## Applied Stochastic Analysis

Weinan E<br>Tiejun Li<br>Eric Vanden-Eijnden

# Applied Stochastic Analysis 

# Applied <br> Stochastic Analysis 

Weinan E<br>Tiejun Li<br>Eric Vanden-Eijnden

AMS
AMERICAN
MATHEMATICAL
SOCIETY
Providence, Rhode Island

# EDITORIAL COMMITTEE 

Daniel S. Freed (Chair)<br>Bjorn Poonen<br>Gigliola Staffilani<br>Jeff A. Viaclovsky

2010 Mathematics Subject Classification. Primary 60-01, 60J22, 60H10, 60H35, 62P10, 62P35, 65C05, 65C10, 82-01.

For additional information and updates on this book, visit
www.ams.org/bookpages/gsm-199

## Library of Congress Cataloging-in-Publication Data

Names: E, Weinan, 1963- author. | Li, Tiejun, 1974- author. | Vanden-Eijnden, Eric, 1968author.
Title: Applied stochastic analysis / Weinan E, Tiejun Li, Eric Vanden-Eijnden.
Description: Providence, Rhode Island : American Mathematical Society, [2019] | Series: Graduate studies in mathematics ; volume 199 | Includes bibliographical references and index.
Identifiers: LCCN 2019000898 | ISBN 9781470449339 (alk. paper)
Subjects: LCSH: Stochastic analysis. | AMS: Probability theory and stochastic processes - Instructional exposition (textbooks, tutorial papers, etc.). msc | Probability theory and stochastic processes - Markov processes - Computational methods in Markov chains. msc | Probability theory and stochastic processes - Stochastic analysis - Stochastic ordinary differential equations. msc | Probability theory and stochastic processes - Stochastic analysis - Computational methods for stochastic equations. msc | Statistics - Applications - Applications to biology and medical sciences. msc | Statistics - Applications - Applications to physics. msc | Numerical analysis - Probabilistic methods, simulation and stochastic differential equations - Monte Carlo methods. msc| Numerical analysis - Probabilistic methods, simulation and stochastic differential equations - Random number generation. msc | Statistical mechanics, structure of matter - Instructional exposition (textbooks, tutorial papers, etc.). msc
Classification: LCC QA274.2 .E23 2019 | DDC 519.2-dc23
LC record available at https://lccn.loc.gov/2019000898

Copying and reprinting. Individual readers of this publication, and nonprofit libraries acting for them, are permitted to make fair use of the material, such as to copy select pages for use in teaching or research. Permission is granted to quote brief passages from this publication in reviews, provided the customary acknowledgment of the source is given.

Republication, systematic copying, or multiple reproduction of any material in this publication is permitted only under license from the American Mathematical Society. Requests for permission to reuse portions of AMS publication content are handled by the Copyright Clearance Center. For more information, please visit www.ams.org/publications/pubpermissions.

Send requests for translation rights and licensed reprints to reprint-permission@ams.org.
(C) 2019 by the authors. All rights reserved.

Printed in the United States of America.


The paper used in this book is acid-free and falls within the guidelines established to ensure permanence and durability.
Visit the AMS home page at https://www.ams.org/

$$
10987654321 \quad 242322212019
$$

To our families

Hongjun, Jane, and Ilene
Xueqing, Baitian, and Baile
Jasna, Colette, Pauline, and Anais et Lilia

## Contents

Introduction to the Series ..... xiii
Preface ..... xvii
Notation ..... xix
Part 1. Fundamentals
Chapter 1. Random Variables ..... 3
§1.1. Elementary Examples ..... 3
§1.2. Probability Space ..... 5
§1.3. Conditional Probability ..... 6
§1.4. Discrete Distributions ..... 7
§1.5. Continuous Distributions ..... 8
§1.6. Independence ..... 12
§1.7. Conditional Expectation ..... 14
§1.8. Notions of Convergence ..... 16
§1.9. Characteristic Function ..... 17
§1.10. Generating Function and Cumulants ..... 19
§1.11. The Borel-Cantelli Lemma ..... 21
Exercises ..... 24
Notes ..... 27
Chapter 2. Limit Theorems ..... 29
§2.1. The Law of Large Numbers ..... 29
§2.2. Central Limit Theorem ..... 31
§2.3. Cramér's Theorem for Large Deviations ..... 32
§2.4. Statistics of Extrema ..... 40
Exercises ..... 42
Notes ..... 44
Chapter 3. Markov Chains ..... 45
§3.1. Discrete Time Finite Markov Chains ..... 46
§3.2. Invariant Distribution ..... 48
§3.3. Ergodic Theorem for Finite Markov Chains ..... 51
§3.4. Poisson Processes ..... 53
§3.5. $\quad Q$-processes ..... 54
§3.6. Embedded Chain and Irreducibility ..... 57
§3.7. Ergodic Theorem for $Q$-processes ..... 59
§3.8. Time Reversal ..... 59
§3.9. Hidden Markov Model ..... 61
§3.10. Networks and Markov Chains ..... 67
Exercises ..... 71
Notes ..... 73
Chapter 4. Monte Carlo Methods ..... 75
§4.1. Numerical Integration ..... 76
§4.2. Generation of Random Variables ..... 77
§4.3. Variance Reduction ..... 83
§4.4. The Metropolis Algorithm ..... 87
§4.5. Kinetic Monte Carlo ..... 91
§4.6. Simulated Tempering ..... 92
§4.7. Simulated Annealing ..... 94
Exercises ..... 96
Notes ..... 98
Chapter 5. Stochastic Processes ..... 101
§5.1. Axiomatic Construction of Stochastic Process ..... 102
§5.2. Filtration and Stopping Time ..... 104
§5.3. Markov Processes ..... 106
§5.4. Gaussian Processes ..... 109
Exercises ..... 113
Notes ..... 114
Chapter 6. Wiener Process ..... 117
§6.1. The Diffusion Limit of Random Walks ..... 118
§6.2. The Invariance Principle ..... 120
§6.3. Wiener Process as a Gaussian Process ..... 121
§6.4. Wiener Process as a Markov Process ..... 125
§6.5. Properties of the Wiener Process ..... 126
$\S 6.6$. Wiener Process under Constraints ..... 130
§6.7. Wiener Chaos Expansion ..... 132
Exercises ..... 135
Notes ..... 137
Chapter 7. Stochastic Differential Equations ..... 139
§7.1. Itô Integral ..... 140
§7.2. Itô's Formula ..... 144
§7.3. Stochastic Differential Equations ..... 148
§7.4. Stratonovich Integral ..... 154
§7.5. Numerical Schemes and Analysis ..... 156
§7.6. Multilevel Monte Carlo Method ..... 162
Exercises ..... 165
Notes ..... 167
Chapter 8. Fokker-Planck Equation ..... 169
§8.1. Fokker-Planck Equation ..... 170
§8.2. Boundary Condition ..... 173
§8.3. The Backward Equation ..... 175
§8.4. Invariant Distribution ..... 176
§8.5. The Markov Semigroup ..... 178
§8.6. Feynman-Kac Formula ..... 180
§8.7. Boundary Value Problems ..... 181
§8.8. Spectral Theory ..... 183
§8.9. Asymptotic Analysis of SDEs ..... 185
§8.10. Weak Convergence ..... 188
Exercises ..... 193
Notes ..... 194

## Part 2. Advanced Topics

Chapter 9. Path Integral ..... 199
§9.1. Formal Wiener Measure ..... 200
§9.2. Girsanov Transformation ..... 203
§9.3. Feynman-Kac Formula Revisited ..... 207
Exercises ..... 208
Notes ..... 208
Chapter 10. Random Fields ..... 209
§10.1. Examples of Random Fields ..... 210
§10.2. Gaussian Random Fields ..... 212
§10.3. Gibbs Distribution and Markov Random Fields ..... 214
Exercise ..... 216
Notes ..... 216
Chapter 11. Introduction to Statistical Mechanics ..... 217
§11.1. Thermodynamic Heuristics ..... 219
§11.2. Equilibrium Statistical Mechanics ..... 224
§11.3. Generalized Langevin Equation ..... 233
§11.4. Linear Response Theory ..... 236
§11.5. The Mori-Zwanzig Reduction ..... 238
§11.6. Kac-Zwanzig Model ..... 240
Exercises ..... 242
Notes ..... 244
Chapter 12. Rare Events ..... 245
§12.1. Metastability and Transition Events ..... 246
§12.2. WKB Analysis ..... 248
§12.3. Transition Rates ..... 249
§12.4. Large Deviation Theory and Transition Paths ..... 250
§12.5. Computing the Minimum Energy Paths ..... 253
§12.6. Quasipotential and Energy Landscape ..... 254
Exercises ..... 259
Notes ..... 260
Chapter 13. Introduction to Chemical Reaction Kinetics ..... 261
§13.1. Reaction Rate Equations ..... 262
§13.2. Chemical Master Equation ..... 263
§13.3. Stochastic Differential Equations ..... 265
§13.4. Stochastic Simulation Algorithm ..... 266
§13.5. The Large Volume Limit ..... 266
§13.6. Diffusion Approximation ..... 268
§13.7. The Tau-leaping Algorithm ..... 269
§13.8. Stationary Distribution ..... 271
§13.9. Multiscale Analysis of a Chemical Kinetic System ..... 272
Exercises ..... 277
Notes ..... 277
Appendix ..... 279
A. Laplace Asymptotics and Varadhan's Lemma ..... 279
B. Gronwall's Inequality ..... 281
C. Measure and Integration ..... 282
D. Martingales ..... 284
E. Strong Markov Property ..... 285
F. Semigroup of Operators ..... 286
Bibliography ..... 289
Index ..... 301

## Introduction to the Series

It is fairly well accepted that to learn pure mathematics, a student has to take analysis, algebra, geometry, and topology. Until now there has not been an equally well-accepted curriculum for applied mathematics. There are many reasons one can think of. For one thing, applied mathematics is truly very diverse. Traditional subjects such as numerical analysis, statistics, operational research, etc., can all be regarded as part of applied mathematics. Beyond that, a huge amount of applied mathematics is practiced in other scientific and engineering disciplines. For example, a large part of fluid dynamics research has become computational. The same can be said about theoretical chemistry, biology, material science, etc. The algorithmic issues that arise in these disciplines are at the core of applied mathematics. Machine learning, a subject that deals with mathematical models and algorithms for complex data, is, at its heart, a very mathematical discipline, although at the moment it is much more commonly practiced in computer science departments.

In 2002, David Cai, Shi Jin, Eric Vanden-Eijnden, Pingwen Zhang, and I started the applied mathematics summer school in Beijing, with the objective of creating a systematic and unified curriculum for students in applied mathematics. Since then, this summer school has been repeated every year at Peking University. The main theme of the summer school has also evolved. But in the early years, the main topics were applied stochastic analysis, differential equations, numerical algorithms, and a mathematical introduction to physics. In recent years, a mathematical introduction to
machine learning has also been added to the list. In addition to the summer school, these courses have also been taught from time to time during regular terms at New York University, Peking University, and Princeton University. The lecture notes from these courses are the main origin of this textbook series. The early participants, including some of the younger people who were students or teaching assistants early on, have also become contributors to this book series.

After many years, this series of courses has finally taken shape. Obviously, this has not come easy and is the joint effort of many people. I would like to express my sincere gratitude to Tiejun Li, Pingbing Ming, Shi Jin, Eric Vanden-Eijnden, Pingwen Zhang, and other collaborators involved for their commitment and dedication to this effort. I am also very grateful to Mrs. Yanyun Liu, Baomei Li, Tian Tian, Yuan Tian for their tireless efforts to help run the summer school. Above all, I would like to pay tribute to someone who dedicated his life to this cause, David Cai. David had a passion for applied mathematics and its applications to science. He believed strongly that one has to find ways to inspire talented young people to go into applied mathematics and to teach them applied mathematics in the right way. For many years, he taught a course on introducing physics to applied mathematicians in the summer school. To create a platform for practicing the philosophy embodied in this project, he cofounded the Institute of Natural Sciences at Shanghai Jiaotong University, which has become one of the most active centers for applied mathematics in China. His passing away last year was an immense loss, not just for all of us involved in this project, but also for the applied mathematics community as a whole.

