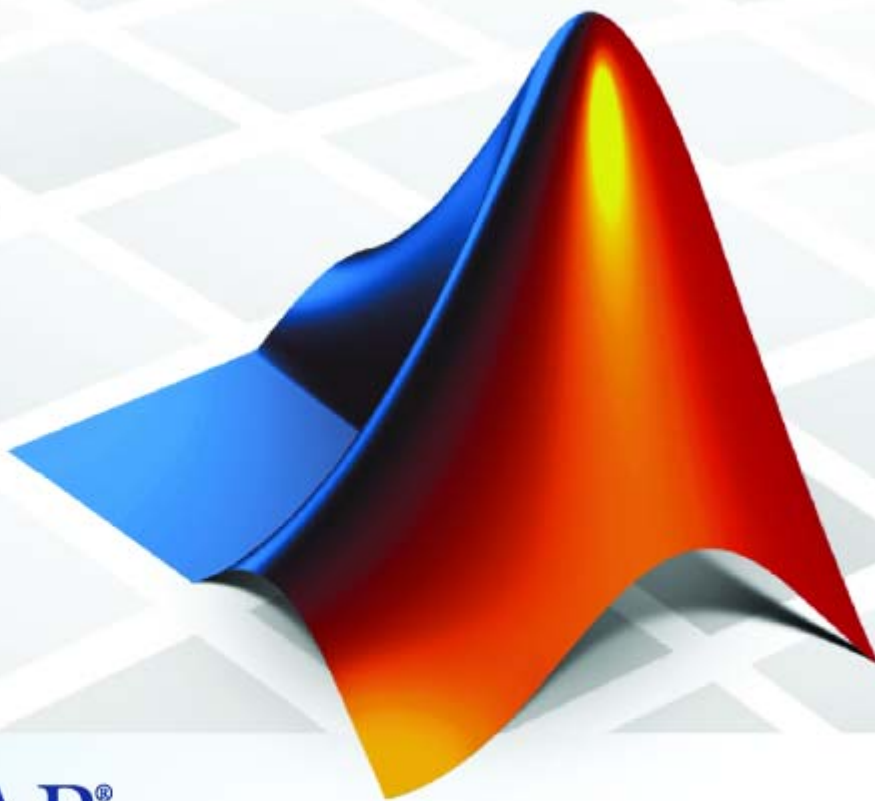


SimBiology 2

Model Reference



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SimBiology Model Reference

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Minimal Cascade Model for a Mitotic Oscillator

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Minimal Cascade Model for a Mitotic Oscillator

Albert Goldbeter modified a model with enzyme cascades (Goldbeter and Koshland 1981) to fit cell cycle data from studies with embryonic cells (Goldbeter 1991). He used this model to demonstrate thresholds with enzyme cascades and periodic behavior caused by negative feedback.

There are two SimBiology model variations using Goldbeter's model. The first model uses the differential rate equations directly from Goldbeter's paper. The second model is built with reactions using Henri-Michaelis-Menten kinetics.

Goldbeter Model (p. 1-2)	Description and graphical representation of a simple enzyme cascade with a feedback loop
SimBiology Model with Rate Rules (p. 1-6)	Enter differential rate equations directly from the literature
SimBiology Model with Reactions (p. 1-10)	Convert differential rate equations to reactions and reaction rates
References (p. 1-21)	Literature references and Web links for additional information

Goldbeter Model

Albert Goldbeter created a simple cell division model from studies with embryonic cells (Goldbeter 1991). This model demonstrates thresholds with enzyme cascades and periodic behavior caused by negative feedback.

Graphic Representation (p. 1-3)

Diagram showing the reactions and relationships between species

Reaction Descriptions and Model Assumptions (p. 1-4)

Brief descriptions of the reactions with some of the simplifying assumptions

Mathematical Model (p. 1-4)

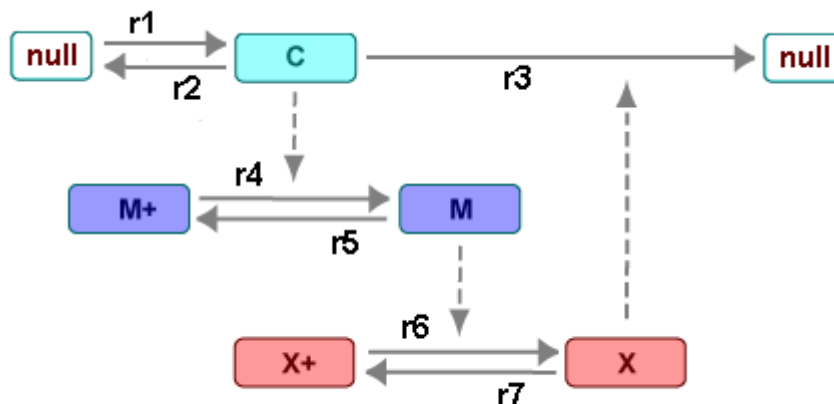
Biochemical pathways defined with differential rate equations and algebraic equations.

Graphic Representation

There are six species in Goldbeter's minimal mitotic oscillator model (Goldbeter 1991).

- C — Cyclin. The periodic behavior of cyclin activates and deactivates an enzyme cascade.
- M+, M — Inactive (phosphorylated) and active forms of cdc2 kinase. Kinases catalyze the addition of phosphate groups onto amino acid residues.
- X+, X — Inactive and active (phosphorylated) forms of a cyclin protease. Proteases degrade proteins by breaking peptide bonds.

The reactions are labeled r1 to r7 on the diagram



This model shows

- How thresholds with cdc2 kinase activation (M+ → M) and protease activation (X+ → X) can occur as the result of covalent modification (for example, phosphorylation or dephosphorylation), but without the need for positive feedback.
- How periodic behavior with cdc2 kinase activation can occur with negative feedback and the time delay associated with activation/deactivation enzyme cascades.

Reaction Descriptions and Model Assumptions

The following list describes each of the reactions in Goldbeter's minimal mitotic oscillator with some of the simplifying assumptions. For a more detailed explanation of the model, see Goldbeter 1991.

- Cyclin (C) is synthesized at a constant rate (r1) and degraded at a constant rate (r2).
- Cyclin (C) does not complex with cdc2 kinase (M).
- Cyclin (C) activates cdc2 kinase (M+ → M) by increasing the velocity of the phosphatase that activates the kinase. Inactive cdc2 kinase (M+) is activated by removing inhibiting phosphate groups (r4).
- The amount of deactivating kinase (not modeled) for the cdc2 kinase (M) is constant. Active cdc2 kinase (M) is deactivated by adding inhibiting phosphate group (r5).
- The activation of cyclin protease (X+ → X) by the active Cdc2 kinase (M) is direct without other intervening cascades. Cyclin protease (X) is activated by adding phosphate groups (r6).
- The amount of deactivating phosphatase (not modeled) for the cyclin protease (X) is constant. Active cyclin protease (X) is deactivated by removing the activating phosphate groups (r7).
- The three species of interest are cyclin (C), active dephosphorylated cdc2 kinase (M), and active phosphorylated protease (X). The total amounts of (M + M+) and (X + X+) are constant.

Mathematical Model

Goldbeter's minimal mitotic oscillator model is defined with three differential rate equations and two algebraic equations that define changing parameters in the rate equations

Differential Rate Equation 1, Cyclin (C)

The following differential rate equation is from Goldbeter 1991 for cyclin (C).

$$\frac{dC}{dt} = v_i - v_d X \frac{C}{K_d + C} - k_d C$$

Differential Rate Equation 2, Kinase (M)

The following differential rate equation is for cdc2 kinase (M). Notice that (1 - M) is the amount of inactive (phosphorylated) cdc2 kinase (M+).

$$\frac{dM}{dt} = V_1 \frac{(1-M)}{K_1+(1-M)} - V_2 \frac{M}{K_2+M}$$

$$V_1 = \frac{VM_1[C]}{K_c + [C]}$$

Differential Rate Equation 3, Protease (X)

Differential rate equations for cyclin protease (X). Notice that (1 - X) is the amount of inactive (unphosphorylated) cyclin protease (X+).

$$\frac{dX}{dt} = V_3 \frac{(1-X)}{K_3+(1-X)} - V_4 \frac{X}{K_4+X}$$

$$V_3 = VM_3[M]$$

SimBiology Model with Rate Rules

In the literature, many biological models are defined using differential rate and algebraic equations. With SimBiology, you can enter the equations directly as SBML rules. The example in this section uses Goldbeter's mitotic oscillator to illustrate this point.

SimBiology Model with Rules (p. 1-6)	Equivalent rate and algebraic rules for the equations
SimBiology Simulation with Rules (p. 1-9)	Model simulation with a deterministic solver

SimBiology Model with Rules

Writing differential rate equations in an unambiguous format that a software program can understand is a fairly simple process.

- Use an asterisk to indicate multiplication. For example, $k[a]$ is written $k*a$.
- Remove square brackets that indicate concentration from around species. The units associated with the species will indicate concentration (moles/liter) or amount (moles, molecules).

SimBiology uses square brackets around species and parameter name to allow names that are not valid MATLAB® variable names. For example, you could have a species named glucose-6-phosphate dehydrogenase but you need to add brackets around the name in reaction rate and rule equations.

- Use parentheses to clarify the order of evaluation for mathematical operations. For example, do not write a Henri-Michaelis-Menten rate as $V_m*C/K_d + C$, because V_m*C is divided by K_d before adding C , and then C is added to the result.

The following equation is the SimBiology rate rule for “Differential Rate Equation 1, Cyclin (C)” on page 1-4:

$$dC/dt = v_i - (v_d*X*C)/(K_d + C) - k_d*C$$

The following equations are the SimBiology rate and algebraic rules for “Differential Rate Equation 2, Kinase (M)” on page 1-5:

$$dM/dt = (V1*Mplus)/(K1 + Mplus) - (V2*M)/(K2 + M)$$

$$V1 = (VM1*C)/(Kc + C)$$

$$Mplus = Mt - M$$

The following equations are the rate and algebraic rules for “Differential Rate Equation 3, Protease (X)” on page 1-5:

$$dX/dt = (V3*Xplus)/(K3 + Xplus) - (V4*X)/(K4 + X)$$

$$V3 = VM3*M$$

$$Xplus = Xt - X$$

Species

The following table is a list of species in the model with their initial amounts.

The two parameters V1 and V3 are in the species list. You could enter the parameters in the parameter table with the ConstantAmount check boxes cleared. Here, the parameters are modeled as species but without reactions.

Name	InitialAmount	ConstantAmount	BoundaryCondition
C	0.01	<input type="checkbox"/>	<input type="checkbox"/>
M	0.01	<input type="checkbox"/>	<input type="checkbox"/>
Mplus	0.99	<input type="checkbox"/>	<input type="checkbox"/>
Mt	1.0	<input type="checkbox"/>	<input type="checkbox"/>
X	0.01	<input type="checkbox"/>	<input type="checkbox"/>
Xplus	0.99	<input type="checkbox"/>	<input type="checkbox"/>
Xt	1.0	<input type="checkbox"/>	<input type="checkbox"/>
V1	0.0	<input type="checkbox"/>	<input type="checkbox"/>
V3	0.0	<input type="checkbox"/>	<input type="checkbox"/>

Parameters

The following table is a list of parameters in the model with their initial values. The **ConstantValue** property is selected for all the parameters.

Name	Value	ConstantValue
vi	0.025	<input checked="" type="checkbox"/>
kd	0.01	<input checked="" type="checkbox"/>
vd	0.25	<input checked="" type="checkbox"/>
Kd	0.02	<input checked="" type="checkbox"/>
VM1	3.0	<input checked="" type="checkbox"/>
K1	0.0050	<input checked="" type="checkbox"/>
Kc	0.5	<input checked="" type="checkbox"/>
V2	1.5	<input checked="" type="checkbox"/>
K2	0.0050	<input checked="" type="checkbox"/>
VM3	1.0	<input checked="" type="checkbox"/>
K3	0.0050	<input checked="" type="checkbox"/>
V4	0.5	<input checked="" type="checkbox"/>
K4	0.0050	<input checked="" type="checkbox"/>

Rules

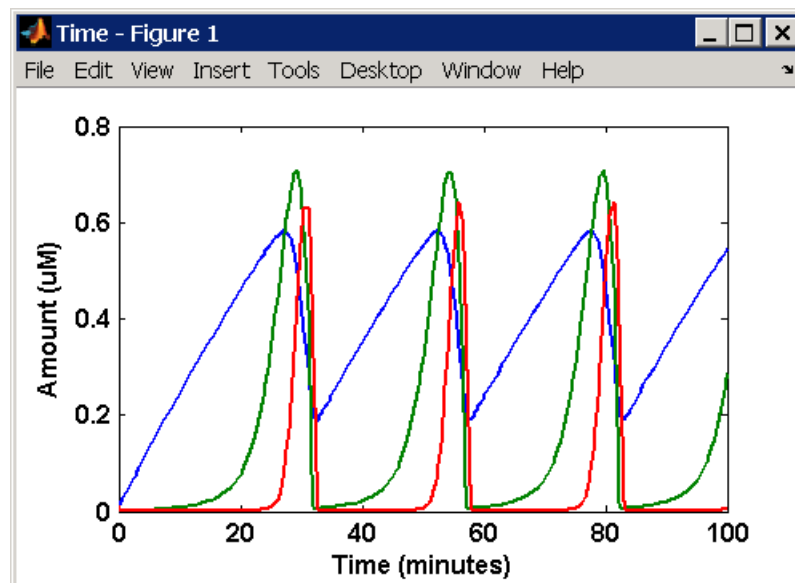
The active (M) and inactive (Mplus) forms of the kinase are assumed to be part of a conserved cycle with the total concentration (Mt) remaining constant during the simulation. You need only one differential rate equation with a mass balance algebraic equation to define the amounts of both species. Similarly, the active (X) and inactive (Xplus) forms of the protease are part of a second conserved cycle.

In the SimBiology desktop, you enter rate rules of the form $\frac{dX}{dt} = \text{Expression}$ as $X = \text{Expression}$, and algebraic rules of the form " $X = \text{Expression}$ ", where X is the independent variable, as $\text{Expression} - X$.

Name ▾	Rule	RuleType
Cyclin	$C = v_i - (v_d * X * C) / (K_d + C) - k_d * C$	rate ▾
Kinase	$M = (V_1 * M_{plus}) / (K_1 + M_{plus}) - (V_2 * M) / (K_2 + M)$	rate ▾
	$M_t - M_{plus} - M$	algebraic ▾
	$(V_{M1} * C) / (K_c + C) - V_1$	algebraic ▾
Protease	$X = (V_3 * X_{plus}) / (K_3 + X_{plus}) - (V_4 * X) / (K_4 + X)$	rate ▾
	$X_t - X_{plus} - X$	algebraic ▾
	$V_{M3} * M - V_3$	algebraic ▾

SimBiology Simulation with Rules

This is a simulation of Goldbeter's minimal mitotic oscillator using differential rate and algebraic equations. Simulate with the ode15s solver and plot species C, M, and X. For a description of the model, see "SimBiology Model with Rules" on page 1-6.



SimBiology Model with Reactions

While in the literature, many models are defined with differential rate equations, creating the differential equations from reactions is unnecessary. With SimBiology, you can enter the reactions and let the software calculate the equations.

Converting Differential Rate Equations to Reactions (p. 1-10)

Simple rules for converting differential rate equations to reactions

Calculating Initial Values for Reactions (p. 1-12)

Calculations for initial values with different units within consistent dimensions

SimBiology Simulation with Reactions (p. 1-20)

Model simulation with a deterministic solver

Converting Differential Rate Equations to Reactions

Some models are defined with differential rate equations, and you might need the reactions to be compatible with your model. Two rules you can use to convert differential rate equations to reactions are

- **For a positive term** — The species described by the equation is placed on the right as a product, and the species in the term are placed on the left as reactants.
- **For a negative term** — The species described by the equation is placed on the left as a product, and the species in the term are also placed on the left as reactants.

You need to determine the products using additional information, for example, a reaction diagram, a description of the model, or an understanding of a reaction. If a reaction is catalyzed by a kinase, then you can conclude that the product has one or more additional phosphate groups.

A simple first order reaction has differential rate equation $dR/dt = +kr[P] - kf[R]$. The negative term implies that the reaction is $R \rightarrow ?$ with an unknown product. The positive term identifies the product and completes the reaction, $R \leftrightarrow P$.

Reactions R1 to R3 from Equation E1

The differential rate equation 1 is repeated here for comparison with the reactions. See “Differential Rate Equation 1, Cyclin (C)” on page 1-4.

$$\frac{dC}{dt} = v_i - v_d X \frac{C}{K_d + C} - k_d C$$

The reaction and reaction rate equations for SimBiology from the differential rate equation E1 are given below.

```
r1      reaction: null -> C
        reaction rate: v_i

r2      reaction: C -> null
        reaction rate: k_d*C

r3      reaction: C -> null
        reaction rate: (v_d*X*C)/(K_d + C)
```

Reactions R4 and R5 from Equation E2

The differential rate equation 2 and algebraic equation 2 are repeated here for comparison with the reactions. See “Differential Rate Equation 2, Kinase (M)” on page 1-5.

$$\frac{dM}{dt} = V_1 \frac{(1-M)}{K_1 + (1-M)} - V_2 \frac{M}{K_2 + M}$$

$$V_1 = \frac{VM_1[C]}{K_c + [C]}$$

The reaction and reaction rate equations for SimBiology from the differential rate equation E2 are given below.

```
r4      reaction: Mplus -> M
        reaction rate: V1*Mplus/(K1 + Mplus)
        algebraic rule: V1 = VM1*C/(Kc + C)

r5      reaction: M -> Mplus
```

reaction rate: $V2 \cdot M / (K2 + M)$

Reactions R6 to R7 from Equation E3

The differential rate equation for equation 3 and algebraic equation 3 is repeated here for comparison with the reactions.

$$\frac{dX}{dt} = V3 \frac{(1-X)}{K3+(1-X)} - V4 \frac{X}{K4+X}$$

$$V3 = VM3 \cdot [M]$$

The reaction and reaction rate equations for SimBiology from the differential rate equation E3 are given below:

r6 reaction: Xplus -> X
 reaction rate: $V3 \cdot Xplus / (K3 + Xplus)$
 algebraic rule: $V3 = VM3 \cdot M$

r7 reaction: X -> Xplus
 reaction rate: $V4 \cdot X / (K4 + X)$

Calculating Initial Values for Reactions

After you converted the differential rate equations to the reactions and reaction rate equations, you can start to fill in initial values for the species (reactants and products) and parameters.

The initial values for parameters and amounts for species are listed with four different units in the same dimension:

- A — Original units in the Goldbeter 1991 paper.
- B — Units of concentration with time converted to second. When converting a to b, use 1 minute = 60 second for parameters.

$$\frac{X \text{ uM}}{\text{minute}} \times \frac{1e-6 \text{ mole/liter}}{1 \text{ uM}} \times \frac{1 \text{ minute}}{60 \text{ second}} = \frac{Y \text{ mole}}{\text{liter} \cdot \text{second}}$$

- C — Units of amount as moles. When converting concentration to moles, use a cell volume of 1e-12 liter and assume that volume does not change.

$$\frac{Y \text{ mole}}{\text{liter*second}} \times \frac{1\text{e-}12 \text{ liter}}{1} = \frac{Z \text{ mole}}{\text{second}}$$

- D — Units of amount as molecules. When converting amount as moles to molecules, use $6.022\text{e}23 \text{ molecules} = 1 \text{ mole}$.

$$\frac{Z \text{ mole}}{\text{second}} \times \frac{6.022\text{e}23 \text{ molecule}}{1 \text{ mole}} = \frac{N \text{ molecules}}{\text{second}}$$

With dimensional analysis on and unit conversion off, select all of the units for one letter. For example, select all of the As. If dimensional analysis and unit conversion are on, you can mix and match letters and get the same answer.

