Preface

Systems biology integrates theoretical and experimental research and applies to various areas related to medicine. However, a few things are known in the medical profession about the theories and techniques behind systems biology.

In the future, as systems biology techniques progress, it may become possible to study complex diseases at a multitude of levels within the cell, from transcriptional changes, to changes in metabolic flux through genetic pathways.

Complete genome sequencing of hundreds of pathogenic and model organisms in the past decade has provided the information required for studies of gene function. Functional genomics and proteomics approaches, when combined with computational biology and the emerging discipline of systems biology, finally allow us to begin comprehensive mapping of cellular and molecular networks and pathways. However, one of the main difficulties we still face is how best to integrate these disparate data sources and use them to better understand, diagnose, and treat biological systems during disease.

The systems biology approach of integrating protein expression data with clinical data such as histopathology, clinical functional measurements, medical imaging scores, patient demographics, and clinical outcome provides a powerful tool for linking biomarker expression with biological processes that can be segmented and linked to disease presentation.

Systems biology and new technologies enable predictive and preventative medicine. This biology is revolutionizing the field of medical research and creating a new breed of medical researchers.Systems biology yields insights that may aid in the treatment of cancer by combining different disciplines and providing an analytical framework. The existence of heterogeneity of treatment effects is apparent when evaluating patient response to a drug in clinical trials and in clinical practice. Adverse drug reactions are being linked to enzymatic deficiencies or mutations. Therefore one of the great challenges for 21st century medicine is to deliver effective therapies that allow clinicians to choose the correct drug, dose, or intervention for any patient before the start of therapy. (Meyer and Zanger, 1997; Eichelbaum and Burk, 2001; Srivastava, 2003, Nicholson J. K., 2006).

The creation of detailed maps of "signaling networks" linkages between various pathways of genes and proteins that resemble complicated wiring diagrams (Hahn C and Weinberg R.A., 2002), provide a better understanding of the disease at a molecular level. Many diseases can be explained by defects in pathways, and new treatments often involve finding drugs that correct those defects. This approach can result to a more individualized, and potentially more effective approach to diagnosis and treatment. Some of these challenges, as well as the development of systems biology techniques and platforms for translating genomic and pathway research into clinical healthcare are discussed in this the handbook.

Systems biology provides us with a common language for both describing and modelling the integrated action of regulatory networks at many levels of biological organization from the subcellular through the cell, tissue, and organ, right up to the whole organism. Molecular epidemiology concerns the measurement of the fundamental biochemical factors that underlie population disease demography

and understanding the health of different nations. This subject naturally lends it to systems biology approaches. Hence, systems biology is certain to play a major role in the future of both the development of personalized medicine and in molecular epidemiological studies.

To access the latest research related to the applications of systems biology in medicine, I decided one year ago to launch a handbook project where researchers from all over the world would assist me in providing the necessary coverage of each respective discipline in systems biology. The primary objective of this project was to define the technologies, terms, and acronyms related to the systems biology and its medical applications.

The handbook will highlight the use of systems approaches including genomic, cellular, proteomic, metabolomic, bioinformatics, molecular, and biochemical, to address fundamental questions in complex diseases like cancer and diabetes, also in ageing.

ORGANISATION OF THE HANDBOOK

The handbook is roughly divided into 13 sections.

Section I, "Basic Concepts in Medical Systems Biology," introduces the readers to some basic concepts in the field of systems biology, and the systematic study of complex interactions in biological systems in order to understand better the entirety of processes that happen in diseases as cancer and diabetes. A cellular network can be modeled mathematically using methods coming from chemical kinetics and control theory. Due to the large number of parameters, variables and constraints in cellular networks, numerical and computational techniques are often used. This Section contains 5 chapters. Chapter I and II introduce the basic concepts in medical systems biology. Chapter I discusses the use of a pathway biology approach to modelling biological processes, providing a new framework for experimental medicine. Chapter II presents principles used in medical systems biology and describe systems and control theory concepts for systems biology and the corresponding implications for medicine. Chapter III describes the inclusion of time delay in pathway cross talk models. Chapter IV explains how deterministic modelling is applied to systems biology. Chapter V introduces Synthetic Biology, as an engineering approach to Systems Biology.

Section II, "Advanced Computational Methods for Systems Biology" serves as a comprehensive introduction to computational methods supporting systems biology research.This part introduces advanced computational methods related to systems biology. Chapter VI describes technical developments in the computational analyses of modern biological data: microarray gene expression data, mass spectrometry data, and bioimaging. Chapter VII provides a perspective on three important collaborative areas in systems biology research, macromolecular crystallization, proteomic biomarker discovery from high-throughput mass spectral technologies and protein structure prediction and complex fold recognition.

