A 2-Dimensional Model of Polynomial Type for Oscillatory ATM-Wip1 Dynamics in p53 Network

Gökhan Demirkıran[1], Güleser Kalaycı Demir[2], and Cüneyt Güzeliş[1]

[1]Department of Electrical and Electronics Engineering, Yaşar University, Bornova, İzmir, 35100, Turkey
gokhan.demirkiran@yasar.edu.tr , cuneyt.guzelis@yasar.edu.tr
[2]Department of Electrical and Electronics Engineering, Dokuz Eylül University, Buca, İzmir, 35160, Turkey
guleser.demir@deu.edu.tr

Abstract

Under gamma irradiation, p53 gene regulatory network is able to exhibit three different modes, namely low state, oscillations, and high state. There are experimental studies demonstrating that oscillatory behaviour of p53 is due to the interaction between upstream mediator of p53, i.e. ATM, and a negative feedback loop formed by Wip1 with that upstream. By proposing a canonical model based on ordinary differential equations made up of polynomial type birth and death terms, we show mathematically that the simple interaction between ATM and Wip1 is indeed able to exhibit three different behaviours relevant to DNA damage response of p53 network. We further carry out bifurcation analysis on the model with the aim of investigating the mutations such as Wip1 overexpression and ATM deficiency. Based on the proposed canonical model, we show that Wip1 is an important target for curing these types of mutations.

1. Introduction

Although mathematical models of gene regulatory networks are helpful in understanding how the system functions, most of the time comprehensive models to describe every detail of chemical processes is infeasible since biological processes in the cell is too complex and there are highly connected components whose interactions are not revealed yet or only known in the form of "repressing" and "enhancing". Therefore, inevitably most of the time, mathematical models proposed in systems biology focus on the motifs arising from the main topological structure of the network omitting some of the chemical reaction details [1]. Nevertheless, this does not diminishes the importance of mathematical models, since the topological structure determines the dynamics of a biological process and provides predictions on the qualitative behavior of the system. Moreover, models focusing on topology is more likely to capture missing nodes or to reveal essential nodes of the system.

As a biological process contains many components, so does the mathematical model of that biological process, making it hard to manage and understand. That's why sometimes we need to simplify the model further just to analyze it easily and grasp how the system functions [2]. Besides, studying a simpler system helps to understand a more comprehensive model of that system. Especially, if there are experimental studies revealing the structure of the system, canonical models derived from this structure can provide an abstraction of the mechanism of the whole system.

It is known that p53 network is responsible from the regulation of the DNA damage response of the cell. Studies show that p53 level in a cell with undamaged DNA is low [3], however upon the exposure of gamma irradiation, double strand breaks in DNA occur, and p53 level starts to oscillate [4,5]. With the starting of oscillation of p53 level, cell cycle is arrested to avoid the proliferation of the damaged cell, while at the same time DNA damage is being repaired by repair molecules. p53 level keeps oscillating along DNA damage repair phase. If DNA damage is not repaired in a certain time, then p53 level goes up to a sustained high level which initiates apoptosis [3,6]. A 17-dimensional two-phase dynamics model is proposed in [7] for describing the aforementioned p53 dynamics showing three qualitative modes: low level (unstressed conditions), oscillations (cell cycle arrest) and a sustained high level (apoptosis). Herein, we propose a 2-dimensional canonical model for two-phase dynamics of p53 network based on the knowledge gained from reducing the two-phase dynamics model [7] in the accompanying paper by the authors and the biological evidence

