SBML Model Report

Model name: “Sarma2012 - Oscillations in MAPK cascade (S1)”

May 6, 2016

1 General Overview

This is a document in SBML Level 2 Version 4 format. This model was created by the following three authors: Nick Juty[1], Vijayalakshmi Chelliah[2] and Uddipan Sarma[3] at March 15th 2013 at 4:53 p. m. and last time modified at April eighth 2016 at 5:23 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	11
events	0	constraints	0
reactions	10	function definitions	10
global parameters	0	unit definitions	2
rules	0	initial assignments	0

Model Notes

Sarma2012 - Oscillations in MAPK cascade (S1)

Two plausible designs (S1 and S2) of coupled positive and negative feedback loops of MAPK cascade has been described in this paper. This model corresponds to model S1 that comprises

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negative feedback from MK-PP to MKKK-P layer coupled to positive feedback from MK-PP to MKK-PP layer.

This model is described in the article:Oscillations in MAPK cascade triggered by two distinct designs of coupled positive and negative feedback loops.Sarma U, Ghosh I.BMC Res Notes. 2012 Jun 13;5:287.

Abstract:

BACKGROUND:
Feedback loops, both positive and negative are embedded in the Mitogen Activated Protein Kinase (MAPK) cascade. In the three layer MAPK cascade, both feedback loops originate from the terminal layer and their sites of action are either of the two upstream layers. Recent studies have shown that the cascade uses coupled positive and negative feedback loops in generating oscillations. Two plausible designs of coupled positive and negative feedback loops can be elucidated from the literature; in one design the positive feedback precedes the negative feedback in the direction of signal flow and vice-versa in another. But it remains unexplored how the two designs contribute towards triggering oscillations in MAPK cascade. Thus it is also not known how amplitude, frequency, robustness or nature (analogous/digital) of the oscillations would be shaped by these two designs.

RESULTS:
We built two models of MAPK cascade that exhibited oscillations as function of two underlying designs of coupled positive and negative feedback loops. Frequency, amplitude and nature (digital/analogous) of oscillations were found to be differentially determined by each design. It was observed that the positive feedback emerging from an oscillating MAPK cascade and functional in an external signal processing module can trigger oscillations in the target module, provided that the target module satisfy certain parametric requirements. The augmentation of the two models was done to incorporate the nuclear-cytoplasmic shuttling of cascade components followed by induction of a nuclear phosphatase. It revealed that the fate of oscillations in the MAPK cascade is governed by the feedback designs. Oscillations were unaffected due to nuclear compartmentalization owing to one design but were completely abolished in the other case.

CONCLUSION:
The MAPK cascade can utilize two distinct designs of coupled positive and negative feedback loops to trigger oscillations. The amplitude, frequency and robustness of the oscillations in presence or absence of nuclear compartmentalization were differentially determined by two designs of coupled positive and negative feedback loops. A positive feedback from an oscillating MAPK cascade was shown to induce oscillations in an external signal processing module, uncovering a novel regulatory aspect of MAPK signal processing.

This model is hosted on BioModels Database and identifiedby: MODEL1112190003 .

To cite BioModels Database, please use: BioModels Database: An enhanced, curated and annotated resourcefor published quantitative kinetic models .

2 Unit Definitions

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

2.1 Unit `volume`

Name volume

Definition ml

2.2 Unit `substance`

Name substance

Definition nmol

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
`compartment_0`	compartment		3	1	litre	☑	

3.1 Compartment compartment_0

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

Name compartment

4 Species

This model contains eleven 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
species_0	MKKK	compartment_0	$\mathrm{nmol \cdot ml^{-1}}$	⊟	⊟
species_1	MKKK_P	compartment_0	$\mathrm{nmol \cdot ml^{-1}}$	⊟	⊟
species_2	MKK	compartment_0	$\mathrm{nmol \cdot ml^{-1}}$	⊟	⊟
species_3	MKK_P	compartment_0	$\mathrm{nmol \cdot ml^{-1}}$	⊟	⊟
species_4	MKK_PP	compartment_0	$\mathrm{nmol \cdot ml^{-1}}$	⊟	⊟
species_5	M	compartment_0	$\mathrm{nmol \cdot ml^{-1}}$	⊟	⊟
species_6	M_P	compartment_0	$\mathrm{nmol \cdot ml^{-1}}$	⊟	⊟
species_7	M_PP	compartment_0	$\mathrm{nmol \cdot ml^{-1}}$	⊟	⊟
species_8	P1	compartment_0	$\mathrm{nmol \cdot ml^{-1}}$	⊟	⊟
species_9	P2	compartment_0	$\mathrm{nmol \cdot ml^{-1}}$	⊟	⊟
species_10	P3	compartment_0	$\mathrm{nmol \cdot ml^{-1}}$	⊟	⊟

5 Function definitions

This is an overview of ten function definitions.

