SBML Model Report

Model name: "Bucher2011_Atorvastatin_Metabolism"

May 6, 2016

1 General Overview

This is a document in SBML Level 2 Version 4 format. This model was created by the following two authors: Lukas Endler[1] and Joachim Bucher[2] at May eleventh 2011 at 8:30 p. m. and last time modified at April eighth 2016 at five o' clock in the afternoon. 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	3
species types	0	species	18
events	0	constraints	0
reactions	29	function definitions	0
global parameters	30	unit definitions	6
rules	0	initial assignments	0

Model Notes

This is the model of atorvastatin metabolism in hepaitc cells described in the article:
A systems biology approach to dynamic modeling and inter-subject variability of statin pharmacokinetics in human hepatocytes

[1]EMBL-EBI, lukas@ebi.ac.uk
[2]Institute of Biochemical Engineering, University of Stuttgart, Stuttgart, Germany, bucher@ibvt.uni-stuttgart.de

Joachim Bucher , Stephan Riedmaier , Anke Schnabel , Katrin Marcus , Gabriele Vacun , Thomas S Weiss , Wolfgang E Thasler , Andreas K Nussler , Ulrich M Zanger and Matthias Reuss. BMC Systems Biology 2011, 5:66. DOI:10.1186/1752-0509-5-66

Abstract:
Background:
The individual character of pharmacokinetics is of great importance in the risk assessment of new drug leads in pharmacological research. Amongst others, it is severely influenced by the properties and inter-individual variability of the enzymes and transporters of the drug detoxification system of the liver. Predicting individual drug biotransformation capacity requires quantitative and detailed models.
Results:
In this contribution we present the de novo deterministic modeling of atorvastatin biotransformation based on comprehensive published knowledge on involved metabolic and transport pathways as well as physicochemical properties. The model was evaluated in primary human hepatocytes and parameter identifiability analysis was performed under multiple experimental constraints. Dynamic simulations of atorvastatin biotransformation considering the inter-individual variability of the two major involved enzymes CYP3A4 and UGT1A3 based on quantitative protein expression data in a large human liver bank (n=150) highlighted the variability in the individual biotransformation profiles and therefore also points to the individuality of pharmacokinetics.
Conclusions:
A dynamic model for the biotransformation of atorvastatin has been developed using quantitative metabolite measurements in primary human hepatocytes. The model comprises kinetics for transport processes and metabolic enzymes as well as population liver expression data allowing us to assess the impact of inter-individual variability of concentrations of key proteins. Application of computational tools for parameter sensitivity analysis enabled us to considerably improve the validity of the model and to create a consistent framework for precise computer-aided simulations in toxicology.

The model is parameterized for patient 1 and reproduces the time courses in figure 2 of the article.

2 Unit Definitions

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

2.1 Unit `time`

Name min

Definition 60 s

2.2 Unit substance

Name pmole

Definition pmol

2.3 Unit volume

Name ml

Definition ml

2.4 Unit nM

Name pmole per ml

Definition $\mathrm{pmol} \cdot \mathrm{ml}^{-1}$

2.5 Unit pmole_per_min

Name pmole per minute

Definition $\mathrm{pmol} \cdot (60\ \mathrm{s})^{-1}$

2.6 Unit ml_per_min

Name ml per minute

Definition $\mathrm{ml} \cdot (60\ \mathrm{s})^{-1}$

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
`compartment`		0000290	3	1	litre	☑	
`medium`		0000290	3	2	ml	☑	
`cell`		0000290	3	0.0142	ml	☑	

3.1 Compartment `compartment`

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

SBO:0000290 physical compartment

3.2 Compartment `medium`

This is a three dimensional compartment with a constant size of two ml.

SBO:0000290 physical compartment

3.3 Compartment `cell`

This is a three dimensional compartment with a constant size of 0.0142 ml.

SBO:0000290 physical compartment

4 Species

This model contains 18 species. 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
AS_m		medium	$\mathrm{pmol \cdot ml^{-1}}$	⊟	⊟
ASL_m		medium	$\mathrm{pmol \cdot ml^{-1}}$	⊟	⊟
ASoOH_m		medium	$\mathrm{pmol \cdot ml^{-1}}$	⊟	⊟
ASLpOH_m		medium	$\mathrm{pmol \cdot ml^{-1}}$	⊟	⊟
ASpOH_m		medium	$\mathrm{pmol \cdot ml^{-1}}$	⊟	⊟
ASLoOH_m		medium	$\mathrm{pmol \cdot ml^{-1}}$	⊟	⊟
AS_c		cell	$\mathrm{pmol \cdot ml^{-1}}$	⊟	⊟
ASL_c		cell	$\mathrm{pmol \cdot ml^{-1}}$	⊟	⊟
ASpOH_c		cell	$\mathrm{pmol \cdot ml^{-1}}$	⊟	⊟
ASoOH_c		cell	$\mathrm{pmol \cdot ml^{-1}}$	⊟	⊟
ASLpOH_c		cell	$\mathrm{pmol \cdot ml^{-1}}$	⊟	⊟
ASLoOH_c		cell	$\mathrm{pmol \cdot ml^{-1}}$	⊟	⊟
ASpOH_b		cell	$\mathrm{pmol \cdot ml^{-1}}$	⊟	⊟
ASoOH_b		cell	$\mathrm{pmol \cdot ml^{-1}}$	⊟	⊟
ASLpOH_b		cell	$\mathrm{pmol \cdot ml^{-1}}$	⊟	⊟
ASLoOH_b		cell	$\mathrm{pmol \cdot ml^{-1}}$	⊟	⊟
AS_b		cell	$\mathrm{pmol \cdot ml^{-1}}$	⊟	⊟
ASL_b		cell	$\mathrm{pmol \cdot ml^{-1}}$	⊟	⊟

5 Parameters

This model contains 30 global parameters.

