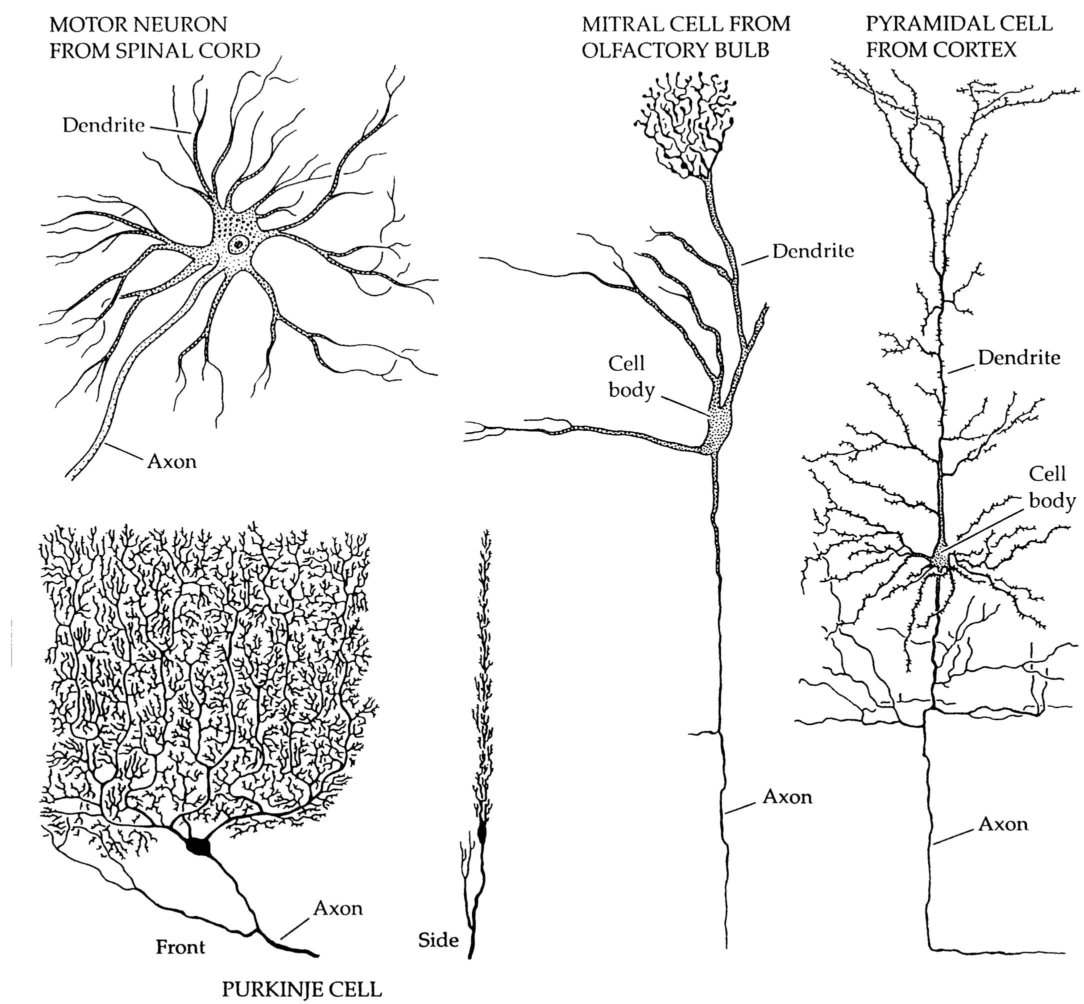
$$C_m \frac{d\phi}{dt} + I_{ion}(\phi, w) = I_{in} \quad \text{where } \frac{dw}{dt} = g(\phi, w), \qquad w \in R^n$$

Examples

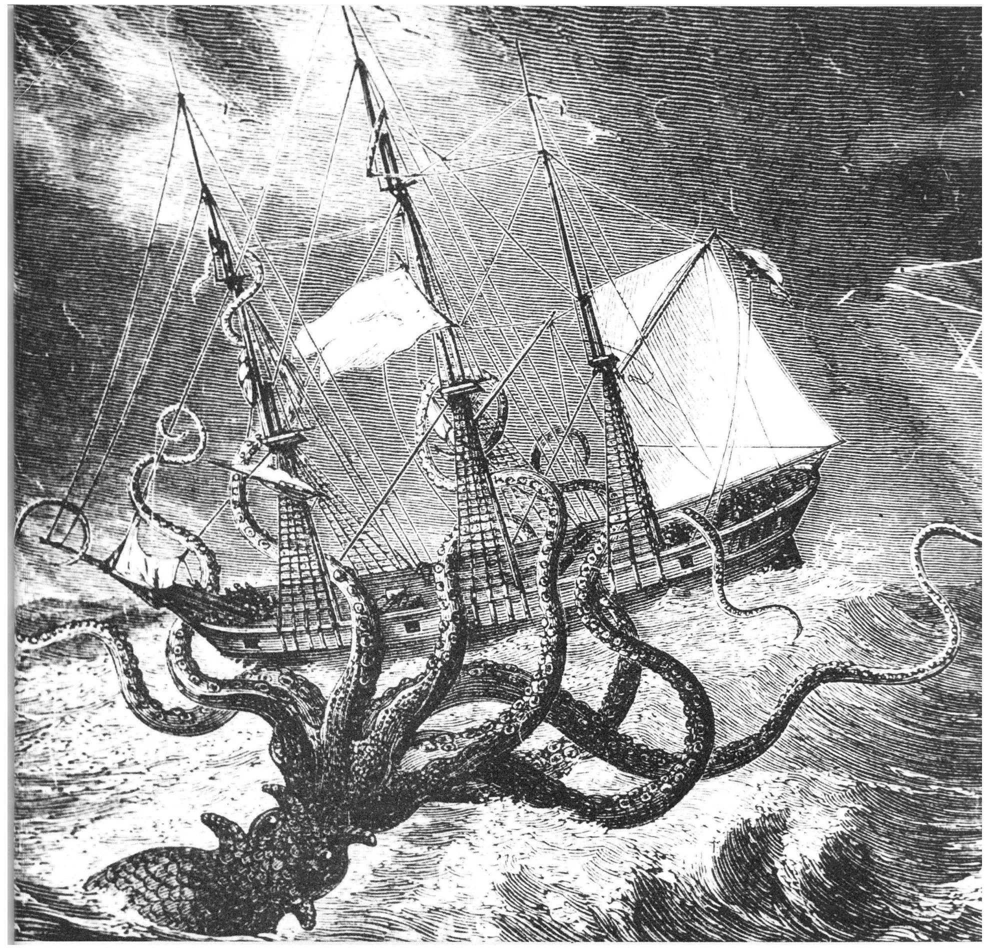
Examples include:

- 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.)

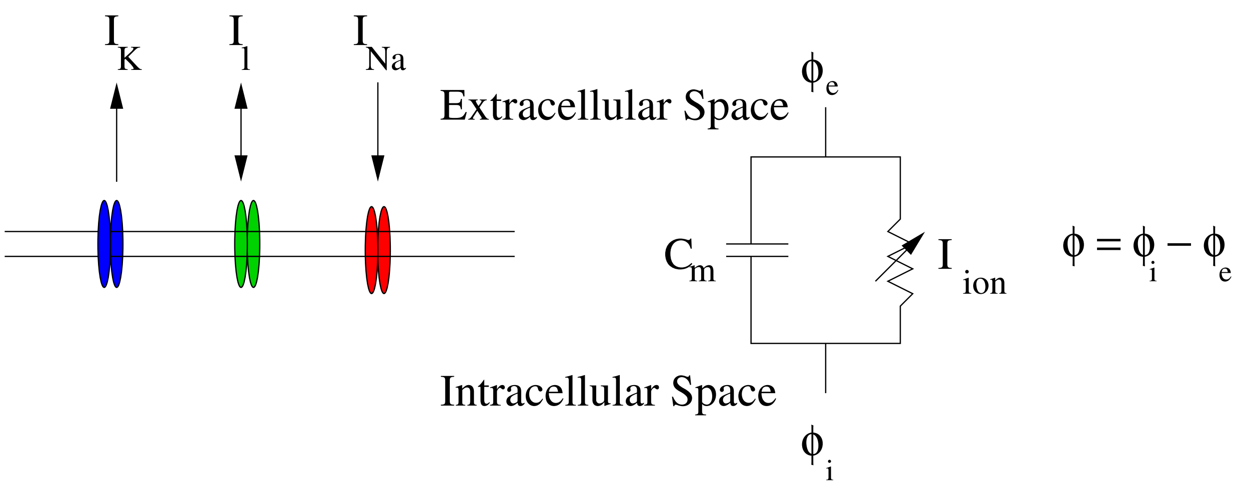
The Squid Giant Axon...



