Fluctuations in network dynamics: SMAR1 can trigger apoptosis

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SMAR1 is a sensitive signaling molecule in p53 regulatory network which can drive p53 network dynamics to three distinct states, namely, stabilized (two), damped and sustain oscillation states. In the interaction of p53 network with SMAR1, p53 network sees SMAR1 as a sub-network with its new complexes formed by SMAR1, where SMAR1 is the central node, and fluctuations in SMAR1 concentration is propagated as a stress signal throughout the network. Excess stress induced by SMAR1 can drive p53 network dynamics to amplitude death scenario which corresponds to apoptotic state. The permutation entropy calculated for normal state is minimum indicating self-organized behavior, whereas for apoptotic state, the value is maximum showing breakdown of self-organization. We also show that the regulation of SMAR1 together with other signaling molecules p300 and HDAC1 in the p53 regulatory network can be engineered to extend the range of stress such that the system can be save from apoptosis.

I. INTRODUCTION

More than three decades of its discovery, p53 protein is still an important and critical molecule to study to explore new insights of cellular functional organization. Several experimental work have been done on p53 to understand how it regulates various cellular functions, but system level organization of these functional pathways controlled by p53 in normal, stress and cancerous cells are still to be investigated rigorously to understand the role of p53 at various cellular states at fundamental level. Due to its importance in cellular mechanisms, it is nominated as molecule of the year and also molecule of the month by the science magazine in 1993. p53 is composed of 393 amino acids [1]. It has a very short half-life of 15-30 minutes [2]. It takes part in many important cellular processes such as cell differentiation, maintaining genome integrity, apoptosis [3] etc. One of the most important negative regulator of the p53 is Mdm2 protein [3, 4]. Mdm2 forms the complex with p53 and then degraded the complex through its enzymatic activity. p53 acts as transcription factor for various important signaling molecules which participate in several important cellular networks and pathways. It helps in the formation of Mdm2 protein through positive feedback, but in turn Mdm2 negatively regulates p53 [5] to maintain minimum p53 level at normal state. These feedbacks lead to the oscillatory behavior of p53 in the regulatory network system. Further, p53 is very sensitive molecule which is generally activated due to several types of cellular stresses, namely DNA damage, interacting with various signaling molecules such as nitric oxide (NO), reactive oxygen synthase (ROS), calcium etc. Once cell comes under the influence of stress the inactive form of ATM kinase get activated and this activated ATM sent the damage information to p53 by interacting with it [6]. Consequently this leads to the phosphorylated p53, and encounters to several statges of reactions network to repair DNA damage and comes back to normal state, otherwise move to apoptosis [7, 8].

p300 is an acetylating agent which acetylate p53 at its c-terminal and this leads to the prevention of p53–Mdm2 interaction and this activity leads to the suppression of p53 degradation [9, 10]. It is also reported that p300 also interact with Mdm2 protein to form p300 – Mdm2 complex as a result of which the level of Mdm2 is decreased in the system [11–13].

On the other hand, HDAC1 is a deacetylating agent which deacetylate the acetylated form of p53. The deacetylation of p53 by HDAC1 is indirect which occurs due to the recruitment of Mdm2 by HDAC1 [14]. However, the deacetylated form of p53 is very vurnable and comes easily in contact with Mdm2, which leads to the degradation of p53 [14, 15].

SMAR1, a p53 target gene, is very a versatile molecule as reported by several experimental study so far [16–18]. It can interact with p53, Mdm2 as well p300 molecule with different affinity [17]. It is reported that it enhances p53 transcriptional activity and stability of p53 [16, 17]. Moreover, it also shows negative impact on both Mdm2 and p300 [17]. This molecule is expressed upon DNA damages in a p53 dependent manner [18]. It is also indicates that the interaction of SMAR1 with p53 in the nucleus helps in stabilizing the p53 by displacing its negative regulator Mdm2 [19]. Further, p53 has been shown to be deacetylated by its interaction with Mdm2 through recruitment of HDAC1 [14]. It can also interact with and deacetylate p53 by recruiting HDAC1 [20]. However, knockdown of HDAC1 only partially rescues p53 acetylation suggesting that SMAR1 employs supplemental mechanisms to regulate p53 acetylation [21]. Hence, SMAR1 can be considered as an important m-
clear matrix binding transcription factor which acts as a repressor by recruiting HDAC1 [22].

There have been several mathematical models constructed from the p53 regulatory network by taking care of various feedback mechanisms in the network [8, 23, 24], incorporating radiotherapy [25], by taking into account apoptosis inhibitors (caps3, caps9) showing various states such as bistability [26], considering DNA damage via irradiation [6, 27], modeling apoptosis from stress p53 [28, 29], taking into account pharmacodynamics target such nutilin [30, 31], incorporating somatogenesis with Wnt, Axin and nutilin [32], embodying signaling molecules such as calcium with NO [32] and p300 and HDAC1 [33], integrating with cell cycle pathway [34]. These studies show that the introduction of stress in the p53 regulatory network allows to switch the stabilized p53 state to oscillatory dynamics via DNA damage [27, 32] and excess stress may lead to apoptosis. It has been observed with evidences that the switching mechanism at different dynamical states of p53 correspond to various cellular states. However, the monitoring of specific reactions in the p53 regulating network could save the system from apoptosis is an open question. The complexity measurement of various possible states of the system could tell many information inherited in the time series and need to be investigated systematically. The study of role of SMAR1 in p53 regulation may open up new understanding in the regulatory network, stress management in the stress system, monitoring apoptosis and switching in cancer phase. We present p53 regulation driven by SMAR1 incorporating p300 and HDAC1 in section II with quasi-steady state approximation technique and permutation entropy description. Results of simulation of the constructed model with discussion in the section III and conclusion based on the simulation results are described in section IV.

