SBML Model Report

Model name: "Heitzler2012_GPCRsignalling"

May 5, 2016

1 General Overview

This is a document in SBML Level 2 Version 4 format. Table 1 gives 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	18
events	0	constraints	0
reactions	26	function definitions	0
global parameters	35	unit definitions	0
rules	0	initial assignments	0

Model Notes

This model is from the article:
Competing G protein-coupled receptor kinases balance G protein and -arrestin signaling
Heitzler D, Durand G, Gallay N, Rizk A, Ahn S, Kim J, Violin JD, Dupuy L, Gauthier C, Piketty V, Crpieux P, Poupon A, Clment F, Fages F, Lefkowitz RJ, Reiter E. Mol Syst Biol. 2012; 8: 590. 22735336 ,
Abstract:
Seven-transmembrane receptors (7TMRs) are involved in nearly all aspects of chemical communications and represent major drug targets. 7TMRs transmit their signals not only via heterotrimeric G proteins but also through -arrestins, whose recruitment to the activated receptor

is regulated by G protein-coupled receptor kinases (GRKs). In this paper, we combined experimental approaches with computational modeling to decipher the molecular mechanisms as well as the hidden dynamics governing extracellular signal-regulated kinase (ERK) activation by the angiotensin II type 1A receptor (AT(1A)R) in human embryonic kidney (HEK)293 cells. We built an abstracted ordinary differential equations (ODE)-based model that captured the available knowledge and experimental data. We inferred the unknown parameters by simultaneously fitting experimental data generated in both control and perturbed conditions. We demonstrate that, in addition to its well-established function in the desensitization of G-protein activation, GRK2 exerts a strong negative effect on -arrestin-dependent signaling through its competition with GRK5 and 6 for receptor phosphorylation. Importantly, we experimentally confirmed the validity of this novel GRK2-dependent mechanism in both primary vascular smooth muscle cells naturally expressing the AT(1A)R, and HEK293 cells expressing other 7TMRs.

2 Unit Definitions

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

2.1 Unit `substance`

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

Definition mol

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
`compartmentOne`			3	1	litre	☑	

3.1 Compartment `compartmentOne`

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

4 Species

This model contains 18 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
HR	H-R	compartmentOne	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
G	G	compartmentOne	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
ERK	ERK	compartmentOne	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
PIP2	PIP2	compartmentOne	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
DAG	DAG	compartmentOne	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
PKC	PKC	compartmentOne	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
PKC_a	PKC_a	compartmentOne	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
GpERK	GpERK	compartmentOne	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
bpERK	bpERK	compartmentOne	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
barr1	barr1	compartmentOne	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
barr2	barr2	compartmentOne	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
G_a	G_a	compartmentOne	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
HRP1	H-R~{P1}	compartmentOne	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
Hbarr1RP1	H-barr1-R~{P1}	compartmentOne	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
Hbarr2RP1	H-barr2-R~{P1}	compartmentOne	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
HRP2	H-R~{P2}	compartmentOne	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
HRbarr2	H-R-barr2	compartmentOne	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
Hbarr2RP2	H-barr2-R~{P2}	compartmentOne	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟

5 Parameters

This model contains 35 global parameters.

Table 4: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k0	k0		$3.11 \cdot 10^{-4}$		⊟
k1	k1		0.018		⊟
k2	k2		7.600		⊟
k3	k3		4.630		⊟
k4	k4		0.079		⊟
k5	k5		2.650		⊟
k6	k6		5.099		⊟
k7	k7		0.461		⊟
k8	k8		1.770		⊟
k9	k9		3.040		⊟
k10	k10		2.270		⊟
k11	k11		2.610		⊟
k12	k12		2.590		⊟
k13	k13		0.006		⊟
k14	k14		0.031		⊟
k15	k15		$6.54 \cdot 10^{-5}$		⊟
k16	k16		0.072		⊟
k17	k17		0.067		⊟
k18	k18		0.590		⊟
k19	k19		0.205		⊟
k20	k20		1.040		⊟
k21	k21		$4.2 \cdot 10^{-4}$		⊟
k22	k22		14.440		⊟
k23	k23		1.050		⊟
k24	k24		0.347		⊟
k25	k25		0.762		⊟
GRK23	GRK23		0.899		⊟
GRK56	GRK56		1.518		⊟
GRK23_si	GRK23_si		0.479		⊟
GRK56_si	GRK56_si		0.001		⊟
P0_Ro	P0_Ro		0.002		⊟
P0_a_Ro	P0_a_Ro		$2.09075206 \cdot 10^{-5}$		⊟
barr2_0_si	barr2_0_si		$1.12306963 \cdot 10^{-4}$		⊟
nDAG	nDAG		4.120		⊟
nPKC	nPKC		7.209		⊟