Section III "Genomics and Bioinformatics for Systems Biology" provides examples of genomics and bioinformatics applications supporting systems biology research. Chapter VIII describes methods for sequence similarity calculation as well as detection of functional contexts by phylogenetic profiling. Chapter IX provide insight into the application of computational tools to calculate the coupling specificity of important receptors like G-protein coupled receptors (GPCRs), which could present novel drug targets. Chapter X describes the importance of identifying Bacterial β-barrel outer membrane proteins in the completely sequenced genomes as these proteins could serve as potential targets for drugs or vaccines.

Section IV describes "Experimental Techniques for Systems Biology" Clustering methods are used to study specific problems in genomics, such as the analysis of time-course experiments. Therefore,

Chapter XI is focused on model-based clusterings of tissue samples and of genes. Chapter XII propose a novel theoretical framework for data and model reduction of gene expression profiles generated by microarray experiments. Chapter XIII introduces the BeadArray™ technology for gene expression profiling, shows possible approaches for data analysis and demonstrates to the reader how the technology performs in comparison to alternative microarray platforms. The authors in Chapter XIV provide a basic understanding of the gene expression data processing with the Affymetrix Technology. Chapter XV illustrate the use of Exon Arrays to detect alternative isoforms, and point out potential problems that may be encountered by researchers using this technology. Chapter XVI focuses on microbial metabolism from a systems biology perspective. Chapter XVII introduces the aspects of alternative splicing in human disease, and its investigation by means of computational large-scale analyses.

In Section V, "Systems Biology and Aging", Chapter XVIII introduces an in vitro model as a means of studying human hormonal aging. In addition, Chapter XIX provide an overview of the aging process, discuss how it relates to system biological concepts and explain how mathematical modelling can improve our understanding of biochemical processes involved in the aging process.

Section VI, "Systems Biology Applications in Medicine" has been streamlined to focus on the topics most relevant to applications of systems biology in medical problems. In Chapter XXI the authors report on their experience with analysis and modelling of data obtained from studies of animal models related to obesity and metabolic syndrome. Chapter XXII describes modelling approaches in Type 2 Diabetes mellitus. The authors in Chapter XXIII list the high throughput biotechnologies generating a wealth of information on the infected cell and some of the immune related databases and finally explain how to extract meaningful information from these sources. Chapter XXIV describes the integration of data from different cellular levels of human-pathogenic fungi and the application of systems biology methodologies.

Section VII, "Systems Biology and Drug Design", provides a thorough overview of novel methodologies in medical research. Chapter XXV focus on a novel methodology of structure-based drug development feasible without prior knowledge of the target structure: analogy modelling. Chapter XXVI introduce a combination of a computer based guided search of novel peptides in sequence space with their biological experimental validation. Chapter XXVII describe metabolic modelling and applications of metabolic flux analysis for antibiotic production.

Section VIII, "Data Integration and Data Mining," confer an understanding of data integration processes in systems biology.Chapter XXVIII describe data integration and data mining techniques in the context of systems biology studies. Chapter XXIX compare different methods and applications for reverse engineering of gene regulatory networks developed in recent years. Data relating to the functioning of individual genes can be drawn from many different and diverse experimental techniques. Chapter XXX introduces the techniques that have been used to identify the genetic regulatory modules by integrating data from various sources.Chapter XXXI presents some particular biological processes modeled as discrete networks to show that the theoretical properties of networks have a clear biological interpretation. In Chapter XXXII the authors review main methods, approaches and models for the analysis of neuronal network data. Chapter XXXIII describes the philosophy behind the SPK tool for Population kinetic analysis (population kinetics) for modelling and analyzing biomedical kinetic, its components and its current implementation as a web service.

The evolution of photosynthesis is driven by selection of genes for photochemical energy conversion that is robust and, yet effective, in a fluctuating light environment. The dynamic regulation of photosynthesis relies on an interplay of multiple sensory, transmission and executive modules that can be studied by the tools of systems biology (Csete and Doyle 2002). Therefore, Section IX, "Systems Biology in Photochemical Processes" is focused on Photochemistry and its applications, highlighting

the new understanding of the genetics of PDT. Chapter XXXIV introduces the theory of optical spectra and excitation energy transfer of light harvesting complexes in photosynthesis. Chapter XXXV focus on studies of Photodynamic Therapy (PDT) that have employed a systems biology approach. Both the nature of the product and the mechanism involved in effecting feedback inhibition remain unknown. Thus, the modelling of porphyrin pathway introduced in Chapter 36 may fill this void and allow researchers to address these questions of importance.

