SBML Model Report

Model name: "Koschorreck2008_InsulinClearance"



May 6, 2016

1 General Overview

This is a document in SBML Level 2 Version 4 format. This model was created by Ishan Ajmera¹ at August fifth 2011 at 9:33 a.m. and last time modified at October tenth 2014 at 10:32 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	13
events	0	constraints	0
reactions	0	function definitions	0
global parameters	58	unit definitions	0
rules	52	initial assignments	0

Model Notes

This model is from the article:

Mathematical modeling and analysis of insulin clearance in vivo.

Koschorreck M, Gilles ED. BMC Syst Biol. 2008 May 13;2:43. 18477391,

Abstract

BACKGROUND: Analyzing the dynamics of insulin concentration in the blood is necessary for a comprehensive understanding of the effects of insulin in vivo. Insulin removal from the blood

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has been addressed in many studies. The results are highly variable with respect to insulin clearance and the relative contributions of hepatic and renal insulin degradation.RESULTS:We present a dynamic mathematical model of insulin concentration in the blood and of insulin receptor activation in hepatocytes. The model describes renal and hepatic insulin degradation, pancreatic insulin secretion and nonspecific insulin binding in the liver. Hepatic insulin receptor activation by insulin binding, receptor internalization and autophosphorylation is explicitly included in the model. We present a detailed mathematical analysis of insulin degradation and insulin clearance. Stationary model analysis shows that degradation rates, relative contributions of the different tissues to total insulin degradation and insulin clearance highly depend on the insulin concentration.CONCLUSION:This study provides a detailed dynamic model of insulin concentration in the blood and of insulin receptor activation in hepatocytes. Experimental data sets from literature are used for the model validation. We show that essential dynamic and stationary characteristics of insulin degradation are nonlinear and depend on the actual insulin concentration.

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To cite BioModels Database, please use: Li C, Donizelli M, Rodriguez N, Dharuri H, Endler L, Chelliah V, Li L, He E, Henry A, Stefan MI, Snoep JL, Hucka M, Le Novre N, Laibe C (2010) BioModels Database: An enhanced, curated and annotated resource for published quantitative kinetic models. BMC Syst Biol., 4:92.

2 Unit Definitions

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

2.1 Unit substance

Notes Mole is the predefined SBML unit for substance.

Definition mol

2.2 Unit volume

Notes Litre is the predefined SBML unit for volume.

Definition 1

2.3 Unit area

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

Definition m²

2.4 Unit length

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

Definition m

2.5 Unit time

Notes Second is the predefined SBML unit for time.

Definition s

3 Compartment

This model contains one compartment.

Table 2: Properties of all compartments.

Id	Name	SBO	Spatial Dimensions	Size	Unit	Constant	Outside
compartment1	compartment1		3	1	litre	Z	

3.1 Compartment compartment1

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

Name compartment1

4 Species

This model contains 13 species. The boundary condition of 13 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
					Condi- tion
R	R	compartment1	$\text{mol} \cdot l^{-1}$		
ins	ins	compartment1	$\text{mol} \cdot l^{-1}$		
IR	IR	compartment1	$\text{mol} \cdot l^{-1}$		$\overline{\mathbf{Z}}$
I2R	I2R	compartment1	$\text{mol} \cdot l^{-1}$	\Box	
Rp	Rp	compartment1	$\text{mol} \cdot l^{-1}$	\Box	
IRp	IRp	compartment1	$\text{mol} \cdot l^{-1}$	\Box	
I2Rp	I2Rp	compartment1	$\text{mol} \cdot l^{-1}$	\Box	
Ren	Ren	compartment1	$\text{mol} \cdot l^{-1}$	\Box	
IRen	IRen	compartment1	$\text{mol} \cdot l^{-1}$	\Box	\square
I2Ren	I2Ren	compartment1	$\text{mol} \cdot l^{-1}$	\Box	
RPen	RPen	compartment1	$\text{mol} \cdot l^{-1}$	\Box	
IRPen	IRPen	compartment1	$\text{mol} \cdot l^{-1}$		$\overline{\mathbf{Z}}$
I2RPen	I2RPen	compartment1	$\operatorname{mol} \cdot 1^{-1}$		$\overline{\mathbf{Z}}$

5 Parameters

This model contains 58 global parameters.

Table 4: Properties of each parameter.

