SBML Model Report

Model name: “Leber2016 - Expanded model of Tfh-Tfr differentiation - Helicobacter pylori infection”

March 1, 2017

1 General Overview

This is a document in SBML Level 2 Version 4 format. This model was created by the following two authors: Andrew Leber[1] and Varun Kothamachu[2] at May 25th 2015 at 11:11 a. m. and last time modified at March first 2017 at 1:11 p. m. 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	19
events	0	constraints	0
reactions	38	function definitions	14
global parameters	0	unit definitions	3
rules	0	initial assignments	0

Model Notes

Leber2016 - Expanded model of Tfh-Tfrdifferentiation - Helicobacter pylori infection
The parameters used in the model wereobtained from experiments conducted by the authors,

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previouspublications [1, 2, 3] andparameter optimisation carried out in the paper using particleswarm and genetic algorithms.

This model is described in the article:Bistability analyses of CD4+ T follicular helper and regulatory cells during Helicobacter pylori infection.Leber A, Abedi V, Hontecillas R, Viladomiu M, Hoops S, Ciupe S, Caughman J, Andrew T, Bassaganya-Riera J.J. Theor. Biol. 2016 Jun; 398: 74-84

Abstract:

T follicular helper (Tfh) cells are a highly plastic subset of CD4+ T cells specialized in providing B cell help and promoting inflammatory and effector responses during infectious and immune-mediate diseases. Helicobacter pylori is the dominant member of the gastric microbiota and exerts both beneficial and harmful effects on the host. Chronic inflammation in the context of H. pylori has been linked to an upregulation in T helper (Th)1 and Th17 CD4+ T cell phenotypes, controlled in part by the cytokine, interleukin-21. This study investigates the differentiation and regulation of Tfh cells, major producers of IL-21, in the immune response to H. pylori challenge. To better understand the conditions influencing the promotion and inhibition of a chronically elevated Tfh population, we used top-down and bottom-up approaches to develop computational models of Tfh and T follicular regulatory (Tfr) cell differentiation. Stability analysis was used to characterize the presence of two bi-stable steady states in the calibrated Tfh/Tfr models. Stochastic simulation was used to illustrate the ability of the parameter set to dictate two distinct behavioral patterns. Furthermore, sensitivity analysis helped identify the importance of various parameters on the establishment of Tfh and Tfr cell populations. The core network model was expanded into a more comprehensive and predictive model by including cytokine production and signaling pathways. From the expanded network, the interaction between TGFB-Induced Factor Homeobox 1 (Tgif1) and the retinoid X receptor (RXR) was displayed to exert control over the determination of the Tfh response. Model simulations predict that Tgif1 and RXR respectively induce and curtail Tfh responses. This computational hypothesis was validated experimentally by assaying Tgif1, RXR and Tfh in stomachs of mice infected with H. pylori.The impulse of RXR as shown in the paper(figure 7C) can be implemented by creating an event in the curatedSBML file.

2 Unit Definitions

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

2.1 Unit volume

Name volume

Definition ml

2.2 Unit time

Name time

Definition 86400 s

2.3 Unit substance

Name substance

Definition item

2.4 Unit area

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

Definition m^2

2.5 Unit length

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

Definition m

3 Compartment

This model contains one compartment.

Table 2: Properties of all compartments.

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

3.1 Compartment compartment

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

Name compartment

4 Species

This model contains 19 species. The boundary condition of two of these species is set to `true` so that these species' amount cannot be changed by any reaction. 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
NaiveCD4	NaiveCD4	compartment	$\mathrm{item} \cdot \mathrm{ml}^{-1}$	☐	☐
nTreg	nTreg	compartment	$\mathrm{item} \cdot \mathrm{ml}^{-1}$	☐	☐
Tfh	Tfh	compartment	$\mathrm{item} \cdot \mathrm{ml}^{-1}$	☐	☐
Tfr	Tfr	compartment	$\mathrm{item} \cdot \mathrm{ml}^{-1}$	☐	☐
Bcl6	Bcl6	compartment	$\mathrm{item} \cdot \mathrm{ml}^{-1}$	☐	☐
Blimp1	Blimp1	compartment	$\mathrm{item} \cdot \mathrm{ml}^{-1}$	☐	☐
FoxP3	FoxP3	compartment	$\mathrm{item} \cdot \mathrm{ml}^{-1}$	☐	☐
STAT3	STAT3	compartment	$\mathrm{item} \cdot \mathrm{ml}^{-1}$	☐	☐
STAT5	STAT5	compartment	$\mathrm{item} \cdot \mathrm{ml}^{-1}$	☑	☑
IL2	IL2	compartment	$\mathrm{item} \cdot \mathrm{ml}^{-1}$	☑	☑
IL4	IL4	compartment	$\mathrm{item} \cdot \mathrm{ml}^{-1}$	☐	☐
IL6	IL6	compartment	$\mathrm{item} \cdot \mathrm{ml}^{-1}$	☐	☐
IL10	IL10	compartment	$\mathrm{item} \cdot \mathrm{ml}^{-1}$	☐	☐
IL21	IL21	compartment	$\mathrm{item} \cdot \mathrm{ml}^{-1}$	☐	☐
CXCR5	CXCR5	compartment	$\mathrm{item} \cdot \mathrm{ml}^{-1}$	☐	☐
ICOS	ICOS	compartment	$\mathrm{item} \cdot \mathrm{ml}^{-1}$	☐	☐
TGFb	TGFb	compartment	$\mathrm{item} \cdot \mathrm{ml}^{-1}$	☐	☐
Tgif1	Tgif1	compartment	$\mathrm{item} \cdot \mathrm{ml}^{-1}$	☐	☐
RXR	RXR	compartment	$\mathrm{item} \cdot \mathrm{ml}^{-1}$	☐	☐

5 Function definitions

This is an overview of 14 function definitions.

5.1 Function definition Molecule_Production__1A_0I__2

Name Molecule Production (1A/0I)_2

Arguments [IL2], sigma

Mathematical Expression

$$\text{sigma} \cdot [\text{IL2}] \tag{1}$$

5.2 Function definition Constant_flux__irreversible

Name Constant flux (irreversible)

Argument v

Mathematical Expression

$$\text{v} \tag{2}$$

5.3 Function definition Molecule_Production__1A_0I__1

Name Molecule Production (1A/0I)_1

Arguments [nTreg], sigma

Mathematical Expression

$$\text{sigma} \cdot [\text{nTreg}] \tag{3}$$

5.4 Function definition Molecule_Production__2A_3I__v2_1

Name Molecule Production (2A/3I) v2_1

Arguments [Blimp1], [ICOS], [RXR], [STAT3], [STAT5], alpha1, alpha2, alpha3, sigma1, sigma2

Mathematical Expression

$$\frac{\text{sigma1} \cdot [\text{ICOS}] + \text{sigma2} \cdot [\text{STAT3}]}{(\text{alpha1} + [\text{Blimp1}]) \cdot (\text{alpha2} + [\text{STAT5}]) \cdot (\text{alpha3} + [\text{RXR}])} \tag{4}$$

5.5 Function definition Molecule_Production__0A_1I__1

Name Molecule Production (0A/1I)_1

Arguments [IL4], alpha1, sigma1

Mathematical Expression

$$\frac{\text{sigma1}}{\text{alpha1} + [\text{IL4}]} \tag{5}$$

5.6 Function definition Molecule_Production__1A_0I__5

Name Molecule Production (1A/0I)_5

Arguments [IL10], sigma

Mathematical Expression

$$\text{sigma} \cdot [\text{IL10}] \tag{6}$$

5.7 Function definition Cell_Differentiation__2A__1

Name Cell Differentiation (2A)_1

Arguments [Bcl6], [CXCR5], gamma1, gamma2, [nTreg]