II. MATERIALS AND METHODS

A. p53 − Mdm2 − SMAR1 regulatory model

p53 maintained at low levels in unstressed cell due to p53 and Mdm2 protein feedback mechanism [4]. It binds to the Mdm2 gene in nucleus which leads to the transcription of Mdm2 messenger RNA (mRNA) with a rate constant k3, subsequently this leads to translation into Mdm2 protein with a rate constant k2 [6]. The half life of the Mdm2 mRNA, Mdm2 is less which occurs with rate k4, k5 respectively. The synthesis of p53 protein in cells varies according to the half life of p53 protein. We considered the rate of p53 synthesis takes place at the rate k6. The interaction of p53 and Mdm2 is reported with rate k8 which leads to formation of Mdm2−p53 complex. It is reported by several research that Mdm2 functions as an E3 ubiquitin ligase and this leads to the degradation of p53 protein with rate k7. Further the dissociation of the Mdm2−p53 complex occurs with a rate k9. When cell experience stress the inactivated form of ATM transform into activated form Mdm2 which supposed to be occurs with a rate k10. Further it is reported that activated form transform into inactivated ATM with a rate k11. The activated form of ATM interact with p53 which leads to phosphorylation of p53 with a rate k12. This phosphorylated form of p53 further dephosphorylates with a rate k13. p300 is an important protein which interact with p53 and forms p53-p300 complex with a rate k15 and this subsequently leads to the production of acetylated p53 with a rate k16. The synthesis of p300 is reported as rate of k23. Similarly due to its short half life the degradation of p300 is reported to occur with a rate k14. p300 is also interact with a rate k20 to form Mdm2−p300 complex. Further it is reported that Mdm2−p300 complex interact with p53 and leads to degradation of complex at rate k1 [5, 9]. It also reported that Mdm2−p53 complex can interact with p300 to form Mdm2−p53−p300 ternary complex with rate k19. Further the dissociation of this complex leads to the formation Mdm2 and p53−p300 complex with a rate k21. HDAC1 deacetylate acetylated p53 with rate k33 by recruiting Mdm2 with rate k32. The synthesis and degradation of the HDAC1 due to its half life occurs with rate k24 and k22. SMAR1 is an important signaling molecule which interact with p53 and phosphorylates it with a rate k29. SMAR1 interact with Mdm2 to form Mdm2−SMAR1 complex with a rate k18. Mdm2−SMAR1 complex interact with HDAC1 to form Mdm2−SMAR1−HDAC1 complex with rate k25. Now this bigger complex interact with acetylated p53 which leads to the formation of deacetylated p53 with a rate k17. The synthesis and degradation of the SMAR1 due to its half life occurs with rate k26 and k27. The degradation of Mdm2−SMAR1 complex takes place with rate k28. SMAR1 interact with p300 and degraded its level with rate k35. The interaction of SMAR1 with Mdm2−p53 complex occurs with a rate k30 which leads to the formation of p53−Mdm2−SMAR1 complex. Further it is reported that the dissociation of this complex with rate k31 leads to the formation of phosphorylated p53 and Mdm2−SMAR1 complex. It is also reported that SMAR1 can interact with p53−p300 complex with rate k34.

The stress p53 − Mdm2 − SMAR1 model network we study is defined by N = 18 (18 molecular species) and M = 35 (35 reaction channels). The molecular species, possible reactions, kinetic laws and the rate constants in this model are listed in Table 1 and Table 2 respectively. The state vector at any instant of time t is given by, ̄x(t) = (x1, . . . , x18)T, where the variables in the vector are various proteins and their complexes which are listed in Table 1. The classical deterministic equations
constructed from these reaction network are given by,

\[
\begin{align*}
\frac{dx_1}{dt} &= -k_1 x_1 x_{14} + k_6 - k_8 x_1 x_2 + k_9 x_4 - k_{12} x_1 x_6 \\
&\quad + k_{13} x_7 + k_{17} x_0 x_{12} - k_{29} x_1 x_{15} \\
&\quad + k_{33} x_9 x_{15} \\
\frac{dx_2}{dt} &= k_2 x_3 - k_5 x_2 + k_7 x_4 - k_8 x_1 x_2 + k_9 x_4 \\
&\quad - k_{18} x_2 x_{15} - k_{20} x_2 x_8 + k_{21} x_{13} \\
&\quad - k_{32} x_2 x_{11} \\
\frac{dx_3}{dt} &= k_3 x_1 - k_4 x_3 \\
\frac{dx_4}{dt} &= -k_7 x_4 + k_8 x_1 x_2 - k_9 x_4 - k_{19} x_4 x_8 \\
&\quad - k_{30} x_4 x_{15} \\
\frac{dx_5}{dt} &= -k_{10} x_5 + k_{11} x_6 \\
\frac{dx_6}{dt} &= k_{10} x_5 - k_{11} x_6 - k_{12} x_1 x_6 \\
\frac{dx_7}{dt} &= k_{12} x_1 x_6 - k_{13} x_7 - k_{15} x_7 x_{18} + k_{29} x_1 x_{15} \\
&\quad + k_{31} x_{17} \\
\frac{dx_8}{dt} &= -k_{14} x_8 - k_{15} x_8 x_7 - k_{19} x_4 x_8 - k_{20} x_2 x_8 \\
&\quad + k_{21} x_{13} + k_3 - k_{35} x_8 x_{15} \\
\frac{dx_9}{dt} &= k_{15} x_8 x_7 - k_{16} x_9 - k_{34} x_9 x_{15} \\
\frac{dx_{10}}{dt} &= k_{16} x_9 - k_{17} x_{10} x_{12} - k_{33} x_{10} x_{18} \\
\frac{dx_{11}}{dt} &= -k_{25} x_{11} x_{16} - k_{22} x_{11} + k_{24} - k_{32} x_2 x_{11} \\
\frac{dx_{12}}{dt} &= -k_{17} x_{10} x_{12} + x_{25} x_{11} x_{16} \\
\frac{dx_{13}}{dt} &= k_{19} x_4 x_8 - k_{21} x_{13} \\
\frac{dx_{14}}{dt} &= -k_1 x_1 x_{14} + k_{20} x_2 x_8 \\
\frac{dx_{15}}{dt} &= -k_{18} x_2 x_{15} + k_{26} - k_{27} x_{15} - k_{29} x_1 x_{15} \\
&\quad - k_{30} x_4 x_{15} \\
\frac{dx_{16}}{dt} &= k_{18} x_2 x_{15} - k_{25} x_{11} x_{16} - k_{28} x_{16} \\
&\quad + k_{31} x_{17} \\
\frac{dx_{17}}{dt} &= k_{30} x_4 x_{15} - k_{31} x_{17} \\
\frac{dx_{18}}{dt} &= k_{32} x_2 x_{11} - k_{33} x_{11} x_{18}
\end{align*}
\]

(1)  
(2)  
(3)  
(4)  
(5)  
(6)  
(7)  
(8)  
(9)  
(10)  
(11)  
(12)  
(13)  
(14)  
(15)  
(16)  
(17)  
(18)  

where, \( \{k_i\} \) and \( \{x_i\}, i = 1, 2, \ldots, N(N = 18) \) represent the sets of rate constants of the reactions listed in Table 2 and concentration variables of the molecular species listed in Table 1. This complicated coupled set of non-linear differential equations can be solved numerically using standard fourth order Runge-Kutta method of numerical integration [39] to get the dynamical behavior of the variables listed in Table 1.

