SBML Model Report

Model name: “Fallon2000 - Interleukin-2 dynamics”

May 17, 2018

1 General Overview

This is a document in SBML Level 2 Version 4 format. This model was created by the following two authors: Matthew Grant Roberts[1] and Catherine Lloyd[2] at June 25th 2010 at noon. and last time modified at June 25th 2010 at noon. 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	8
events	0	constraints	0
reactions	13	function definitions	5
global parameters	13	unit definitions	6
rules	4	initial assignments	0

Model Notes

This a model from the article:
Computational model for effects of ligand/receptor binding properties oninterleukin-2 trafficking dynamics and T cell proliferation response.
Fallon EM, Lauffenburger DA. Biotechnol Prog 2000 Sep-Oct;16(5):905-16 11027188 ,

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Abstract:
Multisubunit cytokine receptors such as the heterotrimeric receptor forinterleukin-2 (IL-2) are ubiquitous in hematopoeitic cell types of importance inbiotechnology and are crucial regulators of cell proliferation anddifferentiation behavior. Dynamics of cytokine/receptor endocytic traffickingcan significantly impact cell responses through effects of receptordown-regulation and ligand depletion, and in turn are governed byligand/receptor binding properties. We describe here a computational model fortrafficking dynamics of the IL-2 receptor (IL-2R) system, which is able topredict T cell proliferation responses to IL-2. This model comprises kineticequations describing binding, internalization, and postendocytic sorting of IL-2and IL-2R, including an experimentally derived dependence of cell proliferationrate on these properties. Computational results from this model predict thatIL-2 depletion can be reduced by decreasing its binding affinity for the IL-2Rbetagamma subunit relative to the alpha subunit at endosomal pH, as a result ofenhanced ligand sorting to recycling vis-a-vis degradation, and that an IL-2analogue with such altered binding properties should exhibit increased potencyfor stimulating the T cell proliferation response. These results are inagreement with our recent experimental findings for the IL-2 analogue termed 2D1[Fallon, E. M. et al. J. Biol. Chem. 2000, 275, 6790-6797]. Thus, this type ofmodel may enable prediction of beneficial cytokine/receptor binding propertiesto aid development of molecular design criteria for improvements in applicationssuch as in vivo cytokine therapies and in vitro hematopoietic cell bioreactors.

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2 Unit Definitions

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

2.1 Unit `time`

Name time

Definition 60 s

2.2 Unit `unit_0`

Name 1/(0.0166667*s)

Definition $(0.0166667\ \mathrm{s})^{-1}$

2.3 Unit `unit_1`

Name 0.06*nl/(mol*s)

Definition $0.06\ \mathrm{nl} \cdot \mathrm{mol}^{-1} \cdot \mathrm{s}^{-1}$

2.4 Unit `unit_2`

Name l

Definition l

2.5 Unit `unit_3`

Name 1/Tmol

Definition Tmol^{-1}

2.6 Unit `unit_4`

Name 1

Definition $\mathrm{dimensionless}^{0}$

2.7 Unit `substance`

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

Definition mol

2.8 Unit volume

Notes Litre is the predefined SBML unit for volume.

Definition l

2.9 Unit area

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

Definition m^2

2.10 Unit length

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

Definition m

3 Compartment

This model contains one compartment.

Table 2: Properties of all compartments.

Id	Name	SBO	Spatial Dimensions	Size	Unit	Constant	Outside
COMpartment	compartment		3	1	litre	☑	

3.1 Compartment COMpartment

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

Name compartment

4 Species

This model contains eight species. The boundary condition of one of these species is set to `true` so that this species' amount cannot be changed by any reaction. Section 9 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
`Rs_0`	Rs	`COMpartment`	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	☐	☐
`Cs_0`	Cs	`COMpartment`	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	☐	☐
`Ri_0`	Ri	`COMpartment`	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	☐	☐
`Ci_0`	Ci	`COMpartment`	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	☐	☐
`Li_0`	Li	`COMpartment`	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	☐	☐
`Ld_0`	Ld	`COMpartment`	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	☐	☐
`L_0`	L	`COMpartment`	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	☐	☐
`Y_0`	Y	`COMpartment`	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	☐	☑

5 Parameters

This model contains 13 global parameters.

