

# **RuleBender 1.1.415 Tutorial**

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# Installing and Launching RuleBender

## Requirements

- Java: Java version 1.5 or greater is required to run RuleBender. It can be acquired from <http://www.oracle.com/technetwork/java/javase/downloads/index.html> by clicking on "Download JRE".
- Perl: OSX and Linux almost always come with perl installed, but the newest version and a free windows version is available <http://www.perl.org/get>
- Before you install and run the program, please be aware that any non-ascii characters in a file path may cause the program to crash.
- Also, it's best to avoid spaces in your path as well.

## OSX Getting Started

Download the [32 bit](#) (most OSX 10.5 or older machines) or [64 bit](#) (most OSX 10.6 machines) OSX distributable file and unzip it. Move the RuleBender directory to your applications directory (or wherever you would like the program to be). Inside of the RuleBender folder you will see the BioNetGen directory and the RuleBender OSX application. To start the tool, double click on the RuleBender application icon.

## Linux Getting Started

Download the [32 bit](#) or [64 bit](#) Linux distributable file and unzip it. Move the RuleBender directory to wherever you would like the program to be. Inside of the RuleBender directory you will see the BioNetGen directory, the RuleBender executable jar, and a script called 'run'. To start the tool, execute the 'run' script in a terminal window.

## Windows Getting Started

Download and unzip the [Windows 32 bit](#) or [Windows 64 bit](#) depending on your Windows installation. Move the RuleBender directory to the Program Files directory (or wherever you would like the program to be). Inside of the RuleBender folder you will see the BioNetGen directory and the RuleBender executable. To start the tool, double click on the RuleBender executable. You may experience errors if you do not have account rights under some configurations. If you are having trouble running simulations or parameter scans try right clicking the exe and selecting "Run As Administrator".

# Using the Editor

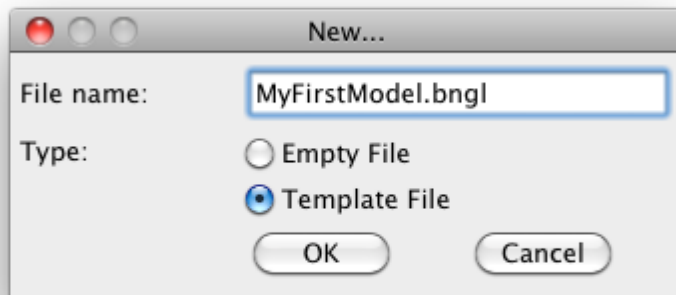
## The Main Window

Launch RuleBender. You should see an empty frame with a console, a toolbar, and a menubar either above the toolbar in Linux or Windows or in the system menubar for OSX.



## Creating and Opening Files

You can create a new file by clicking 'File' -> 'New' in the menubar or 'New' in the toolbar. In the new file dialogue, you can select the 'Template File' radio button to generate a new file with the outline of a bngl model.



For this tutorial, we will be using an existing file, so you can close your new one if you created it. Click on the 'Open' button in the toolbar and open the RuleBender/BioNetGen-2.1.6/Models2/toy-jim.bngl file. This file gives an example of the parameter, seed species, reaction rule, observable, and simulation action definitions. For more clarification on the BioNetGen Language, see the BioNetGen [Documentation](#) page.

Now that the file is loaded in the editor, we can see some of the features of the editor. The 'File' and 'Edit' menu items contain typical text editor functions such as copy, paste, search, replace, print, etc. The Format menu item opens a font chooser which will change the appearance of the text in the editor window. The editor pane supports multiple open tabs, syntax highlighting, and code folding by clicking the - sign next to the beginning of a definition block. All editing of a BNGL model will take place here.

There are a few other menu items and buttons in the main editor window, but we will see those later on in the tutorial.

