

# mathematical modeling in systems biology

Mathematical Modeling in Systems Biology: Unlocking the Complexity of Life

**mathematical modeling in systems biology** serves as a powerful approach to unraveling the intricate networks and dynamic processes that govern living organisms. As biology has evolved from descriptive studies to a more quantitative science, mathematical models have become indispensable tools for understanding how biological systems function at multiple scales. From gene regulation to cellular signaling and metabolic pathways, these models allow scientists to simulate, predict, and manipulate biological behavior in ways that traditional experimentation alone cannot achieve.

## What Is Mathematical Modeling in Systems Biology?

At its core, mathematical modeling in systems biology involves the use of mathematical equations and computational techniques to represent biological processes. Unlike classical biology, which often focuses on isolated components, systems biology seeks to understand how different parts interact as a whole. Models provide a framework to capture these interactions, describing how molecules, cells, and tissues behave over time and under varying conditions.

These models can be deterministic or stochastic, continuous or discrete, depending on the nature of the biological system and the questions being asked. For example, ordinary differential equations (ODEs) are commonly used to model biochemical kinetics, while agent-based models might simulate the behavior of individual cells within a tissue.

## The Role of Mathematical Models in Biological Research

Mathematical models are not just theoretical constructs; they actively guide experiments and help interpret complex datasets. They can:

- Predict the outcome of genetic mutations or drug treatments before conducting costly lab experiments.
- Reveal hidden regulatory mechanisms by fitting models to experimental data.
- Quantify system robustness and identify potential failure points.
- Facilitate the integration of multi-omics data, combining genomics, proteomics, and metabolomics.

By creating a virtual laboratory, researchers can test hypotheses rapidly, refine their understanding, and design better experiments.

## Types of Mathematical Models Used in Systems Biology

Understanding the diversity of models helps appreciate how versatile mathematical modeling in systems biology truly is. Here are some commonly employed frameworks:

## Deterministic Models

Deterministic models rely on fixed equations where the same input leads to the same output every time. These models are often based on ODEs or partial differential equations (PDEs) to describe continuous changes, such as enzyme kinetics or population dynamics. They are particularly useful when dealing with large numbers of molecules where random fluctuations average out.

## Stochastic Models

In contrast, stochastic models account for randomness and noise inherent in biological systems, especially at low molecule counts. For example, gene expression can be highly variable from one cell to another. Stochastic models use probability distributions and methods like the Gillespie algorithm to simulate these fluctuations, providing a more realistic picture of cellular behavior.

## Boolean and Logical Models

When quantitative data is limited, Boolean models come into play. These models simplify components to binary states (on or off) to explore regulatory networks and signal transduction pathways. Despite their simplicity, they can capture essential dynamics and identify key control points within complex networks.

## Agent-Based Models

Agent-based models simulate individual entities, such as cells or molecules, each with their own set of rules governing behavior and interactions. This bottom-up approach is powerful for studying emergent phenomena like tissue morphogenesis or immune responses, where collective behavior arises from numerous individual actions.

## Applications of Mathematical Modeling in Systems Biology

The practical uses of mathematical modeling in systems biology span a wide range of fields and biological scales.

### Understanding Cellular Signaling Networks

Cell signaling is a complex web of interactions that control cell fate decisions like proliferation, differentiation, and apoptosis. Mathematical models help decode these networks by identifying feedback loops, crosstalk between pathways, and potential points of intervention. For example, models of the MAPK/ERK pathway have shed light on cancer progression and therapeutic targets.

# **Metabolic Engineering and Synthetic Biology**

By modeling metabolic pathways, researchers can predict how altering enzyme activities affects the production of metabolites. This insight is key for bioengineering microbes to produce pharmaceuticals, biofuels, or other valuable compounds. Synthetic biology also leverages models to design genetic circuits with desired behaviors, accelerating the development of biological machines.

## **Disease Modeling and Drug Development**

Mathematical models assist in understanding disease mechanisms, from infectious diseases to chronic conditions like diabetes or neurodegeneration. They allow simulation of drug responses, optimization of dosage, and prediction of side effects. In personalized medicine, patient-specific models can tailor treatments based on individual molecular profiles.

