A Modeling Approach of Intercellular Calcium Waves in Glial Cells

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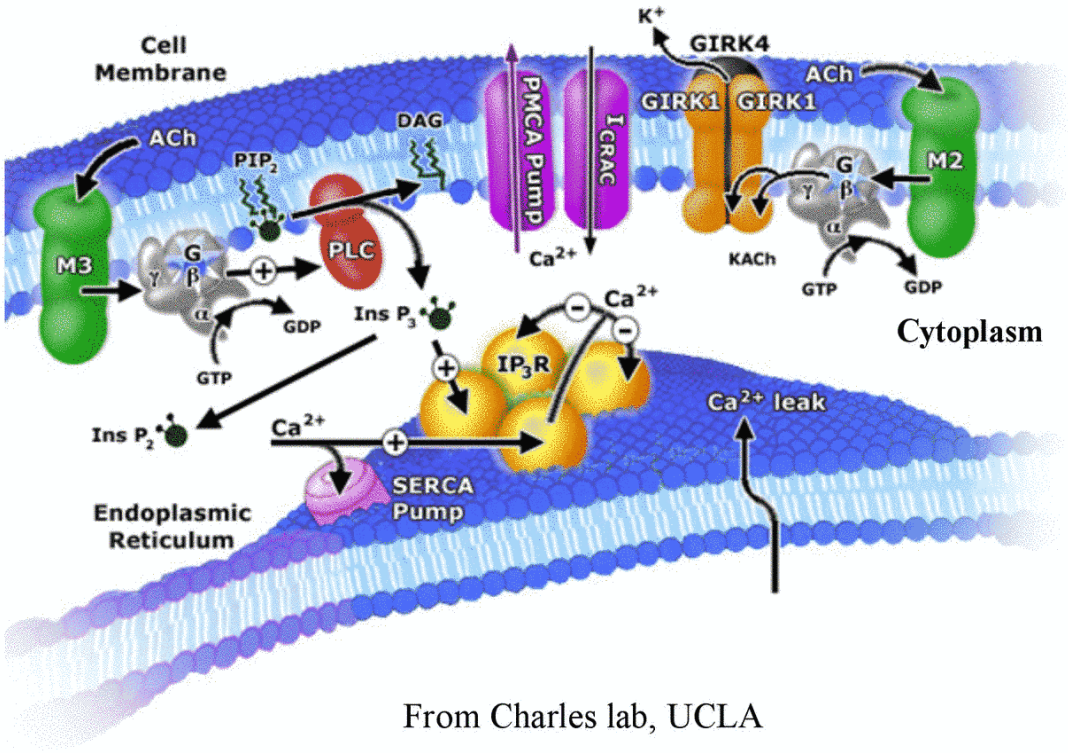
Glial cells

- Supportive elements in the nervous system.
- Calcium-dependent glutamate release
  - Integrate neuronal inputs
  - Modulate synaptic activity
- Glia-glia connection, glia-neuron connection: possible pathways for nervous system functions

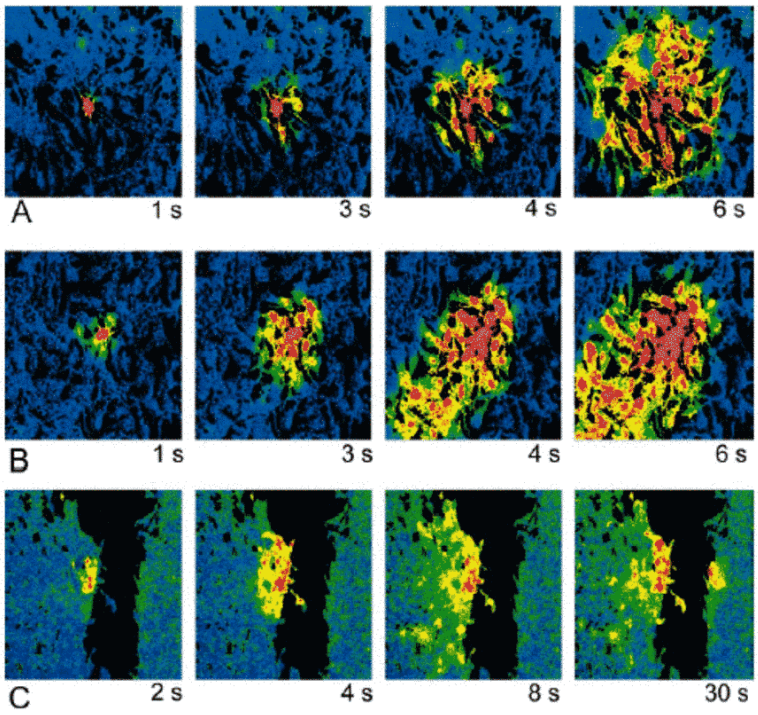
- Intracellular calcium signals
- Intercellular calcium signals: long distance signal with slow spreading speed.