Table 4: Properties of each parameter.							
Id	Name	SBO	Value	Unit	Constan		
kins	kins	0000009	0.001		Z		
kins1d	kins1d	0000180	$4 \cdot 1$	0^{-4}	$ \overline{\mathbf{Z}} $		
kins2d	kins2d	0000180	0.040		$\overline{\mathbf{Z}}$		
kins1den	kins1den	0000180	0.002		$\overline{\mathbf{Z}}$		
kins2den	kins2den	0000180	0.004				
kyd	kyd	0000330	0.004				
kyden	kyden	0000330	0.007				
kyp	kyp	0000216	0.023				
intk1	intk1	0000009	5.5 · 1	0^{-4}			
intk2	intk2	0000009	2 · 1	0^{-4}			
reck1	reck1	0000009	0.002		$ \overline{\mathbf{Z}} $		
Rtotal	Rtotal	0000009	40.000				
k1ub	klub	0000009	0.350				
k2ub	k2ub	0000180	0.200		$\overline{\mathbf{Z}}$		
pansec	pansec	0000009	0.002		$\overline{\mathbf{Z}}$		
Kpan	Kpan	0000009	0.500				
mliver	mliver	0000504	10.000		⊿ ⊟		
vp	vp	0000468	0.007				
rholiver	rholiver	0000226	1051.000				
vhep	vhep	0000468	0.007				
vd	vd	0000468	0.002				
mkidney	mkidney	0000504	1.478		\Box		
Kkidney	Kkidney	0000009	3.32608695652174 · 1	0^{-5}			
r1	r1	0000009	3.538		\Box		
r2	r2	0000009	0.000				
r3	r3	0000009	0.000				
r4	r4	0000009	0.000				
r5	r5	0000009	0.000				
r6	r6	0000009	0.000				
r7	r7	0000009	0.000				
i1	i1	0000216	0.000				
i2	i2	0000216	0.000		\Box		
i3	i3	0000216	0.000				
i 4	i4	0000216	$-1.70974345792274 \cdot 10$	$)^{-17}$			
i 5	i5	0000216	0.000				
i 6	i6	0000216	0.000				
i7	i7	0000216	3.20632409511745 · 10	$)^{-17}$			

Id	Name	SBO	Value	Unit	Constan
f1	f1	0000009	$-4.78999999985533 \cdot 10^{-8}$	3	
f2	f2	0000009	0.000		
f3	f3	0000009	0.000		
f4	f4	0000009	0.000		
f5	f5	0000009	0.000		
f6	f6	0000009	0.000		
bw	bw	0000002	200.000		
$parameter_1$	rliv	0000179	3.890		
$parameter_2$	rkid	0000179	0.493		
$parameter_3$	Ratetotal	0000064	4.383		
$parameter_4$	Fracliver	0000009	88.758		
$parameter_5$	Frackidney	0000009	11.242		
$parameter_6$	Cliver	0000009	1.576		
$parameter_7$	Ckidney	0000009	0.200		
$parameter_8$	Ctotal	0000009	1.775		
$parameter_9$	ReceptorIns	0000064	$-1.11022302462516 \cdot 10^{-10}$	5	
$parameter_10$	ReceptorIns2	0000064	$-1.11022302462516 \cdot 10^{-10}$	5	
$parameter_11$	ReceptorInsPM	0000064	0.000		
parameter_12	ReceptorIns2PM	0000064	0.000		
parameter_13	ReceptorInsEN	0000064	$-1.11022302462516 \cdot 10^{-10}$	5	
parameter_14	ReceptorIns2EN	0000064	$-1.11022302462516 \cdot 10^{-10}$	5	

6 Rules

This is an overview of 52 rules.

6.1 Rule mkidney

Rule mkidney is an assignment rule for parameter mkidney:

$$mkidney = \frac{2 \cdot 0.85 \cdot bw}{230} \tag{1}$$

6.2 Rule mliver

Rule mliver is an assignment rule for parameter mliver:

$$mliver = 0.05 \cdot bw \tag{2}$$

6.3 Rule vp

Rule vp is an assignment rule for parameter vp:

$$vp = 0.03375 \cdot 10^3 \cdot bw (3)$$

6.4 Rule vhep

Rule vhep is an assignment rule for parameter vhep:

$$vhep = \frac{mliver}{rholiver} \cdot 0.78 \tag{4}$$

6.5 Rule vd

Rule vd is an assignment rule for parameter vd:

$$vd = 0.272 \cdot 10^3 \cdot vhep \cdot rholiver \tag{5}$$

6.6 Rule I2RPen

Rule I2RPen is an assignment rule for species I2RPen:

$$I2RPen = Rtotal - [R] - [IR] - [I2R] - [Rp] - [IRp] - [I2Rp] - [Ren] - [IRen] - [I2Ren] - [RPen] - [IRPen]$$
(6)

