

Scientific Frontiers at the Interface of Mathematics and Life Sciences

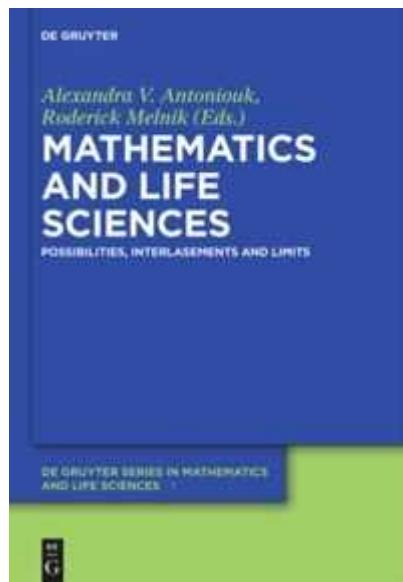
Antoniouk, Alexandra V. and Melnik, Roderick V. N.,

In: "Mathematics and Life Sciences"

(Eds. A. V. Antoniouk and R. V. N. Melnik),

De Gruyter Series in Mathematics and Life Sciences,

Vol. 1, 2013, pp. 3-15.



Mathematics and Life Sciences

Edited by

Alexandra V. Antoniouk
Roderick V. N. Melnik

De Gruyter

Unterstützt von / Supported by



Alexander von Humboldt
Stiftung/Foundation

Mathematics Subject Classification 2010: 97M60, 92C42, 62P10, 35Q92, 37N25, 92C15,
92B05, 92C80, 92-03, 92-02.

ISBN 978-3-11-027372-4
e-ISBN 978-3-11-028853-7

Library of Congress Cataloging-in-Publication Data

A CIP catalog record for this book has been applied for at the Library of Congress.

Bibliographic information published by the Deutsche Nationalbibliothek

The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie;
detailed bibliographic data are available in the Internet at <http://dnb.dnb.de>.

© 2013 Walter de Gruyter GmbH, Berlin/Boston

Typesetting: PTP-Berlin Protago-TEx-Production GmbH, www.ptp-berlin.eu

Printing and binding: Hubert & Co. GmbH & Co. KG, Göttingen

® Printed on acid-free paper

Printed in Germany

www.degruyter.com



Preface

Life sciences provide a significant source of some of the most challenging problems in modern applied mathematics, leading frequently to the necessity of studying complex systems and developing new systems-science-based approaches that are at the forefront of modern scientific thinking. Moreover, since our understanding of the complex systems in life sciences increasingly requires the development of new quantitative approaches, as well as on-going interactions and close collaboration between different disciplines, the fundamental role of interdisciplinary research at the interface of mathematics and life sciences will continue to grow in its importance.

Written by 22 experts from North America, Eurasia, and Australia, this book provides a selection of interdisciplinary areas at the interface of mathematical and life sciences where recent progress has been achieved and where new opportunities exist for exploring this interface. The book is aimed at researchers in academia, practitioners and graduate students who want to foster interdisciplinary collaborations required to meet the challenges at the interface of modern life sciences and mathematics. It can serve as a reference to state-of-the-art original works on the applications of mathematical, statistical and computational methods and tools in seemingly diverse, yet intrinsically connected, areas of life sciences.

The book provides a number of state-of-the-art surveys and topics accessible to graduate students and can serve as a source for graduate student projects. Supported by both rigorous mathematical procedures and examples from life science applications, the book has a strong multidisciplinary focus, promoting the methodology of mathematical analysis, modeling and computational experiment as a ubiquitous tool in applications to life sciences. Both groups of researchers, mathematicians who are interested in advanced applications and life scientists who would like to learn advanced mathematical tools and methodologies applicable in their disciplines, would benefit from this book.

We would like to thank the Alexander von Humboldt Foundation, the NSERC, and the CRC Program for their support. We are grateful to the referees whose help was invaluable. We are thankful to our many colleagues in Europe, North America, Asia, and Australia whose encouragements were vital for the completion of this project. Last but not least, we are thankful to the De Gruyter editors team, and in particular to Mrs. Friederike Dittberner, Mrs. Anja Möbius and Mrs. Hella Behrend, for their continuous support and assistance during the process of publishing this book.

Kyiv – Waterloo – Bilbao, December 2012

Alexandra V. Antoniouk
Roderick V. N. Melnik

Contents

1	Introduction	1
1.1	Scientific Frontiers at the Interface of Mathematics and Life Sciences <i>Alexandra V. Antoniouk and Roderick V. N. Melnik</i>	3
1.1.1	Developing the Language of Science and Its Interdisciplinary Character	3
1.1.2	Challenges at the Interface: Mathematics and Life Sciences ..	5
1.1.3	What This Book Is About	10
1.1.4	Concluding Remarks	14
2	Mathematical and Statistical Modeling of Biological Systems	17
2.1	Ensemble Modeling of Biological Systems	19
	<i>David Swigon</i>	
2.1.1	Introduction	19
2.1.2	Background	21
2.1.3	Ensemble Model	25
2.1.4	Computational Techniques	27
2.1.5	Application to Viral Infection Dynamics	30
2.1.6	Ensemble Models in Biology	34
2.1.7	Conclusions	36
3	Probabilistic Models for Nonlinear Processes and Biological Dynamics	43
3.1	Nonlinear Lévy and Nonlinear Feller Processes: an Analytic Introduction	45
	<i>Vassili N. Kolokoltsov</i>	
3.1.1	Introduction	45
3.1.2	Dual Propagators	49
3.1.3	Perturbation Theory for Weak Propagators	52
3.1.4	T -Products	54
3.1.5	Nonlinear Propagators	57
3.1.6	Linearized Evolution Around a Path of a Nonlinear Semigroup	60
3.1.7	Sensitivity Analysis for Nonlinear Propagators	64