Reaction 1 Cyclin Synthesis

R1		Value	Units
reaction	null -> C	----	----
reaction rate	vi	----	A. uM/minute
		----	B. mole/(liter*second)
		----	C. mole/second
		----	D. molecule/second
parameters	vi	0.025	A. uM/minute
		4.167e-10	B. mole/(liter*second)
		4.167e-22	C. mole/second
		205	D. molecule/second
species	C	0.01	A. uM
		1e-8	B. mole/liter
		1.0e-20	C. mole
		6.022e+3	D. molecule

Reaction 2 Cyclin Undifferentiated Degradation

R2		Value	Units
reaction	C -> null	----	----
reaction rate	kd*C	----	A. uM/minute
		----	B. mole/(liter*second)
		----	C. mole/second
		----	D. molecule/second
parameters	kd	0.010	A. 1/minute
		1.6667e-4	B, C, D. 1/second
species	C	0.01	A. uM
		1e-8	B. mole/liter
		1.0e-20	C. mole
		6.022e+3	D. molecule

Reaction 3 Cyclin Protease Degradation

R3		Value	Units
reaction	C -> null	----	----
reaction rate	$(vd*X*C) / (Kd + C)$	----	A. uM/minute
		----	B. mole/(liter*second)
		----	C. mole/second
		----	D. molecule/second
parameter	vd	0.25	A. 1/minute
		0.0042	B, C, D. 1/second
parameter	Kd	0.02	A. uM
		2.0e-8	B. mole/liter
		2.0e-020	C. mole
		12044	D. molecule

R3		Value	Units
species	C (substrate)	0.01	A. uM
		1e-8	B. mole/liter
		1.0e-20	C. mole
		6.022e+3	D. molecule
species	X (enzyme)	0.01	A. uM
		1e-8	B. mole/liter
		1.0e-20	C. mole
		6.022e+3	D. molecule

Reaction 4 Cdc2 Kinase Activation

R4		Value	Units
reaction	Mplus -> M	----	----
reaction rate	$(V1 * Mplus) / (K1 + Mplus)$	----	A. uM/minute
		----	B. mole/(liter*second)
		----	C. mole/second
		----	D. molecule/second
algebraic rule	$V1 = (VM1 * C) / (Kc + C)$	----	
parameter	V1 (variable by rule)	0.00	A. uM/minute
			B. mole/(liter*second)
			C. mole/second
			D. molecule/second
parameter	VM1	3.0	A. uM/minute
		5.0e-8	B. mole/(liter*second)
		5.0000e-020	C. mole/second

R4		Value	Units
parameter	Kc	30110	D. molecule/second
		0.5	A. uM
		5.0000e-7	B. mole/liter
		5.0e-19	C. mole
parameter	K1	3.011e+5	D. molecule
		0.005	A. uM
		5e-9	B. mole/liter
		5e-21	C. mole
species	Mplus (inactive substrate)	3.011e+3	D. molecule
		0.99	A. uM
		9.9e-7	B. mole/liter
		9.9e-19	C. mole
species	M (active product)	5.962e+5	D. molecule
		0.01	A. uM
		1e-8	B. mole/liter
		1.0e-20	C. mole
species	C	6.022e+3	D. molecule
		0.01	A. uM
		1e-8	B. mole/liter
		1.0e-20	C. mole
		6.022e+3	D. molecule

Reaction 5 Cdc2 Kinase Deactivation

R5		Value	Units
reaction	M -> M_plus	----	----
reaction rate	$(V2 * M) / (K2 + M)$	----	A. uM/minute B. (mole/liter-second) C. mole/second D. molecule/second
parameter	V2	1.5 2.5000e-008 2.5000e-020 15055	A. uM/minute B. mole/liter-second C. mole/second D. molecule/second
parameter	K2	0.005 5.0000e-009 5.0000e-021 3011 1.0e-20	A. uM B. mole/liter C. mole D. molecule
species	Mplus (inactive)	0.99 9.9e-7 9.9e-19 5.962e+5	A. uM B. mole/liter C. mole D. molecule
species	M (active)	0.01 1e-8 1.0e-20 6.022e+3	A. uM B. mole/liter C. mole D. molecule

R6 Protease Activation

R6		Value	Units
reaction	Xplus -> X	----	----
reaction rate	$(V3 \cdot Xplus) / (K3 + Xplus)$	----	A. uM/minute
		----	B. mole/(liter*second)
		----	C. mole/second
		----	D. molecule/second
algebraic rule	$V3 = VM3 \cdot M$	----	
parameter	V3 (variable by rule)		A. uM/minute
			B. mole/liter-second
			C. mole/second
			D. molecule/second
parameter	VM3	1.0	A, 1/minute
		0.0167	B, C, D. 1/second
parameter	K3	0.005	A. uM
		5e-9	B. mole/liter
		5e-21	C. mole
		3.011e+3	D. molecule
species	Xplus (inactive substrate)	0.99	A. uM
		9.9e-7	B. mole/liter
		9.9e-19	C. mole
		5.962e+5	D. molecule
species	X (active product)	0.01	A. uM
		1e-8	B. mole/liter
		1.0e-20	C. mole

R6		Value	Units
		6.022e+3	D. molecule
species	M (enzyme)	0.01	A. uM
		1e-8	B. mole/liter
		1.0e-20	C. mole
		6.022e+3	D. molecule

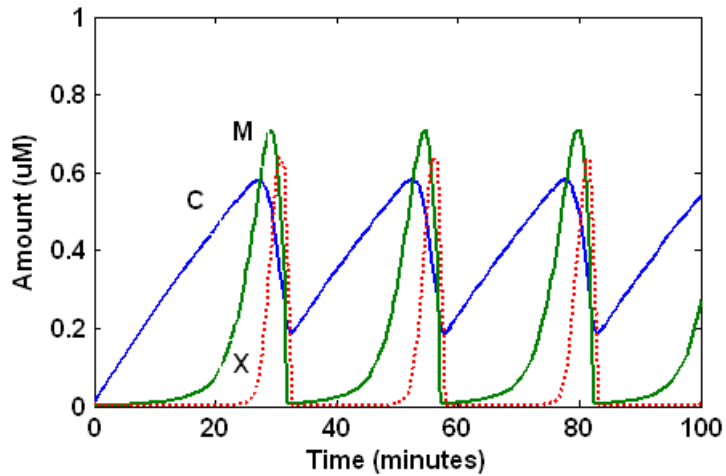
Reaction 7 Protease Deactivation

R7		Value	Units
reaction	$X \rightarrow X_{plus}$	----	----
reaction rate	$(V4 * X) / (K4 + X)$	----	A. uM/minute
		----	B. mole/(liter*second)
		----	C. mole/second
		----	D. molecule/second
parameter	V4	0.5	A. uM/minute
		8.3333e-009	B. mole/(liter*second)
		8.3333e-021	C. mole/second
		5.0183e+003	D. molecule/second
parameter	K4	0.005	A. uM
		5e-9	B. mole/liter
		5e-21	C. mole
		3011	D. molecule
species	Xplus (inactive)	0.99	A. uM
		9.9e-7	B. mole/liter
		9.9e-19	C. mole
		5.962e+5	D. molecule
species	X (active)	0.01	A. uM

R7	Value	Units
	1e-8	B. mole/liter
	1.0e-20	C. mole
	6.022e+3	D. molecule

SimBiology Simulation with Reactions

This is a simulation of Goldbeter's minimal mitotic oscillator with rate and algebraic equations. Simulate with the ode15s solver and plot species C, M, and X. For a description of the model, see "SimBiology Model with Reactions" on page 1-10.



References

- [1] Goldbeter A. (1991), "A minimal cascade model for the mitotic oscillator involving cyclin and cdc2 kinase," *Proceedings of the National Academy of Sciences USA*, 88:9107-9111.
- [2] Goldbeter A., Koshland D. (1981), "An amplified sensitivity arising from covalent modification in biological systems," *Proceedings of the National Academy of Sciences USA*, 78:6840-6844.
- [3] Goldbeter A., Koshland D. (1984), "Ultrasensitivity in biochemical systems controlled by covalent modification," *The Journal of Biological Chemistry*, 259:14441-14447.
- [4] Goldbeter A., home page on the Web,
<http://www.ulb.ac.be/sciences/utc/GOLDBETER/agoldbet.html>
- [5] Murray A.W., Kirschner M.W. (1989), "Cyclin synthesis drives the early embryonic cell cycle," *Nature*, 339:275-280.

Model of the Yeast Heterotrimeric G Protein Cycle

SimBiology lets you build a model using a conceptual framework of biochemical reactions that describe a biological process. You can plot experimental data on top of your model's simulation results to investigate the validity of your model, make predictions based on the model, and test your hypotheses.

Using concepts and data from the published work of Yi and colleagues [Yi et al. 2003], this tutorial shows you how to

- 1** Build a model using the SimBiology graphical user interface (GUI).
- 2** Copy the model and change settings to create a different model.
- 3** Simulate and save the data from the two models.
- 4** Compare the two simulations.
- 5** Compare the simulation results with the experimental data.

Background on G Protein Cycles
(p. 2-3)

Brief overview of G proteins and the G protein cycle in the yeast pheromone response pathway

Modeling a G Protein Cycle (p. 2-5)

Overview of reactions and assumptions

Building the G Protein Cycle Model in SimBiology (p. 2-10)	Describes the goals of this tutorial and explains how to build the model in SimBiology
Completing the SimBiology Model (p. 2-18)	Write the rest of the reactions, determine the reaction rate equations, assign the species initial amounts, and create a rule
Simulating the G Protein Cycle Model in SimBiology (p. 2-27)	Determine the settings for simulation and visualize the simulation results
Building a Model for the Mutant Strain (p. 2-32)	Create a model for the mutant strain (<i>sst2Δ</i>) by copying and changing the existing model
Simulating the G Protein Cycle Model of the Mutant Strain (p. 2-34)	Plot the simulation results for the mutant strain model using a custom plot
Plotting Species from Two Different Data Sets (p. 2-39)	Plot species data from two different simulation runs
Plotting Experimental Data with Simulation Data (p. 2-43)	Store experimental data and use custom plotting to plot experimental and simulation data together
References (p. 2-46)	Reference material used in this tutorial

Background on G Protein Cycles

This section provides a brief overview of G proteins and the G protein cycle in the yeast pheromone response pathway.

G Proteins (p. 2-3)

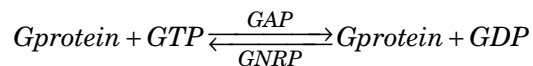
Introduction to G Proteins

G Proteins and Pheromone Response (p. 2-4)

Yeast G protein cycle

G Proteins

Cells rely on signal transduction systems to communicate with each other and to regulate cellular processes. G proteins are GTP-binding proteins that are involved in the regulation of many cellular processes. There are two known classes of G proteins: the monomeric G proteins (one GTPase), and the heterotrimeric G proteins (three different monomers). The G proteins usually facilitate a step requiring energy. This energy is supplied by the hydrolysis of GTP by a GTPase activating protein (GAP). The exchange of GDP for GTP is catalyzed by a guanine nucleotide releasing protein (GNRP) [Alberts et al. (1994)].



G protein coupled receptors (GPCRs) are the targets of many pharmaceutical agents. Some estimates suggest that 40 to 50% of currently marketed drugs target GPCRs and that 40% of current drug discovery focus is on GPCR targets. Some examples include those for reducing stomach acid (ranitidine which targets histamine H2 receptor), migraine (sumatriptan, which targets a serotonin receptor subtype), schizophrenia (olanzapine, which targets serotonin and dopamine receptors), allergies (desloratadine, which targets histamine receptors). One approach in pharmaceutical research is to model signaling pathways to analyze and predict both downstream effects and effects in related pathways. This tutorial examines model building and analysis of the G protein cycle in the yeast pheromone response pathway using SimBiology.

G Proteins and Pheromone Response

In the yeast *Saccharomyces cerevisiae*, G protein signaling in pheromone response is a well characterized signal transduction pathway. The pheromone secreted by *alpha* cells activates the G protein coupled α -factor receptor (Ste2p) in *a* cells which results in a variety of cell responses including cell-cycle arrest and synthesis of new proteins. The authors of the study performed a quantitative analysis of this cycle, compared the regulation of G protein activation in wild-type yeast haploid *a* cells with cells containing mutations that confer supersensitivity to α -factor. They analyzed the data in the context of cell-cycle arrest and pheromone-induced transcriptional activation and developed a mathematical model of the G protein cycle that they used to estimate rates of activation and deactivation of active G protein in the cell.

Modeling a G Protein Cycle

Systems biologists represent biological pathways and processes as reactions with reaction rates and treat the components of these pathways as individual species. In this example, α -factor, α -factor receptor, and the G protein subunits are all treated as species participating in reactions.

Reactions Overview (p. 2-5)

Table of reactions and rate parameters

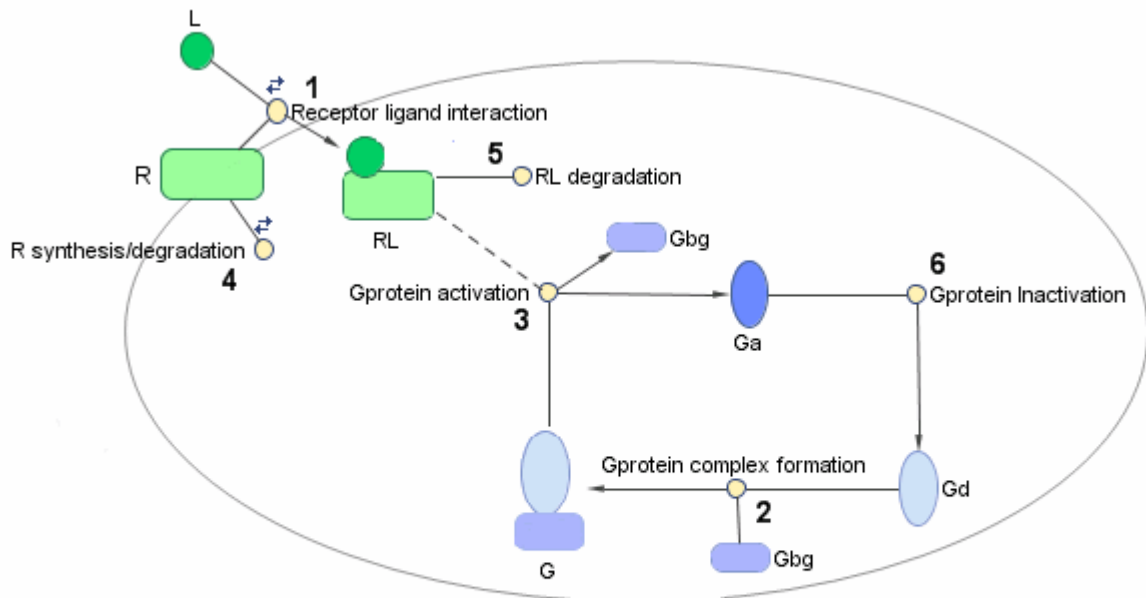
Assumptions, Experimental Data, and Units in the G Protein Model (p. 2-7)

Description of assumptions, and experimental data from the reference paper

Reactions Overview

The G protein cycle in the yeast pheromone-response pathway can be condensed into a set of biochemical reactions. These reactions are complex formation, transformation, or disassociation reactions that Yi and colleagues [Yi et al.2003] use to simplify and describe the system. The system can be graphically represented as follows:

2 Model of the Yeast Heterotrimeric G Protein Cycle



Graphical Representation of the G protein cycle in yeast pheromone response. The numbers represent reaction numbers referenced in the text. L = Ligand (alpha factor), R = alpha-factor receptor, Gbg = free levels of G-beta:G-gamma complex, Ga = active G-alpha-GTP, Gd = inactive G-alpha-GDP, G = inactive Gbg:Gd complex.

The following table shows you the reactions used to model the G protein cycle and the corresponding rate constants (rate parameters) for each reaction. For reversible reactions, the forward rate parameter is listed first.

No.	Name	Reaction	Rate Parameters
1	Receptor-Ligand Interaction	$L + R \leftrightarrow RL$	k_{RLm}, k_{RL}
2	Heterotrimeric G protein formation	$Gd + Gbg \rightarrow G$	k_{G1}
3	G protein activation	$RL + G \rightarrow Ga + Gbg + RL$	k_{Ga}

No.	Name	Reaction	Rate Parameters
4	Receptor synthesis and degradation	$R \leftrightarrow \text{null}$	kRdo, kRs
5	Receptor-Ligand degradation	$RL \rightarrow \text{null}$	kRD1
6	G protein inactivation	$Ga \rightarrow Gd$	kGd

Note that in reaction 3 (G protein activation), RL appears on both sides of the reaction. This is because RL is treated as a modifier or catalyst, and the model assumes that there is no synthesis or consumption of RL in this reaction.

The authors use a set of ordinary differential equations (ODEs) to describe the system. In SimBiology, you can represent the biological pathway as a system of biochemical reactions and the software creates the ODEs for you. Alternatively, if you have a set of ODEs that describe your system you can enter these as rate rules in SimBiology. For an example of modeling using rate rules, see “SimBiology Model with Rate Rules” on page 1-6.

Assumptions, Experimental Data, and Units in the G Protein Model

The authors have obtained experimental data either through their own measurements or through published literature. As with any other model, the G protein cycle model simplifies the biological process while also trying to reconcile the experimental data. There are the following points to consider:

- Reaction 2 - Binding and formation of the heterotrimeric G protein complex is treated as a single step reaction.
- Reaction 3 - Activation of G protein is modeled as a single step. Guanine nucleotide exchange factors (GEFs) are not modeled.
- Reactions 3 and 6 - The parameters for the rate of G protein activation and deactivation (kGa and kGd) have been estimated based on the dose response curves in the reference paper. The SimBiology model being built in this tutorial directly uses those values.

- Reactions 4 and 5 - Receptor synthesis and degradation are handled purely as two simple reaction steps.
- Reaction 6 - Deactivation of G protein by the regulator of G protein signaling (RGS) protein Sst2p is modeled as a single step. Sst2p is not modeled.

The reaction is modeled with an estimated reaction rate of 0.11 s^{-1} in the Sst2p containing wild-type strain. The uncatalyzed reaction rate is estimated to be 0.004 s^{-1} in a strain with a deletion of SST2 (*sst2Δ*, mutant strain).

- Free GDP, GTP, and Pi are not included in the model.

This tutorial shows you how to plot the experimental data over the simulation plot of the active G protein fraction. You can estimate the values of the experimental data of interest for this example from the coordinates of the plots found in Figure 5 of the reference paper [Yi et al. 2003]. The following values were obtained by comparing the coordinates of the standards with those of the unknowns in the figure:

Time	Fraction of Active $G\alpha$ (experimental)
0	0.00
10	0.35
30	0.40
60	0.36
110	0.39
210	0.33
300	0.24
450	0.17
600	0.20

Note The SimBiology **Dimensional Analysis** feature is not used in this tutorial. For this tutorial, the values of all species are converted to have the unit molecule, and all rate parameters are converted to have either the unit 1/second or the units 1/(molecule*second), depending on whether the reaction is first or second order. You should leave the **InitialAmountUnits** box for species, and **ValueUnits** box for rate parameters empty for the models in this tutorial.

Building the G Protein Cycle Model in SimBiology

This section shows you how to build the example yeast heterotrimeric G protein models using SimBiology's graphical user interface (GUI) (SimBiology desktop). For an overview of the SimBiology desktop, [click here](#).

This section assumes that you are starting with an untitled Project and a default Untitled Model Session in the SimBiology desktop.

If you are running the `gprotein.sbproj` file that contains the models in this tutorial, you can refer to “Simulating the G Protein Cycle Model in SimBiology” on page 2-27 for the sections on the simulation and analysis of these models.

Goals of the Tutorial (p. 2-10)	Description of the salient features of the tutorial
Opening the SimBiology Desktop (p. 2-11)	Describes how to open the SimBiology graphical user interface
Saving Your Work as a SimBiology Project File (p. 2-12)	Save your work in the SimBiology project format
Adding a Reaction to the SimBiology Model (p. 2-12)	Add a reaction and determine the reaction rate equation
Determining the Reaction Rate Equation (p. 2-14)	Assign a kinetic law and parameters to determine the reaction rate equation
Setting Initial Amounts of Species (p. 2-16)	Assign the initial values for species amounts

Goals of the Tutorial

This example uses the yeast G protein cycle (Yi et al. 2003) to illustrate model building and analysis in SimBiology. The goals of this tutorial are the following:

- 1 Build a model of the wild-type strain (TMY101) that has the SST2 gene. This strain shows a catalyzed rate of deactivation of $G\alpha$. $G\alpha$ is represented as Ga in the model.

- 2** Copy the model and change settings to create a different model for the mutant strain (*sst2Δ*, TMY111) that shows an uncatalyzed rate of G-Protein inactivation.
- 3** Simulate and save the data from the two models.
- 4** Compare the active G protein fractions in the two simulations.
- 5** Compare the simulation results for active G protein fractions with experimental data.

For additional help in each procedure, select **Help > SimBiology Desktop Help** for context-sensitive help.

Opening the SimBiology Desktop

All of the procedures in this tutorial are performed in the SimBiology desktop. The desktop provides access to command-line functionality through a graphical user interface. You can open the desktop from the MATLAB Command Window.

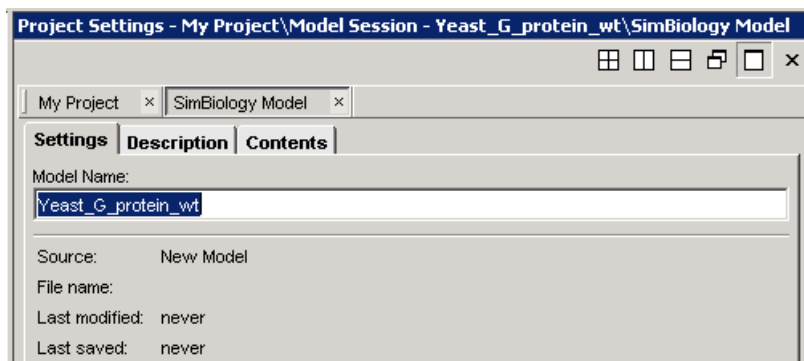
- 1** To open the desktop, at the MATLAB command line, type

```
sbiodesktop
```

The **SimBiology Desktop** opens. Use the **Project Explorer** in the left pane to navigate.

- 2** In the **Project Explorer**, double-click **SimBiology Model**. SimBiology opens the **SimBiology Model** pane.
- 3** In the **SimBiology Model** pane, click the **Settings** tab.
- 4** In the **Model Name** box, enter the name for your model.

```
Yeast_G_Protein_wt
```



Saving Your Work as a SimBiology Project File

Project (.sbproj) is the file format that SimBiology uses to save one or more model sessions. Projects lets you save custom settings, notes, and data associated with your models.

Save your work as a project now so that you can access this file later.

- 1 From the **File** menu, select **Save Project as**.

The Save SimBiology Project dialog box opens.