5.1 Function definition `function_4_1_1`

Name function_4_1_1

Arguments K1, KI, V1, [species_0], [species_7]

Mathematical Expression

$$\frac{\frac{\mathrm{V1}\cdot[\mathrm{species\_0}]}{\mathrm{K1}}}{\left(1+\frac{[\mathrm{species\_0}]}{\mathrm{K1}}\right)\cdot\left(1+\frac{[\mathrm{species\_7}]}{\mathrm{KI}}\right)} \tag{1}$$

5.2 Function definition `function_4_3_1`

Name function_4_3_1

Arguments A, K3, Ka, k3, [species_1], [species_2], [species_3], [species_7]

Mathematical Expression

$$\frac{\frac{\mathrm{k3}\cdot[\mathrm{species\_1}]\cdot[\mathrm{species\_2}]}{\mathrm{K3}}}{1+\frac{[\mathrm{species\_2}]}{\mathrm{K3}}+\frac{[\mathrm{species\_3}]}{\mathrm{K3}}}\cdot\frac{1+\frac{\mathrm{A}\cdot[\mathrm{species\_7}]}{\mathrm{Ka}}}{1+\frac{[\mathrm{species\_7}]}{\mathrm{Ka}}} \tag{2}$$

5.3 Function definition `function_4_4_1`

Name function_4_4_1

Arguments A, K4, Ka, k4, [species_1], [species_2], [species_3], [species_7]

Mathematical Expression

$$\frac{\frac{\mathrm{k4}\cdot[\mathrm{species\_1}]\cdot[\mathrm{species\_3}]}{\mathrm{K4}}}{1+\frac{[\mathrm{species\_3}]}{\mathrm{K4}}+\frac{[\mathrm{species\_2}]}{\mathrm{K4}}}\cdot\frac{1+\frac{\mathrm{A}\cdot[\mathrm{species\_7}]}{\mathrm{Ka}}}{1+\frac{[\mathrm{species\_7}]}{\mathrm{Ka}}} \tag{3}$$

5.4 Function definition `function_4_7_1`

Name function_4_7_1

Arguments K7, k7, [species_4], [species_5], [species_6]

Mathematical Expression

$$\frac{\frac{\mathrm{k7}\cdot[\mathrm{species\_4}]\cdot[\mathrm{species\_5}]}{\mathrm{K7}}}{1+\frac{[\mathrm{species\_5}]}{\mathrm{K7}}+\frac{[\mathrm{species\_6}]}{\mathrm{K7}}} \tag{4}$$

5.5 Function definition function_4_8_1

Name function_4_8_1

Arguments K8, k8, [species_4], [species_5], [species_6]

Mathematical Expression

$$\frac{\frac{\text{k8}\cdot[\text{species\_4}]\cdot[\text{species\_6}]}{\text{K8}}}{1+\frac{[\text{species\_5}]}{\text{K8}}+\frac{[\text{species\_6}]}{\text{K8}}} \tag{5}$$

5.6 Function definition function_4_2_1

Name function_4_2_1

Arguments K2, k2, [species_1], [species_8]

Mathematical Expression

$$\frac{\frac{\text{k2}\cdot[\text{species\_8}]\cdot[\text{species\_1}]}{\text{K2}}}{1+\frac{[\text{species\_1}]}{\text{K2}}} \tag{6}$$

5.7 Function definition function_4_5_1

Name function_4_5_1

Arguments K5, k5, [species_3], [species_4], [species_9]

Mathematical Expression

$$\frac{\frac{\text{k5}\cdot[\text{species\_9}]\cdot[\text{species\_4}]}{\text{K5}}}{1+\frac{[\text{species\_4}]}{\text{K5}}+\frac{[\text{species\_3}]}{\text{K5}}} \tag{7}$$

5.8 Function definition function_4_6_1

Name function_4_6_1

Arguments K6, k6, [species_3], [species_4], [species_9]

Mathematical Expression

$$\frac{\frac{\text{k6}\cdot[\text{species\_9}]\cdot[\text{species\_3}]}{\text{K6}}}{1+\frac{[\text{species\_4}]}{\text{K6}}+\frac{[\text{species\_3}]}{\text{K6}}} \tag{8}$$

5.9 Function definition function_4_9_1

Name function_4_9_1

Arguments K9, k9, [species_10], [species_6], [species_7]

Mathematical Expression

$$\frac{\frac{\mathrm{k9}\cdot[\mathrm{species\_10}]\cdot[\mathrm{species\_7}]}{\mathrm{K9}}}{1+\frac{[\mathrm{species\_7}]}{\mathrm{K9}}+\frac{[\mathrm{species\_6}]}{\mathrm{K9}}} \tag{9}$$

