SBML Model Report

Model name: "Palmer2014 - Effect of IL-1-Blocking therapies in T2DM - Disease Condition"

December 1, 2016

1 General Overview

This is a document in SBML Level 2 Version 4 format. This model was created by the following four authors: Vijayalakshmi Chelliah[1], Vincent Knight-Schrijver[2], Robert Palmr[3] and Balaji Agoram[4] at April 27th 2016 at 5:38 p. m. and last time modified at November tenth 2016 at 11:38 a. m. Table 1 shows an overview of the quantities of all components of this model.

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

Element	Quantity	Element	Quantity
compartment types	0	compartments	1
species types	0	species	35
events	1	constraints	0
reactions	20	function definitions	0
global parameters	52	unit definitions	3
rules	29	initial assignments	0

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Model Notes

Palmer2014 - Effect of IL-1-Blocking therapies in T2DM - Disease Condition

This is the model with disease state initial conditions. A few changes were made to the model equations in order to bypass the circular dependencies apparent in SBML. Coupled algebraic equations for the species Glucose, Insulin and Proinsulin were changed to reactions which represent the ordinary differential equations found in a previously published model by De Gaetanoet al (2008), [MODEL1112110003]. This reference was used by the present authors for the algebraic equations. The original Mathematica code, obtained from the supplementary material of the article can be downloaded from the link below: [Palmer2014_notebook.nb].

This model is described in the article:Effects of IL-1-Blocking Therapies in Type 2 Diabetes Mellitus: A Quantitative Systems Pharmacology Modeling Approach to Explore Underlying Mechanisms.Palmr R, Nyman E, Penney M, Marley A, Cedersund G, Agoram B.CPT Pharmacometrics Syst Pharmacol. 2014 Jun 11;3:e118.

Abstract:

Recent clinical studies suggest sustained treatment effects of interleukin-1 (IL-1)-blocking therapies in type 2 diabetes mellitus. The underlying mechanisms of these effects, however, remain underexplored. Using a quantitative systems pharmacology modeling approach, we combined ex vivo data of IL-1 effects on -cell function and turnover with a disease progression model of the long-term interactions between insulin, glucose, and -cell mass in type 2 diabetes mellitus. We then simulated treatment effects of the IL-1 receptor antagonist anakinra. The result was a substantial and partly sustained symptomatic improvement in -cell function, and hence also in HbA1C, fasting plasma glucose, and proinsulin-insulin ratio, and a small increase in -cell mass. We propose that improved -cell function, rather than mass, is likely to explain the main IL-1-blocking effects seen in current clinical data, but that improved -cell mass might result in disease-modifying effects not clearly distinguishable until >1 year after treatment.

This model is hosted on BioModels Database and identified by: MODEL1604270002.

To cite BioModels Database, please use: BioModels: Content, Features, Functionality and Use.

2 Unit Definitions

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

2.1 Unit `volume`

Definition 1

2.2 Unit `substance`

Definition mol

2.3 Unit `time_unit`

Definition $8.64 \cdot 10^4 \cdot \mathrm{s}$

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

2.6 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
`default_compartment`		0000410	3	1	litre	☑	

3.1 Compartment `default_compartment`

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

SBO:0000410 implicit compartment

4 Species

This model contains 35 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
IL1b		default_compartment	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
IL1Ra		default_compartment	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
Anakinra		default_compartment	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
Proinsulin		default_compartment	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
Insulin		default_compartment	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
TigB		default_compartment	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
B		default_compartment	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
f		default_compartment	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
Anakinrasc		default_compartment	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
Glucose		default_compartment	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
a1c1		default_compartment	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
rbc1		default_compartment	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
a1c2		default_compartment	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
rbc2		default_compartment	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
a1c3		default_compartment	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
rbc3		default_compartment	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
a1c4		default_compartment	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
rbc4		default_compartment	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
a1c5		default_compartment	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
rbc5		default_compartment	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
a1c6		default_compartment	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟

Id	Name	Compartment	Derived Unit	Constant	Boundary Condition
rbc6		default_compartment	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
a1c7		default_compartment	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
rbc7		default_compartment	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
a1c8		default_compartment	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
rbc8		default_compartment	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
a1c9		default_compartment	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
rbc9		default_compartment	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
a1c10		default_compartment	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
rbc10		default_compartment	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
a1c11		default_compartment	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
rbc11		default_compartment	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
a1c12		default_compartment	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
rbc12		default_compartment	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	⊟
hba1c		default_compartment	$\mathrm{mol} \cdot \mathrm{l}^{-1}$	⊟	☑

5 Parameters

This model contains 52 global parameters.

