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CellDesigner™ is being developed by

The Systems Biology Institute
<http://www.systems-biology.org/>

Keio University, Dept. of Biosciences and Informatics,
<http://www.bio.keio.ac.jp/>

Mitsui Knowledge Industry Co., Ltd.
<http://www.mki.co.jp/eng/>

Mizuho Information & Research Institute, Inc.
<http://www.mizuho-ir.co.jp/>

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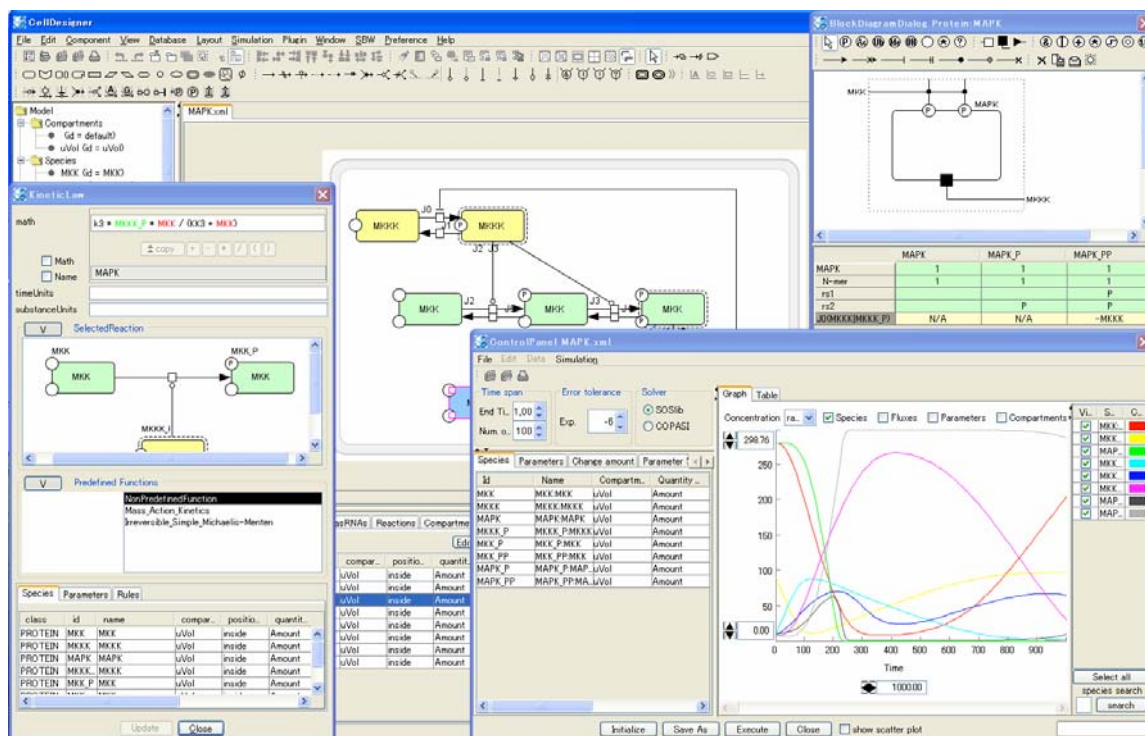
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A. What is CellDesigner™

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 \(SBW\)](#).

SBML + SBGN + Simulation + Databases Connections = CellDesigner

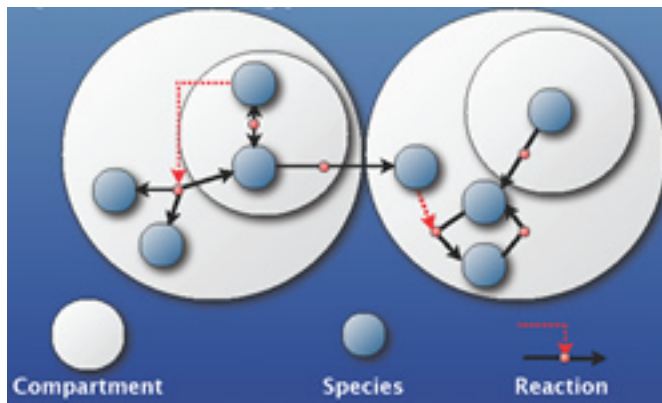


1. CellDesigner Major Features

- Easy-to-understand graphical notation (SBGN)
- SBML-compliant (Level 2 Version 1)
- Built-in simulator (SBML ODE Solver, Copasi)
 - See also: “*Running CellDesigner Simulation with Control Panel – Quick Tutorial*”, or ControlPanel40.pdf under the documents folder.
- 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)
 - Extract the control relationship between Proteins from the pathway diagram.
 - Describe and Verify the Modifications/Activations Logic.
- Plug-in development framework

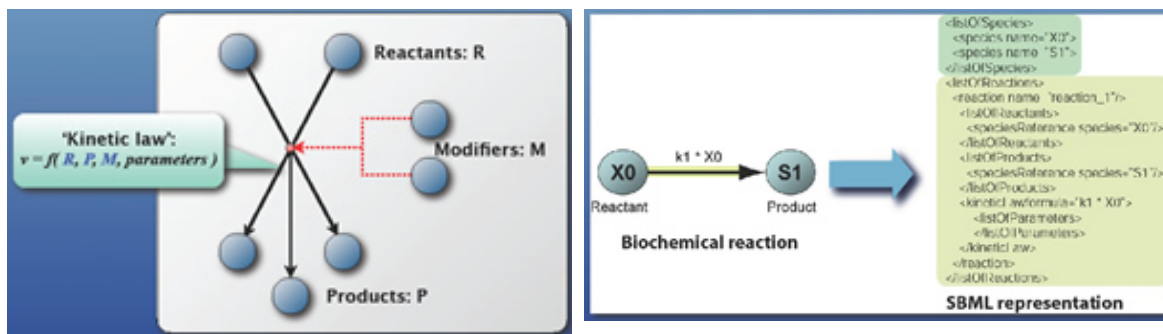
2. CellDesigner and SBML

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

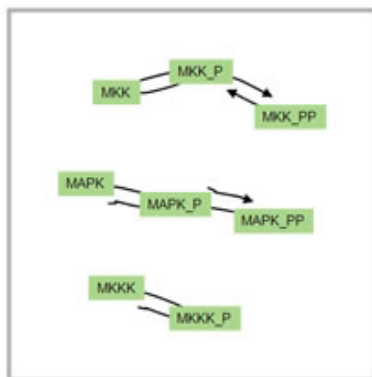
```

<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level1" level="2" version="1">
  <model name="ATitle">
    <listOfCompartments>
      <listOfSpecies>
      </listOfSpecies>
    </listOfCompartments>
  </model>
</sbml>
  
```

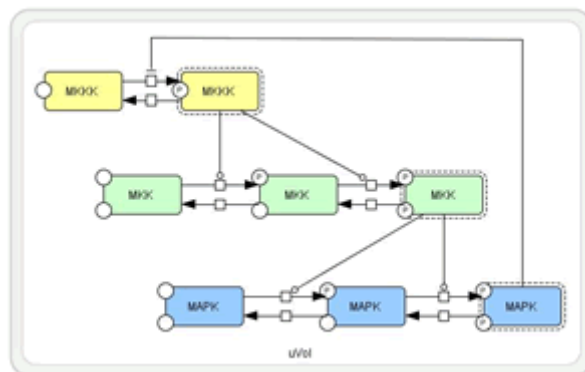

3. CellDesigner and Graphical Notation

SBGN (Systems Biology Graphical Notation) is a graphical notation for representing biological interactions, such as protein-protein interactions and gene regulatory networks.

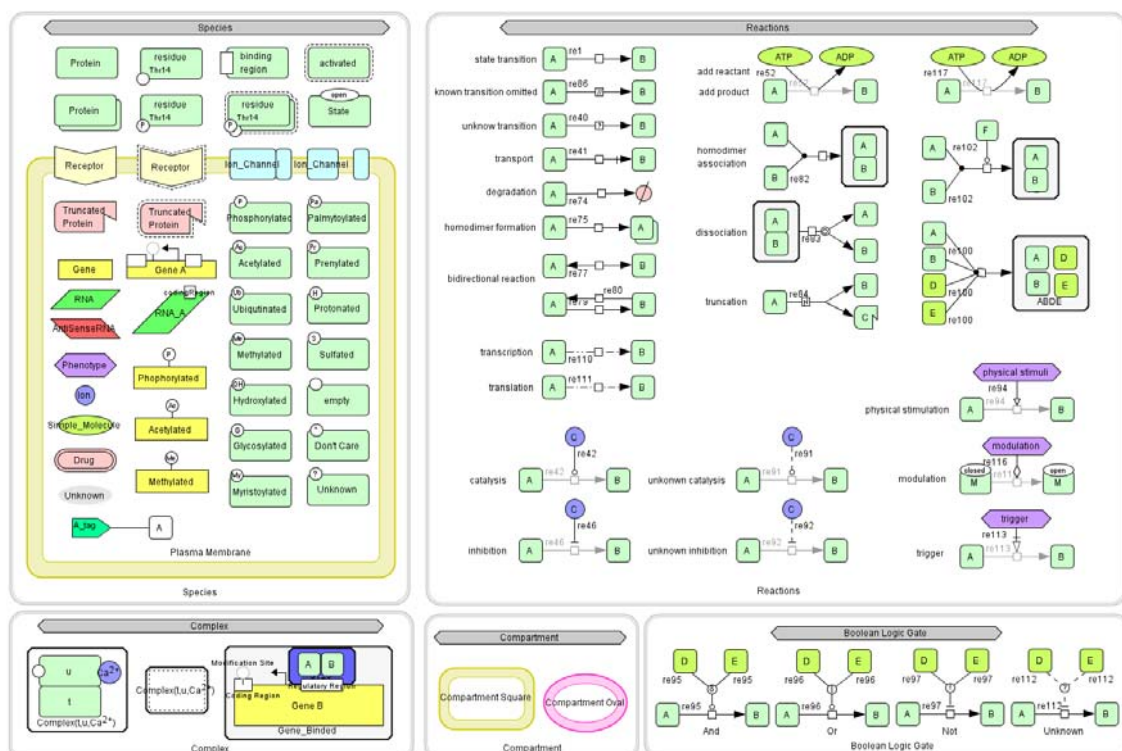
Current discussions on SBGN focus on three graphical notations: process diagram, entity relationship diagram and activity flow. CellDesigner adopts the process diagram as its graphical notation.



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

For details of SBGN, please refer to <http://sbgn.org> website.

4. CellDesigner 4.0 Major Features

CellDesigner 4.0 now supports an updated graphical notation which conforms to SBGN-1 proposal, plug-in development framework, and overall GUI improvement.

* Check <http://celldesigner.org> for details.

Major new features and changes in CellDesigner 4.0 are as follows:

- **Enhanced Graphical Notation**
CellDesigner adopts and supports SBGN (Systems Biology Graphical Notation) Process Diagram Level 1 proposal (April 2008 draft).
 - Protein Residues enhancement
 - Protein / Complex Status, nested Complexes
 - Genes states enhancement
 - Reactions (Modifications, Boolean Logic Gate)
 - New symbols: Drug, Tag
- **Enhanced KineticLaw editing**
 - MathML rendering
- **Simulation – Control Panel enhancement**
 - Copasi integration
 - Solver selection in the ControlPanel : SOSlib and Copasi
 - Simulation results displayed in Table format
 - Show Scatter Plot
- **Export Species/Reactions information including Notes into CSV file**
- **Validation of files when opening (libSBML3)**
- **Native file chooser support for Mac OS X**
- **Layout menu: automatic layout functionality (using yFiles layout library)**
layout automatically when retrieving a SBML file.
- **Enhanced Edit Functions**
 - Macro Functions
 - Change colors of multiple Species/Reactions
 - **Find All** search menu added
 - Components on the list highlighted
 - List sorting function
 - Edit the position of the name of the Compartment display
 - Reaction ID displayed on screen
- **Plug-in Development**
 - ➔ See also “[Plugin Development Tutorial](#)”
- **Layer Function to add text/mark over the model**
 - ➔ **Note:**
 - [Export of Pure Level 1 Version 1 is no more supported.](#)
 - [Windows 2000 is no more supported.](#)

B. Startup Guide

1. Installation and Startup

1.1 Operating Environment

The current version of CellDesigner requires Java5 Runtime Environment (J2SE Runtime Environment 5.0 or later) on Windows (XP or later) or Linux with X Window System (Fedora Core 4 or later).

On Mac OS X 10.4 or later, Java 1.5.0_03 or later is required. On Mac OS X 10.3, Java 1.4.2_05 or later is required. 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.

The installer includes JRE (Java Runtime Environment 1.5.0_07-b03), so you do not have to install Java before your installation.

If SBW and its modules have already been installed, these modules are available. Especially time evolving simulation of the model being edited can be performed.

