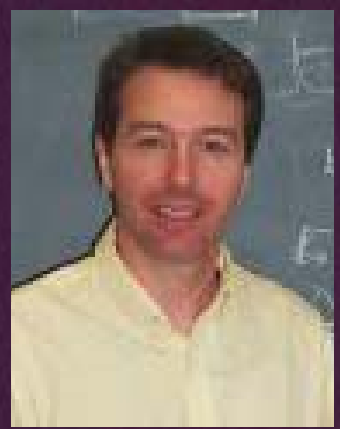
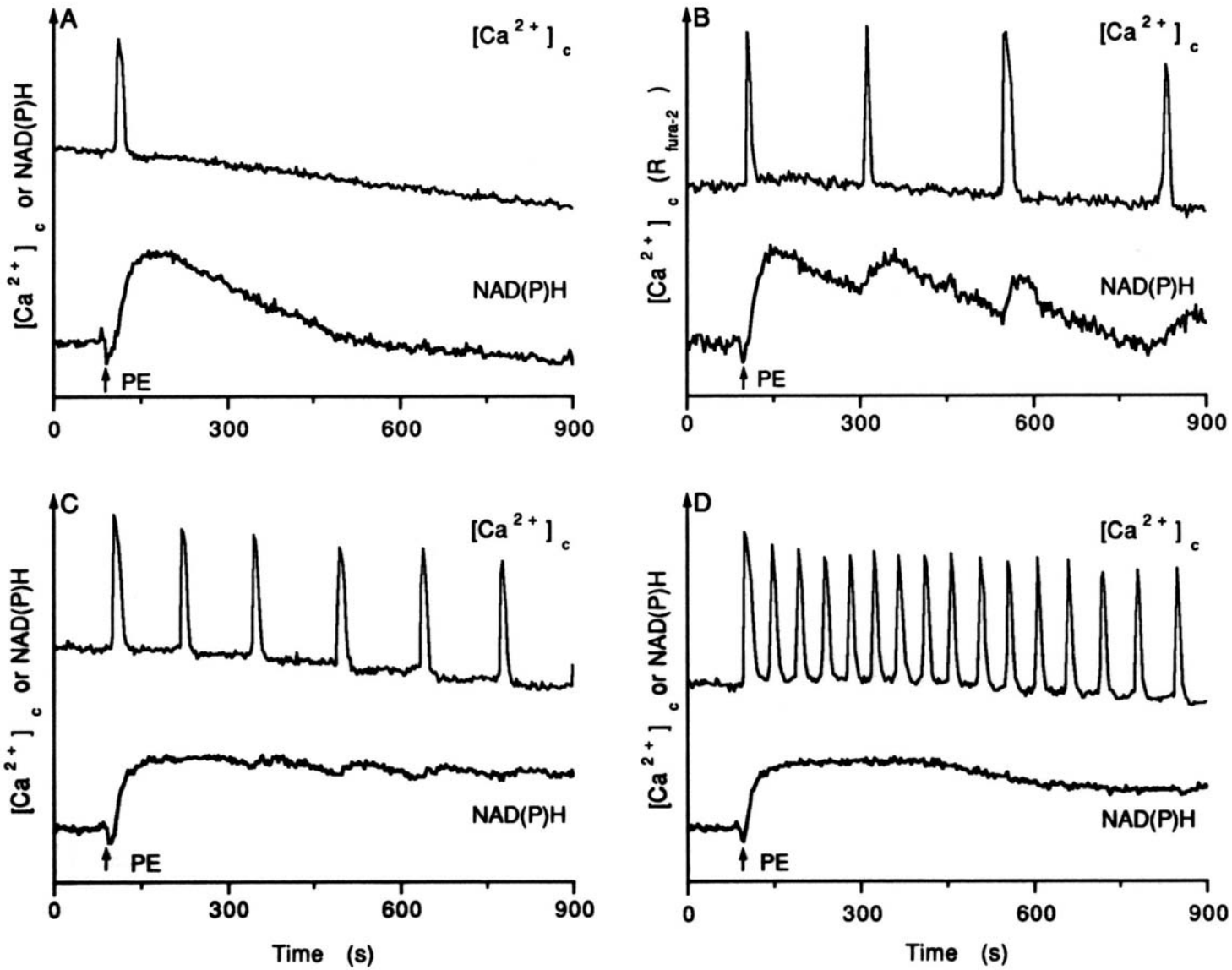
Coupled Oscillations of Calcium and IP3: Identification of Feedback Loops

