SBML Model Report

Model name: “Smith2009 - RGS mediated GTP hydrolysis”

May 6, 2016

1 General Overview

This is a document in SBML Level 2 Version 4 format. This model was created by the following four authors: Nick Juty[1], Manuel Esparza-Franco[2], Wayne Croft[3] and Vijayalakshmi Chelliah[4] at December fifth 2012 at 1:20 p. m. and last time modified at March 18th 2014 at 11:39 a. m. Table 1 shows an overview of the quantities of all components of this model.

Table 1: Number of components in this model, which are described in the following sections.

Element	Quantity	Element	Quantity
compartment types	0	compartments	1
species types	0	species	20
events	1	constraints	0
reactions	21	function definitions	0
global parameters	2	unit definitions	4
rules	0	initial assignments	0

Model Notes

Smith2009 - RGS mediated GTP hydrolysis

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This model is described in the article:Dual positive and negative regulation of GPCR signaling by GTP hydrolysis.Smith B, Hill C, Godfrey EL, Rand D, van den Berg H, Thornton S, Hodgkin M, Davey J, Ladds G.Cell Signal. 2009 Jul;21(7):1151-60.

Abstract:

G protein-coupled receptors (GPCRs) regulate a variety of intracellular pathways through their ability to promote the binding of GTP to heterotrimeric G proteins. Regulator of G protein signaling (RGS) proteins increases the intrinsic GTPase activity of Galpha-subunits and are widely regarded as negative regulators of G protein signaling. Using yeast we demonstrate that GTP hydrolysis is not only required for desensitization, but is essential for achieving a high maximal (saturated level) response. Thus RGS-mediated GTP hydrolysis acts as both a negative (low stimulation) and positive (high stimulation) regulator of signaling. To account for this we generated a new kinetic model of the G protein cycle where Galpha(GTP) enters an inactive GTP-bound state following effector activation. Furthermore, in vivo and in silico experimentation demonstrates that maximum signaling output first increases and then decreases with RGS concentration. This unimodal, non-monotone dependence on RGS concentration is novel. Analysis of the kinetic model has revealed a dynamic network motif that shows precisely how inclusion of the inactive GTP-bound state for the Galpha produces this unimodal relationship.

To reproduce dose-response plots in the publication, the model is simulated with 12 different concentrations (see parameter Ligand_conc). For each concentration, a single value must be obtained from the integral of the trajectory of species z3 from time=0 to time=30. These values are then used to build a dose-response plot (authors used GraphPad Prism). Mutant strains are simulated with alternative parameter values or initial conditions in Table S3.

2 Unit Definitions

This is an overview of nine unit definitions of which five are predefined by SBML and not mentioned in the model.

2.1 Unit `nanoMolar`

Name nM

Definition $\mathrm{nmol} \cdot \mathrm{l}^{-1}$

2.2 Unit `hour`

Name hr

Definition 3600 s

2.3 Unit `FirstOrder`

Name 1/hr

Definition $(3600\ \mathrm{s})^{-1}$

2.4 Unit `SecondOrder`

Name 1/(nM*hr)

Definition $\mathrm{nmol}^{-1} \cdot 1 \cdot (3600\ \mathrm{s})^{-1}$

2.5 Unit `substance`

Notes Mole is the predefined SBML unit for `substance`.

Definition mol

2.6 Unit `volume`

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

Definition l

2.7 Unit `area`

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

Definition m^2

2.8 Unit `length`

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

Definition m

2.9 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`	cell		3	1	litre	☑	

3.1 Compartment `compartment`

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

Name cell

4 Species

This model contains 20 species. Section 8 provides further details and the derived rates of change of each species.

Table 3: Properties of each species.

Id	Name	Compartment	Derived Unit	Constant	Boundary Condition
R	R	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1} \cdot \mathrm{l}^{-1}$	⊟	⊟
L	L	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1} \cdot \mathrm{l}^{-1}$	⊟	⊟
RL	RL	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1} \cdot \mathrm{l}^{-1}$	⊟	⊟
Gabg	Gabg	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1} \cdot \mathrm{l}^{-1}$	⊟	⊟
RGabg	RGabg	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1} \cdot \mathrm{l}^{-1}$	⊟	⊟
RGabgL	RGabgL	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1} \cdot \mathrm{l}^{-1}$	⊟	⊟
GaGTP	GaGTP	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1} \cdot \mathrm{l}^{-1}$	⊟	⊟
Gbg	Gbg	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1} \cdot \mathrm{l}^{-1}$	⊟	⊟
RGS	RGS	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1} \cdot \mathrm{l}^{-1}$	⊟	⊟
RGSGaGTP	RGSGaGTP	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1} \cdot \mathrm{l}^{-1}$	⊟	⊟
GaGDPP	GaGDPP	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1} \cdot \mathrm{l}^{-1}$	⊟	⊟
Effector	Effector	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1} \cdot \mathrm{l}^{-1}$	⊟	⊟
GaGTPEffector	GaGTPEffector	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1} \cdot \mathrm{l}^{-1}$	⊟	⊟
inertGaGTP	inertGaGTP	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1} \cdot \mathrm{l}^{-1}$	⊟	⊟
RGSinertGaGTP	RGSinertGaGTP	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1} \cdot \mathrm{l}^{-1}$	⊟	⊟
GaGDP	GaGDP	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1} \cdot \mathrm{l}^{-1}$	⊟	⊟
P	P	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1} \cdot \mathrm{l}^{-1}$	⊟	⊟
z1	z1	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1} \cdot \mathrm{l}^{-1}$	⊟	⊟
z2	z2	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1} \cdot \mathrm{l}^{-1}$	⊟	⊟
z3	z3	compartment	$\mathrm{nmol} \cdot \mathrm{l}^{-1} \cdot \mathrm{l}^{-1}$	⊟	⊟

