SBML Model Report

Model name: "Nakakuki2010_CellFateDecision_Core"

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: Lukas Endler[1] and Lutz Brusch[2] at May 24th 2010 at 11:49 a. m. and last time modified at June third 2014 at three o' clock in the afternoon. Table 1 gives 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	10
events	0	constraints	0
reactions	9	function definitions	0
global parameters	8	unit definitions	3
rules	1	initial assignments	0

Model Notes

This model describes the activation of immediate early genes such as cFos after EGF or heregulin (HRG) stimulation of the MAPK pathway. Phosphorylated cFos is a key transcription factor triggering downstream cascades of cell fate determination. The model can explain how the

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switch-like response of p-cFos emerges from the spatiotemporal dynamics. The model comprises lumped reaction kinetics of the signal transduction pathway, the transcriptional and the posttranslational feedback and feedforward loops. The parameter set implemented here corresponds to that used for generating Figs. 4 B,C,D (red curves for 10nM HRG) of the below article in Cell (2010). Moreover, we found that the same model described well the dynamics in different cell types (MCF-7 and PC-12), of different ligands (EGF and HRG) and at different doses (0.1nM, 1nM, 10nM) for a unique set of parameter values (as implemented here and reported in Table SD4_1 of the article) except for four parameters characterising the input, cytoplasmic ppERK. These four parameters K1, K2, tau1 and tau2 are used in the two equations involving species x1 and x2. These two equations define a phenomenological input module to describe the ligand-, dose- and cell type-dependent dynamics of ppERKc which are not modelled in mechanistic detail here. The four parameter values can be adjusted to model a specific ligand, dose and cell type. 8 parameter sets for different experiments are given in Table SD4_2 of the article. This SBML file, however, carries just one such parameter set. We have chosen that of MCF-7 cells stimulated by 10nM of HRG. To reproduce all simulations from the article, please replace the parameter values for K1, K2, tau1, tau2 as needed.

Ligand-specific c-Fos expression emerges from the spatiotemporal control of ErbB network dynamics.

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2 Unit Definitions

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

2.1 Unit `volume`

Definition ml

2.2 Unit `time`

Definition 60 s

2.3 Unit `substance`

Definition mmol

2.4 Unit `area`

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

Definition m^2

2.5 Unit `length`

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

Definition m

3 Compartment

This model contains one compartment.

Table 2: Properties of all compartments.

Id	Name	SBO	Spatial Dimensions	Size	Unit	Constant	Outside
`compartment`	compartment	0000290	3	1	litre	☑	

3.1 Compartment `compartment`

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

Name compartment

SBO:0000290 physical compartment

4 Species

This model contains ten species. The boundary condition of one of these species is set to `true` so that this species' amount cannot be changed by any reaction. Section 8 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
x1	x1	compartment	$\mathrm{mmol} \cdot \mathrm{ml}^{-1}$	⊟	⊟
x2	x2	compartment	$\mathrm{mmol} \cdot \mathrm{ml}^{-1}$	⊟	⊟
ppERKn	ppERK(nucleus)	compartment	$\mathrm{mmol} \cdot \mathrm{ml}^{-1}$	⊟	⊟
DUSP	DUSP	compartment	$\mathrm{mmol} \cdot \mathrm{ml}^{-1}$	⊟	⊟
pRSKn	pRSKn	compartment	$\mathrm{mmol} \cdot \mathrm{ml}^{-1}$	⊟	⊟
cFOSp	cFOS preRNA	compartment	$\mathrm{mmol} \cdot \mathrm{ml}^{-1}$	⊟	⊟
cFOS	cFOS	compartment	$\mathrm{mmol} \cdot \mathrm{ml}^{-1}$	⊟	⊟
pcFOS	pc-FOS	compartment	$\mathrm{mmol} \cdot \mathrm{ml}^{-1}$	⊟	⊟
cFOSm	cFOSmRNA	compartment	$\mathrm{mmol} \cdot \mathrm{ml}^{-1}$	⊟	⊟
ppERKc	ppERK(cytosol)	compartment	$\mathrm{mmol} \cdot \mathrm{ml}^{-1}$	⊟	☑

5 Parameters

This model contains eight global parameters.