Mathematical Expression

$$\text{gamma1} \cdot [\text{nTreg}] \cdot [\text{Bcl6}] + \text{gamma2} \cdot [\text{nTreg}] \cdot [\text{CXCR5}] \tag{7}$$

5.8 Function definition Molecule_Production__2A_0I__1

Name Molecule Production (2A/0I)_1

Arguments [IL21], [IL6], sigma1, sigma2

Mathematical Expression

$$\text{sigma1} \cdot [\text{IL6}] + \text{sigma2} \cdot [\text{IL21}] \tag{8}$$

5.9 Function definition Molecule_Production__2A_1I__1

Name Molecule Production (2A/1I)_1

Arguments [Blimp1], [Tfh], [Tfr], alpha, sigma1, sigma2

Mathematical Expression

$$\frac{\text{sigma1} \cdot [\text{Tfh}] + \text{sigma2} \cdot [\text{Tfr}]}{\text{alpha} + [\text{Blimp1}]} \tag{9}$$

5.10 Function definition Molecule_Production__1A_0I__4

Name Molecule Production (1A/0I)_4

Arguments [Tfr], sigma

Mathematical Expression

$$\text{sigma} \cdot [\text{Tfr}] \tag{10}$$

5.11 Function definition Molecule_Production__1A_1I__2

Name Molecule Production (1A/1I)_2

Arguments [TGFb], [Tgif1], alpha, sigma

Mathematical Expression

$$\frac{\text{sigma} \cdot [\text{TGFb}]}{\text{alpha} + [\text{Tgif1}]} \tag{11}$$

5.12 Function definition Molecule_Production__1A_1I__1

Name Molecule Production (1A/1I)_1

Arguments [Bcl6], [Tfr], alpha, sigma

Mathematical Expression

$$\frac{\text{sigma} \cdot [\text{Tfr}]}{\text{alpha} + [\text{Bcl6}]} \tag{12}$$

5.13 Function definition Molecule_Production__1A_0I__3

Name Molecule Production (1A/0I)_3

Arguments [Tfh], sigma

Mathematical Expression

$$\text{sigma} \cdot [\text{Tfh}] \tag{13}$$

5.14 Function definition Cell_Differentiation__1A_1I__1

Name Cell Differentiation (1A/1I)_1

Arguments [Bcl6], [IL10], [NaiveCD4], alpha, gamma

Mathematical Expression

$$\frac{\text{gamma} \cdot [\text{NaiveCD4}] \cdot [\text{Bcl6}]}{\text{alpha} + [\text{IL10}]} \tag{14}$$

6 Reactions

This model contains 38 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	NaiveCD4_Source	NaiveCD4 Source	$\emptyset \longrightarrow$ NaiveCD4	0000393
2	NaiveCD4_Death	NaiveCD4 Death	NaiveCD4 $\longrightarrow \emptyset$	0000291
3	nTreg_Source	nTreg Source	$\emptyset \longrightarrow$ nTreg	0000393
4	nTreg_Death	nTreg Death	nTreg $\longrightarrow \emptyset$	0000291
5	Tfh-_Differentiation	Tfh Differentiation	NaiveCD4 $\xrightarrow{\text{Bcl6, IL10}}$ Tfh	
6	Tfr-_Differentiation	Tfr Differentiation	nTreg $\xrightarrow{\text{Bcl6, CXCR5}}$ Tfr	
7	Tfh_Death	Tfh Death	Tfh $\longrightarrow \emptyset$	0000291
8	Tfr_Death	Tfr Death	Tfr $\longrightarrow \emptyset$	0000291
9	Bcl6_Activation	Bcl6 Activation	$\emptyset \xrightarrow{\text{ICOS, STAT3, Blimp1, STAT5, RXR}}$ Bcl6	0000393
10	Blimp1-_Activation	Blimp1 Activation	$\emptyset \xrightarrow{\text{Tfr, Bcl6}}$ Blimp1	0000393
11	FoxP3-_Activation	FoxP3 Activation	$\emptyset \xrightarrow{\text{nTreg}}$ FoxP3	0000393
12	STAT3-_Activation	STAT3 Activation	$\emptyset \xrightarrow{\text{IL6, IL21}}$ STAT3	0000393
13	STAT5-_Activation	STAT5 Activation	$\emptyset \xrightarrow{\text{IL2}}$ STAT5	0000393

№	Id	Name	Reaction Equation	SBO
14	CXCR5_Production	CXCR5 Production	$\emptyset \xrightarrow{\text{Tfh, Tfr, Blimp1}} \text{CXCR5}$	0000393
15	ICOS_Production	ICOS Production	$\emptyset \xrightarrow{\text{Tfh}} \text{ICOS}$	0000393
16	IL2_Production	IL2 Production	$\emptyset \longrightarrow \text{IL2}$	0000393
17	IL4_Production	IL4 Production	$\emptyset \xrightarrow{\text{Tfh}} \text{IL4}$	0000393
18	IL6_Production	IL6 Production	$\emptyset \xrightarrow{\text{IL4}} \text{IL6}$	0000393
19	IL10_Production	IL10 Production	$\emptyset \xrightarrow{\text{Tfr}} \text{IL10}$	0000393
20	Bcl6_Degradation	Bcl6 Degradation	$\text{Bcl6} \longrightarrow \emptyset$	0000179
21	Blimp1_Degradation	Blimp1 Degradation	$\text{Blimp1} \longrightarrow \emptyset$	0000179
22	FoxP3_Degradation	FoxP3 Degradation	$\text{FoxP3} \longrightarrow \emptyset$	0000179
23	STAT3_Degradation	STAT3 Degradation	$\text{STAT3} \longrightarrow \emptyset$	0000179
24	STAT5_Degradation	STAT5 Degradation	$\text{STAT5} \longrightarrow \emptyset$	0000179
25	CXCR5_Degradation	CXCR5 Degradation	$\text{CXCR5} \longrightarrow \emptyset$	0000179
26	ICOS_Degradation	ICOS Degradation	$\text{ICOS} \longrightarrow \emptyset$	0000179
27	IL2_Degradation	IL2 Degradation	$\text{IL2} \longrightarrow \emptyset$	0000179
28	IL4_Degradation	IL4 Degradation	$\text{IL4} \longrightarrow \emptyset$	0000179
29	IL6_Degradation	IL6 Degradation	$\text{IL6} \longrightarrow \emptyset$	0000179
30	IL10_Degradation	IL10 Degradation	$\text{IL10} \longrightarrow \emptyset$	0000179

№	Id	Name	Reaction Equation	SBO
31	IL21_Degradation	IL21 Degradation	$IL21 \longrightarrow \emptyset$	0000179
32	IL21_Production	IL21 Production	$\emptyset \xrightarrow{Tfh} IL21$	
33	TGFb_Production	TGFb Production	$\emptyset \xrightarrow{IL10} TGFb$	0000393
34	TGFb_Degradation	TGFb Degradation	$TGFb \longrightarrow \emptyset$	0000179
35	RXR_Activation	RXR Activation	$\emptyset \xrightarrow{TGFb,\ Tgif1} RXR$	0000393
36	Tgif1_Production	Tgif1 Production	$\emptyset \xrightarrow{Tfh} Tgif1$	0000393
37	RXR_Degradation	RXR Degradation	$RXR \longrightarrow \emptyset$	0000179
38	Tgif1_Degradation	Tgif1 Degradation	$Tgif1 \longrightarrow \emptyset$	0000179

6.1 Reaction NaiveCD4_Source

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

Name NaiveCD4 Source

SBO:0000393 production

Notes This reaction represents constitutive **naive CD4 cell production**.

Reaction equation

$$\emptyset \longrightarrow \text{NaiveCD4} \tag{15}$$

Product

Table 5: Properties of each product.

