SBML Model Report

Model name: “Proctor2012 - Role of Amyloid-beta dimers in aggregation formation”

May 6, 2016

1 General Overview

This is a document in SBML Level 2 Version 4 format. This model was created by the following two authors: Carole Proctor[1] and Vijayalakshmi Chelliah[2] at June sixth 2013 at 7:51 p. m. and last time modified at October tenth 2014 at 11:22 a. 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	6
events	0	constraints	0
reactions	8	function definitions	0
global parameters	9	unit definitions	1
rules	0	initial assignments	0

Model Notes

Proctor2012 - Amyloid-beta aggregation

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This model supports the current thinking that levels of dimers are important in initiating the aggregation process.

This model is described in the article:Aggregation, impaired degradation and immunization targeting of amyloid-beta dimers in Alzheimer's disease: a stochastic modelling approach.Proctor CJ, Pienaar IS, Elson JL, Kirkwood TBMolecular Neurodegeneration. 2012; 7:32

Abstract:

BACKGROUND: Alzheimer's disease (AD) is the most frequently diagnosed neurodegenerative disorder affecting humans, with advanced age being the most prominent risk factor for developing AD. Despite intense research efforts aimed at elucidating the precise molecular underpinnings of AD, a definitive answer is still lacking. In recent years, consensus has grown that dimerisation of the polypeptide amyloid-beta (A), particularly A, plays a crucial role in the neuropathology that characterise AD-affected post-mortem brains, including the large-scale accumulation of fibrils, also referred to as senile plaques. This has led to the realistic hope that targeting A immunotherapeutically could drastically reduce plaque burden in the ageing brain, thus delaying AD onset or symptom progression. Stochastic modelling is a useful tool for increasing understanding of the processes underlying complex systems-affecting disorders such as AD, providing a rapid and inexpensive strategy for testing putative new therapies. In light of the tool's utility, we developed computer simulation models to examine A turnover and its aggregation in detail and to test the effect of immunization against A dimers.

RESULTS: Our model demonstrates for the first time that even a slight decrease in the clearance rate of A monomers is sufficient to increase the chance of dimers forming, which could act as instigators of protofibril and fibril formation, resulting in increased plaque levels. As the process is slow and levels of A are normally low, stochastic effects are important. Our model predicts that reducing the rate of dimerisation leads to a significant reduction in plaque levels and delays onset of plaque formation. The model was used to test the effect of an antibody mediated immunological response. Our results showed that plaque levels were reduced compared to conditions where antibodies are not present.

CONCLUSION: Our model supports the current thinking that levels of dimers are important in initiating the aggregation process. Although substantial knowledge exists regarding the process, no therapeutic intervention is on offer that reliably decreases disease burden in AD patients. Computer modelling could serve as one of a number of tools to examine both the validity of reliable biomarkers and aid the discovery of successful intervention strategies.

This model is hosted on BioModels Database and identified by: BIOMD0000000462 .

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 four are predefined by SBML and not mentioned in the model.

2.1 Unit substance

Definition item

2.2 Unit volume

Notes Litre is the predefined SBML unit for volume.

Definition l

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
cell			3	1	litre	☑	

3.1 Compartment cell

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

4 Species

This model contains six 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
`Abeta`	AbetaMonomer	`cell`	item	☐	☐
`AbDim`	AbetaDimer	`cell`	item	☐	☐
`AbP`	AbetaPlaque	`cell`	item	☐	☐
`Source`		`cell`	item	☑	☑
`Sink`		`cell`	item	☑	☑
`Nep`	Neprilysin	`cell`	item	☐	☐

5 Parameters

This model contains nine global parameters.

Table 4: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
kprod			$1.86 \cdot 10^{-5}$		☑
kdeg			$2.1 \cdot 10^{-5}$		☑
kdimer			$1.1783 \cdot 10^{-7}$		☑
kdedimer			$8.4655 \cdot 10^{-6}$		☑
kdisagg			$5.4357 \cdot 10^{-5}$		☑
kpf			$2.785 \cdot 10^{-6}$		☑
kpg			0.006		☑
kpghalf			4.000		☑
kdegNep			$1.8 \cdot 10^{-10}$		☑

