

## SBML Model Report

# Model name: “Brown2004 - NGF and EGF signaling”



May 6, 2016

## 1 General Overview

This is a document in SBML Level 2 Version 1 format. This model was created by the following two authors: Nicolas Le Novre<sup>1</sup> and Ryan Gutenkunst<sup>2</sup> at June tenth 2005 at 2:09 p. m. and last time modified at May 18<sup>th</sup> 2015 at 10:58 a. m. Table 1 provides 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	32
events	0	constraints	0
reactions	26	function definitions	0
global parameters	48	unit definitions	2
rules	0	initial assignments	0

## Model Notes

Brown2004 - NGF and EGF signaling

This model is described in the article: [The statistical mechanics of complex signaling networks: nerve growth factor signaling](#). Brown KS, Hill CC, Calero GA, Myers CR, Lee KH, Sethna JP, Cerione RA. Phys Biol 2004 Dec; 1(3-4): 184-195

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## Abstract:

The inherent complexity of cellular signaling networks and their importance to a wide range of cellular functions necessitates the development of modeling methods that can be applied toward making predictions and highlighting the appropriate experiments to test our understanding of how these systems are designed and function. We use methods of statistical mechanics to extract useful predictions for complex cellular signaling networks. A key difficulty with signaling models is that, while significant effort is being made to experimentally measure the rate constants for individual steps in these networks, many of the parameters required to describe their behavior remain unknown or at best represent estimates. To establish the usefulness of our approach, we have applied our methods toward modeling the nerve growth factor (NGF)-induced differentiation of neuronal cells. In particular, we study the actions of NGF and mitogenic epidermal growth factor (EGF) in rat pheochromocytoma (PC12) cells. Through a network of intermediate signaling proteins, each of these growth factors stimulates extracellular regulated kinase (Erk) phosphorylation with distinct dynamical profiles. Using our modeling approach, we are able to predict the influence of specific signaling modules in determining the integrated cellular response to the two growth factors. Our methods also raise some interesting insights into the design and possible evolution of cellular systems, highlighting an inherent property of these systems that we call 'sloppiness.'

The figures in the paper show results from computations performed over an ensemble of all parameter sets that fit the available data. This file contains only the best fit parameters. The full ensemble of parameters is available at <http://www.lassp.cornell.edu/sethna/GeneDynamics/PC12DataFiles/> (Also, the best-fit parameter set produces a curve for DN Rap1 that is less „peakish,, than the ensemble average.)

The conversion factors for EGF and NGF concentrations account for their molecular weights and the density of cells in the culture dish. These concentrations are saturating, so the exact values are not critical.

Because the Erk data fit to measure only fold changes in activity, there is no absolute scale for the y-axes. Thus the curves from this file have different magnitudes than those published.

To reproduce the figures from the paper:

2a) For EGF stimulation, set the initial concentration of EGF to  $100 \text{ ng/ml} * 100020 \text{ (molecule/cell)/(ng/ml)}$   
= 10002000.

For NGF stimulation, set the initial concentration of NGF to  $50 \text{ ng/ml} * 4560 \text{ (molecule/cell)/(ng/ml)}$   
= 456000

5a) To simulate LY294002 addition, set  $k_{PI3KRas}$  and  $k_{PI3K}$  to 0.

5b) To simulate a dominant negative Rap1, set  $k_{Rap1ToBraf}$  to 0.

To simulate a dominant negative Ras, set  $k_{RasToRaf1}$  and  $k_{PI3KRas}$  to 0.

Almost all the data fit with this model by the authors are from Western blots. Given the uncertainties in antibody effectiveness and other factors, one can't a priori derive a conversion between the arbitrary units for a given set of data and molecules per cell. So the authors used an adjustable

„scalefactor,, that converts between molecules per cell and Western blotunits.

For the EGF stimulation data in figure 2a) the scale factorconversion is  $1.414\text{e-}05$  (U/mg)/(molecule/cell).  
For the NGFstimulation data in figure 2a) it is  $7.135\text{e-}06$ (U/mg)/(molecule/cell).

This model is hosted on [BioModels Database](#) and identified by: [BIOMD0000000033](#).

To cite BioModels Database, please use: [BioModels Database: An enhanced, curated and annotated resource for published quantitative kinetic models](#).

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## 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 substance

**Name** item (default)

**Definition** item

### 2.2 Unit time

**Name** minute (default)

**Definition** 60 s

### 2.3 Unit volume

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

**Definition** l

### 2.4 Unit area

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

**Definition**  $\text{m}^2$

### 2.5 Unit length

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

**Definition** m

### 3 Compartment

This model contains one compartment.

Table 2: Properties of all compartments.

Id	Name	SBO	Spatial Dimensions	Size	Unit	Constant	Outside
cell			3	1	litre	<input checked="" type="checkbox"/>	

#### 3.1 Compartment `cell`

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

## 4 Species

This model contains 32 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
EGF		cell	$\text{item} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
NGF		cell	$\text{item} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
freeEGFReceptor		cell	$\text{item} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
boundEGFReceptor		cell	$\text{item} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
freeNGFReceptor		cell	$\text{item} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
boundNGFReceptor		cell	$\text{item} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
SosInactive		cell	$\text{item} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
SosActive		cell	$\text{item} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
P90RskInactive		cell	$\text{item} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
P90RskActive		cell	$\text{item} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
RasInactive		cell	$\text{item} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
RasActive		cell	$\text{item} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
RasGapActive		cell	$\text{item} \cdot \text{l}^{-1}$	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Raf1Inactive		cell	$\text{item} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
Raf1Active		cell	$\text{item} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
BRafInactive		cell	$\text{item} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
BRafActive		cell	$\text{item} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
MekInactive		cell	$\text{item} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
MekActive		cell	$\text{item} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
ErkInactive		cell	$\text{item} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
ErkActive		cell	$\text{item} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
PI3KInactive		cell	$\text{item} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>

Id	Name	Compartment	Derived Unit	Constant	Boundary Condi- tion
PI3KActive		cell	$\text{item} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
AktInactive		cell	$\text{item} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
AktActive		cell	$\text{item} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
C3GInactive		cell	$\text{item} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
C3GActive		cell	$\text{item} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
Rap1Inactive		cell	$\text{item} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
Rap1Active		cell	$\text{item} \cdot \text{l}^{-1}$	<input type="checkbox"/>	<input type="checkbox"/>
RapGapActive		cell	$\text{item} \cdot \text{l}^{-1}$	<input checked="" type="checkbox"/>	<input type="checkbox"/>
PP2AActive		cell	$\text{item} \cdot \text{l}^{-1}$	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Raf1PPtase		cell	$\text{item} \cdot \text{l}^{-1}$	<input checked="" type="checkbox"/>	<input type="checkbox"/>

## 5 Parameters

This model contains 48 global parameters.