The experiments with p53 network shows that the interaction between ATM and Wip1 dynamics plays a key role in forming of p53 oscillations [8,9]. Also in mathematical models, the importance of ATM and Wip1 negative feedback loop in construction of p53 dynamics has been demonstrated [7,8]. When there are DSBs in DNA, repair molecules form a complex with DSBs (DSBCs), thus ATM is activated. ATM is highly sensitive in detection of DSBC activity due to its fast switching bistability property with a positive feedback [10-13]. When DSBs occur in DNA, ATM switches to a high steady state level rapidly. Wip1 is known to provide a negative feedback loop on ATM dynamics and it is observed in wet-lab experiment that Wip1 feedback loop is indispensable for oscillations of p53 [8]. Thus, in this paper, we propose a canonical 2-dimensional polynomial model based on the topological structure between ATM and Wip1 interaction. Since it has been observed in wet-lab experiment [8] that p53 oscillations result from recurrent initiation of ATM, we assume that qualitative behavior of p53 follows the qualitative behavior of ATM. The introduced model consists of only polynomial terms reflecting the interactions between ATM and Wip1. This simple model is demonstrated to be capable of representing three modes of p53 as in [7]: low level, oscillations and a sustained high level. The model equations and bifurcation analysis are provided in the following section.

2. 2-dimensional Model of ATM and Wip1 Interaction

2.1. Model Equations

The equations of the proposed model (1)-(2) describe the properties of ATM and Wip1 interaction in the functional level, just introducing polynomial birth and death terms to reflect

activation and repression, respectively, without addressing enzyme kinetics directly. Equation (1) has the bistable property of ATM, and (2) forms a negative feedback loop with (1). Since the bistability dynamics can be obtained from at least three equilibrium points [14-16], the polynomial right side of (1) would be at least of third order. The parameters of the introduced model are chosen at the end of a trial and error process employing an extensive simulation study and then tuned to have a period of around 6 hours considering the fact that p53 oscillations periods are about 6-8 hours [4]. The resulting parameters are given as $a = 15,\ b = 50, c = 15, d = 70,\ z = 0.5,\ m = 1.25,$ $n = 0.8$. The parameter r is an external signal indicating DSBC activity.

$$\frac{d[ATM]}{dt} = -[ATM](\,r([ATM]^2 - a[ATM] - d) + b + c[Wip1]) \quad (1)$$

$$\frac{d[Wip1]}{dt} = (z + m[ATM] - n[Wip1]\ ) \quad (2)$$

When DSBs occur in DNA, repair molecules form a complex with DSBs (DSBCs) and DSBs are repaired. The parameter r is a term that models the DSBC activity. Its value can be any number between 0 and 1, "0" standing for no DSBC activity and "1" standing for activation of ATM by DSBC activity. Thus, r represents the degree of the activation of ATM.

In the proposed model of (1)-(2), [Wip1] is regulated positively by ATM with the term "$m[ATM]$". In addition, [ATM] has a self-activation property with the term "rd[ATM]". This self-activation property was shown to give the property of rapid activation of ATM [11-12]. Wip1 is known to be a strong inhibitor of ATM [17]. Therefore, the term "$-c[ATM][Wip1]$" is included to represent the strong deactivation property of Wip1. [Wip1] has a constant production rate with the term "z", and a self-degradation term "n".

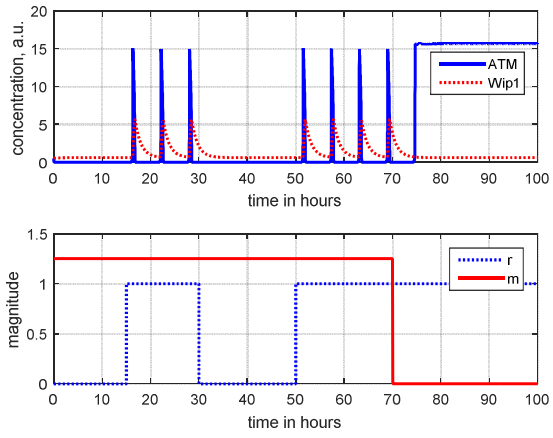

Fig. 1. Numerical simulation of the oscillator model defined by (1) and (2) replicates three essential features of p53 network. In the time intervals between $[15, 30]$ and $[50,100]$ in hours, there are DSBs in DNA indicated by $r = 1$. In addition, when $t > 70, m$ parameter is made zero to simulate the cutting off of $Wip1$ feedback loop. In this case, ATM levels goes to a high level indicating initiation of apoptosis. (Note that a.u. stands for arbitrary unit.)