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

№	Id	Name	Reaction Equation	SBO
1	R_1		$G \xrightarrow{G} G\_a$	
2	R_2		$G + HRP1 \xrightarrow{G,\ HRP1} G\_a + HRP1$	
3	R_3		$G + HR \xrightarrow{G,\ HR} G\_a + HR$	
4	R_4		$G\_a + PIP2 \xrightarrow{G\_a,\ PIP2} DAG + G\_a$	
5	R_5		$DAG + PKC \xrightarrow{DAG,\ PKC} DAG + PKC\_a$	
6	R_6		$ERK + PKC\_a \xrightarrow{ERK,\ PKC\_a} GpERK + PKC\_a$	
7	R_7		$G\_a \xrightarrow{G\_a} G$	
8	R_8		$DAG \xrightarrow{DAG} PIP2$	
9	R_9		$PKC\_a \xrightarrow{PKC\_a} PKC$	
10	R_10		$GpERK \xrightarrow{GpERK} ERK$	
11	R_11		$HR \xrightarrow{HR} HRP1$	
12	R_12		$barr1 + HRP1 \xrightarrow{barr1,\ HRP1} Hbarr1RP1$	
13	R_13		$Hbarr1RP1 \xrightarrow{Hbarr1RP1} barr1 + HRP1$	
14	R_14		$barr2 + HRP1 \xrightarrow{barr2,\ HRP1} Hbarr2RP1$	
15	R_15		$Hbarr2RP1 \xrightarrow{Hbarr2RP1} barr2 + HRP1$	
16	R_16		$Hbarr1RP1 \xrightarrow{Hbarr1RP1} barr1 + HR$	

№	Id	Name	Reaction Equation	SBO
17	R_17		$\text{Hbarr2RP1} \xrightarrow{\text{Hbarr2RP1}} \text{barr2} + \text{HR}$	
18	R_18		$\text{HR} \xrightarrow{\text{HR}} \text{HRP2}$	
19	R_19		$\text{HRP2} \xrightarrow{\text{HRP2}} \text{HR}$	
20	R_20		$\text{barr2} + \text{HR} \xrightarrow{\text{barr2, HR}} \text{HRbarr2}$	
21	R_21		$\text{HRbarr2} \xrightarrow{\text{HRbarr2}} \text{barr2} + \text{HR}$	
22	R_22		$\text{barr2} + \text{HRP2} \xrightarrow{\text{barr2, HRP2}} \text{Hbarr2RP2}$	
23	R_23		$\text{Hbarr2RP2} \xrightarrow{\text{Hbarr2RP2}} \text{barr2} + \text{HRP2}$	
24	R_24		$\text{ERK} + \text{HRbarr2} \xrightarrow{\text{ERK, HRbarr2}} \text{bpERK} + \text{HRbarr2}$	
25	R_25		$\text{ERK} + \text{Hbarr2RP2} \xrightarrow{\text{ERK, Hbarr2RP2}} \text{bpERK} + \text{Hbarr2RP2}$	
26	R_26		$\text{bpERK} \xrightarrow{\text{bpERK}} \text{ERK}$	

6.1 Reaction R_1

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

Reaction equation

$$\mathrm{G} \xrightarrow{\mathrm{G}} \mathrm{G\_a} \tag{1}$$

Reactant

Table 6: Properties of each reactant.

Id	Name	SBO
G	G	

Modifier

Table 7: Properties of each modifier.

Id	Name	SBO
G	G	

Product

Table 8: Properties of each product.

