Cancer Dynamics: Identification of States for Therapeutic Intervention

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We study a minimal model of the stress-driven \( p53 \) regulatory network that includes competition between active and mutant forms of the tumor-suppressor gene \( p53 \). Depending on the nature of the external stress signal, four distinct dynamical states are observed. These states can be distinguished by different dynamical properties and correspond to \textit{active}, \textit{apoptotic}, \textit{pre-malignant} and \textit{cancer} states. Transitions between any two of these states are found to be unidirectional and irreversible if the stress signal is either oscillatory or constant. When the signal decays exponentially, the apoptotic state vanishes, and for low stress the pre-malignant state is bounded by two critical points, allowing the system to transition reversibly from the active to the pre-malignant state. For significantly large stress, the range of the pre-malignant state expands and the system moves to the cancerous state which is a stable attractor. This suggests that identification of the pre-malignant state may be important both for therapeutic intervention as well as for drug discovery.

Keywords: \( p53 \)-Mdm2, mutant \( p53 \), oncogene, stress, regulatory network, cancer dynamics.

Introduction

The tumour suppressor gene \( p53 \), also termed as the guardian of the genome, crucially determines cell fate through various mechanisms \cite{1,2}. \( p53 \) induced different biological outcomes has been studied in detail \cite{4,5}. Activation of the \( p53 \) regulatory pathway by internal and external stress can lead to a number of different outcomes \cite{3,4}. \( p53 \) is known to be mutated in cancer, either in exonic or intronic portion of the gene due to stress \cite{3,6–10}. These mutations eventually lead to disruption in binding DNA. Hence the cell, during transformation, harbours mutated \( p53 \) that may finally develop malignancies. From a network theoretical perspective, \( p53 \) is a key hub controlling important genes as well as essential cellular functions \cite{1,11,12}. Studies on signalling networks have provided identification of many target genes for therapeutic interventions in the context of cancer \cite{1,11,12}, although identification of such genes from a dynamical perspective is still open.

Cancer is a complex disease manifested due to the interaction of nonlinear, nonadditive, and dissipative components \cite{13}. In order to understand the functionality of the cell in this state, it is required to know its behavior in the normal state and in perturbed state. Cancer dynamics has been called an emergent property that arises from these interacting components, the constituting genes, small molecules, and the fluctuating environment \cite{14}. \( p53 \) holds a central point in signal transduction pathways involving a large number of genes that respond to diverse stress signals \cite{15–18}. This reduces the risk of mutation, and prevents circumstances that can lead to cancer or other pathological states \cite{19}. Since the expression and regulation of \( p53 \) depends on its interacting partners in the regulatory pathway, its modeling often involves both negative and positive feedback mechanisms. Mathematical modeling of the \( p53 \) regulatory network can provide dynamical information and patterns in order to predict cellular mechanisms and its behavior \cite{20,21} but a challenge is to capture various cellular phases within a simplified minimal model.

\( p53 \) is maintained at low levels in the normal condition \cite{22}. Emergence of oscillatory behaviour, one such state in \( p53 \) dynamics ("active"), has been extensively studied theoretically and experimentally \cite{27–35}. DNA recovery from low dose of ionizing radiation (IR) corresponds to reversible sustained \( p53 \) oscillations with varied amplitude, whereas high dose IR induce irreversible phase leading to stable state (damped oscillations) which corresponds to apoptosis \cite{16–18,27,28}. The variability in amplitude of oscillation is found to be larger than the changes in period of oscillation both for damped and undamped conditions \cite{29}. Further, persistent DNA damage activates ATM, and ATM activates Chk2, which results into \( p53 \) oscillations to repair damaged DNA \cite{30}. However, what could be the dynamics of \( p53 \) in cancer phase is still debatable question.

Some models of \( p53 \) capture various possible dynamical states. It is well known that \( p53 \) is coupled with Mdm2 via negative feedback loop \cite{27–35}. In these studies it was observed that if negative feedback loop gets activated then DNA repair takes place, whereas, if positive feedback loop gets activated then \( p53 \) activation moves to irreversible apoptotic phase. The other regulators of \( p53 \) sometimes regulate \( p53 \) pulses, for example, inclusion of MDMX in the model system suppress \( p53 \) oscillatory amplitude, whereas, knocking out MDMX significantly enhances this amplitude \cite{32}. In recovery phase of DNA damage, the amplitude of the repetitive \( p53 \) pulses tends to lower level and become stable normal state (oscillation is minimized or vanished) \cite{33}. However, in the case of apoptosis with excess stress, this amplitude of pulse abruptly rise and moves to irreversible stable state. Similarly, the other regulators of \( p53 \) coupled with positive feedback loop (ATM, PTEN, Akt etc) sometimes can induce switching behavior in the \( p53 \) dynamical states. Even though these models could able to capture these various dynamical states (active, recovery and apoptosis) which mimic with experimental results in qualitative sense, these models could not able to capture \( p53 \) behavior in cancer phase.

Once a normal cell becomes cancerous by mutational process, this signal propagates to neighboring cells \cite{23}, thereby a competition is established between normal and cancer cells \cite{24}. The onset, development and propagation of cancer cell population in the normal cell ecology provides a new transformed physico-chemical state, which bears several similarities to first order phase
A simple "competition" model for cancer is based on two types of cells, normal and cancer with population $N_1$ and $N_2$. Their dynamics in the cellular ecology can be modeled by the system of equations [26].

$$\frac{dN_i}{dt} = R_i N_i \left[ 1 - \frac{N_i}{K_i} - C_{ij} \frac{N_j}{K_j} \right] \quad \forall \, i, j = 1, 2 \mid i \neq j. \quad (1)$$

$R_i$, and $K_i$ are the intrinsic growth rate and the carrying capacity of species $i$, and $C_{ij}$ is the competition coefficient measuring the effect on species $i$ by species $j$. The equilibrium point (critical point) of the system is $N_1 = \frac{K_1 - K_2 C_{21}}{1 - C_{12} C_{21}}$, and $N_2 = \frac{K_2 - K_1 C_{12}}{1 - C_{12} C_{21}}$. The normal phase corresponds to the condition $N_1 > 0$, and $N_2 < 0$ which implies that $C_{12} \leq 0$ and $C_{21} \geq K_2/K_1$ assuming that $N_2 << N_1 = K_1$. Biologically this assumption reflects that in the normal phase, population of cancerous cell is small ($\approx 0$), while population of normal cells reaches its carrying capacity. The condition $N_1 < 0$, and $N_2 > 0$ which implies $C_{12} \geq 0$ and $C_{21} \leq K_2/K_1$ corresponds to cancer progression. Apart from normal and cancer phases, there are important dynamical states which may drive the cellular system into various pathologies. Since this dynamical system is function of various species, $\bar{N}_i = E_i(N_1, N_2, \ldots, N_m)$; where $i = 1 \ldots m$, the exact identification of critical point $(\bar{N}_i = 0)$ is difficult.

