

Mathematical Modelling and Scientific Computing in the Biosciences II

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Course webpage

<http://www.ricam.oeaw.ac.at/people/page/jameslu/Teaching/>

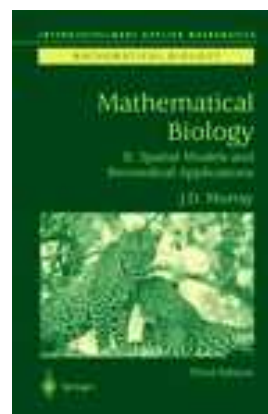
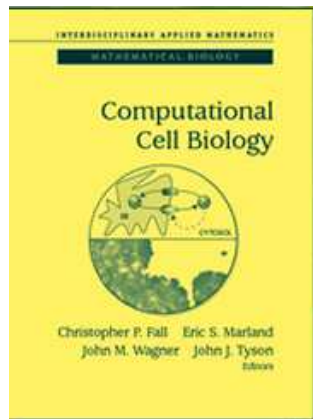
Locations

Lectures: Tues 13:45–15:15, **BA 9907**

Computer room: **HF 107**

Texts

- *Computational Cell Biology*, C. P. Fall, E. S. Maryland, J. M. Wagner, J. J. Tyson, editors. Springer 2002.
- *Mathematical Biology II: Spatial Models and Biomedical Applications*, J. D. Murray. Third Edition, Springer 2003.



Requirement and Grading

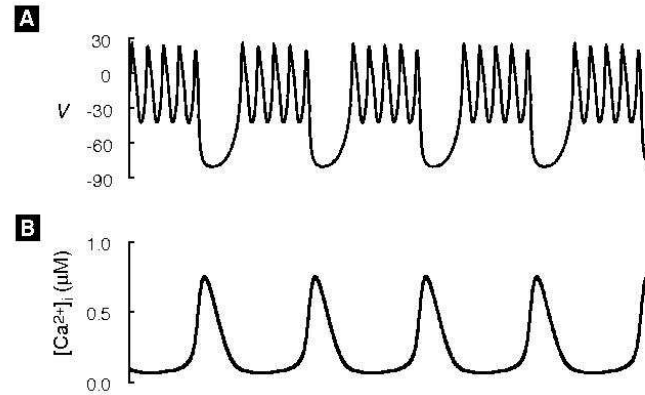
Significant computer assignment, using mathematical software of your choice: *Mathematica* or Matlab

Grade: **40%** exercises, **60%** a small project

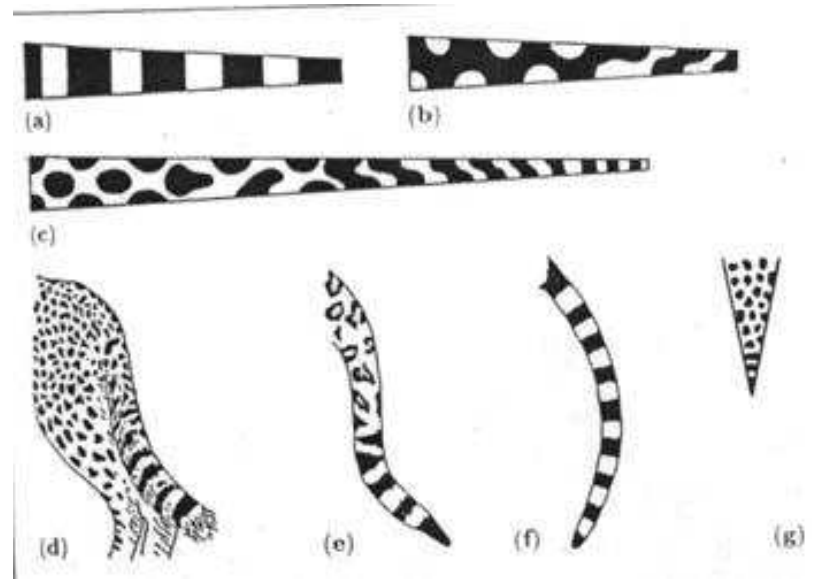
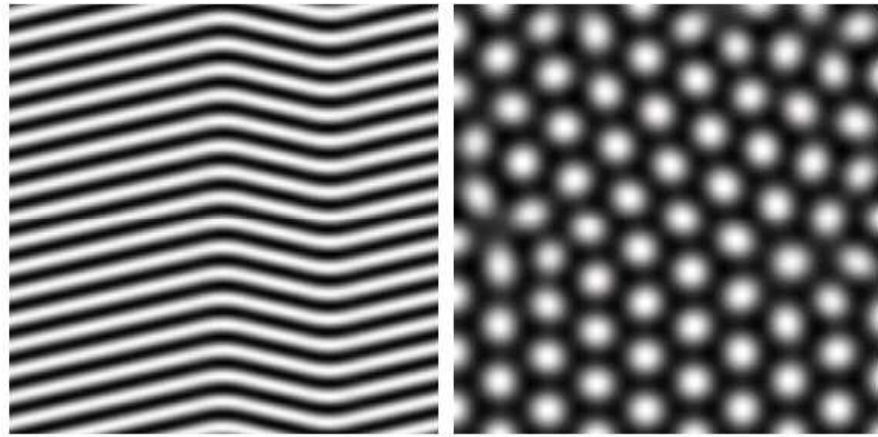


