SBML Model Report

Model name: “Kwang2003 - The influence of RKIP on the ERK signaling pathway”

May 17, 2018

1 General Overview

This is a document in SBML Level 2 Version 4 format. This model was created by the following three authors: Matthew Grant Roberts[1], Varun Kothamachu[2] and Emma Louise Fairbanks[3] at June 20th 2017 at 12:07 a. m. and last time modified at October 26th 2017 at 3:22 p. 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	11
events	0	constraints	0
reactions	11	function definitions	0
global parameters	11	unit definitions	1
rules	0	initial assignments	0

Model Notes

Kwang2003 - The influence of RKIP on the ERKsignaling pathway

[1]EMBL-EBI, mroberts@ebi.ac.uk
[2]Babraham Institute, kothamav@babraham.ac.uk
[3]EMBL-EBI, efairbanks@ebi.ac.uk

This model is described in the article:Mathematical Modeling of the Influence of RKIP on the ERK Signaling PathwayKwang-Hyun Cho, Sung-Young Shin, Hyun-Woo Kim, Olaf Wolkenhauer, Brian McFerran and Walter KolchComputational Methods in Systems Biology: First International Workshop, CMSB 2003 Rovereto, Italy, February 24??26, 2003 Proceedings

Abstract:

This paper investigates the influence of the Raf Kinase Inhibitor Pro- tein (RKIP) on the Extracellular signal Regulated Kinase (ERK) signaling pathway through mathematical modeling and simulation. Using nonlinear ordi- nary differential equations to represent biochemical reactions in the pathway, we suggest a technique for parameter estimation, utilizing time series data of proteins involved in the signaling pathway. The mathematical model allows the simulation the sensitivity of the ERK pathway to variations of initial RKIP and ERK-PP (phosphorylated ERK) concentrations along with time. Throughout the simulation study, we can qualitatively validate the proposed mathematical model compared with experimental results.

This model is hosted on BioModels Database and identified by: BIOMD0000000647.

To cite BioModels Database, please use: Chelliah V et al. BioModels: ten-year anniversary. Nucl. Acids Res. 2015, 43(Database issue):D542-8.

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 substance

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
`cytoplasm`	cytoplasm		3	1	litre	☑	

3.1 Compartment `cytoplasm`

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

Name cytoplasm

4 Species

This model contains eleven species. Section 7 provides further details and the derived rates of change of each species.

Table 3: Properties of each species.

Id	Name	Compartment	Derived Unit	Constant	Boundary Condition
Raf1	Raf1	cytoplasm	$\mu mol \cdot l^{-1}$	⊟	⊟
RKIP	RKIP	cytoplasm	$\mu mol \cdot l^{-1}$	⊟	⊟
Raf1_RKIP	Raf1_RKIP	cytoplasm	$\mu mol \cdot l^{-1}$	⊟	⊟
Raf1_RKIP_ERKPP	Raf1_RKIP_ERKPP	cytoplasm	$\mu mol \cdot l^{-1}$	⊟	⊟
ERK	ERK	cytoplasm	$\mu mol \cdot l^{-1}$	⊟	⊟
RKIPP	RKIPP	cytoplasm	$\mu mol \cdot l^{-1}$	⊟	⊟
MEKPP	MEKPP	cytoplasm	$\mu mol \cdot l^{-1}$	⊟	⊟
MEKPP_ERK	MEKPP_ERK	cytoplasm	$\mu mol \cdot l^{-1}$	⊟	⊟
ERKPP	ERKPP	cytoplasm	$\mu mol \cdot l^{-1}$	⊟	⊟
RP	RP	cytoplasm	$\mu mol \cdot l^{-1}$	⊟	⊟
RKIPP_RP	RKIPP_RP	cytoplasm	$\mu mol \cdot l^{-1}$	⊟	⊟

5 Parameters

This model contains eleven global parameters.