Fluctuations in p53 network dynamics triggered by stress inducing molecular species could highlight some of basic regulatory mechanisms of how regulatory network works and self-organized by itself to maintain normal functioning of the network. The p53 network sees a stress inducing molecular species not as a single species but as a sub-network of that species in which the species itself is the central node (removing this node cause break down of the sub-network). Fluctuations in any one of the reaction channel in the sub-network cause changes in all the components of the sub-network, and then impart that overall perturbation to the main p53 network which alters the topological characteristics and dynamics of the network. These changes in the properties of the network induce fluctuations in the properties of individual behavior of the components of the network.

The state of the dynamical system given by coupled ordinary differential equations (ODE) (1)-(18) at any instant of time ‘t’ is given by state vector, \( \vec{x}(t) = (x_1, x_2, \ldots, x_N)^T \), where, \( T \) is the transpose of the vector and \( N = 18 \). The system of reactions (Table 2), from which the ODEs (1)-(18) are constructed, can be approximately divided into two types of elementary reactions, namely fast and slow reactions [40]. The variables in the state vector \( \vec{x} \) can be divided into fast and slow vectors.
Table 1 - List of molecular species

| S.No. | Species Name | Description | Notation |
|-------|--------------|-------------|----------|
| 1.    | p53          | Unbounded p53 protein | x₁      |
| 2.    | Mdm2        | Unbounded Mdm2 protein | x₂      |
| 3.    | Mdm2_mRNA   | Mdm2 messenger mRNA | x₃      |
| 4.    | Mdm2-p53    | Mdm2 with p53 complex | x₄      |
| 5.    | ATM_p        | Inactivated ATM protein | x₅      |
| 6.    | ATM_p       | Activated ATM protein | x₆      |
| 7.    | p53_P       | Phosphorylated p53 protein | x₇      |
| 8.    | p300        | Unbounded p300 protein | x₈      |
| 9.    | p53_p300_P  | Phosphorylated p53-p300 complex | x₉      |
| 10.   | p53_A       | Acetylated p53 protein | x₁₀     |
| 11.   | HDAC1       | Unbounded HDAC1 protein | x₁₁     |
| 12.   | Mdm2_HDAC1_SMAR1 | Mdm2, HDAC1 and SMAR1 complex | x₁₂     |
| 13.   | Mdm2_p53_p300 | Mdm2, p53 and p300 complex | x₁₃     |
| 14.   | Mdm2_p300   | Mdm2 and p300 complex | x₁₄     |
| 15.   | SMAR1       | Unbounded SMAR1 protein | x₁₅     |
| 16.   | Mdm2_SMAR1  | Mdm2 and SMAR1 complex | x₁₆     |
| 17.   | p53_Mdm2_SMAR1 | p53, Mdm2 and SMAR1 complex | x₁₇     |
| 18.   | HDAC1_Mdm2  | HDAC1 and Mdm2 complex | x₁₈     |

Table 2 - List of chemical reaction, propensity function and their rate constant

| S.No. | Reaction | Name of the process | Kinetic Law | Rate Constant | References |
|-------|----------|---------------------|-------------|---------------|------------|
| 1     | x₁ + x₁₄  | p53 degradation     | k₁⟨x₁⟩⟨x₁₄⟩ | 8.25 × 10⁻⁴ sec⁻¹ | [5, 9]     |
| 2     | x₁ → x₁₃ + x₂ | Mdm2 creation | k₂(x₂)      | 4.95 × 10⁻⁴ sec⁻¹ | [6]        |
| 3     | x₁ → x₁₃ + x₃ | Mdm2_mRNA creation | k₃(x₁)      | 1.0 × 10⁻⁴ sec⁻¹ | [6]        |
| 4     | x₁ → x₁₃ | Mdm2_mRNA degradation | k₄(x₃)      | 1.0 × 10⁻⁴ sec⁻¹ | [6]        |
| 5     | x₂ → x₃ | Mdm2 degradation | k₅(x₂)      | 4.33 × 10⁻⁴ sec⁻¹ | [6]        |
| 6     | φ → x₁ | p53 synthesis | k₀          | 0.078 sec⁻¹ | [6]        |
| 7     | x₄ → x₁₃ | Mdm2_p53 degradation | k₇(x₄)      | 8.25 × 10⁻⁴ sec⁻¹ | [35, 36]  |
| 8     | x₁ + x₂ → x₄ | Mdm2_p53 synthesis | k₈(x₁)⟨x₂⟩ | 11.55 × 10⁻⁴ sec⁻¹ | [6]        |
| 9     | x₄ → x₅ + x₂ | Mdm2_p53 dissociation | k₉(x₄)      | 11.55 × 10⁻⁶ sec⁻¹ | [6]        |
| 10    | x₅ → x₆ | ATM activation | k₁₀(x₅)     | 1.0 × 10⁻⁴ sec⁻¹ | [36, 37]  |
| 11    | x₆ → x₅ | ATM deactivation | k₁₁(x₆)     | 5.0 × 10⁻⁴ sec⁻¹ | [36, 37]  |
| 12    | x₁ + x₆ → x₇ | Phosphorylation of p53 | k₁₂(x₁)⟨x₆⟩ | 5.0 × 10⁻⁴ sec⁻¹ | [36]       |
| 13    | x₇ → x₈ | Dephosphorylation of p53 | k₁₃(x₇)     | 5.0 × 10⁻¹ sec⁻¹ | [36, 37]  |
| 14    | x₈ → x₉ | p300 degradation | k₁₄(x₈)     | 1.0 × 10⁻⁴ sec⁻¹ | [38, 45]  |
| 15    | x₉ → x₁₀ | p53_p300 formation | k₁₅(x₉)⟨x₈⟩ | 1.0 × 10⁻⁴ sec⁻¹ | [11]       |
| 16    | x₉ → x₁₀ | Acetylation of p53 | k₁₆(x₉)     | 1.0 × 10⁻⁴ sec⁻¹ | [10, 12]  |
| 17    | x₁₀ + x₁₂ | Deacetylation of p53 | k₁₇(x₁₀)⟨x₁₂⟩ | 1.0 × 10⁻⁵ sec⁻¹ | [12]       |
| 18    | x₁₂ + x₁₅ | Creation of Mdm2_SMAR1 | k₁₈(x₁₂)⟨x₁₅⟩ | 2.0 × 10⁻⁴ sec⁻¹ | [12]       |
| 19    | x₄ + x₈ | Creation of Mdm2_p53_p300 | k₁₉(x₄)⟨x₈⟩ | 5.0 × 10⁻⁴ sec⁻¹ | [11]       |
| 20    | x₂ + x₈ | Formation of Mdm2_p300 | k₂₀(x₂)⟨x₈⟩ | 5.0 × 10⁻⁴ sec⁻¹ | [5, 6]     |
| 21    | x₁₃ | Dissociation of Mdm2_p53_p300 | k₂₁(x₁₃)     | 1.0 × 10⁻⁴ sec⁻¹ | [11, 35]  |
given by,