In this work, we present a minimal p53 regulatory pathway model in order to study phase transition like behavior of normal and cancer in cellular system at molecular level. We also investigate different cancer progression steps captured in the p53 dynamics and possibility of therapeutic intervention in cancer dynamics. We also discussed various key results in the normal to cancer transition in dynamical sense and observations of various stages of cancer phase.

Materials and methods

**Minimal p53$_A$-p53$_M$-MDM2-ARF regulatory network model**

The proposed model is a minimal regulatory network p53$_A$-p53$_M$-MDM2-ARF under stress condition. This involves the interaction of activated p53 (p53$_A$) and mutated p53 (p53$_M$) along with other key regulators MDM2, ARF and related molecular species as shown in FIG. 1. In the model [35] p53 induces transcription of RNA$_N$ and is also produced in the nucleus with a constant basal rate. After being produced, it is translated at a constant rate after proceeding in the cytoplasm, and this is followed by eventual decay. Cytoplasmic MDM2 is transported to the nucleus, where it regulates p53 via negative feedback in three different ways. First, transcriptional activity by binding to the p53 transactivation domain [36], second it promotes p53 degradation [37, 38], and finally it favours the export of p53 from the nucleus to cytoplasm [39].

Oncogene activation can be incorporated in the model through either structural alterations (such as chromosomal rearrangement, mutation) or epigenetic modification (gene promoter hypomethylation) [40]. In the present model, we have assumed that a certain type of stress signal $S$ causes structural, and epigenetic modification that result in oncogenes activation. The activated oncogene then activates ARF within the nucleus [41, 42] and since ARF is a direct inhibitor of MDM2 activity by binding to the RING finger domain of MDM2 this sequesters MDM2 [43]. Tao, and Levine has observed that ARF blocks the nucleo-cytoplasmic shuttling of MDM2, which is essential for the ability of MDM2 to export p53 into the cytoplasm [44].

Weber and others showed that ARF binds to MDM2 gene and sequesters it into the nucleolus, which in turn prevents p53 regulation by MDM2, and hence leads to the activation of p53 [45]. ARF gets activated due to activation of oncoprotein Myc [45]. It is now well known that activated oncogene, such as c-Myc, leads to the promotion of mutant p53 [46], and this mutated p53 induces the expression of oncogenes [47, 48] as well as inhibits the activity of activated p53 to prevent the cell from apoptosis [49, 49, 51–53]. ARF moves from nucleus to cytoplasm to bind the MDM2 and releases the p53 which is due to activation of oncogene [54].

We incorporate the regulating activity of an oncogene in the p53 network model. In a recent study, it has been shown that regulation/deregulation of c-Myc expression due to stress signal can induce mutation/s in the expression of p53 by binding to CA(C/T)GTG-containing site in the p53 promoter [55]. Hence, it has been suggested that stress induced deregulation of c-Myc expression could increase the expression of mutated p53. On the other hand, it has been observed that mutant p53 is able to regulate c-Myc expression by activating c-Myc promoter through C-terminus [47]. Further, it has been reported that p53 repress the c-Myc expression by inducing tumor suppressor miR-145 [56], because c-Myc repression by p53 is required to control the G1 cell cycle arrest [57], such that activation of c-MYC allows the functioning of mutant p53 [58]. Hence, the oncogene we have incorporated in our model is of c-Myc type which allows to interact p53$_M$ with oncogene and we studied the dynamical behavior of the model system which gives the similar behavior as the main model (see supplementary information). To keep the model simple we have used either hill function or direct interaction between different proteins, and parameters are estimated to observe the qualitative behavior.

**Mathematical framework of the model system**

In the proposed model system (FIG. 1) can be represented by a state vector, $\bar{X} = [x_1, x_2, \ldots, x_8]^T$, where, $\tau$ is the transpose of the vector, and $x_i; i = 1, 2, \ldots, 8$ represents the concentrations of the corresponding molecular species such that $\bar{X} = [p53_A, p53_M, Oncogene, RNA_N, RNA_A, C, MDM2, MDM2, ARF]^T$. Then the model regulatory network is perturbed with a stress with strength $S$ which could be irradiation (IR), molecular (or chemical toxic) fluctuations, environmental fluctuations etc. The amount of stress imparted in the model depends on the $S$ strength, and nature of the $S$ form introduced in the system. In this work, we have taken three different types of nature of stress $S$, 1) constant stress form $S = I$, 2) periodic stress
FIG. 1: Interaction network for p53A-p53M-MDM2-ARF-Stress. Dashed arrow shows movement from nucleus to cytoplasm or vice versa, while solid arrow, and bars corresponds to activation, and inhibition on respective node. (Modified network from [35])

Here, $k_p$ represents the production rate of $p53_A$, $k_1$ is the rate at which MDM2$_N$ ubiquitinates $p53_A$, $d_p$ is the degradation rate of MDM2$_N$ independent of $p53_A$, $\gamma_{x_1}$ is the degradation rate due to $p53_M$ inhibition. Further, $\delta_{x_1}$ shows the rate of mutation in $p53_A$ into $p53_M$ due to pro-oncogene (oncogenic mutation), $n_1$ is Hill coefficient, and $K_1$ is the dissociation constant. $\alpha_{x_2}$ is the production rate of $p53_M$ independent from pro-oncogene (which can be ignored), $\delta_{x_2}$ is mutational transition rate of $p53_A$ into $p53_M$ due to pro-oncogene mutation. Now, $\gamma_{x_2}$ is inhibition due to MDM2$_N$ (MDM2$_N$ dependent degradation), and $\delta_{x_2}$ shows natural degradation rate of $p53_M$ (which can be ignored). $\alpha_{x_3}$ is the production rate of pro-oncogene (ONCO) independent of stress (which can be ignored), $\beta_{x_3}$ is the stress dependent activation rate of pro-oncogene (oncogene), $n_2$ hill coefficient, $K_2$ is dissociation constant, $\delta_{x_3}$ is the mutated $p53_M$ dependent activation rate, $n_3$ is Hill coefficient, $K_3$ is the dissociation constant, and $\gamma_{x_2}$ is the natural degradation rate. $k_m$ represents the production rate of nucleic mRNA, $k_3$ is the maximum production rate of nucleic mRNA, $K_D$ represents dissociation parameter for p53, and $k_0$ is the transportation rate of nucleic mRNA into cytoplasm. $d_{rc}$ represents decay rate of mRNA into cytoplasm, $k_T$ represents the translation rate of MDM2C, while $k_1$ represents nuclear localization of MDM2C. $d_{nn}$ is the rate of MDM2 auto ubiquitination, and $k_3$ is the degradation rate of MDM2$_N$ due to binding ARF to MDM2$_N$. $k_a$ is the production rate of ARF, $\delta$ is the maximum activation rate of ARF due to pro-oncogene activation, $n_4$ is hill coefficient, $K_4$ is the dissociation constant, $d_a$ is the natural degradation rate of ARF, and $k_3$ is the MDM2$_N$ dependent degradation of ARF.

