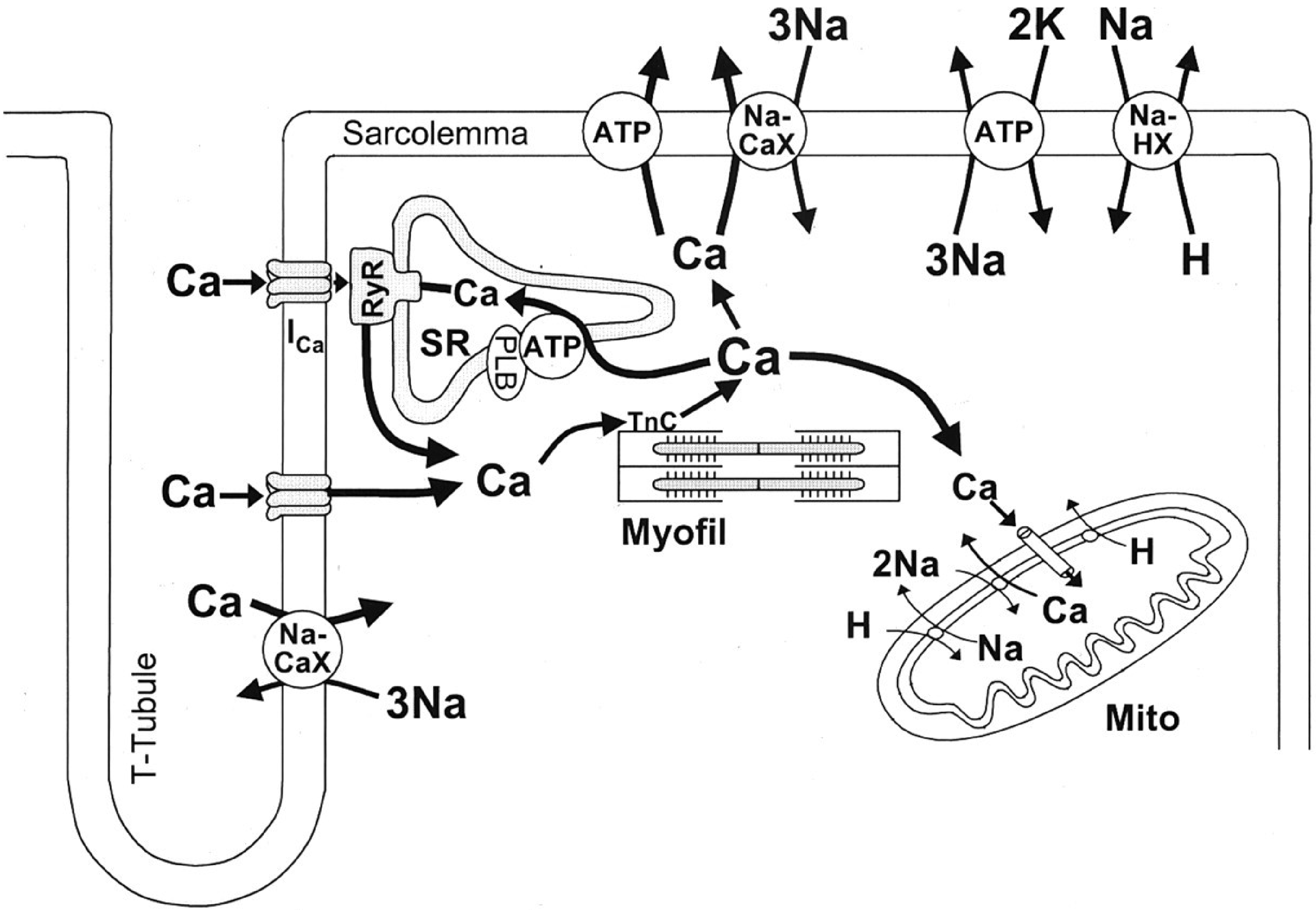
Cellular Calcium Dynamics

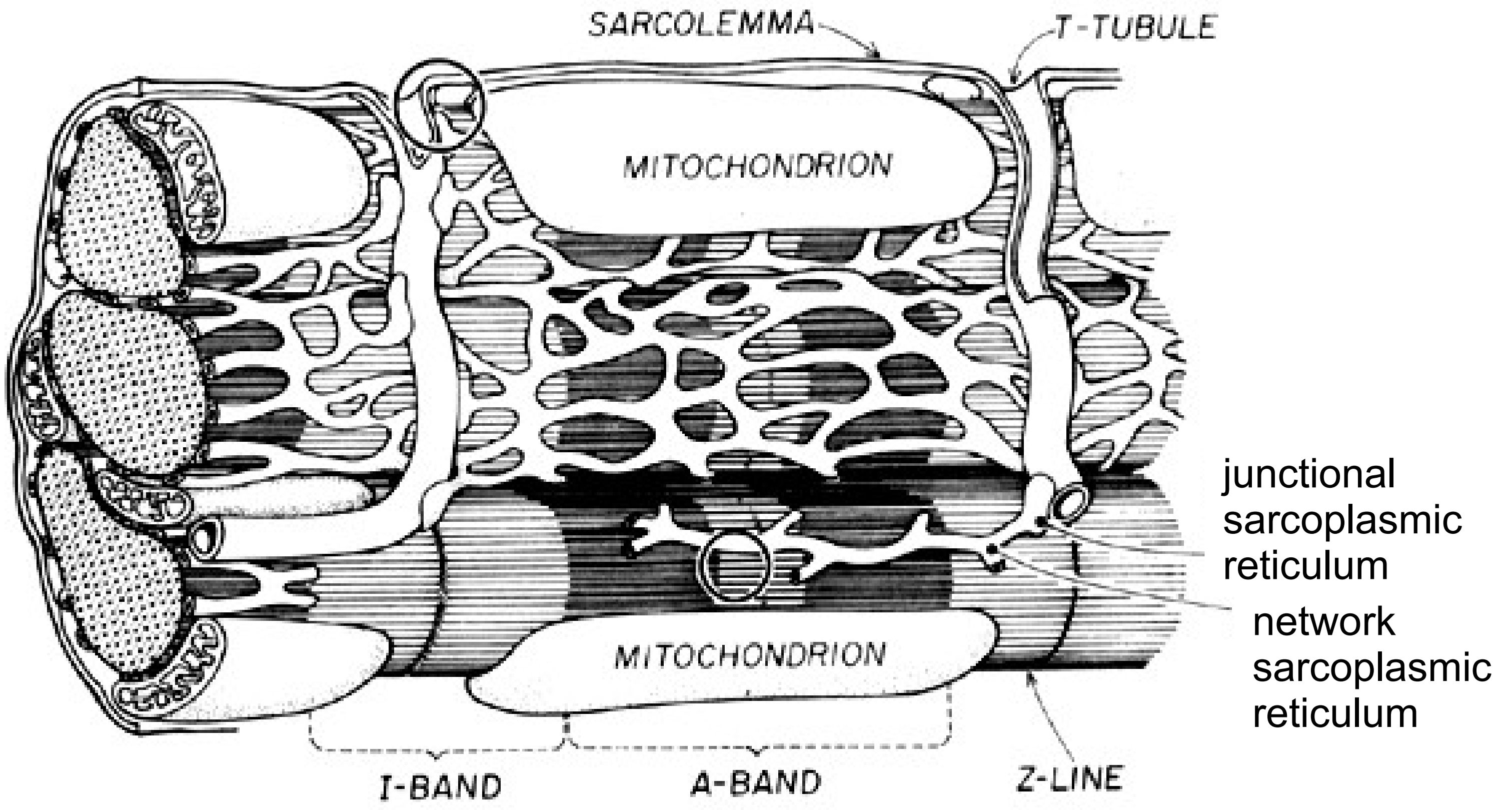
Jussi Koivumäki, Glenn Lines & Joakim Sundnes

