SBML Model Report

Model name: “Kholodenko1999 - EGFR 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: Jacky L Snoep[1] and Lu Li[2] at November 23rd 2005 at 1:53 p. m. and last time modified at February 14th 2014 at 1:52 p. 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	23
events	0	constraints	0
reactions	25	function definitions	0
global parameters	0	unit definitions	1
rules	0	initial assignments	0

Model Notes

Kholodenko1999 - EGFR signaling

This model has been generated by **the JWS Online project by Jacky Snoep using PySCeS Run this model online at http://jjj.biochem.sun.ac.za**

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To cite JWS Online please refer to: Olivier, B.G. and Snoep, J.L. (2004) Web-based modelling using JWS Online , Bioinformatics, 20:2143-2144

This model is described in the article:Quantification of short term signaling by the epidermal growth factor receptor.Kholodenko BN, Demin OV, Moehren G, Hoek JBJ. Biol. Chem. 1999 Oct; 274(42): 30169-30181

Abstract:

During the past decade, our knowledge of molecular mechanisms involved in growth factor signaling has proliferated almost explosively. However, the kinetics and control of information transfer through signaling networks remain poorly understood. This paper combines experimental kinetic analysis and computational modeling of the short term pattern of cellular responses to epidermal growth factor (EGF) in isolated hepatocytes. The experimental data show transient tyrosine phosphorylation of the EGF receptor (EGFR) and transient or sustained response patterns in multiple signaling proteins targeted by EGFR. Transient responses exhibit pronounced maxima, reached within 15-30 s of EGF stimulation and followed by a decline to relatively low (quasi-steady-state) levels. In contrast to earlier suggestions, we demonstrate that the experimentally observed transients can be accounted for without requiring receptor-mediated activation of specific tyrosine phosphatases, following EGF stimulation. The kinetic model predicts how the cellular response is controlled by the relative levels and activity states of signaling proteins and under what conditions activation patterns are transient or sustained. EGFR signaling patterns appear to be robust with respect to variations in many elemental rate constants within the range of experimentally measured values. On the other hand, we specify which changes in the kinetic scheme, rate constants, and total amounts of molecular factors involved are incompatible with the experimentally observed kinetics of signal transfer. Quantitation of signaling network responses to growth factors allows us to assess how cells process information controlling their growth and differentiation.

The model correctly reproduces all the figures from the paper. The curation has been done using SBMLodeSolver.

This model is hosted on BioModels Database and identified by: BIOMD0000000048 .

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

Notes Default unit of substance redefined to 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
`compartment`	cytoplasm		3	$3 \cdot 10^{-12}$	l	☑	

3.1 Compartment `compartment`

This is a three dimensional compartment with a constant size of $3 \cdot 10^{-12}$ litre.

Name cytoplasm

Notes Default size of compartment is 1e-10 litre by comparison with the article.

4 Species

This model contains 23 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
EGF	Epidermal_Growth_Factor	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1}$	⊟	⊟
R	EGFR	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1}$	⊟	⊟
Ra	EGF_EGFR	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1}$	⊟	⊟
R2	(EGF_EGFR)2	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1}$	⊟	⊟
RP	(EGF_EGFR)2-P	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1}$	⊟	⊟
PLCg	PLCg	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1}$	⊟	⊟
RPLCg	(EGF_EGFR)2_PLCg	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1}$	⊟	⊟
RPLCgP	(EGF_EGFR)2_PLCg-P	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1}$	⊟	⊟
PLCgP	PLCg-P	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1}$	⊟	⊟
Grb	Grb2	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1}$	⊟	⊟
RG	(EGF_EGFR)2_Grb2	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1}$	⊟	⊟
SOS	SOS	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1}$	⊟	⊟
RGS	(EGF_EGFR)2_Grb2_SOS	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1}$	⊟	⊟
GS	Grb2_SOS	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1}$	⊟	⊟
Shc	Shc	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1}$	⊟	⊟
RSh	(EGF_EGFR)2_Shc	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1}$	⊟	⊟
RShP	(EGF_EGFR)_Shc-P	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1}$	⊟	⊟
ShP	Shc-P	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1}$	⊟	⊟
RShG	(EGF_EGFR)2_Shc_Grb2	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1}$	⊟	⊟
ShG	Shc_Grb2	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1}$	⊟	⊟
RShGS	(EGF_EGFR)2_Shc_Grb2_SOS	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1}$	⊟	⊟
ShGS	Shc_Grb2_SOS	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1}$	⊟	⊟

