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Systems Biology in Practice

Concepts, Implementation and Application

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Preface

Systems biology is the coordinated study of biological systems by (1) investigating the components of cellular networks and their interactions, (2) applying experimental high-throughput and whole-genome techniques, and (3) integrating computational methods with experimental efforts. In this book we attempt to give a survey of this rapidly developing field. The systematic approach to biology is not new, but it has recently gained new attraction due to emerging experimental and computational methods. This book is intended as an introduction for students of biology, biophysics, and bioinformatics and for advanced researchers approaching systems biology from a different discipline.

We see the origin and the methodological foundations for systems biology (1) in the accumulation of detailed biological knowledge with the prospect of utilization in biotechnology and health care, (2) in the emergence of new experimental techniques in genomics and proteomics, (3) in the tradition of mathematical modeling of biological processes, (4) in the developing computer power as a prerequisite for databases and for the calculation of large systems, and (5) in the Internet as *the* medium for quick and comprehensive exchange of information.

Recently, researchers working in different fields of biology have expressed the need for systematic approaches. They have frequently demanded the establishment of computer models of biochemical and signaling networks in order to arrive at testable quantitative predictions despite the complexity of these networks. For example, Hartwell and colleagues (1999) argue that "[t]he best test of our understanding of cells will be to make quantitative predictions about their behavior and test them. This will require detailed simulations of the biochemical processes taking place within [cells]. ... We need to develop simplifying, higher-level models and find general principles that will allow us to grasp and manipulate the functions of [biochemical networks]." Fraser and Harland (2000) state, "As the sophistication of the data collection improves, so does the challenge of fully harvesting the fruits of these efforts. The results to date show a dizzying array of signaling systems acting within and between cells. ... In such settings, intuition can be inadequate, often giving incomplete or incorrect predictions. ... In the face of such complexity, computational tools must be employed as a tool for understanding." Noble laureate Nurse (2000) writes, "Perhaps a proper understanding of the complex regulatory networks making up cellular systems like the cell cycle will require a ... shift from

common sense thinking. We might need to move into a strange more abstract world, more readily analyzable in terms of mathematics." And Kitano (2002 a) emphasizes that "computational biology, through pragmatic modeling and theoretical exploration, provides a powerful foundation from which to address critical scientific questions head-on."

The requirement to merge experimental techniques and theoretical concepts in the investigation of biological objects has been acknowledged, for example, by Kitano (2002 a): "To understand complex biological systems requires the integration of experimental and computational research – in other words a systems biology approach." Levchenko (2003) recommends "the systems biology approach, relying on computational modeling coupled with various experimental techniques and methodologies, ... combining the dynamical view of rapidly evolving responses and the structural view arising from high-throughput analyses of the interacting species." Ideker and colleagues (2001) state, "Systems biology studies biological systems by systematically perturbing them (biologically, genetically, or chemically); monitoring the gene, protein, and informational pathway responses; integrating these data; and ultimately, formulating mathematical models that describe the structure of the system and its response to individual perturbations."

Aebersold and colleagues (2000) see the fundamental experimental contribution in large-scale facilities for genome-wide analyses, including DNA sequencing, gene expression measurements, and proteomics, while Hood (2003) explains his path to systems biology in the following way: "Our view and how we practice biology have been profoundly changed by the Human Genome Project."

Importantly, it has been discovered that cellular regulation is organized into complex networks and that the various interactions of network elements in time and space must be studied. Kitano (2002 b) stresses that "[t]o understand biology at the system level, we must examine the structure and dynamics of cellular and organismal function, rather than the characteristics of isolated parts of a cell or organism. Properties of systems, such as robustness, emerge as central issues, and understanding these properties may have an impact on the future of medicine." Kholodenko and colleagues want to "untangle the wires" and "trace the functional interactions in signaling and gene networks." Levchenko (2003) sees advantages in understanding signaling: "A new view of signaling networks as systems consisting of multiple complex elements interacting in a multifarious fashion is emerging, a view that conflicts with the single-gene or protein-centric approach common in biological research. The postgenomic era has brought about a different, network-centric methodology of analysis, suddenly forcing researchers toward the opposite extreme of complexity, where the networks being explored are, to a certain extent, intractable and uninterpretable."

There are many fields of application besides the understanding of cellular regulation. With respect to modeling of the heart as whole organ, Noble (2002) discusses that "[s]uccessful physiological analysis requires an understanding of the functional interactions between the key components of cells, organs, and systems, as well as how these interactions change in disease states. This information resides neither in the genome nor even in the individual proteins that genes code for. It lies at the level of protein interactions within the context of subcellular, cellular, tissue, organ, and

system structures." Kirkwood and colleagues (2003) observe a need to apply "e-biology" on aging in order to integrate theory and data.

