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# Regulation of Intercellular Calcium Waves: Predictions of Mathematical Models

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Calcium waves serve as a pathway of intercellular signalling in such diverse systems as the liver and the astrocyte networks of the nervous system. Various schemes for intercellular waves have been proposed, in which wave propagation relies on the diffusion of messengers through gap junctions or across the extracellular space, or both. The schemes differ with respect to the messenger species exchanged and the role of feedback mechanisms that can regenerate the propagating signal. We have studied intercellular wave propagation in a simple reaction-diffusion model accounting for regenerative calcium release and gap-junctional diffusion of calcium or $IP_3$. The analysis shows that the types of signals that can be obtained depend on the diffusivity of the messenger carrying intercellular propagation. If propagation proceeds by calcium-induced calcium release and calcium diffusion, one can find either travelling waves or localized signals that fail to propagate beyond a stimulated cell or its immediate neighbourhood. If propagation relies on the more readily diffusible $IP_3$, one additionally obtains signals with a long yet finite range of propagation. Based on data recorded in rat striatal astrocytes, we developed and analysed a more detailed model of intercellular calcium signalling in astrocyte networks. The kinetic equations account for $IP_3$ generation, including its activation by cytoplasmic calcium, $IP_3$-induced calcium liberation from intracellular stores and various other calcium transports, and both cytoplasmic and gap-junctional diffusion of $IP_3$ and calcium ions. Rate constants for calcium release and sequestration were estimated from experimental data; the kinetic parameters for calcium-activated $IP_3$ production and intercellular $IP_3$ diffusion were taken as control parameters in the analysis of the model. Depending on their values, we find the three types of signals predicted by the simple model: localised diffusive signals, limited regenerative signals, and fully regenerative waves. The gap-junctional permeability for $IP_3$ is the crucial permissive factor for signal propagation, and heterogeneity of gap-junctional coupling yields preferential pathways of propagation. Processes involved in both signal initiation ($IP_3$ production activated by neurotransmitter) and regeneration (activation of $IP_3$ production by calcium, loading of the calcium stores) exert the main control on the signalling range. The refractory period of signalling strongly depends on the refilling kinetics of the calcium stores. Thus the model identifies multiple steps that may be involved in the regulation of this intercellular signalling pathway.

Christian Giaume and Laurent Venance (Collège de France) are gratefully acknowledged for stimulating collaboration.

**Kavli Institute for Theoretical Physics – Symposium on Calcium Dynamics**

## Regulation of intercellular calcium waves: predictions of mathematical models

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## Outline

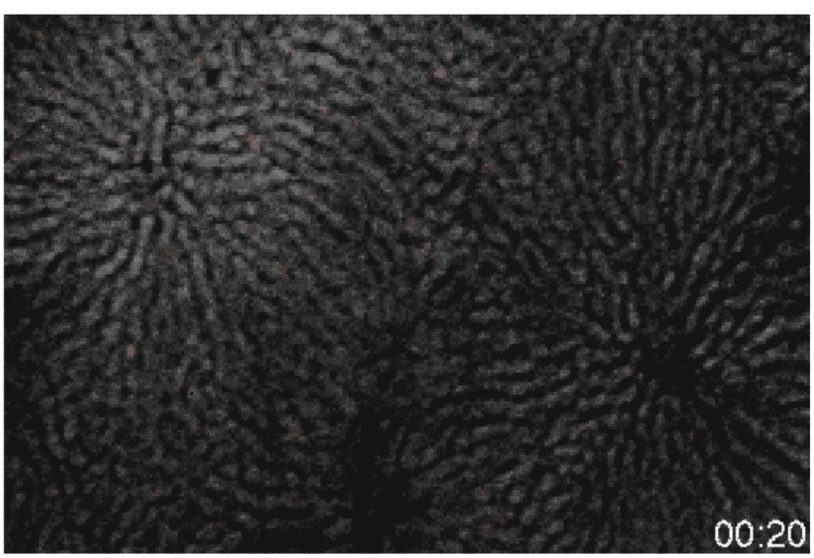
**Experimental observations of cell-to-cell signalling:**
periodic calcium waves in the liver
calcium signals in astrocyte networks

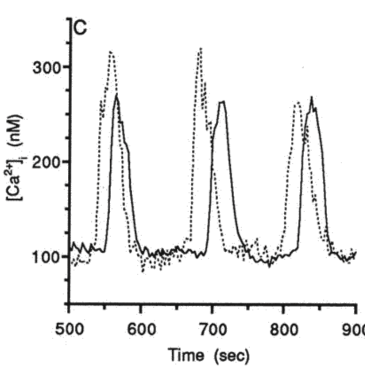
**Simple models of intercellular coupling**

**Gap-junction mediated waves in astrocytes**

**Interactions of calcium signalling and $IP_3$ metabolism**

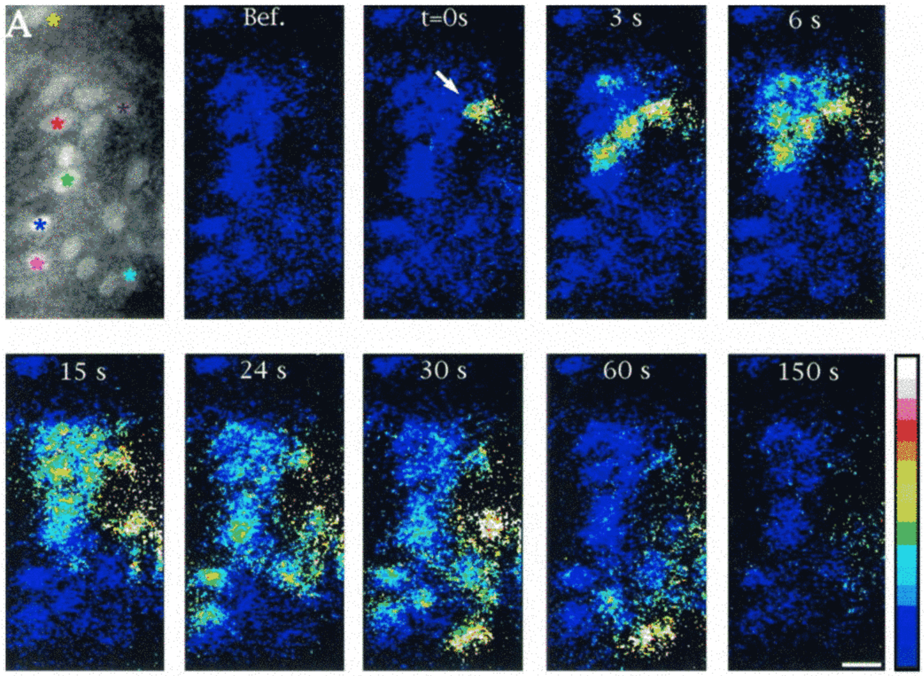
## Calcium waves in the intact rat liver