Id	Name	SBO
G_a	G_a	

Kinetic Law

Derived unit contains undeclared units

$$v_1 = \mathrm{k0} \cdot [\mathrm{G}] \tag{2}$$

6.2 Reaction R_2

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

Reaction equation

$$\mathrm{G} + \mathrm{HRP1} \xrightarrow{\mathrm{G,\ HRP1}} \mathrm{G\_a} + \mathrm{HRP1} \tag{3}$$

Reactants

Table 9: Properties of each reactant.

Id	Name	SBO
G	G	
HRP1	H-R~{P1}	

Modifiers

Table 10: Properties of each modifier.

Id	Name	SBO
G	G	
HRP1	H-R~{P1}	

Products

Table 11: Properties of each product.

Id	Name	SBO
G_a	G_a	
HRP1	H-R~{P1}	

Kinetic Law

Derived unit contains undeclared units

$$v_2 = \mathrm{k1} \cdot [\mathrm{G}] \cdot [\mathrm{HRP1}] \tag{4}$$

6.3 Reaction R_3

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

Reaction equation

$$\mathrm{G} + \mathrm{HR} \xrightarrow{\mathrm{G,\ HR}} \mathrm{G\_a} + \mathrm{HR} \tag{5}$$

Reactants

Table 12: Properties of each reactant.

Id	Name	SBO
G	G	
HR	H-R	

Modifiers

Table 13: Properties of each modifier.

Id	Name	SBO
G	G	
HR	H-R	

Products

Table 14: Properties of each product.

Id	Name	SBO
G_a	G_a	
HR	H-R	

Kinetic Law

Derived unit contains undeclared units

$$v_3 = \mathrm{k2} \cdot [\mathrm{G}] \cdot [\mathrm{HR}] \tag{6}$$

6.4 Reaction R_4

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

Reaction equation

$$\mathrm{G\_a} + \mathrm{PIP2} \xrightarrow{\mathrm{G\_a,\ PIP2}} \mathrm{DAG} + \mathrm{G\_a} \tag{7}$$

Reactants

Table 15: Properties of each reactant.

Id	Name	SBO
G_a	G_a	
PIP2	PIP2	

Modifiers

Table 16: Properties of each modifier.

Id	Name	SBO
G_a	G_a	
PIP2	PIP2	

Products

Table 17: Properties of each product.

Id	Name	SBO
DAG	DAG	
G_a	G_a	

Kinetic Law

Derived unit contains undeclared units

$$v_4 = \mathrm{k3} \cdot [\mathrm{G\_a}] \cdot [\mathrm{PIP2}] \tag{8}$$

6.5 Reaction R_5

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

Reaction equation

$$\mathrm{DAG} + \mathrm{PKC} \xrightarrow{\mathrm{DAG,\ PKC}} \mathrm{DAG} + \mathrm{PKC\_a} \tag{9}$$

Reactants

Table 18: Properties of each reactant.

Id	Name	SBO
DAG	DAG	
PKC	PKC	

Modifiers

Table 19: Properties of each modifier.

Id	Name	SBO
DAG	DAG	
PKC	PKC	

Products

Table 20: Properties of each product.

Id	Name	SBO
DAG	DAG	
PKC_a	PKC_a	

Kinetic Law

Derived unit contains undeclared units

$$v_5 = \mathrm{k4} \cdot [\mathrm{DAG}] \cdot [\mathrm{PKC}] \tag{10}$$

6.6 Reaction R_6

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

Reaction equation

$$\mathrm{ERK} + \mathrm{PKC\_a} \xrightarrow{\mathrm{ERK,\ PKC\_a}} \mathrm{GpERK} + \mathrm{PKC\_a} \tag{11}$$

Reactants

Table 21: Properties of each reactant.

Id	Name	SBO
ERK	ERK	
PKC_a	PKC_a	

Modifiers

Table 22: Properties of each modifier.

Id	Name	SBO
ERK	ERK	
PKC_a	PKC_a	

Products

Table 23: Properties of each product.

Id	Name	SBO
GpERK	GpERK	
PKC_a	PKC_a	

Kinetic Law

Derived unit contains undeclared units

$$v_6 = \mathrm{k5} \cdot [\mathrm{ERK}] \cdot [\mathrm{PKC\_a}] \tag{12}$$

6.7 Reaction R_7

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

Reaction equation

$$\mathrm{G\_a} \xrightarrow{\mathrm{G\_a}} \mathrm{G} \tag{13}$$

Reactant

Table 24: Properties of each reactant.