Intracellular Calcium Oscillation



From Charles lab, UCLA

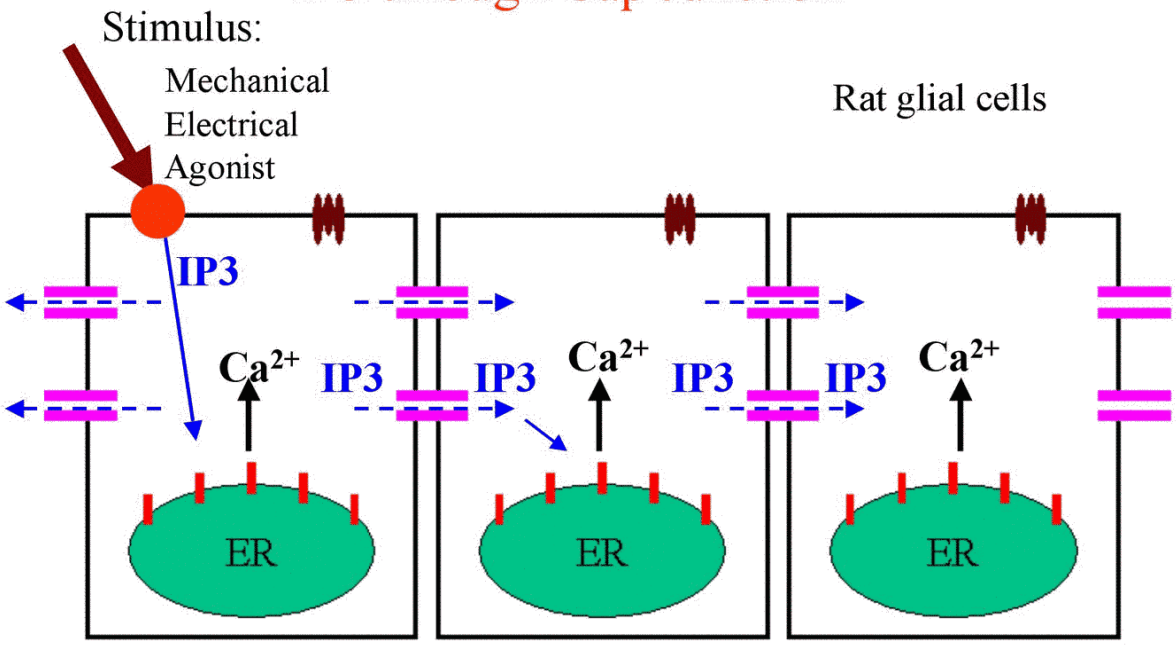
Intercellular Calcium Waves Induced by Mechanical Stimulation in Experiment



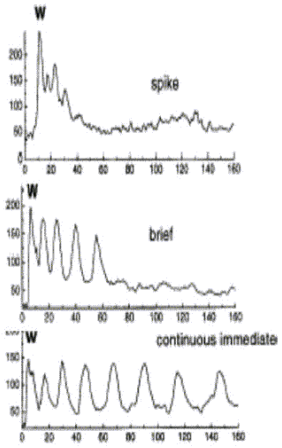
A Charles
Glia, 1998

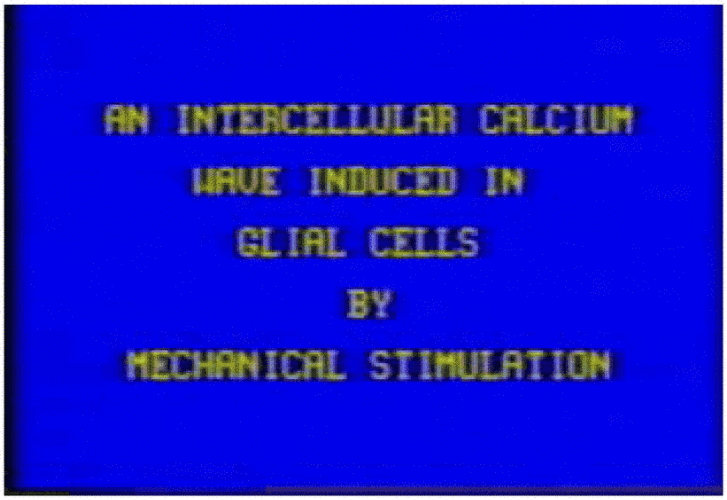
Cell-cell communication

IP3 through Gap Junction

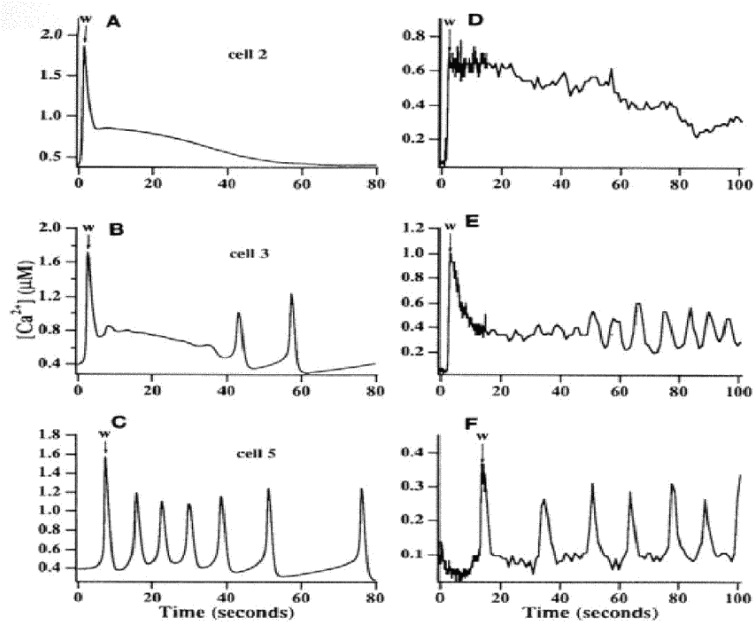


Mechanical Stimulation (Experiment)





Model by J Sneyd, et al

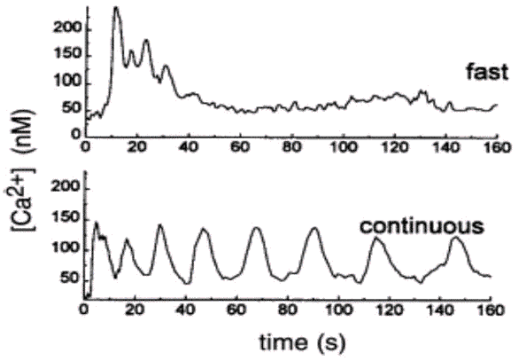


1×5 cells

$29\,\mu m$

Sneyd et al, Am. J. Physiol. 1994

Model by J Sneyd, et al



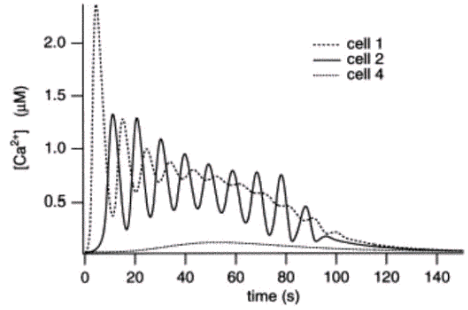
Model assumptions:

