iBioSim: Tutorial

Chris J. Myers

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Contents

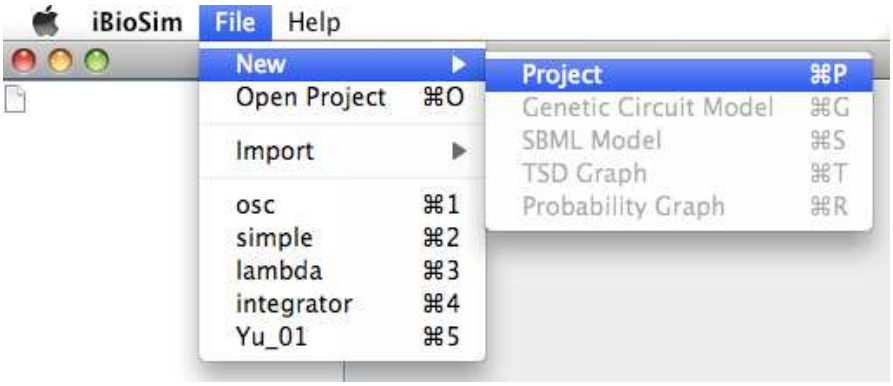
1 Introduction

The example described in this tutorial constructs a simple model for the *cI* and *cII* genes and the P_R and P_{RE} promoters from the phage λ decsion circuit. This example illustrates many of the features of `iBioSim`.

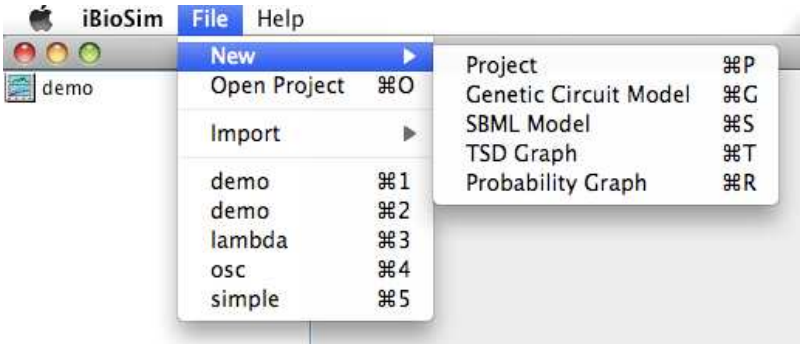
2 SBML Editor

After starting `iBioSim`, complete the following steps to create an SBML model for this example:

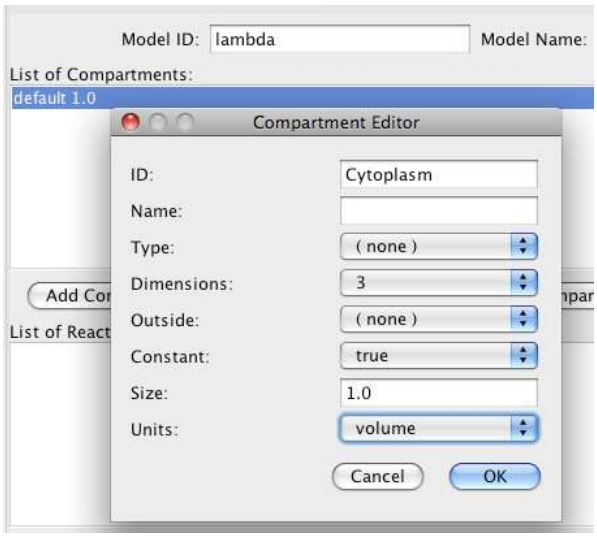
1. Select `File` → `New` → `Project`. Browse to desired path and create a project named `demo`.



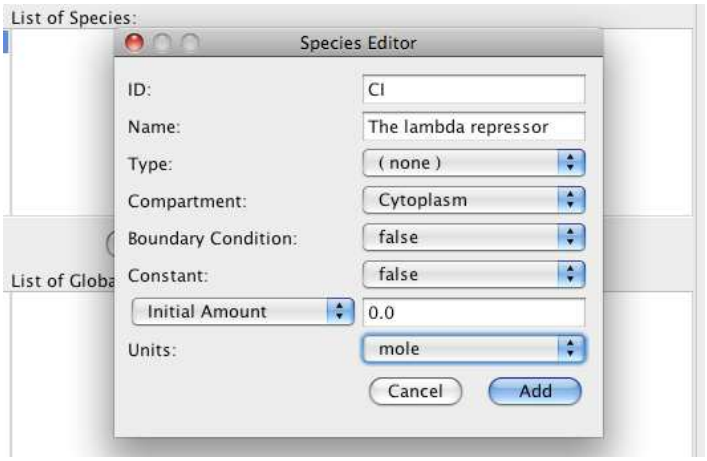
2. Select `File` → `New` → `SBML Model`. Enter `lambda` as the SBML model ID at which point an SBML editor will open.



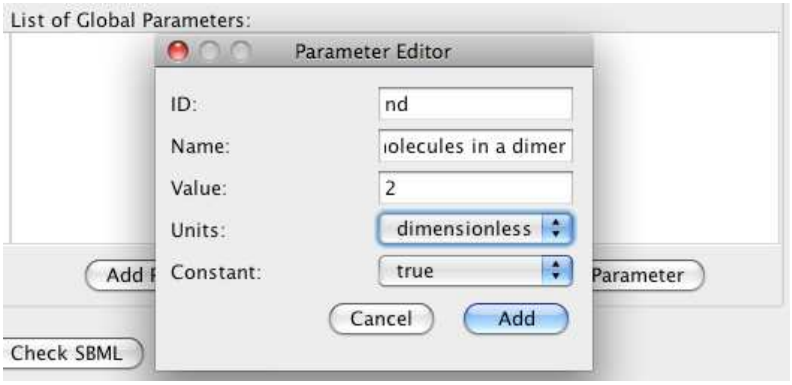
3. Highlight the `default` compartment, select `Edit Compartment`, and change its ID to `Cytoplasm`. Also, change the units to `volume`.



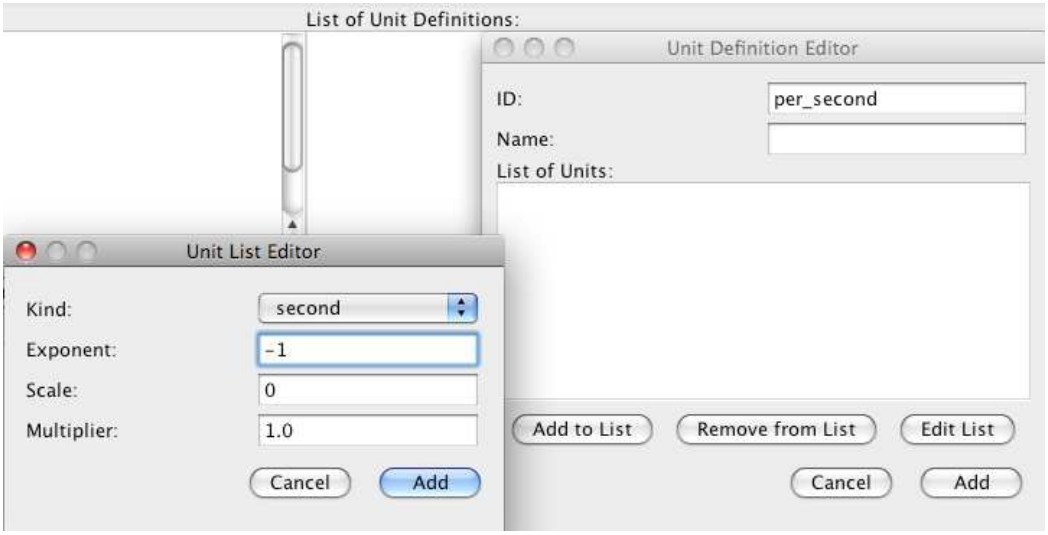
4. Select `Add Species` and enter `CI` as the ID, `The lambda repressor` as the name, and change the units to `mole`. Select `Add Species` again and enter `CI2` as the ID, `CI dimer` as the name, and change the units to `mole`.



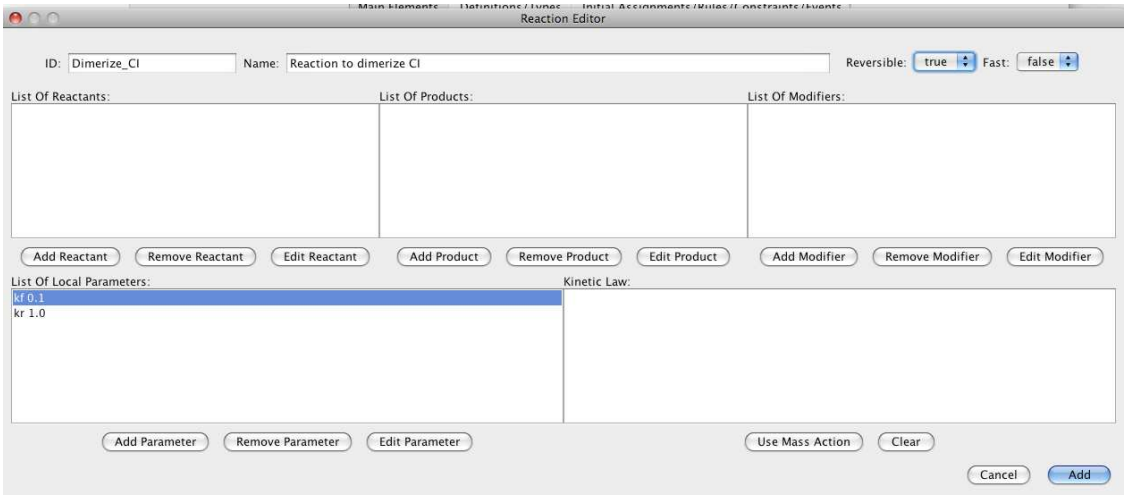
5. Select `Add Parameter` and enter `nd` as the ID, `Number of molecules in dimer` as the name, the value to be 2, and change the units to `dimensionless`.



