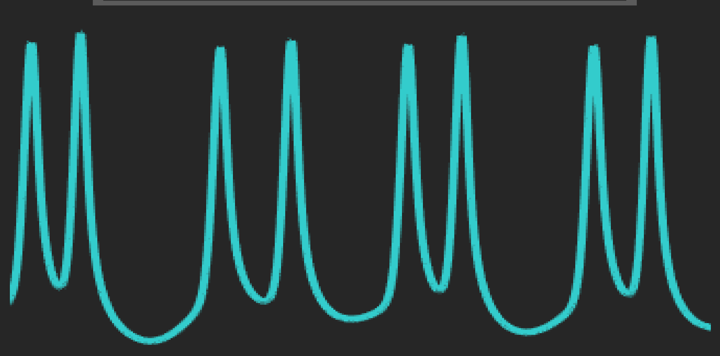
MULTIPLE TIME SCALE DYNAMICS IN CALCIUM OSCILLATIONS

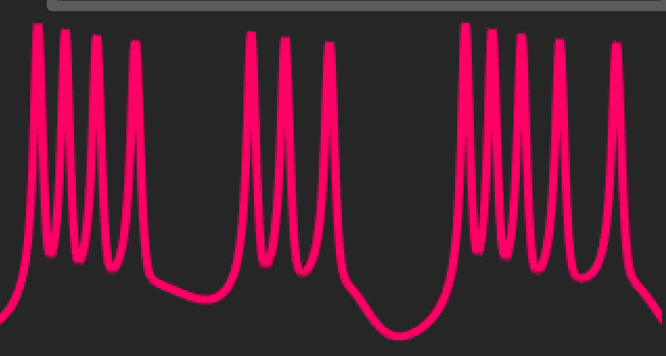
Motivation

BURSTING WITH 2 SPIKES



The natural world is messy, filled with variation. Mathematics on the other hand, is about generalisation and rigor. To truly understand living things we need to consider the underlying principles that govern their behaviour. Many things, including the calcium oscillations in cells, are occurring on multiple time scales. Two time scale systems are relatively well understood, our interest is in those of three time scales. Our research looks closely at bursting (shown to the sides), a phenomena common in neurons. We want to understand the mechanisms that underpin bursting that are intrinsic to three time scales.

BURSTING WITH 3/4 SPIKES



Theory

The area of mathematics concerned with systems that change over time is Dynamical Systems. And in particular to exploit the presence of multiple time scales we familiarise ourselves with Geometric Singular Perturbation Theory (GSPT). Systems of two time scales can be written generally in the following way:

FAST $\frac{dx}{dt} = f(x, y, \varepsilon)$

SLOW $\frac{dy}{dt} = \varepsilon g(x, y, \varepsilon)$

Equations represent the change in arbitrary variables x and y.

When the functions f and g behave 'nicely', and because ε is very small, we're able to take the limit as ε approaches zero and still preserve most of the qualitative behaviour of the system while making it much easier to analyse.

Applications

Interactions on multiple time scales are very prevalent and are frequently observed within a biological context. Calcium encoding is an intracellular signalling pathway used by many cells to transfer, and process information detected by the cell. The concentration of Ca^{2+} ions oscillates, and can be measured. In excitable cells such as neurons, the interaction can sometimes be modelled with variables that evolve on three distinct time scales. Studying such systems mathematically provides fundamental information about the intrinsic nature of cell signalling.

BASIC NEURON MODEL

Fitzhugh-Nagumo Model

EQUATIONS

The FitzHugh-Nagumo Model encapsulates the most basic properties of neurons.

FAST $\frac{dV}{dt} = -V(V-0.1)(V-1) - w + I$

SLOW $\frac{dw}{dt} = \varepsilon(V - w)$

Timescale Parameter

External Current Parameter

V is the voltage across the cell membrane

w is a recovery variable (regulates change in voltage)