3.1.8	Back to Nonlinear Markov Semigroups	66
3.1.9	Concluding Remarks	68
4	New Results in Mathematical Epidemiology and Modeling Dynamics of Infectious Diseases	71
4.1	Formal Solutions of Epidemic Equation	73
	<i>Vitaly A. Stepanenko and Nikolai Tarkhanov</i>	
4.1.1	Introduction	73
4.1.2	Epidemic Models	75
4.1.3	Formal Solutions	76
4.1.4	Separation of Variables	79
4.1.5	Solvability of General Equations	80
4.1.6	Concluding Remarks	84
5	Mathematical Analysis of PDE-based Models and Applications in Cell Biology	87
5.1	Asymptotic Analysis of the Dirichlet Spectral Problems in Thin Perforated Domains with Rapidly Varying Thickness and Different Limit Dimensions	89
	<i>Taras A. Mel'nyk and Andrey V. Popov</i>	
5.1.1	Introduction	89
5.1.2	Description of a Thin Perforated Domain with Quickly Oscillating Thickness and Statement of the Problem	90
5.1.3	Equivalent Problem	92
5.1.4	The Homogenized Theorem	94
5.1.5	Asymptotic Expansions for the Eigenvalues and Eigenfunctions	100
5.1.6	Conclusions	107
6	Axiomatic Modeling in Life Sciences with Case Studies for Virus-immune System and Oncolytic Virus Dynamics	111
6.1	Axiomatic Modeling in Life Sciences	113
	<i>Natalia L. Komarova</i>	
6.1.1	Introduction	113
6.1.2	Boosting Immunity by Anti-viral Drug Therapy: Timing, Efficacy and Success	115
6.1.3	Predictive Modeling of Oncolytic Virus Dynamics	123
6.1.4	Conclusions	138

7 Theory, Applications, and Control of Nonlinear PDEs in Life Sciences	145
7.1 On One Semilinear Parabolic Equation of Normal Type	147
<i>Andrei V. Fursikov</i>	
7.1.1 Introduction	147
7.1.2 Semilinear Parabolic Equation of Normal Type	148
7.1.3 The Structure of NPE Dynamics	153
7.1.4 Stabilization of Solution for NPE by Start Control	158
7.1.5 Concluding Remarks	159
7.2 On some Classes of Nonlinear Equations with L^1 -Data	161
<i>Alexander A. Kovalevsky</i>	
7.2.1 Nonlinear Elliptic Second-order Equations with L^1 -data	162
7.2.2 Nonlinear Fourth-order Equations with Strengthened Coercivity and L^1 -Data	178
7.2.3 Concluding Remarks	185
8 Mathematical Models of Pattern Formation and Their Applications in Developmental Biology	189
8.1 Reaction-Diffusion Models of Pattern Formation in Developmental Biology	191
<i>Anna Marciniak-Czochra</i>	
8.1.1 Introduction	191
8.1.2 Mechanisms of Developmental Pattern Formation	193
8.1.3 Motivating Application: Pattern Control in <i>Hydra</i>	194
8.1.4 Diffusive Morphogens and Turing Patterns	197
8.1.5 Receptor-based Models	200
8.1.6 Multistability	206
8.1.7 Discussion	207
9 Modeling the Dynamics of Genetic Mechanism, Pattern Formation, and the Genetics of “Geometry”	213
9.1 Modeling the Positioning of Trichomes on the Leaves of Plants	215
<i>Robert S. Anderssen, Maureen P. Edwards and Sergiy Pereverzyev Jr.</i>	
9.1.1 Introduction	215
9.1.2 Activator-inhibitor Reaction-diffusion Modeling of the Trichome Positioning	218
9.1.3 Hexagonal Recursion	221
9.1.4 Conclusions	225

10 Statistical Modeling in Life Sciences and Direct Measurements	229
10.1 Error Estimation for Direct Measurements in May–June 1986 of ^{131}I Radioactivity in Thyroid Gland of Children and Adolescents and Their Registration in Risk Analysis	231
<i>Illya Likhtarov, Sergii Masiuk, Mykola Chepurny, Alexander Kukush, Sergiy Shklyar, Andre Bouville and Lina Kovgan</i>	
10.1.1 Introduction	231
10.1.2 Materials and Methods	233
10.1.3 Conclusion and Discussion	239
10.1.4 Appendix. Approximation of Conditional Expectations	240
11 Design and Development of Experiments for Life Science Applications	245
11.1 Physiological Effects of Static Magnetic Field Exposure in an <i>in vivo</i> Acute Visceral Pain Model in Mice	247
<i>János F. László</i>	
11.1.1 Introduction	247
11.1.2 Methods	249
11.1.3 Results	256
11.1.4 Discussion	266
11.1.5 Conclusions	269
12 Mathematical Biomedicine and Modeling Avascular Tumor Growth	277
12.1 Continuum Models of Avascular Tumor Growth	279
<i>Helen M. Byrne</i>	
12.1.1 Introduction	279
12.1.2 Diffusion-limited Models of Avascular Tumor Growth	281
12.1.3 Tumor Invasion	289
12.1.4 Multiphase Models of Avascular Tumor Growth	295
12.1.5 Conclusions	303
Index	313

Alexandra V. Antoniouk and Roderick V. N. Melnik

1.1 Scientific Frontiers at the Interface of Mathematics and Life Sciences

Abstract. Many areas within life sciences are becoming increasingly quantitative and the progress in those areas will be more and more dependent on the successful development of advanced mathematical, statistical and modeling methodologies and techniques. This chapter provides a historical perspective at the interface between mathematics and life sciences and identifies a number of frontier areas where such methodologies and techniques have recently been developed.

