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Editorial overview

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Roy Kishony is a Professor of Systems Biology at Harvard Medical School. He holds a PhD in Physics (2000) from Tel-Aviv University. His group applies Systems Biology approaches to Microbial Evolution and Ecology with specific interest in the emergence of antibiotic resistance.

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Progress in early stages in biotechnology, before the introduction of recombinant DNA technology, was made using the driving forces of evolution. The screening of antibiotic producers and the optimization of bioprocess through statistical experimental design are the most common, early examples of biotechnology using evolutionary methods.

The introduction of rDNA technology and the methods of molecular biotechnology led to 'rational' approaches for the design of metabolic pathways and the optimization of organism performance. These approaches — metabolic engineering, systems biology, and synthetic biology — have been very successful and delivered important industrial results, especially in the area of white biotechnology.

However, as the complexity of the problems is increasing evolutionary approaches are gaining again attention. Until now, direct evolution approaches had been used successfully to optimize protein function, but at the individual protein level. As Woodruff and Gill point out the main challenge in industrial organism development is the engineering of multiple complex traits into a host genome. This can only be achieved through optimization at the systems level, with genome engineering algorithms that draw from the paradigms of directed evolution. Such directed evolutionary approaches can then produce a quantitative map of genetic modifications onto traits of interest.

In industrial and white biotechnology, two of the most desirable traits are stress tolerance (e.g., tolerance to high product concentration and to temperature), and the robust merging of non-native pathways into host metabolism. Portnoy and coworkers discuss adaptive laboratory evolution strategies that have accelerated the development of industrial strain through the combination of rational metabolic engineering, followed by strain evolution in the laboratory in a manner that selects for beneficial mutations in an ''unbiased fashion''. The notion of ''unbiased fashion'' is really critical, because one could argue that every time we evolve strains in the laboratory, we have biased the evolution through the selection pressure. What is really ''unbiased'' in the non-intuitive beneficial mutations occur in many different genes and regulatory regions in parallel is the selection of molecular genomic targets.

The next challenge will be the identification of these non-intuitive events that give rise to beneficial traits. While the identification of the beneficial mutations is now feasible with the use of high-throughput, inexpensive sequencing technologies, the identification of the systemic, regulatory changes that lead to the new traits. Gerosa and Sauer point out that our understanding of the evolutionary fitness of regulatory networks is limited

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by the partial knowledge of detailed molecular mechanisms and of enzyme kinetics. They discuss how evolution towards new traits goes beyond changes in genome sequence and it involves emerging networks of post-translational modifications and enzyme regulations. Therefore, a deeper understanding on the input and feedback signals from metabolism to global regulatory circuits must be the next research frontier in evolutionary systems biology, and novel quantitative experimental and computational methods will be central to these research efforts.

Scott and Hwa and Nam and coworkers discuss how quantitative approaches can be used to analyze laboratory evolution studies in order to understand better the mechanistic origins of the beneficial traits. Growth rate is one of the main traits upon which selection pressure acts in evolution, and it has been one of the main selection criteria in adaptive laboratory evolution experiments. Therefore, quantitative physiology is an important framework for analyzing the results of these experiments. Scott and Hwa review and discuss how advances in systems biology allow the formulation of 'growth laws' that characterize the coupling of gene and protein expression to growth rate. These laws appear to be a promising approach to elucidate the mechanisms of the evolution and engineering of desired traits. And while growth laws lump the details of most of the cellular processes into simple, but powerful mathematical expressions, genome-scale models of metabolism describe the details of the biochemistry based on the reconstruction of metabolic networks. Nam et al. discuss how the integration of genomic technologies, experimental evolution, and network modeling will provide insights on the molecular mechanisms of evolution, and how these mechanisms formulate and optimize the cellular objectives under selective pressure. These insights will be indispensible for advances in biotechnology, where nutritional and stress pressures, such as temperature and pH, are the critical constraints under which industrial strains must perform optimally with respect to cellular and to bioprocess objectives.

While laboratory evolution experiments provide a direct link between biotechnology and evolution, the study of evolution in the natural environment is what has ultimately shaped the structure and function of the cellular systems that drive evolution. Therefore, understanding evolutionary systems biology of the organisms in the wild/outside the lab can provide important insight. Korona takes an approach that it is more of a naturalist than biotechnologist, and he points that many of the genes that have been identified as essential from adaptive laboratory evolution studies have been maintained active because of the selective pressures in environments other than the standard laboratory ones. His observations suggest that there is a lot to be learned from a new evolutionary systems biology approach to better characterize gene dispensability. This is an important consideration, if one considers that the industrial production environment is very different from the ''sanitized'' laboratory where production strains are usually developed; one could argue that the selective pressures in production environment might be closer to those the organisms have encountered in their evolutionary history. Klitgord and Segre review and discuss the recent efforts to apply systems biology approaches for understanding the complex microbe–microbe and microbe–environment interactions. They identify genome-scale modeling, synthetic ecosystems, and metagenomics as the emerging, influential approaches that can enable mechanistic based ecological thinking.

One of the biotechnological applications of microbial ecology, is the mining of microbial communities for bioactive small molecules. O'Brien and Wright review some interesting findings from the study of the chemical basis of phenotype. They argues that if we understand the 'resistome', i.e., the environmental collection of all antibiotic resistant genes, and how it evolves, we might be able to capture the potential for fighting antibiotic resistance in the clinical and human environment. They point that while the focus of natural product research has been largely on the identification of novel molecules, our understanding of why microorganisms produce these remarkable compounds in the first place is lagging. From their discussions becomes clear that, in order to find new sources of novel natural products and mine the chemical ecology of small molecules, we need a systems biology understanding of the individual contributions to biological, genetic and chemical interactions governing the coevolving microcosms in the environment.

Reddy and Georgiou consider a different biological system where adaptive evolution is at play: the immune system. They discuss the developments of high-throughput technologies that have led to a substantial amount of progress in the understanding of adaptive immune responses and opened up a real of possibilities, from answering basic questions on repertoire diversity and selection to monitoring diversity for clinical applications and advancing strategies in monoclonal antibody discovery and engineering. The biophysical and biochemical principles that underlie adaptive immunity are in many respects similar to those in adaptive evolution, and therefore evolutionary systems biology can draw important lessons from the methods and concepts of adaptive immunity.

The common themes and conclusions about the challenges and opportunities in evolutionary systems biology, as they emerge from the papers in this issue, point to the exciting new ways in which new advancement in technologies of genomics, and proteomics and quantitative

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biophysical and biochemical data can be integrated with mathematical modeling to provide new insights to classical evolutionary questions with important biotechnology applications.

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