Table 4: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k1	k1		0.530		☑
k2	k2		0.007		☑
k3	k3		0.625		☑
k4	k4		0.002		☑
k5	k5		0.032		☑
k6	k6		0.800		☑
k7	k7		0.008		☑
k8	k8		0.071		☑
k9	k9		0.920		☑
k10	k10		0.001		☑
k11	k11		0.870		☑

6 Reactions

This model contains eleven 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	Raf1_RKIP-_complex-_formation	Raf1_RKIP complex formation	$\mathrm{Raf1} + \mathrm{RKIP} \longrightarrow \mathrm{Raf1\_RKIP}$	
2	Raf1_RKIP-_complex-_disassembly	Raf1_RKIP complex disassembly	$\mathrm{Raf1\_RKIP} \longrightarrow \mathrm{Raf1} + \mathrm{RKIP}$	
3	Raf1_RKIP-_ERKPP_complex-_formation	Raf1_RKIP_ERKPP complex formation	$\mathrm{Raf1\_RKIP} + \mathrm{ERKPP} \longrightarrow \mathrm{Raf1\_RKIP\_ERKPP}$	
4	Raf1_RKIP-_ERKPP_complex-_disassembly-__ERK-_phosphorylation	Raf1_RKIP_ERKPP complex disassembly (ERK phosphorylation)	$\mathrm{Raf1\_RKIP\_ERKPP} \longrightarrow \mathrm{Raf1\_RKIP} + \mathrm{ERKPP}$	
5	Raf1_RKIP-_ERKPP_complex-_disassembly-__RKIP-_phosphorylation	Raf1_RKIP_ERKPP complex disassembly (RKIP phosphorylation)	$\mathrm{Raf1\_RKIP\_ERKPP} \longrightarrow \mathrm{Raf1} + \mathrm{ERK} + \mathrm{RKIPP}$	
6	MEKPP_ERK-_complex-_formation	MEKPP_ERK complex formation	$\mathrm{ERK} + \mathrm{MEKPP} \longrightarrow \mathrm{MEKPP\_ERK}$	

№	Id	Name	Reaction Equation	SBO
7	MEKPP_ERK-_complex-_disassembly-__ERK-_unphosphorylated	MEKPP_ERK complex disassembly (ERK unphosphorylated)	MEKPP_ERK $\longrightarrow$ ERK + MEKPP	
8	MEKPP_ERK-_complex-_disassembly-__ERK-_phosphorylated	MEKPP_ERK complex disassembly (ERK phosphorylated)	MEKPP_ERK $\longrightarrow$ MEKPP + ERKPP	
9	RKIPP_RP-_comlex-_formation	RKIPP_RP comlex formation	RKIPP + RP $\longrightarrow$ RKIPP_RP	
10	RKIPP_RP-_complex-_disassembly_-_phosphorylated-_RKIP	RKIPP_RP complex disassembly (phosphorylated RKIP)	RKIPP_RP $\longrightarrow$ RP + RKIPP	
11	RKIPP_RP-_complex-_disassembly_-_unphosphorylated-_RKIP	RKIPP_RP complex disassembly (unphosphorylated RKIP)	RKIPP_RP $\longrightarrow$ RP + RKIP	

6.1 Reaction Raf1_RKIP_complex_formation

This is an irreversible reaction of two reactants forming one product.

Name Raf1_RKIP complex formation

Reaction equation

$$\text{Raf1} + \text{RKIP} \longrightarrow \text{Raf1\_RKIP} \tag{1}$$

Reactants

Table 6: Properties of each reactant.

Id	Name	SBO
Raf1	Raf1	
RKIP	RKIP	

Product

Table 7: Properties of each product.

Id	Name	SBO
Raf1_RKIP	Raf1_RKIP	

Kinetic Law

Derived unit contains undeclared units

$$v_1 = \text{vol}\,(\text{cytoplasm}) \cdot \text{k1} \cdot [\text{Raf1}] \cdot [\text{RKIP}] \tag{2}$$

6.2 Reaction Raf1_RKIP_complex_disassembly

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

Name Raf1_RKIP complex disassembly

Reaction equation

$$\text{Raf1\_RKIP} \longrightarrow \text{Raf1} + \text{RKIP} \tag{3}$$

Reactant

Table 8: Properties of each reactant.

Id	Name	SBO
Raf1_RKIP	Raf1_RKIP	

Products

Table 9: Properties of each product.

Id	Name	SBO
Raf1	Raf1	
RKIP	RKIP	

Kinetic Law

Derived unit contains undeclared units

$$v_2 = \mathrm{vol}\,(\mathrm{cytoplasm}) \cdot \mathrm{k2} \cdot [\mathrm{Raf1\_RKIP}] \tag{4}$$

6.3 Reaction Raf1_RKIP_ERKPP_complex_formation

This is an irreversible reaction of two reactants forming one product.

