Synthetic Biology: A New Application Area for Design Automation Research

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December 10, 2009
James Watson

Biology has at least 50 more interesting years (1984).
Michael Samoilov and Adam Arkin
Phage λ Virus

- Phage λ
- E. coli bacterial cell
- Host chromosome
- Attachment
- Penetration
- Lysogeny
- Replication
- Assembly
- Release
- Lysis Pathway
- Lysogeny Pathway
- Induction event
- Cell division

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Phage λ Decision Circuit

[Diagram of the Phage λ Decision Circuit with various components and regulatory interactions, including Cl, Cro, R1, R2, O_R1, O_R2, O_R3, cl, cro, cII, cIII, N, P_L, P_R, P_RM, P_RE, P_I, P_I_CII, P_I_CIII, T_R1, T_L1, NUT_L, NUT_R, R1, R2, R3, R4, R5, Cl_2, Cro_2, and deg nodes.]
Asynchronous Circuit?

Stochastic Circuit?

Arkin/Ross/McAdams, Genetics (1998)

Estimated Fraction Lysogens

1x10^-5
1x10^-4
1x10^-3
1x10^-2
1x10^-1
1x10^0

Poisson-4

Poisson-5

Poisson-6

Arkin/Ross/McAdams, Genetics (1998)
Stochastic Asynchronous Circuit?
Stochastic Asynchronous Circuit Results

SAC results generated in only 7 minutes.
SAC results generated in only 7 minutes.
OK, PAY ATTENTION!
AN INVERTER IS A
COMBINATION OF BASIC
DNA PARTS THAT—

-WORKING
TOGETHER, TURN
SOMETHING UPSIDE
DOWN.

ON BECOMES OFF,
LOW BECOMES HIGH,
AND SO ON.

Parts of an Inverter
1. Ribosome Binding Site (RBS) - Basic elements that start the process of protein synthesis.
2. Repressor - A gene that encodes a particular type of protein that will bind DNA sites in a specific Operator part and cause changes in the rate of gene expression.
3. Terminator - Special elements that decrease the flow of RNA polymerase along DNA, sometimes to zero!
4. Operator - Stretches of DNA that contain Repressor protein binding sites and RNA polymerase binding and initiation sites. With a Repressor protein, the Operator part will be turned OFF. Without a Repressor protein, the Operator part will be turned ON, allowing RNA polymerase to bind and initiate a HIGH output signal.

(From “Adventures in Synthetic Biology” - Endy et al.)
Genetic Engineering vs. Synthetic Biology

- Genetic engineering (last 30 years):
  - Recombinant DNA - constructing artificial DNA through combinations.
  - Polymerase Chain Reaction (PCR) - making many copies of this new DNA.
  - Automated sequencing - checking the resulting DNA sequence.

- Synthetic biology adds:
  - Standards - create repositories of parts that can be easily composed.
  - Abstraction - high-level models to facilitate design.
  - Automated construction - separate design from construction.

(source: Drew Endy)
Genetic Design Automation (GDA)

- Standards, abstraction, and automated construction are the cornerstones of *Electronic Design Automation* (EDA).
- EDA facilitates the design of more complex integrated circuits each year.
- Crucial to the success of synthetic biology is an improvement in methods and tools for *Genetic Design Automation* (GDA).
- Experiences with EDA can jump start the development of GDA.
Registry of standard biological parts used to design synthetic genetic circuits ([http://partsregistry.org](http://partsregistry.org)).

Adequate characterization of these parts is an ongoing effort.

*Systems Biology Markup Language* (SBML) has been proposed as a standard representation for the simulation of biological systems.

Many simulation tools have been developed that accept models in the SBML format (Copasi, Jarnac, CellDesigner, SimBiology, iBioSim, etc.).
Existing SBML-based GDA tools model biological systems at the molecular level.

A typical SBML model is composed of a number of chemical species (i.e., proteins, genes, etc.) and reactions that transform these species.

This is a very low level representation which is roughly equivalent to the layout level for electronic circuits.

Designing and simulating genetic circuits at this level of detail is extremely tedious and time-consuming.
Several companies have formed that will construct a plasmid from an arbitrary DNA sequence.

It is still difficult, however, to separate design and construction issues.

