SBML Model Report

Model name: "Passos2010_DNAdamage-_CellularSenescence"

May 6, 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 Carole J Proctor[2] at March first 2010 at 12:01 a. m. and last time modified at June third 2014 at 9:10 p. 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	1
species types	0	species	23
events	3	constraints	0
reactions	37	function definitions	0
global parameters	36	unit definitions	1
rules	0	initial assignments	0

Model Notes

This is the model described in: **Feedback between p21 and reactive oxygen production is necessary for cell senescence.**
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J, Wipat A, Saretzki G, Rudolph KL, Kirkwood TB, von Zglinicki T. ;Mol Sys Biol2010;6:347. Epub 2010 Feb 16. PMID:20160708 doi:10.1038/msb.2010.5;

Abstract:
Cellular senescence–the permanent arrest of cycling in normally proliferating cells such as fibroblasts–contributes both to age-related loss of mammalian tissue homeostasis and acts as a tumour suppressor mechanism. The pathways leading to establishment of senescence are proving to be more complex than was previously envisaged. Combining in-silico interactome analysis and functional target gene inhibition, stochastic modelling and live cell microscopy, we show here that there exists a dynamic feedback loop that is triggered by a DNA damage response (DDR) and, which after a delay of several days, locks the cell into an actively maintained state of 'deep' cellular senescence. The essential feature of the loop is that long-term activation of the checkpoint gene CDKN1A (p21) induces mitochondrial dysfunction and production of reactive oxygen species (ROS) through serial signalling through GADD45-MAPK14(p38MAPK)-GRB2-TGFBR2-TGFbeta. These ROS in turn replenish short-lived DNA damage foci and maintain an ongoing DDR. We show that this loop is both necessary and sufficient for the stability of growth arrest during the establishment of the senescent phenotype.

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`

Definition item

2.2 Unit `volume`

Notes Litre is the predefined SBML unit for `volume`.

Definition l

2.3 Unit `area`

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

Definition m^2

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
`cell`		0000290	3	1	litre	☑	

3.1 Compartment `cell`

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

SBO:0000290 physical compartment

4 Species

This model contains 23 species. The boundary condition of two of these species is set to `true` so that these 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
Mdm2		cell	item	⊟	⊟
p53		cell	item	⊟	⊟
Mdm2_p53		cell	item	⊟	⊟
Mdm2_mRNA		cell	item	⊟	⊟
p53_mRNA		cell	item	⊟	⊟
ATMA		cell	item	⊟	⊟
ATMI		cell	item	⊟	⊟
p21		cell	item	⊟	⊟
p21_mRNA		cell	item	⊟	⊟
p21step1		cell	item	⊟	⊟
p21step2		cell	item	⊟	⊟
p53_P		cell	item	⊟	⊟
Mdm2_P		cell	item	⊟	⊟
p21_basal		cell	item	⊟	⊟
p38		cell	item	⊟	⊟
p38_P		cell	item	⊟	⊟
GADD45		cell	item	⊟	⊟
IR		cell	item	⊟	⊟
damDNA		cell	item	⊟	⊟
ROS		cell	item	⊟	⊟
basalROS		cell	item	⊟	⊟

Id	Name	Compartment	Derived Unit	Constant	Boundary Condition
`Sink`		`cell`	item	☑	☑
`Source`		`cell`	item	☑	☑

5 Parameters

This model contains 36 global parameters.

Table 4: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
ksynMdm2		0000009	$4.95 \cdot 10^{-4}$		☑
kdegMdm2		0000356	$4.33 \cdot 10^{-4}$		☑
ksynp53		0000009	0.006		☑
kdegp53		0000356	$8.25 \cdot 10^{-4}$		☑
kdegp53mdm2ind		0000282	$8.25 \cdot 10^{-7}$		☑
kbinMdm2p53		0000337	0.001		☑
krelMdm2p53		0000282	$1.155 \cdot 10^{-6}$		☑
ksynMdm2mRNA		0000009	10^{-4}		☑
kdegMdm2mRNA		0000282	10^{-4}		☑
kactATM		0000363	$2 \cdot 10^{-5}$		☑
kdegATMMdm2		0000356	$4 \cdot 10^{-4}$		☑
kinactATM		0000349	$5 \cdot 10^{-4}$		☑
kphosp53		0000009	0.006		☑
kdephosp53		0000009	0.500		☑
kphosMdm2			2.000		☑
kdephosMdm2		0000009	0.500		☑
kphosp38		0000009	0.008		☑
kdephosp38		0000009	0.100		☑
kdam		0000009	0.007		☑
krepair		0000009	$6 \cdot 10^{-5}$		☑
kGADD45		0000009	$4 \cdot 10^{-6}$		☑
kdegGADD45		0000356	10^{-5}		☑
ksynp53mRNA		0000009	0.001		☑
kdegp53mRNA		0000356	10^{-4}		☑
ksynp21mRNAp53P			$6 \cdot 10^{-6}$		☑
ksynp21mRNAp53		0000009	$6 \cdot 10^{-8}$		☑
kdegp21mRNA		0000356	$2.4 \cdot 10^{-5}$		☑
ksynp21step1		0000009	$4 \cdot 10^{-4}$		☑
ksynp21step2		0000009	$4 \cdot 10^{-5}$		☑
ksynp21step3		0000009	$4 \cdot 10^{-5}$		☑
kdegp21		0000356	$1.9 \cdot 10^{-4}$		☑
kremROS		0000356	$3.83 \cdot 10^{-4}$		☑
kgenROSp38		0000009	$4.5 \cdot 10^{-4}$		☑
kdamROS		0000009	10^{-5}		☑
kdamBasalROS		0000009	10^{-9}		☑
kp38ROS		0000009	1.000		☐