ANALYSIS

Phase Space shows varying periodic solutions for different values of I

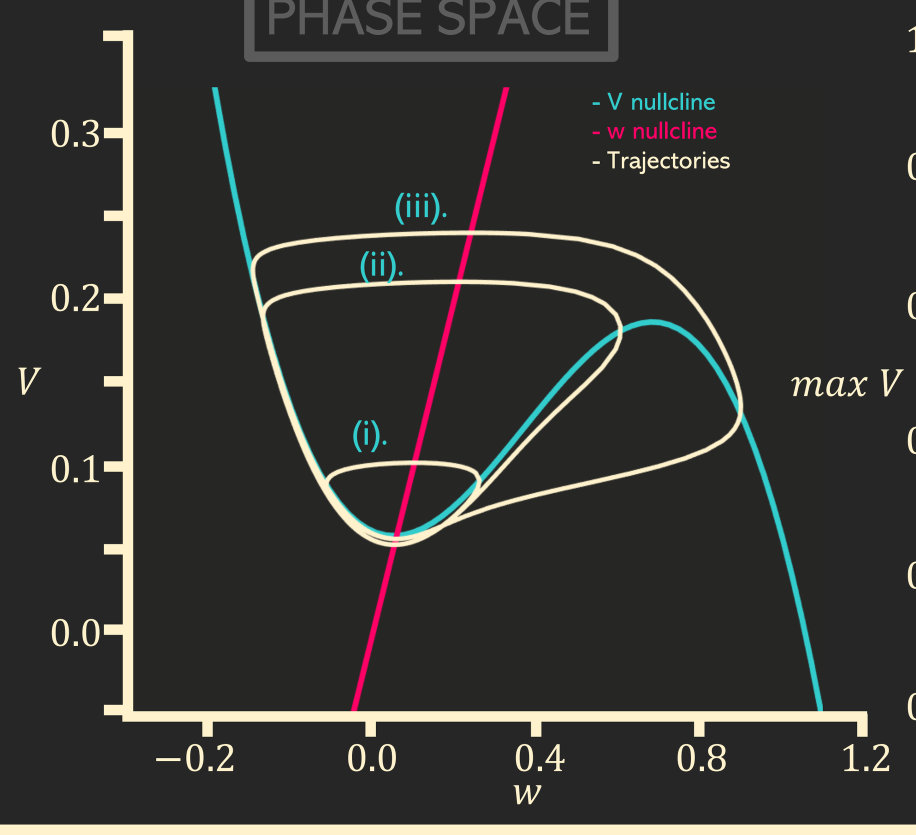
(i). $I = 0.05835$

(ii). $I = 0.058431$

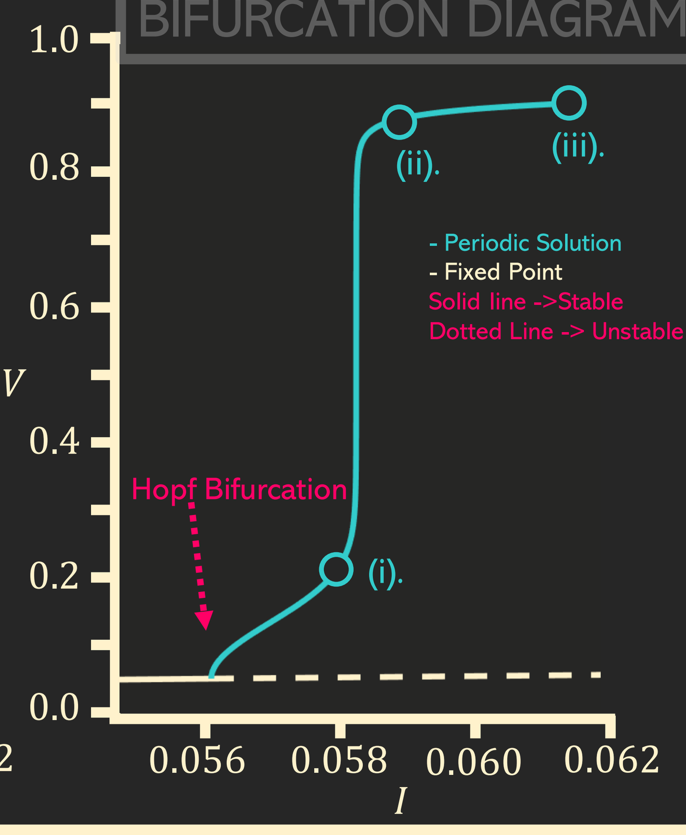
(iii). $I = 0.0625$

Bifurcation Diagram shows onset of periodic solutions by Hopf-Bifurcation, sudden increase in max V amplitude and presence of canard solutions

PHASE SPACE



BIFURCATION DIAGRAM



Three Time-Scale Analysis

EQUATIONS

The model we're investigating is of the following form:

FAST $\frac{dx}{dt} = y - a_3x^3 - a_2x^2 + a_1x + a_0$

MED $\frac{dy}{dt} = \delta(b_2x^2 - b_1x - cy - z + c_0)$

SLOW $\frac{dz}{dt} = \varepsilon\delta(x - \gamma)$

Medium Timescale Parameter

Slowest Timescale Parameter

Bifurcation Parameter

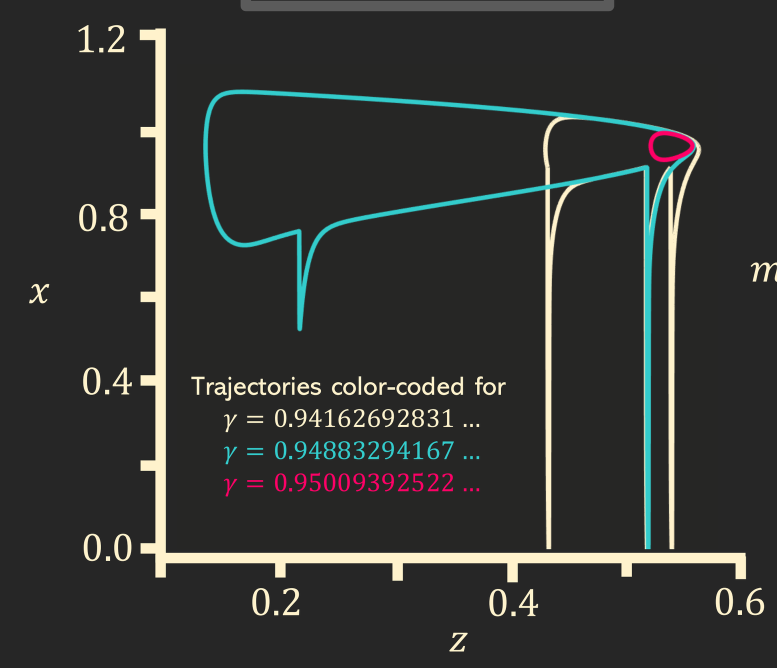
'γ' is our bifurcation parameter, we vary it and observe how the qualitative behaviour changes.

On the right we show the dynamics for different values of β_1 (a grouping parameter for a_1, b_1 which changes the system's structure). We see that for $\beta_1 = 0.70$ we get bursting solutions.

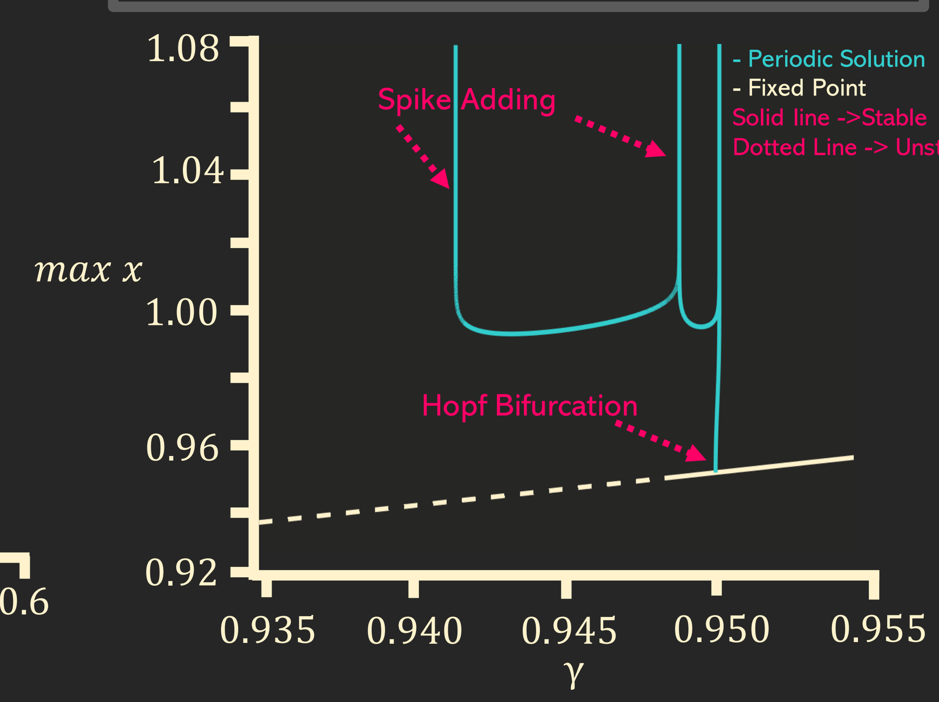
But for $\beta_1 = 0.16$ we don't, just the periodic solutions. We want to identify why one system causes bursting and the other doesn't. Distinguishing the possible mechanisms for bursting in three timescale systems is difficult but a fruitful area of research.

