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CellDesigner™ is being developed by

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Many thanks to the users who kindly provided us bug reports and feature requests!

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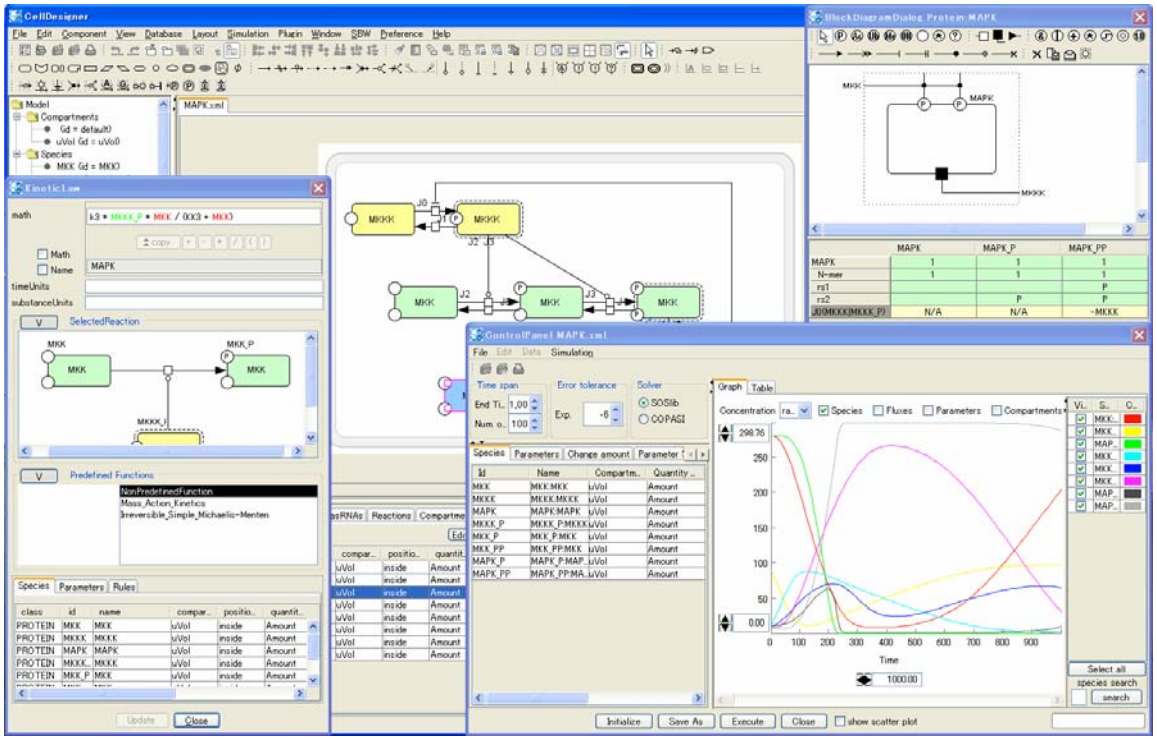
A. What is CellDesigner™

CellDesigner is a process diagram editor for drawing gene-regulatory and biochemical networks. Networks are drawn based on the process diagram, with graphical notation system proposed by Kitano, and are stored using the Systems Biology Markup Language (SBML), a standard for representing models of biochemical and gene-regulatory networks. Networks are able to link with simulation and other analysis packages through Systems Biology Workbench (SBW).

CellDesigner = SBML + SBGN + Simulation + Databases Connections



1. CellDesigner Major Features

- Easy-to-understand graphical notation (SBGN compatible)
- SBML-compliant
- Built-in simulator (SBML ODE Solver, Copasi)
- Integration with analysis tools and other simulators via SBW 2.x
- Database connections
- Intuitive user interface
- Extensive description of Compartments, Species, Reactions, and Proteins
- Export of images in PNG, SVG, JPG, and PDF formats
- Support of Block Diagram (*Proto-type)
- Plug-in development framework

1.1 New Features --- Version 4.1

CellDesigner 4.1 now supports an SBML Level 2 Version 4, export to BioPAX Level3, MIRIAM annotation, SABIO-RK, updating plug-in development framework, and overall GUI improvement.

→ See also: http://celldesigner.org for details.

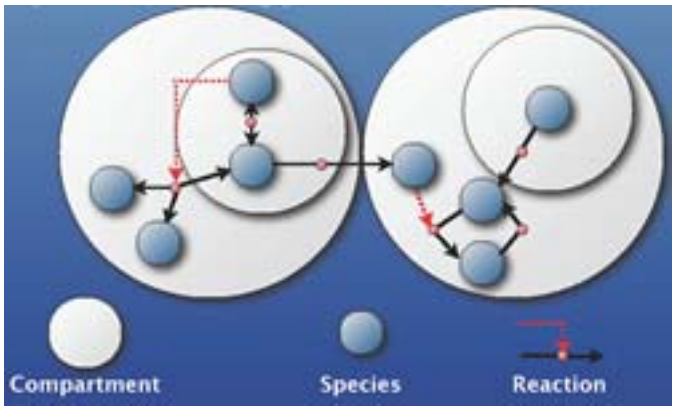
Major new features and changes in CellDesigner 4.1 are as follows:

- SBML Level 2 Version 4 is supported.
  - Validation of files when opening (libSBML3.4.1)
  - SBML Level2 Version4 new information UI
  - SpeciesType
  - CompartmentType
  - Units Definition
- Export to BioPAX Level 3
- MIRIAM Annotation support
- Save SBO (Systems Biology Ontology)Term
- Enhancing SBGN Viewer (Conforms to SGBN Process Diagram Level 1.1 specifitaion)
  - A shape of gene, Association, Dissociation
  - Unit of Information for Components
- Simulation - Control Panel enhancement
- Update SOSLib
- Database Connection
  - Connect to PANTHER Pathways database (http://www.pantherdb.org/pathway/)
  - SABIO-RK support (http://sabio.villa-bosch.de/)
  - Connect to MetaCyc (http://metacyc.org/)
  - Connect to GeneWiki (http://en.wikipedia.org/wiki/Gene)
- Enhanced Edit Functions
  - Zoom Select %
  - The **Find** search menu cover Complexes search
  - Change Species name font size
- Plug-in Development
  - Develop your plugin on Eclipse, and you can call the plugin from **Plugin** menu.

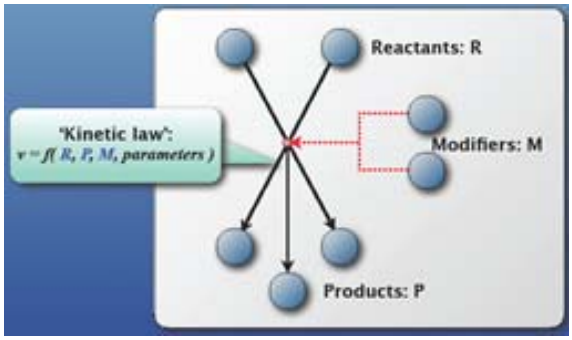
→ See also: “Plugin Development Tutorial”

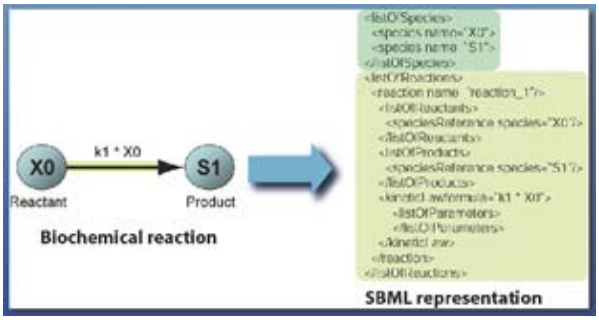
2. CellDesigner and SBML

SBML (Systems Biology Markup Language) is a machine readable format (XML) for representing computational models in systems biology. Over 100 software packages now support SBML. Its focus is to describe the systems of biochemical reactions. Models can also include compartments, events, rules and constraints.



CellDesigner can read/write in SBML format with rich enhanced functions stored as SBML annotations.





For details of SBML, please refer to http://sbml.org website.

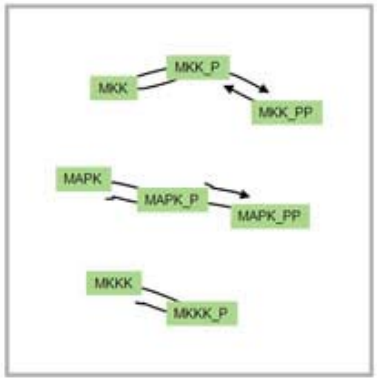
SBML format

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level1" level="2" version="4">
  <model name="ATitle">
    <listOfCompartments>
      <listOfSpecies>
      </listOfSpecies>
    </listOfCompartments>
  </model>
</sbml>
```

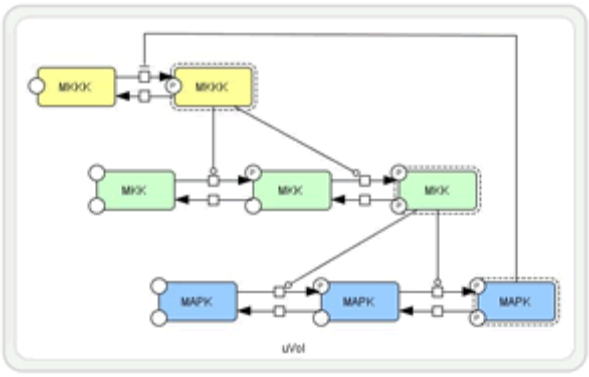
3. CellDesigner and Graphical Notation

CellDesigner supports graphical notation and listing of the symbols based on proposal by Kitano and adopting the most of SBGN (=Systeme Biology Graphical Notation) Process Diagram Level 1.1 notations..

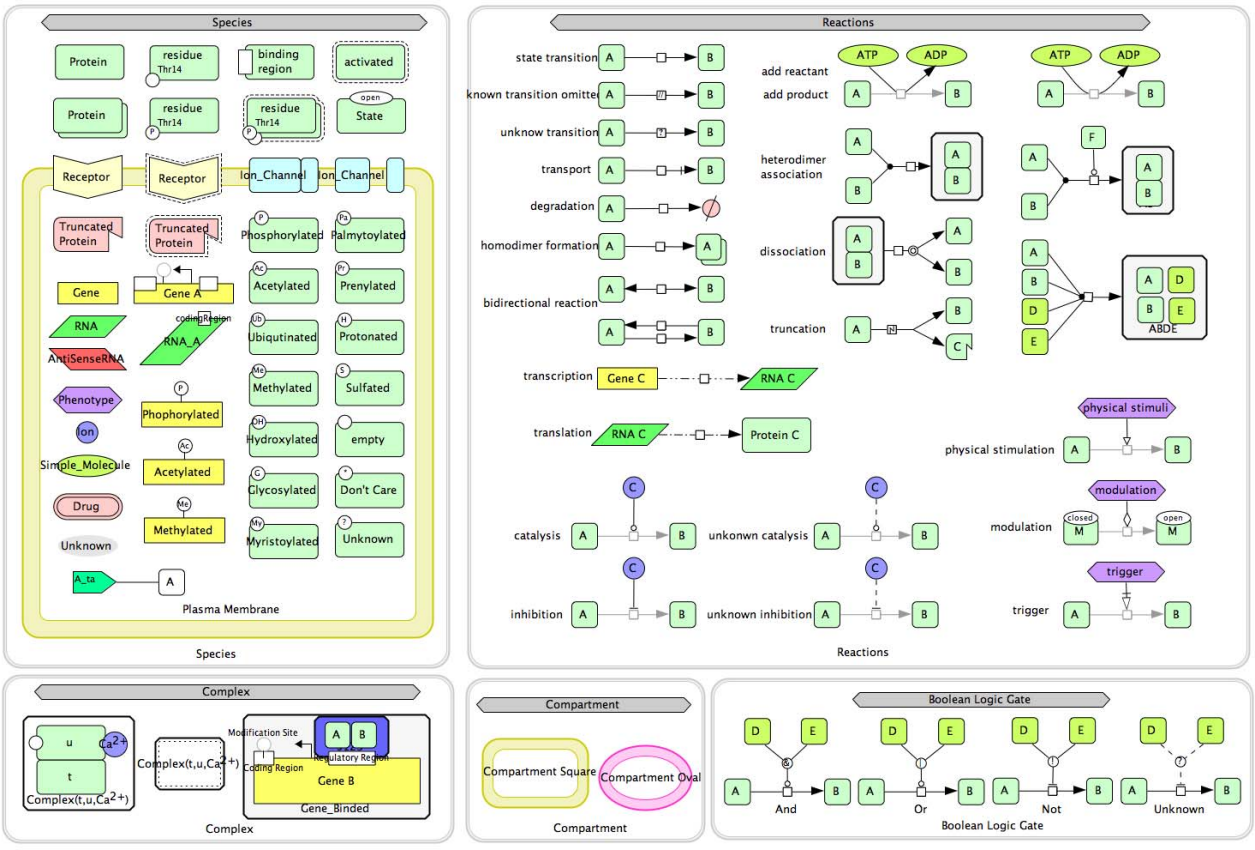
SBGN (Systems Biology Graphical Notation) (http://sbgn.org) is a graphical notation for representing biological interactions, such as protein-protein interactions and gene regulatory networks. Current discussions on SBGN focus on three graphical notations: process diagram, entity relationship diagram and activity flow. CellDesigner adopts the process diagram as its graphical notation.



Pure SBML without notation



SBML with notation



Glyphs used in the graphical notation of CellDesigner

→ See also: [Appendix 1 "Symbols and Expressions] for details on CellDesigner graphical notation

B. Startup Guide

1. Installation and Startup

1.1 Operating Environment

1.1.1 OS

- Windows (XP or later) 32bit only
- Mac OS X (10.5 or later) 32bit, 64bit
- Linux with X Window System (Fedora Core 4 or later is recommended)

On **Linux** platform, due to the version of native libraries, Fedora Core 4 or later is recommended; some problems will arise if you use other than these.

For **64bit Windows** Users, CellDesigner supports 32 bit only. Please install CellDesigner onto 32 bit mode.

1.1.2 Java

The current version of CellDesigner requires JRE (Java Runtime Environment).

The installers for **Windows** and **Linux** include JRE 1.6, so you do not have to install Java before your installation., On **Mac OS X**, Java 1.5 (PowerPC) ; Java 1.5 or 1.6 (Intel) is required.

1.2 Install SBW and SBW Modules

If you are interested in time evolving simulation and analysis on biochemical networks, we recommend you to install the Systems Biology Workbench (SBW) and SBW-powered software before you install CellDesigner.

Please check http://sys-bio.org/ and download the software from **Software Downloads** section.

To install SBW and SBW-powered software, follow their installation instructions.

If you would like to use CellDesigner alone right now, you can postpone this step until you need simulation and/or analysis.

→ Note: For details on SBW information, go to
http://sys-bio.org/research/sbwIntro.htm

1.3 Install CellDesigner

The current release is distributed in archived installer package for each operating system.

Windows:	`CellDesigner-4.1-windows-installer.exe`
Mac OS X:	`CellDesigner-4.1-osx-installer.dmg`
Linux:	`CellDesigner-4.1-linux-installer.bin`

While J2RE is required for CellDesigner to run, the installers include it. Therefore, you do not need to download or install J2RE.

1.3.1 Windows

1. Double click `CellDesigner-41-windows-installer.exe`.
   The installer window should open, and follow the message therein.
2. Follow the instruction of the installer.

1.3.2 Mac OS X

1. Double click `CellDesigner-4.1-osx-installer.dmg`.
   The .dmg file should automatically be mounted and a Finder window should open in which CellDesigner-4.1-osx-installer exists.
2. Then double click it
3. The installer window should open, and follow the message therein.

1.3.3 Linux

1. Open a shell and, cd to the directory where you downloaded the installer.
2. At the prompt, type,
   ```
   % chmod u+x CellDesigner-4.1-linux-installer.bin
   % ./CellDesigner-4.1-linux-installer.bin
   ```
3. The installer window should open, and follow the message therein.

→ Note: In case you have installed **SBW 2.7.6 or later,** and you encounter an error while installing CellDesigner, there might be a possibility that the C++ Broker is up which prevents CellDesigner to start. Please try to kill the broker using the Task Manager, or restart your system before you resume the CellDesigner installation.

1.4 Installed File Images

After installation is finished, you would see the following directories/files in the installation directory (`/CellDesigner4.1` by default).

