iBioSim: Tutorial

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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`.
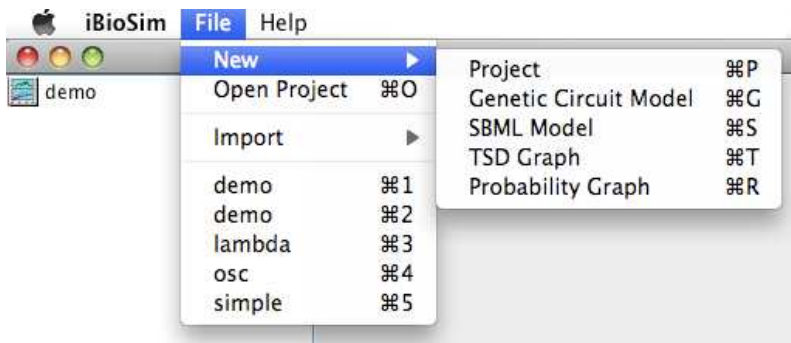
2 SBML Editor

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`.
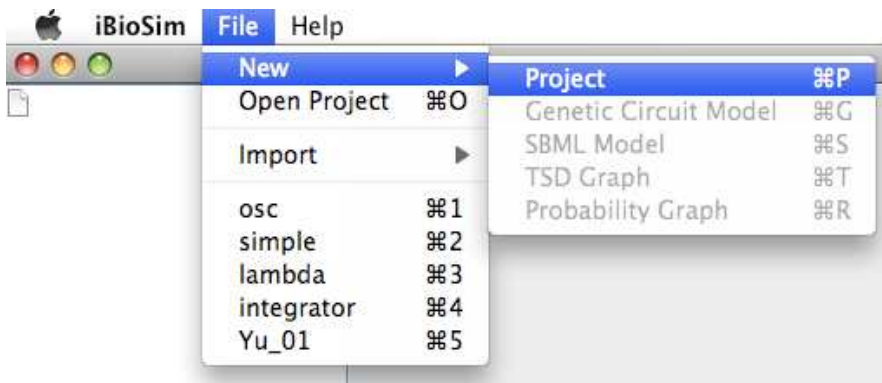