5 Parameters

This model contains two global parameters.

Table 4: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
ka	ka		1.5	$(3600\ \mathrm{s})^{-1}$	☑
Ligand_conc	Ligand_conc		0.1	$\mathrm{nmol} \cdot \mathrm{l}^{-1}$	☑

6 Event

This is an overview of one event. Each event is initiated whenever its trigger condition switches from `false` to `true`. A delay function postpones the effects of an event to a later time point. At the time of execution, an event can assign values to species, parameters or compartments if these are not set to constant.

6.1 Event Ligand_addition

Name Ligand_addition

Notes The model in the publication uses a tanh step function to add ligand, but only because the solver used by the authors did not support Events. Results are identical using this event, and has been changed in agreement with the authors.

Trigger condition

$$\mathrm{time} \geq 14 \tag{1}$$

Assignment

$$\mathrm{L} = [\mathrm{L}] + \mathrm{Ligand\_conc} \tag{2}$$

7 Reactions

This model contains 21 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	R1	Receptor-Ligand association	$R + L \xrightarrow{R,\ L} RL$	0000526
2	R2	Receptor-Gprotein association	$R + Gabg \xrightarrow{R,\ Gabg} RGabg$	0000526
3	R3	RL-Gprotein association	$RL + Gabg \xrightarrow{RL,\ Gabg} RGabgL$	0000526
4	R4	RGabg-Ligand association	$RGabg + L \xrightarrow{RGabg,\ L} RGabgL$	0000526
5	R5	Galpha activation by receptor	$RGabgL \xrightarrow{RGabgL} RL + GaGTP + Gbg$	
6	R6	Galpha activation spontaneous	$Gabg \xrightarrow{Gabg} GaGTP + Gbg$	
7	R7	Galpha-RGS association	$GaGTP + RGS \xrightarrow{GaGTP,\ RGS} RGSGaGTP$	0000526
8	R8	Galpha deactivation by RGS	$RGSGaGTP \xrightarrow{RGSGaGTP} GaGDPP + RGS$	0000169
9	R9	Galpha deactivation spontaneous	$GaGTP \xrightarrow{GaGTP} GaGDPP$	0000169
10	R10	Galpha-Effector association	$Effector + GaGTP \xrightarrow{Effector,\ GaGTP} GaGTPEffector$	0000526
11	R11	Galpha becomes inert	$GaGTPEffector \xrightarrow{GaGTPEffector} inertGaGTP + Effector$	0000169
12	R12	inertGalpha-RGS association	$inertGaGTP + RGS \xrightarrow{inertGaGTP,\ RGS} RGSinertGaGTP$	0000526
13	R13	inertGalpha deactivation by RGS	$RGSinertGaGTP \xrightarrow{RGSinertGaGTP} GaGDPP + RGS$	0000169
14	R14	inertGalpha deactivation spontaneous	$inertGaGTP \xrightarrow{inertGaGTP} GaGDPP$	0000169

№	Id	Name	Reaction Equation	SBO
15	R15	Phosphate release	$\mathrm{GaGDPP} \xrightarrow{\mathrm{GaGDPP}} \mathrm{GaGDP} + \mathrm{P}$	0000393
16	R16	Gprotein subunits association	$\mathrm{GaGDP} + \mathrm{Gbg} \xrightarrow{\mathrm{GaGDP,\ Gbg}} \mathrm{Gabg}$	0000526
17	R17	Phosphate degradation	$\mathrm{P} \xrightarrow{\mathrm{P}} \emptyset$	0000179
18	R18	Delay 1	$\emptyset \xrightarrow{\mathrm{GaGTPEffector,\ GaGTPEffector}} \mathrm{z1}$	0000225
19	R19	Delay 2	$\mathrm{z1} \xrightarrow{\mathrm{z1}} \mathrm{z2}$	0000225
20	R20	Delay 3	$\mathrm{z2} \xrightarrow{\mathrm{z2}} \mathrm{z3}$	0000225
21	R21	Delay 4	$\mathrm{z3} \xrightarrow{\mathrm{z3}} \emptyset$	0000225

7.1 Reaction R1

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

Name Receptor-Ligand association

SBO:0000526 protein complex formation

Reaction equation

$$\mathrm{R} + \mathrm{L} \xrightarrow{\mathrm{R,\ L}} \mathrm{RL} \tag{3}$$

Reactants

Table 6: Properties of each reactant.