```
+00README.txt
|
+CellDesigner4.1.exe  executable application module      (* Windows only)
+CellDesigner4.1.sh   executable application module      (* Linux only)
+CellDesigner4.1      executable application module (* Mac OS X only)
|
+/documents
| +ControlPanel41.pdf       quick tutorial for control panel
| +PluginTutorial41.pdf     quick tutorial for plug in
| +StartupGuide41.pdf       this document
| +/plugin
|   +index.html      Plug-in API document
|
+/exec
| +autolayout_yobf.jar
| +celldesigner.jar  library for CellDesigner application
| +yObf.jar
|
+/jre (1.6)   *(Windows, Linux only)
|
+/lib
| +avalon-framework-4.1.4.jar
| +axis.jar
| +batik.jar
| +browserlauncher.jar
| +collections-generic-4.01.jar
| +Commons-discovery-0.2.jar
| +commons-logging-1.0.4.jar
| +concurrent.jar
| +copasi.jar
| +copasi_gui.jar
| +customizer.jar
| +freehep-export-2.0.3.jar
| +freehep-graphics2d-2.0.jar
| +freehep-graphicsio-2.0.jar
| +freehep-graphicsio-ps-2.0.jar
```

| +freehep-io-2.0.1.jar
| +freehep-swing-2.0.2.jar
| +freehep-util-2.0.1.jar
| +icu4j_3_4,jar
| +iri.jar
| +itext-1.4.6.jar
| +jai_codec.jar
| +jai_core.jar
| +Jakarta-oro.jar
| +jaxrpc.jar
| +jcommon-1.0.0-pre2.jar
| +jeuclid-2.0.jar
| +jfreechart-1.0.0-pre2.jar
| +Jmf.jar
| +junit-4.1.jar
| +log4j-1.2.12.jar
| +mediaplayer.jar
| +mlibwrapper_jai.jar
| +MRJAdapter.jar
| +multiplayer.jar
| +openide-lookup-1.9-patched-1.0.jar
| +pantherConverter.jar
| +paxtools.jar
| +poi-3.0-rc4-20070503.jar
| +quaqua-filechooser-only.jar
| +saaj.jar
| +sabiows.jar
| +sbmlj.jar
| +SBWCore.jar
| +SOSlib.jar
| +wsdl4j-1.5.1.jar
| +xercesImpl.jar
| +xml-apis.jar
|
+bzip2.dll *(Windows only)
+libexpat.dll *(Windows only)
+libsbml.dll *(Windows only)
+sbmlj.dll *(Windows only)
+SOSlibJava.dll *(Windows only)
+zlib.dll *(Windows only)
|
+libbz2.so.1 *(Linux only)
+libexpat.so.1 *(Linux only)
+libsbml.so *(Linux only)
+libsbmlj.so *(Linux only)
+libSOSlibJava.so *(Linux only)
+libz.so.1 *(Linux only)
|
+libbz2.1.0.dylib *(Mac OS X only)
+libexpat.1.dylib *(Mac OS X only)
+libquaqua.jnilib *(Mac OS X only)
+libsbml.dylib *(Mac OS X only)
+libsbmlj.jnilib *(Mac OS X only)
+libSOSlibJava.jnilib *(Mac OS X only)
+libz.1.dylb *(Mac OS X only)
|
+/licenses

| +/celldesigner
| +license.txt
| +/libraries
| +axis.LICENSE.txt
| +batik.LICENSE.txt
| +batik.NOTICE.txt
| +FreeHEP.LGPL.txt
| +FreeHEP.LICENSE.txt
| +itext-MPLICENSE.txt
| +jai.LICENSE.txt
| +jfreechart.LICENSE.txt
| +libsbml.LICENSE.txt
| +mrjadapter.LICENSE.txt
| +quaqua.LICENSE.html
| +xerces.LICENSE.txt
| +xercesImpl.LICENSE.txt
| +xercesImpl.NOTICE.txt
| +xml-apis.LICENSE-SAX.html
| +xml-apis.LICENSE.DOM-documentation.html
| +xml-apis.LICENSE.DOM-software.html
| +xml-apis.LICENSE.txt
| +xml-apis.NOTICE.txt
| +yfiles-3rdPartyLicenses.html
| +yfiles-GeneralLicenseTerms.html
| +yfiles-GeneralTermsandConditions.html
|
+/Microsoft.VC80.CRT *(Windows only)
| +Microsoft.VC80.CRT.manifest
| +msvcm80.dll
| +msvcp80.dll
| +msvcr80.dll
|
+/plugin compiled plugin jar files are added in this directory
| +MappingArrayMass_plugin.jar
|
+/samples
| +components41.xml sample for various components
| +database.xml sample for database connections
| +M-Phase2.xml sample for model editing
| +Macros.xml sample for macros
| +MAPK41.xml sample for simulation provided by SBML ODE Solver
| +SBGNRefCard.xml
| +sim1.xml
| +sim2.xml
| +unitOfInformation.xml sample for unit of information
| +/nbt sample files used in Nature Biotech paper by Kitano
| +/notation sample files for notation
| +/plugin sample source and jar files for plugin
| +/sbml samples from SBML specifications
|
+ mmlctop2_0.xsl
|
+uninstall.exe *(Windows only)
+uninstall *(Linux only)
+Uninstaller *(Mac OS X only)

1.5 Startup CellDesigner

1.5.1 Windows

1. Double click the shortcut icon for CellDesigner4.1 in your desktop.
2. Or double click `CellDesigner4.1.exe` in the directory where you chose to install (`C:/Program Files/CellDesigner4.1` by default).

1.5.2 Mac OS X

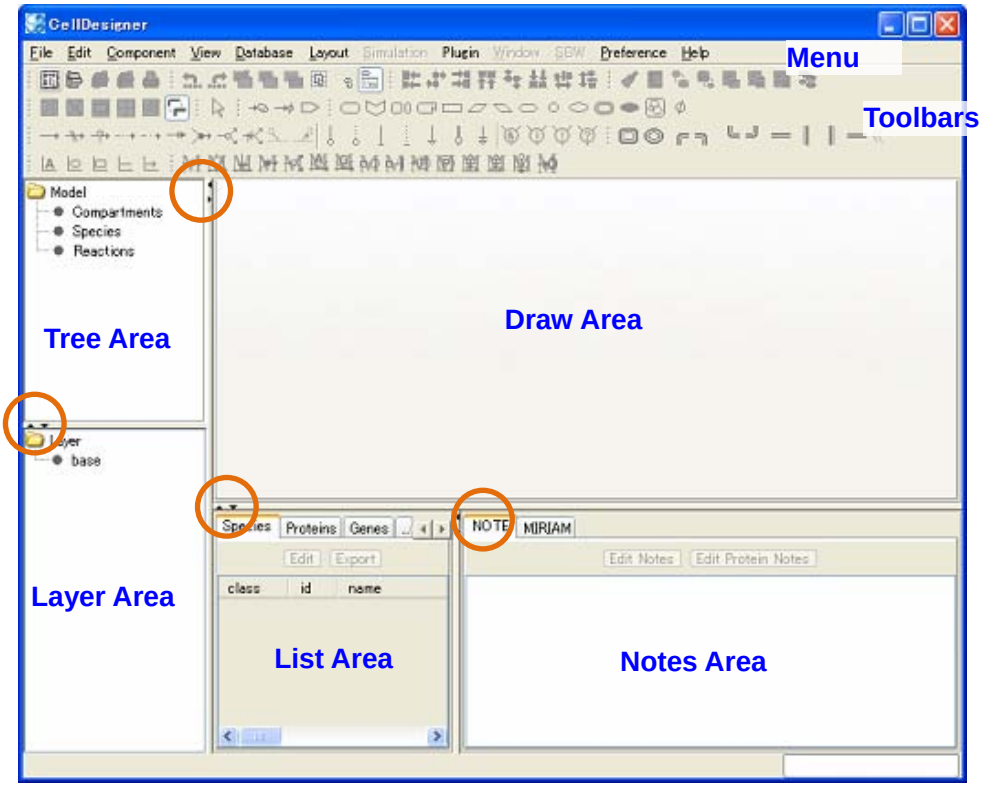
1. Double click the CellDesigner4.1 icon in the folder you chose to install (`/Application/CellDesigner4.1` by default).

1.5.3 Linux

1. On a shell, type `./runCellDesigner4.1` in your home directory.
2. Or type `./runCellDesigner4.1` after changing to the directory where you chose to install (`CellDesigner4.1` in your home directory by default).

1.6 CellDesigner User Interface and Navigation

CellDesigner consists of Menu, Toolbar, and the five areas as shown below



Draw Area:	To draw a model
List Area:	To display and edit the list of the components, functions of a model
Notes Area:	To display and edit the notes of the component
Tree Area:	To display all the list of the components in the tree structure.
Layer Area	To display all the layers of the model.

1.6.1 To change the size of each Area

1. The size of the areas can be changed by dragging the borderlines.
2. To maximize the area, click the triangle icons on the borders.
   (See the orange circles in the above screen.)

1.6.2 To change the position of List and Notes Areas

1. To switch the display position of the List and Notes Areas,
   select **View - List** menu, then select **Right** or **Down**.

1.6.3 To customize Toolbar

1. Each group of the icons can be detached from the Toolbar.
2. It can also be moved to the side (left or right) or the bottom of the main window by dragging the handle.

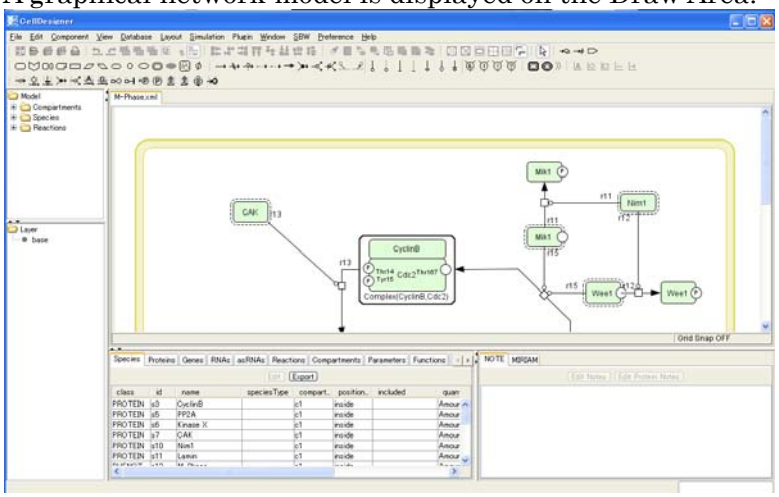
2. Quick Tutorial of Model Building

This section is for beginners, and describes how to edit a model with CellDesigner in brief.

A sample file "`M-Phase.xml`" is used in this tutorial since this model contains most of the essential CellDesigner's expressions of biochemical networks.

2.1 Open a Sample Model

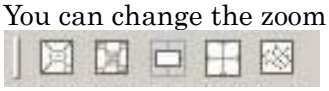
1. Select **File** - **Open** in the Menu to open `M-Phase.xml` in the "`samples`" directory.
2. A graphical network model is displayed on the Draw Area.



3. In the Menu, select **File** – **Save as**⋯ to open the **Save** dialog.
4. In the **File name** text box, type in a new name, e.g. "`M-Phase_Test.xml`".
5. Click **Save**.
6. Drag the borders (left or right) of the Draw Area to change the area size.

2.2 Zoom

1. You can change the zoom view of the model by clicking the following icons.



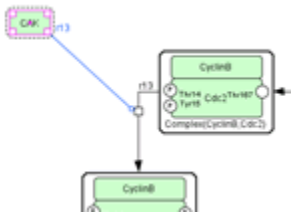
2.3 Select a Component

A **component** is a general term for a **Species** (including a **Complex**), a **Reaction**, or a **Compartment**. Thus, any shape you see on the Draw Area ---a rectangle, an oval, or a line segment--- is a **component**.

2.3.1 To select a Component

1. Confirm that **Select Mode** icon is highlighted. If not, click the arrow icon.

2. Select a component in the Draw Area. For instance, select the green square-shaped component labeled "CAK" which you will find in the upper left corner of the Draw Area. This shape indicates that the component is a Protein.



3. Observe that the green square, a Protein, and also the linked line, called a Reaction, are highlighted.

2.4 Move / Delete a Component

1. Select a Species (e.g. a Protein) and drag it to see the linked Reactions follow as the Species moves.
2. Delete the Species by the Delete key, and see the linked Reactions are deleted as well.
3. To undo the deletion, select **Edit** – **Undo** in the Menu bar.

2.5 Undo / Redo

You can "undo" the previous actions by `Ctrl-Z`, and also "redo" after the undo by `Ctrl-Y` before saving the model.

→ For Mac OS X, use `Command` key instead of `Ctrl` key.

2.5.1 To undo or redo the previous action

1. Undo by `Ctrl-Z`.
2. Redo by `Ctrl-Y`.

2.6 Change the Size of a component

1. When you select a Species or a Reaction, you will find small squares on it. These are the handles to change their size or to bend the line of the Reaction.
2. Select one of the small squares and drag it.

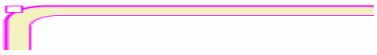
2.7 Compartment

The shape with a thick (and yellow by default) border line is called a **Compartment**.

A **Compartment** is a container for other components and can also hold other Compartments in it. A Compartment represents a generic bounded container, such as a cell or an intracellular compartment. The change in its size and shape only affects its appearance on canvas, and has no effect on semantics of biochemical and gene networks.

2.7.1 To put components in a Compartment

1. To select a Compartment, click on its border line.



2. See the edge of the border line is turned into magenta and the Species inside are shadowed.
3. A Compartment can hold Species and other Compartments inside.
4. Drag the Compartment, and confirm that the Species inside follow it.

2.7.2 To change the shape of a Compartment

1. Select a Compartment.
2. In the Menu, select **Component** – **Change to OVAL**.
3. Observe the shape has changed to an oval.
4. Select the Compartment again.

5. In the Menu, select **Component** – **Change to SQUARE** and observe the shape has changed to a square.

2.7.3 To change the position of the Compartment name

1. Find the Compartment name which is initially located at the bottom of the Compartment.

→ Note: In the `M-Phase_Test.xml` sample model, you will find "cell" as the Compartment name.

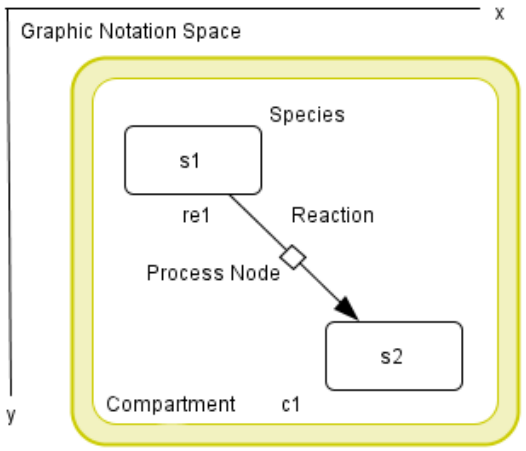
2. Select the Compartment name, drag and drop it wherever you want.

2.8 Species and Reactions

A **Species** represents, for example, a protein or some other molecule in a biochemical network, or a gene in a gene regulatory network.

A **Reaction** represents a state transition of the connected Species such as a biochemical reaction, an interaction between proteins, and a regulatory relation between genes.

The biochemical and genetic meanings of Species and Reactions are distinguished by their symbols. The list of all symbols that can be drawn using CellDesigner and their meanings are described in "Appendix 1: Symbols and Expressions".



Symbolic Process Expression of the CellDesigner

2.8.1 To change the symbol of a Species

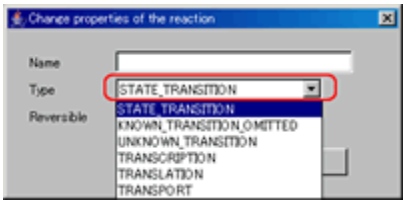
If you double click a Species or a Reaction, a dialog box will appear to alter its properties.

1. Double click a Species, for example, "CAK", then the **Change identity of the species** dialog box will be displayed.

2. Change the value in the **class** drop-down menu. You can switch from Protein to Gene, RNA, Ion, etc., and vice versa.
3. If necessary, type in a name the **name** text box.
4. Click **Apply** button and see the shape has been changed.

2.8.2 To change the symbols of Reactions

1. Double click a Reaction.



2. Change values in the dialog box, and see what have been changed after clicking **OK** button.

2.9 Activate a Species

2.9.1 To activate a Species

1. Select a Species.
2. Type "a" on keyboard.
   Or, select **Component** – **Set Active** in the Menu.
3. See the Species is wrapped by a dashed line.

→ Note: The dashed line has a somewhat ambiguous meaning, indicating only that the Species is “active” without referring to its targets.

→ See also: “Appendix 1.1 “Basic Symbols”.

2.10 Close a Model

2.10.1 To close a file without saving any changes.

1. Select **File** – **Close**.

2.11 Create a New Model

2.11.1 To create a New Model

1. Select **File** - **New** menu or press Ctrl-N.
   The **New Document** dialog will display.
2. Specify **Name**, **Width**, and **Height** of a new model.
3. Click **OK**.

→ Note: For Mac OS X, use Command key instead of Ctrl key.

→ Note: The **Name** you specify here will be not only the **file name** but the **model id** in the xml file when you select **File** – **Save** in the Menu. Therefore, the **Name** needs to conform to SBML convention.
e.g. If you specify "sample" here, the file name will be "sample.xml", in which `<model id="sample">` is written.
However, if you select **File** – **Save As ⋯** in the Menu, you can give a **file name** different from the **model id** in the xml file.
e.g. If you save as "sam ple", the file name will be "sam ple.xml" but the model id is still `<model id="sample">`. See the file name has a space in it but the model id does not.

→ Note: **Naming Convention**
The **model id** only accepts the Type Sid defined in SBML specification as follows:
letter ::= ’a’..’z’,’A’..’Z’
digit ::= ’0’..’9’
idChar ::= letter | digit | ’_’
SId ::= (letter | ’ ’) idChar*

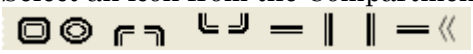
→ See also: Systems Biology Markup Language (SBML) Level 2: Structures and Facilities for Model Definitions

2.12 Create a New Compartment, Species and Reactions

If you want to create a new Species, Reaction, or Compartment, use icons on the tool bar.

→ See also: “Appendix 1: Symbols and Expressions”.

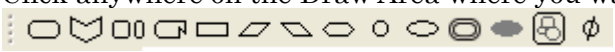
2.12.1 To create a new Compartment

1. Select an icon from the Compartment tool bar (as shown below).

2. Place your cursor anywhere on the Draw Area to make a Compartment of your favorite size.
3. In the **Property of compartment** dialog, specify its **Name** and **Size**.

→ Note: The size may be a volume (if the compartment is a three-dimensional one), or it may be an area (if the compartment is two-dimensional), or a length (if the compartment is one-dimensional).

→ See also: Systems Biology Markup Language (SBML) Level 2: Structures and Facilities for Model Definitions, “4.7 Compartments”

2.12.2 To create a new Species

1. Click and select an icon from the Species tool bar (as shown below).
2. Click anywhere on the Draw Area where you want to place the new Species.


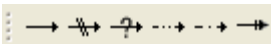
2.12.3 To create a new Reaction

1. Click on an icon from the Reaction tool bar (as shown below).

