SBML Model Report

Model name: "Schmierer2010_FIH_Ankyrins"

May 5, 2016

1 General Overview

This is a document in SBML Level 2 Version 4 format. This model was created by the following two authors: Bernhard Schmierer[1] and Vijayalakshmi Chelliah[2] at August 17th 2010 at 2:11 p. m. and last time modified at February 24th 2015 at 8:27 p. m. Table 1 provides 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	16
events	0	constraints	0
reactions	10	function definitions	5
global parameters	16	unit definitions	3
rules	14	initial assignments	0

Model Notes

This a model from the article:
Hypoxia-dependent sequestration of an oxygen sensor by a widespread structural motif can shape the hypoxic response - a predictive kinetic model
Bernhard Schmierer, Bla Novk1 and Christopher J Schofield BMC Systems Biology2010, 4:139 20955552,

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Abstract:
Background
The activity of the heterodimeric transcription factor hypoxia inducible factor (HIF) is regulated by the post-translational, oxygen-dependent hydroxylation of its -subunit by members of the prolyl hydroxylase domain (PHD or EGLN)-family and by factor inhibiting HIF (FIH). PHD-dependent hydroxylation targets HIF for rapid proteasomal degradation; FIH-catalysed asparaginyl-hydroxylation of the C-terminal transactivation domain (CAD) of HIF suppresses the CAD-dependent subset of the extensive transcriptional responses induced by HIF. FIH can also hydroxylate ankyrin-repeat domain (ARD) proteins, a large group of proteins which are functionally unrelated but share common structural features. Competition by ARD proteins for FIH is hypothesised to affect FIH activity towards HIF; however the extent of this competition and its effect on the HIF-dependent hypoxic response are unknown.
Results
To analyse if and in which way the FIH/ARD protein interaction affects HIF-activity, we created a rate equation model. Our model predicts that an oxygen-regulated sequestration of FIH by ARD proteins significantly shapes the input/output characteristics of the HIF system. The FIH/ARD protein interaction is predicted to create an oxygen threshold for HIF CAD-hydroxylation and to significantly sharpen the signal/response curves, which not only focuses HIF CAD-hydroxylation into a defined range of oxygen tensions, but also makes the response ultrasensitive to varying oxygen tensions. Our model further suggests that the hydroxylation status of the ARD protein pool can encode the strength and the duration of a hypoxic episode, which may allow cells to memorise these features for a certain time period after reoxygenation.
Conclusions
The FIH/ARD protein interaction has the potential to contribute to oxygen-range finding, can sensitise the response to changes in oxygen levels, and can provide a memory of the strength and the duration of a hypoxic episode. These emergent properties are predicted to significantly shape the characteristics of HIF activity in animal cells. We argue that the FIH/ARD interaction should be taken into account in studies of the effect of pharmacological inhibition of the HIF-hydroxylases and propose that the interaction of a signalling sensor with a large group of proteins might be a general mechanism for the regulation of signalling pathways.

There are there models described in the paper. 1) Skeleton Model 1 (SKM1) - HIF CAD-hydroxylation in the absence of the FIH/AR-interaction. 2) Skeleton Model 2 (SKM2) - FIG sequestration by ARD proteins and oxygen-dependent FIH-release. 3) Full Model (Fusion of SKM1 and SKM2) - the effects of the FIH/ARD proteins interaction on HIF CAD-hydroxylation.

This model corresponds to the „Full Model„ described in the paper. The model reproduces figure 5 of the publication.