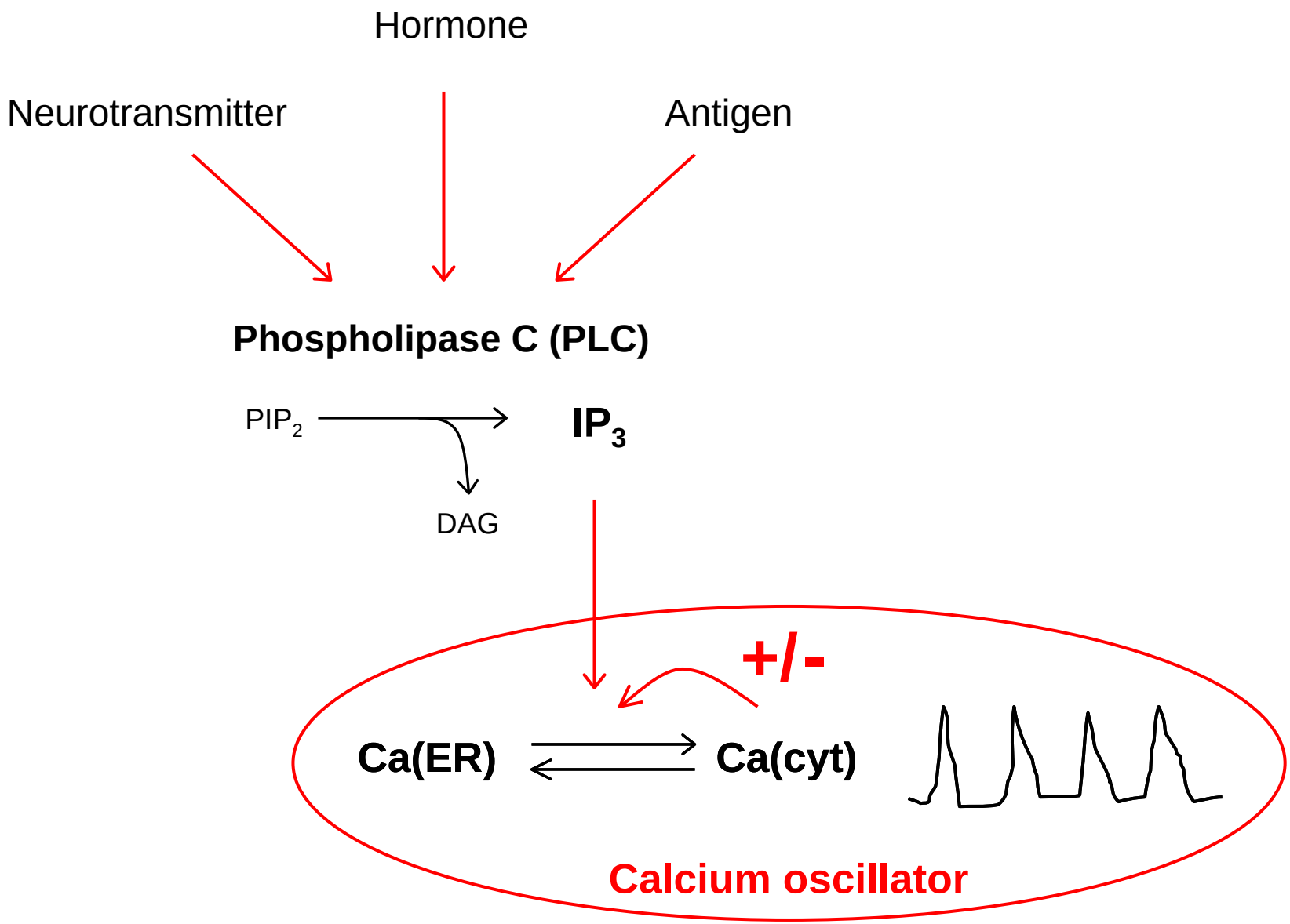
Antonio Politi



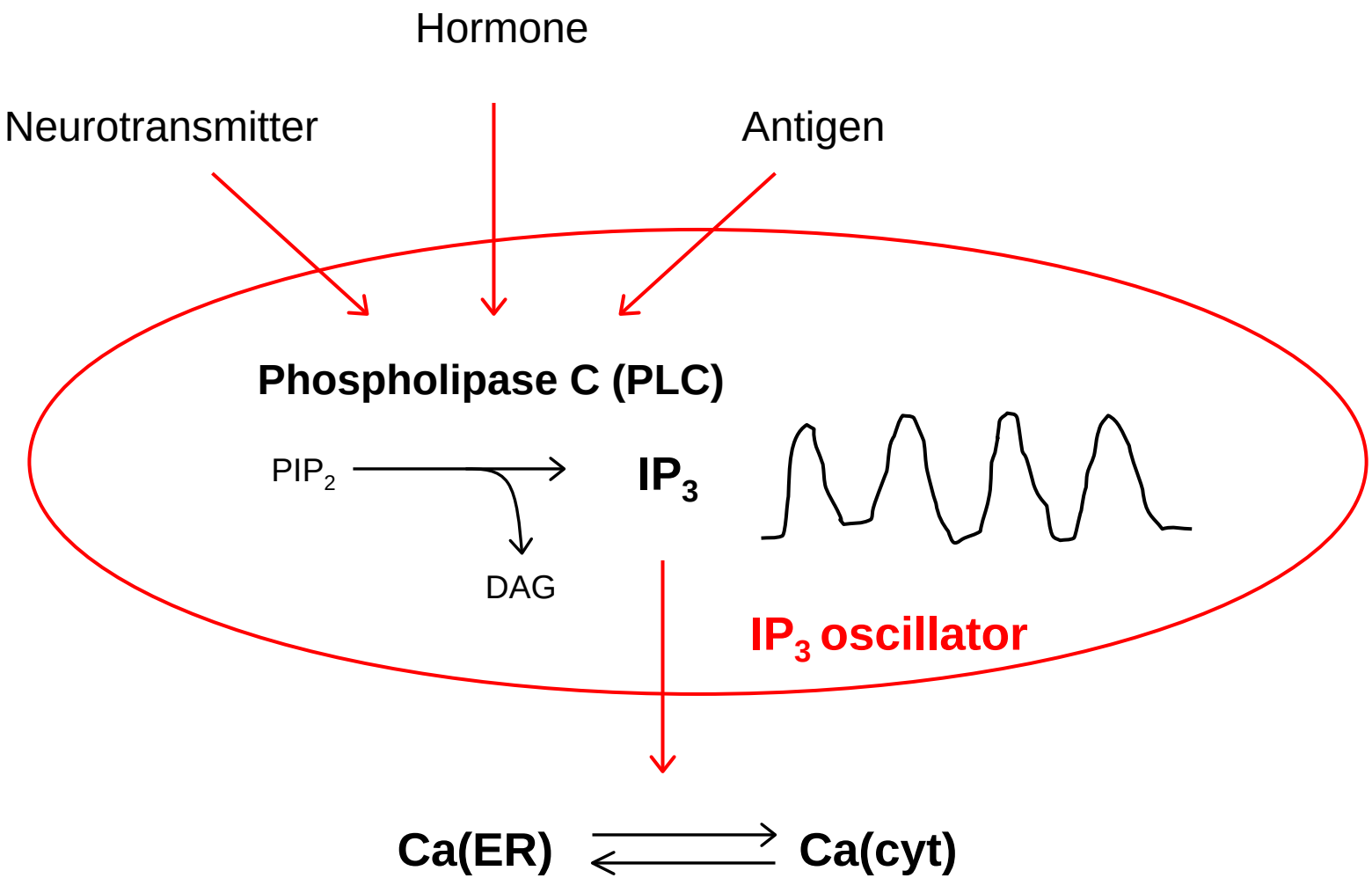
with Andrew Thomas
& Larry Gaspers
New Jersey Med School

Frequency-modulated Ca^{2+} oscillations and control of metabolism in hepatocytes

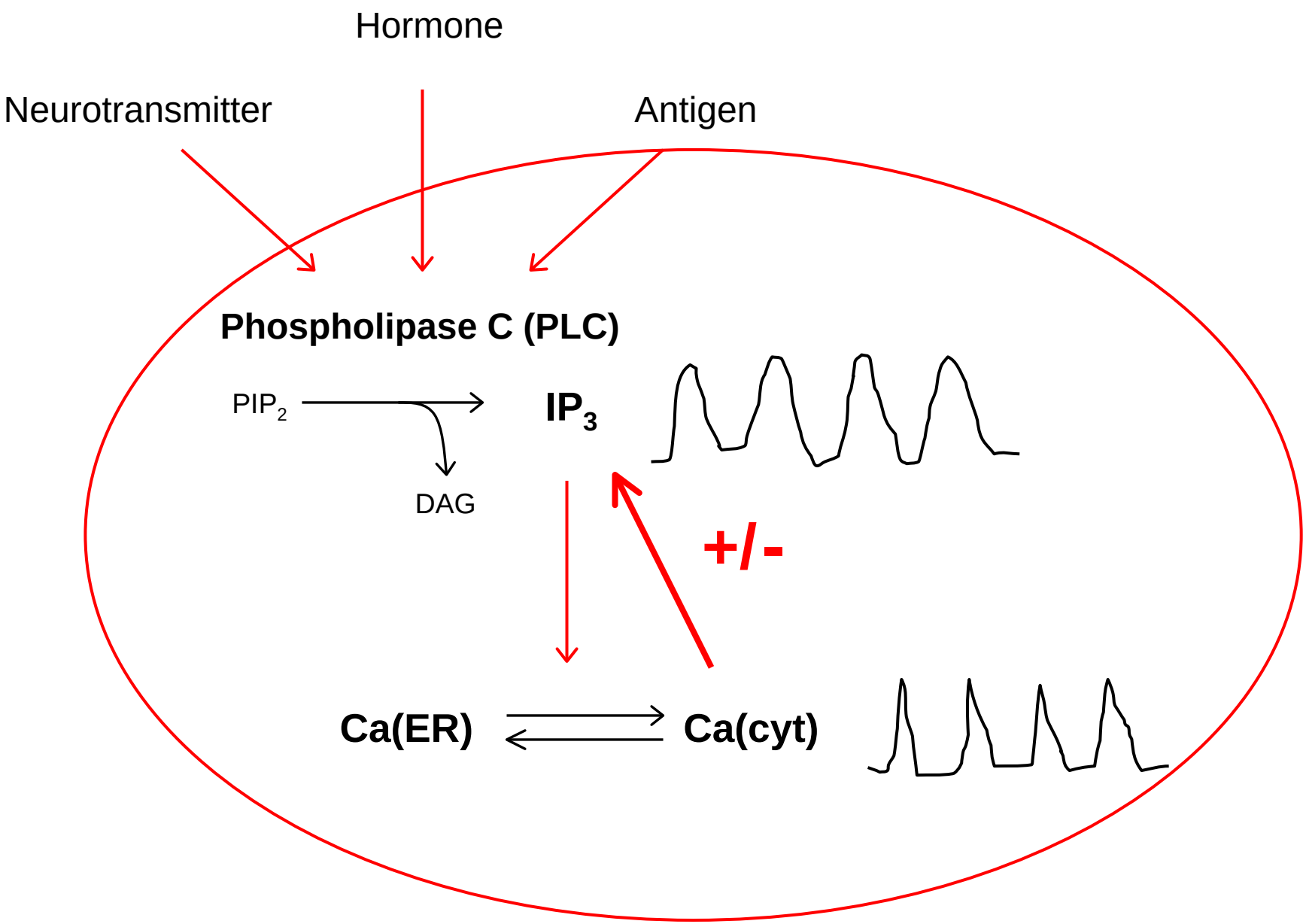




Schuster, Marhl & Höfer, Eur. J. Biochem. (2002)



Schuster, Marhl & Höfer, Eur. J. Biochem. (2002)



Schuster, Marhl & Höfer, Eur. J. Biochem. (2002)

Ca elevates IP3

Haratoonian et al. (1991)

Venance et al. (1997)

Models for Ca/IP3 wave propagation

Höfer, Venance and Giaume (2002)

Dupont and Dummollard (2004)

Wagner et al. (2004)

Models with IP3 oscillations

Meyer and Stryer (1988)

Cuthbertson and Chay (1991)

Kummer et al. (2000)

Dupont and Erneux (1997)

Dupont et al. (2003)

Experiment: IP3/PIP2 oscillate

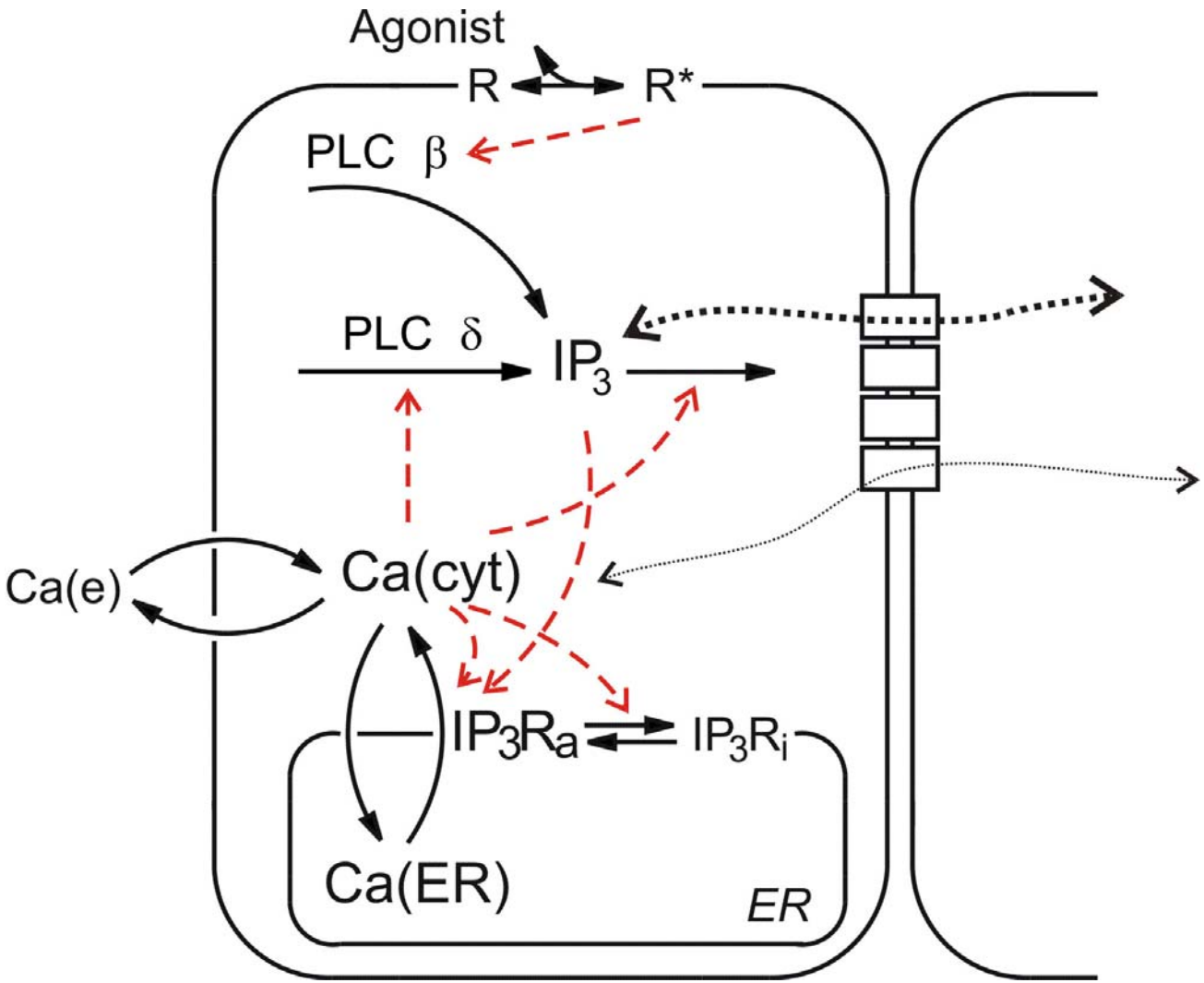
Hirose et al. (1999)

