Stochastic and nonequilibrium processes in cell biology I: Molecular processes

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To Alessandra and Luca
Preface to 2nd edition

This is an extensively updated and expanded version of the first edition. I have continued with the joint pedagogical goals of (i) using cell biology as an illustrative framework for developing the theory of stochastic and nonequilibrium processes, and (ii) providing an introduction to theoretical cell biology. However, given the amount of additional material, the book has been divided into two volumes, with

Mapping from the 1st to the 2nd edition
volume I mainly covering molecular processes and volume II focusing on cellular processes. The latter also includes significantly expanded material on nonequilibrium systems: intracellular pattern formation and reaction-diffusion processes, statistical physics, and the dynamics/self-organization of cellular structures. Hence the term “nonequilibrium” has been added to the title. The mapping from the first to the second edition is shown in the diagram. In volume I, the chapter on intracellular transport processes has been split into two chapters, covering diffusive and active processes, respectively. There are four completely new chapters in volume II: statistical mechanics of polymers and membranes; self-organization and assembly of cellular structures; bacterial population growth and collective behavior; stochastic reaction-diffusion processes. The other three chapters have been significantly expanded.

Major new topics include the following: theory of continuous-time Markov chains (chapter 3); first-passage time problems with (nucleating) sticky boundaries (chapter 4); genetic oscillators, the repressilator, the degrade-and-fire model, delay differential equations, theory of chemical reaction networks, promoter dynamics, transcriptional bursting and queuing theory, epigenetics, gene expression and morphogen gradients (chapter 5); molecular crowding and homogenization theory, percolation theory, narrow capture problems, extreme statistics, diffusion in randomly switching environments, stochastically-gated gap junctions (chapter 6); reversible vesicular transport in axons, distribution of resources across multiple targets and queuing theory, stochastic resetting (chapter 7); metastability in gene networks, Brownian functionals, large deviation theory, generalized central limit theorems and Levy stable distributions (chapter 8); phosphorylation-dephosphorylation cycles and ultrasensitivity, Goldbeter-Koshland model, photoreceptors and photo-transduction, Poisson shot noise, linear response theory, eukaryotic gradient sensing, the local excitation/global inhibition (LEGI) model of adaptation in gradient sensing, maximum likelihood estimation (chapter 10); robustness and accumulation times of protein gradients, non-classical mechanisms for protein gradient formation, pattern formation in mass conserving systems, coupled PDE-ODE systems, cell polarization in fission yeast, pattern formation in hybrid reaction-transport systems, pattern formation on growing domains, synatogenesis in C. elegans, protein clustering in bacteria, multi-spike solutions far from pattern onset, RD models of intracellular traveling waves, pulled and pushed fronts (chapter 11); elastic rod model of flexible polymers, worm-like chains, curvature and torsion, stress and strain tensors, membrane fluctuations and curvature, polymer networks, viscoelasticity and reptation, nuclear organization, Rouse model of DNA dynamics (chapter 12); classical theories of phase separation, spinodal decomposition and Ostwald ripening, phase separation of biological condensates, Becker-Döring model of molecular aggregation, self-assembly of phospholipids, active membranes (chapter 13); doubly stochastic Poisson model of flagellar length control, diffusion-secretion model of filament length control, cell adhesion, motor-clutch model of crawling cells, growth of focal adhesions, variational method for free energy minimization, cytoneme-based morphogen gradients (chapter 14); age-structured models of population growth and cell size regulation, bacterial persistence and phenotypic switching, stochastic mod-
els of population extinction, bacterial quorum sensing, synchronization of genetic oscillators, biofilms (chapter 15); stochastic reaction diffusion processes, stochastic Turing patterns, non-normality and noise-induced pattern amplification, statistical field theory, diagrammatic expansions and the renormalization group, stochastic traveling waves (chapter 16).