Model Editor

New Open Save Save As Find Visualize

/Users/mr\_smith22586/Desktop/RuleBender/BioNetGen-2.1.6/Models2/toy-jim.bngl

toy-jim.bngl

```
6 # When two kinases are juxtaposed through binding to
7 # receptor-associated adapter proteins, one of the kinases can
8 # transphosphorylate the second kinase.
9
10 version("2.0.23");
11
12 + begin parameters
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35 + begin seed species
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56 - begin reaction rules
57 # Ligand binding (L+R)
58 # Note: specifying r in R here means that the r component must not
59 #     be bound. This prevents dissociation of ligand from R
60 #     when R is in a dimer.
61 L(r) + R(l,r) <-> L(r!l).R(l!l,r) kpL, kmL
62
63 # Aggregation (R+R)
64 # Note: R must be bound to ligand to dimerize.
65 L(r!l).R(l!l,r) + L(r!l).R(l!l,r) <-> L(r!l).R(l!l,r!3).L(r!2).R(l!2
66
67 # Receptor binding to adaptor (R+A)
68 # Note: A and R can bind independent of whether A is bound to K or
69 #     whether R is in a dimer.
70 A(r) + R(a) <-> A(r!l).R(a!l) kpA, kmA
```

Console

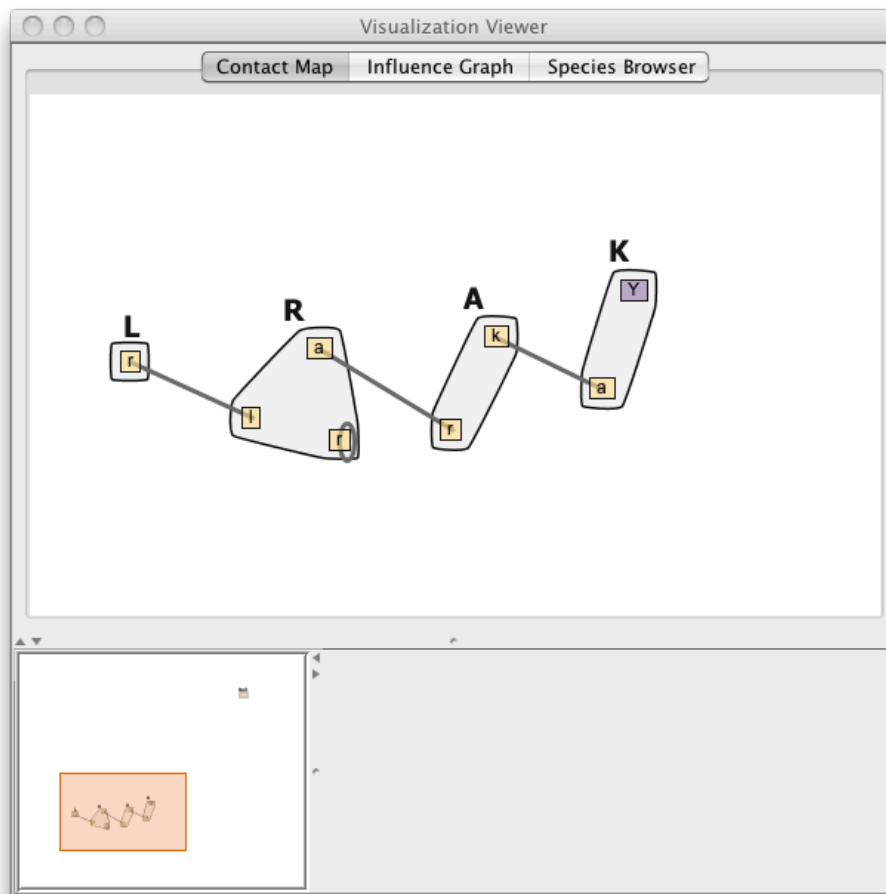
Parsing Contact Map model...  
Contact Map model parsed correctly.  
Parsing file for Influence Graph...  
Influence Graph model parsed correctly.