Nash et al. (2000)

Young et al. (2003)

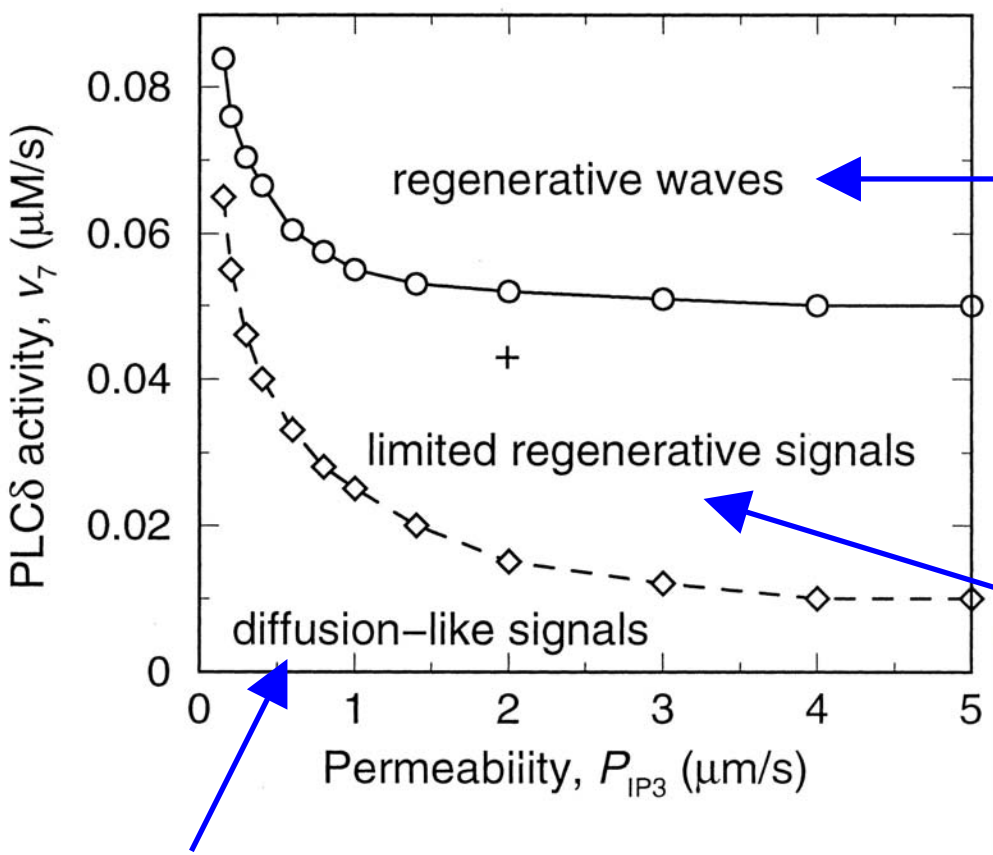
Thore et al. (2004)

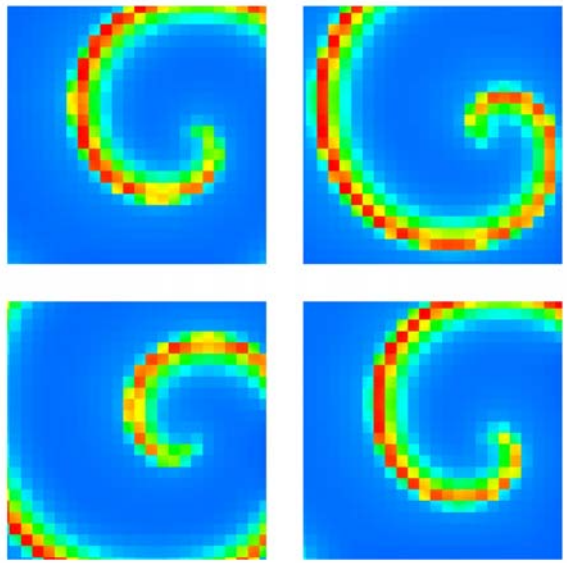
Is dynamic IP3 essential for the calcium oscillator?

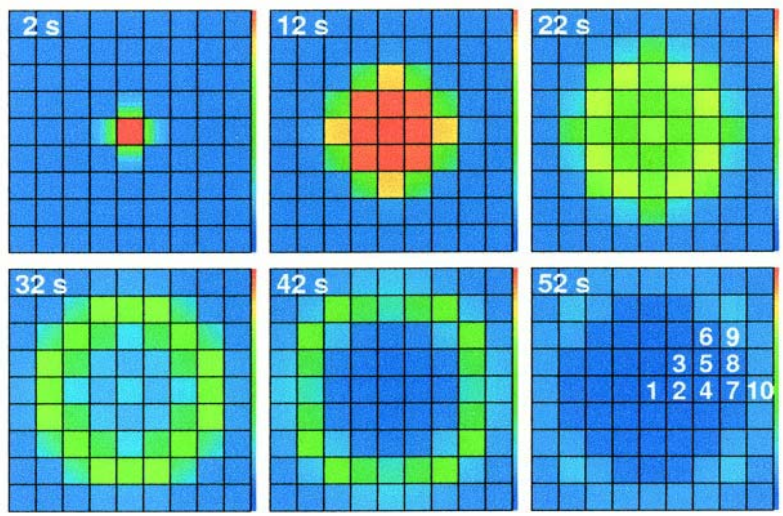


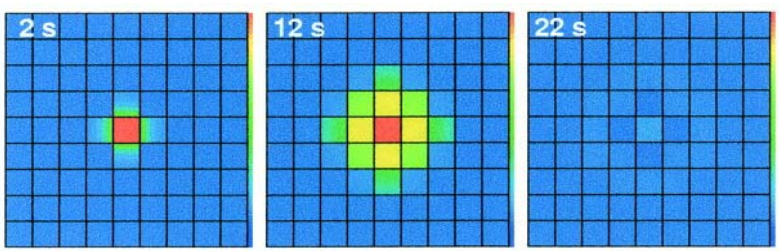
Höfer, Venance & Giaume J. Neurosci. (2002)

