

 **CellDesigner 3.0 alpha**
Preview Version of New Graphical Notation

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0 CellDesigner™ 3.0 alpha Preview Version: Major Features

CellDesigner 3.0 alpha release is a preview version of upcoming formal release. The intention of this preview release is to provide you with a feel of a new notation that enhanced previous process diagram into gene and RNA, as well as protein complex structures.

Please note that functions of this preview version is substantially restricted as the sole purpose of the alpha release is to show the new notation. Version 3.0 implements most part of notations described in Kitano, et al., "Using process diagrams for the graphical representation of biological networks," Nature Biotechnology, August 2005. (*The examples in the above paper are included as the sample files of this preview version.)

For any serious work, please use on-going version CellDesigner 2.2 (or 2.5 which will be released shortly).

Note: You can open and edit your SBML model (which includes a model created by CellDesigner 2.x), but you can **NOT SAVE YOUR MODEL** with this version. Although you can not save your model, you can export your model to image file (JPEG, PNG, SVG) for your publication, CSV and pure SBML file for simulation. The exported pure SBML file doesn't contain graphical information, but other information such as kinetic laws, parameters, initial concentrations etc. are stored.

Please let us know your feedback for the future development. Any information (bug report, request, and question) is greatly helpful. [mailto: info @ celldesigner.org](mailto:info@celldesigner.org)

[CellDesigner 3.0 alpha Major Features]

- New Graphical Notation
 - Complex (Heteromultimer) expression
 - Gene, RNA, AntiSensRNA expressions
 - Unlimited number of homomultimer
 - Reaction
 - ◇ Anchor points
 - ◇ Connection points
 - ◇ Line width control
- Edit Layout Functions Enhancements
 - Right click menu
 - Alignments
 - Fine adjustment by Up/Down/Right/Left keys
 - Select All

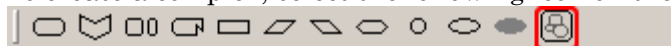
* Check <http://celldesigner.org> for details.

1 Complex – Heteromultimer Expression

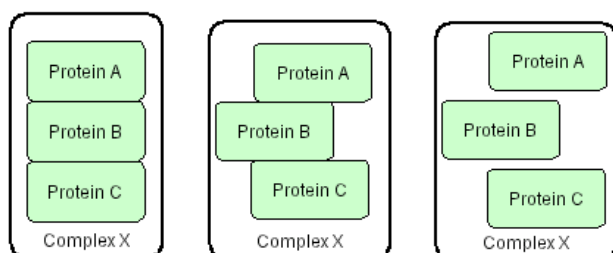
1.1 New type of Species: “Complex”

New type of Species “Complex” box is available.

To create a complex, select the following icon on the tool bar.



To form a complex, you just simply drag and drop the Species you want to add in the complex.



You can name the Complex of your choice. Name can be a simple name or a long name with all the names of the items included.

e.g. Complex(ProteinA,ProteinB,...)

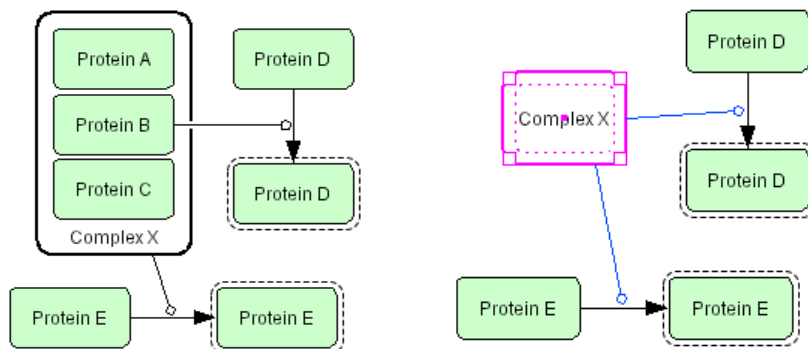
1.2 Relationship between Complex and Species inside

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

The notes of the individual Species will be maintained even though you move the Species in and out of the complex box.

1.3 Complexes and Reactions

Reaction can be connected from the Complex or from the individual component inside the complex. For example, you can distinguish if the activation is initiated by the complex as a whole or an individual Species inside the Complex.



You can pack the Complex view to hide the included components by [Component] – [Change Complex View] menu.

2 Reactions – for better layout

2.1 Connection Point of Reaction

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

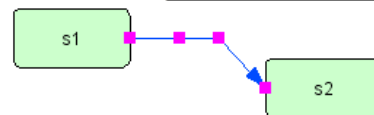
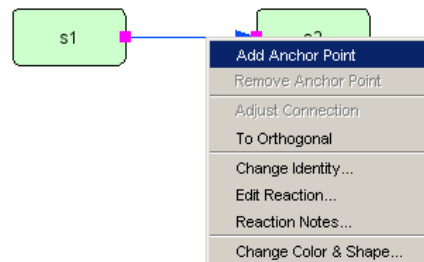


2.2 Anchor Points

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

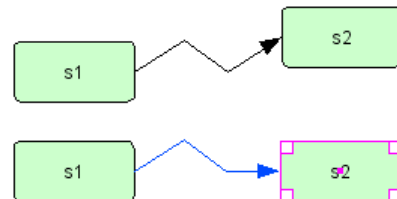
Selecting the point you want to add the anchor, and then click the right mouse button.

To remove the anchor point, click the right mouse button on the target anchor, then select “Remove Anchor Point”.



