SBML Model Report

Model name: "Lockwood2006 - Alzheimer's Disease PBPK model"

May 17, 2018

1 General Overview

This is a document in SBML Level 2 Version 4 format. This model was created by the following two authors: Matthew Grant Roberts[1] and James Lawson[2] at February twelveth 2018 at 12:01 a. m. and last time modified at February 14th 2018 at 3:38 p. m. Table 1 provides 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	0
events	0	constraints	0
reactions	0	function definitions	0
global parameters	29	unit definitions	2
rules	15	initial assignments	0

Model Notes

Lockwood2006 - AlzheimersDisease PBPKmodelA mathematical model to predict theeffectiveness of CI-1017 (muscarinic agonist) for Alzheimer'sdisease by evaluating changes in ADAS-cog score.

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This model is described in the article:Application of clinical trial simulation to compare proof-of-concept study designs for drugs with a slow onset of effect; an example in Alzheimer's disease.Lockwood P, Ewy W, Hermann D, Holford N.Pharm. Res. 2006 Sep; 23(9): 2050-2059

Abstract:

OBJECTIVE: Clinical trial simulation (CTS) was used to select a robust design to test the hypothesis that a new treatment was effective for Alzheimer's disease (AD). Typically, a parallel group, placebo controlled, 12-week trial in 200-400 AD patients would be used to establish drug effect relative to placebo (i.e., Ho: Drug Effect = 0). We evaluated if a crossover design would allow smaller and shorter duration trials. MATERIALS AND METHODS: A family of plausible drug and disease models describing the time course of the AD assessment scale (ADAS-Cog) was developed based on Phase I data and literature reports of other treatments for AD. The models included pharmacokinetic, pharmacodynamic, disease progression, and placebo components. Eight alternative trial designs were explored via simulation. One hundred replicates of each combination of drug and disease model and trial design were simulated. A 'positive trial' reflecting drug activity was declared considering both a dose trend test ($p < 0.05$) and pair-wise comparisons to placebo ($p < 0.025$). RESULTS: A 4 x 4 Latin Square design was predicted to have at least 80% power to detect activity across a range of drug and disease models. The trial design was subsequently implemented and the trial was completed. Based on the results of the actual trial, a conclusive decision about further development was taken. The crossover design provided enhanced power over a parallel group design due to the lower residual variability. CONCLUSION: CTS aided the decision to use a more efficient proof of concept trial design, leading to savings of up to US 4 M dollars in direct costs and a firm decision 8-12 months earlier than a 12-week parallel group trial.

This model is hosted on BioModels Database and identified by: BIOMD0000000673.

To cite BioModels Database, please use: Chelliah V et al. BioModels: ten-year anniversary. Nucl. Acids Res. 2015, 43(Database issue):D542-8.

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2 Unit Definitions

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

2.1 Unit `volume`

Name volume

Definition ml

2.2 Unit `substance`

Name substance

Definition mmol

2.3 Unit `area`

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

Definition m^2

2.4 Unit `length`

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

Definition m

2.5 Unit `time`

Notes Second is the predefined SBML unit for `time`.

Definition s

3 Compartment

This model contains one compartment.

Table 2: Properties of all compartments.

Id	Name	SBO	Spatial Dimensions	Size	Unit	Constant	Outside
`Compartment`	Compartment		3	1	litre	☑	

3.1 Compartment `Compartment`

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

Name Compartment

4 Parameters

This model contains 29 global parameters.

Table 3: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
S0	S0		30.000		☑
alpha	alpha		0.016		☑
MODEL_TIME	MODEL_TIME		1.000		☑
PD_CeP	PD_CeP		−0.311		☐
PD_CeA	PD_CeA		−2.003		☐
epsilon	epsilon		0.000		☑
S	S		27.702		☐
Beta_P	Beta_P		−3.000		☑
Keq_P	Keq_P		0.116		☐
Kel_P	Kel_P		0.099		☐
t_half_eq	t_half_eq		6.000		☑
t_half_el	t_half_el		7.000		☑
Beta_A	Beta_A		−0.047		☑
CeA	CeA		25.000		☑
ECeA_50	ECeA_50		21.000		☑
Emax	Emax		−3.000		☐
n	n		4.000		☐
CeA_U	CeA_U		0.000		☐
ICea_U	ICea_U		0.000		☐
ECea_U50	ECea_U50		18.000		☑
ICea_U50	ICea_U50		38.000		☑
MODEL_TYPE	MODEL_TYPE		3.000		☑
ANT_AGONIST-_COMBINATION	ANT_AGONIST-_COMBINATION		0.000		☑
Model-_Inactive	Model_Inactive		0.000		☐
Model-_active-_Linear	Model_active-_Linear		−1.175		☐
Model-_active-_Hyperbolic	Model_active-_Hyperbolic		−1.630		☐
Model-_active-_Sigmoidal	Model_active-_Sigmoidal		−2.003		☐
Model-_active_U-_Shaped	Model_active_U-_Shaped		0.000		☐
ADAS_COG_P	ADAS_COG_P		−0.311		☐

5 Rules

This is an overview of 15 rules.