Keywords. Coupled Dynamic System, Mathematical Modeling, Monte Carlo Method, Partial Differential Equation, Stochastic Process, Systems-Science-Based Approach

2010 Mathematics Subject Classification. 00A71, 92-02, 92-03, 92B05

1.1.1 Developing the Language of Science and Its Interdisciplinary Character

Mathematics has never been developed in isolation and has always been influenced by other disciplines, in turn offering to these discipline a universal language capable to significantly advance their own fields of knowledge. The intrinsic relationship between mathematics and science goes back to the dawn of human civilizations. For example, scientists in Ancient Egypt deduced their insights into the phenomena observed in nature by using quantitative representations, schemes, and figures. Geometry played a fundamental role in the Ancient World, while the summation series (most likely known in Ancient Egypt at least since the construction of the Chephren Pyramid of Giza in 2500 BCE) was the origin of harmonic design. A well-known example of such series is provided by the Fibonacci sequence, and in the context of life sciences the significance of the latter is hard to overestimate. We all know that the arrangements of leaves, flowers, seeds, petals, just to give a few examples, all demonstrate this sequence. Plenty of examples exist also in zoology, and multiple examples can be given for the human body too. Recall, for example, that the DNA (deoxyribonucleic acid) molecule measures 34 angstroms long by 21 angstroms wide for each full cycle of its double helix spiral. While 21 and 34 are subsequent numbers in the Fibonacci series, the ratio between 34 and 21 provides a good approximation to π .

In Ancient Greece, Pythagoras of Samos taught that reality is, at its deepest level, mathematical in nature and that numbers provide a key to the ultimate reality. Galileo, who later said that “the Book of Nature is written in the language of mathematics,” followed the Pythagorean tradition.

In the Ancient World in general, and in Greece in particular, the initial quantification of life sciences was driven by the development of agriculture and botany as a science. Aristotle himself, who lived during the 300s BCE, collected information about a variety of plants known at that time in the world, while his student Theophrastus classified them. Two other pillars of the initial quantification of life sciences at that time were studies in what was later called natural selection and zoology. Indeed, many Greek philosophers including Aristotle, who studied the manner in which species evolve to fit their environment, were important precursors in the development of modern evolutionary theories. The holistic view, evolving later in the systems science, including systems biology, was originated in the Ancient World. It was Aristotle who taught that “the whole is more than the sum of its parts,” emphasizing the importance of the systems science approach long before it started being developed theoretically.

Through these ancient traditions and first attempts of quantification of life sciences and Galileo’s vision on the fundamental role of mathematics in the description of all phenomena and processes in nature, perhaps one of the greatest stimuli for closer links between mathematics and life sciences was the rediscovery of G. Mendel’s laws in 1900 (originally presented and published in 1865–1866, [2]) and the subsequent growth of genetics. Based on natural selection, C. Darwin’s theory of evolution and the new science of genetics could barely co-exist at the time. It is mathematics that helped to resolve the crisis by what is now known as R. A. Fisher’s Fundamental Theorem of Natural Selection, formulated in his 1930 book [1]. The essence of this theorem is given in the form of a partial differential equation (PDE), expressing the fact that the rate of fitness increase for any living organism is determined by its genetic variance in fitness at the corresponding moment of time. This mathematical result gave a solid foundation for the development of population biology.

Since the beginning of the 20th century, mathematical models have started to play an ever increasing role in the life sciences. Examples include L. Michaelis and M. L. Menten’s equation for enzyme kinetics (1913), J. B. S. Haldane’s equation for genetic mapping (1919), A. J. Lotka and V. Volterra’s predator-prey systems (1925–1931), A. A. Malinovsky’s models for evolutionary genetics and systems analysis (1935), R. Fisher and A. Kolmogorov equation for gene propagation (1937), A. L. Hodgkin and A. F. Huxley’s equations for neural axon membrane potential (1952), and many others. Many such models are based on coupled systems of equations, most typical for life science applications. It is also important to realize that the influence of mathematics on the life sciences has been magnified by the development of mathematics-based new technologies in the applications of these disciplines and medicine. A now classical example of that is A. M. Cormack’s equation for the representation of a function by its line integrals (1963), which inspired the field of computer-assisted tomography,

medical and
already laid i

The devele
matics and th
fact that only
science front
developed by
A. Gierer an
at the interfa
detailed mot
new data-dir
computation.

As we kno
history have
surprise that
time of natu
it “expressed
scientific cor
ness of math.
Moreover, th
tests from di
before in the
the long his
but in the s
places of life
insects new

1.1.2 Ch

Many areas
independen
vided by th
of the two-s
use, while t
benefits fro
surface.

Nowaday
perimental
disciplines as
mathematic
and deliver

medical and biological imaging. Notwithstanding that the fundamentals for this were already laid in 1917 by the mathematical works of J. Radon.

The development of such theories as self-organization and biological pattern formation provides another important example where the cross-fertilization between mathematics and the life sciences has been profoundly influential, clearly demonstrating the fact that only through interdisciplinary efforts can substantial progress be made at the science frontiers. This development is dotted with now classical mathematical models developed by A. J. Lotka, d'A. Thomson, A. Turing, B. Belousov and A. Zhabotinski, A. Gierer and H. Meinhardt, among many others. Much of the current development at the interface of mathematics and life sciences is influenced by the availability of detailed molecular, functional, and genomic data. This leads to the development of new data-driven mathematical models, and the tools of mathematical modeling and computational experiments are becoming largely important in today's life sciences.

As we know, the interactions between mathematics and life sciences through their history have not always been easy. Indeed, to mathematicians it should not come as a surprise that many life scientists would not accept a view that "in every special doctrine of nature only so much science proper can be found as there is mathematics in it," expressed by I. Kant back in 1786. However, there is a growing recognition in the scientific community of what E. Wigner called in 1960 "the unreasonable effectiveness of mathematics in the natural sciences," and the life sciences are not an exception. Moreover, the interdisciplinary nature of science makes collaborations between scientists from different disciplines and mathematicians a necessity that is, more than ever before in the history of science, appreciated by the scientific community. Looking at the long history of interaction between the mathematical and life sciences, it is clear that in this ongoing process mathematics has become pervasive across many disciplines of life sciences, while the interface between these disciplines and mathematics fosters new methods, tools, and approaches in both areas.