## **Challenges and Future Directions**

While mathematical modeling in systems biology holds enormous promise, it also faces several challenges that researchers continually strive to overcome.

## **Data Integration and Model Validation**

Biological data is often noisy, incomplete, and generated from diverse sources. Integrating multi-scale data into coherent models requires sophisticated computational tools and careful validation against experimental results. Without rigorous validation, models risk being oversimplified or misleading.

## **Model Complexity and Interpretability**

As models grow more detailed, they can become computationally expensive and difficult to interpret. Striking a balance between model accuracy and simplicity is essential to maintain usability and generate meaningful biological insights.

## **Bridging Scales from Molecules to Organisms**

One of the ultimate goals is to connect molecular-level events with organism-level phenotypes. This multiscale modeling remains a formidable task due to the vast differences in time scales, spatial organization, and biological complexity.

# Advances in Machine Learning and AI

Emerging technologies like machine learning are increasingly integrated with traditional modeling approaches. AI can help identify patterns in large datasets, optimize model parameters, and even generate hypotheses. This synergy promises to accelerate discoveries in systems biology.

## Tips for Effective Mathematical Modeling in Systems Biology

If you're venturing into mathematical modeling within systems biology, here are some insights to keep in mind:

- **Start Simple:** Begin with the most essential components and gradually add complexity. Simple models often provide valuable intuition.
- **Collaborate Across Disciplines:** Combining expertise from biology, mathematics, and computer science enriches model development and interpretation.
- **Use Open-Source Tools:** Platforms like COPASI, CellDesigner, and SBML facilitate model building, simulation, and sharing within the scientific community.
- **Iterate Between Experiment and Model:** Let experimental data refine your models, and use your models to guide new experiments.
- **Keep Biological Relevance:** Ensure your mathematical assumptions reflect realistic biological behavior to maintain applicability.

Mathematical modeling in systems biology continues to transform our understanding of life's complexity, offering a window into the dynamic interplay of biological components. As computational power and experimental techniques advance, these models will become even more integral to biological discovery and innovation.

## Frequently Asked Questions

### What is mathematical modeling in systems biology?

Mathematical modeling in systems biology involves using mathematical equations and computational techniques to represent and analyze complex biological systems, helping to understand their behavior and predict outcomes.

## **Why is mathematical modeling important in systems biology?**

Mathematical modeling is important because it enables researchers to integrate diverse biological data, simulate complex interactions, generate hypotheses, and guide experimental design, ultimately leading to deeper insights into biological processes.

## **What types of mathematical models are commonly used in systems biology?**

Common types include deterministic models (such as ordinary differential equations), stochastic models, Boolean network models, agent-based models, and hybrid models that combine different approaches.

## **How does mathematical modeling help in understanding cellular processes?**

Mathematical models can simulate the dynamics of cellular components like genes, proteins, and metabolites, allowing researchers to study regulatory networks, signaling pathways, and metabolic fluxes under various conditions.

## **What role do ordinary differential equations (ODEs) play in systems biology modeling?**

ODEs are widely used to represent the continuous change of biological molecules over time, making them ideal for modeling kinetic processes such as enzyme reactions and gene expression dynamics.

## **How can mathematical models in systems biology contribute to drug discovery?**

Models can predict how drugs affect biological pathways, identify potential drug targets, optimize dosing strategies, and reduce the need for costly and time-consuming experiments by simulating drug responses in silico.

## **What challenges are faced in mathematical modeling of biological systems?**

Challenges include incomplete or noisy biological data, high system complexity, parameter estimation difficulties, and computational limitations when simulating large-scale models.

## **How is data integration achieved in mathematical models for systems biology?**

Data integration involves combining heterogeneous datasets such as genomics, proteomics, and metabolomics using statistical and computational methods to inform and validate mathematical models.

# What software tools are commonly used for mathematical modeling in systems biology?

Popular tools include MATLAB, COPASI, CellDesigner, BioNetGen, and Python libraries such as Tellurium and PySB, which provide platforms for model construction, simulation, and analysis.

