Development of the Synthetic Biology Open Language

Herbert Sauro

Synthetic Biology 6.0
July 10, 2013

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Chris J. Myers

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Technology as a Driving Force

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Mesopotamia: Bronze

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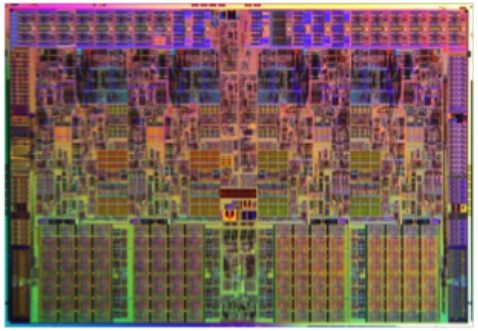

Computing: Silicon

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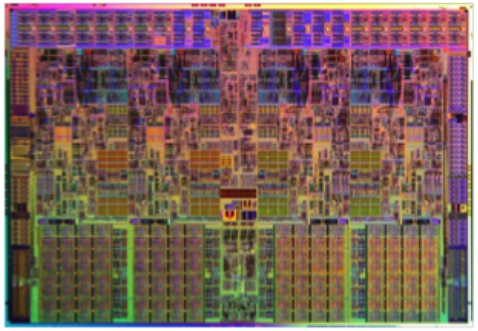

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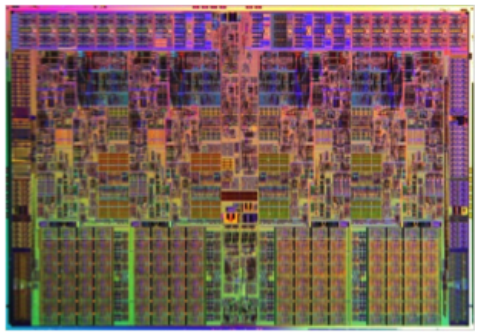

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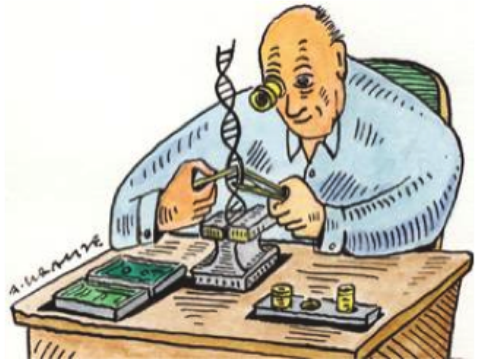

Synthetic Biology

13 Years of Synthetic Biology

Construction of a genetic toggle switch in *Escherichia coli*

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It has been proposed[1] 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 switch[2] and the Cyanobacteria circadian oscillator[3]. 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.

Genetic Toggle

A synthetic oscillatory network of transcriptional regulators

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Networks of interacting biomolecules carry out many essential functions in living cells[1], but the 'design principles' underlying the functioning of such intracellular networks remain poorly understood, despite intensive efforts including quantitative analysis of relatively simple systems[2]. Here we present a complementary approach to this problem: the design and construction of a synthetic network to implement a particular function. We used three transcriptional repressor systems that are not part of any natural biological clock[3–5] to build an oscillating network, termed

Repressilator

Motivation for Developing a Standard

If you take any current publication on a synthetic circuit and try to reproduce it, you typically find there is not sufficient information provided to be successful.

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]

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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).

Motivation for Developing a Standard

- Standards are needed for synthetic biologists to:
  - Exchange DNA level designs with other groups,
  - Round trip designs between software tools without loss,
  - Develop repositories of designs, and
  - Reproduce results found in literature.
- Synthetic biology companies could use standards to offer catalogs of standardized components.

Synthetic Biology Open Language (SBOL)