- 2 Browse to the folder in which you want to save your projects, enter a name for the project file, and then click **Save**.

yeast_g_protein_cycle.sbproj

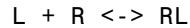
Adding a Reaction to the SimBiology Model

The next steps show you how to add a reaction and determine the reaction rate equation for your model.

This example shows you the first reaction.

Name	Reaction	Rate Parameters
Receptor-Ligand Interaction	$L + R \leftrightarrow RL$	kRLm, kRL

- 1 In the **Project Explorer** double-click **Reactions**.
- 2 In the **Reactions** pane, enter the reaction in the **Enter Reaction** box, and click **Add**.

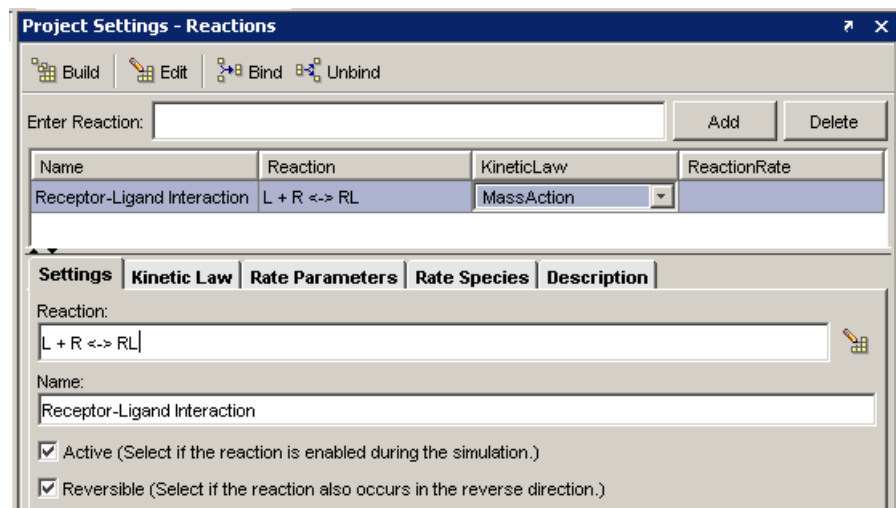


- 3 In the **Name** box, enter the name for your reaction.

Receptor-Ligand Interaction

- 4 In the reaction table, from the **KineticLaw** list, select **MassAction**.

Your screen should now look similar to the figure below:



Note the following in the **Settings** tab:

- Because this reaction is reversible, the **Reversible** check box is selected by default when you enter the reaction.
- All the reactions in this example model are included in the simulation and therefore have the **Active** check box selected by default.

Note Use spaces between the species and the characters in the reaction. If you have a reaction with different stoichiometry, for example $2 A + B \leftrightarrow 3 AB$, you must have a space between the stoichiometric coefficient and the species name for the reaction rate to be accurately determined. Otherwise, the coefficients are considered as part of the species name.

Determining the Reaction Rate Equation

SimBiology populates the reaction rate column once you specify the kinetic law and the rate parameters of the reaction.

To assign and configure the kinetic law and the rate parameters,

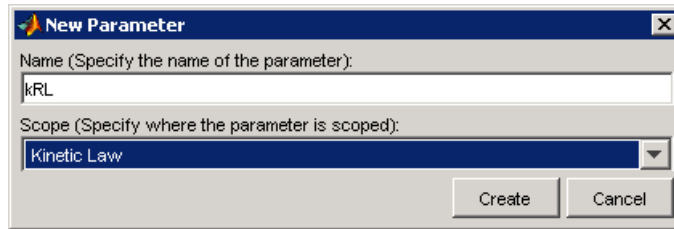
- 1 In the **Reactions** pane, click the **Kinetic Law** tab.
- 2 In the **Specify Corresponding Parameter Names** box, assign names to the parameters by clicking **New**. The New Parameter dialog box opens.
- 3 Specify the name of the parameter in the **Name** box. For **Forward Rate Parameter** enter kRL.
- 4 From the **Scope** list, select **Kinetic Law**. This applies the parameter locally, which means that this parameter is only available for use by this reaction.

If you set the scope of a parameter to **Model**, you can use this parameter in rules, other reactions, and submodels. All the parameters for this model are scoped to their respective kinetic laws.

More about scoping

Scoping lets you overload parameters; you can have parameters with the same name at kinetic law and at model level. Because SimBiology searches up from kinetic law to model level, when a parameter is overloaded, a reaction uses the parameter and parameter value in its kinetic law, however rules and submodels use the parameter value at the model level.

A reaction uses a parameter at the model level, only if a corresponding parameter is not defined at the kinetic law level for the reaction.



New Parameter

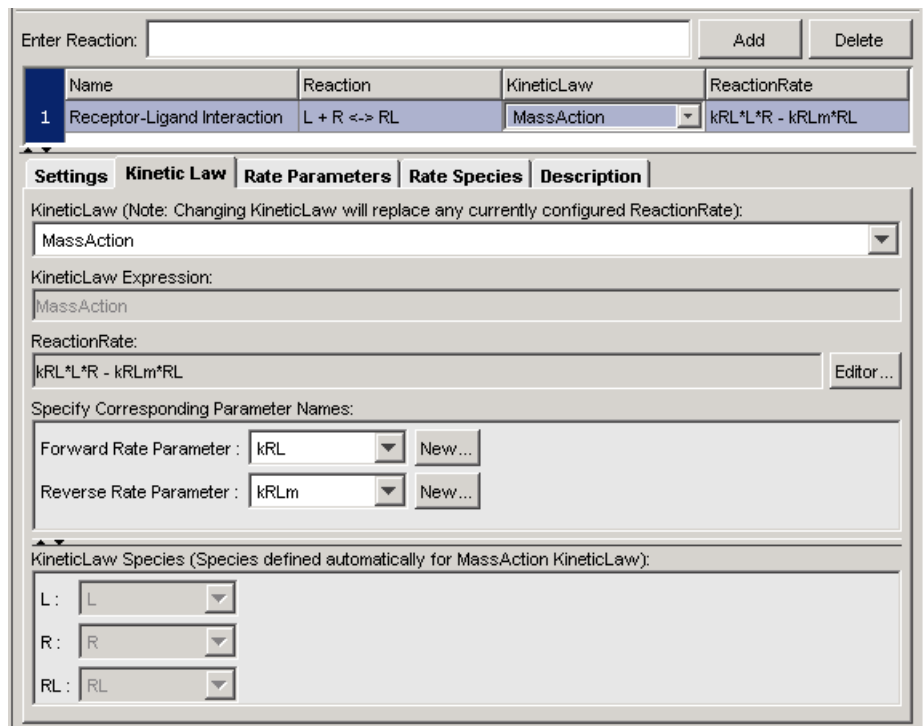
Name (Specify the name of the parameter):

Scope (Specify where the parameter is scoped):
 Kinetic Law

5 Click **Create**.

6 Repeat steps 2 through 5 to create the **Reverse Rate Parameter**. Call the parameter **kRLm**.

Notice that SimBiology updates the **ReactionRate** column.



Enter Reaction:

Name	Reaction	KineticLaw	ReactionRate
1 Receptor-Ligand Interaction	$L + R \leftrightarrow RL$	MassAction	$kRL \cdot L \cdot R - kRLm \cdot RL$

Settings | **Kinetic Law** | **Rate Parameters** | **Rate Species** | **Description**

KineticLaw (Note: Changing KineticLaw will replace any currently configured ReactionRate):

KineticLaw Expression:

ReactionRate:

Specify Corresponding Parameter Names:

Forward Rate Parameter :

Reverse Rate Parameter :

KineticLaw Species (Species defined automatically for MassAction KineticLaw):

L :

R :

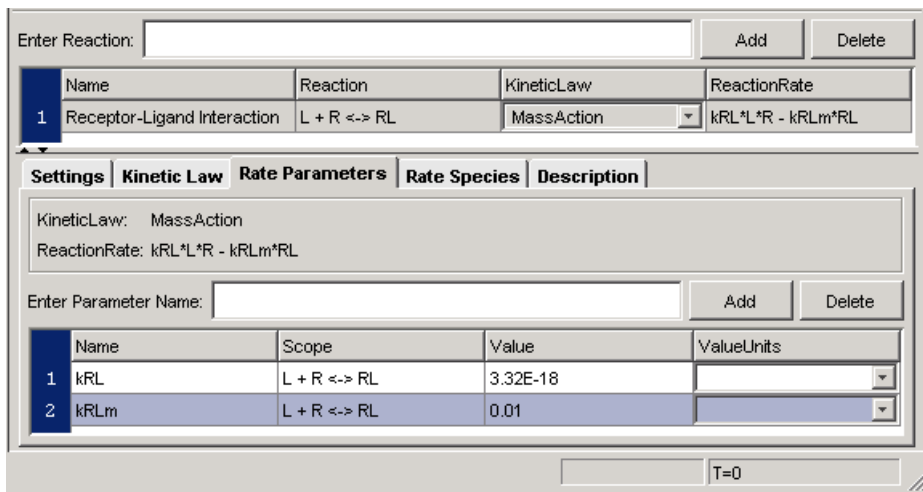
RL :

The species are automatically selected when you MassAction kinetic law.

For other kinetic laws, you would select the species to be included in the rate equation from the **Kinetic Law Species** list.

7 Enter the parameter values in the **Rate Parameters** tab:

$k_{RLm} = 0.01$ and $k_{RL} = 3.32E-18$.



Setting Initial Amounts of Species

SimBiology adds species for you when you add a reaction. You can set the initial amounts of all the model species in the **Species** pane.

Name	InitialAmount
L	6.022E17
R	10000.0
RL	0.0

- 1** In the **Project Explorer**, double-click **Species**. SimBiology opens the **Species** pane.
- 2** In the **Species** pane, double-click in each **InitialAmount** cell and enter the preceding values.

Enter Name:

	Name	InitialAmount	InitialAmountUnits
1	L	6.022E17	<input type="text"/>
2	R	10000.0	<input type="text"/>
3	RL	0.0	<input type="text"/>

T=0

You now have a complete reaction with all components added and defined in SimBiology.

Completing the SimBiology Model

The previous sections of this tutorial show you how to enter the first reaction for the yeast G protein cycle model and configure the reaction rate equation in SimBiology. Repeat the procedures to add the rest of the reactions, parameters, and species values as described in the previous sections, and create a rule to specify the ratio of active G protein that corresponds to the ratio determined experimentally in the referenced study [Yi et al. 2003].

Reactions (p. 2-18)	Table of reactions used in the model
Alternative Ways to Build Reactions in the Desktop (p. 2-19)	Build reactions using the Reaction Builder dialog box; creating binding and unbinding reactions
Parameters (p. 2-21)	Table of parameters and values used in the model
Species (p. 2-22)	Table of species and species initial amounts used in the model
Creating a Rule for the G Protein Model (p. 2-25)	Create a rule in the model to specify the ratio of active G protein
Verifying the Model (p. 2-26)	Verify the model to check if it is ready for simulation

Reactions

Add reactions 2 through 6 listed in the following table, set the kinetic law for each reaction to `MassAction`, create parameters, and configure the reaction rate using the procedure for “Determining the Reaction Rate Equation” on page 2-14.

No.	Name	Reaction	Rate Parameters
1	Receptor-Ligand Interaction	$L + R \leftrightarrow RL$	k_{RLm}, k_{RL}
2	Heterotrimeric G protein formation	$G_d + G_{bg} \rightarrow G$	k_{G1}

No.	Name	Reaction	Rate Parameters
3	G protein activation	$RL + G \rightarrow Ga + Gbg + RL$	kGa
4	Receptor synthesis and degradation	$R \leftrightarrow null$	kRdo, kRs
5	Receptor-Ligand degradation	$RL \rightarrow null$	kRD1
6	G protein inactivation	$Ga \rightarrow Gd$	kGd

Your reaction table should look similar to the following figure:

Name	Reaction	KineticLaw	ReactionRate
Receptor-ligand interaction	$L + R \leftrightarrow RL$	MassAction	$kRL \cdot L \cdot R - kRLm \cdot RL$
Heterotrimeric Gprotein formation	$Gd + Gbg \rightarrow G$	MassAction	$kG1 \cdot Gd \cdot Gbg$
Gprotein activation	$RL + G \rightarrow Ga + Gbg + RL$	MassAction	$kGa \cdot RL \cdot G$
Receptor synthesis-degradation	$R \leftrightarrow null$	MassAction	$kRdo \cdot R - kRs$
Receptor-ligand degradation	$RL \rightarrow null$	MassAction	$kRD1 \cdot RL$
Gprotein inactivation	$Ga \rightarrow Gd$	MassAction	$kGd \cdot Ga$

Alternative Ways to Build Reactions in the Desktop

This optional section shows you some alternative methods to build a reaction in the **Reactions** pane. Use the examples above to try out these methods. If you have finished entering the reactions for the model proceed to “Parameters” on page 2-21

The **Reactions** pane has several dialog boxes that are convenient for building reactions.

Building a Reaction

You can graphically build a reaction using the Reaction Builder.


- 1 If you are not already in the **Reactions** pane, in the **Project Explorer** double-click **Reactions**.
- 2 Click **Build** to open the Reaction Builder dialog box.
- 3 Select a species from the **Available Species** list and click the **Reactant** or **Product** button.
- 4 To edit stoichiometric relationships, click in the **Stoich** column and type.
- 5 Select the **Reversible** check box if the reaction is reversible.
- 6 Click **Add** to continue editing within the Reaction Builder. Click **OK** to finish and return to the **Reactions** pane.

Creating a Binding Reaction

Use the **Bind** button to create a bound product from two reactant species.

- 1 If you are not already in the **Reactions** pane, in the **Project Explorer** double-click **Reactions**.
- 2 In the **Enter Reaction** box, enter the reactant species.

lactose + lactase

- 3 Click the  **Bind** button. SimBiology writes the product as a compound name, with a colon between reactant names to indicate binding.


lactose:lactase

Creating an Unbinding Reaction

Use the **Unbind** button to create two product species from a bound reactant.

- 1 If you are not already in the **Reactions** pane, in the **Project Explorer** double-click **Reactions**.
- 2 In the **Enter Reaction** box, enter the reactant species.

lactose:lactase

- 3 Click  Unbind. SimBiology writes the product names with a + between them to indicate unbinding.

lactose + lactase

Parameters

In the **Reactions** pane, after you create parameters in the **Kinetic Law** tab, you can set the value of the parameter in the **Rate Parameters** tab.

Alternatively, you can set all the parameters in the **Parameters** pane. In the **Project Explorer** double-click **Parameters** to open the **Parameters** pane.

Use the following values for rate parameters:

Parameter Value Table

Name	Value
kRLm	0.01
kRL	3.32E-18
kRdo	4.0E-4
kRs	4.0
kRD1	0.0040
kG1	1.0
kGa	1.0E-5
kGd	0.11

In order to be consistent with units for kRL, RL and L, the value for kRL is converted from the published value, $2.0E6M^{-1}s^{-1}$, to $3.32E-18$ with units $1/(molecule*second)$ (assuming a volume of unity).

Name	Scope	Value	ValueUnits
kRLm	L + R \leftrightarrow RL	0.01	
kRL	L + R \leftrightarrow RL	3.32E-18	
KRdo	R \leftrightarrow null	4.0E-4	
KRs	R \leftrightarrow null	4.0	
kRD1	RL \rightarrow null	0.0040	
kG1	Gd + Gbg \rightarrow G	1.0	
kGa	RL + G \rightarrow Ga + Gbg + RL	1.0E-5	
kGd	Ga \rightarrow Gd	0.11	

Species

Set the species amounts in the **Species** pane. In the **Project Explorer**, double-click **Species** to access this pane.

- Note that the species participating in the reactions have been added automatically to the species list, with default amounts set to 0.0. Double-click each **InitialAmount** cell to change the values to those given in the table.
- The amount of L (α -factor) used in the experiments is 1 M. This value when converted to molecule (assuming a volume of unity) is 6.022E17. This is now internally consistent with the units for the species, RL, and the parameter, kRL.

Species Initial Amounts

Name	InitialAmount (Molecule)
L	6.022E17
R	10000.0
G	7000.0
Gd	3000.0
Gbg	3000.0

Species Initial Amounts (Continued)

Name	InitialAmount (Molecule)
Ga	0.0
RL	0.0

In order to replicate the published results, SimBiology needs the definition of the ratio of active G protein; call this ratio `Ga_frac`. `Ga_frac` is Ga/Gt , where `Ga` is active G protein ($G\alpha$ -GTP) and `Gt` is the total amount of G protein in a cell. This relationship is defined using a rule in SimBiology, and the procedure to create this rule is described in “Creating a Rule for the G Protein Model” on page 2-25.

Define two additional species, called `Ga_frac` and `Gt` in SimBiology.

Additional Species

Name	InitialAmount (molecule)
<code>Ga_frac</code>	0.0
<code>Gt</code>	10000.0

To add a new species,

- 1** In the **Project Explorer**, double-click **Species** to open the **Species** pane.
- 2** In the **Enter name** box, enter the name of a new species, and then click **Add** or press **Enter**.

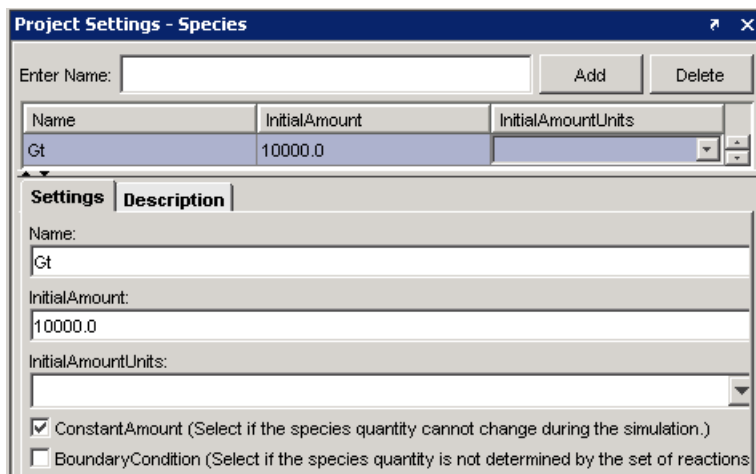
`Ga_frac`

The species table updates with the new entry and its row selected. Note that the species is now available in the **Settings** tab.

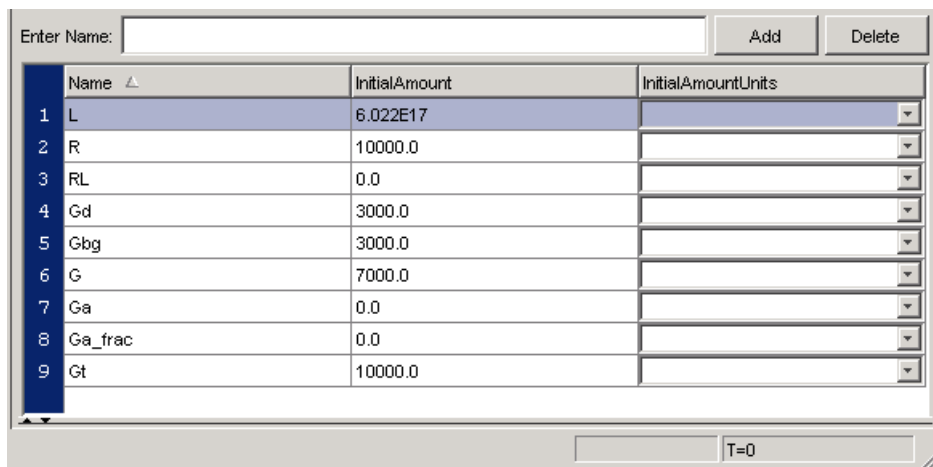
- 3** In the **Initial Amount** cell, enter a value for the amount or concentration of the species.

0.0

- 4** Repeat steps 1 through 3 for Gt. **InitialAmount** = 10000.0
- 5** In the **Settings** tab, select the **ConstantAmount** check box only for Gt, because the amount of Gt does not vary during the simulation.



Your species table should now look similar to this:



For additional help in each procedure, select **Help > SimBiology Desktop Help** for context-sensitive help.

Creating a Rule for the G Protein Model

A SimBiology rule is a mathematical expression that modifies a species amount or a parameter value. Use an algebraic rule to define the value of the species `Ga_frac` in the model.

- 1 In the **Project Explorer**, double-click the **Rules**, to access the **Rules** pane.
- 2 In the **Enter Rule** box, type the expression, and then click **Add** or press **Enter**.

`Ga_frac-Ga/Gt`

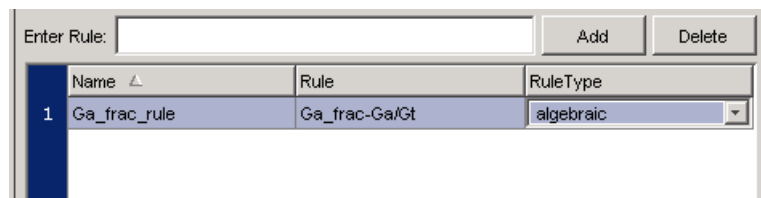
The rule is entered as an expression.

- 3 From the **RuleType** list, select

algebraic

- 4 Give your rule a name (optional). Double-click and type the following in the **Name** box.

