Frontiers in Applied Dynamical Systems: Reviews and Tutorials

Volume 1

More information about this series at http://www.springer.com/series/13763

Frontiers in Applied Dynamical Systems: Reviews and Tutorials

The Frontiers in Applied Dynamical Systems (FIADS) covers emerging topics and significant developments in the field of applied dynamical systems. It is a collection of invited review articles by leading researchers in dynamical systems, their applications and related areas. Contributions in this series should be seen as a portal for a broad audience of researchers in dynamical systems at all levels and can serve as advanced teaching aids for graduate students. Each contribution provides an informal outline of a specific area, an interesting application, a recent technique, or a "how-to" for analytical methods and for computational algorithms, and a list of key references. All articles will be refereed.

Richard Bertram • Joël Tabak • Wondimu Teka
Theodore Vo • Martin Wechselberger
Vivien Kirk • James Sneyd

Mathematical Analysis of Complex Cellular Activity

Review 1: Richard Bertram, Joël Tabak, Wondimu Teka, Theodore Vo, Martin Wechselberger: Geometric Singular Perturbation Analysis of Bursting Oscillations in Pituitary Cells

Review 2: Vivien Kirk, James Sneyd: The Nonlinear Dynamics of Calcium

Springer

Richard Bertram
Department of Mathematics
Florida State University
Tallahasse, FL, USA

Joël Tabak
Department of Mathematics
Florida State University
Tallahassee, FL, USA

Wondimu Teka
Department of Mathematics
Indiana University – Purdue
University Indianapolis
Indianapolis, IN, USA

Theodore Vo
Department of Mathematics and Statistics
Boston University
Boston, MA, USA

Martin Wechselberger
Department of Mathematics
University of Sydney
Sydney, NSW, Australia

Vivien Kirk
Deparment of Mathematics
The University of Auckland
Auckland, New Zealand

James Sneyd
Department of Mathematics
University of Auckland
Auckland, New Zealand

ISSN 2364-4532 ISSN 2364-4931 (electronic)
Frontiers in Applied Dynamical Systems: Reviews and Tutorials
ISBN 978-3-319-18113-4 ISBN 978-3-319-18114-1 (eBook)
DOI 10.1007/978-3-319-18114-1

Library of Congress Control Number: 2015953625

Mathematics Subject Classification (2010): 92C05, 92C30, 92C37, 34C15, 37G15, 37N25

Springer Cham Heidelberg New York Dordrecht London

Printed on acid-free paper

Springer International Publishing AG Switzerland is part of Springer Science+Business Media (www.springer.com)

Preface to the Series

The subject of dynamical systems has matured over a period of more than a century. It began with Poincare's investigation into the motion of the celestial bodies, and he pioneered a new direction by looking at the equations of motion from a qualitative viewpoint. For different motivation, statistical physics was being developed and had led to the idea of ergodic motion. Together, these presaged an area that was to have significant impact on both pure and applied mathematics. This perspective of dynamical systems was refined and developed in the second half of the twentieth century and now provides a commonly accepted way of channeling mathematical ideas into applications. These applications now reach from biology and social behavior to optics and microphysics.

There is still a lot we do not understand and the mathematical area of dynamical systems remains vibrant. This is particularly true as researchers come to grips with spatially distributed systems and those affected by stochastic effects that interact with complex deterministic dynamics. Much of current progress is being driven by questions that come from the applications of dynamical systems. To truly appreciate and engage in this work then requires us to understand more than just the mathematical theory of the subject. But to invest the time it takes to learn a new sub-area of applied dynamics without a guide is often impossible. This is especially true if the reach of its novelty extends from new mathematical ideas to the motivating questions and issues of the domain science.

