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A Mathematical Study of Calcium Oscillations and Waves

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Contents

Abstract xi

Acknowledgements xiii

Preface xv

1 Introduction 1
  1.1 Ca\(^{2+}\) as an intracellular messenger 2
  1.2 Pancreatic Secretion 9
  1.3 The Pancreatic Acinar Cell 12
  1.4 Modelling of Ca\(^{2+}\) oscillations and waves 17
    1.4.1 Previous modelling work 21
  1.5 Summary 35

2 Model Construction 37
  2.1 The homogeneous single cell model 38
CONTENTS

3.8 Experimental verification ........................................ 81

4 Ca$^{2+}$ oscillations and waves in a pancreatic acinus ............ 85

4.1 Model - I .................................................................. 88
  4.1.1 Description of the model ........................................ 88
  4.1.2 Numerical method .................................................. 88
  4.1.3 Results ............................................................... 88

4.2 Model - II .................................................................. 104
  4.2.1 Description of the model ........................................ 104
  4.2.2 Numerical method .................................................. 104
  4.2.3 Results ............................................................... 106

5 Conclusions .................................................................. 117

A Summary of the model equations ....................................... 121
  A.1 Model - I ................................................................. 121
  A.2 Model - II ............................................................... 122

B The Sneyd et al. model ................................................... 125

C The Li-Rinzel model ....................................................... 129
List of Figures

1.1 Principal pathways involved in calcium signalling mediated by production of IP$_3$ ................................. 4
1.2 Typical cytosolic Ca$^{2+}$ oscillations. ........................................... 5
1.3 Experimental data from physiological agonist stimulation [44]. .... 6
1.4 Experimental data from physiological agonist stimulation [51]. .... 7
1.5 Experimental data from physiological agonist stimulation [143]. ... 8
1.6 Pancreas .................................................. 9
1.7 Pancreatic Acinus .............................................. 10
1.8 Pancreatic Acinar Cell. ............................................ 12
1.9 Experimental data. .............................................. 14
1.10 Cluster of Acinar Cells ........................................... 16
1.11 Adapted from DeYoung et al. model [30]. ............................ 23
1.12 Bifurcation diagram for the reference parameters given in Table 1.1. DeYoung et al. [30] ............................. 25
LIST OF FIGURES

1.13 Bifurcation diagram for $\alpha = 0.97$ (left panel). Periodic solutions for $\alpha = 0.97$ and $\nu_4 = 2.8 \text{ s}^{-1}$, solid line denotes $[\text{Ca}^{2+}]$ and broken line denotes $[\text{IP}_3]$ (right panel). DeYoung et al. [30] .......................... 26

1.14 Bifurcation diagrams of Dupont et al. model [33] .......................... 27

1.15 Typical oscillations in Dupont et al. model [36] .......................... 30

1.16 Adapted from LeBeau et al. model [66] .......................... 31

1.17 Bifurcation diagrams of LeBeau et al. model [66] .......................... 32

2.1 Schematic diagram of the model fluxes .......................... 38

2.2 Simplified diagram of the IP$_3$R model [111] .......................... 41

2.3 Schematic diagram of the RyR model [63] .......................... 42

2.4 Schematic diagram of the model of an acinar cell .......................... 45

2.5 Schematic diagram of a cluster of three cells .......................... 50

2.6 The model cluster of three pancreatic acinar cells .......................... 52

3.1 Schematic diagram of the model .......................... 56

3.2 Bifurcation diagram of the closed-cell model .......................... 60

3.3 Two-parameter bifurcation diagram in $(c_t, p)$-space .......................... 61

3.4 Bifurcation diagrams of the open-cell model .......................... 63

3.5 Two-parameter continuation in $(p, \delta)$-space of the Hopf bifurcations of the open-cell model .......................... 64
LIST OF FIGURES

3.6 Typical oscillations, obtained by numerical integration of the open-cell model, for $\delta = 0.1$ and different values of $p$. ......................... 65

3.7 Typical oscillations, obtained by numerical integration of the open-cell model, for $p = 10$ and different values of $\delta$. ......................... 66

