

iBioSim User's Manual

Chris J. Myers, Nathan Barker, Kevin Jones, Hiroyuki Kuwahara,
Curtis Madsen, Nam Nguyen, Tyler Patterson, Nicholas Roehner, Jason Stevens

August 26, 2011

Contents

1	Introduction	2
2	Project Management	3
2.1	Creating and Opening Projects	4
2.2	Creating and Opening Models and Graphs	5
2.3	Importing Models	6
2.4	Exporting Models and Graphs	7
2.5	Editing Project Objects and Creating Tool Views	8
3	Model Editor	9
3.1	Species	12
3.2	Reactions	14
3.3	Components	18
3.4	Promoters	20
3.5	Influences	21
3.6	Compartments	24
3.7	Parameters	26
3.8	Definitions	27
3.9	Assignments	28
3.10	Properties	30
3.11	Events	31
4	SBOL Browser	33
5	Analysis Tool	35
5.1	Simulation Options	35
5.2	Abstraction Options	38
5.3	Schematic	40
5.4	Parameters	43
5.5	SBML Elements	43
6	Learn Tool	44
7	TSD Graph Editor	47
8	Histogram Graph Editor	50
9	Preferences	52
10	Mathematical Formulas	54
11	Continuous Stochastic Logic (CSL) Formulas	54
12	Time Series Data Format	55
13	Tutorial	55
14	Reporting Bugs and Feature Requests	55

1 Introduction

iBioSim has been developed for the modeling, analysis, and design of genetic circuits. While the primary target of **iBioSim** is models of genetic circuits, models representing metabolic networks, cell-signaling pathways, and other biological and chemical systems can also be analyzed. Recently, modeling and visualization support has been added for static multi-cellular and spatial models as well. It is capable of importing and exporting models specified using the *Systems Biology Markup Language* (SBML). It can import all levels and versions while being able to export Level 2 Version 4 or Level 3 Version 1. It supports all SBML modeling constructs except the *delay* function and some types of *fast* reactions. It was the first tool to produce correct results for all examples in the SBML benchmark suite. It has also been tested successfully on the stochastic benchmark suite and the curated models in the *BioModels database*. Finally, it is one of the first tools to also support the *Synthetic Biology Open Language* (SBOL), an emerging standard for information exchange in synthetic biology. **iBioSim** includes the following components:

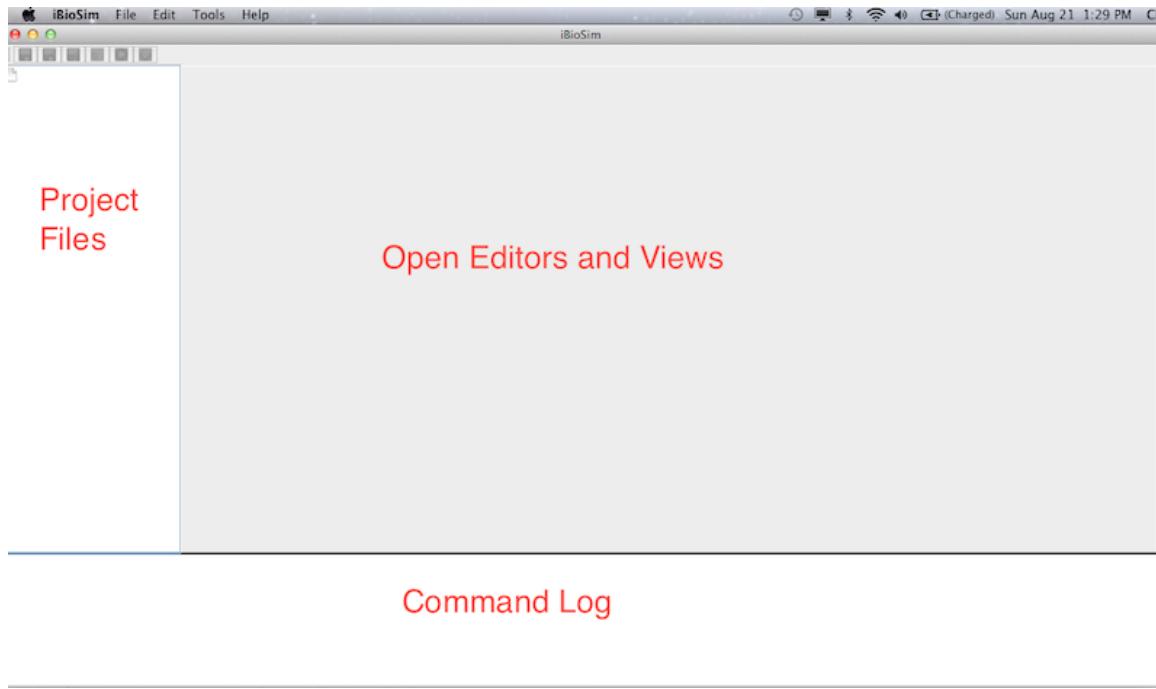
- Model Editor - a tool to create a model of a genetic circuit or other biological system.
- SBOL Browser - a tool to view SBOL files and associate DNA components to model elements.
- Analysis Tool - an abstraction-based ODE, Monte Carlo, and Markov analysis tool.
- Learn Tool - a tool to learn a model from *time series data* (TSD).
- TSD Graph Editor- a tool to visualize TSD files.
- Histogram Graph Editor - a tool to visualize probability data.

Credits

The iBioSim tool is being developed at the University of Utah by Chris Myers, Nathan Barker, Kevin Jones, Hiroyuki Kuwahara, Curtis Madsen, Nam Nguyen, Tyler Patterson, Nicholas Roehner, and Jason Stevens. Nathan Barker is now with Southern Utah University, Kevin Jones is now with Raytheon, Hiroyuki Kuwahara is now with Carnegie Mellon University, and Nam Nguyen is now with the University of Texas in Austin.

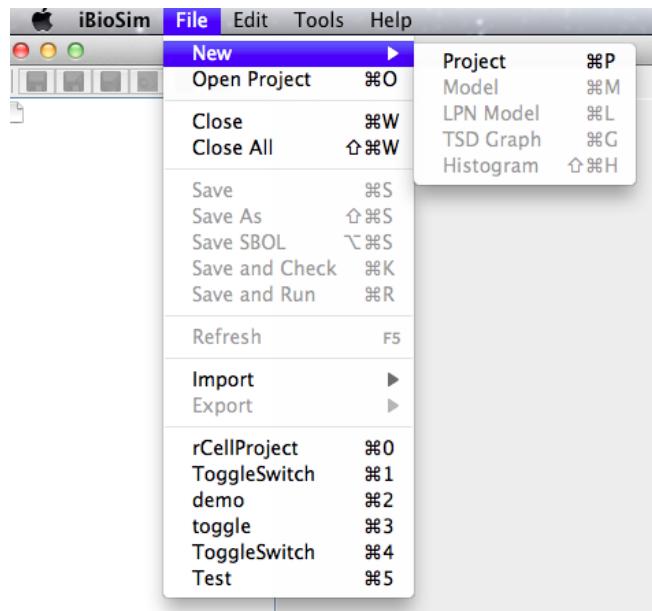
2 Project Management

Within iBioSim, all files are collected within projects. A project is a collection of models, analysis views, learn views, and graphs. As shown below, iBioSim displays all project files on the left; the open models, views, and graphs on the right; and a log of all external commands on the bottom. The menu bar is located on the top of the window in the Windows and Linux versions. It is located on the top of the screen in the MacOS version.



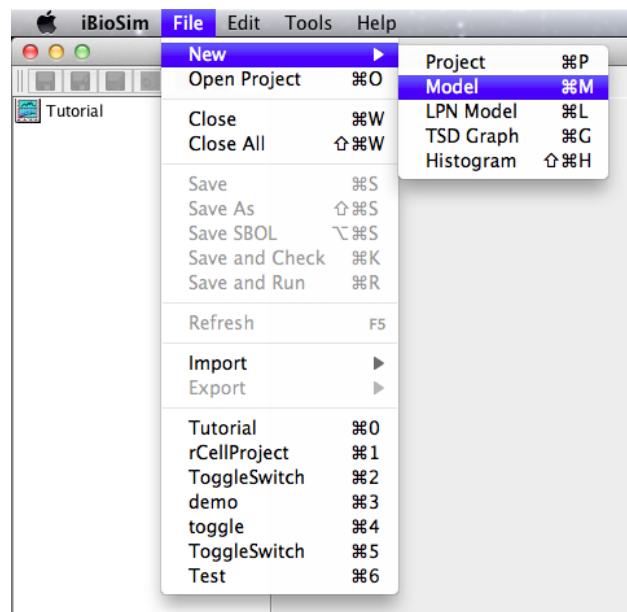
2.1 Creating and Opening Projects

To create a new project, select New → Project from the File menu as shown below. You will then be prompted to browse to a desired location and to give a name to the project directory. After you do this, click the new button and a new project directory will be created. To open a project, select Open → Project from the File menu. You will then be prompted to browse to a project directory to open, and clicking open will open the project. You may also open a project by selecting one of your ten most recently opened projects by selecting the project name shown in the File drop down menu shown below.



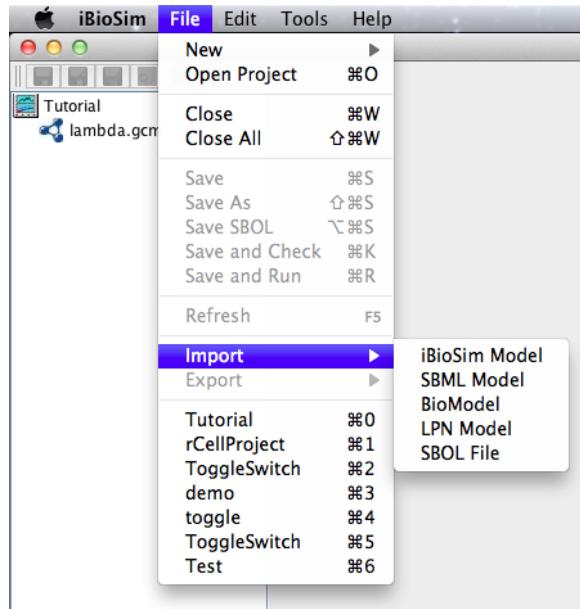
2.2 Creating and Opening Models and Graphs

After you have created or opened a project, you can create a new model or graph to add to the project. To create a new model, select New → Model from the File menu as shown below. You will then be prompted to enter a model ID. At this point, a Model editor (see Section 3) will open in a new tab. To create a new LPN model, select New → LPN Model from the File menu. You will then be prompted to give a model ID. At this point, an LPN model editor will open in a new tab. To create a new TSD graph, select New → TSD Graph from the File menu. You will then be prompted to give a name to the TSD graph. At this point, a TSD graph editor (see Section 7) will open in a new tab. To create a new histogram, select New → Histogram from the File menu. You will then be prompted to give a name to the histogram. At this point, a histogram editor (see Section 8) will open in a new tab. Once a model or graph is created, it can be opened again later by right-clicking on the object in the project window and selecting “View/Edit” or, alternatively, double-clicking on the object. Note that a model can be opened in either a graphical or textual editor. An open model or graph can be closed by either clicking on the “X” in the tab or by selecting File → Close. The File → Close All option will close all tabs.

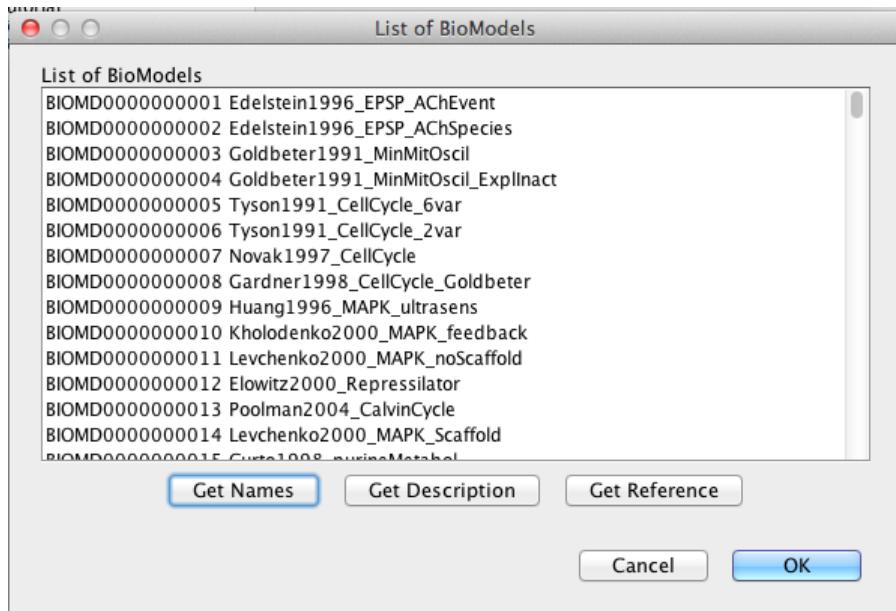


2.3 Importing Models

You can also import models into the current working project. These can be models from other iBioSim projects, models in the *Systems Biology Markup Language* (SBML), models from the *BioModels database*, LPN models, or a *Synthetic Biology Open Language* (SBOL) file (see Section 4). To import an iBioSim model, select File → Import → iBioSim Model. You will then be able to browse to find a model to import. After selecting the desired model, click the import button to bring the model into the project. Before bringing the model into the project, it will be checked to see if it is a valid model file. To import an SBML model, the procedure is the same except use the Import → SBML Model option. Before bringing the model into the project, it will be checked to see if it is a valid SBML file. The model will also be checked for consistency, and any errors or warnings will be reported. These should be corrected before analysis of the model is performed. Importing of an LPN model or an SBOL file are similar in that you are asked to locate the appropriate file to import.



When importing a model from the BioModels database, the window below will open, initially only listing the BioModel numbers. Selecting “Get Names” will fetch the model names from the database. Beware that this can take a significant amount of time. When you click on a model to select it, you can use the “Get Description” button to fetch a description of the model which will open in a browser. Similarly, the “Get Reference” button will fetch the reference describing this model and again open it in a browser.



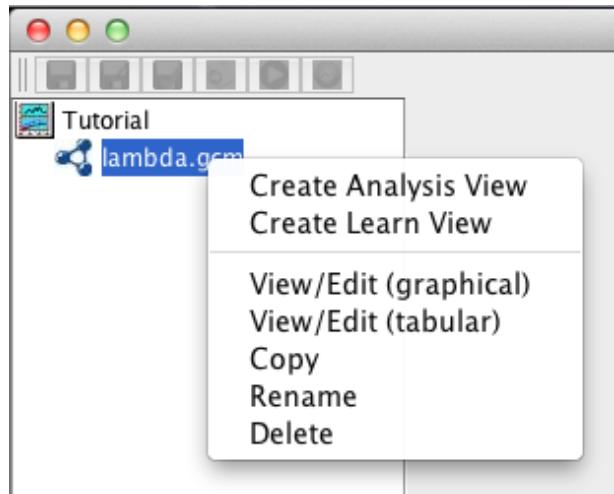
2.4 Exporting Models and Graphs

You can also export a model in either SBML or SBOL format. To export an SBML model, select File → Export → Systems Biology Markup Language (SBML). Then, you will be able to browse to find a location to export the SBML file. Currently, the SBML model generated is a single flattened chemical reaction model. When exporting model as an SBOL component, you must browse to find an SBOL library. The SBOL component will then be added to the selected library. Graphs of time series data or histograms can be exported from the project in many formats. The supported file formats are:

- Time series data format (tsd), see Section 12..
- Comma separated value (csv).
- Column separated data (dat).
- Encapsulated postscript (eps).
- Joint Photographic Experts Group (jpg).
- Portable document format (pdf).
- Portable network graphics (png).
- Scalable vector graphics (svg).

2.5 Editing Project Objects and Creating Tool Views

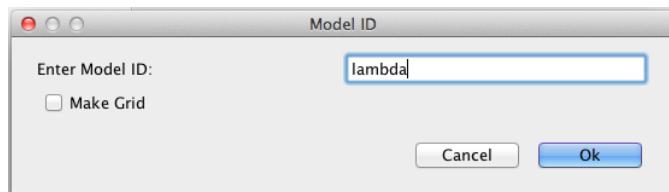
All project objects can be modified by highlighting the object and using a right mouse click to open a menu of options, as shown below. Using this menu, every type of object can be copied, renamed, or deleted (these actions can also be done from the Edit menu). For a model file, the “View/Edit” option opens the model editor (see Section 3). For an LPN model, the “View/Edit” option opens the LPN model editor. For a TSD graph, the “View/Edit” option opens the TSD graph editor (see Section 7). For a histogram, the “View/Edit” option opens the histogram graph editor (see Section 8).



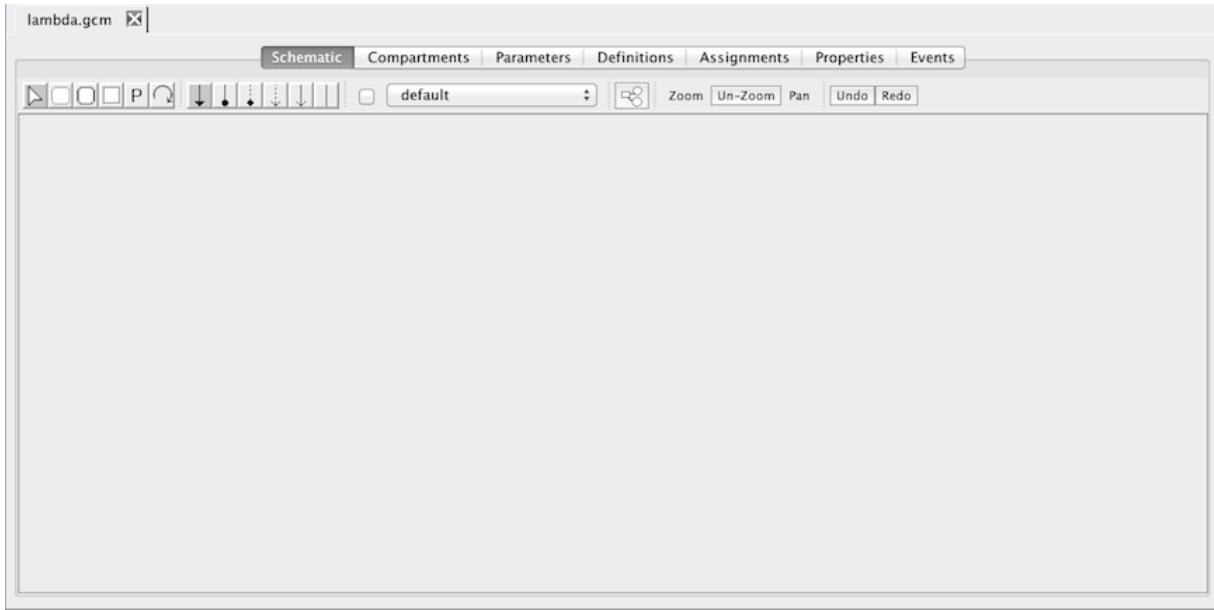
To perform analysis or learning, right-click on a model and select “Create Analysis View” (see Section 5) to perform analysis or “Create Learn View” (see Section 6) to perform learning. You will then be prompted to give a name to your analysis or learn view. After a name is entered, a tab with the newly created view will open. Views can also be created using the Tools menu. Once a view is created, it can be opened again later by right-clicking on an analysis directory and selecting “Open Analysis/Learn View” or, alternatively, double-clicking on the view.

3 Model Editor

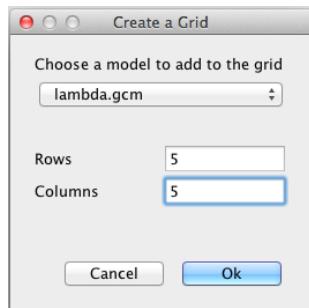
The model editor allows the user to create or modify a model of a genetic circuit or other biochemical system. iBioSim models are based on SBML Level 3 Version 1 models with added features to support visualization, hierarchy, and modeling of genetic regulation. SBML models can be imported and exported to allow interfacing with SBML-compliant tools. When exporting an SBML model, the hierarchy and genetic regulation are flattened to create a single SBML model. The model editor includes both a schematic editor as well as several textual editors. For large models, the schematic portion can also be edited textually instead. As shown below, when creating a new model, you can select whether the model should be on a grid or not. Let us focus initially on models that are not on a grid.



The schematic editor shown below allows one to add *chemical species* (see Section 3.1), *chemical reactions* (see Section 3.2), *components* (see Section 3.3), and *promoters* (see Section 3.4) to a model depending on the icon selected in the toolbar. Chemical species are the molecules such as proteins. Chemical reactions change *reactant* species into *product* species. Components are instances of other models within the project. Finally, promoters are locations on a DNA sequence in which transcription is initiated. There are several types of relationships between species that can be specified. A species may *activate* or *repress* the production of other species (see Section 3.5). One can also specify when there is no influence between two species or when a self-influence exists. Species can also be related by complex-formation reactions which indicate that multiple identical or different species can be combined to form a complex species. A species can also be a reactant or product in a chemical reaction, indicating that the reaction consumes or produces the species, respectively (see Section 3.2). Finally, a species can be a *modifier* to a chemical reaction, indicating that it affects the rate of the reaction but is neither produced nor consumed by the reaction (see Section 3.2). The next item on the toolbar is a checkbox used to indicate if the model is to be considered enclosed within a *compartment*. The combo box is used to select the enclosing compartment for the model. The remaining items on the toolbar allow you to apply an automatic layout routine , zoom, restore to default size (Un-Zoom), pan, undo, and redo. Finally, the additional tabs allow the user to add, edit, or remove compartments (membrane-enclosed objects where reactions take place, see Section 3.6), *parameters* (values used in model generation and within math equations, see Section 3.7), *definitions* (custom functions and units, see Section 3.8), *assignments* (mathematical equations that govern the values of variables in the model, see Section 3.9), *properties* (mathematical equations that describe either desired or undesired behaviors, see Section 3.10), and *events* (objects that describe discrete state changes, see Section 3.11).

