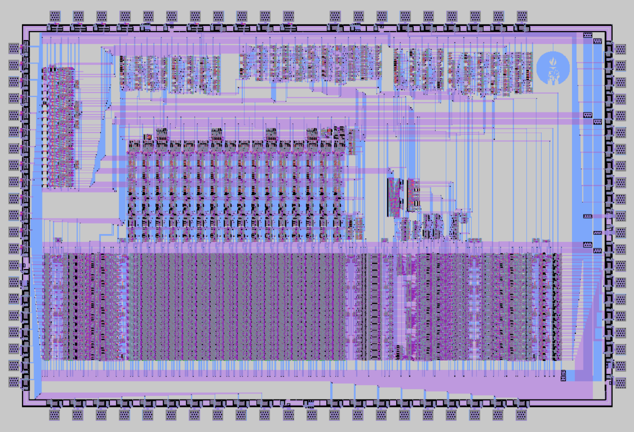
Design of Asynchronous Genetic Circuits

Chris J. Myers

CE Junior Seminar
August 27, 2019

University of Utah

Asynchronous Design at Caltech

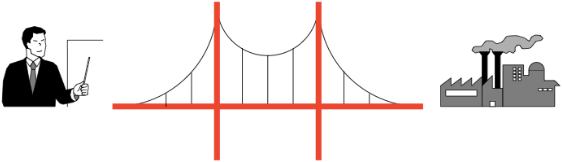


The first fully asynchronous microprocessor
(Designed by Alain Martin's group at Caltech in 1989)

Timed Asynchronous Circuits

Academia	Industry
Timing ignored	Timing critical
Complex-gates	Semi-custom
Systematic methods	Adhoc methods
Verified correct	Extensive simulation
Conservative designs	Unreliable designs

Timed Asynchronous Circuits



Utilize explicit timing information

Semi-custom

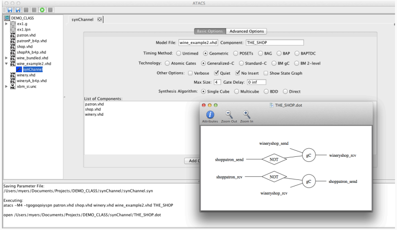
Systematic methods

Verified correct

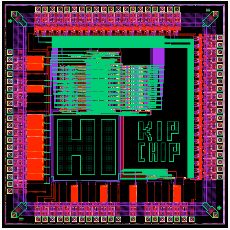
Efficient and reliable designs

(ICCD 1992, IEEE TVLSI 1993, CAV 1994, IEEE TCAD 1999)

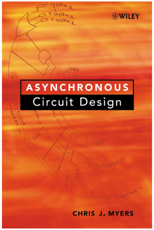
Timed Asynchronous Circuit Design and Verification



ATACS Software



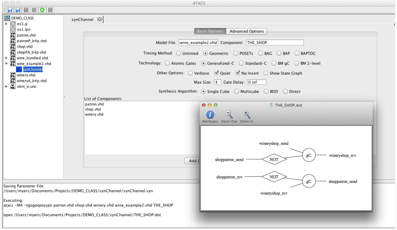
Self-timed Multiplier



Textbook

- 20 journal papers, 4 patents, and 45 conference/workshop papers (including 10 published at this conference).
- 1 postdoc, 5 MS students, and 6 PhD students (3 tenured faculty).

Timed Asynchronous Circuit Design and Verification



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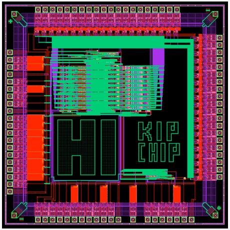

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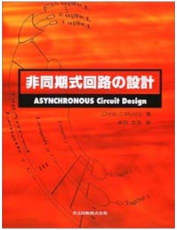

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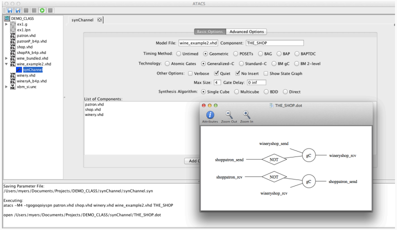

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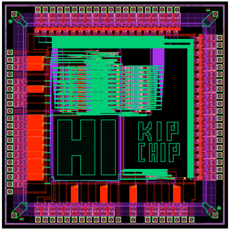

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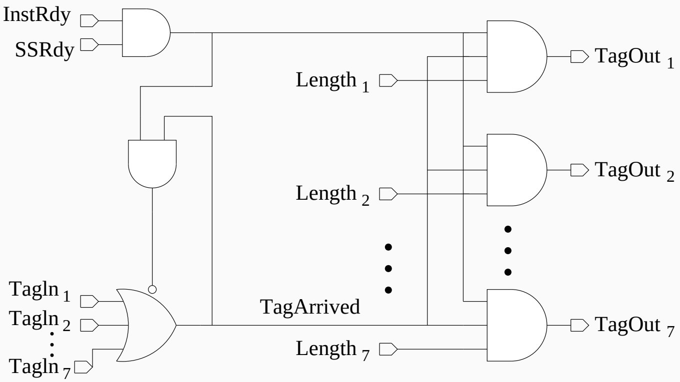
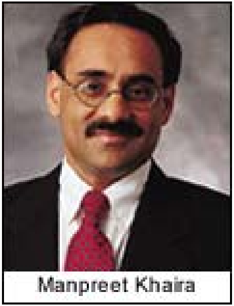
Intel RAPPID Project



ASYNC 1999 (Best Paper Award), IEEE JSSC 2001,
US Patents 5,978,899, 5,948,096, 5,941,982, and 5,931,944.

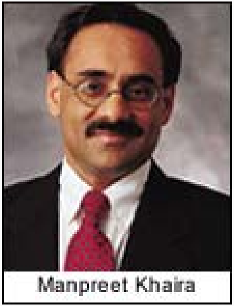
- Test chip fabricated in May 1998 using a 0.25 μm process.
- Three times faster while consuming half the power of the comparable synchronous design.



Manpreet Khaira

Fifth International Symposium on Advanced Research in Asynchronous Circuits and Systems
Barcelona (Spain), 18-21 April 1999

Top 10 Reasons to Hire an Asynchronous Designer



Manpreet Khaira

No. 1 - They are really smart, and we can teach them to do something real.

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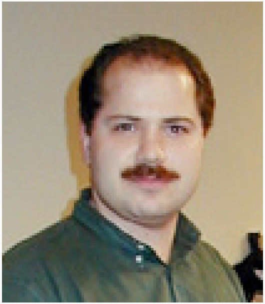
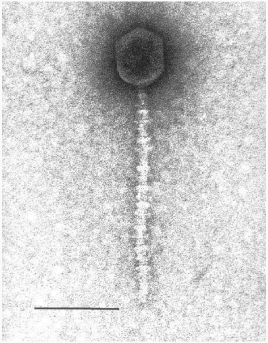
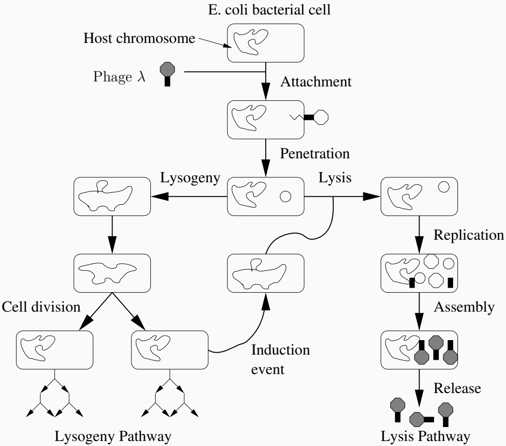


Michael Samoilov

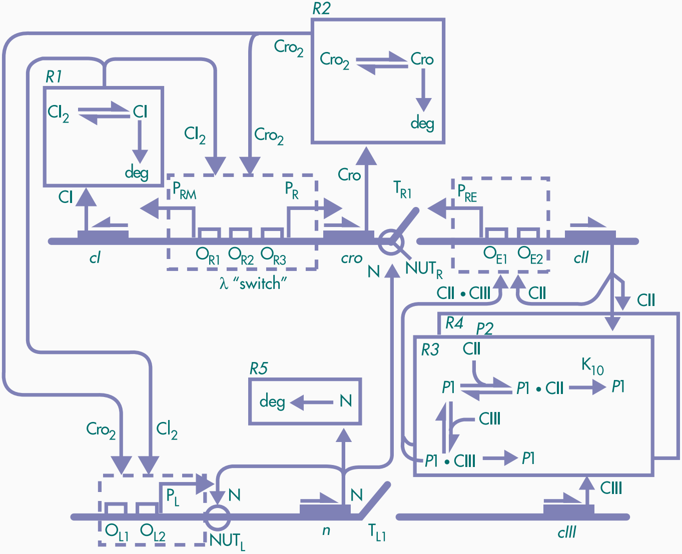
Adam Arkin

Phage λ Virus



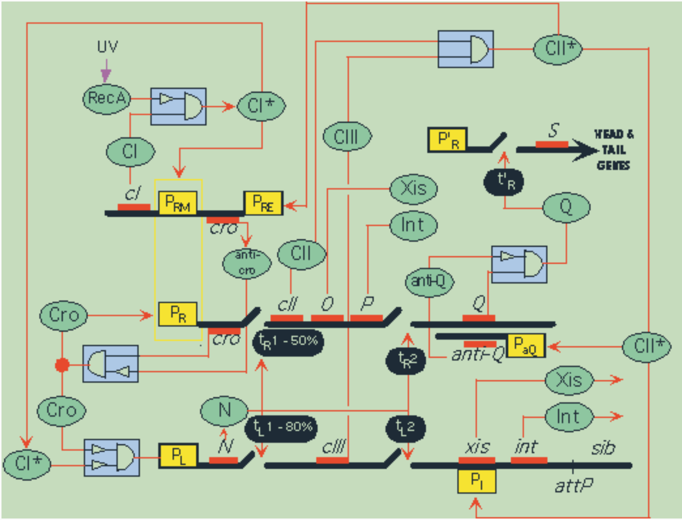


Phage λ Decision Circuit



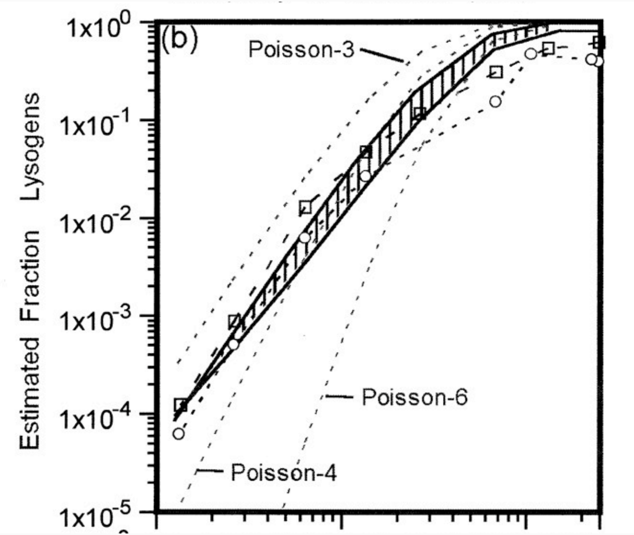
YGG 01-0052

Asynchronous Circuit?



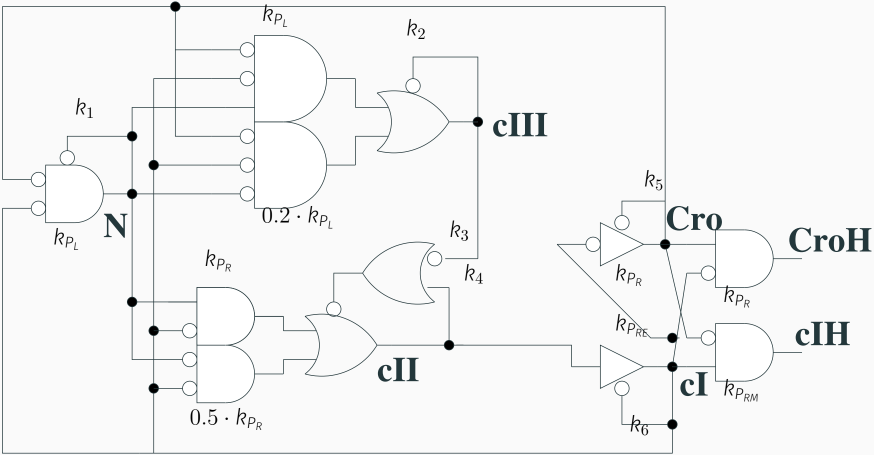
McAdams/Shapiro, Science (1995)

Stochastic Circuit?