Table 4: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
CYP3A4-_ASLpOH_Km1		0000027	1400.000	$\mathrm{pmol} \cdot \mathrm{ml}^{-1}$	☑
CYP3A4-_ASLoOH_Km1		0000027	3900.000	$\mathrm{pmol} \cdot \mathrm{ml}^{-1}$	☑
CYP3A4-_ASpOH_Km1		0000027	25600.000	$\mathrm{pmol} \cdot \mathrm{ml}^{-1}$	☑
CYP3A4-_ASoOH_Km1		0000027	29700.000	$\mathrm{pmol} \cdot \mathrm{ml}^{-1}$	☑
Import-_ASLpOH_k		0000009	0.034	$\mathrm{ml} \cdot (60\ \mathrm{s})^{-1}$	☑
Import-_ASLoOH_k		0000009	0.026	$\mathrm{ml} \cdot (60\ \mathrm{s})^{-1}$	☑
Import_ASL_k		0000009	0.275	$\mathrm{ml} \cdot (60\ \mathrm{s})^{-1}$	☑
fu_ASL		0000540	0.220	dimensionless	☑
fu_AS		0000540	0.220	dimensionless	☑
Import-_ASpOH_k		0000009	0.004	$\mathrm{ml} \cdot (60\ \mathrm{s})^{-1}$	☑
Export-_ASLpOH_k		0000009	0.001	$\mathrm{ml} \cdot (60\ \mathrm{s})^{-1}$	☑
Export-_ASLoOH_k		0000009	0.003	$\mathrm{ml} \cdot (60\ \mathrm{s})^{-1}$	☑
k_CR_ASL_c		0000009	$3.55 \cdot 10^{-5}$	$\mathrm{ml} \cdot (60\ \mathrm{s})^{-1}$	☑
k_CR_ASL_m		0000009	0.005	$\mathrm{ml} \cdot (60\ \mathrm{s})^{-1}$	☑
k_PON_OH_c		0000009	0.004	$\mathrm{ml} \cdot (60\ \mathrm{s})^{-1}$	☑
Export-_ASoOH_k		0000009	0.002	$\mathrm{ml} \cdot (60\ \mathrm{s})^{-1}$	☑
Prot_k1		0000009	8.520	$\mathrm{ml} \cdot (60\ \mathrm{s})^{-1}$	☑
CYP3A4-_ASoOH_Vmax		0000186	47.499	$\mathrm{pmol} \cdot (60\ \mathrm{s})^{-1}$	☑
CYP3A4-_ASLpOH_Vmax		0000186	17.445	$\mathrm{pmol} \cdot (60\ \mathrm{s})^{-1}$	☑
CYP3A4-_ASLoOH_Vmax		0000186	39.134	$\mathrm{pmol} \cdot (60\ \mathrm{s})^{-1}$	☑
UGT1A3_AS-_Vmax		0000186	13.586	$\mathrm{pmol} \cdot (60\ \mathrm{s})^{-1}$	☑

Id	Name	SBO	Value	Unit	Constant
UGT1A3_AS-_Km1		0000027	12000.000	$\mathrm{pmol} \cdot \mathrm{ml}^{-1}$	☑
UGT1A3_AS-_KI1		0000009	75000.000	$\mathrm{pmol} \cdot \mathrm{ml}^{-1}$	☑
k_PON_ASL_c		0000009	0.004	$\mathrm{ml} \cdot (60\ \mathrm{s})^{-1}$	☑
Export_AS_k		0000009	0.002	$\mathrm{ml} \cdot (60\ \mathrm{s})^{-1}$	☑
Export_ASL_k		0000009	0.022	$\mathrm{ml} \cdot (60\ \mathrm{s})^{-1}$	☑
Import_AS_k		0000009	0.020	$\mathrm{ml} \cdot (60\ \mathrm{s})^{-1}$	☑
Import-_ASoOH_k		0000009	$3.8875 \cdot 10^{-4}$	$\mathrm{ml} \cdot (60\ \mathrm{s})^{-1}$	☑
Export-_ASpOH_k		0000009	$7.9526 \cdot 10^{-4}$	$\mathrm{ml} \cdot (60\ \mathrm{s})^{-1}$	☑
CYP3A4-_ASpOH_Vmax		0000186	15.734	$\mathrm{pmol} \cdot (60\ \mathrm{s})^{-1}$	☑

