

# RuleBuilder 1.0

## Getting Started Guide

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# Introduction

RuleBuilder enables you to define, generate, and simulate graphical rule-based models of biochemical systems. Objects and rules created in RuleBuilder are passed to the BioNetGen program in the form of a BioNetGen Language (BNGL) file in order to generate and simulate the reaction network. RuleBuilder enables you to control both the network generation and simulation steps and to view the generated network and plot the simulation results. This guide takes you through all of the basic steps involved in using RuleBuilder.

# RuleBuilder Layout

The screenshot displays the RuleBuilder 1.40 Beta software interface. At the top is a menu bar with 'File', 'Edit', 'View', and 'Help'. Below it is a toolbar with various icons for drawing and editing. The main workspace is divided into several panels:

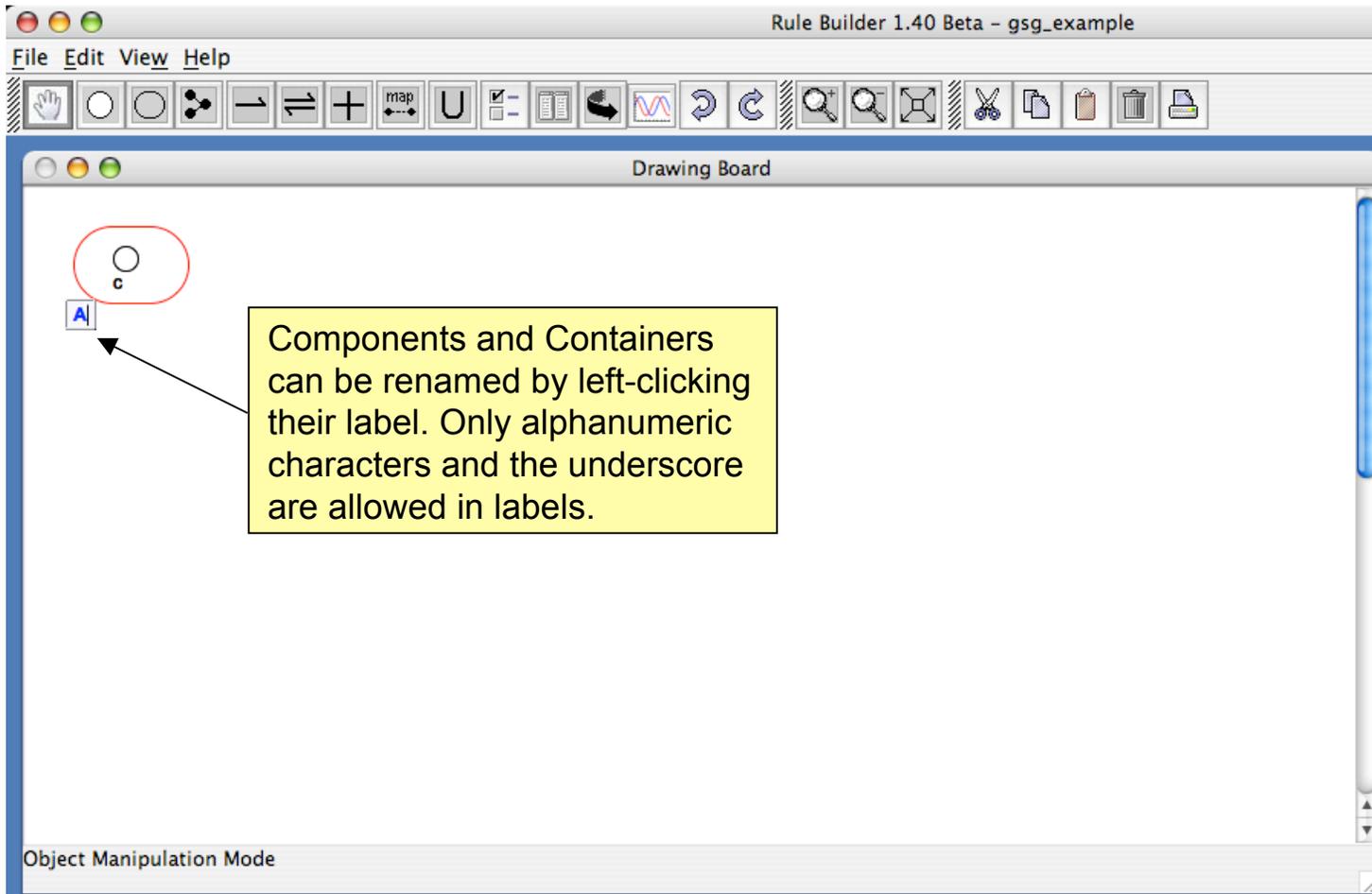
- Drawing Board:** The central area where a reaction rule is being constructed. It shows two reactants, labeled 'A' and 'B', each represented by a circle containing a smaller circle with the letter 'b'. These are followed by a plus sign and an arrow pointing to the products, which are two circles labeled 'A' and 'B' connected by a horizontal line. A yellow callout box explains: "The Drawing Board is where containers, components, edges and operators can be placed in order to create the molecules, species, reaction rules, observables, and patterns that form a BioNetGen model."
- Molecule Templates Palette:** A panel on the right side showing two molecule templates, labeled 'A' and 'B', each consisting of a circle with a smaller circle inside containing the letter 'b'. A yellow callout box states: "Defined objects, such as Molecule Templates, Species, and Reaction Rules are displayed in separate windows."
- Reaction Rules:** A panel at the bottom of the interface, currently empty.

At the bottom left, the text 'Object Manipulation Mode' is visible. The bottom of the window features a blue bar with a small icon of two overlapping windows.

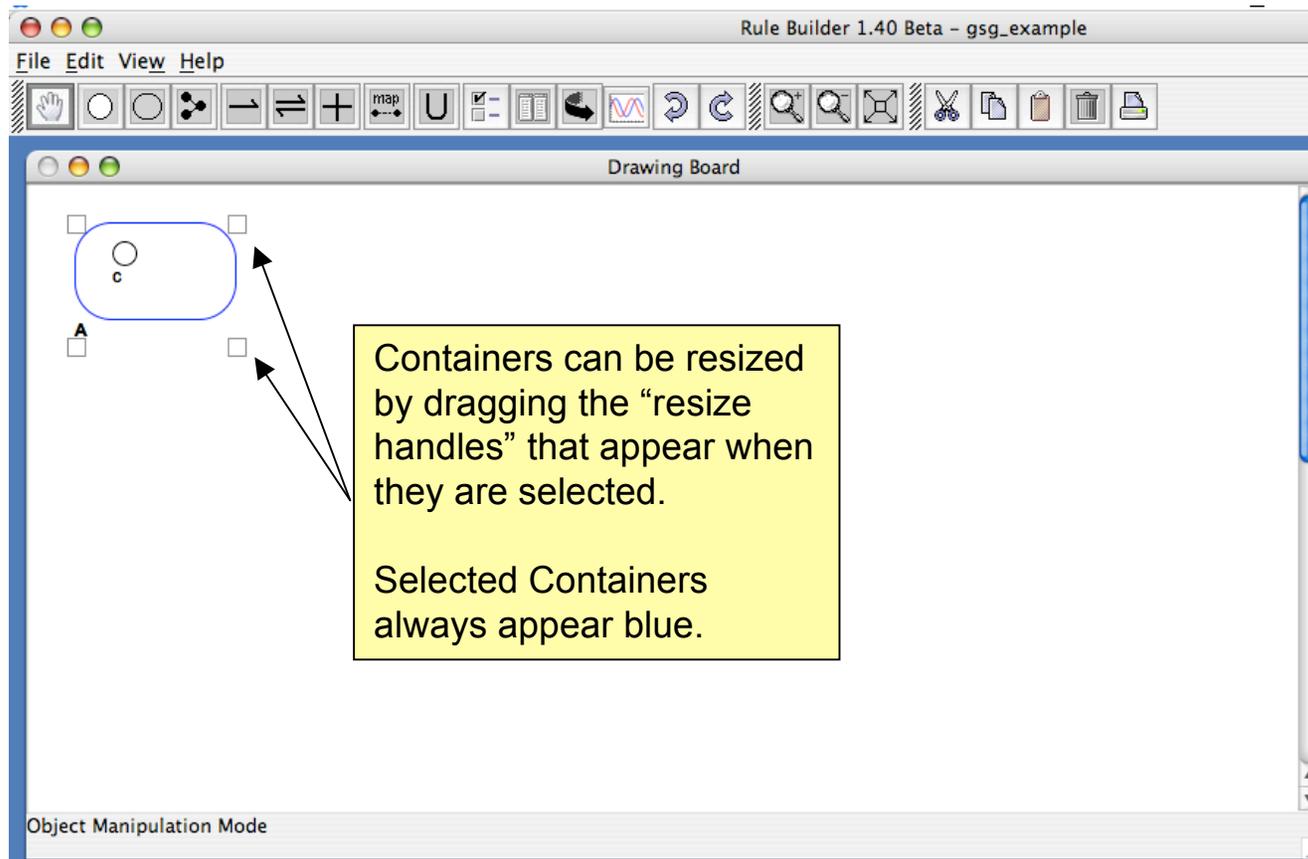
# Adding Containers and Components

The screenshot displays the Rule Builder 1.40 Beta software interface. The main window is titled "Rule Builder 1.40 Beta - gsg\_example" and features a menu bar with "File", "Edit", "View", and "Help". Below the menu bar is a toolbar with various icons for drawing and editing. The central area is the "Drawing Board", which contains a small diagram of a container labeled "c" with a component inside. A yellow callout box points to the "Add Container Mode" icon in the toolbar and contains the text: "Add Container Mode." Another yellow callout box points to the "Add Components" icon in the toolbar and contains the text: "A component is added by entering 'Add Components' mode on the toolbar and left-clicking in the Drawing Board." To the right of the Drawing Board are two panels: "Molecule Templates Palette" and "Seed Species". At the bottom of the interface is a "Reaction Rules" panel. The status bar at the very bottom indicates "Object Manipulation Mode".