To achieve this, a GDA tool that supports higher-levels of abstraction for modeling, analysis, and design of genetic circuits is essential.
Phage $\lambda$ Decision Circuit
Phage λ Decision Circuit
Genetic Circuits

DNA

Pre

$O_E$

$O_R$

Pr

$cl$

$cl II$

Genes

$cI$

$cII$
Genetic Circuits

DNA

Pre

OE

OR

Pr

cl

cll

Promoters

Genes

Prep

CI Dimer

Activation

CI Protein

mRNA

Translation

CII Protein

Operators

Promoters

Genes

CI

cII

O

E

R

Pr

Pre

CI Dimer
Genetic Circuits

DNA

Pre

OE

OR

RNAP

Transcription

cl

cll

Promoters

Genes

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Genetic Circuits

DNA

Promoters
Genes

RNA Polymerase (RNAP)

Repression
Degradation
Dimerization

Pr

CI Dimer

CI Protein

mRNA

Translation

CII Protein

Operator Sites

Pre

Pr

Transcription

Gene

Pre

O

O

cI

cII

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DNA

Pre

O_E

O_R

Pr

RNAP

Transcription

Promoters

Genes

cl

cII

Genes

Transcription

Pr

RNAP

DNA

Pre

O_E

O_R

Pr

RNAP

Promoters

Genes
Genetic Circuits

RNAP

Repression
Degradation
Dimerization

Pr
CI Dimer
Activation
CI Protein

DNA
Promoters
Genes

Pre
Pr
O_E
O_R

O
R

E

Translation
mRNA

cI
Pre
Pr

cII
Promoters
Genes

Transcription

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Genetic Circuits

- **DNA**
- **Pre**
- **Pr**
- **cl**
- **cII**
- **Operator Sites**
- **Promoters**
- **Genes**
- **RNAP**
- **CI Dimer**
- **CI Protein**
- **mRNA**
- **Translation**
- **Transcription**

- **Repression**
- **Degradation**
- **Dimerization**

- **Pr**
- **CI**
- **OE**
- **OR**

- **cI**
- **cII**

- **O**
- **E**
- **R**

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Genetic Circuits

- **RNA Pol (RNAP)**
- **Repression**
- **Degradation**
- **Dimerization**
- **Pr**
- **CI Dimer**
- **CI Protein**
- **DNA**
- **Pre**
- **Activation**
- **Translation**
- **Pr**
- **mRNA**
- **cl**
- **O_E**
- **O_R**
- **cll**
- **Operator Sites**
- **Promoters**
- **Genes**

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Genetic Circuits

DNA → Activation → Transcription → Translation → mRNA

Operator Sites: $O_E$, $O_R$

Cl Protein

Promoters → Genes

Pr, Pre
Genetic Circuits

Repression
Degradation
Dimerization

CI Protein
CI Dimer

Activation
Translation
Transcription
mRNA

DNA

Pre
Pr

OE
OR

cl
cII

Operator Sites
Promoters
Genes

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Genetic Circuits

- **Dimerization**
- **CI Dimer**
- **Cl Protein**
- **CI Dimer**
- **Repression**
- **CII Protein**
- **Activation**
- **DNA**
- **Pre**
- **Pr**
- **Operator Sites**
- **O_E**
- **O_R**
- **Promoters**
- **Genes**
- **cl**
- **cII**
Genetic Circuits

- Repression
- Degradation
- Dimerization
- RNAP
- mRNA
- Translation
- Pr
- CI Dimer
- CII Protein
- CI Protein
- CII Protein
- Operator Sites
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- Genes
- DNA
- Pre
- Pr
- OE
- OR
- cl
- cII
- Activation
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- Synthetic Biology
- Carnegie Mellon University
DNA makes RNA, RNA makes protein, and proteins make us.
The sciences do not try to explain, they hardly even try to interpret, they mainly make models. By a model is meant a mathematical construct which, with the addition of certain verbal interpretations, describes observed phenomena. The justification of such a mathematical construct is solely and precisely that it is expected to work.
There are many methods for predicting the future. For example, you can read horoscopes, tea leaves, tarot cards, or crystal balls. Collectively, these methods are known as “nutty methods.” Or you can put well-researched facts into sophisticated computer models, more commonly referred to as “a complete waste of time.”
Genetic Circuit Model (GCM)

- Provides a higher level of abstraction than SBML.
- Includes only important species and their influences upon each other.
- GCMs also include structural constructs that allow us to connect GCMs for separate modules through species ports.
A Genetic Not Gate

