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Stochastic Biomathematical Models

with Applications to Neuronal Modeling



Springer

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Preface

Why use mathematical or stochastic models to study something as complicated and often poorly understood as dynamics in physiology? Hopefully, this book can provide some partial answers and point to the exciting problems that still remain to be solved, where mathematical and stochastic tools can be useful.

In this book we treat basics of stochastic process theory represented by a stochastic differential equation directed towards biological modeling and review the field of neuronal models. Theoretical models must be relevant physiologically to be useful and interesting, and their analysis can provide biological insight and help summarize and interpret experimental data. Predictions can be extracted from the model, and experiments verifying or invalidating the model can be suggested, thereby enhancing physiological understanding. Even if the mechanisms are well understood, simulations from models can explore the consequences of extreme physiological conditions that might be unethical or impossible to reproduce experimentally. The process of building a theoretical model forces one to consider and decide on the essential characteristics of the physiological dynamics, as well as which variables and mechanisms to include. Analysis and numerical simulations of the model illustrate quantitatively and qualitatively the consequences of the assumptions implied in the model. The unifying aim of theoretical modeling and experimental investigation is the elucidation of the underlying biological processes that result in a particular observed phenomenon.

Many biological systems are highly irregular, and experiments under controlled conditions show a large trial-to-trial variability, even when keeping the experimental setup fixed. This calls for a stochastic, as opposed to deterministic, modeling approach, especially because ignoring the stochastic phenomena in the modeling may hugely affect the conclusions of the studied biological system. In linear systems the noise might only blur the underlying dynamics without qualitatively affecting it, but in nonlinear dynamical systems corrupted by noise, the corresponding deterministic dynamics can be drastically changed. In general, stochastic effects influence the dynamics and may enhance, diminish, or even completely change the dynamic behavior of the system. In certain biological systems, e.g., in auditory

neurons, the noise is even believed to enhance the signal, thus providing a biological justification for the large amount of noise found in living systems.

The book treats stochasticity represented by stochastic differential equations, but is not meant to be a comprehensive textbook on stochastic methods. It is primarily intended for mathematicians and life scientists who are interested in seeing an in-depth and motivated presentation of an important application of stochastic methods. Our goal is to provide an illuminating example of where and how stochastic methods can enter into modeling physiological systems. Life scientists generally, with some background in mathematics, will also be able to benefit by seeing how these two areas are linked, and we point the interested reader to references that fill in missing background information. We hope that the material as presented will provide a useful illustration of interdisciplinary research.

The reader should have a basic background in probability, differential and integral calculus, and ordinary differential equations. We focus on neuronal modeling, where stochastic models have supplemented deterministic dynamical models since the sixties. There exist already many excellent books on nonlinear dynamics, biomathematical modeling, and computational neuroscience. The aim of this volume is to provide a focused, up-to-date presentation of neuronal modeling using stochastic methods, while in addition both motivating the linkage and providing insight into practical issues. More profit will of course be derived from reading the book, if it is combined with the reading of some introductory texts in computational neuroscience or biomathematical modeling.

The book is divided into two parts. The first part introduces some methodology, which is useful when modeling biological systems with stochastic dynamics. Chapter 1 is an introduction to stochastic models and a good place to start if the reader has no background in stochastic processes. Also a short overview of statistical methods to estimate model parameters from data is provided. Chapters 2 and 3 need more mathematical preparation and a basic understanding of stochastic processes and probability theory, as well as some notion of measure theory. In Chap. 2, scale and speed measures of one-dimensional diffusion processes are reviewed, which are used to determine expressions for hitting times or first-escape times, in particular, boundary behaviors. These tools are very useful when dealing with neuronal models, as those presented in the second part of the book. Chapter 3 gives an introduction to the theory of large deviations, providing an asymptotic description of the fluctuations of a stochastic system, in particular, providing exponential estimates for the waiting time to rare events. Chapter 4 closes the methodological part indicating how the theory from Chap. 3 can be implemented in practice. These techniques are natural to use when analyzing stochastic models of biological systems.

The second part of the book treats neuronal models. Chapter 5 provides a timely review of existing methods and available analytical results for the most common one-dimensional stochastic integrate-and-fire models. These models of neuronal activity collapse the neuronal anatomy into a single point in space, sacrificing realism for mathematical tractability, although they often succeed in predicting neuronal response with considerable accuracy. Chapter 6 goes a step further to more realistic models and includes the spatial dimension of neuronal dynamics. Stochastic

partial differential equation models are reviewed, in particular the Hodgkin–Huxley and the FitzHugh–Nagumo models are treated in detail. Chapter 7 is dedicated to a probabilistic treatment of FitzHugh–Nagumo systems. Finally, Chap. 8 implements the tools from Chap. 6 to a specific application of modeling spreading of cortical depression.

This volume was first conceived as a result of the experience of designing and holding a combined summer school/workshop event on the subject of stochastic modeling in physiology. This event was part of a Marie Curie sponsored series of four training events designed to encourage interdisciplinary research in modeling physiological systems. The events brought together mathematicians, bioengineers, statisticians, medical clinicians, physiologists, and other related life science researchers.

The underlying motivation and inspiration for this series of events is that unraveling the complexities of physiological systems and the intricacies of interaction between systems requires development of novel and innovative insights as well as new research approaches and techniques. Furthermore, such new approaches can be strongly stimulated by merging the different perspectives from the mathematical/engineering disciplines on the one side and the life sciences on the other. These observations motivated the design of the events in which summer schools would introduce new and young researches to an interdisciplinary treatment of the modeling of key physiological systems with emphasis on how modeling can address important clinical problems related to these systems. Directly following each summer school an interdisciplinary scientific workshop was held. These workshops focused on the same themes as the preceding summer school and were designed as stand alone scientific events. Students from the school participated in these workshops and in this way new and current researchers could interact and develop contacts for collaboration.

The general web page linking and reflecting all four Marie Curie training events can be found at: <http://www.uni-graz.at/biomedmath/info.html>.

The event related to this volume can be found at the event web page: <http://www.math.ku.dk/~susanne/SummerSchool2008/>

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Acronyms

a.s.	Almost surely
ATP	Adenosine triphosphate
CLT	Central limit theorem
CNS	Central nervous system
CTMC	Continuous-time Markov chain
CV	Coefficient of variation
DCEI	Dynamic contrast enhanced imaging
FET	First entrance time
FIM	Fisher information matrix
FN	FitzHugh–Nagumo
FPT	First passage time
GABA	Gamma-aminobutyric acid
GWN	Gaussian white noise
HH	Hodgkin–Huxley
IF	Integrate and Fire
IG	Inverse Gaussian
iid	independent and identically distributed
IS	Importance sampling
ISI	Interspike interval
LDP	Large deviation principle
LIF	Leaky Integrate and Fire
LLN	Law of large numbers
MC	Monte Carlo
MCMC	Markov Chain Monte Carlo
MLE	Maximum likelihood estimator
MLP	Most likely path
MRI	Magnetic resonance imaging
NMDA	<i>N</i> -methyl D-aspartate
NMSE	Normalized mean-square error
ODE	Ordinary differential equation
OU	Ornstein–Uhlenbeck

PDE	Partial differential equation
pdf	Probability density function
PSP	Postsynaptic potential
r.v.	Random variable
RRW	Randomized Random Walk
SD	Spreading cortical depression
SDE	Stochastic differential equation
SPDE	Stochastic partial differential equation
w.r.t.	With respect to