**SBML Model Report**

# Model name: "Sarma2012 - Interaction topologies of MAPK cascade (M4_K2_QSS_PSEQ)"

May 6, 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 Uddipan Sarma[2] at November 23rd 2012 at 4:21 p. m. and last time modified at May 30th 2014 at 6:21 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 | 2 |
| species types | 0 | species | 11 |
| events | 0 | constraints | 0 |
| reactions | 10 | function definitions | 10 |
| global parameters | 14 | unit definitions | 2 |
| rules | 0 | initial assignments | 0 |

### Model Notes

Sarma2012 - Interaction topologies of MAPK cascade (M4_K2_QSS_PSEQ)


[1]EMBL-EBI, viji@ebi.ac.uk

[2]National Centre for Cell Science, uddipans@gmail.com

The paper presents the various interaction topologies between the kinases and phosphatases of MAPK cascade. They are represented as M1, M2, M3 and M4. The kinases of the cascades are MKKK, MKK and MK, and Phos1, Phos2 and Phos3 are phosphatases of the system. All three kinases in a M1 type network have specific phosphatases Phos1, Phos2 and Phos3 for the dephosphorylation process. In a M2 type system, kinases MKKK and MKK are dephosphorylated by Phos1 and MK is dephosphorylated by Phos2. The architecture of system like M3 is such that MKKK gets dephosphorylated by Phos1, whereas Phos2 dephosphorylates both MKK and MK. Finally, the MAPK cascade exhibiting more complex design of interaction such as M4 is such that MKKK and MKK are dephosphorylated by Phos1 whereas MKK and MK are dephosphorylated by Phos2. In addition, as it is plausible that the kinases can sequester their respective phosphatases by binding to them, this is considered in the design of the systems (PSEQ-sequestrated system; USEQ-Unsequestrated system). The robustness of different interaction designs of the systems is checked, considering both MichaelisMenten type kinetics (K1) and elementary mass action kinetics (K2). In the living systems, the MAPK cascade transmit both short and long duration signals where short duration signals trigger proliferation and long duration signals trigger cell differentiation. These signal variants are considered to interpret the systems behaviour. It is also tested how the robustness and signal response behaviour of K2 models are affected when K2 assumes quasi steady state (QSS). The combinations of the above variants resulted in 40 models (MODEL1204280001-MODEL1204280040). All these 40 models are available from BioModels Database .

Models that correspond to type M4 with mass-action kinetics K2, in four condition 1) USEQ [ MODEL1204280020 - M4_K2_USEQ], 2) PSEQ [ MODEL1204280024 - M4_K2_PSEQ], 3) QSS_USEQ [ MODEL1204280036 - M4_K2_QSS_USEQ] and 4) QSS_PSEQ [ MODEL1204280040 - M4_K2_QSS_PSEQ] are available from the curated branch. The remaining 36 models can be accessed from the non-curated branch.

This model [ MODEL1204280040 - M4_K2_QSS_PSEQ] correspond to type M4 with mass-action kinetics K2, in QSS (quasi steady state) and USEQ (Unsequestrated ) condition. .

This model is described in the article:Different designs of kinase-phosphatase interactions and phosphatase sequestration shapes the robustness and signal flow in the MAPK cascade.Sarma U, Ghosh I.BMC Syst Biol. 2012 Jul 2;6(1):82.

Abstract:

BACKGROUND: The three layer mitogen activated protein kinase (MAPK) signaling cascade exhibits different designs of interactions between its kinases and phosphatases. While the sequential interactions between the three kinases of the cascade are tightly preserved, the phosphatases of the cascade, such as MKP3 and PP2A, exhibit relatively diverse interactions with their substrate kinases. Additionally, the kinases of the MAPK cascade can also sequester their phosphatases. Thus, each topologically distinct interaction design of kinases and phosphatases could exhibit unique signal processing characteristics, and the presence of phosphatase sequestration may lead to further fine tuning of the propagated signal.

RESULTS: We have built four models of the MAPK cascade, each model with identical kinase-kinase interactions but unique kinases-phosphatases interactions. Our simulations unravelled that MAPK cascade's robustness to external perturbations is a function of nature of interaction between its kinases and phosphatases. The cascade's output robustness was enhanced when phosphatases were sequestrated by their target kinases. We uncovered a novel implicit/hidden negative feedback loop from the phosphatase MKP3 to its upstream kinase Raf-1, in a cascade resembling the B cell MAPK cascade. Notably, strength of the feedback loop was reciprocal to the strength of phosphatases' sequestration and stronger sequestration abolished the feedback loop completely. An experimental method to verify the presence of the feedback loop is also proposed. We further showed, when the models were activated by transient signal, memory (total time taken by the cascade output to reach its unstimulated level after removal of signal) of a cascade was determined by the specific designs of interaction among its kinases and phosphatases.

CONCLUSIONS: Differences in interaction designs among the kinases and phosphatases can differentially shape the robustness and signal response behaviour of the MAPK cascade and phosphatase sequestration dramatically enhances the robustness to perturbations in each of the cascade. An implicit negative feedback loop was uncovered from our analysis and we found that strength of the negative feedback loop is reciprocally related to the strength of phosphatase sequestration. Duration of output phosphorylation in response to a transient signal was also found to be determined by the individual cascade's kinase-phosphatase interaction design.

This model is hosted on BioModels Database and identified by: MODEL1204280040 .

To cite BioModels Database, please use: BioModels Database: An enhanced, curated and annotated resource for 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 Compartments

This model contains two compartments.

Table 2: Properties of all compartments.

| Id | Name | SBO | Spatial Dimensions | Size | Unit | Constant | Outside |
|---|---|---|---|---|---|---|---|
| `compartment_1` | compartment | | 3 | 1 | litre | ☑ | |
| `compartment_2` | No Name | | 3 | 1 | litre | ☑ | |

### 3.1 Compartment `compartment_1`

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

**Name** compartment

### 3.2 Compartment `compartment_2`

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

**Name** No Name

## 4 Species

This model contains eleven species. 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 |
|---|---|---|---|---|---|
| species_1 | MKKK | compartment_1 | $\mathrm{nmol} \cdot \mathrm{ml}^{-1}$ | ☐ | ☐ |
| species_2 | MKKK_P | compartment_1 | $\mathrm{nmol} \cdot \mathrm{ml}^{-1}$ | ☐ | ☐ |
| species_3 | MKK | compartment_1 | $\mathrm{nmol} \cdot \mathrm{ml}^{-1}$ | ☐ | ☐ |
| species_4 | MKK_P | compartment_1 | $\mathrm{nmol} \cdot \mathrm{ml}^{-1}$ | ☐ | ☐ |
| species_5 | MKK_PP | compartment_1 | $\mathrm{nmol} \cdot \mathrm{ml}^{-1}$ | ☐ | ☐ |
| species_6 | MK | compartment_1 | $\mathrm{nmol} \cdot \mathrm{ml}^{-1}$ | ☐ | ☐ |
| species_7 | MK_P | compartment_1 | $\mathrm{nmol} \cdot \mathrm{ml}^{-1}$ | ☐ | ☐ |
| species_8 | MK_PP | compartment_1 | $\mathrm{nmol} \cdot \mathrm{ml}^{-1}$ | ☐ | ☐ |
| species_9 | P1 | compartment_1 | $\mathrm{nmol} \cdot \mathrm{ml}^{-1}$ | ☐ | ☐ |
| species_10 | P2 | compartment_1 | $\mathrm{nmol} \cdot \mathrm{ml}^{-1}$ | ☐ | ☐ |
| species_11 | Sig | compartment_1 | $\mathrm{nmol} \cdot \mathrm{ml}^{-1}$ | ☐ | ☐ |

# 5 Parameters

This model contains 14 global parameters.

