Introduction to Physiology IV - Calcium Dynamics

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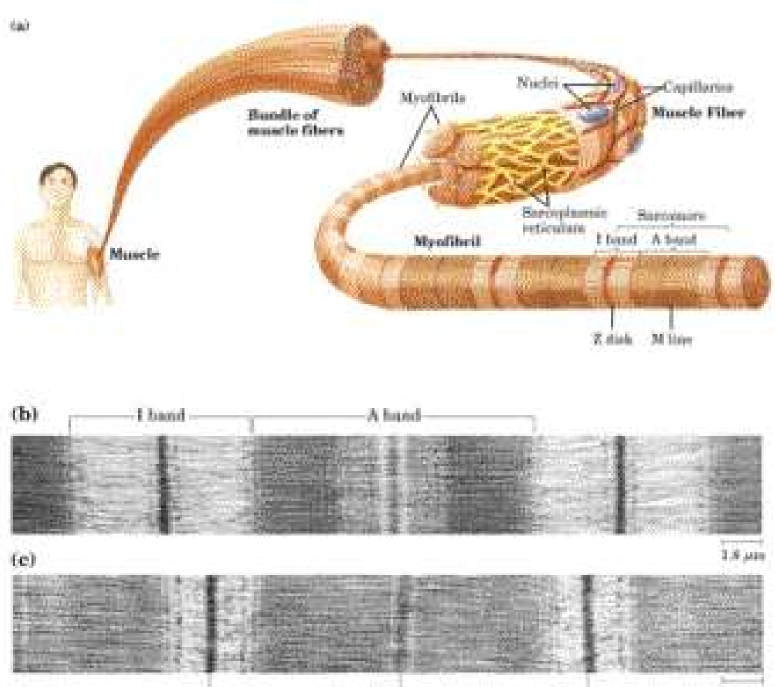
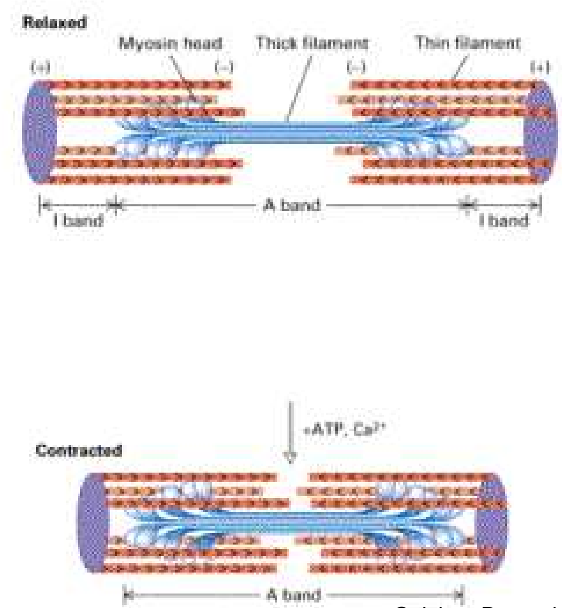
Introduction

- Previous lectures emphasized the role of sodium and potassium in control of membrane size and potential;
- Calcium is equally important in almost every cell type;
- Calcium controls secretion, cell movement, muscular, contraction, cell differentiation, ciliary beating, etc.
- Calcium is important in both excitable and inexcitable cells.

