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Péter Érdi • Gábor Lente

Stochastic Chemical Kinetics

Theory and (Mostly) Systems Biological Applications

Springer

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To our teacher, coworker and friend,
János Tóth

Preface

This book is, of course, about stochastic chemical kinetics. Chemical kinetics is a prototype of nonlinear science, since the rate of reaction is generally a nonlinear function of the quantities of the reacting chemical components.

Stochastic models are able to describe fluctuations around some deterministic values, but also internally random processes without having any deterministic trend (as in small chemical systems). In general, stochastic kinetic models are Markovian jump processes, and the temporal evolution can be described by a Kolmogorov equation, also called the master equation:

$$\frac{dP_n}{dt} = \mathbf{A}P_n(t). \tag{1}$$

Equation (1) is a linear differential-difference equation, and the special structure of $\mathbf{A}$ is governed by the stoichiometry. In spite of the fact that Eq. (1) is linear, it can give rise to *nonlinear phenomena*. The master equation can be converted into nonlinear equations for some macroscopic variables, e.g. by calculating the expectations of concentrations or amounts of substance.

The book deals with spatially homogeneous systems (or a system of spatially homogeneous systems, such as compartmental systems), so reaction-diffusion systems and the related stochastic models based on stochastic partial differential equations and/or on Markov fields are neglected.

There is a generation gap between the two authors. The senior author worked on stochastic kinetics with his mathematician friend János Tóth, mostly in the 1970s, and the cooperation led to a book that is a quarter of a century old now (P.É. and J.T.: Mathematical Models of Chemical Reactions. Theory and applications of deterministic and stochastic models. Manchester Univ. Press., Princeton Univ. Press. 1989). János should have been a natural coauthor of the present book, too, but he has been busy writing another one (Tóth, J., Nagy, A. L., & Papp, D.: Reaction Kinetics: Exercises, Programs and Theorems. Mathematical and Computational Chemistry. New York: Springer Verlag. In preparation.) Many ideas and techniques presented

in this book reflect (we hope) his spirit, too, as we deliberately adopted parts from János's works, and we thank him for his permission to do it.

The more junior author began his involvement in this field a decade ago by re-discovering stochastic kinetics without any knowledge of the previous literature – as a hobby for himself. The primary question for him was the interpretation of the *Soai reaction*, which is connected to efforts to understand the origins of homochirality and, ultimately, life on Earth. His wife, who was his single-member audience at that time, convinced him to try to publish his thoughts and results. The response to his first article from other scientists was sufficiently enthusiastic to keep him busy thinking about stochastic kinetics and writing scientific papers – although his main professional field is still experimental.

The development of the experimental techniques implied the much more extensive application of stochastic models, and we felt we should write a book now, which tries to be a bridge between the theory-induced pioneer period and the present and future somewhat more application-oriented times. Obviously, stochastic kinetics has an increasing popularity, mostly due to the renaissance of systems biology, as it is reflected in the subtitle of the book.

Chapter 1 is a light introduction to the fluctuation phenomena and to the most frequently used concepts of stochastic processes and stochastic kinetics. The scope and limits of the applicability of the deterministic model is discussed. Stochastic modeling grew up from the studies of fluctuation phenomena, particularly of the Brownian motion, famously studied by Einstein. His studies led to the first formulation of the fluctuation-dissipation theorem. Continuous time, discrete state space stochastic models are now often used to describe chemical fluctuations. Systems biology combines new experimental techniques and theoretical/computational methods containing a strong component related to the measurement, analysis and modeling of noise processes.

Chapter 2 is a more formal description of the topic. The mathematical framework of the most often used stochastic models of chemical reactions are discussed. First, a brief overview on and some classification of the stochastic (mostly Markovian) processes is given. The standard stochastic model of homogeneous reaction kinetics is defined, and the construction leads to the most extensively used master equations. The analogies between the deterministic and stochastic models are analyzed, among others, with the concept of the stochastic map. The different methods of obtaining transient and stationary solutions, and then the simulation techniques are reviewed. The deterministic continuation and the continuous state approximation are considered, and finally, a brief hint on the non-Markovian approximation is given.

Chapter 3 reviews the most important applications of stochastic kinetic models. Fluctuations particularly cannot be neglected in small systems and around unstable stationary points. Compartmental systems and enzyme kinetics are popular fields of stochastic kinetics, autocatalytic systems are somewhat neglected despite their historical role. Other fields of systems biology (and related areas), as signal processing, gene expression and chiral symmetry, also convincingly show the necessity of applying stochastic models. After two technical subsections (parameter

estimation and stochastic resonance), the application of stochastic kinetics in the theory of computation is reviewed. Finally, Chapter 4 gives a subjective summary of what is written in the previous three chapters.

Our book is hopefully an organic sprout on the verdant existing scientific literature. Crispin Gardiner's *Stochastic Methods: A Handbook for the Natural and Social Sciences* is an excellent resource for learning (and teaching) concepts, methods and applications of stochastic processes. Peter Schuster has an extremely good textbook on the net (*Stochasticity in Chemistry and Biology*. *When Small Population Sizes Matter and Environments Fluctuate*), Darren Wilkinson's *Stochastic Modelling for Systems Biology* has its second edition, and it is very well usable to learn simulation methods and statistical inference techniques. The literature is now rapidly growing, and we might have overlooked very important items. It is not necessarily reflected in the references, but many papers of Hong Qian were read, and our way of thinking is hopefully not too far from the spirit we spelled out from them. We deliberately adopted text, figures, and ideas from the scientific works of other colleagues. We think precise citation/credit was given.

We benefited from having a wonderful working environment. Kalamazoo College was awarded by a Henry R. Luce Professorship and one of us (P.É.) has had the privilege to serve here to build a program about Complex Systems. The Wigner Research Centre for Physics of the Hungarian Academy of Sciences in Budapest also provides a supportive environment when he spends the summers there. He also benefited from spending the Michaelmas term of 2012 as a fellow of the Institute of Advanced Studies at Durham University. G.L. is expecting to be a full professor at the Department of Inorganic and Analytical Chemistry of the University of Debrecen in Hungary soon. This environment constantly reminds him of the fact that the primary role of scientific theories is to interpret experimental data.

Budapest, Hungary/Debrecen, Hungary/Kalamazoo, USA — Péter Érdi
December 2013 — Gábor Lente

Contents