is not the Giant Squid Axon

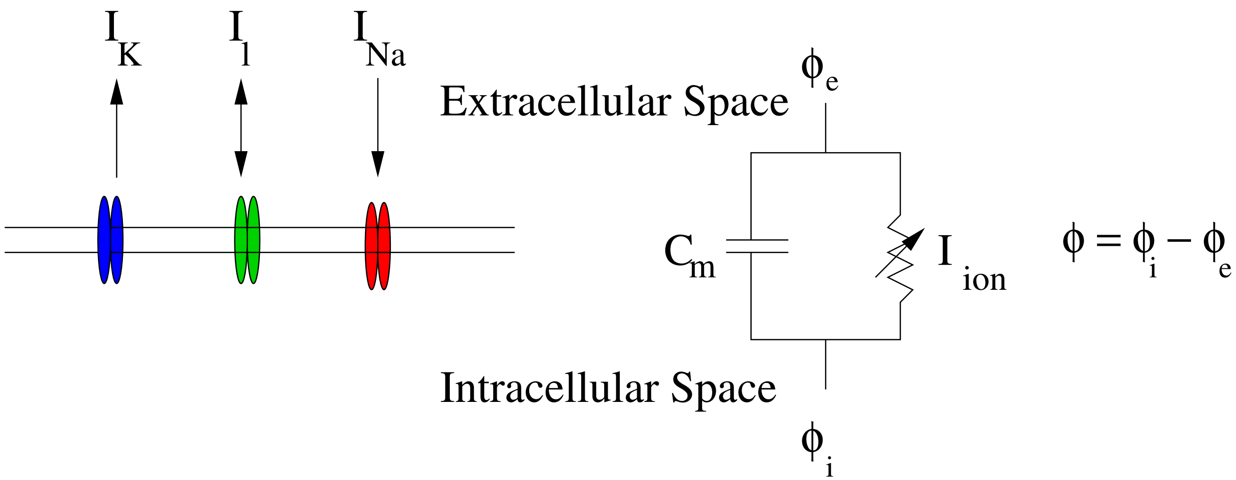


The Hodgkin-Huxley Equations



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

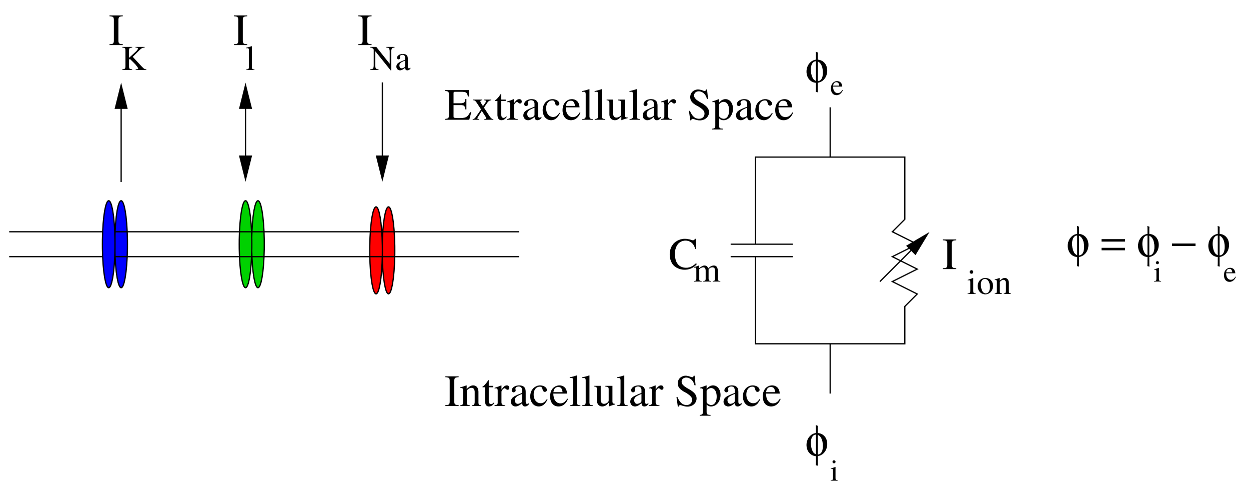
The Hodgkin-Huxley Equations



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

with sodium current $I_{\rm Na}$,

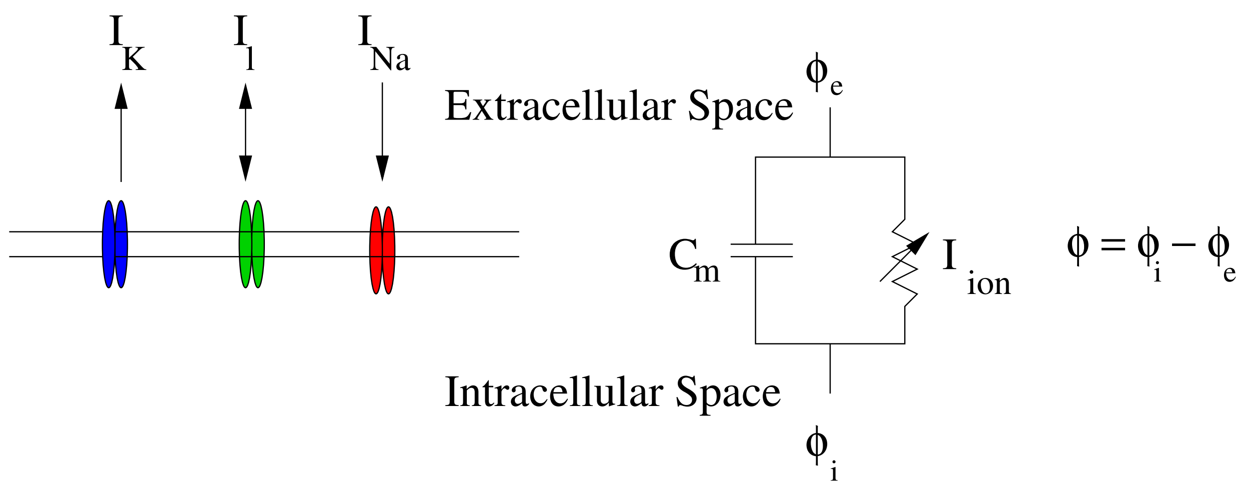
The Hodgkin-Huxley Equations



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

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.

