CALCIUM WAVES

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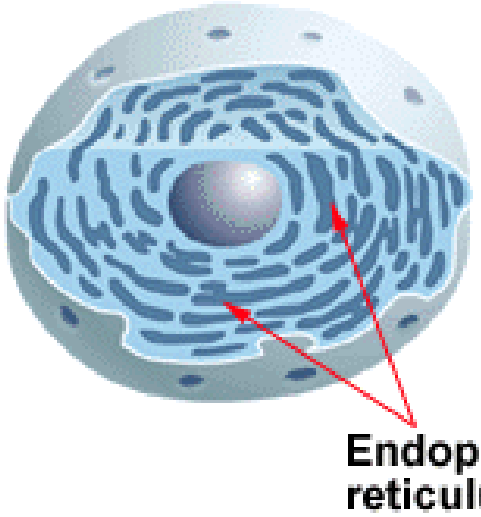
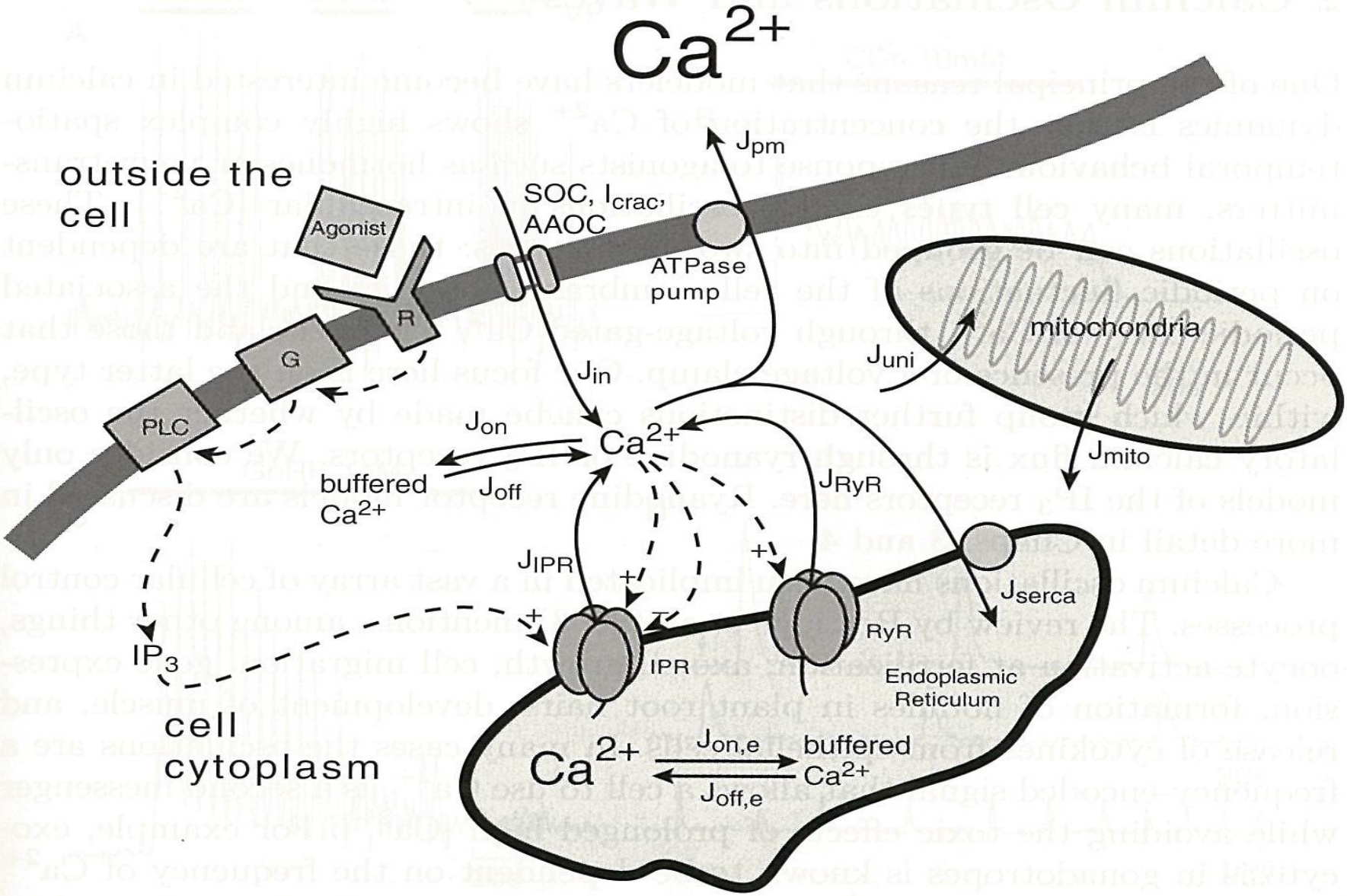
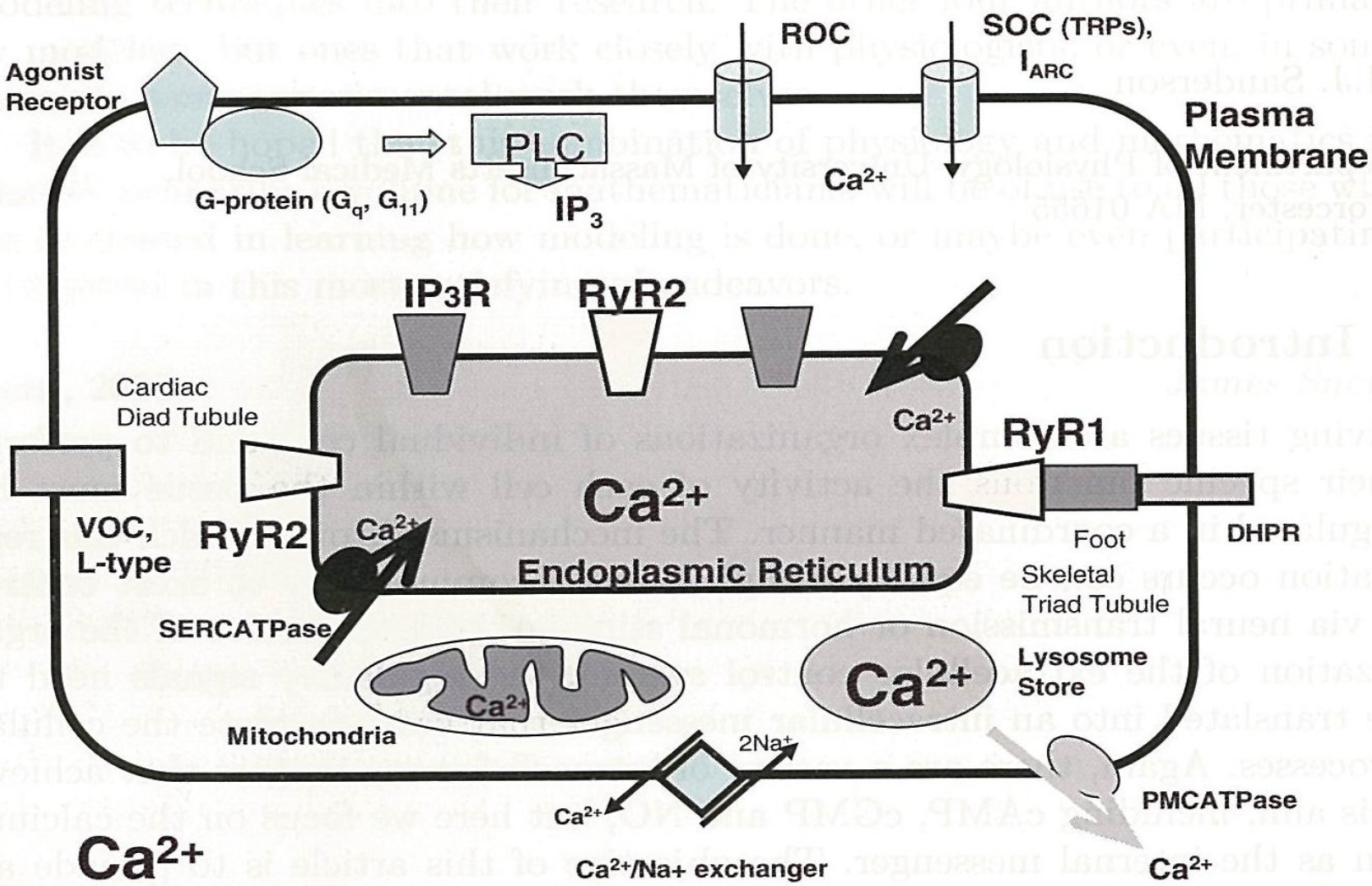