This book is the first in this series, covering probability theory and stochastic processes in a style that we believe is most suited for applied mathematicians. Other subjects covered in this series will include numerical algorithms, the calculus of variations and differential equations, a mathematical introduction to machine learning, and a mathematical introduction to physics and physical modeling. The stochastic analysis and differential equations courses summarize the most relevant aspects of pure mathematics, the algorithms course presents the most important technical tool of applied mathematics, and the learning and physical modeling courses provide a bridge to the real world and to other scientific disciplines. The selection of topics represents a possibly biased view about the true fundamentals of applied mathematics. In particular, we emphasize three themes throughout this textbook series: learning, modeling, and algorithms. Learning is about data and intelligent decision making. Modeling is concerned with physics-based models. The study of algorithms provides the practical tool for building and interrogating the models, whether machine learning-based
or physics-based. We believe that these three themes should be the major pillars of applied mathematics, the applied math analog of algebra, analysis, and geometry.

While physical modeling and numerical algorithms have been the dominating driving force in applied mathematics for years, machine learning is a relatively new comer. However, there are very good reasons to believe that machine learning will not only change AI but also the way we do physical modeling. With this last missing component in place, applied mathematics will become the natural platform for integrating machine learning and physical modeling. This represents a new style for doing scientific research, a style in which the data-driven Keplerian paradigm and the first principle-driven Newtonian paradigm are integrated to give rise to unprecedented technical power. It is our hope that this series of textbooks will be of some help for making that a reality!

Weinan E, Princeton, 2018

## Preface

This book is written for students and researchers in applied mathematics with an interest in science and engineering. Our main purpose is to provide a mathematically solid introduction to the basic ideas and tools in probability theory and stochastic analysis. Starting from the basics of random variables and probability theory, we go on to discuss limit theorems, Markov chains, diffusion processes, and random fields. Since the kind of readers we have in mind typically have some background in differential equations, we put more weight on the differential equation approach. In comparison, we have neglected entirely martingale theory even though it is a very important part of stochastic analysis. The diffusion process occupies a central role in this book. We have presented three different ways of looking at the diffusion process: the approach of using stochastic differential equations, the Fokker-Planck equation approach, and the path integral approach. The first allows us to introduce stochastic calculus. The second approach provides a link between differential equations and stochastic analysis. The path integral approach is very much preferred by physicists and is also suited for performing asymptotic analysis. In addition, it can be extended to random fields.

In choosing the style of the presentation, we have tried to strike a balance between rigor and the heuristic approach. We have tried to give the reader an idea about the kind of mathematical construction or mathematical argument that goes into the subject matter, but at the same time, we often stop short of proving all the theorems we state or we prove the theorems under stronger assumptions. Whenever possible, we have tried to give the intuitive picture behind the mathematical constructions.

Another emphasis is on numerical algorithms, including Monte Carlo methods, numerical schemes for solving stochastic differential equations, and the stochastic simulation algorithm. The book ends with a discussion on two application areas, statistical mechanics and chemical kinetics, and a discussion on rare events, which is perhaps the most important manifestation of the effect of noise.

The material contained in this book has been taught in various forms at Peking University, Princeton University, and New York University since 2001. It is now a required course for the special applied mathematics program at Peking University.

Weinan E<br>Tiejun Li<br>Eric Vanden-Eijnden

December 2018

## Notation

(1) Geometry notation:
(a) $\mathbb{N}$ : Natural numbers, $\mathbb{N}=\{0,1, \ldots\}$.
(b) $\mathbb{Z}$ : Integers.
(c) $\mathbb{Q}$ : Rational numbers.
(d) $\mathbb{R}$ : Real numbers.
(e) $\overline{\mathbb{R}}$ : Extended real numbers, $\overline{\mathbb{R}}=[-\infty, \infty]$.
(f) $\mathbb{R}_{+}$: Nonnegative real numbers.
(g) $\overline{\mathbb{R}}_{+}$: Extended nonnegative real numbers, $\overline{\mathbb{R}}_{+}=[0, \infty]$.
(h) $\mathbb{S}^{n-1}:(n-1)$-dimensional unit sphere in $\mathbb{R}^{n}$.
(i) $\mathbb{R}^{\mathbf{T}}$ : Collection of all real functions on time domain $\mathbf{T}$.
(2) Probability notation:
(a) $\mathbb{P}$ : Probability measure.
(b) $\mathbb{E}$ : Mathematical expectation.
(c) $\mathbb{P}^{i}, \mathbb{P}^{x}$, or $\mathbb{P}^{\mu}$ : Probability distribution conditioned on $X_{0}=i$, $X_{0}=x$, or $X_{0} \sim \mu$.
(d) $\mathbb{E}^{i}, \mathbb{E}^{x}, \mathbb{E}^{\mu}$ : Mathematical expectation with respect to $\mathbb{P}^{i}, \mathbb{P}^{x}$, or $\mathbb{P}^{\mu}$.
(e) $\mathbb{E}^{x, t}$ : Mathematical expectation conditioned on $X_{t}=x$.
(f) $\Omega$ : Sample space.
(g) $\mathcal{F}: \sigma$-algebra in probability space.
(h) $\mathcal{R}, \mathcal{R}^{d}$ : The Borel $\sigma$-algebra on $\mathbb{R}$ or $\mathbb{R}^{d}$.
(i) $\sigma(\mathcal{B})$ : The smallest $\sigma$-algebra generated by sets in $\mathcal{B}$.
(j) $\mathcal{R}^{\mathrm{T}}$ : The product Borel $\sigma$-algebra on $\mathbb{R}^{\mathrm{T}}$.
(k) $\mathcal{U}(A)$ : Uniform distribution on set $A$.
(l) $\mathcal{P}(\lambda)$ : Poisson distribution with mean $\lambda$.
(m) $\mathcal{E}(\lambda)$ : Exponential distribution with mean $\lambda^{-1}$.
(n) $[X, X]_{t}$ : Quadratic variation process of $X$.
(o) $X \sim \mathcal{P}(\lambda)$ : Distribution of $X$. The right-hand side can be distributions like $\mathcal{P}(\lambda)$ or $N\left(\mu, \sigma^{2}\right)$, etc.
(3) Function spaces:
(a) $C_{c}^{\infty}\left(\mathbb{R}^{d}\right)$ or $C_{c}^{k}\left(\mathbb{R}^{d}\right)$ : Smooth or $C^{k}$-functions with compact support in $\mathbb{R}^{d}$.
(b) $C_{0}\left(\mathbb{R}^{d}\right)$ : Continuous functions in $\mathbb{R}^{d}$ that vanish at infinity.
(c) $C_{b}\left(\mathbb{R}^{d}\right)$ : Bounded continuous functions in $\mathbb{R}^{d}$.
(d) $L_{t}^{p}$ or $L^{p}([0, T]): L^{p}$-functions as a function of $t$.
(e) $L_{\omega}^{p}$ or $L^{p}(\Omega): L^{p}$-functions as a function of $\omega$.
(f) $\mathscr{B}, \mathscr{H}$ : Banach or Hilbert spaces.
(g) $\mathscr{B}^{*}$ : Dual space of $\mathscr{B}$.
(4) Operators: $\mathcal{I}, \mathcal{P}, \mathcal{Q}, \mathcal{K}$, etc.
(5) Functions:
(a) $\lceil\cdot\rceil$ : The ceil function. $\lceil x\rceil=m+1$ if $x \in[m, m+1$ ) for $m \in \mathbb{Z}$.
(b) $\lfloor\cdot\rfloor$ : The floor function. $\lfloor x\rfloor=m$ if $x \in[m, m+1)$ for $m \in \mathbb{Z}$.
(c) $|\boldsymbol{x}|: \ell^{2}$-modulus of a vector $\boldsymbol{x} \in \mathbb{R}^{d}:|\boldsymbol{x}|=\left(\sum_{i=1}^{d} x_{i}^{2}\right)^{\frac{1}{2}}$.
(d) $\|f\|$ : Norm of function $f$ in some function space.
(e) $a \vee b$ : Maximum of $a$ and $b: a \vee b=\max (a, b)$.
(f) $a \wedge b$ : Minimum of $a$ and $b: a \wedge b=\min (a, b)$.
(g) $\langle f\rangle$ : The average of $f$ with respect to a measure $\mu$ : $\langle f\rangle=$ $\int f(x) \mu(d x)$.
(h) $(\boldsymbol{x}, \boldsymbol{y})$ : Inner product for $\boldsymbol{x}, \boldsymbol{y} \in \mathbb{R}^{d}:(\boldsymbol{x}, \boldsymbol{y})=\boldsymbol{x}^{T} \boldsymbol{y}$.
(i) $(f, g)$ : Inner product for $L^{2}$-functions $f, g:(f, g)=\int f(x) g(x) d x$.
(j) $\langle f, g\rangle$ : Dual product for $f \in \mathscr{B}^{*}$ and $g \in \mathscr{B}$.
(k) $A: B$ : Twice contraction for second-order tensors, i.e., $A$ : $B=\sum_{i j} a_{i j} b_{j i}$.
(l) $|S|$ : The cardinality of set $S$.
(m) $|\Delta|$ : The subdivision size when $\Delta$ is a subdivision of a domain.
(n) $\chi_{A}(x)$ : Indicator function, i.e., $\chi_{A}(x)=1$ if $x \in A$ and 0 otherwise.
(o) $\delta(x-a)$ : Dirac's delta-function at $x=a$.
(p) Range $(\mathcal{P}), \operatorname{Null}(\mathcal{P})$ : The range and null space of operator $\mathcal{P}$, i.e., Range $(\mathcal{P})=\{y \mid y=\mathcal{P} x\}, \operatorname{Null}(\mathcal{P})=\{x \mid \mathcal{P} x=0\}$.
(q) ${ }^{\perp} \mathscr{C}$ : Perpendicular subspace, i.e., ${ }^{\perp} \mathscr{C}=\left\{x \mid x \in \mathscr{B}^{*},\langle x, y\rangle=\right.$ $0, \forall y \in \mathscr{C}\}$ where $\mathscr{C} \subset \mathscr{B}$.
(6) Symbols:
(a) $c_{\varepsilon} \asymp d_{\varepsilon}$ : Logrithmic equivalence, i.e., $\lim _{\varepsilon \rightarrow 0} \log c_{\varepsilon} / \log d_{\varepsilon}=1$.
(b) $c_{\varepsilon} \sim d_{\varepsilon}$ or $c_{n} \sim d_{n}$ : Equivalence, i.e., $\lim _{\varepsilon \rightarrow 0} c_{\varepsilon} / d_{\varepsilon}=1$ or $\lim _{n \rightarrow \infty} c_{n} / d_{n}=1$.
(c) $\mathcal{D} x$ : Formal infinitesimal element in path space, $\mathcal{D} x=$ $\prod_{0 \leq t \leq T} d x_{t}$.

## Appendix

## A. Laplace Asymptotics and Varadhan's Lemma

Consider the Laplace integral

$$
F(t)=\int_{\mathbb{R}} e^{t h(x)} d x, \quad t \gg 1
$$

where $h(x) \in C^{2}(\mathbb{R}), h(0)$ is the only global maximum, and $h^{\prime \prime}(0) \neq 0$. We further assume that for any $c>0$, there exists $b>0$ such that

$$
h(x)-h(0) \leq-b \quad \text { if }|x| \geq c
$$

Assume also that $h(x) \rightarrow-\infty$ fast enough as $x \rightarrow \infty$ to ensure the convergence of $F$ for $t=1$.

Lemma A. 1 (Laplace method). We have the asymptotics

$$
\begin{equation*}
F(t) \sim \sqrt{2 \pi}\left(-t h^{\prime \prime}(0)\right)^{-\frac{1}{2}} \exp (t h(0)) \quad \text { as } t \rightarrow \infty \tag{A.1}
\end{equation*}
$$

where the equivalence $f(t) \sim g(t)$ means that $\lim _{t \rightarrow \infty} f(t) / g(t)=1$.
The above asymptotic results can be stated as

$$
\lim _{t \rightarrow \infty} \frac{1}{t} \log F(t)=\sup _{x \in \mathbb{R}} h(x) .
$$

This formulation is what we will use in the large deviation theory. Its abstract form in the infinite-dimensional setting is embodied in the so-called Varadhan's lemma to be discussed later [DZ98, DS84, Var84].