Table 4: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
krbEGF			$2.18503 \cdot 10^{-5}$		✓
kruEGF			0.012		✓
krbNGF			$1.38209 \cdot 10^{-7}$		✓
kruNGF			0.007		✓
kEGF			694.731		✓
KmEGF			6086070.000		✓
kNGF			389.428		✓
KmNGF			2112.660		✓
kdSos			1611.970		✓
KmdSos			896896.000		✓
kSos			32.344		✓
KmSos			35954.300		✓
kRasGap			1509.360		✓
KmRasGap			1432410.000		✓
kRasToRaf1			0.884		✓
KmRasToRaf1			62464.600		✓
kpRaf1			185.759		✓
KmpRaf1			4768350.000		✓
kpBRaf			125.089		✓
KmpBRaf			157948.000		✓
kdMek			2.832		✓
KmdMek			518753.000		✓
kpMekCytoplasmic			9.854		✓
KmpMekCytoplasmic			1007340.000		✓
kdErk			8.891		✓
KmdErk			3496490.000		✓
kpP90Rsk			0.021		✓
KmpP90Rsk			763523.000		✓
kPI3K			10.674		✓
KmPI3K			184912.000		✓
kPI3KRas			0.077		✓
KmPI3KRas			272056.000		✓
kAkt			0.057		✓
KmAkt			653951.000		✓
kdRaf1ByAkt			15.121		✓
KmRaf1ByAkt			119355.000		✓
kC3GNGF			146.912		✓

Id	Name	SBO	Value	Unit	Constant
KmC3GNGF			12876.200		<input checked="" type="checkbox"/>
kC3G			1.401		<input checked="" type="checkbox"/>
KmC3G			10965.600		<input checked="" type="checkbox"/>
kRapGap			27.265		<input checked="" type="checkbox"/>
KmRapGap			295990.000		<input checked="" type="checkbox"/>
kRap1ToBRaf			2.210		<input checked="" type="checkbox"/>
KmRap1ToBRaf			1025460.000		<input checked="" type="checkbox"/>
kdRaf1			0.126		<input checked="" type="checkbox"/>
KmdRaf1			1061.710		<input checked="" type="checkbox"/>
kdbRaf			441.287		<input checked="" type="checkbox"/>
KmdBRaf			$1.08795 \cdot 10^7$		<input checked="" type="checkbox"/>



## 6 Reactions

This model contains 26 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

Nº	Id	Name	Reaction Equation	SBO
1	EGFBindingReaction	EGF binding	$\text{EGF} + \text{freeEGFReceptor} \longrightarrow \text{boundEGFReceptor}$	
2	EGFUnbindingReaction	EGF unbinding	$\text{boundEGFReceptor} \longrightarrow \text{EGF} + \text{freeEGFReceptor}$	
3	NGFBindingReaction	NGF binding	$\text{NGF} + \text{freeNGFReceptor} \longrightarrow \text{boundNGFReceptor}$	
4	NGFUnbindingReaction	NGF unbinding	$\text{boundNGFReceptor} \longrightarrow \text{NGF} + \text{freeNGFReceptor}$	
5	SosActivationByEGFReaction	Sos activation by EGF	$\text{SosInactive} \xrightleftharpoons{\text{boundEGFReceptor}} \text{SosActive}$	
6	SosActivationByNGFReaction	Sos activation by NGF	$\text{SosInactive} \xrightleftharpoons{\text{boundNGFReceptor}} \text{SosActive}$	
7	SosDeactivationReaction	Sos deactivation	$\text{SosActive} \xrightleftharpoons{\text{P90RskActive}} \text{SosInactive}$	
8	RasActivationReaction	Ras activation	$\text{RasInactive} \xrightleftharpoons{\text{SosActive}} \text{RasActive}$	
9	RasDeactivationReaction	Ras deactivation	$\text{RasActive} \xrightleftharpoons{\text{RasGapActive}} \text{RasInactive}$	
10	Raf1ByRasActivationReaction	Raf1 activation by Ras	$\text{Raf1Inactive} \xrightleftharpoons{\text{RasActive}} \text{Raf1Active}$	
11	MekbyRaf1ActivationReaction	Mek activation by Raf1	$\text{MekInactive} \xrightleftharpoons{\text{Raf1Active}} \text{MekActive}$	
12	MekbyBRafActivationReaction	Mek activation by B-Raf	$\text{MekInactive} \xrightleftharpoons{\text{BRafActive}} \text{MekActive}$	
13	ErkActivationReaction	Erk activation	$\text{ErkInactive} \xrightleftharpoons{\text{MekActive}} \text{ErkActive}$	
14	MekDeactivationReaction	Mek deactivation	$\text{MekActive} \xrightleftharpoons{\text{PP2AActive}} \text{MekInactive}$	
15	ErkDeactivationReaction	Erk deactivation	$\text{ErkActive} \xrightleftharpoons{\text{PP2AActive}} \text{ErkInactive}$	
16	Raf1byPPtaseDeactivationReaction	Raf1 deactivation by PPase	$\text{Raf1Active} \xrightleftharpoons{\text{Raf1PPtase}} \text{Raf1Inactive}$	