## Additional Resources

Mathematical Modeling in Systems Biology: Unraveling the Complexity of Life

**mathematical modeling in systems biology** has emerged as a pivotal approach in understanding the intricate networks and dynamic processes that govern living organisms. By integrating mathematical frameworks with biological data, researchers aim to decipher the complex interactions within cellular systems, tissues, and entire organisms. This interdisciplinary method allows scientists to simulate biological phenomena, predict system behavior under varying conditions, and generate hypotheses for experimental validation. As the field evolves, mathematical modeling continues to refine our comprehension of biological complexity, providing a bridge between theoretical analysis and practical biomedical applications.

## The Role of Mathematical Modeling in Systems Biology

Systems biology is fundamentally concerned with understanding biological systems as integrated wholes rather than simply collections of individual components. This holistic perspective necessitates tools that can handle complexity, nonlinearity, and multi-scale interactions—criteria that mathematical modeling inherently meets. By representing biological entities such as genes, proteins, metabolites, and signaling pathways as mathematical constructs, researchers can quantify relationships and dynamics that are otherwise challenging to interpret.

Mathematical modeling in systems biology encompasses a wide range of techniques, from ordinary differential equations (ODEs) describing kinetic processes to stochastic models that capture the randomness inherent in molecular interactions. These models serve as invaluable instruments for hypothesis testing, guiding experimental design, and interpreting large-scale omics data.

## Bridging Scales: From Molecular to Organismal Level

One of the unique challenges in systems biology is integrating data and processes across multiple biological scales. Mathematical models enable this integration by linking molecular-level events to cellular behavior, tissue function, and ultimately organismal phenotypes. For example, models of gene regulatory networks can be connected to metabolic pathways to understand how gene expression changes influence cellular metabolism.

Multi-scale modeling approaches often combine discrete and continuous mathematical methods. Cellular automata and agent-based models simulate interactions among individual cells, while partial differential equations (PDEs) describe spatial and temporal changes in tissue environments. By employing such hybrid frameworks, researchers can capture emergent behaviors and complex

feedback loops that define biological systems.

## **Key Approaches and Techniques in Mathematical Modeling of Biological Systems**

The diversity of biological systems necessitates a variety of modeling strategies tailored to specific contexts. Some of the most prevalent approaches include:

### **Deterministic Models**

Deterministic models use differential equations to describe the time evolution of system variables with precise, predictable outcomes. Ordinary differential equations (ODEs) are widely used to model biochemical kinetics, such as enzyme-catalyzed reactions or signaling cascades. For instance, the Michaelis-Menten kinetics model provides a foundational deterministic framework for enzyme activity.

While deterministic models offer clarity and analytical tractability, their limitation lies in the assumption of homogeneity and neglect of stochastic fluctuations, which can be significant in systems with small molecule numbers.

### **Stochastic Models**

Stochastic modeling incorporates randomness and noise, which are inherent in biological processes at the cellular and molecular levels. These models often employ methods such as the Gillespie algorithm to simulate reaction events probabilistically. Stochastic models are especially important when studying gene expression variability, cell differentiation, or signaling pathways with low copy numbers of participating molecules.

Although computationally intensive, stochastic models provide realistic insights into biological variability and robustness that deterministic approaches may overlook.

### **Boolean and Logical Models**

Boolean modeling abstracts biological components into binary states (on/off) and uses logical rules to describe interactions. This approach is particularly useful for analyzing gene regulatory networks where quantitative kinetic parameters are unavailable. Boolean models facilitate the identification of stable states, attractors, and system responses to perturbations.

Their simplicity and scalability make them practical for large networks, but the lack of quantitative dynamics can be a drawback when precise temporal behavior is important.

## Hybrid Modeling

To leverage the strengths of different approaches, hybrid models combine deterministic, stochastic, and logical frameworks. For example, a hybrid model might use deterministic ODEs for metabolic pathways and stochastic simulations for gene regulatory elements. This flexibility enables a more comprehensive representation of biological complexity but requires careful parameterization and validation.

## Applications and Impact of Mathematical Modeling in Systems Biology

Mathematical modeling has transformed various domains within biological research and medicine. Its applications range from fundamental biological discovery to clinical decision support and drug development.