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`

Definition dimensionless

2.2 Unit `time`

Definition dimensionless

2.3 Unit `substance`

Definition dimensionless

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
`compartment_1`	Cell	0000290	3	1	dimensionless	☑	

3.1 Compartment `compartment_1`

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

Name Cell

SBO:0000290 physical compartment

4 Species

This model contains 16 species. The boundary condition of 13 of these species is set to `true` so that these species' amount cannot be changed by any reaction. 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 Condition
species_1	Htot	compartment_1	dimensionless · dimensionless^{-1}	⊟	⊟
species_2	H	compartment_1	dimensionless · dimensionless^{-1}	⊟	⊟
species_3	A	compartment_1	dimensionless · dimensionless^{-1}	⊟	⊟
species_4	HOH	compartment_1	dimensionless · dimensionless^{-1}	⊟	☑
species_5	Atot	compartment_1	dimensionless · dimensionless^{-1}	☑	☑
species_6	AOH	compartment_1	dimensionless · dimensionless^{-1}	⊟	☑
species_7	Ftot	compartment_1	dimensionless · dimensionless^{-1}	☑	☑
species_8	Ptot	compartment_1	dimensionless · dimensionless^{-1}	☑	☑
species_9	HF	compartment_1	dimensionless · dimensionless^{-1}	⊟	☑
species_10	HP	compartment_1	dimensionless · dimensionless^{-1}	⊟	☑

Id	Name	Compartment	Derived Unit	Constant	Boundary Condition
`species_11`	O2	`compartment_1`	dimensionless · dimensionless^{-1}	☑	☑
`species_12`	FIHfree	`compartment_1`	dimensionless · dimensionless^{-1}	⊟	☑
`species_13`	CAD	`compartment_1`	dimensionless · dimensionless^{-1}	⊟	☑
`species_14`	NAD	`compartment_1`	dimensionless · dimensionless^{-1}	⊟	☑
`species_15`	CADOH	`compartment_1`	dimensionless · dimensionless^{-1}	⊟	☑
`species_16`	A for plotting	`compartment_1`	dimensionless · dimensionless^{-1}	⊟	☑

5 Parameters

This model contains 16 global parameters.

Table 4: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
parameter_1	alpha	0000009	0.33	dimensionless	☑
parameter_2	KdFH	0000282	1.00	dimensionless	☑
parameter_3	KdFA	0000282	1.00	dimensionless	☑
parameter_4	KdPH	0000282	1.00	dimensionless	☑
parameter_5	KdHRE	0000282	0.30	dimensionless	☑
parameter_6	gamma	0000009	0.00	dimensionless	☑
parameter_8	kcatPH	0000025	500.00	dimensionless	☑
parameter_10	w	0000009	1.00	dimensionless	☑
parameter_11	eps	0000485	5.00	dimensionless	☑
parameter_14	kdeg_A	0000356	0.20	dimensionless	☐
parameter_16	ksyn_A	0000153	20.00	dimensionless	☐
parameter_7	KiFH	0000261	101.00	dimensionless	☐
parameter_9	KiFA	0000261	1.00	dimensionless	☐
parameter_13	kcatFH	0000025	500.00	dimensionless	☐
parameter_17	kdeg_H	0000356	1.00	dimensionless	☑
parameter_18	ksyn_H	0000153	1.00	dimensionless	☑

6 Function definitions

This is an overview of five function definitions.

6.1 Function definition `function_1`

Name Constant flux (irreversible)

Argument v

Mathematical Expression

$$v \tag{1}$$

6.2 Function definition `function_2`

Name vPH Htot

Arguments kcatPH, Ptot, O2, KdPH, Htot, HP

Mathematical Expression

$$\frac{\frac{\mathrm{Htot} \cdot \mathrm{kcatPH} \cdot \mathrm{Ptot} \cdot \mathrm{O2}}{1+\mathrm{O2}}}{\mathrm{KdPH}+\mathrm{Ptot}+\mathrm{HP}} \tag{2}$$

6.3 Function definition vFH

Name vFH

Arguments Ftot, O2, alpha, H, KiFH, HF, KcatFH

Mathematical Expression

$$\frac{\frac{\mathrm{H} \cdot \mathrm{KcatFH} \cdot \mathrm{Ftot} \cdot \mathrm{O2}}{\mathrm{alpha}+\mathrm{O2}}}{\mathrm{KiFH}+\mathrm{Ftot}+\mathrm{HF}} \tag{3}$$

