SBML Model Report

Model name: "Markevich2004_MAPK-_orderedMM2kinases"

May 6, 2016

1 General Overview

This is a document in SBML Level 2 Version 4 format. This model was created by Nicolas Le Novre[1] at June 30th 2005 at 10:11 a. m. and last time modified at May 15th 2012 at 9:43 p. m. 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	6
events	0	constraints	0
reactions	4	function definitions	0
global parameters	9	unit definitions	1
rules	0	initial assignments	0

Model Notes

The model describes the double phosphorylation of MAP kinase by an ordered mechanism using the Michaelis-Menten formalism. Two different enzymes, MAPKK1 and MAPKK2, successively phosphorylate the MAP kinase, but one and the same phosphatase dephosphorylates both sites.
The model reproduces figure S9 in the supplemental material of the article.

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The model is further described in:
Signaling switches and bistability arising from multisite phosphorylation in protein kinase cascades. Markevich NI, Hoek JB, Kholodenko BN. J Cell Biol. 2004 Feb 2;164(3):353-9.
PMID: 14744999 ; DOI: 10.1083/jcb.200308060
Abstract:
Mitogen-activated protein kinase (MAPK) cascades can operate as bistable switches residing in either of two different stable states. MAPK cascades are often embedded in positive feedback loops, which are considered to be a prerequisite for bistable behavior. Here we demonstrate that in the absence of any imposed feedback regulation, bistability and hysteresis can arise solely from a distributive kinetic mechanism of the two-site MAPK phosphorylation and dephosphorylation. Importantly, the reported kinetic properties of the kinase (MEK) and phosphatase (MKP3) of extracellular signal-regulated kinase (ERK) fulfill the essential requirements for generating a bistable switch at a single MAPK cascade level. Likewise, a cycle where multisite phosphorylations are performed by different kinases, but dephosphorylation reactions are catalyzed by the same phosphatase, can also exhibit bistability and hysteresis. Hence, bistability induced by multisite covalent modification may be a widespread mechanism of the control of protein activity.

2 Unit Definitions

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

2.1 Unit `substance`

Name nanomole (default)

Definition nmol

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
`uVol`			3	1	litre	☑	

3.1 Compartment `uVol`

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

4 Species

This model contains six species. Section 7 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
M		uVol	$\mathrm{nmol} \cdot \mathrm{l}^{-1}$	☐	☐
Mp		uVol	$\mathrm{nmol} \cdot \mathrm{l}^{-1}$	☐	☐
Mpp		uVol	$\mathrm{nmol} \cdot \mathrm{l}^{-1}$	☐	☐
MAPKK1	MAPKK1	uVol	$\mathrm{nmol} \cdot \mathrm{l}^{-1}$	☑	☐
MAPKK2	MAPKK2	uVol	$\mathrm{nmol} \cdot \mathrm{l}^{-1}$	☑	☐
MKP3		uVol	$\mathrm{nmol} \cdot \mathrm{l}^{-1}$	☑	☐

5 Parameters

This model contains nine global parameters.

Table 4: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k1cat			0.010		☑
Km1			50.000		☑
k2cat			15.000		☑
Km2			500.000		☑
k3cat			0.084		☑
Km3			5.000		☑
k4cat			0.060		☑
Km4			18.000		☑
Km5			78.000		☑

6 Reactions

This model contains four 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	v1	phosphorylation of MAPK	$\mathrm{M} \xrightarrow{\mathrm{MAPKK1}} \mathrm{Mp}$	
2	v2	phosphorylation of P-MAPK	$\mathrm{Mp} \xrightarrow{\mathrm{MAPKK2,\ M}} \mathrm{Mpp}$	
3	v3	dephosphorylation of PP-MAPK	$\mathrm{Mpp} \xrightarrow{\mathrm{MKP3,\ M}} \mathrm{Mp}$	
4	v4	dephosphorylation of P-MAPK	$\mathrm{Mp} \xrightarrow{\mathrm{MKP3,\ Mpp}} \mathrm{M}$	

6.1 Reaction v1

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

Name phosphorylation of MAPK

Reaction equation

$$\mathrm{M} \xrightarrow{\mathrm{MAPKK1}} \mathrm{Mp} \tag{1}$$

Reactant

Table 6: Properties of each reactant.

Id	Name	SBO
M		

Modifier

Table 7: Properties of each modifier.

Id	Name	SBO
MAPKK1	MAPKK1	

Product

Table 8: Properties of each product.