5.1 Rule `Keq_P`

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

$$\mathrm{Keq\_P} = \frac{\ln 2}{\mathrm{t\_half\_eq}} \tag{1}$$

5.2 Rule `Kel_P`

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

$$\mathrm{Kel\_P} = \frac{\ln 2}{\mathrm{t\_half\_el}} \tag{2}$$

5.3 Rule `Emax`

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

$$\mathrm{Emax} = \begin{cases} 4 & \text{if MODEL\_TYPE} = 2 \\ \begin{cases} 3 & \text{if MODEL\_TYPE} = 3 \\ \begin{cases} 6 & \text{if MODEL\_TYPE} = 4 \\ 0 & \text{otherwise} \end{cases} & \text{otherwise} \end{cases} & \text{otherwise} \end{cases} \tag{3}$$

5.4 Rule `n`

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

$$\mathrm{n} = \begin{cases} 4 & \text{if MODEL\_TYPE} = 3 \\ \begin{cases} 3 & \text{if MODEL\_TYPE} = 4 \\ 0 & \text{otherwise} \end{cases} & \text{otherwise} \end{cases} \tag{4}$$

5.5 Rule `CeA_U`

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

$$\mathrm{CeA\_U} = \begin{cases} \begin{cases} 0 \cdot \mathrm{CeA} & \text{if ANT\_AGONIST\_COMBINATION} = 0 \\ \begin{cases} 0 \cdot \mathrm{CeA} & \text{if ANT\_AGONIST\_COMBINATION} = 2 \\ 0 & \text{otherwise} \end{cases} & \text{otherwise} \end{cases} & \text{if MOD} \\ 0 & \text{otherwi} \end{cases} \tag{5}$$

5.6 Rule `ICea_U`

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

$$\text{ICea\_U} = \begin{cases} \begin{cases} 0 \cdot \text{CeA} & \text{if ANT\_AGONIST\_COMBINATION} = 1 \\ \begin{cases} 0 \cdot \text{CeA} & \text{if ANT\_AGONIST\_COMBINATION} = 2 \\ 0 & \text{otherwise} \end{cases} & \text{otherwise} \end{cases} & \text{if MOD} \\ 0 & \text{otherwi} \end{cases} \tag{6}$$

5.7 Rule `Model_Inactive`

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

$$\text{Model\_Inactive} = 0 \cdot \text{CeA} \tag{7}$$

5.8 Rule `Model_active_Linear`

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

$$\text{Model\_active\_Linear} = \text{Beta\_A} \cdot \text{CeA} \tag{8}$$

5.9 Rule `Model_active_Hyperbolic`

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

$$\text{Model\_active\_Hyperbolic} = \frac{\text{Emax} \cdot \text{CeA}}{\text{ECeA\_50} + \text{CeA}} \tag{9}$$

5.10 Rule `Model_active_Sigmoidal`

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

$$\text{Model\_active\_Sigmoidal} = \frac{\text{Emax} \cdot \text{CeA}^{\text{n}}}{\text{ECeA\_50}^{\text{n}} + \text{CeA}^{\text{n}}} \tag{10}$$

5.11 Rule `Model_active_U_Shaped`

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

$$\text{Model\_active\_U\_Shaped} = \text{Emax} \cdot \left(\frac{\text{CeA\_U}^{\text{n}}}{\text{ECea\_U50}^{\text{n}} + \text{CeA\_U}^{\text{n}}} - \frac{\text{ICea\_U}^{\text{n}}}{\text{ICea\_U50}^{\text{n}} + \text{ICea\_U}^{\text{n}}} \right) \tag{11}$$

5.12 Rule PD_CeA

Rule PD_CeA is an assignment rule for parameter PD_CeA:

$$\text{PD\_CeA} = \begin{cases} \text{Model\_Inactive} & \text{if MODEL\_TYPE} = 1 \\ \text{Model\_active\_Linear} & \text{if MODEL\_TYPE} = 2 \\ \text{Model\_active\_Hyperbolic} & \text{if MODEL\_TYPE} = 3 \\ \text{Model\_active\_Sigmoidal} & \text{if MODEL\_TYPE} = 4 \\ \begin{cases} \text{Model\_active\_U\_Shaped} & \text{if MODEL\_TYPE} = 4 \\ 0 & \text{otherwise} \end{cases} & \text{otherwise} \end{cases} \tag{12}$$

5.13 Rule ADAS_COG_P

Rule ADAS_COG_P is an assignment rule for parameter ADAS_COG_P:

$$\text{ADAS\_COG\_P} = \frac{\text{Beta\_P} \cdot \text{Keq\_P}}{\text{Keq\_P} - \text{Kel\_P}} \cdot \left(\exp\left(1 \cdot \text{Kel\_P} \cdot \text{MODEL\_TIME}\right) - \exp\left(1 \cdot \text{Keq\_P} \cdot \text{MODEL\_TIME}\right)\right) \tag{13}$$

5.14 Rule PD_CeP

Rule PD_CeP is an assignment rule for parameter PD_CeP:

$$\text{PD\_CeP} = \text{ADAS\_COG\_P} \tag{14}$$

5.15 Rule S

Rule S is an assignment rule for parameter S:

$$\text{S} = \text{S0} + \text{alpha} \cdot \text{MODEL\_TIME} + \text{PD\_CeP} + \text{PD\_CeA} + \text{epsilon} \tag{15}$$

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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