6 Reactions

This model contains 29 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	Import_AS		AS_m ⟶ AS_c	0000185
2	Import_ASL		ASL_m ⟶ ASL_c	0000185
3	CYP3A4_ASpOH		AS_c $\xrightarrow{\text{ASL\_c}}$ ASpOH_c	0000176
4	CYP3A4_ASoOH		AS_c $\xrightarrow{\text{ASL\_c}}$ ASoOH_c	0000176
5	CYP3A4_ASLpOH		ASL_c $\xrightarrow{\text{AS\_c}}$ ASLpOH_c	0000176
6	CYP3A4_ASLoOH		ASL_c $\xrightarrow{\text{AS\_c}}$ ASLoOH_c	0000176
7	Export_ASoOH		ASoOH_c ⟶ ASoOH_m	0000185
8	UGT1A3_AS		AS_c ⟶ ASL_c	0000176
9	R_ASASL_c		ASL_c ⟶ AS_c	0000176
10	CR_oOH		ASLoOH_c ⟶ ASoOH_c	0000176
11	CR_pOH		ASLpOH_c ⟶ ASpOH_c	0000176
12	Export_AS		AS_c ⟶ AS_m	0000185
13	Export_ASL		ASL_c ⟶ ASL_m	0000185
14	Import_ASLpOH		ASLpOH_m ⟶ ASLpOH_c	0000185
15	Import_ASLoOH		ASLoOH_m ⟶ ASLoOH_c	0000185
16	ASpOH_Prot		ASpOH_c ⟶ ASpOH_b	0000176
17	ASoOH_Prot		ASoOH_c ⟶ ASoOH_b	0000176
18	ASLpOH_Prot		ASLpOH_c ⟶ ASLpOH_b	0000176
19	ASLoOH_Prot		ASLoOH_c ⟶ ASLoOH_b	0000176
20	AS_Prot		AS_c ⟶ AS_b	0000176
21	ASL_Prot		ASL_c ⟶ ASL_b	0000176

№	Id	Name	Reaction Equation	SBO
22	Import_ASpOH		ASpOH_m ⟶ ASpOH_c	0000185
23	R_ASASL_m		ASL_m ⟶ AS_m	0000176
24	R_pOH_m		ASLpOH_m ⟶ ASpOH_m	0000176
25	R_oOH_m		ASLoOH_m ⟶ ASoOH_m	0000176
26	Export_ASLpOH		ASLpOH_c ⟶ ASLpOH_m	0000185
27	Export_ASLoOH		ASLoOH_c ⟶ ASLoOH_m	0000185
28	Export_ASpOH		ASpOH_c ⟶ ASpOH_m	0000185
29	Import_ASoOH		ASoOH_m ⟶ ASoOH_c	0000185

6.1 Reaction Import_AS

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

SBO:0000185 transport reaction

Reaction equation

$$\mathrm{AS\_m} \longrightarrow \mathrm{AS\_c} \tag{1}$$

Reactant

Table 6: Properties of each reactant.

Id	Name	SBO
AS_m		

Product

Table 7: Properties of each product.

Id	Name	SBO
AS_c		

Kinetic Law

Derived unit $(60\ \mathrm{s})^{-1} \cdot \mathrm{pmol}$

$$v_1 = \mathrm{Import\_AS\_k} \cdot [\mathrm{AS\_m}] \tag{2}$$

6.2 Reaction Import_ASL

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

SBO:0000185 transport reaction

Reaction equation

$$\mathrm{ASL\_m} \longrightarrow \mathrm{ASL\_c} \tag{3}$$

Reactant

Table 8: Properties of each reactant.

Id	Name	SBO
ASL_m		

Product

Table 9: Properties of each product.

Id	Name	SBO
ASL_c		

Kinetic Law

Derived unit $(60\ \mathrm{s})^{-1} \cdot \mathrm{pmol}$

$$v_2 = \mathrm{Import\_ASL\_k} \cdot [\mathrm{ASL\_m}] \tag{4}$$

6.3 Reaction CYP3A4_ASpOH

This is an irreversible reaction of one reactant forming one product influenced by one modifier.

SBO:0000176 biochemical reaction

Reaction equation

$$\mathrm{AS\_c} \xrightarrow{\mathrm{ASL\_c}} \mathrm{ASpOH\_c} \tag{5}$$

Reactant

Table 10: Properties of each reactant.

Id	Name	SBO
AS_c		

Modifier

Table 11: Properties of each modifier.

Id	Name	SBO
ASL_c		

Product

Table 12: Properties of each product.

Id	Name	SBO
ASpOH_c		

Kinetic Law

Derived unit contains undeclared units

$$v_3 = \frac{\frac{\text{CYP3A4\_ASpOH\_Vmax}}{\text{CYP3A4\_ASpOH\_Km1}} \cdot [\text{AS\_c}]}{1 + \frac{[\text{AS\_c}]}{\text{CYP3A4\_ASpOH\_Km1}} + \frac{[\text{AS\_c}]}{\text{CYP3A4\_ASoOH\_Km1}} + \frac{[\text{ASL\_c}]}{\text{CYP3A4\_ASLpOH\_Km1}} + \frac{[\text{ASL\_c}]}{\text{CYP3A4\_ASLoOH\_Km1}}} \tag{6}$$

6.4 Reaction CYP3A4_ASoOH

This is an irreversible reaction of one reactant forming one product influenced by one modifier.

SBO:0000176 biochemical reaction

Reaction equation

$$\text{AS\_c} \xrightarrow{\text{ASL\_c}} \text{ASoOH\_c} \tag{7}$$

Reactant

Table 13: Properties of each reactant.

Id	Name	SBO
AS_c		

Modifier

Table 14: Properties of each modifier.