# Visualizing a Model

## The Contact Map

With your model still loaded in the editor, Click on the 'Visualize' button on the tool bar to load the visualization pane. While a model is being constructed, the visualization pane displays visual representations of the model. The window contains a main viewing area for the visualizations, a global view of the visualization in the lower left, and an area for additional information on the lower right.

The default visualization is the contact map. The contact map shows the molecules in the model as polygonal nodes in the graph, and bonds between the molecules are shown as edges. Inside of the molecules the bonding sites are displayed as rectangles. You can zoom with the mouse wheel or double clicking the background to fit the graph to the screen. You can pan or rearrange the nodes in the image by clicking and dragging on the background or nodes respectively.



Purple bonding sites have multiple states, while the tan ones do not. Right click on the white background of the visualization to bring up a menu and the select "Show States". The Y bonding

site of the K molecule is now displaying its U (unphosphorelated) and P (phosphorelated) states. In the right click menu you can also save the image to a file or show the compartments that contain the molecules.

Left clicking on a bond will display the rule text and rates in the lower right information pane. Right clicking on a bond will bring up a menu that displays each rule that affects that bond. Selecting a rule from this list will enable a bubble sets overlay that shows the rule center (the components that are changed by the rule) in red and the rule context (the components that are not changed, but are required) in blue.

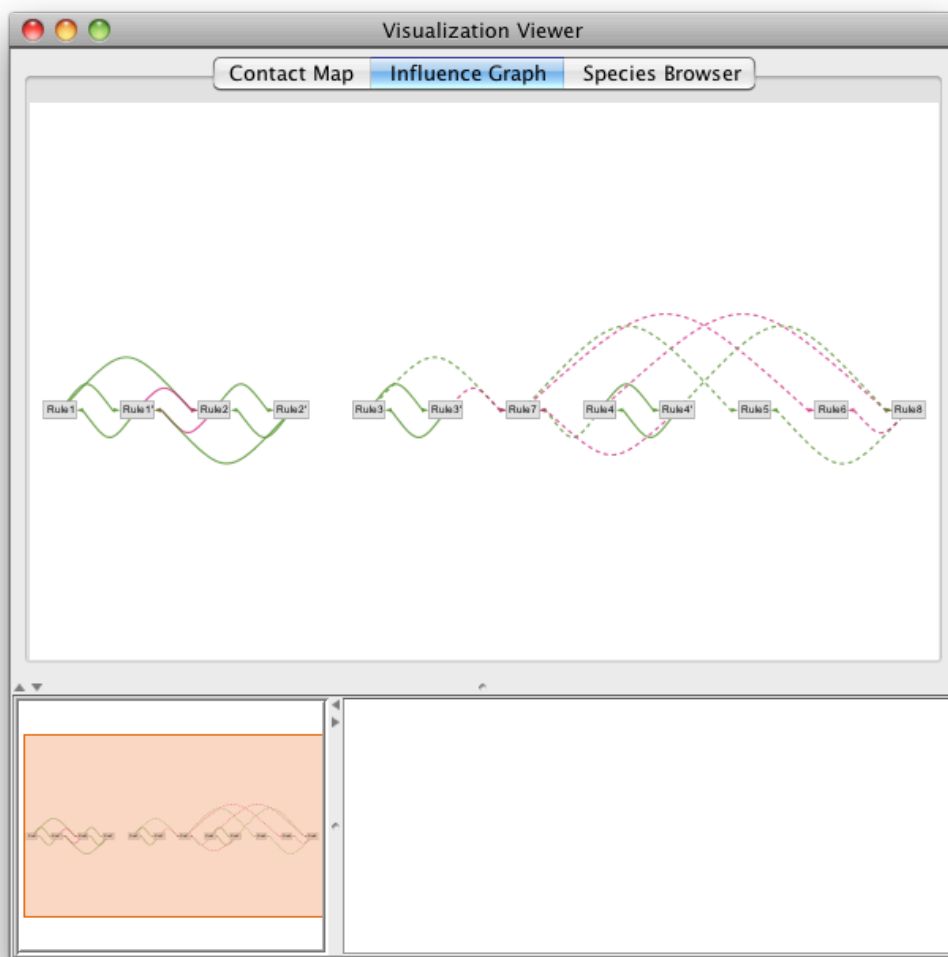
The screenshot shows the 'Visualization Viewer' window. At the top, there are three tabs: 'Contact Map' (selected), 'Influence Graph', and 'Species Browser'. The main area displays a contact map with four molecules: L, R, A, and K. Molecule L is highlighted in red, and molecule R is highlighted in blue. The bottom panel shows the selected rule and its rates.

