

Calcium signaling during osteoclastogenesis

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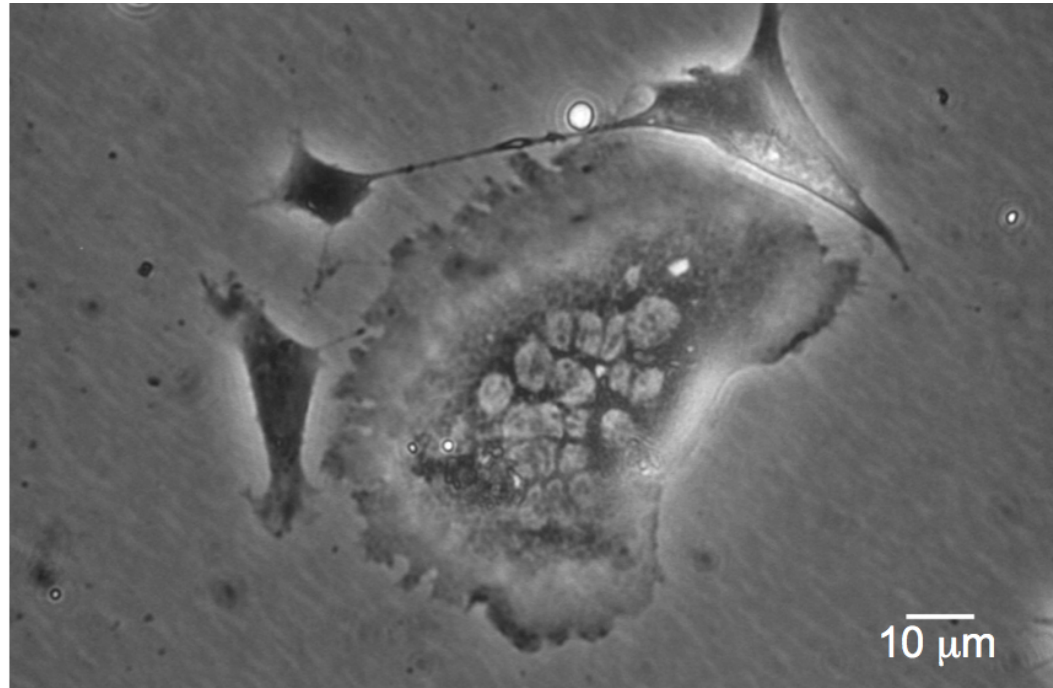
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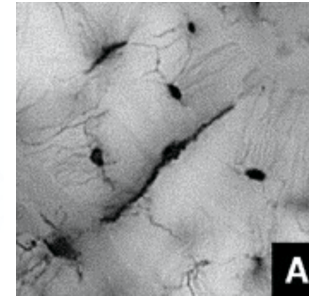
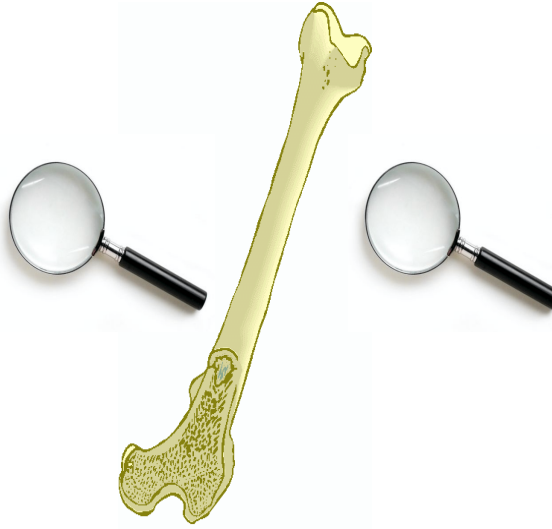
Yi Sui, University of British Columbia

Jiying Wen, University of British Columbia

The protagonist



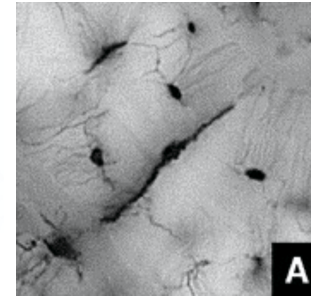
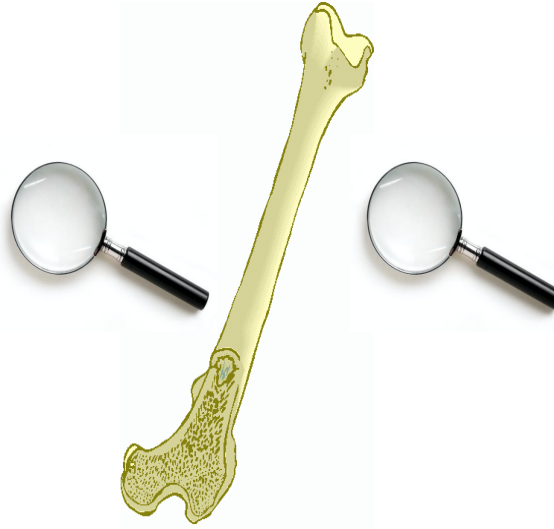
Bigger Picture



Reproduced from S. Qiu et al., Bone, 2005

- Bone \neq static
- Loading \rightarrow mechanical stress \rightarrow micro fractures
- Low calcium \rightarrow release from bones

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Osteoclasts resorb bone

- Bone resorption: part of bone remodeling
- Physiological process
- Various diseases: abnormal osteoclast activity
- Increased resorption in e.g. osteoporosis, bone metastases

How to stop osteoclastic activity?!

Osteoclast formation



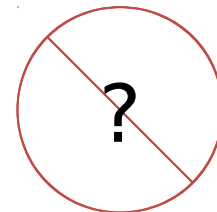
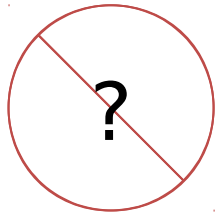
RANKL
(necessary)

Solution 1 (Nobel prize: no)



Solution 2 (Nobel prize: maybe)

downstream of RANKL?