Table 4: Properties of each parameter.

| Id | Name | SBO | Value | Unit | Constant |
|---|---|---|---|---|---|
| parameter_1 | K1 | | 100.00 | | ☑ |
| parameter_2 | K2a | | 54.30 | | ☑ |
| parameter_3 | K3 | | 50.50 | | ☑ |
| parameter_4 | K4 | | 500.00 | | ☑ |
| parameter_5 | K5a | | 24.30 | | ☑ |
| parameter_6 | K6a | | 108.60 | | ☑ |
| parameter_7 | K7 | | 50.50 | | ☑ |
| parameter_8 | K8 | | 500.00 | | ☑ |
| parameter_9 | K9b | | 24.30 | | ☑ |
| parameter_10 | K10b | | 108.60 | | ☑ |
| parameter_11 | Kse1 | | 0.06 | | ☑ |
| parameter_12 | Kse2 | | 0.06 | | ☑ |
| parameter_13 | K5b | | 24.30 | | ☑ |
| parameter_14 | K6b | | 108.60 | | ☑ |

# 6 Function definitions

This is an overview of ten function definitions.

## 6.1 Function definition `function_10`

**Name** 10

**Arguments** MK_P, MKK_PP, MKK_P, MK_PP, MKK, MK, P2, K10b, K5b, K6b, Kse2, K9b, k10b

**Mathematical Expression**

$$\frac{\frac{\mathrm{k10b} \cdot \mathrm{P2} \cdot \mathrm{MK\_P}}{\mathrm{K10b}}}{1 + \frac{\mathrm{MKK\_PP}}{\mathrm{K5b}} + \frac{\mathrm{MKK\_P}}{\mathrm{K6b}} + \frac{\mathrm{MKK}}{\mathrm{Kse2}} + \frac{\mathrm{MK}}{\mathrm{Kse2}} + \frac{\mathrm{MK\_P}}{\mathrm{K10b}} + \frac{\mathrm{MK\_PP}}{\mathrm{K9b}}} \tag{1}$$

## 6.2 Function definition `function_1`

**Name** 1

**Arguments** MKKK, K1, k1, Sig

**Mathematical Expression**

$$\frac{\mathrm{k1} \cdot \mathrm{Sig} \cdot \mathrm{MKKK}}{\mathrm{K1} + \mathrm{MKKK}} \tag{2}$$

## 6.3 Function definition function_6

**Name** 6

**Arguments** P1, MKK_P, MKK_PP, MK_P, MK_PP, MKK, MK, k6a, K6a, MKKK, MKKK_P, P2, K6b, K2a, Kse1, K5a, k6b, K5b, Kse2, K10b, K9b

**Mathematical Expression**

$$\frac{\frac{\mathrm{k6a} \cdot \mathrm{P1} \cdot \mathrm{MKK\_P}}{\mathrm{K6a}}}{1 + \frac{\mathrm{MKKK\_P}}{\mathrm{K2a}} + \frac{\mathrm{MKKK}}{\mathrm{Kse1}} + \frac{\mathrm{MKK\_PP}}{\mathrm{K5a}} + \frac{\mathrm{MKK\_P}}{\mathrm{K6a}} + \frac{\mathrm{MKK}}{\mathrm{Kse1}}} + \frac{\frac{\mathrm{k6b} \cdot \mathrm{P2} \cdot \mathrm{MKK\_P}}{\mathrm{K6b}}}{1 + \frac{\mathrm{MKK\_PP}}{\mathrm{K5b}} + \frac{\mathrm{MKK\_P}}{\mathrm{K6b}} + \frac{\mathrm{MKK}}{\mathrm{Kse2}} + \frac{\mathrm{MK}}{\mathrm{Kse2}} + \frac{\mathrm{MK\_P}}{\mathrm{K10b}} + \frac{\mathrm{MK\_PP}}{\mathrm{K9b}}} \tag{3}$$

## 6.4 Function definition function_2

**Name** 2

**Arguments** MKKK_P, MKKK, P1, MKK_PP, MKK_P, MKK, Kse1, K2a, K5a, K6a, k2a

**Mathematical Expression**

$$\frac{\frac{\mathrm{k2a} \cdot \mathrm{MKKK\_P} \cdot \mathrm{P1}}{\mathrm{K2a}}}{1 + \frac{\mathrm{MKKK\_P}}{\mathrm{K2a}} + \frac{\mathrm{MKKK}}{\mathrm{Kse1}} + \frac{\mathrm{MKK\_PP}}{\mathrm{K5a}} + \frac{\mathrm{MKK\_P}}{\mathrm{K6a}} + \frac{\mathrm{MKK}}{\mathrm{Kse1}}} \tag{4}$$

## 6.5 Function definition function_3

**Name** 3

**Arguments** k3, MKKK_P, MKK, K3, MKK_P, K4

**Mathematical Expression**

$$\frac{\frac{\mathrm{k3} \cdot \mathrm{MKKK\_P} \cdot \mathrm{MKK}}{\mathrm{K3}}}{1 + \frac{\mathrm{MKK}}{\mathrm{K3}} + \frac{\mathrm{MKK\_P}}{\mathrm{K4}}} \tag{5}$$

## 6.6 Function definition `function_4`

**Name** 4

**Arguments** k4, MKKK_P, MKK_P, K4, MKK, K3

**Mathematical Expression**

$$\frac{\frac{\mathrm{k4} \cdot \mathrm{MKKK\_P} \cdot \mathrm{MKK\_P}}{\mathrm{K4}}}{1 + \frac{\mathrm{MKK}}{\mathrm{K3}} + \frac{\mathrm{MKK\_P}}{\mathrm{K4}}} \tag{6}$$

## 6.7 Function definition `function_5`

**Name** 5

**Arguments** MKK_PP, MKK_P, MK_P, MK_PP, P1, MKK, MK, k5a, K5a, MKKK, MKKK_P, k5b, P2, K5b, K6a, Kse1, K2a, K6b, Kse2, K10b, K9b

**Mathematical Expression**

$$\begin{aligned} & \frac{\frac{\mathrm{k5a} \cdot \mathrm{P1} \cdot \mathrm{MKK\_PP}}{\mathrm{K5a}}}{1 + \frac{\mathrm{MKKK\_P}}{\mathrm{K2a}} + \frac{\mathrm{MKKK}}{\mathrm{Kse1}} + \frac{\mathrm{MKK\_PP}}{\mathrm{K5a}} + \frac{\mathrm{MKK\_P}}{\mathrm{K6a}} + \frac{\mathrm{MKK}}{\mathrm{Kse1}}} \\ & + \frac{\frac{\mathrm{k5b} \cdot \mathrm{P2} \cdot \mathrm{MKK\_PP}}{\mathrm{K5b}}}{1 + \frac{\mathrm{MKK\_PP}}{\mathrm{K5b}} + \frac{\mathrm{MKK\_P}}{\mathrm{K6b}} + \frac{\mathrm{MKK}}{\mathrm{Kse2}} + \frac{\mathrm{MK}}{\mathrm{Kse2}} + \frac{\mathrm{MK\_P}}{\mathrm{K10b}} + \frac{\mathrm{MK\_PP}}{\mathrm{K9b}}} \end{aligned} \tag{7}$$