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-40-windows-installer.exe
Mac OS X:	CellDesigner-4.0-osx-installer.zip
Linux:	CellDesigner-4.0-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-40-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-4.0-osx-installer.zip`.
The compressed installer should be recognized by Stuffit Expander and should automatically be expanded to `CellDesigner-4.0-osx-installer`.
2. Then double click it.
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-4.0-linux-installer.bin`
% `./CellDesigner-4.0-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 (`/CellDesigner4.0` by default).

```
+00README.txt
|
+CellDesigner4.0.exe      executable application module (* Windows only)
+CellDesigner4.0.sh      executable application module (* Linux only)
+CellDesigner4.0         executable application module (* Mac OS X only)
|
+documents
| +ControlPanel40.pdf    quick tutorial for control panel
| +PluginTutorial40.pdf  quick tutorial for plug in
| +StartupGuide40.pdf   this document
| +/plugin
|   +index.html          Plug-in document
|
+exec
| +autolayout_yobf.jar
| +celldesigner.jar       library for CellDesigner application
| +yObf.jar
```

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```
+/jre (1.5.0)                *(Windows, Linux only)
|
+ /lib
| +avalon-framework-4.1.4.jar
| +batik.jar
| +browserlauncher.jar
| +copasi.jar
| +copasi_gui.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
| +itext-1.4.6.jar
| +jai_codec.jar
| +jai_core.jar
| +jcommon-1.0.0-pre2.jar
| +jeuclid-2.0.jar
| +jfreechart-1.0.0-pre2.jar
| +mlibwrapper_jai.jar
| +MRJAdapter.jar
| +openide-lookup-1.9-patched-1.0.jar
| +quaqua-filechooser-only.jar
| +sbmlj.jar
| +SEWCore.jar
| +SOSlib.jar
| +xercesImpl.jar
| +xml-apis.jar
|
+libexpat.dll                *(Windows only)
+libsbml.dll                 *(Windows only)
+sbmlj.dll                   *(Windows only)
+SOSlibJava.dll              *(Windows only)
|
+libexpat.so.1               *(Linux only)
+libexpat.1.dylib            *(Linux only)
+libsbml.so                  *(Linux only)
+libsbmlj.so                 *(Linux only)
+libSOSlib.so                *(Linux 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)
|
+ /licenses
| + /celldesigner
| | +license.txt
| + /libraries
| | +batik.LICENSE.txt
| | +batik.NOTICE.txt
| | +FreeHEP.LGPL.txt
| | +FreeHEP.LICENSE.txt
| | +itext-MPLICENSE.txt
| | +jai.LICENSE.txt
```

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```
| +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
| +components40.xml           sample for various components
| +database.xml               sample for database connections
| +M-Phase.xml                sample for model editing
| +M-Phase2.xml               sample for model editing
| +Macros.xml                 sample for macros
| +MAPK.xml                   sample for simulation provided by SBML ODE Solver
| +sim1.xml
| +sim2.xml
| +simulation.xml             sample for simulation
| +/nbt                       sample files used in Nature Biotech paper by Kitano
| +/notation                  sample files for notation
| +/plugin                    sample source and jar files for plugin
+ 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 CellDesigner4.0  in your desktop.
2. Or double click CellDesigner4.0.exe in the directory where you chose to install (C:/Program Files/CellDesigner4.0 by default).

1.5.2 Mac OS X

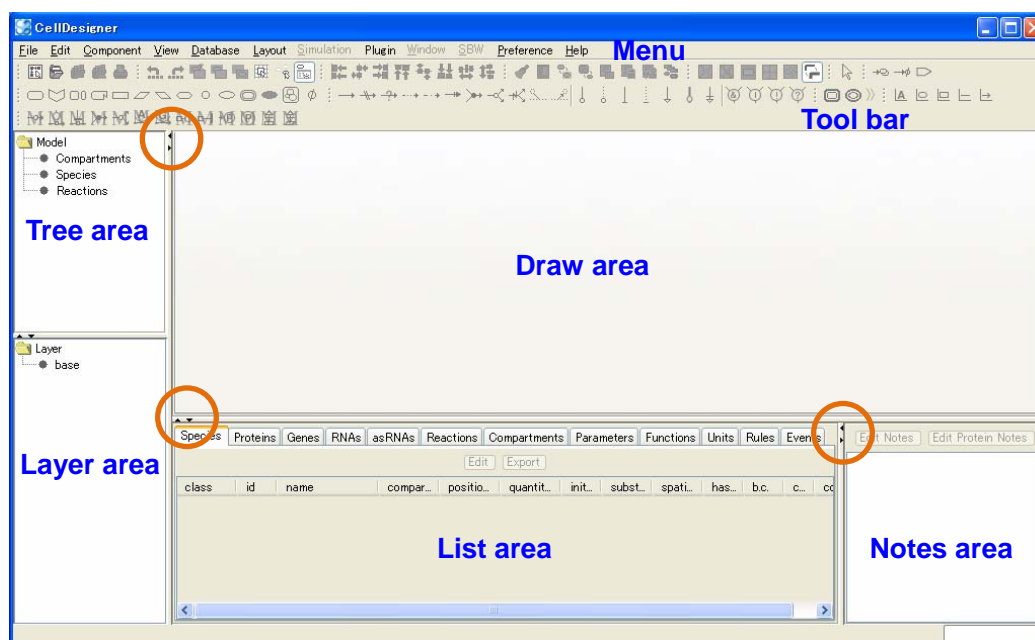
1. Double click the CellDesigner4.0 icon  in the folder you chose to install (/Application/CellDesigner4.0 by default).

1.5.3 Linux

1. On a shell, type `./runCellDesigner4.0` in your home directory.
2. Or type `./runCellDesigner4.0` after changing to the directory where you chose to install (CellDesigner4.0 in you home directory by default).

1.6 CellDesigner User Interface and Navigation

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



Draw area:	To draw a model. (also refer as “canvas” in this guide.)
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 area size

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 List and Notes areas position

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 Tool bar

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

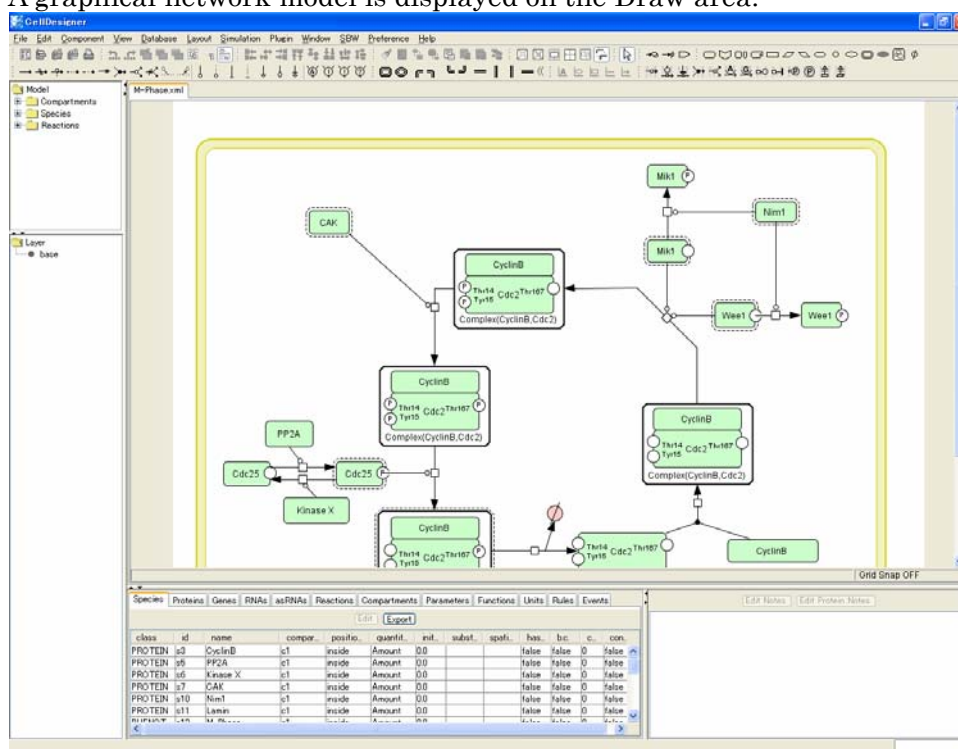
2. Quick Tutorial of Model Building

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 Select a Component

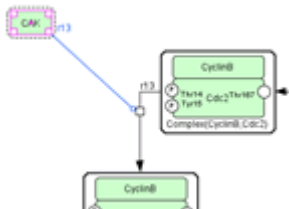
A **Component** is a general term for a **Species**, a **Reaction**, a **Complex** or a **Compartment**. Thus, any shape you see on the Draw area ---a rectangle, an oval, or a line segment--- is a **Component**.

2.2.1 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.

2.3 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.

2.4 Undo / Redo

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

2.4.1 To undo or redo the previous action

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

2.5 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.

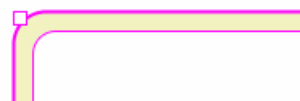
2.6 Compartment

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

A **Compartment** is a container for other Components. Since a **Compartment** is itself a Component, it can hold other Compartments inside.

2.6.1 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 Shape and Name of a Compartment

A **Compartment** represents a generic bounded container, such as a cell or an intracellular compartment. Thus, notational change is only in visual, meaningless to semantics of biochemical and gene networks.

2.7.1 To change the shape of a Compartment

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

2.7.2 To change the position of the Compartment name

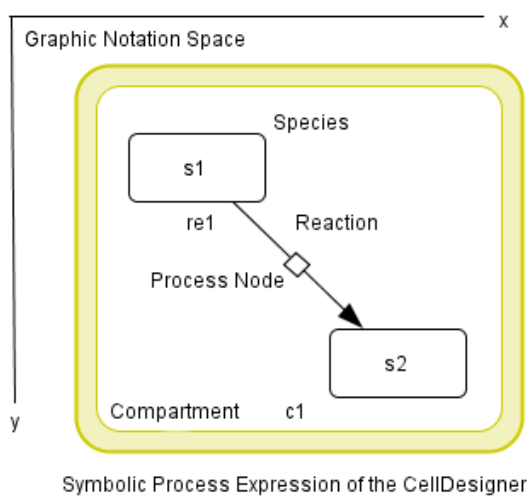
1. Find the Compartment name which is initially located at the bottom of the Compartment.
 → **Note:** In the `M-Phase_Test.xml` sample model, you will find “cell” as the Compartment name.
2. Select the Compartment name, drag and drop it wherever you want.

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](#)”.



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.

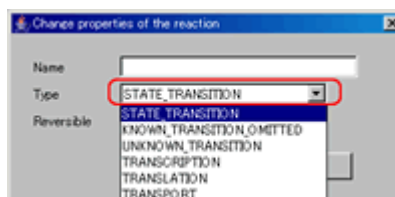
1. Double click a Species, for example, “CAK”, then the **Change identity of the species** dialog box will be displayed.



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 **Apply** 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.

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: The name you specify here will be the file name when saved.
e.g. If you specify "sample" here, the file name would be "sample.xml"

→ 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.

2.12 Create a New Compartment, Species and Reactions

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

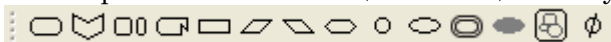
→ See also “Appendix 1: Symbols and Expressions”.

2.12.1 To create a new Compartment


1. Click and select an icon from the Compartment tool bar (as shown below).

2. Place your cursor on any point on the canvas, press and hold your left mouse button, and drag the cursor to make a Compartment of your favorite size.

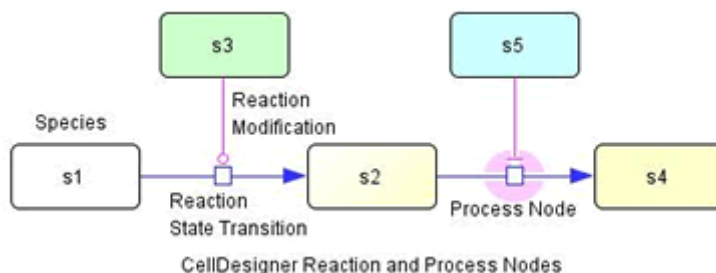
2.12.2 To create a new Species