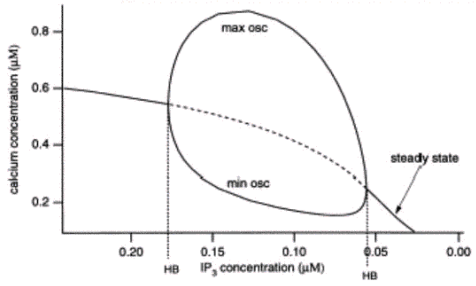
- No calcium-induced IP3 generation
- Supercritical Hopf bifurcation dynamics

Model failure:

The duration of responding waves is too short

Biophys. Chem. 1998
Am. J. Physiol. 1995
Am. J. Physiol. 1994





7×7 cells

$24\,\mu m$

Glial Cell Model: Ca2+

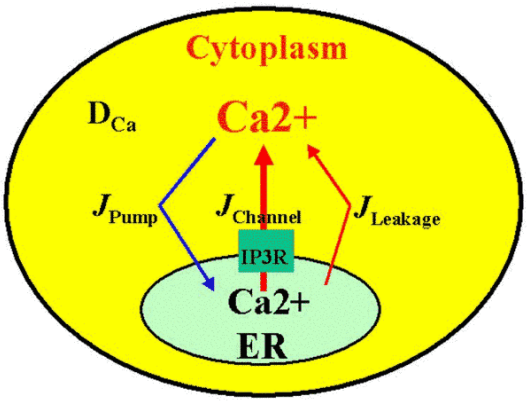
Calcium in cytoplasm

$$\frac{\partial C}{\partial t} = J_{\text{Channel}} - J_{\text{Pump}} + J_{\text{Leakage}} + D_{\text{Ca}}\left(\frac{\partial^2 C}{\partial x^2} + \frac{\partial^2 C}{\partial y^2}\right)$$

$$J_{\text{Channel}} = v_C \left(\frac{C}{d_C + C}\right)^3 \left(\frac{I}{d_I + I}\right)^3 \cdot h^3 \cdot (C_{ER} - C)$$

$$J_{\text{Pump}} = v_{\text{P}} \frac{C^2}{K_{\text{P}}^2 + C^2}$$

$$J_{\text{Leakage}} = v_L (C_{ER} - C)$$



Open fraction of Ca2+ inactivation gate

$$\frac{dh(x,y)}{dt} = \alpha_h (1-h) - \beta_h h$$

Modified from Li-Rinzel model, 1984

Glial Cell Model: IP3

$$\frac{\partial I}{\partial t} = J_{\text{PLC}\beta} + J_{\text{PLC}\delta} - J_{\text{Deg}} + D_{\text{IP3}}\left(\frac{\partial^2 I}{\partial x^2} + \frac{\partial^2 I}{\partial y^2}\right) + J_{\text{MechStim}}$$