6.4 Function definition vFA

Name vFA

Arguments Ftot, O2, alpha, A, gamma, Atot, KiFA, KcatFH

Mathematical Expression

$$\frac{\frac{\mathrm{A} \cdot \mathrm{KcatFH} \cdot \mathrm{Ftot} \cdot \mathrm{O2}}{\mathrm{alpha}+\mathrm{O2}}}{\mathrm{KiFA}+\mathrm{A}+\mathrm{gamma} \cdot (\mathrm{Atot}-\mathrm{A})} \tag{4}$$

6.5 Function definition function_3

Name vPH H

Arguments H, kcatPH, Ptot, O2, KdPH, HP

Mathematical Expression

$$\frac{\frac{\mathrm{H} \cdot \mathrm{kcatPH} \cdot \mathrm{Ptot} \cdot \mathrm{O2}}{1+\mathrm{O2}}}{\mathrm{KdPH}+\mathrm{Ptot}+\mathrm{HP}} \tag{5}$$

7 Rules

This is an overview of 14 rules.

7.1 Rule species_4

Rule species_4 is an assignment rule for species species_4:

$$\mathrm{species\_4} = [\mathrm{species\_1}] - [\mathrm{species\_2}] \tag{6}$$

Derived unit dimensionless^{-1}

7.2 Rule species_6

Rule species_6 is an assignment rule for species species_6:

$$\text{species\_6} = [\text{species\_5}] - [\text{species\_3}] \tag{7}$$

Derived unit dimensionless^{-1}

7.3 Rule species_10

Rule species_10 is an assignment rule for species species_10:

$$\text{species\_10} = 0.5 \cdot \left([\text{species\_1}] - [\text{species\_8}] - \text{parameter\_4} + \sqrt{2}\right) \tag{8}$$

7.4 Rule species_13

Rule species_13 is an assignment rule for species species_13:

$$\text{species\_13} = \frac{[\text{species\_2}]}{\text{parameter\_5} + [\text{species\_1}]} \tag{9}$$

Derived unit dimensionless

7.5 Rule species_14

Rule species_14 is an assignment rule for species species_14:

$$\text{species\_14} = \frac{[\text{species\_1}]}{\text{parameter\_5} + [\text{species\_1}]} \tag{10}$$

Derived unit dimensionless

7.6 Rule species_16

Rule species_16 is an assignment rule for species species_16:

$$\text{species\_16} = \frac{[\text{species\_3}]}{[\text{species\_5}]} \tag{11}$$

Derived unit dimensionless^{-1}

7.7 Rule species_15

Rule species_15 is an assignment rule for species species_15:

$$\text{species\_15} = \frac{[\text{species\_1}] - [\text{species\_2}]}{\text{parameter\_5} + [\text{species\_1}]} \tag{12}$$

Derived unit dimensionless

7.8 Rule parameter_14

Rule parameter_14 is an assignment rule for parameter parameter_14:

$$\text{parameter\_14} = \frac{1}{\text{parameter\_11}} \tag{13}$$

7.9 Rule parameter_16

Rule parameter_16 is an assignment rule for parameter parameter_16:

$$\text{parameter\_16} = \frac{[\text{species\_5}]}{\text{parameter\_11}} \tag{14}$$

Derived unit dimensionless

7.10 Rule parameter_7

Rule parameter_7 is an assignment rule for parameter parameter_7:

$$\begin{aligned} \text{parameter\_7} = & \frac{\text{parameter\_2}}{\text{parameter\_3}} \\ & \cdot (\text{parameter\_3} + [\text{species\_3}] + \text{parameter\_6} \cdot ([\text{species\_5}] - [\text{species\_3}])) \end{aligned} \tag{15}$$

Derived unit dimensionless

7.11 Rule species_9

Rule species_9 is an assignment rule for species species_9:

$$\text{species\_9} = 0.5 \cdot \left([\text{species\_2}] - [\text{species\_7}] - \text{parameter\_7} + \sqrt{2}\right) \tag{16}$$

7.12 Rule species_12

Rule species_12 is an assignment rule for species species_12:

$$\text{species\_12} = \frac{\text{parameter\_2} + [\text{species\_9}]}{\text{parameter\_7} + [\text{species\_9}]} \tag{17}$$