Id	Name	SBO
G_a	G_a	

Modifier

Table 25: Properties of each modifier.

Id	Name	SBO
G_a	G_a	

Product

Table 26: Properties of each product.

Id	Name	SBO
G	G	

Kinetic Law

Derived unit contains undeclared units

$$v_7 = \mathrm{k6} \cdot [\mathrm{G\_a}] \tag{14}$$

6.8 Reaction R_8

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

Reaction equation

$$\mathrm{DAG} \xrightarrow{\mathrm{DAG}} \mathrm{PIP2} \tag{15}$$

Reactant

Table 27: Properties of each reactant.

Id	Name	SBO
DAG	DAG	

Modifier

Table 28: Properties of each modifier.

Id	Name	SBO
DAG	DAG	

Product

Table 29: Properties of each product.

Id	Name	SBO
PIP2	PIP2	

Kinetic Law

Derived unit contains undeclared units

$$v_8 = \mathrm{k7} \cdot [\mathrm{DAG}] \tag{16}$$

6.9 Reaction R_9

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

Reaction equation

$$\mathrm{PKC\_a} \xrightarrow{\mathrm{PKC\_a}} \mathrm{PKC} \tag{17}$$

Reactant

Table 30: Properties of each reactant.

Id	Name	SBO
PKC_a	PKC_a	

Modifier

Table 31: Properties of each modifier.

Id	Name	SBO
PKC_a	PKC_a	

Id	Name	SBO

Product

Table 32: Properties of each product.

Id	Name	SBO
PKC	PKC	

Kinetic Law

Derived unit contains undeclared units

$$v_9 = \mathrm{k8} \cdot [\mathrm{PKC\_a}] \tag{18}$$

6.10 Reaction R_10

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

Reaction equation

$$\mathrm{GpERK} \xrightarrow{\mathrm{GpERK}} \mathrm{ERK} \tag{19}$$

Reactant

Table 33: Properties of each reactant.

Id	Name	SBO
GpERK	GpERK	

Modifier

Table 34: Properties of each modifier.

Id	Name	SBO
GpERK	GpERK	

Product

Table 35: Properties of each product.

Id	Name	SBO
ERK	ERK	

Kinetic Law

Derived unit contains undeclared units

$$v_{10} = \mathrm{k9} \cdot [\mathrm{GpERK}] \tag{20}$$

6.11 Reaction R_11

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

Reaction equation

$$\mathrm{HR} \xrightarrow{\mathrm{HR}} \mathrm{HRP1} \tag{21}$$

Reactant

Table 36: Properties of each reactant.

Id	Name	SBO
HR	H-R	

Modifier

Table 37: Properties of each modifier.

Id	Name	SBO
HR	H-R	

Product

Table 38: Properties of each product.

Id	Name	SBO
HRP1	H-R~{P1}	

Kinetic Law

Derived unit contains undeclared units

$$v_{11} = \mathrm{k10} \cdot \mathrm{GRK23} \cdot [\mathrm{HR}] \tag{22}$$

6.12 Reaction R_12

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

Reaction equation

$$\mathrm{barr1} + \mathrm{HRP1} \xrightarrow{\mathrm{barr1,\ HRP1}} \mathrm{Hbarr1RP1} \tag{23}$$

Reactants

Table 39: Properties of each reactant.

Id	Name	SBO
barr1	barr1	
HRP1	H-R~{P1}	

Modifiers

Table 40: Properties of each modifier.

Id	Name	SBO
barr1	barr1	
HRP1	H-R~{P1}	

Product

Table 41: Properties of each product.

Id	Name	SBO
Hbarr1RP1	H-barr1-R~{P1}	

Kinetic Law

Derived unit contains undeclared units

$$v_{12} = \mathrm{k11} \cdot [\mathrm{barr1}] \cdot [\mathrm{HRP1}] \tag{24}$$

6.13 Reaction R_13

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

Reaction equation

$$\text{Hbarr1RP1} \xrightarrow{\text{Hbarr1RP1}} \text{barr1} + \text{HRP1} \tag{25}$$

Reactant

Table 42: Properties of each reactant.