# Renaming Components and Containers

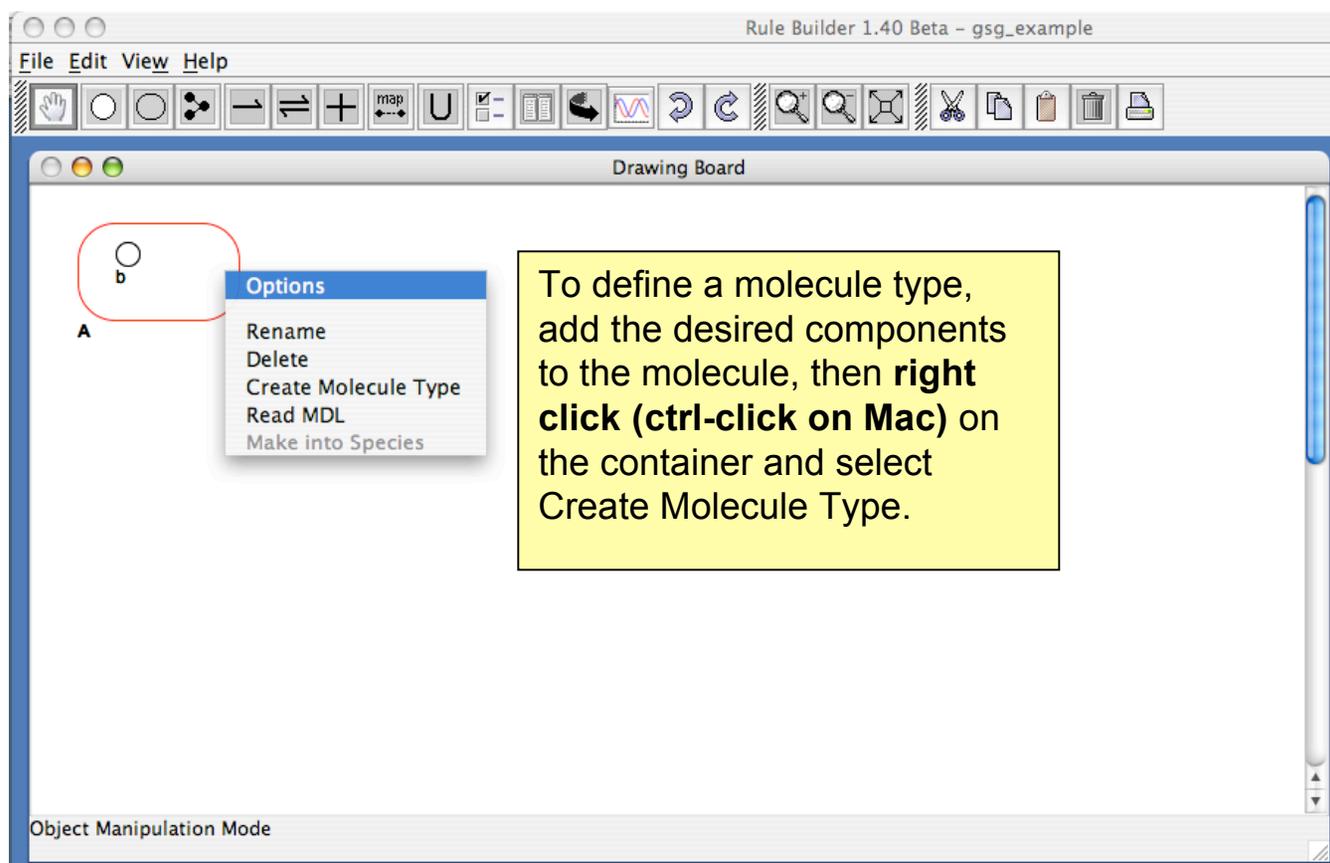


# Resizing Containers



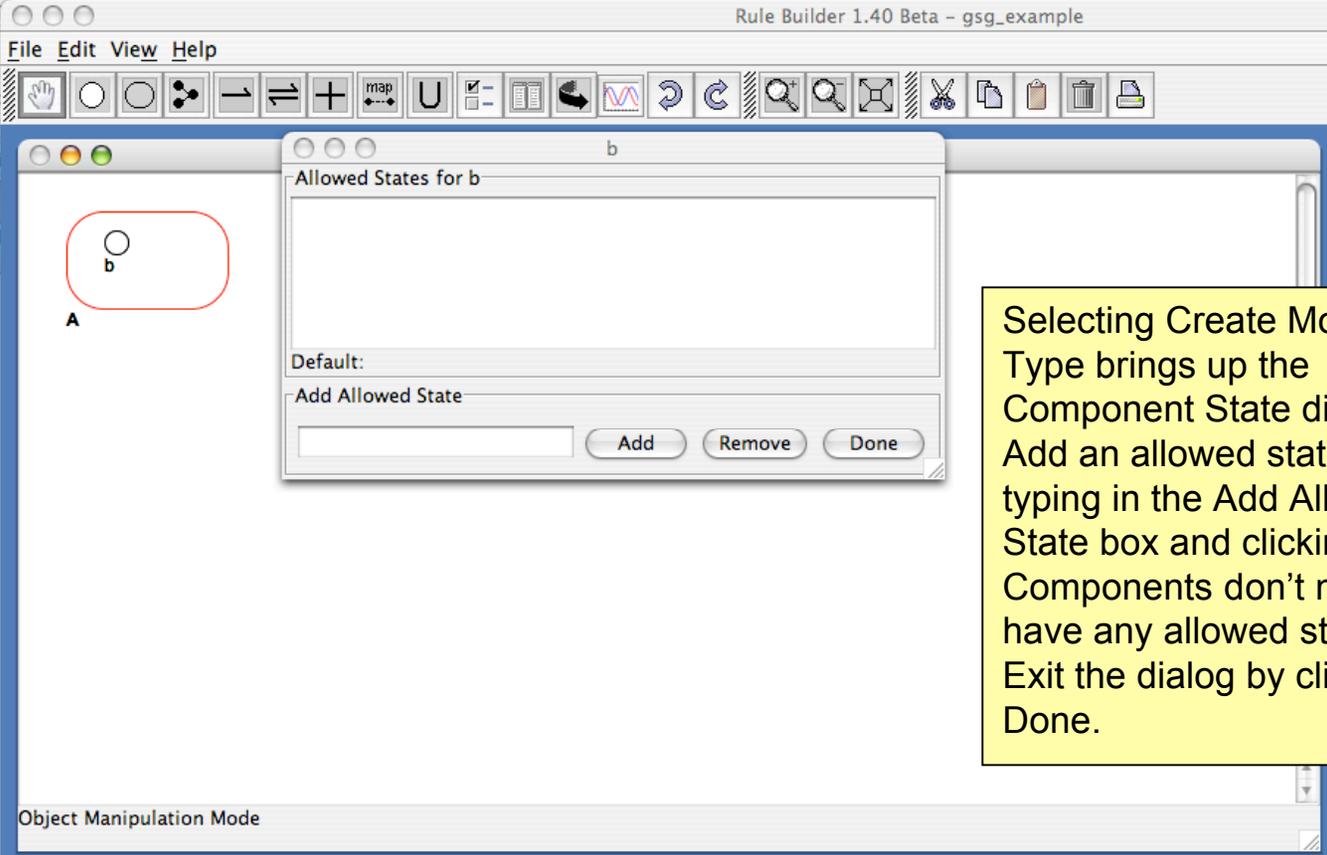
# Creating Molecule Types

Molecules used in a model have to be defined and registered as a “Molecule Type” before they can be used in reaction rules and species.



# Setting Allowed Component States

Components may take on different states to indicate conformation or covalent modification, such as phosphorylation.



The screenshot shows the 'Rule Builder 1.40 Beta - gsg\_example' application window. The main workspace contains a diagram with a component labeled 'b' inside a rounded rectangle labeled 'A'. A dialog box titled 'Allowed States for b' is open, showing a 'Default:' field and an 'Add Allowed State' section with a text input box and 'Add', 'Remove', and 'Done' buttons. The status bar at the bottom indicates 'Object Manipulation Mode'.

Selecting Create Molecule Type brings up the Component State dialog. Add an allowed state by typing in the Add Allowed State box and clicking Add. Components don't need to have any allowed states. Exit the dialog by clicking Done.

# Identifying Valid and Invalid Molecules

The screenshot displays the Rule Builder 1.40 Beta software interface. The main window is titled "Drawing Board" and contains three molecule templates labeled A, B, and A. Template A (top left) is a rounded rectangle with a small circle containing the letter 'b' inside; it is outlined in green. Template B (top right) is a rounded rectangle with a small circle containing the letter 'b' inside; it is outlined in red. Template A (bottom left) is a rounded rectangle with a small circle containing the letter 'b' inside; it is outlined with a dashed green line. To the right of the Drawing Board is a "Molecule Templates Palette" window containing a single rounded rectangle with a small circle containing the letter 'b' inside, labeled A. Below the palette is a "Seed Species" window. The software's menu bar includes "File", "Edit", "View", and "Help". The status bar at the bottom left indicates "Object Manipulation Mode".

File Edit View Help

Rule Builder 1.40 Beta - gsg\_example

Molecule Types appear here

Drawing Board

Molecule Templates Palette

Seed Species

Object Manipulation Mode

A

B

A

A

Containers matching valid types are **green**.

Containers not matching a valid type are **red**.

