6.047/6.878 Lecture 32: Synthetic Biology

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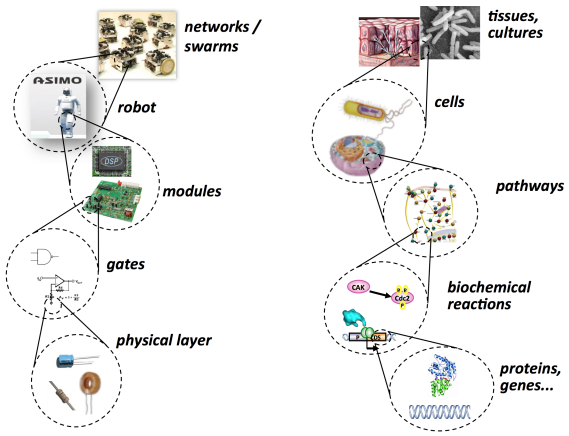
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1 Introduction

A cell is like robot in that it needs to be able to sense it surroundings and internal state, perform computations and make judgments, and complete a task or function. The emerging discipline of synthetic biology aims to make control of biological entities such as cells and proteins similar to designing a robot. Synthetic biology combines technology, science, and engineering to construct biological devices and systems for useful purposes including solutions to world problems in health, energy, environment and, security.

Synthetic biology involves every level of biology, from DNA to tissues. Synthetic biologist aims to create layers of biological abstraction like those in digital computers in order to create biological circuits and programs efficiently. One of the major goals in synthetic biology is development of a standard and well-defined set of tools for building biological systems that allows the level of abstraction available to electrical engineers building complex circuits to be available to synthetic biologists.

Figure 1: The layers of abstraction in robotics compared with those in biology (credit to Ron Weiss).



Synthetic biology is a relatively new field. The size and complexity of synthetic genetic circuits has so far been small, on the order of six to eleven promoters. Synthetic genetic circuits remain small in total size (10^3 - 10^5 base pairs) compared to size of the typical genome in a mammal or other animal (10^5 - 10^7 base pairs) as well.

One of the first milestones in synthetic biology occurred in 2000 with the repressilator. The repressilator [2] is a synthetic genetic regulatory network which acts like an electrical oscillator system with fixed time periods. A green fluorescent protein was expressed within *E. coli* and the fluorescence was measured over time. Three genes in a feedback loop were set up so that each gene repressed the next gene in the loop and was repressed by the previous gene.

The repressilator managed to produce periodic fluctuations in fluorescence. It served as one of the first triumphs in synthetic biology. Other achievements in the past decade include programmed bacterial population control, programmed pattern formation, artificial cell-cell communication in yeast, logic gate creation by chemical complementation with transcription factors, and the complete synthesis, cloning, and assembly of a bacterial genome.

Figure 2: The repressilator genetic regulator network.

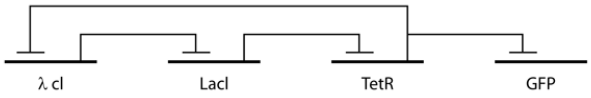
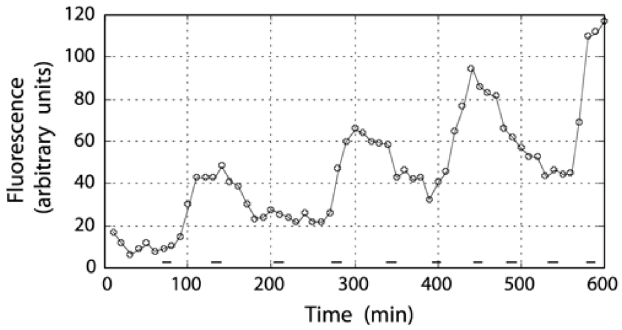