`Ga_frac_rule`



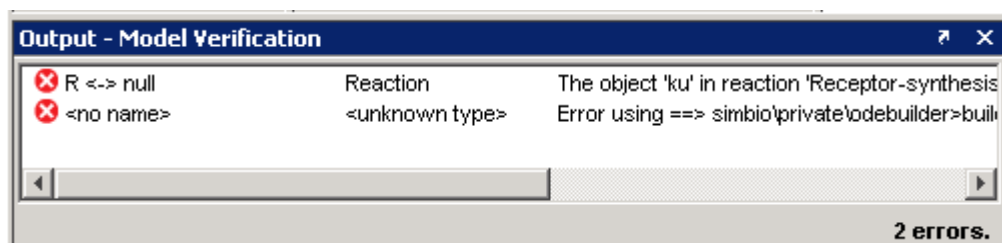
This completes the section on building the G protein cycle model for the wild-type strain.

Verifying the Model

While you are building your model in the SimBiology desktop, you can click



at any time to generate a list of any errors and warnings in the model. The errors and warnings appear in the **Output** pane. Following is an example of the error generated when the reaction rate of a reaction is set to a parameter that you have not defined in SimBiology.



Use **Verify** to see if the example model shows any error or warnings. Double-click the error row to move to the location of the error.

You can interrupt and stop the verification process by clicking **Stop** at any time during verification.

Simulating the G Protein Cycle Model in SimBiology

In the previous sections, this tutorial described building a model in SimBiology for a G protein cycle. This model uses the G protein cycle in the yeast pheromone response pathway. This section describes conditions for simulation and the simulation results for this model.

Setting Conditions Before
Simulating the G Protein Model
(p. 2-27)

Setting conditions for simulation in
the **Simulation Settings** pane

Simulation Results for the Model of
the Wild-Type Strain (p. 2-30)

Simulation results for the G protein
cycle model in the wild-type strain

Setting Conditions Before Simulating the G Protein Model

Consider the following points about simulating this model:

- Yi., et al. show data up to 600s for the active G protein time course. To replicate these results, change the simulation settings from the default 10 second to 600 second. This change remains active for this model unless you change it back to the default.
- The ligand species 'L' has values that are magnitudes higher than those of many of the other species. Don't log data for 'L' so that while plotting you can enable instant visualization of the other species through proper scaling of plots. To do this, define **Data Logging** to stop logging data for 'L'.

The first procedure (below) describes how to change the simulation stop time. The second procedure is about recording a subset of data ("Specifying Which Data Is Recorded by SimBiology" on page 2-28).

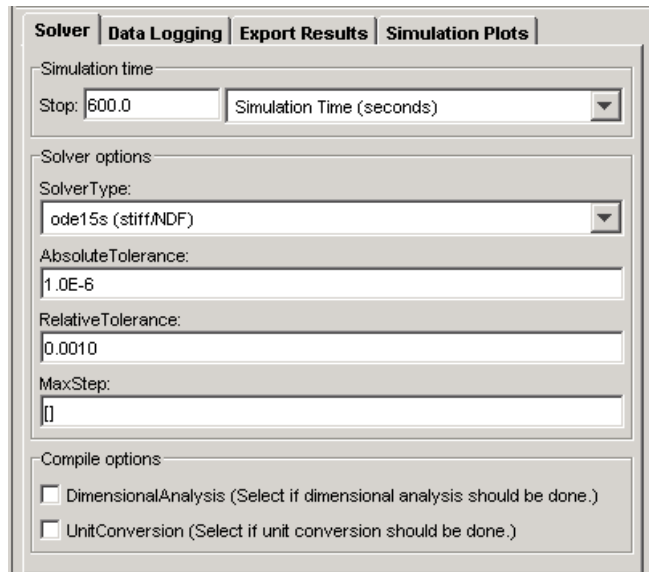
Changing Simulation Stop Time

Change the stop time to replicate the simulation used in the reference paper [Yi et al. 2003], and to facilitate comparison with the experimental results presented in the study.

- 1 Change the time in the SimBiology toolbar to 600 second and press **Enter**. SimBiology applies the new time setting.



- 2 Expand **Simulation and Analysis** in the **Project Explorer** and double-click **Simulation Settings**. SimBiology opens the **Simulation Settings** pane.
- 3 Click the **Solver** tab. (You can also apply your time settings in the **Simulation Time** box.)



- 4 Leave the solver type as the default **SolverType**, `ode15s(stiff/NDF)`, and leave the **AbsoluteTolerance**, **RelativeTolerance**, and **MaxStep** values as the default.

Specifying Which Data Is Recorded by SimBiology

You can specify the species names for which SimBiology should *log* that is record the simulation data. The data set specified is plotted in the figure window.

- 1 Expand **Simulation and Analysis** in the **Project Explorer**, and double-click **Simulation Settings** to open the **Simulation Settings** pane.
- 2 Select the **Data Logging** tab.
- 3 Select the check boxes for the species to log. Because, all the species check boxes are selected by default, clear the check box for 'L'.

Log ▾	Type	State Name	Scope
<input type="checkbox"/>	species	L	Yeast_G_protein_wt
<input checked="" type="checkbox"/>	species	RL	Yeast_G_protein_wt
<input checked="" type="checkbox"/>	species	R	Yeast_G_protein_wt
<input checked="" type="checkbox"/>	species	Gt	Yeast_G_protein_wt
<input checked="" type="checkbox"/>	species	Gd	Yeast_G_protein_wt
<input checked="" type="checkbox"/>	species	Gbg	Yeast_G_protein_wt
<input checked="" type="checkbox"/>	species	Ga_frac	Yeast_G_protein_wt
<input checked="" type="checkbox"/>	species	Ga	Yeast_G_protein_wt
<input checked="" type="checkbox"/>	species	G	Yeast_G_protein_wt

T=0


Alternatively, if you choose to log the data for all the species, you can use the **Plot Browser** to select the subset of species you want to view in your plot. This is described in “Viewing a Subset of Species in the Figure Window” on page 2-31.

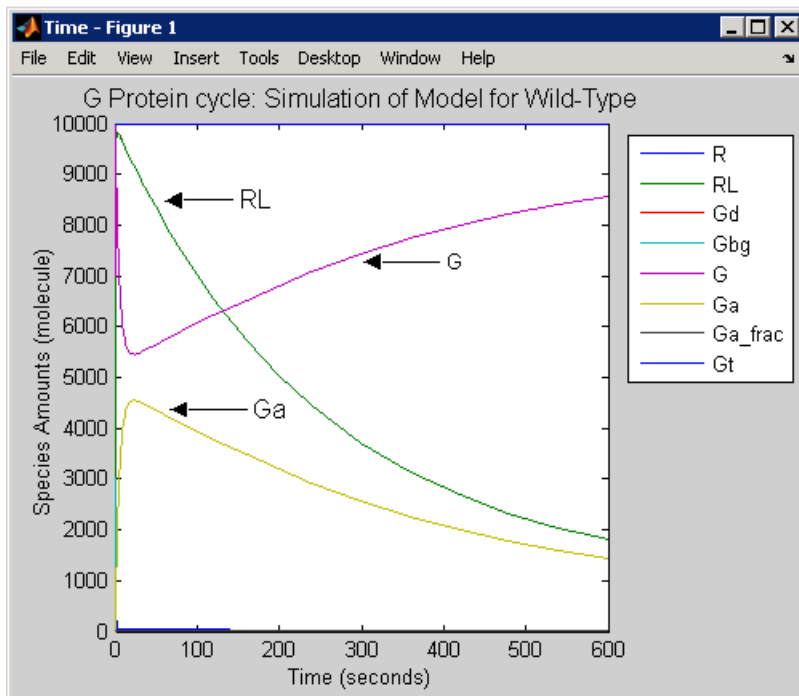
Tips for Use and Some Points to Consider

- You can save all these simulation settings as one custom simulation setting. See the context-sensitive help for **Simulation Settings** to find help on this topic. To access context-sensitive help select **Help > SimBiology Desktop Help**.
- The default ode15s(stiff/NDF), is adequate for modeling of many biological pathways. You might, however, need a different solver for some models. For more information on choosing solver types, see *Selecting a Solver*.

- SimBiology gives you a choice of three stochastic solvers: stochastic (SSA), implicit tau, and explicit tau. Try one of the stochastic solvers with this model and see how it compares with ode15s. For information, see Stochastic Solvers. You can also see how the stochastic solvers compare with each other.
- For a counter that tracks the simulation, look in the lower-right corner of the SimBiology desktop.
- Click the following links to learn more about absolute and relative tolerance. These are links to SimBiology reference pages with definitions for AbsoluteTolerance and RelativeTolerance.

Simulation Results for the Model of the Wild-Type Strain

Simulate the model you have built and see your results. To simulate the model, click  (**Run**) on the simulation toolbar.

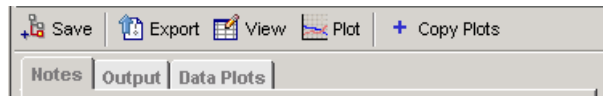


To view all species, see “Viewing a Subset of Species in the Figure Window” on page 2-31 for help on using the **Plot Browser**.

Saving Simulation Data

You can optionally save the data from the most recent simulation run. Unless you save the data for each simulation run, it is overwritten by the data for the next run.

- 1 In the **Project Explorer**, double-click **Data** for the wild-type model.
- 2 In the **Data** pane, click **Save**.



- 3 In the Save Data dialog box, specify a name for your data, and then click **Save**.

wt_model_run1

The saved data is added under **Data** in the **Project Explorer**.

Viewing a Subset of Species in the Figure Window

The **Plot Browser** lets you view all or a subset of the species. This is useful when you log (record) the data for all the species in the model simulation, but you want to view only some of the species.

- 1 On the figure window, from the **View** menu, select **Plot Browser**. The figure window updates with a view of the plotted Y variables.
- 2 Select the variables to view.

To skip to the section on simulating the second model, see “Simulating the G Protein Cycle Model of the Mutant Strain” on page 2-34.

Building a Model for the Mutant Strain

The deletion in SST2, results in uncatalyzed G protein deactivation (Reaction 6; $G_a \rightarrow G_d$). From a modeling perspective this means a change in the rate of the reaction. This section shows you how to copy the previously built model into a new model session, change the parameter to reflect the change in the rate of the reaction, and simulate the new model.

Note An additional simplifying assumption of this model is that there are no changes in the initial amounts of species or the rate of any other reaction.

Copying a Model (p. 2-32)

Copy a model by importing project contents

Changing Model Settings (p. 2-33)

Change the settings in the new model to reflect the pathway in the *sst2Δ* strain

Copying a Model

To copy a model, you first need to save the model to be copied as a SimBiology project. If you have not yet done so, see “Saving Your Work as a SimBiology Project File” on page 2-12.

Use the following procedure to import a model created in your SimBiology project. This is a convenient way to “copy” a model in the project and change the copied model while preserving the previous version.

- 1** From the **File** menu, select **Import Project Contents**.

The Load SimBiology Project dialog box opens.

- 2** Browse and select the project.

`yeast_g_protein_cycle.sbproj`

- 3** Click **Open**. The imported model opens in a new model session.

Changing Model Settings

The copied model has the simulation settings used for the previous model. Therefore, the only settings to change are the name of the model and the value of the parameter kGd. Remember to select the appropriate nodes in the *newly* created model session.

1 Change the name of the model. In the **Project Explorer**, double-click **SimBiology Model** to open the **SimBiology Model**.

2 Click the **Settings** tab. In the **Model Name** box enter the following:

Yeast_G_Protein_mut

3 Locate the parameter kGd for the Yeast_G_Protein_mut using **Find** in the top-right corner of the SimBiology desktop.



- a** In the **Find** box, enter kGd and press **Enter**. SimBiology opens the **Output** pane with the results of the search.
- b** Locate the parameter kGd for the mutant strain. Note that SimBiology organizes the results by model and lists the model component.
- c** Double-click the row containing the parameter kGd under the model Yeast_G_Protein_mut. SimBiology opens the **Parameters** pane with the row containing kGd selected.
- d** Change the value of kGd from 0.11 to 0.004.

Simulating the G Protein Cycle Model of the Mutant Strain

In addition to generating the plot for the model representing the G protein cycle in the *sst2Δ* strain, this section describes how to create and use a custom plot for the data generated in the model simulation.

Creating a Custom Plot (p. 2-34)

Create a custom plot to show simulation results with dashed lines

Plotting Using a Custom Plot (p. 2-35)

Add the custom plot to simulation plots, select the species to be plotted, and plot the results

Simulation Results for the Model of the Mutant Strain (p. 2-37)

Plot the simulation results for the model of the mutant (*sst2Δ*) strain

Creating a Custom Plot

To keep the data plots from each of the model simulations distinct and to facilitate comparison, you can customize one of the plots. This example shows you how to create and save a custom plot to plot the simulation data with dashed lines.

- 1 In the **Project Explorer**, double-click **My Plot Types**.
- 2 In the **My Plot Types** pane, point to the **Copy Plot Type** list and select **Time**.
- 3 Click **Update**.



The **My Plot Types** command window updates:

```

Plot Code with Input Arguments: (tobj, y)
1 % Get the simulation data associated with the species
2 % specified in y.
3 if strcmpi(y, '<all>')
4     [time, data, names] = sbiogetnamedstate(tobj);
5 else
6     [time, data, names] = sbiogetnamedstate(tobj, y);
7 end
8
9 % Error checking.
10 if size(data,2) == 0
11     error('Species specified do not exist.');
```

4 Make the following change to `hline = plot (time,data);` (line 15):

```
hLine = plot (time,data,'LineStyle','--');
```

5 Click **Save**.

The Save Plot Type dialog box opens.

6 Enter a name for the custom plot type and click **Save**.

The new custom plot appears under **My Plot Types** in the **Project Explorer**.

Time plot with dashed line

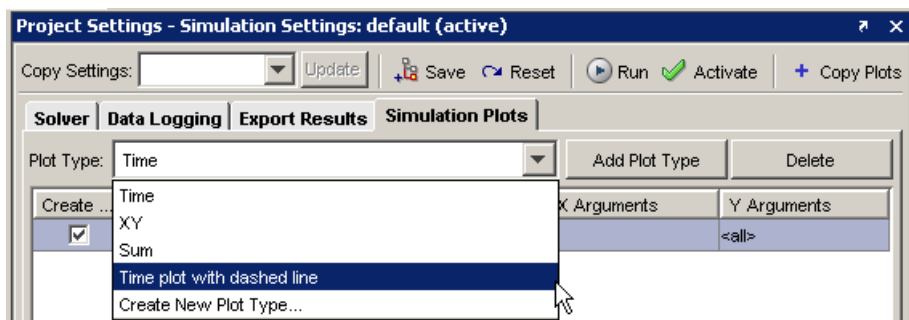
Plotting Using a Custom Plot

Plot the simulation data for the *sst2Δ* model with dashed lines.

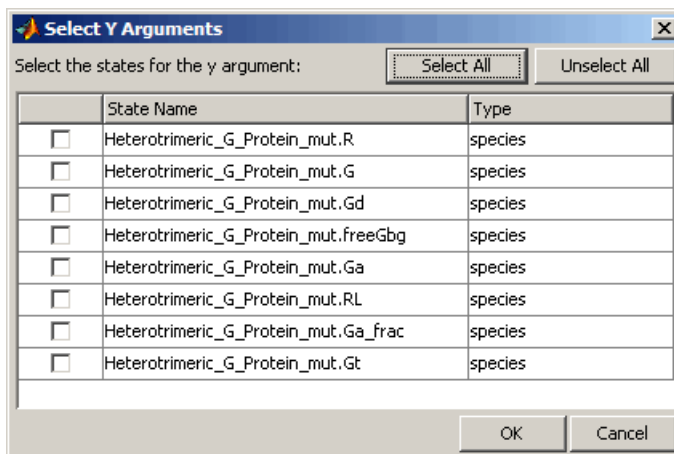
1 In the **Project Explorer**, expand **Simulation and Analysis** for this model and select **Simulation Settings: default (active)**.

2 In the **Simulation Settings: default (active)** pane, click the **Simulation Plots** tab.

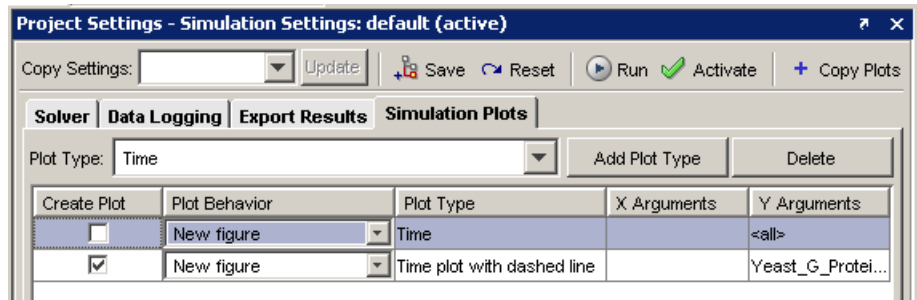
- 3 From the **Plot Type** list, select the new custom plot and click the **Add Plot Type** button.



- 4 In the plot type table, double-click the **Y Arguments** cell for the new entry. This opens the Select Y Arguments dialog box. Click the **Select All** button and then click **OK**.



- 5 In the plot types table, clear the **Create Plot** check box for the Time plot.




When you simulate the model, the plot is generated with dashed lines.

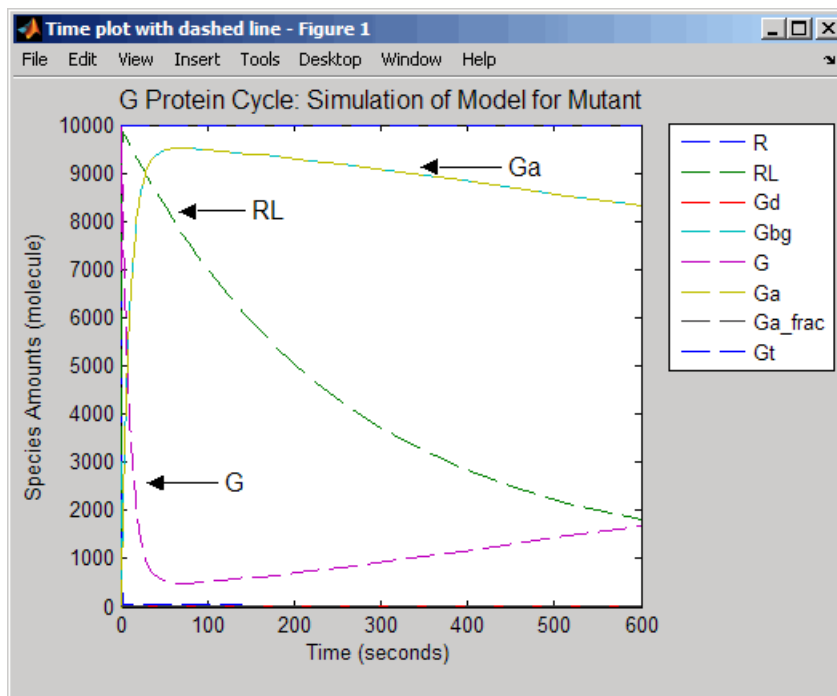
Simulation Results for the Model of the Mutant Strain

To simulate the model,

- 1 In the **Project Explorer**, right-click **Model Session-Yeast_G_Protein_mut** and select **Activate Yeast_G_Protein_mut**.

The model name appears bold in the **Project Explorer** indicating that this model is the active model in the project.

- 2 Click  (**Run**) on the simulation toolbar.



To view each species in the figure window, see “Viewing a Subset of Species in the Figure Window” on page 2-31.

The simulation results for the wild-type strain are described in “Simulation Results for the Model of the Wild-Type Strain” on page 2-30.

Plotting Species from Two Different Data Sets

This section shows you how to compare the active G protein fractions in the two simulations. This example shows you how to plot the data without having to rerun the simulation, and more about how to generate custom plots.

The procedures in this section show you how to create a plot showing species from the two data sets in this tutorial. This example uses the data from the most recent simulation run. Start by plotting the active G protein fraction from the model of wild-type strain. Then, leave the generated figure window open and plot active G protein fraction from the model of the *sst2Δ* strain in the same plot.

Plotting the Active G Protein Fraction from the Model of the Wild-Type Strain (p. 2-39)

Plot active G protein fraction simulation data for the wild-type strain

Creating a Custom Plot to Compare the Data (p. 2-40)

Create a custom plot specifying the species to plot

Plotting the Active G Protein Fraction from the Model of the Mutant Strain (p. 2-41)

Use the custom plot type to plot the *sst2Δ* Ga_frac data in the existing plot

Plotting the Active G Protein Fraction from the Model of the Wild-Type Strain

You can find the simulation data under **Simulation and Analysis** for each model. You can also save the data from previous simulations, see “Saving Simulation Data” on page 2-31 for more information.

To plot data from a previous simulation run,

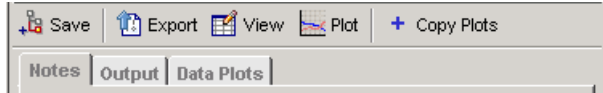
1 In the **Project Explorer**, double-click **Data** to open the **Data** pane.

2 In the **Data** pane, click **Plot**.

SimBiology plots the data from the most recent simulation run.

Specify that the species Ga_frac should be plotted for the wild-type model.

- 1 In the **Project Explorer**, double-click **Data** for the wild-type model.
- 2 In the **Data** pane, select the **Data Plots** tab.



- 3 From the **Plot Type** list, select the Time plot and click the **Add Plot Type** button.
- 4 In the plot type table, double-click the **Y Arguments** cell for the new entry. This opens the Select Y Arguments dialog box.
- 5 Select `Yeast_G_Protein_wt.Ga_frac` and click **OK**.
- 6 In the plot type table, clear the **Create Plot** check boxes for the other plots, and click **Plot**. Leave the figure window open.