There is no need to add another definition of systems biology. More important than such a definition is the operational meaning and the *modus vivendi*. However, we would like to emphasize the view that although the *new* property of systems biology is the computational aspect, the trinity of experimentation, data handling, and mathematical modeling is crucial for further successful development of biological science.

Although deciphering of the DNA sequences of many organisms including man has been acknowledged as an important step towards the exact representation of biology, it is currently not possible to calculate the phenotype of an organism from genotype or to simulate a living cell using only the information encoded in these sequences. We will show in the following chapters what can be achieved at present. An old proverb states, "What you expect is what you will get." Knowledge of different concepts, methodologies, and sources of information will support researchers in interpreting their data in a broader context.

This book is divided into three parts. The first part gives an introduction to three main foundations of systems biology – cell biology, mathematics, and experimental techniques. This will be very basic for advanced readers but will prove helpful for those approaching systems biology from a different scientific discipline.

The second part of the book presents current strategies of computational modeling and data mining. It covers in detail various cellular processes such as metabolism, signaling, the cell cycle, and gene expression, as well as the interactions between them. We introduce different concepts of modeling and discuss how the different models can be used to tackle a number of frequent problems, including such questions as how regulation is organized, how data can be interpreted, or which model to apply under specific settings.

The third part gives an overview on currently available help and resources from the Internet. We represent modeling tools that we frequently use ourselves. We also give an overview on databases that are indispensable for information exchange and therefore constitute an essential support for systems biology.

The ideas presented in this book rely on the work of many colleagues currently or formerly active in the field. Our contribution to systems biology has been influenced by many other scientists and our teachers, whom we wish to acknowledge.

We also thank a number of people who helped us in finishing this book. We are especially grateful to Bente Kofahl, Dr. Wolfram Liebermeister, and Dr. Damini Tapadar for reading and commenting on the manuscript. Hendrik Hache and Mario Drungowski contributed with data analysis. Parts of the experimental data used throughout the book were generated in collaboration with Dr. Marie-Laure Yaspo, Dr. James Adjaye and Dr. Pia Aanstad. We thank Monica Shevack for the artistic preparation of many figures.

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Foreword

Systems biology is an emergent discipline that is gaining increased attention. A desire to understand systems of living organisms is not a new one. It can be traced back a few decades. Walter Cannon's homeostasis, Norbert Wiener's cybernetics, and Ludwig von Bertalanffy's general systems theory all points to essentially the same direction – system-level understanding of biological systems. Since the discovery of double helix structure of DNA and a series of efforts that gave birth to molecular biology, astonishing progress has been made on our understanding on living forms as molecular machinery. The climax came as completion of human genome sequencing.

With accumulating knowledge of genes and proteins, the next natural question to ask is how they are working together? What are principles that govern at the system-level? With the progress of molecular biology, genomics, computer science, and control theory, the old question is now being revisited with new concepts and methodologies.

A system is not just an assembly of components. There are principles that govern at the system-level. Unlike genes and proteins that are rather tangible objects, a system is no tangible. The essence of the system lies in dynamics that is not tangible. This makes the game of systems biology complicated, and may sound alien to many molecular biologists who are accustomed to a molecular-oriented view of the world. Needless to say system-level understanding has to be grounded onto molecular-level so that a continuous spectrum of knowledge can be established.

The enterprise of systems biology research requires both breadth and depth of understanding for various aspects of biological, computational, mathematical, and even engineering issues. So far, there has not been a coherent textbook in the field that covers broad aspects of systems biology. (I wrote a textbook in 2001 perhaps the first textbook in systems biology, but it was only in Japanese.) In this textbook, the authors have successfully covered sufficiently broad aspects of biology and computation that is essential in getting started in systems biology research. It is essential that both computational and experimental aspects of biology are described consistently and seamlessly. The students who learned through this textbook will make no barrier between computation and experiments. They would use advanced computational tools just like using PCR. I am expecting to see a new generation of systems biologists who get the first touch of the field from this book.