6 Events

This is an overview of three events. Each event is initiated whenever its trigger condition switches from `false` to `true`. A delay function postpones the effects of an event to a later time point. At the time of execution, an event can assign values to species, parameters or compartments if these are not set to constant.

6.1 Event `stressCell`

Trigger condition

$$t \geq 172800 \tag{1}$$

Assignment

$$[\mathrm{IR}] = 200 \tag{2}$$

6.2 Event `stopStress`

Trigger condition

$$t \geq 172860 \tag{3}$$

Assignment

$$[\mathrm{IR}] = 0 \tag{4}$$

6.3 Event `stopp38ROS`

Trigger condition

$$t \geq 691200 \tag{5}$$

Assignment

$$\mathrm{kp38ROS} = 0.6 \tag{6}$$

7 Reactions

This model contains 37 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	p53mRNASynthesis		Source ⟶ p53_mRNA	0000183
2	p53mRNADegradation		p53_mRNA ⟶ Sink	0000179
3	Mdm2Synthesis		Mdm2_mRNA ⟶ Mdm2_mRNA + Mdm2	0000184
4	Mdm2mRNASynthesis1		p53 ⟶ p53 + Mdm2_mRNA	0000183
5	Mdm2mRNASynthesis2		p53_P ⟶ p53_P + Mdm2_mRNA	0000183
6	Mdm2mRNADegradation		Mdm2_mRNA ⟶ Sink	0000179
7	Mdm2Degradation		Mdm2 ⟶ Sink	0000179
8	p53Synthesis		p53_mRNA ⟶ p53 + p53_mRNA	0000184
9	p53Degradation		Mdm2_p53 ⟶ Mdm2	0000179
10	p53Mdm2IndepDegradation1		p53_P ⟶ Sink	0000179
11	p53Mdm2IndepDegradation2		p53 ⟶ Sink	0000179
12	P53_Mdm2Binding		p53 + Mdm2 ⟶ Mdm2_p53	0000526
13	P53_Mdm2Release		Mdm2_p53 ⟶ p53 + Mdm2	0000180
14	DNAdamage		IR ⟶ IR + damDNA	0000375
15	DNArepair		damDNA ⟶ Sink	0000179
16	ATMactivation		damDNA + ATMI ⟶ damDNA + ATMA	0000176
17	p53phoshorylation		p53 + ATMA ⟶ p53_P + ATMA	0000216
18	p53dephosorylation		p53_P ⟶ p53	0000216
19	Mdm2phoshorylation		Mdm2 + ATMA ⟶ Mdm2_P + ATMA	0000216
20	Mdm2dephosorylation		Mdm2_P ⟶ Mdm2	0000330
21	Mdm2Pdegradation		Mdm2_P ⟶ Sink	0000179
22	ATMInactivation		ATMA ⟶ ATMI	0000176
23	p21mRNASynthesis1		p53 ⟶ p53 + p21_mRNA	0000183

№	Id	Name	Reaction Equation	SBO
24	p21mRNASynthesis2		p53_P $\longrightarrow$ p53_P + p21_mRNA	0000183
25	p21mRNADegradation		p21_mRNA $\longrightarrow$ Sink	0000179
26	p21Synthesis1		p21_mRNA $\longrightarrow$ p21_mRNA + p21step1	0000184
27	p21Synthesis2		p21step1 $\longrightarrow$ p21step2	0000184
28	p21Synthesis3		p21step2 $\longrightarrow$ p21	0000184
29	p21degradation		p21 $\longrightarrow$ Sink	0000179
30	GADD45activation2		p21 $\longrightarrow$ p21 + GADD45	0000176
31	GADD45degradation		GADD45 $\longrightarrow$ Sink	0000179
32	p38activation		p38 + GADD45 $\longrightarrow$ p38_P + GADD45	0000176
33	p38inactivation		p38_P $\longrightarrow$ p38	0000176
34	ROSgenerationP38		p38_P $\longrightarrow$ p38_P + ROS	0000393
35	ROSremoval		ROS $\longrightarrow$ Sink	0000179
36	ROSDNAdamage		ROS $\longrightarrow$ ROS + damDNA	0000176
37	basalROSDNAdamage		basalROS $\longrightarrow$ basalROS + damDNA	0000176

7.1 Reaction p53mRNASynthesis

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

SBO:0000183 transcription

Reaction equation

$$\text{Source} \longrightarrow \text{p53\_mRNA} \tag{7}$$

Reactant

Table 6: Properties of each reactant.

Id	Name	SBO
Source		

Product

Table 7: Properties of each product.