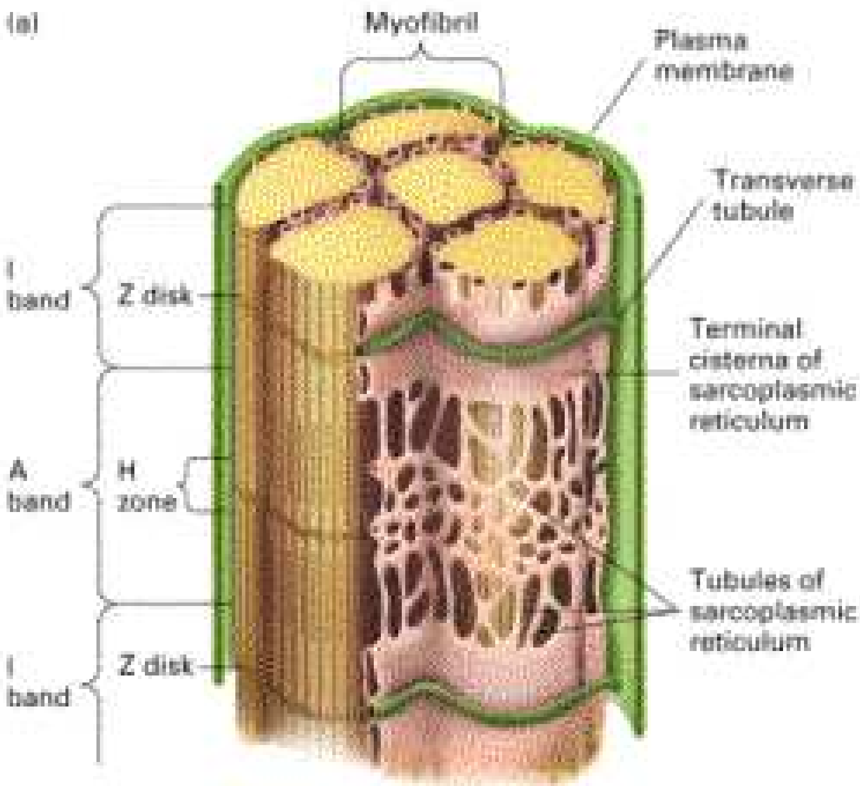
Calcium in muscle: I

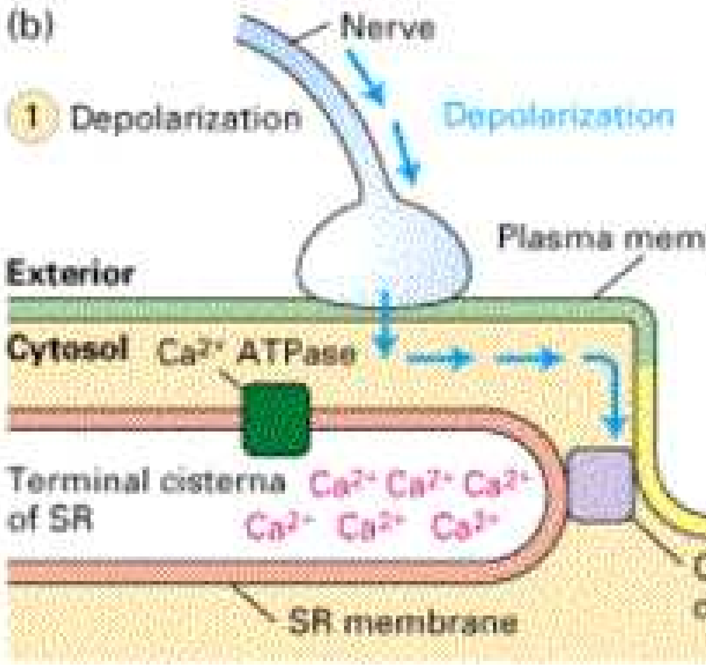
Structure of skeletal muscle



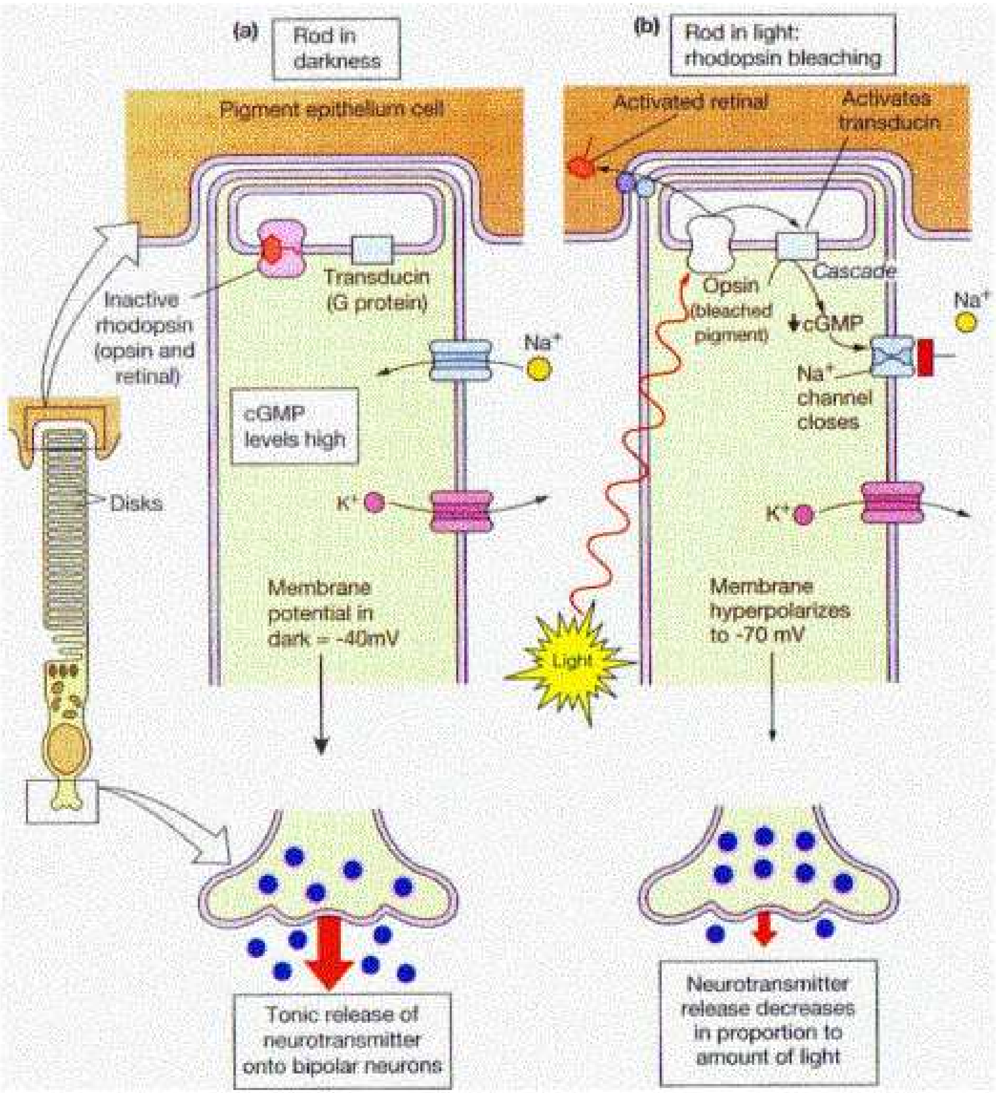


Muscle

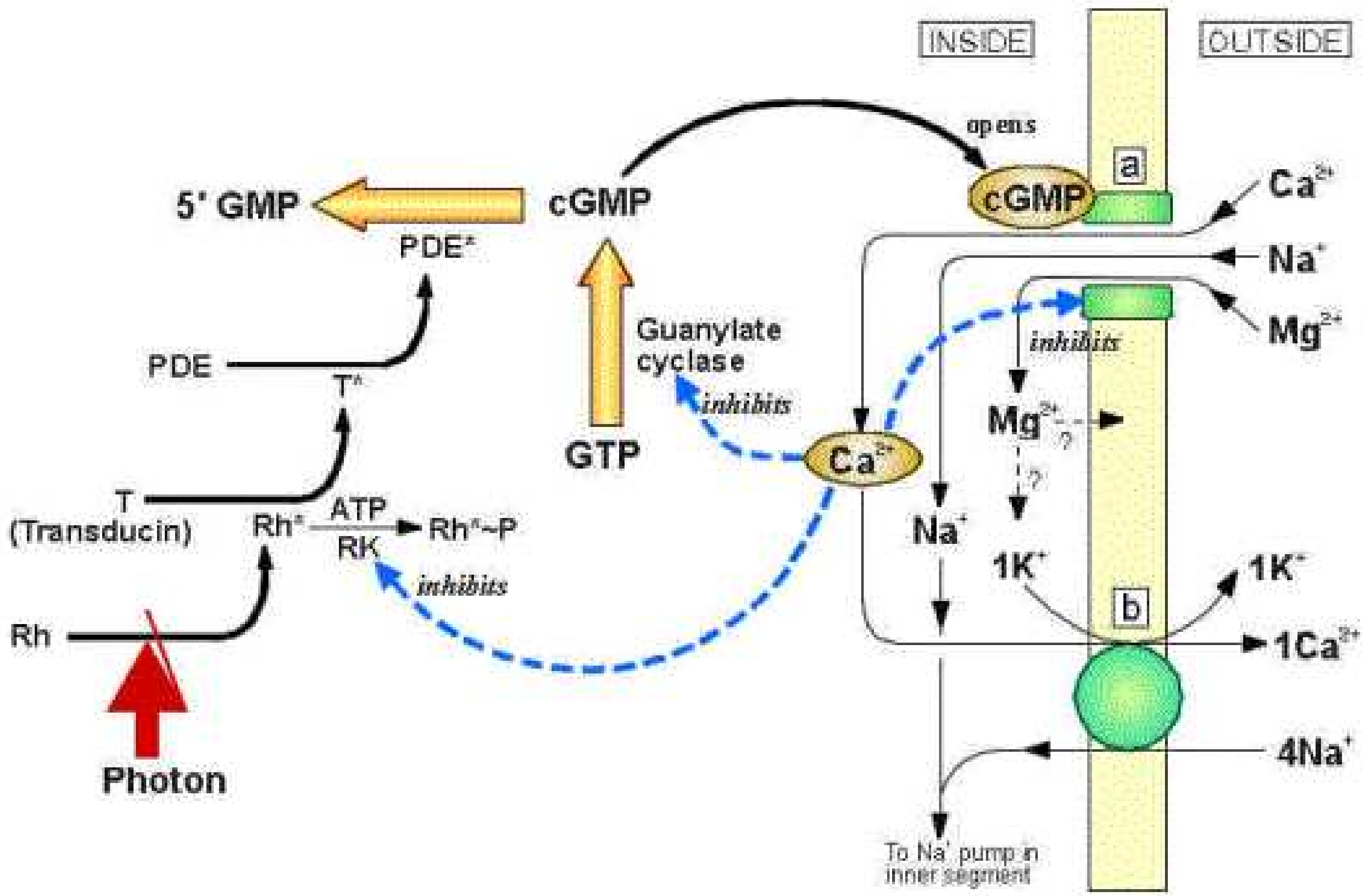

(a)
Myofibril
Plasma membrane
Transverse tubule
I band
Z disk
Terminal cisterna of sarcoplasmic reticulum
A band
H zone
Tubules of sarcoplasmic reticulum
I band
Z disk


(b)
Nerve
1 Depolarization
Depolarization
Plasma mem
Exterior
Cytosol
Ca2+ ATPase
Terminal cisterna of SR
Ca2+ Ca2+ Ca2+
Ca2+ Ca2+ Ca2+
SR membrane