Meaning no disrespect to vegetarians, I do not explicitly cover plant cells. However, many of the mechanisms and concepts developed in this book would still apply. Chapter 15 on bacterial population growth suggests another natural extension of the current book, namely, stochastic and nonequilibrium processes at the multicellular and tissue levels, including biological neural networks, immunology, collective cell migration, cell development, wound healing, and cancer. This would involve additional topics such as cell-to-cell signaling, the propagation of intercellular signals, nonlocal differential and integral equations, physical properties of the extracellular matrix, and network theory. Clearly ripe themes for a possible third volume!

**Acknowledgements**

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. It should also be noted that the relatively large number of self-citations is not a reflection of the significance of my own work in the field, but a consequence of the fact that I am most familiar with my own work! Finally, I would like to thank my wife Alessandra and son Luca (the Shmu) for their continuing love and support.
Preface to 1st edition

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 Alzheimer’s 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 long-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), discrete Markov processes and chemical reaction networks (chapter 3), polymers and molecular motors (chapter 4), gene expression and regulatory networks (chapter 5), and biochemical signaling and adaptation (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 in reaction-diffusion models (chapter 8), self-organization of the cytoskeleton (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.
Organization of volumes I and II

Volume I: Molecular processes

The first volume begins with a short introduction to probability theory and statistical mechanics (chapter 1). Chapter 2 presents two microscopic theories of diffusion in cells, one based on random walks and the other on over-damped Brownian motion. The latter leads to the theory of continuous Markov processes. Two complementary approaches to formulating continuous Markov process are developed, one in terms of the sample paths generated by a stochastic differential equation (SDE) or Langevin equation, and the other in terms of the Fokker-Planck (FP) equation describing the evolution of the probability density of possible paths. In the former case, a basic introduction to stochastic calculus is given, focusing on the rules for integrating an SDE in order to obtain an expression that can be used to generate moments of the stochastic process. The distinction between Ito and Stratonovich interpretations of multiplicative noise is explained in some detail. It is also shown how, in the case of linear SDEs, Fourier methods can be used to determine the power spectrum, which is important in quantifying the linear response properties of a noisy system. The FP equation, which is a deterministic partial differential equation (PDE) that generalizes the diffusion equation, is then analyzed using standard methods in the theory of linear PDEs: separation of variables, transform methods, Green’s functions, and eigenfunction expansions. Many quantities measured by experimentalists can be interpreted mathematically in terms of the solution to a first passage time (FPT) problem. Using the fact that the distribution of first passage times satisfies a backward FP equation, the mean FPT is shown to satisfy a boundary value problem. This is then used to derive the classical Kramer’s rate formula for escape across a potential barrier. Noise-induced changes in the effective potential (quasipotential) in the presence of multiplicative noise are also discussed. Finally, some numerical methods for solving SDEs are reviewed.

Chapter 3 covers some of the main molecular players in cell signaling and transduction, namely, receptors and ion channels. After briefly summarizing the most common types of receptors, some simple kinetic models of cooperative binding are
introduced, including the Monod-Wyman-Changeaux model and the Ising model. These provide one mechanism for a cell to amplify signals from the extracellular environment. Following a description of various single ion channel models, the stochastic dynamics of an ensemble of independent ion-channels is formulated in terms of a birth-death process. The latter is an example of a discrete Markov process or Markov chain. It is shown how the the probability distribution for the number of open ion channels evolves according to a corresponding birth-death master equation. Two models of stochastic ion channels are then explored, a conductance-based model of spontaneous action potential generation in a neuron, which is driven by the random opening and closing of voltage-gated ion channels, and the spontaneous release of calcium puffs and sparks by ligand-gated ion channels. In both cases, the occurrence of spontaneous events can be analyzed in terms of a FPT problem.

Finally, the general theory of continuous-time Markov chains is reviewed, including a discussion of the Perron-Frobenius theorem and an introduction to Poisson processes. There are a number of systems considered in subsequent chapters where the signal received by a biochemical sensor involves a sequence of discrete events that can be modeled as a Poisson process. Examples include the arrival of photons at photoreceptors of the retina, and the arrival of action potentials (spikes) at the synapse of a neuron. Another type of event is the random arrival of customers at some service station, resulting in the formation of a queue. However, these processes are typically non-Markovian.