Table 4: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
kr	kr		0.014	$(0.0166667\ \mathrm{s})^{-1}$	☑
kf	kf		0.001	$0.06\ \mathrm{nl} \cdot \mathrm{mol}^{-1} \cdot \mathrm{s}^{-1}$	⊟
kre	kre		0.110	$(0.0166667\ \mathrm{s})^{-1}$	⊟
kfe	kfe		$1.104 \cdot 10^{-4}$	$0.06\ \mathrm{nl} \cdot \mathrm{mol}^{-1} \cdot \mathrm{s}^{-1}$	⊟
kt	kt		0.007	$(0.0166667\ \mathrm{s})^{-1}$	☑
Vs	Vs		11.000	$(0.0166667\ \mathrm{s})^{-1}$	☑
ksyn	ksyn		0.001	$(0.0166667\ \mathrm{s})^{-1}$	☑
ke	ke		0.040	$(0.0166667\ \mathrm{s})^{-1}$	☑
kx	kx		0.150	$(0.0166667\ \mathrm{s})^{-1}$	☑
kh	kh		0.035	$(0.0166667\ \mathrm{s})^{-1}$	☑
Ve	Ve		10^{-14}	l	☑
NA	NA		$6.022 \cdot 10^{11}$	Tmol^{-1}	☑
IL2	IL2		1.000	$\mathrm{dimensionless}^{0}$	☑

6 Function definitions

This is an overview of five function definitions.

6.1 Function definition Constant_flux__irreversible

Name Constant flux (irreversible)

Argument v

Mathematical Expression

$$\mathrm{v} \tag{1}$$

6.2 Function definition modifier_function_1

Name modifier function 1

Arguments parameter, modifier, substrate

Mathematical Expression

$$\mathrm{parameter} \cdot \mathrm{modifier} \cdot \mathrm{substrate} \tag{2}$$

6.3 Function definition `function_for_Li`

Name function for Li

Arguments kf, Li, Ri, kre, Ci, Ve, Na

Mathematical Expression

$$\frac{\mathrm{kf} \cdot \mathrm{Li} \cdot \mathrm{Ri} - \mathrm{kre} \cdot \mathrm{Ci}}{\mathrm{Ve} \cdot \mathrm{Na}} \tag{3}$$

6.4 Function definition `function_for_L`

Name function for L

Arguments kf, L, Rs, kr, Cs, kx, Li, Ve, Na, Y

Mathematical Expression

$$\frac{(\mathrm{kf} \cdot \mathrm{L} \cdot \mathrm{Rs} - \mathrm{kr} \cdot \mathrm{Cs} - \mathrm{kx} \cdot \mathrm{Li} \cdot \mathrm{Ve} \cdot \mathrm{Na}) \cdot \mathrm{Y}}{\mathrm{Na}} \tag{4}$$

6.5 Function definition `modifier_function_3`

Name modifier function 3

Arguments parameter, modifier

Mathematical Expression

$$\mathrm{parameter} \cdot \mathrm{modifier} \tag{5}$$

7 Rules

This is an overview of four rules.

7.1 Rule `kf`

Rule `kf` is an assignment rule for parameter `kf`:

$$\mathrm{kf} = \begin{cases} \dfrac{\mathrm{kr}}{11.1} & \text{if IL2} = 1 \\ \dfrac{\mathrm{kr}}{8.2} & \text{otherwise} \end{cases} \tag{6}$$

7.2 Rule `kre`

Rule `kre` is an assignment rule for parameter `kre`:

$$\mathrm{kre} = \begin{cases} \mathrm{kr} \cdot 8 & \text{if IL2} = 1 \\ \mathrm{kr} \cdot 5 & \text{otherwise} \end{cases} \tag{7}$$

7.3 Rule kfe

Rule kfe is an assignment rule for parameter kfe:

$$\mathrm{kfe} = \begin{cases} \dfrac{\mathrm{kre}}{1000} & \text{if IL2} = 1 \\ \dfrac{\mathrm{kre}}{3000} & \text{otherwise} \end{cases} \tag{8}$$