Nº	Id	Name	Reaction Equation	SBO
17	P90RskActivationReaction	P90Rsk activation	$\text{P90RskInactive} \xrightleftharpoons{\text{ErkActive}} \text{P90RskActive}$	
18	PI3KbyEGFRActivationReaction	PI3K activation by EGFR	$\text{PI3KInactive} \xrightleftharpoons{\text{boundEGFReceptor}} \text{PI3KActive}$	
19	PI3KbyRasActivationReaction	PI3K activation by Ras	$\text{PI3KInactive} \xrightleftharpoons{\text{RasActive}} \text{PI3KActive}$	
20	AktActivationReaction	Akt activation	$\text{AktInactive} \xrightleftharpoons{\text{PI3KActive}} \text{AktActive}$	
21	Raf1ByAktDeactivationReaction	Raf1 deactivation by Akt	$\text{Raf1Active} \xrightleftharpoons{\text{AktActive}} \text{Raf1Inactive}$	
22	C3GActivationReaction	C3G activation	$\text{C3GInactive} \xrightleftharpoons{\text{boundNGFReceptor}} \text{C3GActive}$	
23	Rap1ActivationReaction	Rap1 activation	$\text{Rap1Inactive} \xrightleftharpoons{\text{C3GActive}} \text{Rap1Active}$	
24	Rap1DeactivationReaction	Rap1 deactivation	$\text{Rap1Active} \xrightleftharpoons{\text{RapGapActive}} \text{Rap1Inactive}$	
25	BRafByRap1ActivationReaction	BRaf activation by Rap1	$\text{BRafInactive} \xrightleftharpoons{\text{Rap1Active}} \text{BRafActive}$	
26	BRafbyPPtaseDeactivationReaction	BRaf deactivation by PPase	$\text{BRafActive} \xrightleftharpoons{\text{Raf1PPtase}} \text{BRafInactive}$	

## 6.1 Reaction `EGFBindingReaction`

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

**Name** EGF binding

### Reaction equation



### Reactants

Table 6: Properties of each reactant.

Id	Name	SBO
EGF		
freeEGFReceptor		

### Product

Table 7: Properties of each product.

Id	Name	SBO
boundEGFReceptor		

### Kinetic Law

**Derived unit** contains undeclared units

$$v_1 = \text{vol}(\text{cell}) \cdot \text{krbEGF} \cdot [\text{EGF}] \cdot [\text{freeEGFReceptor}] \quad (2)$$

## 6.2 Reaction `EGFUnbindingReaction`

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

**Name** EFG unbinding

### Reaction equation



### Reactant

Table 8: Properties of each reactant.

Id	Name	SBO
boundEGFReceptor		

## Products

Table 9: Properties of each product.

Id	Name	SBO
EGF		
freeEGFReceptor		

## Kinetic Law

**Derived unit** contains undeclared units

$$v_2 = \text{vol}(\text{cell}) \cdot \text{kruEGF} \cdot [\text{boundEGFReceptor}] \quad (4)$$

## 6.3 Reaction NGFBindingReaction

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

**Name** NGF binding

## Reaction equation



## Reactants

Table 10: Properties of each reactant.

Id	Name	SBO
NGF		
freeNGFReceptor		

## Product

Table 11: Properties of each product.

Id	Name	SBO
boundNGFReceptor		

**Kinetic Law****Derived unit** contains undeclared units

$$v_3 = \text{krbNGF} \cdot [\text{NGF}] \cdot [\text{freeNGFReceptor}] \cdot \text{vol}(\text{cell}) \quad (6)$$

**6.4 Reaction** NGFUnbindingReaction

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

**Name** NGF unbinding**Reaction equation****Reactant**

Table 12: Properties of each reactant.

Id	Name	SBO
boundNGFReceptor		

**Products**

Table 13: Properties of each product.

Id	Name	SBO
NGF		
freeNGFReceptor		

**Kinetic Law****Derived unit** contains undeclared units

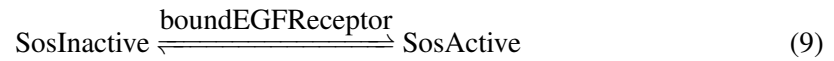
$$v_4 = \text{kruNGF} \cdot [\text{boundNGFReceptor}] \cdot \text{vol}(\text{cell}) \quad (8)$$

## 6.5 Reaction `SosActivationByEGFReaction`

This is a reversible reaction of one reactant forming one product influenced by one modifier.

**Name** SOS activation by EGF

### Reaction equation



### Reactant

Table 14: Properties of each reactant.

Id	Name	SBO
SosInactive		

### Modifier

Table 15: Properties of each modifier.

Id	Name	SBO
boundEGFReceptor		

### Product

Table 16: Properties of each product.

Id	Name	SBO
SosActive		

### Kinetic Law

**Derived unit** contains undeclared units

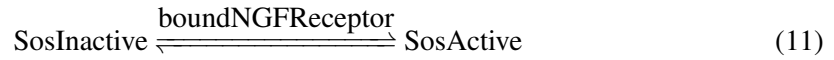
$$v_5 = \text{vol}(\text{cell}) \cdot \frac{k_{\text{EGF}} \cdot [\text{boundEGFReceptor}] \cdot [\text{SosInactive}]}{[\text{SosInactive}] + K_{\text{mEGF}}} \quad (10)$$

## 6.6 Reaction `SosActivationByNGFReaction`

This is a reversible reaction of one reactant forming one product influenced by one modifier.

**Name** SOS activation by NGF

## Reaction equation



## Reactant

Table 17: Properties of each reactant.

Id	Name	SBO
SosInactive		

## Modifier

Table 18: Properties of each modifier.

Id	Name	SBO
boundNGFReceptor		

## Product

Table 19: Properties of each product.

Id	Name	SBO
SosActive		

## Kinetic Law

**Derived unit** contains undeclared units

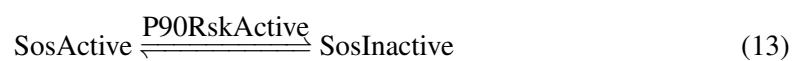
$$v_6 = \text{vol}(\text{cell}) \cdot \frac{k_{\text{NGF}} \cdot [\text{boundNGFReceptor}] \cdot [\text{SosInactive}]}{[\text{SosInactive}] + K_{\text{mNGF}}} \quad (12)$$

## 6.7 Reaction SosDeactivationReaction

This is a reversible reaction of one reactant forming one product influenced by one modifier.