Id	Name	SBO
p53_mRNA		

Kinetic Law

Derived unit contains undeclared units

$$v_1 = \text{ksynp53mRNA} \cdot \text{Source} \tag{8}$$

7.2 Reaction p53mRNADegradation

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

SBO:0000179 degradation

Reaction equation

$$\text{p53\_mRNA} \longrightarrow \text{Sink} \tag{9}$$

Reactant

Table 8: Properties of each reactant.

Id	Name	SBO
p53_mRNA		

Product

Table 9: Properties of each product.

Id	Name	SBO
Sink		

Kinetic Law

Derived unit contains undeclared units

$$v_2 = \text{kdegp53mRNA} \cdot \text{p53\_mRNA} \tag{10}$$

7.3 Reaction Mdm2Synthesis

This is an irreversible reaction of one reactant forming two products.

SBO:0000184 translation

Reaction equation

$$\text{Mdm2\_mRNA} \longrightarrow \text{Mdm2\_mRNA} + \text{Mdm2} \tag{11}$$

Reactant

Table 10: Properties of each reactant.

Id	Name	SBO
Mdm2_mRNA		

Products

Table 11: Properties of each product.

Id	Name	SBO
Mdm2_mRNA		
Mdm2		

Id	Name	SBO

Kinetic Law

Derived unit contains undeclared units

$$v_3 = \text{ksynMdm2} \cdot \text{Mdm2\_mRNA} \tag{12}$$

7.4 Reaction `Mdm2mRNASynthesis1`

This is an irreversible reaction of one reactant forming two products.

SBO:0000183 transcription

Reaction equation

$$\text{p53} \longrightarrow \text{p53} + \text{Mdm2\_mRNA} \tag{13}$$

Reactant

Table 12: Properties of each reactant.

Id	Name	SBO
p53		

Products

Table 13: Properties of each product.

Id	Name	SBO
p53		
Mdm2_mRNA		

Kinetic Law

Derived unit contains undeclared units

$$v_4 = \text{ksynMdm2mRNA} \cdot \text{p53} \tag{14}$$

7.5 Reaction `Mdm2mRNASynthesis2`

This is an irreversible reaction of one reactant forming two products.

SBO:0000183 transcription

Reaction equation

$$\text{p53\_P} \longrightarrow \text{p53\_P} + \text{Mdm2\_mRNA} \tag{15}$$

Reactant

Table 14: Properties of each reactant.

Id	Name	SBO
p53_P		

Products

Table 15: Properties of each product.

Id	Name	SBO
p53_P		
Mdm2_mRNA		

Kinetic Law

Derived unit contains undeclared units

$$v_5 = \text{ksynMdm2mRNA} \cdot \text{p53\_P} \tag{16}$$

7.6 Reaction Mdm2mRNADegradation

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

SBO:0000179 degradation

Reaction equation

$$\text{Mdm2\_mRNA} \longrightarrow \text{Sink} \tag{17}$$

Reactant

Table 16: Properties of each reactant.

Id	Name	SBO
Mdm2_mRNA		

Product

Table 17: Properties of each product.

Id	Name	SBO
Sink		

Kinetic Law

Derived unit contains undeclared units

$$v_6 = \text{kdegMdm2mRNA} \cdot \text{Mdm2\_mRNA} \tag{18}$$

7.7 Reaction Mdm2Degradation

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

SBO:0000179 degradation

Reaction equation

$$\text{Mdm2} \longrightarrow \text{Sink} \tag{19}$$

Reactant

Table 18: Properties of each reactant.

Id	Name	SBO
Mdm2		

Product

Table 19: Properties of each product.

Id	Name	SBO
Sink		

Kinetic Law

Derived unit contains undeclared units

$$v_7 = \text{kdegMdm2} \cdot \text{Mdm2} \tag{20}$$

7.8 Reaction p53Synthesis

This is an irreversible reaction of one reactant forming two products.

SBO:0000184 translation

Reaction equation

$$\text{p53\_mRNA} \longrightarrow \text{p53} + \text{p53\_mRNA} \tag{21}$$

Reactant

Table 20: Properties of each reactant.

Id	Name	SBO
p53_mRNA		

Products

Table 21: Properties of each product.

Id	Name	SBO
p53		
p53_mRNA		

Kinetic Law

Derived unit contains undeclared units

$$v_8 = \text{ksynp53} \cdot \text{p53\_mRNA} \tag{22}$$

7.9 Reaction p53Degradation

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

SBO:0000179 degradation

Reaction equation

$$\text{Mdm2\_p53} \longrightarrow \text{Mdm2} \tag{23}$$

Reactant

Table 22: Properties of each reactant.

Id	Name	SBO
Mdm2_p53		

Product

Table 23: Properties of each product.

Id	Name	SBO
Mdm2		

Kinetic Law

Derived unit contains undeclared units

$$v_9 = \text{kdegp53} \cdot \text{Mdm2\_p53} \tag{24}$$

7.10 Reaction p53Mdm2IndepDegradation1

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

SBO:0000179 degradation

Reaction equation

$$\text{p53\_P} \longrightarrow \text{Sink} \tag{25}$$

Reactant

Table 24: Properties of each reactant.