Ca-induced IP3 generation

$$J_{\text{PLC}\delta} = v_\delta \frac{C^2}{K_\delta^2 + C^2}$$

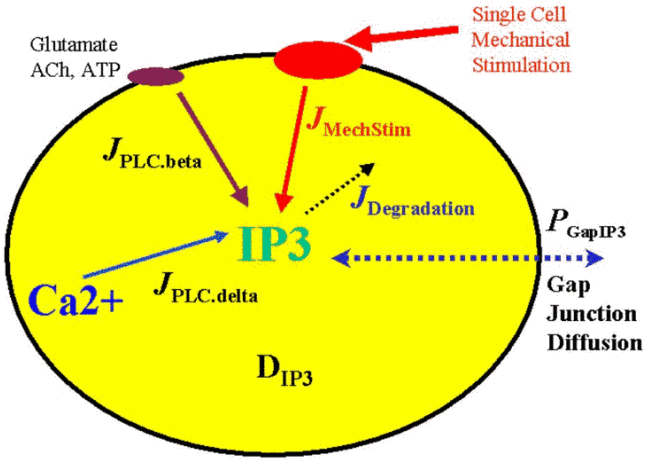
IP3 Degeneration

$$J_{\text{Deg}} = \gamma \frac{I}{K_D + I}$$

with

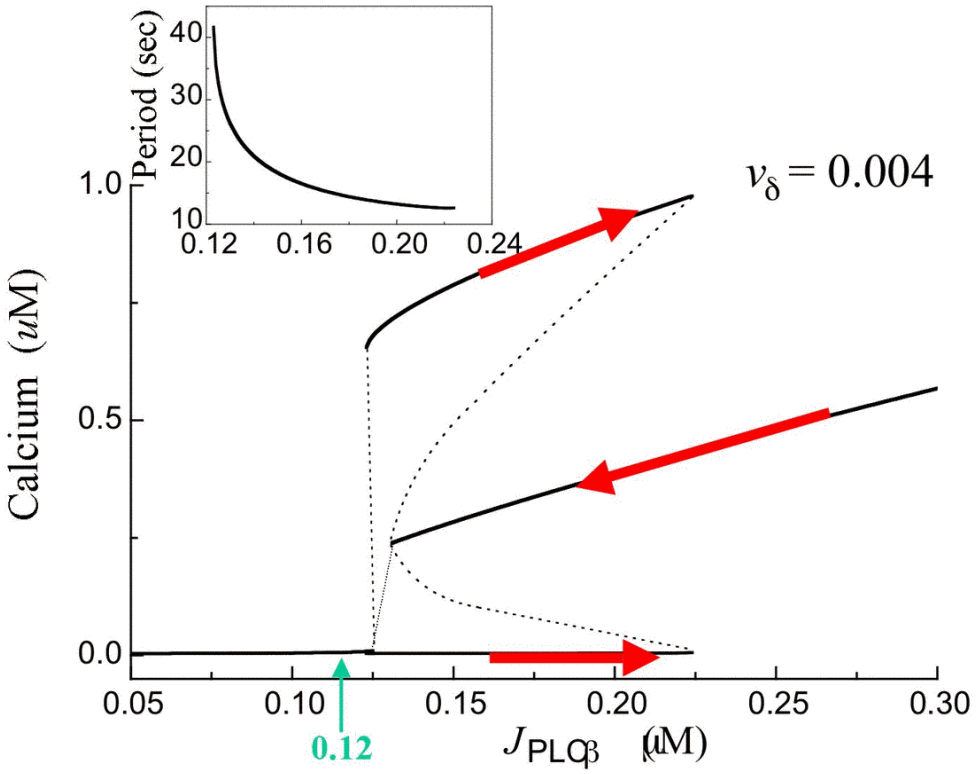
$$v_\delta = 0.004\,\mu\text{M/sec}$$

$$\gamma = 0.05\,\mu\text{M/sec}$$

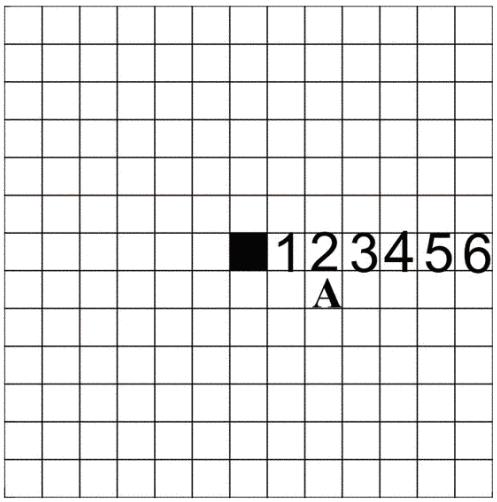


$J_{\text{PLC}\beta}$ is a constant which is determined by the applied bath.

Point model



Glial Cell Networks



Networks:
13×13 **cells**

Each cell:
$24\mu\text{m} \times 24\mu\text{m}$

No-flux boundary

$D_{Ca} = 20.0\mu m^2 / \text{sec}$

$D_{IP3} = 280.0\mu m^2 / \text{sec}$

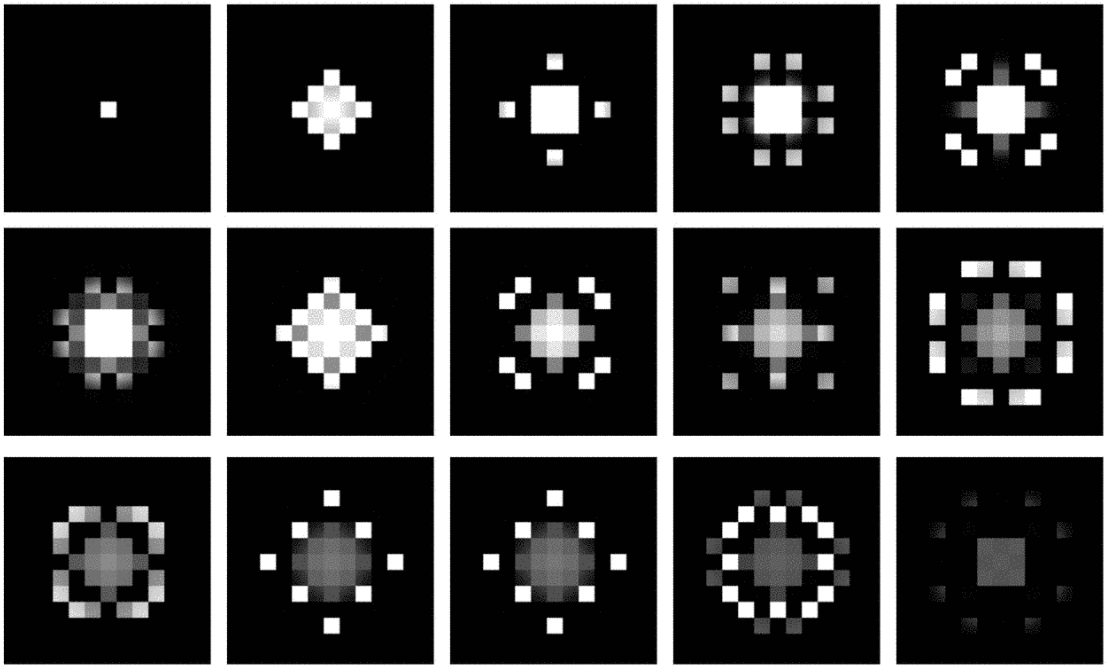
$P_{IP3} = 0.50\mu m / \text{sec}$

IP3 Gap junction diffusion:

$$-D_{IP3}\left.\frac{\partial I}{\partial x}\right|_{x=\xi} = P_{IP3}[I(\xi^-, y, t) - I(\xi^+, y, t)]$$