\[
\vec{x}^f = \begin{bmatrix}
    x_1 \\
    x_2 \\
    x_3 \\
    x_4 \\
    x_5 \\
    x_6 \\
    x_7 \\
    x_8 \\
    x_9 \\
    x_{10} \\
    x_{11} \\
    x_{12} \\
    x_{13} \\
    x_{14} \\
    x_{15} \\
    x_{16} \\
    x_{17} \\
    x_{18}
\end{bmatrix};
\vec{\dot{x}}^f = \begin{bmatrix}
    x_3 \\
    x_4 \\
    x_5 \\
    x_6 \\
    x_7 \\
    x_8 \\
    x_9 \\
    x_{10} \\
    x_{11} \\
    x_{12} \\
    x_{13} \\
    x_{14} \\
    x_{15} \\
    x_{16} \\
    x_{17} \\
    x_{18}
\end{bmatrix}
\]

(19)

\[
\frac{d\vec{x}^f}{dt} \approx 0; \quad \vec{x}^{\ast f} = \frac{d\vec{x}^f}{dt}
\]

(20)

The fast variables are normally corresponding to complex molecular species. Generally, formation of complex molecular species due to fast reactions are followed by fast decay of these complexes, the dynamics of the fast variables reach steady state much quickly as compared to the dynamics of slow variables \[41, 42\]. We then use Henri-Michaelis-Menten-Briggs-Haldane approximation to assume that the time evolution of fast state vector \(\vec{x}^f\) reach equilibrium state defined by \(\vec{x}^{\ast f}\) much faster as compared to the time evolution of slow state vector \(\vec{x}^s\) \[41, 42\]. Applying this approximation, we can reach the following steady state for fast variables,

\[
\frac{d\vec{x}^s}{dt} = \frac{d}{dt} \begin{bmatrix}
    x_1 \\
    x_2 \\
    x_3 \\
    x_4 \\
    x_5 \\
    x_6 \\
    x_7 \\
    x_8 \\
    x_9 \\
    x_{10} \\
    x_{11} \\
    x_{12} \\
    x_{13} \\
    x_{14} \\
    x_{15} \\
    x_{16} \\
    x_{17} \\
    x_{18}
\end{bmatrix}
\approx 0
\]

\[
\frac{d\vec{x}^s}{dt} = \frac{d}{dt} \begin{bmatrix}
    x_1 \\
    x_2 \\
    x_3 \\
    x_4 \\
    x_5 \\
    x_6 \\
    x_7 \\
    x_8 \\
    x_9 \\
    x_{10} \\
    x_{11} \\
    x_{12} \\
    x_{13} \\
    x_{14} \\
    x_{15} \\
    x_{16} \\
    x_{17} \\
    x_{18}
\end{bmatrix}
\]

(21)

The approximate solution of the complex model can be obtained from this reduced model using quasi steady state approximation.
and stabilized (2), damped and sustain oscillation states in all

FIG. 2: (A) The dynamics of $p$ following. The time series of the variable $S$ substituting variable $x$ to slide along the sequence $i$ to find the probabilities of occurrence of each inequality in $w_i$. Since $q$ out of $r!$ permutations are distinct, one can define a normalized permutation entropy $x_{15}(t)$ as $H_i = -\frac{1}{\ln(r)} \sum_{j=1}^{r} p_j \ln(p_j)$ where, $0 \leq H_i(r) \leq 1$. The mapped permutation entropy spectrum of time series $x(t)$ is $H = \{H_1, H_2, ..., H_M\}$ which is the measure of complexity of time series $x(t)$. For self-organized state corresponds to order state giving $H \to 0$.

III. RESULTS AND DISCUSSION

Based on above equation we have obtained from our proposed integrated model, the simulation have been done. Here we only limits our study upto the deterministic solution of the equation. We have solved the set of differential equation using standard runge-kutte 4th order differential equation.

A. Approximate solution of the model

The fast state vector reach steady state quickly and can be taken as constant as compared to slow state variable (equations (20) and (21)). From equations (18) and (20), one can reach $x_2 = \frac{k_{27}}{k_{30}} x_1^*$ showing the direct dependence of $x_2$ on $x_1^*$ is steady state of HDA1-Mdm2 complex. Similarly, from equations (3) and (20) we get $x_1 = \frac{k_{32}}{k_{33}} x_3^*$ indicating direct proportional to the steady state of Mdm2-mRNA complex. Putting these equations to equation (15) and using equation (20), we have the following equation,

$$\frac{dx_{15}}{dt} + U x_{15} = k_{26}$$

where, $U = k_{27} + \frac{k_{1} k_{2}}{k_{32}} x_1^* + \frac{k_{3}}{k_{33}} x_3^* + k_{30} x_1^*$ is a constant within quasi-steady state approximation. The solution of this equation (22) is given by,

$$x_{15}(t) = \frac{k_{26}}{U} \left(1 - e^{-Ut}\right) + x_{15}(0) e^{-Ut}$$

where, $x_{15}(0)$ is the initial concentration of $x_{15}$ at $t = 0$. The solution (23) shows that the rate of increase of $x_{15}$ SMAR1 in the system is restricted by the steady state values of $x_3$, $x_4$ and $x_{18}$ via $U$; and time. The asymptotic value of $x_{15}$ as $t \to \infty$ is found to be $x_{15} \approx \frac{k_{26}}{k_{30}}$ reaching a steady state. For small values of time ‘t’, keeping upto linear terms in the expansion $e^{xt} \sim 1 + xt + O(t^2)$, we get $x_{15}(t) \approx \left[k_{26} - U x_{15}(0)\right] t$ which shows minimal sufficient condition for $x_{15}$ creation is $k_{26} > U x_{15}(0)$.