Id	Name	SBO
R	R	
L	L	

Modifiers

Table 7: Properties of each modifier.

Id	Name	SBO
R	R	
L	L	

Product

Table 8: Properties of each product.

Id	Name	SBO
RL	RL	

Kinetic Law

Derived unit $1^{-2} \cdot 9.999999999999998 \cdot 10^{-10}\ \mathrm{mol} \cdot (3600\ \mathrm{s})^{-1}$

$$v_1 = \mathrm{vol}\,(\mathrm{compartment}) \cdot [\mathrm{R}] \cdot [\mathrm{L}] \cdot \mathrm{k1} \tag{4}$$

Table 9: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k1	k1		0.003	$\text{nmol}^{-1} \cdot 1 \cdot (3600\ \text{s})^{-1}$	☑

7.2 Reaction R2

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

Name Receptor-Gprotein association

SBO:0000526 protein complex formation

Reaction equation

$$\text{R} + \text{Gabg} \xrightarrow{\text{R, Gabg}} \text{RGabg} \tag{5}$$

Reactants

Table 10: Properties of each reactant.

Id	Name	SBO
R	R	
Gabg	Gabg	

Modifiers

Table 11: Properties of each modifier.

Id	Name	SBO
R	R	
Gabg	Gabg	

Product

Table 12: Properties of each product.

Id	Name	SBO
RGabg	RGabg	

Kinetic Law

Derived unit $1^{-2} \cdot 9.999999999999998 \cdot 10^{-10}\ \text{mol} \cdot (3600\ \text{s})^{-1}$

$$v_2 = \text{vol}\,(\text{compartment}) \cdot [\text{R}] \cdot [\text{Gabg}] \cdot \text{k2} \tag{6}$$

Table 13: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k2	k2		0.005	$\text{nmol}^{-1} \cdot 1 \cdot (3600\ \text{s})^{-1}$	☑

7.3 Reaction R3

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

Name RL-Gprotein association

SBO:0000526 protein complex formation

Reaction equation

$$\text{RL} + \text{Gabg} \xrightarrow{\text{RL, Gabg}} \text{RGabgL} \tag{7}$$

Reactants

Table 14: Properties of each reactant.

Id	Name	SBO
RL	RL	
Gabg	Gabg	

Modifiers

Table 15: Properties of each modifier.

Id	Name	SBO
RL	RL	
Gabg	Gabg	

Product

Table 16: Properties of each product.

Id	Name	SBO
RGabgL	RGabgL	

Kinetic Law

Derived unit $1^{-2} \cdot 9.999999999999998 \cdot 10^{-10}\ \text{mol} \cdot (3600\ \text{s})^{-1}$

$$v_3 = \text{vol}\,(\text{compartment}) \cdot [\text{RL}] \cdot [\text{Gabg}] \cdot \text{k3} \tag{8}$$

Table 17: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k3	k3		0.02	$\text{nmol}^{-1} \cdot 1 \cdot (3600\ \text{s})^{-1}$	☑

7.4 Reaction R4

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

Name RGabg-Ligand association

SBO:0000526 protein complex formation

Reaction equation

$$\text{RGabg} + \text{L} \xrightarrow{\text{RGabg, L}} \text{RGabgL} \tag{9}$$

Reactants

Table 18: Properties of each reactant.

Id	Name	SBO
RGabg	RGabg	
L	L	

Modifiers

Table 19: Properties of each modifier.

Id	Name	SBO
RGabgL	RGabgL	

Product

Table 20: Properties of each product.

Id	Name	SBO
RGabgL	RGabgL	

Kinetic Law

Derived unit $1^{-2} \cdot 9.999999999999998 \cdot 10^{-10}\ \mathrm{mol} \cdot (3600\ \mathrm{s})^{-1}$

$$v_4 = \mathrm{vol}\,(\mathrm{compartment}) \cdot [\mathrm{RGabg}] \cdot [\mathrm{L}] \cdot \mathrm{k4} \tag{10}$$

Table 21: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k4	k4		0.005	$\mathrm{nmol}^{-1} \cdot 1 \cdot (3600\ \mathrm{s})^{-1}$	☑

7.5 Reaction R5

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

Name Galpha activation by receptor

Reaction equation

$$\mathrm{RGabgL} \xrightarrow{\mathrm{RGabgL}} \mathrm{RL} + \mathrm{GaGTP} + \mathrm{Gbg} \tag{11}$$

Reactant

Table 22: Properties of each reactant.