1.1.2 Challenges at the Interface: Mathematics and Life Sciences

Many areas of life sciences have been profoundly influenced by mathematics, while indispensable stimuli for new advances in mathematical disciplines have been provided by fundamental challenges coming from the life sciences. The current breadth of the two-way interaction between mathematics and life sciences is already impressive, while the potential of this interaction is virtually unlimited. Moreover, substantial benefits from the continuous deepening of such interaction lie on both sides of the interface.

Nowadays, many disciplines in life sciences routinely apply mathematics-based experimental techniques. The design and increasing quality of measurements in such disciplines as structural, cellular and molecular biology require the development of new mathematical algorithms, methods, and tools. For example, in the area of drug design and delivery, optimization and control tools, along with graph theoretical approaches,

have become ubiquitous. Mathematics has played an important role in the areas ranging from genetic mapping and cell dynamics to the study of functions of biological systems, from the study of organs to the study of organisms, covering a wide spectrum of life science disciplines, from medicine to ecology, from physiology to neuroscience and to bio-nanotechnological innovations.

Mathematical modeling tools, ranging from continuum-mechanics based models to Molecular Dynamics Simulation and Monte Carlo procedures, are fundamental to the progress made in the areas of bio-mechanics and bio-tissue engineering, membrane and cell biology, studying properties of macromolecules, such as DNA, RNA, proteins, and complex biophysical phenomena in biological systems. Apart from more traditional applications of approximation theory and statistics, other mathematical disciplines such as differential geometry and topology are becoming increasingly important in life sciences. In turn, such problems as sequencing macromolecules, already present in biological databases, provide an important catalyst for the development of new mathematics, new efficient algorithms and methods. The influence of mathematics on life sciences can be both direct and indirect, sometimes appreciated many years later. The importance of Euclidian geometry in life sciences that has been with us since 300 BCE is hard to overestimate. Only in 1830 did the mathematical world come to know the non-Euclidian geometries of J. Bolyai and N. I. Lobachevsky. Yet it was many years later (around 1999–2003) when scientists realized that these seemingly very abstract mathematical constructs can be applied in the flat mapping of the human cerebellum. Similarly, it was in the 1970s when we learned about B. Mandelbrot's fractal geometry where symmetry across scales plays a fundamental role. But it was only years later when life scientists found that many biological processes and systems, including human organs from the bronchi to the liver, can be well described by using methods of fractal geometry. A classical example of the impact of life sciences on mathematics is the discovery of what is now called Brownian motion. The microscope was discovered in the late 17th century and in 1827, R. Brown, a Scottish botanist, was examining under a microscope grains of pollen of Clarkia pulchella plant suspended in water. Years later, it was the basis for the development of a mathematical theory that nowadays is pivotal in probability theory and numerous applied branches of mathematics. New challenges in life sciences provide a great impetus for dynamical systems theory, differential equations (partial, stochastic, integro-differential), mathematical modeling, geometry and topology, data mining, mathematical and numerical analysis, and other branches of modern mathematics.

It is also well known that the development of game theory, and contributions by von Neumann in particular, as well as the development of control theory and cybernetics by N. Wiener, were influenced by the development in life sciences. In turn, the growth of the systems science has provided one of the fundamental corner stones for the development of systems biology where biological systems (e.g., cells, organisms) are considered in a holistic way (recall Aristotle's quote from our Section 1.1.1). This new discipline aims at accounting the interactions between different components of a

biological system and the behavior of the system are a consideration is a complex systems is often once said "If the contribution of mathematics in biology would be known, it would be nowdays for granted."

Present day life science application of mathematics are rapidly. They include:

- Systems biology in life fields, e.g., cells, organs, their systems, studies of human diseases;
- Dynamics of complex interactions: mathematical biology, & cell biology;
- Mathematical modeling of evolution and evolution;
- Mathematical biology dealing infectious diseases and resistance;
- Genomics and proteomics: synthesis in control, regulation, gene decisions, and the genome;
- Self-assembly and order waves and collective phases in biology;
- Mathematical modeling of properties, dynamics, and structures;
- Mathematical modeling of data, including tomography and imaging.

biological system at different scales (e.g., from the molecular to the systemic level). Mathematically speaking, we have to account for a multiscale spatio-temporal character of the system and an intrinsic interplay of its components. What comes out of such a consideration is one of the important examples of complex systems. Mathematics of complex systems is at the beginning of its development. On the other hand, as J. E. Cohen once said “if every biologist who plotted data on x–y coordinates acknowledged the contribution of Descartes to biological understanding, the key role of mathematics in biology would be uncontested.” Recall that this link of geometry and algebra, taken nowadays for granted, was made by René Descartes back in 1637.