Course Content

- Modelling and bifurcation analysis
 - Calcium oscillation in whole-cell models
 - Intercellular communication



- Spatial models
 - Reaction diffusion/Turing mechanism
 - Pattern formation

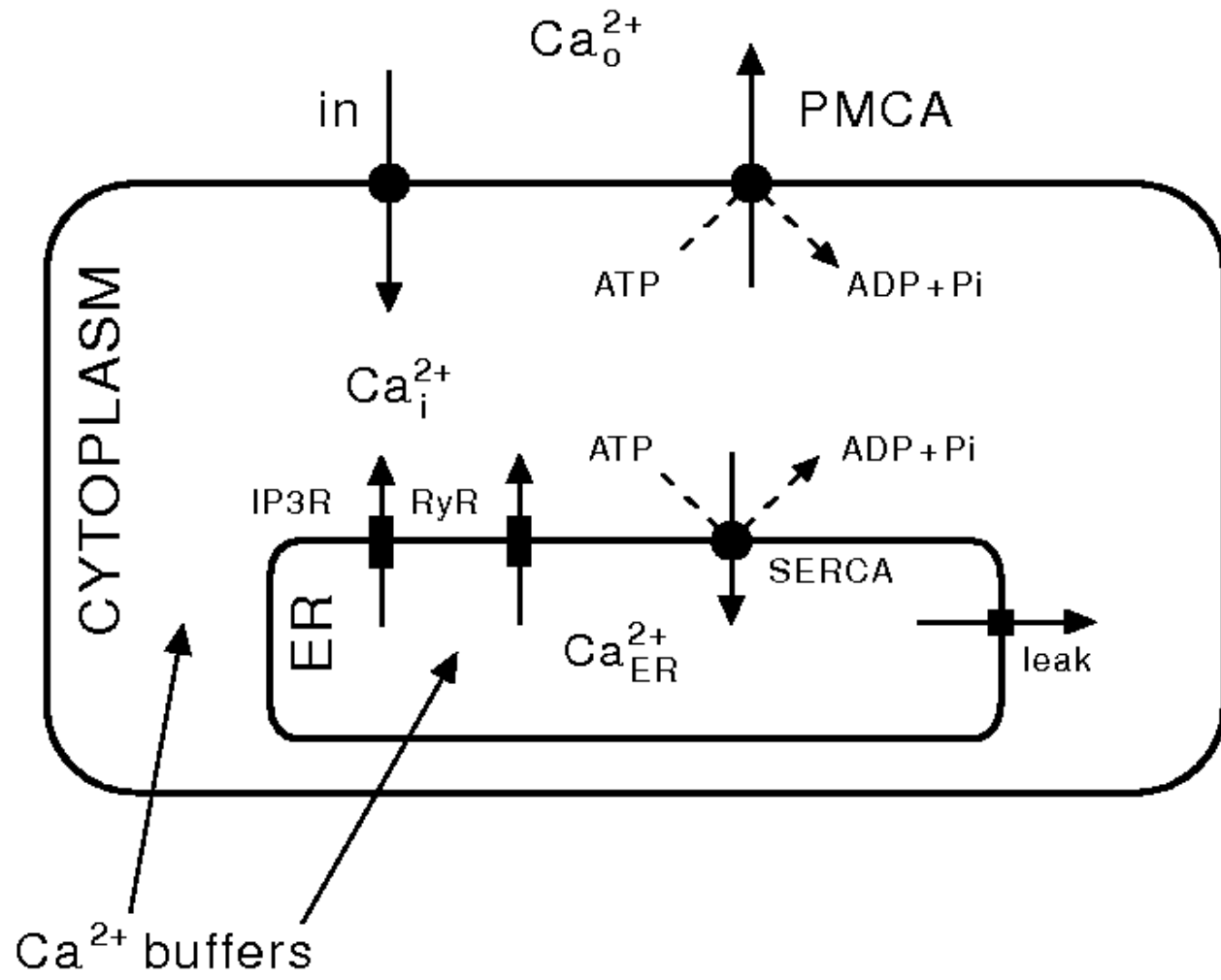


Whole Cell Modelling: Control of Calcium Oscillations

Calcium binds to many proteins and modifies their enzymatic properties; thus, need to control and localize Ca^{2+}