5.10 Function definition function_4_10_1

Name function_4_10_1

Arguments K10, k10, [species_10], [species_6], [species_7]

Mathematical Expression

$$\frac{\frac{\mathrm{k10}\cdot[\mathrm{species\_10}]\cdot[\mathrm{species\_6}]}{\mathrm{K10}}}{1+\frac{[\mathrm{species\_7}]}{\mathrm{K10}}+\frac{[\mathrm{species\_6}]}{\mathrm{K10}}} \tag{10}$$

6 Reactions

This model contains ten 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 4: Overview of all reactions

№	Id	Name	Reaction Equation	SBO
1	reaction_0	1	species_0 $\xrightarrow{\text{species\_7, species\_0, species\_7}}$ species_1	
2	reaction_1	3	species_2 $\xrightarrow{\text{species\_1, species\_3, species\_7, species\_1, species\_2, species\_3, species\_7}}$ spe	
3	reaction_2	4	species_3 $\xrightarrow{\text{species\_1, species\_2, species\_7, species\_1, species\_2, species\_3, species\_7}}$ spe	
4	reaction_3	7	species_5 $\xrightarrow{\text{species\_4, species\_6, species\_4, species\_5, species\_6}}$ species_6	
5	reaction_4	8	species_6 $\xrightarrow{\text{species\_4, species\_5, species\_4, species\_5, species\_6}}$ species_7	
6	reaction_5	2	species_1 $\xrightarrow{\text{species\_8, species\_1, species\_8}}$ species_0	
7	reaction_6	5	species_4 $\xrightarrow{\text{species\_9, species\_3, species\_3, species\_4, species\_9}}$ species_3	
8	reaction_7	6	species_3 $\xrightarrow{\text{species\_9, species\_4, species\_3, species\_4, species\_9}}$ species_2	
9	reaction_8	9	species_7 $\xrightarrow{\text{species\_10, species\_6, species\_5, species\_10, species\_6, species\_7}}$ species_6	
10	reaction_9	10	species_6 $\xrightarrow{\text{species\_10, species\_7, species\_5, species\_10, species\_6, species\_7}}$ species_5	

6.1 Reaction reaction_0

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

Name 1

Reaction equation

$$\text{species\_0} \xrightarrow{\text{species\_7, species\_0, species\_7}} \text{species\_1} \tag{11}$$

Reactant

Table 5: Properties of each reactant.

Id	Name	SBO
species_0	MKKK	

Modifiers

Table 6: Properties of each modifier.

Id	Name	SBO
species_7	M_PP	
species_0	MKKK	
species_7	M_PP	

Product

Table 7: Properties of each product.

Id	Name	SBO
species_1	MKKK_P	

Kinetic Law

Derived unit contains undeclared units

$$v_1 = \text{vol}\left(\text{compartment\_0}\right) \cdot \text{function\_4\_1\_1}\left(\text{K1}, \text{KI}, \text{V1}, [\text{species\_0}], [\text{species\_7}]\right) \tag{12}$$

$$\text{function\_4\_1\_1}\left(\text{K1}, \text{KI}, \text{V1}, [\text{species\_0}], [\text{species\_7}]\right) = \frac{\frac{\text{V1} \cdot [\text{species\_0}]}{\text{K1}}}{\left(1 + \frac{[\text{species\_0}]}{\text{K1}}\right) \cdot \left(1 + \frac{[\text{species\_7}]}{\text{KI}}\right)} \tag{13}$$

$$\text{function\_4\_1\_1}\left(\text{K1}, \text{KI}, \text{V1}, [\text{species\_0}], [\text{species\_7}]\right) = \frac{\frac{\text{V1} \cdot [\text{species\_0}]}{\text{K1}}}{\left(1 + \frac{[\text{species\_0}]}{\text{K1}}\right) \cdot \left(1 + \frac{[\text{species\_7}]}{\text{KI}}\right)} \quad (14)$$

Table 8: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
K1	K1		20.0		☑
KI	KI		9.0		☑
V1	V1		2.5		☑

6.2 Reaction reaction_1

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

Name 3

Reaction equation

$$\text{species\_2} \xrightarrow{\text{species\_1, species\_3, species\_7, species\_1, species\_2, species\_3, species\_7}} \text{species\_3} \quad (15)$$

Reactant

Table 9: Properties of each reactant.

Id	Name	SBO
species_2	MKK	

Modifiers

Table 10: Properties of each modifier.

Id	Name	SBO
species_1	MKKK_P	
species_3	MKK_P	
species_7	M_PP	
species_1	MKKK_P	
species_2	MKK	
species_3	MKK_P	

Id	Name	SBO
species_7	M_PP	

Product

Table 11: Properties of each product.

