CellDesigner™ Startup Guide

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Acknowledgements

- Rainer Machné and Christoph Flamm at University of Vienna for providing us a library version of SBML ODE Solver (SOSlib).
- Ralph Gauges, Sven Sahle and Ursula Kummer at University of Heidelberg for the development of a library version of COPASI.
- Frank Bergmann and Herbert Sauro at University of Washington for helping us support SBW-2.x on CellDesigner.
- Many thanks to the users who kindly provided us bug reports and feature requests!
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A. What is CellDesigner™

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

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](http://sbml.org) website.

SBML format

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

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](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.

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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 library for CellDesigner application
  | +celldesigner.jar
  | +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 |
  + sbmlj.jar |
  + SBWCore.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 |
  + /celledesigner |
  + 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 sample for various components |
| +components40.xml sample for database connections |
| +database.xml sample for model editing |
| +M-Phase.xml sample for model editing |
| +M-Phase2.xml sample for macros |
| +Macros.xml sample for simulation provided by SBML ODE Solver |
| +MAPK.xml |
| +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 CellDesigner 4.0 in your desktop.
2. Or double click \texttt{CellDesigner4.0.exe} in the directory where you chose to install (\texttt{C:/Program Files/CellDesigner4.0} by default).

1.5.2 Mac OS X

1. Double click the CellDesigner 4.0 icon in the folder you chose to install (\texttt{/Applications/CellDesigner4.0} by default).

1.5.3 Linux

1. On a shell, type \texttt{./runCellDesigner4.0} in your home directory.
2. Or type \texttt{./runCellDesigner4.0} after changing to the directory where you chose to install (\texttt{CellDesigner4.0} in your 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] | [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
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.

   ![Diagram of two species and a reaction](image)

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

   ![Tool bar icons](image)

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.

   ![Diagram of a complex reaction](image)

2.13 Create a Complex

2.13.1 To create a Complex

1. Click a Complex icon on the tool bar.

   ![Complex icon](image)

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.

   ![Diagram of species in complex](image)

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

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 Gene, 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](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.)
- **SGD** (Saccharomyces Genome Database)
  [http://yeastgenome.org/](http://yeastgenome.org/)
- **iHOP** (Information Hyperlinked over Proteins)
- **Genome Network Platform**
- **PubMed**
- **Entrez Gene**
- **BioModels.net**
  [http://www.biocass model.net](http://www.biocass model.net), [http://www.ebi.ac.uk/biomodels/](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).
3. 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](http://biomodels.net)) is a data resource that allows biologists to store, search and retrieve published mathematical models of biological interests. Models present in BioModels Database are annotated and linked to relevant data resources, such as publications, databases of compounds and pathways.

1. 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.

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.

<table>
<thead>
<tr>
<th>Modification Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphorylated</td>
</tr>
<tr>
<td>Acetylated</td>
</tr>
<tr>
<td>Ubiquitinated</td>
</tr>
<tr>
<td>Methylated</td>
</tr>
<tr>
<td>Hydroxylated</td>
</tr>
<tr>
<td>Glycosylated</td>
</tr>
<tr>
<td>Myristoylated</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>id</th>
<th>type</th>
<th>name</th>
</tr>
</thead>
<tbody>
<tr>
<td>pr1</td>
<td>GENERIC</td>
<td>p1</td>
</tr>
<tr>
<td>pr2</td>
<td>GENERIC</td>
<td>mySpecies</td>
</tr>
</tbody>
</table>

### 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

1. In the Menu, click **File – New** to create a new model.
2. Click on any type of Species icon from the Tool bar and place it on the canvas.
3. 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.
4. Select **File – Save as...** in the Menu.
5. Save the file in XML format.
6. 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="sal" 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_αβγ_endsub_

3) Complex of Cdc2 and CyclinB ("Cdc2" followed by "+CyclinB" in the new line).
   Cdc2_br__plus_CyclinB
   Cdc2_br_+CyclinB

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

6.1 Reaction ID

6.1.1 To show Reaction ID on canvas

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

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.

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.

![Diagram of Proteins A and B](image)

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”.

![Species table](image)

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.

![KineticLaw dialog](image)

10. The *Formula* dialog will be displayed.

![Formula dialog](image)

11. Type in “0.3” in the *k* text box, then click *OK*.
12. See that “sn*kn” has been entered in math field, then click Update, then Close.

![Kinetic Law](image)

13. 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

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

![Simulation Graph](image)
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.

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.

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.

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

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

![Diagram of MAPK pathway]
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.
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.

   \[ k_3 \times \text{MKK}_P \times \text{MKK} / (k_3 + \text{MKK}) \]

   - 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.