- in vertebrates majority of body Ca^{2+} stored in bones
- extracellular concentration - about 1-2 mM
- intracellular concentration - about 0.1 μM
- E(S)R - endoplasmic(sarcoplasmic) reticulum - internal reservoirs from which Ca^{2+} can be released. Concentration range: 10 - 100 μM



Major fluxes involved in the control of cytoplasmic Calcium



The same but more schematically

CALCIUM WAVES and OSCILLATIONS

Enable communication from one side of a cell to another or between cells

Synchronize a global multicellular response to a local stimulus

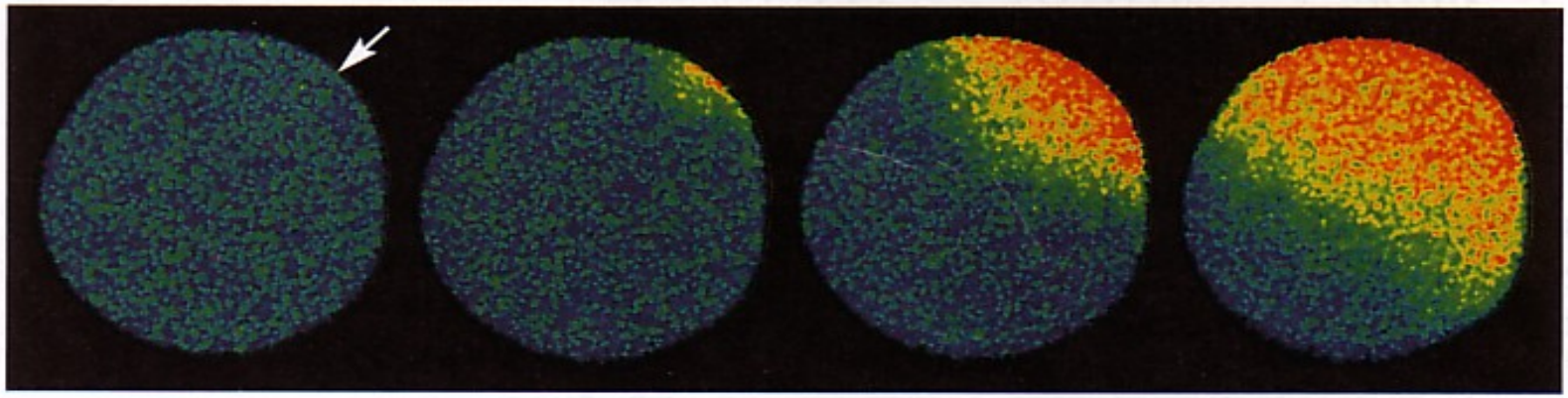
- *Many processes are Ca^{2+} dependent (regulated)*
- *Many extracellular signals induce an increase in cytosolic Ca^{2+}*