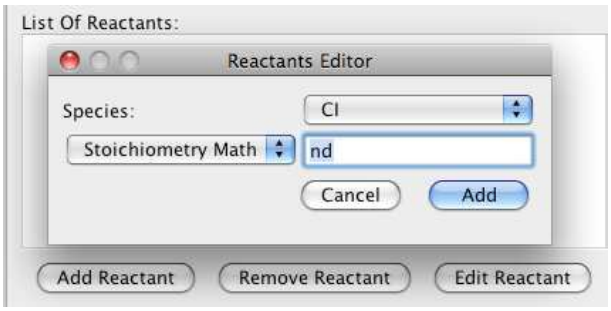
6. Select `Definitions/Types` tab, and select `Add Unit` and enter `per_second` as the ID. Select `Add to List`, select `second` as the kind, change the exponent to -1, and click `Add`. Click `Add` in the `Unit Definition Editor`. Repeat these steps to create a `per_second_mole` unit (i.e., $(\text{second})^{-1}(\text{mole})^{-1}$).



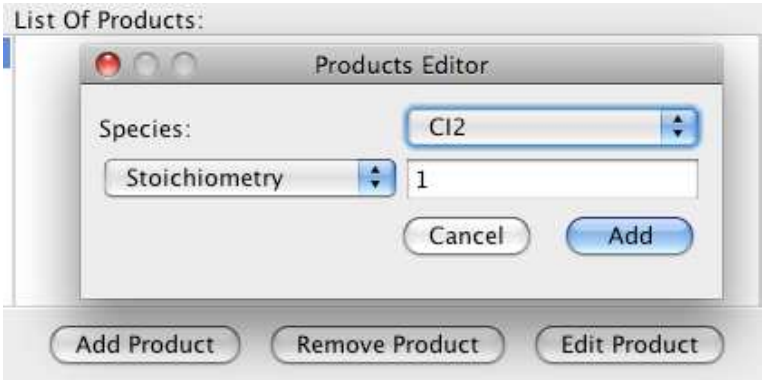
7. Select `Main Elements` tab. Select `Add Reaction` and enter `Dimerize_CI` as the ID, `Reaction to dimerize CI` as the name, and change reversible to `true`.



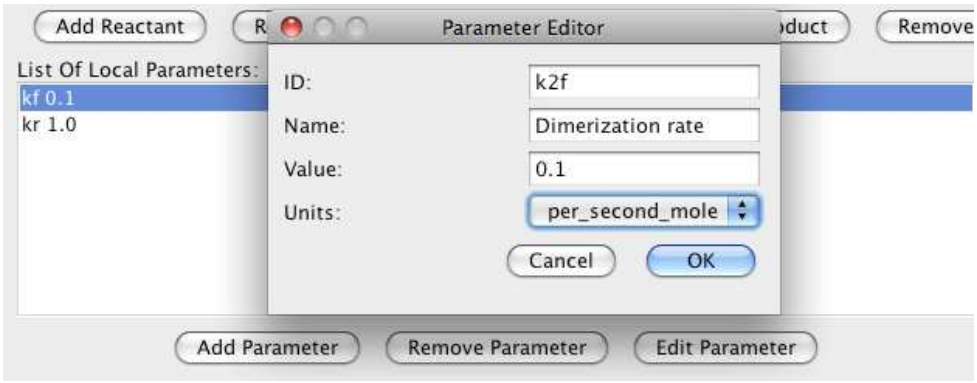
8. Select `Add Reactant` and select `CI` as the species, change `Stoichiometry` to `Stoichiometry math`, and set its value to `nd`.



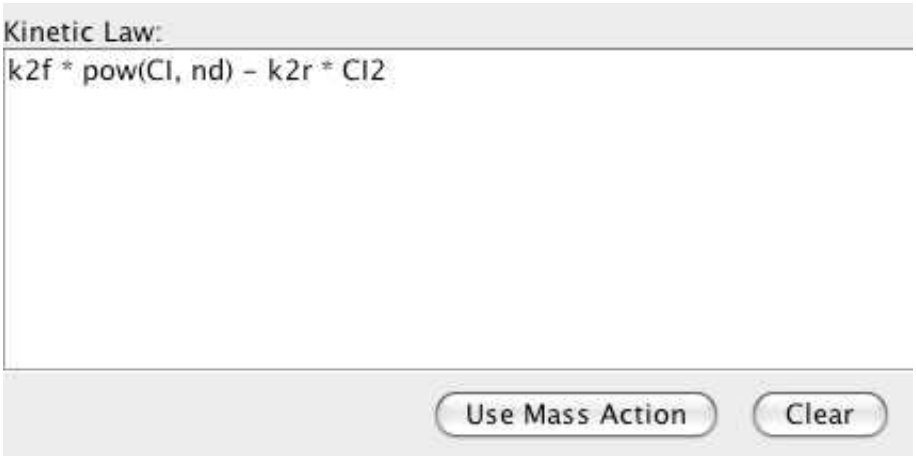
9. Select `Add Product` and select `CI2` as the species. Leave the stoichiometry as 1.



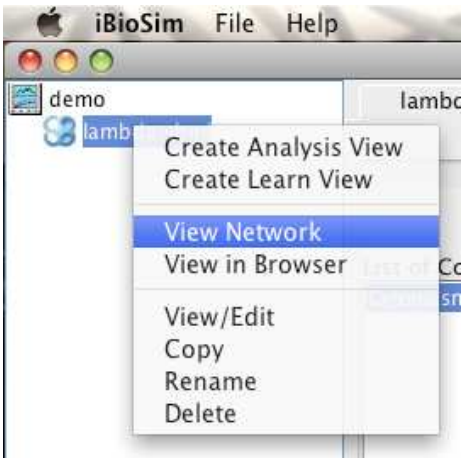
10. Highlight `kf` and select `Edit Selected Parameter`, change `kf` to `k2f`, and change the units to `per_second_mole`. Highlight `kr` and select `Edit Selected Parameter`, change `kr` to `k2r`, and change the units to `per_second`.



11. Select `Use Mass Action`, select `Add`, and select `Save and Check SBML`. There should be no errors.

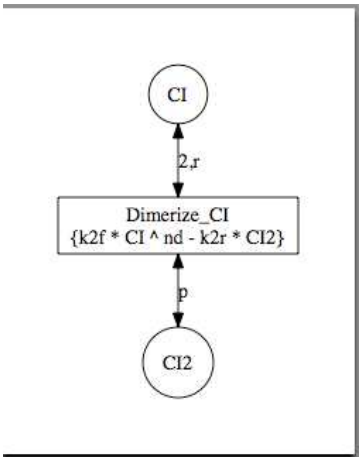


12. Highlight `lambda.sbml`, using right mouse button, select `View Network`. Highlight `lambda.sbml`, using right mouse button, select `View in Browser`.



Unit ID	Definition
per_second	$(\text{second})^{-1}$
per_second_mole	$(\text{mole})^{-1} \bullet (\text{second})^{-1}$

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		$k2f * CI^{nd} - k2r * CI2$

13. Go back to the SBML editor complete the construction of the chemical reaction network shown below:

$$
\begin{aligned}
PRE + \text{RNAP} &\overset{KPRE2}{\longleftrightarrow} PRE\_\text{RNAP} \\
PRE + \text{CII} + \text{RNAP} &\overset{KPRE4}{\longleftrightarrow} PRE\_\text{CII\_RNAP} \\
PRE\_\text{RNAP} &\overset{kPREb}{\longrightarrow} PRE\_\text{RNAP} + n\text{CI} \\
PRE\_\text{CII\_RNAP} &\overset{kPRE}{\longrightarrow} PRE\_\text{CII\_RNAP} + n\text{CI} \\
PR + \text{RNAP} &\overset{KOR9}{\longleftrightarrow} PR\_\text{RNAP} \\
PR + 2\text{CI2} &\overset{KOR10}{\longleftrightarrow} PR\_2\text{CI2} \\
PR\_\text{RNAP} &\overset{kPR}{\longrightarrow} PR\_\text{RNAP} + n\text{CII} \\
2\text{CI} &\overset{K2}{\longleftrightarrow} \text{CI2} \\
\text{CI} &\overset{k1}{\longrightarrow} () \\
\text{CII} &\overset{k10}{\longrightarrow} ()
\end{aligned}
$$