2. Select `File` → `New` → `SBML Model`. Enter `lambda` as the SBML model ID at which point an SBML editor will open.

3. Select `Edit Compartment` and change ID from `default` to `Cytoplasm`. Also, change Units to `volume`.
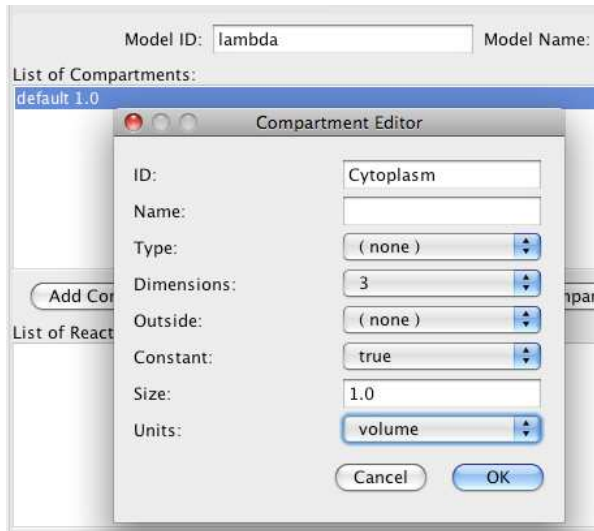
4. Select `Add Species` and enter `CI` as the ID, `The lambda repressor` as the name, and change the units to `mole`. Select `Add Species` again and enter `CI2` as the ID, `CI dimer` as the name, and change the units to `mole`.
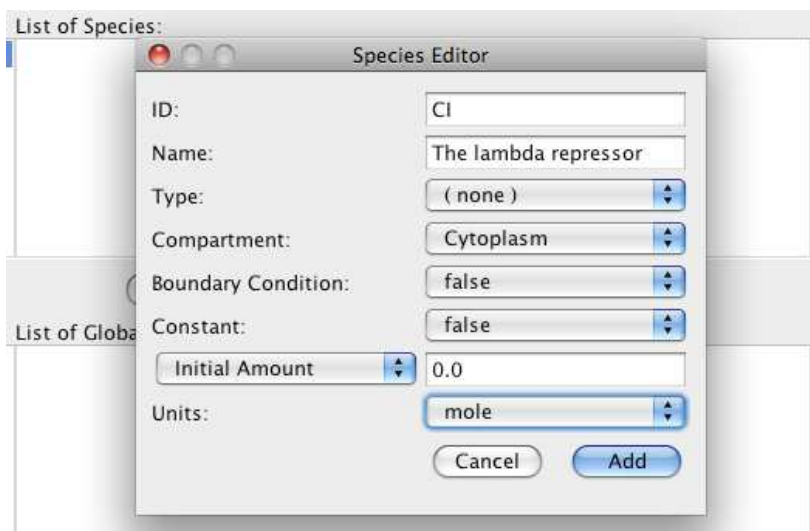
5. Select `Add Parameter` and enter `nd` as the ID, `Number of molecules in dimer` as the name, and change the units to `dimensionless`.
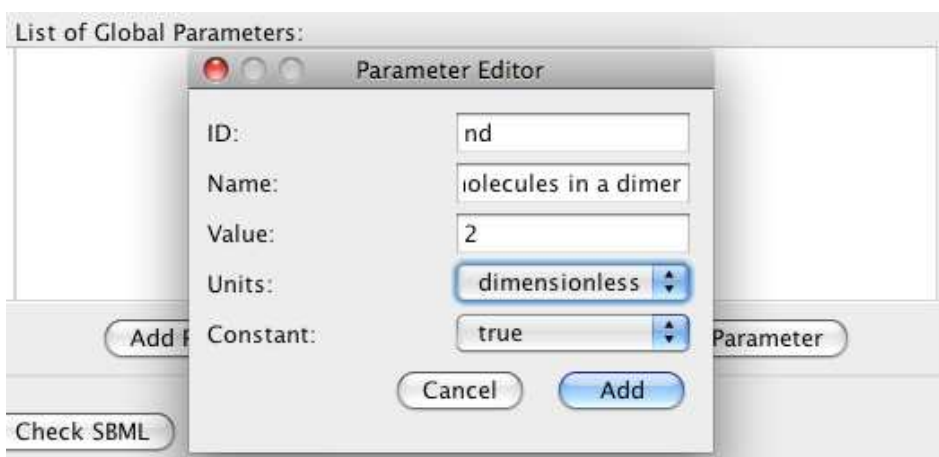
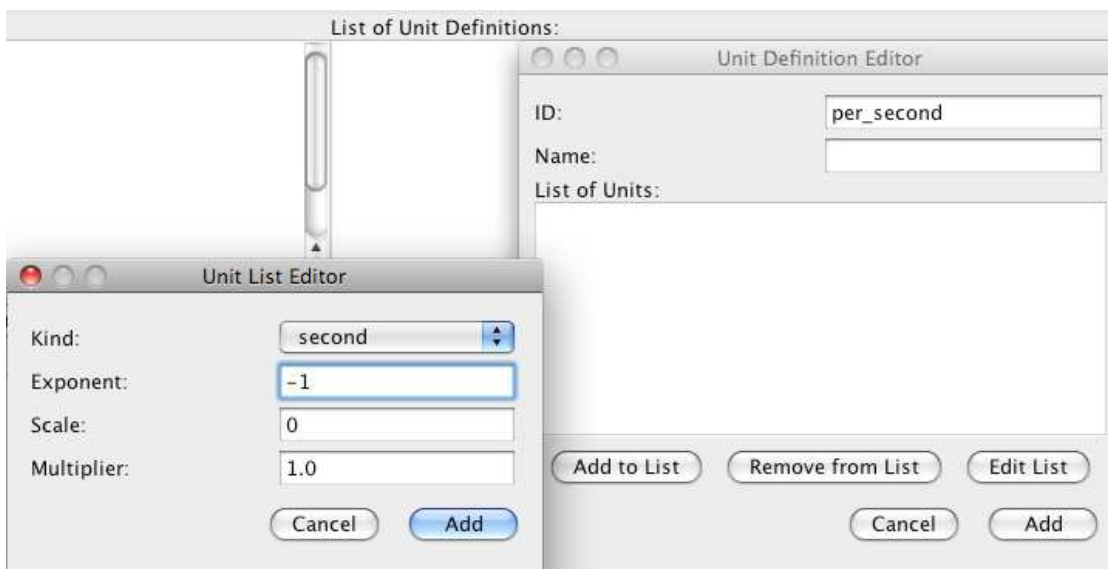6. Select `Definitions/Types` tab, and select `Add Unit` and enter `per_second` as the ID. Select `Add to List`, select `second` as the kind, change the exponent to -1, and click `Add`. Click `Add` in the `Unit Definition Editor`. Repeat these steps to create a `per_second_mole` unit (i.e., $(\text{second})^{-1}(\text{mole})^{-1}$).