Chapter 4 describes how random walks and SDEs are used to model polymerization and molecular motor dynamics. Polymerization plays a major role in the self-organization of cytoskeletal structures, whereas molecular motors “walking” along polymer filaments is a major active component of intracellular transport. The analysis of polymerization focuses on the Dogterom-Leibler model of microtubule catastrophes, which takes the form of a two-state velocity-jump process for the length of a microtubule. The effects of nucleation and constrained growth are taken into account, and FPT problems with “sticky” boundaries are analyzed using the theory of conditional expectations, stopping times and strong Markov processes. The FP equation for a Brownian particle moving in a periodic ratchet (asymmetric) potential is then analyzed. It is shown that the mean velocity of the Brownian particle is zero, which implies that the periodicity of the potential must be broken for a molecular motor to perform useful work against an applied load. One such mechanism is to rectify the motion, as exemplified by polymerization and translocation ratchets. A qualitative model of processive molecular motors is then introduced, based on a flashing Brownian ratchet. It is shown how useful work can be generated if the motor switches between different conformational states (and corresponding potentials) at rates that do not satisfy detailed balance; this is achieved via the hydrolysis of adenosine triphosphate (ATP). The theory of molecular motors is further developed by considering two examples of the collective motion of an ensemble of molecular motors: (i) the tug-of-war model of bidirectional vesicular transport by opposing groups of processive motors; (ii) a model of interacting motors attached to a rigid cytoskeletal backbone.
Chapter 5 covers the basics of stochastic gene expression and chemical reaction networks. First, various deterministic rate models of gene regulatory networks are described, including autoregulatory networks, the toggle switch, the lac operon, the repressilator, NK-βB oscillators, and the circadian clock. Brief reviews of linear stability analysis, Hopf bifurcation theory, and oscillations in delay differential equations are also given. The analysis of molecular noise associated with low copy numbers is then developed, based on the chemical master equation. Since chemical master equations are difficult to analyze directly, a system-size expansion is used to approximate the chemical master equation by an FP equation and its associated chemical Langevin equation. Gillespie’s stochastic simulation algorithm for generating exact sample paths of a continuous-time Markov chain is also summarized. Various effects of molecular noise on gene expression are then explored, including translational bursting, noise-induced switching, and noise-induced oscillations. One of the assumptions of many stochastic models of gene networks is that the binding/unbinding of transcription factors at promoter sites is faster than the rates of synthesis and degradation. If this assumption is relaxed, then there exists another source of intrinsic noise known as promoter noise. The latter is modeled in terms of a stochastic hybrid system, also known as a piecewise-deterministic Markov process. This involves the coupling between a continuous-time Markov chain and a continuous process that may be deterministic or stochastic. The evolution of the system is now described by a differential Chapman-Kolmogorov (CK) equation, which is a mixture of a master equation and an FP equation. In the limit of fast switching, a quasi-steady-state approximation is used to reduce the CK equation to an effective FP equation. This is analogous to the system-size expansion of chemical master equations. Various examples of networks with promoter noise are presented, including a stochastic version of the toggle switch. It is shown how one of the major effects of promoter noise, namely transcriptional bursting, can be analyzed using queuing theory. Some time-limiting steps in gene regulation are then described, including kinetic proofreading based on enzymatic reactions, and DNA transcription times. The penultimate chapter consists of a brief introduction to epigenetics. This concerns phenotypic states that are not encoded as genes, but as inherited patterns of gene expression originating from environmental factors, and maintained over multiple cell generations when the original environmental stimuli have been removed. A number of epigenetic mechanisms are discussed, including the infection of E. coli by the λ phage DNA virus, and local mechanisms such as DNA methylation and gene silencing by nucleosome modifications. Finally, the role of gene expression in interpreting morphogen gradients during early development is discussed.

