

ECE/CS/BioEn 6760

Engineering Genetic Circuits

Chris J. Myers

Lecture 0: Course Overview

Course Information

- Webpage: access using CANVAS
- Meeting time: TTh 2-3:20pm
- Meeting place: MEB 2325
- Office hours: TTh 3:30-4:30pm or by appointment
- Email: myers@ece.utah.edu
- Office: MEB 4112 / 581-6490

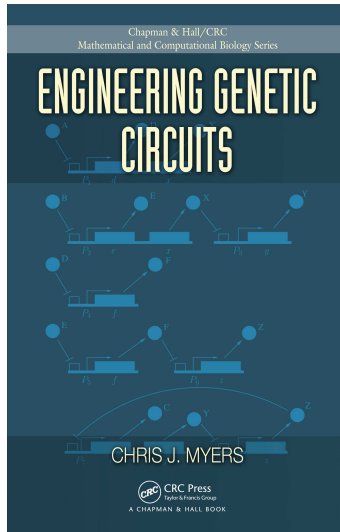
Prerequisites

- Students should have some familiarity with:
 - Genetics, cell biology, molecular biology, or biochemistry, OR
 - Engineering methods for modeling, analysis, and design.

Grading Policy

- Participation - 10 percent
 - Attend class.
 - Participate in class discussions.
- Homework - 40 percent
 - Will learn how to use and create modeling, analysis, and design tools.
 - Use simple system for tutorial.
 - Choose a genetic circuit to use in your assignments.
 - Model, analyze, and design your genetic circuit with these tools.
- Project - 50 percent
 - Design a genetic circuit, or
 - Design and implement a software tool.

Recommended Textbook



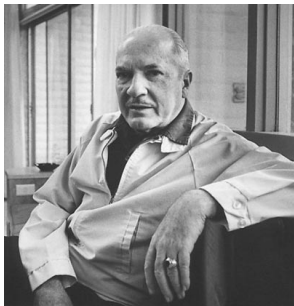
What is Engineering?



Samuel Florman

Engineering is the art or science of making practical.

What is Engineering?



Robert Heinlein

One man's "magic" is another man's engineering.

What are Genetic Circuits?

- A cell includes three main types of biological networks (circuits):
 - *Metabolic networks* are enzymatic processes that transform food into energy, and perform both biosynthesis and biodegradation.
 - *Protein networks* are communication and signaling networks which are composed of basic reactions between two or more proteins.
 - *Genetic regulatory networks*, or *genetic circuits*, regulate gene expression at many molecular levels.

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- **The focus of this course is the application of engineering methods to the modeling, analysis, and design of genetic circuits.**

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- **The focus of this course is the application of engineering methods to the modeling, analysis, and design of genetic circuits.**
- **GOAL: facilitate collaborations between engineers and biologists.**

What is Bioinformatics?

- Biology is now both a lab-based science and an information science.
- Biologists have had to draw assistance from those in mathematics, computer science, and engineering.
- Result was development of *bioinformatics* and *computational biology*.
- Major goal is to extract new biological insights from large and noisy sets of data generated by high throughput technologies.
- Must create and maintain databases with massive amounts of data.
- Must be able to efficiently access, submit, and revise this data.
- Latest software must even analyze and interpret this data.
- Bioinformatics refers to the analysis of *static* data such as sequence analysis of DNA and protein sequences, techniques for finding genes or evolutionary patterns, and *cluster analysis* of microarray data.
- Bioinformatics algorithms are not explicitly covered in this course.

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- Bioinformatics algorithms are not explicitly covered in this course.
- **Results of bioinformatics research are important to this course.**

What is Systems Biology?

- *Systems biology* is the study of the mechanisms underlying complex molecular processes as integrated into systems or pathways made up of many interacting genes and proteins.
- Concerned with the analysis of *dynamic* models.
- Made possible by new experimental methods such as:
 - cDNA microarrays and oligonucleotide chips.
 - Mass spectrometric identification of gel-separated proteins.
 - 2-hybrid systems.
 - Genome-wide location analysis (ChIP-to-chip)
- Systems biology involves:
 - Collection of large experimental data sets,
 - Constructing mathematical models from this data,
 - Designing software to accurately and efficiently analyze these models *in silico* (i.e., on a computer), and
 - Comparing numerical simulations with the experimental data.

What is Systems Biology? (cont)

- Ultimate goal is to develop methods which can give reasonable predictions of experimental results.
- While it will never replace experimental methods, may help experimentalists make better use of their time.
- Also may gain insight into mechanisms used by these biological processes which may not be obtained by experiments.
- Eventually, may be possible that they could have substantial impact on our society such as aiding in drug discovery.
- Systems biology was focus of previous iterations of this course.