Proof. Without loss of generality, we can assume $h(0)=0$ by shifting $h(x)$ correspondingly. With this condition, if $h(x)=h^{\prime \prime}(0) x^{2} / 2, h^{\prime \prime}(0)<0$, we
have

$$
\int_{\mathbb{R}} e^{t h(x)} d x=\sqrt{2 \pi}\left(-t h^{\prime \prime}(0)\right)^{-\frac{1}{2}}
$$

In general, for any $\epsilon>0$, there exists $\delta>0$ such that if $|x| \leq \delta$,

$$
\left|h(x)-\frac{h^{\prime \prime}(0)}{2} x^{2}\right| \leq \epsilon x^{2}
$$

It follows that

$$
\begin{aligned}
\int_{[-\delta, \delta]} \exp \left(\frac{t x^{2}}{2}\left(h^{\prime \prime}(0)-2 \epsilon\right)\right) d x & \leq \int_{[-\delta, \delta]} \exp (t h(x)) d x \\
& \leq \int_{[-\delta, \delta]} \exp \left(\frac{t x^{2}}{2}\left(h^{\prime \prime}(0)+2 \epsilon\right)\right) d x
\end{aligned}
$$

By assumption, for this $\delta>0$, there exists $\eta>0$ such that $h(x) \leq-\eta$ if $|x| \geq \delta$. Thus

$$
\int_{|x| \geq \delta} \exp (t h(x)) d x \leq e^{-(t-1) \eta} \int_{\mathbb{R}} e^{h(x)} d x \sim \mathcal{O}\left(e^{-\alpha t}\right), \alpha>0, \quad \text { for } \quad t>1
$$

We first prove the upper bound:

$$
\begin{aligned}
\int_{\mathbb{R}} \exp (t h(x)) d x \leq & \int_{\mathbb{R}} \exp \left(\frac{t x^{2}}{2}\left(h^{\prime \prime}(0)+2 \epsilon\right)\right) d x \\
& -\int_{|x| \geq \delta} \exp \left(\frac{t x^{2}}{2}\left(h^{\prime \prime}(0)+2 \epsilon\right)\right) d x+\mathcal{O}\left(e^{-\alpha t}\right) \\
= & \sqrt{2 \pi}\left[t\left(-h^{\prime \prime}(0)-2 \epsilon\right)\right]^{-\frac{1}{2}}+\mathcal{O}\left(e^{-\beta t}\right)
\end{aligned}
$$

where $\beta>0$. In fact, we ask for $\epsilon<-h^{\prime \prime}(0) / 2$ here.
The proof of the lower bound is similar. By the arbitrary smallness of $\epsilon$, we have

$$
\lim _{t \rightarrow \infty} F(t) / \sqrt{2 \pi}\left(-t h^{\prime \prime}(0)\right)^{-\frac{1}{2}}=1
$$

which completes the proof.
Definition A. 2 (Large deviation principle). Let $\mathscr{X}$ be a complete separable metric space and let $\left\{\mathbb{P}^{\varepsilon}\right\}_{\varepsilon \geq 0}$ be a family of probability measures on the Borel subsets of $\mathscr{X}$. We say that $\mathbb{P}^{\varepsilon}$ satisfies the large deviation principle if there exists a rate functional $I: \mathscr{X} \rightarrow[0, \infty]$ such that:
(i) For any $\ell<\infty$,

$$
\{x: I(x) \leq \ell\} \text { is compact. }
$$

(ii) Upper bound. For each closed set $F \subset \mathscr{X}$,

$$
\varlimsup_{\varepsilon \rightarrow 0} \varepsilon \ln \mathbb{P}^{\varepsilon}(F) \leq-\inf _{x \in F} I(x)
$$

(iii) Lower bound. For each open set $G \subset \mathscr{X}$,

$$
\varliminf_{\varepsilon \rightarrow 0} \varepsilon \ln \mathbb{P}^{\varepsilon}(G) \geq-\inf _{x \in G} I(x)
$$

Theorem A. 3 (Varadhan's lemma). Suppose that $\mathbb{P}^{\varepsilon}$ satisfies the large deviation principle with rate functional $I(\cdot)$ and $F \in C_{b}(\mathscr{X})$. Then

$$
\begin{equation*}
\lim _{\varepsilon \rightarrow 0} \varepsilon \ln \int_{\mathscr{X}} \exp \left(\frac{1}{\varepsilon} F(x)\right) \mathbb{P}^{\varepsilon}(d x)=\sup _{x \in \mathscr{X}}(F(x)-I(x)) . \tag{A.2}
\end{equation*}
$$

The proof of Varadhan's lemma can be found in DZ98, Var84.

## B. Gronwall's Inequality

Theorem B. 1 (Gronwall's inequality). Assume that the function $f:[0, \infty)$ $\rightarrow \mathbb{R}^{+}$satisfies the inequality

$$
f(t) \leq a(t)+\int_{0}^{t} b(s) f(s) d s
$$

where $a(t), b(t) \geq 0$. Then we have

$$
\begin{equation*}
f(t) \leq a(t)+\int_{0}^{t} a(s) b(s) \exp \left(\int_{s}^{t} b(u) d u\right) d s \tag{B.1}
\end{equation*}
$$

Proof. Let $g(t)=\int_{0}^{t} b(s) f(s) d s$. We have

$$
g^{\prime}(t) \leq a(t) b(t)+b(t) g(t)
$$

Define $h(t)=g(t) \exp \left(-\int_{0}^{t} b(s) d s\right)$. We obtain

$$
h^{\prime}(t) \leq a(t) b(t) \exp \left(-\int_{0}^{t} b(s) d s\right)
$$

Integrating both sides from 0 to $t$, we get

$$
g(t) \leq \int_{0}^{t} a(s) b(s) \exp \left(\int_{s}^{t} b(u) d u\right) d s
$$

which yields the desired estimate.
In the case when $a(t) \equiv a$ and $b(t) \equiv b$, we have

$$
f(t) \leq a \exp (b t)
$$

Theorem B. 2 (Discrete Gronwall's inequality). Assume that $F_{n}$ satisfies

$$
\begin{equation*}
F_{n+1} \leq\left(1+b_{n} \delta t\right) F_{n}+a_{n}, \quad F_{0} \geq 0 \tag{B.2}
\end{equation*}
$$

where $\delta t, a_{n}, b_{n} \geq 0$. Then we have
(B.3) $\quad F_{n} \leq \exp \left(\left(\sum_{k=0}^{n-1} b_{k}\right) \delta t\right) F_{0}+\sum_{k=0}^{n-1}\left(a_{k} \exp \left(\left(\sum_{l=k+1}^{n-1} b_{l}\right) \delta t\right)\right)$.

Proof. From ( $\bar{B} .2$ ), we have

$$
F_{n} \leq \prod_{k=0}^{n-1}\left(1+b_{k} \delta t\right) F_{0}+\sum_{k=0}^{n-1}\left(a_{k} \sum_{l=k+1}^{n-1}\left(1+b_{l} \delta t\right)\right)
$$

The estimate ( $\bar{B} .2$ ) follows by a straightforward application of the inequality $1+x \leq e^{x}$.

When $F_{0} \leq C \delta t^{p}, b_{n} \equiv b, a_{n}=K \delta t^{p+1}$, and $n \delta t \leq T$, we have

$$
F_{n} \leq C e^{b T} \delta t^{p}+K e^{b T} \frac{\delta t^{p+1}}{1-e^{-b \delta t}}
$$

This is the commonly used $p$ th-order error estimate in numerical analysis.

## C. Measure and Integration

Let $(\Omega, \mathcal{F})$ be a measurable space.
Definition C. 1 (Measure). The measure $\mu: \mathcal{F} \rightarrow \overline{\mathbb{R}}_{+}=[0, \infty]$ is a set function defined on $\mathcal{F}$ that satisfies
(a) $\mu(\emptyset)=0$;
(b) the countable additivity; i.e., for pairwise disjoint sets $A_{n} \in \mathcal{F}$, we have

$$
\mu\left(\bigcup_{n=1}^{\infty} A_{n}\right)=\sum_{n=1}^{\infty} \mu\left(A_{n}\right)
$$

where we assume the arithmetic rules (2.7) on the extended reals $\overline{\mathbb{R}}_{+}$.
When the set function $\mu$ takes values in $\overline{\mathbb{R}}=[-\infty, \infty]$ and only the countable additivity condition is assumed, $\mu$ is called a signed measure.

Definition C. 2 (Algebra). An algebra (or field) $\mathcal{F}_{0}$ is a collection of subsets of $\Omega$ that satisfies the following conditions:
(i) $\Omega \in \mathcal{F}_{0}$;
(ii) if $A \in \mathcal{F}_{0}$, then $A^{c} \in \mathcal{F}_{0}$;
(iii) if $A, B \in \mathcal{F}_{0}$, then $A \cup B \in \mathcal{F}_{0}$.

Theorem C. 3 (Measure extension). A finite measure $\mu$ on an algebra $\mathcal{F}_{0} \subset$ $\mathcal{F}$, i.e., $\mu(\Omega)<\infty$, can be uniquely extended to a measure on $\sigma\left(\mathcal{F}_{0}\right)$.

Definition C. 4 (Measurable function). A function $f: \Omega \rightarrow \mathbb{R}$ is called measurable or $\mathcal{F}$-measurable if $f^{-1}(A) \in \mathcal{F}$ for any $A \in \mathcal{R}$.

Definition C. 5 (Simple function). A function $f: \Omega \rightarrow \mathbb{R}$ is called a simple function if it has the representation

$$
f(\omega)=\sum_{i=1}^{n} a_{i} \chi_{A_{i}}(\omega)
$$

where $a_{i} \in \mathbb{R}$ and $A_{i} \in \mathcal{F}$ for $i=1, \ldots, n$.
Theorem C.6. Any nonnegative measurable function $f$ on space $(\Omega, \mathcal{F})$ can be approximated by a sequence of monotonically increasing nonnegative functions $\left\{f_{n}\right\}$; that is, $0 \leq f_{n}(\omega) \leq f_{n+1}(\omega)$ for any $n$ and

$$
\lim _{n \rightarrow \infty} f_{n}(\omega)=f(\omega)
$$

We will denote such a monotone approximation as $f_{n} \uparrow f$ for short.
Definition C. 7 (Integration of a simple function). The integral of the simple function $f(\omega)=\sum_{i=1}^{n} a_{i} \chi_{A_{i}}(\omega)$ is defined as

$$
\mu(f)=\int_{\Omega} f \mu(d \omega)=\sum_{i=1}^{n} a_{i} \mu\left(A_{i}\right) .
$$

Theorem C. 8 (Properties of the integral of simple functions). Suppose that $f_{n}, g_{n}, f$, and $g$ are nonnegative simple functions. Then we have:
(a) $\mu(\alpha f+\beta g)=\alpha \mu(f)+\beta \mu(g)$ for any $\alpha, \beta \in \mathbb{R}_{+}$.
(b) If $f \leq g$, then $\mu(f) \leq \mu(g)$.
(c) If $f_{n} \uparrow f$, then $\lim _{n \rightarrow \infty} \mu\left(f_{n}\right)=\mu(f)$.
(d) If $f_{n}$ and $g_{n}$ are monotonically increasing and $\lim _{n \rightarrow \infty} f_{n} \leq$ $\lim _{n \rightarrow \infty} g_{n}$, then $\lim _{n \rightarrow \infty} \mu\left(f_{n}\right) \leq \lim _{n \rightarrow \infty} \mu\left(g_{n}\right)$.

Definition C.9. Let $f$ be a nonnegative measurable function. The integral of $f$ is defined as

$$
\mu(f)=\int_{\Omega} f(\omega) \mu(d \omega)=\lim _{n \rightarrow \infty} \mu\left(f_{n}\right)
$$

where $f_{n} \uparrow f$ are nonnegative functions.
It is easy to see that the integral is well-defined, say using Theorem C.8(d).

Definition C.10. Let $f$ be a measurable function. The integral of $f$ is defined as

$$
\mu(f)=\int_{\Omega} f(\omega) \mu(d \omega)=\mu\left(f^{+}\right)-\mu\left(f^{-}\right)
$$

where $f^{+}=f \vee 0$ and $f^{-}=(-f) \vee 0$ are both nonnegative measurable functions. If both $\mu\left(f^{+}\right)$and $\mu\left(f^{-}\right)$are finite, $f$ is called an integrable function.

