SBML Model Report

# Model name: "Kholodenko2000 - Ultrasensitivity and negative feedback bring oscillations 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 Herbert Sauro[1] at February twelveth 2005 at 0:18 a. m. and last time modified at June second 2015 at 12:03 a. m. Table 1 shows 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 | 8 |
| events | 0 | constraints | 0 |
| reactions | 10 | function definitions | 0 |
| global parameters | 0 | unit definitions | 1 |
| rules | 0 | initial assignments | 0 |

### Model Notes

Kholodenko2000 - Ultrasensitivity and negative feedback bring oscillations in MAPK cascade

The combination of ultrasensitivity and negative feedback bring sustained oscillations in the mitogen-activated protein kinase cascades.

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This model is described in the article:Negative feedback and ultrasensitivity can bring about oscillations in the mitogen-activated protein kinase cascades.Kholodenko BNEur. J. Biochem. 2000; 267(6):1583-8

Abstract:

Functional organization of signal transduction into protein phosphorylation cascades, such as the mitogen-activated protein kinase (MAPK) cascades, greatly enhances the sensitivity of cellular targets to external stimuli. The sensitivity increases multiplicatively with the number of cascade levels, so that a tiny change in a stimulus results in a large change in the response, the phenomenon referred to as ultrasensitivity. In a variety of cell types, the MAPK cascades are imbedded in long feedback loops, positive or negative, depending on whether the terminal kinase stimulates or inhibits the activation of the initial level. Here we demonstrate that a negative feedback loop combined with intrinsic ultrasensitivity of the MAPK cascade can bring about sustained oscillations in MAPK phosphorylation. Based on recent kinetic data on the MAPK cascades, we predict that the period of oscillations can range from minutes to hours. The phosphorylation level can vary between the base level and almost 100% of the total protein. The oscillations of the phosphorylation cascades and slow protein diffusion in the cytoplasm can lead to intracellular waves of phospho-proteins.

This model is hosted on BioModels Database and identified by: BIOMD0000000010 .

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 four are predefined by SBML and not mentioned in the model.

### 2.1 Unit `substance`

**Name** nanomole

**Definition** nmol

### 2.2 Unit `volume`

**Notes** Litre is the predefined SBML unit for `volume`.

**Definition** l

### 2.3 Unit `area`

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

**Definition** $m^2$

### 2.4 Unit `length`

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

**Definition** m

### 2.5 Unit `time`

**Notes** Second is the predefined SBML unit for `time`.

**Definition** s

## 3 Compartment

This model contains one compartment.

Table 2: Properties of all compartments.

| Id | Name | SBO | Spatial Dimensions | Size | Unit | Constant | Outside |
|---|---|---|---|---|---|---|---|
| `uVol` | | | 3 | 1 | litre | ☑ | |

### 3.1 Compartment `uVol`

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

## 4 Species

This model contains eight species. Section 6 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 |
|---|---|---|---|---|---|
| MKKK | Mos | uVol | $\mathrm{nmol} \cdot \mathrm{l}^{-1}$ | ⊟ | ⊟ |
| MKKK_P | Mos-P | uVol | $\mathrm{nmol} \cdot \mathrm{l}^{-1}$ | ⊟ | ⊟ |
| MKK | Mek1 | uVol | $\mathrm{nmol} \cdot \mathrm{l}^{-1}$ | ⊟ | ⊟ |
| MKK_P | Mek1-P | uVol | $\mathrm{nmol} \cdot \mathrm{l}^{-1}$ | ⊟ | ⊟ |
| MKK_PP | Mek1-PP | uVol | $\mathrm{nmol} \cdot \mathrm{l}^{-1}$ | ⊟ | ⊟ |
| MAPK | Erk2 | uVol | $\mathrm{nmol} \cdot \mathrm{l}^{-1}$ | ⊟ | ⊟ |
| MAPK_P | Erk2-P | uVol | $\mathrm{nmol} \cdot \mathrm{l}^{-1}$ | ⊟ | ⊟ |
| MAPK_PP | Erk2-PP | uVol | $\mathrm{nmol} \cdot \mathrm{l}^{-1}$ | ⊟ | ⊟ |