6.7 Rule Kkidney

Rule Kkidney is an assignment rule for parameter Kkidney:

$$Kkidney = 0.0225 \cdot 10^3 \cdot mkidney \tag{7}$$

6.8 Rule r1

Rule r1 is an assignment rule for parameter r1:

$$r1 = kins \cdot [R] \cdot [ins] - kins1d \cdot [IR]$$
(8)

6.9 Rule r2

Rule r2 is an assignment rule for parameter r2:

$$r2 = kins \cdot [Rp] \cdot [ins] - kins1d \cdot [IRp]$$
(9)

6.10 Rule r3

Rule r3 is an assignment rule for parameter r3:

$$r3 = kins \cdot [IR] \cdot [ins] - kins2d \cdot [I2R]$$
(10)

6.11 Rule r4

Rule r4 is an assignment rule for parameter r4:

$$r4 = kins \cdot [IRp] \cdot [ins] - kins2d \cdot [I2Rp]$$
(11)

6.12 Rule r5

Rule r5 is an assignment rule for parameter r5:

$$r5 = kyd \cdot [Rp] \tag{12}$$

6.13 Rule r6

Rule r6 is an assignment rule for parameter r6:

$$r6 = kyp \cdot [IR] - kyd \cdot [IRp] \tag{13}$$

6.14 Rule r7

Rule r7 is an assignment rule for parameter r7:

$$r7 = kyp \cdot [I2R] - kyd \cdot [I2Rp] \tag{14}$$

6.15 Rule i1

Rule i1 is an assignment rule for parameter i1:

$$i1 = kins1den \cdot [IRen]$$
 (15)

6.16 Rule i2

Rule i2 is an assignment rule for parameter i2:

$$i2 = kins1den \cdot [IRPen]$$
 (16)

6.17 Rule i3

Rule i3 is an assignment rule for parameter i3:

$$i3 = kins2den \cdot [I2Ren]$$
 (17)

6.18 Rule i4

Rule i4 is an assignment rule for parameter i4:

$$i4 = kins2den \cdot [I2RPen]$$
 (18)

6.19 Rule 15

Rule i5 is an assignment rule for parameter i5:

$$i5 = kyden \cdot [RPen] \tag{19}$$

6.20 Rule i6

Rule i6 is an assignment rule for parameter i6:

$$i6 = kyp \cdot [IRen] - kyden \cdot [IRPen]$$
 (20)

6.21 Rule i7

Rule i7 is an assignment rule for parameter i7:

$$i7 = kyp \cdot [I2Ren] - kyden \cdot [I2RPen]$$
 (21)

6.22 Rule f1

Rule f1 is an assignment rule for parameter f1:

$$f1 = intk2 \cdot [R] - reck1 \cdot [Ren]$$
 (22)

6.23 Rule f2

Rule f2 is an assignment rule for parameter f2:

$$f2 = intk2 \cdot [IR] \tag{23}$$

6.24 Rule f3

Rule f3 is an assignment rule for parameter f3:

$$f3 = intk2 \cdot [I2R] \tag{24}$$

6.25 Rule f4

Rule f4 is an assignment rule for parameter f4:

$$f4 = intk1 \cdot [Rp] - reck1 \cdot [RPen]$$
 (25)

6.26 Rule f5

Rule f5 is an assignment rule for parameter f5:

$$f5 = intk1 \cdot [IRp] \tag{26}$$

6.27 Rule f6

Rule f6 is an assignment rule for parameter f6:

$$f6 = intk1 \cdot [I2Rp] \tag{27}$$

6.28 Rule parameter_1

Rule parameter_1 is an assignment rule for parameter parameter_1:

$$parameter_{-}1 = \frac{(r1 - r2 - r3 - r4) \cdot vhep}{vp}$$
 (28)

6.29 Rule parameter_2

Rule parameter_2 is an assignment rule for parameter parameter_2:

$$parameter_2 = \frac{Kkidney \cdot [ins]}{vp}$$
 (29)

6.30 Rule parameter_3

Rule parameter_3 is an assignment rule for parameter parameter_3:

$$parameter_3 = parameter_2 + parameter_1$$
 (30)