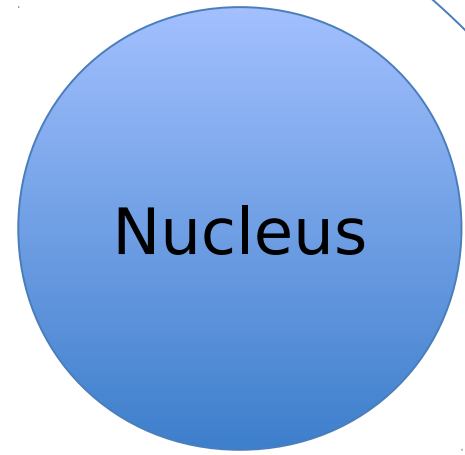
Status Quo

RANKL

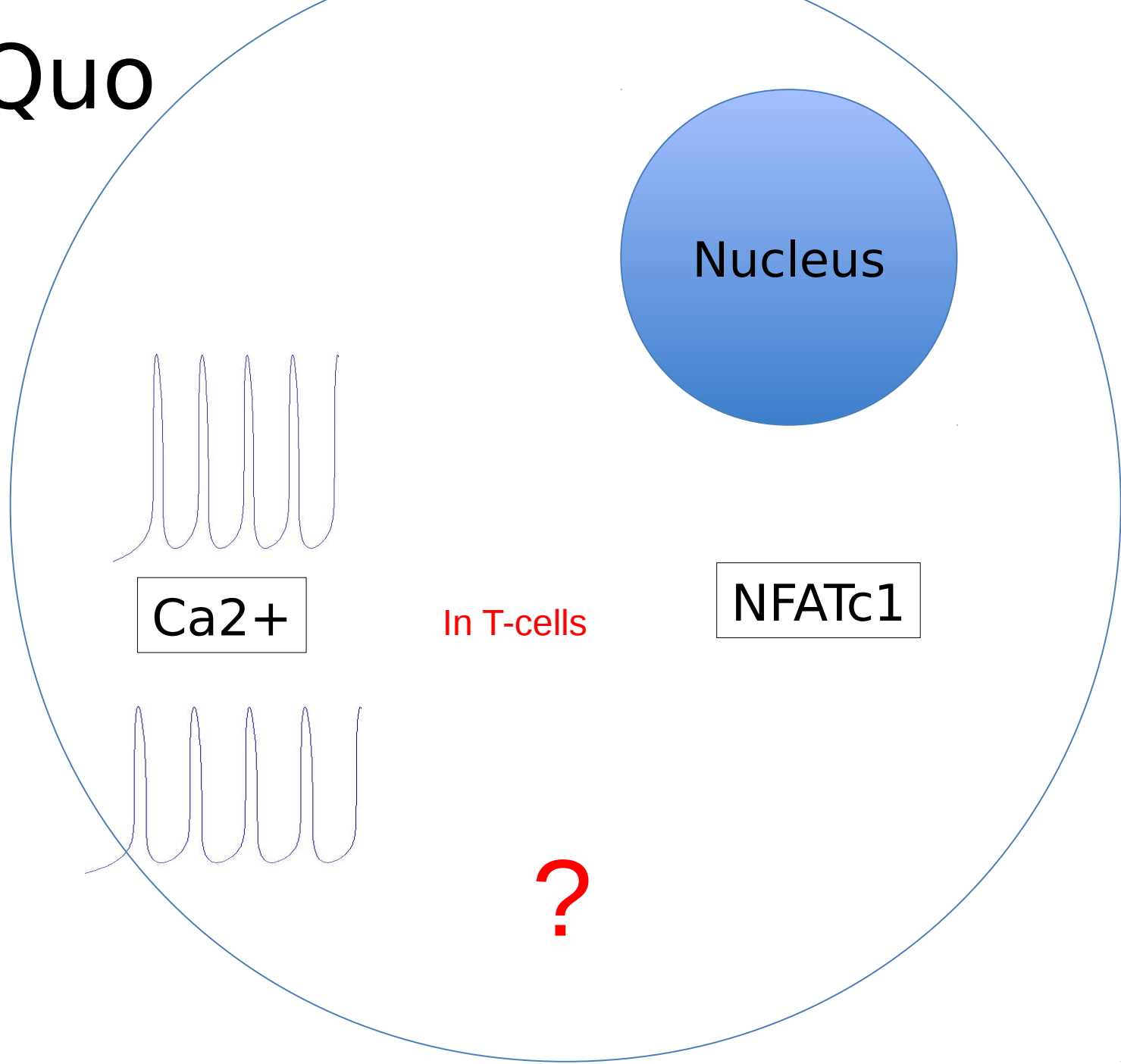
Ca²⁺

In T-cells

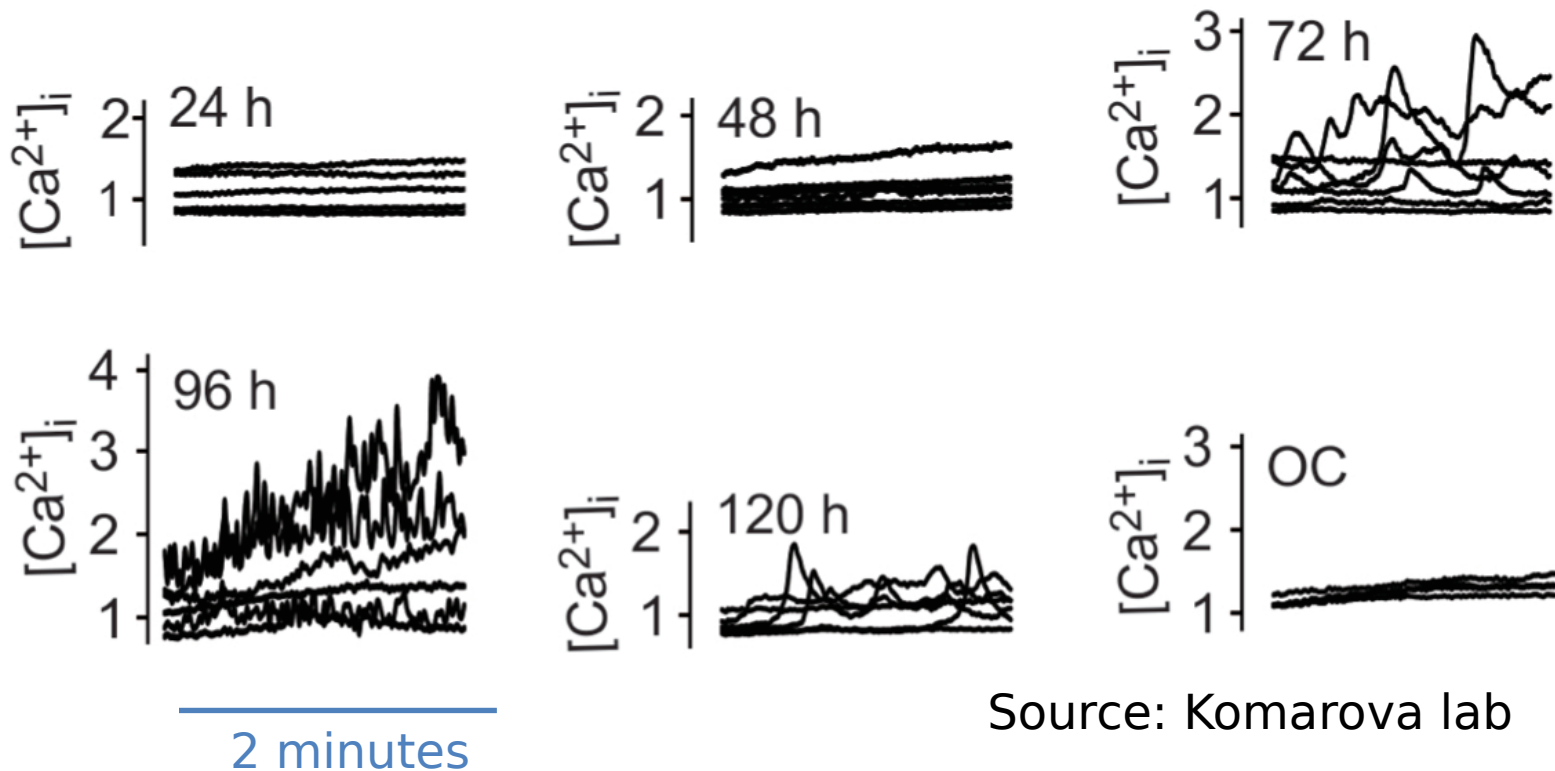
NFATc1



?



Data: a messy affair

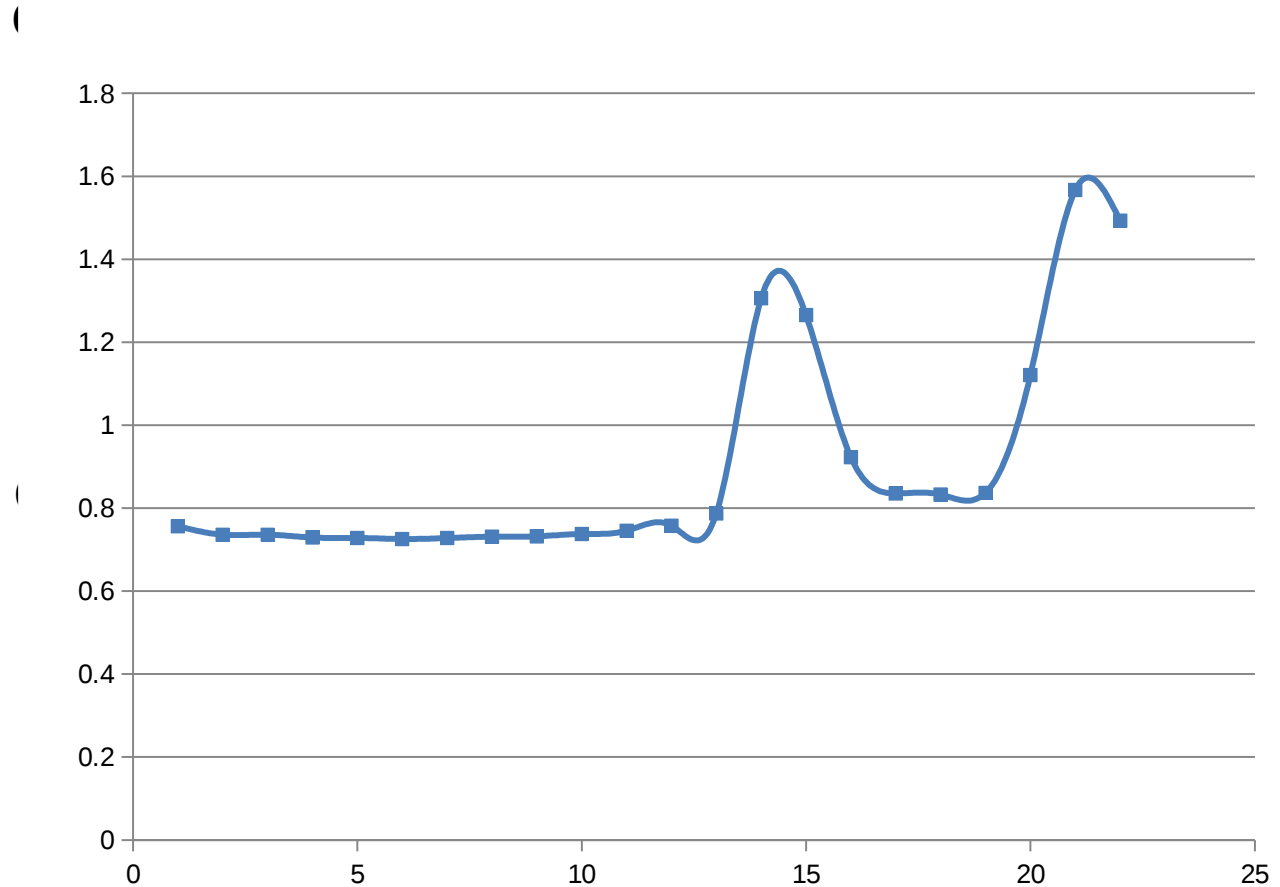


Oscillations, or just noise?

Interpretation: 2 cell types?