Id	Name	SBO
Hbarr1RP1	H-barr1-R~{P1}	

Modifier

Table 43: Properties of each modifier.

Id	Name	SBO
Hbarr1RP1	H-barr1-R~{P1}	

Products

Table 44: Properties of each product.

Id	Name	SBO
barr1	barr1	
HRP1	H-R~{P1}	

Kinetic Law

Derived unit contains undeclared units

$$v_{13} = \text{k13} \cdot [\text{Hbarr1RP1}] \tag{26}$$

6.14 Reaction R_14

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

Reaction equation

$$\text{barr2} + \text{HRP1} \xrightarrow{\text{barr2, HRP1}} \text{Hbarr2RP1} \tag{27}$$

Reactants

Table 45: Properties of each reactant.

Id	Name	SBO
barr2	barr2	
HRP1	H-R~{P1}	

Modifiers

Table 46: Properties of each modifier.

Id	Name	SBO
barr2	barr2	
HRP1	H-R~{P1}	

Product

Table 47: Properties of each product.

Id	Name	SBO
Hbarr2RP1	H-barr2-R~{P1}	

Kinetic Law

Derived unit contains undeclared units

$$v_{14} = \text{k12} \cdot [\text{barr2}] \cdot [\text{HRP1}] \tag{28}$$

6.15 Reaction R_15

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

Reaction equation

$$\text{Hbarr2RP1} \xrightarrow{\text{Hbarr2RP1}} \text{barr2} + \text{HRP1} \tag{29}$$

Reactant

Table 48: Properties of each reactant.

Id	Name	SBO
Hbarr2RP1	H-barr2-R~{P1}	

Modifier

Table 49: Properties of each modifier.

Id	Name	SBO
Hbarr2RP1	H-barr2-R~{P1}	

Products

Table 50: Properties of each product.

Id	Name	SBO
barr2	barr2	
HRP1	H-R~{P1}	

Kinetic Law

Derived unit contains undeclared units

$$v_{15} = \mathrm{k14} \cdot [\mathrm{Hbarr2RP1}] \tag{30}$$

6.16 Reaction R_16

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

Reaction equation

$$\mathrm{Hbarr1RP1} \xrightarrow{\mathrm{Hbarr1RP1}} \mathrm{barr1} + \mathrm{HR} \tag{31}$$

Reactant

Table 51: Properties of each reactant.

Id	Name	SBO
Hbarr1RP1	H-barr1-R~{P1}	

Modifier

Table 52: Properties of each modifier.

Id	Name	SBO
Hbarr1RP1	H-barr1-R~{P1}	

Products

Table 53: Properties of each product.

Id	Name	SBO
barr1	barr1	
HR	H-R	

Kinetic Law

Derived unit contains undeclared units

$$v_{16} = \mathrm{k15} \cdot [\mathrm{Hbarr1RP1}] \tag{32}$$

6.17 Reaction R_17

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

Reaction equation

$$\mathrm{Hbarr2RP1} \xrightarrow{\mathrm{Hbarr2RP1}} \mathrm{barr2} + \mathrm{HR} \tag{33}$$

Reactant

Table 54: Properties of each reactant.

Id	Name	SBO
Hbarr2RP1	H-barr2-R~{P1}	

Modifier

Table 55: Properties of each modifier.

Id	Name	SBO
Hbarr2RP1	H-barr2-R~{P1}	

Products

Table 56: Properties of each product.

Id	Name	SBO
barr2	barr2	
HR	H-R	

Kinetic Law

Derived unit contains undeclared units

$$v_{17} = \mathrm{k16} \cdot [\mathrm{Hbarr2RP1}] \tag{34}$$

6.18 Reaction R_18

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

Reaction equation

$$\mathrm{HR} \xrightarrow{\mathrm{HR}} \mathrm{HRP2} \tag{35}$$

Reactant

Table 57: Properties of each reactant.

Id	Name	SBO
HR	H-R	

Modifier

Table 58: Properties of each modifier.

Id	Name	SBO
HR	H-R	

Product

Table 59: Properties of each product.