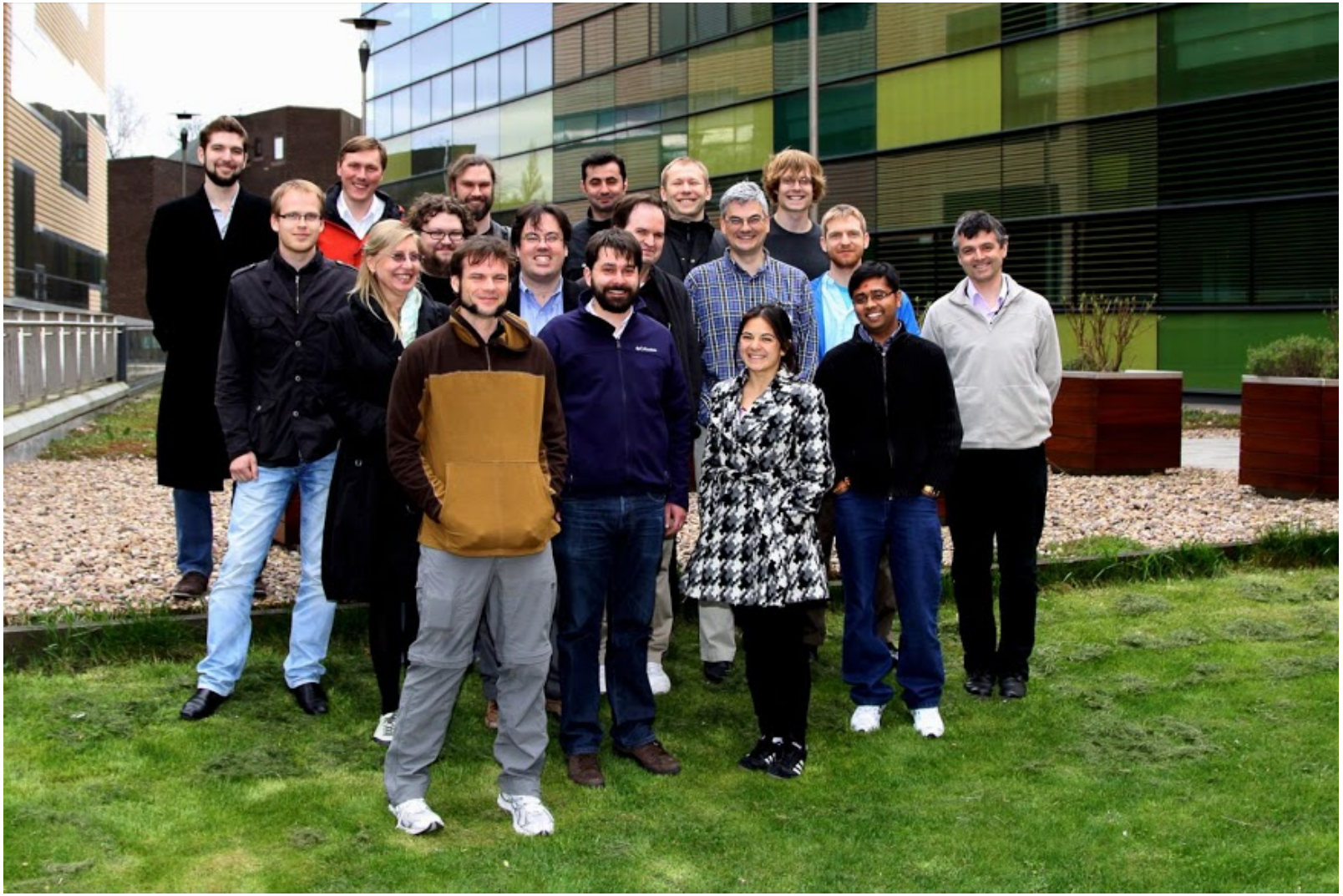
- In 2008, a small group of researchers proposed the development of the *synthetic biology open language* (SBOL), an open-source standard for the exchange of genetic designs.
- In 2011, the first version of the SBOL Core Data Model was released.
- In 2013, the first version of the SBOL Visual standard was released.
- Leveraging `libSBOLj`, a java-based library for SBOL's Core Data Model, 18 *genetic design automation* (GDA) software tools now support SBOL.