Theorem C. 11 (Monotone convergence theorem). Suppose that $\left\{f_{n}\right\}$ are nonnegative integrable functions and $f_{n} \uparrow f$ almost everywhere. Then

$$
\lim _{n \rightarrow \infty} \mu\left(f_{n}\right)=\mu(f)
$$

Theorem C. 12 (Fatou lemma). Let $\left\{f_{n}\right\}$ be nonnegative integrable functions. We have

$$
\mu\left(\liminf _{n \rightarrow \infty} f_{n}\right) \leq \liminf _{n \rightarrow \infty} \mu\left(f_{n}\right)
$$

Theorem C. 13 (Dominated convergence theorem). Suppose that $\left\{f_{n}\right\}$ are integrable functions and $f_{n} \rightarrow f$ almost everywhere. If $\left|f_{n}\right| \leq g$ for any $n$ and $\mu(g)<\infty$, then

$$
\lim _{n \rightarrow \infty} \mu\left(f_{n}\right)=\mu(f)
$$

Definition C. 14 ( $\sigma$-finite measure). A measure $\mu$ on $(\Omega, \mathcal{F})$ is $\sigma$-finite if there exists a countable partition of $\Omega$; i.e., $\Omega=\bigcup_{n=1}^{\infty} A_{n}$ where $\left\{A_{n}\right\}$ are pairwise disjoint, such that $\mu\left(A_{n}\right)<\infty$ for any $n$.
Definition C. 15 (Absolute continuity). Let $\mu, \eta$ be a $\sigma$-finite measure and a signed measure, respectively. Here $\eta$ is called absolutely continuous with respect to $\mu$ if $\mu(A)=0$ implies $\eta(A)=0$ for any $A \in \mathcal{F}$. It is also denoted as $\eta \ll \mu$ for short.

Theorem C. 16 (Radon-Nikodym theorem). Let $\mu$ be a $\sigma$-finite measure on $(\Omega, \mathcal{F})$ and let $\eta$ be a signed measure which is absolutely continuous with respect to $\mu$. Then there exists a measurable function $f$ such that

$$
\eta(A)=\int_{A} f(\omega) \mu(d \omega)
$$

for any $A \in \mathcal{F}$. Here $f$ is unique in the $\mu$-equivalent sense; i.e., $f \stackrel{\mu}{\sim} g$ if $\mu(f=g)=1$. It is also called the Radon-Nikodym derivative of $\eta$ with respect to $\mu$, abbreviated as $f=d \eta / d \mu$.

The readers may refer to Bil79, Cin11, Hal50] for more details.

## D. Martingales

Consider the probability space $(\Omega, \mathcal{F}, \mathbb{P})$ and a filtration $\left\{\mathcal{F}_{n}\right\}_{n \in \mathbb{N}}$ or $\left\{\mathcal{F}_{t}\right\}_{t \geq 0}$. Definition D. 1 (Martingale). A continuous time stochastic process $X_{t}$ is called an $\mathcal{F}_{t}$-martingale if $X_{t} \in L_{\omega}^{1}$ for any $t, X_{t}$ is $\mathcal{F}_{t}$-adapted, and

$$
\begin{equation*}
\mathbb{E}\left(X_{t} \mid \mathcal{F}_{s}\right)=X_{s} \quad \text { for all } s \leq t \tag{D.1}
\end{equation*}
$$

$X_{t}$ is called a submartingale or supermartigale if the above equality is replaced by $\geq$ or $\leq$. These concepts can be defined for discrete time stochastic processes if we replace (D.1) by $\mathbb{E}\left(X_{n} \mid \mathcal{F}_{m}\right)=X_{m}$ for any $m \leq n$. The discrete submartingale or supermartingale can be defined similarly.

The following theorem is a straightforward application of the conditional Jensen inequality
Theorem D.2. Assume $\phi$ is a convex function such that $\phi\left(X_{t}\right) \in L_{\omega}^{1}$ for any $t$. Then $\phi\left(X_{t}\right)$ is a submartingale.

The simplest choices of $\phi$ include $\phi(x)=|x|, x^{+}:=x \vee 0$, or $x^{2}$ if $X_{t}$ is a square-integrable martingale.
Theorem D. 3 (Martingale inequalities). Let $X_{t}$ be a submartingale with continuous paths. Then for any $[s, t] \subset[0, \infty)$ and $\lambda>0$, we have:
(i) Doob's inequality:

$$
\mathbb{P}\left(\sup _{u \in[s, t]} X_{u} \geq \lambda\right) \leq \frac{\mathbb{E} X_{t}^{+}}{\lambda}
$$

(ii) Doob's $L^{p}$-maximal inequality:

$$
\mathbb{E}\left(\sup _{u \in[s, t]} X_{u}\right)^{p} \leq\left(\frac{p}{p-1}\right)^{p} \mathbb{E} X_{t}^{p}, \quad p>1
$$

Useful results follow immediately if we take $X_{t}=\left|Y_{t}\right|$ where $Y_{t}$ is a martingale. Similar inequalities also hold for discrete time martingales. See Chu01, Dur10, KS91 for more details.

## E. Strong Markov Property

Consider a finite Markov chain $\left\{X_{n}\right\}_{n \in \mathbb{N}}$ on $S$ with initial distribution $\mu$ and transition probability matrix $\boldsymbol{P}$.
Theorem E. 1 (Markov property). Conditional on $X_{m}=i(m \in \mathbb{N})$, $\left\{X_{m+n}\right\}_{n \in \mathbb{N}}$ is Markovian with initial distribution $\delta_{i}$ and transition probability matrix $\boldsymbol{P}$, and it is independent of $\left(X_{0}, X_{1}, \ldots, X_{m}\right)$.
Theorem E. 2 (Strong Markov property). Let $N$ be a stopping time. Conditional on $\{N<\infty\}$ and $X_{N}=i,\left\{X_{N+n}\right\}_{n \in \mathbb{N}}$ is Markovian with initial distribution $\delta_{i}$ and transition probability matrix $\boldsymbol{P}$.

The above results also hold for the $Q$-process $\left\{X_{t}\right\}_{t \geq 0}$ with generator $\boldsymbol{Q}$.
Theorem E. 3 (Markov property). Conditional on $X_{t}=i(t \geq 0),\left\{X_{t+s}\right\}_{s \geq 0}$ is Markovian with initial distribution $\delta_{i}$ and generator $\boldsymbol{Q}$, and it is independent of $\left\{X_{r}, r \leq t\right\}$.

Theorem E. 4 (Strong Markov property). Let $T$ be a stopping time. Conditional on $\{T<\infty\}$ and $X_{T}=i,\left\{X_{T+t}\right\}_{t \geq 0}$ is Markovian with initial distribution $\delta_{i}$ and generator $\boldsymbol{Q}$.

See Dur10, Nor97 for more details.

## F. Semigroup of Operators

Let $\mathscr{B}$ be a Banach space equipped with the norm $\|\cdot\|$.
Definition F. 1 (Operator semigroup). A family of bounded linear operators $\{S(t)\}_{t \geq 0}: \mathscr{B} \rightarrow \mathscr{B}$ forms a strongly continuous semigroup if for any $f \in \mathscr{B}:$
(i) $S(0) f=f$; i.e., $S(0)=I$.
(ii) $S(t) S(s) f=S(s) S(t) f=S(t+s) f$ for any $s, t \geq 0$.
(iii) $\|S(t) f-f\| \rightarrow 0$ for any $f \in \mathscr{B}$ as $t \rightarrow 0+$.

We will call $\{S(\cdot)\}$ a contraction semigroup if $\|S(t)\| \leq 1$ for any $t$, where $\|S(t)\|$ is the operator norm induced by the metric $\|\cdot\|$.

The simplest examples of semigroups include the solution operator for the system

$$
\frac{d \boldsymbol{u}(t)}{d t}=\boldsymbol{A} \boldsymbol{u}(t)
$$

where $\boldsymbol{u} \in \mathbb{R}^{n}, \boldsymbol{A} \in \mathbb{R}^{n \times n}, \mathscr{B}=\mathbb{R}^{n}$, and $S(t) \boldsymbol{f}:=\boldsymbol{u}(t)$ by solving the ODE with initial condition $\left.\boldsymbol{u}(t)\right|_{t=0}=\boldsymbol{f}$. Similarly, consider the PDE

$$
\partial_{t} u=\Delta u \quad \text { in } U, \quad u=0 \quad \text { on } \partial U,
$$

where $U$ is a bounded open set with smooth boundary. We can take $\mathscr{B}=$ $L^{2}(U)$ and $S(t) f:=u(t)$, where $u(t)$ is the solution of the above PDE with initial condition $u(x, t=0)=f$.

Definition F. 2 (Infinitesimal generator). Denote

$$
D(\mathcal{A})=\left\{f \in \mathscr{B}: \lim _{t \rightarrow 0+} \frac{S(t) f-f}{t} \text { exits in } \mathscr{B}\right\}
$$

and

$$
\mathcal{A} f:=\lim _{t \rightarrow 0+} \frac{1}{t}(S(t) f-f), \quad f \in D(\mathcal{A})
$$

The operator $\mathcal{A}$ is called the infinitesimal generator of the semigroup $S(t)$; $D(\mathcal{A})$ is the domain of the operator $\mathcal{A}$.

It can be shown that the infinitesimal generators of the two examples above are $\mathcal{A}=\boldsymbol{A}$ and $\mathcal{A}=\Delta$ and their domains are $\mathbb{R}^{n}$ and the Sobolev space $H_{0}^{1}(U) \cup H^{2}(U)$, respectively.

Theorem F. 3 (Basic properties). Let $f \in D(\mathcal{A})$. We have:
(i) $S(t) f \in D(\mathcal{A})$ and $S(t) \mathcal{A} f=\mathcal{A} S(t) f$ for any $t \geq 0$.
(ii) $f(t):=S(t) f$ is differentiable on $(0, \infty)$ and

$$
\frac{d f(t)}{d t}=\mathcal{A} f(t), \quad t>0
$$

Theorem F.4. The generator $\mathcal{A}$ is a closed operator and $D(\mathcal{A})$ is dense in $\mathscr{B}$.

In general, the generator $\mathcal{A}$ is unbounded, e.g., $\mathcal{A}=\Delta$ in the previous PDE example, so we only have $D(\mathcal{A}) \subsetneq \mathscr{B}$.

Definition F. 5 (Resolvent set and operator). Let $\mathcal{A}$ be a closed linear operator with domain $D(\mathcal{A})$. The resolvent set of $\mathcal{A}$ is defined by

$$
\rho(\mathcal{A})=\{\lambda: \lambda \in \mathbb{R} \text { and } \lambda I-\mathcal{A} \text { is bijective from } D(\mathcal{A}) \text { to } \mathscr{B}\}
$$

If $\lambda \in \rho(\mathcal{A})$, the resolvent operator $R_{\lambda}: \mathscr{B} \rightarrow \mathscr{B}$ is defined by

$$
R_{\lambda} f:=(\lambda I-\mathcal{A})^{-1} f
$$

The closed graph theorem ensures that $(\lambda I-\mathcal{A})^{-1}$ is a bounded linear operator if $\lambda \in \rho(\mathcal{A})$.
Theorem F. 6 (Hille-Yosida theorem). Let $\mathcal{A}$ be a closed, densely defined linear operator on $\mathscr{B}$. Then $\mathcal{A}$ generates a contraction semigroup $\{S(t)\}_{t \geq 0}$ if and only if

$$
\lambda \in \rho(\mathcal{A}) \quad \text { and } \quad\left\|R_{\lambda}\right\| \leq \frac{1}{\lambda} \quad \text { for all } \lambda>0
$$

Interested readers are referred to Eva10, Paz83, Yos95 for more details on semigroup theory.