Results
The system of coupled ordinary differential equations are numerically integrated using ODEINT Python. Numerical simulations are carried out for an arbitrary set of initial values for the variables, and after discarding transients the system dynamics is examined. Initial values of mutant p53, and oncogene are kept zero for each form of the new stress discussed above assuming

$$S = I(1 + \sin(2\pi t))/T, \quad (T = 6 \text{ hrs through out the model }), \quad \text{and} \quad 3) \text{ exponentially decaying stress } S = Ie^{-\lambda t}.$$ Based on the proposed model system, we arrived at the following set of coupled ordinary differential equations,

\[
\begin{align*}
\frac{dx_1}{dt} &= k_p \left( k_1 x_7 + d_p + \gamma_{x_1} x_2 + \delta_{x_1} \frac{x_3^{n_1}}{K_1^{n_1} + x_3^{n_1}} \right) x_1 \\
\frac{dx_2}{dt} &= \alpha_{x_2} + \delta_{x_1} \frac{x_3^{n_1}}{K_1^{n_1} + x_3^{n_1}} x_1 - \gamma_{x_2} x_7 x_2 - \delta_{x_2} x_2 \\
\frac{dx_3}{dt} &= \alpha_{x_3} + \beta_{x_3} \frac{x_2^{n_3}}{K_2^{n_3} + x_2^{n_3}} + \delta_{x_3} \frac{x_2^{n_3}}{K_3^{n_3} + x_2^{n_3}} - \gamma_{x_3} x_3 \\
\frac{dx_4}{dt} &= k_m + k_2 \frac{x_1^{n_8}}{K_D^{n_8} + x_1^{n_8}} - k_0 x_4 \\
\frac{dx_5}{dt} &= k_0 x_4 - d_{rc} x_5 \\
\frac{dx_6}{dt} &= k_T x_5 - k_3 x_6 \\
\frac{dx_7}{dt} &= k_1 x_6 - d_{nn} x_6 - k_3 x_7 x_8 \\
\frac{dx_8}{dt} &= k_a + \delta \frac{x_3^{n_4}}{K_4^{n_4} + x_3^{n_4}} x_8 - d_a x_8 - k_3 x_7 x_8
\end{align*}
\]
initially there is no mutant p53, and oncogene.

**Phase transition driven by Stress**

Panels A<sub>1</sub>, A<sub>2</sub>, and A<sub>3</sub> in FIG. 2 show the time course of p53<sub>A</sub> and p53<sub>M</sub> for constant stress signal for three different magnitudes \( I = 1.0, I = 1.75, \) and \( I = 2.5 \) respectively. For small magnitude of stress signal \( (S = 1, \text{FIG. 2 panel } A_1) \) both p53<sub>A</sub> and p53<sub>M</sub> dynamics show sustained oscillations in which amplitude of oscillations of activated p53 is very high, while the amplitude of mutated p53 is negligibly small. This scenario indicates the possibility of repairing damaged DNA induced by stress signal via p53-MDM2. In such situation, repetitive pulses of p53<sub>A</sub>, which dominate those of p53<sub>M</sub> in the system, will be generated if damaged DNA is not properly repaired after delivering first pulse. Once the stress is removed, cell comes to the normal state. Hence sustained oscillations of p53<sub>A</sub> may correspond to the repeated repair efforts of the system to fix damaged DNA.

If the magnitude of the stress signal is significantly high \( (I = 1.75 \text{ panel } A_2 \text{ FIG. 2}) \). The system attempts to repair damaged DNA by generating few pulses (five) of activated p53 (indicated by damped oscillations in p53<sub>A</sub> and p53<sub>M</sub> dynamics). This could be the indication that after first pulse, the system sees that the damage is not repairable, it delivers the followed pulses with smaller amplitudes, and moves to amplitude death state \[59\], \( A_{p53_A} \to 0, A_{p53_M} \to 0 \) (when cell dies out due to apoptosis) with
p53_3 > p53M. Then p53 pathway activates many apoptogenic genes, by delivering a constant pulse of activated p53, to kill the cell before mutated p53 gets uncontrolled over the p53_3 at stress condition [60, 61]. Alternatively, p53 can also trigger apoptosis by inhibiting antiapoptotic genes (surviving), thus promoting caspase activation [62]. This phase corresponds to apoptotic phase (amplitude death [59] after damped oscillations), where the concentration of p53A still dominates that of p53M in the cellular dynamics.

In the third phase p53A and p53M dynamics, for high stress (S = 2.5), are different from earlier two phases (panel A, FIG. 2). In this phase, p53M concentration grows rapidly, and is high compared to p53A in the normal phase, indicating uncontrolled behavior of p53M. This dynamical behavior is qualitatively similar to the experimental observation of higher expression of mutated p53 leads to cancer [63], and in some cancers mutated p53 has dominated effect over active p53 [64]. The normal to cancer transition (NCT) is irreversible: the stress S imparted to the system is able to drive the system into three distinct dynamical states in addition active, apoptosis (indicated by dominant p53A, and low p53M) and cancer (p53M concentration rapidly increasing behavior, and low concentration of p53A with slow decay) states (FIG. 2).

We studied the system dynamics driven by periodic stress of magnitude I = 1.0,1.5,2.5 (panel B1, B2 and B3 FIG. 2 respectively). We observed three different dynamical phases, active, apoptosis, and cancer phase (panels B1, B2 and B3 FIG. 2 respectively), which are qualitatively similar to the constant stress case (panels A1, A2 and A3 FIG. 2 respectively). However, the behavior of p53A and p53M in FIG. 2 panel B2 after successive four pulses (with decaying pulses amplitudes), we still observed small amplitude oscillations which do not die out with time which are negligible to the oscillation of active state. Increasing the magnitude, this oscillatory behavior dies out (not shown here). In the case of cancer phase, the monotonically growth of p53M is a little slower as compared to constant stress signal case indicating periodic signal helps the cell to prevent moving to either apoptosis or cancer phase.

The scenario of the behavior of the system dynamics is different in the case of exponentially decay stress. Panel C1, C2 and C3 FIG. 2 show the time course of p53A, and p53M for the magnitude I = 1.0,3.5,4.5. For I = 1.0, we observed active state with sustain oscillations (panel C1 FIG. 2). Increasing the stress (I = 3.5), the dynamics shows that first, the stress provides a shock to the system allowing p53A moves to amplitude death [59] (Ap53A → constant) for small interval of time Tps → [9.8-37] hrs, whereas p53M concentration is suddenly increased dominating p53A concentration during Tps. Since p53M dominates over p53A during Tps, this state could be considered as a premalignant signature of the system dynamics which can be termed as critical state [25]. During this short time interval (Tps → finite and Ap53A → constant), the active state of the system is collapsed, and p53M becomes uncontrollable, and if Tps → ∞, then the system moves towards cancer phase. Identification of this critical state in cancer patients is very crucial for possible therapeutic intervention for preventing from cancer. After this time interval, the system regains its active state, where, p53A attains its sustain oscillation state by suppressing p53M concentration level, and then the system repairs damaged DNA. Significantly high dose of the stress signal triggers higher expression of mutated p53 protein as compared to activated p53 which corresponds to the cancer phase. Hence, in case of exponentially decaying stress signal, we are able to observe only two phases active, and cancer phase. Dynamics on the phase plane, for the time series used in the FIG. 2, are shown in FIG. 3. Green color indicates active state (panel A1, B1, C1, and C2), blue color apoptotic (panel A2, and B2), and red color cancer state (panel A3, B3, and C3). The dot shows the attractor (end point of the trajectory).