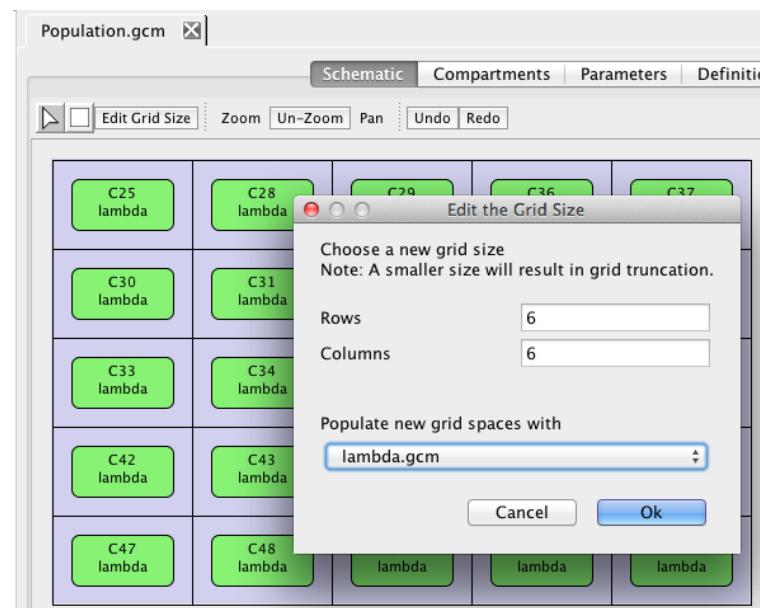


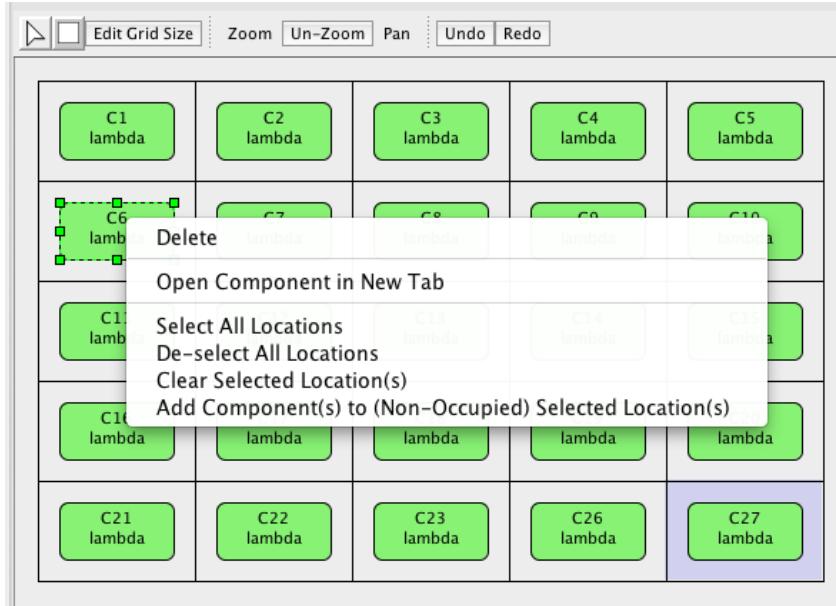
iBioSim also supports the creation of models on a grid. The idea of a grid is to provide a coarse-grain spatial representation. A single model can be instantiated within each grid location. The models can be for individual cells, allowing one to model population dynamics. The models can also be different segments of a single cell, allowing one to model diffusion within a cell. Key to grid-based modeling are diffusible species, described in Section 3.1. When the models within grid locations are compartment-enclosed components, reactions are added to represent the movement of these diffusible species between the compartment and the area outside the compartment within the grid location (i.e., membrane diffusion). When performing analysis, reactions are also automatically added to represent the movement of these diffusible species between the grid locations. To use a grid, check the Make Grid option when creating the model. A window will then open asking for the number of rows and columns in the grid. It also asks which model to use to populate the grid. You can select “none” if you wish to populate it later.



The schematic for a model on a grid is a bit different than for an ordinary model, which is evident from the toolbar. Namely, a grid-based model can only include components, with at most one component per grid location. By pressing the Add Component icon and clicking on an empty grid location, you are allowed to select a model to instantiate within that grid location. You can also select Edit Grid Size to change the size of the grid. If the grid is larger in one or more dimensions than before, you can select a model to populate the new grid locations. A smaller grid size simply removes the component instantiations that fall outside the new grid. You can also edit the grid by selecting individual grid locations by clicking on them. When you then use the right

mouse button, it brings up the menu shown below. This menu allows you to delete the component that was right-clicked on or to open its model in a Model Editor. You can also use this menu to select or de-select all grid locations, and you can either clear occupied, or populate non-occupied, selected grid locations.



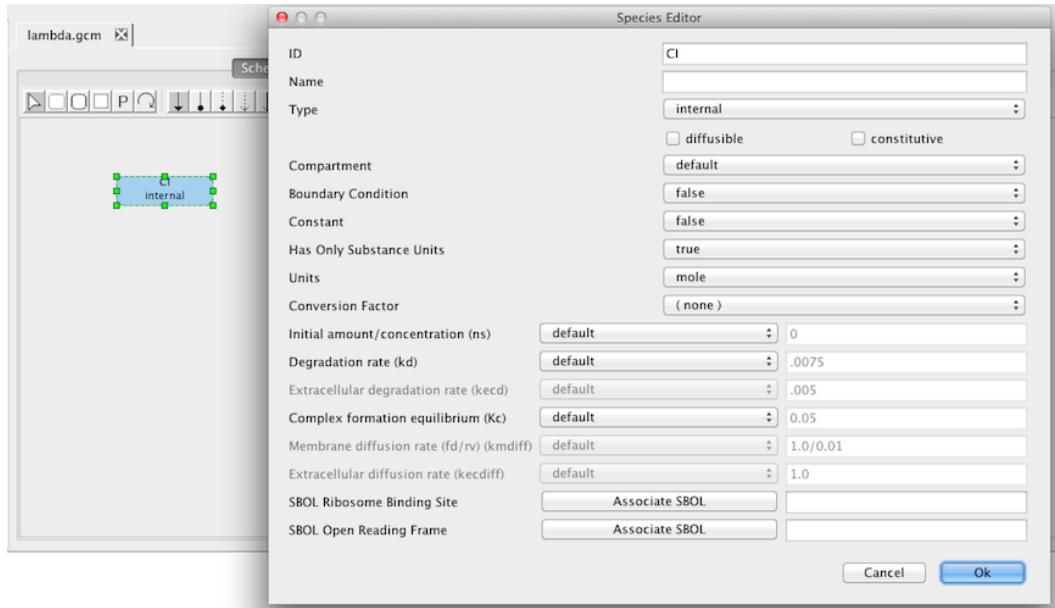


3.1 Species

Species are the molecules, such as proteins, that are produced by genes or chemical reactions. To add a species to the model, select the Add Species icon and click on the schematic canvas. This will drop a new species with default ID and other values. You may change these defaults by double-clicking on the species to open the Species Editor. A species has the following elements:

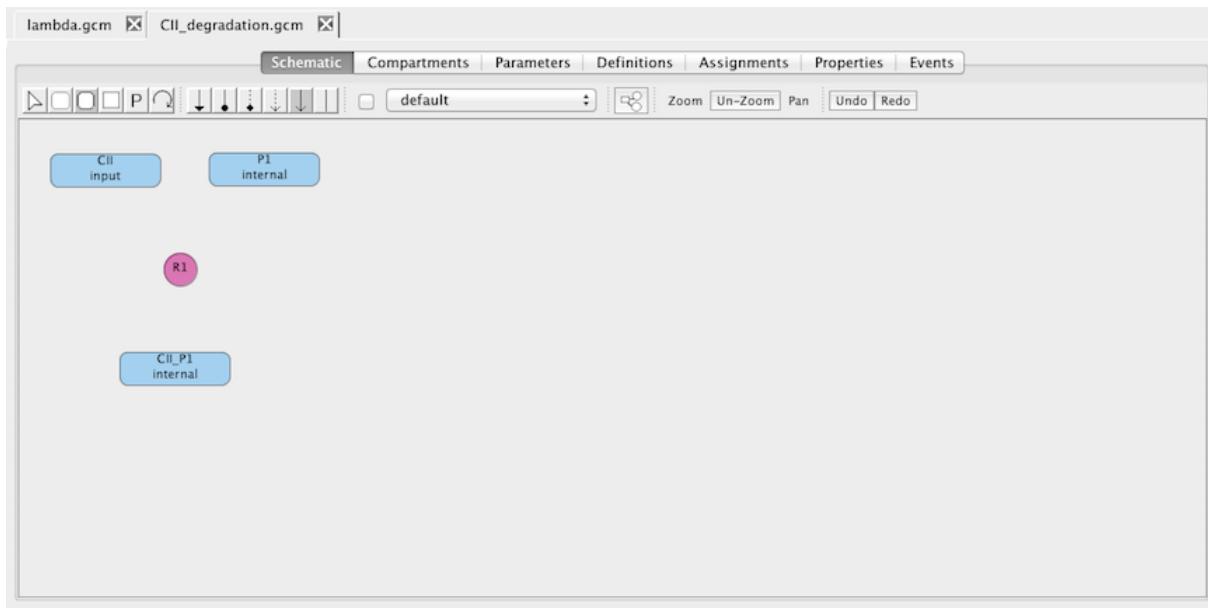
- ID: a unique ID composed of only alphanumeric characters and underscores.
- Name: an arbitrary string description of the species (optional).
- Type: used to indicate how this species can be connected in hierarchical models. The *input* type is used to indicate a species that is produced outside this model, the *internal* type is used to indicate that a species is produced inside this model but cannot be used in other models, and the *output* type is used to indicate that a species is produced by this model and can be used in other models.
- Diffusible: this checkbox indicates if this species can diffuse in multi-compartment and grid-based models.
- Constitutive: this checkbox indicates that a default production reaction should be created for this species.
- Compartment: location of the species (default=default).
- Boundary Condition: Boolean indicating if the species amount/concentration cannot be changed by reactions (default=false).
- Constant: Boolean indicating if the species amount/concentration is constant (default=false).
- Has Only Substance Units: Boolean indicating if the species is to be considered an amount in mathematical equations (default=true).
- Units: the units for the amount/concentration (default=none).

- Conversion Factor: is a constant global parameter, the value of which is used to convert this species' units into the units used for extent (i.e., the units of change due to reactions).
- Initial amount/concentration (ns): initial value of the amount or concentration of the species. If the value is enclosed in brackets (i.e., [number]), it is a concentration, otherwise it is an amount. The default is the value of the global parameter ns.
- Degradation rate (kd): the degradation rate for this species. The default is the value of the global parameter kd. Note that a value of 0 will result in no degradation reaction being produced for this species.
- Extracellular degradation rate (kecd): the rate at which this species degrades when it is outside a cell (i.e., on the grid level). If a species is present in different models (i.e., has the same ID), be sure to keep these rates consistent. The default is the global parameter kecd.
- Complex formation equilibrium (Kc): the equilibrium constant for formation of this species when it is produced by a complex formation reaction. The default is the global parameter Kc. The equilibrium constant can be specified as a forward and reverse rate constant using the <forward rate>/<reverse rate> form.
- Membrane diffusion rate (fd/rv) (kmdiff): the forward (in to out) and reverse (out to in) rate constants (slash-separated) for diffusion of this species through its compartment's membrane. Note that when membrane diffusion reactions are generated, the rates are taken from the inner species. If no reverse rate is given, a default of 1.0 is used. The default is the global parameter kmdiff.
- Extracellular diffusion rate (kecdiff): the rate at which this species diffuses between grid locations in a grid-based model. This rate is used for both the forward and reverse diffusion reactions. If a species is present in different models (i.e., has the same ID), be sure to keep these rates consistent. The default is the global parameter kecdiff.
- SBOL Ribosome Binding Site: the DNA component for the ribosome binding site that is associated with this species. Either a full path can be specified (i.e., <filename> / <collection> / <DNA component>) or clicking on the Associate SBOL button opens the SBOL browser described in Section 4.
- SBOL Open Reading Frame: the DNA component for the open reading frame (gene) that is associated with this species. Either a full path can be specified (i.e., <filename> / <collection> / <DNA component>) or clicking on the Associate SBOL button opens the SBOL browser described in Section 4.



3.2 Reactions

Reactions are used to create or destroy molecular species in a biochemical reaction network. To add a reaction, select the Add Reaction icon and click on the schematic canvas which drops a new reaction with a default ID and parameter values.

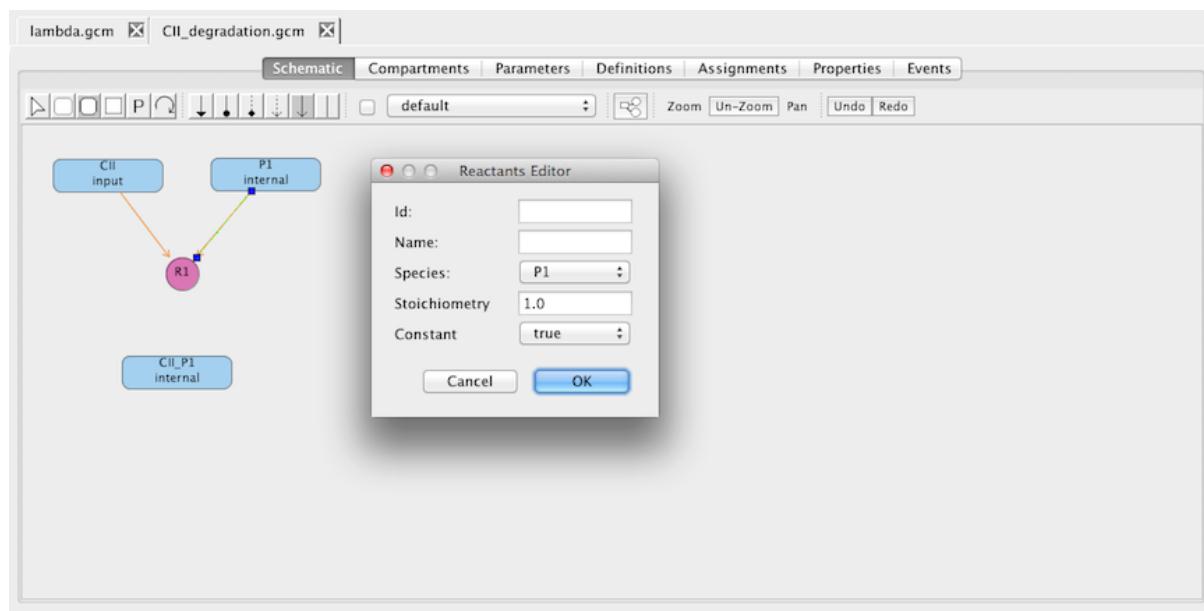


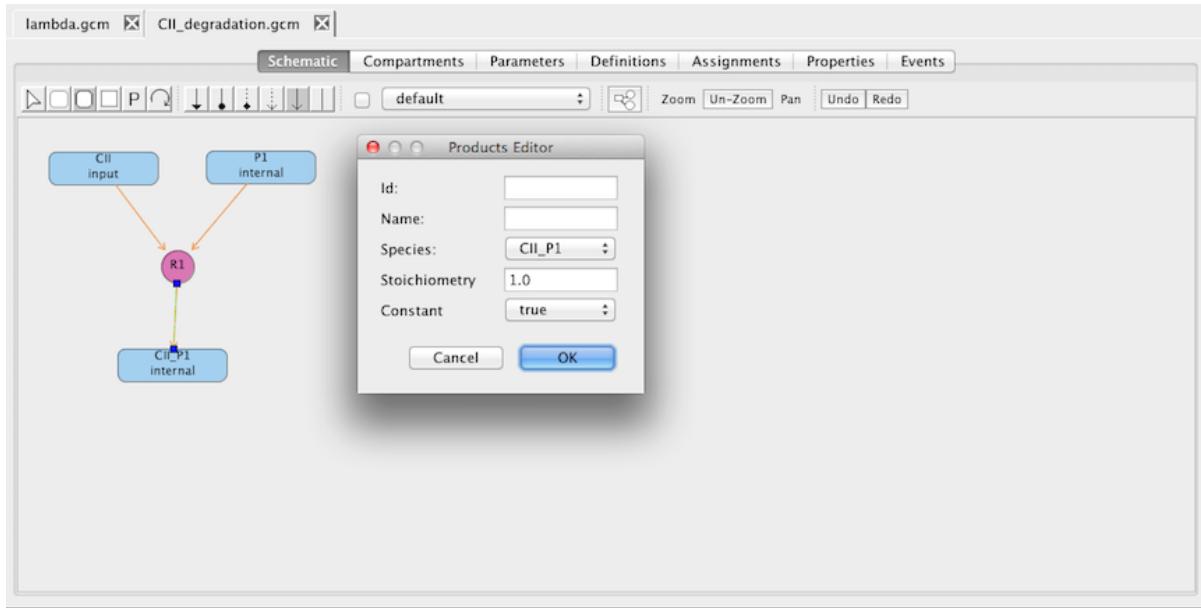
Reactions convert reactant species into product species with perhaps modifier species (e.g., enzymes or catalysts) affecting the rate of this conversion. The next step, therefore, is to indicate which species are reactants, products, and modifiers for the reaction. This is accomplished by selecting the Reaction icon or Modifier icon . With the Reaction icon selected, selecting a species, holding the mouse button, and dragging the arc to a reaction makes the selected species a reactant in that reaction. Similarly, selecting a reaction, holding the mouse button, and dragging

the arc to a species makes the species a product in the selected reaction. Finally, with the Modifier icon selected, dragging an arc between a species and reaction (in either direction) adds the species as a modifier in the reaction. When you select a reactant edge, it opens a Reactants Editor. This editor allows you to change the following things:

- ID: this is the ID for this reactant and should not be confused with the Species ID. This ID can be used in equations such as initial, rule, or event assignments. Use this ID when you want the stoichiometry to be determined by an equation or used in an equation. The ID is optional.
- Name: an arbitrary string description of the species (optional).
- Species: the ID of the reactant species.
- Stoichiometry: the number of molecules consumed by the reaction. Note that this value will be overridden when the reactant ID is used on the left-hand side of an assignment.
- Constant: indicates whether the stoichiometry can change dynamically.

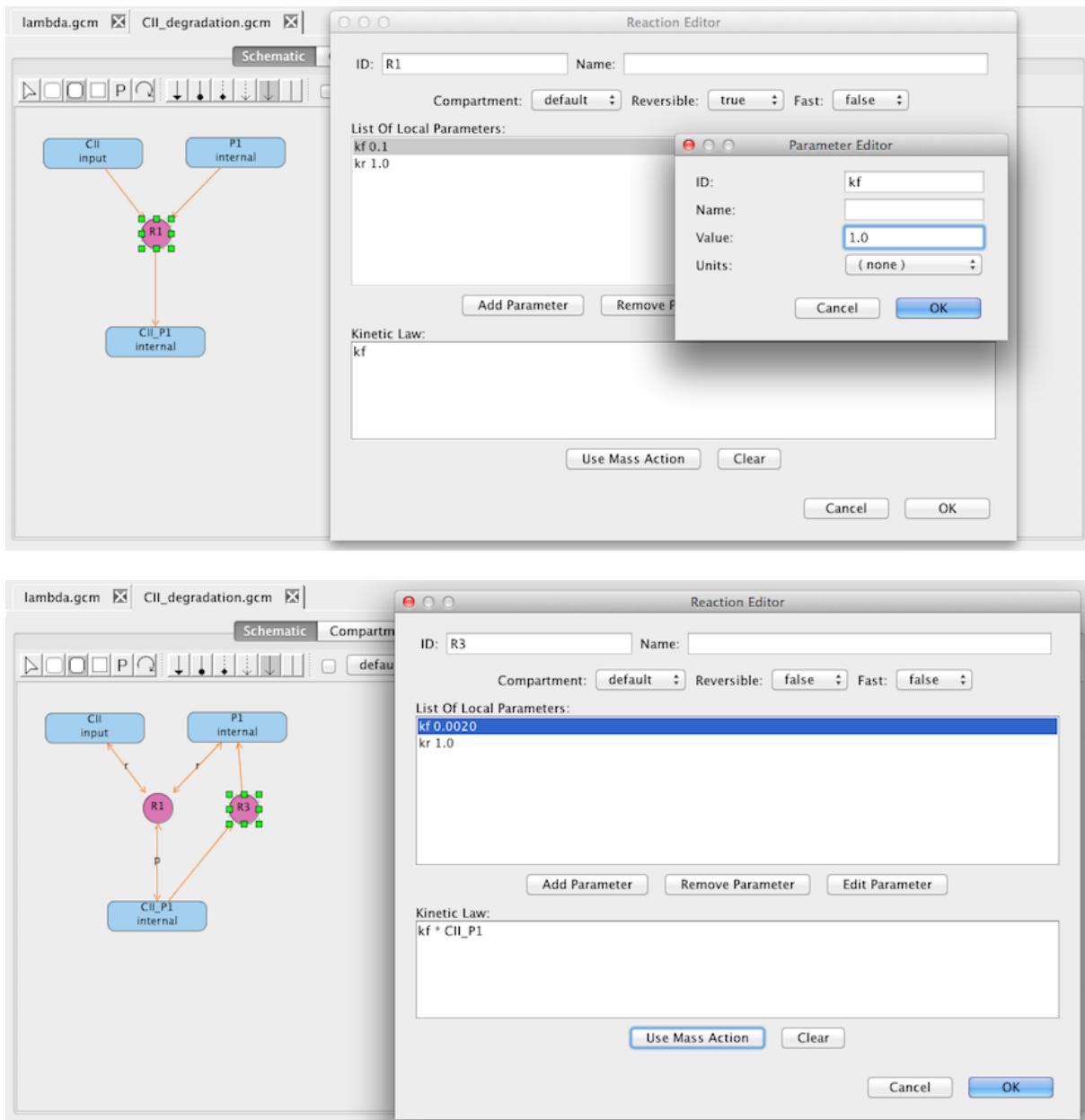
Similarly, the ID, Name, Species, Stoichiometry, and Constant fields can be edited for a Product edge as shown below. Modifier edges do not have any of these fields, so they cannot be edited.