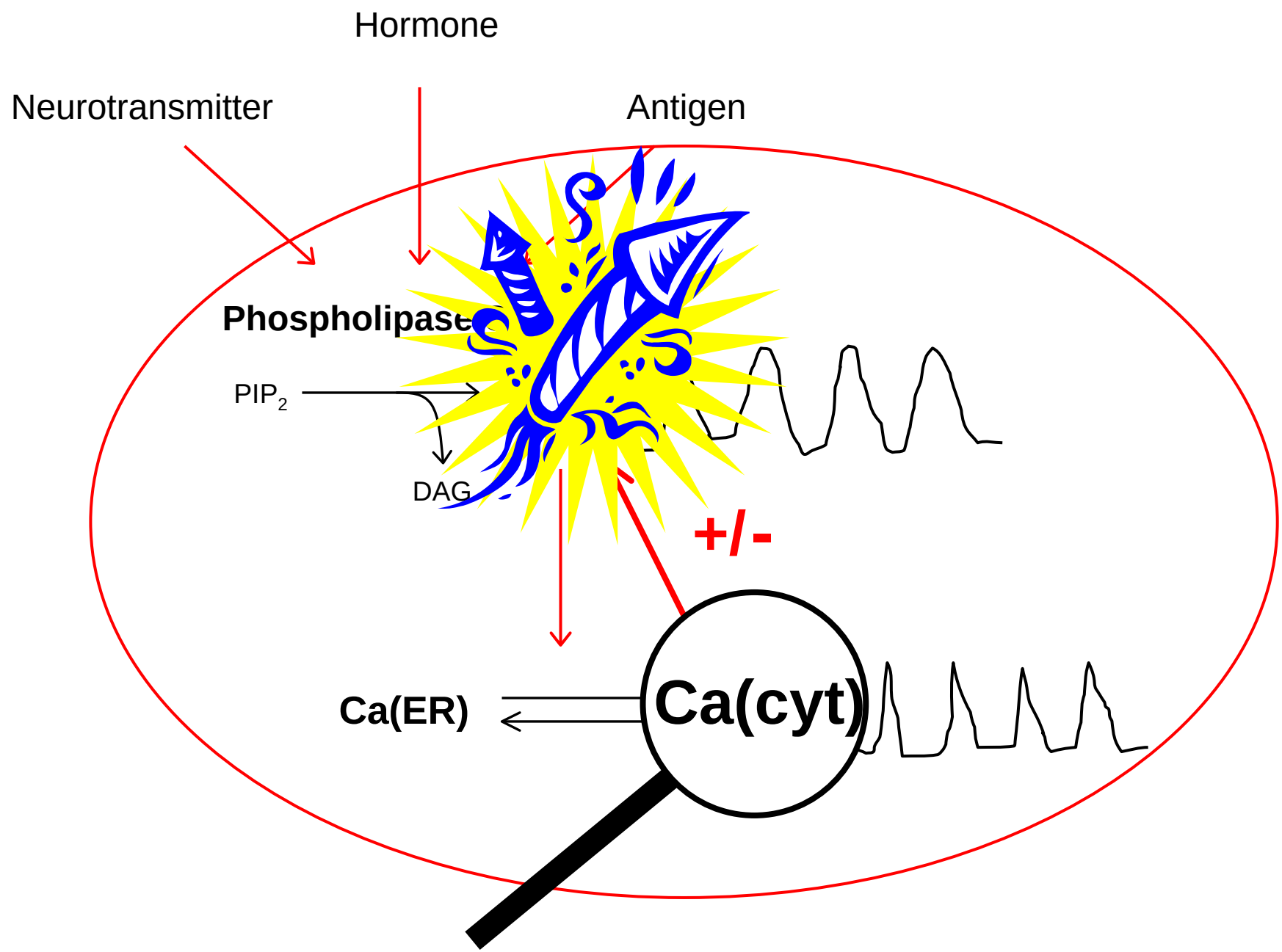
3 modes of intercellular signaling







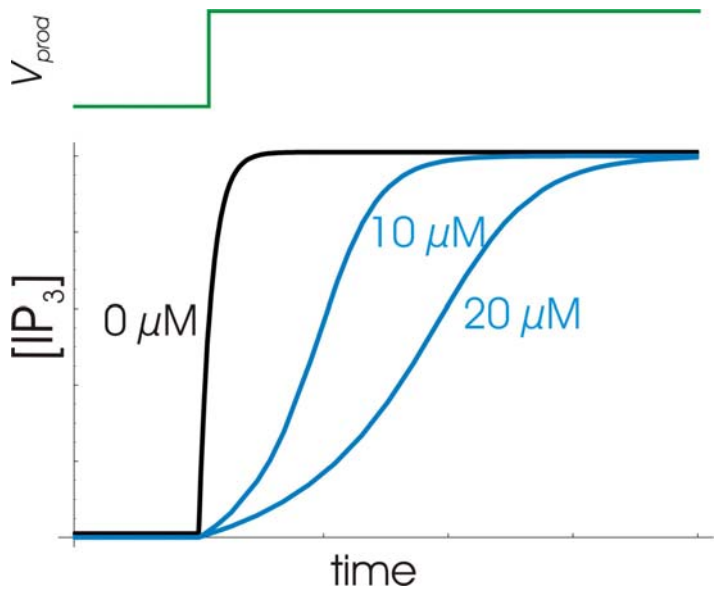



Hormone
Neurotransmitter
Antigen
Phospholipase
PIP2
DAG
+/-
Ca(ER)
Ca(cyt)

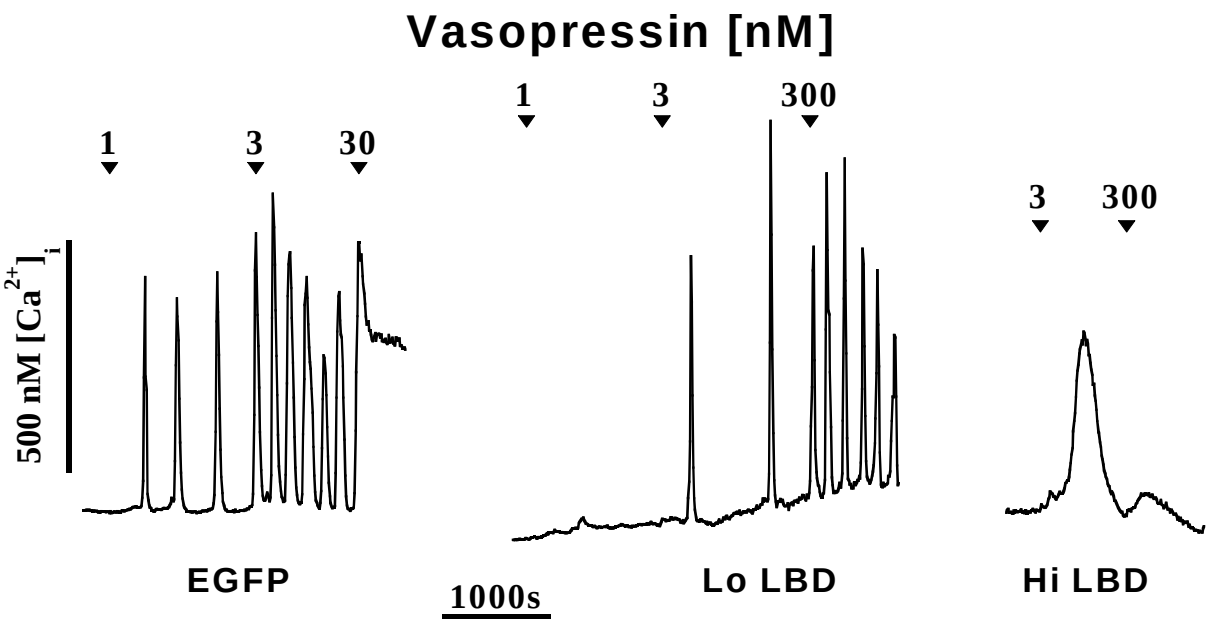
Slowing IP3 turnover with a buffer protein

$$\frac{d[IP_3]}{dt} = \frac{1}{\tau_P}\left(V_{prod} - V_{deg}\right)$$

$$\tau_P = \frac{1}{k_P}\left(1 + \frac{K_d B_T}{(K_d + [IP_3])^2}\right)$$



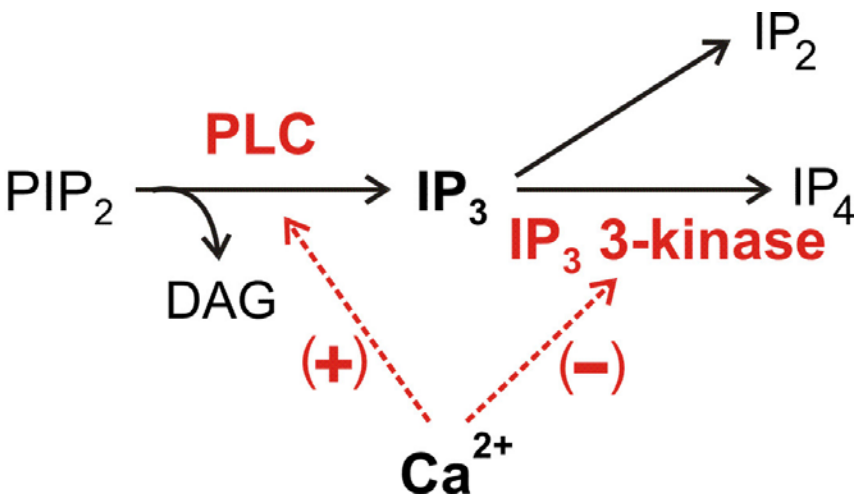
Response to IP3 buffer in hepatocytes

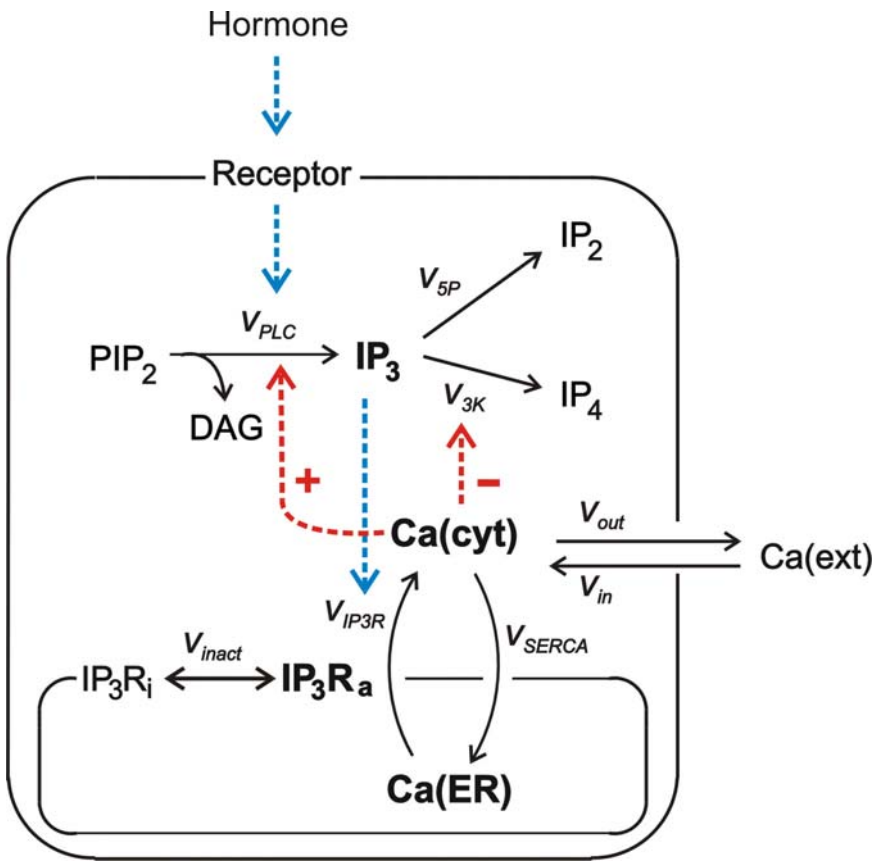


How are IP3 oscillations mediated?

