SBML Model Report

Model name: “Proctor2008 - p53/Mdm2 circuit - p53 stablisation by p14ARF”

May 5, 2016

1 General Overview

This is a document in SBML Level 2 Version 3 format. This model was created by the following three authors: Carole Proctor[1], Vijayalakshmi Chelliah[2] and Douglas A Gray[3] at September fifth 2008 at 1:47 p. m. and last time modified at April eleventh 2016 at 4:06 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	18
events	2	constraints	0
reactions	14	function definitions	0
global parameters	16	unit definitions	5
rules	2	initial assignments	0

Model Notes

Proctor2008 - p53/Mdm2 circuit - p53 stabilisation by p14ARF

This model is described in the article:Explaining oscillations and variability in the p53-Mdm2 system.Proctor CJ, Gray DA.BMC Syst Biol 2008; 2: 75

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Abstract:

BACKGROUND: In individual living cells p53 has been found to be expressed in a series of discrete pulses after DNA damage. Its negative regulator Mdm2 also demonstrates oscillatory behaviour. Attempts have been made recently to explain this behaviour by mathematical models but these have not addressed explicit molecular mechanisms. We describe two stochastic mechanistic models of the p53/Mdm2 circuit and show that sustained oscillations result directly from the key biological features, without assuming complicated mathematical functions or requiring more than one feedback loop. Each model examines a different mechanism for providing a negative feedback loop which results in p53 activation after DNA damage. The first model (ARF model) looks at the mechanism of p14ARF which sequesters Mdm2 and leads to stabilisation of p53. The second model (ATM model) examines the mechanism of ATM activation which leads to phosphorylation of both p53 and Mdm2 and increased degradation of Mdm2, which again results in p53 stabilisation. The models can readily be modified as further information becomes available, and linked to other models of cellular ageing. RESULTS: The ARF model is robust to changes in its parameters and predicts undamped oscillations after DNA damage so long as the signal persists. It also predicts that if there is a gradual accumulation of DNA damage, such as may occur in ageing, oscillations break out once a threshold level of damage is acquired. The ATM model requires an additional step for p53 synthesis for sustained oscillations to develop. The ATM model shows much more variability in the oscillatory behaviour and this variability is observed over a wide range of parameter values. This may account for the large variability seen in the experimental data which so far has examined ARF negative cells. CONCLUSION: The models predict more regular oscillations if ARF is present and suggest the need for further experiments in ARF positive cells to test these predictions. Our work illustrates the importance of systems biology approaches to understanding the complex role of p53 in both ageing and cancer.

This model is hosted on BioModels Database and identified by: BIOMD0000000188.

To cite BioModels Database, please use: BioModels Database: An enhanced, curated and annotated resource for published quantitative kinetic models.

2 Unit Definitions

This is an overview of ten unit definitions of which five are predefined by SBML and not mentioned in the model.

2.1 Unit `molepsecpdGy`

Name molepsecpdGy

Definition $\text{mol} \cdot \text{s}^{-1} \cdot (10\,\text{Gy})^{-1}$

2.2 Unit decagray

Name dGy

Definition 10 Gy

2.3 Unit molepsec

Name molepsec

Definition $\mathrm{mol} \cdot \mathrm{s}^{-1}$

2.4 Unit pmolepsec

Name pmolepsec

Definition $\mathrm{mol}^{-1} \cdot \mathrm{s}^{-1}$

2.5 Unit psec

Name psec

Definition s^{-1}

2.6 Unit substance

Notes Mole is the predefined SBML unit for `substance`.

Definition mol

2.7 Unit volume

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

Definition l

2.8 Unit area

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

Definition m^2

2.9 Unit length

Notes Metre is the predefined SBML unit for `length` since SBML Level 2 Version 1.

Definition m

2.10 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`			3	1	litre	☑	

3.1 Compartment `cell`

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

4 Species

This model contains 18 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 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
Mdm2		cell	mol	☐	☐
p53		cell	mol	☐	☐
Mdm2_p53		cell	mol	☐	☐
Mdm2_mRNA		cell	mol	☐	☐
ARF		cell	mol	☐	☐
ARF_Mdm2		cell	mol	☐	☐
damDNA		cell	mol	☐	☐
Sink		cell	mol	☑	☑
Source		cell	mol	☑	☑
p53deg		cell	mol	☐	☐
p53syn		cell	mol	☐	☐
mdm2deg		cell	mol	☐	☐
mdm2syn		cell	mol	☐	☐
Mdm2mRNAdeg		cell	mol	☐	☐
Mdm2mRNAsyn		cell	mol	☐	☐
totdamDNA		cell	mol	☐	☐
totp53		cell	mol	☐	☐
totMdm2		cell	mol	☐	☐

5 Parameters

This model contains 16 global parameters.