Derived unit dimensionless

7.13 Rule parameter_9

Rule parameter_9 is an assignment rule for parameter parameter_9:

$$\text{parameter\_9} = \frac{\text{parameter\_3}}{\text{parameter\_2}} \cdot (\text{parameter\_2} + [\text{species\_9}]) \tag{18}$$

Derived unit dimensionless

7.14 Rule parameter_13

Rule parameter_13 is an assignment rule for parameter parameter_13:

$$\mathrm{parameter\_13} = \mathrm{parameter\_8} \cdot \mathrm{parameter\_10} \tag{19}$$

Derived unit dimensionless

8 Reactions

This model contains ten 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	reaction_1	Htot synthesis	$\emptyset \longrightarrow \text{species\_1}$	0000393
2	reaction_2	Htot basal degradation	$\text{species\_1} \longrightarrow \emptyset$	0000179
3	reaction_3	Htot induced degradation	$\text{species\_1} \xrightarrow{\text{species\_8, species\_11, species\_10}} \emptyset$	0000179
4	reaction_4	H synthesis	$\emptyset \longrightarrow \text{species\_2}$	0000393
5	reaction_5	H basal degardation	$\text{species\_2} \longrightarrow \emptyset$	0000179
6	reaction_6	H induced degradation	$\text{species\_2} \xrightarrow{\text{species\_8, species\_11, species\_10}} \emptyset$	0000179
7	reaction_7	H hydroxylation	$\text{species\_2} \xrightarrow{\text{species\_7, species\_11, species\_9}} \emptyset$	0000233
8	reaction_8	A synthesis	$\emptyset \longrightarrow \text{species\_3}$	0000393
9	reaction_9	A degradation	$\text{species\_3} \longrightarrow \emptyset$	0000179
10	reaction_10	A hydroxylation	$\text{species\_3} \xrightarrow{\text{species\_7, species\_11, species\_5}} \emptyset$	0000233

8.1 Reaction reaction_1

This is an irreversible reaction of no reactant forming one product.

Name Htot synthesis

SBO:0000393 production

Reaction equation

$$\emptyset \longrightarrow \text{species\_1} \tag{20}$$

Product

Table 6: Properties of each product.

Id	Name	SBO
species_1	Htot	

Kinetic Law

Derived unit dimensionless

$$v_1 = \text{vol}\left(\text{compartment\_1}\right) \cdot \text{function\_1}\left(\text{parameter\_18}\right) \tag{21}$$

$$\text{function\_1}\left(\text{v}\right) = \text{v} \tag{22}$$

$$\text{function\_1}\left(\text{v}\right) = \text{v} \tag{23}$$

8.2 Reaction reaction_2

This is an irreversible reaction of one reactant forming no product.

Name Htot basal degradation

SBO:0000179 degradation

Reaction equation

$$\text{species\_1} \longrightarrow \emptyset \tag{24}$$

Reactant

Table 7: Properties of each reactant.

Id	Name	SBO
species_1	Htot	

Kinetic Law

Derived unit dimensionless^{-1}

$$v_2 = \mathrm{vol}\left(\mathrm{compartment\_1}\right) \cdot \mathrm{parameter\_17} \cdot [\mathrm{species\_1}] \tag{25}$$

8.3 Reaction `reaction_3`

This is an irreversible reaction of one reactant forming no product influenced by three modifiers.

Name Htot induced degradation

SBO:0000179 degradation

Reaction equation

$$\mathrm{species\_1} \xrightarrow{\mathrm{species\_8},\ \mathrm{species\_11},\ \mathrm{species\_10}} \emptyset \tag{26}$$

Reactant

Table 8: Properties of each reactant.

Id	Name	SBO
species_1	Htot	

Modifiers

Table 9: Properties of each modifier.

