SBML Model Report

Model name: “Morris2009 - -Synuclein aggregation variable temperature and pH”

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 January 16th 2015 at 4:30 p. m. and last time modified at January 23rd 2015 at 4:57 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	1
species types	0	species	2
events	0	constraints	0
reactions	2	function definitions	0
global parameters	4	unit definitions	3
rules	2	initial assignments	0

Model Notes

Morris2008 - Fitting protein aggregation datavia F-W 2-step mechanism

This model is described in the article:Fitting neurological protein aggregation kinetic data via a 2-step, minimal/„Ockham’s razor„ model: the Finke-Watzky mechanism of nucleation followed by autocatalytic surface growth.Morris AM, Watzky MA, Agar JN, Finke RG.Biochemistry 2008 Feb; 47(8): 2413-2427

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Abstract:

The aggregation of proteins has been hypothesized to be an underlying cause of many neurological disorders including Alzheimer's, Parkinson's, and Huntington's diseases; protein aggregation is also important to normal life function in cases such as G to F-actin, glutamate dehydrogenase, and tubulin and flagella formation. For this reason, the underlying mechanism of protein aggregation, and accompanying kinetic models for protein nucleation and growth (growth also being called elongation, polymerization, or fibrillation in the literature), have been investigated for more than 50 years. As a way to concisely present the key prior literature in the protein aggregation area, Table 1 in the main text summarizes 23 papers by 10 groups of authors that provide 5 basic classes of mechanisms for protein aggregation over the period from 1959 to 2007. However, and despite this major prior effort, still lacking are both (i) anything approaching a consensus mechanism (or mechanisms), and (ii) a generally useful, and thus widely used, simplest/„Ockham's razor„ kinetic model and associated equations that can be routinely employed to analyze a broader range of protein aggregation kinetic data. Herein we demonstrate that the 1997 Finke-Watzky (F-W) 2-step mechanism of slow continuous nucleation, A –> B (rate constant k1), followed by typically fast, autocatalytic surface growth, A + B –> 2B (rate constant k2), is able to quantitatively account for the kinetic curves from all 14 representative data sets of neurological protein aggregation found by a literature search (the prion literature was largely excluded for the purposes of this study in order provide some limit to the resultant literature that was covered). The F-W model is able to deconvolute the desired nucleation, k1, and growth, k2, rate constants from those 14 data sets obtained by four different physical methods, for three different proteins, and in nine different labs. The fits are generally good, and in many cases excellent, with R2 values >or=0.98 in all cases. As such, this contribution is the current record of the widest set of protein aggregation data best fit by what is also the simplest model offered to date. Also provided is the mathematical connection between the 1997 F-W 2-step mechanism and the 2000 3-step mechanism proposed by Sait and co-workers. In particular, the kinetic equation for Sait's 3-step mechanism is shown to be mathematically identical to the earlier, 1997 2-step F-W mechanism under the 3 simplifying assumptions Sait and co-workers used to derive their kinetic equation. A list of the 3 main caveats/limitations of the F-W kinetic model is provided, followed by the main conclusions from this study as well as some needed future experiments.

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 Compartment

This model contains one compartment.

Table 2: Properties of all compartments.

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

3.1 Compartment Brain

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

Name Brain

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 8 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
`B`	B	`Brain`	$\mathrm{mmol} \cdot \mathrm{ml}^{-1}$	⊟	☑
`A`	A	`Brain`	$\mathrm{mmol} \cdot \mathrm{ml}^{-1}$	☑	☑

5 Parameters

This model contains four global parameters.

Table 4: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k1	k1		$4 \cdot 10^{-5}$		☑
k2	k2		$1.57 \cdot 10^{-6}$		☑
A0	A0		184713.376		☐
k2A0	k2A0		0.290		☑

6 Rules

This is an overview of two rules.

6.1 Rule A0

Rule A0 is an assignment rule for parameter A0:

$$\mathrm{A0} = \frac{\mathrm{k2A0}}{\mathrm{k2}} \tag{1}$$

6.2 Rule B

Rule B is an assignment rule for species B:

$$\mathrm{B} = \mathrm{A0} - \frac{\frac{\mathrm{k1}}{\mathrm{k2}} + \mathrm{A0}}{1 + \frac{\mathrm{k1}}{\mathrm{k2} \cdot \mathrm{A0}} \cdot \exp\left((\mathrm{k1} + \mathrm{k2} \cdot \mathrm{A0}) \cdot \mathrm{time}\right)} \tag{2}$$

7 Reactions

This model contains two 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	`Nucleation`	Nucleation	$\mathrm{A} \xrightarrow{\mathrm{A}} \mathrm{B}$	
2	`Growth`	Growth	$\mathrm{A} + \mathrm{B} \xrightarrow{\mathrm{A,\ B}} 2\,\mathrm{B}$	

7.1 Reaction `Nucleation`

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

Name Nucleation

Reaction equation

$$\mathrm{A} \xrightarrow{\mathrm{A}} \mathrm{B} \tag{3}$$

Reactant

Table 6: Properties of each reactant.

Id	Name	SBO
`A`	A	

Modifier

Table 7: Properties of each modifier.

Id	Name	SBO
`A`	A	

Product

Table 8: Properties of each product.

Id	Name	SBO
`B`	B	

Kinetic Law

Derived unit contains undeclared units

$$v_1 = \mathrm{vol}\,(\mathrm{Brain}) \cdot \mathrm{k1} \cdot [\mathrm{A}] \tag{4}$$

7.2 Reaction `Growth`

This is an irreversible reaction of two reactants forming one product influenced by two modifiers.

Name Growth

Reaction equation

$$\mathrm{A} + \mathrm{B} \xrightarrow{\mathrm{A,\ B}} 2\,\mathrm{B} \tag{5}$$

Reactants

Table 9: Properties of each reactant.

Id	Name	SBO
A	A	
B	B	

Modifiers

Table 10: Properties of each modifier.

Id	Name	SBO
A	A	
B	B	

Product

Table 11: Properties of each product.

Id	Name	SBO
B	B	

Kinetic Law

Derived unit contains undeclared units

$$v_2 = \mathrm{vol}\,(\mathrm{Brain}) \cdot \mathrm{k2} \cdot [\mathrm{A}] \cdot [\mathrm{B}] \tag{6}$$

8 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.

8.1 Species B

Name B

Notes `Polymeric form of the -Synuclein (Tht Fluorescence)`

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

Involved in rule B

This species takes part in four reactions (as a reactant in Growth and as a product in Nucleation, Growth and as a modifier in Growth). Not these but one rule determines the species' quantity because this species is on the boundary of the reaction system.

8.2 Species A

Name A

Notes `Monomeric form of the -Synuclein (M)`

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

This species takes part in four reactions (as a reactant in Nucleation, Growth and as a modifier in Nucleation, Growth), which do not influence its rate of change because this constant species is on the boundary of the reaction system:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{A} = 0 \tag{7}$$

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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