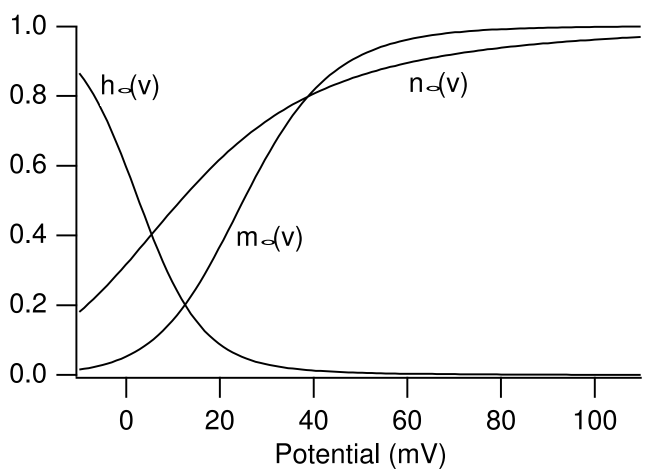
Currents

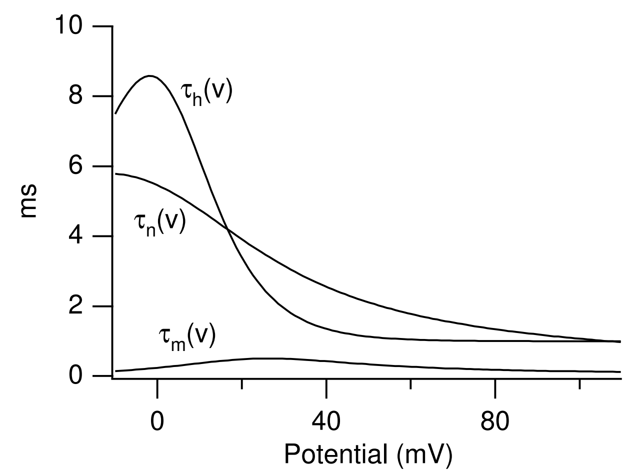
Hodgkin and Huxley found that

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

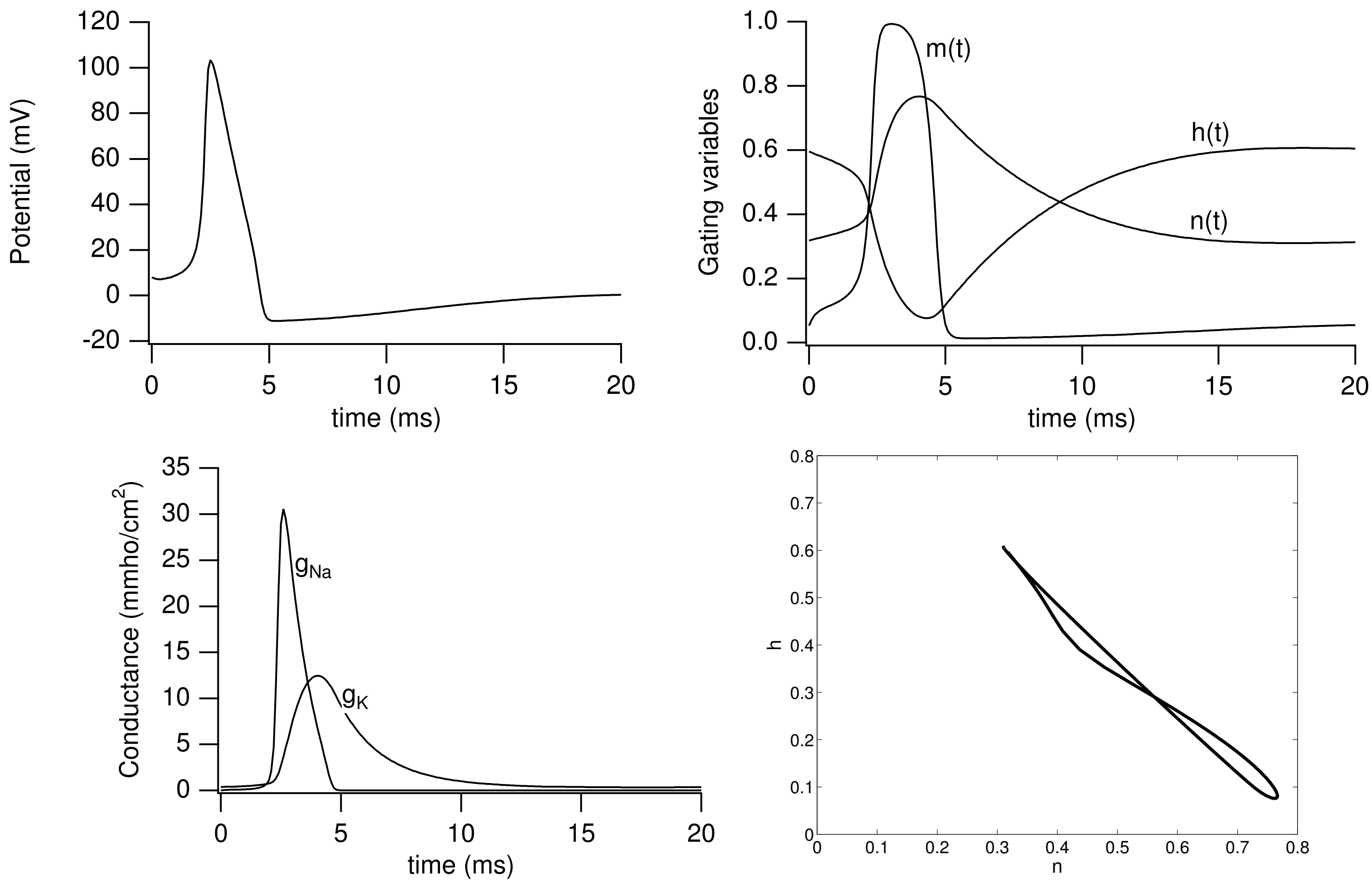
where

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



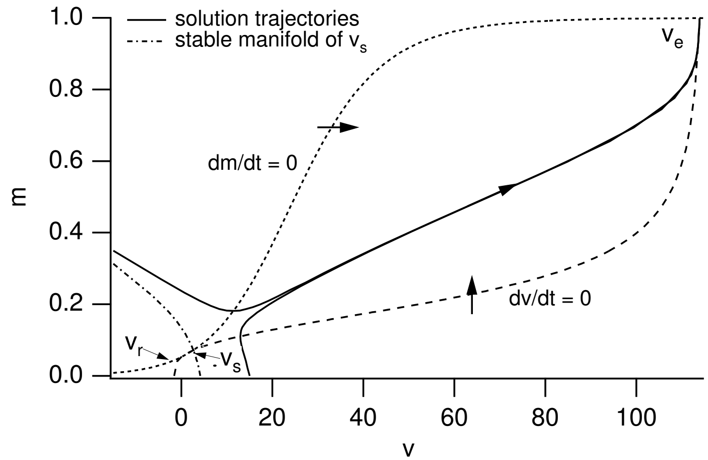


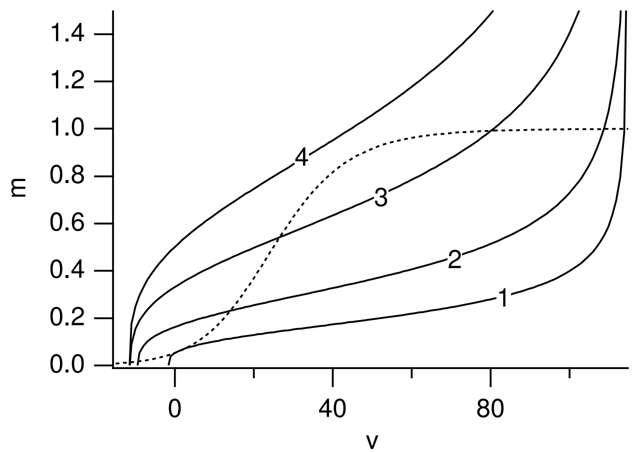
Action Potential Dynamics



Fast-Slow Subsystem Dynamics

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





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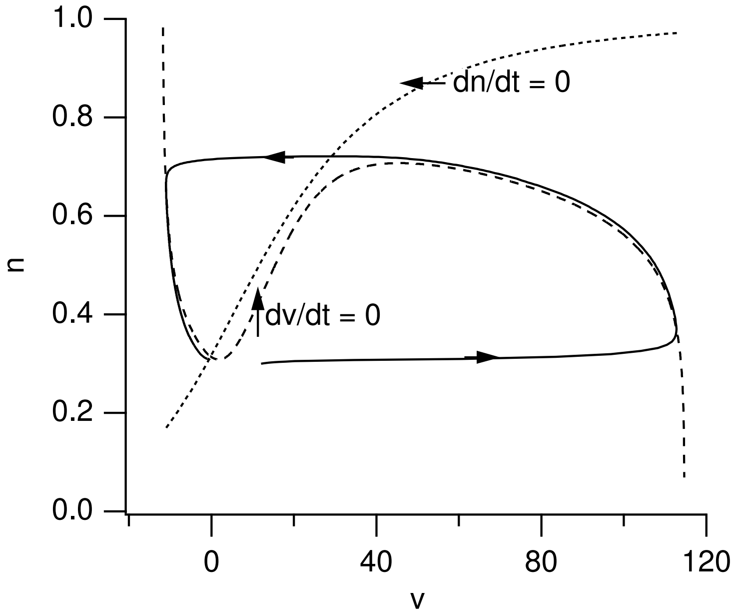
Two Variable Reduction of HH Eqns

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

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



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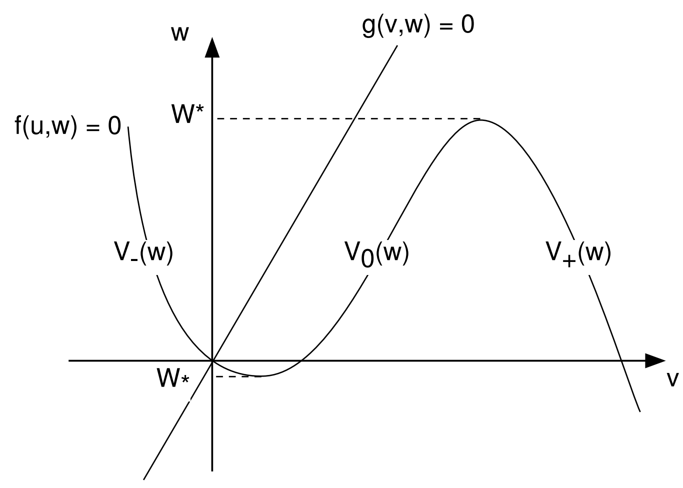
Two Variable Models

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.



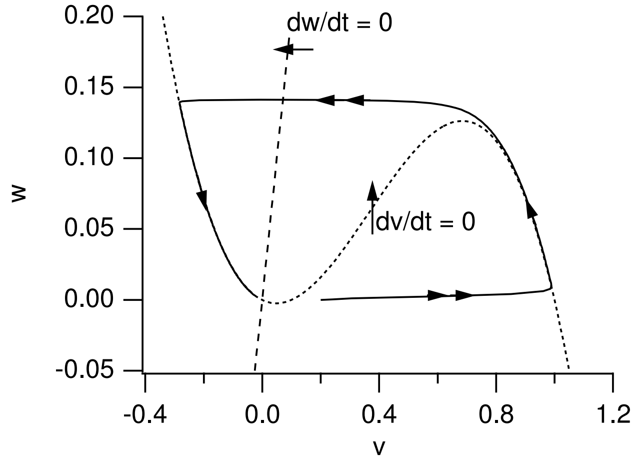
Cubic FitzHugh-Nagumo

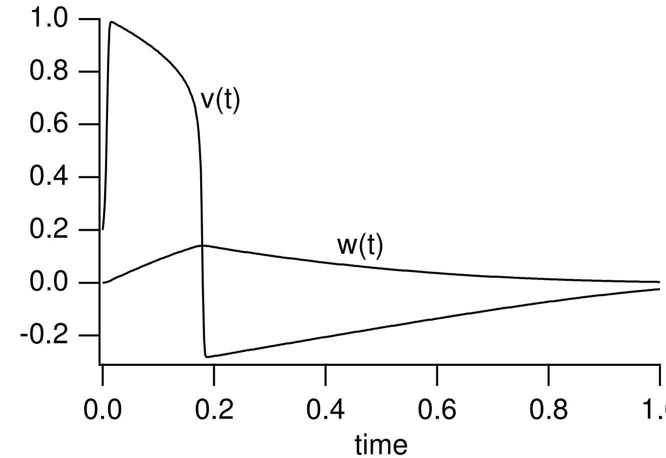
The model that started the whole business uses a cubic polynomial (a variant of the van der Pol equation).

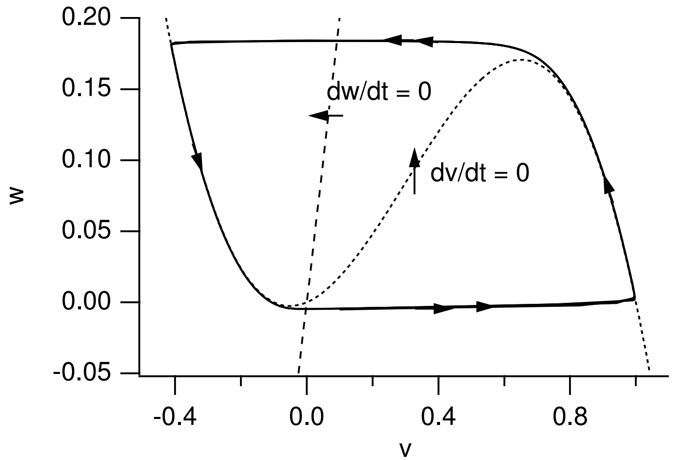
$$
\begin{aligned}
F(v,w) &= Av(v-\alpha)(1-v) - w, \\
G(v,w) &= \epsilon(v-\gamma w).
\end{aligned}
$$

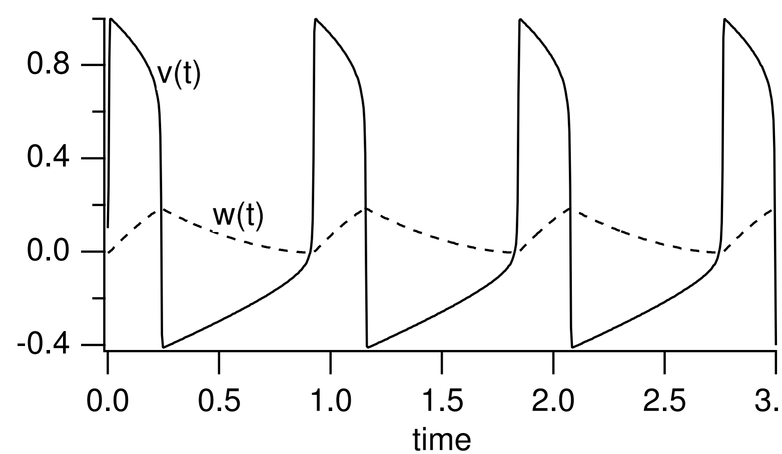
with $0 < \alpha < \frac{1}{2}$, and ϵ “small”.