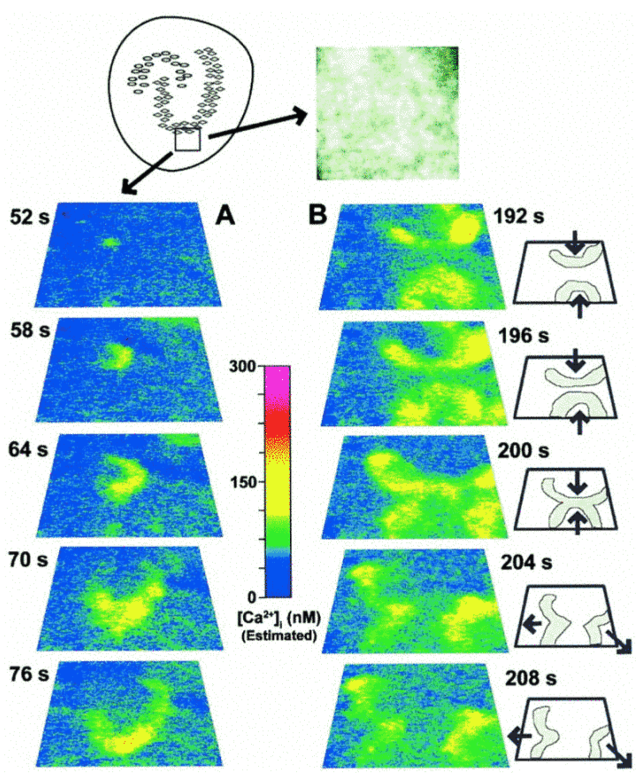

Larry Gaspers, Andrew Thomas

## Neurotransmitters induced-calcium waves in astrocytes




Laurent Venance, Christian Giaume

## Calcium waves in hippocampal slice cultures




Andrew Charles lab

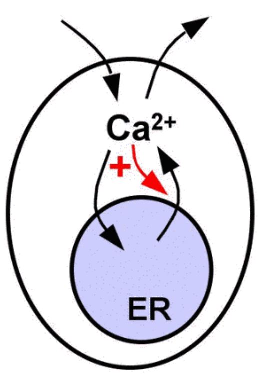
# Intercellular calcium waves

**Diffusion:**
- cytoplasmic ($Ca^{2+}$, $IP_3$)
- gap-junctional ($Ca^{2+}$, $IP_3$)
- paracrine (ATP)

**Regeneration:**
- CICR – sensitized $IP_3R$, RyR
- IICR and $Ca^{2+}$-acticated $IP_3$ generation

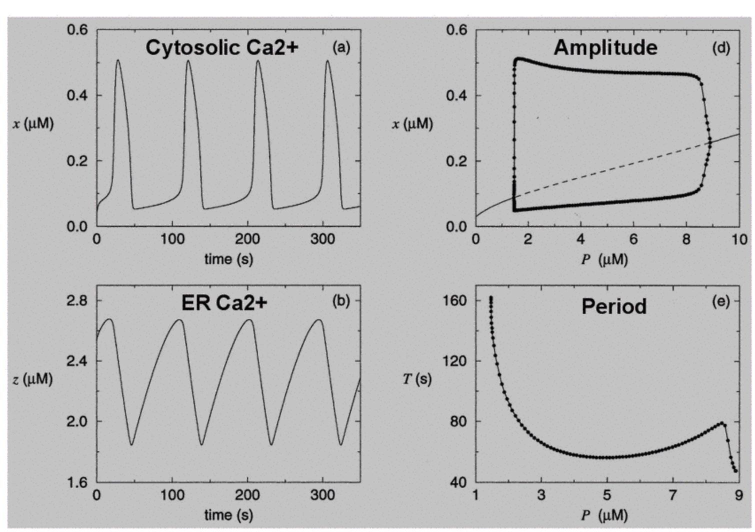
**Inhibition:**
- $Ca^{2+}$- induced inhibition of $IP_3R$
- $Ca^{2+}$-mediated activation of $IP_3$ degradation

# Simple model 1: coupling of $Ca^{2+}$ oscillators

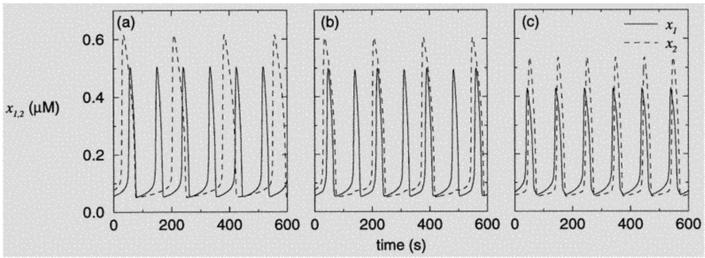



$$dc/dt = v_{\mathrm{PM-leak}} + v_{\mathrm{release}} - v_{\mathrm{SERCA}} - v_{\mathrm{PMCA}}$$

$$ds/dt = \frac{V_{\mathrm{Cyt}}}{V_{\mathrm{ER}}}\left(v_{\mathrm{SERCA}} - v_{\mathrm{release}}\right)$$