### Decoding Cellular Signaling Networks

Cell signaling pathways consist of intricate networks of interactions that regulate cellular responses to external stimuli. Mathematical models help unravel these networks by simulating signal transduction dynamics, feedback loops, and cross-talk between pathways. For example, models of the MAPK/ERK pathway have provided insights into how cells interpret growth signals and make fate decisions, which are critical in cancer biology.

### Metabolic Engineering and Synthetic Biology

In metabolic engineering, mathematical models predict how modifications to enzymatic pathways affect metabolite production. Constraint-based modeling, such as flux balance analysis (FBA), is widely used to optimize microbial strains for biofuel or pharmaceutical production. Similarly, synthetic biology relies on modeling to design genetic circuits with desired behaviors, enhancing the predictability of engineered systems.

### Personalized Medicine and Systems Pharmacology

Mathematical modeling facilitates the integration of patient-specific data to tailor treatments. Systems pharmacology models simulate drug interactions, metabolism, and effects on biological networks, enabling prediction of efficacy and toxicity. These tools support the development of personalized therapeutic strategies, improving clinical outcomes.



# Understanding Disease Mechanisms

By modeling complex disease-related networks, such as tumor microenvironments or immune responses, researchers can identify key regulatory nodes and potential drug targets. Models of infectious disease dynamics also guide public health interventions by simulating pathogen spread and host immune responses.

## Challenges and Future Directions

Despite its transformative potential, mathematical modeling in systems biology faces several challenges. Parameter estimation remains a significant hurdle, as many biological parameters are difficult to measure experimentally or exhibit high variability. Models can become computationally expensive and complex, limiting accessibility and interpretability.

Furthermore, the integration of heterogeneous data types—from genomics, proteomics, metabolomics, and imaging—requires advanced data harmonization and model calibration techniques. Ensuring reproducibility and standardization in model development is also crucial for building robust and widely applicable frameworks.

Looking ahead, advances in machine learning and artificial intelligence offer promising avenues to enhance model construction, parameter inference, and predictive accuracy. The coupling of data-driven approaches with mechanistic models may accelerate discovery and application in systems biology.

Collaborative efforts between experimentalists, mathematicians, computer scientists, and clinicians will continue to drive innovation, fostering models that not only explain biological complexity but also translate into tangible benefits for health and disease management.

Mathematical modeling in systems biology remains a dynamic and evolving discipline, integral to decoding the fundamental principles of life and harnessing biological systems for transformative scientific and medical advancements.

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**mathematical modeling in systems biology:** *Mathematical Modeling in Systems Biology*  
Brian P. Ingalls, 2013-07-05 An introduction to the mathematical concepts and techniques needed for the construction and analysis of models in molecular systems biology. Systems techniques are integral to current research in molecular cell biology, and system-level investigations are often accompanied by mathematical models. These models serve as working hypotheses: they help us to understand and predict the behavior of complex systems. This book offers an introduction to

mathematical concepts and techniques needed for the construction and interpretation of models in molecular systems biology. It is accessible to upper-level undergraduate or graduate students in life science or engineering who have some familiarity with calculus, and will be a useful reference for researchers at all levels. The first four chapters cover the basics of mathematical modeling in molecular systems biology. The last four chapters address specific biological domains, treating modeling of metabolic networks, of signal transduction pathways, of gene regulatory networks, and of electrophysiology and neuronal action potentials. Chapters 3-8 end with optional sections that address more specialized modeling topics. Exercises, solvable with pen-and-paper calculations, appear throughout the text to encourage interaction with the mathematical techniques. More involved end-of-chapter problem sets require computational software. Appendixes provide a review of basic concepts of molecular biology, additional mathematical background material, and tutorials for two computational software packages (XPPAUT and MATLAB) that can be used for model simulation and analysis.