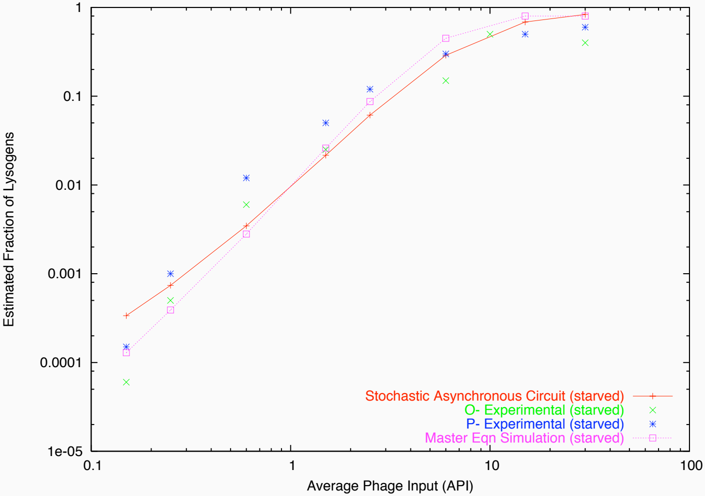


Arkin / Ross / McAdams, Genetics (1998)

Stochastic Asynchronous Circuit?



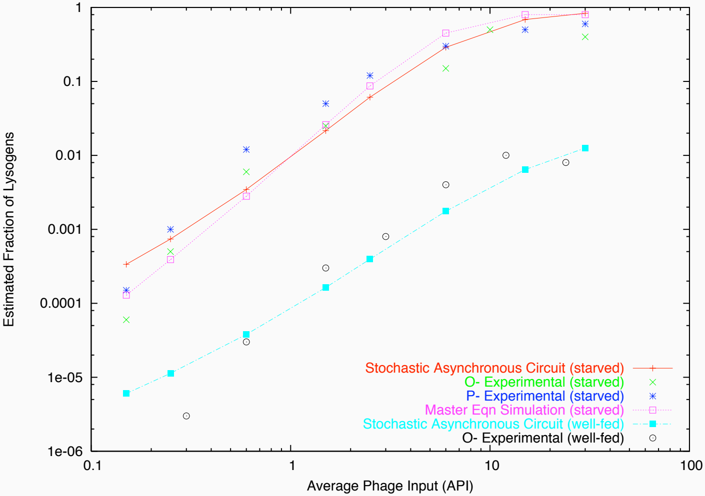
Stochastic Asynchronous Circuit Results



SAC results generated in only 7 minutes.

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

Stochastic Asynchronous Circuit Results



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Systems Biology Versus Synthetic Biology

Drew Endy

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Synthetic biology applications:

- Produce drugs and bio-fuels.
- Consume toxic waste.
- Destroy tumors.

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- Synthetic biology adds *standards*, *abstraction*, and *decoupling* to genetic engineering practice.

Systems Biology Versus Synthetic Biology

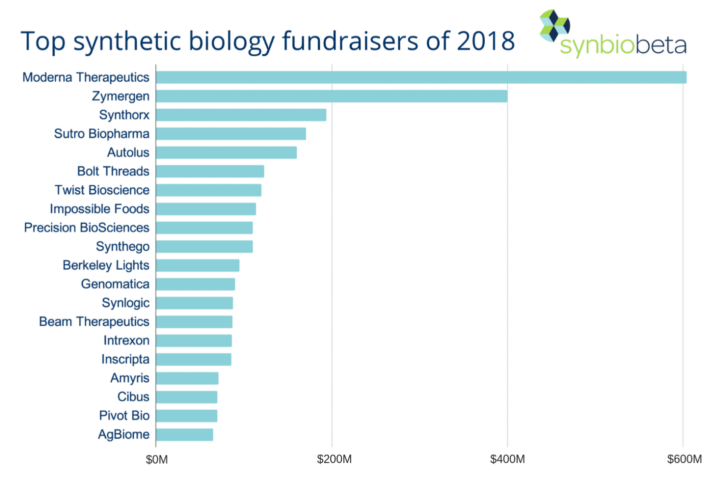
Drew Endy

Synthetic biology applications:

- Produce drugs and bio-fuels.
- Consume toxic waste.
- Destroy tumors.

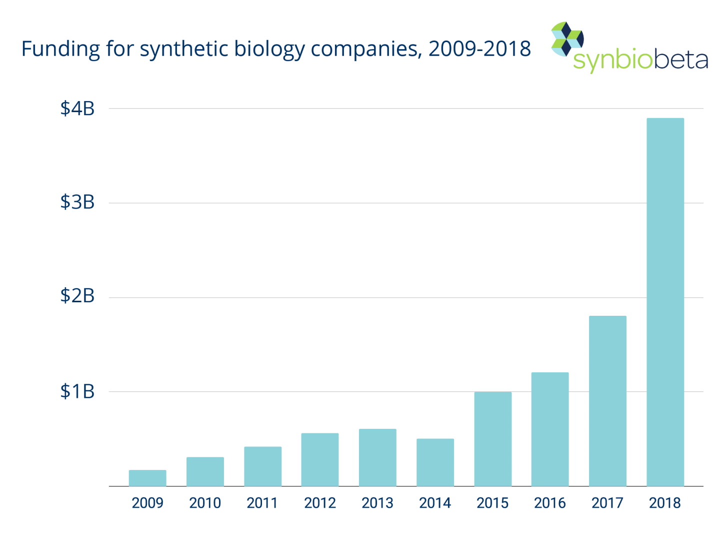
- Synthetic biology adds *standards*, *abstraction*, and *decoupling* to genetic engineering practice.
- Since *genetic circuits* are inherently asynchronous, seems appropriate to leverage asynchronous design and verification methodologies.

Synthetic Biology Startups



98 Synthetic Biology Companies
Raised More Than $3.8 Billion in 2018

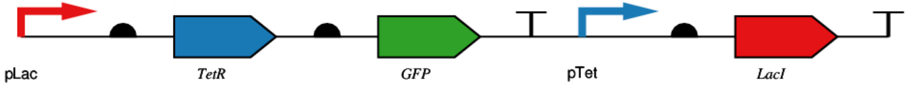
Synthetic Biology Startups



Genetic Circuit Designs

- Genetic circuits are created from biological components that mimic the behavior of Boolean logic gates.
- Genetic circuits can be built inside of a living organism (*in vivo*) or in a test tube (*in vitro*).
- Most genetic circuits that have been built are *combinational circuits*.
- Some *sequential memory circuits* have been constructed.

Genetic Toggle Switch (Gardner et al. 2000)



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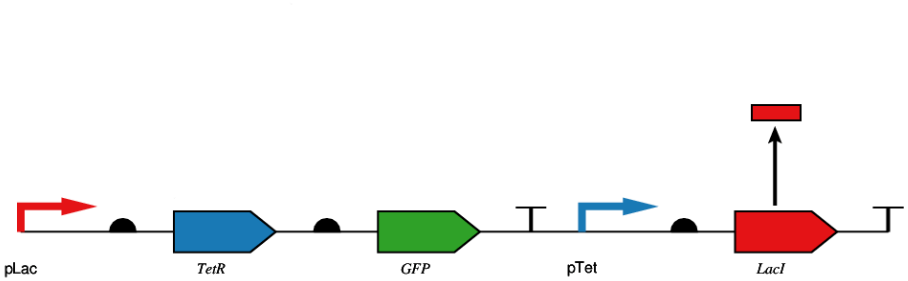

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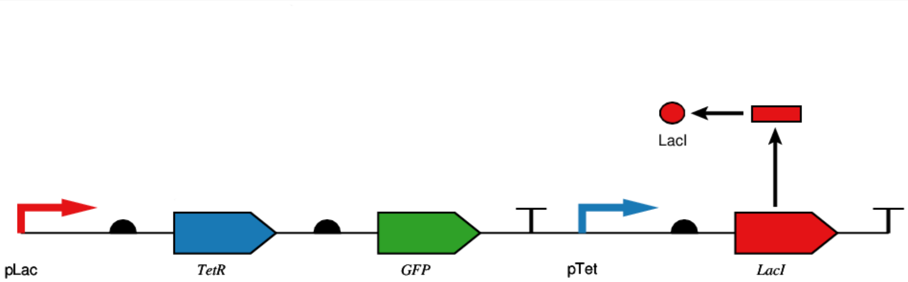

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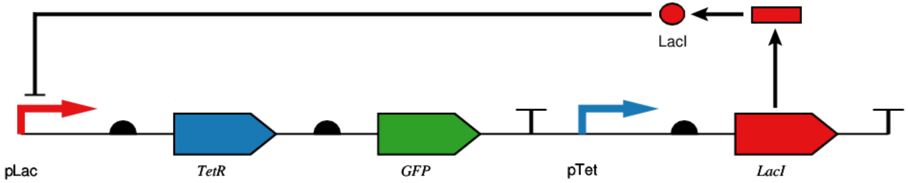

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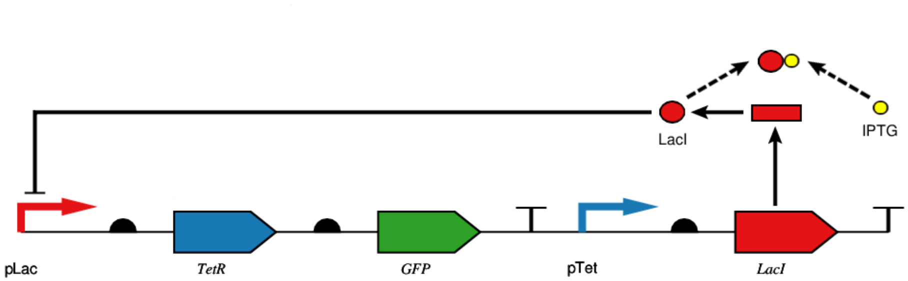

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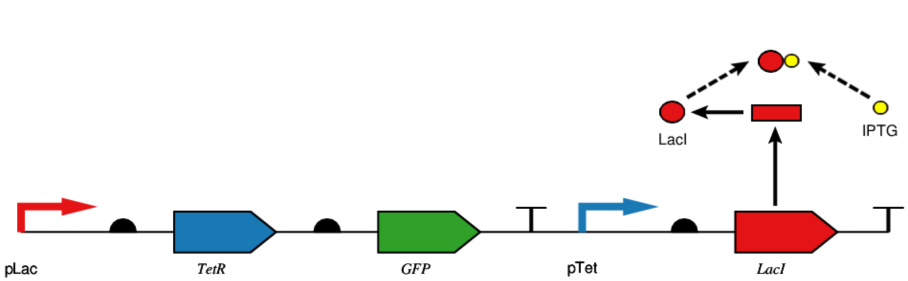

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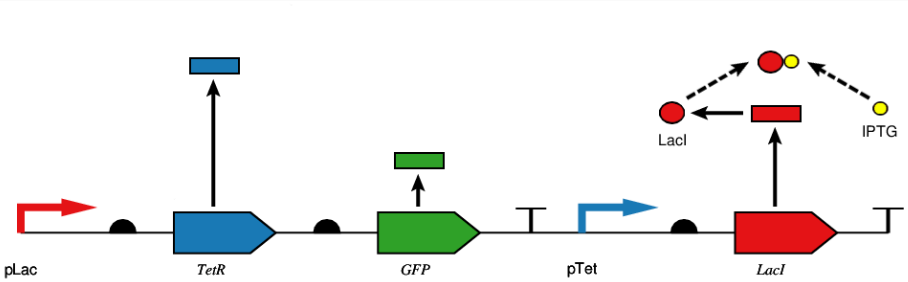

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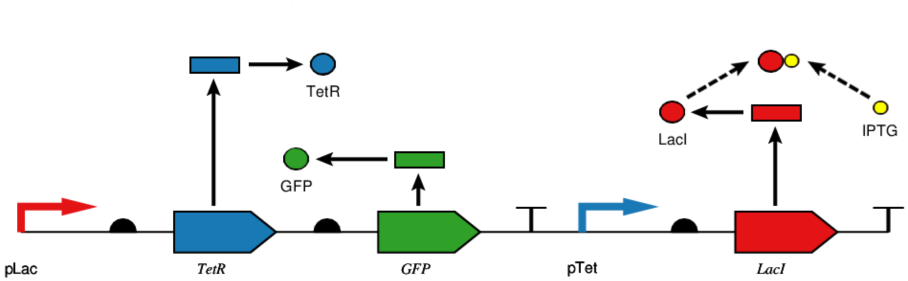