6.31 Rule parameter_4

Rule parameter_4 is an assignment rule for parameter parameter_4:

$$parameter_{4} = \frac{parameter_{1}}{parameter_{1} + parameter_{2}} \cdot 100$$
 (31)

6.32 Rule parameter_5

Rule parameter_5 is an assignment rule for parameter parameter_5:

$$parameter_5 = \frac{parameter_2}{parameter_2 + parameter_1} \cdot 100$$
 (32)

6.33 Rule parameter_6

Rule parameter_6 is an assignment rule for parameter parameter_6:

$$parameter_6 = \frac{parameter_1 \cdot vp \cdot 6000}{[ins]}$$
 (33)

6.34 Rule parameter_7

Rule parameter_7 is an assignment rule for parameter parameter_7:

$$parameter_{7} = \frac{parameter_{2} \cdot vp \cdot 6000}{[ins]}$$
 (34)

6.35 Rule parameter_8

Rule parameter_8 is an assignment rule for parameter parameter_8:

$$parameter_8 = parameter_7 + parameter_6$$
 (35)

6.36 Rule parameter_9

Rule parameter_9 is an assignment rule for parameter parameter_9:

$$parameter_9 = \frac{Rtotal - [R] - [Rp] - [Ren] - [RPen]}{Rtotal}$$
 (36)

6.37 Rule parameter_11

Rule parameter_11 is an assignment rule for parameter parameter_11:

$$parameter_{-}11 = \frac{[IR] + [I2R] + [IRp] + [I2Rp]}{Rtotal}$$
(37)

6.38 Rule parameter_10

Rule parameter_10 is an assignment rule for parameter parameter_10:

$$parameter_{-}10 = \frac{[I2R] + [I2Ren] + [I2Rp] + [I2RPen]}{Rtotal}$$
(38)

6.39 Rule parameter_12

Rule parameter_12 is an assignment rule for parameter parameter_12:

$$parameter_{12} = \frac{[I2R] + [I2Rp]}{Rtotal}$$
 (39)

6.40 Rule parameter_13

Rule parameter_13 is an assignment rule for parameter parameter_13:

$$parameter_13 = parameter_9 - parameter_11$$
 (40)

6.41 Rule parameter_14

Rule parameter_14 is an assignment rule for parameter parameter_14:

$$parameter_14 = parameter_10 - parameter_12$$
 (41)

6.42 Rule R

Rule R is a rate rule for species R:

$$\frac{\mathrm{d}}{\mathrm{d}t}R = r1 + r5 - f1\tag{42}$$

6.43 Rule IR

Rule IR is a rate rule for species IR:

$$\frac{d}{dt}IR = r1 - r3 - r6 - f2 \tag{43}$$

6.44 Rule I2R

Rule I2R is a rate rule for species I2R:

$$\frac{d}{dt}I2R = r3 - r7 - f3 \tag{44}$$

6.45 Rule Rp

Rule Rp is a rate rule for species Rp:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Rp} = \mathrm{r}2 - \mathrm{r}5 - \mathrm{f}4\tag{45}$$

6.46 Rule IRp

Rule IRp is a rate rule for species IRp:

$$\frac{d}{dt}IRp = r2 - r4 + r6 - f5 \tag{46}$$

6.47 Rule I2Rp

Rule I2Rp is a rate rule for species I2Rp:

$$\frac{d}{dt}I2Rp = r4 + r7 - f6 (47)$$

6.48 Rule Ren

Rule Ren is a rate rule for species Ren:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Ren} = \mathrm{i}1 + \mathrm{i}5 + \mathrm{f}1\tag{48}$$

6.49 Rule IRen

Rule IRen is a rate rule for species IRen:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{IRen} = \mathrm{i}1 + \mathrm{i}3 - \mathrm{i}6 + \mathrm{f}2\tag{49}$$

6.50 Rule I2Ren

Rule I2Ren is a rate rule for species I2Ren:

$$\frac{\mathrm{d}}{\mathrm{d}t} 12 \mathrm{Ren} = \mathrm{i}3 - \mathrm{i}7 + \mathrm{f}3 \tag{50}$$

6.51 Rule RPen

Rule RPen is a rate rule for species RPen:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{RPen} = \mathrm{i}2 - \mathrm{i}5 + \mathrm{f}4\tag{51}$$

6.52 Rule IRPen

Rule IRPen is a rate rule for species IRPen:

$$\frac{d}{dt}$$
IRPen = i2 + i4 + i6 + f5 (52)

7 Derived Rate Equations

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

7.1 Species R

Name R

SBO:0000244 receptor

Initial concentration $35.3837 \text{ mol} \cdot l^{-1}$

Involved in rule R

One rule determines the species' quantity.

