Radiation-induced robust oscillation and non-Gaussian fluctuation*

Liu Bo(刘 波)[a)b)c)†], Yan Shi-Wei(晏世伟)[c)d)e)], and Geng Yi-Zhao(耿轶钊)[c)]

[a)] *Key Laboratory for Biomedical Effects of Nanomaterials and Nanosafety, Institute of High Energy Physics, Chinese Academy of Sciences, Beijing* 100049, *China*

[b)] *Key Laboratory of Beam Technology and Material Modification of Ministry of Education, Beijing Normal University, Beijing* 100875, *China*

[c)] *College of Nuclear Science and Technology, Beijing Normal University, Beijing* 100875, *China*

[d)] *Beijing Radiation Centre, Beijing* 100875, *China*

[e)] *Centre of Theoretical Physics, National Laboratory of Heavy Ion Accelerator of Lanzhou, Lanzhou* 730000, *China*

(Received 7 September 2010; revised manuscript received 16 August 2011)

There have been many recent studies devoted to the consequences of stochasticity in protein circuitry. Stress conditions, including DNA damage, hypoxia, heat shock, nutrient deprivation, and oncogene activation, can result in the activation and accumulation of p53. Several experimental studies show that oscillations can be induced by DNA damage following nuclear irradiation. To explore the underlying dynamical features and the role of stochasticity, we discuss the oscillatory dynamics in the well-studied regulatory network motif. The fluctuations around the fixed point of a delayed system are Gaussian in the limit of sufficiently weak delayed feedback, and remain Gaussian along a limit cycle when viewed tangential to the trajectory. The experimental results are recapitulated in this study. We illustrate several features of the p53 activities, which are robust when the parameters change. Furthermore, the distribution in protein abundance can be characterized by its non-Gaussian nature.

Keywords: nuclear radiation, DNA damage, non-Gaussian activity, robustness

PACS: 87.16.Yc, 87.18.Tt, 05.40.–a **DOI:** 10.1088/1674-1056/20/12/128702

1. Introduction

There are numerous new methods capable of counting individual mRNAs and proteins at the single-cell level.[1−4] p53 acts mainly as a transcriptional regulator and promotes the synthesis of its main antagonist, the ubiquitin ligase Mdm2, which degrades p53. The negative feedback circuit between p53 and Mdm2 can maintain p53 at a low level under normal conditions. However, when cells are exposed to stresses, this homeostasis is destroyed, and the level of p53 increases, which results in growth arrest, DNA repair or synthesis of pro-apoptotic proteins. The challenge we are facing now is to understand which dynamical mechanism is responsible for the oscillatory behaviours[5−12] in experimental observations, their robustness, and the possible distribution of protein with delayed feedback. In many cases the number of molecules is small, especially when it involves transcription and translation, so we use the Gillespie algorithm to simulate the system and introduce stochastic effects into the model.

2. Features and robustness

In order to illustrate the problem, we introduce the interaction of p53 and Mdm2, whose populations are denoted by $P(t)$ and $M(t)$,

$$\begin{aligned} P &\xrightarrow{\alpha_P M(t)(1-\gamma_P \mathcal{S}(t))+\mu_P} \varnothing \xrightarrow{S_P} P, \\ M &\xrightarrow{\mu_M} \varnothing \xrightarrow{S_M+\alpha_M \Gamma(t)} M, \end{aligned} \tag{1}$$

where $\varnothing$ denotes a vacant state, and $\Gamma(t)$ is a Hill function incorporating time delay τ between the activation of p53 and the induction of Mdm2. S_P, α_P, γ_P, μ_P,

*Project supported by the National Natural Science Foundation of China (Grant No. 10975019), the Scientific Research Foundation for the Returned Overseas Chinese Scholars, Ministry of Personnel of China (Grant No. MOP2006138), the Fundamental Research Funds for the Central Universities, and the Science Foundation of the Ministry of Science and Technology of China (Grant No. 2012CB934001).

†Corresponding author. E-mail: bliu@mail.bnu.edu.cn

© 2011 Chinese Physical Society and IOP Publishing Ltd

S_M, α_M, μ_M, K, N are constant parameters reflecting various mechanisms as described in our previous papers,[13−15] $\mathcal{S}(t)$ denotes the radiation-derived signal and makes an on-or-off response to irradiation, and wherein $\tau_{\rm th}$ is the duration of the oscillatory scheme.