## 6.8 Function definition `function_7`

**Name** 7

**Arguments** k7, MKK_PP, MK, K7, MK_P, K8

**Mathematical Expression**

$$\frac{\frac{\mathrm{k7} \cdot \mathrm{MKK\_PP} \cdot \mathrm{MK}}{\mathrm{K7}}}{1 + \frac{\mathrm{MK}}{\mathrm{K7}} + \frac{\mathrm{MK\_P}}{\mathrm{K8}}} \tag{8}$$

## 6.9 Function definition `function_9`

**Name** 9

**Arguments** MK_PP, MKK_PP, MKK_P, MK_P, MKK, MK, P2, K9b, K5b, K6b, Kse2, K10b, k9b

**Mathematical Expression**

$$\frac{\frac{\mathrm{k9b} \cdot \mathrm{P2} \cdot \mathrm{MK\_PP}}{\mathrm{K9b}}}{1 + \frac{\mathrm{MKK\_PP}}{\mathrm{K5b}} + \frac{\mathrm{MKK\_P}}{\mathrm{K6b}} + \frac{\mathrm{MKK}}{\mathrm{Kse2}} + \frac{\mathrm{MK}}{\mathrm{Kse2}} + \frac{\mathrm{MK\_P}}{\mathrm{K10b}} + \frac{\mathrm{MK\_PP}}{\mathrm{K9b}}} \tag{9}$$

## 6.10 Function definition `function_8`

**Name** 8

**Arguments** k7, MKK_PP, MK_P, K8, MK, K7

**Mathematical Expression**

$$\frac{\frac{\mathrm{k7}\cdot \mathrm{MKK\_PP}\cdot \mathrm{MK\_P}}{\mathrm{K8}}}{1+\frac{\mathrm{MK}}{\mathrm{K7}}+\frac{\mathrm{MK\_P}}{\mathrm{K8}}} \tag{10}$$

# 7 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 5: Overview of all reactions

| № | Id | Name | Reaction Equation | SBO |
|---|---|---|---|---|
| 1 | `reaction_1` | 1 | species_1 $\xrightarrow{\text{species\_11, species\_1, species\_11}}$ species_2 | |
| 2 | `reaction_2` | 2 | species_2 $\xrightarrow{\text{species\_1, species\_9, species\_5, species\_4, species\_3, species\_2, species\_1, sp}}$ | |
| 3 | `reaction_3` | 3 | species_3 $\xrightarrow{\text{species\_2, species\_4, species\_2, species\_3, species\_4}}$ species_4 | |
| 4 | `reaction_4` | 4 | species_4 $\xrightarrow{\text{species\_2, species\_3, species\_2, species\_4, species\_3}}$ species_5 | |
| 5 | `reaction_5` | 5 | species_5 $\xrightarrow{\text{species\_4, species\_7, species\_8, species\_9, species\_3, species\_6, species\_1, sp}}$ | |
| 6 | `reaction_6` | 6 | species_4 $\xrightarrow{\text{species\_9, species\_5, species\_7, species\_8, species\_3, species\_6, species\_1, sp}}$ | |
| 7 | `reaction_7` | 7 | species_6 $\xrightarrow{\text{species\_5, species\_7, species\_5, species\_6, species\_7}}$ species_7 | |
| 8 | `reaction_8` | 8 | species_7 $\xrightarrow{\text{species\_5, species\_6, species\_5, species\_7, species\_6}}$ species_8 | |
| 9 | `reaction_9` | 9 | species_8 $\xrightarrow{\text{species\_9, species\_4, species\_7, species\_3, species\_6, species\_10, species\_8, s}}$ | |
| 10 | `reaction_10` | 10 | species_7 $\xrightarrow{\text{species\_5, species\_4, species\_8, species\_3, species\_6, species\_10, species\_7, s}}$ | |

## 7.1 Reaction reaction_1

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

**Name** 1

### Reaction equation

$$\text{species\_1} \xrightarrow{\text{species\_11, species\_1, species\_11}} \text{species\_2} \tag{11}$$

### Reactant

Table 6: Properties of each reactant.

| Id | Name | SBO |
|---|---|---|
| species_1 | MKKK | |

### Modifiers

Table 7: Properties of each modifier.

| Id | Name | SBO |
|---|---|---|
| species_11 | Sig | |
| species_1 | MKKK | |
| species_11 | Sig | |

### Product

Table 8: Properties of each product.

| Id | Name | SBO |
|---|---|---|
| species_2 | MKKK_P | |

### Kinetic Law

**Derived unit** contains undeclared units

$$v_1 = \text{vol}(\text{compartment\_1}) \cdot \text{function\_1}([\text{species\_1}], \text{parameter\_1}, \text{k1}, [\text{species\_11}]) \tag{12}$$

$$\text{function\_1}(\text{MKKK}, \text{K1}, \text{k1}, \text{Sig}) = \frac{\text{k1} \cdot \text{Sig} \cdot \text{MKKK}}{\text{K1} + \text{MKKK}} \tag{13}$$

$$\text{function\_1}(\text{MKKK}, \text{K1}, \text{k1}, \text{Sig}) = \frac{\text{k1} \cdot \text{Sig} \cdot \text{MKKK}}{\text{K1} + \text{MKKK}} \quad (14)$$

Table 9: Properties of each parameter.

| Id | Name | SBO | Value | Unit | Constant |
|---|---|---|---|---|---|
| k1 | k1 | | 1.0 | | ☑ |

## 7.2 Reaction reaction_2

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

**Name** 2

### Reaction equation

$$\text{species\_2} \xrightarrow{\text{species\_1, species\_9, species\_5, species\_4, species\_3, species\_2, species\_1, species\_9, species\_5, species\_4,}} \quad (15)$$

### Reactant

Table 10: Properties of each reactant.

| Id | Name | SBO |
|---|---|---|
| species_2 | MKKK_P | |

### Modifiers

Table 11: Properties of each modifier.

| Id | Name | SBO |
|---|---|---|
| species_1 | MKKK | |
| species_9 | P1 | |
| species_5 | MKK_PP | |
| species_4 | MKK_P | |
| species_3 | MKK | |
| species_2 | MKKK_P | |
| species_1 | MKKK | |
| species_9 | P1 | |
| species_5 | MKK_PP | |

| Id | Name | SBO |
|---|---|---|
| species_4 | MKK_P | |
| species_3 | MKK | |

### Product

Table 12: Properties of each product.

| Id | Name | SBO |
|---|---|---|
| species_1 | MKKK | |

### Kinetic Law

**Derived unit** contains undeclared units

$$v_2 = \mathrm{vol}(\mathrm{compartment\_1}) \cdot \mathrm{function\_2}([\mathrm{species\_2}], [\mathrm{species\_1}], [\mathrm{species\_9}], [\mathrm{species\_5}], [\mathrm{species\_4}], [\mathrm{species\_3}], \mathrm{parameter\_11}, \mathrm{parameter\_2}, \mathrm{parameter\_5}, \mathrm{parameter\_6}, \mathrm{k2a}) \quad (16)$$

$$\mathrm{function\_2}(\mathrm{MKKK\_P}, \mathrm{MKKK}, \mathrm{P1}, \mathrm{MKK\_PP}, \mathrm{MKK\_P}, \mathrm{MKK}, \mathrm{Kse1}, \mathrm{K2a}, \mathrm{K5a}, \mathrm{K6a}, \mathrm{k2a}) = \frac{\frac{\mathrm{k2a} \cdot \mathrm{MKKK\_P} \cdot \mathrm{P1}}{\mathrm{K2a}}}{1 + \frac{\mathrm{MKKK\_P}}{\mathrm{K2a}} + \frac{\mathrm{MKKK}}{\mathrm{Kse1}} + \frac{\mathrm{MKK\_PP}}{\mathrm{K5a}} + \frac{\mathrm{MKK\_P}}{\mathrm{K6a}} + \frac{\mathrm{MKK}}{\mathrm{Kse1}}} \quad (17)$$