Id	Name	Compartment	Derived Unit	Constant	Boundary Condition
PLCgl	PLCgP-I	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1}$	⊟	⊟

5 Reactions

This model contains 25 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	v1	EGF_binds_to_EGFR	$R + EGF \rightleftharpoons Ra$	
2	v2	association_of_2_Ra_into_dimer	$2\,Ra \rightleftharpoons R2$	
3	v3	phosphorylation_of_R2	$R2 \rightleftharpoons RP$	
4	v4	dephosphorylation_of_RP	$RP \longrightarrow R2$	
5	v5	binding_of_PLCg_to_RP	$RP + PLCg \rightleftharpoons RPLCg$	
6	v6	phosphorylation_of_PLCg	$RPLCg \rightleftharpoons RPLCgP$	
7	v7	dissociation_of_RPLCgP	$RPLCgP \rightleftharpoons PLCgP + RP$	
8	v8	dephosphorylation_of_PLCgP	$PLCgP \longrightarrow PLCg$	
9	v9	binding_of_Grb2_to_RP	$Grb + RP \rightleftharpoons RG$	
10	v10	binding_of_SOS_to_RG	$RG + SOS \rightleftharpoons RGS$	
11	v11	dissociation_of_RGS	$RGS \rightleftharpoons GS + RP$	
12	v12	dissociation_of_GS	$GS \rightleftharpoons Grb + SOS$	
13	v13	binding_of_Shc_to_RP	$Shc + RP \rightleftharpoons RSh$	
14	v14	phosphorylation_of_RSh	$RSh \rightleftharpoons RShP$	
15	v15	dissociation_of_RShp	$RShP \rightleftharpoons RP + ShP$	
16	v16	dephosphorylation_of_ShP	$ShP \longrightarrow Shc$	
17	v17	binding_of_Grb2_to_RShP	$RShP + Grb \rightleftharpoons RShG$	
18	v18	dissociation_of_RShG	$RShG \rightleftharpoons ShG + RP$	
19	v19	binding_of_SOS_to_RShG	$SOS + RShG \rightleftharpoons RShGS$	
20	v20	dissociation_of_RShGS	$RShGS \rightleftharpoons ShGS + RP$	
21	v21	binding_of_Grb2_to_ShP	$Grb + ShP \rightleftharpoons ShG$	
22	v22	binding_of_SOS_to_ShG	$ShG + SOS \rightleftharpoons ShGS$	
23	v23	dissociation_of_ShGS	$ShGS \rightleftharpoons GS + ShP$	

№	Id	Name	Reaction Equation	SBO
24	v24	association_of_RShP_and_GS	$\mathrm{RShP} + \mathrm{GS} \rightleftharpoons \mathrm{RShGS}$	
25	v25	translocation_of_PLCgP	$\mathrm{PLCgP} \rightleftharpoons \mathrm{PLCgl}$	

5.1 Reaction v1

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

Name EGF_binds_to_EGFR

Reaction equation

$$\mathrm{R} + \mathrm{EGF} \rightleftharpoons \mathrm{Ra} \tag{1}$$

Reactants

Table 5: Properties of each reactant.

Id	Name	SBO
R	EGFR	
EGF	Epidermal_Growth_Factor	

Product

Table 6: Properties of each product.

Id	Name	SBO
Ra	EGF_EGFR	

Kinetic Law

Derived unit contains undeclared units

$$v_1 = (\mathrm{k1f} \cdot [\mathrm{R}] \cdot [\mathrm{EGF}] - \mathrm{k1b} \cdot [\mathrm{Ra}]) \cdot \mathrm{vol}\,(\mathrm{compartment}) \tag{2}$$

Table 7: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k1f			0.003		☑
k1b			0.060		☑

5.2 Reaction v2

This is a reversible reaction of one reactant forming one product.

Name association_of_2_Ra_into_dimer

Reaction equation

$$2\,\mathrm{Ra} \rightleftharpoons \mathrm{R2} \tag{3}$$

Reactant

Table 8: Properties of each reactant.

Id	Name	SBO
Ra	EGF_EGFR	

Product

Table 9: Properties of each product.