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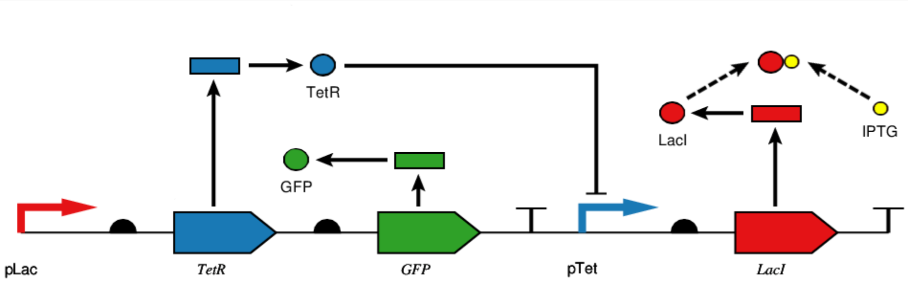

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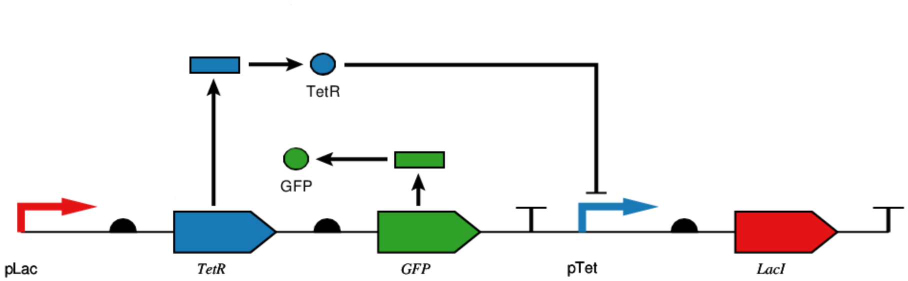

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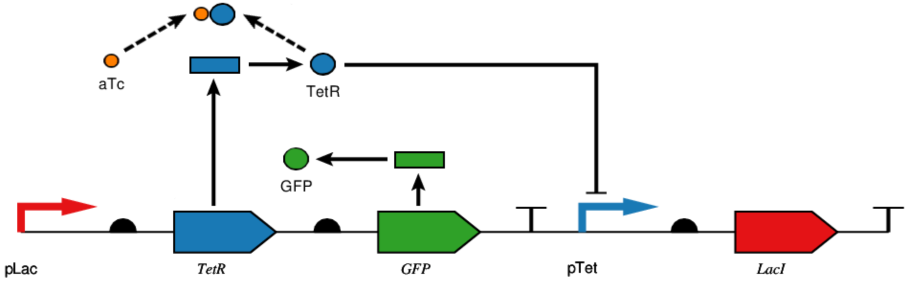

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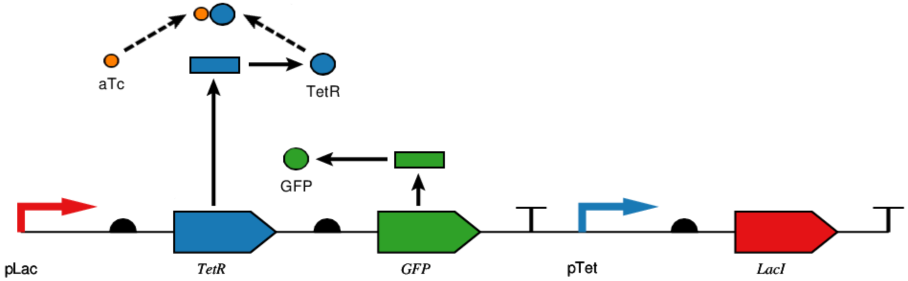

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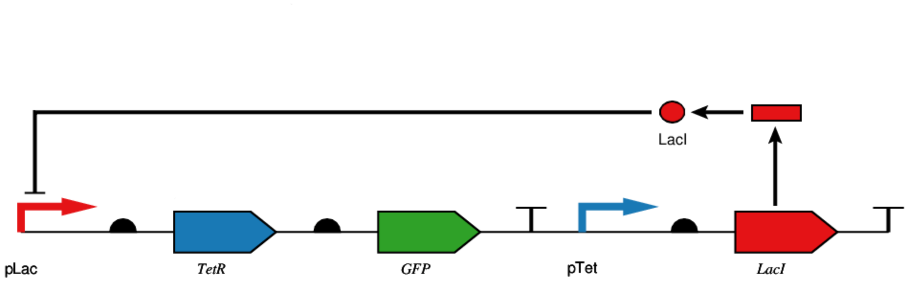
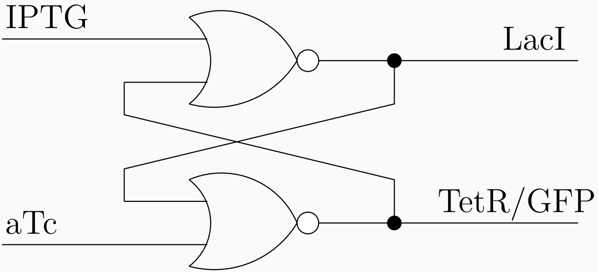


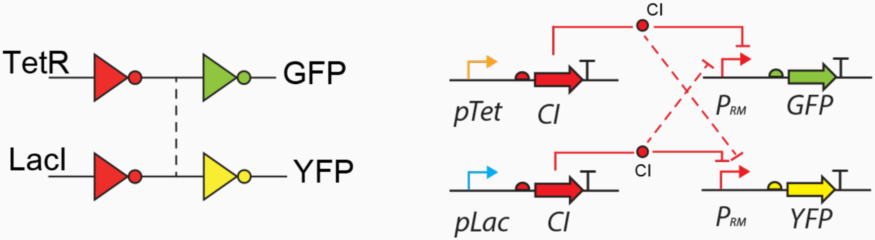
Genetic Toggle Switch (SR Latch) Logic Diagram



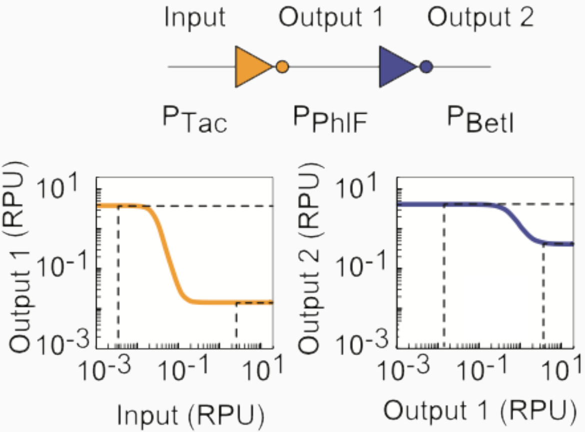
Genetic Design Constraints

- Crosstalk
- Signal Mismatch
- Roadblocking
- Context Effects

Crosstalk

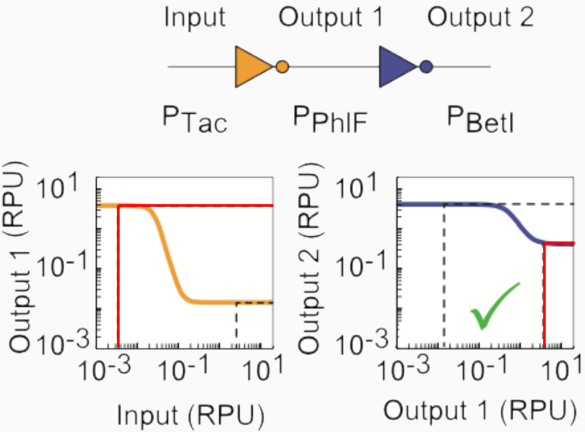


Signal Mismatch



Nielsen et al., *Science*, 2016

Signal Mismatch



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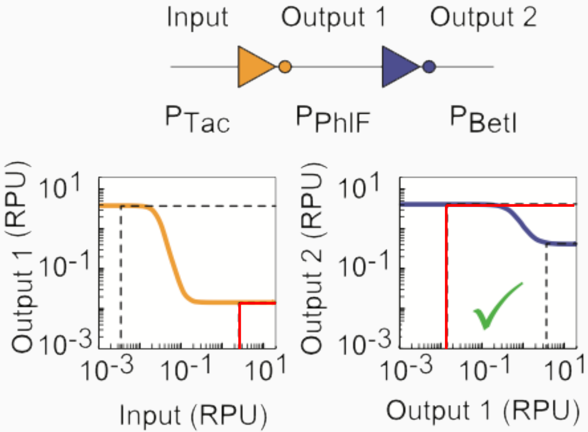

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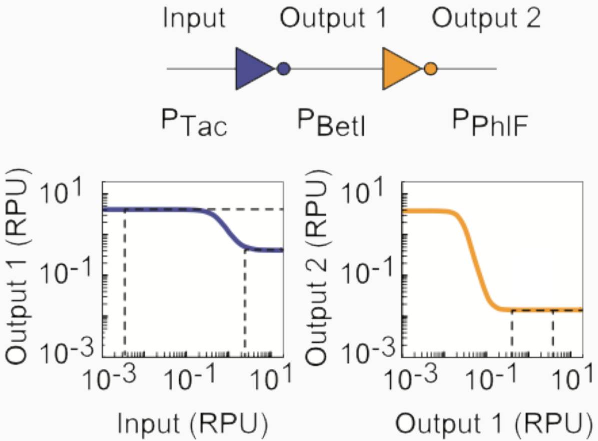

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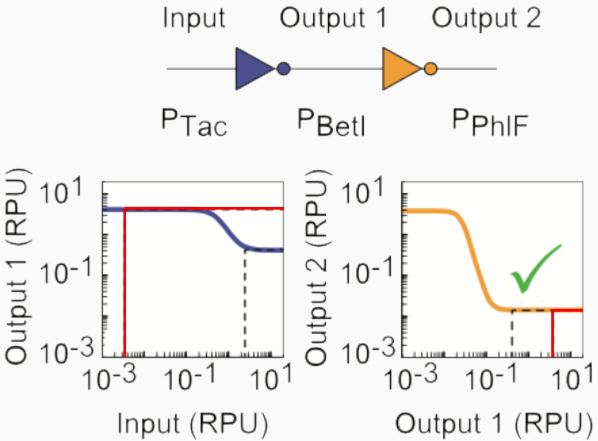

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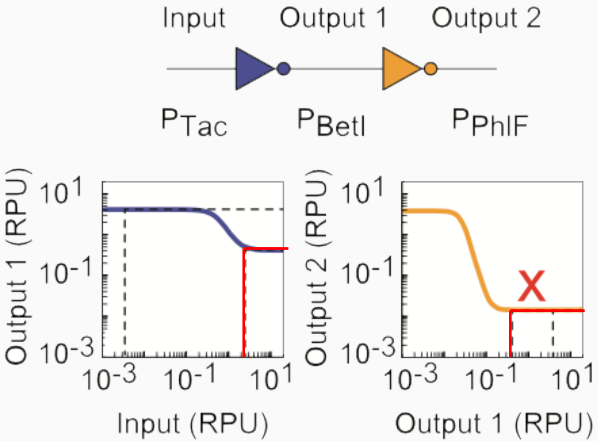
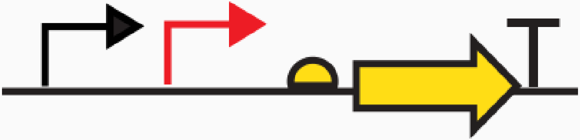


Nielsen et al., *Science*, 2016

Roadblocking



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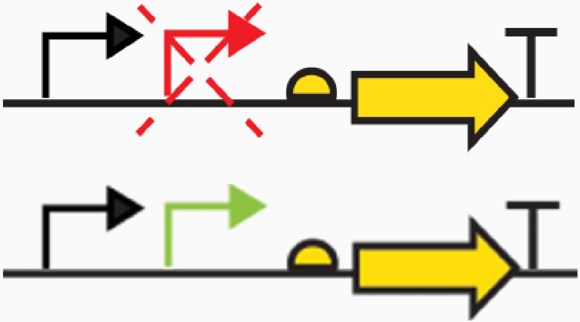
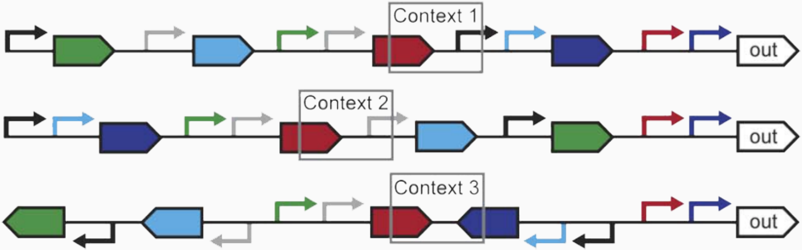


Nielsen et al., *Science*, 2016

Context Effects



Vaidyanathan et al., *IEEE*, 2015

Genetic Design Automation (GDA)

- Building a complex circuit that operates correctly under the genetic design constraints is time consuming.
- *Genetic design automation* (GDA) can help refine the design space before building a circuit in the laboratory.
- Models can be generated programatically and analysis of these models can help evaluate design alternatives on a computer (*in silico*).

