SBML Model Report

Model name: “Grange2001 - L Dopa PK model”

May 5, 2016

1 General Overview

This is a document in SBML Level 2 Version 3 format. This model was created by the following two authors: Lukas Endler[1] and Vijayalakshmi Chelliah[2] at October 27th 2009 at 2:45 p. m. and last time modified at October tenth 2014 at 11:18 a. 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	3
species types	0	species	3
events	0	constraints	0
reactions	6	function definitions	0
global parameters	18	unit definitions	5
rules	8	initial assignments	1

Model Notes

Grange2001 - L-dopa PK model

A pharmacokinetics of L-dopa in rats after administration of L-dopa alone (this model: BIOMD0000000321) or L-dopa combined with a peripheral AADC (amino-acid-decarboxylase) inhibitor (BIOMD0000000320) has been studied using noncompartmental analysis.

[1]EMBL-EBI, lukas@ebi.ac.uk
[2]EMBL-EBI, viji@ebi.ac.uk

This model is described in the article:A pharmacokinetic model to predict the PK interaction of L-dopa and benserazide in rats.Grange S, Holford NH, Guentert TWPharmaceutical Research [2001, 18(8):1174-1184]

Abstract:

PURPOSE: To study the PK interaction of L-dopa/benserazide in rats. METHODS: Male rats received a single oral dose of 80 mg/kg L-dopa or 20 mg/kg benserazide or 80/20 mg/kg L-dopa/benserazide. Based on plasma concentrations the kinetics of L-dopa, 3-O-methyldopa (3-OMD), benserazide, and its metabolite Ro 04-5127 were characterized by noncompartmental analysis and a compartmental model where total L-dopa clearance was the sum of the clearances mediated by amino-acid-decarboxylase (AADC), catechol-O-methyltransferase and other enzymes. In the model Ro 04-5127 inhibited competitively the L-dopa clearance by AADC.

RESULTS: The coadministration of L-dopa/benserazide resulted in a major increase in systemic exposure to L-dopa and 3-OMD and a decrease in L-dopa clearance. The compartmental model allowed an adequate description of the observed L-dopa and 3-OMD concentrations in the absence and presence of benserazide. It had an advantage over noncompartmental analysis because it could describe the temporal change of inhibition and recovery of AADC.

CONCLUSIONS: Our study is the first investigation where the kinetics of benserazide and Ro 04-5127 have been described by a compartmental model. The L-dopa/benserazide model allowed a mechanism-based view of the L-dopa/benserazide interaction and supports the hypothesis that Ro 04-5127 is the primary active metabolite of benserazide.

The model has a species (A-dopa) whose initial concentration is calculated from a *listOfInitialAssignments* . While running for the first time the time-course (24hrs) for this model in COPASI (up to version 4.6, Build 33), the resulting graph displays only straight lines for all the species. Any subsequent runs should provide proper plots (i.e. without making any change to the model, just by clicking the „run„ button again).

The above issue is caused by some initial assignments which are not calculated when COPASI imports the file. This issue should not be present in newer releases of COPASI.

This model is hosted on BioModels Database and identified by: MODEL1103250000 .

To cite BioModels Database, please use: BioModels Database: An enhanced, curated and annotated resource for published quantitative kinetic models .

2 Unit Definitions

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

2.1 Unit `substance`

Name micromole

Definition nmol

2.2 Unit umol_per_kg

Name micromole_per_kg

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

2.3 Unit per_h

Name per_h

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

2.4 Unit l_per_h

Name l_per_h

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

2.5 Unit time

Name hours

Definition 3600 s

2.6 Unit volume

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

Definition l

2.7 Unit area

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

Definition m^2

2.8 Unit length

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

Definition m

3 Compartments

This model contains three compartments.

Table 2: Properties of all compartments.