$$\mathrm{function\_2}(\mathrm{MKKK\_P}, \mathrm{MKKK}, \mathrm{P1}, \mathrm{MKK\_PP}, \mathrm{MKK\_P}, \mathrm{MKK}, \mathrm{Kse1}, \mathrm{K2a}, \mathrm{K5a}, \mathrm{K6a}, \mathrm{k2a}) = \frac{\frac{\mathrm{k2a} \cdot \mathrm{MKKK\_P} \cdot \mathrm{P1}}{\mathrm{K2a}}}{1 + \frac{\mathrm{MKKK\_P}}{\mathrm{K2a}} + \frac{\mathrm{MKKK}}{\mathrm{Kse1}} + \frac{\mathrm{MKK\_PP}}{\mathrm{K5a}} + \frac{\mathrm{MKK\_P}}{\mathrm{K6a}} + \frac{\mathrm{MKK}}{\mathrm{Kse1}}} \quad (18)$$

Table 13: Properties of each parameter.

| Id | Name | SBO | Value | Unit | Constant |
|---|---|---|---|---|---|
| k2a | k2a | | 0.086 | | ☑ |

## 7.3 Reaction reaction_3

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

**Name** 3

## Reaction equation

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

## Reactant

Table 14: Properties of each reactant.

| Id | Name | SBO |
|---|---|---|
| species_3 | MKK | |

## Modifiers

Table 15: Properties of each modifier.

| Id | Name | SBO |
|---|---|---|
| species_2 | MKKK_P | |
| species_4 | MKK_P | |
| species_2 | MKKK_P | |
| species_3 | MKK | |
| species_4 | MKK_P | |

## Product

Table 16: Properties of each product.

| Id | Name | SBO |
|---|---|---|
| species_4 | MKK_P | |

## Kinetic Law

**Derived unit** contains undeclared units

$$v_3 = \text{vol}(\text{compartment\_1}) \cdot \text{function\_3}(\text{k3}, [\text{species\_2}], [\text{species\_3}], \text{parameter\_3}, [\text{species\_4}], \text{parameter\_4}) \tag{20}$$

$$\text{function\_3}(\text{k3}, \text{MKKK\_P}, \text{MKK}, \text{K3}, \text{MKK\_P}, \text{K4}) = \frac{\frac{\text{k3}\cdot\text{MKKK\_P}\cdot\text{MKK}}{\text{K3}}}{1 + \frac{\text{MKK}}{\text{K3}} + \frac{\text{MKK\_P}}{\text{K4}}} \tag{21}$$

$$\text{function\_3}(\text{k3}, \text{MKKK\_P}, \text{MKK}, \text{K3}, \text{MKK\_P}, \text{K4}) = \frac{\frac{\text{k3}\cdot\text{MKKK\_P}\cdot\text{MKK}}{\text{K3}}}{1 + \frac{\text{MKK}}{\text{K3}} + \frac{\text{MKK\_P}}{\text{K4}}} \tag{22}$$

Table 17: Properties of each parameter.

| Id | Name | SBO | Value | Unit | Constant |
|---|---|---|---|---|---|
| k3 | k3 | | 0.01 | | ☑ |

## 7.4 Reaction reaction_4

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

**Name** 4

### Reaction equation

$$\text{species\_4} \xrightarrow{\text{species\_2, species\_3, species\_2, species\_4, species\_3}} \text{species\_5} \quad (23)$$

### Reactant

Table 18: Properties of each reactant.

| Id | Name | SBO |
|---|---|---|
| species_4 | MKK_P | |

### Modifiers

Table 19: Properties of each modifier.

| Id | Name | SBO |
|---|---|---|
| species_2 | MKKK_P | |
| species_3 | MKK | |
| species_2 | MKKK_P | |
| species_4 | MKK_P | |
| species_3 | MKK | |

### Product

Table 20: Properties of each product.

| Id | Name | SBO |
|---|---|---|
| species_5 | MKK_PP | |

### Kinetic Law

**Derived unit** contains undeclared units

$$v_4 = \mathrm{vol}(\mathrm{compartment\_1}) \cdot \mathrm{function\_4}(\mathrm{k4}, [\mathrm{species\_2}], [\mathrm{species\_4}], \mathrm{parameter\_4}, [\mathrm{species\_3}], \mathrm{parameter\_3}) \quad (24)$$

$$\mathrm{function\_4}(\mathrm{k4}, \mathrm{MKKK\_P}, \mathrm{MKK\_P}, \mathrm{K4}, \mathrm{MKK}, \mathrm{K3}) = \frac{\frac{\mathrm{k4} \cdot \mathrm{MKKK\_P} \cdot \mathrm{MKK\_P}}{\mathrm{K4}}}{1 + \frac{\mathrm{MKK}}{\mathrm{K3}} + \frac{\mathrm{MKK\_P}}{\mathrm{K4}}} \quad (25)$$

$$\mathrm{function\_4}(\mathrm{k4}, \mathrm{MKKK\_P}, \mathrm{MKK\_P}, \mathrm{K4}, \mathrm{MKK}, \mathrm{K3}) = \frac{\frac{\mathrm{k4} \cdot \mathrm{MKKK\_P} \cdot \mathrm{MKK\_P}}{\mathrm{K4}}}{1 + \frac{\mathrm{MKK}}{\mathrm{K3}} + \frac{\mathrm{MKK\_P}}{\mathrm{K4}}} \quad (26)$$

Table 21: Properties of each parameter.

| Id | Name | SBO | Value | Unit | Constant |
|---|---|---|---|---|---|
| k4 | k4 | | 15.0 | | ☑ |

## 7.5 Reaction reaction_5

This is an irreversible reaction of one reactant forming one product influenced by 19 modifiers.

**Name** 5

### Reaction equation

$$\mathrm{species\_5} \xrightarrow{\mathrm{species\_4,\ species\_7,\ species\_8,\ species\_9,\ species\_3,\ species\_6,\ species\_1,\ species\_2,\ species\_10,\ species\_5}} \quad (27)$$

### Reactant

Table 22: Properties of each reactant.

| Id | Name | SBO |
|---|---|---|
| species_5 | MKK_PP | |

### Modifiers

Table 23: Properties of each modifier.

| Id | Name | SBO |
|---|---|---|
| species_4 | MKK_P | |
| species_7 | MK_P | |
| species_8 | MK_PP | |
| species_9 | P1 | |
| species_3 | MKK | |
| species_6 | MK | |
| species_1 | MKKK | |
| species_2 | MKKK_P | |
| species_10 | P2 | |
| species_5 | MKK_PP | |
| species_4 | MKK_P | |
| species_7 | MK_P | |
| species_8 | MK_PP | |
| species_9 | P1 | |
| species_3 | MKK | |
| species_6 | MK | |
| species_1 | MKKK | |
| species_2 | MKKK_P | |
| species_10 | P2 | |

### Product

Table 24: Properties of each product.