Professor David Donoho
Stanford University

An article about computational science in a scientific publication is not the scholarship itself, it is merely advertising of the scholarship. The actual scholarship is the complete ... set of instructions [and data] which generated the figures.

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 Biodesign 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 application[1] 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 GenBank[3]. 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 sequence[8]. 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 oscillators[9]. 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 Peccoud[1], J Christopher Anderson[2], Deepak Chandran[3], Douglas Densmore[4], Michal Galdzicki[5], Matthew W Lux[1], Cesar A Rodriguez[6], Guy-Bart Stan[7] & Herbert M Sauro[3]

[1]Virginia Bioinformatics Institute, Virginia Tech, Blacksburg, Virginia, USA. [2]Department of Bioengineering, QB3: California Institute for Quantitative Biological Research, University of California, Berkeley, California, USA. [3]Department of Bioengineering, University of Washington, Seattle, Washington, USA. [4]Department of Electrical and Computer Engineering, Boston University, Boston, Massachusetts, USA. [5]Biomedical and Health Informatics, University of Washington, Seattle, Washington, USA. [6]BIOFAB, Emeryville, California, USA. [7]Department 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. & Weiss, R. *Nature* **434**, 1130–1134 (2005).

Synthetic Biology Open Language (SBOL) Version 1 Released in 2011

nature biotechnology

NATURE BIOTECHNOLOGY | COMPUTATIONAL BIOLOGY | PERSPECTIVE

日本語要約

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, Bryan A Bartley, Jacob Beal, Deepak Chandran, Joanna Chen, Douglas Densmore, Drew Endy, Raik Grünberg, Jennifer Hallinan, Nathan J Hillson, Jeffrey D Johnson, Allan Kuchinsky, Matthew Lux, Goksel Misirli, Jean Peccoud, Hector A Plahar, Evren Sirin, Guy-Bart Stan, Alan Villalobos, Anil Wipat, John H Gennari, Chris J Myers & Herbert M Sauro

− Show fewer authors

Affiliations | Contributions | Corresponding author

Nature Biotechnology **32**, 545–550 (2014) | doi:10.1038/nbt.2891
Received 09 November 2013 | Accepted 20 December 2013 | Published online 06 June 2014

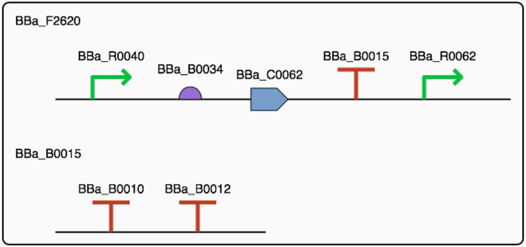
SBOL Visual Version 1 Released in 2013

PLOS | BIOLOGY

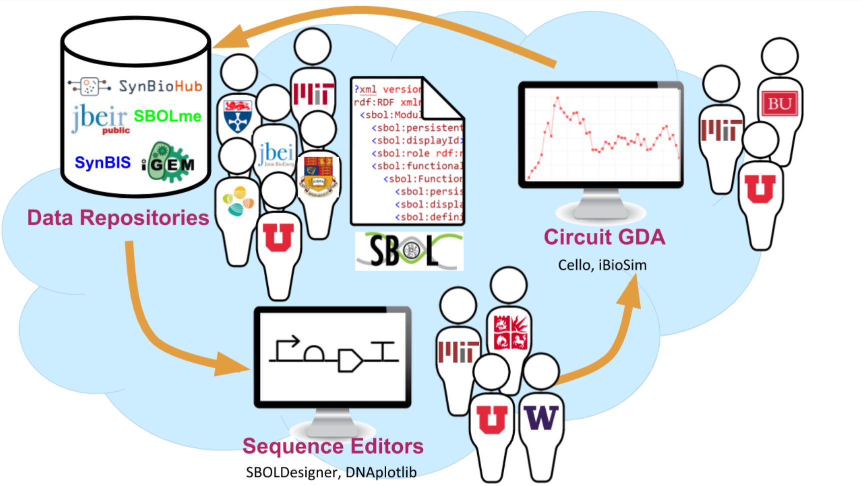
COMMUNITY PAGE

SBOL Visual: A Graphical Language for Genetic Designs

Jacqueline Y. Quinn[1☯], Robert Sidney Cox III[2☯], Aaron Adler[3], Jacob Beal[3], Swapnil Bhatia[4], Yizhi Cai[5], Joanna Chen[6,7], Kevin Clancy[8], Michal Galdzicki[9], Nathan J. Hillson[6,7], Nicolas Le Novère[10], Akshay J. Maheshwari[11], James Alastair McLaughlin[12], Chris J. Myers[13], Umesh P[14], Matthew Pocock[12,15], Cesar Rodriguez[16], Larisa Soldatova[17], Guy-Bart V. Stan[18], Neil Swainston[19], Anil Wipat[12], Herbert M. Sauro[20]*



Synthetic Biology Workflow Using SBOL



Myers et al., *Biochemical Society Transactions* (2017).

International Genetically Engineered Machine (iGEM) Competition

Started in 2004 with 5 teams and 31 participants.

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

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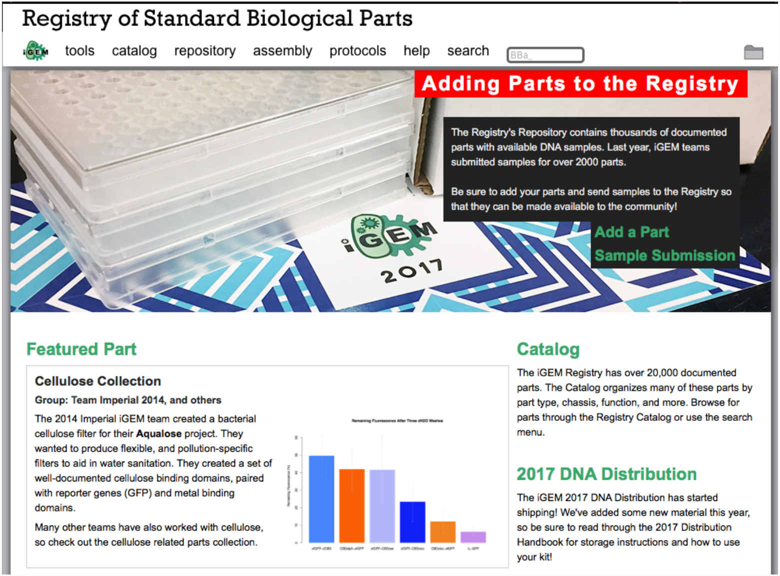
iGEM Registry of Standard Biological Parts (BioBricks)



http://parts.igem.org

Data Repositories (SynBioHub)

Newcastle University

James McLaughlin

Anil Wipat

The University of Utah®

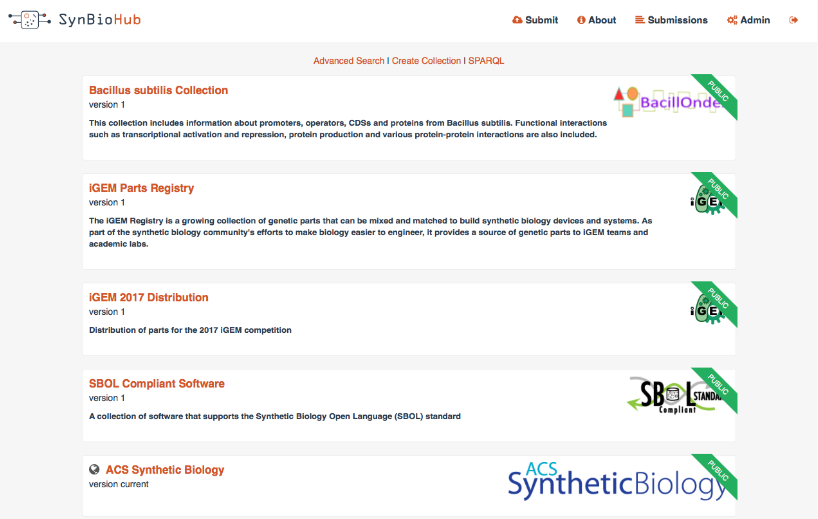
Zach Zundel

Chris Myers

Version 1.0 released
June 14, 2017

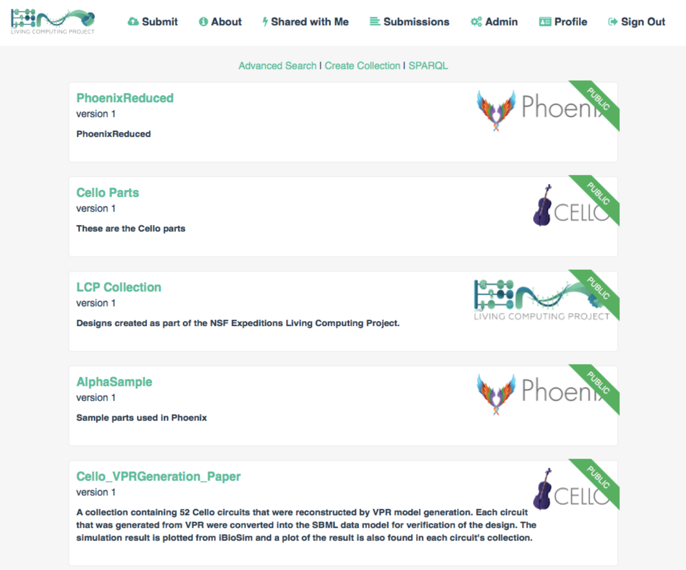
McLaughlin et al., *ACS Synthetic Biology* (2018).

Reference Instance



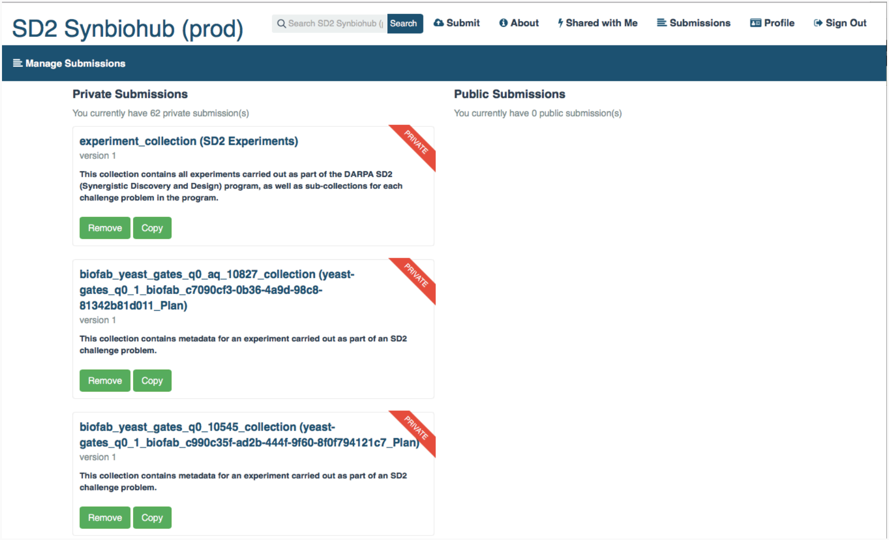
https://synbiohub.org

NSF Expeditions Living Computing Project



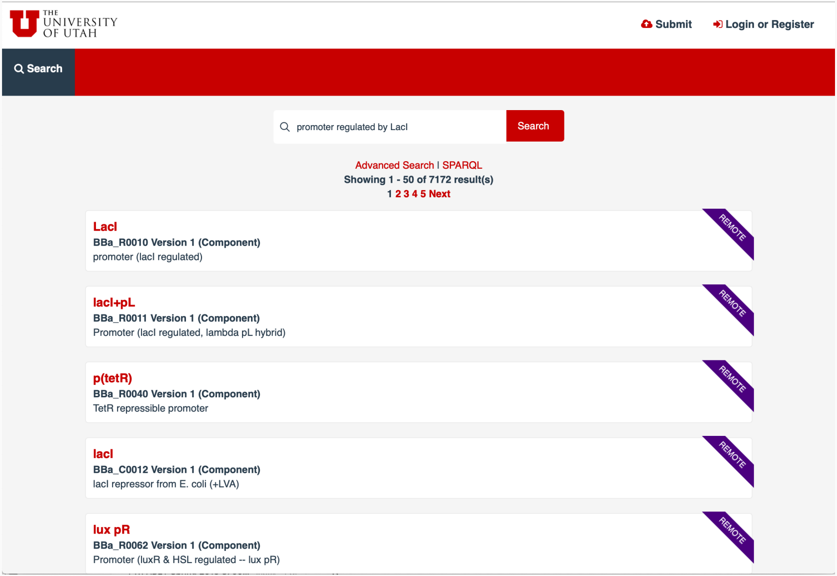
https://synbiohub.programmingbiology.org

