

iBioSim 1.0: A Tool for the Analysis and Design of Genetic Circuits

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iBioSim 1.0: The Intelligent Biological Simulator

- Project management support.
- SBML Editor - creates models using the *Systems Biology Markup Language* (SBML).
- GCM Editor - creates *Genetic Circuit Models* (GCM).
- reb2sac - abstraction-based ODE, Monte Carlo, and Markov analysis.
- TSD Graph Editor - visualizes TSD files.
- Probability Graph Editor - visualizes probability data.
- GeneNet - learns GCMs from time series data (TSD).

SBML Editor

The screenshot displays the iBioSim SBML Editor interface. The window title is "iBioSim" and the file name is "lambda.sbml". The interface is divided into several sections:

- Left Panel:** A file browser showing a "demo" folder containing files like "learn", "sim", "Cl_Cll.gcm", "lambda.sbml" (selected), "prob.prb", and "SSA.grf".
- Top Panel:** Tabs for "Main Elements", "Definitions/Types", and "Initial Assignments/Rules/Constraints/Events".
- Model Information:** "Model ID: lambda" and "Model Name: A model of the phage lambda decision circuit".
- List of Compartments:** "Cytoplasm 1.0 volume".
- List of Species:** A list of species including "Cl Cytoplasm 0.0 mole", "Cl2 Cytoplasm 0.0 mole", "Cll Cytoplasm 0.0", "Clll Cytoplasm 0.0", "Cro Cytoplasm 0.0", "Cro2 Cytoplasm 0.0", "N Cytoplasm 0.0", and "PR Cytoplasm 0.0".
- List of Reactions:** A list of reactions including "Degradate_Cl", "Degradate_Cll", "Degradate_Clll", "Degradate_Cro", "Degradate_N", "Dimerize_Cl", "Dimerize_Cro", and "RNAP_Binding_PR".
- List of Global Parameters:** "nd 2.0 dimensionless".

Buttons for "Add", "Remove", and "Edit" are provided for compartments, species, reactions, and parameters. At the bottom, there are "Save SBML", "Save and Check SBML", and "Save As" buttons.

SBML Species Editor

List of Species:

List of Global

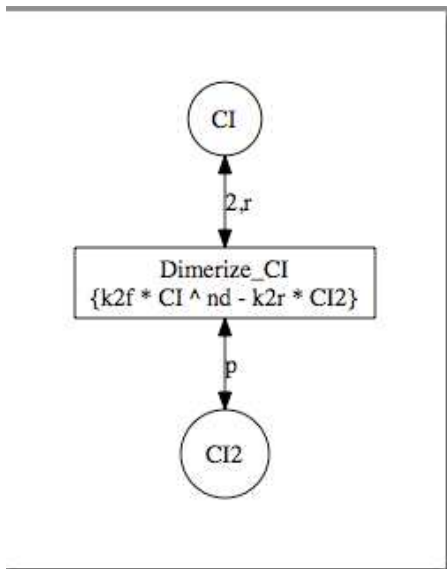
Species Editor

ID:	<input type="text" value="Cl"/>
Name:	<input type="text" value="The lambda repressor"/>
Type:	<input type="text" value="(none)"/>
Compartment:	<input type="text" value="Cytoplasm"/>
Boundary Condition:	<input type="text" value="false"/>
Constant:	<input type="text" value="false"/>
<input type="text" value="Initial Amount"/>	<input type="text" value="0.0"/>
Units:	<input type="text" value="mole"/>

iBioSim Random Functions

- iBioSim adds support for random functions.
- Continuous random functions:
 - uniform(a,b)
 - normal(m,s)
 - exponential(mu)
 - gamma(a,b)
 - lognormal(z,s)
 - chisq(nu)
 - laplace(a)
 - cauchy(a)
 - rayleigh(s)
- Discrete random functions:
 - poisson(mu)
 - binomial(p,n)
 - bernoulli(p)

Viewing SBML as Network Graph



Viewing SBML in Browser

Unit ID	Definition
per_second	(second) ⁻¹
per_second_mole	(mole) ⁻¹ •(second) ⁻¹

Compartment ID	Type	Dimensions	Initial Size	Units	Outside	Constant
Cytoplasm	none	3	1	none	none	True