**mathematical modeling in systems biology: Systems Biology** Andreas Kremling, 2013-11-12 Drawing on the latest research in the field, *Systems Biology: Mathematical Modeling and Model Analysis* presents many methods for modeling and analyzing biological systems, in particular cellular systems. It shows how to use predictive mathematical models to acquire and analyze knowledge about cellular systems. It also explores how the models are sy

**mathematical modeling in systems biology: Mathematical Modeling in Systems Biology**, 2023-10-27

**mathematical modeling in systems biology: *Dynamic Systems Biology Modeling and Simulation*** Joseph DiStefano III, 2015-01-10 *Dynamic Systems Biology Modeling and Simulation* consolidates and unifies classical and contemporary multiscale methodologies for mathematical modeling and computer simulation of dynamic biological systems - from molecular/cellular, organ-system, on up to population levels. The book pedagogy is developed as a well-annotated, systematic tutorial - with clearly spelled-out and unified nomenclature - derived from the author's own modeling efforts, publications and teaching over half a century. Ambiguities in some concepts and tools are clarified and others are rendered more accessible and practical. The latter include novel qualitative theory and methodologies for recognizing dynamical signatures in data using structural (multicompartmental and network) models and graph theory; and analyzing structural and measurement (data) models for quantification feasibility. The level is basic-to-intermediate, with much emphasis on biomodeling from real biodata, for use in real applications. - Introductory coverage of core mathematical concepts such as linear and nonlinear differential and difference equations, Laplace transforms, linear algebra, probability, statistics and stochastics topics - The pertinent biology, biochemistry, biophysics or pharmacology for modeling are provided, to support understanding the amalgam of math modeling with life sciences - Strong emphasis on quantifying as well as building and analyzing biomodels: includes methodology and computational tools for parameter identifiability and sensitivity analysis; parameter estimation from real data; model distinguishability and simplification; and practical bioexperiment design and optimization - Companion website provides solutions and program code for examples and exercises using Matlab, Simulink, VisSim, SimBiology, SAAMII, AMIGO, Copasi and SBML-coded models - A full set of PowerPoint slides are available from the author for teaching from his textbook. He uses them to teach a 10 week quarter upper division course at UCLA, which meets twice a week, so there are 20 lectures. They can easily be augmented or stretched for a 15 week semester course - Importantly, the slides are editable, so they can be readily adapted to a lecturer's personal style and course content needs. The lectures are based on excerpts from 12 of the first 13 chapters of DSBMS. They are designed to highlight the key course material, as a study guide and structure for students following the full text content - The complete PowerPoint slide package (~25 MB) can be obtained by instructors (or prospective instructors) by emailing the author directly, at: joed@cs.ucla.edu

**mathematical modeling in systems biology: Mathematical Modeling of Biological Systems, Volume II** Andreas Deutsch, Rafael Bravo de la Parra, Rob J. de Boer, Odo Diekmann,

Peter Jagers, Eva Kisdi, Mirjam Kretzschmar, Petr Lansky, Hans Metz, 2007-10-12 Volume II of this two-volume, interdisciplinary work is a unified presentation of a broad range of state-of-the-art topics in the rapidly growing field of mathematical modeling in the biological sciences. Highlighted throughout are mathematical and computational approaches to examine central problems in the life sciences, ranging from the organization principles of individual cells to the dynamics of large populations. The chapters are thematically organized into the following main areas: epidemiology, evolution and ecology, immunology, neural systems and the brain, and innovative mathematical methods and education. The work will be an excellent reference text for a broad audience of researchers, practitioners, and advanced students in this rapidly growing field at the intersection of applied mathematics, experimental biology and medicine, computational biology, biochemistry, computer science, and physics.

**mathematical modeling in systems biology:** *A Guide to Numerical Modelling in Systems Biology* Peter Deuffhard, Susanna Röblitz, 2015-07-06 This book is intended for students of computational systems biology with only a limited background in mathematics. Typical books on systems biology merely mention algorithmic approaches, but without offering a deeper understanding. On the other hand, mathematical books are typically unreadable for computational biologists. The authors of the present book have worked hard to fill this gap. The result is not a book on systems biology, but on computational methods in systems biology. This book originated from courses taught by the authors at Freie Universität Berlin. The guiding idea of the courses was to convey those mathematical insights that are indispensable for systems biology, teaching the necessary mathematical prerequisites by means of many illustrative examples and without any theorems. The three chapters cover the mathematical modelling of biochemical and physiological processes, numerical simulation of the dynamics of biological networks and identification of model parameters by means of comparisons with real data. Throughout the text, the strengths and weaknesses of numerical algorithms with respect to various systems biological issues are discussed. Web addresses for downloading the corresponding software are also included.