Id	Name	SBO
R2	(EGF_EGFR)2	

Kinetic Law

Derived unit contains undeclared units

$$v_2 = (\mathrm{k2f} \cdot [\mathrm{Ra}] \cdot [\mathrm{Ra}] - \mathrm{k2b} \cdot [\mathrm{R2}]) \cdot \mathrm{vol}\,(\mathrm{compartment}) \tag{4}$$

Table 10: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k2f			0.01		☑
k2b			0.10		☑

5.3 Reaction v3

This is a reversible reaction of one reactant forming one product.

Name phosphorylation_of_R2

Reaction equation

$$\mathrm{R2} \rightleftharpoons \mathrm{RP} \tag{5}$$

Reactant

Table 11: Properties of each reactant.

Id	Name	SBO
R2	(EGF_EGFR)2	

Product

Table 12: Properties of each product.

Id	Name	SBO
RP	(EGF_EGFR)2-P	

Kinetic Law

Derived unit contains undeclared units

$$v_3 = (\mathrm{k3f} \cdot [\mathrm{R2}] - \mathrm{k3b} \cdot [\mathrm{RP}]) \cdot \mathrm{vol}\,(\mathrm{compartment}) \tag{6}$$

Table 13: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k3f			1.00		☑
k3b			0.01		☑

5.4 Reaction v4

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

Name dephosphorylation_of_RP

Notes According to the artical, this dephosphorylation of RP should be irriversible.

Reaction equation

$$\mathrm{RP} \longrightarrow \mathrm{R2} \tag{7}$$

Reactant

Table 14: Properties of each reactant.

Id	Name	SBO
RP	(EGF_EGFR)2-P	

Id	Name	SBO

Product

Table 15: Properties of each product.

Id	Name	SBO
R2	(EGF_EGFR)2	

Kinetic Law

Derived unit contains undeclared units

$$v_4 = \frac{\mathrm{V4} \cdot [\mathrm{RP}]}{\mathrm{K4} + [\mathrm{RP}]} \cdot \mathrm{vol}\,(\mathrm{compartment}) \tag{8}$$

Table 16: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
V4			450.0		☑
K4			50.0		☑

5.5 Reaction v5

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

Name binding_of_PLCg_to_RP

Reaction equation

$$\mathrm{RP} + \mathrm{PLCg} \rightleftharpoons \mathrm{RPLCg} \tag{9}$$

Reactants

Table 17: Properties of each reactant.

Id	Name	SBO
RP	(EGF_EGFR)2-P	
PLCg	PLCg	

Product

Table 18: Properties of each product.

Id	Name	SBO
RPLCg	(EGF_EGFR)2_PLCg	

Kinetic Law

Derived unit contains undeclared units

$$v_5 = (\mathrm{k5f} \cdot [\mathrm{RP}] \cdot [\mathrm{PLCg}] - \mathrm{k5b} \cdot [\mathrm{RPLCg}]) \cdot \mathrm{vol}\,(\mathrm{compartment}) \tag{10}$$

Table 19: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k5f			0.06		☑
k5b			0.20		☑

5.6 Reaction v6

This is a reversible reaction of one reactant forming one product.

Name phosphorylation_of_PLCg

Reaction equation

$$\mathrm{RPLCg} \rightleftharpoons \mathrm{RPLCgP} \tag{11}$$

Reactant

Table 20: Properties of each reactant.

Id	Name	SBO
RPLCg	(EGF_EGFR)2_PLCg	

Product

Table 21: Properties of each product.

Id	Name	SBO
RPLCgP	(EGF_EGFR)2_PLCg-P	

Kinetic Law

Derived unit contains undeclared units

$$v_6 = (\text{k6f} \cdot [\text{RPLCg}] - \text{k6b} \cdot [\text{RPLCgP}]) \cdot \text{vol}(\text{compartment}) \tag{12}$$

Table 22: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k6f			1.00		☑
k6b			0.05		☑

5.7 Reaction v7

This is a reversible reaction of one reactant forming two products.

Name dissociation_of_RPLCgP

Reaction equation

$$\text{RPLCgP} \rightleftharpoons \text{PLCgP} + \text{RP} \tag{13}$$

Reactant

Table 23: Properties of each reactant.

Id	Name	SBO
RPLCgP	(EGF_EGFR)2_PLCg-P	

Products

Table 24: Properties of each product.

