SBML Model Report

Model name: “Huang1996 - Ultrasensitivity in MAPK cascade”

May 6, 2016

1 General Overview

This is a document in SBML Level 2 Version 4 format. This model was created by Rainer Machne[1] at February tenth 2005 at 11:39 p. m. and last time modified at June second 2015 at noon. 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	26
events	0	constraints	0
reactions	20	function definitions	0
global parameters	1	unit definitions	1
rules	4	initial assignments	0

Model Notes

Huang1996 - Ultrasensitivity in MAPK cascade

The temporal sequence of kinase activation, from MAPKKK (activated RAF) to the final effector MAPK (activated ERK), is described here. It is observed from the model that there is an increase in sensitivity along the levels of the cascade, where the activity of MAPK reaches its maximal before MAPKKK.

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This model is described in the article:Ultrasensitivity in the mitogen-activated protein kinase cascade.Huang CY, Ferrell JE JrProc. Natl. Acad. Sci. U.S.A. 1996:93(19):10078-83

Abstract:

The mitogen-activated protein kinase (MAPK) cascade is a highly conserved series of three protein kinases implicated in diverse biological processes. Here we demonstrate that the cascade arrangement has unexpected consequences for the dynamics of MAPK signaling. We solved the rate equations for the cascade numerically and found that MAPK is predicted to behave like a highly cooperative enzyme, even though it was not assumed that any of the enzymes in the cascade were regulated cooperatively. Measurements of MAPK activation in Xenopus oocyte extracts confirmed this prediction. The stimulus/response curve of the MAPK was found to be as steep as that of a cooperative enzyme with a Hill coefficient of 4-5, well in excess of that of the classical allosteric protein hemoglobin. The shape of the MAPK stimulus/ response curve may make the cascade particularly appropriate for mediating processes like mitogenesis, cell fate induction, and oocyte maturation, where a cell switches from one discrete state to another.

The species K_PP_norm, KKK_P_norm and KK_PP_norm are the relative concentrations of the active MAPK, MAPKK and MAPKKK, that is the double, or single resp. phophorylated forms divided by the total concentrations of each kinase. For MAPK additionally the also active MAPK divided by the maximal concentration of active MAPK is given by rel_K_PP_max. The parameter K_PP_norm_max, the maximal ratio of active MapK, has to be calculated for each change of parameters.

This model is hosted on BioModels Database and identified by: BIOMD0000000009 .

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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 micromole

Definition μmol

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
`compartment`			3	$4 \cdot 10^{-12}$	l	☑	

3.1 Compartment `compartment`

This is a three dimensional compartment with a constant size of $4 \cdot 10^{-12}$ litre.

4 Species

This model contains 26 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
E1	MAPKKK activator (Ras)	compartment	$\mu mol \cdot l^{-1}$	⊟	⊟
E2	MAPKKK inactivator	compartment	$\mu mol \cdot l^{-1}$	⊟	⊟
KKK	Mos	compartment	$\mu mol \cdot l^{-1}$	⊟	⊟
P_KKK	Mos-P	compartment	$\mu mol \cdot l^{-1}$	⊟	⊟
KK	Mek1	compartment	$\mu mol \cdot l^{-1}$	⊟	⊟
P_KK	Mek1-P	compartment	$\mu mol \cdot l^{-1}$	⊟	⊟
PP_KK	Mek1-PP	compartment	$\mu mol \cdot l^{-1}$	⊟	⊟
K	Erk2	compartment	$\mu mol \cdot l^{-1}$	⊟	⊟
P_K	Erk2-P	compartment	$\mu mol \cdot l^{-1}$	⊟	⊟
PP_K	Erk2-PP	compartment	$\mu mol \cdot l^{-1}$	⊟	⊟
KPase	MAPK-Pase	compartment	$\mu mol \cdot l^{-1}$	⊟	⊟
KKPase	MAPKK-Pase	compartment	$\mu mol \cdot l^{-1}$	⊟	⊟
E1_KKK	E1_Mos	compartment	$\mu mol \cdot l^{-1}$	⊟	⊟
E2_P_KKK	E2_Mos-P	compartment	$\mu mol \cdot l^{-1}$	⊟	⊟
P_KKK_KK	P-Mos_Mek1	compartment	$\mu mol \cdot l^{-1}$	⊟	⊟
P_KKK_P_KK	P-Mos_P-Mek1	compartment	$\mu mol \cdot l^{-1}$	⊟	⊟
PP_KK_K	PP-Mek1_Erk2	compartment	$\mu mol \cdot l^{-1}$	⊟	⊟
PP_KK_P_K	PP-Mek1_P-Erk2	compartment	$\mu mol \cdot l^{-1}$	⊟	⊟
KKPase_PP_KK	MAPKK-Pase_PP-Mek1	compartment	$\mu mol \cdot l^{-1}$	⊟	⊟
KKPase_P_KK	MAPKK-Pase_P-Mek1	compartment	$\mu mol \cdot l^{-1}$	⊟	⊟
KPase_PP_K	MAPK-Pase_PP-Erk2	compartment	$\mu mol \cdot l^{-1}$	⊟	⊟
KPase_P_K	MAPK-Pase_P-Erk2	compartment	$\mu mol \cdot l^{-1}$	⊟	⊟

