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Stochastic processes in cell biology

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To my wife Alessandra

Contents

1	Introduction	1
1.1	Stochastic processes in living cells	1
1.2	Experimental studies of noise in cells	11
1.3	A brief introduction to probability theory	17
1.4	Statistical mechanics and the Boltzmann-Gibbs distribution	22
1.5	Organization of the book	26
 Part I Foundations		
2	Diffusion in cells: random walks and Brownian motion	35
2.1	Discrete-time random walk	36
2.1.1	Continuum limit of a random walk	44
2.2	Continuous stochastic processes and the Fokker-Planck (FP) equation	48
2.2.1	Derivation of the FP equation from a Langevin equation	48
2.2.2	Boundary conditions for the FP equation	53
2.2.3	The Ornstein-Uhlenbeck process	54
2.2.4	Multiplicative noise	57
2.2.5	Correlations and the power spectrum	58
2.3	First passage time density and the backward FP equation	61
2.4	Diffusion-limited reaction rates	65
2.4.1	Smoluchowski reaction rate	65
2.4.2	Chemoreception	67
2.5	Boundary value problems	69
2.5.1	Eigenfunction expansions	70
2.5.2	Green's functions and steady-state analysis	73
2.6	Appendix: An informal introduction to stochastic calculus	78
2.6.1	What is a continuous stochastic process?	78
2.6.2	Ito stochastic integrals	80
2.6.3	Simulation of stochastic differential equations	88
2.7	Exercises	93

3	Stochastic ion channels	103
3.1	Single ion channel kinetics	104
3.1.1	Voltage-gated ion channels	104
3.1.2	Ligand-gated ion channel	108
3.1.3	Monod-Wyman-Changeux (MWC) model	110
3.2	Master equation for an ensemble of ion channels	112
3.2.1	Diffusion approximation of a birth-death master equation ...	115
3.3	Population channel bistability and mean escape times	118
3.4	Stochastic models of Ca^{2+} release	123
3.4.1	Stochastic model of Ca^{2+} puffs in a cluster of IP_3Rs	125
3.4.2	Stochastic model of Ca^{2+} sparks in cardiac myocytes	128
3.5	Membrane voltage fluctuations and spontaneous action potentials ..	134
3.5.1	Conductance-based model of neural excitability	134
3.5.2	Neural excitability and phase-plane analysis	139
3.5.3	Stochastic conductance-based model	142
3.6	Stochastic gating model of confinement	147
3.7	Exercises	151
4	Polymers and molecular motors	161
4.1	Polymerization	167
4.1.1	Simple model of a single polymer filament	167
4.1.2	Microtubule catastrophes	171
4.2	Brownian motion in a periodic potential	178
4.2.1	Polymerization ratchet	181
4.2.2	Translocation ratchet	183
4.3	Brownian ratchet model of a processive molecular motor	185
4.4	Collective effects of multiple molecular motors	192
4.4.1	Intracellular cargo transport by multiple motors	192
4.4.2	Tug-of-war model	195
4.4.3	Collective extraction of membrane nanotubes	199
4.4.4	Rigidly linked molecular motors	209
4.5	Appendix: Statistical mechanics of polymers	214
4.6	Exercises	220
5	Sensing the environment: adaptation and amplification in cells	229
5.1	Physical limits of biochemical signaling due to noise	230
5.2	Fluctuation-dissipation theorem	233
5.3	Bacterial chemotaxis	239
5.3.1	Receptor clustering and signal amplification	243
5.3.2	Adaptation in signal transduction pathways	247
5.3.3	Bacterial chemotaxis as a velocity-jump process	248
5.4	Hair cells and active mechanotransduction	253
5.4.1	Gating-spring model	255
5.4.2	Channel compliance, myosin motors and spontaneous oscillations	258

5.4.3	Active amplification close to a Hopf bifurcation	262
5.5	Exercises	264
6	Stochastic gene expression and regulatory networks	269
6.1	Basics of gene expression.	270
6.2	Unregulated transcription and translation	274
6.3	Simple models of gene regulation	278
6.3.1	Transcriptional bursting in a two-state model	279
6.3.2	Protein fluctuations and the linear noise approximation	282
6.3.3	Autoregulatory network	287
6.4	Genetic switches and oscillators	290
6.4.1	Mutual repressor model of a genetic switch	290
6.4.2	The <i>lac</i> operon	294
6.4.3	Genetic oscillator network	297
6.4.4	The circadian clock and molecular noise	299
6.4.5	Quasi-cycles in a biochemical oscillator	304
6.5	Information transmission in regulatory networks	308
6.5.1	Entropy and mutual information	310
6.5.2	Optimizing mutual information in a simple regulatory network	312
6.6	Fluctuations in DNA transcription	316
6.7	Kinetic proofreading	321
6.7.1	Kinetic proofreading in protein synthesis	324
6.7.2	Kinetic proofreading in T-cell activation	326
6.8	Stochastic algorithms for chemical kinetics	328
6.9	Exercises	330