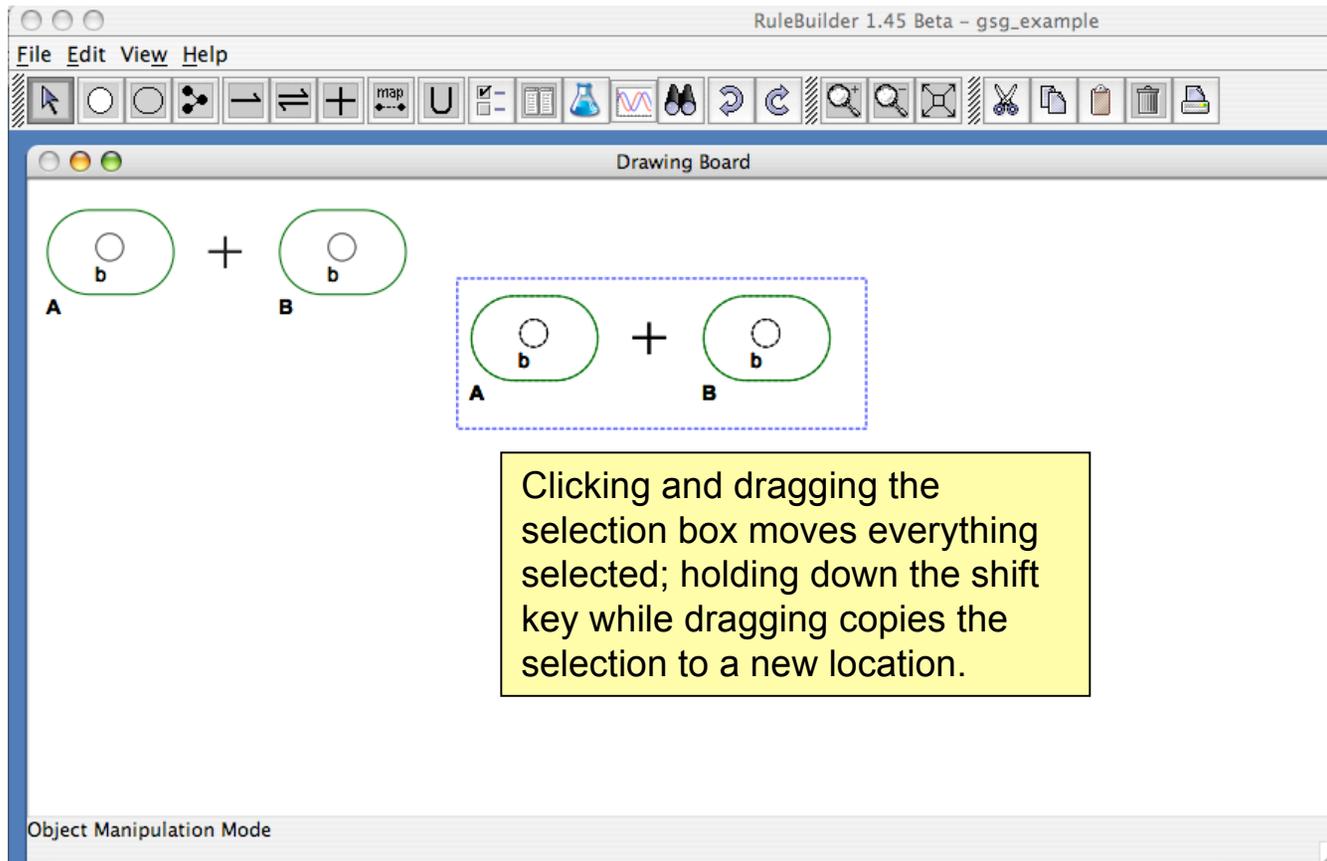
Dashed line indicates an incomplete match.

# Copying Objects with the Selection Box

Draw a box around objects on the Drawing Board to select them. Partially enclosed objects are not selected.

Object Manipulation Mode

# Copying Objects with the Selection Box



# Creating a Reaction Rule

Reaction rules are created by arranging containers and operators to construct a formula for the reaction.

The screenshot displays the 'Rule Builder 1.40 Beta - gsg\_example' application window. The main 'Drawing Board' contains two rounded rectangular containers, 'A' and 'B'. Container 'A' contains a small circle with the letter 'b' inside, and container 'B' contains a small circle with the letter 'a' inside. A red '+' operator is positioned between containers 'A' and 'B', and a red '-' operator is positioned to the right of container 'B'. Two yellow callout boxes provide explanations: one points to the '+' operator with the text 'The '+' operator separates reactants or products in a list.', and another points to the '-' operator with the text 'The arrow operator separates reactants and products.'. The software interface includes a menu bar (File, Edit, View, Help), a toolbar with various icons, and two side panels: 'Molecule Templates Palette' and 'Seed Species'. The status bar at the bottom indicates 'Object Manipulation Mode'.

# Creating a Reaction Rule

The type of arrow determines whether a reaction is reversible or irreversible.

The screenshot displays the Rule Builder 1.40 Beta software interface. The main window is titled "Rule Builder 1.40 Beta - gsg\_example" and features a menu bar with "File", "Edit", "View", and "Help". Below the menu bar is a toolbar with various icons, including a red box highlighting the irreversible arrow ( $\rightarrow$ ) and the reversible arrow ( $\rightleftharpoons$ ). The central "Drawing Board" shows a reaction rule: a rounded rectangle labeled "A" containing a small circle with the letter "b" inside, followed by a plus sign, another rounded rectangle labeled "B" containing a small circle with the letter "a" inside, and finally an irreversible arrow ( $\rightarrow$ ). To the right of the drawing board are two palettes: "Molecule Templates Palette" and "Seed Species". The "Molecule Templates Palette" contains two rounded rectangles, one with a circle labeled "b" and another with a circle labeled "a". The "Seed Species" palette is currently empty. At the bottom left of the interface, the text "Object Manipulation Mode" is visible.

# Defining Products

RuleBuilder 1.45 Beta - gsg\_example

File Edit View Help

Drawing Board

A + B → A B

Use Add Edges to create a bond between the components

Object Manipulation Mode

# Defining Products

RuleBuilder 1.45 Beta - gsg\_example

File Edit View Help

Drawing Board

A + B → A B

Create the bond by clicking on the two components to be linked.

Add Edge Mode

# Creating the Rule

The screenshot shows the RuleBuilder 1.45 Beta software interface. The main window is titled "RuleBuilder 1.45 Beta - gsg\_example" and contains a "Drawing Board" window. On the drawing board, a chemical rule is shown: two separate green ovals labeled 'A' and 'B', each containing a smaller white circle with the letter 'b' inside. These are followed by a plus sign and an arrow pointing to a single green oval containing two such 'b' circles, labeled 'A' and 'B' respectively. A blue dashed selection box encloses the entire rule diagram. A context menu is open over the diagram, listing three actions: "Make Rule" (highlighted in blue), "Make Species", and "Make Observable".

File Edit View Help

RuleBuilder 1.45 Beta - gsg\_example

Drawing Board

A + B → A B

Actions

- Make Rule
- Make Species
- Make Observable

Draw a selection box enclosing the rule, right-click (ctrl-click on Mac), and select Make Rule.

If Make Rule is grayed out, make sure all of the objects are valid and the box is enclosing all of the elements.

Object Manipulation Mode

# Make Rule Dialog

The screenshot shows the 'RuleBuilder 1.45 Beta - gsg\_example' window. The 'Drawing Board' contains a reaction diagram with a reactant 'b' (a circle with a smaller circle inside) and a product 'b' (a circle with a smaller circle inside). A plus sign is between them. A 'Reaction Properties' dialog box is open, showing the following fields:

- Rule Name: [ ]
- Label: Rule1
- Forward Rate Name: kp1
- Forward Rate Rate: [ ]
- BNGL Annotation: [ ]

Buttons for 'Done' and 'Cancel' are at the bottom of the dialog. A yellow callout box with an arrow pointing to the 'Rate' field contains the following text:

Set Rule Name, rate constants, and optional annotation in the dialog box.

For a parameter being used for the first time, set a numerical value in the Rate box.

Object Manipulation Mode

# Reaction Rules Window

The screenshot displays the RuleBuilder 1.45 Beta software interface. The main window is titled "RuleBuilder 1.45 Beta - gsg\_example" and contains several panels:

- Drawing Board:** Shows a chemical reaction rule. On the left, two separate molecules are shown, each consisting of a circle with a smaller circle inside, labeled 'A' and 'B' respectively. A plus sign is between them. An arrow points to the right, where the two molecules are now connected by a horizontal line, still labeled 'A' and 'B'.
- Molecule Templates Palette:** Located on the right side, it contains two templates: one labeled 'A' and one labeled 'B', each represented by a circle with a smaller circle inside.
- Seed Species:** A panel below the Molecule Templates Palette, currently empty.
- Reaction Rules Window:** Located at the bottom, it shows the same reaction rule as the Drawing Board, but with the rate constant 'kp1' above the arrow. The label 'Rule1' is positioned below the first molecule on the left.

A yellow callout box with a black border is positioned over the Reaction Rules Window, containing the text: "Rule now appears in the Reaction Rules Window."

# Defining Seed Species

The network is defined by applying the reaction rules to a set of seed species.