Id	Name	SBO
p53_P		

Product

Table 25: Properties of each product.

Id	Name	SBO
Sink		

Kinetic Law

Derived unit contains undeclared units

$$v_{10} = \text{kdegp53mdm2ind} \cdot \text{p53\_P} \tag{26}$$

7.11 Reaction p53Mdm2IndepDegradation2

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

SBO:0000179 degradation

Reaction equation

$$\text{p53} \longrightarrow \text{Sink} \tag{27}$$

Reactant

Table 26: Properties of each reactant.

Id	Name	SBO
p53		

Product

Table 27: Properties of each product.

Id	Name	SBO
Sink		

Kinetic Law

Derived unit contains undeclared units

$$v_{11} = \text{kdegp53mdm2ind} \cdot \text{p53} \tag{28}$$

7.12 Reaction P53_Mdm2Binding

This is an irreversible reaction of two reactants forming one product.

SBO:0000526 protein complex formation

Reaction equation

$$\text{p53} + \text{Mdm2} \longrightarrow \text{Mdm2\_p53} \tag{29}$$

Reactants

Table 28: Properties of each reactant.

Id	Name	SBO
p53		
Mdm2		

Product

Table 29: Properties of each product.

Id	Name	SBO
Mdm2_p53		

Kinetic Law

Derived unit contains undeclared units

$$v_{12} = \text{kbinMdm2p53} \cdot \text{p53} \cdot \text{Mdm2} \tag{30}$$

7.13 Reaction P53_Mdm2Release

This is an irreversible reaction of one reactant forming two products.

SBO:0000180 dissociation

Reaction equation

$$\text{Mdm2\_p53} \longrightarrow \text{p53} + \text{Mdm2} \tag{31}$$

Reactant

Table 30: Properties of each reactant.

Id	Name	SBO
Mdm2_p53		

Products

Table 31: Properties of each product.

Id	Name	SBO
p53		
Mdm2		

Kinetic Law

Derived unit contains undeclared units

$$v_{13} = \text{krelMdm2p53} \cdot \text{Mdm2\_p53} \tag{32}$$

7.14 Reaction DNAdamage

This is an irreversible reaction of one reactant forming two products.

SBO:0000375 process

Reaction equation

$$\text{IR} \longrightarrow \text{IR} + \text{damDNA} \tag{33}$$

Reactant

Table 32: Properties of each reactant.

Id	Name	SBO
IR		

Products

Table 33: Properties of each product.

Id	Name	SBO
IR		
damDNA		

Kinetic Law

Derived unit contains undeclared units

$$v_{14} = \text{kdam} \cdot \text{IR} \tag{34}$$

7.15 Reaction DNArepair

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

SBO:0000179 degradation

Reaction equation

$$\text{damDNA} \longrightarrow \text{Sink} \tag{35}$$

Reactant

Table 34: Properties of each reactant.

Id	Name	SBO
damDNA		

Product

Table 35: Properties of each product.

Id	Name	SBO
Sink		

Kinetic Law

Derived unit contains undeclared units

$$v_{15} = \text{krepair} \cdot \text{damDNA} \tag{36}$$

7.16 Reaction ATMactivation

This is an irreversible reaction of two reactants forming two products.

SBO:0000176 biochemical reaction

Reaction equation

$$\text{damDNA} + \text{ATMI} \longrightarrow \text{damDNA} + \text{ATMA} \tag{37}$$

Reactants

Table 36: Properties of each reactant.

Id	Name	SBO
damDNA		
ATMI		

Products

Table 37: Properties of each product.

Id	Name	SBO
damDNA		
ATMA		

Kinetic Law

Derived unit contains undeclared units

$$v_{16} = \text{kactATM} \cdot \text{damDNA} \cdot \text{ATMI} \tag{38}$$

7.17 Reaction p53phoshorylation

This is an irreversible reaction of two reactants forming two products.

SBO:0000216 phosphorylation

Reaction equation

$$\text{p53} + \text{ATMA} \longrightarrow \text{p53\_P} + \text{ATMA} \tag{39}$$

Reactants

Table 38: Properties of each reactant.

Id	Name	SBO
p53		
ATMA		

Products

Table 39: Properties of each product.

Id	Name	SBO
p53_P		
ATMA		

Kinetic Law

Derived unit contains undeclared units

$$v_{17} = \text{kphosp53} \cdot \text{p53} \cdot \text{ATMA} \tag{40}$$

7.18 Reaction p53dephosorylation

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

SBO:0000216 phosphorylation

Reaction equation

$$\text{p53\_P} \longrightarrow \text{p53} \tag{41}$$

Reactant

Table 40: Properties of each reactant.

Id	Name	SBO
p53_P		

Product

Table 41: Properties of each product.

Id	Name	SBO
p53		

Kinetic Law

Derived unit contains undeclared units

$$v_{18} = \text{kdephosp53} \cdot \text{p53\_P} \tag{42}$$

7.19 Reaction Mdm2phoshorylation

This is an irreversible reaction of two reactants forming two products.