## Bibliography

[AC08] A. Abdulle and S. Cirilli, S-ROCK: Chebyshev methods for stiff stochastic differential equations, SIAM J. Sci. Comput. 30 (2008), no. 2, 997-1014, DOI 10.1137/070679375. MR 2385896
[ACK10] D. F. Anderson, G. Craciun, and T. G. Kurtz, Product-form stationary distributions for deficiency zero chemical reaction networks, Bull. Math. Biol. 72 (2010), no. 8, 1947-1970, DOI 10.1007/s11538-010-9517-4. MR2734052
[AGK11] D. F. Anderson, A. Ganguly, and T. G. Kurtz, Error analysis of tau-leap simulation methods, Ann. Appl. Probab. 21 (2011), no. 6, 2226-2262, DOI 10.1214/10AAP756. MR2895415
[AH12] D. F. Anderson and D. J. Higham, Multilevel Monte Carlo for continuous time Markov chains, with applications in biochemical kinetics, Multiscale Model. Simul. 10 (2012), no. 1, 146-179, DOI 10.1137/110840546. MR 2902602
[AL08] A. Abdulle and T. Li, S-ROCK methods for stiff Itô SDEs, Commun. Math. Sci. 6 (2008), no. 4, 845-868. MR2511696
[And86] H. L. Anderson, Metropolis, Monte Carlo and the MANIAC, Los Alamos Science 14 (1986), 96-108.
[App04] D. Applebaum, Lévy processes and stochastic calculus, Cambridge Studies in Advanced Mathematics, vol. 93, Cambridge University Press, Cambridge, 2004. MR 2072890
[ARLS11] M. Assaf, E. Roberts, and Z. Luthey-Schulten, Determining the stability of genetic switches: Explicitly accounting for mrna noise, Phys. Rev. Lett. 106 (2011), 248102.
[ARM98] A. Arkin, J. Ross, and H. H. McAdams, Stochastic kinetic analysis of developmental pathway bifurcation in phage lambda-infected Escherichia coli cells, Genetics 149 (1998), 1633-1648.
[Arn89] V. I. Arnol'd, Mathematical methods of classical mechanics, 2nd ed., translated from the Russian by K. Vogtmann and A. Weinstein, Graduate Texts in Mathematics, vol. 60, Springer-Verlag, New York, 1989. MR997295
[BB01] P. Baldi and S. Brunak, Bioinformatics, 2nd ed., The machine learning approach; A Bradford Book, Adaptive Computation and Machine Learning, MIT Press, Cambridge, MA, 2001. MR 1849633
[BE67] L. E. Baum and J. A. Eagon, An inequality with applications to statistical estimation for probabilistic functions of Markov processes and to a model for ecology, Bull. Amer. Math. Soc. 73 (1967), 360-363, DOI 10.1090/S0002-9904-1967-117518. MR0210217
[Bil79] P. Billingsley, Probability and measure, Wiley Series in Probability and Mathematical Statistics, John Wiley \& Sons, New York-Chichester-Brisbane, 1979. MR534323
[BKL75] A. B. Bortz, M. H. Kalos, and J. L. Lebowitz, New algorithm for Monte Carlo simulations of Ising spin systems, J. Comp. Phys. 17 (1975), 10-18.
[Bou95] C. A. Bouman, Markov random fields and stochastic image models, available from http://dynamo.ecn.purdue.edu/~bouman, 1995.
[BP98] S. Brin and L. Page, The anatomy of a large-scale hypertextual web search engine, Computer Networks and ISDN Systems 30 (1998), 107-117.
[BP06] Z. P. Bažant and S. Pang, Mechanics-based statistics of failure risk of quasibrittle structures and size effect of safety factors, Proc. Nat. Acad. Sci. USA 103 (2006), 9434-9439.
[BPN14] G. R. Bowman, V. S. Pande, and F. Noé (eds.), An introduction to Markov state models and their application to long timescale molecular simulation, Advances in Experimental Medicine and Biology, vol. 797, Springer, Dordrecht, 2014. MR 3222039
[Bre92] L. Breiman, Probability, corrected reprint of the 1968 original, Classics in Applied Mathematics, vol. 7, Society for Industrial and Applied Mathematics (SIAM), Philadelphia, PA, 1992. MR 1163370
[Cam12] M. K. Cameron, Finding the quasipotential for nongradient SDEs, Phys. D 241 (2012), no. 18, 1532-1550, DOI 10.1016/j.physd.2012.06.005. MR 2957825
[CGP05] Y. Cao, D. Gillespie, and L. Petzold, Multiscale stochastic simulation algorithm with stochastic partial equilibrium assumption for chemically reacting systems, J. Comput. Phys. 206 (2005), no. 2, 395-411, DOI 10.1016/j.jcp.2004.12.014. MR 2143324
[CGP06] Y. Cao, D. Gillespie, and L. Petzold, Efficient stepsize selection for the tau-leaping method, J. Chem. Phys. 124 (2006), 044109.
[CH13] A. J. Chorin and O. H. Hald, Stochastic tools in mathematics and science, 3rd ed., Texts in Applied Mathematics, vol. 58, Springer, New York, 2013. MR3076304
[Cha78] D. Chandler, Statistical mechanics of isomerization dynamics in liquids and the transition state approximation, J. Chem. Phys. 68 (1978), 2959-2970.
[Cha87] D. Chandler, Introduction to modern statistical mechanics, The Clarendon Press, Oxford University Press, New York, 1987. MR913936
[CHK02] A. J. Chorin, O. H. Hald, and R. Kupferman, Optimal prediction with memory, Phys. D 166 (2002), no. 3-4, 239-257, DOI 10.1016/S0167-2789(02)00446-3. MR 1915310
[Cho03] A. J. Chorin, Conditional expectations and renormalization, Multiscale Model. Simul. 1 (2003), no. 1, 105-118, DOI 10.1137/S1540345902405556. MR1960842
[Chu97] F. R. K. Chung, Spectral graph theory, CBMS Regional Conference Series in Mathematics, vol. 92, Published for the Conference Board of the Mathematical Sciences, Washington, DC; by the American Mathematical Society, Providence, RI, 1997. MR 1421568
[Chu01] K. L. Chung, A course in probability theory, 3rd ed., Academic Press, Inc., San Diego, CA, 2001. MR1796326
[Cin11] E. Çınlar, Probability and stochastics, Graduate Texts in Mathematics, vol. 261, Springer, New York, 2011. MR2767184
[CKVE11] M. Cameron, R. V. Kohn, and E. Vanden-Eijnden, The string method as a dynamical system, J. Nonlinear Sci. 21 (2011), no. 2, 193-230, DOI 10.1007/s00332-010-9081-y. MR2788855
[CLP04] Y. Cao, H. Li, and L. Petzold, Efficient formulation of the stochastic simulation algorithm for chemically reacting systems, J. Chem. Phys. 121 (2004), 4059-4067.
[CM47] R. H. Cameron and W. T. Martin, The orthogonal development of non-linear functionals in series of Fourier-Hermite functionals, Ann. of Math. (2) 48 (1947), 385-392, DOI 10.2307/1969178. MR0020230
[CT06] T. M. Cover and J. A. Thomas, Elements of information theory, 2nd ed., WileyInterscience [John Wiley \& Sons], Hoboken, NJ, 2006. MR2239987
[CVK05] A. Chatterjee, D. G. Vlachos, and M. A. Katsoulakis, Binomial distribution based tau-leap accelerated stochastic simulation, J. Chem. Phys. 122 (2005), 024112.
[CW05] K. L. Chung and J. B. Walsh, Markov processes, Brownian motion, and time symmetry, 2nd ed., Grundlehren der Mathematischen Wissenschaften [Fundamental Principles of Mathematical Sciences], vol. 249, Springer, New York, 2005. MR 2152573
[DE86] M. Doi and S. F. Edwards, The theory of polymer dynamics, Oxford University Press, New York, 1986.
[DLR77] A. P. Dempster, N. M. Laird, and D. B. Rubin, Maximum likelihood from incomplete data via the EM algorithm, J. Roy. Statist. Soc. Ser. B 39 (1977), no. 1, $1-38$. With discussion. MR0501537
[DMRH94] M. I. Dykman, E. Mori, J. Ross, and P. M. Hunt, Large fluctuations and optimal paths in chemical kinetics, J. Chem. Phys. 100 (1994), 5735-5750.
[Doo42] J. L. Doob, The Brownian movement and stochastic equations, Ann. of Math. (2) 43 (1942), 351-369, DOI 10.2307/1968873. MR0006634
[Doo84] J. L. Doob, Classical potential theory and its probabilistic counterpart, Grundlehren der Mathematischen Wissenschaften [Fundamental Principles of Mathematical Sciences], vol. 262, Springer-Verlag, New York, 1984. MR 731258
[DPZ92] G. Da Prato and J. Zabczyk, Stochastic equations in infinite dimensions, Encyclopedia of Mathematics and its Applications, vol. 44, Cambridge University Press, Cambridge, 1992. MR 1207136
[DS84] J.-D. Deuschel and D. W. Stroock, Large deviations, Pure and Applied Mathematics, vol. 137, Academic Press, Inc., Boston, MA, 1989. MR997938
[DSK09] E. Darve, J. Solomon, and A. Kia, Computing generalized Langevin equations and generalized Fokker-Planck equations, Proc. Nat. Acad. Sci. USA 106 (2009), 10884-10889.
[Dur10] R. Durrett, Probability: theory and examples, 4th ed., Cambridge Series in Statistical and Probabilistic Mathematics, vol. 31, Cambridge University Press, Cambridge, 2010. MR2722836
[DZ98] A. Dembo and O. Zeitouni, Large deviations techniques and applications, 2nd ed., Applications of Mathematics (New York), vol. 38, Springer-Verlag, New York, 1998. MR 1619036
[E11] W. E, Principles of multiscale modeling, Cambridge University Press, Cambridge, 2011. MR 2830582
[EAM95] R. J. Elliott, L. Aggoun, and J. B. Moore, Hidden Markov models: Estimation and control, Applications of Mathematics (New York), vol. 29, Springer-Verlag, New York, 1995. MR 1323178
[Eck87] R. Eckhardt, Stan Ulam, John von Neumann, and the Monte Carlo method, with contributions by Tony Warnock, Gary D. Doolen, and John Hendricks; Stanislaw Ulam, 1909-1984, Los Alamos Sci. 15, Special Issue (1987), 131-137. MR935772
[Ein05] A. Einstein, On the movement of small particles suspended in a stationary liquid demanded by the molecular kinetic theory of heat, Ann. Phys. (in German) 322 (1905), 549-560.
[EK86] S. N. Ethier and T. G. Kurtz, Markov processes: Characterization and convergence, Wiley Series in Probability and Mathematical Statistics: Probability and Mathematical Statistics, John Wiley \& Sons, Inc., New York, 1986. MR838085
[El185] R. S. Ellis, Entropy, large deviations, and statistical mechanics, Grundlehren der Mathematischen Wissenschaften [Fundamental Principles of Mathematical Sciences], vol. 271, Springer-Verlag, New York, 1985. MR 793553
[ELSS02] M. B. Elowitz, A. J. Levine, E. D. Siggia, and P. S. Swain, Stochastic gene expression in a single cell, Science 297 (2002), 1183-1186.
[ELVE05a] W. E, D. Liu, and E. Vanden-Eijnden, Analysis of multiscale methods for stochastic differential equations, Comm. Pure Appl. Math. 58 (2005), no. 11, 1544-1585, DOI 10.1002/cpa.20088. MR2165382
[ELVE05b] W. E, D. Liu, and E. Vanden-Eijnden, Nested stochastic simulation algorithm for chemical kinetic systems with disparate rates, J. Chem. Phys. 123 (2005), 194107.
[ELVE07] W. E, D. Liu, and E. Vanden-Eijnden, Nested stochastic simulation algorithms for chemical kinetic systems with multiple time scales, J. Comput. Phys. 221 (2007), no. 1, 158-180, DOI 10.1016/j.jcp.2006.06.019. MR2290567
[ELVE08] W. E, T. Li, and E. Vanden-Eijnden, Optimal partition and effective dynamics of complex networks, Proc. Natl. Acad. Sci. USA 105 (2008), no. 23, 7907-7912, DOI 10.1073/pnas. 0707563105 . MR 2415575
[ERVE02] W. E, W. Ren, and E. Vanden-Eijnden, String method for the study of rare events, Phys. Rev. B 66 (2002), 052301.
[ERVE03] W. E, W. Ren, and E. Vanden-Eijnden, Energy landscape and thermally activated switching of submicron-sized ferromagnetic elements, J. Appl. Phys. 93 (2003), 2275-2282.
[ERVE07] W. E, W. Ren, and E. Vanden-Eijnden, Simplified and improved string method for computing the minimum energy paths in barrier-crossing events, J. Chem. Phys. 126 (2007), 164103.
[Eva10] L. C. Evans, Partial differential equations, 2nd ed., Graduate Studies in Mathematics, vol. 19, American Mathematical Society, Providence, RI, 2010. MR 2597943
[EVE10] W. E and E. Vanden-Eijnden, Transition-path theory and path-finding algorithms for the study of rare events, Ann. Rev. Phys. Chem. 61 (2010), 391-420.
