CELLDESIGNER™ 1.0 STARTUP GUIDE

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http://www.systems-biology.org/

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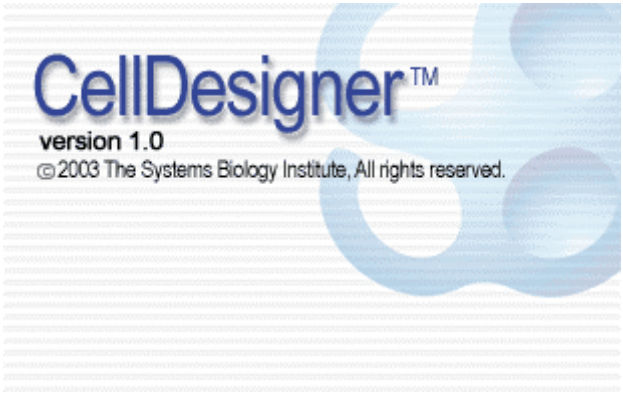

Acknowledgements:

This product includes software developed by the Apache Software Foundation (http://www.apache.org/).

This product also includes a graphics library developed by ANCL, Inc. (http://www.ancl.co.jp/ [in Japanese]).

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0 Introduction

CellDesigner's feature:

- Biochemical, Gene Regulatory Networks Modeling with GUI
- Visual Representation of Biochemical Semantics
- Detailed Description of State Transition of Protein
- SBML Compliant (SBML Level 1 Version 1 Format)
- Linkage to SBW Powered Simulator Modules
- Extreme Portability as a JAVA Application

1 Operating Environment

The current version of CellDesigner requires Java2 Runtime Environment (JRE1.3.x) on Windows (95 or later), MacOSX, and Linux with X Window System. On Linux platform, running under twm and windowmaker window managers is recommended; some problems will arise if you use window environments other than these.

If SBW and its modules have already been installed, these modules are available. Especially time evolving simulation of editing models can be performed.

2 Installation and Startup

2.1 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 first (*1).

Go and see http://www.sbw-sbml.org/index.html and download the software from Software/Download section. To install SBW and SBW-powered software, follow installation instructions therein and/or attached to the software. Note that the current release of CellDesigner requires SBW to be installed into, the default path prompted by SBW installer (`C:\ERATO\`) for Windows, or the user home directory ($HOME/SBW) for Linux (*2).

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

(*1) Currently, (June 9th, 2003) SBW is available on Windows and Linux.

(*2) Currently, (June 9th, 2003) the number of SBW-powered simulator module on Linux is limited.

2.2 Install CellDesigner

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

Windows: `CDinstall_win.exe`
MacOSX: `CDinstall_mac.zip`
Linux: `CDinstall_linux.bin`

While J2RE is required for CellDesigner to run, the installers for Windows and Linux include it, and MacOSX has a Java runtime environment initially. Therefore, you do not need to download or install J2RE. (If you installed SBW, you have already had it anyway.) Download the one for your operating system and follow instructions below to install CellDesigner for each environment.

Windows

Double click `CDinstall_win.exe`.

MacOSX

Double click `CDinstall_mac.zip`. The compressed installer should be recognized by Stuffit Expander and should automatically be expanded to `CDinstall_mac`. Then double click it.

Linux

Open a shell and, `cd` to the directory where you downloaded the installer. At the prompt type: `sh ./CDinstall.bin`.

After then, an installer window should open, and follow the message therein.

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

```
+00README.txt
|
+CelDesigner1.0executable application module
|
+documents/
|     +startup_guide.pdf    this document
|
+exec/
|     +ancl_graphics.jar    graphics library by ANCL, Inc.
|     +graph.jar       library for handling graph structure
|     +sbedit.jar            library for CellDesigner application
|     +sbml.jar        library for SBML I/O
|     +xerces.jar      XML library by The Apache Software Foundation
|
+licenses/
|     +xerces/
|          +LICENCE
|          +LICENCE-DOM.html
|          +LICENCE-SAX.html
|
+samples/
      +auto.xml
      +M-Phase.xml          sample for model editing
      +simulation.xmlsample for simulation
```

2.3 Startup CellDesigner

- Windows:

Double click shortcut icon `CellDesigner1.0` in your desktop. Or double click `CellDesigner1.0.exe` in the directory where you chose to install (`C:\Program Files\CellDesigner` by default).