| Id | Name | SBO |
|---|---|---|
| species_4 | MKK_P | |

### Kinetic Law

**Derived unit** contains undeclared units

$$
\begin{aligned}
v_5 = \mathrm{vol}\left(\mathrm{compartment\_1}\right) \cdot \mathrm{function\_5}\left([\mathrm{species\_5}], [\mathrm{species\_4}], [\mathrm{species\_7}], [\mathrm{species\_8}],\right. \\
[\mathrm{species\_9}], [\mathrm{species\_3}], [\mathrm{species\_6}], \mathrm{k5a}, \mathrm{parameter\_5}, [\mathrm{species\_1}], [\mathrm{species\_2}], \mathrm{k5b}, \\
[\mathrm{species\_10}], \mathrm{parameter\_13}, \mathrm{parameter\_6}, \mathrm{parameter\_11}, \mathrm{parameter\_2}, \mathrm{parameter\_14}, \\
\left.\mathrm{parameter\_12}, \mathrm{parameter\_10}, \mathrm{parameter\_9}\right)
\end{aligned}
\tag{28}
$$

$$\begin{aligned}&\mathrm{function\_5}\left(\mathrm{MKK\_PP}, \mathrm{MKK\_P}, \mathrm{MK\_P}, \mathrm{MK\_PP}, \mathrm{P1}, \mathrm{MKK}, \mathrm{MK}, \mathrm{k5a}, \right.\\ &\quad \mathrm{K5a}, \mathrm{MKKK}, \mathrm{MKKK\_P}, \mathrm{k5b}, \mathrm{P2}, \mathrm{K5b}, \mathrm{K6a}, \mathrm{Kse1}, \mathrm{K2a}, \mathrm{K6b}, \mathrm{Kse2},\\ &\quad \left.\mathrm{K10b}, \mathrm{K9b}\right) = \frac{\frac{\mathrm{k5a} \cdot \mathrm{P1} \cdot \mathrm{MKK\_PP}}{\mathrm{K5a}}}{1 + \frac{\mathrm{MKKK\_P}}{\mathrm{K2a}} + \frac{\mathrm{MKKK}}{\mathrm{Kse1}} + \frac{\mathrm{MKK\_PP}}{\mathrm{K5a}} + \frac{\mathrm{MKK\_P}}{\mathrm{K6a}} + \frac{\mathrm{MKK}}{\mathrm{Kse1}}}\\ &\quad + \frac{\frac{\mathrm{k5b} \cdot \mathrm{P2} \cdot \mathrm{MKK\_PP}}{\mathrm{K5b}}}{1 + \frac{\mathrm{MKK\_PP}}{\mathrm{K5b}} + \frac{\mathrm{MKK\_P}}{\mathrm{K6b}} + \frac{\mathrm{MKK}}{\mathrm{Kse2}} + \frac{\mathrm{MK}}{\mathrm{Kse2}} + \frac{\mathrm{MK\_P}}{\mathrm{K10b}} + \frac{\mathrm{MK\_PP}}{\mathrm{K9b}}}\end{aligned} \tag{29}$$

$$\begin{aligned}&\mathrm{function\_5}\left(\mathrm{MKK\_PP}, \mathrm{MKK\_P}, \mathrm{MK\_P}, \mathrm{MK\_PP}, \mathrm{P1}, \mathrm{MKK}, \mathrm{MK}, \mathrm{k5a}, \right.\\ &\quad \mathrm{K5a}, \mathrm{MKKK}, \mathrm{MKKK\_P}, \mathrm{k5b}, \mathrm{P2}, \mathrm{K5b}, \mathrm{K6a}, \mathrm{Kse1}, \mathrm{K2a}, \mathrm{K6b}, \mathrm{Kse2},\\ &\quad \left.\mathrm{K10b}, \mathrm{K9b}\right) = \frac{\frac{\mathrm{k5a} \cdot \mathrm{P1} \cdot \mathrm{MKK\_PP}}{\mathrm{K5a}}}{1 + \frac{\mathrm{MKKK\_P}}{\mathrm{K2a}} + \frac{\mathrm{MKKK}}{\mathrm{Kse1}} + \frac{\mathrm{MKK\_PP}}{\mathrm{K5a}} + \frac{\mathrm{MKK\_P}}{\mathrm{K6a}} + \frac{\mathrm{MKK}}{\mathrm{Kse1}}}\\ &\quad + \frac{\frac{\mathrm{k5b} \cdot \mathrm{P2} \cdot \mathrm{MKK\_PP}}{\mathrm{K5b}}}{1 + \frac{\mathrm{MKK\_PP}}{\mathrm{K5b}} + \frac{\mathrm{MKK\_P}}{\mathrm{K6b}} + \frac{\mathrm{MKK}}{\mathrm{Kse2}} + \frac{\mathrm{MK}}{\mathrm{Kse2}} + \frac{\mathrm{MK\_P}}{\mathrm{K10b}} + \frac{\mathrm{MK\_PP}}{\mathrm{K9b}}}\end{aligned} \tag{30}$$

Table 25: Properties of each parameter.

| Id | Name | SBO | Value | Unit | Constant |
|---|---|---|---|---|---|
| k5a | k5a | | 0.092 | | ☑ |
| k5b | k5b | | 0.092 | | ☑ |

## 7.6 Reaction reaction_6

This is an irreversible reaction of one reactant forming one product influenced by 19 modifiers.

**Name** 6

### Reaction equation

$$\mathrm{species\_4} \xrightarrow{\mathrm{species\_9},\ \mathrm{species\_5},\ \mathrm{species\_7},\ \mathrm{species\_8},\ \mathrm{species\_3},\ \mathrm{species\_6},\ \mathrm{species\_1},\ \mathrm{species\_2},\ \mathrm{species\_10},\ \mathrm{species\_9}} \tag{31}$$

### Reactant

Table 26: Properties of each reactant.

| Id | Name | SBO |
|---|---|---|
| species_4 | MKK_P | |

### Modifiers

Table 27: Properties of each modifier.

| Id | Name | SBO |
|---|---|---|
| species_9 | P1 | |
| species_5 | MKK_PP | |
| species_7 | MK_P | |
| species_8 | MK_PP | |
| species_3 | MKK | |
| species_6 | MK | |
| species_1 | MKKK | |
| species_2 | MKKK_P | |
| species_10 | P2 | |
| species_9 | P1 | |
| species_4 | MKK_P | |
| species_5 | MKK_PP | |
| species_7 | MK_P | |
| species_8 | MK_PP | |
| species_3 | MKK | |
| species_6 | MK | |
| species_1 | MKKK | |
| species_2 | MKKK_P | |
| species_10 | P2 | |

### Product

Table 28: Properties of each product.