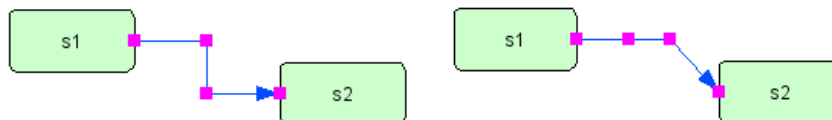
2.3 Move Segment

When the Species connected to the reaction is being moved, the last segment of the Reactions will be followed.

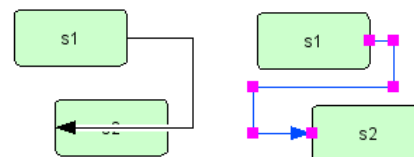


2.4 Drawing styles of the Connection

The drawing shape of the Reaction can be changed to Orthogonal / to Polyline.

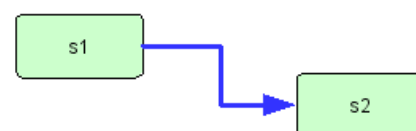


After you move the Species connected to the reaction, you can adjust the drawing line by selecting “Adjust Connection” menu. (Valid for Orthogonal style only.)



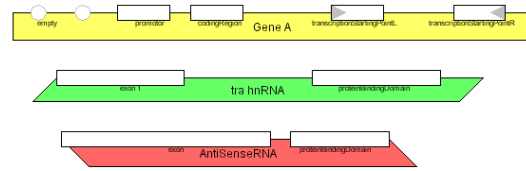
2.5 Line width and Colour Setting

Colors and line width of each Reaction can be specified as well as Species, and Compartment.



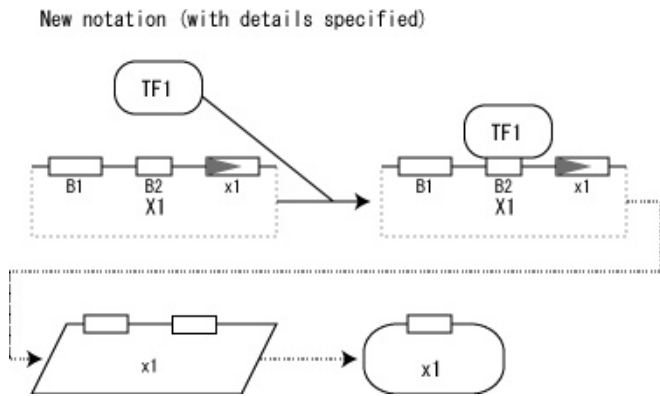
3 Gene / RNA / AntiSenseRNA Structure Expressions

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, exon segments, and other detailed structure for genes and RNAs.

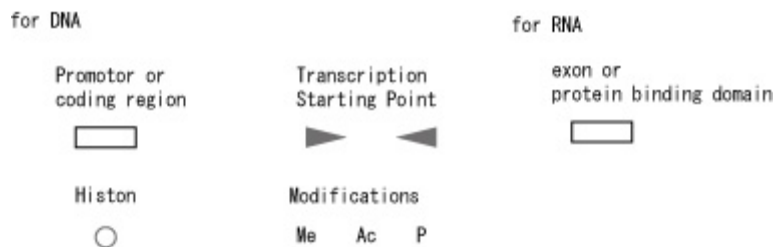


3.1 Promoter Structure Representation

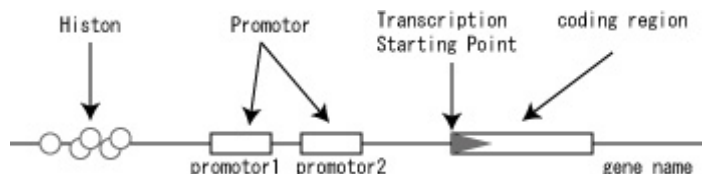
A new extension allows user to define structure of promoter region, exon, and histons. Specific promoter regions, exon, and histon are represented on upper part of the box. When such structure information is defined, lines for both sides and lower part of the box are either not shown or dimmed to highlight structures represented on the upper line.



3.1.1 Symbols related to transcription and translation



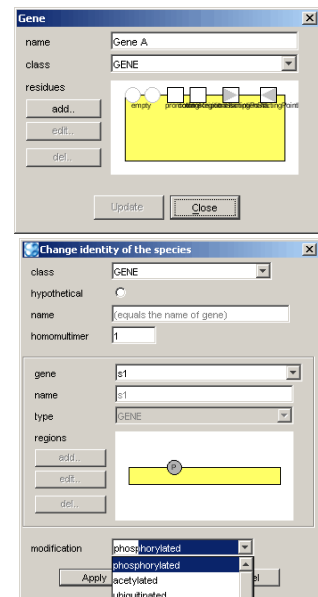
3.1.2 A usage example transcription related symbols



3.1.3 Specifying Region symbols and status

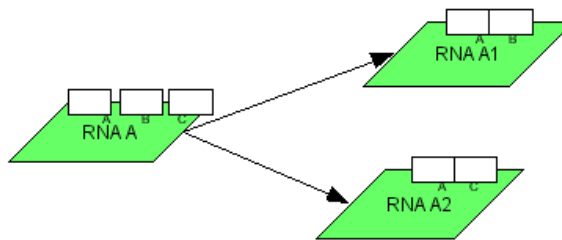
To specify the regions, click the target items and from the right click menu, select [Edit Gene/RNA/asRNA...]. Alternatively select the target from the Gene/RNA/asRNA lists. Add the region; select the type and location of your choice in the dialog box.

To change the status of the “empty” region of the gene, Select [Change Identity...] menu, click the target empty region and change the modification status.



3.2 Alternative Splicing

Alternative splicing can be represented as transition of RNA from original state to multiple RNA with different splicing patterns.