7.4 Rule Y_0

Rule Y_0 is a rate rule for species Y_0:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Y\_0} = \begin{cases} \left(\dfrac{600 \cdot [\mathrm{Cs\_0}]}{250 + [\mathrm{Cs\_0}]} - 200\right) \cdot 1000 & \text{if } \dfrac{600 \cdot [\mathrm{Cs\_0}]}{250 + [\mathrm{Cs\_0}]} - 200 > 0 \\ 0 & \text{otherwise} \end{cases} \tag{9}$$

8 Reactions

This model contains 13 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	Receptor_binding_to_Ligand	Receptor binding to Ligand	$Rs\_0 \xrightarrow{L\_0} Cs\_0$	
2	Receptor_Ligand_complex_dissocation	Receptor/Ligand complex dissocation	$Cs\_0 \longrightarrow Rs\_0$	
3	Upregulation_of_Receptor_Synthesis	Upregulation of Receptor Synthesis	$\emptyset \xrightarrow{Cs\_0} Rs\_0$	
4	Receptor_Internalisation	Receptor Internalisation	$Rs\_0 \longrightarrow Ri\_0$	
5	Receptor_Synthesis	Receptor Synthesis	$\emptyset \longrightarrow Rs\_0$	
6	Endocytosis_of_Receptor_Ligand_complex	Endocytosis of Receptor/Ligand complex	$Cs\_0 \longrightarrow Ci\_0$	
7	IL_2_binding_to_free_BetaGamma_heterodimer_1	IL-2 binding to free BetaGamma heterodimer	$Ri\_0 \xrightarrow{Li\_0} Ci\_0$	

№	Id	Name	Reaction Equation	SBO
8	Dissocation_of_IL_2_Heterodimer_complex	Dissocation of IL-2/Heterodimer complex	$\mathrm{Ci\_0} \longrightarrow \mathrm{Ri\_0}$	
9	Degradation_of_heterodimer	Degradation of heterodimer	$\mathrm{Ri\_0} \longrightarrow \emptyset$	
10	Degradation_of_IL_2_heterodimer_complex	Degradation of IL-2/heterodimer complex	$\mathrm{Ci\_0} \longrightarrow \mathrm{Ld\_0}$	
11	IL_2_binding_dissociating	IL-2 binding/dissociating	$\mathrm{Li\_0} \xrightarrow{\mathrm{Ri\_0,\ Ci\_0}} \emptyset$	
12	Ligand_recycling	Ligand recycling	$\mathrm{Li\_0} \longrightarrow \emptyset$	
13	Ligand_Binding_Dissociation_Recycling	Ligand Binding/Dissociation/Recycling	$\mathrm{L\_0} \xrightarrow{\mathrm{Rs\_0,\ Cs\_0,\ Li\_0,\ Y\_0}} \emptyset$	

8.1 Reaction Receptor_binding_to_Ligand

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

Name Receptor binding to Ligand

Reaction equation

$$\mathrm{Rs\_0} \xrightarrow{\mathrm{L\_0}} \mathrm{Cs\_0} \tag{10}$$

Reactant

Table 6: Properties of each reactant.

Id	Name	SBO
Rs_0	Rs	

Modifier

Table 7: Properties of each modifier.

Id	Name	SBO
L_0	L	

Product

Table 8: Properties of each product.

Id	Name	SBO
Cs_0	Cs	

Kinetic Law

Derived unit $\mathrm{s}^{-1} \cdot \mathrm{mol}$

$$v_1 = \mathrm{vol}\left(\mathrm{COMpartment}\right) \cdot \mathrm{modifier\_function\_1}\left(\mathrm{kf}, [\mathrm{L\_0}], [\mathrm{Rs\_0}]\right) \tag{11}$$

$$\mathrm{modifier\_function\_1}\left(\mathrm{parameter}, \mathrm{modifier}, \mathrm{substrate}\right) = \mathrm{parameter} \cdot \mathrm{modifier} \cdot \mathrm{substrate} \tag{12}$$

$$\mathrm{modifier\_function\_1}\left(\mathrm{parameter}, \mathrm{modifier}, \mathrm{substrate}\right) = \mathrm{parameter} \cdot \mathrm{modifier} \cdot \mathrm{substrate} \tag{13}$$

8.2 Reaction Receptor_Ligand_complex_dissocation

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

Name Receptor/Ligand complex dissocation

Reaction equation

$$\mathrm{Cs\_0} \longrightarrow \mathrm{Rs\_0} \tag{14}$$

Reactant

Table 9: Properties of each reactant.