1. Click and select an icon from the Species tool bar (as shown below).
2. Click a point on the canvas (draw area) where you want to place the new Species.



2.12.3 To create a new Reaction

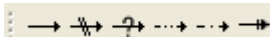
1. Click and select an icon from the Reaction tool bar (as shown below).

2. Depending on the type of Reaction you have chosen, follow the appropriate steps below.
 - A. State Transitions - Connect between Species / Complexes
 - B. Modifications - Connect to a “Process Node” on a reaction
 - C. Boolean Logic Gates - Show the relationship among the modifications



→ See also: “A1.1.7 Logical Operation”

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

1. On the Reaction Tool bar, 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 - a State Transition <Two to One type>

1. On the Reaction Tool bar,

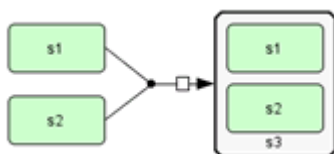


click the following icon.



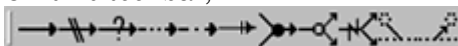
- Heterodimer Association

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 - a State Transition < One to Two type >

1. On this tool bar,



click one of the following icons.

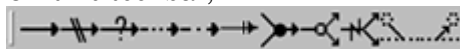


- Dissociation
- Truncation

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 add a new Reactant to a Reaction

1. On this tool bar,



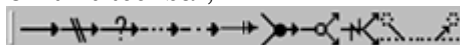
click the **Add Reactant** icon.



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 add a new Product to a Reaction

1. On this tool bar,



click the **Add Product** icon.

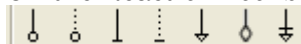


2. Place the cursor on a Reaction and find a blue point.
3. Click on it.
4. Click a Species to end at, and see a Reaction line is drawn.



2.12.9 To create a new Reaction ---a Modification

1. On the Reaction Tool bar, 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.

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).

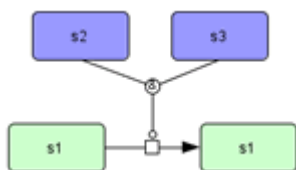
Or, on the Tool bar, click the **State Transition** macro icon. 



2. Draw two more Species.
3. On the tool bar, click one of the icons below.

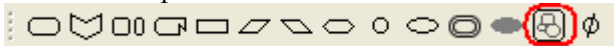


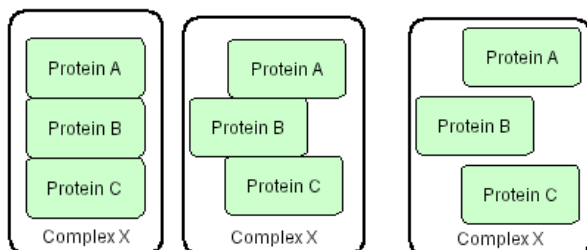
4. Click the two Species painted last.
5. Then click a square (“process node”) on the Reaction (State Transition), and see a Reaction line is drawn.



2.13 Create a Complex

2.13.1 To create a Complex

1. Click a Complex icon on the tool bar. 
2. Move the cursor onto the canvas 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

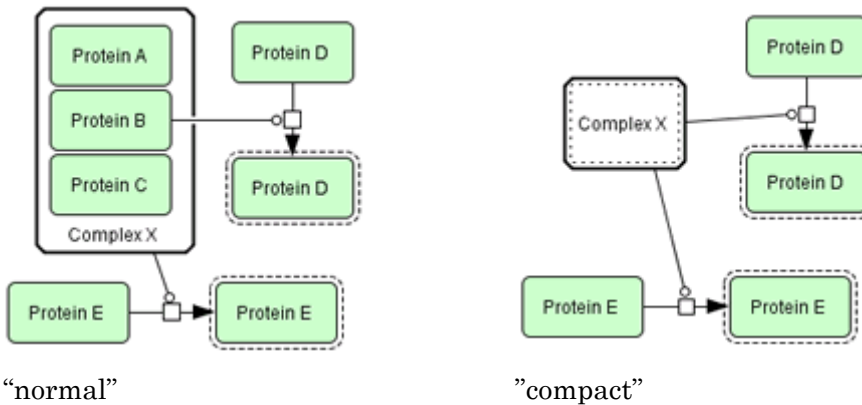
1. Note: You can modify the individual Species inside a Complex box at any time. For example, you can add a residue, change the residue status, or change the name or the class of the Species.
 - Note: The Notes information of the individual Species will be maintained even though you move the Species in and out of the complex box.
 - See also: [3.4 “Add Notes to the Components”] and [4 “Edit Proteins”].

2.14 Complexes and Reactions

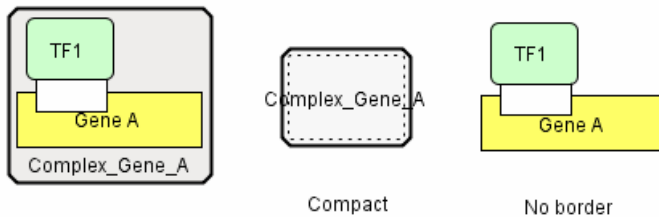
A Reaction can be connected to a Complex or to an individual Species/Reaction inside the Complex. Thus, you can distinguish if the activation is initiated by the Complex, or by an individual Species inside the Complex.

2.14.1 To change the appearance of a Complex

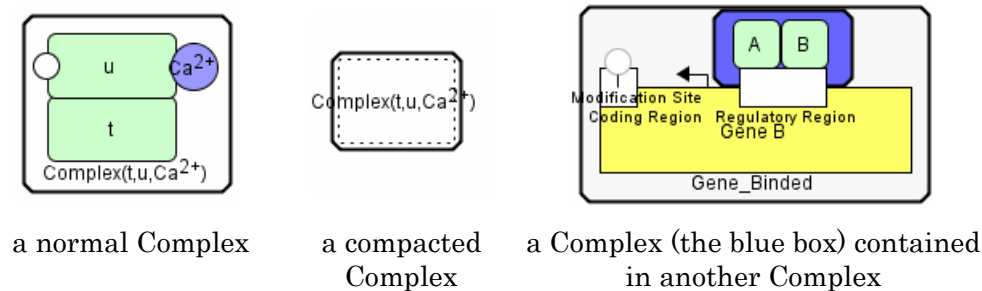
1. Select a Complex and type “C” to make it compact.
2. Type the “C” key again to have the border line invisible. (no border)
3. Type the “C” key again to get back to the original shape.
4. You can do the same steps as above by selecting **Component - Change Complex View** menu.



→ Note: You can set the Complex to be displayed with no border. This option is useful when you create a Complex with Gene/RNA/Antisense RNA. Below is an example which you can find in Complex40.xml in /samples/notation folder.



→ Note: A Complex can be contained within another Complex. Below is an example which you can find in components40.xml in /samples folder.



2.15 Edit Reactions

2.15.1 To change connection points of Reaction on Species

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

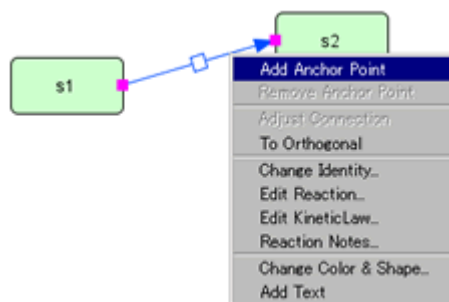
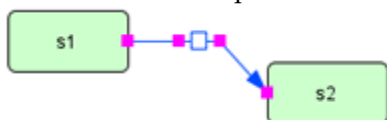
1. Select a Reaction and try to change the connection point.



2.15.2 To add Anchor points

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

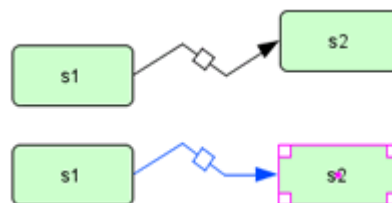
1. Click a point on a Reaction where you want to add an anchor.
2. Click the right mouse button and select **Add Anchor Point**.
3. See a new anchor point has been added.



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

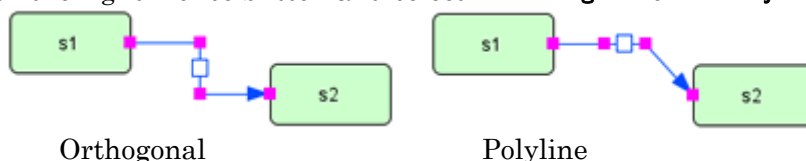
2.15.3 To move a Species with a Reaction

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



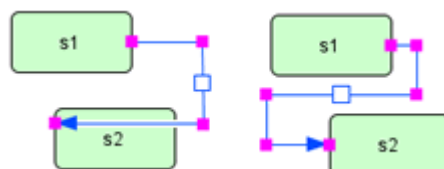
2.15.4 To change the shape of a Reaction line segment

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



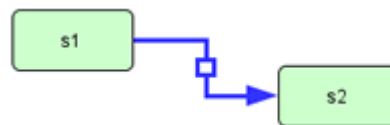
2.15.5 To adjust a Reaction line automatically

1. Select a Reaction which has already been set **To Orthogonal**.
2. Right-click your mouse and select **Adjust Connection** in the menu.



2.15.6 To change line width and color setting of a Reaction

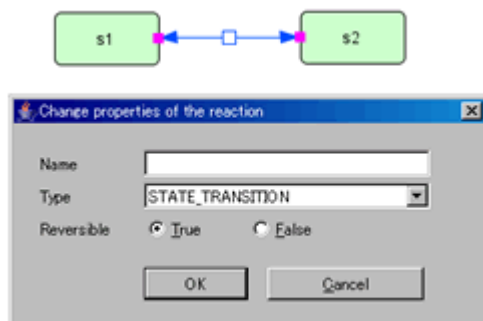
1. Select a Reaction.
2. Right-click on it and select **Change Color & Shape...** from the context menu.
3. Change the color and line width.



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

2.15.7 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**.

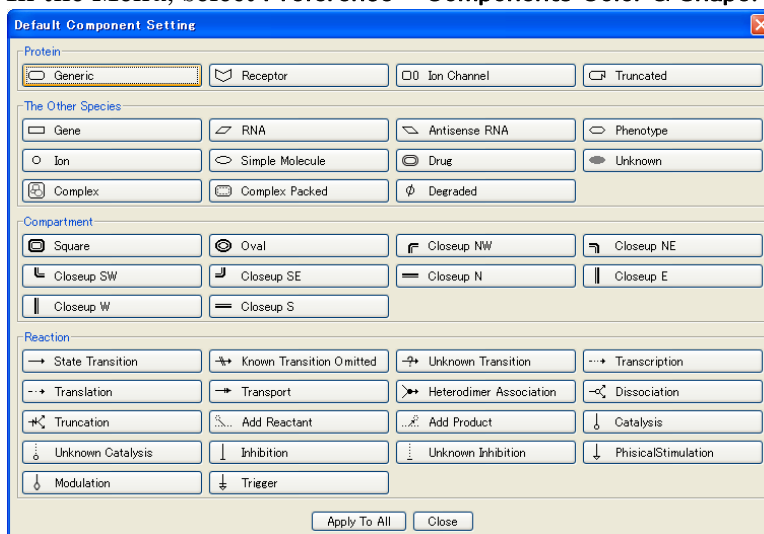


2.16 Change Color and Shape of Components

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


2.16.1 To change the default settings of the color and shape

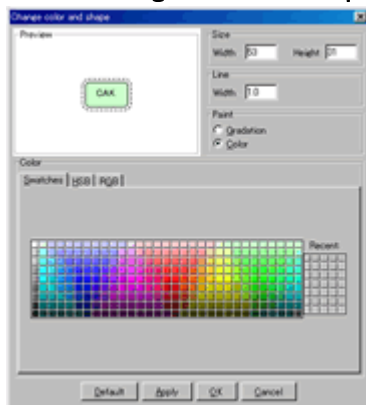
1. In the Menu, select **Preference – Components Color & Shape**.



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

2.16.2 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.



2.17 Export Image

2.17.1 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.

2.18 Save a Model

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

2.18.1 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.

2.18.2 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.

2.19 Export and Import a Model in pure SBML format

To open the xml file with another SBML-compliant application, you should export the model in a pure SBML file.

2.19.1 To export the model on the canvas:

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

2.19.2 To import any SBML file:

1. Select **File - Open**.

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

CellDesigner's "export" / "SBML" functions:

- CellDesigner stores all information only in a SBML file.
- Though SBML does not support layout information, CellDesigner stores layout information inside <annotations> tags in SBML, which is CellDesigner specific extension.
- Though these extensions are enclosed in <annotations> tags, generated SBML files are still "SBML Validated" documents.
- CellDesigner has a feature to export "pure" SBML document which 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.

2.20 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: [5.11 "Automatic Layout"].