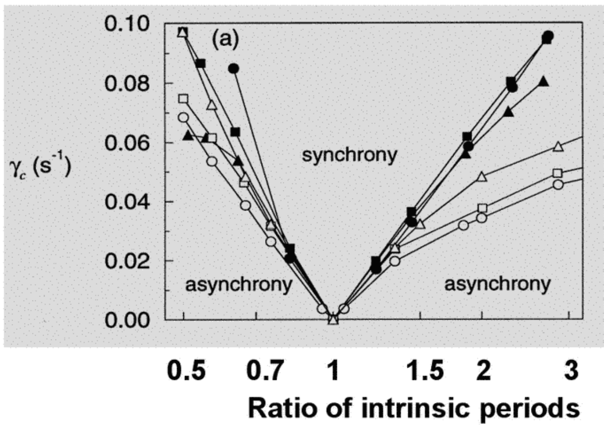


# Critical gap-junctional coupling

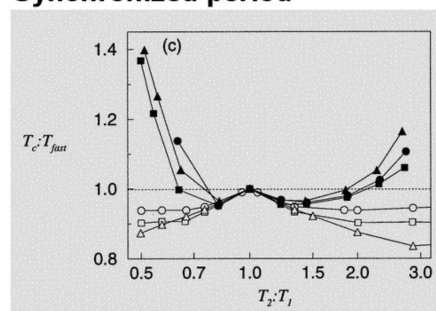



Gap-junctional permeability increases

Permeability



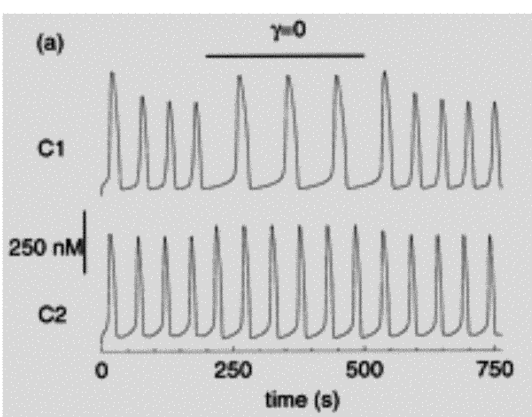

Synchronized period

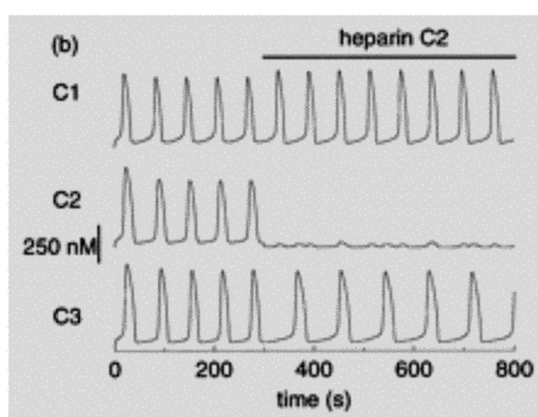



# Model experiments

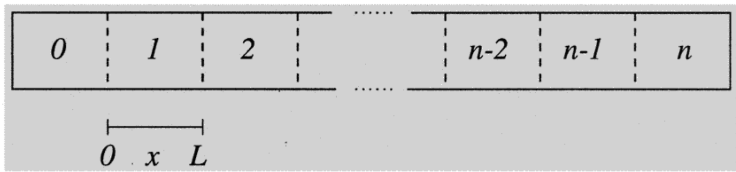
Transient gap junction blockade desynchronizes transiently

CICR inhibition abolishes oscillations



# Simple model 2: diffusion and regeneration



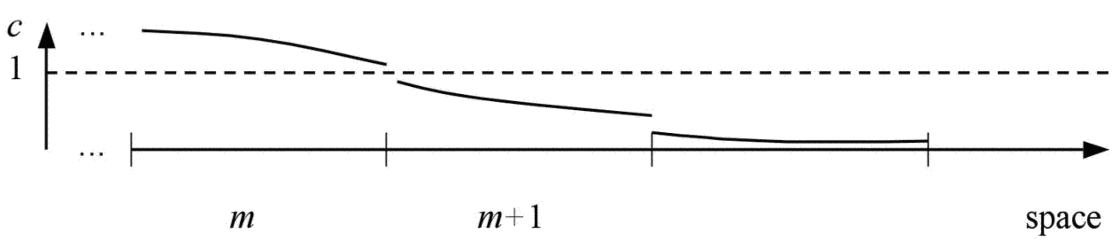

Intracellular dynamics:

$$\frac{\partial}{\partial t} c_i(x,t) = \underbrace{\alpha\, h(x)\,\Theta(c_i - 1)}_{\text{IP3R-mediated release}} - \underbrace{k c_i}_{\text{SERCA}} + \underbrace{D \frac{\partial^2 c_i}{\partial x^2}}_{\text{buffered diffusion}}$$

Gap-junctional fluxes:

$$-D \left.\frac{\partial c_i}{\partial x}\right|_{x=0,L} = P \Delta c_{gj,i}(x = 0, L)$$