RuleBuilder 1.45 Beta - gsg\_example

File Edit View Help

Drawing Board

Molecule Templates Palette

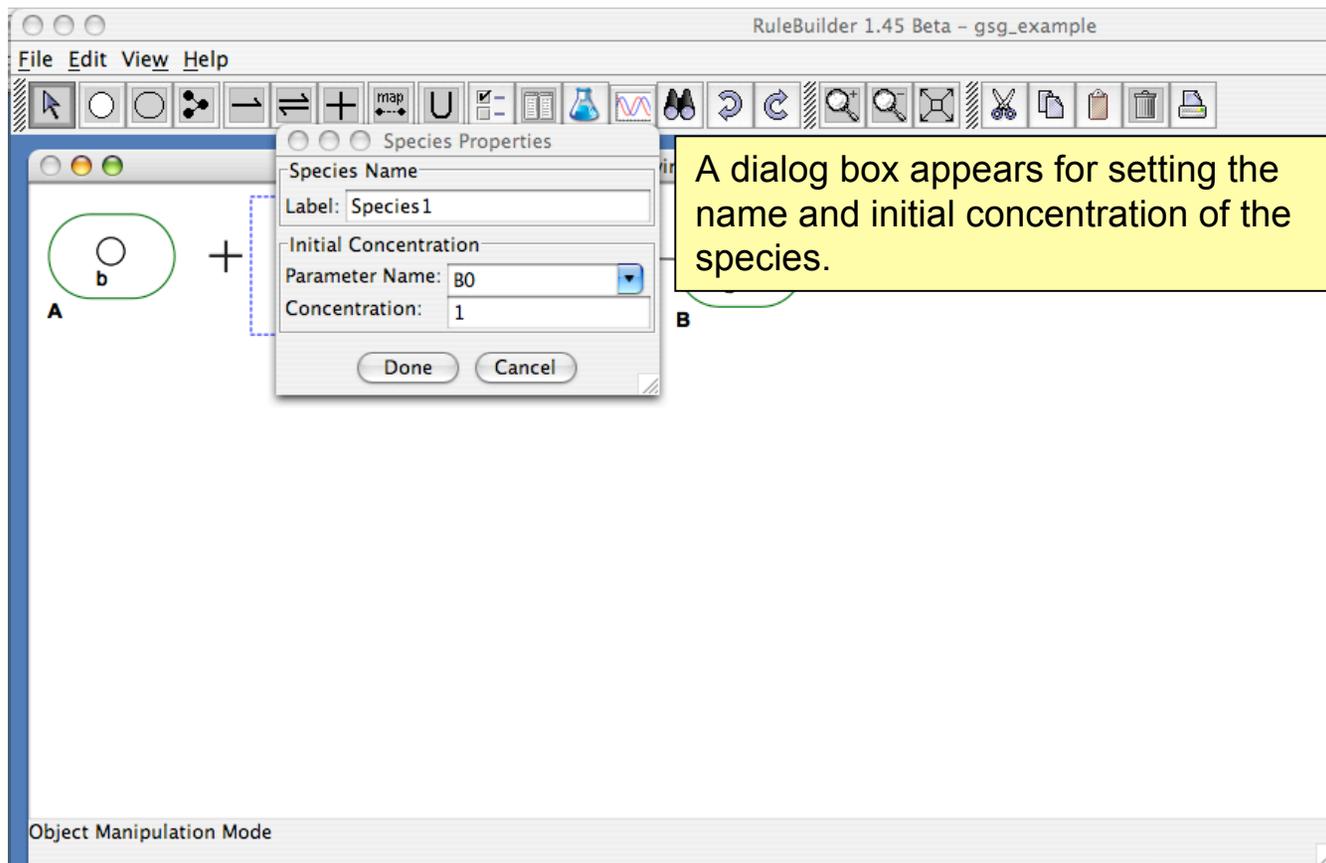
Seed Species

Object Manipulation M

Draw a selection box around a connected set of molecules and right-click (ctrl-click on Mac) to define a species.

All items in selection box should have solid green lines, indicating the the molecules are fully defined.

# Species Dialog Box



# Seed Species Window

The screenshot displays the RuleBuilder 1.45 Beta interface. The main window, titled "RuleBuilder 1.45 Beta - gsg\_example", contains a "Drawing Board" and a "Molecule Templates Palette".

The Drawing Board shows a chemical reaction: two separate molecules, labeled A and B, each consisting of a small circle 'b' inside a larger oval, are added together (+). An arrow points to the product, which consists of two such molecules, A and B, connected by a horizontal line.

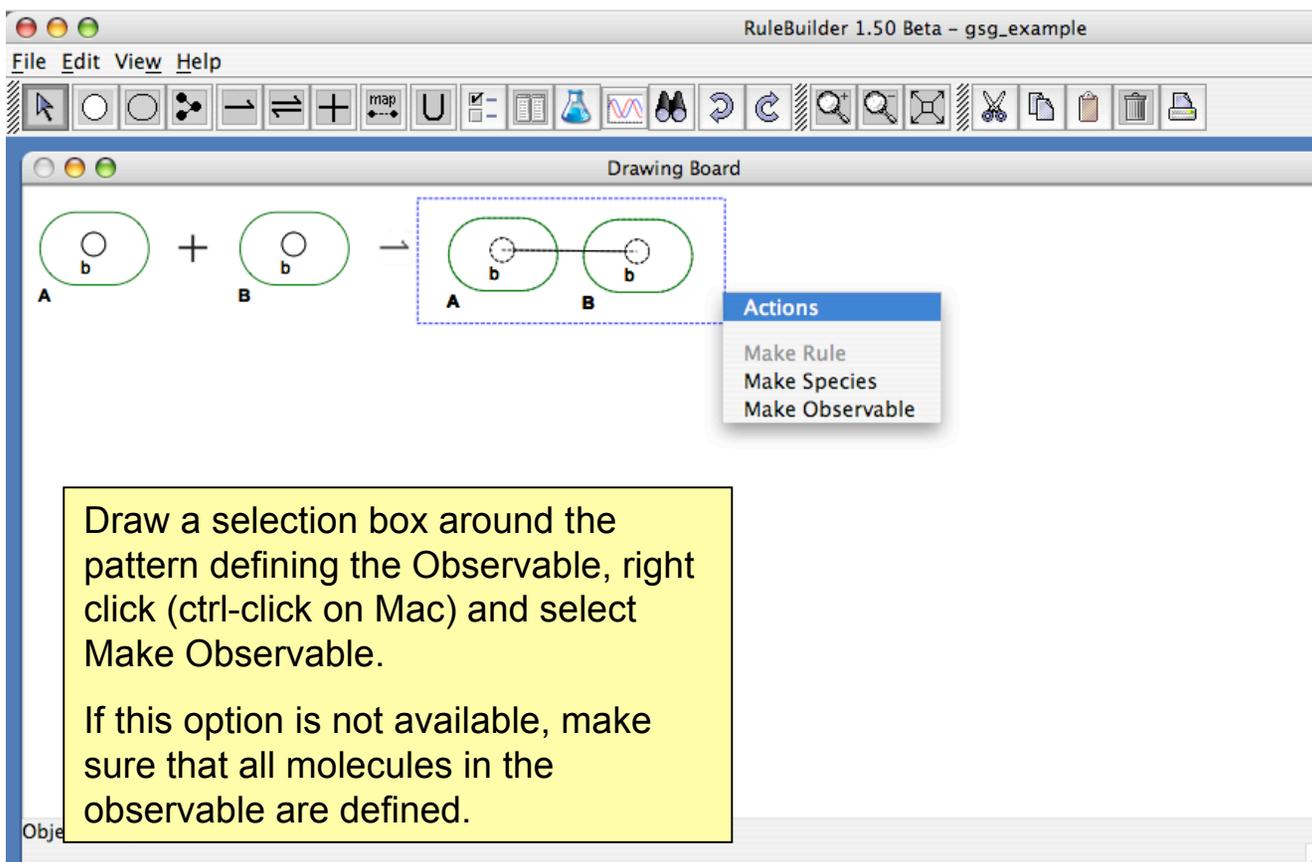
The Molecule Templates Palette on the right shows two templates: A (a small circle 'b' inside a larger oval) and B (a small circle 'b' inside a larger oval).

The Seed Species window, located below the Molecule Templates Palette, shows two species: A Species0 and B Species1. Each species is represented by a small circle 'b' inside a larger oval. A yellow callout box with the text "New species appears in the Seed Species Window." has an arrow pointing to the B Species1 entry.

At the bottom left of the interface, the text "Object Manipulation Mode" is visible.

# Defining Observables

Observables are concentration sums over species with particular properties and correspond to model outputs, such as total phosphorylation of a protein.



The screenshot shows the RuleBuilder 1.50 Beta software interface. The main window is titled "RuleBuilder 1.50 Beta - gsg\_example" and contains a "Drawing Board" window. On the drawing board, a chemical reaction is shown: two molecules, labeled A and B, each containing a smaller circle labeled 'b', are combined to form a single molecule consisting of two such units connected by a horizontal line. A dashed blue selection box is drawn around the product molecule. A context menu is open over the product, with the following options: "Make Rule", "Make Species", and "Make Observable".

Draw a selection box around the pattern defining the Observable, right click (ctrl-click on Mac) and select Make Observable.

If this option is not available, make sure that all molecules in the observable are defined.

# Make Observables Dialog

RuleBuilder 1.50 Beta - gsg\_example

File Edit View Help

Properties

Name:

Type: Molecules

Done

**Set Rule Name and Type.**

Type **Molecules** weights the concentration of each matching species by the number of times the defined pattern matches the species.

