

DOWNLOAD PDF INVESTIGATING BIOLOGICAL SYSTEMS USING MODELING

Chapter 1 : Model Systems in Biology

Investigating Biological Systems Using Modeling describes how to apply software to analyze and interpret data from biological systems. It is written for students and investigators in lay person's terms, and will be a useful reference book and textbook on mathematical modeling in the design and interpretation of kinetic studies of biological systems.

Advanced Search Abstract Mathematical and computational models are increasingly used to help interpret biomedical data produced by high-throughput genomics and proteomics projects. The application of advanced computer models enabling the simulation of complex biological processes generates hypotheses and suggests experiments. Appropriately interfaced with biomedical databases, models are necessary for rapid access to, and sharing of knowledge through data mining and knowledge discovery approaches. These advances are changing the way biomedical research, development and applications are conducted. Clinical data complements biological data, enabling detailed descriptions of both healthy and diseased states, as well as disease progression and response to therapies. The availability of data representing various biological states, processes and their time dependencies enables the study of biological systems at various levels of organization, from molecules to organism and even up to the population level [3â€”5]. Multiple sources of data support a rapidly growing body of biomedical knowledge, however, our ability to analyze and interpret this data lags far behind data generation and storage capacity. Mathematical and computational models are increasingly used to help interpret biomedical data produced by high-throughput genomics and proteomics projects. Computational models are set to exploit the wealth of data stored on biomedical databases through text mining and knowledge discovery approaches. Modeling is the human activity consisting of representing, manipulating and communicating real-world daily life objects. As one can easily realize, there are many ways to observe an object or, equivalently, there are many different observers for the same object. Each different observer collects data and generates hypothesis that are consistent with the data. Abduction is not infallible, though; with respect to a scientific unknown, we are all blind. A system is a collection of interrelated objects. For example, a biological system could be a collection of different cellular compartments e. An object is some elemental unit upon which observation can be made but whose internal structure is either unknown or does not exist. The choice of the elemental unit defines the representation scale of the system. A model is a description of a system in terms of constitutive objects and the relationships among them, where the description itself is, in general, decodable or interpretable by humans. Using this general definition, one can identify three primary scientific uses of models [12]: Secondary uses of models account for conceptual frameworks to design new experiments, methods to summarize or synthesize large quantities of data, tools to discover relationships among objects. In this article, we analyze models and modeling processes specific for the biology. We mainly focus on the use of models aiming at the points i and ii as tools for knowledge discovering in biology. The mathematical methods used in modeling biological systems vary according to different steps of the process. We focus on the mathematical representation of the system. However, other important steps in the modeling processes are parameters fitting and model selection. We will not analyze the mathematical methods in those two important aspects as these would require separate review papers. Methods for parameters fitting refer to wide area of mathematical optimization, whereas methods for model selection mainly use statistical techniques. On top of these, sensitivity analysis and phaseâ€”space analysis of the models may be required. Interested readers may find more information in these references: Models for technical use are formal models, but the strategy for building them is quite different and therefore, we leave them out of the present discussion. It is worth pointing out that, as we will mention later on, alternative systems can be considered parts of a large model to account for effects whose origin can be neglected without compromising the understanding of the whole phenomena. This article is organized as follows: Actually, one can identify four different types of models: In this article, we focus mainly on diagrammatic and formal models and we concentrate on the model building process. Verbal models In verbal models the system is described in words. These models, based on