## 5 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 | J0 | MAPKKK activation | $\mathrm{MKKK} \xrightarrow{\mathrm{MAPK\_PP}} \mathrm{MKKK\_P}$ | |
| 2 | J1 | MAPKKK inactivation | $\mathrm{MKKK\_P} \longrightarrow \mathrm{MKKK}$ | |
| 3 | J2 | phosphorylation of MAPKK | $\mathrm{MKK} \xrightarrow{\mathrm{MKKK\_P}} \mathrm{MKK\_P}$ | |
| 4 | J3 | phosphorylation of MAPKK-P | $\mathrm{MKK\_P} \xrightarrow{\mathrm{MKKK\_P}} \mathrm{MKK\_PP}$ | |
| 5 | J4 | dephosphorylation of MAPKK-PP | $\mathrm{MKK\_PP} \longrightarrow \mathrm{MKK\_P}$ | |
| 6 | J5 | dephosphorylation of MAPKK-P | $\mathrm{MKK\_P} \longrightarrow \mathrm{MKK}$ | |
| 7 | J6 | phosphorylation of MAPK | $\mathrm{MAPK} \xrightarrow{\mathrm{MKK\_PP}} \mathrm{MAPK\_P}$ | |
| 8 | J7 | phosphorylation of MAPK-P | $\mathrm{MAPK\_P} \xrightarrow{\mathrm{MKK\_PP}} \mathrm{MAPK\_PP}$ | |
| 9 | J8 | dephosphorylation of MAPK-PP | $\mathrm{MAPK\_PP} \longrightarrow \mathrm{MAPK\_P}$ | |
| 10 | J9 | dephosphorylation of MAPK-P | $\mathrm{MAPK\_P} \longrightarrow \mathrm{MAPK}$ | |

## 5.1 Reaction J0

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

**Name** MAPKKK activation

### Reaction equation

$$\mathrm{MKKK} \xrightarrow{\mathrm{MAPK\_PP}} \mathrm{MKKK\_P} \tag{1}$$

### Reactant

Table 5: Properties of each reactant.

| Id | Name | SBO |
|---|---|---|
| MKKK | Mos | |

### Modifier

Table 6: Properties of each modifier.

| Id | Name | SBO |
|---|---|---|
| MAPK_PP | Erk2-PP | |

### Product

Table 7: Properties of each product.

| Id | Name | SBO |
|---|---|---|
| MKKK_P | Mos-P | |

### Kinetic Law

**Derived unit** contains undeclared units

$$v_1 = \frac{\mathrm{vol}\,(\mathrm{uVol}) \cdot \mathrm{V1} \cdot [\mathrm{MKKK}]}{\left(1 + \left(\frac{[\mathrm{MAPK\_PP}]}{\mathrm{Ki}}\right)^{\mathrm{n}}\right) \cdot (\mathrm{K1} + [\mathrm{MKKK}])} \tag{2}$$

Table 8: Properties of each parameter.

| Id | Name | SBO | Value | Unit | Constant |
|---|---|---|---|---|---|
| V1 | | | 2.5 | | ☑ |
| Ki | | | 9.0 | | ☑ |
| n | | | 1.0 | | ☑ |
| K1 | | | 10.0 | | ☑ |

## 5.2 Reaction J1

This is an irreversible reaction of one reactant forming one product.

**Name** MAPKKK inactivation

### Reaction equation

$$\text{MKKK\_P} \longrightarrow \text{MKKK} \tag{3}$$

### Reactant

Table 9: Properties of each reactant.

| Id | Name | SBO |
|---|---|---|
| MKKK_P | Mos-P | |

### Product

Table 10: Properties of each product.

| Id | Name | SBO |
|---|---|---|
| MKKK | Mos | |

### Kinetic Law

**Derived unit** contains undeclared units

$$v_2 = \frac{\text{vol}\,(\text{uVol}) \cdot \text{V2} \cdot [\text{MKKK\_P}]}{\text{KK2} + [\text{MKKK\_P}]} \tag{4}$$

Table 11: Properties of each parameter.

| Id | Name | SBO | Value | Unit | Constant |
|---|---|---|---|---|---|
| V2 | | | 0.25 | | ☑ |
| KK2 | | | 8.00 | | ☑ |