Id	Name	SBO
Cs_0	Cs	

Product

Table 10: Properties of each product.

Id	Name	SBO
Rs_0	Rs	

Kinetic Law

Derived unit $(0.0166667\ \mathrm{s})^{-1} \cdot \mathrm{mol}$

$$v_2 = \mathrm{vol}\,(\mathrm{COMpartment}) \cdot \mathrm{kr} \cdot [\mathrm{Cs\_0}] \tag{15}$$

8.3 Reaction Upregulation_of_Receptor_Synthesis

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

Name Upregulation of Receptor Synthesis

Reaction equation

$$\emptyset \xrightarrow{\mathrm{Cs\_0}} \mathrm{Rs\_0} \tag{16}$$

Modifier

Table 11: Properties of each modifier.

Id	Name	SBO
Cs_0	Cs	

Product

Table 12: Properties of each product.

Id	Name	SBO
Rs_0	Rs	

Kinetic Law

Derived unit $(0.0166667\ \mathrm{s})^{-1} \cdot \mathrm{mol}$

$$v_3 = \mathrm{vol}\,(\mathrm{COMpartment}) \cdot \mathrm{modifier\_function\_3}\,(\mathrm{ksyn}, [\mathrm{Cs\_0}]) \tag{17}$$

$$\mathrm{modifier\_function\_3}\,(\mathrm{parameter}, \mathrm{modifier}) = \mathrm{parameter} \cdot \mathrm{modifier} \tag{18}$$

$$\mathrm{modifier\_function\_3}\,(\mathrm{parameter}, \mathrm{modifier}) = \mathrm{parameter} \cdot \mathrm{modifier} \tag{19}$$

8.4 Reaction Receptor_Internalisation

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

Name Receptor Internalisation

Reaction equation

$$\mathrm{Rs\_0} \longrightarrow \mathrm{Ri\_0} \tag{20}$$

Reactant

Table 13: Properties of each reactant.

Id	Name	SBO
Rs_0	Rs	

Product

Table 14: Properties of each product.

Id	Name	SBO
Ri_0	Ri	

Kinetic Law

Derived unit $(0.0166667\ \mathrm{s})^{-1} \cdot \mathrm{mol}$

$$v_4 = \mathrm{vol}(\mathrm{COMpartment}) \cdot \mathrm{kt} \cdot [\mathrm{Rs\_0}] \tag{21}$$

8.5 Reaction Receptor_Synthesis

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

Name Receptor Synthesis

Reaction equation

$$\emptyset \longrightarrow \mathrm{Rs\_0} \tag{22}$$

Product

Table 15: Properties of each product.

Id	Name	SBO
Rs_0	Rs	

Kinetic Law

Derived unit $1 \cdot (0.0166667\ \mathrm{s})^{-1}$

$$v_5 = \mathrm{vol}(\mathrm{COMpartment}) \cdot \mathrm{Constant\_flux\_\_irreversible}(\mathrm{Vs}) \tag{23}$$

$$\mathrm{Constant\_flux\_\_irreversible}(\mathrm{v}) = \mathrm{v} \tag{24}$$

$$\mathrm{Constant\_flux\_\_irreversible}(\mathrm{v}) = \mathrm{v} \tag{25}$$

8.6 Reaction Endocytosis_of_Receptor_Ligand_complex

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

Name Endocytosis of Receptor/Ligand complex

Reaction equation

$$\mathrm{Cs\_0} \longrightarrow \mathrm{Ci\_0} \tag{26}$$

Reactant

Table 16: Properties of each reactant.

Id	Name	SBO
Cs_0	Cs	

Product

Table 17: Properties of each product.

