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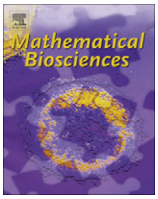

Special issue on biological design principles

Systems biology aims at understanding how the molecular networks of a cell behave collectively as a whole and how these networks came to be as they are. The first aspect requires studying the coordinated operation of the different cellular components as they work together, rather than studying each component individually. This need to study the cooperation of components was already identified in the early decades of the twentieth century [1,2], but it was difficult to address, due to the lack of efficient analytical tools and computational power. Indeed, throughout the twentieth century, systems biology was essentially identical to mathematical biology, because the only tools available for studying complex systems in biology were abstract (and highly simplified) mathematical models.

Even though the roots of systems biology reach back many decades, it was the invention of large scale 'omics' technologies that moved systems biology toward the center of biology, because these technologies made it possible to measure significant fractions of all cellular components directly and simultaneously. Most of the researchers taking advantage of these technical advances came from molecular biology and were therefore not familiar with the decades-old entwining between mathematical and systems biology. As a consequence, systems biology was, in a way, reinvented around the turn of the millennium. However, as data from the large-scale omics approaches accumulated, it quickly became evident to the new practitioners of systems biology that mathematical and computational methods were not only needed to organize the wealth of data but that they were fundamental for making sense of the vast information that was being generated and for achieving a deeper understanding of how biological systems work. This recognition led to an emerging and widening awareness that systems biology must draw from all its many scientific roots, if we are to understand the collective and integrated behavior of cellular components.

The second aim of systems biology addresses the need to understand how evolution shaped the molecular networks of living organisms. Given that evolution preferentially selects the fittest organisms and that fitness at the organism level is, ultimately, a consequence of fitness at the molecular level, we must ask: What are the selection criteria for functional effectiveness at the level of a molecular circuit? In addition, can these criteria be used to explain objectively why different circuits have been selected in different contexts to perform similar functions?

Questions of this nature were first formally addressed in the nineteen seventies by a small cohort of researchers who intended to decipher why natural systems had evolved to work as they do. This type of investigation was pioneered by Michael Savageau [3], who proposed the notion of *design principles* in molecular biology [4]. Such principles objectively and rigorously associate specific aspects of qualitative and/or quantitative design elements in molecular networks to the effectiveness of network performance. While appearing at random during evolution, these elements have the potential to generate networks that have improved fitness because they are more effective than networks in which these elements are either absent, differently structured, or organized in a different fashion.

The early work on design principles was mostly theoretical. An early success story in this line of research was demand theory. This theory relates the fraction of an organism's life cycle in which a gene product is needed to the mode of regulation for the expression of the gene [5–7]. Additional work in recent years has furthermore related the mode of regulation to the error tolerance of gene expression [8] and the filtering of noise in signal transduction [9]. Experimental work during the past decade verified some of the early predictions pertaining to specific design elements and their influence on the effectiveness of molecular circuits [10].

In more recent years, research on design principles went through a solid expansion, parallel to the growth of systems biology. New design principles are now reported with increasing frequency, and often experimentally verified, in a variety of molecular systems. Because of this growing interest, and celebrating the fortieth anniversary of the first paper on design principles [3], it seems timely to dedicate a special issue of *Mathematical Biosciences* to the subject. The goal of this volume is to review the current state of the art and to present some new results on the subject that indicate future directions.

The volume begins with an extensive review by Salvado et al., who presents different theoretical methods used to study design principles as well as some of the design principles that have indeed been identified in molecular systems [11]. The article begins with a short historical view of the subject and then discusses the concept of design principles and its importance for the evolution of molecular networks.

Following this overview is a set of methodological papers that highlight some of the prevalent and novel techniques in more detail and illustrate how they may be applied to the study of design principles. Savageau reviews the concept of design spaces, which can be used to characterize regions within the functional output space of a system that correspond to different types of dynamical behaviors (phenotypical regions) and connect them to the different regions in the parameter space of the system. Savageau demonstrates the applicability of the method with the analysis of hysteretic behavior in the lac operon of microbes growing on natural substrates [12]. He shows that hysteresis is only possible if non-metabolizable substrates, such as IPTG, are used to induce expression of the operon. Shinar and Feinberg present a review of their work on Reaction Network Theory. Methods based on this theory

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permit determining some of the constraints that the structure of a molecular reaction network imposes on its dynamic behavior. The authors use the method to study which network structures enable absolute concentration robustness of an element of the network [13]. Voit and colleagues present alternative methods for determining operating principles that govern how a system may move from one steady state to another, following an alteration in the environmental milieu. They exemplify the methods with a study of operating strategies in the heat stress response of yeast [14].

The final set of papers reviews design principles in specific types of molecular systems. Wall presents a review of design principles associated with gene expression circuits. By exploring a number of specific designs, this work addresses the important issue of how the transcription factor interaction network that regulates gene expression is organized and why it is challenging to predict how the interactions in this network determine cellular behavior [15]. Mittenthal and Zou analyze the most effective way in which a signal transduction pathway can integrate simultaneous input signals. They focus on understanding the design principles that may explain selection of positive or negative regulation for signaling transduction in response to multiple simultaneous inputs. Their results suggest that cells are likely to use negative regulation – a gating network based on a logical disjunction of signals for the absence of prerequisites –rather than positive regulation – a logical conjunction of signals for their presence [16]. Tiwari and colleagues review work on design principles in bacterial genetic networks. They focus on the question of how the design of the circuits influences the possibility of hysteresis in bacterial two component systems, phosphorelays, and sigma factor transcriptional networks [17]. Finally, Rué and Garcia–Ojalvo present a study of design principles in three alternative types of excitable gene circuits. They discuss which of the three alternative designs are likely to perform more efficiently in generating different types of excitable dynamics. Their study suggests that different types of excitable dynamics are possible for all designs, depending on the parameter values of the system [18]. This result could imply that either the different designs are functionally equivalent or that not all criteria for functional effectiveness have been identified for excitable responses in gene circuits.

Collectively, this set of papers, written by leading experts in the field, will provide an overview of the efforts for identifying design principles in molecular networks. Because of the general character of these articles, this volume is hoped to be of interest to both experimental and theoretical biologists and to attract new ideas and insights into this fascinating area of science.

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