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`.
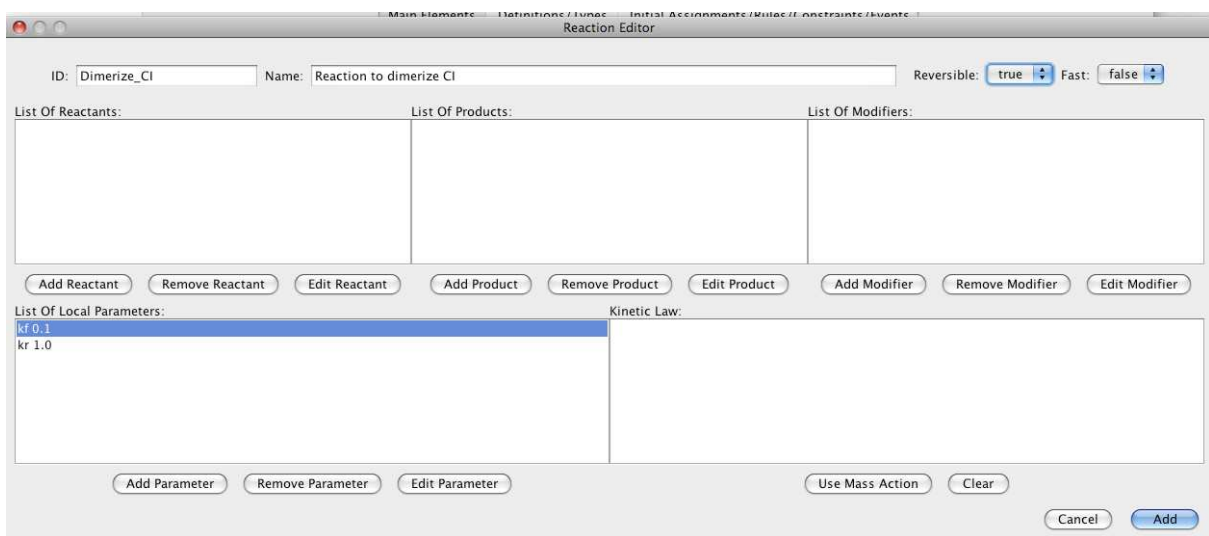
8. Select `Add Reactant` and select `CI` as the species, `Stoichiometry` to `Stoichiometry math`, and set its value to `nd`.
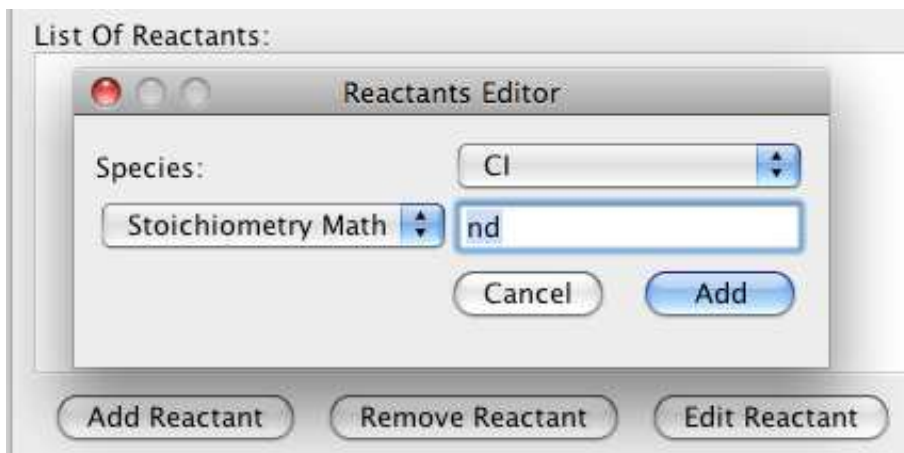
9. Select `Add Product` and select `CI2` as the species. Leave the stoichiometry as 1.
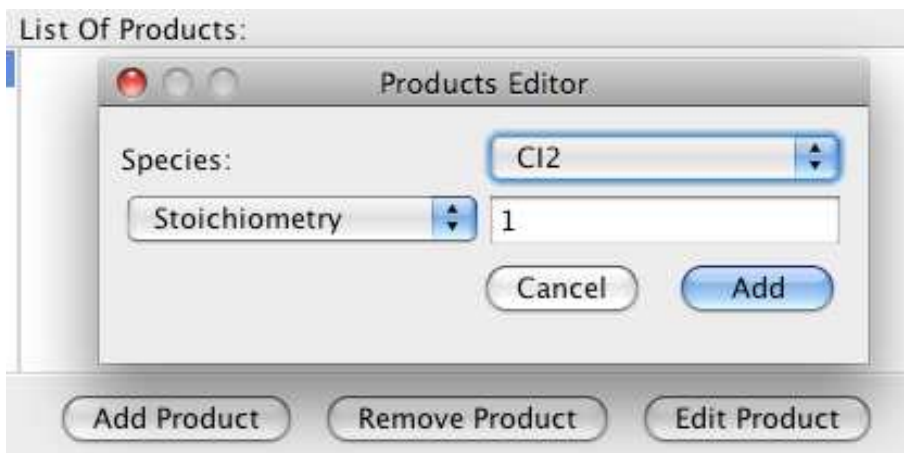
10. Highlight `kf` and select `Edit Selected Parameter`, change `kf` to `k2f`, and change the units to `per_second_mole`. Highlight `kr` and select `Edit Selected Parameter`, change `kr` to `k2r`,