[Fel68] W. Feller, An introduction to probability theory and its applications, Third edition, John Wiley \& Sons, Inc., New York-London-Sydney, 1968. MR0228020
[Fre85] M. Freidlin, Functional integration and partial differential equations, Annals of Mathematics Studies, vol. 109, Princeton University Press, Princeton, NJ, 1985. MR 833742
[Fri75a] A. Friedman, Stochastic differential equations and applications. Vol. 1, Probability and Mathematical Statistics, Vol. 28, Academic Press [Harcourt Brace Jovanovich, Publishers], New York-London, 1975. MR0494490
[Fri75b] A. Friedman, Stochastic differential equations and applications. Vol. 2, Probability and Mathematical Statistics, Vol. 28, Academic Press [Harcourt Brace Jovanovich, Publishers], New York-London, 1976. MR0494491
[FS02] D. Frenkel and B. Smit, Understanding molecular simulations: From algorithms to applications, 2nd ed., Academic Press, San Diego, 2002.
[FW98] M. I. Freidlin and A. D. Wentzell, Random perturbations of dynamical systems, 2nd ed., translated from the 1979 Russian original by Joseph Szücs, Grundlehren
der Mathematischen Wissenschaften [Fundamental Principles of Mathematical Sciences], vol. 260, Springer-Verlag, New York, 1998. MR1652127
[Gal99] G. Gallavotti, Statistical mechanics: A short treatise, Texts and Monographs in Physics, Springer-Verlag, Berlin, 1999. MR 1707309
[Gar09] C. Gardiner, Stochastic methods: A handbook for the natural and social sciences, 4th ed., Springer Series in Synergetics, Springer-Verlag, Berlin, 2009. MR 2676235
[GB00] M. A. Gibson and J. Bruck, Efficient exact stochastic simulation of chemical systems with many species and channels, J. Phys. Chem. A 104 (2000), 18761889.
[Gey91] C. Geyer, Markov chain Monte Carlo maximum likelihood, Computing Science and Statistics: Proceedings of the 23rd Symposium on the interface (New York) (E. Keramigas, ed.), American Statistical Association, 1991, pp. 156-163.
[GHO17] R. Ghanem, D. Higdon, and H. Owhadi (eds.), Handbook of uncertainty quantification, Springer International Publishing, Switzerland, 2017.
[GHP13] D. Gillespie, A. Hellander, and L. Petzold, Perspective: Stochastic algorithms for chemical kinetics, J. Chem. Phys. 138 (2013), 170901.
[Gil76] D. T. Gillespie, A general method for numerically simulating the stochastic time evolution of coupled chemical reactions, J. Computational Phys. 22 (1976), no. 4, 403-434, DOI 10.1016/0021-9991(76)90041-3. MR0503370
[Gi192] D. T. Gillespie, Markov processes: An introduction for physical scientists, Academic Press, Inc., Boston, MA, 1992. MR1133392
[Gil00] D. Gillespie, The chemical Langevin equation, J. Chem. Phys. 113 (2000), 297.
[Gil01] D. Gillespie, Approximate accelerated stochastic simulation of chemically reacting systems, J. Chem. Phys. 115 (2001), 1716-1733.
[Gil08] M. B. Giles, Multilevel Monte Carlo path simulation, Oper. Res. 56 (2008), no. 3, 607-617, DOI 10.1287/opre.1070.0496. MR2436856
[Gil14] M. B. Giles, Multilevel Monte Carlo methods, Monte Carlo and quasi-Monte Carlo methods 2012, Springer Proc. Math. Stat., vol. 65, Springer, Heidelberg, 2013, pp. 83-103, DOI 10.1007/978-3-642-41095-6_4. MR3145560
[GJ87] J. Glimm and A. Jaffe, Quantum physics: A functional integral point of view, 2nd ed., Springer-Verlag, New York, 1987. MR887102
[Gla04] P. Glasserman, Monte Carlo methods in financial engineering: Stochastic modelling and applied probability, Applications of Mathematics (New York), vol. 53, Springer-Verlag, New York, 2004. MR1999614
[Gol80] H. Goldstein, Classical mechanics, 2nd ed., Addison-Wesley Publishing Co., Reading, Mass., 1980. Addison-Wesley Series in Physics. MR 575343
[Gol92] N. Goldenfeld, Lectures on phase transitions and the renormalization group, Perseus Books Publishing, Massachusetts, 1992.
[GS66] I. M. Gelfand and G. E. Shilov, Generalized functions, vols. 1-5, Academic Press, New York and London, 1964-1966.
[GS12] R. Ghanem and P. Spanos, Stochastic finite elements: A spectral approach, revised ed., Dover Publications Inc., Mineola, 2012.
[GT95] C. Geyer and E. Thompson, Annealing Markov chain Monte Carlo with applications to ancestral inference, J. Amer. Stat. Assoc. 90 (1995), 909-920.
[Hal50] P. R. Halmos, Measure Theory, D. Van Nostrand Company, Inc., New York, N. Y., 1950. MR0033869
[HEnVEDB10] C. Hijón, P. Español, E. Vanden-Eijnden, and R. Delgado-Buscalioni, MoriZwanzig formalism as a practical computational tool, Faraday Disc. 144 (2010), 301-322.
[HJ85] R. A. Horn and C. R. Johnson, Matrix analysis, Cambridge University Press, Cambridge, 1985. MR832183
[HJ99] G. Henkelman and H. Jónsson, A dimer method for finding saddle points on high dimensional potential surfaces using only first derivatives, J. Chem. Phys. 111 (1999), 7010-7022.
[HJ00] G. Henkelman and H. Jónsson, Improved tangent estimate in the nudged elastic band method for finding minimum energy paths and saddle points, J. Chem. Phys. 113 (2000), 9978-9985.
[HNW08] E. Hairer, S. P. Norsett, and G. Wanner, Solving ordinary differential equations I: Nonstiff problems, 2nd ed., Springer-Verlag, Berlin and Heidelberg, 2008.
[HPM90] P. Hanggi, P. Talkner, and M. Borkovec, Reaction-rate theory: fifty years after Kramers, Rev. Modern Phys. 62 (1990), no. 2, 251-341, DOI 10.1103/RevModPhys.62.251. MR 1056234
[HR02] E. L. Haseltine and J. B. Rawlings, Approximate simulation of coupled fast and slow reactions for stochastic kinetics, J. Chem. Phys. 117 (2002), 6959-6969.
[HS08] T. Hida and S. Si, Lectures on white noise functionals, World Scientific Publishing Co. Pte. Ltd., Hackensack, NJ, 2008. MR 2444857
[HVE08] M. Heymann and E. Vanden-Eijnden, The geometric minimum action method: a least action principle on the space of curves, Comm. Pure Appl. Math. 61 (2008), no. 8, 1052-1117, DOI 10.1002/cpa.20238. MR2417888
[IW81] N. Ikeda and S. Watanabe, Stochastic differential equations and diffusion processes, North-Holland Mathematical Library, vol. 24, North-Holland Publishing Co., Amsterdam-New York; Kodansha, Ltd., Tokyo, 1981. MR 637061
[Jel97] F. Jelinek, Statistical methods for speech recognition, MIT Press, Cambridge, 1997.
[JM09] D. Jurafsky and J. H. Martin, Speech and language processing: An introduction to natural language processing, computational linguistics, and speech recognition, 2nd ed., Pearson Prentice Hall, Upper Saddle River, 2009.
[JQQ04] D.-Q. Jiang, M. Qian, and M.-P. Qian, Mathematical theory of nonequilibrium steady states: On the frontier of probability and dynamical systems, Lecture Notes in Mathematics, vol. 1833, Springer-Verlag, Berlin, 2004. MR 2034774
[Kal97] O. Kallenberg, Foundations of modern probability, Probability and its Applications (New York), Springer-Verlag, New York, 1997. MR1464694
[Kes80] H. Kesten, The critical probability of bond percolation on the square lattice equals $\frac{1}{2}$, Comm. Math. Phys. 74 (1980), no. 1, 41-59. MR 575895
[KK80] C. Kittel and H. Kroemer, Thermal physics, 2nd ed., W. H. Freeman and Company, New York, 1980.
[Kle06] H. Kleinert, Path integrals in quantum mechanics, statistics, polymer physics, and financial markets, 4th ed., World Scientific Publishing Co. Pte. Ltd., Hackensack, NJ, 2006. MR2255818
[Knu98] D. E. Knuth, The art of computer programming. Vol. 2, Addison-Wesley, Reading, MA, 1998. Seminumerical algorithms, third edition [of MR0286318]. MR3077153
[Kol56] A. N. Kolmogorov, Foundations of the theory of probability, translation edited by Nathan Morrison, with an added bibliography by A. T. Bharucha-Reid, Chelsea Publishing Co., New York, 1956. MR0079843
[KP92] P. E. Kloeden and E. Platen, Numerical solution of stochastic differential equations, Applications of Mathematics (New York), vol. 23, Springer-Verlag, Berlin, 1992. MR 1214374
[Kra40] H. A. Kramers, Brownian motion in a field of force and the diffusion model of chemical reactions, Physica 7 (1940), 284-304. MR0002962
[KS76] J. G. Kemeny and J. L. Snell, Finite Markov chains, reprinting of the 1960 original, Undergraduate Texts in Mathematics, Springer-Verlag, New York-Heidelberg, 1976. MR 0410929
[KS91] I. Karatzas and S. E. Shreve, Brownian motion and stochastic calculus, 2nd ed., Graduate Texts in Mathematics, vol. 113, Springer-Verlag, New York, 1991. MR 1121940
[KS07] L. B. Koralov and Y. G. Sinai, Theory of probability and random processes, 2nd ed., Universitext, Springer, Berlin, 2007. MR2343262
[KS09] J. Keener and J. Sneyd, Mathematical physiology, 2nd ed., Springer-Verlag, New York, 2009.
[KTH95] R. Kubo, M. Toda, and N. Hashitsume, Statistical physics, vol. 2, Springer-Verlag, Berlin, Heidelberg and New York, 1995.
[Kub66] R. Kubo, The fluctuation-dissipation theorem, Rep. Prog. Phys. 29 (1966), 255.
[Kur72] T. G. Kurtz, The relation between stochastic and deterministic models for chemical reactions, J. Chem. Phys. 57 (1972), 2976-2978.
[KW08] M. H. Kalos and P. A. Whitlock, Monte Carlo methods, 2nd ed., Wiley-Blackwell, Weinheim, 2008. MR2503174
[KZW06] S. C. Kou, Q. Zhou, and W. H. Wong, Equi-energy sampler with applications in statistical inference and statistical mechanics, with discussions and a rejoinder by the authors, Ann. Statist. 34 (2006), no. 4, 1581-1652, DOI 10.1214/009053606000000515. MR 2283711
[Lam77] J. Lamperti, Stochastic processes: A survey of the mathematical theory, Applied Mathematical Sciences, Vol. 23, Springer-Verlag, New York-Heidelberg, 1977. MR0461600
[Lax02] P. D. Lax, Functional analysis, Pure and Applied Mathematics (New York), Wiley-Interscience [John Wiley \& Sons], New York, 2002. MR 1892228
[LB05] D. P. Landau and K. Binder, A guide to Monte Carlo simulations in statistical physics, 2nd ed., Cambridge University Press, Cambridge, 2005.
[LBL16] H. Lei, N. A. Baker, and X. Li, Data-driven parameterization of the generalized Langevin equation, Proc. Natl. Acad. Sci. USA 113 (2016), no. 50, 14183-14188, DOI 10.1073/pnas. 1609587113 . MR 3600515
[Li07] T. Li, Analysis of explicit tau-leaping schemes for simulating chemically reacting systems, Multiscale Model. Simul. 6 (2007), no. 2, 417-436, DOI 10.1137/06066792X. MR2338489
[Liu04] J. S. Liu, Monte Carlo strategies in scientific computing, Springer-Verlag, New York, 2004.
[LL17] T. Li and F. Lin, Large deviations for two-scale chemical kinetic processes, Commun. Math. Sci. 15 (2017), no. 1, 123-163, DOI 10.4310/CMS.2017.v15.n1.a6. MR 3605551
[LLLL14] C. Lv, X. Li, F. Li, and T. Li, Constructing the energy landscape for genetic switching system driven by intrinsic noise, PLoS One 9 (2014), e88167.
[LLLL15] C. Lv, X. Li, F. Li, and T. Li, Energy landscape reveals that the budding yeast cell cycle is a robust and adaptive multi-stage process, PLoS Comp. Biol. 11 (2015), e1004156.
[LM15] B. Leimkuhler and C. Matthews, Molecular dynamics: With deterministic and stochastic numerical methods, Interdisciplinary Applied Mathematics, vol. 39, Springer, Cham, 2015. MR3362507
[Loè77] M. Loève, Probability theory. I, 4th ed., Graduate Texts in Mathematics, Vol. 45, Springer-Verlag, New York-Heidelberg, 1977. MR0651017
