SBML Model Report

Model name: “Shi1993_Caffeine_pressor_tolerance”

May 5, 2016

1 General Overview

This is a document in SBML Level 2 Version 4 format. This model was created by Lukas Endler[1] at January eighth 2010 at eleven o’ clock in the morning. and last time modified at April eighth 2016 at 4:07 p. 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	5
species types	0	species	5
events	1	constraints	0
reactions	0	function definitions	0
global parameters	19	unit definitions	8
rules	6	initial assignments	0

Model Notes

described in: **Pharmacokinetic-pharmacodynamic modeling of caffeine: Tolerance to pressor effects**
Shi J, Benowitz NL, Denaro CP and Sheiner LB. ;Clin. Pharmacol. Ther. 1993 Jan;53(1):6-14.
PMID:8422743;
Abstract:

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We propose a parametric pharmacokinetic-pharmacodynamic model for caffeine that quantifies the development of tolerance to the pressor effect of the drug and characterizes the mean behavior and inter-individual variation of both pharmacokinetics and pressor effect. Our study in a small group of subjects indicates that acute tolerance develops to the pressor effect of caffeine and that both the pressor effect and tolerance occur after some time delay relative to changes in plasma caffeine concentration. The half-life of equilibration of effect with plasma caffeine concentration is about 20 minutes. The half-life of development and regression of tolerance is estimated to be about 1 hour, and the model suggests that tolerance, at its fullest, causes more than a 90 percent reduction of initial (nontolerant) effect. Whereas tolerance to the pressor effect of caffeine develops in habitual coffee drinkers, the pressor response is regained after relatively brief periods of abstinence. Because of the rapid development and regression of tolerance, the pressor response to caffeine depends on how much caffeine is consumed, the schedule of consumption, and the elimination half-life of caffeine.

Caffeine intake in this version is modelled as cups of coffee drunk at regular intervals (parameter t_interval). The amount of caffeine per cup is determined by the parameter cupsize. The body weight of the person drinking is given by the parameter bodyweight.
The even coffee cup occures delayed to the drinking of each cup, as the availability of the caffeine in the digestive tract is assumed to be delayed to the ingestion by the time t_lag.

2 Unit Definitions

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

2.1 Unit substance

Name mg

Definition mg

2.2 Unit time

Name hr

Definition 3600 s

2.3 Unit per_hour

Name per_hour

Definition $(3600\ \mathrm{s})^{-1}$

2.4 Unit l_per_kg

Name liter_per_kg

Definition $\mathrm{l} \cdot \mathrm{kg}^{-1}$

2.5 Unit mm_Hg

Name mm_Hg

Notes unit for blood pressure

Definition mm

2.6 Unit mm_Hg_l_per_mg

Name mm_Hg per (mg/l)

Definition $\mathrm{mm} \cdot \mathrm{l} \cdot \mathrm{mg}^{-1}$

2.7 Unit mg_per_l

Name mg/l

Definition $\mathrm{mg} \cdot \mathrm{l}^{-1}$

2.8 Unit mg_per_kg

Name mg_per_kg

Definition dimensionless

2.9 Unit volume

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

Definition l

2.10 Unit area

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

Definition m^2

2.11 Unit `length`

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

Definition m

3 Compartments

This model contains five compartments.

Table 2: Properties of all compartments.

Id	Name	SBO	Spatial Dimensions	Size	Unit	Constant	Outside
`Gut`	Gut	0000290	3	1	litre	☑	
`C`	C	0000290	3	0.31	l	☑	
`P`	P	0000290	3	1	litre	☑	
`Tol`	Tol	0000289	3	1	litre	☑	
`Eff`	Eff	0000289	3	1	litre	☑	

3.1 Compartment `Gut`

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

Name Gut

SBO:0000290 physical compartment

Notes gut compartment, the digestive tract

3.2 Compartment `C`

This is a three dimensional compartment with a constant size of 0.31 litre.

Name C

SBO:0000290 physical compartment

Notes the central compartment, corresponding mainly to the plasma. Its apparant volume is given by the parameter **V_C**

3.3 Compartment `P`

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

Name P

SBO:0000290 physical compartment

Notes peripheral compartment

3.4 Compartment `Tol`

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

Name Tol

SBO:0000289 functional compartment

Notes virtual compartment to account for tolerance effects

3.5 Compartment `Eff`

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

Name Eff

SBO:0000289 functional compartment

Notes virtual effect compartment

4 Species

This model contains five species. Section 8 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
`X_gut`	X_gut	`Gut`	dimensionless	$\boxminus$	$\boxminus$
`C_p`	C_p	`C`	$\mathrm{mg} \cdot \mathrm{l}^{-1}$	$\boxminus$	$\boxminus$
`C_per`	C_per	`P`	$\mathrm{mg} \cdot \mathrm{l}^{-1}$	$\boxminus$	$\boxminus$
`C_e`	C_e	`Eff`	$\mathrm{mg} \cdot \mathrm{l}^{-1}$	$\boxminus$	$\boxminus$
`C_t`	C_t	`Tol`	$\mathrm{mg} \cdot \mathrm{l}^{-1}$	$\boxminus$	$\boxminus$

5 Parameters

This model contains 19 global parameters.