FitzHugh-Nagumo Equations









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Mitchell-Schaeffer

Mitchell-Schaeffer two-variable model (also in a slightly different but equivalent form by Karma)

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

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

Notice that $F(v,w)$ is cubic in v, and w is an inactivation variable (like h in HH).

Mitchell-Schaeffer Revised

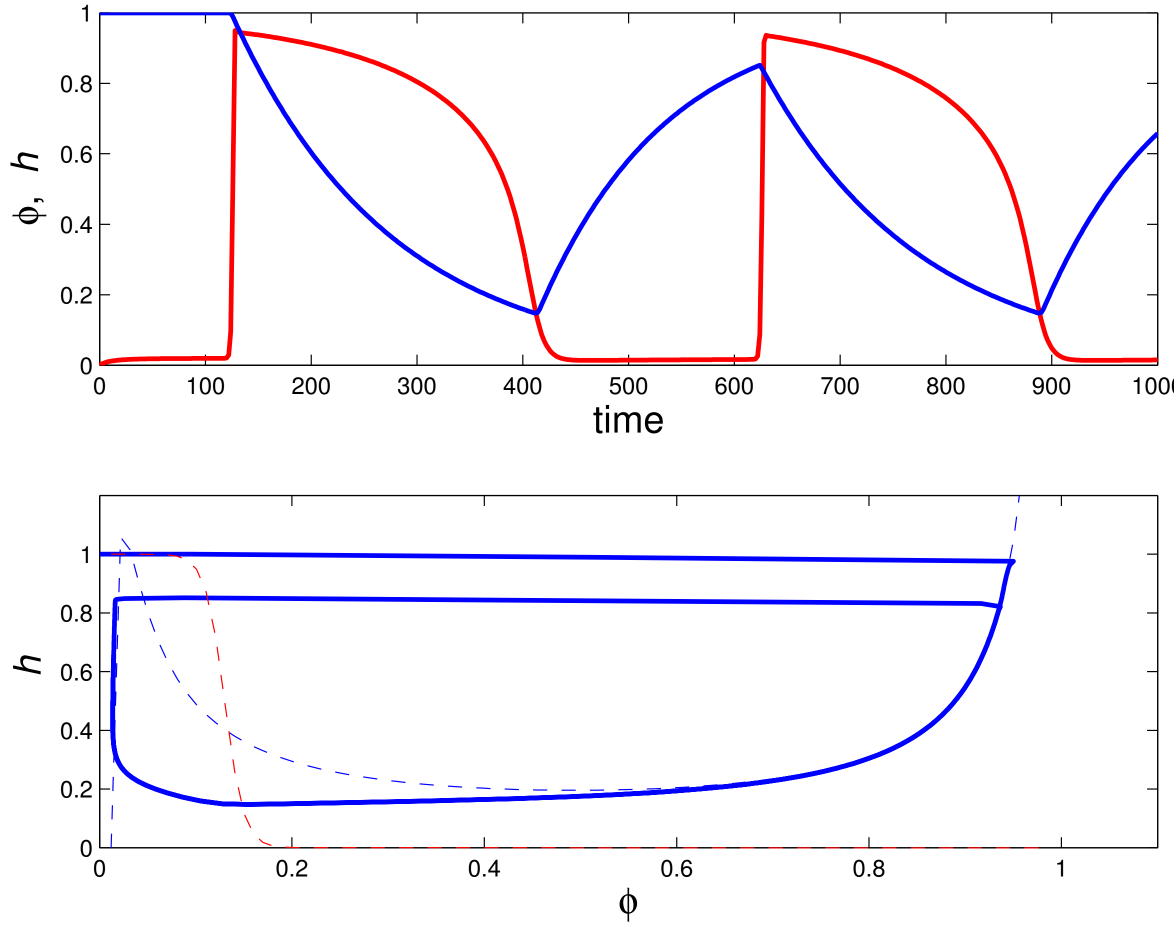
To make the Mitchell-Schaeffer look like an ionic model, take

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

where

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

Mitchell-Schaeffer Revised-II



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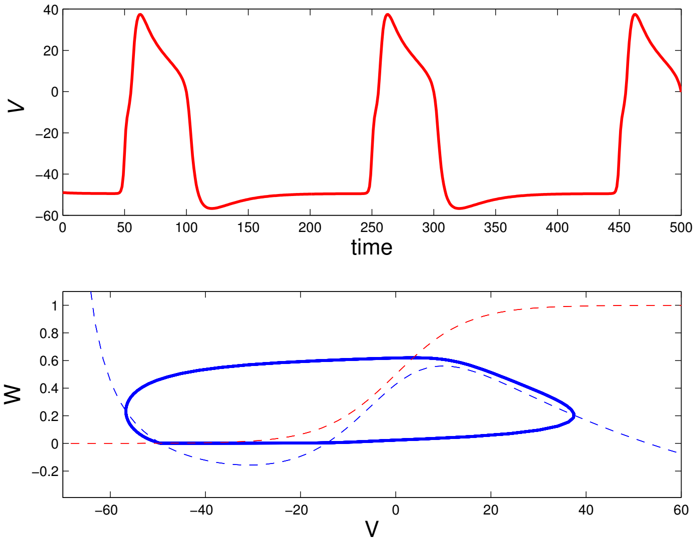
Morris-Lecar

This model was devised for barnacle muscle fiber.

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

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



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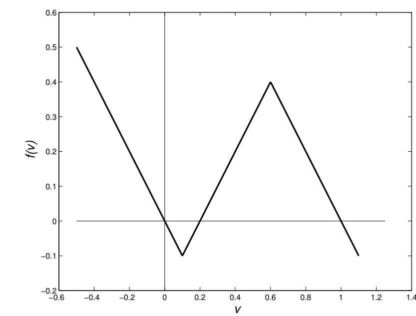
McKean

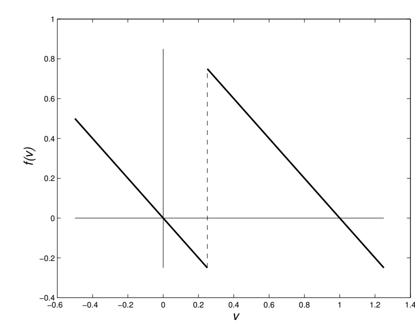
McKean suggested two piecewise linear models with $F(v,w) = f(v) - w$ and $G(v,w) = \epsilon(v - \gamma w)$. For the first,

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



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)

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

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

Tyson-Fife

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

$$F(v,w) = v - v^2 - (fw + \phi_0)\frac{v-q}{v+q} \qquad \text{(-9)}$$

$$G(v,w) = \epsilon(v - w) \qquad \text{(-9)}$$

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

Imagine the Possibilities

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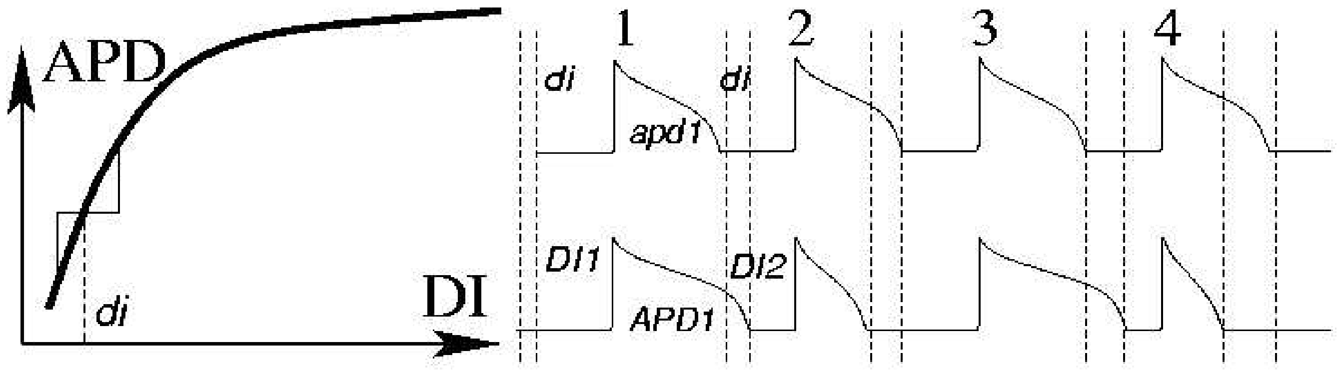
Features of Excitable Systems