3.3 Identification of Gene, RNA, and AntiSenseRNA.

In the model, Genes, RNA and AntiSenseRNA are identified by their name. If the name of the newly created component is already available in the mode, the representation will become the same as the existing one.

4 Edit / Layout Assisting Functions

Not only new graphical notation scheme, CellDesigner 3.0 alpha provides some enhancement to assist in editing and layout your models.

4.1 Right Click Menu

Click on the target Species or Reaction with the right mouse button, the pop-up menu will be displayed. All the operations which can be conducted with the target are displayed in the menu.

4.2 Alignment

The following icons are available to adjust the alignment of the components. Select the multiple Species to adjust, and then click the icon of your choice.



4.3 Fine tuning by keyboard operation.

Species location can also be adjusted bit by bit using UP, DOWN, RIGHT, LEFT keys.

4.4 Select All

Select All [Ctrl + A]

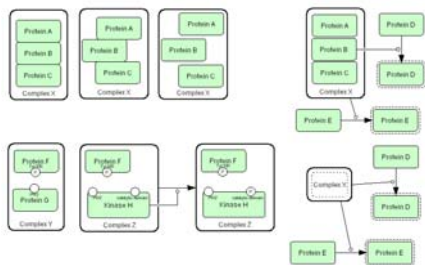
5 Sample Files

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

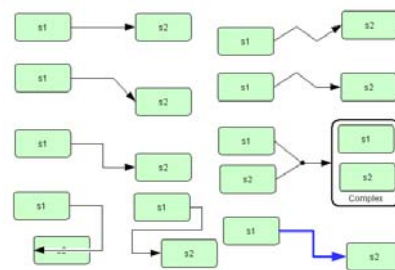
Caution: You cannot save the model in this preview version. You can export the images of the model or export the SBML files which saves the basic model data but without CellDesigner specific layout information.

5.1 Examples used in this document

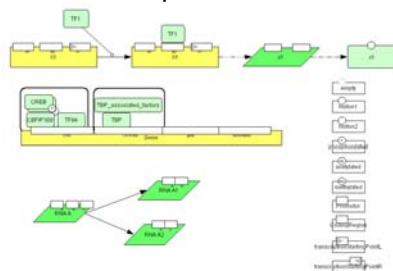
Complex.xml



geneRNA.xml



ReactionShape.xml



5.2 Examples for Graphical Notation

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

Fig1b_ProcessDiagram_3

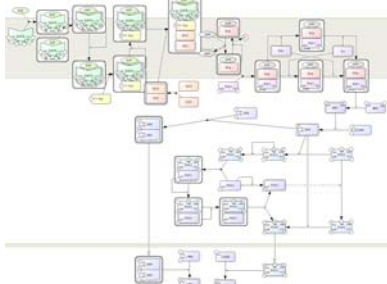


Fig3abcd_AndOr_3

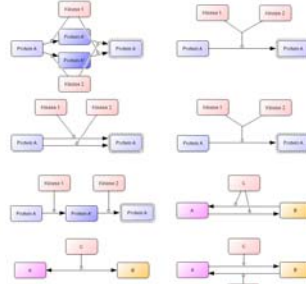
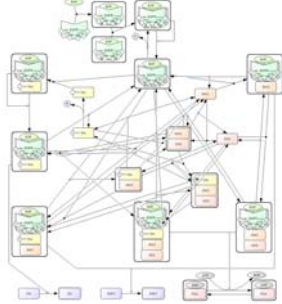
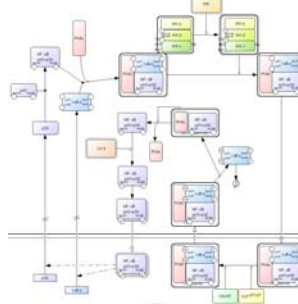