Simulation Results

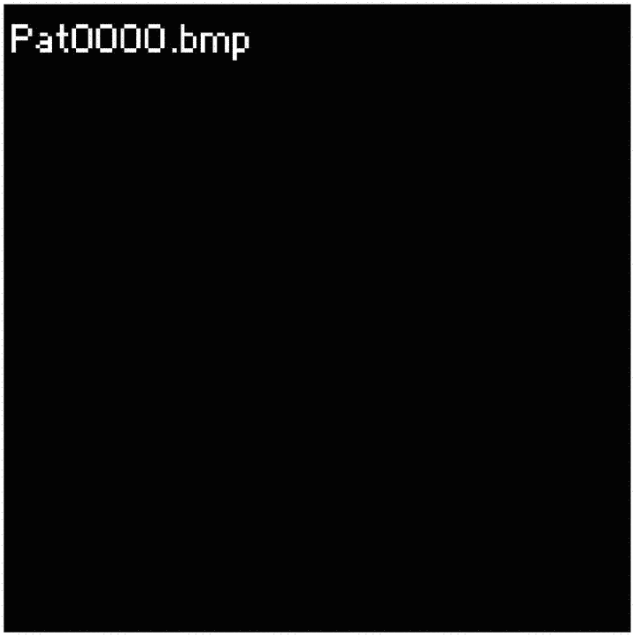
Mechanical Stimulation

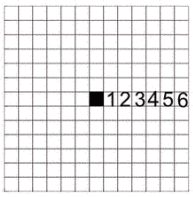


dt = 10 sec

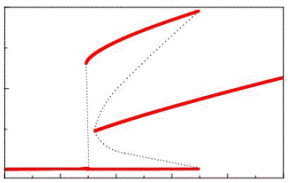
Mechanical stimulation

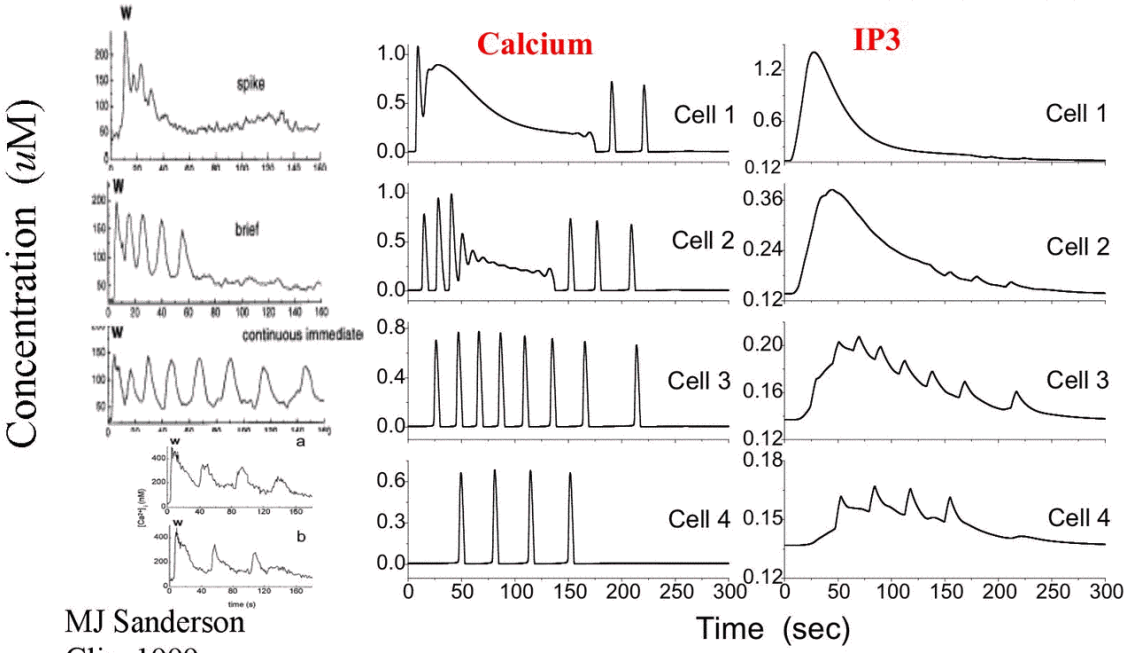
Simulation movie





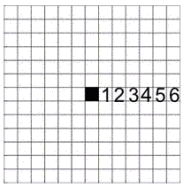
Trajectories

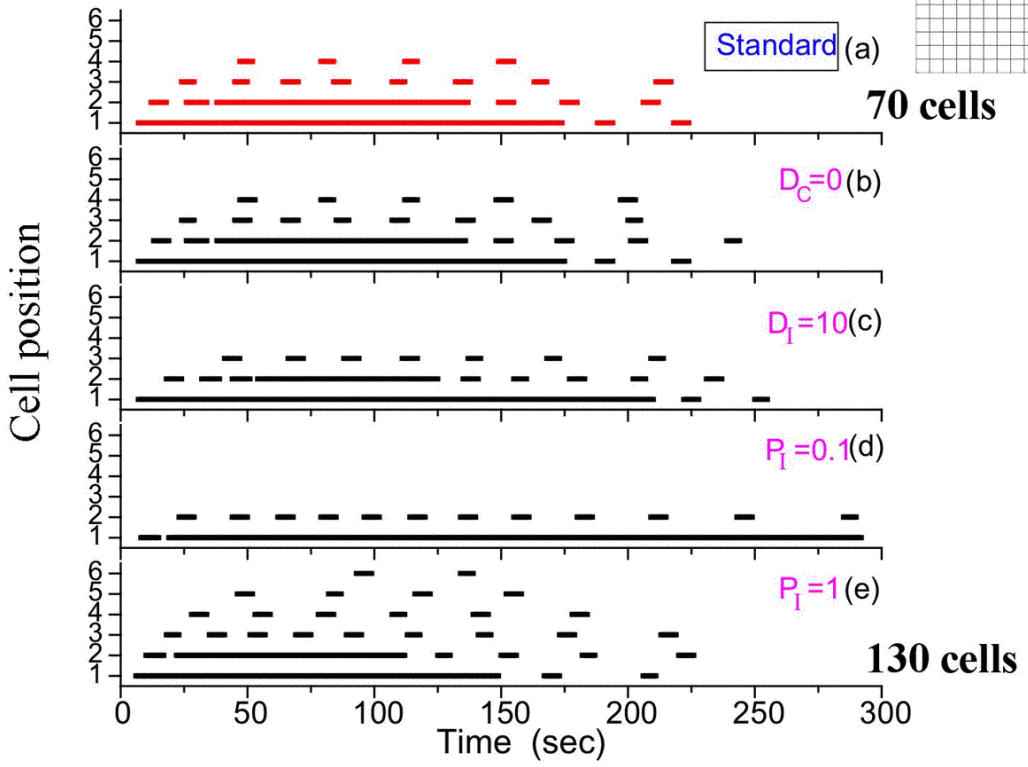


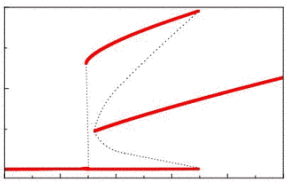


MJ Sanderson
Glia, 1999