and change the units to `per_second`.
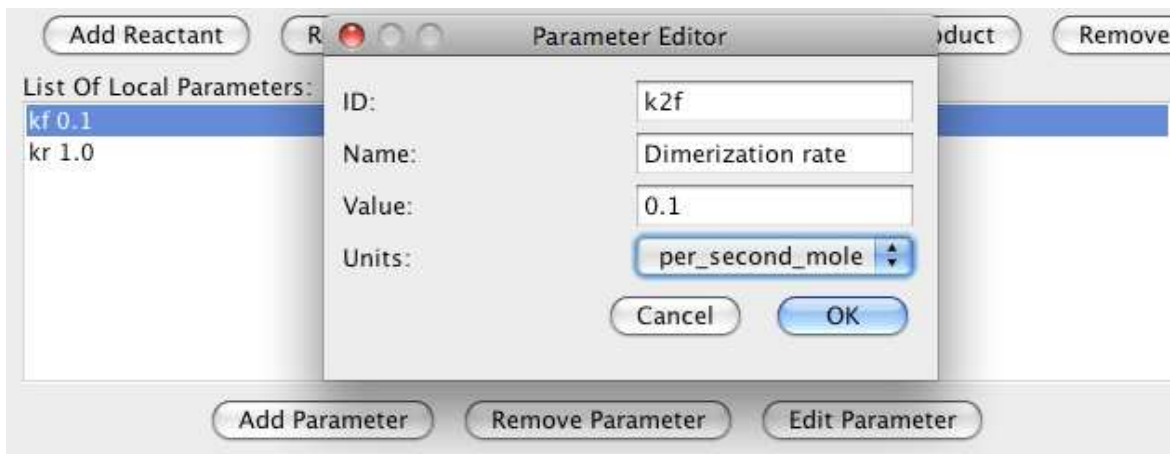
11. Select `Use Mass Action`, select `Add`, and select `Save and Check SBML`. There should be no errors.
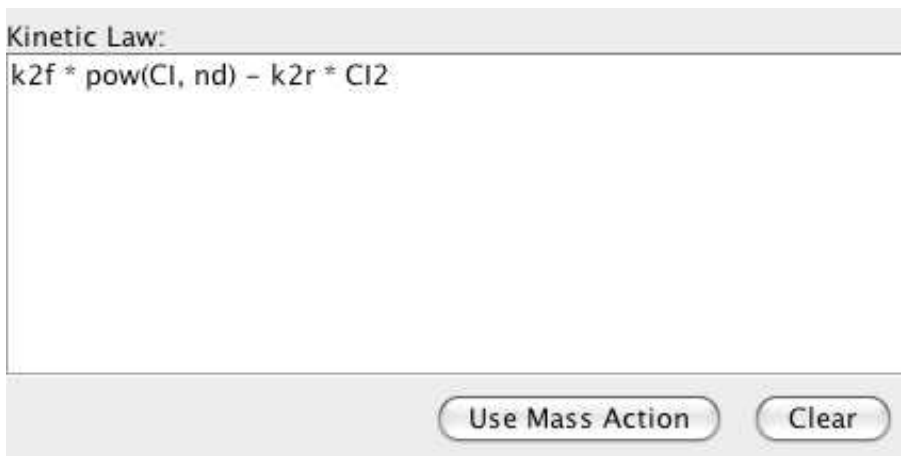
12. Add a new species "CI_total" with units of `mole`. Click on the "Initial Assignments/Rules/Constraints/Events" tab and press the "Add Rule" button. Select Assignment Type, select Variable "CI_total", and enter the following as the Rule:

$$2 * CI2 + CI$$

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

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

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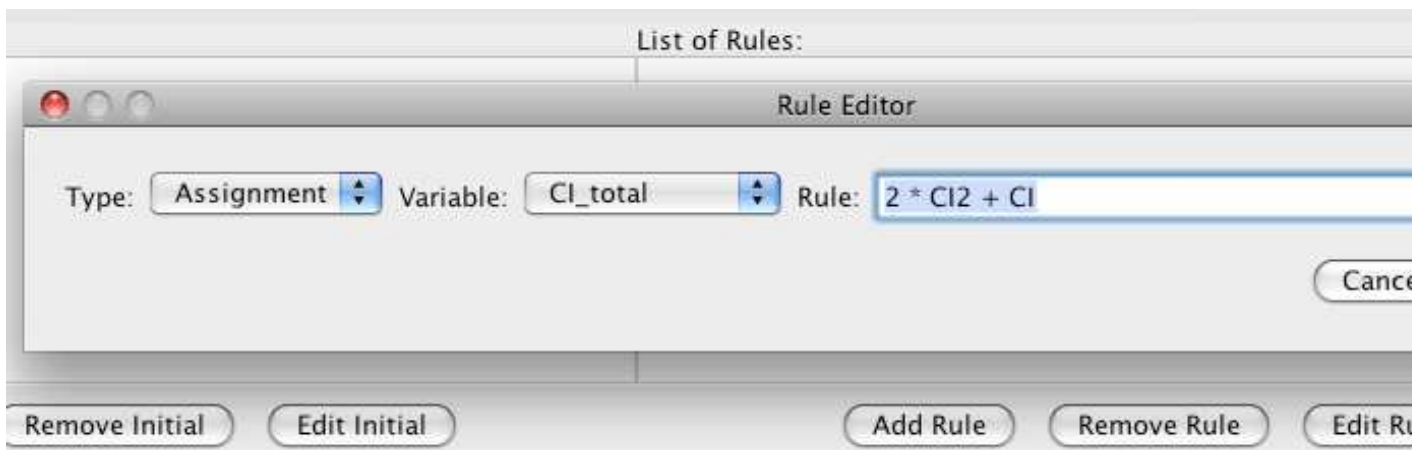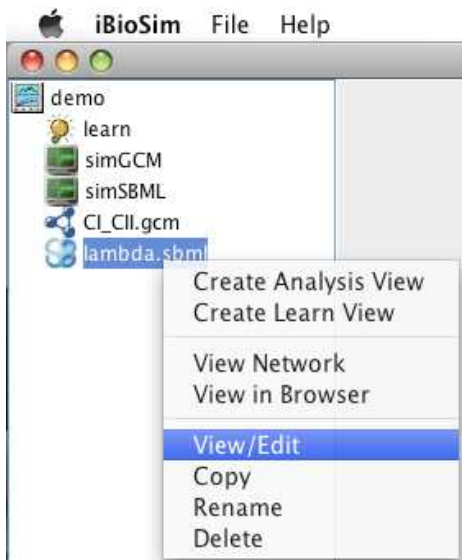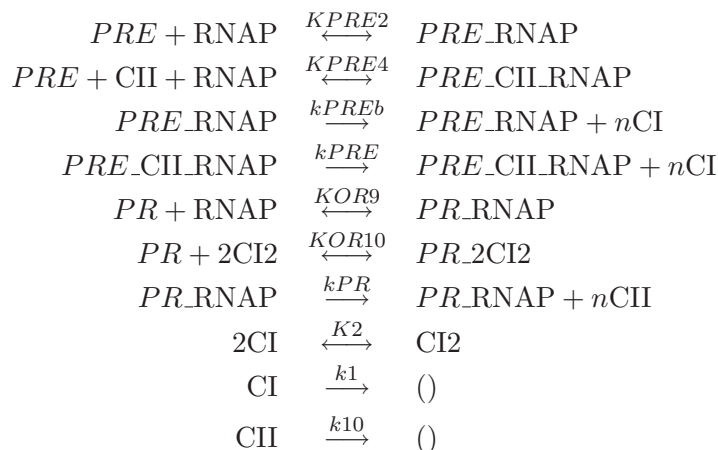$$PRE\_\text{RNAP} \overset{kPREb}{\longrightarrow} PRE\_\text{RNAP} + n\text{CI}$$
$$PRE\_\text{CII}\_\text{RNAP} \overset{kPRE}{\longrightarrow} PRE\_\text{CII}\_\text{RNAP} + n\text{CI}$$
$$PR + \text{RNAP} \overset{KOR9}{\longleftrightarrow} PR\_\text{RNAP}$$
$$PR + 2\text{CI2} \overset{KOR10}{\longleftrightarrow}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