## 5.3 Reaction J2

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

**Name** phosphorylation of MAPKK

### Reaction equation

$$\mathrm{MKK} \xrightarrow{\mathrm{MKKK\_P}} \mathrm{MKK\_P} \tag{5}$$

### Reactant

Table 12: Properties of each reactant.

| Id | Name | SBO |
|---|---|---|
| MKK | Mek1 | |

### Modifier

Table 13: Properties of each modifier.

| Id | Name | SBO |
|---|---|---|
| MKKK_P | Mos-P | |

### Product

Table 14: Properties of each product.

| Id | Name | SBO |
|---|---|---|
| MKK_P | Mek1-P | |

### Kinetic Law

**Derived unit** contains undeclared units

$$v_3 = \frac{\mathrm{vol}\,(\mathrm{uVol}) \cdot \mathrm{k3} \cdot [\mathrm{MKKK\_P}] \cdot [\mathrm{MKK}]}{\mathrm{KK3} + [\mathrm{MKK}]} \tag{6}$$

Table 15: Properties of each parameter.

| Id | Name | SBO | Value | Unit | Constant |
|---|---|---|---|---|---|
| k3 | | | 0.025 | | ☑ |
| KK3 | | | 15.000 | | ☑ |

## 5.4 Reaction J3

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

**Name** phosphorylation of MAPKK-P

### Reaction equation

$$\mathrm{MKK\_P} \xrightarrow{\mathrm{MKKK\_P}} \mathrm{MKK\_PP} \tag{7}$$

### Reactant

Table 16: Properties of each reactant.

| Id | Name | SBO |
|---|---|---|
| MKK_P | Mek1-P | |

### Modifier

Table 17: Properties of each modifier.

| Id | Name | SBO |
|---|---|---|
| MKKK_P | Mos-P | |

### Product

Table 18: Properties of each product.

| Id | Name | SBO |
|---|---|---|
| MKK_PP | Mek1-PP | |

### Kinetic Law

**Derived unit** contains undeclared units

$$v_4 = \frac{\mathrm{vol}\,(\mathrm{uVol}) \cdot \mathrm{k4} \cdot [\mathrm{MKKK\_P}] \cdot [\mathrm{MKK\_P}]}{\mathrm{KK4} + [\mathrm{MKK\_P}]} \tag{8}$$

Table 19: Properties of each parameter.

| Id | Name | SBO | Value | Unit | Constant |
|---|---|---|---|---|---|
| k4 | | | 0.025 | | ☑ |
| KK4 | | | 15.000 | | ☑ |

## 5.5 Reaction J4

This is an irreversible reaction of one reactant forming one product.

**Name** dephosphorylation of MAPKK-PP

### Reaction equation

$$\mathrm{MKK\_PP} \longrightarrow \mathrm{MKK\_P} \tag{9}$$

### Reactant

Table 20: Properties of each reactant.

| Id | Name | SBO |
|---|---|---|
| MKK_PP | Mek1-PP | |

### Product

Table 21: Properties of each product.

| Id | Name | SBO |
|---|---|---|
| MKK_P | Mek1-P | |

### Kinetic Law

**Derived unit** contains undeclared units

$$v_5 = \frac{\mathrm{vol}\,(\mathrm{uVol}) \cdot \mathrm{V5} \cdot [\mathrm{MKK\_PP}]}{\mathrm{KK5} + [\mathrm{MKK\_PP}]} \tag{10}$$

Table 22: Properties of each parameter.

| Id | Name | SBO | Value | Unit | Constant |
|---|---|---|---|---|---|
| V5 | | | 0.75 | | ☑ |
| KK5 | | | 15.00 | | ☑ |

## 5.6 Reaction J5

This is an irreversible reaction of one reactant forming one product.