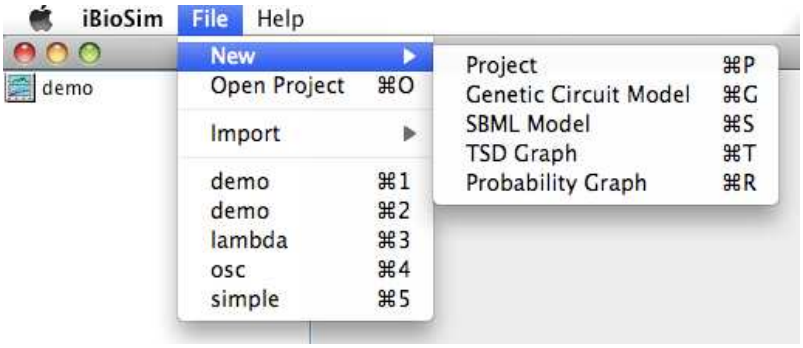
Constant	*Value*	*Constant*	*Value*	*Constant*	*Value*
$KPRE2$	0.01 M^{-1}	$KPRE4$	0.00161 M^{-2}	$kPREb$	0.00004 sec^{-1}
$kPRE$	0.015 sec^{-1}	$KOR9$	0.69422 M^{-1}	$KOR10$	0.06568 M^{-2}
kPR	0.014 sec^{-1}	$K2$	$0.1M^{-1}$	$k1$	0.0007 sec^{-1}
$k10$	0.002 sec^{-1}	n	10		

Set an initial amount of 1.0 for PRE and OR, 30.0 for RNAP, and 0.0 for the rest.

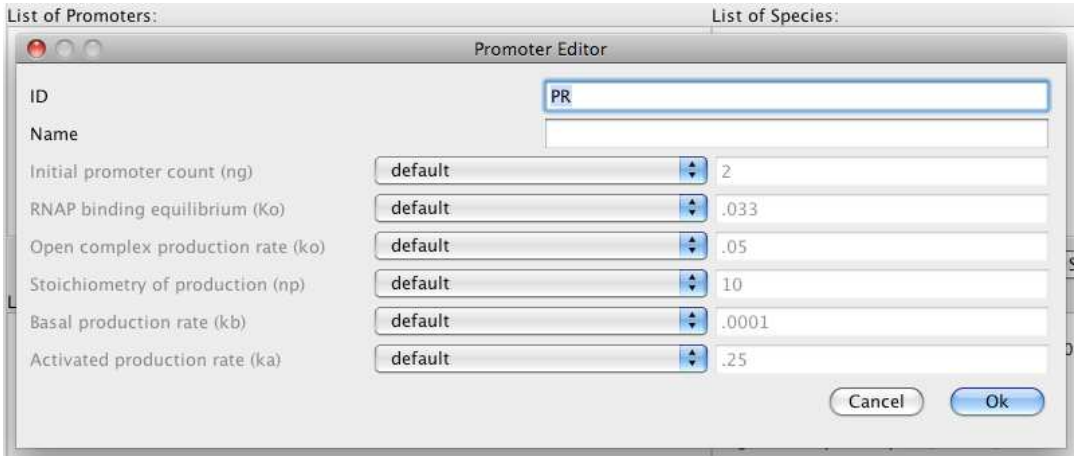
3 GCM Editor

This section describes how to construct a GCM model for this example:

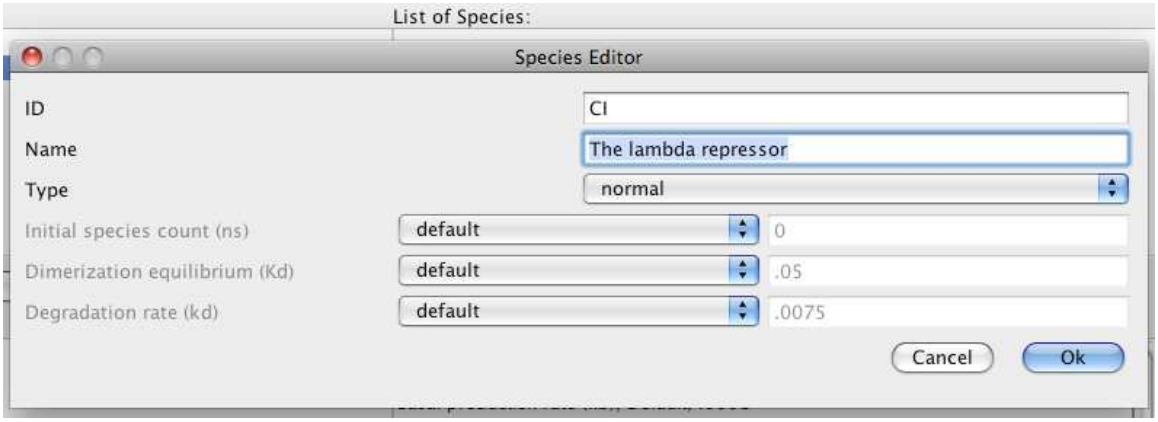
1. Select `File` → `New` → `Genetic Circuit Model`. Enter `CI_CII` as the GCM model ID at which point a GCM editor will open.



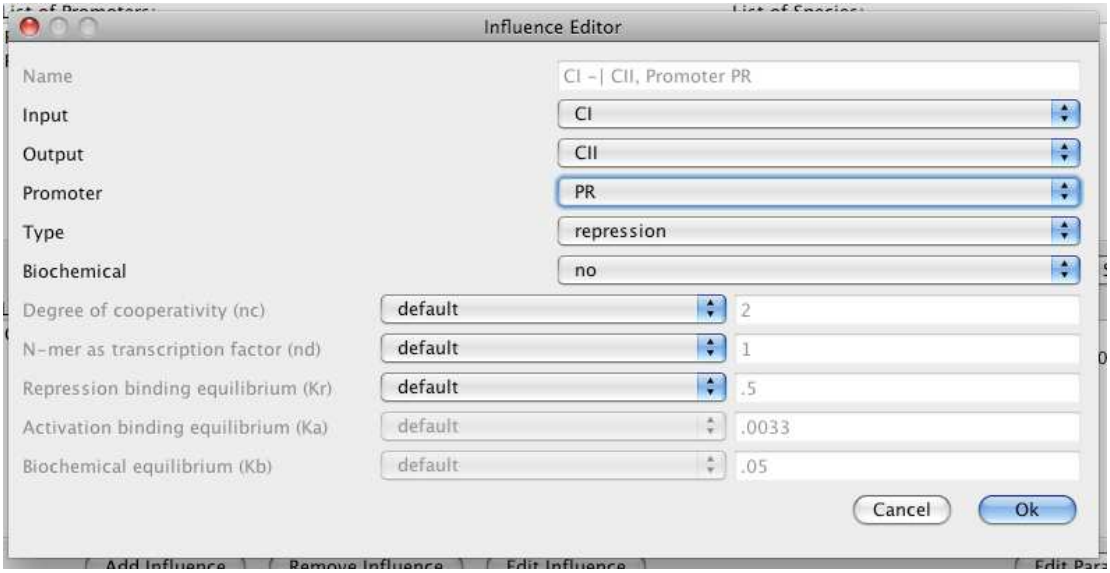
2. Select `Add Promoter`, enter `PR` as the ID, and press `Ok`. Next, add the `PRE` promoter in the same way.



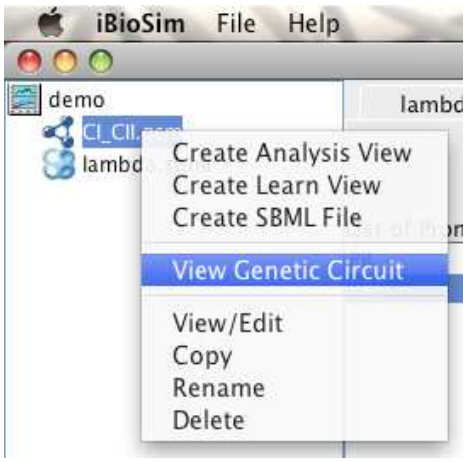
3. Select `Add Species`, enter `CI` as the ID, and press `Ok`. Next, add the `CII` species in the same way.

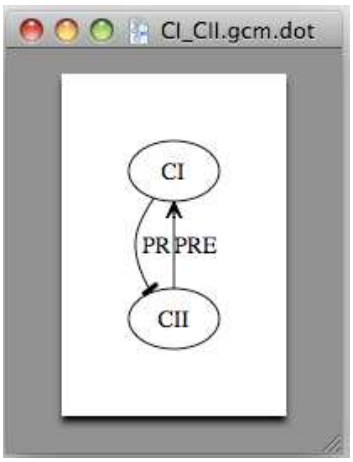


4. Select `Add Influence`, change the input to `CI`, change the output to `CII`, change the promoter to `PR`, and the type to `repression`. Next, add an activation influence between `CII` and `CI` on promoter `PRE`.