Part II Advanced Topics

7	Transport processes in cells	343
7.1	Anomalous diffusion.	347
7.1.1	Molecular crowding, diffusion-trapping, and long-time correlations	347
7.1.2	Diffusion-trapping model of protein trafficking in dendrites	350
7.1.3	Continuous-time random walks	355
7.1.4	Diffusion in the plasma membrane.	359
7.2	Narrow escape problems, small targets, and singular perturbation methods	361
7.2.1	Narrow escape problems	361
7.2.2	Diffusion to a small target	365
7.3	Membrane transport through nanopores and channels	368
7.3.1	Confined diffusion and the Fick-Jacobs equation	370
7.3.2	Nuclear transport	373
7.3.3	Single-file diffusion	379
7.3.4	Translocation of DNA through a nanopore	382

7.4	PDE models of active transport	385
7.4.1	Active transport on a 1D track	386
7.4.2	Active transport on microtubular networks	390
7.5	Exclusion processes	396
7.5.1	Asymmetric exclusion process and the hydrodynamic limit	396
7.5.2	Steady-state analysis	398
7.5.3	Method of characteristics and shocks	401
7.6	Random intermittent search processes	407
7.6.1	Diffusive search for a protein-DNA binding site	409
7.6.2	Optimal unbiased search on a 1D track	415
7.6.3	Biased intermittent search	419
7.6.4	Effects of local chemical signaling	421
7.6.5	Virus trafficking	425
7.7	Exercises	428
8	Self-organization in cells I: active processes	439
8.1	Cellular length regulation by molecular motors	440
8.1.1	Filament length regulation by depolymerization	441
8.1.2	Filament length regulation by altering the frequency of catastrophes	445
8.1.3	Length regulation by intraflagellar transport	446
8.2	Cell mitosis	447
8.2.1	Search-and-capture model of chromosome/kinetochore attachment	450
8.2.2	Chromosome movements and directional instability	455
8.2.3	Force balance and spindle length control	467
8.3	Cell motility	473
8.3.1	Tethered ratchet model	474
8.3.2	Crawling cells and lamellipodial motility	478
8.3.3	Stochastic model of integrin-mediated cell protrusion	480
8.4	Cooperative transport of proteins between cellular organelles	483
8.5	Exercises	489
9	Self-organization in cells II: reaction-diffusion models	495
9.1	Intracellular protein concentration gradients	496
9.1.1	Spatially distributed signaling cascades	498
9.1.2	Robustness of concentration gradients	502
9.2	Theory of Turing pattern formation	506
9.2.1	Linear stability analysis	508
9.2.2	Amplitude equations and bifurcation theory	510
9.3	Stochastic pattern formation and the RD master equation	521
9.3.1	Turing instability in the Brusselator model	522
9.3.2	Linear-noise approximation of RD master equation	524
9.4	Protein self-organization of Min proteins in <i>E. coli</i>	529
9.5	Cell polarization	534

9.5.1	Positive feedback model: deterministic analysis	540
9.5.2	Positive feedback model: stochastic analysis	545
9.5.3	Active transport models	550
9.5.4	Turing-like mechanism for cell polarization	557
9.5.5	Wave-pinning and cell polarity in a bistable reaction-diffusion model	559
9.6	Exercises	563
10	The WKB method and large deviation theory	573
10.1	The Wentzel-Kramers-Brillouin (WKB) method.	575
10.1.1	WKB method for a birth-death master equation	575
10.1.2	WKB method for a stochastic hybrid system	583
10.1.3	Stochastic ion channels revisited	587
10.2	Path integral representation of an SDE	589
10.3	Path integral representation of a birth-death master equation	595
10.4	Path-integral representation of a stochastic hybrid system	600
10.5	Excitability in the stochastic Morris-Lecar model	605
10.6	Exercises	610
	Probability theory and martingales	613
11.1	Probability spaces, random variables and conditional expectations . .	613
11.2	Definitions and examples of martingales	615
11.3	Stopping times	618
11.4	Martingale convergence theorems	620
11.5	The Galton-Watson branching process	621
11.6	Modeling chemical reaction networks as counting processes	629
	References	639
	Index	1

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 meth-

ods 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.

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