SBML Model Report

Model name: "Bai2003_G1phaseRegulation"

May 5, 2016

1 General Overview

This is a document in SBML Level 2 Version 4 format. This model was created by the following two authors: Vijayalakshmi Chelliah[1] and Mandri Obeyeseker[2] at March fifth 2010 at 4:22 p. m. and last time modified at February 14th 2014 at 1:22 p. m. Table 1 provides an overview of the quantities of all components of this model.

Table 1: Number of components in this model, which are described in the following sections.

Element	Quantity	Element	Quantity
compartment types	0	compartments	1
species types	0	species	6
events	0	constraints	0
reactions	12	function definitions	1
global parameters	26	unit definitions	0
rules	1	initial assignments	0

Model Notes

This a model from the article:
Theoretical and experimental evidence for hysteresis in cell proliferation.
Bai S, Goodrich D, Thron CD, Tecarro E, Obeyesekere M. Cell Cycle. 2003 Jan-Feb;2(1):46-52. 12695688 ,
Abstract:

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We propose a mathematical model for the regulation of the G1-phase of the mammalian cell cycle taking into account interactions of cyclin D/cdk4, cyclin E/cdk2, Rb and E2F. Mathematical analysis of this model predicts that a change in the proliferative status in response to a change in concentrations of serum growth factors will exhibit the property of hysteresis: the concentration of growth factors required to induce proliferation is higher than the concentration required to maintain proliferation. We experimentally confirmed this prediction in mouse embryonic fibroblasts in vitro. In agreement with the mathematical model, this indicates that changes in proliferative mode caused by small changes in concentrations of growth factors are not easily reversible. Based on this study, we discuss the importance of proliferation hysteresis for cell cycle regulation.
The original model was taken from the Cell Cycle DataBase (CCDB).

Variable added: assignment rule for denoting phosphorylated Rb (Rb_phosphorylated i.e(RT-RS-R)) created.

2 Unit Definitions

This is an overview of five unit definitions which are all predefined by SBML and not mentioned in the model.

2.1 Unit `substance`

Notes Mole is the predefined SBML unit for `substance`.

Definition mol

2.2 Unit `volume`

Notes Litre is the predefined SBML unit for `volume`.

Definition l

2.3 Unit `area`

Notes Square metre is the predefined SBML unit for `area` since SBML Level 2 Version 1.

Definition m^2

2.4 Unit `length`

Notes Metre is the predefined SBML unit for `length` since SBML Level 2 Version 1.

Definition m

2.5 Unit `time`

Notes Second is the predefined SBML unit for `time`.

Definition s

3 Compartment

This model contains one compartment.

Table 2: Properties of all compartments.

Id	Name	SBO	Spatial Dimensions	Size	Unit	Constant	Outside
`cell`	cell		3	1	litre	☑	

3.1 Compartment `cell`

This is a three dimensional compartment with a constant size of one litre.

Name cell

4 Species

This model contains six species. Section 9 provides further details and the derived rates of change of each species.

Table 3: Properties of each species.

Id	Name	Compartment	Derived Unit	Constant	Boundary Condition
D_1	D	cell	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
E_1	E	cell	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
R_1	R	cell	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
RS_1	RS	cell	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
theta_1	theta	cell	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
X_1	X	cell	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟

5 Parameters

This model contains 26 global parameters.

Table 4: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
GF_1	GF		6.300		☑
k1_1	k1		0.050		☑
dD_1	dD		0.400		☑
aD_1	aD		0.400		☑
aE_1	aE		0.160		☑
k2_1	k2		1000.000		☑
aF_1	aF		0.900		☑
pX_1	pX		0.480		☑
RT_1	RT		2.500		☑
qX_1	qX		0.800		☑
pS_1	pS		0.600		☑
pD_1	pD		0.480		☑
qD_1	qD		0.600		☑
pE_1	pE		0.096		☑
qE_1	qE		0.600		☑
atheta_1	atheta		0.050		☑
k3_1	k3		1.500		☑
dtheta_1	dtheta		0.120		☑
qtheta_1	qtheta		0.300		☑
aX_1	aX		0.080		☑
f_1	f		0.350		☑
g_1	g		0.528		☑
dX_1	dX		1.040		☑
dE_1	dE		0.200		☑
fC_1_1	fe		0.003		☑
Rb_phos	Rb_phosphorylated		0.000		☐

6 Function definition

This is an overview of one function definition.