Do they serve a function?

Negative and positive feedbacks of calcium on IP3





Ca^{2+} activation of PLC

$$\frac{dp}{dt} = \frac{1}{\tau_p}\left[v_{PLC,1} + v_{PLC,2}\frac{c^2}{K_{PLC}^2 + c^2} - p \right]$$

Ca activation

$$\frac{dc}{dt} = \frac{1}{\tau_c}\left[\left(\frac{(rpc)^3}{(K_p + p)^3 (K_a + c)^3} + k_2 \right)(c_{ER} - c) - v_S \frac{c^2}{K_S^2 + c^2} \right]$$

$$\frac{dr}{dt} = \frac{1}{\tau_r}\left[1 - (1 + c/K_i)r\right]$$

$$W_c\, c + W_{ER}\, c_{ER} = n_{tot}$$

Ca^{2+} activation IP_3 3-kinase

$$\frac{dp}{dt} = \frac{1}{\tau_p}\left[v_{PLC,1} - \left(1 - \eta + \eta \frac{c^2}{K_{3K}^2 + c^2} \right) p \right], \quad 0 \le \eta \le 1$$

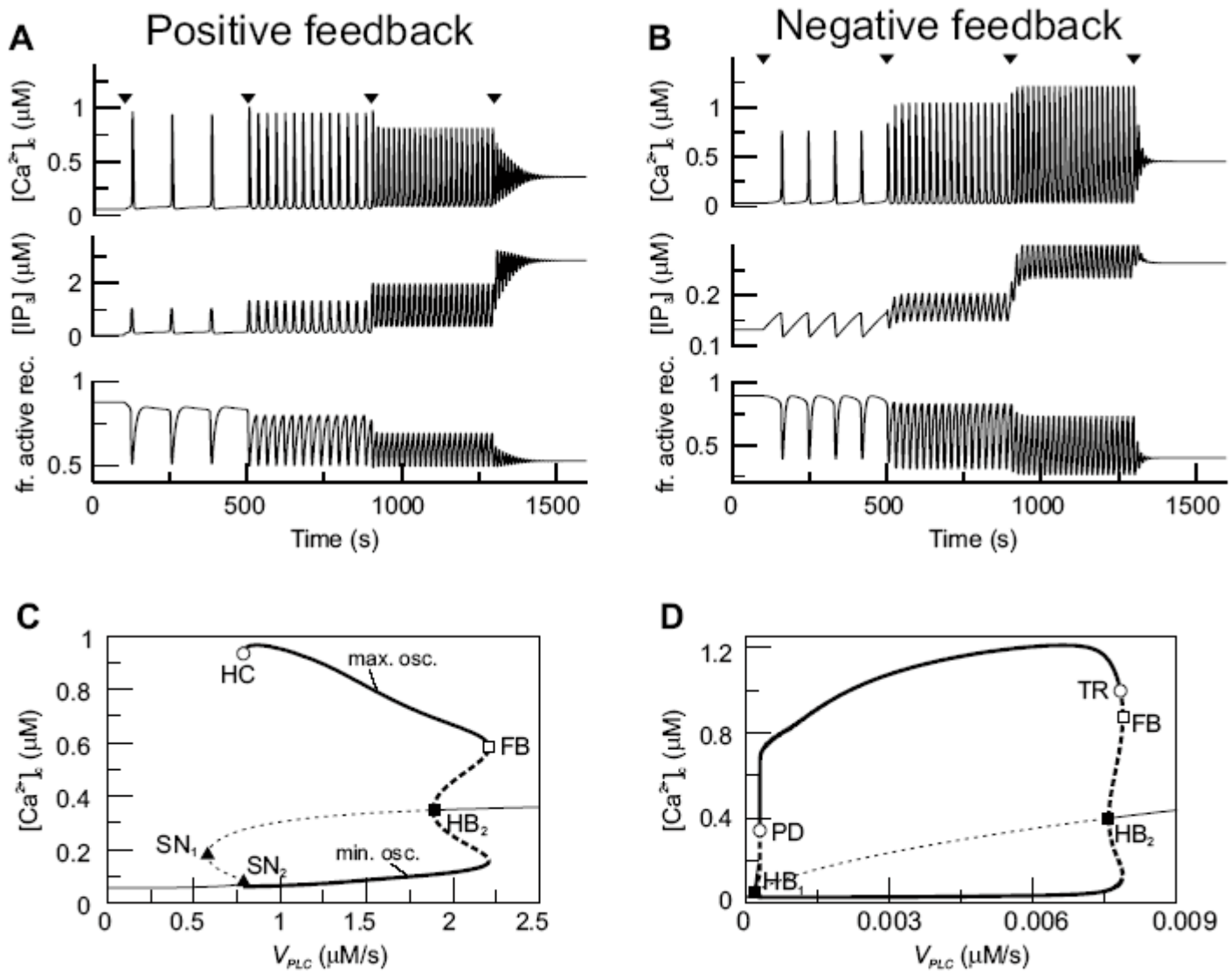
Ca activation

$$\frac{dc}{dt} = \frac{1}{\tau_c}\left[\left(\frac{(rpc)^3}{(K_p + p)^3 (K_a + c)^3} + k_2 \right)(c_{ER} - c) - v_S \frac{c^2}{K_S^2 + c^2} \right]$$