Id	Name	SBO
NaiveCD4	NaiveCD4	

Kinetic Law

Derived unit contains undeclared units

$$v_1 = \text{vol}\left(\text{compartment}\right) \cdot \text{Constant\_flux\_\_irreversible}\left(\text{v}\right) \tag{16}$$

$$\text{Constant\_flux\_\_irreversible}\left(\text{v}\right) = \text{v} \tag{17}$$

$$\text{Constant\_flux\_\_irreversible}\left(\text{v}\right) = \text{v} \tag{18}$$

Table 6: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
v	v	0000485	100.0		☑

6.2 Reaction NaiveCD4_Death

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

Name NaiveCD4 Death

SBO:0000291 empty set

Notes This reaction represents the constitutive **naiveCD4 cell death**.

Reaction equation

$$\text{NaiveCD4} \longrightarrow \emptyset \tag{19}$$

Reactant

Table 7: Properties of each reactant.

Id	Name	SBO
NaiveCD4	NaiveCD4	

Kinetic Law

Derived unit contains undeclared units

$$v_2 = \text{vol}\,(\text{compartment}) \cdot \text{k1} \cdot [\text{NaiveCD4}] \tag{20}$$

Table 8: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k1	k1	0000485	0.036		☑

6.3 Reaction nTreg_Source

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

Name nTreg Source

SBO:0000393 production

Notes This reaction represents constitutive **nTreg cell production**.

Reaction equation

$$\emptyset \longrightarrow \text{nTreg} \tag{21}$$

Product

Table 9: Properties of each product.

Id	Name	SBO
nTreg	nTreg	

Kinetic Law

Derived unit contains undeclared units

$$v_3 = \text{vol}\,(\text{compartment}) \cdot \text{Constant\_flux\_\_irreversible}\,(\text{v}) \tag{22}$$

$$\text{Constant\_flux\_\_irreversible}\,(\text{v}) = \text{v} \tag{23}$$

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

Table 10: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
v	v	0000485	10.0		☑

6.4 Reaction nTreg_Death

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

Name nTreg Death

SBO:0000291 empty set

Notes This reaction represents the constitutive **nTreg cell death**.

Reaction equation

$$\text{nTreg} \longrightarrow \emptyset \tag{25}$$

Reactant

Table 11: Properties of each reactant.

Id	Name	SBO
nTreg	nTreg	

Kinetic Law

Derived unit contains undeclared units

$$v_4 = \mathrm{vol}\,(\mathrm{compartment}) \cdot \mathrm{k1} \cdot [\mathrm{nTreg}] \tag{26}$$

Table 12: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k1	k1	0000485	0.03		☑

6.5 Reaction Tfh_Differentiation

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

Name Tfh Differentiation

Reaction equation

$$\mathrm{NaiveCD4} \xrightarrow{\mathrm{Bcl6,\ IL10}} \mathrm{Tfh} \tag{27}$$

Reactant

Table 13: Properties of each reactant.

Id	Name	SBO
NaiveCD4	NaiveCD4	

Modifiers

Table 14: Properties of each modifier.

Id	Name	SBO
Bcl6	Bcl6	
IL10	IL10	

Product

Table 15: Properties of each product.

Id	Name	SBO
`Tfh`	Tfh	

Kinetic Law

Derived unit contains undeclared units

$$v_5 = \mathrm{vol}\,(\mathrm{compartment}) \cdot \mathrm{Cell\_Differentiation\_\_1A\_1I\_\_1}\,([\mathrm{Bcl6}], [\mathrm{IL10}], [\mathrm{NaiveCD4}], \mathrm{alpha}, \mathrm{gamma}) \tag{28}$$

$$\mathrm{Cell\_Differentiation\_\_1A\_1I\_\_1}\,([\mathrm{Bcl6}], [\mathrm{IL10}], [\mathrm{NaiveCD4}], \mathrm{alpha}, \mathrm{gamma}) = \frac{\mathrm{gamma} \cdot [\mathrm{NaiveCD4}] \cdot [\mathrm{Bcl6}]}{\mathrm{alpha} + [\mathrm{IL10}]} \tag{29}$$

$$\mathrm{Cell\_Differentiation\_\_1A\_1I\_\_1}\,([\mathrm{Bcl6}], [\mathrm{IL10}], [\mathrm{NaiveCD4}], \mathrm{alpha}, \mathrm{gamma}) = \frac{\mathrm{gamma} \cdot [\mathrm{NaiveCD4}] \cdot [\mathrm{Bcl6}]}{\mathrm{alpha} + [\mathrm{IL10}]} \tag{30}$$

Table 16: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
`alpha`	alpha		0.100		☑
`gamma`	gamma		0.364		☑

6.6 Reaction `Tfr_Differentiation`

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

Name Tfr Differentiation

Notes This reaction represents differentiation of **Treg to Tfr** by Bcl-6 and CXCR-5 .

Reaction equation

$$\mathrm{nTreg} \xrightarrow{\mathrm{Bcl6,\ CXCR5}} \mathrm{Tfr} \tag{31}$$

Reactant

Table 17: Properties of each reactant.

Id	Name	SBO
nTreg	nTreg	

Modifiers

Table 18: Properties of each modifier.

Id	Name	SBO
Bcl6	Bcl6	
CXCR5	CXCR5	

Product

Table 19: Properties of each product.

Id	Name	SBO
Tfr	Tfr	

Kinetic Law

Derived unit contains undeclared units

$$v_6 = \mathrm{vol}\,(\mathrm{compartment}) \cdot \mathrm{Cell\_Differentiation\_\_2A\_\_1}\,([\mathrm{Bcl6}], [\mathrm{CXCR5}], \mathrm{gamma1}, \mathrm{gamma2}, [\mathrm{nTreg}]) \tag{32}$$

$$\begin{aligned}&\mathrm{Cell\_Differentiation\_\_2A\_\_1}\,([\mathrm{Bcl6}], [\mathrm{CXCR5}], \mathrm{gamma1}, \mathrm{gamma2}, [\mathrm{nTreg}]) \\ &\quad = \mathrm{gamma1} \cdot [\mathrm{nTreg}] \cdot [\mathrm{Bcl6}] + \mathrm{gamma2} \cdot [\mathrm{nTreg}] \cdot [\mathrm{CXCR5}]\end{aligned} \tag{33}$$

$$\begin{aligned}&\mathrm{Cell\_Differentiation\_\_2A\_\_1}\,([\mathrm{Bcl6}], [\mathrm{CXCR5}], \mathrm{gamma1}, \mathrm{gamma2}, [\mathrm{nTreg}]) \\ &\quad = \mathrm{gamma1} \cdot [\mathrm{nTreg}] \cdot [\mathrm{Bcl6}] + \mathrm{gamma2} \cdot [\mathrm{nTreg}] \cdot [\mathrm{CXCR5}]\end{aligned} \tag{34}$$

Table 20: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
gamma1	gamma1		0.056		☑
gamma2	gamma2		0.111		☑

6.7 Reaction Tfh_Death

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

Name Tfh Death

SBO:0000291 empty set

Reaction equation

$$\mathrm{Tfh} \longrightarrow \emptyset \tag{35}$$

Reactant

Table 21: Properties of each reactant.

Id	Name	SBO
Tfh	Tfh	

Kinetic Law

Derived unit contains undeclared units

$$v_7 = \mathrm{vol}\,(\mathrm{compartment}) \cdot \mathrm{k1} \cdot [\mathrm{Tfh}] \tag{36}$$

Table 22: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k1	k1	0000485	0.03		☑

6.8 Reaction Tfr_Death

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

Name Tfr Death

SBO:0000291 empty set

Reaction equation

$$\mathrm{Tfr} \longrightarrow \emptyset \tag{37}$$

Reactant

Table 23: Properties of each reactant.