A

\[ \text{P1} \]

C

A

\[ \text{A} \]

P1

C

\[ \text{c} \]
A Genetic Nor Gate

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A Genetic Nand Gate

A genetic nand gate is a biological circuit that functions similarly to a digital nand gate. It is composed of two inputs, A and B, and one output, C. The expression of the output C is determined by the simultaneous absence of both inputs A and B. Mathematical expression of a nand gate is: 

\[ C = \overline{A \land B} \]

where \( A \) and \( B \) are the inputs, \( C \) is the output, and \( \overline{\cdot} \) denotes the logical negation.}

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A Genetic Oscillator

CI

Pre

Pr

CII

Cl Dimer

CI Protein

CII Protein

Pre

OE

OR

Pr

cl

cII

CI

CII
SBML: Main Elements

- **Species**
- **Global parameters** (ex. \(k_1=0.1\))
- **Reactions**
  - Reactants
  - Products
  - Modifiers
  - Stoichiometry
  - Reversible
  - Kinetic laws
SBML: Main Elements

- **Species**
  - Global parameters (ex. k1=0.1)

- **Reactions**
  - Reactants
  - Products
  - Modifiers
  - Stoichiometry
  - Reversible
  - Kinetic laws

![Diagram of SBML reactions]

- Reactants: S1, S2
- Products: S3, S4
- Stoichiometry: r1 \( k1 \cdot S1 \cdot S2 \), r2 \( k2 \cdot S3 - k3 \cdot S4 \)
- Reversible: r, m
- Kinetic laws: p
Species

Global parameters (ex. k1=0.1)

Reactions
- Reactants
- Products
- Modifiers
- Stoichiometry
- Reversible
- Kinetic laws
- Species
- Global parameters (ex. $k1=0.1$)
- Reactions
  - Reactants
  - Products
  - Modifiers
  - Stoichiometry
  - Reversible
  - Kinetic laws
**SBML: Main Elements**

- **Species**
- **Global parameters** (ex. k1=0.1)
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- **Species**
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SBML: Main Elements

- Species
- Global parameters (ex. k1=0.1)
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**SBML: Main Elements**

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![Diagram showing SBML elements](image)
SBML: Main Elements

- **Species**
- **Global parameters (ex. k1=0.1)**
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SBML: Main Elements

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  - Kinetic laws

```
S1 -> r1 -> S3 -> r2 -> S4
\nS2 -> m

r1 = k1 * S1 * S2
r2 = k2 * S3 - k3 * S4
```

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Create degradation reactions
Create open complex formation reactions
Create dimerization reactions
Create repression reactions
Create activation reactions
GCM Example

\[
\text{Pre} \rightarrow \text{Cl} \rightarrow \text{Pr} \rightarrow \text{CII}
\]
Degradation Reactions

\[
\begin{align*}
\text{CI} & \quad \text{r} \quad \text{Decay of CI} \\
& \quad \text{kd} \ast \text{CI} \\
\text{CII} & \quad \text{r} \quad \text{Decay of CII} \\
& \quad \text{kd} \ast \text{CII}
\end{align*}
\]
Dimerization Reactions

\[
\text{CI} \xrightarrow{2, \, r} \text{Dimerization of CI} \xrightarrow{K_d \times \text{CI}^2 - \text{CI}_2} \text{CI}_2
\]
Repression Reactions

Repression of Pr
$Kr \ast Pr \ast Cl2^{nc} - S3$

$S3$
Activation Reactions

Activated Open Complex Pre
Ka * Pre * CII\(^{nc}\) * RNAP - S4

Activated Production of CI
ka * S4

CI
Uses *ordinary differential equations* (ODE) to represent the system to be analyzed, and it assumes:
- Molecule counts are high, so concentrations can be continuous variables.
- Reactions occur continuously and deterministically.

Genetic circuits have:
- Small molecule counts which must be considered as discrete variables.
- Gene expression reactions that occur sporadically.

ODEs do not capture non-deterministic behavior.
A philosopher once said “It is necessary for the very existence of science that the same conditions always produce the same results.” Well, they do not. You set up the circumstances, with the same conditions every time, and you cannot predict behind which hole you will see the electron.
A colony of genetically identical E. coli is actually a mob of individuals. Under identical conditions, they behave in different ways.