$$\frac{dr}{dt} = \frac{1}{\tau_r}\left[1 - (1 + c/K_i) r \right]$$

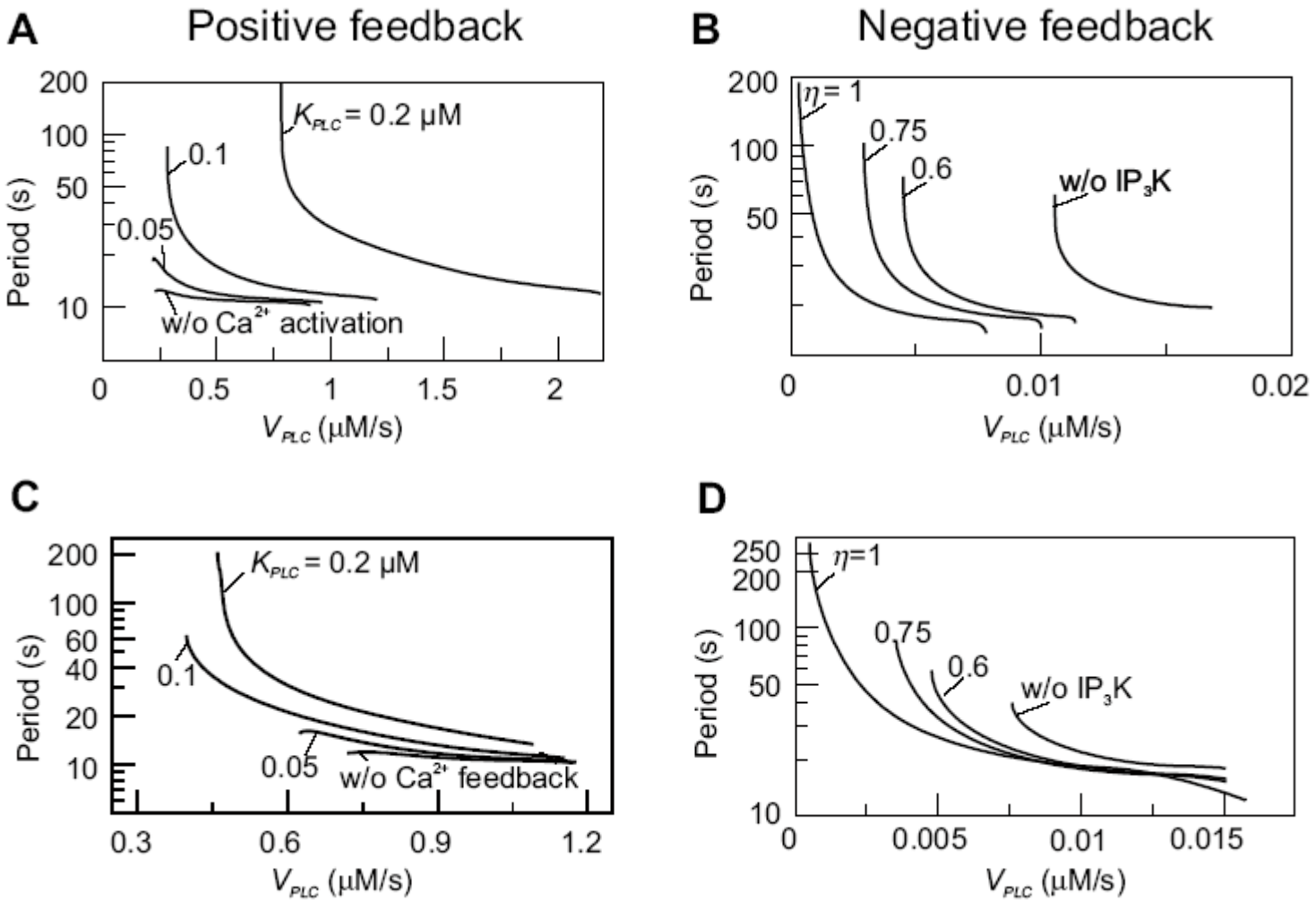
$$W_c\, c + W_{ER}\, c_{ER} = n_{tot}$$

Agonist

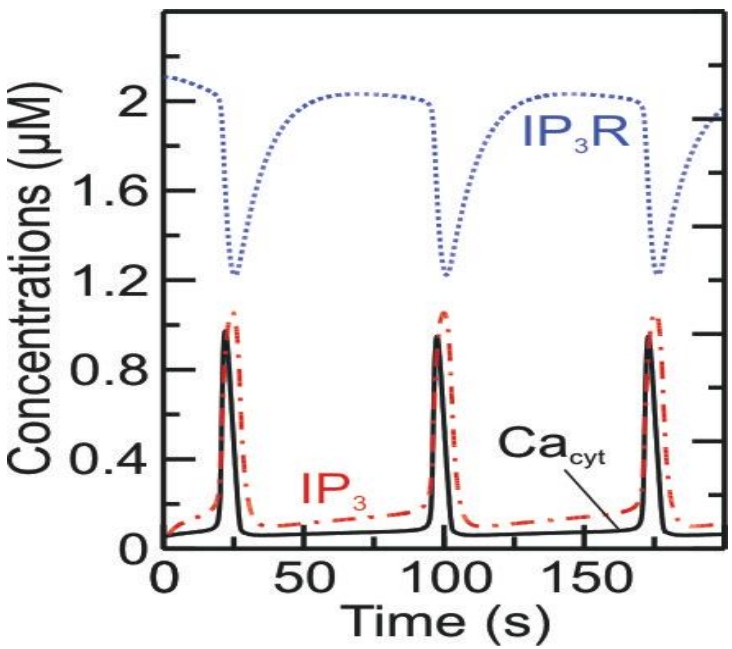

A
Positive feedback
B
Negative feedback
[Ca2+]c (μM)
[IP3] (μM)
fr. active rec.
Time (s)
C
D
HC
max. osc.
FB
HB2
SN1
SN2
min. osc.
TR
PD
HB1
VPLC (μM/s)