Rule	Rate1	Rate2
$L(r) + R(l,r) \leftrightarrow L(r!1).R(!1,r)$	kpL	kmL

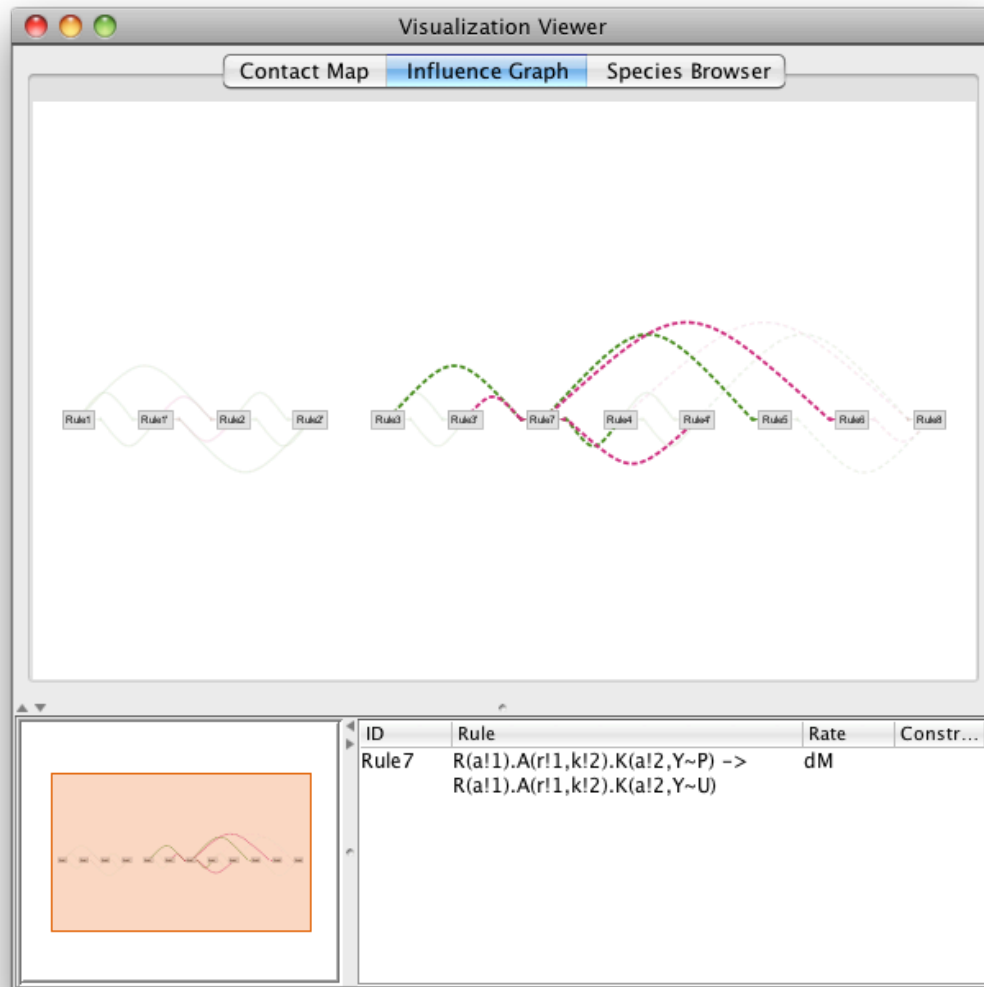
## The Influence Graph



The second visualization that is available can be seen by clicking the 'Influence Graph' tab of the visualization viewer. The influence graph represents the interactions between the rules of a model. Rules can interact by either producing or consuming the structures required by another rule. If rule 1 consumes the reactants rule 2, then rule 1 inhibites rule 2. Conversely, if rule 1 produces the reactants of rule 2, then rule 1 activates rule 2. In the influence graph each node is a rule and activation and inhibition are shown as green or red edges respectively. The edges that appear above the nodes are directed to the right, and the edges that appear below the nodes are directed to the left.



The influence graph also has the zooming and panning capabilities present in the contact map. Right clicking on the background will bring up a menu that allows you to save the image, or disable the activation or inhibition edges in the graph. Clicking on a node will display the rule text in the lower left information pane. Clicking on a node will also highlight the edges that are connected to it and fade the edges that are not connected to it.