Name Raf1_RKIP_ERKPP complex formation

Reaction equation

$$\mathrm{Raf1\_RKIP} + \mathrm{ERKPP} \longrightarrow \mathrm{Raf1\_RKIP\_ERKPP} \tag{5}$$

Reactants

Table 10: Properties of each reactant.

Id	Name	SBO
Raf1_RKIP	Raf1_RKIP	
ERKPP	ERKPP	

Product

Table 11: Properties of each product.

Id	Name	SBO
Raf1_RKIP_ERKPP	Raf1_RKIP_ERKPP	

Kinetic Law

Derived unit contains undeclared units

$$v_3 = \mathrm{vol}\,(\mathrm{cytoplasm}) \cdot \mathrm{k3} \cdot [\mathrm{Raf1\_RKIP}] \cdot [\mathrm{ERKPP}] \tag{6}$$

6.4 Reaction Raf1_RKIP_ERKPP_complex_disassembly__ERK_phosphorylation

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

Name Raf1_RKIP_ERKPP complex disassembly (ERK phosphorylation)

Reaction equation

$$\mathrm{Raf1\_RKIP\_ERKPP} \longrightarrow \mathrm{Raf1\_RKIP} + \mathrm{ERKPP} \tag{7}$$

Reactant

Table 12: Properties of each reactant.

Id	Name	SBO
Raf1_RKIP_ERKPP	Raf1_RKIP_ERKPP	

Products

Table 13: Properties of each product.

Id	Name	SBO
Raf1_RKIP	Raf1_RKIP	
ERKPP	ERKPP	

Kinetic Law

Derived unit contains undeclared units

$$v_4 = \mathrm{vol}\,(\mathrm{cytoplasm}) \cdot \mathrm{k4} \cdot [\mathrm{Raf1\_RKIP\_ERKPP}] \tag{8}$$

6.5 Reaction Raf1_RKIP_ERKPP_complex_disassembly__RKIP_phosphorylation

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

Name Raf1_RKIP_ERKPP complex disassembly (RKIP phosphorylation)

Reaction equation

$$\text{Raf1\_RKIP\_ERKPP} \longrightarrow \text{Raf1} + \text{ERK} + \text{RKIPP} \tag{9}$$

Reactant

Table 14: Properties of each reactant.

Id	Name	SBO
Raf1_RKIP_ERKPP	Raf1_RKIP_ERKPP	

Products

Table 15: Properties of each product.

Id	Name	SBO
Raf1	Raf1	
ERK	ERK	
RKIPP	RKIPP	

Kinetic Law

Derived unit contains undeclared units

$$v_5 = \text{vol}\,(\text{cytoplasm}) \cdot \text{k5} \cdot [\text{Raf1\_RKIP\_ERKPP}] \tag{10}$$

6.6 Reaction MEKPP_ERK_complex_formation

This is an irreversible reaction of two reactants forming one product.

Name MEKPP_ERK complex formation

Reaction equation

$$\text{ERK} + \text{MEKPP} \longrightarrow \text{MEKPP\_ERK} \tag{11}$$

Reactants

Table 16: Properties of each reactant.

Id	Name	SBO
ERK	ERK	
MEKPP	MEKPP	

Product

Table 17: Properties of each product.

Id	Name	SBO
MEKPP_ERK	MEKPP_ERK	

Kinetic Law

Derived unit contains undeclared units

$$v_6 = \mathrm{vol}\,(\mathrm{cytoplasm}) \cdot \mathrm{k6} \cdot [\mathrm{ERK}] \cdot [\mathrm{MEKPP}] \tag{12}$$

6.7 Reaction MEKPP_ERK_complex_disassembly__ERK_unphosphorylated

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

Name MEKPP_ERK complex disassembly (ERK unphosphorylated)

Reaction equation

$$\mathrm{MEKPP\_ERK} \longrightarrow \mathrm{ERK} + \mathrm{MEKPP} \tag{13}$$

Reactant

Table 18: Properties of each reactant.

Id	Name	SBO
MEKPP_ERK	MEKPP_ERK	

Products

Table 19: Properties of each product.