Id	Name	SBO
ASL_c		

Product

Table 15: Properties of each product.

Id	Name	SBO
ASoOH_c		

Kinetic Law

Derived unit contains undeclared units

$$v_4 = \frac{\frac{\text{CYP3A4\_ASoOH\_Vmax}}{\text{CYP3A4\_ASoOH\_Km1}} \cdot [\text{AS\_c}]}{1 + \frac{[\text{AS\_c}]}{\text{CYP3A4\_ASpOH\_Km1}} + \frac{[\text{AS\_c}]}{\text{CYP3A4\_ASoOH\_Km1}} + \frac{[\text{ASL\_c}]}{\text{CYP3A4\_ASLpOH\_Km1}} + \frac{[\text{ASL\_c}]}{\text{CYP3A4\_ASLoOH\_Km1}}} \tag{8}$$

6.5 Reaction CYP3A4_ASLpOH

This is an irreversible reaction of one reactant forming one product influenced by one modifier.

SBO:0000176 biochemical reaction

Reaction equation

$$\text{ASL\_c} \xrightarrow{\text{AS\_c}} \text{ASLpOH\_c} \tag{9}$$

Reactant

Table 16: Properties of each reactant.

Id	Name	SBO
ASL_c		

Modifier

Table 17: Properties of each modifier.

Id	Name	SBO
AS_c		

Product

Table 18: Properties of each product.

Id	Name	SBO
ASLpOH_c		

Kinetic Law

Derived unit contains undeclared units

$$v_5 = \frac{\frac{\text{CYP3A4\_ASLpOH\_Vmax}}{\text{CYP3A4\_ASLpOH\_Km1}} \cdot [\text{ASL\_c}]}{1 + \frac{[\text{AS\_c}]}{\text{CYP3A4\_ASpOH\_Km1}} + \frac{[\text{AS\_c}]}{\text{CYP3A4\_ASoOH\_Km1}} + \frac{[\text{ASL\_c}]}{\text{CYP3A4\_ASLpOH\_Km1}} + \frac{[\text{ASL\_c}]}{\text{CYP3A4\_ASLoOH\_Km1}}} \tag{10}$$

6.6 Reaction CYP3A4_ASLoOH

This is an irreversible reaction of one reactant forming one product influenced by one modifier.

SBO:0000176 biochemical reaction

Reaction equation

$$\text{ASL\_c} \xrightarrow{\text{AS\_c}} \text{ASLoOH\_c} \tag{11}$$

Reactant

Table 19: Properties of each reactant.

Id	Name	SBO
ASL_c		

Modifier

Table 20: Properties of each modifier.

Id	Name	SBO
AS_c		

Product

Table 21: Properties of each product.

Id	Name	SBO
ASLoOH_c		

Kinetic Law

Derived unit contains undeclared units

$$v_6 = \frac{\frac{\text{CYP3A4\_ASLoOH\_Vmax}}{\text{CYP3A4\_ASLoOH\_Km1}} \cdot [\text{ASL\_c}]}{1 + \frac{[\text{AS\_c}]}{\text{CYP3A4\_ASpOH\_Km1}} + \frac{[\text{AS\_c}]}{\text{CYP3A4\_ASoOH\_Km1}} + \frac{[\text{ASL\_c}]}{\text{CYP3A4\_ASLpOH\_Km1}} + \frac{[\text{ASL\_c}]}{\text{CYP3A4\_ASLoOH\_Km1}}} \tag{12}$$

6.7 Reaction Export_ASoOH

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

SBO:0000185 transport reaction

Reaction equation

$$\text{ASoOH\_c} \longrightarrow \text{ASoOH\_m} \tag{13}$$

Reactant

Table 22: Properties of each reactant.

Id	Name	SBO
ASoOH_c		

Product

Table 23: Properties of each product.

Id	Name	SBO
ASoOH_m		

Kinetic Law

Derived unit $(60\ \text{s})^{-1} \cdot \text{pmol}$

$$v_7 = \text{Export\_ASoOH\_k} \cdot [\text{ASoOH\_c}] \tag{14}$$

6.8 Reaction UGT1A3_AS

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

SBO:0000176 biochemical reaction

Reaction equation

$$\mathrm{AS\_c} \longrightarrow \mathrm{ASL\_c} \tag{15}$$

Reactant

Table 24: Properties of each reactant.

Id	Name	SBO
AS_c		

Product

Table 25: Properties of each product.

Id	Name	SBO
ASL_c		

Kinetic Law

Derived unit $10^{-12}\ \mathrm{mol} \cdot (60\ \mathrm{s})^{-1}$

$$v_8 = \frac{\mathrm{UGT1A3\_AS\_Vmax} \cdot [\mathrm{AS\_c}]}{\mathrm{UGT1A3\_AS\_Km1} + [\mathrm{AS\_c}] + \frac{[\mathrm{AS\_c}] \cdot [\mathrm{AS\_c}]}{\mathrm{UGT1A3\_AS\_KI1}}} \tag{16}$$

6.9 Reaction R_ASASL_c

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

SBO:0000176 biochemical reaction

Reaction equation

$$\mathrm{ASL\_c} \longrightarrow \mathrm{AS\_c} \tag{17}$$

Reactant

Table 26: Properties of each reactant.