Produced by SBML2LaTeX

Id	Name	Compartment	Derived Unit	Constant	Boundary Condition
K_PP_norm	K_PP_norm	compartment	$\mu mol \cdot l^{-1}$	⊟	⊟
KK_PP_norm	KK_PP_norm	compartment	$\mu mol \cdot l^{-1}$	⊟	⊟
KKK_P_norm	KKK_P_norm	compartment	$\mu mol \cdot l^{-1}$	⊟	⊟
rel_K_PP_max	relative maximal K_PP	compartment	$\mu mol \cdot l^{-1}$	⊟	⊟

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5 Parameter

This model contains one global parameter.

Table 4: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
K_PP_norm_max			0.900		☑

6 Rules

This is an overview of four rules.

6.1 Rule K_PP_norm

Rule K_PP_norm is an assignment rule for species K_PP_norm:

$$\text{K\_PP\_norm} = \frac{[\text{PP\_K}] + [\text{KPase\_PP\_K}]}{[\text{PP\_K}] + [\text{P\_K}] + [\text{K}] + [\text{PP\_KK\_K}] + [\text{PP\_KK\_P\_K}] + [\text{KPase\_PP\_K}] + [\text{KPase\_P\_K}]} \tag{1}$$

Derived unit dimensionless

6.2 Rule rel_K_PP_max

Rule rel_K_PP_max is an assignment rule for species rel_K_PP_max:

$$\text{rel\_K\_PP\_max} = \frac{[\text{K\_PP\_norm}]}{\text{K\_PP\_norm\_max}} \tag{2}$$

6.3 Rule KK_PP_norm

Rule KK_PP_norm is an assignment rule for species KK_PP_norm:

$$\text{KK\_PP\_norm} = \frac{[\text{PP\_KK}] + [\text{PP\_KK\_K}] + [\text{PP\_KK\_P\_K}] + [\text{KKPase\_PP\_KK}]}{[\text{PP\_KK}] + [\text{P\_KK}] + [\text{KK}] + [\text{PP\_KK\_K}] + [\text{PP\_KK\_P\_K}] + [\text{P\_KKK\_KK}] + [\text{P\_KKK\_P\_KK}] + [\text{KKPase\_PP\_KK}]} \tag{3}$$

Derived unit dimensionless

6.4 Rule KKK_P_norm

Rule KKK_P_norm is an assignment rule for species KKK_P_norm:

$$\text{KKK\_P\_norm} = \frac{[\text{P\_KKK}] + [\text{P\_KKK\_KK}] + [\text{P\_KKK\_P\_KK}]}{[\text{KKK}] + [\text{P\_KKK}] + [\text{P\_KKK\_KK}] + [\text{P\_KKK\_P\_KK}]} \tag{4}$$

