SBML Model Report

Model name: "Walsh2014 - Inhibition kinetics of DAPT on APP Cleavage"

October 10, 2016

1 General Overview

This is a document in SBML Level 3 Version 1 format. This model was created by Thawfeek Varusai[1] at September second 2016 at 11:09 a. m. and last time modified at October tenth 2016 at 3:39 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	2
species types	0	species	1
events	0	constraints	0
reactions	4	function definitions	4
global parameters	26	unit definitions	5
rules	4	initial assignments	0

Model Notes

Walsh2014 - Inhibition kinetics of DAPT onAPP Cleavage

This model is described in the article:Are improper kinetic models hampering drug development?Walsh R.PeerJ 2014; 2: e649

Abstract:

[1]EMBL-EBI, tvarusai@ebi.ac.uk

Reproducibility of biological data is a significant problem in research today. One potential contributor to this, which has received little attention, is the over complication of enzyme kinetic inhibition models. The over complication of inhibitory models stems from the common use of the inhibitory term (1 + [I]/Ki), an equilibrium binding term that does not distinguish between inhibitor binding and inhibitory effect. Since its initial appearance in the literature, around a century ago, the perceived mechanistic methods used in its production have spurred countless inhibitory equations. These equations are overly complex and are seldom compared to each other, which has destroyed their usefulness resulting in the proliferation and regulatory acceptance of simpler models such as IC50s for drug characterization. However, empirical analysis of inhibitory data recognizing the clear distinctions between inhibitor binding and inhibitory effect can produce simple logical inhibition models. In contrast to the common divergent practice of generating new inhibitory models for every inhibitory situation that presents itself. The empirical approach to inhibition modeling presented here is broadly applicable allowing easy comparison and rational analysis of drug interactions. To demonstrate this, a simple kinetic model of DAPT, a compound that both activates and inhibits ?-secretase is examined using excel. The empirical kinetic method described here provides an improved way of probing disease mechanisms, expanding the investigation of possible therapeutic interventions.

This model is hosted on BioModels Database and identified by: BIOMD0000000617.

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 five unit definitions.

2.1 Unit `volume`

Definition ml

2.2 Unit `substance`

Definition mmol

2.3 Unit `length`

Name length

Definition m

2.4 Unit area

Name area

Definition m^2

2.5 Unit time

Name time

Definition s

3 Compartments

This model contains two compartments.

Table 2: Properties of all compartments.

Id	Name	SBO	Spatial Dimensions	Size	Unit	Constant	Outside
default_compartment	default_compartment	0000410	3	1	litre	☑	
Compartment_	Compartment_	0000410	3	1	litre	☑	

3.1 Compartment default_compartment

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

Name default_compartment

SBO:0000410 implicit compartment

3.2 Compartment Compartment_

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

Name Compartment_

SBO:0000410 implicit compartment

4 Species

This model contains one 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
v	v	`default_compartment`	$\mathrm{mmol} \cdot \mathrm{ml}^{-1}$	⊟	⊟

5 Parameters

This model contains 26 global parameters.

Table 4: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
V1s	V1s		64.681		☐
S	S		61.000		☑
K1s	K1s		37.340		☐
V2s	V2s		32.427		☐
H1	H1		1.710		☑
K2s	K2s		126.236		☐
H2	H2		2.690		☑
K3s	K3s		605.010		☑
V2	V2		443.680		☑
V2i	V2i		0.000		☑
Ii	Ii		1000.000		☑
Hxx	Hxx		0.960		☑
Kxx1	Kxx1		70.930		☑
K2	K2		225.490		☑
K2i	K2i		118.410		☑
V1	V1		20.060		☑
V1is	V1is		451.780		☑
Hx1	Hx1		1.020		☑
Kx1	Kx1		30.180		☑
Hx2	Hx2		2.690		☑
Kx2	Kx2		553.640		☑
V1ii	V1ii		0.000		☑
K1	K1		177.760		☑
K1is	K1is		29.520		☑
K1ii	K1ii		34.050		☑
V3	V3		0.000		☑

6 Function definitions

This is an overview of four function definitions.