Species ID	Type	Compartment	Initial Value	Units	Boundary	Constant
CI		Cytoplasm	0	mole	False	False
CI2		Cytoplasm	0	mole	False	False

Parameter ID	Initial Value	Units	Constant
nd	2	dimensionless	True
k2f	0.1	per_second_mole	True
k2r	1	per_second	True

Reaction ID	Rev	Fast	Reactants	Products	Modifiers	Kinetic Law
Dimerize_CI	True	False	2CI	CI2		$k2f * CI^{nd} - k2r * CI2$

Genetic Circuit Model (GCM) Editor

Cl_CII.gcm [x]

GCM Id: Cl_CII SBML File: Cl_CIIenv.sbml Biochemical abstraction: Dimerization abstraction:

List of Promoters:	List of Species:
PR	CI
PRE	CII

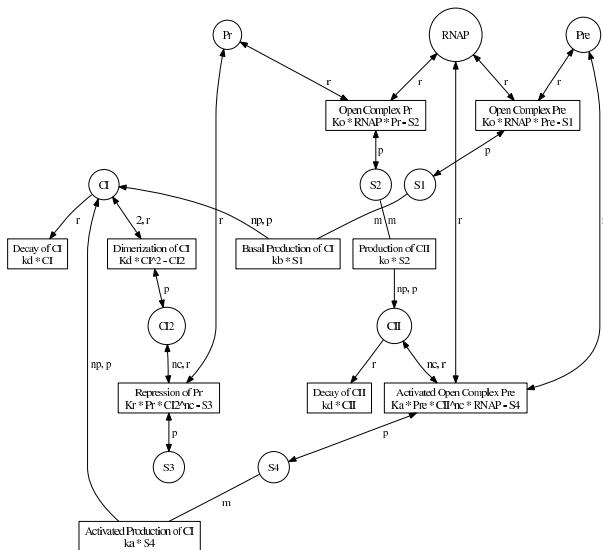
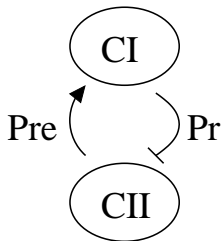
Add Promoter Remove Promoter Edit Promoter Add Species Remove Species Edit Species

List of Influences:	List of Parameters:
CI - CII, Promoter PR CII -> CI, Promoter PRE	Activated production rate (ka), Default, .25 Activation binding equilibrium (Ka), Default, .0033 Basal production rate (kb), Default, .0001 Biochemical equilibrium (Kb), Default, .05 Degradation rate (kd), Default, .0075 Degree of cooperativity (nc), Default, 2 Dimerization equilibrium (Kd), Default, .05 Initial RNAP count (nr), Default, 30 Initial promoter count (ng), Default, 2

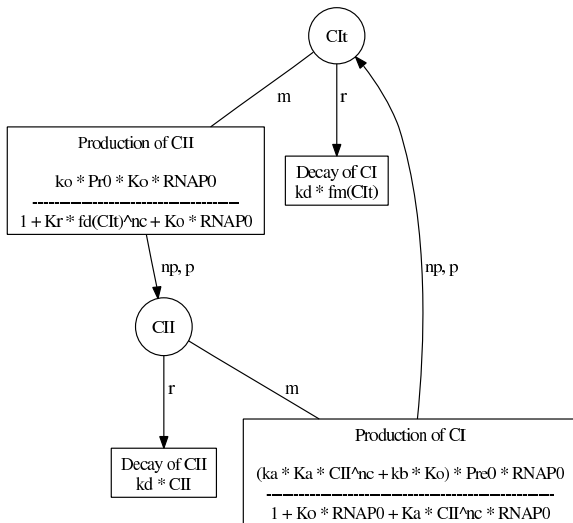
Add Influence Remove Influence Edit Influence Edit Parameter