It was from this challenge facing us that the idea for the *Frontiers in Applied Dynamics* was born. Our hope is that through the editions of this series, both new and seasoned dynamicists will be able to get into the applied areas that are defining modern dynamical systems. Each article will expose an area of current interest and excitement, and provide a portal for learning and entering the area. Occasionally we will combine more than one paper in a volume if we see a related audience as we have done in the first few volumes. Any given paper may contain new ideas and results. But more importantly, the papers will provide a survey of recent activity and the necessary background to understand its significance, open questions and mathematical challenges.

Editors-in-Chief
Christopher K R T Jones, Björn Sandstede, Lai-Sang Young

Preface

In the world of cell biology, there is a myriad of oscillatory processes, with periods ranging from the day of a circadian rhythm to the milliseconds of a neuronal action potential. To one extent or another they all interact, mostly in ways that we do not understand at all, and for at least the past 70 years, they have provided a fertile ground for the joint investigations of theoreticians and experimentalists. Experimentalists study them because they are physiologically important, while theoreticians tend to study them, not only for this reason, but also because such complex dynamic processes provide an opportunity to use, as their tools of investigation, the methods of mathematical analysis.

In this volume, we are concerned with two of these oscillatory processes: calcium oscillations and bursting electrical oscillations. These two are not chosen at random. Not only have they both been studied in depth by modellers and mathematicians, but we also have a good understanding – although not a complete one – of how they interact, and how one oscillatory process affects the other. They thus make an excellent example of how multiple oscillatory processes interact within a cell, and how mathematical methods can be used to understand such interactions better.

The theoretical study of electrical oscillations in cells began, to all intents and purposes, with the classic work of Hodgkin and Huxley in the 1950s. In a famous series of papers they showed how action potentials in neurons arose from the time-dependent control of the conductance of Na^+ and K^+ channels. The model they wrote down, a system of four coupled nonlinear ordinary differential equations, became one of the most influential models in all of physiology. It was quickly taken up by other modellers, who extended the model to study oscillations of electric potential in neurons, and over the last few decades the theoretical study of neurons and groups of neurons has expanded to become one of the largest and most active areas in all of mathematical biology.

More traditional applied mathematicians were also strongly influenced, albeit at one remove, by the Hodgkin-Huxley equations. The simplification by FitzHugh in the 1960s led to the FitzHugh-Nagumo model of excitability (Nagumo, a Japanese engineer, derived the same equation independently at the same time, from entirely different first principles) which formed the basis of more theoretical studies of excitability across many different areas, both inside and outside cell biology.

Oscillations in the cytosolic concentration of free Ca^{2+} (usually simply called Ca^{2+} oscillations) have a more recent history, not having been discovered until the development of Ca^{2+} fluorescent dyes in the 1980s allowed the measurement of intracellular Ca^{2+} concentrations with enough temporal precision. But since then, the number of theoretical and experimental investigations of Ca^{2+} oscillations has expanded rapidly. Calcium oscillations are now known to control a wide variety of cellular functions, including muscular contraction, water transport, gene differentiation, enzyme and neurotransmitter secretion, and cell differentiation. Indeed, the more we learn about intracellular Ca^{2+}, the more we realize how important it is for cellular function. Conversely, the intricate spatial and temporal behaviors exhibited by the intracellular Ca^{2+} concentration, including periodic plane waves, spiral waves, complex whole-cell oscillations, phase waves, stochastic resonance, and spiking, have encouraged theoreticians to use their skills, in collaboration with the experimentalists, to try and understand the dynamics of this ubiquitous ion.

Many cell types, however, contain both a membrane oscillator and a Ca^{2+} oscillator. The best-known examples of this, and the most widely studied, are the neuroendocrine cells of the hypothalamus and pituitary, as well as the endocrine cells of the pancreas, the pancreatic β cells. In these cell types, membrane oscillators and calcium oscillators are indissolubly linked; fast oscillations of the membrane potential open voltage-gated Ca^{2+} channels which allow Ca^{2+} to flow into the cell, which in turn activates the exocytotic machinery to secrete insulin (in the case of pancreatic β cells) or a variety of hormones (in the case of hypothalamic and pituitary cells). However, in each of these cell types, cytosolic Ca^{2+} also controls the conductance of membrane ion channels, particularly Ca^{2+}-sensitive K^+ and Cl^- channels, which in turn affect the membrane potential oscillations. In these endocrine cells, it is thus necessary to understand both types of cellular oscillator in order to understand overall cellular behavior.

