Calcium Dynamics

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Calcium Dynamics: Why we care

New experimental approaches that enable the study of astrocyte physiology at higher spatialtemporal resolution in intact brain preparations are beginning to reveal an unexpected level of compartmentalization and sophistication in astrocytic Ca^{2+} dynamics. This newly revealed complexity needs to be attentively considered in order to understand how astrocytes may contribute to brain information processing. -Volterra et al. (Nature Reviews Neuroscience 2014)

- Signaling is done almost exclusively through Ca^{2+} dynamics
- Understanding the how Astrocytes can effect neural dynamics starts with understanding the mechanisms behind this signaling process
- Novel perspectives of how to create efficient and powerful NN can come from this type of biological inspiration
- We will go through work by Dr James 'the calcium guy' Sneyd

Calcium Dynamics: Introduction

Calcium plays a role in almost every cell type
Timescale can be short or looooong: much more variability
Amplitude vs Frequency
Great for modelers

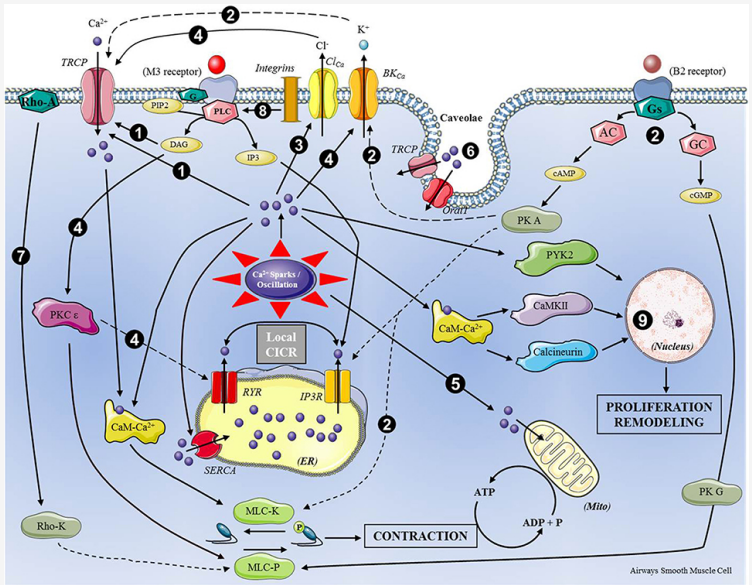


Figure: Calcium Signaling: a lot going on[1]

[1] Tanguy S (2015) Calcium, a multitasking signaling actor in airway smooth muscle cells, as a target of novel strategies to limit airway disease? Front. Pharmacol.

Ways To Model

There are a lot of ways to model Calcium and one must be wary of being overly simplistic/complicated. You need to use your judgement.
First off: you got to bring in the DE

- Homogeneous vs Inhomogeneous
  - How "real" does it need to be
- Stochastic vs Deterministic
  - Evidence suggests stochastic
  - Don't need stochasticity to understand mechanisms
- Excitability

Example: Astrocyte Compartmentalization

Investigating the internal workings (mechanisms) of an simplistic astrocyte

- homogeneous: with a twist
  - individually simple representation of calcium
  - compartments allow spatial 'impression'
- deterministic
  - not needed at this stage of development

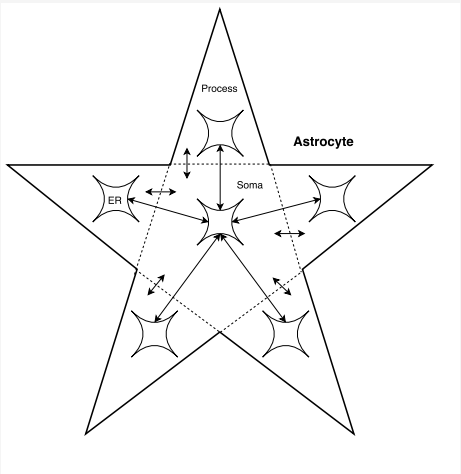


Figure: Calcium Dynamics in a Compartmentalized Astrocyte

Basic Fluxes of Calcium

Flow into Cell: channels
- voltage-gated Ca^{2+} channels
- receptor-operated channels item store operated channels

Flow out of cell: pumps (ER or PM)
- into the Endoplasmic/Sarcoplasmic Recticulum: SERCA Pumps
- ATPase pumps across cell membrane