DARPA Synergistic Data & Discovery (SD2) Project



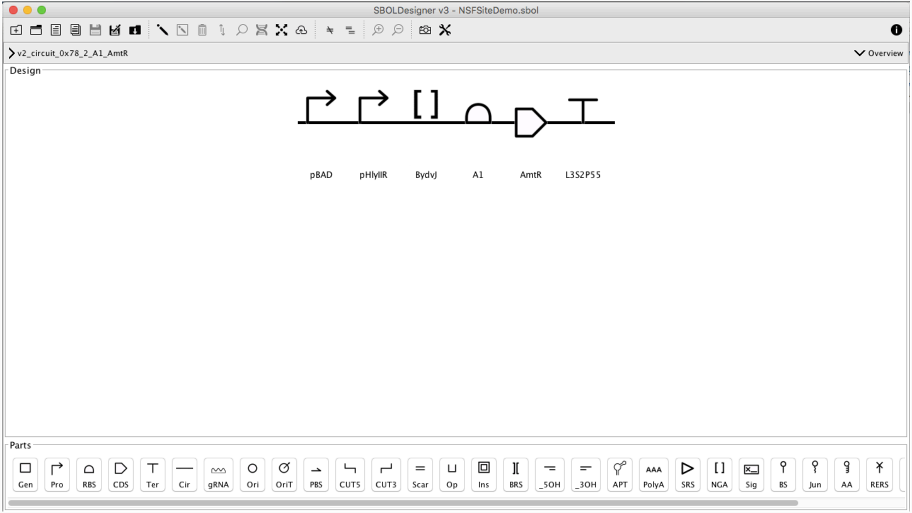
`https://hub.sd2e.org`

SBOLExplorer



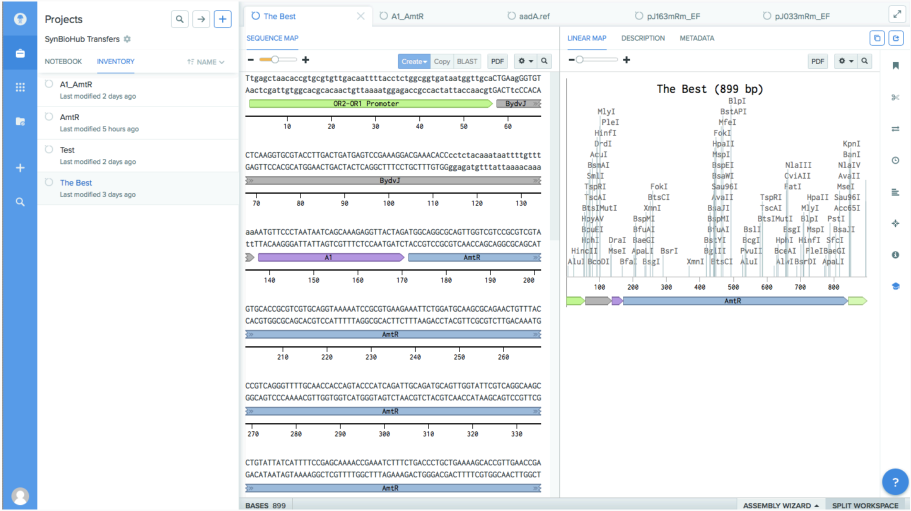
https://synbiohub.utah.edu

Sequence Editors (SBOLDesigner)



Zhang et al., *ACS Synthetic Biology* (2017)

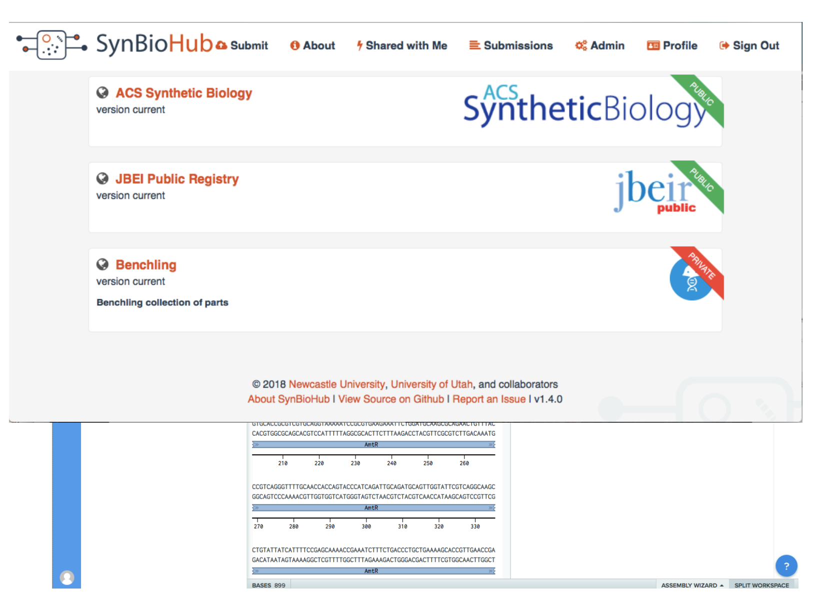
Sequence Editors (Benchling)

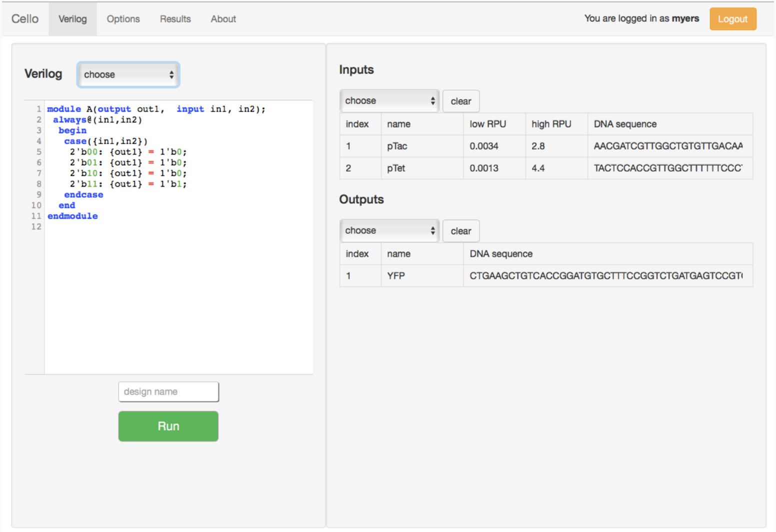


Other sequence editors that support SBOL:

DeviceEditor, J5, VectorEditor (JBEI), DNAPlotLib (MIT/UW/Bristol), Eugene (Boston), GenoCAD (VBI), BOOST (JGI), etc.

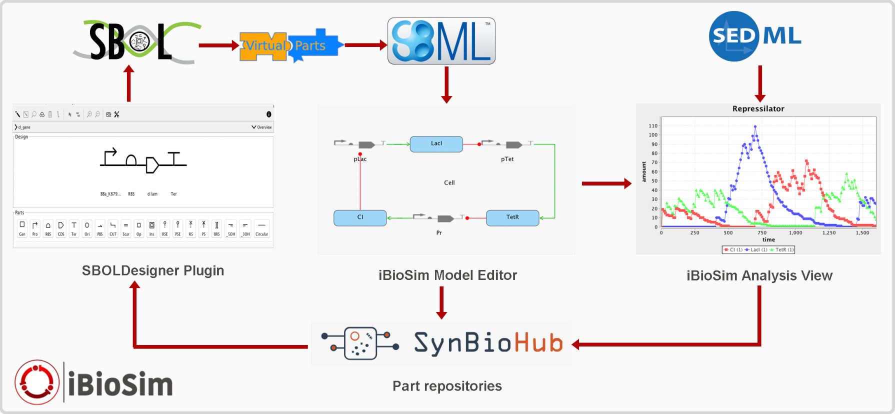
Sequence Editors (Benchling)





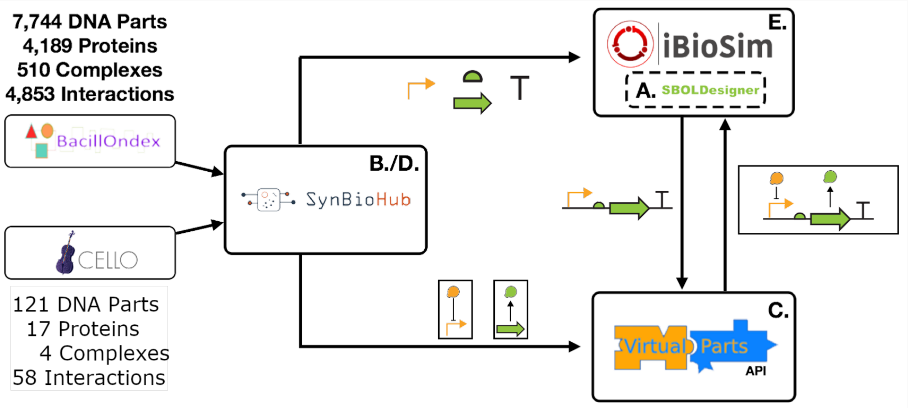
Nielsen et al., *Science* (2016)

Circuit GDA Tools (iBioSim)



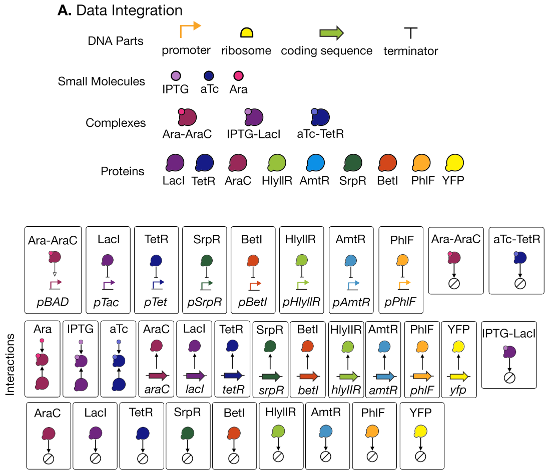
Myers et al., *Bioinformatics* (2009)
Madsen et al., *IEEE Design & Test* (2012)
Watanabe et al., *ACS Synthetic Biology* (2018)

Model Generation Workflow



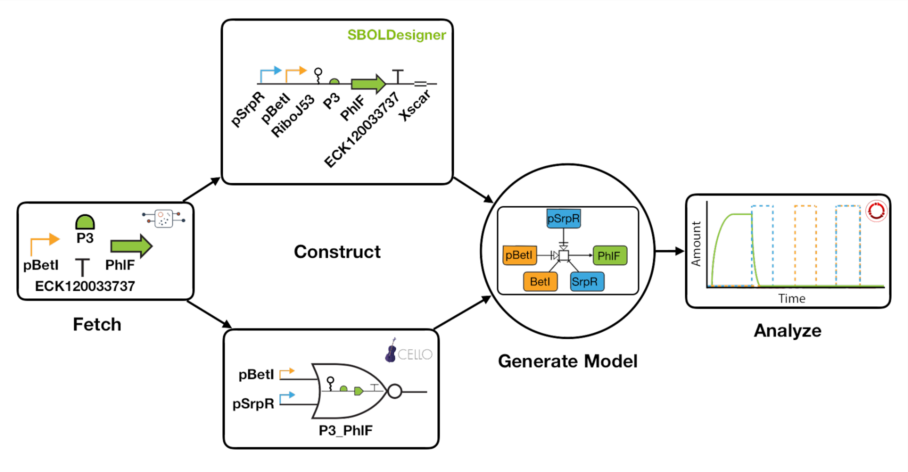
Mısırlı et al., *ACS Synthetic Biology* (2018).

Data Integration: Cello Part Library



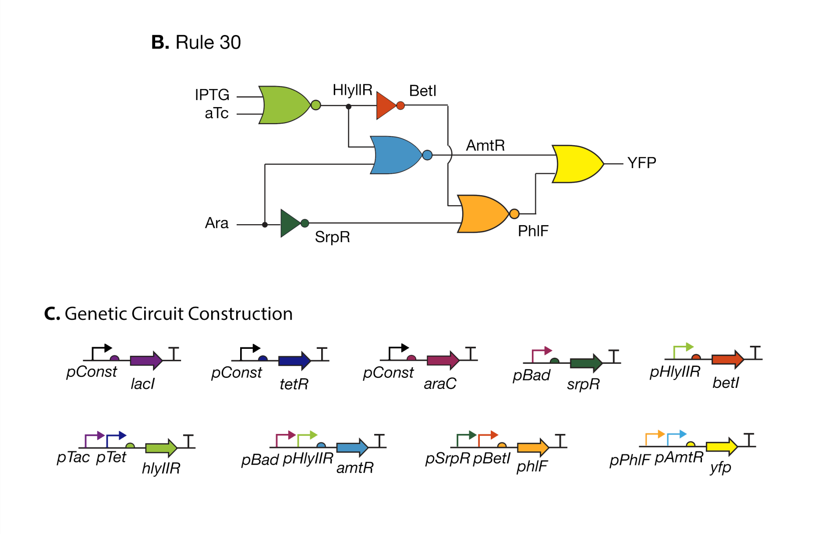
Mısırlı et al., *ACS Synthetic Biology* (2018).