Id	Name	SBO
Tfr	Tfr	

Kinetic Law

Derived unit contains undeclared units

$$v_8 = \mathrm{vol}\,(\mathrm{compartment}) \cdot \mathrm{k1} \cdot [\mathrm{Tfr}] \tag{38}$$

Table 24: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k1	k1	0000485	0.03		☑

6.9 Reaction Bcl6_Activation

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

Name Bcl6 Activation

SBO:0000393 production

Notes This reaction represents **Bcl6 activation** by STAT3 and ICOS, and inhibition of Bcl6 activation by STAT5, RXR and Blimp1.

Reaction equation

$$\emptyset \xrightarrow{\text{ICOS, STAT3, Blimp1, STAT5, RXR}} \text{Bcl6} \tag{39}$$

Modifiers

Table 25: Properties of each modifier.

Id	Name	SBO
ICOS	ICOS	
STAT3	STAT3	
Blimp1	Blimp1	
STAT5	STAT5	
RXR	RXR	

Product

Table 26: Properties of each product.

Id	Name	SBO
Bcl6	Bcl6	

Kinetic Law

Derived unit contains undeclared units

$$v_9 = \mathrm{vol}\,(\mathrm{compartment}) \cdot \mathrm{Molecule\_Production\_\_2A\_3I\_\_v2\_1}\,([\mathrm{Blimp1}], [\mathrm{ICOS}], [\mathrm{RXR}], [\mathrm{STAT3}], [\mathrm{STAT5}], \mathrm{alpha1}, \mathrm{alpha2}, \mathrm{alpha3}, \mathrm{sigma1}, \mathrm{sigma2}) \tag{40}$$

$$\mathrm{Molecule\_Production\_\_2A\_3I\_\_v2\_1}\,([\mathrm{Blimp1}], [\mathrm{ICOS}], [\mathrm{RXR}], [\mathrm{STAT3}], [\mathrm{STAT5}], \mathrm{alpha1}, \mathrm{alpha2}, \mathrm{alpha3}, \mathrm{sigma1}, \mathrm{sigma2}) = \frac{\mathrm{sigma1} \cdot [\mathrm{ICOS}] + \mathrm{sigma2} \cdot [\mathrm{STAT3}]}{(\mathrm{alpha1} + [\mathrm{Blimp1}]) \cdot (\mathrm{alpha2} + [\mathrm{STAT5}]) \cdot (\mathrm{alpha3} + [\mathrm{RXR}])} \tag{41}$$

$$\mathrm{Molecule\_Production\_\_2A\_3I\_\_v2\_1}\,([\mathrm{Blimp1}], [\mathrm{ICOS}], [\mathrm{RXR}], [\mathrm{STAT3}], [\mathrm{STAT5}], \mathrm{alpha1}, \mathrm{alpha2}, \mathrm{alpha3}, \mathrm{sigma1}, \mathrm{sigma2}) = \frac{\mathrm{sigma1} \cdot [\mathrm{ICOS}] + \mathrm{sigma2} \cdot [\mathrm{STAT3}]}{(\mathrm{alpha1} + [\mathrm{Blimp1}]) \cdot (\mathrm{alpha2} + [\mathrm{STAT5}]) \cdot (\mathrm{alpha3} + [\mathrm{RXR}])} \tag{42}$$

Table 27: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
alpha1	alpha1		0.200		☑
alpha2	alpha2		1.368		☑
alpha3	alpha3		0.125		☑
sigma1	sigma1		3.244		☑
sigma2	sigma2		3.220		☑

6.10 Reaction Blimp1_Activation

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

Name Blimp1 Activation

SBO:0000393 production

Notes This reaction represents **Blimp1 activation** by Tfr, and inhibition of Blimp1 activation by Bcl-6

Reaction equation

$$\emptyset \xrightarrow{\text{Tfr, Bcl6}} \text{Blimp1} \tag{43}$$

Modifiers

Table 28: Properties of each modifier.

Id	Name	SBO
`Tfr`	Tfr	
`Bcl6`	Bcl6	

Product

Table 29: Properties of each product.

Id	Name	SBO
`Blimp1`	Blimp1	

Kinetic Law

Derived unit contains undeclared units

$$v_{10} = \text{vol}\left(\text{compartment}\right) \cdot \text{Molecule\_Production\_\_1A\_1I\_\_1}\left(\left[\text{Bcl6}\right], \left[\text{Tfr}\right], \text{alpha}, \text{sigma}\right) \tag{44}$$

$$\text{Molecule\_Production\_\_1A\_1I\_\_1}\left(\left[\text{Bcl6}\right], \left[\text{Tfr}\right], \text{alpha}, \text{sigma}\right) = \frac{\text{sigma} \cdot \left[\text{Tfr}\right]}{\text{alpha} + \left[\text{Bcl6}\right]} \tag{45}$$

$$\text{Molecule\_Production\_\_1A\_1I\_\_1}\left(\left[\text{Bcl6}\right], \left[\text{Tfr}\right], \text{alpha}, \text{sigma}\right) = \frac{\text{sigma} \cdot \left[\text{Tfr}\right]}{\text{alpha} + \left[\text{Bcl6}\right]} \tag{46}$$

Table 30: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
`alpha`	alpha		2.386		☑
`sigma`	sigma		3.600		☑

6.11 Reaction FoxP3_Activation

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

Name FoxP3 Activation

SBO:0000393 production

Notes This reaction represents **FoxP3 activation** by nTreg

Reaction equation

$$\emptyset \xrightarrow{\text{nTreg}} \text{FoxP3} \tag{47}$$

Modifier

Table 31: Properties of each modifier.

Id	Name	SBO
nTreg	nTreg	

Product

Table 32: Properties of each product.

Id	Name	SBO
FoxP3	FoxP3	

Kinetic Law

Derived unit contains undeclared units

$$v_{11} = \text{vol}\left(\text{compartment}\right) \cdot \text{Molecule\_Production\_\_1A\_0I\_\_1}\left(\left[\text{nTreg}\right], \text{sigma}\right) \tag{48}$$

$$\text{Molecule\_Production\_\_1A\_0I\_\_1}\left(\left[\text{nTreg}\right], \text{sigma}\right) = \text{sigma} \cdot \left[\text{nTreg}\right] \tag{49}$$

$$\text{Molecule\_Production\_\_1A\_0I\_\_1}\left(\left[\text{nTreg}\right], \text{sigma}\right) = \text{sigma} \cdot \left[\text{nTreg}\right] \tag{50}$$

Table 33: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
sigma	sigma		0.1		☑

6.12 Reaction STAT3_Activation

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

Name STAT3 Activation

SBO:0000393 production

Notes This reaction represents **STAT3 activation** by IL6 and IL21.

Reaction equation

$$\emptyset \xrightarrow{\text{IL6, IL21}} \text{STAT3} \tag{51}$$

Modifiers

Table 34: Properties of each modifier.

Id	Name	SBO
IL6	IL6	
IL21	IL21	

Product

Table 35: Properties of each product.

Id	Name	SBO
STAT3	STAT3	

Kinetic Law

Derived unit contains undeclared units

$$v_{12} = \text{vol}\,(\text{compartment}) \cdot \text{Molecule\_Production\_\_2A\_0I\_\_1}\,([\text{IL21}], [\text{IL6}], \text{sigma1}, \text{sigma2}) \tag{52}$$

$$\text{Molecule\_Production\_\_2A\_0I\_\_1}\,([\text{IL21}], [\text{IL6}], \text{sigma1}, \text{sigma2}) = \text{sigma1} \cdot [\text{IL6}] + \text{sigma2} \cdot [\text{IL21}] \tag{53}$$

$$\text{Molecule\_Production\_\_2A\_0I\_\_1}\,([\text{IL21}], [\text{IL6}], \text{sigma1}, \text{sigma2}) = \text{sigma1} \cdot [\text{IL6}] + \text{sigma2} \cdot [\text{IL21}] \tag{54}$$

Table 36: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
sigma1	sigma1		0.125		☑
sigma2	sigma2		0.100		☑

6.13 Reaction STAT5_Activation

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

Name STAT5 Activation

SBO:0000393 production

Notes This reaction represents **STAT5 activation** by IL21.

