Synthetic Biology: A New Application Area for Design Automation Research

Chris Myers[1], Nathan Barker[2], Hiroyuki Kuwahara[3],
Curtis Madsen[1], Nam Nguyen[4], Chris Winstead[5]

[1]University of Utah
[2]Southern Utah University
[3]Microsoft Research, Trento, Italy
[4]University of Texas at Austin
[5]Utah State University

NSF EDA Workshop
July 8, 2009

Synthetic Biology

- Increasing number of labs are designing more ambitious and mission critical *synthetic biology* projects.
- These projects construct synthetic *genetic circuits* from DNA.
- These synthetic *genetic circuits* can potentially result in:
  - More efficient pathways for the production of antimalarial drugs (Dae et al.).
  - Bacteria that can metabolize toxic chemicals (Brazil et al.).
  - Bacteria that can hunt and kill tumors (Anderson et al.).

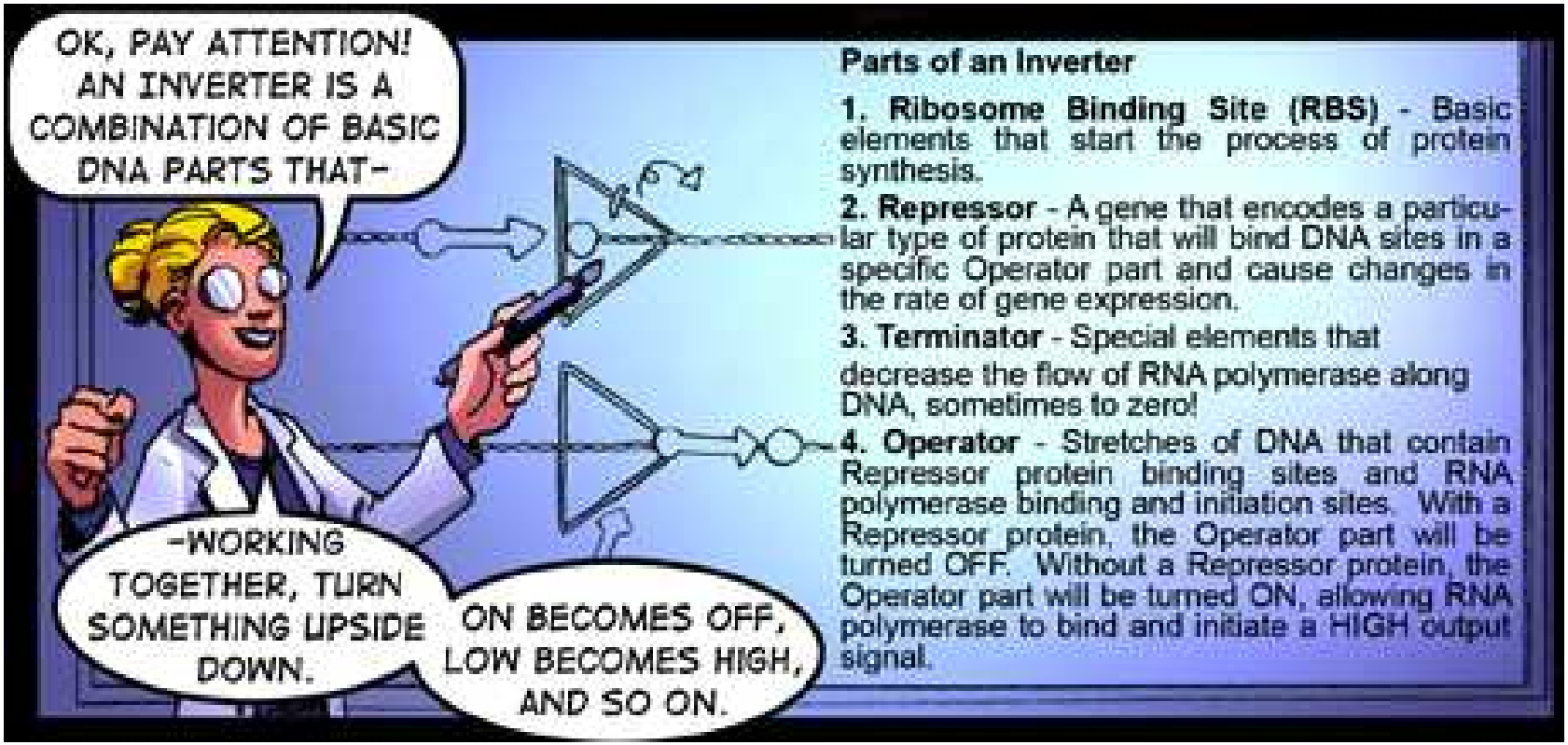
Genetic Engineering vs. Synthetic Biology

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

Genetic Design Automation (GDA)

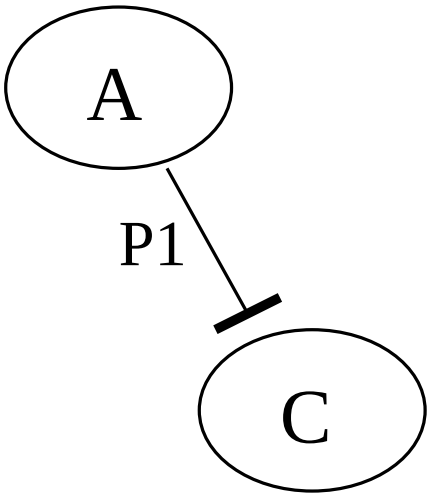
- *Electronic Design Automation* (EDA) tools have facilitated the design of ever more complex integrated circuits each year.
- Crucial to the success of synthetic biology is an improvement in methods and tools for *Genetic Design Automation* (GDA).
- Existing GDA tools require biologists to design at the molecular level.
- Roughly equivalent to designing electronic circuits at the layout level.
- Analysis of genetic circuits is also performed at this very low level.
- A GDA tool that supports higher levels of abstraction is essential.

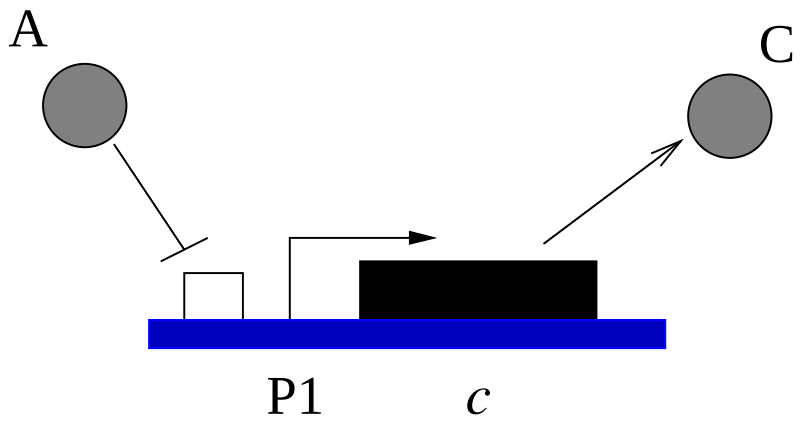
Adventures in Synthetic Biology

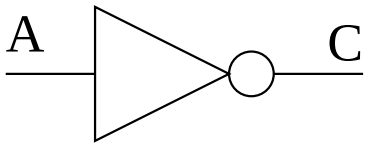


(From “Adventures in Synthetic Biology” - Endy et al.)