Both the contact map and the influence graph are update every time that the bngl file is saved. To see the effects of change the model, try commenting out (with the '#' character) the first rule in the model and then save while watching the influence graph. Be sure to uncomment the line afterwards so that the model will be complete for the rest of the tutorial.

# Simulation and Results Analysis

## Running a Simulation

After a model has been constructed with the assistance of the visualization window, it can be executed from the main editor window. In the menu bar, select the 'Actions' menu and then click on 'Run Simulation' option. There will be a lot of output displayed to the console, and then when the simulation completes the results viewer window will appear.

## The Results Viewer Window

The upper left pane of the results window contains a tree browser of all of the simulation results. The simulations are organized by date and time, and are all managed by the tool. The large center pane is used for displaying results data. The bottom left pane displays a list of the chemical species in the file being viewed.

## Results File Types

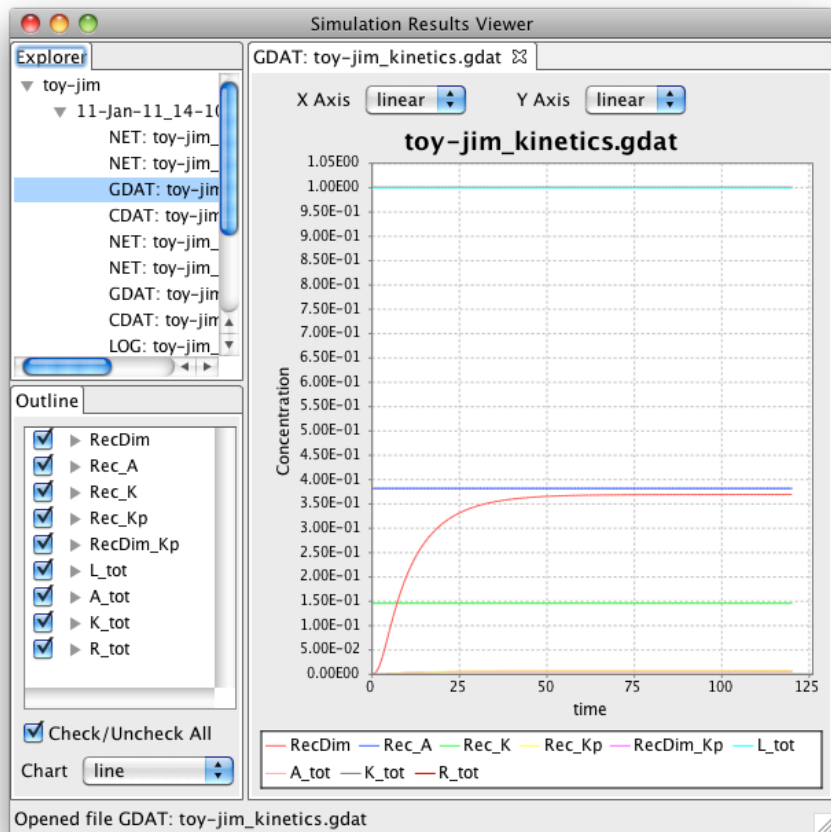
There are 4 different types of results files:

- GDAT: The concentrations of the observable molecules.
- CDAT: The concentrations of all of the molecules generated in the simulation.
- NET: The textual representation of the network after a simulation is complete.
- LOG: Output from the simulator.

In addition, XML (SBML) and M (Matlab) models can be produced by BioNetGen for use in other tools.

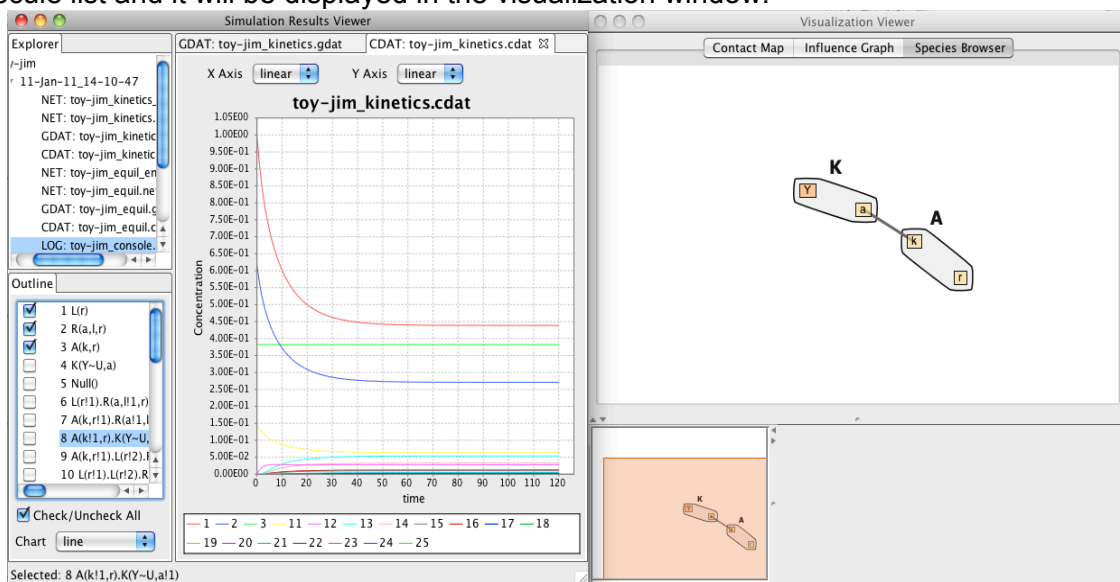
## Displaying Results

Double clicking on a file will display it in the large viewer area. LOG and NET files are displayed as text, and the GDAT and CDAT files are viewed as line/point plots of the concentrations of the molecules in the files. You can change the axes to linear plotting using the drop down menus above the graph. Clicking and dragging to the right and down produces a rectangle over the graph that will zoom into the selected area when it is released. Click and drag to the left in order to zoom back out. You can select the molecules to display in the main results area by selecting or deselecting the checkboxes next to the molecules in the lower left molecules list.