Id	Name	SBO
species_3	MKK_P	

Kinetic Law

Derived unit contains undeclared units

$$v_2 = \mathrm{vol}\,(\mathrm{compartment\_0}) \cdot \mathrm{function\_4\_3\_1}\,(\mathrm{A}, \mathrm{K3}, \mathrm{Ka}, \mathrm{k3}, [\mathrm{species\_1}], [\mathrm{species\_2}], [\mathrm{species\_3}], [\mathrm{species\_7}]) \tag{16}$$

$$\mathrm{function\_4\_3\_1}\,(\mathrm{A}, \mathrm{K3}, \mathrm{Ka}, \mathrm{k3}, [\mathrm{species\_1}], [\mathrm{species\_2}], [\mathrm{species\_3}], [\mathrm{species\_7}]) = \frac{\frac{\mathrm{k3}\cdot[\mathrm{species\_1}]\cdot[\mathrm{species\_2}]}{\mathrm{K3}}}{1 + \frac{[\mathrm{species\_2}]}{\mathrm{K3}} + \frac{[\mathrm{species\_3}]}{\mathrm{K3}}} \cdot \frac{1 + \frac{\mathrm{A}\cdot[\mathrm{species\_7}]}{\mathrm{Ka}}}{1 + \frac{[\mathrm{species\_7}]}{\mathrm{Ka}}} \tag{17}$$

$$\mathrm{function\_4\_3\_1}\,(\mathrm{A}, \mathrm{K3}, \mathrm{Ka}, \mathrm{k3}, [\mathrm{species\_1}], [\mathrm{species\_2}], [\mathrm{species\_3}], [\mathrm{species\_7}]) = \frac{\frac{\mathrm{k3}\cdot[\mathrm{species\_1}]\cdot[\mathrm{species\_2}]}{\mathrm{K3}}}{1 + \frac{[\mathrm{species\_2}]}{\mathrm{K3}} + \frac{[\mathrm{species\_3}]}{\mathrm{K3}}} \cdot \frac{1 + \frac{\mathrm{A}\cdot[\mathrm{species\_7}]}{\mathrm{Ka}}}{1 + \frac{[\mathrm{species\_7}]}{\mathrm{Ka}}} \tag{18}$$

Table 12: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
A	A		10.0		☑
K3	K3		20.0		☑
Ka	Ka		500.0		☑
k3	k3		0.1		☑

6.3 Reaction reaction_2

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

Name 4

Reaction equation

$$\text{species\_3} \xrightarrow{\text{species\_1, species\_2, species\_7, species\_1, species\_2, species\_3, species\_7}} \text{species\_4} \tag{19}$$

Reactant

Table 13: Properties of each reactant.

Id	Name	SBO
species_3	MKK_P	

Modifiers

Table 14: Properties of each modifier.

Id	Name	SBO
species_1	MKKK_P	
species_2	MKK	
species_7	M_PP	
species_1	MKKK_P	
species_2	MKK	
species_3	MKK_P	
species_7	M_PP	

Product

Table 15: Properties of each product.

Id	Name	SBO
species_4	MKK_PP	

Kinetic Law

Derived unit contains undeclared units

$$\begin{aligned} v_3 = {} & \text{vol}\left(\text{compartment\_0}\right) \\ & \cdot \text{function\_4\_4\_1}\left(\text{A}, \text{K4}, \text{Ka}, \text{k4}, [\text{species\_1}], [\text{species\_2}], [\text{species\_3}], [\text{species\_7}]\right) \end{aligned} \tag{20}$$

$$\text{function\_4\_4\_1}(\mathrm{A}, \mathrm{K4}, \mathrm{Ka}, \mathrm{k4}, [\text{species\_1}], [\text{species\_2}], [\text{species\_3}], [\text{species\_7}]) = \frac{\frac{\mathrm{k4} \cdot [\text{species\_1}] \cdot [\text{species\_3}]}{\mathrm{K4}}}{1 + \frac{[\text{species\_3}]}{\mathrm{K4}} + \frac{[\text{species\_2}]}{\mathrm{K4}}} \cdot \frac{1 + \frac{\mathrm{A} \cdot [\text{species\_7}]}{\mathrm{Ka}}}{1 + \frac{[\text{species\_7}]}{\mathrm{Ka}}} \tag{21}$$

$$\text{function\_4\_4\_1}(\mathrm{A}, \mathrm{K4}, \mathrm{Ka}, \mathrm{k4}, [\text{species\_1}], [\text{species\_2}], [\text{species\_3}], [\text{species\_7}]) = \frac{\frac{\mathrm{k4} \cdot [\text{species\_1}] \cdot [\text{species\_3}]}{\mathrm{K4}}}{1 + \frac{[\text{species\_3}]}{\mathrm{K4}} + \frac{[\text{species\_2}]}{\mathrm{K4}}} \cdot \frac{1 + \frac{\mathrm{A} \cdot [\text{species\_7}]}{\mathrm{Ka}}}{1 + \frac{[\text{species\_7}]}{\mathrm{Ka}}} \tag{22}$$