Bon voyage

Tokyo, Japan, September 26 2004 *Hiroaki Kitano*

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Part III Computer-based Information Retrieval and Examination

Part I
General Introduction

1
Basic Principles

1.1
Systems Biology is Biology!

Life is one of the most complex phenomena in the universe. It has been studied by using systematic approaches in botany, zoology, and ecology as well as by investigating the composition and molecular biology of single cells. For a long time biologists have thoroughly investigated how parts of the cell work: they have studied the biochemistry of small and large molecules, the structure of proteins, the structure of DNA and RNA, and the principles of DNA replication as well as transcription and translation and the structure and function of membranes. In addition, theoretical concepts about the interaction of elements in different types of networks have been developed. The next step in this line of research is further effort towards a systematic investigation of cells, organs, and organisms and of (mainly) cellular processes such as cellular communication, cell division, homeostasis, and adaptation. This approach has been termed systems biology.

Now the time has come to integrate different fields of biology and natural science in order to better understand how cells work, how cellular processes are regulated, and how cells react to environmental perturbations or even anticipate those changes. The development of a more systematic view of biological processes is accompanied by and based on a revolution of experimental techniques and methodologies. New high-throughput methods allow measurement of the expression levels of all genes of a cell at the same time and with reasonable temporal resolution, although this is still very expensive. Fluorescence labeling and sophisticated microscopic techniques allow tracing individual molecules within a single cell. A fine-grained study of cell components and cell processes in time and in space is an important prerequisite for the further elucidation of cellular regulation.

Systems biology is driven partly by the curiosity of scientists, but even more so by the high potential of its applications. Biotechnological production requires tools with high predictive power to design cells with desired properties cheaply and reliably. There are many promises for health care: models of regulatory networks are necessary to understand their alterations in the case of disease and to develop methods to cure the disease. Furthermore, since there is an observable trend in health care towards individualized and predictive medicine (Weston and Hood 2004), there will be

an increasing need for the exact formulation of cellular networks and the prediction of systems behavior in the areas of drug development, drug validation, diagnostics, and therapy monitoring. For example, it has been shown that the epidermal growth factor receptor, which is targeted by a new generation of cancer drugs, belongs to a family of at least four related receptors. These receptors can be turned on by more than 30 different molecules. Thus, such a complex setup makes it necessary to derive the wiring diagram to understand how each component plays its role in responding to various stimuli and causing disease. Once a detailed model has been constructed, all effects of possible perturbations can be predicted fairly cheaply *in silico*. Furthermore, models gained by systems biology approaches can be used for prediction of the behavior of the biological system even under conditions that are not easily accessible with experiments.

Systems biology approaches offer the chance to predict the outcome of complex processes, e. g., the effect of different possible courses of cancer treatment on the tumor (how effectively the treatment eliminates the tumor as well as possible metastatic cells) and the patient (what the cancer treatment does to other rapidly growing tissues, how bad the predicted side effects of a specific treatment in a specific patient are).

These and many other problems that could have enormous effects on our survival, our health, our food supplies, and many other issues that are essential to our existence and our well being might very well be almost impossible to approach without the tools of systems biology that are currently being developed. E. g., to optimize the treatment of an individual cancer patient, we have to be able to accurately predict the outcome of the possible courses of treatment. This would be easy if we were able to understand the complex processes (drug effects, drug side effects, drug metabolism, etc.) the way that we understand some processes in physics (e. g., the famous equation $E = mc^2$ describing the dependence of mass and energy) or even some of the basic processes in biology (the genetic code). This is very unlikely for the complex, highly connected systems we are faced with in many real-world problems in biology. It is not even clear whether our current approach of studying such systems – analyzing small segments (often one or a few genes at a time) – will ever give us enough insight to be able to make useful prediction, as, at least in mathematics, many systems cannot be subdivided in that form. The only option we have might therefore very well be to generate as much information as possible on the system, using the tools of functional genomics, and to model the entire process in as much detail as necessary to allow quantitative predictions of the parameters we are interested in.

Systems biology relies on the integration of experimentation, data processing, and modeling. Ideally, this is an iterative process. Experimentally obtained knowledge about the system under study together with open questions lead to an initial model. The initial model allows predictions that can be verified or falsified in new experiments. Disagreements stimulate the next step of model development, which again results in experimentally testable predictions. This iteration continues until a good agreement is achieved between the data obtained in the experiment and the model predictions.

A major topic of current systems biology is the analysis of networks: gene networks, protein interaction networks, metabolic networks, signaling networks, etc. Initially, investigation of abstract networks was fashionable. However, it has become

clear that it is necessary to study more realistic and detailed networks in order to uncover the peculiarities of biological regulation. Different theoretical attempts have been made to study the different types of networks. For example, gene regulatory networks are sometimes described by Boolean logic assigning to genes one of two states, on or off; protein relations are mainly characterized by a static view of putative interactions measured by yeast two-hybrid methods, and metabolic networks are determined by the set of catalyzing enzymes and the possible metabolic fluxes and intrinsic modes of regulation.

