SBML Model Report

Model name: "Lebeda2008_BoTN_Paralysis_4stepModel"

May 6, 2016

1 General Overview

This is a document in SBML Level 2 Version 3 format. This model was created by the following two authors: Lukas Endler[1] and Frank Lebeda[2] at August eighth 2008 at 3:57 p. m. and last time modified at October tenth 2014 at 11:34 a. 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	3
species types	0	species	6
events	0	constraints	0
reactions	4	function definitions	0
global parameters	1	unit definitions	4
rules	2	initial assignments	0

Model Notes

This model is the 4-step model from the article:
Onset dynamics of type A botulinum neurotoxin-induced paralysis.
Lebeda FJ, Adler M, Erickson K, Chushak Y J Pharmacokinet Pharmacodyn2008 Jun; 35(3):

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Abstract:
Experimental studies have demonstrated that botulinum neurotoxin serotype A (BoNT/A) causes flaccid paralysis by a multi-step mechanism. Following its binding to specific receptors at peripheral cholinergic nerve endings, BoNT/A is internalized by receptor-mediated endocytosis. Subsequently its zinc-dependent catalytic domain translocates into the neuroplasm where it cleaves a vesicle-docking protein, SNAP-25, to block neurally evoked cholinergic neurotransmission. We tested the hypothesis that mathematical models having a minimal number of reactions and reactants can simulate published data concerning the onset of paralysis of skeletal muscles induced by BoNT/A at the isolated rat neuromuscular junction (NMJ) and in other systems. Experimental data from several laboratories were simulated with two different models that were represented by sets of coupled, first-order differential equations. In this study, the 3-step sequential model developed by Simpson (J Pharmacol Exp Ther 212:16-21,1980) was used to estimate upper limits of the times during which anti-toxins and other impermeable inhibitors of BoNT/A can exert an effect. The experimentally determined binding reaction rate was verified to be consistent with published estimates for the rate constants for BoNT/A binding to and dissociating from its receptors. Because this 3-step model was not designed to reproduce temporal changes in paralysis with different toxin concentrations, a new BoNT/A species and rate (k(S)) were added at the beginning of the reaction sequence to create a 4-step scheme. This unbound initial species is transformed at a rate determined by k(S) to a free species that is capable of binding. By systematically adjusting the values of k(S), the 4-step model simulated the rapid decline in NMJ function (k(S) >or= 0.01), the less rapid onset of paralysis in mice following i.m. injections (k (S) = 0.001), and the slow onset of the therapeutic effects of BoNT/A (k(S) < 0.001) in man. This minimal modeling approach was not only verified by simulating experimental results, it helped to quantitatively define the time available for an inhibitor to have some effect (t(inhib)) and the relation between this time and the rate of paralysis onset. The 4-step model predicted that as the rate of paralysis becomes slower, the estimated upper limits of (t(inhib)) for impermeable inhibitors become longer. More generally, this modeling approach may be useful in studying the kinetics of other toxins or viruses that invade host cells by similar mechanisms, e.g., receptor-mediated endocytosis.

Model updated by Viji on 07/09/2010.

This model is the extended model of BIOMD0000000267, which itself is the reduced form of the model developed by Simpson 1980; PMID 6243359.

2 Unit Definitions

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

2.1 Unit `substance`

Name relative concentration

Definition dimensionless

2.2 Unit `volume`

Name normalized volume

Definition dimensionless

2.3 Unit `time`

Name min

Definition 60 s

2.4 Unit `pmin`

Name perminute

Definition $(60\ \mathrm{s})^{-1}$

2.5 Unit `area`

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

Definition m^2

2.6 Unit `length`

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

Definition m

3 Compartments

This model contains three compartments.

Table 2: Properties of all compartments.

Id	Name	SBO	Spatial Dimensions	Size	Unit	Constant	Outside
`extracellular`	extracellular		3	1	dimensionless	☑	
`endosome`	endosome		3	1	dimensionless	☑	
`neuroplasm`	neuroplasm		3	1	dimensionless	☑	

3.1 Compartment `extracellular`

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

Name extracellular

3.2 Compartment `endosome`

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

Name endosome

3.3 Compartment `neuroplasm`

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

Name neuroplasm

4 Species

This model contains six species. The boundary condition of one of these species is set to `true` so that this 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
`BoNT`	tot_free_BoNT/A	`extracellular`	dimensionless · dimensionless^{-1}	⊟	☑
`bulk`	bulk_BoNT/A	`extracellular`	dimensionless · dimensionless^{-1}	⊟	⊟
`free`	free_BoNT/A	`extracellular`	dimensionless · dimensionless^{-1}	⊟	⊟
`bound`	bound_BoNT/A	`extracellular`	dimensionless · dimensionless^{-1}	⊟	⊟
`translocate`	transloc_BoNT/A	`endosome`	dimensionless · dimensionless^{-1}	⊟	⊟
`lytic`	lytic_BoNT/A	`neuroplasm`	dimensionless · dimensionless^{-1}	⊟	⊟

5 Parameter

This model contains one global parameter.

Table 4: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
`tension`			0.0		⊟

6 Rules

This is an overview of two rules.

