SBML Model Report

Model name: “Sluka2016 - Acetaminophen metabolism”

December 6, 2016

1 General Overview

This is a document in SBML Level 2 Version 4 format. This model was created by James Sluka[1] at July 29th 2014 at noon. and last time modified at October 26th 2015 at noon. 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	7
events	0	constraints	0
reactions	5	function definitions	0
global parameters	9	unit definitions	6
rules	0	initial assignments	0

Model Notes

Sluka2016 - Acetaminophen metabolism**Liver metabolism of Acetaminophen:** Acetaminophen (APAP) ismetabolized in the liver in both Phase I and Phase II reactions.Phase II reactions convert APAP to APAP-glucuronide andAPAP-sulfate. Phase I reactions involve Cytochrome P450 mediated(mostly Cyp450-2E1 and -1A2) conversion of APAP toN-acetyle-p-quinoneimine (NAPQI),

[1] Indiana University, jsluka@indiana.edu

which goes on to react withcellular nucleophiles such as glutathione (GSH). At high doses ofA-PAP significant GSH depletion in hepatocyte occurs resulting incell necrosis and and in extreme cases death.

This model is described in the article:A Liver-Centric Multiscale Modeling Framework for Xenobiotics.Sluka JP, Fu X, Swat M, Belmonte JM, Cosmanescu A, Clendenon SG, Wambaugh JF, Glazier JA.PLoS ONE 2016; 11(9): e0162428

Abstract:

We describe a multi-scale, liver-centric in silico modeling framework for acetaminophen pharmacology and metabolism. We focus on a computational model to characterize whole body uptake and clearance, liver transport and phase I and phase II metabolism. We do this by incorporating sub-models that span three scales; Physiologically Based Pharmacokinetic (PBPK) modeling of acetaminophen uptake and distribution at the whole body level, cell and blood flow modeling at the tissue/organ level and metabolism at the sub-cellular level. We have used standard modeling modalities at each of the three scales. In particular, we have used the Systems Biology Markup Language (SBML) to create both the whole-body and sub-cellular scales. Our modeling approach allows us to run the individual sub-models separately and allows us to easily exchange models at a particular scale without the need to extensively rework the sub-models at other scales. In addition, the use of SBML greatly facilitates the inclusion of biological annotations directly in the model code. The model was calibrated using human in vivo data for acetaminophen and its sulfate and glucuronate metabolites. We then carried out extensive parameter sensitivity studies including the pairwise interaction of parameters. We also simulated population variation of exposure and sensitivity to acetaminophen. Our modeling framework can be extended to the prediction of liver toxicity following acetaminophen overdose, or used as a general purpose pharmacokinetic model for xenobiotics.

This model is hosted on BioModels Database and identified by: BIOMD0000000624.

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 nine unit definitions of which three are predefined by SBML and not mentioned in the model.

2.1 Unit `substance`

Name millimole

Definition mmol

2.2 Unit time

Name second

Definition s

2.3 Unit first_order_rate_constant

Name first_order_rate_constant

Definition s^{-1}

2.4 Unit second_order_rate_constant

Name second_order_rate_constant

Definition $mmol^{-1} \cdot s^{-1}$

2.5 Unit flux

Name flux

Definition $mmol \cdot s^{-1}$

2.6 Unit millimolar

Name millimolar

Definition $mmol \cdot l^{-1}$

2.7 Unit volume

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

Definition l

2.8 Unit area

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

Definition m^2

2.9 Unit length

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

Definition m

3 Compartment

This model contains one compartment.

Table 2: Properties of all compartments.

Id	Name	SBO	Spatial Dimensions	Size	Unit	Constant	Outside
`compartment`	Hepatocyte		3	1		☑	