Id	Name	SBO
species_8	Ptot	
species_11	O2	
species_10	HP	

Kinetic Law

Derived unit contains undeclared units

$$v_3 = \mathrm{vol}\left(\mathrm{compartment\_1}\right) \cdot \mathrm{function\_2}\left(\mathrm{parameter\_8}, [\mathrm{species\_8}], [\mathrm{species\_11}], \mathrm{parameter\_4}, [\mathrm{species\_1}], [\mathrm{species\_10}]\right) \tag{27}$$

$$\mathrm{function\_2}\left(\mathrm{kcatPH}, \mathrm{Ptot}, \mathrm{O2}, \mathrm{KdPH}, \mathrm{Htot}, \mathrm{HP}\right) = \frac{\frac{\mathrm{Htot} \cdot \mathrm{kcatPH} \cdot \mathrm{Ptot} \cdot \mathrm{O2}}{1+\mathrm{O2}}}{\mathrm{KdPH} + \mathrm{Ptot} + \mathrm{HP}} \tag{28}$$

$$\mathrm{function\_2}\left(\mathrm{kcatPH}, \mathrm{Ptot}, \mathrm{O2}, \mathrm{KdPH}, \mathrm{Htot}, \mathrm{HP}\right) = \frac{\frac{\mathrm{Htot} \cdot \mathrm{kcatPH} \cdot \mathrm{Ptot} \cdot \mathrm{O2}}{1+\mathrm{O2}}}{\mathrm{KdPH} + \mathrm{Ptot} + \mathrm{HP}} \tag{29}$$

8.4 Reaction `reaction_4`

This is an irreversible reaction of no reactant forming one product.

Name H synthesis

SBO:0000393 production

Reaction equation

$$\emptyset \longrightarrow \mathrm{species\_2} \tag{30}$$

Product

Table 10: Properties of each product.

Id	Name	SBO
`species_2`	H	

Kinetic Law

Derived unit dimensionless

$$v_4 = \mathrm{vol}\left(\mathrm{compartment\_1}\right) \cdot \mathrm{function\_1}\left(\mathrm{parameter\_18}\right) \tag{31}$$

$$\mathrm{function\_1}\left(\mathrm{v}\right) = \mathrm{v} \tag{32}$$

$$\mathrm{function\_1}\left(\mathrm{v}\right) = \mathrm{v} \tag{33}$$

8.5 Reaction `reaction_5`

This is an irreversible reaction of one reactant forming no product.

Name H basal degardation

SBO:0000179 degradation

Reaction equation

$$\text{species\_2} \longrightarrow \emptyset \quad (34)$$

Reactant

Table 11: Properties of each reactant.

Id	Name	SBO
species_2	H	

Kinetic Law

Derived unit dimensionless^{-1}

$$v_5 = \text{vol}\left(\text{compartment\_1}\right) \cdot \text{parameter\_17} \cdot [\text{species\_2}] \quad (35)$$

8.6 Reaction reaction_6

This is an irreversible reaction of one reactant forming no product influenced by three modifiers.

Name H induced degradation

SBO:0000179 degradation

Reaction equation

$$\text{species\_2} \xrightarrow{\text{species\_8, species\_11, species\_10}} \emptyset \quad (36)$$

Reactant

Table 12: Properties of each reactant.

Id	Name	SBO
species_2	H	

Modifiers

Table 13: Properties of each modifier.

Id	Name	SBO
species_8	Ptot	

Id	Name	SBO
species_11	O2	
species_10	HP	

Kinetic Law

Derived unit contains undeclared units

$$v_6 = \mathrm{vol}(\mathrm{compartment\_1}) \cdot \mathrm{function\_3}([\mathrm{species\_2}], \mathrm{parameter\_8}, [\mathrm{species\_8}], [\mathrm{species\_11}], \mathrm{parameter\_4}, [\mathrm{species\_10}]) \tag{37}$$

$$\mathrm{function\_3}(\mathrm{H}, \mathrm{kcatPH}, \mathrm{Ptot}, \mathrm{O2}, \mathrm{KdPH}, \mathrm{HP}) = \frac{\frac{\mathrm{H} \cdot \mathrm{kcatPH} \cdot \mathrm{Ptot} \cdot \mathrm{O2}}{1+\mathrm{O2}}}{\mathrm{KdPH} + \mathrm{Ptot} + \mathrm{HP}} \tag{38}$$

$$\mathrm{function\_3}(\mathrm{H}, \mathrm{kcatPH}, \mathrm{Ptot}, \mathrm{O2}, \mathrm{KdPH}, \mathrm{HP}) = \frac{\frac{\mathrm{H} \cdot \mathrm{kcatPH} \cdot \mathrm{Ptot} \cdot \mathrm{O2}}{1+\mathrm{O2}}}{\mathrm{KdPH} + \mathrm{Ptot} + \mathrm{HP}} \tag{39}$$

8.7 Reaction `reaction_7`

This is an irreversible reaction of one reactant forming no product influenced by three modifiers.