6.1 Function definition Mass_Action_2_1

Name Mass_Action_2

Arguments k1, S1, S2

Mathematical Expression

$$k1 \cdot S1 \cdot S2 \tag{1}$$

7 Rule

This is an overview of one rule.

7.1 Rule `Rb_phos`

Rule `Rb_phos` is an assignment rule for parameter `Rb_phos`:

$$\text{Rb\_phos} = \text{RT\_1} - [\text{RS\_1}] - [\text{R\_1}] \tag{2}$$

8 Reactions

This model contains twelve reactions. All reactions are listed in the following table and are subsequently described in detail. If a reaction is affected by a modifier, the identifier of this species is written above the reaction arrow.

Table 5: Overview of all reactions

№	Id	Name	Reaction Equation	SBO
1	_1	cyclinD synthesis	$\emptyset \longrightarrow \mathrm{D\_1}$	
2	cyclinD_1	cyclinD degradation	$\mathrm{D\_1} \xrightarrow{\mathrm{D\_1,\ E\_1}} \emptyset$	
3	cyclinEsynthesis_1	cyclinE synthesis	$\emptyset \xrightarrow{\mathrm{theta\_1}} \mathrm{E\_1}$	
4	cyclinEdegradation_1	cyclinE degradation	$\mathrm{E\_1} \xrightarrow{\mathrm{X\_1,\ E\_1}} \emptyset$	
5	pRBsynthesis_1	pRB synthesis	$\emptyset \xrightarrow{\mathrm{RS\_1,\ R\_1,\ X\_1}} \mathrm{R\_1}$	
6	pRBdeplation_1	pRB/E2F complex association	$\mathrm{R\_1} + \mathrm{theta\_1} \longrightarrow \mathrm{RS\_1}$	
7	_2	pRB/E2F complex dissociation via cyclin D	$\mathrm{RS\_1} \xrightarrow{\mathrm{RS\_1,\ D\_1}} \mathrm{theta\_1}$	
8	null2_1	pRB/E2F complex dissociation via cyclin E	$\mathrm{RS\_1} \xrightarrow{\mathrm{RS\_1,\ E\_1}} \mathrm{theta\_1}$	
9	null3_1	E2F synthesis	$\emptyset \xrightarrow{\mathrm{theta\_1}} \mathrm{theta\_1}$	
10	E2Fdegradationviacellcycle_1	E2F degradation via cell cycle progression	$\mathrm{theta\_1} \xrightarrow{\mathrm{theta\_1,\ X\_1}} \emptyset$	
11	cellcycleprogressiongo_1	cell cycle progression go	$\emptyset \xrightarrow{\mathrm{E\_1,\ theta\_1,\ X\_1}} \mathrm{X\_1}$	
12	cellcycleprogressionslow_1	cell cycle progression slow	$\mathrm{X\_1} \xrightarrow{\mathrm{X\_1}} \emptyset$	

8.1 Reaction _1

This is an irreversible reaction of no reactant forming one product.

Name cyclinD synthesis

Reaction equation

$$\emptyset \longrightarrow \mathrm{D\_1} \tag{3}$$

Product

Table 6: Properties of each product.

Id	Name	SBO
D_1	D	

Kinetic Law

Derived unit contains undeclared units

$$v_1 = \mathrm{vol}\,(\mathrm{cell}) \cdot \mathrm{aD\_1} \cdot \frac{\mathrm{GF\_1}}{\mathrm{k1\_1}^1 + \mathrm{GF\_1}} \tag{4}$$

8.2 Reaction cyclinD_1

This is an irreversible reaction of one reactant forming no product influenced by two modifiers.

Name cyclinD degradation

Reaction equation

$$\mathrm{D\_1} \xrightarrow{\mathrm{D\_1,\ E\_1}} \emptyset \tag{5}$$

Reactant

Table 7: Properties of each reactant.

Id	Name	SBO
D_1	D	

Modifiers

Table 8: Properties of each modifier.