- MacOSX

Click icon for CellDesigner1.0 in dock. Or double click `CellDesigner1.0` in the folder you chose to install (`Application/CellDesigner` in you home directory by default).

- Linux

On a shell, `cd` to the directory where you chose to create links and type `./CellDesigner1.0`. Or, type `./CellDesigner1.0` after `cd` to the directory where you chose to install (`CellDesigner` in you home directory by defulat).

3 Quick Tutorial of Model Building

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

In the beginning, open `M-Phase.xml` in `samples` directory by selecting File—Open in main menu bar, and a graphical network model is displayed on an edit canvas. This model has almost all of essentials of CellDesigner's expression of biochemical networks.

Confirm "select/move" button is highlighted (in select/move mode). If not, click it, and try

- Select shapes (not arrows, not rounding overall; called **Species** in SBML), and see what are highlighted.

  [Ans. The shapes and linked arrows.]
- Select arrows (called **Reaction** in SBML), and see what are highlighted.

  [Ans. The arrows and attached arrows.]

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

- Drag and move the **Species**,
- Delete the **Species** and **Reaction**s by using Backspace and/or Delete keys.

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

- Click the **Compartment** (click inside without any other shapes), and see what are and how highlighted.

  [Ans. The **Compartment** highlighted in magenta, **Species** inside highlighted in Green]

A **Compartment** can place **Species** and other **Compartment**s inside.

- Drag and move the **Compartment**, and confirm **Species** inside are on it.

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

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

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

- Drag the small squares and move.

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 **Reaction**s are distinguished by their symbols. The list of all symbols that can be drawn using CellDesigner and their meanings are described in [].

If you want to change these symbol, double click **Species** and **Reaction**s and use a dialog box to appear.

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

For the other changes,

- Select the **Compartment**,
  And select Edit—Change to OVAL,
  Then select Edit—Change to SQUARE.

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.

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

[Ans. The Species are wrapped by dashed line.]

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

(From this part, use buttons other than "select/move".)

If you want to create new **Species**, **Reaction**, or **Compartment**, use buttons on “Components” and “Compartments” palettes.

New **Species**:

Select a button (placed upper in “Components” palette) by click and then click a point on the canvas, where you want to place the new.

New **Compartment**:

Select a button (placed in “Compartments” palette) by click and then drag a point to another on the canvas until the new becomes suitable size.

New **Reaction**:

Select a button with an arrow on it, and then click **Species** on canvas you want to link by the **Reaction** in the order of start-point(s) to end-point(s). **Reaction**s themselves are allowed to be endpoints of other **Reaction**s.

- Create new **Species**: select button and click a point of canvas.
- Create new **Compartment**: select button and drag a point to another on canvas.
- Create new **Reaction**: select button and link **Species** to **Species**/**Reaction** on canvas.

There are some buttons with actions not mentioned above.

Try the followings after select the buttons and see what happens.

- Create heterodimer: click several **Species**.
- Release heterodimer: click several **Species**.
- Homodimer formation: click several **Species**.

- Degradation: click several **Species**.
- Add reactant: click a **Species** and then a **Reaction**.
- Add product: click a **Reaction** and then a **Species**.

4 Edit Proteins

In this section, how to edit proteins with modification sites, like "Cdc2" in above sample, `M-Phase.xml`, is 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 1 format with CellDesigner’s extended tags.

The model `M-Phase.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**.

You can see this **Protein** data by selecting Window—Show <listOfProteins> on the main menu. Selecting "Cdc2" in the list and clicking Edit button make a dialog for **Protein** 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 **Heterodimer**s (complex of several **Species**) including such **Species**, as you expect.

How residues of proteins are modified (phosphorylated, etc.) is NOT **Protein**’s property, but **Species**. Therefore, modifications are edited by double-clicking **Species** in “select/move” mode. In the dialog to appear, you can change modification types only, cannot add, edit, or delete modification residues. A **Protein** referred by the **Species** can be selected in the protein pulldown in the dialog, and if you want new protein, not listed in the pulldown, select [New Protein] listed at the last and you can edit the new **Protein** here (see known bugs (a) in section 8.2). Only in this case you can add, edit, and delete residues.