2.20.1 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: [3.5 "Connect to Databases"].

3. Edit Species

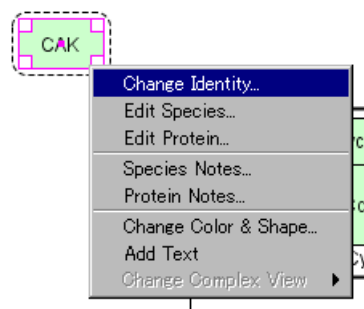
3.1 Edit Species

A **Species** represents, for example, a Protein, a Complex or some other Molecule in a biochemical network, or a gene in a gene regulatory network.

3.1.1 To edit a Species

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

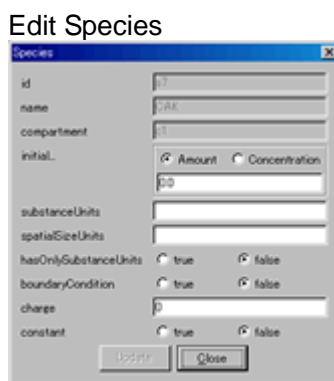
→ Note: The third menu item (e.g. **Edit Protein** in the above screen) is content-dependent. The menu would be only displayed if the target Species is a Protein, a Genes, an RNA, or an asRNA.



3. Change the values in the dialog box.



Change Identity dialog can specify the class, name, type, modification, state of a Species.



Edit Species dialog can view the id, name and compartment name in which Species resides, and set the value of initial amount / concentration, substance units, charge etc.



Edit Protein dialog can specify name and type of a Protein, add residues or binding blocks and edit block diagram.

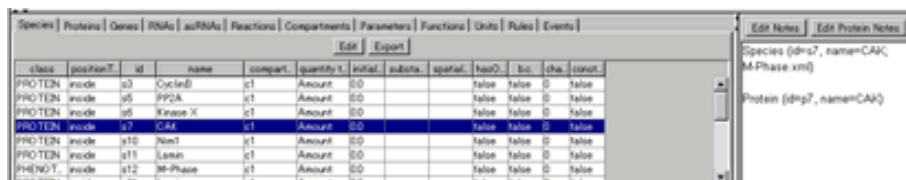
→ See also: CellDesigner.org Online Help **Species** section:
http://celldesigner.org/help/CDH_Species_T.html .

→ See also: [4 “Edit Proteins”].

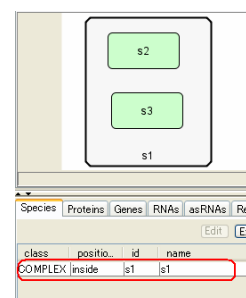
→ See also: [8 “Gene/RNA/AntisenseRNA Structure Expressions”].

3.2 Check the Species in the List

You can view all the data concerning a Species in the Species list. This is useful when you want to check all the items specified in the model. You can swap the column by drag-and-drop.



→ Note: If Species are contained in a Complex, only the Complex information will be displayed in the list and the Species will NOT.

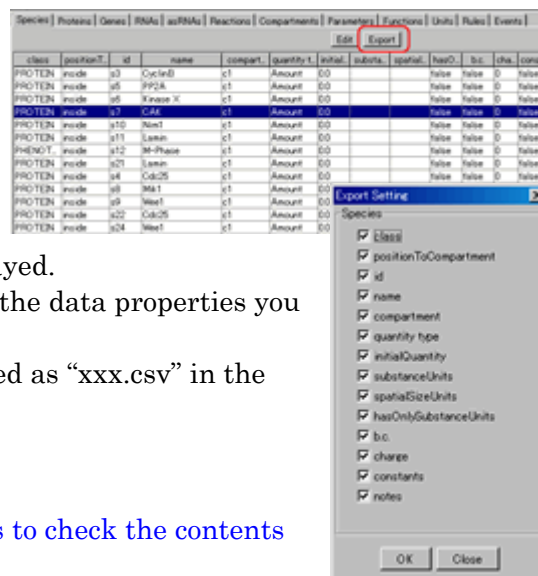


3.3 Export Lists to CSV file

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.

3.3.1 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.
The **Export Setting** dialog will be displayed.
3. In the **Export Setting** dialog box, check the data properties you want to export, then click **OK**.
4. The file name is automatically specified as “xxx.csv” in the **Save** dialog.
5. Click **Save** to save the CSV file.



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

3.4 Add Notes to the Components (Compartments, Species and Reactions)

You can add a note to a component (Compartment, Species or Reaction,) except some Species types (Phenotype, Ion, Simple Molecule, Drug, Unknown and Tag).

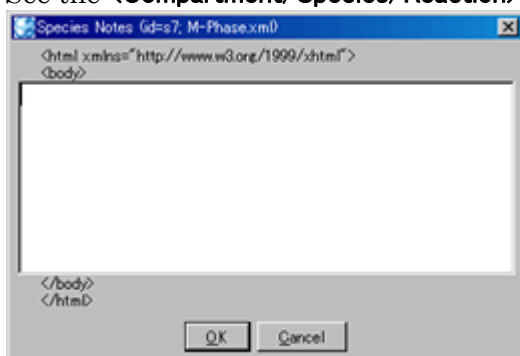
The Notes should be written in XHTML format. For details on XHTML tags and attributes, please check the XHTML 1.0 specification provided at <http://www.w3.org/TR/xhtml1/>

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

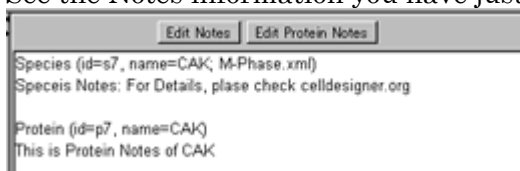
→ See also [3.5 “Connect to Database”].

3.4.1 To add Notes to a component

1. Select the target component.
2. See that the Notes of the component is displayed in the Notes Area in the right-bottom corner of the window.
3. On the target component, click on the right mouse button to display the popup menu and select **<Compartment/Species/Reaction> Notes**, or click **Edit Notes** button in the Notes Area.
 - Note: If your target component is a Species of the following types, namely, Protein, RNA, asRNA or Gene, you will also find **<type of Species> Notes** in the right-click menu or **Edit <type of Species > Notes** button in the Notes Area.
4. See the **<Compartment/Species/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.



3.5 Connect to Databases

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

- **DBGET**
(a simple database retrieval system for a diverse range of molecular biology databases.)
<http://www.genome.jp/dbget/>
- **SGD (Saacharomyces Genome Database)**
<http://yeastgenome.org/>
- **iHOP (Information Hyperlinked over Proteins)**
<http://www.ihop-net.org/UniPub/iHOP/>
- **Genome Network Platform**
<http://genomenetwork.nig.ac.jp/public/sys/gnppub/portal.do>
- **PubMed**
<http://www.ncbi.nlm.nih.gov/sites/entrez>
- **Entrez Gene**
<http://www.ncbi.nlm.nih.gov/sites/entrez?db=gene>
- **BioModels.net**
<http://www.biomodels.net>, <http://www.ebi.ac.uk/biomodels/>

3.5.1 To connect to the databases using Species Name

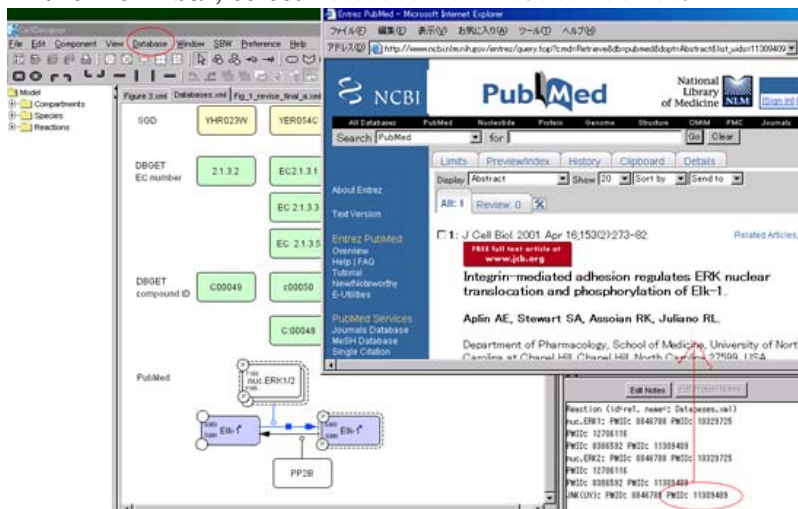
1. Select the component (Species, Reaction or Compartment)
2. Select the database to connect to: **Database** –
Connect to SGD, Connect to DBGET, Connect to iHOP,
Connect to Genome Network Platform,
Connect to PubMed, or Connect to Entrez Gene.
3. See your web browser pop up and open the page relevant 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.

3.5.2 To connect to PubMed or Entrez Gene via the ID written in the Notes

1. Specify the PubMed ID / Entrez Gene ID in the Notes of Species, Reaction, or Compartment as follows;
PMID: 12345 PMID: 67890
GeneID: 22954 GeneID: 493761
2. Select the component (Species, Reaction or Compartment).

- In the menu bar, select **Database - Connect to PubMed**.



3.5.3 To connect to the databases to download the models

CellDesigner can connect directly to BioModels.net, and import various annotated models.

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.

- Select the menu **Database – Import model from BioModels.net...** to retrieve a model.



4. Edit Proteins

In this section, how to edit proteins with modification sites, such as "Cdc2" in the sample "M-Phase2.xml", is being described.

With CellDesigner, you can edit symbols of proteins with modification residues on a network diagram, and hence, describe detailed state transitions between Species of an identical protein with different modifications. 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 model M-Phase2.xml, you see, describes state transition of "Cdc2," where there are five "Cdc2"s. The five represent different Species, while 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".

4.1 Check and Change Protein Property

You can see this Protein data by selecting the **Proteins** tab in the List Area.

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

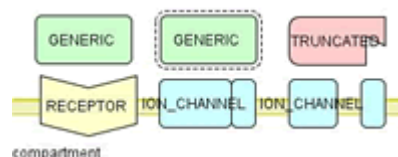
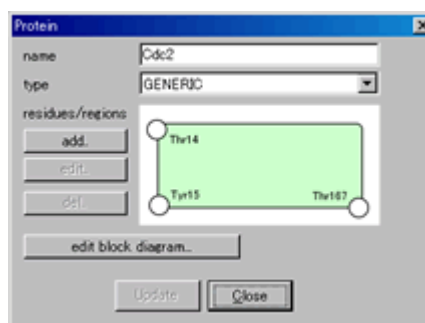
id	type	name
p11	GENERIC	APC
p5	GENERIC	CAK
p2	GENERIC	Cdc13
p1	GENERIC	Cdc2
p7	GENERIC	Cdc25
p6	GENERIC	Lamin
p8	GENERIC	PP2A
p10	GENERIC	Skp1

For individual Protein, you can view the properties by clicking on the target Species to open a **Protein** dialog. In the dialog, you can edit properties of Protein, such as name, type, and residues and binding regions (add, edit, and delete).

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

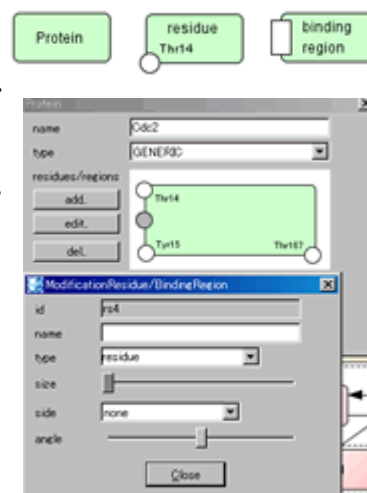
4.1.1 To edit the Protein property

1. Select "Cdc2" in the list and click **Edit** button. Alternatively, you can click on the target Protein with the right mouse button, to select **Edit Protein...** menu. The **Protein** dialog will appear.
2. Select **type** of a Protein.
 - GENERIC
 - RECEPTOR
 - ION_CHANNEL
 - TRUNCATED



4.2 Add Residue / Binding Region to a Protein