What is Systems Biology? (cont)

- Ultimate goal is to develop methods which can give reasonable predictions of experimental results.
- While it will never replace experimental methods, may help experimentalists make better use of their time.
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- Eventually, may be possible that they could have substantial impact on our society such as aiding in drug discovery.
- Systems biology was focus of previous iterations of this course.
- **Modeling and analysis methods for systems biology are important for this course, but the applications considered will be different.**

Systems Biology Example: Phage λ



Esther Lederberg



Andre Lwoff



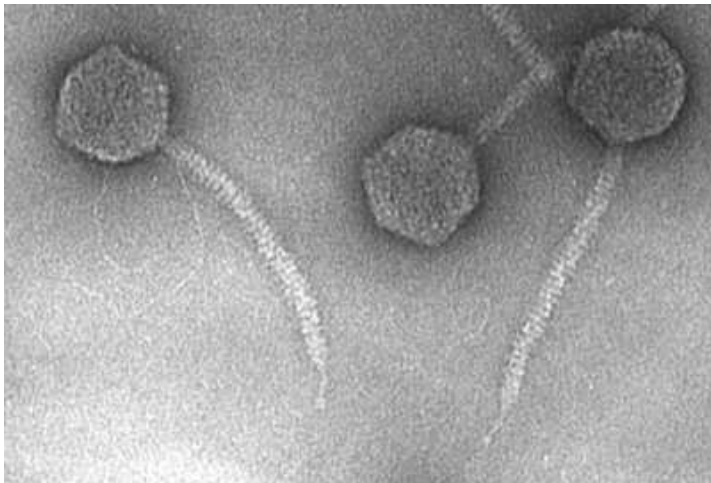
Francois Jacob



Jacques Monod

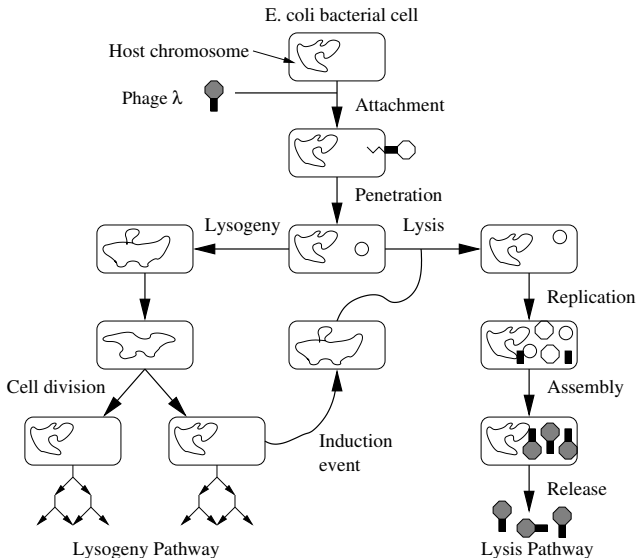
- In 1953, Lwoff et al. discovered that a strain of *E. Coli* when exposed to UV light lyse spewing forth λ viruses.
- Some of the newly infected *E. Coli* would soon lyse while others grow and divide normally until exposed to UV light.
- In other words, some cells follow a *lysis* pathway while other followed a *lysogeny* pathway.
- The decision between the lysis and the lysogeny developmental pathway is made by a fairly simple genetic circuit.

Systems Biology Example: Phage λ

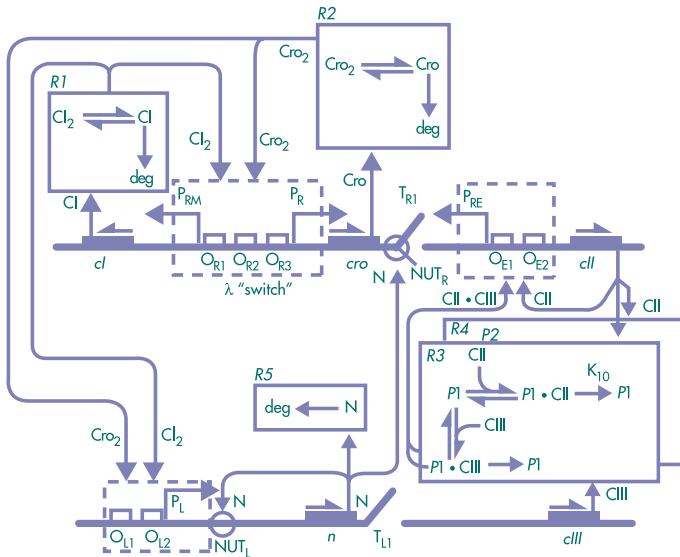


(Courtesy of Maria Schnos and Ross Inman, Institute for Molecular Virology, University of Wisconsin, Madison)