Reaction equation

$$\emptyset \xrightarrow{\text{IL2}} \text{STAT5} \tag{55}$$

Modifier

Table 37: Properties of each modifier.

Id	Name	SBO
IL2	IL2	

Product

Table 38: Properties of each product.

Id	Name	SBO
STAT5	STAT5	

Kinetic Law

Derived unit contains undeclared units

$$v_{13} = \text{vol}\,(\text{compartment}) \cdot \text{Molecule\_Production\_\_1A\_0I\_\_2}\,([\text{IL2}], \text{sigma}) \tag{56}$$

$$\text{Molecule\_Production\_\_1A\_0I\_\_2}\,([\text{IL2}], \text{sigma}) = \text{sigma} \cdot [\text{IL2}] \tag{57}$$

$$\text{Molecule\_Production\_\_1A\_0I\_\_2}\,([\text{IL2}], \text{sigma}) = \text{sigma} \cdot [\text{IL2}] \tag{58}$$

Table 39: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
sigma	sigma		10.0		☑

6.14 Reaction CXCR5_Production

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

Name CXCR5 Production

SBO:0000393 production

Notes This reaction represents **CXCR5 production** by Tfh and Tfr, and the inhibition of CXCR5 activation by Blimp1.

Reaction equation

$$\emptyset \xrightarrow{\text{Tfh, Tfr, Blimp1}} \text{CXCR5} \tag{59}$$

Modifiers

Table 40: Properties of each modifier.

Id	Name	SBO
Tfh	Tfh	
Tfr	Tfr	
Blimp1	Blimp1	

Product

Table 41: Properties of each product.

Id	Name	SBO
CXCR5	CXCR5	

Kinetic Law

Derived unit contains undeclared units

$$\begin{aligned} v_{14} = {} & \text{vol}\,(\text{compartment}) \\ & \cdot \text{Molecule\_Production\_\_2A\_1I\_\_1}\,([\text{Blimp1}], [\text{Tfh}], [\text{Tfr}], \text{alpha}, \text{sigma1}, \text{sigma2}) \end{aligned} \tag{60}$$

$$\text{Molecule\_Production\_\_2A\_1I\_\_1}\left([\text{Blimp1}], [\text{Tfh}], [\text{Tfr}], \text{alpha}, \text{sigma1}, \text{sigma2}\right) = \frac{\text{sigma1} \cdot [\text{Tfh}] + \text{sigma2} \cdot [\text{Tfr}]}{\text{alpha} + [\text{Blimp1}]} \tag{61}$$

$$\text{Molecule\_Production\_\_2A\_1I\_\_1}\left([\text{Blimp1}], [\text{Tfh}], [\text{Tfr}], \text{alpha}, \text{sigma1}, \text{sigma2}\right) = \frac{\text{sigma1} \cdot [\text{Tfh}] + \text{sigma2} \cdot [\text{Tfr}]}{\text{alpha} + [\text{Blimp1}]} \tag{62}$$

Table 42: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
`alpha`	alpha		0.054		☑
`sigma1`	sigma1		3.040		☑
`sigma2`	sigma2		2.922		☑

6.15 Reaction `ICOS_Production`

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

Name ICOS Production

SBO:0000393 production

Notes This reaction represents **ICOS production** by Tfh.

Reaction equation

$$\emptyset \xrightarrow{\text{Tfh}} \text{ICOS} \tag{63}$$

Modifier

Table 43: Properties of each modifier.

Id	Name	SBO
`Tfh`	Tfh	

Product

Table 44: Properties of each product.

Id	Name	SBO
ICOS	ICOS	

Kinetic Law

Derived unit contains undeclared units

$$v_{15} = \mathrm{vol}\,(\mathrm{compartment}) \cdot \mathrm{Molecule\_Production\_\_1A\_0I\_\_3}\,([\mathrm{Tfh}], \mathrm{sigma}) \tag{64}$$

$$\mathrm{Molecule\_Production\_\_1A\_0I\_\_3}\,([\mathrm{Tfh}], \mathrm{sigma}) = \mathrm{sigma} \cdot [\mathrm{Tfh}] \tag{65}$$

$$\mathrm{Molecule\_Production\_\_1A\_0I\_\_3}\,([\mathrm{Tfh}], \mathrm{sigma}) = \mathrm{sigma} \cdot [\mathrm{Tfh}] \tag{66}$$

Table 45: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
sigma	sigma		0.018		☑

6.16 Reaction IL2_Production

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

Name IL2 Production

SBO:0000393 production

Reaction equation

$$\emptyset \longrightarrow \mathrm{IL2} \tag{67}$$

Product

Table 46: Properties of each product.

Id	Name	SBO
IL2	IL2	

Kinetic Law

Derived unit contains undeclared units

$$v_{16} = \mathrm{vol}\left(\mathrm{compartment}\right) \cdot \mathrm{Constant\_flux\_\_irreversible}\left(\mathrm{v}\right) \tag{68}$$

$$\mathrm{Constant\_flux\_\_irreversible}\left(\mathrm{v}\right) = \mathrm{v} \tag{69}$$

$$\mathrm{Constant\_flux\_\_irreversible}\left(\mathrm{v}\right) = \mathrm{v} \tag{70}$$

Table 47: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
v	v	0000485	0.1		☑

6.17 Reaction `IL4_Production`

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

Name IL4 Production

SBO:0000393 production

Notes This reaction represents **IL4 production**, positively regulated by Tfh.

Reaction equation

$$\emptyset \xrightarrow{\mathrm{Tfh}} \mathrm{IL4} \tag{71}$$

Modifier

Table 48: Properties of each modifier.

Id	Name	SBO
`Tfh`	Tfh	

Product

Table 49: Properties of each product.

Id	Name	SBO
IL4	IL4	

Kinetic Law

Derived unit contains undeclared units

$$v_{17} = \mathrm{vol}\,(\mathrm{compartment}) \cdot \mathrm{Molecule\_Production\_\_1A\_0I\_\_3}\,([\mathrm{Tfh}], \mathrm{sigma}) \tag{72}$$

$$\mathrm{Molecule\_Production\_\_1A\_0I\_\_3}\,([\mathrm{Tfh}], \mathrm{sigma}) = \mathrm{sigma} \cdot [\mathrm{Tfh}] \tag{73}$$

$$\mathrm{Molecule\_Production\_\_1A\_0I\_\_3}\,([\mathrm{Tfh}], \mathrm{sigma}) = \mathrm{sigma} \cdot [\mathrm{Tfh}] \tag{74}$$

Table 50: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
sigma	sigma		0.015		☑

6.18 Reaction IL6_Production

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

Name IL6 Production

SBO:0000393 production

Notes This reaction represents **IL6 production** inhibited by IL4.

Reaction equation

$$\emptyset \xrightarrow{\mathrm{IL4}} \mathrm{IL6} \tag{75}$$

Modifier

Table 51: Properties of each modifier.

Id	Name	SBO
IL4	IL4	

Product

Table 52: Properties of each product.