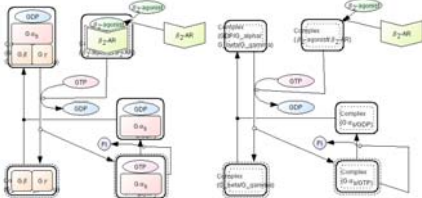
Fig3e_EGFR_league_3



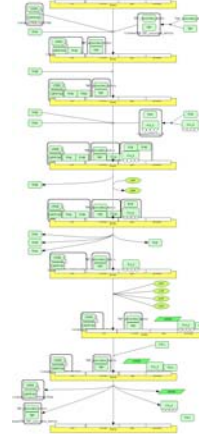
SuplFig3_NF-kappaB(p65+p50)_3



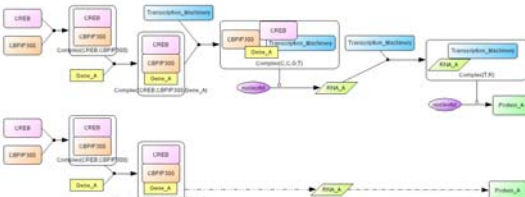
SuplFig2_GPCR beta2-AR_3



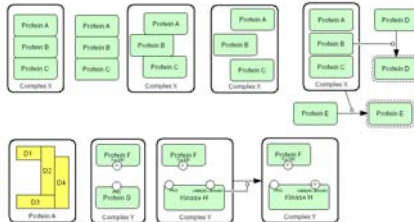
SuplFig4b_transcription_3



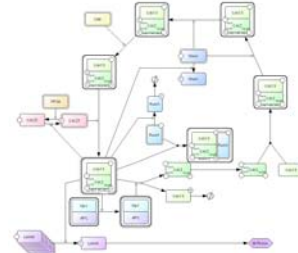
SuplFig4a_TranscriptionTranslation_3



SuplFig5_StructureofComplex_3

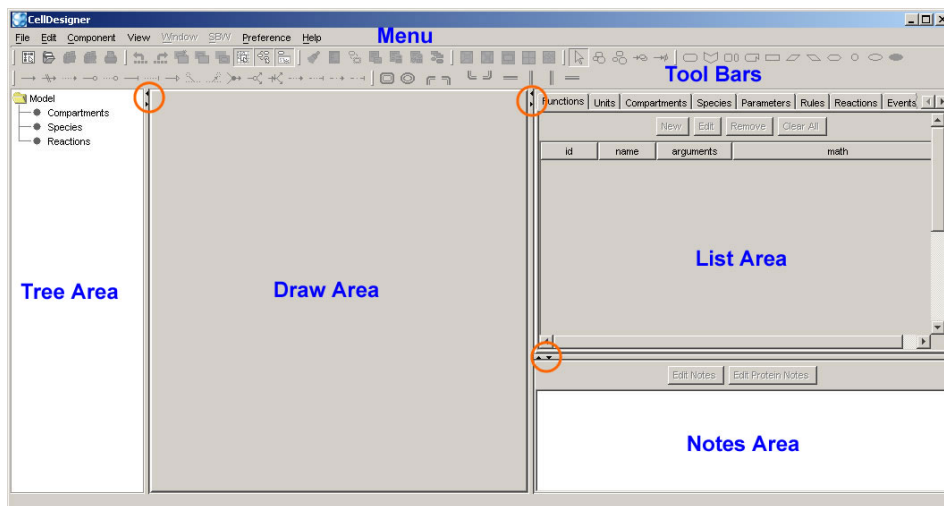


SuplFig7_M-Phase_3



6 Basics of CellDesigner

6.1 CellDesigner Screen and Navigation



CellDesigner consists of four areas as shown above:

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

Change the area size:

- The size of the area can be changed by dragging the border lines.
- To maximize the area, click the triangle icons on the borders.

Customize Tool bar:

- Each group of the icons can be detached from the Tool Bar.
- It can also move to the left side of the screen by dragging the handle to the left boundaries.

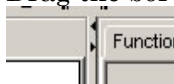
7 Quick Tutorials for Testing New Graphical Notation

This section is for beginners, and describes how to edit and what kind of model to be edited with CellDesigner in brief.

7.1 Open a File:

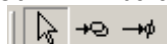
1. Select File – Open in main menu bar to open a sample file in samples directory.
A graphical network model is displayed on the Draw Area.

2. Drag the borders (left or right) of the draw area to change the area size



7.2 Select an Item:

3. Confirm "select/move" icon is highlighted (in select/move mode).



If not, click the icon.

7.3 Move / Delete an Item:

The objects highlighted in magenta are influenced by "move" and "delete" actions to the selected object.

Now,

4. Drag and move the **Species**,
5. Delete the **Species** and **Reactions** by using Backspace and / or Delete keys.

7.4 Compartment:

The other shape rounding overall is called **Compartment** in SBML.

6. Click the Compartment (click inside without any other shapes),
and see what are and how highlighted.
A **Compartment** can place **Species** and other **Compartments** inside.
7. Drag and move the Compartment, and confirm **Species** inside are on it.

7.5 Undo / Redo:

You can "undo" all of the past actions by [CTRL]-z, and then "redo" after undo by [CTRL]-y before saving the model. Try

8. Undo by [CTRL]-z,
9. Redo by [CTRL]-y.

7.6 Change the size of an item:

When selecting the **Species** and **Reactions**, you can see small squares appear. These are handles to change the size of **Species** and to bend the arrows of **Reactions**.

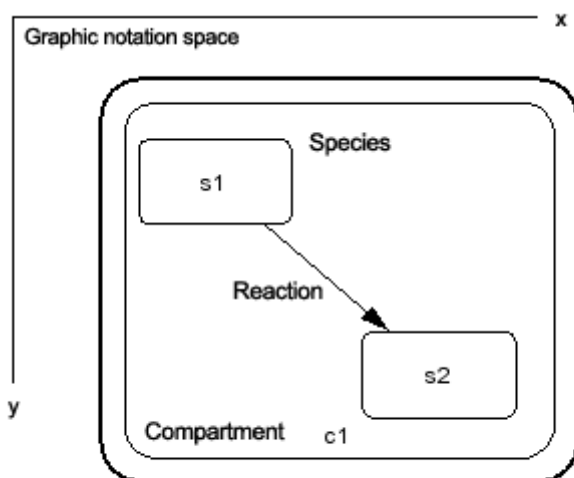
10. Drag the small squares and move.

7.7 Species and Reactions:

The **Species** represents, for example, proteins and other molecules in biochemical networks and genes in gene regulatory networks.

The **Reaction** represents, for example, biochemical reactions literally, interaction between proteins, and regulatory relations 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 [Section “Symbols and Expressions”].



Symbolic process expression of the CellDesigner

To change the symbols of **Species** / **Reactions**:

If you double click **Species** and **Reactions**, the dialog box will appear to alter its type.

11. Double click a **Species** (especially decorated one), click and change anything in the dialog box, and then, see what is changed after click "Apply" button.

7.8 Change the Shape of Compartments:

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

To change the shape of **Compartment**:

12. Select the **Compartment**,
13. Select Edit—Change to OVAL,
14. Then select Edit—Change to SQUARE.

7.9 Activate a Species:

15. Select **Species** and type "a" on keyboard, and see how it changes.

The **Species** are wrapped by dashed line.]

The dashed line has somewhat ambiguous meanings, indicating that **Species** are “active” without referring their targets.