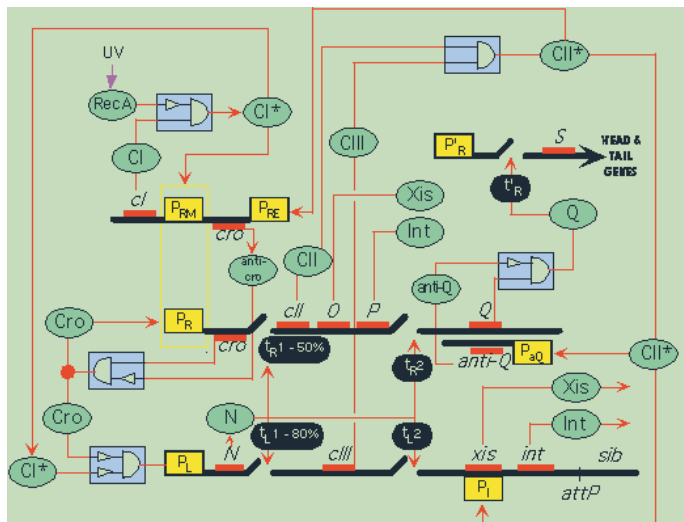
Phage λ Developmental Pathways



Phage λ Decision Circuit

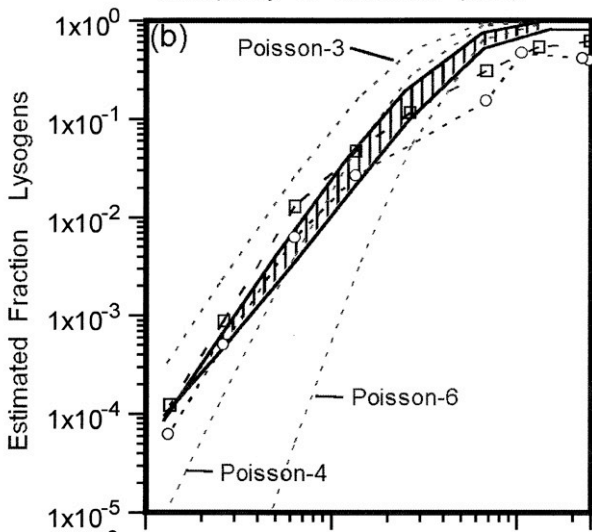


Another Representation of the Phage λ Decision Circuit



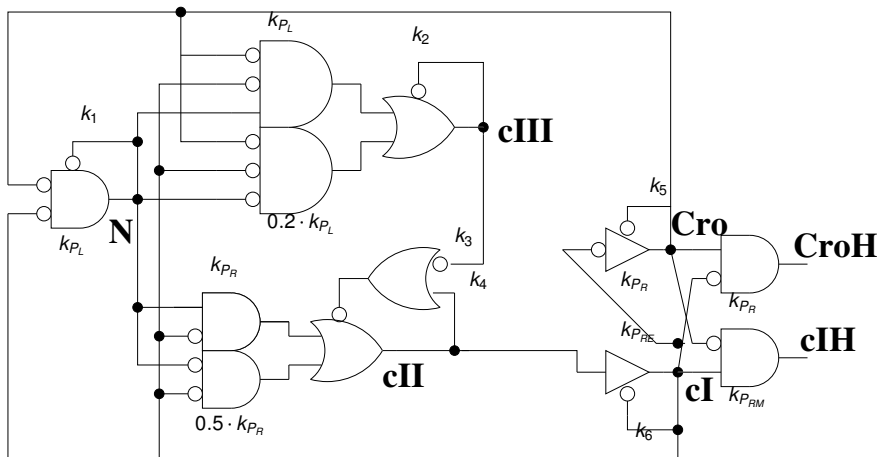
McAdams/Shapiro, Science (1995)

Stochastic Simulation Results for the Phage λ Circuit

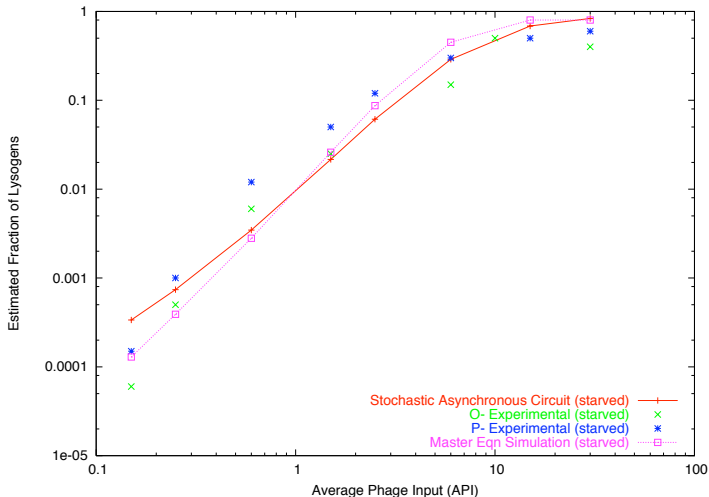


Arkin/Ross/McAdams, Genetics (1998)