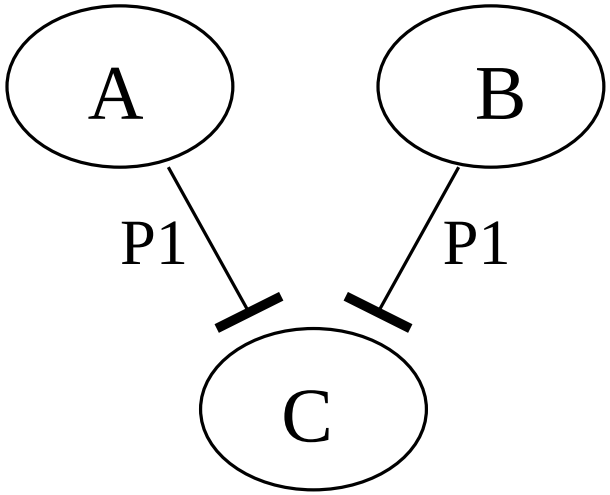
A Genetic Not Gate

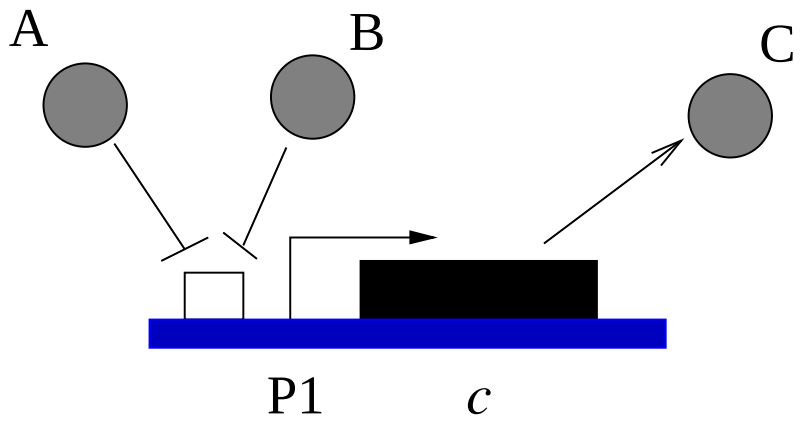


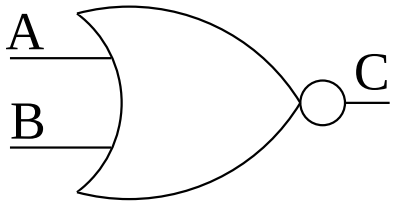




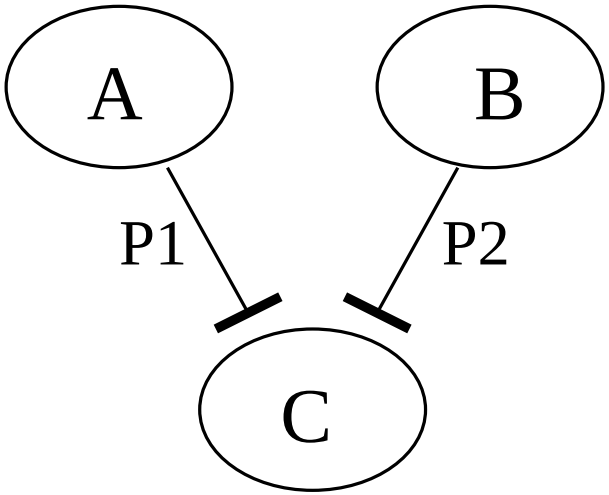
A Genetic Nor Gate

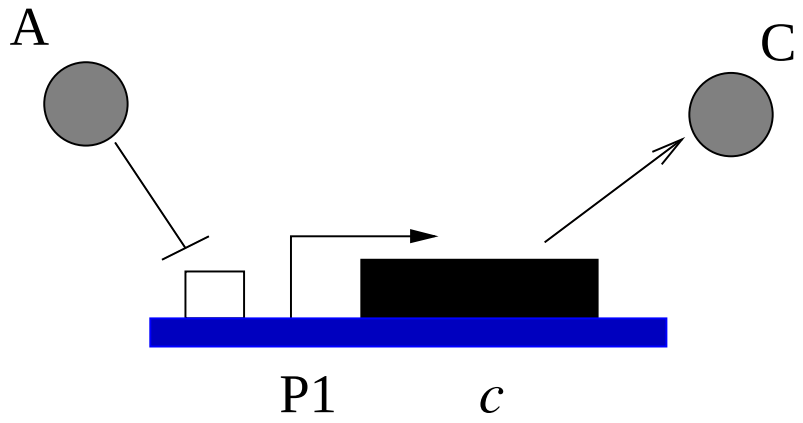


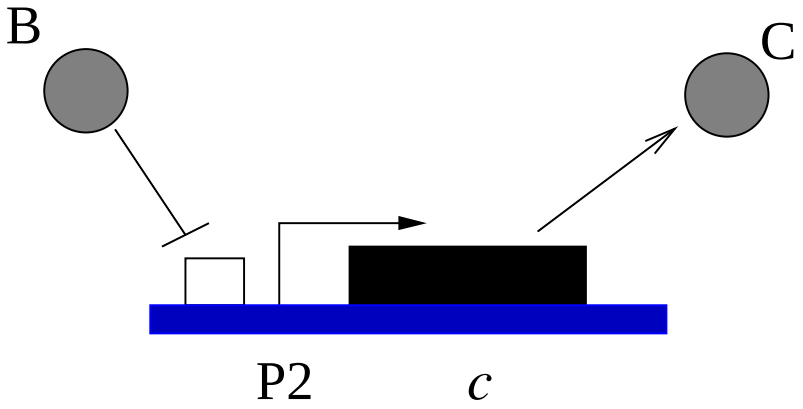


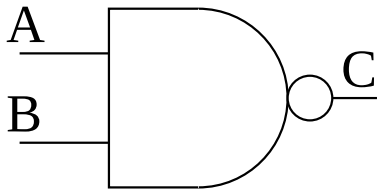


A Genetic Nand Gate

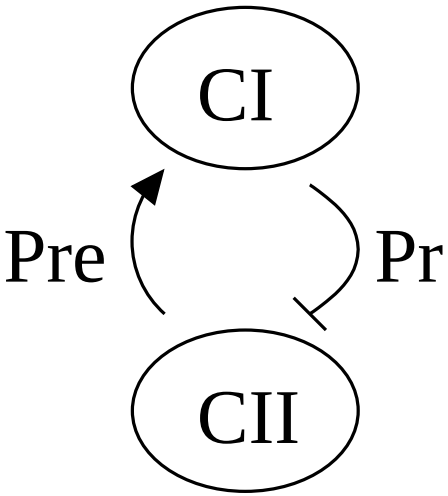


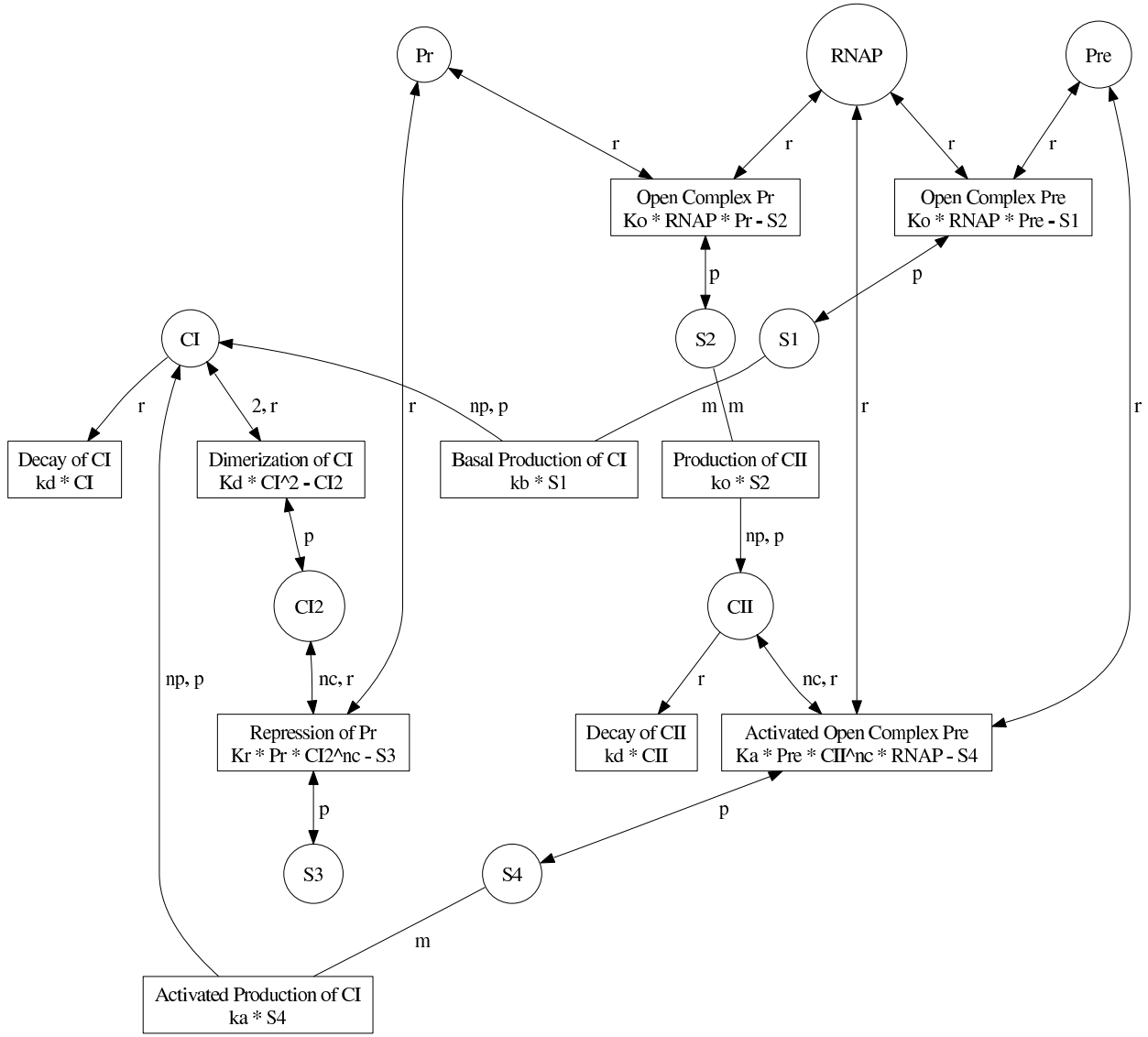




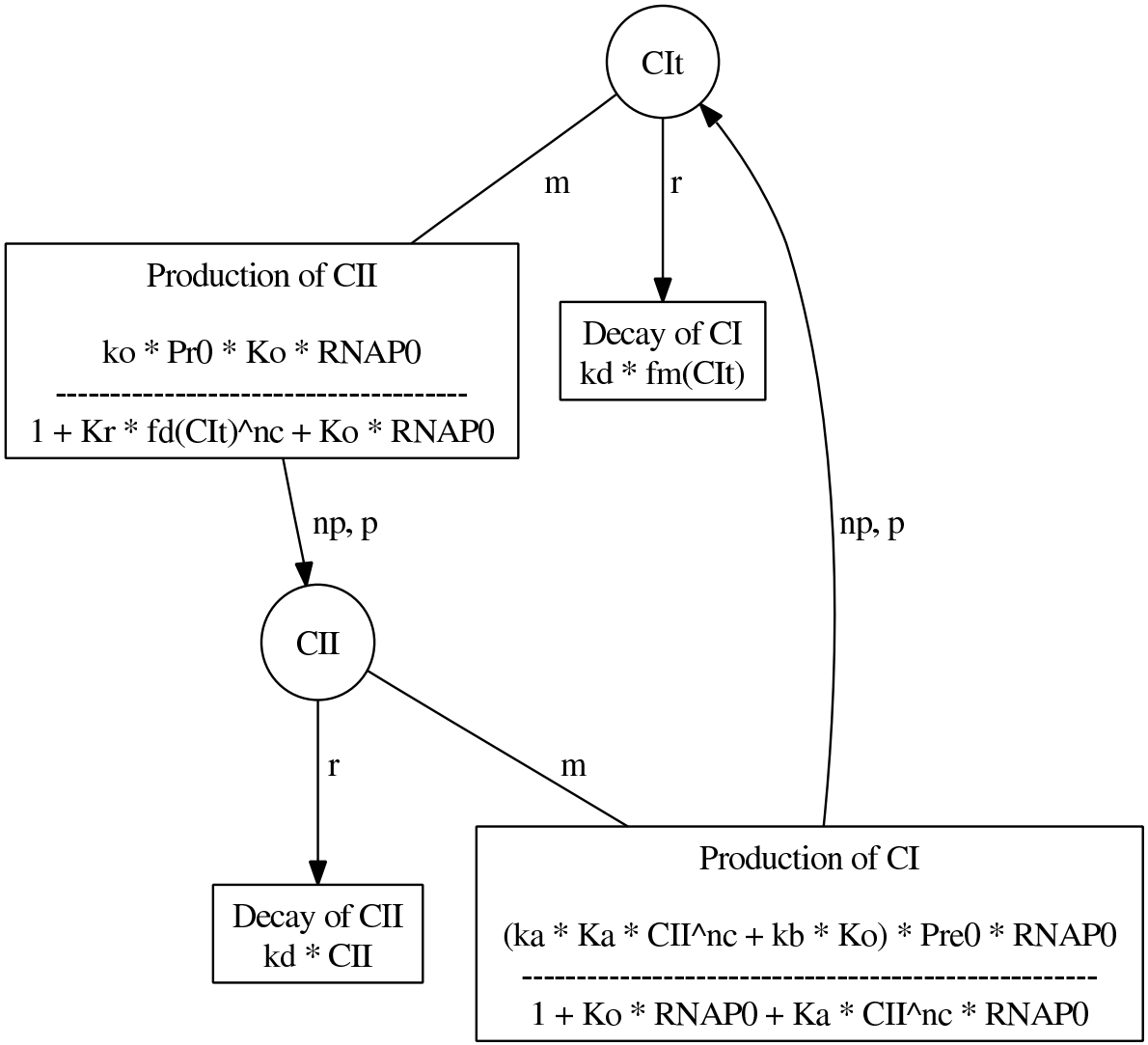


Genetic Circuit versus Molecular Representation





Final Molecular Model After Abstraction



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

Classical Chemical Kinetics

- 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.

