

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Introductory Chapter: Systems Biology Consolidating State of the Art Genetics and Bioinformatics

*Eleni Papakonstantinou, Katerina Pierouli,
Elias Eliopoulos and Dimitrios Vlachakis*

1. Biological systems and computational tools in systems biology

A biological system is defined as the network of biological entities with a specific function. Although the study of the genome and its expression process remains important, in recent years, researchers have focused on studying the structure and dynamics of an entire biological system. The operation of a system determines the interactions of its individual elements. Understanding the function and interactions of a system is accomplished by comprehension of four basic attributes:

(1) structures of the system, including the gene interactions and biochemical pathways, as well as the control mechanisms of the above procedures, (2) system dynamics, containing patterns of the system behavior over time, and the identification of the main mechanisms that control specific behaviors under various conditions, (3) the control method, including configuration of cellular mechanisms in order to reduce dysfunctions, (4) the design method, including techniques for designing and modifying biological systems to reduce errors. The definition of systems biology has not yet been clarified; many different definitions are depending on the researcher. In general, systems biology is an interdisciplinary field of biology that involves the computational and mathematical modeling of complex biological systems. The purpose of this field is to understand the complex interactions and functions at the organism, tissue or cell level with direct application in biomedical research. Therefore, systems biology comprises an approach that diverges from heretofore reductive biological research.

Systems biology examines the interactions between several components rather than the individual features of the molecules, in order to understand the phenotype resulting from the components of the system. To this end, computational approaches are employed in systems biology to create possible *in silico* models that can also be verified experimentally *in vivo* or *in vitro*, thus allowing the analysis of a large number of data [1–5]. In the study of biological systems, various computational tools are used including techniques for sequence alignment and for recording molecular dynamics, molecular interactions and discovering or predicting the molecular structure [6].

The computational techniques are divided into two categories; those guided by data and those guided by hypothesis. Network modeling is based on data to provide information on the interactions of numerous molecular components. On the other hand, dynamic modeling is based on a hypothesis in order to characterize the quantitative relations and interactions between the molecular components (**Figure 1**).

This category of computational techniques includes strategies that involve smaller biological systems with fewer molecular components [7].

In the context of the computational models' employment in systems biology, there is a correlation between the design of a biological model and the development of a computer program. Thus, the researcher can visualize the internal processes and flows of system reactions, as well as to study the changes that occur depending on the conditions of the system [8].

In a biological network in systems biology, the molecular components are considered as “nodes”, while their interactions as “edges”. Molecular components include genes, proteins, metabolites, drugs, and can also be diseases and phenotypes [9]. On the other hand, the dynamical modeling of a biological system involves the representation of known molecular paths in a mathematical form. Mathematical equations are intended to describe biological processes based on the physicochemical properties that determine the rate of reaction and the affinity of the interaction. In order to achieve the most efficient performance of a dynamic model, the initial concentrations of cellular components must be given, and their connectivity is then established. In this way, through dynamic modeling, the concentrations of the components can be calculated at subsequent times and can be compared with those that occur in experimental time [5]. A dynamic model can be definitive when the initial data and parameters are determined and lead to a particular path or can be stochastic when it is able to proceed to different conditions with different probabilities according to its primary data [10].

Various tools have been developed for analyzing and modeling biological systems. An indicative example is the biological tool COPASI, which is suitable for mathematical simulation and analysis of the dynamics of biochemical processes [11].