| Id | Name | SBO |
|---|---|---|
| species_3 | MKK | |

### Kinetic Law

**Derived unit** contains undeclared units

$$v_6 = \mathrm{vol}\left(\mathrm{compartment\_1}\right) \cdot \mathrm{function\_6}\left([\mathrm{species\_9}], [\mathrm{species\_4}], [\mathrm{species\_5}], [\mathrm{species\_7}], [\mathrm{species\_8}], [\mathrm{species\_3}], [\mathrm{species\_6}], \mathrm{k6a}, \mathrm{parameter\_6}, [\mathrm{species\_1}], [\mathrm{species\_2}], [\mathrm{species\_10}], \mathrm{parameter\_14}, \mathrm{parameter\_2}, \mathrm{parameter\_11}, \mathrm{parameter\_5}, \mathrm{k6b}, \mathrm{parameter\_13}, \mathrm{parameter\_12}, \mathrm{parameter\_10}, \mathrm{parameter\_9}\right) \quad (32)$$

$$\mathrm{function\_6}\left(\mathrm{P1}, \mathrm{MKK\_P}, \mathrm{MKK\_PP}, \mathrm{MK\_P}, \mathrm{MK\_PP}, \mathrm{MKK}, \mathrm{MK}, \mathrm{k6a}, \mathrm{K6a}, \mathrm{MKKK}, \mathrm{MKKK\_P}, \mathrm{P2}, \mathrm{K6b}, \mathrm{K2a}, \mathrm{Kse1}, \mathrm{K5a}, \mathrm{k6b}, \mathrm{K5b}, \mathrm{Kse2}, \mathrm{K10b}, \mathrm{K9b}\right) = \frac{\frac{\mathrm{k6a} \cdot \mathrm{P1} \cdot \mathrm{MKK\_P}}{\mathrm{K6a}}}{1 + \frac{\mathrm{MKKK\_P}}{\mathrm{K2a}} + \frac{\mathrm{MKKK}}{\mathrm{Kse1}} + \frac{\mathrm{MKK\_PP}}{\mathrm{K5a}} + \frac{\mathrm{MKK\_P}}{\mathrm{K6a}} + \frac{\mathrm{MKK}}{\mathrm{Kse1}}} + \frac{\frac{\mathrm{k6b} \cdot \mathrm{P2} \cdot \mathrm{MKK\_P}}{\mathrm{K6b}}}{1 + \frac{\mathrm{MKK\_PP}}{\mathrm{K5b}} + \frac{\mathrm{MKK\_P}}{\mathrm{K6b}} + \frac{\mathrm{MKK}}{\mathrm{Kse2}} + \frac{\mathrm{MK}}{\mathrm{Kse2}} + \frac{\mathrm{MK\_P}}{\mathrm{K10b}} + \frac{\mathrm{MK\_PP}}{\mathrm{K9b}}} \tag{33}$$

$$\mathrm{function\_6}\left(\mathrm{P1}, \mathrm{MKK\_P}, \mathrm{MKK\_PP}, \mathrm{MK\_P}, \mathrm{MK\_PP}, \mathrm{MKK}, \mathrm{MK}, \mathrm{k6a}, \mathrm{K6a}, \mathrm{MKKK}, \mathrm{MKKK\_P}, \mathrm{P2}, \mathrm{K6b}, \mathrm{K2a}, \mathrm{Kse1}, \mathrm{K5a}, \mathrm{k6b}, \mathrm{K5b}, \mathrm{Kse2}, \mathrm{K10b}, \mathrm{K9b}\right) = \frac{\frac{\mathrm{k6a} \cdot \mathrm{P1} \cdot \mathrm{MKK\_P}}{\mathrm{K6a}}}{1 + \frac{\mathrm{MKKK\_P}}{\mathrm{K2a}} + \frac{\mathrm{MKKK}}{\mathrm{Kse1}} + \frac{\mathrm{MKK\_PP}}{\mathrm{K5a}} + \frac{\mathrm{MKK\_P}}{\mathrm{K6a}} + \frac{\mathrm{MKK}}{\mathrm{Kse1}}} + \frac{\frac{\mathrm{k6b} \cdot \mathrm{P2} \cdot \mathrm{MKK\_P}}{\mathrm{K6b}}}{1 + \frac{\mathrm{MKK\_PP}}{\mathrm{K5b}} + \frac{\mathrm{MKK\_P}}{\mathrm{K6b}} + \frac{\mathrm{MKK}}{\mathrm{Kse2}} + \frac{\mathrm{MK}}{\mathrm{Kse2}} + \frac{\mathrm{MK\_P}}{\mathrm{K10b}} + \frac{\mathrm{MK\_PP}}{\mathrm{K9b}}} \tag{34}$$

Table 29: Properties of each parameter.

| Id | Name | SBO | Value | Unit | Constant |
|---|---|---|---|---|---|
| k6a | k6a | | 0.086 | | ☑ |
| k6b | k6b | | 0.086 | | ☑ |

## 7.7 Reaction reaction_7

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

**Name** 7

### Reaction equation

$$\mathrm{species\_6} \xrightarrow{\mathrm{species\_5},\ \mathrm{species\_7},\ \mathrm{species\_5},\ \mathrm{species\_6},\ \mathrm{species\_7}} \mathrm{species\_7} \tag{35}$$

### Reactant

Table 30: Properties of each reactant.

| Id | Name | SBO |
|---|---|---|
| species_6 | MK | |

### Modifiers

Table 31: Properties of each modifier.

| Id | Name | SBO |
| --- | --- | --- |
| species_5 | MKK_PP | |
| species_7 | MK_P | |
| species_5 | MKK_PP | |
| species_6 | MK | |
| species_7 | MK_P | |

### Product

Table 32: Properties of each product.

| Id | Name | SBO |
| --- | --- | --- |
| species_7 | MK_P | |

### Kinetic Law

**Derived unit** contains undeclared units

$$v_7 = \mathrm{vol}\left(\mathrm{compartment\_1}\right) \cdot \mathrm{function\_7}\left(\mathrm{k7}, [\mathrm{species\_5}], [\mathrm{species\_6}], \mathrm{parameter\_7}, [\mathrm{species\_7}], \mathrm{parameter\_8}\right) \quad (36)$$

$$\mathrm{function\_7}\left(\mathrm{k7}, \mathrm{MKK\_PP}, \mathrm{MK}, \mathrm{K7}, \mathrm{MK\_P}, \mathrm{K8}\right) = \frac{\frac{\mathrm{k7} \cdot \mathrm{MKK\_PP} \cdot \mathrm{MK}}{\mathrm{K7}}}{1 + \frac{\mathrm{MK}}{\mathrm{K7}} + \frac{\mathrm{MK\_P}}{\mathrm{K8}}} \quad (37)$$

$$\mathrm{function\_7}\left(\mathrm{k7}, \mathrm{MKK\_PP}, \mathrm{MK}, \mathrm{K7}, \mathrm{MK\_P}, \mathrm{K8}\right) = \frac{\frac{\mathrm{k7} \cdot \mathrm{MKK\_PP} \cdot \mathrm{MK}}{\mathrm{K7}}}{1 + \frac{\mathrm{MK}}{\mathrm{K7}} + \frac{\mathrm{MK\_P}}{\mathrm{K8}}} \quad (38)$$

Table 33: Properties of each parameter.

| Id | Name | SBO | Value | Unit | Constant |
| --- | --- | --- | --- | --- | --- |
| k7 | k7 | | 0.01 | | ☑ |

## 7.8 Reaction reaction_8

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

**Name** 8

### Reaction equation

$$\text{species\_7} \xrightarrow{\text{species\_5, species\_6, species\_5, species\_7, species\_6}} \text{species\_8} \tag{39}$$

### Reactant

Table 34: Properties of each reactant.

| Id | Name | SBO |
|---|---|---|
| species_7 | MK_P | |

### Modifiers

Table 35: Properties of each modifier.

| Id | Name | SBO |
|---|---|---|
| species_5 | MKK_PP | |
| species_6 | MK | |
| species_5 | MKK_PP | |
| species_7 | MK_P | |
| species_6 | MK | |

### Product

Table 36: Properties of each product.