When you select a reaction, it opens the Reaction Editor which allows you to edit the following reaction fields:

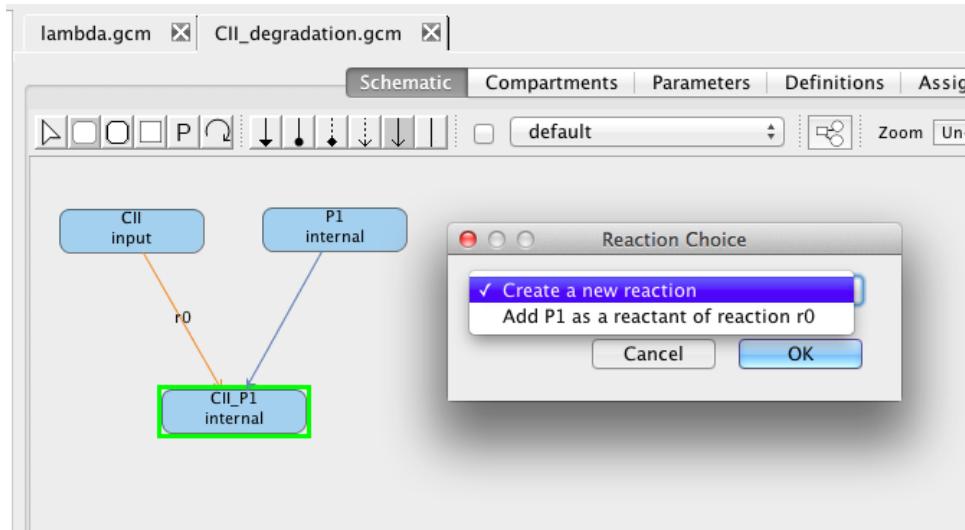
- ID: a unique ID composed only of alphanumeric characters and underscores.
- Name: an arbitrary string description (optional).
- Compartment: the location where this reaction takes place.
- Reversible: a Boolean indicating if the reaction is reversible (default=false). Note that reversible reactions are indicated in the schematic with double headed arrows.
- Fast: a Boolean indicating if the reaction reaches equilibrium rapidly (default=false). Note that this only has limited support in analysis, so it should be used sparingly.
- List of Local Parameters: symbolic values that can be used in the *kinetic law* for this reaction. Their IDs only need to be unique to this reaction. Local parameters can be added, removed, and edited using the appropriate buttons. Each parameter is composed of an ID, Name (optional), Value, and Units (optional). The list of parameters begins with a default forward reaction rate (kf) and reverse reaction rate (kr). These names and their values should likely be edited.
- Kinetic Law: a mathematical formula (see Section 10) describing the rate or probability for this reaction. The kinetic law can either be automatically generated using the Use Mass Action button or manually entered. The Use Mass Action button creates a rate law using the law of mass action assuming that the first parameter in the list is the forward reaction rate and the second parameter in the list is the reverse reaction rate. The Clear button clears the kinetic law editor. Note that the kinetic law formula can only include species IDs that are reactants, products, or modifiers to this reaction.



To simplify a schematic, one can use implicit reactions in some limited situations. To create an implicit reaction, with the Reaction icon highlighted and the mouse button selected, drag a reaction edge between two species. This action creates a reaction with a default ID and parameters, including the source species as a reactant and sink species as a product. If you connect an additional reaction edge to either species, you are asked if you wish to create a new reaction or add this new relationship to an existing reaction on the source and/or sink species. Implicit reactions can only be used when the following conditions hold:

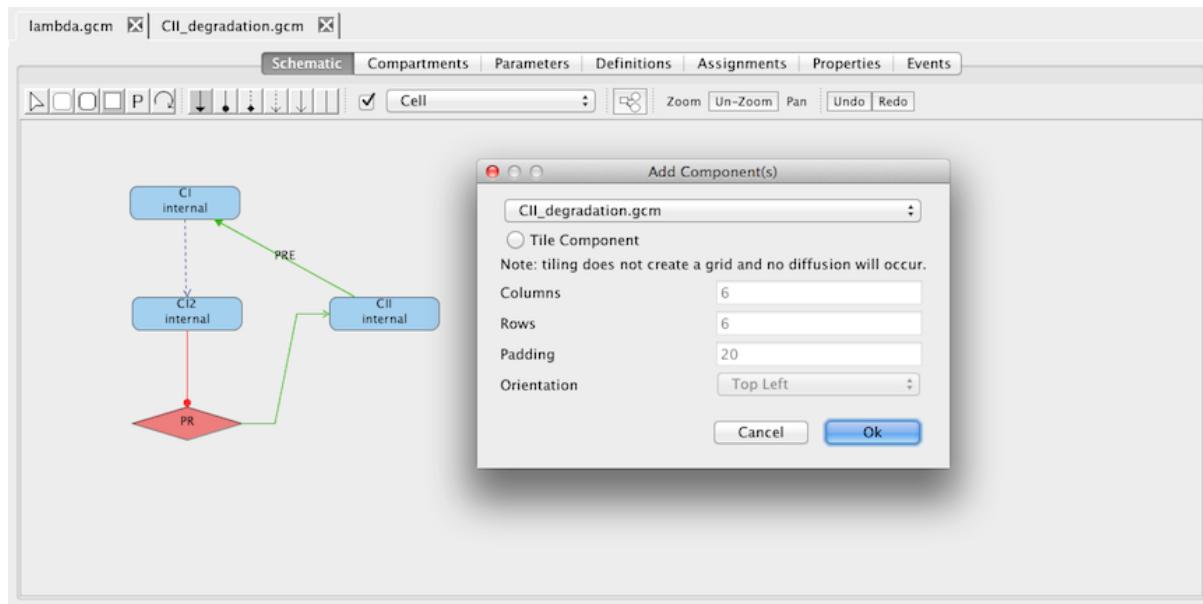
- The stoichiometry of all reactants and products for the reaction is 1.
- The reaction has either a single reactant OR a single product.
- The reaction has no modifier species.

The first condition is a default and cannot be changed. Adding edges can, however, cause a violation of the second or third condition. If this violation occurs, an explicit reaction is created to replace the implicit reaction.

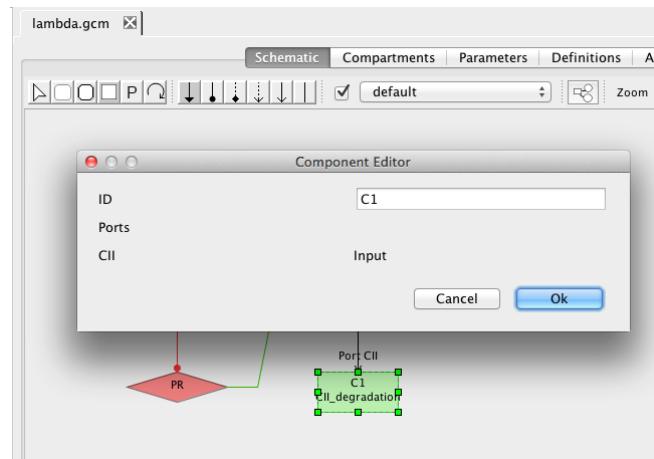


3.3 Components

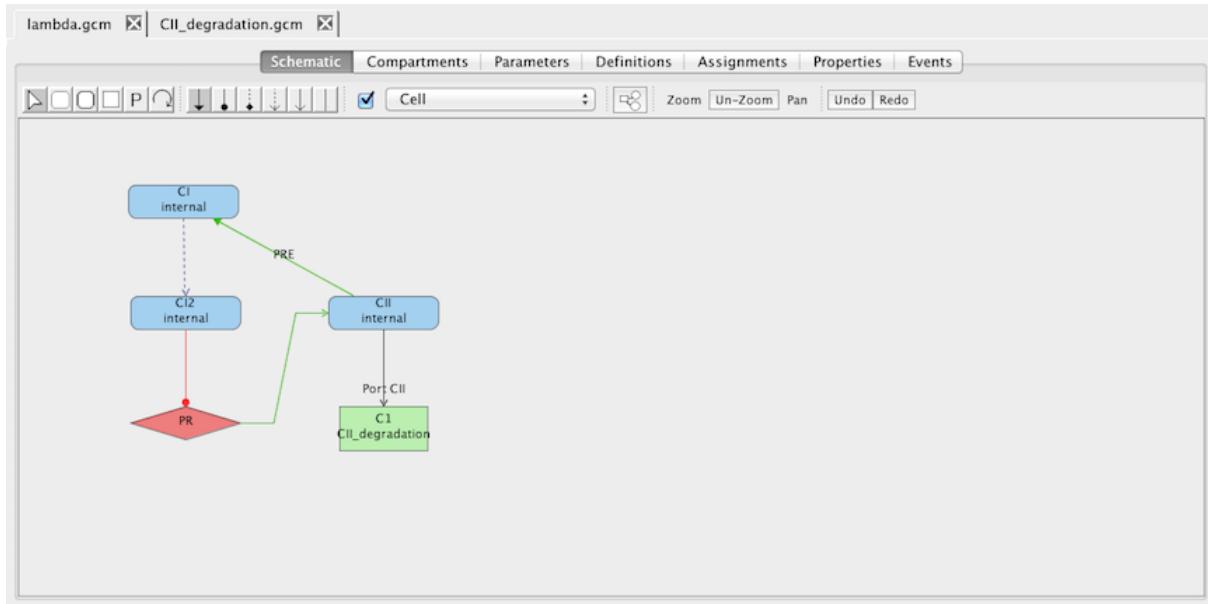
Components are instances of other models within the project, and they are used to create hierarchical, multi-compartment, and cellular population models. To add a component, select the Add Component icon and click on the schematic canvas. You are then prompted to select the model for the component that you wish to add. This window also allows you to add multiple instances of the component at one time. To do this, select Tile Component and specify how many Columns, Rows, the Padding between them that you want, and whether to start the tiling in the top left corner of the schematic or at the mouse location.



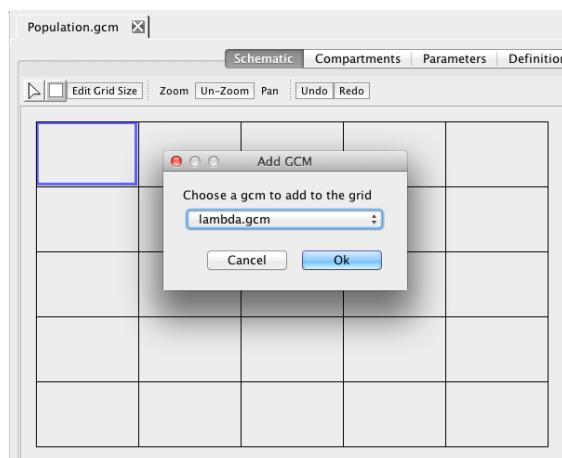
When a component is added, it appears in the schematic either with sharp or rounded corners. A component with sharp corners is not enclosed within a compartment, so it may have ports to which species may be connected. In other words, this is likely part of a hierarchical model. On the other hand, rounded corners indicate that it is enclosed within a compartment, so it cannot have any ports. In this case, the component is likely to be part of either a multi-compartment or cellular population model. If a diffusible species with the same ID exists inside and outside of a compartment-enclosed component, a membrane diffusion reaction will be created, allowing the species to be transported to/from the compartment-enclosed component. If the compartment-enclosed component is on a grid, the outside diffusible species will be automatically created if the inside diffusible species exists. Clicking on the component opens the Component Editor, which allows you to change the instance name for the component as well as see a list of the components ports.



When a component has ports, connections to input ports can be made by selecting a species and, while holding the mouse button, drag an arc to the component. If there are multiple input ports, you are asked which input port to connect this species to. To connect to output ports, begin by selecting the component and drag an arc to the species to be connected to the output port. Note that when you make these connections you are specifying that the species in the top-level model is the same species as the one in the component that it is connected too.



When adding a component to a grid, you are simply asked which model to instantiate, and you cannot connect to ports as species are not allowed on a grid.

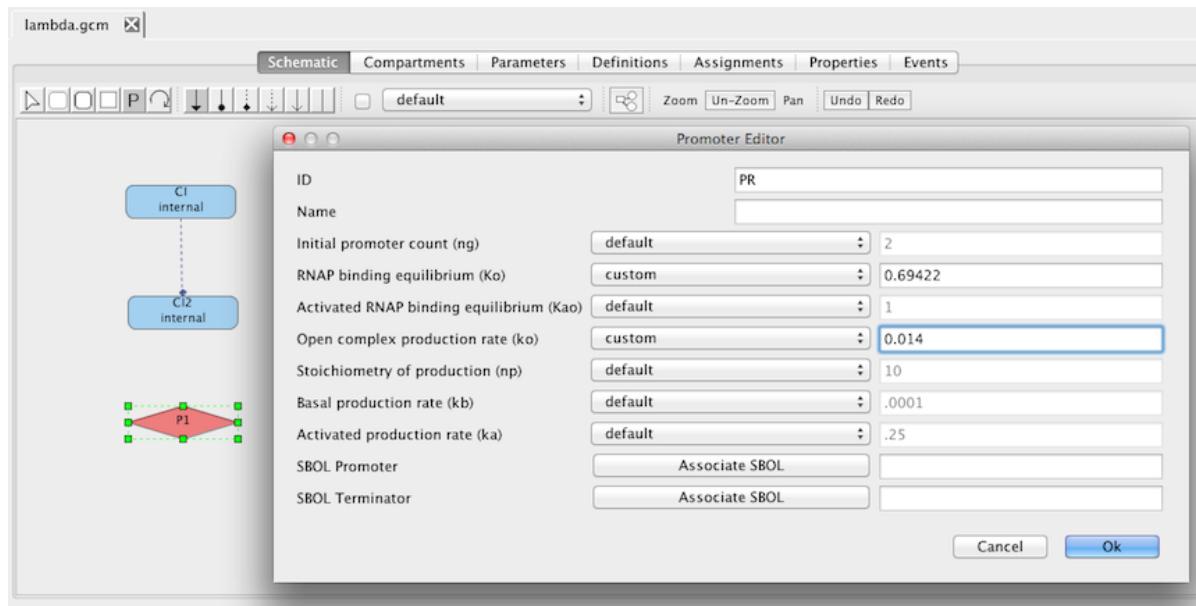


3.4 Promoters

Promoters are the locations on a DNA sequence in which transcription is initiated to create a *message* RNA (mRNA), which can then be translated by a ribosome into a protein. To add a promoter to a model, select the Add Promoter icon **P** and click on the schematic canvas, which creates a new promoter with a default ID and parameter values. Clicking on the promoter opens the Promoter Editor and allows you to edit the following fields:

- ID: a unique ID composed only of alphanumeric characters and underscores.
- Name: an arbitrary string description (optional).
- Initial promoter count (ng): the number of copies of this promoter. The default is the value of the global parameter ng.

- RNAP binding equilibrium (Ko): the equilibrium constant to use for the binding of RNAP to this promoter. The default value is the global parameter Ko. Note that this can either be specified as a single equilibrium constant or as a forward rate “/” reverse rate.
- Open complex production rate (ko): once RNAP binds to this promoter, this is the rate at which transcription is initiated. Note that this production rate is only used for promoters with no activators. The default value is the global parameter ko.
- Stoichiometry of production (np): the average number of proteins that are produced by an mRNA before it degrades. The default value is the global parameter np.
- Basal production rate (kb): once RNAP binds to an activated promoter, this is the rate at which transcription is initiated without the activator also being bound. The default value is the global parameter kb.
- Activated production rate (ka): once RNAP binds to an activated promoter, this is the rate at which transcription is initiated when the activator is also bound to the promoter. The default value is the global value ka.
- SBOL Promoter: the DNA component that is associated with this promoter. Either a full path can be specified (i.e., < filename > / < collection > / < DNA component >) or clicking on the Associate SBOL button opens the SBOL browser described in Section 4.
- SBOL Terminator: the DNA component that is associated with the terminator for the transcription initiated by this promoter. Either a full path can be specified (i.e., < filename > / < collection > / < DNA component >) or clicking on the Associate SBOL button opens the SBOL browser described in Section 4.

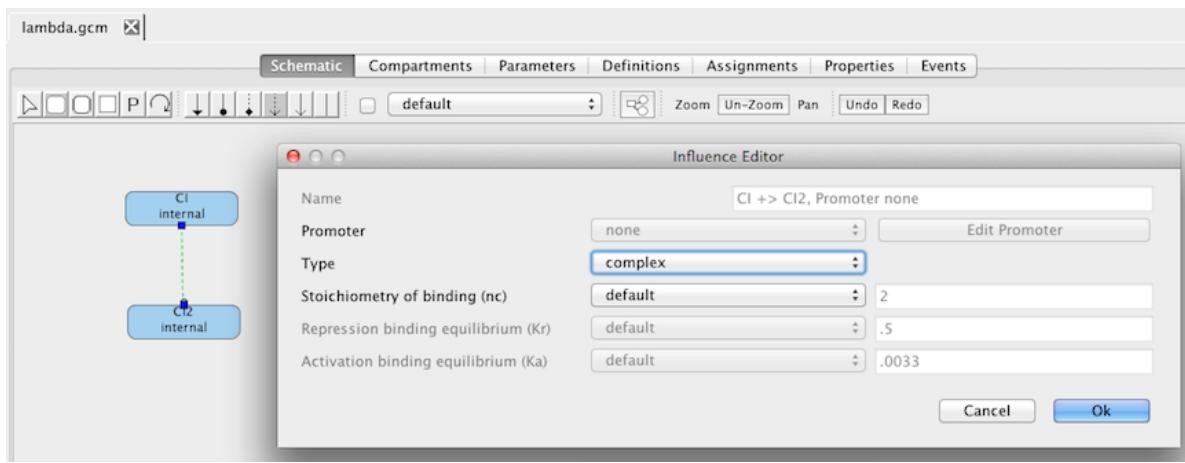


3.5 Influences

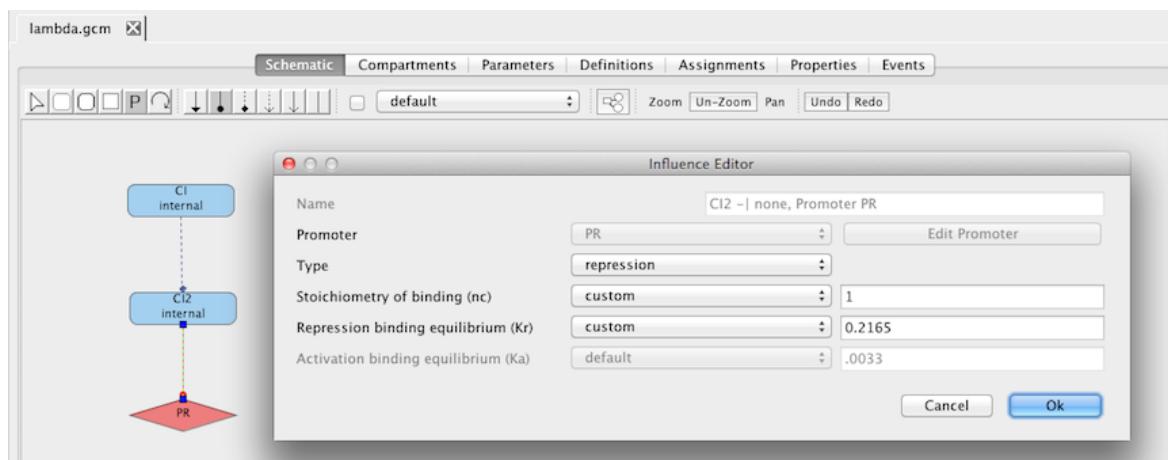
There are several types of influences between species that can be specified. A species may *activate* or *repress* the production of other species. This relationship is made from a species to the promoter that it activates or represses. It can also be made directly between two species with an

implicit promoter annotating the edge. One can also specify when there is no influence between two species. An activating or repressing self-influence can also be specified. Species can also be related by complex formation reactions which indicate that multiple identical or different species can be combined to form a complex species.

To add a complex formation reaction, select the complex formation icon , highlight a species that is part of a complex, and while holding the mouse button stretch the complex formation arc to the complex species. If you double click on the complex formation arc, an influence editor will open which indicates that this is a complex formation arc and the stoichiometry of binding (i.e., the number of molecules of the source species used to construct the sink species) is 2 which you can customize, if desired.

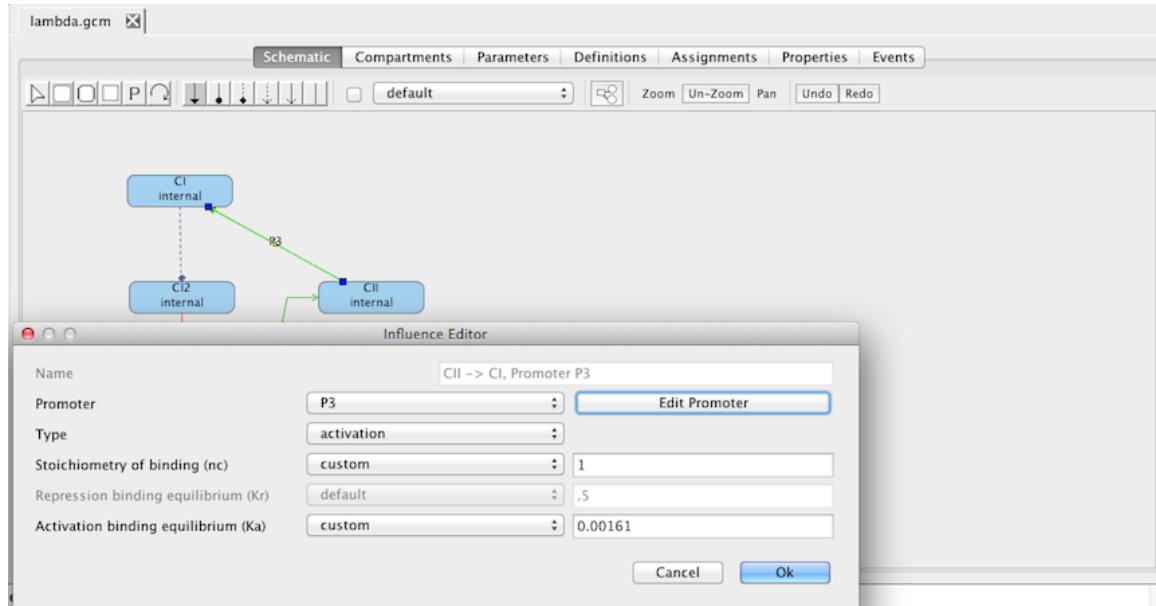


To create a repression influence, select the Repression icon , highlight the species that is acting as a repressor, and while holding the mouse button stretch the repression arc to either the promoter or another species. In the later, case, an implicit promoter is added. Double clicking on the repression arc brings up an influence editor. In this editor, you can customize the stoichiometry of binding as well as the repression binding equilibrium.