The residues or binding regions of a protein can be added / delete in the **Protein** dialog. You can adjust the position of the residues and regions in the dialog. However, to change the modification of the residue status (such as phosphorylated, etc.) should be made in the Species' identity dialog.



4.2.1 To add a residue to a Protein

1. Open a **Edit Protein** dialog.
2. Click **add**, **edit** button to add / edit a residue/region.
3. You can select the type from **residue** or **binding region**, name it, and set the properties such as size and position.

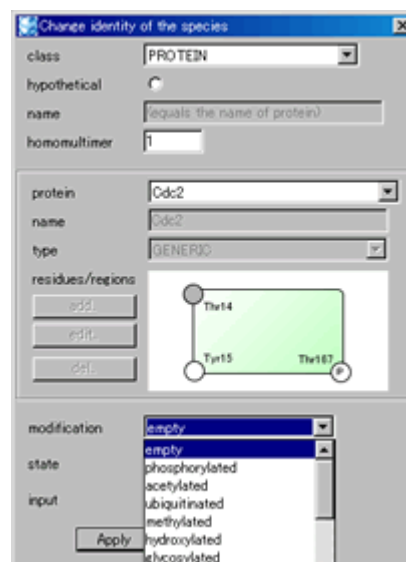
You can also delete a residue or a binding region in this dialog.

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

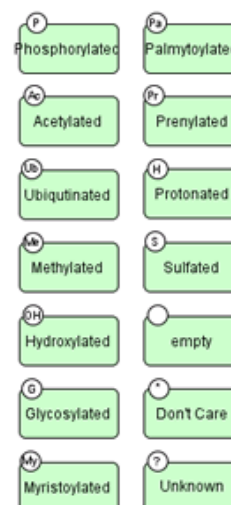
4.2.2 To specify the modification of a residue

Once you add a residue to a Protein, you can specify the modification status for a specific alias. As you specify the status per Species, use **Change identity of the Species** dialog instead of **Protein** dialog.

1. Double-click a Species to open **Change identity of the species** dialog.
2. In the dialog, click on the target residue in **residues/regions** diagram in the middle.
3. Change the modification type in the **modification** drop-down menu.



- | | |
|----------------|--------------|
| Phosphorylated | Palmtoylated |
| Acetylated | Prenylated |
| Ubiquitinated | 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 **Edit Protein** dialog instead.

4.3 State of Proteins

The state of the protein can be changed to Open / Close / User defined text. Here again, you will use **Change identity of the Species** dialog instead of **Protein** dialog.

4.3.1 To specify the modification of a residue



1. Double-click a Species to open **Change identity of the species** dialog.
2. In the dialog, select **state** from the drop-down menu.

4.4 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.

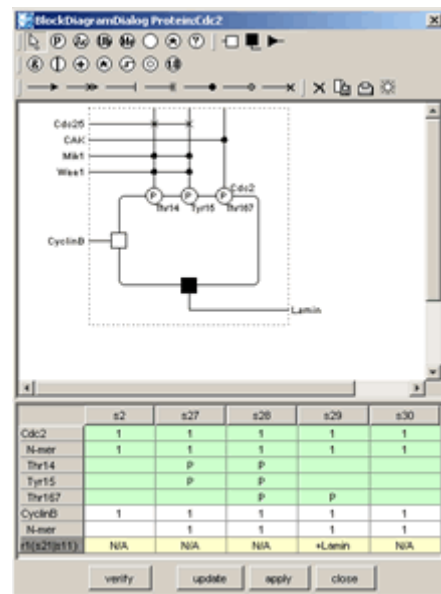
→ Note: The editor is still prototype and user interface for editing is not fully functional.

4.4.1 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. (See [4.1]).
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.



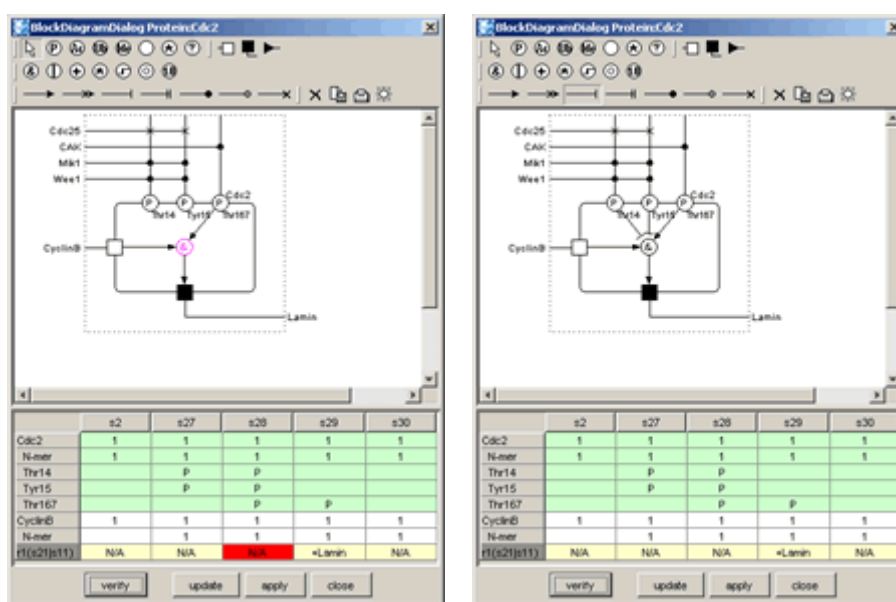
→ See also Kitano (Biosilico 1, No.5 (2003) pp.169—176), For notation details of the block diagram.

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).

4.4.2 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.)

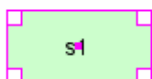
5. Draw a Model using the Edit Menu

In this section, convenient functions for editing models are introduced. CellDesigner provides several functions that are generally seen in drawing software.

5.1 Cut, Copy and Paste

5.1.1 To cut and paste a Species

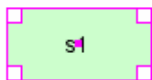
1. Select a Species by clicking on it.



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.

5.1.2 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 canvas by selecting **Edit – Paste**, or typing `Ctrl-V`.
4. In the Notes area, observe that the Notes content is the same as the original.

5.1.3 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, i.e. “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.

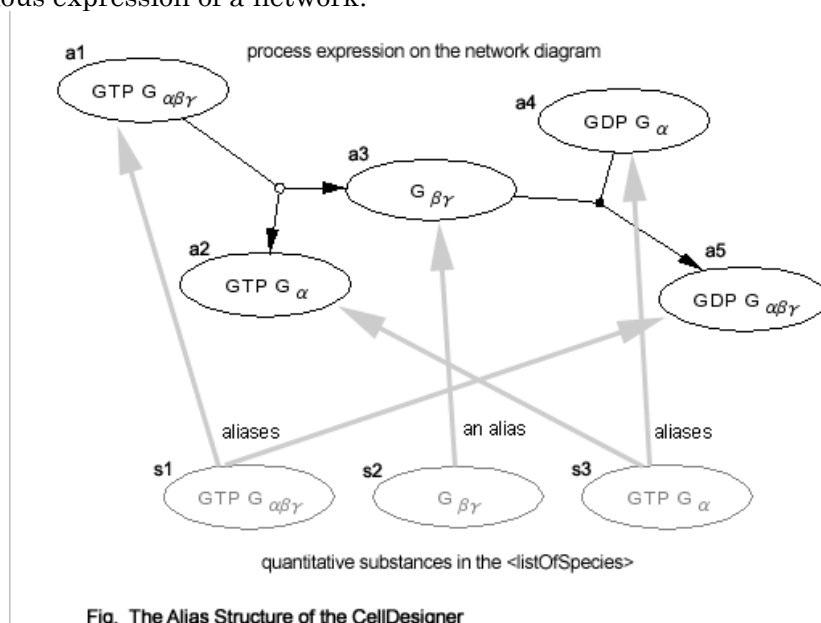
Species			
class	position...	id	name
PROTEIN	inside	s1	s1
PROTEIN	inside	s2	mySpecies

- 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

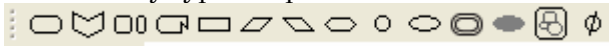
5.1.4 SpeciesAlias

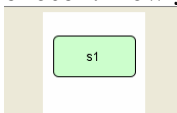
The copy-and-paste action makes “real” copies of the selected Species, which are SpeciesAliases in CellDesigner’s terminology, referring to the original Species. Strictly speaking, all of the Species on the canvas are SpeciesAliases, each referring to the original Species. By this feature, CellDesigner has multiple copies of the same Species on the canvas (i.e. a model), to possess ability to make various expression of a network.



When you have created a new Species, what you see on the canvas is not the Species itself but an Alias of it.

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

- In the Menu, click **File – New** to create a new model.
- Click on any type of Species icon from the Tool bar and place it on the canvas.

- Move the cursor and click anywhere on the canvas to place the Species you have chosen. Now you have the simplest model on your canvas.




- Select **File – Save as...** in the Menu.
- Save the file in XML format.
- With a web browser, 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 id="s1" name="s1" compartment="default" initialAmount="0">`

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

5.2 Select Mode


After you have put a new component on canvas, 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 canvas first and then rearrange them as you like.

5.2.1 To avoid the automatic Select Mode

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

5.2.2 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.

5.3 Select All

5.3.1 To select all the components

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

5.4 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 resembled to the situation, Species on a Compartment, while it has nothing to do with structure of the model. Therefore, if these two conflict each other in the canvas, “Species on a Compartment” structure has priority.

5.4.1 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.

5.4.2 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.

5.5 Alignment

5.5.1 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 Tool bar.



5.5.2 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.

5.6 Set Grid Snap ON/OFF

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

5.6.1 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.

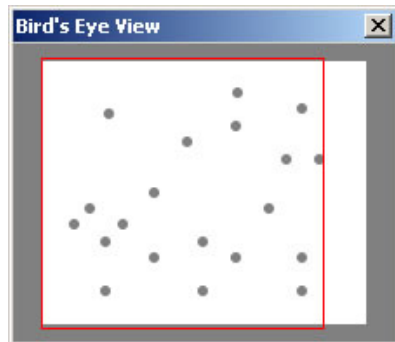
5.7 Zoom IN/OUT, Bird's Eye View

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



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 Tool bar. When you drag the red square in the Bird's Eye View, observe that the view of the Draw area moves accordingly.

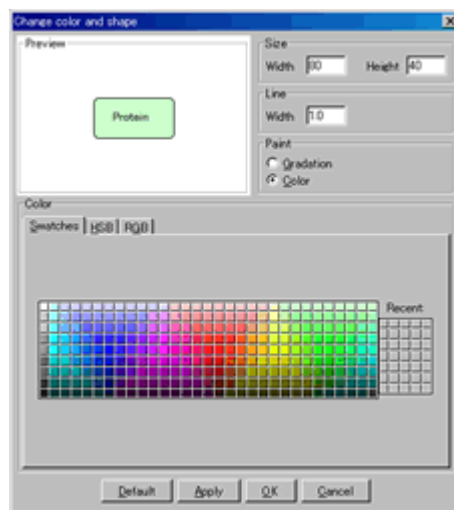


5.8 Change Color and Shape


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

5.8.1 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.



5.8.2 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.

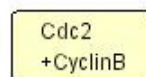
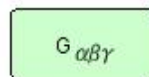
5.9 Display special characters in Component name

As CellDesigner is compliant with SBML, all names of components in a model must conform to the SBML convention. CellDesigner 4.0 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.

5.9.1 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_alpha_beta_gamma_endsub_

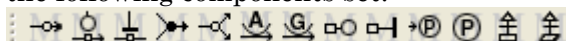
- 3) Complex of Cdc2 and CyclinB ("Cdc2" followed by "+CyclinB" in the new line).
Cdc2_br_plus_CyclinB
Cdc2_br_+CyclinB

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.

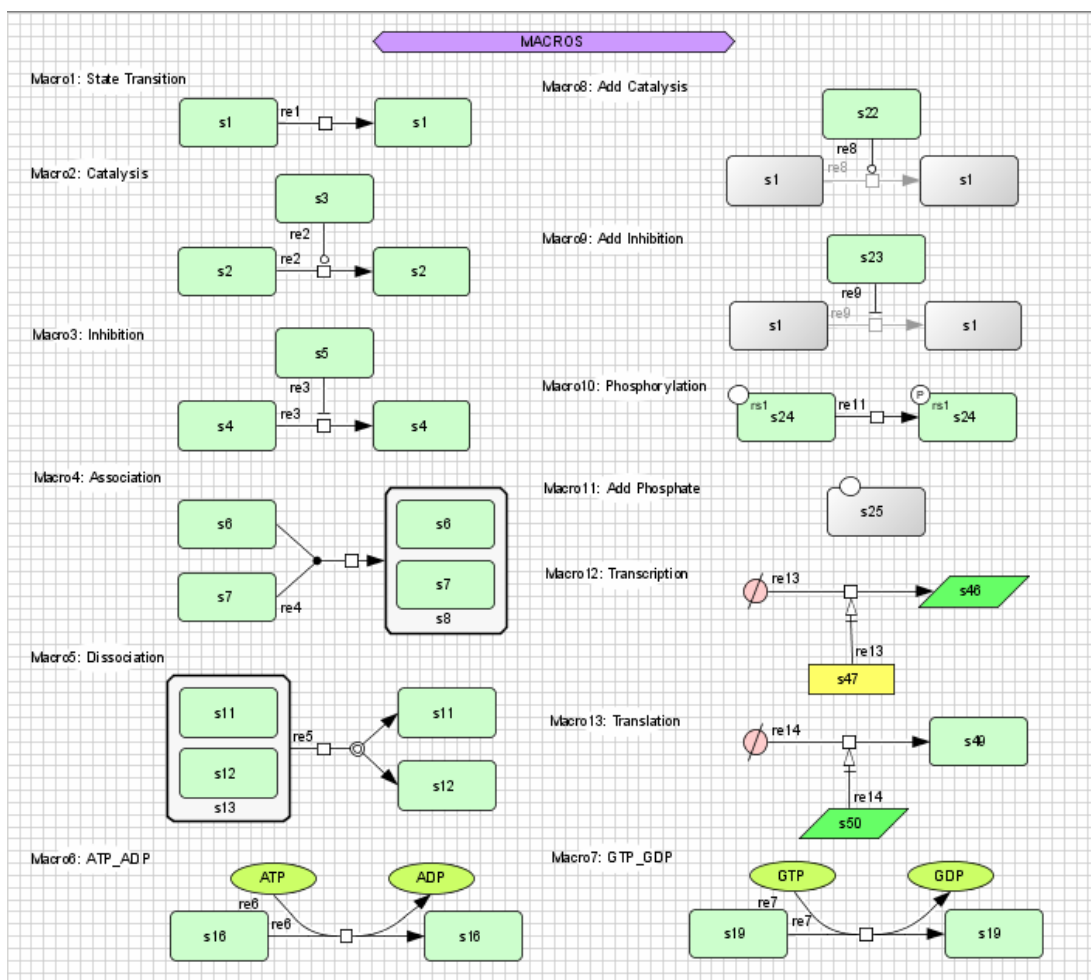
5.10 Macros

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.



5.10.1 To view how each macro paint 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.



“Macros.xml” in the “samples” folder

5.10.2 To change the Macro Set

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

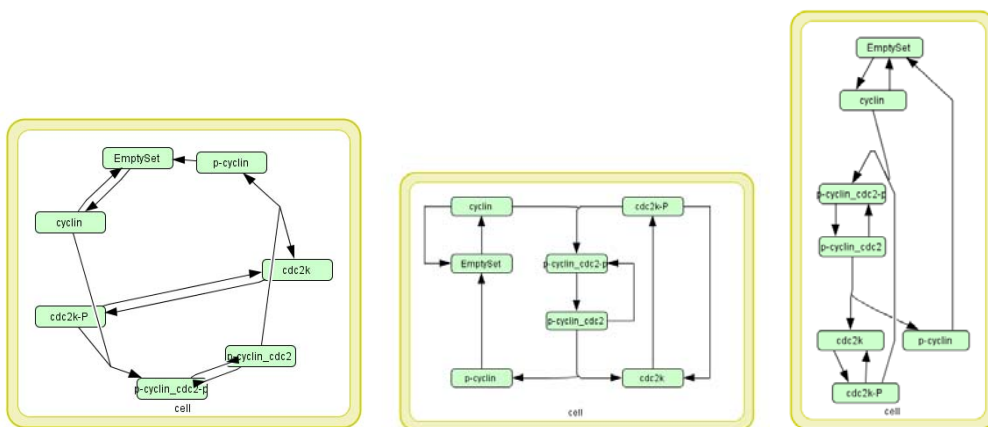