**mathematical modeling in systems biology:** *Systems Biology: Mathematical Modeling and Model Analysis* Lynda Feidan, 2019-06-05 Systems biology is the mathematical and computational modeling of complex biological systems. It is an interdisciplinary field of study concerned with complex interactions within biological systems. One of the primary objectives of systems biology is to discover and model emergent properties and explore the properties of cells, tissues and organisms functioning as a system. The foundations of systems biology are control theory and cybernetics, quantitative modeling of enzyme kinetics, synergetics, simulations for the study of neurophysiology and the mathematical modeling of population dynamics. The topics covered in this extensive book deal with the core aspects of mathematical modeling and model analysis in the discipline of systems biology. For all readers who are interested in this field, the case studies included in this book will serve as an excellent guide to develop a comprehensive understanding. It aims to equip students and experts with the advanced topics and upcoming concepts in this area of study.

**mathematical modeling in systems biology:** *Kinetic Modelling in Systems Biology* Oleg Demin, Igor Goryanin, 2008-10-24 With more and more interest in how components of biological systems interact, it is important to understand the various aspects of systems biology. Kinetic Modelling in Systems Biology focuses on one of the main pillars in the future development of systems biology. It explores both the methods and applications of kinetic modeling in this emerging field. The book introduces the basic biological cellular network concepts in the context of cellular functioning, explains the main aspects of the Edinburgh Pathway Editor (EPE) software package, and discusses the process of constructing and verifying kinetic models. It presents the features, user interface, and examples of DBSolve as well as the principles of modeling individual enzymes and transporters. The authors describe how to construct kinetic models of intracellular systems on the basis of models of individual enzymes. They also illustrate how to apply the principles of kinetic modeling to collect all available information on the energy metabolism of whole organelles, construct a kinetic model, and predict the response of the organelle to changes in external

conditions. The final chapter focuses on applications of kinetic modeling in biotechnology and biomedicine. Encouraging readers to think about future challenges, this book will help them understand the kinetic modeling approach and how to apply it to solve real-life problems. Downloadable Resources Features Extensively used throughout the text for pathway visualization and illustration, the EPE software is available on the accompanying downloadable resources. The downloadable resources also include pathway diagrams in several graphical formats, DBSolve installation with examples, and all models from the book with dynamic visualization of simulation results, allowing readers to perform in silico simulations and use the models as templates for further applications.

**mathematical modeling in systems biology: Stochastic Modelling for Systems Biology, Third Edition** Darren J. Wilkinson, 2018-12-07 Since the first edition of Stochastic Modelling for Systems Biology, there have been many interesting developments in the use of likelihood-free methods of Bayesian inference for complex stochastic models. Having been thoroughly updated to reflect this, this third edition covers everything necessary for a good appreciation of stochastic kinetic modelling of biological networks in the systems biology context. New methods and applications are included in the book, and the use of R for practical illustration of the algorithms has been greatly extended. There is a brand new chapter on spatially extended systems, and the statistical inference chapter has also been extended with new methods, including approximate Bayesian computation (ABC). Stochastic Modelling for Systems Biology, Third Edition is now supplemented by an additional software library, written in Scala, described in a new appendix to the book. New in the Third Edition New chapter on spatially extended systems, covering the spatial Gillespie algorithm for reaction diffusion master equation models in 1- and 2-d, along with fast approximations based on the spatial chemical Langevin equation Significantly expanded chapter on inference for stochastic kinetic models from data, covering ABC, including ABC-SMC Updated R package, including code relating to all of the new material New R package for parsing SBML models into simulatable stochastic Petri net models New open-source software library, written in Scala, replicating most of the functionality of the R packages in a fast, compiled, strongly typed, functional language Keeping with the spirit of earlier editions, all of the new theory is presented in a very informal and intuitive manner, keeping the text as accessible as possible to the widest possible readership. An effective introduction to the area of stochastic modelling in computational systems biology, this new edition adds additional detail and computational methods that will provide a stronger foundation for the development of more advanced courses in stochastic biological modelling.