3.1 Compartment `compartment`

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

Name Hepatocyte

Notes **A single liver hepatocyte (parenchymal) cell.**

`FMA:68646 Cell`
`FMA:14515 Hepatocyte`
`GO:0005623 Cell`

4 Species

This model contains seven 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 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 Condition
X1	X1	compartment	$\mathrm{mmol} \cdot \mathrm{l}^{-1}$	⊟	☑
APAP	APAP	compartment	$\mathrm{mmol} \cdot \mathrm{l}^{-1}$	⊟	⊟
NAPQI	NAPQI	compartment	$\mathrm{mmol} \cdot \mathrm{l}^{-1}$	⊟	⊟
GSH	GSH	compartment	$\mathrm{mmol} \cdot \mathrm{l}^{-1}$	⊟	⊟
NAPQIGSH	NAPQIGSH	compartment	$\mathrm{mmol} \cdot \mathrm{l}^{-1}$	⊟	⊟
APAPconj_Glu	APAPconj_Glu	compartment	$\mathrm{mmol} \cdot \mathrm{l}^{-1}$	⊟	⊟
APAPconj_Sul	APAPconj_Sul	compartment	$\mathrm{mmol} \cdot \mathrm{l}^{-1}$	⊟	⊟

5 Parameters

This model contains nine global parameters.

Table 4: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
Vmax_2E1_APAP		0000186	$2 \cdot 10^{-5}$	$\text{mmol} \cdot \text{s}^{-1}$	☑
Km_2E1_APAP		0000027	1.290	$\text{mmol} \cdot \text{l}^{-1}$	☑
kNapqiGsh		0000017	0.100	$\text{mmol}^{-1} \cdot \text{s}^{-1}$	☑
kGsh		0000022	10^{-4}	s^{-1}	☑
GSHmax			10.000	$\text{mmol} \cdot \text{l}^{-1}$	☑
Vmax_PhaseIIEnzGlu_APAP		0000186	0.001	$\text{mmol} \cdot \text{s}^{-1}$	☑
Km_PhaseIIEnzGlu_APAP		0000027	1.000	$\text{mmol} \cdot \text{l}^{-1}$	☑
Vmax_PhaseIIEnzSul_APAP		0000186	$1.75 \cdot 10^{-4}$	$\text{mmol} \cdot \text{s}^{-1}$	☑
Km_PhaseIIEnzSul_APAP		0000027	0.200	$\text{mmol} \cdot \text{l}^{-1}$	☑

6 Reactions

This model contains five 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	J0	J0	APAP $\longrightarrow$ NAPQI	0000201
2	J1	J1	GSH + NAPQI $\longrightarrow$ NAPQIGSH	0000210
3	J2	J2	X1 $\longrightarrow$ GSH	0000176
4	J3	J3	APAP $\longrightarrow$ APAPconj_Glu	0000210
5	J4	J4	APAP $\longrightarrow$ APAPconj_Sul	0000210

6.1 Reaction J0

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

Name J0

SBO:0000201 oxidation

Notes J0: APAP -> NAPQI

Metabolic conversion of APAP to NAPQI by oxidation via Cyp450's such 1A2 and 2E1. Phase I metabolism.

MESH.2013:D050216 Metabolic Detoxication, Phase I
isDescribedBy PubMed:19219744 Acetaminophen bioactivation by human cytochrome P450 enzymes and animal microsomes. (2009)
isDescribedBy PubMed:6424115 N-acetyl-p-benzoquinone imine: a cytochrome P-450-mediated oxidation product of acetaminophen. (1984)
isPartOf GO:0045333 cellular respiration
is GO:0044237 cellular metabolic process, biological_process
is GO:0071704 organic substance metabolic process

Reaction equation

$$\mathrm{APAP} \longrightarrow \mathrm{NAPQI} \tag{1}$$

Reactant

Table 6: Properties of each reactant.

Id	Name	SBO
APAP	APAP	

Product

Table 7: Properties of each product.

Id	Name	SBO
NAPQI	NAPQI	

Kinetic Law

Derived unit $0.0010\ \mathrm{mol} \cdot \mathrm{s}^{-1}$

$$v_1 = \frac{\text{Vmax\_2E1\_APAP} \cdot [\text{APAP}]}{\text{Km\_2E1\_APAP} + [\text{APAP}]} \tag{2}$$

6.2 Reaction J1

This is an irreversible reaction of two reactants forming one product.

Name J1

SBO:0000210 addition of a chemical group

Notes J1: GSH + NAPQI -> NAPQIGSH

Reaction of (scavenging of) NAPQI by cellular GSH.

is PW:0000373 glutathione conjugation pathway

Reaction equation

$$\text{GSH} + \text{NAPQI} \longrightarrow \text{NAPQIGSH} \tag{3}$$

Reactants

Table 8: Properties of each reactant.

Id	Name	SBO
GSH	GSH	
NAPQI	NAPQI	

Product

Table 9: Properties of each product.