Id	Name	SBO
RGabgL	RGabgL	

Id	Name	SBO

Modifier

Table 23: Properties of each modifier.

Id	Name	SBO
RGabgL	RGabgL	

Products

Table 24: Properties of each product.

Id	Name	SBO
RL	RL	
GaGTP	GaGTP	
Gbg	Gbg	

Kinetic Law

Derived unit $\mathrm{l}^{-1} \cdot \mathrm{nmol} \cdot (3600\ \mathrm{s})^{-1}$

$$v_5 = \mathrm{vol}\,(\mathrm{compartment}) \cdot [\mathrm{RGabgL}] \cdot \mathrm{k5} \tag{12}$$

Table 25: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k5	k5		50.0	$(3600\ \mathrm{s})^{-1}$	☑

7.6 Reaction R6

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

Name Galpha activation spontaneous

Reaction equation

$$\mathrm{Gabg} \xrightarrow{\mathrm{Gabg}} \mathrm{GaGTP} + \mathrm{Gbg} \tag{13}$$

Reactant

Table 26: Properties of each reactant.

Id	Name	SBO
Gabg	Gabg	

Modifier

Table 27: Properties of each modifier.

Id	Name	SBO
Gabg	Gabg	

Products

Table 28: Properties of each product.

Id	Name	SBO
GaGTP	GaGTP	
Gbg	Gbg	

Kinetic Law

Derived unit $1^{-1} \cdot \text{nmol} \cdot (3600\ \text{s})^{-1}$

$$v_6 = \text{vol}\,(\text{compartment}) \cdot [\text{Gabg}] \cdot \text{k6} \tag{14}$$

Table 29: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k6	k6		0.2	$(3600\ \text{s})^{-1}$	☑

7.7 Reaction R7

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

Name Galpha-RGS association

SBO:0000526 protein complex formation

Reaction equation

$$\mathrm{GaGTP} + \mathrm{RGS} \xrightarrow{\mathrm{GaGTP,\ RGS}} \mathrm{RGSGaGTP} \tag{15}$$

Reactants

Table 30: Properties of each reactant.

Id	Name	SBO
GaGTP	GaGTP	
RGS	RGS	

Modifiers

Table 31: Properties of each modifier.

Id	Name	SBO
GaGTP	GaGTP	
RGS	RGS	

Product

Table 32: Properties of each product.

Id	Name	SBO
RGSGaGTP	RGSGaGTP	

Kinetic Law

Derived unit $1^{-2} \cdot 9.999999999999998 \cdot 10^{-10}\ \mathrm{mol} \cdot (3600\ \mathrm{s})^{-1}$

$$v_7 = \mathrm{vol}\,(\mathrm{compartment}) \cdot [\mathrm{GaGTP}] \cdot [\mathrm{RGS}] \cdot \mathrm{k7} \tag{16}$$

Table 33: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k7	k7		500.0	$\mathrm{nmol}^{-1} \cdot 1 \cdot (3600\ \mathrm{s})^{-1}$	☑

7.8 Reaction R8

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

Name Galpha deactivation by RGS

SBO:0000169 inhibition

Reaction equation

$$\mathrm{RGSGaGTP} \xrightarrow{\mathrm{RGSGaGTP}} \mathrm{GaGDPP} + \mathrm{RGS} \tag{17}$$

Reactant

Table 34: Properties of each reactant.

Id	Name	SBO
RGSGaGTP	RGSGaGTP	

Modifier

Table 35: Properties of each modifier.

Id	Name	SBO
RGSGaGTP	RGSGaGTP	

Products

Table 36: Properties of each product.

Id	Name	SBO
GaGDPP	GaGDPP	
RGS	RGS	

Kinetic Law

Derived unit $\mathrm{l}^{-1} \cdot \mathrm{nmol} \cdot (3600\ \mathrm{s})^{-1}$

$$v_8 = \mathrm{vol}\,(\mathrm{compartment}) \cdot [\mathrm{RGSGaGTP}] \cdot \mathrm{k8} \tag{18}$$

Table 37: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k8	k8		2.5	$(3600\ \mathrm{s})^{-1}$	☑

7.9 Reaction R9

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

Name Galpha deactivation spontaneous

SBO:0000169 inhibition

Reaction equation

$$\mathrm{GaGTP} \xrightarrow{\mathrm{GaGTP}} \mathrm{GaGDPP} \tag{19}$$

Reactant

Table 38: Properties of each reactant.

Id	Name	SBO
GaGTP	GaGTP	

Modifier

Table 39: Properties of each modifier.