Creating a Custom Plot to Compare the Data

Create a custom plot that specifies that the species `Ga_frac` should be plotted with dashed lines for the `sst2Δ` model, and add a legend indicating `Ga_frac` from wild-type (`Ga_frac_wt`) and `Ga_frac` from `sst2Δ` (`Ga_frac_mut`).

- 1 In the **Project Explorer**, double-click **My Plot Types**.
- 2 In the **My Plot Types** pane, point to the **Copy Plot Type** list and select Time plot with dashed line.
- 3 Click **Update**.

The **My Plot Types** editor window is updated with the code for this plot.

- 4 Make the following changes to the code:

Under `% Show legend` add the `%` symbol to make these lines of code into comments.

```
%h = legend(names, 'Location', 'NorthEastOutside');  
%set(h, 'Interpreter', 'none')
```


Specify the legend.

```
legend({'Ga_frac_wt', 'Ga_frac_mut'}, 'Location', 'NorthEastOutside', 'Interpreter', 'none');
```

5 Click **Save**.

A Save Plot Type dialog box opens. Enter a name for the custom plot type and click **Save**.

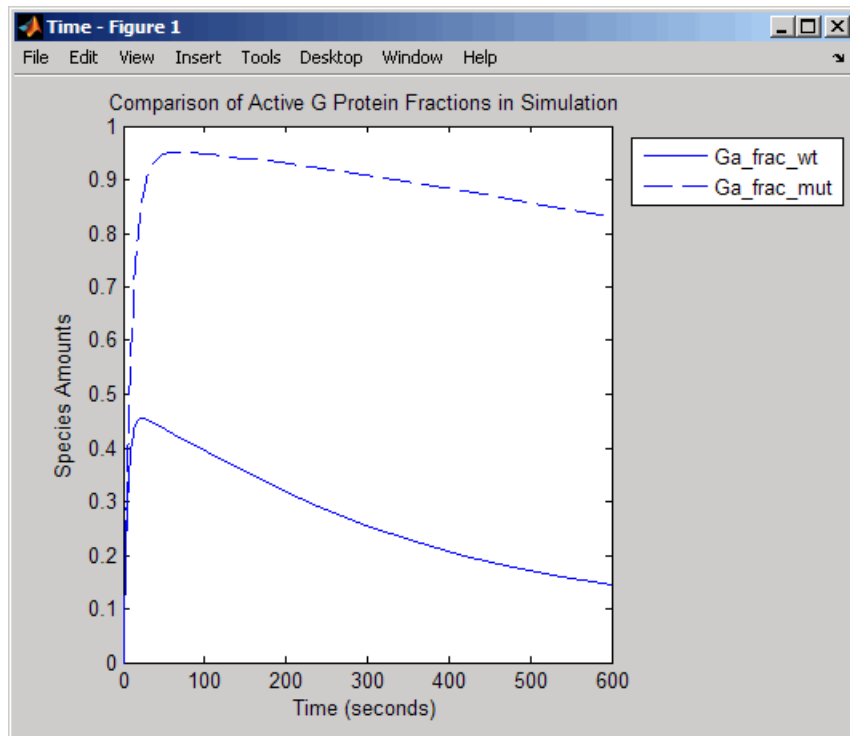
```
Time plot for Ga_frac comparisons
```

The new custom plot appears under **My Plot Types** in the **Project Explorer**. Now you can plot Ga_frac data from the wild-type strain with Ga_frac data from the *sst2Δ*.

Plotting the Active G Protein Fraction from the Model of the Mutant Strain

Use the new plot type to plot the *sst2Δ* Ga_frac data.

- 1 In the **Project Explorer**, double-click **Data** for the *sst2Δ* model.
- 2 In the **Data** pane, select the **Data Plots** tab.
- 3 From the **Plot Type** list, select the Time plot for Ga_frac comparisons plot and click the **Add Plot Type** button.
- 4 In the plot type table, double-click the **Y Arguments** cell for the new entry. This opens the Select Y Arguments dialog box. Select Yeast_G_Protein_mut.Ga_frac and click **OK**.
- 5 In the plot type table, clear the **Create Plot** check box for the other plots.
- 6 From the **Plot Behavior** list select Add to current axes and click **Plot**. This option lets you add data to the most recently generated plot. You must have the figure window open to exercise this option.



Plotting Experimental Data with Simulation Data

SimBiology enables you to work with your experimental data and plot your data from the SimBiology desktop. The section describes how to store the experimental data and use the custom plotting features to plot the data with your simulation data.

This example uses the yeast G protein model built in this tutorial, using a reference paper published by Yi and colleagues (Yi et al. 2003). The experimental data used here are also from the same reference paper.

Creating a Custom Plot for
Experimental Data (p. 2-43)

Working with experimental data in
My Plot Types

Plotting the Data (p. 2-44)

Plotting the experimental data with
the simulation data

Creating a Custom Plot for Experimental Data

- 1** In the **Project Explorer**, double-click **My Plot Types**.
- 2** In the **My Plot Types** pane, copy the following code into the plot types editor window:

```
% 1. Store the time and state data
%(Obtained from Fig. 5 of reference paper.)
x = [0 10 30 60 110 210 300 450 600];
y = [0 0.35 0.4 0.36 0.39 0.33 0.24 0.17 0.2];

% 2. Store the estimated error values.
%(Obtained from Fig. 5 of reference paper.)
L = [0 0.0100 0 0.0100 0.0200 0.0200 0.0300 0.0200 0.0200];
U = [0 0.0100 0 0.0200 0.0100 0.0180 0.0350 0.0300 0.0100];

% 3. Plot the experimental data.
errorbar(x,y,L,U,'LineStyle','none', 'Marker', '.');
legH3 = legend('Ga_frac_sim','Ga_frac_exp' , 'Location','NorthEastOutside');
set(legH3, 'Interpreter','none')
```

```
% To make a better picture,  
axis([0 600 0 0.5]);
```

Explanation of the code

In step 1 you store the data as vectors in two variables, one for the experimental values of active G protein fractions (x), and the other for the time points (y). By writing scripts in this command window, you can store and process your experimental data before plotting.

In step 2 you store the estimated upper (U) and lower (L) bounds of the error values of each data point.

In step 3, the function `errorbar` enables you to plot x versus y with error bars $L(i)+U(i)$ long. x , y , L , and U must be the same size. When they are vectors, each error bar is a distance of $L(i)$ below and $U(i)$ above the point defined by $(x(i),y(i))$. For more information, see `errorbar`.

The code also specifies legend location, marker style, line style, and axis scale. For more information, see `legend` and `axis`.

3 Clear the **X Arguments must be specified** and **Y Arguments must be specified** check boxes. The x and y arguments are already specified in the code that you entered in the second step.

4 Click **Save**.

The Save Plot Type dialog box opens. Enter a name for the custom plot type and click **Save**.

```
Ga_frac Experimental Data Plot
```

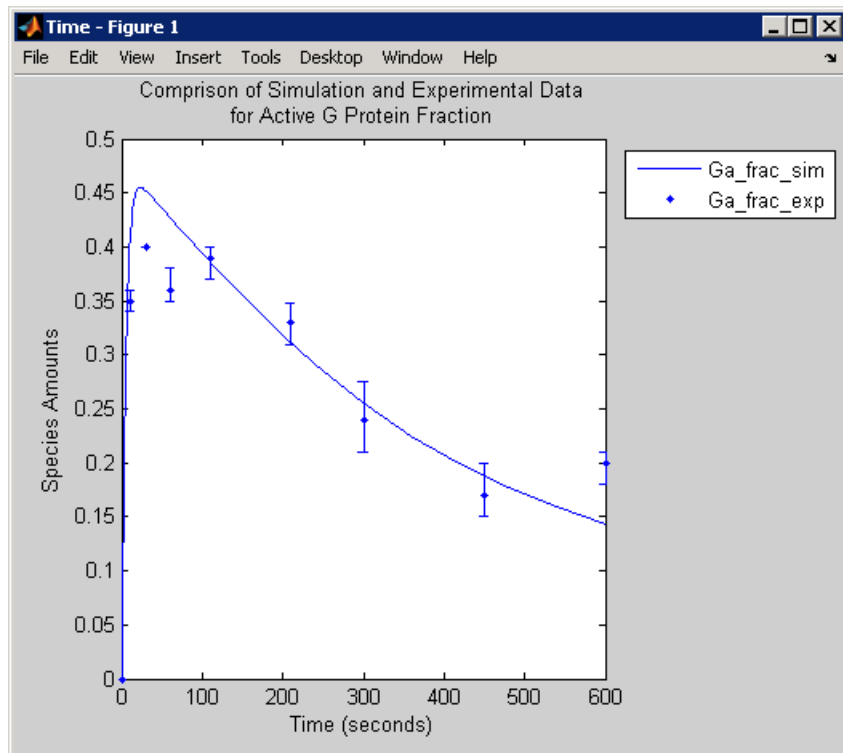
The new custom plot appears under **My Plot Types** in the **Project Explorer**.

Plotting the Data

You can add the new custom plot to the data plot for the model of the wild-type strain and plot the simulation data for `Ga_frac` with the experimental data.

1 In the **Project Explorer**, double-click **Data** for the wild-type model.

- 2 In the **Data** pane, click the **Data Plots** tab.
- 3 From the **Plot Type** list, select the Ga_frac Experimental Data Plot plot and click the **Add Plot Type** button.
- 4 Select the **Create Plot** check box for the following:
 - a Time plot with the Y arguments limited to Yeast_G_Protein_wt.Ga_frac and choose New Figure from the **Plot Behavior** list for this plot.
 - b Ga_frac Experimental Data Plot and choose Add to current axes from the **Plot Behavior** list, for this plot.
- 5 In the plot type table, clear the **Create Plot** check boxes for the other plots and click **Plot**.



References

- [1] Tau-Mu Yi, Hiroaki Kitano, and Melvin I. Simon. A quantitative characterization of the yeast heterotrimeric G protein cycle. PNAS (2003) vol. 100, 10764-10769.
- [2] Alberts, B., Bray, D., Lewis, J., Raff, M., Roberts, K., and Watson, J.D. Molecular Biology of the Cell, 3rd edition, Garland Publishing, 1994.

M-Phase Control in *Xenopus* Oocyte Extracts

John Tyson's Computational Cell Biology Lab created a mathematical model for M-phase control in *Xenopus* oocyte (frog egg) extracts (Marlovits et. al. 1998). The M-phase control model shows principles by which you can apply phosphorylation and regulatory loops in your own models. Publications typically list systems of ordinary differential equations (ODEs) that represent a model system. This example shows you how to interpret these ODEs in the form of reaction pathways that are easier to represent and visualize in SimBiology.

M-Phase Control Model (p. 3-2)	Diagram of reaction pathways and model assumptions
M-Phase Control Equations (p. 3-4)	Differential rate equations for each varying species and supporting algebraic equations
SimBiology Model with Rate and Algebraic Rules (p. 3-14)	Enter differential rate equations directly from the literature
SimBiology Model with Reactions and Algebraic Rules (p. 3-22)	Convert differential rate equations to reactions and reaction rates
References (p. 3-40)	Literature references and Web links for additional information

M-Phase Control Model

The model is centered around M-phase promoting factor (MPF). There are two positive feedback loops where MPF increases its synthesis and a negative feedback loop where MPF decreases its amount by increasing its degradation.

Synthesis Reactions (p. 3-2)

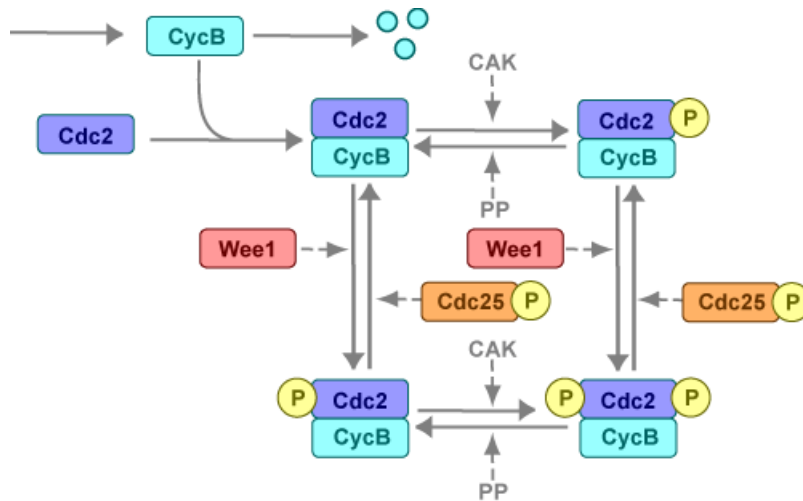
Synthesis of Cyclin B, dimerization of Cyclin B with Cdc2 protein kinase, and covalent modification with phosphate groups

Regulation Reactions with Active MPF (p. 3-3)

Positive and negative feedback loops with M-phase promoting factor (MPF), Wee1 kinase, Cdc25 phosphatase, and anaphase promoting complex (APC)

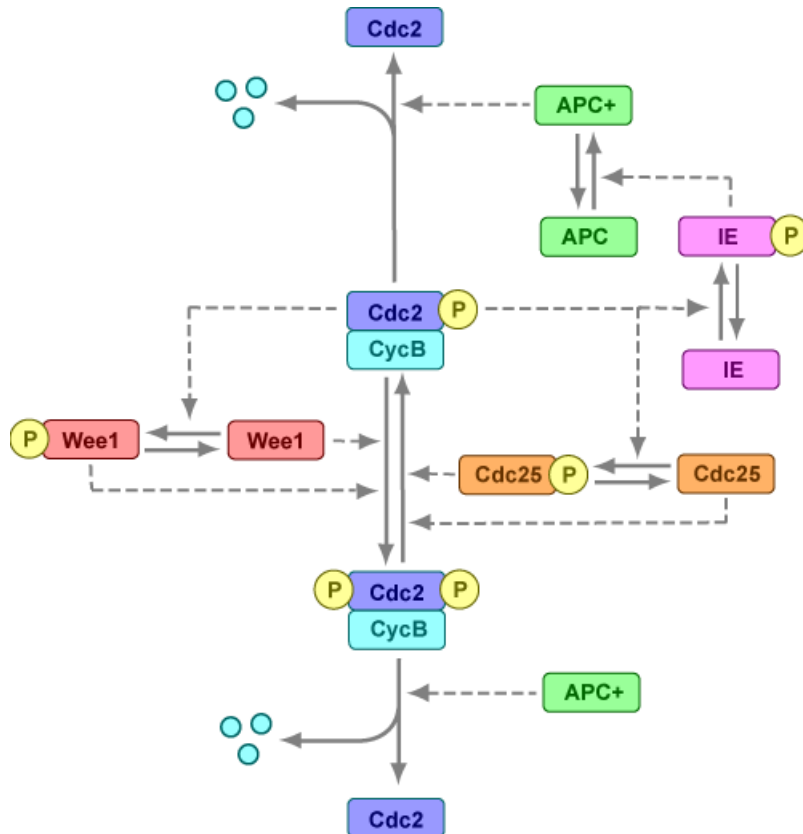
Synthesis Reactions

Cyclin B (CycB) dimerizes with Cdc2 kinase (Cdc2) to form M-phase promoting factor (MPF).



Regulation Reactions with Active MPF

Positive feedback loops with M-phase promoting factor (MPF) activate the Cdc25 phosphatase and deactivate the Wee1 kinase. A negative feedback loop with MPF activates anaphase-promoting complex (APC) that regulates the degradation of the Cyclin B subunit.



M-Phase Control Equations

Models in systems biology are commonly described in the literature with differential rate equations. However, SimBiology defines a model using reactions. This section shows you how to convert models published in the literature to a SimBiology format. The equation numbers match the published paper for this model (Marlovits et. al. 1998). Equations that are missing in the sequence involve the Cdk inhibitor protein (CKI), which is not currently modeled in the SimBiology version.

Converting Differential Equations to Reactions (p. 3-5)	Write the reaction and reaction rate equations from the differential rate equations
Equation 1 Cyclin B (p. 3-6)	Synthesis and degradation of Cyclin B
Equation 2 M-Phase Promoting Factor (MPF) (p. 3-7)	Synthesis, degradation, and removal of phosphate groups
Equation 3 Inhibited M-Phase Promoting Factor (pMPF) (p. 3-7)	Degradation with addition and removal of phosphate groups
Equation 4 Inhibited and Activated M-Phase Promoting Factor (pMPFp) (p. 3-8)	Degradation with addition and removal of phosphate groups
Equation 5 Activated M-Phase Promoting Factor (MPFp) (p. 3-9)	Degradation with addition and removal of phosphate groups
Equation 11 Cell Division Control 25 (Cdc25) (p. 3-10)	Activation of Cdc25 phosphatase by active M-phase promoting factor (MPFp) and deactivation by an unknown phosphatase
Equation 12 Wee1 Activation/Deactivation (p. 3-10)	Deactivation of Wee1 kinase by active M-phase promoting factor (MPFp) and activation by an unknown kinase
Equation 13 Intermediate Enzyme (IE) Activation/Deactivation (p. 3-11)	Activation of an intermediate enzyme by active M-phase promoting factor (MPFp) and deactivation by an unknown phosphatase

Equation 14 APC Activation/Deactivation (p. 3-11)	Activation of anaphase-promoting factor (APC) by an intermediate enzyme (IE) and deactivation
Equation 17 Rate Parameter K2 (p. 3-12)	Variable rate parameter for the degradation of Cyclin B defined by an algebraic equation
Equation 18 Rate Parameter Kcdc25 (p. 3-12)	Variable rate parameter for the activation of Cdc25 phosphatase defined by an algebraic equation
Equation 19 Rate Parameter Kwee1 (p. 3-13)	Variable rate parameter for the activation of Wee1 kinase defined by an algebraic equation

Converting Differential Equations to Reactions

The rules for writing reaction and reaction rate equations from differential rate equations include not only the equations but also an understanding of the reactions. dx/dt refers to the species the differential rate equation is defining. *kinetics* refers to the species in the reaction rate.

- Positive terms: rate species are placed on right side of the reactions; reaction rate equation species are placed on the right.

$$\text{kinetics} \rightarrow \frac{dx}{dt}$$

- Negative terms: rate species are placed on the left side of the reaction because the species are being used up in some way; reaction rate equation species are placed on left. You need to deduce the products from additional information about the model.

$$\text{kinetics or } \left(\frac{dx}{dt}\right) \rightarrow \text{products?}$$

The following table will help you to deduce the products for a reaction. In this example, by convention, phosphate groups on the right side of a species name are activating while phosphate groups on left are inhibiting.

Enzyme	Description	Reaction
wee1	Kinase, add inhibiting phosphate group	MPF → P-MPF
cdc25	Phosphatase, remove inhibitory phosphate group	P-MPF → MPF + P
kcak	Kinase, add activating phosphate group	MPF → MPFp
kpp	Phosphatase, remove activating phosphate group	MPF-P → MPF + P
MPF	Kinase, add activating or inhibiting phosphate group	Wee1/Cdc25/IE → X-P or P-X
ki	Add inhibiting Cki	Cki + MPF → Cki:MPF
kir	Remove inhibiting Cki	Cki:MPF → Cki + MPF

Equation 1 Cyclin B

Differential rate equation for Cyclin B (Marlovits et. al. 1998).

$$\frac{d[\text{CycB}]}{dt} = +k_1 - k_2[\text{CycB}] - k_3[\text{Cdc2}][\text{CycB}]$$

Rate rule using SimBiology format for the differential rate equation 1. For a model using this rule, see “SimBiology Model with Rate and Algebraic Rules” on page 3-14.

$$\text{Rule 1 } [\text{CycB}] = k_1 - K_2 * [\text{CycB}] - k_3 * [\text{Cdc2}] * [\text{CycB}]$$

Reaction and reaction rate equations derived from the differential rate equation. For a model using these reactions, see “SimBiology Model with Reactions and Algebraic Rules” on page 3-22.

Reaction 1	AA -> CycB	v = k1
Reaction 2	CycB -> AA	v = K2* [CycB]
Reaction 3	Cdc2 + CycB -> MPF	v = k3* [Cdc2] * [CycB]

Equation 2 M-Phase Promoting Factor (MPF)

Differential rate equation for M-phase promoting factor (MPF) (Marlovits 1998). Note, the parameter name k_{cacr} (Marlovits 1998) is changed to k_{pp} (Borisuk 1998) in the following reaction equations. MPF is a heterodimer of Cdc2 kinase and Cyclin B.

$$\begin{aligned} \frac{d[\text{MPF}]}{dt} = & +k_3[\text{Cdc2}][\text{CycB}] -K_2[\text{MPF}] \\ & +k_{pp}[\text{MPFp}] -k_{cak}[\text{MPF}] \\ & +K_{cdc25}[\text{pMPF}] -K_{wee1}[\text{MPF}] \\ & +k_{ir}[\text{Cki:MPF}] -k_i[\text{MPF}][\text{Cki}] \end{aligned}$$

Rate rule using SimBiology format for the differential rate equation 1. For a model using this rule, see “SimBiology Model with Rate and Algebraic Rules” on page 3-14.

$$\begin{aligned} \text{Rule 2 MPF} = & k_{pp} \cdot \text{MPFp} - (K_{wee1} + k_{cak} + K_2) \cdot \text{MPF} + \\ & K_{cdc25} \cdot \text{pMPF} + k_3 \cdot \text{Cdc2} \cdot \text{CycB} \end{aligned}$$

Reaction and reaction rate equations derived from the differential rate equation. For a model using these reactions, see “SimBiology Model with Reactions and Algebraic Rules” on page 3-22. A reaction name in parentheses denotes a reaction repeated in another differential rate equation.