5.11 Automatic Layout

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.

5.11.1 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**.

5.11.2 To change the Default Setting:

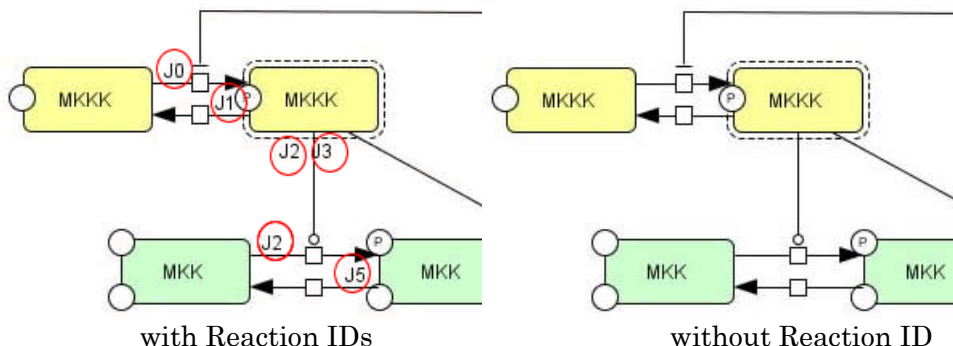
1. On the **Layout** menu, click **Default Automatic Graph Layout**.
2. Select a layout you want set as default.

6. Reaction and KineticLaw

6.1 Reaction ID

6.1.1 To show Reaction ID on canvas

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



6.2 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 items 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	$V1 * MKKK / ((1 + \text{pow}(\text{MAPK_PP} / K1, n)) * (K1 + MKKK))$	
STATE_TRANSITIO...	J1	J1	false	false	MKKK_P	MKKK		$V2 * MKKK_P / (K2 + MKKK_P)$	
STATE_TRANSITIO...	J2	J2	false	false	MKK	MKK_P	MKKK_P	$k3 * MKKK_P * MKK / (K3 + MKK)$	
STATE_TRANSITIO...	J3	J3	false	false	MKK_P	MKK_PP	MKKK_P	$k4 * MKKK_P * MKK_P / (K4 + MKK_P)$	
STATE_TRANSITIO...	J4	J4	false	false	MKK_PP	MKK_P		$V5 * MKK_PP / (K5 + MKK_PP)$	
STATE_TRANSITIO...	J5	J5	false	false	MKK_P	MKK		$V6 * MKK_P / (K6 + MKK_P)$	
STATE_TRANSITIO...	J6	J6	false	false	MAPK	MAPK_P	MKK_PP	$k7 * MKK_PP * MAPK / (K7 + MAPK)$	
STATE_TRANSITIO...	J7	J7	false	false	MAPK_P	MAPK_PP	MKK_PP	$k8 * MKK_PP * MAPK_P / (K8 + MAPK_P)$	
STATE_TRANSITIO...	J8	J8	false	false	MAPK_PP	MAPK_P		$V9 * MAPK_PP / (K9 + MAPK_PP)$	
STATE_TRANSITIO...	J9	J9	false	false	MAPK_P	MAPK		$V10 * MAPK_P / (K10 + MAPK_P)$	

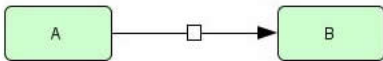
You can export the contents of the list into .CSV file format by clicking **Export** button on the top of the list.

6.3 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.

6.3.1 To add a KineticLaw to a Reaction

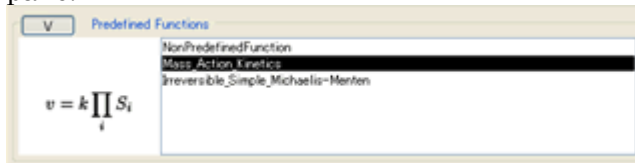
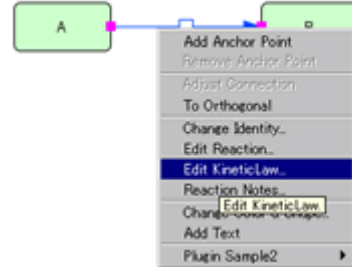
1. Create a model with Proteins A and B, with State Transition reaction in-between. Or, just open the file `sim1.xml` in the `samples` folder.



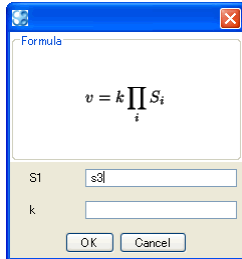
2. In the List area, click on the **Species** tab.
3. Select the row for the protein A.
4. Double click on the cell under **InitialQuantity** column.
5. Set the value to “0.1”.

class	positionT	id	name	compart.	quantity t.	initial	substa.	spatial.	hasO.	b.c.	cha.
PROTEIN	inside	s1	A	default	Amount	0.1			false	false	0
PROTEIN	inside	s2	B	default	Amount	0.0			false	false	0

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 or **Edit** button. Or click on the Reaction with the right mouse button, then select **Edit KineticLaw...** menu.
8. The **KineticLaw** dialog will open.
9. In the middle of the dialog, click **Mass Action Kinetics** in the **Predefined Functions** pane.

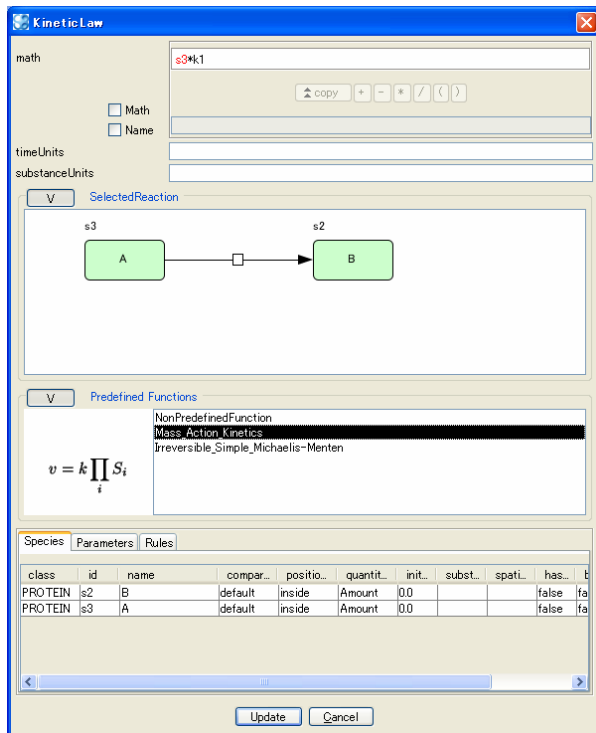


10. The **Formula** dialog will be displayed.



11. Type in “0.3” in the **k** text box, then click **OK**.

- See that “ $s3*k1$ ” has been entered in **math** field, then click **Update**, then **Close**.

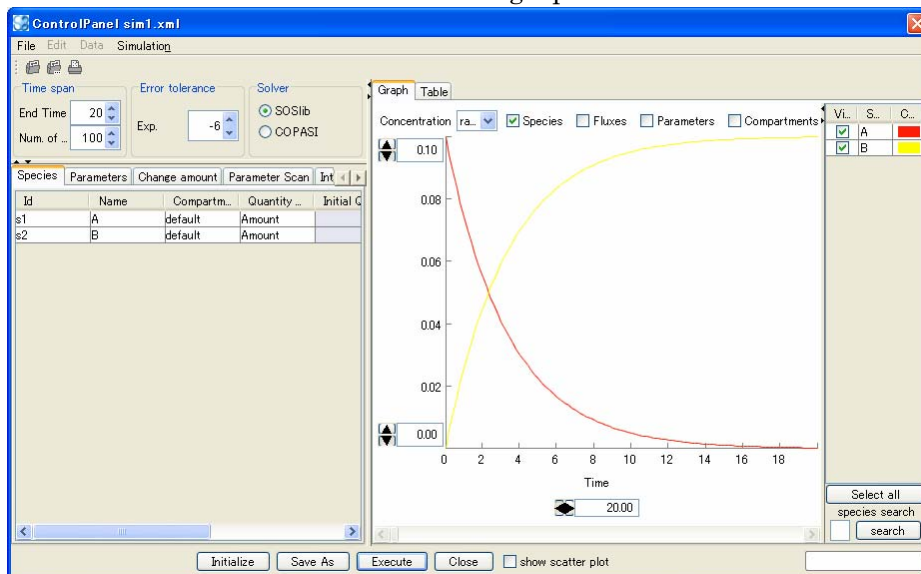


- In the **Reaction** dialog, click **Close**.

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

6.3.2 To run the simulation

- Do the previous walkthrough “To add a KineticLaw to a Reaction”.
- On the **Simulation** menu, click **Control Panel**.
- In the **ControlPanel <filename>** dialog, set **End Time** to “20”.
- Click **Execute** button. You will obtain a graph like this.



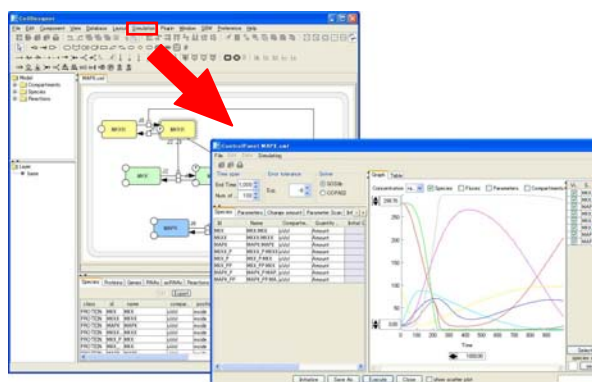
7. Simulation

This section describes how to simulate a model.

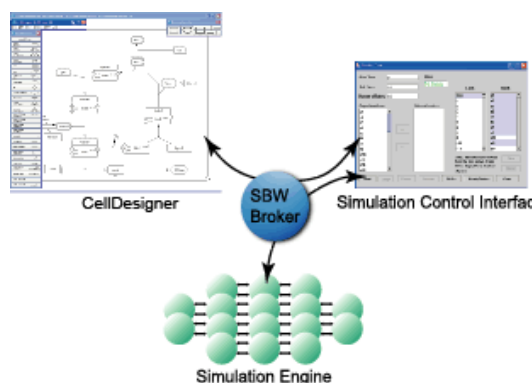
CellDesigner can be used as a kind of SBML file editors for simulators.

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 Solver



SBW menu
to call SBML compliant simulator.

If you select the **Simulation** menu, you can call SBML ODE Solver 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.

To conduct time evolving simulation, you also need to know some basics of the SBML specification. Here in this document, describes the minimum requirements for simulation.

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

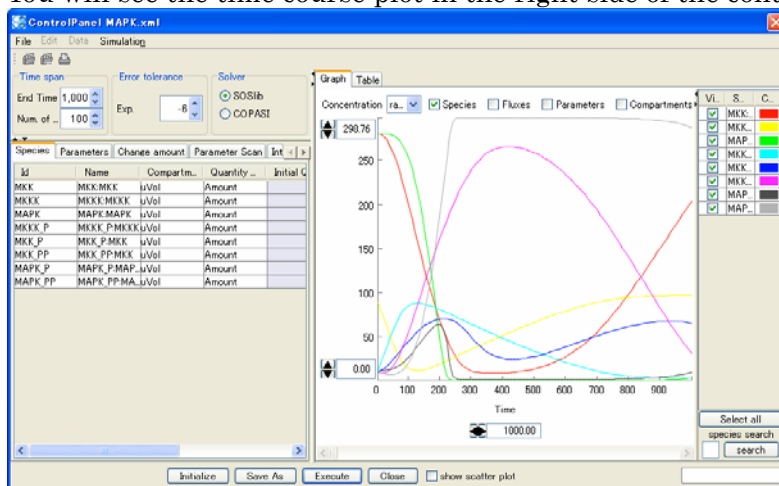
→ **See also:** for more details on SBML specifications, <http://sbml.org/Documents/Specifications>

→ **See also:** [Section 3.5 “Connect to Database”].

7.1 Simulation by Control Panel

7.1.1 To simulate a model using the Control Panel

1. Open the sample file “MAPK.xml” in the “samples” folder.
2. In the Menu, select **Simulation - Control Panel**.
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.



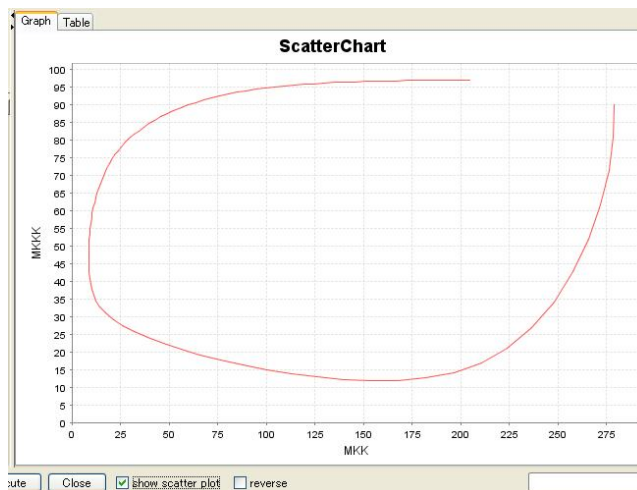
→ See also:
 For more details on how to use control panel, please refer to the document “*Running CellDesigner™ Simulation with ControlPanel*” in the /documents directory.

7.1.2 To change the solver to COPASI

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

7.1.3 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.



7.2 Simulation by SBW

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 “Section 1.2 Install SBW and SBW Modules”.

7.2.1 To set up SBW for simulation

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.

7.2.2 To simulate a model using SBW

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

7.3 Data required for Simulation

In terms of SBML model building, you should specify first at least some Species and its attributes, and Reaction and its attribute for simulation. 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:	-formula,	
		-parameter,	

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

7.3.1 Species Attributes

The attribute “initialAmount” should usually be changed to a positive value. The attribute “formula” should be text string according to SBML Level 2 specification, probably including id (name in SBML Level 2) attribute of Species and parameters defined by the attribute “parameter.” These attributes can be set at the Species list shown in the List Area.

7.3.2 Reaction Attributes

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

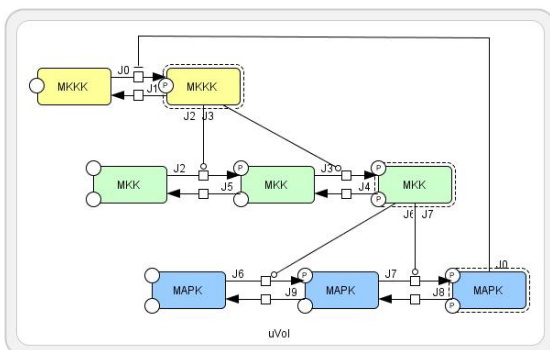
For the other parameters, the default values specified in SBML Level 2 are used.

7.4 Data for 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.

7.4.1 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											
class	positionT...	id	name	compart...	quantity t	initialQuantity	substa...	spatial...	hasO...	b.c.	cha...const...
PROTEIN	inside	MKK	MKK	uVol	Amount	280.0			false	false	0 false
PROTEIN	inside	MKKK	MKKK	uVol	Amount	90.0			false	false	0 false
PROTEIN	inside	MAPK	MAPK	uVol	Amount	280.0			false	false	0 false
PROTEIN	inside	MKKK_P	MKKK_P	uVol	Amount	10.0			false	false	0 false
PROTEIN	inside	MKK_P	MKK_P	uVol	Amount	10.0			false	false	0 false
PROTEIN	inside	MKK_PP	MKK_PP	uVol	Amount	10.0			false	false	0 false
PROTEIN	inside	MAPK_PP	MAPK_PP	uVol	Amount	10.0			false	false	0 false
PROTEIN	inside	MAPK_P	MAPK_P	uVol	Amount	10.0			false	false	0 false

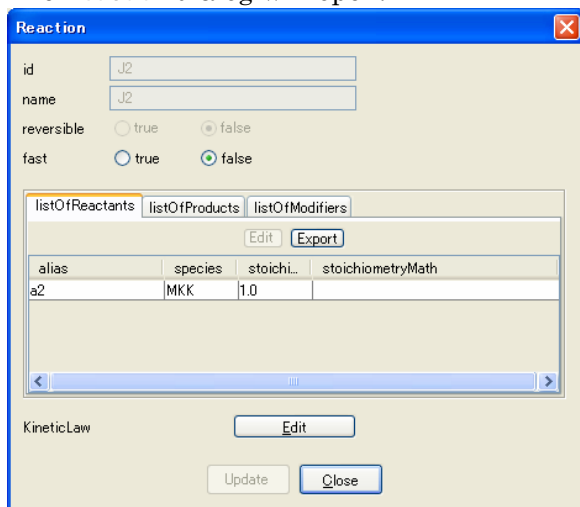
3. Check the **Reactions** tab in the List area to see how the kinetic laws and parameters are specified.

Reactions											
type	id	name	rever...	fast	reactants	products	modifiers	math			
STATE_TRANSITIO...	J0	J0	false	false	MKKK	MKKK_P	MAPK_PP	$V1 * MKKK / ((1 + \text{pow}(\text{MAPK_PP} / K1, n)) * (K1 + MKKK))$			
