SBML Model Report

Model name: "Phillips2003 - The Mechanism of Ras GTPase Activation by Neurofibromin"



May 17, 2018

1 General Overview

This is a document in SBML Level 2 Version 4 format. This model was created by Matthew Grant Roberts¹ at March 19th 2018 at 3:37 p.m. and last time modified at March 19th 2018 at 4:08 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	8
events	0	constraints	0
reactions	5	function definitions	5
global parameters	2	unit definitions	1
rules	2	initial assignments	0

Model Notes

Phillips2003 - The Mechanism of Ras GTPaseActivation by NeurofibrominA mathematical model for Ras-GTPactivation by neurofibromin and the kinetic rates of the relevantreactions.

This model is described in the article: The mechanism of Ras GTPase activation by neurofibromin. Phillips RA, Hunter JL, Eccleston JF, Webb MR. Biochemistry 2003 Apr; 42(13): 3956-3965

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Abstract:

Individual rate constants have been determined for each step of the Ras.GTP hydrolysis mechanism, activated by neurofibromin. Fluorescence intensity and anisotropy stopped-flow measurements used the fluorescent GTP analogue, mantGTP (2'(3')-O-(N-methylanthraniloyl)GTP), to determine rate constants for binding and release of neurofibromin. Quenched flow measurements provided the kinetics of the hydrolytic cleavage step. The fluorescent phosphate sensor, MDCC-PBP was used to measure phosphate release kinetics. Phosphate-water oxygen exchange, using (18)O-substituted GTP and inorganic phosphate (P(i)), was used to determine the extent of reversal of the hydrolysis step and of P(i) binding. The data show that neurofibromin and P(i) dissociate from the NF1.Ras.GDP.P(i) complex with identical kinetics, which are 3-fold slower than the preceding cleavage step. A model is presented in which the P(i) release is associated with the change of Ras from "GTP,, to "GDP,, conformation. In this model, the conformation change on P(i) release causes the large change in affinity of neurofibromin, which then dissociates rapidly.

This model is hosted on BioModels Database and identified by: BIOMD0000000692.

To cite BioModels Database, please use: Chelliah V et al. BioModels: ten-year anniversary. Nucl. Acids Res. 2015, 43(Database issue):D542-8.

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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

Name substance

Definition µmol

2.2 Unit volume

Notes Litre is the predefined SBML unit for volume.

Definition 1

2.3 Unit area

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

Definition m²

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
geometry	E. coli		3	$5.236 \cdot 10^{-13}$	1	Ø	

3.1 Compartment geometry

This is a three dimensional compartment with a constant size of $5.236 \cdot 10^{-13}$ litre.

Name E. coli

4 Species

This model contains eight species. Section 9 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 Condi- tion
Pi	Pi	geometry	μ mol·l ⁻¹		\Box
RasGTP	RasGTP	geometry	μ mol · l ⁻¹		\Box
RasGTP_minus_NF1	RasGTP_minus_NF1	geometry	μ mol · l ⁻¹		\Box
RasGTP_minus_NF1- _star_	RasGTP_minus_NF1_star_	geometry	$\mu mol \cdot l^{-1}$		
RasGDP_minus_NF1- _Pi	RasGDP_minus_NF1_Pi	geometry	$\mu mol \cdot l^{-1}$		
RasGDP_NF1	RasGDP_NF1	geometry	μ mol · l ⁻¹		\Box
RasGDP	RasGDP	geometry	$\mu mol \cdot l^{-1}$		\Box
NF1	NF1	geometry	$\mu mol \cdot l^{-1}$		

5 Parameters

This model contains two global parameters.

Table 4: Properties of each parameter.

Id	Name	SBO Value	Unit	Constant
Pi_curve	Pi_curve	0.0		В
${\tt hplc_curve}$	hplc_curve	100.0		

6 Function definitions

This is an overview of five function definitions.