6.1 Function definition Function_for_R3

Name Function for R3

Arguments vol (Compartment_), H1, K2s, S, V1s

Mathematical Expression

$$\mathrm{vol}\left(\mathrm{Compartment\_}\right) \cdot \mathrm{V1s} \cdot \frac{\mathrm{S}^{\mathrm{H1}}}{\mathrm{S}^{\mathrm{H1}} + \mathrm{K2s}^{\mathrm{H1}}} \tag{1}$$

6.2 Function definition `Function_for_R4`

Name Function for R4

Arguments $\mathrm{vol}\left(\mathrm{Compartment\_}\right)$, H2, K3s, S, V2s

Mathematical Expression

$$\mathrm{vol}\left(\mathrm{Compartment\_}\right) \cdot \mathrm{V2s} \cdot \frac{\mathrm{S}^{\mathrm{H2}}}{\mathrm{S}^{\mathrm{H2}} + \mathrm{K3s}^{\mathrm{H2}}} \tag{2}$$

6.3 Function definition `Function_for_R1`

Name Function for R1

Arguments $\mathrm{vol}\left(\mathrm{Compartment\_}\right)$, K1s, S, V1s

Mathematical Expression

$$\mathrm{vol}\left(\mathrm{Compartment\_}\right) \cdot \mathrm{V1s} \cdot \frac{\mathrm{S}}{\mathrm{S} + \mathrm{K1s}} \tag{3}$$

6.4 Function definition `Function_for_R2`

Name Function for R2

Arguments $\mathrm{vol}\left(\mathrm{Compartment\_}\right)$, H1, K2s, S, V2s

Mathematical Expression

$$\mathrm{vol}\left(\mathrm{Compartment\_}\right) \cdot \mathrm{V2s} \cdot \frac{\mathrm{S}^{\mathrm{H1}}}{\mathrm{S}^{\mathrm{H1}} + \mathrm{K2s}^{\mathrm{H1}}} \tag{4}$$

7 Rules

This is an overview of four rules.

7.1 Rule `K2s`

Rule `K2s` is an assignment rule for parameter `K2s`:

$$\mathrm{K2s} = \mathrm{K2} - \left(\mathrm{K2} - \mathrm{K2i}\right) \cdot \frac{\mathrm{Ii}^{\mathrm{Hxx}}}{\mathrm{Ii}^{\mathrm{Hxx}} + \mathrm{Kxx1}^{\mathrm{Hxx}}} \tag{5}$$

7.2 Rule `V1s`

Rule `V1s` is an assignment rule for parameter `V1s`:

$$\begin{aligned} \mathrm{V1s} = \mathrm{V1} - (\mathrm{V1} - \mathrm{V1is}) \cdot \frac{\mathrm{Ii}^{\mathrm{Hx1}}}{\mathrm{Ii}^{\mathrm{Hx1}} + \mathrm{Kx1}^{\mathrm{Hx1}}} + (\mathrm{V1} - \mathrm{V1is}) \\ \cdot \frac{\mathrm{Ii}^{\mathrm{Hx2}}}{\mathrm{Ii}^{\mathrm{Hx2}} + \mathrm{Kx2}^{\mathrm{Hx2}}} - (\mathrm{V1} - \mathrm{V1ii}) \cdot \frac{\mathrm{Ii}^{\mathrm{Hx2}}}{\mathrm{Ii}^{\mathrm{Hx2}} + \mathrm{Kx2}^{\mathrm{Hx2}}} \end{aligned} \tag{6}$$

7.3 Rule `K1s`

Rule `K1s` is an assignment rule for parameter `K1s`:

$$\begin{aligned} \mathrm{K1s} = \mathrm{K1} - (\mathrm{K1} - \mathrm{K1is}) \cdot \frac{\mathrm{Ii}^{\mathrm{Hx1}}}{\mathrm{Ii}^{\mathrm{Hx1}} + \mathrm{Kx1}^{\mathrm{Hx1}}} + (\mathrm{K1} - \mathrm{K1is}) \\ \cdot \frac{\mathrm{Ii}^{\mathrm{Hx2}}}{\mathrm{Ii}^{\mathrm{Hx2}} + \mathrm{Kx2}^{\mathrm{Hx2}}} - (\mathrm{K1} - \mathrm{K1ii}) \cdot \frac{\mathrm{Ii}^{\mathrm{Hx2}}}{\mathrm{Ii}^{\mathrm{Hx2}} + \mathrm{Kx2}^{\mathrm{Hx2}}} \end{aligned} \tag{7}$$