$\beta_1 = 0.70$

PHASE SPACE

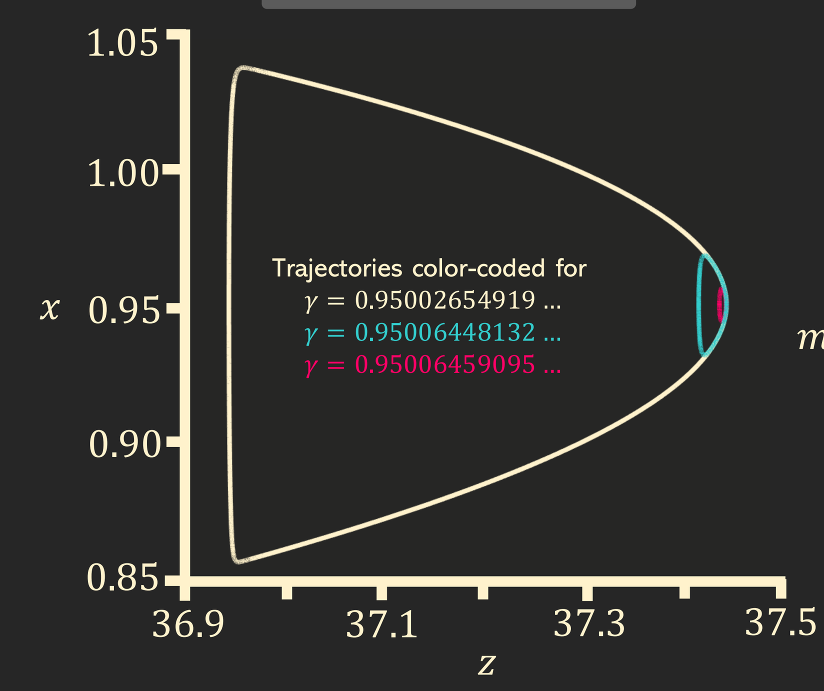


PARTIAL BIFURCATION DIAGRAM

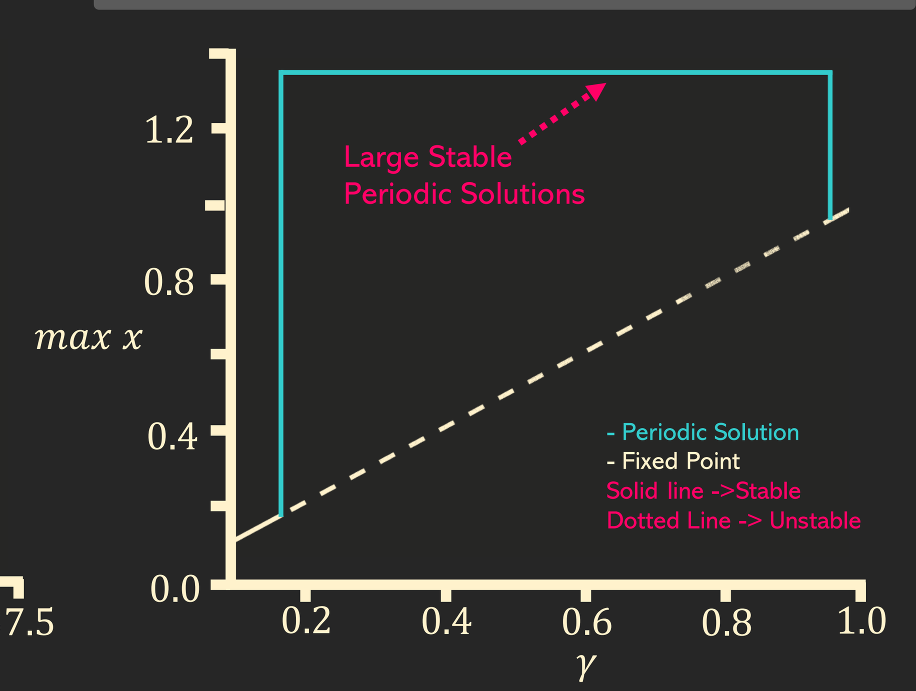


$\beta_1 = 0.16$

PHASE SPACE



PARTIAL BIFURCATION DIAGRAM



References

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- 'Spike-Adding in a Canonical Three-Time-Scale Model: Superslow Explosion and Folded-Saddle Canards' – Mathieu Desroches and Vivien Kirk, Applied Dynamical Systems Vol. 17, No. 3, pp. 1987 – 2017
- 'The Effect of Geometry on the Dynamics of a Three Timescale System' – Uzma Atiq, Master's thesis, UoA, 2018
- 'Dynamical Systems Analysis of Biophysical models with Multiple Time Scales' – Pingyu Nan, Doctoral Thesis, UoA, 2014

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