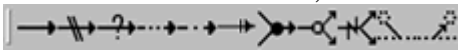
For the detail of each icon, see the following sections.

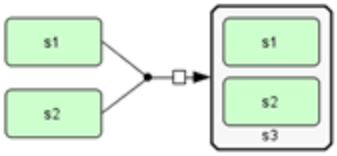
→ See also: “Appendix 1.1.6 Reaction (State Transitions and others)”
→ See also: “Appendix 1.1.7 Reaction (Modifications)”
→ See also: “Appendix 1.1.8 Reaction (Logical Operations)”

2.12.4 To create a new Reaction - State Transition <One to One type>

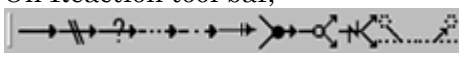
1. On the Reaction Toolbar, click one of the following icons. (from left to right)

-State Transition
-Known Transition Omitted
-Unknown Transition
-Transcription
-Translation
-Transport
2. Click a Species as the start-point.
3. Click another Species as the end-point, and see a Reaction line has been drawn.

2.12.5 To create a new Reaction - State Transition <Two to One type>

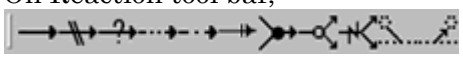
1. On the Reaction Toolbar,

click the following icon.

-Heterodimer Association
2. Click a Species and then another for start-points.
3. Click a Species for an end-point, and see a merged Reaction line is drawn.


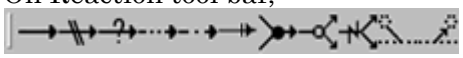
2.12.6 To create a new Reaction - State Transition < One to Two type >

1. On Reaction tool bar,
   
   click one of the following icons.
   
   -**Dissociation**
   -**Truncation**
2. Click a Species for a start-point.
3. Click a Species and then another for end-points, and see a forked Reaction line is drawn.

2.12.7 To create a new Reaction - Add Reactant

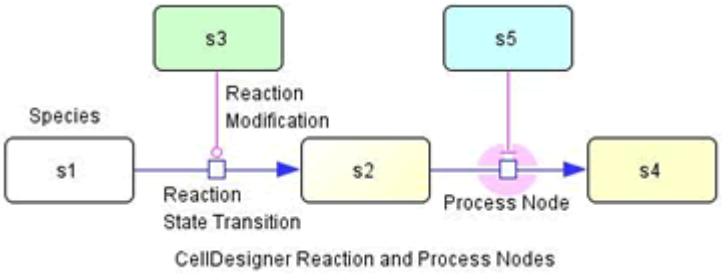
1. On Reaction tool bar,
   
   click the **Add Reactant** icon.
   
2. Click a Species to start at.
3. Place the cursor on a Reaction and find a blue point.
4. Click on it, and see a Reaction line is drawn.

2.12.8 To create a new Reaction - Add Product

1. On Reaction tool bar,
   
   click the **Add Product** icon.
   
2. Place the cursor on a Reaction and find a blue point.
3. Click on it.
4. Click a Species to end at, and see a Reaction line is drawn. 

2.12.9 To create a new Reaction - Modification

1. On the Reaction Toolbar, click one of the following icons,
   
   -**Catalysis**
   -**Unknown Catalysis**
   -**Inhibition**
   -**Unknown Inhibition**
   -**Physical Stimulation**
   -**Modulation**
   -**Trigger**
2. Click a Species for a start-point.
3. Click a square ("**process node**") on a Reaction for an end-point, and see a Reaction line is drawn.



CellDesigner Reaction and Process Nodes

→ Note: You can connect Modification arc to Species "Phenotype" directly.

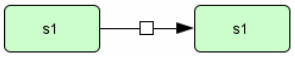
2.12.10 To create a Homodimer/ degradation / tag

There are some icons with actions not mentioned above. Try the followings after selecting the icons and see what happens.

1. To create a Homodimer Formation, click the **Homodimer Formation** icon  , then click a target **Species.**
2. To create a Degradation, click the **Degradation** icon  , then click a target **Species..**
3. To create a Tag, click the **Auto Create Tag** icon  , then click a target **Species.**

2.12.11 To create a Boolean logic gates

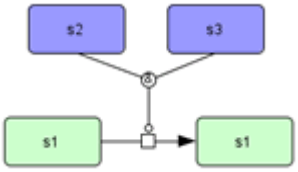
1. Draw two Species and connect them with a Reaction (State Transition).



2. Or equivalently, on the Toolbar, select the **State Transition** macro icon  and then click anywhere on the Draw Area.
3. Draw two more Species.
4. On the tool bar, click one of the icons below.

 Select the two Species painted last.

5. Then click a square (“process node”) on the Reaction (State Transition), and see a Reaction line is drawn.

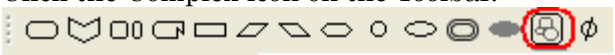


→ See also: “Appendix 1.1.8 Reaction (Logical Operations)”

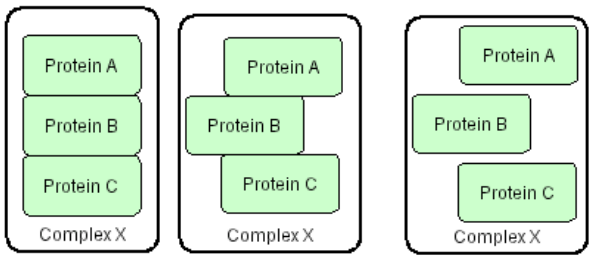
2.13 Create a Complex

2.13.1 To create a Complex

1. Click the Complex icon on the Toolbar.



2. Move the cursor onto the Draw Area and click the left mouse button to place a Complex.
3. In the **Name of the species** dialog box, type in a name of your choice. The name can be a simple name as well as a long name which includes the names of the species contained in the Complex, e.g. “Complex(ProteinA, ProteinB, ProteinC)”.
4. To place Species in the Complex, just drag and drop them into the Complex.



2.13.2 To modify the Species within a Complex

Note: You can modify the individual Species inside a Complex box at any time. For example, you can add a residue, change the residue status, or change the name or the class of the Species.

→ Note: The Notes information of the individual Species will be maintained even though you move the Species in and out of the complex box.

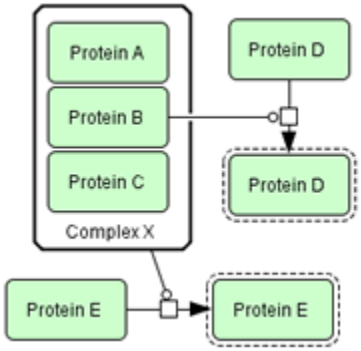
→ See also: [5 Species---Protein, Gene, RNA and asRNA].

2.14 Complexes and Reactions

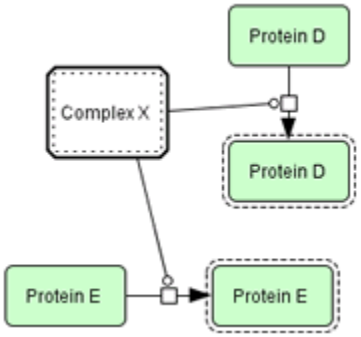
A Reaction can be connected to a Complex or to an individual Species/Reaction inside the Complex. Thus, you can distinguish if the activation is initiated by the Complex, or by an individual Species inside the Complex.

2.14.1 To change the appearance of a Complex

1. Select a Complex and type “C” to make it compact.
2. Type the “C” key again to have the border line invisible. (no border)
3. Type the “C” key again to get back to the original shape.
4. You can do the same steps as above by selecting **Component - Change Complex View** menu.

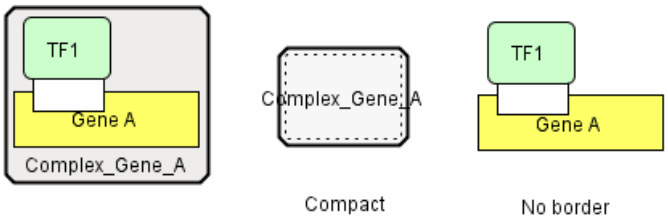


“normal”

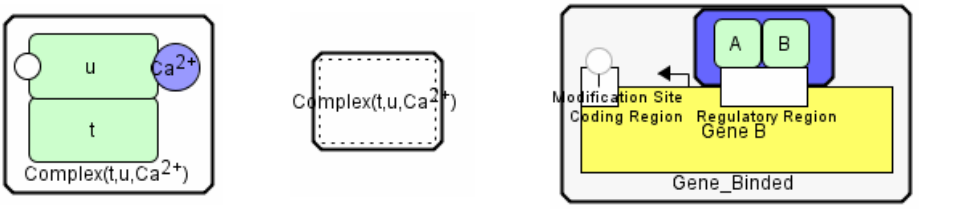


”compact”

→ Note: You can set a Complex to be displayed with no border. This option is useful when you create a Complex with Gene/RNA/Antisense RNA inside. Below is an example which you can find in `Complex41.xml` in `/samples/notation` folder.



→ Note: A Complex can be contained within another Complex. Below is an example which you can find in `components41.xml` in `/samples` folder.



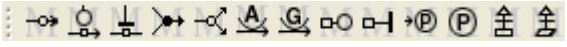
a normal Complex

a compacted Complex

a Complex (the blue box) contained in another Complex

2.15 Macros

To draw the diagram easier, some of the most frequently used components sets are available as “macros”. You can select the macros from the tool bar to draw the following components set.



→ See also: [6.2 Macros]

2.16 Edit Reactions

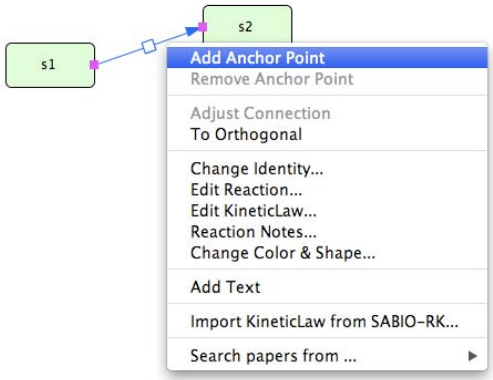
2.16.1 To change connection points of Reaction on Species

A Reaction can be connected to one of the 16 connection points around a Species.

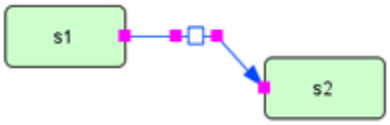
1. Select a Reaction and try to change the connection point.

2.16.2 To add Anchor points

You can add and remove Anchor points by the right click menu.



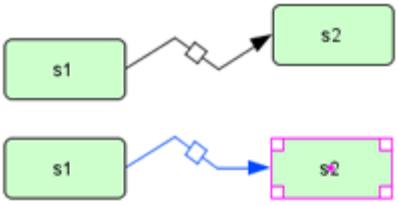
1. Click a point on a Reaction where you want to add an anchor.
2. Click the right mouse button and select **Add Anchor Point**.
3. See a new anchor point has been added.



4. To remove the anchor point, click the right mouse button on the target anchor, and then select **Remove Anchor Point**.

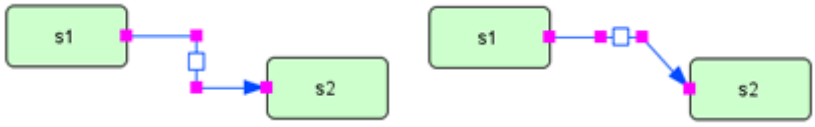
2.16.3 To move a Species with a Reaction

1. Select a Species with a Reaction attached,
2. Move it around and see the last segment of the Reaction follow the Species.



2.16.4 To change the shape of a Reaction line segment

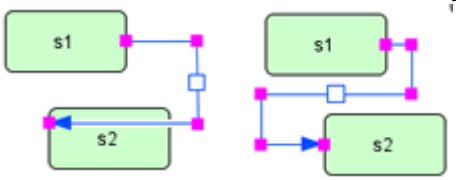
1. Select a Reaction
2. Click the right mouse button and select **To Orthogonal** or **To Polyline**.



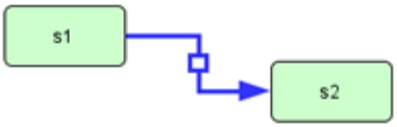
Orthogonal Polyline

2.16.5 To adjust a Reaction line automatically

1. Select a Reaction which has already been set **To Orthogonal**.



2. Right-click your mouse and select **Adjust Connection** in the menu.



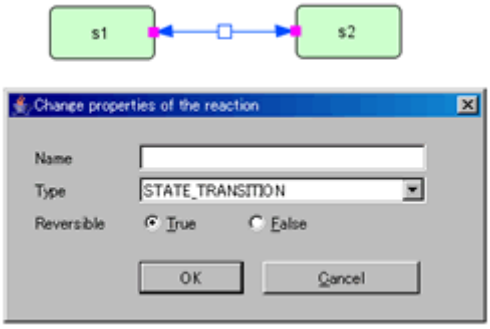
2.16.6 To change line width and color setting of a Reaction

1. Select a Reaction.
2. Right-click on it and select **Change Color & Shape…** from the context menu.
3. Change the color and line width.

→ Note: The color and line width of Species and Compartments can be changed in the same way.

2.16.7 To make a reversible Reaction

1. To make a Reaction reversible, double-click the Reaction
2. On the **Change property of the reaction** dialog box, set **Reversible** option to **True**.

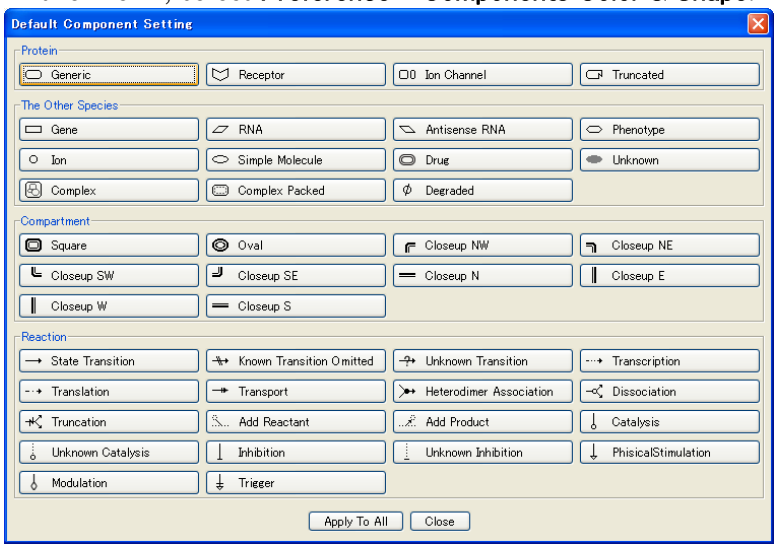


2.17 Change Color and Shape of Components

You can change the color and shape of a component individually or collectively.

2.17.1 To change the default settings of the color and shape

1. In the Menu, select **Preference** – **Components Color & Shape**.

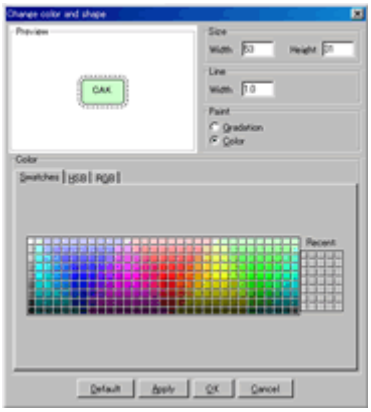


2. Click the icon of the component whose color or shape you want to change.

2.17.2 To change the color and shape of the individual components

1. Select the component(s) to edit, and then click the icon of **(Change Color & Shape)** in the tool bar.

2. In the **Change color and shape** dialog box, change the values as you like.



2.18 Export Image

2.18.1 To export the model image in PNG, JPEG, EPS, SVG or PDF format

1. Select **File** – **Export Image…** on the Menu bar.
2. Specify the name and the file format.

→ Note: The image saved here is the same as the one displayed on the screen.

2.19 Add Model Description

Before you save your model, you can add the description / MIRIAM information to the model.

2.19.1 To add Model Description

1. Select **Component – Model Description** menu.
   The **Model Description** dialog will display.
2. Specify **Creator information, File information** to a new model.

→ For adding MIRIAM information, See also: [8. Notes and MIRIAM],

2.20 Save a Model

CellDesigner stores all the information on the model you create to an SBML format file.

2.20.1 To save a model

1. Select **File** – **Save** or **Save As…**.

→ Note: CellDesigner's specific functions will be stored under <annotation> tag in the SBML file.

2.20.2 To save a model in a pure SBML format

1. Select **File - Export Pure Level x Version x…**.

→ Note: **Naming Convention**
The Model ID or/and the File Name only accept the following characters:
(_|[a-z]|[A-Z])(_|[a-z]|[A-Z]|[0-9])*. No blank space is accepted.
This is the SBML convention.

2.21 Import a Model

2.21.1 To import an SBML file:

1. Select **File - Open**.
2. In the **Open** dialog, select a .sbml or .xml file.

3. Click **Open**.

2.22 Export a Model

CellDesigner supports export the model to SBML (.xml) as well as BioPAX level 3 formats (.owl).

2.22.1 To export a model to a pure SBML file (.sbml, .xml)

1. In the Menu, select **File - Export Pure Level x Version x…**.
2. **Save** dialog opens. Specify a file name and Click **Save**.

→ See also: http://sbml.org/ for more details on SBML Levels.

CellDesigner's file format and pure SBML file format:

CellDesigner stores all information in a SBML file format. While pure SBML format does not support layout information, CellDesigner stores layout information inside <annotations> tags in SBML, which is CellDesigner specific extension.
When you export the model into "pure" SBML document, the exported SBML file doesn't contain any layout information. You may use this feature if you find any trouble when you tried to open your SBML document with other SBML compliant software.

2.22.2 To export a model to a BioPAX format file (.owl)

1. In the Menu, select **File**, then **Export to BioPAX Level 3…**
2. In **Export to BioPAX Level 3…** dialog, change the file name if needed.
3. Click **Save**.
4. **Error** dialog will list the Species that were not converted.
5. Click **OK**.

→ See also: http://www.biopax.org/ for more details on BioPAX levels.

2.23 Open an SBML File

You can open an SBML file with CellDesigner.

When you retrieve an SBML file created by some other tool than CellDesigner without any layout information, it will automatically adjust the layout of the model with the layout schemes.

→ See also: [6.11 "Automatic Layout"].

2.23.1 To open an SBML file:

1. Select **File - Open**, then specify the target SBML file.

→ Note: You can also import the SBML models from BioModels.net database. (http://biomodels.net)

→ See also: [9 "Connect to External Databases"].

2.24 Save SBO Terms

"The Systems Biology Ontology (http://www.ebi.ac.uk/sbo/) is a set of controlled vocabularies and ontologies tailored specifically for the kinds of problems being faced in Systems Biology, especially in the context of computational modeling."

CellDesigner can save the SBO Term automatically.

2.24.1 To save a model with SBO Terms

1. In the Menu, select **Edit – SBO Term Value.**
2. Check **Save with SBO Term Value** option.
3. When you save, SBO Terms will automatically be allocated and written in the model file.

3. Compartments

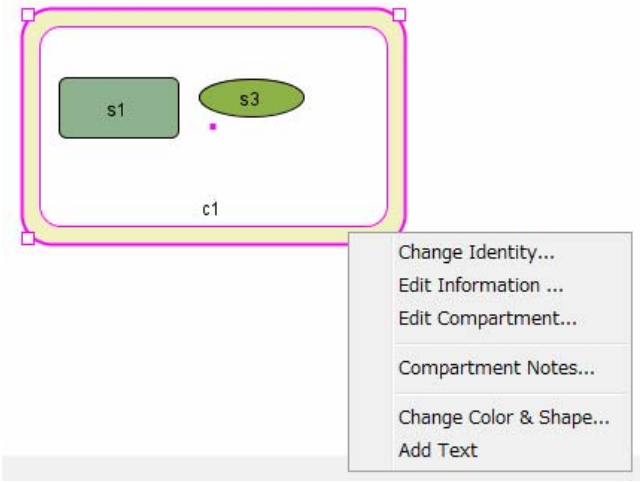
3.1 Edit a Compartment

The SBML Level 2 Version 4 specification defines a compartment as follows:
"A compartment in SBML represents a bounded space in which species are located. Compartments do not necessarily have to correspond to actual structures inside or outside of a biological cell, although models are often designed that way."

→ See also:
"Systems Biology Markup Language (SBML) Level 2: Structures and Facilities for Model Definitions" found in http://sbml.org/Documents/Specifications

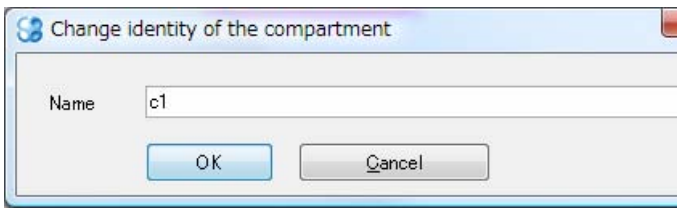
3.1.1 To edit a Compartment

1. Right click on a Compartment.
2. Select a menu item from the right-click context menu. See the following pictures for detail.

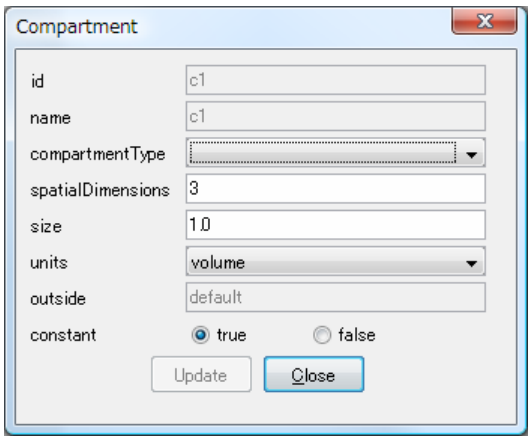


3. Depending on the menu item you have selected, one of the following dialogs will pop up.

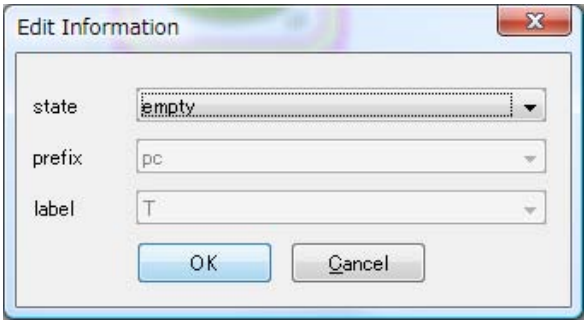
4. **Change identity of the compartment** dialog



5. **Compartment** dialog



6. **Edit Information** dialog