Table 4: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
IR			0.000	10 Gy	☐
ksynMdm2			$4.95 \cdot 10^{-4}$	s^{-1}	☑
kdegMdm2			$4.33 \cdot 10^{-4}$	s^{-1}	☑
ksynp53			0.078	s^{-1}	☑
kdegp53			$8.25 \cdot 10^{-4}$	s^{-1}	☑
kbinMdm2p53			0.001	$mol^{-1} \cdot s^{-1}$	☑
krelMdm2p53			$1.155 \cdot 10^{-5}$	s^{-1}	☑
ksynMdm2mRNA			10^{-4}	s^{-1}	☑
kdegMdm2mRNA			10^{-4}	s^{-1}	☑
kbinARFMdm2			0.010	$mol^{-1} \cdot s^{-1}$	☑
kdegARFMdm2			0.001	s^{-1}	☑
kdegARF			10^{-4}	s^{-1}	☑
kactARF			$3.3 \cdot 10^{-5}$	s^{-1}	☑
kdam			0.080	$mol \cdot s^{-1} \cdot (10\,Gy)^{-1}$	☑
krepair			$2 \cdot 10^{-5}$	s^{-1}	☑
kproteff			1.000	dimensionless	☑

6 Rules

This is an overview of two rules.

6.1 Rule totp53

Rule totp53 is an assignment rule for species totp53:

$$[\text{totp53}] = \text{p53} + \text{Mdm2\_p53} \tag{1}$$

Derived unit mol

6.2 Rule totMdm2

Rule totMdm2 is an assignment rule for species totMdm2:

$$[\text{totMdm2}] = \text{Mdm2} + \text{Mdm2\_p53} + \text{ARF\_Mdm2} \tag{2}$$

Derived unit mol

7 Events

This is an overview of two 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.

7.1 Event `stressCell`

Trigger condition

$$\mathrm{t} \geq 3600 \tag{3}$$

Assignment

$$\mathrm{IR} = 25 \tag{4}$$

7.2 Event `stopStress`

Trigger condition

$$\mathrm{t} \geq 3660 \tag{5}$$

Assignment

$$\mathrm{IR} = 0 \tag{6}$$

8 Reactions

This model contains 14 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	Mdm2Synthesis		$\text{Mdm2\_mRNA} \longrightarrow \text{Mdm2\_mRNA} + \text{Mdm2} + \text{mdm2syn}$	
2	Mdm2mRNASynthesis		$\text{p53} \longrightarrow \text{p53} + \text{Mdm2\_mRNA} + \text{Mdm2mRNAsyn}$	
3	Mdm2mRNADegradation		$\text{Mdm2\_mRNA} \longrightarrow \text{Sink} + \text{Mdm2mRNAdeg}$	
4	Mdm2Degradation		$\text{Mdm2} \longrightarrow \text{Sink} + \text{mdm2deg}$	
5	p53Synthesis		$\text{Source} \longrightarrow \text{p53} + \text{p53syn}$	
6	p53Degradation		$\text{Mdm2\_p53} \longrightarrow \text{Mdm2} + \text{p53deg}$	
7	P53_Mdm2Binding		$\text{p53} + \text{Mdm2} \longrightarrow \text{Mdm2\_p53}$	
8	P53_Mdm2Release		$\text{Mdm2\_p53} \longrightarrow \text{p53} + \text{Mdm2}$	
9	DNAdamage		$\emptyset \longrightarrow \text{damDNA} + \text{totdamDNA}$	
10	DNArepair		$\text{damDNA} \longrightarrow \text{Sink}$	
11	ARFactivation		$\text{damDNA} \longrightarrow \text{damDNA} + \text{ARF}$	
12	ARF_Mdm2Binding		$\text{ARF} + \text{Mdm2} \longrightarrow \text{ARF\_Mdm2}$	
13	ARF-_Mdm2Degradation		$\text{ARF\_Mdm2} \longrightarrow \text{ARF} + \text{mdm2deg}$	
14	ARFDegradation		$\text{ARF} \longrightarrow \text{Sink}$	

8.1 Reaction Mdm2Synthesis

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

Reaction equation

$$\mathrm{Mdm2\_mRNA} \longrightarrow \mathrm{Mdm2\_mRNA} + \mathrm{Mdm2} + \mathrm{mdm2syn} \tag{7}$$

Reactant

Table 6: Properties of each reactant.