Id	Name	SBO	Spatial Dimensions	Size	Unit	Constant	Outside
gut		0000290	3	1	litre	☑	
Vdopa	V_L_Dopa	0000290	3	0.496	l	☑	
V_3_OMD		0000290	3	0.196	l	☑	

3.1 Compartment gut

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

SBO:0000290 physical compartment

3.2 Compartment Vdopa

This is a three dimensional compartment with a constant size of 0.496 litre.

Name V_L_Dopa

SBO:0000290 physical compartment

3.3 Compartment V_3_OMD

This is a three dimensional compartment with a constant size of 0.196 litre.

SBO:0000290 physical compartment

4 Species

This model contains three species. 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
A_dopa		gut	nmol	⊟	⊟
C_dopa		Vdopa	$\mathrm{nmol} \cdot \mathrm{l}^{-1}$	⊟	⊟
C_OMD	C_3-OMD	V_3_OMD	$\mathrm{nmol} \cdot \mathrm{l}^{-1}$	⊟	⊟

5 Parameters

This model contains 18 global parameters.

Table 4: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
F_b		0000381	0.000	dimensionless	⊟
F_H		0000381	0.000	dimensionless	⊟
F_G		0000381	0.240	dimensionless	☑
CL_H		0000035	0.000	$1 \cdot (3600\ \mathrm{s})^{-1}$	⊟
Q		0000002	0.828		☑
f_H		0000381	0.130	dimensionless	☑
CL_dopa		0000035	0.000	$1 \cdot (3600\ \mathrm{s})^{-1}$	⊟
f_rest		0000381	0.000	dimensionless	⊟
f_AADC		0000381	0.690	dimensionless	☑
f_COMT		0000381	0.100	dimensionless	☑
CL_AADC		0000035	0.000	$1 \cdot (3600\ \mathrm{s})^{-1}$	⊟
CL_rest		0000035	0.000	$1 \cdot (3600\ \mathrm{s})^{-1}$	⊟
CL_COMT		0000035	0.000	$1 \cdot (3600\ \mathrm{s})^{-1}$	⊟
CL_dopa0		0000035	0.823	$1 \cdot (3600\ \mathrm{s})^{-1}$	☑
ka_b		0000035	2.110	$(3600\ \mathrm{s})^{-1}$	☑
CL_OMD	CL_3_OMD	0000035	0.012		☑
L_Dopa_per_kg_rat		0000197	404.000		☑
rat_body_mass		0000002	0.250		☑

6 Initialassignment

This is an overview of one initialassignment.

6.1 Initialassignment A_dopa

Derived unit contains undeclared units

Math $\mathrm{L\_Dopa\_per\_kg\_rat} \cdot \mathrm{rat\_body\_mass}$

7 Rules

This is an overview of eight rules.

7.1 Rule F_b

Rule F_b is an assignment rule for parameter F_b:

$$\mathrm{F\_b} = \mathrm{F\_H} \cdot \mathrm{F\_G} \tag{1}$$

Derived unit dimensionless

7.2 Rule F_H

Rule F_H is an assignment rule for parameter F_H:

$$\mathrm{F\_H} = 1 - \frac{\mathrm{CL\_H}}{\mathrm{Q}} \tag{2}$$

7.3 Rule CL_H

Rule CL_H is an assignment rule for parameter CL_H:

$$\mathrm{CL\_H} = \mathrm{f\_H} \cdot \mathrm{CL\_dopa} \tag{3}$$

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

7.4 Rule CL_dopa

Rule CL_dopa is an assignment rule for parameter CL_dopa:

$$\mathrm{CL\_dopa} = \mathrm{CL\_AADC} + \mathrm{CL\_rest} + \mathrm{CL\_COMT} \tag{4}$$