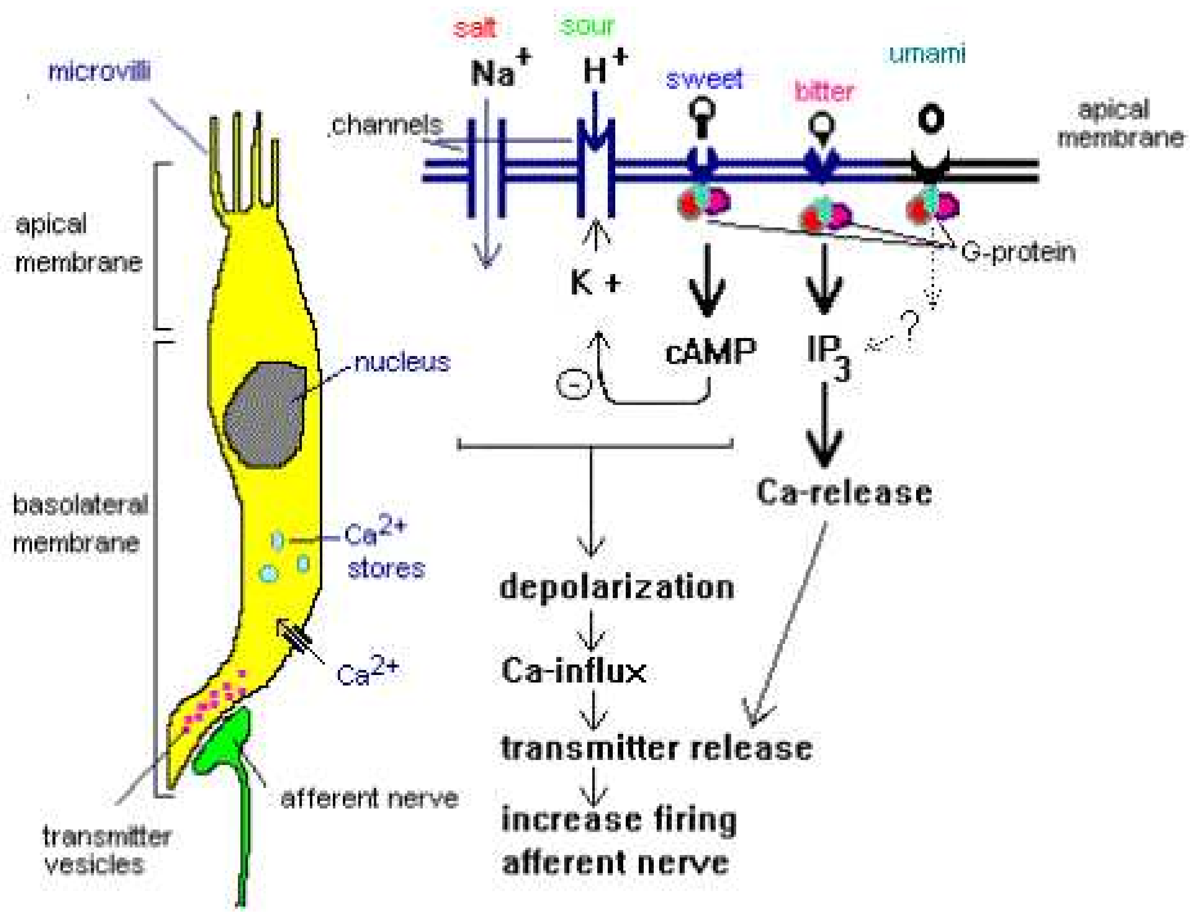
Phototransduction



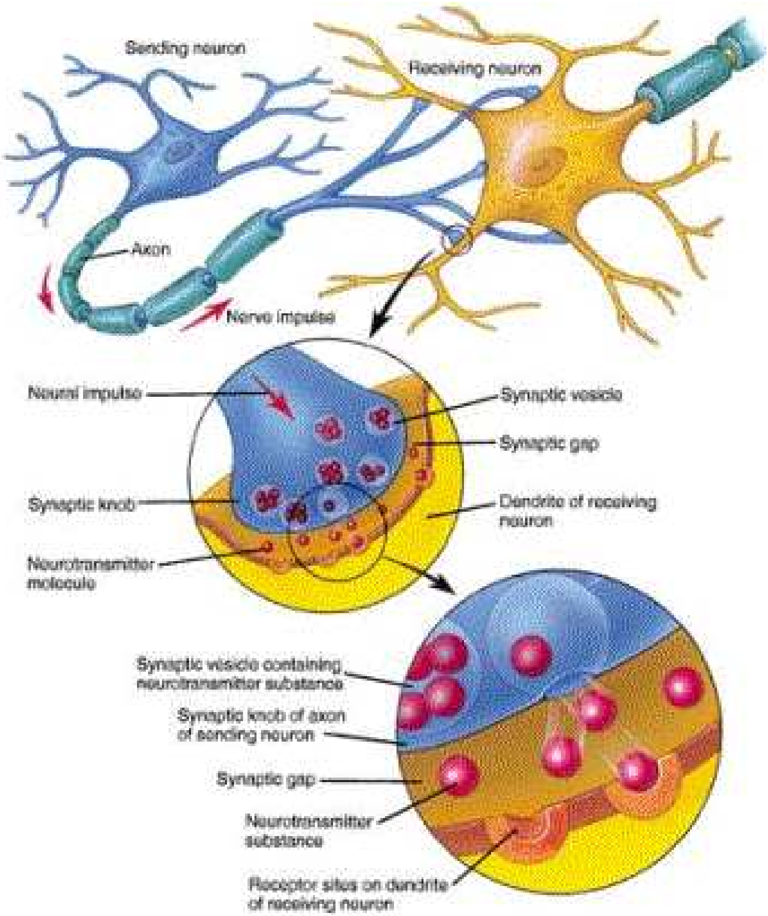
Phototransduction



Taste


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

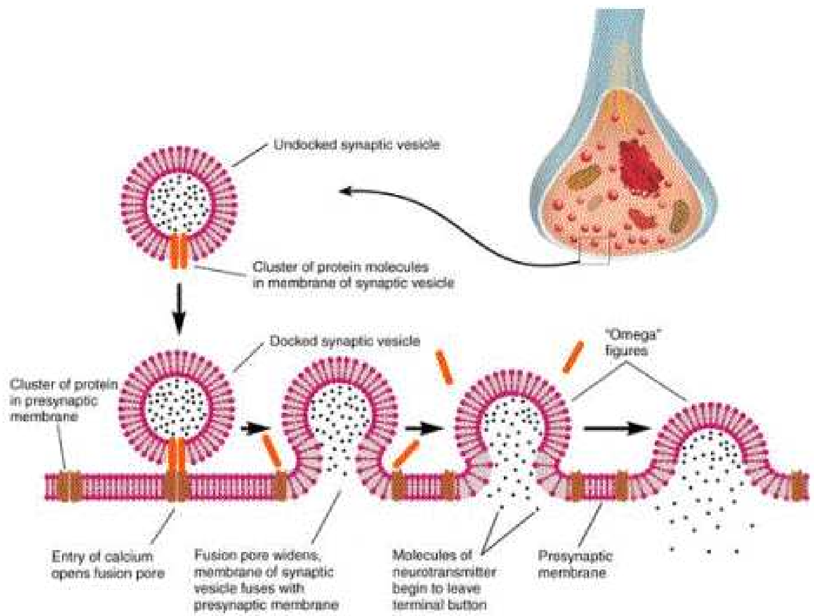
Synaptic Transmission



Synaptic Transmission

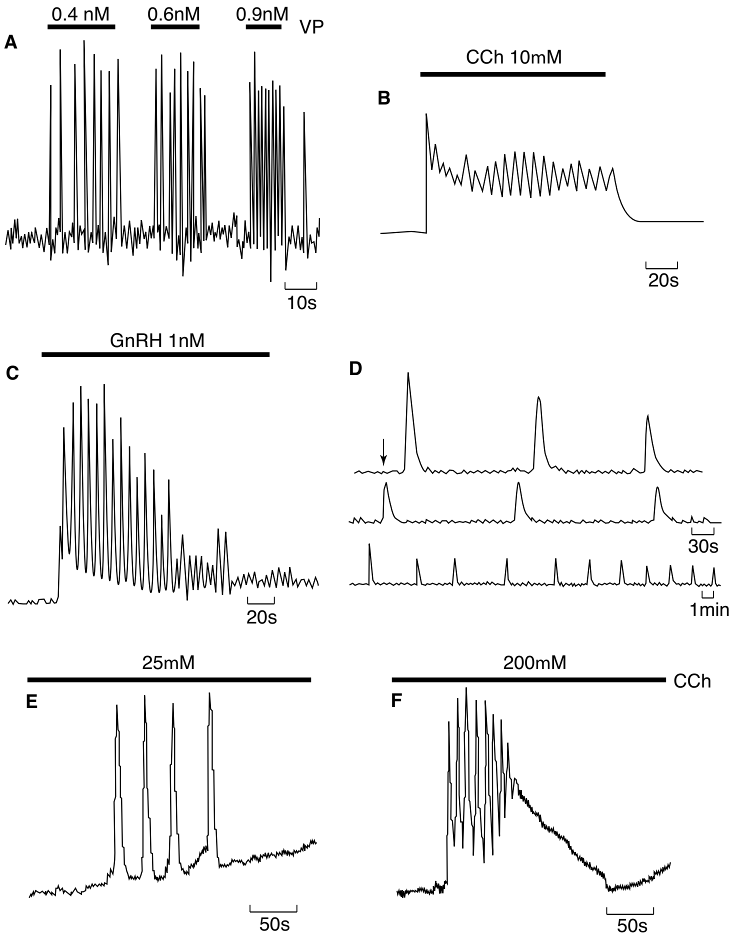
Calcium and synapses: II

- Release of Neurotransmitter



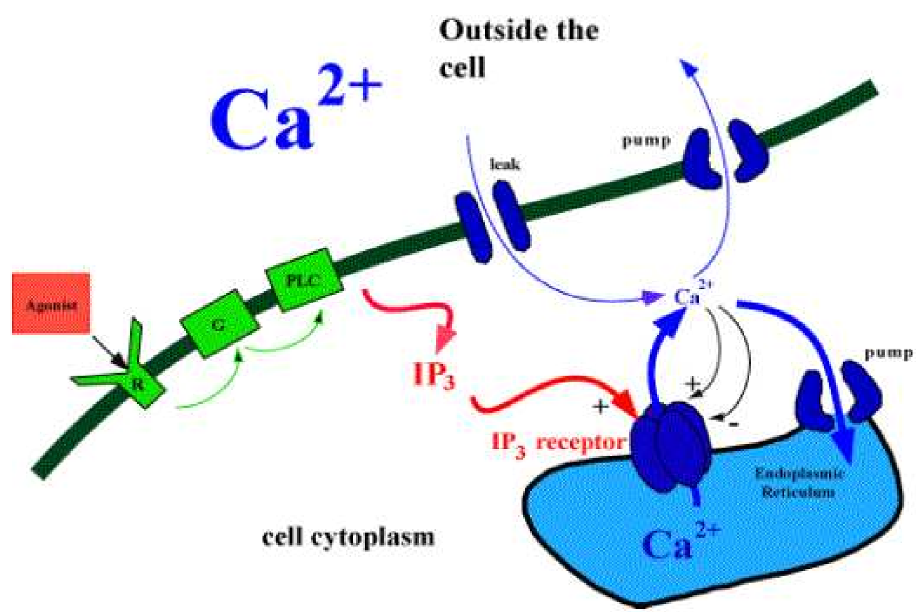
Calcium Oscillations

- A) Hepatocytes
- B) Rat parotid gland
- C) Gonadotropes
- D) Hamster eggs
- E, F) Insulinoma Cells



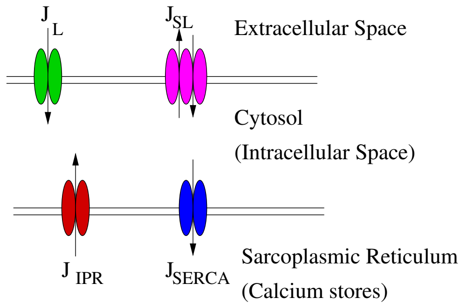
Calcium Handling

IP_3 Receptor pathway



IPR Calcium Handling

$$v\frac{dc}{dt} = J_{IPR} - J_{SERCA} + J_L - J_{SL}$$