Id	Name	SBO
HRP2	H-R~{P2}	

Kinetic Law

Derived unit contains undeclared units

$$v_{18} = \mathrm{k18} \cdot \mathrm{GRK56} \cdot [\mathrm{HR}] \tag{36}$$

6.19 Reaction R_19

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

Reaction equation

$$\mathrm{HRP2} \xrightarrow{\mathrm{HRP2}} \mathrm{HR} \tag{37}$$

Reactant

Table 60: Properties of each reactant.

Id	Name	SBO
HRP2	H-R~{P2}	

Modifier

Table 61: Properties of each modifier.

Id	Name	SBO
HRP2	H-R~{P2}	

Product

Table 62: Properties of each product.

Id	Name	SBO
HR	H-R	

Id	Name	SBO

Kinetic Law

Derived unit contains undeclared units

$$v_{19} = \mathrm{k17} \cdot [\mathrm{HRP2}] \tag{38}$$

6.20 Reaction R_20

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

Reaction equation

$$\mathrm{barr2} + \mathrm{HR} \xrightarrow{\mathrm{barr2,\ HR}} \mathrm{HRbarr2} \tag{39}$$

Reactants

Table 63: Properties of each reactant.

Id	Name	SBO
barr2	barr2	
HR	H-R	

Modifiers

Table 64: Properties of each modifier.

Id	Name	SBO
barr2	barr2	
HR	H-R	

Product

Table 65: Properties of each product.

Id	Name	SBO
HRbarr2	H-R-barr2	

Kinetic Law

Derived unit contains undeclared units

$$v_{20} = \mathrm{k19} \cdot [\mathrm{barr2}] \cdot [\mathrm{HR}] \tag{40}$$

6.21 Reaction R_21

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

Reaction equation

$$\mathrm{HRbarr2} \xrightarrow{\mathrm{HRbarr2}} \mathrm{barr2} + \mathrm{HR} \tag{41}$$

Reactant

Table 66: Properties of each reactant.

Id	Name	SBO
HRbarr2	H-R-barr2	

Modifier

Table 67: Properties of each modifier.

Id	Name	SBO
HRbarr2	H-R-barr2	

Products

Table 68: Properties of each product.

Id	Name	SBO
barr2	barr2	
HR	H-R	

Kinetic Law

Derived unit contains undeclared units

$$v_{21} = \mathrm{k23} \cdot [\mathrm{HRbarr2}] \tag{42}$$

6.22 Reaction R_22

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

Reaction equation

$$\text{barr2} + \text{HRP2} \xrightarrow{\text{barr2, HRP2}} \text{Hbarr2RP2} \tag{43}$$

Reactants

Table 69: Properties of each reactant.

Id	Name	SBO
barr2	barr2	
HRP2	H-R~{P2}	

Modifiers

Table 70: Properties of each modifier.

Id	Name	SBO
barr2	barr2	
HRP2	H-R~{P2}	

Product

Table 71: Properties of each product.

Id	Name	SBO
Hbarr2RP2	H-barr2-R~{P2}	

Kinetic Law

Derived unit contains undeclared units

$$v_{22} = \text{k20} \cdot [\text{barr2}] \cdot [\text{HRP2}] \tag{44}$$

6.23 Reaction R_23

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

Reaction equation

$$\text{Hbarr2RP2} \xrightarrow{\text{Hbarr2RP2}} \text{barr2} + \text{HRP2} \tag{45}$$

Reactant

Table 72: Properties of each reactant.

Id	Name	SBO
Hbarr2RP2	H-barr2-R~{P2}	

Modifier

Table 73: Properties of each modifier.

Id	Name	SBO
Hbarr2RP2	H-barr2-R~{P2}	

Products

Table 74: Properties of each product.

Id	Name	SBO
barr2	barr2	
HRP2	H-R~{P2}	

Kinetic Law

Derived unit contains undeclared units

$$v_{23} = \text{k24} \cdot [\text{Hbarr2RP2}] \tag{46}$$

6.24 Reaction R_24

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

Reaction equation

$$\text{ERK} + \text{HRbarr2} \xrightarrow{\text{ERK, HRbarr2}} \text{bpERK} + \text{HRbarr2} \tag{47}$$

Reactants

Table 75: Properties of each reactant.

Id	Name	SBO
ERK	ERK	
HRbarr2	H-R-barr2	

Modifiers

Table 76: Properties of each modifier.