NYTimes: Expressing Our Individuality, the Way E. Coli Do

The New York Times

Research

Health All NYT Search

Ameriprise Financial

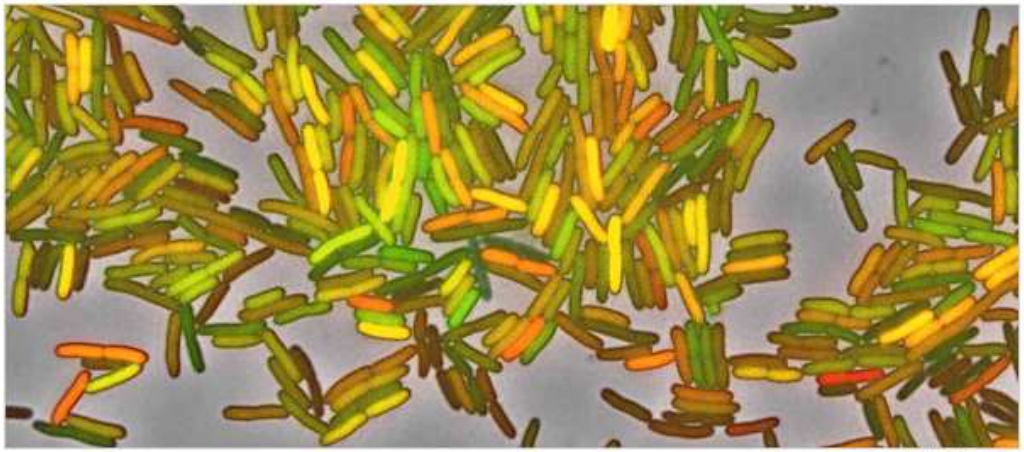
WORLD | U.S. | N.Y. / REGION | BUSINESS | TECHNOLOGY | SCIENCE | HEALTH | SPORTS | OPINION | ARTS | STYLE | TRAVEL | JOBS | REAL ESTATE | AUTOS

RESEARCH | FITNESS & NUTRITION | MONEY & POLICY | VIEWS | HEALTH GUIDE

Search Health 3,000+ Topics

Go

Expressing Our Individuality, the Way E. Coli Do



Dr. Michael Elowitz

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, 2008

SIGN IN TO E-MAIL

Well
Tara Parker-Pope on Health

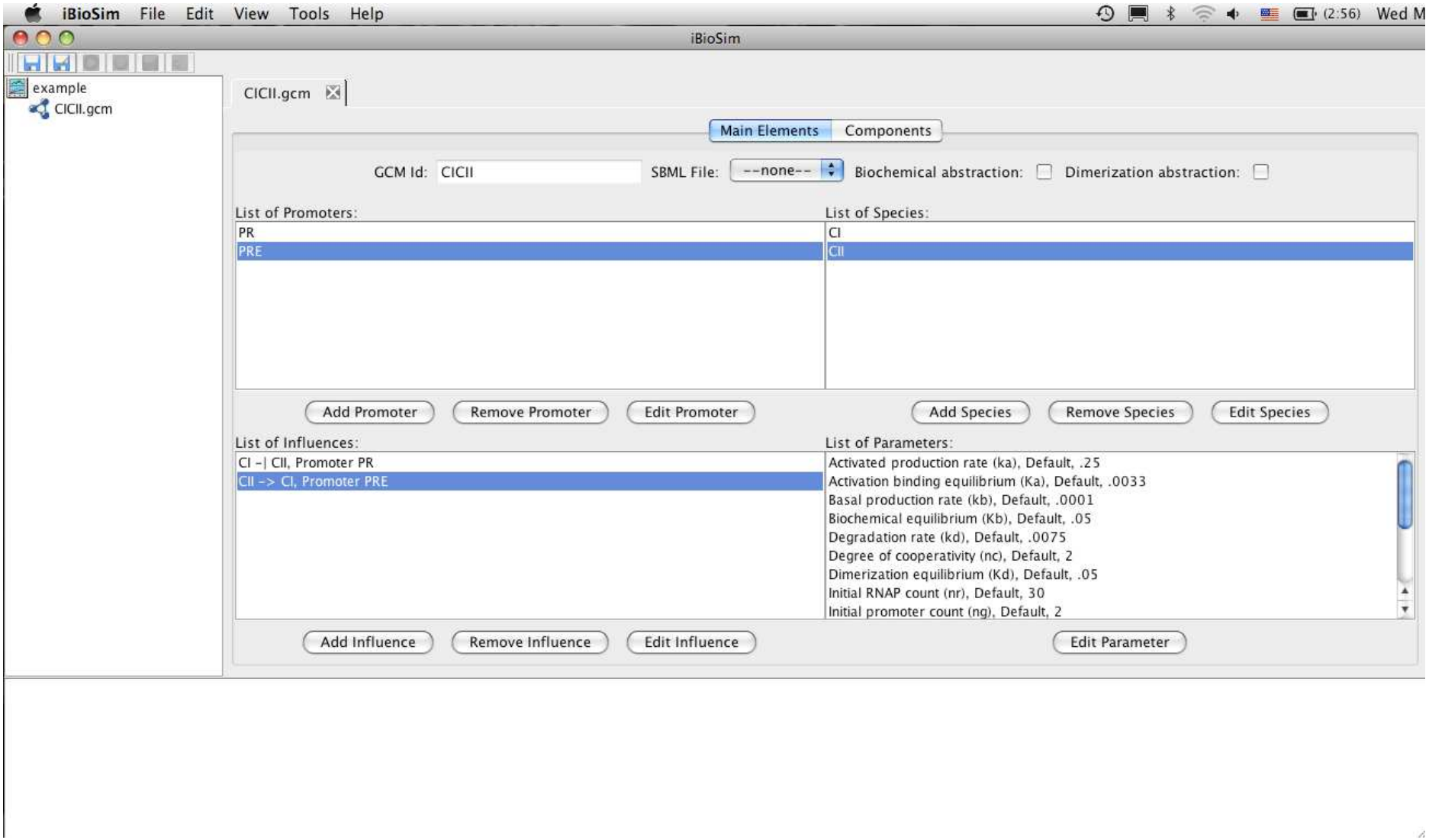
- **Socializing Appears to Delay Memory Problems**
  June 4, 2008, 12:34 PM
- **Colon Cancer in Family Predicts Better Survival**
  June 3, 2008
- **Jane Brody's New Knees**
  June 3, 2008
- **Brain Surgeons and Cellphones**
  June 2, 2008
- **Cleaner Classrooms Mean Fewer Sick Kids**
  June 2, 2008

Rainbow and CC

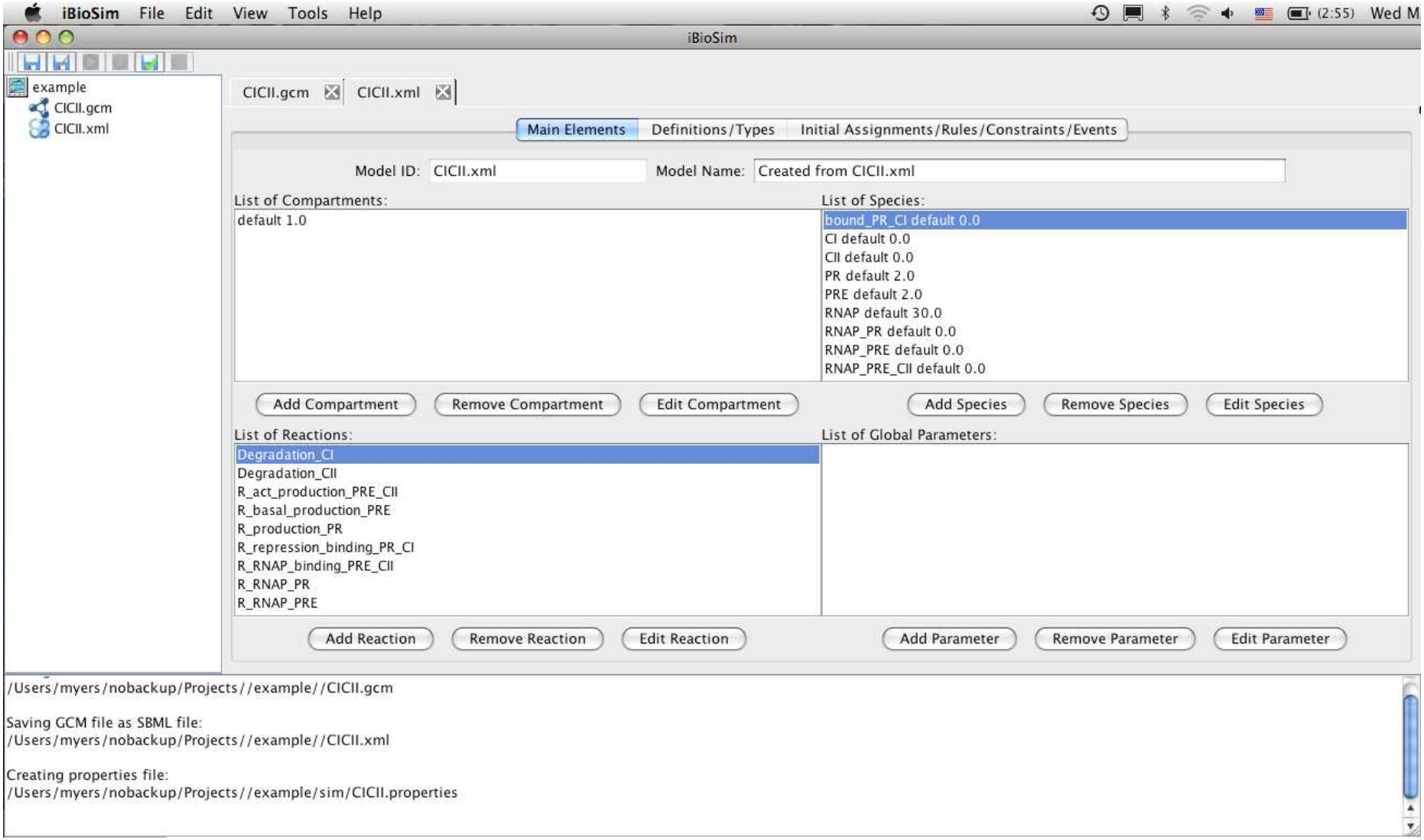
Stochastic Chemical Kinetics

- 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.

