Calcium Dynamics

Evan Cresswell
Florida State University
2nd February 2016
Calcium Dynamics: Why we care

New experimental approaches that enable the study of astrocyte physiology at higher spatial-temporal 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 looooonng: much more variability
Amplitude vs Frequency
Great for modelers

Figure: Calcium Signaling: a lot going on

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
- store operated channels

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

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

Figure: Calcium Signaling: significant dynamics

---

$^1$James Sneyd (2015) Mathematical Analysis of Complex Cellular Activity Springer
This leads to simple formulation of the Calcium in a cell:

\[
\frac{dc}{dt} = J_{IPR} - J_{SERCA} + J_{in} - J_{pm}
\]

\[
\frac{dc_e}{dt} = \gamma(-J_{IPR} + J_{SERCA})
\]

where \( \gamma \) 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 critical feature: a bell-shaped function, of which two techniques are most popular

*IP*<sub>3</sub> receptor subunits: a Hodgkin-Huxely formulation

fast calcium activation followed by a slow calcium inactivation

emphasises the mathematical similarities between IP and the *Na*<sup>+</sup> channel in HH

multi modal IPR

much more complicated (yields similar results)

**Figure:** Calcium Signaling: significant 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

\[ J_{\text{SERCA}} = \frac{V_m c^2}{K_m^2 + c^2} \]

can be more detailed (not typical)

\(^{1}\text{reddit} \)
Membrane fluxes

Can be very complicated and controlled by a variety of factors

- Voltage-dependent channels
  - in response to depolarization of the cell
  - electrically excitable cells

- Receptor-operated receptor operated channels
  - in response to agonist stimulation
  - exact mechanisms are unknown

- Store-operated channels (depletion of ER/SR)

- Can be approximated within model parameters
Model Classification

Let's 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 $Ca^{2+}$

$\nu$ is the maximal rate of $IP_3$ production
Bifurcation Structure of Class I/Class II Models

Bifurcation analysis shows you how the model acts as you vary a specific parameter (in this case $\nu$)

**Figure**: Class I (Sneyd)
Bifurcation analysis shows you how the model acts as you vary a specific parameter (in this case $\nu$)

**Figure:** Class II (Sneyd)