- Threshold Behavior, Refractoriness
- Alternans
- Wenckebach Patterns

APD Alternans



Action Potential Duration Restitution Curve

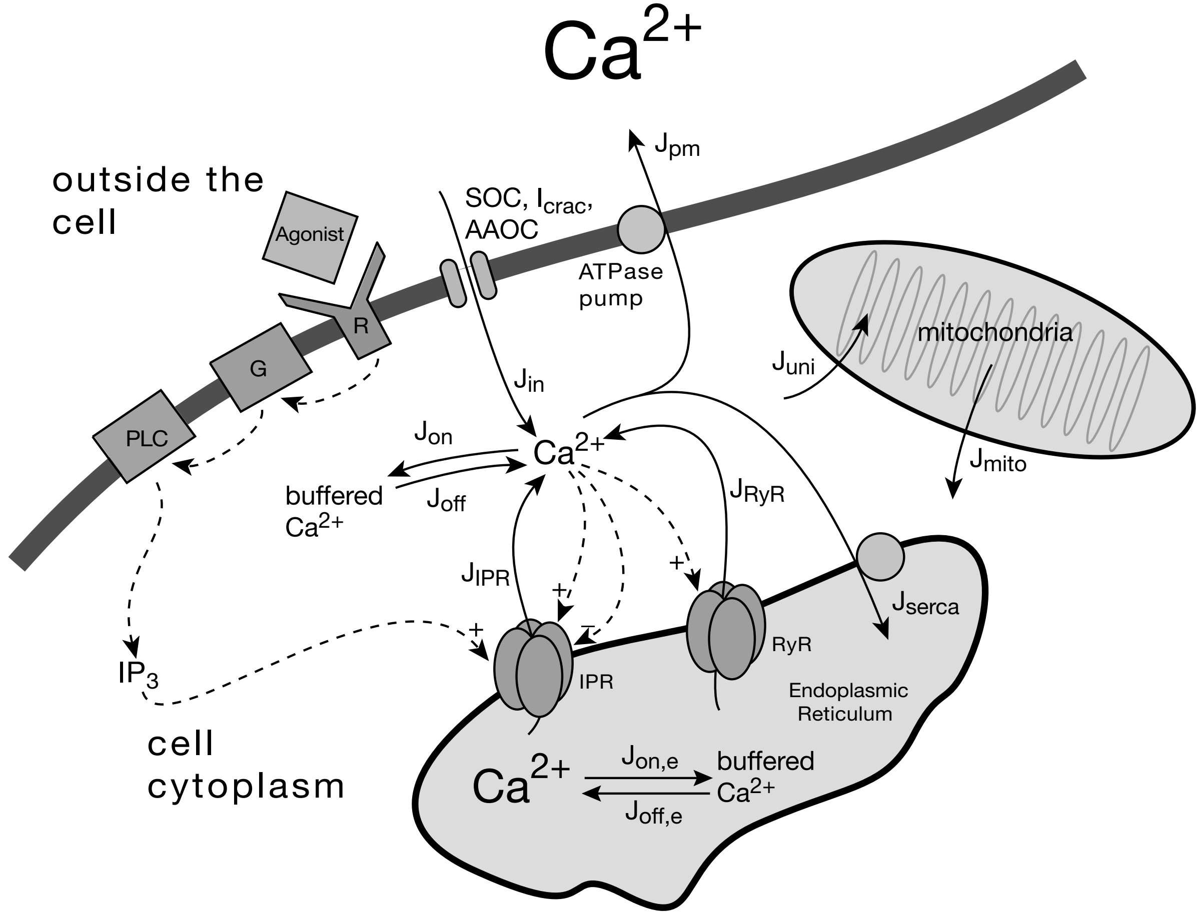
$$APD_n + DI_n = BCL.$$

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

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

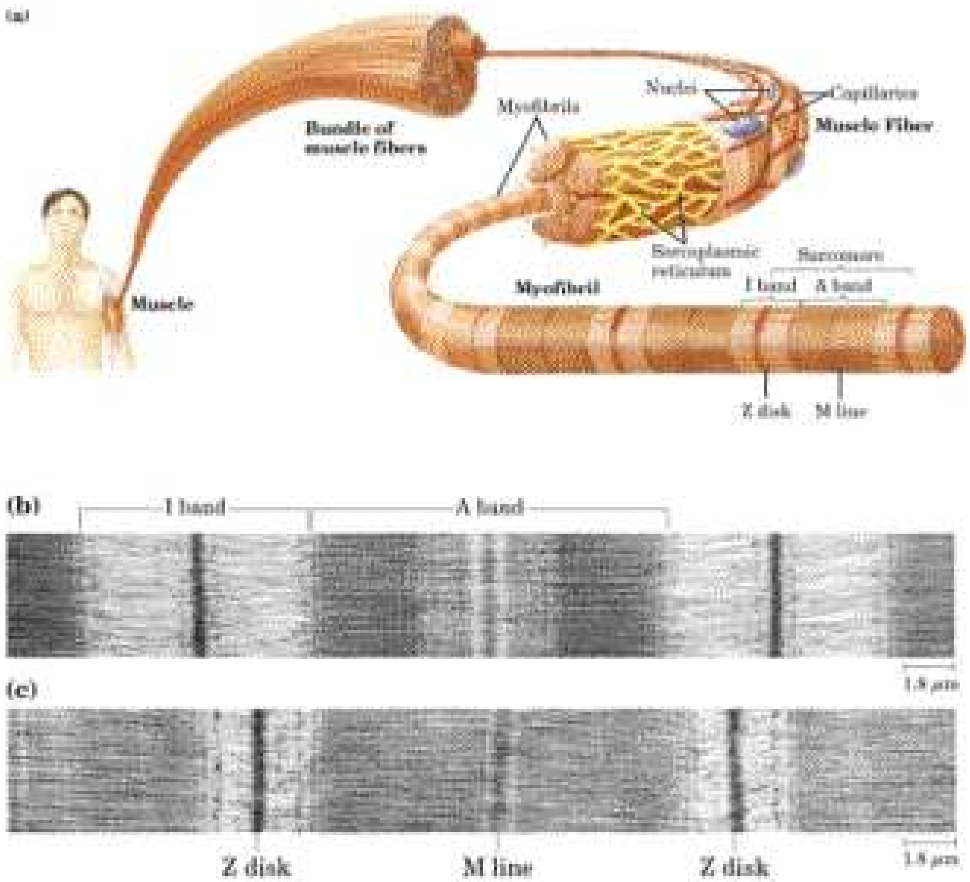
APD Map Animated

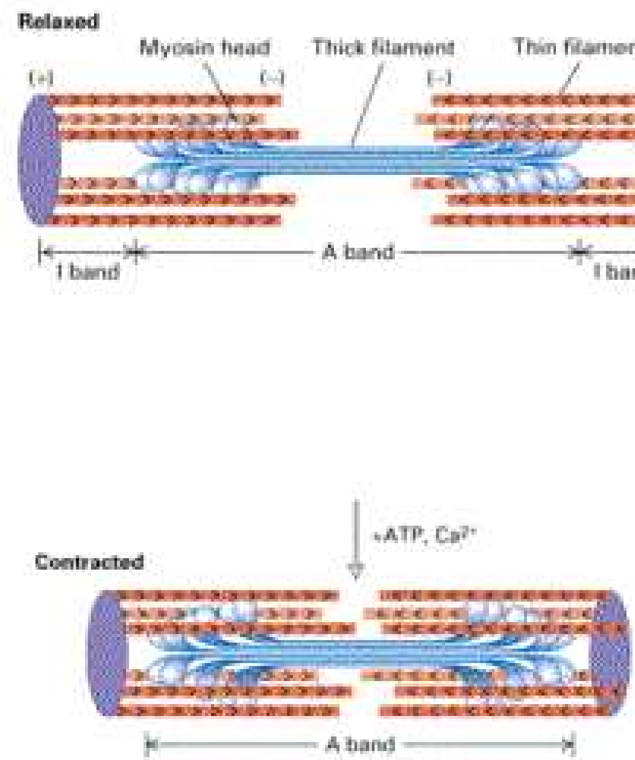
Intracellular Calcium



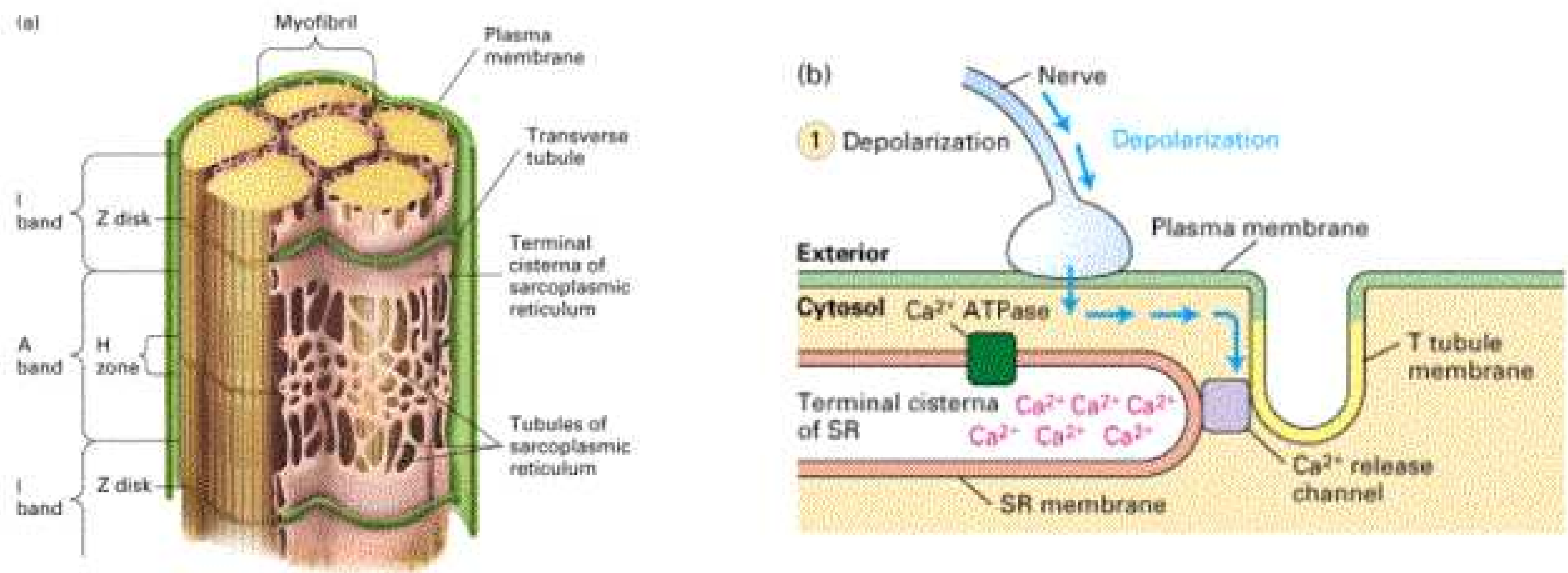
Muscle

Structure of skeletal muscle





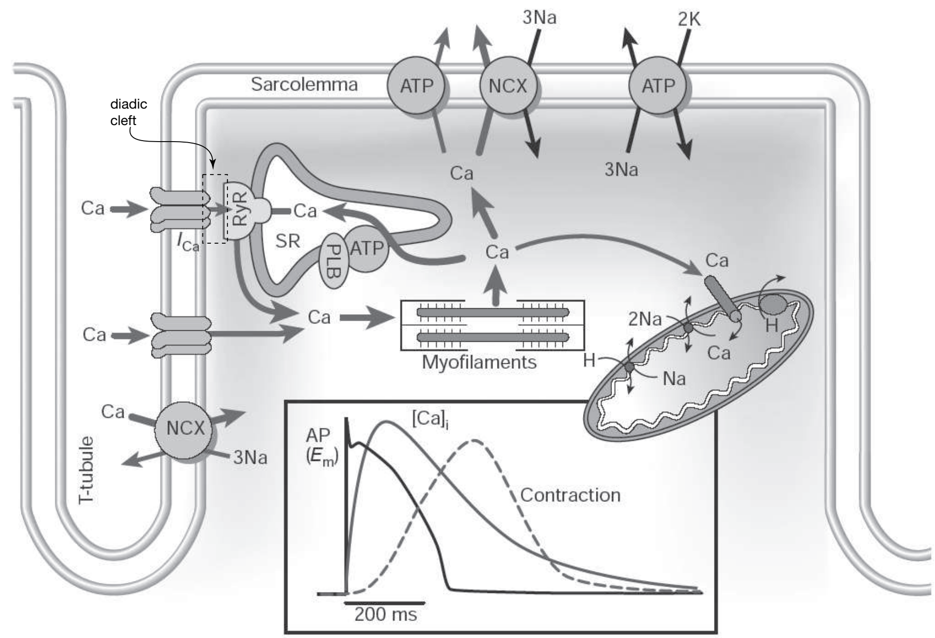
Muscle - II


(a)
Myofibril
Plasma membrane
Transverse tubule
Terminal cisterna of sarcoplasmic reticulum