Id	Name	SBO
GaGTP	GaGTP	

Product

Table 40: Properties of each product.

Id	Name	SBO
GaGDPP	GaGDPP	

Kinetic Law

Derived unit $\mathrm{l}^{-1} \cdot \mathrm{nmol} \cdot (3600\ \mathrm{s})^{-1}$

$$v_9 = \mathrm{vol}\,(\mathrm{compartment}) \cdot [\mathrm{GaGTP}] \cdot \mathrm{k9} \tag{20}$$

Table 41: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k9	k9		0.005	$(3600\ \mathrm{s})^{-1}$	☑

7.10 Reaction R10

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

Name Galpha-Effector association

SBO:0000526 protein complex formation

Reaction equation

$$\mathrm{Effector} + \mathrm{GaGTP} \xrightarrow{\mathrm{Effector,\ GaGTP}} \mathrm{GaGTPEffector} \tag{21}$$

Reactants

Table 42: Properties of each reactant.

Id	Name	SBO
Effector	Effector	
GaGTP	GaGTP	

Modifiers

Table 43: Properties of each modifier.

Id	Name	SBO
Effector	Effector	
GaGTP	GaGTP	

Product

Table 44: Properties of each product.

Id	Name	SBO
GaGTPEffector	GaGTPEffector	

Id	Name	SBO

Kinetic Law

Derived unit $1^{-2} \cdot 9.999999999999998 \cdot 10^{-10}\ \mathrm{mol} \cdot (3600\ \mathrm{s})^{-1}$

$$v_{10} = \mathrm{vol}\,(\mathrm{compartment}) \cdot [\mathrm{Effector}] \cdot [\mathrm{GaGTP}] \cdot \mathrm{k10} \tag{22}$$

Table 45: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k10	k10		10.0	$\mathrm{nmol}^{-1} \cdot 1 \cdot (3600\ \mathrm{s})^{-1}$	☑

7.11 Reaction R11

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

Name Galpha becomes inert

SBO:0000169 inhibition

Reaction equation

$$\mathrm{GaGTPEffector} \xrightarrow{\mathrm{GaGTPEffector}} \mathrm{inertGaGTP} + \mathrm{Effector} \tag{23}$$

Reactant

Table 46: Properties of each reactant.

Id	Name	SBO
GaGTPEffector	GaGTPEffector	

Modifier

Table 47: Properties of each modifier.

Id	Name	SBO
GaGTPEffector	GaGTPEffector	

Products

Table 48: Properties of each product.

Id	Name	SBO
`inertGaGTP`	inertGaGTP	
`Effector`	Effector	

Kinetic Law

Derived unit $1^{-1} \cdot \text{nmol} \cdot (3600\ \text{s})^{-1}$

$$v_{11} = \text{vol}(\text{compartment}) \cdot [\text{GaGTPEffector}] \cdot \text{k11} \tag{24}$$

Table 49: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
`k11`	k11		1.0	$(3600\ \text{s})^{-1}$	☑

7.12 Reaction `R12`

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

Name inertGalpha-RGS association

SBO:0000526 protein complex formation

Reaction equation

$$\text{inertGaGTP} + \text{RGS} \xrightarrow{\text{inertGaGTP, RGS}} \text{RGSinertGaGTP} \tag{25}$$

Reactants

Table 50: Properties of each reactant.

Id	Name	SBO
`inertGaGTP`	inertGaGTP	
`RGS`	RGS	

Modifiers

Table 51: Properties of each modifier.

Id	Name	SBO
inertGaGTP	inertGaGTP	
RGS	RGS	

Product

Table 52: Properties of each product.

Id	Name	SBO
RGSinertGaGTP	RGSinertGaGTP	

Kinetic Law

Derived unit $1^{-2} \cdot 9.999999999999998 \cdot 10^{-10}\ \text{mol} \cdot (3600\ \text{s})^{-1}$

$$v_{12} = \text{vol}\,(\text{compartment}) \cdot [\text{inertGaGTP}] \cdot [\text{RGS}] \cdot \text{k12} \tag{26}$$

Table 53: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k12	k12		50.0	$\text{nmol}^{-1} \cdot \text{l} \cdot (3600\ \text{s})^{-1}$	☑

7.13 Reaction R13

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

Name inertGalpha deactivation by RGS

SBO:0000169 inhibition

Reaction equation

$$\text{RGSinertGaGTP} \xrightarrow{\text{RGSinertGaGTP}} \text{GaGDPP} + \text{RGS} \tag{27}$$

Reactant

Table 54: Properties of each reactant.

Id	Name	SBO
RGSinertGaGTP	RGSinertGaGTP	

Modifier

Table 55: Properties of each modifier.

Id	Name	SBO
RGSinertGaGTP	RGSinertGaGTP	

Products

Table 56: Properties of each product.