<table>
<thead>
<tr>
<th>Species</th>
<th>Parameters</th>
<th>Rules</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>scope</td>
<td>id name</td>
<td>value</td>
</tr>
<tr>
<td>local Reaction(k)</td>
<td>k3</td>
<td>0.025</td>
</tr>
<tr>
<td>local Reaction(k)</td>
<td>kr3</td>
<td>15.0</td>
</tr>
</tbody>
</table>

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

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

id | initialQuantity |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MKK</td>
<td>280</td>
</tr>
<tr>
<td>MKKK</td>
<td>90</td>
</tr>
<tr>
<td>MAPK</td>
<td>280</td>
</tr>
<tr>
<td>MKKK_P</td>
<td>10</td>
</tr>
<tr>
<td>MKK_P</td>
<td>10</td>
</tr>
<tr>
<td>MAPK_PP</td>
<td>10</td>
</tr>
<tr>
<td>MAPK_P</td>
<td>10</td>
</tr>
</tbody>
</table>

id | name | value |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>V1</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>Ki</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>K1</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>V2</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>KK2</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>
### 7.5 Simulation by COPASI

COPASI ([http://www.copasi.org/](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

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.

<table>
<thead>
<tr>
<th>Activated -&gt; State Active</th>
<th>CellDesigner</th>
<th>SBGN Viewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>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).</td>
<td><img src="image1" alt="CellDesigner Activated State" /></td>
<td><img src="image2" alt="SBGN Activated State" /></td>
</tr>
<tr>
<td>• Protein–Generic type (activated)</td>
<td><img src="image3" alt="CellDesigner Generic Activated Protein" /></td>
<td><img src="image4" alt="SBGN Generic Activated Protein" /></td>
</tr>
<tr>
<td>• Protein–Ion_Channel type (activated)</td>
<td><img src="image5" alt="CellDesigner Ion_Channel Activated" /></td>
<td><img src="image6" alt="SBGN Ion_Channel Activated" /></td>
</tr>
</tbody>
</table>

### Various Species Types -> Generic Species

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

<table>
<thead>
<tr>
<th>Species Type</th>
<th>CellDesigner</th>
<th>SBGN Viewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Protein –Receptor type</td>
<td><img src="image7" alt="CellDesigner Receptor" /></td>
<td><img src="image8" alt="SBGN Receptor" /></td>
</tr>
<tr>
<td>• Protein –Truncated type</td>
<td><img src="image9" alt="CellDesigner Truncated Protein" /></td>
<td><img src="image10" alt="SBGN Truncated Protein" /></td>
</tr>
<tr>
<td>• Protein –Ion_Channel type</td>
<td><img src="image11" alt="CellDesigner Ion_Channel" /></td>
<td><img src="image12" alt="SBGN Ion_Channel" /></td>
</tr>
<tr>
<td>• RNA</td>
<td><img src="image13" alt="CellDesigner RNA" /></td>
<td><img src="image14" alt="SBGN RNA" /></td>
</tr>
<tr>
<td>• Antisense RNA</td>
<td>AntSenseRNA</td>
<td>AntSenseRNA</td>
</tr>
</tbody>
</table>

### Clone Marker

If a Species is duplicated on a map, it is indicated by using the clone marker (bottom part shaded)

<table>
<thead>
<tr>
<th>Species Type</th>
<th>CellDesigner</th>
<th>SBGN Viewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Ion</td>
<td><img src="image15" alt="CellDesigner Ion" /></td>
<td><img src="image16" alt="SBGN Ion" /></td>
</tr>
</tbody>
</table>
### 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.

- **Transcription**
- **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:


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.

<table>
<thead>
<tr>
<th>Species</th>
<th>not activated</th>
<th>activated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Generic</td>
<td>Protein</td>
<td>Protein</td>
</tr>
<tr>
<td>-Receptor</td>
<td>Receptor</td>
<td>Receptor</td>
</tr>
<tr>
<td>-Ion channel</td>
<td>Ion Channel</td>
<td>Ion Channel</td>
</tr>
<tr>
<td>-Truncated</td>
<td>Truncated Protein</td>
<td>Truncated Protein</td>
</tr>
<tr>
<td>Complex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gene</td>
<td>Gene</td>
<td>n/a</td>
</tr>
<tr>
<td>RNA</td>
<td>RNA</td>
<td>n/a</td>
</tr>
<tr>
<td>Anti-sense RNA</td>
<td>Anti_Sense_RNA</td>
<td>n/a</td>
</tr>
<tr>
<td>Phenotype</td>
<td>Phenotype</td>
<td>n/a</td>
</tr>
<tr>
<td>Ion</td>
<td>Ion</td>
<td>n/a</td>
</tr>
<tr>
<td>Simple Molecule</td>
<td>Simple_Molecule</td>
<td>n/a</td>
</tr>
<tr>
<td>Drug</td>
<td>Drug</td>
<td>n/a</td>
</tr>
<tr>
<td>Unknown</td>
<td>unknown</td>
<td>n/a</td>
</tr>
<tr>
<td>Tag</td>
<td>Tag</td>
<td>n/a</td>
</tr>
</tbody>
</table>
### 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.