Derived unit dimensionless

7 Reactions

This model contains 20 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	r1a	binding of MAPKKK activator	$KKK + E1 \rightleftharpoons E1\_KKK$	
2	r1b	MAPKKK activation	$E1\_KKK \longrightarrow E1 + P\_KKK$	
3	r2a	binding of MAPKKK inactivator	$P\_KKK + E2 \rightleftharpoons E2\_P\_KKK$	
4	r2b	MAPKKK inactivation	$E2\_P\_KKK \longrightarrow E2 + KKK$	
5	r3a	binding P-MAPKKK and MAPKK	$KK + P\_KKK \rightleftharpoons P\_KKK\_KK$	
6	r3b	phosphorylation of MAPKK	$P\_KKK\_KK \longrightarrow P\_KK + P\_KKK$	
7	r4a	binding MAPKK-Pase and P-MAPKK	$P\_KK + KKPase \rightleftharpoons KKPase\_P\_KK$	
8	r4b	dephosphorylation of P-MAPKK	$KKPase\_P\_KK \longrightarrow KK + KKPase$	
9	r5a	binding P-MAPKKK and P-MAPKK	$P\_KK + P\_KKK \rightleftharpoons P\_KKK\_P\_KK$	
10	r5b	phosphorylation of P-MAPKK	$P\_KKK\_P\_KK \longrightarrow PP\_KK + P\_KKK$	
11	r6a	binding MAPKK-Pase and PP-MAPKK	$PP\_KK + KKPase \rightleftharpoons KKPase\_PP\_KK$	
12	r6b	dephosphorylation of PP-MAPKK	$KKPase\_PP\_KK \longrightarrow P\_KK + KKPase$	
13	r7a	binding MAPK and PP-MAPKK	$K + PP\_KK \rightleftharpoons PP\_KK\_K$	
14	r7b	phosphorylation of MAPK	$PP\_KK\_K \longrightarrow P\_K + PP\_KK$	
15	r8a	binding MAPK-Pase and P-MAPK	$P\_K + KPase \rightleftharpoons KPase\_P\_K$	
16	r8b	dephosphorylation of P-MAPK	$KPase\_P\_K \longrightarrow K + KPase$	
17	r9a	binding PP-MAPKK and P-MAPK	$P\_K + PP\_KK \rightleftharpoons PP\_KK\_P\_K$	
18	r9b	phosphorylation of P-MAPK	$PP\_KK\_P\_K \longrightarrow PP\_KK + PP\_K$	
19	r10a	binding MAPK-Pase and PP-MAPK	$PP\_K + KPase \rightleftharpoons KPase\_PP\_K$	
20	r10b	dephosphorylation of PP-MAPK	$KPase\_PP\_K \longrightarrow P\_K + KPase$	

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7.1 Reaction r1a

This is a reversible reaction of two reactants forming one product.

Name binding of MAPKKK activator

Reaction equation

$$\mathrm{KKK} + \mathrm{E1} \rightleftharpoons \mathrm{E1\_KKK} \tag{5}$$

Reactants

Table 6: Properties of each reactant.

Id	Name	SBO
KKK	Mos	
E1	MAPKKK activator (Ras)	

Product

Table 7: Properties of each product.

Id	Name	SBO
E1_KKK	E1_Mos	

Kinetic Law

Derived unit contains undeclared units

$$v_1 = \mathrm{vol}\,(\mathrm{compartment}) \cdot (\mathrm{a1} \cdot [\mathrm{E1}] \cdot [\mathrm{KKK}] - \mathrm{d1} \cdot [\mathrm{E1\_KKK}]) \tag{6}$$

Table 8: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
a1			1000.0		☑
d1			150.0		☑

7.2 Reaction r1b

This is an irreversible reaction of one reactant forming two products.

Name MAPKKK activation

Reaction equation

$$\mathrm{E1\_KKK} \longrightarrow \mathrm{E1} + \mathrm{P\_KKK} \tag{7}$$

Reactant

Table 9: Properties of each reactant.

Id	Name	SBO
E1_KKK	E1_Mos	

Products

Table 10: Properties of each product.

Id	Name	SBO
E1	MAPKKK activator (Ras)	
P_KKK	Mos-P	

Kinetic Law

Derived unit contains undeclared units

$$v_2 = \mathrm{vol}\,(\mathrm{compartment}) \cdot \mathrm{k2} \cdot [\mathrm{E1\_KKK}] \tag{8}$$

Table 11: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k2			150.0		☑

7.3 Reaction r2a

This is a reversible reaction of two reactants forming one product.

Name binding of MAPKKK inactivator

Reaction equation

$$\mathrm{P\_KKK} + \mathrm{E2} \rightleftharpoons \mathrm{E2\_P\_KKK} \tag{9}$$

Reactants

Table 12: Properties of each reactant.

Id	Name	SBO
P_KKK	Mos-P	
E2	MAPKKK inactivator	

Product

Table 13: Properties of each product.

Id	Name	SBO
E2_P_KKK	E2_Mos-P	

Kinetic Law

Derived unit contains undeclared units

$$v_3 = \mathrm{vol}\,(\mathrm{compartment}) \cdot (\mathrm{a2} \cdot [\mathrm{E2}] \cdot [\mathrm{P\_KKK}] - \mathrm{d2} \cdot [\mathrm{E2\_P\_KKK}]) \tag{10}$$

Table 14: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
a2			1000.0		☑
d2			150.0		☑

7.4 Reaction r2b

This is an irreversible reaction of one reactant forming two products.

Name MAPKKK inactivation

Reaction equation

$$\mathrm{E2\_P\_KKK} \longrightarrow \mathrm{E2} + \mathrm{KKK} \tag{11}$$

Reactant

Table 15: Properties of each reactant.

Id	Name	SBO
E2_P_KKK	E2_Mos-P	

Products

Table 16: Properties of each product.