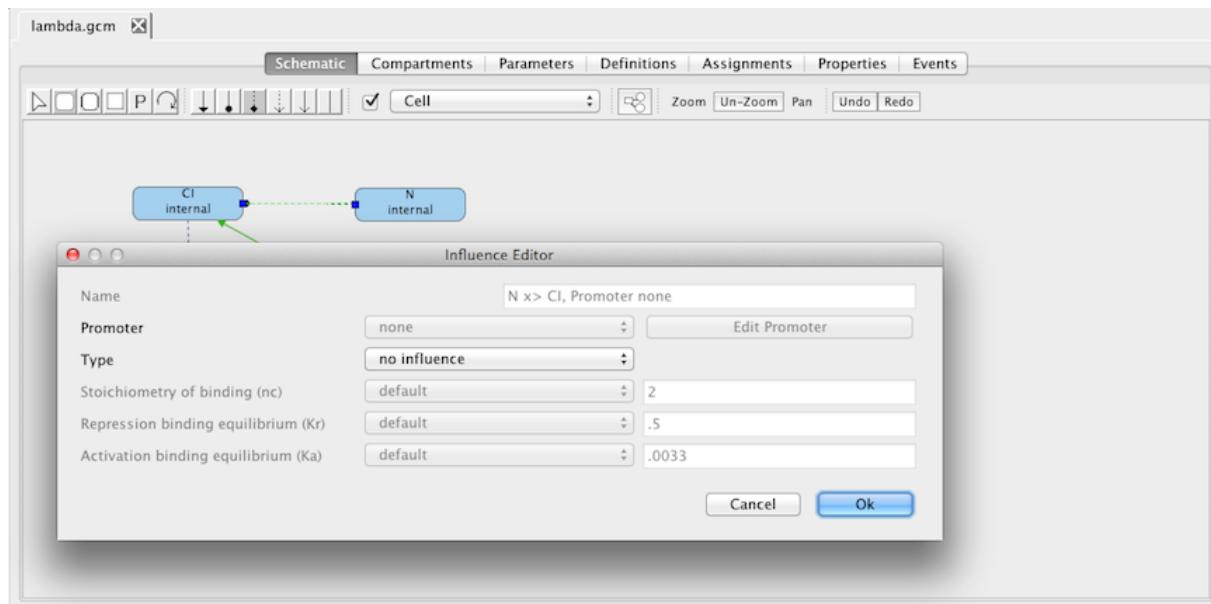


To create an activation influence, select the Activation icon , highlight the species that is acting as an activator, and while holding the mouse button stretch the activation arc to either the promoter or another species. In the later, case, an implicit promoter is added. Double clicking on

the activation arc brings up an influence editor. In this editor, you can customize the stoichiometry of binding as well as the activation binding equilibrium.

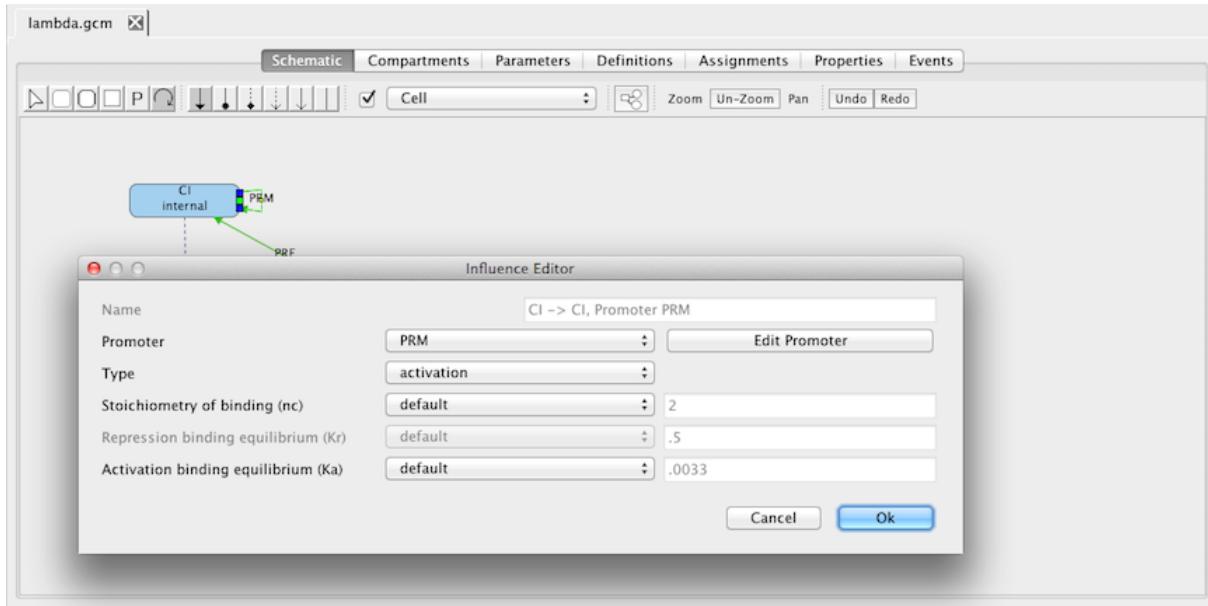


To indicate that a species has no influence on another species, select the No Influence icon , highlight the species that has no influence, and while holding the mouse button stretch the no influence arc to the species it has no influence upon. Double clicking on the no influence arc brings up an influence editor. In this editor, you can change its type to indicate that it actually has an influence, if you like, and the edit accordingly. No influence arcs are used by the Learn Tool to avoid adding influences where you are certain there is none.



The last type of influence is a self-influence. A self-influence can be either activation or repression. To create a self-influence, select the Self-influence icon , select the appropriate Activation

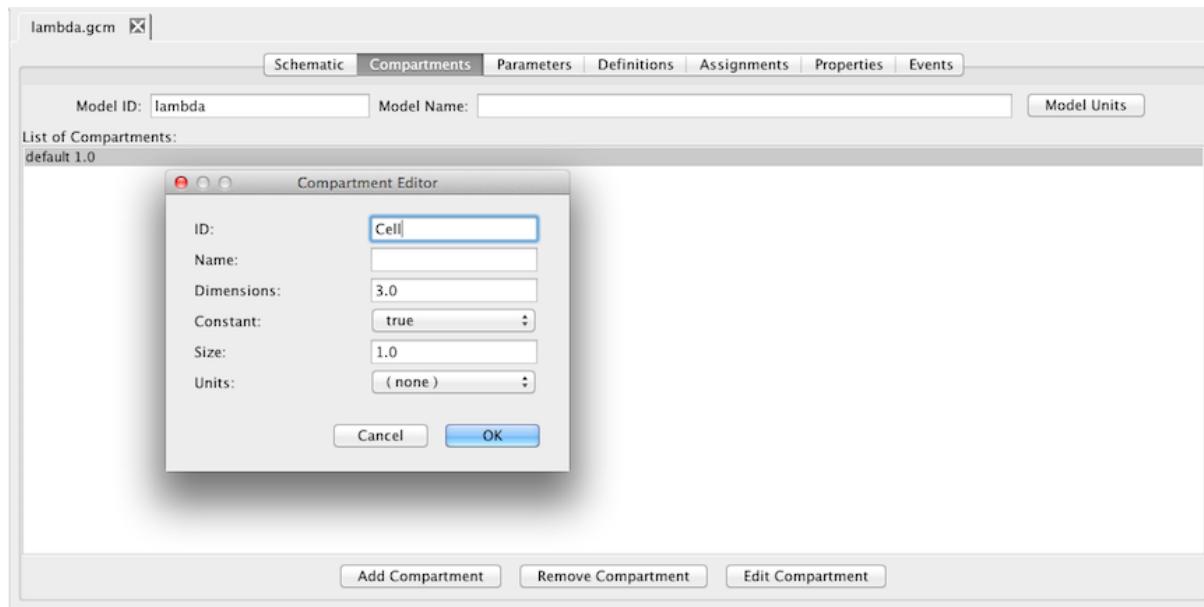
or Repression icon, and click on the species that influences itself. If you click on a self-influence, you will be able to edit its promoter, its type of influence, its stoichiometry of binding, as well as the appropriate binding equilibrium.



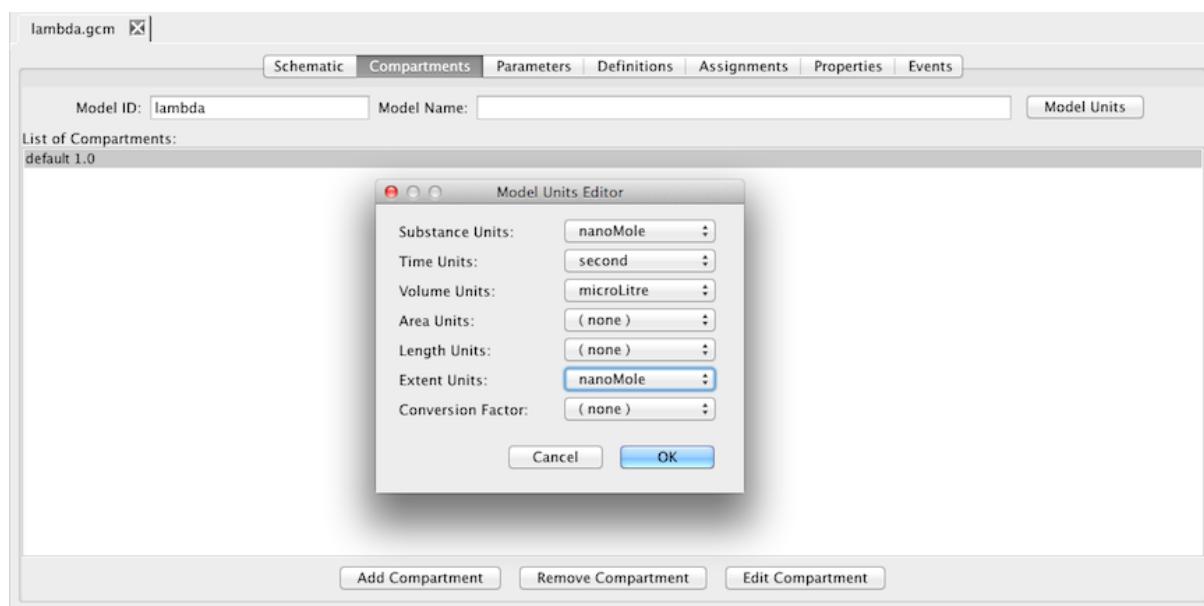
3.6 Compartments

Compartments are used to specify membrane enclosed regions where species are found. Every model must include at least one compartment. A new model includes a compartment named `default`. While its ID and other parameters can be changed, it cannot be removed unless a new compartment is added. A compartment to which species or reactions have been assigned also cannot be removed. As shown below, a compartment has the following fields:

- ID: a unique ID composed of only alphanumeric characters and underscores.
- Name: an arbitrary string description (optional).
- Dimensions: number of spatial dimensions (default=3).
- Constant: Boolean indicating if the size is constant (default=true).
- Size: initial size of the compartment (default=1.0).
- Units: the units for the size (default=none).

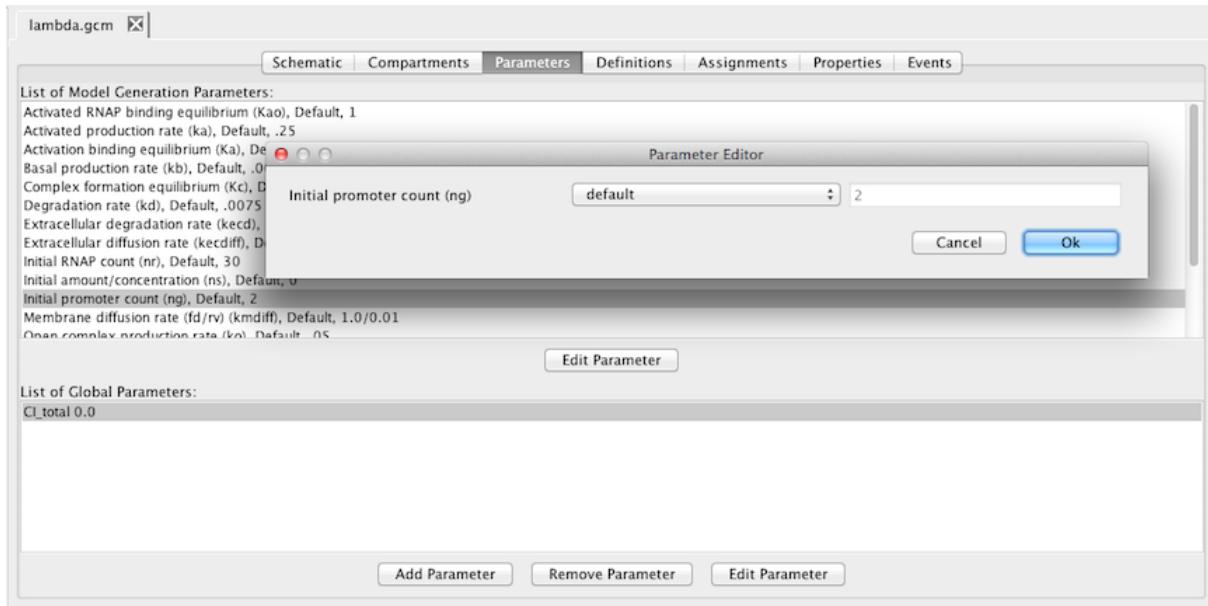


In addition to the list of compartments, this tab also includes the Model ID (which cannot be changed), the Model Name (an arbitrary string description of this model), and the Model Units. Clicking on the Model Units button allows you to see and edit this model's default units. The substance units is the default units for species, the time units is the default units for time, the volume units are the default units for 3-dimensional compartments, the area units are the default units for 2-dimensional compartments, the length units are the default units for 1-dimensional compartments, the extent units are the defaults units for what the amount changed due to a reaction. Kinetic laws have a default units of extent units / time units. The conversion factor is the constant global parameter to be used as the default conversion factor to convert species units into extent units.



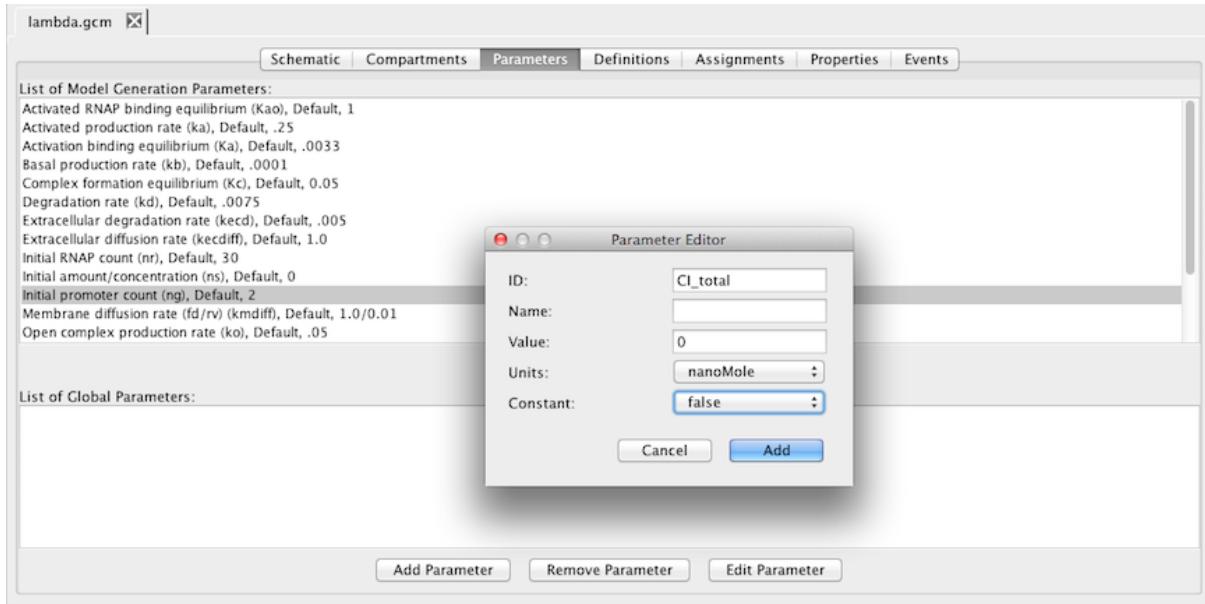
3.7 Parameters

There are two types of parameters: model generation parameters and global parameters. The model generation parameters provide default parameter values when converting a model into a reaction-based model for analysis. In the Species, Promoter, and Influence Editors, any parameter set to default uses the value found in this list. These defaults can be modified in the user preferences (see Section 9). The user can also edit these parameters for an individual model by changing the default to custom, then changing the value.



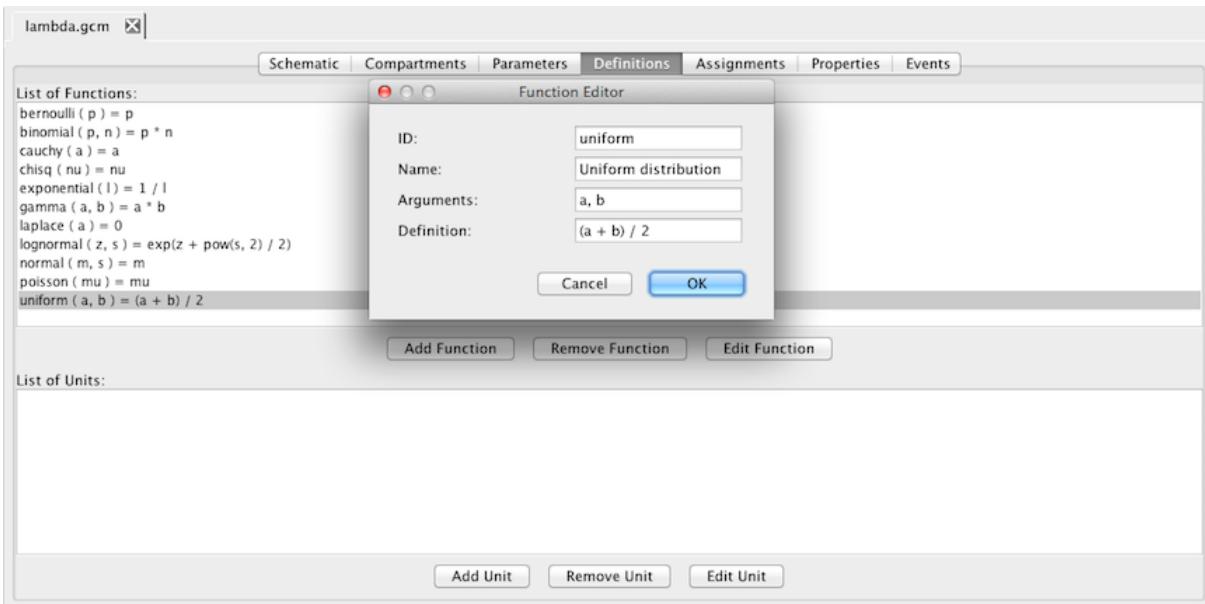
Global Parameters are variables that can be used in math formulas (see Section 10). A parameter includes the following:

- ID: a unique ID composed only of alphanumeric characters and underscores.
- Name: an arbitrary string description (optional).
- Value: initial value for the parameter.
- Units: the units for the parameter value (default=none).
- Constant: Boolean indicating if the parameter value is constant (default=true).



3.8 Definitions

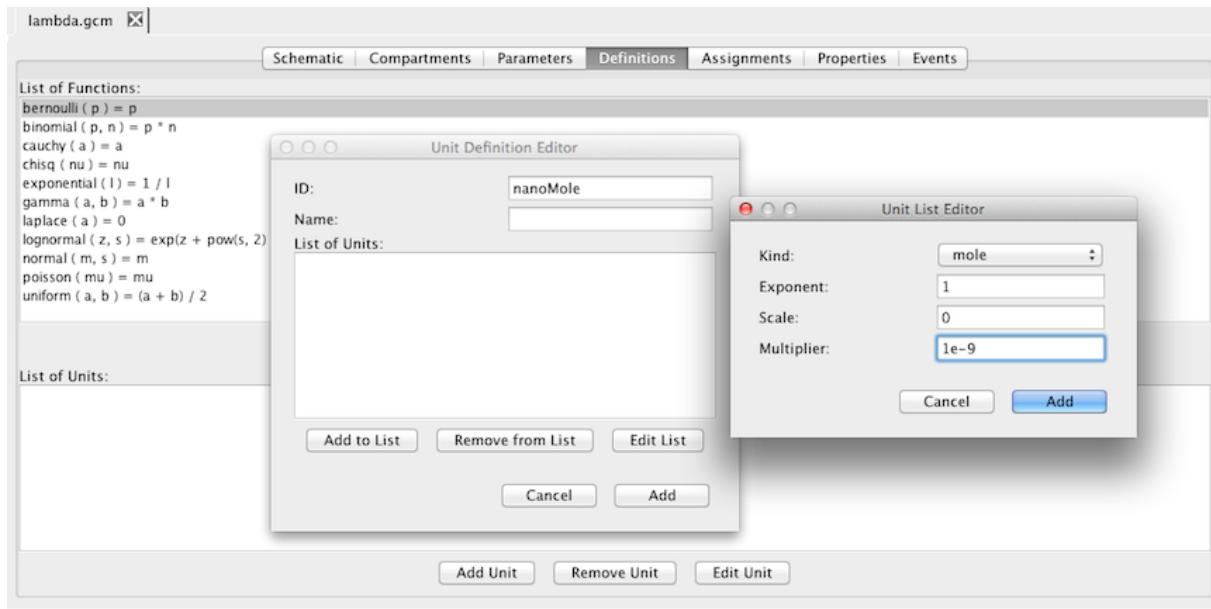
The Definitions tab allows users to provide function and unit definitions. Function definitions are used to create user defined functions that can then be used in math formulas (see Section 10). As shown below, function definitions include an ID, an optional name field, a comma-separated list of arguments, and its definition. The definition is a math formula though it is restricted to only use variable names which are arguments to the function. While functions can call other functions, they cannot be recursive (i.e., call themselves) either directly or indirectly (i.e., through a cycle of function calls). Several random functions supported by iBioSim's simulators are added automatically to every model.