By CARL ZIMMER
Published: April 22, 2003
To more accurately predict the temporal behavior of genetic circuits, *stochastic chemical kinetics* formalism can be used.

Use Gillespie’s *Stochastic Simulation Algorithm* which tracks the quantities of each molecular species and treats each reaction as a separate random event.

Only practical for small systems with no major time-scale separations.

Abstraction is essential for efficient analysis of any realistic system.
Begins with a *reaction-based model* in SBML.

Automatically abstracts this model leveraging the quasi-steady state assumption, whenever possible.

Encodes chemical species concentrations into Boolean (or n-ary) levels to produce a *stochastic asynchronous circuit* (SAC) model.

Can now utilize Markov chain analysis.

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Automatic Abstraction

- Begins with a *reaction-based model* in SBML.
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Dimerization Reduction

- **Clit**
  - Decay of Cl: $kd \times fm(Cl_t)$

- **Pr**
  - Repression of Pr: $Kr \times Pr \times fd(Cl_t)^{nc} - S3$

- $p$ (production)
  - $S3$ (sink)
Operator Site Reduction (PR)

Repression of Pr
Kr * Pr * fd(CIt) * nc - S3

Open Complex PR
Ko * RNAP * Pr - S2

Production of CII
ko * S2

\[ \text{S3} \]
\[ \text{S2} \]
\[ \text{CII} \]
Operator Site Reduction (PR)

Production of CII

\[ \frac{\text{ko} \times \text{Pr} \times \text{Ko} \times \text{RNAP}}{1 + \text{Kr} \times \text{fd(CIt)}^{\text{nc}} + \text{Ko} \times \text{RNAP}} \]

np, p

CII
Activated Production of CI

\[ka \cdot \text{Pre} \cdot Ka \cdot \text{CII}^{\text{nc}} \cdot \text{RNAP}\]

\[1 + Ko \cdot \text{RNAP} + Ka \cdot \text{CII}^{\text{nc}} \cdot \text{RNAP}\]

Basal Production of CI

\[kb \cdot \text{Pre} \cdot Ko \cdot \text{RNAP}\]

\[1 + Ko \cdot \text{RNAP} + Ka \cdot \text{CII}^{\text{nc}} \cdot \text{RNAP}\]
Similar Reaction Combination

Production of CI

\[(ka \times Ka \times CII^{nc} + kb \times Ko) \times Pre \times RNAP\]

\[1 + Ko \times RNAP + Ka \times CII^{nc} \times RNAP\]

np, p

CII

Pre

RNAP

CIt

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Production of CI

\[(ka \cdot Ka \cdot CII^{nc} + kb \cdot Ko) \cdot Pre0 \cdot RNAP0 \]

\[1 + Ko \cdot RNAP0 + Ka \cdot CII^{nc} \cdot RNAP0\]
Final SBML Model

10 species and 10 reactions reduced to 2 species and 4 reactions

Production of CII

\[ \text{Production of CII} \]
\[ \text{Decay of CI} \]

Production of CI

\[ \text{Production of CI} \]

\[ \text{Decay of CII} \]
GCM Advantages

- Greatly increases the speed of model development and reduces the number of errors in the resulting models.
- Allows efficient exploration of the effects of parameter variation.
- Constrains SBML model such that it can be more easily abstracted resulting in substantial improvement in simulation time.
Project management support.

GCM Editor - creates Genetic Circuit Models (GCM).

SBML Editor - creates models using the Systems Biology Markup Language (SBML).

reb2sac - abstraction-based ODE, Monte Carlo, and Markov analysis.

TSD Graph Editor - visualizes time series data (TSD).

Probability Graph Editor - visualizes probability data.

GeneNet - learns GCMs from TSD.