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observations, usually evidence in a simple way the objects and relations among the objects in the system. A verbal model is a rough and sometime ambiguous qualitative representation of the knowledge of the system. These kinds of models are used in the first approach to the analysis of biological system. Conceptual or diagrammatic models. In conceptual or diagrammatic models the system is described by a graphical representation of the objects and the relationships describing the underlying dynamical processes. To develop these kind of models the understanding of the available data needs to be sufficient to have a detailed even if not exhaustive idea of the objects or entities and relations. In computer science, CM are also referred to as domain models. A CM is expressly independent from the design and free from implementation concerns. The CM aims to clarify the meaning of the usually ambiguous terms to minimize as much as possible problems arising from different interpretations of terms and concepts. Once the domain concepts have been modeled, the model becomes a stable basis for subsequent development of applications in that specific domain. Furthermore, the concepts behind the conceptual model can be mapped to physical design or implementation constructs using either manual or automated code generation approaches. In UML notation, the conceptual model is often described with a class diagram in which classes represent concepts, associations represent relationships between concepts and role-type of an association represents role types taken by instances of the modeled concepts in various situations. Physical models In physical models the representation is done using a mock-up of a real system or object like a scale model of an aircraft or of a ship. These type of models are mostly of interest for engineers. Formal models Formal models represent the knowledge of the system using mathematical structures. The mathematical representation of the model depends on the knowledge of the system, on some modeling choices for instance, the spatial scale of representation and the aim of the modeling process. Those questions are mainly related to the description of the system with respect to its different parts or components, the physical variables space and time, the type of relations between objects and the object representation per se. In systems biology, a system is viewed as an assembly of different parts or compartments i. Models can also represent physical variables in different ways. Besides, the model may or not consider the evolution of the system with respect to time dynamic versus static models. Time can be treated as continuous or discrete variable time-continuous versus time-discrete models. Likewise, spatial distribution of objects in each compartment may or not be relevant spatially-heterogeneous versus homogeneous models. Finally, similar objects may be treated as individuals or taken in bulk particle models versus population models. In the first case, individual objects are identified by a unique state or by a large, but finite number of states one-state particle versus finite-state automata. Lastly, the relations between objects can be described as deterministic or stochastic rules deterministic versus stochastic models. According to the different modeling choices, one can get single versus multicompartment models, including transport, evolutionary differential equations versus algebraic equations or spatial partial differential equation, differential equations versus difference equations, ordinary differential equations ODE versus partial differential equations PDE , kinetic methods, agent-based methods ABM or cellular automata CA versus ODE or PDE; deterministic methods ODE or PDE, etc. Statistical and artificial intelligence-based models A statistical model is a formalization of the relationships between variables i. When the relationship between two objects is too complex to be easily guessed, one can resort to probabilistic measures and statistical or artificial intelligence methods to reproduce the response relationship see e. Examples of this approach are the lumped models using equivalent circuits, neural network, etc. To find a good model is an issue. Modeling is a hard problem in itself and failure is not a rare event. The modeling procedure is a process in itself that follows a semi-formal set of rules. The methodology lean on four macro steps [31]: This step includes knowledge and data acquisition from field experts and literature, model structure, model hypothesis, conceptual model, choosing the appropriate mathematical formalism, solving the formal model, get the results, check model results matching to available data and so on; iii execute the plan, i. This last point is a major test to evaluate the hypothesis formulated when setting the model. As mentioned before, we are mostly interested in models for the analysis and predictions. For these models, the classical description of modeling process is shown in Figure 1. It is worth to mention

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that the schema illustrated in Figure 1 does not have the pretense to be the most general one: Figure 1 View large Download slide The description of the modeling process. The top part of the figure refers to the formulation of the model, i. Central part of the figure refers to calibration i. Finally, the bottom of the figure refers to analysis and evaluation, i. Model objectives As we already pointed out, a proper definition of the model objectives is a fundamental step as it implies a certain level of comprehension of the problem. The reason for building a model should be clear and a proper clarification of the objective must answer to major questions: All these questions need to be clarified before we proceed in searching the current knowledge on the system we wish to model, as some informations may be more relevant than the others. Current knowledge A second crucial step in the modeling process is to collect the knowledge on the system under investigation. In the biomedical field, data sets of literature record e. Pubmed can highly facilitate the task of browsing the vast amount of information available nowadays. In this respect, methods of data mining and data extraction may be very useful [17]. Model structure A model is a representation of a real system and has its own structure. Realism, Precision and Generality are competing properties. Each of these properties trades-off against the other two. Deciding a model structure is to find a proper balance between those competing properties, which satisfy the model objectives. Decision on the model structure is crucial for defining the model hypothesis, diagrammatic model construction and mathematical formulation. Hypotheses The next step in the modeling process is to translate objectives and current knowledge we wish to include in the model in a list of specific working hypothesis. These are usually verbal statements, but could also be quantitative relationships. Working hypotheses are the basis of the model we are going to built and model results will depend on them. In doing the cycle refinement of model, the starting hypothesis should be critically, repeatedly analyzed. Conceptual model The conceptual model is a graphical representation of the relevant system knowledge and model objectives that have been identified in the hypotheses. In the conceptual model compartments, objects and relations will be described in a diagram where the set of objects are fully clarified and relations bounded. Mathematical formulation This is usually the trickiest part of the modeling process, requiring the choice of a mathematical structure, which is appropriate for the model objectives and is able to describe in quantitative form the hypotheses. This step of the process requires a certain level of mathematical sophistication and, more importantly, it requires to define vague concepts and loose relations in strict mathematical terms. Noticeably, model objectives play an important role because, a detailed description of the biological system may turn out to be useless if not required by the model objectives. Choosing a mathematical formulations is a mapping of the model into the mathematical domain to obtain a formal model.