Id	Name	SBO
PLCgP	PLCg-P	
RP	(EGF_EGFR)2-P	

Kinetic Law

Derived unit contains undeclared units

$$v_7 = (\mathrm{k7f} \cdot [\mathrm{RPLCgP}] - \mathrm{k7b} \cdot [\mathrm{RP}] \cdot [\mathrm{PLCgP}]) \cdot \mathrm{vol}\,(\mathrm{compartment}) \tag{14}$$

Table 25: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k7f			0.300		☑
k7b			0.006		☑

5.8 Reaction v8

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

Name dephosphorylation_of_PLCgP

Notes Dephosphorylation is irriversible, according to article.

Reaction equation

$$\mathrm{PLCgP} \longrightarrow \mathrm{PLCg} \tag{15}$$

Reactant

Table 26: Properties of each reactant.

Id	Name	SBO
PLCgP	PLCg-P	

Product

Table 27: Properties of each product.

Id	Name	SBO
PLCg	PLCg	

Kinetic Law

Derived unit contains undeclared units

$$v_8 = \frac{\mathrm{V8} \cdot [\mathrm{PLCgP}]}{\mathrm{K8} + [\mathrm{PLCgP}]} \cdot \mathrm{vol}\,(\mathrm{compartment}) \tag{16}$$

Table 28: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
V8			1.0		☑
K8			100.0		☑

5.9 Reaction v9

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

Name binding_of_Grb2_to_RP

Reaction equation

$$\mathrm{Grb} + \mathrm{RP} \rightleftharpoons \mathrm{RG} \tag{17}$$

Reactants

Table 29: Properties of each reactant.

Id	Name	SBO
Grb	Grb2	
RP	(EGF_EGFR)2-P	

Product

Table 30: Properties of each product.

Id	Name	SBO
RG	(EGF_EGFR)2_Grb2	

Kinetic Law

Derived unit contains undeclared units

$$v_9 = (\mathrm{k9f} \cdot [\mathrm{RP}] \cdot [\mathrm{Grb}] - \mathrm{k9b} \cdot [\mathrm{RG}]) \cdot \mathrm{vol}\,(\mathrm{compartment}) \tag{18}$$

Table 31: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k9f			0.003		☑
k9b			0.050		☑

5.10 Reaction v10

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

Name binding_of_SOS_to_RG

Reaction equation

$$\mathrm{RG} + \mathrm{SOS} \rightleftharpoons \mathrm{RGS} \tag{19}$$

Reactants

Table 32: Properties of each reactant.

Id	Name	SBO
RG	(EGF_EGFR)2_Grb2	
SOS	SOS	

Product

Table 33: Properties of each product.

Id	Name	SBO
RGS	(EGF_EGFR)2_Grb2_SOS	

Kinetic Law

Derived unit contains undeclared units

$$v_{10} = (\mathrm{k10f} \cdot [\mathrm{RG}] \cdot [\mathrm{SOS}] - \mathrm{k10b} \cdot [\mathrm{RGS}]) \cdot \mathrm{vol}(\mathrm{compartment}) \tag{20}$$

Table 34: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k10f			0.01		☑
k10b			0.06		☑

5.11 Reaction v11

This is a reversible reaction of one reactant forming two products.

Name dissociation_of_RGS

Reaction equation

$$\mathrm{RGS} \rightleftharpoons \mathrm{GS} + \mathrm{RP} \tag{21}$$

Reactant

Table 35: Properties of each reactant.

Id	Name	SBO
RGS	(EGF_EGFR)2_Grb2_SOS	

Products

Table 36: Properties of each product.

Id	Name	SBO
GS	Grb2_SOS	
RP	(EGF_EGFR)2-P	

Kinetic Law

Derived unit contains undeclared units

$$v_{11} = (\mathrm{k11f} \cdot [\mathrm{RGS}] - \mathrm{k11b} \cdot [\mathrm{RP}] \cdot [\mathrm{GS}]) \cdot \mathrm{vol}\,(\mathrm{compartment}) \tag{22}$$

Table 37: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k11f			0.030		☑
k11b			0.005		☑

5.12 Reaction v12

This is a reversible reaction of one reactant forming two products.

Name dissociation_of_GS

Reaction equation

$$\mathrm{GS} \rightleftharpoons \mathrm{Grb} + \mathrm{SOS} \tag{23}$$

Reactant

Table 38: Properties of each reactant.

Id	Name	SBO
GS	Grb2_SOS	

Products

Table 39: Properties of each product.