We make a linkage between the single-cell (stochastic) oscillatory behaviour and averaged behaviour (population level). It has been observed that they behave as sustained oscillations in individual cells (Figs. 1(a) and 1(b)) and dampened oscillations in population (Figs. 1(c) and 1(d)). This type of dephasing in collective phenomena[16] is the Green–Kubo relation from standard transport theory.[17,18] Furthermore, modeling macroscopic ODEs that follow mass action law and averaged master equations explains that ODE simulation converges to sustained oscillation, whereas the averaged master equations converge to a steady-state point through dampened oscillation. Bifurcation analysis of the deterministic model that describes the same process has been done in our previous paper,[19] and a limit cycle exists when the delay exceeds the critical value. If the equations are nonlinear, in the whole parameter region simulations according to the ODE model and averaged master equations do not co-exist. This phenomenon occurs not only when the parameter space is very close to the Hopf bifurcation point, but also elsewhere in the oscillatory region. Numerical calculation has shown that when the parameters change, the behaviour is robust as shown in Fig. 1(d). The damping can be ascribed to the noise in the network motif. It is intriguing to note that the delay-induced resonant phenomenon is related to the destabilizing of the nonlinear dynamical system (1), and to the onset of Hopf bifurcation in the solutions of the corresponding deterministic equations.