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

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

3 Analysis

The following instructions describe how to analyze the SBML file just created.

1. Highlight `lambda.sbml`, using the right mouse button, select `Create Analysis View`, and enter the name `sim`.
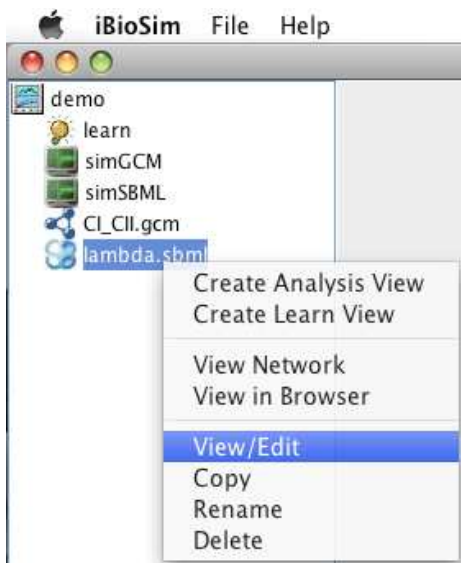
2. In the newly opened window, select `Monte Carlo`. Also, in this window, change the time limit to 2100.0, print interval to 100.0, and runs to 20. Finally, select `Save and Run` at the bottom of the window.
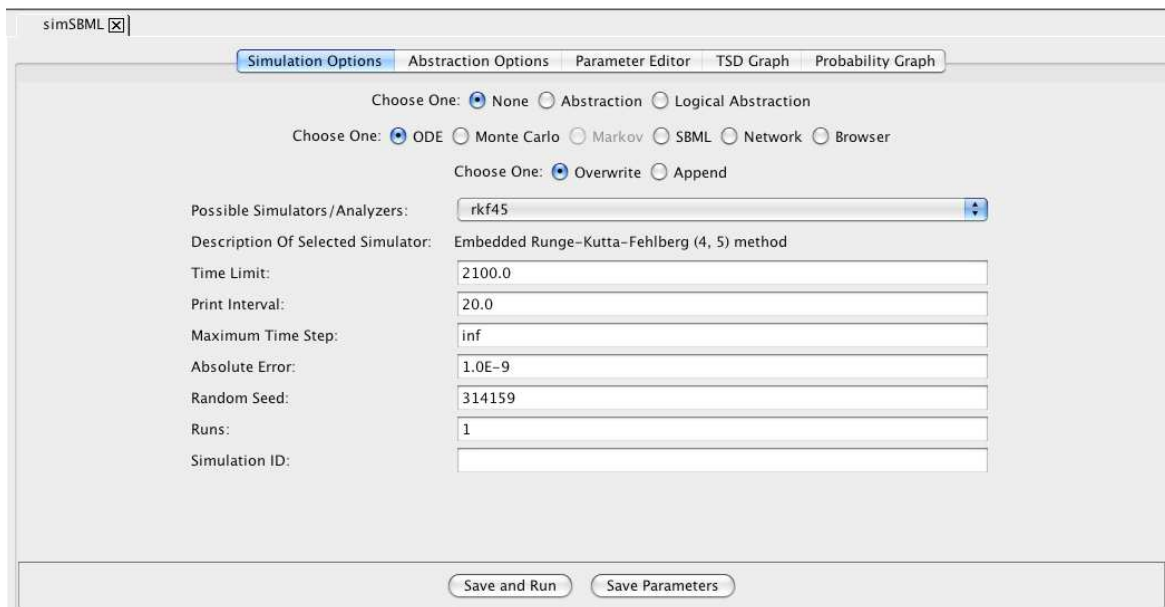
3. After the simulation completes (it may take a little while), click on the graph tab.