Id	Name	SBO
E2	MAPKKK inactivator	
KKK	Mos	

Kinetic Law

Derived unit contains undeclared units

$$v_4 = \mathrm{vol}\,(\mathrm{compartment}) \cdot \mathrm{k2} \cdot [\mathrm{E2\_P\_KKK}] \tag{12}$$

Table 17: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k2			150.0		☑

7.5 Reaction r3a

This is a reversible reaction of two reactants forming one product.

Name binding P-MAPKKK and MAPKK

Reaction equation

$$\mathrm{KK} + \mathrm{P\_KKK} \rightleftharpoons \mathrm{P\_KKK\_KK} \tag{13}$$

Reactants

Table 18: Properties of each reactant.

Id	Name	SBO
KK	Mek1	
P_KKK	Mos-P	

Product

Table 19: Properties of each product.

Id	Name	SBO
P_KKK_KK	P-Mos_Mek1	

Kinetic Law

Derived unit contains undeclared units

$$v_5 = \mathrm{vol}\,(\mathrm{compartment}) \cdot (\mathrm{a3} \cdot [\mathrm{KK}] \cdot [\mathrm{P\_KKK}] - \mathrm{d3} \cdot [\mathrm{P\_KKK\_KK}]) \tag{14}$$

Table 20: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
a3			1000.0		☑
d3			150.0		☑

7.6 Reaction r3b

This is an irreversible reaction of one reactant forming two products.

Name phosphorylation of MAPKK

Reaction equation

$$\mathrm{P\_KKK\_KK} \longrightarrow \mathrm{P\_KK} + \mathrm{P\_KKK} \tag{15}$$

Reactant

Table 21: Properties of each reactant.

Id	Name	SBO
P_KKK_KK	P-Mos_Mek1	

Products

Table 22: Properties of each product.

Id	Name	SBO
P_KK	Mek1-P	
P_KKK	Mos-P	

Kinetic Law

Derived unit contains undeclared units

$$v_6 = \mathrm{vol}\,(\mathrm{compartment}) \cdot \mathrm{k3} \cdot [\mathrm{P\_KKK\_KK}] \tag{16}$$

Table 23: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k3			150.0		☑

7.7 Reaction r4a

This is a reversible reaction of two reactants forming one product.

Name binding MAPKK-Pase and P-MAPKK

Reaction equation

$$\mathrm{P\_KK} + \mathrm{KKPase} \rightleftharpoons \mathrm{KKPase\_P\_KK} \tag{17}$$

Reactants

Table 24: Properties of each reactant.

Id	Name	SBO
P_KK	Mek1-P	
KKPase	MAPKK-Pase	

Product

Table 25: Properties of each product.

Id	Name	SBO
KKPase_P_KK	MAPKK-Pase_P-Mek1	

Kinetic Law

Derived unit contains undeclared units

$$v_7 = \mathrm{vol}\,(\mathrm{compartment}) \cdot (\mathrm{a4} \cdot [\mathrm{P\_KK}] \cdot [\mathrm{KKPase}] - \mathrm{d4} \cdot [\mathrm{KKPase\_P\_KK}]) \tag{18}$$

Table 26: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
a4			1000.0		☑
d4			150.0		☑

7.8 Reaction r4b

This is an irreversible reaction of one reactant forming two products.

Name dephosphorylation of P-MAPKK

Reaction equation

$$\text{KKPase\_P\_KK} \longrightarrow \text{KK} + \text{KKPase} \tag{19}$$

Reactant

Table 27: Properties of each reactant.

Id	Name	SBO
KKPase_P_KK	MAPKK-Pase_P-Mek1	

Products

Table 28: Properties of each product.

Id	Name	SBO
KK	Mek1	
KKPase	MAPKK-Pase	

Kinetic Law

Derived unit contains undeclared units

$$v_8 = \text{vol}\,(\text{compartment}) \cdot \text{k4} \cdot [\text{KKPase\_P\_KK}] \tag{20}$$

Table 29: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k4			150.0		☑

7.9 Reaction r5a

This is a reversible reaction of two reactants forming one product.

Name binding P-MAPKKK and P-MAPKK

Reaction equation

$$\text{P\_KK} + \text{P\_KKK} \rightleftharpoons \text{P\_KKK\_P\_KK} \tag{21}$$

Reactants

Table 30: Properties of each reactant.

Id	Name	SBO
P_KK	Mek1-P	
P_KKK	Mos-P	

Product

Table 31: Properties of each product.