Present day life sciences comprise a vast range of different disciplines where the application of mathematical, statistical and computational science tools is growing rapidly. They include, but are not limited to, the following (frequently interconnected) areas:

- Systems biology and medicine, including direct and inverse problems applied to specific fields, e.g. cellular systems biology, systems oncology, etc., studies of various organs, their systems and functions, e.g., cardiac and skeletal-muscular functions, studies of human tissues and blood flow, etc.;
- Dynamics of complex biological networks, including regulatory networks, their interactions; mathematical models for cell biology, including cell dynamics, membrane biology; developing complex signaling models and their applications;
- Mathematical models in neuroscience and physiology, developmental biology, evolution and evolutionary dynamics of biological games;
- Mathematical biomedicine, including immunology problems, epidemiology, modeling infectious diseases, mathematics of clinical trials, drug development, delivery, and resistance;
- Genomics and genetics research, including the analysis of the mechanism of protein synthesis in control of gene expression (and in cells), molecular machines and gene regulation, gene regulatory networks governing cell proliferation and differentiation decisions, and the developing strategies to control genetic expressions;
- Self-assembly and spatio-temporal pattern formation in biological systems; nonlinear waves and excitable systems, including nonlinear reaction-diffusion systems, phases in biological systems, phase transitions, etc.;
- Mathematical models for bio-macromolecules, including DNA, RNA, proteins, their properties, dynamics, and interactions at various length and time scales;
- Mathematical models for industrial biotechnology and biotechnological applications, including bio-nanotechnology, bio-imaging, reconstructions of computerized tomography scans, etc.;

- Bionics and using nature's ideas in creating artificial bio-tissues, bio-sensors and bio-actuators, etc.; studies into coupled systems and coupled effects in biological systems, e.g., piezoeffect, chemotaxis, phototaxis, new biophysical phenomena and new models for photosynthesis, biological fluid dynamics and fluid-structure interactions in biological systems, etc.;
- Mathematics in other areas of life sciences, including ecology in general and microbial (food, environment) ecology in particular, protecting ecosystems, homeland security, sustainability, plant biology and agriculture, etc.

The problems we encounter in these areas require a variety of methods and tools from mathematical, statistical and computational sciences. For example, probabilistic graphical models are essential in the analysis of cellular networks, while computational methods are playing a fundamental role in studies of cellular signaling, pathways, and signal transduction. Ordinary, partial, integro-differential, functional, and stochastic differential equations, methods of dynamical systems theory, neural networks, singularity theory, discrete mathematics approaches, tools from statistics and algebraic geometry, to name just a few, have all brought their invaluable contributions to life sciences, enriching the body of knowledge so important in our further progress.

While these mathematical, statistical and computational tools are ubiquitous and are frequently applied in other areas of human endeavors, their applications in life sciences have certain specifics.

Firstly, compared to many physical or engineering systems, where mathematical theories, tools and methods have long played a profound role in their understanding and quantification, well beyond the descriptive level (still typical for many life science disciplines), our knowledge of biological systems is quite limited. It should not come as a surprise as most biological theories are of recent origin, now undergoing profound transformations.

Secondly, one of the consequences of biological system complexity lies with the fact that most systems we have to deal with are highly heterogeneous with their parts interacting on a large range of spatio-temporal scales, often exhibiting non-deterministic behavior. Indeed, many problems that appear in life sciences involve systems that are only partially understood. They are inherently uncertain, demanding their studies with new mathematical tools. Attempts to analyze such systems with conventional methods of mathematical analysis almost inevitably lead to a situation where our models remain often over-simplified, compared to their real-world biological prototypes. Therefore, while in the analysis of physical and engineering systems we often look for simplified mathematical models to understand and explain the data we have, in life sciences it may not always be the case (as many historical examples, including A. Turing's example, clearly show). Similarly to physical and engineering sciences, the development of more realistic mathematical models in life sciences leads frequently to coupled systems of equations, e.g., coupled PDEs. Efficient mathematical and computational methodologies for their solutions have to often account for the multiscale character of

the problem. In their development the study of the networks and governing the dynamics are usually in models not being cells, is influenced, the models to deal with the mechanical mechanics, from corresponds.

Mathematics result, the role of indeed, mathematics need for better to the model so data that can using algorithms, algorithms and extract from of and modeling phenomena, part of life sciences in the analysis step should be predictive capability of mathematics efficient discus

At the same spatio-temporal may lead to set parameter idea more close in experimental techniques but

Finally, we areas of life science limited number This view not their modern c

the problem. In a large variety of situations such methodologies are at the beginning of their development. Typical examples of such problems are coming from cell biology, the study of metabolic pathways, and complex networks (e.g., biochemical reaction networks and genomic interactions via gene regulatory networks). Moreover, in studying the dynamics of such complex biological networks, stochastic mathematical models are usually needed, with non-equilibrium mathematical and statistical mechanics models not being uncommon. Indeed, any biological system, comprising interacting cells, is influenced (already at the cell level) by a variety of external factors. As a result, the models and approaches developed for physical systems may not be sufficient to deal with this biological complexity. However, based on non-equilibrium statistical mechanics, we can still get a flavor of system behavior at the macroscopic level from corresponding moments of the distribution function taken over the microscopic states.

Mathematical models are at the heart of predictive capabilities of life sciences. As a result, the role of mathematical modeling in life sciences has continued to increase. Indeed, mathematical modeling not only can support theories, but can often suggest the need for better experiments and more focused observations, providing in turn a check to the model accuracy. Observations and experiments may produce large amounts of data that can only be intelligently processed with efficient mathematical data mining algorithms, powerful statistical and visualization tools. The application of these algorithms and tools require a close collaboration between mathematicians and scientists from other respective disciplines. Thus, observations and experiments, theory and modeling reinforce each other, leading together to our better understanding of phenomena, processes, and systems we study. With the increase in data in some areas of life sciences (e.g., genomic research), bioinformatics has played an important role in the analysis of such data. This increase in data has also clearly shown that the next step should lie with the integration of this data with mathematical models possessing predictive capabilities. Indeed, this step is essential in making us closer to the application of mathematics in such important areas as clinical research and practice, including efficient disease treatments.

At the same time, many complex biological systems are still hard to measure on spatio-temporal scales required for their understanding. This lack of measurements may lead to serious constraints on the application of conventional methods for systems parameter identification and estimation. At the same time, it leads to the necessity of more close interactions between mathematical modeling, computational analyses and experimental approaches, paving the way for the development of new mathematical techniques based on inverse problem analysis and their applications in life sciences.

