SBML Model Report

Model name: “Cloutier2012 - Feedback motif for Parkinson’s disease”

May 5, 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 November 26th 2014 at 11:29 a. m. and last time modified at December twelveth 2014 at 3:08 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	1
species types	0	species	2
events	0	constraints	0
reactions	4	function definitions	3
global parameters	8	unit definitions	3
rules	1	initial assignments	0

Model Notes

Cloutier2012 - Feedback motif for Parkinson’sdisease

This model is described in the article:Feedback motif for the pathogenesis of Parkinson’s disease.Cloutier M, Middleton R, Wellstead P.IET Syst Biol 2012 Jun; 6(3): 86-93

Abstract:

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Previous article on the integrative modelling of Parkinson's disease (PD) described a mathematical model with properties suggesting that PD pathogenesis is associated with a feedback-induced biochemical bistability. In this article, the authors show that the dynamics of the mathematical model can be extracted and distilled into an equivalent two-state feedback motif whose stability properties are controlled by multi-factorial combinations of risk factors and genetic mutations associated with PD. Based on this finding, the authors propose a principle for PD pathogenesis in the form of the switch-like transition of a bistable feedback process from 'healthy' homeostatic levels of reactive oxygen species and the protein ?-synuclein, to an alternative 'disease' state in which concentrations of both molecules are stable at the damagingly high-levels associated with PD. The bistability is analysed using the rate curves and steady-state response characteristics of the feedback motif. In particular, the authors show how a bifurcation in the feedback motif marks the pathogenic moment at which the 'healthy' state is lost and the 'disease' state is initiated. Further analysis shows how known risks (such as: age, toxins and genetic predisposition) modify the stability characteristics of the feedback motif in a way that is compatible with known features of PD, and which explain properties such as: multi-factorial causality, variability in susceptibility and severity, multi-timescale progression and the special cases of familial Parkinson's and Parkinsonian symptoms induced purely by toxic stress.Stress of 2.6 obtained by optimization(parameter S1) was imposed between days 10 and 150 in order toreproduce the Figure.

This model is hosted on BioModels Database and identified by: BIOMD0000000558.

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 86400 s

2.3 Unit substance

Name substance

Definition µmol

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 Compartment

This model contains one compartment.

Table 2: Properties of all compartments.

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

3.1 Compartment Neuron

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

Name Neuron

Notes Type cell: Neuron

4 Species

This model contains two 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
`ROS`	ROS	`Neuron`	$\mu mol \cdot ml^{-1}$	⊟	⊟
`alpha_syn`	alpha-syn	`Neuron`	$\mu mol \cdot ml^{-1}$	⊟	⊟

5 Parameters

This model contains eight global parameters.

Table 4: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k1	k1		17280.000		☑
k2	k2		17280.000		☑
k3	k3		0.168		☑
k4	k4		0.168		☑
dalphasyn	dalphasyn		15.000		☑
kalphasyn	kalphasyn		8.500		☑
S1	S1		0.000		☐
S2_4	S2-4		1.000		☑

6 Function definitions

This is an overview of three function definitions.

6.1 Function definition V2_4

Name V2-4

Arguments k, S, Sx

Mathematical Expression

$$k \cdot S \cdot Sx \tag{1}$$

6.2 Function definition V3

Name V3

Arguments k, S, Sx

Mathematical Expression

$$k \cdot S \cdot Sx \tag{2}$$

6.3 Function definition V1

Name V1

Arguments k1, Sx, d, S, k2

Mathematical Expression

$$\mathrm{k1} \cdot \left(1 + \mathrm{Sx} + \mathrm{d} \cdot \frac{\left(\frac{\mathrm{S}}{\mathrm{k2}}\right)^4}{1 + \left(\frac{\mathrm{S}}{\mathrm{k2}}\right)^4}\right) \tag{3}$$

7 Rule

This is an overview of one rule.

7.1 Rule S1

Rule S1 is an assignment rule for parameter S1:

$$\mathrm{S1} = \begin{cases} 2.6 & \text{if } (\mathrm{time} > 10) \land (\mathrm{time} < 150) \\ 0 & \text{otherwise} \end{cases} \tag{4}$$

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	ROS_1	ROS 1	$\emptyset \xrightarrow{\text{alpha\_syn, alpha\_syn}} \text{ROS}$	
2	ROS_2	ROS 2	$\text{ROS} \xrightarrow{\text{ROS}} \emptyset$	
3	aSyn_1	aSyn 1	$\emptyset \xrightarrow{\text{ROS, ROS}} \text{alpha\_syn}$	
4	aSyn_2	aSyn 2	$\text{alpha\_syn} \xrightarrow{\text{alpha\_syn}} \emptyset$	

8.1 Reaction ROS_1

This is an irreversible reaction of no reactant forming one product influenced by two modifiers.

Name ROS 1

Reaction equation

$$\emptyset \xrightarrow{\text{alpha\_syn, alpha\_syn}} \text{ROS} \tag{5}$$

Modifiers

Table 6: Properties of each modifier.

Id	Name	SBO
alpha_syn	alpha-syn	
alpha_syn	alpha-syn	

Product

Table 7: Properties of each product.