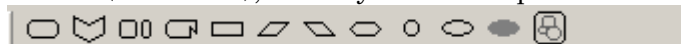
→ **See also** [Section 6.1.1 “Symbols and Expressions” “Basic Symbols”].

7.10 Create New Species, Reactions, and Compartment:

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

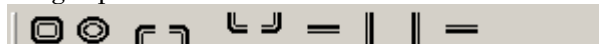
New Species:

17. Select an icon (placed in the tool bar) by click and then click a point on the canvas (draw area), where you want to place the new.



New Compartment:

18. Select an icon from the compartment bar (as shown below) by click and then drag a point to another on the canvas until the new becomes suitable size.



New Reaction:

19. Select an icon with an arrow on it,



and then link **Species** to **Species**/Reaction on canvas.

(in details) Click **Species** on canvas you want to link by the **Reaction** in the order of start-point(s) to end-point(s). **Reactions** themselves are allowed to be endpoints of other **Reactions**.

7.11 Add Notes to the Components:

You can add a note to any component (Species, Reaction, Compartment, and Protein).

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** [Section “Connect to Database”].

To add a note to the component:

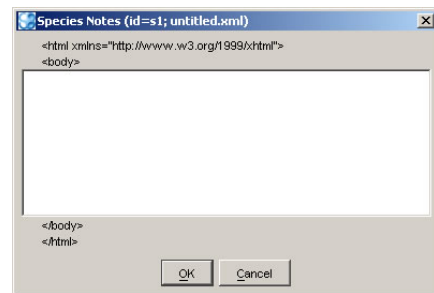
20. Select the target component (any Species, Reaction, Compartment, and Protein).

The current notes of the target component are displayed in the Notes window in the right-bottom corner of the window.

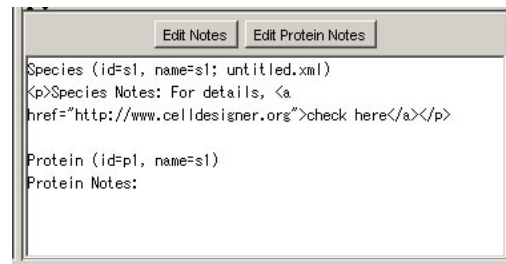
21. Click [Edit Notes] button.
Species Notes dialog will pop-up.

Note: If the target is a protein, you can also select [Edit Protein Notes].

22. Type the text you want to add as the notes to the component.
The text should be in XHTML format.



23. Then Click [OK] to close the dialog
The notes you have just added will be displayed in the notes window.



You can export the image of the model to either .PNG, .JPEG or .SVG format.

24. Select [File] – [Export Image...]
25. Then specify the name and the file format.
The image saved here is the same as displayed on screen.

7.13 Export List to CSV file:

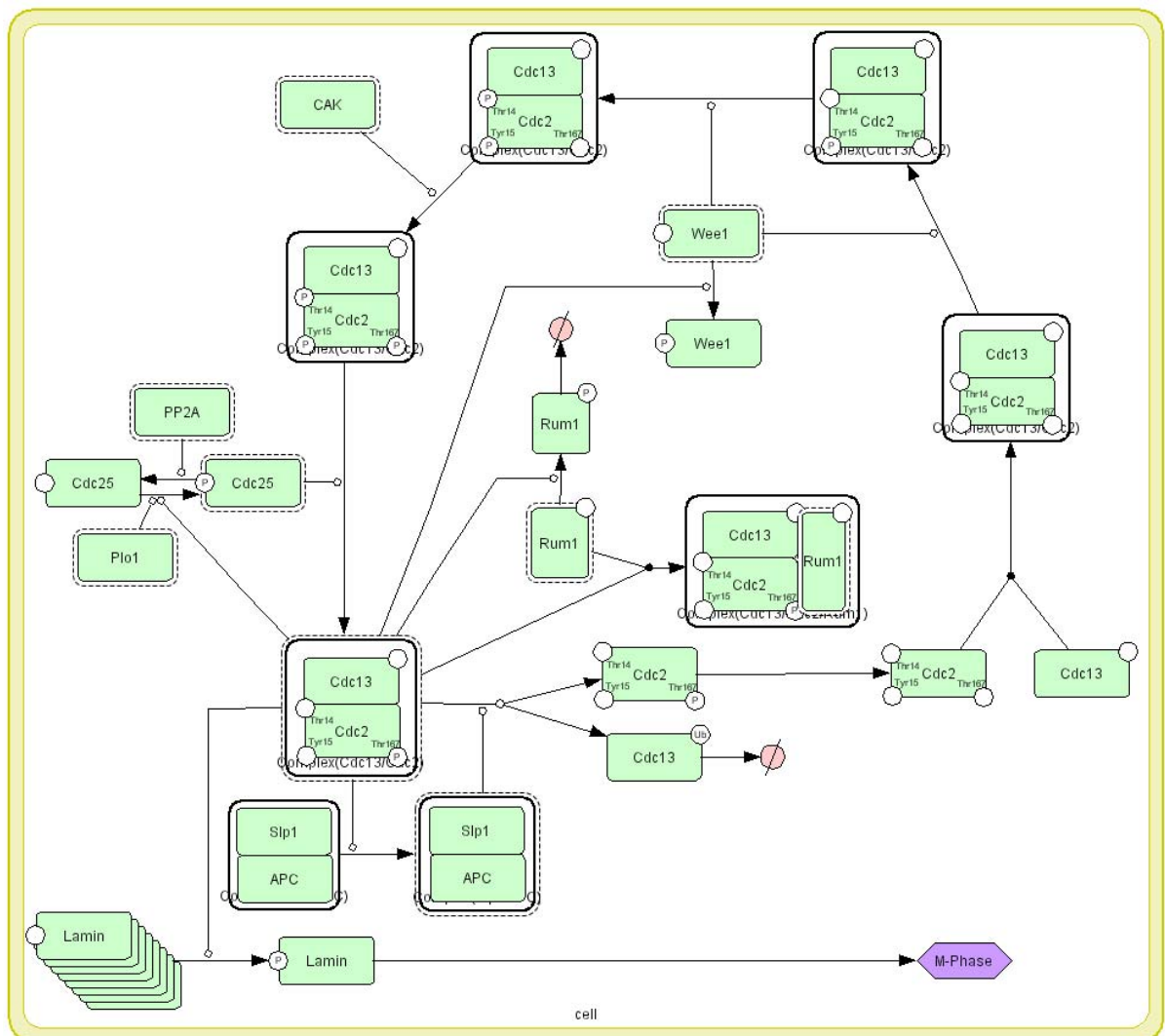
You can export the contents of the list into .CSV file format. This is useful when you want to check all the items specified in the model.