Finally, we mention that the development of a holistic view already pursued in many areas of life sciences and generically termed as systems biology, opens a practically unlimited number of avenues for exploring the interface of mathematics and life sciences. This view not only is crucial in a large body of disciplines within life sciences to meet their modern challenges, but also provides an important stimulus for the development

of new models, methods and techniques in mathematical sciences in response to those challenges.

1.1.3 What This Book Is About

The book contains 12 state-of-the-art surveys and research articles at the interface of mathematics and life sciences. It is based on selected invited contributions by researchers from Europe, North America, Asia, and Australia. The book presents a broad spectrum of mathematical, statistical and computational methods important in life sciences, as well as some representative examples of modern problems from life sciences where the development of new mathematical approaches is required. After this introductory chapter, each remaining chapter stands alone as a survey or in-depth research within a specific area, exploring the interface of mathematics and life sciences. In what follows, we highlight the main features of each such chapter.

- **Mathematical and Statistical Modeling of Biological Systems.** A survey of a new type of mathematical models in life sciences, termed ensemble models, is given by D. Swigon (Pittsburg, USA). These models are extensions of conventional deterministic or stochastic mathematical models to the situations where we have small or extensive amount of data. Such models are identified and their parameters are estimated by using Bayesian techniques. Examples are given for viral infection dynamics modeling. Computational techniques, implementation of ensemble models, as well as open problems are also discussed.
- **Probabilistic Models for Nonlinear Processes and Biological Dynamics.** An introductory survey to the important analytical aspects of mathematical models based on general non-linear Markov processes is given by V. N. Kolokoltsov (Warwick, UK). Among such processes are Levy and Feller processes, as well as nonlinear Markov chains. The author demonstrates mathematical tools that are important in the study of replicator dynamics in evolutionary biology and have potential for applications in many other areas of life sciences.
- **New Results in Mathematical Epidemiology and Modeling Dynamics of Infectious Diseases.** A detailed mathematical analysis leading to formal solutions of general epidemic equations is carried out by V. A. Stepanenko (Krasnoyarsk, Russia) and N. Tarkhanov (Potsdam, Germany). The authors' analysis is, in fact, performed even for a more general equation describing Markov stochastic processes, of which an epidemic equation is a particular example. Their explicit solution may provide a new efficient way for modeling the transmission of infectious diseases in living organisms.
- **Mathematical Analysis of PDE-based Models and Applications in Cell Biology.** Spectral problems with rapidly oscillating coefficients are analyzed by T. A. Mel'nyk and A. V. Popov (Kyiv, Ukraine). Such problems arise in numerous life science

applications and
ncular, certain b
processes) can b
with a rapidly o
assess in the dev
amisms for dam
ensions for the
complete asymp
useful in other a

• **Axiomatic Model**
tem and Oncol
iomatic modelin
ges that, unlike
stance to the a
time, mathemat
formulate assun
ited biologic
allows us to mo
sponding mode
boosting immu
ficiency and suc
data for hepatic
can also be appl
virus (HIV). Th
for oncolytic vi
spread, as well a
nations of the a

• **Theory, Appli**
area encompasses
ematics, and is
and computatio
us get further in
cesses. The wo
the basis of PD
tions of normal
is on the devel
find importan
ematically, the
solution to the
tion of normal

applications and the authors focus on one of them, pertinent to cell biology. In particular, certain biophysical processes within biological cells (e.g., some metabolic processes) can be described by boundary value problems in thin perforated domains with a rapidly oscillating boundary. The corresponding mathematical models may assist in the development of new methods of diagnostics and new healing mechanisms for damaged cells. The analysis of such models, based on asymptotic expansions for the eigenvalues and eigenfunctions, is carried out for different limit dimensions and a new homogenization theorem is established. These results and the complete asymptotic expansions constructed by the authors may also prove to be useful in other areas of life sciences.

- **Axiomatic Modeling in Life Sciences with Case Studies for Virus-Immune System and Oncolytic Virus Dynamics.** Approaches based on what is termed as “axiomatic modeling” are surveyed by N. L. Komarova (Irvine, USA). The author argues that, unlike physics or chemistry, life sciences still demonstrate notable resistance to the application of conventional mathematical approaches. At the same time, mathematical modeling provides an appropriate framework in these fields to formulate assumptions in a quantitative way. It is demonstrated that despite very limited biological knowledge about the systems of interest, the axiomatic approach allows us to make some nontrivial statements based on the analysis of the corresponding models. The first case study is considered in the context of strategies for boosting immunity by anti-viral drug therapy and discusses the issues of timing, efficacy and success of such a therapy. The model is considered on the example of data for hepatitis C virus (HCV). However, the developed theoretical framework can also be applied to other situations, e.g., in the case of human immunodeficiency virus (HIV). The second case study concerns the construction of a predictive model for oncolytic virus dynamics where the author analyzes different scenarios of virus spread, as well as stability properties of equilibrium solutions. Advantages and limitations of the axiomatic modeling approach are also discussed.
- **Theory, Applications, and Control of Nonlinear PDEs in Life Sciences.** This area encompasses many different topics at the interface of life sciences and mathematics, and is represented in this chapter by two papers. Mathematical modeling and computational experiments help better understand biological systems, as well as get further insight into many biophysical and biochemical phenomena and processes. The workhorse for many mathematical models in life sciences is built on the basis of PDEs. In this chapter, a detailed analysis of semilinear parabolic equations of normal type is given by A. V. Fursikov (Moscow, Russia). The main focus is on the development of various tools for damping turbulence in fluid flows which find important applications in biology and medicine, among other disciplines. Mathematically, the problem is studied in the context of theory of stabilization of the solution to the Navier–Stokes equations by feedback control. Details of the derivation of normal parabolic equations, the structure of dynamics of such equations and

stabilization of their solutions by starting control are discussed. The tools developed could be important in a range of applications of biological fluid dynamics. The other paper in this chapter, by A. A. Kovalevsky (Donetsk, Ukraine), focuses on nonlinear PDE equations with L^1 data. The author provides a survey of results on the existence and properties of solutions to several classes of nonlinear second- and fourth-order equations. As many applied mathematics problems in life sciences do not possess higher regularity, the analysis provided here is important. The author notes that in particular cases, the principal parts of analyzed equations can be generalized by the p-Laplacian operator, which arises naturally in the context of the Navier–Stokes equations describing the motion of non-Newtonian fluids. The author describes different kinds of solutions to his PDE-based models such as entropy and proper entropy solutions. Among other areas, the applications of these results are important in the study of the motion of non-Newtonian fluids, e.g., blood flow, synovial fluid, saliva, etc. Other applications include problems related to modeling biological pattern formations, as well as the interaction of diffusing biological species.