SBOL Community

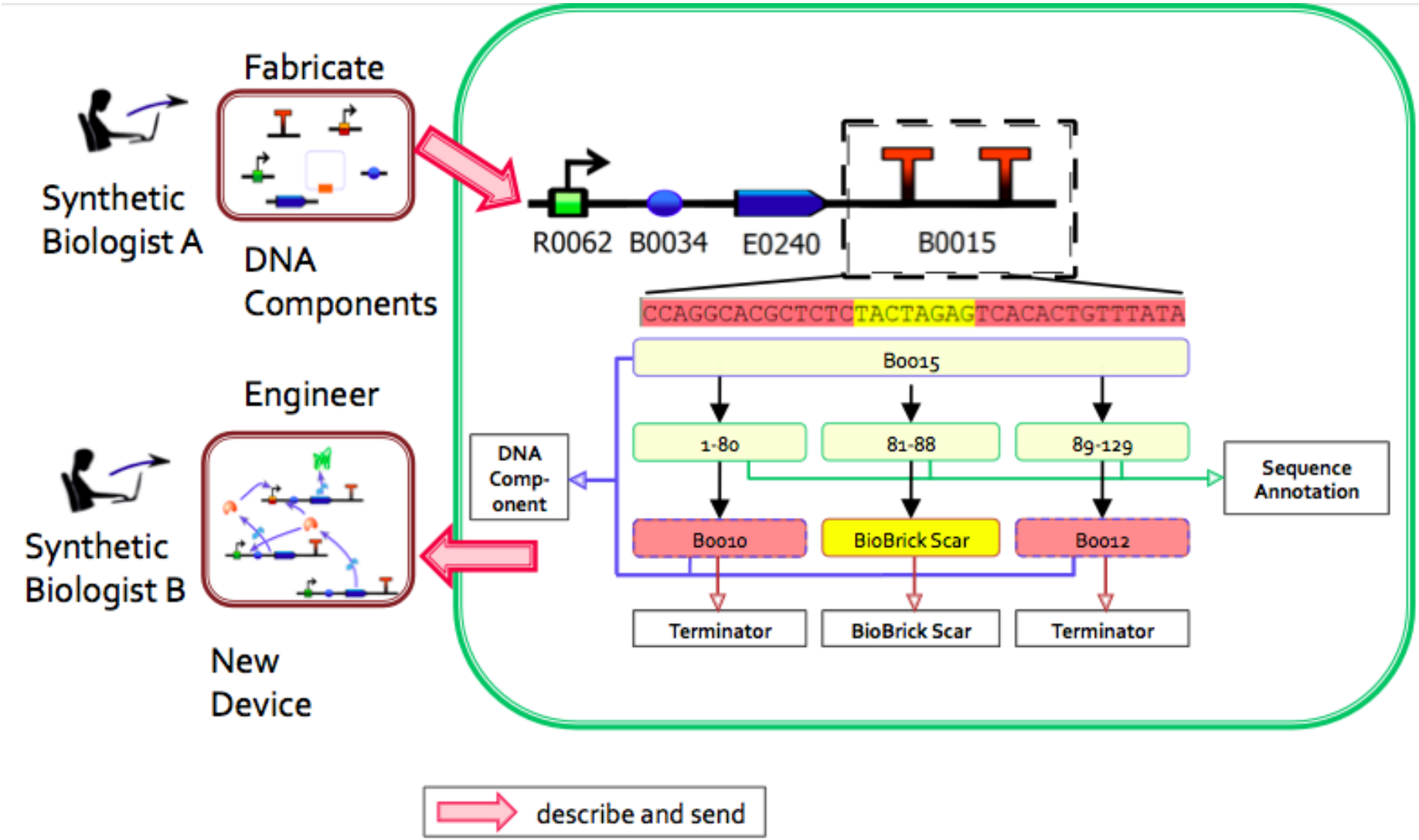
- SBOL Chair - Herbert Sauro (U. of Washington)
- SBOL Editors - Kevin Clancy (Life Tech.), Ernst Oberortner (Boston), Mathew Pocock (Newcastle), Jacqueline Quinn (Autodesk), and Nicholas Roehner (Utah).
- Past SBOL Editors - Michal Galdzicki (U. of Washington), Mandy Wilson (VBI), and Cesar Rodriguez (Autodesk).
- SBOL Developers Group includes 80 members from 29 organizations.
  - Academia - Boston, ETH Zurich, Imperial College London, Newcastle, Stanford, Berkeley, Kerala, Montreal, Utah, Washington, VBI, etc.
  - Industry - Agilent, Amyris, Autodesk, BBN, Clark & Parsia, DNA 2.0, Genome Compiler, JBEI, Life Technologies, etc.