Id	Name	SBO
Ci_0	Ci	

Kinetic Law

Derived unit $(0.0166667\ \mathrm{s})^{-1} \cdot \mathrm{mol}$

$$v_6 = \mathrm{vol}\,(\mathrm{COMpartment}) \cdot \mathrm{ke} \cdot [\mathrm{Cs\_0}] \tag{27}$$

8.7 Reaction IL_2_binding_to_free_BetaGamma_heterodimer_1

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

Name IL-2 binding to free BetaGamma heterodimer

Reaction equation

$$\mathrm{Ri\_0} \xrightarrow{\mathrm{Li\_0}} \mathrm{Ci\_0} \tag{28}$$

Reactant

Table 18: Properties of each reactant.

Id	Name	SBO
Ri_0	Ri	

Modifier

Table 19: Properties of each modifier.

Id	Name	SBO
Li_0	Li	

Product

Table 20: Properties of each product.

Id	Name	SBO
Ci_0	Ci	

Kinetic Law

Derived unit $\mathrm{s}^{-1} \cdot \mathrm{mol}$

$$v_7 = \mathrm{vol}\left(\mathrm{COMpartment}\right) \cdot \mathrm{modifier\_function\_1}\left(\mathrm{kfe}, [\mathrm{Li\_0}], [\mathrm{Ri\_0}]\right) \tag{29}$$

$$\mathrm{modifier\_function\_1}\left(\mathrm{parameter}, \mathrm{modifier}, \mathrm{substrate}\right) = \mathrm{parameter} \cdot \mathrm{modifier} \cdot \mathrm{substrate} \tag{30}$$

$$\mathrm{modifier\_function\_1}\left(\mathrm{parameter}, \mathrm{modifier}, \mathrm{substrate}\right) = \mathrm{parameter} \cdot \mathrm{modifier} \cdot \mathrm{substrate} \tag{31}$$

8.8 Reaction Dissocation_of_IL_2_Heterodimer_complex

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

Name Dissocation of IL-2/Heterodimer complex

Reaction equation

$$\mathrm{Ci\_0} \longrightarrow \mathrm{Ri\_0} \tag{32}$$

Reactant

Table 21: Properties of each reactant.

Id	Name	SBO
Ci_0	Ci	

Product

Table 22: Properties of each product.

Id	Name	SBO
Ri_0	Ri	

Kinetic Law

Derived unit $(0.0166667\ \mathrm{s})^{-1} \cdot \mathrm{mol}$

$$v_8 = \mathrm{vol}\,(\mathrm{COMpartment}) \cdot \mathrm{kre} \cdot [\mathrm{Ci\_0}] \tag{33}$$

8.9 Reaction Degradation_of_heterodimer

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

Name Degradation of heterodimer

Reaction equation

$$\mathrm{Ri\_0} \longrightarrow \emptyset \tag{34}$$

Reactant

Table 23: Properties of each reactant.

Id	Name	SBO
Ri_0	Ri	

Kinetic Law

Derived unit $(0.0166667\ \mathrm{s})^{-1} \cdot \mathrm{mol}$

$$v_9 = \mathrm{vol}\,(\mathrm{COMpartment}) \cdot \mathrm{kh} \cdot [\mathrm{Ri\_0}] \tag{35}$$

8.10 Reaction Degradation_of_IL_2_heterodimer_complex

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

Name Degradation of IL-2/heterodimer complex

Reaction equation

$$\text{Ci\_0} \longrightarrow \text{Ld\_0} \tag{36}$$

Reactant

Table 24: Properties of each reactant.

Id	Name	SBO
Ci_0	Ci	

Product

Table 25: Properties of each product.

Id	Name	SBO
Ld_0	Ld	

Kinetic Law

Derived unit $(0.0166667\ \text{s})^{-1} \cdot \text{mol}$

$$v_{10} = \text{vol}\,(\text{COMpartment}) \cdot \text{kh} \cdot [\text{Ci\_0}] \tag{37}$$

8.11 Reaction IL_2_binding_dissociating

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

Name IL-2 binding/dissociating

Reaction equation

$$\text{Li\_0} \xrightarrow{\text{Ri\_0, Ci\_0}} \emptyset \tag{38}$$

Reactant

Table 26: Properties of each reactant.