Cellular calcium dynamics



A real cardiomyocyte is obviously not an empty cylinder, where Ca^{2+} just diffuses freely...

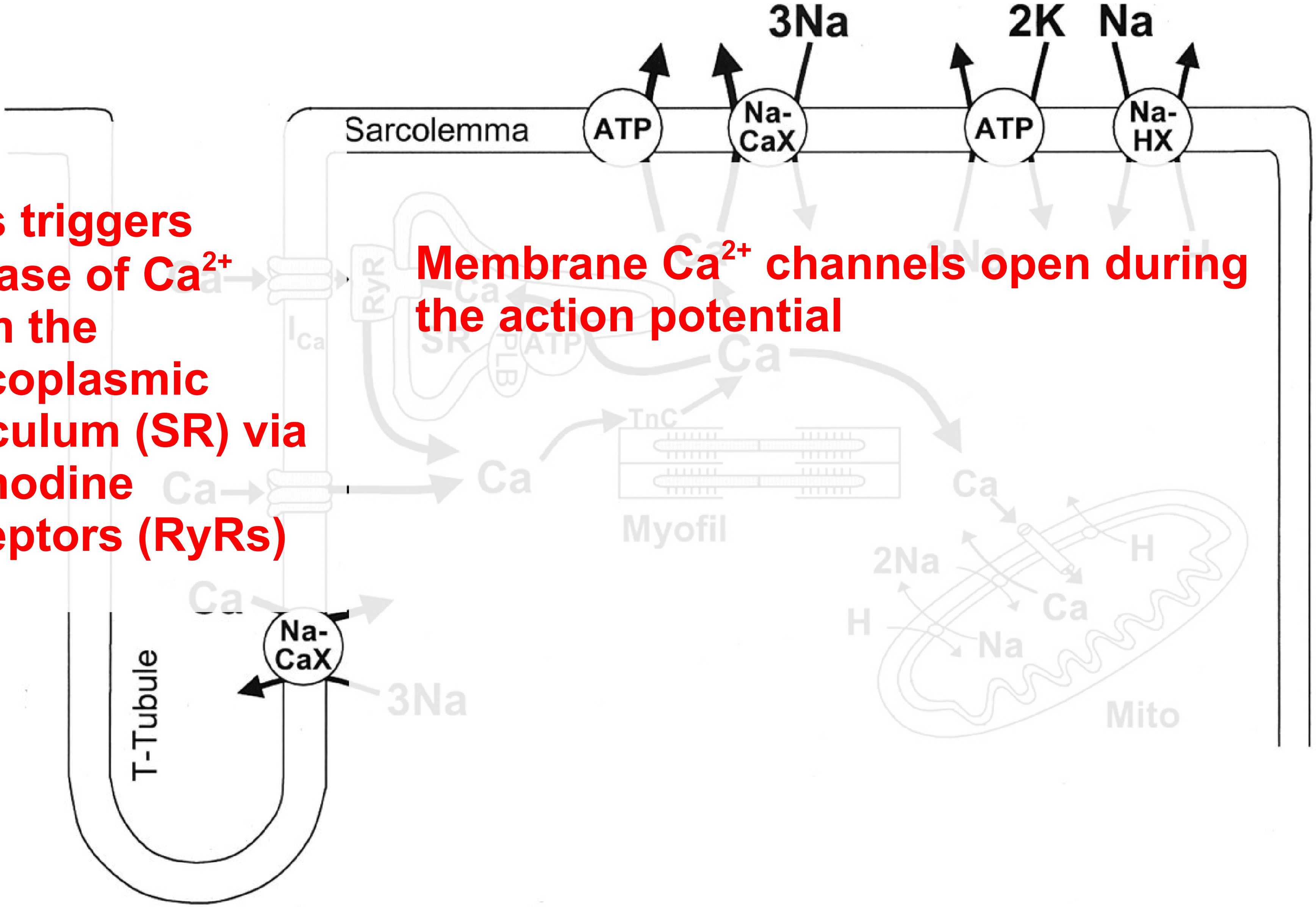
...instead it's filled with myofibrils, mitochondria, sarcoplasmic reticulum, t-tubule, etc.