Table 16: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
A	A		10.0		☑
K4	K4		20.0		☑
Ka	Ka		500.0		☑
k4	k4		0.1		☑

6.4 Reaction reaction_3

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

Name 7

Reaction equation

$$\text{species\_5} \xrightarrow{\text{species\_4, species\_6, species\_4, species\_5, species\_6}} \text{species\_6} \tag{23}$$

Reactant

Table 17: Properties of each reactant.

Id	Name	SBO
species_5	M	

Modifiers

Table 18: Properties of each modifier.

Id	Name	SBO
species_4	MKK_PP	
species_6	M_P	
species_4	MKK_PP	
species_5	M	
species_6	M_P	

Product

Table 19: Properties of each product.

Id	Name	SBO
species_6	M_P	

Kinetic Law

Derived unit contains undeclared units

$$v_4 = \mathrm{vol}\left(\mathrm{compartment\_0}\right) \cdot \mathrm{function\_4\_7\_1}\left(\mathrm{K7}, \mathrm{k7}, [\mathrm{species\_4}], [\mathrm{species\_5}], [\mathrm{species\_6}]\right) \quad (24)$$

$$\mathrm{function\_4\_7\_1}\left(\mathrm{K7}, \mathrm{k7}, [\mathrm{species\_4}], [\mathrm{species\_5}], [\mathrm{species\_6}]\right) = \frac{\frac{\mathrm{k7} \cdot [\mathrm{species\_4}] \cdot [\mathrm{species\_5}]}{\mathrm{K7}}}{1 + \frac{[\mathrm{species\_5}]}{\mathrm{K7}} + \frac{[\mathrm{species\_6}]}{\mathrm{K7}}} \quad (25)$$

$$\mathrm{function\_4\_7\_1}\left(\mathrm{K7}, \mathrm{k7}, [\mathrm{species\_4}], [\mathrm{species\_5}], [\mathrm{species\_6}]\right) = \frac{\frac{\mathrm{k7} \cdot [\mathrm{species\_4}] \cdot [\mathrm{species\_5}]}{\mathrm{K7}}}{1 + \frac{[\mathrm{species\_5}]}{\mathrm{K7}} + \frac{[\mathrm{species\_6}]}{\mathrm{K7}}} \quad (26)$$

Table 20: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
K7	K7		20.0		☑
k7	k7		0.1		☑

6.5 Reaction reaction_4

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

Name 8

Reaction equation

$$\text{species\_6} \xrightarrow{\text{species\_4, species\_5, species\_4, species\_5, species\_6}} \text{species\_7} \tag{27}$$

Reactant

Table 21: Properties of each reactant.

Id	Name	SBO
species_6	M_P	

Modifiers

Table 22: Properties of each modifier.

Id	Name	SBO
species_4	MKK_PP	
species_5	M	
species_4	MKK_PP	
species_5	M	
species_6	M_P	

Product

Table 23: Properties of each product.

Id	Name	SBO
species_7	M_PP	

Kinetic Law

Derived unit contains undeclared units

$$v_5 = \text{vol}\left(\text{compartment\_0}\right) \cdot \text{function\_4\_8\_1}\left(\text{K8}, \text{k8}, [\text{species\_4}], [\text{species\_5}], [\text{species\_6}]\right) \tag{28}$$

$$\text{function\_4\_8\_1}\left(\text{K8}, \text{k8}, [\text{species\_4}], [\text{species\_5}], [\text{species\_6}]\right) = \frac{\frac{\text{k8} \cdot [\text{species\_4}] \cdot [\text{species\_6}]}{\text{K8}}}{1 + \frac{[\text{species\_5}]}{\text{K8}} + \frac{[\text{species\_6}]}{\text{K8}}} \tag{29}$$

$$\text{function\_4\_8\_1}\left(\text{K8}, \text{k8}, [\text{species\_4}], [\text{species\_5}], [\text{species\_6}]\right) = \frac{\frac{\text{k8} \cdot [\text{species\_4}] \cdot [\text{species\_6}]}{\text{K8}}}{1 + \frac{[\text{species\_5}]}{\text{K8}} + \frac{[\text{species\_6}]}{\text{K8}}} \tag{30}$$

Table 24: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
K8	K8		20.0		☑
k8	k8		0.1		☑

6.6 Reaction reaction_5

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

Name 2

Reaction equation

$$\text{species\_1} \xrightarrow{\text{species\_8, species\_1, species\_8}} \text{species\_0} \tag{31}$$

Reactant

Table 25: Properties of each reactant.