Id	Name	SBO
ASL_c		

Product

Table 27: Properties of each product.

Id	Name	SBO
AS_c		

Kinetic Law

Derived unit $(60\ \mathrm{s})^{-1} \cdot \mathrm{pmol}$

$$v_9 = (\mathrm{k\_CR\_ASL\_c} + \mathrm{k\_PON\_ASL\_c}) \cdot [\mathrm{ASL\_c}] \tag{18}$$

6.10 Reaction CR_oOH

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

SBO:0000176 biochemical reaction

Reaction equation

$$\mathrm{ASLoOH\_c} \longrightarrow \mathrm{ASoOH\_c} \tag{19}$$

Reactant

Table 28: Properties of each reactant.

Id	Name	SBO
ASLoOH_c		

Product

Table 29: Properties of each product.

Id	Name	SBO
ASoOH_c		

Kinetic Law

Derived unit $(60\ \mathrm{s})^{-1} \cdot \mathrm{pmol}$

$$v_{10} = (\mathrm{k\_CR\_ASL\_c} + \mathrm{k\_PON\_OH\_c}) \cdot [\mathrm{ASLoOH\_c}] \tag{20}$$

6.11 Reaction CR_pOH

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

SBO:0000176 biochemical reaction

Reaction equation

$$\mathrm{ASLpOH\_c} \longrightarrow \mathrm{ASpOH\_c} \tag{21}$$

Reactant

Table 30: Properties of each reactant.

Id	Name	SBO
ASLpOH_c		

Product

Table 31: Properties of each product.

Id	Name	SBO
ASpOH_c		

Kinetic Law

Derived unit $(60\ \mathrm{s})^{-1} \cdot \mathrm{pmol}$

$$v_{11} = (\mathrm{k\_CR\_ASL\_c} + \mathrm{k\_PON\_OH\_c}) \cdot [\mathrm{ASLpOH\_c}] \tag{22}$$

6.12 Reaction Export_AS

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

SBO:0000185 transport reaction

Reaction equation

$$\mathrm{AS\_c} \longrightarrow \mathrm{AS\_m} \tag{23}$$

Reactant

Table 32: Properties of each reactant.

Id	Name	SBO
AS_c		

Product

Table 33: Properties of each product.

Id	Name	SBO
AS_m		

Kinetic Law

Derived unit $(60\ \mathrm{s})^{-1} \cdot \mathrm{pmol}$

$$v_{12} = \mathrm{Export\_AS\_k} \cdot [\mathrm{AS\_c}] \tag{24}$$

6.13 Reaction Export_ASL

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

SBO:0000185 transport reaction

Reaction equation

$$\mathrm{ASL\_c} \longrightarrow \mathrm{ASL\_m} \tag{25}$$

Reactant

Table 34: Properties of each reactant.

Id	Name	SBO
ASL_c		

Product

Table 35: Properties of each product.

Id	Name	SBO
ASL_m		

Kinetic Law

Derived unit $(60\ \mathrm{s})^{-1} \cdot \mathrm{pmol}$

$$v_{13} = \mathrm{Export\_ASL\_k} \cdot [\mathrm{ASL\_c}] \tag{26}$$

6.14 Reaction Import_ASLpOH

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

SBO:0000185 transport reaction

Reaction equation

$$\mathrm{ASLpOH\_m} \longrightarrow \mathrm{ASLpOH\_c} \tag{27}$$

Reactant

Table 36: Properties of each reactant.

Id	Name	SBO
ASLpOH_m		

Product

Table 37: Properties of each product.

Id	Name	SBO
ASLpOH_c		

Kinetic Law

Derived unit $(60\ \mathrm{s})^{-1} \cdot \mathrm{pmol}$

$$v_{14} = \mathrm{Import\_ASLpOH\_k} \cdot [\mathrm{ASLpOH\_m}] \tag{28}$$

6.15 Reaction Import_ASLoOH

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

SBO:0000185 transport reaction

Reaction equation

$$\text{ASLoOH\_m} \longrightarrow \text{ASLoOH\_c} \tag{29}$$

Reactant

Table 38: Properties of each reactant.

Id	Name	SBO
ASLoOH_m		

Product

Table 39: Properties of each product.

Id	Name	SBO
ASLoOH_c		

Kinetic Law

Derived unit $(60\ \text{s})^{-1} \cdot \text{pmol}$

$$v_{15} = \text{Import\_ASLoOH\_k} \cdot [\text{ASLoOH\_m}] \tag{30}$$

6.16 Reaction ASpOH_Prot

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

SBO:0000176 biochemical reaction

Reaction equation

$$\text{ASpOH\_c} \longrightarrow \text{ASpOH\_b} \tag{31}$$

Reactant

Table 40: Properties of each reactant.

Id	Name	SBO
ASpOH_c		

Product

Table 41: Properties of each product.

Id	Name	SBO
ASpOH_b		

Kinetic Law

Derived unit contains undeclared units

$$v_{16} = \text{Prot\_k1} \cdot \left(\frac{1 - \text{fu\_AS}}{\text{fu\_AS}} \cdot [\text{ASpOH\_c}] - [\text{ASpOH\_b}] \right) \tag{32}$$

6.17 Reaction ASoOH_Prot

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

SBO:0000176 biochemical reaction

Reaction equation

$$\text{ASoOH\_c} \longrightarrow \text{ASoOH\_b} \tag{33}$$

Reactant

Table 42: Properties of each reactant.

