Synthetic biology: from bacteria to stem cells

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ABSTRACT

Synthetic biology is revolutionizing how we conceptualize and approach the engineering of biological systems. Recent advances in the field are allowing us to expand beyond the construction and analysis of small gene networks towards the implementation of complex multicellular systems with a variety of applications. We have developed an integrated computational/experimental approach to engineering complex behavior in living systems ranging from bacteria to stem cells. In our research, we appropriate useful design principles from electrical engineering and other well established fields. These principles include abstraction, standardization, modularity, and computer aided design. But we also spend considerable effort towards understanding what makes synthetic biology different from all other existing engineering disciplines and discovering new design and construction rules that are effective for this unique discipline.

Categories and Subject Descriptors

C.1.3 [**Computer Systems Organizations**]: Processor Architectures – Other Architecture Styles

General Terms

Experimentation

Keywords

Synthetic biology, genetic engineering

1. INTRODUCTION

With recent advances in our understanding of cellular processes and DNA synthesis methods, we can now regard cells as "programmable matter." Through genetic engineering, we are equipping cells with new sophisticated capabilities for gene regulation, information processing, and communication. These new capabilities serve as catalysts for Synthetic Biology, an emerging engineering discipline to program cell behaviors as easily as we program computers. Synthetic biology will improve our quantitative understanding of natural biological processes and will also have biotechnology applications in areas such as biosensing, synthesis of pharmaceutical products, molecular fabrication of biomaterials and nanostructures, and tissue engineering.

We implemented genetic circuits with finely-tuned digital and analog behavior and used artificial cell-cell communication to coordinate the behavior of cell populations for programmed pattern formation [1, 2, 3, 4]. In our research, we use computer engineering principles of abstraction, composition, and interface specifications to build programmable organisms with sensors and actuators precisely controlled by analog and digital logic circuitry [5]. Here, recombinant DNA-binding proteins represent signals, and recombinant genes perform the computation by regulating protein expression. We have built synthetic gene networks that implement biochemical logic circuits in a variety of cell types including *Escherichia coli*, *Saccharomyces cerevisiae* (yeast), and mammalian stem cells. These circuits incorporate a variety of digital and analog devices including the AND, NOT, and IMPLIES logic gates and analog signal amplifiers. We have used both rational design [1] and directed evolution [6] for the construction of complex but reliable biochemical logic circuits.

Through the construction of transcriptional cascades, we studied how information flows through regulatory networks in single cells by examining noise propagation, ultrasensitivity, and impedance matching [2]. Understanding these issues is critical for the analysis and de novo engineering of complex gene networks. We also constructed several synthetic multicellular systems that have been programmed to exhibit unique coordinated cell behavior. The first of these systems is the pulse generator where sender cells communicate to nearby receiver cells, which then respond with a transient burst of gene expression whose amplitude and duration depends on the distance from the senders [3]. In the second system, receiver cells have been engineered to respond to cell-cell communication signals only within prespecified ranges [4]. This system has been used to generate a variety of interesting spatial patterns. In the third system, cells have been engineered to play "Conway's Game of Life", where cells live or die based on the density of their neighbors. This system exhibits complex global emergent behavior that arises from the interaction of cells based on simple local rules.

DAC 2007, June 4–8, 2007, San Diego, California, USA.

Some of the most significant contributions of synthetic biology will likely focus on medical applications such as tissue engineering. Recently, we have obtained preliminary experimental results towards demonstrating precise spatiotemporal control over stem cell differentiation. For this purpose, we couple elements for gene regulation, cell fate determination, signal processing, and artificial cellcell communication. We have implemented two types of mammalian communication systems, one that uses bacterial quorum sensing enzymes and response elements and one that is based on the secretion and endocytosis of transcription factors. We have also initiated work for creating an artificial tissue homeostasis system where genetically engineered stem cells maintain indefinitely a desired level of pancreatic beta cells despite attacks by the autoimmune response. The system, which relies on artificial cell-cell communication, various regulatory network motifs, and programmed differentiation into beta cells, may one day be useful for the treatment (or cure) of diabetes.

2. REFERENCES

[1] R. Weiss and S. Basu. The device physics of cellular logic gates. In *NSC-1: The First Workshop of Non-Silicon Computing*, Boston, Massachusetts, February 2002.

[2] S. Hooshangi, S. Thiberge, and R. Weiss. Ultrasensitivity and noise propagation in a synthetic transcriptional cascade. *Proceedings of the National Academy of Science*, 102(10):3581–3586, March 2005.

[3] S. Basu, R. Mehreja, S. Thiberge, M. Chen, and R. Weiss. Spatiotemporal control of gene expression with pulse-generating networks. *Proceedings of the National Academy of Science*, 101(17):6355–6360, 2004.

[4] S. Basu, Y. Gerchman, C. H. Collins, F. H. Arnold, and R. Weiss. A synthetic multicellular system for programmed pattern formation. *Nature*, 434(7037):1130–1134, 2005.

[5] R. Weiss, G. Homsy, and T. F. Knight Jr. Toward in-vivo digital circuits. In *Dimacs Workshop on Evolution as Computation*, Princeton, NJ, January 1999.

[6] Y. Yokobayashi, R. Weiss, and F. H. Arnold. Directed evolution of a genetic circuit. *Proceedings of the National Academy of Science*, 99:16587–16591, 2002.