SBOL Workshops

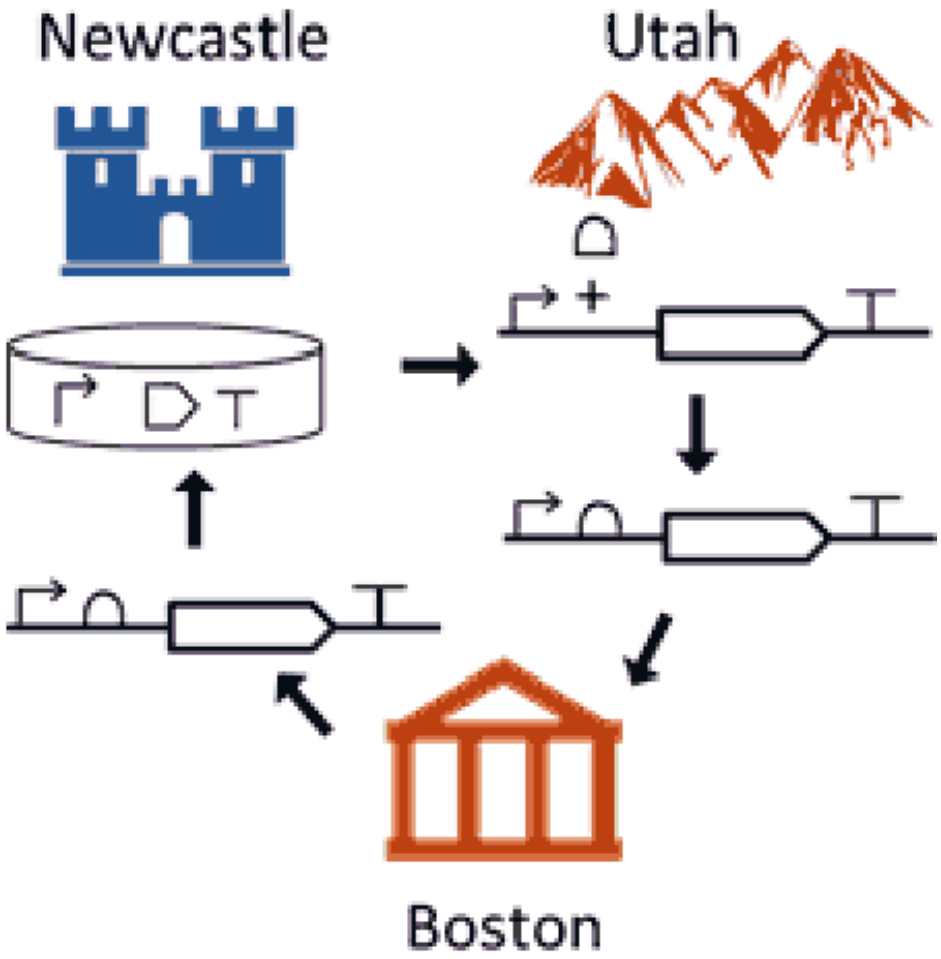
In April 2013, several members of the *SBOL Developers Group* met at Newcastle University to discuss SBOL's next steps.



SBOL Core Data Model



SBOL Core Data Model Demonstration



SBOL Visual

ACS SyntheticBiology

Letter

pubs.acs.org/synthbio

Dynamic Modeling of Cellular Populations within iBioSim

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Supporting

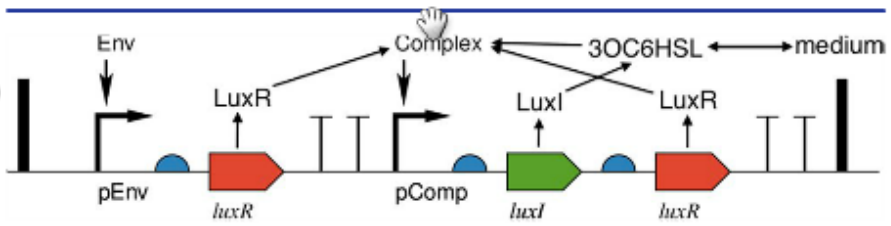
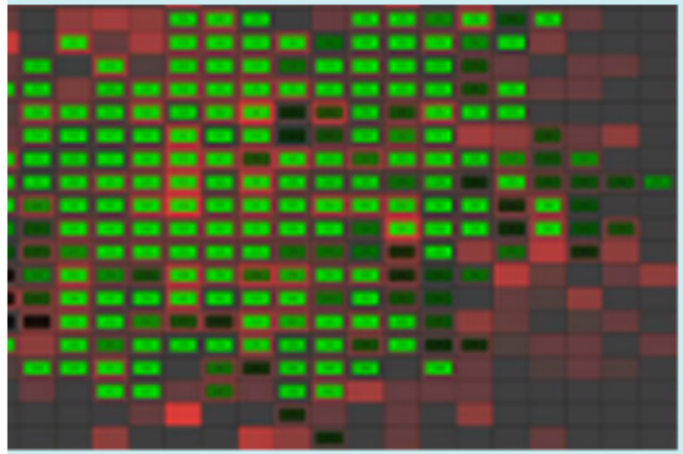