The equations (11), (21), (20) and $x_2 = \frac{k_{32}}{k_{33}} x_1^*$ can be used to get the following ODE of variable $x_{11},$

$$\frac{dx_{11}}{dt} + V x_{11} = k_{24}$$

where, $V = k_{22} + k_{25} x_{16} + k_{33} x_3^*$ is a constant. Then the solution of the ODE (24) can be obtained given by,

$$x_{11}(t) = \frac{k_{24}}{V} \left(1 - e^{-Vt}\right) + x_{11}(0) e^{-Vt}$$
where, $x_{11}(0)$ is the initial value of $x_{11}$ at $t = 0$. The asymptotic value of $x_{11}$ at $t \to \infty$ is given by $x_{11} \approx \frac{k_{24}}{V}$ which is the steady state. At small time limit where exponential expansion is approximated upto linear terms, we obtain $x_{11}(t) \sim \left[ k_{24} - V x_{11}(0) \right] t$. The minimal sufficient condition for formation of $x_{11}$ is $k_{24} > V x_{11}(0)$.

Similarly, using equations (8), (21) and (20) we can reach the following ODE,

$$\frac{dx_8}{dt} + x_8 \left[ W + k_{35} \left( \frac{k_{26}}{U} + W e^{-Ut} \right) \right] = k_{23} + k_{13} k_{21}$$

(26)

where, $W = k_{14} + k_{15} x_{17}^* + k_{19} x_{13}^* + k_{32} x_{18}^*$ is a constant.

The solution of this ODE can be obtained by taking $f \to f_0^\infty$ which is also true for positive values of $x_8$, and is given by,

$$x_8(t) = \left[ C_1 - G \left( \frac{U}{W} \right)^{H/U} \Gamma \left( \frac{H}{U} \right) \right] e^{-Ht + \frac{W}{U} e^{-Ut}}$$

(27)

where, $G = \frac{k_{23} + k_{13} x_{17}^*}{U}$ and $H = W + \frac{k_{32} x_{18}^*}{U}$ are constants. The constant $C_1$ can be obtained by using initial condition i.e. $t = 0$. Putting back the expression for $C_1$ to equation (27), we get,

$$x_8(t) = x_8(0) e^{-W} e^{-Ht + \frac{W}{U} e^{-Ut}}$$

(28)

It is observed that for large value of $t$, the term $Ht$ dominates $e^{-Ut}$, and therefore we have $x_8(t) \propto e^{-Ht}$. However, for small $t$, we have $x_8(t) \sim x_8(0) e^{-W/U} [1 - (H + W)t]$, which indicates that the minimal existence of $x_8$ will have the condition $(H + W)t < 1$.

Now, to get the solution for $x_2$, the equations (12) and (16) using (20) are added, and the result is substituted in equation (2). The simplified ODE of $x_2$ is given by,

$$\frac{dx_2}{dt} + x_2 \left[ R + \frac{S}{e^{Vt}} \right] = D$$

(29)

where, $R = k_5 + \frac{k_{14} k_{25}}{k_{33}}$, $S = k_{32} \left( x_{11} - \frac{k_{23}}{V} \right)$ and $D = k_2 x_3^* + k_7 x_4^* + k_6 x_{13} + k_{31} x_{17} - \frac{k_{32}}{k_{33}} x_5^* - k_{17} x_{10} x_{12} - k_{28} x_{16}^* - \frac{k_{32} k_{33} x_{18}^*}{k_3}$ are constants. The solution of the equation (29) is given by,

$$x_2(t) = \left[ C_2 - D S V \left( \frac{V}{S} \right)^{P-1} \Gamma \left( \frac{R}{V} \right) \right] e^{-Rt + \frac{S}{V e^{Vt}}}$$

(30)

where, $C_2$ is a constant which can be obtained from initial condition $t = 0$. Then putting back the expression for $C_2$ to the equation (30), we get,

$$x_2(t) = x_2(0) e^{-\frac{S}{V} e^{-Rt + \frac{S}{V e^{Vt}}}$$

(31)

The large $t$ limit in the equation (31) show that $x_2(t) \sim x_2(0) e^{-S/V e^{-Rt}}$ which shows that $x_2(t) \propto e^{-Rt}$. However, it further indicates that $\lim_{t \to \infty} x_2(t) = 0$. Small $t$ approximation to the equation (31) leads to the expression $x_2(t) \sim x_2(0) e^{-S/V} [1 - (R + S)t]$, which shows that minimal condition for existence of $x_2$ is $1 > (R + S)t$.

Similarly, proceeding same way as above, from equations (1), (7), (9) and (steady) we obtain the following ODE for $x_1$,

$$\frac{dx_1}{dt} + F x_1 = G + P e^{-Vt}$$

(32)

where, $F = k_1 x_{14}^* + \frac{k_{15} k_{25}}{k_{33}}$, $G = k_6 + k_{31} x_{17}^* + k_{17} x_{10} x_{12}^* + k_{31} x_{17}^* - k_{13} x_7^* - k_{16} x_{18}^* + \frac{k_{32} k_{33} k_{18}}{k_3}$, and $P = k_{32} k_{18}$ are constants. The solution of the equation (32) is given by,

$$x_1(t) = \frac{G}{F} \left( 1 - e^{-Ft} \right) + \frac{P}{F - V} \left( e^{-Vt} - e^{-Ft} \right) + x_1(0) e^{-Ft}$$

(33)

Now, the small $t$ approximation allows to simplify equation (33) to obtain $x_1(t) \sim x_1(0) + t[P - G - F x_1(0)]$. The minimal condition for $x_1$ existence in the system is given by, $x_1(0) > |t[G + F x_1(0) - P]|$. However, in the large $t$ approximation, we have, $x_1(t) = \frac{G}{F} (1 - e^{-Ft})$ and for non-negative value of $x_1$ the condition is, $e^{Ft} \leq 1$. However, we have $\lim_{t \to \infty} x_1(t) = -\infty$. 