Table 4: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
Kxg			$1.6 \cdot 10^{-5}$		☑
Kxi			0.050		☑
Gh			9.000		☑
vh			4.000		☑
Ktr			0.120		☑
Kin			1.050		☑
lambda			0.743		☑
Kglucose			$2.92 \cdot 10^{-4}$		☑
vs			0.700		☑
kms			0.021		☑
taus			0.500		☑
kmf			0.021		☑
tauf			0.500		☑
vfg			4.000		☑
xfg			4.000		☑
kmfg			9.000		☑
vf			0.400		☑
vlr			1.800		☑
kmlr			0.001		☑
xlr			3.000		☑
vhr			2.700		☑
kmhr			0.018		☑
xhr			0.500		☑
vla			0.650		☑
kmla			$1.8 \cdot 10^{-4}$		☑
xla			3.000		☑
vha			4.600		☑
kmha			0.155		☑
xha			0.667		☑
km			8.500		☑
ki			1.700		☑
ka			$5.52022 \cdot 10^{-4}$		☑
kr			$3.76393 \cdot 10^{-4}$		☑
kf			0.010		☑
ks			0.291		☑
Tgl			0.025		☑
Kxgi			$2.24 \cdot 10^{-5}$		☑

Id	Name	SBO	Value	Unit	Constant
il1bH			0.050		☑
il1b0			5.000		☐
kplacebo			0.001		☑
k1			0.200		☑
k2			0.003		☑
kab			3.940		☑
CL			432.000		☑
Vp			48.000		☑
apoptosis			$7.543653797 \cdot 10^{-4}$		☐
IL1R			0.023		☐
replication			$5.12314779 \cdot 10^{-4}$		☐
Ana_on			1.000		☑
placebo_on			0.000		☑
Anakinra-_dose_counter			0.500		☐
PI_I			0.430		☐

6 Rules

This is an overview of 29 rules.

6.1 Rule a1c1

Rule a1c1 is a rate rule for species a1c1:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{a1c1} = \mathrm{Kglucose} \cdot [\mathrm{Glucose}]^{\mathrm{lambda}} \cdot [\mathrm{rbc1}] - \mathrm{Ktr} \cdot [\mathrm{a1c1}] \tag{1}$$

6.2 Rule rbc1

Rule rbc1 is a rate rule for species rbc1:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{rbc1} = \mathrm{Kin} - \mathrm{Ktr} \cdot [\mathrm{rbc1}] - \mathrm{Kglucose} \cdot [\mathrm{Glucose}]^{\mathrm{lambda}} \cdot [\mathrm{rbc1}] \tag{2}$$

6.3 Rule a1c2

Rule a1c2 is a rate rule for species a1c2:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{a1c2} = \mathrm{Kglucose} \cdot [\mathrm{Glucose}]^{\mathrm{lambda}} \cdot [\mathrm{rbc2}] + \mathrm{Ktr} \cdot [\mathrm{a1c1}] - \mathrm{Ktr} \cdot [\mathrm{a1c2}] \tag{3}$$

6.4 Rule `rbc2`

Rule `rbc2` is a rate rule for species `rbc2`:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{rbc2} = \mathrm{Ktr} \cdot [\mathrm{rbc1}] - \mathrm{Ktr} \cdot [\mathrm{rbc2}] - \mathrm{Kglucose} \cdot [\mathrm{Glucose}]^{\mathrm{lambda}} \cdot [\mathrm{rbc2}] \tag{4}$$

6.5 Rule `a1c3`

Rule `a1c3` is a rate rule for species `a1c3`:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{a1c3} = \mathrm{Kglucose} \cdot [\mathrm{Glucose}]^{\mathrm{lambda}} \cdot [\mathrm{rbc3}] + \mathrm{Ktr} \cdot [\mathrm{a1c2}] - \mathrm{Ktr} \cdot [\mathrm{a1c3}] \tag{5}$$

6.6 Rule `rbc3`

Rule `rbc3` is a rate rule for species `rbc3`:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{rbc3} = \mathrm{Ktr} \cdot [\mathrm{rbc2}] - \mathrm{Ktr} \cdot [\mathrm{rbc3}] - \mathrm{Kglucose} \cdot [\mathrm{Glucose}]^{\mathrm{lambda}} \cdot [\mathrm{rbc3}] \tag{6}$$

6.7 Rule `a1c4`

Rule `a1c4` is a rate rule for species `a1c4`:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{a1c4} = \mathrm{Kglucose} \cdot [\mathrm{Glucose}]^{\mathrm{lambda}} \cdot [\mathrm{rbc4}] + \mathrm{Ktr} \cdot [\mathrm{a1c3}] - \mathrm{Ktr} \cdot [\mathrm{a1c4}] \tag{7}$$

6.8 Rule `rbc4`

Rule `rbc4` is a rate rule for species `rbc4`:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{rbc4} = \mathrm{Ktr} \cdot [\mathrm{rbc3}] - \mathrm{Ktr} \cdot [\mathrm{rbc4}] - \mathrm{Kglucose} \cdot [\mathrm{Glucose}]^{\mathrm{lambda}} \cdot [\mathrm{rbc4}] \tag{8}$$

6.9 Rule `a1c5`

Rule `a1c5` is a rate rule for species `a1c5`:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{a1c5} = \mathrm{Kglucose} \cdot [\mathrm{Glucose}]^{\mathrm{lambda}} \cdot [\mathrm{rbc5}] + \mathrm{Ktr} \cdot [\mathrm{a1c4}] - \mathrm{Ktr} \cdot [\mathrm{a1c5}] \tag{9}$$