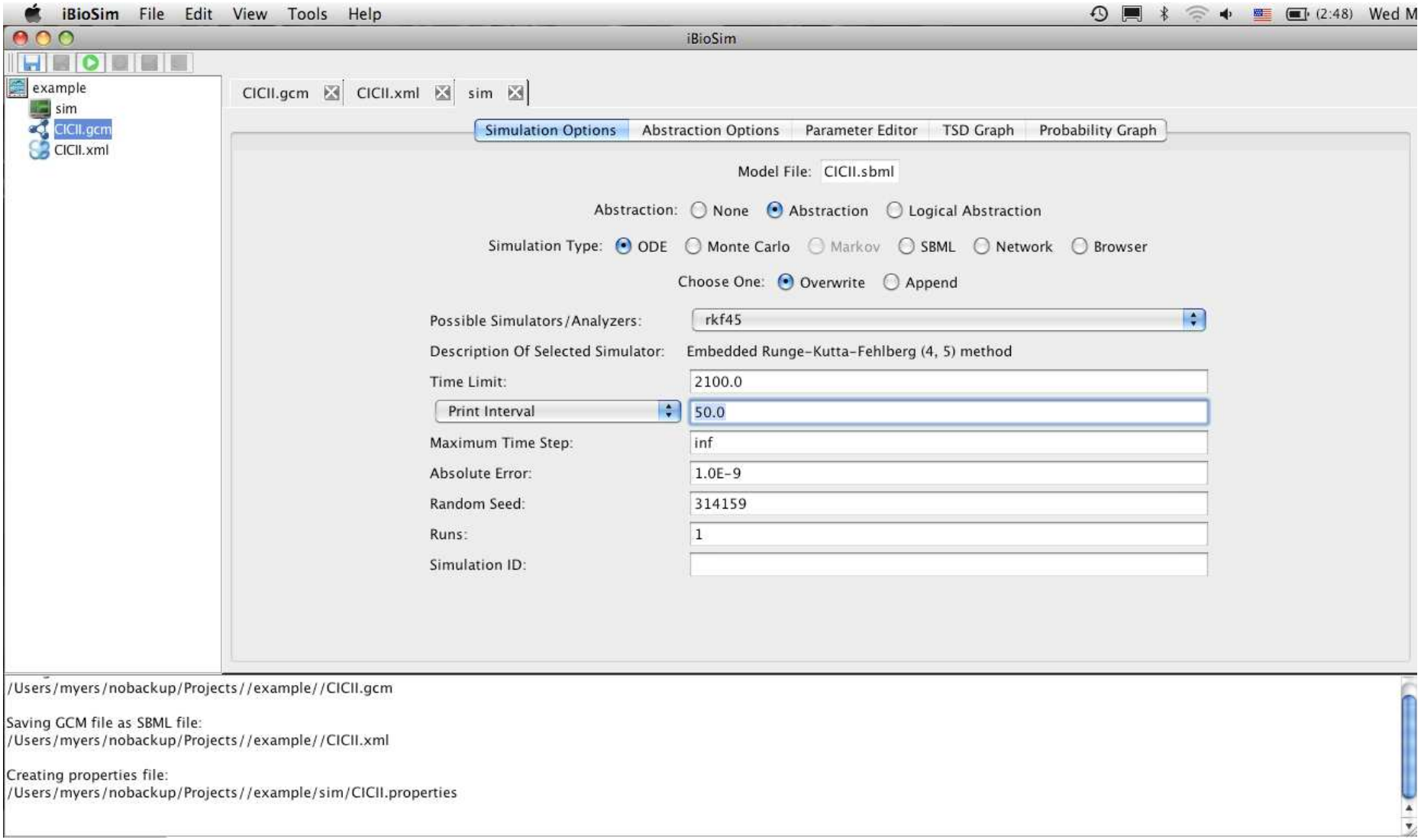
iBioSim: Genetic Circuit Editor



iBioSim: SBML Editor

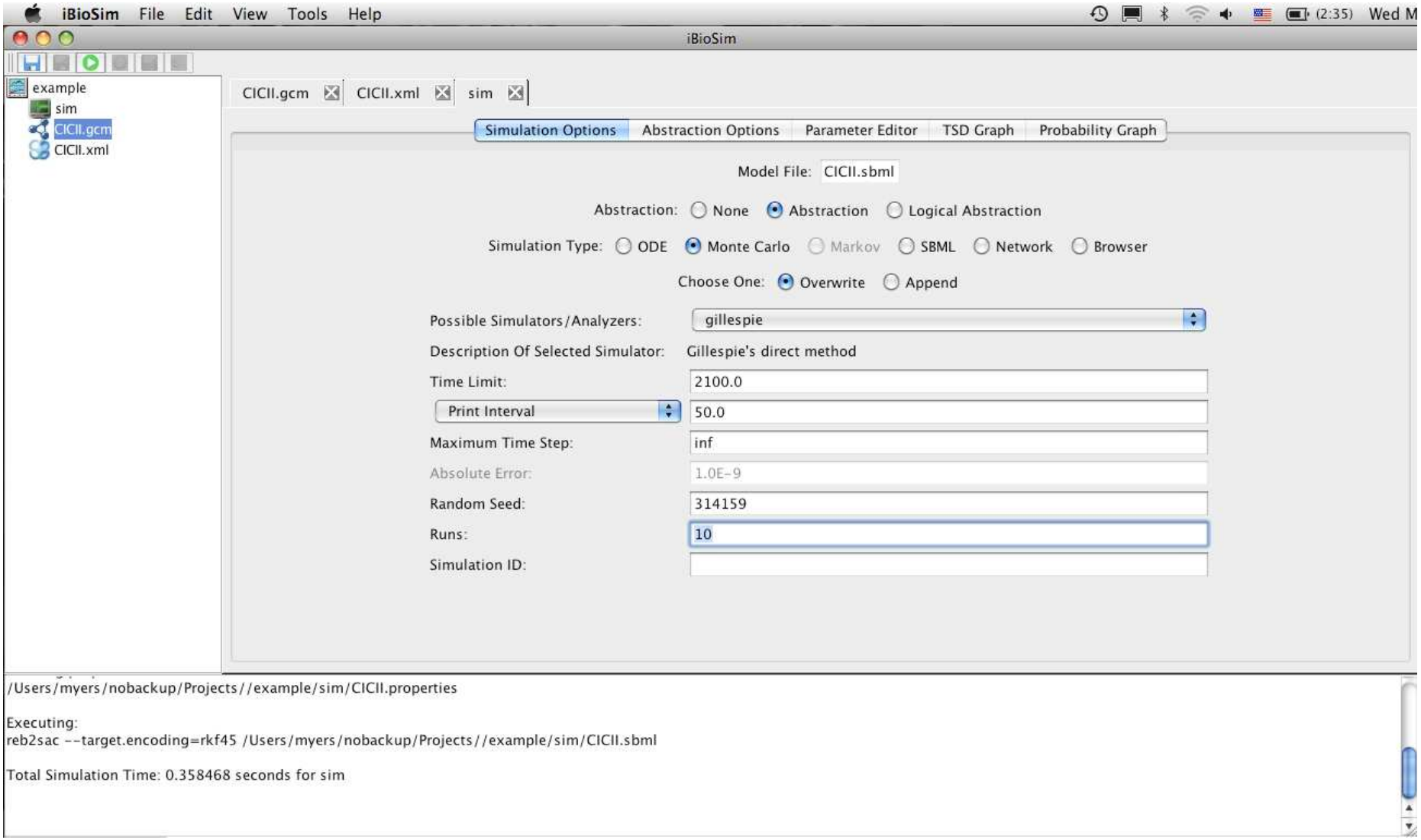


iBioSim: ODE Analysis

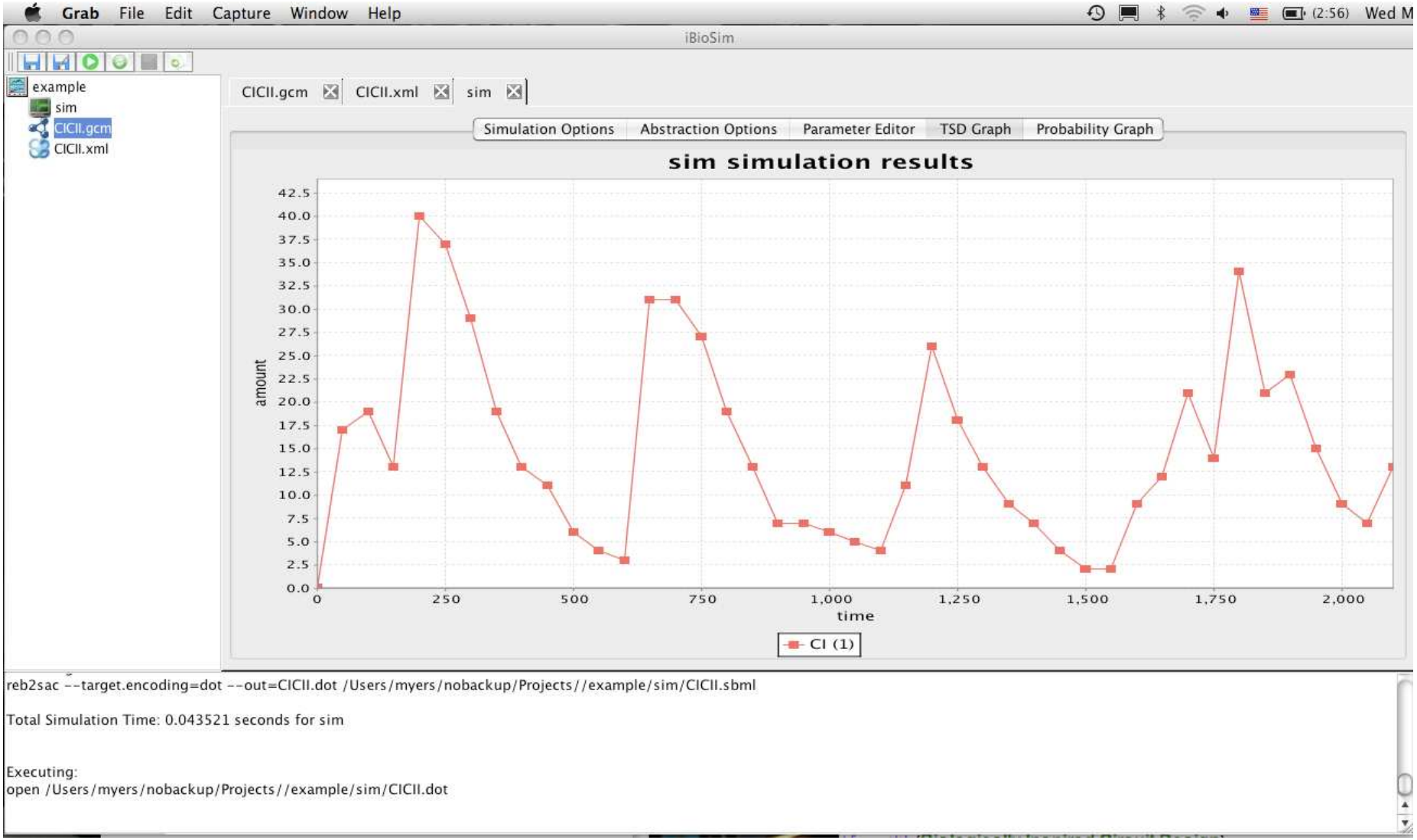


iBioSim: ODE Simulation Results

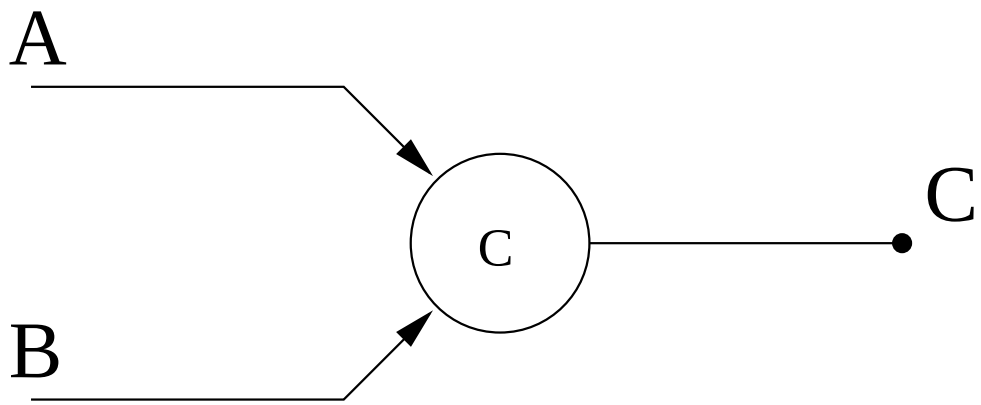
iBioSim: Gillespie Analysis