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Chapter 2 : Scientific modelling - Wikipedia

Investigating Biological Systems Using Modeling describes how to apply software to analyze and interpret data from biological systems. It is written for students and investigators in lay person's terms, and will be a useful reference book and textbook on mathematical modeling in the design and interpretation of kinetic studies of biological.

Overview[edit] A scientific model seeks to represent empirical objects, phenomena, and physical processes in a logical and objective way. All models are in simulacra, that is, simplified reflections of reality that, despite being approximations, can be extremely useful. Complete and true representation may be impossible, but scientific debate often concerns which is the better model for a given task, e. The aim of these attempts is to construct a formal system that will not produce theoretical consequences that are contrary to what is found in reality. Predictions or other statements drawn from such a formal system mirror or map the real world only insofar as these scientific models are true. Such computer models are in silico. Other types of scientific models are in vivo living models, such as laboratory rats and in vitro in glassware, such as tissue culture. Direct measurement of outcomes under controlled conditions see Scientific method will always be more reliable than modelled estimates of outcomes. Within modelling and simulation , a model is a task-driven, purposeful simplification and abstraction of a perception of reality, shaped by physical, legal, and cognitive constraints. Simplifications leave all the known and observed entities and their relation out that are not important for the task. Abstraction aggregates information that is important, but not needed in the same detail as the object of interest. Both activities, simplification and abstraction, are done purposefully. However, they are done based on a perception of reality. This perception is already a model in itself, as it comes with a physical constraint. There are also constraints on what we are able to legally observe with our current tools and methods, and cognitive constraints which limit what we are able to explain with our current theories. This model comprises the concepts, their behavior, and their relations in formal form and is often referred to as a conceptual model. In order to execute the model, it needs to be implemented as a computer simulation. This requires more choices, such as numerical approximations or the use of heuristics. A steady state simulation provides information about the system at a specific instant in time usually at equilibrium, if such a state exists. A dynamic simulation provides information over time. A simulation brings a model to life and shows how a particular object or phenomenon will behave. Such a simulation can be useful for testing, analysis, or training in those cases where real-world systems or concepts can be represented by models. In general, a system is a construct or collection of different elements that together can produce results not obtainable by the elements alone. There are two types of system models: Typically a model will deal with only some aspects of the phenomenon in question, and two models of the same phenomenon may be essentially different—that is to say, that the differences between them comprise more than just a simple renaming of components. In any case, users of a model need to understand the assumptions made that are pertinent to its validity for a given use. Building a model requires abstraction. Assumptions are used in modelling in order to specify the domain of application of the model. For example, the special theory of relativity assumes an inertial frame of reference. This assumption was contextualized and further explained by the general theory of relativity. A model makes accurate predictions when its assumptions are valid, and might well not make accurate predictions when its assumptions do not hold. Such assumptions are often the point with which older theories are succeeded by new ones the general theory of relativity works in non-inertial reference frames as well. The term "assumption" is actually broader than its standard use, etymologically speaking. The Oxford English Dictionary OED and online Wiktionary indicate its Latin source as *assumere* "accept, to take to oneself, adopt, usurp" , which is a conjunction of *ad-* "to, towards, at" and *sumere* to take. The root survives, with shifted meanings, in the Italian *sumere* and Spanish *sumir*. One way to modify the model is by restricting the domain over which it is credited with having high validity. A case in point is Newtonian physics, which is highly useful except for the very small, the very fast, and the very massive phenomena of the universe. However, a fit