Unit definitions are used to construct user-defined units which are derived from the set of base units. As shown below, a unit definition includes an ID, an optional name, and a list of units that

define it. There are buttons to add, remove, and edit elements in the list of units. Each unit is composed of a kind, exponent, scale, and multiplier. The kind is selected from the list of base units in the table below. The exponent and multiplier are real numbers, and the scale is an integer that specifies the relationship between the derived unit and the base unit using the relation below:

$$\text{unit} = (\text{multiplier} * 10^{\text{scale}} * \text{baseUnit})^{\text{exponent}}$$



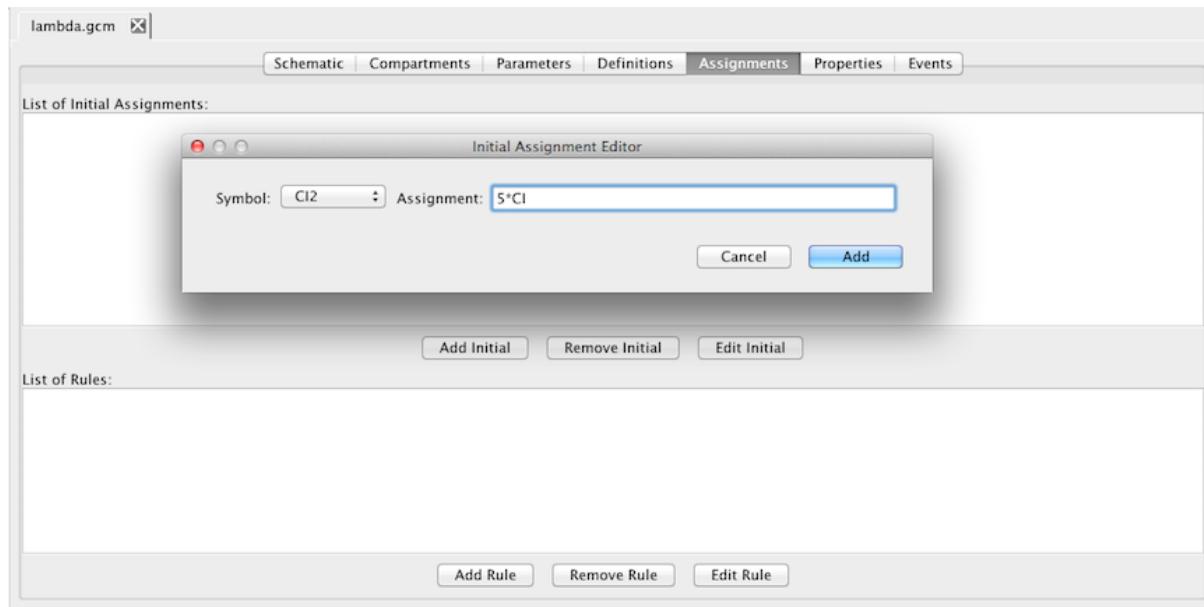
ampere	farad	joule	lux	radian	volt
avogadro	gram	katal	metre	second	watt
bacquerel	gray	kelvin	mole	siemens	weber
candela	henry	kilogram	newton	sievert	
coulomb	hertz	litre	ohm	steradian	
dimensionless	item	lumen	pascal	tesla	

3.9 Assignments

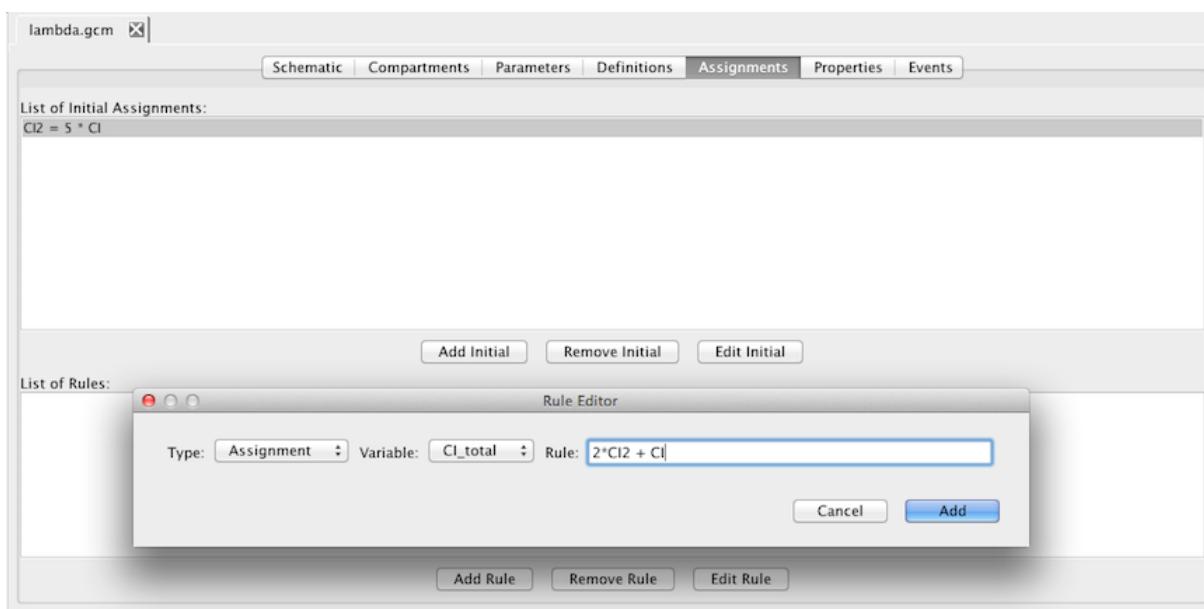
There are two types of assignments: initial assignments and rules. Initial assignments as shown below are used to provide a mathematical formula (see Section 10) that is evaluated at time 0 to determine the initial value of a compartment size, species amount or concentration, or parameter. The value of this formula takes precedence over the initial value specified in the object.

There are three types of rules: algebraic, assignment, and rate rules:

Algebraic	left-hand side is zero	$0 = f(W)$
Assignment	left-hand side is a scalar	$x = f(W)$
Rate	left-hand side is a rate-of-change	$\frac{dx}{dt} = f(W)$

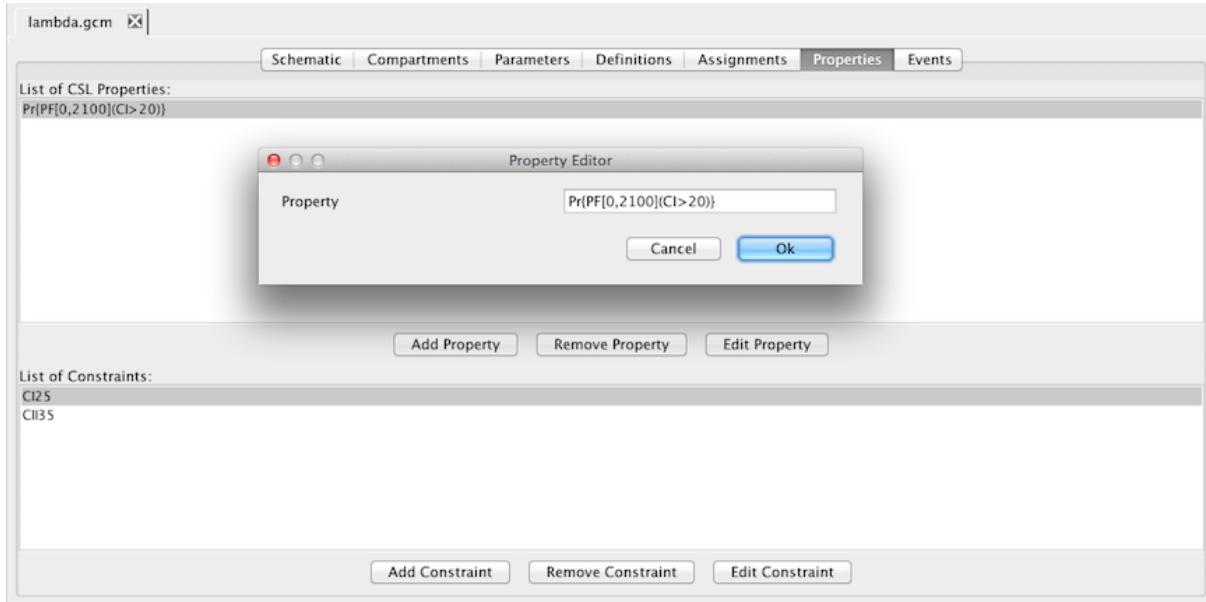


Algebraic rules specify relationships which must be maintained. Assignment rules specify the value of a compartment size, species amount or concentration, or parameter in terms of a mathematical formula (see Section 10). A variable cannot be determined by both an assignment rule and initial assignment. Rate rules specify the rate of change of a compartment size, species amount or concentration, or parameter in terms of a mathematical formula (see Section 10). A variable cannot be determined by both an assignment rule and a rate rule. A species that is a reactant or a product of any reaction cannot be updated by either an assignment rule or rate rule. When adding a rule, the user first selects the type of rule as shown below. This automatically restricts the set of variables available for the left-hand side to those that are valid. The user should then select a variable (except in the case of an algebraic rule), and enter a mathematical formula (see Section 10) for the rule. When editing a rule, the user cannot modify the rule type.

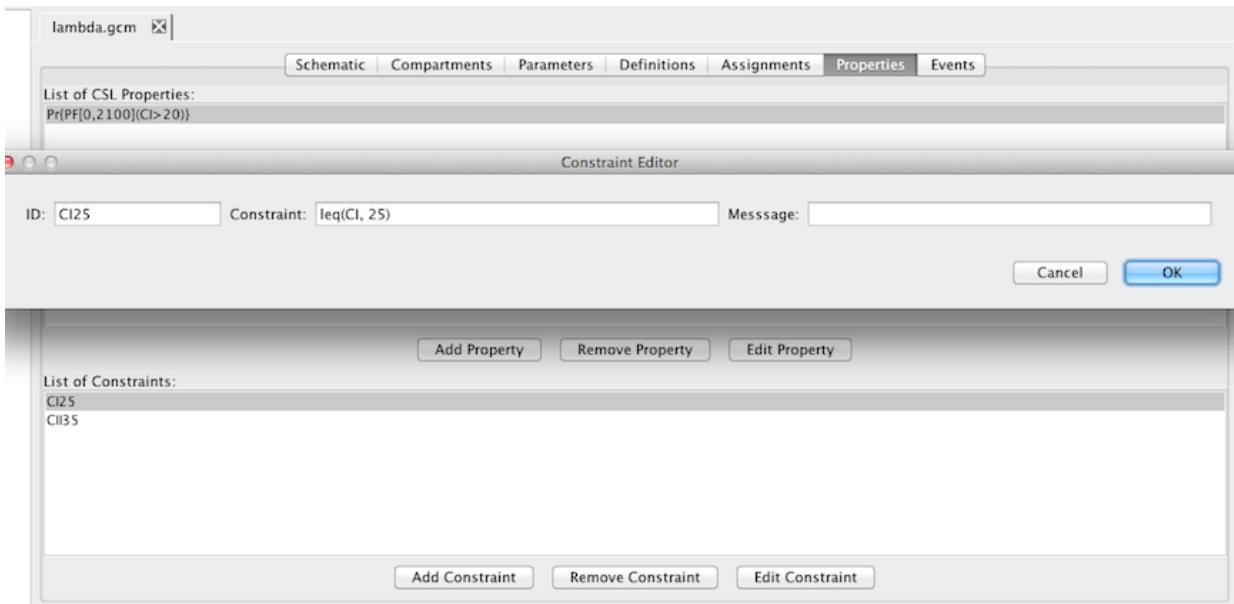


3.10 Properties

The properties tab allows users to provide formula for either desired or un-desired behavior. These formula can be provided in two forms as either a *Continuous Stochastic Logic* (CSL) property (see Section 11) or as a constraint. CSL is a temporal logic which allows one to specify probabilistic temporal logic properties. Analysis of a CSL property should return the probability that the property is true. These properties can either be transient properties to ask if something happens within a certain amount of time, or steady-state properties to ask the probability of a given state as time goes to infinity. The syntax for our CSL properties is given in Section 11.



Constraints are used to specify properties that should cause simulation to terminate. As shown below, each constraint is composed of an ID which is used to identify it in graphs, a constraint given as a mathematical formula (see Section 10), and a message describing the constraint. A default id is automatically generated when a new constraint is created.

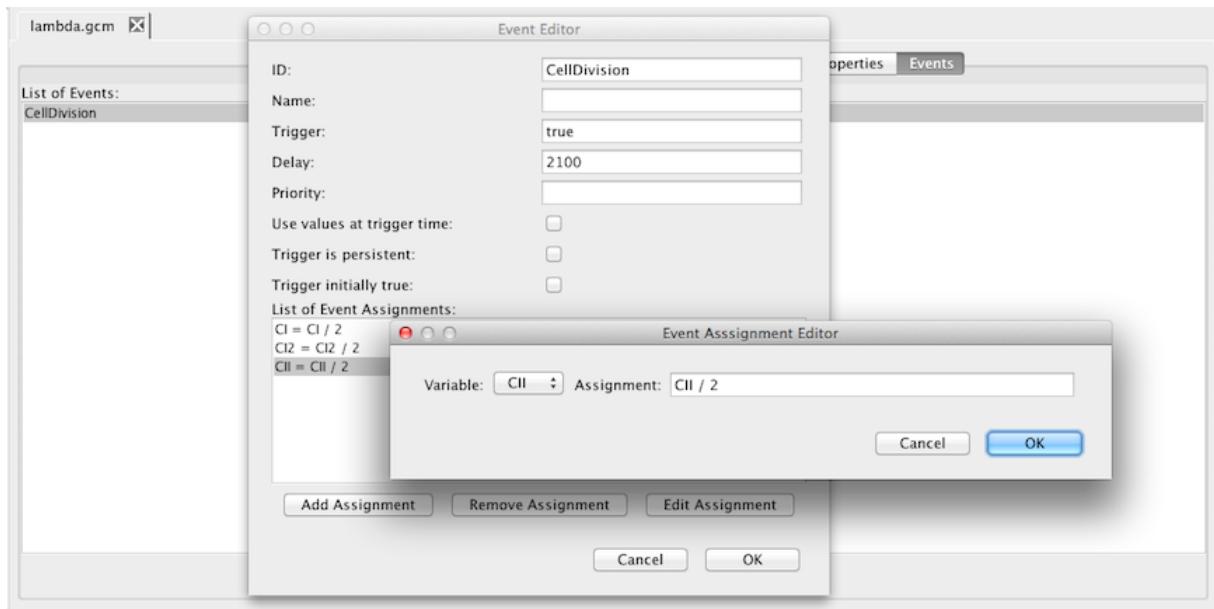


Our analysis methods can provide histograms that show the proportion of simulations that either satisfy a CSL property or are terminated due to a constraint. Analysis can also show time series plots showing the proportion of simulations at each time point that have either satisfied a CSL property or terminated due to a constraint.

3.11 Events

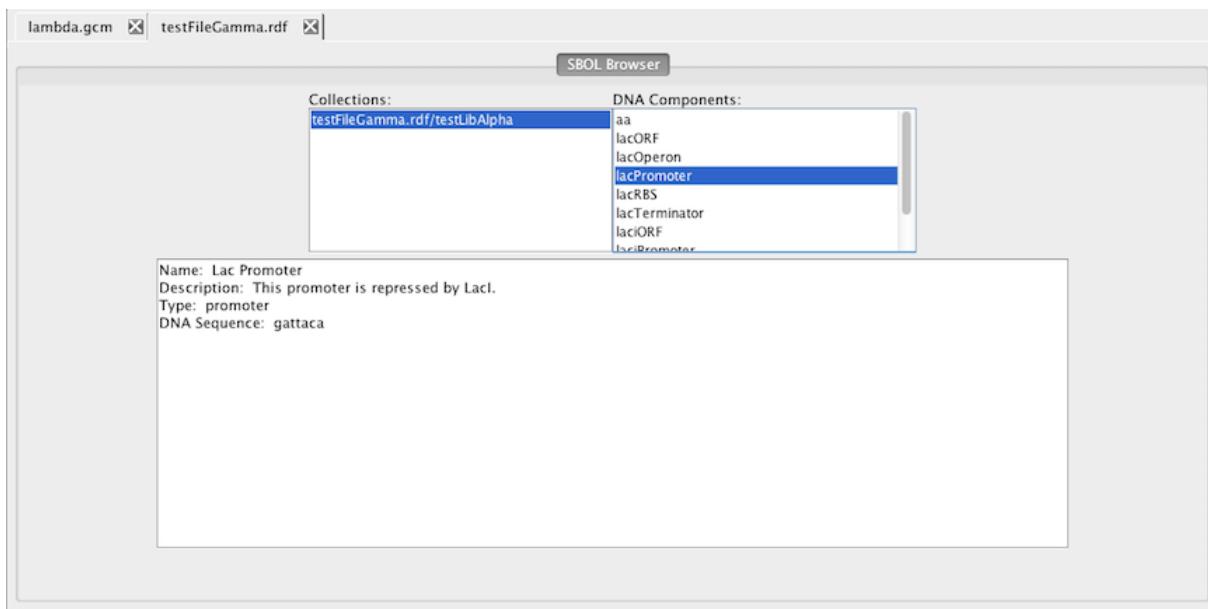
Events are used to specify discrete changes of compartment sizes, species amounts or concentrations, and parameter values. Each event is composed of the following items:

- ID: a unique ID composed only of alphanumeric characters and underscores.
- Name: an arbitrary string description (optional).
- Trigger: a mathematical formula which when it changes evaluation from false to true indicates that the event is triggered.
- Delay: a mathematical formula which is evaluated when an event is triggered, and the result is the amount of time before the event is to be executed.
- Priority: a mathematical formula which sets the priority for this event when multiple events are scheduled to be executed simultaneously. In this situation, the event with the highest priority is the next to be executed.
- Use values at trigger time: this Boolean indicates if values for the event assignments should be calculated at trigger time or execution time (default=false).
- Trigger is persistent: this Boolean indicates the behavior when a trigger expression becomes false before an event is executed. If it is persistent, then it still executes when ready. If it is not persistent, then the event is disabled and no longer scheduled to execute (default=false).
- Trigger is initially true: this Boolean indicates the behavior when a trigger evaluates to true at time 0. If it is initially true, there is no change in evaluation, so the event is not triggered. If it is not initially true, there is now a change in evaluation, so the event is triggered.
- List of Event Assignments: these indicate how the state is supposed to change when the event executes. The add, remove, and edit assignment buttons to update them. In the event assignment editor, the variable to change must be selected and the assignment to be performed must be specified as a mathematical formula.

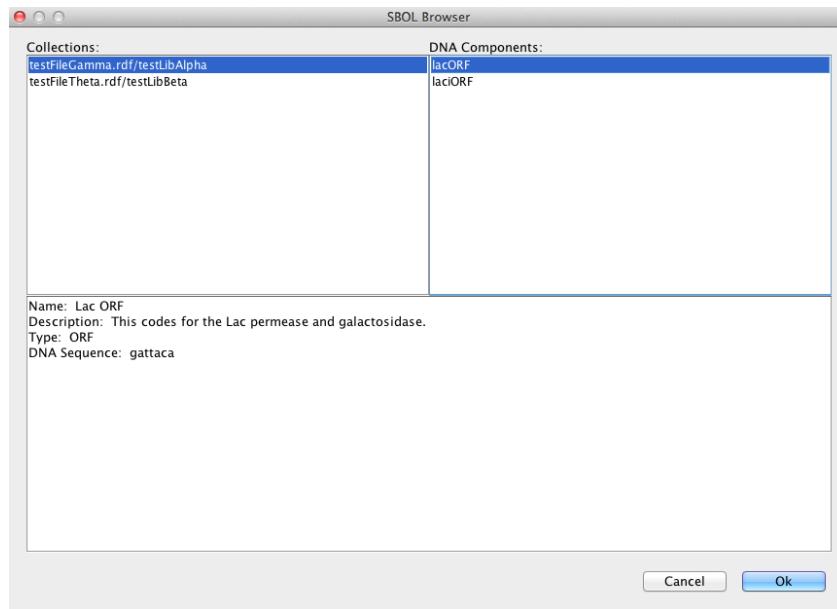


4 SBOL Browser

SBOL is an emerging standard under development for the exchange of information about synthetic biology designs. An SBOL file includes *Collections of DNA Components*. Each DNA component has a unique ID, name, description, type, and a DNA sequence. A DNA component can be a simple sequence feature like a promoter, ribosome binding site, open reading frame (i.e., gene), or terminator. It can also be an annotated DNA sequence that includes a several of these individual features perhaps organized hierarchically. For example, a DNA component may include a promoter followed by a ribosome binding site followed by a open reading frame followed by a terminator. iBioSim includes an SBOL browser that allows the user to view an individual SBOL file by clicking on it in the list of project files. In this browser, you can highlight individual DNA components and see the information stored about them.