6.10 Rule `rbc5`

Rule `rbc5` is a rate rule for species `rbc5`:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{rbc5} = \mathrm{Ktr} \cdot [\mathrm{rbc4}] - \mathrm{Ktr} \cdot [\mathrm{rbc5}] - \mathrm{Kglucose} \cdot [\mathrm{Glucose}]^{\mathrm{lambda}} \cdot [\mathrm{rbc5}] \tag{10}$$

6.11 Rule `a1c6`

Rule `a1c6` is a rate rule for species `a1c6`:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{a1c6} = \mathrm{Kglucose} \cdot [\mathrm{Glucose}]^{\mathrm{lambda}} \cdot [\mathrm{rbc6}] + \mathrm{Ktr} \cdot [\mathrm{a1c5}] - \mathrm{Ktr} \cdot [\mathrm{a1c6}] \tag{11}$$

6.12 Rule `rbc6`

Rule `rbc6` is a rate rule for species `rbc6`:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{rbc6} = \mathrm{Ktr} \cdot [\mathrm{rbc5}] - \mathrm{Ktr} \cdot [\mathrm{rbc6}] - \mathrm{Kglucose} \cdot [\mathrm{Glucose}]^{\mathrm{lambda}} \cdot [\mathrm{rbc6}] \tag{12}$$

6.13 Rule `a1c7`

Rule `a1c7` is a rate rule for species `a1c7`:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{a1c7} = \mathrm{Kglucose} \cdot [\mathrm{Glucose}]^{\mathrm{lambda}} \cdot [\mathrm{rbc7}] + \mathrm{Ktr} \cdot [\mathrm{a1c6}] - \mathrm{Ktr} \cdot [\mathrm{a1c7}] \tag{13}$$

6.14 Rule `rbc7`

Rule `rbc7` is a rate rule for species `rbc7`:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{rbc7} = \mathrm{Ktr} \cdot [\mathrm{rbc6}] - \mathrm{Ktr} \cdot [\mathrm{rbc7}] - \mathrm{Kglucose} \cdot [\mathrm{Glucose}]^{\mathrm{lambda}} \cdot [\mathrm{rbc7}] \tag{14}$$

6.15 Rule `a1c8`

Rule `a1c8` is a rate rule for species `a1c8`:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{a1c8} = \mathrm{Kglucose} \cdot [\mathrm{Glucose}]^{\mathrm{lambda}} \cdot [\mathrm{rbc8}] + \mathrm{Ktr} \cdot [\mathrm{a1c7}] - \mathrm{Ktr} \cdot [\mathrm{a1c8}] \tag{15}$$

6.16 Rule `rbc8`

Rule `rbc8` is a rate rule for species `rbc8`:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{rbc8} = \mathrm{Ktr} \cdot [\mathrm{rbc7}] - \mathrm{Ktr} \cdot [\mathrm{rbc8}] - \mathrm{Kglucose} \cdot [\mathrm{Glucose}]^{\mathrm{lambda}} \cdot [\mathrm{rbc8}] \tag{16}$$

6.17 Rule `a1c9`

Rule `a1c9` is a rate rule for species `a1c9`:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{a1c9} = \mathrm{Kglucose} \cdot [\mathrm{Glucose}]^{\mathrm{lambda}} \cdot [\mathrm{rbc9}] + \mathrm{Ktr} \cdot [\mathrm{a1c8}] - \mathrm{Ktr} \cdot [\mathrm{a1c9}] \tag{17}$$

6.18 Rule `rbc9`

Rule `rbc9` is a rate rule for species `rbc9`:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{rbc9} = \mathrm{Ktr} \cdot [\mathrm{rbc8}] - \mathrm{Ktr} \cdot [\mathrm{rbc9}] - \mathrm{Kglucose} \cdot [\mathrm{Glucose}]^{\mathrm{lambda}} \cdot [\mathrm{rbc9}] \tag{18}$$

6.19 Rule `a1c10`

Rule `a1c10` is a rate rule for species `a1c10`:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{a1c10} = \mathrm{Kglucose} \cdot [\mathrm{Glucose}]^{\mathrm{lambda}} \cdot [\mathrm{rbc10}] + \mathrm{Ktr} \cdot [\mathrm{a1c9}] - \mathrm{Ktr} \cdot [\mathrm{a1c10}] \tag{19}$$

6.20 Rule `rbc10`

Rule `rbc10` is a rate rule for species `rbc10`:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{rbc10} = \mathrm{Ktr} \cdot [\mathrm{rbc9}] - \mathrm{Ktr} \cdot [\mathrm{rbc10}] - \mathrm{Kglucose} \cdot [\mathrm{Glucose}]^{\mathrm{lambda}} \cdot [\mathrm{rbc10}] \tag{20}$$

6.21 Rule `a1c11`

Rule `a1c11` is a rate rule for species `a1c11`:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{a1c11} = \mathrm{Kglucose} \cdot [\mathrm{Glucose}]^{\mathrm{lambda}} \cdot [\mathrm{rbc11}] + \mathrm{Ktr} \cdot [\mathrm{a1c10}] - \mathrm{Ktr} \cdot [\mathrm{a1c11}] \tag{21}$$