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to empirical data alone is not sufficient for a model to be accepted as valid. Other factors important in evaluating a model include: Visualization[edit] Visualization is any technique for creating images, diagrams, or animations to communicate a message. Visualization through visual imagery has been an effective way to communicate both abstract and concrete ideas since the dawn of man. Space mapping[edit] Space mapping refers to a methodology that employs a "quasi-global" modeling formulation to link companion "coarse" ideal or low-fidelity with "fine" practical or high-fidelity models of different complexities. In engineering optimization , space mapping aligns maps a very fast coarse model with its related expensive-to-compute fine model so as to avoid direct expensive optimization of the fine model. The alignment process iteratively refines a "mapped" coarse model surrogate model. Types of scientific modelling[edit].

Chapter 3 : Mathematical Modeling of Complex Biological Systems

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This article has been cited by other articles in PMC. Abstract To understand complex biological systems such as cells, tissues, or even the human body, it is not sufficient to identify and characterize the individual molecules in the system. It also is necessary to obtain a thorough understanding of the interaction between molecules and pathways. Mathematical models allow researchers to investigate how complex regulatory processes are connected and how disruptions of these processes may contribute to the development of disease. In addition, computational models help investigators to systematically analyze systems perturbations, develop hypotheses to guide the design of new experimental tests, and ultimately assess the suitability of specific molecules as novel therapeutic targets. Numerous mathematical methods have been developed to address different categories of biological processes, such as metabolic processes or signaling and regulatory pathways. Today, modeling approaches are essential for biologists, enabling them to analyze complex physiological processes, as well as for the pharmaceutical industry, as a means for supporting drug discovery and development programs. Systems biology, human biology, complex biological systems, mathematical modeling, computational models, transcriptomics, proteomics, metabolomics Over the last decade, DNA-sequencing technologies have advanced tremendously, culminating in the deciphering of the complete human genome in Landers et al. This achievement is a major milestone in the understanding of human biology, as the human genome provides a catalogue of all human genes and associated molecules that are required for creating a living human being. Moreover, the hope that with the knowledge of the human genome sequence researchers would be able to readily develop new therapies for treating human disease as yet has only partially been fulfilled. In the meantime, further technological advances have led to a considerable increase in the understanding of the workings of the human body under normal conditions and in various disease states. For example, transcriptomic 1 studies are shedding light on which genes are active in a given cell at a given time, proteomic studies are discovering which proteins are present and in what amounts, and analyses of the metabolome have begun to examine which metabolic processes occur under different conditions. Most importantly, however, this work has highlighted the fact that human genes and the proteins they encode do not work in isolation but are connected at various levels in networks and pathways of varying complexity. A deeper understanding of these interactions is pivotal for understanding human diseases and developing appropriate therapeutic approaches. One crucial element in this process is the generation of mathematical models that capture the often-unexpected features of complex biological systems. The development of these models is intimately linked to the generation of experimental data using various high-throughput genomic, transcriptomic, proteomic, and metabolomic experimental strategies. This article summarizes the challenges associated with the study of complex biological systems, the benefits of systems biology approaches, and the ways in which computational models can help consolidate and interpret the experimental data obtained using these approaches. These principles are exemplified by some concrete examples from current research projects.