→ See also: “Species” section of the CellDesigner.org Online Help http://celldesigner.org/help/CDH_Species_T.html.

→ See also: [5. “Species---Protein, Gene, RNA and asRNA”].

→ See also: [10 “Gene/RNA/AntisenseRNA Structure Expressions”]

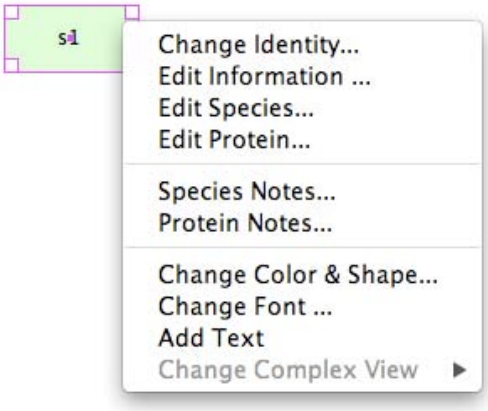
4. Species---General

4.1 Edit Species

A **Species** is a term defined in the Systems Biology Markup Language (SBML) and represents an entity in general used in a model. CellDesigner subdivides Species into several categories, i.e. Complexes, Proteins, Genes, RNAs, or some other Molecules.

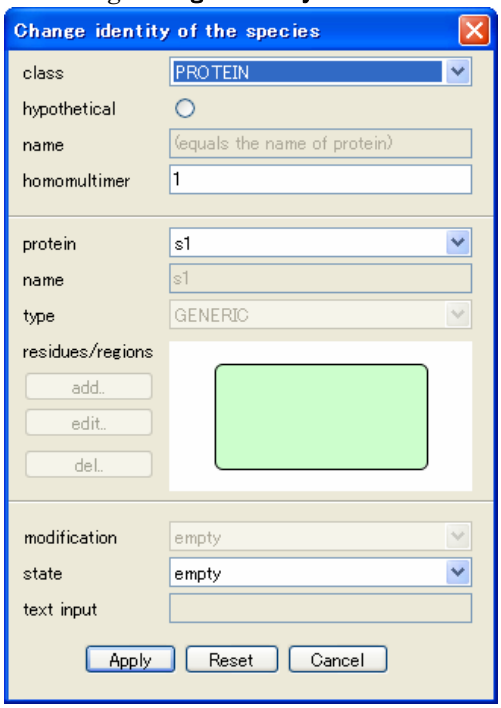
4.1.1 To edit a Species

1. Right click on a Species
2. Select a menu item from the right-click context menu.

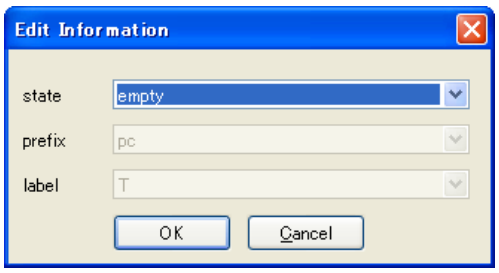


→ Note: The fourth menu item (e.g. **Edit Protein...** in the above figure) is content-dependent. It will only be displayed if the Species is a Protein, Gene, RNA, or asRNA.

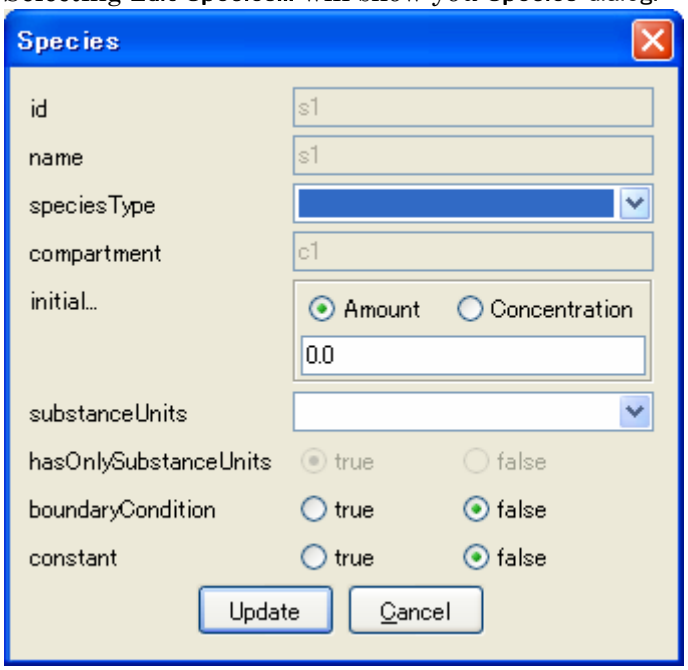
3. Select a menu item depending on which value you want to edit. See the following pictures for detail.
4. Selecting **Change Identity...** menu will show you **Change Identity of the species** dialog.



5. Selecting **Edit Information...**will show you **Edit Information** dialog.



6. Selecting **Edit Species...** will show you **Species** dialog.



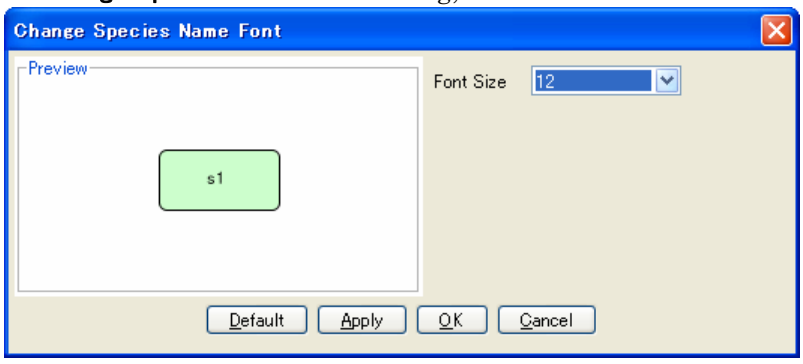
→ See also: "Species" section of the CellDesigner.org Online Help http://celldesigner.org/help/CDH_Species_T.html.

→ See also: [5. "Species---Protein, Gene, RNA and asRNA"].

→ See also: [10 "Gene/RNA/AntisenseRNA Structure Expressions"].

4.1.2 To change font size

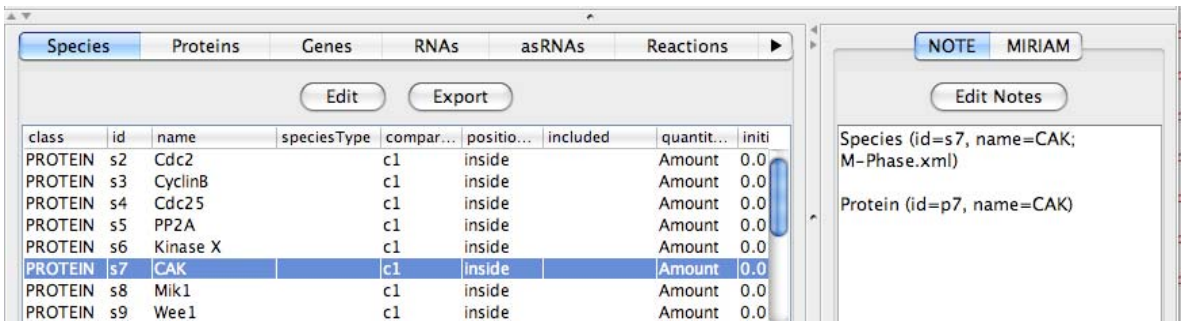
1. On the Draw Area, right-click on a Species to show the context menu.
2. Select **Change font ....**
3. In **Change Species Name Font** dialog, select a font size.



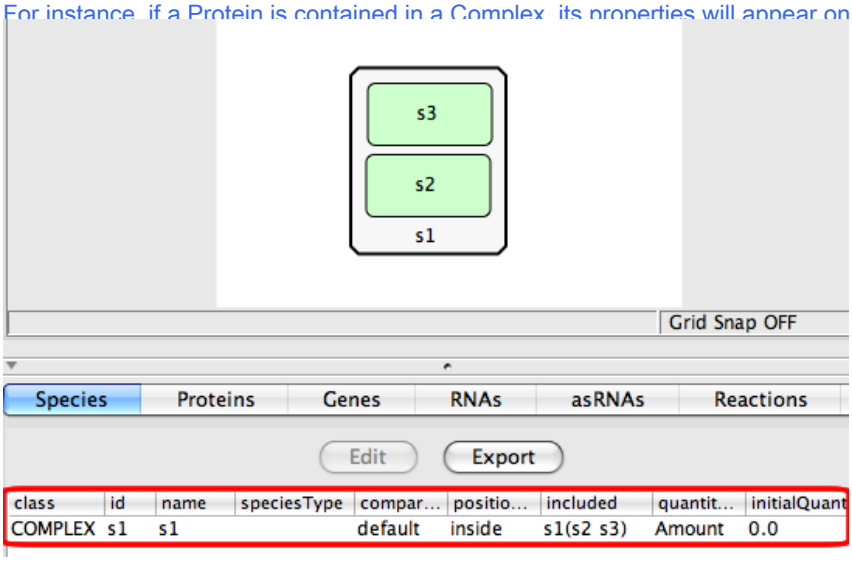
4.2 Find a Species in the List Area

You can view all the data concerning a Species tab in the List Area. This is useful when you want to glance over all the Species specified in the model.

You can swap the column by drag-and-drop.



→ Note: In the **Species** list, you will only find a Complex even if the Complex contains other Species. Properties for the contained Species will appear on other lists correspoding to the Species, and not on the Species list. For instance, if a Protein is contained in a Complex, its properties will appear on the Proteins list.



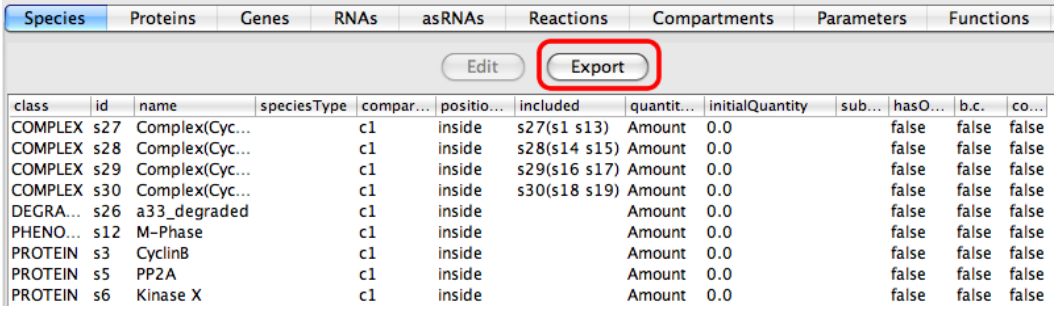
→ Note: In the Species list, the "included" column shows the list of Speices included in a complex. For example, s1(s2, s3) means the complex s1 includes the Species s2 and s3.

4.3 Export Lists to CSV file

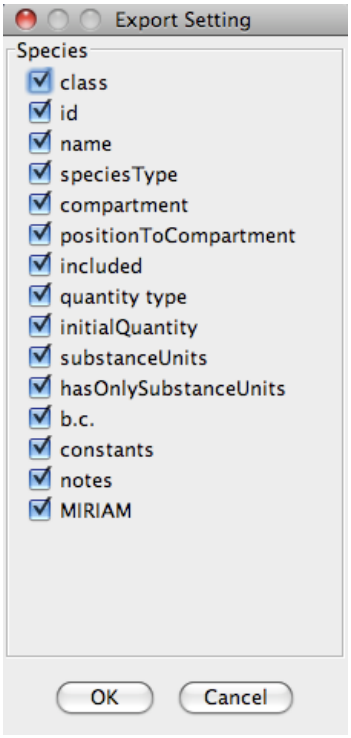
You can export the contents of the list into .CSV file format. All the other lists you can see in the List Area, such as the Protein list, the Reaction list, can be exported to a CSV file.

4.3.1 To export the list

1. Select the **Species** tab in the List Area.
2. Click **Export** button on the list or select **File** – **Export List to CSV…** from the menu bar.



3. The **Export Setting** dialog will be displayed.



4. In the **Export Setting** dialog box, check the data properties you want to export, then click **OK**.
5. The file name is automatically specified as "xxx.csv" in the **Save** dialog.
6. Click **Save** to save the CSV file.

→ Note: You may use other applications to check the contents of the CSV file.

5. Species---Protein, Gene, RNA and asRNA

In this section, we shall edit a Protein, Gene, RNA, or asRNA with modification sites. You can use a sample file "`M-Phase2.xml`" to go through the following steps.

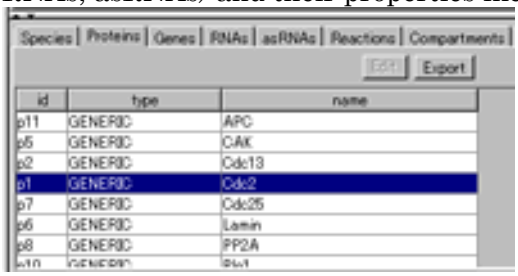
CellDesigner allows you to add modification residues to a graphical symbol of specific Species types (Protein/Gene/RNA/asRNA). Hence, you can describe a state transition of a Species in such a way that two graphical symbols of an identical Species with different modifications are connected by a Reaction. The structure of modification residues, states, and state transitions of proteins are also stored in SBML Level 2 format with CellDesigner's extended tags.

The sample model `M-Phase2.xml`, which you will find in `/samples` folder, describes state transition of "Cdc2," where there are eight "Cdc2"s. The eight represent different Species, while they are essentially the same protein. Therefore, CellDesigner should handle data structure describing each protein in a model, so that several protein-type Species could have references to the same protein data. This data structure is called "Protein".

→ Note: (New in ver. 4.1) In SBML Level 2 Version 4, a new object called "SpeciesType" is being introduced. SpeciesType is intended to relate the same type of the Species on the model together. This concept corresponds to the Ids for "Protein", "Gene", "RNA" and "asRNA" in CellDesigner.

5.1 Check and Change the Properties on a Protein/Gene/RNA/asRNA

Proteins tab (and also **Genes**, **RNAs**, **asRNAs** tabs) in the List Area shows you all Proteins (Genes, RNAs, asRNAs) and their properties included in the model.



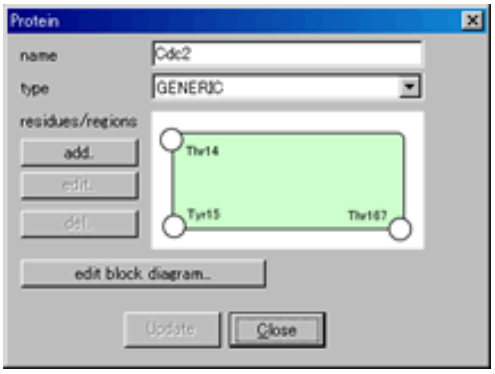
If you cannot see the **Proteins** tab in the List Area, click on the right arrow in the upper right corner of the List Area, and adjust the size of the List Area appropriately.

For an individual Protein, you can view its properties by double-clicking on the Protein row to open the **Protein** dialog. In the dialog, you can edit the properties of the Protein, such as name and type, and also add, edit and delete a residue or a binding region.

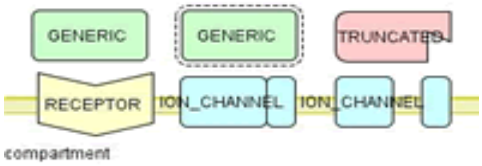
→ Note: Changes in this dialog will be reflected to all Species referring to this Protein, including those inside Complexes.

5.1.1 To change the type of Protein

1. In the List Area, click **Proteins** tab.
2. Select "Cdc2" in the list and click **Edit** button.
   Alternatively, you can click one of the "Cdc2" proteins on the Draw Area, click the right mouse button, and then select **Edit Protein…** menu item.
3. The **Protein** dialog will appear.

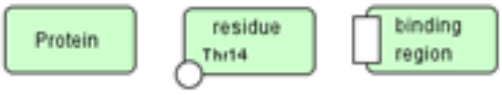


4. Select the **type** of Protein from the drop-down list.
   - GENERIC
   - RECEPTOR
   - ION_CHANNEL
   - TRUNCATED



5.2 Residue / Binding Region of a Protein/Gene/RNA/asRNA

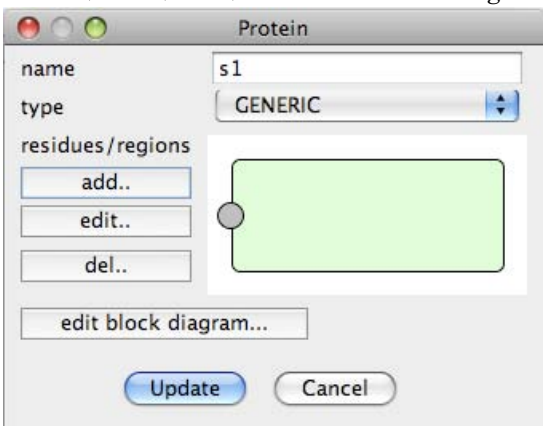
In the **Protein/Gene/RNA/asRNA** dialog, you can add and delete residues and binding regions. You can also adjust the position of the residues and binding regions in the dialog.



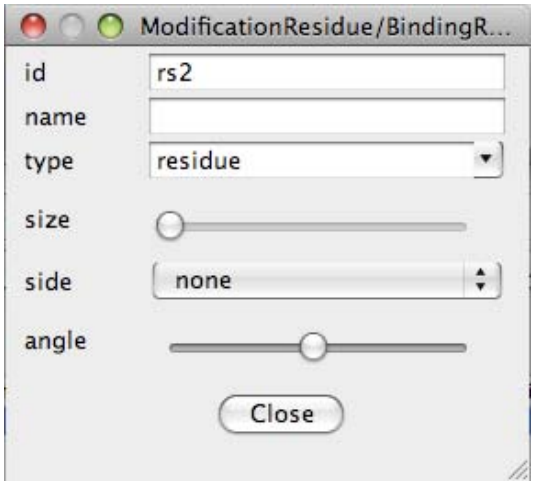
→ Note: Changes in the modification of residue status (such as phosphorylated, etc.) should be made in the Change identity of the species dialog.

5.2.1 To add a residue/region to a Protein/Gene/RNA/asRNA

1. On Draw Area, right-click on a Protein, Gene, RNA or asRNA.
2. Select **Edit Protein/Gene/RNA/asRNA...**.
3. **Protein/Gene/RNA/AntisenseRNA** dialog will appear.



4. Click **add** or **edit** button.
5. In the **Modification Region** dialog (or **ModificationResidue / Binding Region** dialog when editing a Protein), specify the **name**, **type**, **size**, and **position**.



→ Note: Name of the dialog is dependent on the Species type.

6. Click Close.
7. In the **Protein/Gene/RNA/AntisenseRNA** dialog, click **Update** then **Cancel**.

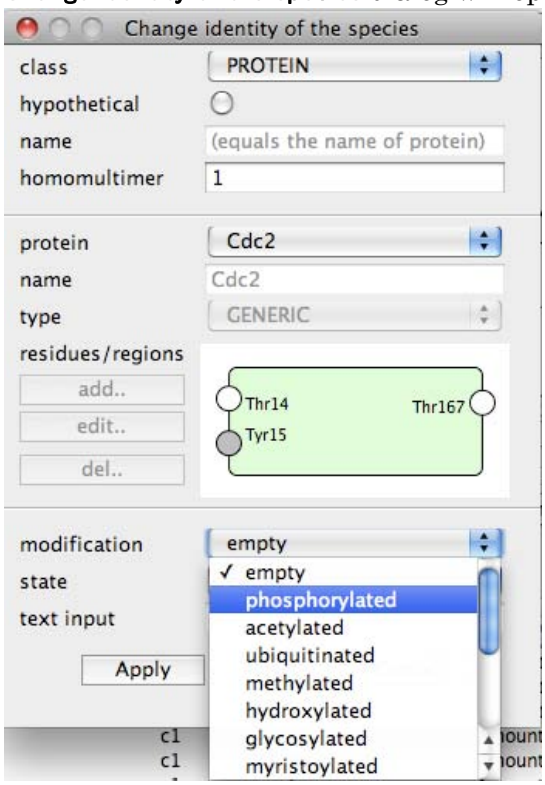
→ Note: You can also delete a residue or a binding region in this dialog.

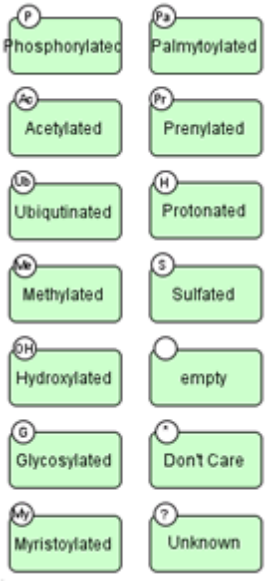
→ Note: Changes in this dialog will be reflected to all Species referring to this Protein, including those inside Complexes.

5.2.2 To specify the modification of a residue

Once you add a residue to a Protein/Gene/RNA/asRNA, you can specify the modification status for a specific Species. To specify the status per Species, use **Change identity of the Species** dialog instead of **Protein/Gene/RNA/AntisenseRNA** dialog.

1. On the Draw Area, double-click a Protein/Gene/RNA/AntisenseRNA which has a residue. Or, select **Change Identity...** from the right-click context menu.
2. **Change identity of the species** dialog will open.





3. In the dialog, click on the target residue in **residues/regions** (or **regions**) diagram in the middle.
4. Select a modification type from the **modification** drop-down list.

Phosphorylated
Palmtoylated
Acetylated
Prenylated
Ubiqutinated
Protonated
Methylated
Sulfated
Hydoxylated
Empty
Glycosylated
Don't care
Myristoylated
Unknown

→ Note: You cannot add, edit, or delete modification residues in this **Change identity of the species** dialog. To add/ delete a residue, use **Protein/Gene/RNA/AntisenseRNA** dialog instead.

5.3 State of a Protein

The state of a Protein can be changed to "open", "close" or "user defined text". Here again, you will use **Change identity of the Species** dialog instead of **Protein** dialog.

→ See also: [2.4 Activate a Species]

5.3.1 To change the state of a Protein

1. Double-click on a Protein to open **Change identity of the species** dialog.
2. In the **state** drop-down list, select an option from **empty**, **open**, **closed** or **user defined text**.

5.4 Add Notes to a Protein, Gene, RNA or asRNA

Protein/Gene/RNA/asRNA Notes allows you to type in additional text information and save it in the xml file.

→ Note: Each Protein, Gene, RNA or asRNA has the Species Notes as well as the Protein/Gene/RNA/asRNA Notes. You should be careful which Notes you want to change when editing.

→ See also: [8. **エラー! 参照元が見つかりません。**Notes and MIRIAM annotation]

5.5 Block Diagram –to check Relationship of a Species (*Proto-type)

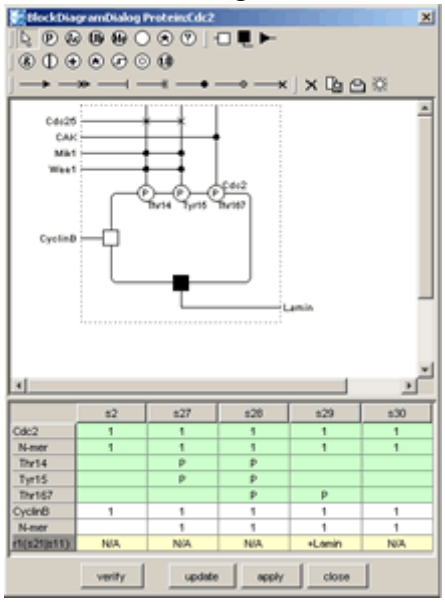
Block diagram gives a summary view of interactions with respect to a specific Species (especially **Protein**) and relation between its modification and activity as enzyme. Using this block diagram editor, complex relations between Proteins can be understood at a glance and the relation between modification states enzymic activity can easily be constructed.

→ Note: The editor is still a prototype and user interface for edittin is not fully functional.

5.5.1 To extract Regulation

CellDesigner extracts the interactions where the Species regulates or is regulated by other Species, from process diagram, and displays its block diagram.

1. Open M-Phase.xml.
2. Right click on Species "Cdc2" then select **Edit Protein** menu.
3. Click **edit block diagram** button and you can see the diagram as shown below.



At the top side of the rectangle placed in center, states of modification residues of Cdc2 and proteins that cause change of the states (phosphorylate or dephosphorylate) are shown. At the left and bottom sides, binding to CyclinB enzymic activity to Lamina are shown respectively.

→ See also Kitano (Biosilico 1, No.5 (2003) pp.169—176), For notation details of the block diagram.

List in the dialog shows all the Species of Cdc2 and Complexes with other Species in process diagram (column) and their modification states and enzymic activity (row).

5.5.2 Modifications/Activations Relation

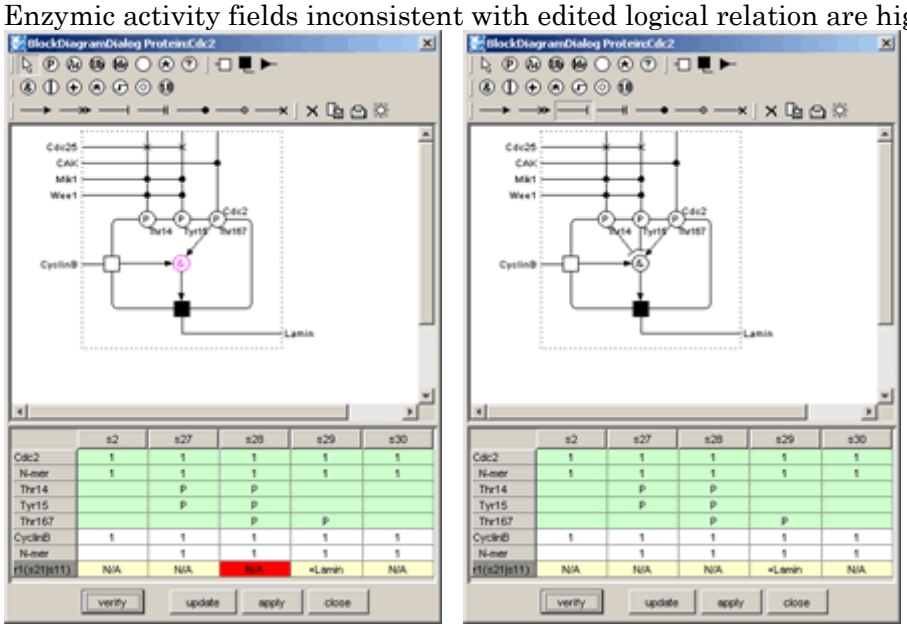
You can edit logical relation between modification states and enzymic activity.

1. Select the symbol "&" and then place them on the diagram.
2. Select the arrow, and link "P", "&", "□" and "■".
3. To delete a placed symbol, select the symbol and press × button in the toolbar.

→ Note: The arrows represent causal relationship and "&" , "|", etc. are logical operators. Created logical relation can also be verified by checking consistency with contents of process diagram.

4. Press **verify** button.

5. Enzymic activity fields inconsistent with edited logical relation are highlighted in red.



The above figures, the left is depicted by logical relation inferred by Species s29 only and the enzymic activity field of Species s28 is highlighted. The right is corrected by using the information of s28. (Note that the way of correction is not unique.)

6. Edit a Model

In this section, convenient functions for editing models are introduced.

CellDesigner provides several functions that are generally seen in drawing software.

6.1 Cut, Copy and Paste

6.1.1 To cut and paste a Species

1. Select a Species by clicking on it.

2. On the **Edit** menu, click **Cut**. Or type `Ctrl-X`.
   The Species has been cut.
3. On the **Edit** menu, click **Paste**.
   The Species reappears.
4. In the Notes Area, observe that the Notes content is the same as the original.

→ Note: For Mac OS X, use Command key instead of Ctrl key.

6.1.2 To copy and paste a Species

1. Select a Species by clicking on it.

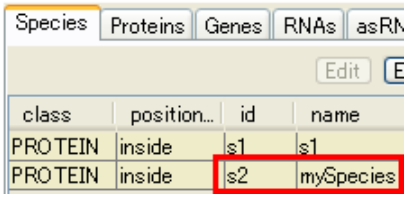
2. On the **Edit** menu, click **Copy**. Or type `Ctrl-C`.
3. Paste it on the Draw Area by selecting **Edit** – **Paste**, or typing `Ctrl-V`.
4. In the Notes Area, observe that the Notes content is the same as the original.

→ Note: For Mac OS X, use Command key instead of Ctrl key.

6.1.3 To change the identity of a Species

1. Right click on one of the Species shown in the previous procedure, and select **Change Identity**.
2. If **Residues Caution** dialog appears, click **Close**.
   The **Change identity of the species** dialog appears.
3. In the **protein** list, click **New Protein**.
4. In the **name** textbox, type any name, e.g. “mySpecies”. Click **Apply**.
5. Click **No**. The name of the Species has been changed to “mySpecies”.
   Its id has also been changed but not shown.

6. In the List Area, select **Species** tab.
   See that the id and name of the Species has been changed.



7. In the List Area, select **Proteins** tab.