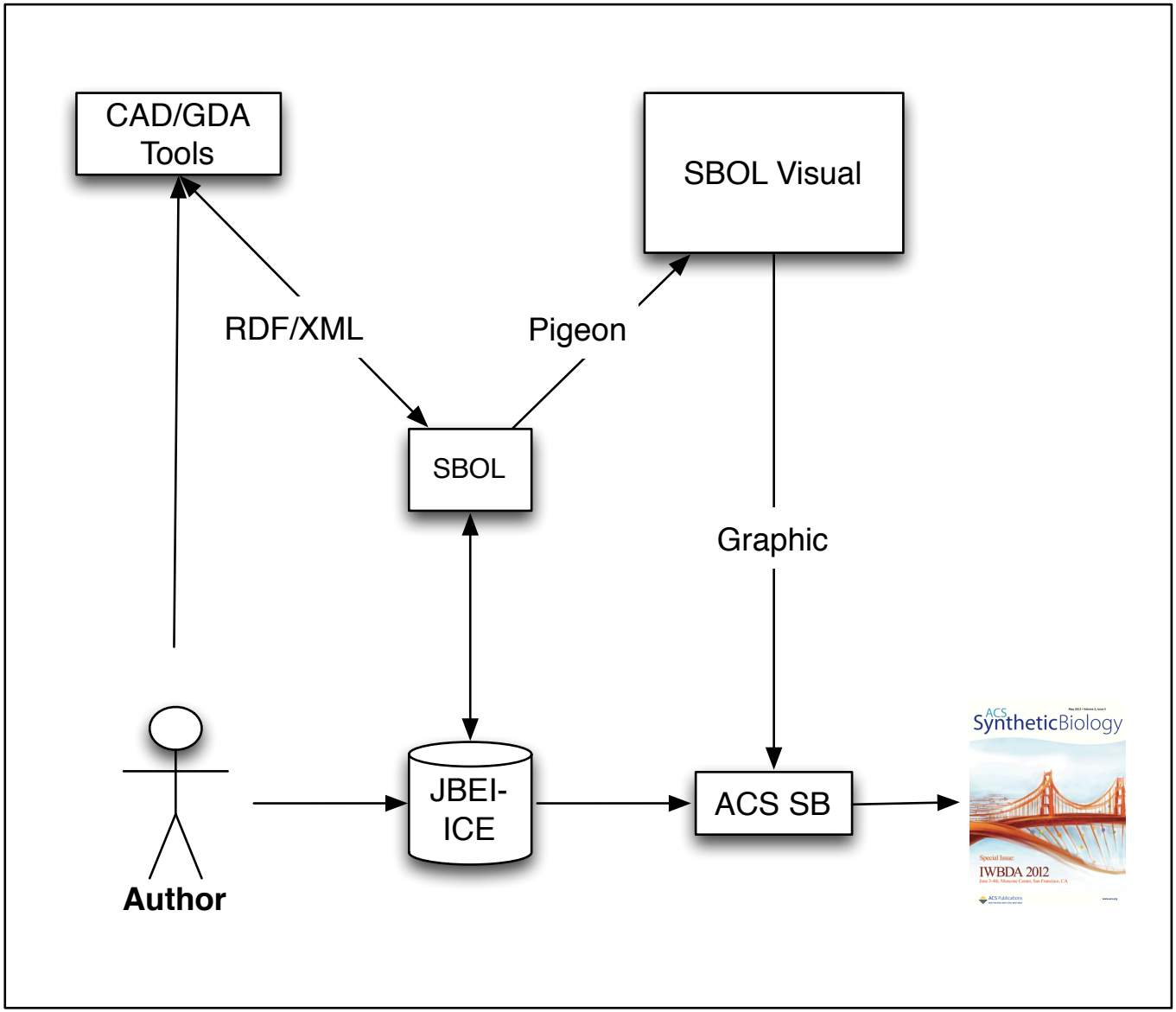
Figure 2. The genetic circuit diagram for the quorum trigger represented using SBOL visual symbols. This circuit is designed to produce a density-dependent response to an environmental signal (Env). This response is achieved using the quorum sensing molecule 3OC6HSL. The 3OC6HSL molecule can either come from LuxI generated at the basal rate of the pComp promoter, or it can come from diffusion into the cell from 3OC6HSL available in the medium that is produced by other cells.