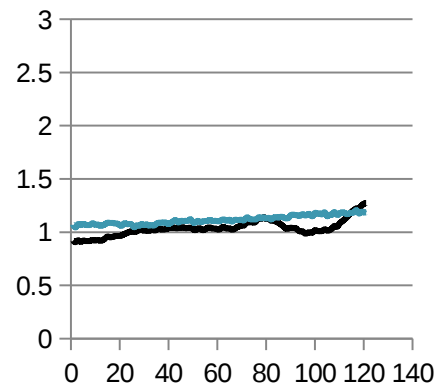
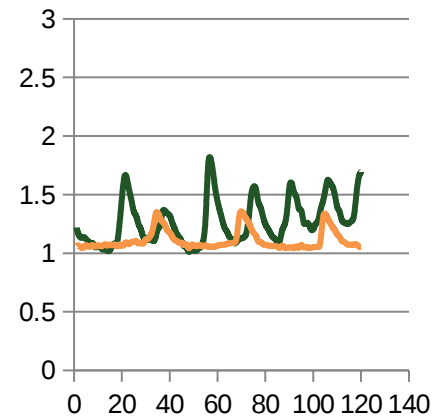
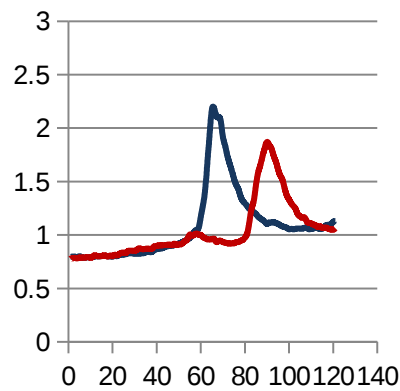
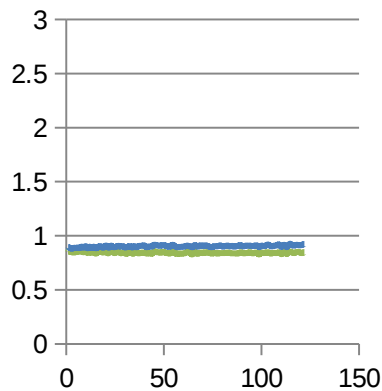
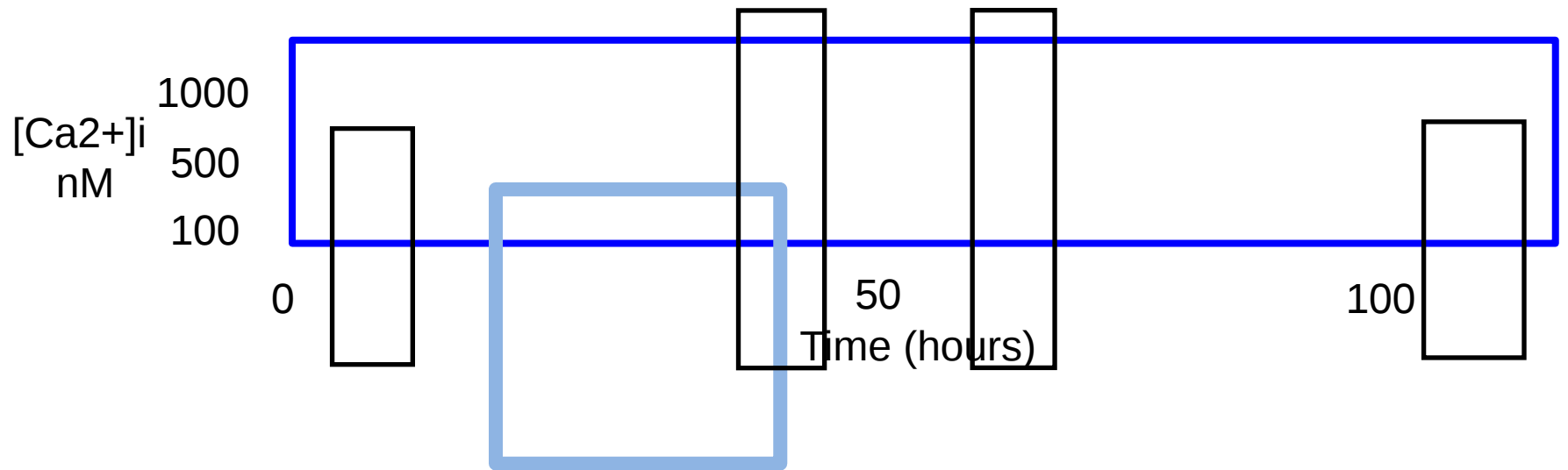
Type 1

Type 2



Not plausible: reject

Working hypothesis



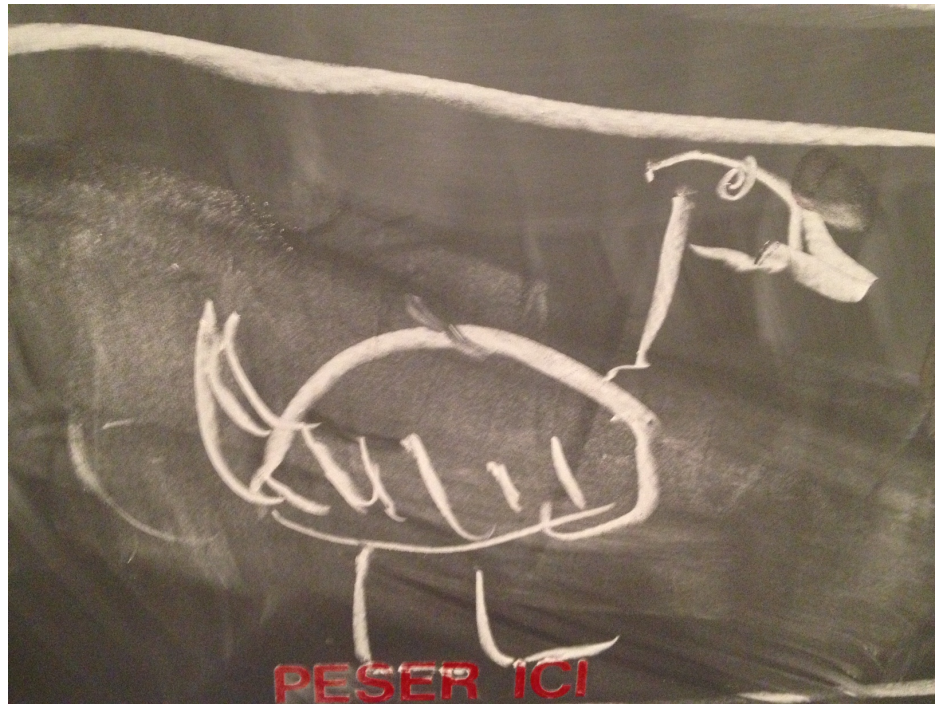
Time (s). Each plot is 120 s of recording

Fluorescence intensity (reflects $[Ca^{2+}]_i$)

Hence...

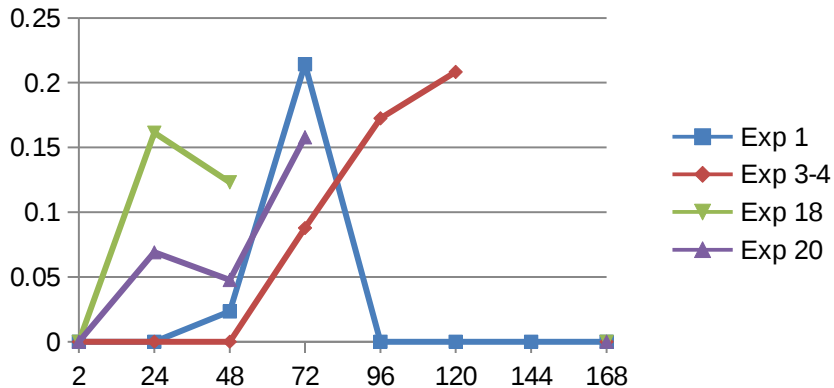
Focus on oscillations between perturbations

Pleiotropic
Canard

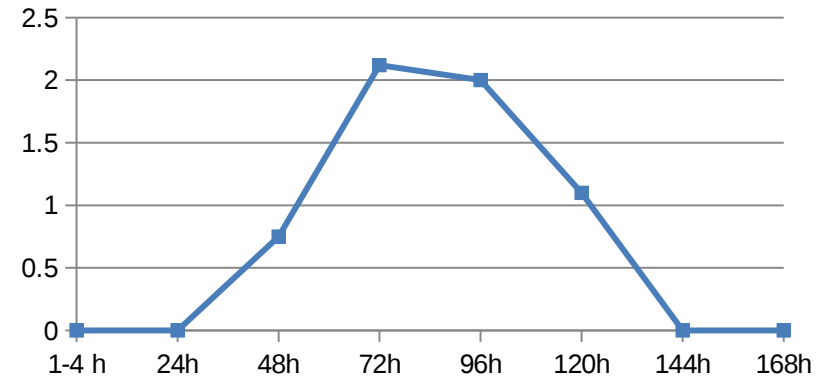


What to learn from the data?

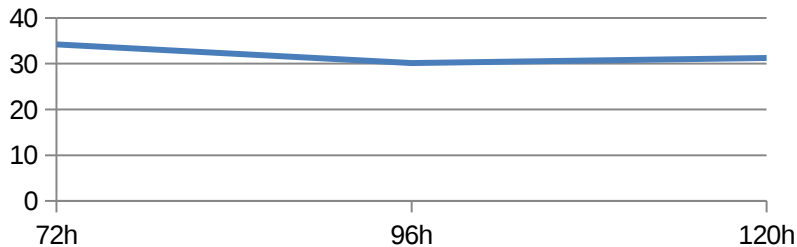
Fraction of oscillating cells



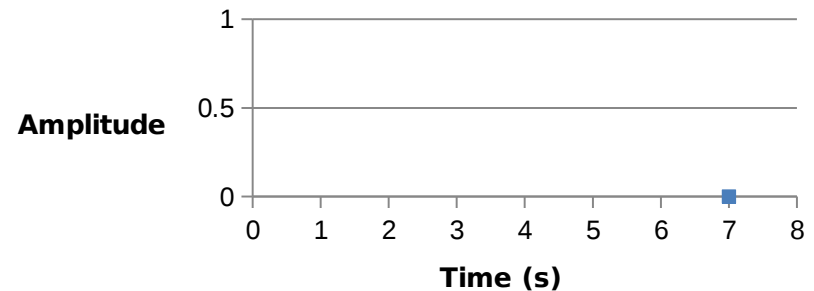
peaks (per 120 seconds)



Period [seconds]



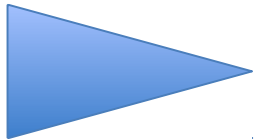
Amplitude



When they oscillate, they oscillate.