iBioSim: Stochastic Simulation Results

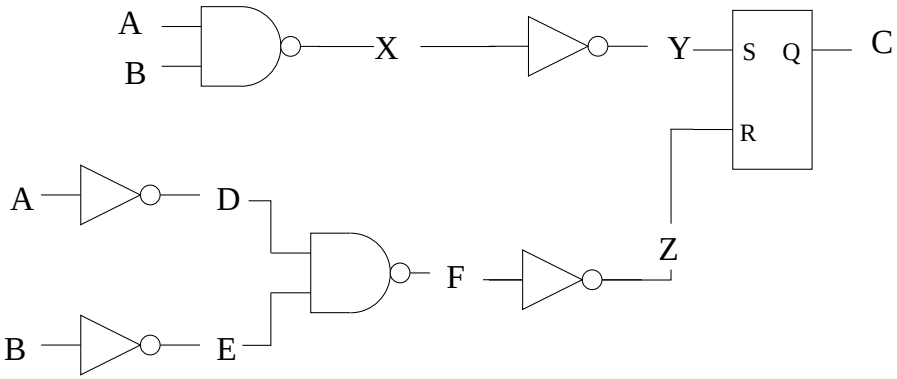


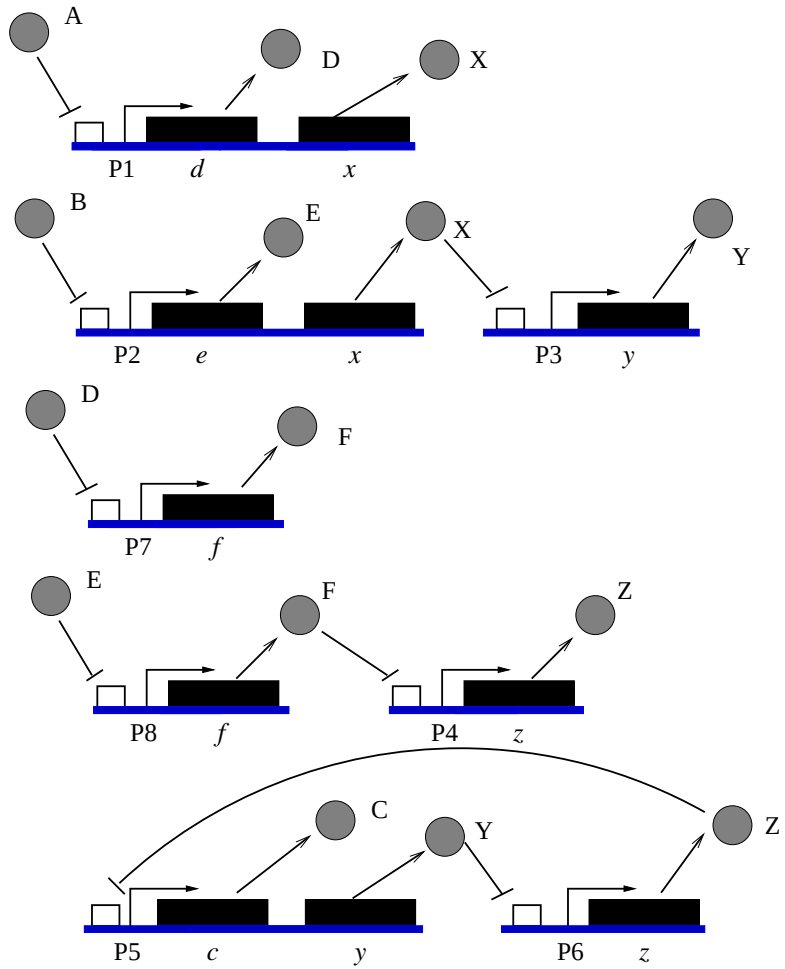
Genetic Muller C-Element



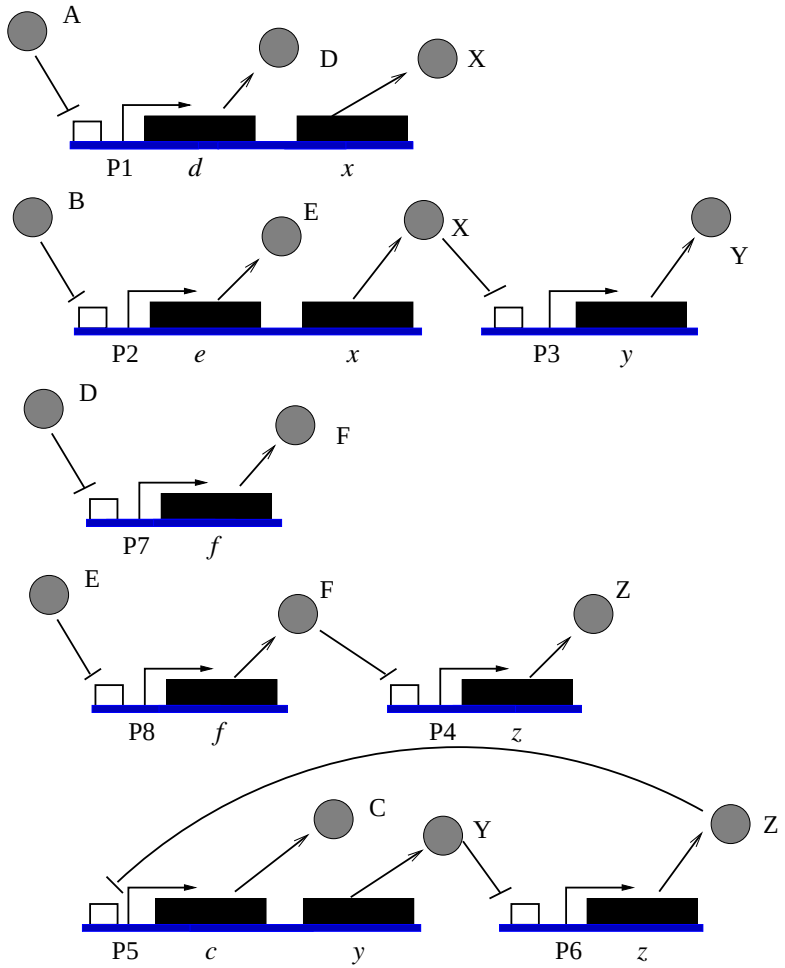
A	B	C’
0	0	0
0	1	C
1	0	C
1	1	1

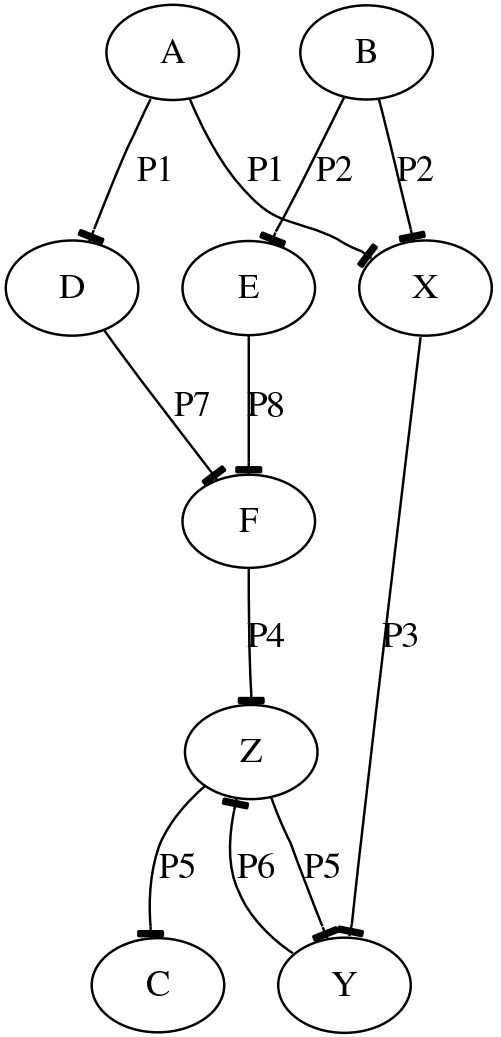
Toggle Switch C-Element (Genetic Circuit)