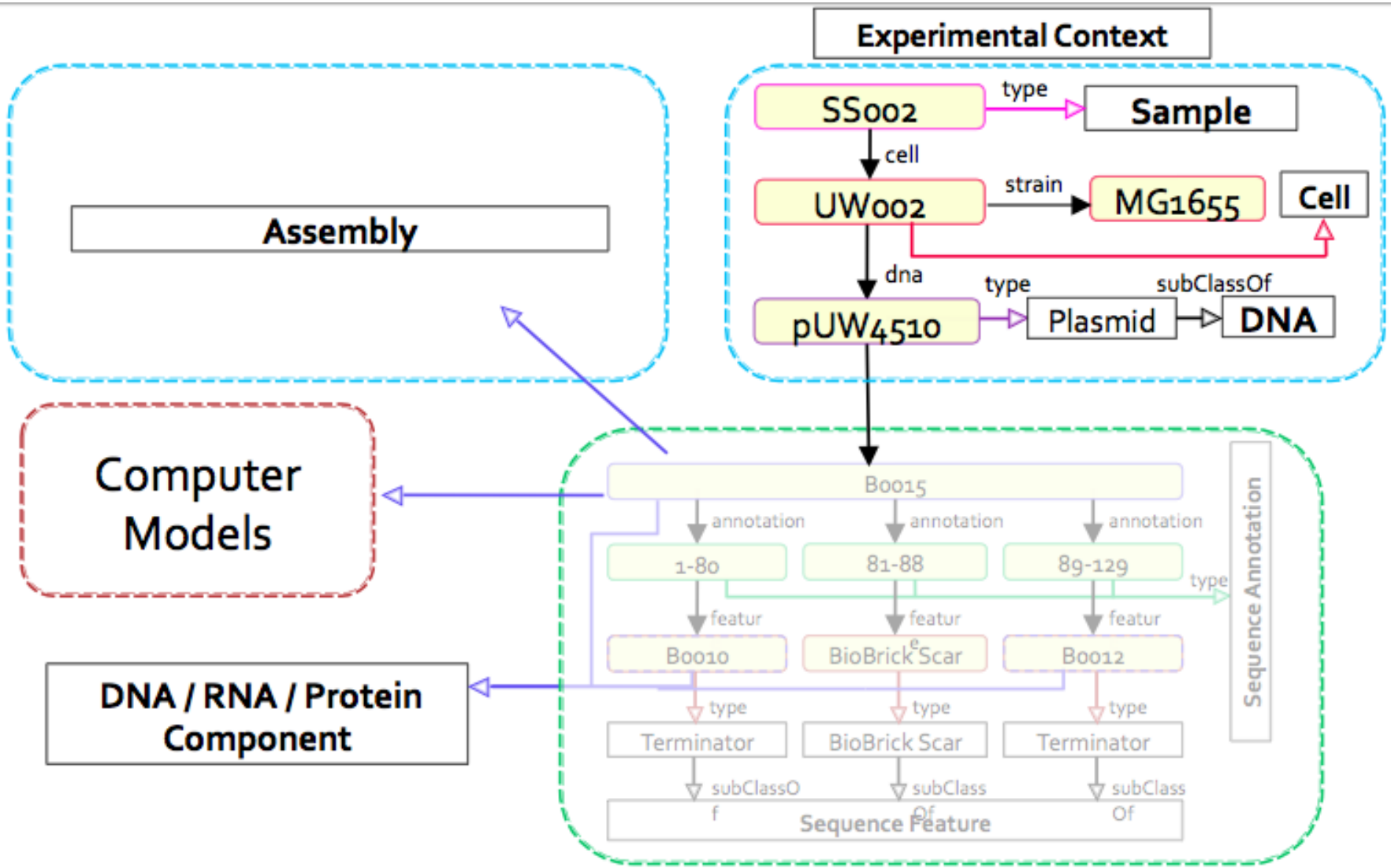
ABSTRACT: increases, mod subsequent ex automation cc tional tools f analyzing new existing softwa cell level, wit address this enhanced to visualizing dyr space. This capitalizing on iBioSim's strengths in modeling, simulating, and analyzing single-celled systems.

KEYWORDS: *spatial modeling, dynamic modeling, multicellular modeling, stochastic simulation, genetic circuits, SBML*