## Look for stationary, spatially confined signals:

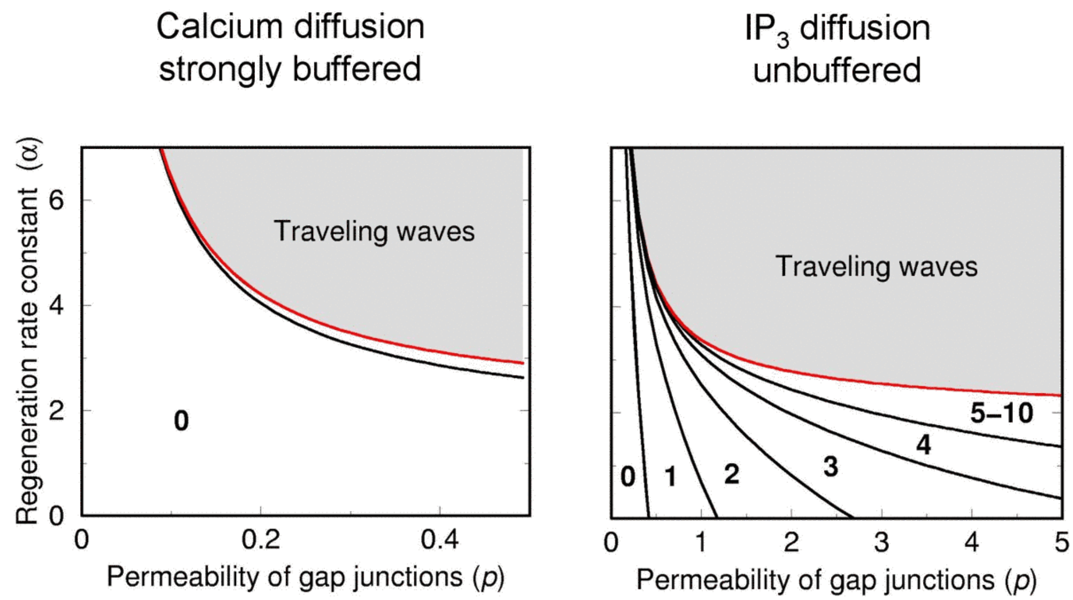



## Intercellular travelling waves:

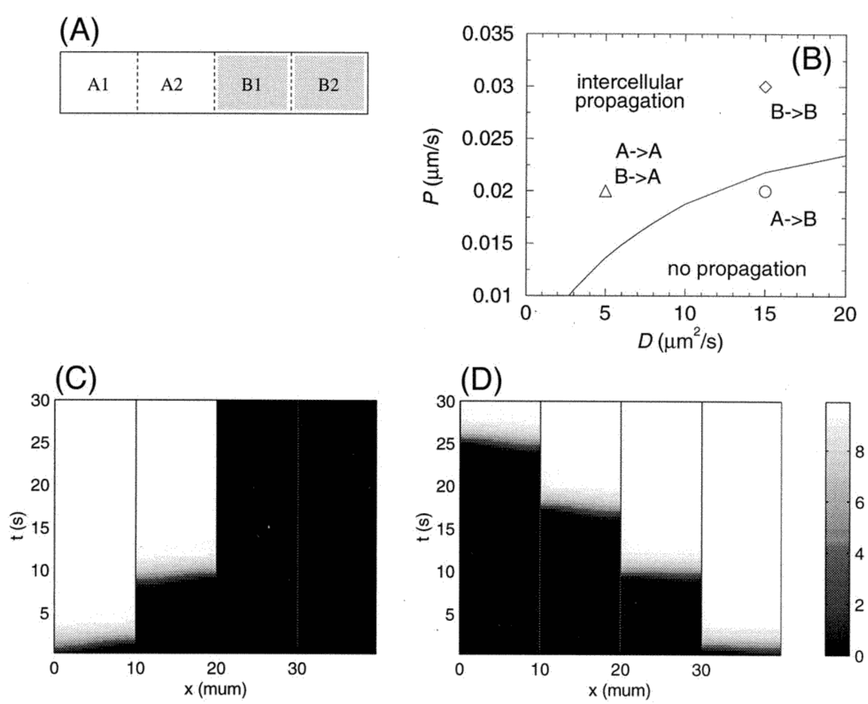
$$\lim_{m \to \infty} c_{m+1}(0) = 1$$

$$h \equiv 0: \quad P > \frac{\sqrt{kD}}{\alpha / k - 2}$$

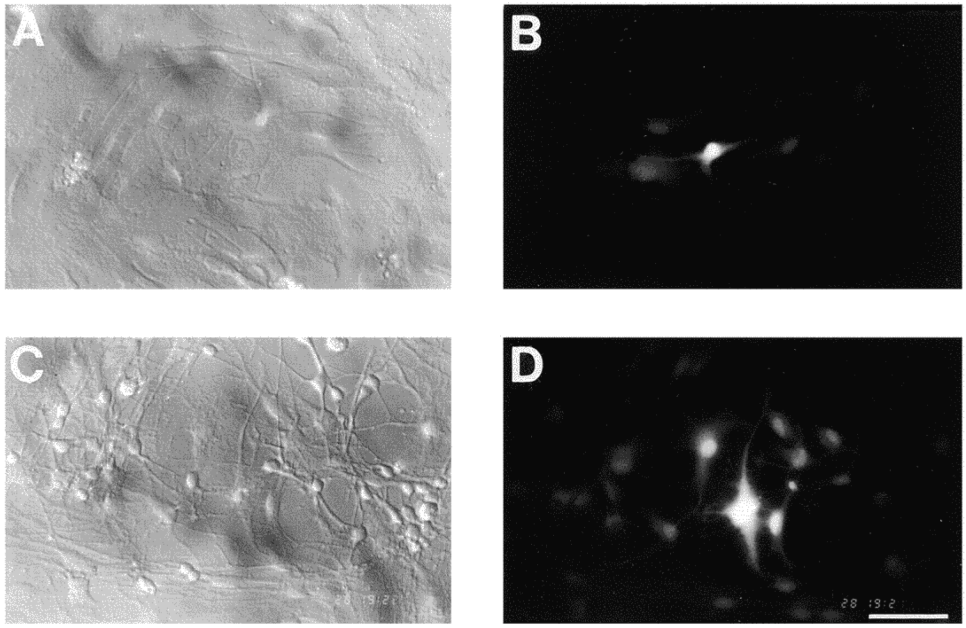
# Travelling waves and finite-range signals




# Unidirectional signaling

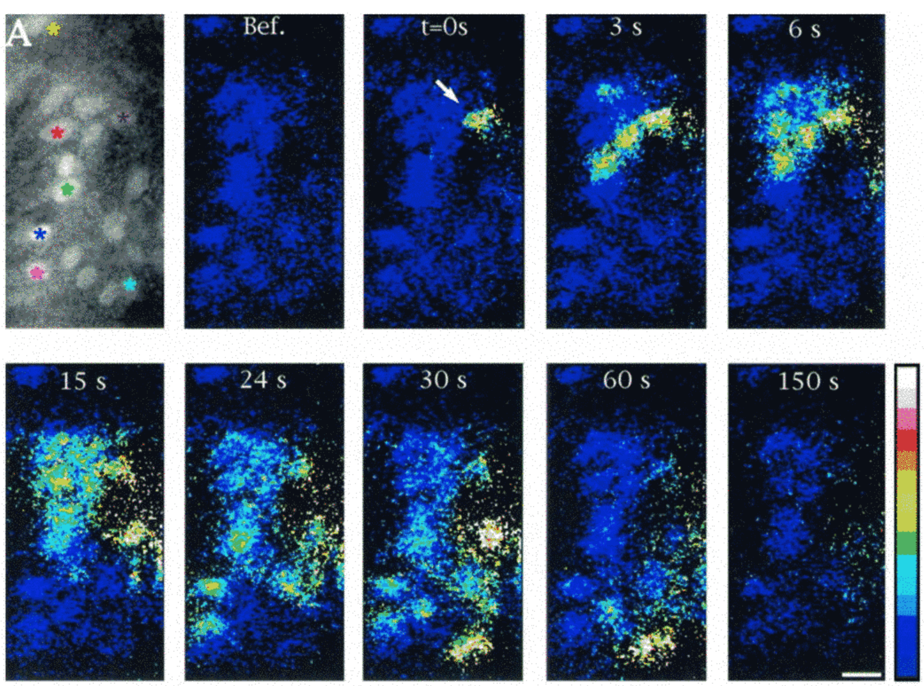


## Astrocytes in the CNS communicate through gap junction channels




Nathalie Rouach, Christian Giaume

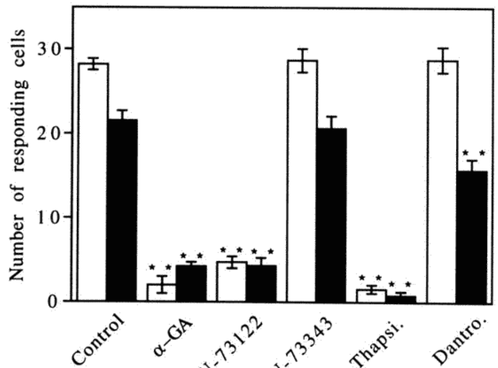
## Neurotransmitters induced-calcium waves in astrocytes