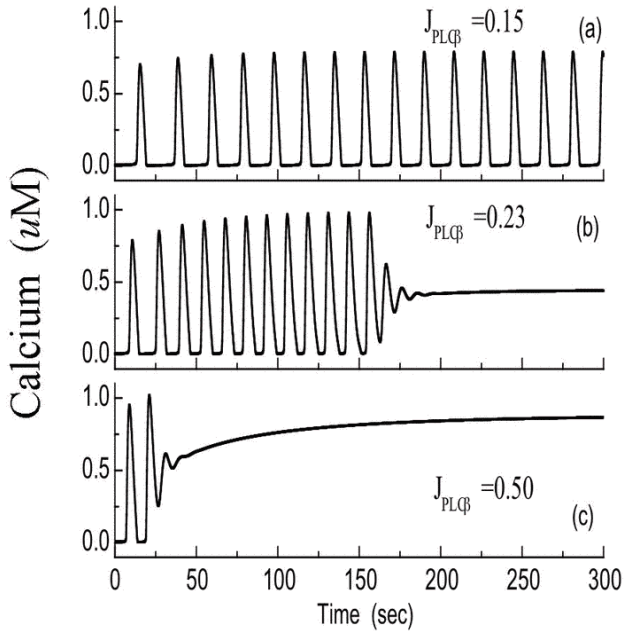
Effect of diffusion parameters on waves

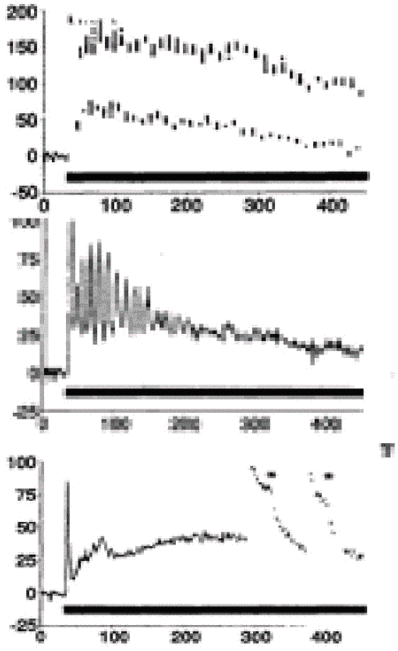




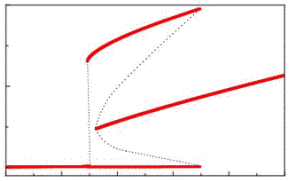


Glutamate application

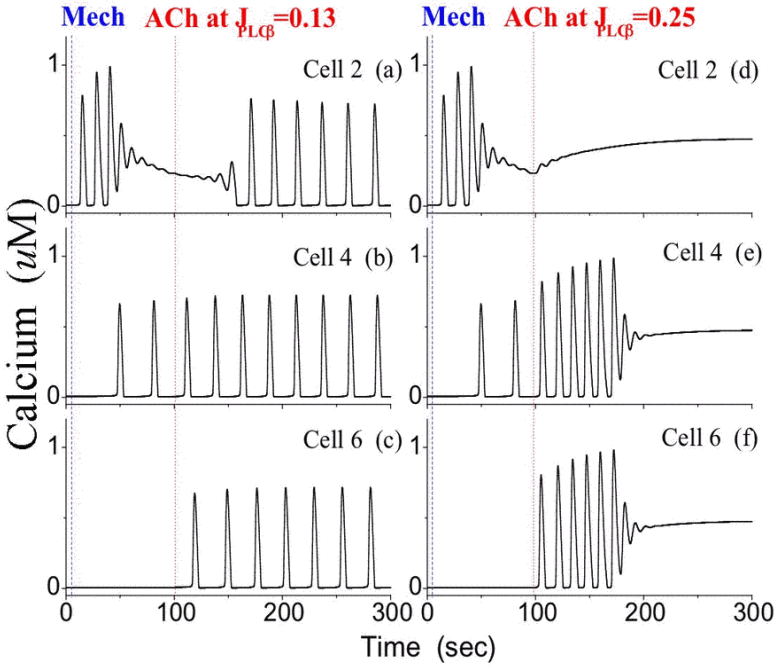


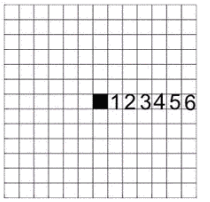


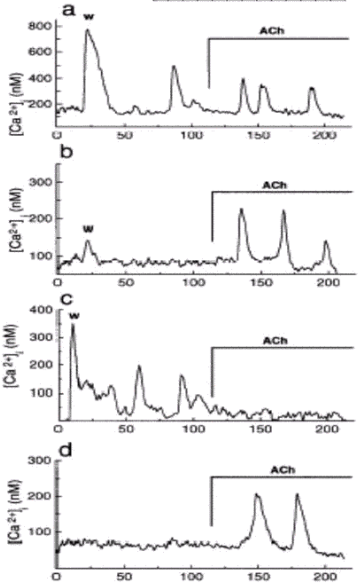
AH Cornell-Bell, et al. Science 1990



Mechanical stimulation followed by ACh



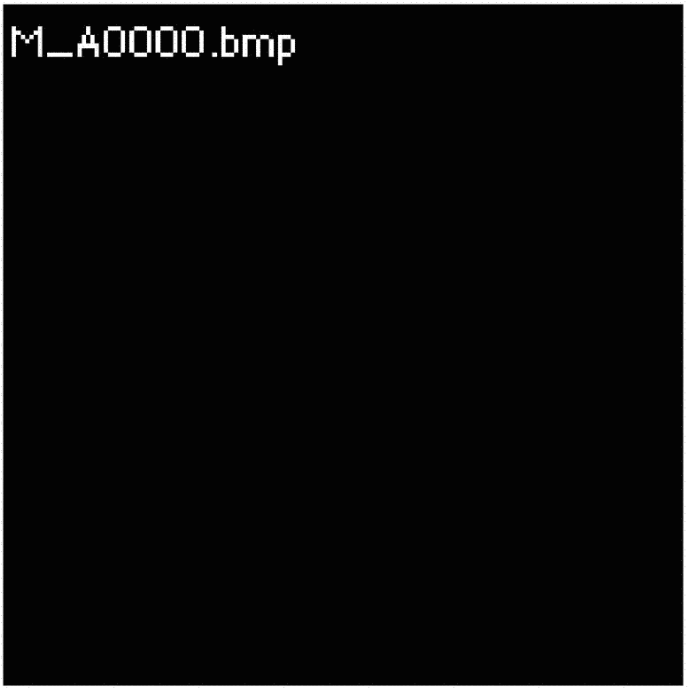


