Preface

During the last decade, life sciences have experienced a major shift from *analytical* to *integrative* approaches that can be globally defined as *Systems Biology*. In this overall new landscape, the importance of complex systems and whole-system approaches has become paramount.

The volume that you have in your hands represents the collective effort of a group of dedicated and accomplished researchers in the nascent field of systems biology. Although a rather recent *renaissant* research endeavor, systems biology has a long ancestry that goes back as far as Newton, Leibniz, Mendel, Poincaré, Bernard, Wiener, and von Bertalanffy, amongst many others. The roots are not only strong but diverse; they encompass mathematics, computer science, physiology, genetics, engineering, and biology.

Cells, organisms, and ecosystems consist of a large number of usually nonlinearly interacting parts that exhibit complex behavior while exchanging matter and energy with their environment. *Systems biology* represents a holistic approach for analyses of structural and functional interactions between components rather than individual elements. Vast data gathering from -omics technologies (i.e., gen-, transcript-, prote-, and metabol-omics), together with the growing capability of generating computational models, have allowed for a massive integration and interpretation of new information. Noninvasive imaging technologies used together with intracellular probes are increasing our ability to monitor the spatiotemporal dynamics of cellular, metabolic, and signaling processes in living systems. As such, systems biology can integrate multiple spatial and temporal scales and has the potential to allow new insights into fundamental mechanisms involved in, e.g., human health and disease.

Cellular mass–energy transformations comprise networks of metabolic and transport processes represented by the metabolome and fluxome, which account for the complete set of metabolites and fluxes in a cell. The information-carrying networks include the genome, transcriptome, and proteome that represent the whole set of genes, transcripts, and proteins, respectively, present in a cell. Signaling networks mediate between the genome–transcriptome–proteome and metabolome–fluxome and, as such, play the crucial role of influencing the unfolding of cell function in space and time.

Network is a central concept to systems biology. The study of network properties, and how these control the behavior of cells and organisms, constitutes a main focus of systems biology. A major unsolved biological problem is to understand how a cell works and what goes wrong in pathology. However, in order to achieve this goal we need to unravel how the mass–energy and information networks of the cell interact with each other while being modulated (activated or repressed) by signaling networks to produce a certain phenotype or (patho)physiological response. This novel perspective constitutes a distinctive feature of this volume, thus allowing it to differ from previously published books on systems biology.

If *information* is organized data (and we have a plethora), *knowledge* organized information, and *wisdom* organized knowledge, then systems biology is at the interphase between information and knowledge. We are learning to think and act systemically, to organize catalogs of data into meaningful information, and to distil knowledge from that learning process. To what kind of new wisdom is this emerging knowledge leading us? Although we are far from being there yet, a few lessons have been learned along the way.

Certainly, life is more complex and far-reaching than our genes, at least by the numbers. This is one of the first lessons gleaned from sequencing the genome of species with diverse lineage and evolutionary paths: the number of genes and core proteomes does not correlate with their apparent complexity. For example, the basic proteome of the human genome is not much larger than that of the fly and the worm, but human complexity is. Therefore, where does complexity lie? If diversity and number of functions cannot be directly connected to genes, then we have at least two possibilities. One is that genes are subjected to some combinatorial process that elevates exponentially their numbers (e.g., by alternative splicing), coding diversity, and functional outcomes. Another is the spatiotemporal unfolding of gene expression that, in interaction with the environment, modifies and is modified in a combinatorial manner to give rise to multiple functions. The unfolding in space and time of gene expression would proceed as presciently suggested by the philosopher-scientist Evelyn Fox Keller who wrote, right at the turn of this century, these words referring to developmental genetics:

> . . .we could describe the fertilized egg as a massively parallel and multilayered processor in which both programs (or networks) and data are distributed throughout the cell. The roles of data and program here are relative, for what counts as data for one program is often the output of a second program, and the output of the first is data for yet another program, or even for the very program that provided its own initial data. For some developmental stages, the DNA might be seen as encoding programs or switches that process the data provided by gradients of transcription activators. Or, alternatively, one might say that DNA sequences provide data for the machinery of transcription activation (some of which is acquired directly from the cytoplasm of the egg). In later developmental stages, the products of transcription serve as data for splicing machines, translation machines, and so on. In turn, the output from these processes make up the very machinery or programs needed to process the data in the first place.

More than a decade later we could translate these ideas into the more precise concept about iteratively interacting networks of mass–energy, information, and

signaling, which is precisely the subject of this book. A basic principle of living systems is worth noting at this point: unicellular or multicellular organisms make themselves. This essential defining property of living systems, in general, demands a circular causality in which these different networks are both input and output data, i.e., they provide metabolite precursors, second messengers, and transcriptional factors, and they are supplied with substrates, effectors, and signals—as suggested by Fox Keller's quotation. In these circular loops lies the self-determination of the living, and from their nonlinear dynamics involving feed-back and feed-forward autocatalysis and other interactions, with their potential for self-organization and emergent novelties, results the diversity and distinctiveness of life. According to this perspective then, we should probably look much more into the dynamics of how these different networks evolve and interact in time and space in order to find the unique complexity of yeast, mice, flies, worm, or humans.

The book comprises 13 chapters: the first two introductory and the remaining ones organized in four blocks devoted to the systems biology of signaling networks, cellular structures and fluxes, organ function, and microorganisms.

Chapter 1 explores the historical roots of the twenty-first century approach to systems biology tracing from its origins in dynamics and the invention of differential calculus, physiology, self-organized systems, biochemistry, bioenergetics, and molecular biology to the currently accepted networks approach. Chapter 2 gives an overview of the three types of networks involved in the interactive unfolding of the spatiotemporal organization of living systems: mass–energy, information, and signaling. Chapter 3 describes a quantitative approach to signaling from the perspective of metabolic control analysis. Chapter 4 addresses the novel regulatory features bestowed by microRNAs to the mass–energy transducing networks. Chapter 5 analyzes (from a combined experimental–computational approach) the energetic and redox behavior of mitochondrial networks, along with the signaling role of reactive oxygen species. Chapter 6 highlights the role of adenylate kinase in metabolic AMP-dependent signaling involved in cellular sensing of energetic status and the response to stress. Chapters 7–9 address from different viewpoints the systems biology of the organization in space and time of cellular macromolecular structures and its impact on fluxes through mass–energy networks. Chapters 10 and 11 describe systems organization across and between different temporal and spatial scales from the molecular to the organ levels, namely, as applied to the heart. Chapters 12 and 13 approach the systems biology of network organization from two different angles; in the case of yeast the overall temporal organization of mass–energy, information, and signaling networks exhibited by this unicellular eukaryote in self-synchronized chemostat cultures is presented and analyzed, as the sole model example of in vivo deconvolution of the time structure of a living system at present available, whereas Chap. 13 reviews systems biology approaches as applied to the engineering of mass–energy transforming networks.

Miguel A. Aon
Valdur Saks
Uwe Schlattner

http://www.springer.com/978-3-642-38504-9

Systems Biology of Metabolic and Signaling Networks
Energy, Mass and Information Transfer
Aon, M.A.; Saks, V.; Schlattner, U. (Eds.)
2014, X, 375 p. 90 illus., 67 illus. in color., Hardcover
ISBN: 978-3-642-38504-9