3.8 Experimentally observed oscillations in mouse pancreatic acinar cells. 67

3.9 Dynamic modulation of the cytosolic calcium oscillations. ............... 68

3.10 A spiking cycle projected onto the $(c, c_t)$ plane for value of $p = 10$. 69

3.11 The effects of changing membrane transport. ............................. 71

3.12 Bifurcation diagram of the open-cell model superimposed on the two-parameter bifurcation diagram of the closed-cell model. ................. 74

3.13 Two-parameter bifurcation diagram of the open-cell model in $(\alpha_1 - p)$ plane. ................................................. 75

3.14 Analogue of Figures 3.12 and 3.13 for the Li-Rinzel model. ............ 76

3.15 Analogue of Figures 3.12 and 3.13 for the Atri et al. model. ............ 77

3.16 Model simulations ...................................................... 80

3.17 Experimental traces - model prediction 1.................................. 82

3.18 Experimental traces - model prediction 2.................................. 83

3.19 Experimental traces ...................................................... 84

4.1 Bifurcation diagram of the single cell model. ................................ 92

4.2 Bifurcation diagrams of the homogeneous model I. ....................... 95
<table>
<thead>
<tr>
<th>FIGURE</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.3</td>
<td>Typical oscillations in the homogeneous model I.</td>
</tr>
<tr>
<td>4.4</td>
<td>Two-parameter bifurcation diagrams in ((p_{st}, \epsilon))-space (identical cells).</td>
</tr>
<tr>
<td>4.5</td>
<td>Two-parameter bifurcation diagrams in ((p_{st}, \epsilon))-space (non-identical cells).</td>
</tr>
<tr>
<td>4.6</td>
<td>Typical synchronised oscillations in the model in the case of weak coupling.</td>
</tr>
<tr>
<td>4.7</td>
<td>Typical synchronised oscillations in the model in the case of strong coupling.</td>
</tr>
<tr>
<td>4.8</td>
<td>Experimental image of a cluster of three pancreatic acinar cells.</td>
</tr>
<tr>
<td>4.9</td>
<td>Two-parameter diagram in ((p_f, c_f))-space.</td>
</tr>
<tr>
<td>4.10</td>
<td>Intercellular oscillations in the triplet.</td>
</tr>
<tr>
<td>4.11</td>
<td>Typical intercellular oscillations in a heterogeneous in terms of stimulation cluster.</td>
</tr>
<tr>
<td>4.12</td>
<td>Experimental traces.</td>
</tr>
<tr>
<td>4.13</td>
<td>Typical oscillations in a structurally heterogeneous cluster.</td>
</tr>
<tr>
<td>E.1</td>
<td>The FEM Mesh of Three Cells</td>
</tr>
<tr>
<td>E.2</td>
<td>Numbering Scheme of the Master Element</td>
</tr>
<tr>
<td>E.3</td>
<td>The Interface Boundary</td>
</tr>
</tbody>
</table>
List of Tables

1.1 Parameter values of DeYoung et al. model [30] ................... 24

1.2 Values of the parameters characterising Ins-1,4,5-P$_3$ synthesis and metabolism used in Dupont et al. model [36] ................... 29

A.1 Steady state values of the system variables ................... 123

A.2 Model parameters ........................................ 124

B.1 Parameter values of the Sneyd et al. model [114] ............ 128

C.1 Parameter values of the Li-Rinzel model [72] ................. 130

D.1 Parameter values of the Atri et al. model [6] ................. 132

E.1 Gauss points and quadrature weights ........................ 142
Abstract

In this thesis we study theoretically the dynamics of the free cytosolic Ca\(^{2+}\) concentration. We construct a mathematical model of the Ca\(^{2+}\) dynamics in pancreatic acinar cells. Although this model refers to a particular cell type, it also allows us to study some aspects of Ca\(^{2+}\) signalling in general. We begin by analysing the dependence of the Ca\(^{2+}\) oscillations on the plasma membrane transport. Further we study the propagation of intercellular Ca\(^{2+}\) waves in a pancreatic acinus.