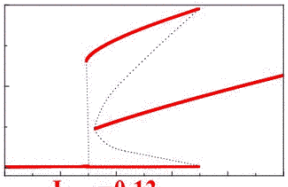


MJ Sanderson, Glia. 1999

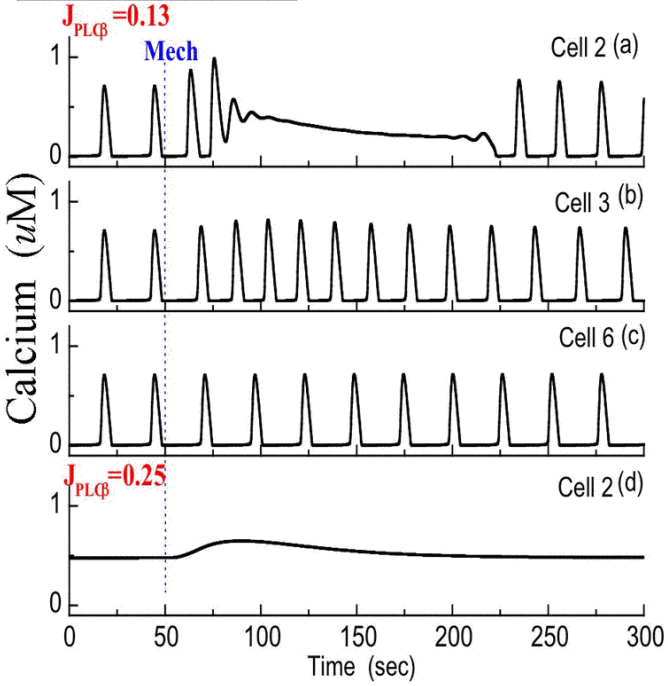
Mechanical stimulation followed by Ach

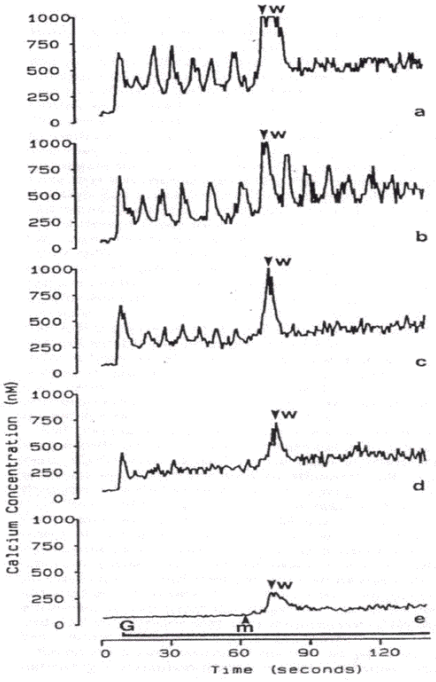
Simulation movie





Glutamate followed by Mechanical stimulation

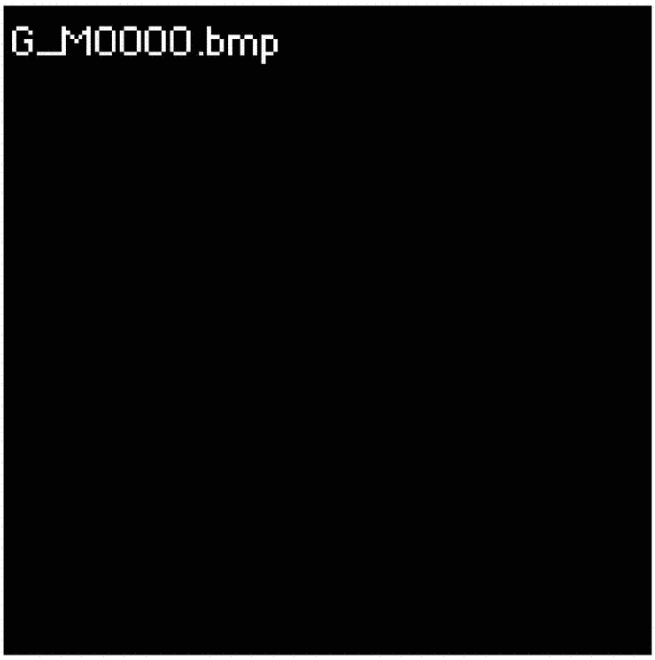




AC Charles, et al, Neuron 1991

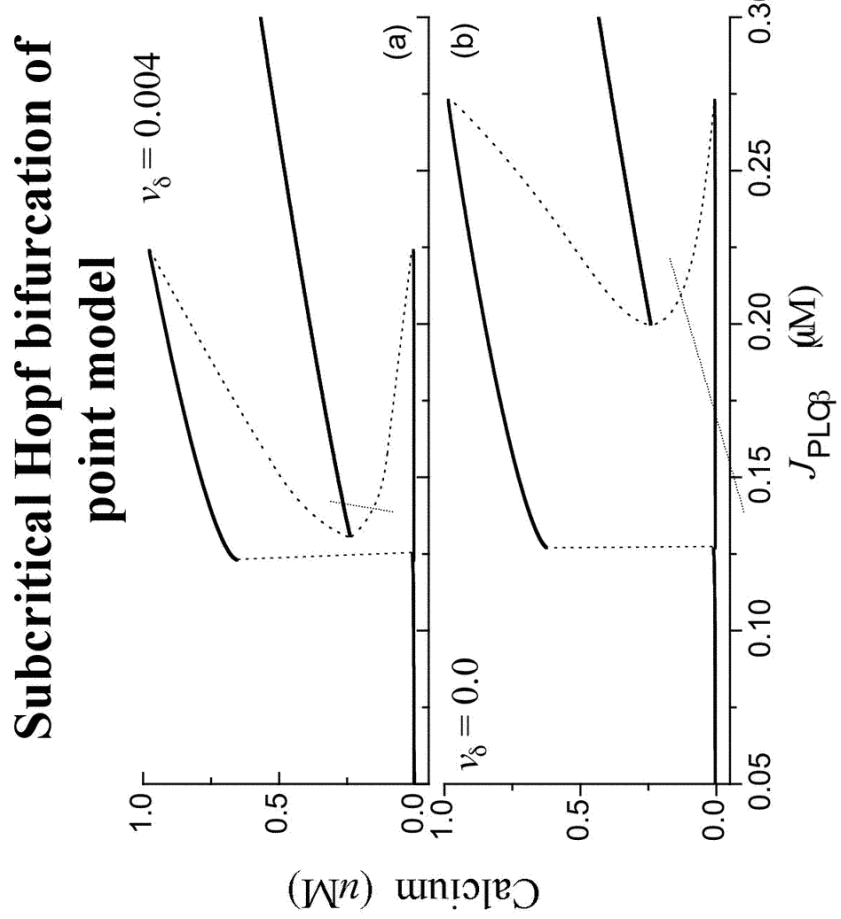
Glutamate followed by Mechanical stimulation