7.2 Species ins

Name ins

SBO:0000252 polypeptide chain

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

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{ins} = 0 \tag{53}$$

7.3 Species IR

Name IR

SBO:0000297 protein complex

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

Involved in rule IR

One rule determines the species' quantity.

7.4 Species I2R

Name I2R

SBO:0000297 protein complex

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

Involved in rule I2R

One rule determines the species' quantity.

7.5 Species Rp

Name Rp

SBO:0000244 receptor

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

Involved in rule Rp

One rule determines the species' quantity.

7.6 Species IRp

Name IRp

SBO:0000297 protein complex

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

Involved in rule IRp

One rule determines the species' quantity.

7.7 Species I2Rp

Name I2Rp

SBO:0000297 protein complex

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

Involved in rule 12Rp

One rule determines the species' quantity.

7.8 Species Ren

Name Ren

SBO:0000244 receptor

Initial concentration $4.6163 \text{ mol} \cdot l^{-1}$

Involved in rule Ren

One rule determines the species' quantity.

7.9 Species IRen

Name IRen

SBO:0000297 protein complex

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

Involved in rule IRen

One rule determines the species' quantity.

7.10 Species I2Ren

Name I2Ren

SBO:0000297 protein complex

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

Involved in rule 12Ren

One rule determines the species' quantity.

7.11 Species RPen

Name RPen

SBO:0000297 protein complex

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

Involved in rule RPen

One rule determines the species' quantity.

7.12 Species IRPen

Name IRPen

SBO:0000297 protein complex

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

Involved in rule IRPen

One rule determines the species' quantity.

7.13 Species I2RPen

Name I2RPen

SBO:0000297 protein complex

Initial concentration $-4.44089209850063 \cdot 10^{-15} \ mol \cdot l^{-1}$

Involved in rule I2RPen

One rule determines the species' quantity.

A Glossary of Systems Biology Ontology Terms

SBO:0000002 quantitative systems description parameter: A numerical value that defines certain characteristics of systems or system functions. It may be part of a calculation, but its value is not determined by the form of the equation itself, and may be arbitrarily assigned

SBO:000009 kinetic constant: Numerical parameter that quantifies the velocity of a chemical reaction

SBO:000064 mathematical expression: Formal representation of a calculus linking parameters and variables of a model

- SBO:0000179 degradation: Complete disappearance of a physical entity
- **SBO:0000180 dissociation:** Transformation of a non-covalent complex that results in the formation of several independent biochemical entitie
- **SBO:0000216 phosphorylation:** Addition of a phosphate group (-H2PO4) to a chemical entity
- **SBO:0000226 density of an entity pool:** A quantitative measure of an amount or property of an entity expressed in terms of another dimension, such as unit length, area or volume
- **SBO:0000244 receptor:** Participating entity that binds to a specific physical entity and initiates the response to that physical entity. The original concept of the receptor was introduced independently at the end of the 19th century by John Newport Langley (1852-1925) and Paul Ehrlich (1854-1915). Langley JN. On the reaction of cells and of nerve-endings to certain poisons, chiefly as regards the reaction of striated muscle to nicotine and to curari. J Physiol. 1905 Dec 30;33(4-5):374-413
- **SBO:0000252 polypeptide chain:** Naturally occurring macromolecule formed by the repetition of amino-acid residues linked by peptidic bonds. A polypeptide chain is synthesized by the ribosome. CHEBI:1654
- **SBO:0000297 protein complex:** Macromolecular complex containing one or more polypeptide chains possibly associated with simple chemicals. CHEBI:3608
- **SBO:0000330 dephosphorylation:** Removal of a phosphate group (-H2PO4) from a chemical entity.
- **SBO:0000468 volume:** A quantity representing the three-dimensional space occupied by all or part of an object
- **SBO:0000504** mass of an entity pool: The mass that comprises an entity pool

 $\mathfrak{BML2}$ ATEX was developed by Andreas Dräger^a, Hannes Planatscher^a, Dieudonné M Wouamba^a, Adrian Schröder^a, Michael Hucka^b, Lukas Endler^c, Martin Golebiewski^d and Andreas Zell^a. Please see http://www.ra.cs.uni-tuebingen.de/software/SBML2LaTeX for more information.

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