A mathematical model of a P53 oscillation network triggered by DNA damage*

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Taking the interaction between a DNA damage repair module, an ATM module, and a P53–MDM2 oscillation module into account, this paper presents a mathematical model of a P53 oscillation network triggered by a DNA damage signal in individual cells. The effects of the DNA damage signal and the delay time of P53-induced MDM2 expression on the behaviours of the P53 oscillation network are studied. In the oscillatory state of the P53–MDM2 oscillator, it is found that the pulse number of P53–P oscillation increases with the increase of the initial DNA damage signal, whereas the amplitude and the period of P53–P oscillation are fixed for different initial DNA damage signals, and the period numbers of P53–P oscillations decrease with the increase of time delay of MDM2 expression induced by P53. These theoretical predictions are consistent with previous experimental results. The combined negative feedback of P53–MDM2 with the time delay of P53-induced MDM2 expression causes oscillation behaviour in the P53 network.

Keywords: P53 oscillation network, DNA damage signal, time delay, kinetic model

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P53 is well known as a tumor-suppressor protein. In normal unstressed cells, the level of active P53 is kept low[1] through the P53–MDM2 negative feedback loop.[2] However, in stressed cells, the active P53 as a transcription factor can transcribe some downstream genes.[3,4] Ionizing radiation (IR) can cause DNA damage that triggers[5] the kinase activity of ataxia telangiectasia mutated (ATM). The primary function of ATM is to act as a kinase detecting[6] and transmitting the DNA damage signal.[7] Phosphorylated ATM (ATM–P) can phosphorylate P53 into active P53–P[8] which turns on the P53 network of transcription. When DNA damage is repaired, ATM activation disappears, and cannot phosphorylate the P53, then the network of transcription is shut down. ATM shows switch characteristics for the P53 network.

Recent experimental results have showed that in response to DNA damage, the P53 and MDM2 proteins levels exhibit damped oscillatory behaviour[9] in a population of cells and undamped behaviour[10] in individual cells. In individual cells, the fluorescence measurements revealed that in response to IR, P53 and MDM2 proteins exhibit a digital response (i.e. discrete pulses of these two proteins), and the average height and duration of P53 and MDM2 proteins are fixed, whereas the mean pulse number of P53 and MDM2 increases with the strength of the DNA damage signal.[10]

Some mathematical models[9,11−20] of the P53 network have been presented to describe the oscillatory behaviour of P53 and MDM2 proteins, and the theoretical results consist partly with the experimental data. In order to generate oscillations, different mechanisms have been proposed. The model in Ref. [9] based on ordinary differential equations has to include a hypothetical intermediate component. The models in Refs. [13] and [18]–[20] are based on dual-feedback mechanisms which combine a negative feedback loop and a positive one. The models in Refs. [11], [12] and [14]–[17] are based on delayed differential equations including explicit time delay. In particular, a unified theoretical model of the P53–MDM2 negative feedback loop with the aim of describing the dynamical behaviours of protein levels both in individuals and populations of cells in a self-consistent and unified way was proposed in Ref. [16]. It can be found that most of these models[9,11,13−17] focus on the research of the P53–MDM2 module; however, the production, detection, and control of DNA damage have not been simultaneously considered and studied in previous models. Although the DNA damage repair module, the ATM module, and the P53–MDM2 core

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oscillation module have been simultaneously considered in Refs. [12], [18] and [19], in which the models involve the production, detection, and control of DNA damage, these models are too complicated.

Based on the DNA damage repair module, the ATM module, and the P53–MDM2 core oscillation module,[12,18,20] in this paper, we have proposed a simple mathematical model to describe the dynamical behaviour of an undamped oscillation P53 and MDM2 network triggered by DNA damage in individual cells, and the effects of the DNA damage signal and the delay time of P53-induced MDM2 expression on the behaviours of the P53 oscillation network are discussed.