Id	Name	SBO
ERK	ERK	
MEKPP	MEKPP	

Kinetic Law

Derived unit contains undeclared units

$$v_7 = \mathrm{vol}\,(\mathrm{cytoplasm}) \cdot \mathrm{k7} \cdot [\mathrm{MEKPP\_ERK}] \tag{14}$$

6.8 Reaction MEKPP_ERK_complex_disassembly__ERK_phosphorylated

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

Name MEKPP_ERK complex disassembly (ERK phosphorylated)

Reaction equation

$$\mathrm{MEKPP\_ERK} \longrightarrow \mathrm{MEKPP} + \mathrm{ERKPP} \tag{15}$$

Reactant

Table 20: Properties of each reactant.

Id	Name	SBO
MEKPP_ERK	MEKPP_ERK	

Products

Table 21: Properties of each product.

Id	Name	SBO
MEKPP	MEKPP	
ERKPP	ERKPP	

Kinetic Law

Derived unit contains undeclared units

$$v_8 = \mathrm{vol}\,(\mathrm{cytoplasm}) \cdot \mathrm{k8} \cdot [\mathrm{MEKPP\_ERK}] \tag{16}$$

6.9 Reaction RKIPP_RP_comlex_formation

This is an irreversible reaction of two reactants forming one product.

Name RKIPP_RP comlex formation

Reaction equation

$$\mathrm{RKIPP} + \mathrm{RP} \longrightarrow \mathrm{RKIPP\_RP} \tag{17}$$

Reactants

Table 22: Properties of each reactant.

Id	Name	SBO
RKIPP	RKIPP	
RP	RP	

Product

Table 23: Properties of each product.

Id	Name	SBO
RKIPP_RP	RKIPP_RP	

Kinetic Law

Derived unit contains undeclared units

$$v_9 = \mathrm{vol}\,(\mathrm{cytoplasm}) \cdot \mathrm{k9} \cdot [\mathrm{RKIPP}] \cdot [\mathrm{RP}] \tag{18}$$

6.10 Reaction RKIPP_RP_complex_disassembly__phosphorylated_RKIP

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

Name RKIPP_RP complex disassembly (phosphorylated RKIP)

Reaction equation

$$\mathrm{RKIPP\_RP} \longrightarrow \mathrm{RP} + \mathrm{RKIPP} \tag{19}$$

Reactant

Table 24: Properties of each reactant.

Id	Name	SBO
RKIPP_RP	RKIPP_RP	

Products

Table 25: Properties of each product.

Id	Name	SBO
RP	RP	
RKIPP	RKIPP	

Kinetic Law

Derived unit contains undeclared units

$$v_{10} = \mathrm{vol}\,(\mathrm{cytoplasm}) \cdot \mathrm{k10} \cdot [\mathrm{RKIPP\_RP}] \tag{20}$$

6.11 Reaction RKIPP_RP_complex_disassembly__unphosphorylated_RKIP

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

Name RKIPP_RP complex disassembly (unphosphorylated RKIP)

Reaction equation

$$\mathrm{RKIPP\_RP} \longrightarrow \mathrm{RP} + \mathrm{RKIP} \tag{21}$$

Reactant

Table 26: Properties of each reactant.

Id	Name	SBO
RKIPP_RP	RKIPP_RP	

Products

Table 27: Properties of each product.

Id	Name	SBO
RP	RP	
RKIP	RKIP	

Kinetic Law

Derived unit contains undeclared units

$$v_{11} = \mathrm{vol}\,(\mathrm{cytoplasm}) \cdot \mathrm{k11} \cdot [\mathrm{RKIPP\_RP}] \tag{22}$$

7 Derived Rate Equations

When interpreted as an ordinary differential equation framework, this model implies the following set of equations for the rates of change of each species.

Identifiers for kinetic laws highlighted in gray cannot be verified to evaluate to units of SBML `substance` per `time`. As a result, some SBML interpreters may not be able to verify the consistency of the units on quantities in the model. Please check if

- parameters without an unit definition are involved or
- volume correction is necessary because the `hasOnlySubstanceUnits` flag may be set to `false` and `spacialDimensions`> 0 for certain species.