Table 4: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k7	k7		0.50		☑
k11	k11		0.11		☑
k13	k13		0.06		☑
L	L		1.00		☑
K1	K1		1.09		☑
tau1	tau1		3.07		☑
K2	K		2.89		☑
tau2	tau		472.00		☑

6 Rule

This is an overview of one rule.

6.1 Rule ppERKc

Rule ppERKc is an assignment rule for species ppERKc:

$$\text{ppERKc} = [\text{x1}] - [\text{x2}] \tag{1}$$

Derived unit $\text{mmol} \cdot \text{ml}^{-1}$

7 Reactions

This model contains nine 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	reaction_1	1 PhIM 1	$\emptyset \longrightarrow$ x1	
2	reaction_2	1 PhIM 2	$\emptyset \longrightarrow$ x2	
3	reaction_3	2a ppERKn	$\emptyset \xrightarrow{\text{ppERKc, DUSP}}$ ppERKn	
4	reaction_4	2b DUSP	$\emptyset \xrightarrow{\text{ppERKn}}$ DUSP	
5	reaction_5	3 pRSKn	$\emptyset \xrightarrow{\text{ppERKn}}$ pRSKn	
6	reaction_6	4 cFOSp	$\emptyset \xrightarrow{\text{ppERKn, pRSKn}}$ cFOSp	
7	reaction_7	5 cFOSm	$\emptyset \xrightarrow{\text{cFOSp}}$ cFOSm	
8	reaction_8	6 cFOS	$\emptyset \xrightarrow{\text{cFOSm, ppERKc, pcFOS}}$ cFOS	
9	reaction_9	7 pcFOS	$\emptyset \xrightarrow{\text{cFOS, ppERKc}}$ pcFOS	

7.1 Reaction reaction_1

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

Name 1 PhIM 1

Reaction equation

$$\emptyset \longrightarrow \mathrm{x1} \tag{2}$$

Product

Table 6: Properties of each product.

Id	Name	SBO
x1	x1	

Kinetic Law

Derived unit contains undeclared units

$$v_1 = \mathrm{vol}\,(\mathrm{compartment}) \cdot \left(\frac{[\mathrm{x1}]}{\mathrm{tau1}} + \frac{\mathrm{K1} \cdot \mathrm{L}}{\mathrm{tau1}} \right) \tag{3}$$

7.2 Reaction reaction_2

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

Name 1 PhIM 2

Reaction equation

$$\emptyset \longrightarrow \mathrm{x2} \tag{4}$$

Product

Table 7: Properties of each product.

Id	Name	SBO
x2	x2	

Kinetic Law

Derived unit contains undeclared units

$$v_2 = \text{vol}\,(\text{compartment}) \cdot \left(\frac{[\text{x2}]}{\text{tau2}} + \frac{\text{K2} \cdot \text{L}}{\text{tau2}} \right) \tag{5}$$

7.3 Reaction `reaction_3`

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

Name 2a ppERKn

Reaction equation

$$\emptyset \xrightarrow{\text{ppERKc, DUSP}} \text{ppERKn} \tag{6}$$

Modifiers

Table 8: Properties of each modifier.

Id	Name	SBO
`ppERKc`	ppERK(cytosol)	
`DUSP`	DUSP	

Product

Table 9: Properties of each product.

Id	Name	SBO
`ppERKn`	ppERK(nucleus)	

Kinetic Law

Derived unit contains undeclared units

$$v_3 = \text{vol}\,(\text{compartment}) \cdot (\text{k1} \cdot [\text{ppERKc}] - \text{k2} \cdot [\text{ppERKn}] - \text{k3} \cdot [\text{DUSP}] \cdot [\text{ppERKn}]) \tag{7}$$

Table 10: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
`k1`	k1		15.0		☑
`k2`	k2		50.0		☑
`k3`	k3		14.0		☑

7.4 Reaction reaction_4

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

Name 2b DUSP

Reaction equation

$$\emptyset \xrightarrow{\text{ppERKn}} \text{DUSP} \tag{8}$$

Modifier

Table 11: Properties of each modifier.

Id	Name	SBO
ppERKn	ppERK(nucleus)	

Product

Table 12: Properties of each product.