STATE_TRANSITIO...	J1	J1	false	false	MKKK_P	MKKK		$V2 * MKKK_P / (K2 + MKKK_P)$			
STATE_TRANSITIO...	J2	J2	false	false	MKK	MKK_P	MKKK_P	$k3 * MKKK_P * MKK / (K3 + MKK)$			
STATE_TRANSITIO...	J3	J3	false	false	MKK_P	MKK_PP	MKKK_P	$k4 * MKKK_P * MKK_P / (K4 + MKK_P)$			
STATE_TRANSITIO...	J4	J4	false	false	MKK_PP	MKK_P		$V5 * MKK_PP / (K5 + MKK_PP)$			
STATE_TRANSITIO...	J5	J5	false	false	MKK_P	MKK		$V6 * MKK_P / (K6 + MKK_P)$			
STATE_TRANSITIO...	J6	J6	false	false	MAPK	MAPK_PP	MKK_PP	$k7 * MKK_PP * MAPK / (K7 + MAPK)$			
STATE_TRANSITIO...	J7	J7	false	false	MAPK_PP	MAPK_P	MKK_PP	$k8 * MKK_PP * MAPK_P / (K8 + MAPK_P)$			
STATE_TRANSITIO...	J8	J8	false	false	MAPK_PP	MAPK_P		$V9 * MAPK_PP / (K9 + MAPK_PP)$			
STATE_TRANSITIO...	J9	J9	false	false	MAPK_P	MAPK		$V10 * MAPK_P / (K10 + MAPK_P)$			

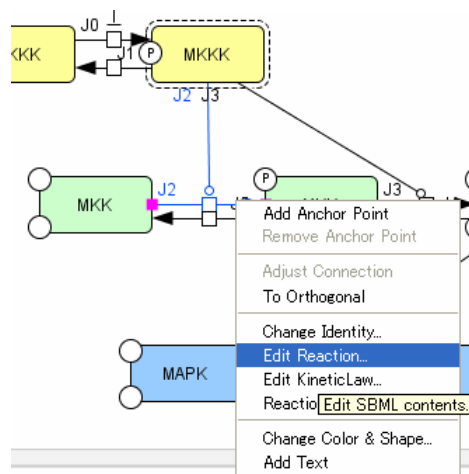
4. In the **Reactions** list, double-click on the third row whose id is “J2”.

Reactions					
Species	Proteins	Genes	RNAs	asRNAs	Reactions
Species ID					
type	id	name	rev...	fast	
STATE_TRANSITION	J0	J0	false	false	
STATE_TRANSITION	J1	J1	false	false	
STATE_TRANSITION	J2	J2	false	false	
STATE_TRANSITION	J3	J3	false	false	

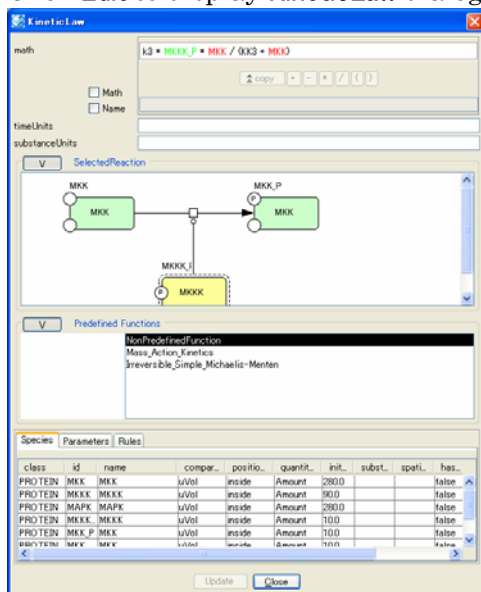
5. The **Reaction** dialog will open.



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



7. Click **Edit** to display **KineticLaw** dialog.



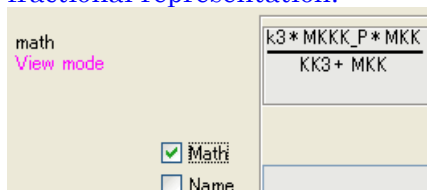
8. In the **math** text box, you can change the formula.

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.

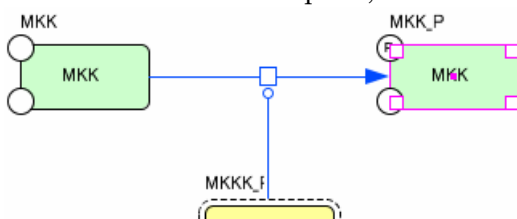


- Note: Ticking **Math** checkbox will show the variables in the **math** text box in fractional representation.

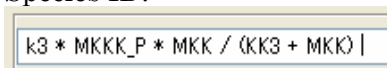


7.4.2 To add a Species ID in the math text box

1. In the **SelectedReaction** pane, select the target Species (e.g. MKK_P).

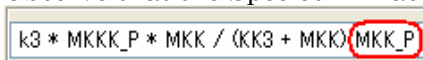


2. In the **math** text box, put the cursor to the place where you want to add the Species ID.



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

3. Press the **copy** button.
4. Observe that the Species ID has been added.



7.4.3 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.

Species Parameters Rules					
<input type="button" value="New"/> <input type="button" value="Edit"/> <input type="button" value="Remove"/> <input type="button" value="Clear All"/>					
scope	id	name	value	units	constant
local:Reaction(J2)	k3		0.025		true
local:Reaction(J2)	KK3		15.0		true

7.4.4 To specify 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 easily.

→ See also: [Edit Reaction / Add KineticLaw section](#).

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 – Control Panel** from the Menu, then conduct the simulation.

→ See also: “Running CellDesigner™ Simulation with ControlPanel” in the /documents directory.

Reference: MAPK.XML

id	Math
J0	$V1 * MKKK / ((1 + \text{pow}(\text{MAPK_PP} / K_i, n)) * (K1 + MKKK))$
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	$k7 * MKK_PP * \text{MAPK} / (KK7 + \text{MAPK})$
J7	$k8 * MKK_PP * \text{MAPK_P} / (KK8 + \text{MAPK_P})$
J8	$V9 * \text{MAPK_PP} / (KK9 + \text{MAPK_PP})$
J9	$V10 * \text{MAPK_P} / (KK10 + \text{MAPK_P})$
id	Math
J0	$V1 * MKKK / ((1 + \text{pow}(\text{MAPK_PP} / K_i, n)) * (K1 + MKKK))$

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

id	name	value
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

7.5 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.

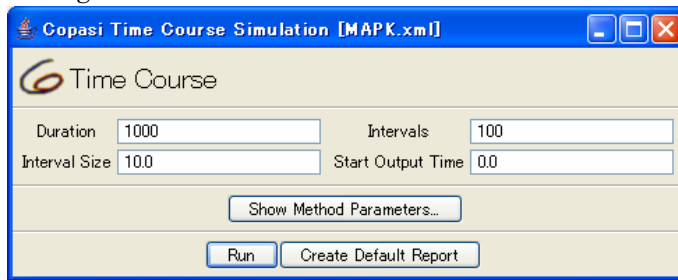
7.5.1 To setup COPASI to use with CellDesigner

1. Visit the Copasi web site at <http://www.copasi.org/>.
2. Download the Language Binding for Java
(e.g. `copasi-java-buildxx-win32.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.

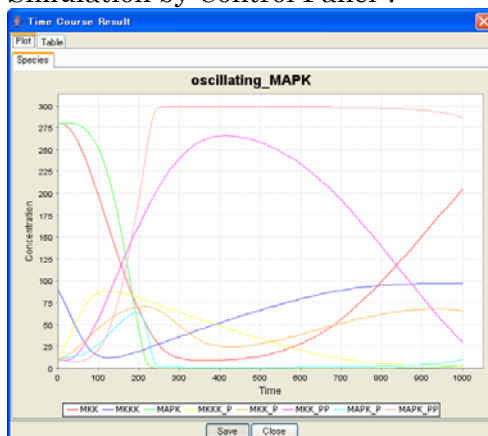
7.5.2 To simulate a model with COPASI

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”.

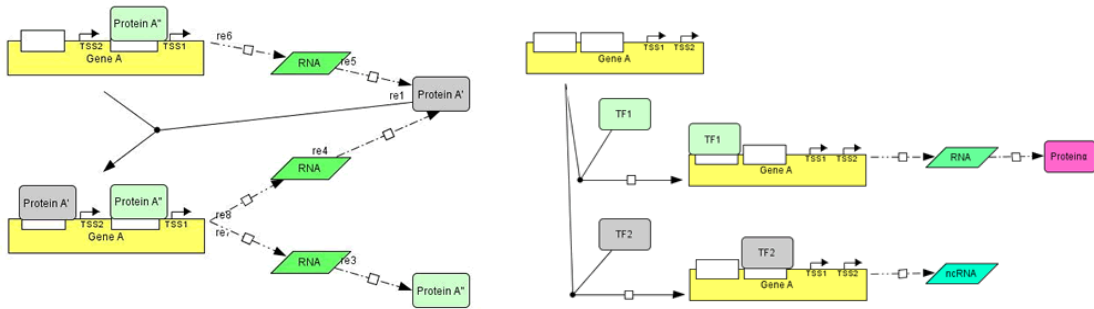


5. Click **Run**.
6. In the **Time Course Result** window, compare the result with the section “7.1 Simulation by Control Panel”.



8. Gene / RNA / AntiSenseRNA Structure Expressions

The graphical notation is extended and redefined to enhance representation capability for transcription and translation processes. The most salient feature is capability to describe promoter structure, and other detailed structure for genes and RNAs.

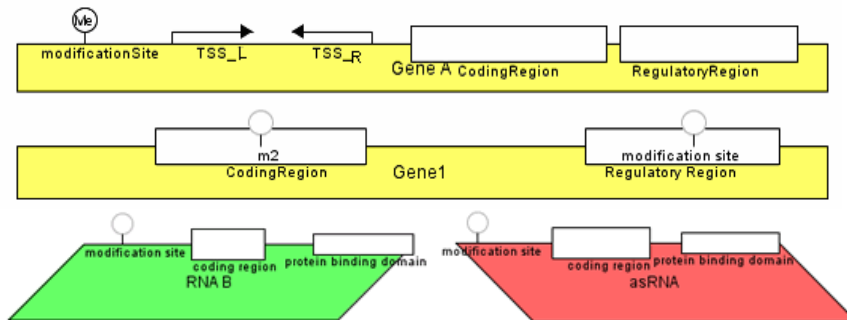


→ See also: [Appendix 2: Sample Files for Graphical Notation].

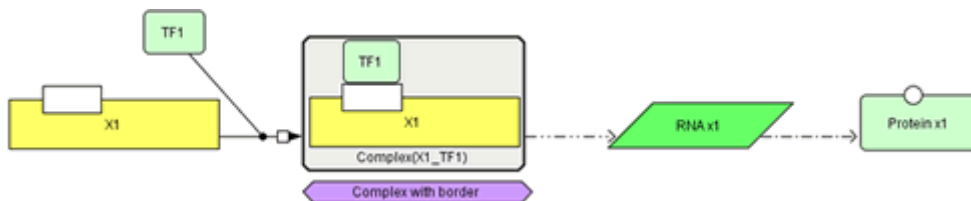
8.1 Promoter Structure Representation

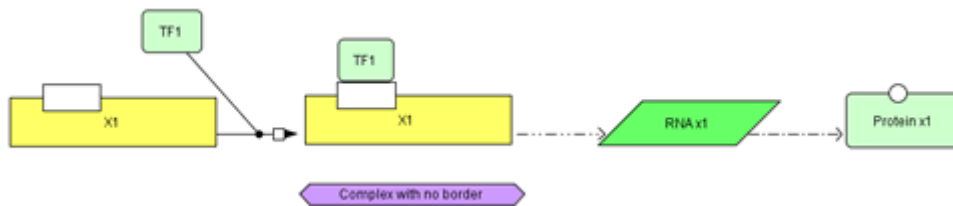
CellDesigner allows users to define the structure of promoter regions. Specific promoter regions are represented on upper part of the box. When such structure information is defined, lines for both sides and lower part of the box are either not shown or dimmed to highlight structures represented on the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

8.1.1 Symbols related to transcription and translation



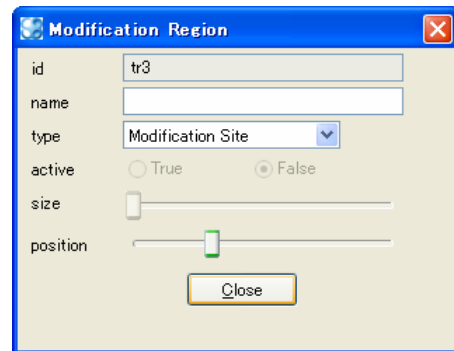
8.1.2 A usage example transcription related symbols





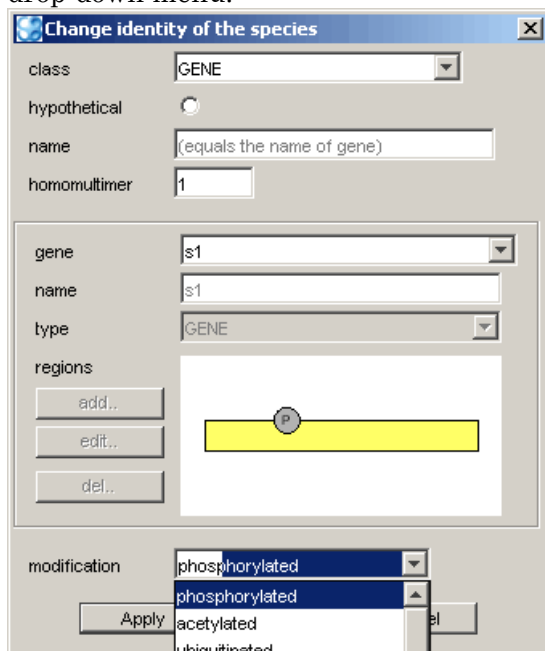
8.1.3 To specify region symbols

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**.
4. Click **Close**.
5. Click **Update**.



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

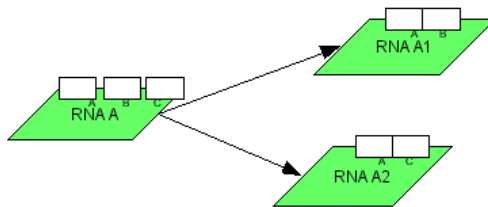
1. Right-click on a Gene.
2. Select **Change Identity...** from the menu.
3. Click the target empty region and change the **modification** status from the drop-down menu.



4. Click **Apply**.

8.2 Alternative Splicing

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



8.3 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.

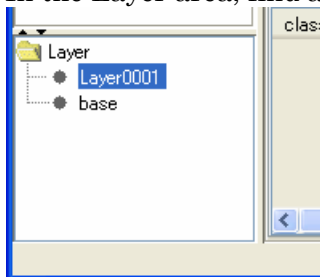
9. Layer

You can add a layer to give comments to the components. 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.

9.1 Add a Layer

9.1.1 To add a layer

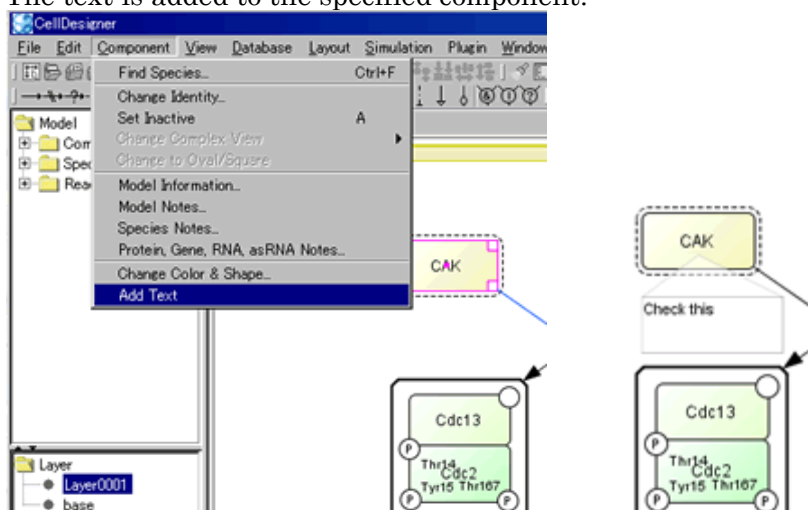
1. Select **Edit** → **Add Layer** in the Menu.
2. **LayerNameInputDialog** is displayed.
3. Specify the **Layer Name**, then click **Add Layer** button.
4. In the Layer area, find a new layer has been added to the list.




9.2 Add Text and Shapes on a Layer

9.2.1 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.



9.2.2 To add a Layer Object onto a layer

1. In the Tool bar, select an icon out of the different Layer Objects.

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

9.2.3 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**

9.3 Manage a Layer

9.3.1 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.

9.3.2 To set invisible the Layer Objects on a layer

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.

9.3.3 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.

10. 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 Diagram Level 1 draft as of May 2008.

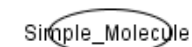
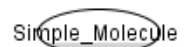
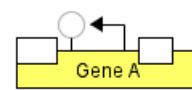
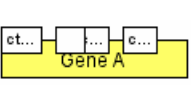
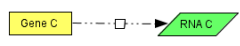

10.1 Use the SBGN Viewer

10.1.1 To view a model with the SBGN Viewer

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