6.1 Function definition Function_for_GTP_hydrolysis_sbo_2_sbc

Name Function for GTP_hydrolysis_sbo_2_sbc_

Arguments [Pi], [RasGDP_NF1], [RasGDP_minus_NF1_Pi], vol (geometry), kb, kf

Mathematical Expression

$$\frac{kf \cdot [RasGDP_minus_NF1_Pi] - kb \cdot [Pi] \cdot [RasGDP_NF1]}{vol\left(geometry\right)} \tag{1}$$

6.2 Function definition Function_for_NF1_binding

Name Function for NF1_binding

Arguments [NF1], [RasGTP], [RasGTP_minus_NF1], vol (geometry), kb, kf

Mathematical Expression

$$\frac{\text{kf} \cdot [\text{RasGTP}] \cdot [\text{NF1}] - \text{kb} \cdot [\text{RasGTP_minus_NF1}]}{\text{vol}(\text{geometry})}$$
 (2)

6.3 Function definition Function_for_Ras_activation

Name Function for Ras_activation

Arguments [RasGTP_minus_NF1], [RasGTP_minus_NF1_star_], vol (geometry), kb, kf

Mathematical Expression

$$\frac{kf \cdot [RasGTP_minus_NF1] - kb \cdot [RasGTP_minus_NF1_star_]}{vol(geometry)}$$
 (3)

6.4 Function definition Function_for_GAP_dissociation

Name Function for GAP_dissociation

Arguments [NF1], [RasGDP], [RasGDP_NF1], vol (geometry), kb, kf

Mathematical Expression

$$\frac{kf \cdot [RasGDP_NF1] - kb \cdot [RasGDP] \cdot [NF1]}{vol (geometry)} \tag{4}$$

6.5 Function definition Function_for_GTP_hydrolysis_sbo_1_sbc

Name Function for GTP_hydrolysis_sbo_1_sbc_

Arguments [RasGDP_minus_NF1_Pi], [RasGTP_minus_NF1_star_], vol (geometry), kb, kf

Mathematical Expression

$$\frac{\text{kf} \cdot [\text{RasGTP_minus_NF1_star_}] - \text{kb} \cdot [\text{RasGDP_minus_NF1_Pi}]}{\text{vol}(\text{geometry})}$$
 (5)

7 Rules

This is an overview of two rules.

7.1 Rule Pi_curve

Rule Pi_curve is an assignment rule for parameter Pi_curve:

$$Pi_curve = \frac{100 \cdot ([Pi] - 1)}{1}$$
 (6)

7.2 Rule hplc_curve

Rule hplc_curve is an assignment rule for parameter hplc_curve:

$$hplc_curve = \frac{[RasGTP] \cdot 100}{1}$$
 (7)

8 Reactions

This model contains five 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

N₀	Id	Name	Reaction Equation	SBO
1	GTP_hydrolysis- _sbo_1_sbc_	GTP_hydrolysis_sbo_1_sbc_	RasGTP_minus_NF1_star_ \improx RasGDP_minus_NF1_	_Pi
2	GTP_hydrolysis- _sbo_2_sbc_	GTP_hydrolysis_sbo_2_sbc_	$RasGDP_minus_NF1_Pi \Longrightarrow Pi + RasGDP_NF1$	
3	${\tt Ras_activation}$	Ras_activation	RasGTP_minus_NF1 \Rightarrow RasGTP_minus_NF1_star_	
4	GAP- _dissociation	GAP_dissociation	$RasGDP_NF1 \Longrightarrow RasGDP + NF1$	
5	${ m NF1_binding}$	NF1_binding	$RasGTP+NF1 \Longrightarrow RasGTP_minus_NF1$	

8.1 Reaction GTP_hydrolysis_sbo_1_sbc_

This is a reversible reaction of one reactant forming one product.

Name GTP_hydrolysis_sbo_1_sbc_

Notes First step in hydrolysis of GTP bound to Ras complexed with NF1 - a mammalian GAP Kf = 19.5 / sec Kb = 0.22 / sec Table 3, Phillips RA et al 2003 Biochemistry 3956-3965

Reaction equation

$$RasGTP_minus_NF1_star_ \Longrightarrow RasGDP_minus_NF1_Pi \tag{8}$$

Reactant

Table 6: Properties of each reactant.

