6.047 / 6.878 Computational Biology: Genomes, Networks, Evolution
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Lecture 25: Synthetic Biology

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1 Introduction

Compared to human-engineered artifacts, biological systems are strikingly powerful: they are reliable and flexible, capable of storing information at incredible density, and — most importantly — able to self-replicate. In many ways, biology, when viewed as a technology, is vastly superior to any other.

Scientists have been modifying biological systems for many years — both to better understand them and to make them do useful work. Though often called 'genetic engineering', these traditional approaches lack the rigor and power of true engineering disciplines. Synthetic biology is a new discipline that aims to truly *engineer* biology: synthetic biologists develop techniques and genetic parts, with a focus on standardization, characterization, and modularity.

2 The Analogy Between Electrical Engineering and Synthetic Biology

The analogy between electrical engineering and synthetic biology is strong. Electrical engineering splintered off from physics in the early twentieth century because electrical engineers were building circuits instead of studying quantum physics. Similarly, synthetic biology has splintered off from traditional biology and bioengineering in this century because synthetic biologists are engineering organisms instead of investigating natural ones.

This analogy extends beyond history: in many ways, synthetic biologists are actively modeling their discipline on electrical engineering (among other fields). The power of modern digital systems is largely due to the idease of hierarchy, abstraction, standardization, etc. Consider the hierarchy in modern EECS:

- atoms and transistors, where physicists work
- transistors and connections, where layout engineers work
- abstract logic gates, where computer architects work
- assembly and C programming, where system programmers work
- high-level programming, where application programmers work

It would be impossible to understand all these levels at once — who could understand an OS kernel as a quantum mechanical system? Instead, engineers working at one level of the hierarchy abstract the level below: computer architects treat a handful of transistors as an abstract logic gate, application programmers treat a series of complicated interactions with a hard drive as a simple system call. Standards play a critical role in this hierarchy: the standard x86 instruction set allows operating systems to run on both AMD and Intel hardware and the POSIX standard allows a great deal of software to compile and run on any UNIX-like system.

Synthetic biologists have put much effort into the development of modular, standardized 'biological parts' (usually genes or sets of genes.) The BioBrick standard, a 'packaging' for DNA that allows easy assembly of subparts, is perhaps the most widely used [4]. Families of logic gates have been implemented using both RNA [6] and DNA [5], and work has been done on producing spec sheets for genetic parts [1].

3 Complexity Reduction

Electrical engineers and computer scientists have a host of design and modeling tools at their disposal; modern hardware design would be impossible without them. A major barrier to the development of analogous tools for synthetic biologists is the complexity of biological systems. The most popular organisms for engineering are *E. coli* and *S. cerevisiae*; though both are well-studied, they are complex and are not yet understood to the degree that would permit accurate computational modeling.

One solution to this problem is to *engineer* a simple, well-understood organism — to design a 'chassis' for synthetic biology. Multiple teams are working toward this goal; most are focusing on reengineering Mycoplasmas, a group of bacteria with some of the smallest known genomes.

3.1 Minimal Cells

One approach to the reduction of complexity is the attempt to design a minimal cell: a cell with the smallest possible genome. Most notable is the team at JCVI attempting to design a minimal cell based on the bacterium *Mycoplasma genitalium* [3] [2].

3.2 Simple Cells

A second approach, that taken by Dr. Knight, is to design a cell that is as *simple* as possible. This differs from a minimal cell: a cell where many proteins have multiple roles will likely have a smaller genome than a cell where every protein has a single role, but the latter is conceptually much simpler.

Dr. Knight has chosen to engineer a simple cell starting from the bacterium *Mesoplasma florum* (another mycoplasma), which has a number of advantages:

- short doubling time
- no growth at 37 °C
- a unique genetic code (like other mycoplasmas)

As a first step in the process of engineering a simplified cell, Dr. Knight's lab has determined the essential genes in the genome of *M. florum* by creating and sequencing a library of knockout mutants. The next steps in the process include adding a plasmid system, adding a recET recombination system, and developing a kit of recoded parts (e.g. GFP, antibiotic resistance genes).

4 Biosafety

Synthetic biological systems pose at least three potential dangers: uncontrolled growth, horizontal gene transfer *from* natural organisms, and horizontal gene transfer *to* natural organisms. Uncontrolled growth could be checked by designing synthetic biological systems to require pairs of nutrients: though evolution might circumvent a single nutrient requirement, it is unlikely to circumvent two simultaneously.

Engineered organisms based on *M. florum* would be naturally resistant to horizontal gene transfer (in either direction). UGA, normally a stop codon, is the preferred tryptophan codon in *M. florum*; thus, gene transfer to natural organisms is unlikely. Similarly, gene transfer from natural organisms is prevented by the fact that CGG is a nonsense codon in *M. florum*. Further altering the genetic code in synthetic biological systems could increase this natural barrier.

References

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