→ **Note:** Difference In Graphical Notations---CellDesigner's Original and SBGN
There are some differences in graphical representation between the two.

	CellDesigner	SBGN Viewer
Activated -> State Active		
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).		
<ul style="list-style-type: none"> • Protein-Generic type (activated) • Protein-Ion_Channel type (activated) 		
Various Species Types -> Generic Species		
In SBML viewer, various Species shapes are represented by rounded square.		
<ul style="list-style-type: none"> • Protein-Receptor type • Protein-Truncated type • Protein-Ion_Channel type • RNA • Antisense RNA 		
Clone Marker		
If a Species is duplicated on a map, it is indicated by using the clone marker (bottom part shaded)		
<ul style="list-style-type: none"> • Ion 		

<ul style="list-style-type: none"> • Simple molecule 		
Resides/Domains etc -> Information box		
Gene / RNA / asRNA with Coding Region, Modification Site, Transcription Starting Site, and Regulatory Region		
Transcription / Translation		
Reactions of Transcription and translation are converted into the reactions with triggers.		
<ul style="list-style-type: none"> • Transcription 		
<ul style="list-style-type: none"> • Translation 		

11. Limitations and Known Issues

11.1 Limitations

Available actions of UNDO and REDO are limited to actions making change on the draw canvas.

11.2 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

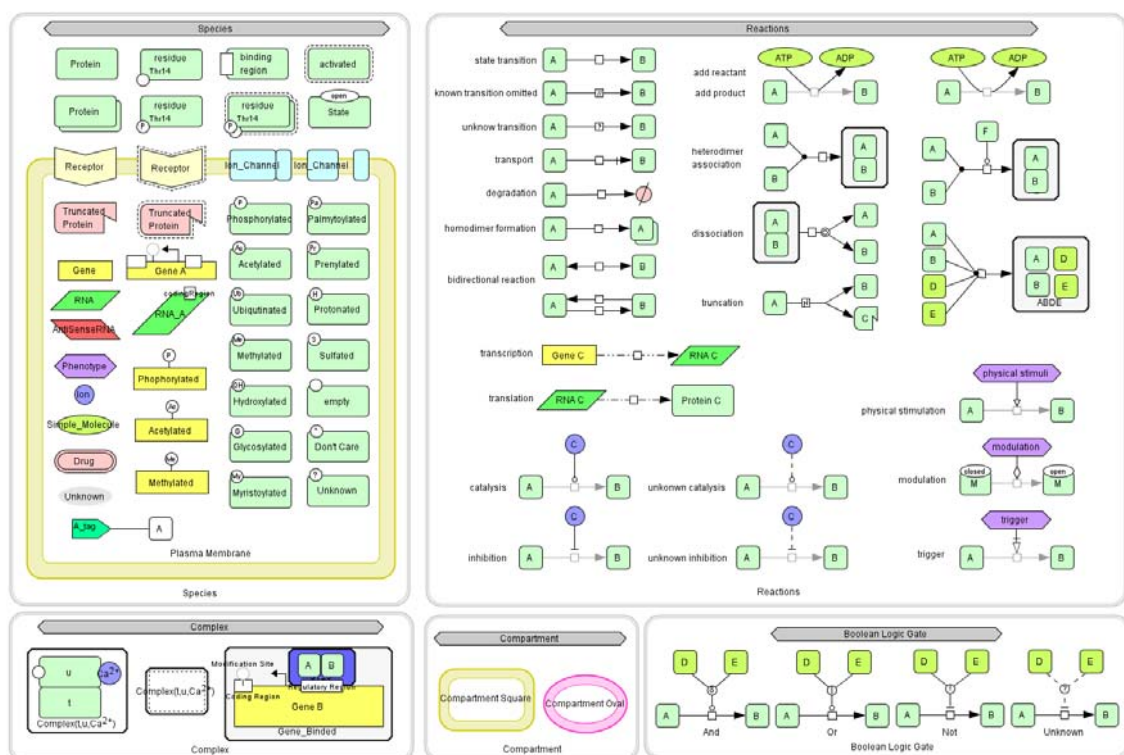
This section lists up all the symbols for building models with CellDesigner.

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.)



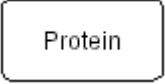
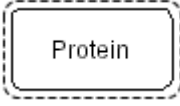
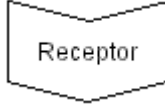





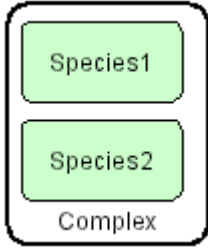

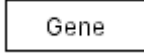
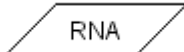
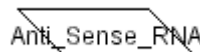
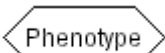

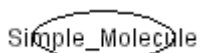
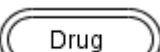
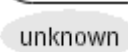

A sample file : Components40.xml

→ Note: All the graphical symbols used in CellDesigner will be found in the file “<your CellDesigner folder>/samples/components40.xml”.

A1.1 Basic Symbols

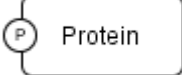
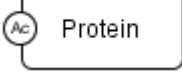
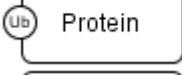
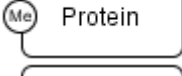
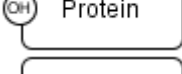
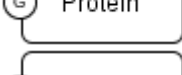
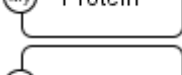
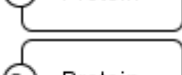
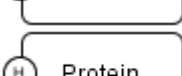
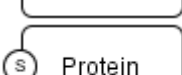
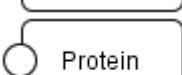
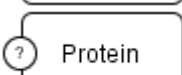
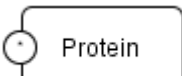

A1.1.1 Species

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

Species	not activated	activated
Protein -Generic		
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		n/a


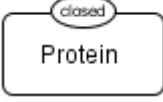
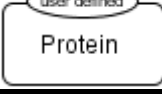
A1.1.2 Modifications of Protein Residues

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

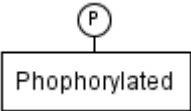

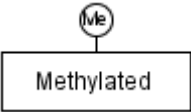

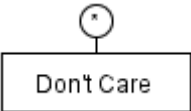
A1.1.3 State of Proteins

New to Version 4.0: Now you can define the State of the Species.

State	Symbol
Open	
Closed	
User defined	

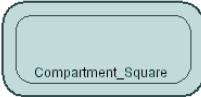


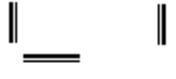
A1.1.4 Modifications of Gene / RNA / AntiSenseRNA Residues

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	

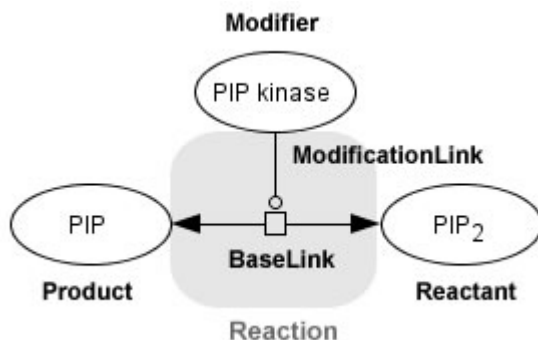
A1.1.5 Compartment

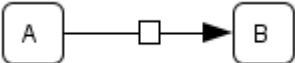

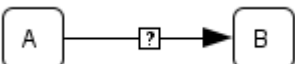
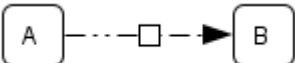
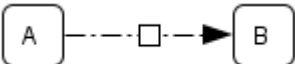
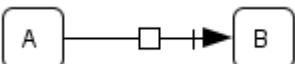
There are 4 types of Compartment symbols. For each type, the thick line indicates outside of its boundary.

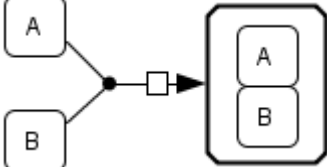
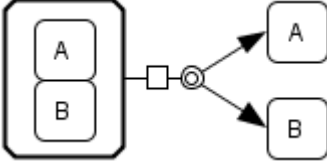
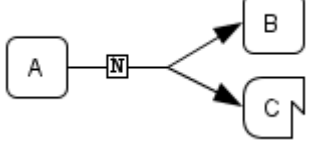
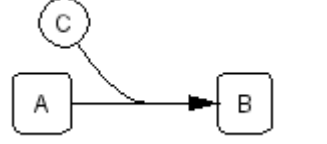
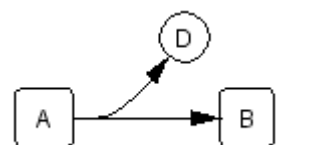
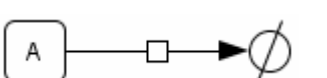
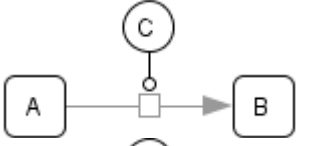
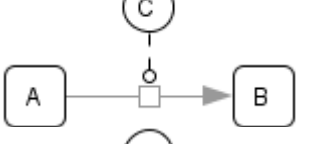
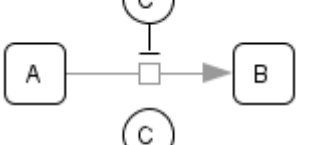
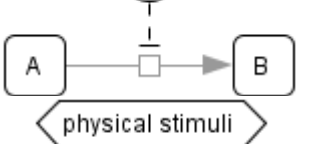
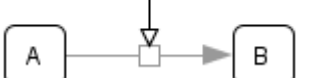
Type	Symbol	Note
Square		
Oval		
Close-up type		Northwest, Northeast Southwest, Southeast
Close-up type		West, East North, South

A1.1.6 Reaction

Symbols for Reactions are as follows.



Reactions	Symbol	Note
State Transition		
Known Transition Omitted		Abbreviated symbol of several Reactions
Unknown Transition		
Transcription		
Translation		
Transport		

Reactions	Symbol	Note
Heterodimer Association		
Dissociation		
Truncation		Dissociation of Proteins by truncation.
Add Reactant		
Add Product		
Degradation		
Modifications		
Catalysis		
Unknown Catalysis		
Inhibition		
Unknown Inhibition		
Physical Stimulation		

Reactions	Symbol	Note
Modulation		
Trigger		

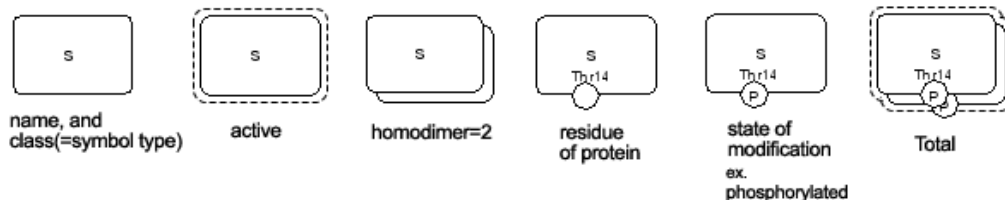
A1.1.7 Logical Operation

There are 4 types of **Logical Operation** symbols.

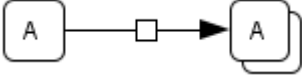
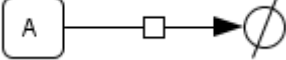
Logical Operations	Symbol
And	
Or	
Not	
Unknown	

A1.2 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 .
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. Set Change Complex View to normal / compact / no border .
Complex		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.

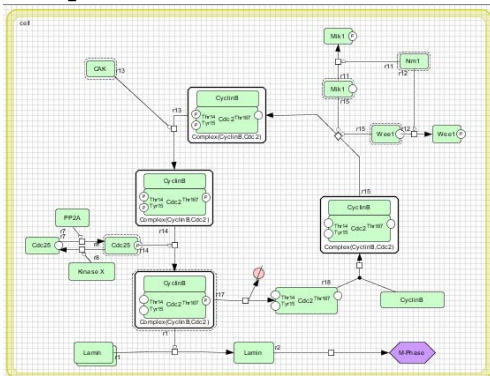
Expression	Symbol	Note
Homodimer Formation		Click the icon of Homodimer Formation .
Degradation of Species		Click the icon of Degradation .

Appendix 2: Sample Files for Graphical Notation

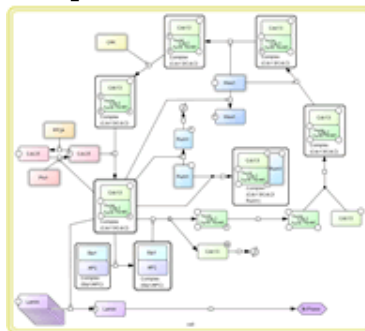
To explore new graphical notation scheme, there are sample files available in this version. Please open the files in the /samples directory and try editing the model.

A2.1 Examples of the sample files contained in the CellDesigner

/samples/M-Phase.xml



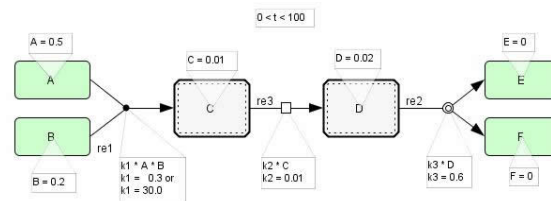
/samples/M-Phase2.xml



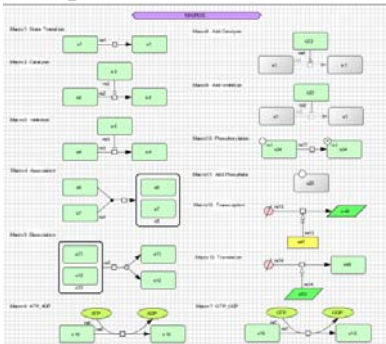
/samples/MAPK.xml



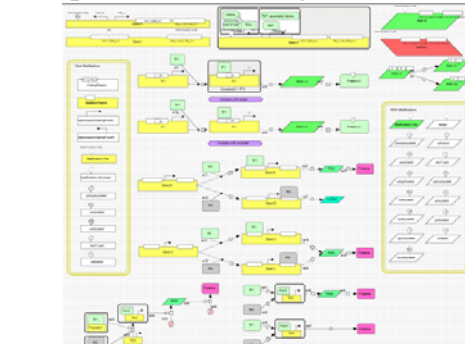
/samples/sim2.xml



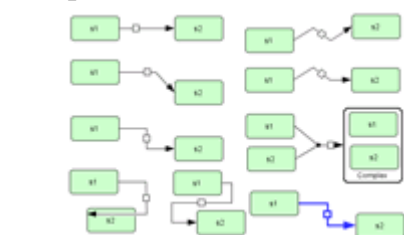
/samples/Macros.xml



/samples/notation/generNA40.xml



/samples/notation/ReactionShape.xml



/samples/notation/Complex40.xml



A2.2 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

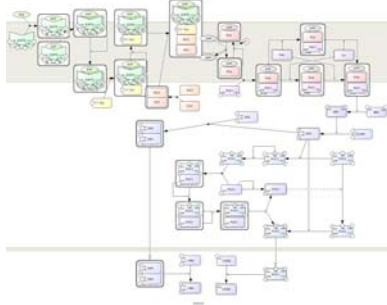


Fig3abcd_AndOr_4

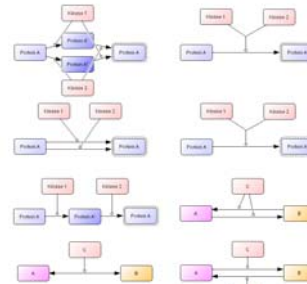
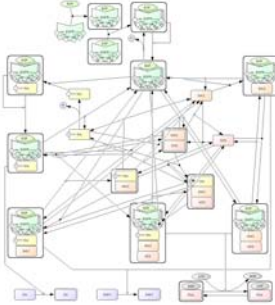
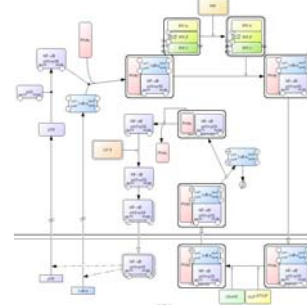


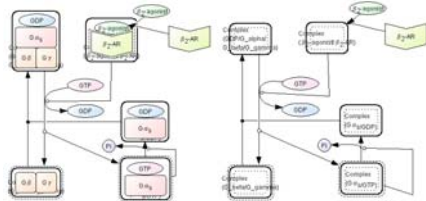
Fig3e_EGFR_league_4



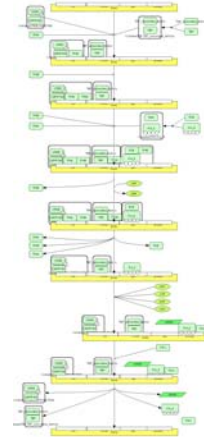
SuplFig3_NF-kappaB(p65+p50)_4



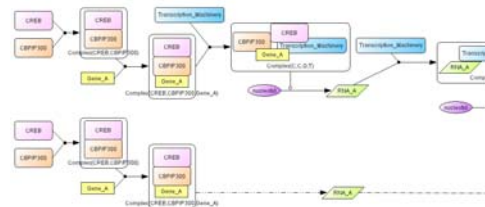
SuplFig2_GPCR beta2-AR_4



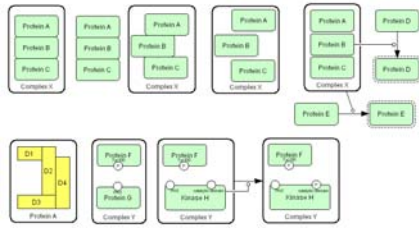
SuplFig4b_transcription_4



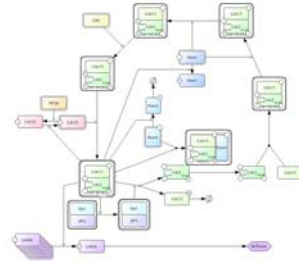
SuplFig4a_TranscriptionTranslation_4



SuplFig5_StructureofComplex_4



SuplFig7_M-Phase_4



A2.3 CellDesigner Species / Reactions Conventions