   See that the id (as a protein) and name of the Species has been changed.

id	type	name
pr1	GENERIC	s1
pr2	GENERIC	mySpecies

6.2 SpeciesAlias

The copy-and-paste action makes a duplicate figure of the original Species. The duplicated figure is called a **SpeciesAlias** in CellDesigner's terminology. Strictly speaking, all of the Species on the Draw Area, including the original Species figure, are SpeciesAliases, each referring to the original Species object class. In other words, when you have created a new Species, what you see on the Draw Area is not the Species itself but an Alias of it. This feature enables CellDesigner to have multiple copies of the same Species object class on the Draw Area, and make various expressions of a network.

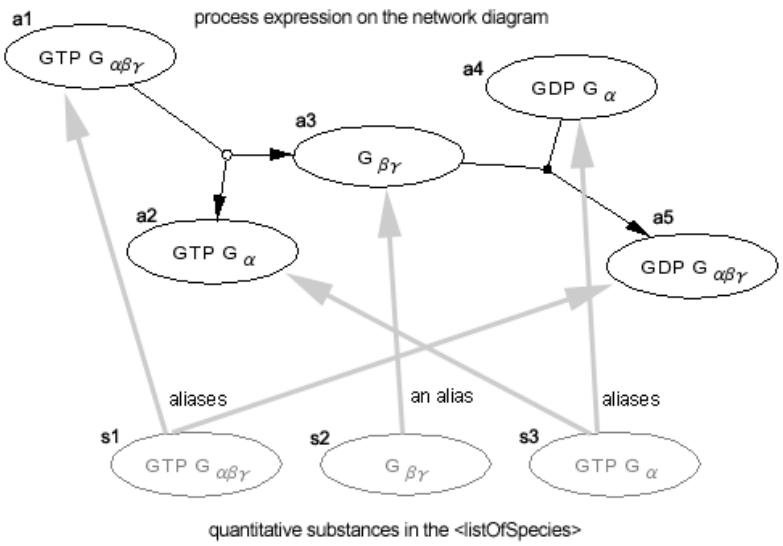
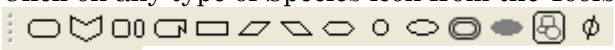
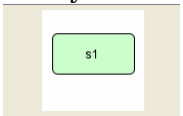


Fig. The Alias Structure of the CellDesigner

6.2.1 To see the relationship between a Species and a SpeciesAlias in XML

1. In the Menu, click **File** – **New** to create a new model.
2. Click on any type of Species icon from the Toolbar and place it on the Draw Area.

3. Move the cursor and click anywhere on the Draw Area to place the Species you have chosen. Now you have a model with only one Species.


4. Select **File** – **Save as⋯** in the Menu.
5. Save the file in XML format.
6. With a text editor, open the XML file you have just saved.
7. Find the `<celldesigner:listOfSpeciesAliases>` tag, under which is a child element that specifies the Alias of the Species. `<celldesigner:speciesAlias id="sa1" species="s1">`
8. Near the bottom of the XML file, find the `<listOfSpecies>` tag which lists up all the Species in your model.
9. Find a tag as below which indicates the Species itself.
```
<species metaid="s1" id="s1" name="s1" compartment="default" initialAmount="0">
```

→ Note: A Complex is a type of Species but a ComplexSpeciesAlias is NOT a SpeciesAlias.

6.3 Select Mode

After you have put a new component on Draw Area, the **Select Mode** icon  will automatically be selected so that you can immediately select and move the component. This is the initial setting of CellDesigner.

You might want to change this setting so as to create several components on Draw Area first and then rearrange them as you like.

6.3.1 To avoid the automatic Select Mode

1. Select **Edit** menu in the Menu.
2. Select **Input Repeat**.

6.3.2 To switch temporarily to the Select Mode

1. While the **Select Mode** icon  is NOT selected, hold down the "s" key on your keyboard.
2. Select a component and move it.
3. Release the "s" key to go back to the previous mode.

6.4 Select All

6.4.1 To select all the components

1. Select **Edit** and then **Select All** in the Menu
2. You can also use `Ctrl-A`.

→ Note: For Mac OS X, use Command key instead of Ctrl key.

6.5 Grouping

In Select Mode, by clicking multiple Species while holding the SHIFT key down, you can make a temporal group of the selected Species. Moving, cutting, and copying them in a group are available. If you want the group to be permanent (saved to SBML), use Ctrl-G while the temporary group is formed. This grouping feature is similar to placing several Species within a Compartment but they are different. Grouping has no effect on the structure of the model. Therefore, if these two apparently seem to conflict each other in the Draw Area, "Species within a Compartment" structure has priority.

→ Note: Tags cannot include in a group

6.5.1 To create a temporary group of components

1. Click multiple Species while holding the SHIFT key down.
2. You can move, cut or copy them together.

6.5.2 To create a permanent group of components

1. Click multiple Species while holding the SHIFT key down.
2. Select **Edit** and then **Create Group** in the Menu. Or use `Ctrl-G`.
3. When saved, this group information will be written in the SBML file.

→ Note: For Mac OS X, use Command key instead of Ctrl key.

6.6 Alignment

6.6.1 To adjust the alignment of the components

1. Select the multiple Species you want to adjust.
2. Click **Edit** menu, point to **Alignment**, and select an alignment type.
   You can also click an icon in the Toolbar.

6.6.2 To adjust the position of a component by keyboard operation

1. Select a component.
2. Use UP, DOWN, RIGHT, LEFT keys to move the component pixel by pixel.

6.7 Set Grid Snap ON/OFF

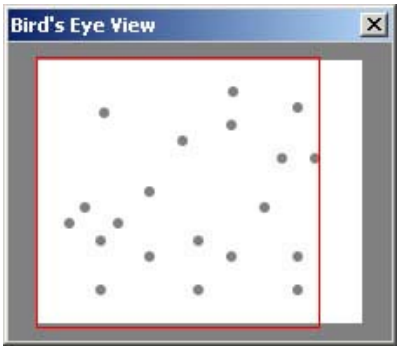
Snapping your components on the grid makes it easier to layout the pathway diagram.

6.7.1 To use Grid Snap

1. On the **Edit** menu, click **Grid Snap**.
2. To show the grid, click **Grid Visible on the Edit menu.**
3. **To change the grid size, click Set Grid Size... on the Edit menu.**

6.8 Zoom IN/OUT, Bird's Eye View

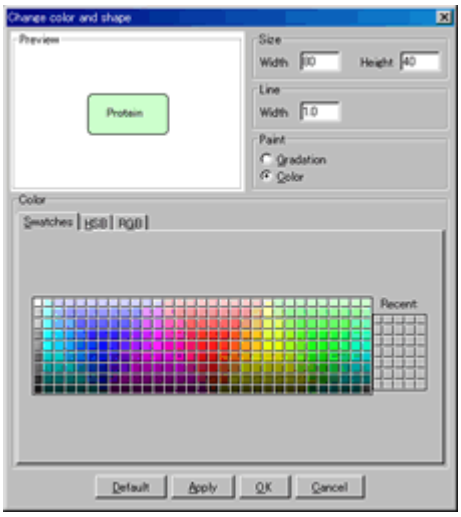
You can change the zoom view of the model by clicking the following icons. or use the menu [View] –[Zoom Select] to specify the zoom %.



When you create a big model, it would be convenient to use the Bird's Eye View to navigate inside the model.

The Bird's Eye View can be displayed by clicking the icon  (**Show Bird' s Eye View**) in the above Toolbar. When you drag the red square in the Bird's Eye View, observe that the view of the Draw Area moves accordingly.

6.9 Change Color and Shape



You can change the color and size of the components, such as Species, Reactions and Compartments, individually or to their default settings.

6.9.1 To change the default settings

1. On the **Preference** menu, select **Components Color & Shape....**
2. In the **Default Component Setting** dialog, click on a Species of which you want to change the default settings.
3. In the **Default setting of <species name>** dialog, change

parameters.

6.9.2 To change the color and shape of the individual component(s)

1. Select a component, or components of the same type.
2. In the **Component** menu, select **Change Color & Shape...**, or Click the **Change Color & Shape** icon  in the tool bar.

6.10 Change Species font size

6.10.1 To change font size

1. On the Draw Area, right-click on a Species to show the context menu.
2. Select **Change font ....**
3. In **Change Species Name Font** dialog, select a font size.

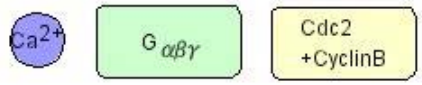
6.11 Display special characters in Component name

As CellDesigner is compliant with SBML, all names of components in a model must conform to the SBML convention. CellDesigner 4.1 is compliant with SBML Level 2 Version 1; any character that can be mapped to UTF-8 encoding can be used for the component names. If you want the special characters, such as + plus, line break, superscript and subscript, you should follow the special rules to input such characters.

6.11.1 Examples

A special character is expressed by a sequence of characters with precedent and follow up '_'s. Here are some examples:

1) Ca2+ ("Ca" with "2+" superscript)



Ca_super_2_plus__endsuper_

Ca_super_2+_endsuper_

2) G alpha beta gamma ("G" with Greek "αβγ" subscripts)

G_sub__alpha__beta__gamma__endsub_

G_sub_αβγ_endsub_

3) Complex of Cdc2 and CyclinB ("Cdc2" followed by "+CyclinB" in the new line).

Cdc2_br__plus_CyclinB

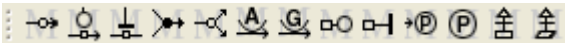
Cdc2_br_+CyclinB

For more details on displaying special characters, click **Name Expression** in the **Help** menu.

→ Note: CellDesigner uses the "name" attributes as information to distinguish Species. Therefore, even if the rendered names look the same, the different "name" attributes, for example, "Gα" and "G_alpha_", mean different Species.

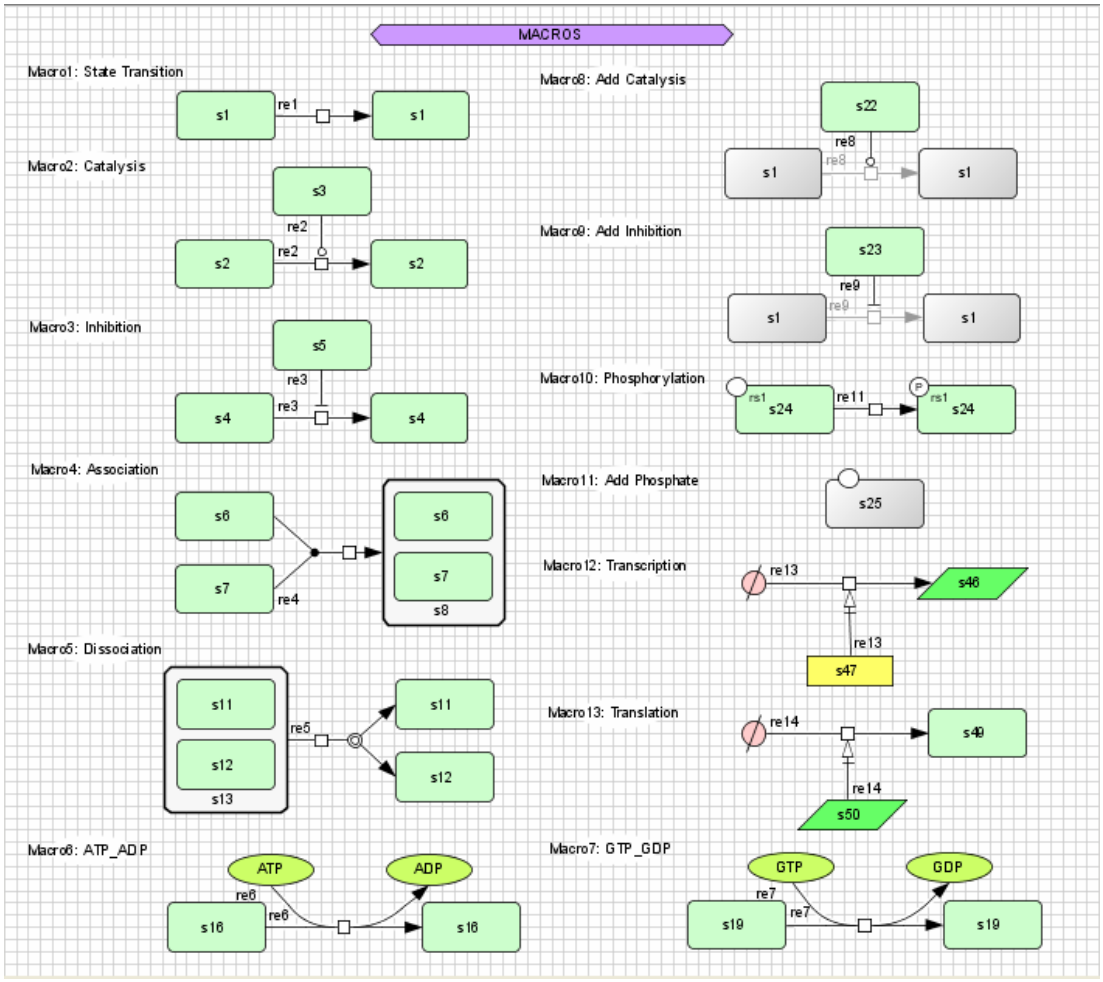
6.12 Macros

To draw the diagram easier, some of the most frequently used components sets are available as “macros”. You can select the macros from the tool bar to draw the following components set.



6.12.1 To view how each macro draws the components

1. In the **File** menu, click **Open**.
2. In the **Open** dialog, go to “samples” folder in your CellDesigner directory.
3. Double-click “Macro.xml” in the “samples” directory.



6.12.2 To change the Macro Setting

1. In the **Preference** menu, click **Set Macro UI...**
2. In the **Macro UI Setting** dialog, change the settings.

6.13 Automatic Layout

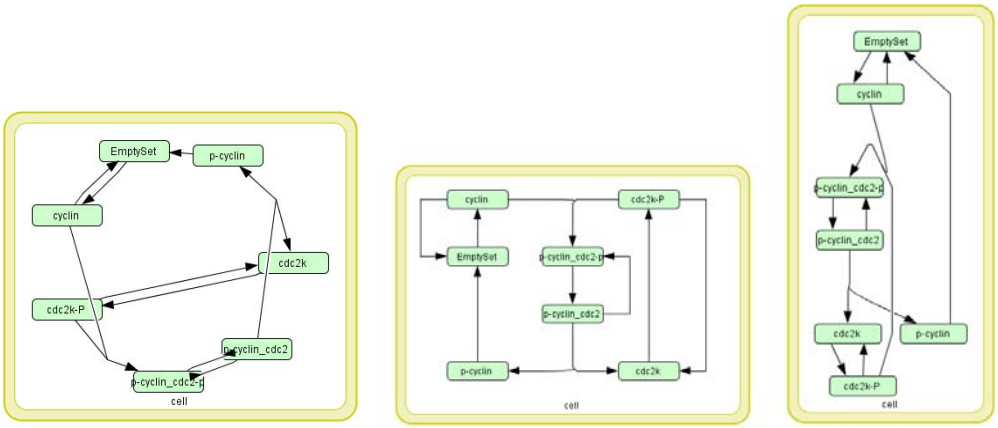
Automatic layout function is available for adjusting the model outlook.

When you retrieve SBML files without any layout information created by other tools, CellDesigner will automatically adjust the layout with its layout schemes.

6.13.1 To change the layout of your working model

1. On the **Layout** menu, select one of the layout types

Orthogonal Layout
Organic Layout
Smart Organic Layout
Hierarchic Layout
Incremental Hierarchic Layout
Circular Layout
Tree Layout
Edge Router



You can change the detail settings for the above types as well as default settings adopted when you retrieve SBML files.

The default setting is **Smart Organic Layout**.

6.13.2 To change the Default Setting:

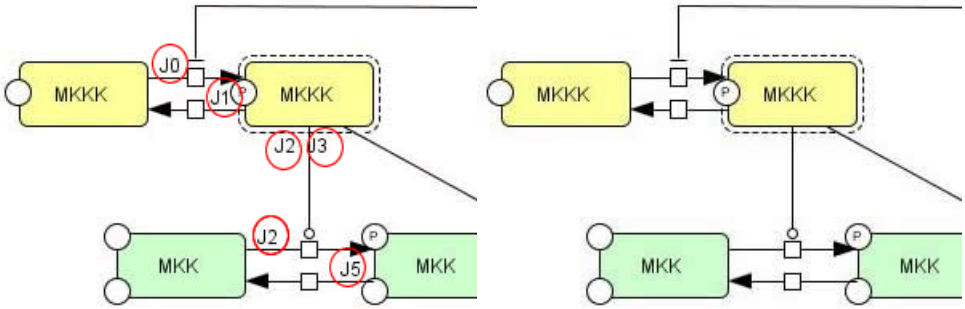
1. On the **Layout** menu, click **Default Automatic Graph Layout**.
2. Select a layout you want set as default.

7. Reaction and KineticLaw

7.1 Reaction ID

7.1.1 To show Reaction ID on Draw Area

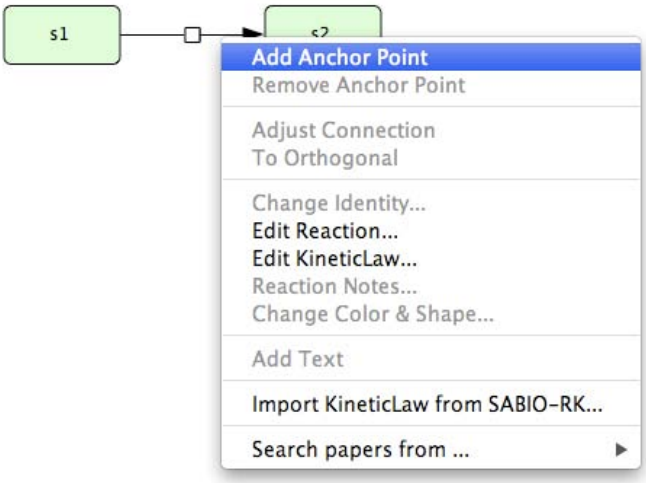
1. On the **View** menu, select **Show Reaction ID**.



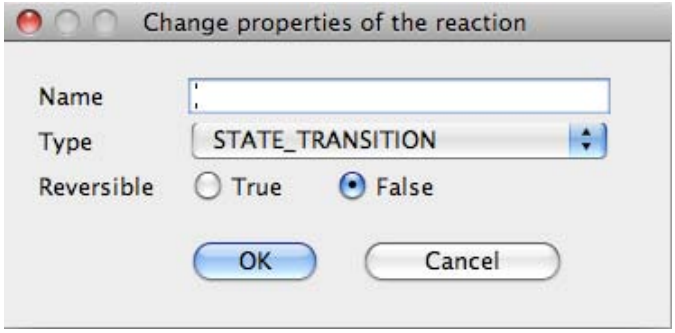
with Reaction IDs　　without Reaction ID

7.2 Edit a Reaction

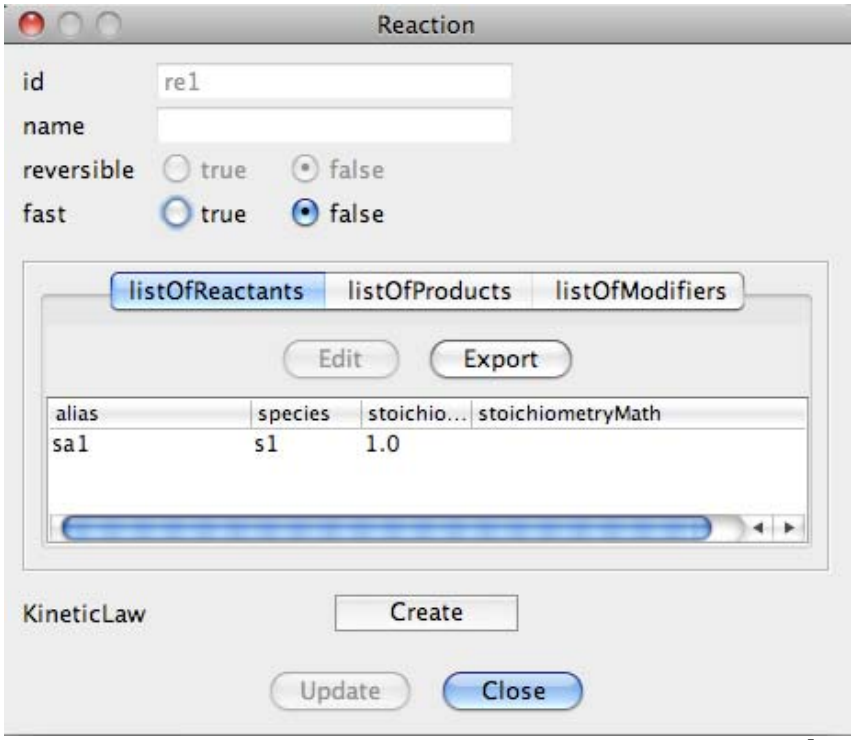
1. Right click on a Reaction.
2. Select a menu item from the right-click context menu.



3. Select a menu item depending on which value you want to edit.
4. Selecting **Change Identity** will show you **Change properties of the reaction** dialog.



5. Selecting **Edit Reaction** will show you **Reaction** dialog.



6. Selecting **Edit KineticLaw...** will show you **KineticLaw** dialog. See [7.4 KineticLaw] for detail.

→ See also: "Species" section of the CellDesigner.org Online Help http://celldesigner.org/help/CDH_Species_T.html.

→ See also: [10. "Gene/RNA/AntisenseRNA Structure Expressions"].

7.3 Reactions List

You can view all the data concerning a Reaction in the **Reactions** tab in the List Area. This is useful when you want to check all the Reactions specified in the model.

You can swap columns by drag-and-drop.

Species | Proteins | Genes | RNAs | asRNAs | Reactions | Compartments | Parameters | Functions | Units | Rules | Events

Species ID | Edit | Export

type	id	name	rever...	fast	reactants	products	modifiers	math
STATE_TRANSITIO...	J0	J0	false	false	MKKK	MKKK_P	MAPK_PP	V1 * MKKK / ((1 + pow(MAPK_PP / K1, n)) * (K1 + MKKK))
STATE_TRANSITIO...	J1	J1	false	false	MKKK_P	MKKK		V2 * MKKK_P / (KK2 + MKKK_P)
STATE_TRANSITIO...	J2	J2	false	false	MKK	MKK_P	MKKK_P	k3 * MKKK_P * MKK / (KK3 + MKK)
STATE_TRANSITIO...	J3	J3	false	false	MKK_P	MKK_PP	MKKK_P	k4 * MKKK_P * MKK_P / (KK4 + MKK_P)
STATE_TRANSITIO...	J4	J4	false	false	MKK_PP	MKK_P		V5 * MKK_PP / (KK5 + MKK_PP)
STATE_TRANSITIO...	J5	J5	false	false	MKK_P	MKK		V6 * MKK_P / (KK6 + MKK_P)
STATE_TRANSITIO...	J6	J6	false	false	MAPK	MAPK_P	MKK_PP	k7 * MKK_PP * MAPK / (KK7 + MAPK)
STATE_TRANSITIO...	J7	J7	false	false	MAPK_P	MAPK_PP	MKK_PP	k8 * MKK_PP * MAPK_P / (KK8 + MAPK_P)
STATE_TRANSITIO...	J8	J8	false	false	MAPK_PP	MAPK_P		V9 * MAPK_PP / (KK9 + MAPK_PP)
STATE_TRANSITIO...	J9	J9	false	false	MAPK_P	MAPK		V10 * MAPK_P / (KK10 + MAPK_P)

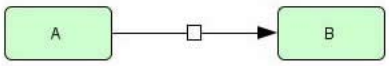
You can export the contents of the list into .CSV file format by clicking **Export** button on the top of the list.

7.4 KineticLaw

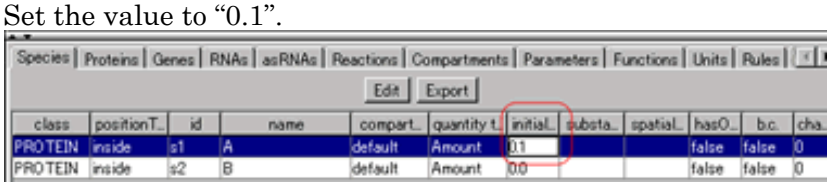
You can specify a KineticLaw to a Reaction using the **KineticLaw** dialog. You can input your own math functions, or you can use the predefined functions from the **KineticLaw** dialog.

7.4.1 To add a KineticLaw to a Reaction

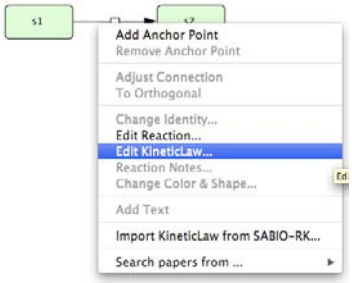
1. Create a model with Proteins A and B, with a State Transition Reaction in-between.



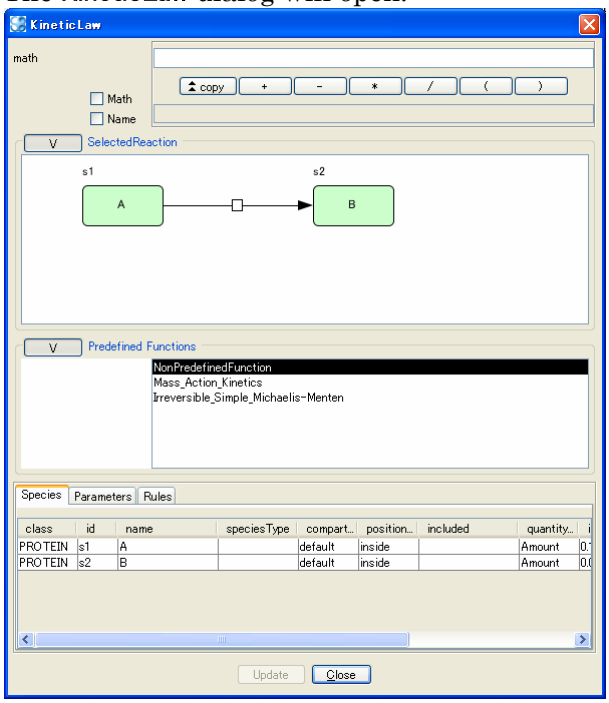
2. In the List Area, click on the **Species** tab.
3. Select the row for the Protein A.
4. Double click on the cell under **InitialQuantity** column.
5. Set the value to “0.1”.



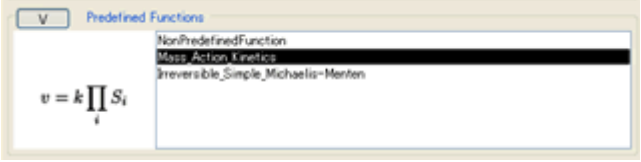
6. In the List Area, click on the **Reactions** tab and double click on the STATE_TRANSITION Reaction to open the **Reaction** dialog.
7. Click KineticLaw **Create** button.
8. Instead of doing the steps 6 and 7, you can also click on the Reaction with the right mouse button, and then select **Edit KineticLaw...** menu.



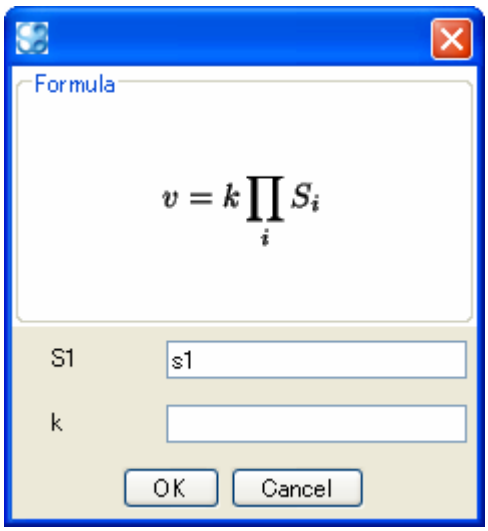
9. The **KineticLaw** dialog will open.



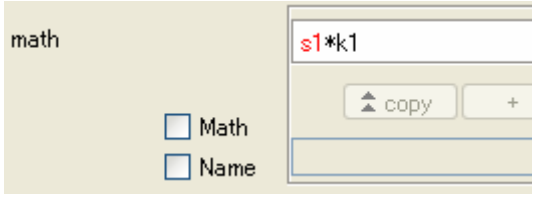
10. In the **Predefined Functions** pane, click **Mass_Action_Kinetics**.



11. The **Formula** dialog will be displayed.



12. Type in "0.3" in the **k** text box, then click **OK**.
13. See that "s*1**k*1*" has been entered in **math** field, then click **Update,** then **Close.**

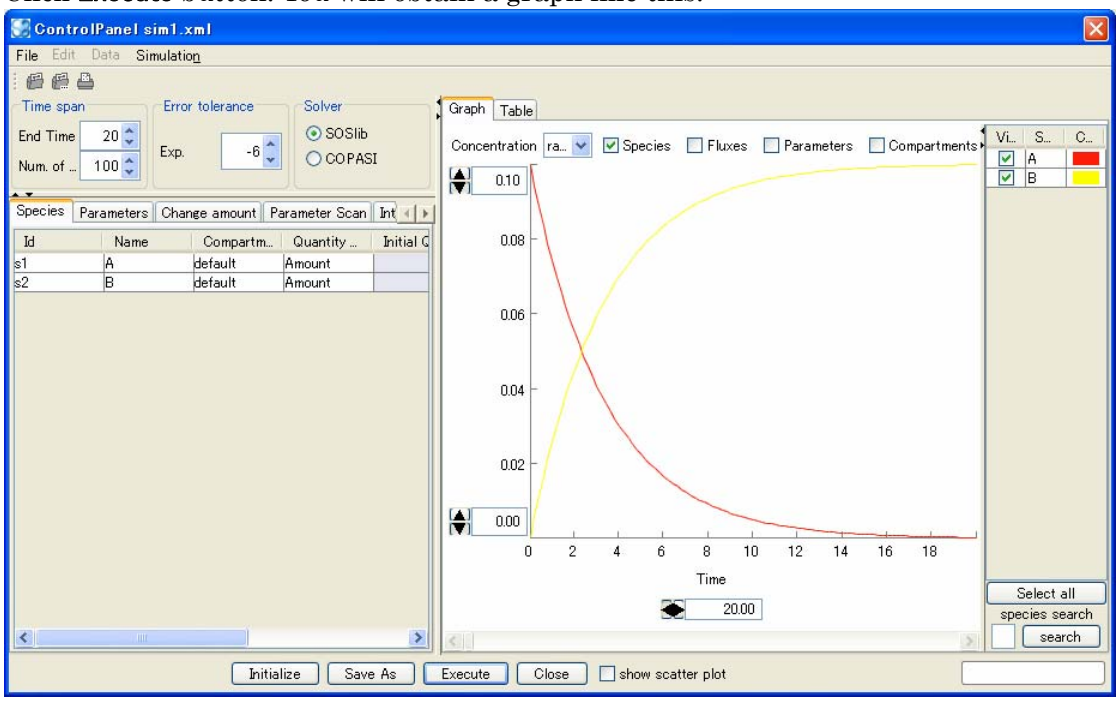


14. In the **Reaction** dialog, click **Close**.

The KineticLaw for the Reaction was successfully set.
Now you can run the simulation.

7.4.2 To run the simulation

1. Do the previous walkthrough "To add a KineticLaw to a Reaction". Or, just open the file `sim1.xml` in the `samples` folder.
2. On the **Simulation** menu, click **Control Panel**.
3. In the **Control Panel <filename>** dialog, set **End Time** to "20".
4. Click **Execute** button. You will obtain a graph like this.



8. Notes and MIRIAM annotation

There are two ways to annotate a Component (Compartment, Species, or Reaction); by adding free text Notes and by adding MIRIAM information.