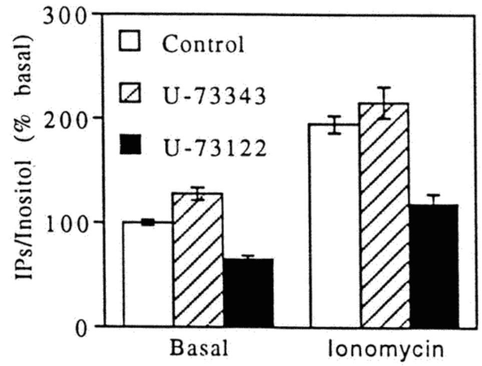

Laurent Venance, Christian Giaume

# Calcium waves in rat striatal astrocytes: pharmacology

## Gap junctions and PLC required



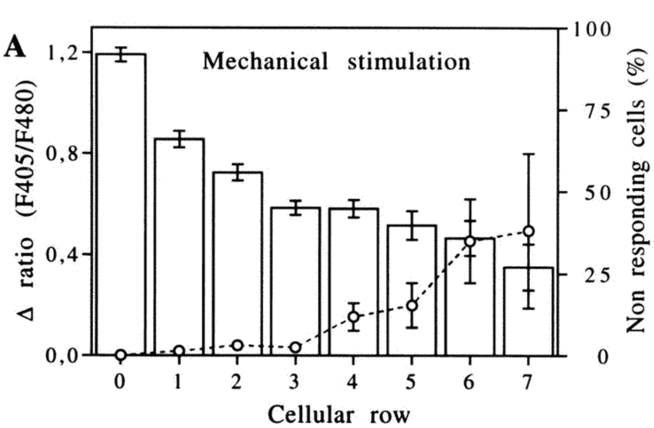

## Calcium activates PLC

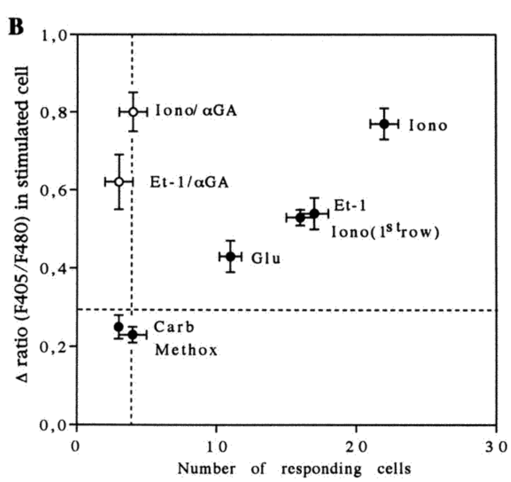



Laurent Venance, Christian Giaume

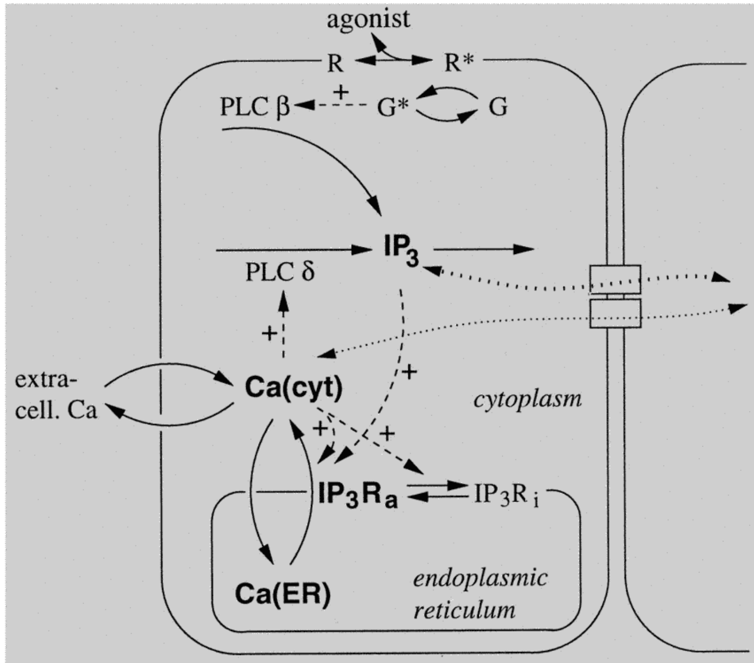
## IP3-mediated calcium release
## Ca-activated IP3 generation
## gap-junctional coupling

## Wave range restricted and well-defined:



# Model of $IP_3$ and $Ca^{2+}$ dynamics in astrocytes




## Dynamics in the cell

$$\frac{\partial c}{\partial t} = v_{\text{release}} + v_{\text{influx}} - v_{\text{sequestration}} - v_{\text{extrusion}} + D_{\text{c}}\left(\frac{\partial^2 c}{\partial x^2} + \frac{\partial^2 c}{\partial y^2}\right)$$

$$\frac{\partial s}{\partial t} = \rho(-v_{\text{release}} + v_{\text{sequestration}})$$

$$\frac{\partial p}{\partial t} = v_{\text{synthesis}} - v_{\text{degradation}} + D_{\text{p}}\left(\frac{\partial^2 p}{\partial x^2} + \frac{\partial^2 p}{\partial y^2}\right)$$

$$\frac{\partial r}{\partial t} = v_{\text{rec}} - v_{\text{inact}}$$

## Intercellular diffusion

$$-D_c \frac{\partial c}{\partial x} = P_c \Delta c (\text{across membrane})$$

$$-D_p \frac{\partial p}{\partial x} = P_p \Delta p (\text{across membrane})$$

**Rate equations**

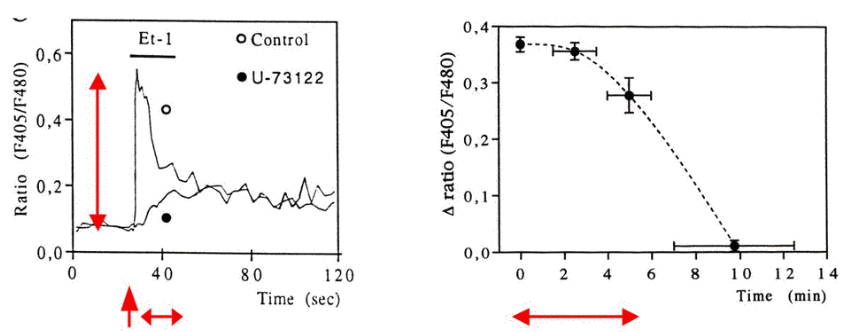
Ca [2+] release $$v_{\text{release}} = \left( k_1 + k_2 r \frac{c^2 p^2}{\left(K_a^2 + c^2\right)\left(K_p^2 + p^2\right)} \right)(s - c)$$