Genetic Circuit Construction



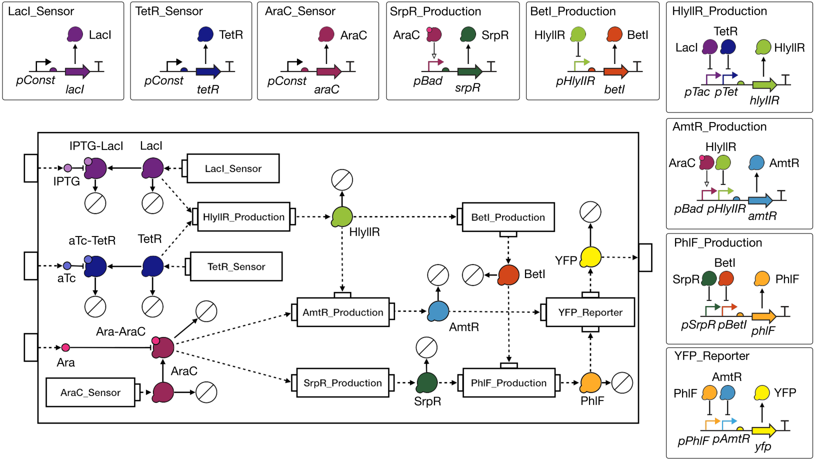
Mısırlı et al., *ACS Synthetic Biology* (2018).

Genetic Circuit Construction: Rule 30 Example



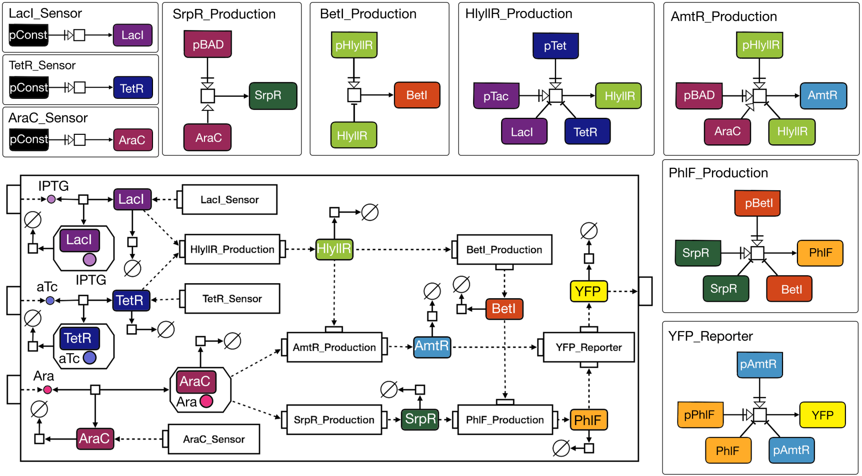
Mısırlı et al., *ACS Synthetic Biology* (2018).

Enriched SBOL Representation: Rule 30 Example



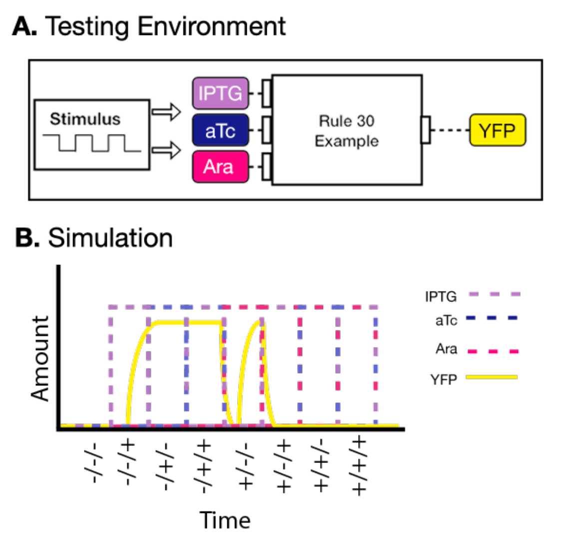
Mısırlı et al., *ACS Synthetic Biology* (2018).

Dynamic SBML Model: Rule 30 Example



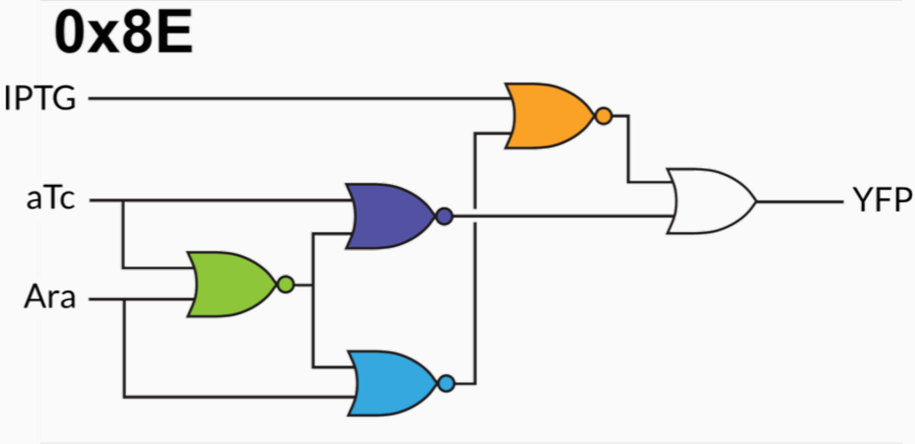
Mısırlı et al., *ACS Synthetic Biology* (2018).

Simulation: Rule 30 Example



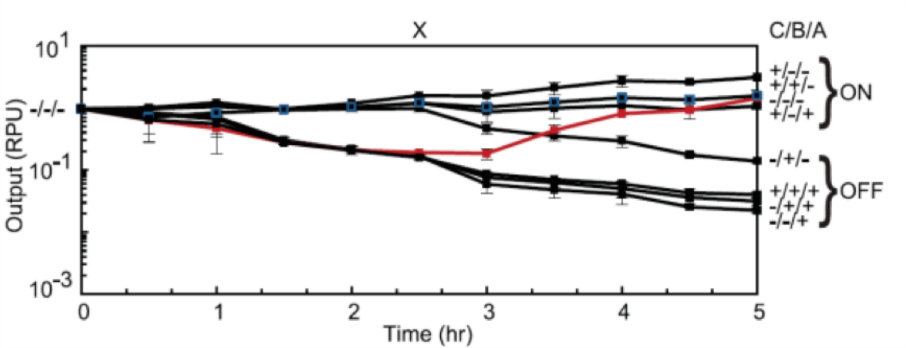
Mısırlı et al., *ACS Synthetic Biology* (2018).

Circuit0x8E



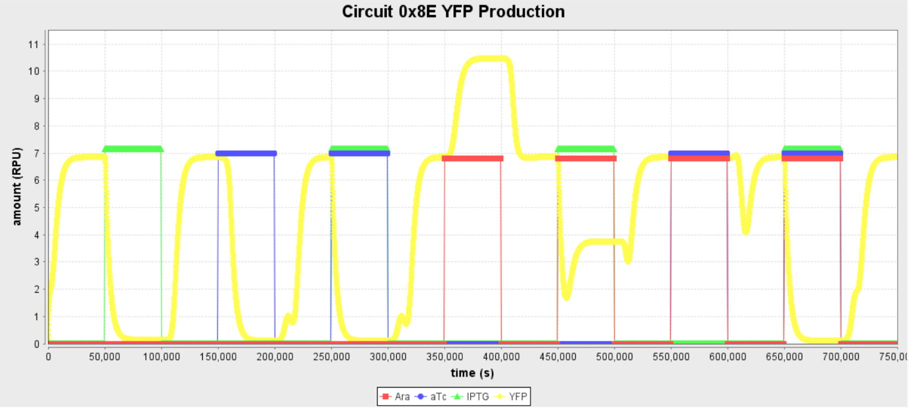
Nielsen et al., *Science* (2016).

Circuit0x8E: Experimental Results



Nielsen et al., *Science* (2016).

Circuit0x8E: Simulation



Fontanarrosa, Hosseini, Borujeni, Dorfan, Voigt, and Myers, “Analyzing Genetic Circuits for Hazards and Glitches”, in preparation for *ASC Synthetic Biology*.

Circuit0x8E: Logic Function

Truth Table for circuit 0x8E:

Ara	IPTG	aTc	YFP
0	0	0	**1**
0	0	1	**0**
0	1	0	**0**
0	1	1	**0**
1	0	0	**1**
1	0	1	**1**
1	1	0	**1**
1	1	1	**0**

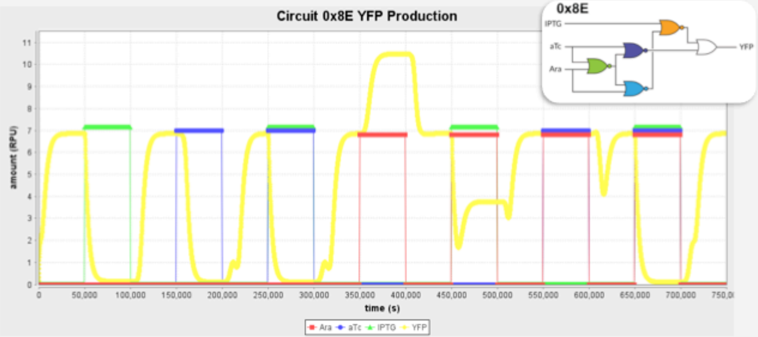
Karnaugh map for circuit 0x8E:

Ara \ IPTG aTc	0 0	0 1	1 1	1 0
0	1	0	0	0
1	1	1	0	1

Fontanarrosa, Hosseini, Borujeni, Dorfan, Voigt, and Myers, “Analyzing Genetic Circuits for Hazards and Glitches”, in preparation for *ASC Synthetic Biology*.

Circuit0x8E: Hazard Analysis

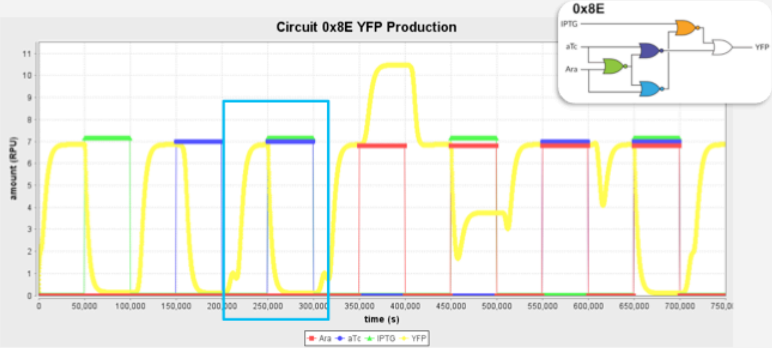
Ara \ IPTG aTc	0 0	0 1	1 1	1 0
0	1	0	0	0
1	1	1	0	1



Fontanarrosa, Hosseini, Borujeni, Dorfan, Voigt, and Myers, “Analyzing Genetic Circuits for Hazards and Glitches”, in preparation for *ASC Synthetic Biology*.