5 Convenient Edit Functions

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

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

- Temporal “select/move” mode

When constructing a model using buttons on “Components” and “Compartments” palettes to create new **Species**, **Reaction**s, and **Compartment**s (in “create new“ mode), you cannot move any components unless click the select/move button. 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.

- 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 **SpeciesAlias**es in CellDesigner’s terminology, referring the original **Species**. Strictly speaking, all of the **Species** on edit canvas are **SpeciesAlias**es 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.

- 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.

- Other convenient functions

Snapping components on grid: try the followings from Edit menu.
  Set Grid Snap ON/OFF
  Set Grids Size...
  Set Grids Visible
Setting default size of components: try the followings from Window menu.
  Show Palette Option
Displaying special characters in **Species** name:
  See Name Expression from Help menu.

6 Simulation

In this section, how to do simulation of an editing model is described.

CellDesigner is a kind of SBML file editors for simulators. To do time evolving simulation, you'd better to know some specification of SBML Level 1. Here describes minimum requirement for doing simulation and not detailed SBML specification. If you would like to know more about SBML Level 1, go http://www.sbw-sbml.org/sbml/docs/papers/sbml-level-1/sbml-level-1.pdf to obtain the SBML Level 1 specification document.

From software side, it is necessary that the SBW and SBW-powered simulator modules have been installed in the path mentioned in section 2.1. After starting CellDesigner and some model opened, SBW menu in the main menu is enabled if your setup has correctly been done. In addition, in the SBW menu, some simulators are listed if simulators you selected have correctly been installed. The following is the SBW menu in typical environment on Windows.

Save Network Object Model Clipboard
Simulation Service
Save Model as Matlab ODE Function File
Save Model as Matlab SimuLink Function File
Gibson Simulator

"Simulation Service" appears if Jarnac has been installed. The others are default-installed. For trial, open `simulation.xml` in "`samples`" directory, and then choose Simulation Service. This wakes Jarnac up and gives the model `simulation.xml` to it.

To know how to start simulation, please read the usage attached to the simulator modules.

From side of SBML model building, **Species** and its attributes, and **Reaction** and its attribute are required at least 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,	

where the rightmost of each line is required to be input. The attribute “initialAmount” should usually be changed to a positive value. The attribute “formula” should be text string according to SBML Level 1 specification, probably including id (name in SBML Level 1) attribute of **Species** and parameters defined by the attribute “parameter.” These attributes are set by Window—Show <listOfSpecies> and Window—Show

<listOfReactions> menus and their child dialogs. Open and see `simulation.xml` in `samples` directory, for example.

For the other parameters required, the default values specified in SBML Level 1 are used.

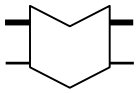
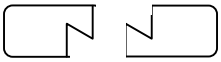
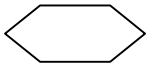
7 Symbols and Expressions

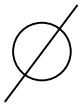
In this section, symbols for building models with CellDesigner are listed. Graphical notation and listing of the symbols are based on proposal by Kitano (http://www.sbw-sbml.org/workshops/sixth/sbmlsbwstockholm.htm). The symbol system for state-transition diagram and the residue state representation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

7.1 Basic Symbols

7.1.1 Species

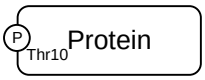
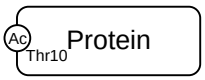
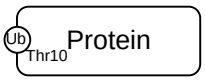
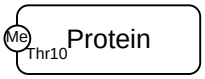
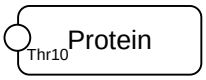
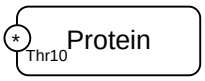
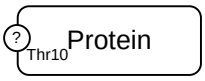
There are twelve types of **Species** symbols.