Tubules of sarcoplasmic reticulum
I band
Z disk
A band
H zone
I band
Z disk
(b)
Nerve
1 Depolarization
Depolarization
Plasma membrane
Exterior
Cytosol
Ca2+ ATPase
T tubule membrane
Terminal cisterna of SR
Ca2+ Ca2+ Ca2+
Ca2+ Ca2+ Ca2+
Ca2+ release channel
SR membrane

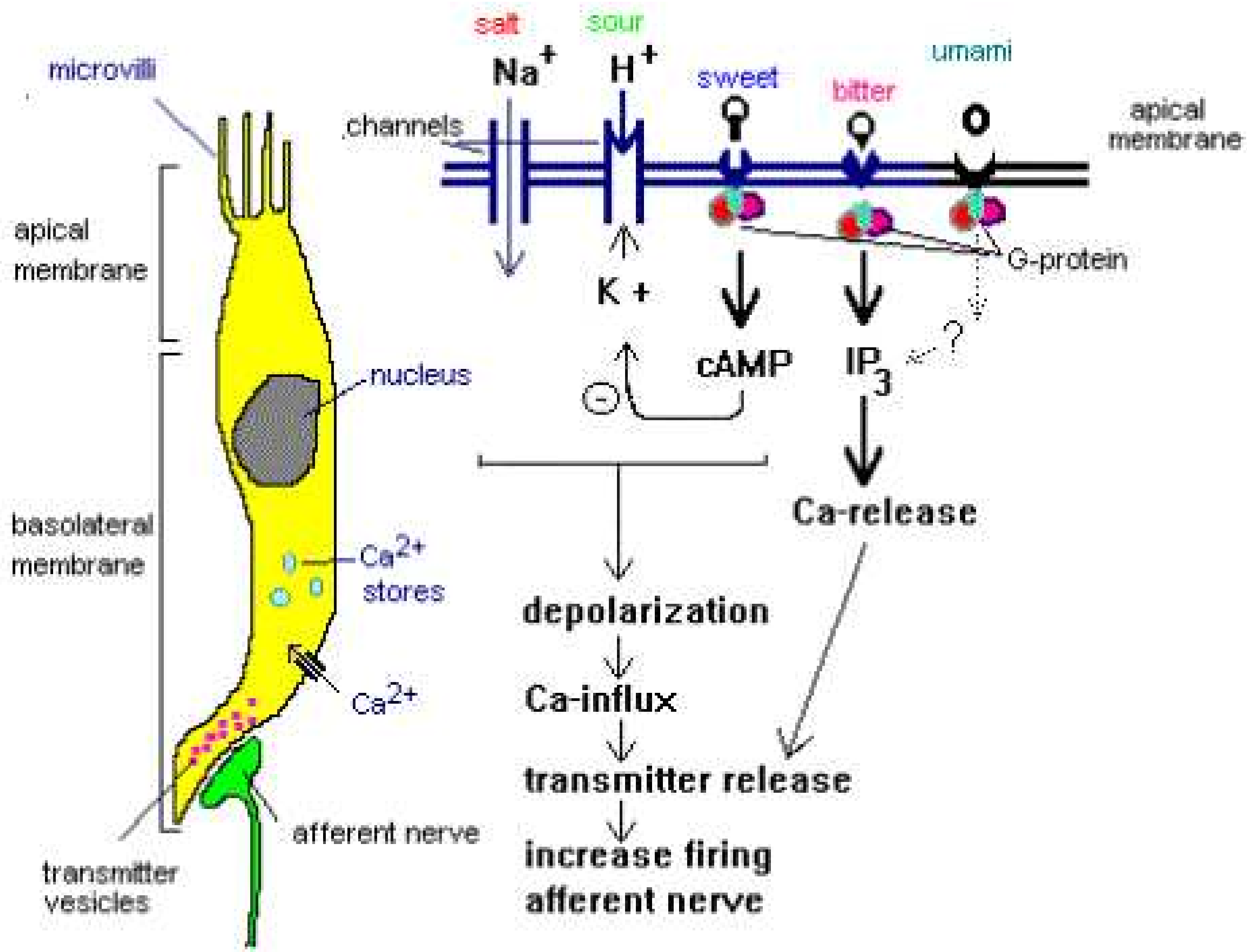
Excitation-Contraction Coupling

Cardiac cells are interesting because they contain TWO excitable systems that are interconnected

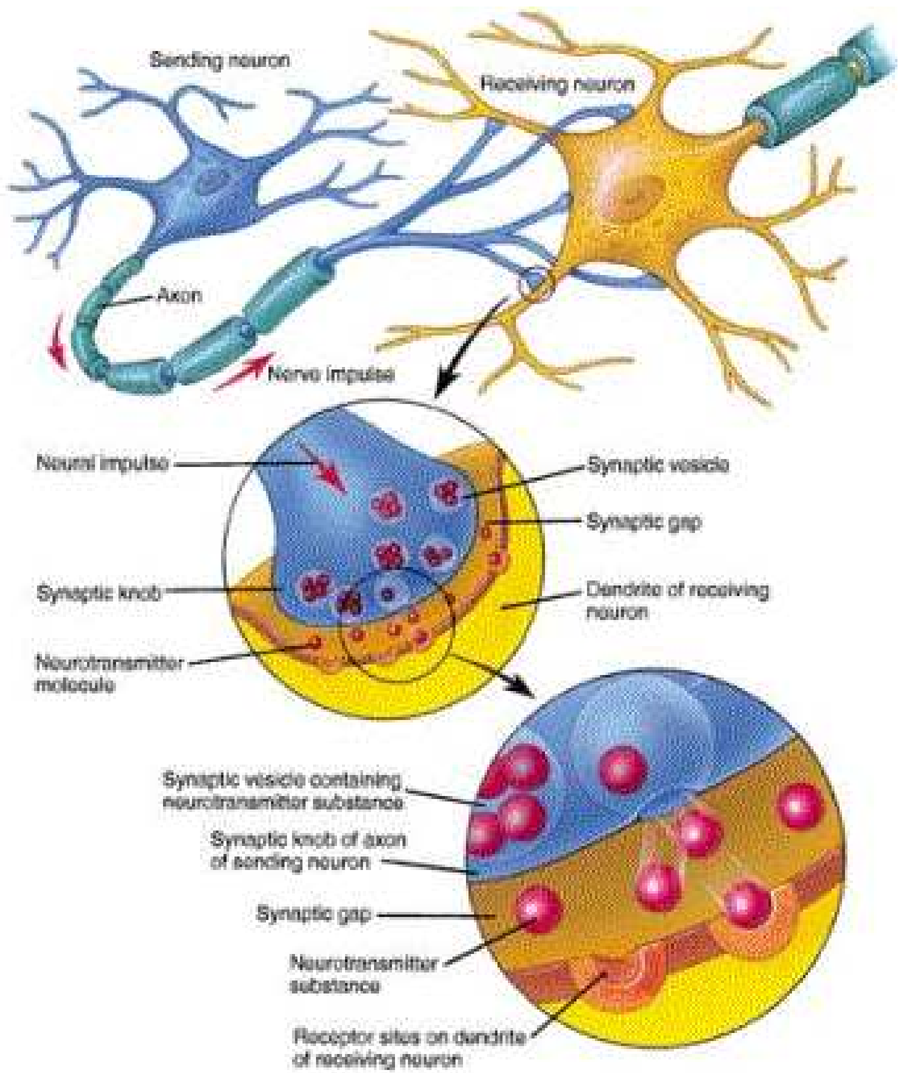
- The sodium-potassium electrical action potential, that stimulates an inward calcium flux
- which excites CICR
- which causes muscles to contract.