**Name** SOS deactivation

## Reaction equation



## Reactant

Table 20: Properties of each reactant.

Id	Name	SBO
SosActive		

## Modifier

Table 21: Properties of each modifier.

Id	Name	SBO
P90RskActive		

## Product

Table 22: Properties of each product.

Id	Name	SBO
SosInactive		

## Kinetic Law

**Derived unit** contains undeclared units

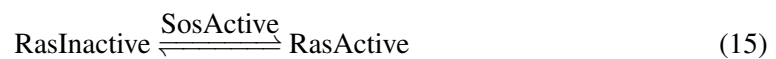
$$v_7 = \text{vol}(\text{cell}) \cdot \frac{\text{kdSos} \cdot [\text{P90RskActive}] \cdot [\text{SosActive}]}{[\text{SosActive}] + \text{KmdSos}} \quad (14)$$

## 6.8 Reaction `RasActivationReaction`

This is a reversible reaction of one reactant forming one product influenced by one modifier.

**Name** Ras activation

### Reaction equation



## Reactant



Table 23: Properties of each reactant.

Id	Name	SBO
RasInactive		

## Modifier

Table 24: Properties of each modifier.

Id	Name	SBO
SosActive		

## Product

Table 25: Properties of each product.

Id	Name	SBO
RasActive		

## Kinetic Law

**Derived unit** contains undeclared units

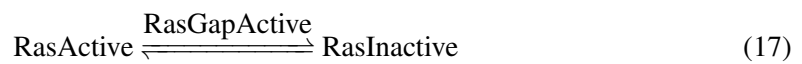
$$v_8 = \text{vol}(\text{cell}) \cdot \frac{k_{\text{Sos}} \cdot [\text{SosActive}] \cdot [\text{RasInactive}]}{[\text{RasInactive}] + K_{\text{mSos}}} \quad (16)$$

## 6.9 Reaction RasDeactivationReaction

This is a reversible reaction of one reactant forming one product influenced by one modifier.

**Name** Ras deactivation

### Reaction equation



## Reactant

Table 26: Properties of each reactant.

Id	Name	SBO
RasActive		

## Modifier

Table 27: Properties of each modifier.

Id	Name	SBO
RasGapActive		

## Product

Table 28: Properties of each product.

Id	Name	SBO
RasInactive		

## Kinetic Law

**Derived unit** contains undeclared units

$$v_9 = \text{vol}(\text{cell}) \cdot \frac{k_{\text{RasGap}} \cdot [\text{RasGapActive}] \cdot [\text{RasActive}]}{[\text{RasActive}] + K_{\text{mRasGap}}} \quad (18)$$

### 6.10 Reaction [Raf1ByRasActivationReaction](#)

This is a reversible reaction of one reactant forming one product influenced by one modifier.

**Name** Raf1 activation by Ras

#### Reaction equation



## Reactant

Table 29: Properties of each reactant.

Id	Name	SBO
Raf1Inactive		

## Modifier

Table 30: Properties of each modifier.

Id	Name	SBO
RasActive		

## Product

Table 31: Properties of each product.

Id	Name	SBO
Raf1Active		

## Kinetic Law

**Derived unit** contains undeclared units

$$v_{10} = \text{vol}(\text{cell}) \cdot \frac{k_{\text{RasToRaf1}} \cdot [\text{RasActive}] \cdot [\text{Raf1Inactive}]}{[\text{Raf1Inactive}] + K_{\text{mRasToRaf1}}} \quad (20)$$

### 6.11 Reaction [MekbyRaf1ActivationReaction](#)

This is a reversible reaction of one reactant forming one product influenced by one modifier.

**Name** Mek activation by Raf1

#### Reaction equation



## Reactant

Table 32: Properties of each reactant.

Id	Name	SBO
MekInactive		

## Modifier

Table 33: Properties of each modifier.

Id	Name	SBO
Raf1Active		

## Product

Table 34: Properties of each product.

Id	Name	SBO
MekActive		

## Kinetic Law

**Derived unit** contains undeclared units

$$v_{11} = \text{vol}(\text{cell}) \cdot \frac{\text{kpRaf1} \cdot [\text{Raf1Active}] \cdot [\text{MekInactive}]}{[\text{MekInactive}] + \text{KmpRaf1}} \quad (22)$$

### 6.12 Reaction `MekbyBRafActivationReaction`

This is a reversible reaction of one reactant forming one product influenced by one modifier.

**Name** Mek activation by B-Raf

#### Reaction equation



## Reactant

Table 35: Properties of each reactant.

Id	Name	SBO
MekInactive		

## Modifier

Table 36: Properties of each modifier.

Id	Name	SBO
BRafActive		

## Product

Table 37: Properties of each product.

Id	Name	SBO
MekActive		

## Kinetic Law

**Derived unit** contains undeclared units

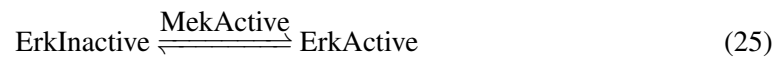
$$v_{12} = \text{vol}(\text{cell}) \cdot \frac{\text{kpBRaf} \cdot [\text{BRafActive}] \cdot [\text{MekInactive}]}{[\text{MekInactive}] + \text{KmpBRaf}} \quad (24)$$

### 6.13 Reaction `ErkActivationReaction`

This is a reversible reaction of one reactant forming one product influenced by one modifier.

**Name** Erk activation

#### Reaction equation



## Reactant

Table 38: Properties of each reactant.

Id	Name	SBO
ErkInactive		

## Modifier

Table 39: Properties of each modifier.

Id	Name	SBO
MekActive		

## Product

Table 40: Properties of each product.