Section X, "Modeling Cellular Physiology" deals with the study of cellular microstructures in biology by microscopy. Chapter XXXVII describes the application of interference microscopy and double-wavelet analysis to the non-invasive study of cell structure and function. Chapter XXXVIII deals with the stress response of mitochondria to heat which is the central agent of thermotherapy.

Section XI, "Tools for Molecular Networks," includes two chapters. Chapter XXXIX reviews the mechanisms leading to diseases and involving protein interactions and refers to specific diseases such as Huntington's disease and cancer. Chapter XL introduce a network systems resource, Reactome which is also starting to provide powerful and robust tools to investigate tissue-specific biology and steer targeted drug design.

Section XII, "Mathematical Modeling Approaches," includes mathematical modeling that allows us to link epidemiology, physiology and physics to systems biology. Chapter XLI gives an overview of the utility of a more rigorous treatment of thermodynamics at the molecular level to understand protein folding and receptor-ligand binding. Chapter XLII introduces some modelling fundamentals that are applied to the model development of the human menstrual cycle. Chapter XLIII describes mathematical model which deals with the dynamics of human infection by avian influenza both in birds and in humans. Chapter XLIV presents a mathematical model with immunization is proposed to simulate the succession of two epidemics with variable human populations.

Section XIII, "Data Processing in Histopathology", presents automated image analysis approaches which can serve as a valuable aide to clinical pathologists and systems biology researchers in the domain of histopathology. Chapter XLV discusses some of the most important techniques and given examples of their use in the area up to now.

The handbook covers basic biological and mathematical concepts important for systems biology. The chapters are oriented to describe the relation between basic science and medical issues. Topics that are covered in this handbook are (a) Foundations of systems biology (2) Pathophysiology of complex diseases and systems biology approach to therapy.

The Handbook of Research on Systems Biology Applications in Medicine contains over three hundred pages of information and more than hundred figures. Besides having the traditional text, this information source also has a glossary of terms and definitions, contributions from more than 90 international experts, in-depth analysis of issues, concepts, new trends, and advanced technologies. This handbook allows the inclusion of more than 100 high-quality illustrations. While providing the information that is critical to an understanding of the basic of systems biology, this edition focuses more directly and extensively than ever on applications of medical systems biology.

The diverse and comprehensive coverage of multiple disciplines in the field of systems biology in this handbook will contribute to a better understanding all topics, research, and discoveries in this evolving, significant field of study. This handbook provides information for both science and biotechnology researchers and also medical doctors in obtaining a greater understanding of the concepts, issues, problems, trends, challenges and opportunities related to this field of study.

In shaping this book, I committed myself to making the textbook as useful as possible to students and advanced researchers coping with the demands of modern medical research. I hope will make the Handbook of Research on Systems Biology Applications in Medicine a helpful tool-not only for the student

who needs an expert source of basic knowledge in systems biology, but also for the advanced medical researcher who needs clear, concise, and balanced information on which to conduct his research

Thanks to a very hard-working advisory editorial board of scientists, excellent authors who fulfilled our invitations, and a very efficient publisher providing clear procedures and practices for a quality production, readers may now enjoy Chapters on some of the major ideas that have concerned systems biology applications in medicine.

Andriani Daskalaki
Max Planck Institute, Berlin, Germany
July 2008

REFERENCES

Csete, M.E., Doyle, J.C. (2002). Reverse Engineering of Biological Complexity. *Science*, 295: 1664-1669.

Eichelbaum M, Burk O (2001) CYP3A (2001). Genetics in drug metabolism. *Nat Med,* 7: 285–288.

Hahn C. and Weinberg Robert A**.** (2002). A Subway Map of Cancer Pathways. *Nature Reviews Cancer.*

Klipp E. Klipp E., Herwig R., Kowald A., Wierling C., Lehrach H. (2005). *Systems Biology in Practice: Concepts, Implementation and Applications*.

Nicholson J. K. (2006). Global systems biology, personalized medicine and molecular epidemiology *Mol Syst Biol*, *2*, 52

Meyer UA, Zanger UM (1997). Molecular mechanisms of genetic polymorphisms of drug metabolism. *Annu Rev Pharmacol Toxicol*, *37*, 269–296

Srivastava P. (2003). Drug metabolism and individualized medicine. *Curr Drug Metab*, *4*, 33–44