5. Select `Save GCM`, highlight `CI_CII.gcm` file, and right click to select `View Genetic Circuit`.

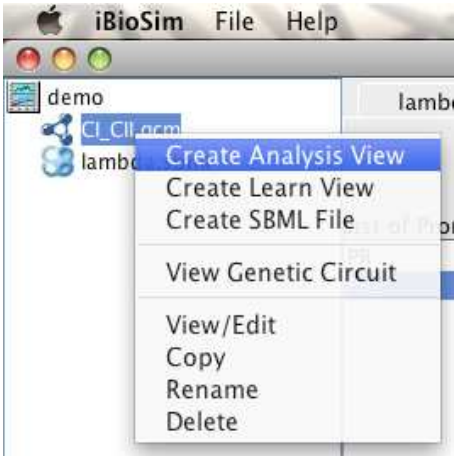




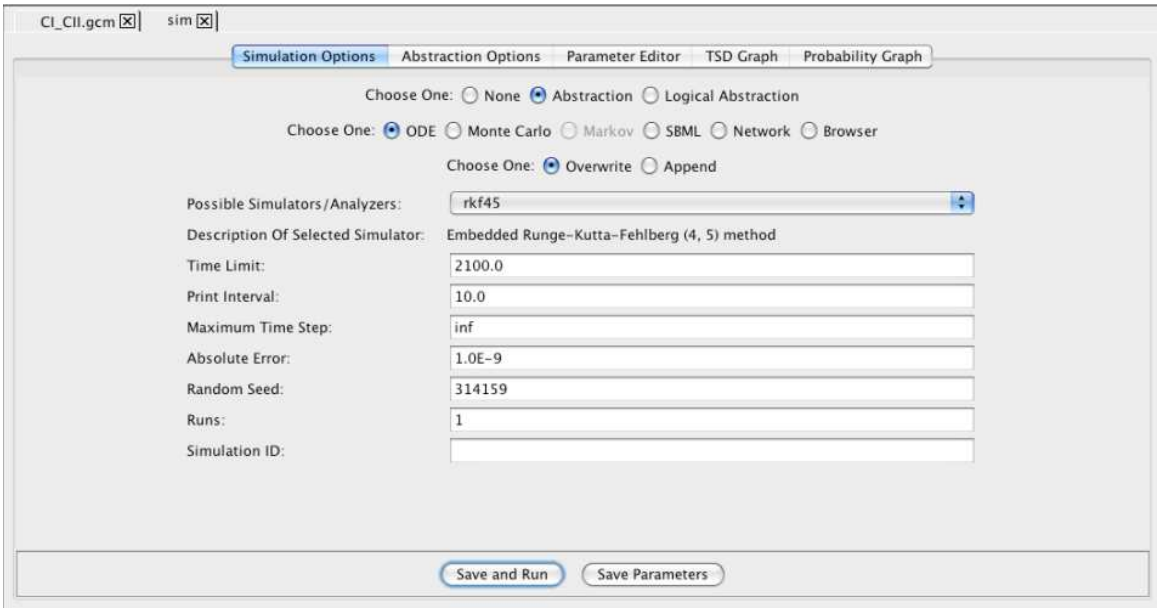
4 Analysis

The following instructions describe how to analyze the GCM file just created. The SBML file can also be simulated using the following steps.

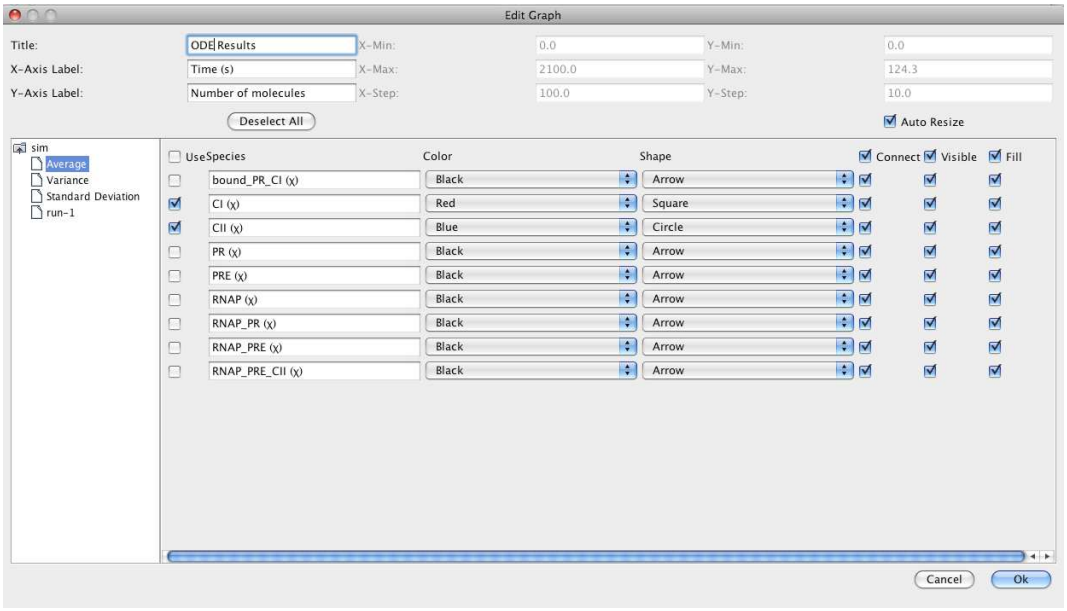
1. Select `Save GCM`, highlight `CI_CII.gcm` file, right click to select `Create Analysis View`, and set the analysis ID to `sim`.

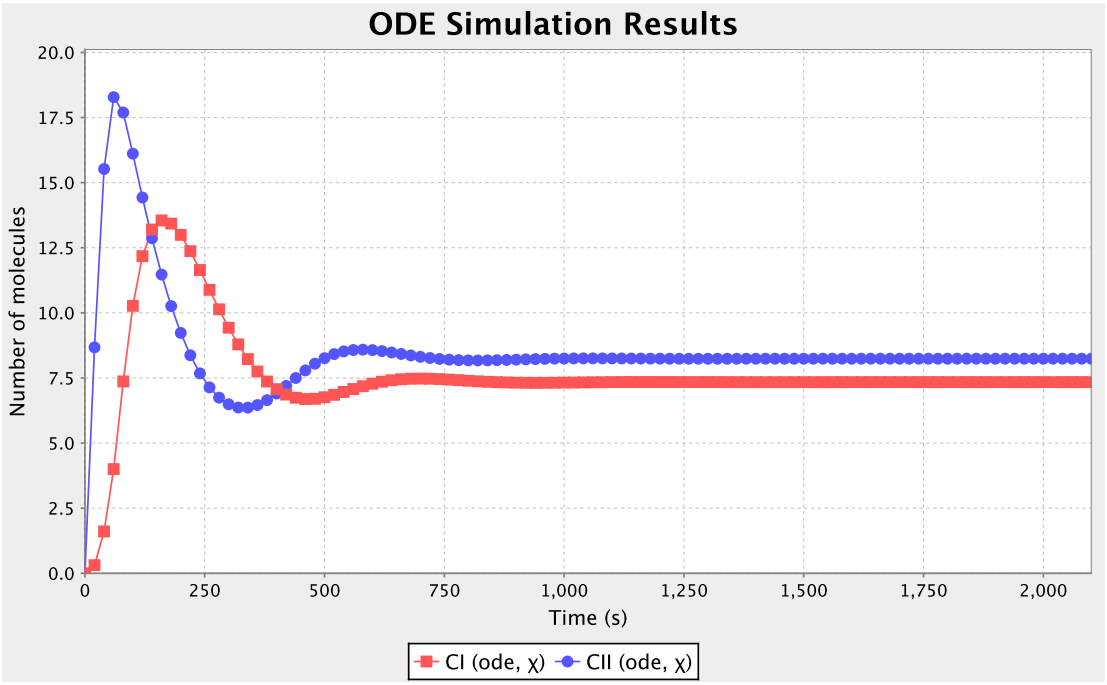


2. In the newly opened window, select `ODE`. Also, in this window, change the time limit to 2100.0 and print interval to 10.0. Finally, select `Save and Run` at the bottom of the window.