**Oncogenic regulation of normal and cancer dynamics**

In this section we study the cooperative impact of oncogene on the dynamics of p53A and p53M in the regulating pathway. We consider microscopic dissociation parameter K3, which is an equilibrium constant that amounts to the probability per unit time to dissociate molecular complex [65]. FIG. 4 shows steady state behavior of P53A, and P53M as a function of magnitude of stress (I) for three different values of K3 = 1000,500,100. The system’s behavior and transition of the states can be studied from steady state behavior (FIG. 4). For oscillatory behavior of p53A and p53M, the mean population is the average of the maxima and minima of the oscillation calculated in time window of t = 145.82hr – 166.66hr (removing transients) while, in case of no oscillations, population of p53A, and p53M were taken at time 166.66 hrs (end point of trajectory).

We observed different phases/states (FIG. 4 panels A1, A2 and A3) in the dynamics of p53A and p53M driven by constant stress for three different values of K3 = 1000,500,100. For small I values (I<1.19), the criteria for this was as average value of p53A reduces by 5% to its maximum averaged value in the case of without stress, both p53A and p53M exhibit oscillatory behavior (FIG. 4 panel A, K3 = 1000) with the concentration of p53M maintained at minimum level as compared to that of p53A. This phase may be considered as active phase of the cellular system, where, p53M delivers successive pulses to activate various genes which are involved in the pathway to repair damaged DNA. In this case, one can see that difference between x1 and x2 is almost constant (Δx12 → constant). Increasing the strength of the stress I (I → [1.19 – 2.04]), we get that Δx12 becomes variable where, p53A > p53M and Ap53A, Ap53M → constant exhibits amplitude death (cell programme death) scenario in both p53A and p53M dynamics. This state may correspond to apoptotic state (cyan area) in the system dynamics.

In apoptotic phase, the system is not able to repair damaged DNA thereby, p53A activates apoptogenic genes favoring to program cell death. It can also be observed that the concentration levels of both p53A and p53M are converged to a critical level xc as I → Ic = 2.04, which is termed as critical point (FIG. 4 panel A1). This critical point can be defined such as: \( \lim_{i \to \infty} x_{i+1} = 2.04 \). Slight increase in I (I > Ic = 2.04) triggers slow dominance of p53M over p53A, which is the beginning of new departure to the cancer phase. This new stage can be termed as pre-malignant regime (magenta area). Further increasing I, p53M is found to rapidly increased, while p53A is decreased significantly low, indicating p53A can no longer control p53M signal such that Δx12 rapidly increased and then becomes stable. Hence, this phase may be considered as cancer phase (grey area) [25, 66]. In this case, critical point can be seen as the point of departure to either in apoptotic phase or cancer phase.

Decreasing the value of dissociation parameter K3 = 500, we observe similar behavior in p53A and p53M dynamics (FIG. 4 panel A2), but critical point can be obtained at smaller value of magnitude of stress signal, Ic = 1.79 and range of apoptotic...
FIG. 4: The left column show three different form of stress discussed about. A1, A2, and A3 display the steady state behaviour against magnitude of stress for different $K_3$ values 1000.0, 500.0, and 100.0 respectively driven with constant stress. B1, B2, and B3 display the steady state behaviour against magnitude of stress for different $K_3$ values 1000.0, 500.0, and 100.0 respectively driven with oscillatory stress. C1, C2, and C3 display the steady state behaviour against amplitude for different $K_3$ values 1000.0, 500.0, and 100.0 respectively driven with decaying stress. Yellow region, cyan region, and grey region correspond to active, apoptotic, premalignant, and cancer state respectively. In panel C1, and C2 (wheat region) black line (upper line), and blue line (lower line) show maximum of $p53_M$, and maximum of $p53_A$ in $T_{ps}$ (see the text) time region, which corresponds to the initial cancer condition.

and pre-malignant state get shrinked and the range of cancer phase increased as compared to the case $K_3 = 1000$ (FIG. 4 panel A1). For comparatively small value of dissociation parameter $K_3 = 100$, $\Delta_{1s} \approx 0$ and $\Delta_{1c} \rightarrow \infty$ (FIG. 4 panel A3). In such situation, a stress state suddenly moves from active to cancer phase crossing critical point without showing the signatures of apoptotic and pre-malignant states, and then become steady ($\Delta_{1c} \rightarrow \text{constant}$) both in $p53_A$ and $p53_M$. It may lead to first order phase transition. In case of c-Myc we did not observe pre-malignant regime In constant stress case (supplementary information, panel A1, A2, and A3 FIG. 2).

In case of periodic stress, and for same values of $K_3 = 1000, 500, 100$ (FIG. 4 panels B1, B2 and B3), we observed the similar pattern of four states along with critical point as we found in the case of constant stress. This results also show that all the four states can be obtained at significantly smaller values of stress signal $I$ as compared to those of constant stress case.

We observed different scenario for exponentially decay stress. In this case, we only get three states, active, pre-malignant and cancer state for $K_3 = 1000, 500$ and for $K_3 = 100$ we get only two states (FIG. 4 panels C1, C2 and C3). We have also observed that there are two critical points, $x_a$, and $x_c$ ($x_a > x_c$) in the range $\Delta I = I_{c1} - I_{a1}$ (wheat region, FIG. 4 panels C1 and C2). In this range $\Delta I$, $p53_A$ dominates over $p53_M$ for a certain time interval $T_{ps}$ (previous section), which is a signature of pre-malignant or critical state, which comes back to the active state after $T_{ps}$ time interval if $I \in [I_{c1}, I_{c2}]$, where $I_{c2} = 5.80$ for $K_3 = 1000$ and $I_{c2} = 3.83$ for $K_3 = 500$. In the dynamical system study, the identification of this critical point/s and pre-malignant regime of any cancer type are quite important for therapeutic intervention of the cancer [25]. The reason could be if system dynamics is in this regime $I \in [I_{c1}, I_{c2}]$, there is a possibility of repairing damaged DNA. For lower value of $K_3$ parameter ($K_3 = 100$), if $I > I_{c2}$, the two critical points become single $I_{c1} = I_{a2} > I_{ps}$, and the active state directly jumps to cancer state ($T_{ps} \rightarrow \infty$) via $I_{a2}$ (FIG. 4 panels C3). These critical points can be seen as the points of departure to either in active state or cancer state. All these results indicate that the impact of oncogene is quite significant in regulating normal and cancer dynamics as well as their phase transition.