Id	Name	SBO
IL6	IL6	

Kinetic Law

Derived unit contains undeclared units

$$v_{18} = \mathrm{vol}\,(\mathrm{compartment}) \cdot \mathrm{Molecule\_Production\_\_0A\_1I\_\_1}\,([\mathrm{IL4}], \mathrm{alpha1}, \mathrm{sigma1}) \quad (76)$$

$$\mathrm{Molecule\_Production\_\_0A\_1I\_\_1}\,([\mathrm{IL4}], \mathrm{alpha1}, \mathrm{sigma1}) = \frac{\mathrm{sigma1}}{\mathrm{alpha1} + [\mathrm{IL4}]} \quad (77)$$

$$\mathrm{Molecule\_Production\_\_0A\_1I\_\_1}\,([\mathrm{IL4}], \mathrm{alpha1}, \mathrm{sigma1}) = \frac{\mathrm{sigma1}}{\mathrm{alpha1} + [\mathrm{IL4}]} \quad (78)$$

Table 53: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
alpha1	alpha1		0.435		☑
sigma1	sigma1		0.990		☑

6.19 Reaction IL10_Production

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

Name IL10 Production

SBO:0000393 production

Notes This reaction represents **IL10 production** by Tfr

Reaction equation

$$\emptyset \xrightarrow{\mathrm{Tfr}} \mathrm{IL10} \quad (79)$$

Modifier

Table 54: Properties of each modifier.

Id	Name	SBO
Tfr	Tfr	

Product

Table 55: Properties of each product.

Id	Name	SBO
IL10	IL10	

Kinetic Law

Derived unit contains undeclared units

$$v_{19} = \text{vol}\left(\text{compartment}\right) \cdot \text{Molecule\_Production\_\_1A\_0I\_\_4}\left(\left[\text{Tfr}\right], \text{sigma}\right) \tag{80}$$

$$\text{Molecule\_Production\_\_1A\_0I\_\_4}\left(\left[\text{Tfr}\right], \text{sigma}\right) = \text{sigma} \cdot \left[\text{Tfr}\right] \tag{81}$$

$$\text{Molecule\_Production\_\_1A\_0I\_\_4}\left(\left[\text{Tfr}\right], \text{sigma}\right) = \text{sigma} \cdot \left[\text{Tfr}\right] \tag{82}$$

Table 56: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
sigma	sigma	0000485	0.068		☑

6.20 Reaction Bcl6_Degradation

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

Name Bcl6 Degradation

SBO:0000179 degradation

Reaction equation

$$\text{Bcl6} \longrightarrow \emptyset \tag{83}$$

Reactant

Table 57: Properties of each reactant.

Id	Name	SBO
Bcl6	Bcl6	

Kinetic Law

Derived unit contains undeclared units

$$v_{20} = \mathrm{vol}\,(\mathrm{compartment}) \cdot \mathrm{k1} \cdot [\mathrm{Bcl6}] \tag{84}$$

Table 58: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k1	k1	0000485	0.164		☑

6.21 Reaction Blimp1_Degradation

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

Name Blimp1 Degradation

SBO:0000179 degradation

Reaction equation

$$\mathrm{Blimp1} \longrightarrow \emptyset \tag{85}$$

Reactant

Table 59: Properties of each reactant.

Id	Name	SBO
Blimp1	Blimp1	

Kinetic Law

Derived unit contains undeclared units

$$v_{21} = \mathrm{vol}\,(\mathrm{compartment}) \cdot \mathrm{k1} \cdot [\mathrm{Blimp1}] \tag{86}$$

Table 60: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k1	k1	0000485	0.111		☑

6.22 Reaction FoxP3_Degradation

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

Name FoxP3 Degradation

SBO:0000179 degradation

Reaction equation

$$\text{FoxP3} \longrightarrow \emptyset \tag{87}$$

Reactant

Table 61: Properties of each reactant.

Id	Name	SBO
FoxP3	FoxP3	

Kinetic Law

Derived unit contains undeclared units

$$v_{22} = \text{vol}\,(\text{compartment}) \cdot \text{k1} \cdot [\text{FoxP3}] \tag{88}$$

Table 62: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k1	k1	0000485	0.1		☑

6.23 Reaction STAT3_Degradation

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

Name STAT3 Degradation

SBO:0000179 degradation

Reaction equation

$$\text{STAT3} \longrightarrow \emptyset \tag{89}$$

Reactant

Table 63: Properties of each reactant.

Id	Name	SBO
STAT3	STAT3	

Kinetic Law

Derived unit contains undeclared units

$$v_{23} = \text{vol}\,(\text{compartment}) \cdot \text{k1} \cdot [\text{STAT3}] \tag{90}$$

Table 64: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k1	k1	0000485	0.1		☑

6.24 Reaction STAT5_Degradation

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

Name STAT5 Degradation

SBO:0000179 degradation

Reaction equation

$$\text{STAT5} \longrightarrow \emptyset \tag{91}$$

Reactant

Table 65: Properties of each reactant.

Id	Name	SBO
STAT5	STAT5	

Kinetic Law

Derived unit contains undeclared units

$$v_{24} = \mathrm{vol}\,(\mathrm{compartment}) \cdot \mathrm{k1} \cdot [\mathrm{STAT5}] \tag{92}$$

Table 66: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k1	k1	0000485	0.1		☑

6.25 Reaction CXCR5_Degradation

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

Name CXCR5 Degradation

SBO:0000179 degradation

Reaction equation

$$\mathrm{CXCR5} \longrightarrow \emptyset \tag{93}$$

Reactant

Table 67: Properties of each reactant.

Id	Name	SBO
CXCR5	CXCR5	

Kinetic Law

Derived unit contains undeclared units

$$v_{25} = \mathrm{vol}\,(\mathrm{compartment}) \cdot \mathrm{k1} \cdot [\mathrm{CXCR5}] \tag{94}$$

Table 68: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k1	k1	0000485	0.1		☑

6.26 Reaction ICOS_Degradation

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

Name ICOS Degradation

SBO:0000179 degradation

Reaction equation

$$\text{ICOS} \longrightarrow \emptyset \tag{95}$$

Reactant

Table 69: Properties of each reactant.

Id	Name	SBO
ICOS	ICOS	

Kinetic Law

Derived unit contains undeclared units

$$v_{26} = \text{vol}\left(\text{compartment}\right) \cdot \text{k1} \cdot [\text{ICOS}] \tag{96}$$

Table 70: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k1	k1	0000485	0.1		☑

6.27 Reaction IL2_Degradation

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

Name IL2 Degradation

SBO:0000179 degradation

Reaction equation

$$\text{IL2} \longrightarrow \emptyset \tag{97}$$

Reactant

Table 71: Properties of each reactant.

Id	Name	SBO
IL2	IL2	

Kinetic Law

Derived unit contains undeclared units

$$v_{27} = \mathrm{vol}\,(\mathrm{compartment}) \cdot \mathrm{k1} \cdot [\mathrm{IL2}] \tag{98}$$

Table 72: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k1	k1	0000485	0.1		☑

6.28 Reaction IL4_Degradation

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

Name IL4 Degradation

SBO:0000179 degradation

Reaction equation

$$\mathrm{IL4} \longrightarrow \emptyset \tag{99}$$

Reactant

Table 73: Properties of each reactant.

Id	Name	SBO
IL4	IL4	

Kinetic Law

Derived unit contains undeclared units

$$v_{28} = \mathrm{vol}\,(\mathrm{compartment}) \cdot \mathrm{k1} \cdot [\mathrm{IL4}] \tag{100}$$

Table 74: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k1	k1	0000485	0.1		☑

6.29 Reaction IL6_Degradation

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

Name IL6 Degradation

SBO:0000179 degradation

Reaction equation

$$\mathrm{IL6} \longrightarrow \emptyset \tag{101}$$

Reactant

Table 75: Properties of each reactant.