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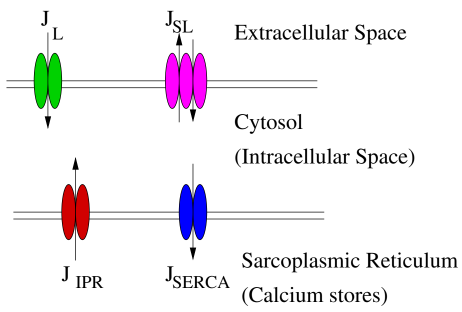

with

J_{IPR} IP$_3$ Receptor - calcium regulated calcium channel,

IPR Calcium Handling

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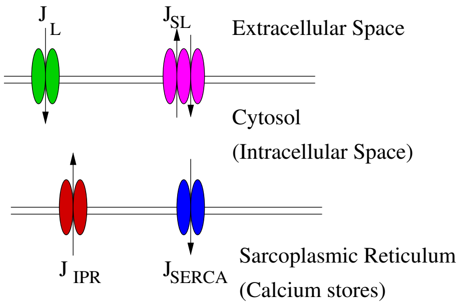

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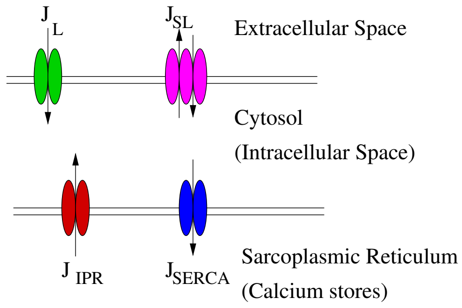

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J_{SERCA} Sarco- and Endoplasmic Reticulum Calcium ATPase,

J_L L-calcium leak,

IPR Calcium Handling

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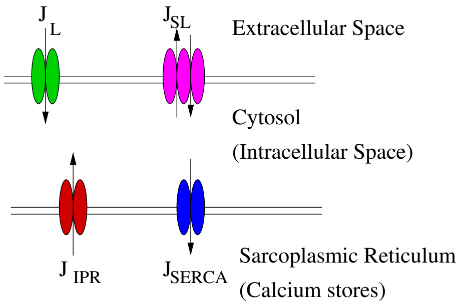

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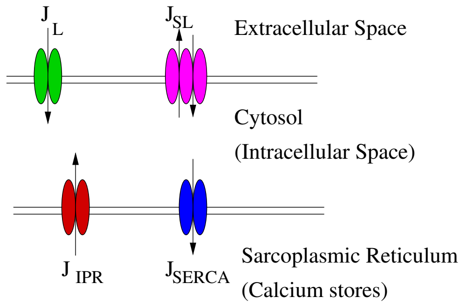