The scheme considered here includes three basic module structures; the integrated model is shown in Fig. 1. In the first module, IR can lead the initial DNA damage signal, which inhibits the process of dephosphorylation of ATM–P. In the second module, ATM activation (i.e. ATM–P) is autocatalytic with positive feedback rapidly activating the pool of ATM. In the third module, there is a well-known P53 and MDM2 negative feedback loop, that is, MDM2-dependent degradation of P53. Active P53 (P53–P) is activated by ATM–P, and able to transcribe (after a time delay) MDM2, and activates the repair of DNA damage in the meanwhile.

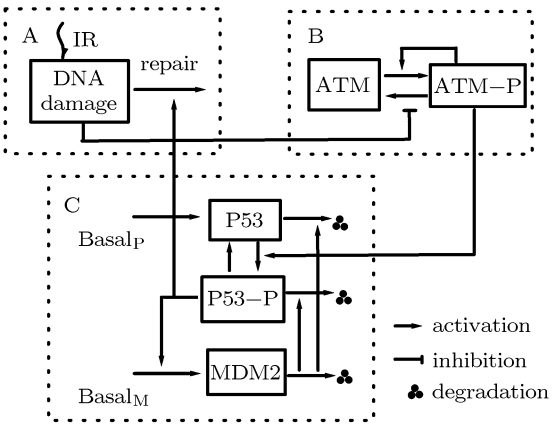


Fig. 1. Scheme of the P53 core regulatory network which is composed of three modules (A represents DNA damage repair module, B represents ATM module, C represents P53–MDM2 core oscillation module).

According to the scheme of Fig. 1, we assume that the concentrations of the DNA damage signal ([S_D]), active ATM ([ATM–P]), P53 ([P53]), active P53 ([P53–P]), and MDM2 ([MDM2]) proteins obey the following dimensionless kinetic equations

$$\frac{\mathrm{d}[S_D](t)}{\mathrm{d}t} = -\alpha_D[\mathrm{P53-P}][S_D], \tag{1}$$

$$\frac{\mathrm{d}[\mathrm{ATM-P}](t)}{\mathrm{d}t} = [\mathrm{ATM-P}]\frac{[\mathrm{ATM}]}{[\mathrm{ATM}]+h_1} - \left(\frac{\alpha_0}{[S_D]+h_0}\right)\left(\frac{[\mathrm{ATM-P}]}{[\mathrm{ATM-P}]+h_2}\right) + \alpha, \tag{2}$$

$$\frac{\mathrm{d}[\mathrm{P53}](t)}{\mathrm{d}t} = \nu_1 - k_1[\mathrm{P53}] - k_2[\mathrm{MDM2}][\mathrm{P53}] - k_3[\mathrm{ATM-P}][\mathrm{P53}] + k_4[\mathrm{P53-P}] - \beta, \tag{3}$$

$$\frac{\mathrm{d}[\mathrm{P53-P}](t)}{\mathrm{d}t} = k_5[\mathrm{ATM-P}][\mathrm{P53}] - k_6[\mathrm{P53-P}] - k_7[\mathrm{MDM2}][\mathrm{P53-P}] + \beta, \tag{4}$$

$$\frac{\mathrm{d}[\mathrm{MDM2}](t)}{\mathrm{d}t} = \nu_2 + \nu_3\frac{[\mathrm{P53-P}]^n(t-\tau)}{[\mathrm{P53-P}]^n(t-\tau)+K^n} - k_8[\mathrm{MDM2}], \tag{5}$$

where τ is the P53-induced transcriptional-translational time delay of the MDM2 protein, and there exists a conservation relationship [ATM]+[ATM–P]=1. On the right-hand side of Eq. (1), the first term describes P53–P-dependent repair of S_D. In Eq. (2), the first term represents the autocatalytic mechanism of ATM–P, the second term describes S_D-dependent dephosphorylation of ATM–P, and the last term describes the basal rate of phosphorylation due to stochastic fluctuations in ATM. In Eq. (3), the first term represents the basal synthesis rate of P53, the second term describes MDM2-independent degradation of P53, the third term describes MDM2-dependent degradation of P53, the fourth term describes ATM–P-dependent phosphorylation of P53, the fifth term describes dephosphorylation of P53–P, and the last term describes the basal rate of phosphorylation due to stochastic fluctuations in P53. In Eq. (4), the second term describes dephosphorylation of P53–P and MDM2-independent degradation of P53–P, and the third term describes MDM2-dependent degradation of P53–P. In Eq. (5),