Feedbacks support frequency encoding of hormone dose

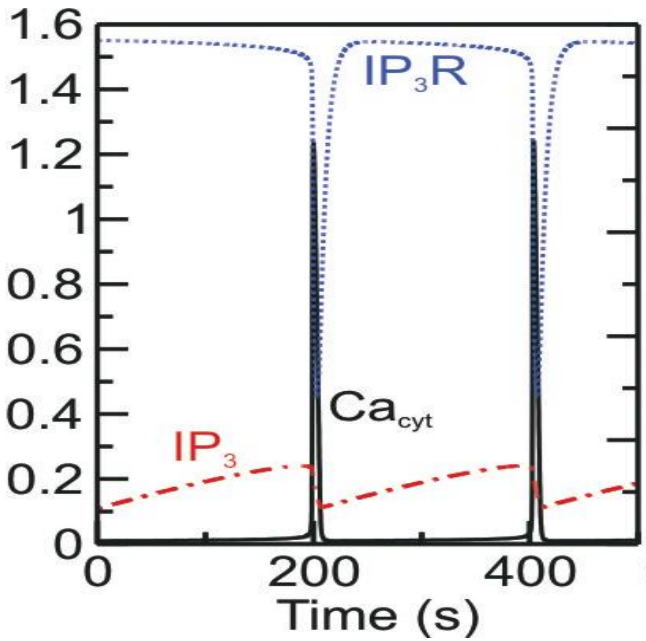
With Ca^{2+}
PM fluxes



Positive feedback

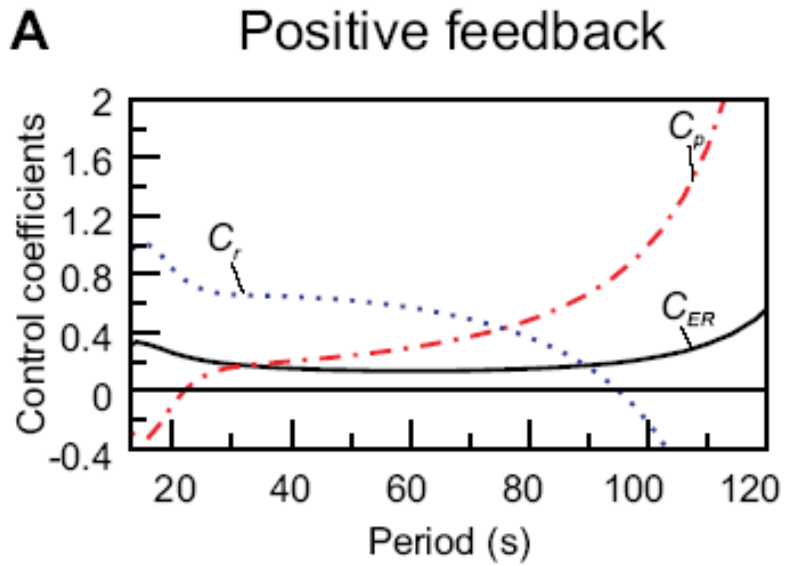


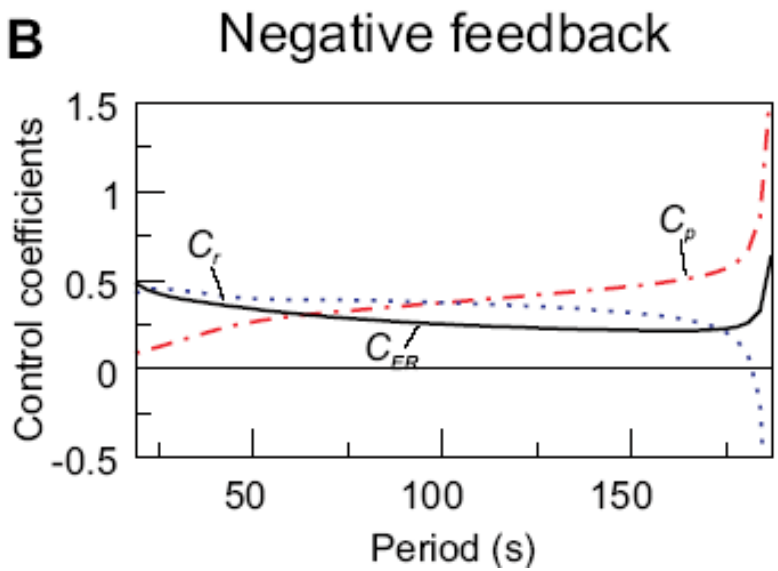
Negative feedback

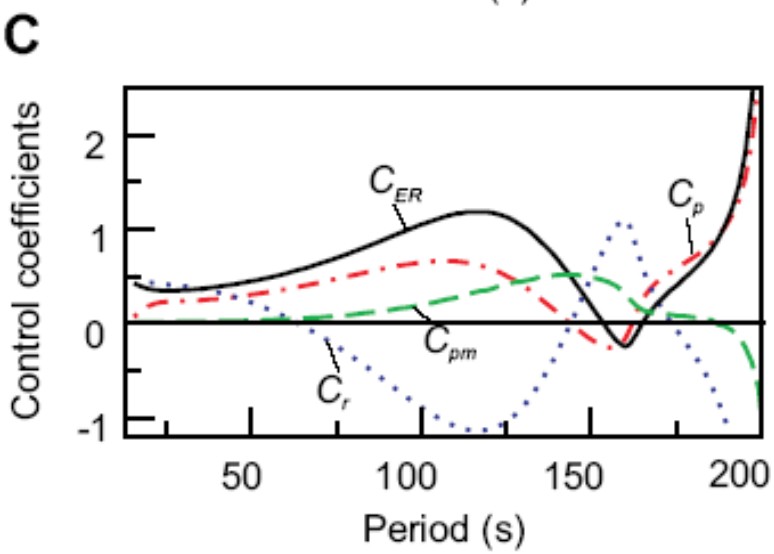


Period control

$$C_i^T = \frac{\partial \ln T}{\partial \ln \tau_i}$$



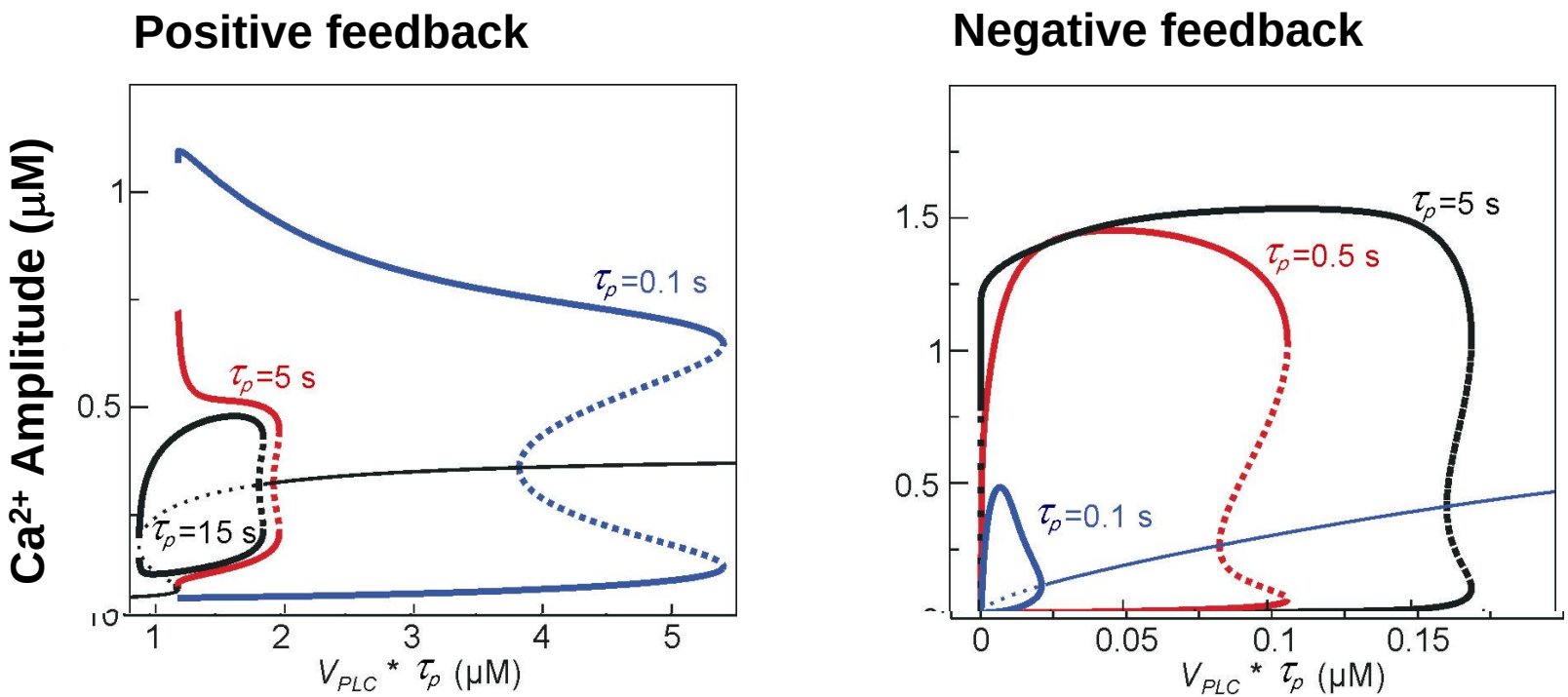




With Ca^{2+}

PM fluxes

Sensitivity to IP3 turnover differs

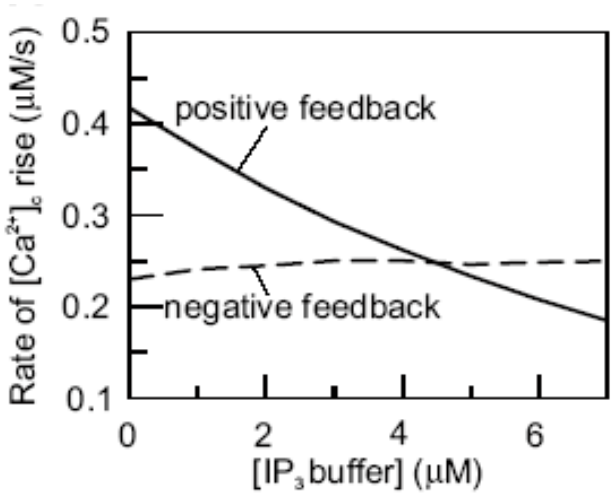


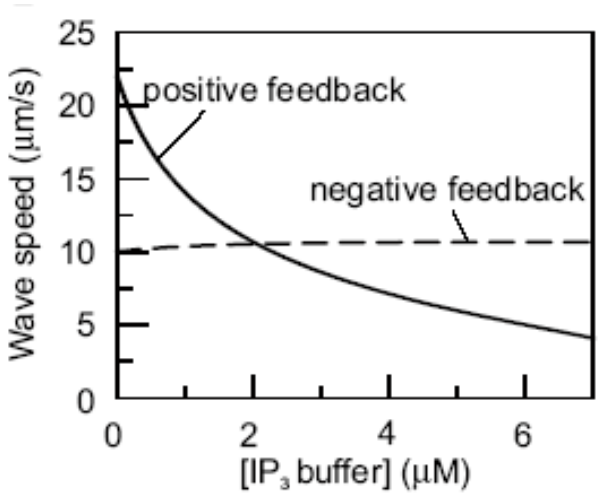
Agonist stimulus ⟶

Range of oscillations for fast, intermediate, slow IP_3 turnover

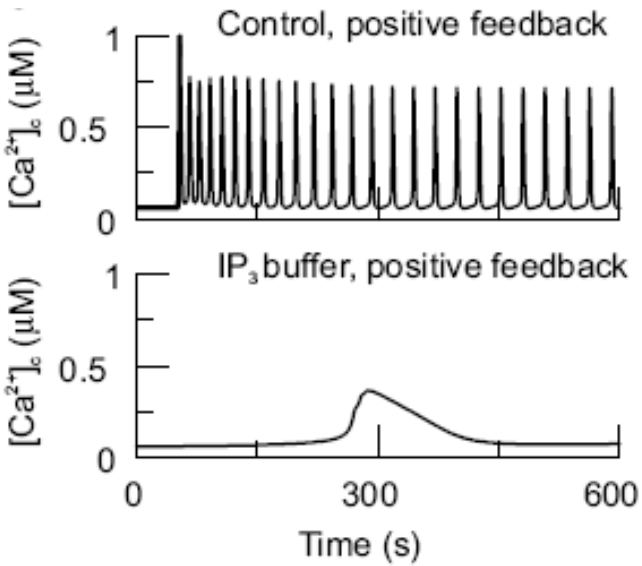
IP_3 buffer affects Ca^{2+} oscillations differently in the positive and negative feedback models