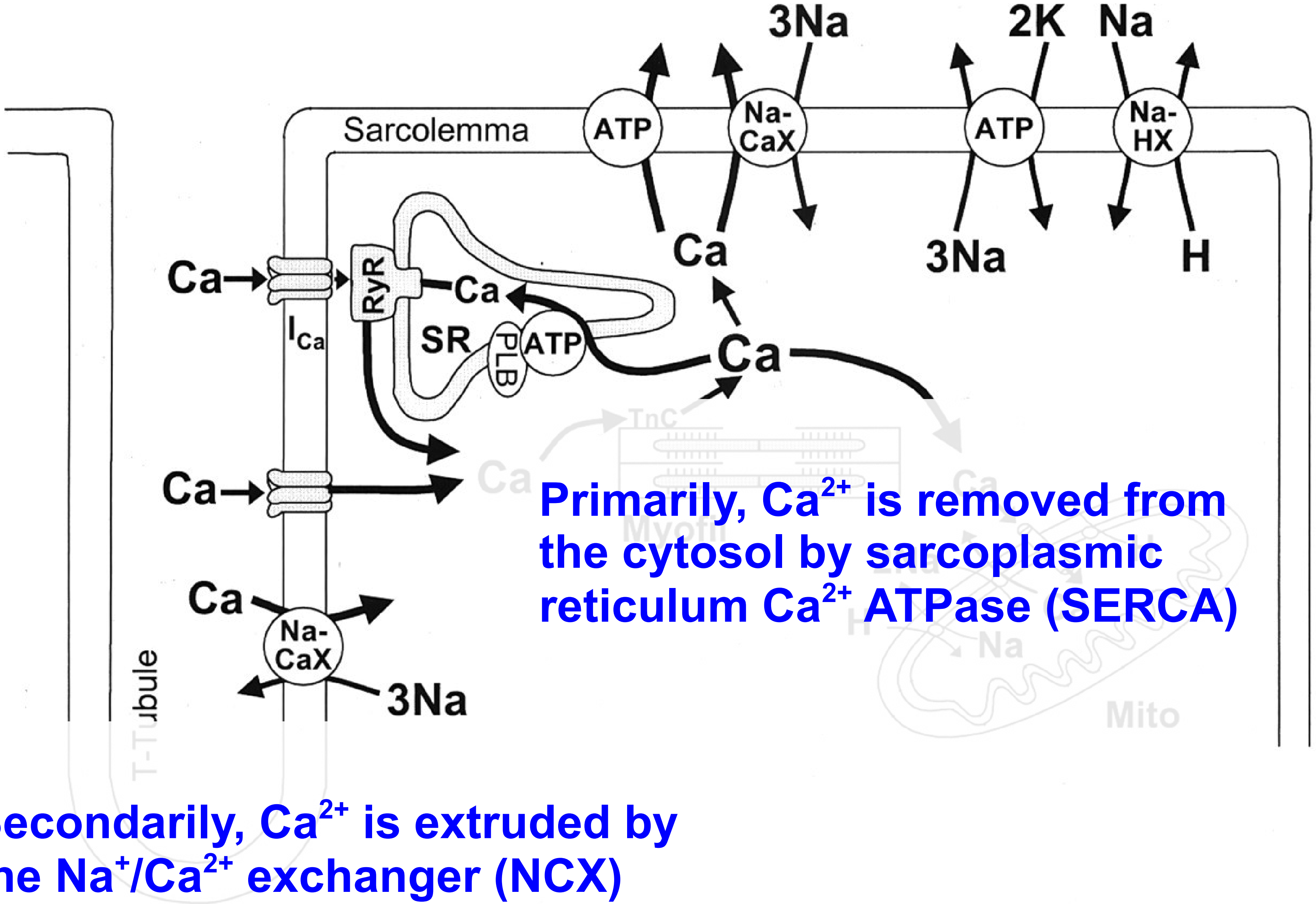
Cellular calcium dynamics: influx

This triggers release of Ca^{2+} from the sarcoplasmic reticulum (SR) via ryanodine receptors (RyRs)