**Name** dephosphorylation of MAPKK-P

### Reaction equation

$$\mathrm{MKK\_P} \longrightarrow \mathrm{MKK} \tag{11}$$

### Reactant

Table 23: Properties of each reactant.

| Id | Name | SBO |
|---|---|---|
| MKK_P | Mek1-P | |

### Product

Table 24: Properties of each product.

| Id | Name | SBO |
|---|---|---|
| MKK | Mek1 | |

### Kinetic Law

**Derived unit** contains undeclared units

$$v_6 = \frac{\mathrm{vol}\,(\mathrm{uVol}) \cdot \mathrm{V6} \cdot [\mathrm{MKK\_P}]}{\mathrm{KK6} + [\mathrm{MKK\_P}]} \tag{12}$$

Table 25: Properties of each parameter.

| Id | Name | SBO | Value | Unit | Constant |
|---|---|---|---|---|---|
| V6 | | | 0.75 | | ☑ |
| KK6 | | | 15.00 | | ☑ |

## 5.7 Reaction J6

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

**Name** phosphorylation of MAPK

### Reaction equation

$$\text{MAPK} \xrightarrow{\text{MKK\_PP}} \text{MAPK\_P} \tag{13}$$

### Reactant

Table 26: Properties of each reactant.

| Id | Name | SBO |
|---|---|---|
| MAPK | Erk2 | |

### Modifier

Table 27: Properties of each modifier.

| Id | Name | SBO |
|---|---|---|
| MKK_PP | Mek1-PP | |

### Product

Table 28: Properties of each product.

| Id | Name | SBO |
|---|---|---|
| MAPK_P | Erk2-P | |

### Kinetic Law

**Derived unit** contains undeclared units

$$v_7 = \frac{\mathrm{vol}\,(\mathrm{uVol}) \cdot \mathrm{k7} \cdot [\mathrm{MKK\_PP}] \cdot [\mathrm{MAPK}]}{\mathrm{KK7} + [\mathrm{MAPK}]} \tag{14}$$

Table 29: Properties of each parameter.

| Id | Name | SBO | Value | Unit | Constant |
|---|---|---|---|---|---|
| k7 | | | 0.025 | | ☑ |
| KK7 | | | 15.000 | | ☑ |

## 5.8 Reaction J7

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

**Name** phosphorylation of MAPK-P

### Reaction equation

$$\mathrm{MAPK\_P} \xrightarrow{\mathrm{MKK\_PP}} \mathrm{MAPK\_PP} \tag{15}$$

### Reactant

Table 30: Properties of each reactant.

| Id | Name | SBO |
|---|---|---|
| MAPK_P | Erk2-P | |

### Modifier

Table 31: Properties of each modifier.

| Id | Name | SBO |
|---|---|---|
| MKK_PP | Mek1-PP | |

### Product

Table 32: Properties of each product.

| Id | Name | SBO |
|---|---|---|
| MAPK_PP | Erk2-PP | |

### Kinetic Law

**Derived unit** contains undeclared units

$$v_8 = \frac{\mathrm{vol}\,(\mathrm{uVol}) \cdot \mathrm{k8} \cdot [\mathrm{MKK\_PP}] \cdot [\mathrm{MAPK\_P}]}{\mathrm{KK8} + [\mathrm{MAPK\_P}]} \tag{16}$$

Table 33: Properties of each parameter.

| Id | Name | SBO | Value | Unit | Constant |
|---|---|---|---|---|---|
| k8 | | | 0.025 | | ☑ |
| KK8 | | | 15.000 | | ☑ |

## 5.9 Reaction J8

This is an irreversible reaction of one reactant forming one product.

**Name** dephosphorylation of MAPK-PP

### Reaction equation

$$\mathrm{MAPK\_PP} \longrightarrow \mathrm{MAPK\_P} \tag{17}$$

### Reactant

Table 34: Properties of each reactant.

| Id | Name | SBO |
|---|---|---|
| MAPK_PP | Erk2-PP | |

### Product

Table 35: Properties of each product.

| Id | Name | SBO |
|---|---|---|
| MAPK_P | Erk2-P | |

### Kinetic Law

**Derived unit** contains undeclared units

$$v_9 = \frac{\mathrm{vol}\,(\mathrm{uVol}) \cdot \mathrm{V9} \cdot [\mathrm{MAPK\_PP}]}{\mathrm{KK9} + [\mathrm{MAPK\_PP}]} \tag{18}$$

Table 36: Properties of each parameter.

| Id | Name | SBO | Value | Unit | Constant |
|---|---|---|---|---|---|
| V9 | | | 0.5 | | ☑ |
| KK9 | | | 15.0 | | ☑ |

## 5.10 Reaction J9

This is an irreversible reaction of one reactant forming one product.