Two basic mechanisms:

- **Buffering:** specialized Ca^{2+} binding proteins that soak up most of the calcium in the cytosol
- **Sequestration:** in internal stores, such as the endoplasmic reticulum (ER); via
 - SERCA pumps
 - channels such as ryanodine receptor (RyR), IP3R receptors



Whole Cell Modelling: Control of Calcium Oscillations

Flux Balance Equations

The number of ions in the cytoplasm and endoplasmic reticulum (ER) changes due to fluxes across plasma membrane (PM) and ER:

$$\frac{d [Ca^{2+}]_i^{tot}}{dt} = \frac{1}{\bar{V}} \left(J_{PM}^{in} - J_{PM}^{out} - J_{ER}^{in} + J_{ER}^{out} \right)$$

$$\frac{d [Ca^{2+}]_{ER}^{tot}}{dt} = \frac{1}{\bar{V}_{ER}} \left(J_{ER}^{in} - J_{ER}^{out} \right)$$

Buffering Equations

Total calcium equals free Ca^{2+} plus those bound to buffer **B**: in the cytosol,

$$[Ca^{2+}]_i + [Ca^{2+} \cdot B]_i = [Ca^{2+}]_i^{tot}$$

$$[B]_i + [Ca^{2+} \cdot B]_i = [B]_i^{tot}$$

Whole Cell Modelling: Control of Calcium Oscillations

Buffer: Rapid Equilibrium Assumption

We assume rapid equilibrium between **buffer** and Ca^{2+} with equilibrium constant K_i , thereby avoiding writing down the additional differential equation for the reaction:

$$[\text{Ca}^{2+}]_i = \frac{K_i [\text{Ca}^{2+} \cdot \text{B}]_i}{[\text{B}]_i}$$

When combined with TotalBufferEqn

$$[\text{Ca}^{2+}]_i^{\text{tot}} = [\text{Ca}^{2+}]_i \left(1 + \frac{[\text{B}]_i}{K_i} \right)$$

Hence the ODE for Ca^{2+} is:

$$\begin{aligned} \frac{d [\text{Ca}^{2+}]_i^{\text{tot}}}{dt} &= \frac{d [\text{Ca}^{2+}]_i^{\text{tot}}}{d [\text{Ca}^{2+}]_i} \frac{d [\text{Ca}^{2+}]_i}{dt} \\ &= \left(1 + \frac{\kappa_i [\text{B}]_i^{\text{tot}}}{(\kappa_i + [\text{Ca}^{2+}]_i)^2} \right) \frac{d [\text{Ca}^{2+}]_i}{dt} \end{aligned}$$

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Whole Cell Modelling: Control of Calcium Oscillations

Buffer: Low Affinity Assumption

We further assume that the buffer has low affinity, i.e., total free buffer concentrations are essentially the same

Combining previous equations

$$[B]_i + [Ca^{2+} \cdot B]_i = [B]_i^{tot}, \quad [Ca^{2+}]_i^{tot} = [Ca^{2+}]_i \left(1 + \frac{[B]_i}{K_i} \right)$$

we get the relation between the concentrations of total and free buffer:

$$[B]_i^{tot} = [B]_i \left(1 + \frac{[Ca^{2+}]_i}{K_i} \right)$$

Thus low affinity assumption corresponds to:

$$K_i \gg [Ca^{2+}]_i$$

and thus Total Calcium to Free Calcium Rates becomes

$$\frac{d [\text{Ca}^{2+}]_i^{\text{tot}}}{dt} = \left(1 + \frac{1}{[\text{B}]_i^{\text{tot}} / K_i} \right)^{-1} \frac{d [\text{Ca}^{2+}]_i}{dt}$$



Whole Cell Modelling: Control of Calcium Oscillations

Expression for Fluxes

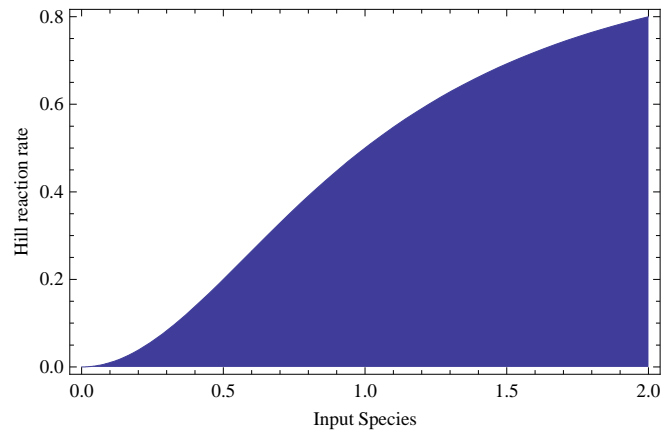
Now we should relate the flux terms

$$J_{PM}^{in}, J_{PM}^{out}, J_{ER}^{in}, J_{ER}^{out}$$

to expressions involving the concentrations of Ca^{2+} .