the first term represents the basal synthesis rate of P53–P-independent MDM2 transcription and translation, the second term describes P53–P-dependent synthesis of MDM2, and the last term describes degradation of MDM2. Descriptions and values of the other parameters in Eqs. (1)–(5) are listed in Table 1. In the following computation, equations (1)–(5) are integrated by using an Euler forward scheme. Our results which can be drawn from the computations of the integrated model Eqs. (1)–(5) are as follows.

The role of ATM is to act as a kinase detecting DNA damage. The experimental results show that ATM is ultra-sensitive as a DNA damage detector.[12] In Fig. 2, we plot the steady-state value of ATM–P versus the parameter DNA damage signal $[S_{\rm D}]$ according to Eq. (2). With the increase of $[S_{\rm D}]$, it can be seen that ATM–P transits from 0 (OFF) to 1 (ON) at the threshold $[S_{\rm D}] \approx 0.27$. That is, ATM–P shows a switch-like behaviour and relays the DNA damage signal.

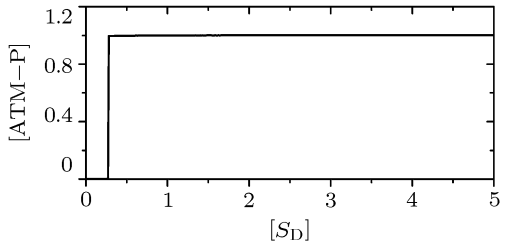


Fig. 2. Steady-state value of ATM–P as a function of DNA damage signal $[S_{\rm D}]$.

The core regulatory circuitry of P53 is a loop formed by P53 and its principal antagonist, MDM2, a P53-specific ubiquitous ligase that is transactivated by P53.[12] On the one hand, ATM–P transits from 0 to 1 with an increasing DNA damage signal $[S_{\rm D}]$ as shown in Fig.2. On the other hand, in the P53–MDM2 core oscillation module, the bifurcation diagram of P53–P as a function of the ATM–P shows that increasing ATM–P produces an abrupt onset of P53–P oscillations (see Fig. 3) where the Hopf bifurcation occurs at [ATM–P]$\approx$ 0.6. It can be seen from Fig. 3 that P53–P is the steady-state at [ATM–P]=0 (OFF, see Fig. 2), while P53–P is the oscillatory state at [ATM–P]=1.0 (ON). Therefore, one can use the DNA damage signal to regulate the oscillation behaviour of the P53–MDM2 core oscillation module very well by finely controlling the ATM module.

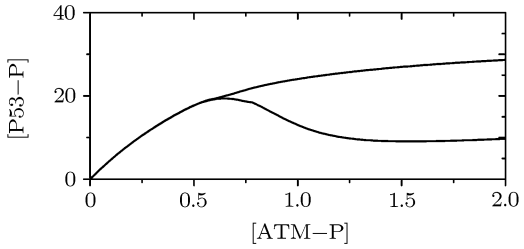


Fig. 3. Bifurcation diagram of P53–P as a function of the parameter ATM–P.

In normal unstressed cells, [ATM–P](t = 0)=0, the initial values of [P53](t), [P53–P](t) and [MDM2](t) can be obtained from a steady-state solution of Eqs. (3)–(5)

$$[\text{P53}](0) = \frac{v_1 + k_4[\text{P53–P}](0) - \beta}{k_1 + k_2[\text{MDM2}](0)}, \tag{6}$$

$$[\text{P53–P}](0) = \frac{\beta}{k_6 + k_7[\text{MDM2}](0)}, \tag{7}$$

$$[\text{MDM2}](0) = \frac{\nu_2}{k_8}, \tag{8}$$

where [P53](0), [P53–P](0) and [MDM2](0) represent initial vaules of P53, P53–P and MDM2, respectively. Inserting the parameter values [see Table 1] into Eqs. (6)–(8), one can obtain [P53](0)=10.45, [P53–P](0)=0.00048, [MDM2](0)=0.047.

