**SBML Model Report**

# Model name: "Lebeda2008_BoNT_Paralysis_3stepModel"

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## 1 General Overview

This is a document in SBML Level 2 Version 4 format. This model was created by the following three authors: Lukas Endler[1], Vijayalakshmi Chelliah[2] and Frank Lebeda[3] at September seventh 2010 at 2:22 p. m. and last time modified at April first 2014 at 9:17 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 | 3 |
| species types | 0 | species | 4 |
| events | 0 | constraints | 0 |
| reactions | 3 | function definitions | 0 |
| global parameters | 1 | unit definitions | 4 |
| rules | 1 | initial assignments | 0 |

### Model Notes

This model is the 3-step model from the article:
**Onset dynamics of type A botulinum neurotoxin-induced paralysis.**

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Lebeda FJ, Adler M, Erickson K, Chushak Y J Pharmacokinet Pharmacodyn 2008 Jun; 35(3): 251-67 18551355 ,

**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.

This model is the reduced form of the model developed my Simpson 1980; PMID: 6243359 , i.e., it omits three unknown parameters that represents the binding sites for each species of the toxin.

## 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** $\mathrm{m}^2$

### 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 four species. 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 |
|---|---|---|---|---|---|
| `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 Rule

This is an overview of one rule.

## 6.1 Rule `tension`

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

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

## 7 Reactions

This model contains three 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 | |

## 7.1 Reaction `endocytosis`

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

### Reaction equation

$$\text{bound} \longrightarrow \text{translocate} \tag{2}$$

### 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** $(60\ \text{s})^{-1}$

$$v_1 = \text{kT} \cdot [\text{bound}] \cdot \text{vol}(\text{extracellular}) \tag{3}$$

Table 8: Properties of each parameter.

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

## 7.2 Reaction `translocation`

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

### Reaction equation

$$\text{translocate} \longrightarrow \text{lytic} \tag{4}$$

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

$$v_2 = \mathrm{kL} \cdot [\mathrm{translocate}] \cdot \mathrm{vol}\,(\mathrm{endosome}) \tag{5}$$

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

$$\mathrm{free} \longrightarrow \mathrm{bound} \tag{6}$$

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

$$v_3 = \mathrm{kB} \cdot [\mathrm{free}] \cdot \mathrm{vol}\,(\mathrm{extracellular}) \tag{7}$$

Table 14: Properties of each parameter.

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

## 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 `free`

**Name** free_BoNT/A

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

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

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{free} = -v_3 \tag{8}$$

## 8.2 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).

$$\frac{\mathrm{d}}{\mathrm{d}t}\text{bound} = v_3 - v_1 \tag{9}$$

## 8.3 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).

$$\frac{\mathrm{d}}{\mathrm{d}t}\text{translocate} = v_1 - v_2 \tag{10}$$

## 8.4 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).

$$\frac{\mathrm{d}}{\mathrm{d}t}\text{lytic} = v_2 \tag{11}$$

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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