Id	Name	SBO
P_KKK_P_KK	P-Mos_P-Mek1	

Kinetic Law

Derived unit contains undeclared units

$$v_9 = \text{vol}\,(\text{compartment}) \cdot (\text{a5} \cdot [\text{P\_KK}] \cdot [\text{P\_KKK}] - \text{d5} \cdot [\text{P\_KKK\_P\_KK}]) \tag{22}$$

Table 32: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
a5			1000.0		☑
d5			150.0		☑

7.10 Reaction r5b

This is an irreversible reaction of one reactant forming two products.

Name phosphorylation of P-MAPKK

Reaction equation

$$\text{P\_KKK\_P\_KK} \longrightarrow \text{PP\_KK} + \text{P\_KKK} \tag{23}$$

Reactant

Table 33: Properties of each reactant.

Id	Name	SBO
P_KKK_P_KK	P-Mos_P-Mek1	

Products

Table 34: Properties of each product.

Id	Name	SBO
PP_KK	Mek1-PP	
P_KKK	Mos-P	

Kinetic Law

Derived unit contains undeclared units

$$v_{10} = \text{vol}\,(\text{compartment}) \cdot \text{k5} \cdot [\text{P\_KKK\_P\_KK}] \tag{24}$$

Table 35: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k5			150.0		☑

7.11 Reaction r6a

This is a reversible reaction of two reactants forming one product.

Name binding MAPKK-Pase and PP-MAPKK

Reaction equation

$$\text{PP\_KK} + \text{KKPase} \rightleftharpoons \text{KKPase\_PP\_KK} \tag{25}$$

Reactants

Table 36: Properties of each reactant.

Id	Name	SBO
PP_KK	Mek1-PP	
KKPase	MAPKK-Pase	

Product

Table 37: Properties of each product.

Id	Name	SBO
KKPase_PP_KK	MAPKK-Pase_PP-Mek1	

Kinetic Law

Derived unit contains undeclared units

$$v_{11} = \mathrm{vol}\,(\mathrm{compartment}) \cdot (\mathrm{a6} \cdot [\mathrm{PP\_KK}] \cdot [\mathrm{KKPase}] - \mathrm{d6} \cdot [\mathrm{KKPase\_PP\_KK}]) \qquad (26)$$

Table 38: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
a6			1000.0		☑
d6			150.0		☑

7.12 Reaction r6b

This is an irreversible reaction of one reactant forming two products.

Name dephosphorylation of PP-MAPKK

Reaction equation

$$\mathrm{KKPase\_PP\_KK} \longrightarrow \mathrm{P\_KK} + \mathrm{KKPase} \qquad (27)$$

Reactant

Table 39: Properties of each reactant.

Id	Name	SBO
KKPase_PP_KK	MAPKK-Pase_PP-Mek1	

Products

Table 40: Properties of each product.

Id	Name	SBO
P_KK	Mek1-P	
KKPase	MAPKK-Pase	

Kinetic Law

Derived unit contains undeclared units

$$v_{12} = \mathrm{vol}\,(\mathrm{compartment}) \cdot \mathrm{k6} \cdot [\mathrm{KKPase\_PP\_KK}] \tag{28}$$

Table 41: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k6			150.0		☑

7.13 Reaction r7a

This is a reversible reaction of two reactants forming one product.

Name binding MAPK and PP-MAPKK

Reaction equation

$$\mathrm{K} + \mathrm{PP\_KK} \rightleftharpoons \mathrm{PP\_KK\_K} \tag{29}$$

Reactants

Table 42: Properties of each reactant.

Id	Name	SBO
K	Erk2	
PP_KK	Mek1-PP	

Product

Table 43: Properties of each product.

Id	Name	SBO
PP_KK_K	PP-Mek1_Erk2	

Kinetic Law

Derived unit contains undeclared units

$$v_{13} = \mathrm{vol}\,(\mathrm{compartment}) \cdot (\mathrm{a7} \cdot [\mathrm{K}] \cdot [\mathrm{PP\_KK}] - \mathrm{d7} \cdot [\mathrm{PP\_KK\_K}]) \tag{30}$$

Table 44: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
a7			1000.0		☑
d7			150.0		☑

7.14 Reaction r7b

This is an irreversible reaction of one reactant forming two products.

Name phosphorylation of MAPK

Reaction equation

$$\mathrm{PP\_KK\_K} \longrightarrow \mathrm{P\_K} + \mathrm{PP\_KK} \tag{31}$$

Reactant

Table 45: Properties of each reactant.

Id	Name	SBO
PP_KK_K	PP-Mek1_Erk2	

Products

Table 46: Properties of each product.

Id	Name	SBO
P_K	Erk2-P	
PP_KK	Mek1-PP	

Kinetic Law

Derived unit contains undeclared units

$$v_{14} = \mathrm{vol}\,(\mathrm{compartment}) \cdot \mathrm{k7} \cdot [\mathrm{PP\_KK\_K}] \tag{32}$$

Table 47: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k7			150.0		☑

7.15 Reaction r8a

This is a reversible reaction of two reactants forming one product.