Chapters 6 and 7 consider various aspects of intracellular transport, focusing on diffusive and active transport, respectively. Chapter 6 begins by describing the anomalous effects of molecular crowding and trapping, where the differences in diffusive behavior at multiple timescales are highlighted. The classical Smoluchowski theory of diffusion-limited reactions is then developed, with applications to chemoreception and to facilitated diffusion, which occurs when a protein searches for specific DNA binding sites. Extensions of the classical theory to stochastically-gated diffusion limited reactions and ligand rebinding in enzymatic reactions are also consid-
Next it is shown how Green’s functions and singular perturbation theory can be used to analyze narrow escape and narrow capture problems. The former concerns the escape of a particle from a bounded domain through small openings in the boundary of the domain, whereas the latter refers to a diffusion-trapping problem in which the interior traps are much smaller than the size of the domain. An alternative measure of the timescale for diffusive search processes is then introduced, based on the FPT of the fastest particle to find a target amongst a large population of independent Brownian particles, which is an example of an extreme statistic. This leads to the so-called “redundancy principle,” which provides a possible explanation for the apparent redundancy in the number of molecules involved in various cellular processes, namely, that it accelerates search processes. In certain examples of diffusive search, regions of a boundary may randomly switch between open and closed states, which requires the analysis of PDEs in randomly switching environments. In particular, it is shown how a common switching environment can induce statistical correlations between non-interacting particles. The analysis of randomly switching environments is then extended to the case of molecular diffusion between cells that are coupled by stochastically-gated gap junctions. Finally, diffusive transport through narrow membrane pores and channels is analyzed using the Fick-Jacobs equation and models of single-file diffusion. Applications to transport through the nuclear pore complex are considered.

Chapter 7 begins by considering population models of axonal transport in neurons. The stochastic dynamics of a single motor-complex is then modeled in terms of a velocity jump process, which focuses on the transitions between different types of motion (e.g., anterograde vs. retrograde active transport, diffusion vs. active transport) rather than the microscopic details of how a motor performs a single step. Transport on a 1D track and on higher-dimensional cytoskeletal networks are considered, including a model of virus trafficking. Next, the efficiency of transport processes in delivering vesicular cargo to a particular subcellular domain is analyzed in terms of the theory of random search-and-capture processes. The latter describe a particle that randomly switches between a slow search phase (e.g., diffusion) and a faster non-search phase (e.g., ballistic transport). In certain cases it can be shown that there exists an optimal search strategy, in the sense that the mean time to find a target can be minimized by varying the rates of switching between the different phases. The case of multiple search-and-capture events, whereby targets accumulate resources, is then analyzed using queuing theory. Another example of a random search process is then introduced, in which the position of a particle (searcher) is reset randomly in time at a constant rate. One finds that the MFPT to find a target is finite and has an optimal value as a function of the resetting rate. Stochastic resetting also arises in models of cell adhesion and morphogen gradient formation. Finally, it is shown how the effects of molecular crowding of motors on a filament track can be modeled in terms of asymmetric exclusion processes. In the mean-field limit, molecular crowding can be treated in terms of quasilinear PDEs that support shock waves.

Chapters 8 and 9 cover more advanced topics. Chapter 8 focuses on methods for analyzing noise-induced transitions in multistable systems, such as Wentzel-Kramers-
Brillouin (WKB) methods, path-integrals, and large deviation theory. First, WKB theory and asymptotic methods are used to analyze noise-induced escape in an SDE with weak noise. It is shown how the most likely paths of escape can be interpreted in terms of least action paths of a path integral representation of the SDE. An analogous set of analyses are also carried out for birth-death processes and stochastic hybrid systems, which are illustrated using the examples of an autoregulatory gene network and a conductance-based neuron model. The path-integral representation of an SDE is then used to derive the Feynman-Kac formula for Brownian functionals. The latter are random variables defined by some integral measure of a Brownian path. Chapter 8 ends with a brief introduction to large deviation theory, as well as a discussion of generalized central limit theorems and Lévy stable distributions. Finally, chapter 9 briefly reviews the theory of martingales and applications to branching processes and counting processes.