Thus, this current volume. In it we first see how the interaction of Ca^{2+} cytosolic with membrane ion channels can result in the complex patterns of electrical spiking that we see in cells. We then discuss the basic theory of Ca^{2+} oscillations (common to almost all cell types), including spatio-temporal behaviors such as waves, and then review some of the theory of mathematical models of electrical bursting pituitary cells.

Although our understanding of how cellular oscillators interact remains rudimentary at best, this coupled oscillator system has been instrumental in developing our understanding of how the cytosol interacts with the membrane to form complex electrical firing patterns. In addition, from the theoretical point of view it has provided the motivation for the development and use of a wide range of mathematical methods, including geometric singular perturbation theory, nonlinear bifurcation theory, and multiple-time-scale analysis.

It is thus an excellent example of how mathematics and physiology can learn from each other, and work jointly towards a better understanding of complex cellular processes.

Tallahasse, FL, USA	Richard Bertram
Auckland, New Zealand	Vivien Kirk
Auckland, New Zealand	James Sneyd
Tallahasse, FL, USA	Joël Tabak
Indianapolis, IN, USA	Wondimu Teka
Boston, MA, USA	Theodore Vo
Sydney, NSW, Australia	Martin Wechselberger

Contents

1 Geometric Singular Perturbation Analysis of Bursting Oscillations in Pituitary Cells 1
Richard Bertram, Joël Tabak, Wondimu Teka, Theodore Vo, and Martin Wechselberger
1 Introduction 2
2 The Lactotroph/Somatotroph Model 5
3 The Standard Fast/Slow Analysis 8
4 The 1-Fast/2-Slow Analysis 13
4.1 Reduced, Desingularized, and Layer Systems 13
4.2 Folded Singularities and the Origin of Pseudo-Plateau Bursting 16
4.3 Phase-Plane Analysis of the Desingularized System 19
4.4 Bursting Boundaries 21
4.5 Spike-Adding Transitions 23
4.6 Prediction Testing on Real Cells 26
5 Relationship Between the Fast/Slow Analysis Structures 28
5.1 The $f_c \to 0$ Limit 30
5.2 The $C_m \to 0$ Limit 31
5.3 The Double Limit 33
6 Store-Generated Bursting in Stimulated Gonadotrophs 35
6.1 Closed-Cell Dynamics 35
6.2 Open-Cell Dynamics 40
6.3 Store-Generated Bursting 43
7 Conclusion 46
8 Appendix 46
8.1 The Chay-Keizer Model 46
8.2 The Lactotroph Model with an A-Type K^+ Current 47
References 48

2 The Nonlinear Dynamics of Calcium 53
Vivien Kirk and James Sneyd
1 Introduction 53
1.1 Some background physiology 56
1.2 Overview of calcium models 61
1.3 Stochastic versus deterministic models 62
1.4 Excitability 63
2 ODE models 64
2.1 Calcium buffering 66
2.2 Modelling the calcium fluxes 68
2.3 Model classification 72
2.4 A simple example: the combined model 73
3 Bifurcation structure of ODE models 75
3.1 Fast-slow reductions 78
3.2 Pulse experiments and GSPT 84
4 Merging calcium dynamics and membrane electrical excitability 87
5 Calcium diffusion and waves 88
5.1 Basic equations 88
5.2 Fire-diffuse-fire models 90
5.3 Another simple example 91
5.4 CU systems 92
5.5 Calcium excitability and comparison to the FitzHugh-Nagumo equations 95
5.6 The effects on wave propagation of calcium buffers 98
6 Conclusion 100
Appendix 100
References 100