Name binding MAPK-Pase and P-MAPK

Reaction equation

$$\mathrm{P\_K} + \mathrm{KPase} \rightleftharpoons \mathrm{KPase\_P\_K} \tag{33}$$

Reactants

Table 48: Properties of each reactant.

Id	Name	SBO
P_K	Erk2-P	
KPase	MAPK-Pase	

Product

Table 49: Properties of each product.

Id	Name	SBO
KPase_P_K	MAPK-Pase_P-Erk2	

Kinetic Law

Derived unit contains undeclared units

$$v_{15} = \mathrm{vol}\,(\mathrm{compartment}) \cdot (\mathrm{a8} \cdot [\mathrm{P\_K}] \cdot [\mathrm{KPase}] - \mathrm{d8} \cdot [\mathrm{KPase\_P\_K}]) \tag{34}$$

Table 50: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
a8			1000.0		☑
d8			150.0		☑

7.16 Reaction r8b

This is an irreversible reaction of one reactant forming two products.

Name dephosphorylation of P-MAPK

Reaction equation

$$\text{KPase\_P\_K} \longrightarrow \text{K} + \text{KPase} \tag{35}$$

Reactant

Table 51: Properties of each reactant.

Id	Name	SBO
KPase_P_K	MAPK-Pase_P-Erk2	

Products

Table 52: Properties of each product.

Id	Name	SBO
K	Erk2	
KPase	MAPK-Pase	

Kinetic Law

Derived unit contains undeclared units

$$v_{16} = \text{vol}\,(\text{compartment}) \cdot \text{k8} \cdot [\text{KPase\_P\_K}] \tag{36}$$

Table 53: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k8			150.0		☑

7.17 Reaction r9a

This is a reversible reaction of two reactants forming one product.

Name binding PP-MAPKK and P-MAPK

Reaction equation

$$\mathrm{P\_K} + \mathrm{PP\_KK} \rightleftharpoons \mathrm{PP\_KK\_P\_K} \tag{37}$$

Reactants

Table 54: Properties of each reactant.

Id	Name	SBO
P_K	Erk2-P	
PP_KK	Mek1-PP	

Product

Table 55: Properties of each product.

Id	Name	SBO
PP_KK_P_K	PP-Mek1_P-Erk2	

Kinetic Law

Derived unit contains undeclared units

$$v_{17} = \mathrm{vol}\,(\mathrm{compartment}) \cdot (\mathrm{a9} \cdot [\mathrm{P\_K}] \cdot [\mathrm{PP\_KK}] - \mathrm{d9} \cdot [\mathrm{PP\_KK\_P\_K}]) \tag{38}$$

Table 56: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
a9			1000.0		☑
d9			150.0		☑

7.18 Reaction r9b

This is an irreversible reaction of one reactant forming two products.

Name phosphorylation of P-MAPK

Reaction equation

$$\text{PP\_KK\_P\_K} \longrightarrow \text{PP\_KK} + \text{PP\_K} \tag{39}$$

Reactant

Table 57: Properties of each reactant.

Id	Name	SBO
PP_KK_P_K	PP-Mek1_P-Erk2	

Products

Table 58: Properties of each product.

Id	Name	SBO
PP_KK	Mek1-PP	
PP_K	Erk2-PP	

Kinetic Law

Derived unit contains undeclared units

$$v_{18} = \text{vol}\,(\text{compartment}) \cdot \text{k9} \cdot [\text{PP\_KK\_P\_K}] \tag{40}$$

Table 59: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k9			150.0		☑

7.19 Reaction r10a

This is a reversible reaction of two reactants forming one product.

Name binding MAPK-Pase and PP-MAPK

Reaction equation

$$\text{PP\_K} + \text{KPase} \rightleftharpoons \text{KPase\_PP\_K} \tag{41}$$

Reactants

Table 60: Properties of each reactant.

Id	Name	SBO
PP_K	Erk2-PP	
KPase	MAPK-Pase	

Product

Table 61: Properties of each product.

Id	Name	SBO
KPase_PP_K	MAPK-Pase_PP-Erk2	

Kinetic Law

Derived unit contains undeclared units

$$v_{19} = \mathrm{vol}\,(\mathrm{compartment}) \cdot (\mathrm{a10} \cdot [\mathrm{PP\_K}] \cdot [\mathrm{KPase}] - \mathrm{d10} \cdot [\mathrm{KPase\_PP\_K}]) \tag{42}$$

Table 62: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
a10			1000.0		☑
d10			150.0		☑

7.20 Reaction r10b

This is an irreversible reaction of one reactant forming two products.