7.4 Rule `V2s`

Rule `V2s` is an assignment rule for parameter `V2s`:

$$\mathrm{V2s} = \mathrm{V2} - (\mathrm{V2} - \mathrm{V2i}) \cdot \frac{\mathrm{Ii}^{\mathrm{Hxx}}}{\mathrm{Ii}^{\mathrm{Hxx}} + \mathrm{Kxx1}^{\mathrm{Hxx}}} \tag{8}$$

8 Reactions

This model contains four 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	R1	R1	$\emptyset \longrightarrow v$	
2	R2	R2	$\emptyset \longrightarrow v$	
3	R3	R3	$v \longrightarrow \emptyset$	
4	R4	R4	$v \longrightarrow \emptyset$	

8.1 Reaction R1

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

Name R1

Reaction equation

$$\emptyset \longrightarrow \mathrm{v} \tag{9}$$

Product

Table 6: Properties of each product.

Id	Name	SBO
v	v	

Kinetic Law

Derived unit contains undeclared units

$$v_1 = \mathrm{vol}\left(\mathrm{default\_compartment}\right) \cdot \mathrm{Function\_for\_R1}\left(\mathrm{vol}\left(\mathrm{Compartment\_}\right), \mathrm{K1s}, \mathrm{S}, \mathrm{V1s}\right) \tag{10}$$

$$\mathrm{Function\_for\_R1}\left(\mathrm{vol}\left(\mathrm{Compartment\_}\right), \mathrm{K1s}, \mathrm{S}, \mathrm{V1s}\right) = \mathrm{vol}\left(\mathrm{Compartment\_}\right) \cdot \mathrm{V1s} \cdot \frac{\mathrm{S}}{\mathrm{S} + \mathrm{K1s}} \tag{11}$$

$$\mathrm{Function\_for\_R1}\left(\mathrm{vol}\left(\mathrm{Compartment\_}\right), \mathrm{K1s}, \mathrm{S}, \mathrm{V1s}\right) = \mathrm{vol}\left(\mathrm{Compartment\_}\right) \cdot \mathrm{V1s} \cdot \frac{\mathrm{S}}{\mathrm{S} + \mathrm{K1s}} \tag{12}$$

8.2 Reaction R2

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

Name R2

Reaction equation

$$\emptyset \longrightarrow \mathrm{v} \tag{13}$$

Product

Table 7: Properties of each product.

Id	Name	SBO
v	v	

Kinetic Law

Derived unit contains undeclared units

$$v_2 = \mathrm{vol}\left(\mathrm{default\_compartment}\right) \cdot \mathrm{Function\_for\_R2}\left(\mathrm{vol}\left(\mathrm{Compartment\_}\right), \mathrm{H1}, \mathrm{K2s}, \mathrm{S}, \mathrm{V2s}\right) \quad (14)$$

$$\begin{aligned} &\mathrm{Function\_for\_R2}\left(\mathrm{vol}\left(\mathrm{Compartment\_}\right), \mathrm{H1}, \mathrm{K2s}, \mathrm{S}, \mathrm{V2s}\right) \\ &= \mathrm{vol}\left(\mathrm{Compartment\_}\right) \cdot \mathrm{V2s} \cdot \frac{\mathrm{S}^{\mathrm{H1}}}{\mathrm{S}^{\mathrm{H1}} + \mathrm{K2s}^{\mathrm{H1}}} \end{aligned} \quad (15)$$

$$\begin{aligned} &\mathrm{Function\_for\_R2}\left(\mathrm{vol}\left(\mathrm{Compartment\_}\right), \mathrm{H1}, \mathrm{K2s}, \mathrm{S}, \mathrm{V2s}\right) \\ &= \mathrm{vol}\left(\mathrm{Compartment\_}\right) \cdot \mathrm{V2s} \cdot \frac{\mathrm{S}^{\mathrm{H1}}}{\mathrm{S}^{\mathrm{H1}} + \mathrm{K2s}^{\mathrm{H1}}} \end{aligned} \quad (16)$$

8.3 Reaction R3

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

Name R3

Reaction equation

$$\mathrm{v} \longrightarrow \emptyset \quad (17)$$

Reactant

Table 8: Properties of each reactant.