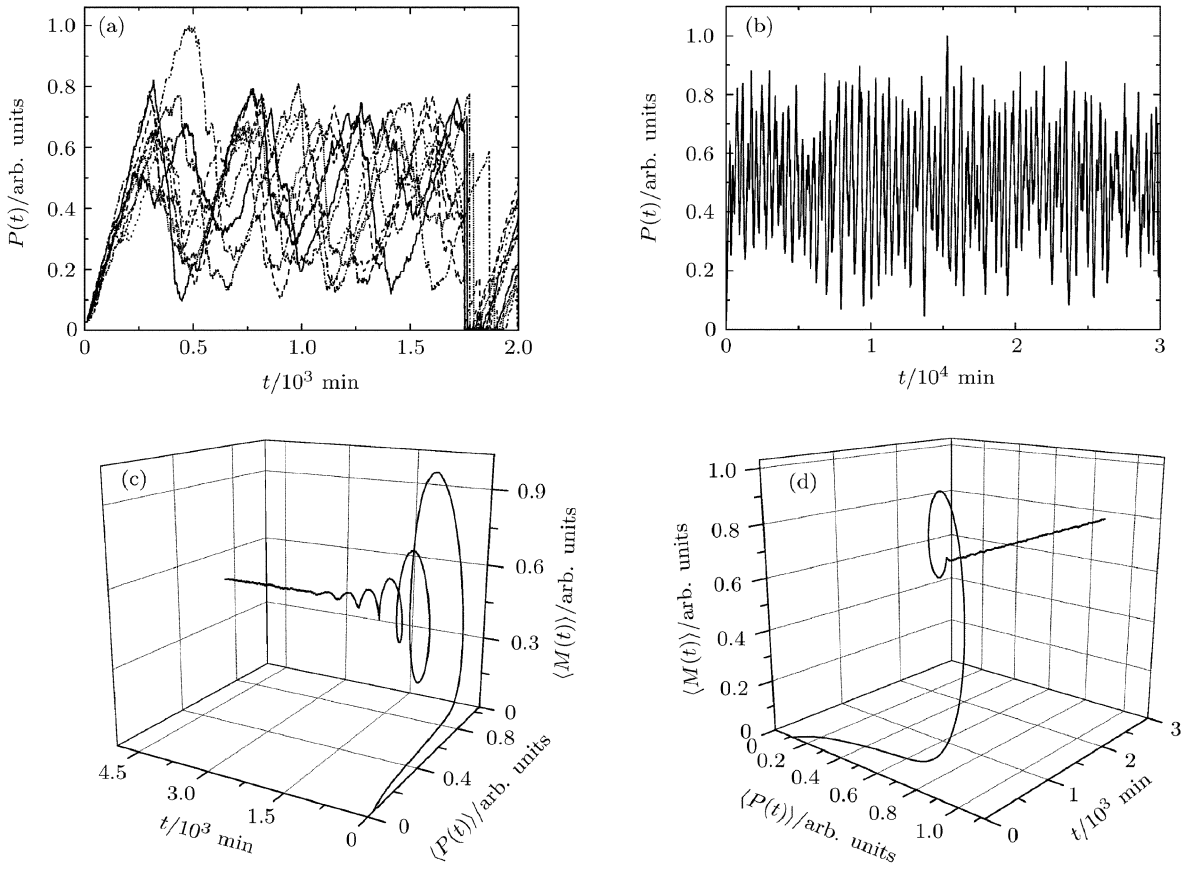


Fig. 1. Nuclear evolution of normalized p53 and Mdm2 populations. (a) Oscillations of p53 populations in 10 isogenic cells with $\tau_{\rm th} = 1750$ min. (b) p53 population in a single cell over 3×10^4 min. (c) and (d) Phase plots of p53 and Mdm2 mean populations at the cell population level. The parameters for panels (a), (b), and (c) are $S_P = 0.5$ min^{-1}, $\alpha_P = 1.8$ min^{-1}, $\gamma_P = 0.996$, $\mu_P = 2.5 \times 10^{-4}$ min^{-1}, $S_M = 2.35 \times 10^{-3}$ min^{-1}, $\alpha_M = 0.1$ min^{-1}, $\mu_M = 0.05$ min^{-1}, $K = 120$, $N = 10$, and $\tau = 100$ min. The parameters for panel (d) are $S_P = 0.5$ min^{-1}, $\alpha_P = 2.5$ min^{-1}, $\gamma_P = 0.968$, $\mu_P = 2.5 \times 10^{-4}$ min^{-1}, $S_M = 2.35 \times 10^{-3}$ min^{-1}, $\alpha_M = 0.03$ min^{-1}, $\mu_M = 0.05$ min^{-1}, $K = 25$, $N = 20$, and $\tau = 25$ min. $\tau_{\rm th} \to +\infty$ for panels (b), (c), and (d). Abscissa t represents a time in units of minute (min).

Now we discuss the statistical characteristics of probabilities of proteins. With respect to a linear delay biochemical motif driven by a Gaussian Langevin force $\xi(t)$ with $\langle\xi(t)\rangle = 0$ and $\langle\xi(t)\xi(t')\rangle = \delta(t - t')$,[20,21] the stochastic delay equation for a random variable $P(t)$, defined on the real line $\Omega = \mathbb{R}$, can be taken as the form

$$\frac{\mathrm{d}P(t)}{\mathrm{d}t} = -AP(t) - BP(t-\tau) + \sqrt{G}\xi(t), \quad (2)$$

where $t \geq 0$, $\tau \geq 0$ denotes the delay of the system, and $P(t) = \varphi(t)$ for $t \in [-\tau, 0]$. The probability density of $P(t)$ is given by $\Pr(n_P, t) = \langle\delta(n_P - P(t))\rangle$, and similarly, the joint probability can be defined as $\Pr(n_P, t; n'_P, t - \tau) = \langle\delta(n_P - P(t))\delta(n'_P - P(t-\tau))\rangle$. Then the delay Fokker–Planck equation associated with Eq. (2) reads

$$\begin{aligned}\frac{\partial \Pr(n_P,t)}{\partial t} = {} & \frac{\partial}{\partial n_P}\Big(An_P\Pr(n_P,t) \\ & + B\int n'_P \Pr(n_P,t;n'_P,t-\tau)\mathrm{d}n'_P\Big) \\ & + \frac{G}{2}\frac{\partial^2 \Pr(n_P,t)}{\partial {n_P}^2}. \end{aligned} \quad (3)$$

Since in Eq. (2) the fluctuation force is Gaussian distributed and the shift force is linear, a Gaussian-like stationary distribution in the state variable can be taken as

$$\Pr_{\mathrm{s}}(n_P) = \frac{1}{\sqrt{2\pi V(\tau)}}\exp\left(-\frac{{n_P}^2}{2V(\tau)}\right), \quad (4)$$

in which the variance $V(\tau)$ is obtained by derivation as

$$V(\tau) = \begin{cases} \dfrac{G}{2}\left(\dfrac{1 + B\omega^{-1}\sin(\omega\tau)}{A + B\cos(\omega\tau)}\right), & B > A \geq 0, \\ \dfrac{G}{2}\left(\dfrac{1 + B\omega^{-1}\sinh(\omega\tau)}{A + B\cosh(\omega\tau)}\right), & A > B \geq 0, \\ \dfrac{G}{4A}(1 + A\tau), & A = B > 0, \end{cases} \quad (5)$$

where $\omega = \sqrt{|A^2 - B^2|}$. The variance and maximum of the probability are tuned by delay. Figure 2(a) shows the stationary distribution in the p53 and Mdm2 populations without delay, which is defined by

$$\Pr_{\mathrm{s}}(n_P, n_M) = \lim_{t\to\infty}\Pr(n_P, n_M, t), \quad (6)$$

and it is seen that $\Pr_{\mathrm{s}}(n_P, n_M)$ is Gaussian. The p53 motif (1) is very nonlinear in contrast to the linear delay one-species system (2), so with delay, figure 2(b) shows strong non-Gaussian nature. It has been shown using a careful perturbation scheme that the fluctuations around the fixed point of a delayed system, in the limit of sufficiently weak delayed feedback, are Gaussian, and along a limit cycle, remain Gaussian when viewed tangential to the trajectory.[22–25]