Name dephosphorylation of PP-MAPK

Reaction equation

$$\mathrm{KPase\_PP\_K} \longrightarrow \mathrm{P\_K} + \mathrm{KPase} \tag{43}$$

Reactant

Table 63: Properties of each reactant.

Id	Name	SBO
KPase_PP_K	MAPK-Pase_PP-Erk2	

Products

Table 64: Properties of each product.

Id	Name	SBO
P_K	Erk2-P	
KPase	MAPK-Pase	

Kinetic Law

Derived unit contains undeclared units

$$v_{20} = \mathrm{vol}\,(\mathrm{compartment}) \cdot \mathrm{k10} \cdot [\mathrm{KPase\_PP\_K}] \tag{44}$$

Table 65: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k10			150.0		☑

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 E1

Name MAPKKK activator (Ras)

Initial concentration $3 \cdot 10^{-5}$ µmol$\cdot$l^{-1}

This species takes part in two reactions (as a reactant in r1a and as a product in r1b).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{E1} = v_2 - v_1 \tag{45}$$

8.2 Species E2

Name MAPKKK inactivator

Initial concentration $3 \cdot 10^{-4}$ µmol · l^{-1}

This species takes part in two reactions (as a reactant in r2a and as a product in r2b).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{E2} = v_4 - v_3 \tag{46}$$

8.3 Species KKK

Name Mos

Initial concentration 0.0030 µmol · l^{-1}

This species takes part in two reactions (as a reactant in r1a and as a product in r2b).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{KKK} = v_4 - v_1 \tag{47}$$

8.4 Species P_KKK

Name Mos-P

Initial concentration 0 µmol · l^{-1}

This species takes part in six reactions (as a reactant in r2a, r3a, r5a and as a product in r1b, r3b, r5b).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{P\_KKK} = v_2 + v_6 + v_{10} - v_3 - v_5 - v_9 \tag{48}$$

8.5 Species KK

Name Mek1

Initial concentration 1.2 µmol · l^{-1}

This species takes part in two reactions (as a reactant in r3a and as a product in r4b).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{KK} = v_8 - v_5 \tag{49}$$

8.6 Species P_KK

Name Mek1-P

Initial concentration 0 µmol · l^{-1}

This species takes part in four reactions (as a reactant in r4a, r5a and as a product in r3b, r6b).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{P\_KK} = v_6 + v_{12} - v_7 - v_9 \tag{50}$$

8.7 Species PP_KK

Name Mek1-PP

Initial concentration $0\ \mu\text{mol}\cdot\text{l}^{-1}$

This species takes part in six reactions (as a reactant in r6a, r7a, r9a and as a product in r5b, r7b, r9b).

$$\frac{\text{d}}{\text{d}t}\text{PP\_KK} = v_{10} + v_{14} + v_{18} - v_{11} - v_{13} - v_{17} \tag{51}$$

8.8 Species K

Name Erk2

Initial concentration $1.2\ \mu\text{mol}\cdot\text{l}^{-1}$

This species takes part in two reactions (as a reactant in r7a and as a product in r8b).

$$\frac{\text{d}}{\text{d}t}\text{K} = v_{16} - v_{13} \tag{52}$$

8.9 Species P_K

Name Erk2-P

Initial concentration $0\ \mu\text{mol}\cdot\text{l}^{-1}$

This species takes part in four reactions (as a reactant in r8a, r9a and as a product in r7b, r10b).

$$\frac{\text{d}}{\text{d}t}\text{P\_K} = v_{14} + v_{20} - v_{15} - v_{17} \tag{53}$$

8.10 Species PP_K

Name Erk2-PP

Initial concentration $0\ \mu\text{mol}\cdot\text{l}^{-1}$

This species takes part in two reactions (as a reactant in r10a and as a product in r9b).

$$\frac{\text{d}}{\text{d}t}\text{PP\_K} = v_{18} - v_{19} \tag{54}$$

8.11 Species KPase

Name MAPK-Pase

Initial concentration $0.12\ \mu\text{mol}\cdot\text{l}^{-1}$

This species takes part in four reactions (as a reactant in r8a, r10a and as a product in r8b, r10b).

$$\frac{\mathrm{d}}{\mathrm{d}t}\text{KPase} = v_{16} + v_{20} - v_{15} - v_{19} \tag{55}$$

8.12 Species KKPase

Name MAPKK-Pase

Initial concentration $3\cdot 10^{-4}\ \mu\text{mol}\cdot\text{l}^{-1}$

This species takes part in four reactions (as a reactant in r4a, r6a and as a product in r4b, r6b).