Table 1. Parameters of Eqs.(1)-(5).

parameter	value	description
$\alpha_{\rm D}$	0.0002	rate of the decay in damage signal
h_0	0.1	Michaelis–Menten constant
h_1	0.01	Michaelis–Menten constant
h_2	1.0	Michaelis–Menten constant
α_0	0.3	scaling parameter
α	0.0001	basal rate of phosphorylation in ATM
β	0.0001	basal rate of phosphorylation in P53
k_1	0.0004	degradation rate of P53
k_2	1.0	MDM2-dependent degradation rate of P53
k_3	1.0	ATM–P-dependent degradation rate of P53
k_4	0.2	dephosphorylation rate of P53–P
k_5	1.0	ATM–P-dependent synthesis rate of P53–P
k_6	0.208	dephosphorylation/degradation rate of P53–P
k_7	0.005	MDM2-dependent degradation rate of P53–P
k_8	0.05	degradation rate of MDM2
ν_1	0.5	basal synthesis rate of P53 from gene
ν_2	0.0235	basal synthesis rate of MDM2 from gene
ν_3	0.03	P53–P-dependent transcription rate of MDM2
K	25.0	threshold-for-activation constant
n	20	Hill coefficient

For a given initial DNA damage signal $[S_{\rm D}](0) = 10$ and a given P53-induced transcriptional-translational time delay of MDM2 τ = 45 min, the time-series of the protein concentrations, P53–P, MDM2, ATM, ATM–P, and the DNA damage

signal are plotted in Fig. 4. First, IR leads the initial DNA damage signal which inhibits the process of dephosphorylation of ATM–P. The ATM–P level is rapidly increased, and transits from 0 (OFF) to 1 (ON) after a short time interval, then the P53 oscillations occur. Second, the ATM–P phosphorylates P53 into active P53–P which turns on the P53–MDM2 oscillator, meanwhile, the DNA damage signal is reduced by P53–P through the DNA damage repair. Finally, with a decreasing DNA damage signal [$S_{\rm D}$], ATM–P transits from 1 (ON) to 0 (OFF) at [$S_{\rm D}$] $\approx$ 0.27 (the threshold of the DNA damage signal, see Fig. 2), and then the oscillation of the P53–MDM2 oscillator is turned off. In the oscillatory state, it can be found from Fig. 4 that the amplitude and the period of oscillations of P53–P and MDM2 are fixed since the ATM–P is always 1 (ON). Moreover, the first maximum value of P53–P appears earlier than that of MDM2, which means that there is a time delay in the P53–MDM2 oscillator.[9,10] Thus, the DNA damage signal [$S_{\rm D}$] and the P53-induced transcriptional-translational time delay τ of MDM2 play a very important role in the oscillation of the P53–MDM2 oscillator. In what follows the effects of the DNA damage signal and the delay time of P53-induced MDM2 expression on the behaviours of the P53 oscillation network are studied.

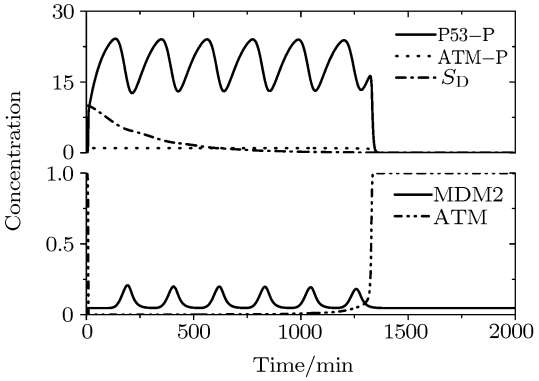


Fig. 4. Time-series of P53–P, MDM2, ATM, ATM–P, and DNA damage signal [$S_{\rm D}$]. The initial concentrations are [P53](0)=10.54, [P53–P](0)=0.00048, [MDM2](0)=0.047, [ATM–P](0)=0, [$S_{\rm D}$](0) = 10, and τ = 45 min.