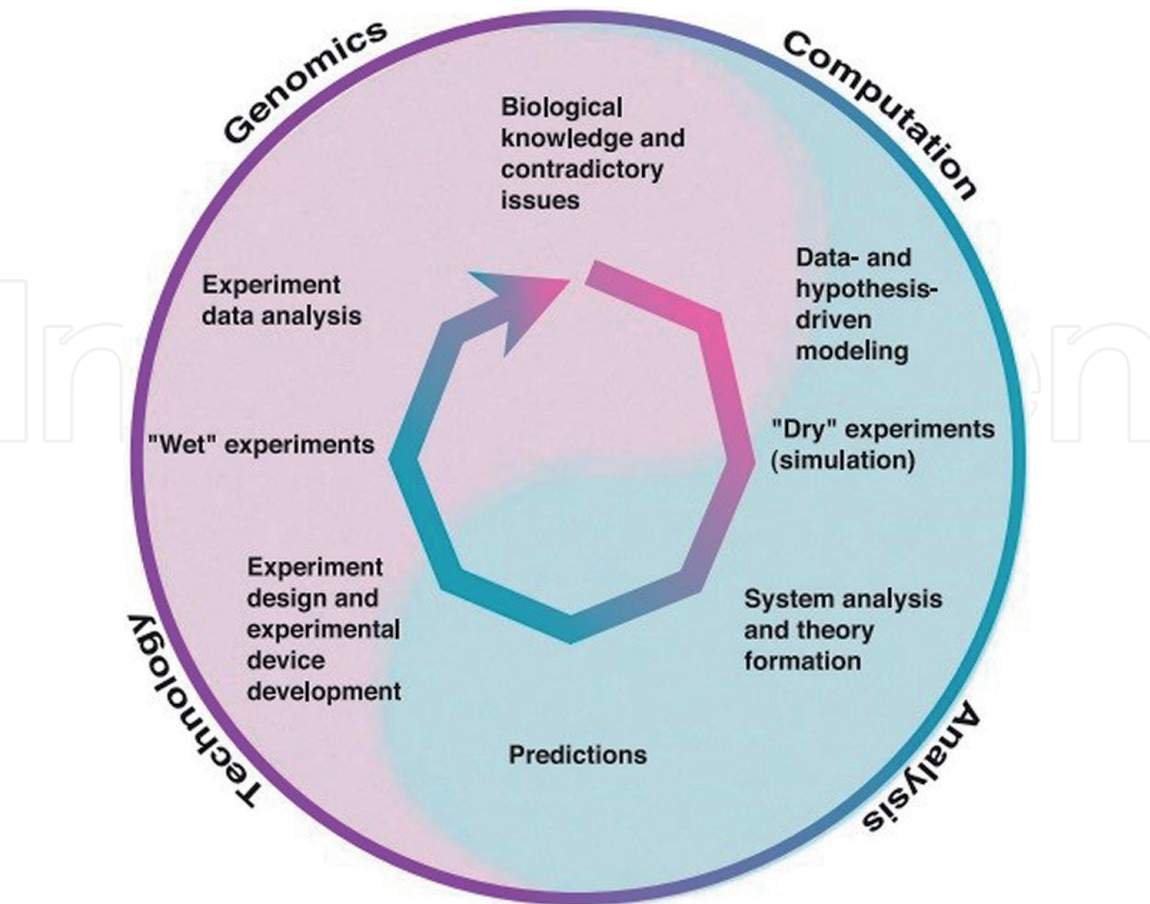


Figure 1.
Hypothesis-driven research in systems biology [2].

BioModel Analyzer (BMA) is a graphical tool for the structure and analysis of biological systems. It aims to combine the simple analysis offered by formal-verification tools to the biologists' expectations of examining systems spatially and temporally and studying the modifications of system interactions according to several conditions [12].

BioDiVinE is a tool for parallel study and analysis of biological systems. The tool analyzes the model based on its chemical reactions, through the following main features: (a) the specificity of models according to their chemical equations through the user interface, (b) the representation of models based on the various ordinary differential equations (ODEs), (c) adjustment of the initial kinetic parameters and conditions, (d) regulation of the discrete abstraction parameters, (e) graphic simulation of model's discrete stages and (f) model controlling [13].

Another example is BoolNet, a computational tool which studies the biological Boolean networks (BNs) that describe the gene regulation where the genes exhibit dual "on/off" behavior, i.e., whether they are expressed or not. The tool can analyze new functions for attractor search, robustness and binarization for three categories of BNs: (i) synchronous BNs, consisting of a set of genes (variables) and a set of transition functions, (ii) asynchronous BNs, where a single transition function is selected, and the corresponding variable is updated, and (iii) probabilistic BNs, that allow the specification of various transition functions per variable [14].

2. Applications of systems biology

While traditional reductionist methods provide an invaluable insight into the molecular mechanisms of a disease, a systems-level approach has been widely used in recent years based on the integration of large-scale data emerging from omics technologies. The acquired high-dimensional data produced by genomic, transcriptomic, proteomic, lipidomic and metabolomic technologies can be processed and analyzed by employing novel techniques in data analysis and data mining, bioinformatics and machine learning approaches. The ultimate goal is the design of a refined computational model that can reflect on the dynamic perturbations of the system in a predictive mode.

Systems biology approaches have been implemented in the study of many diseases, such as cancer and neurodegenerative diseases. Carcinogenesis, tumor progression, and metastasis have long been a challenging field of research, since high complexity interaction networks govern them at a genetic, epigenetic, cellular, tissue and environmental level [15]. The wide availability of high-throughput genomic, epigenomic and transcriptomic data on different types of cancer in large repositories, such as "The Cancer Genome Atlas (TCGA)," has empowered research in the context of cancer systems biology. The use of such data in parallel with computational models has been employed in a number of successful stories, identifying new key regulators, establishing predictive biomarkers and designing optimized or novel therapeutic strategies against cancer [16–19].

Another application of systems biology includes the computational analysis on extensive experimental data in the field of pharmacology, namely systems pharmacology. Systems pharmacology is focused on the study of drugs, identifying new drug targets, repurposing of existing drugs and analyzing the properties and effects of known drugs in a systems-level. Addressing the complexity of the cellular networks and the mode of action of a drug can lead to a better understanding of side effects and adverse events of a drug and the identification of off-targets, improving the safety and effectiveness of disease treatment [20]. In the past decade, systems-based applications have proved to gain better insights into drug-drug interactions,

drug-target networks, drug-target interactions, and drug side-effects, leading to novel drug discovery [21–23].

Finally, in the field of virology, a systems-level approach is required to address the extremely complex viral and host processes that follow upon viral infection. Systems virology encompasses the study of virus-host interaction networks through the process and analysis of high-throughput data, such as next-generation sequencing, mass spectrometry, microarray technologies, and protein-protein interactions, aiming towards the generation of a representative dynamic model of virus-host interactions [24]. Such methods may reveal key network components that can be used as potential targets during viral infection and replication and lead to novel preventive or therapeutic antiviral strategies [25].