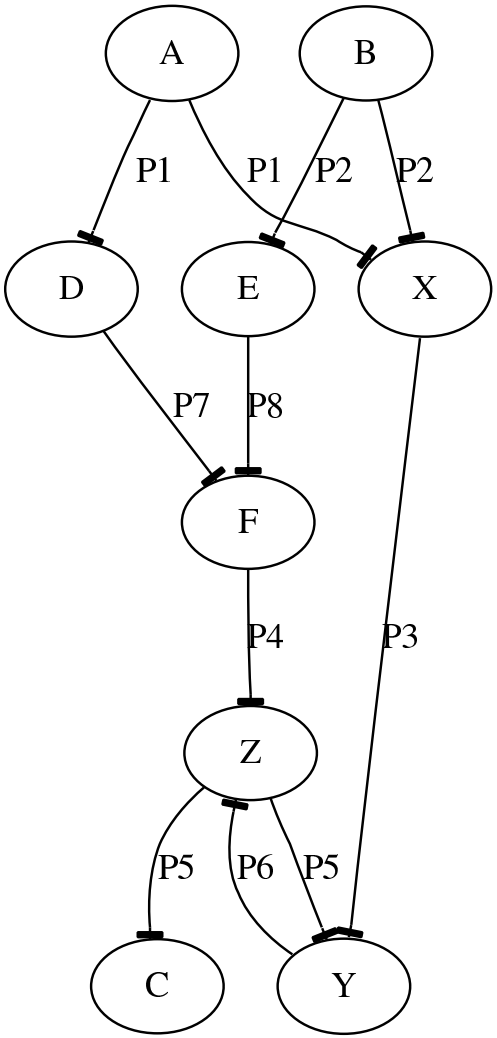


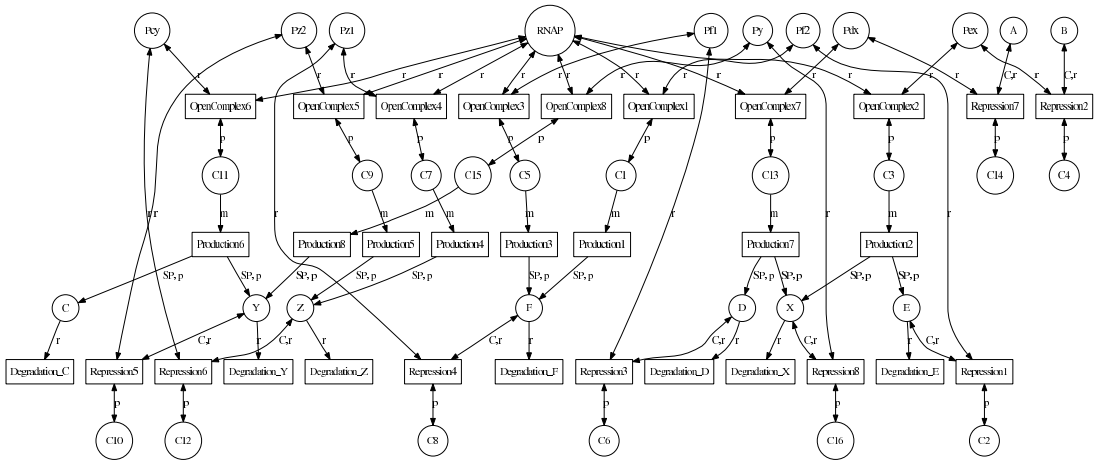
Toggle Switch C-Element (GCM)



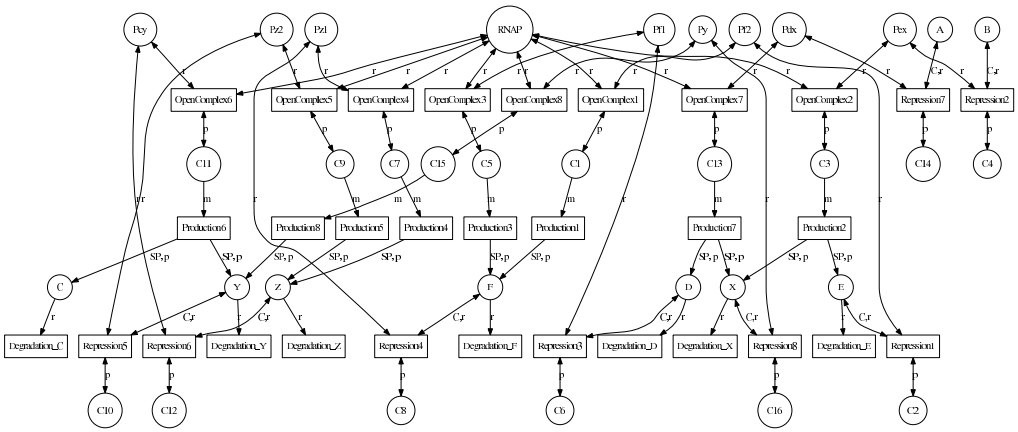


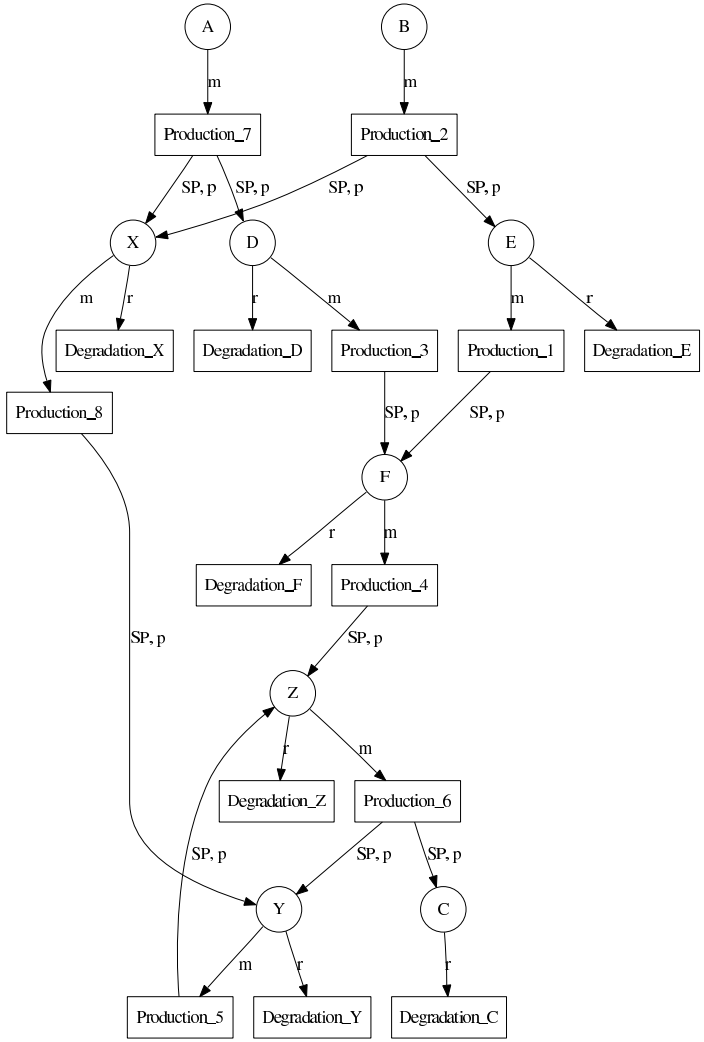
Toggle Switch C-Element (SBML)





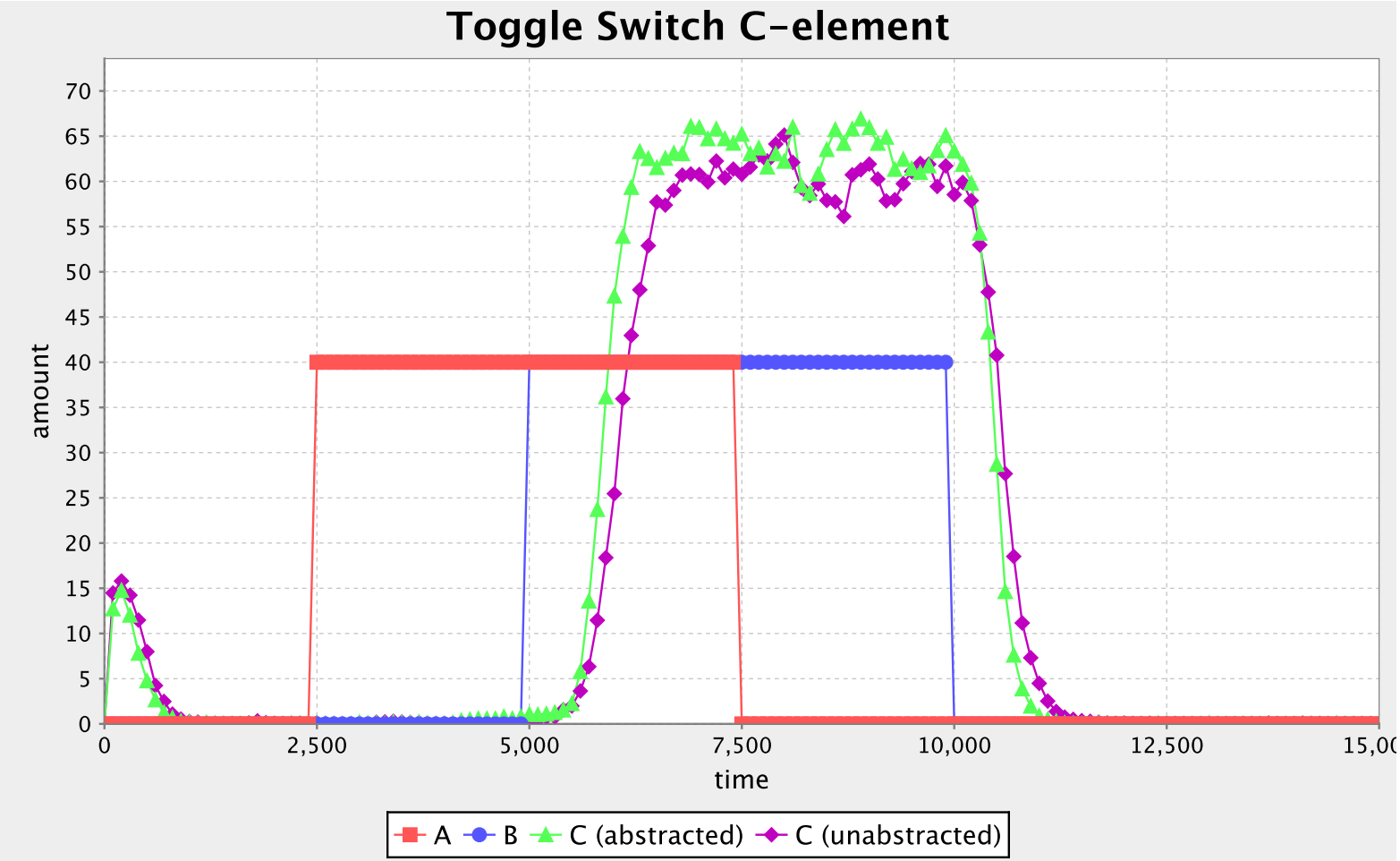
Toggle Switch C-Element (Abstracted)