26. Select the [Species] tab in the list window.
27. Select [File] – [Export List to CSV...].then click [Save] to save the CSV file.
You may use other applications to check the contents of the CSV file.

8 Edit Proteins

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.

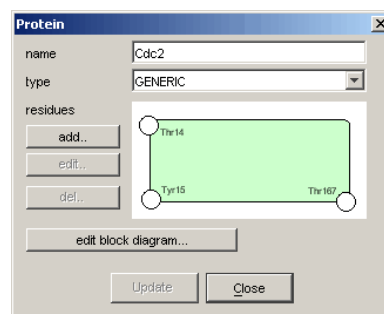
The model M-Phase2.xml, you see, describes state transition of "Cdc2," where there are five "Cdc2"s. The five represent different **Species**, while essentially the same protein. Therefore, CellDesigner should handle data structure describing each protein in a model, so that several protein-type **Species** could have references to the same protein data. This data structure is called **Protein**.



8.1 Check and Change Protein Property

You can see this Protein data by selecting the Protein tab in the List Area. If you cannot see the Protein tab, click on the right arrow in the upper right corner of the List Area, and adjust the size of the List window appropriately.

1. Select "Cdc2" in the list and click Edit button. The Protein dialog will appear. In this dialog, you can edit several properties of Protein, name, class, and residues (add, edit, and delete).



Changes in this dialog are reflected to all **Species** referring to this Protein.

The changes are also reflected to Heterodimers (complex of several **Species**) including such **Species**, as you expect.

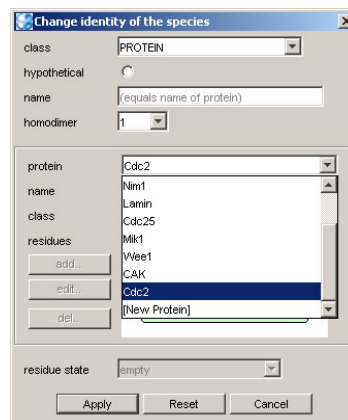
8.2 Residue of Proteins

The residues of proteins can be added in the Protein dialog, but the modification of the residue status (such as phosphorylated, etc.) is NOT maintained as Protein's property, but as **Species**' identity.

1. Therefore, modifications are edited by
2. Double-click **Species** in "select/move" mode. In the dialog appeared, you can change the modification types.

Note: You cannot add, edit, or delete modification residues in "Change Species Identity" dialog.

A Protein referred by the **Species** can be selected in the "Protein" pulldown in the dialog. If you want new protein, not listed in the "Protein" pulldown, select [New Protein] listed at the last and you can edit the new Protein here. Only in this case you can add, edit, and delete residues.



9 Convenient Edit Functions

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

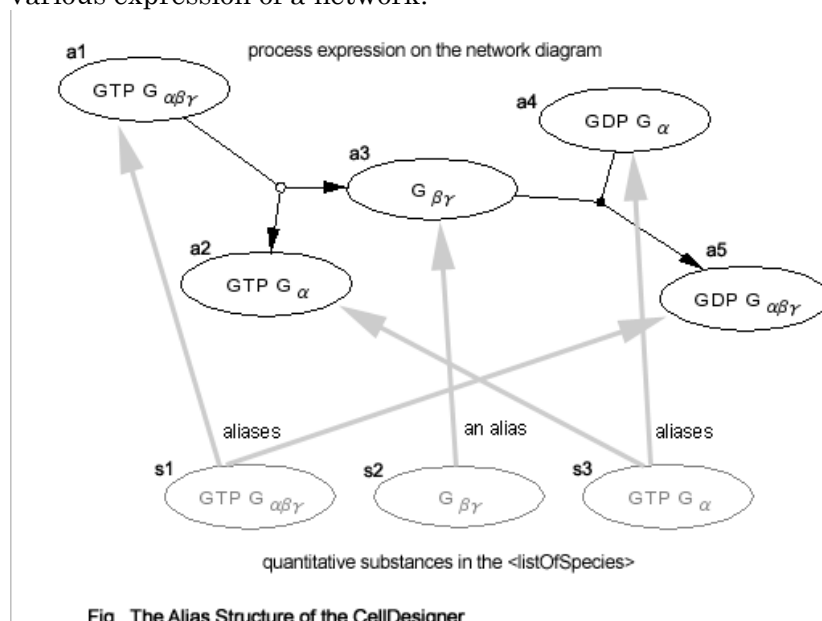
9.1 Temporal “select/move” mode

When constructing a model using buttons on toolbars to create new **Species**, **Reactions**, and **Compartments** (in “create new” mode), you cannot move any components unless click the select/move icon. In model building, creating new components and layout them are likely to be repeated successively. In such case, holding “s” key on your keyboard down makes the current edit mode to “select/move” temporally. After moving some components by drag, releasing the key makes the edit mode to “create new” immediately.