Stochastic Asynchronous Circuit Model for Phage λ



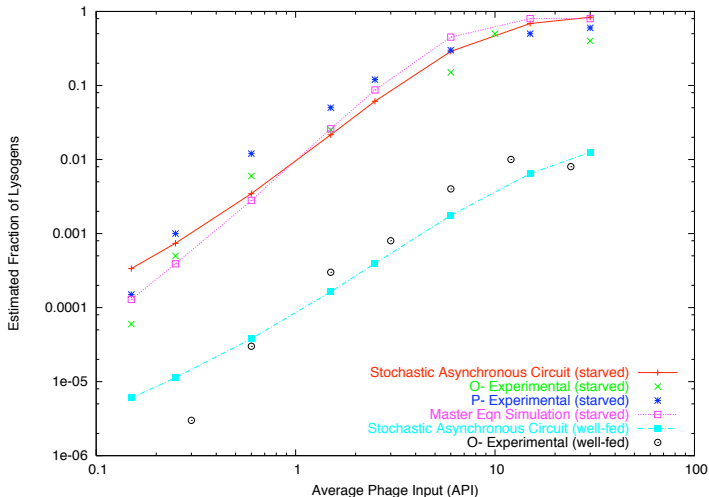
Stochastic Asynchronous Circuit Results



SAC results generated in only 7 minutes.

Kuwahara et al., Trans. on Comp. Sys. Bio. (2006)

Stochastic Asynchronous Circuit Results



SAC results generated in only 7 minutes.

Kuwahara et al., Trans. on Comp. Sys. Bio. (2006)

Systems Biology Versus Synthetic Biology



Drew Endy

What is Synthetic Biology?



Biology has at least 50 more
interesting years
– James Watson (1984).

What is Synthetic Biology?



Biology has at least 50 more
interesting years
– James Watson (1984).

- *Synthetic biology* has likely extended this much further.
- Synthetic biology involves:
 - Designing new biological systems to achieve a desired function.
 - Creating systems that actually agree with our models.
- Potential applications:
 - Produce drugs and bio-fuels.
 - Consume toxic waste.
 - Destroy tumors.
- **Synthetic biology is the focus of this course.**

Genetic Engineering vs. Synthetic Biology

- *Genetic engineering* (last 40 years) consists of experimental techniques to produce artificial DNA sequences.
- Synthetic biology adds:
 - *Standards* - create repositories of parts that can be easily composed.
 - *Abstraction* - high-level models to facilitate design.
 - *Decoupling* - separate design from construction.

(source: Drew Endy)

Genetic Engineering vs. Synthetic Biology

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- Synthetic biology adds:
 - *Standards* - create repositories of parts that can be easily composed.
 - *Abstraction* - high-level models to facilitate design.
 - *Decoupling* - separate design from construction.
- **In other words, synthetic biology makes genetic engineering a “real” engineering discipline.**

(source: Drew Endy)

nature International weekly journal of science

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Nature Research

Letters to Nature

Nature **403**, 339–342 (20 January 2000) | doi:10.1038/35002131; Received 15 September 1999; Accepted 23 November 1999

Construction of a genetic toggle switch in *Escherichia coli*

Timothy S. Gardner^{1,2}, Charles R. Cantor¹ & James J. Collins^{1,2}

1. Department of Biomedical Engineering,
2. Center for BioDynamics and
3. Center for Advanced Biotechnology, Boston University, 44 Cumming Street, Boston, Massachusetts 02215, USA

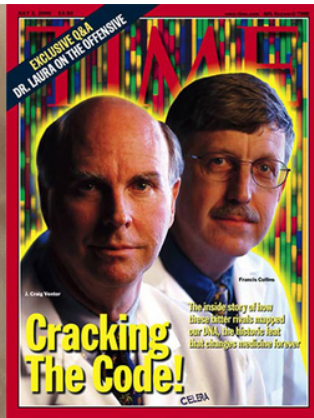
Correspondence to: James J. Collins^{1,2} Correspondence and requests for materials should be addressed to J.J.C. (e-mail: Email: jcollins@bu.edu). Plasmid sequences are available at <http://cbd.bu.edu/abl/toggle>.

It has been proposed¹ that gene-regulatory circuits with virtually any desired property can be constructed from networks of simple regulatory elements. These properties, which include multistability and oscillations, have been found in specialized gene circuits such as the bacteriophage λ switch² and the *Cyanobacteria* circadian oscillator³. However, these behaviours have not been demonstrated in networks of non-specialized regulatory components. Here we present the construction of a genetic toggle switch—a synthetic, bistable gene-regulatory network—in *Escherichia coli* and provide a simple theory that predicts the conditions necessary for bistability. The toggle is constructed from any two repressible promoters arranged in a mutually inhibitory network. It is flipped between stable states using transient chemical or thermal induction and exhibits a nearly ideal switching threshold. As a practical device, the toggle switch forms a synthetic, addressable cellular memory unit and has implications for biotechnology, biocomputing and gene therapy.

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The Beginning: January 2000

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Human Genome Project
Published February 2001
Cost of \$3 billion
1990 → 2003

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Synthetic Biology 1.0

The First International Meeting on Synthetic Biology

June 10-12, 2004
at the
Massachusetts Institute of Technology
Cambridge, MA

Synthetic Biology 1.0 brought together, for the first time, researchers who are working to:

1. design and build biological parts, devices and integrated biological systems,
2. develop technologies that enable such work, and
3. place this scientific and engineering research within its current and future social context.