Id	Name	SBO
D_1	D	
E_1	E	

Kinetic Law

Derived unit contains undeclared units

$$v_2 = \mathrm{vol}\,(\mathrm{cell}) \cdot \mathrm{dD\_1} \cdot [\mathrm{E\_1}] \cdot [\mathrm{D\_1}] \tag{6}$$

8.3 Reaction cyclinEsynthesis_1

This is an irreversible reaction of no reactant forming one product influenced by one modifier.

Name cyclinE synthesis

Reaction equation

$$\emptyset \xrightarrow{\mathrm{theta\_1}} \mathrm{E\_1} \tag{7}$$

Modifier

Table 9: Properties of each modifier.

Id	Name	SBO
theta_1	theta	

Product

Table 10: Properties of each product.

Id	Name	SBO
E_1	E	

Kinetic Law

Derived unit contains undeclared units

$$v_3 = \mathrm{vol}\,(\mathrm{cell}) \cdot \mathrm{aE\_1} \cdot \left(\frac{\mathrm{GF\_1}}{\mathrm{k2\_1}^1 + \mathrm{GF\_1}} + \mathrm{aF\_1} \cdot [\mathrm{theta\_1}] \right) \tag{8}$$

8.4 Reaction cyclinEdegradation_1

This is an irreversible reaction of one reactant forming no product influenced by two modifiers.

Name cyclinE degradation

Reaction equation

$$\mathrm{E\_1} \xrightarrow{\mathrm{X\_1,\ E\_1}} \emptyset \tag{9}$$

Reactant

Table 11: Properties of each reactant.

Id	Name	SBO
E_1	E	

Modifiers

Table 12: Properties of each modifier.

Id	Name	SBO
X_1	X	
E_1	E	

Kinetic Law

Derived unit contains undeclared units

$$v_4 = \mathrm{vol}\,(\mathrm{cell}) \cdot \mathrm{dE\_1} \cdot [\mathrm{X\_1}] \cdot [\mathrm{E\_1}] \tag{10}$$

8.5 Reaction pRBsynthesis_1

This is an irreversible reaction of no reactant forming one product influenced by three modifiers.

Name pRB synthesis

Reaction equation

$$\emptyset \xrightarrow{\mathrm{RS\_1,\ R\_1,\ X\_1}} \mathrm{R\_1} \tag{11}$$

Modifiers

Table 13: Properties of each modifier.

Id	Name	SBO
RS_1	RS	
R_1	R	
X_1	X	

Product

Table 14: Properties of each product.

Id	Name	SBO
R_1	R	

Kinetic Law

Derived unit contains undeclared units

$$v_5 = \mathrm{vol}\,(\mathrm{cell}) \cdot \frac{\mathrm{pX\_1} \cdot (\mathrm{RT\_1} - [\mathrm{RS\_1}] - [\mathrm{R\_1}]) \cdot [\mathrm{X\_1}]}{\mathrm{qX\_1} + \mathrm{RT\_1} - [\mathrm{RS\_1}] - [\mathrm{R\_1}] + [\mathrm{X\_1}]} \tag{12}$$

8.6 Reaction pRBdeplation_1

This is an irreversible reaction of two reactants forming one product.

Name pRB/E2F complex association

Reaction equation

$$\mathrm{R\_1} + \mathrm{theta\_1} \longrightarrow \mathrm{RS\_1} \tag{13}$$

Reactants

Table 15: Properties of each reactant.

Id	Name	SBO
R_1	R	
theta_1	theta	

Product

Table 16: Properties of each product.

Id	Name	SBO
RS_1	RS	

Kinetic Law

Derived unit contains undeclared units

$$v_6 = \text{vol}\,(\text{cell}) \cdot \text{Mass\_Action\_2\_1}\,(\text{pS\_1}, [\text{R\_1}], [\text{theta\_1}]) \tag{14}$$

$$\text{Mass\_Action\_2\_1}\,(\text{k1}, \text{S1}, \text{S2}) = \text{k1} \cdot \text{S1} \cdot \text{S2} \tag{15}$$

$$\text{Mass\_Action\_2\_1}\,(\text{k1}, \text{S1}, \text{S2}) = \text{k1} \cdot \text{S1} \cdot \text{S2} \tag{16}$$

8.7 Reaction _2

This is an irreversible reaction of one reactant forming one product influenced by two modifiers.