Id	Name	SBO
species_1	MKKK_P	

Modifiers

Table 26: Properties of each modifier.

Id	Name	SBO
species_8	P1	
species_1	MKKK_P	
species_8	P1	

Product

Table 27: Properties of each product.

Id	Name	SBO
species_0	MKKK	

Kinetic Law

Derived unit contains undeclared units

$$v_6 = \mathrm{vol}\left(\mathrm{compartment\_0}\right) \cdot \mathrm{function\_4\_2\_1}\left(\mathrm{K2}, \mathrm{k2}, [\mathrm{species\_1}], [\mathrm{species\_8}]\right) \tag{32}$$

$$\mathrm{function\_4\_2\_1}\left(\mathrm{K2}, \mathrm{k2}, [\mathrm{species\_1}], [\mathrm{species\_8}]\right) = \frac{\frac{\mathrm{k2} \cdot [\mathrm{species\_8}] \cdot [\mathrm{species\_1}]}{\mathrm{K2}}}{1 + \frac{[\mathrm{species\_1}]}{\mathrm{K2}}} \tag{33}$$

$$\mathrm{function\_4\_2\_1}\left(\mathrm{K2}, \mathrm{k2}, [\mathrm{species\_1}], [\mathrm{species\_8}]\right) = \frac{\frac{\mathrm{k2} \cdot [\mathrm{species\_8}] \cdot [\mathrm{species\_1}]}{\mathrm{K2}}}{1 + \frac{[\mathrm{species\_1}]}{\mathrm{K2}}} \tag{34}$$

Table 28: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
K2	K2		200.000		☑
k2	k2		0.025		☑

6.7 Reaction reaction_6

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

Name 5

Reaction equation

$$\mathrm{species\_4} \xrightarrow{\mathrm{species\_9,\ species\_3,\ species\_3,\ species\_4,\ species\_9}} \mathrm{species\_3} \tag{35}$$

Reactant

Table 29: Properties of each reactant.

Id	Name	SBO
species_4	MKK_PP	

Modifiers

Table 30: Properties of each modifier.

Id	Name	SBO
species_9	P2	
species_3	MKK_P	
species_3	MKK_P	
species_4	MKK_PP	
species_9	P2	

Product

Table 31: Properties of each product.

Id	Name	SBO
species_3	MKK_P	

Kinetic Law

Derived unit contains undeclared units

$$v_7 = \mathrm{vol}\left(\mathrm{compartment\_0}\right) \cdot \mathrm{function\_4\_5\_1}\left(\mathrm{K5}, \mathrm{k5}, [\mathrm{species\_3}], [\mathrm{species\_4}], [\mathrm{species\_9}]\right) \quad (36)$$

$$\mathrm{function\_4\_5\_1}\left(\mathrm{K5}, \mathrm{k5}, [\mathrm{species\_3}], [\mathrm{species\_4}], [\mathrm{species\_9}]\right) = \frac{\frac{\mathrm{k5} \cdot [\mathrm{species\_9}] \cdot [\mathrm{species\_4}]}{\mathrm{K5}}}{1 + \frac{[\mathrm{species\_4}]}{\mathrm{K5}} + \frac{[\mathrm{species\_3}]}{\mathrm{K5}}} \quad (37)$$

$$\mathrm{function\_4\_5\_1}\left(\mathrm{K5}, \mathrm{k5}, [\mathrm{species\_3}], [\mathrm{species\_4}], [\mathrm{species\_9}]\right) = \frac{\frac{\mathrm{k5} \cdot [\mathrm{species\_9}] \cdot [\mathrm{species\_4}]}{\mathrm{K5}}}{1 + \frac{[\mathrm{species\_4}]}{\mathrm{K5}} + \frac{[\mathrm{species\_3}]}{\mathrm{K5}}} \quad (38)$$

Table 32: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
K5	K5		200.0		☑
k5	k5		0.1		☑

6.8 Reaction reaction_7

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

Name 6

Reaction equation

$$\text{species\_3} \xrightarrow{\text{species\_9, species\_4, species\_3, species\_4, species\_9}} \text{species\_2} \tag{39}$$

Reactant

Table 33: Properties of each reactant.

Id	Name	SBO
species_3	MKK_P	

Modifiers

Table 34: Properties of each modifier.

Id	Name	SBO
species_9	P2	
species_4	MKK_PP	
species_3	MKK_P	
species_4	MKK_PP	
species_9	P2	

Product

Table 35: Properties of each product.