A unified view of a cellular network is currently emerging in the sense that each action of a cell involves different levels of cellular organization, including genes, proteins, metabolism, or signaling pathways. Therefore, the current description of the individual networks must be integrated into a larger framework.

Systems biology also employs theoretical concepts that are only rough representations of their biological counterparts. For example, the representation of gene regulatory networks by Boolean networks, the description of complex enzyme kinetics by simple mass action laws, or the simplification of multifarious reaction schemes by black boxes proved to be helpful understatements. Although being a simplification, these models elucidate possible network properties and help to check the reliability of basic assumptions and to discover possible design principles in nature. Simplified models can be used to test mathematically formulated hypothesis about system dynamics. And simplifying models are easier to understand and to apply to different questions.

Computational models serve as repositories of the current knowledge, both established and hypothetical, on how pathways might operate, providing one with quantitative codification of this knowledge and with the ability to simulate the biological processes according to this codification (Levchenko 2003). The attempt to formulate current knowledge and open problems in mathematical terms often uncovers a lack of knowledge and requirements for clarification. On the other hand, computational models can be used to test whether different hypotheses about the true process are reliable.

Many current approaches pay tribute to the fact that biological items are subject to evolution. This concerns on one hand the similarity of biological organisms from different species. This similarity allows for the use of model organisms and for the critical transfer of insights gained from one cell type to other cell types. Applications include, e.g., prediction of protein function from similarity, prediction of network properties from optimality principles, reconstruction of phylogenetic trees, or identification of regulatory DNA sequences through cross-species comparisons. On the other hand, the evolutionary process leads to genetic variations within species. Therefore, personalized medicine and research is an important new challenge for biomedical research.

1.2
Systems Biology is Modeling

Observation of the real world and, especially, of biological processes confronts us with many simple and complex processes that cannot be explained with elementary

principles and the outcome of which cannot reliably be foreseen from experience. Mathematical modeling and computer simulations can help us to understand the internal nature and dynamics of these processes and to arrive at well-founded predictions about their future development and the effect of interactions with the environment.

What is a model? The answer will differ among communities of researchers. In the broadest sense, a model is an abstract representation of objects or processes that explains features of these objects or processes. For instance, the strings composed of the letters A, C, G, and T are used as a model for DNA sequences. In some cases a cartoon of a reaction network showing dots for metabolites and arrows for reactions is a model, while in other cases a system of differential equations is employed to describe the dynamics of that network. In experimental biology, the term model is also used to denote species that are especially suitable for experiments. For example the mouse Ts65DN serves as a model for human trisomy 21 (Reeves et al. 1995).

1.2.1 Properties of Models

1.2.1.1 Model Assignment is not Unique

Biological phenomena can be described in mathematical terms. Many examples have been presented during the past few decades (from the description of glycolytic oscillations with ordinary differential equations, to populations growth with difference equations, to stochastic equations for signaling pathways, to Boolean networks for gene expression). It is important to note that a certain process can be described in more than one way.

- A biological object can be investigated with different experimental methods.
- Each biological process can be described with different (mathematical) models.
- A mathematical formalism may be applied to different biological instances.
- The choice of a mathematical model or an algorithm to describe a biological object depends on the problem, the purpose, and the intention of the investigator.
- Modeling has to reflect essential properties of the system. Different models may highlight different aspects of the same instance.

This ambiguity has the advantage that different ways of studying a problem also provide different insights into the system. An important disadvantage is that the diversity of modeling approaches makes it very difficult to merge established models (e. g., for individual metabolic pathways) into larger super-models (e. g., for the complete cellular metabolism).

1.2.1.2 System State

An important notion in dynamical systems theory is the *state*. The state of a system is a snapshot of the system at a given time that contains enough information to predict the behavior of the system for all future times. The state of the system is described by the set of variables that must be kept track of in a model.

Different modeling approaches have different representations of the state: in a differential equation model for a metabolic network, the state is a list of concentrations of each chemical species. In the respective stochastic model, it is a probability distribution and/or a list of the current number of molecules of a species. In a Boolean model of gene regulation, the state is a string of bits indicating for each gene whether it is expressed ("1") or not expressed ("0"). Thus, each model defines what it means by the state of the system. Given the current state, the model predicts which state or states can occur next, thereby describing the change of state.