Phase transition and key to therapeutic intervention
In this section we study the dynamical behavior of $p53_A$, and $p53_M$ in two parameter space driven by different stress (FIG. 5 panel A). Each point in two parameter space (Magnitude of stress, $K_3$) (FIG. 5 panel A) are calculated concentrations of $p53_A$ in the dynamics: for oscillatory dynamics each point is the average of maxima and minima obtained in the time interval [145.82, 166.66] hrs, otherwise (no oscillation) concentration are measured at time 166.66 hrs. FIG. 5 A (with constant stress) shows three distinct regimes/phases active (green region), apoptosis (yellow region) and cancer (red region). For large value of $K_3$, transition from active to cancer state is through apoptotic phase, while for low value of $K_3$, the range of apoptotic regime is so thin that slight increase in stress magnitude ($I$) might lead to direct cancer phase. Transition from active to apoptotic state is one directional. Figure A1, A2, A3, and A4 are the time course at different point on the heat map (FIG. 5 A).

Similar behavior was observed in the patterns of two parameter space in case of periodic stress (FIG. 5 panel B). The panels B1, B2, B3, and B4 show the corresponding time series for the parameter set (0.5, 500.0), (1.3, 500.0), (0.96, 100.0), and (2.0, 200.0) respectively on the heat map. It is also observed that in case of periodic stress, less magnitude of stress is required for...
In case of exponentially decay stress, we observed only two states active (green region), and cancer (red region) (FIG. 5 panels A, B, C) respectively. First, and second term in the parameter set correspond to magnitude of stress ($I_2$, $I_3$), and $K_3$ for the parameter set (0.5,500.0), (1.3, 500.0), (0.96, 100.0), and (2.0, 200.0) respectively on the heat map A. B, C, and D correspond to the time course for the parameter set (0.5,500.0), (1.3, 500.0), (0.96, 100.0), and (2.0, 200.0) respectively on the heat map B. And C, D, E, and F for the parameter set (2.0,500.0), (4.0, 500.0), (2.0, 100.0), and (4.0, 100.0) respectively on the heat map C. First, and second term in the parameter set correspond to magnitude of stress ($I_1$, $I_2$), and $K_3$ respectively. Green, yellow, and red region indicate active, apoptotic, and cancer phase respectively on the heap map (A, B, and C).

In case of exponentially decay stress, we observed only two states active (green region), and cancer (red region) (FIG. 5 panels C) unlike constant, and periodic stress. The significantly small yellow region as compared to active and cancer regions is observed in the phase diagram indicating either active state or cancer state (due to 166.66 hrs window). Further, the behavior also suggests that increasing the magnitude of stress signal, and decreasing $K_3$ parameter value enhances the chance of inducing cancer phase in the system dynamics. Hence, $K_3$ parameter is a crucial parameter for cancer dynamics where low value of $K_3$ leads to more chances of having cancer [66].

The results discussed above indicate that apart from different stress, introduced in the system, there are various other factors which can drive the system to cancer state, for example, oncogene and its associated pathway/s. These factors are in fact the key to sustain the system at active state or bring back to active state from pre-malignant state by regulating these parameters and their associated pathways. Moreover, the identification of these critical point/s and pre-malignant state is very important.

Cancer recovery phase: dynamics of pre-malignant state

In this section we focus on the properties of the pre-malignant, and critical point/s, and their importance in therapeutic intervention to prevent the cancer. As we have discussed in previous sections, we could able to find only one critical point ($T_c$) for constant, and periodic stress driven system (FIG. 2, 4 and 5). In these cases the pre-malignant state is just the beginning of cancer state, and it is hard to bring back to normal state. The scenario is quite different for exponentially decay stress. Here, we study the recovery time behavior for three different set of parameters such as ($magnitude of stress$, and $K_3$), ($magnitude of stress$, and $K_4$), and ($magnitude of stress$, and $\lambda$) (FIG. 6). In this case, we observed two critical points $T_{c1} > 0$ and $T_{c2} > 0$.
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FIG. 6: The left column show decaying stress. Second column, A, B, and C, show two parameter cancer recovery behavior for the parameter set (magnitude of stress, $K_4$), (magnitude of stress, $K_3$), and (magnitude of stress, $\lambda$) respectively driven with same decaying stress. $A_1$, $A_2$, $A_3$, and $A_4$ correspond to the time course for the parameter set (3.25,700.0), (3.8, 700.0), (3.25, 500.0), and (3.8, 500.0) respectively on the heat map A. $B_1$, $B_2$, $B_3$, and $B_4$ correspond to the time course for the parameter set (3.25,300.0), (3.8, 300.0), (3.25, 1.0), and (3.8, 1.0) respectively on the heat map B ($K_3 = 500.0$). $C_1$, $C_2$, $C_3$, and $C_4$ correspond to the time course for the parameter set (3.0,0.07), (3.0,0.03), and (6.0,0.03) respectively on the heat map C ($K_3 = 1000.0$, $K_4 = 10.0$). On the heat map green color shoes lowest recovery time, while red shows highest recovery time or no recovery (in case of cancer).

With $T_{c_2} > T_{c_1}$ separated by a time interval $T_{ps} = T_{c_2} - T_{c_1} \geq 0$ in the $p53_A$ and $p53_M$ dynamics. However, for time $< T_{c_1}$ and time $> T_{c_2}$, the system dynamics will be in active state, where $p53_A$ dynamics showed sustain oscillatory behavior controlling $p53_M$ dynamics to maintain at minimum concentration level ($p53_M < p53_A$). This particular state is termed as pre-malignant state (discussed earlier), and is shown in FIG. 6. For certain values of the parameter set we observed that the system dynamics show a situation, $T_{ps} \rightarrow \infty$, $T_{c_1} \rightarrow T_{c_2} \rightarrow T_{c}$ and $p53_M > p53_A$ exhibit stable attractor, then the dynamical system becomes cancer state. In this case, we did not observed apoptotic state.

We observe that by decreasing $K_3$ and increasing the magnitude of stress $I$, $T_{ps}$ is increased, but $T_{c_1} \rightarrow$ constant(same), which is pre-malignant state (FIG. 6 panels $A_1$ – $A_4$) in the parameter space of $I$, and $K_3$. In such situation, there is always a possibility of bringing back into active state. However, for significantly small $K_3 \leq K_3^c$ and large $I \geq I^c$, where, $K_3^c$ and $I^c$ being critical values, we could able to observe the cancer state condition: $\lim_{(K_3 \leq K_3^c, I \geq I^c)} T_{ps} \rightarrow \infty$, $T_{c_1} \rightarrow T_{c_2} \rightarrow T_{c}$ and $p53_M > p53_A$ exhibiting stable attractor. Once the system reaches this phase, the dynamical process of the system becomes irreversible, and the system could not back to active state. Similar behavior and dynamical patterns can be found for set of ($I$, and $K_4$) in FIG. 6 panel B and $B_1 - B_4$, and for set of ($I$, $\lambda$) in FIG. 6 panels C, $C_1 - C_4$, where we could see the three states distinctly.

