Many applications require cells to integrate multiple environmental signals and to implement synthetic control over biological processes. Genetic circuits enable cells to perform computational operations, interfacing biosensors and actuators. Despite advances in the rational construction of genetic circuits, practical applications of genetic circuits have yet to be realized. Cells equipped with an “internal cell state controller” may respond quickly to fluctuation of pH and O₂/acetate/redox levels in a heterogeneous large bioreactor, leading to less stress and more production. Autonomously navigating cells can be created to detect and destroy toxic chemicals, pathogens, and tumor cells. Engineering cells in a lab scale is entirely different from creating microbial cell factories and environmental janitors that face various changing signals. For such real-world applications, systems must be robust and resistant to mutations for an extended use. In addition, orthogonal genetic parts are needed to build complex circuits. My long term goal is constructing programmable cells that are able to process multiple input signals and to produce desirable outputs to solve energy, environment, and health problems. It is time to create useful biological systems rather than toy systems.

**Keywords:** Synthetic Biology; Systems Biology; Metabolic Engineering; Protein Engineering; Genetic Circuits