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

7.5 Rule f_rest

Rule f_rest is an assignment rule for parameter f_rest:

$$\mathrm{f\_rest} = 1 - (\mathrm{f\_AADC} + \mathrm{f\_COMT}) \tag{5}$$

7.6 Rule CL_AADC

Rule CL_AADC is an assignment rule for parameter CL_AADC:

$$\mathrm{CL\_AADC} = \mathrm{CL\_dopa0} \cdot \mathrm{f\_AADC} \tag{6}$$

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

7.7 Rule CL_rest

Rule CL_rest is an assignment rule for parameter CL_rest:

$$\mathrm{CL\_rest} = \mathrm{CL\_dopa0} \cdot \mathrm{f\_rest} \tag{7}$$

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

7.8 Rule CL_COMT

Rule CL_COMT is an assignment rule for parameter CL_COMT:

$$\mathrm{CL\_COMT} = \mathrm{CL\_dopa0} \cdot \mathrm{f\_COMT} \tag{8}$$

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

8 Reactions

This model contains six 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	l_dopa_absorption	L_Dopa absorption from gut	A_dopa ⟶ C_dopa	0000185
2	l_dopa_blood_hepa_clearance	hepatic and blood L-Dopa clearance	A_dopa ⟶ ∅	0000179
3	AADC_clearance	L-Dopa clearance via AADC	C_dopa ⟶ ∅	0000399
4	COMT_clearance	L-Dopa clearance via COMT	C_dopa ⟶ C_OMD	0000214
5	rest_clearance	rest clearance of L-Dopa	C_dopa ⟶ ∅	0000179
6	_3_OMD_clearance	3-OMD clearance	C_OMD ⟶ ∅	0000179

8.1 Reaction `l_dopa_absorption`

This is an irreversible reaction of one reactant forming one product.

Name L_Dopa absorption from gut

SBO:0000185 transport reaction

Reaction equation

$$\text{A\_dopa} \longrightarrow \text{C\_dopa} \tag{9}$$

Reactant

Table 6: Properties of each reactant.

Id	Name	SBO
A_dopa		

Product

Table 7: Properties of each product.

Id	Name	SBO
C_dopa		

Kinetic Law

SBO:0000049 mass action rate law for first order irreversible reactions, continuous scheme

Derived unit $(3600\ \text{s})^{-1} \cdot \text{nmol}$

$$v_1 = \text{ka\_b} \cdot \text{A\_dopa} \cdot \text{F\_b} \tag{10}$$

8.2 Reaction `l_dopa_blood_hepa_clearance`

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

Name hepatic and blood L-Dopa clearance

SBO:0000179 degradation

Reaction equation

$$\text{A\_dopa} \longrightarrow \emptyset \tag{11}$$

Reactant

Table 8: Properties of each reactant.

Id	Name	SBO
A_dopa		

Kinetic Law

SBO:0000049 mass action rate law for first order irreversible reactions, continuous scheme

Derived unit contains undeclared units

$$v_2 = \text{ka\_b} \cdot \text{A\_dopa} \cdot (1 - \text{F\_b}) \tag{12}$$

8.3 Reaction AADC_clearance

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

Name L-Dopa clearance via AADC

SBO:0000399 decarboxylation

Reaction equation

$$\text{C\_dopa} \longrightarrow \emptyset \tag{13}$$

Reactant

Table 9: Properties of each reactant.

Id	Name	SBO
C_dopa		

Kinetic Law

SBO:0000049 mass action rate law for first order irreversible reactions, continuous scheme

Derived unit $(3600\ \text{s})^{-1} \cdot \text{nmol}$

$$v_3 = \text{CL\_AADC} \cdot [\text{C\_dopa}] \tag{14}$$

8.4 Reaction COMT_clearance

This is an irreversible reaction of one reactant forming one product.

Name L-Dopa clearance via COMT

SBO:0000214 methylation

Reaction equation

$$\text{C\_dopa} \longrightarrow \text{C\_OMD} \tag{15}$$

Reactant

Table 10: Properties of each reactant.

Id	Name	SBO
C_dopa		

Product

Table 11: Properties of each product.