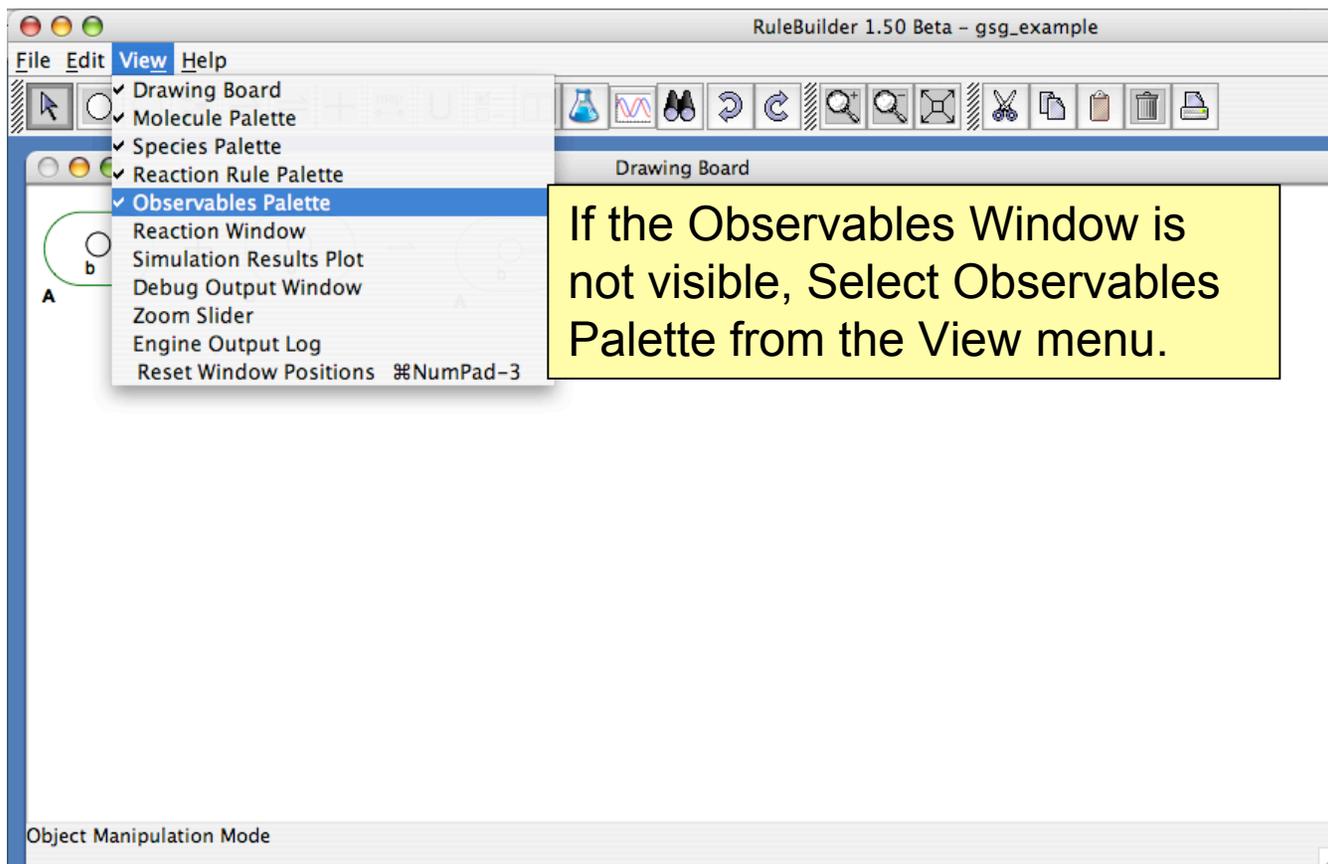
Use this for quantities like total phosphorylation of a site on a protein or total number of receptors in aggregates.

Type **Species** gives unit weight to the concentration of each matching species.

Use this type to get the concentration of complexes of a particular type.

Object Manipulation Mode

# Observables Window



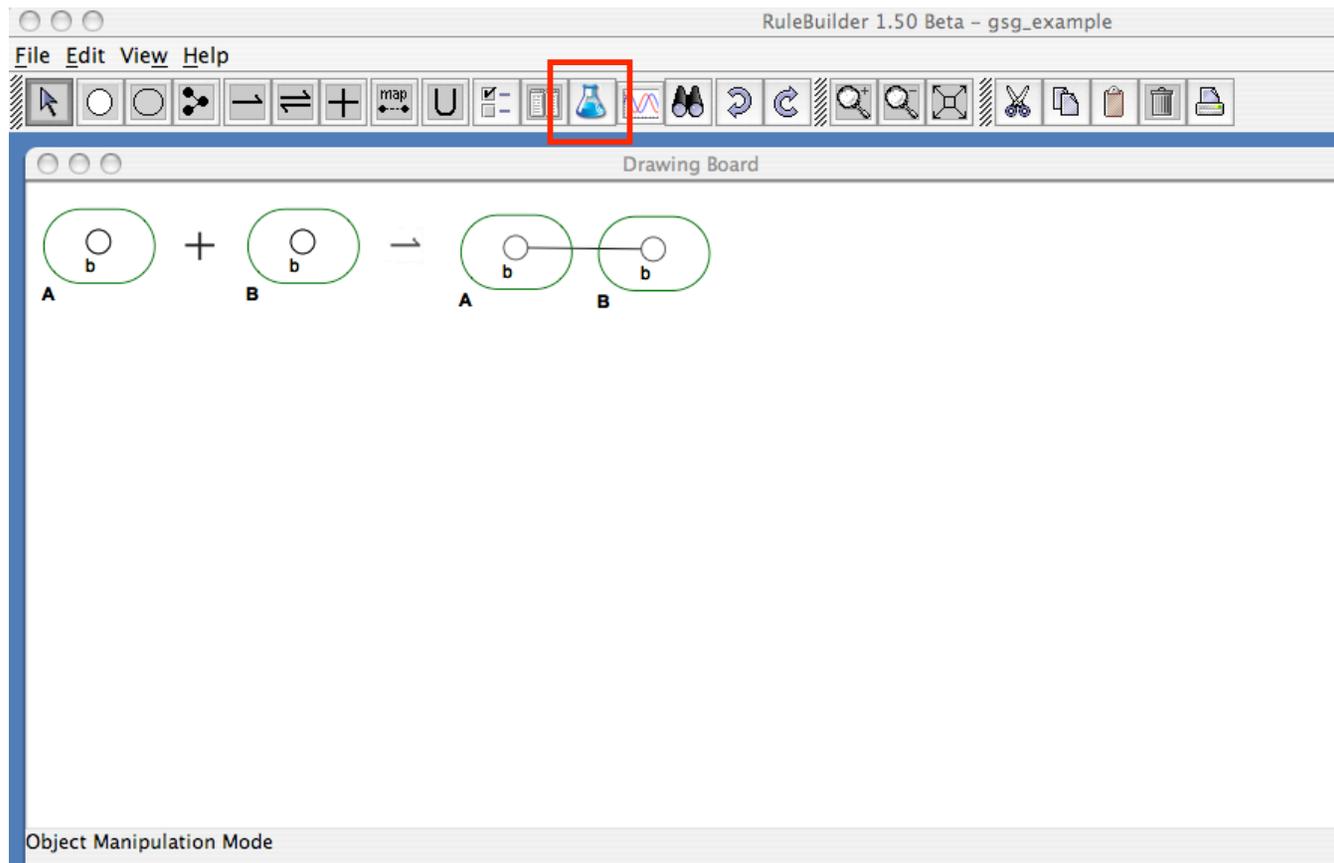
# Observables Window

The screenshot displays the RuleBuilder 1.50 Beta software interface. The main window is titled "RuleBuilder 1.50 Beta - gsg\_example" and contains several panels:

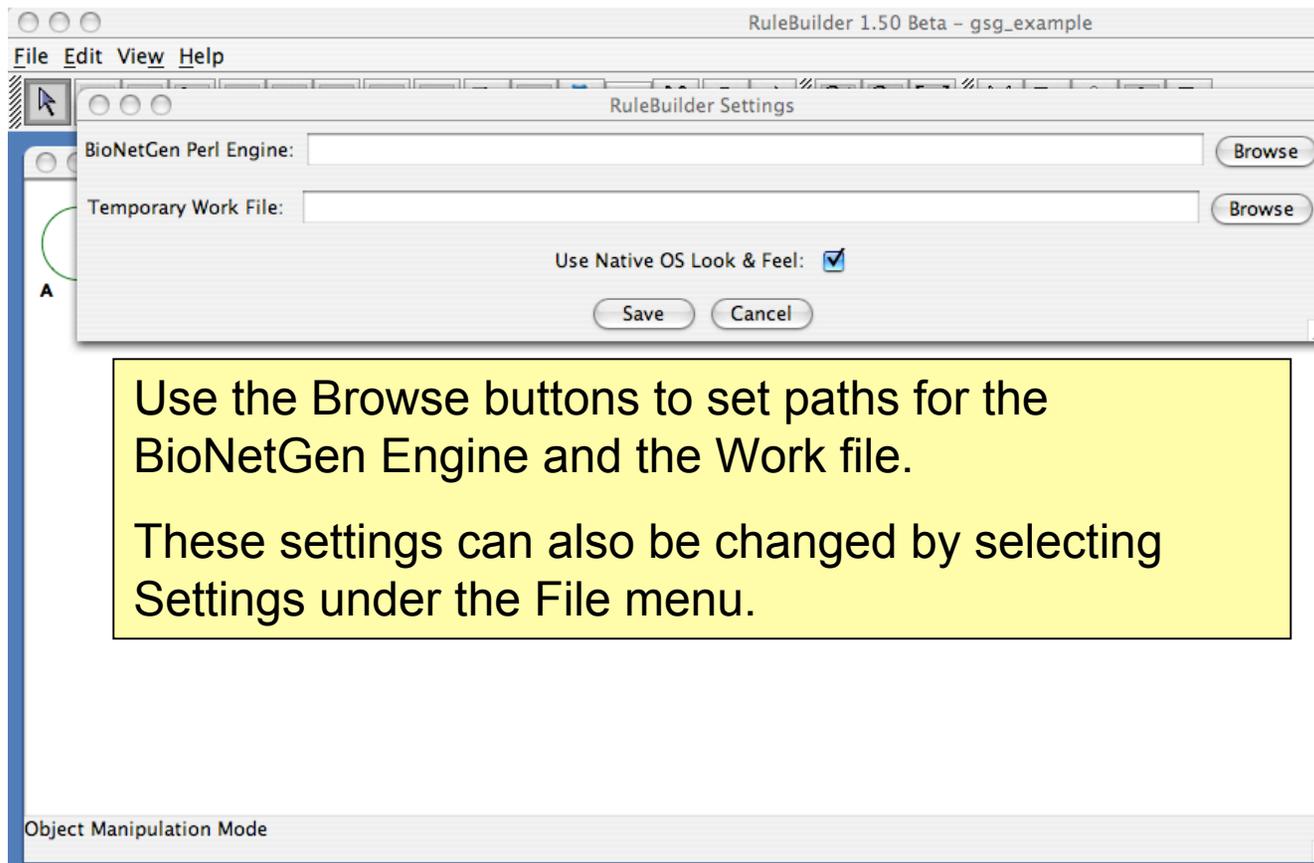
- File Edit View Help**: A menu bar at the top.
- Drawing Board**: A central workspace showing a chemical reaction rule. On the left, two separate molecules, labeled "A" and "B", each consisting of a circle with a smaller circle inside and the letter "b" below it, are separated by a plus sign. An arrow points to the right, where the two molecules are now connected by a horizontal line, with "A" and "B" labels below them.
- Molecule Templates Palette**: A panel on the right side containing two templates, labeled "A" and "B", identical to the molecules in the drawing board.
- Seed Species**: A panel below the palette containing two species, labeled "Species0" and "Species1", also identical to the templates.
- Object Manipulation Mode**: A horizontal bar below the drawing board.
- Reaction Rules**: A panel at the bottom left showing the reaction rule "Rule1" with the same visual representation as the drawing board.
- Observables**: A panel at the bottom right, highlighted with a yellow background and labeled "The Observables Window". It displays the connected molecule from the drawing board, with labels "A" and "B" below it, and "AB" centered below the two molecules.