**Name** dephosphorylation of MAPK-P

### Reaction equation

$$\mathrm{MAPK\_P} \longrightarrow \mathrm{MAPK} \tag{19}$$

### Reactant

Table 37: Properties of each reactant.

| Id | Name | SBO |
|---|---|---|
| MAPK_P | Erk2-P | |

### Product

Table 38: Properties of each product.

| Id | Name | SBO |
|---|---|---|
| MAPK | Erk2 | |

### Kinetic Law

**Derived unit** contains undeclared units

$$v_{10} = \frac{\mathrm{vol}\,(\mathrm{uVol}) \cdot \mathrm{V10} \cdot [\mathrm{MAPK\_P}]}{\mathrm{KK10} + [\mathrm{MAPK\_P}]} \tag{20}$$

Table 39: Properties of each parameter.

| Id | Name | SBO | Value | Unit | Constant |
|---|---|---|---|---|---|
| V10 | | | 0.5 | | ☑ |
| KK10 | | | 15.0 | | ☑ |

# 6 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.

## 6.1 Species MKKK

**Name** Mos

**Initial concentration** $90\ \mathrm{nmol}\cdot\mathrm{l}^{-1}$

This species takes part in two reactions (as a reactant in J0 and as a product in J1).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{MKKK} = v_2 - v_1 \tag{21}$$

## 6.2 Species MKKK_P

**Name** Mos-P

**Initial concentration** $10\ \mathrm{nmol}\cdot\mathrm{l}^{-1}$

This species takes part in four reactions (as a reactant in J1 and as a product in J0 and as a modifier in J2, J3).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{MKKK\_P} = v_1 - v_2 \tag{22}$$

### 6.3 Species MKK

**Name** Mek1

**Initial concentration** $280\ \mathrm{nmol}\cdot\mathrm{l}^{-1}$

This species takes part in two reactions (as a reactant in J2 and as a product in J5).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{MKK} = v_6 - v_3 \tag{23}$$

### 6.4 Species MKK_P

**Name** Mek1-P

**Initial concentration** $10\ \mathrm{nmol}\cdot\mathrm{l}^{-1}$

This species takes part in four reactions (as a reactant in J3, J5 and as a product in J2, J4).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{MKK\_P} = v_3 + v_5 - v_4 - v_6 \tag{24}$$

### 6.5 Species MKK_PP

**Name** Mek1-PP

**Initial concentration** $10\ \mathrm{nmol}\cdot\mathrm{l}^{-1}$

This species takes part in four reactions (as a reactant in J4 and as a product in J3 and as a modifier in J6, J7).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{MKK\_PP} = v_4 - v_5 \tag{25}$$

### 6.6 Species MAPK

**Name** Erk2

**Initial concentration** $280\ \mathrm{nmol}\cdot\mathrm{l}^{-1}$

This species takes part in two reactions (as a reactant in J6 and as a product in J9).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{MAPK} = v_{10} - v_7 \tag{26}$$

### 6.7 Species MAPK_P

**Name** Erk2-P

**Initial concentration** $10\ \mathrm{nmol}\cdot\mathrm{l}^{-1}$

This species takes part in four reactions (as a reactant in J7, J9 and as a product in J6, J8).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{MAPK\_P} = v_7 + v_9 - v_8 - v_{10} \tag{27}$$

## 6.8 Species MAPK_PP

**Name** Erk2-PP

**Initial concentration** $10\ \mathrm{nmol} \cdot \mathrm{l}^{-1}$

This species takes part in three reactions (as a reactant in J8 and as a product in J7 and as a modifier in J0).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{MAPK\_PP} = v_8 - v_9 \tag{28}$$

SBML2LaTeX was developed by Andreas Dräger[a], Hannes Planatscher[a], Dieudonné M Wouamba[a], Adrian Schröder[a], Michael Hucka[b], Lukas Endler[c], Martin Golebiewski[d] and Andreas Zell[a]. Please see http://www.ra.cs.uni-tuebingen.de/software/SBML2LaTeX for more information.

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