Id	Name	SBO
RasGTP_minus_NF1_star_	RasGTP_minus_NF1_star_	

Product

Table 7: Properties of each product.

Id	Name	SBO
RasGDP_minus_NF1_Pi	RasGDP_minus_NF1_Pi	

Kinetic Law

Derived unit contains undeclared units

$$v_1 = \text{vol}(\text{geometry}) \cdot \text{Function_for_GTP_hydrolysis_sbo_1_sbc}([\text{RasGDP_minus_NF1_Pi}], (9)$$

$$[\text{RasGTP_minus_NF1_star_}], \text{vol}(\text{geometry}), \text{kb}, \text{kf})$$

$$Function_for_GTP_hydrolysis_sbo_1_sbc ([RasGDP_minus_NF1_Pi], \\ [RasGTP_minus_NF1_star_], vol (geometry), kb, \\ kf) = \frac{kf \cdot [RasGTP_minus_NF1_star_] - kb \cdot [RasGDP_minus_NF1_Pi]}{vol (geometry)}$$
 (10)

$$Function_for_GTP_hydrolysis_sbo_1_sbc ([RasGDP_minus_NF1_Pi], \\ [RasGTP_minus_NF1_star_], vol (geometry), kb, \\ kf) = \frac{kf \cdot [RasGTP_minus_NF1_star_] - kb \cdot [RasGDP_minus_NF1_Pi]}{vol (geometry)}$$
 (11)

Table 8: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
kb kf	kb kf		$1.15192 \cdot 10^{-1}$ $1.02102 \cdot 10^{-1}$		

8.2 Reaction GTP_hydrolysis_sbo_2_sbc_

This is a reversible reaction of one reactant forming two products.

Name GTP_hydrolysis_sbo_2_sbc_

Notes Second step in hydrolysis of GTP bound to Ras is complexed with NF1 - a mammalian GAP Kf = 40 /sec Kb = 108 /M/sec = 1.08e-04 /uM/sec Phillips RA et al 2003 Biochemistry 3956-3965

Reaction equation

$$RasGDP_minus_NF1_Pi \Longrightarrow Pi + RasGDP_NF1$$
 (12)

Reactant

Table 9: Properties of each reactant.

Id	Name	SBO
RasGDP_minus_NF1_Pi	RasGDP_minus_NF1_Pi	

Products

Table 10: Properties of each product.

Id	Name	SBO
Pi	Pi	
RasGDP_NF1	RasGDP_NF1	

Id	Name	SBO

Kinetic Law

Derived unit contains undeclared units

$$v_2 = \text{vol}(\text{geometry}) \cdot \text{Function_for_GTP_hydrolysis_sbo_2_sbc}([\text{Pi}], [\text{RasGDP_NF1}], \\ [\text{RasGDP_minus_NF1_Pi}], \text{vol}(\text{geometry}), \text{kb}, \text{kf})$$

$$(13)$$

$$Function_for_GTP_hydrolysis_sbo_2_sbc ([Pi], [RasGDP_NF1], [RasGDP_minus_NF1_Pi], \\ vol (geometry), kb, kf) = \frac{kf \cdot [RasGDP_minus_NF1_Pi] - kb \cdot [Pi] \cdot [RasGDP_NF1]}{vol (geometry)}$$
 (14)

$$Function_for_GTP_hydrolysis_sbo_2_sbc ([Pi], [RasGDP_NF1], [RasGDP_minus_NF1_Pi], \\ vol (geometry), kb, kf) = \frac{kf \cdot [RasGDP_minus_NF1_Pi] - kb \cdot [Pi] \cdot [RasGDP_NF1]}{vol (geometry)}$$
 (15)

Table 11: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
kb kf	kb kf		$5.65482 \cdot 10^{-1}$ $2.0944 \cdot 10^{-1}$		

8.3 Reaction Ras_activation

This is a reversible reaction of one reactant forming one product.

Name Ras_activation

Notes Activation of Ras by GAP (i.e NF1) Kf = 418 /sec Kb = 5.5 /sec Table 3, Phillips RA et al 2003 Biochemistry 3956-3965

Reaction equation

$$RasGTP_minus_NF1 \Longrightarrow RasGTP_minus_NF1_star_$$
 (16)

Reactant

Table 12: Properties of each reactant.