Id	Name	SBO
GaGDPP	GaGDPP	
RGS	RGS	

Kinetic Law

Derived unit $1^{-1} \cdot \mathrm{nmol} \cdot (3600\ \mathrm{s})^{-1}$

$$v_{13} = \mathrm{vol}\,(\mathrm{compartment}) \cdot [\mathrm{RGSinertGaGTP}] \cdot \mathrm{k13} \tag{28}$$

Table 57: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k13	k13		0.3	$(3600\ \mathrm{s})^{-1}$	☑

7.14 Reaction R14

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

Name inertGalpha deactivation spontaneous

SBO:0000169 inhibition

Reaction equation

$$\text{inertGaGTP} \xrightarrow{\text{inertGaGTP}} \text{GaGDPP} \tag{29}$$

Reactant

Table 58: Properties of each reactant.

Id	Name	SBO
`inertGaGTP`	inertGaGTP	

Modifier

Table 59: Properties of each modifier.

Id	Name	SBO
`inertGaGTP`	inertGaGTP	

Product

Table 60: Properties of each product.

Id	Name	SBO
`GaGDPP`	GaGDPP	

Kinetic Law

Derived unit $\mathrm{l}^{-1} \cdot \mathrm{nmol} \cdot (3600\ \mathrm{s})^{-1}$

$$v_{14} = \mathrm{vol}\,(\mathrm{compartment}) \cdot [\mathrm{inertGaGTP}] \cdot \mathrm{k14} \tag{30}$$

Table 61: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
`k14`	k14		0.005	$(3600\ \mathrm{s})^{-1}$	☑

7.15 Reaction `R15`

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

Name Phosphate release

SBO:0000393 production

Reaction equation

$$\mathrm{GaGDPP} \xrightarrow{\mathrm{GaGDPP}} \mathrm{GaGDP} + \mathrm{P} \tag{31}$$

Reactant

Table 62: Properties of each reactant.

Id	Name	SBO
GaGDPP	GaGDPP	

Modifier

Table 63: Properties of each modifier.

Id	Name	SBO
GaGDPP	GaGDPP	

Products

Table 64: Properties of each product.

Id	Name	SBO
GaGDP	GaGDP	
P	P	

Kinetic Law

Derived unit $\mathrm{l}^{-1} \cdot \mathrm{nmol} \cdot (3600\ \mathrm{s})^{-1}$

$$v_{15} = \mathrm{vol}\,(\mathrm{compartment}) \cdot [\mathrm{GaGDPP}] \cdot \mathrm{k15} \tag{32}$$

Table 65: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k15	k15		1000.0	$(3600\ \mathrm{s})^{-1}$	☑

7.16 Reaction R16

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

Name Gprotein subunits association

SBO:0000526 protein complex formation

Reaction equation

$$\mathrm{GaGDP} + \mathrm{Gbg} \xrightarrow{\mathrm{GaGDP,\ Gbg}} \mathrm{Gabg} \tag{33}$$

Reactants

Table 66: Properties of each reactant.

Id	Name	SBO
GaGDP	GaGDP	
Gbg	Gbg	

Modifiers

Table 67: Properties of each modifier.

Id	Name	SBO
GaGDP	GaGDP	
Gbg	Gbg	

Product

Table 68: Properties of each product.

Id	Name	SBO
Gabg	Gabg	

Kinetic Law

Derived unit $1^{-2} \cdot 9.999999999999998 \cdot 10^{-10}\ \mathrm{mol} \cdot (3600\ \mathrm{s})^{-1}$

$$v_{16} = \mathrm{vol}\,(\mathrm{compartment}) \cdot [\mathrm{GaGDP}] \cdot [\mathrm{Gbg}] \cdot \mathrm{k16} \tag{34}$$

Table 69: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k16	k16		1000.0	$\text{nmol}^{-1} \cdot \text{l} \cdot (3600\ \text{s})^{-1}$	☑

7.17 Reaction R17

This is an irreversible reaction of one reactant forming no product influenced by one modifier.

Name Phosphate degradation

SBO:0000179 degradation

Reaction equation

$$\text{P} \xrightarrow{\text{P}} \emptyset \tag{35}$$

Reactant

Table 70: Properties of each reactant.

Id	Name	SBO
P	P	

Modifier

Table 71: Properties of each modifier.

Id	Name	SBO
P	P	

Kinetic Law

Derived unit $\text{l}^{-1} \cdot \text{nmol} \cdot (3600\ \text{s})^{-1}$

$$v_{17} = \text{vol}(\text{compartment}) \cdot [\text{P}] \cdot \text{k17} \tag{36}$$

Table 72: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k17	k17		10.0	$(3600\ \mathrm{s})^{-1}$	☑

7.18 Reaction R18

This is an irreversible reaction of no reactant forming one product influenced by two modifiers.