Volume II: Cellular processes

Chapter 10 explores the general problem of detecting weak signals in noisy environments. Illustrative examples include photoreceptors and shot noise, inner hair cells and active mechano-transduction, and cellular chemotaxis. Various mechanisms for signal amplification and adaptation are described, such as phosphorylation-dephosphorylation cycles, ultrasensitivity, and receptor clustering. The basic principles of linear response theory are also introduced. The fundamental physical limits of cell signaling are developed in some detail, covering the classical Berg-Purcell analysis of temporal signal integration, and more recent developments based on linear response theory, and maximum likelihood estimation. One of the useful features of the latter approach is that it can be extended to take into account temporal concentration changes, such as those that arise during bacterial chemotaxis. Bacteria are too small to detect differences in concentrations across their cell bodies, so they proceed by measuring and comparing concentrations over time along their swimming trajectories. Some simple PDE models of bacterial chemotaxis, based on velocity jump processes, are also considered. In contrast to bacterial cells, eukaryotic cells such as the social amoeba *Dictyostelium discoideum* are sufficiently large so that they can measure the concentration differences across their cell bodies without temporal integration. Various models of spatial gradient sensing in eukaryotes are investigated, including the local excitation, global inhibition (LEGI) model, which takes into account the fact that cells adapt to background concentrations.

Chapter 11 explores intracellular pattern formation based on reaction-diffusion processes. First, various mechanisms for the formation of intracellular protein concentration gradients are considered, and the issue of robustness is discussed. Next, after reviewing the general theory of Turing pattern formation, two particular aspects are highlighted that are specific to intracellular pattern formation: (i) mass-conservation and (ii) the dynamical exchange of proteins between the cytoplasm and plasma membrane. Various examples of mass-conserving reaction-diffusion models of cell
polarization and division are then described, including Min protein oscillations in *E. coli*, cell polarization in budding and fission yeast, and cell polarization in motile eukaryotic cells. An alternative mechanism for intracellular pattern formation is then introduced, based on a hybrid transport model where one chemical species diffuses and the other undergoes active transport. Evolving the model on a slowly growing domain leads to a spatial pattern that is consistent with the distribution of synaptic puncta during the development of *C. elegans*. Next, asymptotic methods are used to study the existence and stability of multi-spike solutions far from pattern onset.; the latter consist of strongly localized regions of high concentration of a slowly diffusing activator. The theory is also applied to a model of the self-positioning of structural maintenance of chromosomes (SMC) protein complexes in *E. coli*, which are required for correct chromosome condensation, organization and segregation. Finally, various examples of intracellular traveling waves are analyzed, including polarization fronts in motile eukaryotic cells, mitotic waves, and CamKII translocation waves in dendrites. An introduction to the theory of bistable and unstable waves is also given.

Chapter 12 presents an introduction to the statistical mechanics and dynamics of polymers, membranes and polymer networks such as the cytoskeleton. First, the statistical mechanics of single polymers is considered, covering random walk models such as the freely-jointed chain, and elastic rod models (worm-like chains). The latter type of model treats a polymer as a continuous curve, whose free energy contributions arise from the stretching, bending and twisting of the polymer. The continuum mechanics of elastic rods is briefly reviewed in terms of curvature and torsion in the Frenet-Serret frame. A generalized worm-like chain model is used to account for experimentally obtained force-displacement curves for DNA. The statistical mechanics of membranes is then developed along analogous lines to flexible polymers, by treating membranes as thin elastic sheets. In order to construct the bending energy of the membrane, some basic results form membrane elasticity are reviewed, including stress and strain tensors, bending/compression moduli, and the theory of curved surfaces. The corresponding partition function is used to estimate the size of thermally driven membrane fluctuations. Since the membrane is modeled as an infinite-dimensional continuum, the partition function takes the form of a path-integral whose associated free energy is a functional. The analysis of statistical properties thus requires the use of functional calculus. The next topic is the statistical dynamics of systems at or close to equilibrium. This is developed by generalizing the theory of Brownian motion to more complex structures with many internal degrees of freedom. Various results and concepts from classical non-equilibrium statistical physics are introduced, including Onsager’s reciprocal relations, non-equilibrium forces, time correlations and susceptibilities, and a general version of the fluctuation-dissipation theorem. The theory is illustrated by deriving Langevin equations for fluctuating polymers and membranes. The chapter then turns to polymer network models, which are used extensively by biophysicists to understand the rheological properties of the cytoskeleton. Only the simplest classical models are considered: the rubber elasticity of a cross-linked polymer network, swelling of a polymer gel, and the macroscopic theory of viscoelasticity in uncross-
linked polymer fluids. Reptation theory, which is used to model the dynamics of entangled polymers, is also briefly discussed. Finally, the dynamics of DNA within the nucleus is considered. After describing some of the key features of nuclear organization, a classical stochastic model of a Gaussian polymer chain (the Rouse model) is introduced. The latter is used to model the subdiffusive motion of chromosomal loci, and to explore mechanisms for spontaneous DNA loop formation. The mean time to form a loop requires solving an FP equation with non-trivial absorbing boundary condition. The Wilemski-Fixman theory of diffusion-controlled reactions is used to solve the problem by replacing the boundary condition with a sink term in the FP equation.