Release from ER: IPR
- agonist $\rightarrow$ IP_3 $\rightarrow$ IPR release

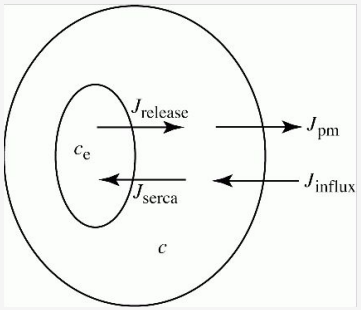


Figure: Calcium Signaling: signifcant dynamics[2]

[1] James Sneyd (2015) Mathematical Analysis of Complex Cellular Activity Springer

Basic Model

This leads to simple formulation of the Calcium in a cell:

$$\frac{dc}{dt} = J_{IPR} - J_{SERCA} + J_{in} - Jpm$$
$$\frac{dc_e}{dt} = \gamma(-J_{IPR} + J_{SERCA})$$

where γ is a factor relating the difference in concentrations between the cytoplasm and the ER

IPR fluxes

Coolest and most difficult to model!

All models share one crititcal feature: a bell-shaped function, of which two techniques are most popular

- IP_3 receptor subunits: a Hodgkin-Huxely formulation
  - fast calcium activation followed by a slow calcium inactivation
  - emphasises the mathematical similarities between IP and the Na^+ channel in HH
- multi modal IPR
  - much more complicated (yields similar results)

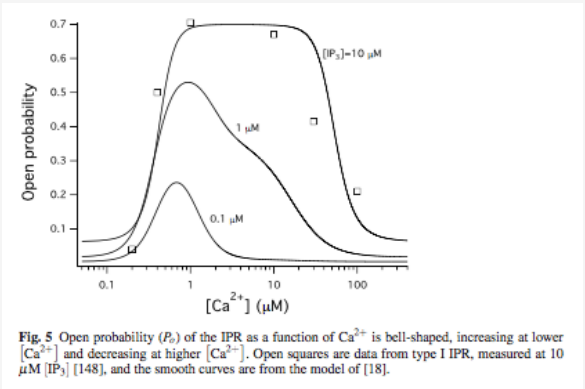


Fig. 5 Open probability (P_o) of the IPR as a function of Ca^{2+} is bell-shaped, increasing at lower $[Ca^{2+}]$ and decreasing at higher $[Ca^{2+}]$. Open squares are data from type I IPR, measured at 10 μM $[IP_3]$ [148], and the smooth curves are from the model of [18].

Figure: Calcium Signaling: signifcant dynamics (Sneyd)

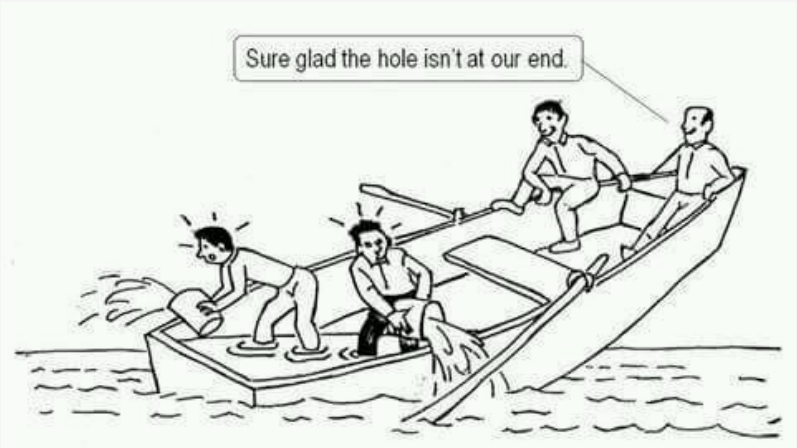
Pump fluxes

SERCA pumps transfer 2 ions per cycle and can therefore be represented through a Hill Function

Hill function with Hill-coefficient 2

$$J_{SERCA} = \frac{V_m c^2}{K_m^2 + c^2}$$

can be more detailed (not typical)



[1] reddit

Membrane fluxes

Can be very complicated and controlled by a variety of factors

- Votage-dependent channels
  - in responce to depolarization of the cell
  - electrically excitable cells
- Receptor-operated receptor operated channels
  - in responce to agonist stimulation
  - exact mechanisms are unknown
- Store-operated channels (depletion of ER/SR)
- Can be approximated within model parameters

Model Classification

Lets consider an important classification and the show an example.

