SBML Model Report

Model name: "Overgaard2007_PDmodel_IL21"

May 5, 2016

1 General Overview

This is a document in SBML Level 2 Version 4 format. This model was created by the following three authors: Catherine Lloyd[1], Vijayalakshmi Chelliah[2] and Rune Viig Overgaard[3] at November twelveth 2009 at 2:29 p. m. and last time modified at February 24th 2015 at 8:28 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	0
events	0	constraints	0
reactions	0	function definitions	0
global parameters	56	unit definitions	0
rules	27	initial assignments	0

Model Notes

This a model from the article:
PKPD model of interleukin-21 effects on thermoregulation in monkeys–application and evaluation of stochastic differential equations.

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Overgaard RV, Holford N, Rytved KA, Madsen H. Pharm Res.2007 Feb;24(2):298-309. PUBMED,

Abstract:

PURPOSE: To describe the pharmacodynamic effects of recombinant human interleukin-21 (IL-21) on core body temperature in cynomolgus monkeys using basic mechanisms of heat regulation. A major effort was devoted to compare the use of ordinary differential equations (ODEs) with stochastic differential equations (SDEs) in pharmacokinetic pharmacodynamic (PKPD) modelling. METHODS: A temperature model was formulated including circadian rhythm, metabolism, heat loss, and a thermoregulatory set-point. This model was formulated as a mixed-effects model based on SDEs using NONMEM. RESULTS: The effects of IL-21 were on the set-point and the circadian rhythm of metabolism. The model was able to describe a complex set of IL-21 induced phenomena, including 1) disappearance of the circadian rhythm, 2) no effect after first dose, and 3) high variability after second dose. SDEs provided a more realistic description with improved simulation properties, and further changed the model into one that could not be falsified by the autocorrelation function. CONCLUSIONS: The IL-21 induced effects on thermoregulation in cynomolgus monkeys are explained by a biologically plausible model. The quality of the model was improved by the use of SDEs.

To cite BioModels Database, please use Le Novre N., Bornstein B., Broicher A., Courtot M., Donizelli M., Dharuri H., Li L., Sauro H., Schilstra M., Shapiro B., Snoep J.L., Hucka M. (2006) BioModels Database: A Free, Centralized Database of Curated, Published, Quantitative Kinetic Models of Biochemical and Cellular Systems Nucleic Acids Res., 34: D689-D691.

2 Unit Definitions

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

2.1 Unit `substance`

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

Definition mol

2.2 Unit `volume`

Notes Litre is the predefined SBML unit for `volume`.

Definition l

2.3 Unit `area`

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

Definition m^2

2.4 Unit `length`

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

Definition m

2.5 Unit `time`

Notes Second is the predefined SBML unit for `time`.

Definition s

3 Compartment

This model contains one compartment.

Table 2: Properties of all compartments.

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

3.1 Compartment `COMpartment`

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

4 Parameters

This model contains 56 global parameters.

Table 3: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
`M`	Metabolic rate		3.500		☐
`T`	Temperature		38.785		☐
`BR`	Bound Receptor		0.000		☐
`E_slow`	Slow Effect		0.000		☐
`E_fast`	Fast Effect		0.000		☐
`f_prime`	Priming		0.000		☐
`T_a`	ambient temperature		21.000		☑

Id	Name	SBO	Value	Unit	Constant
T_b	basiline temperature		38.000		☑
delta_T	temperature difference		1.570		☑
kinc	kinc		0.026		☑
tdose1	tdose1		24.000		☑
tdose2	tdose2		72.000		☑
tdose3	tdose3		120.000		☑
M_c	circadian rhythm		0.000		⊟
t_day	t_day		17.500		☑
t_night	t_night		6.730		☑
tprime	tprime		0.000		⊟
day_length	day_length		86400.000		☑
km	rate constant Metabolism		1.138		☑
c	specific heat constant		3.470		☑
k	heat conductance		0.000		⊟
pEtot	pEtot		0.144		☑
kR	kR		5.350		☑
AMT_dose	AMT_dose		3.000		☑
pEf1	pEf1		1.000		☑
pEs1	pEs1		0.200		☑
pEf2	pEf2		3.570		☑
pEs2	pEs2		2.430		☑
pEf3	pEf3		8.000		☑
pEs3	pEs3		50.000		☑
f2_drug	f2_drug		0.000		⊟
T_day	T_day		0.000		⊟
T_night	T_night		0.000		⊟
kb	heat conductance baselinevalue		0.000		⊟
M_b	M_b		3.000		☑
M_day	M_day		0.000		⊟
M_night	M_night		0.000		⊟
t_prime	t_prime		45.120		☑
alpha	alpha		0.223		☑
delta_high_dose	delta_high_dose		1.000		☑
M_night_baseline	M_night_baseline		0.000		⊟
gNsTs1	gNsTs1		0.000		⊟