Id	Name	SBO
Grb	Grb2	
SOS	SOS	

Kinetic Law

Derived unit contains undeclared units

$$v_{12} = (\mathrm{k12f} \cdot [\mathrm{GS}] - \mathrm{k12b} \cdot [\mathrm{Grb}] \cdot [\mathrm{SOS}]) \cdot \mathrm{vol}\,(\mathrm{compartment}) \tag{24}$$

Table 40: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k12f			0.002		☑
k12b			10^{-4}		☑

5.13 Reaction v13

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

Name binding_of_Shc_to_RP

Reaction equation

$$\mathrm{Shc} + \mathrm{RP} \rightleftharpoons \mathrm{RSh} \tag{25}$$

Reactants

Table 41: Properties of each reactant.

Id	Name	SBO
Shc	Shc	
RP	(EGF_EGFR)2-P	

Product

Table 42: Properties of each product.

Id	Name	SBO
RSh	(EGF_EGFR)2_Shc	

Kinetic Law

Derived unit contains undeclared units

$$v_{13} = (\mathrm{k13f} \cdot [\mathrm{RP}] \cdot [\mathrm{Shc}] - \mathrm{k13b} \cdot [\mathrm{RSh}]) \cdot \mathrm{vol}\,(\mathrm{compartment}) \tag{26}$$

Table 43: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k13f			0.09		☑
k13b			0.60		☑

5.14 Reaction v14

This is a reversible reaction of one reactant forming one product.

Name phosphorylation_of_RSh

Reaction equation

$$\mathrm{RSh} \rightleftharpoons \mathrm{RShP} \tag{27}$$

Reactant

Table 44: Properties of each reactant.

Id	Name	SBO
RSh	(EGF_EGFR)2_Shc	

Product

Table 45: Properties of each product.

Id	Name	SBO
RShP	(EGF_EGFR)_Shc-P	

Kinetic Law

Derived unit contains undeclared units

$$v_{14} = (\mathrm{k14f} \cdot [\mathrm{RSh}] - \mathrm{k14b} \cdot [\mathrm{RShP}]) \cdot \mathrm{vol}(\mathrm{compartment}) \tag{28}$$

Table 46: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k14f			6.00		☑
k14b			0.06		☑

5.15 Reaction v15

This is a reversible reaction of one reactant forming two products.

Name dissociation_of_RShp

Reaction equation

$$\mathrm{RShP} \rightleftharpoons \mathrm{RP} + \mathrm{ShP} \tag{29}$$

Reactant

Table 47: Properties of each reactant.

Id	Name	SBO
RShP	(EGF_EGFR)_Shc-P	

Products

Table 48: Properties of each product.

Id	Name	SBO
RP	(EGF_EGFR)2-P	
ShP	Shc-P	

Kinetic Law

Derived unit contains undeclared units

$$v_{15} = (\mathrm{k15f} \cdot [\mathrm{RShP}] - \mathrm{k15b} \cdot [\mathrm{ShP}] \cdot [\mathrm{RP}]) \cdot \mathrm{vol}\,(\mathrm{compartment}) \tag{30}$$

Table 49: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k15f			0.300		☑
k15b			$9 \cdot 10^{-4}$		☑

5.16 Reaction v16

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

Name dephosphorylation_of_ShP

Notes Dephosphorylation is irriversible, according to artical.

Reaction equation

$$\mathrm{ShP} \longrightarrow \mathrm{Shc} \tag{31}$$

Reactant

Table 50: Properties of each reactant.

Id	Name	SBO
ShP	Shc-P	

Product

Table 51: Properties of each product.

Id	Name	SBO
Shc	Shc	

Kinetic Law

Derived unit contains undeclared units

$$v_{16} = \frac{\mathrm{V16} \cdot [\mathrm{ShP}]}{\mathrm{K16} + [\mathrm{ShP}]} \cdot \mathrm{vol}\,(\mathrm{compartment}) \tag{32}$$

Table 52: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
V16			1.7		☑
K16			340.0		☑

5.17 Reaction v17

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

Name binding_of_Grb2_to_RShP

Reaction equation

$$\mathrm{RShP} + \mathrm{Grb} \rightleftharpoons \mathrm{RShG} \tag{33}$$

Reactants

Table 53: Properties of each reactant.

Id	Name	SBO
RShP	(EGF_EGFR)_Shc-P	
Grb	Grb2	

Product

Table 54: Properties of each product.

