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Peter E. Kloeden • Christian Pötzsche
Editors

Nonautonomous Dynamical Systems in the Life Sciences

Editors

Peter E. Kloeden
Institut für Mathematik
Goethe-Universität Frankfurt
Frankfurt am Main, Germany

Christian Pötzsche
Institut für Mathematik
Alpen-Adria Universität Klagenfurt
Klagenfurt am Wörthersee, Austria

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Preface

The theory of dynamical systems is a well-developed and successful mathematical framework to describe time-varying phenomena. Its applications in the life sciences range from simple predator–prey models to complicated signal transduction pathways in biological cells, in physics from the motion of a pendulum to complex climate models, and beyond that to further fields as diverse as chemistry (reaction kinetics), economics, engineering, sociology, demography, and biosciences. Indeed, Systems Biology relies heavily on methods from Dynamical Systems. Moreover, these diverse applications have provided a significant impact on the theory of dynamical systems itself and is one of the main reasons for its popularity over the last decades.

As a general principle, before abstract mathematical tools can be applied to real-world phenomena from the above areas, one needs corresponding models in terms of some kind of evolutionary difference or differential equation. Their goal is to provide a realistic and tractable picture for the actual behavior of, e.g., a biodynamical system. A thorough understanding helps to optimize time-consuming and costly experiments, like the development of harvesting or dosing strategies and might even enable field studies to be avoided.

From a conceptional level, in developing such models one distinguishes an actual dynamical *system* from its surrounding *environment*. The system is given in terms of physical or internal feedback laws that yield an evolutionary equation. The parameters in this equation describe the current state of the environment. The latter may or may not vary in time, but is assumed to be unaffected by the system.

For *autonomous dynamical systems* the basic law of evolution is static in the sense that the environment does not change with time. However, in many applications such a static approach is too restrictive and a temporally fluctuating environment is required:

- Parameters in real-world situations and particularly in the life sciences are rarely constant over time. This has various reasons, like absence of lab conditions, adaption processes, seasonal effects on different time scales, changes in nutrient supply, or an intrinsic “background noise.”

- On the other hand, sometimes it is desirable to include regulation or control strategies into a model (e.g., harvesting and fishing, dosing of drugs or radiation, stimulating chemicals or catalytic submissions), as well as extrinsic noise, and to study their effects. In particular, biochemical signaling within and into cells is a nonautonomous process.
- Several problems can be decomposed into coupled subsystems. Provided the influence of some of them is understood, without the requirement to precisely know their explicit form, they can be seen as a non-constant time-varying input.

These temporal fluctuations might be deterministic or random and in the first case often more than just periodic in time. The evidence of time-dependent parameters can also be verified statistically, when it comes to the problem of fitting parameters to actual measured data or in phenomena like cardiovascular ageing.

Consequently, in reasonable models that are adapted to and well suited for problems in temporally fluctuating environments, the resulting evolutionary equations have to depend explicitly on time. In order to study such realistic problems, the classical theory of dynamical systems has to be extended. The field of *nonautonomous and random dynamical systems* has thus received a wide attraction over the recent 10–15 years and is expected to develop to further maturity. Both the fields of nonautonomous and of random dynamical systems are parallel theories featuring very similar concepts.

In the area of biomathematics, for example, the corresponding contributions deal with nonautonomous equations and have provided major progress in our understanding of classical boundedness, global stability, persistence, permanence, or positivity aspects. Nevertheless, often more subtle questions are crucial. For instance, it is of utmost importance to identify “key players” in biodynamical processes, i.e., the variables or parameters crucially affecting the long-term behavior of a system. Knowing these quantities enables researchers to reduce the dimension of a system significantly and thus makes it amenable for analytical tools, as opposed to sometimes problematic numerical methods and simulations. Such questions clearly fit into the framework of *bifurcation theory* describing qualitative changes. However, when dealing with nonautonomous and random equations new ideas and concepts are required: For instance, the classical notions of invariance, attraction, hyperbolicity, and invariant manifolds have had to be extended.

Despite being well motivated, one rarely finds biological processes modeled using nonautonomous equations. A cause seems to be the problem that classical methods from autonomous dynamical systems theory do not apply to them, while more recent tools tailor-made for time-dependent problems still need to be popularized.

For these reasons, the contemporary fields of nonautonomous and random dynamical systems on the one side, and biodynamics on the other side, strongly benefit from each other. Actually, it is essential to

- illustrate such a modern theory using successful and convincing real-world applications,

- gain input from real-life application inducing a further development of the theory into directions of a broader interest.

On the other hand, researchers interested in mathematical approaches to life sciences will

- find suitable mathematical methods promising and fruitful in various applications,
- obtain a solid toolbox for an understanding and iterative refinement of models in fluctuating environments,
- lower an inhibition threshold to use nonautonomous models from the beginning.