Id	Name	SBO
Li_0	Li	

Modifiers

Table 27: Properties of each modifier.

Id	Name	SBO
Ri_0	Ri	
Ci_0	Ci	

Kinetic Law

Derived unit $1^{-1} \cdot s^{-1} \cdot (1000000\ \text{mol})^2$

$$v_{11} = \text{vol}(\text{COMpartment}) \cdot \text{function\_for\_Li}(\text{kf}, [\text{Li\_0}], [\text{Ri\_0}], \text{kre}, [\text{Ci\_0}], \text{Ve}, \text{NA}) \quad (39)$$

$$\text{function\_for\_Li}(\text{kf}, \text{Li}, \text{Ri}, \text{kre}, \text{Ci}, \text{Ve}, \text{Na}) = \frac{\text{kf} \cdot \text{Li} \cdot \text{Ri} - \text{kre} \cdot \text{Ci}}{\text{Ve} \cdot \text{Na}} \quad (40)$$

$$\text{function\_for\_Li}(\text{kf}, \text{Li}, \text{Ri}, \text{kre}, \text{Ci}, \text{Ve}, \text{Na}) = \frac{\text{kf} \cdot \text{Li} \cdot \text{Ri} - \text{kre} \cdot \text{Ci}}{\text{Ve} \cdot \text{Na}} \quad (41)$$

8.12 Reaction Ligand_recycling

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

Name Ligand recycling

Reaction equation

$$\text{Li\_0} \longrightarrow \emptyset \quad (42)$$

Reactant

Table 28: Properties of each reactant.

Id	Name	SBO
Li_0	Li	

Kinetic Law

Derived unit $(0.0166667\ \mathrm{s})^{-1} \cdot \mathrm{mol}$

$$v_{12} = \mathrm{vol}\,(\mathrm{COMpartment}) \cdot \mathrm{kx} \cdot [\mathrm{Li\_0}] \tag{43}$$

8.13 Reaction Ligand_Binding_Dissociation_Recycling

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

Name Ligand Binding/Dissociation/Recycling

Reaction equation

$$\mathrm{L\_0} \xrightarrow{\mathrm{Rs\_0,\ Cs\_0,\ Li\_0,\ Y\_0}} \emptyset \tag{44}$$

Reactant

Table 29: Properties of each reactant.

Id	Name	SBO
L_0	L	

Modifiers

Table 30: Properties of each modifier.

Id	Name	SBO
Rs_0	Rs	
Cs_0	Cs	
Li_0	Li	
Y_0	Y	

Kinetic Law

Derived unit $1^{-1} \cdot \mathrm{s}^{-1} \cdot (9999.999999999995\ \mathrm{mol})^3$

$$v_{13} = \mathrm{vol}\,(\mathrm{COMpartment}) \cdot \mathrm{function\_for\_L}\,(\mathrm{kf}, [\mathrm{L\_0}], [\mathrm{Rs\_0}], \mathrm{kr}, [\mathrm{Cs\_0}], \mathrm{kx}, [\mathrm{Li\_0}], \mathrm{Ve}, \mathrm{NA}, [\mathrm{Y\_0}]) \tag{45}$$

$$\mathrm{function\_for\_L}\,(\mathrm{kf}, \mathrm{L}, \mathrm{Rs}, \mathrm{kr}, \mathrm{Cs}, \mathrm{kx}, \mathrm{Li}, \mathrm{Ve}, \mathrm{Na}, \mathrm{Y}) = \frac{(\mathrm{kf} \cdot \mathrm{L} \cdot \mathrm{Rs} - \mathrm{kr} \cdot \mathrm{Cs} - \mathrm{kx} \cdot \mathrm{Li} \cdot \mathrm{Ve} \cdot \mathrm{Na}) \cdot \mathrm{Y}}{\mathrm{Na}} \tag{46}$$

$$\mathrm{function\_for\_L}\,(\mathrm{kf}, \mathrm{L}, \mathrm{Rs}, \mathrm{kr}, \mathrm{Cs}, \mathrm{kx}, \mathrm{Li}, \mathrm{Ve}, \mathrm{Na}, \mathrm{Y}) = \frac{(\mathrm{kf} \cdot \mathrm{L} \cdot \mathrm{Rs} - \mathrm{kr} \cdot \mathrm{Cs} - \mathrm{kx} \cdot \mathrm{Li} \cdot \mathrm{Ve} \cdot \mathrm{Na}) \cdot \mathrm{Y}}{\mathrm{Na}} \tag{47}$$

9 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.