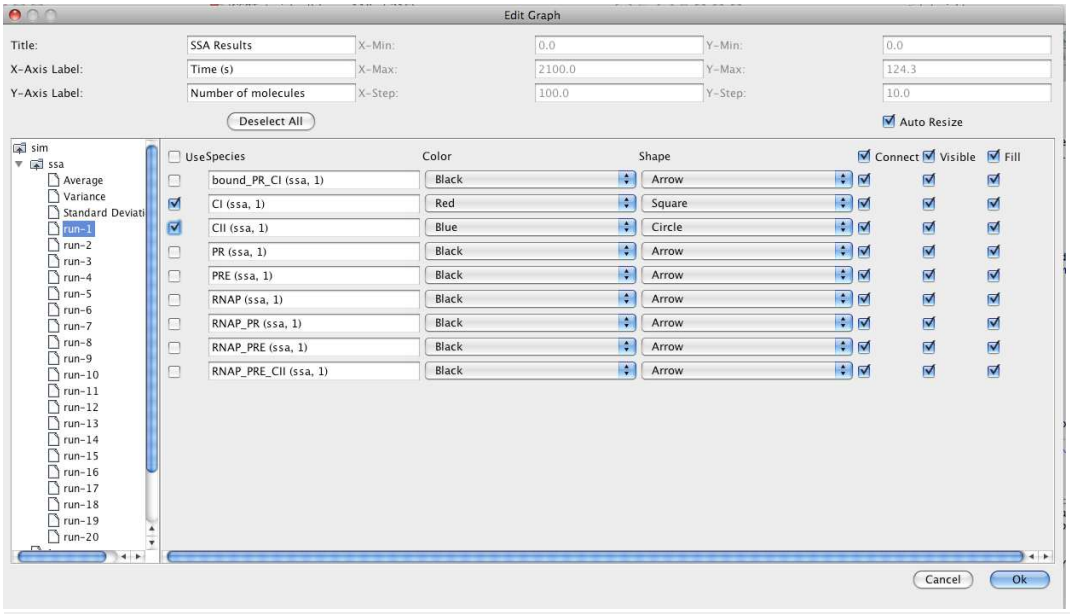


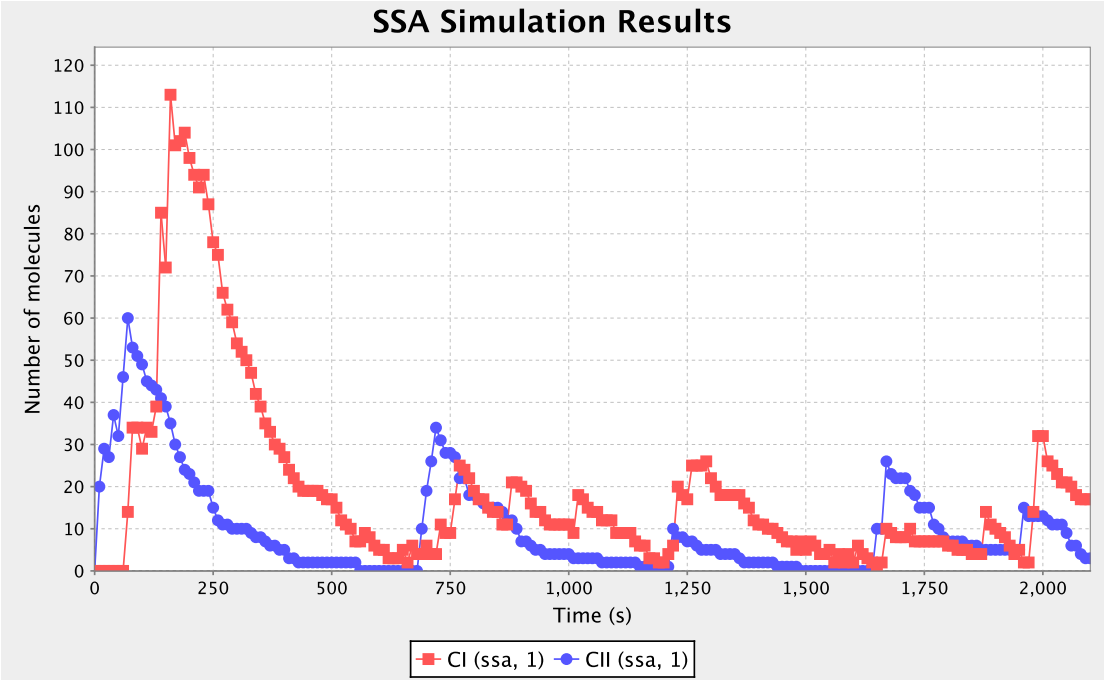
3. After the simulation completes, click on the `TSD Graph` tab. Double click on the graph to bring up the graph editor. Highlight Average, if not already highlighted, select CI and CII, change the Title to "ODE Simulation Results", change the X-Axis Label to "Time (seconds)", and change the Y-Axis Label to "Number of Molecules". Press the OK button. Click on Export and enter file name of `ode.jpg`.



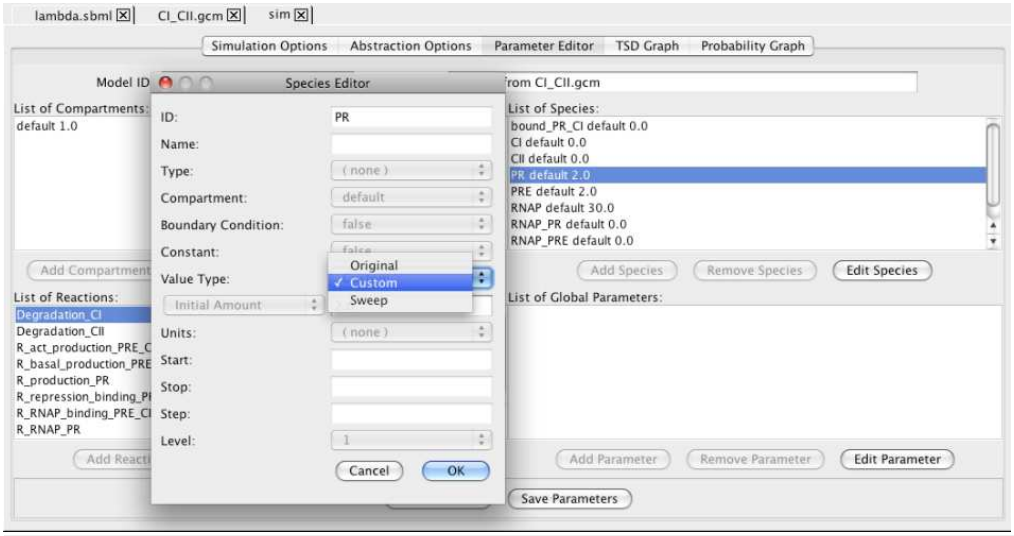


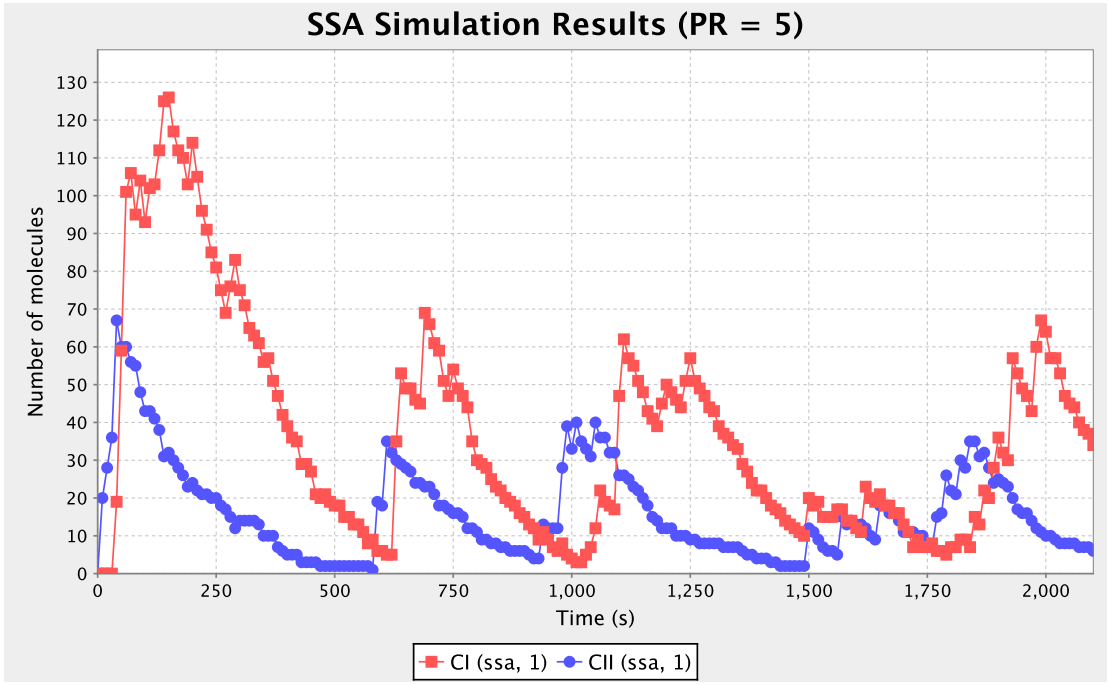
4. Select the simulation options tab again, select `Monte Carlo`, change the number of runs to 100, and set the simulation ID to `ssa`. Click on `Save and Run`. Click on the `TSD Graph` tab. Double click on the graph to bring up the graph editor. Open the ssa simulation directory, and highlight `run-1`. Select CI and CII, change Title to "SSA Simulation Results", change the X-Axis Label to "Time (seconds)", and change the Y-Axis Label to "Number of Molecules". Press the OK button. Click on Export and enter file name of `ssa-1.jpg`. Repeat these steps to generate graphs for the average (`average.jpg`) and standard deviation (`stddev.jpg`). Note that you can use the "Deselect All" button to remove all items from the graph.