Note: If you want to create components one by one, select “Input Repeat” in Edit menu to OFF the checkmark.

9.2 Cut, Copy and Paste

In “select/move” mode, selected **Species** can be cut / copied to CellDesigner’s internal clipboard by [CTRL]-x / [CTRL]-c, and pasted to the edit canvas by [CTRL]-v. The copy-and-paste action makes “real” copies of the selected **Species**, which are **SpeciesAliases** in CellDesigner’s terminology, referring the original **Species**. Strictly speaking, all of the **Species** on edit canvas are **SpeciesAliases** referring each original **Species**. By this feature, CellDesigner has multiple copies of the same **Species** on an edit canvas (i.e. a model), to possess ability to make various expression of a network.



9.3 Select All

To select All the components in the model, [Ctrl]+A or specify [Select All] in the [Component] menu.

9.4 Grouping

In “select/move” mode, by clicking multiple **Species** while holding the SHIFT key down, you can make a temporal group of the selecting **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.

9.5 Alignment

The following icons are available to adjust the alignment of the components. Select the multiple Species to adjust, and then click the icon of your choice.



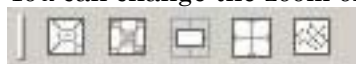
9.6 Set Grid Snap ON/OFF

Snapping components on grid makes it easier to layout the pathway diagram. Try the followings from Edit menu.

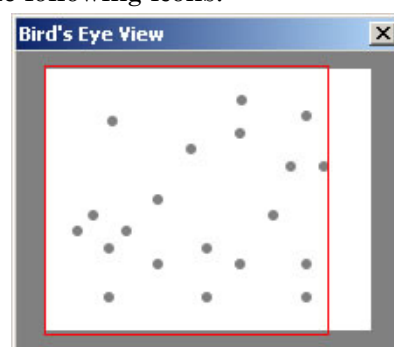
- Set Grids Size...
- Grid Snap
- Grid Visible

9.7 Zoom IN/OUT, Bird's Eye View

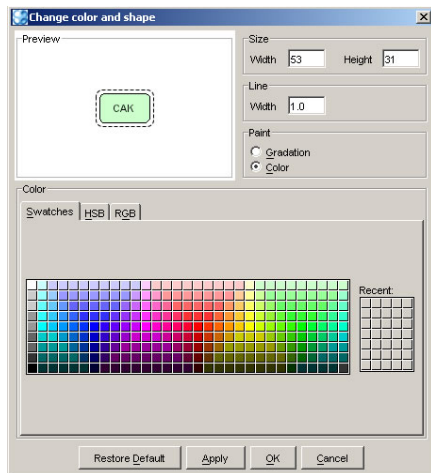
You can change the zoom of the display by clicking the following icons.



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 right most icon of the above tool bar. When you click the position you want to display in the Bird's Eye View, you can move to the specified position.



9.8 Change Color and Shape



You can change the color and shape of the **Species**, **Compartments** and **Reactions** individually or their default settings.

To change the default settings of the color and shape, select the Preference menu.

To change the color and shape of the individual components, select the components to edit, and then select the icon of Change Color & Shape



in the tool bar.

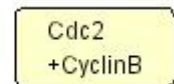
9.9 Display special characters in Component name

As CellDesigner is compliant to SBML, all names of components in a model must be conforming to the SBML convention. CellDesigner 2.0 is now compliant to 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.

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, check [“Name Expression” at Help menu](#).

Caution: 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.

10 Symbols and Expressions

In this section, symbols for building models with CellDesigner are listed. Graphical notation and listing of the symbols are based on proposal by Kitano (<http://www.sbw-sbml.org/workshops/sixth/sbmlsbwstockholm.htm>) and (Nature Biotech. Xxxxxx). The symbol system for state-transition diagram and the residue state representation among the proposal are almost realized with CellDesigner.

10.1 Basic Symbols

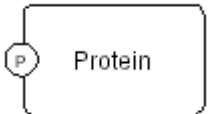
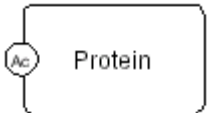
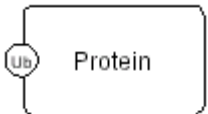
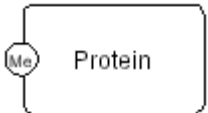

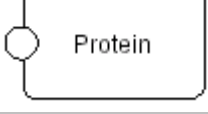
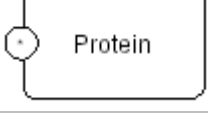
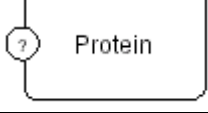
10.1.1 Species

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

Species		activated
protein Generic		
protein Receptor		
protein Ion channel		
protein truncated		
gene		
RNA		
Anti-sense RNA		
phenotype		
ion		
simple molecule		


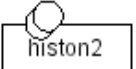
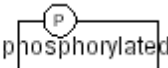
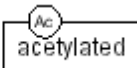
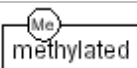
10.1.2 Modifications of Protein Residues

There are seven 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**.

