Journal of Theoretical Biology 258 (2009) 561–577

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

From structure to dynamics: Frequency tuning in the p53–Mdm2 network I. Logical approach

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ARTICLE INFO

Article history:
Received 10 September 2008
Received in revised form
19 January 2009
Accepted 11 February 2009
Available online 21 February 2009

Keywords:
p53
DNA-damage response
Feedback loops
Post-translational modifications
Network dynamics
Mathematical modelling

ABSTRACT

We investigate the dynamical properties of a simple four-variable model describing the interactions between the tumour suppressor protein p53, its main negative regulator Mdm2 and DNA damage, a model inspired by the work of Ciliberto et al. [2005. Steady states and oscillations in the p53/Mdm2 network. Cell Cycle 4(3), 488–493]. Its core consists of an antagonist circuit between p53 and nuclear Mdm2 embedded in a three-element negative circuit involving p53, cytoplasmic and nuclear Mdm2. A major concern has been to develop an integrated approach in which various types of descriptions complement each other. Here we present the logical analysis of our network and briefly discuss the corresponding differential model. Introducing the new notion of "logical bifurcation diagrams", we show that the essential qualitative dynamical properties of our network can be summarized by a small number of bifurcation scenarios, which can be understood in terms of the balance between the positive and negative circuits of the core network. The model displays a wide variety of behaviours depending on the level of damage, the efficiency of damage repair and, importantly, the DNA-binding affinity and transcriptional activity of p53, which are both stress- and cell-type specific. Our results qualitatively account for several experimental observations such as p53 pulses after irradiation, failure to respond to irradiation, shifts in the frequency of the oscillations, or rapid dampening of the oscillations in a cell population. They also suggest a great variability of behaviour from cell to cell and between different cell-types on the basis of different post-translational modifications and transactivation properties of p53. Finally, our differential analysis provides an interpretation of the high and low frequency oscillations observed by Geva-Zatorsky et al. [2006. Oscillations and variability in the p53 system. Mol. Syst. Biol. 2, 2006.0033] depending on the irradiation dose. A more detailed analysis of our differential model as well as its stochastic analysis will be developed in a next paper.

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1. Introduction

Protein p53 is a transcriptional regulator of a large number of genes involved notably in growth arrest, DNA repair, apoptosis and cellular senescence (Gatz and Wiesmüller, 2006; Oren, 2003; Vogelstein et al., 2000). It therefore plays an essential role in the control of the proliferation of abnormal cells. The level of this key tumour suppressor protein is tightly regulated by the ubiquitin ligase Mdm2 through a negative feedback circuit. This negative circuit prevents the permanent presence of high levels of p53 that would be lethal for the cells. Normally, the level of p53 remains low. It becomes elevated only when cells are stressed or damaged, for example by ionizing radiations, aberrant growth signals or drugs. In particular, the DNA damage resulting from ionizing radiations leads to an increase in the level of active p53, which in turn activates the damage repair process or the synthesis of pro-apoptotic proteins, thereby preventing the proliferation of genetically unstable cells.

The importance of the regulation of p53 for ensuring an appropriate response to various genotoxic and cytotoxic stresses has led to an impressive amount of experimental investigations, some of which deal with the kinetics of the p53 response to DNA damage. In particular, experimental studies on irradiated cells in culture have shown the occurrence of damped oscillations of p53 at the level of cell populations (Bar-Or et al., 2000) and repeated p53 pulses in single cells (Lahav et al., 2004). In these first experiments on single cells, performed with a short time scale, the pulse amplitudes and interpulse intervals were initially reported to remain almost constant, with an average number of peaks increasing with irradiation intensity. Damped p53 oscillations following irradiation were also observed *in vivo* in an Mdm2-luciferase transgenic mouse model (Hamstra et al., 2006), confirming the pulsatile behaviour observed *in vitro*. In more recent experiments, over longer times of observation, Geva-Zatorsky et al. (2006) highlighted several new

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0022-5193/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jtbi.2009.02.005

characteristics of the p53 oscillatory response to DNA damage. They reported, in particular, that under identical conditions, individual cells show a great variability in response to radiation damage, with some cells showing undamped oscillations for at least 3 days while others do not respond or show irregular fluctuations. The oscillations have a regular periodicity and peak width but highly variable amplitudes. A Fourier analysis of the oscillations revealed that the oscillation period decreases with increasing irradiation intensity, with a typical cycling time of about 10 h at low irradiation doses and about 6 h at high irradiation doses. The same group also observed that, in some cells, the oscillations stopped or changed frequency after one or two days. On the other hand, in an experimental study of the kinetics of the p53–Mdm2 response for different production rates of p53 and Mdm2, Hu et al. (2007) reported that oscillations only occurred when the basal levels of p53 and Mdm2 are within an optimal range.