The Notes allows you to type in additional text information for your Component and save it in the xml file.

→ Note: Each Protein, Gene, RNAs or asRNA has a Protein/Gene/RNA/asRNA Notes as well as Species Notes. You should be careful which Notes you want to change when editing.

The Notes should be written in XHTML format. For details on XHTML tags and attributes, please check the XHTML 1.0 specification provided at http://www.w3.org/TR/xhtml1/

You can enter PubMed ID in the Notes, and directly link to the relevant reference.

→ See also [9. "Connect to External Databases"].

MIRIAM (the Minimal Information Requested In the Annotation of Models) is a standard to annotate and curate computational models in biology. http://www.ebi.ac.uk/miriam/. SBML Level 2 Version 4 recommends using MIRIAM as an annotation scheme. CellDesigner 4.1 now supports MIRIAM annotation.

MAPK41.xml is a sample file installed with CellDesigner. The file already contains MIRIAM information to give you a picture of how MIRIAM information is added on a model.

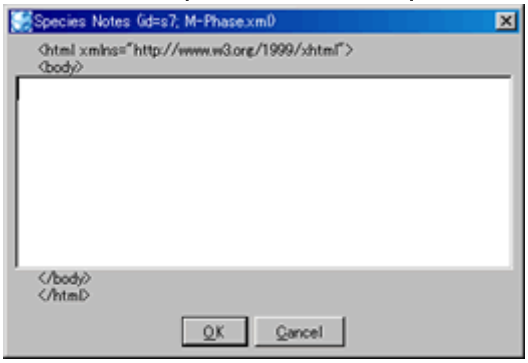
8.1 Notes

8.1.1 To add Notes to a Component (i.e. Compartment, Species or Reaction)

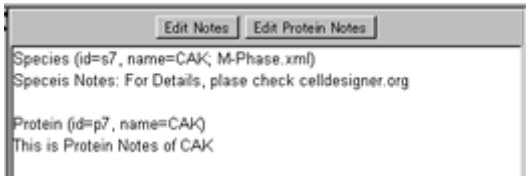
1. Select a Component.
2. Click on the right mouse button to display the popup menu and select **Species Notes...** (**Compartment Notes...** or **Reaction Notes...**).
3. Or, click **NOTE** tab in the Notes Area (at the bottom right corner of the Main Window) and click **Edit Notes** button.

→ Note: If you select a Protein, Gene, RNA or asRNA, you will also find **[Protein | Gene | RNA | asRNA] Notes** menu item in the right-click menu, as well as **Edit [Protein | Gene | RNA | asRNA] Notes** button in the Notes Area. See the next procedure "To add Notes to a Protein, Gene, RNA or asRNA" on how to use them.

4. See that the **Species Notes** (**Compartment Notes...** or **Reaction Notes...**) dialog pops up.



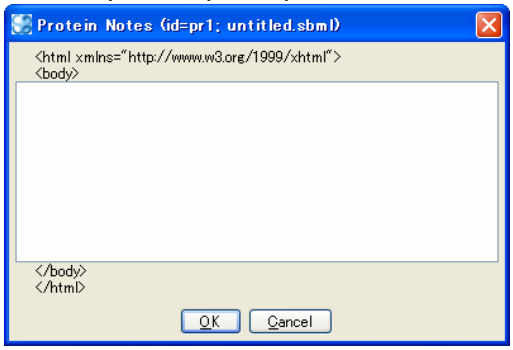
5. Type the text you want to add in XHTML format.
6. Click **OK** to close the dialog
7. See the Notes information you have just added is displayed in the Notes Area.



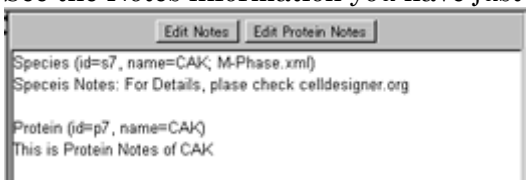
8.1.2 To add Notes to a Protein, Gene, RNA or asRNA

If your target Species is one of the following types, namely, Protein, Gene, RNA or asRNA, you can add the [Protein | Gene | RNA | asRNA] Notes as well as the Species Notes.

1. Select a Protein, Gene, RNA or asRNA.
2. Click on the right mouse button to display the popup menu and select **Edit [Protein | Genes | RNA | asRNA] Notes**, or click **Edit [Protein | Genes | RNA | asRNA] Notes** button in the Notes Area (on the bottom right corner of the window).
3. **[Protein | Genes | RNA | asRNA] Notes** dialog pops up.



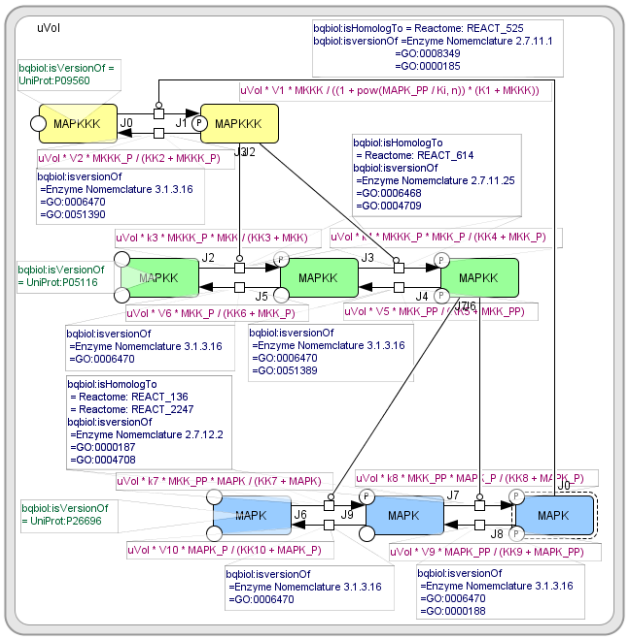
4. Type the text you want to add in XHTML format.
5. Click **OK** to close the dialog
6. See the Notes information you have just added is displayed in the Notes Area.



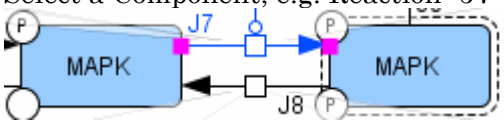
8.2 MIRIAM annotation

8.2.1 To see MIRIAM annotation on a sample file MAPK41.xml

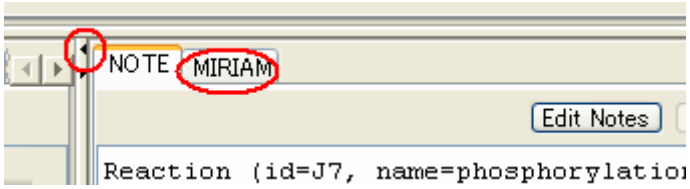
1. In the Menu, select **File**, then **Open**.
2. In the **Open** dialog, find `MAPK41.xml` in `/<your CellDesigner directory>/samples/` folder and Click **Open**.
3. `MAPK41.xml` opens. We shall modify this file, so if you wish to keep the original file, make its duplicate.



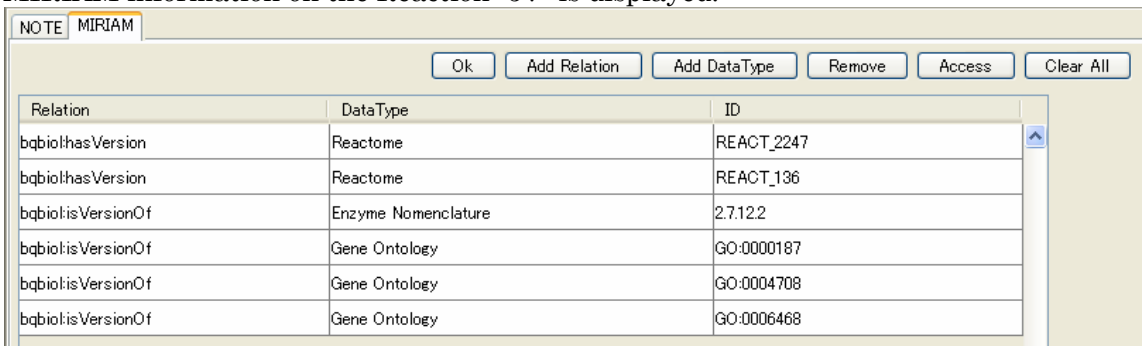
4. Select a Component, e.g. Reaction “J7”.



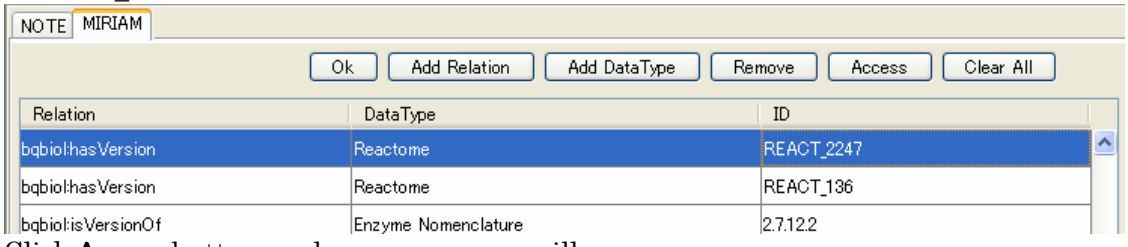
5. In the Notes Area, click **MIRIAM** tab. To have a wider view, click the left-pointing arrow.



6. MIRIAM information on the Reaction “J7” is displayed.



7. Select the first row where **Relation** is “bqbiol:hasVersion”, **DataType** is “Reactome” and **ID** is “REACT_2247”.

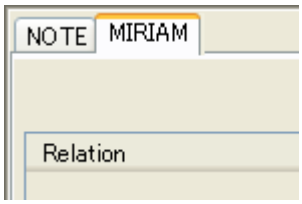


8. Click **Access** button, and a pop-up menu will appear.
9. In the pop-up menu, select “MIR;00100026”.
10. Your web browser will be launched and show you a Reactome web page explaining “MEK2 phosphorylates ERK-2 [Homo sapiens]”.
11. Back to CellDesigner Main Window, in the MIRIAM list, select the third row where **Relation** is “bqbiol:isVersionOf”, **DataType** is “Enzyme Nomenclature” and **ID** is “2.7.12.2”.
12. Click **Access** button, and a pop-up menu will appear.

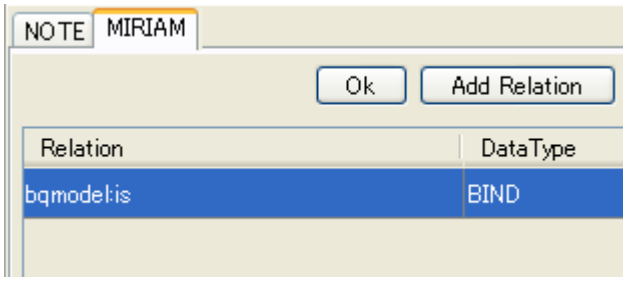
13. In the pop-up menu, select one of the followings:
    "MIR;00100001" to access an EBI web page
    "MIR;00100002" to access a KEGG web page
    "MIR;00100003" to access an ExPASy Proteomics Server web page
14. Whichever web page you go to, you will find information on Mitogen-activated protein kinase kinase (EC 2.7.12.2).

8.2.2 To add MIRIAM information to a Component

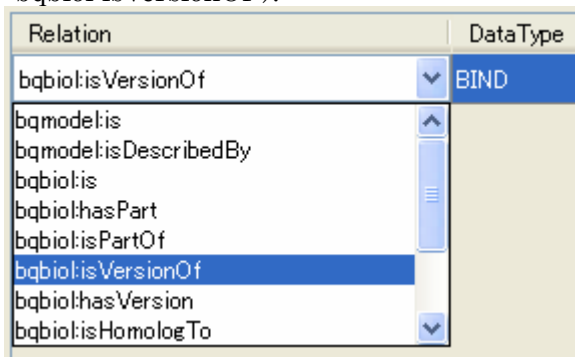
1. On the Draw Area (Canvas), select a Component (i.e. Compartment, Species or Reaction).
2. Click on the **MIRIAM** tab in the Notes Area.



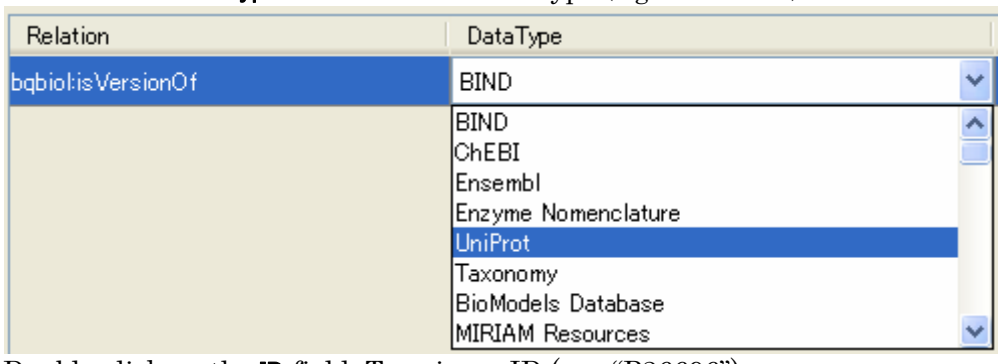
3. Click **Add Relation** button.
4. A Relation will be added to the list.



5. Click on the **Relation** field. Select a Relation from the pull-down menu (e.g. "bqbiol:isVersionOf").



6. Click on the **DataType** field. Select a DataType (e.g. "UniProt").



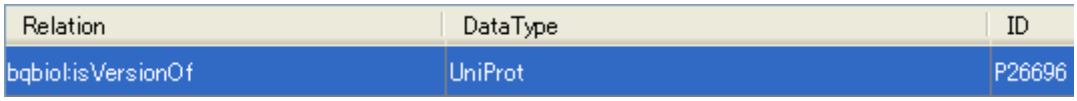
7. Double-click on the **ID** field. Type in an ID (e.g. "P26696").

→ Note: If you do not know the ID, click **Access** button. It will show MIRIAM site IDs, select one to access the website and find the ID for the DataType.

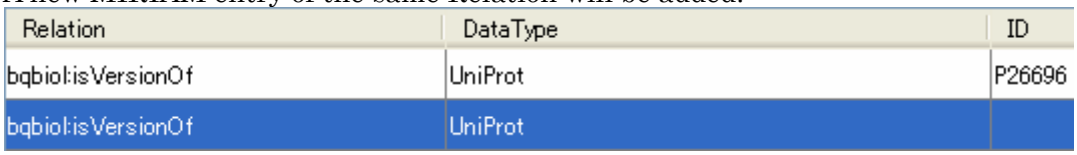
8. Click **OK** to save the MIRIAM information.

8.2.3 To add a new DataType for an existing Relation

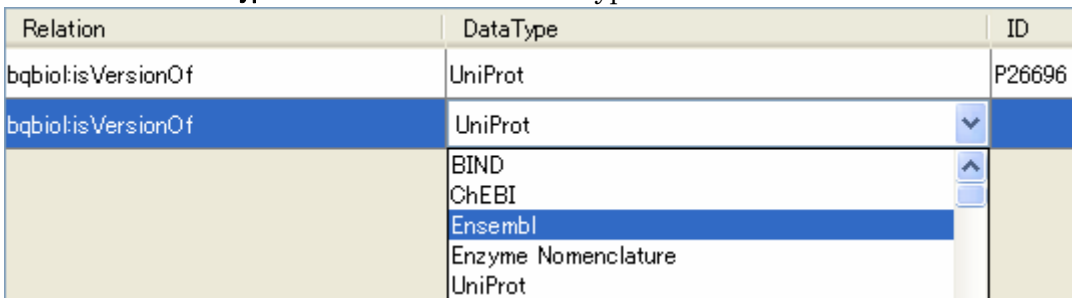
1. Select a Component which has MIRIAM information.
2. In the Notes Area, click **MIRIAM** tab.
3. Select a Relation from the list.



4. Click **Add DataType** button.
5. A new MIRIAM entry of the same Relation will be added.



6. Click on the **DataType** field and select a DataType from the list.



7. Double-click on the **ID** field and type in an ID for the DataType.
8. Click **OK** to save the MIRIAM information.

8.2.4 To delete MIRIAM information

1. Select a Component having MIRIAM entry. of the same Relation.
2. In the Notes Area, click **MIRIAM** tab.
3. Select an entry to delete.
4. Click **Remove**.

→ Note: If you want to undo the Remove action, just click the Component on the Draw Area without clicking **OK** button. MIRIAM information for the Component will not be saved until you click the OK button.

5. Click **OK** to save the MIRIAM information.

9. Connect to External Databases

You can connect to external databases using the Species name or ID specified in the Notes. Currently we support the connections to the following databases.

Importing models and information		
BioModels.net	http://www.biomodels.net, http://www.ebi.ac.uk/biomodels/	
PANTHER Pathways database	http://www.pantherdb.org/pathway/	
SABIO-RK	http://sabio.villa-bosch.de/index2.jsp	
Use Species Names for query		
DBGET	http://www.genome.jp/dbget/	a simple database retrieval system for a diverse range of molecular biology databases
SGD	http://yeastgenome.org/	Saacharomyces Genome Database
iHOP	http://www.ihop-net.org/UniPub/iHOP/	Information Hyperlinked over Proteins
Genome Network Platform	http://genomenetwork.nig.ac.jp/public/sys/gnppub/portal.do	
Use IDs for query		
PubMed	http://www.ncbi.nlm.nih.gov/sites/entrez	
Entrez Gene	http://www.ncbi.nlm.nih.gov/sites/entrez?db=gene	
MetaCyc	http://www.metacyc.org/	
GeneWiki	http://en.wikipedia.org/wiki/Portal:Gene_Wiki	

9.1 Database Query

9.1.1 To use Species Names for database query

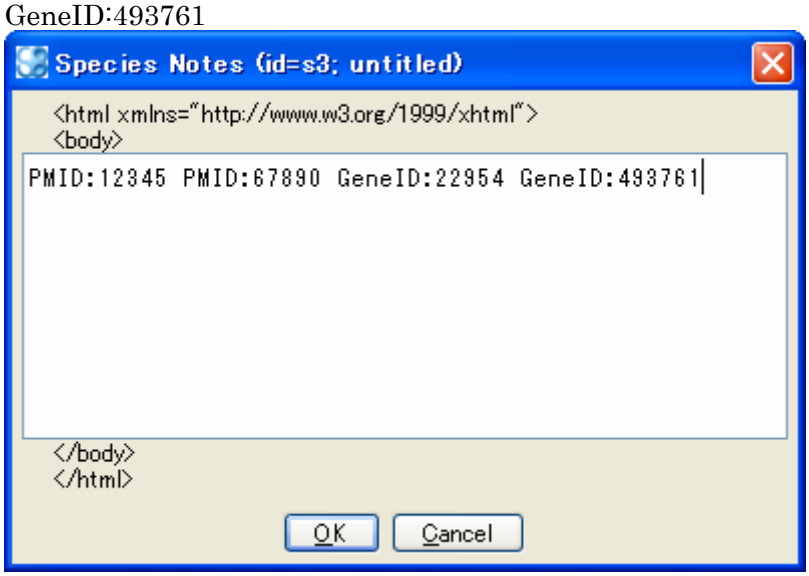
1. Select a component (Species, Reaction or Compartment).
2. In the Menu, select **Database**, and then **Connect to** *<database name>*.
3. See your web browser pop up and open the page relevant to the Species.

→ Note: In case of DBGET, search is conducted according to the format of the name. If the name is written as "2.1.3.1", "EC2.1.3.1", "EC: 2.1.3.1", and "EC 2.1.3.1" for EC number, while the name start with "C", "C00010", "C 00010", "C: 00010" , search for compound ID.

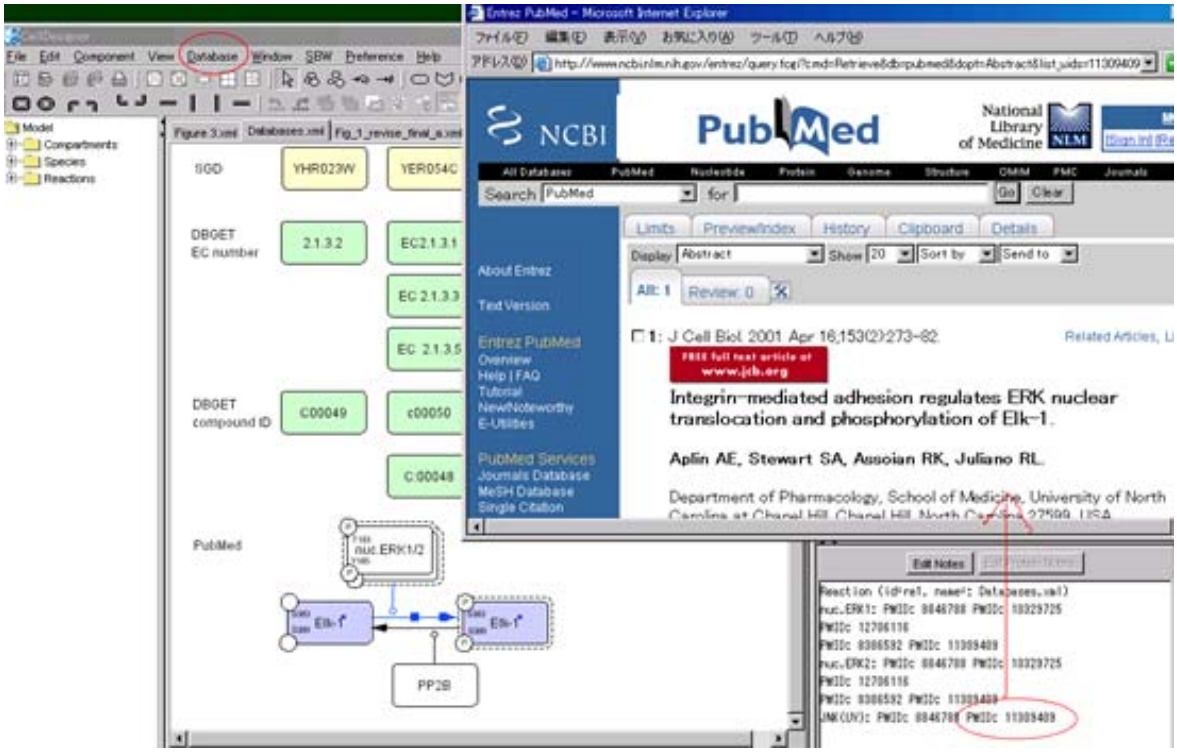
9.1.2 To use PubMed ID and Entrez Gene ID for database query

1. Select a component (Species, Reaction or Compartment).
2. In the Notes Area, click **Edit Notes**.
3. Specify the PubMed ID / Entrez Gene ID as follows:
   PMID:12345
   PMID:67890
   GeneID:22954

GeneID:493761



4. In the menu bar, select **Database** - **Connect to PubMed**.
5. Your browser will be launched and show the PubMed web site.
6. In the menu bar, select **Database** - **Connect to Entrez Gene**.
7. Your browser will be launched and show the Entrez Gene web site.



9.2 Importing Models and Information

9.2.1 To import models from BioModels.net

BioModels Database (http://biomodels.net) is a data resource that allows biologists to store, search and retrieve published mathematical models of biological interests. Models present in BioModels Database are annotated and linked to relevant data resources, such as publications, databases of compounds and pathways.

1. In the Menu, select **Database**, then **Import model from BioModels.net...**
2. The **BioModels.net** dialog opens.
3. Select a model in the list and click **OK**.

4. If **Notice** dialog opens, just click **OK**.
5. The model will open.

9.2.2 To import models from pantherdb.org

Panther Pathway Database (http://www.pantherdb.org/pathway) consists of primarily signaling, pathways, each with subfamilies and protein sequences mapped to individual pathway components. Pathways are drawn using CellDesigner, capturing molecular level events in both signaling and metabolic pathways, and can be exported in SBML format. The images of SBGN view of the diagram can also be exported.

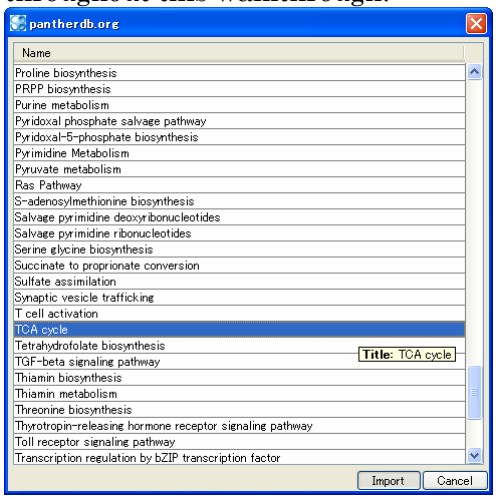
1. In the Menu, select **Database**, then **Import model from pantherdb.org...**
2. The **pantherdb.org** dialog opens.
3. Select a model in the list and click **Import**.
4. If **libSBML Consistency Check** dialog opens, read the message and click **OK**.
5. If **File conversion needed** dialog opens, read the message and click **Yes** or **Cancel**. Even if you click **Cancel**, you can still open the model.
6. If **Notice** dialog opens, just click **OK**.
7. If **Compartment's size attribute is undefined.** dialog opens, click **OK** or **No**. Even if you click **No**, you can still open the model.
8. The model will open.

9.2.3 To import the reaction information from SABIO-RK database

The SABIO-RK (System for the Analysis of Biochemical Pathways - Reaction Kinetics) is a web-based application based on the SABIO relational database that contains information about biochemical reactions, their kinetic equations with their parameters, and the experimental conditions under which these parameters were measured. It aims to support modellers in the setting-up of models of biochemical networks, but it is also useful for experimentalists or researchers with interest in biochemical reactions and their kinetics. Information about reactions and their kinetics can be exported in SBML format.

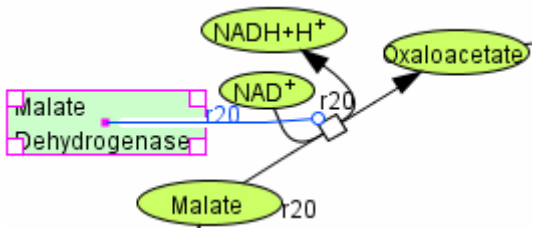
→ See also: 7.4. KineticLaw.

1. Import the model **TCA cycle** from pantherdb.org. We will use the model as a sample throughout this walkthrough.

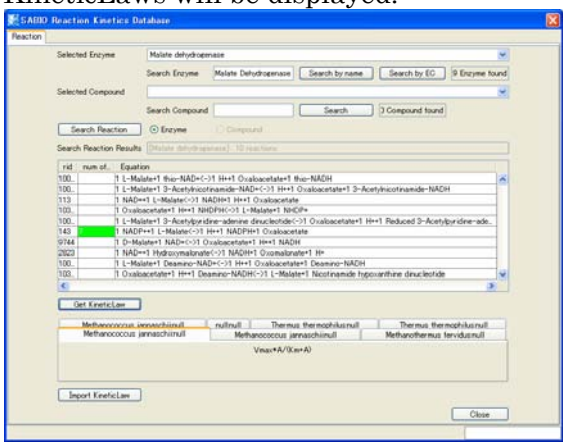


→ See also: 9.2.2 To import models from pantherdb.org

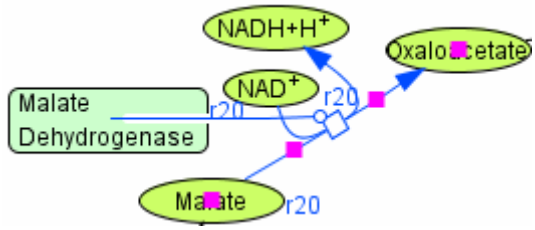
2. On the Draw Area, select **Malate Dehydrogenase**.



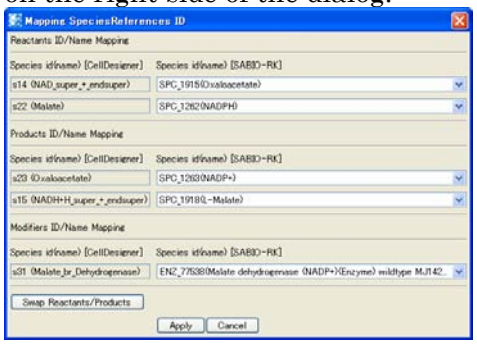
3. In the Menu, select **Database - Import reaction information from SABIO-RK...**
4. The **SABIO Reaction Kinetics Database** dialog will appear.
5. Verify that **Malate Dehydrogenase** is already been typed in **Search Enzyme** textbox.
6. Click **Search by name** button.
7. From **Selected Enzyme** drop-down list, select **Malate Dehydrogenase**.
8. Verify that **Enzyme** radio button is selected and click **Search Reaction**.
9. From the returned list, select a row where **rid** is **143**.
10. Click **Get KineticLaw**.
11. KineticLaws will be displayed.



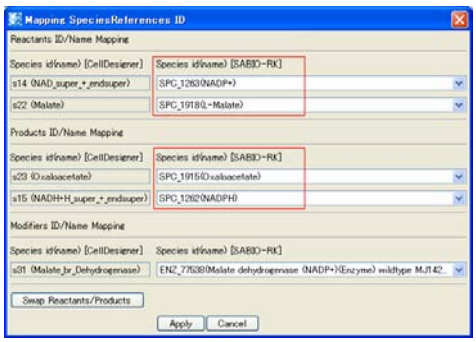
12. On the Draw Area, click the Reaction **r20**.



13. In the **SABIO Reaction Kinetics Database** dialog, click **Import KineticLaw**.
14. **Mapping SpeciesReferences ID** dialog will appear. Imported data from SABIO-RK is displayed on the right side of the dialog.



15. If necessary, click **Swap Reactants/Products** to exchange the imported Reactants and Products.



16. Confirm that the type of each Species on the left side (CellDesigner side) meets that of the right side (SABIO-RK side). If not, select another Species from the drop-down list.
17. Click **Apply**.
18. In the **Confirmation Dialog**, read the message and click **OK**.
19. In the **SABIO Reaction Kinetics Database** dialog, click **Close**.
20. On the Draw Area, right-click on the Reaction **r20**.
21. Select **Edit KineticLaw** from the list.
22. In the **KineticLaw** dialog, confirm that the Kinetic Law is successfully imported.

10. Simulation

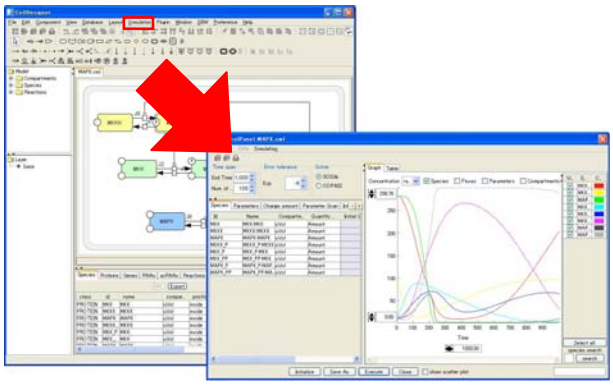
This section describes how to simulate a model.

CellDesigner can be used as an SBML file editor for simulators.

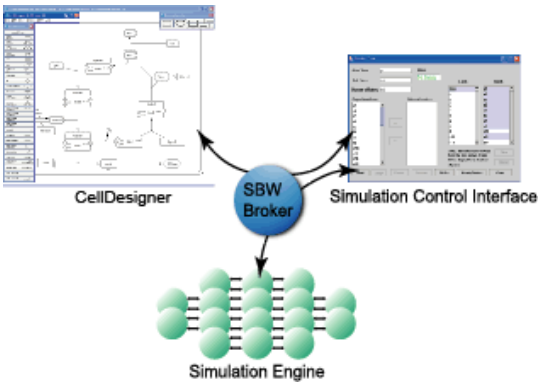
There are two ways to conduct the simulation by CellDesigner:

using Simulation menu to call SBML ODE Solver seamlessly. The conditions can be set using the Control Panel directly.