Phosphorylated	
Acetylated	
Ubiquitinated	
Methylated	
Hydroxylated	
Empty	
Don't Care	
Unknown	




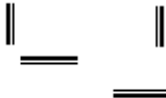
10.1.3 Modifications of Gene Region

There are seven types of symbols for Gene region modification states.

histon1	
histon2	
phosphorylated	
acetylated	
methylated	

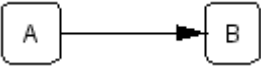
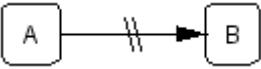
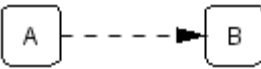
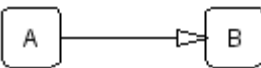
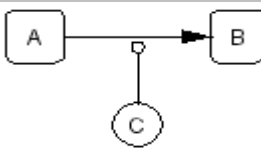
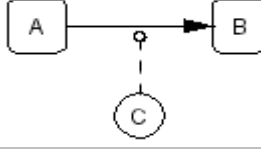
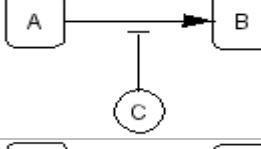
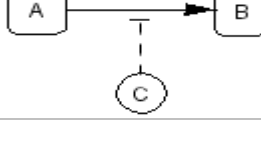
10.1.4 Compartment

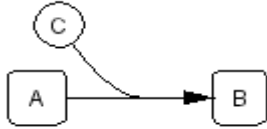
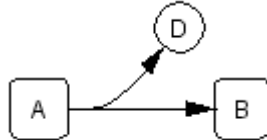
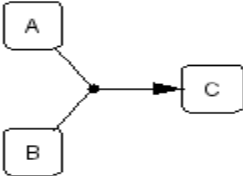
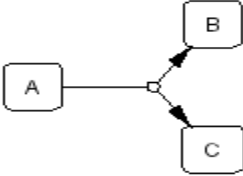
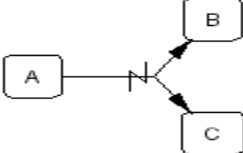
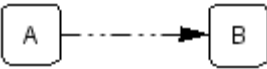
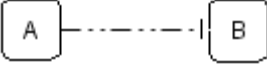

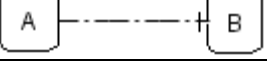
There are ten types of Compartment symbols. For each type, the thick line indicates outside of its boundary.

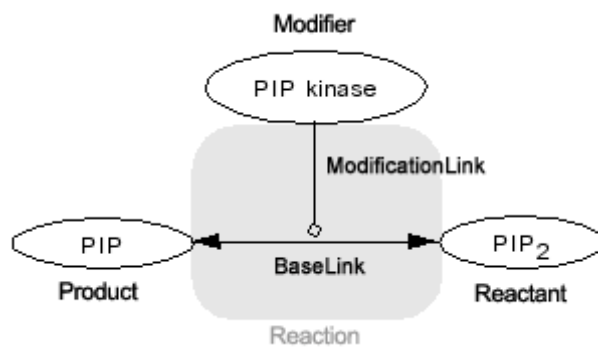
Square		
Oval		
Close-up type		Northwest, Northeast Southwest, Southeast
Close-up type		West, East North, South

10.1.5 Reaction

There are thirteen types of **Reaction** symbols.

Reactions		
State Transition		
Known Transition Omitted		Abbreviated symbol of several Reactions
Unknown Transition		
Transport		
Catalysis		
Unknown Catalysis		
Inhibition		
Unknown Inhibition		

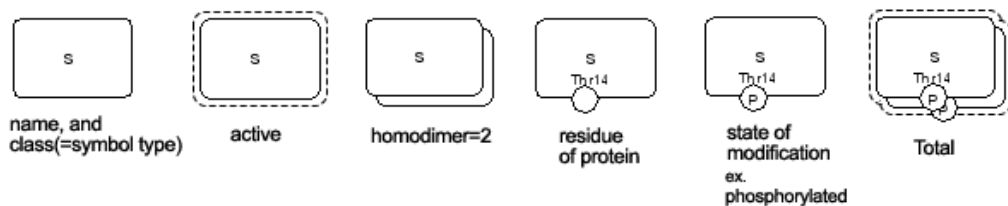
Add Reactant		
Add Product		
Heterodimer Association		
Dissociation		
Truncation		Dissociation of Proteins by truncation.
Transcriptional Activation		
Transcriptional Inhibition		
Translational Activation		
Translational Inhibition		



10.2 Expressions

Here are symbols acquiring additional semantics by shape, combination of symbols, or change in drawings. Active if the **Species** is active.

Active		
Channel Open		Activate Ion_Channel.
Homodimer formed		Double-click the Species to open the identity dialog, then set the Homodimer number.
Complex (Heterodimer formed)		
Hypothetical Species		Double-click the Species to open the identity dialog, then check the hypothetical ON.
Reversible Reactions		Double-click the Reaction, then set "reversible" to "true"
Bidirectional Reactions		Simply draw two state transitions and reposition them
Homodimer formation		Click the icon of Homodimer formation.
Degradation of Species		Click the icon of Degradation.



11 Limitations and Known Issues

11.1 Limitations

- (a) You can open and edit your SBML model (which includes a model created by CellDesigner 2.x), but you **can NOT SAVE YOUR MODEL with this version**. Although you can not save your model, you can export your model to image file (JPEG, PNG, SVG) for your publication, CSV and pure SBML file for simulation. The exported pure SBML file doesn't contain graphical information, but other information such as kinetic laws, parameters, initial concentrations etc. are stored.

11.2 Known Issues

- (a) The problems are reported in printing / exporting images of the huge model due to the lack of the memory.
- (b) When using CellDesigner in non-English environment on MacOSX and Linux, letters on dialog boxes from File menu are not correctly displayed.
 - **For MacOSX**, 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.