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Stochastic processes in cell biology

May 22, 2014

Springer

To my wife Alessandra

Contents

Part I Foundations

Part II Advanced Topics

Preface

In recent years there has been an explosion of interest in the effects of noise in cell biology. This has partly been driven by rapid advances in experimental techniques, including high-resolution imaging and molecular-level probes. However, it is also driven by fundamental questions raised by the ubiquity of noise. For example, how does noise at the molecular and cellular levels translate into reliable or robust behavior at the macroscopic level? How do microscopic organisms detect weak environmental signals in the presence of noise? Have single-cell and more complex organisms evolved to exploit noise to enhance performance? In light of the above, there is a growing need for mathematical biologists and other applied mathematicians interested in biological problems to have some background in applied probability theory and stochastic processes. Traditional mathematical courses and textbooks in cell biology and cell physiology tend to focus on deterministic models based on differential equations such as the Hodgkin-Huxley and FitzHugh-Nagumo equations, chemical kinetic equations, and reaction-diffusion equations. Although there are a number of well-known textbooks on applied stochastic processes, they are written primarily for physicists and chemists or for population biologists. There are also several excellent books on cell biology written from a biophysics perspective. However, these assume some background in statistical physics and a certain level of physical intuition. Therefore, I felt that it was timely to write a textbook for applied mathematicians interested in learning stochastic processes within the context of cell biology, which could also serve as an introduction to mathematical cell biology for statistical physicists and applied probabilists.

I started my interest in stochastic cell biology, as distinct from my work in mathematical neuroscience, around eight years ago when I volunteered to teach a course in biophysics for the mathematical biology graduate program at Utah. I was immediately fascinated by the molecular processes underlying the operation of a cell, particularly the mechanisms for transporting proteins and other macromolecules to the correct subcellular targets at the correct times. Such an issue is particularly acute for neurons, which are amongst the largest and most complex cells in biology. In healthy cells, the regulation of protein trafficking within a neuron provides an important mechanism for modifying the strength of synaptic connections between neurons, and synaptic plasticity is generally believed to be the cellular substrate of learning and memory. On the other hand, various types of dysfunction in protein trafficking appear to be a major contributory factor to a number of neurodegenerative diseases associated with memory loss including Alzheimers disease.

In writing this book, I have gone back to my roots in theoretical physics, but refracted through the lens formed by many years working in applied mathematics. Hence, the book provides extensive coverage of analytical methods such as initial boundary value problems for partial differential equations, singular perturbation theory, slow/fast analysis and quasi-steady-state approximations, Green's functions, WKB methods and Hamilton-Jacobi equations, homogenization theory and multi-scale analysis, the method of characteristics and shocks, and reaction-diffusion equations. I have also endeavored to minimize the use of statistical mechanics, which is not usually part of a mathematician's tool-kit and requires a certain level of physical intuition. It is not possible to avoid this topic completely, since many experimental and theoretical papers in cell biology assume some familiarity with terms such as entropy, free energy and chemical potential. The reason is that microscopic systems often operate close to thermodynamic equilibrium or asymptotically approach thermodynamic equilibrium in the large-time limit. This then imposes constraints on any model of the underlying stochastic process. In most cases, one can understand these constraints by considering the Boltzmann-Gibbs distribution of a macromolecule in thermodynamic equilibrium, which is the approach I take in this book.

There are two complementary approaches to modeling biological systems. One involves a high level of biological detail and computational complexity, which means that it is usually less amenable to mathematical analysis than simpler reduced models. The focus tends to be on issues such as parameter searches and data fitting, sensitivity analysis, model reductions, numerical convergence, and computational efficiency. This is exemplified by the rapidly growing field of systems biology. The other approach is based on relatively simple conceptual or "toy" models, which are analytically tractable and, hopefully, capture essential features of the phenomena of interest. In this book I focus on the latter for pedagogical reasons and because of my own personal tastes. In the introductory chapter, I summarize some of the basic concepts in stochastic processes and non-equilibrium systems that are used throughout the book, describe various experimental methods for probing noise at the molecular and cellular levels, give a brief review of basic probability theory and statistical mechanics, and then highlight the structure of the book. In brief, the book is divided into two parts: Part I (Foundations) and Part II (Advanced Topics). Part I provides the basic foundations of both discrete and continuous stochastic processes in cell biology. It's five chapters deal with diffusion, random walks and the Fokker-Planck equation (chapter 2), stochastic ion channels (chapter 3), polymers and molecular motors (chapter 4), biochemical signaling and adaptation (chapter 5), and gene expression and regulatory networks (chapter 6). Part II covers more advanced topics that build upon the ideas and techniques from part I. Topics include transport processes in cells (chapter 7), self-organization of the cytoskeleton (chapter 8), self-organization in reaction-diffusion models (chapter 9), WKB methods for escape problems (chapter 10), and some more advanced topics in probability theory (chapter 11). The chapters are supplemented by additional background material highlighted in gray boxes, and numerous exercises that reinforce the analytical methods and models introduced in the main body of the text. I have attempted to make the book as self-contained as possible. However, some introductory background in partial differential equations, integral transforms, and applied probability theory would be advantageous.

Finally, this book should come with a "government health warning." That is, throughout most of the book, I review the simplest mechanistic models that have been constructed in order to investigate a particular biological phenomenon or illustrate a particular mathematical method. Although I try to make clear the assumptions underlying each model, I do not carry out a comparative study of different models in terms of the degree of quantitative agreement with experimental data. Therefore, the reader should be cautioned that the models are far from the last word on a given phenomenon, and the real biological system is usually way more complicated than stated. However, it is hoped that the range of modeling and analytical techniques presented in this book, when combined with efficient numerical methods, provide the foundations for developing more realistic, quantitative models in stochastic cell biology.

Acknowledgements

Much of my recent research on stochastic processes in cell biology has been done in a very fruitful and enjoyable collaboration with my ex-graduate student Jay Newby. There are many applied mathematicians, physical scientists, and life scientists upon whose sturdy shoulders I have stood during the writing of this book, and whose work is featured extensively in the following pages. I apologize in advance if I have excluded anyone or didn't do proper justice to their contributions. Finally, I would like to thank my wife Alessandra and son Luca (the Shmu) for their love and support, and for putting up with my hermit-like existence over the past year.