Id	Name	SBO
Mdm2_mRNA		

Products

Table 7: Properties of each product.

Id	Name	SBO
Mdm2_mRNA		
Mdm2		
mdm2syn		

Kinetic Law

Derived unit $\mathrm{s}^{-1} \cdot \mathrm{mol}$

$$v_1 = \mathrm{ksynMdm2} \cdot \mathrm{Mdm2\_mRNA} \tag{8}$$

8.2 Reaction Mdm2mRNASynthesis

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

Reaction equation

$$\mathrm{p53} \longrightarrow \mathrm{p53} + \mathrm{Mdm2\_mRNA} + \mathrm{Mdm2mRNAsyn} \tag{9}$$

Reactant

Table 8: Properties of each reactant.

Id	Name	SBO
p53		

Products

Table 9: Properties of each product.

Id	Name	SBO
p53		
Mdm2_mRNA		
Mdm2mRNAsyn		

Kinetic Law

Derived unit $s^{-1} \cdot mol$

$$v_2 = \mathrm{ksynMdm2mRNA} \cdot \mathrm{p53} \tag{10}$$

8.3 Reaction Mdm2mRNADegradation

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

Reaction equation

$$\mathrm{Mdm2\_mRNA} \longrightarrow \mathrm{Sink} + \mathrm{Mdm2mRNAdeg} \tag{11}$$

Reactant

Table 10: Properties of each reactant.

Id	Name	SBO
Mdm2_mRNA		

Products

Table 11: Properties of each product.

Id	Name	SBO
Sink		

Id	Name	SBO
Mdm2mRNAdeg		

Kinetic Law

Derived unit $\mathrm{s}^{-1} \cdot \mathrm{mol}$

$$v_3 = \mathrm{kdegMdm2mRNA} \cdot \mathrm{Mdm2\_mRNA} \tag{12}$$

8.4 Reaction Mdm2Degradation

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

Reaction equation

$$\mathrm{Mdm2} \longrightarrow \mathrm{Sink} + \mathrm{mdm2deg} \tag{13}$$

Reactant

Table 12: Properties of each reactant.

Id	Name	SBO
Mdm2		

Products

Table 13: Properties of each product.

Id	Name	SBO
Sink		
mdm2deg		

Kinetic Law

Derived unit $\mathrm{s}^{-1} \cdot \mathrm{mol}$

$$v_4 = \mathrm{kdegMdm2} \cdot \mathrm{Mdm2} \cdot \mathrm{kproteff} \tag{14}$$

8.5 Reaction p53Synthesis

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

Reaction equation

$$\text{Source} \longrightarrow \text{p53} + \text{p53syn} \tag{15}$$

Reactant

Table 14: Properties of each reactant.

Id	Name	SBO
Source		

Products

Table 15: Properties of each product.

Id	Name	SBO
p53		
p53syn		

Kinetic Law

Derived unit $\text{s}^{-1} \cdot \text{mol}$

$$v_5 = \text{ksynp53} \cdot \text{Source} \tag{16}$$

8.6 Reaction `p53Degradation`

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

Reaction equation

$$\text{Mdm2\_p53} \longrightarrow \text{Mdm2} + \text{p53deg} \tag{17}$$

Reactant

Table 16: Properties of each reactant.

Id	Name	SBO
Mdm2_p53		

Products

Table 17: Properties of each product.

Id	Name	SBO
Mdm2		
p53deg		

Kinetic Law

Derived unit $s^{-1} \cdot mol$

$$v_6 = \text{kdegp53} \cdot \text{Mdm2\_p53} \cdot \text{kproteff} \tag{18}$$

8.7 Reaction P53_Mdm2Binding

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

Reaction equation

$$\text{p53} + \text{Mdm2} \longrightarrow \text{Mdm2\_p53} \tag{19}$$

Reactants

Table 18: Properties of each reactant.

Id	Name	SBO
p53		
Mdm2		

Product

Table 19: Properties of each product.

Id	Name	SBO
Mdm2_p53		

Kinetic Law

Derived unit $s^{-1} \cdot mol$

$$v_7 = \text{kbinMdm2p53} \cdot \text{p53} \cdot \text{Mdm2} \tag{20}$$

8.8 Reaction P53_Mdm2Release

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

Reaction equation

$$\text{Mdm2\_p53} \longrightarrow \text{p53} + \text{Mdm2} \tag{21}$$

Reactant

Table 20: Properties of each reactant.