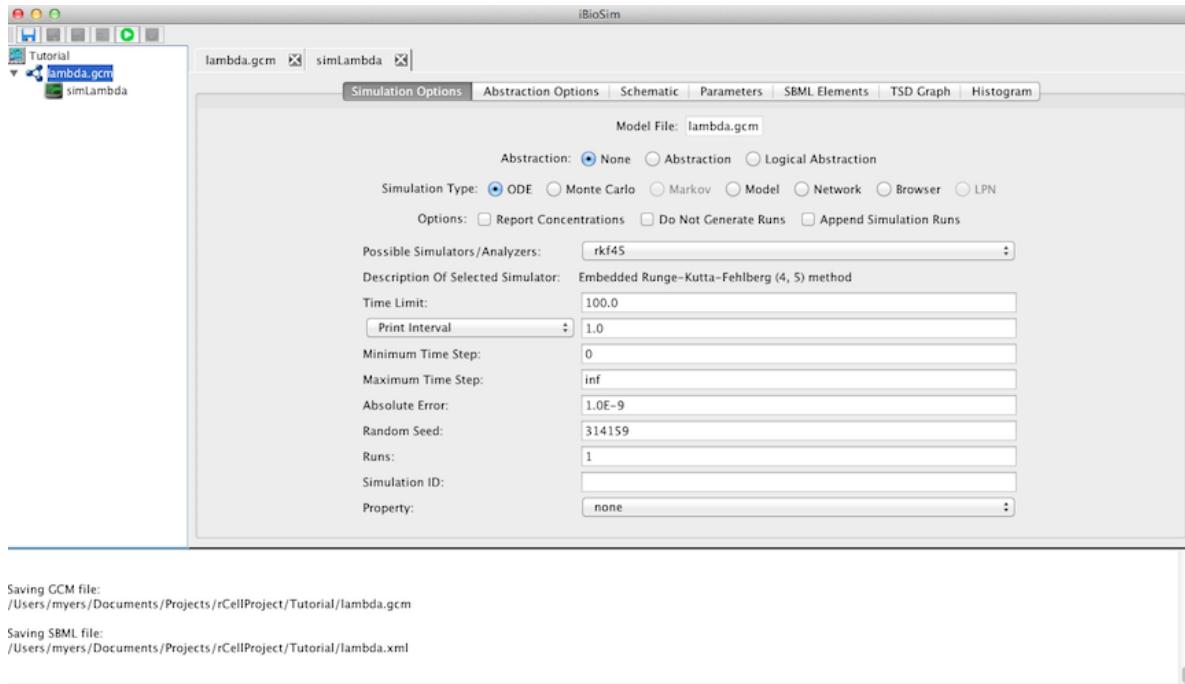


A similar SBOL browser is available for associating DNA components to a model. Namely, for a promoter, you can associate both a DNA component to the promoter as well as a terminator for the transcription initiated at this promoter. For a species, you can associate both a DNA component for the open reading frame for the gene that produces this species as well as the ribosome binding site where translation begins for this gene. This SBOL browser is opened by clicking on an Associate SBOL button within either the Species Editor (see Section 3.1) or Promoter Editor (see Section 3.4). This browser only shows DNA components of the appropriate type. For example, when associating a species to its open reading frame, only DNA components of the type open reading frame are shown.



5 Analysis Tool

The analysis tool is used to analyze biochemical reaction network models. iBioSim comes with a number of simulation methods, ranging from continuous-deterministic (ODE) simulation methods to discrete-stochastic (Monte Carlo) simulation methods. In order to perform efficient temporal behavior analysis, various model abstractions can also be automatically applied. Many of the analysis and abstraction routines are implemented within the reb2sac tool described in Kuwahara's PhD Dissertation (UofUtah 2007). An analysis view includes several tabs. The Simulation Options tab described in Section 5.1 selects the different simulation methods and parameters. The Abstraction Options tab described in Section 5.2 configures model abstraction. The Schematic tab described in Section 5.3 allows the user to modify or sweep various parameters on the schematic. It also provides an alternative way of visualizing simulation data upon the schematic. The Parameters tab allows the user to modify or sweep model generation and global parameters, and it is described in Section 5.4. The SBML elements tab described in Section 5.5 allows the user to add or remove parts of the model during analysis. The TSD Graph tab is a graph editor for some series data, and it is described in Section 7. Finally, the Histogram tab is a graph editor for probability data, and it is described in Section 8.



5.1 Simulation Options

The first set of radio buttons in this tab specifies the type of abstraction.

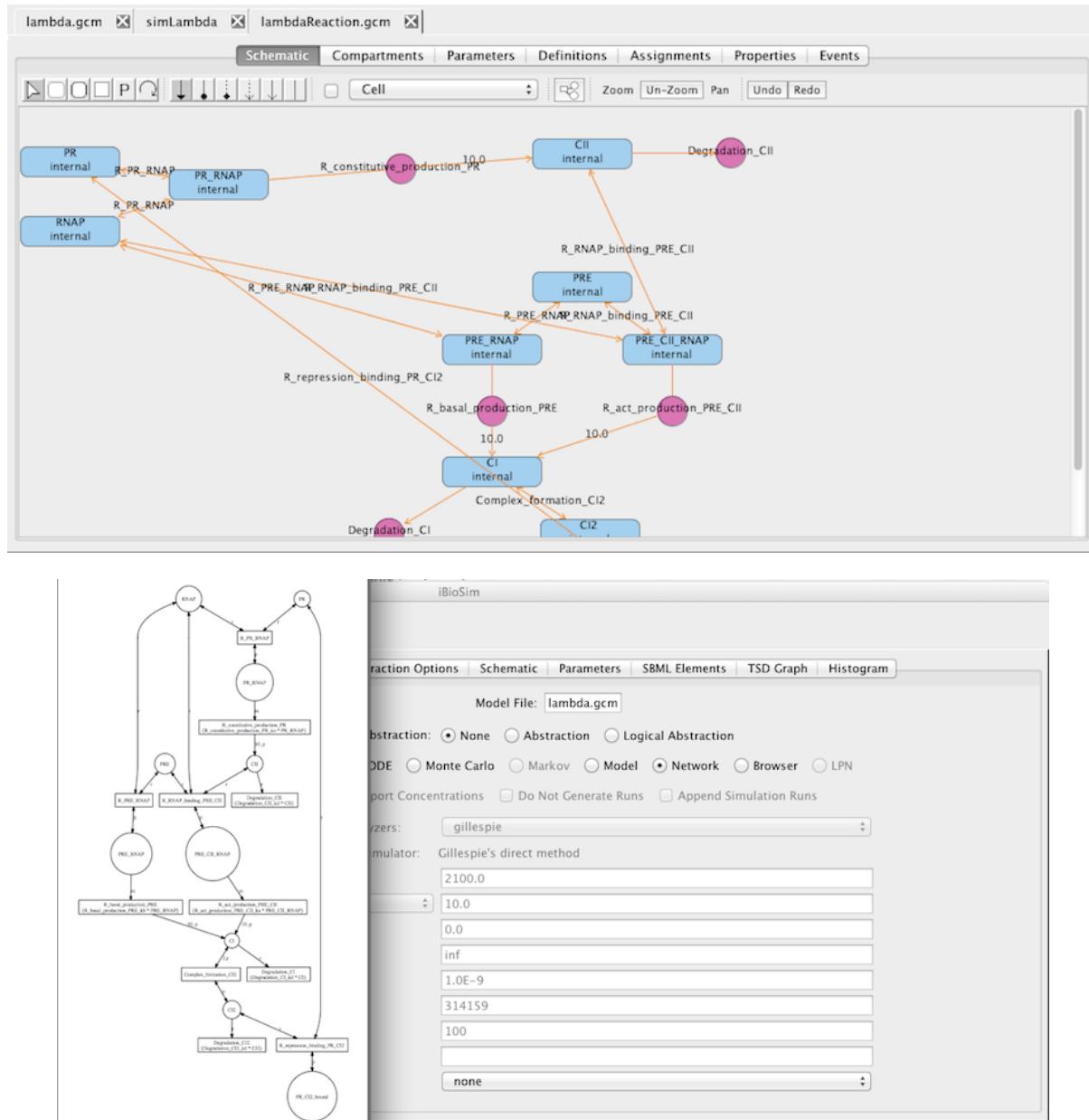
- None: use no abstraction.
- Abstraction: perform reaction-based abstraction.
- Logical Abstraction: perform both reaction-based and logical abstractions.

The second set of radio buttons specify the type of analysis.

- ODE: continuous-deterministic simulation.

- Monte Carlo: discrete-stochastic simulation.
- Markov performs temporal probability distribution analysis on finite-state Markov chain models (this requires logical abstraction).
- Model: produces a flattened model and puts it in the list of project files.
- Network: outputs the model in the GraphViz format for display by dotty.
- Browser outputs the model in xhtml format for display in a web browser.
- LPN: produces an LPN model and puts it in the list of project files (this requires logical abstraction).

Some results selecting Model, Network, and Browser are shown below.



Unit ID	Definition
u_1_mole_n1	(mole) ⁻¹
microLitre	0.001•litre
nanoMole	1e-09•mole
u_1_second_n1	(second) ⁻¹
u_1_mole_n1_1_second_n1	(mole) ⁻¹ •(second) ⁻¹

Compartment ID	Dimensions	Initial Size	Units	Constant
Cell	3	1	none	True

Species ID	Compartment	Initial Value	Units	Conversion Factor	Boundary	Constant	HasOnlySubstanceUnits
CI	Cell	0 (amount)	mole	none	False	False	True
CI2	Cell	$5^* CI$	mole	none	False	False	True
CII	Cell	0 (amount)	mole	none	False	False	True
PRE	Cell	1 (amount)	none	none	False	False	True
PRE_RNAP	Cell	0 (amount)	none	none	False	False	True
PRE_CII_RNAP	Cell	0 (amount)	none	none	False	False	True
PR	Cell	1 (amount)	none	none	False	False	True
PR_RNAP	Cell	0 (amount)	none	none	False	False	True
PR_CI2_bound	Cell	0 (amount)	none	none	False	False	True
RNAP	Cell	30 (amount)	none	none	False	False	True

Parameter ID	Initial Value	Units	Constant
R_repression_binding_PR_CI2_kr_r	1	u_1_second_n1	True
R_RNAP_binding_PRE_CII_Ka	0.00161	u_1_mole_n1	True

The next group of options are for simulation based analysis only.

- Report concentrations: if checked, report concentrations rather than amounts (default=amounts).
- Do Not Generate Runs: if checked, simulation data is not produced though summary probabilistic data is still produced (default=Generate Runs).
- Append Simulation Runs: if checked, additional simulation runs are added to the existing set of simulation runs rather than first removing the previous runs (default=overwrite). Note that the seed changes automatically when this gets checked because otherwise the additional runs will likely be the same as the previous set.

The next field specifies the simulation method you want to use based on the simulation type you specified. The methods available are:

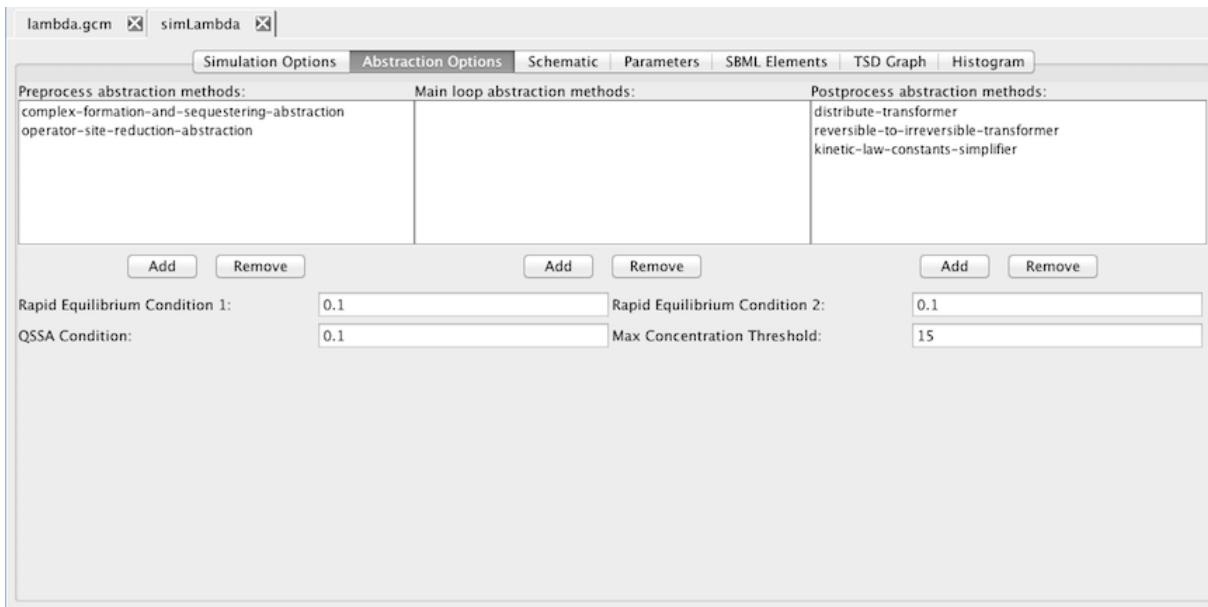
Type	Method ID	Description
ODE	Euler	The forward Euler Method
ODE	gear1	Gear Method M=1
ODE	gear2	Gear Method M=2
ODE	rk4imp	Implicit 4th order Runge-Kutta at Gaussian points
ODE	rk8pd	Embedded Runge-Kutta Prince-Dormand (8,9) method
ODE	rkf45	Embedded Runge-Kutta-Fehlberg (4, 5) method
Monte carlo	Gillespie	Gillespie's SSA direct method
Monte carlo	GillespieJava	Java implementation of Gillespie's SSA direct method
Monte carlo	mpde	iSSA using marginal probability density evolution
Monte carlo	mp	iSSA using the mean path
Monte carlo	mp-adaptive	iSSA using the mean path and adaptive step size
Monte carlo	mp-event	iSSA using the mean path and event count step size
Monte carlo	emc-sim	Use jump count as next reaction time
Monte carlo	bunker	Uses mean for next reaction time
Monte carlo	nmc	Uses normally distributed next reaction time
Markov	steady-state	Steady-state Markov chain analysis
Markov	transient	Transient Markov chain analysis
Markov	reachability	Only perform reachability analysis
Markov	atacs	Use <code>atacs</code> steady-state Markov analysis engine
Markov	ctmc-transient	Transient distribution analysis

There are some properties that need to be set for simulation. The table below specifies these:

Field	Description
Time Limit	The simulation time limit
Choose one:	
Print Interval	The print time interval for each simulation run
Minimum Print Interval	Print on change but no more often than this interval
Number of Steps	Number of steps to print
Minimum Time Step	The smallest time step allowed
Maximum Time Step	The largest time step allowed (also the time step used for the Euler method)
Absolute Error	Used by the adaptive time step ODE methods
Random Seed	An integer number as a seed to generate random numbers
Runs	The number of random simulation runs to perform
Simulation ID	Creates a simulation directory with the ID name

5.2 Abstraction Options

Abstraction is performed in three steps. There is a preprocess step which is a sequence of abstractions performed once on the initial model. The main loop iterates through a group of abstractions until there is no change in the model. Finally, there is a postprocess step which is a sequence of abstractions performed once at the end. Clicking on the Add button brings up a list of all the possible abstraction methods. The selected abstraction method is added after the highlighted abstraction method in the list. If not method is highlighted, it makes it the first abstraction in the list.



iBioSim supports many different types of abstraction. However, there are a few critical ones that we list here:

- complex-formation-and-sequestering-abstraction: this attempts to remove complex formation reactions. It replaces the complex species in rate laws with a function of its constituent species.
- operator-site-reduction-abstraction: this removes reactions and corresponding species involved in the binding of transcription factors to operator sites.
- distribute-transformer: applies the distributive law to kinetic law formula to make them easier to identify the forward and reverse rates within a reversible reaction.
- reversible-to-irreversible-transformer: this converts a reversible reaction into two irreversible reaction. This is critical for the Monte Carlo simulation methods that require there to be no reversible reactions.
- kinetic-law-constants-simplifier: this replaces constant parameters within kinetic laws with their values to improve their evaluation time.

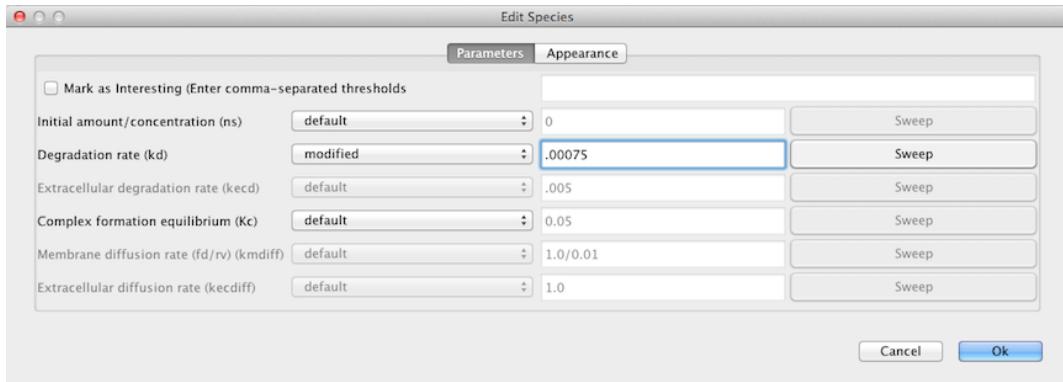
This tab also includes a few parameters for the abstraction methods.

- Rapid Equilibrium Condition 1 specifies threshold T1 such that the rapid equilibrium condition fails when $T1 > E0/(S0 + k - 1/k1)$.
- Rapid Equilibrium Condition 2 specifies threshold T2 such that the rapid equilibrium condition fails when $T1 > k2/k - 1$.
- The QSSA condition specifies threshold T used by the QSSA abstraction method where $T > E0/(S0 + KM)$.
- The Max concentration threshold specifies the maximum number of molecules that a species can have initially and still be considered an operator site by the operator site reduction.

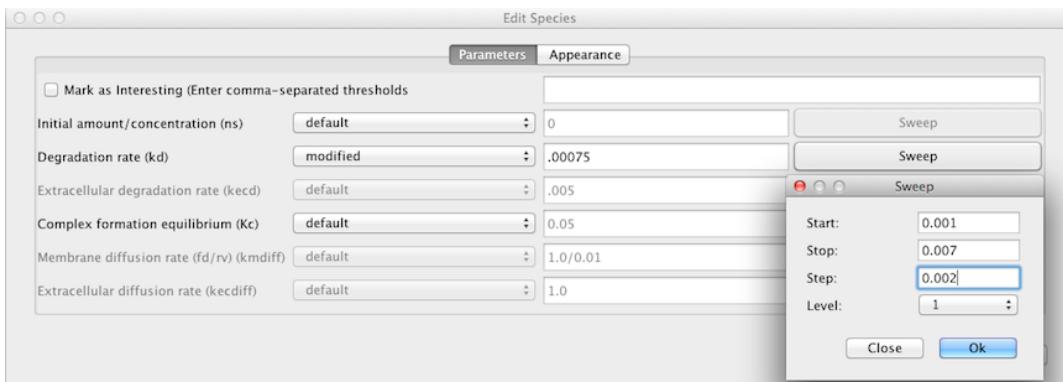
Note that these are not used by the common abstractions listed above.

5.3 Schematic

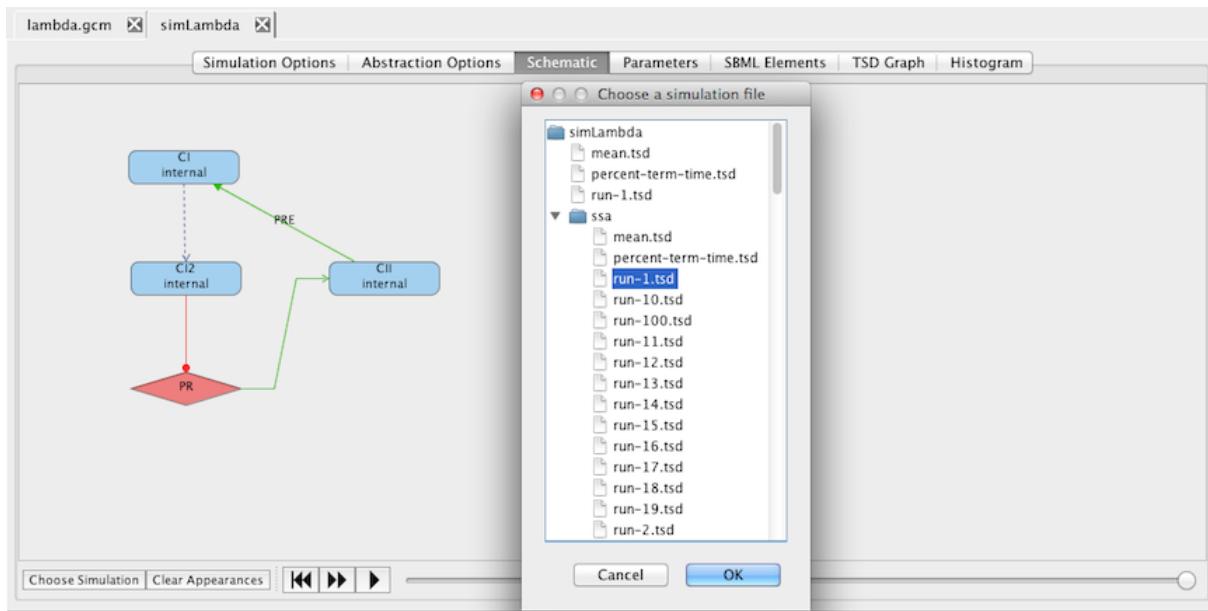
Using the schematic tab, you can adjust initial values and parameters allowing one to perform simulations to determine the effect of these changes. Clicking on any species, promoter, reaction, or influence brings up the corresponding editor. To change a value, switch the corresponding combo box to modified which will then allow you to change the value.



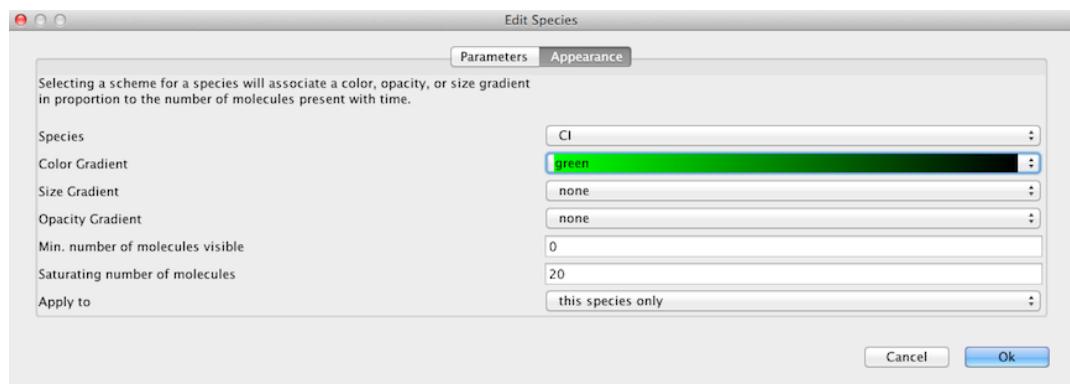
In addition to making single changes, you can also sweep a value as shown below. When you click on the Sweep button, it brings up a window where you can select the start value, the stop value, and the step value. The level indicates how the sweep should perform when multiple variables are swept at the same time. All variables at the same level are changed at the same time. Furthermore, all variables on level 2 are stepped through all their values before changing the values of those variables on level 1. After the values on level 1 are changed, the values on level 2 are stepped through all their values again.