Membrane Ca^{2+} channels open during the action potential



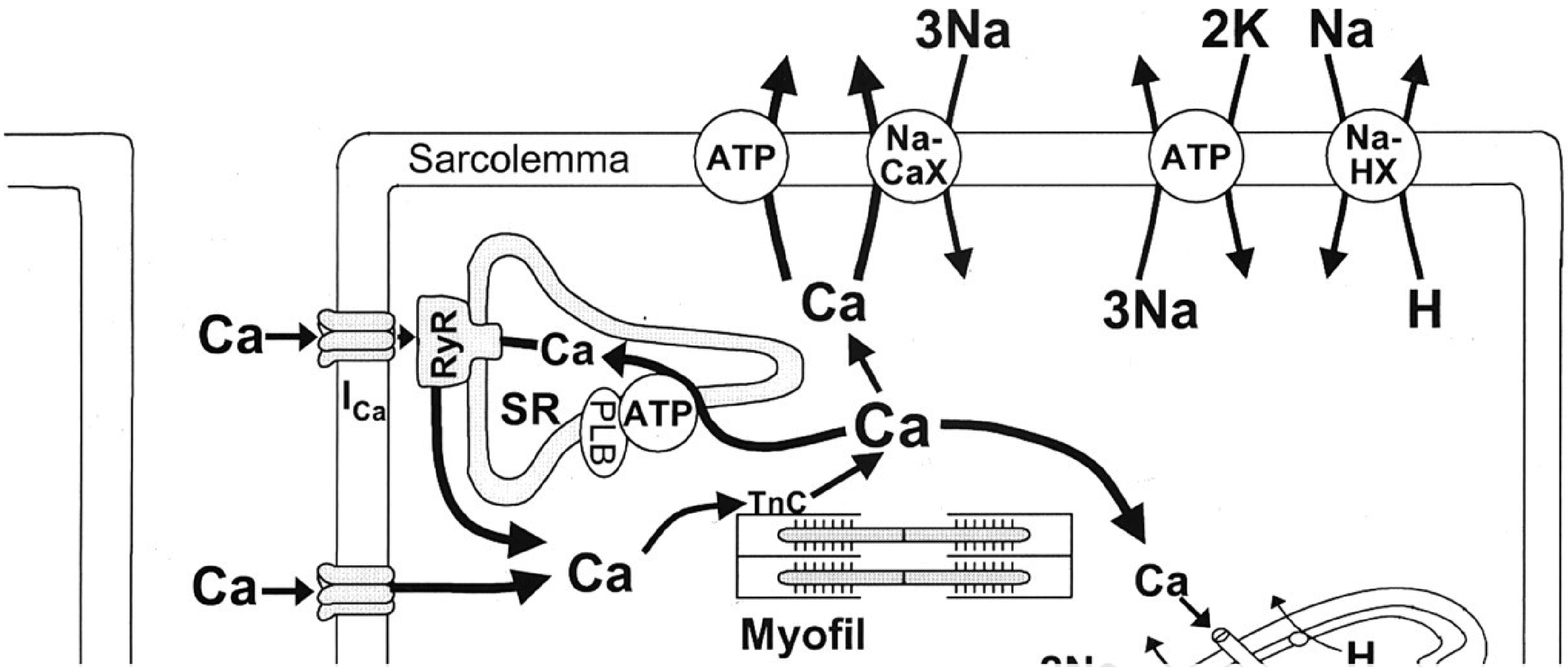
Cellular calcium dynamics: efflux



Primarily, Ca^{2+} is removed from the cytosol by sarcoplasmic reticulum Ca^{2+} ATPase (SERCA)

Secondarily, Ca^{2+} is extruded by the Na^{+}/Ca^{2+} exchanger (NCX)

Cellular calcium dynamics



Let's take a step back and view development…

Why has calcium dynamics evolved to be so complex?

In addition to actions on the contractile filaments, calcium signals also regulate

- the activity of kinases, phosphatases, ion channels, exchangers and transporters, as well as

- function, growth, gene expression, differentiation, and development of cardiac muscle cells.

- The multifunctional roles require
  1) high dynamic gain, as well as
  2) fast propagation and
  3) accurate spatial control of the calcium signals.

What does “high dynamic gain” mean in the context of calcium dynamics?

- In the adult mammalian heart, calcium-induced calcium release establishes an outstanding dynamic range of calcium signals
  - up to 1000-fold increase in the calcium concentration in only tens of milliseconds.

- This is a totally different scale than, for example, intracellular Na+ and K+ concentrations,
  - which vary by some tens of percent, at most.

What defines propagation speed of calcium signals in the cytosol?

- In all biological systems, diffusion is a ubiquitous mechanism equalizing the concentration gradients of all moving particles in the cells cytosol.
  - It forms also the basis for distribution of Ca^{2+} ions in the cytosol.

- In general, in muscle cells diffusion of ions (K+, Na+, Cl-) in cytosol is relatively fast, only 2-fold slower than in water.

- However, diffusion of Ca2+ is an exception from this rule, it is 50-times slower in the cytosol than in pure water.
  - This is due to the stationary and mobile calcium buffers that slow down the calcium diffusion remarkably.

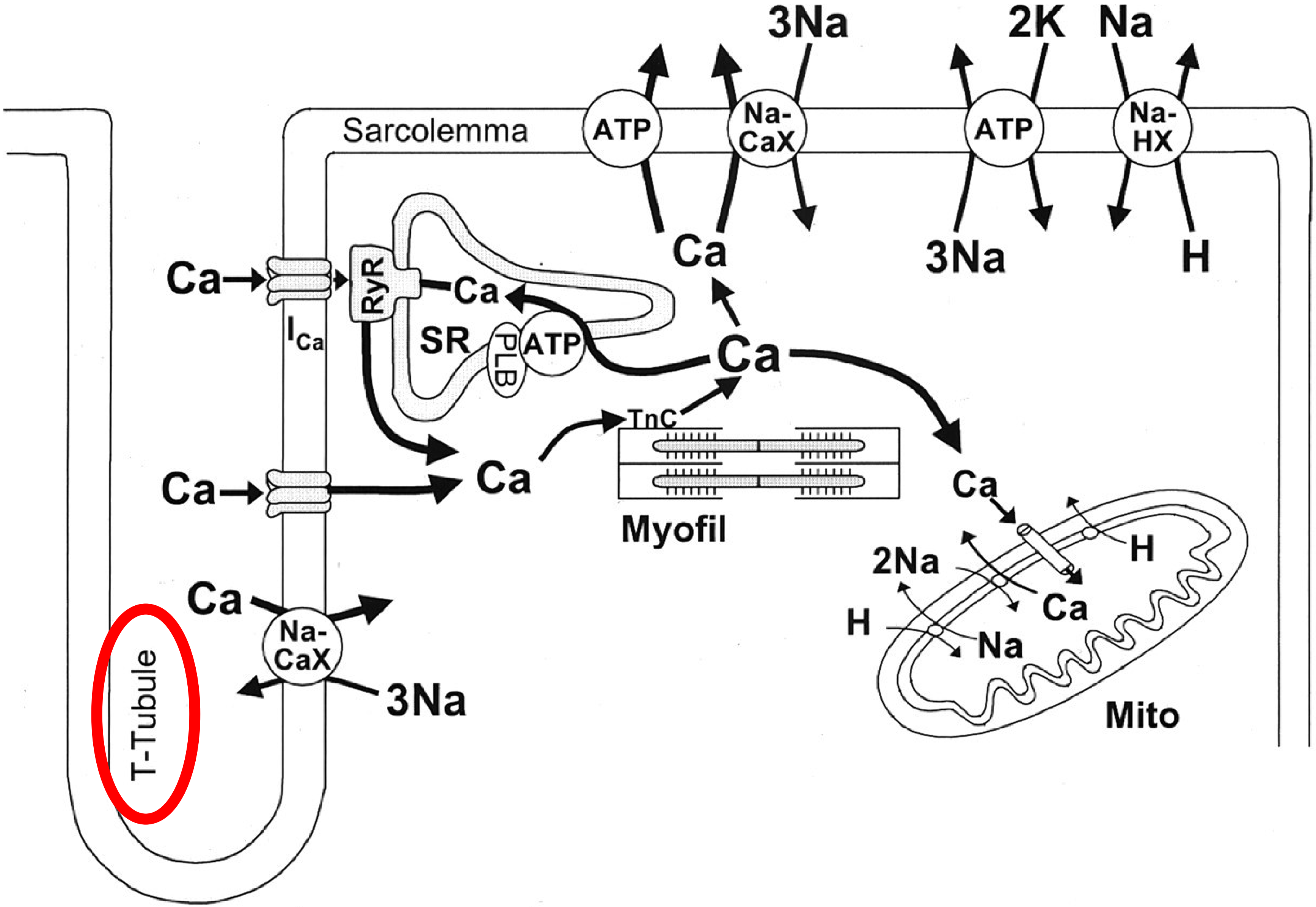
Why is the propagation speed of calcium signals in the cytosol so slow?