Id	Name	SBO	Value	Unit	Constant
gNsTs2	gNsTs2		0.000		☐
gNsTs3	gNsTs3		0.000		☐
gNfTf1	gNfTf1		0.000		☐
gNfTf2	gNfTf2		0.000		☐
gNfTf3	gNfTf3		0.000		☐
Ns	No. of transit compartment (slow)		4.000		☑
Nf	No. of transit compartment (fast)		4.000		☑
Ts	mean total delay (slow)		2.450		☑
Tf	mena total delay (fast)		0.368		☑
X1	X1		0.000		☐
X2	X2		0.000		☐
X3	X3		0.000		☐
Kf	Kf		0.000		☐
Ks	Ks		0.000		☐

5 Rules

This is an overview of 27 rules.

5.1 Rule M

Rule M is a rate rule for parameter M:

$$\frac{d}{dt}\mathrm{M} = \mathrm{km} \cdot (\mathrm{M} - \mathrm{M\_c}) \tag{1}$$

5.2 Rule T

Rule T is a rate rule for parameter T:

$$\frac{d}{dt}\mathrm{T} = \mathrm{c}^{-1} \cdot (\mathrm{M} - \mathrm{k} \cdot (\mathrm{T} - \mathrm{T\_a})) \tag{2}$$

5.3 Rule BR

Rule BR is a rate rule for parameter BR:

$$\frac{d}{dt}\mathrm{BR} = \mathrm{f\_prime} \cdot (\mathrm{E\_slow} + \mathrm{E\_fast}) \cdot (1 - \mathrm{BR}) - \mathrm{kR} \cdot \mathrm{BR} \tag{3}$$

5.4 Rule tprime

Rule tprime is an assignment rule for parameter tprime:

$$\text{tprime} = \text{time} \cdot 3600 \cdot 1 - \left\lfloor \frac{\text{time} \cdot 3600 \cdot 1}{\text{day\_length}} \right\rfloor \cdot \text{day\_length} \tag{4}$$

5.5 Rule kb

Rule kb is an assignment rule for parameter kb:

$$\text{kb} = \frac{\text{M\_b}}{\text{T\_b} - \text{T\_a}} \tag{5}$$

5.6 Rule T_day

Rule T_day is an assignment rule for parameter T_day:

$$\text{T\_day} = \text{T\_b} + \frac{\text{delta\_T}}{2} \tag{6}$$

5.7 Rule M_day

Rule M_day is an assignment rule for parameter M_day:

$$\text{M\_day} = (\text{kb} + \text{kinc} \cdot (\text{T\_day} - \text{T\_b})) \cdot (\text{T\_day} - \text{T\_a}) \tag{7}$$

5.8 Rule f_prime

Rule f_prime is an assignment rule for parameter f_prime:

$$\text{f\_prime} = \text{delta\_high\_dose} \cdot (1 + \exp(\text{alpha} \cdot (\text{time} - (\text{tdose1} + \text{t\_prime}))))^{-1} \tag{8}$$

5.9 Rule T_night

Rule T_night is an assignment rule for parameter T_night:

$$\text{T\_night} = \text{T\_b} - \frac{\text{delta\_T}}{2} \tag{9}$$

5.10 Rule M_night_baseline

Rule M_night_baseline is an assignment rule for parameter M_night_baseline:

$$\text{M\_night\_baseline} = (\text{kb} + \text{kinc} \cdot (\text{T\_night} - \text{T\_b})) \cdot (\text{T\_night} - \text{T\_a}) \tag{10}$$

5.11 Rule M_night

Rule M_night is an assignment rule for parameter M_night:

$$\text{M\_night} = (1 - \text{f\_prime}) \cdot \text{M\_night\_baseline} + \text{f\_prime} \cdot \text{M\_day} \tag{11}$$

5.12 Rule M_c

Rule M_c is an assignment rule for parameter M_c:

$$\text{M\_c} = \begin{cases} \text{M\_night} & \text{if } \left(\frac{\text{tprime}}{3600} \geq \text{t\_night}\right) \land \left(\frac{\text{tprime}}{3600} < \text{t\_day}\right) \\ \text{M\_day} & \text{otherwise} \end{cases} \tag{12}$$

5.13 Rule f2_drug

Rule f2_drug is an assignment rule for parameter f2_drug:

$$\text{f2\_drug} = 0 \tag{13}$$

5.14 Rule k

Rule k is an assignment rule for parameter k:

$$\text{k} = \text{kb} + \text{kinc} \cdot (\text{T} - \text{T\_b} \cdot (1 + \text{pEtot} \cdot \text{BR})) + \text{f2\_drug} \tag{14}$$