$IP_3$ synthesis $$v_{\text{synthesis}} = v_{\text{PLC}\beta} + v_{\text{PLC}\delta} \frac{c^2}{K_{Ca}^2 + c^2}$$

$IP_3R$ inactivation $$v_{rec} - v_{inact} = k_r \left( \frac{1}{1 + \left(c/K_i\right)^2} - r \right)$$

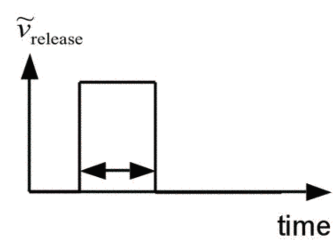
all other rates mass action, linear in concentrations

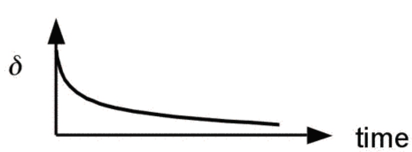
**Parameter estimates:**




$$\frac{\partial c}{\partial t} = \tilde{v}_{\text{release}}(s - c) + k_2(c_0 - c) - k_3 c$$

$$\frac{\partial s}{\partial t} = \rho\left(k_3 c - \tilde{v}_{\text{release}}(s - c)\right)$$



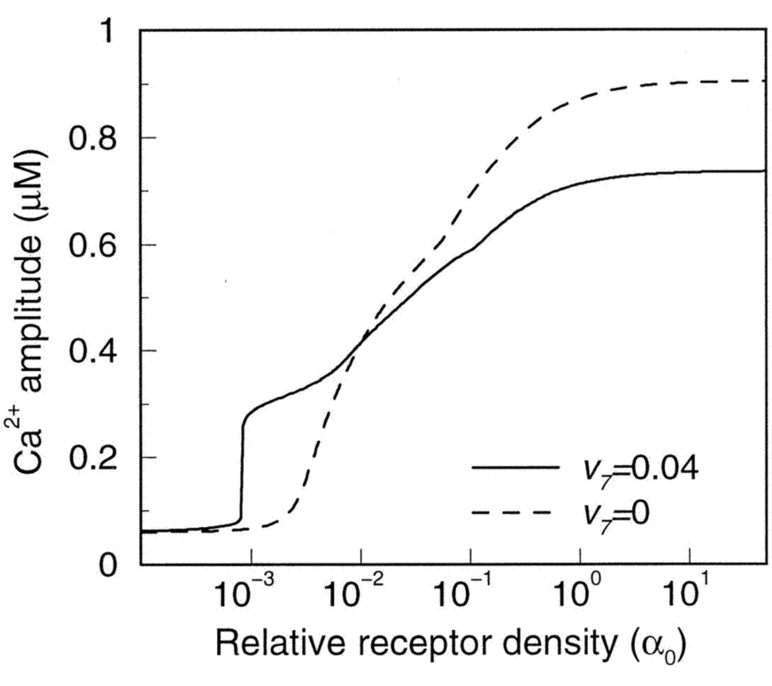




$$\tau = \int_0^\infty \delta(t)\,dt$$

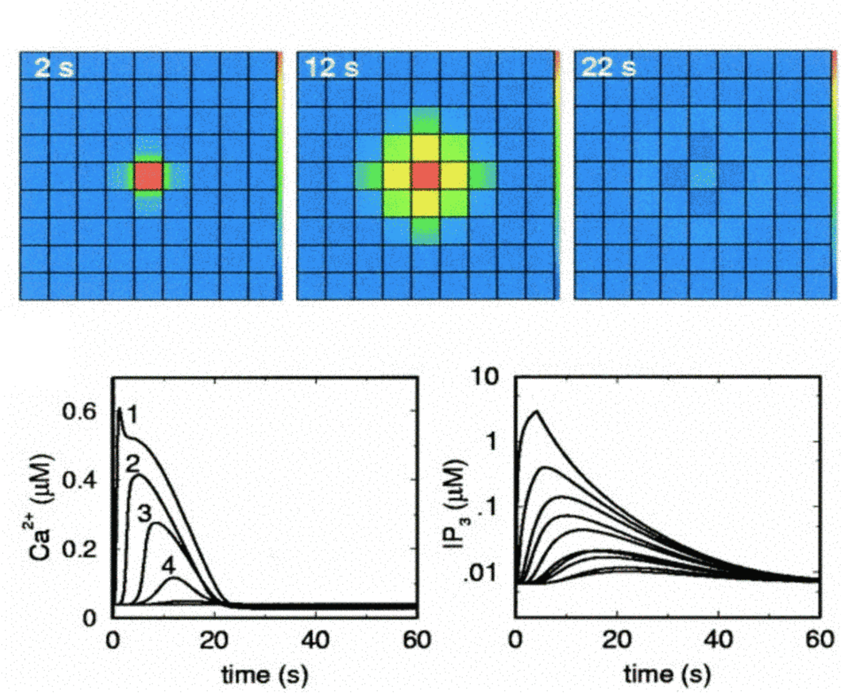
## Parameter estimates

| Parameter | Symbol | Value |
|---|---|---|
| Rate constant of calcium leak from ER | *k*1 | 0.0004/s |
| Rate constant of calcium release through IP3R | *k*2 | 0.08/s |
| Rate constant of SERCA pump | *k*3 | 0.5/s |
| Rate of calcium leak across the plasma membrane | *v*40 | 0.025 M/s |
| Maximal rate of activation-dependent calcium influx | *v*41 | 0.2 M/s |