Id	Name	SBO
DUSP	DUSP	

Kinetic Law

Derived unit contains undeclared units

$$v_4 = \text{vol}\,(\text{compartment}) \cdot \text{k} \cdot [\text{ppERKn}] \tag{9}$$

Table 13: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k	k		1.0		☑

7.5 Reaction reaction_5

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

Name 3 pRSKn

Reaction equation

$$\emptyset \xrightarrow{\text{ppERKn}} \text{pRSKn} \tag{10}$$

Modifier

Table 14: Properties of each modifier.

Id	Name	SBO
ppERKn	ppERK(nucleus)	

Product

Table 15: Properties of each product.

Id	Name	SBO
pRSKn	pRSKn	

Kinetic Law

Derived unit contains undeclared units

$$v_5 = \text{vol}\,(\text{compartment}) \cdot (\text{k4} \cdot [\text{ppERKn}] - \text{k5} \cdot [\text{pRSKn}]) \tag{11}$$

Table 16: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k4	k4		0.10		☑
k5	k5		0.15		☑

7.6 Reaction reaction_6

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

Name 4 cFOSp

Reaction equation

$$\emptyset \xrightarrow{\text{ppERKn, pRSKn}} \text{cFOSp} \tag{12}$$

Modifiers

Table 17: Properties of each modifier.

Id	Name	SBO
ppERKn	ppERK(nucleus)	
pRSKn	pRSKn	

Product

Table 18: Properties of each product.

Id	Name	SBO
cFOSp	cFOS preRNA	

Kinetic Law

Derived unit contains undeclared units

$$v_6 = \mathrm{vol}\,(\mathrm{compartment}) \cdot \left(\frac{([\mathrm{ppERKn}] \cdot [\mathrm{pRSKn}])^{\mathrm{n}}}{\mathrm{k6}^{\mathrm{n}} + ([\mathrm{ppERKn}] \cdot [\mathrm{pRSKn}])^{\mathrm{n}}} - \mathrm{k7} \cdot [\mathrm{cFOSp}] \right) \tag{13}$$

Table 19: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k6	k6		0.13		☑
n	n		1.10		☑

7.7 Reaction reaction_7

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

Name 5 cFOSm

Reaction equation

$$\emptyset \xrightarrow{\mathrm{cFOSp}} \mathrm{cFOSm} \tag{14}$$

Modifier

Table 20: Properties of each modifier.

Id	Name	SBO
cFOSp	cFOS preRNA	

Product

Table 21: Properties of each product.

Id	Name	SBO
cFOSm	cFOSmRNA	

Kinetic Law

Derived unit contains undeclared units

$$v_7 = \text{vol}\,(\text{compartment}) \cdot (\text{k7} \cdot [\text{cFOSp}] - \text{k8} \cdot [\text{cFOSm}]) \tag{15}$$

Table 22: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k8	k8		0.08		☑

7.8 Reaction reaction_8

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

Name 6 cFOS

Reaction equation

$$\emptyset \xrightarrow{\text{cFOSm, ppERKc, pcFOS}} \text{cFOS} \tag{16}$$

Modifiers

Table 23: Properties of each modifier.

Id	Name	SBO
cFOSm	cFOSmRNA	
ppERKc	ppERK(cytosol)	
pcFOS	pc-FOS	

Product

Table 24: Properties of each product.

Id	Name	SBO
cFOS	cFOS	

Kinetic Law

Derived unit contains undeclared units

$$v_8 = \mathrm{vol}\,(\mathrm{compartment}) \cdot (\mathrm{k9} \cdot [\mathrm{cFOSm}] - \mathrm{k10} \cdot [\mathrm{cFOS}] - \mathrm{k11} \cdot [\mathrm{cFOS}] \cdot [\mathrm{ppERKc}] + \mathrm{k13} \cdot [\mathrm{pcFOS}]) \tag{17}$$

Table 25: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k10	k10		0.3		☑
k9	k9		0.3		☑

7.9 Reaction reaction_9

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

Name 7 pcFOS

Reaction equation

$$\emptyset \xrightarrow{\text{cFOS, ppERKc}} \text{pcFOS} \tag{18}$$

Modifiers

Table 26: Properties of each modifier.

Id	Name	SBO
cFOS	cFOS	
ppERKc	ppERK(cytosol)	

Product

Table 27: Properties of each product.