SBO:0000216 phosphorylation

Reaction equation

$$\text{Mdm2} + \text{ATMA} \longrightarrow \text{Mdm2\_P} + \text{ATMA} \tag{43}$$

Reactants

Table 42: Properties of each reactant.

Id	Name	SBO
Mdm2		
ATMA		

Products

Table 43: Properties of each product.

Id	Name	SBO
Mdm2_P		
ATMA		

Kinetic Law

Derived unit contains undeclared units

$$v_{19} = \text{kphosMdm2} \cdot \text{Mdm2} \cdot \text{ATMA} \tag{44}$$

7.20 Reaction Mdm2dephosorylation

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

SBO:0000330 dephosphorylation

Reaction equation

$$\text{Mdm2\_P} \longrightarrow \text{Mdm2} \tag{45}$$

Reactant

Table 44: Properties of each reactant.

Id	Name	SBO
Mdm2_P		

Product

Table 45: Properties of each product.

Id	Name	SBO
Mdm2		

Kinetic Law

Derived unit contains undeclared units

$$v_{20} = \text{kdephosMdm2} \cdot \text{Mdm2\_P} \tag{46}$$

7.21 Reaction Mdm2Pdegradation

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

SBO:0000179 degradation

Reaction equation

$$\text{Mdm2\_P} \longrightarrow \text{Sink} \tag{47}$$

Reactant

Table 46: Properties of each reactant.

Id	Name	SBO
Mdm2_P		

Product

Table 47: Properties of each product.

Id	Name	SBO
Sink		

Kinetic Law

Derived unit contains undeclared units

$$v_{21} = \text{kdegATMMdm2} \cdot \text{Mdm2\_P} \tag{48}$$

7.22 Reaction ATMInactivation

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

SBO:0000176 biochemical reaction

Reaction equation

$$\text{ATMA} \longrightarrow \text{ATMI} \tag{49}$$

Reactant

Table 48: Properties of each reactant.

Id	Name	SBO
ATMA		

Product

Table 49: Properties of each product.

Id	Name	SBO
ATMI		

Kinetic Law

Derived unit contains undeclared units

$$v_{22} = \text{kinactATM} \cdot \text{ATMA} \tag{50}$$

7.23 Reaction p21mRNASynthesis1

This is an irreversible reaction of one reactant forming two products.

SBO:0000183 transcription

Reaction equation

$$\text{p53} \longrightarrow \text{p53} + \text{p21\_mRNA} \tag{51}$$

Reactant

Table 50: Properties of each reactant.

Id	Name	SBO
p53		

Products

Table 51: Properties of each product.

Id	Name	SBO
p53		
p21_mRNA		

Kinetic Law

Derived unit contains undeclared units

$$v_{23} = \text{ksynp21mRNAp53} \cdot \text{p53} \tag{52}$$

7.24 Reaction p21mRNASynthesis2

This is an irreversible reaction of one reactant forming two products.

SBO:0000183 transcription

Reaction equation

$$\text{p53\_P} \longrightarrow \text{p53\_P} + \text{p21\_mRNA} \tag{53}$$

Reactant

Table 52: Properties of each reactant.

Id	Name	SBO
p53_P		

Products

Table 53: Properties of each product.

Id	Name	SBO
p53_P		
p21_mRNA		

Kinetic Law

Derived unit contains undeclared units

$$v_{24} = \text{ksynp21mRNAp53P} \cdot \text{p53\_P} \tag{54}$$

7.25 Reaction p21mRNADegradation

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

SBO:0000179 degradation

Reaction equation

$$\text{p21\_mRNA} \longrightarrow \text{Sink} \tag{55}$$

Reactant

Table 54: Properties of each reactant.

Id	Name	SBO
p21_mRNA		

Product

Table 55: Properties of each product.

Id	Name	SBO
Sink		

Kinetic Law

Derived unit contains undeclared units

$$v_{25} = \text{kdegp21mRNA} \cdot \text{p21\_mRNA} \tag{56}$$

7.26 Reaction p21Synthesis1

This is an irreversible reaction of one reactant forming two products.

SBO:0000184 translation

Reaction equation

$$\text{p21\_mRNA} \longrightarrow \text{p21\_mRNA} + \text{p21step1} \tag{57}$$

Reactant

Table 56: Properties of each reactant.

Id	Name	SBO
p21_mRNA		

Products

Table 57: Properties of each product.

Id	Name	SBO
p21_mRNA		
p21step1		

Kinetic Law

Derived unit contains undeclared units

$$v_{26} = \text{ksynp21step1} \cdot \text{p21\_mRNA} \tag{58}$$

7.27 Reaction p21Synthesis2

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

SBO:0000184 translation

Reaction equation

$$\text{p21step1} \longrightarrow \text{p21step2} \tag{59}$$

Reactant

Table 58: Properties of each reactant.

Id	Name	SBO
p21step1		

Product

Table 59: Properties of each product.

Id	Name	SBO
p21step2		

Kinetic Law

Derived unit contains undeclared units

$$v_{27} = \text{ksynp21step2} \cdot \text{p21step1} \tag{60}$$

7.28 Reaction p21Synthesis3

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

SBO:0000184 translation

Reaction equation

$$\text{p21step2} \longrightarrow \text{p21} \tag{61}$$

Reactant

Table 60: Properties of each reactant.