**mathematical modeling in systems biology: Model-Based Hypothesis Testing in Biomedicine** Rikard Johansson, 2017-10-03 The utilization of mathematical tools within biology and medicine has traditionally been less widespread compared to other hard sciences, such as physics and chemistry. However, an increased need for tools such as data processing, bioinformatics, statistics, and mathematical modeling, have emerged due to advancements during the last decades. These advancements are partly due to the development of high-throughput experimental procedures and techniques, which produce ever increasing amounts of data. For all aspects of biology and medicine, these data reveal a high level of inter-connectivity between components, which operate on many levels of control, and with multiple feedbacks both between and within each level of control. However, the availability of these large-scale data is not synonymous to a detailed mechanistic understanding of the underlying system. Rather, a mechanistic understanding is gained first when we construct a hypothesis, and test its predictions experimentally. Identifying interesting predictions that are quantitative in nature, generally requires mathematical modeling. This, in turn, requires that the studied system can be formulated into a mathematical model, such as a series of ordinary differential equations, where different hypotheses can be expressed as precise mathematical expressions that influence the output of the model. Within specific sub-domains of biology, the utilization of mathematical models have had a long tradition, such as the modeling done on electrophysiology by Hodgkin and Huxley in the 1950s. However, it is only in recent years, with the

arrival of the field known as systems biology that mathematical modeling has become more commonplace. The somewhat slow adaptation of mathematical modeling in biology is partly due to historical differences in training and terminology, as well as in a lack of awareness of showcases illustrating how modeling can make a difference, or even be required, for a correct analysis of the experimental data. In this work, I provide such showcases by demonstrating the universality and applicability of mathematical modeling and hypothesis testing in three disparate biological systems. In Paper II, we demonstrate how mathematical modeling is necessary for the correct interpretation and analysis of dominant negative inhibition data in insulin signaling in primary human adipocytes. In Paper III, we use modeling to determine transport rates across the nuclear membrane in yeast cells, and we show how this technique is superior to traditional curve-fitting methods. We also demonstrate the issue of population heterogeneity and the need to account for individual differences between cells and the population at large. In Paper IV, we use mathematical modeling to reject three hypotheses concerning the phenomenon of facilitation in pyramidal nerve cells in rats and mice. We also show how one surviving hypothesis can explain all data and adequately describe independent validation data. Finally, in Paper I, we develop a method for model selection and discrimination using parametric bootstrapping and the combination of several different empirical distributions of traditional statistical tests. We show how the empirical log-likelihood ratio test is the best combination of two tests and how this can be used, not only for model selection, but also for model discrimination. In conclusion, mathematical modeling is a valuable tool for analyzing data and testing biological hypotheses, regardless of the underlying biological system. Further development of modeling methods and applications are therefore important since these will in all likelihood play a crucial role in all future aspects of biology and medicine, especially in dealing with the burden of increasing amounts of data that is made available with new experimental techniques.