Id	Name	SBO
C_OMD	C_3-OMD	

Kinetic Law

SBO:0000049 mass action rate law for first order irreversible reactions, continuous scheme

Derived unit $(3600\ \text{s})^{-1} \cdot \text{nmol}$

$$v_4 = \text{CL\_COMT} \cdot [\text{C\_dopa}] \tag{16}$$

8.5 Reaction `rest_clearance`

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

Name rest clearance of L-Dopa

SBO:0000179 degradation

Reaction equation

$$\text{C\_dopa} \longrightarrow \emptyset \tag{17}$$

Reactant

Table 12: Properties of each reactant.

Id	Name	SBO
C_dopa		

Kinetic Law

SBO:0000049 mass action rate law for first order irreversible reactions, continuous scheme

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

$$v_5 = \mathrm{CL\_rest} \cdot [\mathrm{C\_dopa}] \tag{18}$$

8.6 Reaction _3_OMD_clearance

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

Name 3-OMD clearance

SBO:0000179 degradation

Reaction equation

$$\mathrm{C\_OMD} \longrightarrow \emptyset \tag{19}$$

Reactant

Table 13: Properties of each reactant.

Id	Name	SBO
C_OMD	C_3-OMD	

Kinetic Law

SBO:0000049 mass action rate law for first order irreversible reactions, continuous scheme

Derived unit contains undeclared units

$$v_6 = \mathrm{CL\_OMD} \cdot [\mathrm{C\_OMD}] \tag{20}$$

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 A_dopa

SBO:0000247 simple chemical

Notes amount of L-Dopa in the gut

Initial assignment A_dopa

This species takes part in two reactions (as a reactant in l_dopa_absorption, l_dopa_blood-_hepa_clearance).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{A\_dopa} = -v_1 - v_2 \tag{21}$$

9.2 Species C_dopa

SBO:0000247 simple chemical

Notes amount of L-Dopa in the central compartment

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

This species takes part in four reactions (as a reactant in AADC_clearance, COMT_clearance, rest_clearance and as a product in l_dopa_absorption).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{C\_dopa} = v_1 - v_3 - v_4 - v_5 \tag{22}$$

9.3 Species C_OMD

Name C_3-OMD

SBO:0000247 simple chemical

Notes amount of 3-OMD in the central compartment

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

This species takes part in two reactions (as a reactant in _3_OMD_clearance and as a product in COMT_clearance).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{C\_OMD} = v_4 - v_6 \tag{23}$$

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:0000035 forward unimolecular rate constant, continuous case: Numerical parameter that quantifies the forward velocity of a chemical reaction involving only one reactant. This parameter encompasses all the contributions to the velocity except the quantity of the reactant. It is to be used in a reaction modelled using a continuous framework

SBO:0000049 mass action rate law for first order irreversible reactions, continuous scheme: Reaction scheme where the products are created from the reactants and the change of a product quantity is proportional to the product of reactant activities. The reaction scheme does not include any reverse process that creates the reactants from the products. The change of a product quantity is proportional to the quantity of one reactant. It is to be used in a reaction modelled using a continuous framework.

SBO:0000179 degradation: Complete disappearance of a physical entity

SBO:0000185 transport reaction: Movement of a physical entity without modification of the structure of the entity

SBO:0000197 specific concentration of an entity: Concentration of an object divided by the value of another parameter having the dimension of a concentration

SBO:0000214 methylation: Addition of a methyl group (-CH3) to a chemical entity

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

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

SBO:0000381 biochemical proportionality coefficient: A multiplicative factor for quantities, expressions or functions

SBO:0000399 decarboxylation: A process in which a carboxyl group (COOH) is removed from a molecule as carbon dioxide

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.

[a]Center for Bioinformatics Tübingen (ZBIT), Germany
[b]California Institute of Technology, Beckman Institute BNMC, Pasadena, United States
[c]European Bioinformatics Institute, Wellcome Trust Genome Campus, Hinxton, United Kingdom
[d]EML Research gGmbH, Heidelberg, Germany