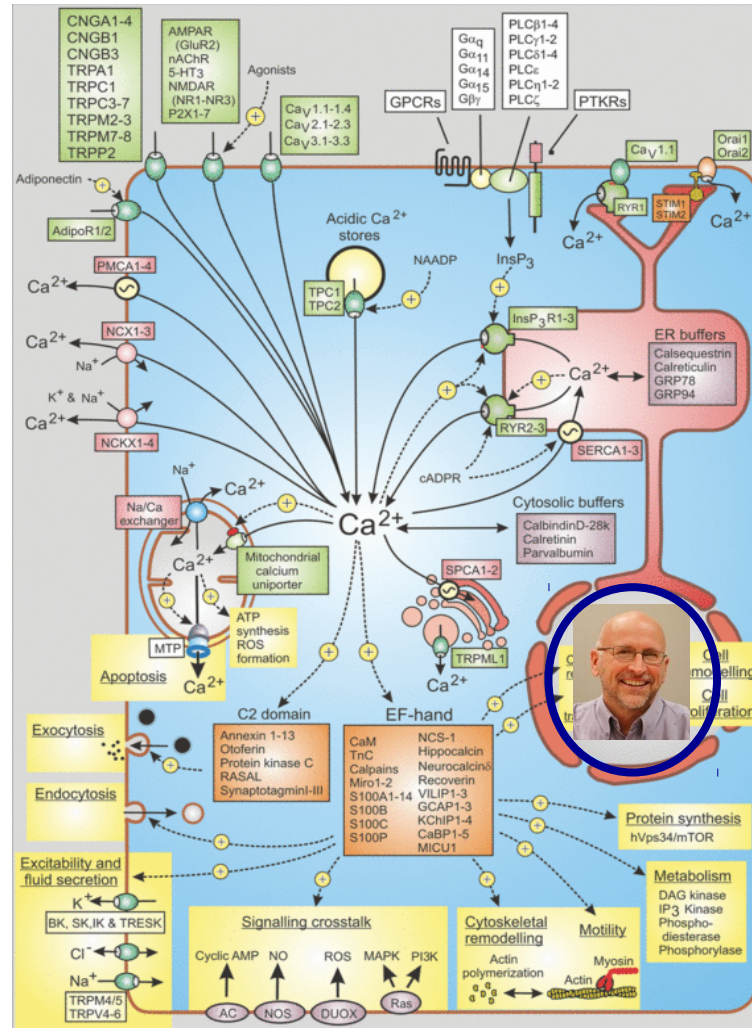
Next step?

- Ok, we have control data
- Need to start manipulating the oscillations and quantify impact on osteoclastogenesis
- Big question: **how** to manipulate oscillations?



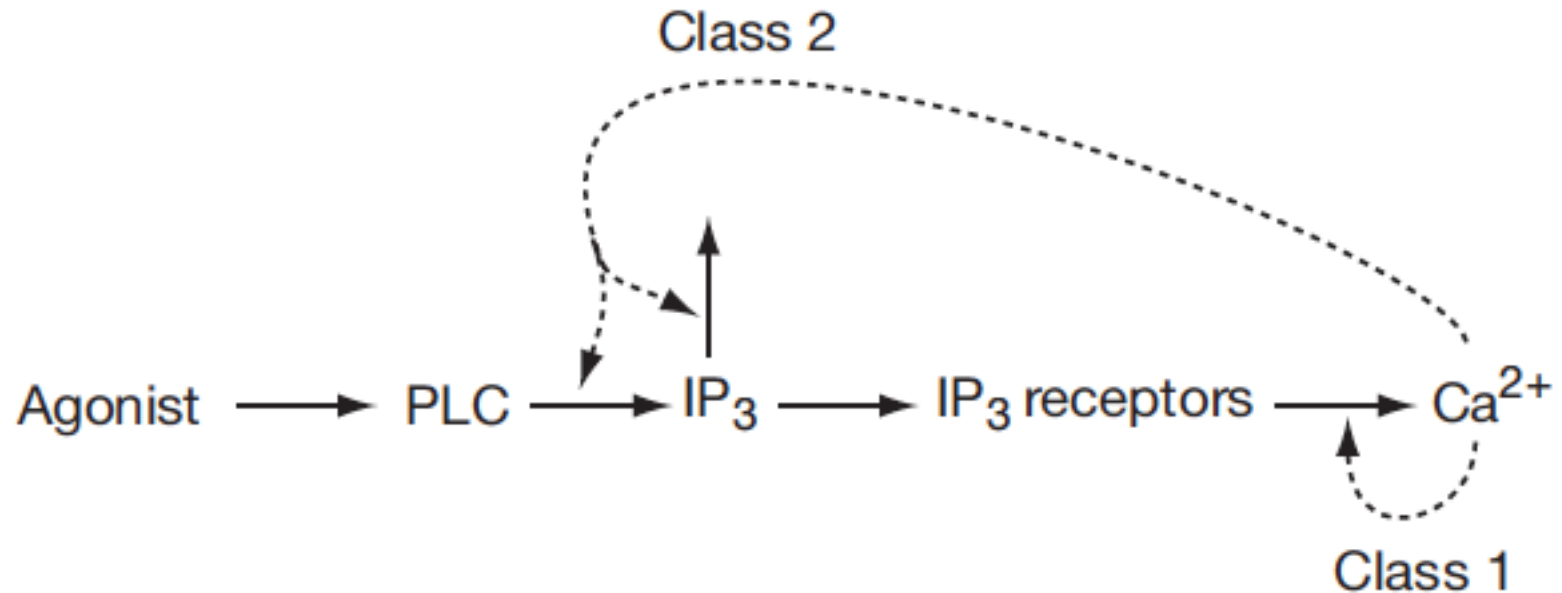
Mathematical modeling!

Mathematical model



Nucleus
(of group 1)

Calcium oscillation model (Atri)