Id	Name	SBO
p21step2		

Product

Table 61: Properties of each product.

Id	Name	SBO
p21		

Kinetic Law

Derived unit contains undeclared units

$$v_{28} = \text{ksynp21step3} \cdot \text{p21step2} \tag{62}$$

7.29 Reaction `p21degradation`

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

SBO:0000179 degradation

Reaction equation

$$\text{p21} \longrightarrow \text{Sink} \tag{63}$$

Reactant

Table 62: Properties of each reactant.

Id	Name	SBO
p21		

Product

Table 63: Properties of each product.

Id	Name	SBO
Sink		

Kinetic Law

Derived unit contains undeclared units

$$v_{29} = \text{kdegp21} \cdot \text{p21} \tag{64}$$

7.30 Reaction `GADD45activation2`

This is an irreversible reaction of one reactant forming two products.

SBO:0000176 biochemical reaction

Reaction equation

$$\text{p21} \longrightarrow \text{p21} + \text{GADD45} \tag{65}$$

Reactant

Table 64: Properties of each reactant.

Id	Name	SBO
p21		

Products

Table 65: Properties of each product.

Id	Name	SBO
p21		
GADD45		

Kinetic Law

Derived unit contains undeclared units

$$v_{30} = \text{kGADD45} \cdot \text{p21} \tag{66}$$

7.31 Reaction GADD45degradation

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

SBO:0000179 degradation

Reaction equation

$$\text{GADD45} \longrightarrow \text{Sink} \tag{67}$$

Reactant

Table 66: Properties of each reactant.

Id	Name	SBO
GADD45		

Product

Table 67: Properties of each product.

Id	Name	SBO
Sink		

Kinetic Law

Derived unit contains undeclared units

$$v_{31} = \text{kdegGADD45} \cdot \text{GADD45} \tag{68}$$

7.32 Reaction p38activation

This is an irreversible reaction of two reactants forming two products.

SBO:0000176 biochemical reaction

Reaction equation

$$\text{p38} + \text{GADD45} \longrightarrow \text{p38\_P} + \text{GADD45} \tag{69}$$

Reactants

Table 68: Properties of each reactant.

Id	Name	SBO
p38		
GADD45		

Products

Table 69: Properties of each product.

Id	Name	SBO
p38_P		
GADD45		

Kinetic Law

Derived unit contains undeclared units

$$v_{32} = \text{kphosp38} \cdot \text{p38} \cdot \text{GADD45} \tag{70}$$

7.33 Reaction p38inactivation

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

SBO:0000176 biochemical reaction

Reaction equation

$$\text{p38\_P} \longrightarrow \text{p38} \tag{71}$$

Reactant

Table 70: Properties of each reactant.

Id	Name	SBO
p38_P		

Product

Table 71: Properties of each product.

Id	Name	SBO
p38		

Kinetic Law

Derived unit contains undeclared units

$$v_{33} = \text{kdephosp38} \cdot \text{p38\_P} \tag{72}$$

7.34 Reaction ROSgenerationP38

This is an irreversible reaction of one reactant forming two products.

SBO:0000393 production

Reaction equation

$$\text{p38\_P} \longrightarrow \text{p38\_P} + \text{ROS} \tag{73}$$

Reactant

Table 72: Properties of each reactant.

Id	Name	SBO
p38_P		

Products

Table 73: Properties of each product.

Id	Name	SBO
p38_P		
ROS		

Kinetic Law

Derived unit contains undeclared units

$$v_{34} = \text{kgenROSp38} \cdot \text{p38\_P} \cdot \text{kp38ROS} \tag{74}$$

7.35 Reaction ROSremoval

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

SBO:0000179 degradation

Reaction equation

$$\text{ROS} \longrightarrow \text{Sink} \tag{75}$$

Reactant

Table 74: Properties of each reactant.

Id	Name	SBO
ROS		

Product

Table 75: Properties of each product.

Id	Name	SBO
Sink		

Id	Name	SBO

Kinetic Law

Derived unit contains undeclared units

$$v_{35} = \text{kremROS} \cdot \text{ROS} \tag{76}$$

7.36 Reaction ROSDNAdamage

This is an irreversible reaction of one reactant forming two products.

SBO:0000176 biochemical reaction

Reaction equation

$$\text{ROS} \longrightarrow \text{ROS} + \text{damDNA} \tag{77}$$

Reactant

Table 76: Properties of each reactant.

Id	Name	SBO
ROS		

Products

Table 77: Properties of each product.

Id	Name	SBO
ROS		
damDNA		

Kinetic Law

Derived unit contains undeclared units

$$v_{36} = \text{kdamROS} \cdot \text{ROS} \tag{78}$$

7.37 Reaction basalROSDNAdamage

This is an irreversible reaction of one reactant forming two products.

SBO:0000176 biochemical reaction

Reaction equation

$$\text{basalROS} \longrightarrow \text{basalROS} + \text{damDNA} \tag{79}$$

Reactant

Table 78: Properties of each reactant.