6.1 Rule `tension`

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

$$\text{tension} = 1 - [\text{lytic}] \tag{1}$$

6.2 Rule `BoNT`

Rule `BoNT` is an assignment rule for species `BoNT`:

$$\text{BoNT} = [\text{bulk}] + [\text{free}] \tag{2}$$

Derived unit $\text{dimensionless}^{-1}$

7 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	`endocytosis`		bound ⟶ translocate	
2	`translocation`		translocate ⟶ lytic	
3	`binding`		free ⟶ bound	
4	`bulk_movement`		bulk ⟶ free	

7.1 Reaction `endocytosis`

This is an irreversible reaction of one reactant forming one product.

Reaction equation

$$\text{bound} \longrightarrow \text{translocate} \tag{3}$$

Reactant

Table 6: Properties of each reactant.

Id	Name	SBO
`bound`	bound_BoNT/A	

Product

Table 7: Properties of each product.

Id	Name	SBO
`translocate`	transloc_BoNT/A	

Kinetic Law

Derived unit $(60\ \mathrm{s})^{-1}$

$$v_1 = \mathrm{kT} \cdot [\text{bound}] \cdot \mathrm{vol}\,(\text{extracellular}) \tag{4}$$

Table 8: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
kT			0.141	$(60\ \mathrm{s})^{-1}$	☑

7.2 Reaction `translocation`

This is an irreversible reaction of one reactant forming one product.

Reaction equation

$$\text{translocate} \longrightarrow \text{lytic} \tag{5}$$

Reactant

Table 9: Properties of each reactant.

Id	Name	SBO
`translocate`	transloc_BoNT/A	

Product

Table 10: Properties of each product.

Id	Name	SBO
`lytic`	lytic_BoNT/A	

Kinetic Law

Derived unit $(60\ \mathrm{s})^{-1}$

$$v_2 = \mathrm{kL} \cdot [\mathrm{translocate}] \cdot \mathrm{vol}\,(\mathrm{endosome}) \tag{6}$$

Table 11: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
kL			0.013	$(60\ \mathrm{s})^{-1}$	☑

7.3 Reaction `binding`

This is an irreversible reaction of one reactant forming one product.

Reaction equation

$$\mathrm{free} \longrightarrow \mathrm{bound} \tag{7}$$

Reactant

Table 12: Properties of each reactant.

Id	Name	SBO
`free`	free_BoNT/A	

Product

Table 13: Properties of each product.

Id	Name	SBO
bound	bound_BoNT/A	

Kinetic Law

Derived unit $(60\ \mathrm{s})^{-1}$

$$v_3 = \mathrm{kB} \cdot [\mathrm{free}] \cdot \mathrm{vol}\,(\mathrm{extracellular}) \tag{8}$$

Table 14: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
kB			0.058	$(60\ \mathrm{s})^{-1}$	☑

7.4 Reaction bulk_movement

This is an irreversible reaction of one reactant forming one product.

Reaction equation

$$\mathrm{bulk} \longrightarrow \mathrm{free} \tag{9}$$

Reactant

Table 15: Properties of each reactant.

Id	Name	SBO
bulk	bulk_BoNT/A	

Product

Table 16: Properties of each product.

Id	Name	SBO
free	free_BoNT/A	

Kinetic Law

Derived unit $(60\ \mathrm{s})^{-1}$

$$v_4 = \mathrm{kS} \cdot [\mathrm{bulk}] \cdot \mathrm{vol}\,(\mathrm{extracellular}) \tag{10}$$

Table 17: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
kS			$1.5 \cdot 10^{-4}$	$(60\ \mathrm{s})^{-1}$	☑

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 `BoNT`

Name tot_free_BoNT/A

Involved in rule `BoNT`

One rule determines the species' quantity.

8.2 Species `bulk`

Name bulk_BoNT/A

Initial concentration $1\ \mathrm{dimensionless} \cdot \mathrm{dimensionless}^{-1}$

This species takes part in one reaction (as a reactant in `bulk_movement`).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{bulk} = -\,v_4 \tag{11}$$

8.3 Species free

Name free_BoNT/A

Initial concentration $0\ \text{dimensionless} \cdot \text{dimensionless}^{-1}$

This species takes part in two reactions (as a reactant in binding and as a product in bulk_movement).

$$\frac{\mathrm{d}}{\mathrm{d}t}\text{free} = v_4 - v_3 \tag{12}$$

8.4 Species bound

Name bound_BoNT/A

Initial concentration $0\ \text{dimensionless} \cdot \text{dimensionless}^{-1}$

This species takes part in two reactions (as a reactant in endocytosis and as a product in binding).

$$\frac{\mathrm{d}}{\mathrm{d}t}\text{bound} = v_3 - v_1 \tag{13}$$

8.5 Species translocate

Name transloc_BoNT/A

Initial concentration $0\ \text{dimensionless} \cdot \text{dimensionless}^{-1}$

This species takes part in two reactions (as a reactant in translocation and as a product in endocytosis).

$$\frac{\mathrm{d}}{\mathrm{d}t}\text{translocate} = v_1 - v_2 \tag{14}$$

8.6 Species lytic

Name lytic_BoNT/A

Initial concentration $0\ \text{dimensionless} \cdot \text{dimensionless}^{-1}$

This species takes part in one reaction (as a product in translocation).

$$\frac{\mathrm{d}}{\mathrm{d}t}\text{lytic} = v_2 \tag{15}$$

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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