Id	Name	SBO
v	v	

Kinetic Law

Derived unit contains undeclared units

$$v_3 = \mathrm{vol}\left(\mathrm{default\_compartment}\right) \cdot \mathrm{Function\_for\_R3}\left(\mathrm{vol}\left(\mathrm{Compartment\_}\right), \mathrm{H1}, \mathrm{K2s}, \mathrm{S}, \mathrm{V1s}\right) \quad (18)$$

$$\begin{aligned}&\text{Function\_for\_R3}\left(\text{vol}\left(\text{Compartment\_}\right),\text{H1},\text{K2s},\text{S},\text{V1s}\right)\\&=\text{vol}\left(\text{Compartment\_}\right)\cdot\text{V1s}\cdot\frac{\text{S}^{\text{H1}}}{\text{S}^{\text{H1}}+\text{K2s}^{\text{H1}}}\end{aligned}\tag{19}$$

$$\begin{aligned}&\text{Function\_for\_R3}\left(\text{vol}\left(\text{Compartment\_}\right),\text{H1},\text{K2s},\text{S},\text{V1s}\right)\\&=\text{vol}\left(\text{Compartment\_}\right)\cdot\text{V1s}\cdot\frac{\text{S}^{\text{H1}}}{\text{S}^{\text{H1}}+\text{K2s}^{\text{H1}}}\end{aligned}\tag{20}$$

8.4 Reaction R4

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

Name R4

Reaction equation

$$\text{v}\longrightarrow\emptyset\tag{21}$$

Reactant

Table 9: Properties of each reactant.

Id	Name	SBO
v	v	

Kinetic Law

Derived unit contains undeclared units

$$v_4=\text{vol}\left(\text{default\_compartment}\right)\cdot\text{Function\_for\_R4}\left(\text{vol}\left(\text{Compartment\_}\right),\text{H2},\text{K3s},\text{S},\text{V2s}\right)\tag{22}$$

$$\begin{aligned}&\text{Function\_for\_R4}\left(\text{vol}\left(\text{Compartment\_}\right),\text{H2},\text{K3s},\text{S},\text{V2s}\right)\\&=\text{vol}\left(\text{Compartment\_}\right)\cdot\text{V2s}\cdot\frac{\text{S}^{\text{H2}}}{\text{S}^{\text{H2}}+\text{K3s}^{\text{H2}}}\end{aligned}\tag{23}$$

$$\begin{aligned}&\text{Function\_for\_R4}\left(\text{vol}\left(\text{Compartment\_}\right),\text{H2},\text{K3s},\text{S},\text{V2s}\right)\\&=\text{vol}\left(\text{Compartment\_}\right)\cdot\text{V2s}\cdot\frac{\text{S}^{\text{H2}}}{\text{S}^{\text{H2}}+\text{K3s}^{\text{H2}}}\end{aligned}\tag{24}$$

9 Derived Rate Equation

When interpreted as an ordinary differential equation framework, this model implies the following set of equations for the rate of change of the following 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 v

Name v

SBO:0000268 enzymatic rate law

Notes `Rate of APP cleavage in the presence of DAPT`

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

This species takes part in four reactions (as a reactant in R3, R4 and as a product in R1, R2).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{v} = v_1 + v_2 - v_3 - v_4 \tag{25}$$

A Glossary of Systems Biology Ontology Terms

SBO:0000268 enzymatic rate law: Enzyme kinetics is the study of the rates of chemical reactions that are catalysed by enzymes, how this rate is controlled, and how drugs and poisons can inhibit its activity.

SBO:0000410 implicit compartment: A compartment whose existence is inferred due to the presence of known material entities which must be bounded, allowing the creation of material entity pools

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