(Reaction 3)	$\text{Cdc2} + \text{CycB} \rightarrow \text{MPF}$	$v = k_3 \cdot [\text{Cdc2}] \cdot [\text{CycB}]$
Reaction 4	$\text{MPF} \rightarrow \text{Cdc2} + \text{AA}$	$v = K_2 \cdot [\text{MPF}]$
Reaction 5	$\text{MPFp} \rightarrow \text{MPF}$	$v = k_{pp} \cdot [\text{MPFp}]$
Reaction 6	$\text{MPF} \rightarrow \text{MPFp}$	$v = k_{cak} \cdot [\text{MPF}]$
Reaction 7	$\text{pMPF} \rightarrow \text{MPF}$	$v = K_{cdc25} \cdot [\text{pMPF}]$
Reaction 8	$\text{MPF} \rightarrow \text{pMPF}$	$v = K_{wee1} \cdot [\text{MPF}]$

Equation 3 Inhibited M-Phase Promoting Factor (pMPF)

Differential rate equation for inhibited M-phase promoting factor (pMPF) (Marlovits 1998).

$$\begin{aligned} \frac{d[\text{pMPF}]}{dt} = & -K2[\text{pMPF}] \\ & +kpp[\text{pMPFp}] -kcak[\text{pMPF}] \\ & +Kwee1[\text{MPF}] -Kcdc25[\text{pMPF}] \\ & +kd[\text{Cki:pMPF}] \end{aligned}$$

Rate rule using SimBiology format for the differential rate equation 3. For a model using this rule, see “SimBiology Model with Rate and Algebraic Rules” on page 3-14.

$$\text{Rule 3 pMPF} = Kwee1*MPF - (Kcdc25 + kcak + K2)*pMPF + kpp*pMPFp$$

Reaction and reaction rate equations derived from the differential rate equation. For a model using these reactions, see “SimBiology Model with Reactions and Algebraic Rules” on page 3-22.

Reaction 11	pMPF -> Cdc2 + AA	v = K2*[pMPF]
Reaction 12	pMPFp -> pMPF	v = kpp*[pMPFp]
Reaction 13	pMPF -> pMPFp	v = kcak*[pMPF]
(Reaction 8)	MPF -> pMPF	v = Kwee1*[MPF]
(Reaction 7)	pMPF -> MPF	v = Kcdc25*[pMPF]

Equation 4 Inhibited and Activated M-Phase Promoting Factor (pMPFp)

Differential rate equation for inhibited and activated M-phase promoting Factor (pMPFp) (Marlovits 1998).

$$\begin{aligned} \frac{d[\text{pMPFp}]}{dt} = & -K2[\text{pMPFp}] \\ & +kcak[\text{pMPF}] -kpp[\text{pMPFp}] \\ & +Kwee1[\text{MPFp}] -Kcdc25[\text{pMPFp}] \\ & +kd[\text{Cki:pMPFp}] \end{aligned}$$

Rate rule using SimBiology format for the differential rate equation. For a model using this rule, see “SimBiology Model with Rate and Algebraic Rules” on page 3-14.

Rule 4 $pMPFp = K_{wee1} * MPFp - (k_{pp} + K_{cdc25} + K_2) * pMPFp + k_{cak} * MPF$

Reaction and reaction rate equations derived from the differential rate equation. For a model using these reactions, see “SimBiology Model with Reactions and Algebraic Rules” on page 3-22.

Reaction 15	$pMPFp \rightarrow Cdc2 + AA$	$v = K_2 * [pMPFp]$
(Reaction 13)	$pMPF \rightarrow pMPFp$	$v = k_{cak} * [pMPF]$
(Reaction 12)	$pMPFp \rightarrow pMPF$	$v = k_{pp} * [pMPFp]$
Reaction 16	$MPFp \rightarrow pMPFp$	$v = K_{wee1} * [MPFp]$
Reaction 17	$pMPFp \rightarrow MPFp$	$v = K_{cdc25} * [pMPFp]$

Equation 5 Activated M-Phase Promoting Factor (MPFp)

Differential rate equation for activated M-phase promoting factor (MPFp) (Marlovits 1998).

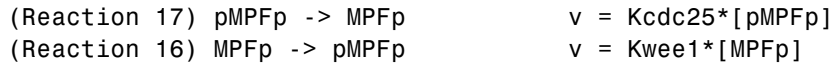
$$\frac{d[MPFp]}{dt} = -K_2[MPFp] + k_{cak}[MPF] - k_{pp}[MPFp] + K_{cdc25}[pMPFp] - K_{wee1}[MPFp] + k_{ir}[CKI:MPFp] - k_i[CKI][MPFp]$$

Rate rule using SimBiology format for the differential rate equation 1. For a model using this rule, see “SimBiology Model with Rate and Algebraic Rules” on page 3-14.

Rule 5 $MPFp = k_{cak} * MPF - (k_{pp} + K_{wee1} + K_2) * MPFp + K_{cdc25} * pMPFp$

Reaction and reaction rate equations derived from the differential rate equation. For a model using these reactions, see “SimBiology Model with Reactions and Algebraic Rules” on page 3-22.

Reaction 19	$MPFp \rightarrow MPF + AA$	$v = K_2 * [MPFp]$
(Reaction 6)	$MPF \rightarrow MPFp$	$v = k_{cak} * [MPF]$
(Reaction 5)	$MPFp \rightarrow MPF$	$v = k_{pp} * [MPFp]$



Equation 11 Cell Division Control 25 (Cdc25)

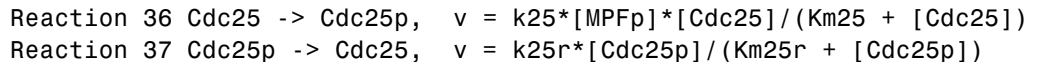
Differential rate equation for activating and deactivating Cdc25 (Marlovits 1998).

$$\frac{d[Cdc25p]}{dt} = + \frac{k25[MPFp][Cdc25]}{Km25+[Cdc25]} - \frac{k25r[Cdc25p]}{Km25r+[Cdc25p]}$$

Rate rule in SimBiology format for the differential rate equation 1. For a model using this rule, see “SimBiology Model with Rate and Algebraic Rules” on page 3-14. Note that, since there isn’t a rate rule for Cdc25, its amount is written as (TotalCdc25 - Cdc25p).

$$\text{Rule 11 Cdc25p} = (k25*MPFp*(TotalCdc25 - Cdc25p))/(Km25 + (TotalCdc25 - Cdc25p)) - (k25r*PPase*Cdc25p)/(Km25r + Cdc25p)$$

Reaction and reaction rate equations derived from the differential rate equation. For a model using these reactions, see “SimBiology Model with Reactions and Algebraic Rules” on page 3-22.



Equation 12 Wee1 Activation/Deactivation

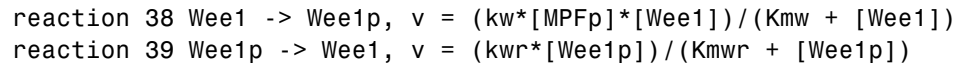
Differential rate equation for activating and deactivating Wee1 kinase (Marlovits 1998). The kinase (MPFp) phosphorylates active Wee1 (Wee1) to its inactive form (Wee1p). The dephosphorylation of inactive Wee1 (Wee1p) is by an unknown phosphatase.

$$\frac{d[Wee1]}{dt} = - \frac{k_w[MPFp][Wee1]}{K_{mw} + [Wee1]} + \frac{k_{wr}[Wee1P]}{K_{mwr} + [Wee1P]}$$

Rate rule in SimBiology format for the differential rate equation 1. For a model using this rule, see “SimBiology Model with Rate and Algebraic Rules” on page 3-14.

$$\text{Rule 12 } \text{Wee1p} = (\text{kw} * \text{MPFp} * (\text{TotalWee1} - \text{Wee1p})) / (\text{Kmw} + (\text{TotalWee1} - \text{Wee1p})) \\ - (\text{kwr} * \text{Wee1p}) / (\text{Kmr} + \text{Wee1p})$$

Reaction and reaction rate equations derived from the differential rate equation. For a model using these reactions, see “SimBiology Model with Reactions and Algebraic Rules” on page 3-22.



Equation 13 Intermediate Enzyme (IE) Activation/Deactivation

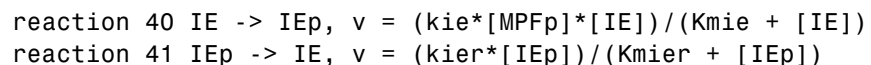
Differential rate equation for activating and deactivating the intermediate enzyme (IE) (Marlovits 1998). The active kinase (MPFp) phosphorylates the inactive intermediate enzyme (IE) to its active form (IEp).

$$\frac{d[\text{IEp}]}{dt} = + \frac{\text{kie}[\text{MPFp}][\text{IE}]}{\text{Kmie} + [\text{IE}]} - \frac{\text{kier}[\text{IEp}]}{\text{Kmier} + [\text{IEp}]}$$

Rate rule in SimBiology format for the differential rate equation 1. For a model using this rule, see “SimBiology Model with Rate and Algebraic Rules” on page 3-14.

$$\text{Rule 13 } \text{IEp} = (\text{kie} * \text{MPFp} * (\text{TotalIE} - \text{IEp})) / (\text{Kmie} + (\text{TotalIE} - \text{IEp})) \\ - (\text{kier} * \text{IEp}) / (\text{Kmier} + \text{IEp})$$

Reaction and reaction rate equations derived from the differential rate equation. For a model using these reactions, see “SimBiology Model with Reactions and Algebraic Rules” on page 3-22.



Equation 14 APC Activation/Deactivation

Differential rate equation for (Marlovits 1998).

$$\frac{d[APCa]}{dt} = + \frac{k_{ap}[IEP][APCi]}{K_{map} + [APCi]} - \frac{k_{apr}[APCa]}{K_{mapr} + [APCa]}$$

Rate rule in SimBiology format for the differential rate equation 1. For a model using this rule, see “SimBiology Model with Rate and Algebraic Rules” on page 3-14.

```
Rule 14 APCa = (kap*IEp*(TotalAPC - APCa))/(Kmap + (TotalAPC - APCa))
              - (kapr*APCa)/(Kmapr + APCa)
```

Reaction and reaction rate equations derived from the differential rate equation. For a model using these reactions, see “SimBiology Model with Reactions and Algebraic Rules” on page 3-22.

```
Reaction 42 APCi -> APCa, v = (kap*[IEp]*[APCi])/(Kmap + [APCi])
Reaction 43 APCa -> APCi, v = (kapr*[APCa])/(Kmapr + [APCa])
```

Equation 17 Rate Parameter K2

Algebraic equation to define the rate parameter K2 (Marlovits 1998). Inactive APC (APCi) is catalyzed by IE (intermediate enzyme) to active APC (APCa).

$$k2 = V2'[APC] + V2''[APC']$$

Algebraic rule in SimBiology format for the algebraic equation 17. For a model using this rule, see “SimBiology Model with Rate and Algebraic Rules” on page 3-14.

```
Algebraic Rule 17 V2i*(TotalAPC - APCa) + V2a*APCa - K2
```

Algebraic rule when simulating with reactions. For a model using this rule with reactions, see “SimBiology Model with Reactions and Algebraic Rules” on page 3-22. V2' is renamed to V2i and V2 is renamed to V2a. APCi (APC) is the inactive form of the enzyme while APCa (APC') is the active form. K2 is the independent variable.

```
Algebraic Rule 1 (V2i*APCi) + (V2a*APCa) - K2
```

Equation 18 Rate Parameter Kcdc25

Algebraic equation to define the rate parameter Kcdc25 (Marlovits 1998). Inactive Cdc25 (Cdc25) is phosphorylated by MPF to active Cdc25 (Cdc25p).

$$kcdc25 = V25'[Cdc25] + V25''[Cdc25p]$$

Algebraic rule in SimBiology format for the algebraic equation 18. For a model using this rule, see “SimBiology Model with Rate and Algebraic Rules” on page 3-14.

$$\text{Algebraic Rule 18 } V25i*(TotalCdc25 - Cdc25p) + V25a*Cdc25p - Kcdc25$$

Algebraic rule when simulating with reactions. Kcdc25 is the independent variable. For a model using this rule with reactions, see “SimBiology Model with Reactions and Algebraic Rules” on page 3-22.

$$\text{Algebraic Rule 2 } (V25i*Cdc25) + (V25a*Cdc25p) - Kcdc25$$

Equation 19 Rate Parameter Kwee1

Algebraic equation to define the rate parameter (Marlovits 1998). Active Wee1 (Wee1) is phosphorylated by MPF to inactive Wee1 (Wee1p).

$$kwee1 = Vwee1'[Wee1p] + Vwee1''[Wee1]$$

Algebraic rule in SimBiology format for rate parameter equation 19. For a model using this rule, see “SimBiology Model with Rate and Algebraic Rules” on page 3-14.

$$\text{Algebraic Rule 19 } Vwee1i*Wee1p + Vwee1a*(TotalWee1 - Wee1p) - Kwee1$$

Algebraic rule when simulating with reactions. Kwee1 is the independent variable. For a model using this rule with reactions, see “SimBiology Model with Reactions and Algebraic Rules” on page 3-22.

$$\text{Algebraic Rule 3 } (Vwee1i*Wee1p) + (Vwee1a*Wee1) - Kwee1$$

SimBiology Model with Rate and Algebraic Rules

There is one rate rule for each equation defining a species and one algebraic rule for each variable parameter in the M-phase control model (Marlovits 1998). For a list and description of the equations, see “M-Phase Control Equations” on page 3-4.

A basic model includes rate rules 1 through 5 and 11 through 14 with algebraic rules 17, 18, and 19.

- “Writing Differential Rate Equations as Rate Rules” on page 3-14
- “Species” on page 3-15
- “Parameters” on page 3-16
- “Rate Rule 1 Cyclin B (CycB)” on page 3-17
- “Rate Rule 2 M-Phase Promoting Factor (MPF)” on page 3-18
- “Rate Rule 3 Inhibited M-Phase Promoting Factor (pMPF)” on page 3-18
- “Rate Rule 4 Activated but Inhibited M-Phase Promoting Factor (pMPFp)” on page 3-19
- “Rate Rule 5 Activated M-Phase Promoting Factor (MPFp)” on page 3-19
- “Rate Rule 11 Activated Cdc25 (Cdc25p)” on page 3-19
- “Rate Rule 12 Inhibited Wee1 (Wee1p)” on page 3-19
- “Rate Rule 13 Activated Intermediate Enzyme (IEp)” on page 3-19
- “Rate Rule 14 Activated APC (APCa)” on page 3-19
- “Algebraic Rule 17 Rate Parameter K2” on page 3-20
- “Algebraic Rule 18 Rate Parameter Kcdc25” on page 3-20
- “Algebraic Rule 19 Rate Parameter Kwee1” on page 3-20
- “Simulation of the M-Phase Control Model with Rules” on page 3-20

Writing Differential Rate Equations as Rate Rules

Writing differential rate equations in an unambiguous format that a software program can understand is a simple process when you follow the syntax rules for programming languages.

- Use an asterisk to indicate multiplication. For example, $k[A]$ is written $k*A$ or $k*[A]$. The brackets around the species A do not indicate concentration.
- SimBiology uses square brackets around species and parameter name to allow names that are not valid MATLAB® variable names. For example, you could have a species named `glucose-6-phosphate dehydrogenase` but you need to add brackets around the name in reaction rate and rule equations.

`[glucose-6-phosphate dehydrogenase]`

- Use parentheses to clarify the order of evaluation for mathematical operations. For example, do not write Henri-Michaelis-Menten reaction rates as $V_m*C/K_d + C$, because V_m*C is divided by K_d before adding C to the result. Instead, write this reaction rate as $(V_m*C)/(K_d + C)$.

Species

The following table lists species in the model with their initial amounts. There are three variable parameters modeled as species (`K2`, `Kcdc25`, and `KWee1`). You could also model the variable parameters as parameters with the property **ConstantAmount** cleared.

Name	InitialAmount ▲	InitialAmountUnits	ConstantAmount
CycB	0.0		<input type="checkbox"/>
MPF	0.0		<input type="checkbox"/>
pMPF	0.0		<input type="checkbox"/>
pMPFp	0.0		<input type="checkbox"/>
MPFp	0.0		<input type="checkbox"/>
Cdc25p	0.0		<input type="checkbox"/>
Wee1p	0.0		<input type="checkbox"/>
IEp	0.0		<input type="checkbox"/>
APCa	0.0		<input type="checkbox"/>
Kcdc25	0.0		<input type="checkbox"/>
Kwee1	0.0		<input type="checkbox"/>
K2	0.0		<input type="checkbox"/>
Wee1	0.0		<input type="checkbox"/>
TotalCdc25	1.0		<input checked="" type="checkbox"/>
TotalWee1	1.0		<input checked="" type="checkbox"/>
TotalAPC	1.0		<input checked="" type="checkbox"/>
TotalIE	1.0		<input type="checkbox"/>
PPase	1.0		<input checked="" type="checkbox"/>
AntiAPC	1.0		<input checked="" type="checkbox"/>
Cdc2	100.0		<input checked="" type="checkbox"/>

Parameters

The following table lists parameters in the model with their initial values. The property **ConstantValue** is selected for all of the parameters.

Name	Value ▾	ValueUnits	ConstantValue
Vweea	1.0		<input checked="" type="checkbox"/>
k1	1.0		<input checked="" type="checkbox"/>
Kmwr	1.0		<input checked="" type="checkbox"/>
Kmapr	1.0		<input checked="" type="checkbox"/>
Km25r	1.0		<input checked="" type="checkbox"/>
kcak	0.64		<input checked="" type="checkbox"/>
V2a	0.25		<input checked="" type="checkbox"/>
V25a	0.17		<input checked="" type="checkbox"/>
kier	0.15		<input checked="" type="checkbox"/>
kapr	0.13		<input checked="" type="checkbox"/>
kap	0.13		<input checked="" type="checkbox"/>
kwr	0.1		<input checked="" type="checkbox"/>
k25r	0.1		<input checked="" type="checkbox"/>
Kmw	0.1		<input checked="" type="checkbox"/>
Km25	0.1		<input checked="" type="checkbox"/>
kie	0.02		<input checked="" type="checkbox"/>
kw	0.02		<input checked="" type="checkbox"/>
k25	0.02		<input checked="" type="checkbox"/>
V25i	0.017		<input checked="" type="checkbox"/>
Vweei	0.01		<input checked="" type="checkbox"/>
Kmier	0.01		<input checked="" type="checkbox"/>
Kmie	0.01		<input checked="" type="checkbox"/>
Kmap	0.01		<input checked="" type="checkbox"/>
V2i	0.0050		<input checked="" type="checkbox"/>
k3	0.0050		<input checked="" type="checkbox"/>
kpp	0.0040		<input checked="" type="checkbox"/>

Rate Rule 1 Cyclin B (CycB)

The rate rule is from “Equation 1 Cyclin B” on page 3-6.

$$\text{rate rule: CycB} = k1 - K2 \cdot \text{CycB} - k3 \cdot \text{Cdc2} \cdot \text{CycB}$$

```
species: CycB = 0 nM
         Cdc2 = 100 nM, [x]constant
parameters: k1 = 1 nM/minute
           K2 = 0 1/minute, []constant
           k3 = 0.005 1/(nM*minute)
```

K2 is a variable rate parameter whose value is defined by an algebraic rule. See “Algebraic Rule 17 Rate Parameter K2” on page 3-20. Its value varies from 0.005 to 0.25 1/minute.

Rate Rule 2 M-Phase Promoting Factor (MPF)

The rate rule is from “Equation 2 M-Phase Promoting Factor (MPF)” on page 3-7.

```
rate rule: MPF = kpp*MPFp - (Kwee1 + kcak + K2)*MPF + Kcdc25*pMPF
           + k3*Cdc2*CycB
species: MPF = 0 nM
        MPFp = 0 nM
        pMPF = 0 nM
parameters: kpp = 0.004 1/minute
           kcak = 0.64 1/minute
           k3 = 0.005 1/(nM*minute)
           K2 = 0 1/minute
           Kcdc25 = 0 1/minute
           Kwee1 = 0 1/minute
```

K2, Kcdc25, and Kwee1 are variable rate parameters whose values are defined by algebraic rules. See “Algebraic Rule 17 Rate Parameter K2” on page 3-20, “Algebraic Rule 18 Rate Parameter Kcdc25” on page 3-20, and “Algebraic Rule 19 Rate Parameter Kwee1” on page 3-20.