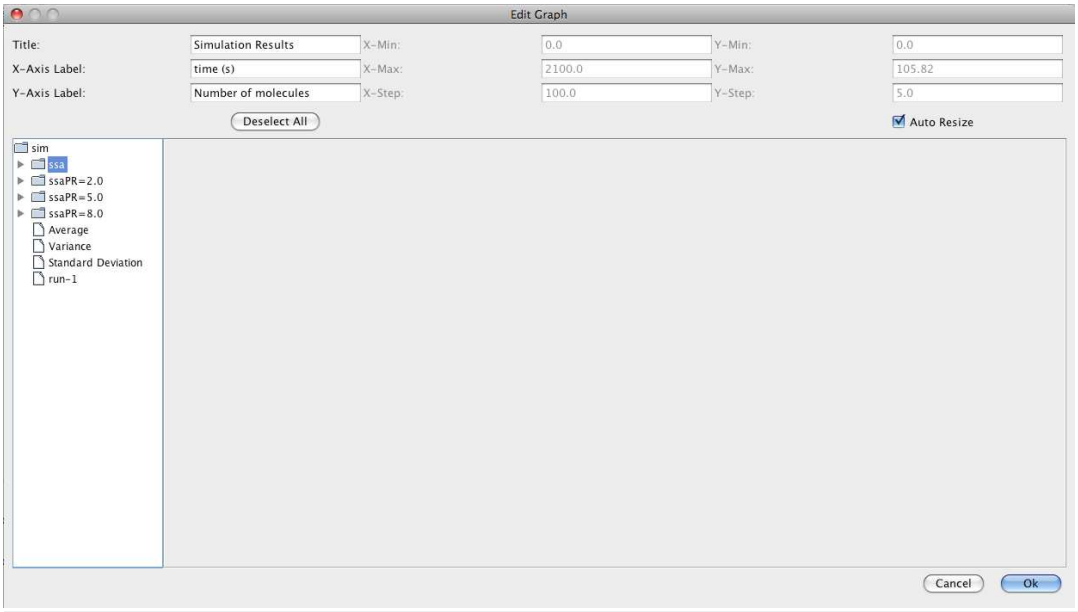


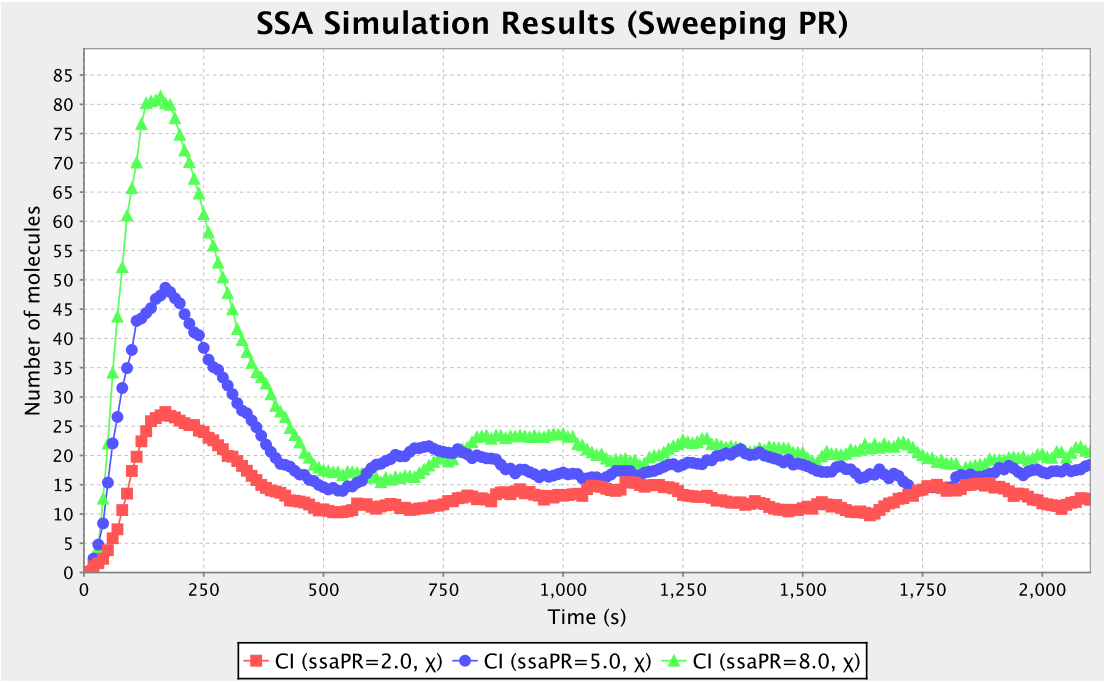
5. Click on the parameter editor tab. Highlight the `PR` species, and select `Edit Species`. Select `Custom` for the initial amount of `PR` and change it to 5. Press the Save and Run button. Click on the `TSD Graph` tab and following the steps above, create the following plots `ssa-1_5.jpg`, `average_5.jpg`, and `stddev_5.jpg`.



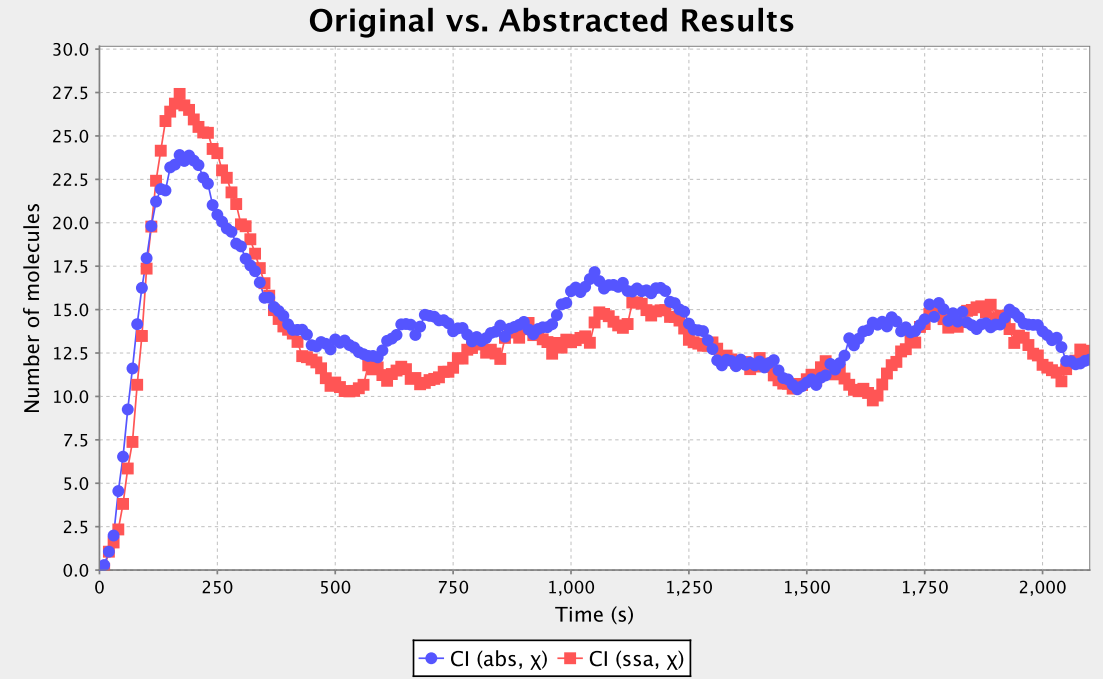


6. Now go back to the parameter editor tab, and change the initial amount for `PR` to `Sweep`, set the start to 2, stop to 8, step to 3. Press the save and run button. Click on the `TSD Graph` tab and double click on the graph to open the graph editor. Notice the new simulations id's generated for each of the run with PR of 2, PR of 5, and PR of 8. Deselect all from the current graph, and go and add the average value of `CI` from each of these simulation runs.





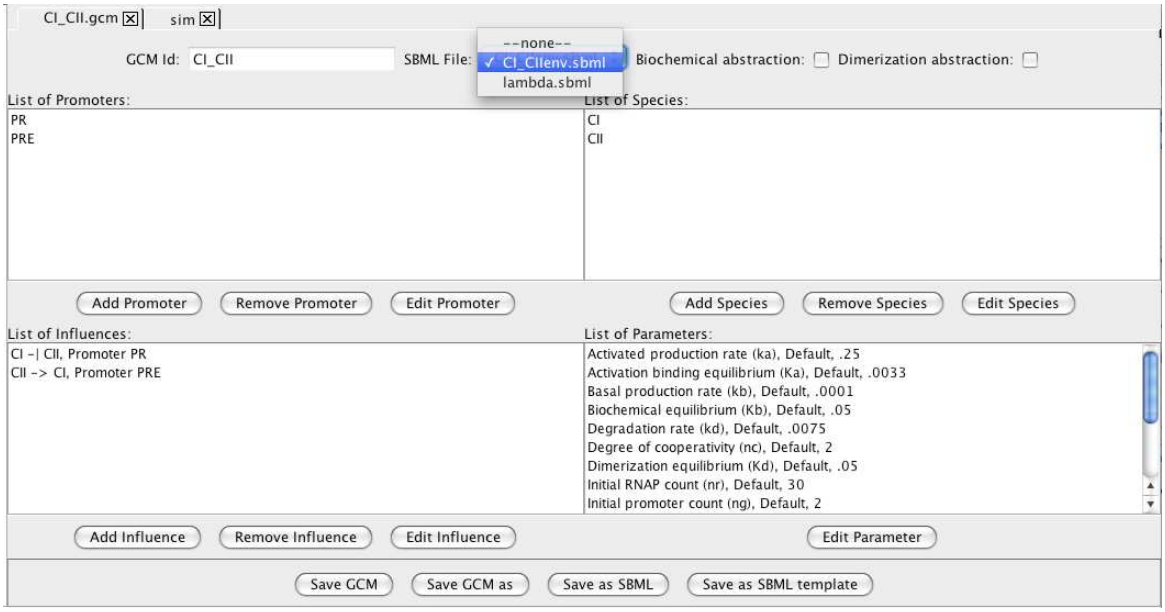
7. Go back to the Parameter Editor tab and change `PR` back to `Original` value type. Go back to the Simulation Options tab, select `Abstraction` and change the simulation ID to `abs`. Press `Save and Run` and note that the simulation time should be substantially faster. Go back to the `TSD Graph` tab and double click on the graph to bring up the graph editor. Deselect all and add the average value of `CI` from both the `abs` and `ssa` simulations.



