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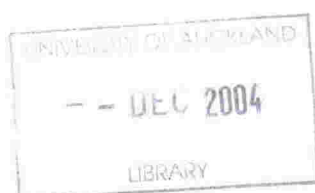
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A Mathematical Study of Calcium Oscillations and Waves

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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^{2+} and IP_3 in the intercellular Ca^{2+} signalling has been made.

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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.