Save GCM Save GCM as Save as SBML Save as SBML template

GCM versus SBML Representation

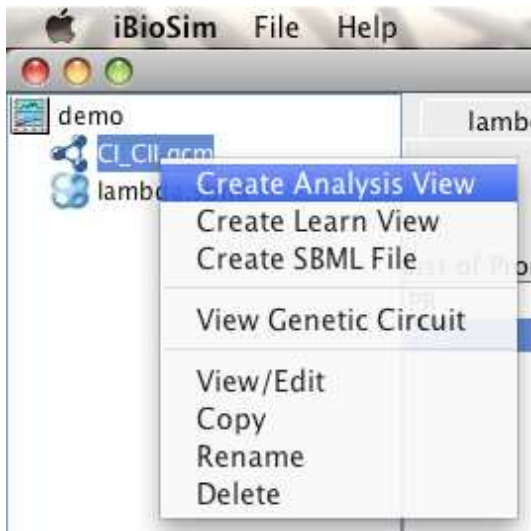


Automatic Abstraction



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

Create Analysis View



Analysis View

Cl_CII.gcm [x] | sim [x]

Simulation Options | Abstraction Options | Parameter Editor | TSD Graph | Probability Graph

Choose One: None Abstraction Logical Abstraction

Choose One: ODE Monte Carlo Markov SBML Network Browser

Choose One: Overwrite Append

Possible Simulators/Analyzers:

Description Of Selected Simulator: Embedded Runge-Kutta-Fehlberg (4, 5) method

Time Limit:

Print Interval:

Maximum Time Step:

Absolute Error:

Random Seed:

Runs:

Simulation ID:

TSD Graph Editor

Edit Graph

Title: X-Min: Y-Min:
X-Axis Label: X-Max: Y-Max:
Y-Axis Label: X-Step: Y-Step:

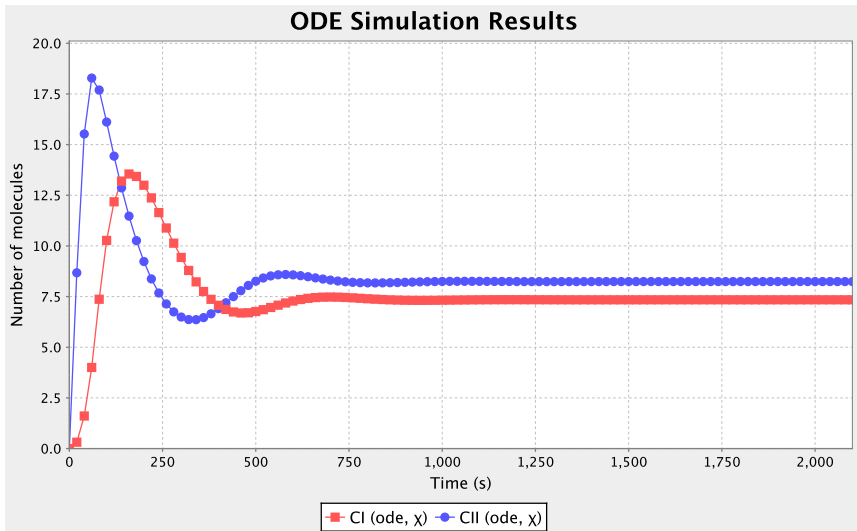
Auto Resize

sim

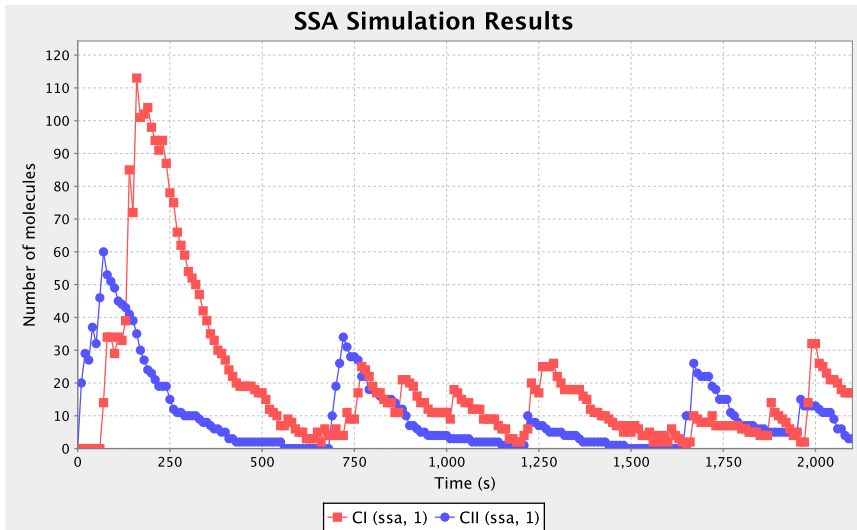
- Average
- Variance
- Standard Deviation
- run-1