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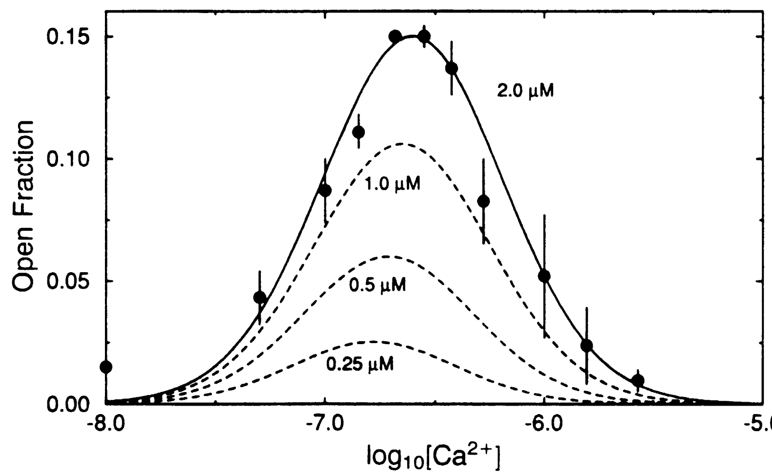
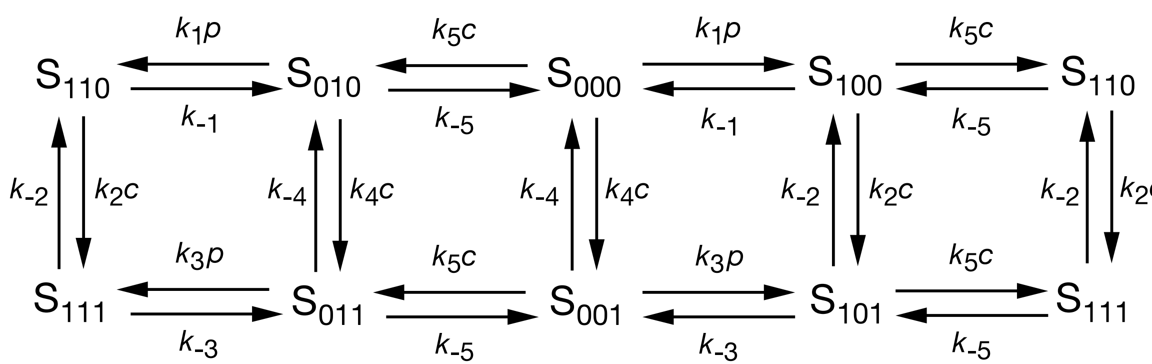
Challenge: Determine the flux terms.

Calcium Handling

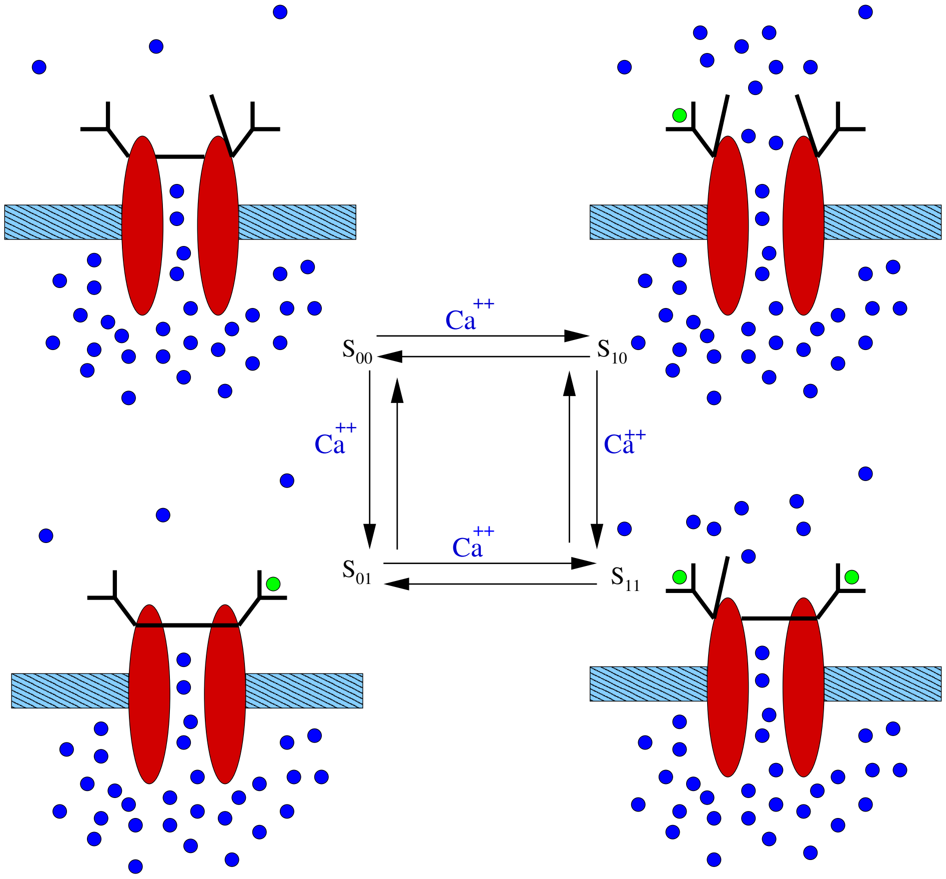


group I



group II

IP_3 Receptors



IP_3 Receptors

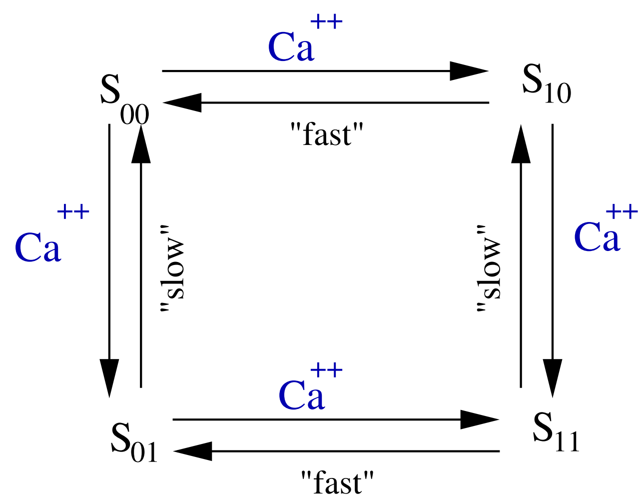
Flux through IP_3 receptor is diffusive,

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

where $P_o = S_{10}^3 = m^3 h^3$ is the open probability, and

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

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



Consequently, (h is reminiscent of HH h)....