6 Reactions

This model contains eight 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	`Abetaproduction`		$\text{Source} \xrightarrow{\text{Source}} \text{Abeta}$	
2	`AbetaDegradation`		$\text{Abeta} + \text{Nep} \xrightarrow{\text{Abeta, Nep}} \text{Sink} + \text{Nep}$	
3	`AbetaDimerisation`		$2\,\text{Abeta} \xrightarrow{\text{Abeta}} \text{AbDim}$	
4	`AbetaDedimerisation`		$\text{AbDim} \xrightarrow{\text{AbDim}} 2\,\text{Abeta}$	
5	`AbetaPlaqueFormation`		$2\,\text{AbDim} \xrightarrow{\text{AbDim}} 4\,\text{AbP}$	
6	`AbetaPlaqueGrowth`		$\text{Abeta} + \text{AbP} \xrightarrow{\text{Abeta, AbP}} 2\,\text{AbP}$	
7	`AbetaDisaggregation`		$\text{AbP} \xrightarrow{\text{AbP}} \text{Abeta}$	
8	`NepDegradation`		$\text{Nep} \xrightarrow{\text{Nep}} \text{Sink}$	

6.1 Reaction `Abetaproduction`

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

Reaction equation

$$\text{Source} \xrightarrow{\text{Source}} \text{Abeta} \tag{1}$$

Reactant

Table 6: Properties of each reactant.

Id	Name	SBO
`Source`		

Modifier

Table 7: Properties of each modifier.

Id	Name	SBO
`Source`		

Product

Table 8: Properties of each product.

Id	Name	SBO
`Abeta`	AbetaMonomer	

Kinetic Law

Derived unit contains undeclared units

$$v_1 = \text{kprod} \cdot \text{Source} \tag{2}$$

6.2 Reaction `AbetaDegradation`

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

Reaction equation

$$\text{Abeta} + \text{Nep} \xrightarrow{\text{Abeta, Nep}} \text{Sink} + \text{Nep} \tag{3}$$

Reactants

Table 9: Properties of each reactant.

Id	Name	SBO
`Abeta`	AbetaMonomer	
`Nep`	Neprilysin	

Modifiers

Table 10: Properties of each modifier.

Id	Name	SBO
`Abeta`	AbetaMonomer	
`Nep`	Neprilysin	

Products

Table 11: Properties of each product.

Id	Name	SBO
`Sink`		
`Nep`	Neprilysin	

Kinetic Law

Derived unit contains undeclared units

$$v_2 = \text{kdeg} \cdot \text{Abeta} \cdot \text{Nep} \cdot 0.0010 \tag{4}$$

6.3 Reaction `AbetaDimerisation`

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

Reaction equation

$$2\,\text{Abeta} \xrightarrow{\text{Abeta}} \text{AbDim} \tag{5}$$

Reactant

Table 12: Properties of each reactant.

Id	Name	SBO
Abeta	AbetaMonomer	

Modifier

Table 13: Properties of each modifier.

Id	Name	SBO
Abeta	AbetaMonomer	

Product

Table 14: Properties of each product.

Id	Name	SBO
AbDim	AbetaDimer	

Kinetic Law

Derived unit contains undeclared units

$$v_3 = \text{kdimer} \cdot \text{Abeta} \cdot (\text{Abeta} - 1) \cdot 0.5 \tag{6}$$

6.4 Reaction AbetaDedimerisation

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

Reaction equation

$$\text{AbDim} \xrightarrow{\text{AbDim}} 2\,\text{Abeta} \tag{7}$$

Reactant

Table 15: Properties of each reactant.

Id	Name	SBO
AbDim	AbetaDimer	

Modifier

Table 16: Properties of each modifier.

Id	Name	SBO
AbDim	AbetaDimer	

Product

Table 17: Properties of each product.

Id	Name	SBO
Abeta	AbetaMonomer	

Kinetic Law

Derived unit contains undeclared units

$$v_4 = \text{kdedimer} \cdot \text{AbDim} \tag{8}$$

6.5 Reaction AbetaPlaqueFormation

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

Reaction equation

$$2\,\text{AbDim} \xrightarrow{\text{AbDim}} 4\,\text{AbP} \tag{9}$$

Reactant

Table 18: Properties of each reactant.

Id	Name	SBO
AbDim	AbetaDimer	

Modifier

Table 19: Properties of each modifier.

Id	Name	SBO
AbDim	AbetaDimer	

Id	Name	SBO

Product

Table 20: Properties of each product.

Id	Name	SBO
AbP	AbetaPlaque	

Kinetic Law

Derived unit contains undeclared units

$$v_5 = \text{kpf} \cdot \text{AbDim} \cdot (\text{AbDim} - 1) \cdot 0.5 \tag{10}$$

6.6 Reaction AbetaPlaqueGrowth

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

Reaction equation

$$\text{Abeta} + \text{AbP} \xrightarrow{\text{Abeta, AbP}} 2\,\text{AbP} \tag{11}$$

Reactants

Table 21: Properties of each reactant.