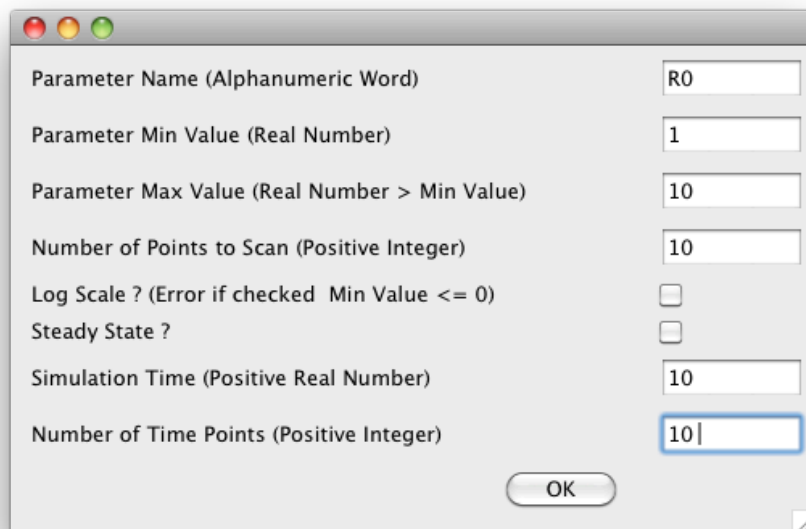
## Molecule Visualization

To see a visual representation of a chemical species, click on the molecule in the lower left molecule list and it will be displayed in the visualization window.



## Parameter Scanning

A parameter scan runs several simulations while varying the value of a parameter, and then reports how it affects the concentrations of observable species. To start a parameter scan, click on the Actions menu and select Parameter Scan. You will see the window below, and you should fill in the name of the parameter to vary, its minimum and maximum values, the number of points to scan, the simulation time, and the number of time points. Also, you can select the checkboxes to set the log scale and steady state options. Click OK to run the scan.

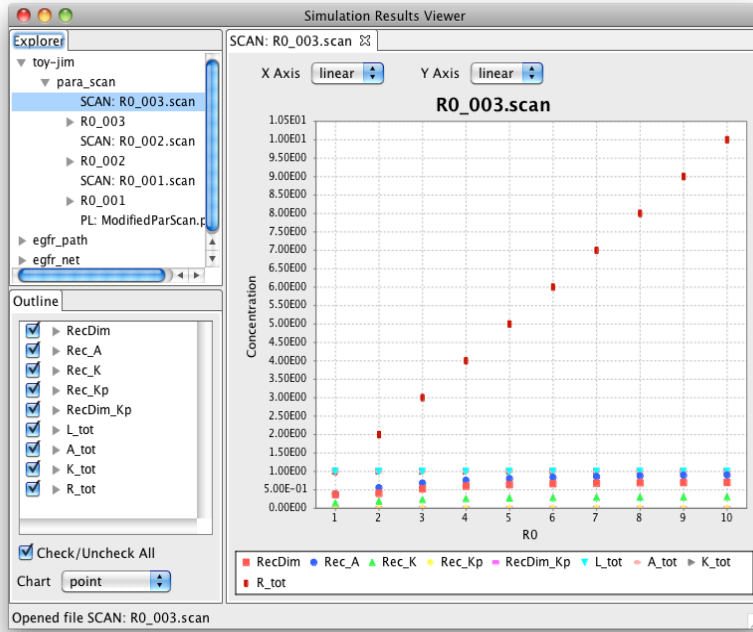


The image shows a dialog box for parameter scanning. It contains the following fields and options:

Parameter Name (Alphanumeric Word)	R0
Parameter Min Value (Real Number)	1
Parameter Max Value (Real Number > Min Value)	10
Number of Points to Scan (Positive Integer)	10
Log Scale ? (Error if checked Min Value <= 0)	<input type="checkbox"/>
Steady State ?	<input type="checkbox"/>
Simulation Time (Positive Real Number)	10
Number of Time Points (Positive Integer)	10

An OK button is located at the bottom right of the dialog box.

After the scan has completed, the results window will display a plot of the initial value of the parameter vs concentration. Each observable that was defined the bngl file will have a colored plot on this graph. In our results you can see that changing R0 from 1 to 10 gradually increases the concentration of the RecDim observable. This makes sense because R0 is the starting concentration of RecDim.



Changing the Y axis to log mode makes it easier to see the effect of changing R0.