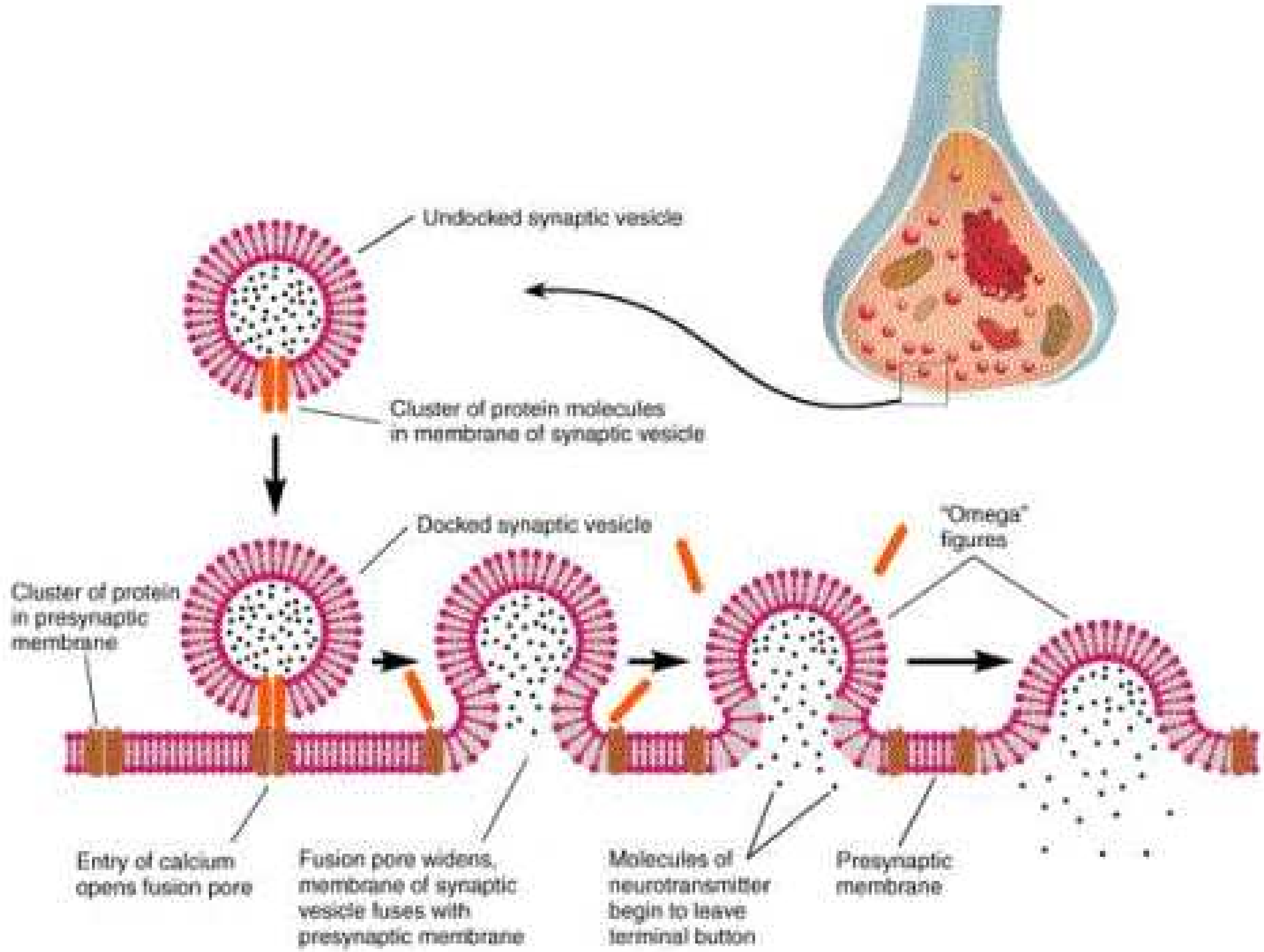
Taste Buds


salt
sour
umami
microvilli
Na+
H+
sweet
bitter
channels
apical membrane
apical membrane
G-protein
K +
cAMP
IP3
?
nucleus
Ca-release
basolateral membrane
Ca2+ stores
depolarization
Ca2+
Ca-influx
transmitter release
afferent nerve
increase firing afferent nerve
transmitter vesicles