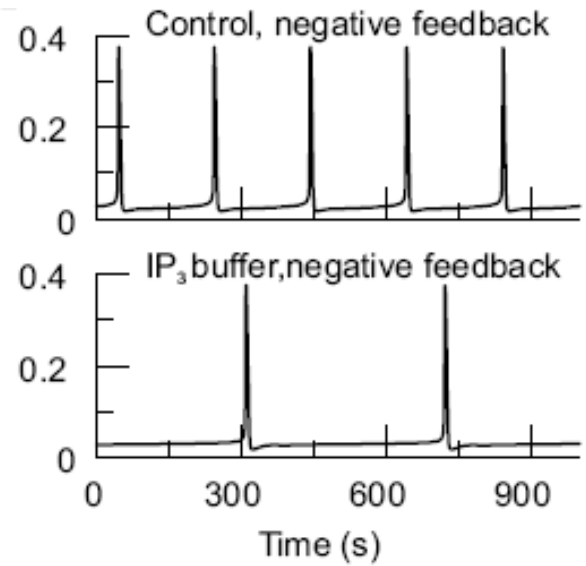
Low IP_3 buffer



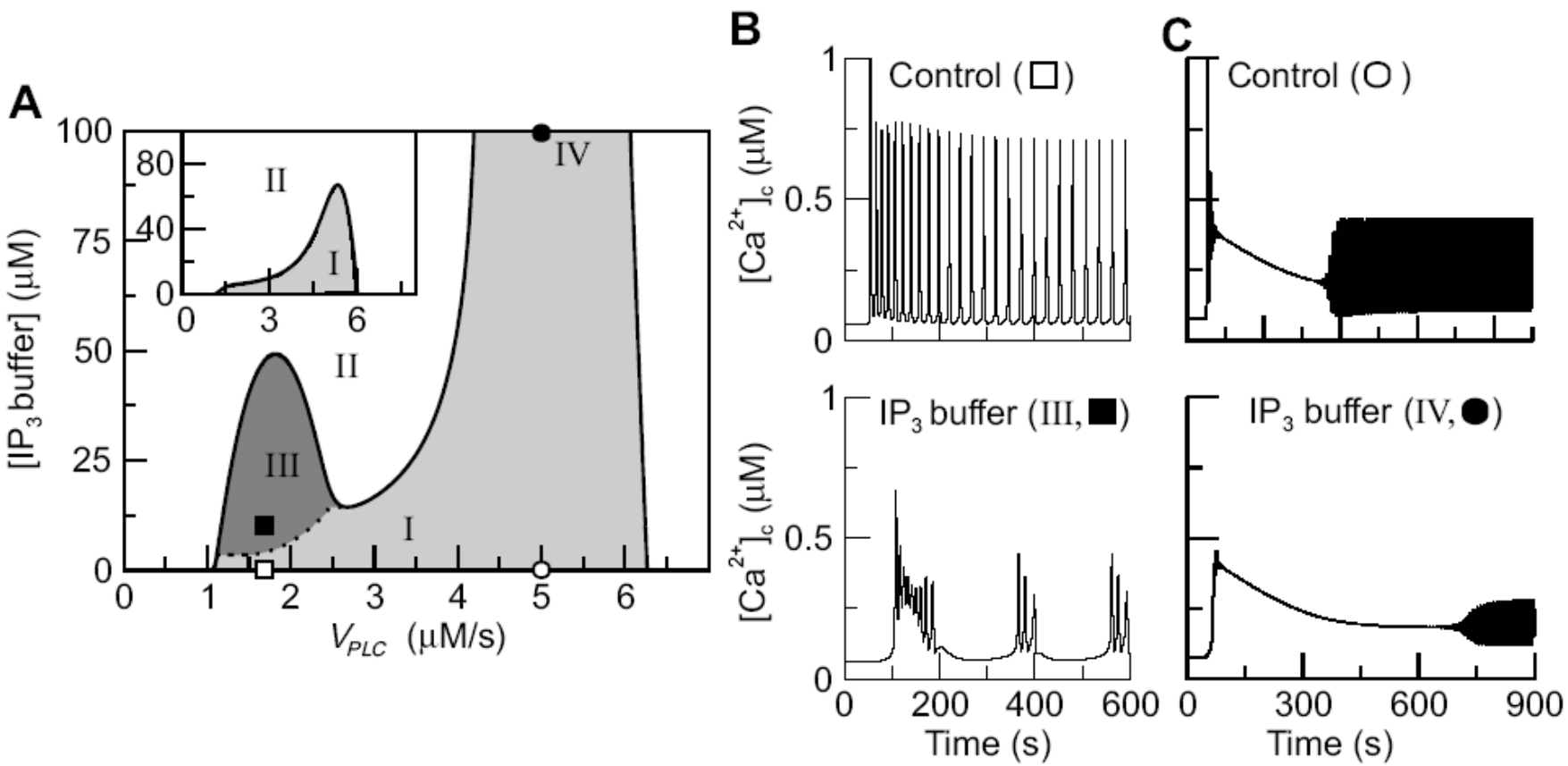


High IP_3 buffer

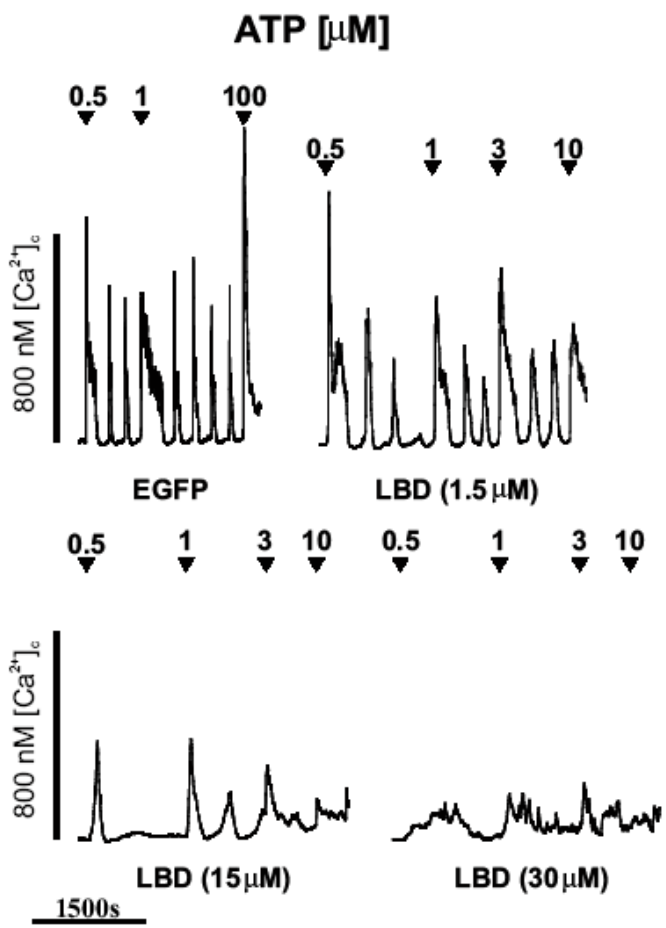




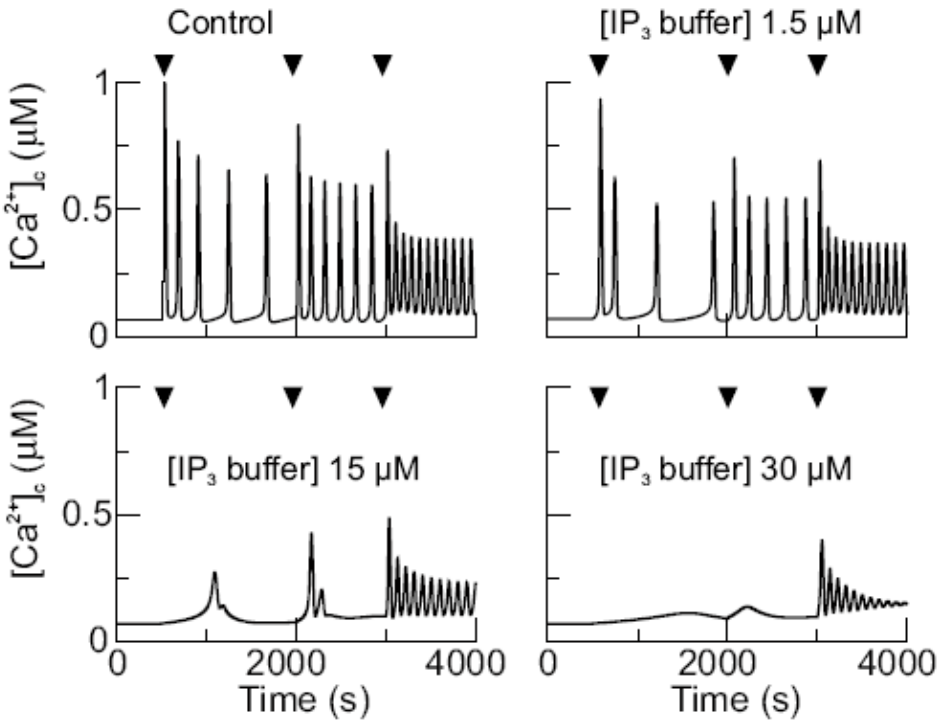
Complex buffer effects



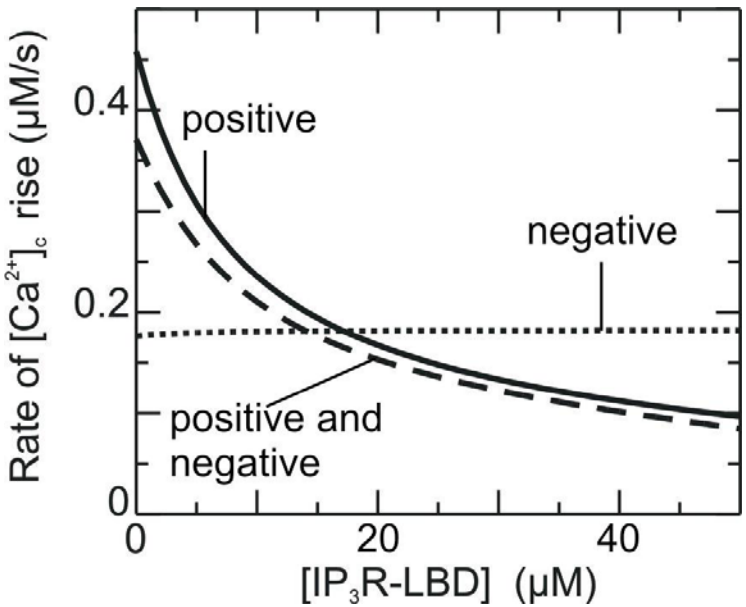
Experiment 3 – CHO cells

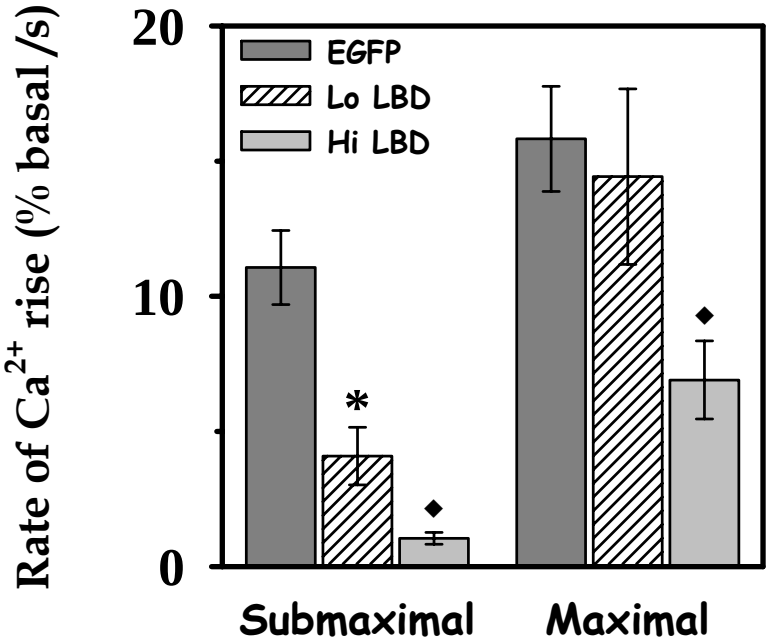


Model (+ve feedback, strong PM fluxes)



Rate of calcium rise depends on IP3 buffer





Politi, Gaspers, Thomas & Höfer, Biophys. J. (2006)