Name Delay 1

SBO:0000225 delay

Reaction equation

$$\emptyset \xrightarrow{\text{GaGTPEffector, GaGTPEffector}} \text{z1} \tag{37}$$

Modifiers

Table 73: Properties of each modifier.

Id	Name	SBO
GaGTPEffector	GaGTPEffector	
GaGTPEffector	GaGTPEffector	

Product

Table 74: Properties of each product.

Id	Name	SBO
z1	z1	

Kinetic Law

Derived unit $1^{-1} \cdot \mathrm{nmol} \cdot (3600\ \mathrm{s})^{-1}$

$$v_{18} = \mathrm{vol}\,(\mathrm{compartment}) \cdot [\mathrm{GaGTPEffector}] \cdot \mathrm{ka} \tag{38}$$

7.19 Reaction R19

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

Name Delay 2

SBO:0000225 delay

Reaction equation

$$\mathrm{z1} \xrightarrow{\mathrm{z1}} \mathrm{z2} \tag{39}$$

Reactant

Table 75: Properties of each reactant.

Id	Name	SBO
z1	z1	

Modifier

Table 76: Properties of each modifier.

Id	Name	SBO
z1	z1	

Product

Table 77: Properties of each product.

Id	Name	SBO
z2	z2	

Kinetic Law

Derived unit $\mathrm{l}^{-1} \cdot \mathrm{nmol} \cdot (3600\ \mathrm{s})^{-1}$

$$v_{19} = \mathrm{vol}\,(\mathrm{compartment}) \cdot [\mathrm{z1}] \cdot \mathrm{ka} \tag{40}$$

7.20 Reaction R20

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

Name Delay 3

SBO:0000225 delay

Reaction equation

$$\mathrm{z2} \xrightarrow{\mathrm{z2}} \mathrm{z3} \tag{41}$$

Reactant

Table 78: Properties of each reactant.

Id	Name	SBO
z2	z2	

Modifier

Table 79: Properties of each modifier.

Id	Name	SBO
z2	z2	

Product

Table 80: Properties of each product.

Id	Name	SBO
z3	z3	

Kinetic Law

Derived unit $\mathrm{l}^{-1} \cdot \mathrm{nmol} \cdot (3600\ \mathrm{s})^{-1}$

$$v_{20} = \mathrm{vol}\,(\mathrm{compartment}) \cdot [\mathrm{z2}] \cdot \mathrm{ka} \tag{42}$$

7.21 Reaction R21

This is an irreversible reaction of one reactant forming no product influenced by one modifier.

Name Delay 4

SBO:0000225 delay

Reaction equation

$$\mathrm{z3} \xrightarrow{\mathrm{z3}} \emptyset \tag{43}$$

Reactant

Table 81: Properties of each reactant.

Id	Name	SBO
z3	z3	

Modifier

Table 82: Properties of each modifier.

Id	Name	SBO
z3	z3	

Kinetic Law

Derived unit $\mathrm{l}^{-1} \cdot \mathrm{nmol} \cdot (3600\ \mathrm{s})^{-1}$

$$v_{21} = \mathrm{vol}\,(\mathrm{compartment}) \cdot [\mathrm{z3}] \cdot \mathrm{ka} \tag{44}$$

8 Derived Rate Equations

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

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

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

8.1 Species R

Name R

SBO:0000244 receptor

Initial concentration $205\ \mathrm{nmol} \cdot \mathrm{l}^{-1} \cdot \mathrm{l}^{-1}$

This species takes part in four reactions (as a reactant in R1, R2 and as a modifier in R1, R2).

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

8.2 Species L

Name L

SBO:0000280 ligand

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

Involved in event Ligand_addition

This species takes part in four reactions (as a reactant in R1, R4 and as a modifier in R1, R4).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{L} = -\,v_1 - v_4 \tag{46}$$

Furthermore, one event influences this species' rate of change.

8.3 Species RL

Name RL

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

This species takes part in four reactions (as a reactant in R3 and as a product in R1, R5 and as a modifier in R3).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{RL} = v_1 + v_5 - v_3 \tag{47}$$

8.4 Species Gabg

Name Gabg

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

This species takes part in seven reactions (as a reactant in R2, R3, R6 and as a product in R16 and as a modifier in R2, R3, R6).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Gabg} = v_{16} - v_2 - v_3 - v_6 \tag{48}$$

8.5 Species RGabg

Name RGabg

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

This species takes part in three reactions (as a reactant in R4 and as a product in R2 and as a modifier in R4).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{RGabg} = v_2 - v_4 \tag{49}$$

8.6 Species RGabgL

Name RGabgL

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

This species takes part in four reactions (as a reactant in R5 and as a product in R3, R4 and as a modifier in R5).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{RGabgL} = v_3 + v_4 - v_5 \tag{50}$$