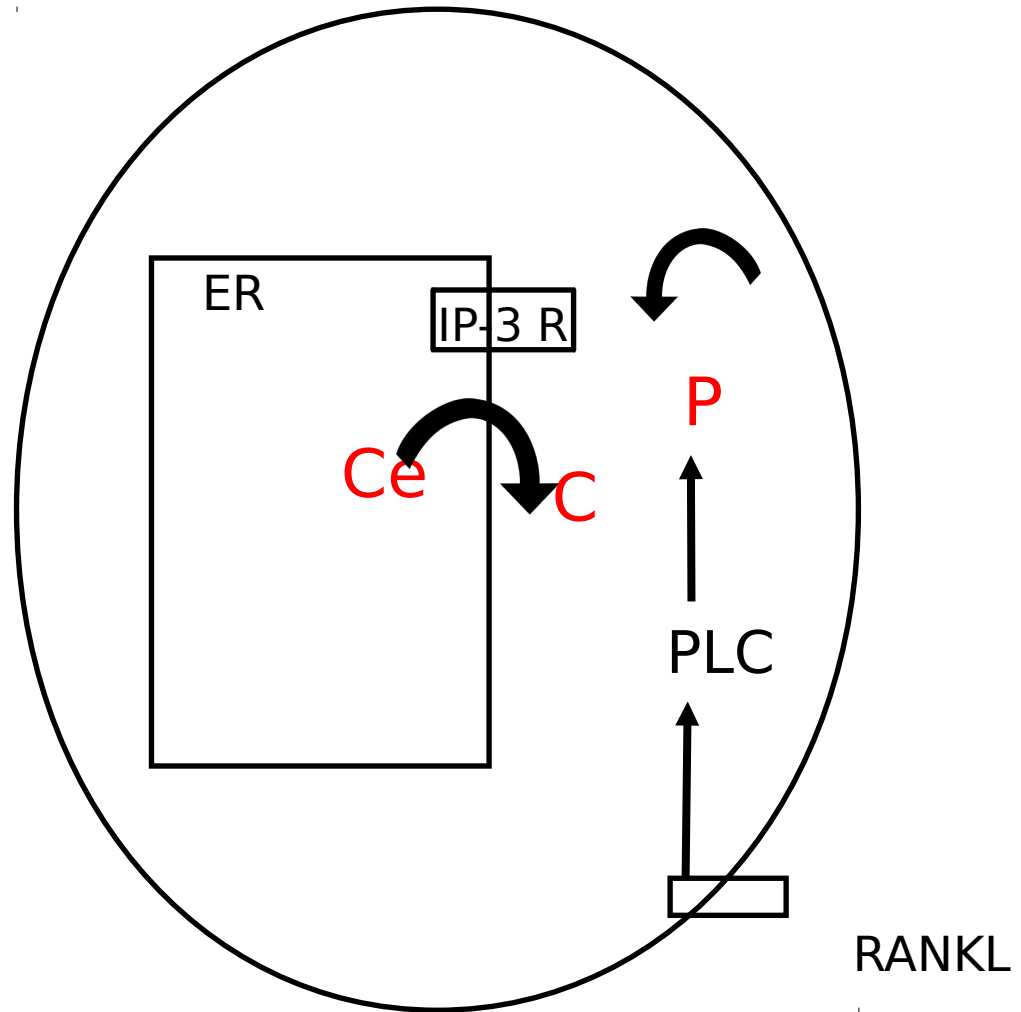


Dynamical Probing of the Mechanisms Underlying Calcium Oscillations

M. Domijan,¹ R. Murray,¹ and J. Sneyd²

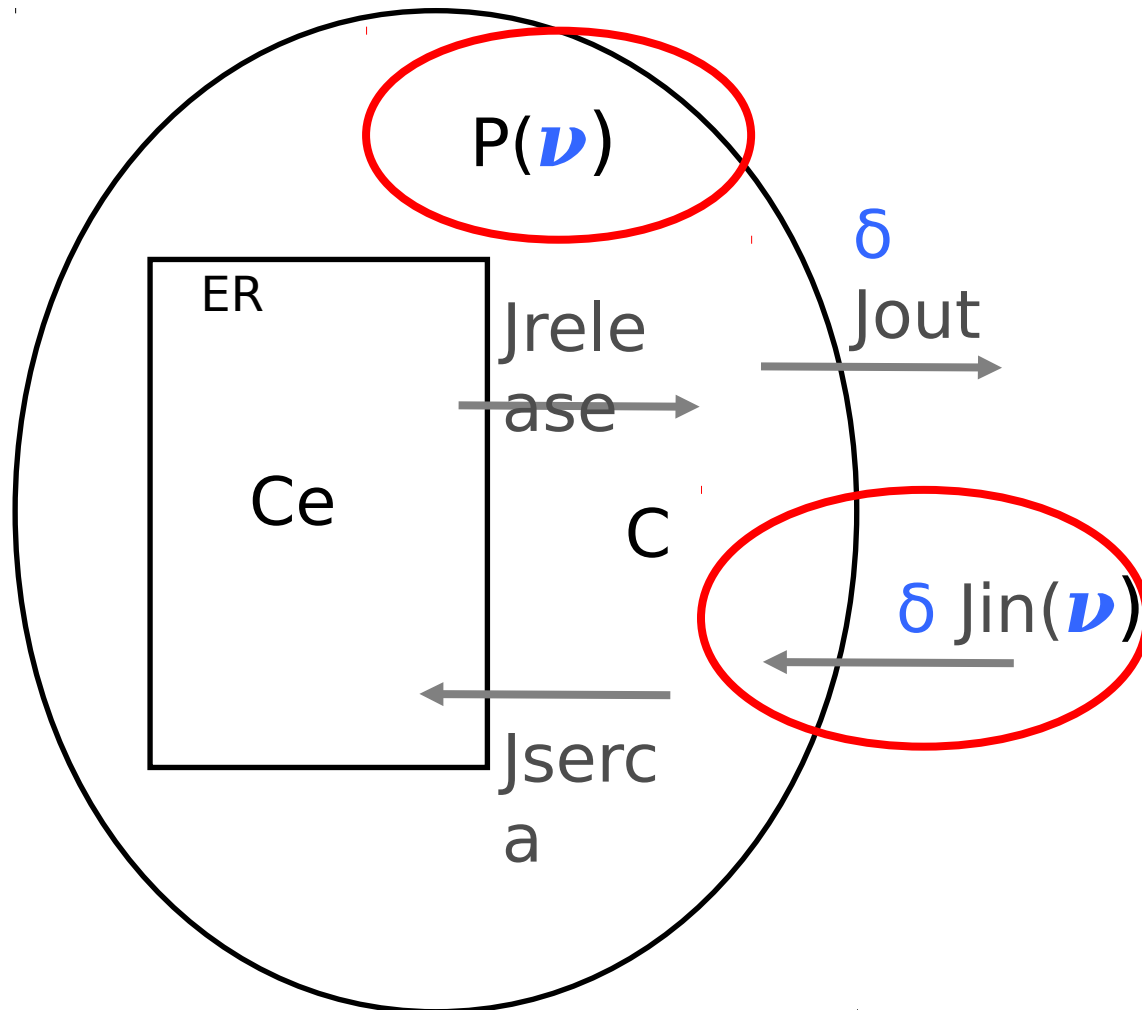
J. Nonlinear Sci. Vol. 16: pp. 483–506 (2006)

Calcium oscillation model (Atri)



Ce [Ca²⁺] in ER
C [Ca²⁺] in cytoplasm
P [IP-3] in cytoplasm

Important parameters



ν : IP-3 production capacity

Calcium oscillation model

$$\frac{dc}{dt} = K\{(\bar{J}_{release} - \bar{J}_{serca}) + \delta(\bar{J}_{in} - \bar{J}_{pm})\}$$

$$\frac{dc_e}{dt} = \gamma K(\bar{J}_{serca} - \bar{J}_{release})$$

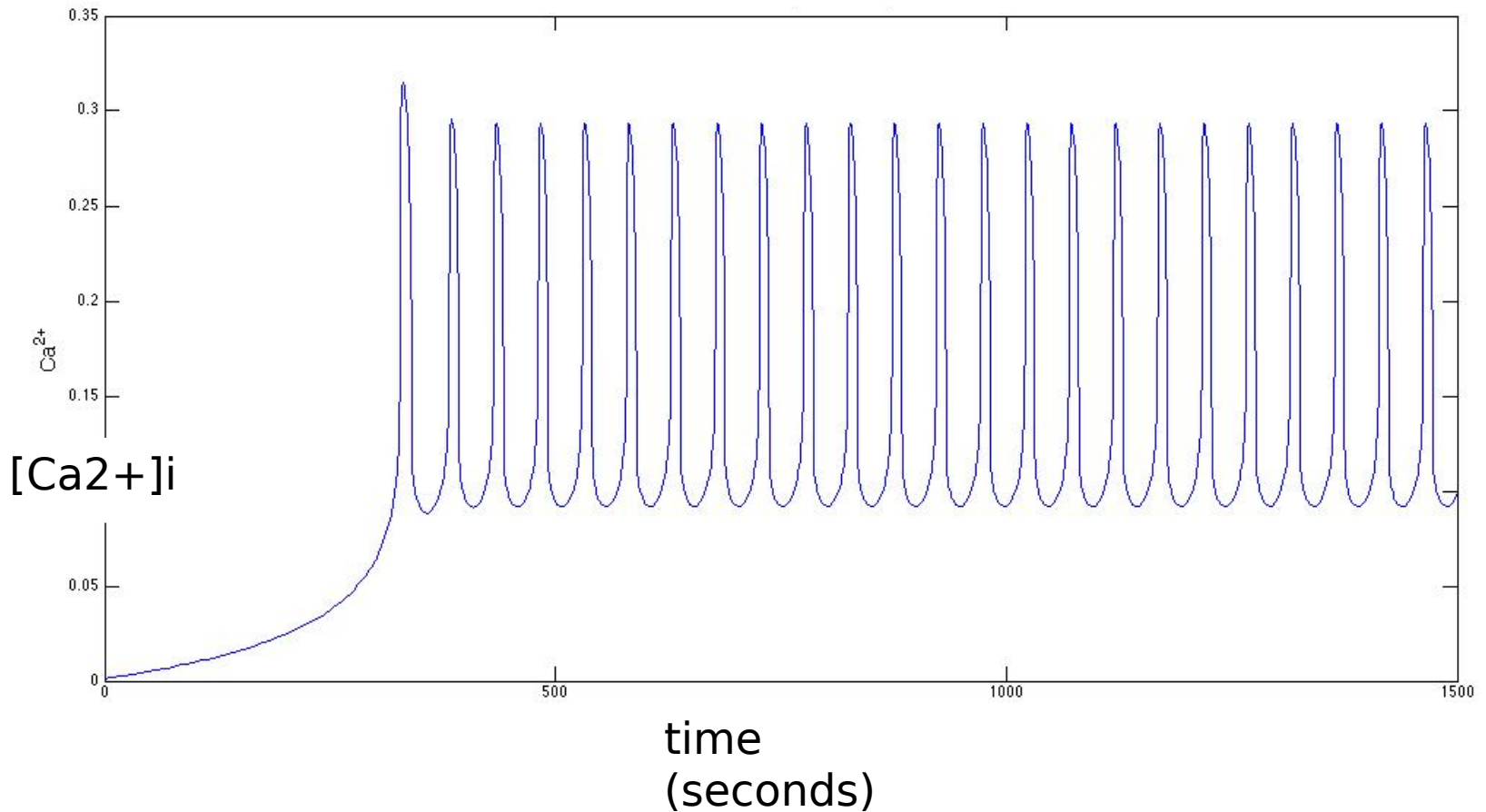
$$\frac{dn}{dt} = \frac{1}{\hat{\tau}} \left(\frac{k_2^2}{k_2^2 + Q_c^2 c^2} - n \right)$$