Name H hydroxylation

SBO:0000233 hydroxylation

Reaction equation

$$\mathrm{species\_2} \xrightarrow{\mathrm{species\_7},\ \mathrm{species\_11},\ \mathrm{species\_9}} \emptyset \tag{40}$$

Reactant

Table 14: Properties of each reactant.

Id	Name	SBO
species_2	H	

Modifiers

Table 15: Properties of each modifier.

Id	Name	SBO
species_7	Ftot	
species_11	O2	
species_9	HF	

Kinetic Law

Derived unit dimensionless

$$v_7 = \mathrm{vol}\left(\mathrm{compartment\_1}\right) \cdot \mathrm{vFH}\left([\mathrm{species\_7}], [\mathrm{species\_11}], \mathrm{parameter\_1}, [\mathrm{species\_2}], \mathrm{parameter\_7}, [\mathrm{species\_9}], \mathrm{parameter\_13}\right) \quad (41)$$

$$\mathrm{vFH}\left(\mathrm{Ftot}, \mathrm{O2}, \mathrm{alpha}, \mathrm{H}, \mathrm{KiFH}, \mathrm{HF}, \mathrm{KcatFH}\right) = \frac{\frac{\mathrm{H} \cdot \mathrm{KcatFH} \cdot \mathrm{Ftot} \cdot \mathrm{O2}}{\mathrm{alpha} + \mathrm{O2}}}{\mathrm{KiFH} + \mathrm{Ftot} + \mathrm{HF}} \quad (42)$$

$$\mathrm{vFH}\left(\mathrm{Ftot}, \mathrm{O2}, \mathrm{alpha}, \mathrm{H}, \mathrm{KiFH}, \mathrm{HF}, \mathrm{KcatFH}\right) = \frac{\frac{\mathrm{H} \cdot \mathrm{KcatFH} \cdot \mathrm{Ftot} \cdot \mathrm{O2}}{\mathrm{alpha} + \mathrm{O2}}}{\mathrm{KiFH} + \mathrm{Ftot} + \mathrm{HF}} \quad (43)$$

8.8 Reaction `reaction_8`

This is an irreversible reaction of no reactant forming one product.

Name A synthesis

SBO:0000393 production

Reaction equation

$$\emptyset \longrightarrow \mathrm{species\_3} \quad (44)$$

Product

Table 16: Properties of each product.

Id	Name	SBO
species_3	A	

Kinetic Law

Derived unit dimensionless

$$v_8 = \text{vol}\,(\text{compartment\_1}) \cdot \text{function\_1}\,(\text{parameter\_16}) \tag{45}$$

$$\text{function\_1}\,(\text{v}) = \text{v} \tag{46}$$

$$\text{function\_1}\,(\text{v}) = \text{v} \tag{47}$$

8.9 Reaction `reaction_9`

This is an irreversible reaction of one reactant forming no product.

Name A degradation

SBO:0000179 degradation

Reaction equation

$$\text{species\_3} \longrightarrow \emptyset \tag{48}$$

Reactant

Table 17: Properties of each reactant.

Id	Name	SBO
`species_3`	A	

Kinetic Law

Derived unit dimensionless^{-1}

$$v_9 = \text{vol}\,(\text{compartment\_1}) \cdot \text{parameter\_14} \cdot [\text{species\_3}] \tag{49}$$

8.10 Reaction `reaction_10`

This is an irreversible reaction of one reactant forming no product influenced by three modifiers.