6.22 Rule `rbc11`

Rule `rbc11` is a rate rule for species `rbc11`:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{rbc11} = \mathrm{Ktr} \cdot [\mathrm{rbc10}] - \mathrm{Ktr} \cdot [\mathrm{rbc11}] - \mathrm{Kglucose} \cdot [\mathrm{Glucose}]^{\mathrm{lambda}} \cdot [\mathrm{rbc11}] \tag{22}$$

6.23 Rule `a1c12`

Rule `a1c12` is a rate rule for species `a1c12`:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{a1c12} = \mathrm{Kglucose} \cdot [\mathrm{Glucose}]^{\mathrm{lambda}} \cdot [\mathrm{rbc12}] + \mathrm{Ktr} \cdot [\mathrm{a1c11}] - \mathrm{Ktr} \cdot [\mathrm{a1c12}] \tag{23}$$

6.24 Rule `rbc12`

Rule `rbc12` is a rate rule for species `rbc12`:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{rbc12} = \mathrm{Ktr} \cdot [\mathrm{rbc11}] - \mathrm{Ktr} \cdot [\mathrm{rbc12}] - \mathrm{Kglucose} \cdot [\mathrm{Glucose}]^{\mathrm{lambda}} \cdot [\mathrm{rbc12}] \tag{24}$$

6.25 Rule `hba1c`

Rule `hba1c` is an assignment rule for species `hba1c`:

$$
\begin{aligned}
&\mathrm{hba1c} \qquad (25)\\
&= \frac{100 \cdot ([\mathrm{a1c1}] + [\mathrm{a1c2}] + [\mathrm{a1c3}] + [\mathrm{a1c4}] + [\mathrm{a1c5}] + [\mathrm{a1c6}] + [}{[\mathrm{a1c1}] + [\mathrm{a1c2}] + [\mathrm{a1c3}] + [\mathrm{a1c4}] + [\mathrm{a1c5}] + [\mathrm{a1c6}] + [\mathrm{a1c7}] + [\mathrm{a1c8}] + [\mathrm{a1c9}] + [\mathrm{a1c10}] + [\mathrm{a1c11}] + [\mathrm{a1c12}] +}
\end{aligned}
$$

6.26 Rule `apoptosis`

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

$$\mathrm{apoptosis} = \mathrm{ka} \cdot \left(1 + \frac{\mathrm{vha} \cdot \mathrm{IL1R}^{\mathrm{xha}}}{\mathrm{kmha}^{\mathrm{xha}} + \mathrm{IL1R}^{\mathrm{xha}}} - \frac{\mathrm{vla} \cdot \mathrm{IL1R}^{\mathrm{xla}}}{\mathrm{kmla}^{\mathrm{xla}} + \mathrm{IL1R}^{\mathrm{xla}}}\right) \qquad (26)$$

6.27 Rule `IL1R`

Rule `IL1R` is an assignment rule for parameter `IL1R`:

$$\mathrm{IL1R} = \frac{[\mathrm{IL1b}]}{[\mathrm{IL1b}] + \mathrm{km} \cdot \left(1 + \frac{[\mathrm{IL1Ra}] + [\mathrm{Anakinra}]}{\mathrm{ki}}\right)} \qquad (27)$$

6.28 Rule `replication`

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

$$\mathrm{replication} = \mathrm{kr} \cdot \left(1 - \frac{\mathrm{vhr} \cdot \mathrm{IL1R}^{\mathrm{xhr}}}{\mathrm{kmhr}^{\mathrm{xhr}} + \mathrm{IL1R}^{\mathrm{xhr}}} + \frac{\mathrm{vlr} \cdot \mathrm{IL1R}^{\mathrm{xlr}}}{\mathrm{kmlr}^{\mathrm{xlr}} + \mathrm{IL1R}^{\mathrm{xlr}}}\right) \qquad (28)$$

6.29 Rule `PI_I`

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

$$\mathrm{PI\_I} = \frac{[\mathrm{Proinsulin}]}{[\mathrm{Insulin}]} \qquad (29)$$

Derived unit dimensionless

7 Event

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

7.1 Event Anakinra_Administration_event

Notes Dose event for anakinra. The value for the dose is considered to be 100mg which is assumed to be converted into ng / ml.

Trigger condition

$$(\mathrm{time} = \mathrm{Anakinra\_dose\_counter}) \wedge (\mathrm{Anakinra\_dose\_counter} < 91) \tag{30}$$

Delay

$$0 \tag{31}$$

Assignments

$$\mathrm{Anakinrasc} = [\mathrm{Anakinrasc}] + 100000 \cdot \mathrm{Ana\_on} \tag{32}$$

$$\mathrm{Anakinra\_dose\_counter} = \mathrm{Anakinra\_dose\_counter} + 1 \tag{33}$$