- The “job” of a cardiomyocyte is to contract upon electrical stimulus and not to diffuse calcium as fast as possible...

1) Assembly of contractile elements is progressively augmented during development to fulfill the demand for more forceful contraction
2) Capacity of SR calcium stores is synchronously increased to provide more calcium release for activating contraction.

- Both of these developmental steps lead to increased cytosolic calcium buffering.

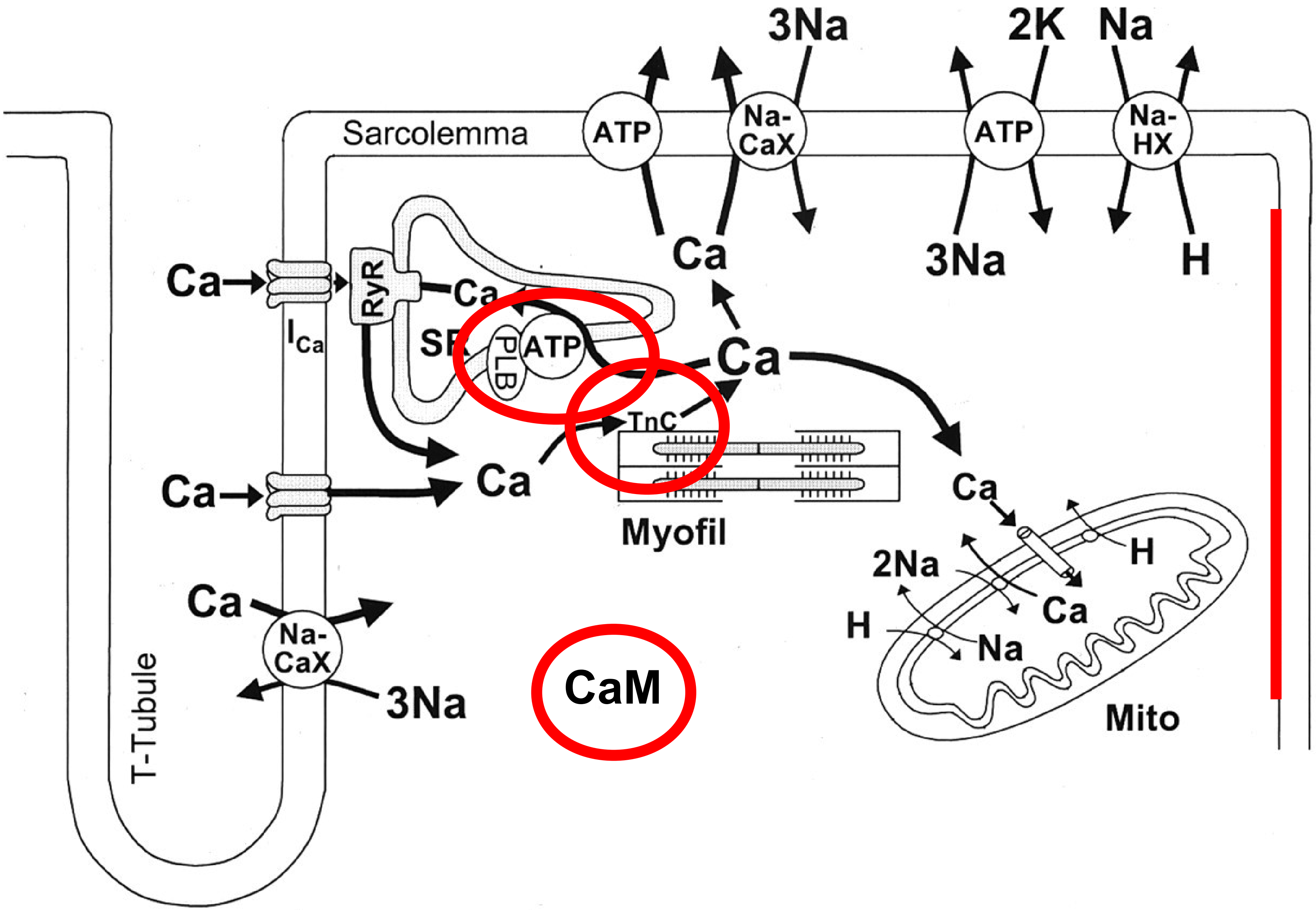
How to ensure fast (enough) propagation of calcium signals in the cytosol?

