SBML Model Report

Model name: “Das2010 - Effect of a gamma-secretase inhibitor on Amyloid-beta dynamics”

May 6, 2016

1 General Overview

This is a document in SBML Level 2 Version 4 format. This model was created by Audald Lloret i Villas[1] at September 23rd 2014 at 11:29 a. m. and last time modified at April eighth 2016 at 5:42 p. 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	2
species types	0	species	2
events	0	constraints	0
reactions	0	function definitions	0
global parameters	17	unit definitions	3
rules	5	initial assignments	0

Model Notes

Das2010 - Effect of a gamma-secretaseinhibitor on Amyloid-beta dynamics

This model is described in the article:Modeling effect of a ?-secretase inhibitor on amyloid-? dynamics reveals significant role of an amyloid clearance mechanism.Das R, Nachbar RB,

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Edelstein-Keshet L, Saltzman JS, Wiener MC, Bagchi A, Bailey J, Coombs D, Simon AJ, Hargreaves RJ, Cook JJ.Bull. Math. Biol. 2011 Jan; 73(1): 230-247

Abstract:

Aggregation of the small peptide amyloid beta (A?) into oligomers and fibrils in the brain is believed to be a precursor to Alzheimer's disease. A? is produced via multiple proteolytic cleavages of amyloid precursor protein (APP), mediated by the enzymes ?- and ?-secretase. In this study, we examine the temporal dynamics of soluble (unaggregated) A? in the plasma and cerebral-spinal fluid (CSF) of rhesus monkeys treated with different oral doses of a ?-secretase inhibitor. A dose-dependent reduction of A? concentration was observed within hours of drug ingestion, for all doses tested. A? concentration in the CSF returned to its predrug level over the monitoring period. In contrast, A? concentration in the plasma exhibited an unexpected overshoot to as high as 200% of the predrug concentration, and this overshoot persisted as late as 72 hours post-drug ingestion. To account for these observations, we proposed and analyzed a minimal physiological model for A? dynamics that could fit the data. Our analysis suggests that the overshoot arises from the attenuation of an A? clearance mechanism, possibly due to the inhibitor. Our model predicts that the efficacy of A? clearance recovers to its basal (pretreatment) value with a characteristic time of >48 hours, matching the time-scale of the overshoot. These results point to the need for a more detailed investigation of soluble A? clearance mechanisms and their interaction with A?-reducing drugs.

This model is hosted on BioModels Database and identified by: BIOMD0000000551.

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 of which two are predefined by SBML and not mentioned in the model.

2.1 Unit `volume`

Name volume

Definition ml

2.2 Unit `time`

Name time

Definition 3600 s

2.3 Unit substance

Name substance

Definition mmol

2.4 Unit area

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

Definition m^2

2.5 Unit length

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

Definition m

3 Compartments

This model contains two compartments.

Table 2: Properties of all compartments.

Id	Name	SBO	Spatial Dimensions	Size	Unit	Constant	Outside
CSF	CSF		3	1	litre	☑	
Plasma	Plasma		3	1	litre	☑	

3.1 Compartment CSF

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

Name CSF

3.2 Compartment Plasma

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

Name Plasma

4 Species

This model contains two species. The boundary condition of two of these species is set to `true` so that these 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
`C`	C	`CSF`	$\mathrm{mmol} \cdot \mathrm{ml}^{-1}$	⊟	☑
`P`	P	`Plasma`	$\mathrm{mmol} \cdot \mathrm{ml}^{-1}$	⊟	☑

5 Parameters

This model contains 17 global parameters.

Table 4: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
l	l		1.000		☐
Sc	Sc		1.160		☑
g_t	g(t)		0.000		☐
Ki	Ki		0.023		☑
k1	k1		1.130		☑
J	J		0.000		☑
r	r		0.430		☑
deltap	deltap		0.550		☑
epsilon	epsilon		0.021		☑
alpha	alpha		0.522		☑
f_t	f(t)		0.000		☐
aplasma	aplasma		187.000		☑
bplasma	bplasma		0.089		☑
tauplasma	tauplasma		1.660		☑
aCSF	aCSF		4.920		☑
bCSF	bCSF		0.259		☑
tauCSF	tauCSF		2.060		☑

6 Rules

This is an overview of five rules.

6.1 Rule g_t

Rule g_t is an assignment rule for parameter g_t:

$$\mathrm{g\_t} = \begin{cases} \dfrac{\mathrm{time}}{\mathrm{tauCSF}} \cdot \mathrm{aCSF} \cdot \exp\left(\mathrm{bCSF} \cdot \mathrm{tauCSF}\right) & \text{if time} < \mathrm{tauCSF} \\ \mathrm{aCSF} \cdot \exp\left(\mathrm{bCSF} \cdot \mathrm{time}\right) & \text{otherwise} \end{cases} \tag{1}$$

6.2 Rule f_t

Rule f_t is an assignment rule for parameter f_t:

$$\mathrm{f\_t} = \begin{cases} \dfrac{\mathrm{time}}{\mathrm{tauplasma}} \cdot \mathrm{aplasma} \cdot \exp\left(\mathrm{bplasma} \cdot \mathrm{tauplasma}\right) & \text{if time} < \mathrm{tauplasma} \\ \mathrm{aplasma} \cdot \exp\left(\mathrm{bplasma} \cdot \mathrm{time}\right) & \text{otherwise} \end{cases} \tag{2}$$

6.3 Rule C

Rule C is a rate rule for species C:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{C} = \frac{\mathrm{Sc}}{1 + \frac{\mathrm{g\_t}}{\mathrm{Ki}}} - \mathrm{k1} \cdot [\mathrm{C}] + \mathrm{J} \tag{3}$$

6.4 Rule P

Rule P is a rate rule for species P:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{P} = \mathrm{k1} \cdot \mathrm{r} \cdot [\mathrm{C}] - \mathrm{J} \cdot \mathrm{r} - \mathrm{deltap} \cdot [\mathrm{P}] \cdot \mathrm{l} \tag{4}$$

6.5 Rule l

Rule l is a rate rule for parameter l:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{l} = \mathrm{epsilon} \cdot \left(\frac{1}{1 + \mathrm{alpha} \cdot \mathrm{f\_t}} - \mathrm{l} \right) \tag{5}$$

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 C

Name C

Notes Abeta concentration in CSF

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

Involved in rule C

One rule determines the species' quantity.

7.2 Species P

Name P

Notes Abeta concentration in plasma

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

Involved in rule P

One rule determines the species' quantity.

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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