Id	Name	SBO
basalROS		

Products

Table 79: Properties of each product.

Id	Name	SBO
basalROS		
damDNA		

Kinetic Law

Derived unit contains undeclared units

$$v_{37} = \text{kdamBasalROS} \cdot \text{basalROS} \tag{80}$$

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 `Mdm2`

SBO:0000245 macromolecule

Initial amount 5 item

This species takes part in seven reactions (as a reactant in Mdm2Degradation, P53_Mdm2Binding, Mdm2phoshorylation and as a product in Mdm2Synthesis, p53Degradation, P53_Mdm2Release, Mdm2dephosorylation).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Mdm2} = v_3 + v_9 + v_{13} + v_{20} - v_7 - v_{12} - v_{19} \tag{81}$$

8.2 Species p53

SBO:0000245 macromolecule

Initial amount 5 item

This species takes part in ten reactions (as a reactant in Mdm2mRNASynthesis1, p53Mdm2IndepDegradation2, P53_Mdm2Binding, p53phoshorylation, p21mRNASynthesis1 and as a product in Mdm2mRNASynthesis1, p53Synthesis, P53_Mdm2Release, p53dephosorylation, p21mRNASynthesis1).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{p53} = v_4 + v_8 + v_{13} + v_{18} + v_{23} - v_4 - v_{11} - v_{12} - v_{17} - v_{23} \tag{82}$$

8.3 Species Mdm2_p53

SBO:0000296 macromolecular complex

Initial amount 95 item

This species takes part in three reactions (as a reactant in p53Degradation, P53_Mdm2Release and as a product in P53_Mdm2Binding).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Mdm2\_p53} = v_{12} - v_9 - v_{13} \tag{83}$$

8.4 Species Mdm2_mRNA

SBO:0000278 messenger RNA

Initial amount 10 item

This species takes part in five reactions (as a reactant in Mdm2Synthesis, Mdm2mRNADegradation and as a product in Mdm2Synthesis, Mdm2mRNASynthesis1, Mdm2mRNASynthesis2).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Mdm2\_mRNA} = v_3 + v_4 + v_5 - v_3 - v_6 \tag{84}$$

8.5 Species p53_mRNA

SBO:0000278 messenger RNA

Initial amount 10 item

This species takes part in four reactions (as a reactant in p53mRNADegradation, p53Synthesis and as a product in p53mRNASynthesis, p53Synthesis).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{p53\_mRNA} = v_1 + v_8 - v_2 - v_8 \tag{85}$$

8.6 Species ATMA

SBO:0000245 macromolecule

Initial amount 0 item

This species takes part in six reactions (as a reactant in p53phoshorylation, Mdm2phoshorylation, ATMInactivation and as a product in ATMactivation, p53phoshorylation, Mdm2phoshorylation).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{ATMA} = v_{16} + v_{17} + v_{19} - v_{17} - v_{19} - v_{22} \tag{86}$$

8.7 Species ATMI

SBO:0000245 macromolecule

Initial amount 200 item

This species takes part in two reactions (as a reactant in ATMactivation and as a product in ATMInactivation).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{ATMI} = v_{22} - v_{16} \tag{87}$$

8.8 Species p21

SBO:0000245 macromolecule

Initial amount 0 item

This species takes part in four reactions (as a reactant in p21degradation, GADD45activation2 and as a product in p21Synthesis3, GADD45activation2).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{p21} = v_{28} + v_{30} - v_{29} - v_{30} \tag{88}$$

8.9 Species p21_mRNA

SBO:0000278 messenger RNA

Initial amount 1 item

This species takes part in five reactions (as a reactant in p21mRNADegradation, p21Synthesis1 and as a product in p21mRNASynthesis1, p21mRNASynthesis2, p21Synthesis1).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{p21\_mRNA} = v_{23} + v_{24} + v_{26} - v_{25} - v_{26} \tag{89}$$

8.10 Species p21step1

SBO:0000245 macromolecule

Initial amount 0 item

This species takes part in two reactions (as a reactant in p21Synthesis2 and as a product in p21Synthesis1).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{p21step1} = v_{26} - v_{27} \tag{90}$$

8.11 Species p21step2

SBO:0000245 macromolecule

Initial amount 0 item

This species takes part in two reactions (as a reactant in p21Synthesis3 and as a product in p21Synthesis2).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{p21step2} = v_{27} - v_{28} \tag{91}$$

8.12 Species p53_P

SBO:0000245 macromolecule

Initial amount 0 item

This species takes part in seven reactions (as a reactant in Mdm2mRNASynthesis2, p53Mdm2IndepDegradation1, p53dephosorylation, p21mRNASynthesis2 and as a product in Mdm2mRNASynthesis2, p53phoshorylation, p21mRNASynthesis2).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{p53\_P} = v_5 + v_{17} + v_{24} - v_5 - v_{10} - v_{18} - v_{24} \tag{92}$$

8.13 Species Mdm2_P

SBO:0000245 macromolecule

Initial amount 0 item

This species takes part in three reactions (as a reactant in Mdm2dephosorylation, Mdm2Pdegradation and as a product in Mdm2phoshorylation).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Mdm2\_P} = v_{19} - v_{20} - v_{21} \tag{93}$$