Id	Name	SBO
RShG	(EGF_EGFR)2_Shc_Grb2	

Kinetic Law

Derived unit contains undeclared units

$$v_{17} = (\mathrm{k17f} \cdot [\mathrm{RShP}] \cdot [\mathrm{Grb}] - \mathrm{k17b} \cdot [\mathrm{RShG}]) \cdot \mathrm{vol}\,(\mathrm{compartment}) \tag{34}$$

Table 55: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k17f			0.003		☑
k17b			0.100		☑

5.18 Reaction v18

This is a reversible reaction of one reactant forming two products.

Name dissociation_of_RShG

Reaction equation

$$\mathrm{RShG} \rightleftharpoons \mathrm{ShG} + \mathrm{RP} \tag{35}$$

Reactant

Table 56: Properties of each reactant.

Id	Name	SBO
RShG	(EGF_EGFR)2_Shc_Grb2	

Products

Table 57: Properties of each product.

Id	Name	SBO
ShG	Shc_Grb2	
RP	(EGF_EGFR)2-P	

Kinetic Law

Derived unit contains undeclared units

$$v_{18} = (\mathrm{k18f} \cdot [\mathrm{RShG}] - \mathrm{k18b} \cdot [\mathrm{RP}] \cdot [\mathrm{ShG}]) \cdot \mathrm{vol}\,(\mathrm{compartment}) \tag{36}$$

Table 58: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k18f			0.300		☑
k18b			$9 \cdot 10^{-4}$		☑

5.19 Reaction v19

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

Name binding_of_SOS_to_RShG

Reaction equation

$$\mathrm{SOS} + \mathrm{RShG} \rightleftharpoons \mathrm{RShGS} \tag{37}$$

Reactants

Table 59: Properties of each reactant.

Id	Name	SBO
SOS	SOS	
RShG	(EGF_EGFR)2_Shc_Grb2	

Product

Table 60: Properties of each product.

Id	Name	SBO
RShGS	(EGF_EGFR)2_Shc_Grb2_SOS	

Kinetic Law

Derived unit contains undeclared units

$$v_{19} = (\mathrm{k19f} \cdot [\mathrm{RShG}] \cdot [\mathrm{SOS}] - \mathrm{k19b} \cdot [\mathrm{RShGS}]) \cdot \mathrm{vol}\,(\mathrm{compartment}) \tag{38}$$

Table 61: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k19f			0.010		☑
k19b			0.021		☑

5.20 Reaction v20

This is a reversible reaction of one reactant forming two products.

Name dissociation_of_RShGS

Reaction equation

$$\mathrm{RShGS} \rightleftharpoons \mathrm{ShGS} + \mathrm{RP} \tag{39}$$

Reactant

Table 62: Properties of each reactant.

Id	Name	SBO
RShGS	(EGF_EGFR)2_Shc_Grb2_SOS	

Products

Table 63: Properties of each product.

Id	Name	SBO
ShGS	Shc_Grb2_SOS	
RP	(EGF_EGFR)2-P	

Kinetic Law

Derived unit contains undeclared units

$$v_{20} = (\mathrm{k20f} \cdot [\mathrm{RShGS}] - \mathrm{k20b} \cdot [\mathrm{ShGS}] \cdot [\mathrm{RP}]) \cdot \mathrm{vol}(\mathrm{compartment}) \tag{40}$$

Table 64: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k20f			0.120		☑
k20b			$2.4 \cdot 10^{-4}$		☑

5.21 Reaction v21

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

Name binding_of_Grb2_to_ShP

Reaction equation

$$\mathrm{Grb} + \mathrm{ShP} \rightleftharpoons \mathrm{ShG} \tag{41}$$

Reactants

Table 65: Properties of each reactant.

Id	Name	SBO
Grb	Grb2	
ShP	Shc-P	

Product

Table 66: Properties of each product.

Id	Name	SBO
ShG	Shc_Grb2	

Kinetic Law

Derived unit contains undeclared units

$$v_{21} = (\mathrm{k21f} \cdot [\mathrm{ShP}] \cdot [\mathrm{Grb}] - \mathrm{k21b} \cdot [\mathrm{ShG}]) \cdot \mathrm{vol}\,(\mathrm{compartment}) \tag{42}$$

Table 67: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k21f			0.003		☑
k21b			0.100		☑

5.22 Reaction v22

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

Name binding_of_SOS_to_ShG

Reaction equation

$$\mathrm{ShG} + \mathrm{SOS} \rightleftharpoons \mathrm{ShGS} \tag{43}$$

Reactants

Table 68: Properties of each reactant.

Id	Name	SBO
ShG	Shc_Grb2	
SOS	SOS	

Product

Table 69: Properties of each product.