Rate Rule 3 Inhibited M-Phase Promoting Factor (pMPF)

The rate rule is from “Equation 3 Inhibited M-Phase Promoting Factor (pMPF)” on page 3-7.

```
rate rule: pMPF = Kwee1*MPF - (Kcdc25 + kcak + K2)*pMPF + kpp*pMPFp
```


Rate Rule 4 Activated but Inhibited M-Phase Promoting Factor (pMPFp)

The rate rule is from “Equation 4 Inhibited and Activated M-Phase Promoting Factor (pMPFp)” on page 3-8.

$$\text{rate rule: pMPFp} = \text{Kwee1} * \text{MPFp} - (\text{kpp} + \text{Kcdc25} + \text{K2}) * \text{pMPFp} + \text{kca} * \text{MPF}$$

Rate Rule 5 Activated M-Phase Promoting Factor (MPFp)

The rate rule is from “Equation 5 Activated M-Phase Promoting Factor (MPFp)” on page 3-9.

$$\text{rate rule: MPFp} = \text{kca} * \text{MPF} - (\text{kpp} + \text{Kwee1} + \text{K2}) * \text{MPFp} + \text{Kcdc25} * \text{pMPFp}$$

Rate Rule 11 Activated Cdc25 (Cdc25p)

The rate rule is from “Equation 11 Cell Division Control 25 (Cdc25)” on page 3-10.

$$\begin{aligned} \text{rate rule: Cdc25p} = & (\text{k25} * \text{MPFp} * (\text{TotalCdc25} - \text{Cdc25p})) / (\text{Km25} + (\text{TotalCdc25} - \text{Cdc25p})) \\ & - (\text{k25r} * \text{PPase} * \text{Cdc25p}) / (\text{Km25r} + \text{Cdc25p}) \end{aligned}$$

Rate Rule 12 Inhibited Wee1 (Wee1p)

The rate rule is from “Equation 12 Wee1 Activation/Deactivation” on page 3-10.

$$\begin{aligned} \text{rate rule: Wee1p} = & (\text{kw} * \text{MPFp} * (\text{TotalWee1} - \text{Wee1p})) / (\text{Kmw} + (\text{TotalWee1} - \text{Wee1p})) \\ & - (\text{kwr} * \text{PPase} * \text{Wee1p}) / (\text{Kmwr} + \text{Wee1p}) \end{aligned}$$

Rate Rule 13 Activated Intermediate Enzyme (IEp)

The rate rule is from “Equation 13 Intermediate Enzyme (IE) Activation/Deactivation” on page 3-11.

$$\begin{aligned} \text{rate rule: IEp} = & (\text{kie} * \text{MPFp} * (\text{TotalIE} - \text{IEp})) / (\text{Kmie} + (\text{TotalIE} - \text{IEp})) \\ & - (\text{kier} * \text{PPase} * \text{IEp}) / (\text{Kmier} + \text{IEp}) \end{aligned}$$

Rate Rule 14 Activated APC (APCa)

The rate rule is from “Equation 14 APC Activation/Deactivation” on page 3-11.

```
rate rule: APCa = (kap*IEp*(TotalAPC - APCa))/(Kmap + (TotalAPC - APCa))  
            - (kapr*AntiAPC*APCa)/(Kmapr + APCa)
```

Algebraic Rule 17 Rate Parameter K2

K2 is a variable rate parameter whose value is determined by the amount of active and inactive APC. The algebraic rule is from “Equation 17 Rate Parameter K2” on page 3-12.

```
algebraic rule: V2i*(TotalAPC - APCa) + V2a*APCa - K2  
species: APCi = 1 nM  
          APCa = 0 nM  
          TotalAPC = 1 nM [x]constant  
parameters: K2 = 0 or 0.25 1/minute, []constant  
            V2i = 0.005 1/(nM*minute)  
            V2a = 0.25 1/(nM*minute)
```

Algebraic Rule 18 Rate Parameter Kcdc25

Kcdc25 is a variable rate parameter whose value is determined by the amount of active and inactive Cdc25. The algebraic rule is from “Algebraic Rule 18 Rate Parameter Kcdc25” on page 3-20.

```
algebraic rule: V25i*(TotalCdc25 - Cdc25p) + V25a*Cdc25p - Kcdc25
```

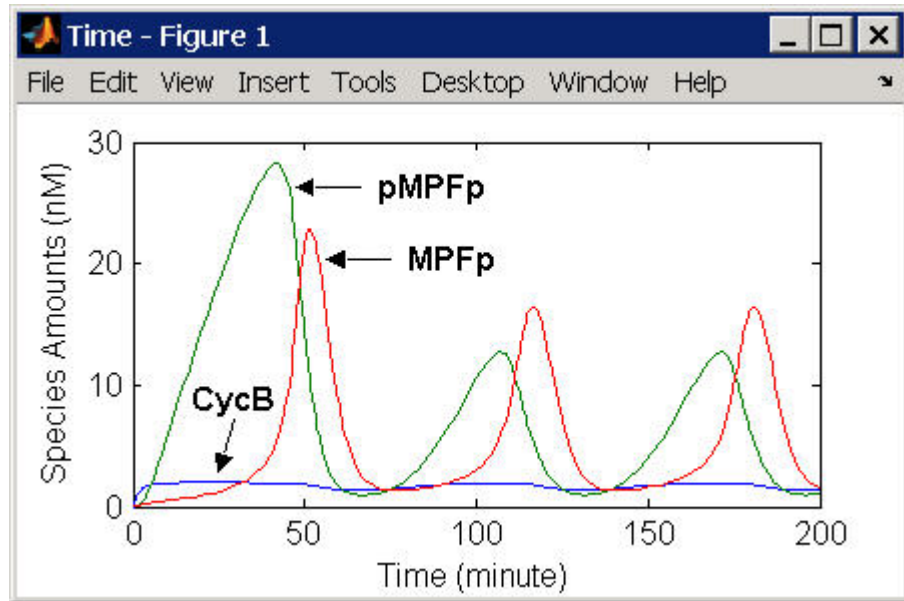
Algebraic Rule 19 Rate Parameter Kwee1

Kwee1 is a variable rate parameter whose value is determined by the amount of active and inactive Wee1. The algebraic rule is from “Equation 19 Rate Parameter Kwee1” on page 3-13.

```
algebraic rule: Vweei*Wee1p + Vweea*(TotalWee1 - Wee1p) - Kwee1
```

Simulation of the M-Phase Control Model with Rules

This is a simulation of the M-phase control model using rate and algebraic rules. Simulate with the ode15s solver and plot species CycB, pMPFp, and MPFp. For a description of the model, see “SimBiology Model with Rate and Algebraic Rules” on page 3-14.



If you want to run the simulation, you can open the model within the SimBiology desktop.

- 1 Open the SimBiology desktop using the function `sbiodesktop`.
- 2 From the **File** menu, select **Open Project**.
- 3 Browse to the file `m_phase_xenopus.sbproj` in the following directory:

```
matlabroot/toolbox/simbio/simbiodemos/m_phase_xenopus.sbproj
```

For a model using reactions and algebraic rules, see “SimBiology Model with Reactions and Algebraic Rules” on page 3-22.

SimBiology Model with Reactions and Algebraic Rules

There can be one or more reactions for an equation defining a species and one algebraic rule for each variable parameter in the M-phase control model (Marlovits 1998). For a list and description of the equations, see “M-Phase Control Equations” on page 3-4.

A basic model includes reactions 1 through 8, 11 through 13, 15 through 17, 19, and 36 through 43 with algebraic rules from equations 17, 18, and 19.

- “Reaction 1 Synthesis of Cyclin B ” on page 3-23
- “Reaction 2 Degradation of Cyclin B ” on page 3-24
- “Reaction 3 Dimerization of Cyclin B with Cdc2 Kinase” on page 3-25
- “Reaction 4 Degradation of Cyclin B on MPF” on page 3-26
- “Reaction 5 Deactivation of Active MPF” on page 3-27
- “Reaction 6 Activation of MPF” on page 3-28
- “Reaction 7 Remove Inhibiting Phosphate from Inhibited MPF” on page 3-29
- “Reaction 8 Inhibition of MPF by Phosphorylation” on page 3-30
- “Reaction 11 Degradation of Cyclin B on Inhibited MPF” on page 3-32
- “Reaction 12 Deactivation of MPF to Inhibited MPF” on page 3-32
- “Reaction 13 Activation of Inhibited MPF” on page 3-32
- “Reaction 15 Degradation of Cyclin B on Active but Inhibited MPF” on page 3-33
- “Reaction 16 Inhibit MPF by Phosphorylation” on page 3-33
- “Reaction 17 Remove Inhibiting Phosphate from Activated MPF” on page 3-34
- “Reaction 19 Degradation of Cyclin B on Activated MPF” on page 3-34
- “Reaction 36 Activation of Cdc25 by Activated MPF” on page 3-34
- “Reaction 37 Deactivation of Cdc25” on page 3-35
- “Reaction 38 Deactivation of Wee1 by Active MPF” on page 3-35

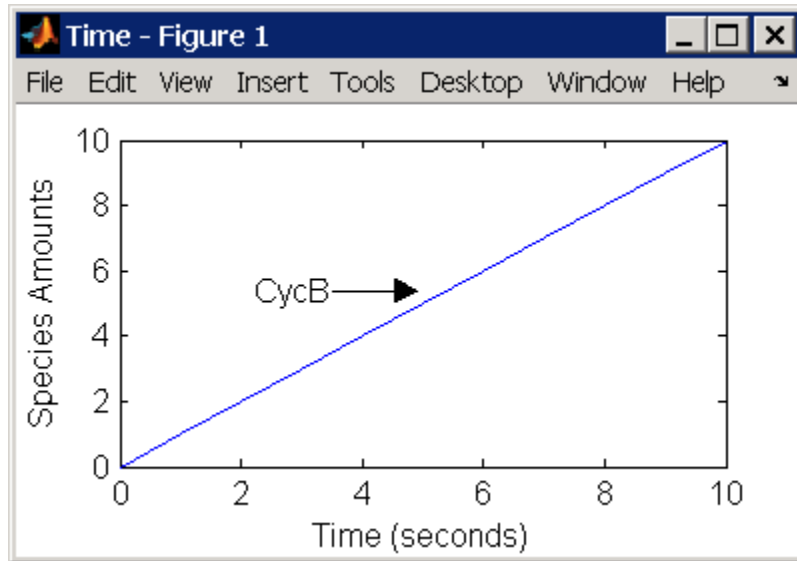
- “Reaction 39 Activation of Wee1” on page 3-35
- “Reaction 40 Activation of Intermediate Enzyme by Active MPF ” on page 3-36
- “Reaction 41 Deactivation of IE” on page 3-36
- “Reaction 42 APC Activation by IEp” on page 3-36
- “Reaction 43 APC Deactivation” on page 3-36
- “Block Diagram of the M-Phase Control Model with Reactions” on page 3-37
- “Simulation of the M-Phase Control Model with Reactions” on page 3-39

Reaction 1 Synthesis of Cyclin B

Cyclin B is synthesized at a constant rate.

```
reaction: AA -> CycB
reaction rate: k1 nM/minute
parameter: k1 = 1 nM/minute
species: CycB = 0 nM
          AA = 100 nM [x]constant [x]boundary
```

Simulate reaction 1 with the ode15s solver.



Reaction 2 Degradation of Cyclin B

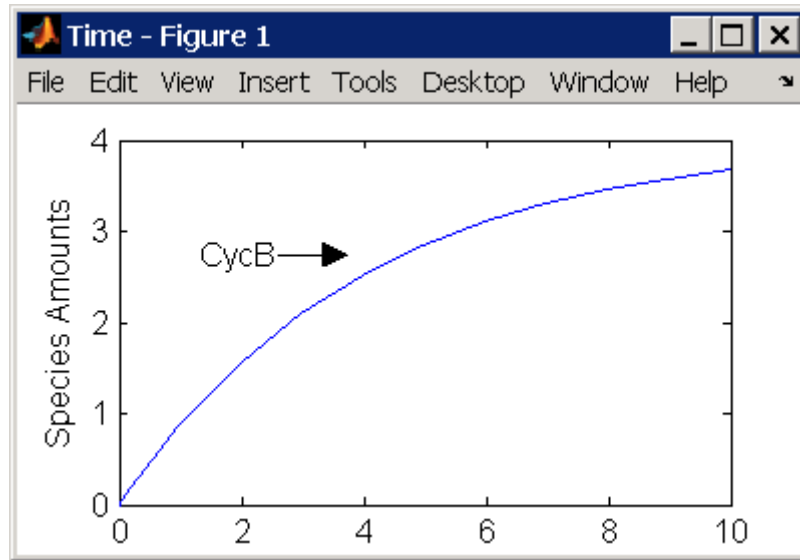
Cyclin B is degraded at the end of the M-phase.

```

reaction: CycB -> AA
reaction rate: K2*CycB nM/minute
parameters: K2 = 0 1/minute, []constant, variable by rule
            V2i = 0.005 1/nM*minute
            V2a = 0.25 1/nM*minute
species: CycB = 0 nM
         APCi = 1 nM
         APCa = 0 nM
         AA = 100 nM [x]constant [x]boundary
algebraic rule: (V2i*APCi) + (V2a*APCa) - K2
    
```

Initially, Cyclin B degradation is low. This implies the amount of active APC (APCa) = 0 and inactive APC (APCi) = APCtotal = 1 nM.

Test the algebraic rule by simulating reactions 1 and 2 with APCi = 0 and APCa = 1.



Reaction 3 Dimerization of Cyclin B with Cdc2 Kinase

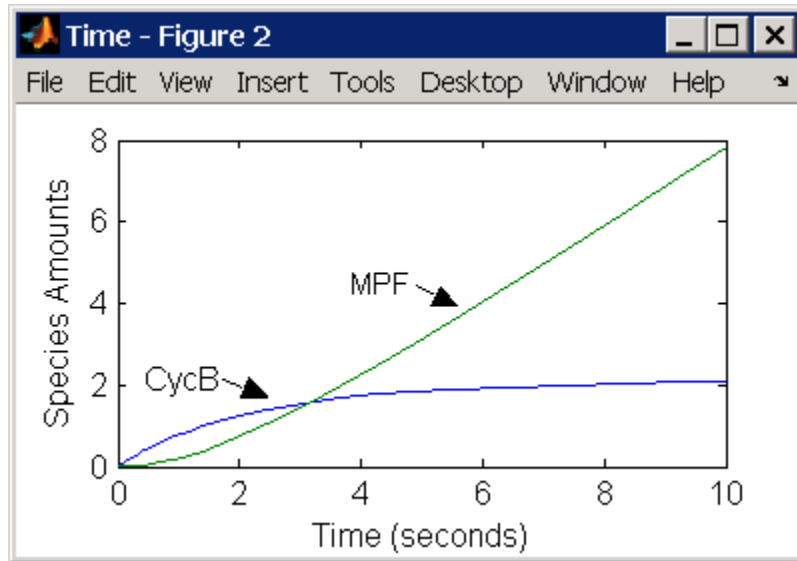
Cyclin B dimerizes with Cdc2 kinase to form M-phase promoting factor (MPF).

```

reaction: Cdc2 + CycB -> MPF
reaction rate: k3*Cdc2*CycB nM/minute
parameters: k3 = 0.005 1/(nM*minute)
species: Cdc2 = 100 nM
          CycB = 0 nM
          MPF = 0 nM

```

Test the model by simulating with $K2 = 0.25$.



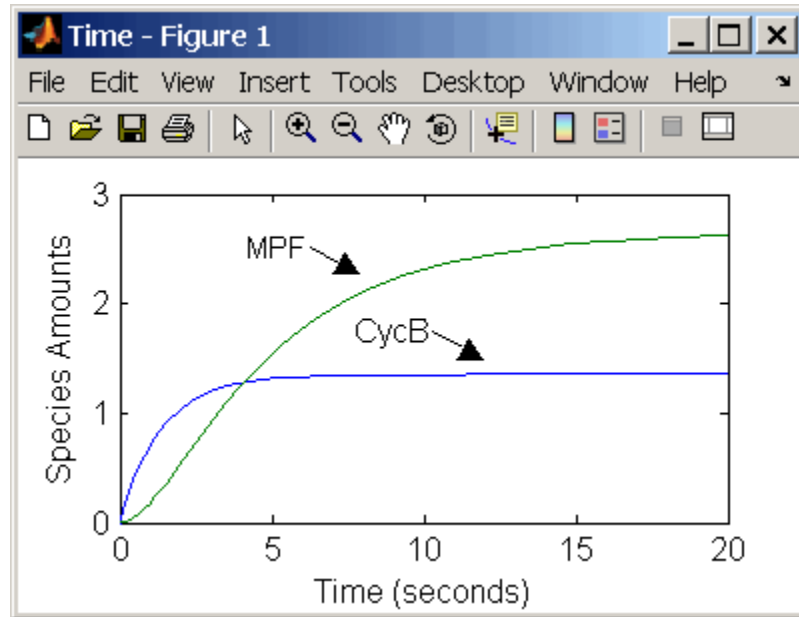
Reaction 4 Degradation of Cyclin B on MPF

Cyclin B is tagged with ubiquitin groups and degrades while bound to Cdc2.

```

reaction: MPF -> Cdc2 + AA
reaction rate: K2*[MPF]
parameters: K2 = 0 or 0.25 1/minute, variable by rule
             v2i = 0.005 1/(nM*minute)
             v2a = 0.25 1/(nM*minute)
species: MPF = 0 nM
          APCi = 1 nM
          APCa = 0 nM
          AA = 100 nM [x]constant [x]boundary
algebraic rule: (v2i*APCi) + (v2a*APCa) - K2
    
```

Test the simulation with $APCa = 1$ and $APCi = 0$. Because the amount of $APCa$ (active) is high, $K2$ increases and the degradation starts to balance the synthesis of MPF.



Reaction 5 Deactivation of Active MPF

Active MPF (MPFp) is dephosphorylated on Thr-161 by an unknown phosphatase (PP) to inactive MPF (MPF).

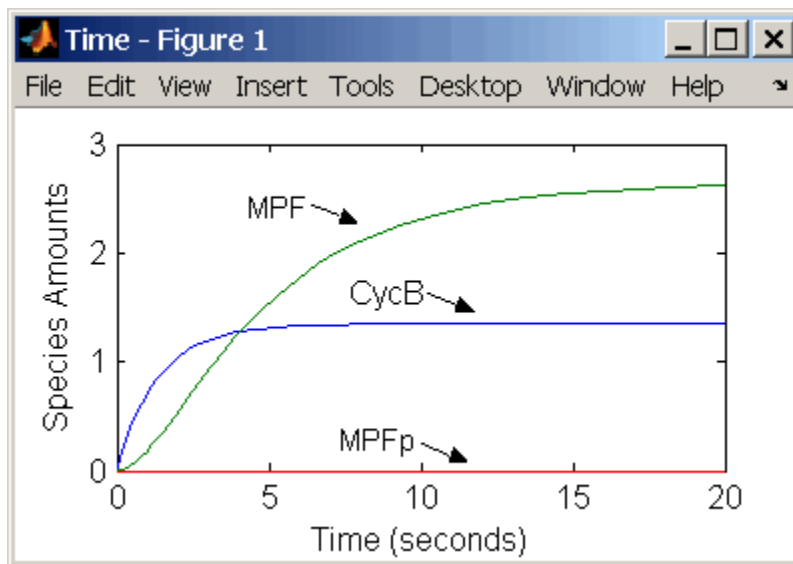
```

reaction: MPFp -> MPF
reaction rate: kpp*[MPFp]
parameters: kpp = 0.004 1/minute
species: MPFp = 0 nM
          MPF = 0 nM

```

$k_{cacr} = 0.004$ 1/minute (Marlovits 1998, p 175), but is renamed to k_{pp} (Borisuk 1998).

Test simulation with $APCa = 1$ and $APCi = 0$. MPF increases without reaching steady-state.



Reaction 6 Activation of MPF

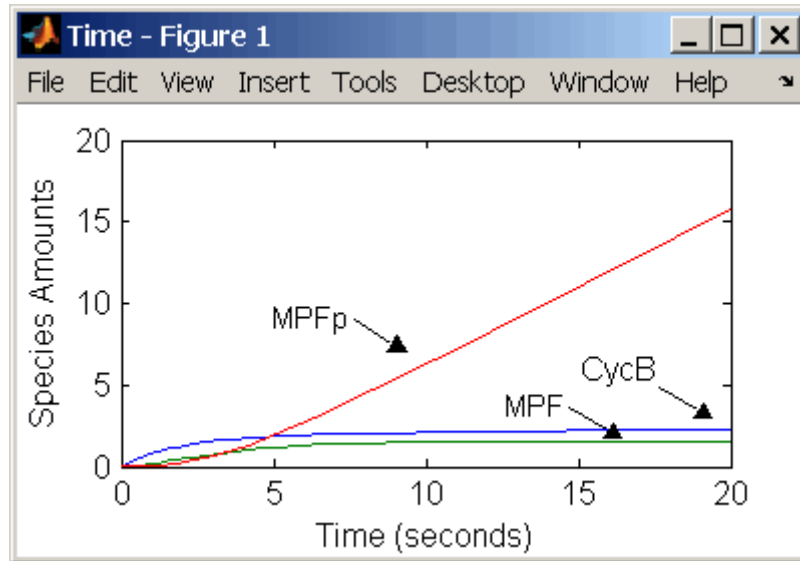
Inactive MPF (MPF) is phosphorylated on Thr-161 by an unknown cyclin activating kinase (CAK).

```

reaction: MPF -> MPFp
reaction rate: kcak*[MPF]
parameters: kcak = 0.64 1/minute
species: MPF = 0 nM
          MPFp = 0 nM
    
```

The kinase reaction that phosphorylates MPF to the active form is 160 times faster than the phosphatase reaction that dephosphorylates active MPF.

Simulate the model with reactions 1 through 6. Notice that after adding reaction 6, most of the product goes to active MPF (MPFp).



Reaction 7 Remove Inhibiting Phosphate from Inhibited MPF

Cdc25 phosphatase removes the inhibiting phosphate groups at the threonine 14 and tyrosine 15 residues on Cdc2 kinase.

```

reaction: pMPF -> MPF
reaction rate: Kcdc25*[pMPF]
parameters: Kcdc25 = 0.0 1/minute or 0.017 1/minute, variable by
                                                    algebraic rule
            V25i = 0.017 1/(mM*minute)
            V25a = 0.17 1/mM*minute
species: pMPF = 0 nM
        MPF = 0 nM
        Cdc25 = 1 nM (inactive)
        Cdc25p = 0 nM (active)
algebraic rule: (V25i*Cdc25) + (V25a*Cdc25p) - Kcdc25

```

Initially, all of the Cdc25 phosphatase is in the inactive form (Cdc25).

