SBML Model Report

Model name: "Morris2008 - Fitting protein aggregation data via F-W 2-step mechanism"

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 January 16th 2015 at 4:18 p. m. and last time modified at April eighth 2016 at 5:52 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	2	function definitions	0
global parameters	3	unit definitions	3
rules	1	initial assignments	0

Model Notes

Morris2009 - -Synuclein aggregationvariable temperature and pH

This model is described in the article:Alpha-synuclein aggregation variable temperature and variable pH kinetic data: a re-analysis using the Finke-Watzky 2-step model of nucleation and autocatalytic growth.Morris AM, Finke RG.Biophys. Chem. 2009 Mar; 140(1-3): 9-15

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Abstract:

The aggregation of proteins is believed to be intimately connected to many neurodegenerative disorders. We recently reported an „Ockham's razor„/minimalistic approach to analyze the kinetic data of protein aggregation using the Finke-Watzky (F-W) 2-step model of nucleation (A–>B, rate constant k(1)) and autocatalytic growth (A+B–>2B, rate constant k(2)). With that kinetic model we have analyzed 41 representative protein aggregation data sets in two recent publications, including amyloid beta, alpha-synuclein, polyglutamine, and prion proteins (Morris, A. M., et al. (2008) Biochemistry 47, 2413-2427; Watzky, M. A., et al. (2008) Biochemistry 47, 10790-10800). Herein we use the F-W model to reanalyze protein aggregation kinetic data obtained under the experimental conditions of variable temperature or pH 2.0 to 8.5. We provide the average nucleation (k(1)) and growth (k(2)) rate constants and correlations with variable temperature or varying pH for the protein alpha-synuclein. From the variable temperature data, activation parameters DeltaG(double dagger), DeltaH(double dagger), and DeltaS(double dagger) are provided for nucleation and growth, and those values are compared to the available parameters reported in the previous literature determined using an empirical method. Our activation parameters suggest that nucleation and growth are energetically similar for alpha-synuclein aggregation (DeltaG(double dagger)(nucleation)=23(3) kcal/mol; DeltaG(double dagger)(growth)=22(1) kcal/mol at 37 degrees C). From the variable pH data, the F-W analyses show a maximal k(1) value at pH approximately 3, as well as minimal k(1) near the isoelectric point (pI) of alpha-synuclein. Since solubility and net charge are minimized at the pI, either or both of these factors may be important in determining the kinetics of the nucleation step. On the other hand, the k(2) values increase with decreasing pH (i.e., do not appear to have a minimum or maximum near the pI) which, when combined with the k(1) vs. pH (and pI) data, suggest that solubility and charge are less important factors for growth, and that charge is important in the k(1), nucleation step of alpha-synuclein. The chemically well-defined nucleation (k(1)) rate constants obtained from the F-W analysis are, as expected, different than the 1/lag-time empirical constants previously obtained. However, k(2)x[A](0) (where k(2) is the rate constant for autocatalytic growth and [A](0) is the initial protein concentration) is related to the empirical constant, k(app) obtained previously. Overall, the average nucleation and average growth rate constants for alpha-synuclein aggregation as a function of pH and variable temperature have been quantitated. Those values support the previously suggested formation of a partially folded intermediate that promotes aggregation under high temperature or acidic conditions.

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 three global parameters.

Table 4: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k1	k1		$8 \cdot 10^{-6}$		☑
k2	k2		0.034		☑
A0	A0		3.550		☑

6 Rule

This is an overview of one rule.

6.1 Rule B

Rule B is an assignment rule for species B:

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

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

$$\mathrm{A} \xrightarrow{\mathrm{A}} \mathrm{B} \tag{2}$$

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

$$v_1 = \mathrm{vol}\,(\mathrm{Brain}) \cdot \mathrm{k1} \cdot [\mathrm{A}] \tag{3}$$

7.2 Reaction `Growth`

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

Name Growth

Reaction equation

$$\mathrm{A} + \mathrm{B} \xrightarrow{\mathrm{A},\ \mathrm{B}} 2\,\mathrm{B} \tag{4}$$

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

$$v_2 = \mathrm{vol}\,(\mathrm{Brain}) \cdot \mathrm{k2} \cdot [\mathrm{A}] \cdot [\mathrm{B}] \tag{5}$$

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 protein`

Initial concentration $-4.44089209850063 \cdot 10^{-16}\ \mathrm{mmol} \cdot \mathrm{ml}^{-1}$

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 protein`

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:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{A} = 0 \tag{6}$$

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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