The model successfully shows the rest state in normal unstressed conditions of the cell (i.e. $r = 0$), oscillations in case of DSBC activity (i.e. $r = 1$), and a high steady state in unrepaired DNA damage case (modelled as $r = 1, m = 0$) as shown in Fig. 1. If DSBs are not repaired in certain amount of time, indicating that DNA damage is too severe, then Wip1 feedback loop is distracted ($m = 0$), thus ATM is driven into high steady state (See Fig.1) [7,18,19].

2.2. Analysis of the model

Bifurcation parameters are the parameters that cause a qualitative change in the dynamics of the system. In the proposed model, passing from the rest state to oscillations under DNA damage is such a change in the dynamics of the system. In cancer studies, the parameters which are sensitive, i.e. causing qualitative change in the dynamics of a gene regulatory network, are chosen as the bifurcation parameters quantifying the mutations [20]. Thus, we test our model's validity by showing that sensitive parameters of the model correspond to the relevant mutations reported in the literature [21-24].

Wip1 overexpression: Wip1 overexpression is a mutation that is known to cause cancer [21]. This mutation can be embedded into our model by increasing the parameter z which is the Wip1 constant production term. As depicted in Fig. 2, we evaluate the sensitivity of the parameter z by taking it as a bifurcation parameter in order to test if it causes a qualitative change in dynamics. As can be deduced from Fig. 2, the system is highly sensitive to the parameter z. Its increase destroys the cell's ability to oscillate and pulls ATM level down to zero. Since oscillations are required to arrest cell cycle [6] and defective cell cycle arrest may lead to tumor formation, we conclude that the changes in the sensitive parameter z may cause cancer by removing cell's ability to arrest cell cycle. This prediction requires further wet-lab experiments, since, to the best of our knowledge, it is not known if Wip1 overexpression causes cancer due to the removal of p53 oscillations as a consequence of Wip1 overexpression.

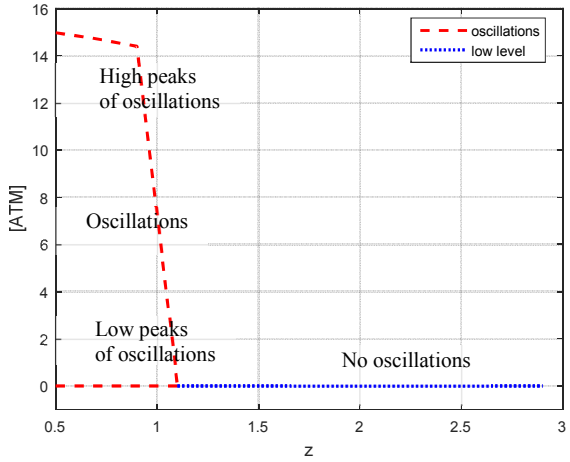

Fig. 2. The parameter z is taken as a bifurcation parameter. [ATM] level stops oscillating if z is over increased.

ATM deficiency: ATM deficiency is a mutation that is characterized by the decrease in its sensitiveness to the DNA damage [22-23]. Thus, mutated ATM has difficulty in sensing the DNA damage. We embed this mutation by decreasing the parameter r, as assuming that this decrease is not due to a low DSBC activity, but due to ATM's deficiency in sensing the DSBC activity. Thus, by doing this, we decrease the degree of activation of ATM, while assuming that it should be fully activated. By taking the parameter r as a bifurcation parameter, we show that the decrease in r causes oscillations to stop as shown in Fig. 3. In

this case, cell loses its ability to arrest cell cycle. This finding is in agreement with biological findings which state that mutations in ATM cause defective cell cycle arrest [23-24].

