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James Sneyd (Ed.)

Tutorials in Mathematical Biosciences II

Mathematical Modeling of Calcium Dynamics and Signal Transduction

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Mathematical Modeling of Calcium Dynamics and Signal Transduction

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Preface

This is the second volume in the series "Lectures in Mathematical Biosciences". These lectures are based on material which was presented in tutorials or developed by visitors and postdoctoral fellows of the Mathematical Bioscience Institute (MBI), at The Ohio State University. The aim of this series is to introduce graduate students and researchers with just a little background in either mathematics or biology to mathematical modeling of biological processes. The present volume is devoted to Mathematical Modeling of Calcium Dynamics and Signal Transduction, which was the focus of the MBI program in the winter of 2004; documentation of that program, including streaming videos of the workshops, can be found on the website http://mbi.osu.edu.

This volume was organized and edited by James Sneyd. Sneyd is a world leader in mathematical physiology and biology, and has been working extensively on modeling biological processes of signal transduction induced by calcium oscillations.

Some of the chapters describe mathematical models of calcium dynamics as they occur in signal transduction. However, more attention is given in this volume to the underlying physiology, since, as Sneyd says, "Mathematical physiology is not possible without the physiology."

I wish to express my thanks to the contributors, all of whom served also as tutorial lecturers at the MBI. Special thanks are due to James Sneyd, who took it upon himself to organize this volume. I hope this volume will serve as a useful introduction to those who are interested in learning about mathematical physiology, and maybe even participating in this exciting field of research.

April, 2005 *Avner Friedman*

Introduction

The question of how cells respond to their environment and coordinate their behavior with that of other cells is one that can naturally be studied using mathematical models. In order for cells to communicate with each other or with the outside world they have developed a large number of transduction mechanisms, whereby extracellular signals can be translated into intracellular signals, or a signal of one type can be changed into a signal of another type. For instance, muscle cells change an electrical signal into a force; photoreceptors change a light signal into an electrical signal; neurosecretory cells change an electrical signal into a hormonal signal; while in many cell types binding of a neurotransmitter or a hormone leads to oscillations in the concentration of intracellular free calcium, oscillations which control a variety of intracellular processes, including secretion, gene expression, cell movement, or wound repair. For instance, in muscle cells, the release of calcium from the sarcoplasmic reticulum controls muscle contraction, while in olfactory neurons and photoreceptors calcium forms an important negative feedback loop that controls adaptation. In neurosecretory cells, oscillations of the cytoplasmic calcium concentration lead to hormone secretion, while in neurons, calcium is not only crucial for synaptic communication, it is also an important modulator of synaptic plasticity.

In this volume we present a number of examples of signal transduction, showing how physiology and mathematical modeling interact to give a detailed quantitative understanding of such complex phenomena. Because of the widespread importance of calcium, all the chapters here will necessarily include discussion of calcium dynamics. Thus, we begin by showing how mathematical models of calcium dynamics can be constructed and analyzed. This is followed by descriptions of excitation-contraction coupling (i.e., how calcium forms a link between the muscle action potential and the contractile proteins), how the muscle proteins themselves work, and, finally, chapters on the physiology and modeling of olfactory neurons and of neuronal synapses.

Although this volume is part of a series of Tutorials in Mathematics, readers will soon notice that much of what is presented here is not mathematics at all, but physiology. This is entirely deliberate. It cannot be emphasized too strongly that mathematical physiology is not possible without the physiology. Without a detailed understanding of the physiology of the system under discussion it is simply not possible to say anything very interesting about it, no matter how clever is the mathematics used. Three of the authors here (Sanderson, Shannon and Reisert) are experimental physiologists, each of whom works closely with mathematical modelers to incorporate sophisticated modeling techniques into their research. The other four authors are primarily modelers, but ones that work closely with physiologists, or even, in some cases, do some experimental work themselves.

It is to be hoped that this combination of physiology and mathematics in what is, primarily, a volume for mathematicians, will be of use to all those who are interested in learning how modeling is done, or maybe even participating themselves in this most satisfying of endeavors.

April, 2005 *James Sneyd*

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Contents

Basic Concepts of Ca^{2+} Signaling in Cells and Tissues

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1 Introduction

Living tissues are complex organizations of individual cells and to perform their specific functions the activity of each cell within the tissue must be regulated in a coordinated manner. The mechanisms through which this regulation occurs can be equally complex, but a common way to exert control is via neural transmission or hormonal stimulation. Irrespective of the organization of the extracellular control system, the regulatory signals need to be translated into an intracellular messenger that can modulate the cellular processes. Again, there are a variety of intracellular messengers that achieve this aim, including cAMP, cGMP and NO, but here we focus on the calcium ion as the internal messenger. The objective of this article is to provide an overview of the basic mechanisms of how Ca^{2+} serves as a signaling messenger. For greater detail, the reader must refer to the many extensive reviews (for example, Berridge et al., 2003; Berridge et al., 2002). The details of the individual mechanisms are extremely important since they can confer specificity on the signaling model. As a result, model simulations of Ca^{2+} signaling are most useful when the model is designed for a specific cell type and sufficient experimental detail can be incorporated.