| Id | Name | SBO |
|---|---|---|
| species_8 | MK_PP | |

### Kinetic Law

**Derived unit** contains undeclared units

$$\begin{aligned} v_8 = & \operatorname{vol}(\text{compartment\_1}) \\ & \cdot \text{function\_8}(\text{k7}, [\text{species\_5}], [\text{species\_7}], \text{parameter\_8}, [\text{species\_6}], \text{parameter\_7}) \end{aligned} \tag{40}$$

$$\mathrm{function\_8}\left(\mathrm{k7}, \mathrm{MKK\_PP}, \mathrm{MK\_P}, \mathrm{K8}, \mathrm{MK}, \mathrm{K7}\right) = \frac{\frac{\mathrm{k7} \cdot \mathrm{MKK\_PP} \cdot \mathrm{MK\_P}}{\mathrm{K8}}}{1 + \frac{\mathrm{MK}}{\mathrm{K7}} + \frac{\mathrm{MK\_P}}{\mathrm{K8}}} \tag{41}$$

$$\mathrm{function\_8}\left(\mathrm{k7}, \mathrm{MKK\_PP}, \mathrm{MK\_P}, \mathrm{K8}, \mathrm{MK}, \mathrm{K7}\right) = \frac{\frac{\mathrm{k7} \cdot \mathrm{MKK\_PP} \cdot \mathrm{MK\_P}}{\mathrm{K8}}}{1 + \frac{\mathrm{MK}}{\mathrm{K7}} + \frac{\mathrm{MK\_P}}{\mathrm{K8}}} \tag{42}$$

Table 37: Properties of each parameter.

| Id | Name | SBO | Value | Unit | Constant |
|---|---|---|---|---|---|
| k7 | k7 | | 15.0 | | ☑ |

## 7.9 Reaction reaction_9

This is an irreversible reaction of one reactant forming one product influenced by 13 modifiers.

**Name** 9

### Reaction equation

$$\mathrm{species\_8} \xrightarrow{\mathrm{species\_9},\ \mathrm{species\_4},\ \mathrm{species\_7},\ \mathrm{species\_3},\ \mathrm{species\_6},\ \mathrm{species\_10},\ \mathrm{species\_8},\ \mathrm{species\_9},\ \mathrm{species\_4},\ \mathrm{species\_7}} \tag{43}$$

### Reactant

Table 38: Properties of each reactant.

| Id | Name | SBO |
|---|---|---|
| species_8 | MK_PP | |

### Modifiers

Table 39: Properties of each modifier.

| Id | Name | SBO |
|---|---|---|
| species_9 | P1 | |
| species_4 | MKK_P | |
| species_7 | MK_P | |
| species_3 | MKK | |
| species_6 | MK | |
| species_10 | P2 | |

| Id | Name | SBO |
|---|---|---|
| species_8 | MK_PP | |
| species_9 | P1 | |
| species_4 | MKK_P | |
| species_7 | MK_P | |
| species_3 | MKK | |
| species_6 | MK | |
| species_10 | P2 | |

## Product

Table 40: Properties of each product.

| Id | Name | SBO |
|---|---|---|
| species_7 | MK_P | |

## Kinetic Law

**Derived unit** contains undeclared units

$$v_9 = \mathrm{vol}\left(\mathrm{compartment\_1}\right) \cdot \mathrm{function\_9}\left([\mathrm{species\_8}], [\mathrm{species\_9}], [\mathrm{species\_4}], [\mathrm{species\_7}], [\mathrm{species\_3}], [\mathrm{species\_6}], [\mathrm{species\_10}], \mathrm{parameter\_9}, \mathrm{parameter\_13}, \mathrm{parameter\_14}, \mathrm{parameter\_12}, \mathrm{parameter\_10}, \mathrm{k9b}\right) \quad (44)$$

$$\mathrm{function\_9}\left(\mathrm{MK\_PP}, \mathrm{MKK\_PP}, \mathrm{MKK\_P}, \mathrm{MK\_P}, \mathrm{MKK}, \mathrm{MK}, \mathrm{P2}, \mathrm{K9b}, \mathrm{K5b}, \mathrm{K6b}, \mathrm{Kse2}, \mathrm{K10b}, \mathrm{k9b}\right) = \frac{\frac{\mathrm{k9b} \cdot \mathrm{P2} \cdot \mathrm{MK\_PP}}{\mathrm{K9b}}}{1 + \frac{\mathrm{MKK\_PP}}{\mathrm{K5b}} + \frac{\mathrm{MKK\_P}}{\mathrm{K6b}} + \frac{\mathrm{MKK}}{\mathrm{Kse2}} + \frac{\mathrm{MK}}{\mathrm{Kse2}} + \frac{\mathrm{MK\_P}}{\mathrm{K10b}} + \frac{\mathrm{MK\_PP}}{\mathrm{K9b}}} \quad (45)$$

$$\mathrm{function\_9}\left(\mathrm{MK\_PP}, \mathrm{MKK\_PP}, \mathrm{MKK\_P}, \mathrm{MK\_P}, \mathrm{MKK}, \mathrm{MK}, \mathrm{P2}, \mathrm{K9b}, \mathrm{K5b}, \mathrm{K6b}, \mathrm{Kse2}, \mathrm{K10b}, \mathrm{k9b}\right) = \frac{\frac{\mathrm{k9b} \cdot \mathrm{P2} \cdot \mathrm{MK\_PP}}{\mathrm{K9b}}}{1 + \frac{\mathrm{MKK\_PP}}{\mathrm{K5b}} + \frac{\mathrm{MKK\_P}}{\mathrm{K6b}} + \frac{\mathrm{MKK}}{\mathrm{Kse2}} + \frac{\mathrm{MK}}{\mathrm{Kse2}} + \frac{\mathrm{MK\_P}}{\mathrm{K10b}} + \frac{\mathrm{MK\_PP}}{\mathrm{K9b}}} \quad (46)$$

Table 41: Properties of each parameter.

| Id | Name | SBO | Value | Unit | Constant |
|---|---|---|---|---|---|
| k9b | k9b | | 0.092 | | ☑ |

## 7.10 Reaction reaction_10

This is an irreversible reaction of one reactant forming one product influenced by 13 modifiers.

**Name** 10

### Reaction equation

$$\text{species\_7} \xrightarrow{\text{species\_5, species\_4, species\_8, species\_3, species\_6, species\_10, species\_7, species\_5, species\_4, species\_8}} \tag{47}$$

### Reactant

Table 42: Properties of each reactant.

| Id | Name | SBO |
|---|---|---|
| species_7 | MK_P | |

### Modifiers

Table 43: Properties of each modifier.

| Id | Name | SBO |
|---|---|---|
| species_5 | MKK_PP | |
| species_4 | MKK_P | |
| species_8 | MK_PP | |
| species_3 | MKK | |
| species_6 | MK | |
| species_10 | P2 | |
| species_7 | MK_P | |
| species_5 | MKK_PP | |
| species_4 | MKK_P | |
| species_8 | MK_PP | |
| species_3 | MKK | |
| species_6 | MK | |
| species_10 | P2 | |

### Product

Table 44: Properties of each product.