- **Mathematical Models of Pattern Formation and Their Applications in Developmental Biology.** Developmental biology deals with the entire range of biological complexity of living organisms, e.g., from egg to embryo. This area provides a very fertile ground for the formulation of mathematical models, their analysis, developing efficient numerical techniques, and subsequent computational experiments. This area is represented in this chapter by a paper aiming at a better understanding of developmental processes via the study of pattern formation. Based on reaction-diffusion equations, the paper by A. Marciniak-Czochra (Heidelberg, Germany) focuses on the study of a symmetry break and formation of spatially heterogeneous structures during development. A detailed analysis is given for two important cases of pattern formation: (a) diffusion-driven instability (Turing instability) and (b) a hysteresis-driven mechanism. The author demonstrates main possibilities of these mechanisms and their constraints in explaining different aspects of structure formation in cell systems. The results are discussed in the context of morphogenesis of a fresh water polyp, known as a model organism in developmental biology.
- **Modeling the Dynamics of Genetic Mechanisms, Pattern Formation, and the “Genetics of Geometry”.** One of the challenging problems in life sciences in general, and in plant science in particular, is the recovery of information about the dynamics of genetic mechanisms by which biological systems (e.g., plants) can control the development of their various topological/geometrical features. In this chapter, R. S. Anderssen (Canberra, Australia), M. P. Edwards (Wollongong, Australia), and S. Pereverzyev Jr. (Linz, Austria) address this problem in the context of the positioning of trichomes on the leaves of plants. The authors compare the application of reaction-diffusion models to this problem with cellular signaling and switching models. It is demonstrated that in order to better understand genetic control mechanisms,

leading to significant biological effects is essential to understand the underlying mechanisms of a new Andean plant species. The sorting of the seeds is done by hand.

- **Statistical Methods for Nonparametric Data.** Nonparametric methods represent an important class of statistical methods. They are used to analyze data sets where the underlying distribution is not specified or is not fully known. The development of nonparametric methods has been driven by many areas of application, including medical statistics, engineering, and economics. In this chapter, S. Shklyar (Lviv, Ukraine) and V. Chepurnyj (Lviv, Ukraine) present a review of nonparametric methods for regression analysis. They develop a unified approach to nonparametric regression, which involves both parametric and nonparametric methods. The Berkson error model is needed for the construction of nonparametric regression models. They also discuss the use of nonparametric methods in medical statistics, where they provide a nonparametric approach to the analysis of survival data.
- **Design and Development of Diagnostic Tools for Clinical Applications.** Diagnostic tools are an important part of modern medicine. They help to detect diseases early and to monitor their progression. In this chapter, J. C. Gómez (Budapest, Hungary) presents a review of diagnostic tools for clinical applications. He discusses the design and development of diagnostic tools for various diseases, including cancer, heart disease, and diabetes. He also discusses the use of machine learning and deep learning for the development of diagnostic tools. The author shows how machine learning can be used to improve the accuracy and efficiency of diagnostic tools. He also discusses the challenges and opportunities for the development of diagnostic tools in the future.
- **Mathematical Models of Plant Growth and Development.** Plants are one of the biggest sources of biomass on Earth. They play a crucial role in the environment, providing oxygen, removing carbon dioxide, and producing food and fiber. In this chapter, S. Pereverzyev Jr. (Linz, Austria) presents a review of mathematical models of plant growth and development. He discusses the basic principles of plant growth and development, including the regulation of gene expression, the control of cell division, and the control of cell differentiation. He also discusses the use of mathematical models to predict plant growth and development under different environmental conditions. The author shows how mathematical models can be used to optimize plant growth and development for various applications, such as agriculture and biotechnology.

leading to signaling and switching between cells to produce the observed patterns, it is essential to utilize cellular models of the plant organ. Furthermore, the authors put their research on the positioning of trichomes on the leaves of plants in the context of a new Anderssen–Pereverzyev framework for performing the biocombinatorial sorting of the known genes to be involved into biomechanistic categories.

- **Statistical Modeling in Life Sciences and Direct Measurements.** Measurements represent an important part of research tools intrinsic to life sciences. A natural question that arises once such measurements are completed is that of error estimations. The development of statistical models for such estimations is fundamental to many areas of life sciences. This is the subject of a paper presented by the group of researchers from the Center for Radiation Medicine (I. Likhtarov, S. Masiuk, M. Chepurny, L. Kovgan), National T. Shevchenko University of Kyiv (A. Kukush, S. Shklyar) in Ukraine and the National Cancer Institute (A. Bouville) in the USA. They develop a new statistical model for radioactivity measurements. The model involves both classical and Berkson measurement errors. While in the estimation of the Berkson error the Monte Carlo method can be applied, a new methodology is needed for the classical error estimation. They carry out a detailed risk analysis where they propose two methods to characterize dose uncertainty, based on parametric and non-parametric calibrations.
- **Design and Development of Experiments for Life Science Applications.** A vast range of mathematical, statistical, and operation research tools are required in this area which is represented in this chapter by a new quantitative study of *in vivo* biological responses to static magnetic field exposure. In a paper by J. F. László (Debrecen, Hungary) this study is largely motivated by an ever increasing interest in this topic due to the proliferation of high field magnetic resonance tomography in medical diagnostics. It is an important example of the situations where it is fundamental to optimize the experiment in methods, in materials, as well as conceptually. In doing so, we are making a step toward increasing the interest of clinical practitioners to the results of mathematical, statistical and computational modeling. In the current paper, the author deals with mathematical modeling in physiology, which is frequently defined as the science of the function of living systems. The study involves the analysis of static magnetic field known to induce a wide range of biological responses. In particular, this field can induce analgesic effects in humans. Since pain is a very complex state that involves both central and peripheral mechanisms, to study such effects is an extremely difficult task. The author provides a detailed account on recent progress in this field, focusing on statistical and experimental models. Based on his finding, suggestions for SMF-based devices for therapy are also given.
- **Mathematical Biomedicine and Modeling Avascular Tumor Growth.** One of the biggest challenges in life sciences in general, and in biomedicine in particular, lies with the development of mathematical models for various diseases in order to