Id	Name	SBO
ERK	ERK	
HRbarr2	H-R-barr2	

Products

Table 77: Properties of each product.

Id	Name	SBO
bpERK	bpERK	
HRbarr2	H-R-barr2	

Kinetic Law

Derived unit contains undeclared units

$$v_{24} = \mathrm{k21} \cdot [\mathrm{ERK}] \cdot [\mathrm{HRbarr2}] \tag{48}$$

6.25 Reaction R_25

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

Reaction equation

$$\mathrm{ERK} + \mathrm{Hbarr2RP2} \xrightarrow{\mathrm{ERK,\ Hbarr2RP2}} \mathrm{bpERK} + \mathrm{Hbarr2RP2} \tag{49}$$

Reactants

Table 78: Properties of each reactant.

Id	Name	SBO
ERK	ERK	
Hbarr2RP2	H-barr2-R~{P2}	

Modifiers

Table 79: Properties of each modifier.

Id	Name	SBO
ERK	ERK	
Hbarr2RP2	H-barr2-R~{P2}	

Products

Table 80: Properties of each product.

Id	Name	SBO
bpERK	bpERK	
Hbarr2RP2	H-barr2-R~{P2}	

Kinetic Law

Derived unit contains undeclared units

$$v_{25} = \mathrm{k22} \cdot [\mathrm{ERK}] \cdot [\mathrm{Hbarr2RP2}] \tag{50}$$

6.26 Reaction R_26

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

Reaction equation

$$\mathrm{bpERK} \xrightarrow{\mathrm{bpERK}} \mathrm{ERK} \tag{51}$$

Reactant

Table 81: Properties of each reactant.

Id	Name	SBO
bpERK	bpERK	

Modifier

Table 82: Properties of each modifier.

Id	Name	SBO
bpERK	bpERK	

Product

Table 83: Properties of each product.

Id	Name	SBO
ERK	ERK	

Kinetic Law

Derived unit contains undeclared units

$$v_{26} = \text{k25} \cdot [\text{bpERK}] \tag{52}$$

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 HR

Name H-R

Initial concentration $0.08\ \text{mol} \cdot \text{l}^{-1}$

This species takes part in 13 reactions (as a reactant in R_3, R_11, R_18, R_20 and as a product in R_3, R_16, R_17, R_19, R_21 and as a modifier in R_3, R_11, R_18, R_20).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{HR} = v_3 + v_{16} + v_{17} + v_{19} + v_{21} - v_3 - v_{11} - v_{18} - v_{20} \tag{53}$$

7.2 Species G

Name G

Initial concentration $56.99\ \mathrm{mol}\cdot\mathrm{l}^{-1}$

This species takes part in seven reactions (as a reactant in R_1, R_2, R_3 and as a product in R_7 and as a modifier in R_1, R_2, R_3).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{G} = v_7 - v_1 - v_2 - v_3 \tag{54}$$

7.3 Species ERK

Name ERK

Initial concentration $4.243\ \mathrm{mol}\cdot\mathrm{l}^{-1}$

This species takes part in eight reactions (as a reactant in R_6, R_24, R_25 and as a product in R_10, R_26 and as a modifier in R_6, R_24, R_25).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{ERK} = v_{10} + v_{26} - v_6 - v_{24} - v_{25} \tag{55}$$

7.4 Species PIP2

Name PIP2

Initial concentration $0.997\ \mathrm{mol}\cdot\mathrm{l}^{-1}$

This species takes part in three reactions (as a reactant in R_4 and as a product in R_8 and as a modifier in R_4).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{PIP2} = v_8 - v_4 \tag{56}$$

7.5 Species DAG

Name DAG

Initial concentration $0.0090\ \mathrm{mol}\cdot\mathrm{l}^{-1}$

This species takes part in six reactions (as a reactant in R_5, R_8 and as a product in R_4, R_5 and as a modifier in R_5, R_8).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{DAG} = v_4 + v_5 - v_5 - v_8 \tag{57}$$

7.6 Species PKC

Name PKC

Initial concentration $8.842\ \mathrm{mol}\cdot\mathrm{l}^{-1}$

This species takes part in three reactions (as a reactant in R_5 and as a product in R_9 and as a modifier in R_5).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{PKC} = v_9 - v_5 \tag{58}$$