Name A hydroxylation

SBO:0000233 hydroxylation

Reaction equation

$$\text{species\_3} \xrightarrow{\text{species\_7, species\_11, species\_5}} \emptyset \tag{50}$$

Reactant

Table 18: Properties of each reactant.

Id	Name	SBO
species_3	A	

Modifiers

Table 19: Properties of each modifier.

Id	Name	SBO
species_7	Ftot	
species_11	O2	
species_5	Atot	

Kinetic Law

Derived unit dimensionless

$$v_{10} = \mathrm{vol}\left(\mathrm{compartment\_1}\right) \cdot \mathrm{vFA}\left([\mathrm{species\_7}], [\mathrm{species\_11}], \mathrm{parameter\_1}, [\mathrm{species\_3}], \mathrm{parameter\_6}, [\mathrm{species\_5}], \mathrm{parameter\_9}, \mathrm{parameter\_13}\right) \quad (51)$$

$$\mathrm{vFA}\left(\mathrm{Ftot}, \mathrm{O2}, \mathrm{alpha}, \mathrm{A}, \mathrm{gamma}, \mathrm{Atot}, \mathrm{KiFA}, \mathrm{KcatFH}\right) = \frac{\frac{\mathrm{A} \cdot \mathrm{KcatFH} \cdot \mathrm{Ftot} \cdot \mathrm{O2}}{\mathrm{alpha} + \mathrm{O2}}}{\mathrm{KiFA} + \mathrm{A} + \mathrm{gamma} \cdot \left(\mathrm{Atot} - \mathrm{A}\right)} \quad (52)$$

$$\mathrm{vFA}\left(\mathrm{Ftot}, \mathrm{O2}, \mathrm{alpha}, \mathrm{A}, \mathrm{gamma}, \mathrm{Atot}, \mathrm{KiFA}, \mathrm{KcatFH}\right) = \frac{\frac{\mathrm{A} \cdot \mathrm{KcatFH} \cdot \mathrm{Ftot} \cdot \mathrm{O2}}{\mathrm{alpha} + \mathrm{O2}}}{\mathrm{KiFA} + \mathrm{A} + \mathrm{gamma} \cdot \left(\mathrm{Atot} - \mathrm{A}\right)} \quad (53)$$

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 species_1

Name Htot

SBO:0000245 macromolecule

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

This species takes part in three reactions (as a reactant in reaction_2, reaction_3 and as a product in reaction_1).

$$\frac{\mathrm{d}}{\mathrm{d}t}\text{species\_1} = v_1 - v_2 - v_3 \tag{54}$$

9.2 Species species_2

Name H

SBO:0000245 macromolecule

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

This species takes part in four reactions (as a reactant in reaction_5, reaction_6, reaction_7 and as a product in reaction_4).

$$\frac{\mathrm{d}}{\mathrm{d}t}\text{species\_2} = v_4 - v_5 - v_6 - v_7 \tag{55}$$

9.3 Species species_3

Name A

SBO:0000245 macromolecule

Initial concentration $100 \text{ dimensionless} \cdot \text{dimensionless}^{-1}$

This species takes part in three reactions (as a reactant in reaction_9, reaction_10 and as a product in reaction_8).

$$\frac{\mathrm{d}}{\mathrm{d}t}\text{species\_3} = v_8 - v_9 - v_{10} \tag{56}$$

9.4 Species species_4

Name HOH

SBO:0000245 macromolecule

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

Involved in rule species_4

One rule determines the species' quantity.

9.5 Species species_5

Name Atot

SBO:0000245 macromolecule

Initial concentration $100 \text{ dimensionless} \cdot \text{dimensionless}^{-1}$

This species takes part in one reaction (as a modifier in reaction_10), which does not influence its rate of change because this constant species is on the boundary of the reaction system:

$$\frac{d}{dt}\text{species\_5} = 0 \tag{57}$$

9.6 Species species_6

Name AOH

SBO:0000245 macromolecule

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

Involved in rule species_6

One rule determines the species' quantity.