Use empirical, *Hill-type* formulas (see notes from previous course), i.e.,

$$J_{SERCA} = \bar{V} \frac{v_{SERCA} \cdot [Ca^{2+}]_i^2}{K_{SERCA}^2 + [Ca^{2+}]_i^2}$$



Efflux from ER to cytosol includes constant, unregulated leak of the form:

$$J_{\text{LEAK}} = \bar{V} \cdot \nu_{\text{SERCA}} \cdot \left([\text{Ca}^{2+}]_{\text{ER}} - [\text{Ca}^{2+}]_{\text{i}} \right)$$

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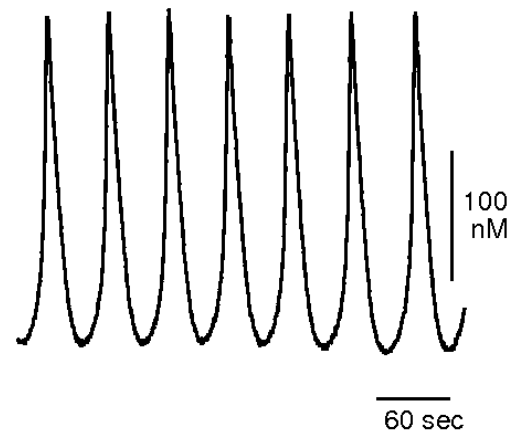
Whole Cell Modelling: Control of Calcium Oscillations

Bullfrog Sympathetic Ganglion Neuron

The Ca^{2+} oscillations are driven by nonlinearity in the ER

Rhythmic hyperpolarizations of the resting membrane potential has been observed when neurons were exposed to caffeine:

$[\text{Ca}^{2+}]$ oscillations of a bullfrog sympathetic ganglion neuron during continuous exposure to caffeine



Caffeine has been found to activate Ryanodine Receptor (RyR) by shifting down Ca^{2+} dependence of channel opening to lower concentrations

The caffeine induced oscillations also occur when membrane voltage is clamped at a fixed value, suggesting that voltage-gated ion channels are not involved in producing oscillations

Whole Cell Modelling: Control of Calcium Oscillations

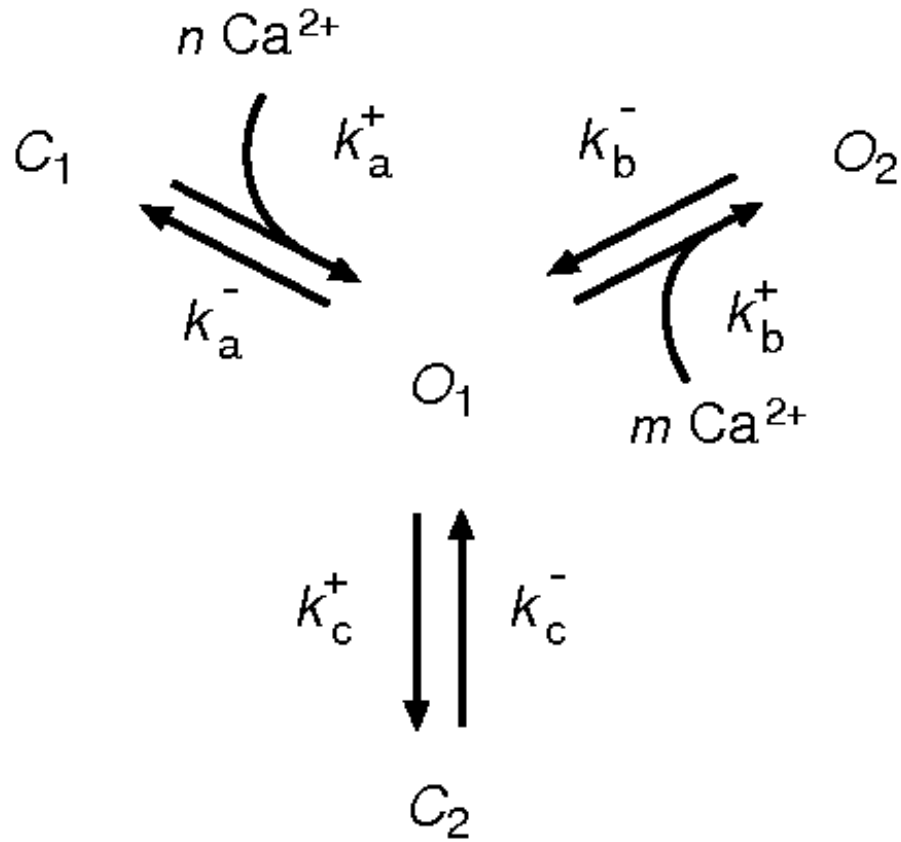
Ryanodine Receptor Kinetics: Keizer–Levine Model