5.15 Rule X1

Rule X1 is an assignment rule for parameter X1:

$$\text{X1} = \frac{\text{time} - \text{tdose1}}{24} \tag{15}$$

5.16 Rule X2

Rule X2 is an assignment rule for parameter X2:

$$\text{X2} = \frac{\text{time} - \text{tdose2}}{24} \tag{16}$$

5.17 Rule X3

Rule X3 is an assignment rule for parameter X3:

$$\text{X3} = \frac{\text{time} - \text{tdose3}}{24} \tag{17}$$

5.18 Rule Kf

Rule Kf is an assignment rule for parameter Kf:

$$\text{Kf} = \frac{\text{Nf}}{\text{Tf}} \tag{18}$$

5.19 Rule Ks

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

$$\mathrm{Ks} = \frac{\mathrm{Ns}}{\mathrm{Ts}} \tag{19}$$

5.20 Rule gNsTs1

Rule `gNsTs1` is an assignment rule for parameter `gNsTs1`:

$$\mathrm{gNsTs1} = \begin{cases} \frac{\mathrm{Ks}^{\mathrm{Ns}}}{6} \cdot \exp\left(\mathrm{Ks} \cdot \mathrm{X1}\right) \cdot \mathrm{X1}^{\mathrm{Ns}-1} & \text{if } \mathrm{X1} > 0 \\ 0 & \text{otherwise} \end{cases} \tag{20}$$

5.21 Rule gNsTs2

Rule `gNsTs2` is an assignment rule for parameter `gNsTs2`:

$$\mathrm{gNsTs2} = \begin{cases} \frac{\mathrm{Ks}^{\mathrm{Ns}}}{6} \cdot \exp\left(\mathrm{Ks} \cdot \mathrm{X2}\right) \cdot \mathrm{X2}^{\mathrm{Ns}-1} & \text{if } \mathrm{X2} > 0 \\ 0 & \text{otherwise} \end{cases} \tag{21}$$

5.22 Rule gNsTs3

Rule `gNsTs3` is an assignment rule for parameter `gNsTs3`:

$$\mathrm{gNsTs3} = \begin{cases} \frac{\mathrm{Ks}^{\mathrm{Ns}}}{6} \cdot \exp\left(\mathrm{Ks} \cdot \mathrm{X3}\right) \cdot \mathrm{X3}^{\mathrm{Ns}-1} & \text{if } \mathrm{X3} > 0 \\ 0 & \text{otherwise} \end{cases} \tag{22}$$

5.23 Rule gNfTf1

Rule `gNfTf1` is an assignment rule for parameter `gNfTf1`:

$$\mathrm{gNfTf1} = \begin{cases} \frac{\mathrm{Kf}^{\mathrm{Nf}}}{6} \cdot \exp\left(\mathrm{Kf} \cdot \mathrm{X1}\right) \cdot \mathrm{X1}^{\mathrm{Nf}-1} & \text{if } \mathrm{X1} > 0 \\ 0 & \text{otherwise} \end{cases} \tag{23}$$

5.24 Rule gNfTf2

Rule `gNfTf2` is an assignment rule for parameter `gNfTf2`:

$$\mathrm{gNfTf2} = \begin{cases} \frac{\mathrm{Kf}^{\mathrm{Nf}}}{6} \cdot \exp\left(\mathrm{Kf} \cdot \mathrm{X2}\right) \cdot \mathrm{X2}^{\mathrm{Nf}-1} & \text{if } \mathrm{X2} > 0 \\ 0 & \text{otherwise} \end{cases} \tag{24}$$

5.25 Rule gNfTf3

Rule gNfTf3 is an assignment rule for parameter gNfTf3:

$$\mathrm{gNfTf3} = \begin{cases} \frac{\mathrm{Kf}^{\mathrm{Nf}}}{6} \cdot \exp\left(\mathrm{Kf} \cdot \mathrm{X3}\right) \cdot \mathrm{X3}^{\mathrm{Nf}-1} & \text{if } \mathrm{X3} > 0 \\ 0 & \text{otherwise} \end{cases} \tag{25}$$

5.26 Rule E_slow

Rule E_slow is an assignment rule for parameter E_slow:

$$\mathrm{E\_slow} = \mathrm{AMT\_dose} \cdot \mathrm{pEs2} \cdot \left(\mathrm{gNsTs1} + \mathrm{gNsTs2} + \mathrm{gNsTs3}\right) \tag{26}$$

5.27 Rule E_fast

Rule E_fast is an assignment rule for parameter E_fast:

$$\mathrm{E\_fast} = \mathrm{pEf2} \cdot \left(\mathrm{gNfTf1} + \mathrm{gNfTf2} + \mathrm{gNfTf3}\right) \tag{27}$$

SBML2LaTeX 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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