[Lov96] L. Lovász, Random walks on graphs: a survey, Combinatorics, Paul Erdős is eighty, Vol. 2 (Keszthely, 1993), Bolyai Soc. Math. Stud., vol. 2, János Bolyai Math. Soc., Budapest, 1996, pp. 353-397. MR 1395866
[LX11] G. Li and X. S. Xie, Central dogma at the single-molecule level in living cells, Nature 475 (2011), 308-315.
[Mar68] G. Marsaglia, Random numbers fall mainly in the planes, Proc. Nat. Acad. Sci. U.S.A. 61 (1968), 25-28, DOI 10.1073/pnas.61.1.25. MR0235695
[MD10] D. Mumford and A. Desolneux, Pattern theory: The stochastic analysis of realworld signals, Applying Mathematics, A K Peters, Ltd., Natick, MA, 2010. MR 2723182
[Mey66] P.-A. Meyer, Probability and potentials, Blaisdell Publishing Co. Ginn and Co., Waltham, Mass.-Toronto, Ont.-London, 1966. MR0205288
[MN98] M. Matsumoto and T. Nishimura, Mersenne twister: A 623-dimensionally equidistributed uniform pseudo-random number generator, ACM Trans. Mod. Comp. Simul. 8 (1998), 3-30.
[MP92] E. Marinari and G. Parisi, Simulated tempering: A new Monte Carlo scheme, Europhys. Lett. 19 (1992), 451-458.
[MP10] P. Mörters and Y. Peres, Brownian motion, with an appendix by Oded Schramm and Wendelin Werner, Cambridge Series in Statistical and Probabilistic Mathematics, vol. 30, Cambridge University Press, Cambridge, 2010. MR2604525
[MPRV08] U. M. B. Marconi, A. Puglisi, L. Rondoni, and A. Vulpiani, Fluctuationdissipation: Response theory in statistical physics, Phys. Rep. 461 (2008), 111195.
[MS99] C. D. Manning and H. Schütze, Foundations of statistical natural language processing, MIT Press, Cambridge, MA, 1999. MR 1722790
[MS01] M. Meila and J. Shi, A random walks view of spectral segmentation, Proceedings of the Eighth International Workshop on Artificial Intelligence and Statistics (San Francisco), 2001, pp. 92-97.
[MT93] S. P. Meyn and R. L. Tweedie, Markov chains and stochastic stability, Communications and Control Engineering Series, Springer-Verlag London, Ltd., London, 1993. MR 1287609
[MT04] G. N. Milstein and M. V. Tretyakov, Stochastic numerics for mathematical physics, Scientific Computation, Springer-Verlag, Berlin, 2004. MR 2069903
[MTV16] A. Moraes, R. Tempone, and P. Vilanova, Multilevel hybrid Chernoff tau-leap, BIT 56 (2016), no. 1, 189-239, DOI 10.1007/s10543-015-0556-y. MR3486459
[Mul56] M. E. Muller, Some continuous Monte Carlo methods for the Dirichlet problem, Ann. Math. Statist. 27 (1956), 569-589, DOI 10.1214/aoms/1177728169. MR 0088786
[MY71] A. S. Monin and A. M. Yaglom, Statistical fluid mechanics: Mechanics of turbulence, vol. 1, MIT Press, Cambridge, 1971.
[Nor97] J. R. Norris, Markov chains, Cambridge University Press, Cambridge, 1997.
[Oks98] B. Øksendal, Stochastic differential equations: An introduction with applications, 5th ed., Universitext, Springer-Verlag, Berlin, 1998. MR1619188
[Pap77] G. C. Papanicolaou, Introduction to the asymptotic analysis of stochastic equations, Modern modeling of continuum phenomena (Ninth Summer Sem. Appl. Math., Rensselaer Polytech. Inst., Troy, N.Y., 1975), Lectures in Appl. Math., Vol. 16, Amer. Math. Soc., Providence, R.I., 1977, pp. 109-147. MR0458590
[Pav14] G. A. Pavliotis, Stochastic processes and applications: Diffusion processes, the Fokker-Planck and Langevin equations, Texts in Applied Mathematics, vol. 60, Springer, New York, 2014. MR3288096
[Paz83] A. Pazy, Semigroups of linear operators and applications to partial differential equations, Applied Mathematical Sciences, vol. 44, Springer-Verlag, New York, 1983. MR 710486
[PTVF95] W. H. Press, S. A. Teukolsky, W. T. Vetterling, and B. P. Flannery, Numerical recipes in C, 2nd ed., Cambridge University Press, Cambridge, New York, Port Chester, Melbourne and Sydney, 1995.
[Rö3] A. Rößler, Runge-Kutta methods for the numerical solution of stochastic differential equation, Shaker-Verlag, Aachen, 2003.
[Rab89] L. R. Rabiner, A tutorial on hidden Markov models and selected applications in speech recognition, Proceedings of the IEEE 77 (1989), 257-286.
[Ram69] J. F. Ramaley, Buffon's noodle problem, Amer. Math. Monthly 76 (1969), 916918, DOI 10.2307/2317945. MR0254893
[RC04] C. P. Robert and G. Casella, Monte Carlo statistical methods, 2nd ed., Springer Texts in Statistics, Springer-Verlag, New York, 2004. MR2080278
[Rea10] A. Rukhin et al., A statistical test suite for random and pseudorandom number generators for cryptographic applications, available from https://nvlpubs.nist. gov/nistpubs/legacy/sp/nistspecialpublication800-22r1a.pdf, April 2010.
[Rei98] L. E. Reichl, A modern course in statistical physics, 2nd ed., A Wiley-Interscience Publication, John Wiley \& Sons, Inc., New York, 1998. MR1600476
[Ris89] H. Risken, The Fokker-Planck equation: Methods of solution and applications, 2nd ed., Springer Series in Synergetics, vol. 18, Springer-Verlag, Berlin, 1989. MR 987631
[Roc70] R. T. Rockafellar, Convex analysis, Princeton Mathematical Series, No. 28, Princeton University Press, Princeton, N.J., 1970. MR0274683
[Roz82] Yu. A. Rozanov, Markov random fields, translated from the Russian by Constance M. Elson, Applications of Mathematics, Springer-Verlag, New York-Berlin, 1982. MR676644
[RSN56] F. Riesz and B. Sz.-Nagy, Functional analysis, Blackie \& Son Limited, London and Glasgow, 1956.
[RVE13] W. Ren and E. Vanden-Eijnden, A climbing string method for saddle point search, J. Chem. Phys. 138 (2013), 134105.
[RW94a] L. C. G. Rogers and D. Williams, Diffusions, Markov processes, and martingales: Foundations, Vol. 1, 2nd ed., Wiley Series in Probability and Mathematical Statistics: Probability and Mathematical Statistics, John Wiley \& Sons, Ltd., Chichester, 1994. MR1331599
[RW94b] L. C. G. Rogers and D. Williams, Diffusions, Markov processes, and martingales: Itô calculus, Vol. 2, Wiley Series in Probability and Mathematical Statistics: Probability and Mathematical Statistics, John Wiley \& Sons, Inc., New York, 1987. MR 921238
[RW09] R. T. Rockafellar and R. J-B. Wets, Variational analysis, Springer-Verlag, Berlin and Heidelberg, 2009.
[RY05] D. Revuz and M. Yor, Continuous martingales and Brownian motion, 3rd ed., Springer-Verlag, Berlin and Heidelberg, 2005.
[Sch80] Z. Schuss, Singular perturbation methods in stochastic differential equations of mathematical physics, SIAM Rev. 22 (1980), no. 2, 119-155, DOI 10.1137/1022024. MR 564560
[Sei12] U. Seifert, Stochastic thermodynamics, fluctuation theorems and molecular machines, Rep. Prog. Phys. 75 (2012), 126001.
[Sek10] K. Sekimoto, Stochastic energetics, Lecture Notes in Physics, vol. 799, SpringerVerlag, Heidelberg, 2010.
[Shi92] A. N. Shiryaev (ed.), Selected works of A.N. Kolmogorov, vol. II, Kluwer Academic Publishers, Dordrecht, 1992.
[Shi96] A. N. Shiryaev, Probability, 2nd ed., translated from the first (1980) Russian edition by R. P. Boas, Graduate Texts in Mathematics, vol. 95, Springer-Verlag, New York, 1996. MR 1368405
[Sin89] Y. Sinai (ed.), Dynamical systems II: Ergodic theory with applications to dynamical systems and statistical mechanics, Encyclopaedia of Mathematical Sciences, vol. 2, Springer-Verlag, Berlin and Heidelberg, 1989.
[SM00] J. Shi and J. Malik, Normalized cuts and image segmentation, IEEE Trans. Pattern Anal. Mach. Intel. 22 (2000), 888-905.
[Soa94] P. M. Soardi, Potential theory on infinite networks, Lecture Notes in Mathematics, vol. 1590, Springer-Verlag, Berlin, 1994. MR 1324344
[Sus78] H. J. Sussmann, On the gap between deterministic and stochastic ordinary differential equations, Ann. Probability 6 (1978), no. 1, 19-41. MR0461664
[SW95] A. Shwartz and A. Weiss, Large deviations for performance analysis, Queues, communications, and computing, with an appendix by Robert J. Vanderbei, Stochastic Modeling Series, Chapman \& Hall, London, 1995. MR 1335456
[Szn98] A.-S. Sznitman, Brownian motion, obstacles and random media, Springer Monographs in Mathematics, Springer-Verlag, Berlin, 1998. MR1717054
[Tai04] K. Taira, Semigroups, boundary value problems and Markov processes, Springer Monographs in Mathematics, Springer-Verlag, Berlin, 2004. MR2019537
[Tan96] M. A. Tanner, Tools for statistical inference: Methods for the exploration of posterior distributions and likelihood functions, 3rd ed., Springer Series in Statistics, Springer-Verlag, New York, 1996. MR 1396311
[TB04] T. Tian and K. Burrage, Binomial leap methods for simulating stochastic chemical kinetics, J. Chem. Phys. 121 (2004), 10356-10364.
[TKS95] M. Toda, R. Kubo, and N. Saitô, Statistical physics, vol. 1, Springer-Verlag, Berlin, Heidelberg and New York, 1995.
[Tou09] H. Touchette, The large deviation approach to statistical mechanics, Phys. Rep. 478 (2009), no. 1-3, 1-69, DOI 10.1016/j.physrep.2009.05.002. MR2560411
[TT90] D. Talay and L. Tubaro, Expansion of the global error for numerical schemes solving stochastic differential equations, Stochastic Anal. Appl. 8 (1990), no. 4, 483-509 (1991), DOI 10.1080/07362999008809220. MR1091544
[Van83] E. Vanmarcke, Random fields: Analysis and synthesis, MIT Press, Cambridge, MA, 1983. MR761904
[Var84] S. R. S. Varadhan, Large deviations and applications, CBMS-NSF Regional Conference Series in Applied Mathematics, vol. 46, Society for Industrial and Applied Mathematics (SIAM), Philadelphia, PA, 1984. MR 758258
[VK04] N. G. Van Kampen, Stochastic processes in physics and chemistry, 2nd ed., Elsevier, Amsterdam, 2004.
[Wal02] D. F. Walnut, An introduction to wavelet analysis, Applied and Numerical Harmonic Analysis, Birkhäuser Boston, Inc., Boston, MA, 2002. MR1854350
[Wel03] L. R. Welch, Hidden Markov models and the Baum-Welch algorithm, IEEE Infor. Theory Soc. Newslett. 53 (2003), 10-13.
[Wie23] N. Wiener, Differential space, J. Math. and Phys. 2 (1923), 131-174.
[Win03] G. Winkler, Image analysis, random fields and Markov chain Monte Carlo methods, 2nd ed., A mathematical introduction, with 1 CD-ROM (Windows), Stochastic Modelling and Applied Probability, Applications of Mathematics (New York), vol. 27, Springer-Verlag, Berlin, 2003. MR 1950762
[WZ65] E. Wong and M. Zakai, On the convergence of ordinary integrals to stochastic integrals, Ann. Math. Statist. 36 (1965), 1560-1564, DOI 10.1214/aoms/1177699916. MR0195142
[XK02] D. Xiu and G. E. Karniadakis, The Wiener-Askey polynomial chaos for stochastic differential equations, SIAM J. Sci. Comput. 24 (2002), no. 2, 619-644, DOI 10.1137/S1064827501387826. MR 1951058
[YLAVE16] T. Yu, J. Lu, C. F. Abrams, and E. Vanden-Eijnden, Multiscale implementation of infinite-swap replica exhange molecular dynamics, Proc. Nat. Acad. Sci. USA 113 (2016), 11744-11749.
[Yos95] K. Yosida, Functional analysis, reprint of the sixth (1980) edition, Classics in Mathematics, Springer-Verlag, Berlin, 1995. MR1336382
[ZD12] J. Zhang and Q. Du, Shrinking dimer dynamics and its applications to saddle point search, SIAM J. Numer. Anal. 50 (2012), no. 4, 1899-1921, DOI 10.1137/110843149. MR3022203
[ZJ07] J. Zinn-Justin, Phase transitions and renormalization group, Oxford Graduate Texts, Oxford University Press, Oxford, 2007. MR2345069
[ZL16] P. Zhou and T. Li, Construction of the landscape for multi-stable systems: Potential landscape, quasi-potential, A-type integral and beyond, J. Chem. Phys. 144 (2016), 094109.