Id	Name	SBO
Mdm2_p53		

Products

Table 21: Properties of each product.

Id	Name	SBO
p53		
Mdm2		

Kinetic Law

Derived unit $\text{s}^{-1} \cdot \text{mol}$

$$v_8 = \text{krelMdm2p53} \cdot \text{Mdm2\_p53} \tag{22}$$

8.9 Reaction DNAdamage

This is an irreversible reaction of no reactant forming two products.

Reaction equation

$$\emptyset \longrightarrow \text{damDNA} + \text{totdamDNA} \tag{23}$$

Products

Table 22: Properties of each product.

Id	Name	SBO
damDNA		

Id	Name	SBO
totdamDNA		

Kinetic Law

Derived unit $\mathrm{mol} \cdot \mathrm{s}^{-1}$

$$v_9 = \mathrm{kdam} \cdot \mathrm{IR} \tag{24}$$

8.10 Reaction DNArepair

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

Reaction equation

$$\mathrm{damDNA} \longrightarrow \mathrm{Sink} \tag{25}$$

Reactant

Table 23: Properties of each reactant.

Id	Name	SBO
damDNA		

Product

Table 24: Properties of each product.

Id	Name	SBO
Sink		

Kinetic Law

Derived unit $\mathrm{s}^{-1} \cdot \mathrm{mol}$

$$v_{10} = \mathrm{krepair} \cdot \mathrm{damDNA} \tag{26}$$

8.11 Reaction ARFactivation

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

Reaction equation

$$\mathrm{damDNA} \longrightarrow \mathrm{damDNA} + \mathrm{ARF} \tag{27}$$

Reactant

Table 25: Properties of each reactant.

Id	Name	SBO
damDNA		

Products

Table 26: Properties of each product.

Id	Name	SBO
damDNA		
ARF		

Kinetic Law

Derived unit $\mathrm{s}^{-1} \cdot \mathrm{mol}$

$$v_{11} = \mathrm{kactARF} \cdot \mathrm{damDNA} \tag{28}$$

8.12 Reaction ARF_Mdm2Binding

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

Reaction equation

$$\mathrm{ARF} + \mathrm{Mdm2} \longrightarrow \mathrm{ARF\_Mdm2} \tag{29}$$

Reactants

Table 27: Properties of each reactant.

Id	Name	SBO
ARF		
Mdm2		

Product

Table 28: Properties of each product.

Id	Name	SBO
ARF_Mdm2		

Kinetic Law

Derived unit $\mathrm{s}^{-1} \cdot \mathrm{mol}$

$$v_{12} = \mathrm{kbinARFMdm2} \cdot \mathrm{ARF} \cdot \mathrm{Mdm2} \tag{30}$$

8.13 Reaction ARF_Mdm2Degradation

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

Reaction equation

$$\mathrm{ARF\_Mdm2} \longrightarrow \mathrm{ARF} + \mathrm{mdm2deg} \tag{31}$$

Reactant

Table 29: Properties of each reactant.

Id	Name	SBO
ARF_Mdm2		

Products

Table 30: Properties of each product.

Id	Name	SBO
ARF		
mdm2deg		

Kinetic Law

Derived unit $\mathrm{s}^{-1} \cdot \mathrm{mol}$

$$v_{13} = \mathrm{kdegARFMdm2} \cdot \mathrm{ARF\_Mdm2} \cdot \mathrm{kproteff} \tag{32}$$

8.14 Reaction ARFDegradation

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

Reaction equation

$$\text{ARF} \longrightarrow \text{Sink} \tag{33}$$

Reactant

Table 31: Properties of each reactant.

Id	Name	SBO
ARF		

Product

Table 32: Properties of each product.

Id	Name	SBO
Sink		

Kinetic Law

Derived unit $\text{s}^{-1} \cdot \text{mol}$

$$v_{14} = \text{kdegARF} \cdot \text{ARF} \cdot \text{kproteff} \tag{34}$$

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.