Id	Name	SBO
ASoOH_c		

Product

Table 43: Properties of each product.

Id	Name	SBO
ASoOH_b		

Id	Name	SBO

Kinetic Law

Derived unit contains undeclared units

$$v_{17} = \text{Prot\_k1} \cdot \left(\frac{1 - \text{fu\_AS}}{\text{fu\_AS}} \cdot [\text{ASoOH\_c}] - [\text{ASoOH\_b}] \right) \tag{34}$$

6.18 Reaction ASLpOH_Prot

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

SBO:0000176 biochemical reaction

Reaction equation

$$\text{ASLpOH\_c} \longrightarrow \text{ASLpOH\_b} \tag{35}$$

Reactant

Table 44: Properties of each reactant.

Id	Name	SBO
ASLpOH_c		

Product

Table 45: Properties of each product.

Id	Name	SBO
ASLpOH_b		

Kinetic Law

Derived unit contains undeclared units

$$v_{18} = \text{Prot\_k1} \cdot \left(\frac{1 - \text{fu\_ASL}}{\text{fu\_ASL}} \cdot [\text{ASLpOH\_c}] - [\text{ASLpOH\_b}] \right) \tag{36}$$

6.19 Reaction ASLoOH_Prot

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

SBO:0000176 biochemical reaction

Reaction equation

$$\text{ASLoOH\_c} \longrightarrow \text{ASLoOH\_b} \tag{37}$$

Reactant

Table 46: Properties of each reactant.

Id	Name	SBO
ASLoOH_c		

Product

Table 47: Properties of each product.

Id	Name	SBO
ASLoOH_b		

Kinetic Law

Derived unit contains undeclared units

$$v_{19} = \text{Prot\_k1} \cdot \left(\frac{1 - \text{fu\_ASL}}{\text{fu\_ASL}} \cdot [\text{ASLoOH\_c}] - [\text{ASLoOH\_b}] \right) \tag{38}$$

6.20 Reaction AS_Prot

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

SBO:0000176 biochemical reaction

Reaction equation

$$\text{AS\_c} \longrightarrow \text{AS\_b} \tag{39}$$

Reactant

Table 48: Properties of each reactant.

Id	Name	SBO
AS_c		

Product

Table 49: Properties of each product.

Id	Name	SBO
AS_b		

Kinetic Law

Derived unit contains undeclared units

$$v_{20} = \text{Prot\_k1} \cdot \left(\frac{1 - \text{fu\_AS}}{\text{fu\_AS}} \cdot [\text{AS\_c}] - [\text{AS\_b}] \right) \tag{40}$$

6.21 Reaction ASL_Prot

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

SBO:0000176 biochemical reaction

Reaction equation

$$\text{ASL\_c} \longrightarrow \text{ASL\_b} \tag{41}$$

Reactant

Table 50: Properties of each reactant.

Id	Name	SBO
ASL_c		

Product

Table 51: Properties of each product.

Id	Name	SBO
ASL_b		

Kinetic Law

Derived unit contains undeclared units

$$v_{21} = \text{Prot\_k1} \cdot \left(\frac{1 - \text{fu\_ASL}}{\text{fu\_ASL}} \cdot [\text{ASL\_c}] - [\text{ASL\_b}] \right) \tag{42}$$

6.22 Reaction Import_ASpOH

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

SBO:0000185 transport reaction

Reaction equation

$$\text{ASpOH\_m} \longrightarrow \text{ASpOH\_c} \tag{43}$$

Reactant

Table 52: Properties of each reactant.

Id	Name	SBO
ASpOH_m		

Product

Table 53: Properties of each product.

Id	Name	SBO
ASpOH_c		

Kinetic Law

Derived unit $(60\ \text{s})^{-1} \cdot \text{pmol}$

$$v_{22} = \text{Import\_ASpOH\_k} \cdot [\text{ASpOH\_m}] \tag{44}$$

6.23 Reaction R_ASASL_m

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

SBO:0000176 biochemical reaction

Reaction equation

$$\text{ASL\_m} \longrightarrow \text{AS\_m} \tag{45}$$

Reactant

Table 54: Properties of each reactant.

Id	Name	SBO
ASL_m		

Product

Table 55: Properties of each product.

Id	Name	SBO
AS_m		

Kinetic Law

Derived unit $(60\ \mathrm{s})^{-1} \cdot \mathrm{pmol}$

$$v_{23} = \mathrm{k\_CR\_ASL\_m} \cdot [\mathrm{ASL\_m}] \tag{46}$$

6.24 Reaction R_pOH_m

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

SBO:0000176 biochemical reaction

Reaction equation

$$\mathrm{ASLpOH\_m} \longrightarrow \mathrm{ASpOH\_m} \tag{47}$$

Reactant

Table 56: Properties of each reactant.

Id	Name	SBO
ASLpOH_m		

Product

Table 57: Properties of each product.

Id	Name	SBO
ASpOH_m		

Kinetic Law

Derived unit $(60\ \mathrm{s})^{-1} \cdot \mathrm{pmol}$

$$v_{24} = \mathrm{k\_CR\_ASL\_m} \cdot [\mathrm{ASLpOH\_m}] \tag{48}$$

6.25 Reaction R_oOH_m

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

SBO:0000176 biochemical reaction

Reaction equation

$$\mathrm{ASLoOH\_m} \longrightarrow \mathrm{ASoOH\_m} \tag{49}$$

Reactant

Table 58: Properties of each reactant.