Användandet av matematiska verktyg har inom biologi och medicin traditionellt sett varit mindre utbredd jämfört med andra ämnen inom naturvetenskapen, såsom fysik och kemi. Ett ökat behov av verktyg som databehandling, bioinformatik, statistik och matematisk modellering har trätt fram tack vare framsteg under de senaste decennierna. Dessa framsteg är delvis ett resultat av utvecklingen av storskaliga datainsamlingstekniker. Inom alla områden av biologi och medicin så har dessa data avslöjat en hög nivå av interkonnektivitet mellan komponenter, verksamma på många kontrollnivåer och med flera återkopplingar både mellan och inom varje nivå av kontroll. Tillgång till storskaliga data är emellertid inte synonymt med en detaljerad mekanistisk förståelse för det underliggande systemet. Snarare uppnås en mekanisk förståelse först när vi bygger en hypotes vars prediktioner vi kan testa experimentellt. Att identifiera intressanta prediktioner som är av kvantitativ natur, kräver generellt sett matematisk modellering. Detta kräver i sin tur att det studerade systemet kan formuleras till en matematisk modell, såsom en serie ordinära differentialekvationer, där olika hypoteser kan uttryckas som precisa matematiska uttryck som påverkar modellens output. Inom vissa delområden av biologin har utnyttjandet av matematiska modeller haft en lång tradition, såsom den modellering gjord inom elektrofysiologi av Hodgkin och Huxley på 1950-talet. Det är emellertid just på senare år, med ankomsten av fältet systembiologi, som matematisk modellering har blivit ett vanligt inslag. Den något långsamma adapteringen av matematisk modellering inom biologi är bl.a. grundad i historiska skillnader i träning och terminologi, samt brist på medvetenhet om exempel som illustrerar hur modellering kan göra skillnad och faktiskt ofta är ett krav för en korrekt analys av experimentella data. I detta arbete tillhandahåller jag sådana exempel och demonstrerar den matematiska modelleringens och hypotestestningens allmängiltighet och tillämpbarhet i tre olika biologiska system. I Arbete II visar vi hur matematisk modellering är nödvändig för en korrekt tolkning och analys av dominant-negativ-inhiberingsdata vid insulinsignaler i primära humana adipocyter. I Arbete III använder vi modellering för att bestämma transporthastigheter över cellkärnmembranet i jästceller, och vi visar hur denna teknik är överlägsen traditionella kurvpassningsmetoder. Vi demonstrerar också frågan om populationsheterogenitet och behovet av att ta hänsyn till individuella skillnader mellan celler och befolkningen som helhet. I Arbete IV använder vi matematisk modellering för att förkasta tre hypoteser om hur fenomenet facilitering

uppstår i pyramidala nervceller hos råttor och möss. Vi visar också hur en överlevande hypotes kan beskriva all data, inklusive oberoende valideringsdata. Slutligen utvecklar vi i Arbete I en metod för modellselektion och modelldiskriminering med hjälp av parametrisk "bootstrapping" samt kombinationen av olika empiriska fördelningar av traditionella statistiska tester. Vi visar hur det empiriska "log-likelihood-ratio-testet" är den bästa kombinationen av två tester och hur testet är applicerbart, inte bara för modellselektion, utan också för modelldiskriminering.

Sammanfattningsvis är matematisk modellering ett värdefullt verktyg för att analysera data och testa biologiska hypoteser, oavsett underliggande biologiskt system. Vidare utveckling av modelleringsmetoder och tillämpningar är därför viktigt eftersom dessa sannolikt kommer att spela en avgörande roll i framtiden för biologi och medicin, särskilt när det gäller att hantera belastningen från ökande datamängder som blir tillgänglig med nya experimentella tekniker.

**mathematical modeling in systems biology: Stochastic Modelling for Systems Biology**

Darren J. Wilkinson, 2011-11-09 Since the first edition of Stochastic Modelling for Systems Biology, there have been many interesting developments in the use of likelihood-free methods of Bayesian inference for complex stochastic models. Re-written to reflect this modern perspective, this second edition covers everything necessary for a good appreciation of stochastic kinetic modelling of biological networks in the systems biology context. Keeping with the spirit of the first edition, all of the new theory is presented in a very informal and intuitive manner, keeping the text as accessible as possible to the widest possible readership. New in the Second Edition All examples have been updated to Systems Biology Markup Language Level 3 All code relating to simulation, analysis, and inference for stochastic kinetic models has been re-written and re-structured in a more modular way An ancillary website provides links, resources, errata, and up-to-date information on installation and use of the associated R package More background material on the theory of Markov processes and stochastic differential equations, providing more substance for mathematically inclined readers Discussion of some of the more advanced concepts relating to stochastic kinetic models, such as random time change representations, Kolmogorov equations, Fokker-Planck equations and the linear noise approximation Simple modelling of extrinsic and intrinsic noise An effective introduction to the area of stochastic modelling in computational systems biology, this new edition adds additional mathematical detail and computational methods that will provide a stronger foundation for the development of more advanced courses in stochastic biological modelling.

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