using SBW menu to call SBML compliant simulators.



Simulation menu
for direct control over SBML ODE solvers.



SBW menu
to call SBML compliant simulator.

If you select the **Simulation** menu, you can call SBML ODE solvers (SOSLib and Copasi) directly. The ControlPanel enables you to specify the details of parameters, changing amount, conducting parameter search, and interactive simulation with intuitive manner.

If you select **SBW** menu, you can pass the SBML data from CellDesigner to the SBML compliant simulators via SBW. You can conduct simulation seamlessly from CellDesigner via SBW to evoke such SBML compliant simulators.

→ Note: You need to set up SBW before you conduct simulation.

→ See also: [1.2 “Install SBW and SBW modules”]

To conduct time evolving simulation, you also need to know some basics of the SBML specification. This section describes the minimum requirements for simulation.

→ Note: There are various annotated sample models at BioModels.net for simulation.

→ See also: for more details on SBML specifications, http://sbml.org/Documents/Specifications

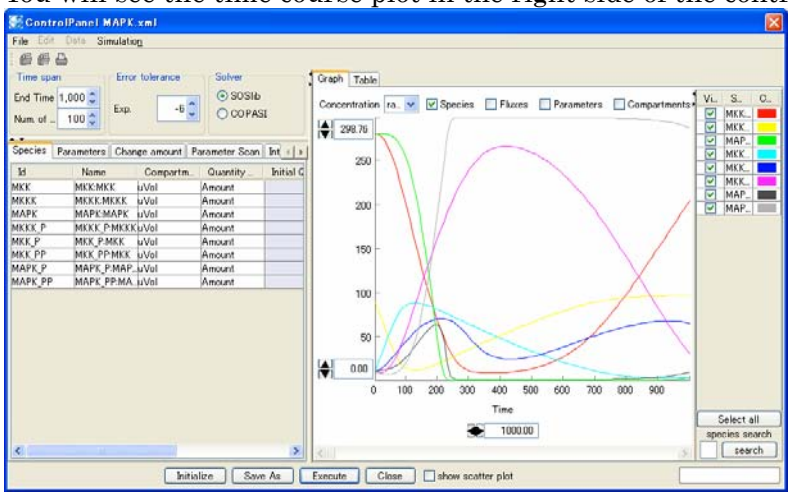
→ See also: [9 “Connect to External Databases”].

10.1 Simulation by ControlPanel

10.1.1 To simulate a model using the ControlPanel

1. Open the sample file “`MAPK.xml`” in the “`samples`” folder.
2. In the Menu, select **Simulation** - **ControlPanel**.
3. The **Control Panel** will open.
4. Change the **End Time** value to “1000”.

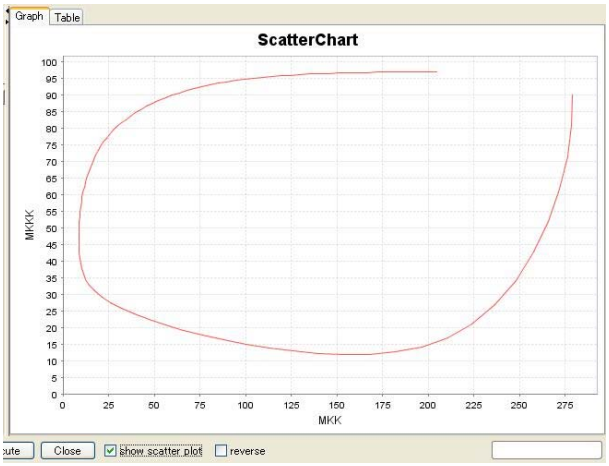
5. Click **Execute** button.
6. You will see the time course plot in the right side of the control panel.



→ See also: For more details on Control Panel, please refer to the document "*Running CellDesigner™ Simulation with ControlPanel*" found in the `/documents` folder.

10.1.2 To convert the graph to a scatter plot

1. In the **ControlPanel**, select any two Species by ticking the checkboxes in the **Visible** column.
2. Observe that the graph has been reduced to two curves.
3. Tick the **show scatter plot** checkbox.
4. Observe that in the new graph the x-axis does not indicate time series any more.
5. Select the **reverse** checkbox to change the x- and y- axes.



10.2 Simulation by COPASI

COPASI (http://www.copasi.org/) is a software application for simulation and analysis of biochemical networks. COPASI is free for non commercial use. You can use Copasi engine via CellDesigner's control panel, or Copasi's own GUI.

10.2.1 To setup COPASI to use with CellDesigner

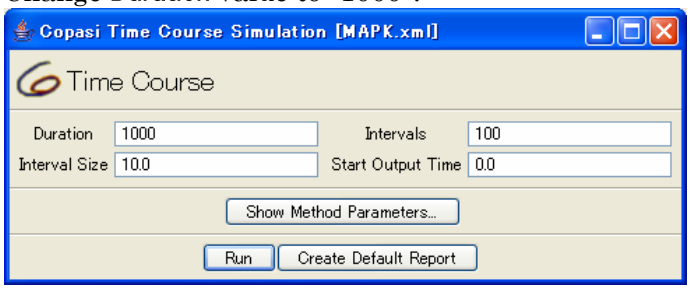
1. Visit the Copasi web site at `http://www.copasi.org/`.
2. Download the Language Binding for Java (e.g. `copasi_java_win32_buildxx.zip` for Windows 32bit).
3. Extract the downloaded file.
4. In the extracted folder, find
   `CopasiJava.dll` for Windows.
   `libCopasiJava.jnilib` for MacOS X.
   `libCopasiJava.so` for Linux.
5. Copy the file into the CellDesigner's root folder.

10.2.2 To simulate a model via CellDesigner's Control Panel, changing the solver to COPASI

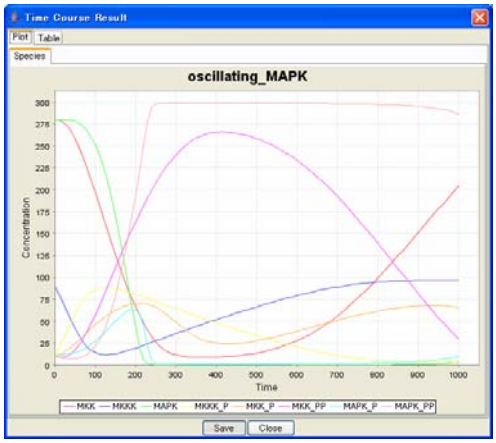
1. Click the **COPASI** radio button.
2. Click **Execute**

10.2.3 To simulate a model with COPASI

1. Open the sample file "MAPK.xml".
2. On the **Simulation** menu, select **COPASI GUI**.
3. The **Copasi Time Course Simulation** dialog will open.
4. Change **Duration** value to "1000".



5. Click **Run**.
6. In the **Time Course Result** window, compare the result with the section "9.1 Simulation by Control Panel".



10.3 Simulation by SBW modules

If you want to simulate the model with SBW modules you need to check if the SBW and SBW-powered simulator modules are installed in the path mentioned in the section "1.2 Install SBW and SBW Modules".

10.3.1 To confirm the installation of SBW

1. To check if the SBW is properly installed, start CellDesigner and open a model. The **SBW** menu in the main Menu should be activated if your setup has correctly been done.
2. Check if there are any simulators listed in the **SBW** menu.
3. If you have installed the simulators of your choice correctly, they are listed under **SBW** menu.

→ Note: "**Jarnac Simulation Service**" appears if Jarnac has been installed. The others are default-installed.

10.3.2 To simulate a model using SBW component

1. Open the sample file MAPK.xml in "samples" directory.
2. In the Menu, select **SBW** – **Jarnac Simulation Service** as an example.
   This wakes Jarnac up.
3. Check the help or manual of the simulator to learn how to start the simulation.

10.4 Data required for Simulation

For simulation, you should specify at least some Species, Reactions and their attributes. The minimum requirement of their attributes might be:

Species: -initialAmount (default=0.0),

Reaction:	-reactant:	-SpeciesReference:	-stoichiometry (default=1),
	-product:	-SpeciesReference:	-stoichiometry (default=1),
	-kineticLaw:	-math, -parameter,	

→ Note: the rightmost of each line is required to be input.

10.4.1 Species Attributes

The attribute "initialAmount" should usually be changed to a positive value.
According to SBML Level 2 specification, the attribute "math" should be a text string in which the id of Species and the parameters are written. These attributes can be set at the Species list shown in the List Area.

10.4.2 Reaction Attributes

The attributes and parameters of the Reaction can be specified in the Reaction dialog and their child dialogs.

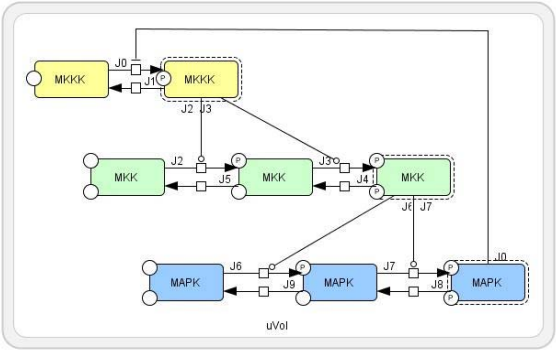
For the other parameters, the default values specified in SBML Level 2 are used.

10.5 Simulation Sample: MAPK.xml

Let us use the sample file "`MAPK.xml`" to see how the data required for simulation is specified in the model.

10.5.1 To check the data required for simulation

1. Open `MAPK.xml` in "`samples`" directory.



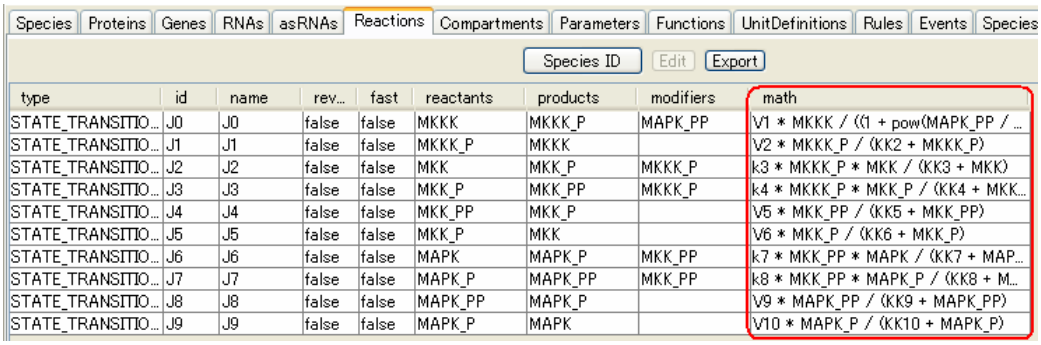
2. Select the **Species** tab in the List Area and observe the initial quantities.

Species | Proteins | Genes | RNAs | asRNAs | Reactions | Compartments | Parameters | Functions | UnitDefinitions | Rules | Events | SpeciesTypes | Compartm

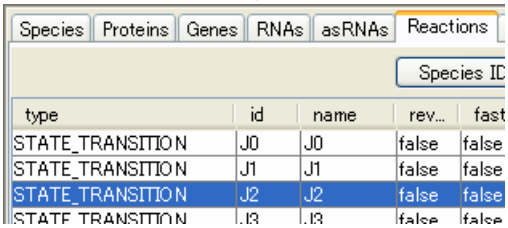
Edit | Export

class	id	name	speciesType	compart...	position...	included	quantity...	initialQuantity	sub...	hasO...	b.c.	c...
PROTEIN	MKK	MKK		uVol	inside		Amount	280.0		false	false	false
PROTEIN	MKKK	MKKK		uVol	inside		Amount	90.0		false	false	false
PROTEIN	MAPK	MAPK		uVol	inside		Amount	280.0		false	false	false
PROTEIN	MKKK...	MKKK		uVol	inside		Amount	10.0		false	false	false
PROTEIN	MKK_P	MKK		uVol	inside		Amount	10.0		false	false	false
PROTEIN	MKK_...	MKK		uVol	inside		Amount	10.0		false	false	false
PROTEIN	MAPK...	MAPK		uVol	inside		Amount	10.0		false	false	false
PROTEIN	MAPK...	MAPK		uVol	inside		Amount	10.0		false	false	false

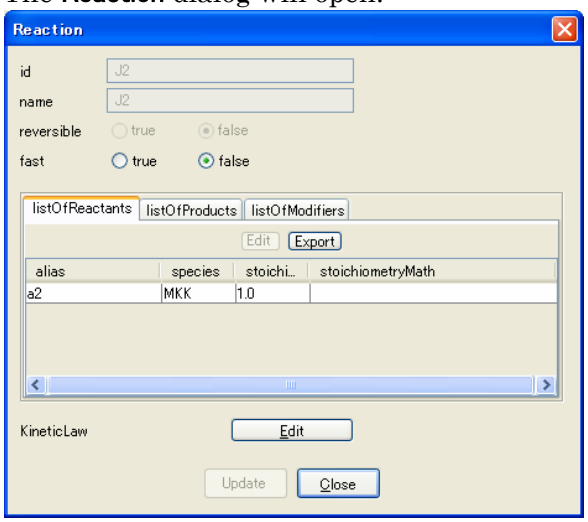
3. Select the **Reactions** tab in the List Area to see how the kinetic laws and parameters are specified.



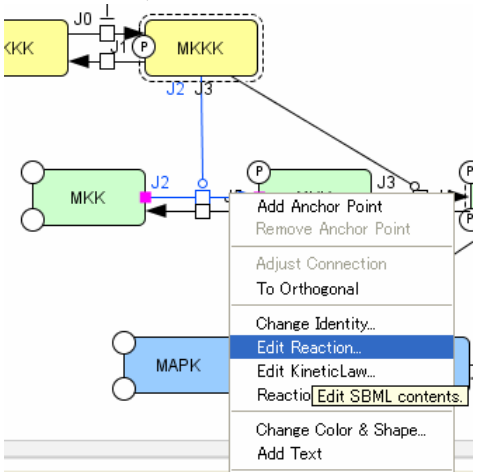
4. In the **Reactions** list, double-click on the third row whose id is "J2".



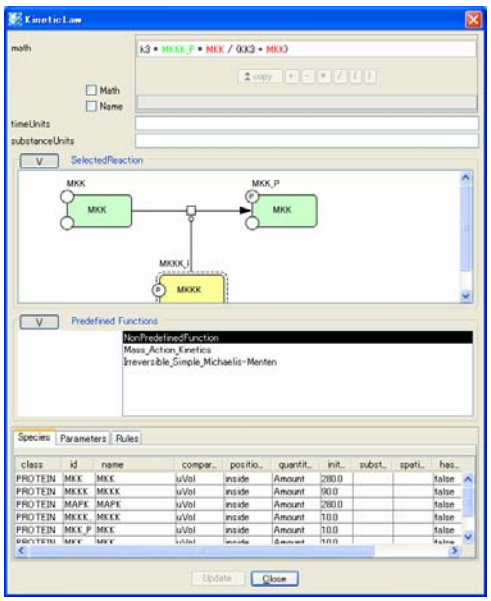
5. The **Reaction** dialog will open.



6. You can also open the **Reaction** dialog by clicking on the Reaction on Draw Area with the right-mouse button, then select **Edit Reaction...** menu. If the Reaction ID is not displayed on Draw Area, select **View** – **Show Reaction Id** in the Menu.



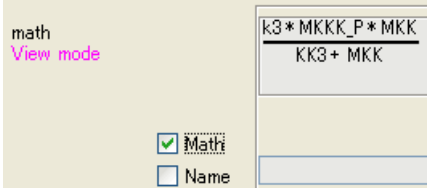
7. Click Edit to display KineticLaw dialog.



8. In the **math** text box, you can change the formula.
9. In the **Parameters** tab, you can change the parameter values.

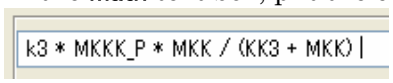
→ Note: Ticking **Name** checkbox will show the variables in the **math** text box in Species name rather than Species ID

→ Note: Ticking **Math** checkbox will show the variables in the **math** text box in fractional representation.



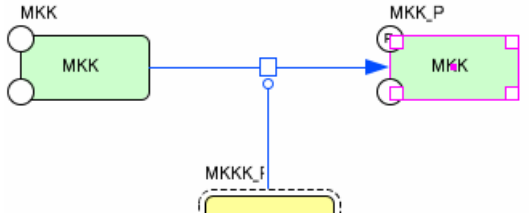
10.5.2 To add a Species ID in the math text box

1. In the **math** text box, put the cursor into the place where you want to add the Species ID.

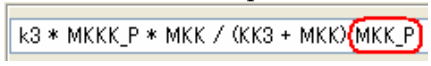


→ Note: Verify that the Math checkbox is NOT selected, otherwise you cannot edit the math expression.

2. In the KineticLaw dialog, in the **SelectedReaction** pane, select a Species (e.g. MKK_P).

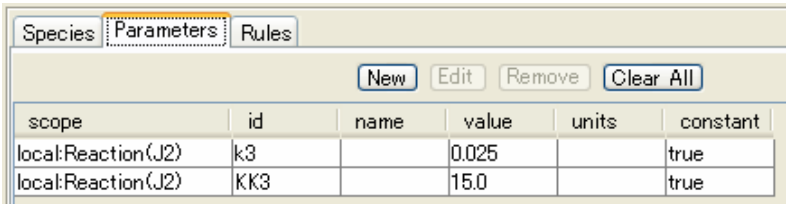


3. Observe that the Species ID has been added.



10.5.3 To edit parameters

1. Click on the **Parameters** tab at the bottom of the **KineticLaw** dialog.
2. All the parameters related to the selected Reaction are listed.



10.5.4 To use a Predefined Function

You can use some predefined functions such as Mass Action or irreversible simple Michaelis-Menten, by using Predefined Functions section on the dialog.

→ See also: [7 "Reaction and KineticLaw"]

10.5.5 To run the simulation

1. After checking all the reactions and KineticLaw formulas, close the **KineticLaw** dialog and the **Reaction** dialog.
2. You can double check all the specified **Reactions**, **Parameters**, etc in the List Area.
3. Select **Simulation** – **ControlPanel** from the Menu, and then conduct the simulation. You can view the graph as well as the simulated values in the Graph and Table tabs respectively.

→ See also: "Running CellDesigner Simulation with ControlPanel" found in the `documents` folder.

10.5.6 To save or print the simulated Graph

1. Select **File – Save Image / Print** menu.
2. **Image Config Dialog** will be displayed.
3. Click **Config**, and display **Chart Properties** dialog.
4. Specify **Title, Legend, Plot** and **Other**, then click **OK**.
5. Click either **Save Image** or **Print**.

10.5.7 To save the simulation results

1. Click **SaveAs** button or select **File – SaveAs** menu.
2. Specify where you save the results.
3. Modified model as well as the simulation results (with `.sim` extension) are stored in the specified folder.

10.6 Reference: MAPK.XML

Reactions

id	Math
J0	V1 * MKKK / ((1 + pow(MAPK_PP / Ki, n)) * (K1 + MKKK))
J1	V2 * MKKK_P / (KK2 + MKKK_P)
J2	k3 * MKKK_P * MKK / (KK3 + MKK)
J3	k4 * MKKK_P * MKK_P / (KK4 + MKK_P)
J4	V5 * MKK_PP / (KK5 + MKK_PP)
J5	V6 * MKK_P / (KK6 + MKK_P)
J6	k7 * MKK_PP * MAPK / (KK7 + MAPK)
J7	k8 * MKK_PP * MAPK_P / (KK8 + MAPK_P)
J8	V9 * MAPK_PP / (KK9 + MAPK_PP)
J9	V10 * MAPK_P / (KK10 + MAPK_P)

Species

id	initialQuantity
MKK	280

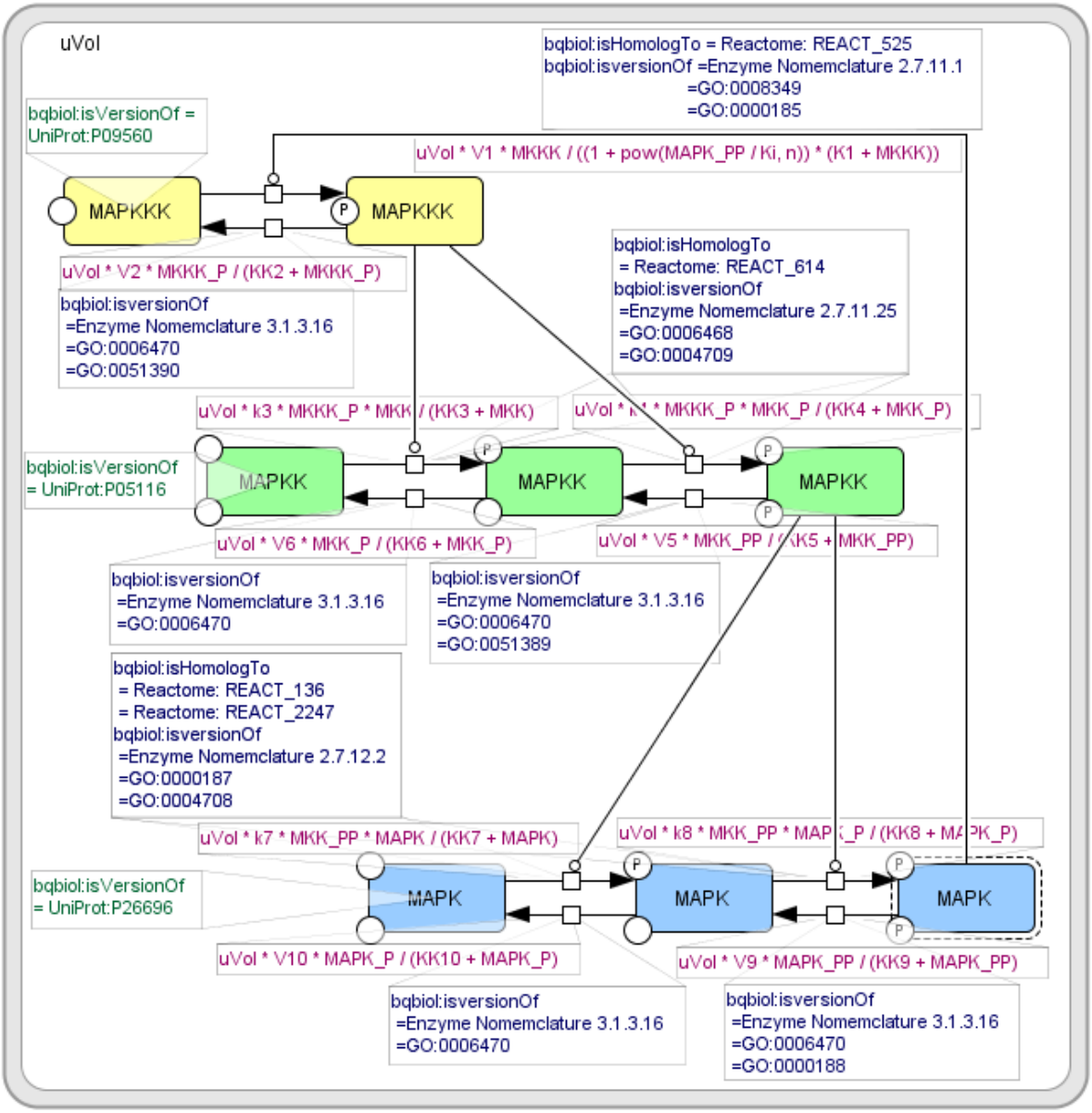
MKKK	90
MAPK	280
MKKK_P	10
MKK_P	10
MKK_PP	10
MAPK_P	10
MAPK_PP	10

Parameters

id	name	value
V1		2.5
Ki		9
n		1
K1		10
V2		0.25
KK2		8
k3		0.025
KK3		15
V0	V0	111
K0	K0	1
k4		0.025
KK4		15
V5		0.75
KK5		15
V6		0.75
KK6		15
k7		0.025
KK7		15
k8		0.025
KK8		15
V9		0.5
KK9		15
V10		0.5
KK10		15

10.7 MAPK41.xml

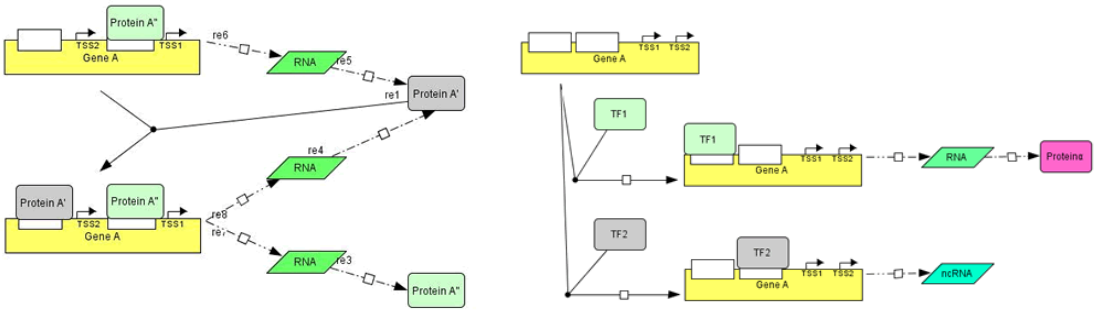
MAPK41.xml is identical to MAPK.xml except that it contains KineticLaw and MIRIAM information displayed as layered text.



→ See also: [12. Layer]

11. Gene / RNA / AntiSenseRNA Structure Expressions

In CellDesigner 4.x, graphical notation is extended and redefined to enhance representation capability for transcription and translation processes. The most salient feature is the capability to describe promoter structure, and other detailed structure for genes and RNA's.

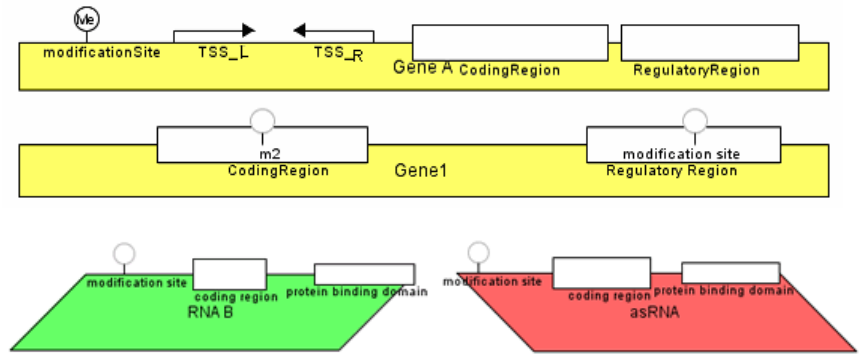


→ See also: [Appendix 2: Sample Files for Graphical Notation].

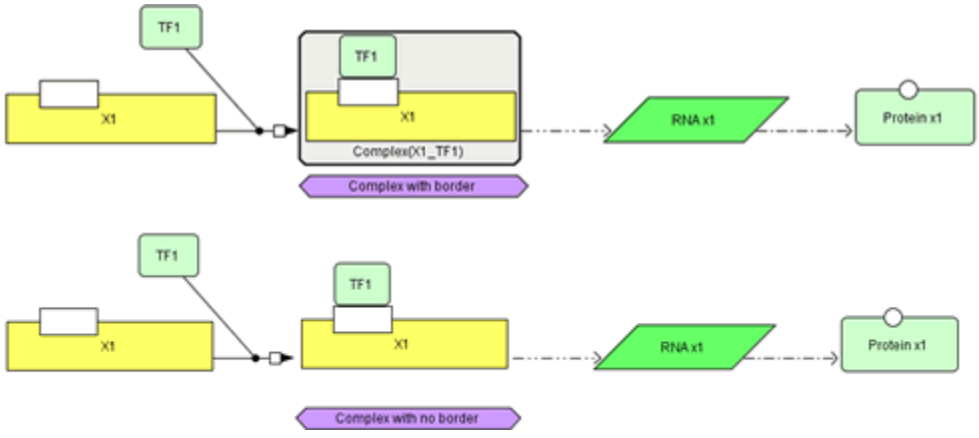
11.1 Promoter Structure Representation

CellDesigner allows users to define the structure of promoter regions. Specific promoter regions are represented on upper part of the box. When such structure information is defined, lines for both sides and lower part of the box are either not shown or dimmed to highlight structures represented on the upper line.

11.1.1 Symbols related to transcription and translation

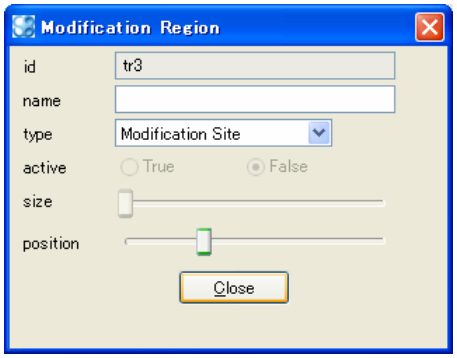


11.1.2 An example of transcription related symbols



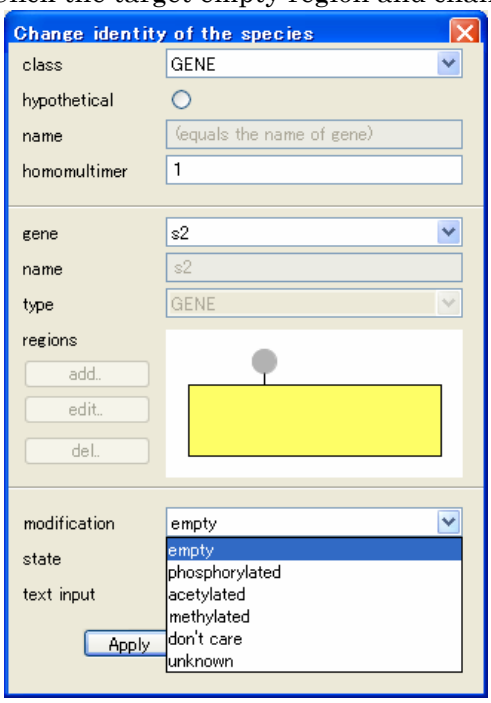
11.1.3 To specify region symbols

1. Right-click on a Species.
2. Select **Edit <*Gene or RNA or asRNA*>…** from the menu.
   Alternatively, select the Species from the List Area and click the **add** button.
3. In the **Modification Region** dialog, select a **type** from the drop-down menu and change the **size** and **position**.
   Click **Close**.
4. Click **Update**.



11.1.4 To change the modification of the modification site of a Gene

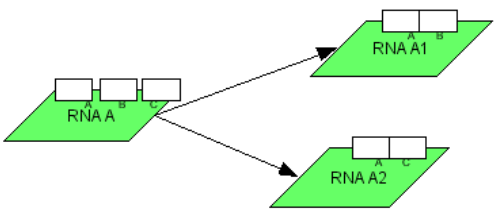
1. Right-click on a Gene.
2. Select **Change Identity…** from the menu.
3. Click the target empty region and change the **modification** status from the drop-down menu.



4. Click **Apply**.

11.2 Alternative Splicing

Alternative splicing can be represented as transition of an RNA in the original state to multiple RNAs with different splicing patterns.



11.3 Identification of Gene, RNA, and AntiSenseRNA.

In the model, Genes, RNAs and AntiSenseRNAs are identified by their name. If the name of the newly created component is already used in the model, the representation will become the same as the existing one.

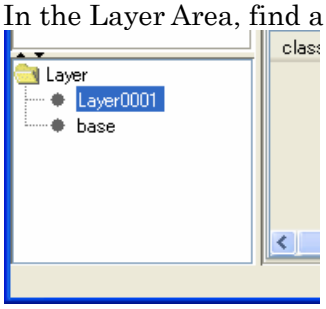
12. Layer – displaying comments over the model

You can add a layer to give comments to the components and over the model. The “base” layer is the layer where the components are displayed. Additional layers can hold free text to those components, or draw the circle or square. You can choose to display or to hide the layers.

12.1 Add a Layer

12.1.1 To add a layer

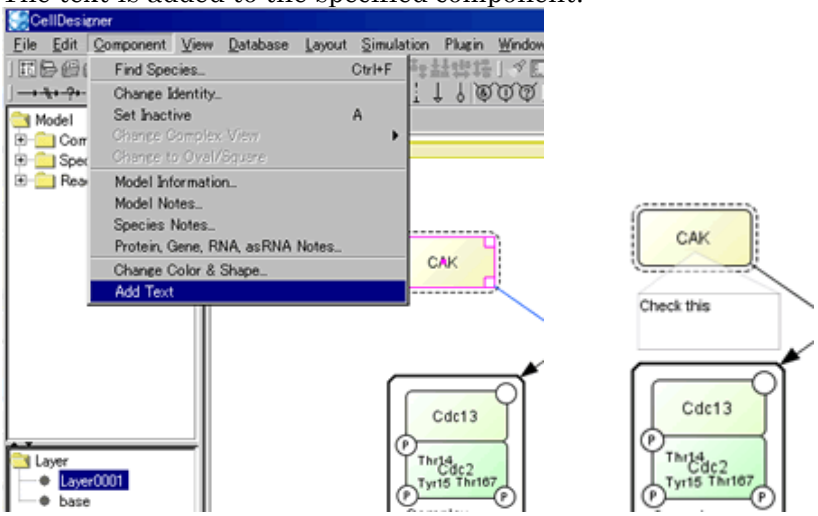
1. Select **Edit** → **Add Layer** in the Menu.
2. **LayerNameInputDialog** is displayed.
3. Specify the **Layer Name**, then click **Add Layer** button.