It has been observed experimentally that, in many cell types, calcium fluxes across the plasma membrane affect inositol trisphosphate IP\(_3\)-induced calcium oscillations. Since IP\(_3\)-induced calcium oscillations involve the cycling of calcium to and from the endoplasmic reticulum, it is not well understood how they can be so strongly affected by membrane fluxes. We use a mathematical model to answer this question; a model that relies on the introduction of a slow variable, the Ca\(^{2+}\) load of the cell. Our model predictions are confirmed by experimental results. Since similar behaviour is observed in two other models of IP\(_3\)-induced Ca\(^{2+}\) oscillations, it is possible that this bifurcation structure is a generic feature of Ca\(^{2+}\) oscillation models.

The effect of intercellular coupling on the oscillatory dynamics is investigated theoretically. It is demonstrated that junctional calcium diffusion can account for the co-ordination and synchronisation of cytosolic calcium oscillations in a coupled triplet of cells under the assumption of constant IP\(_3\) concentration in each individual cell. Furthermore a two dimensional version of that model, where Ca\(^{2+}\) and IP\(_3\) are assumed to diffuse within as well as between the cells, has been studied numerically. Compared to the results from the analysis of the ODE model, the results from the
analysis of the PDE model (in two spatial dimensions) reveal some interesting spatial effects of the diffusion, and of the geometry of the cells on the collective oscillatory behaviour of the system. Based on this combined approach, a suggestion about the specific role of both Ca\textsuperscript{2+} and IP\textsubscript{3} in the intercellular Ca\textsuperscript{2+} signalling has been made.
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I wish to thank Dr. Vivien Kirk for sharing with me her wealth of knowledge in the area of dynamical systems and bifurcation analysis. Her generous assistance and the productive scientific discussions have helped me a lot during the course of my research.

My appreciation goes to Dr. David Yule for inviting me to visit the University of Rochester Medical Center. I should emphasise how much the opportunity to perform real experiments has contributed to a better understanding of the non mathematical part of my work. I owe a great deal to him, Prof. Trevor Shuttleworth and the many student workers in their labs. Without them, I would not have had any data to analyse and from which to develop theories about cytosolic calcium signalling.

I started my graduate degree at Massey University, so I would like to thank some people from IIMS at Albany. Prof. Robert McKibbin, Merrill Bowers, and my colleagues and friends Cynthia Wang, Maha Shakir, Amal Al-Dujaily were among those who kept me going at the beginning. I also appreciate the assistance I received from the students and faculty from the Department of Mathematics at the University of
Finally, I would like to thank my parents, for their absolute confidence in me. Most of all I would like to acknowledge the great level of understanding and endless patience given to me by my husband Atanas and my daughter Deyana.
Preface

The work presented in this thesis illustrates on one hand how mathematics can be used to answer physiological questions, and on the other hand it is an example of how physiological questions may pose very interesting mathematical problems. It is an interdisciplinary study which requires solid mathematical knowledge as well as a very good understanding of the physiological processes underlying the problems under investigation. Although coming from pure mathematics background I have always been interested in learning more about its applications. The opportunity to work with Prof. James Sneyd was an excellent chance to do this, and I really enjoyed it!

This thesis consists of 4 chapters:

Chapter 1 gives a general introduction to the physiology of the pancreatic acinar cells and the calcium signalling. It also contains a brief overview of previous modelling work done in this field.

Chapter 2 explains the modelling details. Mathematical analyses of the model described in this chapter have been published in [113, 115].

Chapter 3 addresses a particular physiological question about the role of the plasma membrane transport for the calcium oscillations which are based on fluxes across the endoplasmic reticulum. This work has appeared in [114, 129].

Chapter 4 contains a mathematical study of calcium oscillations and waves in a
triplet of pancreatic acinar cells. The results from this study have been submitted for publication to the Biophysical Journal.

All the work presented in this thesis has been done in close collaboration with Dr. David Yule and his colleagues from the University of Rochester Medical Center, USA.