Quick Tutorial

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1. Introduction

The "Control Panel" is designed to assist the users to simulate directly from CellDesigner controlling the amounts and parameters of the Species.

Calling directly SBML ODE Solver (<u>http://www.tbi.univie.ac.at/~raim/odeSolver/</u>) from CellDesigner, ControlPanel enables you to specify the details of parameters, changing amount, conducting parameter search, and interactive simulation with intuitive manner.

You can also choose COPASI (<u>http://www.copasi.org/</u>) as an alternative solver.



→ See also: Startup Guide

Sample file used in this document:

This document uses a sample model "MAPK.xml" originally provided with SBML ODE Solver. When you install CellDesigner, MAPK.xml is deployed in the /<your CellDesigner directory>/samples/folder.

This MAPK.xml model has been slightly modified from a model obtained from <u>http://sbml.org/models/</u>.

The model has been published in Kholodenko BN. Negative feedback and ultrasensitivity can bring about oscillations in the mitogen-activated protein kinase cascades. Eur. J. Biochem. 267: 1583-1588 (2000).

2. Quick Tutorial of Simulation

2.1 Before you start simulation

Throughout this tutorial, we will use MAPK.xml which can be found in the <CeI I Designer i nstal I ation directory>/sampl es/ folder. All the formulae necessary for the simulation are already embedded in the Reactions. You can check the formulae in the CellDesigner's Reactions list.

→ See also: Startup Guide or CellDesigner Online Help.



KineticLaw

id	name	reactants	products	modifiers	math
10	10	MKKK	MKKK D		V1 * MKKK / ((1 + pow(MAPK_PP / Ki, n))
30	30	IVITATATA		MAEK_FF	* (K1 + MKKK))
J1	J1	MKKK_P	MKKK		V2 * MKKK_P / (KK2 + MKKK_P)
J2	J2	MKK	MKK_P	MKKK_P	k3 * MKKK_P * MKK / (KK3 + MKK)
J3	J3	MKK_P	MKK_PP	MKKK_P	k4 * MKKK_P * MKK_P / (KK4 + MKK_P)
J4	J4	MKK_PP	MKK_P		V5 * MKK_PP / (KK5 + MKK_PP)
J5	J5	MKK_P	MKK		V6 * MKK_P / (KK6 + MKK_P)
J6	J6	MAPK	MAPK_P	MKK_PP	k7 * MKK_PP * MAPK / (KK7 + MAPK)
17	17				k8 * MKK_PP * MAPK_P / (KK8 +
J7	37	WAFR_F			MAPK_P)
J8	J8	MAPK_PP	MAPK_P		V9 * MAPK_PP / (KK9 + MAPK_PP)
J9	J9	MAPK_P	MAPK		V10 * MAPK_P / (KK10 + MAPK_P)

CD10D00

class	id	name	compartment	quantity type	initialQuantity
PROTEIN	MKK	MKK	uVol	Amount	280
PROTEIN	MKKK	MKKK	uVol	Amount	90
PROTEIN	MAPK	MAPK	uVol	Amount	280
PROTEIN	MKKK_P	MKKK	uVol	Amount	10
PROTEIN	MKK_P	MKK	uVol	Amount	10
PROTEIN	MKK_PP	MKK	uVol	Amount	10
PROTEIN	MAPK_P	MAPK	uVol	Amount	10
PROTEIN	MAPK_PP	MAPK	uVol	Amount	10