To characterize the effects of the DNA damage signal on the P53–MDM2 oscillator, figure 5 shows time-series of P53–P under different initial DNA damage signals [$S_{\rm D}$]. It is shown that the pulse number (digital) of P53–P oscillation is increased with the increase of initial DNA damage signal; for example, the pulse number is 7 for [$S_{\rm D}$](0) = 10, 9 for [$S_{\rm D}$](0) = 30, and 10 for [$S_{\rm D}$](0) = 60. However, the amplitude and the period of P53–P oscillation are unchanged in each case. Recent *in vivo* fluorescence measurements in individual cells revealed that the average height and duration of P53 and MDM2 proteins are fixed, whereas the mean pulse number of P53 and MDM2 increases with the strength of the DNA damage signal.[10,12] Our theoretical predictions are consistent with the previous experimental results.

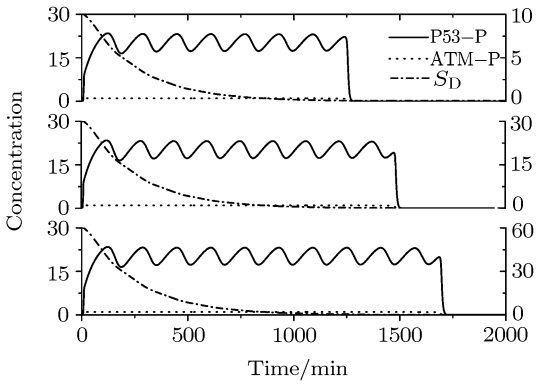


Fig. 5. Time-series of P53–P, ATM–P, and DNA damage signal for different initial DNA damage levels. From top to bottom: [$S_{\rm D}$](0) = 10, 30, and 60 (see the vertical scales on the right). τ = 30 min.

To characterize the effects of the P53-induced transcriptional-translational time delay of MDM2 on the P53–MDM2 oscillator, figure 6 shows the time-series of P53–P and ATM–P under different time delays τ. It is shown that the period numbers of P53–P oscillations are decreased with the increase of τ; for example, the period number of P53–P oscillation is 9 for τ = 30, 7 for τ = 50, and 6 for τ = 70.

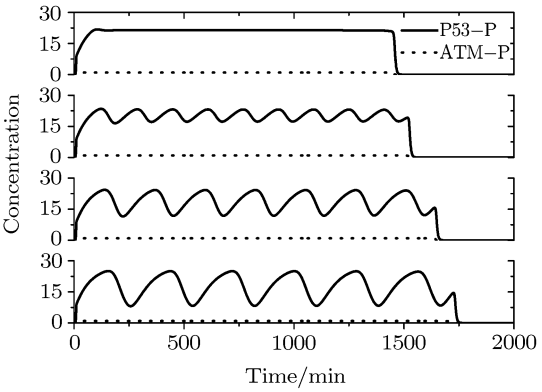


Fig. 6. Time-series plots of P53–P, ATM–P, and DNA damage signal for different transcription time delays. From top to bottom: τ = 0, 30, 50, and 70. Initial DNA damage level [$S_{\rm D}$](0) = 30.

However, the amplitude of P53–P is increased with the increase of τ. It is interesting that P53–P does not oscillate when τ = 0. Therefore, the oscillation behaviour of P53–MDM2 is caused by cooperating the

negative feedback mechanism of P53–MDM2 with the time delay of P53-induced MDM2 expression, which is the same as that of Refs.[14]–[16].