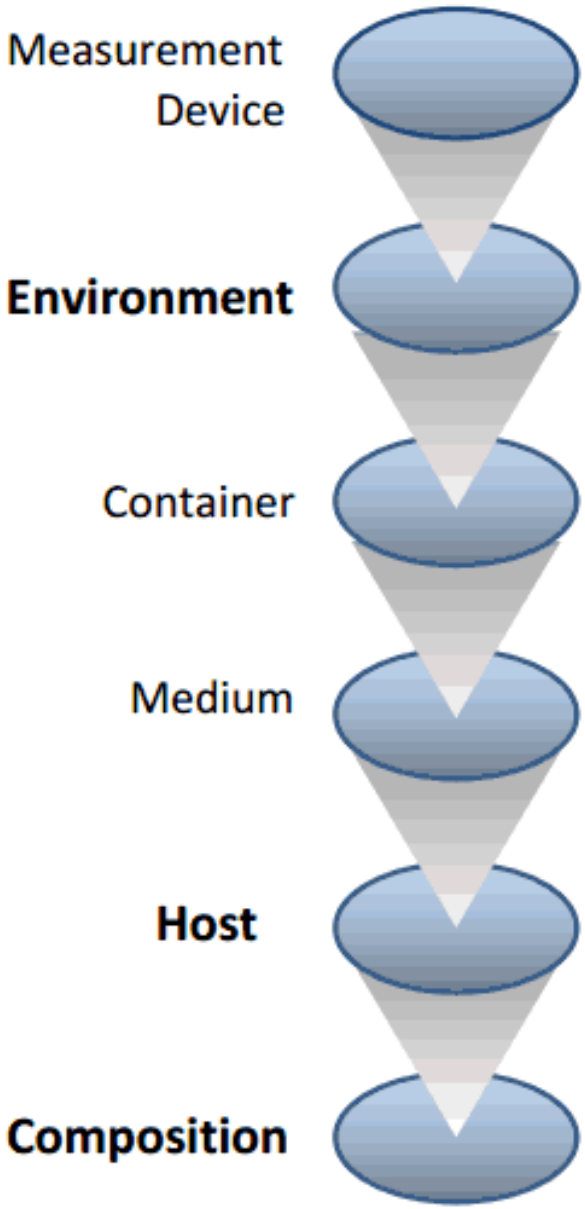
SBOL Adoption Plan



SBOL Extensions



Experimental Context



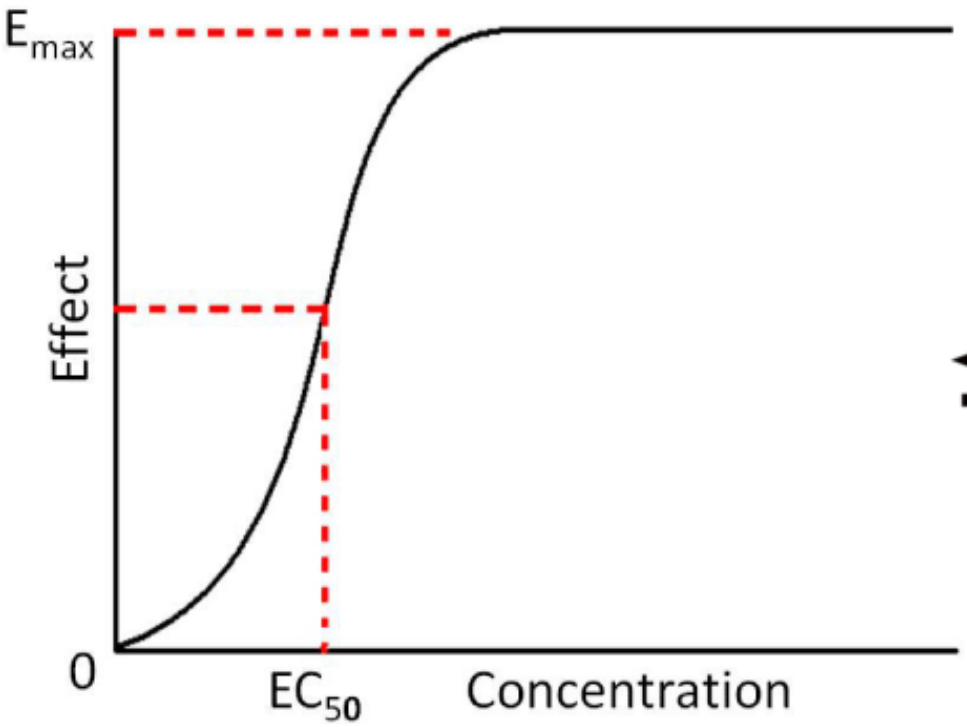
Context: What is needed to reproduce the intended function of a DNA design

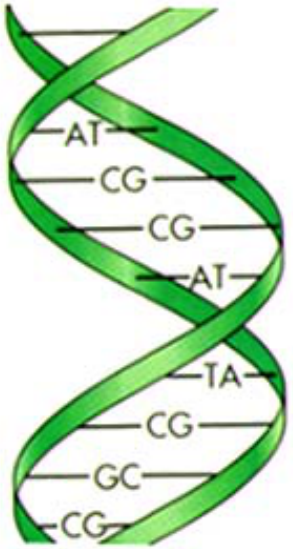
Cardinale S and Arkin AP. *Contextualizing context for synthetic biology – identifying causes of failure of synthetic biological systems*. Biotechnol J. 2012 July; 7(7): 856–866.

Experimental Context: Repressilator Example

Measurement Device	Zeiss Axiovert 135TV microscope
Environment	The temperature of the samples was maintained at 30–32 °C by using Peltier devices (Melcor)
Container	coverslip and microscope slide
Medium	minimal media 1 ml of liquid 2% SeaPlaque low-melt agarose (FMC) in media 100 uM IPTG inducer antibiotic 20 g ml-1 kanamycin or 20 g ml -1 ampicillin) minimum initial cell density OD = 0.1
Host	*E. coli* lac- strain MC4100
Composition	Genome, Repressilator and Reporter plasmids