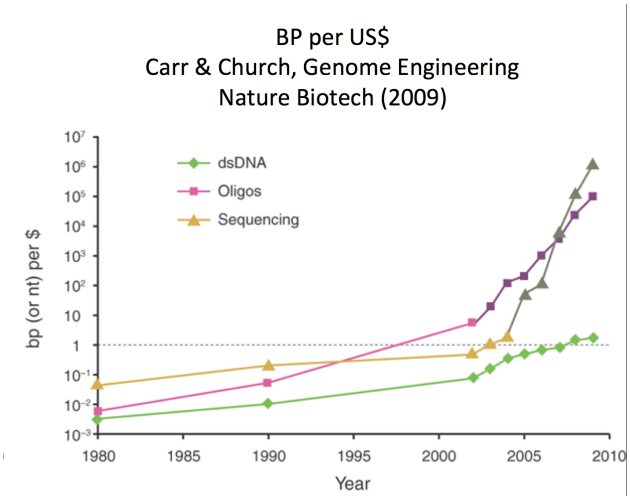
Figure 3: Fluorescence of a single cell with the repressilator circuit over a period of 10 hours.



2 Current Research Directions

Encoding functionality in DNA is one way synthetic biologists program cells. As the price of sequencing and synthesis of DNA continues to decrease, coding DNA strands has become more feasible. In fact, the number of base pairs that can be synthesized per US$ has increased exponentially, akin to Moore's Law.

Figure 4: Cost of synthesizing a base pair versus US dollar



This has made the process of designing, building, and testing biological circuits much faster and cheaper. One of the major research areas in synthetic biology is the creation of fast, automated synthesis of DNA molecules and the creation of cells with the desired DNA sequence. The goal of creating a such a system is speeding up the design and debugging of making a biological system so that synthetic biological systems can be prototyped and tested in a quick, iterative process.

Synthetic biology also aims to develop abstract biological components that have standard and well-defined behavior like a part an electrical engineer might order from a catalogue. To accomplish this, the Registry of Standard Biological Parts (http://partsregistry.org) [4] was created in 2003 and currently contains over 7000 available parts for users. The research portion of creating such a registry includes the classification and description of biological parts. The goal is to find parts that have desirable characteristics such as:

Orthogonality Regulators should not interfere with each other. They should be independent.

Composability Regulators can be fused to give composite function.

Connectivity Regulators can be chained together to allow cascades and feedback.

Homogeneity Regulators should obey very similar physics. This allows for predictability and efficiency.

Synthetic biology is still developing, and research can still be done by people with little background in the field. The International Genetically Modified Machine (iGEM) Foundation (http://igem.org) [3] created the iGEM competition where undergraduate and high school students compete to design and build biological systems that operate within living cells. The student teams are given a kit of biological parts at the beginning of the summer and work at their own institutions to create biological system. Some interesting projects include:

Arsenic Biodetector The aim was to develop a bacterial biosensor that responds to a range of arsenic concentrations and produces a change in pH that can be calibrated in relation to arsenic concentration. The team's goal was to help many under-developed countries, in particular Bangladesh, to detect arsenic contamination in water. The proposed device was intended be more economical, portable and easier to use in comparison with other detectors.

BactoBlood The UC Berkeley team worked to develop a cost-effective red blood cell substitute constructed from engineered E. coli bacteria. The system is designed to safely transport oxygen in the bloodstream without inducing sepsis, and to be stored for prolonged periods in a freeze-dried state.

E. Chromi The Cambridge team project strived to facilitate biosensor design and construction. They designed and characterised two types of parts - Sensitivity Tuners and Colour Generators – E. coli engineered to produce different pigments in response to different concentrations of an inducer. The availability of these parts revolutionized the path of future biosensor design.

3 Further Reading

4 Tools and Techniques

Synthetic biology combines many fields, and the techniques used are not particular to synthetic biology. Much like the process of solving other engineering problems, the process of creating a useful biological system has designing, building, testing, and improving phases. Once a design or statement of the desired properties of a biological system are created, the problem becomes finding the proper biological components to build such a system.