In conclusion, the main motivation for this book is to bring readers' attention to various recent developments and methods from the field of nonautonomous and random dynamical systems and promising applications originating in life sciences. For this reason we collected three articles (Chaps. 1–3) illustrating theoretical aspects, as well as six further papers (Chaps. 4–8) focussing on more concrete applications, where these new ideas and tools could be used:

1. The introductory contribution of the editors shares the title with this book and surveys several key concepts from the mathematical theory of deterministic nonautonomous dynamical systems. They are exemplified using various simple models from the life sciences.
2. The chapter on *Random Dynamical Systems with Inputs* by Michael Marcondes de Freitas and Eduardo D. Sontag describes the concept of a random dynamical system and extends it to problems with inputs and outputs. Applications to feedback connections are given.
3. Multiple time scales are an important feature of physiological systems and functions. Martin Wechselberger, John Mitry, and John Rinzel give a modern introduction to the basic geometrical singular perturbation theory and use it in their chapter *Canard Theory and Excitability* to tackle related problems and their transient behavior.
4. *Stimulus-Response Reliability of Biological Networks* by Kevin K. Lin reviews some basic concepts and results from the ergodic theory of random dynamical systems and explains how these ideas can be used (partly in combination with numerical simulations) to study the reliability of networks, i.e., the reproducibility of a network's response when repeatedly presented with a given stimulus.
5. The "Lancaster group" Philip Clemson, Spase Petkoski, Tomislav Stankovski, and Aneta Stefanovska explain how networks of nonautonomous self-sustained oscillators can model a virtual physiological human. Their chapter *Coupled Nonautonomous Oscillators* includes novel methods suitable to reconstruct nonautonomous dynamics using data from a real living system by studying time-dependent coupling between cardiac and respiratory rhythms.
6. Germán Enciso's contribution *Multisite Mechanisms for Ultrasensitivity in Signal Transduction* gives a mathematical review of the most important molecular models featuring ultrasensitive behavior.

7. The chapter *Mathematical Concepts in Pharmacokinetics and Pharmacodynamics with Application to Tumor Growth* by Gilbert Koch and Johannes Schropp describes corresponding models and their applications in the pharmaceutical industry. Moreover, a model for tumor growth and anticancer effects is developed and discussed.
8. In *Viral Kinetic Modeling of Chronic Hepatitis C and B Infection*, Eva Herrmann and Yusuke Asai demonstrate the interplay between mathematical and statistical analysis of compartment ODE models for hepatitis B and C. They give an account of clinical use of models in treatment. Moreover, the most relevant models for such infections are surveyed.
9. Finally, Christina and Nicolae Surulescu study *Some Classes of Stochastic Differential Equations as an Alternative Modeling Approach to Biomedical Problems*. In detail, models for an intracellular signaling pathway, a radio-oncological treatment, and cell dispersal are presented and studied.

Finally, we cordially thank all the contributors to this volume and hope to have contributed to building a bridge between nonautonomous/random dynamics and the life sciences.

Frankfurt am Main, Germany
Klagenfurt, Austria
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Peter E. Kloeden
Christian Pötzsche

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Nonautonomous and Random Dynamical Systems in Life Sciences

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List of Contributors

Yusuke Asai Department of Medicine, Institute of Biostatistics and Mathematical Modeling, Goethe University Frankfurt, Deutschland

Philip Clemson Physics Department, Lancaster University, Lancaster, UK

Germán A. Enciso Department of Mathematics, University of California, Irvine, Irvine, CA, USA

Eva Herrmann Department of Medicine, Institute of Biostatistics and Mathematical Modeling, Goethe University Frankfurt, Deutschland

Peter E. Kloeden Institut für Mathematik, Goethe-Universität Frankfurt, Postfach, Frankfurt am Main, Deutschland

Gilbert Koch Department of Pharmaceutical Sciences, School of Pharmacy and Pharmaceutical Sciences, State University of New York at Buffalo, Buffalo, NY, USA

Kevin K. Lin Department of Mathematics, University of Arizona, Tucson, AZ, USA

Michael Marcondes de Freitas Department of Mathematics, Rutgers University, Piscataway, NJ, USA

John Mitry School of Mathematics and Statistics, University of Sydney, NSW, Australia

Spase Petkoski Physics Department, Lancaster University, Lancaster, UK

Christian Pötzsche Institut für Mathematik, Alpen-Adria Universität Klagenfurt, Universitätsstr., Klagenfurt am Wörthersee, Österreich

John Rinzel Courant Institute, New York University, New York, NY, USA

Johannes Schropp FB Mathematik und Statistik, Universität Konstanz, Postfach, Konstanz, Deutschland

Eduardo D. Sontag Department of Mathematics, Rutgers University, Piscataway, NJ, USA

Tomislav Stankovski Physics Department, Lancaster University, Lancaster, UK

Aneta Stefanovska Physics Department, Lancaster University, Lancaster, UK

Christina Surulescu Felix Klein Zentrum für Mathematik, Universität Kaiserslautern, Kaiserslautern, Deutschland

Nicolae Surulescu Mathematisches Institut, Universität Münster, Münster, Deutschland

Martin Wechselberger School of Mathematics and Statistics, University of Sydney, NSW, Australia