$$\frac{dp}{dt} = \nu \left(\frac{Q_c c}{Q_c c + k_4} \right) - p.$$

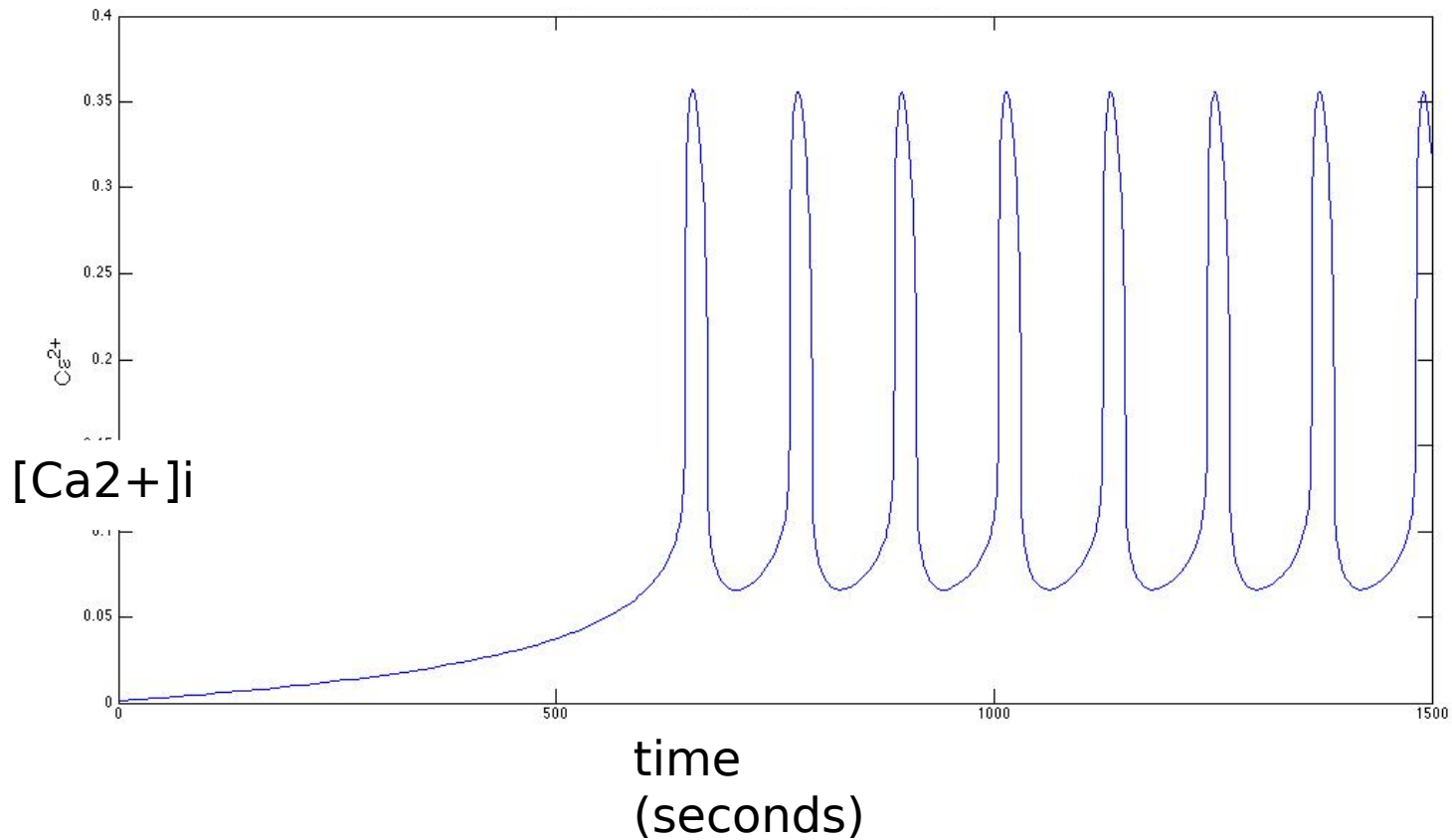
where $K = \frac{V_p T}{Q_c}$, $T = \frac{1}{\beta}$ and Q_c is a typical Ca^{2+} concentration scale.

Calcium oscillation model (Class 2)

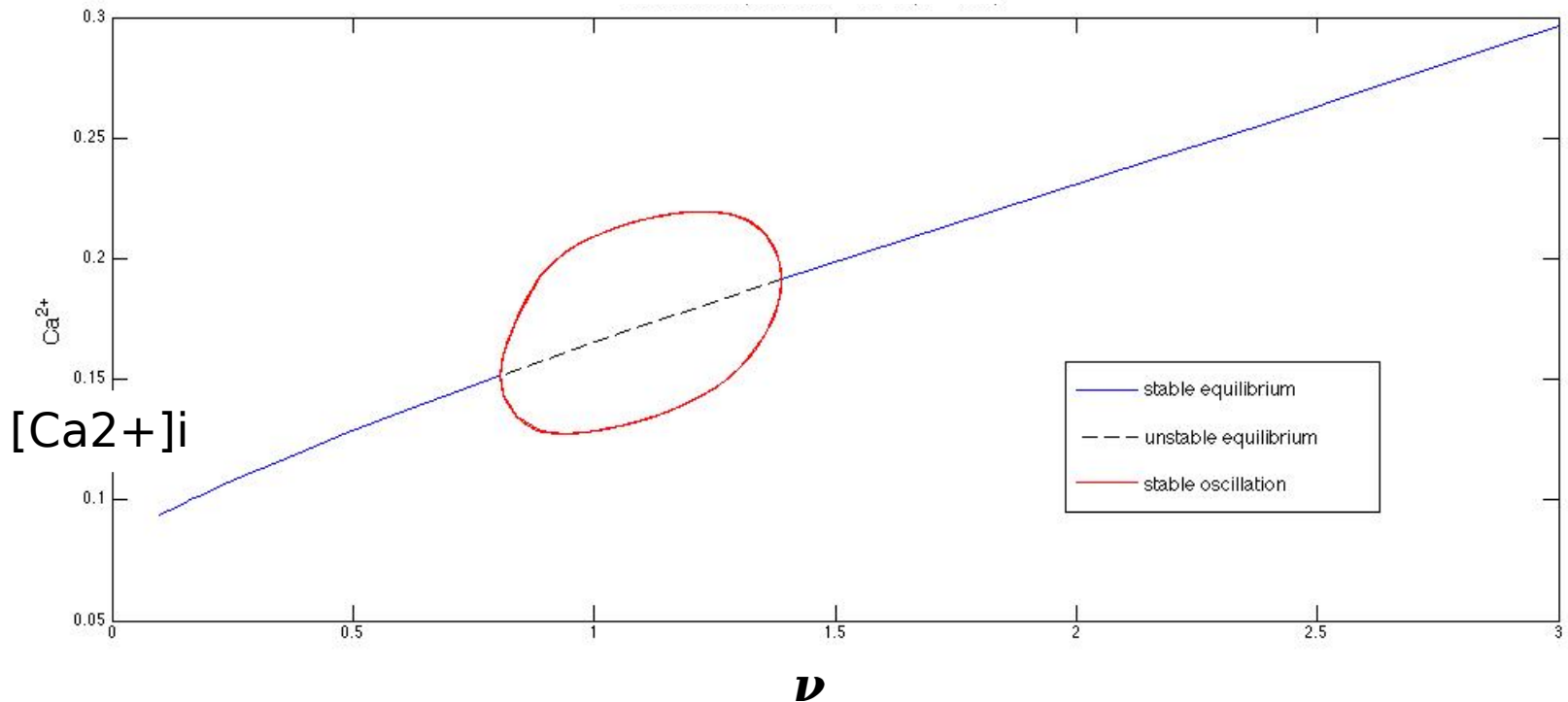
$$\delta=0.004, \nu=0.7$$



Decreasing Ca^{2+} - flux (δ) \rightarrow increasing
period
(through membrane)
 $\delta=0.002$, $\nu=0.7$

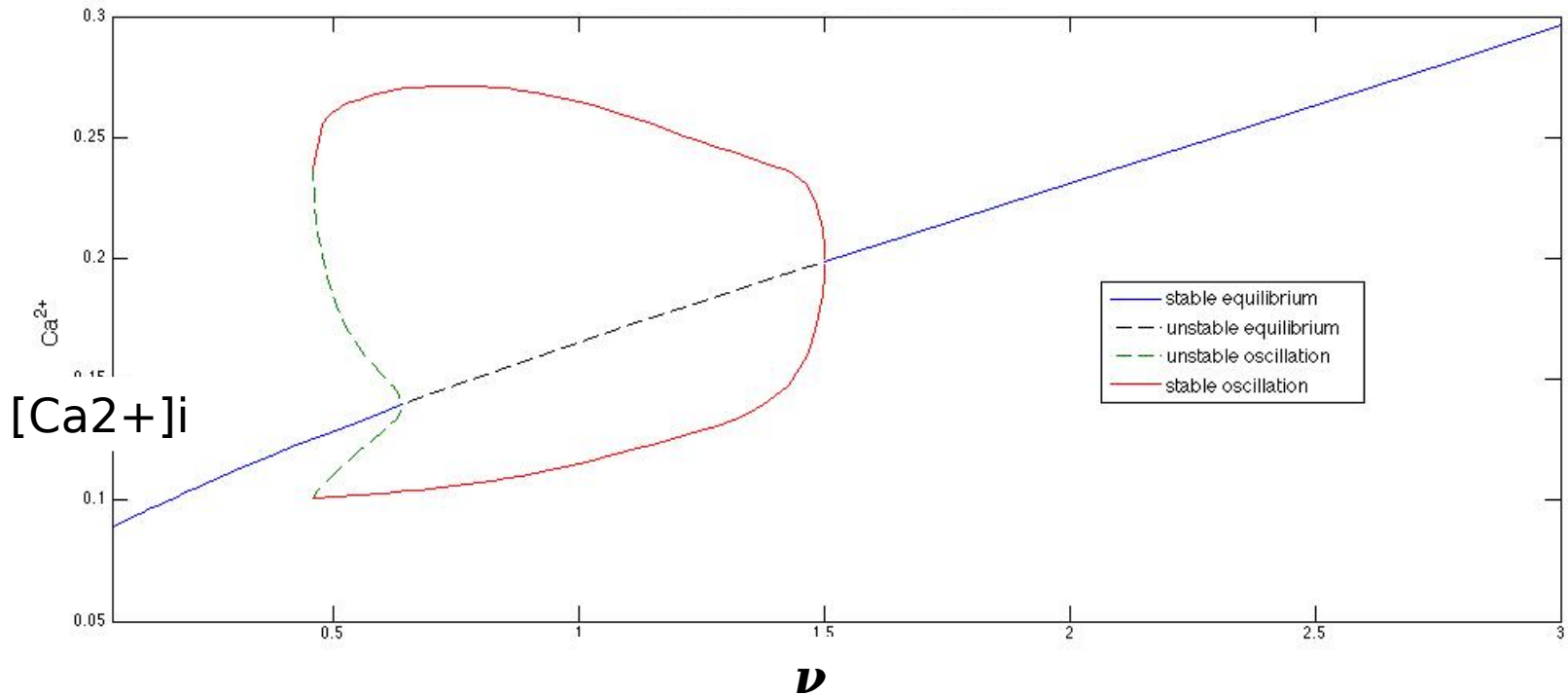


Bifurcation diagram ($\delta=0.01$)