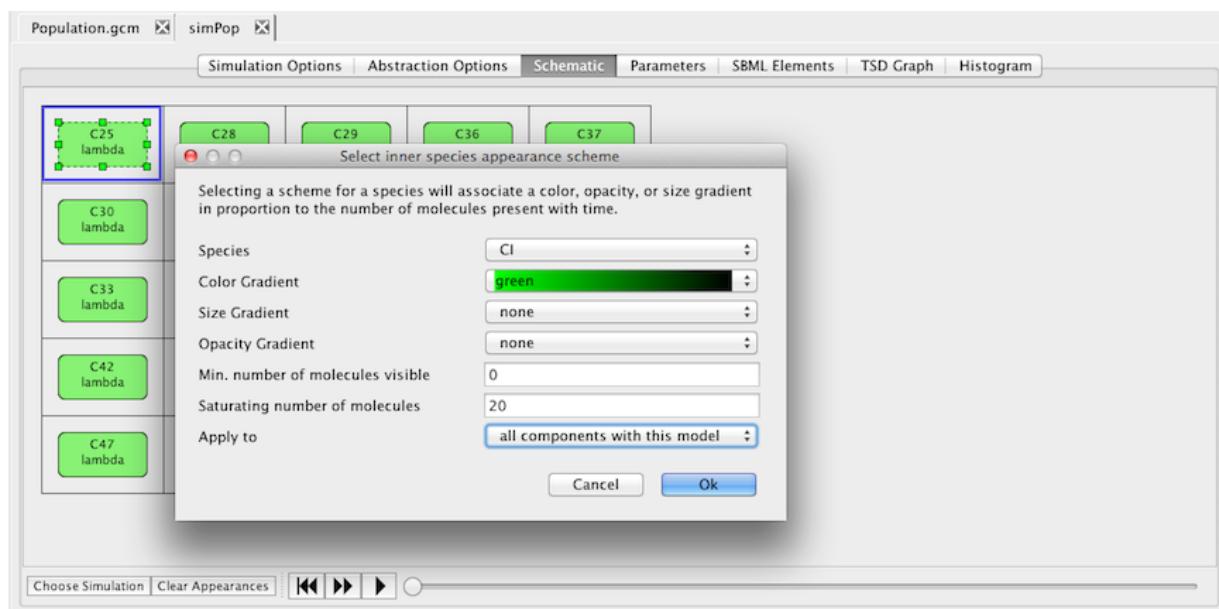
The schematic tab can also be used to visualize simulation results. To do this, after you have generated some simulation results, you can press the Choose Simulation button to bring up a window with all the simulations in this analysis view. You can then select the data that you would like to visualize.



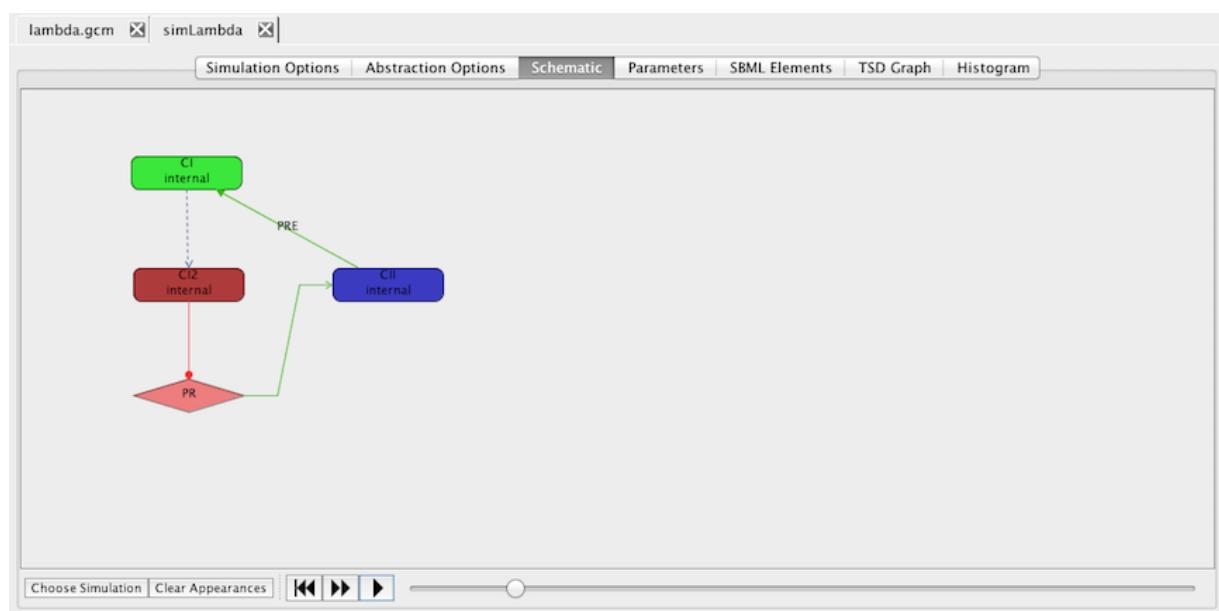
If you now click on a species, component, or grid location, you can modify how it appears as you playback the simulation. You can have it change color on a gradient, change size, or change opacity. You can also select the range of molecule counts to use for the gradients. Finally, you can indicate that these selections are either for this species or all species in the model.



The appearances editor for components and grid locations is similar. The differences are that you can select any species within the component (or diffusible species for the grid location). You also can copy the settings to all instantiations of the same model.

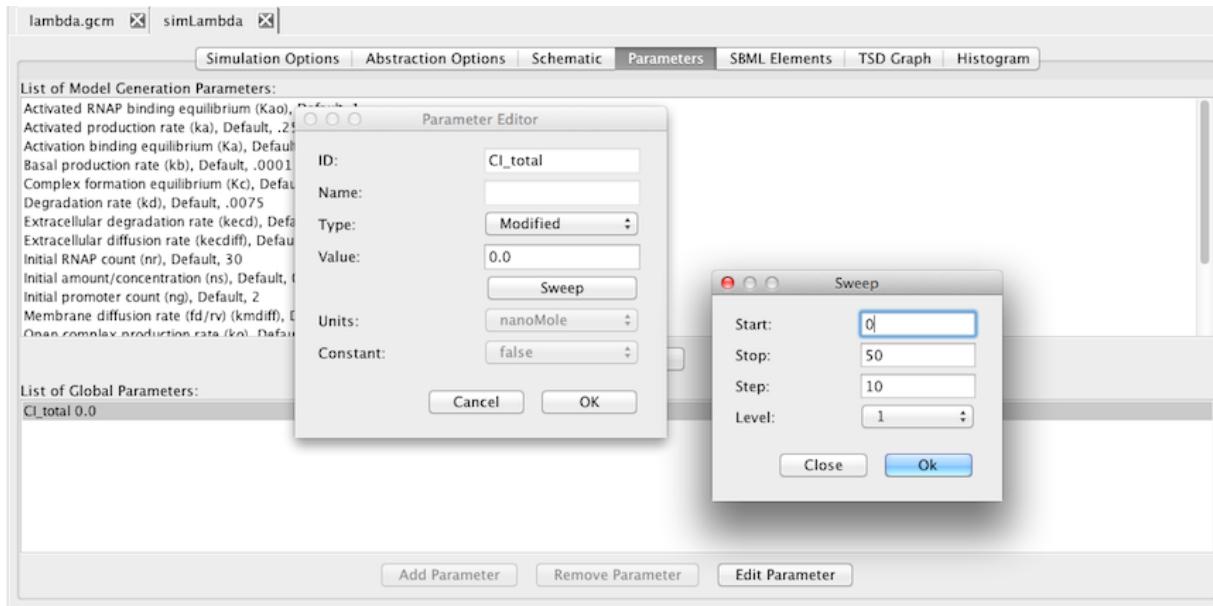


Once you have made your selections, you can now playback the simulation. You can either single step the simulation by pressing the icon or play continuously by pressing the icon. The playback can also be paused by pressing the icon and restarted by pressing the icon.



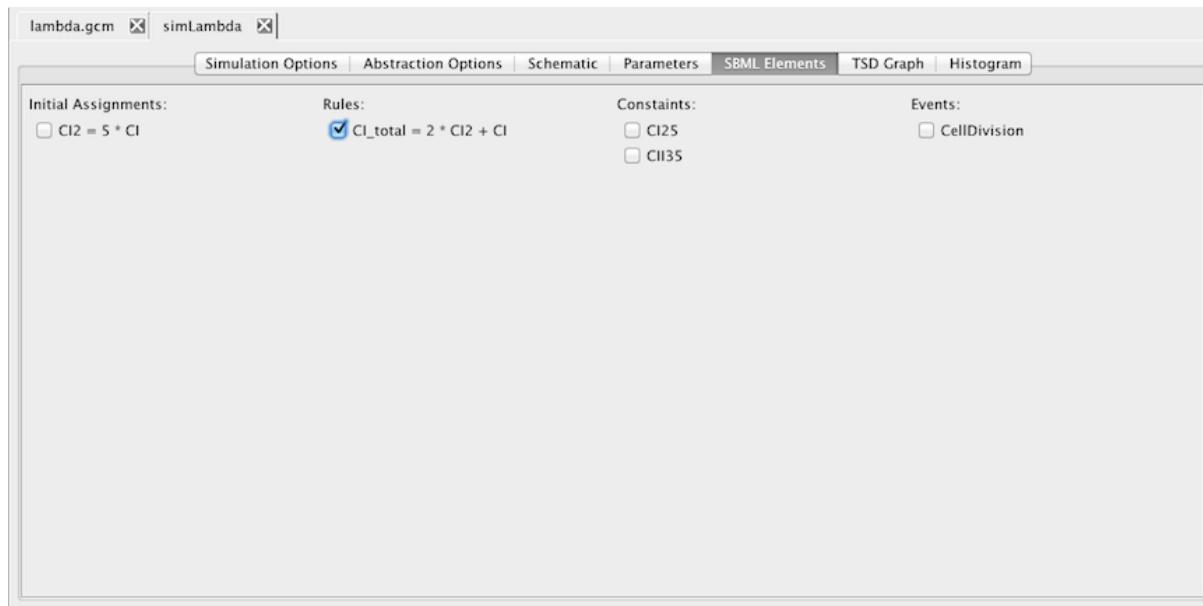
5.4 Parameters

The parameter tab allows the user to modify the value of any model generation or global parameter for a given analysis. Like the values on the schematic tab, they can also be swept to generate multiple simulation runs stepping through different values.



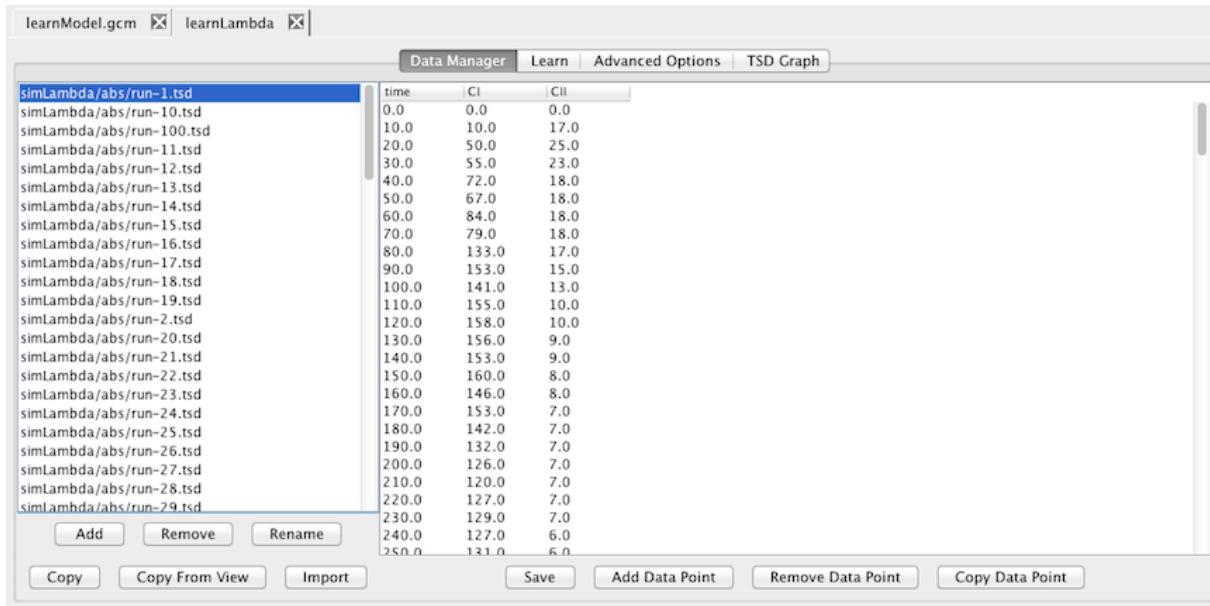
5.5 SBML Elements

The SBML elements tab allows you to select which SBML model elements to include in your analysis. This includes initial assignments, rules, constraints, and events. Elements that are checked are used during analysis. Otherwise, they are not used.



6 Learn Tool

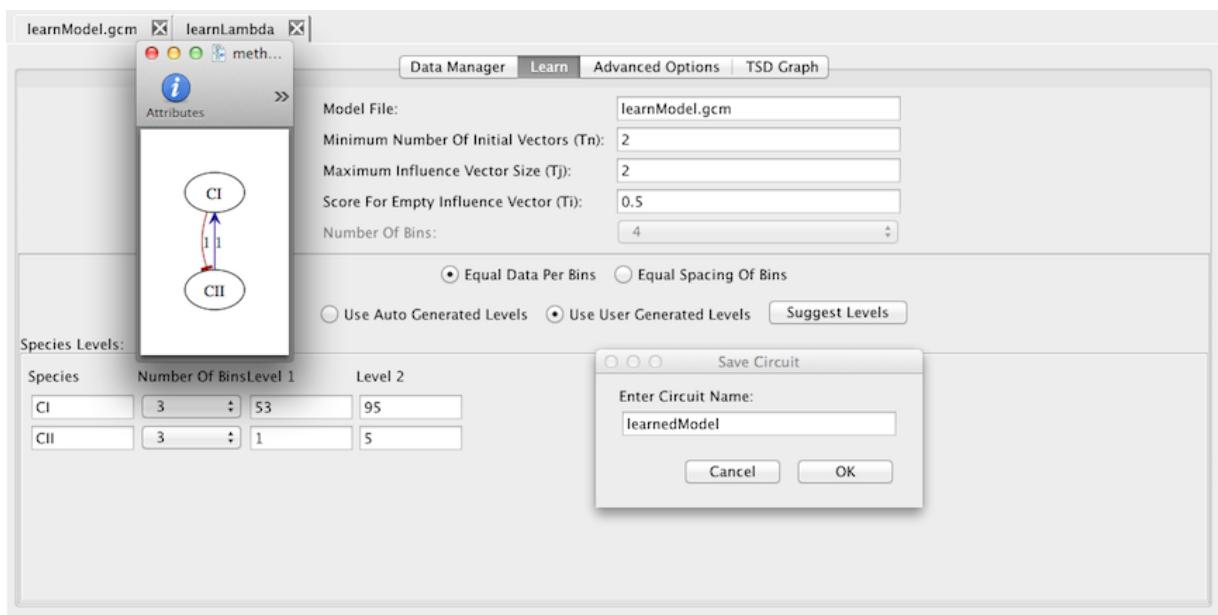
The Learn Tool is used to discover genetic circuit connectivity from time series data. This tool uses the GeneNet algorithm described in Barker's PhD dissertation (University of Utah 2007). The first tab of the Learn Tool is the *data manager* which is shown below. It is used to both enter time series experimental data as well as bring data into the learn view. The Add button is used to create a new data file. After pressing this button, enter the name of the new data file, and then enter the data for this file using the data editor to the right. The Remove button deletes all highlighted files. Note that after highlighting one file, you can use the ctrl key to highlight additional files or the shift key to highlight a range of files. The Rename button is used to change the name of a data file. The Copy button copies a data file. The Copy From View button brings up a list of all analysis and learn views in the current project, and data from the selected view will be copied into this learn view. Finally, the Import button brings up a file browser, and it allows you to import a data file from outside this project. These files can be in time series data (TSD) format (see Section 12), comma separated value (CSV) format, or tab delimited format (DAT). The contents of the data file highlighted on the left appear in the data editor on the right. Individual data entries can be modified, new data points can be added using the Add Data Point button, data points can be removed using the Remove Data Point button, and data points can be copied using the Copy Data Point button. When you are satisfied with all your changes, you should press the Save button to record your changes.



The second tab allows the user to configure the basic options for the Learn Tool. The basic options include:

- Minimum Number of Initial Vectors (T_n) (default=2):
T_n is a threshold value used in the CreateInfluenceVectorSet algorithm and represents the minimum number of influence vectors constructed in this algorithm.
- Maximum Influence Vector Size (T_j) (default=2):
T_j is a threshold value used in the CombineInfluenceVectors algorithm to determine the maximal size of merged influence vectors.

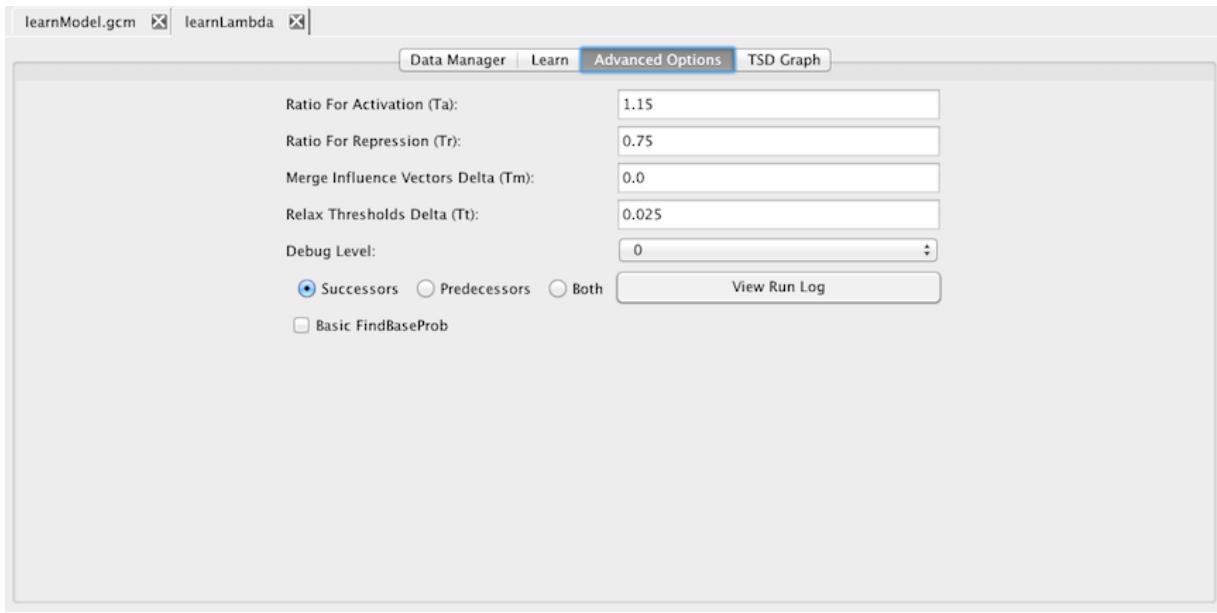
- Score for Empty Influence Vector (Ti) (default=0.5):
The score for an influence vector with no influences in it.
- Number of Bins (default=4):
The number of bins value specifies how many values the encoded time series data can assume.
- Equal Data Per Bins / Equal Spacing of Bins:
This radio button selects whether the auto generated levels should be determined by equally dividing the data between the bins or by equally dividing the range of the data.
- Use Auto Generated Levels / Use User Generated Levels:
This radio button allows the user to select whether they want the levels separating the bins to be auto generated or the user would like to provide them.
- When using user provided levels, the Suggest Levels button will provide the levels that would have been auto generated as a suggestion. These levels can then be edited by the user. The number of bins for each species can also be individually adjusted.



The third tab allow the user to select some advanced options for the Learn Tool. These include:

- Ratio for Activation (Ta) (default=1.15):
A probability ratio above this value results in a vote for an influence vector that has a majority of activation influences.
- Ratio for Repression (Tr) (default=0.75):
A probability ratio above this value results in a vote for an influence vector that has a majority of repression influences.
- Merge Influence Vectors Delta (Tm) (default=0.0):
Two influence vectors cannot be merged unless the difference in their scores is less than this value.
- Relax Thresholds Delta (Tt) (default=0.025):
The values of Ta and Tr are modified by this amount when these thresholds are relaxed.

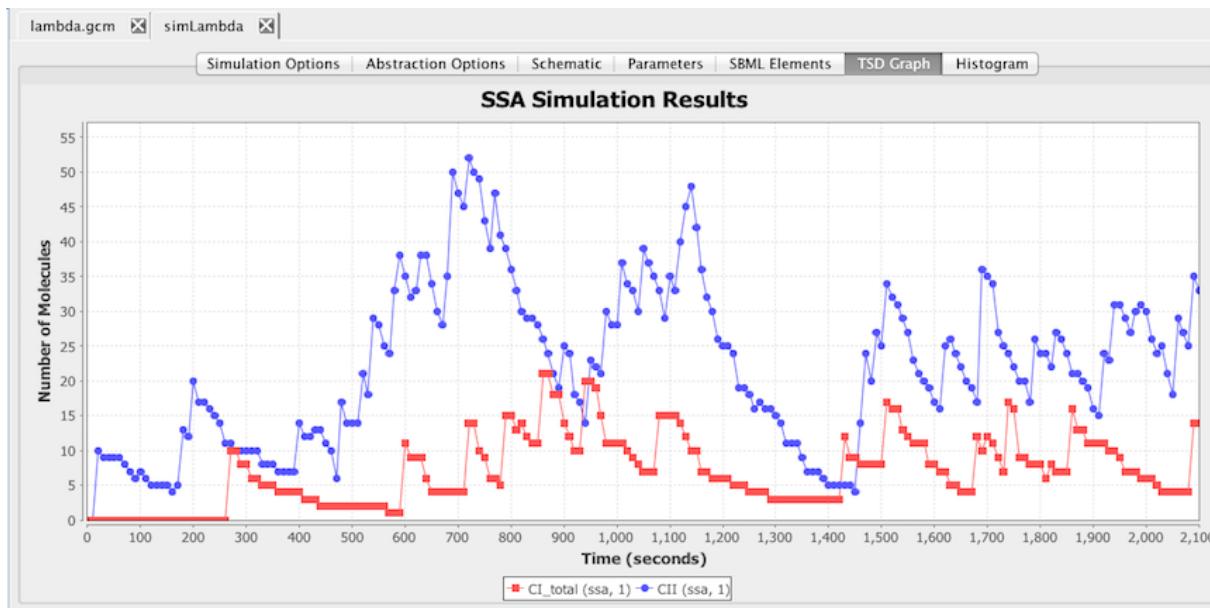
- Debug Level (default=0):
This controls how much information is displayed by the GeneNet algorithm when it runs.
- Successors / Predecessors / Both (default=Successors):
This radio button selects whether successor data point pairs, predecessor data point pairs, or both are used.
- Basic FindBaseProb (default=unchecked):
When selected, the basic FindBaseProb function is used.
- View Log button:
Opens a window contain the log file generated by GeneNet during the learn process for debugging purposes.