Id	Name	SBO
Abeta	AbetaMonomer	
AbP	AbetaPlaque	

Modifiers

Table 22: Properties of each modifier.

Id	Name	SBO
Abeta	AbetaMonomer	
AbP	AbetaPlaque	

Product

Table 23: Properties of each product.

Id	Name	SBO
AbP	AbetaPlaque	

Kinetic Law

Derived unit contains undeclared units

$$v_6 = \frac{\text{kpg} \cdot \text{Abeta} \cdot \text{AbP}^2}{\text{kpghalf}^2 + \text{AbP}^2} \tag{12}$$

6.7 Reaction AbetaDisaggregation

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

Reaction equation

$$\text{AbP} \xrightarrow{\text{AbP}} \text{Abeta} \tag{13}$$

Reactant

Table 24: Properties of each reactant.

Id	Name	SBO
AbP	AbetaPlaque	

Modifier

Table 25: Properties of each modifier.

Id	Name	SBO
AbP	AbetaPlaque	

Product

Table 26: Properties of each product.

Id	Name	SBO
Abeta	AbetaMonomer	

Kinetic Law

Derived unit contains undeclared units

$$v_7 = \text{kdisagg} \cdot \text{AbP} \tag{14}$$

6.8 Reaction `NepDegradation`

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

Reaction equation

$$\text{Nep} \xrightarrow{\text{Nep}} \text{Sink} \tag{15}$$

Reactant

Table 27: Properties of each reactant.

Id	Name	SBO
`Nep`	Neprilysin	

Modifier

Table 28: Properties of each modifier.

Id	Name	SBO
`Nep`	Neprilysin	

Product

Table 29: Properties of each product.

Id	Name	SBO
`Sink`		

Kinetic Law

Derived unit contains undeclared units

$$v_8 = \text{kdegNep} \cdot \text{Nep} \tag{16}$$

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.

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.

7.1 Species `Abeta`

Name AbetaMonomer

Initial amount 0 item

This species takes part in nine reactions (as a reactant in `AbetaDegradation`, `AbetaDimerisation`, `AbetaPlaqueGrowth` and as a product in `Abetaproduction`, `AbetaDedimerisation`, `AbetaDisaggregation` and as a modifier in `AbetaDegradation`, `AbetaDimerisation`, `AbetaPlaqueGrowth`).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Abeta} = v_1 + 2\,v_4 + v_7 - v_2 - 2\,v_3 - v_6 \tag{17}$$

7.2 Species `AbDim`

Name AbetaDimer

Initial amount 0 item

This species takes part in five reactions (as a reactant in `AbetaDedimerisation`, `AbetaPlaqueFormation` and as a product in `AbetaDimerisation` and as a modifier in `AbetaDedimerisation`, `AbetaPlaqueFormation`).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{AbDim} = v_3 - v_4 - 2\,v_5 \tag{18}$$

7.3 Species `AbP`

Name AbetaPlaque

Initial amount 0 item

This species takes part in six reactions (as a reactant in `AbetaPlaqueGrowth`, `AbetaDisaggregation` and as a product in `AbetaPlaqueFormation`, `AbetaPlaqueGrowth` and as a modifier in `AbetaPlaqueGrowth`, `AbetaDisaggregation`).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{AbP} = 4\,v_5 + 2\,v_6 - v_6 - v_7 \tag{19}$$

7.4 Species Source

SBO:0000291 empty set

Initial amount 1 item

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

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Source} = 0 \tag{20}$$

7.5 Species Sink

SBO:0000291 empty set

Initial amount 1 item

This species takes part in two reactions (as a product in AbetaDegradation, NepDegradation), which do not influence its rate of change because this constant species is on the boundary of the reaction system:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Sink} = 0 \tag{21}$$

7.6 Species Nep

Name Neprilysin

Initial amount 1000 item

This species takes part in five reactions (as a reactant in AbetaDegradation, NepDegradation and as a product in AbetaDegradation and as a modifier in AbetaDegradation, NepDegradation).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Nep} = v_2 - v_2 - v_8 \tag{22}$$

A Glossary of Systems Biology Ontology Terms

SBO:0000291 empty set: Entity defined by the absence of any actual object. An empty set is often used to represent the source of a creation process or the result of a degradation process.

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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