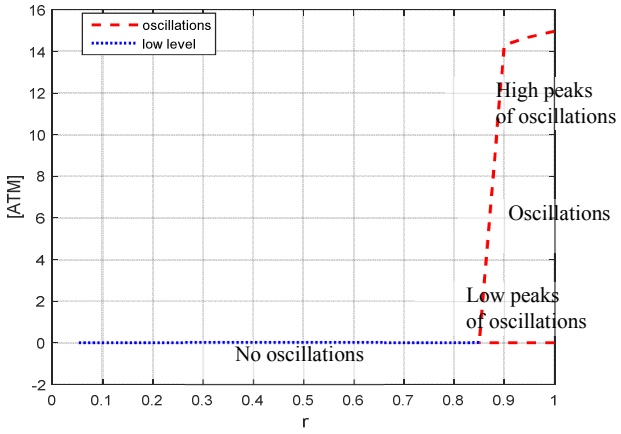

Fig. 3. The parameter r is taken as a bifurcation parameter. Decrease in r, causes the oscillations to stop, so yielding defective cell cycle arrest.

We further show that ATM deficient cell can still go to apoptosis like normal cells, if Wip1 feedback loop is distracted (i.e. m = 0) (See Fig. 5d.). Since the model parameters corresponds to idealized reactions in the cell, making "m =0" would be interpreted as any approach that decreases the activity of Wip1, such as using Wip1 inhibitors, deletion of PPM1D (gene encoding Wip1). There are several experiments indicating that inhibition of Wip1 drive cancerous cells to apoptosis [18-19] or deletion of PPM1D (gene encoding Wip1) make cells resistant to tumors [22]. Recently Wip1 has been recognized as a new candidate for cancer treatment [25-27].

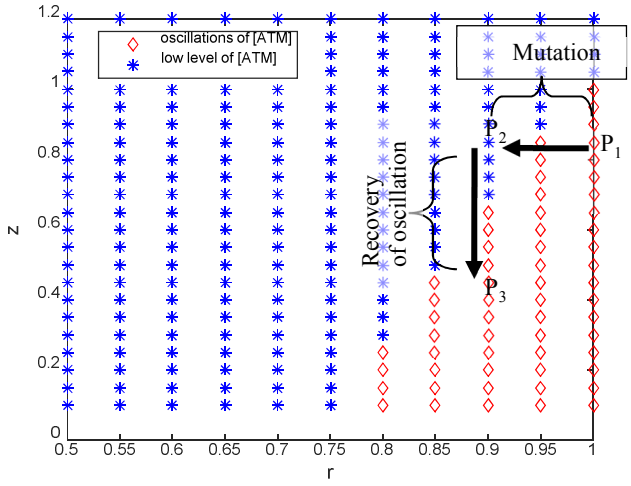

Fig. 4. The parameter z and r together taken as bifurcation parameters. The parameter combinations that result in oscillations or low level of ATM are shown. P_1 corresponds to the parameters $(r, z) = (1,0.8)$ where [ATM] oscillates. However, if ATM deficiency occurs, then the cell moves to P_2 (0.9,0.8) and [ATM] oscillation stops. Thus, the cell becomes defective in cell cycle arrest. This situation is healed by decreasing the parameter z and moving the cell to P_3(0.9,0.4). In this case, the oscillations are recovered.