Calcium Dynamics

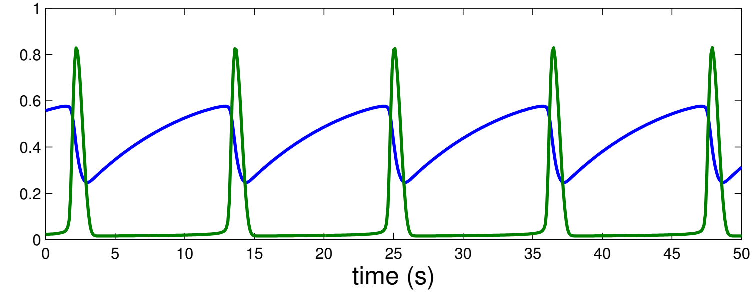
$$\frac{dc}{dt} = (g_{max}P_o + J_{er})(c_e - c) - J_{SERCA},$$

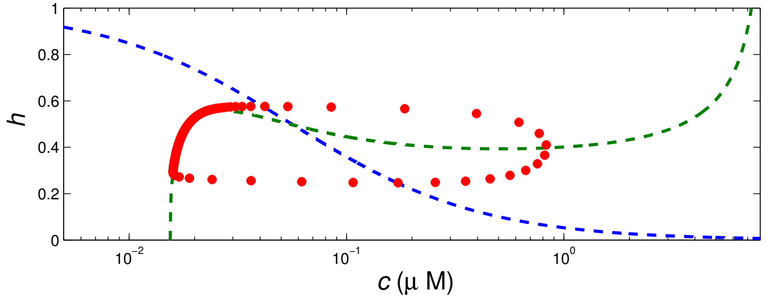
$$\frac{dh}{dt} = \phi_h(c)(1-h) - \psi_h(c)h,$$

where

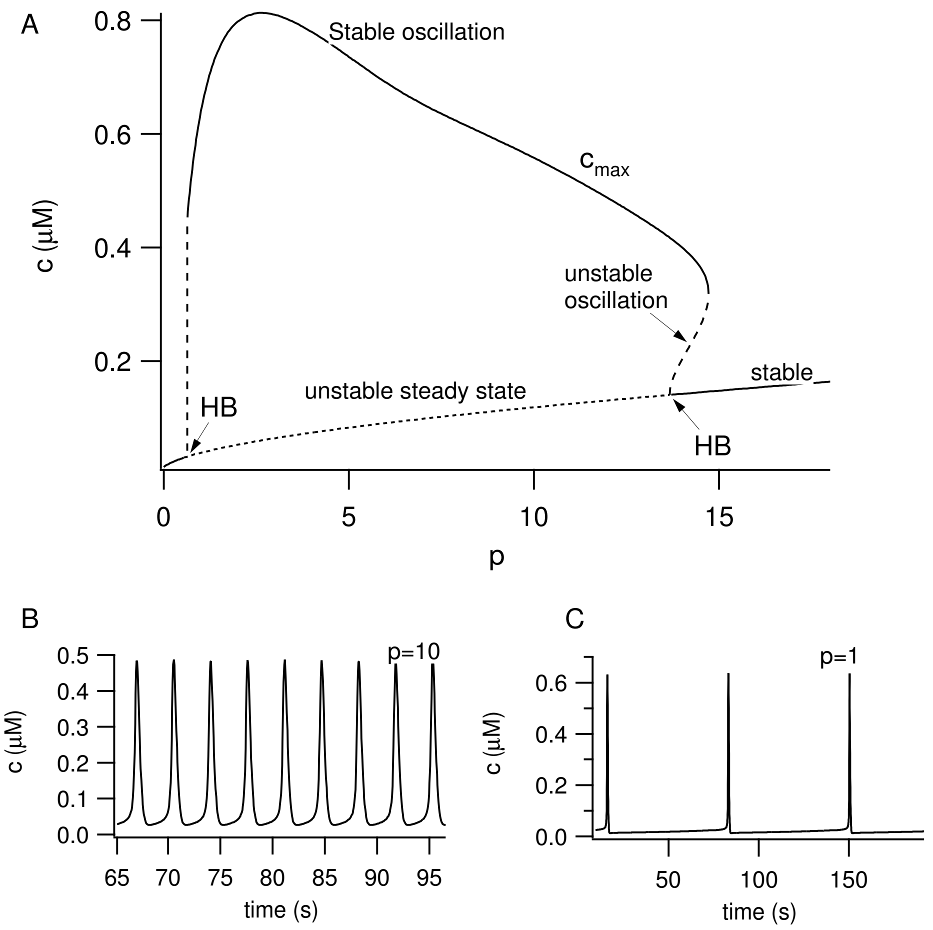
$$J_{SERCA} = V_{max}\frac{c^2}{K_s^2+c^2},$$

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



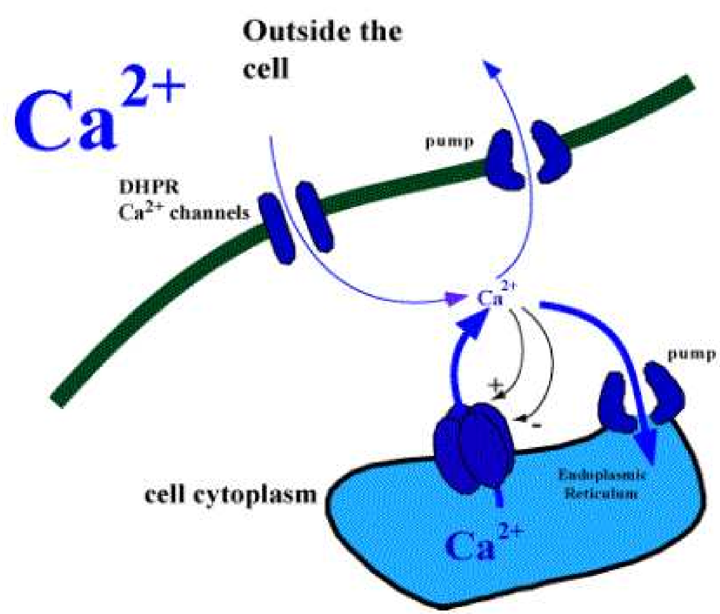


Bifurcation Diagram



RYR Calcium Handling

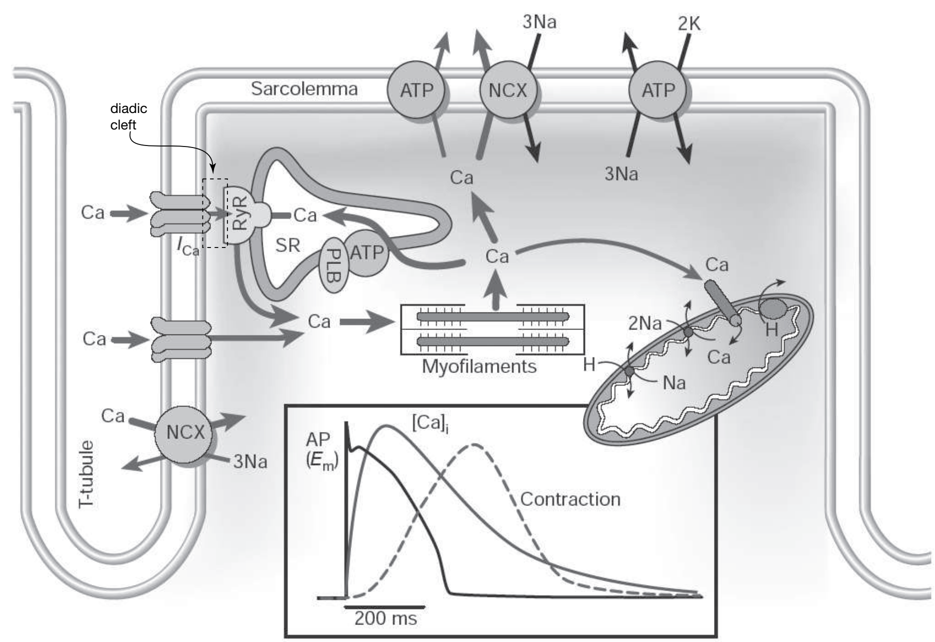
Ryanodine Receptor pathway



Excitation-Contraction Coupling

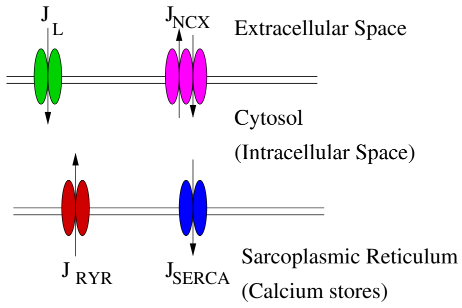
Cardiac cells are interesting because they contain TWO excitable systems that are interconnected