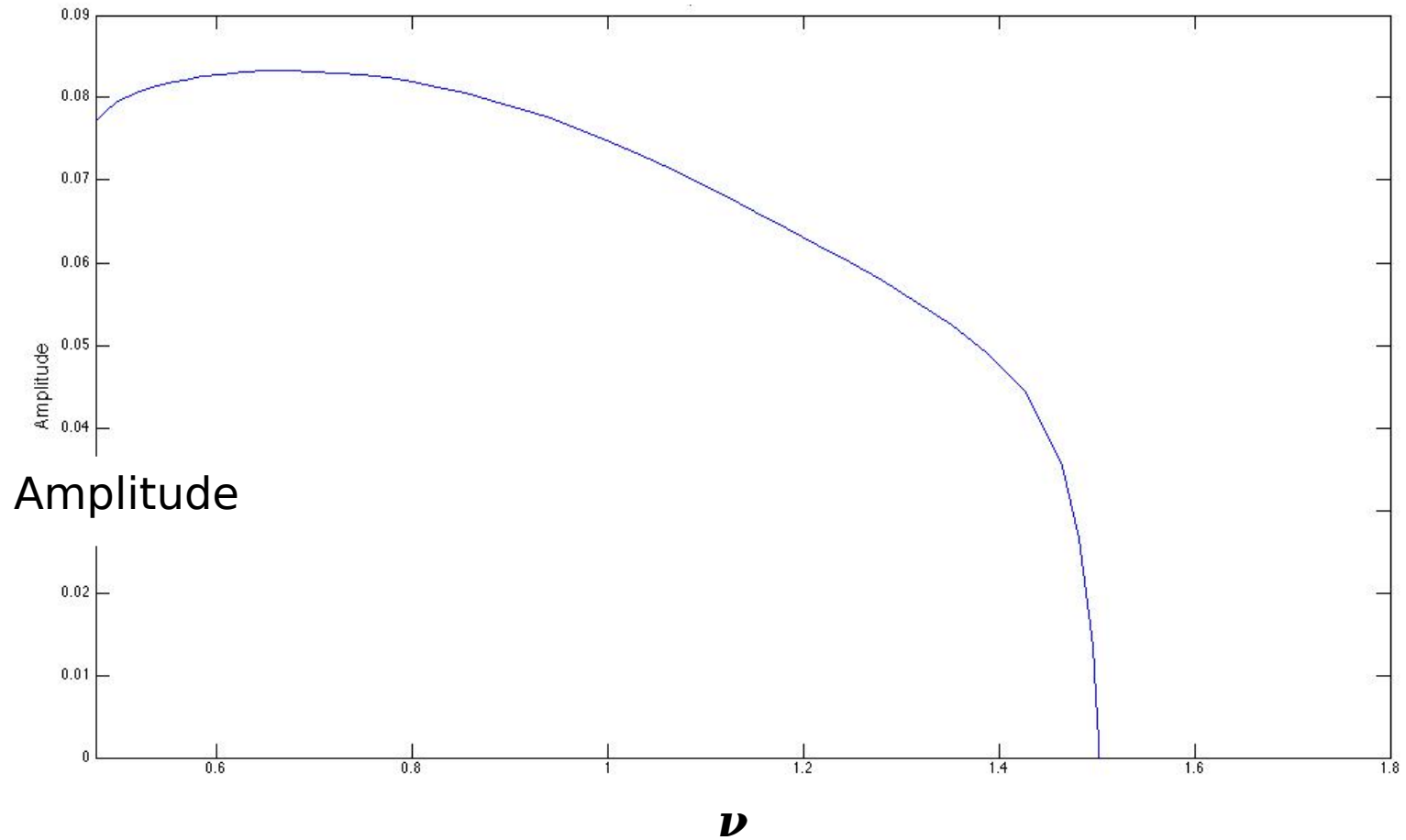
- Stable oscillations emerge (supercritical Hopf bifurcation)
- Narrow amplitude and frequency range

Bifurcation diagram ($\delta=0.005$)

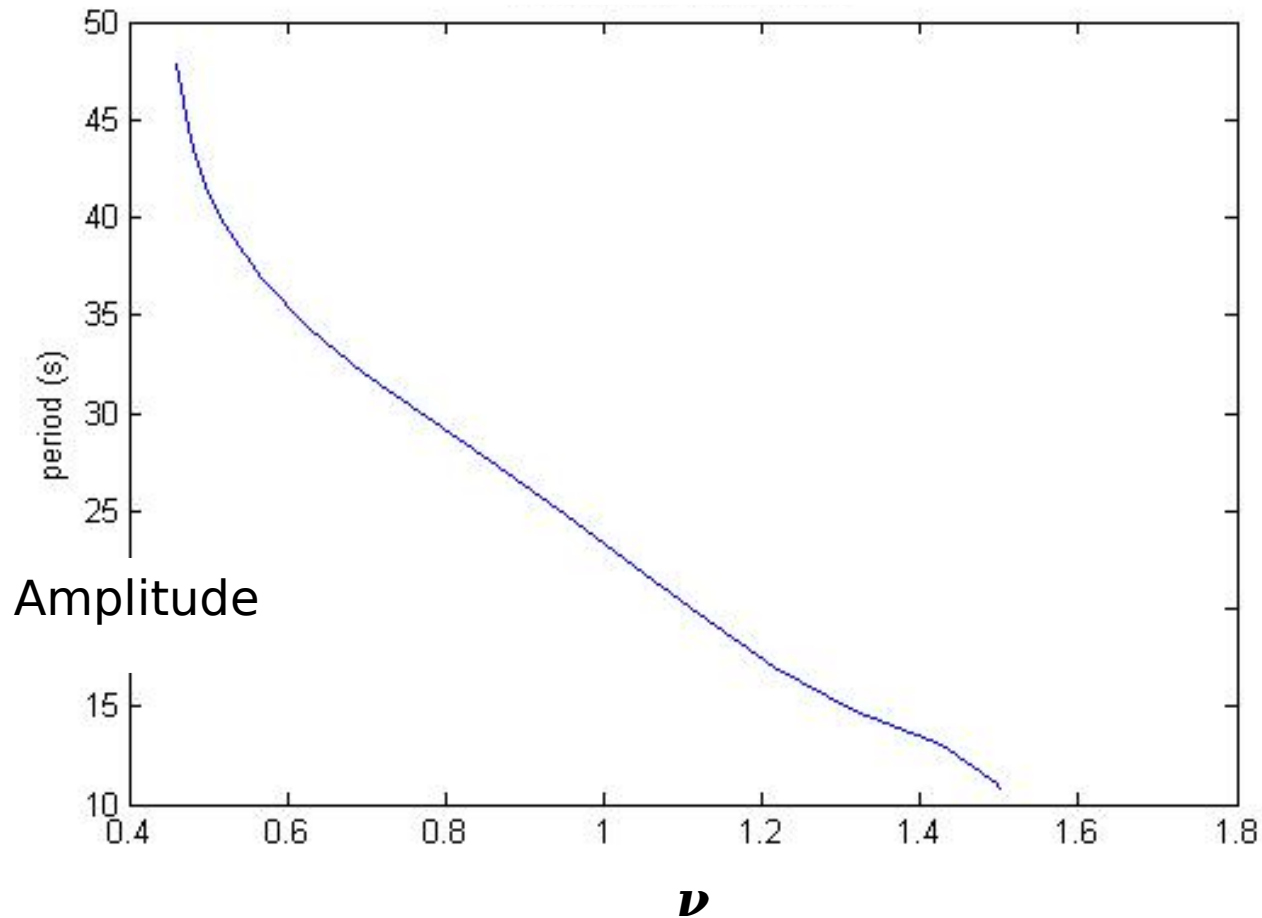


- Multistability region (subcritical Hopf bifurcation)
- Wide amplitude and frequency range

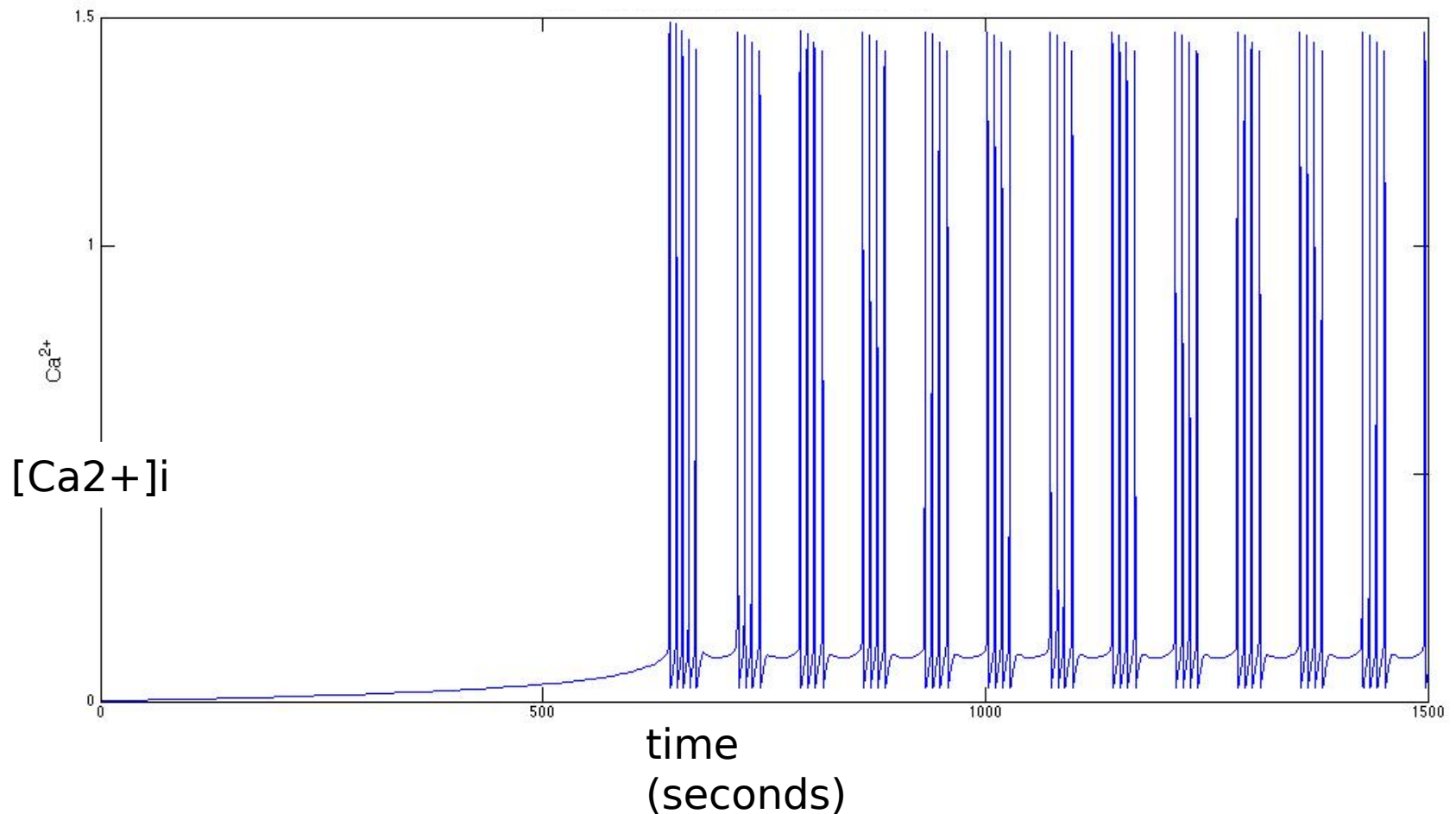
Amplitude versus IP-3 production capacity