Circuit0x8E: Hazard Analysis

Ara \ IPTG aTc	00	01	11	10
0	1	0	0	0
1	1	1	0	1



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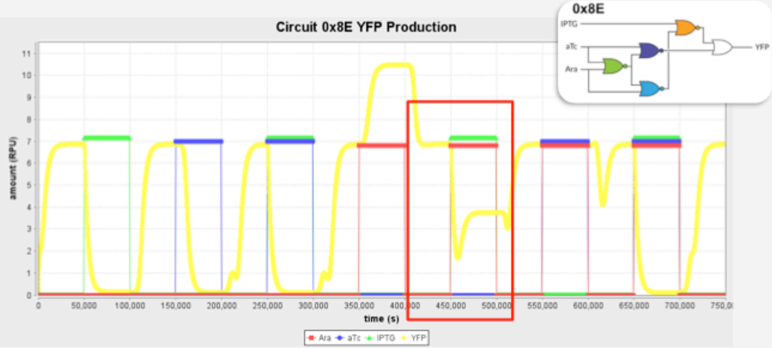
Circuit0x8E: Hazard Analysis

Ara \ IPTG aTc	00	01	11	10
0	1	0	0	0
1	1	1	0	1



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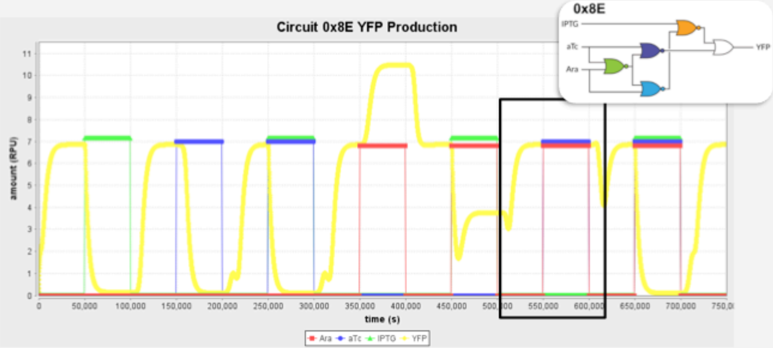
Circuit0x8E: Hazard Analysis

Ara \ IPTG aTc	00	01	11	10
0	1	0	0	0
1	1	1	0	1



Fontanarrosa, Hosseini, Borujeni, Dorfan, Voigt, and Myers, “Analyzing Genetic Circuits for Hazards and Glitches”, in preparation for *ASC Synthetic Biology*.

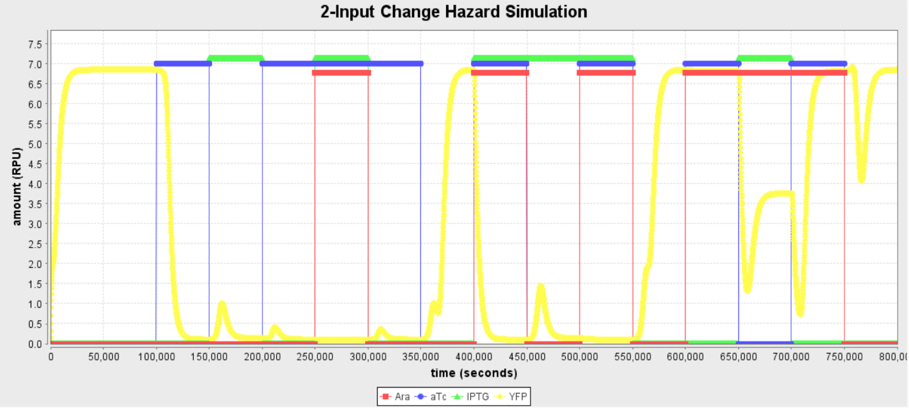
Circuit0x8E: 2-Input Function Hazards

Ara \ IPTG aTc	00	01	11	10
0	1	0	0	0
1	1	1	0	1

Case	2 input change hazards			
Case 1-2	IPTG	0	1	0
	aTc	1	1	1
	Ara	0	1	0
Case 3-4	IPTG	0	1	0
	aTc	1	0	1
	Ara	0	0	0
Case 5-6	IPTG	1	1	1
	aTc	1	0	1
	Ara	1	0	1
Case 7-8	IPTG	0	1	0
	aTc	1	0	1
	Ara	1	1	1

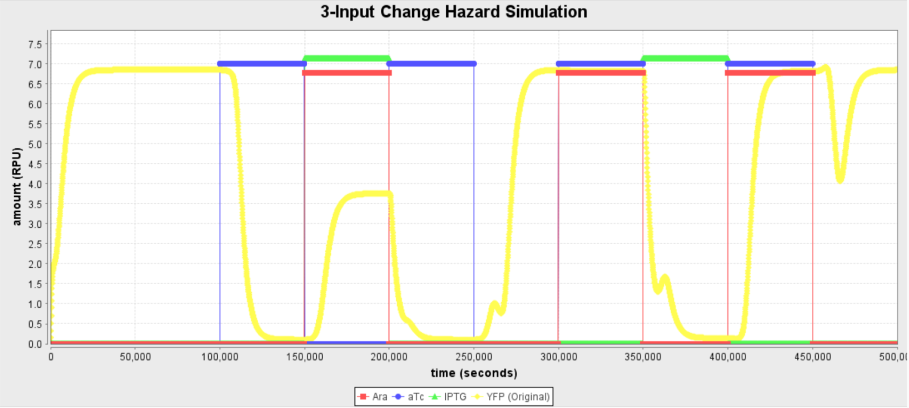
Fontanarrosa, Hosseini, Borujeni, Dorfan, Voigt, and Myers, “Analyzing Genetic Circuits for Hazards and Glitches”, in preparation for *ASC Synthetic Biology*.

Circuit0x8E: 2-Input Function Hazards



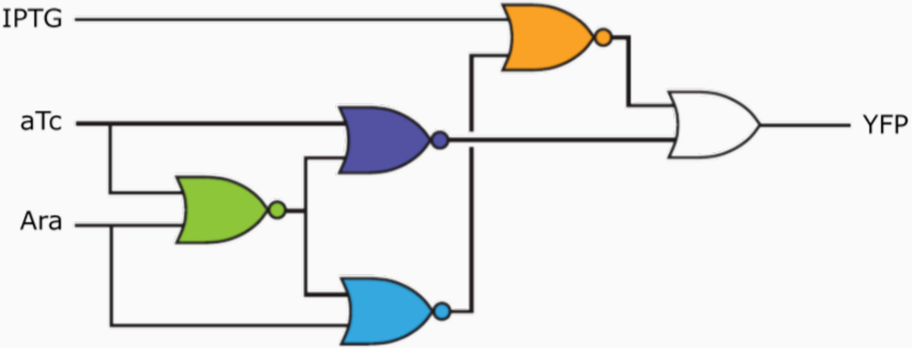
Fontanarrosa, Hosseini, Borujeni, Dorfan, Voigt, and Myers, "Analyzing Genetic Circuits for Hazards and Glitches", in preparation for *ASC Synthetic Biology*.

Circuit0x8E: 3-Input Function Hazards



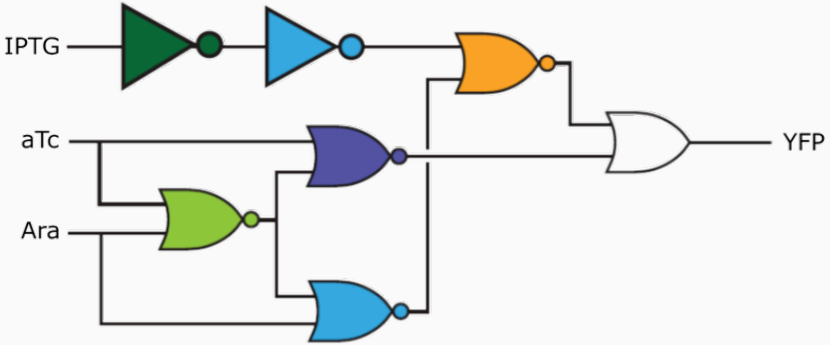
Fontanarrosa, Hosseini, Borujeni, Dorfan, Voigt, and Myers, “Analyzing Genetic Circuits for Hazards and Glitches”, in preparation for *ASC Synthetic Biology*.

CIRCUIT0X8E: REDUNDANT LOGIC



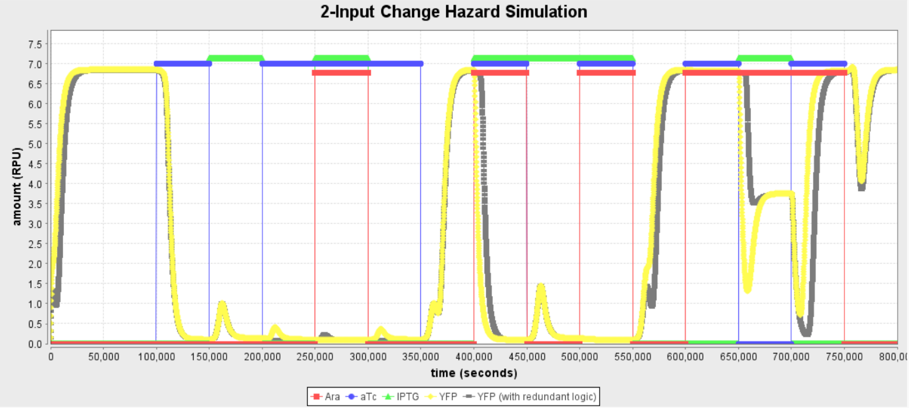
Fontanarrosa, Hosseini, Borujeni, Dorfan, Voigt, and Myers, “Analyzing Genetic Circuits for Hazards and Glitches”, in preparation for *ASC Synthetic Biology*.

Circuit0x8E: Redundant Logic



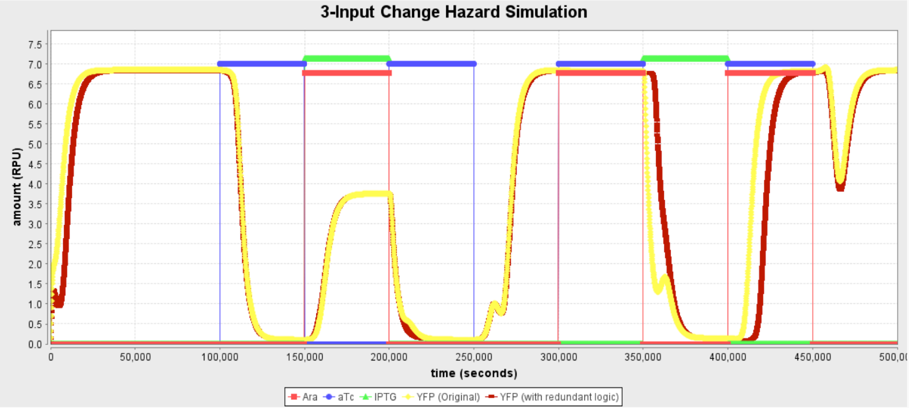
Fontanarrosa, Hosseini, Borujeni, Dorfan, Voigt, and Myers, “Analyzing Genetic Circuits for Hazards and Glitches”, in preparation for *ASC Synthetic Biology*.

Circuit0x8E: Redundant Logic



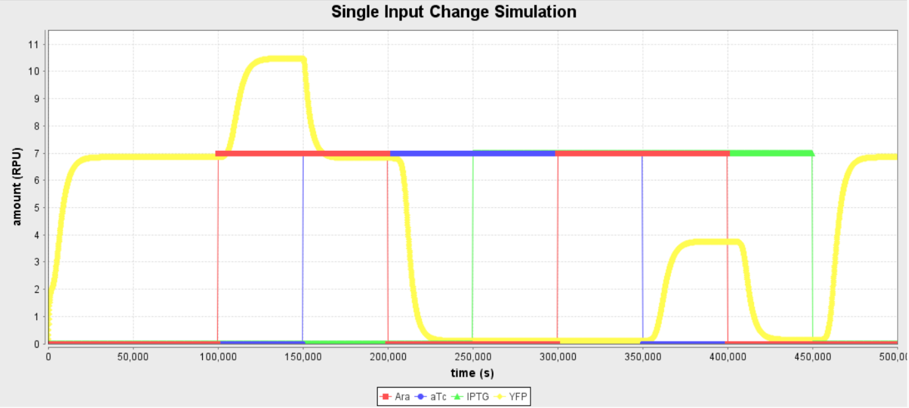
Fontanarrosa, Hosseini, Borujeni, Dorfan, Voigt, and Myers, “Analyzing Genetic Circuits for Hazards and Glitches”, in preparation for *ASC Synthetic Biology*.

Circuit0x8E: Redundant Logic



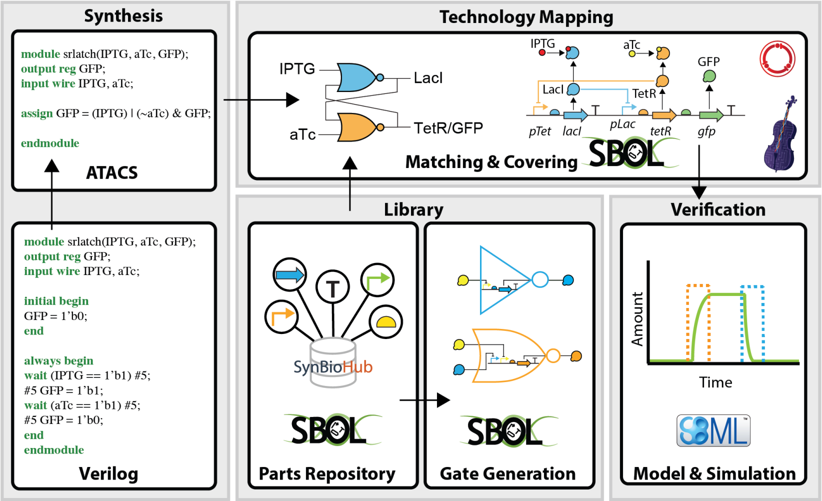
Fontanarrosa, Hosseini, Borujeni, Dorfan, Voigt, and Myers, "Analyzing Genetic Circuits for Hazards and Glitches", in preparation for *ASC Synthetic Biology*.