The oscillations are characterized by: sharp upstroke, followed by a plateau phase, and subsequent downstroke

The state diagram consists of 2 closed states (C_1, C_2) and 2 open states (O_1, O_2)

The net open probability is $P_O = P_{O1} + P_{O2}$

Kinetic states of Keizer–Levine model for Ryanodine Receptor
C: closed, O: open



Whole Cell Modelling: Control of Calcium Oscillations

Ryanodine Receptor Kinetics: Keizer–Levine Model

Without going into the derivations, the equation for the fraction of non-inactivated receptors, w , is:

$$\frac{dw}{dt} = \frac{(w_{\infty} - w)}{\tau},$$

$$w_{\infty} = \frac{1 + (K_a / [Ca^{2+}]_i)^4 + ([Ca^{2+}]_i / K_b)^3}{1 + (1 / K_c) + (K_a / [Ca^{2+}]_i)^4 + ([Ca^{2+}]_i / K_b)^3}, \quad \tau = \frac{w_{\infty}}{k_c^-}$$

where the (slow) time-scale τ

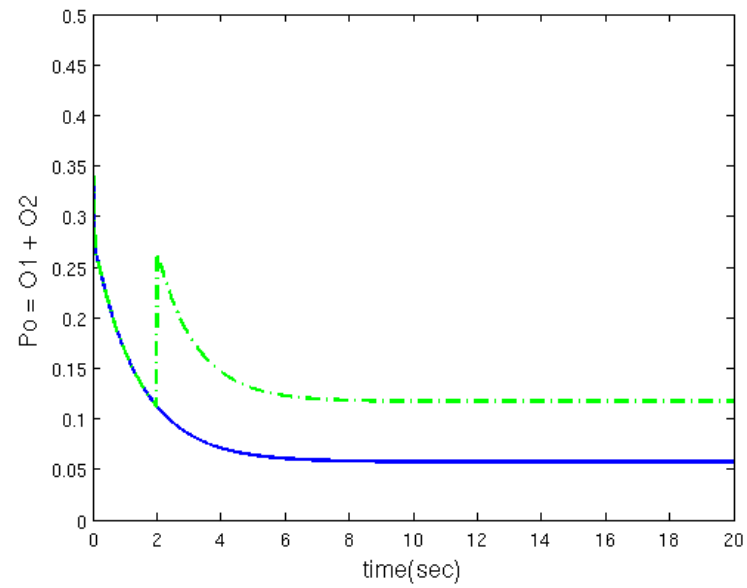
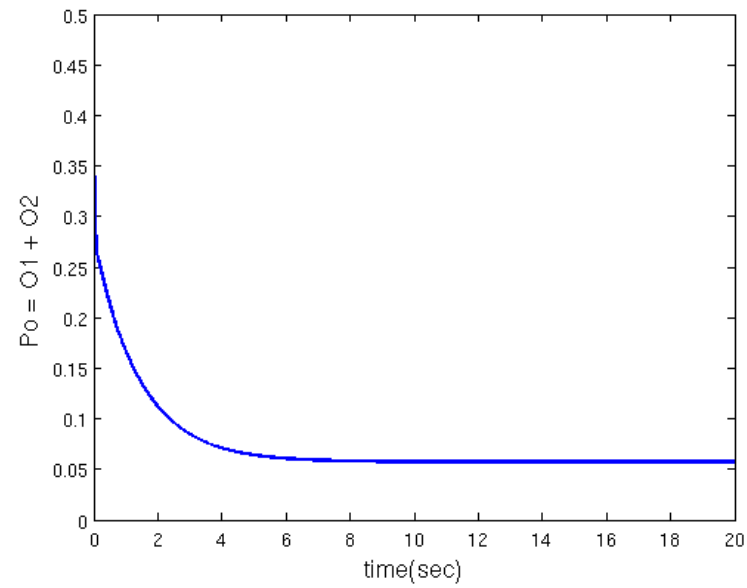
is inversely proportional to k_c^+ , the rate of transition out of closed state C_2