Coupling Models to DNA

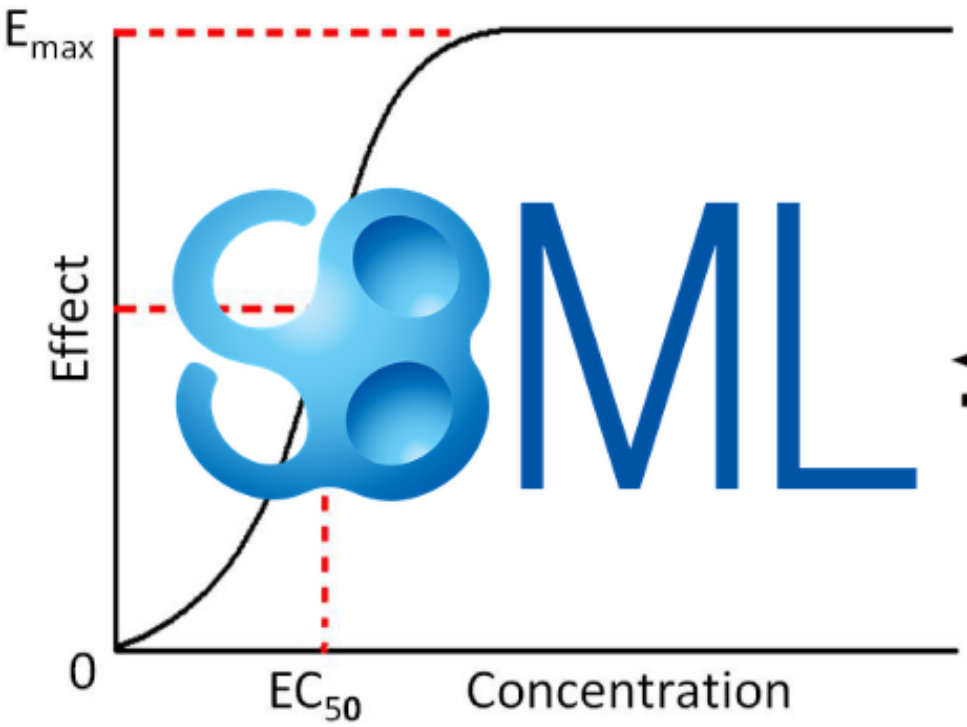




Model

DNA Component

Coupling Models to DNA



SBML

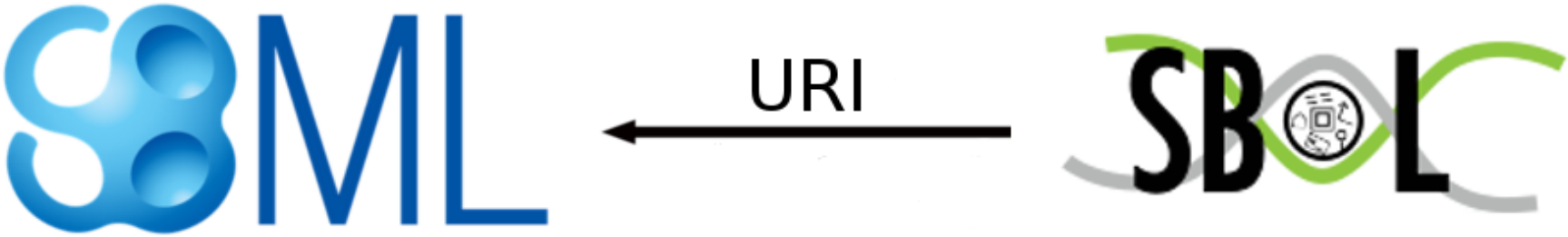
SBOL

Model

DNA Component

Connection from SBML to SBOL

Connection from SBOL to SBML



Challenges in Building SBOL

- Must identify and engage stakeholders while maintaining consensus.
- Fast pace of in the field:
  - Terminology evolution - “BioBricks” $\rightarrow$ “Parts” $\rightarrow$ “DNA components”.
  - Stability of use cases - standard and research needs seem contradictory.
  - Software for synthetic biology is new.
- Scarcity of data sources:
  - Quality “knowledge” about elements is very limited.
  - Heterogeneity of existing annotations is problematic.
- Funding

An Invitation

- SBOL is developed by the synthetic biology community.
- We hope you will join our discussions and support SBOL by:
  - Submitting your designs to a SBOL repository, such as `JBEI-ICE`.
  - Using SBOL in your GDA tools leveraging `libSBOLj`, when applicable.
  - Joining the SBOL Developers Group by emailing `sbol-editors@googlegroups.org`.
- More information: `http://www.sbolstandard.org`.

Acknowledgments

Agilent Technologies

CLARK PARSIA

Stardog

Raytheon BBN Technologies

AUTODESK.

life technologies™

DNA 2.0

GENOME COMPILER
TOOLS FOR DESIGNING LIFE

National Human Genome Research Institute

Special Issue Synthetic Biology for the ACM Journal on Emerging Technologies in Computing Systems

- Guest editors: Chris J. Myers, Herbert Sauro, and Anil Wipat
- Topics of interest include, but are not limited to:
  - Domain specific languages
  - Methodologies for automated model driven design
  - Data exchange standards
  - Efficient modeling and analysis methods
  - Abstraction techniques
  - Automated assembly techniques
  - Experimental validations of genetic designs
- Submission deadline: December 15, 2013.
- More information: `http://jetc.acm.org`.