8.7 Species GaGTP

Name GaGTP

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

This species takes part in eight reactions (as a reactant in R7, R9, R10 and as a product in R5, R6 and as a modifier in R7, R9, R10).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{GaGTP} = v_5 + v_6 - v_7 - v_9 - v_{10} \tag{51}$$

8.8 Species Gbg

Name Gbg

Initial concentration $205\ \mathrm{nmol}\cdot 1^{-1}\cdot 1^{-1}$

This species takes part in four reactions (as a reactant in R16 and as a product in R5, R6 and as a modifier in R16).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Gbg} = v_5 + v_6 - v_{16} \tag{52}$$

8.9 Species RGS

Name RGS

Notes NoRGS=0, 1xRGS=60, 2xRGS=120, 3xRGS=180

Initial concentration $60\ \mathrm{nmol}\cdot 1^{-1}\cdot 1^{-1}$

This species takes part in six reactions (as a reactant in R7, R12 and as a product in R8, R13 and as a modifier in R7, R12).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{RGS} = v_8 + v_{13} - v_7 - v_{12} \tag{53}$$

8.10 Species RGSGaGTP

Name RGSGaGTP

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

This species takes part in three reactions (as a reactant in R8 and as a product in R7 and as a modifier in R8).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{RGSGaGTP} = v_7 - v_8 \tag{54}$$

8.11 Species GaGDPP

Name GaGDPP

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

This species takes part in six reactions (as a reactant in R15 and as a product in R8, R9, R13, R14 and as a modifier in R15).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{GaGDPP} = v_8 + v_9 + v_{13} + v_{14} - v_{15} \tag{55}$$

8.12 Species Effector

Name Effector

Initial concentration $205\ \mathrm{nmol}\cdot\mathrm{l}^{-1}\cdot\mathrm{l}^{-1}$

This species takes part in three reactions (as a reactant in R10 and as a product in R11 and as a modifier in R10).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Effector} = v_{11} - v_{10} \tag{56}$$

8.13 Species GaGTPEffector

Name GaGTPEffector

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

This species takes part in five reactions (as a reactant in R11 and as a product in R10 and as a modifier in R11, R18, R18).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{GaGTPEffector} = v_{10} - v_{11} \tag{57}$$

8.14 Species inertGaTP

Name inertGaTP

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

This species takes part in five reactions (as a reactant in R12, R14 and as a product in R11 and as a modifier in R12, R14).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{inertGaTP} = v_{11} - v_{12} - v_{14} \tag{58}$$

8.15 Species RGSinertGaTP

Name RGSinertGaTP

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

This species takes part in three reactions (as a reactant in R13 and as a product in R12 and as a modifier in R13).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{RGSinertGaTP} = v_{12} - v_{13} \tag{59}$$

8.16 Species GaGDP

Name GaGDP

Initial concentration $205\ \mathrm{nmol}\cdot 1^{-1}\cdot 1^{-1}$

This species takes part in three reactions (as a reactant in R16 and as a product in R15 and as a modifier in R16).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{GaGDP} = v_{15} - v_{16} \tag{60}$$

8.17 Species P

Name P

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

This species takes part in three reactions (as a reactant in R17 and as a product in R15 and as a modifier in R17).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{P} = v_{15} - v_{17} \tag{61}$$

8.18 Species z1

Name z1

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

This species takes part in three reactions (as a reactant in R19 and as a product in R18 and as a modifier in R19).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{z1} = v_{18} - v_{19} \tag{62}$$

8.19 Species z2

Name z2

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

This species takes part in three reactions (as a reactant in R20 and as a product in R19 and as a modifier in R20).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{z2} = v_{19} - v_{20} \tag{63}$$

8.20 Species z3

Name z3

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

This species takes part in three reactions (as a reactant in R21 and as a product in R20 and as a modifier in R21).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{z3} = v_{20} - v_{21} \tag{64}$$

A Glossary of Systems Biology Ontology Terms

SBO:0000169 inhibition: Negative modulation of the execution of a process

SBO:0000179 degradation: Complete disappearance of a physical entity

SBO:0000225 delay: Time during which some action is awaited

SBO:0000244 receptor: Participating entity that binds to a specific physical entity and initiates the response to that physical entity.The original concept of the receptor was introduced independently at the end of the 19th century by John Newport Langley (1852-1925) and Paul Ehrlich (1854-1915). Langley JN.On the reaction of cells and of nerve-endings to certain poisons, chiefly as regards the reaction of striated muscle to nicotine and to curari. J Physiol. 1905 Dec 30;33(4-5):374-413

SBO:0000280 ligand: In biochemistry, a ligand is an effector, a physical entity that binds to a site on a receptor's surface by intermolecular forces

SBO:0000393 production: Generation of a material or conceptual entity.

SBO:0000526 protein complex formation: The process by which two or more proteins interact non-covalently to form a protein complex (SBO:0000297)

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