The speed of intracellular and intercellular plane waves : 5-20 *m*

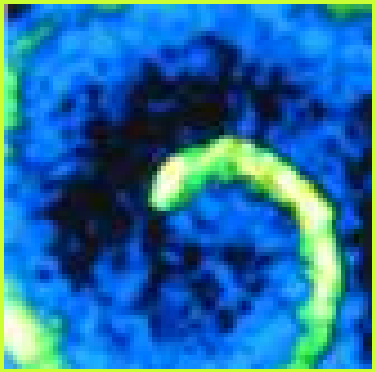
Concentration of intracellular (cytosol) calcium oscillate with periods ranging from a few seconds to more than a

EXAMPLES

1. Calcium waves during the fertilization of a starfish egg

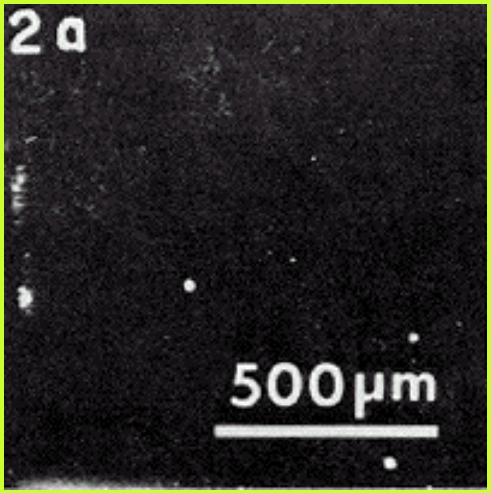


2. (Spiral) Waves in Xenopus oocyte (600 m)

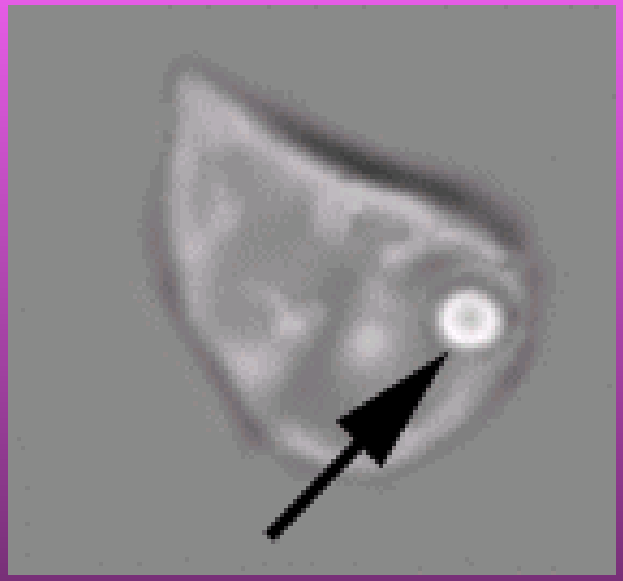


3. Waves in Medaka eggs (1000 m)

[connected with mechanical deformation]

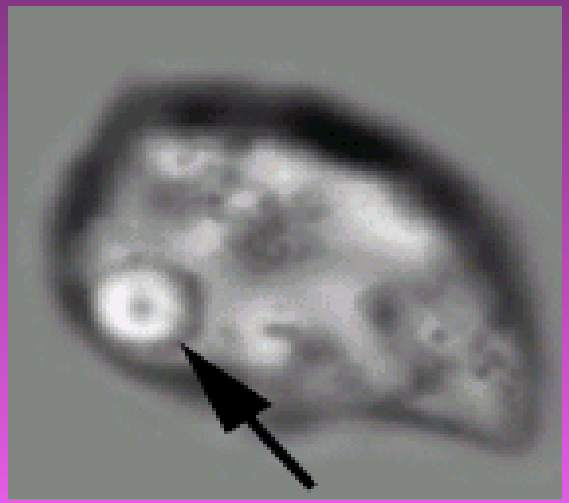


6.Calcium Waves in Phagocytosis (Petty, Kindzelskii, 2003)



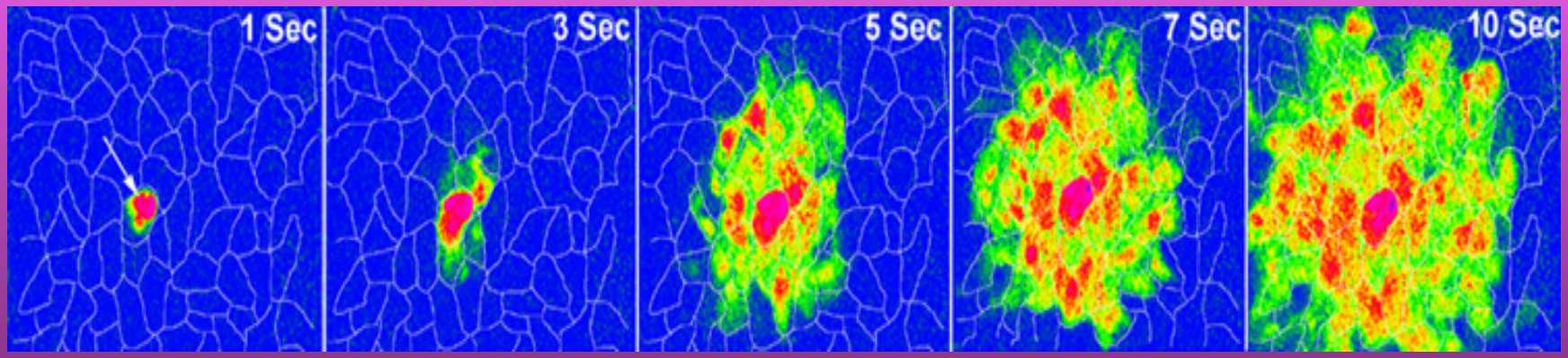
A wave traveling around the cell's perimeter splits in two, with the second wave encircling the phagosome. This second wave allows the digestive enzymes to enter the phagosome and destroy the target.