Myers et al., Bioinformatics (2009)
iBioSim: Genetic Circuit Editor

Myers et al., Bioinformatics (2009)
Myers et al., Bioinformatics (2009)
Myers et al., Bioinformatics (2009)
ODE Results for the Simple Genetic Oscillator

Comparison of ODE to SSA Results

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SSA Results for the Simple Genetic Oscillator

Comparison of ODE to SSA Results

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Toggle Switch C-Element (Genetic Circuit)

Nguyen et al., 13th Symposium on Async. Ckts. & Sys., 2007 (best paper)
Nguyen et al., to appear in the Journal of Theoretical Biology
Toggle Switch C-Element (GCM)
Toggle Switch C-Element (SBML)
Reduced from 34 species and 31 reactions to 9 species and 15 reactions.
Simulation time improved from 312 seconds to 20 seconds.
Majority Gate C-Element (Genetic Circuit)
Speed-Independent C-Element (Genetic Circuit)
Comparison of Failure Rates for the C-element Designs

Failure Rate for Each C-Element Design

- Majority Gate (High to Low)
- Speed-Independent (High to Low)
- Toggle Switch (High to Low)

Time (s) | 0 | 500 | 1000 | 1500 | 2000
---|---|---|---|---|---
Failure Rate | 0 | 0.005 | 0.01 | 0.015 | 0.02

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Effects of Decay Rates on Failure Rates

Failure Rate Versus Decay Rate (Toggle Switch C-element)

High to Low

Low to High

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Effects of Decay Rates on Switching Time

Switching Time Versus Decay Rate (Toggle Switch C-element)

Switching Time (s) vs Decay Rate

High 
Low

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One interesting application for synthetic biology is the design of bacteria that can hunt and kill tumor cells (Anderson et al.). Care must be taken in determining when to attack potential tumor cells. Can use a genetic Muller C-element and a bacterial consensus mechanism known as *quorum sensing*. C-element combines a noisy environmental trigger signal and a density dependent quorum sensing signal. Activated bacteria signal their neighbors to reach consensus.

Winstead et al., IBE Conference (2008)
A noisy C-element with a confidence-feedback loop:

The output “rails” to maximum confidence, even if $E$ has low confidence.

This configuration only works if the C-element is “noisy”. Otherwise, the circuit is permanently stuck in its initial state.
Inactive Trigger Circuits
Env signal applied

(HSL concentration low)
One circuit randomly activates

(HSL concentration increases)

Env

(HSL concentration increases)
More circuits activate due to HSL

(HSL concentration increases sharply)
Avalanche effect: most cells activate

(HSL concentration saturates)
Env signal is removed.

(Circuits stay active)
Time passes.

(Circuits randomly switch off)

(Circuits randomly switch off)
Quorum Trigger Simulation Results

Probability of Toggle gate stimuli, E=0.005000

- Environmental Trigger
- Consensus Activator

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Quorum Trigger Simulation Results

Probability of Toggle gate stimuli, \( E=0.050000 \)

- Environmental Trigger
- Consensus Activator

Time Steps

Probability

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Quorum Trigger Simulation Results

Probability of Toggle gate stimuli, E=0.000000

- Environmental Trigger
- Consensus Activator

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Quorum Trigger Design

Env

Complex

LuxR

LuxI

3OC6HSL

medium

lacI+pLRBS

luxR

lux pR

GFP

RBS

luxR

RBS

luxI

→

→

↓↓

↓↓

↓↓

↓↓

→

→

→

→

/octagon/octagon

R0011

B0034

C0062

B0015

R0062

B0034

E0040

B0034

C0062

B0015

F2622

K116634

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Quorum Trigger Design

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Future GDA Research Directions

- Genetic circuits have no signal isolation.
- Circuit products may interfere with each other and host cell.
- Gates in a genetic circuit library usually can only be used once.
- Behavior of circuits are non-deterministic in nature.
- No global clock, so timing is difficult to characterize.
- To address these challenges, we are investigating soft logic models based on *factor graphs* and adapting asynchronous synthesis tools to a genetic circuit technology.
Human inner ear performs the equivalent of one billion floating point operations per second and consumes only 14 µW while a game console with similar performance burns about 50 W (Sarpeshkar, 2006).

We believe this difference is due to over designing components in order to achieve an extremely low probability of failure in every device.

Future silicon and nano-devices will be much less reliable.

For Moore’s law to continue, future design methods should support the design of reliable systems using unreliable components.

Biological systems constructed from very noisy and unreliable devices.

GDA tools may be useful for future integrated circuit technologies.
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.
Linux/Windows/Mac versions of iBioSim are freely available from:
http://www.async.ece.utah.edu/iBioSim/

Publications:
http://www.async.ece.utah.edu/publications/

Course materials:
http://www.async.ece.utah.edu/~myers/ece6760/
http://www.async.ece.utah.edu/~myers/math6790/
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Curtis Madsen  Nam Nguyen  Chris Winstead

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