From the perspective of dynamical system analysis, identification of these three states obtained in any type of cancer is quite important in view of prevention from that cancer. The reason could be due to the possibility of bringing back to normal condition from pre-malignant signature. Proper therapeutic intervention and drug administration needed to be done during the time $T_{ps}$ to prevent from cancer phase. It may not be able to cure the cancer once proper intervention and preventive measures are not taken up. Further, for the sake of cancer drug discovery, this pre-malignant state could be proper stage of investigation.
Discussion and Summary
A dynamical systems approach can offer fresh insights to understanding cancer progression, and therefore suggest new protocols in therapeutic intervention. Cancer can be treated in broadly in two ways by exploring dynamical behavior along with hidden patterns of cancer and associated cellular states, and second to explore proper cellular state and time for therapeutic intervention or drug discovery. In the present work we have studied a model that incorporates the dynamics of both active and mutant p53 that are driven by different forms of time-dependent stress, and have considered the impact of ARF and oncogenes through different feedback mechanisms. This simple model has four distinct final states that can be characterised by the asymptotic dynamics: these have experimental validation [29, 67] and variously correspond to active, apoptotic, pre-malignant and cancer states.

Sustained oscillations in $p53_A$ and $p53_M$ dynamics can be seen as repeated pulses that occur in the system when DNA damage is repaired. Such oscillations persist until the DNA repair is completed [33]. Stress that triggers the system to the active state is a reversible process, the dynamics reverting to normal when the stress is removed. For high stress or when there are $p53_M$ activators such as oncogene and/or ARF, the amplitude of $p53_A$ oscillation with be large enough to arrest the cell cycle. In this situation, the amplitude of $p53_M$ reaches a critical level, although lower than the amplitude of $p53_A$ [68]. Oscillatory dynamics vanishes [59] for both $p53_A$ and $p53_M$; this is a state of amplitude death leading to a stable fixed-point attractor. This corresponds to apoptosis since the system cannot revert to oscillatory dynamics: this is an irreversible transition [25].

For large stress the production of mutant $p53_M$ becomes rapid and uncontrolled. The concentration level of $p53_M$ exceeds a critical apoptotic threshold, and this can be seen as a stress-induced premature senescence. This suppresses apoptosis and triggers cancer progression [69]. For constant or a periodic stress signal, we were able to find a condition where $p53_A$ and $p53_M$ coincide. We term this a critical point of the dynamical system, and this can be considered as leading to a new, cancer, state: mutant $p53_M$ is uncontrollable ($p53_M > p53_A$). Furthermore, there is no possibility of DNA repair and the process is irreversible. However, there is a small range of stress where the concentration of mutant p53 increases slowly, compared to the monotonic increase in the cancer regime. This we term pre-malignant. For constant or periodic stress there is a single critical point and hence the system, having transitioned to the cancer state cannot revert to the normal state.

For exponentially decaying stress only three states can be observed: active, pre-malignant or cancer. There are two critical points in this case, indicating the possibility of reversing from the pre-malignant to the active state. The width of the transition region depends on the stress inducing parameters with respect to oncogene, ARF, and other mechanisms. Identification of this range of the pre-malignant state, along with critical points, is important for therapeutic intervention.

Our study provides a qualitative picture of the dynamical properties of states observed in various experiments on cellular dynamics. The present results indicate the possibility of measuring how much stress suffices to lead to cancer. It will be important to explore the role of noise in driving the dynamics to see how robust these results are to extrinsic or intrinsic stochasticity.

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Author Contributions
AJ and MZM conceived the model. AJ, MZM, RR and RKBS did analytical work. AJ, MZM, RR and RKBS did the numerical experiment and prepared the figures of the numerical results. AJ, MZM, RR and RKBS analyzed and interpreted the analytical as well as simulation results. All authors wrote and approve the final manuscript.

Additional Information
Additional information is available at

Conflict of Interest Statement
None declared.