Several theoretical models have been proposed to account for the oscillatory behaviour observed experimentally after exposure to stress, either at the level of cell populations (Bar-Or et al., 2000; Ma et al., 2005; Monk, 2003; Ogunnaike, 2006; Tiana et al, 2002) or at the level of individual cells (Bottani and Grammaticos, 2007; Chickarmane et al., 2005; Ciliberto et al., 2005; Geva-Zatorsky et al., 2006; Ma et al., 2005; Puszyński et al., 2008; Wagner et al., 2005; Zhang et al., 2007). They all rely on the well-established negative feedback circuit between p53 and its main antagonist Mdm2, but differ by how this negative circuit is assumed to generate robust large amplitude pulses in the presence of DNA damage. Two broad classes of models can be distinguished. In a first class of models, the occurrence of a robust oscillatory response to stress is ensured by the presence of a sufficiently long time delay between the accumulation of active p53 and the p53-dependent activation of the *Mdm*2 gene. In the framework of this type of models, based on ordinary differential equations involving several intermediate steps (Bar-Or et al., 2000; Chickarmane et al., 2005; Puszyński et al., 2008) or on time delayed differential equations (Bottani and Grammaticos, 2007; Ma et al., 2005; Monk, 2003; Ramalingam et al., 2007; Tiana et al., 2002; Wagner et al., 2005), the transition between a stable steady state with low p53 level and stable oscillations of p53 takes place through a Hopf bifurcation and the onset of large amplitude oscillations requires considering highly nonlinear, switch like, DNA-damage response functions (Chickarmane et al., 2005; Ma et al., 2005). More recently, Batchelor et al. (2008) proposed that repeated, large amplitude p53 pulses would result from the interplay between the basic negative p53–Mdm2 feedback loop and a second negative loop involving upstream regulators of p53. In a second class of models, first developed by Ciliberto et al. (2005), the negative p53–Mdm2 feedback circuit is combined with positive feedback circuits, which upon damage induction leads to an abrupt transition from the homeostatic rest state to oscillations of large and roughly constant amplitude (Zhang et al., 2007). In particular, in the differential model of Ciliberto et al. (2005), as well as in the recent stochastic model of Puszyński et al. (2008), p53 indirectly amplifies its own level via a PTEN-dependent inhibitory effect on the nuclear entry of Mdm2.

The possible implications of p53 oscillations for the regulation of p53-induced apoptosis still remain an open question and are the subject of a number of recent theoretical analyses (Bose and Ghosh, 2007; Puszyński et al., 2008; Zhang et al., 2007).

In our work, we focused on a simple four-variable model describing the interactions between protein p53, its negative regulator Mdm2 and DNA damage, a model inspired by the work of Ciliberto et al. (2005). Its core consists of an antagonist circuit between p53 and nuclear Mdm2 embedded in a three-element negative circuit involving p53, cytoplasmic and nuclear Mdm2. To study the dynamics of this network upon damage induction, we combined a multilevel logical modelling method with differential and stochastic approaches. The logical description provided a powerful way of grasping the main qualitative dynamical properties to be expected for our network, without having to specify the details of the molecular interactions or to introduce precise kinetic parameter values. The differential approach allowed us relaxing the high nonlinearity intrinsic to the discrete description and provided more quantitative information on the evolution dynamics. Stochastic simulations further enabled us to account for the effect of molecular fluctuations due to a small number of molecules.

This paper deals with the logical analysis of our model and briefly presents some results of the differential analysis. It introduces new developments of the logical method initially formulated by Thomas (1973, 1991), Thomas and D'Ari (1990), namely: (1) the concept of "logical bifurcation diagrams", which enables a systematic characterization of all the asymptotic behaviours compatible with a given set of interactions and (2) the use of on/off time delays that vary in the course of the evolution of the system for describing the dynamics. Using these tools, we show that the main qualitative dynamical properties of our network can be summarized in terms of a small number of logical bifurcation diagrams that correspond to different bifurcation scenarios and rely on the balance between the positive and negative circuits involving p53. The same simple model displays a wide variety of behaviours depending on the level of damage, the efficiency of damage repair and, importantly, the DNA-binding affinity and transcriptional activity of p53, which are both stress- and cell-type specific (Feng et al., 2007; Mayo, et al., 2005; Singh et al., 2002).

Our results reproduce several qualitative features of the experimental observations for single cells and cell populations and, in particular, the high and low frequency oscillations observed by Geva-Zatorsky et al. (2006) depending on the irradiation dose. They also suggest a high variability of behaviour from cell to cell and between different cell types characterized, for example, by different post-translational modifications and trans-activation properties of p53.

This study further emphasizes the link between the structure of a regulatory network and its main dynamical properties as well as the complementarities between the logical and differential approaches. A detailed analysis of our differential model and its stochastic analysis are developed in a next paper.

The outline of the paper is as follows. After a brief presentation of the biological bases of our model in the next section, we summarize the main principles of our logical formalism in Section 3. Section 4 deals with the logical bifurcation analysis of the core of our network and gives some illustrations of the dynamics of single cells upon damage induction as a function of the level of damage and the rate of damage repair. Stochastic logical simulations account for damped oscillations at the level of cell populations. In Section 5, we introduce the differential counterpart of our logical model. We show that the essential results of our logical analysis are preserved for more realistic nonlinearities and parameter values and propose a mechanism for the adjustment of the oscillation frequency as a function of the damage level and repair efficiency.

2. The model

In the present study, we investigate the dynamical properties of a four-variable model derived from the work of Ciliberto et al. (2005). This model describes the interactions between protein p53, the ubiquitin ligase Mdm2 and DNA damage, and is based on

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