8 Reactions

This model contains 20 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	`TigB_up`		$\emptyset \longrightarrow \text{TigB}$	
2	`TigB_down`		$\text{TigB} \longrightarrow \emptyset$	
3	`Bcell_replication`		$\emptyset \longrightarrow \text{B}$	
4	`Bcell_apoptosis`		$\text{B} \longrightarrow \emptyset$	
5	`proinsulin_sec_up`		$\emptyset \xrightarrow{\text{Glucose}} \text{f}$	
6	`proinsulin_sec_down`		$\text{f} \longrightarrow \emptyset$	
7	`IL1b_treatment`		$\emptyset \longrightarrow \text{IL1b}$	
8	`IL1b_degradation`		$\text{IL1b} \longrightarrow \emptyset$	
9	`IL1b_placebo`		$\emptyset \longrightarrow \text{IL1b}$	
10	`AnakinraSC_elimination`		$\text{Anakinrasc} \longrightarrow \emptyset$	
11	`Anakinra_absorption`		$\emptyset \xrightarrow{\text{Anakinrasc}} \text{Anakinra}$	
12	`Anakinra_elimination`		$\text{Anakinra} \longrightarrow \emptyset$	
13	`Glucose_production`		$\emptyset \longrightarrow \text{Glucose}$	

№	Id	Name	Reaction Equation	SBO
14	`Basal_glucose-_uptake`		Glucose $\longrightarrow \emptyset$	
15	`Insulin-_dependent-_glucose_uptake`		Glucose $\xrightarrow{\text{Insulin}} \emptyset$	
16	`Proinsulin-_dependent-_glucose_uptake`		Glucose $\xrightarrow{\text{Proinsulin}} \emptyset$	
17	`Glucose-_dependent-_insulin-_secretion`		$\emptyset \xrightarrow{\text{TigB, B, Glucose}}$ Insulin	
18	`Insulin-_elimination`		Insulin $\longrightarrow \emptyset$	
19	`Glucose-_dependent-_proinsulin-_secretion`		$\emptyset \xrightarrow{\text{TigB, B, f, Glucose}}$ Proinsulin	
20	`Proinsulin-_elimination`		Proinsulin $\longrightarrow \emptyset$	

8.1 Reaction TigB_up

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

Reaction equation

$$\emptyset \longrightarrow \text{TigB} \tag{34}$$

Product

Table 6: Properties of each product.

Id	Name	SBO
TigB		

Kinetic Law

Derived unit not available

$$v_1 = \text{taus} \cdot \text{ks} \cdot \left(1 - \frac{\text{vs} \cdot \text{IL1R}}{\text{kms} + \text{IL1R}}\right) \tag{35}$$

8.2 Reaction TigB_down

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

Reaction equation

$$\text{TigB} \longrightarrow \emptyset \tag{36}$$

Reactant

Table 7: Properties of each reactant.

Id	Name	SBO
TigB		

Kinetic Law

Derived unit contains undeclared units

$$v_2 = \text{taus} \cdot [\text{TigB}] \tag{37}$$

8.3 Reaction `Bcell_replication`

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

Reaction equation

$$\emptyset \longrightarrow \mathrm{B} \tag{38}$$

Product

Table 8: Properties of each product.

Id	Name	SBO
B		

Kinetic Law

Derived unit contains undeclared units

$$v_3 = \mathrm{replication} \cdot [\mathrm{B}] \tag{39}$$

8.4 Reaction `Bcell_apoptosis`

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

Reaction equation

$$\mathrm{B} \longrightarrow \emptyset \tag{40}$$

Reactant

Table 9: Properties of each reactant.

Id	Name	SBO
B		

Kinetic Law

Derived unit contains undeclared units

$$v_4 = \mathrm{apoptosis} \cdot [\mathrm{B}] \tag{41}$$

8.5 Reaction `proinsulin_sec_up`

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

Reaction equation

$$\emptyset \xrightarrow{\text{Glucose}} \text{f} \tag{42}$$

Modifier

Table 10: Properties of each modifier.

Id	Name	SBO
`Glucose`		

Product

Table 11: Properties of each product.

Id	Name	SBO
`f`		

Kinetic Law

Derived unit contains undeclared units

$$v_5 = \text{tauf} \cdot \text{kf} \cdot \left(1 + \frac{\text{vfg} \cdot [\text{Glucose}]^{\text{xfg}}}{\text{kmfg}^{\text{xfg}} + [\text{Glucose}]^{\text{xfg}}}\right) \cdot \left(1 + \frac{\text{vf} \cdot \text{IL1R}}{\text{kmf} + \text{IL1R}}\right) \tag{43}$$

8.6 Reaction `proinsulin_sec_down`

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

Reaction equation

$$\text{f} \longrightarrow \emptyset \tag{44}$$

Reactant

Table 12: Properties of each reactant.

Id	Name	SBO
f		

Kinetic Law

Derived unit contains undeclared units

$$v_6 = \mathrm{tauf} \cdot [\mathrm{f}] \tag{45}$$

8.7 Reaction IL1b_treatment

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

Reaction equation

$$\emptyset \longrightarrow \mathrm{IL1b} \tag{46}$$

Product

Table 13: Properties of each product.

Id	Name	SBO
IL1b		

Kinetic Law

Derived unit not available

$$v_7 = \begin{cases} (1 - \mathrm{placebo\_on}) \cdot \mathrm{k1} \cdot \mathrm{il1bH} & \text{if time} < 91 \\ (1 - \mathrm{placebo\_on}) \cdot \mathrm{k2} \cdot (\mathrm{il1b0} + \mathrm{kplacebo} \cdot \mathrm{time}) & \text{otherwise} \end{cases} \tag{47}$$

8.8 Reaction IL1b_degradation

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

Reaction equation

$$\mathrm{IL1b} \longrightarrow \emptyset \tag{48}$$

Reactant

Table 14: Properties of each reactant.