<table>
<thead>
<tr>
<th>Modification</th>
<th>Symbol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphorylated</td>
<td>🥤 Protein</td>
</tr>
<tr>
<td>Acetylated</td>
<td>🍬 Protein</td>
</tr>
<tr>
<td>Ubiquitinated</td>
<td>🍤 Protein</td>
</tr>
<tr>
<td>Methylated</td>
<td>ℹ️ Protein</td>
</tr>
<tr>
<td>Hydroxylated</td>
<td>🍥 Protein</td>
</tr>
<tr>
<td>Glycosylated</td>
<td>🍺 Protein</td>
</tr>
<tr>
<td>Myristoylated</td>
<td>🍬 Protein</td>
</tr>
<tr>
<td>Palmytoylated</td>
<td>🍬 Protein</td>
</tr>
<tr>
<td>Prenylated</td>
<td>🍬 Protein</td>
</tr>
<tr>
<td>Protonated</td>
<td>ℹ️ Protein</td>
</tr>
<tr>
<td>Sulfated</td>
<td>ℹ️ Protein</td>
</tr>
<tr>
<td>Empty</td>
<td>🥤 Protein</td>
</tr>
<tr>
<td>Unknown</td>
<td>🍬 Protein</td>
</tr>
<tr>
<td>Don’t Care</td>
<td>🥤 Protein</td>
</tr>
</tbody>
</table>
A1.1.3 State of Proteins

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

<table>
<thead>
<tr>
<th>State</th>
<th>Symbol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open</td>
<td>Protein</td>
</tr>
<tr>
<td>Closed</td>
<td>Protein</td>
</tr>
<tr>
<td>User defined</td>
<td>Protein</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Modification Region</th>
<th>Symbol</th>
</tr>
</thead>
<tbody>
<tr>
<td>phosphorylated</td>
<td>Phosphorylated</td>
</tr>
<tr>
<td>acetylated</td>
<td>Acetylated</td>
</tr>
<tr>
<td>methylated</td>
<td>Methylated</td>
</tr>
<tr>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Don’t care</td>
<td>Don’t Care</td>
</tr>
</tbody>
</table>
A1.1.5 Compartment

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

<table>
<thead>
<tr>
<th>Type</th>
<th>Symbol</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Square</td>
<td><img src="Compartment_Square.png" alt="Compartment_Square.png" /></td>
<td></td>
</tr>
<tr>
<td>Oval</td>
<td><img src="Compartment_Oval.png" alt="Compartment_Oval.png" /></td>
<td></td>
</tr>
<tr>
<td>Close-up type</td>
<td><img src="Compartment_Close-up.png" alt="Compartment_Close-up.png" /></td>
<td>Northwest, Northeast Southwest, Southeast</td>
</tr>
<tr>
<td>Close-up type</td>
<td><img src="Compartment_Close-up.png" alt="Compartment_Close-up.png" /></td>
<td>West, East North, South</td>
</tr>
</tbody>
</table>

A1.1.6 Reaction

Symbols for Reactions are as follows.

![Reaction Diagram](Reaction_Diagram.png)

<table>
<thead>
<tr>
<th>Reactions</th>
<th>Symbol</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>State Transition</td>
<td><img src="State_Transition_Symbol.png" alt="State Transition Symbol" /></td>
<td></td>
</tr>
<tr>
<td>Known Transition Omitted</td>
<td><img src="Known_Transition_Omitted_Symbol.png" alt="Known Transition Omitted Symbol" /></td>
<td>Abbreviated symbol of several Reactions</td>
</tr>
<tr>
<td>Unknown Transition</td>
<td><img src="Unknown_Transition_Symbol.png" alt="Unknown Transition Symbol" /></td>
<td></td>
</tr>
<tr>
<td>Transcription</td>
<td><img src="Transcription_Symbol.png" alt="Transcription Symbol" /></td>
<td></td>
</tr>
<tr>
<td>Translation</td>
<td><img src="Translation_Symbol.png" alt="Translation Symbol" /></td>
<td></td>
</tr>
<tr>
<td>Transport</td>
<td><img src="Transport_Symbol.png" alt="Transport Symbol" /></td>
<td></td>
</tr>
</tbody>
</table>
### Reactions