Id	Name	SBO
ASLoOH_m		

Product

Table 59: Properties of each product.

Id	Name	SBO
ASoOH_m		

Kinetic Law

Derived unit $(60\ \mathrm{s})^{-1} \cdot \mathrm{pmol}$

$$v_{25} = \mathrm{k\_CR\_ASL\_m} \cdot [\mathrm{ASLoOH\_m}] \tag{50}$$

6.26 Reaction Export_ASLpOH

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

SBO:0000185 transport reaction

Reaction equation

$$\text{ASLpOH\_c} \longrightarrow \text{ASLpOH\_m} \tag{51}$$

Reactant

Table 60: Properties of each reactant.

Id	Name	SBO
ASLpOH_c		

Product

Table 61: Properties of each product.

Id	Name	SBO
ASLpOH_m		

Kinetic Law

Derived unit $(60\ \mathrm{s})^{-1} \cdot \mathrm{pmol}$

$$v_{26} = \text{Export\_ASLpOH\_k} \cdot [\text{ASLpOH\_c}] \tag{52}$$

6.27 Reaction Export_ASLoOH

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

SBO:0000185 transport reaction

Reaction equation

$$\text{ASLoOH\_c} \longrightarrow \text{ASLoOH\_m} \tag{53}$$

Reactant

Table 62: Properties of each reactant.

Id	Name	SBO
ASLoOH_c		

Product

Table 63: Properties of each product.

Id	Name	SBO
ASLoOH_m		

Kinetic Law

Derived unit $(60\ \mathrm{s})^{-1} \cdot \mathrm{pmol}$

$$v_{27} = \mathrm{Export\_ASLoOH\_k} \cdot [\mathrm{ASLoOH\_c}] \tag{54}$$

6.28 Reaction Export_ASpOH

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

SBO:0000185 transport reaction

Reaction equation

$$\mathrm{ASpOH\_c} \longrightarrow \mathrm{ASpOH\_m} \tag{55}$$

Reactant

Table 64: Properties of each reactant.

Id	Name	SBO
ASpOH_c		

Product

Table 65: Properties of each product.

Id	Name	SBO
ASpOH_m		

Kinetic Law

Derived unit $(60\ \mathrm{s})^{-1} \cdot \mathrm{pmol}$

$$v_{28} = \mathrm{Export\_ASpOH\_k} \cdot [\mathrm{ASpOH\_c}] \tag{56}$$

6.29 Reaction Import_ASoOH

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

SBO:0000185 transport reaction

Reaction equation

$$\text{ASoOH\_m} \longrightarrow \text{ASoOH\_c} \tag{57}$$

Reactant

Table 66: Properties of each reactant.

Id	Name	SBO
ASoOH_m		

Product

Table 67: Properties of each product.

Id	Name	SBO
ASoOH_c		

Kinetic Law

Derived unit $(60\ \text{s})^{-1} \cdot \text{pmol}$

$$v_{29} = \text{Import\_ASoOH\_k} \cdot [\text{ASoOH\_m}] \tag{58}$$

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 AS_m

SBO:0000298 synthetic chemical compound

Initial concentration $8797.15\ \text{pmol} \cdot \text{ml}^{-1}$

This species takes part in three reactions (as a reactant in Import_AS and as a product in Export_AS, R_ASASL_m).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{AS\_m} = v_{12} + v_{23} - v_1 \tag{59}$$

7.2 Species ASL_m

SBO:0000298 synthetic chemical compound

Initial concentration $30.56\ \mathrm{pmol \cdot ml^{-1}}$

This species takes part in three reactions (as a reactant in Import_ASL, R_ASASL_m and as a product in Export_ASL).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{ASL\_m} = v_{13} - v_2 - v_{23} \tag{60}$$

7.3 Species ASoOH_m

SBO:0000298 synthetic chemical compound

Initial concentration $0\ \mathrm{pmol \cdot ml^{-1}}$

This species takes part in three reactions (as a reactant in Import_ASoOH and as a product in Export_ASoOH, R_oOH_m).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{ASoOH\_m} = v_7 + v_{25} - v_{29} \tag{61}$$

7.4 Species ASLpOH_m

SBO:0000298 synthetic chemical compound

Initial concentration $0\ \mathrm{pmol \cdot ml^{-1}}$

This species takes part in three reactions (as a reactant in Import_ASLpOH, R_pOH_m and as a product in Export_ASLpOH).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{ASLpOH\_m} = v_{26} - v_{14} - v_{24} \tag{62}$$

7.5 Species ASpOH_m

SBO:0000298 synthetic chemical compound

Initial concentration $0\ \mathrm{pmol \cdot ml^{-1}}$

This species takes part in three reactions (as a reactant in Import_ASpOH and as a product in R_pOH_m, Export_ASpOH).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{ASpOH\_m} = v_{24} + v_{28} - v_{22} \tag{63}$$