c

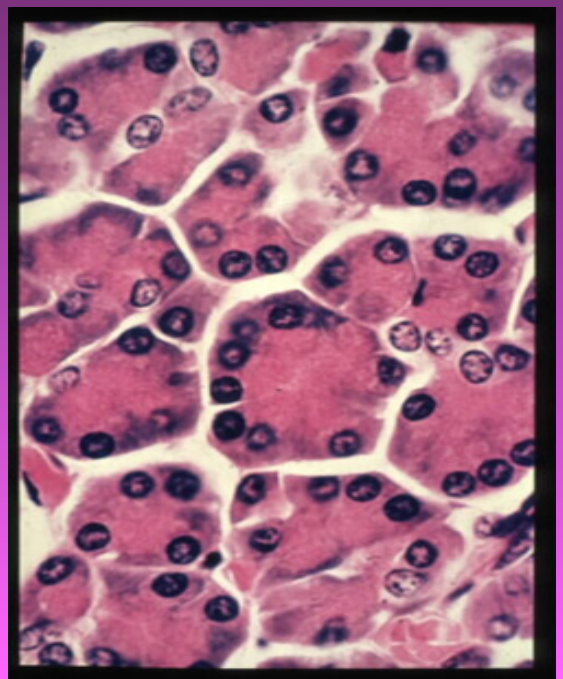


When a mutation is introduced, phagocytosis is not completed because the calcium wave circles the cell and bypasses the phagosome altogether.

4. Intercellular calcium waves in epithelial cells



5. Traveling Waves of Calcium in Pancreatic Acinar Cells



Ca2+ wave travels from cell to cell around the acinus.

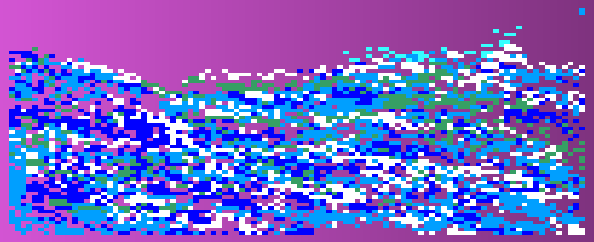
Its function is to increase the efficiency of enzyme secretion of the acinus, presumably by coordinating the secretion of each individual cell with that of its neighbours.