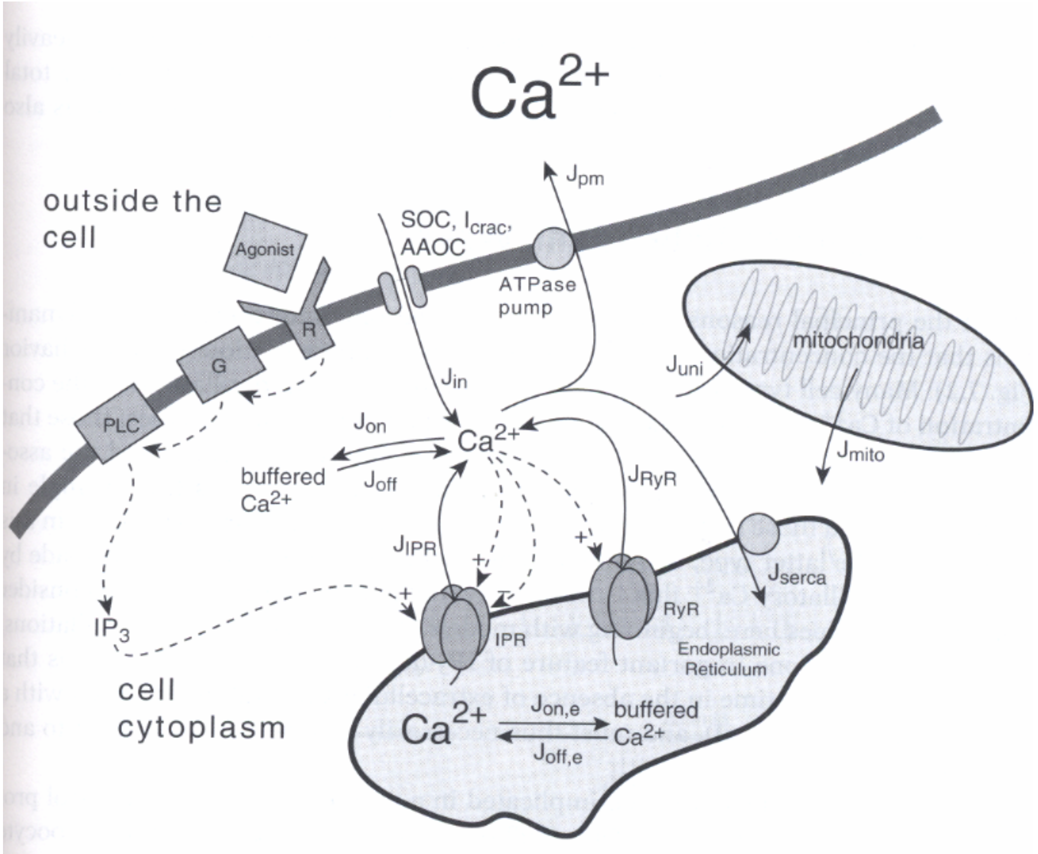


Main players in calcium handling are:

- Buffers
- Pumps
- Transporters/exchangers
- Ion channels

Calcium buffers are large Ca^{2+} binding proteins.





Ca^{2+}
J_{pm}
outside the cell
Agonist
SOC, I_{crac}, AAOC
ATPase pump
R
G
PLC
J_{in}
mitochondria
J_{uni}
J_{mito}
J_{on}
Ca^{2+}
buffered Ca^{2+}
J_{off}
J_{RyR}
J_{IPR}
J_{serca}
IP_3
IPR
RyR
Endoplasmic Reticulum
cell cytoplasm
Ca^{2+}
$J_{on,e}$
buffered Ca^{2+}
$J_{off,e}$

Well mixed concentrations

If we assume a well mixed solution the concentration only vary with time, not space:

$$\frac{dc}{dt} = J_{\text{IPR}} + J_{\text{RyR}} + J_{\text{in}} + J_{\text{pm}} - J_{\text{serca}} - J_{\text{on}} + J_{\text{off}}$$

Where c is the calcium concentration, similarly for the endoplasmic content:

$$\frac{dc_e}{dt} = \gamma(J_{\text{serca}} - J_{\text{IPR}} - J_{\text{RyR}}) - J_{\text{on},e} + J_{\text{off},e}$$

where $\gamma = v_{cyt}/v_e$

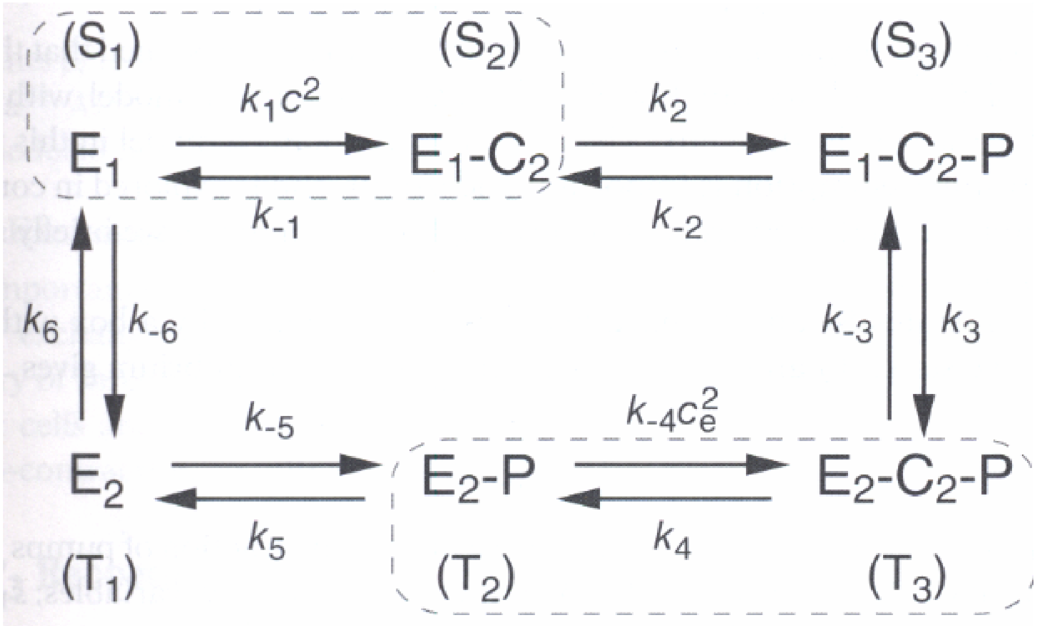
Calcium pumps

Early model based on Hill-type formulation:

$$J_{\text{serca}} = \frac{V_p c^2}{K_p^2 + c^2}$$

Draw backs: Independent of c_e and always positive, which is not the case when c_e is large.