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Symbol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterodimer Association</td>
<td><img src="image" alt="Diagram" /></td>
</tr>
<tr>
<td>Dissociation</td>
<td><img src="image" alt="Diagram" /></td>
</tr>
<tr>
<td>Truncation</td>
<td><img src="image" alt="Diagram" /></td>
</tr>
<tr>
<td>Add Reactant</td>
<td><img src="image" alt="Diagram" /></td>
</tr>
<tr>
<td>Add Product</td>
<td><img src="image" alt="Diagram" /></td>
</tr>
<tr>
<td>Degradation</td>
<td><img src="image" alt="Diagram" /></td>
</tr>
</tbody>
</table>

### Note
- Dissociation of Proteins by truncation.

### Modifications

<table>
<thead>
<tr>
<th>Modification</th>
<th>Symbol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catalysis</td>
<td><img src="image" alt="Diagram" /></td>
</tr>
<tr>
<td>Unknown Catalysis</td>
<td><img src="image" alt="Diagram" /></td>
</tr>
<tr>
<td>Inhibition</td>
<td><img src="image" alt="Diagram" /></td>
</tr>
<tr>
<td>Unknown Inhibition</td>
<td><img src="image" alt="Diagram" /></td>
</tr>
<tr>
<td>Physical Stimulation</td>
<td><img src="image" alt="Diagram" /></td>
</tr>
</tbody>
</table>
Reactions | Symbol | Note
---|---|---
Modulation

![Modulation Diagram](image)

Trigger

![Trigger Diagram](image)

A1.1.7 Logical Operation

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

<table>
<thead>
<tr>
<th>Logical Operations</th>
<th>Symbol</th>
</tr>
</thead>
</table>
| And

![And Diagram](image)

| Or

![Or Diagram](image)

| Not

![Not Diagram](image)

| Unknown

![Unknown Diagram](image)
A1.2 Expressions

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

<table>
<thead>
<tr>
<th>Expression</th>
<th>Symbol</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active</td>
<td><img src="image" alt="Protein" /> <img src="image" alt="Receptor" /></td>
<td>Select a Protein and, in the Component menu, select Set Active.</td>
</tr>
<tr>
<td>Channel Open</td>
<td><img src="image" alt="Ion Channel" /></td>
<td>Select an Ion Channel and, in the Component menu, select Set Active.</td>
</tr>
<tr>
<td>Species State Open / Closed</td>
<td><img src="image" alt="Protein" /> <img src="image" alt="Protein" /> <img src="image" alt="Protein" /></td>
<td>Double-click the Species to open the identity dialog, then set the Homodimer number. Set Change Complex View to normal / compact / no border. compact is used to hide the contents of the Complex. no border is mainly used for a Complex with Genes etc.</td>
</tr>
<tr>
<td>Homodimer formed</td>
<td><img src="image" alt="Protein" /> <img src="image" alt="CyclinB" /></td>
<td>Double-click the Species to open the identity dialog, then set Homodimer number.</td>
</tr>
<tr>
<td>Complex</td>
<td><img src="image" alt="Complex" /></td>
<td>Double-click the Species to open the Change identity of the species dialog, then select hypothetical. Double-click the Reaction, then set Reversible to True. Simply draw two state transitions and reposition them.</td>
</tr>
<tr>
<td>Complex in a Complex</td>
<td><img src="image" alt="hypothetical" /></td>
<td>Double-click the Species to open the Change identity of the species dialog, then select hypothetical. Double-click the Reaction, then set Reversible to True. Simply draw two state transitions and reposition them.</td>
</tr>
<tr>
<td>Reversible Reactions</td>
<td><img src="image" alt="A to B" /></td>
<td>Double-click the Species to open the Change identity of the species dialog, then select hypothetical. Double-click the Reaction, then set Reversible to True. Simply draw two state transitions and reposition them.</td>
</tr>
<tr>
<td>Bidirectional Reactions</td>
<td><img src="image" alt="A to B" /></td>
<td>Double-click the Species to open the Change identity of the species dialog, then select hypothetical. Double-click the Reaction, then set Reversible to True. Simply draw two state transitions and reposition them.</td>
</tr>
<tr>
<td>Expression</td>
<td>Symbol</td>
<td>Note</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>--------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Homodimer Formation</td>
<td><img src="image1.png" alt="Symbol" /></td>
<td>Click the icon of Homodimer Formation.</td>
</tr>
<tr>
<td>Degradation of Species</td>
<td><img src="image2.png" alt="Symbol" /></td>
<td>Click the icon of Degradation.</td>
</tr>
</tbody>
</table>
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
A2.3 CellDesigner Species / Reactions Conventions