Id	Name	SBO
RasGTP_minus_NF1	RasGTP_minus_NF1	

Product

Table 13: Properties of each product.

Id	Name	SBO
RasGTP_minus_NF1_star_	RasGTP_minus_NF1_star_	

Kinetic Law

Derived unit contains undeclared units

$$v_3 = \text{vol (geometry)} \cdot \text{Function_for_Ras_activation ([RasGTP_minus_NF1],}$$

$$[RasGTP_minus_NF1_star_], \text{vol (geometry)}, \text{kb, kf})$$
(17)

$$\begin{aligned} & Function_for_Ras_activation ([RasGTP_minus_NF1], [RasGTP_minus_NF1_star_], \\ & vol (geometry) \, , kb, kf) = \frac{kf \cdot [RasGTP_minus_NF1] - kb \cdot [RasGTP_minus_NF1_star_]}{vol (geometry)} \end{aligned} \tag{18}$$

$$\begin{aligned} & Function_for_Ras_activation\left([RasGTP_minus_NF1],[RasGTP_minus_NF1_star_],\\ & vol\left(geometry\right),kb,kf\right) = \frac{kf \cdot [RasGTP_minus_NF1] - kb \cdot [RasGTP_minus_NF1_star_]}{vol\left(geometry\right)} \end{aligned} \tag{19}$$

Table 14: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
kb	kb		$2.8798 \cdot 10^{-1}$		
kf	kf	2	$2.18865 \cdot 10^{-1}$	0	\square

8.4 Reaction GAP_dissociation

This is a reversible reaction of one reactant forming two products.

Name GAP_dissociation

Notes Dissociation of NF1 from Ras.GDP NF1 is a mammalian GAP Kf = 46.5 /sec Kb = 1.2 /sec/uM Table 3, Phillips RA et al 2003 Biochemistry 3956-3965

Reaction equation

$$RasGDP_NF1 \Longrightarrow RasGDP + NF1 \tag{20}$$

Reactant

Table 15: Properties of each reactant.

Id	Name	SBO
RasGDP_NF1	RasGDP_NF1	

Products

Table 16: Properties of each product.

Id	Name	SBO
RasGDP NF1	RasGDP NF1	

Kinetic Law

Derived unit contains undeclared units

$$v_4 = \text{vol} (\text{geometry}) \cdot \text{Function_for_GAP_dissociation} ([\text{NF1}], [\text{RasGDP}], [\text{RasGDP_NF1}], \\ \text{vol} (\text{geometry}), \text{kb, kf})$$
 (21)

$$\begin{aligned} & Function_for_GAP_dissociation ([NF1], [RasGDP], [RasGDP_NF1], \\ & vol (geometry), kb, kf) = \frac{kf \cdot [RasGDP_NF1] - kb \cdot [RasGDP] \cdot [NF1]}{vol (geometry)} \end{aligned} \tag{22}$$

$$Function_for_GAP_dissociation([NF1], [RasGDP], [RasGDP_NF1], \\ vol(geometry), kb, kf) = \frac{kf \cdot [RasGDP_NF1] - kb \cdot [RasGDP] \cdot [NF1]}{vol(geometry)}$$
 (23)

Table 17: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
kb	kb	6	$5.28318 \cdot 10^{-1}$	3	\overline{Z}
kf	kf	2	$2.43474 \cdot 10^{-1}$	1	

8.5 Reaction NF1_binding

This is a reversible reaction of two reactants forming one product.

Name NF1_binding

Notes Binding of NF1 to Ras.GTP NF1 is a mammalian GAP Kd = 5.3 uM Table 3, Phillips RA et al 2003 Biochemistry 3956-3965

Reaction equation

$$RasGTP + NF1 \Longrightarrow RasGTP_minus_NF1$$
 (24)

Reactants

Table 18: Properties of each reactant.

Id	Name	SBO
RasGTP NF1	RasGTP NF1	

Product

Table 19: Properties of each product.

