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EDITORIAL

Special collection of synthetic biology, aiming for quantitative control of cellular systems

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Over the past 15 years, the field of synthetic biology has seen a rapid rise in research activities and innovation, as evident by the increase of publications that quote the term "synthetic biology" from one in 2002 to ~1400 in 2016 (from PubMed). Furthermore, synthetic biology projects now involve biological parts that work at wide length-scales and synthetic cells that are created from the bottom-up. With the expansion of synthetic biology in terms of project scale and research activity, have we fulfilled the initial goals of the field? In my personal perspective, there are at least two primary goals of synthetic biology that differentiate it from other fields*. First, synthetic biology will enable rational and quantitative control of biological systems that are robust to their environmental context. Second, synthetic biology will expand our ability to create and program biological systems from the bottom-up.* Achieving the goals has broad impact on applications of synthetic biology in the manufacturing of therapeutic cells, production of biological commodities, disease diagnostics, and therapeutic treatment. However, assessing our overall advancement toward the goals is non-trivial. We do not use a standard metric to report functions of engineered cells, and we do not study the same model system within the same context. My own research has met similar obstacles in pursuing the goals. A meta-analysis of plate-reader protocols in synthetic biology reveals a lack of consistent protocols and consensus reporting of the protocols, which may affect their reproducibility [1]. In addition, my lab synthesizes artificial cells that mimic living cells from the bottom-up [2]. Despite the minimality of the artificial cells, it remains difficult to rationally control the cells in varying environmental conditions due to the lack of knowledge on how their parts interact with one another and with environmental factors.

When I was asked to edit this special issue, my first thought was to assemble a group of emerging leaders in the field to address the two main goals from their own perspective. In contrast to other special issues in synthetic biology, this special issue focuses primarily on quantitative approaches in synthetic biology that aim to advance rational control of biological systems. The special issue covers four areas of synthetic biology: phage engineering, gene expression control, nonlinear dynamics of cells, and metabolic networks.

Brown *et al.* review the role of synthetic biology in promoting phage therapy, and discuss challenges involved in expanding host range of bacteriophages, reducing side effect of phages, and modifying bacteria using engineered phages. Based on single-cell microscopy, Guan *et al.* quantify the degradation of phage DNA by the CRISPR/Cas system. Their results may open the door toward predictive model of phage-bacteria interactions in the future. Three papers in this special issue cover the quantitative control and assays of nucleic acids. Guo *et al.* review the application of DNA strand displacement reaction in DNA nanotechnology. Meng *et al.* present a machine learning approach that predicts expression strength of promoters. Choudhary *et al.* review the structural profiling of RNA, as well as current approaches and challenges in using the profiling data for prediction of RNA structure. Synthetic biological parts can also be integrated to generate nonlinear dynamics of biological systems. Sadeghpour *et al.* study the emergence of bistability in co-repressive microbial consortia and the impact of spatial interactions on the bistability. Along the same line, Menn[1)] *et al.* review temporal and spatial dynamics of gene regulatory networks, as well as synthetic biology approaches to analyze and control the dynamics. Li and Yang[2)] review recent progress in understanding oscillations of natural systems through synthetic biology approaches. In addition, biological systems can be controlled using outer membrane proteins and nucleic acids. Heyde *et al.* use mathematical models to study the *ex vivo* assembly of genetic circuits on microparticles. To this end, surface assembly of biological molecules requires new engineering tools, which are reviewed by Park and Sun[3)] who discuss the methodology and applications of genetically-encoded click chemistry. Finally, in the area of metabolic engineering, Tu *et al.* demonstrate a three dimensional visualization method for analyzing metabolism networks of *Escherichia coli*.

Readers of the special issue will be able to learn quantitative methodologies that are used to study and predict dynamics of biological systems, ranging from biological molecules to cellular populations. Readers will observe some general principles of applying quantitative approaches in synthetic biology. First, the control of biological systems requires the integration of rigorous mathematics with fundamental understanding of biology. Second, quantitative studies of different biological systems may rely on the same fundamental mathematical techniques, but they use specific model assumptions, variables, or boundary conditions for each system. Third, quantitative approaches with broad scientific impact often yield novel insights that improve our control and understanding of biological systems. Fourth, wet-lab experimentation and validation are critical to broadening the scientific impact of quantitative methods in synthetic biology.

This special issue offers a glimpse into the advancement of synthetic biology. Based on the advancement, are we ready to tackle the major challenges in quantitative control of biological systems? Context-dependency is a long-standing issue that has plagued the field of synthetic biology. A synthetic cellular circuit often works within one environmental context, and may operate differently or fail to function in another environmental context. This issue impacts reproducibility of engineered cells in biomanufacturing, and affects predictive control of biological systems in open environments. To overcome the issue, we may need to further understand mechanisms that underlie context-dependency of living cells, and to incorporate bioinspired mechanisms that reduce context-dependency of engineered biological systems. In addition, multi-scale (from nanometer to meter) and multi-modal (*e.g.*, chemical, mechanical, and electromagnetical) control of biological systems may finally become possible due to the ever-expanding collection of synthetic molecular parts. However, quantitative control of such multi-modal systems may require fundamental innovation in mathematical and measurement methods that handle different modes of molecular interactions.

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[1), 2), 3)] The papers will be published in future issues.