Period versus IP-3 production capacity

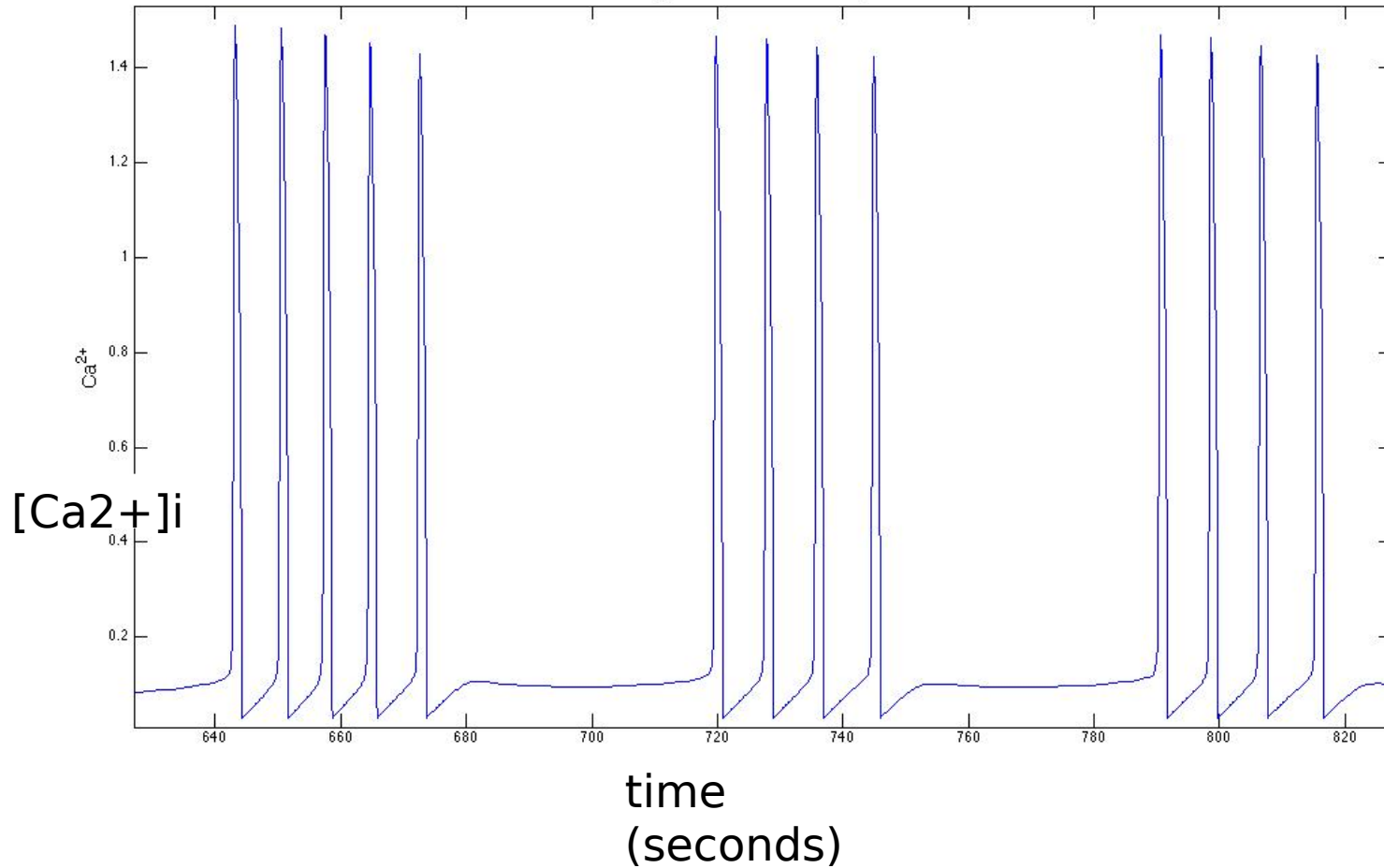


Calcium oscillation (Class 1+2)



Predicts bursts of activity

Predicts bursts of activity (zoom in)



Big question: **how** to manipulate oscillations?

Cell Metabolism
Article

2013

Cell
PRESS

Tmem64 Modulates Calcium Signaling during RANKL-Mediated Osteoclast Differentiation

Hyunsoo Kim,^{1,8} Taesoo Kim,^{3,8} Byung-Chul Jeong,^{1,4,8} Il-Taeg Cho,¹ Daehee Han,¹ Noriko Takegahara,¹ Takako Negishi-Koga,⁵ Hiroshi Takayanagi,⁵ Jae Hee Lee,² Jai-Yoon Sul,² Vikram Prasad,⁶ Seoung Hoon Lee,⁷ and Yongwon Choi^{1,*}

Systematic approach!

Take-home message 1

δ

Flux of calcium across plasma membrane

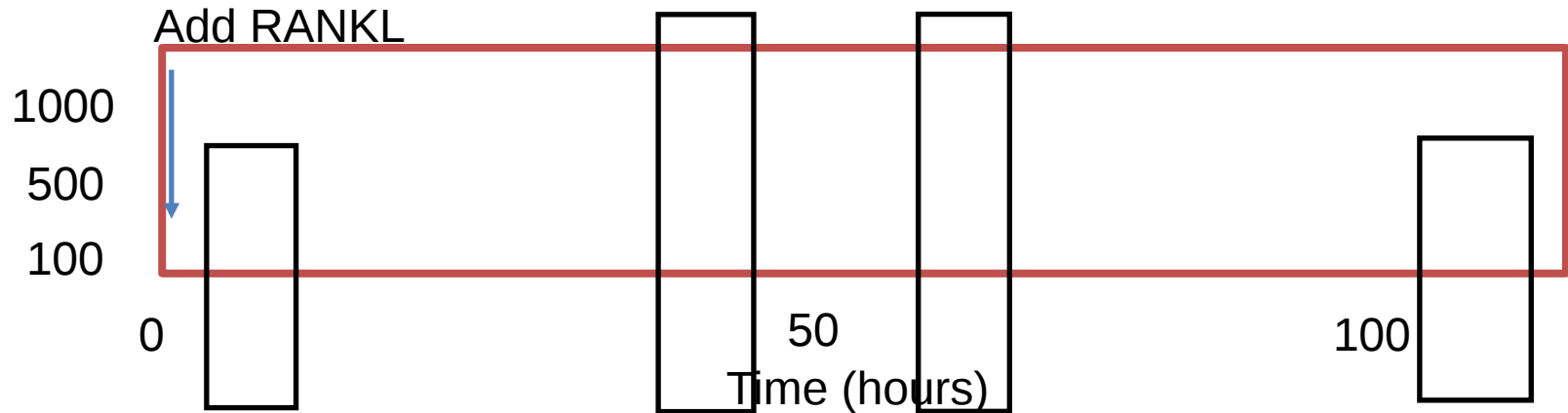
Manipulate Ca^{2+} channels

ν

IP-3 production capacity

Manipulate the agonist receptors

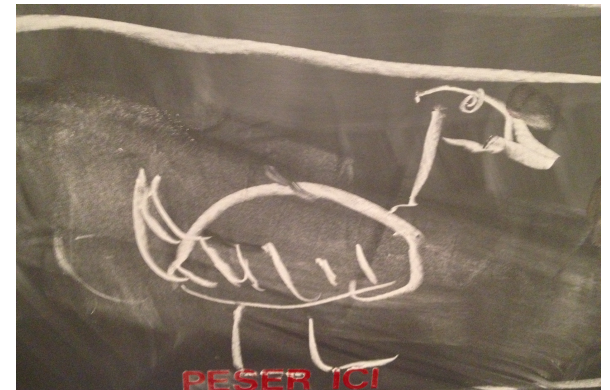
Take-home message 2



- Working hypothesis: we only see small windows of intermittent but regular oscillations
- Measure larger time windows!

Quack...une bien belle semaine

- Special thanks to...
- The organizing committee and CRM staff
- S. Sims, S.J. Dixon, K. Tiedemann, S.V. Komarova





That's all Folks!