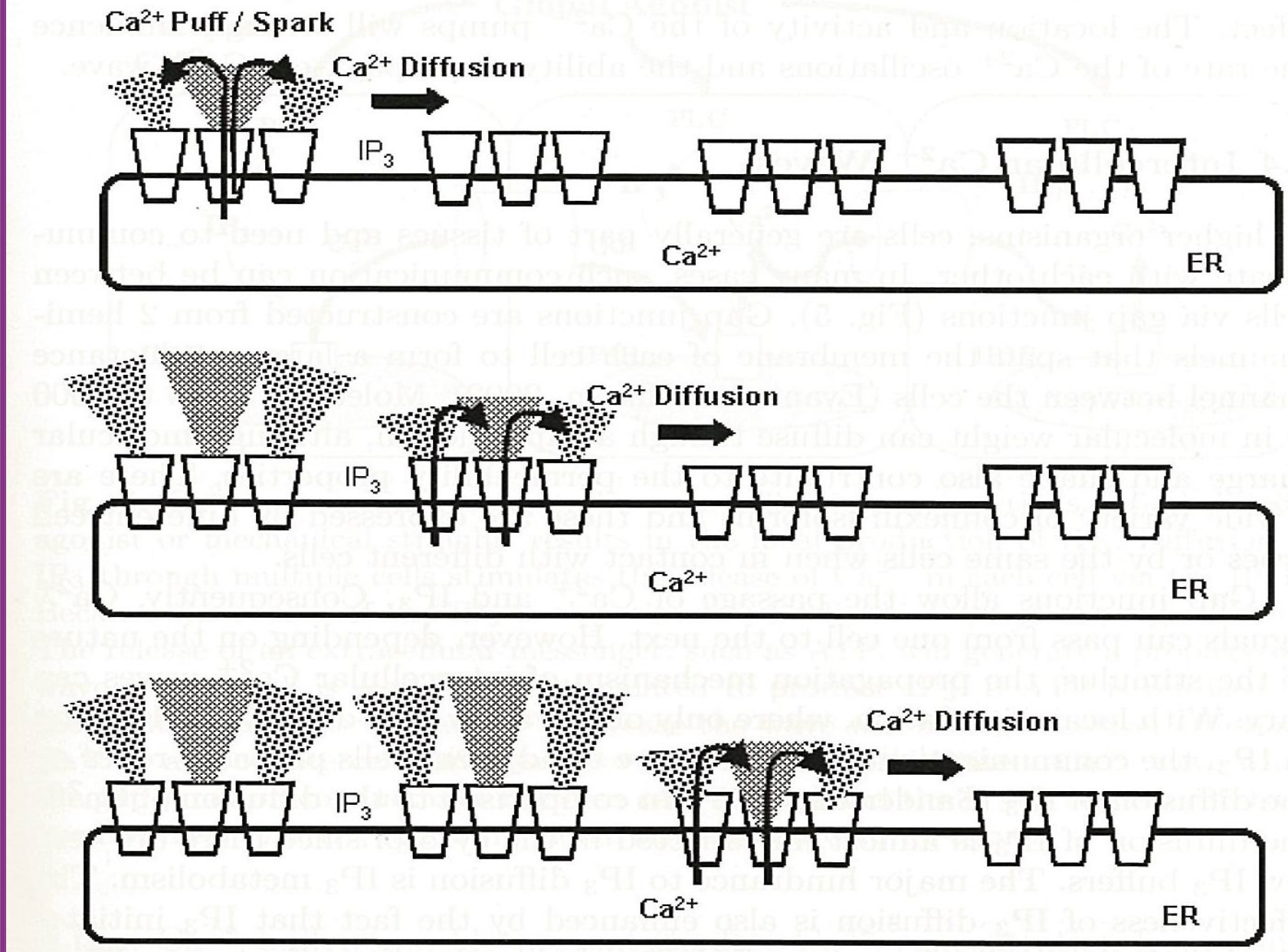
Mechanisms of Calcium propagation

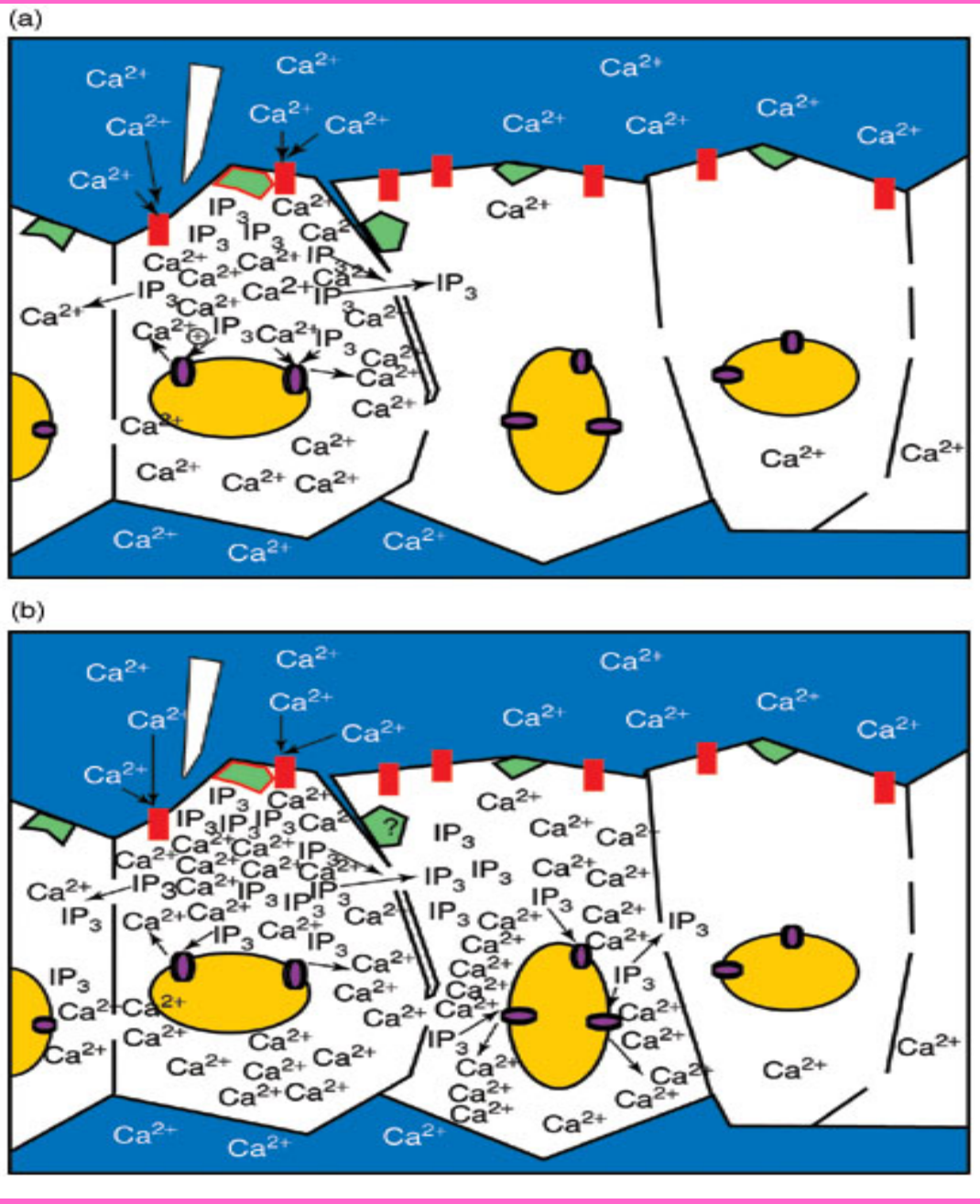
Simplified mechanism:

Diffusion of calcium between release sites. Ca^{2+} released from one Ca^{2+} - sensitive pool diffuses to neighbouring pools and initiates further release via calcium induced calcium release. Repetition of this process generate an advancing front of high calcium concentration.

Additional factors: the role of IP3 and Ryanodine receptors




Ca2+ Puff / Spark
Ca2+ Diffusion
IP3
Ca2+
ER
Ca2+ Diffusion
IP3
Ca2+
ER
Ca2+ Diffusion
IP3
Ca2+
ER



Intercellular calcium waves:

The transitions between the cells are due of the diffusion of IP_3

THE TWO-POOL MODEL

$$\frac{dc}{d\tau} = r - kc - \widetilde{f}(c, c_s),$$

$$\frac{dc_s}{d\tau} = \widetilde{f}(c, c_s)$$

c - concentration of calcium inside the cytoplasm
c_s - concentration of calcium in the Ca^{2+}-sensitive pool

$$\widetilde{f}(c, c_s) = J_{uptake} - J_{release} - k_f c_s,$$

r - a steady flux of Ca^{2+} caused by IP_3 from IP_3-sensitive stores
kc - the flux pumped out of the cytoplasm
$k_f c_s$ - the rate Ca^{2+} leaks from Ca^{2+}-sensitve pools

$$J_{uptake} = \frac{V_1 c^n}{K_1^n + c^n},$$

$$J_{release} = \left(\frac{V_2 c_s^m}{K_2^m + c_s^m}\right)\left(\frac{c^p}{K_3^p + c^p}\right).$$

The parameters for the two-pool model:

k=10/s; K_1 = 1 M ; K_2 = 2 M ; K_3 = 0.9 M ;

V_1 = 65 M/s; V_2 = 500 M/s ; k_f = 1/s ;

m=2 ; n = 2; p = 4 ;