Id	Name	SBO
IL6	IL6	

Kinetic Law

Derived unit contains undeclared units

$$v_{29} = \mathrm{vol}\,(\mathrm{compartment}) \cdot \mathrm{k1} \cdot [\mathrm{IL6}] \tag{102}$$

Table 76: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k1	k1	0000485	0.697		☑

6.30 Reaction IL10_Degradation

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

Name IL10 Degradation

SBO:0000179 degradation

Reaction equation

$$\text{IL10} \longrightarrow \emptyset \tag{103}$$

Reactant

Table 77: Properties of each reactant.

Id	Name	SBO
IL10	IL10	

Kinetic Law

Derived unit contains undeclared units

$$v_{30} = \text{vol}\,(\text{compartment}) \cdot \text{k1} \cdot [\text{IL10}] \tag{104}$$

Table 78: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k1	k1	0000485	0.1		☑

6.31 Reaction IL21_Degradation

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

Name IL21 Degradation

SBO:0000179 degradation

Reaction equation

$$\text{IL21} \longrightarrow \emptyset \tag{105}$$

Reactant

Table 79: Properties of each reactant.

Id	Name	SBO
IL21	IL21	

Kinetic Law

Derived unit contains undeclared units

$$v_{31} = \mathrm{vol}\,(\mathrm{compartment}) \cdot \mathrm{k1} \cdot [\mathrm{IL21}] \tag{106}$$

Table 80: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k1	k1	0000485	0.1		☑

6.32 Reaction IL21_Production

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

Name IL21 Production

Notes This reaction represents **IL21 production**, positively regulated by Tfh.

Reaction equation

$$\emptyset \xrightarrow{\mathrm{Tfh}} \mathrm{IL21} \tag{107}$$

Modifier

Table 81: Properties of each modifier.

Id	Name	SBO
Tfh	Tfh	

Product

Table 82: Properties of each product.

Id	Name	SBO
IL21	IL21	

Kinetic Law

Derived unit contains undeclared units

$$v_{32} = \mathrm{vol}\,(\mathrm{compartment}) \cdot \mathrm{Molecule\_Production\_\_1A\_0I\_\_3}\,([\mathrm{Tfh}], \mathrm{sigma}) \tag{108}$$

$$\text{Molecule\_Production\_\_1A\_0I\_\_3}\left([\text{Tfh}], \text{sigma}\right) = \text{sigma} \cdot [\text{Tfh}] \tag{109}$$

$$\text{Molecule\_Production\_\_1A\_0I\_\_3}\left([\text{Tfh}], \text{sigma}\right) = \text{sigma} \cdot [\text{Tfh}] \tag{110}$$

Table 83: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
sigma	sigma		0.060		☑

6.33 Reaction TGFb_Production

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

Name TGFb Production

SBO:0000393 production

Notes This reaction represents **TGFb activation** by IL10.

Reaction equation

$$\emptyset \xrightarrow{\text{IL10}} \text{TGFb} \tag{111}$$

Modifier

Table 84: Properties of each modifier.

Id	Name	SBO
IL10	IL10	

Product

Table 85: Properties of each product.

Id	Name	SBO
TGFb	TGFb	

Kinetic Law

Derived unit contains undeclared units

$$v_{33} = \text{vol}\left(\text{compartment}\right) \cdot \text{Molecule\_Production\_\_1A\_0I\_\_5}\left([\text{IL10}], \text{sigma}\right) \tag{112}$$

$$\text{Molecule\_Production\_\_1A\_0I\_\_5}\left([\text{IL10}], \text{sigma}\right) = \text{sigma} \cdot [\text{IL10}] \tag{113}$$

$$\text{Molecule\_Production\_\_1A\_0I\_\_5}\left([\text{IL10}], \text{sigma}\right) = \text{sigma} \cdot [\text{IL10}] \tag{114}$$

Table 86: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
sigma	sigma		0.1		☑

6.34 Reaction TGFb_Degradation

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

Name TGFb Degradation

SBO:0000179 degradation

Reaction equation

$$\text{TGFb} \longrightarrow \emptyset \tag{115}$$

Reactant

Table 87: Properties of each reactant.

Id	Name	SBO
TGFb	TGFb	

Kinetic Law

Derived unit contains undeclared units

$$v_{34} = \text{vol}\left(\text{compartment}\right) \cdot \text{k1} \cdot [\text{TGFb}] \tag{116}$$

Table 88: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k1	k1	0000485	0.1		☑

6.35 Reaction RXR_Activation

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

Name RXR Activation

SBO:0000393 production

Reaction equation

$$\emptyset \xrightarrow{\text{TGFb, Tgif1}} \text{RXR} \tag{117}$$

Modifiers

Table 89: Properties of each modifier.

Id	Name	SBO
TGFb	TGFb	
Tgif1	Tgif1	

Product

Table 90: Properties of each product.

Id	Name	SBO
RXR	RXR	

Kinetic Law

Derived unit contains undeclared units

$$v_{35} = \text{vol}\,(\text{compartment}) \cdot \text{Molecule\_Production\_\_1A\_1I\_\_2}\,([\text{TGFb}], [\text{Tgif1}], \text{alpha}, \text{sigma}) \tag{118}$$

$$\text{Molecule\_Production\_\_1A\_1I\_\_2}\,([\text{TGFb}], [\text{Tgif1}], \text{alpha}, \text{sigma}) = \frac{\text{sigma} \cdot [\text{TGFb}]}{\text{alpha} + [\text{Tgif1}]} \tag{119}$$

$$\text{Molecule\_Production\_\_1A\_1I\_\_2}\,([\text{TGFb}], [\text{Tgif1}], \text{alpha}, \text{sigma}) = \frac{\text{sigma} \cdot [\text{TGFb}]}{\text{alpha} + [\text{Tgif1}]} \tag{120}$$

Table 91: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
alpha	alpha		3.050		☑
sigma	sigma		0.050		☑

6.36 Reaction Tgif1_Production

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

Name Tgif1 Production

SBO:0000393 production

Notes This reaction represents **Tgif1 activation** positively regulated by Tfh.

Reaction equation

$$\emptyset \xrightarrow{\text{Tfh}} \text{Tgif1} \tag{121}$$

Modifier

Table 92: Properties of each modifier.

Id	Name	SBO
Tfh	Tfh	

Product

Table 93: Properties of each product.

Id	Name	SBO
Tgif1	Tgif1	

Kinetic Law

Derived unit contains undeclared units

$$v_{36} = \text{vol}\,(\text{compartment}) \cdot \text{Molecule\_Production\_\_1A\_0I\_\_3}\,([\text{Tfh}], \text{sigma}) \tag{122}$$

$$\text{Molecule\_Production\_\_1A\_0I\_\_3}\,([\text{Tfh}], \text{sigma}) = \text{sigma} \cdot [\text{Tfh}] \tag{123}$$

$$\text{Molecule\_Production\_\_1A\_0I\_\_3}\,([\text{Tfh}], \text{sigma}) = \text{sigma} \cdot [\text{Tfh}] \tag{124}$$

Table 94: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
sigma	sigma		0.1		☑

6.37 Reaction RXR_Degradation

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

Name RXR Degradation

SBO:0000179 degradation

Reaction equation

$$\mathrm{RXR} \longrightarrow \emptyset \tag{125}$$

Reactant

Table 95: Properties of each reactant.

Id	Name	SBO
RXR	RXR	

Kinetic Law

Derived unit contains undeclared units

$$v_{37} = \mathrm{vol}\,(\mathrm{compartment}) \cdot \mathrm{k1} \cdot [\mathrm{RXR}] \tag{126}$$

Table 96: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k1	k1	0000485	0.085		☑

6.38 Reaction Tgif1_Degradation

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

Name Tgif1 Degradation

SBO:0000179 degradation

Reaction equation

$$\text{Tgif1} \longrightarrow \emptyset \tag{127}$$

Reactant

Table 97: Properties of each reactant.