Once the Learn Tool has been provided data and configured as desired, pressing the Save and Run icon causes the tool to attempt to produce a model that may have produced this data. The resulting model is displayed using GraphViz, and the user is prompted to provide a model ID for the resulting model. If learning fails, an error message will be reported instead.

7 TSD Graph Editor

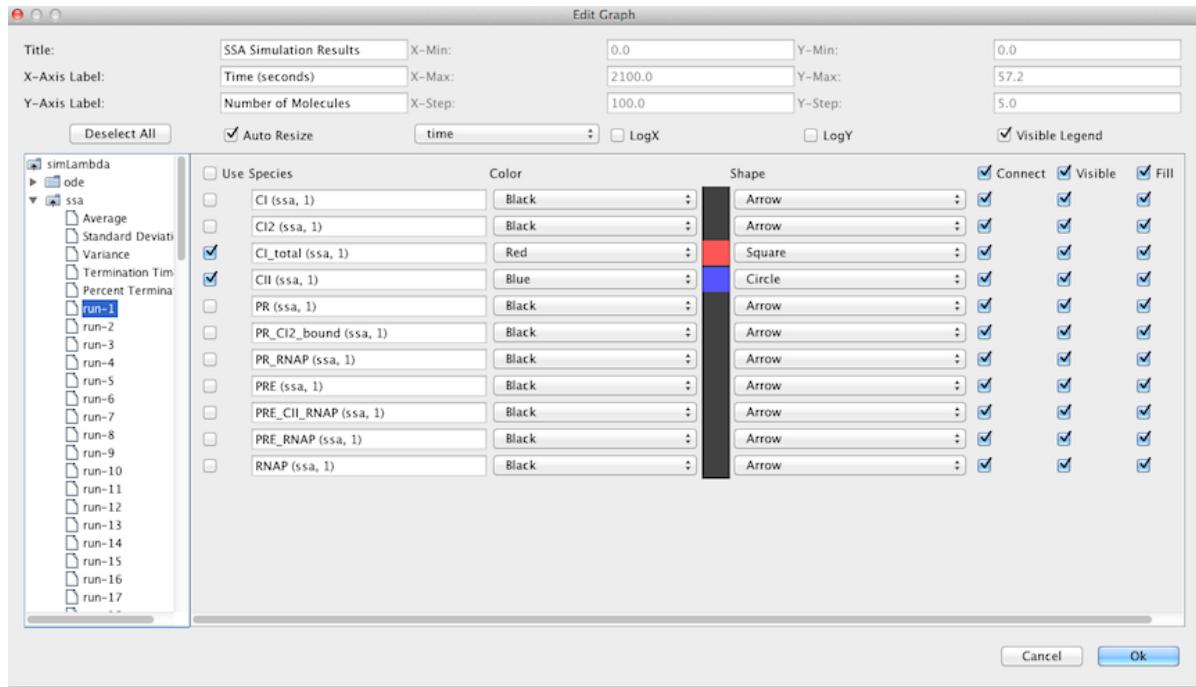
The TSD graph editor appears as a tab in both analysis and learn views. TSD graphs can also be created at the top-level of the project to allow you to integrate results from several analysis or learn views. These graphs can be created using the New → TSD Graph menu option in the File menu. Once created, they can be viewed and edited by double clicking on the graph in the project window. An example graph is shown below.



In the TSD graph editor, a graph is created by double clicking on the graph. You can then set various parameters and select what values you would like to have graphed. The parameters that you can select for a graph include:

- Title - the title of the graph.
- X-Axis Label - the label displayed for the x-axis.
- Y-Axis Label - the label displayed for the y-axis.
- X-Min - the starting value for the x-axis.
- X-Max - the ending value for the x-axis.
- X-Step - the increment for the x-axis.
- Y-Min - the starting value for the y-axis.
- Y-Max - the ending value for the y-axis.
- Y-Step - the increment for the y-axis.
- Auto Resize Check Box - determines whether to automatically resize the graph for best fit.
- X-Axis Combo Box - selects which variable to use for the x-axis (default=time).
- LogX - selects that the scale of the x-axis should be logarithmic.

- LogY - selects that the scale of the y-axis should be logarithmic.
- Visible Legend - selects that the legend should appear on the graph.



The data selection menu on the left displays all of the available sets of data that can be graphed. For a top-level graph, these data sets are organized hierarchically. Hierarchy is also introduced when different simulations in an analysis view are given different simulation IDs or after performing an analysis while sweeping parameter values. In addition to being able to plot results from individual simulation runs, the average, standard deviation, and variance are also provided. Finally, when constraints are used, the Termination Time and Percent Termination data is also computed. The Termination Time gives a plot of the number of runs that have terminated versus time while Percent Termination gives the percentage of runs that have terminated versus time. After selecting a data set, one can select individual variables (typically species) to graph and how they are to be displayed. In other words, for each species, there are the following options:

- Use Check Box - determines whether or not this species is displayed on the graph. Checking or unchecking the box at the top changes the state for all species in the data set.
- Species Label - the name displayed in the legend.
- Drop Down Menu Of Colors - the color that is used for this species.
- Color Palette - clicking on the color palette lets one customize the color selection.
- Drop Down Menu Of Shapes - the shape that is used to mark the data points.
- Connect Check Box - determines whether to connect the points with a line. Checking or unchecking the box at the top changes the state for all species in the data set.
- Visible Check Box - determines whether shapes are visible on the line. Checking or unchecking the box at the top changes the state for all species in the data set.

- Fill Check Box - determines whether shapes are filled on the line. Checking or unchecking the box at the top changes the state for all species in the data set.

Note that a check mark appears on a data set to indicate that some species have been selected in that data set. Also, all species can be deselected by pressing the Deselect All button.

When in a TSD graph editor, pressing the Save icon  saves the settings for the graph to a file, so when you re-open the graph, it will reload this data and display in the same way as before. Pressing the Save As icon  prompts for a new filename and creates a new top-level graph with that name. Finally, pressing the Export icon  prompts for a filename and exports the data to the given name. The extension provided for the filename is used to determine how the graph is to be exported. The supported file types are:

- Time series data format (tsd), see Section 12..
- Comma separated value (csv).
- Column separated data (dat).
- Encapsulated postscript (eps).
- Joint Photographic Experts Group (jpg).
- Portable document format (pdf).
- Portable network graphics (png).
- Scalable vector graphics (svg).

If no extension is given, then the file type is the one specified in the file filter (default is pdf). For image (i.e., not data) file types, you will be prompted to give a desired pixel height and width for the file before the file is exported.

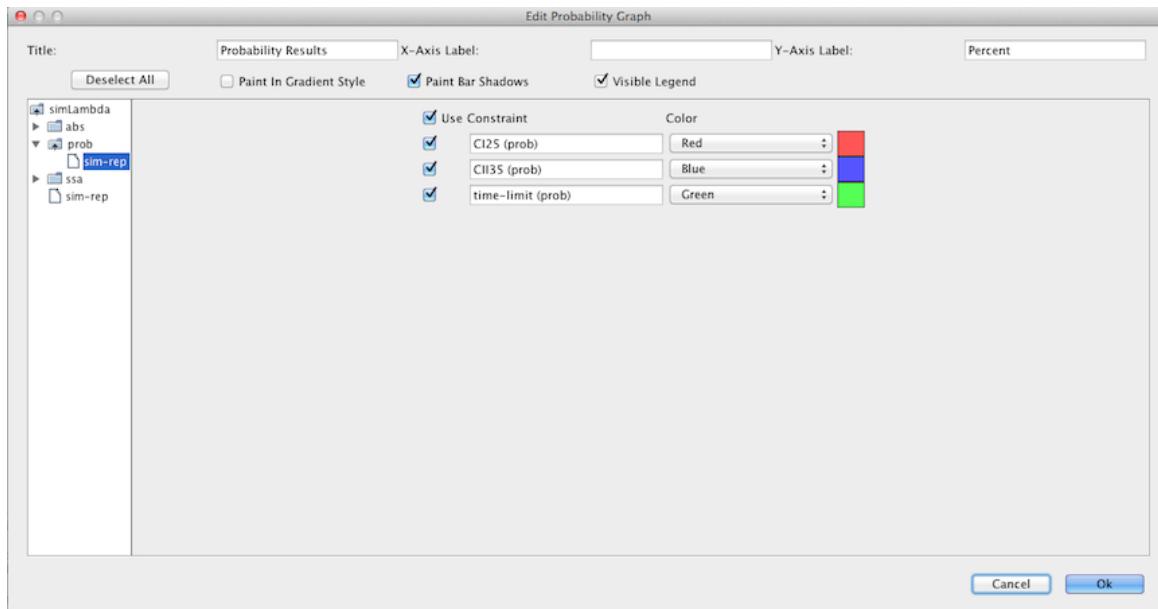
8 Histogram Graph Editor

iBioSim includes a histogram graph editor for visualizing probability data. In particular, this editor can display the reasons that a simulation terminated. Namely, it displays statistics on which constraint failed to hold allowing the user to determine the likelihood of various conditions. The histogram graph editor appears as a tab in analysis views. Histograms can also be created at the top-level of the project to allow you to integrate results from several analysis views. These graphs can be created using the New → Histogram menu option in the File menu. Once created, they can be viewed and edited by double clicking on the graph in the project window. An example histogram is shown below.



In the histogram graph editor, a graph is created by double clicking on the graph. You can then set various parameters and select what values you would like to have graphed. The parameters that you can select for a graph include:

- Title - the title of the graph.
- X-Axis Label - the label displayed for the x-axis.
- Y-Axis Label - the label displayed for the y-axis.
- Paint in Gradient Style - creates a color gradient in the bars.
- Paint Bar Shadows - enables the bars to cast shadows.
- Visible Legend - selects whether a legend should be included in the graph.



The data selection menu on the left displays all of the available sets of data that can be graphed. For a top-level graph, these data sets are organized hierarchically. Hierarchy is also introduced when different simulations in an analysis view are given different simulation IDs or after performing an analysis while sweeping parameter values. After selecting a data set, one can select individual constraints to graph. The constraint labeled time-limit indicates that the simulation terminated while all constraints were still satisfied. One can also select how each result is to be displayed. In other words, for each constraint, there are the following options:

- Use Check Box - determines whether or not this constraint is displayed on the graph. Checking or unchecking the box at the top changes the state for all constraints in the data set.
- Constraint Label - sets the name displayed in the legend.
- Drop Down Menu Of Colors - the color of the bar used for this constraint.
- Color Palette - clicking on the color palette lets one customize the color selection.

Note that a check mark appears on a data set to indicate that some constraints have been selected in that data set. Also, all constraints can be deselected by pressing the Deselect All button.

When in a histogram graph editor, pressing the Save icon saves the settings for the graph to a file, so when you re-open the graph, it will reload this data and display in the same way as before. Pressing the Save As icon prompts for a new filename and creates a new top-level graph with that name. Finally, pressing the Export icon prompts for a filename and exports the data to the given name. The extension provided for the filename is used to determine how the graph is to be exported. The supported file types are:

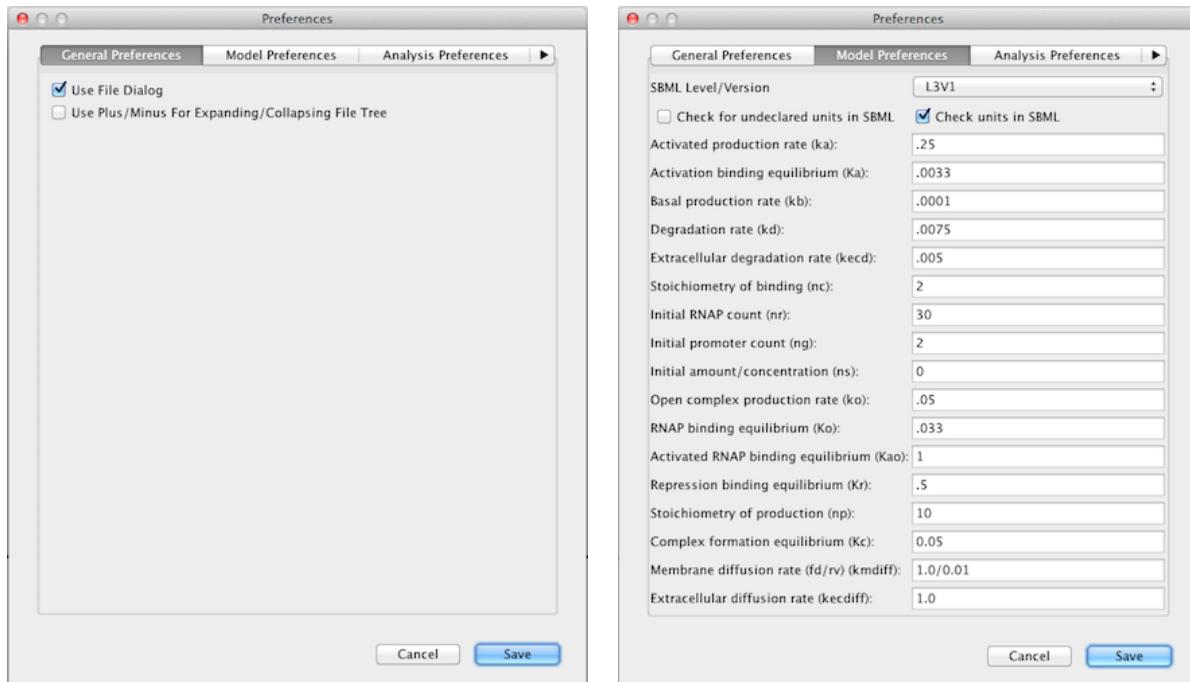
- Encapsulated postscript (eps).
- Joint Photographic Experts Group (jpg).
- Portable document format (pdf).
- Portable network graphics (png).

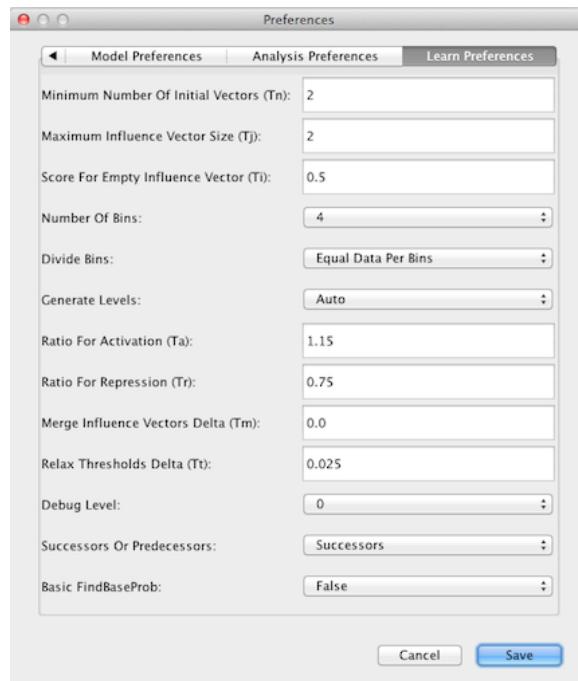
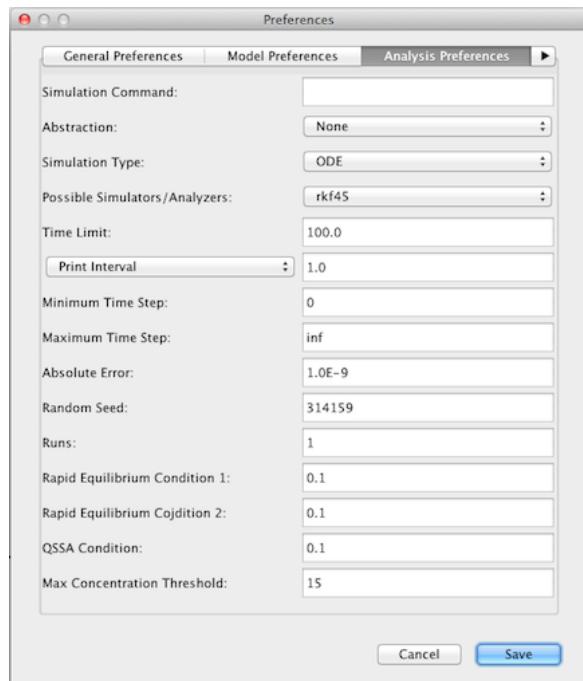
- Scalable vector graphics (svg).

If no extension is given, then the file type is the one specified in the file filter (default is pdf). For image (i.e., not data) file types, you will be prompted to give a desired pixel height and width for the file before the file is exported.

9 Preferences

User preferences can be set by selecting the **Preferences** option under the **File** menu on Linux and Windows or the **iBioSim** menu on MacOS. As shown below, under the General Preferences tab, the user can decide whether they wish to use a File Dialog for selecting files. If this is not checked, files are selected using the default Java File Chooser. One can also choose whether or not they want to use plus/minus for expanding and collapsing file trees. The Model Preferences tab allows users to select between Level 3 Version 1 of SBML or Level 2 Version 4. One can also select whether they wish to see warnings about undeclared units in SBML and whether they wish to check units at all. Finally, it allows users to change the default model generation parameter values. The Analysis Preferences tab allows users to change the default values used by the analysis tool. The simulation command in particular can be useful to either select an alternative simulator. We've used it to select a script that executes the simulation on a compute server. Finally, the Learn Preferences tab allows users to change the default values used by the learn tool.





10 Mathematical Formulas

Math formulas appear in many model constructs. These formulas are expressed as text strings using a simple syntax. In particular, model math formulas can include:

- Variables (compartment, species, parameter IDs, and reaction IDs)
- Real Numbers
- Built-in constants: exponentiale, pi, true, and false.
- Special variable time or t which returns the current simulation time.
- Mathematical operators including add (+), subtract (-), multiply (*), divide (/), and power (pow(x,y)).
- A function defined in the list of function definitions.
- Logical functions: and, or, xor, not.
- Relational functions: eq, neq, geq, gt, leq, and lt.
- Unary functions: abs, ceiling, exp, factorial, floor, ln, log, sqr, and sqrt.
- Trigonometric functions: cos, cosh, sin, sinh, tan, tanh, cot, coth, csc, csch, sec, sech, arccos, arccosh, arcsin, arcsinh, arctan, arctanh, arccot, arccoth, arccsc, arccsch, arcsec, and arcsech.
- The delay(expr1,expr2) function which returns the value of expr1 at a time expr2 time units earlier (not currently supported by analysis).
- The piecewise(value1, case1, value2, case2, ..., otherwise) function returns value1 if case1 is true, value2 if case2 is true, etc. If no cases are true, it returns the otherwise value.

iBioSim's simulators also support several random functions which are added by default to any model file. The following random functions, therefore, can also be used in model math formula:

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

11 Continuous Stochastic Logic (CSL) Formulas

To analyze probabilistic models using **iBioSim**, it is necessary to specify one or more properties of the model. **iBioSim** accepts property specifications using a subset of probabilistic temporal logic called *Continuous Stochastic Logic* (CSL). There are four types of CSL properties currently supported:

- Transient global formula of the form $\text{Pr}\{\text{PG} [\psi](\Psi)\}$ where ψ is a time bound and Ψ is state formula. This formula determines the probability that Ψ is always true in the interval defined by ψ .
- Transient eventually formula of the form $\text{Pr}\{\text{PF} [\psi](\Psi)\}$ where ψ is a time bound and Ψ is a state formula. This formula determines the probability that Ψ becomes true during the interval defined by ψ .

- Transient until formula of the form $\text{Pr}\{\Psi_1 \text{ PU } [\psi] \Psi_2\}$ where ψ is a time bound and Ψ_1 and Ψ_2 are state formula. This formula determines the probability that Ψ_1 remains true until Ψ_2 becomes true during the interval defined by ψ .
- Steady-state formula of the form $\text{St}\{\Psi\}$ where Ψ is a state formula. This formula determines the probability of being in a state that satisfies Ψ as time goes to infinity.

The time bound, ψ , can either be a relational operator ($<$, \leq , $=$, \geq , $>$) followed by a constant real time value or a time bound of the form $[l, u]$ where l and u are constant real time values. The state formula, Ψ , should evaluate to a Boolean, and it can include:

- Variables (compartment IDs, species IDs, parameter IDs, and reaction IDs)
- Real Numbers
- Mathematical operators: add (+), subtract (-), multiply (*), divide (/), and power (^).
- Logical functions: and (&), or (|), and not (~).
- Relational functions: equals (=), greater-than-or-equals (\geq), greater-than ($>$), less-than-or-equals (\leq), and less-than ($<$).

12 Time Series Data Format

The time series data (tsd) format is composed of a parenthesized and comma-separated set of time points. Each time point is composed of a parenthesized and comma-separated set of data for that time point. This first time point is composed of a set of strings that are the labels for the data entries. The first entry in each time point is by convention the time for that time point. Below is an example simulation of the species CI and CII from 0 to 1000 seconds with time points separated by 100 seconds.

```
(("time","CI","CII"), (0,0,0), (100,0,19), (200,20,25), (300,19,18), (400,17,20), (500,17,46),
(600,26,40), (700,43,43), (800,63,28), (900,72,34), (1000,72,28))
```

13 Tutorial

A detailed tutorial is available in the `docs` directory that comes with the distribution.

14 Reporting Bugs and Feature Requests

In order to report a bug or to request a change or feature, please send an email to:

`atacs-bugs@vlsigroup.ece.utah.edu`.

The subject line must begin with one of the following keywords or the mail will be filtered by our spam filters:

- BUG - error or crash of the software
- CHANGE - something which can be improved
- FEATURE - something new