FIG. 3: (A) The Mdm2 dynamics induced by stress inducers, $k_{SMAR1}$, $k_{p300}$ and $k_{HDAC1}$ showing three different distinct states as obtained in the case of p53. (B) The permutation entropy spectrum of the three states of Mdm2 dynamics induced by SMAR1.
The changes in the states of the dynamics of p53 are triggered by various signaling molecules, namely, SMAR1, p300 and HDAC1 respectively (Fig. 2) and found three distinct states, two steady states, damped oscillation state and sustain oscillation states. When p53 regulatory network interacts with one of the signaling molecules, the network saw that signaling molecule as a sub-network (see Fig. 1) which involves a number of interaction and a number of complexes due to the interaction. So the changes in the p53 dynamics are due to the fluctuations in the sub-network associated with the signaling molecule.

The concentration of HDAC1 in the system depends on the value of creation rate of it \( k_{26} \) which we have taken as \( k_{HDAC1} \) in our simulation. At low concentration of HDAC1 (small value of \( k_{HDAC1} \)) allows p53 to maintain its normal state (stabilized state) in the system (Fig. 2 left upper panels). As one increase the concentration of HDAC1 in the system (increasing the value of \( k_{HDAC1} \)), HDAC1 starts active interaction with Mdm2 and SMAR1 forming various complexes followed by indirect interaction with p53 (Table 2). This indirect interaction of HDAC1 and p53 impart stress in p53 dynamics which starts exhibit damped oscillation (mixture of stress and stabilized state) indicating the induction of stress by the available HDAC1 concentration in the system and then come back to the normal state\[14, 45]\.

The range of damped oscillation increases as \( k_{HDAC1} \) value increases and after sufficient value of \( k_{HDAC1} \), p53 dynamics become sustain oscillation for a certain range of \( k_{HDAC1} \rightarrow [0.007 − 0.05] \). This sustain oscillation state corresponds to strong activated or stress state which is found to be maximum at \( k_{HDAC1} = 0.07 \) (where amplitude of p53 of the corresponding sustain oscillation is maximum \( \sim 123.2 \pm 2 \)), then start decreasing as \( k_{HDAC1} \) increases. After \( k_{HDAC1} > 0.05 \), the dynamics of p53 become damped oscillation, which indicates that large HDAC1 concentration in the system trigger large stress which can’t be repair back and may probably go to apoptosis. This range of stress in this case decreases with amplitude as the value of \( k_{HDAC1} \) increases. Excess HDAC1 concentration in the system may trigger immediate apoptosis of the system (stabilized state)\[46–48]\.

Similarly, the three states of p53 are also found when the p53 regulatory network is perturbed by sub-network of SMAR1 (Fig. 2 middle panels) which is composed of SMAR1 and its interaction partners i.e. associated complexes (Fig. 1) and acts as main hub in the sub-network. The rate constant of formation of SMAR1 in the system \( k_{26} \), which we take \( k_{SMAR1} \) as notation, corresponds to the availability of SMAR1 concentration in the system to induce perturbation in p53 network\[17]\.

This accessible concentration of SMAR1 affects the dynamics its own sub-network, and then impart perturbation to p53 network. The results of perturbation, similar to that of HDAC1, shows nearly normal state for \( k_{SMAR1} < 0.0001 \) for fixed values of \( k_{HDAC1} = 0.01 \) and \( k_{p300} = 0.1 \), damped states in two ranges \( [0.0001 − 0.005] \) (increasing range of damped oscillation as \( k_{SMAR1} \) increases) and \( [0.06 − 0.2] \) (decreasing range of damped oscillation as \( k_{SMAR1} \) increases), and sustain oscillation in the range \( [0.051 − 0.058] \) which decreases p53 amplitude as \( k_{SMAR1} \) increases. Therefore, excess SMAR1 concentration in the system triggers apoptosis. Similar behavior is found in Mdm2 case (Fig. 3).

Similar behavior of these three states is found for the case of p300 induced p53 dynamics (Fig. 2 right panels). Similar behavior is found in Mdm2 case (Fig. 3). This reveals that this signaling molecule has also the tendency to induce apoptosis in the system\[12, 33]\.

The permutation entropies \( H_{p53} \) of the three states of p53 driven by SMAR1 are calculated for p53 dynamics to understand complexity of the perturbed network (Fig. 2 lowermost panel). We took embedded dimension \( r = 3 \) and window size to be \( w_s = 512 \). We also tried for other values of embedded dimension i.e. \( 4, 5 \) and \( 6, \) and found the results almost the same. The results show that for normal state (low value of \( k_{SMAR1} = 0.0001 \)) the values of \( H_{p53} \) is low, with large gaps among nearly periodic curves which consist of large number of near zero points. This low values of \( H_{p53} \) indicates more self-organized behavior at normal state of the system. If we increase the values of \( k_{SMAR1} \) (\( k_{SMAR1} = 0.001, 0.01, 0.04 \)) the \( H_{p53} \) values start increasing, and the gap between neighbouring curves decreases, showing significant increase of \( H_{p53} \).
taining oscillation. Larger values of stress parameter than this range, the transition of sustain to damped oscillation states takes place. Further larger values of stress parameter force the dynamics to amplitude death scenario again (Fig. 4 and Fig. 5). This transition of various oscillating states as a function of stress parameter give corresponding signatures of the state of the system [34].