Id	Name	SBO
pcFOS	pc-FOS	

Kinetic Law

Derived unit contains undeclared units

$$v_9 = \mathrm{vol}\,(\mathrm{compartment}) \cdot (\mathrm{k11} \cdot [\mathrm{cFOS}] \cdot [\mathrm{ppERKc}] - \mathrm{k12} \cdot [\mathrm{pcFOS}] - \mathrm{k13} \cdot [\mathrm{pcFOS}]) \quad (19)$$

Table 28: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k12	k12		0.001		☑

8 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.

8.1 Species x1

Name x1

SBO:0000236 physical entity representation

Initial concentration $0\ \mathrm{mmol} \cdot \mathrm{ml}^{-1}$

This species takes part in one reaction (as a product in `reaction_1`).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{x1} = v_1 \quad (20)$$

8.2 Species x2

Name x2

SBO:0000236 physical entity representation

Initial concentration $0\ \mathrm{mmol} \cdot \mathrm{ml}^{-1}$

This species takes part in one reaction (as a product in reaction_2).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{x2} = v_2 \tag{21}$$

8.3 Species ppERKn

Name ppERK(nucleus)

SBO:0000252 polypeptide chain

Initial concentration $0\ \mathrm{mmol} \cdot \mathrm{ml}^{-1}$

This species takes part in four reactions (as a product in reaction_3 and as a modifier in reaction_4, reaction_5, reaction_6).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{ppERKn} = v_3 \tag{22}$$

8.4 Species DUSP

Name DUSP

SBO:0000252 polypeptide chain

Initial concentration $0\ \mathrm{mmol} \cdot \mathrm{ml}^{-1}$

This species takes part in two reactions (as a product in reaction_4 and as a modifier in reaction_3).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{DUSP} = v_4 \tag{23}$$

8.5 Species pRSKn

Name pRSKn

SBO:0000252 polypeptide chain

Initial concentration $0\ \mathrm{mmol} \cdot \mathrm{ml}^{-1}$

This species takes part in two reactions (as a product in reaction_5 and as a modifier in reaction_6).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{pRSKn} = v_5 \tag{24}$$

8.6 Species cFOSp

Name cFOS preRNA

SBO:0000250 ribonucleic acid

Initial concentration $0\ \mathrm{mmol} \cdot \mathrm{ml}^{-1}$

This species takes part in two reactions (as a product in reaction_6 and as a modifier in reaction_7).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{cFOSp} = v_6 \tag{25}$$

8.7 Species cFOS

Name cFOS

SBO:0000252 polypeptide chain

Initial concentration $0\ \mathrm{mmol} \cdot \mathrm{ml}^{-1}$

This species takes part in two reactions (as a product in reaction_8 and as a modifier in reaction_9).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{cFOS} = v_8 \tag{26}$$

8.8 Species pcFOS

Name pc-FOS

SBO:0000252 polypeptide chain

Initial concentration $0\ \mathrm{mmol} \cdot \mathrm{ml}^{-1}$

This species takes part in two reactions (as a product in reaction_9 and as a modifier in reaction_8).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{pcFOS} = v_9 \tag{27}$$

8.9 Species cFOSm

Name cFOSmRNA

SBO:0000250 ribonucleic acid

Initial concentration $0\ \mathrm{mmol} \cdot \mathrm{ml}^{-1}$

This species takes part in two reactions (as a product in reaction_7 and as a modifier in reaction_8).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{cFOSm} = v_7 \tag{28}$$

8.10 Species ppERKc

Name ppERK(cytosol)

SBO:0000252 polypeptide chain

Involved in rule ppERKc

This species takes part in three reactions (as a modifier in reaction_3, reaction_8, reaction_9). Not these but one rule determines the species' quantity because this species is on the boundary of the reaction system.

A Glossary of Systems Biology Ontology Terms

SBO:0000236 physical entity representation: Representation of an entity that may participate in an interaction, a process or relationship of significance.

SBO:0000250 ribonucleic acid: Macromolecule formed by a repetition of ribonucleosides linked by phosphodiester bonds. CHEBI:3369

SBO:0000252 polypeptide chain: Naturally occurring macromolecule formed by the repetition of amino-acid residues linked by peptidic bonds. A polypeptide chain is synthesized by the ribosome. CHEBI:1654

SBO:0000290 physical compartment: Specific location of space, that can be bounded or not. A physical compartment can have 1, 2 or 3 dimensions

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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