assist clinical practitioners and help the advancement of strategies for disease treatments. In this chapter a comprehensive survey of a series of increasingly complex mathematical models for avascular tumor growth is given by H. Byrne (Oxford, UK), with the major focus on continuum models. These include two-dimensional models that can be used to determine the stability of radially-symmetric solutions to symmetry-breaking perturbations, allowing the establishment of conditions under which the growth remains localized or invasive. Tumor growth is one of the primary challenges of cancer research. Its dynamics features a range of different scales, from molecular to macroscopic, and its treatment seems to require new, systems biomedicine based, approaches. In this chapter the author explains how the existing models are inter-related as well as the biophysical insight that they provide. A discussion of the theoretical challenges that lie ahead is also given.

1.1.4 Concluding Remarks

In this chapter we have presented a selection of topics, representing part of a vast spectrum of the interface between mathematics and life sciences. The chapters that follow provide a unique collection of in-depth mathematical, statistical, and modeling methods and techniques for life sciences, as well as their applications in a number of areas within life sciences. They also provide a range of new ideas that represent emerging frontiers in life sciences where the application of such quantitative methods and techniques is becoming increasingly important. It is hoped that many mathematical, statistical, and computational tools presented in this book will help address current and future challenges in life sciences. Such challenges lie in different spatio-temporal scales, from genetic and molecular levels to cells, to whole organisms and to the level of entire ecosystems, from fractions of a second to the evolutionary scale. Therefore, we also hope that problems arising in life sciences will provide an exciting ground and continuous stimulus for the development of new theories, methods, and tools in mathematical, statistical, and computational sciences.

We are convinced that since our understanding of the complex systems we encounter in life sciences increasingly requires the development of new quantitative approaches, as well as on-going interactions and close collaboration between different disciplines, the fundamental role of interdisciplinary research at the interface of mathematics and life sciences will continue to grow in its importance.

Bibliography

- [1] R. A. Fisher: *The Genetical Theory of Natural Selection*. Clarendon Press, Oxford, 1930.
- [2] G. Mendel: Versuche über Pflanzen-Hybriden. *Verhandlungen des Naturforschenden Vereins zu Brünn* **4** (1866), 3–47.

Author Information

Alexandra V. Antonevich
Ukraine, Kyiv, Ukraine
E-mail: antonio@kpf.kiev.ua

Roderick V.N. Melnik
ON, Canada
Borja Ibarbaque, Basque Country
E-mail: rmelnik@umanitoba.ca

Author Information

Alexandra V. Antoniouk, Institute of Mathematics National Academy of Sciences
Ukraine, Kyiv, Ukraine
E-mail: antoniouk@imath.kiev.ua

Roderick V. N. Melnik, M²NeT Laboratory, Wilfrid Laurier University, Waterloo,
ON, Canada;
Ikerbasque, Basque Foundation for Science and BCAM, Bilbao, Spain
E-mail: rmelnik@wlu.ca

This book contains 12 state-of-the-art surveys and research articles at the interface of mathematics and life sciences. It is based on selected invited contributions by researchers from Europe, North America, Asia, and Australia. The book presents a broad spectrum of mathematical, statistical and computational methods important in life sciences, as well as some representative examples of modern problems from life sciences where the development of new mathematical approaches is required. After an introductory chapter, each remaining chapter stands alone as a survey or in-depth research within a specific area, exploring the interface of mathematics and life sciences.

The main areas covered in this book are: mathematical and statistical modelling of biological systems, probabilistic models for nonlinear processes and biological dynamics, new results in mathematical epidemiology and modelling dynamics of infectious diseases, mathematical analysis of PDE-based models and applications in cell biology, axiomatic modelling in life sciences with case studies for virus-immune system and oncolytic virus dynamics, theory, applications, and control of nonlinear PDEs in life sciences, mathematical models of pattern formation and their applications in developmental biology, modeling the dynamics of genetic mechanisms, pattern formation, and the „genetics of geometry“, statistical modeling in life sciences and direct measurements, design and development of experiments for life science applications, mathematical biomedicine and modelling avascular tumour growth.

THE SERIES: DE GRUYTER SERIES IN MATHEMATICS AND LIFE SCIENCES

The De Gruyter Series in Mathematics and Life Sciences is devoted to the publication of monographs in the field. They cover topics and methods in fields of current interest that use mathematical approaches to understand and explain, model and influence phenomena in all areas of life sciences. This includes, among others, theory and application of biological mathematical modeling, complex systems biology, bio-informatics, computational biomodeling stochastic modeling, biostatistics, computational evolutionary biology, comparative genomics, or structural bioinformatics. Also, new types of mathematical problems that arise from biological knowledge shall be covered.



www.degruyter.com

ISBN 978-3-11-027372-4

9 783110 273724