Let $\gamma = K_2/K_1$, $w = u + \gamma u$ (i.e. $w = K_1^{-1}(c + c_s)$). Then

$$\frac{dw}{dt} = \mu - (w - \gamma w),$$

$$\frac{dv}{dt} = \varepsilon^{-1} f(w - \gamma v, v) = \varepsilon^{-1} F(w, v).$$

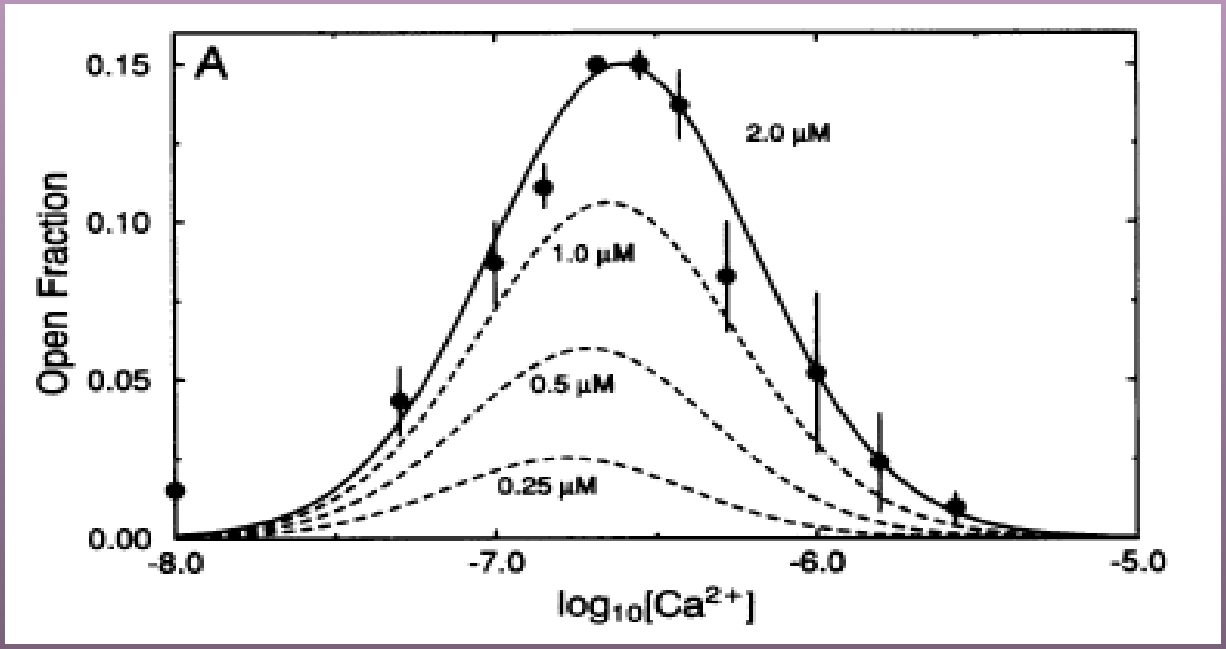
$$\varepsilon \cong 0.04.$$

$\varepsilon = kK_2/V_2$

Some other models:

1. Atri model (1993, e.g. Spiral waves in Xenopus oocyte)

2. De Young – Keizer model (1992)

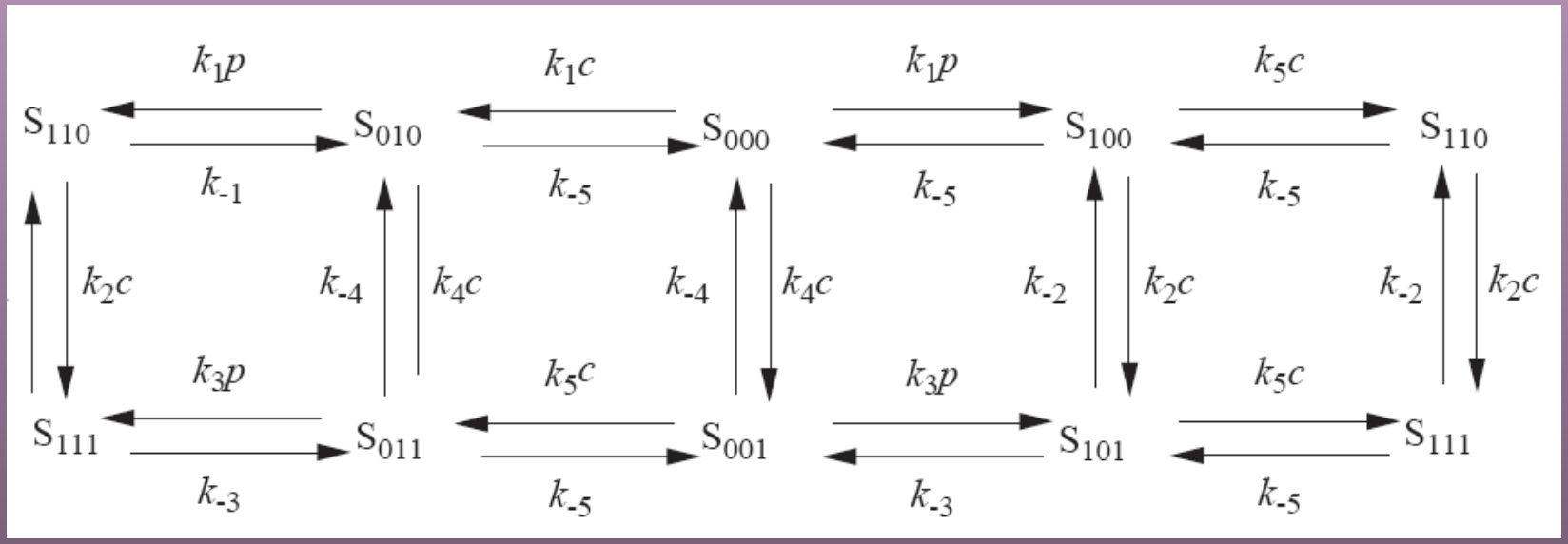


The open probability of the IP_3 receptor as a function of $[Ca^{2+}]$.