7.1 Species `Raf1`

Name Raf1

Initial concentration $2\ \mu\mathrm{mol} \cdot \mathrm{l}^{-1}$

This species takes part in three reactions (as a reactant in `Raf1_RKIP_complex_formation` and as a product in `Raf1_RKIP_complex_disassembly`, `Raf1_RKIP_ERKPP_complex_disassembly__RKIP_phosphorylation`).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Raf1} = v_2 + v_5 - v_1 \tag{23}$$

7.2 Species `RKIP`

Name RKIP

Initial concentration $2.5\ \mu\mathrm{mol} \cdot \mathrm{l}^{-1}$

This species takes part in three reactions (as a reactant in Raf1_RKIP_complex_formation and as a product in Raf1_RKIP_complex_disassembly, RKIPP_RP_complex_disassembly_-_unphosphorylated_RKIP).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{RKIP} = v_2 + v_{11} - v_1 \tag{24}$$

7.3 Species Raf1_RKIP

Name Raf1_RKIP

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

This species takes part in four reactions (as a reactant in Raf1_RKIP_complex_disassembly, Raf1_RKIP_ERKPP_complex_formation and as a product in Raf1_RKIP_complex_formation, Raf1_RKIP_ERKPP_complex_disassembly__ERK_phosphorylation).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Raf1\_RKIP} = v_1 + v_4 - v_2 - v_3 \tag{25}$$

7.4 Species Raf1_RKIP_ERKPP

Name Raf1_RKIP_ERKPP

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

This species takes part in three reactions (as a reactant in Raf1_RKIP_ERKPP_complex_disassembly-_ERK_phosphorylation, Raf1_RKIP_ERKPP_complex_disassembly__RKIP_phosphorylation and as a product in Raf1_RKIP_ERKPP_complex_formation).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Raf1\_RKIP\_ERKPP} = v_3 - v_4 - v_5 \tag{26}$$

7.5 Species ERK

Name ERK

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

This species takes part in three reactions (as a reactant in MEKPP_ERK_complex_formation and as a product in Raf1_RKIP_ERKPP_complex_disassembly__RKIP_phosphorylation, MEKPP-_ERK_complex_disassembly__ERK_unphosphorylated).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{ERK} = v_5 + v_7 - v_6 \tag{27}$$

7.6 Species RKIPP

Name RKIPP

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

This species takes part in three reactions (as a reactant in RKIPP_RP_comlex_formation and as a product in Raf1_RKIP_ERKPP_complex_disassembly__RKIP_phosphorylation, RKIPP-_RP_complex_disassembly__phosphorylated_RKIP).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{RKIPP} = v_5 + v_{10} - v_9 \tag{28}$$

7.7 Species MEKPP

Name MEKPP

Initial concentration $2.5\ \mu\text{mol}\cdot\text{l}^{-1}$

This species takes part in three reactions (as a reactant in MEKPP_ERK_complex_formation and as a product in MEKPP_ERK_complex_disassembly__ERK_unphosphorylated, MEKPP_ERK-_complex_disassembly__ERK_phosphorylated).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{MEKPP} = v_7 + v_8 - v_6 \tag{29}$$

7.8 Species MEKPP_ERK

Name MEKPP_ERK

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

This species takes part in three reactions (as a reactant in MEKPP_ERK_complex_disassembly-_-ERK_unphosphorylated, MEKPP_ERK_complex_disassembly__ERK_phosphorylated and as a product in MEKPP_ERK_complex_formation).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{MEKPP\_ERK} = v_6 - v_7 - v_8 \tag{30}$$

7.9 Species ERKPP

Name ERKPP

Initial concentration $2.5\ \mu\text{mol}\cdot\text{l}^{-1}$

This species takes part in three reactions (as a reactant in Raf1_RKIP_ERKPP_complex_formation and as a product in Raf1_RKIP_ERKPP_complex_disassembly__ERK_phosphorylation, MEKPP-_ERK_complex_disassembly__ERK_phosphorylated).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{ERKPP} = v_4 + v_8 - v_3 \tag{31}$$

7.10 Species RP

Name RP

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

This species takes part in three reactions (as a reactant in RKIPP_RP_comlex_formation and as a product in RKIPP_RP_complex_disassembly__phosphorylated_RKIP, RKIPP_RP_complex_disassembly__unphosphorylated_RKIP).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{RP} = v_{10} + v_{11} - v_9 \tag{32}$$

7.11 Species RKIPP_RP

Name RKIPP_RP

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

This species takes part in three reactions (as a reactant in RKIPP_RP_complex_disassembly__phosphorylated_RKIP, RKIPP_RP_complex_disassembly__unphosphorylated_RKIP and as a product in RKIPP_RP_comlex_formation).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{RKIPP\_RP} = v_9 - v_{10} - v_{11} \tag{33}$$

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