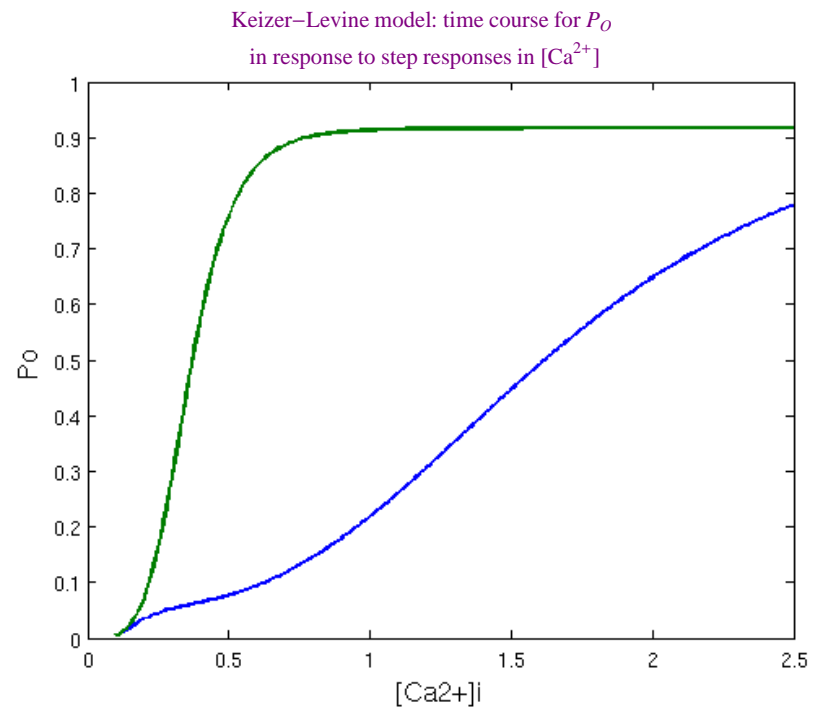
Lets now look at the typical behavior of this equation...

Whole Cell Modelling: Control of Calcium Oscillations

Ryanodine Receptor Kinetics: Keizer–Levine Model

Keizer–Levine model: time course for P_O in response to step responses in $[Ca^{2+}]$





Whole Cell Modelling: Control of Calcium Oscillations

Bullfrog Sympathetic Ganglion Neuron

Next, we look at 2 models incorporating RyR dynamics:

- **Closed Cell Model**
- **Open Cell Model**

For the **closed cell model**, we show that the model is able to exhibit *bistability*; however, oscillations are not possible

For the model to oscillate as observed in experiments, we consider an **open cell model**, where an additional slower process is used to take the system around the bistable bifurcation diagram

That is, we build a relaxation oscillator, combining a **slow** and a **fast** process

Whole Cell Modelling: Control of Calcium Oscillations

Bullfrog Sympathetic Ganglion Neuron: Closed Cell Model

With no plasma membrane currents, $j_{PM}^{in} = 0$, $j_{PM}^{out} = 0$

$$\frac{d [Ca^{2+}]_i}{dt} = f_i (j_{RyR} + j_{LEAK} - j_{SERCA})$$

where

$$j_{RyR} = v_{RyR} \cdot P_o \cdot ([Ca^{2+}]_{ER} - [Ca^{2+}]_i),$$

$$j_{LEAK} = v_{LEAK} \cdot ([Ca^{2+}]_{ER} - [Ca^{2+}]_i),$$

$$j_{SERCA} = v_{SERCA} \cdot \frac{[Ca^{2+}]_i^2}{[Ca^{2+}]_i^2 + K_{SERCA}^2},$$

Obtain 2-dimensional ODE system for calcium, and w

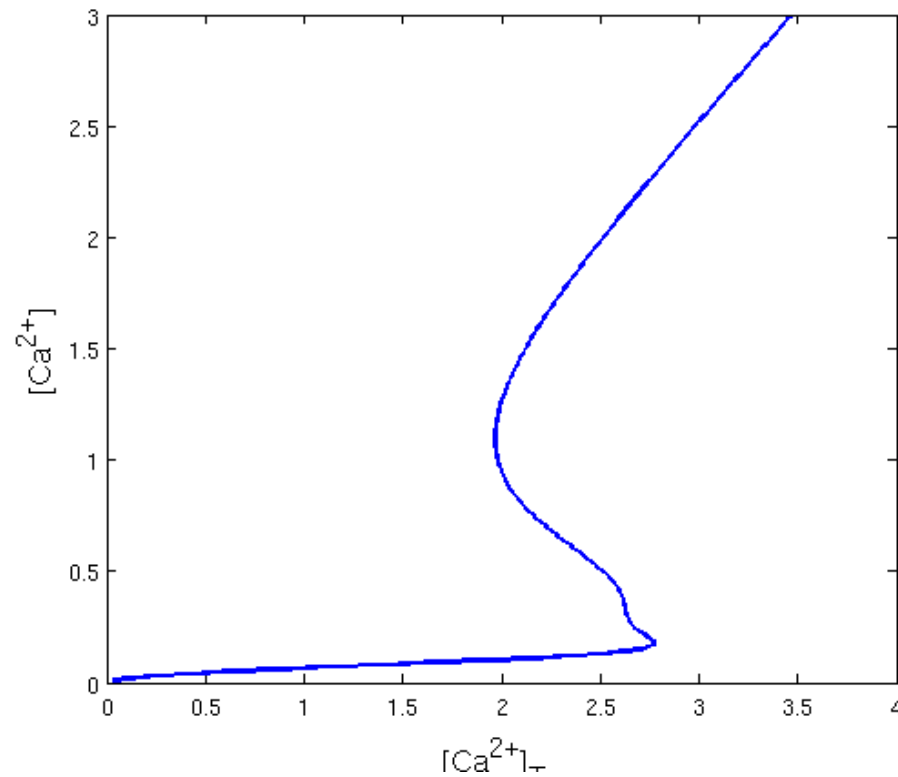
In this closed cell model, the total calcium $[Ca^{2+}]_T$ is constant; hence natural to choose it as a *bifurcation parameter*