4. Click on the graph to bring up the graph editor. Highlight Average, if not already highlighted, select CI2 and CII, change T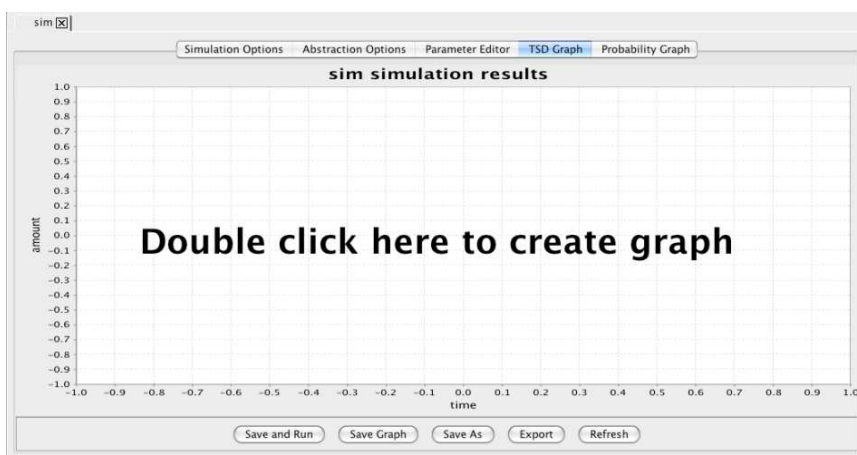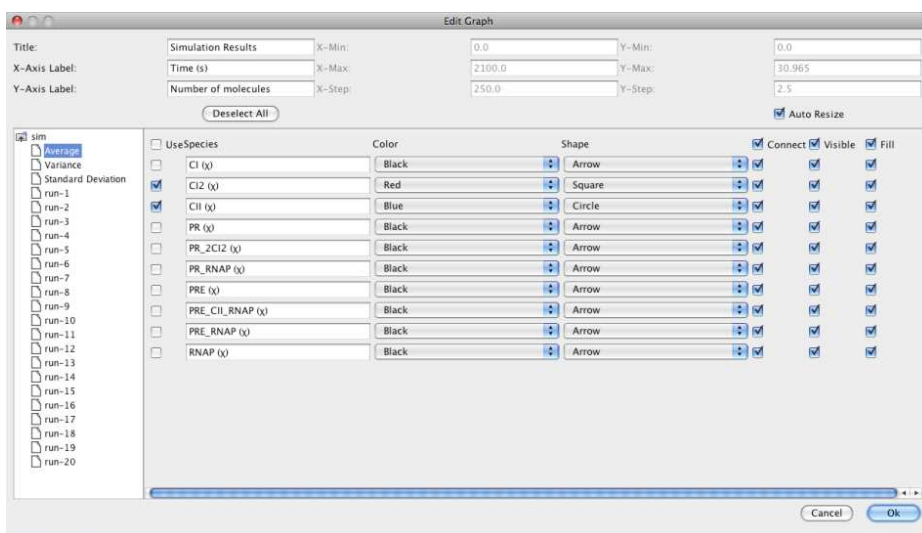itle to "Average", change X-Axis Label to "Time (seconds)", and change Y-Axis Label to "Number of Molecules". Press the OK button. Click on Export and enter file name of `average.jpg`. Repeat these steps to generate graphs for the standard deviation `stddev.jpg` and run-1 `run1.jpg`. Note that you can use the "Deselect All" button to remove all items from the graph.

5. Click on the SBML editor tab. Change the initial amounts of OR and PRE to 10. Press the Save and Run button. Click on the graph tab and following the steps above, create the following plots `average_10.jpg`, `run1_10.jpg`, and `stddev_10.jpg`.
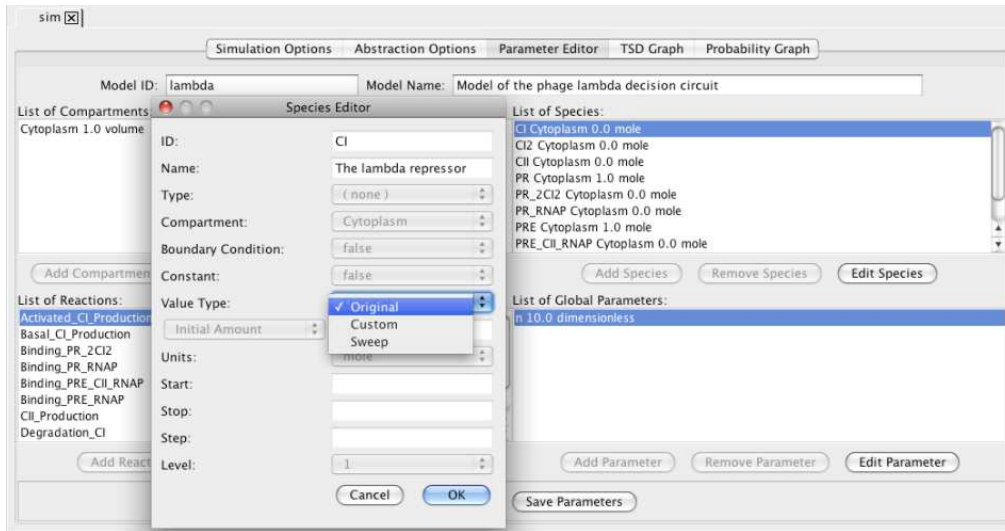
6. Simulate your lambda model with BioSim using the ODE method rkf45 with a time limit of 2100 and print interval of 50. Make a note of the simulation time and plot CI2 and CII. Next, simulate using the Euler method. Make a note of the simulation time and add CI2 and CII from the euler results to your graph. How do the simulation times and results compare? Change the time step and rerun the Euler method. Repeat until the results match up well. What time step is required for a good match? How do the simulation times compare?