Experiment (Bezprozvanny) and De Young-Keizer model

De Young andKeizer model

IPR_3 - 3 equivalent and independent subunits. Each subunit has an $IP3$ binding site, an activating Ca binding site, and an inactivating Ca binding site. The state of the subunit S_{ijk}, $i, j, k = 0, 1$. The conducting state - S_{110}. x_{ijk} - the fraction of units in the state S_{ijk}.



$$\frac{dc}{dt} = (r_1 x_{110}^3 + r_2)(c_s - c) - \frac{r_3 c^2}{c^2 k_p^2}$$

$$\frac{dy}{dt} = \frac{(k_{-4}K_2K_1 + k_{-2}pK_4)c}{K_4K_2(p + K_1)}(1-y) - \frac{k_{-4}p + k_{-2}K_3}{p + K_3}y$$

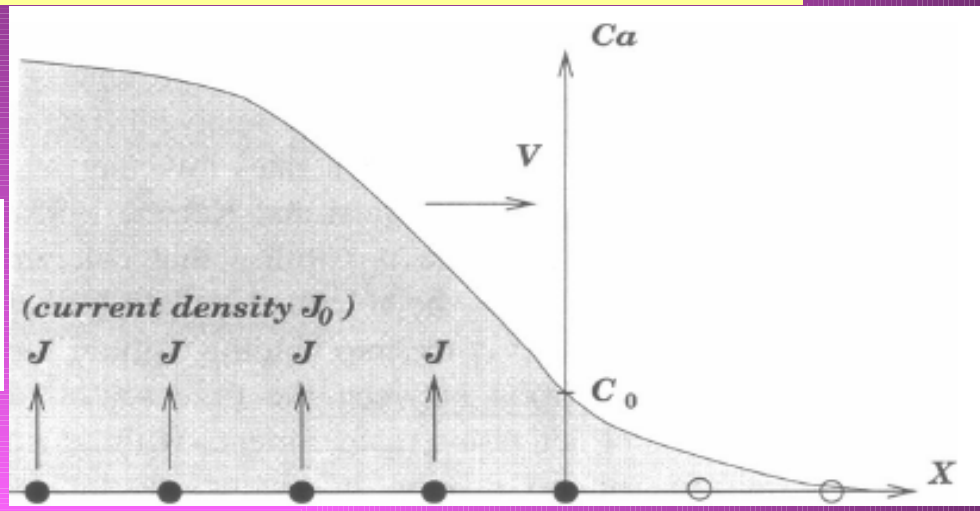
$$x_{110} = \frac{pc(1-y)}{(pK_1)(c + K_5)}$$

$$(1 - y) = x_{000} + x_{010} + x_{100} + x_{110}.$$

To analyze the propagation of calcium waves we must consider diffusion of calcium ions

The Kupferman model

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} - \Gamma C + J_0 H(C - C_0)$$



1) The Ca^{2+} source is continuously and uniformly distributed throughout the cell volume. **2)** The concentration of IP_3 is sufficiently large. **3)** The channels are closed if the local Ca^{2+} concentration is below a critical threshold, C_0, and are activated instantaneously when the concentration exceeds C_0. **4)** Ca^{2+} is pumped out from the cytosol at a rate proportional to the concentration, with rate constant Γ. **5)** Buffers and calcium inactivation channels are ignored.

Buffers

Big proteins (e.g. calmodulin, parvalbumin, calsequestrin, calretinin or EGTA) which can bind free calcium (up to 99%).

$$B_i + Ca^{2+} \rightleftarrows Ca^{2+}B_i.$$

$$\begin{aligned}
\frac{\partial u}{\partial t} &= D\Delta u + f(u) + \sum_{i=1}^{n}[k_-^i v_i - k_+^i u(b_0^i - v_i)],\\
\frac{\partial v_i}{\partial t} &= D_i \Delta v_i - [k_-^i v_i - k_+^i u(b_0^i - v_i)],
\end{aligned} \tag{1}$$

$$i = 1, \ldots, n, \quad v_i = [Ca^{2+}\ B_i].$$

$f(\cdot)$ is of bistable type: $f(u) = 0$ has exactly three solutions: u_1, $u_3 > u_1$ and $u_2 \in (u_1, u_3)$.

Calmodulin binds 0,2,4 Ca ions; atomic mass 16700 Da

Constant steady states

$$P_k = (u_k, v_1^k, \ldots, v_n^k), \quad k = 1, 2, 3,$$

where

$$v_j^k = u^k \frac{k_+^j b_0^j}{(k_-^j + k_+^j u^k)}.$$

$$v_j^1 < v_j^2 < v_j^3, \quad j = 1, \ldots, n,$$

$$P_1 < P_2 < P_3.$$

$$c(x,t) = c(x \cdot n - vt), \quad b(x,t) = b(x \cdot n - vt)$$

(Kazmierczak, Peradzynski, Volpert)

THEOREM 1. *Let $D, D_1, \ldots, D_n$ be positive. Then there exists a unique heteroclinic travelling wave solution to the system satisfying*

$$\lim_{\xi \to -\infty}(u(\xi), v_1(\xi), \ldots, v_n(\xi)) = (u^1, v_1^1, \ldots, v_n^1) = P_1,$$

$$\lim_{\xi \to \infty}(u(\xi), v_1(\xi), \ldots, v_n(\xi)) = (u^3, v_1^3, \ldots, v_n^3) = P_3,$$

$$\lim_{|\xi| \to \infty}(u'(\xi), v_1'(\xi), \ldots, v_n'(\xi)) = (0, 0, \ldots, 0).$$

Immobile buffers

For $D_i \longrightarrow 0$ the above solution tends to a unique heteroclinic travelling wave solution of the degenerate system.