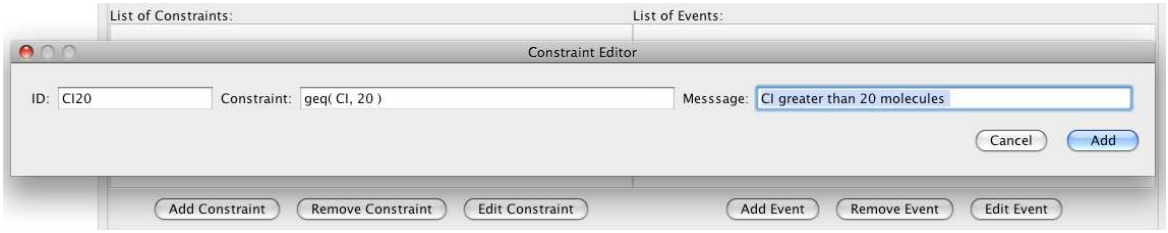
5 Probabilistic Analysis

This example illustrates how `iBioSim` can be used for probabilistic analysis.

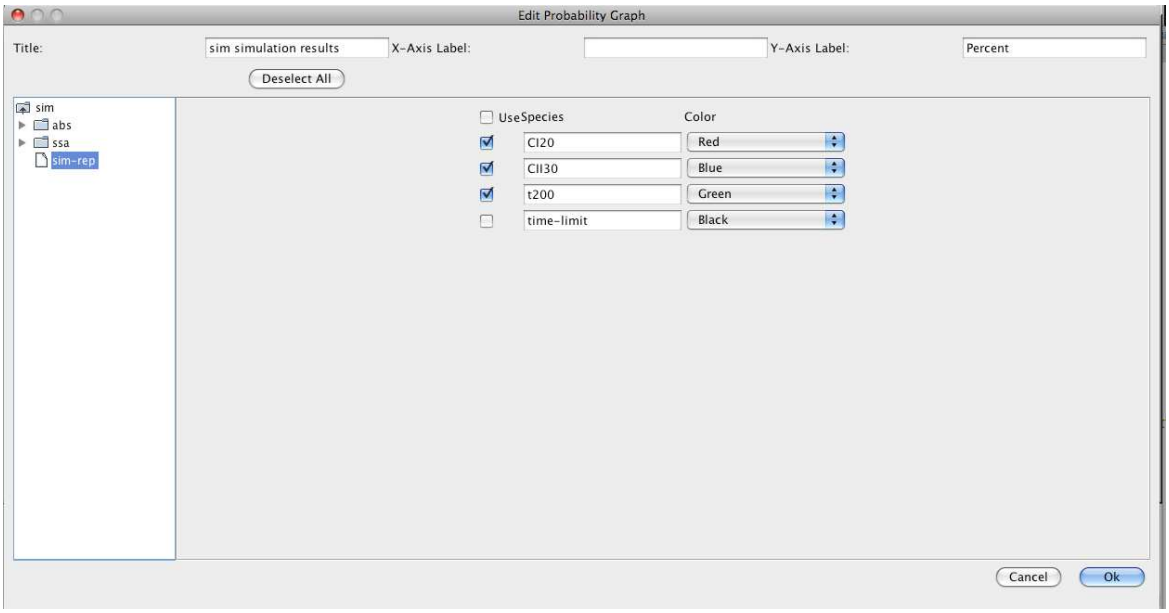
1. Go back to the GCM editor for `CI_CII`. Select `Save as SBML Template` and give it the name `CI_CIIenv`. Use the `SBML File` pulldown menu to select `CI_CIIenv.sbml` to associate with this GCM. Press the `Save GCM` button.



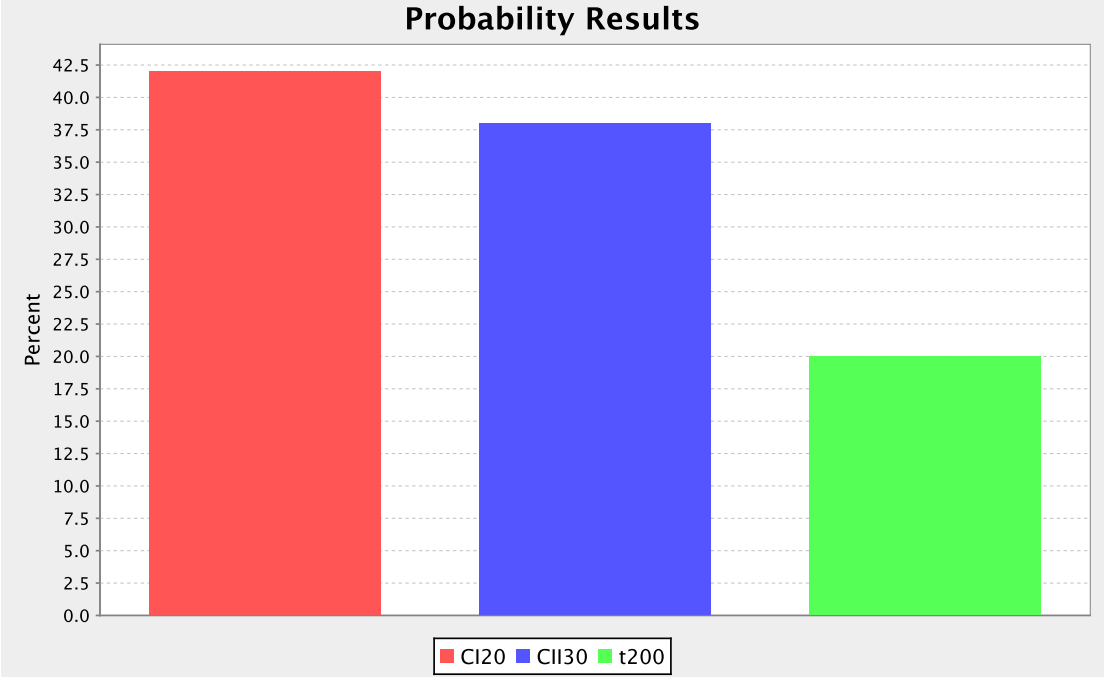
2. Double click on the `CI_CIIenv.sbml` file to open it in an SBML editor. Select the `Initial Assignments/Rules/Constraints/Events` tab, and select `Add Constraint`. Add a constraint with ID `CI20`, constraint `geq(CI, 20)`, and message `CI greater than 20 molecules`. Repeat these steps to add constraints for $CII \geq 30$, and $t \geq 200$. Be sure to press the `Save SBML` button when you are done.



3. Go back to your analysis view by clicking on the `sim` tab. Remove the simulation ID and press `Save and Run`. Click on the `Probability Graph` tab. Double click on the graph to bring up the probability graph editor. Change the title to `Probability Results` and the Y-axis label to `Percent`. Click on the `sim-rep` file on the left-hand side. Select `CI20`, `CII30`, and `t200` to graph them. Press `Ok`.



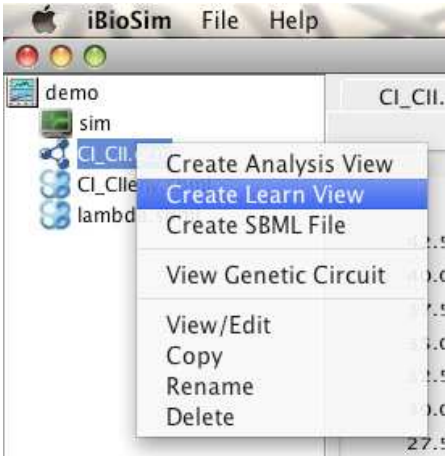
4. Export the graph as a jpg file by selecting the `Export` button and entering the filename `prob.jpg`.