Id	Name	SBO
ErkActive		

## Kinetic Law

**Derived unit** contains undeclared units

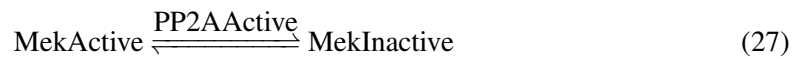
$$v_{13} = \text{vol}(\text{cell}) \cdot \frac{\text{kpMekCytoplasmic} \cdot [\text{MekActive}] \cdot [\text{ErkInactive}]}{[\text{ErkInactive}] + \text{KmpMekCytoplasmic}} \quad (26)$$

### 6.14 Reaction `MekDeactivationReaction`

This is a reversible reaction of one reactant forming one product influenced by one modifier.

**Name** Mek deactivation

#### Reaction equation



## Reactant

Table 41: Properties of each reactant.

Id	Name	SBO
MekActive		

## Modifier

Table 42: Properties of each modifier.

Id	Name	SBO
PP2AActive		

## Product

Table 43: Properties of each product.

Id	Name	SBO
MekInactive		

## Kinetic Law

**Derived unit** contains undeclared units

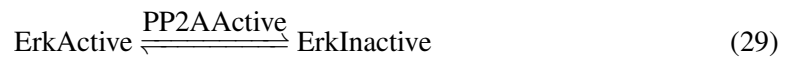
$$v_{14} = \text{vol}(\text{cell}) \cdot \frac{\text{kdMek} \cdot [\text{PP2AActive}] \cdot [\text{MekActive}]}{[\text{MekActive}] + \text{KmdMek}} \quad (28)$$

### 6.15 Reaction ErkDeactivationReaction

This is a reversible reaction of one reactant forming one product influenced by one modifier.

**Name** Erk deactivation

#### Reaction equation



## Reactant

Table 44: Properties of each reactant.

Id	Name	SBO
ErkActive		

## Modifier

Table 45: Properties of each modifier.

Id	Name	SBO
PP2AActive		

## Product

Table 46: Properties of each product.

Id	Name	SBO
ErkInactive		

## Kinetic Law

**Derived unit** contains undeclared units

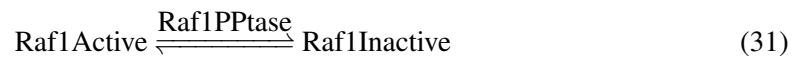
$$v_{15} = \text{vol}(\text{cell}) \cdot \frac{\text{kdErk} \cdot [\text{PP2AActive}] \cdot [\text{ErkActive}]}{[\text{ErkActive}] + \text{KmdErk}} \quad (30)$$

### 6.16 Reaction [Raf1byPPtaseDeactivationReaction](#)

This is a reversible reaction of one reactant forming one product influenced by one modifier.

**Name** Raf1 deactivation by PPase

#### Reaction equation



## Reactant



Table 47: Properties of each reactant.

Id	Name	SBO
Raf1Active		

## Modifier

Table 48: Properties of each modifier.

Id	Name	SBO
Raf1PPtase		

## Product

Table 49: Properties of each product.

Id	Name	SBO
Raf1Inactive		

## Kinetic Law

**Derived unit** contains undeclared units

$$v_{16} = \text{vol}(\text{cell}) \cdot \frac{\text{kdRaf1} \cdot [\text{Raf1PPtase}] \cdot [\text{Raf1Active}]}{[\text{Raf1Active}] + \text{KmdRaf1}} \quad (32)$$

### 6.17 Reaction P90RskActivationReaction

This is a reversible reaction of one reactant forming one product influenced by one modifier.

**Name** P90Rsk activation

#### Reaction equation



## Reactant

Table 50: Properties of each reactant.

Id	Name	SBO
P90RskInactive		

## Modifier

Table 51: Properties of each modifier.

Id	Name	SBO
ErkActive		

## Product

Table 52: Properties of each product.

Id	Name	SBO
P90RskActive		

## Kinetic Law

**Derived unit** contains undeclared units

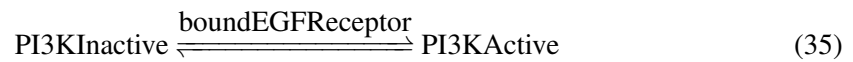
$$v_{17} = \text{vol}(\text{cell}) \cdot \frac{k_{\text{pP90Rsk}} \cdot [\text{ErkActive}] \cdot [\text{P90RskInactive}]}{[\text{P90RskInactive}] + K_{\text{mpP90Rsk}}} \quad (34)$$

### 6.18 Reaction `PI3KbyEGFRActivationReaction`

This is a reversible reaction of one reactant forming one product influenced by one modifier.

**Name** PI3K activation by EGFR

#### Reaction equation



## Reactant

Table 53: Properties of each reactant.

Id	Name	SBO
PI3KInactive		

## Modifier

Table 54: Properties of each modifier.

Id	Name	SBO
boundEGFReceptor		

## Product

Table 55: Properties of each product.

Id	Name	SBO
PI3KActive		

## Kinetic Law

**Derived unit** contains undeclared units

$$v_{18} = \text{vol}(\text{cell}) \cdot \frac{k_{\text{PI3K}} \cdot [\text{boundEGFReceptor}] \cdot [\text{PI3KInactive}]}{[\text{PI3KInactive}] + K_{\text{mPI3K}}} \quad (36)$$

### 6.19 Reaction [PI3KbyRasActivationReaction](#)

This is a reversible reaction of one reactant forming one product influenced by one modifier.

**Name** PI3K activation by Ras

#### Reaction equation



## Reactant

Table 56: Properties of each reactant.

Id	Name	SBO
PI3KInactive		

## Modifier

Table 57: Properties of each modifier.

Id	Name	SBO
RasActive		

## Product

Table 58: Properties of each product.

Id	Name	SBO
PI3KActive		

## Kinetic Law

**Derived unit** contains undeclared units

$$v_{19} = \text{vol}(\text{cell}) \cdot \frac{k_{\text{PI3KRas}} \cdot [\text{RasActive}] \cdot [\text{PI3KInactive}]}{[\text{PI3KInactive}] + K_{\text{mPI3KRas}}} \quad (38)$$

## 6.20 Reaction AktActivationReaction

This is a reversible reaction of one reactant forming one product influenced by one modifier.

**Name** Akt activation

### Reaction equation



## Reactant

Table 59: Properties of each reactant.

Id	Name	SBO
AktInactive		

## Modifier

Table 60: Properties of each modifier.