Whole Cell Modelling: Control of Calcium Oscillations

Bullfrog Sympathetic Ganglion Neuron: Closed Cell Model

Look at how the number of steady-state solutions vary as $[Ca^{2+}]_T$ varies:

Bifurcation diagram for Closed Cell Model



From the diagram, we see:

- For low values of $[Ca^{2+}]_T$, the steady-state solution of $[Ca^{2+}]$ is low (correspondingly, w is high)

- For high values of $[Ca^{2+}]_T$, the steady-state solution of $[Ca^{2+}]$ is high (correspondingly, w is low)
- For intermediate values of $[Ca^{2+}]_T$, there are 2 stable solutions and 1 unstable solution; i.e., region of bistability bracketed by 2 *saddle-node* bifurcation points

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Whole Cell Modelling: Control of Calcium Oscillations

Bullfrog Sympathetic Ganglion Neuron: Open Cell Model

We saw that adaptation of RyR is not the source of mechanism behind the cell

However, the model is bistable. Can an oscillatory model be constructed by building on the bistable module?

Yes, construct a *relaxation oscillator* by introducing an additional variable that moves about the bistable bifurcation diagram; i.e., the **closed cell model** is the fast subsystem of the **open cell model**

In particular, introduce an equation for total calcium concentration, $[Ca^{2+}]_T$

$$\frac{d [Ca^{2+}]_T}{dt} = f_i (j_{in} - j_{PMCA})$$

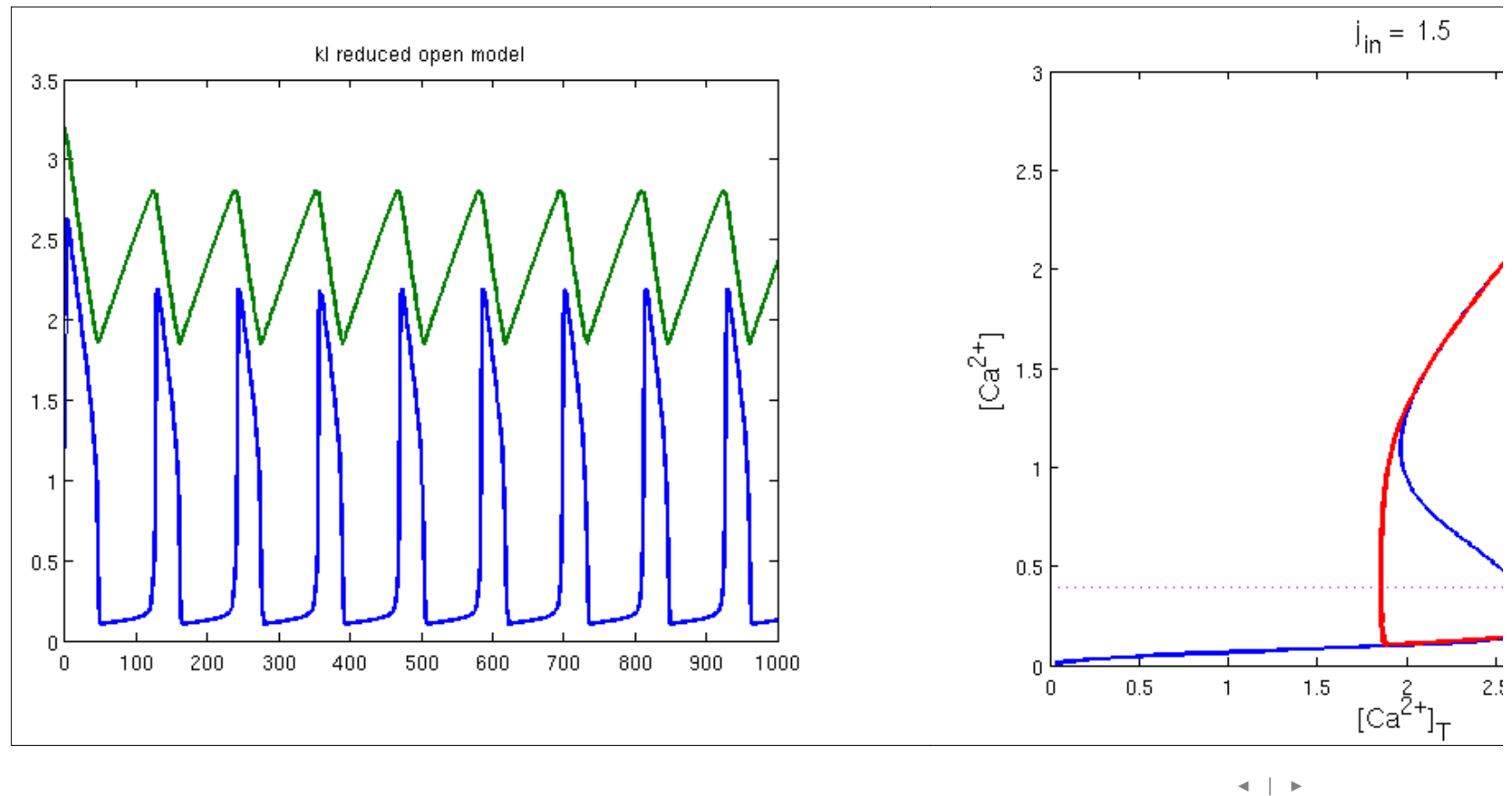
where j_{in} describes the fluxes into the cell, j_{PMCA} the flux pumping Ca^{2+} from the cell, given by expression