Normal state of \( p53 \) dynamics (small values of stress parameter) show amplitude death scenario of \( p53 \) as a function of \( k_{HDAC1} \) for different values of \( k_{SMAR1} \) (Fig. 4 upper left panel). The transition from amplitude death (normal state) to damped state (mixture of stress then come back to normal after removing of stress) is for small range of \( k_{HDAC1} \) only, and suddenly move to the sustain oscillation state (we took long time series of 500 hours i.e. 5 days duration after removing transients). Within the range of sustain oscillation state, the amplitude of \( p53 \) (\( A_{p53} \)) increases as a function of \( k_{HDAC1} \) (equation (33)). The amplitude \( A_{p53} \) suddenly drops to zero (amplitude death scenario) after a short range \( k_{HDAC1} \). This second regime of amplitude death scenario could be the apoptotic state of the modeled system. Further, it can also be seen that for the same range of \( k_{HDAC1} \), as \( k_{SMAR1} \) increases the range of sustain oscillation decreases and on the other hand the amplitude of \( p53 \) decreases. It reveals that if the value of \( k_{SMAR1} \) is large enough the the system will go to amplitude death (apoptotic) regime directly. Similar transition the states can also be found in the case of \( Mdm2 \) dynamics also (Fig. 5).

The transition of the states can also be seen in the parameter space of \( p53 \) and \( k_{HDAC1} \) for different values of \( k_{p300} \) and for fixed value of \( k_{SMAR1} \) (Fig. 4 upper right panel). The different in behavior in this is the increase in the regime of sustain oscillation as \( k_{p300} \) increases until \( k_{p300} = 0.1 \). This indicates that within this range of \( k_{p300} \), increasing \( k_{p300} \) can able to increase the range of \( k_{HDAC1} \) before reaching apoptosis. After this value the \( A_{p53} \) behavior does not usual transition and goes to zero amplitude quickly (Fig. 4 upper right panel). This means that one can engineer the modeled system in such a way that increasing \( k_{p300} \) can able to increase the accessible \( k_{HDAC1} \) to save the system from apoptosis.

The behavior of \( A_{p53} \) as a function of \( k_{p300} \) for various values of \( k_{HDAC1} \) and for a fixed value of \( k_{SMAR1} \) shows two states transition, namely sustain oscillation and amplitude death (apoptotic state) (Fig. 4 left middle panel). This is due to the choice of value of \( k_{SMAR1} \) is to induce sustain oscillation. The increase in \( k_{HDAC1} \) allow the system to reach amplitude death regime quickly. Same is true for the case of \( A_{p53} \) versus \( k_{p300} \) for various values of \( k_{SMAR1} \) (Fig. 4 right middle panel).

The scenario of transition of the states is different in the case of \( A_{p53} \) as a function of \( k_{SMAR1} \) for various values of \( k_{HDAC1} \) which shows the increase in the range of accessible \( k_{SMAR1} \) as \( k_{HDAC1} \) increases (Fig. 4 lower left panel). However, increase in \( k_{p300} \) forces \( A_{p53} \) to reach amplitude death regime (apoptotic) quicker (Fig. 4 lower right panel). Similar scenario of transition of

C. Amplitude death: signature of apoptosis

The amplitude of \( p53 \) oscillatory dynamics due to fluctuations induced by changes in some part of the network (for example changes in concentration of \( SMAR1 \), \( p300 \), \( HDAC1 \) with corresponding sub-networks associated with them) refers to the amount of stress induced in its dynamics. The amount of stress imparted in the system allows active interaction of this \( p53 \) with the respective fluctuated molecular species directly or indirectly, and once the stress is removed, the active interaction stays for sometime with damped oscillation which we call "Restoration time" and come back to normal situation where the amplitude becomes zero (amplitude death) (Fig. 2 and Fig. 3). The relaxation time increases as the amount of stress is increased, and become infinite for certain range of value of stress parameter \((k_{SMAR1}, k_{p300}, k_{HDAC1} etc)\) which is the case of sustained oscillation. Larger values of stress parameter than this range, the transition of sustain to damped oscillation states takes place. Further larger values of stress parameter force the dynamics to amplitude death scenario again (Fig. 4 and Fig. 5). This transition of various oscillating states as a function of stress parameter give corresponding signatures of the state of the system [34].

Normal state of \( p53 \) dynamics (small values of stress parameter) show amplitude death scenario of \( p53 \) as a function of \( k_{HDAC1} \) for different values of \( k_{SMAR1} \) (Fig. 4 upper left panel). The transition from amplitude death (normal state) to damped state (mixture of stress then come back to normal after removing of stress) is for small range of \( k_{HDAC1} \) only, and suddenly move to the sustain oscillation state (we took long time series of 500 hours i.e. 5 days duration after removing transients). Within the range of sustain oscillation state, the amplitude of \( p53 \) (\( A_{p53} \)) increases as a function of \( k_{HDAC1} \) (equation (33)). The amplitude \( A_{p53} \) suddenly drops to zero (amplitude death scenario) after a short range \( k_{HDAC1} \). This second regime of amplitude death scenario could be the apoptotic state of the modeled system. Further, it can also be seen that for the same range of \( k_{HDAC1} \), as \( k_{SMAR1} \) increases the range of sustain oscillation decreases and on the other hand the amplitude of \( p53 \) decreases. It reveals that if the value of \( k_{SMAR1} \) is large enough the the system will go to amplitude death (apoptotic) regime directly. Similar transition the states can also be found in the case of \( Mdm2 \) dynamics also (Fig. 5).

The transition of the states can also be seen in the parameter space of \( p53 \) and \( k_{HDAC1} \) for different values of \( k_{p300} \) and for fixed value of \( k_{SMAR1} \) (Fig. 4 upper right panel). The different in behavior in this is the increase in the regime of sustain oscillation as \( k_{p300} \) increases until \( k_{p300} = 0.1 \). This indicates that within this range of \( k_{p300} \), increasing \( k_{p300} \) can able to increase the range of \( k_{HDAC1} \) before reaching apoptosis. After this value the \( A_{p53} \) behavior does not usual transition and goes to zero amplitude quickly (Fig. 4 upper right panel). This means that one can engineer the modeled system in such a way that increasing \( k_{p300} \) can able to increase the accessible \( k_{HDAC1} \) to save the system from apoptosis.