Id	Name	SBO
PI3KActive		

## Product

Table 61: Properties of each product.

Id	Name	SBO
AktActive		

## Kinetic Law

**Derived unit** contains undeclared units

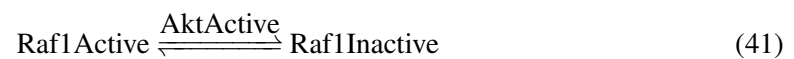
$$v_{20} = \text{vol}(\text{cell}) \cdot \frac{k_{\text{Akt}} \cdot [\text{PI3KActive}] \cdot [\text{AktInactive}]}{[\text{AktInactive}] + K_{\text{mAkt}}} \quad (40)$$

### 6.21 Reaction [Raf1ByAktDeactivationReaction](#)

This is a reversible reaction of one reactant forming one product influenced by one modifier.

**Name** Raf1 deactivation by Akt

#### Reaction equation



## Reactant

Table 62: Properties of each reactant.

Id	Name	SBO
Raf1Active		

## Modifier

Table 63: Properties of each modifier.

Id	Name	SBO
AktActive		

## Product

Table 64: Properties of each product.

Id	Name	SBO
Raf1Inactive		

## Kinetic Law

**Derived unit** contains undeclared units

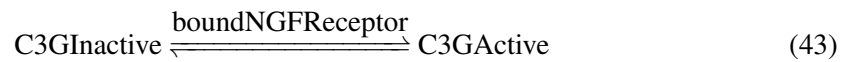
$$v_{21} = \text{vol}(\text{cell}) \cdot \frac{\text{kdRaf1ByAkt} \cdot [\text{AktActive}] \cdot [\text{Raf1Active}]}{[\text{Raf1Active}] + \text{KmRaf1ByAkt}} \quad (42)$$

### 6.22 Reaction C3GActivationReaction

This is a reversible reaction of one reactant forming one product influenced by one modifier.

**Name** C3G activation

#### Reaction equation



## Reactant

Table 65: Properties of each reactant.

Id	Name	SBO
C3GInactive		

## Modifier

Table 66: Properties of each modifier.

Id	Name	SBO
boundNGFReceptor		

## Product

Table 67: Properties of each product.

Id	Name	SBO
C3GActive		

## Kinetic Law

**Derived unit** contains undeclared units

$$v_{22} = \text{vol}(\text{cell}) \cdot \frac{k_{\text{C3GNGF}} \cdot [\text{boundNGFReceptor}] \cdot [\text{C3GInactive}]}{[\text{C3GInactive}] + K_{\text{mC3GNGF}}} \quad (44)$$

### 6.23 Reaction `Rap1ActivationReaction`

This is a reversible reaction of one reactant forming one product influenced by one modifier.

**Name** Rap1 activation

#### Reaction equation



## Reactant

Table 68: Properties of each reactant.

Id	Name	SBO
Rap1Inactive		

## Modifier

Table 69: Properties of each modifier.

Id	Name	SBO
C3GActive		

## Product

Table 70: Properties of each product.

Id	Name	SBO
Rap1Active		

## Kinetic Law

**Derived unit** contains undeclared units

$$v_{23} = \text{vol}(\text{cell}) \cdot \frac{k_{\text{C3G}} \cdot [\text{C3GActive}] \cdot [\text{Rap1Inactive}]}{[\text{Rap1Inactive}] + K_{\text{mC3G}}} \quad (46)$$

### 6.24 Reaction `Rap1DeactivationReaction`

This is a reversible reaction of one reactant forming one product influenced by one modifier.

**Name** Rap1 deactivation

#### Reaction equation



## Reactant



Table 71: Properties of each reactant.

Id	Name	SBO
Rap1Active		

## Modifier

Table 72: Properties of each modifier.

Id	Name	SBO
RapGapActive		

## Product

Table 73: Properties of each product.

Id	Name	SBO
Rap1Inactive		

## Kinetic Law

**Derived unit** contains undeclared units

$$v_{24} = \text{vol}(\text{cell}) \cdot \frac{k_{\text{RapGap}} \cdot [\text{RapGapActive}] \cdot [\text{Rap1Active}]}{[\text{Rap1Active}] + K_{\text{mRapGap}}} \quad (48)$$

### 6.25 Reaction BRafByRap1ActivationReaction

This is a reversible reaction of one reactant forming one product influenced by one modifier.

**Name** BRaf activation by Rap1

#### Reaction equation



## Reactant

Table 74: Properties of each reactant.

Id	Name	SBO
	BRafInactive	

## Modifier

Table 75: Properties of each modifier.

Id	Name	SBO
	Rap1Active	

## Product

Table 76: Properties of each product.

Id	Name	SBO
	BRafActive	

## Kinetic Law

**Derived unit** contains undeclared units

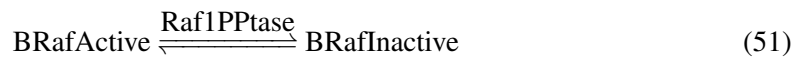
$$v_{25} = \text{vol}(\text{cell}) \cdot \frac{k_{\text{Rap1ToBRaf}} \cdot [\text{Rap1Active}] \cdot [\text{BRafInactive}]}{[\text{BRafInactive}] + K_{\text{mRap1ToBRaf}}} \quad (50)$$

### 6.26 Reaction BRafbyPPtaseDeactivationReaction

This is a reversible reaction of one reactant forming one product influenced by one modifier.

**Name** BRaf deactivation by PPase

#### Reaction equation



## Reactant

Table 77: Properties of each reactant.

Id	Name	SBO
BRafActive		

## Modifier

Table 78: Properties of each modifier.

Id	Name	SBO
Raf1PPtase		

## Product

Table 79: Properties of each product.