Id	Name	SBO
ROS	ROS	

Kinetic Law

Derived unit contains undeclared units

$$v_1 = \text{vol}\left(\text{Neuron}\right) \cdot \text{V1}\left(\text{k1}, \text{S1}, \text{dalphasyn}, [\text{alpha\_syn}], \text{kalphasyn}\right) \tag{6}$$

$$\text{V1}\left(\text{k1}, \text{Sx}, \text{d}, \text{S}, \text{k2}\right) = \text{k1} \cdot \left(1 + \text{Sx} + \text{d} \cdot \frac{\left(\frac{\text{S}}{\text{k2}}\right)^4}{1 + \left(\frac{\text{S}}{\text{k2}}\right)^4}\right) \tag{7}$$

$$\text{V1}\left(\text{k1}, \text{Sx}, \text{d}, \text{S}, \text{k2}\right) = \text{k1} \cdot \left(1 + \text{Sx} + \text{d} \cdot \frac{\left(\frac{\text{S}}{\text{k2}}\right)^4}{1 + \left(\frac{\text{S}}{\text{k2}}\right)^4}\right) \tag{8}$$

8.2 Reaction ROS_2

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

Name ROS 2

Reaction equation

$$\mathrm{ROS} \xrightarrow{\mathrm{ROS}} \emptyset \tag{9}$$

Reactant

Table 8: Properties of each reactant.

Id	Name	SBO
ROS	ROS	

Modifier

Table 9: Properties of each modifier.

Id	Name	SBO
ROS	ROS	

Kinetic Law

Derived unit contains undeclared units

$$v_2 = \mathrm{vol}\,(\mathrm{Neuron}) \cdot \mathrm{V2\_4}\,(\mathrm{k2}, [\mathrm{ROS}], \mathrm{S2\_4}) \tag{10}$$

$$\mathrm{V2\_4}\,(\mathrm{k}, \mathrm{S}, \mathrm{Sx}) = \mathrm{k} \cdot \mathrm{S} \cdot \mathrm{Sx} \tag{11}$$

$$\mathrm{V2\_4}\,(\mathrm{k}, \mathrm{S}, \mathrm{Sx}) = \mathrm{k} \cdot \mathrm{S} \cdot \mathrm{Sx} \tag{12}$$

8.3 Reaction aSyn_1

This is an irreversible reaction of no reactant forming one product influenced by two modifiers.

Name aSyn 1

Reaction equation

$$\emptyset \xrightarrow{\mathrm{ROS},\ \mathrm{ROS}} \mathrm{alpha\_syn} \tag{13}$$

Modifiers

Table 10: Properties of each modifier.

Id	Name	SBO
ROS	ROS	
ROS	ROS	

Product

Table 11: Properties of each product.

Id	Name	SBO
alpha_syn	alpha-syn	

Kinetic Law

Derived unit contains undeclared units

$$v_3 = \mathrm{vol}\left(\mathrm{Neuron}\right) \cdot \mathrm{V3}\left(\mathrm{k3}, [\mathrm{ROS}], \mathrm{S2\_4}\right) \tag{14}$$

$$\mathrm{V3}\left(\mathrm{k}, \mathrm{S}, \mathrm{Sx}\right) = \mathrm{k} \cdot \mathrm{S} \cdot \mathrm{Sx} \tag{15}$$

$$\mathrm{V3}\left(\mathrm{k}, \mathrm{S}, \mathrm{Sx}\right) = \mathrm{k} \cdot \mathrm{S} \cdot \mathrm{Sx} \tag{16}$$

8.4 Reaction aSyn_2

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

Name aSyn 2

Reaction equation

$$\mathrm{alpha\_syn} \xrightarrow{\mathrm{alpha\_syn}} \emptyset \tag{17}$$

Reactant

Table 12: Properties of each reactant.

Id	Name	SBO
alpha_syn	alpha-syn	

Modifier

Table 13: Properties of each modifier.

Id	Name	SBO
alpha_syn	alpha-syn	

Kinetic Law

Derived unit contains undeclared units

$$v_4 = \mathrm{vol}\,(\mathrm{Neuron}) \cdot \mathrm{V2\_4}\,(\mathrm{k4}, [\mathrm{alpha\_syn}], \mathrm{S2\_4}) \tag{18}$$

$$\mathrm{V2\_4}\,(\mathrm{k}, \mathrm{S}, \mathrm{Sx}) = \mathrm{k} \cdot \mathrm{S} \cdot \mathrm{Sx} \tag{19}$$

$$\mathrm{V2\_4}\,(\mathrm{k}, \mathrm{S}, \mathrm{Sx}) = \mathrm{k} \cdot \mathrm{S} \cdot \mathrm{Sx} \tag{20}$$

9 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.

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 ROS

Name ROS

Notes `Reactive oxygen species`

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

This species takes part in five reactions (as a reactant in ROS_2 and as a product in ROS_1 and as a modifier in ROS_2, aSyn_1, aSyn_1).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{ROS} = v_1 - v_2 \tag{21}$$

9.2 Species alpha_syn

Name alpha-syn

Notes Misfolded alpha-synuclein

Initial concentration $1\ \mu\text{mol} \cdot \text{ml}^{-1}$

This species takes part in five reactions (as a reactant in aSyn_2 and as a product in aSyn_1 and as a modifier in ROS_1, ROS_1, aSyn_2).

$$\frac{\mathrm{d}}{\mathrm{d}t}\text{alpha\_syn} = v_3 - v_4 \tag{22}$$

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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