Model simulation
Numerical integration were carried out using Python ODEINT.
[1] D. P. Lane. p53, guardian of the genome. *Nature*, 358:15–16, 1992.
[2] H. V. Karen. p53: Death star. *Cell*, 104(5):691 – 694, 2000.
[3] T. B. Mark and V. Nikolina. p53: a molecular marker for the detection of cancer. *Expert Opinion on Medical Diagnostics*, 2(9):1013–1024, 2008. PMID: 23495923.
[4] N. Issaeva. p53 Signaling in Cancers. *Cancers*, 11(3), 2019. doi:10.3390/cancers11030332.
[5] K. H. Voussen and X. Lu. Live or let die: the cell’s response to p53. *Nat. Rev. Cancer*, 2:594–604, 2002.
[6] A. J. Levine. The many faces of p53: something for everyone. *J Mol Cell Biol*, 11(7):524–530, 2019. doi: 10.1093/jmcb/mjz026.
[7] D. W. Meek. Regulation of the p53 response and its relationship to cancer1. *Biochemical Journal*, 469(3):325–346, 07 2015.
[8] A. V. Golgurov and E. A. Komarova. The role of p53 in determining sensitivity to radiotherapy. *Nature Reviews Cancer*, 3(2):117–129, 2003.
[9] M. Oren. Decision making by p53: life, death and cancer. *Cell Death Differentiation*, 10(4):431–442, 2003.
[10] T. Soussi. The p53 pathway and human cancer. *BJIS*, 92(11):1331–1332, 2005.
[11] K. Hiroaki. Foundations of Systems Biology. 2001.
[12] B. Alberts, A. Johnson, J. Lewis, M. Ra, K. Roberts, P. Walter, and N. Chaey. *Molecular biology of the cell*. 4th edn. Annals of Botany, 91(3):401–401, 1991.
[13] L. Reinhard, H. Valerie, J. Abdul, V. T. Suzy, S. Vladimir, M. Pedro, M. T. Frank, and A. Steven. A systems biology view of cancer. *Biochimica et Biophysica Acta (BBA) - Reviews on Cancer*, 1796(2):129 – 139, 2009.
[14] E. E. Schadt. Molecular networks as sensors and drivers of common human diseases. *Annals of Botany*, 461:218–223, 2009.
[15] C. J. Proctor and D. A. Gray. Explaining oscillations and variability in the p53-mdm2 system. *BMC Systems Biology*, 2:75, 2008.
[16] M. Z. Malik, S. Ali, S. S. Singh, R. Ishrat, and R. K. B. Singh. Dynamical states, possibilities and propagation of stress signal. *Scientific Reports*, 7:40596, 2017.
[17] M. Z. Malik, S. Ali, M. J. Alam, R. Ishrat, and R. K. B. Singh. Dynamics of p53 and wnt cross talk. *Computational Biology and Chemistry*, 59:55 – 66, 2015. *Advances in Systems Biology*.
[18] M. Z. Malik, M. J. Alam, R. Ishrat, S. M. A garwal, and R. K. B. Singh. Control of apoptosis by smar1. *Mol. BioSyst.*, 13:350–362, 2017.
[19] A. J. Levine, W. Hu, and Z. Feng. The p53 pathway: what questions remain to be explored. *Cell Death Differentiation*, 13:1027–1036, 2006.
[20] H. M. Byrne. Dissecting cancer through mathematics: from the cell to the animal model. *Nature Reviews Cancer*, 10:221–230, 2010.
[21] P. M. Altrock, L. L. Liu, and F. Michor. The mathematics of cancer: integrating quantitative models. *Nature Reviews Cancer*, 15:730–745, 2015.
[22] A. J. Levine, and M. Oren. The first 30 years of p53: growing ever more complex. *Cell Death Dierentiation*, 17(2):554–564, 2010.
[23] R. Lev Bar-Or, R. Maya, L. A. Segel, U. Alon, A. J. Levine, and M. Oren. Generation of oscillations by the p53-mdm2 feedback loop: A theoretical and experimental study. *Proceedings of the National Academy of Sciences*, 97(21):11250–11255, 2000.
[24] 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*, 102(40):14266–14271, 2005.
[25] N. Geva-Zatorsky, N. Rosenfeld, S. Itzkovitz, R. Milo, A. Sigal, E. Dekel, T. Yarnitzky, Y. Liron, P. Polak, G. Lahav, and U. Alon. Oscillations and variability in the p53 system. *Molecular Systems Biology*, 2(1), 2006.
[26] 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*, 30(3):277 – 289, 2008.
[27] K. PuszyAski, B. Hat, and T. Lipniacki. Oscillations and bistability in the stochastic model of p53 regulation. *Journal of Theoretical Biology*, 254(2):452 – 465, 2008.
[28] X. Cai and Z. M. Yuan. Stochastic modeling and simulation of the p53-mdm2/mdmx loop. *Journal of Computational Biology*, 16(7):917–933, 2009. PMID: 19580521.
[29] 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*, 108(22):8990–8995, 2011.
[30] E. Batchelor, A. Loewer, C. Mock, and G. Lahav. Stimulus-dependent dynamics of p53 in single cells. *Molecular Systems Biology*, 7(1):488, 2011.
[31] G. B. Leenders and J. A. Tusznyski. Stochastic and deterministic models of cellular p53 regulation. *Frontiers in oncology*, 3:1229–1244, 2013.
[32] J. Momand, G. P. Zambetti, D. C. Olson, D. George, and A. J. Levine. The mdm-2 oncogene product forms a complex with the p53 protein and inhibits p53-mediated transactivation. *Cell*, 69(7):1237 – 1245, 1992.
[33] S. Fang, J. P. Jensen, R. L. Ludwig, K. H. Voussen, and A. M. Weissman. Mdm2 is a ring nger-dependent ubiquitin protein ligase for itself and p53. *Journal of Biological Chemistry*, 275(12):8945–8951, 2000.
[34] R. Honda and H. Yasuda. Activity of mdm2, a ubiquitin ligase, toward p53 or itself is dependent on the ring nger domain of the ligase. *Oncogene*, 19(11):1473 – 1476, 2000.
[35] J. Roth, M. Dobbekstein, D. A. Freedman, T. Shenk, and A. J. Levine. Nucleo-cytoplasmic shuttling of the hdm2 oncoprotein regulates the levels of the p53 protein via a pathway used by the human immunodeficiency virus rev protein. *The EMBO Journal*, 17(2):554–564, 1998.
[36] Donald W. K. et al. *Holland-Frei Cancer Medicine*, 6th edition. 2003.
[37] H. Mellert, S. M. Sykes, M. E. Murphy, and S. B. McMahon. The arf/oncopathway activates p53 acetylation within the dna binding domain. *Cell Cycle*, 6(11):1304–1306, 2007. PMID: 17534149.
[38] I. Palmero, M. Murga, A. Zubiaga, and M. Serrano. Activation of arf by oncogenic stress in mouse broblasts is independent of e2f1 and e2f2. *Oncogene*, 21(19):2939–2947, 2002.
[39] R. Honda and H. Yasuda. Association of p19arf with mdm2 inhibits ubiquitin ligase activity of mdm2 for tumor suppressor p53. *The EMBO Journal*, 18(1):22 – 27, 1999.
[40] W. Tao and A. J. Levine. P19arf stabilizes p53 by blocking nucleo-cytoplasmic shuttling of mdm2. *Proceedings of the National Academy of Sciences*, 96(12):6937–6941, 1999.
A. Willis, E. J. Jung, T. Wakeeld, and X. Chen. Mutant p53 exerts a dominant negative effect by preventing wild-type p53 from binding to the promoter of its target genes. *Oncogene*, 23(13):2330–2338, 2004.

A. de Vries, E. R. Flores, B. Miranda, H. M. Hsieh, C. T. M. van Oostrom, J. Sage, and T. Jacks. Targeted point mutations of p53 lead to dominant-negative inhibition of wild-type p53 function. *Proceedings of the National Academy of Sciences*, 99(5):2948–2953, 2002.

T. Ozaki and A. Nakagawara. Role of p53 in cell death and human cancers. *Cancers*, 3(1):994–1013, 2011.

A. Sigal and V. Rotter. Oncogenic mutations of the p53 tumor suppressor: The demons of the guardian of the genome. *Cancer Research*, 60(24):6785–6793, 2000.

C. Prives and E. White. Does control of mutant p53 by mdm2 complicate cancer therapy? *Genes Dev.*, 22:1259–1264, 2008.

A. Suzuki, R. Kogo, K. Kawahara, M. Sasaki, M. Nishio, T. Maehama, T. Sasaki, K. Mimori, and M. Mori. A new picture of nucleolar stress. *Cancer Science*, 103(4):632–637, 2012.

B. Roy, J. Beamon, E. Balint, and D. Reisman. Transactivation of the human p53 tumor suppressor gene by c-myc/max contributes to elevated mutant p53 expression in some tumors. *Molecular and Cellular Biology*, 14(12):7805–7815, 1994.

M. Sachdeva, S. Zhu, F. Wu, H. Wu, V. Wallia, S. Kumar, R. Elble, K. Watabe, and Y. Y. Mo. p53 repression by c-myc through induction of the tumor suppressor mir-145. *Proceedings of the National Academy of Sciences*, 106(9):3207–3212, 2009.

J. S. L. Ho, W. Ma, D. Y. L. Mao, and S. Benchimol. p53-dependent transcriptional repression of c-myc is required for G1 cell cycle arrest. *Molecular and Cellular Biology*, 25(17):7423–7431, 2005.

P. Liao, S. X. Zeng, X. Zhou, T. Chen, F. Zhou, B. Cao, J. H. Jung, G. D. Sal, S. Luo, and H. Lu. Mutant p53 gains its function via c-myc activation upon cdk4 phosphorylation at serine 249 and consequent pin1 binding. *Molecular Cell*, 68(6):1134 – 1146.e6, 2017.

G. Saxena, A. Prasad, and R. Ramasamy. Amplitude death: The emergence of stationarity in coupled nonlinear systems. *Physics Reports*, 521(5), 205–228, 2012. doi:10.1016/j.physrep.2012.09.003.