Species

Parameters

scope	id	name	value	units	constant
local:Reaction(J0)	V1		2.5		TRUE
local:Reaction(J0)	Ki		9		TRUE
local:Reaction(J0)	n		1		TRUE
local:Reaction(J0)	K1		10		TRUE
local:Reaction(J1)	V2		0.25		TRUE
local:Reaction(J1)	KK2		8		TRUE
local:Reaction(J2)	k3		0.025		TRUE
local:Reaction(J2)	KK3		15		TRUE
local:Reaction(J2)	V0	V0	111		TRUE
local:Reaction(J2)	K0	K0	1		TRUE
local:Reaction(J3)	k4		0.025		TRUE
local:Reaction(J3)	KK4		15		TRUE
local:Reaction(J4)	V5		0.75		TRUE
local:Reaction(J4)	KK5		15		TRUE
local:Reaction(J5)	V6		0.75		TRUE
local:Reaction(J5)	KK6		15		TRUE
local:Reaction(J6)	k7		0.025		TRUE
local:Reaction(J6)	KK7		15		TRUE
local:Reaction(J7)	k8		0.025		TRUE
local:Reaction(J7)	KK8		15		TRUE
local:Reaction(J8)	V9		0.5		TRUE
local:Reaction(J8)	KK9		15		TRUE
local:Reaction(J9)	V10		0.5		TRUE
local:Reaction(J9)	KK10		15		TRUE

2.2 To run a basic simulation:

- 1. Open the sample file MAPK. xml in the samples folder.
- 2. In the Menu, select Simulation Control Panel.
- 3. The **ControlPanel** will open.



- 4. Click **Execute** button.
- 5. A graph will be drawn in the right window.

Gantro	Panel MAPK xml								2
File Elli	Data Simulation								
#1 #1 6	4								
Time man	Firm tolerance	Techer.		Couch Tax					
Time spec		One		Graph Table					-
End Time	100 0	€ SOSI6		Concentration ra	V P Spec	es EFkures	Parameter	a Compartmen	VL S. C.
Nun. of	100 C Ltp0	 O COPAC 	1	La Participation of the second			-	-	MKK.
1000	201			280.10					MKK_
Species F	Parameters Change amount	Parameter Scan	ht)	250					MAP_
1d	Name Compartm	Quantity	Initial C						MKK.
MKK	MKKMKK UV01	Amount		1.000					W MKK
MKKK	MEREMERE UVol	Amount		200 -					MAP_
MAPK	MAPKMAPK UVol	Amount							MAP_
MKKK_P	MKKK_P:MKKKuVo1	Amount		10000					
MKK_P	MKK_P-MKK uVol	Amount		150					
MKK PP	MKK_PP:MKK_UVol	Amount		1.1201					
MAPK_P	MAPK_P.MAP_UVol	Amount							
MAPK, PP	MAPK_PP.MA_UVol	Amount		100 -					
							-		-
				80 -				-	=
				A 000	-				=
				IN	1	3.	1	1	
				0	20	40	60	80	
						Time			
						-	1		Select all
						100.00	8		species search
2			5	100					search

- 6. By default, the simulation **End Time** is set to "100" and **Num. of Points** to plot is "100". You can enter different values into **End Time** and **Num. of Points** to change these values.
- 7. Change End Time to "1000".

ControlPanel MAPK.xml								
File Edit Date	 Simulation 							
FEA								
Time span								
End Time	1,000 🛨							
Num. of Points	100 -							

- 8. Click **Execute** button.
- 9. A graph is drawn with a longer time.

Contro	IPanel MAPK.xml		
File Edit	Data Simulation		
65 65 6	3		
Time upon	From tolerance	Soluer	Courts File
		(C) COORIN	J origin Lobie
End time 1	Fvn 6	0 00000	Concentration ra. V. S. C
Num. of _	100 0	OCOPASI	
			₹ 298.70 × MAX
Species P	arameters Change amount F	arameter Scan Int	
ы	Name Compartm.	Quantity_ Initia	2 XXX .
MKK	MKKMKK WVol	Anount	₩CK.
MKKK	MKKKMKKK UVol	Anount	MAP.
MAPK	MAPKMAPK UVol	Amount	W MAP_
MKKK P	MKKK P.MKKKuVol	Anount	
MKK_P	MKK_PMKK uVol	Amount	
MKK_PP	MKK_PP:MKK_uVol	Amount	150
MAPK P	MAPK P.MAP uVol	Amount	
MAPK_PP	MAPK PP.MA. uVol	Amount	
			100
			60-
			♦ 0.00
			0 100 000 000 000 000 000 000 000
			0 100 200 300 400 500 800 700 800 500
			Time
			2 100000 Select all
			species search
			search