Alternative formulation



Two main configurations:

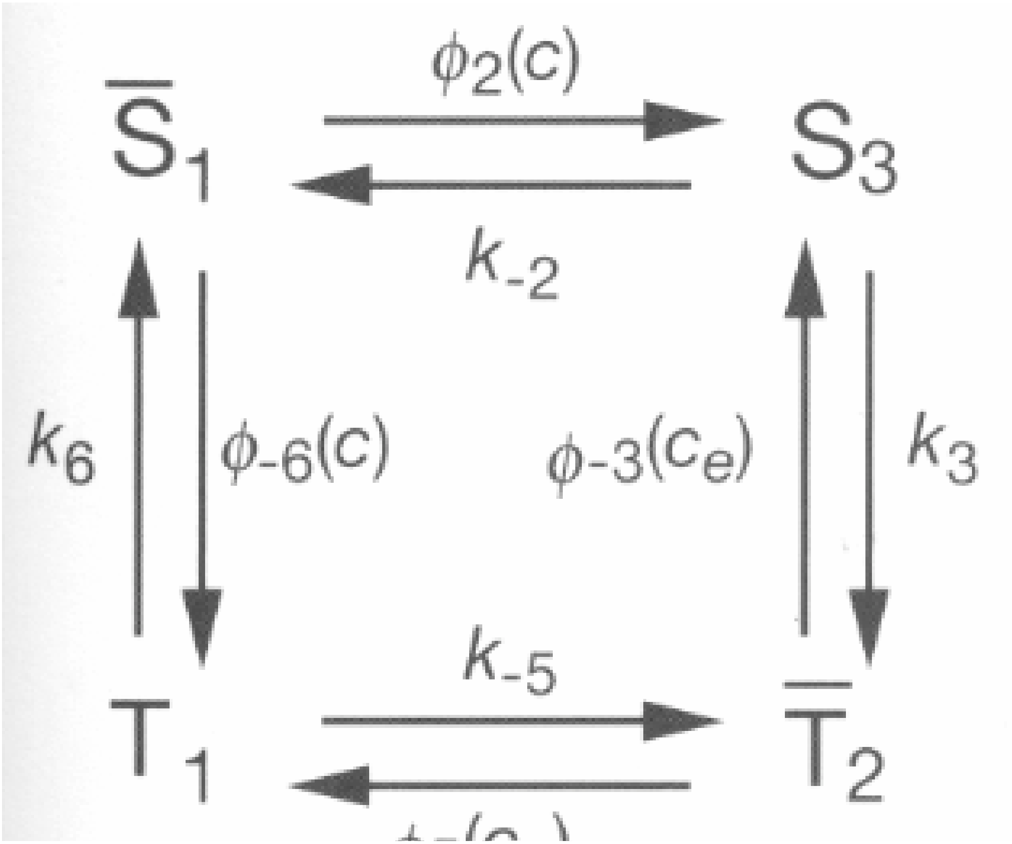
- E1 Calcium binding sites exposed to cytoplasma
- E2 Calcium binding sites exposed to endoplasmic reticulum

Model reduction

Assuming steady state between s_1 and s_2, and t_2 and t_3. And introduce $\bar{s}_1 = s_1 + s_2$ and $\bar{t}_2 = t_2 + t_3$,

$$s_1 = \frac{K_1}{c^2} s_2$$

$$\bar{s}_1 = s_1 \left(1 + \frac{c^2}{K_1}\right) = s_2 \left(1 + \frac{K_1}{c^2}\right)$$



Calcium release

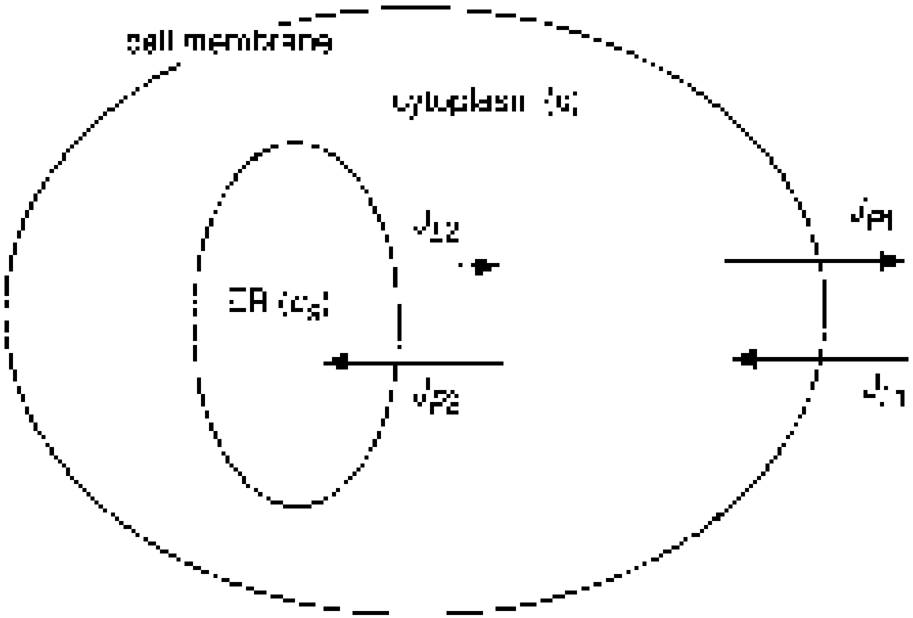
Calcium released from internal stores is mediated by 2 types of channels (receptors)

- Inositol (1,4,5)-triphosphate (IP_3) receptors
- Ryanodine receptors

Ryanodine Receptors, 7.2.9

- Sits at the surface of intra cellular calcium stores
  - Endoplasmic Reticulum (ER)
  - Sarcoplasmic Reticulum (SR)
- Sensitive to calcium. Both activation and inactivation.
- Upon stimulation calcium is released from the stores.
- To different pathways
  - Triggering from action potential through extra cellular calcium inflow.
  - Calcium oscillations observed in some neurons at fixed membrane potentials.