Download a one-page [summary \(pdf\)](#) about the conference.

MIT's Biology Department, Biological Engineering Division, Electrical Engineering & Computer Science Department, Computer Science & Artificial Intelligence Laboratory, and MIT Synthetic Biology Working Group helped to support the meeting.

We hope that you enjoyed the conference.

If you would like to give us feedback about the conference, use this [web form](#) to email us.

Please note that the conference proceedings will not be released.

Some of the talks are now available online:

- [George Poste](#)
- [Paul Rabinow](#)

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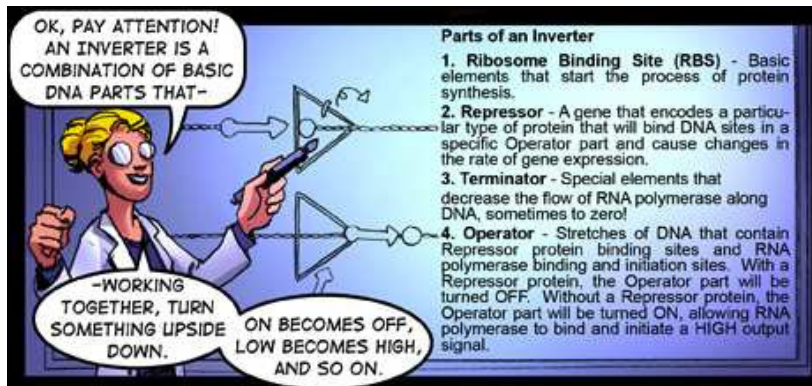


iGEM 2004: 5 teams, 31 participants, ~50 parts

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(From "Adventures in Synthetic Biology" - Endy et al.)

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iGEM 2005: 13 teams, 125 participants, \sim 125 parts

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Synthetic Biology 2.0

The Second International Meeting on Synthetic Biology

May 20-22, 2006

at the

University of California, Berkeley

Berkeley, CA

[Official Conference Website](#)

Taken from the [Official Conference Website](#)

The Second International Conference on Synthetic Biology (SB2.0) will take place on May 20-22, 2006, at the University of California, Berkeley. The conference will bring together a diverse group of participants from a variety of disciplines, including some of the world's leaders in biological engineering, biochemistry, quantitative biology, biophysics, molecular and cellular biology, bioethics, policy and governance, and the biotech industry. A collaborative effort among Berkeley Lab, MIT, UC Berkeley, and UCSF, the conference will promote and guide the further, constructive development of the field.

SB2.0 will begin with two days of plenary talks and discussions focused on five research areas: energy, chemistry, health, materials, and foundational technologies. The [third day of the conference](#) will be dedicated to presentation, discussion, and deliberation of the four key societal issues associated with synthetic biology: biosecurity & risk, public understanding & perception, ownership, sharing & innovation, and community organization. All conferees will be expected to participate in these conversations.

This site is hosted on [OpenWetWare](#) and can be edited by all members of the Synthetic Biology community.

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iGEM 2006: 32 teams, 723 participants, ~724 parts

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iGEM 2007: 54 teams, 777 participants, ~800 parts

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iGEM 2008: 88 teams, 1248 participants, 1387 parts

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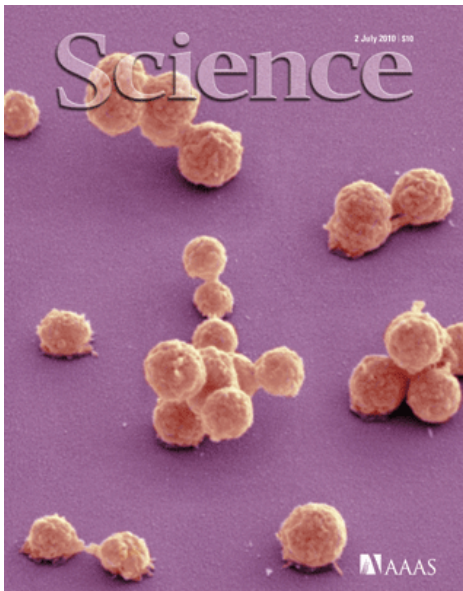


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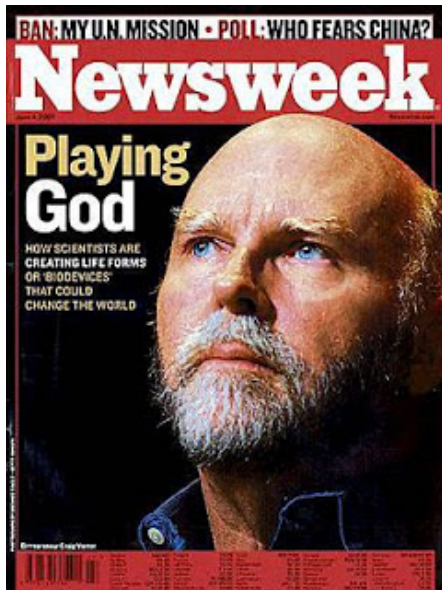


iGEM 2009: 113 teams, 1840 participants, 1348 parts

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iGEM 2010: 128 teams, 2327 participants, 1863 parts

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SB 5.0, Stanford University, June 2011

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Essential information for synthetic DNA sequences

To the Editor:

Following a discussion by the workgroup for Data Standards in Synthetic Biology, which met in June 2010 during the Second Workshop on Bidesign Automation in Anaheim, California, we wish to highlight a problem relating to the reproducibility of the synthetic biology literature. In particular, we have noted the very small number of articles reporting synthetic gene networks that disclose the complete sequence of all the constructs they describe.