8.14 Species p21_basal

SBO:0000245 macromolecule

Initial amount 7 item

This species does not take part in any reactions. Its quantity does hence not change over time:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{p21\_basal} = 0 \tag{94}$$

8.15 Species p38

SBO:0000245 macromolecule

Initial amount 100 item

This species takes part in two reactions (as a reactant in p38activation and as a product in p38inactivation).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{p38} = v_{33} - v_{32} \tag{95}$$

8.16 Species p38_P

SBO:0000245 macromolecule

Initial amount 0 item

This species takes part in four reactions (as a reactant in p38inactivation, ROSgenerationP38 and as a product in p38activation, ROSgenerationP38).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{p38\_P} = v_{32} + v_{34} - v_{33} - v_{34} \tag{96}$$

8.17 Species GADD45

SBO:0000245 macromolecule

Initial amount 0 item

This species takes part in four reactions (as a reactant in GADD45degradation, p38activation and as a product in GADD45activation2, p38activation).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{GADD45} = v_{30} + v_{32} - v_{31} - v_{32} \tag{97}$$

8.18 Species IR

SBO:0000405 perturbing agent

Initial amount 0 item

Involved in events stressCell, stopStress

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

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{IR} = v_{14} - v_{14} \tag{98}$$

Furthermore, two events influence this species' rate of change.

8.19 Species damDNA

SBO:0000251 deoxyribonucleic acid

Initial amount 0 item

This species takes part in six reactions (as a reactant in DNArepair, ATMactivation and as a product in DNAdamage, ATMactivation, ROSDNAdamage, basalROSDNAdamage).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{damDNA} = v_{14} + v_{16} + v_{36} + v_{37} - v_{15} - v_{16} \tag{99}$$

8.20 Species ROS

SBO:0000327 non-macromolecular ion

Initial amount 0 item

This species takes part in four reactions (as a reactant in ROSremoval, ROSDNAdamage and as a product in ROSgenerationP38, ROSDNAdamage).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{ROS} = v_{34} + v_{36} - v_{35} - v_{36} \tag{100}$$

8.21 Species basalROS

SBO:0000327 non-macromolecular ion

Initial amount 10 item

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

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{basalROS} = v_{37} - v_{37} \tag{101}$$

8.22 Species Sink

SBO:0000291 empty set

Initial amount 1 item

This species takes part in eleven reactions (as a product in p53mRNADegradation, Mdm2mRNADegradation, Mdm2Degradation, p53Mdm2IndepDegradation1, p53Mdm2IndepDegradation2, DNArepair, Mdm2Pdegradation, p21mRNADegradation, p21degradation, GADD45degradation, ROSremoval), which do not influence its rate of change because this constant species is on the boundary of the reaction system:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Sink} = 0 \tag{102}$$

8.23 Species Source

SBO:0000291 empty set

Initial amount 1 item

This species takes part in one reaction (as a reactant in p53mRNASynthesis), which does not influence its rate of change because this constant species is on the boundary of the reaction system:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Source} = 0 \tag{103}$$

A Glossary of Systems Biology Ontology Terms

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

SBO:0000176 biochemical reaction: An event involving one or more chemical entities that modifies the electrochemical structure of at least one of the participants.

SBO:0000179 degradation: Complete disappearance of a physical entity

SBO:0000180 dissociation: Transformation of a non-covalent complex that results in the formation of several independent biochemical entitie

SBO:0000183 transcription: Process through which a DNA sequence is copied to produce a complementary RNA

SBO:0000184 translation: Process in which a polypeptide chain is produced from a messenger RNA

SBO:0000216 phosphorylation: Addition of a phosphate group (-H2PO4) to a chemical entity

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

SBO:0000251 deoxyribonucleic acid: Polymer composed of nucleotides containing deoxyribose and linked by phosphodiester bonds. CHEBI:16991

SBO:0000278 messenger RNA: A messenger RNA is a ribonucleic acid synthesized during the transcription of a gene, and that carries the information to encode one or several proteins

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:0000291 empty set: Entity defined by the absence of any actual object. An empty set is often used to represent the source of a creation process or the result of a degradation process.

SBO:0000296 macromolecular complex: Non-covalent complex of one or more macromolecules and zero or more simple chemicals

SBO:0000327 non-macromolecular ion: Chemical entity having a net electric charge

SBO:0000330 dephosphorylation: Removal of a phosphate group (-H2PO4) from a chemical entity.

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:0000349 inactivation rate constant: Kinetic constant describing the rate of an irreversible enzyme inactivation by decay of the active enzyme into its inactive form

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:0000363 activation constant: Dissociation constant of a potentiator (activator) from a target (e.g. an enzyme) of which it activates the function

SBO:0000375 process: A sequential series of actions, motions, or occurrences, such as chemical reactions, that affect one or more entities in a phenomenologically characteristic manner

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

SBO:0000405 perturbing agent: A material entity that is responsible for a perturbing effec

SBO:0000526 protein complex formation: The process by which two or more proteins interact non-covalently to form a protein complex (SBO:0000297)

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