Name pRB/E2F complex dissociation via cyclin D

Reaction equation

$$\text{RS\_1} \xrightarrow{\text{RS\_1, D\_1}} \text{theta\_1} \tag{17}$$

Reactant

Table 17: Properties of each reactant.

Id	Name	SBO
RS_1	RS	

Modifiers

Table 18: Properties of each modifier.

Id	Name	SBO
RS_1	RS	
D_1	D	

Product

Table 19: Properties of each product.

Id	Name	SBO
theta_1	theta	

Kinetic Law

Derived unit contains undeclared units

$$v_7 = \mathrm{vol}\,(\mathrm{cell}) \cdot \frac{\mathrm{pD\_1} \cdot [\mathrm{RS\_1}] \cdot [\mathrm{D\_1}]}{\mathrm{qD\_1} + [\mathrm{RS\_1}] + [\mathrm{D\_1}]} \tag{18}$$

8.8 Reaction null2_1

This is an irreversible reaction of one reactant forming one product influenced by two modifiers.

Name pRB/E2F complex dissociation via cyclin E

Reaction equation

$$\mathrm{RS\_1} \xrightarrow{\mathrm{RS\_1,\ E\_1}} \mathrm{theta\_1} \tag{19}$$

Reactant

Table 20: Properties of each reactant.

Id	Name	SBO
RS_1	RS	

Modifiers

Table 21: Properties of each modifier.

Id	Name	SBO
RS_1	RS	
E_1	E	

Product

Table 22: Properties of each product.

Id	Name	SBO
theta_1	theta	

Kinetic Law

Derived unit contains undeclared units

$$v_8 = \mathrm{vol}\,(\mathrm{cell}) \cdot \frac{\mathrm{pE\_1} \cdot [\mathrm{RS\_1}] \cdot [\mathrm{E\_1}]}{\mathrm{qE\_1} + [\mathrm{RS\_1}] + [\mathrm{E\_1}]} \tag{20}$$

8.9 Reaction null3_1

This is an irreversible reaction of no reactant forming one product influenced by one modifier.

Name E2F synthesis

Reaction equation

$$\emptyset \xrightarrow{\mathrm{theta\_1}} \mathrm{theta\_1} \tag{21}$$

Modifier

Table 23: Properties of each modifier.

Id	Name	SBO
theta_1	theta	

Product

Table 24: Properties of each product.

Id	Name	SBO
theta_1	theta	

Kinetic Law

Derived unit contains undeclared units

$$v_9 = \mathrm{vol}\,(\mathrm{cell}) \cdot \mathrm{atheta\_1} \cdot \left(\frac{\mathrm{GF\_1}}{\mathrm{k3\_1}^1 + \mathrm{GF\_1}} + \mathrm{fC\_1\_1} \cdot [\mathrm{theta\_1}] \right) \tag{22}$$

8.10 Reaction E2Fdegradationviacellcycleprogression_1

This is an irreversible reaction of one reactant forming no product influenced by two modifiers.

Name E2F degradation via cell cycle progression

Reaction equation

$$\text{theta\_1} \xrightarrow{\text{theta\_1, X\_1}} \emptyset \tag{23}$$

Reactant

Table 25: Properties of each reactant.

Id	Name	SBO
theta_1	theta	

Modifiers

Table 26: Properties of each modifier.

Id	Name	SBO
theta_1	theta	
X_1	X	

Kinetic Law

Derived unit contains undeclared units

$$v_{10} = \text{vol}(\text{cell}) \cdot \text{dtheta\_1} \cdot \frac{[\text{X\_1}]}{\text{qtheta\_1} + [\text{X\_1}]} \cdot [\text{theta\_1}] \tag{24}$$

8.11 Reaction cellcycleprogression_1

This is an irreversible reaction of no reactant forming one product influenced by three modifiers.

Name cell cycle progression go

Reaction equation

$$\emptyset \xrightarrow{\text{E\_1, theta\_1, X\_1}} \text{X\_1} \tag{25}$$

Modifiers

Table 27: Properties of each modifier.

Id	Name	SBO
E_1	E	
theta_1	theta	
X_1	X	

Product

Table 28: Properties of each product.