$$j_{PMCA} = v_{PMCA} \cdot \frac{[Ca^{2+}]_i^2}{[Ca^{2+}]_i^2 + K_{PMCA}^2}$$

Whole Cell Modelling: Control of Calcium Oscillations

Bullfrog Sympathetic Ganglion Neuron: Open Cell Model

One can understand the coupling of fast/slow components (which is typical in relaxation oscillators) by super-imposing time-series on bifurcation diagram

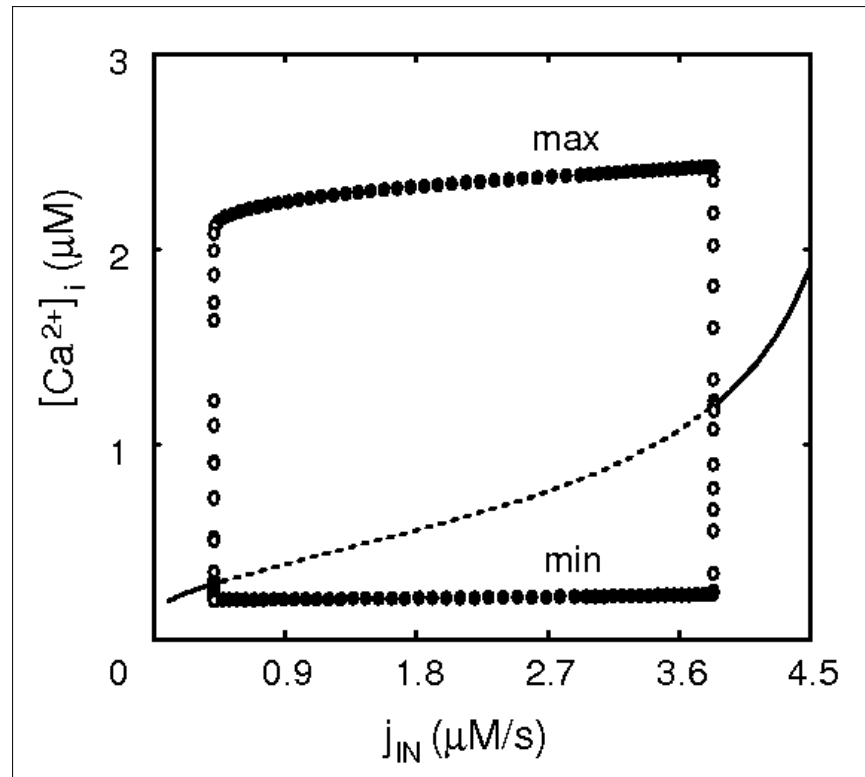


Whole Cell Modelling: Control of Calcium Oscillations

Bullfrog Sympathetic Ganglion Neuron: Open Cell Model

Bifurcation analysis shows that amplitude of oscillation is essentially independent of input current, j_{in}

This follows from the relaxation oscillator character of the model: the amplitude in $[Ca^{2+}]_i$ is given by the bistable bifurcation diagram of closed cell model



Bifurcation diagram, with respect to parameter $[Ca^{2+}]_T$

Conclusions

- Modelling involving buffering, multi-compartment
- Construction of a relaxation type oscillator using slow/fast sub-systems

- Next time: model showing *bursting* behavior
- **Exercise 1** will entail using Matlab program, MATCONT, to reproduce bifurcation diagrams, etc