The behavior of \( A_{p53} \) as a function of \( k_{p300} \) for various values of \( k_{HDAC1} \) and for a fixed value of \( k_{SMAR1} \) shows two states transition, namely sustain oscillation and amplitude death (apoptotic state) (Fig. 4 left middle panel). This is due to the choice of value of \( k_{SMAR1} \) is to induce sustain oscillation. The increase in \( k_{HDAC1} \) allow the system to reach amplitude death regime quickly. Same is true for the case of \( A_{p53} \) versus \( k_{p300} \) for various values of \( k_{SMAR1} \) (Fig. 4 right middle panel).

The scenario of transition of the states is different in the case of \( A_{p53} \) as a function of \( k_{SMAR1} \) for various values of \( k_{HDAC1} \) which shows the increase in the range of accessible \( k_{SMAR1} \) as \( k_{HDAC1} \) increases (Fig. 4 lower left panel). However, increase in \( k_{p300} \) forces \( A_{p53} \) to reach amplitude death regime (apoptotic) quicker (Fig. 4 lower right panel). Similar scenario of transition of

FIG. 5: The variation of amplitude of \( Mdm2 \) dynamics induced by \( k_{SMAR1} \), \( k_{p300} \) and \( k_{HDAC1} \) which shows three different states: stabilized state (one for normal and the other for apoptotic states, indicated by amplitude death case), damped states and sustain states.
states is found in the case of $A_{Mdm2}$ (Fig. 5)[50].

D. Regulation of apoptosis

Taming stress imparted in a system by stress induced parameters is important to save the system from apoptosis. The calculated critical value of $k_{SMAR1}$, $k_{SMAR1}^c$, at which the amplitude of $p53$ is zero, and larger than this value the system goes to apoptosis, corresponds to a value of $k_{HDAC1}$ for each $k_{SMAR1}$ (Fig. 6 upper panel). The phase diagram in the parameter space $(k_{HDAC1}, k_{SMAR1})$ show the distinct demarcation of stress and apoptotic states (Fig. 6 upper panel). The result indicates that even for large value of $k_{SMAR1}$ which drives the system to apoptotic state, one can vary $k_{HDAC1}$ so that the range of stress state be broaden such that the system can be pull back to normal state once the stress is removed.

The average value of mid-value of sustain oscillation regime $p53$ amplitude ($A_{p53}^{av}$) for ten ensembles with different initial conditions modulated by $HDAC1$ as a function of $k_{SMAR1}$ shows monotonous decrease $A_{p53}^{av}$, as $k_{SMAR1}$ increases and will reach amplitude death for sufficiently large value of $k_{SMAR1}$ (Fig. 6 lower panel). Even though $k_{SMAR1}$ drives the $p53$ network to apoptosis (Fig. 6 lower panel), this apoptotic state can be regulated by $HDAC1$ interaction to save from apoptosis[48, 51].

Similar study of the impact of $k_{SMAR1}$ on $p53$ network in regulating apoptotic phase in the presence of another stress inducer $p300$ via $k_{p300}$ shows different scenario. The apoptotic phase diagram in the parameter space $(k_{p300}, k_{SMAR1})$ indicate two distinct scenarios, first $k_{SMAR1}^c$ increases as $k_{p300}$ increases up to a maximum value, and secondly $k_{SMAR1}^c$ decreases as $k_{p300}$ increases (Fig. 7 upper panel). In the first case, for any critical value of $k_{SMAR1}^c$, one can extend the range of stress regime by increasing the concentration of $p300$ (increasing the value of $k_{p300}$) in the system and save the system from apoptosis after removing the stress. In the second case, the range of stress can be increased for any value of $k_{SMAR1}^c$ by decreasing concentration of $p300$ and can save from apoptotic state.

The value of $A_{p53}^{av}$ modulated by $p300$ decays slowly as a function of $k_{SMAR1}$ (exponential decay) as compared to the case of $HDAC1$ (Fig. 7 lower panel). The amplitude death scenario can be seen in this case also but with slow variation.

IV. CONCLUSION

Fluctuations imparted in a network, due to interaction of stress inducing molecular species in the form of a sub-network where the stress inducer species is the central in the sub-network, are propagated throughout the network and dynamical as well as topological properties of each individual component in the network get changed. However, the amount of perturbation signal in the form of stress recieved by various components in the network are not equal, and depend on how far the components are from the stress epicentre in the network. Biological network, corresponding to a certain biological function, is generally self-organized and tries to protect the network organization to maintain its own normal functioning. However, if the stress is large enough the network functioning of the organization will break down and move to apoptosis.

$SMAR1$ is found to be a very dynamic and stress inducer signaling molecule which interfere the $p53$ regulatory network. It also interacts with many other signaling molecules such as $p300$, $HDAC1$ etc in the $p53$ network and regulate $p53$ dynamics. The concentration of this signaling molecular species in the network trigger the $p53$ dynamics to different states, which correspond to different cellular states, and even it can induce apoptosis to the cell. The mathematical modeling of this network provides various dynamical properties of the network which
is reflected in the dynamics of the state vector which is the vector of molecular species variables in the system. The complexity of these states can be determined by calculating the permutation entropies of these states, and found that normal state corresponds to smallest value of permutation entropy. As stress increases, complexity also increases and permutation entropy is increased correspondingly, and surprisingly the permutation entropy of second stabilized state, which corresponds to apoptotic state, has highest value. This indicates that at apoptotic state the self-organization of the network has lost and become disorder in the network organization.

The amplitude death scenario obtained from the dynamical study of the p53 regulatory network model could be used as the signature of apoptosis. Because the dynamics of this state has large complexity due to the lost of self-organization at this state. On the other hand, the amplitude death for the case of normal state (stabilized state) has minimum complexity due to the maintainance of self-organization of the system.

Abnormality in one signaling molecule in a system may trigger apoptosis to the system. However, since the network involves a number of other signaling molecules which can regulate the network, one can probably use other signaling molecules to save the system from apoptosis. The reason is that even though abnormality of one signaling molecule drives the system to apoptosis, a change in another signaling molecule may extend the range of stress and save the system from apoptosis. Thus even though SMAR1 can trigger apoptosis to p53 regulatory network, regulating other signaling molecule p300 or HDAC1 or both can possibly save the system from apoptosis. However, one needs experimental investigation and engineering of the signaling molecules in p53 regulatory network on such issues. Experimental and theoretical investigations in this direction are needed because these study will open up new understanding in the disease dynamics caused by abnormalities in signaling molecules, their preventive measures and cancer engineering.

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