Id	Name	SBO
BRafInactive		

## Kinetic Law

**Derived unit** contains undeclared units

$$v_{26} = \text{vol}(\text{cell}) \cdot \frac{\text{kdBRaf} \cdot [\text{Raf1PPtase}] \cdot [\text{BRafActive}]}{[\text{BRafActive}] + \text{KmdBRaf}} \quad (52)$$

## 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 EGF

**Initial concentration**  $1.0002 \cdot 10^7 \text{ item} \cdot \text{l}^{-1}$

This species takes part in two reactions (as a reactant in [EGFBindingReaction](#) and as a product in [EGFUnbindingReaction](#)).

$$\frac{d}{dt}\text{EGF} = v_2 - v_1 \quad (53)$$

## 7.2 Species NGF

**Initial concentration** 456000 item · l<sup>-1</sup>

This species takes part in two reactions (as a reactant in [NGFBindingReaction](#) and as a product in [NGFUnbindingReaction](#)).

$$\frac{d}{dt}\text{NGF} = v_4 - v_3 \quad (54)$$

## 7.3 Species freeEGFReceptor

**Initial concentration** 80000 item · l<sup>-1</sup>

This species takes part in two reactions (as a reactant in [EGFBindingReaction](#) and as a product in [EGFUnbindingReaction](#)).

$$\frac{d}{dt}\text{freeEGFReceptor} = v_2 - v_1 \quad (55)$$

## 7.4 Species boundEGFReceptor

**Initial concentration** 0 item · l<sup>-1</sup>

This species takes part in four reactions (as a reactant in [EGFUnbindingReaction](#) and as a product in [EGFBindingReaction](#) and as a modifier in [SosActivationByEGFReaction](#), [PI3KbyEGFActivationReaction](#)).

$$\frac{d}{dt}\text{boundEGFReceptor} = v_1 - v_2 \quad (56)$$

## 7.5 Species freeNGFReceptor

**Initial concentration** 10000 item · l<sup>-1</sup>

This species takes part in two reactions (as a reactant in [NGFBindingReaction](#) and as a product in [NGFUnbindingReaction](#)).

$$\frac{d}{dt}\text{freeNGFReceptor} = v_4 - v_3 \quad (57)$$

## 7.6 Species boundNGFReceptor

**Initial concentration**  $0 \text{ item} \cdot \text{l}^{-1}$

This species takes part in four reactions (as a reactant in [NGFUnbindingReaction](#) and as a product in [NGFBindingReaction](#) and as a modifier in [SosActivationByNGFReaction](#), [C3GActivationReaction](#)).

$$\frac{d}{dt} \text{boundNGFReceptor} = v_3 - v_4 \quad (58)$$

## 7.7 Species SosInactive

**Initial concentration**  $120000 \text{ item} \cdot \text{l}^{-1}$

This species takes part in three reactions (as a reactant in [SosActivationByEGFReaction](#), [SosActivationByNGFReaction](#) and as a product in [SosDeactivationReaction](#)).

$$\frac{d}{dt} \text{SosInactive} = v_7 - v_5 - v_6 \quad (59)$$

## 7.8 Species SosActive

**Initial concentration**  $0 \text{ item} \cdot \text{l}^{-1}$

This species takes part in four reactions (as a reactant in [SosDeactivationReaction](#) and as a product in [SosActivationByEGFReaction](#), [SosActivationByNGFReaction](#) and as a modifier in [RasActivationReaction](#)).

$$\frac{d}{dt} \text{SosActive} = v_5 + v_6 - v_7 \quad (60)$$

## 7.9 Species P90RskInactive

**Initial concentration**  $120000 \text{ item} \cdot \text{l}^{-1}$

This species takes part in one reaction (as a reactant in [P90RskActivationReaction](#)).

$$\frac{d}{dt} \text{P90RskInactive} = -v_{17} \quad (61)$$

## 7.10 Species P90RskActive

**Initial concentration**  $0 \text{ item} \cdot \text{l}^{-1}$

This species takes part in two reactions (as a product in [P90RskActivationReaction](#) and as a modifier in [SosDeactivationReaction](#)).

$$\frac{d}{dt} \text{P90RskActive} = v_{17} \quad (62)$$

### 7.11 Species `RasInactive`

**Initial concentration** 120000 item · l<sup>-1</sup>

This species takes part in two reactions (as a reactant in `RasActivationReaction` and as a product in `RasDeactivationReaction`).

$$\frac{d}{dt}\text{RasInactive} = v_9 - v_8 \quad (63)$$

### 7.12 Species `RasActive`

**Initial concentration** 0 item · l<sup>-1</sup>

This species takes part in four reactions (as a reactant in `RasDeactivationReaction` and as a product in `RasActivationReaction` and as a modifier in `Raf1ByRasActivationReaction`, `PI3KbyRasActivationReaction`).

$$\frac{d}{dt}\text{RasActive} = v_8 - v_9 \quad (64)$$

### 7.13 Species `RasGapActive`

**Initial concentration** 120000 item · l<sup>-1</sup>

This species takes part in one reaction (as a modifier in `RasDeactivationReaction`).

$$\frac{d}{dt}\text{RasGapActive} = 0 \quad (65)$$

### 7.14 Species `Raf1Inactive`

**Initial concentration** 120000 item · l<sup>-1</sup>

This species takes part in three reactions (as a reactant in `Raf1ByRasActivationReaction` and as a product in `Raf1byPPtaseDeactivationReaction`, `Raf1ByAktDeactivationReaction`).

$$\frac{d}{dt}\text{Raf1Inactive} = v_{16} + v_{21} - v_{10} \quad (66)$$

### 7.15 Species `Raf1Active`

**Initial concentration** 0 item · l<sup>-1</sup>

This species takes part in four reactions (as a reactant in `Raf1byPPtaseDeactivationReaction`, `Raf1ByAktDeactivationReaction` and as a product in `Raf1ByRasActivationReaction` and as a modifier in `MekbyRaf1ActivationReaction`).

$$\frac{d}{dt}\text{Raf1Active} = v_{10} - v_{16} - v_{21} \quad (67)$$

### 7.16 Species BRafInactive

**Initial concentration** 120000 item · l<sup>-1</sup>

This species takes part in two reactions (as a reactant in [BRafByRap1ActivationReaction](#) and as a product in [BRafbyPPTaseDeactivationReaction](#)).