Id	Name	SBO
Tgif1	Tgif1	

Kinetic Law

Derived unit contains undeclared units

$$v_{38} = \text{vol}\,(\text{compartment}) \cdot \text{k1} \cdot [\text{Tgif1}] \tag{128}$$

Table 98: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k1	k1	0000485	0.1		☑

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 NaiveCD4

Name NaiveCD4

Initial concentration $200\ \text{item} \cdot \text{ml}^{-1}$

This species takes part in three reactions (as a reactant in NaiveCD4_Death, Tfh_Differentiation and as a product in NaiveCD4_Source).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{NaiveCD4} = v_1 - v_2 - v_5 \tag{129}$$

7.2 Species nTreg

Name nTreg

Initial concentration $100\ \mathrm{item} \cdot \mathrm{ml}^{-1}$

This species takes part in four reactions (as a reactant in nTreg_Death, Tfr_Differentiation and as a product in nTreg_Source and as a modifier in FoxP3_Activation).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{nTreg} = v_3 - v_4 - v_6 \tag{130}$$

7.3 Species Tfh

Name Tfh

Initial concentration $1\ \mathrm{item} \cdot \mathrm{ml}^{-1}$

This species takes part in seven reactions (as a reactant in Tfh_Death and as a product in Tfh_Differentiation and as a modifier in CXCR5_Production, ICOS_Production, IL4-_Production, IL21_Production, Tgif1_Production).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Tfh} = v_5 - v_7 \tag{131}$$

7.4 Species Tfr

Name Tfr

Initial concentration $1\ \mathrm{item} \cdot \mathrm{ml}^{-1}$

This species takes part in five reactions (as a reactant in Tfr_Death and as a product in Tfr-_Differentiation and as a modifier in Blimp1_Activation, CXCR5_Production, IL10-_Production).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Tfr} = v_6 - v_8 \tag{132}$$

7.5 Species Bcl6

Name Bcl6

Initial concentration $1\ \mathrm{item} \cdot \mathrm{ml}^{-1}$

This species takes part in five reactions (as a reactant in Bcl6_Degradation and as a product in Bcl6_Activation and as a modifier in Tfh_Differentiation, Tfr_Differentiation, Blimp1_Activation).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Bcl6} = v_9 - v_{20} \tag{133}$$

7.6 Species Blimp1

Name Blimp1

Initial concentration $1\ \text{item} \cdot \text{ml}^{-1}$

This species takes part in four reactions (as a reactant in Blimp1_Degradation and as a product in Blimp1_Activation and as a modifier in Bcl6_Activation, CXCR5_Production).

$$\frac{\mathrm{d}}{\mathrm{d}t}\text{Blimp1} = v_{10} - v_{21} \tag{134}$$

7.7 Species FoxP3

Name FoxP3

Initial concentration $1\ \text{item} \cdot \text{ml}^{-1}$

This species takes part in two reactions (as a reactant in FoxP3_Degradation and as a product in FoxP3_Activation).

$$\frac{\mathrm{d}}{\mathrm{d}t}\text{FoxP3} = v_{11} - v_{22} \tag{135}$$

7.8 Species STAT3

Name STAT3

Initial concentration $1\ \text{item} \cdot \text{ml}^{-1}$

This species takes part in three reactions (as a reactant in STAT3_Degradation and as a product in STAT3_Activation and as a modifier in Bcl6_Activation).

$$\frac{\mathrm{d}}{\mathrm{d}t}\text{STAT3} = v_{12} - v_{23} \tag{136}$$

7.9 Species STAT5

Name STAT5

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

This species takes part in three reactions (as a reactant in STAT5_Degradation and as a product in STAT5_Activation and as a modifier in Bcl6_Activation), which do not influence its rate of change because this constant species is on the boundary of the reaction system:

$$\frac{\mathrm{d}}{\mathrm{d}t}\text{STAT5} = 0 \tag{137}$$

7.10 Species IL2

Name IL2

Initial concentration 10^{-4} item $\cdot$ ml^{-1}

This species takes part in three reactions (as a reactant in IL2_Degradation and as a product in IL2_Production and as a modifier in STAT5_Activation), which do not influence its rate of change because this constant species is on the boundary of the reaction system:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{IL2} = 0 \tag{138}$$

7.11 Species IL4

Name IL4

Initial concentration 1 item $\cdot$ ml^{-1}

This species takes part in three reactions (as a reactant in IL4_Degradation and as a product in IL4_Production and as a modifier in IL6_Production).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{IL4} = v_{17} - v_{28} \tag{139}$$

7.12 Species IL6

Name IL6

Initial concentration 1 item $\cdot$ ml^{-1}

This species takes part in three reactions (as a reactant in IL6_Degradation and as a product in IL6_Production and as a modifier in STAT3_Activation).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{IL6} = v_{18} - v_{29} \tag{140}$$

7.13 Species IL10

Name IL10

Initial concentration 1 item $\cdot$ ml^{-1}

This species takes part in four reactions (as a reactant in IL10_Degradation and as a product in IL10_Production and as a modifier in Tfh_Differentiation, TGFb_Production).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{IL10} = v_{19} - v_{30} \tag{141}$$

7.14 Species IL21

Name IL21

Initial concentration $1\ \text{item} \cdot \text{ml}^{-1}$

This species takes part in three reactions (as a reactant in IL21_Degradation and as a product in IL21_Production and as a modifier in STAT3_Activation).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{IL21} = v_{32} - v_{31} \tag{142}$$

7.15 Species CXCR5

Name CXCR5

Initial concentration $1\ \text{item} \cdot \text{ml}^{-1}$

This species takes part in three reactions (as a reactant in CXCR5_Degradation and as a product in CXCR5_Production and as a modifier in Tfr_Differentiation).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{CXCR5} = v_{14} - v_{25} \tag{143}$$

7.16 Species ICOS

Name ICOS

Initial concentration $1\ \text{item} \cdot \text{ml}^{-1}$

This species takes part in three reactions (as a reactant in ICOS_Degradation and as a product in ICOS_Production and as a modifier in Bcl6_Activation).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{ICOS} = v_{15} - v_{26} \tag{144}$$

7.17 Species TGFb

Name TGFb

Initial concentration $1\ \text{item} \cdot \text{ml}^{-1}$

This species takes part in three reactions (as a reactant in TGFb_Degradation and as a product in TGFb_Production and as a modifier in RXR_Activation).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{TGFb} = v_{33} - v_{34} \tag{145}$$

7.18 Species Tgif1

Name Tgif1

Initial concentration $1\ \text{item} \cdot \text{ml}^{-1}$

This species takes part in three reactions (as a reactant in Tgif1_Degradation and as a product in Tgif1_Production and as a modifier in RXR_Activation).

$$\frac{\mathrm{d}}{\mathrm{d}t}\text{Tgif1} = v_{36} - v_{38} \tag{146}$$

7.19 Species RXR

Name RXR

Initial concentration $1\ \text{item} \cdot \text{ml}^{-1}$

This species takes part in three reactions (as a reactant in RXR_Degradation and as a product in RXR_Activation and as a modifier in Bcl6_Activation).

$$\frac{\mathrm{d}}{\mathrm{d}t}\text{RXR} = v_{35} - v_{37} \tag{147}$$

A Glossary of Systems Biology Ontology Terms

SBO:0000179 degradation: Complete disappearance of a physical entity

SBO:0000291 empty set: Entity defined by the absence of any actual object. An empty set is often used to represent the source of a creation process or the result of a degradation process.

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

SBO:0000485 basal rate constant: The minimal velocity observed under defined conditions, which may or may not include the presence of an effector. For example in an inhibitory system, this would be the residual velocity observed under full inhibition. In non-essential activation, this would be the velocity in the absence of any activator

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