9.1 Species `Rs_0`

Name Rs

Notes `Initial value of 1500 from paper`

Initial concentration $1500\ \mathrm{mol} \cdot 1^{-1}$

This species takes part in six reactions (as a reactant in `Receptor_binding_to_Ligand`, `Receptor_Internalisation` and as a product in `Receptor_Ligand_complex_dissocation`, `Upregulation_of_Receptor_Synthesis`, `Receptor_Synthesis` and as a modifier in `Ligand_Binding_Dissociation_Recycling`).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Rs\_0} = v_2 + v_3 + v_5 - v_1 - v_4 \tag{48}$$

9.2 Species Cs_0

Name Cs

Notes SBML file uploaded with initial value set to 1

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

This species takes part in five reactions (as a reactant in Receptor_Ligand_complex_dissocation, Endocytosis_of_Receptor_Ligand_complex and as a product in Receptor_binding_to_Ligand and as a modifier in Upregulation_of_Receptor_Synthesis, Ligand_Binding_Dissociation_Recycling).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Cs\_0} = v_1 - v_2 - v_6 \tag{49}$$

9.3 Species Ri_0

Name Ri

Notes Initial value of 300 from paper

Initial concentration $300\ \mathrm{mol}\cdot\mathrm{l}^{-1}$

This species takes part in five reactions (as a reactant in IL_2_binding_to_free_BetaGamma_heterodimer_1, Degradation_of_heterodimer and as a product in Receptor_Internalisation, Dissocation_of_IL_2_Heterodimer_complex and as a modifier in IL_2_binding_dissociating).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Ri\_0} = v_4 + v_8 - v_7 - v_9 \tag{50}$$

9.4 Species Ci_0

Name Ci

Notes SBML file uploaded with initial value set to 1

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

This species takes part in five reactions (as a reactant in Dissocation_of_IL_2_Heterodimer_complex, Degradation_of_IL_2_heterodimer_complex and as a product in Endocytosis_of_Receptor_Ligand_complex, IL_2_binding_to_free_BetaGamma_heterodimer_1 and as a modifier in IL_2_binding_dissociating).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Ci\_0} = v_6 + v_7 - v_8 - v_{10} \tag{51}$$

9.5 Species Li_0

Name Li

Notes SBML file uploaded with initial value set to 0.01

Initial concentration $0.01\ \mathrm{mol}\cdot\mathrm{l}^{-1}$

This species takes part in four reactions (as a reactant in IL_2_binding_dissociating, Ligand_recycling and as a modifier in IL_2_binding_to_free_BetaGamma_heterodimer_1, Ligand_Binding_Dissociation_Recycling).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Li\_0} = -\,v_{11} - v_{12} \tag{52}$$

9.6 Species Ld_0

Name Ld

Notes SBML file uploaded with initial value set to 1

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

This species takes part in one reaction (as a product in Degradation_of_IL_2_heterodimer_complex).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Ld\_0} = v_{10} \tag{53}$$

9.7 Species L_0

Name L

Notes SBML file uploaded with initial value set to 10

Initial concentration $10\ \mathrm{mol}\cdot\mathrm{l}^{-1}$

This species takes part in two reactions (as a reactant in Ligand_Binding_Dissociation_Recycling and as a modifier in Receptor_binding_to_Ligand).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{L\_0} = -\,v_{13} \tag{54}$$

9.8 Species Y_0

Name Y

Initial concentration $2.5\cdot 10^{8}\ \mathrm{mol}\cdot\mathrm{l}^{-1}$

Involved in rule Y_0

This species takes part in one reaction (as a modifier in Ligand_Binding_Dissociation_Recycling). Not this but one rule determines the species' quantity because this species is on the boundary of the reaction system.

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