2.3 To view the values of the simulation results:

- 1. Click the Table Tab behind the Graph tab on the right panel.
- 2. You can view the results of the simulation in a table format. You can switch **species**, **fluxes**, **parameters** and **compartment** by clicking the relevant tabs.

Contro	IPanel MAP	(.xm)										X
File Edit	Data Simulat	iog.										
69 69 6	2											
Time span	En En	or tolerance	Solver		Graph Table							
End Time	1,000 2	E CONTRACTOR	⊙ SOSIb		species flux	es parameter	s compartme	inte				
Num of _	100 C	-6	O COPAS	t i	time / names	MKK	MKKK	MAPK	MKKK P	MKK P	MKK PP	1
and the second					00	280.0	90.0	280.0	100	100	100	10
Species p	Parameters Chu	ore amount F	arameter Scan	be die	10.0	279.6623903	00.71005964.	279.8795776.	19,28194015.	11.65649409.	8.681114904.	
A COLORED	are units out a grant	and another t			20.0	277.4105421.	71.26419001	290.0123660	28.73581998.	13.87921551	8.710242296	
1d	Name	Conpartm.	Quantity_	Initial C	30.0	273.2337896.	61.62264580.	280.0497661	38.37736419.	16.68953532	10.07667606.	
MKK	MKKMKK	uVol	Amount	1000	40.0	267.1211936.	51.97394200.	279.6672963.	48.02605799.	20.07727090.	12.00153539.	-
MKKK	MEREMERE	uVol	Amount		50.0	259 1053508	42.65937771	278.5508577	57.34062228.	23.96592952	16.92871962	
MAPK	MAPKMAPK	uVal	Amount		60.0	249.3000217.	34.12662769.	276.3906686.	65.87337240.	28.21993826.	22.48003999.	-
MKKK_P	MKKK P.MKK	KuVol	Amount	1	70.0	237.9211842	26.82384551.	272.8854367.	73.17615448.	32.67360127.	29.40521446.	
MKK_P	MKK_P-MKK	uVol	Amount		80.0	225.2767963	21.06130968.	267.7549262	78.93869031	37.16335890.	37.55985470	
MKK_PP	MKK_PP:MKK	uVol	Amount		90.0	211.7238266.	16.90943551	260.7551132	83.09056448	41.55221384	46.72395947.	18
MAPK_P	MAPK_P:MAR	P_uVol	Amount	1	100.0	197.6112907.	14.20497291.	251.6899795.	85.79502700	45.74111638	56.64759286.	-
MAPK PP	MAPK_PP:MA	LiuVol	Amount		110.0	180.2367610.	12.65732077.	240.4165320.	07.34267922	49.66764328.	67.09559406	-
100					120.0	168.8313279	11.96799785	226.8439846	8803200214	5329690809	7787176392	
					130.0	154.5667568.	11.89575921.	210.9306021.	88.10424078.	56.61086612	08.82237702	-10
					140.0	140.5710931.	12.26763168	192.6817132	87.73236831.	59.59965679.	99.82925009	-
					150.0	126.9434262	12.96541968	172.1517431	8703458031	62.25584396	110.8007298	
					160.0	113.7650338.	13.90864168.	149.4634931.	86.09135831.	64.57082219.	121.6641439.	
					170.0	101.1070506.	15.04130490.	124.7815530	84.95869509.	66.53257895.	132.3603705	-
					180.0	89.03567537	16.32337110.	98.45690081	83.67662889	68.12419597	142.8401286	1
					190.0	77.61611797.	17.72621376.	71.10913762	82.27478623.	69.32261282	163.0612692	
					200.0	66.91537844.	19.22415030.	43.94130762	80.77584969.	70.09776721	162,9968543.	-
					210.0	57.00409685	20.80215590	19.90139362	79.19784409	70.41224180	172,5836613	
					220.0	47.95693647	22 44387267	5.253885660	7755612732	70.22201752	181.8210460	-
<				5		<	THE PROPAGA	to approximations			IS AN ABAAAPP	5
		(T144)	line Com		Evente	Char I El	how exatter of			-		-
1.00		Pine	inte Coave		Execute		scow scower bi	O1				