Y. Ohira, I. Garkavtsev, S. Kobayashi, K. R. Sreekumar, R. Nantz, B. T. Higashikubo, S. L. Duy, R. Higashikubo, A. Usheva, D. Gius, N. Kley, and N. Horikoshi. A novel p53-inducible apoptogenic gene, prg3, encodes a homologue of the apoptosis-inducing factor (aif). *FEBS Letters*, 524(1-3):163–171, 2002.

Q. Luo, J. M. Beaver, Y. Liu, and Z. Zhang. Dynamics of p53: A master决定er of cell fate. *Genes*, 8(2), 2017.

W. H. Homan, S. Biade, J. T. Zilfou, J. Chen, and M. Murphy. Transcriptional repression of the anti-apoptotic surviving gene by wild type p53*. *The Journal of Biological Chemistry*, 277(5):3247–3257, 2002.

K. Huang, L. Chen, J. Zhang, and et al. Elevated p53 expression levels correlate with tumor progression and poor prognosis in patients exhibiting esophageal squamous cell carcinoma. *Oncol Lett*, 8(4):1441–1446, 2014.

P. A. J. Muller, and K. H. Vousden. Mutant p53 in Cancer: New Functions and Therapeutic Opportunities. *Cancer Cell*, 25: 304-317 (2014).

M. I. Stefan and N. Le Nov’ere. Cooperative binding. *PLOS Computational Biology*, 9(6):1–6, 06 2013.

P. Ao, D. Galas, L. Hood, and X. Zhu. Cancer as robust intrinsic state of endogenous molecular-cellular network shaped by evolution. *Medical Hypotheses*, 70(3):678 – 684, 2008.

T. N. Wong, G. Ramsingh, A. L. Young, C. A. Miller, W. Touma, J. S. Welch, T. L. Lamprecht, D. Shen, J. Hundal, R. S. Fulton, S. Heath, J. D. Baty, J. M. Klco, L. Ding, E. R. Mardis, P. Westervelt, J. F. DiPersio, M. J. Walter, T. A. Graubert, T. J. Ley, T. E. Druley, D. C. Link, and R. K. Wilson. Role of tp53 mutations in the origin and evolution of therapy-related acute myeloid leukaemia. *Nature*, 518(7540):552–555, 2015.

B. Hat, M. Kochanczyk, M. N. Bogdal, and T. Lipniacki. Feedbacks, bifurcations, and cell fate decision-making in the p53 system. *PLoS Comput Biol* 12(2):1–28, 02-2016.

R. Mirzayans, B. Andrais, A. Scott, and D. Murray. New insights into p53 signaling and cancer cell response to dna damage: Implications for cancer therapy. *Journal of Biomedicine and Biotechnology*, 2012: 1-16, 2012.

Y. Shetzer, H. Solomon, G. Koifman, A. Molchadsky, S. Horesh, V. Rotter. The paradigm of mutant p53-expressing cancer stem cells and drug resistance. *Carcinogenesis* 35(6): 1196–1208, 2014.
| S. No. | Parameter | Value | Description | References |
|--------|-----------|-------|-------------|------------|
| 1.     | $k_p$     | 0.5 proteins/s | [p53$_A$] production | [35] |
| 2.     | $k_1$     | $9.963 \times 10^{-6}$ | [MDM2$_{N}$] dependent [p53$_A$] decay | [35] |
| 3.     | $d_p$     | $1.925 \times 10^{-6}$ | [p53$_A$] decay | [35] |
| 4.     | $\gamma_{x_2}$ | $9.963 \times 10^{-7}$ | [p53$_M$] dependent [p53$_A$] decay | Estimated |
| 5.     | $\delta_{x_1}$ | $4.963 \times 10^{-9}$ | [GENE] dependent [p53$_A$] decay | Estimated |
| 6.     | $K_1$     | 50 | Cooperative coefficient | Estimated |
| 7.     | $n_1$     | 4 | Hill coefficient | Estimated |
| 8.     | $\alpha_{x_2}$ | $1.5 \times 10^{-7}$ | [p53$_M$] production | Estimated |
| 9.     | $\gamma_{x_2}$ | $9.963 \times 10^{-6}$ | [MDM2$_{N}$] dependent [p53$_M$] decay | Estimated |
| 10.    | $\delta_{x_2}$ | $1.925 \times 10^{-6}$ | [p53$_M$] decay | Estimated |
| 11.    | $\alpha_{x_3}$ | $1.5 \times 10^{-7}$ | [GENE] production | Estimated |
| 12.    | $\beta_{x_3}$ | $5.5 \times 10^{-3}$ | Stress dependent maximum [GENE] activation rate | Estimated |
| 13.    | $K_2$     | 3 | Cooperative coefficient | Estimated |
| 14.    | $n_2$     | 3 | Hill coefficient | Estimated |
| 15.    | $\delta_{x_3}$ | $2.0635 \times 10^{-3}$ | [p53$_M$] dependent maximum [GENE] activation rate | Estimated |
| 16.    | $K_3$     | 1000 | Cooperative coefficient for oncogene | Estimated |
| 17.    | $n_3$     | 3 | Hill coefficient | Estimated |
| 18.    | $\gamma_{x_3}$ | $1.925 \times 10^{-6}$ | [GENE] decay | Estimated |
| 19.    | $k_m$     | $1.5 \times 10^{-3}$ | [RNA$_N$] production | [35] |
| 20.    | $k_2$     | $1.5 \times 10^{-2}$ | [p53$_A$] dependent maximum [RNA$_N$] activation rate | [35] |
| 21.    | $k_D$     | 740.0 | Cooperative coefficient | [35] |
| 22.    | $k_0$     | $8.0 \times 10^{-4}$ | [RNA$_N$] decay and [RNA$_C$] production | [35] |
| 23.    | $d_c$     | $1.444 \times 10^{-4}$ | [RNA$_C$] decay | [35] |
| 24.    | $k_T$     | $1.66 \times 10^{-4}$ | [MDM2$_C$] production | [35] |
| 25.    | $k_1$     | $9.0 \times 10^{-4}$ | [MDM2$_C$] decay and [MDM2$_N$] production | [35] |
| 26.    | $d_{mn}$  | $1.66 \times 10^{-4}$ | [MDM2$_N$] decay | [35] |
| 27.    | $k_3$     | $9.963 \times 10^{-6}$ | [ARF] dependent [MDM2$_N$] decay | [35] |
| 28.    | $k_a$     | 0.5 proteins/s | [ARF] production | Estimated |
| 29.    | $K_4$     | 10 | Cooperative coefficient for ARF | Estimated |
| 30.    | $n_4$     | 3 | Hill coefficient | Estimated |
| 31.    | $\delta$ | $3.5 \times 10^{-4}$ | [ARF] activation rate due to stress | Estimated |
| 32.    | $d_a$     | $3.209 \times 10^{-4}$ | [ARF] decay | [35] |
| 33.    | $k_3$     | $9.963 \times 10^{-6}$ | [MDM2$_N$] dependent [ARF] decay | [35] |