Id	Name	SBO
X_1	X	

Kinetic Law

Derived unit contains undeclared units

$$v_{11} = \mathrm{vol}\,(\mathrm{cell}) \cdot \left(\mathrm{aX\_1} \cdot [\mathrm{E\_1}] + \mathrm{f\_1} \cdot [\mathrm{theta\_1}] + \mathrm{g\_1} \cdot [\mathrm{X\_1}]^2 \cdot [\mathrm{E\_1}]\right) \tag{26}$$

8.12 Reaction cellcycleprogressionslow_1

This is an irreversible reaction of one reactant forming no product influenced by one modifier.

Name cell cycle progression slow

Reaction equation

$$\mathrm{X\_1} \xrightarrow{\mathrm{X\_1}} \emptyset \tag{27}$$

Reactant

Table 29: Properties of each reactant.

Id	Name	SBO
X_1	X	

Modifier

Table 30: Properties of each modifier.

Id	Name	SBO
X_1	X	

Kinetic Law

Derived unit contains undeclared units

$$v_{12} = \mathrm{vol}\,(\mathrm{cell}) \cdot \mathrm{dX\_1} \cdot [\mathrm{X\_1}] \tag{28}$$

9 Derived Rate Equations

When interpreted as an ordinary differential equation framework, this model implies the following set of equations for the rates of change of each species.

Identifiers for kinetic laws highlighted in gray cannot be verified to evaluate to units of SBML `substance` per `time`. As a result, some SBML interpreters may not be able to verify the consistency of the units on quantities in the model. Please check if

- parameters without an unit definition are involved or
- volume correction is necessary because the `hasOnlySubstanceUnits` flag may be set to `false` and `spacialDimensions`> 0 for certain species.

9.1 Species D_1

Name D

Initial amount 0 mol

This species takes part in four reactions (as a reactant in cyclinD_1 and as a product in _1 and as a modifier in cyclinD_1, _2).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{D\_1} = v_1 - v_2 \tag{29}$$

9.2 Species E_1

Name E

Initial amount 0 mol

This species takes part in six reactions (as a reactant in cyclinEdegradation_1 and as a product in cyclinEsynthesis_1 and as a modifier in cyclinD_1, cyclinEdegradation_1, null2_1, cellcycleprogression_1).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{E\_1} = v_3 - v_4 \tag{30}$$

9.3 Species R_1

Name R

Initial amount 2.5 mol

This species takes part in three reactions (as a reactant in pRBdeplation_1 and as a product in pRBsynthesis_1 and as a modifier in pRBsynthesis_1).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{R\_1} = v_5 - v_6 \tag{31}$$

9.4 Species RS_1

Name RS

Initial amount 0 mol

This species takes part in six reactions (as a reactant in _2, null2_1 and as a product in pRBdeplation_1 and as a modifier in pRBsynthesis_1, _2, null2_1).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{RS\_1} = v_6 - v_7 - v_8 \tag{32}$$

9.5 Species theta_1

Name theta

Initial amount 0 mol

This species takes part in nine reactions (as a reactant in pRBdeplation_1, E2Fdegradationviacellcycleprogre_1 and as a product in _2, null2_1, null3_1 and as a modifier in cyclinEsynthesis_1, null3_1, E2Fdegradationviacellcycleprogression_1, cellcycleprogression_1).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{theta\_1} = v_7 + v_8 + v_9 - v_6 - v_{10} \tag{33}$$

9.6 Species X_1

Name X

Initial amount 0 mol

This species takes part in seven reactions (as a reactant in cellcycleprogressionslow_1 and as a product in cellcycleprogression_1 and as a modifier in cyclinEdegradation_1, pRBsynthesis_1, E2Fdegradationviacellcycleprogression_1, cellcycleprogression_1, cellcycleprogressionslow_1).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{X\_1} = v_{11} - v_{12} \tag{34}$$

SBML2LaTeX was developed by Andreas Dräger[a], Hannes Planatscher[a], Dieudonné M Wouamba[a], Adrian Schröder[a], Michael Hucka[b], Lukas Endler[c], Martin Golebiewski[d] and Andreas Zell[a]. Please see http://www.ra.cs.uni-tuebingen.de/software/SBML2LaTeX for more information.

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