4   Abstraction

The example in this section illustrates abstraction-based synthesis.

1. Press the Save SBML button.

2. Create or open an analysis view on your lambda model.

3. Select "None" and "Network", and press the Save and Run button. Count the number of species and reactions in your model.

4. Select "Monte Carlo", set the Time Limit to 2100.0, Print Interval to 100.0, and Runs to 20. Press the Save and Run button and record the simulation time.

5. Create a new analysis view for your lambda model and select "Abstraction" this time.

6. In the abstraction tab, change rapid equilibrium conditions 1 and 2 to 1000.0 as well as QSSA condition to 1000.0. Select "Network" then save and run. Count the number of species and reactions in your model.

7. Select "Monte Carlo", set the Time Limit to 2100.0, Print Interval to 100.0, and Runs to 20. Press the Save and Run button and record the simulation time.

8. Select File → New → Graph and enter a name for your new top-level graph.

9. Click on the graph and find the average simulation results from your orginal model and graph CII and CIt. Also, add to this graph from your abstracted model CII and CI. How well do they compare? Send me by email a jpg of your result.

10. Go back to your analysis view in which you did abstraction and change all the conditions back to 0.1. Regenerate the network and record the number of species and reactions. Regenerate the simulation results and record the simulation time.

11. Go back to the top-level graph which should have updated results. How does it compare now?

5 GCM Editor

This section gives an example using the GCM editor.

1. Create a new project named "xor", select File → New → Genetic Circuit Model, and enter the name `xor`.

2. Add species A and B of type constant. Be sure to fill in both the ID and Name fields.

3. Add species $Abar$, $Bbar$, X, Y, and C of type normal. Again, fill in the ID and Name fields.

4. Add an influence of type repression with input A and output $Abar$ and dimer of 2. You have just created an inverter. Create another inverter from B to $Bbar$.

5. Add a promoter named PX1 and another promoter named PX2.

6. Add a repression influence from A to X and use the promoter PX1 with dimer of 2.

7. Add a repression influence from $Bbar$ to X and use the promoter PX2 with dimer of 2. You have just created a NAND gate.

8. Create another NAND gate with inputs $Abar$ and B and output Y.

9. Finally, create another NAND gate with inputs X and Y and output C.

10. Change the `decay` parameter to 0.01.

11. Press the "Save GCM" and "Save as SBML" buttons.

12. Create an analysis view for your `xor.sbml` file.

13. Select the User Defined Data tab and click on the "Use User Defined Data" button.

14. Add a data point for A at time step 1000 to go to 20.

15. Add a data point for B at time step 2000 to go to 20.

16. Add a data point for A at time step 3000 to go to 0.

17. Add a data point for B at time step 4000 to go to 0.

18. Select the options tab, select "abstraction", and set a time limit of 5000, a print interval of 200, and 20 runs.

19. Select the abstraction tab, and add species C to the interesting species list.

20. Press the "Save Parameters" button then "Save and Run" button.

21. Create a graph that includes A, B, and C. Email a jpg of this graph to me.

22. Close your analysis view and edit your `xor.gcm`. Try adjusting some of the global parameters. Remember to save both your `gcm sbml` files. Reopen your analysis view and re-run your simulation. Send me a few different graphs. Change the titles of the graphs and provide a description in your email of the graphs as to what you changed.