Systems biology - Advances in disease understanding and in metabolic engineering

Sarah-Maria Fendt and Costas D. Maranas

Systems biology provides a unifying framework for biological data collection, analysis and informed intervention. In both biotechnology and biomedicine the ultimate goal is to understand and redirect or repair biological processes. For example, the goal could be the design of a production strain that converts a cheap, renewable, and ecological worthwhile substrate with the theoretical maximum possible yield into a desired product or a drug that reverts the aberrant cellular processes in diseased cells back to normal with no side effects and no resistance mechanism. In contrast to other systems, biological processes are characterized by irreducible complexity at multiple time and spatial scales which hinders our ability to reliably predict, test, learn and redesign. Nevertheless, our understanding of select cellular processes has advanced dramatically over the past decade and their complex interactions are unveiled at an ever accelerated pace. However, our ability to functionally and rationally control these highly connected cellular processes and to predict as well as counter regulate non-anticipated consequences is still limited. Therefore, a number of overarching themes are emerging across systems biology that could serve as stepping stones to the ideal drug or production strain developmental pipeline. For example, we would like to know how a cell reacts to multiple and partially contradicting cellular inputs; or why some inputs are in one condition of dominance while the same input is rather of no consequence in another condition. Systems biology provides the appropriate framework for conceptualizing the integration of multiple regulatory layers with downstream cellular responses, the formalization of event hierarchies in computational models, and the integration of information and tools into actionable interventions.

Tools and concepts across disciplines

Experimental tools and concepts used in one area can frequently open up new vistas in other areas of research. Two such tools that are more and more applied across disciplines are ^{13}C tracer analysis and ^{13}C flux analysis. **Buescher *et al.*** and **Niedenführ *et al.*** outline roadmaps for ^{13}C tracer analysis and ^{13}C flux analysis, respectively, to provide researchers a quick start in applying these tools to their biological system of interest. Moreover, not only tools are exchanged between disciplines but also concepts. **Trefois *et al.*** highlights the concept of critical transition, which describes the effect of nonlinear events on systems in general. This concept from ecology has been increasingly applied to elucidate chronic disease onset.

From data to systems level concept

A decade ago the generation of large-scale omics datasets was in the center of the systems biology research. Now, we are looking at the question of what are the biological insight and systems-level lessons we can generate from large-scale omics data. The integration of different omics datasets with cellular processes is of critical importance to progress towards systems level concepts. **Sevin *et al.*** and **Boersema *et al.*** analyzed the advances in the interpretation of metabolomics and proteomics data, respectively, beyond a simple inventory exercise. The analysis of single-cell events compared to population-based conclusions is a further stepping-stone in generating multi-layered and high-resolution interaction concepts for cellular processes. **De Vargas Roditi & Claassen** review state of the art computational and biological techniques that allow the elucidation of intra- and intercellular single cell dynamics. Short and long term regulatory responses enable cells to adapt to multiple stress conditions. Control over adaptation and stress response critically contributes to a systems level understanding. **Voordeckers *et al.*** highlight that the flexibility to adapt to various stimuli is supported by the evolution in gene regulation. In their review they specifically focus on the role of gene duplication versus gene mutation in the evolution of regulatory networks. Moving from understanding to leveraging for engineering regulatory loops, **Venayak *et al.*** discuss how to deploy dynamic control over gene circuits in metabolic engineering. Moreover, **Leavitt & Alper** describe the advances and needs in translating transcriptional regulation to transcriptional engineering and thus the progression in moving from a concept to an application.

Computational biology at the systems level

Computations as an engine of discovery is manifested with a number of contributions that bridge the gap between computational and systems biology. **Mardinoglu & Nielsen** describe recent advances in the development of human cell type-specific genome-scale models of metabolism. They provide convincing evidence that modeling and computations can be used to identify targets for therapeutic interventions. **Heavner & Price** emphasize the need for the systematization and the development of standards for the reconstruction of genome-scale models and make the case that these reconstructions can serve as pipelines of discovery. **O'Brien & Palsson** highlight exciting new developments in computing the functional proteome and the development of metabolism and gene expression (ME) models that account not only for metabolism but also for the assembly and disassembly of all cellular catalytic and macromolecular entities. Finally, **Long *et al.***, provide an overview on recent computational methods in metabolic engineering for strain design.

Metabolism - a multi functional network

Metabolism is connected to virtually any cellular process by providing *e.g.* energy equivalents and precursors for posttranslational modifications, or by affecting signaling pathway activity via metabolite concentration alterations. Thus, metabolism plays an integral role in understanding and causally controlling cell

function. This multi-dimensional impact of metabolism on cellular processes is highlighted by several contributions. **Wegner *et al.*** analyze the auto-regulation within metabolism focusing on the question how metabolite concentrations control metabolic pathway fluxes. **Gomes & Blenis** review the regulatory interplay between signaling events and metabolism, while **Carrer & Wellen** highlight the interdependence of epigenetics and metabolic precursors on the example of cancer cells. Moreover, **Zecchin *et al.*** focus on the often forgotten fact that metabolism is not uniformly distributed within a cell but that a spatial distribution *e.g.* between compartments occurs and is of critical importance for normal homeostasis. Finally, **Keller *et al.*** provide an overview of the often neglected though important role that non-enzymatic reactions play in biological processes. They comment on how these reactions help shape the structure and stability of metabolic networks and their implications in drug design.