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



EC Calcium Handling

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



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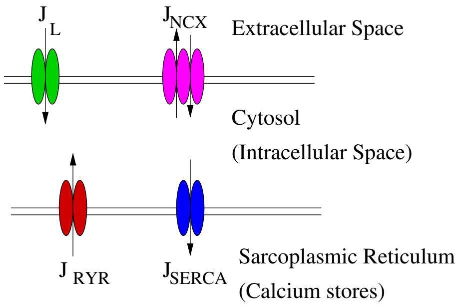

with

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EC Calcium Handling

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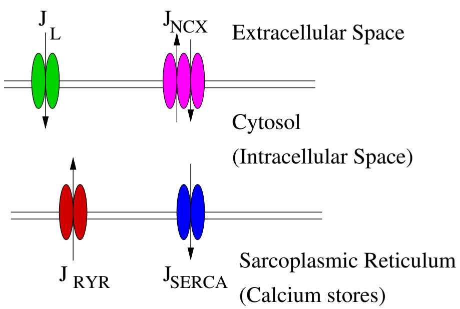

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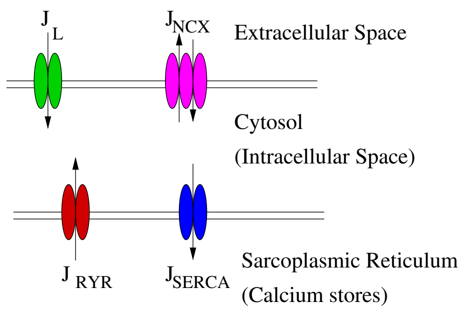

with

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

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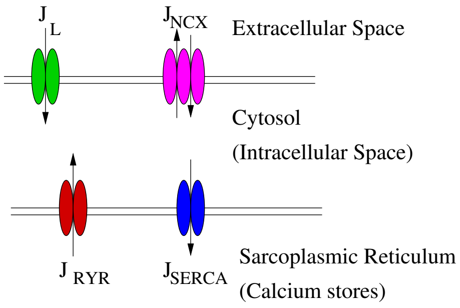
J_L L-type voltage regulated calcium channel,

EC Calcium Handling

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



with

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

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J_L L-type voltage regulated calcium channel,

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

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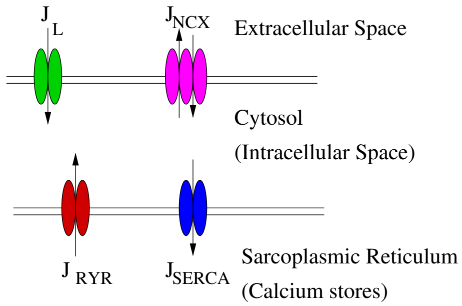

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J_L L-type voltage regulated calcium channel,

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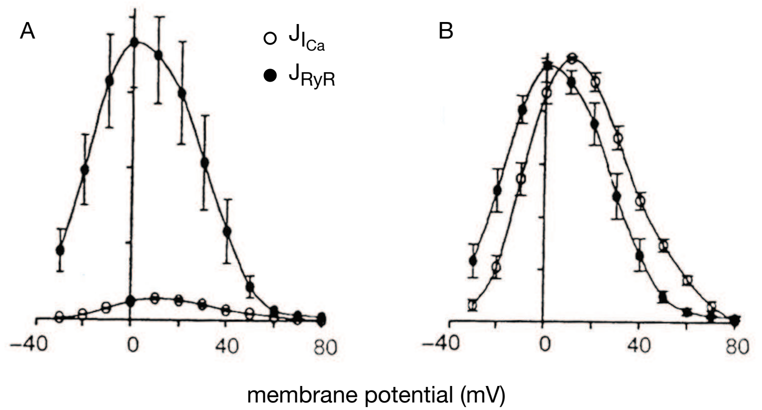
Challenge: Determine the flux terms.

Serious Problems

There are (at least) three problems with this (and all similar) models:

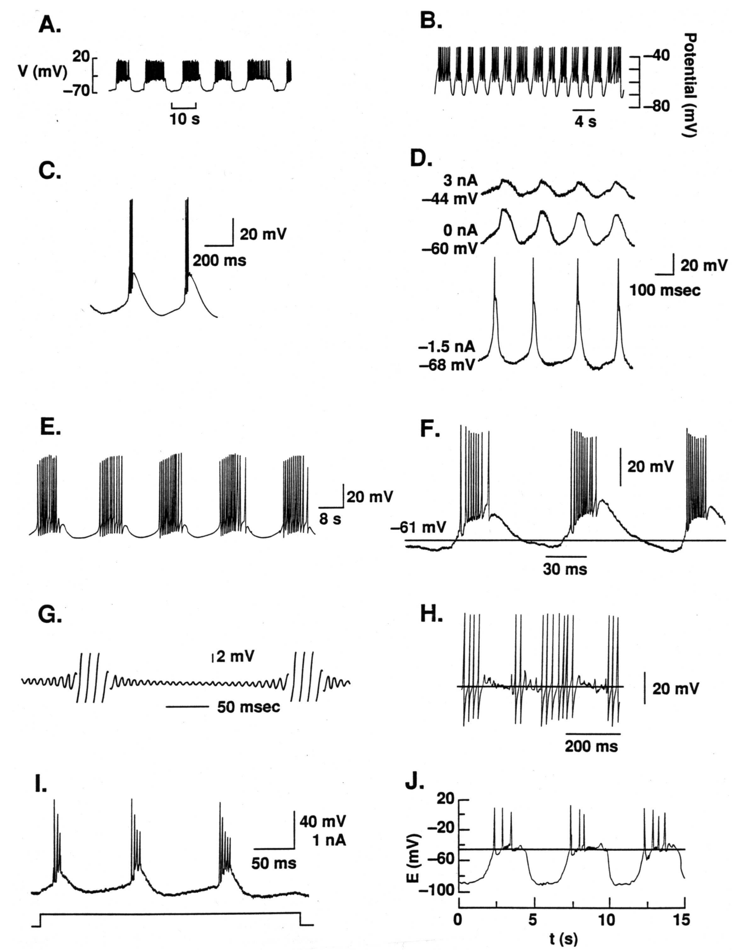
- Graded response



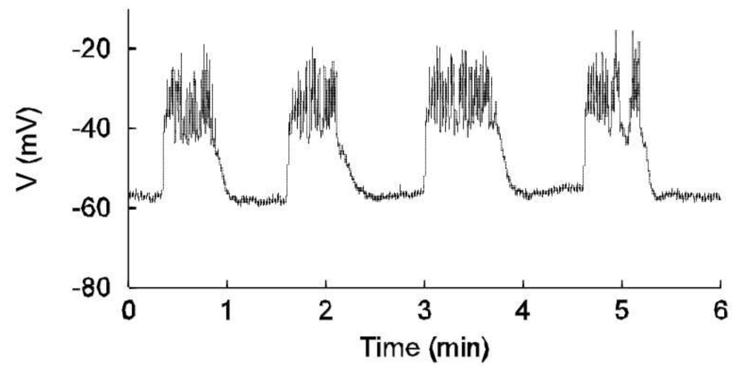
- Calcium is not spatially homogenious; channels are controlled by **local** calcium concentration. Thus, whole cell models are inappropriate - geometry mattters.
- Channel openings are not deterministic and numbers are not large. Stochastic modeling is needed.