Id	Name	SBO
IL1b		

Kinetic Law

Derived unit contains undeclared units

$$v_8 = \begin{cases} (1 - \text{placebo\_on}) \cdot \text{k1} \cdot [\text{IL1b}] & \text{if time} < 91 \\ (1 - \text{placebo\_on}) \cdot \text{k2} \cdot [\text{IL1b}] & \text{otherwise} \end{cases} \tag{49}$$

8.9 Reaction IL1b_placebo

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

Reaction equation

$$\emptyset \longrightarrow \text{IL1b} \tag{50}$$

Product

Table 15: Properties of each product.

Id	Name	SBO
IL1b		

Kinetic Law

Derived unit not available

$$v_9 = \text{placebo\_on} \cdot \text{kplacebo} \tag{51}$$

8.10 Reaction AnakinraSC_elimination

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

Reaction equation

$$\text{Anakinrasc} \longrightarrow \emptyset \tag{52}$$

Reactant

Table 16: Properties of each reactant.

Id	Name	SBO
Anakinrasc		

Kinetic Law

Derived unit contains undeclared units

$$v_{10} = \mathrm{kab} \cdot [\mathrm{Anakinrasc}] \tag{53}$$

8.11 Reaction Anakinra_absorption

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

Reaction equation

$$\emptyset \xrightarrow{\mathrm{Anakinrasc}} \mathrm{Anakinra} \tag{54}$$

Modifier

Table 17: Properties of each modifier.

Id	Name	SBO
Anakinrasc		

Product

Table 18: Properties of each product.

Id	Name	SBO
Anakinra		

Kinetic Law

Derived unit contains undeclared units

$$v_{11} = \frac{\mathrm{kab} \cdot [\mathrm{Anakinrasc}]}{\mathrm{Vp}} \tag{55}$$

8.12 Reaction Anakinra_elimination

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

Reaction equation

$$\text{Anakinra} \longrightarrow \emptyset \tag{56}$$

Reactant

Table 19: Properties of each reactant.

Id	Name	SBO
Anakinra		

Kinetic Law

Derived unit contains undeclared units

$$v_{12} = \frac{\text{CL}}{\text{Vp}} \cdot [\text{Anakinra}] \tag{57}$$

8.13 Reaction Glucose_production

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

Reaction equation

$$\emptyset \longrightarrow \text{Glucose} \tag{58}$$

Product

Table 20: Properties of each product.

Id	Name	SBO
Glucose		

Kinetic Law

Derived unit not available

$$v_{13} = \text{Tgl} \tag{59}$$

8.14 Reaction Basal_glucose_uptake

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

Reaction equation

$$\text{Glucose} \longrightarrow \emptyset \tag{60}$$

Reactant

Table 21: Properties of each reactant.

Id	Name	SBO
Glucose		

Kinetic Law

Derived unit contains undeclared units

$$v_{14} = \text{Kxg} \cdot [\text{Glucose}] \tag{61}$$

8.15 Reaction Insulin_dependent_glucose_uptake

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

Reaction equation

$$\text{Glucose} \xrightarrow{\text{Insulin}} \emptyset \tag{62}$$

Reactant

Table 22: Properties of each reactant.

Id	Name	SBO
Glucose		

Modifier

Table 23: Properties of each modifier.

Id	Name	SBO
Insulin		

Kinetic Law

Derived unit contains undeclared units

$$v_{15} = \text{Kxgi} \cdot [\text{Insulin}] \cdot [\text{Glucose}] \quad (63)$$

8.16 Reaction Proinsulin_dependent_glucose_uptake

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

Reaction equation

$$\text{Glucose} \xrightarrow{\text{Proinsulin}} \emptyset \quad (64)$$

Reactant

Table 24: Properties of each reactant.

Id	Name	SBO
Glucose		

Modifier

Table 25: Properties of each modifier.

Id	Name	SBO
Proinsulin		

Kinetic Law

Derived unit contains undeclared units

$$v_{16} = 0.1 \cdot \text{Kxgi} \cdot [\text{Proinsulin}] \cdot [\text{Glucose}] \quad (65)$$

8.17 Reaction Glucose_dependent_insulin_secretion

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

Reaction equation

$$\emptyset \xrightarrow{\text{TigB, B, Glucose}} \text{Insulin} \quad (66)$$

Modifiers

Table 26: Properties of each modifier.

Id	Name	SBO
TigB		
B		
Glucose		

Product

Table 27: Properties of each product.

Id	Name	SBO
Insulin		

Kinetic Law

Derived unit contains undeclared units

$$v_{17} = \frac{\left(\frac{[\mathrm{Glucose}]}{\mathrm{Gh}}\right)^{\mathrm{vh}}}{1 + \left(\frac{[\mathrm{Glucose}]}{\mathrm{Gh}}\right)^{\mathrm{vh}}} \cdot [\mathrm{TigB}] \cdot [\mathrm{B}] \tag{67}$$

8.18 Reaction Insulin_elimination

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

Reaction equation

$$\mathrm{Insulin} \longrightarrow \emptyset \tag{68}$$

Reactant

Table 28: Properties of each reactant.