9.7 Species species_7

Name Ftot

SBO:0000245 macromolecule

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

This species takes part in two reactions (as a modifier in reaction_7, reaction_10), which do not influence its rate of change because this constant species is on the boundary of the reaction system:

$$\frac{d}{dt}\text{species\_7} = 0 \tag{58}$$

9.8 Species species_8

Name Ptot

SBO:0000245 macromolecule

Initial concentration $0.2 \text{ dimensionless} \cdot \text{dimensionless}^{-1}$

This species takes part in two reactions (as a modifier in reaction_3, reaction_6), which do not influence its rate of change because this constant species is on the boundary of the reaction system:

$$\frac{d}{dt}\text{species\_8} = 0 \tag{59}$$

9.9 Species species_9

Name HF

SBO:0000245 macromolecule

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

Involved in rule species_9

This species takes part in one reaction (as a modifier in reaction_7). Not this but one rule determines the species' quantity because this species is on the boundary of the reaction system.

9.10 Species species_10

Name HP

SBO:0000245 macromolecule

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

Involved in rule species_10

This species takes part in two reactions (as a modifier in reaction_3, reaction_6). Not these but one rule determines the species' quantity because this species is on the boundary of the reaction system.

9.11 Species species_11

Name O2

SBO:0000247 simple chemical

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

This species takes part in four reactions (as a modifier in reaction_3, reaction_6, reaction_7, reaction_10), which do not influence its rate of change because this constant species is on the boundary of the reaction system:

$$\frac{\mathrm{d}}{\mathrm{d}t}\text{species\_11} = 0 \tag{60}$$

9.12 Species species_12

Name FIHfree

SBO:0000245 macromolecule

Initial concentration $0.0099009900990099\ \text{dimensionless}\cdot\text{dimensionless}^{-1}$

Involved in rule species_12

One rule determines the species' quantity.

9.13 Species species_13

Name CAD

SBO:0000245 macromolecule

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

Involved in rule species_13

One rule determines the species' quantity.

9.14 Species species_14

Name NAD

SBO:0000247 simple chemical

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

Involved in rule species_14

One rule determines the species' quantity.

9.15 Species species_15

Name CADOH

SBO:0000245 macromolecule

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

Involved in rule species_15

One rule determines the species' quantity.

9.16 Species species_16

Name A for plotting

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

Involved in rule species_16

One rule determines the species' quantity.

A Glossary of Systems Biology Ontology Terms

SBO:0000009 kinetic constant: Numerical parameter that quantifies the velocity of a chemical reaction

SBO:0000025 catalytic rate constant: Numerical parameter that quantifies the velocity of an enzymatic reaction

SBO:0000153 forward rate constant: Numerical parameter that quantifies the forward velocity of a chemical reaction. This parameter encompasses all the contributions to the velocity except the quantity of the reactants

SBO:0000179 degradation: Complete disappearance of a physical entity

SBO:0000233 hydroxylation: Addition of an hydroxyl group (-OH) to a chemical entity.

SBO:0000245 macromolecule: Molecular entity mainly built-up by the repetition of pseudo-identical units. CHEBI:3383

SBO:0000247 simple chemical: Simple, non-repetitive chemical entity

SBO:0000261 inhibitory constant: Dissociation constant of a compound from a target of which it inhibits the function.

SBO:0000282 dissociation constant: Equilibrium constant that measures the propensity of a larger object to separate (dissociate) reversibly into smaller components, as when a complex falls apart into its component molecules, or when a salt splits up into its component ions. The dissociation constant is usually denoted Kd and is the inverse of the affinity constant.

SBO:0000290 physical compartment: Specific location of space, that can be bounded or not. A physical compartment can have 1, 2 or 3 dimensions

SBO:0000356 decay constant: Kinetic constant characterising a mono-exponential decay. It is the inverse of the mean lifetime of the continuant being decayed. Its unit is“per tim”.

SBO:0000393 production: Generation of a material or conceptual entity.

SBO:0000485 basal rate constant: The minimal velocity observed under defined conditions, which may or may not include the presence of an effector. For example in an inhibitory system, this would be the residual velocity observed under full inhibition. In non-essential activation, this would be the velocity in the absence of any activator

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