Id	Name	SBO
Mp		

Kinetic Law

Derived unit contains undeclared units

$$v_1 = \mathrm{vol}\,(\mathrm{uVol}) \cdot \frac{\frac{\mathrm{k1cat} \cdot [\mathrm{MAPKK1}] \cdot [\mathrm{M}]}{\mathrm{Km1}}}{1 + \frac{[\mathrm{M}]}{\mathrm{Km1}}} \tag{2}$$

6.2 Reaction v2

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

Name phosphorylation of P-MAPK

Reaction equation

$$\mathrm{Mp} \xrightarrow{\mathrm{MAPKK2,\ M}} \mathrm{Mpp} \tag{3}$$

Reactant

Table 9: Properties of each reactant.

Id	Name	SBO
Mp		

Modifiers

Table 10: Properties of each modifier.

Id	Name	SBO
MAPKK2	MAPKK2	
M		

Product

Table 11: Properties of each product.

Id	Name	SBO
Mpp		

Kinetic Law

Derived unit contains undeclared units

$$v_2 = \mathrm{vol}\,(\mathrm{uVol}) \cdot \frac{\frac{\mathrm{k2cat} \cdot [\mathrm{MAPKK2}] \cdot [\mathrm{Mp}]}{\mathrm{Km2}}}{1 + \frac{[\mathrm{Mp}]}{\mathrm{Km2}}} \tag{4}$$

6.3 Reaction v3

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

Name dephosphorylation of PP-MAPK

Reaction equation

$$\mathrm{Mpp} \xrightarrow{\mathrm{MKP3,\ M}} \mathrm{Mp} \tag{5}$$

Reactant

Table 12: Properties of each reactant.

Id	Name	SBO
Mpp		

Modifiers

Table 13: Properties of each modifier.

Id	Name	SBO
MKP3		
M		

Product

Table 14: Properties of each product.

Id	Name	SBO
Mp		

Kinetic Law

Derived unit contains undeclared units

$$v_3 = \mathrm{vol}\,(\mathrm{uVol}) \cdot \frac{\frac{\mathrm{k3cat} \cdot [\mathrm{MKP3}] \cdot [\mathrm{Mpp}]}{\mathrm{Km3}}}{1 + \frac{[\mathrm{Mpp}]}{\mathrm{Km3}} + \frac{[\mathrm{Mp}]}{\mathrm{Km4}} + \frac{[\mathrm{M}]}{\mathrm{Km5}}} \tag{6}$$

6.4 Reaction v4

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

Name dephosphorylation of P-MAPK

Reaction equation

$$\mathrm{Mp} \xrightarrow{\mathrm{MKP3,\ Mpp}} \mathrm{M} \tag{7}$$

Reactant

Table 15: Properties of each reactant.

Id	Name	SBO
Mp		

Modifiers

Table 16: Properties of each modifier.

Id	Name	SBO
MKP3		
Mpp		

Product

Table 17: Properties of each product.

Id	Name	SBO
M		

Kinetic Law

Derived unit contains undeclared units

$$v_4 = \mathrm{vol}\,(\mathrm{uVol}) \cdot \frac{\frac{\mathrm{k4cat}\cdot[\mathrm{MKP3}]\cdot[\mathrm{Mp}]}{\mathrm{Km4}}}{1 + \frac{[\mathrm{Mpp}]}{\mathrm{Km3}} + \frac{[\mathrm{Mp}]}{\mathrm{Km4}} + \frac{[\mathrm{M}]}{\mathrm{Km5}}} \tag{8}$$

7 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.

7.1 Species M

Initial amount 500 nmol

This species takes part in four reactions (as a reactant in v1 and as a product in v4 and as a modifier in v2, v3).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{M} = v_4 - v_1 \tag{9}$$

7.2 Species Mp

Initial amount 0 nmol

This species takes part in four reactions (as a reactant in v2, v4 and as a product in v1, v3).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Mp} = v_1 + v_3 - v_2 - v_4 \tag{10}$$

7.3 Species Mpp

Initial amount 0 nmol

This species takes part in three reactions (as a reactant in v3 and as a product in v2 and as a modifier in v4).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Mpp} = v_2 - v_3 \tag{11}$$

7.4 Species MAPKK1

Name MAPKK1

Initial amount 100 nmol

This species takes part in one reaction (as a modifier in v1).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{MAPKK1} = 0 \tag{12}$$

7.5 Species MAPKK2

Name MAPKK2

Initial amount 1 nmol

This species takes part in one reaction (as a modifier in v2).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{MAPKK2} = 0 \tag{13}$$

7.6 Species MKP3

Initial amount 100 nmol

This species takes part in two reactions (as a modifier in v3, v4).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{MKP3} = 0 \tag{14}$$

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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