Id	Name	SBO
Insulin		

Kinetic Law

Derived unit contains undeclared units

$$v_{18} = \mathrm{Kxi} \cdot [\mathrm{Insulin}] \tag{69}$$

8.19 Reaction Glucose_dependent_proinsulin_secretion

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

Reaction equation

$$\emptyset \xrightarrow{\text{TigB, B, f, Glucose}} \text{Proinsulin} \tag{70}$$

Modifiers

Table 29: Properties of each modifier.

Id	Name	SBO
TigB		
B		
f		
Glucose		

Product

Table 30: Properties of each product.

Id	Name	SBO
Proinsulin		

Kinetic Law

Derived unit contains undeclared units

$$v_{19} = \frac{[\text{f}] \cdot \left(\frac{[\text{Glucose}]}{\text{Gh}}\right)^{\text{vh}}}{1 + \left(\frac{[\text{Glucose}]}{\text{Gh}}\right)^{\text{vh}}} \cdot [\text{TigB}] \cdot [\text{B}] \tag{71}$$

8.20 Reaction Proinsulin_elimination

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

Reaction equation

$$\text{Proinsulin} \longrightarrow \emptyset \tag{72}$$

Reactant

Table 31: Properties of each reactant.

Id	Name	SBO
Proinsulin		

Kinetic Law

Derived unit contains undeclared units

$$v_{20} = 0.1 \cdot \mathrm{Kxi} \cdot [\mathrm{Proinsulin}] \quad (73)$$

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 `IL1b`

Notes Units: ng / ml

Initial concentration $5 \text{ mol} \cdot \text{l}^{-1}$

This species takes part in three reactions (as a reactant in `IL1b_degradation` and as a product in `IL1b_treatment`, `IL1b_placebo`).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{IL1b} = v_7 + v_9 - v_8 \quad (74)$$

9.2 Species `IL1Ra`

Notes Units: ng / ml

Initial concentration $40 \text{ mol} \cdot \text{l}^{-1}$

This species does not take part in any reactions. Its quantity does hence not change over time:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{IL1Ra} = 0 \quad (75)$$

9.3 Species Anakinra

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

This species takes part in two reactions (as a reactant in Anakinra_elimination and as a product in Anakinra_absorption).

$$\frac{d}{dt}\text{Anakinra} = v_{11} - v_{12} \tag{76}$$

9.4 Species Proinsulin

Notes Units: pM

Initial concentration $43 \text{ mol} \cdot \text{l}^{-1}$

This species takes part in three reactions (as a reactant in Proinsulin_elimination and as a product in Glucose_dependent_proinsulin_secretion and as a modifier in Proinsulin_dependent_glucose_uptake).

$$\frac{d}{dt}\text{Proinsulin} = v_{19} - v_{20} \tag{77}$$

9.5 Species Insulin

Notes Units: pM

Initial concentration $100 \text{ mol} \cdot \text{l}^{-1}$

This species takes part in three reactions (as a reactant in Insulin_elimination and as a product in Glucose_dependent_insulin_secretion and as a modifier in Insulin_dependent_glucose_uptake).

$$\frac{d}{dt}\text{Insulin} = v_{17} - v_{18} \tag{78}$$

9.6 Species TigB

Notes Units: pM min-1 (% beta-cells)-1

Initial concentration $0.1865 \text{ mol} \cdot \text{l}^{-1}$

This species takes part in four reactions (as a reactant in TigB_down and as a product in TigB_up and as a modifier in Glucose_dependent_insulin_secretion, Glucose_dependent_proinsulin_secretion).

$$\frac{d}{dt}\text{TigB} = v_1 - v_2 \tag{79}$$

9.7 Species B

Notes Units: % of healthy

Initial concentration $40 \text{ mol} \cdot \text{l}^{-1}$

This species takes part in four reactions (as a reactant in Bcell_apoptosis and as a product in Bcell_replication and as a modifier in Glucose_dependent_insulin_secretion, Glucose_dependent_proinsulin_secretion).

$$\frac{\mathrm{d}}{\mathrm{d}t} \mathrm{B} = v_3 - v_4 \tag{80}$$

9.8 Species f

Initial concentration $0.0427776 \text{ mol} \cdot \text{l}^{-1}$

This species takes part in three reactions (as a reactant in proinsulin_sec_down and as a product in proinsulin_sec_up and as a modifier in Glucose_dependent_proinsulin_secretion).

$$\frac{\mathrm{d}}{\mathrm{d}t} \mathrm{f} = v_5 - v_6 \tag{81}$$

9.9 Species Anakinrasc

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

Involved in event Anakinra_Administration_event

This species takes part in two reactions (as a reactant in AnakinraSC_elimination and as a modifier in Anakinra_absorption).

$$\frac{\mathrm{d}}{\mathrm{d}t} \mathrm{Anakinrasc} = -v_{10} \tag{82}$$

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

9.10 Species Glucose

Notes Units: pM

Initial concentration $10.8 \text{ mol} \cdot \text{l}^{-1}$

This species takes part in seven reactions (as a reactant in Basal_glucose_uptake, Insulin_dependent_glucose_uptake, Proinsulin_dependent_glucose_uptake and as a product in Glucose_production and as a modifier in proinsulin_sec_up, Glucose_dependent_insulin_secretion, Glucose_dependent_proinsulin_secretion).

$$\frac{\mathrm{d}}{\mathrm{d}t} \mathrm{Glucose} = v_{13} - v_{14} - v_{15} - v_{16} \tag{83}$$

9.11 Species a1c1

Initial concentration $0.122997 \text{ mol} \cdot \text{l}^{-1}$

Involved in rule a1c1

One rule which determines this species' quantity.