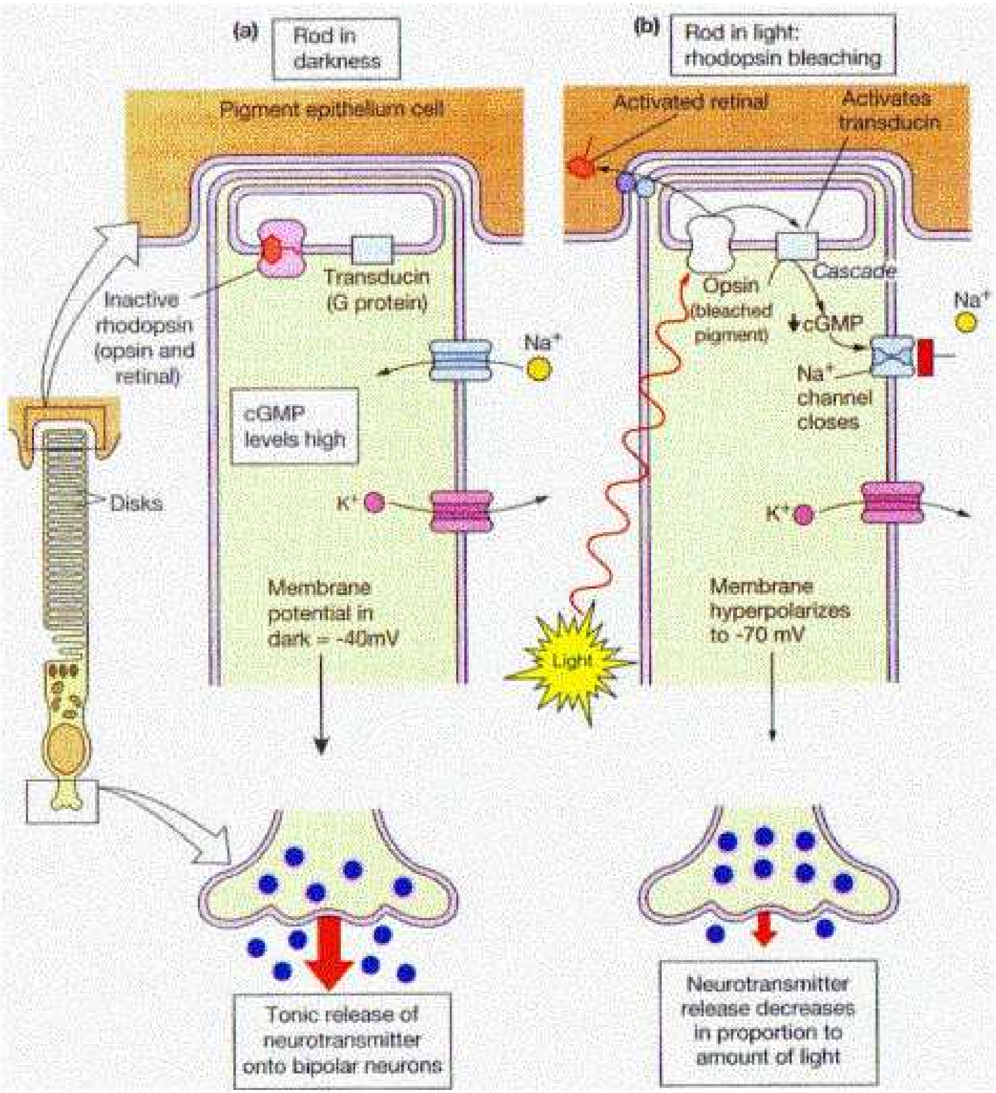
Neural Synapses



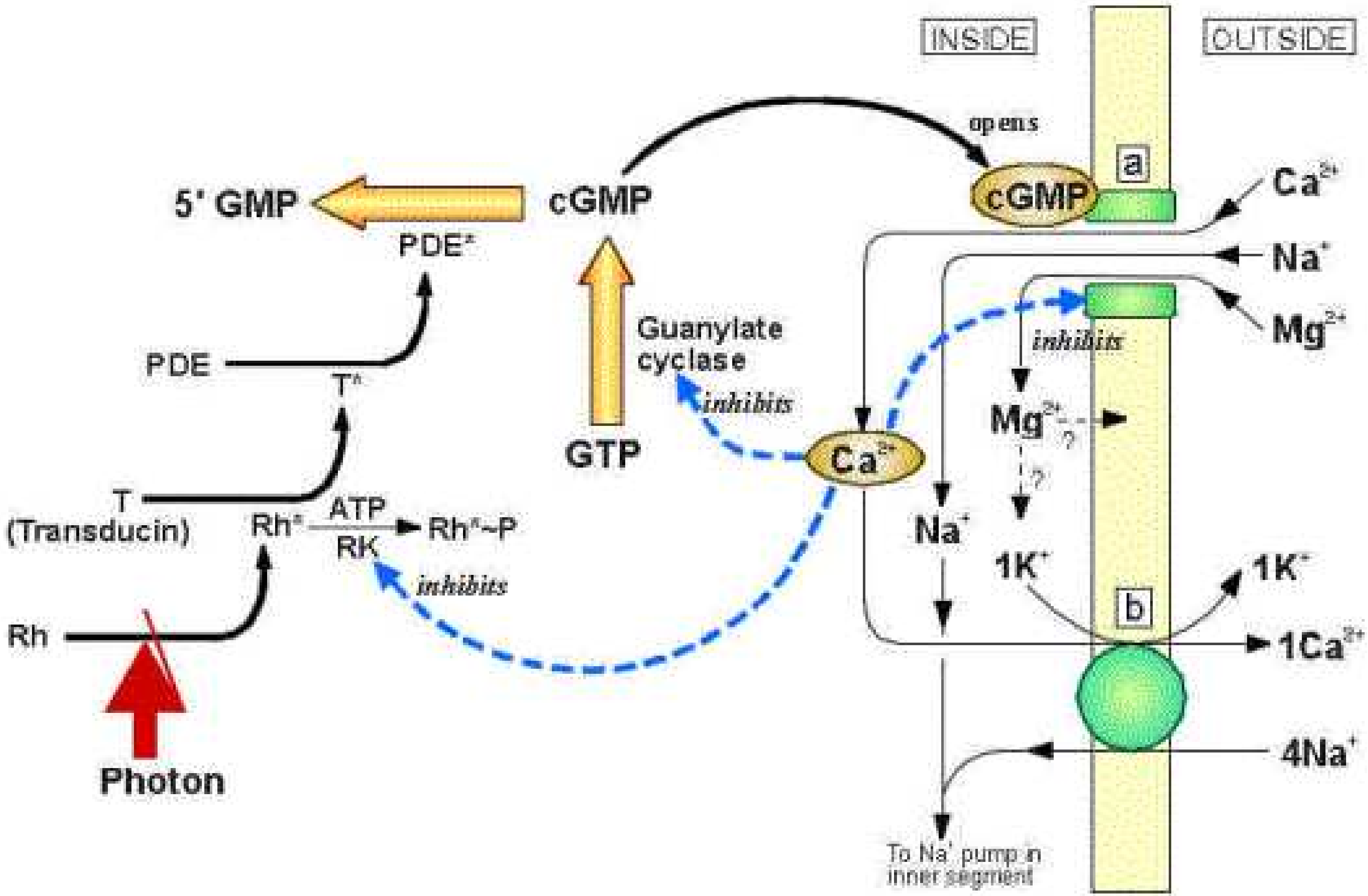
Neurotransmitter - II



Phototransduction

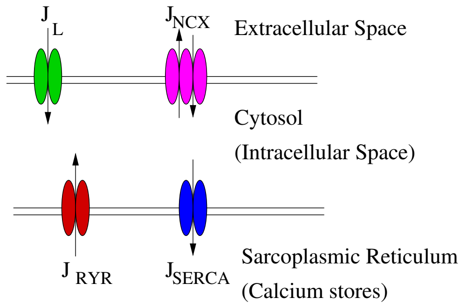


Phototransduction



Calcium Handling

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



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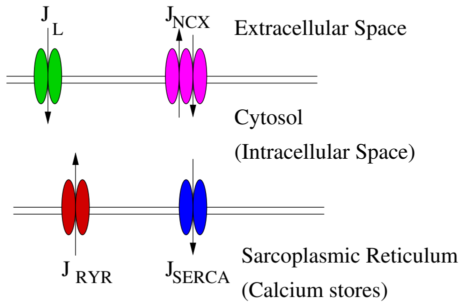

with

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

Calcium Handling

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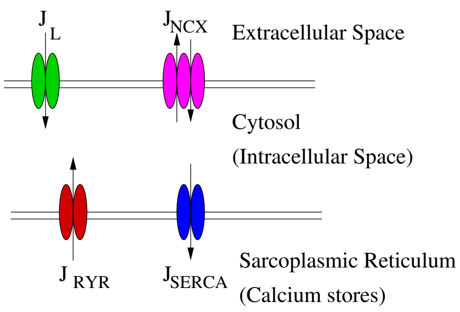

with

J_{RYR} Ryanodine Receptor - calcium regulated calcium channel,

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

Calcium Handling

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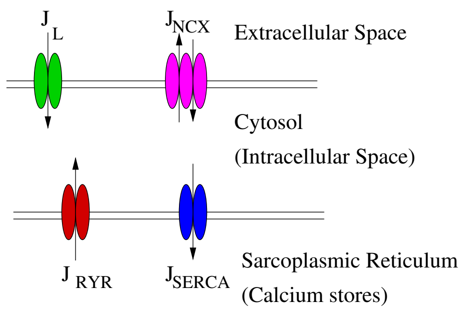

with

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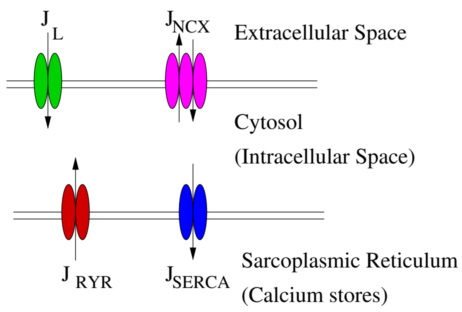
J_{SERCA} Sarco- and Endoplasmic Reticulum Calcium ATPase,

J_L L-type voltage regulated calcium channel,

Calcium Handling

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



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J_{RYR} Ryanodine Receptor - calcium regulated calcium channel,

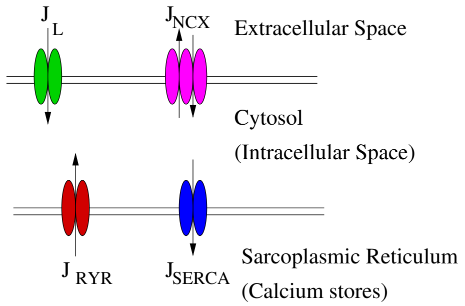
J_{SERCA} Sarco- and Endoplasmic Reticulum Calcium ATPase,

J_L L-type voltage regulated calcium channel,

J_{NCX} sodium(Na^{++})- Calcium eXchanger .

Calcium Handling

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



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J_L L-type voltage regulated calcium channel,

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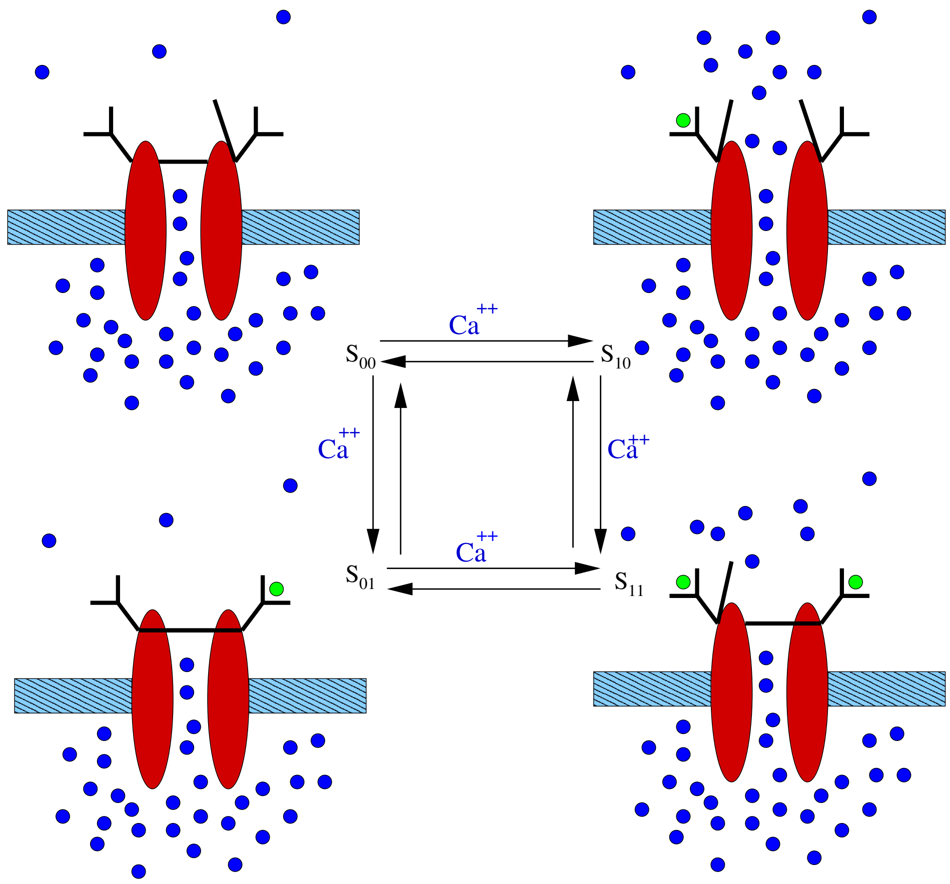
Challenge: Determine the flux terms.

Ryanodine Receptors



Ryanodine Receptors

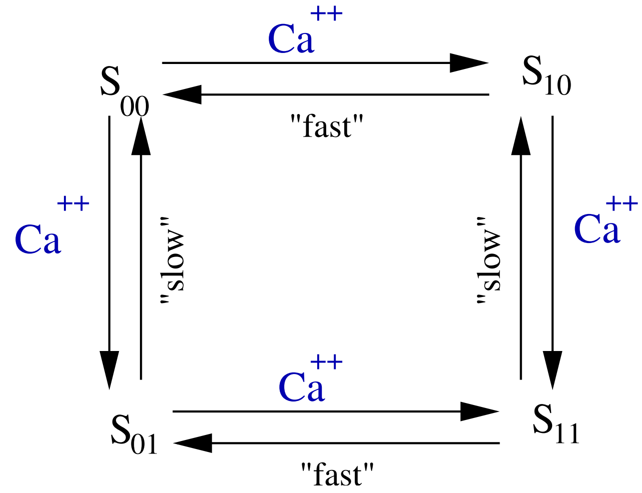
Flux through ryanodine receptor is diffusive,

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

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

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

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