To our knowledge, there are only a few examples where full sequences have been released. In 2005, a patent application¹ disclosed the sequences of the toggle switches published four years earlier in a paper by Gardner *et al.*². The same year, Basu *et al.*³ deposited their construct sequences for programmed pattern formation into GenBank³. Examples of synthetic DNA sequences derived from standardized parts that have been made available in GenBank include the refactored genome of the bacteriophage

gaps between key components are almost never reported, presumably because they are not considered crucial to the report. Yet, synthetic biology relies on the premise that synthetic DNA can be engineered with base-level precision.

Missing sequence information in papers hurts reproducibility, limits reuse of past work and incorrectly assumes that we know fully which sequence segments are important. For example, many synthetic biologists are currently realizing that translation initiation rates are dependent on more than the Shine-Dalgarno sequence⁴. Sequences upstream of the

start codon are crucial for translation rates, yet are underreported. Similarly, it has been demonstrated that intron length can affect the dynamics of genetic oscillators⁵. Many more such examples are likely to emerge.

Because full sequence disclosure is critical, we wonder why the common requirement by many journals to provide GenBank entries

for genomes and natural sequences has

and welcome contributions from the greater community.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

Jean Peccoud¹, J Christopher Anderson², Deepak Chandran³, Douglas Densmore⁴, Michal Galdzicki⁵, Matthew W Lux¹, Cesar A Rodriguez⁶, Guy-Bart Stan⁷ & Herbert M Sauro³

¹Virginia Bioinformatics Institute, Virginia Tech, Blacksburg, Virginia, USA. ²Department of Bioengineering, QB3: California Institute for Quantitative Biological Research, University of California, Berkeley, California, USA.

³Department of Bioengineering, University of Washington, Seattle, Washington, USA.

⁴Department of Electrical and Computer Engineering, Boston University, Boston, Massachusetts, USA. ⁵Biomedical and Health Informatics, University of Washington, Seattle, Washington, USA. ⁶BIOFAB, Emeryville, California, USA. ⁷Department of Bioengineering and Centre for Synthetic Biology and Innovation, Imperial College London, London, UK.
e-mail: peccoud@vt.edu

1. Gardner, T.S. & Collins, J.J. US patent 6,841,376 (2005).
2. Gardner, T.S., Cantor, C.R. & Collins, J.J. *Nature* **403**, 339–342 (2000).
3. Basu, S., Gerchman, Y., Collins, C.H., Arnold, F.H. & Woicik, B. *Nature* **434**, 1125–1129 (2006).



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The Synthetic Biology Open Language (SBOL) provides a community standard for communicating designs in synthetic biology

[Michal Galdzicki](#), [Kevin P Clancy](#), [Ernst Oberortner](#), [Matthew Pocock](#), [Jacqueline Y Quinn](#),
[Cesar A Rodriguez](#), [Nicholas Roehner](#), [Mandy L Wilson](#), [Laura Adam](#), [J Christopher Anderson](#),
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Endy](#), [Raik Grünberg](#), [Jennifer Hallinan](#), [Nathan J Hillson](#), [Jeffrey D Johnson](#), [Allan Kuchinsky](#),
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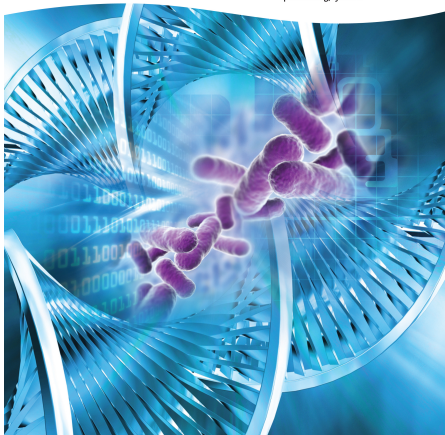
iGEM 2011: 165 teams, 2586 participants, 1355 parts

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ACS SyntheticBiology

January 2012 • Volume 1, Issue 1

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Theory

A Whole-Cell Computational Model Predicts Phenotype from Genotype

Jonathan R. Karr,^{1,4} Jayodita C. Sanghvi,^{2,4} Derek N. Macklin,² Miriam V. Gutschow,² Jared M. Jacobs,² Benjamin Bolival, Jr.,² Nacyra Assad-Garcia,³ John I. Glass,³ and Markus W. Covert^{2,*}

¹Graduate Program in Biophysics

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⁴These authors contributed equally to this work