 \rightarrow Note: You can copy the data from the table by specifying the area in the table. The data is treated as

CSV format so you can paste it directly to the spreadsheet.

2.4 To save an image of the simulation result:

You can save the graph image into five types of graphical file format: BMP, JPEG, PNG, TIFF, and PNM file format: (".bmp", ".jpg", ".png", ".tif" and ".pnm".)

- 1. Select Save Image / Print from the File menu.
- 2. The Image Config Dialog pops up.



3. Select **Config** button to specify the graph items such as **Title**, **Legend** and **Plot** ranges.



- 4. Click OK.
- 5. Select **Save Image** button, then select the file format and specify the file name for a graph image.



2.5 To change the solver to COPASI:

COPASI is a software application for simulation and analysis of biochemical networks. COPASI is free for non-commercial use. If you want to use COPASI with CellDesigner as a simulation solver, setup COPASI before you run the simulation.

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

💽 ControlPanel MAPK.xml	X
File Edit Data Simulation	
664	
Time span Error tolerance Solver	Graph Table
Fed Time 100	
Exp6 OCOND	Concentration ra VI. S C
Num. of 100 🗢	
	V MAP.
Species Parameters Change amount Parameter Scan Int	200 MKK
Id Name Compartm Quantity Initial Q	MKK
MKK MKK uVol Amount	MKK.
MKKK MKKK:MKKK uVol Amount	ZUU MAP.
MAPK MAPK:MAPK uVol Amount	
MKKK_P MKKK_P:MKKKµVol Amount	150
MKK_P MKK_P:MKK_uVol Amount	100
MARK P MARK PMAR Wol Amount	
MAPK PP MAPK PP:MA.uVol Amount	
	100
	50
	0 20 40 60 80
	-
	Select all
	100.00 species search
< >	search
Initialize Save As	Execute Close show scatter plot

→ To install Copasi, see also README.txt or "Installation and Startup" section in

CellDesigner's Startup Guide,

3. Change the Initial Quantities of Species and Parameter Values

It is possible to run the simulation with the values in **Species** and **Parameters** tabs changed. The values changed in the ControlPanel are updated to the corresponding values in the CellDesigner itself.

3.1 To change the initial quantity for Species:

1. Click the **Species** tab.

Species Parameters Change amount Parameter Scan Interactive Simulation Results									
ld	Name	Compartment	Quantity Type	Initial Quantity	Substance				
MKK	MKK:MKK	uVol	0	280.0					
MKKK	MKKK:MKKK	uVol	0	90.0					
MAPK	MAPK:MAPK	uVol	0	280.0					
MKKK_P	MKKK_P:MKKK	uVol	0	10.0					
MKK_P	MKK_P:MKK	uVol	0	10.0					
MKK_PP	MKK_PP:MKK	uVol	0	10.0					
MAPK_P	MAPK_P:MAPK	uVol	0	10.0					
MAPK_PP	MAPK_PP:M	uVol	0	10.0					

- 2. Change the initial quantity by clicking each blue cell for the values to be modified.
- 3. Click the **Execute** button to run the simulation with the new values.