| Id | Name | SBO |
|---|---|---|
| species_6 | MK | |

### Kinetic Law

**Derived unit** contains undeclared units

$$v_{10} = \mathrm{vol}(\mathrm{compartment\_1}) \cdot \mathrm{function\_10}([\mathrm{species\_7}], [\mathrm{species\_5}], [\mathrm{species\_4}], [\mathrm{species\_8}], [\mathrm{species\_3}], [\mathrm{species\_6}], [\mathrm{species\_10}], \mathrm{parameter\_10}, \mathrm{parameter\_13}, \mathrm{parameter\_14}, \mathrm{parameter\_12}, \mathrm{parameter\_9}, \mathrm{k10b}) \quad (48)$$

$$\mathrm{function\_10}(\mathrm{MK\_P}, \mathrm{MKK\_PP}, \mathrm{MKK\_P}, \mathrm{MK\_PP}, \mathrm{MKK}, \mathrm{MK}, \mathrm{P2}, \mathrm{K10b}, \mathrm{K5b}, \mathrm{K6b}, \mathrm{Kse2}, \mathrm{K9b}, \mathrm{k10b}) = \frac{\frac{\mathrm{k10b} \cdot \mathrm{P2} \cdot \mathrm{MK\_P}}{\mathrm{K10b}}}{1 + \frac{\mathrm{MKK\_PP}}{\mathrm{K5b}} + \frac{\mathrm{MKK\_P}}{\mathrm{K6b}} + \frac{\mathrm{MKK}}{\mathrm{Kse2}} + \frac{\mathrm{MK}}{\mathrm{Kse2}} + \frac{\mathrm{MK\_P}}{\mathrm{K10b}} + \frac{\mathrm{MK\_PP}}{\mathrm{K9b}}} \quad (49)$$

$$\mathrm{function\_10}(\mathrm{MK\_P}, \mathrm{MKK\_PP}, \mathrm{MKK\_P}, \mathrm{MK\_PP}, \mathrm{MKK}, \mathrm{MK}, \mathrm{P2}, \mathrm{K10b}, \mathrm{K5b}, \mathrm{K6b}, \mathrm{Kse2}, \mathrm{K9b}, \mathrm{k10b}) = \frac{\frac{\mathrm{k10b} \cdot \mathrm{P2} \cdot \mathrm{MK\_P}}{\mathrm{K10b}}}{1 + \frac{\mathrm{MKK\_PP}}{\mathrm{K5b}} + \frac{\mathrm{MKK\_P}}{\mathrm{K6b}} + \frac{\mathrm{MKK}}{\mathrm{Kse2}} + \frac{\mathrm{MK}}{\mathrm{Kse2}} + \frac{\mathrm{MK\_P}}{\mathrm{K10b}} + \frac{\mathrm{MK\_PP}}{\mathrm{K9b}}} \quad (50)$$

Table 45: Properties of each parameter.

| Id | Name | SBO | Value | Unit | Constant |
|---|---|---|---|---|---|
| k10b | k10b | | 0.086 | | ☑ |

## 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 species_1

**Name** MKKK

**Initial concentration** $300\ \mathrm{nmol} \cdot \mathrm{ml}^{-1}$

This species takes part in nine reactions (as a reactant in reaction_1 and as a product in reaction_2 and as a modifier in reaction_1, reaction_2, reaction_2, reaction_5, reaction_5, reaction_6, reaction_6).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{species\_1} = v_2 - v_1 \tag{51}$$

## 8.2 Species species_2

**Name** MKKK_P

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

This species takes part in eleven reactions (as a reactant in reaction_2 and as a product in reaction_1 and as a modifier in reaction_2, reaction_3, reaction_3, reaction_4, reaction_4, reaction_5, reaction_5, reaction_6, reaction_6).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{species\_2} = v_1 - v_2 \tag{52}$$

## 8.3 Species species_3

**Name** MKK

**Initial concentration** $1199.99994221325\ \mathrm{nmol} \cdot \mathrm{ml}^{-1}$

This species takes part in 15 reactions (as a reactant in reaction_3 and as a product in reaction_6 and as a modifier in reaction_2, reaction_2, reaction_3, reaction_4, reaction_4, reaction_5, reaction_5, reaction_6, reaction_6, reaction_9, reaction_9, reaction_10, reaction_10).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{species\_3} = v_6 - v_3 \tag{53}$$

## 8.4 Species species_4

**Name** MKK_P

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

This species takes part in 16 reactions (as a reactant in reaction_4, reaction_6 and as a product in reaction_3, reaction_5 and as a modifier in reaction_2, reaction_2, reaction_3, reaction_3, reaction_4, reaction_5, reaction_5, reaction_6, reaction_9, reaction_9, reaction_10, reaction_10).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{species\_4} = v_3 + v_5 - v_4 - v_6 \tag{54}$$

## 8.5 Species species_5

**Name** MKK_PP

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

This species takes part in 13 reactions (as a reactant in reaction_5 and as a product in reaction_4 and as a modifier in reaction_2, reaction_2, reaction_5, reaction_6, reaction_6, reaction_7, reaction_7, reaction_8, reaction_8, reaction_10, reaction_10).

$$\frac{\mathrm{d}}{\mathrm{d}t}\text{species\_5} = v_4 - v_5 \tag{55}$$

## 8.6 Species species_6

**Name** MK

**Initial concentration** $1199.99994221325 \text{ nmol} \cdot \text{ml}^{-1}$

This species takes part in 13 reactions (as a reactant in reaction_7 and as a product in reaction_10 and as a modifier in reaction_5, reaction_5, reaction_6, reaction_6, reaction_7, reaction_8, reaction_8, reaction_9, reaction_9, reaction_10, reaction_10).

$$\frac{\mathrm{d}}{\mathrm{d}t}\text{species\_6} = v_{10} - v_7 \tag{56}$$

## 8.7 Species species_7

**Name** MK_P

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

This species takes part in 14 reactions (as a reactant in reaction_8, reaction_10 and as a product in reaction_7, reaction_9 and as a modifier in reaction_5, reaction_5, reaction_6, reaction_6, reaction_7, reaction_7, reaction_8, reaction_9, reaction_9, reaction_10).

$$\frac{\mathrm{d}}{\mathrm{d}t}\text{species\_7} = v_7 + v_9 - v_8 - v_{10} \tag{57}$$

## 8.8 Species species_8

**Name** MK_PP

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

This species takes part in nine reactions (as a reactant in reaction_9 and as a product in reaction_8 and as a modifier in reaction_5, reaction_5, reaction_6, reaction_6, reaction_9, reaction_10, reaction_10).

$$\frac{\mathrm{d}}{\mathrm{d}t}\text{species\_8} = v_8 - v_9 \tag{58}$$

### 8.9 Species species_9

**Name** P1

**Initial concentration** $100 \text{ nmol} \cdot \text{ml}^{-1}$

This species takes part in eight reactions (as a modifier in reaction_2, reaction_2, reaction_5, reaction_5, reaction_6, reaction_6, reaction_9, reaction_9).

$$\frac{\mathrm{d}}{\mathrm{d}t}\text{species\_9} = 0 \tag{59}$$

### 8.10 Species species_10

**Name** P2

**Initial concentration** $200 \text{ nmol} \cdot \text{ml}^{-1}$

This species takes part in eight reactions (as a modifier in reaction_5, reaction_5, reaction_6, reaction_6, reaction_9, reaction_9, reaction_10, reaction_10).

$$\frac{\mathrm{d}}{\mathrm{d}t}\text{species\_10} = 0 \tag{60}$$

### 8.11 Species species_11

**Name** Sig

**Initial concentration** $20 \text{ nmol} \cdot \text{ml}^{-1}$

This species takes part in two reactions (as a modifier in reaction_1, reaction_1).

$$\frac{\mathrm{d}}{\mathrm{d}t}\text{species\_11} = 0 \tag{61}$$

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.

[a]Center for Bioinformatics Tübingen (ZBIT), Germany
[b]California Institute of Technology, Beckman Institute BNMC, Pasadena, United States
[c]European Bioinformatics Institute, Wellcome Trust Genome Campus, Hinxton, United Kingdom
[d]EML Research gGmbH, Heidelberg, Germany