Bursting

- A) Pancreatic β-cell
- B) Rat midbrain
- C) Cat Thalamocortical relay neuron
- D) Guinea pig olivary neuron
- E Aplysia R15 neuroon
- F) Cat thalamic reticular neuron
- G) *Sepia* giant axon
- H) Rat thalamic reticular neuron
- I) Mouse neocortical pyramidal neuron
- J) Pituitary gonadotropin re-lasing cell



Pancreatic β cells



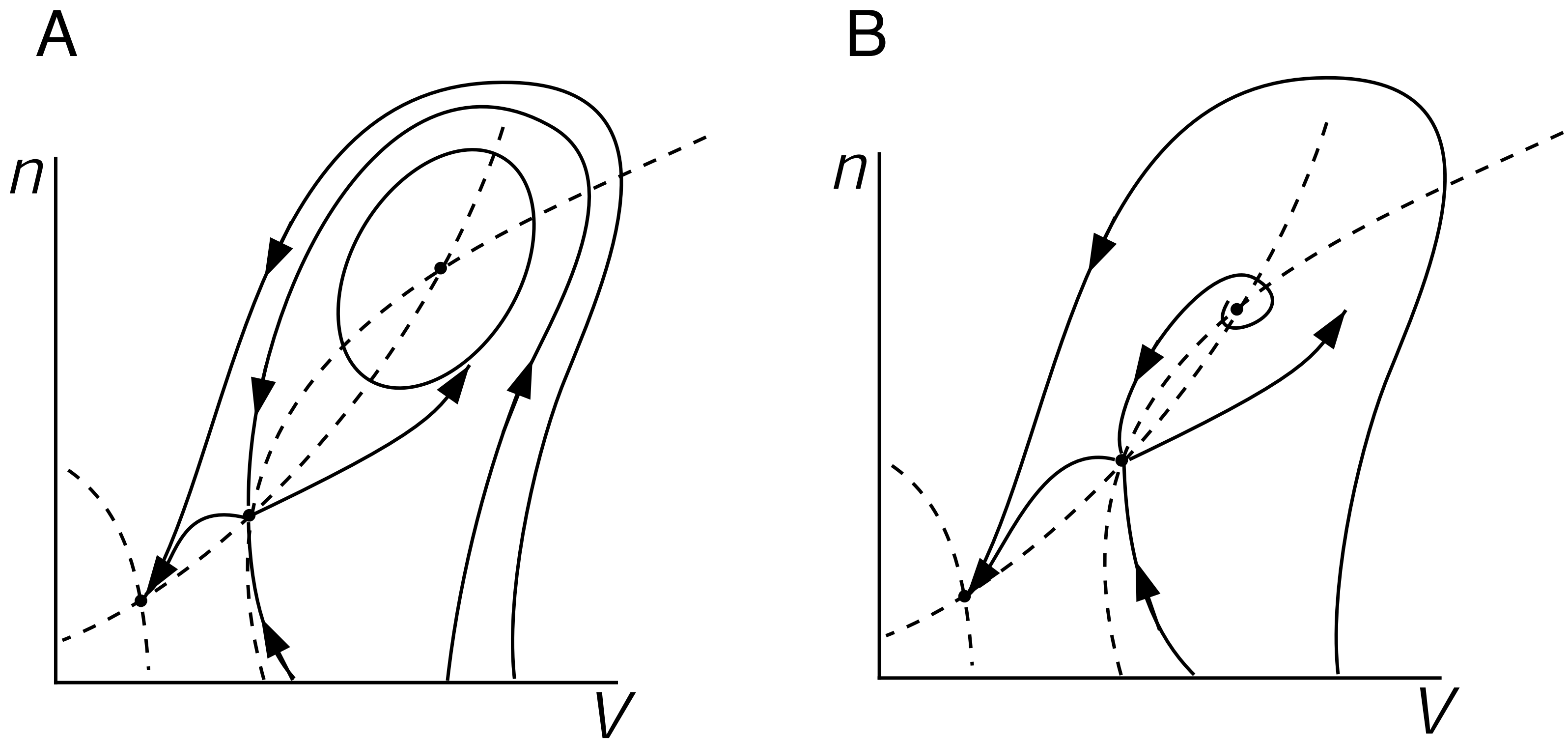
$$C_m \frac{dV}{dt} = -I_{\mathrm{Ca}}(V) - \left(\bar{g}_{\mathrm{K}} n^4 + \frac{\bar{g}_{\mathrm{K,Ca}} c}{K_d + c}\right)(V - V_{\mathrm{K}}) - \bar{g}_{\mathrm{L}}(V - V_{\mathrm{L}})$$

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

$$\frac{dc}{dt} = f(-k_1 I_{\mathrm{Ca}}(V) - k_c c),$$

where $I_{\mathrm{Ca}} = \bar{g}_{\mathrm{Ca}} m_\infty^3(V) h_\infty(V)(V - V_{\mathrm{Ca}})$.

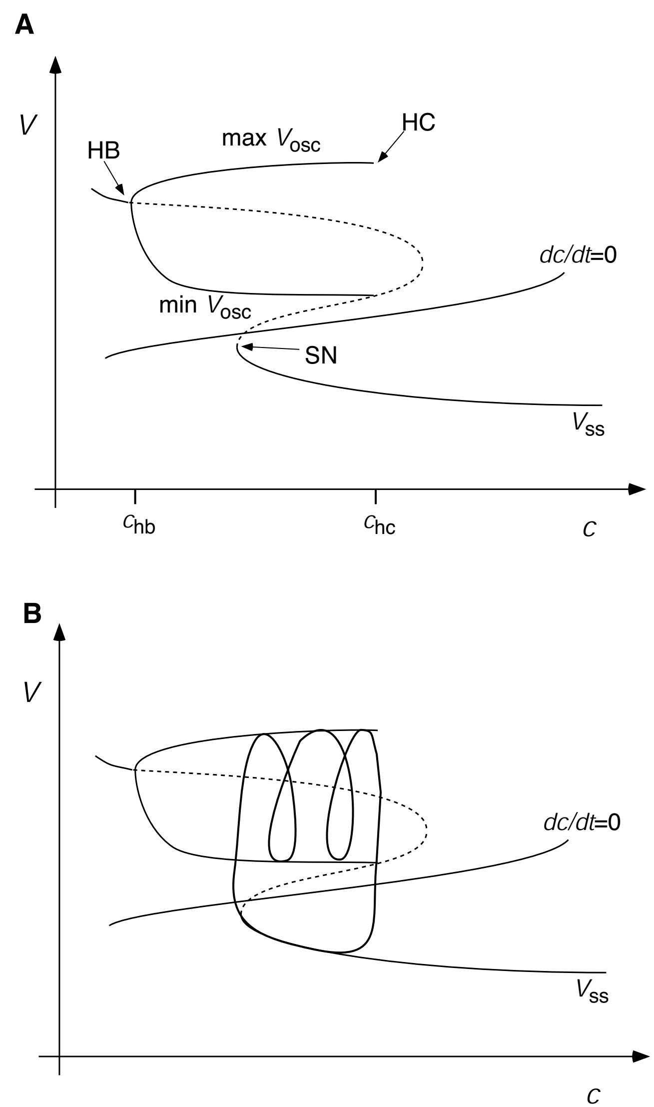
Fast Phase Plane



Low Ca^{++}

High Ca^{++}

Bifurcation Diagram



Bursting Oscillations