Id	Name	SBO
RasGTP_minus_NF1	RasGTP_minus_NF1	

Kinetic Law

Derived unit contains undeclared units

$$v_5 = \text{vol}(\text{geometry}) \cdot \text{Function_for_NF1_binding}([\text{NF1}], [\text{RasGTP}], \\ [\text{RasGTP_minus_NF1}], \text{vol}(\text{geometry}), \text{kb}, \text{kf})$$
 (25)

$$\begin{aligned} & Function_for_NF1_binding ([NF1], [RasGTP], [RasGTP_minus_NF1], \\ & vol (geometry), kb, kf) = \frac{kf \cdot [RasGTP] \cdot [NF1] - kb \cdot [RasGTP_minus_NF1]}{vol (geometry)} \end{aligned} \tag{26}$$

$$Function_for_NF1_binding([NF1], [RasGTP], [RasGTP_minus_NF1], \\ vol(geometry), kb, kf) = \frac{kf \cdot [RasGTP] \cdot [NF1] - kb \cdot [RasGTP_minus_NF1]}{vol(geometry)}$$
 (27)

Table 20: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
kb	kb		$3.3301 \cdot 10^{-1}$	2	$\overline{\mathbf{A}}$
kf	kf	ϵ	$6.28318 \cdot 10^{-1}$.3	$\overline{\mathbf{Z}}$

9 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.

9.1 Species Pi

Name Pi

Initial concentration $1 \mu mol \cdot l^{-1}$

This species takes part in one reaction (as a product in GTP_hydrolysis_sbo_2_sbc_).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Pi} = v_2 \tag{28}$$

9.2 Species RasGTP

Name RasGTP

Initial concentration $1 \mu mol \cdot l^{-1}$

This species takes part in one reaction (as a reactant in NF1_binding).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Ras}\mathrm{GTP} = -v_5 \tag{29}$$

9.3 Species RasGTP_minus_NF1

Name RasGTP_minus_NF1

Initial concentration $0 \ \mu mol \cdot l^{-1}$

This species takes part in two reactions (as a reactant in Ras_activation and as a product in NF1_binding).

$$\frac{\mathrm{d}}{\mathrm{d}t} \mathrm{RasGTP_minus_NF1} = |v_5| - |v_3| \tag{30}$$

9.4 Species RasGTP_minus_NF1_star_

Name RasGTP_minus_NF1_star_

Initial concentration $0 \mu mol \cdot l^{-1}$

This species takes part in two reactions (as a reactant in GTP_hydrolysis_sbo_1_sbc_ and as a product in Ras_activation).

$$\frac{d}{dt}RasGTP_minus_NF1_star_ = v_3 - v_1$$
 (31)

9.5 Species RasGDP_minus_NF1_Pi

Name RasGDP_minus_NF1_Pi

Initial concentration $0 \mu mol \cdot l^{-1}$

This species takes part in two reactions (as a reactant in GTP_hydrolysis_sbo_2_sbc_ and as a product in GTP_hydrolysis_sbo_1_sbc_).

$$\frac{\mathrm{d}}{\mathrm{d}t} \mathrm{RasGDP_minus_NF1_Pi} = |v_1| - |v_2| \tag{32}$$

9.6 Species RasGDP_NF1

Name RasGDP_NF1

Initial concentration $0 \mu mol \cdot l^{-1}$

This species takes part in two reactions (as a reactant in GAP_dissociation and as a product in GTP_hydrolysis_sbo_2_sbc_).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{RasGDP_NF1} = |v_2| - |v_4| \tag{33}$$

9.7 Species RasGDP

Name RasGDP

Initial concentration $0 \mu mol \cdot l^{-1}$

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

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{RasGDP} = v_4 \tag{34}$$

9.8 Species NF1

Name NF1

Initial concentration $9.99936338171632 \ \mu mol \cdot l^{-1}$

This species takes part in two reactions (as a reactant in NF1_binding and as a product in GAP_dissociation).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{NF1} = |v_4| - |v_5| \tag{35}$$

 $\mathfrak{BML2}^{d}$ 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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