| Rate constant of calcium extrusion | *k*5 | 0.5/s |
| Rate constant of IP3R inactivation | *k*6 | 4/s |
| Maximal rate of PLC | *v*7 | 0–0.05 M/s |
| Rate of PLC | *v*8 | 0–3 M/s |
| Rate constant of IP3 degradation | *k*9 | 0.08/s |
| Half-saturation constant for IP3 activation of IP3R | *K*IP3 | 0.3 μM |
| Half-saturation constant for calcium activation of IP3R | *K*a | 0.2 μM |
| Half-saturation constant for calcium inhibition of IP3R | *K*i | 0.2 μM |
| Half-saturation constant for calcium activation of PLC | *K*Ca | 0.3 μM |
| Half-saturation constant for agonist-dep. calcium entry | *K*r | 1 μM |
| Diffusion coefficient of IP3 | *D*IP3 | 280 μm2/s |
| Effective diffusion coefficient of calcium | *D*Ca | 20 μm2/s |
| Gap-junctional permeability of IP3 | *P*IP3 | 1–5 μm/s |
| Effective gap-junctional permeability of calcium | *P*Ca | 0.01 *P*IP3 |
| Ratio of the effective volumes for Ca2 cytoplasm/ER | $\rho$ | 20 |

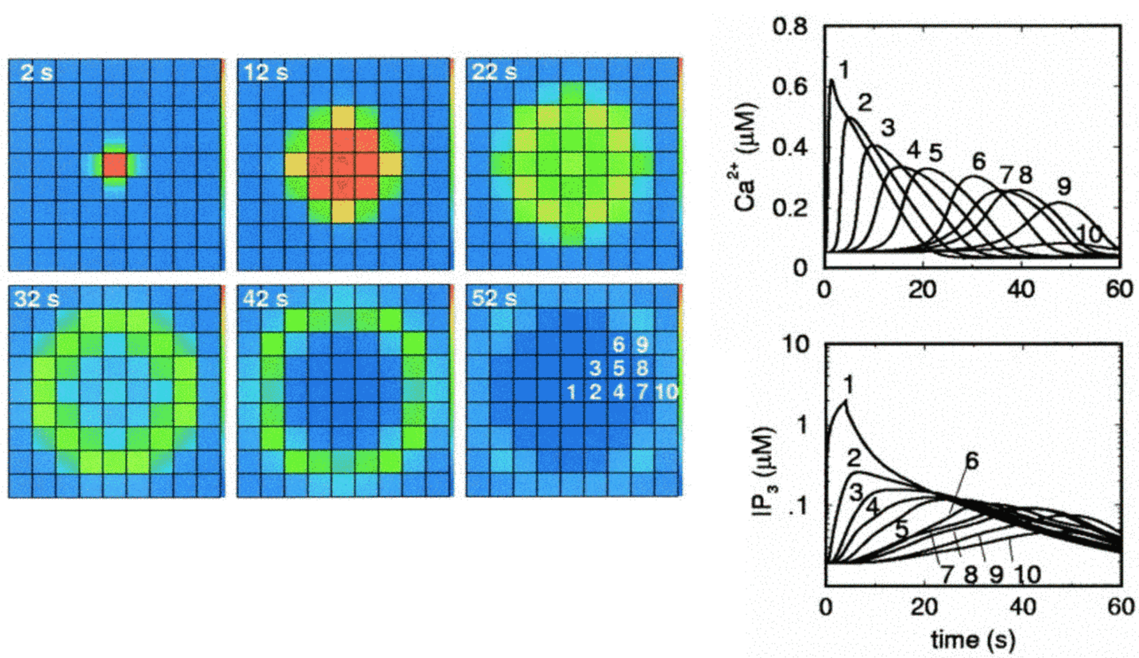
## Single cell stimulus-response curve



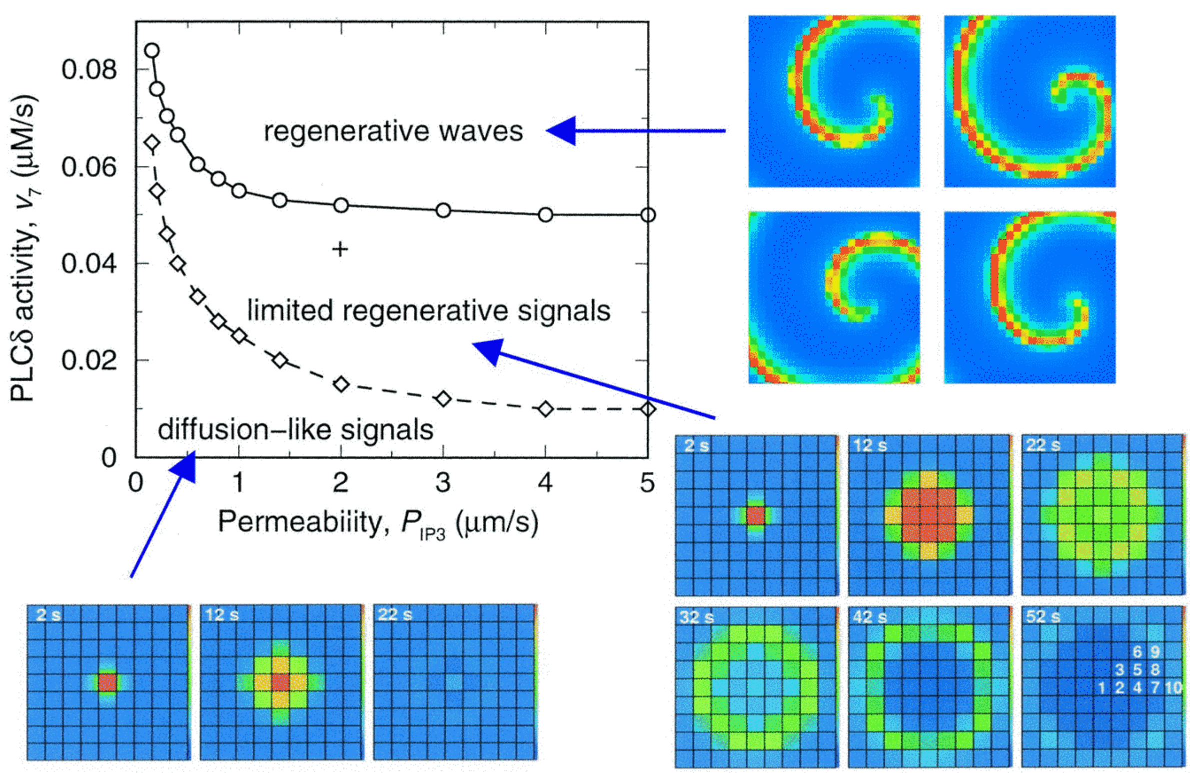
## No PLCδ activity: diffusive intercellular calcium signals