Chapter 13 considers the self-organization and assembly of a number of distinct cellular structures. First, there is a detailed discussion of the theory of liquid-liquid phase separation and the formation of biological condensates. This introduces various classical concepts in non-equilibrium systems, such as coexistence curves, spinodal decomposition, nucleation and coarsening, Ostwald ripening, and Onsager's principle. Recent developments that are specific to biological condensates are also described, including the effects of non-equilibrium chemical reactions and protein concentration gradients. The chapter then turns to the Becker and Döring model of molecular aggregation and fragmentation, which provides a framework for investigating the processes of nucleation and coarsening. An application of the model to the self-assembly of phospholipids in the plasma membrane is also included. Finally, a model for the cooperative transport of proteins between cellular organelles is introduced, which represents a self-organizing mechanism for organelles to maintain their distinct identities while constantly exchanging material.

Chapter 14 considers various models for the dynamics and regulation of the cytoskeleton. First, several mechanisms for filament length regulation are presented, including molecular motor-based control, protein concentration gradients, and diffusion based secretion in bacterial flagella. The role of intraflagellar transport (IFT) in the length control of eukaryotic flagella is analyzed in terms of a doubly stochastic Poisson process. The dynamics of the mitotic spindle during various stages of cell mitosis is then described, including the search-and-capture model of microtubule-chromosome interactions and force-balance equations underlying chromosomal oscillations. Finally, various models of biophysical mechanisms underlying cell motility are considered. These includes the tethered ratchet model of cell protrusion and the motor-clutch mechanism for crawling cells. The latter describes the dynamical interplay between retrograde flow of the actin cytoskeleton and the assembly and disassembly of focal adhesions. The resulting dynamics exhibits a number of behaviors that are characteristic of physical systems involving friction at moving interfaces, including biphasic force-velocity curves and stick-slip motion. A mean-field analysis is used to show how these features can be captured by a relatively simple stochastic model of focal adhesions. In addition, a detailed model of the force-induced growth of focal adhesions is analyzed using a variational method for free energy minimization. Finally, a detailed account of cytoneme-based morphogenesis is given. Cytonemes are thin, actin-rich filaments that can dynamically
extend up to several hundred microns to form direct cell-to-cell contacts. There is increasing experimental evidence that these direct contacts allow the active transport of morphogen to embryonic cells during development. Two distinct models of active transport are considered. The first involves active motor-driven transport of morphogen along static cytonemes with fixed contacts between a source cell and a target cell. The second is based on nucleating cytonemes from a source cell that dynamically grow and shrink until making temporary contact with a target cell and delivering a burst of morphogen. The delivery of a single burst is modeled in terms of a FPT problem for a search process with stochastic resetting, while the accumulation of morphogen following multiple rounds of cytoneme search-and-capture and degradation is analyzed using queuing theory.