# Running the Model

Once Reaction Rules, Seed Species, and Observables (optional) have been defined, the model can be simulated by pressing Run BioNetGen button.

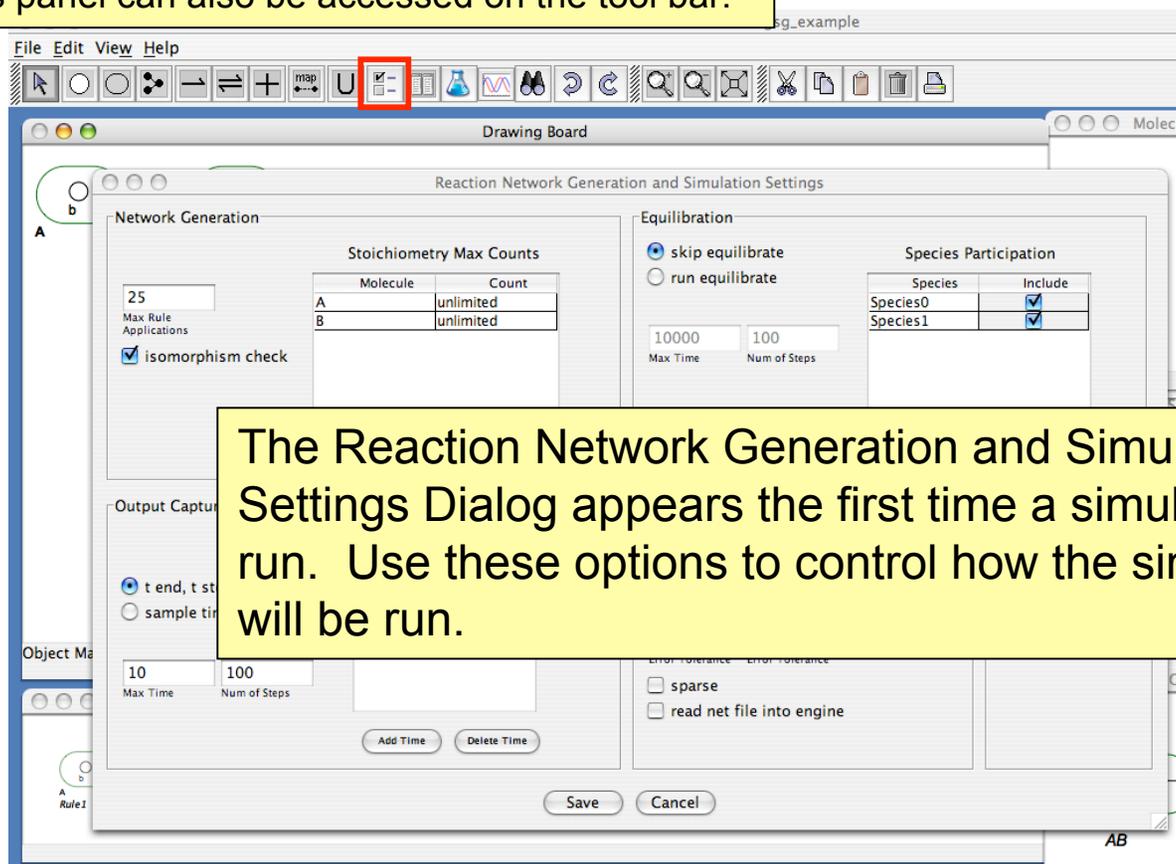


# BioNetGen Engine Settings



# The SimConfig Panel

This panel can also be accessed on the tool bar.



The Reaction Network Generation and Simulation Settings Dialog appears the first time a simulation is run. Use these options to control how the simulation will be run.

# The SimConfig Panel

RuleBuilder 1.50 Beta - gsg\_example

File Edit View Help

Drawing Board

Reaction Network Generation and Simulation Settings

Network Generation

25  
Max Rule Applications

isomorphism check

Molecule	Count
A	unlimited
B	unlimited

Equilibration

skip equilibrate  
 run equilibrate

10000 100  
Max Time Num of Steps

Species Participation

Species	Include
Species0	<input checked="" type="checkbox"/>
Species1	<input checked="" type="checkbox"/>