Id	Name	SBO
ShGS	Shc_Grb2_SOS	

Kinetic Law

Derived unit contains undeclared units

$$v_{22} = (\mathrm{k22f} \cdot [\mathrm{ShG}] \cdot [\mathrm{SOS}] - \mathrm{k22b} \cdot [\mathrm{ShGS}]) \cdot \mathrm{vol}\,(\mathrm{compartment}) \tag{44}$$

Table 70: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k22f			0.030		☑
k22b			0.064		☑

5.23 Reaction v23

This is a reversible reaction of one reactant forming two products.

Name dissociation_of_ShGS

Reaction equation

$$\mathrm{ShGS} \rightleftharpoons \mathrm{GS} + \mathrm{ShP} \tag{45}$$

Reactant

Table 71: Properties of each reactant.

Id	Name	SBO
ShGS	Shc_Grb2_SOS	

Products

Table 72: Properties of each product.

Id	Name	SBO
GS	Grb2_SOS	
ShP	Shc-P	

Kinetic Law

Derived unit contains undeclared units

$$v_{23} = (\mathrm{k23f} \cdot [\mathrm{ShGS}] - \mathrm{k23b} \cdot [\mathrm{ShP}] \cdot [\mathrm{GS}]) \cdot \mathrm{vol}\,(\mathrm{compartment}) \tag{46}$$

Table 73: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k23f			0.100		☑
k23b			0.021		☑

5.24 Reaction v24

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

Name association_of_RShP_and_GS

Reaction equation

$$\mathrm{RShP} + \mathrm{GS} \rightleftharpoons \mathrm{RShGS} \tag{47}$$

Reactants

Table 74: Properties of each reactant.

Id	Name	SBO
RShP	(EGF_EGFR)_Shc-P	
GS	Grb2_SOS	

Product

Table 75: Properties of each product.

Id	Name	SBO
RShGS	(EGF_EGFR)2_Shc_Grb2_SOS	

Kinetic Law

Derived unit contains undeclared units

$$v_{24} = (\mathrm{k24f} \cdot [\mathrm{RShP}] \cdot [\mathrm{GS}] - \mathrm{k24b} \cdot [\mathrm{RShGS}]) \cdot \mathrm{vol}\,(\mathrm{compartment}) \tag{48}$$

Table 76: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k24f			0.009		☑
k24b			0.043		☑

5.25 Reaction v25

This is a reversible reaction of one reactant forming one product.

Name translocation_of_PLCgP

Reaction equation

$$\mathrm{PLCgP} \rightleftharpoons \mathrm{PLCgl} \tag{49}$$

Reactant

Table 77: Properties of each reactant.

Id	Name	SBO
PLCgP	PLCg-P	

Product

Table 78: Properties of each product.

Id	Name	SBO
PLCgl	PLCgP-I	

Kinetic Law

Derived unit contains undeclared units

$$v_{25} = (\mathrm{k25f} \cdot [\mathrm{PLCgP}] - \mathrm{k25b} \cdot [\mathrm{PLCgl}]) \cdot \mathrm{vol}\,(\mathrm{compartment}) \tag{50}$$

Table 79: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k25f			1.00		☑
k25b			0.03		☑

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 EGF

Name Epidermal_Growth_Factor

Initial concentration $680\ \mathrm{nmol} \cdot \mathrm{l}^{-1}$

This species takes part in one reaction (as a reactant in v1).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{EGF} = -v_1 \tag{51}$$

6.2 Species R

Name EGFR

Initial concentration $100\ \mathrm{nmol}\cdot\mathrm{l}^{-1}$

This species takes part in one reaction (as a reactant in v1).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{R} = -v_1 \tag{52}$$

6.3 Species Ra

Name EGF_EGFR

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

This species takes part in two reactions (as a reactant in v2 and as a product in v1).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Ra} = v_1 - 2\,v_2 \tag{53}$$

6.4 Species R2

Name (EGF_EGFR)2

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

This species takes part in three reactions (as a reactant in v3 and as a product in v2, v4).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{R2} = v_2 + v_4 - v_3 \tag{54}$$

6.5 Species RP

Name (EGF_EGFR)2-P

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

This species takes part in ten reactions (as a reactant in v4, v5, v9, v13 and as a product in v3, v7, v11, v15, v18, v20).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{RP} = v_3 + v_7 + v_{11} + v_{15} + v_{18} + v_{20} - v_4 - v_5 - v_9 - v_{13} \tag{55}$$