Compartments and fluxes in the model



Model equations

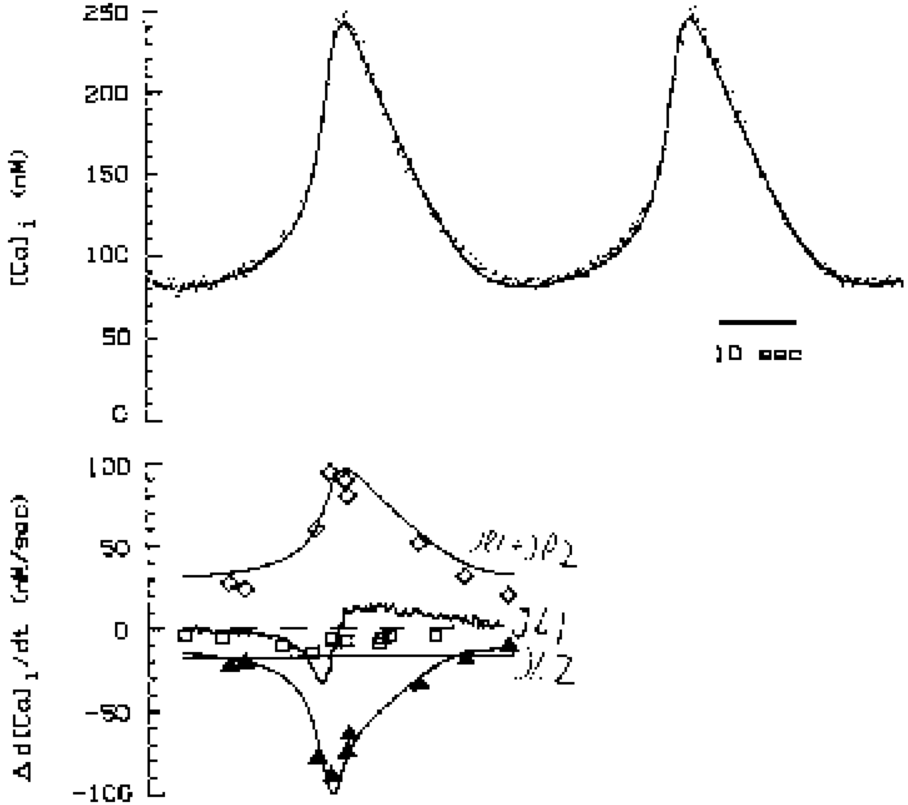
$$\begin{aligned}
\frac{d[c]}{dt} &= J_{\mathrm{L1}} - J_{\mathrm{P1}} + J_{\mathrm{L2}} - J_{\mathrm{P2}} \\
\frac{d[c_s]}{dt} &= \gamma(J_{\mathrm{P2}} - J_{\mathrm{L2}}) \\
J_{\mathrm{L1}} &= k_1(c_e - c), \quad \mathrm{Ca}^{2+} \text{ entry} \\
J_{\mathrm{P1}} &= k_2 c, \quad \mathrm{Ca}^{2+} \text{ extrusion} \\
J_{\mathrm{L2}} &= k_3(c_s - c), \quad \mathrm{Ca}^{2+} \text{ release} \\
J_{\mathrm{P2}} &= k_4 c, \quad \mathrm{Ca}^{2+} \text{ uptake}
\end{aligned}$$

The calcium sensitivity

Release modelled with Hill type dynamics:

$$J_{L2} = k_3(c_s - c) = (\kappa_1 + \frac{\kappa_2 c^n}{K_d^n + c^n})(c_s - c)$$

Experiments and simulations



- Good agreement between experiments and simulations
- Inactivation through calcium not included, but does not seem to be an important aspect

Buffered diffusion, 2.2.5

Consider buffering of calcium:

$$[Ca^{2+}] + [B] \underset{k_-}{\overset{k_+}{\rightleftharpoons}} [CB]$$

Conservation implies:

$$\begin{aligned}
\frac{\partial c}{\partial t} &= D_c \frac{\partial^2 c}{\partial x^2} + k_- w - k_+ cv + f(t, x, c) \\
\frac{\partial v}{\partial t} &= D_b \frac{\partial^2 v}{\partial x^2} + k_- w - k_+ cv \\
\frac{\partial w}{\partial t} &= D_b \frac{\partial^2 w}{\partial x^2} - k_- w + k_+ cv
\end{aligned}$$

where $c = [Ca^{2+}]$, $v = [B]$, and $w = [CB]$.
Buffer is large compared to Ca^{2+} so D_b is used for both bound and unbound state.

Quasi static assumption

Adding the buffer equations yields,

$$\frac{\partial(v+w)}{\partial t} = D_b \frac{\partial^2(v+w)}{\partial x^2}$$

Thus if $v + w$ is initially uniform, it will stay uniform, $v(x) + w(x) = w_0$

If buffering is fast compared to f:

$$k_-(w_0 - v) - k_+ c v = 0$$

so:

$$v = \frac{K_{eq} w_0}{K_{eq} + c}, \text{ where } K_{eq} = k_-/k_+$$

Eliminating v and w

Subtracting the equations for c_t and v_t and then eliminating v and w yields:

$$c_t = \frac{D_c + \phi(c) D_b}{1+\phi(c)} c_{xx} + \frac{D_b \phi'(c)}{1+\phi(c)} (c_x)^2 + \frac{f(t,x,c)}{1+\phi(c)}$$

where

$$\phi(c) = \mathrm{K}_{eq} w_0 / (\mathrm{K}_{eq} + c)^2$$

Buffering thus gives rise to a non-linear transport equation with non-linear diffusion coefficient. If $c << \mathrm{K}_{eq}$, then $\phi(c) \approx w_0/\mathrm{K}_{eq}$.

$$D_{\mathrm{eff}} = \frac{D_c + D_b \frac{w_0}{\mathrm{K}_{eq}}}{1 + \frac{w_0}{\mathrm{K}_{eq}}}$$

I.e. a linear combination of D_c and D_b. Reaction rate is slowed by $1/(1 + w_0/\mathrm{K}_{eq})$