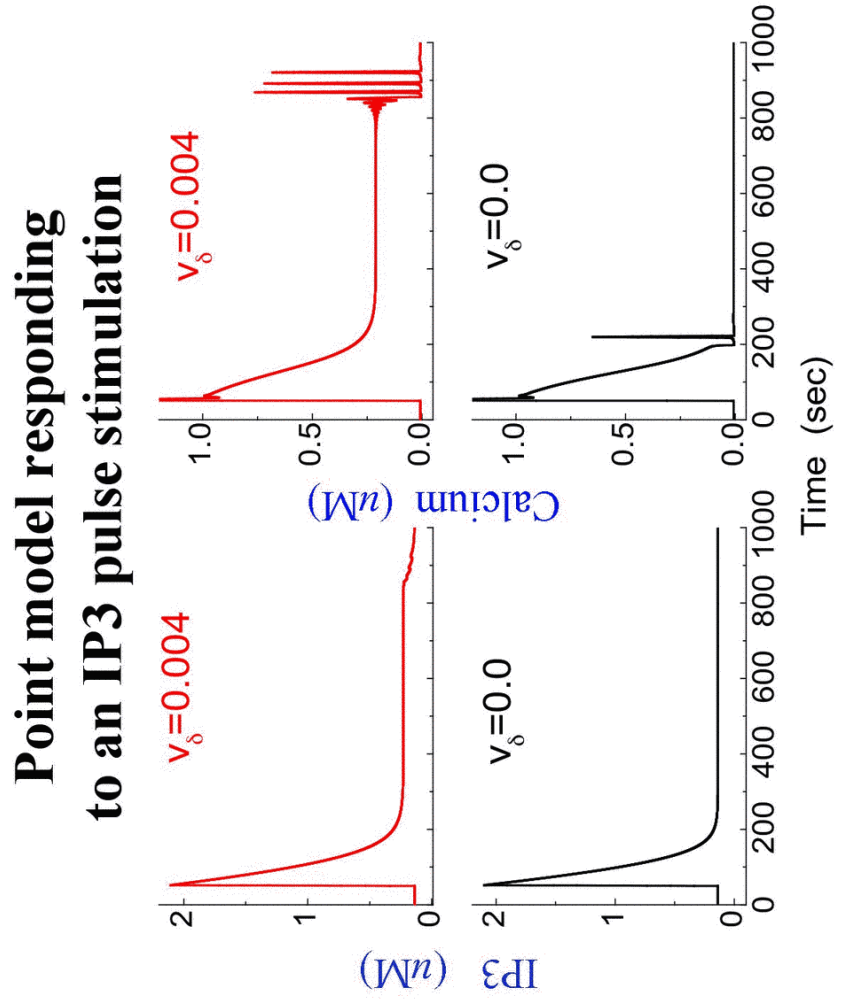
Simulation movie



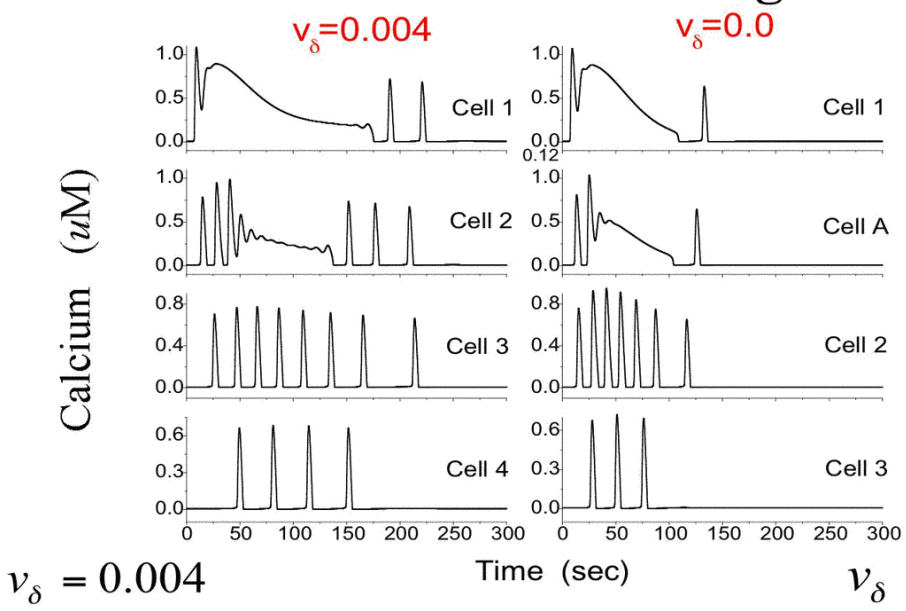
Predictions

- A small **Calcium-induced IP3 generation** term is required
  - To cause a prolonged wave responding to the mechanical stimulation.
  - To generate a large bistable regime.
- The **bistable dynamics** is predicated
  - To generate a prolonged Ca2+ plateau in the cells nearby the mechanically stimulated cell.


Subcritical Hopf bifurcation of point model
$\nu_\delta = 0.004$
$\nu_\delta = 0.0$
(a)
(b)
Calcium (μM)
1.0
0.5
0.0
0.05
0.10
0.15
0.20
0.25
0.30
$J_{PLC\beta}$ (μM)


Point model responding to an IP3 pulse stimulation
v_δ=0.004
v_δ=0.0
Calcium (μM)
IP3 (μM)
Time (sec)
0
200
400
600
800
1000
1.0
0.5
0.0
2
1

Effect of Ca2+ induced IP3 generation



$v_\delta = 0.004$

Duration of responding Ca2+ signals is 230 sec; Duration of high Ca2+ plateau is 170 sec.

$v_\delta = 0.0$

Duration of responding Ca2+ signal is 140 sec; Duration of high Ca2+ plateau is 110 sec.

Conclusions

- Proposed a glial cell network model with IP3 diffusion between cells.
- Reproduced the experimental results with four different types of stimulations.
- A **small calcium-induced IP3 generation** term is required in glial cell model.
- The glial cell model has a large regime of **bistable dynamics** with subcritical Hopf bifurcation.

Thanks

Prof. Peter Jung

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S. Nadkarni
S. Zeng

NSF