## Index

$Q$-process, 54108
waiting time, 56
$\sigma$-algebra, 5
Borel, 8
generated by a random variable, 15
infinite product, 103
accessible state, 50
action functional, 200
algebra, 282
Arrhenius's law, 250
backward stochastic integral, 166, 194
Bayes's theorem, 7
Bayesian inference, 90
BKL algorithm, see also kinetic Monte
Carlo
Bochner's theorem, 19
Boltzmann constant, 12
Borel-Cantelli lemma, 21, 30
Brownian bridge, 113, 136
Brownian dynamics, 171, 234
Brownian motion on sphere, 172
Brownian sheet, 136
central limit theorem, 31
Chapman-Kolmogorov equation, 47, 55
characteristic function, 17
chemical master equation, 264
chemical potential, 172,223
chemical reaction kinetics
diffusion approximation, 268
multiscale, 272
closed system, 218
colored noise, 139
compound Poisson process, 72
conditional expectation, 14, 239
conditional probability, 6
convergence
almost sure, 16
in $L^{p}, 16$
in distribution, 16
in probability, 16
relations, 17
coordinate process, 103
covariance, 9
covariance function, 235
Cramér's theorem, 33, 37
cross-correlation function, 237
cylinder set, 102
density of states, 221
detailed balance, 87,176
diffusion coefficient, 118
diffusion process, 154
Dirichlet form, 61
distribution, 8
Bernoulli, 724
binomial, 8, 24
Cauchy-Lorentz, 31
exponential, 11
Fréchet, 41
gamma, 72
Gaussian, 11
Gibbs, 12, 77, 89, 95, 176, 216, 221
229236
Gumbel, 41
normal, 11
Poisson, 8 , 24
uniform, 10
Weibull, 41
distribution function, 12
Dynkin's formula, 182
Dyson's formula, 239
Ehrenfest's diffusion model, 46
Einstein relation, 234 238
emission matrix, 61
ensemble
canonical, 218, 222, 226
grand canonical, 218, 222
isothermal-isobaric, 224
microcanonical, 218, 225
entropy
Boltzmann, 38, 219
Gibbs, 219
ideal gas, 227
mixing, 225
relative, 37
Shannon, 26 43
ergodic theorem, 52
$Q$-process, 59
finite Markov chain, 51
Euler-Maruyama scheme, 157
strong convergence, 161
weak convergence, 190
exit problem, 182249
expectation, 9
extremal statistics, 40
Feynman-Kac formula, 180, 207
filtration, 104
augmented filtration, 105141
first passage time, 72
Fisher-Tippett-Gnedenko theorem, 41
fluctuation-dissipation relation, 234
Fokker-Planck equation, 170
boundary conditions, 175
fractional Brownian motion, 114, 136
free energy, 39
Gibbs, 224
Helmholtz, 221
Landau, 223
Gärtner-Ellis theorem, 231
Gaussian process, 109, 242
characteristic function, 110
covariance function, 109
mean function, 109

Gaussian random field, 212
generalized Langevin equation, 234 242
generating function, 19
moment, 20
generator, see also infinitesimal generator
geometric Brownian motion, 153
Gibbs distribution, see also distribution, Gibbs
Gillespie's algorithm, see also stochastic simulation algorithm
Girko's circular law, 27
Girsanov theorem, 206, 207
grand potential, see also free energy, Landau
Green-Kubo relation, 238
Hamilton-Jacobi equation, 255
Hammersley-Clifford theorem, 215
heat capacity, 222
hidden Markov model, 61
backward algorithm, 65
Baum-Welch algorithm, 66
forward algorithm, 63
Viterbi algorithm, 64
Hille-Yosida theorem, 287
HMM, see also hidden Markov model
holding time, 57
i.o. set, 21
ideal gas, 226
discrete, 227
independence, 1213
inequality
Boole, 6
Burkholder-Davis-Gundy, 148
Chebyshev, 10
conditional Jensen, 15
discrete Gronwall, 281
Doob's maximal, 151
Fenchel, 33
Gronwall, 281
Hölder, 9
Jensen, 10
martingale, 285
Minkowski, 9
Schwartz, 10
infinitesimal generator, 55, [108, 170, 286
information theory, 43
internal energy, 39
invariance principle, 120
invariant distribution, 48 56 176) 271
invariant measure, 48
Ising model, 88 228, 243
isolated system, 218
Itô integral, 140
Itô isometry, 141143
Itô process, 145
Itô-Taylor expansion, 156
Itô's formula, 145147
discrete, 160
jump chain, 57
jump matrix, 57
jump time, 57
Kac-Zwanzig model, 240
Karhunen-Loève expansion, 112
kinetic Monte Carlo, 91
Kolmogorov equation
backward, [55, 175) 179, 268
forward, [55 171264
Kolmogorov's continuity theorem, 129
Kolmogorov's extension theorem, 104
Kullback-Leibler distance, see also entropy, relative

Langevin dynamics, see also Langevin equation
Langevin equation, 153,233
Laplace lemma, 34 279
single-sided, 42
Laplacian matrix, 61
large deviation theory, 32, 33, 250,280
large volume limit, 266
law of large numbers, 241
strong, 30
weak, 4, 29
law of mass action, 263
Legendre-Fenchel transform, 33,224 , $230 \quad 249$
Lévy's continuity theorem, 19
likelihood function, 62,90
limit theorem, 29
linear response theory, 236
admittance, 238
Markov chain
coarse-graining, 69
communicate, 50
continuous time, 53, 54]
discrete time, 46
embedded, 57
irreducible, 4958
lumpable, 69
primitive, 51
reducible, 49
reversible, 60
stationary, 47
time reversal, 59
Markov process, 106
homogeneous in time, 107
transition density, 107
transition function, 106
transition kernel, 107, 126, 179
Markov random field, 214
martingale, 148 , 151,284
maximum entropy principle, 242
maximum likelihood estimate, 6590
MCMC, see also Metropolis algorithm
mean, 7 , 9
mean first passage time, 183,249
measurable
$\mathcal{F}$-measurable, 8 , 14
measurable space, [5, 282
Mercer's theorem, 111
metastability, [246
Metropolis algorithm, 87
Gibbs sampling, 89
Glauber dynamics, 88
Metropolis-Hastings, 90
Milstein scheme, 158
minimum action path, 252,256
minimum energy path, see also minimum action path
moment, 920
exponential, 32
Monte Carlo integration, 76
Monte Carlo method, 32
Mori-Zwanzig formalism, 238
multilevel Monte Carlo method, 162
network, 67
chemical reaction, 263
community structure, 69
numerical SDEs
strong convergence, 159
weak convergence, 159190
open system, 218
order statistics, 2672
Ornstein-Uhlenbeck process, 113,114
152177193
OU process, see also
Ornstein-Uhlenbeck process
over-damped dynamics, 242
partition function, 12, 221
grand, 223
path integral, 203, 252
Perron-Frobenius theorem, 50, 230
phase transition, 231
Poisson process, 53, 109
waiting time, 54
posterior probability, 7
pressure, 225
prior probability, 7
probability current density, 172
probability density function, 9
probability distribution
continuous, 8
discrete, 7
probability measure, 5
absolutely continuous, 9
probability space, 5
quadratic variation, 127
quasipotential, 254, 256
global, 259
local, 259
Radon-Nikodym derivative, 9
random field, 209
random number generation, 77
acceptance-rejection, 82
Box-Muller, 81
composition, 81
inverse transformation, 79
linear congruential generator, 78
squeezing acceptance-rejection, 97
random telegraph process, 185
random variable, 8
random vector, 9
random walk, 46, 118
arcsine law, 120
rare events, 245
rate function, 33, 39
reaction rate equation, 262
reflection principle, 131
resistor network, 72
response function, 237
Runge-Kutta scheme, 158
semigroup, 108, 178, 286
Feller, 179
spectral theory, 183
simple function, 141
simulated annealing, 94
convergence, 96
simulated tempering, 92
Smoluchowski equation, 172
spectral radius, 49
SSA, see also stochastic simulation algorithm
stable laws, 26, 32
stationary distribution, see also invariant distribution
stationary measure, see also invariant measure
Stirling's formula, 3
stochastic differential equation
averaging, 185275
chemical reaction, 265
existence and uniqueness, 149
stochastic matrix, 47
stochastic process, 102
adapted, 105
modification, 128
stochastic simulation algorithm, 57, 266
nested SSA, 276
stoichiometric matrix, 263
stopping time, 105
Stratonovich integral, 154
string method, 253
strong Markov property, 58, 285
tau-leaping algorithm, 269
thermodynamic average, 12, 89
transfer matrix, 230
transition kernel, see also Markov process, transition kernel
transition path, 247, 258
transition probability matrix, 47, 49. 55, 61
transition rate, 249
transition state, 247 260
uncorrelated random variables, 9
variance, 77
variance identity, 26
variance reduction, 83
antithetic variable, 97
control variates, 86
importance sampling, 84
Rao-Blackwellization, 86
stratified sampling, 97
white noise, 139
Wick's theorem, 26
Wiener chaos expansion, 132
Wiener measure, 200

Wiener process, 117121,125
absorbing wall, 131
finite-dimensional distribution, 125
generator, 126
local law of the iterated logarithm, 129
properties, 127
reflecting barrier, 130
Witten Laplacian, 185
WKB analysis, 248

This is a textbook for advanced undergraduate students and beginning graduate students in applied mathematics. It presents the basic mathematical foundations of stochastic analysis (probability theory and stochastic processes) as well as some important practical tools and applications (e.g., the connection with differential equations, numerical methods, path integrals, random fields, statistical physics, chemical kinetics, and rare events). The book strikes a nice balance between mathematical formalism and intuitive arguments, a style that is most suited for applied mathematicians. Readers can learn both the rigorous treatment of stochastic analysis as well as practical applications in modeling and simulation. Numerous exercises nicely supplement the main exposition.


For additional information
and updates on this book, visit www.ams.org/bookpages/gsm-199

