SBML Model Report

Model name: "Hunziker2010_p53-_StressSpecificResponse"

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: Vijayalakshmi Chelliah[1] and Alexander Hunziker[2] at July 16th 2010 at 1:06 p. m. and last time modified at February 25th 2015 at 12:12 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	4
events	0	constraints	0
reactions	0	function definitions	0
global parameters	9	unit definitions	3
rules	4	initial assignments	0

Model Notes

This a model from the article:
Stress-specific response of the p53-Mdm2 feedback loop
Alexander Hunziker, Mogens H Jensen and Sandeep Krishna BMC Systems Biology 2010, Jul 12;4(1):94 20624280,

[1]EMBL-EBI, viji@ebi.ac.uk
[2]Niels Bohr Institute, alex.hunziker@nbi.dk

Abstract:
ABSTRACT: BACKGROUND: The p53 signalling pathway has hundreds of inputs and outputs. It can trigger cellular senescence, cell-cycle arrest and apoptosis in response to diverse stress conditions, including DNA damage, hypoxia and nutrient deprivation. Signals from all these inputs are channeled through a single node, the transcription factor p53. Yet, the pathway is flexible enough to produce different downstream gene expression patterns in response to different stresses. RESULTS: We construct a mathematical model of the negative feedback loop involving p53 and its inhibitor, Mdm2, at the core of this pathway, and use it to examine the effect of different stresses that trigger p53. In response to DNA damage, hypoxia, etc., the model exhibits a wide variety of specific output behaviour – steady states with low or high levels of p53 and Mdm2, as well as spiky oscillations with low or high average p53 levels. CONCLUSIONS: We show that even a simple negative feedback loop is capable of exhibiting the kind of flexible stress-specific response observed in the p53 system. Further, our model provides a framework for predicting the differences in p53 response to different stresses and single nucleotide polymorphisms.

The parameters of the model corresponds to the resting state, with delta = $11hr^{-1}$, gamma = $0.2hr^{-1}$, $k_t = 0.03nM^{-1}hr^{-1}$ and $k_f = 5000nM^{-1}hr^{-1}$.

To simulate different stress conditions as in figure 2A (also look at the curation figure of this model) of the reference publication, the above parameter should be changed. The parameter values corresponding to different stress conditions are shown in the following table.

Stress Condition/Parameter	delta	gamma	k_t	k_f
Nutlin	$11hr^{-1}$	$0.2hr^{-1}$	$0.03nM^{-1}hr^{-1}$	$500nM^{-1}hr^{-1}$
Oncogene	$2hr^{-1}$	$0.2hr^{-1}$	$0.03nM^{-1}hr^{-1}$	$5000nM^{-1}hr^{-1}$
DNA damage	$2hr^{-1}$	$0.5hr^{-1}$	$0.03nM^{-1}hr^{-1}$	$2500nM^{-1}hr^{-1}$
Hypoxia	$2hr^{-1}$	$0.2hr^{-1}$	$0.01nM^{-1}hr^{-1}$	$5000nM^{-1}hr^{-1}$

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 3600 s

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 3: Properties of all compartments.

Id	Name	SBO	Spatial Dimensions	Size	Unit	Constant	Outside
compartment_1	cell		3	1	dimensionless	☑	

3.1 Compartment compartment_1

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

Name cell

4 Species

This model contains four species. The boundary condition of four 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 4: Properties of each species.

Id	Name	Compartment	Derived Unit	Constant	Boundary Condition
p	p	compartment_1	dimensionless · dimensionless^{-1}	⊟	☑
mm	mm	compartment_1	dimensionless · dimensionless^{-1}	⊟	☑
m	m	compartment_1	dimensionless · dimensionless^{-1}	⊟	☑
pm	pm	compartment_1	dimensionless · dimensionless^{-1}	⊟	☑

5 Parameters

This model contains nine global parameters.

Table 5: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
S	S		1000.00		☑
alpha	alpha	0000356	0.10		☑
k_t	k_t	0000009	0.03		☑
k_tl	k_tl	0000009	1.40		☑
k_b	k_b	0000282	7200.00		☑
k_f	k_f	0000337	5000.00		☑
beta	beta	0000356	0.60		☑
gamma	gamma	0000356	0.20		☑
delta	delta	0000356	11.00		☑

6 Rules

This is an overview of four rules.

6.1 Rule p

Rule p is a rate rule for species p:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{p} = \mathrm{S} - \mathrm{k\_f} \cdot [\mathrm{p}] \cdot [\mathrm{m}] - \mathrm{alpha} \cdot [\mathrm{p}] + (\mathrm{k\_b} + \mathrm{gamma}) \cdot [\mathrm{pm}] \tag{1}$$

6.2 Rule mm

Rule mm is a rate rule for species mm:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{mm} = \mathrm{k\_t} \cdot [\mathrm{p}]^2 - \mathrm{beta} \cdot [\mathrm{mm}] \tag{2}$$

6.3 Rule m

Rule m is a rate rule for species m:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{m} = \mathrm{k\_tl} \cdot [\mathrm{mm}] - \mathrm{k\_f} \cdot [\mathrm{p}] \cdot [\mathrm{m}] + (\mathrm{k\_b} + \mathrm{delta}) \cdot [\mathrm{pm}] - \mathrm{gamma} \cdot [\mathrm{m}] \tag{3}$$

6.4 Rule pm

Rule pm is a rate rule for species pm:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{pm} = \mathrm{k\_f} \cdot [\mathrm{p}] \cdot [\mathrm{m}] - (\mathrm{k\_b} + \mathrm{delta}) \cdot [\mathrm{pm}] - \mathrm{gamma} \cdot [\mathrm{pm}] \tag{4}$$

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.

7.1 Species p

Name p

SBO:0000252 polypeptide chain

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

Involved in rule p

One rule determines the species' quantity.

7.2 Species mm

Name mm

SBO:0000250 ribonucleic acid

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

Involved in rule mm

One rule determines the species' quantity.

7.3 Species m

Name m

SBO:0000252 polypeptide chain

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

Involved in rule m

One rule determines the species' quantity.

7.4 Species pm

Name pm

SBO:0000297 protein complex

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

Involved in rule pm

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:0000250 ribonucleic acid: Macromolecule formed by a repetition of ribonucleosides linked by phosphodiester bonds. CHEBI:3369

SBO:0000252 polypeptide chain: Naturally occurring macromolecule formed by the repetition of amino-acid residues linked by peptidic bonds. A polypeptide chain is synthesized by the ribosome. CHEBI:1654

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:0000297 protein complex: Macromolecular complex containing one or more polypeptide chains possibly associated with simple chemicals. CHEBI:3608

SBO:0000337 association constant: Equilibrium constant that measures the propensity of two objects to assemble (associate) reversibly into a larger component. The association constant is usually denoted Ka and is the inverse of the dissociation constant.

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”.

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.

[a]Center for Bioinformatics Tübingen (ZBIT), Germany
[b]California Institute of Technology, Beckman Institute BNMC, Pasadena, United States
[c]European Bioinformatics Institute, Wellcome Trust Genome Campus, Hinxton, United Kingdom
[d]EML Research gGmbH, Heidelberg, Germany