Emergent Properties of a System

The human body consists of approximately individual cells, each of which is itself a complex system comprising thousands of different proteins and other biomolecules. The information specifying the composition and structure of virtually all of these molecules is encoded in the DNA. Although researchers now have information on all genes at hand, they still lack a deeper understanding of many seemingly common biological effects. The reason for this can be exemplified by an analogy with a modern passenger jet, another complex, yet man-made, system. Modern passenger jets consist of thousands of individual components, such as screws, wheels, cables, and other components that perform a specific function in a specific technical context. However, knowledge of those

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individual components does not reveal functions that arise through interactions with other components, such as those related to takeoff, navigation, communication, or landing. Similarly, the processes that occur in living organisms during growth, metabolism, and regulation of cell functions also are interrelated and require equally tight and coordinated control mechanisms. The characteristics of a complex system that arise from the interaction of various components are referred to as the emergent properties of the system. Because they are the result of interactions between the different parts, these emergent properties cannot be attributed to any single part of the system. Thus, the ability of a passenger jet to fly is not the consequence of one particular screw even though this particular screw may be necessary for the plane to function. Similarly, the development of a complex disease e. Such a system is considered irreducible—that is, the system is unlikely to be fully understood by taking it apart and studying each part on its own. To understand irreducible systems and fully appreciate their emergent properties, one must study the systems as a whole. The publication of the human genome sequence provided biological scientists with a list of all the individual parts that make up the human body. However, just like having a pile of all the pieces of a passenger jet does not allow a technician to put together a functional plane without having a blueprint of the wiring scheme, this genome sequence is not sufficient to understand the interactions between the genes and their products. Advances over the last few years in transcriptomics, proteomics, and metabolomics that allow investigators to monitor the biological response of cells, however, will allow studies of physiological systems as a whole in order to identify higher-level biological mechanisms encoded in the human genome Brent see figure 1.

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Chapter 4 : Modelling biological systems - Wikipedia

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A sample time-series of the Lotka–Volterra model. Note that the two populations exhibit cyclic behaviour. Creating a cellular model has been a particularly challenging task of systems biology and mathematical biology. It involves the use of computer simulations of the many cellular subsystems such as the networks of metabolites and enzymes which comprise metabolism, signal transduction pathways and gene regulatory networks to both analyze and visualize the complex connections of these cellular processes. Craig Venter Institute and published on 20 July in Cell. Multi-cellular organism simulation[edit] An open source simulation of C. So far the physics engine Gepetto has been built and models of the neural connectome and a muscle cell have been created in the NeuroML format. It is one of the most important goals pursued by bioinformatics and theoretical chemistry. Protein structure prediction is of high importance in medicine for example, in drug design and biotechnology for example, in the design of novel enzymes. Every two years, the performance of current methods is assessed in the CASP experiment. Human biological systems[edit] Brain model[edit] The Blue Brain Project is an attempt to create a synthetic brain by reverse-engineering the mammalian brain down to the molecular level. Model of the immune system[edit] The last decade has seen the emergence of a growing number of simulations of the immune system. The goal is to produce a virtual liver, a dynamic mathematical model that represents human liver physiology, morphology and function. Simulated growth of plants Electronic trees e-trees usually use L-systems to simulate growth. L-systems are very important in the field of complexity science and A-life. A universally accepted system for describing changes in plant morphology at the cellular or modular level has yet to be devised. Ecosystem model Ecosystem models are mathematical representations of ecosystems. Models in ecotoxicology[edit] The purpose of models in ecotoxicology is the understanding, simulation and prediction of effects caused by toxicants in the environment. Most current models describe effects on one of many different levels of biological organization e. A challenge is the development of models that predict effects across biological scales. Ecotoxicology and models discusses some types of ecotoxicological models and provides links to many others. Modelling of infectious disease[edit] Main articles: Mathematical modelling of infectious disease and Epidemic model It is possible to model the progress of most infectious diseases mathematically to discover the likely outcome of an epidemic or to help manage them by vaccination. This field tries to find parameters for various infectious diseases and to use those parameters to make useful calculations about the effects of a mass vaccination programme.

Chapter 5 : Wolfram and Mathematica Solutions for Biological Sciences

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Chapter 6 : Mathematical modeling of biological systems | Briefings in Bioinformatics | Oxford Academic

Models describing biological systems generally are too complex to be solved analytically ("manually") and therefore typically are solved numerically—that is, using computers to solve the mathematical equations that help predict the response of a biological system.