1.2.1.3 Steady States

The concept of stationary states is important for the modeling of dynamical systems. *Stationary states* (other terms are *steady states* or *fixed points*) are determined by the fact that the values of all state variables remain constant in time. The asymptotic behavior of dynamic systems, i. e., the behavior after a sufficiently long time, is often stationary. Other types of asymptotic behavior are oscillatory or chaotic regimes.

The consideration of steady states is actually an abstraction that is based on a separation of time scales. In nature, everything flows. Fast and slow processes – ranging from formation and release of chemical bonds within nanoseconds to growth of individuals within years – are coupled in the biological world. While fast processes often reach a quasi-steady state after a short transition period, the change of the value of slow variables is often negligible in the time window of consideration. Thus each steady state can be regarded as a quasi-steady state of a system that is embedded in a larger non-stationary environment. Although the concept of stationary states is a mathematical idealization, it is important in kinetic modeling since it points to typical behavioral modes of the investigated system and the respective mathematical problems are frequently easier to solve.

1.2.1.4 Variables, Parameters, and Constants

The quantities involved in a model can be classified as variables, parameters, and constants. A *constant* is a quantity with a fixed value, such as the natural number e or Avogadro's number $N_A = 6.02 \cdot 10^{23}$ (number of molecules per mole). *Parameters* are quantities that are assigned a value, such as the K_m value of an enzyme in a reaction. This value depends on the method used and on the experimental conditions and may change. *Variables* are quantities with a changeable value for which the model establishes relations. The *state variables* are a set of variables that describe the system behavior completely. They are independent of each other and each of them is necessary to define the system state. Their number is equivalent to the dimension of the system. For example, diameter d and volume V of a sphere obey the relation $V = \pi d^3/6$. π and 6 are constants and V and d are variables, but only one of them is a state variable, since the mentioned relation uniquely determines the other one.

Whether a quantity is a variable or a parameter depends on the model. The enzyme concentration is frequently considered a parameter in biochemical reaction kinetics. That is no longer valid if, in a larger model, the enzyme concentration may change due to gene expression or protein degradation.

1.2.1.5 Model Behavior

There are two fundamental causes that determine the behavior of a system or its changes: (1) influences from the environment (input) and (2) processes within the system. The system structure, i.e., the relation among variables, parameters, and constants, determines how endogenous and exogenous forces are processed. It must be noted that different system structures may produce similar system behavior (output). The structure determines the behavior, not the other way around. Therefore, the system output is often not sufficient to predict the internal organization. Generally, system limits are set such that the system output has no impact on the input.

1.2.1.6 Process Classification

For modeling, processes are classified with respect to a set of criteria. *Reversibility* determines whether a process can proceed in a forward and backward direction. Irreversible means that only one direction is possible. *Periodicity* indicates that a series of states may be assumed in the time interval $\{t, t + \Delta t)$ and again in the time interval $\{t + i \cdot \Delta t, t + (i + 1) \cdot \Delta t\}$ for $i = 1, 2, \ldots$ With respect to the randomness of the predictions, deterministic modeling is distinct from stochastic modeling. A description is *deterministic* if the motion through all following states can be predicted from the knowledge of the current state. *Stochastic* description gives instead a probability distribution for the succeeding states. The nature of values that time, state, or space may assume distinguishes a *discrete* model (where values are taken from a discrete set) from a *continuous* model (where values belong to a continuum).

1.2.1.7 Purpose and Adequateness of Models

Models represent only specific aspects of the reality. The intention of modeling is to answer particular questions. Modeling is, therefore, a subjective and selective procedure. It may, for example, aim at predicting the system output. In this case it might be sufficient to obtain precise input-output relation, while the system internals can be regarded as black box. However, if the function of an object is to be elucidated, then its structure and the relations between its parts must be described realistically. One may intend to formulate a model that is generally applicable to many similar objects (e.g., Michaelis-Menten kinetics holds for many enzymes, the promoter-operator concept is applicable to many genes, and gene regulatory motifs are common) or that is specific to one special object (e.g., the 3D structure of a protein, the sequence of a gene, or a model of deteriorating mitochondria during aging). The mathematical part can be kept as simple as possible to allow for easy implementation and comprehensible results. Or it can be modeled very realistically and be much more complicated. None of the characteristics mentioned above makes a model wrong or right, but they determine whether a model is appropriate to the problem to be solved.

1.2.1.8 Advantages of Computational Modeling

Models gain their reference to reality from comparison with experiments, and their benefits are, therefore, somewhat dependent on experimental performance. Nevertheless, modeling has a lot of advantages.