4. In the Layer Area, find a new layer has been added to the list.



12.2 Add Text and Shapes on a Layer

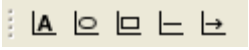
12.2.1 To add a textbox to a component

1. Select a component (Species, Reaction, or Compartment).
2. In the Layer Area, select the target layer.
3. In the Menu, select **Component**→ **Add Text**.
   Or, right-click on the component and select **Add Text.**
4. In the **Input text** dialog, type in any text, then press **OK**.
5. The text is added to the specified component.



12.2.2 To add a Layer Object onto a layer

1. In the Layer Toolbar, select an icon from the different Layer Objects.



2. Place your cursor on Draw Area, click-hold the mouse button, and drag the cursor to the size and shape you like.

12.2.3 To change the color and shape of a Layer Object

1. Right-click on a Layer Object to open the **Change Color & Shape...** dialog.
2. Change the parameters and click **OK**

12.3 Edit a Layer

12.3.1 To lock the Layer Objects on a layer

1. In the Layer Area, select a layer.

   → Note: The base layer cannot be locked, deleted nor set invisible. For it contains all the components (Species, Reactions and Compartments) and holds no Layer Objects in it.

2. In the right-click menu, select **Lock**.

3. Verify that all the Layer Objects on the layer cannot be selected.

12.3.2 To set the Layer Objects invisible

1. In the Layer Area, select a layer.
2. In the right-click menu, select **Invisible**.
3. See that the Layer Objects belonging to the layer are invisible.

12.3.3 To delete a layer

1. In the Layer Area, select a layer.
2. In the right-click menu, select **Delete Layer**.
3. See that the Layer Objects belonging to the layer have been deleted.

13. SBGN Viewer

With the SBGN Viewer, you can readily obtain an SBGN graphical representation for the model created with the CellDesigner.

→ Note: CellDesigner's SBGN Viewer adopts the SBGN Process Description Diagram Level 1.1.

13.1 Use the SBGN Viewer

13.1.1 To view a model with the SBGN Viewer

1. Open a model.
2. On the **View** menu, select **Convert to SBGN Viewer**.

13.2 Difference In Graphical Notations---CellDesigner and SBGN Viewer

There are some differences in graphical representation between the two.

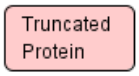
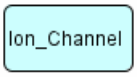
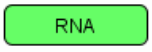
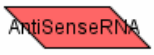
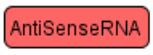
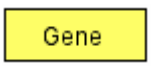
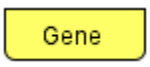
Difference in Activated State

In CellDesigner's notation, activated proteins are surrounded by dotted line. (or open state for Ion_channel.
In SBGN notation, activated proteins will have an oval at the bottom (States).

Protein–Generic (activated)		
Protein–Ion Channel (activated)		

Difference in Various Species Shapes

In SBML viewer, various Species shapes are represented by rounded square.

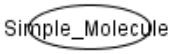
Protein –Receptor type		
Protein –Truncated type		
Protein –Ion_Channel type		
RNA		
Antisense RNA		
Gene		

Difference in Notation of Clone Marker

If a Species is duplicated, both the original and the duplicates will be marked by the clone marker (bottom part shaded).

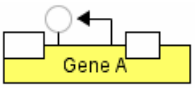
Ion

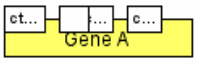
Simple molecule



Resides/Domains etc -> Information box

Gene / RNA / asRNA with
Coding Region, Modification Site,
Transcription Starting Site,
and Regulatory Region

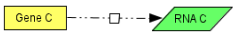


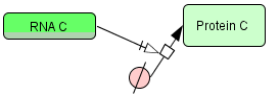


Difference in Notation of Transcription/Translation

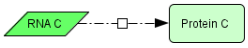
Reactions of Transcription and translation are converted into the reactions with triggers.

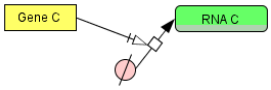
Transcription





Translation

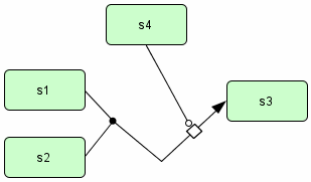


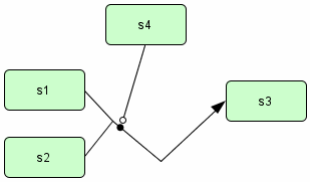


Difference in Association/Dissociation

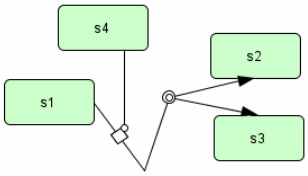
In the SBGN Viewer, a process node is positioned near the fork.

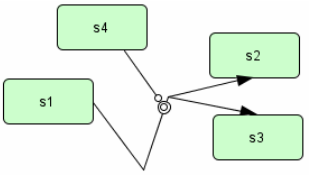
Association





Dissociation





14. Limitations and Known Issues

14.1 Limitations

Available actions of UNDO and REDO are limited to actions making change on the Draw Area.

14.2 Known Issues

- The problems are reported in printing / exporting images of the huge model due to the lack of the memory.
- When using CellDesigner in non-English environment on Mac OS X and Linux, letters on dialog boxes from File menu are not correctly displayed.
- **For Mac OS X**, open “System Preferences” and click “International” icon from “Personal” row, and then click “Language” tab. In the window for choosing language, place “English” at the top. (Note: The terms quoted by “_“ depend on your environment.) Then start CellDesigner.
- **For Linux**, unset LANG in the shell, then starts CellDesigner.

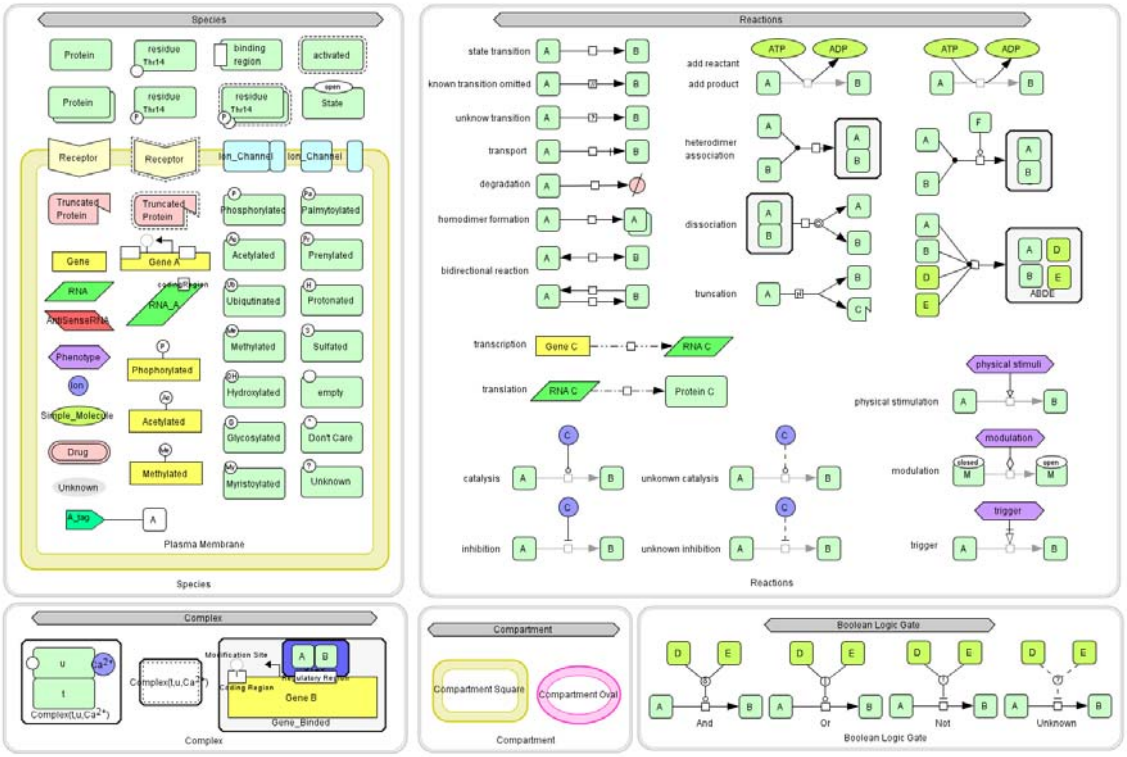
Appendix 1: Symbols and Expressions

This section lists up all the symbols for building models with CellDesigner. Graphical notation and the list of the symbols are based on the proposals by Kitano:

"Using process diagram for the graphical representation of biological networks", Nature Biotechnology 23(8), 961-966 (2005).

The symbol system for state-transition diagram and the residue state representation in these proposals are mostly realized with CellDesigner.

→ See Also: http://sbgn.org for SBGN (Systems Biology Graphical Notation scheme.)



A sample file: Components41.xml

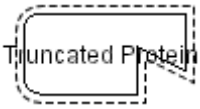
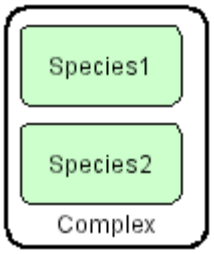
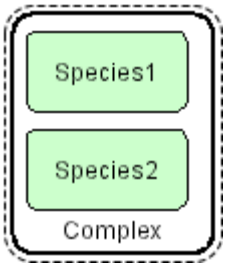
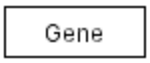
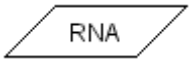
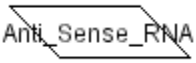
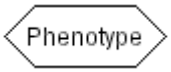
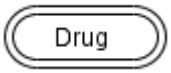
→ Note: All the graphical symbols used in CellDesingner will be found in the file "<your CellDesigner folder>/samples/components41.xml".

Appendix 1.1 Basic Symbols

Appendix 1.1.1 Species

There are 14 types of **Species** symbols.

Species	not activated	activated
Protein -Generic	Protein	Protein

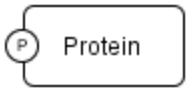
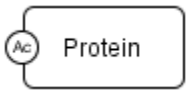
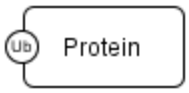
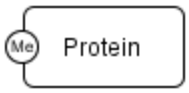
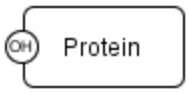
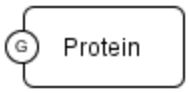
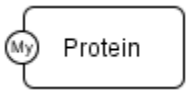
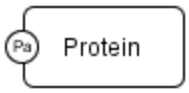
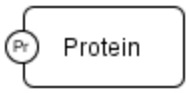
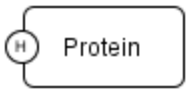
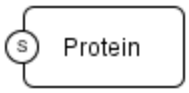
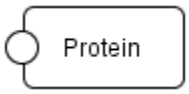
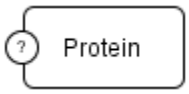
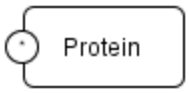
Species	not activated	activated
Protein -Receptor		
Protein -Ion channel		
Protein -Truncated		
Complex		
Gene		n/a
RNA		n/a
Anti-sense RNA		n/a
Phenotype		n/a
Ion		n/a
Simple Molecule		n/a
Drug		n/a
Unknown		n/a

Tag	

Appendix 1.1.2 Modifications of Protein Residues

There are 14 types of symbols for residue modification states. The residue symbols accompanied with their label (used for residue name and position in amino acid sequence) can be attached to all protein-type Species.

Modification	Symbol

Modification	Symbol
Phosphorylated	
Acetylated	
Ubiquitinated	
Methylated	
Hydroxylated	
Glycosylated	
Myristoylated	
Palmytoylated	
Prenylated	
Protonated	
Sulfated	
Empty	
Unknown	
Don't Care	

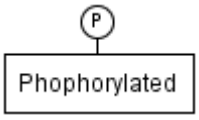
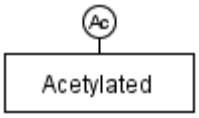
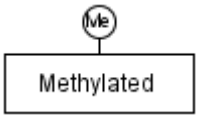
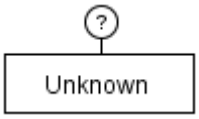
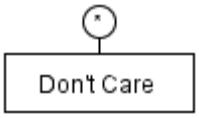
Appendix 1.1.3 State of Proteins

State	Symbol
Open	

State	Symbol
Closed	
User defined	

Appendix 1.1.4 Modifications of Gene / RNA / AntiSenseRNA Residues

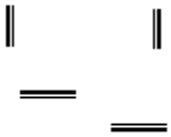
There are 5 types of symbols for residue modification states. The residue symbols accompanied with their label (used for residue name and position in amino acid sequence) can be attached to Gene / RNA / AntiSenseRNA.

Modification Region	Symbol
phosphorylated	
acetylated	
methylated	
Unknown	
Don't care	

Appendix 1.1.5 Compartment

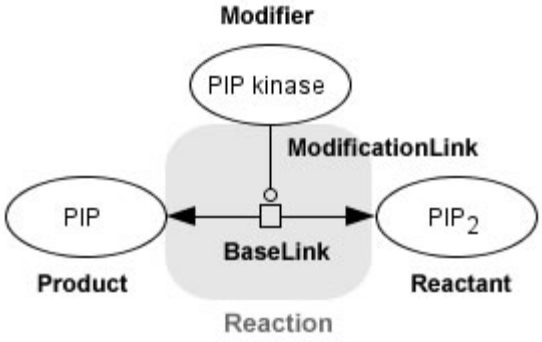
There are 4 types of Compartment symbols. For each type, the thick line indicates outside of its boundary.

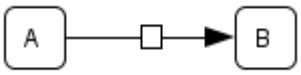
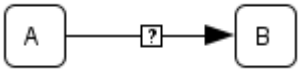
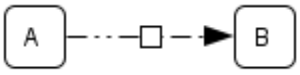
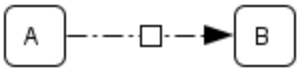
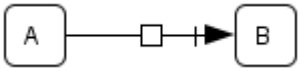
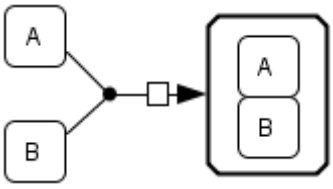
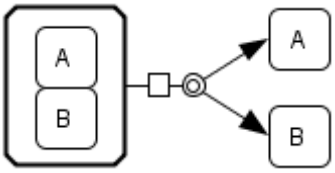
Type	Symbol	Note
Square		
Oval		
Close-up type		Northwest, Northeast Southwest, Southeast

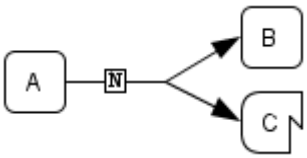
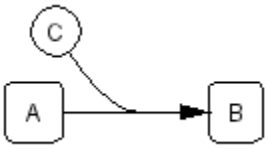
Type	Symbol	Note
Close-up type		West, East North, South

Appendix 1.1.6 Reaction (State Transitions and others)

There are 11 symbols representing State Transitions and other types of Reactions.

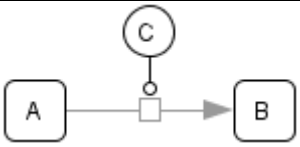
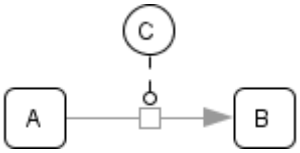
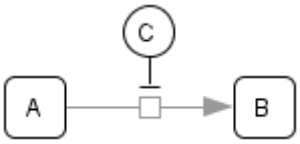
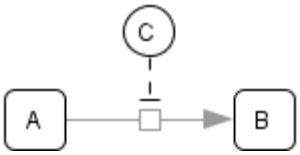
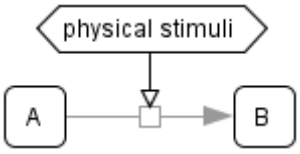
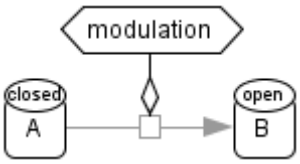
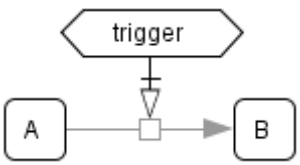


Reaction (State Transitions and others)	Symbols	Note
State Transition		
Known Transition Omitted		Abbreviated symbol of several Reactions
Unknown Transition		
Transcription		
Translation		
Transport		
Heterodimer Association		
Dissociation		

Reaction (State Transitions and others)	Symbols	Note
Truncation		Dissociation of Proteins by truncation.
Add Reactant		

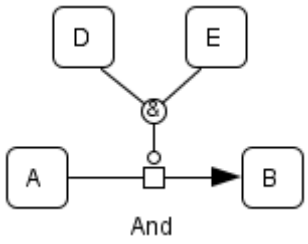
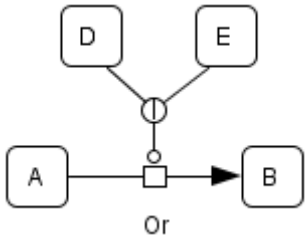
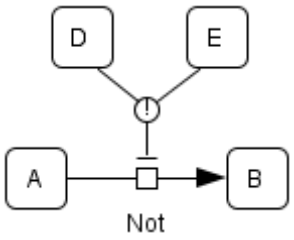
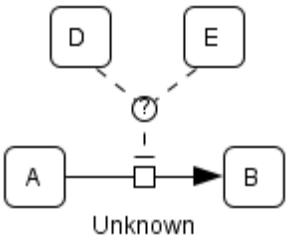
Appendix 1.1.7 Reaction (Modifications)

There are 7 symbols representing Modifications.

Reaction (Modifications)	Symbols	Note
Catalysis		
Unknown Catalysis		
Inhibition		
Unknown Inhibition		
Physical Stimulation		
Modulation		
Trigger		

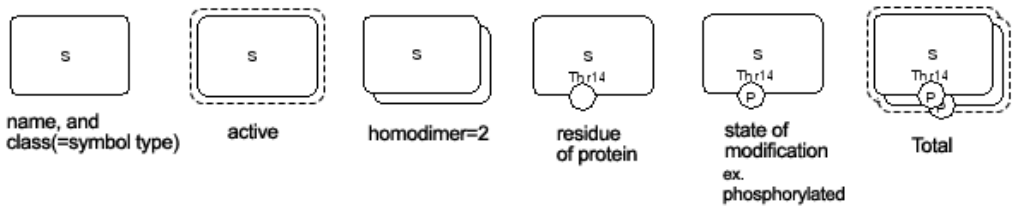
Appendix 1.1.8 Reaction (Logical Operations)

There are 4 symbols representing **Logical Operations**.

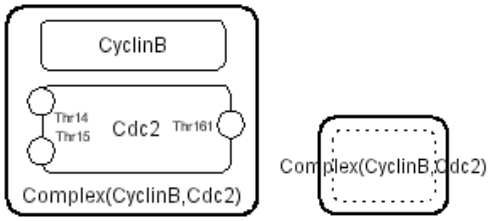
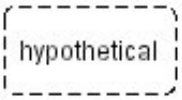
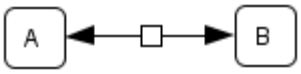
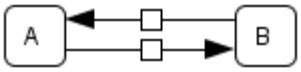
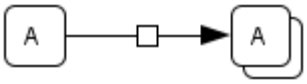
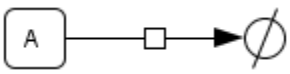
Reactions (Logical Operations)	Symbols	Note
And		
Or		
Not		
Unknown		

Appendix 1.2 Expressions

Here are symbols acquiring additional semantics by shape, combination of symbols, or change in drawings.



Expression	Symbol	Note
Active		Select a Protein and, in the **Component** menu, select **Set Active**.

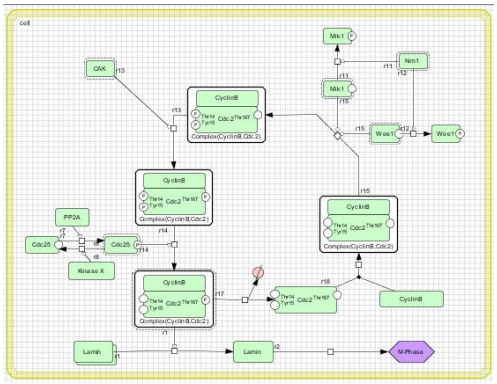
Expression	Symbol	Note
		
Channel Open		Select an Ion Channel and, in the **Component** menu, select **Set Active**.
Species State Open / Closed		
Homodimer formed		Double-click the Species to open the identity dialog, then set the Homodimer number.
Complex		Set **Change Complex View** to **normal** / **compact** / **no border**. **compact** is used to hide the contents of the Complex. **no border** is mainly used for a Complex with Genes etc.
Complex in a Complex		
Hypothetical Species		Double-click the Species to open the **Change identity of the species** dialog, then select **hypothetical**.
Reversible Reactions		Double-click the Reaction, then set **Reversible** to **True**.
Bidirectional Reactions		Simply draw two state transitions and reposition them.
Homodimer Formation		Click the icon of **Homodimer Formation**.
Degradation of Species		Click the icon of **Degradation**.

Appendix 2: Sample Files for Graphical Notation

To explore new graphical notation scheme, there are sample files available in this version. Please open the files in the `/samples` directory and try editing the model.

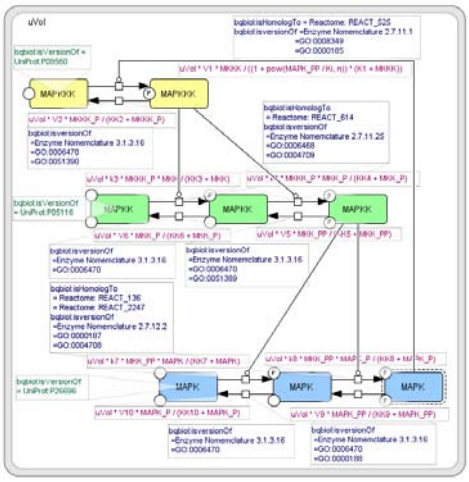
Appendix 2.1 Examples of the sample files contained in the CellDesigner

`/samples/M-Phase.xml`

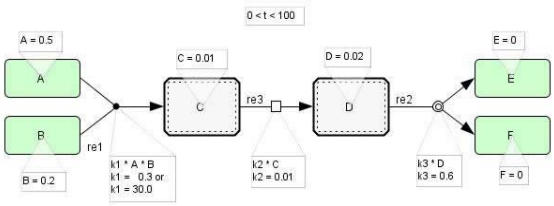


`/samples/M-Phase2.xml`

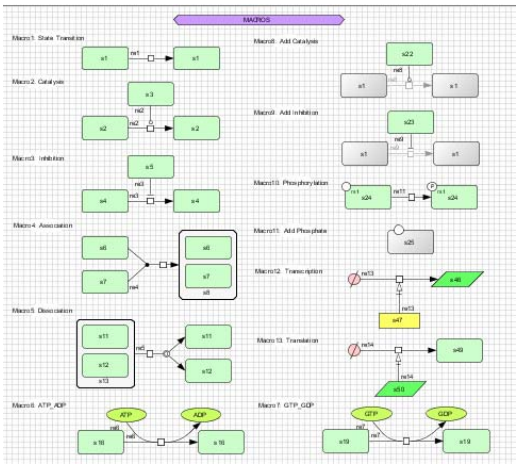
`/samples/MAPK41.xml`



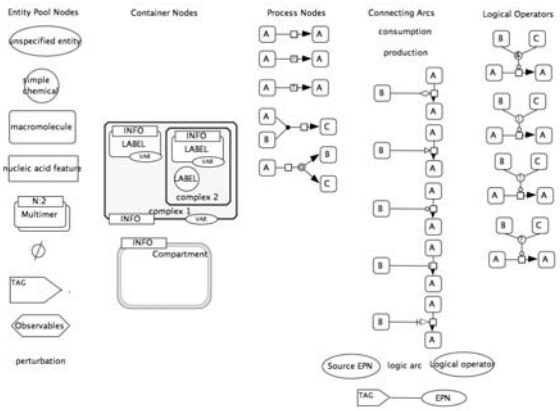
`/samples/sim2.xml`



`/samples/Macros.xml`

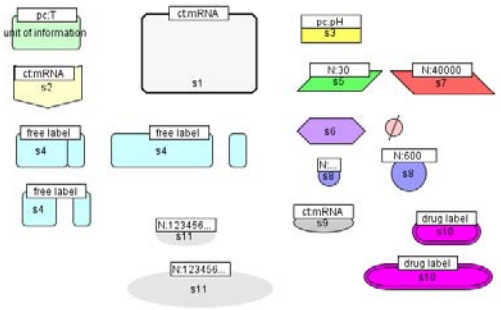


`/samples/SBGNRefCard.xml`

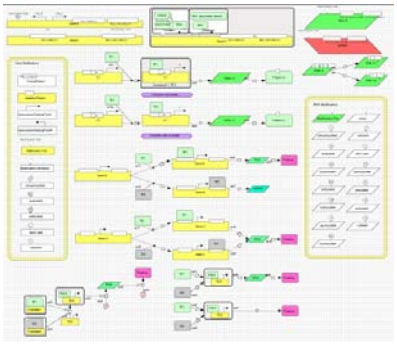


`/samples/UnitOfInformation.xml`

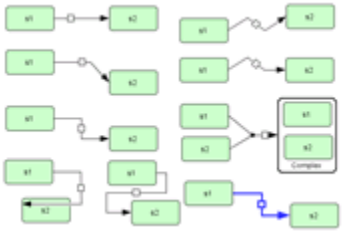
`/samples/notation/geneRNA41.xml`

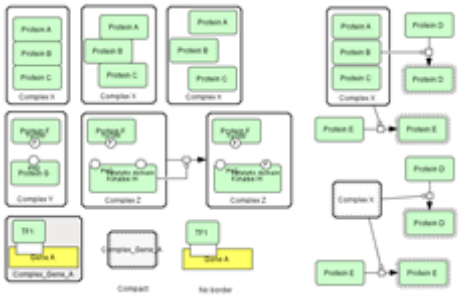


/samples/notation/ReactionShape.xml



/samples/notation/Complex41.xml





Appendix 2.2 Examples for Graphical Notation

These are the examples used in the paper
"The Process Diagram for Graphical Representation of Biological Networks," Kitano, H. et al. Nature Biotechnology, August 2005.

Fig1b_ProcessDiagram_4

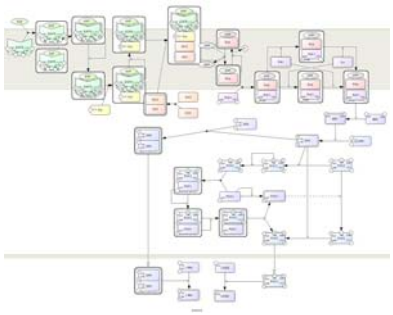


Fig3abcd_AndOr_4

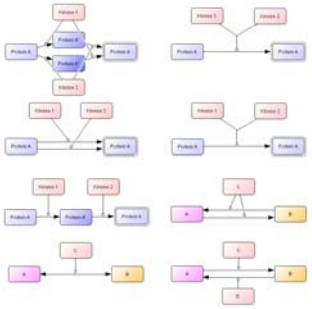
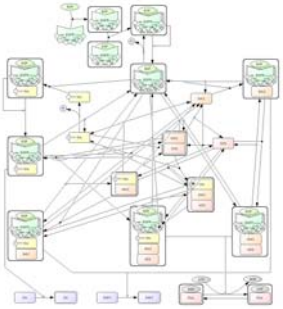
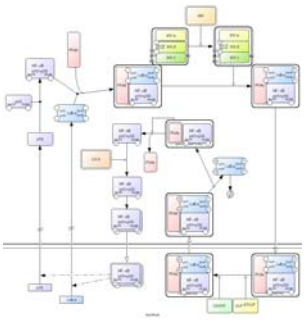


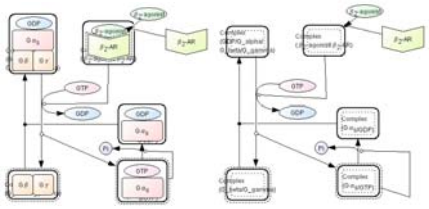
Fig3e_EGFR_league_4



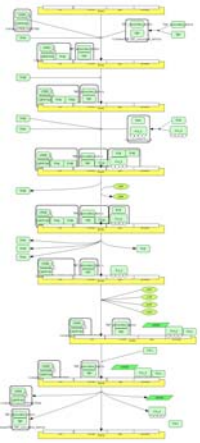
SuplFig3_NF-kappaB(p65+p50)_4



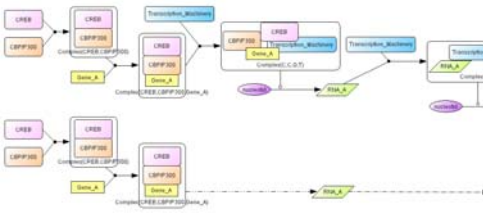
SuplFig2_GPCR beta2-AR_4



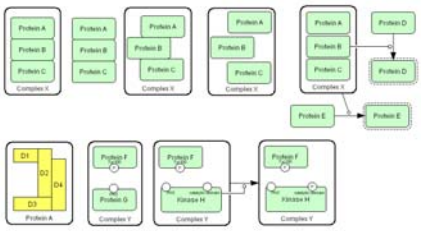
SuplFig4b_transcription_4



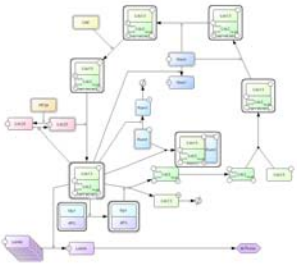
SuplFig4a_TranscriptionTranslation_4



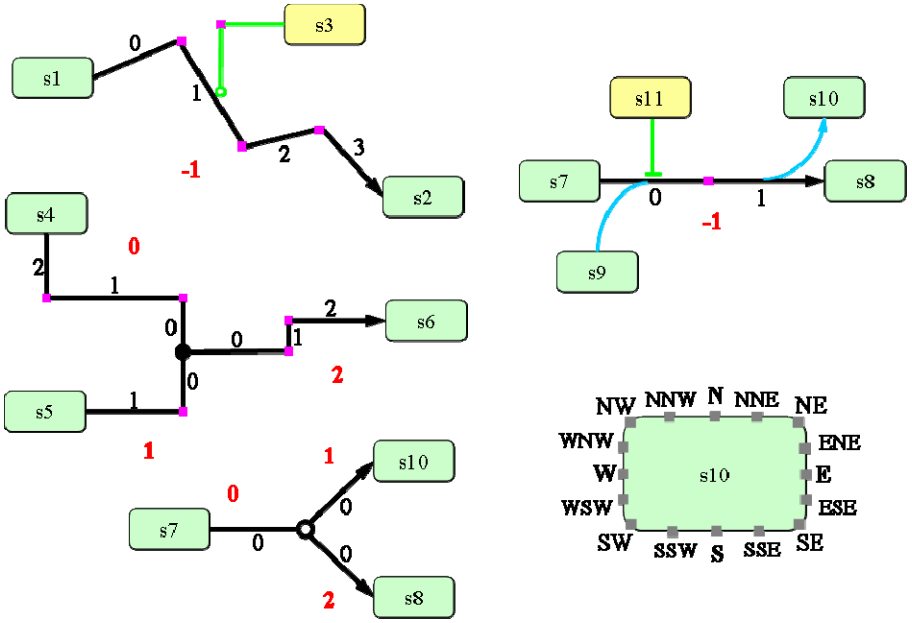
SuplFig5_StructureofComplex_4

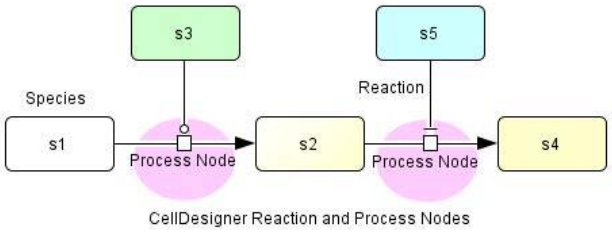


SuplFig7_M-Phase_4



Appendix 2.3 CellDesigner Species / Reactions Conventions





CellDesigner Reaction and Process Nodes