<input type="checkbox"/> UseSpecies		Color	Shape	<input checked="" type="checkbox"/> Connect	<input checked="" type="checkbox"/> Visible	<input checked="" type="checkbox"/> Fill
<input type="checkbox"/>	bound_PR_CI (x)	Black	Arrow	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
<input checked="" type="checkbox"/>	CI (x)	Red	Square	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
<input checked="" type="checkbox"/>	CII (x)	Blue	Circle	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
<input type="checkbox"/>	PR (x)	Black	Arrow	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
<input type="checkbox"/>	PRE (x)	Black	Arrow	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
<input type="checkbox"/>	RNAP (x)	Black	Arrow	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
<input type="checkbox"/>	RNAP_PR (x)	Black	Arrow	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
<input type="checkbox"/>	RNAP_PRE (x)	Black	Arrow	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
<input type="checkbox"/>	RNAP_PRE_CII (x)	Black	Arrow	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>

TSD Graph (ODE)



TSD Graph (Monte Carlo)



Parameter Editor

lambda.sbml | CI_CII.gcm | sim

Simulation Options | Abstraction Options | Parameter Editor | TSD Graph | Probability Graph

Model ID: Species Editor

List of Compartments:
default 1.0

Add Compartment

List of Reactions:
Degradation_CI
Degradation_CII
R_act_production_PRE_C
R_basal_production_PRE
R_production_PR
R_repression_binding_PR
R_RNAP_binding_PRE_C
R_RNAP_PR

Add Reaction

ID: PR

Name:

Type: (none)

Compartment: default

Boundary Condition: false

Constant: false

Value Type: Initial Amount

Units: (none)

Start:

Stop:

Step:

Level: 1

Cancel OK

List of Species:
bound_PR_CI default 0.0
CI default 0.0
CII default 0.0
PR default 2.0
PRE default 2.0
RNAP default 30.0
RNAP_PR default 0.0
RNAP_PRE default 0.0

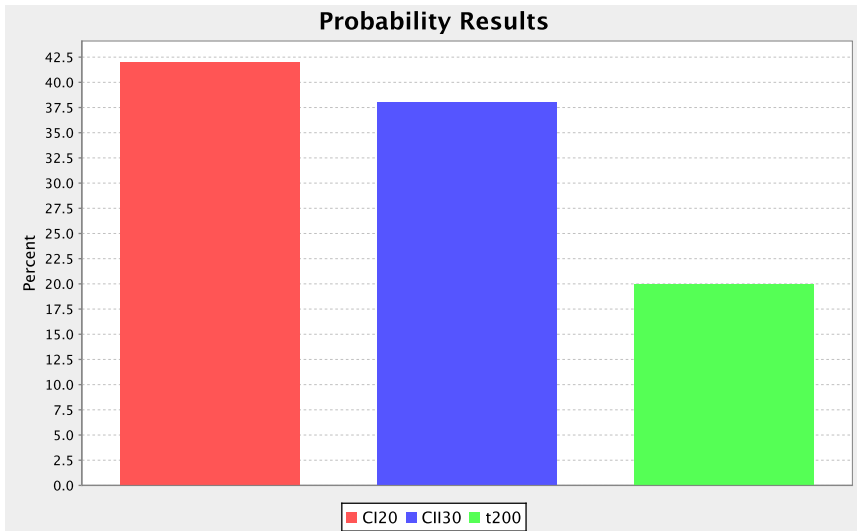
Add Species Remove Species Edit Species

List of Global Parameters:

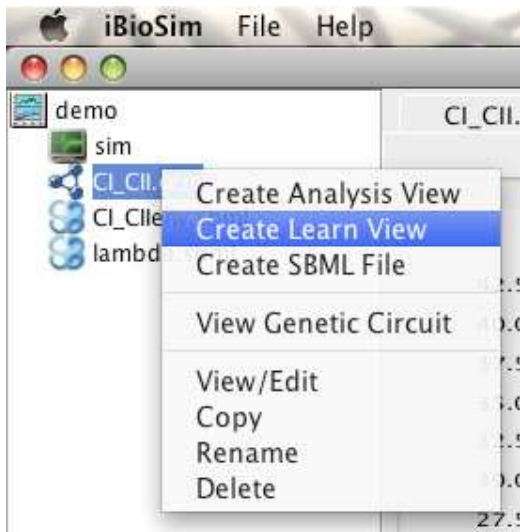
Add Parameter Remove Parameter Edit Parameter

Save Parameters

Probability Graph



Create Learn View



Data Manager

The screenshot shows the Data Manager window with three tabs: Data Manager (selected), Learn, and TSD Graph. The Data Manager tab displays a list of simulation runs on the left and a data table on the right. The data table has columns for time, CI, and CII. Below the table are several control buttons: Add, Remove, Rename, Copy, Copy From View, Import, Save, Add Data Point, Remove Data Point, and Copy Data Point.

	time	CI	CII
sim/ssa/run-1.tsd	0.0	0.0	0.0
sim/ssa/run-10.tsd	10.0	0.0	20.0
sim/ssa/run-100.tsd	20.0	0.0	29.0
sim/ssa/run-11.tsd	30.0	0.0	27.0
sim/ssa/run-12.tsd	40.0	0.0	37.0
sim/ssa/run-13.tsd	50.0	0.0	32.0
sim/ssa/run-14.tsd	60.0	0.0	46.0
sim/ssa/run-15.tsd	70.0	14.0	60.0
sim/ssa/run-16.tsd	80.0	34.0	53.0
sim/ssa/run-17.tsd	90.0	34.0	51.0
sim/ssa/run-18.tsd	100.0	29.0	49.0
sim/ssa/run-19.tsd	110.0	34.0	45.0
sim/ssa/run-2.tsd	120.0	33.0	44.0
sim/ssa/run-20.tsd	130.0	39.0	43.0
sim/ssa/run-21.tsd	140.0	85.0	41.0
sim/ssa/run-22.tsd	150.0	72.0	39.0
sim/ssa/run-23.tsd	160.0	113.0	35.0
sim/ssa/run-24.tsd	170.0	101.0	30.0
sim/ssa/run-25.tsd	180.0	102.0	27.0
sim/ssa/run-26.tsd	190.0	104.0	24.0
sim/ssa/run-27.tsd	200.0	98.0	23.0
sim/ssa/run-27.tsd	210.0	94.0	21.0
sim/ssa/run-28.tsd	220.0	91.0	19.0
sim/ssa/run-29.tsd	230.0	94.0	19.0
	240.0	87.0	19.0
	250.0	78.0	15.0

Learn Tool

CI_CII.gcm [x] sim [x] learn [x]

Data Manager Learn TSD Graph

Basic Options Advanced Options

Minimum Number of Initial Vectors (Tn):

Maximum Influence Vector Size (Tj):

Score for Empty Influence Vector (Ti):

Number Of Bins:

Equal Data Per Bins Equal Spacing Of Bins

Use Auto Generated Levels Use User Generated Levels

Species Levels:

Species	Number Of Bins	Level 1	Level 2
CI	<input type="text" value="3"/>	<input type="text" value="6"/>	<input type="text" value="15"/>
CII	<input type="text" value="3"/>	<input type="text" value="5"/>	<input type="text" value="11"/>

```
graph TD; CII((CII)) -- 10.833 --> CI((CI)); CI --> CII;
```

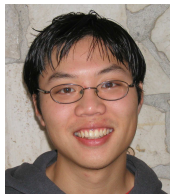
Acknowledgments



Nathan Barker



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Nam Nguyen



Curtis Madsen



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More Information

- Versions available for Windows, Linux, and MacOS.
- Available for free download from:
<http://www.async.ece.utah.edu/iBioSim>
- Publications and course materials available from our website:
<http://www.async.ece.utah.edu>
- Forthcoming textbook: *Engineering Genetic Circuits*, accepted for publication by Taylor and Francis Publishing Group.