3.2 To change the parameter values:

1. Click the **Parameters** tab.

Scope	ld	Name	Value	Units	const	ant
local:Reactio	V1		2.500		true	-
local Reactio	Ki		9.000		true	
local:Reactio	n		1.000		true	
local:Reactio	K1		10.000		true	
local Reactio	V2		0.250		true	
local Reactio	KK2		8.000		true	
local Reactio	k3		0.025		true	
local:Reactio	KK3		15.000		true	
local:Reactio	k:4		0.025		true	
local Reactio	KK4		15.000		true	
local Reactio	V5		0.750		true	
local:Reactio	KK5		15.000		true	
local:Reactio	V6		0.750		true	
local Reactio	KK6		15.000		true	

- 2. Change the initial parameters by clicking each blue cell for the values to be modified.
- 3. Click the **Execute** button to run the simulation with the new parameters.

4. Change Amount for Simulation

In order to simulate the time course of Specie resulting from forced expression of a gene/genes on a certain time, ControlPanel implements the **Change amount** functionality. By this functionality you can run a simulation with the amount of Species at a specific time being changed to a desired value.

 \rightarrow Note: COPASI does not support the Change Amount functionality.

4.1 To run simulation changing the amount of Species at specific time:

- 1. Click the Change amount tab.
- 2. Check the **Change amount** checkbox.
- 3. In the **Change amount** matrix, enter the amount of **Species** at the time specified at the header row.



4. Click the **Execute** button.

4.2 To export and import the Change amount matrix:

The **Change amount** matrix can be edited by external software such as MS Excel by exporting the matrix to a CSV file. Conversely, a CSV file edited outside can be imported to ControlPanel.

- 1. Select **Export** from the **Data** menu.
- Enter a file name and click the Save button.
 (A CSV file will be created with the specified file name.)
- 3. Open the CSV file using other software such as MS Excel, edit values, and save them.

Span	100			
Step	30			
species/time point	0	30	60	90
MKKK	90			
MKKK_P	10			
MKK	280			
MKK_P	10		100	
MKK_PP	10			
MAPK	280			
MAPK_P	10			
MAPK_PP	10			

e.g. an example of .CSV file exported from Control Panel. $% \left[{{\left[{{{\rm{CSV}}} \right]}_{\rm{TOT}}}} \right]$

- 4. Select **Import** from the **Data** menu.
- 5. Select the file that you have just edited and click the **Open** button.

5. Parameter Scan

You can run simulations in a batch job to scan parameters. By setting the range and interval of each parameter to scan, ControlPanel runs the simulation with each parameter changing within the specified range with the value incremented by the specified interval.

5.1 To scan parameters:

- 1. Click the Parameter Scan tab.
- 2. Check the Scan parameter checkbox.
- 3. Select the Initial value or Parameter value option.
- 4. Select the name of a parameter to change from the **Name** list.
- 5. Input values into **From**, **To**, and **Interval** for a parameter scan, which correspond to the start value, the end value, and the interval respectively.
- 6. Click **Execute** button to start simulation scanning the specified parameters.

ecies Parameters Change	amount Paramete	r Scan Interactive Sim	Jation Res
Simulation1			
Scan parameter	Name	мюжмюж	¥
Initial value	From		0 ×
C Parameter value	То		10 +
	Interval		1 ×
Simulation2			
Scan parameter	Name	J0:V1	¥
C Initial value	From		0 *
Parameter value	То		10 +
	Interval		1

ightarrow Note: In case you check two Scan parameter checkboxes, you can scan two parameters. The

simulations are executed using the combination of the two parameters.

5.2 To see the results of parameter scan:

- 1. In the **Information** dialog saying "The simulation was completed" is displayed, click **OK**.
- 2. Click the blinking **Result** tab. (The right most tab)
- 3. Select the result you wish to see and click the **Show Graph** button.
- → Note: If you specify only one parameter on parameter scanning, you should specify Overlay Setting to

view the graph.