9.1 Species Mdm2

SBO:0000245 macromolecule

Initial amount 5 mol

This species takes part in six reactions (as a reactant in Mdm2Degradation, P53_Mdm2Binding, ARF_Mdm2Binding and as a product in Mdm2Synthesis, p53Degradation, P53_Mdm2Release).

$$\frac{\text{d}}{\text{d}t}\text{Mdm2} = v_1 + v_6 + v_8 - v_4 - v_7 - v_{12} \tag{35}$$

9.2 Species p53

SBO:0000245 macromolecule

Initial amount 5 mol

This species takes part in five reactions (as a reactant in Mdm2mRNASynthesis, P53_Mdm2Binding and as a product in Mdm2mRNASynthesis, p53Synthesis, P53_Mdm2Release).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{p53} = v_2 + v_5 + v_8 - v_2 - v_7 \tag{36}$$

9.3 Species Mdm2_p53

Initial amount 95 mol

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

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Mdm2\_p53} = v_7 - v_6 - v_8 \tag{37}$$

9.4 Species Mdm2_mRNA

Initial amount 0 mol

This species takes part in four reactions (as a reactant in Mdm2Synthesis, Mdm2mRNADegradation and as a product in Mdm2Synthesis, Mdm2mRNASynthesis).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Mdm2\_mRNA} = v_1 + v_2 - v_1 - v_3 \tag{38}$$

9.5 Species ARF

Initial amount 0 mol

This species takes part in four reactions (as a reactant in ARF_Mdm2Binding, ARFDegradation and as a product in ARFactivation, ARF_Mdm2Degradation).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{ARF} = v_{11} + v_{13} - v_{12} - v_{14} \tag{39}$$

9.6 Species ARF_Mdm2

Initial amount 0 mol

This species takes part in two reactions (as a reactant in ARF_Mdm2Degradation and as a product in ARF_Mdm2Binding).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{ARF\_Mdm2} = v_{12} - v_{13} \tag{40}$$

9.7 Species damDNA

Initial amount 0 mol

This species takes part in four reactions (as a reactant in DNArepair, ARFactivation and as a product in DNAdamage, ARFactivation).

$$\frac{d}{dt}\text{damDNA} = v_9 + v_{11} - v_{10} - v_{11} \tag{41}$$

9.8 Species Sink

Initial amount 1 mol

This species takes part in four reactions (as a product in Mdm2mRNADegradation, Mdm2Degradation, DNArepair, ARFDegradation), which do not influence its rate of change because this constant species is on the boundary of the reaction system:

$$\frac{d}{dt}\text{Sink} = 0 \tag{42}$$

9.9 Species Source

Initial amount 1 mol

This species takes part in one reaction (as a reactant in p53Synthesis), which does not influence its rate of change because this constant species is on the boundary of the reaction system:

$$\frac{d}{dt}\text{Source} = 0 \tag{43}$$

9.10 Species p53deg

Initial amount 0 mol

This species takes part in one reaction (as a product in p53Degradation).

$$\frac{d}{dt}\text{p53deg} = v_6 \tag{44}$$

9.11 Species p53syn

Initial amount 0 mol

This species takes part in one reaction (as a product in p53Synthesis).

$$\frac{d}{dt}\text{p53syn} = v_5 \tag{45}$$

9.12 Species mdm2deg

Initial amount 0 mol

This species takes part in two reactions (as a product in Mdm2Degradation, ARF_Mdm2Degradation).

$$\frac{d}{dt}\text{mdm2deg} = v_4 + v_{13} \tag{46}$$

9.13 Species mdm2syn

Initial amount 0 mol

This species takes part in one reaction (as a product in Mdm2Synthesis).

$$\frac{d}{dt}\text{mdm2syn} = v_1 \tag{47}$$

9.14 Species Mdm2mRNAdeg

Initial amount 0 mol

This species takes part in one reaction (as a product in Mdm2mRNADegradation).

$$\frac{d}{dt}\text{Mdm2mRNAdeg} = v_3 \tag{48}$$

9.15 Species Mdm2mRNAsyn

Initial amount 0 mol

This species takes part in one reaction (as a product in Mdm2mRNASynthesis).

$$\frac{d}{dt}\text{Mdm2mRNAsyn} = v_2 \tag{49}$$

9.16 Species totdamDNA

Initial amount 0 mol

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

$$\frac{d}{dt}\text{totdamDNA} = v_9 \tag{50}$$

9.17 Species totp53

Initial amount 0 mol

Involved in rule totp53

One rule which determines this species' quantity.

9.18 Species totMdm2

Initial amount 0 mol

Involved in rule totMdm2

One rule which determines this species' quantity.

A Glossary of Systems Biology Ontology Terms

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

SBML2LaTeX was developed by Andreas Dräger[a], Hannes Planatscher[a], Dieudonné M Wouamba[a], Adrian Schröder[a], Michael Hucka[b], Lukas Endler[c], Martin Golebiewski[d] and Andreas Zell[a]. Please see http://www.ra.cs.uni-tuebingen.de/software/SBML2LaTeX for more information.

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