Circuit0x8E: Gray Code



Fontanarrosa, Hosseini, Borujeni, Dorfan, Voigt, and Myers, “Analyzing Genetic Circuits for Hazards and Glitches”, in preparation for *ASC Synthetic Biology*.

Asynchronous Genetic Circuit Design Methodology



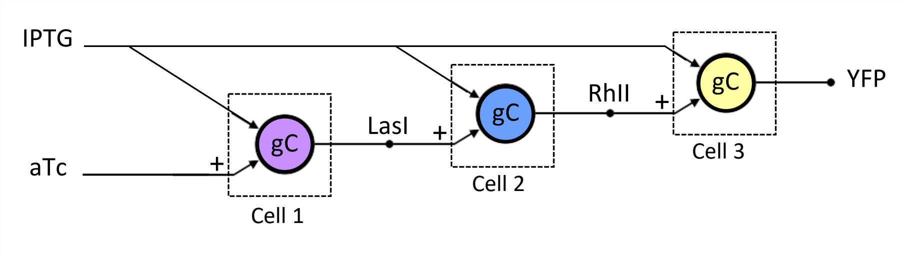
Nguyen, Jones, Vaidyanathan, Densmore, and Myers, "Design of Asynchronous Genetic Circuits", in *Proceedings of the IEEE* (2019).

Genetic Sensor Specification

```
module async_sensor(Start, Sensor, Actuator);
    input wire Start, Sensor;
    output reg Actuator;
    initial begin
        Actuator = 1'b0;
    end
    always begin
        wait (Start == 1'b1 && Sensor == 1'b1);
        #5 Actuator = 1'b1;
        wait (Sensor == 1'b0);
        #5 Actuator = 1'b0;
    end
endmodule
```

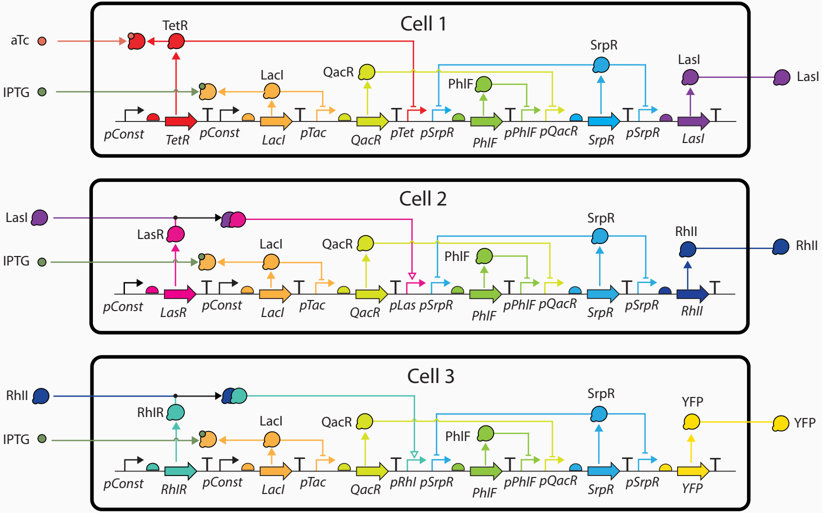
Nguyen, Jones, Vaidyanathan, Densmore, and Myers, "Design of Asynchronous Genetic Circuits", in *Proceedings of the IEEE* (2019).

Genetic Sensor Design

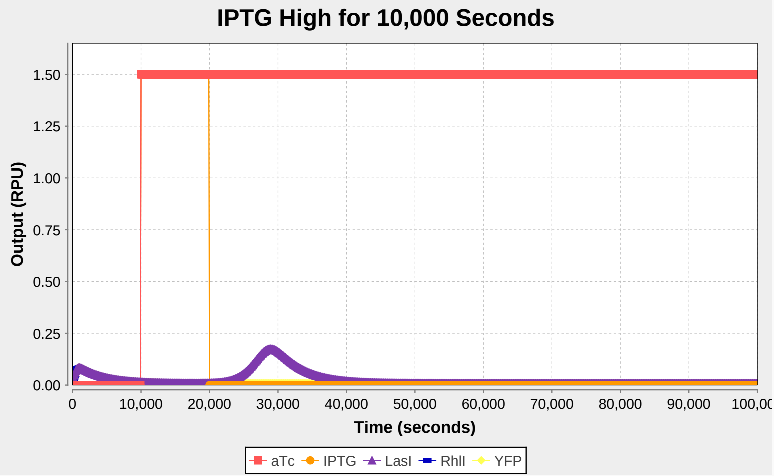


Nguyen, Jones, Vaidyanathan, Densmore, and Myers, "Design of Asynchronous Genetic Circuits", in *Proceedings of the IEEE* (2019).

Genetic Sensor Design

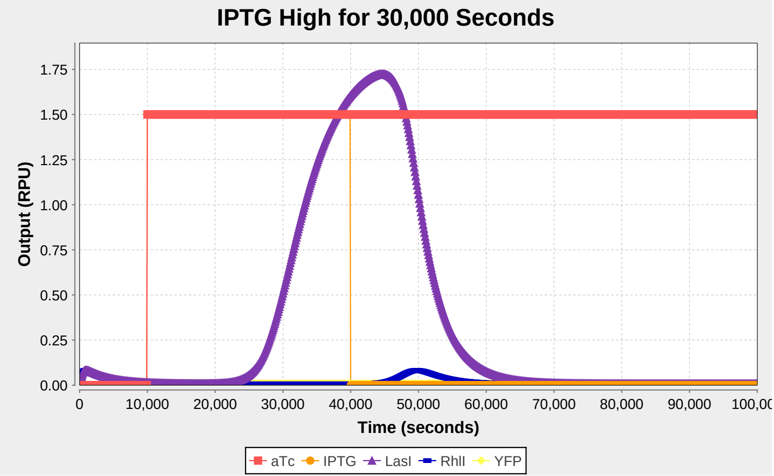


Nguyen, Jones, Vaidyanathan, Densmore, and Myers, “Design of Asynchronous Genetic Circuits”, in *Proceedings of the IEEE* (2019).



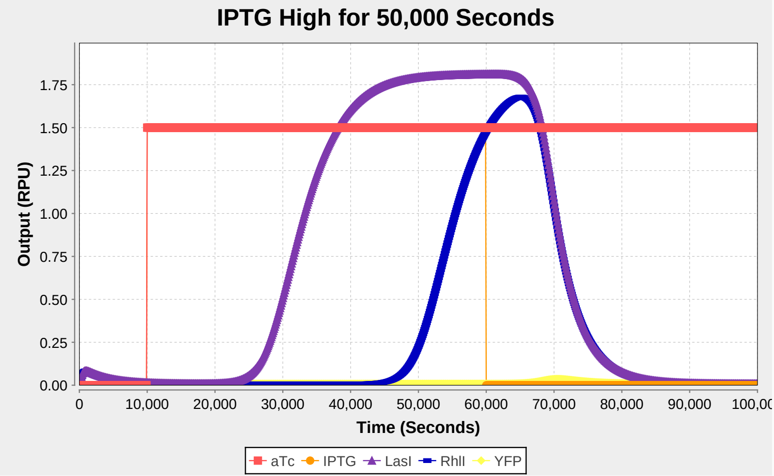
Nguyen, Jones, Vaidyanathan, Densmore, and Myers, “Design of Asynchronous Genetic Circuits”, in *Proceedings of the IEEE* (2019).

Genetic Sensor Simulation



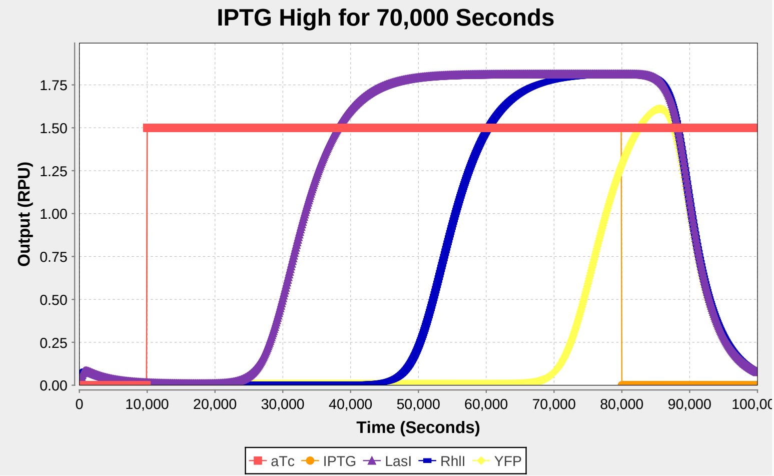
Nguyen, Jones, Vaidyanathan, Densmore, and Myers, “Design of Asynchronous Genetic Circuits”, in *Proceedings of the IEEE* (2019).

Genetic Sensor Simulation



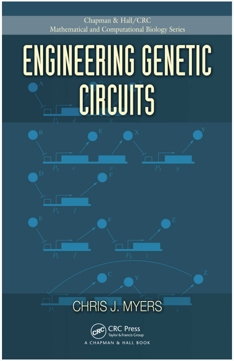
Nguyen, Jones, Vaidyanathan, Densmore, and Myers, "Design of Asynchronous Genetic Circuits", in *Proceedings of the IEEE* (2019).

Genetic Sensor Simulation



Nguyen, Jones, Vaidyanathan, Densmore, and Myers, “Design of Asynchronous Genetic Circuits”, in *Proceedings of the IEEE* (2019).

More Information



Textbook

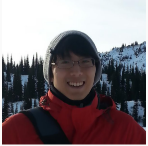
- ECE/CS/BioEn 6760
  Offered in Fall 2020
- Our research work:
  `http://www.async.ece.utah.edu`
- SBOL standard:
  `http://sbolstandard.org`
  Checkout our Youtube channel for demos
- SynBioHub Repository:
  `https://synbiohub.org`

Adam Arkin

Since the engineering principles by which such circuitry is constructed in cells comprise a super-set of that used in electrical engineering, it is, in turn, possible that we will learn more about how to design asynchronous, robust electronic circuitry as well.

Acknowledgements (University of Washington)

Dr. Bryan Bartley
(Now with BBN/Raytheon)



Kiri Choi

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Acknowledgements (Newcastle University)

James McLaughlin

Dr. Goksel Misirli
(Now with Keele University)

Dr Angel Goni-Moreno

Prof. Anil Wipat

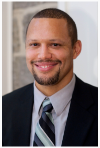
Acknowledgements (Boston University)

Dr. Timothy Jones

Dr. Curtis Madsen

Dr. Nicholas Roehner (Now with BBN/Raytheon)

Prashant Vaidyanathan



Prof. Douglas Densmore

Acknowledgements (Other Institutions)

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(BBN/Raytheon)

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(University of Bristol)

Dr Hiroyuki Kuwahara
(KAUST)

Dr. Ernst Oberortner
(Joint Genome Institute)

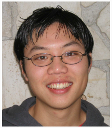
Acknowledgements (University of Utah / Graduated Students)

Nathan Barker (SUU/Chair CS)

Scott Glass (BS/CE)

Hiroyuki Kuwahara (KAUST)

Curtis Madsen (Sandia)



Nam Nguyen (UCSD/Postdoc)

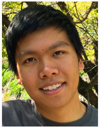
Tyler Patterson (BS/CE)

Nicholas Roehner (BBN/Raytheon)

Meher Samineni (Amazon)

Jason Stevens (UWash/PhD)

Leandro Watanabe (Google)



Michael Zhang (Google)

Zhen Zhang (Utah State U.)

Supported by National Science Foundation Grants ECCS-0331270, CCF-07377655, CCF-0916042, CCF-1218095, and DBI-1356041.

Acknowledgements (University of Utah / Current Students)

Samuel Bridge (BS/CS)

Oliver Flatt (BS/CS)

Pedro Fontanarrosa (PhD/BioEn)

Jet Mante (PhD/BioEn)

Tramy Nguyen (Phd/ECE)

James Scholz (BS/CS)

Zach Zundel (BS/CS/BioEn)

Supported by National Science Foundation Grants DBI-1356041, CCF-1748200, and CCF-1522074 (sub-award from BU), and DARPA FA8750-17-C-0229 (sub-award from MIT).