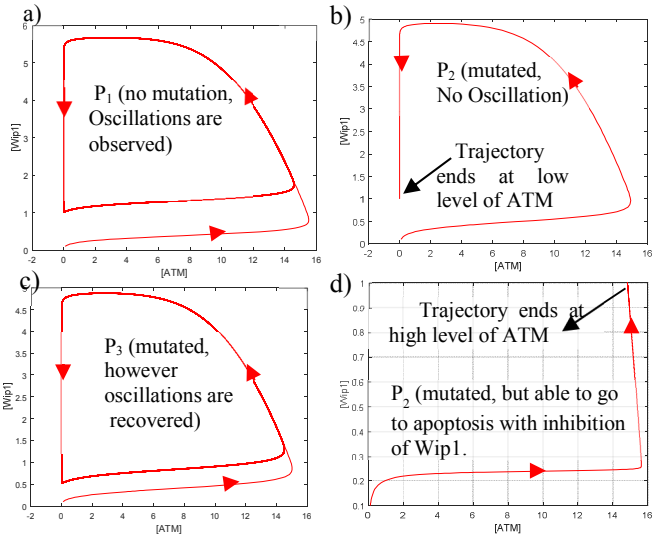

Fig. 5. Simulations of ATM deficiency. a) In P_1, ATM is not mutated and oscillations are observed in case of DSBC activity. b) In P_2 , ATM is mutated and oscillations are no longer observed in case of DSBC activity. c) Mutated cell is moved to point P_3 by decreasing the parameter z. In this case, oscillations are observed even if ATM is mutated. d) An ATM deficient cell in P_2 still can go to apoptosis by inhibiting Wip1 (m=0.1), even if the cell is deficient in cell cycle arrest (i.e. no [ATM] oscillation possible). Thus, the analysis indicates that degradation of Wip1 may be a cancer treatment strategy for ATM deficient patients.

3. Conclusion

This study proposes a 2-dimensional model that is able to replicate the behaviors of ATM dynamics in p53 network. The results obtained by the introduced model emphasizes the importance of ATM and Wip1 in p53 dynamics. Due to its simplicity, the model has the potential of being used in other gene regulatory networks such as circadian system that have interaction with p53 network. The bifurcation analyses reveal that the production rate of Wip1 and sensitivity of ATM to DNA damage are sensitive parameters that are related to cancer. Wip1 feedback loop is important for different behaviors of p53 dynamics. Thus, Wip1 feedback loop may be a control element which other networks control p53 dynamics. This perspective is important since cancer treatment strategies can use Wip1 feedback loop as a target to control mutated cells.

References

[1] U. Alon, "Network motifs: theory and experimental approaches," *Nature Reviews Genetics,* pp. 450-461, 2007.

[2] L. H. Hartwell, J. J. Hopfield, S. Leibler and A. W. Murray, "From molecular to modular cell biology," *Nature,* pp. C47-C52, 1999.

[3] A. Loewer, E. Batchelor, G. Gaglia and G. Lahav, " Basal dynamics of p53 reveal transcriptionally

attenuated pulses in cycling cells," *Cell,* pp. 89-100, 2010.

[4] G. Lahav, N. Rosenfeld, A. Sigal, N. Geva-Zatorsky, A. J. Levine, M. B. Elowitz and U. Alon, "Dynamics of the p53-Mdm2 feedback loop in individual cells," *Nature Genetics,* pp. 147-150, 2004.

[5] Bar-Or, R. Lev, R. Maya, L. A. Segel, U. Alon, A. J. Levine and a. M. Oren, "Generation of oscillations by the p53-Mdm2 feedback loop: a theoretical and experimental study," *Proceedings of the National Academy of Sciences,* pp. 11250-11255, 2000.

[6] J. E. Purvis, K. W. Karhohs, C. Mock, E. Batchelor, A. Loewer and G. Lahav, "p53 dynamics control cell fate," *Science,* pp. 1440-1444, 2012.

[7] X.-P. Zhang, F. Liu and W. Wang, "Two-phase dynamics of p53 in the DNA damage response," *Proceedings of the National Academy of Sciences,* pp. 8990-8995, 2011.

[8] E. Batchelor, A. Loewer, C. Mock and G. Lahav, "Stimulus-dependent dynamics of p53 in single cells," *Molecular systems biology,* p. 488, 2011.

[9] E. Batchelor, C. S. Mock, I. Bhan, A. Loewer and G. Lahav, "Recurrent initiation: a mechanism for triggering p53 pulses in response to DNA damage," *Molecular cell,* pp. 277-289, 2008.

[10] E. U. Kurz and S. P. Lees-Miller, "DNA damage-induced activation of ATM and ATM-dependent signaling pathways," *DNA repair ,* pp. 889-900, 2004 .

[11] T. Uziel, Y. Lerenthal, L. Moyal, Y. Andegeko, L. Mittelman and Y. Shiloh, "Requirement of the MRN complex for ATM activation by DNA damage," *The EMBO journal,* pp. 5612-5621, 2003.