Table 4: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
CL	CL		0.110		☑
V_C	V_C		0.320	$\mathrm{l} \cdot \mathrm{kg}^{-1}$	☑
k_a	k_a		12.000	$(3600\ \mathrm{s})^{-1}$	☑
t_lag	t_lag		0.150	3600 s	☑
k10	k10		0.340	$(3600\ \mathrm{s})^{-1}$	☑
k12	k12		1.640	$(3600\ \mathrm{s})^{-1}$	☑
k21	k21		1.190	$(3600\ \mathrm{s})^{-1}$	☑
t_half	t_half		3.980	3600 s	☑
F	F		0.984		☑
k_eo	k_eo		2.030	$(3600\ \mathrm{s})^{-1}$	☑
k_tol	k_tol		0.750	$(3600\ \mathrm{s})^{-1}$	☑
E_0	E_0		83.300	mm	☑
S	S		19.070	$\mathrm{mm} \cdot \mathrm{l} \cdot \mathrm{mg}^{-1}$	☑
T_50	T_50		0.260	$\mathrm{mg} \cdot \mathrm{l}^{-1}$	☑
E	MAP		0.000	mm	☐
t_int	t_intervall		2.000	3600 s	☑
cupsize	cupsize		90.000	mg	☑
bodyweight	bodyweight		80.000	kg	☑
cups	cups		0.000	dimensionless	☐

6 Rules

This is an overview of six rules.

6.1 Rule X_gut

Rule X_gut is a rate rule for species X_gut:

$$\frac{\mathrm{d}}{\mathrm{d}t}[\mathrm{X\_gut}] = \mathrm{k\_a} \cdot \mathrm{X\_gut} \tag{1}$$

Derived unit $(3600\ \mathrm{s})^{-1}$

6.2 Rule `C_p`

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

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{C\_p} = \frac{\mathrm{k\_a} \cdot \mathrm{F} \cdot \mathrm{X\_gut}}{\mathrm{V\_C}} - \mathrm{k12} \cdot [\mathrm{C\_p}] + \mathrm{k21} \cdot [\mathrm{C\_per}] - \mathrm{k10} \cdot [\mathrm{C\_p}] \tag{2}$$

6.3 Rule `C_per`

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

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{C\_per} = \mathrm{k12} \cdot [\mathrm{C\_p}] - \mathrm{k21} \cdot [\mathrm{C\_per}] \tag{3}$$

Derived unit $(3600\ \mathrm{s})^{-1} \cdot \mathrm{mg} \cdot \mathrm{l}^{-1}$

6.4 Rule `C_e`

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

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{C\_e} = \mathrm{k\_eo} \cdot ([\mathrm{C\_p}] - [\mathrm{C\_e}]) \tag{4}$$

Derived unit $(3600\ \mathrm{s})^{-1} \cdot \mathrm{mg} \cdot \mathrm{l}^{-1}$

6.5 Rule `C_t`

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

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{C\_t} = \mathrm{k\_tol} \cdot ([\mathrm{C\_p}] - [\mathrm{C\_t}]) \tag{5}$$

Derived unit $(3600\ \mathrm{s})^{-1} \cdot \mathrm{mg} \cdot \mathrm{l}^{-1}$

6.6 Rule `E`

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

$$\mathrm{E} = \mathrm{E\_0} + \frac{\mathrm{S} \cdot [\mathrm{C\_e}]}{1 + \frac{[\mathrm{C\_t}]}{\mathrm{T\_50}}} \tag{6}$$

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 coffecup

Name coffee cup

Notes availability of caffeine in gut after drinking a cup

Trigger condition

$$\text{time} \geq \text{t\_int} \cdot \text{cups} + \text{t\_lag} \tag{7}$$

Assignments

$$\text{cups} = \text{cups} + 1 \tag{8}$$

$$[\text{X\_gut}] = \text{X\_gut} + \frac{\text{cupsize}}{\text{bodyweight}} \tag{9}$$

8 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.

8.1 Species X_gut

Name X_gut

SBO:0000241 functional entity

Initial amount $0\ Unknownunitmg_{p}er_{k}g$

Involved in event coffecup

Involved in rule X_gut

One rule which determines this species' quantity. Furthermore, one event influences this species' rate of change.

8.2 Species C_p

Name C_p

SBO:0000247 simple chemical

Initial amount 0 mg

Involved in rule C_p

One rule which determines this species' quantity.

8.3 Species `C_per`

Name C_per

SBO:0000247 simple chemical

Initial concentration $0\ \mathrm{mg} \cdot \mathrm{l}^{-1}$

Involved in rule `C_per`

One rule which determines this species' quantity.

8.4 Species `C_e`

Name C_e

SBO:0000241 functional entity

Notes hypothetical effect-site concentration

Initial concentration $0\ \mathrm{mg} \cdot \mathrm{l}^{-1}$

Involved in rule `C_e`

One rule which determines this species' quantity.

8.5 Species `C_t`

Name C_t

SBO:0000241 functional entity

Notes hypothetical antagonistic metabolite to account for tolerance development

Initial concentration $0\ \mathrm{mg} \cdot \mathrm{l}^{-1}$

Involved in rule `C_t`

One rule which determines this species' quantity.

A Glossary of Systems Biology Ontology Terms

SBO:0000241 **functional entity:** A real thing, defined by its properties or the actions it performs, rather than it physico-chemical structure

SBO:0000247 **simple chemical:** Simple, non-repetitive chemical entity

SBO:0000289 functional compartment: Logical or physical subset of the event space that contains pools, that is sets of participants considered identical when it comes to the event they are involved into. A compartment can have any number of dimensions, including 0, and be of any size including null

SBO:0000290 physical compartment: Specific location of space, that can be bounded or not. A physical compartment can have 1, 2 or 3 dimensions

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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