Id	Name	SBO
NAPQIGSH	NAPQIGSH	

Kinetic Law

Derived unit $\text{s}^{-1} \cdot \text{mmol}$

$$v_2 = \text{kNapqiGsh} \cdot [\text{NAPQI}] \cdot [\text{GSH}] \cdot \text{vol}(\text{compartment}) \cdot \text{vol}(\text{compartment}) \tag{4}$$

6.3 Reaction J2

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

Name J2

SBO:0000176 biochemical reaction

Notes J2: X1 -> GSH

Synthesis of GSH, including via reduction of oxidized GSH (GSSG).

is GO:0004363 glutathione synthase activity

Reaction equation

$$\mathrm{X1} \longrightarrow \mathrm{GSH} \tag{5}$$

Reactant

Table 10: Properties of each reactant.

Id	Name	SBO
X1	X1	

Product

Table 11: Properties of each product.

Id	Name	SBO
GSH	GSH	

Kinetic Law

Derived unit $\mathrm{s}^{-1} \cdot \mathrm{mmol}$

$$v_3 = \mathrm{kGsh} \cdot (\mathrm{GSHmax} - [\mathrm{GSH}]) \cdot \mathrm{vol}\,(\mathrm{compartment}) \tag{6}$$

6.4 Reaction J3

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

Name J3

SBO:0000210 addition of a chemical group

Notes J3: APAP -> APAPconj_Glu

Conjugation of APAP with Glucuronic Acid.
Phase II metabolism.

is GO:0052697 xenobiotic glucuronidation

Reaction equation

$$\text{APAP} \longrightarrow \text{APAPconj\_Glu} \tag{7}$$

Reactant

Table 12: Properties of each reactant.

Id	Name	SBO
APAP	APAP	

Product

Table 13: Properties of each product.

Id	Name	SBO
APAPconj_Glu	APAPconj_Glu	

Kinetic Law

Derived unit $0.0010\ \text{mol} \cdot \text{s}^{-1}$

$$v_4 = \frac{\text{Vmax\_PhaseIIEnzGlu\_APAP} \cdot [\text{APAP}]}{\text{Km\_PhaseIIEnzGlu\_APAP} + [\text{APAP}]} \tag{8}$$

6.5 Reaction J4

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

Name J4

SBO:0000210 addition of a chemical group

Notes J4: APAP -> APAPconj_Sul

Conjugation of APAP with Sulfate.
Phase II metabolism.

is GO:0051923 sulfations (phase II metabolism)

Reaction equation

$$\text{APAP} \longrightarrow \text{APAPconj\_Sul} \tag{9}$$

Reactant

Table 14: Properties of each reactant.

Id	Name	SBO
APAP	APAP	

Product

Table 15: Properties of each product.

Id	Name	SBO
APAPconj_Sul	APAPconj_Sul	

Kinetic Law

Derived unit $0.0010\ \text{mol} \cdot \text{s}^{-1}$

$$v_5 = \frac{\text{Vmax\_PhaseIIEnzSul\_APAP} \cdot [\text{APAP}]}{\text{Km\_PhaseIIEnzSul\_APAP} + [\text{APAP}]} \tag{10}$$

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 X1

Name X1

Notes Generic precursor to GSH.

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

This species takes part in one reaction (as a reactant in J2), which does not influence its rate of change because this species is on the boundary of the reaction system:

$$\frac{\text{d}}{\text{d}t}\text{X1} = 0 \tag{11}$$

7.2 Species APAP

Name APAP

Notes Acetaminophen (N-acetyl-p-aminophenol APAP).

Formula: C8H9NO2
Mol. mass: 151.163 g/mol
InChIKey: RZVAJINKPMORJF-UHFFFAOYSA-N

Also known as: Paracetamol, 4-Acetamidophenol, Tylenol, APAP, Acetaminofen, Panadol, Datril, 4'-Hydroxyacetanilide, Algotropyl

CHEBI:46195

Initial concentration $0.1\ \mathrm{mmol}\cdot\mathrm{l}^{-1}$

This species takes part in three reactions (as a reactant in J0, J3, J4).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{APAP} = -v_1 - v_4 - v_5 \tag{12}$$

7.3 Species NAPQI

Name NAPQI

Notes N-Acetyl paraquinone imine (NAPQI)

Also known as: N-acetyl-4-benzoquinoneimine, Acetimidoquinone, N-Acetylbenzoquinoneimine, N-Acetyl-P-benzoquinoneimine, N-Acetyl-p-benzoquinone imine, N-acetyl-1,4-benzoquinone imine

A CypP450 oxidation product of Acetaminophen.

