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Editorial overview

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Editorial Overview: Systems Biology for Biotechnology

About 15 years ago, systems biology was introduced as a novel approach to biological research. On the one side, its introduction was a result of the recognition that through solely the reductionist approach, we would ultimately not be able to understand how biological systems function as a whole. On the other side, new high-throughput technologies for large-scale experimental assessment and perturbation of biological systems, which emerged at around the same time, were embraced by this new field, or gave it additional momentum.

Although specially earmarked funding opportunities for systems biology, having boosted the early systems biology research, have largely vanished, systems biology has found its place next to the more classical biological research approaches. Today, new experimental and computational systems biology approaches are still being developed, indicating that the field's toolbox continues to growing. Despite being a relatively young field, systems biology has also already greatly contributed in advancing biotechnology, for instance by generating system-level insights about complex systems, or by providing system-level perturbation and analyses tools of either experimental or computational nature.

This systems biology issue of Current Opinion of Biotechnology highlights this fact. In this issue, we focus on two important areas, where biotechnology aims to contribute in solving important societal issues. The first area is the area of biomedicine, where ultimately new medical treatments or prevention measures are the goal, and the second area is the one of industrial biotechnology, where the ambition is to develop cell-factories, through which our current economy, still largely relying on fossil resources, could ultimately be transformed into a more sustainable one.

With regards to the area of biomedicine, Lukacisinova and Bollenbach covered the topic of antimicrobial resistance. In their article, they argue that key towards solving this problem is a deeper understanding of the underlying dynamics of resistance evolution. They demonstrate that a combination of experimental and theoretical approaches from different disciplines, for instance new technology for studying evolution in the laboratory, can yield insights that might be crucial to develop effective strategies for combating resistance. A related topic was covered in an article by Radzikowski et al., namely the topic of bacterial persistence, a phenotype that is characterized by temporal tolerance against antibiotics, without any genetic resistance. While most research in the persistence field has adopted a reductionist approach, Radzikowski et al. sketched a novel systems-level perspective of bacterial persistence, integrating the current knowledge and recent findings generated by high-throughput experimental methods. Interestingly, both reviews provide some initial indication that eventually both areas – the one of antimicrobial resistance and the one of persistence – could eventually even be connected.

In another biomedically oriented article, Moor and Itzkovitz covered the topic of tissue organization, considering tissues as complex systems composed of diverse cell types that interact to yield anatomical units. The authors highlight recent advances in spatial transcriptomics. They show how this approach opens the way for tissue-level systems biology towards unraveling the principles that govern the division of labor between the diverse cell of the tissue. Finally, in the last article in the biomedical area of this issue, Zhang et al. reviewed exciting advances on host–microbiota interactions, having important roles in human health as well as in mitigating disease. Through highlighting recent large-scale and high-throughput genetic screening studies, the authors show that the nematode *C. elegans* and its bacterial diet has turned out to be excellent model for investigations on host–microbiota interactions. Together, these contributions on the one hand highlight the scientific challenges at hand, and on the other side also

demonstrate the power of systems biology to further advance our understanding of these complex systems. Such improved understanding will surely lead to biomedical exploitation at some point.

In the second set of articles, four reviews highlight advances that have the potential to fuel the necessary transition to a more sustainable economy. These articles do not cover specific industrial applications, but rather highlight advances the development of large-scale experimental and modeling tools. CRISPR/Cas9 is currently revolutionizing the biosciences. Jakociunas et al. review how the CRISPR/Cas9 system can be used as a tool for system-level perturbations of cell metabolism, indicating the power of this tool for metabolic engineering. Next to being able to generate genetic diversity - system-wide and in a targeted manner - screening and selection of genotypes with desired phenotypes is also necessary for industrial biotechnology. Vervoort et al. demonstrate in their article how lab-on-chip strategies miniaturize the screening and selection process to the nanoliter scale and the single- cell level, allowing for massive parallelization of this important process in strain development.

Next to expanding our capabilities for high-throughput experimentation, which is exploited for industrial biotechnology, systems-biology has also contributed approaches for rational strain development and optimization, for instance by means of modeling approaches. Covering different methodologies, Chen et al. reviewed the recent progress in modeling approaches for improvement of cell factories ranging from stoichiometric approaches to approaches also considering enzyme kinetics, through which different issues in metabolic systems, such as pathway robustness, can be addressed. To build kinetic models on cellular metabolism, which could be used for the design of cell factories, information about the kinetics of enzymes is required. In their contribution, Davidi and Milo show how recent quantitative proteomics can be leveraged to gain novel insight into in vivo enzyme kinetics. Further, they demonstrate how recently gained understanding about the use of enzymes can explain metabolic strategies.

From the collection of these reviews, it is clear that systems biology greatly contributes to the advances of biotechnology in generating novel system-level insights and as well as tools for system analysis and system-level experimental perturbation.

CV

Matthias Heinemann received a PhD in Biochemical Engineering in 2003. After a postdoc in the Bioprocess lab at ETH Zurich, he took up a position as a junior group leader at the Institute of Molecular Systems Biology at ETH. Since 2009, he is Professor for Molecular Systems Biology at the University of Groningen. His research is geared towards generating a fundamental understanding about microbial metabolism, for which his labs exploits a broad range of experimental techniques as well as mathematical modeling.

Yitzhak Pilpel received a PhD in Molecular genetics in 2000 with Doron Lancet and Ephraim Katzir. He did a post-doctoral training with George Church at Harvard Medical School and he then took a group leader position at the department of Molecular Genetics at the Weizmann Institute in 2003. His lab studies genome evolution taking a systems level approach to deciphering mechanisms of protein translation. The lab combines theoretical, computational and genome-wide experimental approaches to obtain new insight on the biological systems.