6.6 Species PLCg

Name PLCg

Initial concentration $105\ \mathrm{nmol}\cdot\mathrm{l}^{-1}$

This species takes part in two reactions (as a reactant in v5 and as a product in v8).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{PLCg} = v_8 - v_5 \tag{56}$$

6.7 Species RPLCg

Name (EGF_EGFR)2_PLCg

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

This species takes part in two reactions (as a reactant in v6 and as a product in v5).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{RPLCg} = v_5 - v_6 \tag{57}$$

6.8 Species RPLCgP

Name (EGF_EGFR)2_PLCg-P

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

This species takes part in two reactions (as a reactant in v7 and as a product in v6).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{RPLCgP} = v_6 - v_7 \tag{58}$$

6.9 Species PLCgP

Name PLCg-P

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

This species takes part in three reactions (as a reactant in v8, v25 and as a product in v7).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{PLCgP} = v_7 - v_8 - v_{25} \tag{59}$$

6.10 Species Grb

Name Grb2

Initial concentration $85\ \mathrm{nmol}\cdot\mathrm{l}^{-1}$

This species takes part in four reactions (as a reactant in v9, v17, v21 and as a product in v12).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Grb} = v_{12} - v_9 - v_{17} - v_{21} \tag{60}$$

6.11 Species RG

Name (EGF_EGFR)2_Grb2

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

This species takes part in two reactions (as a reactant in v10 and as a product in v9).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{RG} = v_9 - v_{10} \tag{61}$$

6.12 Species SOS

Name SOS

Initial concentration $34\ \mathrm{nmol}\cdot\mathrm{l}^{-1}$

This species takes part in four reactions (as a reactant in v10, v19, v22 and as a product in v12).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{SOS} = v_{12} - v_{10} - v_{19} - v_{22} \tag{62}$$

6.13 Species RGS

Name (EGF_EGFR)2_Grb2_SOS

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

This species takes part in two reactions (as a reactant in v11 and as a product in v10).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{RGS} = v_{10} - v_{11} \tag{63}$$

6.14 Species GS

Name Grb2_SOS

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

This species takes part in four reactions (as a reactant in v12, v24 and as a product in v11, v23).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{GS} = v_{11} + v_{23} - v_{12} - v_{24} \tag{64}$$

6.15 Species Shc

Name Shc

Initial concentration $150\ \mathrm{nmol}\cdot\mathrm{l}^{-1}$

This species takes part in two reactions (as a reactant in v13 and as a product in v16).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Shc} = v_{16} - v_{13} \tag{65}$$

6.16 Species RSh

Name (EGF_EGFR)2_Shc

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

This species takes part in two reactions (as a reactant in v14 and as a product in v13).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{RSh} = v_{13} - v_{14} \tag{66}$$

6.17 Species RShP

Name (EGF_EGFR)_Shc-P

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

This species takes part in four reactions (as a reactant in v15, v17, v24 and as a product in v14).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{RShP} = v_{14} - v_{15} - v_{17} - v_{24} \tag{67}$$

6.18 Species ShP

Name Shc-P

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

This species takes part in four reactions (as a reactant in v16, v21 and as a product in v15, v23).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{ShP} = v_{15} + v_{23} - v_{16} - v_{21} \tag{68}$$

6.19 Species RShG

Name (EGF_EGFR)2_Shc_Grb2

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

This species takes part in three reactions (as a reactant in v18, v19 and as a product in v17).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{RShG} = v_{17} - v_{18} - v_{19} \tag{69}$$

6.20 Species ShG

Name Shc_Grb2

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

This species takes part in three reactions (as a reactant in v22 and as a product in v18, v21).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{ShG} = v_{18} + v_{21} - v_{22} \tag{70}$$

6.21 Species RShGS

Name (EGF_EGFR)2_Shc_Grb2_SOS

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

This species takes part in three reactions (as a reactant in v20 and as a product in v19, v24).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{RShGS} = v_{19} + v_{24} - v_{20} \tag{71}$$

6.22 Species ShGS

Name Shc_Grb2_SOS

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

This species takes part in three reactions (as a reactant in v23 and as a product in v20, v22).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{ShGS} = v_{20} + v_{22} - v_{23} \tag{72}$$

6.23 Species PLCgl

Name PLCgP-I

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

This species takes part in one reaction (as a product in v25).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{PLCgl} = v_{25} \tag{73}$$

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