2 Ca^{2+} Stores and Pumps

A key characteristic determining how Ca^{2+} serves as a signaling molecule is that, unlike organic messengers (i.e. cAMP, NO), Ca^{2+} ions cannot be created or metabolized. Consequently, cell signaling with Ca^{2+} ions requires a strategy of accumulation or storage coupled with Ca^{2+} release. The cell exploits two major Ca^{2+} stores, the external environment that contains a virtually infinite supply of Ca^{2+} at a concentration of about 1–2 mM and an internal store, usually contained within the endoplasmic (ER) or muscle-equivalent sarcoplasmic (SR) reticulum (Petersen et al., 2001). The storage capacity of the E/SR is enhanced by the presence of Ca^{2+} buffering proteins (e.g. calsequestrin and calretinin) that can bind large quantities of Ca^{2+}. The free Ca^{2+} concentration in the ER is in the 10–100 μM range. Mitochondria can also serve as a Ca^{2+} reservoir, taking up Ca^{2+} in times of excess and releasing Ca^{2+} when cytosolic Ca^{2+} falls. Another, but less-well defined, secondary Ca^{2+} store is the lysosome-related store (Fig. 1).

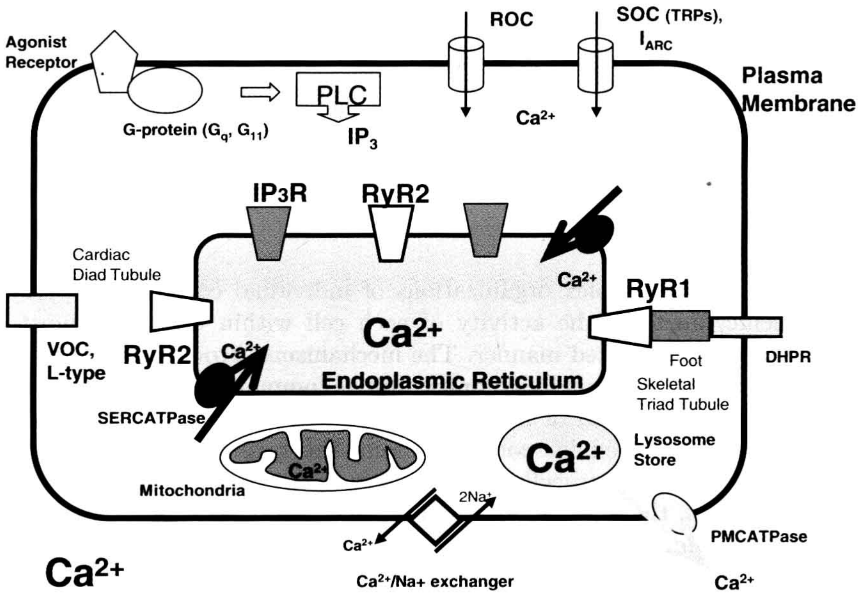

Fig. 1. A schematic of a generalized cell illustrating the fundamental elements of the Ca^{2+} signaling machinery. Ca^{2+} stores exist in the extracellular medium, the endoplasmic reticulum, the mitochondria and the lysosome. Ca^{2+} is moved to these stores by a Ca^{2+}/Na^{+} exchanger, plasma membrane Ca^{2+} pumps and SERCA pumps. Ca^{2+} can enter the cytoplasm via receptor-operated channels (ROC), store-operated channels (SOC), voltage-operated channels (VOC), ryanodine receptors (RyR) and inositol trisphosphate receptors (IP_3R). Agonist stimulation acts via G-proteins to stimulate phospholipase C (PLC) to produce IP_3. RyR receptors are coupled with VOCs in cardiac muscle or with the DHPR in skeletal muscle

To maintain the necessary electrochemical gradient that drives Ca^{2+} release from these stores, the cell membranes separating the stores must be relatively impermeable to Ca^{2+}. In addition, the cell must be able to lower the cytoplasmic Ca^{2+} concentration and re-load the stores to turn off the signal to reset the system. This is achieved by energy-dependent Ca^{2+} pumps (Ca^{2+} ATPases) or Ca^{2+} exchangers located in the cell membranes. There are 2 basic forms of Ca^{2+} ATPase; outer plasma cell membrane ATPases (PCMAs) and sacroplasmic/endoplasmic reticulum calcium ATPase (SERCA) pumps