Chapter 15 presents various topics related to bacterial population growth and collective behavior. First, a continuum model of bacterial population growth is developed using an age-structured evolution equation. Such an equation supplements the continuously varying observational time by a second time variable that specifies the age of an individual cell since the last division. Whenever a cell divides, the age of the daughter cells is reset to zero. Although the total number of cells grows exponentially with time, the normalized age distribution approaches a steady-state. The latter determines the effective population growth rate via a self-consistency condition. The age-structured model is then extended in order to keep track of both the age and volume distribution of cells. This is used to explore various forms of cell length regulation, including timer, sizer and adder mechanisms. Further aspects of cell size regulation are analyzed in terms of a discrete-time stochastic map that tracks changes across cell generations. The chapter then turns to another important issue, namely, to what extent single-cell molecular variation play a role in population-level function. This is explored within the context of phenotypic switching in switching environments, which is thought to be an important factor in the phenomenon of persistent bacterial infections following treatment with antibiotics. At the population level, phenotypic switching is modeled in terms of a stochastic hybrid system. The chapter then turns to a discussion of bacterial quorum sensing (QS). This is a form of collective cell behavior that is triggered by the population density reaching a critical threshold, which requires that individual cells sense their local environment. The next topic is an analysis of synchronization in a population of synthetic gene oscillators that are dynamically coupled to an external medium via a QS mechanism. In particular a continuity equation for the distribution of oscillator phases is constructed in the thermodynamic limit, and various methods of analysis are presented, including the Ott-Antonsen dimensional reduction ansatz. The chapter ends with a review of some mathematical models of bacterial biofilms.

Chapter 16 discusses various analytical methods for studying stochastic reaction-diffusion processes. First, the effects of intrinsic noise on intracellular pattern formation are investigated using the notion of a reaction-diffusion master equation. The latter is obtained by discretizing space and treating spatially discrete diffusion as a hopping reaction. Carrying out a linear noise approximation of the master equation leads to an effective Langevin equation, whose power spectrum provides
a means of extending the definition of a Turing instability to stochastic systems, namely, in terms of the existence of a peak in the power spectrum at a non-zero spatial frequency. It is also shown how the interplay between intrinsic noise and transient growth of perturbations can amplify the weakly fluctuating patterns. The source of transient growth is the presence of a non-normal matrix in the linear evolution operator. Next, using the canonical example of pair annihilation with diffusion, various well-known techniques from statistical field theory are used to capture the dimension-dependent asymptotic decay of the system. These include moment generating functionals, diagrammatic perturbation expansions (Feynman diagrams), and the renormalization group. Finally, a formal perturbation method is used to analyze bistable front solutions of a stochastic reaction-diffusion equation, which exploits a separation of time scales between fast fluctuations of the front profile and a slowly diffusing phase shift in the mean location of the front.

At the end of most chapters there is a set of exercises that further develops the mathematical models and analysis introduced within the body of the text. Additional comments and background material are scattered throughout the text in the form of framed boxes.

Introductory lecture notes based on the contents of this book can be found at http://www.math.utah.edu/bresslof/
11. Intracellular pattern formation and reaction-diffusion processes
• intracellular protein gradients
• Turing pattern formation
• mass-conserving systems
• coupled PDE/ODE systems
• cell polarization and division
• hybrid reaction-transport models
• intracellular traveling waves

15. Bacterial population growth and collective behavior
• age-structured models
• cell size control
• bacterial persistence/phenotypic switching
• extinction in bacterial populations
• bacterial quorum sensing
• biofilms
• stochastic Turing patterns
• path integral of RD master equation
• statistical field theory
• diagramatic expansions
• renormalization theory and scaling
• stochastic traveling waves

14. Regulation of the cytoskeleton
• filament length control
• intraflagellar transport
• doubly stochastic poisson processes
• cell mitosis
• cell motility
• cell adhesion
• cytoneme-based morphogenesis

13. Self-organization and assembly of cellular structures
• phase separation/biological condensates
• active membranes
• nucleation and growth of molecular clusters
• self-assembly of micelles

10. Sensing the environment
• phosphorylation and ultrasensitivity
• photoreceptors and shot noise
• linear response theory
• hair cell mechanotransduction
• bacterial chemotaxis
• physical limits of chemical sensing
• spatial gradient sensing

9. Probability theory and martingales
• filtrations, martingales and stopping times
• branching processes
• counting process and biochemical networks

8. WKB method, path integrals...
• WKB method for noise-induced escape
• path-integral for SDEs
• Doi-Peliti path integral of a birth death process
• path integral for hybrid systems
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