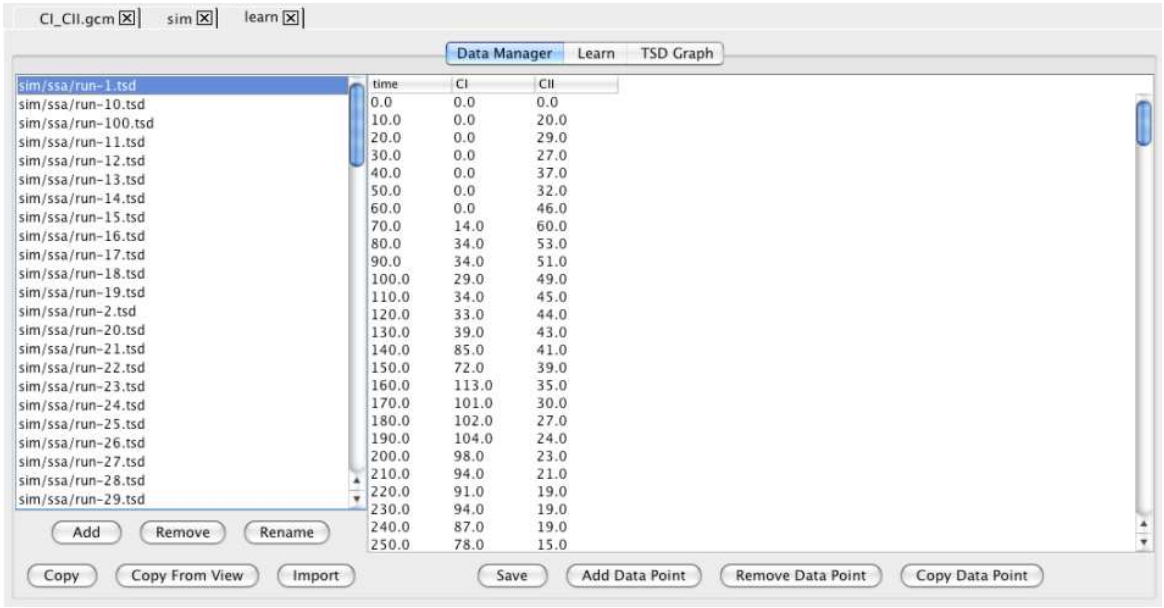
6 GCM Learning

This section describes how a GCM can be learned from time series data.

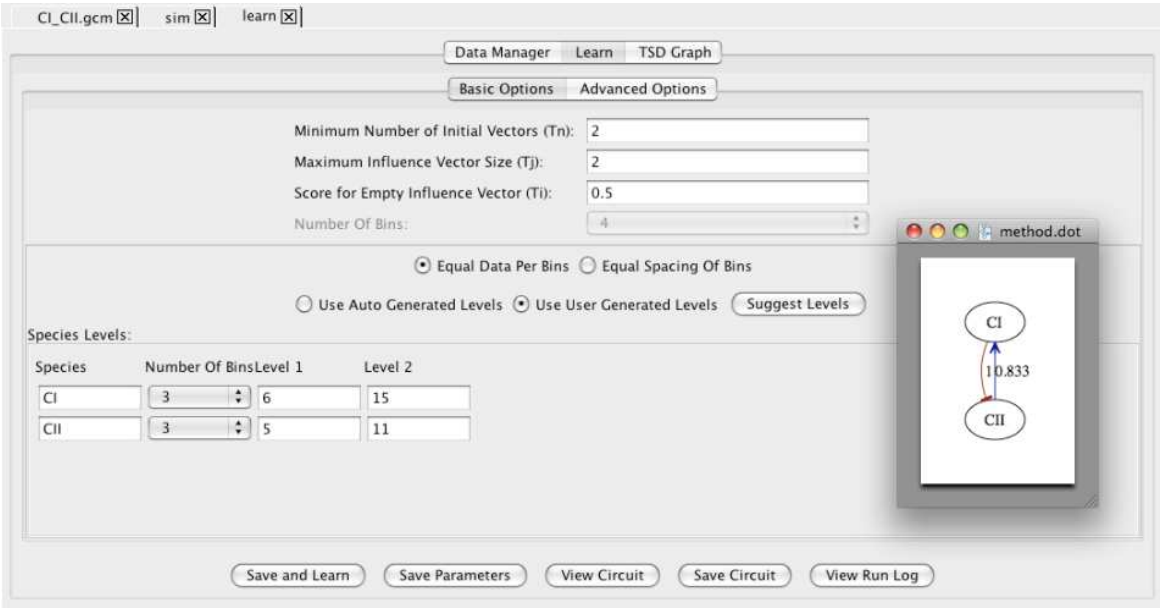
1. Highlight `CI_CII.gcm`, right click on it, and select `Create Learn View`. Give the learn view the ID `learn`.



2. At this point a `Learn View` will open, and you could begin to add your experimental data. In this demo, we will just utilize our simulation data as synthetic experimental data. To do this, click `Copy From View`, and select `sim/ssa`. Highlight `sim/ssa/run-1.tsd`, and you should see the simulation data for `CI` and `CII` appear on the right in the data editor.



3. Click on the `Learn` tab. Here you can edit the various learning options. For example, you can either use auto generated levels or user generated levels for your data encoding. Select `Use User Generated Levels` which will make the levels below editable. You can also select how many bins to use. Change the number of bins for both `CI` and `CII` to 3. At this point, you can ask the tool to suggest levels by clicking on the `Suggest Levels` button. Finally, press `Save and Learn` which will bring up the GCM that has been learned from this experimental data using Graphviz's dotty program.



7 Genetic Circuit Design

This last section describes how `iBioSim` can be used to design genetic logic gates.

1. Select `File` → `New` → `Genetic Circuit Model` and give it the ID `gate`.

2. Add promoters `P1` and `P2`, species `A`, `B`, and `C` (make `A` and `B` type `boundary` and `C` type normal), and repression influences from `A` to `C` on `P1` and `B` to `C` on `P2`. Save as an SBML template named `gateEnv`, and associate that SBML file with this GCM. Finally, save the GCM.

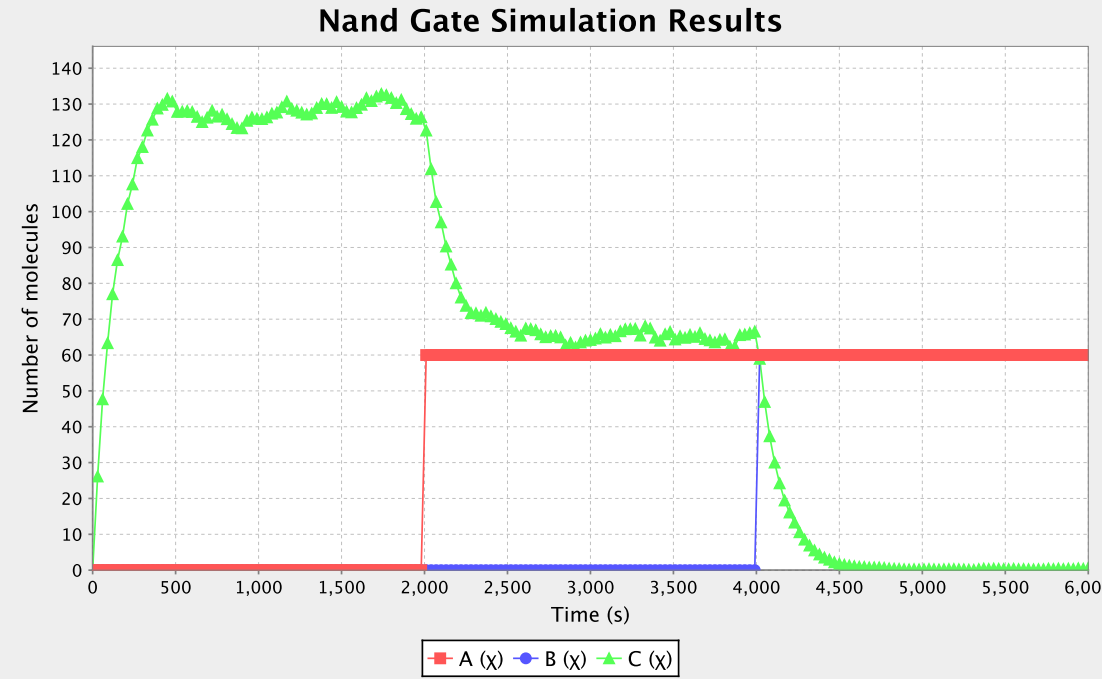
3. Open `gateEnv.sbml` in an SBML editor. Click on the `Initial Assignments/Rules/Constraints/Events` tab, and select `Add Event`.

4. In the event editor, give a trigger of `geq(t,2000)`. Press `Add Assignment`, select variable `A`, and enter 60 in the `Assignment` field. Press `Add` for the event assignment and `Add` for the event. Repeat these steps to create an assignment to `B` of 60 at time 4000. Note that you may ignore the warnings. These can be suppressed by changing your preferences and deselecting `Check for undeclared units in SBML`. Be sure to prese `Save SBML` when you are done.

5. Highlight `gate.gcm`, right-click, and select `Create Analysis View`. Give it the ID `simGate`.

6. In the analysis view, change the options to `Monte Carlo`, time limit of 6000, print interval of 30, runs of 100. Press `Save and Run`.

7. Select the `TSD Graph` tab and graph the averages of `A`, `B`, and `C`. The behavior should be that of a Nand gate.



8. Go back to the GCM editor for `gate`. Change the promoter on the influence from `B` to `C` to `P1`, and save the GCM. Go back to your analysis view and press `Save and Run`. The behavior should now be that of a Nor gate.