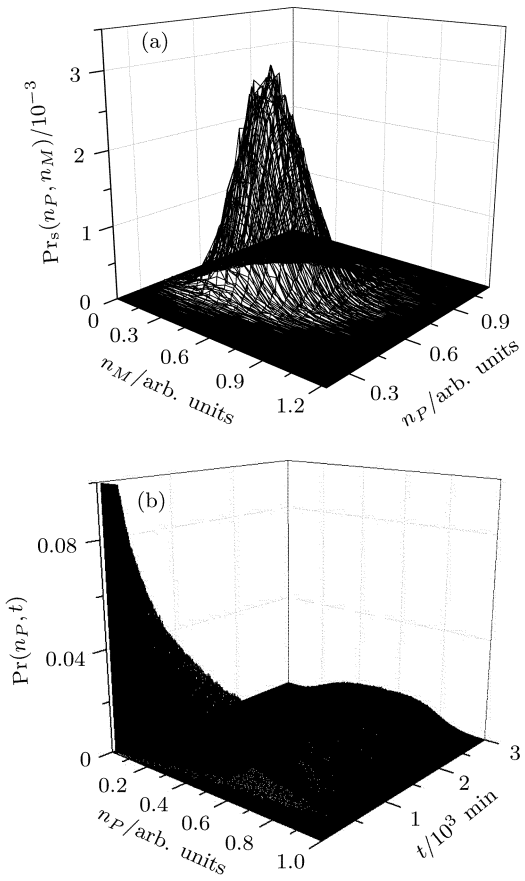


Fig. 2. Probabilities of normalized populations: (a) distribution in the p53 and Mdm2 populations in steady state with $\tau = 0$ min and (b) evolution of the probability of p53 population with $\tau = 100$ min, where $\Pr(n_P, t) = \sum_{n_M=0}^{\infty}\Pr(n_P, n_M, t)$. The other parameters are chosen to be the same as those in Fig. 1(b).

References

[1] Elowitz M, Levine A, Siggia E and Swain P 2002 *Science* **297** 1183

[2] Bar-Even A, Paulsson J, Maheshri N, Carmi M, O'Shea E, Pilpel Y and Barkai N 2006 *Nat. Genet.* **38** 636

[3] Newman J, Ghaemmaghami S, Ihmels J, Breslow D, Noble M, DeRisi J and Weissman J 2006 *Nature* **441** 840

[4] Raj A and van Oudenaarden A 2009 *Ann. Rev. Biophys.* **38** 255

[5] Lev Bar-Or R, Maya R, Segel L, Alon U, Levine A and Oren M 2000 *Proc. Natl. Acad. Sci. USA* **97** 11250

[6] Lahav G, Rosenfeld N, Sigal A, Geva-Zatorsky N, Levine A, Elowitz M and Alon U 2004 *Nat. Genet.* **36** 147

[7] Tyson J J 2004 *Nat. Genet.* **36** 113

[8] Ma L, Wagner J, Rice J, Hu W, Levine A and Stolovitzky G 2005 *Proc. Natl. Acad. Sci. USA* **102** 14266

[9] Geva-Zatorsky N, Rosenfeld N, Itzkovitz S, Milo R, Sigal A, Dekel E, Yarnitzky T, Liron Y, Polak P, Lahav G and Alon U 2006 *Mol. Syst. Biol.* **2** 2006.0033

[10] Tyson J J 2006 *Mol. Syst. Biol.* **2** 2006.0032

[11] Batchelor E, Mock C, Bhan I, Loewer A and Lahav G 2008 *Mol. Cell* **30** 277

[12] Proctor C and Gray D 2008 *BMC Syst. Biol.* **2** 75

[13] Yan S W and Zhuo Y Z 2006 *Physica* D **220** 157

[14] Yan S W 2007 *J. Biol. Syst.* **15** 123

[15] Wilkinson D J 2009 *Nat. Rev. Genet.* **10** 122

[16] Yan S W, Sakata F and Zhuo Y Z 2002 *Phys. Rev.* E **65** 031111

[17] Green M S 1954 *J. Chem. Phys.* **22** 398

[18] Kubo R 1957 *J. Phys. Soc. Jpn.* **12** 570

[19] Yan S W, Wang Q, Xie B S and Zhang F S 2007 *Chin. Phys. Lett.* **24** 1771

[20] Risken H 1989 *The Fokker–Planck Equation: Methods of Solution and Applications* 2nd edn. (Berlin: Springer)

[21] Frank T D, Beek P J and Friedrich R 2003 *Phys. Rev.* E **68** 021912

[22] Dieterich P, Klages R, Preuss R and Schwab A 2008 *Proc. Natl. Acad. Sci. USA* **105** 459

[23] Gheorghiu S and Coppens M O 2004 *Proc. Natl. Acad. Sci. USA* **101** 15852

[24] Liu B and Goree J 2008 *Phys. Rev. Lett.* **100** 055003

[25] Scott M 2009 *Phys. Rev.* E **80** 031129