Reduced from 34 species and 31 reactions to 9 species and 15 reactions.

Toggle Switch C-Element (Simulation)

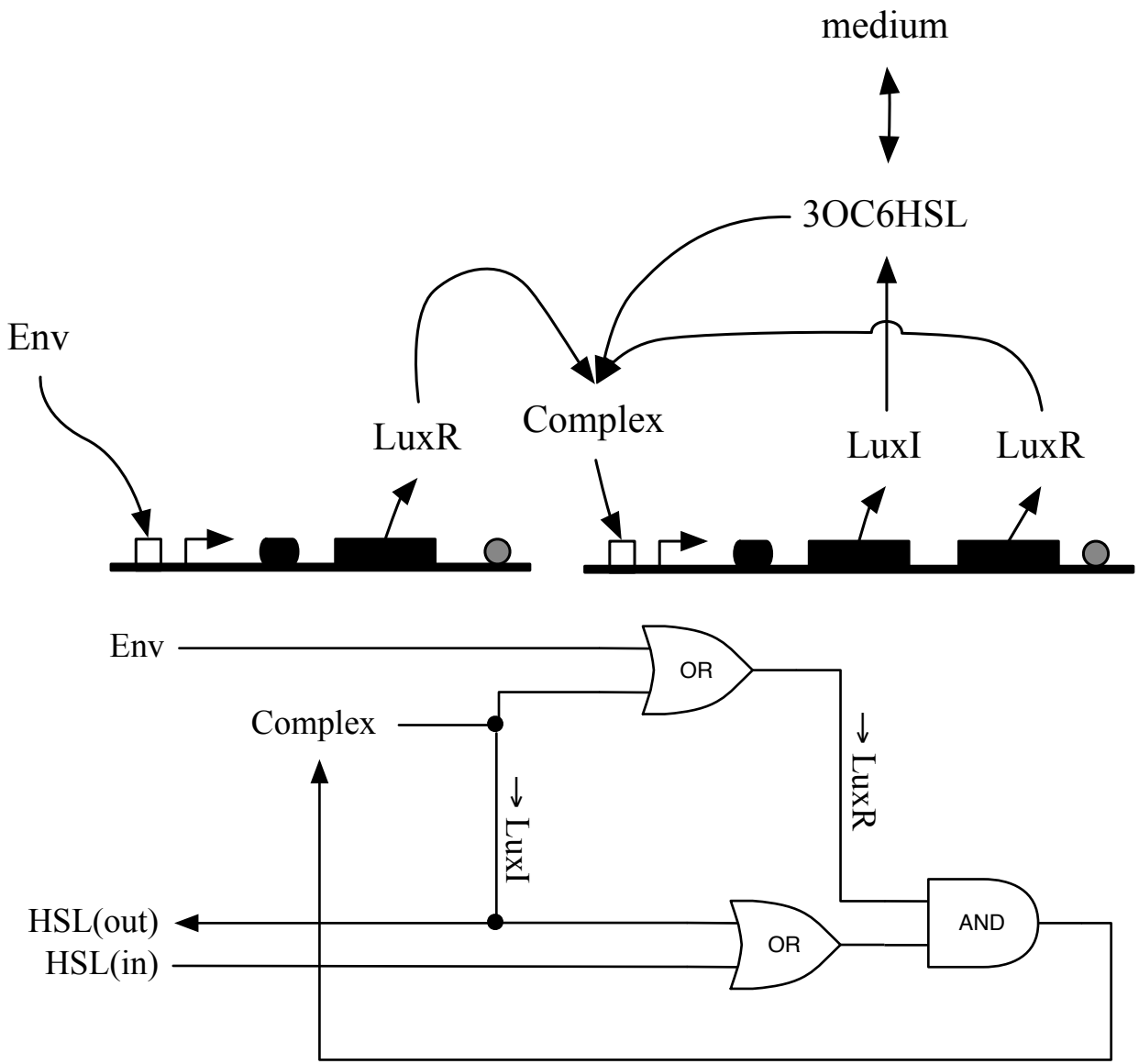


Simulation time improved from 312 seconds to 20 seconds.

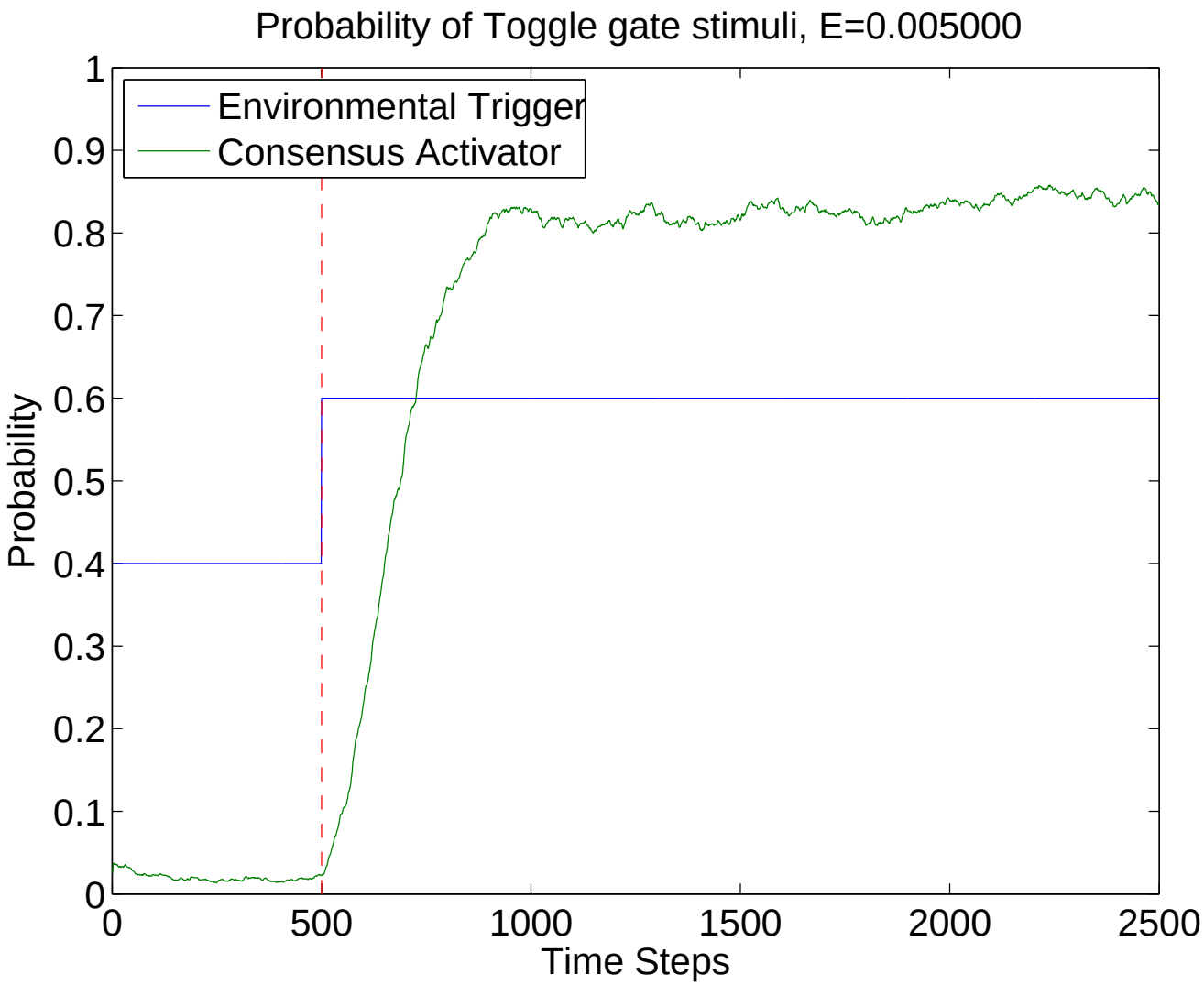
Application: Bacterial Consensus

- One interesting application is designing 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.
- C-elements behave unreliably (i.e., have probability of switching state).