Molecular Formula: C8H7NO2
Molecular Weight: 149.14668
InChIKey: URNSECGXFRDEDC-UHFFFAOYSA-N

CHEBI:29132

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

This species takes part in two reactions (as a reactant in J1 and as a product in J0).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{NAPQI} = v_1 - v_2 \tag{13}$$

7.4 Species GSH

Name GSH

Notes **Glutathione (GSH), reduced.**

gamma-L-Glutamyl-L-Cysteinyl-Glycine.

Molecular formula: C10H17N3O6S
Molar mass: 307.32 g/mol

Initial concentration $10\ \mathrm{mmol}\cdot\mathrm{l}^{-1}$

This species takes part in two reactions (as a reactant in J1 and as a product in J2).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{GSH} = v_3 - v_2 \tag{14}$$

7.5 Species NAPQIGSH

Name NAPQIGSH

Notes **N-Acetyl paraquinone imine - Glutathione Conjugate (NAPQIGSH)**

Product of the reaction of NAPQI and glutathion.

Also known as:3-(glutathion-S-yl)acetaminophen, AA-Glutathion, AA-Gsh, Acetaminophen glutathion, Glutathione-S-acetaminophen conjugate, 3-Gsh-acetaminophen, 64889-81-2

Molecular Formula: C18H24N4O8S
Molecular Weight: 456.47016
InChIKey: VFNAXGMNFCUWCI-RYUDHWBXSA-N

CHEBI:32639

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

This species takes part in one reaction (as a product in J1).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{NAPQIGSH} = v_2 \tag{15}$$

7.6 Species APAPconj_Glu

Name APAPconj_Glu

Notes **Acetaminophen glucuronide**

4-acetamidophenyl beta-D-glucopyranosiduronic acid
Metabolic product of liver metabolism of Acetaminophen (APAP). Typically about 50%

of an APAP dose ends up as the glucuronide.

Molecular Formula: C14H17NO8
Molecular Weight: 327.28668 grams/mol
InChIKey: IPROLSVTVHAQLE-BYNIDDHOSA-N

CHEBI:32636

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

This species takes part in one reaction (as a product in J3).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{APAPconj\_Glu} = v_4 \tag{16}$$

7.7 Species APAPconj_Sul

Name APAPconj_Sul

Notes Acetaminophen sulfate

4-acetamidophenyl beta-D-glucopyranosiduronic acid
Metabolic product of liver metabolism of Acetaminophen (APAP). Typically about 25% of an APAP dose ends up as the sulfate.

Also known as: Paracetamol Sulfate, N-Acetyl-4-aminophenol sulfate, N-(4-(Sulfooxy)phenyl)acetamide, Acetamide, N-(4-(sulfooxy)phenyl)-

Molecular Formula: C8H9NO5S
Molecular Weight: 231.22576
InChIKey: IGTYILLPRJOVFY-UHFFFAOYSA-N

CHEBI:32635

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

This species takes part in one reaction (as a product in J4).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{APAPconj\_Sul} = v_5 \tag{17}$$

A Glossary of Systems Biology Ontology Terms

SBO:0000017 bimolecular rate constant: Numerical parameter that quantifies the velocity of a chemical reaction involving two reactants

SBO:0000022 forward unimolecular rate constant: 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

SBO:0000027 Michaelis constant: Substrate concentration at which the velocity of reaction is half its maximum. Michaelis constant is an experimental parameter. According to the underlying molecular mechanism it can be interpreted differently in terms of microscopic constants

SBO:0000176 biochemical reaction: An event involving one or more chemical entities that modifies the electrochemical structure of at least one of the participants.

SBO:0000186 maximal velocity: Limiting maximal velocity of an enzymatic reaction, reached when the substrate is in large excess and all the enzyme is complexed.

SBO:0000201 oxidation: Chemical process during which a molecular entity loses electrons

SBO:0000210 addition of a chemical group: Covalent reaction that results in the addition of a chemical group on a molecule

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