7.7 Species PKC_a

Name PKC_a

Initial concentration $0.0020\ \mathrm{mol}\cdot\mathrm{l}^{-1}$

This species takes part in six reactions (as a reactant in R_6, R_9 and as a product in R_5, R_6 and as a modifier in R_6, R_9).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{PKC\_a} = v_5 + v_6 - v_6 - v_9 \tag{59}$$

7.8 Species GpERK

Name GpERK

Initial concentration $0.015\ \mathrm{mol}\cdot\mathrm{l}^{-1}$

This species takes part in three reactions (as a reactant in R_10 and as a product in R_6 and as a modifier in R_10).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{GpERK} = v_6 - v_{10} \tag{60}$$

7.9 Species bpERK

Name bpERK

Initial concentration $0.015\ \mathrm{mol}\cdot\mathrm{l}^{-1}$

This species takes part in four reactions (as a reactant in R_26 and as a product in R_24, R_25 and as a modifier in R_26).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{bpERK} = v_{24} + v_{25} - v_{26} \tag{61}$$

7.10 Species barr1

Name barr1

Initial concentration $0.858\ \mathrm{mol}\cdot\mathrm{l}^{-1}$

This species takes part in four reactions (as a reactant in R_12 and as a product in R_13, R_16 and as a modifier in R_12).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{barr1} = v_{13} + v_{16} - v_{12} \tag{62}$$

7.11 Species barr2

Name barr2

Initial concentration $0.483\ \mathrm{mol}\cdot\mathrm{l}^{-1}$

This species takes part in ten reactions (as a reactant in R_14, R_20, R_22 and as a product in R_15, R_17, R_21, R_23 and as a modifier in R_14, R_20, R_22).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{barr2} = v_{15} + v_{17} + v_{21} + v_{23} - v_{14} - v_{20} - v_{22} \tag{63}$$

7.12 Species G_a

Name G_a

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

This species takes part in eight reactions (as a reactant in R_4, R_7 and as a product in R_1, R_2, R_3, R_4 and as a modifier in R_4, R_7).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{G\_a} = v_1 + v_2 + v_3 + v_4 - v_4 - v_7 \tag{64}$$

7.13 Species HRP1

Name H-R~{P1}

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

This species takes part in ten reactions (as a reactant in R_2, R_12, R_14 and as a product in R_2, R_11, R_13, R_15 and as a modifier in R_2, R_12, R_14).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{HRP1} = v_2 + v_{11} + v_{13} + v_{15} - v_2 - v_{12} - v_{14} \tag{65}$$

7.14 Species Hbarr1RP1

Name H-barr1-R˜{P1}

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

This species takes part in five reactions (as a reactant in R_13, R_16 and as a product in R_12 and as a modifier in R_13, R_16).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Hbarr1RP1} = v_{12} - v_{13} - v_{16} \tag{66}$$

7.15 Species Hbarr2RP1

Name H-barr2-R˜{P1}

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

This species takes part in five reactions (as a reactant in R_15, R_17 and as a product in R_14 and as a modifier in R_15, R_17).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Hbarr2RP1} = v_{14} - v_{15} - v_{17} \tag{67}$$

7.16 Species HRP2

Name H-R˜{P2}

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

This species takes part in six reactions (as a reactant in R_19, R_22 and as a product in R_18, R_23 and as a modifier in R_19, R_22).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{HRP2} = v_{18} + v_{23} - v_{19} - v_{22} \tag{68}$$

7.17 Species HRbarr2

Name H-R-barr2

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

This species takes part in six reactions (as a reactant in R_21, R_24 and as a product in R_20, R_24 and as a modifier in R_21, R_24).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{HRbarr2} = v_{20} + v_{24} - v_{21} - v_{24} \tag{69}$$

7.18 Species Hbarr2RP2

Name H-barr2-R~{P2}

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

This species takes part in six reactions (as a reactant in R_23, R_25 and as a product in R_22, R_25 and as a modifier in R_23, R_25).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Hbarr2RP2} = v_{22} + v_{25} - v_{23} - v_{25} \tag{70}$$

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