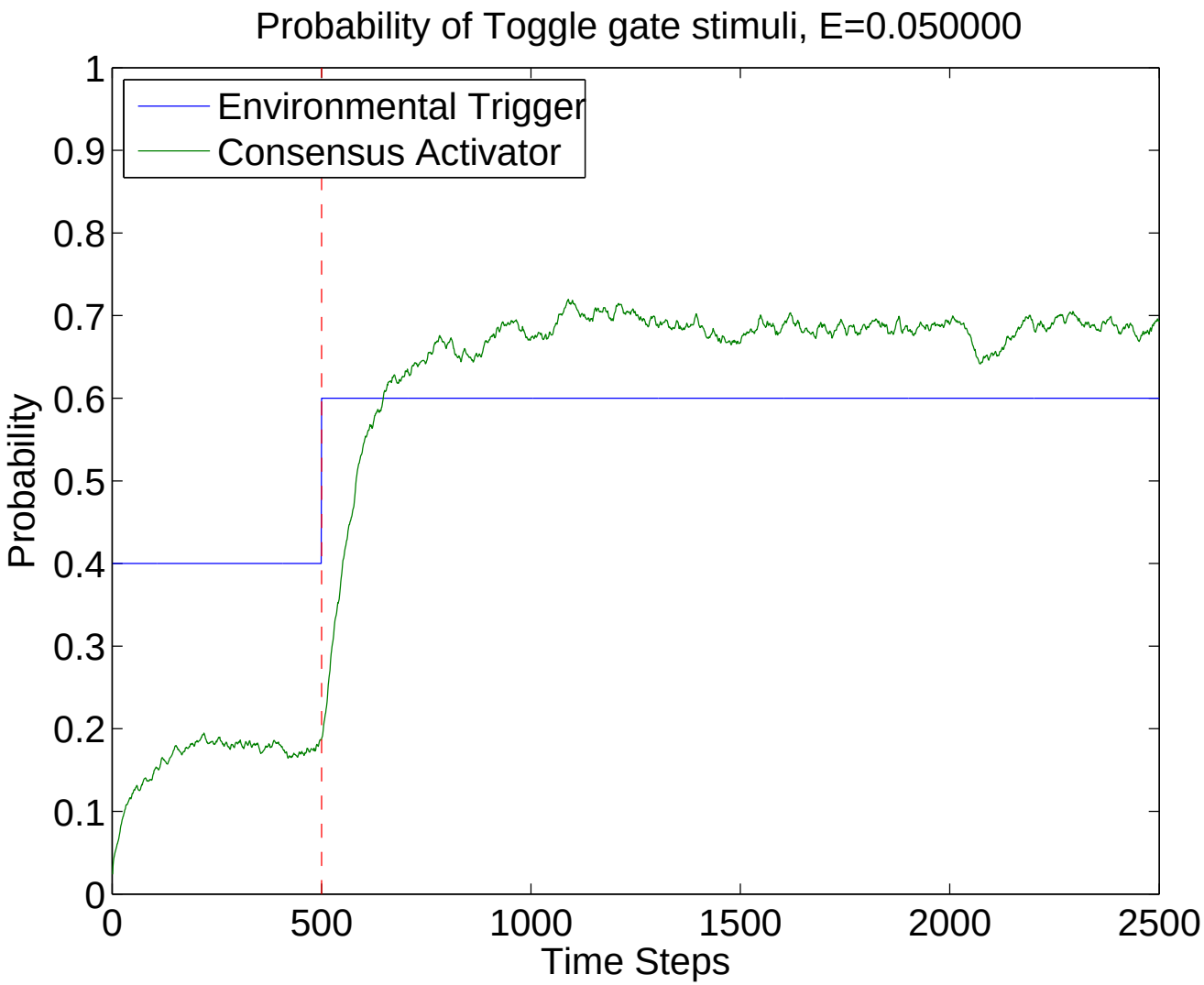
Quorum Trigger Circuit



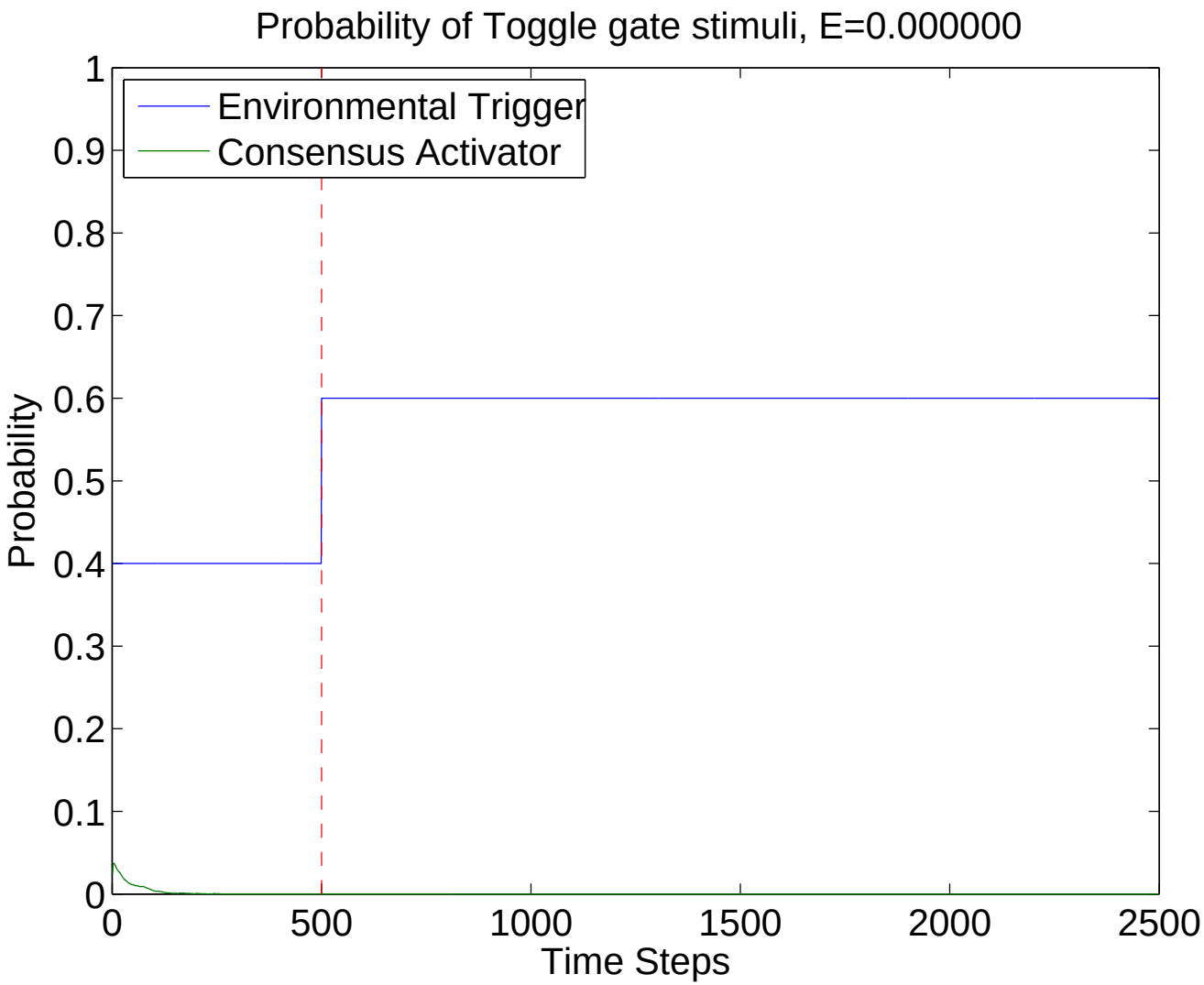
Application: Results



Application: Results



Application: Results



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.
- We plan to adapt asynchronous tools to genetic circuit technology.

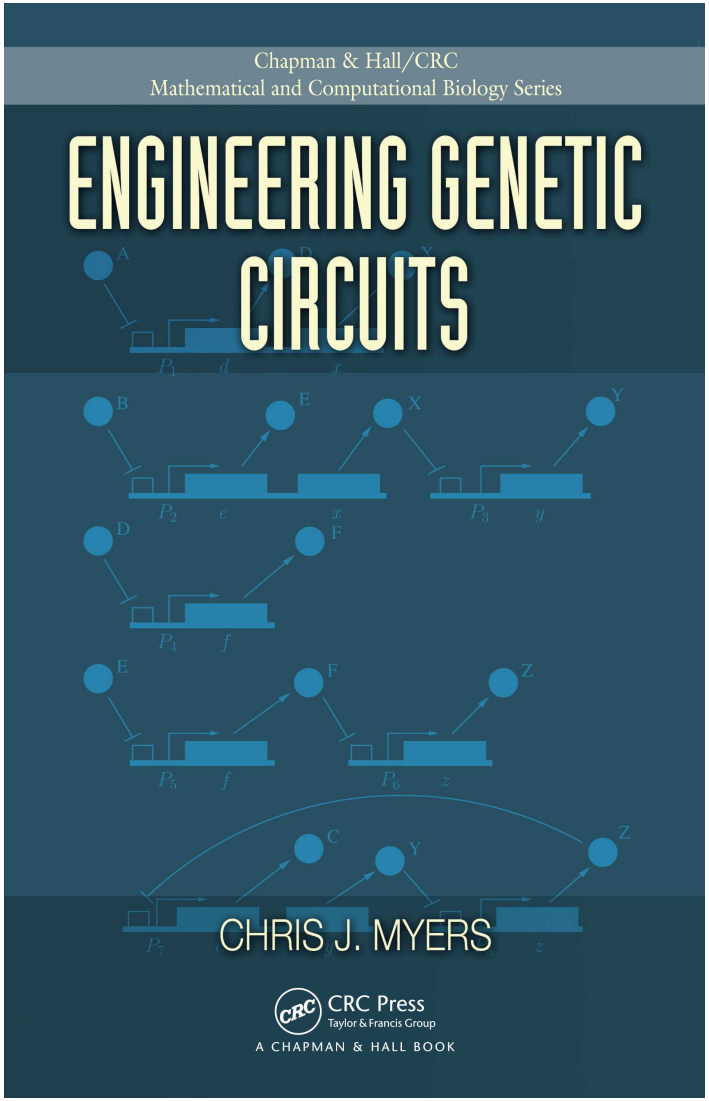
Biologically Inspired Circuit Design

- 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.

More Information

- 1st International Workshop on Bio-Design Automation
  July 27th in San Francisco at DAC.
- 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/`

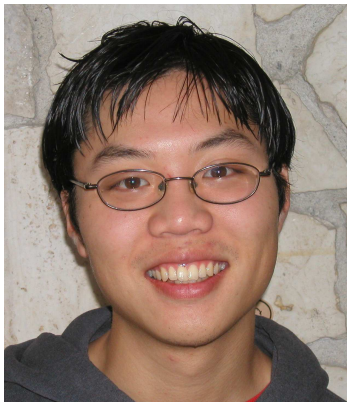
Engineering Genetic Circuits



Acknowledgments

Nathan Barker

Hiroyuki Kuwahara



Nam Nguyen

Curtis Madsen

Chris Winstead

This work is supported by the National Science Foundation under Grants No. 0331270 and CCF07377655.