7.6 Species ASLoOH_m

SBO:0000298 synthetic chemical compound

Initial concentration $0\ \mathrm{pmol} \cdot \mathrm{ml}^{-1}$

This species takes part in three reactions (as a reactant in Import_ASLoOH, R_oOH_m and as a product in Export_ASLoOH).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{ASLoOH\_m} = v_{27} - v_{15} - v_{25} \tag{64}$$

7.7 Species AS_c

SBO:0000298 synthetic chemical compound

Initial concentration $0\ \mathrm{pmol} \cdot \mathrm{ml}^{-1}$

This species takes part in nine reactions (as a reactant in CYP3A4_ASpOH, CYP3A4_ASoOH, UGT1A3_AS, Export_AS, AS_Prot and as a product in Import_AS, R_ASASL_c and as a modifier in CYP3A4_ASLpOH, CYP3A4_ASLoOH).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{AS\_c} = v_1 + v_9 - v_3 - v_4 - v_8 - v_{12} - v_{20} \tag{65}$$

7.8 Species ASL_c

SBO:0000298 synthetic chemical compound

Initial concentration $0\ \mathrm{pmol} \cdot \mathrm{ml}^{-1}$

This species takes part in nine reactions (as a reactant in CYP3A4_ASLpOH, CYP3A4_ASLoOH, R_ASASL_c, Export_ASL, ASL_Prot and as a product in Import_ASL, UGT1A3_AS and as a modifier in CYP3A4_ASpOH, CYP3A4_ASoOH).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{ASL\_c} = v_2 + v_8 - v_5 - v_6 - v_9 - v_{13} - v_{21} \tag{66}$$

7.9 Species ASpOH_c

SBO:0000298 synthetic chemical compound

Initial concentration $0\ \mathrm{pmol} \cdot \mathrm{ml}^{-1}$

This species takes part in five reactions (as a reactant in ASpOH_Prot, Export_ASpOH and as a product in CYP3A4_ASpOH, CR_pOH, Import_ASpOH).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{ASpOH\_c} = v_3 + v_{11} + v_{22} - v_{16} - v_{28} \tag{67}$$

7.10 Species ASoOH_c

SBO:0000298 synthetic chemical compound

Initial concentration $0\ \mathrm{pmol}\cdot\mathrm{ml}^{-1}$

This species takes part in five reactions (as a reactant in Export_ASoOH, ASoOH_Prot and as a product in CYP3A4_ASoOH, CR_oOH, Import_ASoOH).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{ASoOH\_c} = v_4 + v_{10} + v_{29} - v_7 - v_{17} \tag{68}$$

7.11 Species ASLpOH_c

SBO:0000298 synthetic chemical compound

Initial concentration $0\ \mathrm{pmol}\cdot\mathrm{ml}^{-1}$

This species takes part in five reactions (as a reactant in CR_pOH, ASLpOH_Prot, Export_ASLpOH and as a product in CYP3A4_ASLpOH, Import_ASLpOH).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{ASLpOH\_c} = v_5 + v_{14} - v_{11} - v_{18} - v_{26} \tag{69}$$

7.12 Species ASLoOH_c

SBO:0000298 synthetic chemical compound

Initial concentration $0\ \mathrm{pmol}\cdot\mathrm{ml}^{-1}$

This species takes part in five reactions (as a reactant in CR_oOH, ASLoOH_Prot, Export_ASLoOH and as a product in CYP3A4_ASLoOH, Import_ASLoOH).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{ASLoOH\_c} = v_6 + v_{15} - v_{10} - v_{19} - v_{27} \tag{70}$$

7.13 Species ASpOH_b

SBO:0000298 synthetic chemical compound

Initial concentration $0\ \mathrm{pmol}\cdot\mathrm{ml}^{-1}$

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

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{ASpOH\_b} = v_{16} \tag{71}$$

7.14 Species ASoOH_b

SBO:0000298 synthetic chemical compound

Initial concentration $0\ \mathrm{pmol}\cdot\mathrm{ml}^{-1}$

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

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{ASoOH\_b} = v_{17} \tag{72}$$

7.15 Species ASLpOH_b

SBO:0000298 synthetic chemical compound

Initial concentration $0\ \mathrm{pmol}\cdot\mathrm{ml}^{-1}$

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

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{ASLpOH\_b} = v_{18} \tag{73}$$

7.16 Species ASLoOH_b

SBO:0000298 synthetic chemical compound

Initial concentration $0\ \mathrm{pmol}\cdot\mathrm{ml}^{-1}$

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

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{ASLoOH\_b} = v_{19} \tag{74}$$

7.17 Species AS_b

SBO:0000298 synthetic chemical compound

Initial concentration $0\ \mathrm{pmol}\cdot\mathrm{ml}^{-1}$

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

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{AS\_b} = v_{20} \tag{75}$$

7.18 Species ASL_b

SBO:0000298 synthetic chemical compound

Initial concentration $0\ \mathrm{pmol}\cdot\mathrm{ml}^{-1}$

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

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{ASL\_b} = v_{21} \tag{76}$$

A Glossary of Systems Biology Ontology Terms

SBO:0000009 kinetic constant: Numerical parameter that quantifies the velocity of a chemical reaction

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

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

SBO:0000298 synthetic chemical compound: Chemical entity that is engineered by a human-designed process ex-vivo rather than a produced by a living entity

SBO:0000540 fraction of an entity pool: A ratio that represents the quantity of a defined constituent entity over the total number of all constituent entities present.

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