Options

SBML output

1e-12 1e-12  
Abs Integration Error Tolerance Rel Integration Error Tolerance

sparse  
 read net file into engine

10 100  
Max Time Num of Steps

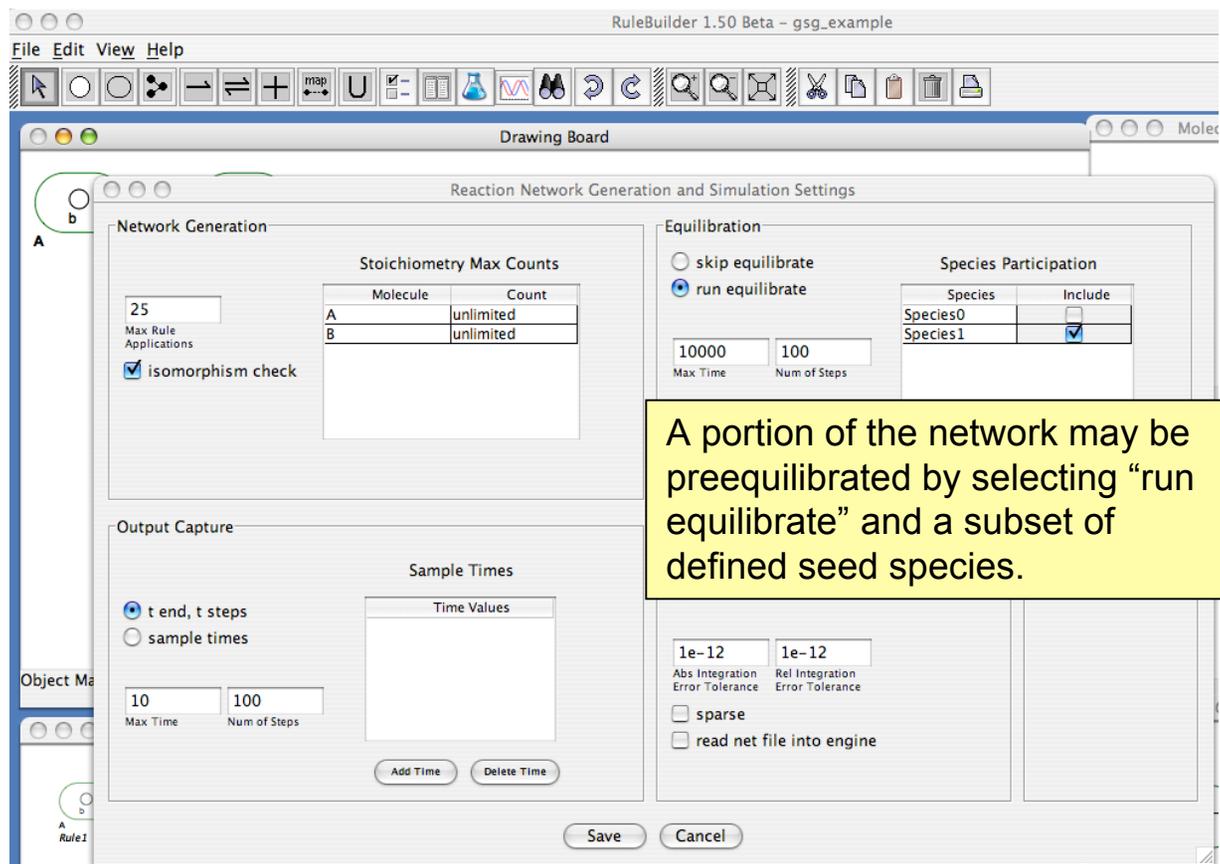
Add Time Delete Time

Save Cancel

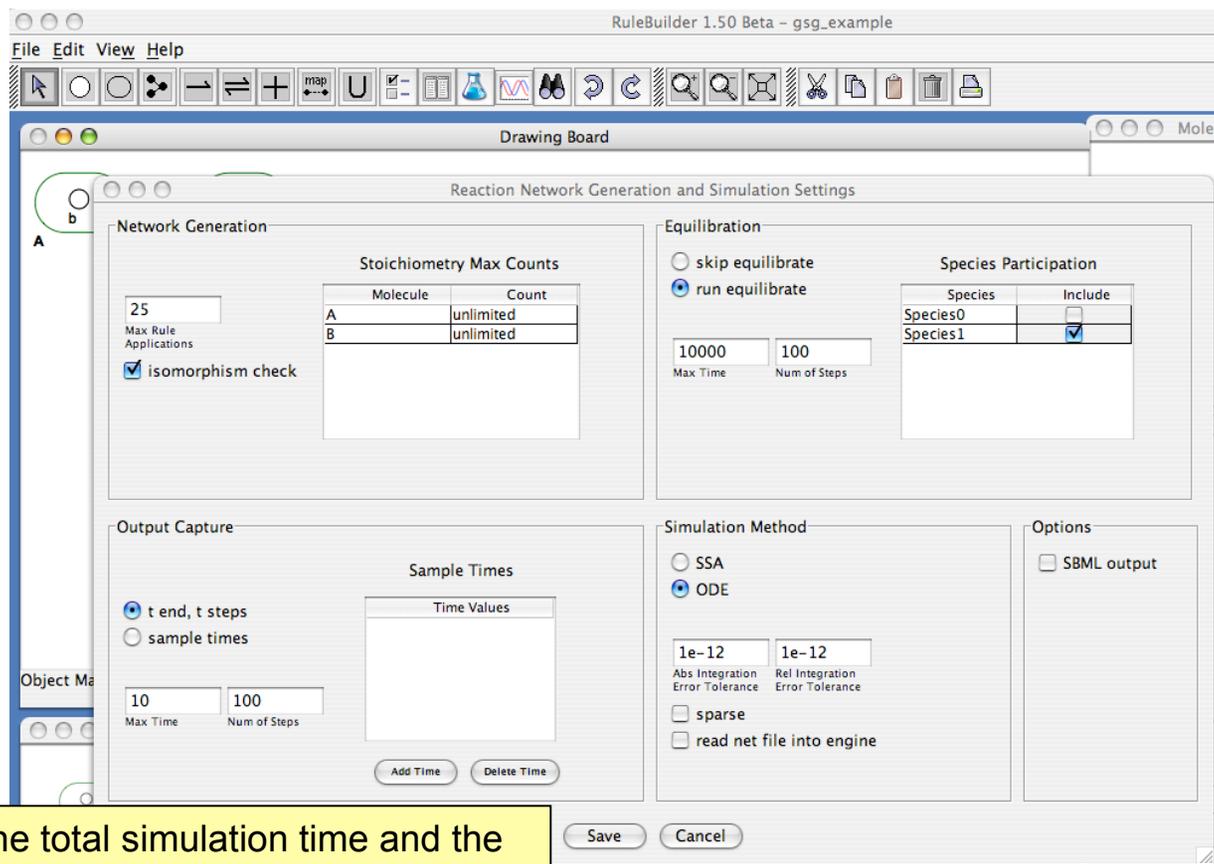
AB

The size of complexes and the reaction network can be limited by setting maximum values for the stoichiometry of molecules.

# The SimConfig Panel

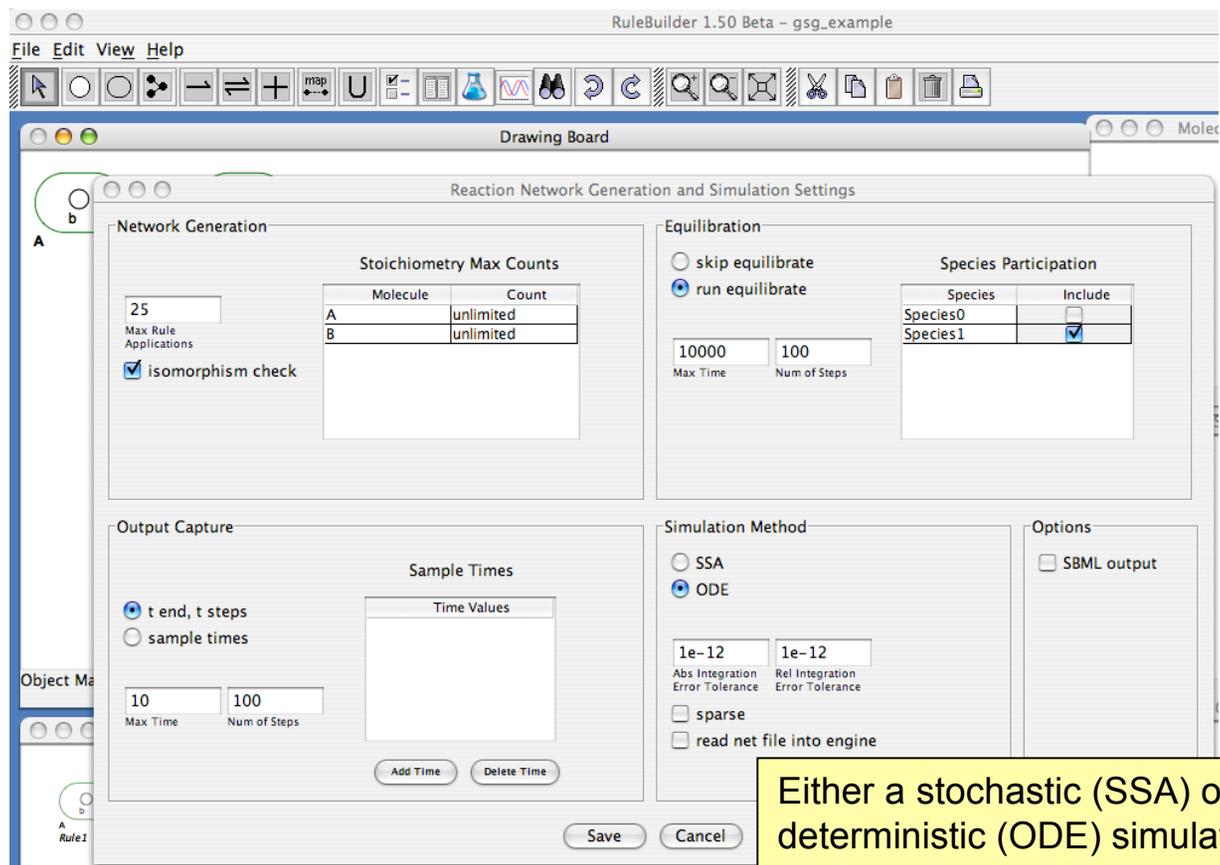


# The SimConfig Panel



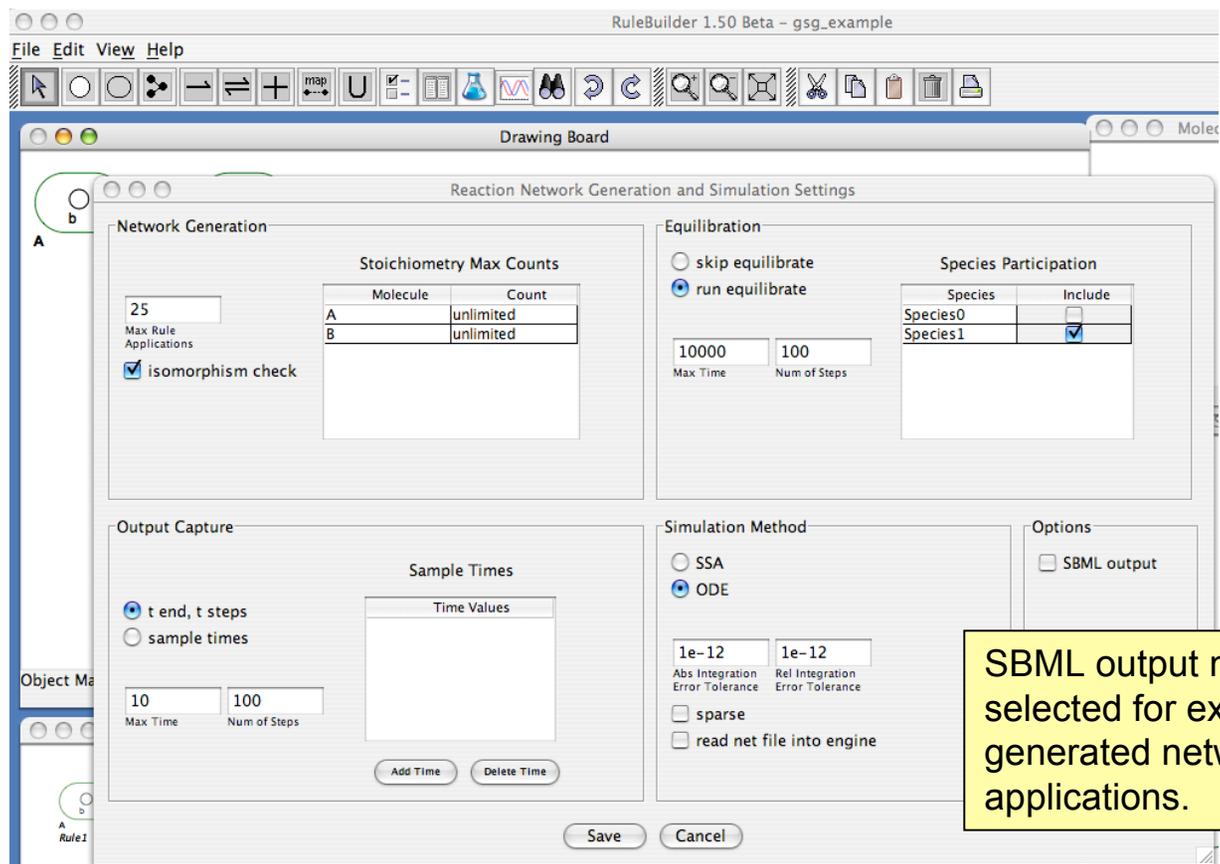
The total simulation time and the times at which concentrations are sampled are set here.