Id	Name	SBO
species_2	MKK	

Kinetic Law

Derived unit contains undeclared units

$$v_8 = \text{vol}\left(\text{compartment\_0}\right) \cdot \text{function\_4\_6\_1}\left(\text{K6}, \text{k6}, [\text{species\_3}], [\text{species\_4}], [\text{species\_9}]\right) \tag{40}$$

$$\text{function\_4\_6\_1}\left(\text{K6}, \text{k6}, [\text{species\_3}], [\text{species\_4}], [\text{species\_9}]\right) = \frac{\frac{\text{k6} \cdot [\text{species\_9}] \cdot [\text{species\_3}]}{\text{K6}}}{1 + \frac{[\text{species\_4}]}{\text{K6}} + \frac{[\text{species\_3}]}{\text{K6}}} \tag{41}$$

$$\text{function\_4\_6\_1}\left(\text{K6}, \text{k6}, [\text{species\_3}], [\text{species\_4}], [\text{species\_9}]\right) = \frac{\frac{\text{k6} \cdot [\text{species\_9}] \cdot [\text{species\_3}]}{\text{K6}}}{1 + \frac{[\text{species\_4}]}{\text{K6}} + \frac{[\text{species\_3}]}{\text{K6}}} \tag{42}$$

Table 36: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
K6	K6		200.0		☑
k6	k6		0.1		☑

6.9 Reaction reaction_8

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

Name 9

Reaction equation

$$\text{species\_7} \xrightarrow{\text{species\_10, species\_6, species\_5, species\_10, species\_6, species\_7}} \text{species\_6} \quad (43)$$

Reactant

Table 37: Properties of each reactant.

Id	Name	SBO
species_7	M_PP	

Modifiers

Table 38: Properties of each modifier.

Id	Name	SBO
species_10	P3	
species_6	M_P	
species_5	M	
species_10	P3	
species_6	M_P	
species_7	M_PP	

Product

Table 39: Properties of each product.

Id	Name	SBO
species_6	M_P	

Kinetic Law

Derived unit contains undeclared units

$$v_9 = \mathrm{vol}\left(\mathrm{compartment\_0}\right) \cdot \mathrm{function\_4\_9\_1}\left(\mathrm{K9}, \mathrm{k9}, [\mathrm{species\_10}], [\mathrm{species\_6}], [\mathrm{species\_7}]\right) \quad (44)$$

$$\mathrm{function\_4\_9\_1}\left(\mathrm{K9}, \mathrm{k9}, [\mathrm{species\_10}], [\mathrm{species\_6}], [\mathrm{species\_7}]\right) = \frac{\frac{\mathrm{k9} \cdot [\mathrm{species\_10}] \cdot [\mathrm{species\_7}]}{\mathrm{K9}}}{1 + \frac{[\mathrm{species\_7}]}{\mathrm{K9}} + \frac{[\mathrm{species\_6}]}{\mathrm{K9}}} \quad (45)$$

$$\mathrm{function\_4\_9\_1}\left(\mathrm{K9}, \mathrm{k9}, [\mathrm{species\_10}], [\mathrm{species\_6}], [\mathrm{species\_7}]\right) = \frac{\frac{\mathrm{k9} \cdot [\mathrm{species\_10}] \cdot [\mathrm{species\_7}]}{\mathrm{K9}}}{1 + \frac{[\mathrm{species\_7}]}{\mathrm{K9}} + \frac{[\mathrm{species\_6}]}{\mathrm{K9}}} \quad (46)$$

Table 40: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
K9	K9		200.0		☑
k9	k9		0.1		☑

6.10 Reaction reaction_9

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

Name 10

Reaction equation

$$\mathrm{species\_6} \xrightarrow{\mathrm{species\_10},\ \mathrm{species\_7},\ \mathrm{species\_5},\ \mathrm{species\_10},\ \mathrm{species\_6},\ \mathrm{species\_7}} \mathrm{species\_5} \quad (47)$$

Reactant

Table 41: Properties of each reactant.

Id	Name	SBO
species_6	M_P	

Modifiers

Table 42: Properties of each modifier.

Id	Name	SBO
species_10	P3	
species_7	M_PP	
species_5	M	
species_10	P3	
species_6	M_P	
species_7	M_PP	

Product

Table 43: Properties of each product.