5.3 To output the results of parameter scan:

- 1. Click Writing.
- 2. Specify the file name and the directory to save the file.
- 3. The output of the parameter scan results will be saved in the text file format.

6. Interactive Simulation

ControlPanel allows you to see real-time results of simulations. You should use "Interactive simulation" for this purpose.

6.1 To run interactive simulations:

- 1. Click the Interactive Simulation tab.
- 2. Select the Initial value or Parameter value option.
- 3. To change a parameter, slide each slider bar or input a value into a box on the right side of the slider bar for the parameter.



→ Note: The minimum and maximum values of slider bar were automatically defined based on the initial values of SBML. However, you can change the data range of slider bars.

6.2 To change the data range of slider bars:

- 1. Click the **Define Range** button.
- 2. In the **Define Slider Range** dialog, change the minimum and maximum values and click the **OK** button.

~	Min	Max	Current
MKICMIK	0.0	560.0	278.84
MKKKK MKKK	0.0	180.0	90.00
MAPKMAPK	0.0	560.0	280.00
MKKK_P:MKKK	0.0	20.0	10.00
MKK_P:MKK	0.0	20.0	10.00
MKK_PP:MKK	0.0	20.0	10.00
MAPK_P:MAPK	0.0	20.0	10.00
MAPK_PP:M	0.0	20.0	10.00

7. Graph Area

7.1 To highlight a Species in the Graph Area:

- 1. In the Control Panel, click **Graph** tab.
- 2. Click a cell in the **Species** column in the table.
- 3. The corresponding line in the **Graph** will be highlighted.
- 4. Next, click on a line in the **Graph**.
- 5. The corresponding table row on the right panel will be highlighted.



7.2 To show/hide Species displayed in the Graph Area:

- 1. In the Control Panel, click **Graph** tab.
- 2. Select/unselect checkboxes in the Visible column in the right panel.
- 3. The checked Species are displayed/hidden on the **Graph**.



7.3 To change the line color of the graph:

- 1. In the Control Panel, click **Graph** tab.
- 2. Click a cell in the **Color** column on the right panel.
- 3. Pick a Color dialog appears.
- 4. Select a color and click the OK button.



7.4 To search for species:

- 1. In the ControlPanel, in the species search textbox, enter your search word
- 2. Click search.

0	100	200	300	400	500	600	700	800	900		
				Time							Select all
			۰	100	0.00						species search
										3	search

7.5 To convert the graph to a scatter plot:

You can convert the line chart to a scatter plot and compare the data of an arbitrary pair of Species.

- 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.



8. Save/Open the Results of Simulation (File I/O)

The result of a simulation is stored in three file types:

- a model file (*.xml; SBML)
- a simulation condition file (*.sim)
- simulation result files (*.txt)

The model file (SBML) has a one-to-one correspondence with the simulation condition file (*.sim).

For example, if you stored the results of two simulations run by model1.xml and newmodel.xml into the "models" directory, the contents of the directory will be:

[mo	dels]
	+model1.xml (SBML)
	+model1.sim(parameters setting for the model 1)
	+[model1](the result folder for the model 1)
	+result1.txt (simulation result 1)
	+result2.txt (simulation result 2)
	+
	+newmodel.xml (a new model)
	+newmodel.sim(parameters setting for the new model)
	+[newmodel](the result folder for the new model)
	+result1.txt(simulation result 1)
	+result2.txt(simulation result 2)

8.1 To save a simulation result into files:

- 1. Select Save As from the File menu of ControlPanel.
- 2. Enter the file name for a simulation result and click the **save** button.
- 3. Then three types of file having extensions ".xml", ".sim", and ".txt" are created.

8.2 To open a result saved in files:

- 1. Select **Open** from the **File** menu of CellDesigner.
- 2. Select an SBML (.xml) file and click the Open button.
- 3. The corresponding conditon (.sim) file and result files (*.txt) are automatically imported so that you can start the ControlPanel and see the result.