BioCompiler [1] is a tool developed to allow the programming of biological circuits using a high-level programming language. One can write programs in a language similar to LISP and compile their program into a biological circuit. BioCompiler uses a process similar to that of a compiler for a programming language. It uses a human-written program as a high-level description of the genetic circuit, then generates a formal description of the program. From there, it looks up abstract genetic regulatory network pieces that can be combined to create the genetic circuit and goes through its library of DNA parts to find appropriate sequences to match the functionality of the abstract genetic regulatory network pieces. Assembly instructions can then be generated for creating cells with the appropriate genetic regulatory network.

BioBrick standard biologic parts (biobricks.org)are another tool used in synthetic biology. Similar to the parts in the Registry of Standard Biological Parts, BioBrick standard biological parts are DNA sequences of defined structure and function. Each BioBrick part is a DNA sequence held together in a circular plasmid. At either end of the BioBrick contains a known and well-defined sequence with restriction enzymes that can cut open the plasmid at known positions. This allows for the creation of larger BioBrick parts by chaining together smaller ones. Some competitors in the iGEM competition used BioBrick systems to develop an *E. coli* line that produced scents such as banana or mint.

Figure 5: An example of a BioCompiler program and the process of actualizing it (credit to Ron Weiss)

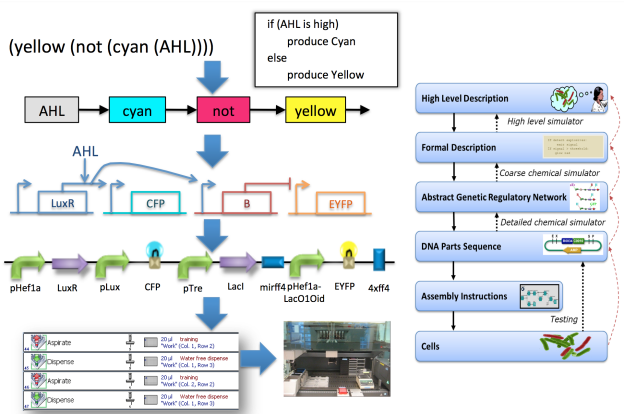
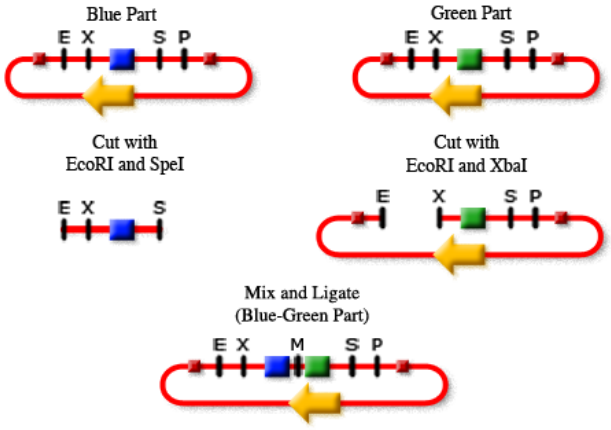


Figure 6: An example of combining BioBrick Pieces taken from http://2006.igem.org/wiki/index.php/Standard_Assembly



5 What Have We Learned?

Synthetic biology is an emerging disciplines that aims to create useful biological systems to solve problems in energy, medicine, environment, and many more fields. Synthetic biologists attempt to use abstraction to enable them to build more complex systems from simpler ones in a similar way to how a software engineer or an electrical engineer would make a computer program or a complex circuit. The Registry of Standard Biological Parts and BioBrick standard biological parts aim to characterize and standardize biological pieces just as one would a transistor or logic gate to enable abstraction. Tools such as BioCompiler allow people to describe a genetic circuit using a high-level language and actually build a genetic circuit with the described functionality. Synthetic biology is still new, and research can be done by those unfamiliar with the field, as demonstrated by the iGEM competition.

References

[1] J. Beal and J. Bachrach. Cells are plausible targets for high-level spatial languages, 2008.

[2] M. Elowitz and S. Leibler. A synthetic oscillatory network of transcriptional regulators. *Nature*, 403:335–338, 2000.

[3] iGEM. igem: Synthetic biology based on standard parts, December 2012.

[4] Registry of Standard Biological Parts. Registry of standard biological parts, December 2012.