## PLCδ activity: regenerative intercellular calcium signals

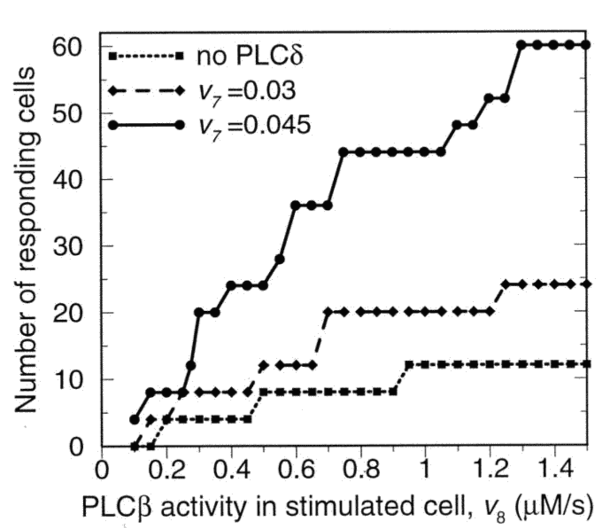


## Three modes of intercellular signalling

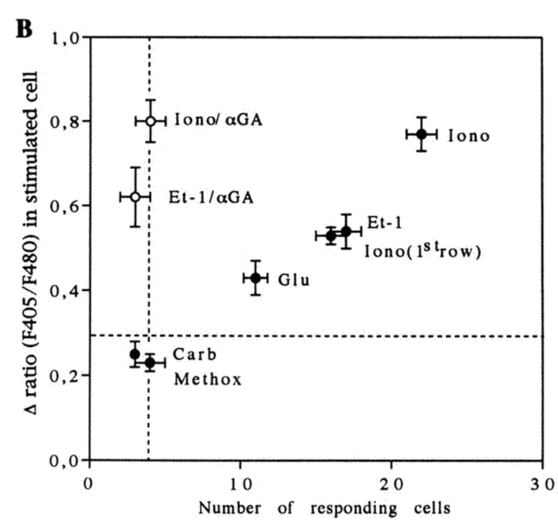



## Control of signalling by stimulus

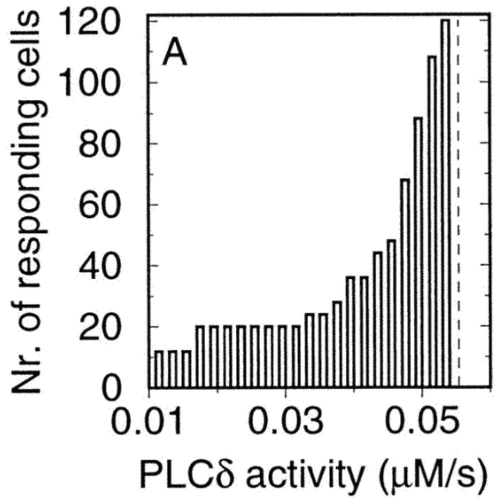
### Theory

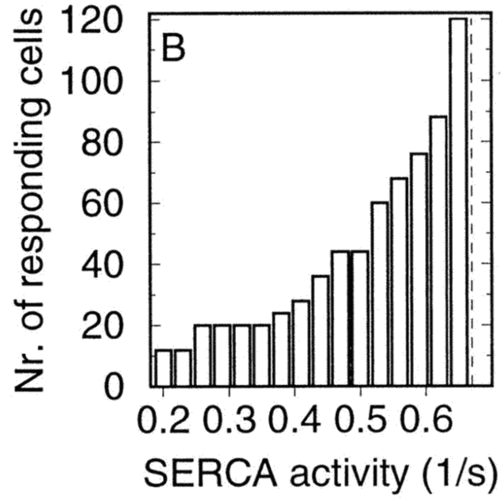



### Experiment

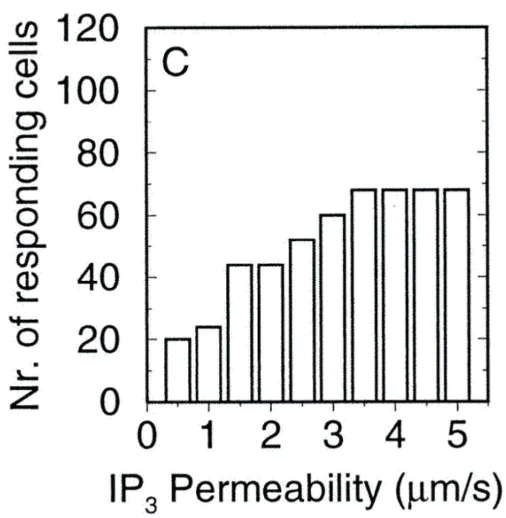


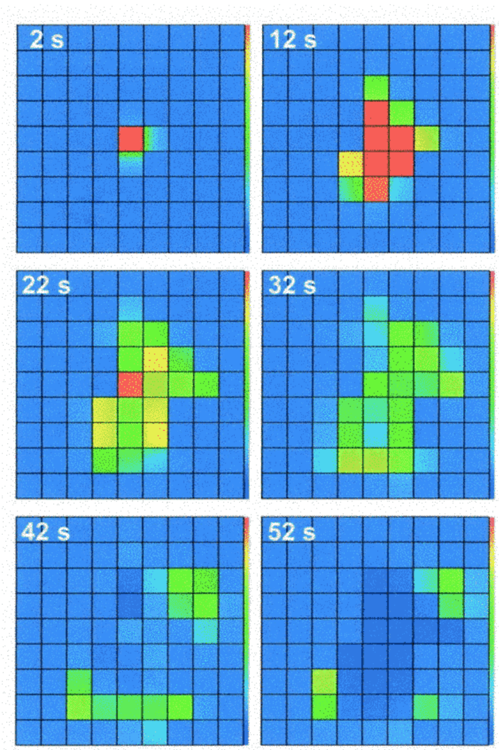
# Regeneration controls range of propagation




# $IP_3$ diffusion is permissive for propagation




Experiments:
Rouach/Giaume (JCB 2000)

# Refractory period