Enter the initial value for Kcdc25 as 0.0 and let the first time step calculate the value from the rule, or enter an initial value using the rule.

Initially, set **ConstantAmount** for Cdc25 and Cdc25p to test reactions 1 through 7. Then after you can add the reactions to regulate the Cdc25 phosphatase by clearing the **ConstantAmount** property.

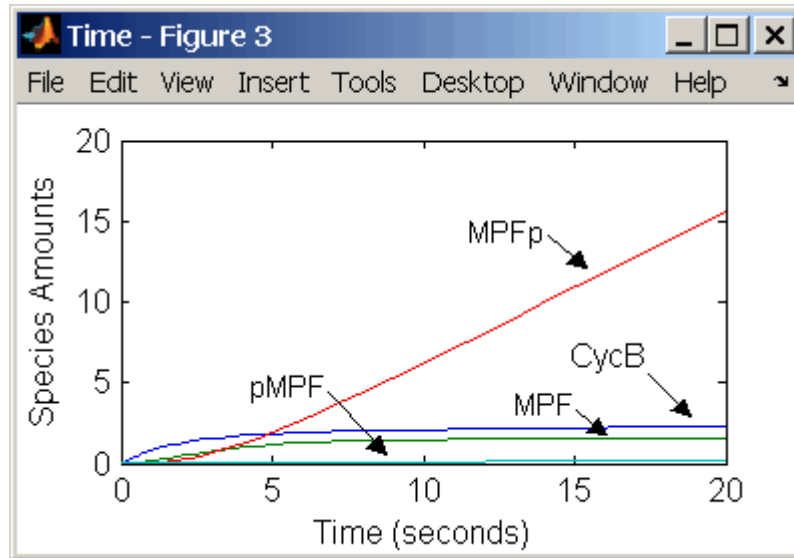
Reaction 8 Inhibition of MPF by Phosphorylation

Addition of inhibiting phosphate groups by Wee1 kinase to inhibit active M-phase promoting factor (MPF). Myt1 kinase is also involved with the phosphorylation, but its contribution is grouped with Wee1.

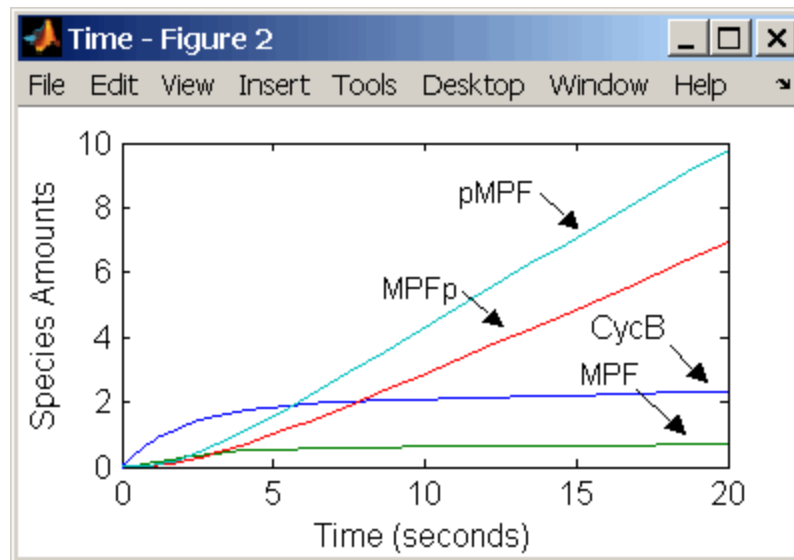
```
reaction: MPF -> pMPF
reaction rate: Kwee1*[MPF]
parameters: Kwee1 = 0.0 1/minute or 0.01 1/minute, variable by
                                                    algebraic rule
            Vwee1i = 0.01 1/(nM*minute)
            Vwee1a = 1.0 1/(nM*minute)
species: MPF = 0 nM
        pMPF = 0 nM
        Wee1p = 1 nM (inactive)
        Wee1 = 0 nM (active)
algebraic rule: (Vwee1i*Wee1p) + (Vwee1a*Wee1) - Kwee1
```

The initial capitalization for the parameter Kwee1 is a convention to indicate that this value changes during the simulation.

Test the simulation for reactions 1 through 8 with Wee1p (inactive) = 1 and Wee1 (active) = 0.



Test the simulation with Wee1p (inactive) = 0 and Wee1 (active) = 1.



Reaction 11 Degradation of Cyclin B on Inhibited MPF

Degradation of Cyclin B (CycB) on inhibited MPF (pMPF). Cyclin B is tagged with ubiquitin groups and degrades while bound to Cdc2.

```

reaction: pMPF -> Cdc2 + AA
reaction rate: K2*[pMPF] nM/minute
parameters: K2 = 0 or 0.25 1/minute, variable by rule
            V2i = 0.005 1/nM*minute
            V2a = 0.25 1/nM*minute
species: MPF = 0 nM
         APCi = 1 nM
         APCa = 0 nM
         AA = 100 nM [x]constant [x]boundary
         Cdc2 = 100 nm
algebraic rule: (V2i*APCi) + (V2a*APCa) - K2
    
```

Test the simulation with Wee1 active (Wee1 = 1) and APC active (APCi = 1).

Reaction 12 Deactivation of MPF to Inhibited MPF

Inhibited/Active MPF (pMPFp) is dephosphorylated on Thr-161 by an unknown phosphatase (PP) to inhibited MPF (pMPF). Compare reaction 12 with reaction 5.

```

reaction: pMPFp -> pMPF
reaction rate: kpp*[pMPFp]
parameters: kpp = 0.004 1/minute
species: pMPFp = 0 nM
         pMPF = 0 nM
    
```

Reaction 13 Activation of Inhibited MPF

Inhibited MPF (pMPF) is phosphorylated on Thr - 161 by an unknown cyclin activating kinase (CAK). Compare reaction 13 with reaction 6.

```

reaction: pMPF -> pMPFp
reaction rate: kcak*[pMPF] nM/minute
parameters: kcak = 0.64 1/minute
species: pMPF = 0 nM
         pMPFp = 0 nM
    
```

Test the simulation with Wee1p = 1 (inactive)/ Wee1 = 0 and then test with Wee1p = 0 (inactive)/ Wee1 = 1.

Reaction 15 Degradation of Cyclin B on Active but Inhibited MPF

Degradation of Cyclin B (CycB) on inhibited MPF (pMPF). Cyclin B is tagged with ubiquitin groups and degrades while bound to Cdc2 kinase.

```

reaction: pMPFp -> Cdc2 + AA
reaction rate: K2*[pMPFp] nM/minute
parameters: K2 = 0 or 0.25 1/minute, variable by rule
            v2i = 0.005 1/nM*minute
            v2a = 0.25 1/nM*minute
species: MPF = 0 nM
         APCi = 1 nM
         APCa = 0 nM
         AA = 100 nM [x]constant [x]boundary
         Cdc2 = 100 nm
algebraic rule: (V2i*APCi) + (V2a*APCa) - K2

```

Reaction 16 Inhibit MPF by Phosphorylation

Addition of inhibiting phosphate groups by Wee1 kinase to inhibit active M-phase promoting factor (MPF). Myt1 kinase is also involved with the phosphorylation, but its contribution is grouped with Wee1.

```

reaction: MPFp -> pMPFp
reaction rate: Kwee1*[MPFp] nM/minute
parameters: Kwee1 = 1/minute [x]constant, variable by rule
            Vweei = 0.01 1/nM*minute
            Vweea = 1 1/nM*minute
species: MPFp = 0 nM
         pMPFp = 0 nM
         Wee1p = 1 nM (inactive)
         Wee1 = 0 nM (active)
algebraic rule: (Vweei*Wee1p) + (Vweea*Wee1) - Kwee1

```

Reaction 17 Remove Inhibiting Phosphate from Activated MPF

Remove the inhibiting phosphate group from pMPFp with Cdc25 phosphatase.

```

reaction: pMPFp -> MPFp
reaction rate: Kcdc25*[pMPFp]
parameters: Kcdc25 = 0 1/minute, [x]constant, variable by rule
            V25i = 0.017 1/nM*minute
            V25a = 0.17 1/nM*minute
species: pMPFp = 0 nM
         MPFp = 0 nM
algebraic rule: (V25i*Cdc25) + (V25a*Cdc25p) - Kcdc25
    
```

Reaction 19 Degradation of Cyclin B on Activated MPF

Degradation of Cyclin B (CycB) on inhibited MPF (pMPF). Cyclin B is tagged with ubiquitin groups and degrades while bound to Cdc2 kinase.

```

reaction: MPFp -> MPF + AA
reaction rate: K2*[MPFp] nM/minute
parameters: K2 = 0 or 0.25 1/minute, variable by rule
            V2i = 0.005 1/nM*minute
            V2a = 0.25 1/nM*minute
species: MPF = 0 nM
         MPFp = 0 nM
         APCi = 1 nM
         APCa = 0 nM
         AA = 100 nM [x]constant [x]boundary
         Cdc2 = 100 nm
algebraic rule: (V2i*APCi) + (V2a*APCa) - K2
    
```

Reaction 36 Activation of Cdc25 by Activated MPF

Activation of Cdc25 phosphatase by phosphorylation with active M-phase promoting factor (MPFp).

```

reaction: Cdc25 + (MPFp) -> Cdc25p + (MPFp)
reaction rate: (k25*[MPFp]*[Cdc25])/(Km25 + [Cdc25])
parameters: k25 = 0.02 1/minute
    
```



```

Km25 = 0.1 nM
species: Cdc25 = 1 nM (inactive)
        Cdc25p = 0 nM (active)

```

Initially MPF is inhibited (MPF* reacts to pMPF*).

Reaction 37 Deactivation of Cdc25

Deactivation of Cdc25 phosphatase by dephosphorylation with an unknown phosphatase.

```

reaction: Cdc25p -> Cdc25
reaction rate: (k25r*[Cdc25p])/(Km25r + [Cdc25p])
parameters: k25r = 0.1 nM/minute
            Km25r = 1 nM
species: Cdc25 = 1 nM (inactive)
        Cdc25p = 0 nM (active)

```

Reaction 38 Deactivation of Wee1 by Active MPF

Deactivation of Wee1 kinase by phosphorylation with active M-phase promoting factor (MPFp).

```

reaction: Wee1 + (MPFp) -> Wee1p + (MPFp)
reaction rate: (kw*[MPFp]*[Wee1])/(Kmw + [Wee1]) nM/minute
parameters: kw = 0.02 1/minute
            Kmw = 0.1 nM
species: Wee1p = 1 nM (inactive)
        Wee1 = 0 nM (active)

```

Initially MPF is inhibited (MPF* reacts to pMPF*).

Reaction 39 Activation of Wee1

Activation of Wee1 kinase by dephosphorylation with an unknown kinase.

```

reaction: Wee1p -> Wee1
reaction rate: (kwr*[Wee1p])/(Kmwr + [Wee1p]) nM/minute
parameters: kwr = 0.1 nM/minute
            Kmwr = 1 nM
species: Wee1p = 1 nM (inactive)

```

Wee1 = 0 nM (active)

Reaction 40 Activation of Intermediate Enzyme by Active MPF

The inactive intermediate enzyme (IE) is activated by phosphorylation with active M-phase promoting factor (MPFp).

```
reaction: IE + (MPFp) -> IEp + (MPFp)
reaction rate: (kie*[MPFp]*[IE])/(Kmie + [IE])
parameters: kie = 0.02 1/minute
             Kmie = 0.01nM
species: IE = 1 nM (inactive)
        IEp = 0 nM (active)
```

Reaction 41 Deactivation of IE

The active intermediate enzyme (IE) is deactivated by dephosphorylation.

```
reaction: IEp -> IE
reaction rate: (kier*[IEp])/(Kmier + [IEp])
parameters: kier = 0.15 nM/minute
             Kmier = 0.01 nM
species: IE = 1 nM (inactive)
        IEp = 0 nM (active)
```

Reaction 42 APC Activation by IEp

Anaphase promoting complex (APC) is activated by an active intermediate enzyme (IEp).

```
reaction: APCi + IEp -> APCa + IEp
reaction rate: (kap*[IEp]*[APCi])/(Kmap + [APCi])
parameters: kap = 0.13 1/minute
             Kmap = 0.01 nM
species : APCi = 1 nM
        APCa = 0 nM
```

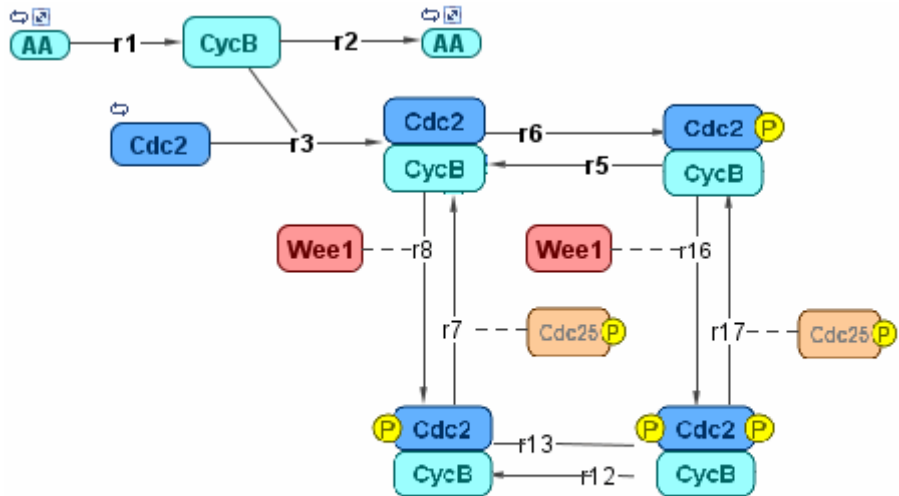
Reaction 43 APC Deactivation

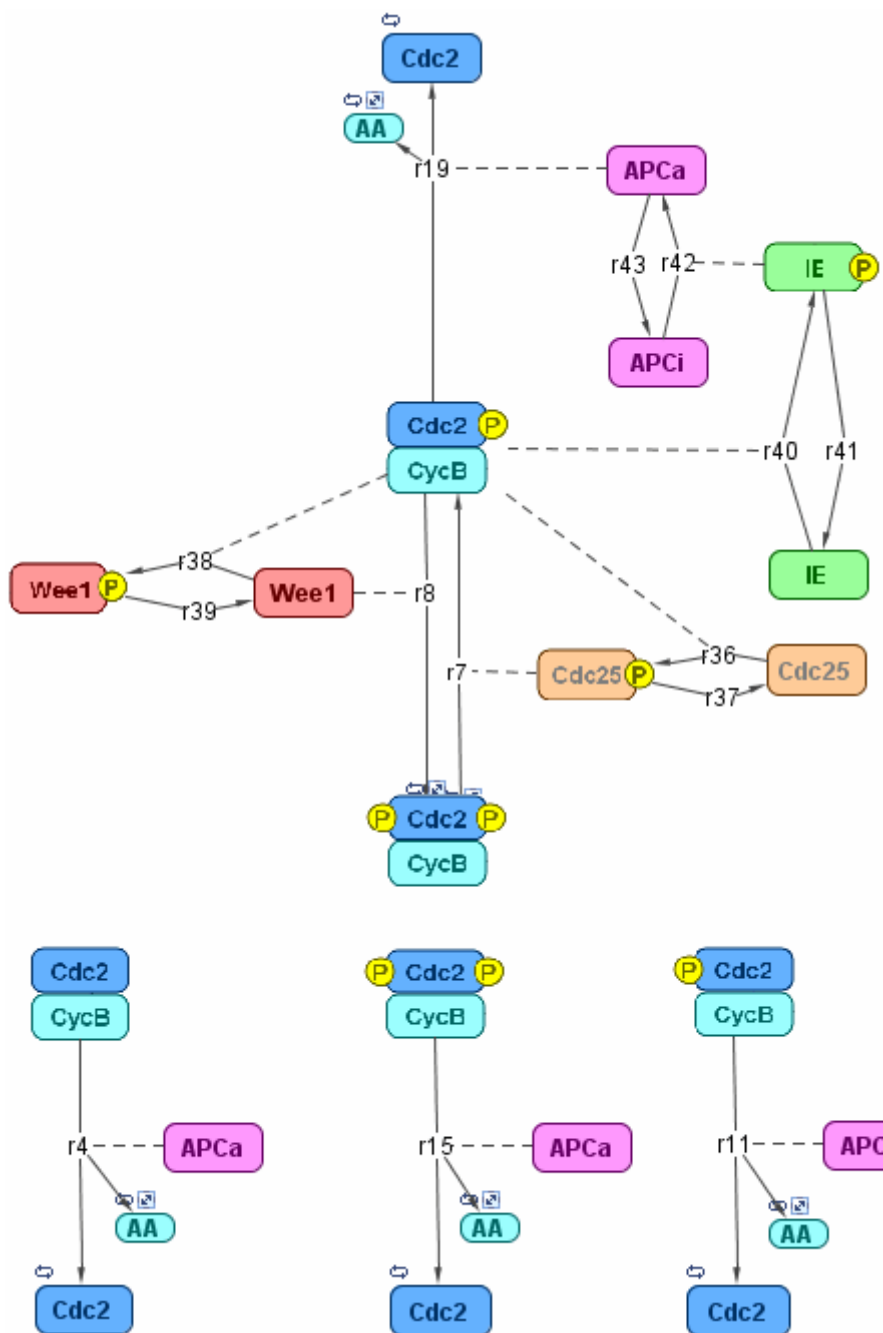
Anaphase promoting complex (APC) is deactivated.

```
reaction: APCa -> APCi
```

reaction rate: $(k_{apr} * [APCa]) / (K_{mapr} + [APCa])$
 parameters: $k_{apr} = 0.13$ nM/minute
 $K_{mapr} = 1$ nM
 species : $APCi = 1$ nM
 $APCa = 0$ nM

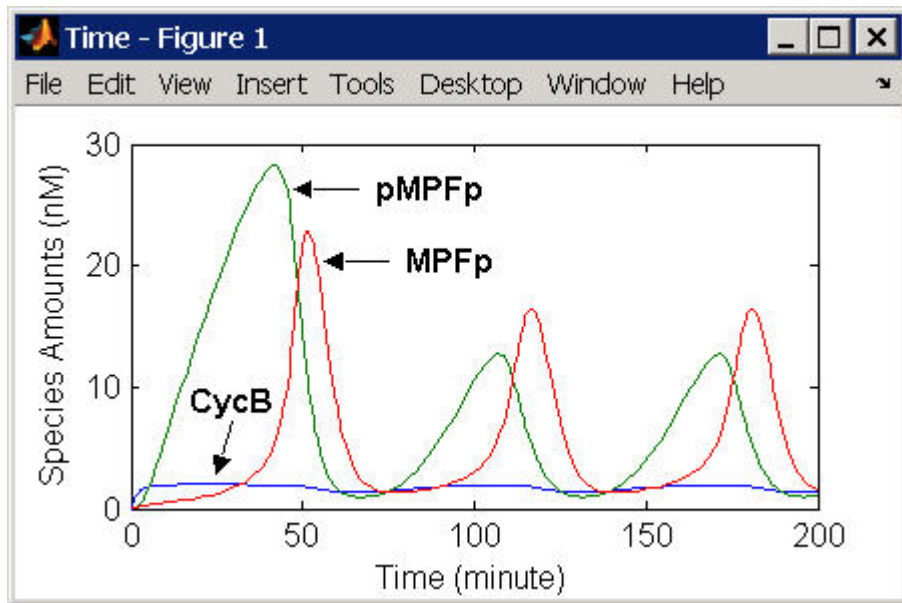
Block Diagram of the M-Phase Control Model with Reactions





Simulation of the M-Phase Control Model with Reactions

This is a simulation of the M-phase control model using reactions and algebraic rules. Simulate with the ode15s solver and plot species CycB, pMPFp, and MPFp. For a description of the model, see “SimBiology Model with Reactions and Algebraic Rules” on page 3-22.



If you want to run the simulation, you can open the model within the SimBiology Desktop.

- 1 Open the Desktop using the function `sbiodesktop`.
- 2 From the **File** menu, select **Open Project**.
- 3 Browse to the file `m_phase_xenopus.sbproj` in the following directory

```
matlabroot/toolbox/simbio/simbiodemodemos/m_phase_xenopus.sbproj
```

For a model using reactions and algebraic rules, see “SimBiology Model with Reactions and Algebraic Rules” on page 3-22.

References

- [1] Borisuk M, Tyson J (1998), “Bifurcation analysis of a model of mitotic control in frog eggs,” *Journal of Theoretical Biology*, 195(1):69–85, PubMed 9802951.

- [2] Marlovits G, Tyson C, Novak B, Tyson J (1998), “Modeling M-phase control in *Xenopus* oocyte extracts: the surveillance mechanism for unreplicated DNA,” *Biophysical Chemistry*, 72(1-2):169–184, PubMed 9652093.

- [3] Novák B, Tyson J (1993), “Numerical analysis of a comprehensive model of M-phase control in *Xenopus* oocyte extracts and intact embryos,” *Journal of Cell Science*, 106(4):1153–1168, PubMed 8126097.

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