9.12 Species rbc1

Initial concentration $8.627 \text{ mol} \cdot \text{l}^{-1}$

Involved in rule rbc1

One rule which determines this species' quantity.

9.13 Species a1c2

Initial concentration $0.244266 \text{ mol} \cdot \text{l}^{-1}$

Involved in rule a1c2

One rule which determines this species' quantity.

9.14 Species rbc2

Initial concentration $8.50573 \text{ mol} \cdot \text{l}^{-1}$

Involved in rule rbc2

One rule which determines this species' quantity.

9.15 Species a1c3

Initial concentration $0.363829 \text{ mol} \cdot \text{l}^{-1}$

Involved in rule a1c3

One rule which determines this species' quantity.

9.16 Species rbc3

Initial concentration $8.38617 \text{ mol} \cdot \text{l}^{-1}$

Involved in rule rbc3

One rule which determines this species' quantity.

9.17 Species a1c4

Initial concentration $0.481712\ \mathrm{mol} \cdot \mathrm{l}^{-1}$

Involved in rule a1c4

One rule which determines this species' quantity.

9.18 Species rbc4

Initial concentration $8.26829\ \mathrm{mol} \cdot \mathrm{l}^{-1}$

Involved in rule rbc4

One rule which determines this species' quantity.

9.19 Species a1c5

Initial concentration $0.597938\ \mathrm{mol} \cdot \mathrm{l}^{-1}$

Involved in rule a1c5

One rule which determines this species' quantity.

9.20 Species rbc5

Initial concentration $8.15206\ \mathrm{mol} \cdot \mathrm{l}^{-1}$

Involved in rule rbc5

One rule which determines this species' quantity.

9.21 Species a1c6

Initial concentration $0.71253\ \mathrm{mol} \cdot \mathrm{l}^{-1}$

Involved in rule a1c6

One rule which determines this species' quantity.

9.22 Species rbc6

Initial concentration $8.03747\ \mathrm{mol} \cdot \mathrm{l}^{-1}$

Involved in rule rbc6

One rule which determines this species' quantity.

9.23 Species `a1c7`

Initial concentration $0.825512 \text{ mol} \cdot l^{-1}$

Involved in rule `a1c7`

One rule which determines this species' quantity.

9.24 Species `rbc7`

Initial concentration $7.92449 \text{ mol} \cdot l^{-1}$

Involved in rule `rbc7`

One rule which determines this species' quantity.

9.25 Species `a1c8`

Initial concentration $0.936905 \text{ mol} \cdot l^{-1}$

Involved in rule `a1c8`

One rule which determines this species' quantity.

9.26 Species `rbc8`

Initial concentration $7.8131 \text{ mol} \cdot l^{-1}$

Involved in rule `rbc8`

One rule which determines this species' quantity.

9.27 Species `a1c9`

Initial concentration $1.04673 \text{ mol} \cdot l^{-1}$

Involved in rule `a1c9`

One rule which determines this species' quantity.

9.28 Species `rbc9`

Initial concentration $7.70327 \text{ mol} \cdot l^{-1}$

Involved in rule `rbc9`

One rule which determines this species' quantity.

9.29 Species a1c10

Initial concentration $1.15502 \text{ mol} \cdot \text{l}^{-1}$

Involved in rule a1c10

One rule which determines this species' quantity.

9.30 Species rbc10

Initial concentration $7.59498 \text{ mol} \cdot \text{l}^{-1}$

Involved in rule rbc10

One rule which determines this species' quantity.

9.31 Species a1c11

Initial concentration $1.26178 \text{ mol} \cdot \text{l}^{-1}$

Involved in rule a1c11

One rule which determines this species' quantity.

9.32 Species rbc11

Initial concentration $7.48822 \text{ mol} \cdot \text{l}^{-1}$

Involved in rule rbc11

One rule which determines this species' quantity.

9.33 Species a1c12

Initial concentration $1.36704 \text{ mol} \cdot \text{l}^{-1}$

Involved in rule a1c12

One rule which determines this species' quantity.

9.34 Species rbc12

Initial concentration $7.38296 \text{ mol} \cdot \text{l}^{-1}$

Involved in rule rbc12

One rule which determines this species' quantity.

9.35 Species hba1c

Initial concentration $8.7 \text{ mol} \cdot \text{l}^{-1}$

Involved in rule hba1c

One rule determines the species' quantity.

A Glossary of Systems Biology Ontology Terms

SBO:0000410 implicit compartment: A compartment whose existence is inferred due to the presence of known material entities which must be bounded, allowing the creation of material entity pools

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