Engineering Biological Computers

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Over the last 50 years, exponential increases in our ability to manipulate electrons and engineer electronic systems spawned the information technology revolution. Similarly rapid improvements in technologies for reading and writing DNA are now transforming our capacity to engineer biological systems. Leveraging these technologies, synthetic biology is an emerging discipline for designing biological systems with novel functionalities. Despite major improvements in our ability to engineer biological systems over the last two decades, there remain major needs for more robust, scalable, and complex synthetic gene circuit technologies to program cell function.

This field has opened up new strategies for interrogating and understanding biology, as well as for diagnosing and treating human diseases. For example, we established a massively parallel functional genomics screening platform called Combinatorial Genetics *En Masse* (CombiGEM) that is orders of magnitude more efficient than existing strategies. CombiGEM was used to discover novel high-order combinatorial therapies with enhanced efficacy against antibiotic-resistant bacteria as well as ovarian cancer. Furthermore, CombiGEM enables the efficient, scalable, and high-throughput mapping of genetic interactions in human cells, thus allowing for cellular gene networks to be mapped in detail and deciphered.

In addition, I will discuss several examples where we have created digital and analog synthetic gene circuits to implement sophisticated sense-and-respond behaviors for applications in microbiome engineering and next-generation human cell therapies. For example, we engineered probiotic bacteria capable of sensing disease states in the gut and treating serious systemic diseases through the microbiome. These engineered probiotic bacteria are being advanced into clinical trials.