In conclusion, taking the interaction between the DNA damage repair module, ATM module, and P53–MDM2 oscillation module into account in individual cells, we have proposed a mathematical model of the P53 oscillation network triggered by a DNA damage signal in this paper. By virtue of the numerical computation of the integrated model, it is found that (i) there is a threshold of DNA damage signal at which the ATM–P transits from 0 (OFF) to 1 (ON), ATM–P shows a switch-like behaviour and relays the DNA damage signal; (ii) the bifurcation diagram of P53–P as a function of the ATM–P shows that one can regulate the oscillation behaviour of the P53–MDM2 core oscillation module very well by controlling the ATM module; (iii) in the oscillatory state of the P53–MDM2 oscillator, the pulse number of P53–P oscillation increases with increasing initial DNA damage signal; however, the amplitude and the period of P53–P oscillation is fixed for different initial DNA damage signals; (iv) the period numbers of P53–P oscillations decrease with increasing time delay of MDM2 expression-induced by P53; the theoretical predictions (iii) and (iv) obtained here are consistent with some previous experimental results;[9,10,12] (v) the model also shows that the combined negative feedback of P53–MDM2 with the time delay of P53-induced MDM2 expression causes oscillation behaviour of the P53 network triggered by the DNA damage signal.

The model discussed here exhibits the strong switch-like behaviour of ATM–P relaying the DNA damage signal. Using the switch-like behaviour of the ATM module, one can use the DNA damage signal to regulate the oscillation behaviour of the P53–MDM2 core oscillation module. The model may provide a mechanism for the digital response behaviour of P53 and MDM2 proteins in single cells.

References

[1] Kubbutat M H G, Jones S N and Vousden K H 1997 *Nature* **378** 299
[2] Freedman D A, Wu L and Levine A J 1999 *Cell. Mol. Life Sci.* **55** 96
[3] Vogelstein V, Lane D and Levine J 2000 *Nature* **408** 307
[4] Oren M 2003 *Cell Death and Differentiation* **10** 431
[5] Lee J H and Paull T T 2005 *Science* **22** 551
[6] Mckinnon P J 2004 *EMBO Reports* **5** 772
[7] Rouse J and Jackson S P 2002 *Science* **297** 547
[8] Banin S, Moyal L, Shieh S Y, Taya Y, Anderson C W, Chessa L, Smorodinsky N I, Prives C, Reiss Y, Shiloh Y and Ziv Y 1998 *Science* **281** 1674
[9] Bar-Or R L, Maya R, Segel L A, Alon U, Levine A J and Oren M 2000 *Proc. Nat. Acad. Sci.* USA **97** 11250
[10] Lahav G, Rosenfeld N, Sigal A, Geva-Zatorsky N, Levine A, Elowitz M B and Alon U 2004 *Nat. Genet.* **36** 113
[11] Monk N A M 2003 *Current Biology* **13** 1409
[12] Ma L, Wagner J, Rice J J, Hu W, Levime A J and Stolovitzky G A 2005 *Proc. Nat. Acad. Sci.* USA **102** 14266
[13] Ciliberto A, Novak B and Tyson J J 2005 *Cell Cycle* **4** 488
[14] Tiana G, Jensen M H and Sneppen K 2002 *Euro. Phys. J.* **29** 135
[15] Wagner J, Ma L, Rice J J, Hu W, Levine A J and Stolovitzky G A 2005 *Systems Biology* **152** 109
[16] Yan S W and Zhuo Y Z 2006 *Physica* D **220** 157
[17] Bottani S and Grammaticos B 2007 *J. Theor. Biol.* **249** 235
[18] Chickarmane V, Nadim A, Ray A and Sauro H M arXiv:q-bio/0510002v1
[19] Qi J P, Shao S H, Li D D and Zhou G P 2007 *Amino Acids* **33** 75
[20] Chickarmane V, Ray A, Sauro H M and Nadim A 2007 *SIAM J. Appl. Dyn. Syst.* **6** 61