*Correspondence: mcovert@stanford.edu

<http://dx.doi.org/10.1016/j.cell.2012.05.044>

SUMMARY

Understanding how complex phenotypes arise from individual molecules and their interactions is a primary challenge in biology that computational approaches are poised to tackle. We report a whole-cell computational model of the life cycle of the human pathogen *Mycoplasma genitalium* that

First, until recently, not enough has been known about the individual molecules and their interactions to completely model any one organism. The advent of genomics and other high-throughput measurement techniques has accelerated the characterization of some organisms to the extent that comprehensive modeling is now possible. For example, the mycoplasmas, a genus of bacteria with relatively small genomes that includes several pathogens, have recently been the subject of an exhaustive experimental effort by a European consortium to determine

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iGEM 2012: 190 teams, 3696 participants, 1708 parts

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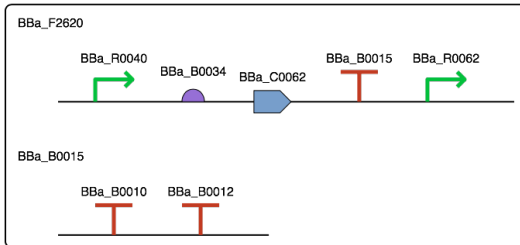


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COMMUNITY PAGE

SBOL Visual: A Graphical Language for Genetic Designs

Jacqueline Y. Quinn¹*, Robert Sidney Cox III²*, Aaron Adler³, Jacob Beal³, Swapnil Bhatia⁴, Yizhi Cai⁵, Joanna Chen^{6,7}, Kevin Clancy⁸, Michal Galdzicki⁹, Nathan J. Hillson^{6,7}, Nicolas Le Novère¹⁰, Akshay J. Maheshwari¹¹, James Alastair McLaughlin¹², Chris J. Myers¹³, Umesh P¹⁴, Matthew Pocock^{12,15}, Cesar Rodriguez¹⁶, Larisa Soldatova¹⁷, Guy-Bart V. Stan¹⁸, Neil Swainston¹⁹, Anil Wipat¹², Herbert M. Sauro²⁰*



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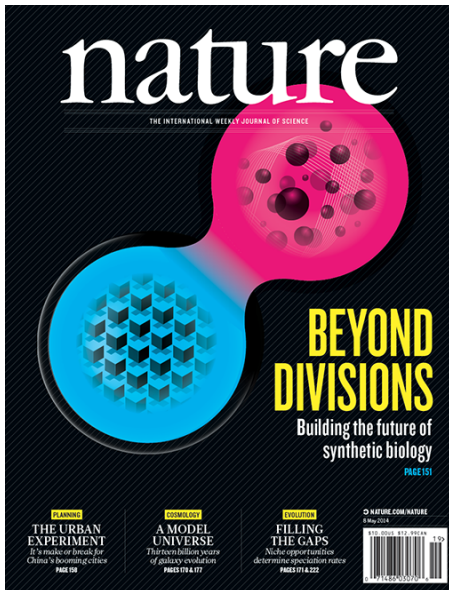


iGEM 2013: 215 teams, 4027 participants, 1708 parts

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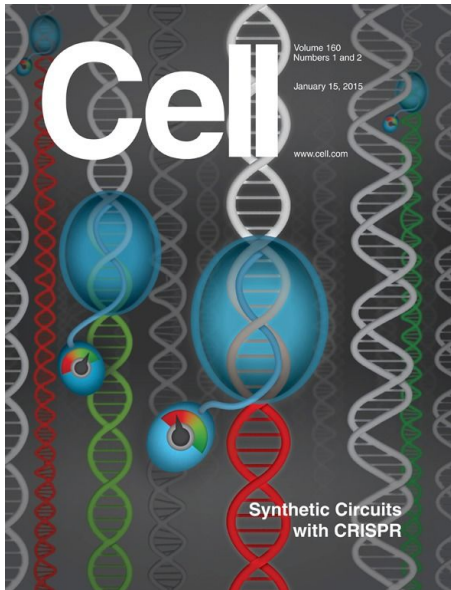


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iGEM 2014: 245 teams, 4515 participants

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Sharing Structure and Function in Biological Design with SBOL 2.0

Nicholas Roehner,^{*,†} Jacob Beal,[‡] Kevin Clancy,[§] Bryan Bartley,[⊥] Goksel Misirli,^{||} Raik Grünberg,[¶]
Ernst Oberortner,[#] Matthew Pocock,[▽] Michael Bissell,[⊗] Curtis Madsen,^{||} Tramy Nguyen,[■]
Michael Zhang,[■] Zhen Zhang,[■] Zach Zundel,[▲] Douglas Densmore,[†] John H. Gennari,[●] Anil Wipat,^{||}
Herbert M. Sauro,[⊥] and Chris J. Myers[■]

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iGEM 2015: 280 teams, 5018 participants