Summarizing, systems biology is a field that aims to analyze and model the molecular pathways and interactions of a broader set of several molecular components. The study of a system can be achieved by computational tools that enable scientists to visualize and record the progress of functions in a system over time. The ultimate ambition is the prediction of potential changes and interactions according to the dynamic conditions, making it possible to lead to the development of more effective therapies and handling several diseases.

Author details

Eleni Papakonstantinou, Katerina Pierouli, Elias Eliopoulos
and Dimitrios Vlachakis*

Department of Biotechnology, Genetics and Computational Biology Group,
Laboratory of Genetics, Agricultural University of Athens, Athens, Greece

*Address all correspondence to: dimvl@aua.gr

IntechOpen

© 2019 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] Hillmer RA. Systems biology for biologists. *PLoS Pathogens*. 2015;**11**(5):e1004786
- [2] Kitano H. Systems biology: A brief overview. *Science*. 2002;**295**(5560):1662-1664
- [3] Wanjek C. Systems biology as defined by NIH. *National Institutes of Health*. 2011;**19**(6):1-10
- [4] Bartocci E, Lio P. Computational modeling, formal analysis, and tools for systems biology. *PLoS Computational Biology*. 2016;**12**(1):e1004591
- [5] Zou J et al. Advanced systems biology methods in drug discovery and translational biomedicine. *BioMed Research International*. 2013;**2013**:742835
- [6] Nobile MS et al. Graphics processing units in bioinformatics, computational biology and systems biology. *Briefings in Bioinformatics*. 2017;**18**(5):870-885
- [7] Faratian D et al. Systems pathology—Taking molecular pathology into a new dimension. *Nature Reviews. Clinical Oncology*. 2009;**6**(8):455-464
- [8] Gay S, Soliman S, Fages F. A graphical method for reducing and relating models in systems biology. *Bioinformatics*. 2010;**26**(18):i575-i581
- [9] Maayan A. Introduction to network analysis in systems biology. *Science Signaling*. 2011;**4**(190):tr5
- [10] Sobie EA et al. Systems biology—Biomedical modeling. *Science Signaling*. 2011;**4**(190):tr2
- [11] Hoops S et al. Copasi—A complex pathway simulator. *Bioinformatics*. 2006;**22**(24):3067-3074
- [12] Benque D, Bourton S, Cockerton C, Cook B, Fisher J, Ishtiaq S, et al. Bma: Visual Tool for Modeling and Analyzing Biological Networks. Heidelberg: Springer-Verlag; 2012. pp. 686-692. 7358 of LNCS. Berlin
- [13] Barnat J, Brim L, Cern I, Drazan S, et al. BioDiVinE: A framework for parallel analysis of biological models. *Electronic Proceedings in Theoretical Computer Science*. 2009;**9**:31-45
- [14] Mussel C, Hopfensitz M, Kestler HA. BoolNet—An R package for generation, reconstruction and analysis of Boolean networks. *Bioinformatics*. 2010;**26**(10):1378-1380
- [15] Du W, Elemento O. Cancer systems biology: Embracing complexity to develop better anticancer therapeutic strategies. *Oncogene*. 2015;**34**(25):3215-3225
- [16] Agrawal P et al. A systems biology approach identifies FUT8 as a driver of melanoma metastasis. *Cancer Cell*. 2017;**31**(6):804-819 e7
- [17] Chakraborty S et al. Onco-multi-OMICS approach: A new frontier in cancer research. *BioMed Research International*. 2018;**2018**:9836256
- [18] Selvarajoo K. A systems biology approach to overcome TRAIL resistance in cancer treatment. *Progress in Biophysics and Molecular Biology*. 2017;**128**:142-154
- [19] Walsh LA et al. An integrated systems biology approach identifies TRIM25 as a key determinant of breast cancer metastasis. *Cell Reports*. 2017;**20**(7):1623-1640
- [20] Berger SI, Iyengar R. Role of systems pharmacology in understanding drug adverse events. *Wiley Interdisciplinary Reviews. Systems Biology and Medicine*. 2011;**3**(2):129-135

- [21] Li P et al. Transcriptome inference and systems approaches to polypharmacology and drug discovery in herbal medicine. *Journal of Ethnopharmacology*. 2017;**195**:127-136
- [22] Perez-Nueno VI. Using quantitative systems pharmacology for novel drug discovery. *Expert Opinion on Drug Discovery*. 2015;**10**(12):1315-1331
- [23] Wu Z et al. Network-based methods for prediction of drug-target interactions. *Frontiers in Pharmacology*. 2018;**9**:1134
- [24] Law GL et al. Systems virology: Host-directed approaches to viral pathogenesis and drug targeting. *Nature Reviews. Microbiology*. 2013;**11**(7):455-466
- [25] Petit MJ, Shah PS. Mapping Arbovirus-Vector interactions using systems biology techniques. *Frontiers in Cellular and Infection Microbiology*. 2018;**8**:440