[12] L. Ma, J. Wagner, J. J. Rice, W. Hu, A. J. Levine and G. A. Stolovitzky., "A plausible model for the digital response of p53 to DNA damage," *Proceedings of the National Academy of Sciences of the United States of America,* pp. 14266-14271, 2005.

[13] K. Mouri, J. C. Nacher and T. Akutsu, "A mathematical model for the detection mechanism of DNA double-strand breaks depending on autophosphorylation of ATM," *PLoS One 4.4 (2009): e5131.,* p. e5131, 2009.

[14] N. Avcu, G. DEMİR, F. Pekergin, H. ALYÜRÜK, L. ÇAVAŞ and C. GÜZELİŞ, "Discriminant-based bistability analysis of a TMG-induced lac operon model supported with boundedness and local stability results," *Turkish Journal of Electrical Engineering & Computer Sciences,* pp. 719-732, 2016.

[15] N. Avcu, N. Pekergin, F. Pekergin and C. Guzelis, "Aggregation for Computing Multi-Modal Stationary Distributions in 1-D Gene Regulatory Networks," *IEEE/ACM Transactions on Computational Biology and Bioinformatics,* 2017.

[16] N. Avcu, H. Alyürük, G. K. Demir, F. Pekergin, L. Cavas and C. Güzeliş., "Determining the bistability parameter ranges of artificially induced lac operon using the root locus method.," *Computers in biology and medicine,* pp. 75-91, 2015.

[17] S. Shreeram, W. K. Hee, O. N. Demidov, C. Kek, H. Yamaguchi, A. J. Fornace and D. V. Bulavin, "Regulation of ATM/ P53-dependent suppression of myc-induced lymphomas by Wip1 phosphatase," *The Journal of experimental medicine,* pp. 2793-2799, 2006.

[18] Y. Xia, P. Ongusaha, S. Lee and Y. Liou, "Loss of Wip1 sensitizes cells to stress-and DNA damage-induced apoptosis," *Journal of Biological Chemistry,* pp. 17428-17437, 2009.

[19] C. Spinnler, E. Hedström, H. Li, J. de Lange, F. Nikulenkov, A. F. Teunisse and G. ... Selivanova, "Abrogation of Wip1 expression by RITA-activated p53 potentiates apoptosis induction via activation of ATM and inhibition of HdmX," *Cell Death & Differentiation,* pp. 1736-1745, 2011.

[20] J. Chen, H. Yue and Q. Ouyang, "Correlation between oncogenic mutations and parameter sensitivity of the apoptosis pathway model," *PLOS Computational Biology,* p. e1003451, 2014.

[21] R. C. Castellino, M. D. Bortoli, X. Lu, S.-H. Moon, T.-A. Nguyen, M. A. Shepard, P. H. Rao, L. A. Donehower and J. Y. Kim, "Medulloblastomas overexpress the p53-inactivating oncogene WIP1/PPM1D," *Journal of neuro-oncology,* pp. 245-256, 2008.

[22] Y. Darlington, T. Nguyen, S. Moon, A. Herron, P. Rao, C. Zhu, X. Lu and L. Donehower, "Absence of Wip1 partially rescues Atm deficiency phenotypes in mice," *Oncogene,* pp. 1155-1165, 2012.

[23] M. Lavin and S. Kozlov, "TM activation and DNA damage response," *Cell cycle,* pp. 931-942, 2007.

[24] D. Delia, E. Fontanella, C. Ferrario, L. Chessa and S. Mizutani, "DNA damage-induced cell-cycle phase regulation of p53 and p21waf1 in normal and ATM-defective cells," *Oncogene,* pp. 7866-7869, 2003.

[25] D. Filipponi and D. V. Bulavin, "Wip1 and ATM in tumor evolution: role for BRCA1," *Oncotarget,* p. 2170, 2013.

[26] T. O. Bakhshaiesh, K. Majidzadeh-A and R. Esmaeili, "Wip1: A candidate phosphatase for cancer diagnosis and treatment," *DNA repair,* 2017.

[27] A. Emelyanov and D. V. Bulavin, "Wip1 phosphatase in breast cancer," *Oncogene,* pp. 4429-4438, 2015.