# The SimConfig Panel



Either a stochastic (SSA) or a deterministic (ODE) simulation method may be chosen.

# The SimConfig Panel



# The Log Window

Running the simulation brings up the BioNetGen Output Log or Log Window

RuleBuilder 1.40 Beta - gsg\_example

Drawing Board  
BioNetGen Output Log

7.70	594	646
7.80	596	648
7.90	598	650
8.00	600	652
8.10	602	654
8.20	604	656
8.30	606	658
8.40	608	663
8.50	611	666
8.60	613	668
8.70	615	670
8.80	617	672
8.90	619	674
9.00	621	676
9.10	623	678
9.20	625	680
9.30	627	682
9.40	630	685
9.50	632	687
9.60	634	689
9.70	636	691
9.80	638	693
9.90	640	695
10.00	642	697

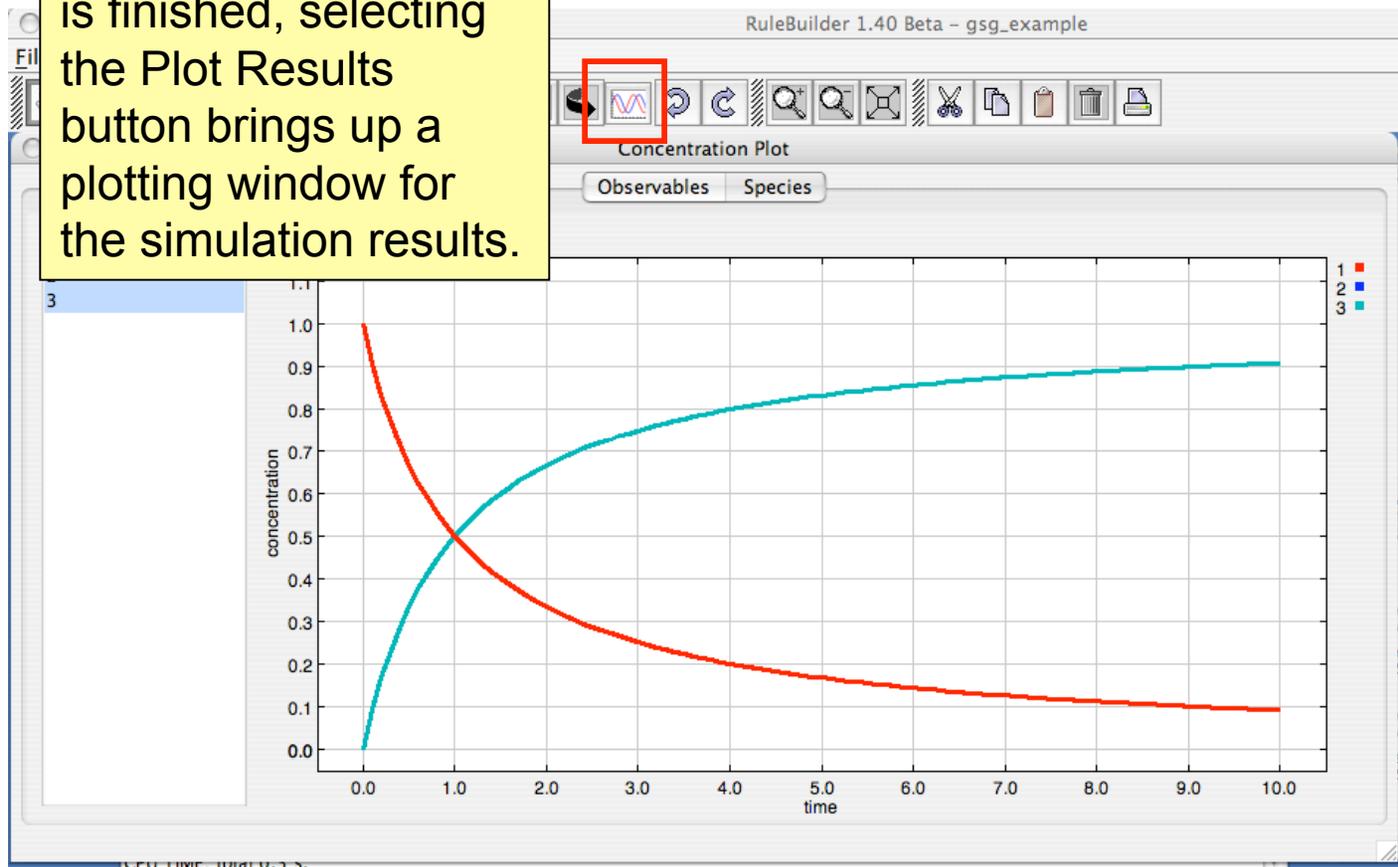
Time course of concentrations written to file /Users/faeder/shared/Projects/BioNetGen\_develop/temp.cdat.  
Propagation took 0.00 CPU seconds  
Program times: 0.01 CPU s 0.00 clock s  
Updating species concentrations from /Users/faeder/shared/Projects/BioNetGen\_develop/temp.cdat  
CPU TIME: simulate\_ode 0.0 s.  
Finished processing file /Users/faeder/shared/Projects/BioNetGen\_develop/temp.bngl  
CPU TIME: total 0.3 s.

Object Ma

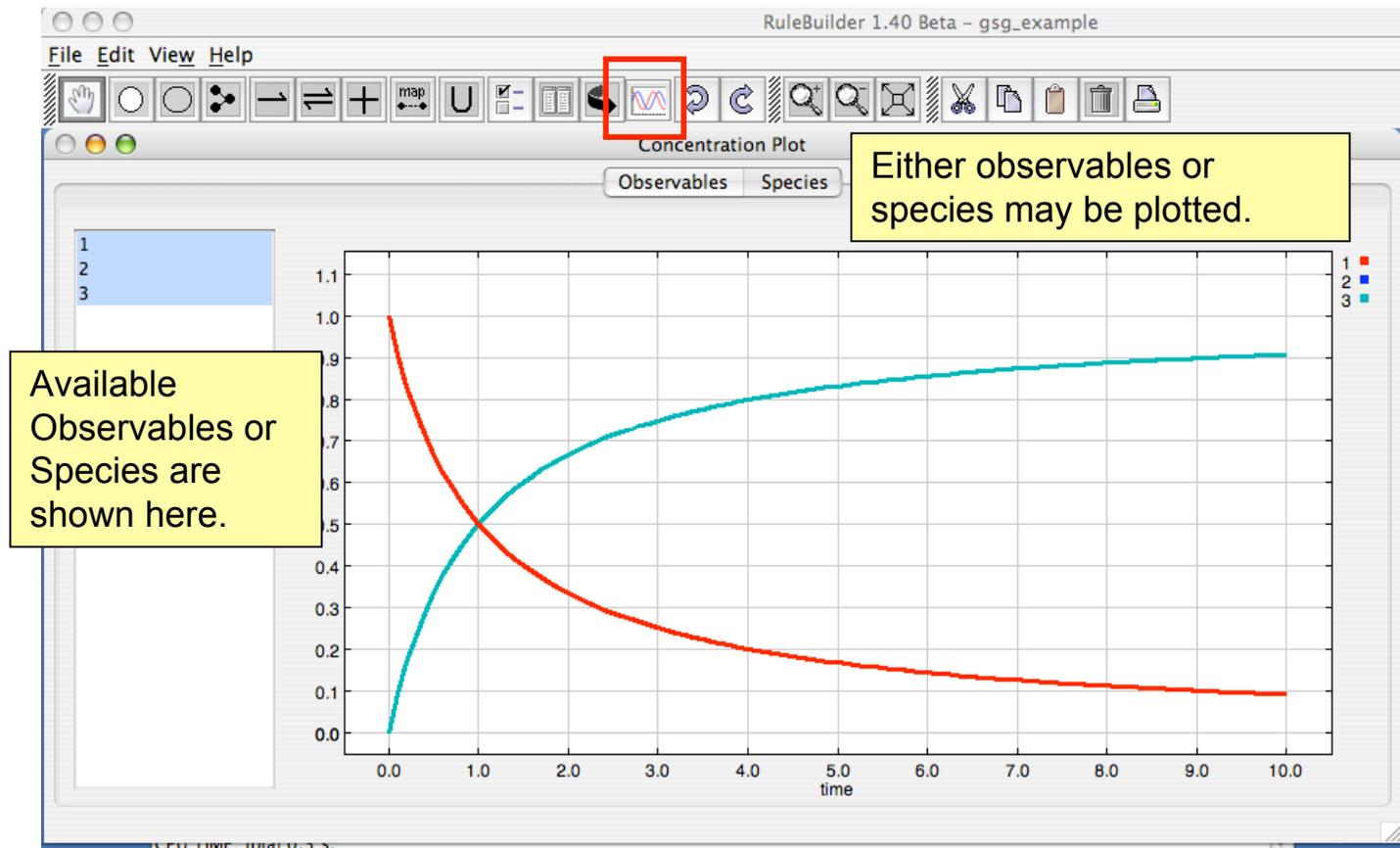
The Log Window displays the output of BioNetGen.

# Plotting the Results

Once the simulation is finished, selecting the Plot Results button brings up a plotting window for the simulation results.



# Plotting the Results



# Plotting the Results