Id	Name	SBO
species_5	M	

Kinetic Law

Derived unit contains undeclared units

$$v_{10} = \mathrm{vol}\left(\mathrm{compartment\_0}\right) \cdot \mathrm{function\_4\_10\_1}\left(\mathrm{K10}, \mathrm{k10}, [\mathrm{species\_10}], [\mathrm{species\_6}], [\mathrm{species\_7}]\right) \tag{48}$$

$$\mathrm{function\_4\_10\_1}\left(\mathrm{K10}, \mathrm{k10}, [\mathrm{species\_10}], [\mathrm{species\_6}], [\mathrm{species\_7}]\right) = \frac{\frac{\mathrm{k10} \cdot [\mathrm{species\_10}] \cdot [\mathrm{species\_6}]}{\mathrm{K10}}}{1 + \frac{[\mathrm{species\_7}]}{\mathrm{K10}} + \frac{[\mathrm{species\_6}]}{\mathrm{K10}}} \tag{49}$$

$$\mathrm{function\_4\_10\_1}\left(\mathrm{K10}, \mathrm{k10}, [\mathrm{species\_10}], [\mathrm{species\_6}], [\mathrm{species\_7}]\right) = \frac{\frac{\mathrm{k10} \cdot [\mathrm{species\_10}] \cdot [\mathrm{species\_6}]}{\mathrm{K10}}}{1 + \frac{[\mathrm{species\_7}]}{\mathrm{K10}} + \frac{[\mathrm{species\_6}]}{\mathrm{K10}}} \tag{50}$$

Table 44: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
K10	K10		200.0		☑
k10	k10		0.1		☑

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 species_0

Name MKKK

Initial concentration $999.999903688753\ \mathrm{nmol \cdot ml^{-1}}$

This species takes part in three reactions (as a reactant in reaction_0 and as a product in reaction_5 and as a modifier in reaction_0).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{species\_0} = v_6 - v_1 \tag{51}$$

7.2 Species species_1

Name MKKK_P

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

This species takes part in seven reactions (as a reactant in reaction_5 and as a product in reaction_0 and as a modifier in reaction_1, reaction_1, reaction_2, reaction_2, reaction_5).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{species\_1} = v_1 - v_6 \tag{52}$$

7.3 Species species_2

Name MKK

Initial concentration $3999.99961475501\ \mathrm{nmol \cdot ml^{-1}}$

This species takes part in five reactions (as a reactant in reaction_1 and as a product in reaction_7 and as a modifier in reaction_1, reaction_2, reaction_2).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{species\_2} = v_8 - v_2 \tag{53}$$

7.4 Species species_3

Name MKK_P

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

This species takes part in ten reactions (as a reactant in reaction_2, reaction_7 and as a product in reaction_1, reaction_6 and as a modifier in reaction_1, reaction_1, reaction_2, reaction_6, reaction_6, reaction_7).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{species\_3} = v_2 + v_7 - v_3 - v_8 \tag{54}$$

7.5 Species species_4

Name MKK_PP

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

This species takes part in nine reactions (as a reactant in reaction_6 and as a product in reaction_2 and as a modifier in reaction_3, reaction_3, reaction_4, reaction_4, reaction_6, reaction_7, reaction_7).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{species\_4} = v_3 - v_7 \tag{55}$$

7.6 Species species_5

Name M

Initial concentration $999.999903688753\ \mathrm{nmol \cdot ml^{-1}}$

This species takes part in seven reactions (as a reactant in reaction_3 and as a product in reaction_9 and as a modifier in reaction_3, reaction_4, reaction_4, reaction_8, reaction_9).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{species\_5} = v_{10} - v_4 \tag{56}$$

7.7 Species species_6

Name M_P

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

This species takes part in ten reactions (as a reactant in reaction_4, reaction_9 and as a product in reaction_3, reaction_8 and as a modifier in reaction_3, reaction_3, reaction_4, reaction_8, reaction_8, reaction_9).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{species\_6} = v_4 + v_9 - v_5 - v_{10} \tag{57}$$

7.8 Species species_7

Name M_PP

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

This species takes part in eleven reactions (as a reactant in reaction_8 and as a product in reaction_4 and as a modifier in reaction_0, reaction_0, reaction_1, reaction_1, reaction_2, reaction_2, reaction_8, reaction_9, reaction_9).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{species\_7} = v_5 - v_9 \tag{58}$$

7.9 Species species_8

Name P1

Initial concentration $99.9999903688752\ \mathrm{nmol} \cdot \mathrm{ml}^{-1}$

This species takes part in two reactions (as a modifier in reaction_5, reaction_5).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{species\_8} = 0 \tag{59}$$

7.10 Species species_9

Name P2

Initial concentration $499.999951844377\ \mathrm{nmol} \cdot \mathrm{ml}^{-1}$

This species takes part in four reactions (as a modifier in reaction_6, reaction_6, reaction_7, reaction_7).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{species\_9} = 0 \tag{60}$$

7.11 Species species_10

Name P3

Initial concentration $499.999951844377\ \mathrm{nmol} \cdot \mathrm{ml}^{-1}$

This species takes part in four reactions (as a modifier in reaction_8, reaction_8, reaction_9, reaction_9).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{species\_10} = 0 \tag{61}$$

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