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SYNTHETIC BIOLOGY

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Cello

Verilog

Options

Results

About

You are logged in as **myers**

Logout

Verilog

choose

```
1 module A(output out1, input in1, in2);
2   always@(in1,in2)
3   begin
4     case({in1,in2})
5       2'b00: {out1} = 1'b0;
6       2'b01: {out1} = 1'b0;
7       2'b10: {out1} = 1'b0;
8       2'b11: {out1} = 1'b1;
9     endcase
10    end
11  endmodule
12
```

design name

Run

Inputs

choose

clear

index	name	low RPU	high RPU	DNA sequence
1	pTac	0.0034	2.8	AACGATCGTTGGCTGTGTTGACAA
2	pTet	0.0013	4.4	TACTCCACCGTTGGCTTTTTCCTCC

Outputs

choose

clear

index	name	DNA sequence
1	YFP	CTGAAGCTGTACCGGATGTGCTTCCGGTCTGATGAGTCCGT

Nielsen et al., Science (2016)

Improving Synthetic Biology Communication: Recommended Practices for Visual Depiction and Digital Submission of Genetic Designs

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iGEM 2016: 300 teams, 4432 participants

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Synthetic Biology Funding in 2016

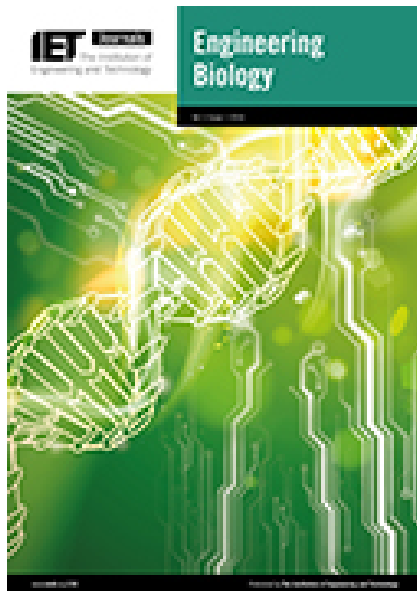


**These 33 Synthetic Biology Companies
Raised More Than \$900 Million in 2016**

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iGEM 2017: 310 teams with nearly 5400 participants from 44 countries.

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These Synthetic Biology Companies Raised \$1.7B in 2017



Gene/Genome Synthesis



Genome/Protein Engineering



Organism Engineering



Tools and Automation



Software



Biopharma and Health



Food and Agriculture



Materials



Aquaculture



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Synthetic biology companies raised over \$650 million in Q1 2018

Gene/Genome Synthesis



Genome/Protein Engineering



Organism Engineering



Food and Agriculture



Tools and Automation



Biopharma and Health



Materials



Environment

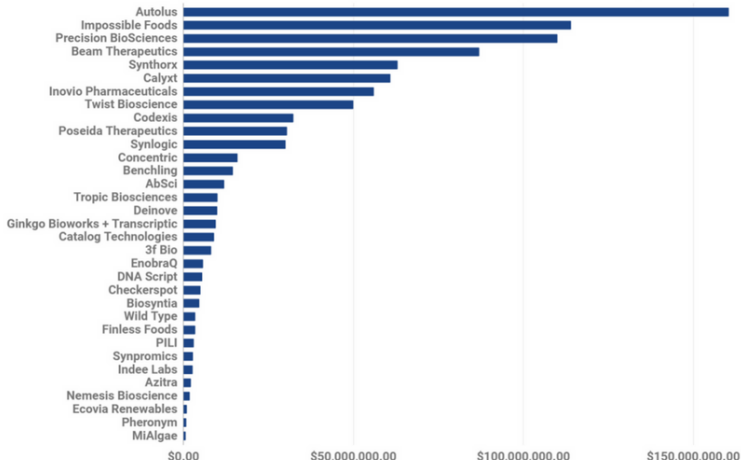


Chemicals



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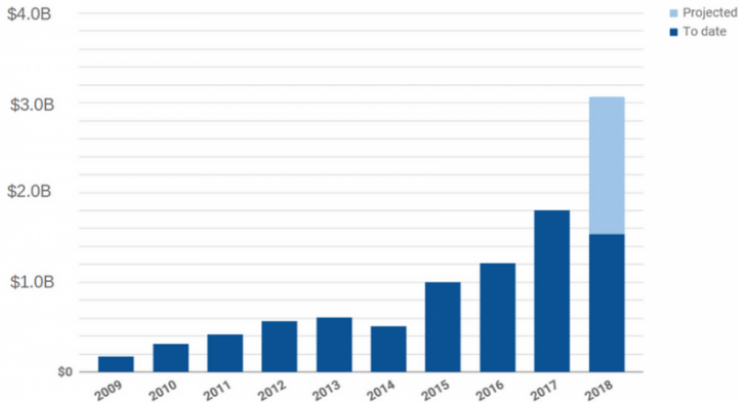
Funding for Synthetic Biology Companies - Q2 2018



**These 33 Synthetic Biology Companies
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Funding for Synthetic Biology Companies



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- An Engineer's Guide to Genetic Circuits
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