Protein Generic		
Protein Receptor		
Protein Ion channel		
Protein Truncated		
Gene		
RNA		
Anti-sense RNA		
Phenotype		
Ion		

Small Molecule		
Unknown		
Degraded		

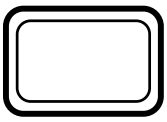
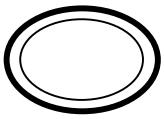
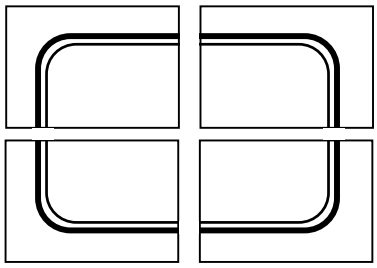
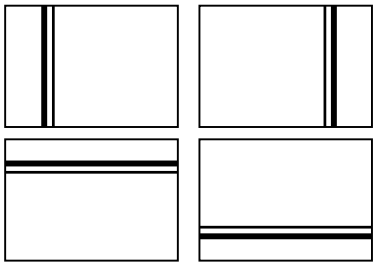
7.1.2 Modifications of Protein Residues

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		
Empty		
Don’t care		
Unknown		

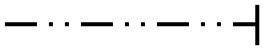
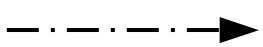
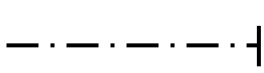
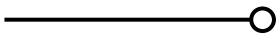
7.1.3 Compartment

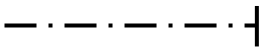
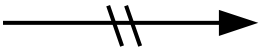
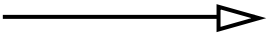
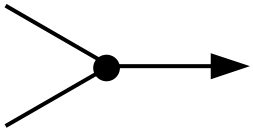
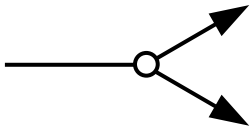
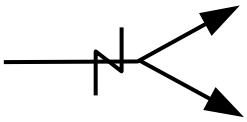
There are ten types of **Compartment** symbols. For each type, the thick line indicates outside of its boundary.

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

7.1.4 Reaction

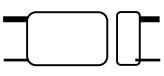
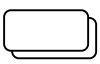
There are thirteen types of **Reaction** symbols.

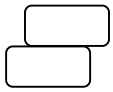
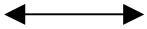
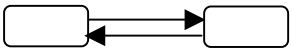
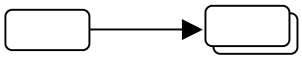
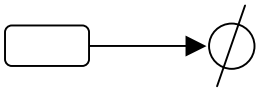
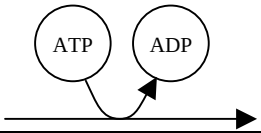
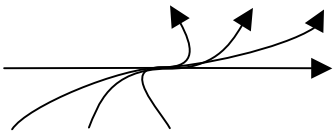
Transcriptional activation		
Transcriptional inhibition		
Translational activation		
Translational inhibition		
Catalysis		

Inhibition		
State transition		
Known transition omitted		Abbreviated symbol of several **Reaction**s
Unknown transition		
Transport		
Heterodimer formation		
Dissociation		
Truncation		Dissociation of Proteins by truncation.

7.2 Expressions

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

Active		Indicates that the **Species** is active.
Channel Open		Indicate the ion channel is open.
Homodimer formed		Indicates dimer of the same **Species**.

Heterodimer formed		Indicate dimer of different **Species**.
Hypothetical **Species**		
Reversible **Reaction**		
Bidirectional **Reaction**		
Homodimer formation		
Degradation of **Specie**s		
Reaction accompanied by transformation		
Reaction of multiple reactants and multiple products		

8 Limitations and Known Bugs

8.1 Limitations

(a) For the changes, not appeared in the edit canvas, through dialogs opened by Window-><listOf___> in the main menu bar, such as initialAmount of **Species**, UNDO and REDO are not available.

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

8.2 Known Bugs

(a) When [New Protein] is selected in protein pulldown in a dialog to appear by double-clicking **Species**, no default shape of proteins appears at the center of the dialog.

Please select class before editing residues, and its shape becomes visible.

(b) Active PROTEIN **Species** with a dashed line around it can be changed to non-PROTEIN **Species**, such as RNA. However, the dashed line remains unnaturally.

Please change species type after delete a dashed line by typing "a" on keyboard when selected.

8.3 Known Issues

(a) 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 start CellDesigner.