J. Tsai, J. Sneyd, Existence and stability of traveling waves in buffered systems, *SIAM J. Appl. Math.*, **66** (2005)

Mechanochemical effects

Murray, Oster, Maini

$$\frac{\partial c}{\partial t} = D_c \nabla^2 c + f(c) + \gamma\theta + \zeta[k_- b - k_+ c(b_* - b)],$$

$$\frac{\partial b}{\partial t} = D_b \nabla^2 b - \zeta[k_- b - k_+ c(b_* - b)],$$

$\theta = \nabla \cdot \mathbf{u}$ -dilation, $\mathbf{u}$ - displacement field

Mechanical forces

$$\nabla \cdot \left\{ \frac{E}{1+\nu} \left[\varepsilon + \frac{\nu}{1-2\nu} \theta \mathbf{I} \right] + \mu_1 \frac{\partial \varepsilon}{\partial t} + \mu_2 \frac{\partial \theta}{\partial t} \mathbf{I} + \tau(c)\mathbf{I} \right\} = \rho \mathbf{u}$$

$\varepsilon = 1/2(\nabla \mathbf{u} + \nabla \mathbf{u}^T)$

$\frac{E}{1+\nu} \left[\varepsilon + \frac{\nu}{1-2\nu} \theta \mathbf{I} \right]$ - elastic part of the stress tensor

$\mu_1 \frac{\partial \varepsilon}{\partial t} + \mu_2 \frac{\partial \theta}{\partial t} \mathbf{I}$ - viscous part

$\tau(c)\mathbf{I}$ - traction tensor, $\rho \mathbf{u}$ - volume forces

$$\theta(x,t) = \theta(x \cdot n - vt), \quad c(x,t) = c(x \cdot n - vt),$$

$$b(x,t) = b(x \cdot n - vt).$$

For $\rho = 0$ one obtains:

– –

$$-\mu v\theta' + K(c)\theta + \tau(c) = \sigma$$

$$D_c c'' + vc' + f(c) + \gamma\theta + (1/\beta^2)[k_- b - k_+ c(b_* - b)] = 0$$

$$D_b b'' + vb' - (1/\beta^2)[k_- b - k_+ c(b_* - b)] = 0,$$

– –

where $' = \frac{d}{d\xi}$, $\xi = x \cdot n - vt$.

Assumption 1. *The function* $f(c) + \gamma K^{-1}(c)(\sigma - \tau(c))$ *is bistable with* c_1, $c_3 > c_1$ *the stable zeros and* $c_2 \in (c_1, c_3)$ *the unstable zero.* □

Objective: for all $\mu > 0$ and $\beta > 0$ sufficiently small prove the existence of a travelling wave such that

$$\lim_{s\to-\infty} c(s) = c_1, \quad \lim_{s\to\infty} c(s) = c_3,$$

$$\lim_{s\to-\infty} \theta(s) = K^{-1}(c_1)(\sigma - \tau(c_1)),$$

$$\lim_{s\to\infty} \theta(s) = K^{-1}(c_3)(\sigma - \tau(c_3)),$$

$$\lim_{s\to-\infty} b(s) = b_* k_+ \frac{c_1}{k_+ c_1 + k_-}, \quad \lim_{s\to\infty} b(s) = b_* k_+ \frac{c_3}{k_+ c_3 + k_-}.$$

$$D_1(c,\eta)c'' - D_2(c)c'^2 + vc' +$$

$$(1+S(c))^{-1}\left[f(c) + \gamma[h + (\sigma - \tau(c))K^{-1}]\right] +$$

$$F_c(\eta,\eta',\eta'',c,c',v) = 0$$

$$\eta'' - W(c,\eta)\beta^{-2}\eta + F_\eta(\eta,\eta',c,c',v) = 0,$$

where

$$\eta = k_- b - k_+ c(b_* - b).$$

$$S(c) = \frac{b_*\mathcal{L}}{(\mathcal{L}+c)^2}\ , \quad \mathcal{L} = \frac{k_-}{k_+},$$

$$D_1(c,\eta) = \frac{D_c + D_b S - D_b k_+ m^{-2}\eta}{1+S}, \quad m = (k_- + k_+ c),$$

$$D_2(c) = \frac{2D_b S}{(\mathcal{L}+c)(1+S)},$$

Theorem *Let us consider the system*

$$\frac{\partial U}{\partial t} = A\Delta U + F(U),$$

where $u = (u_1, ..., u_N)$ *is a vector-valued function,* A *is a diagonal nonnegative-definite matrix and* $C^1 \ni F(\cdot) : \mathbb{R}^N \to \mathbb{R}^N$. *Let*

$$\frac{\partial F_i}{\partial U_j} \geq 0, \qquad i, j = 1, ..., N, i \neq j.$$

Further, let the function $F(u)$ *vanish in a finite number of points* w_-, w_+, u_k, $(k = 1, ..., m)$ *with* $w_- < u_k < w_+$. *Let us assume that all the eigenvalues of the matrices* $F(w_-)$ *and* $F(w_+)$ *lie in the left half-plane, and that the matrices* $F(u_k)$, $(k = 1, ..., m)$ *are irreducible and have at least one eigenvalue in the right half-plane. Then there exists a unique monotone traveling wave, i.e., a constant* q *and a twice continuously differentiable monotone vector-valued function* $U(\xi)$, $\xi = x - qt$, *satisfying system*

$$AU'' + qU' + F(U) = 0,$$

and such that

$$\lim_{\xi \to \pm\infty} U(\xi) = w_\pm, \qquad \lim_{\xi \to \pm\infty} U'(\xi) = 0.$$

$$K = \begin{bmatrix} a - \sum_{i=1}^{n} a_i & b_1 & \dots & b_n \\ a_1 & -b_1 & \dots & 0 \\ .. & .. & \dots & .. \\ a_n & 0 & \dots & -b_n \end{bmatrix}$$

$$a = f_{,c}(c^k), \quad a_i = -k_+^i(b_0^i - v_i^k), \quad b_i = k_-^i + k_+^i c^k$$