$$\frac{d}{dt}\text{BRafInactive} = v_{26} - v_{25} \quad (68)$$

### 7.17 Species BRafActive

**Initial concentration** 0 item · l<sup>-1</sup>

This species takes part in three reactions (as a reactant in [BRafbyPPTaseDeactivationReaction](#) and as a product in [BRafByRap1ActivationReaction](#) and as a modifier in [MekbyBRafActivationReaction](#)).

$$\frac{d}{dt}\text{BRafActive} = v_{25} - v_{26} \quad (69)$$

### 7.18 Species MekInactive

**Initial concentration** 600000 item · l<sup>-1</sup>

This species takes part in three reactions (as a reactant in [MekbyRaf1ActivationReaction](#), [MekbyBRafActivationReaction](#) and as a product in [MekDeactivationReaction](#)).

$$\frac{d}{dt}\text{MekInactive} = v_{14} - v_{11} - v_{12} \quad (70)$$

### 7.19 Species MekActive

**Initial concentration** 0 item · l<sup>-1</sup>

This species takes part in four reactions (as a reactant in [MekDeactivationReaction](#) and as a product in [MekbyRaf1ActivationReaction](#), [MekbyBRafActivationReaction](#) and as a modifier in [ErkActivationReaction](#)).

$$\frac{d}{dt}\text{MekActive} = v_{11} + v_{12} - v_{14} \quad (71)$$

### 7.20 Species ErkInactive

**Initial concentration** 600000 item · l<sup>-1</sup>

This species takes part in two reactions (as a reactant in [ErkActivationReaction](#) and as a product in [ErkDeactivationReaction](#)).

$$\frac{d}{dt}\text{ErkInactive} = v_{15} - v_{13} \quad (72)$$

### 7.21 Species `ErkActive`

**Initial concentration** 0 item · l<sup>-1</sup>

This species takes part in three reactions (as a reactant in `ErkDeactivationReaction` and as a product in `ErkActivationReaction` and as a modifier in `P90RskActivationReaction`).

$$\frac{d}{dt}\text{ErkActive} = v_{13} - v_{15} \quad (73)$$

### 7.22 Species `PI3KInactive`

**Initial concentration** 120000 item · l<sup>-1</sup>

This species takes part in two reactions (as a reactant in `PI3KbyEGFRActivationReaction`, `PI3KbyRasActivationReaction`).

$$\frac{d}{dt}\text{PI3KInactive} = -v_{18} - v_{19} \quad (74)$$

### 7.23 Species `PI3KActive`

**Initial concentration** 0 item · l<sup>-1</sup>

This species takes part in three reactions (as a product in `PI3KbyEGFRActivationReaction`, `PI3KbyRasActivationReaction` and as a modifier in `AktActivationReaction`).

$$\frac{d}{dt}\text{PI3KActive} = v_{18} + v_{19} \quad (75)$$

### 7.24 Species `AktInactive`

**Initial concentration** 120000 item · l<sup>-1</sup>

This species takes part in one reaction (as a reactant in `AktActivationReaction`).

$$\frac{d}{dt}\text{AktInactive} = -v_{20} \quad (76)$$

### 7.25 Species `AktActive`

**Initial concentration** 0 item · l<sup>-1</sup>

This species takes part in two reactions (as a product in `AktActivationReaction` and as a modifier in `Raf1ByAktDeactivationReaction`).

$$\frac{d}{dt}\text{AktActive} = v_{20} \quad (77)$$



### 7.26 Species C3GInactive

**Initial concentration** 120000 item · l<sup>-1</sup>

This species takes part in one reaction (as a reactant in [C3GActivationReaction](#)).

$$\frac{d}{dt}C3GInactive = -v_{22} \quad (78)$$

### 7.27 Species C3GActive

**Initial concentration** 0 item · l<sup>-1</sup>

This species takes part in two reactions (as a product in [C3GActivationReaction](#) and as a modifier in [Rap1ActivationReaction](#)).

$$\frac{d}{dt}C3GActive = v_{22} \quad (79)$$

### 7.28 Species Rap1Inactive

**Initial concentration** 120000 item · l<sup>-1</sup>

This species takes part in two reactions (as a reactant in [Rap1ActivationReaction](#) and as a product in [Rap1DeactivationReaction](#)).

$$\frac{d}{dt}Rap1Inactive = v_{24} - v_{23} \quad (80)$$

### 7.29 Species Rap1Active

**Initial concentration** 0 item · l<sup>-1</sup>

This species takes part in three reactions (as a reactant in [Rap1DeactivationReaction](#) and as a product in [Rap1ActivationReaction](#) and as a modifier in [BRafByRap1ActivationReaction](#)).

$$\frac{d}{dt}Rap1Active = v_{23} - v_{24} \quad (81)$$

### 7.30 Species RapGapActive

**Initial concentration** 120000 item · l<sup>-1</sup>

This species takes part in one reaction (as a modifier in [Rap1DeactivationReaction](#)).

$$\frac{d}{dt}RapGapActive = 0 \quad (82)$$

### 7.31 Species PP2AActive

**Initial concentration** 120000 item · l<sup>-1</sup>

This species takes part in two reactions (as a modifier in [MekDeactivationReaction](#), [ErkDeactivationReaction](#)

$$\frac{d}{dt} \text{PP2AActive} = 0 \quad (83)$$

### 7.32 Species Raf1PPtase

**Initial concentration** 120000 item · l<sup>-1</sup>

This species takes part in two reactions (as a modifier in [Raf1byPPtaseDeactivationReaction](#), [BRafbyPPtaseDeactivationReaction](#)).

$$\frac{d}{dt} \text{Raf1PPtase} = 0 \quad (84)$$

SBML2<sup>AT</sup>EX was developed by Andreas Dräger<sup>a</sup>, Hannes Planatscher<sup>a</sup>, Dieudonné M Wouamba<sup>a</sup>, Adrian Schröder<sup>a</sup>, Michael Hucka<sup>b</sup>, Lukas Endler<sup>c</sup>, Martin Golebiewski<sup>d</sup> and Andreas Zell<sup>a</sup>. Please see <http://www.ra.cs.uni-tuebingen.de/software/SBML2LaTeX> for more information.

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