$$\frac{\mathrm{d}}{\mathrm{d}t}\text{KKPase} = v_{8} + v_{12} - v_{7} - v_{11} \tag{56}$$

8.13 Species E1_KKK

Name E1_Mos

Initial concentration $0\ \mu\text{mol}\cdot\text{l}^{-1}$

This species takes part in two reactions (as a reactant in r1b and as a product in r1a).

$$\frac{\mathrm{d}}{\mathrm{d}t}\text{E1\_KKK} = v_{1} - v_{2} \tag{57}$$

8.14 Species E2_P_KKK

Name E2_Mos-P

Initial concentration $0\ \mu\text{mol}\cdot\text{l}^{-1}$

This species takes part in two reactions (as a reactant in r2b and as a product in r2a).

$$\frac{\mathrm{d}}{\mathrm{d}t}\text{E2\_P\_KKK} = v_{3} - v_{4} \tag{58}$$

8.15 Species P_KKK_KK

Name P-Mos_Mek1

Initial concentration $0\ \mu\text{mol}\cdot\text{l}^{-1}$

This species takes part in two reactions (as a reactant in r3b and as a product in r3a).

$$\frac{\mathrm{d}}{\mathrm{d}t}\text{P\_KKK\_KK} = v_{5} - v_{6} \tag{59}$$

8.16 Species P_KKK_P_KK

Name P-Mos_P-Mek1

Initial concentration $0\ \mu\text{mol}\cdot\text{l}^{-1}$

This species takes part in two reactions (as a reactant in r5b and as a product in r5a).

$$\frac{\text{d}}{\text{d}t}\text{P\_KKK\_P\_KK} = v_9 - v_{10} \tag{60}$$

8.17 Species PP_KK_K

Name PP-Mek1_Erk2

Initial concentration $0\ \mu\text{mol}\cdot\text{l}^{-1}$

This species takes part in two reactions (as a reactant in r7b and as a product in r7a).

$$\frac{\text{d}}{\text{d}t}\text{PP\_KK\_K} = v_{13} - v_{14} \tag{61}$$

8.18 Species PP_KK_P_K

Name PP-Mek1_P-Erk2

Initial concentration $0\ \mu\text{mol}\cdot\text{l}^{-1}$

This species takes part in two reactions (as a reactant in r9b and as a product in r9a).

$$\frac{\text{d}}{\text{d}t}\text{PP\_KK\_P\_K} = v_{17} - v_{18} \tag{62}$$

8.19 Species KKPase_PP_KK

Name MAPKK-Pase_PP-Mek1

Initial concentration $0\ \mu\text{mol}\cdot\text{l}^{-1}$

This species takes part in two reactions (as a reactant in r6b and as a product in r6a).

$$\frac{\text{d}}{\text{d}t}\text{KKPase\_PP\_KK} = v_{11} - v_{12} \tag{63}$$

8.20 Species KKPase_P_KK

Name MAPKK-Pase_P-Mek1

Initial concentration $0\ \mu\text{mol}\cdot\text{l}^{-1}$

This species takes part in two reactions (as a reactant in r4b and as a product in r4a).

$$\frac{\text{d}}{\text{d}t}\text{KKPase\_P\_KK} = v_7 - v_8 \tag{64}$$

8.21 Species KPase_PP_K

Name MAPK-Pase_PP-Erk2

Initial concentration $0\ \mu\text{mol} \cdot \text{l}^{-1}$

This species takes part in two reactions (as a reactant in r10b and as a product in r10a).

$$\frac{\text{d}}{\text{d}t}\text{KPase\_PP\_K} = v_{19} - v_{20} \tag{65}$$

8.22 Species KPase_P_K

Name MAPK-Pase_P-Erk2

Initial concentration $0\ \mu\text{mol} \cdot \text{l}^{-1}$

This species takes part in two reactions (as a reactant in r8b and as a product in r8a).

$$\frac{\text{d}}{\text{d}t}\text{KPase\_P\_K} = v_{15} - v_{16} \tag{66}$$

8.23 Species K_PP_norm

Name K_PP_norm

Involved in rule K_PP_norm

One rule which determines this species' quantity.

8.24 Species KK_PP_norm

Name KK_PP_norm

Involved in rule KK_PP_norm

One rule which determines this species' quantity.

8.25 Species KKK_P_norm

Name KKK_P_norm

Involved in rule KKK_P_norm

One rule which determines this species' quantity.

8.26 Species rel_K_PP_max

Name relative maximal K_PP

Involved in rule rel_K_PP_max

One rule which determines this species' quantity.

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