Class I/Class II

whether Ca^{2+} oscillations are dependent on behavior of IP_3
All cells use a combination of both types of oscillation but it is still important to look at pure models

$$J_{IPR} = (k_{flux}(\mu_0 + \frac{\mu_1 p}{k_\mu + p})(b + \frac{V_1 c}{k_1 + c})r)(c_e - c)$$

$$\frac{dp}{dt} = \nu(1 - \frac{\alpha k_4}{c + k_4}) - \beta p$$

$$\frac{dr}{dt} = \frac{1}{\tau}(\frac{k_2^2}{k_2^2 + c} - r)$$

p is the IP_3 concentration

r is the fraction of IPR that have not been inactivated by Ca^{2+}

ν is the maximal rate of IP_3 production

Bifurcation Structure of Class I/Class II Models

Bifurcation anlysis shows you how the model acts as you vary a specific parameter (in this case ν)

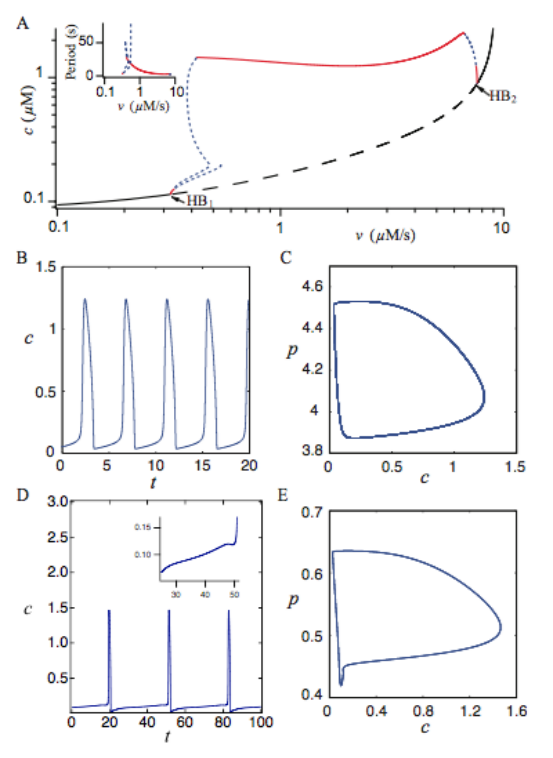


Figure: Class I (Sneyd)

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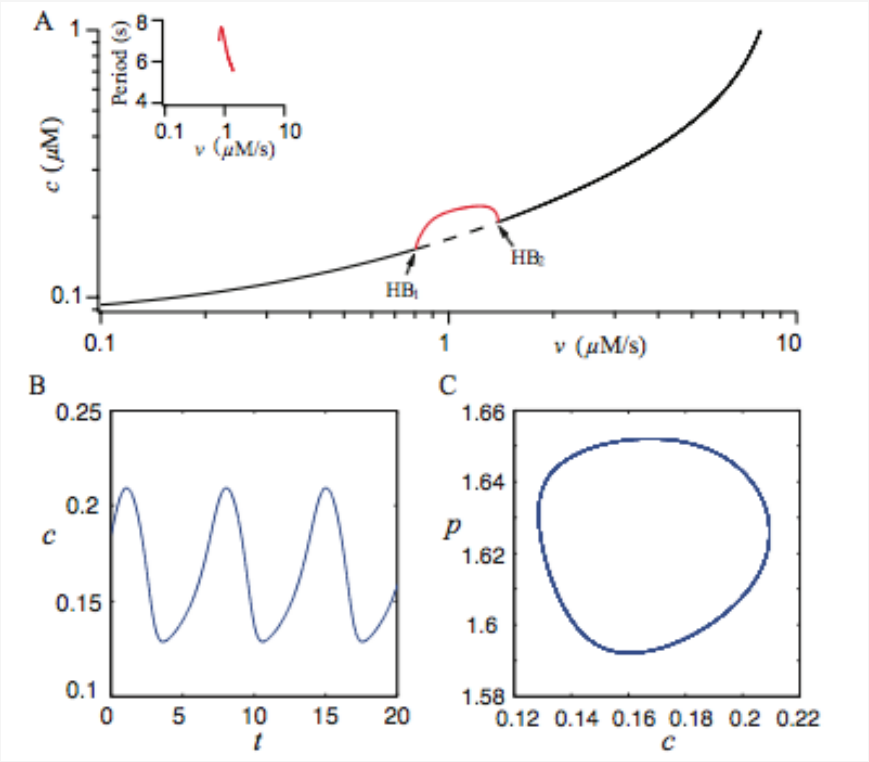

Figure: Class II (Sneyd)