 doi:10.20944/preprints202005.0063.v1

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 *active*, *apoptotic*, *pre-malignant* and *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 mechanism [1, 2]. p53 induced different biological outcomes has been studied in detail [4, 5]. Activation of the p53 regulatory pathway by internal and external stress can lead to a number of different outcomes [3, 4]. p53 is known to be mutated in cancer, either in exonic or intronic portion of the gene due to stress [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 [1, 11, 12]. Studies on signalling networks have provided identification of many target genes for therapeutic interventions in the context of cancer [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 [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 [14]. p53 holds a central point in signal transduction pathways involving a large number of genes that respond to diverse stress signals [15–18]. This reduces the risk of mutation, and prevents circumstances that can lead to cancer or other pathological states [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 [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 [22]. Emergence of oscillatory behaviour, one such state in p53 dynamics ("active"), has been extensively studied theoretically and experimentally[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 [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 [29]. Further, persistent DNA damage activates ATM, and ATM activates Chk2, which results into p53 oscillations to repair damaged DNA[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 [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 [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) [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 [23], thereby a competition is established between normal and cancer cells [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

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transition [25]. 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].

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

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 $N_1 = \frac{K_1 - K_2 C_{12}}{1 - C_{12}C_{21}}$, and $N_2 = \frac{K_2 - K_1 C_{21}}{1 - C_{12}C_{21}}$. The normal phase corresponds to the condition $\dot{N}_1 > 0$, and $\dot{N}_2 < 0$ 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 (≈ 0), while population of normal cells reaches its carrying capacity. The condition $\dot{N}_1 < 0$, and $\dot{N}_2 > 0$ 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, $\dot{N}_i = F_i(N_1, N_2, \ldots, N_m)$; where $i = 1 \ldots m$, the exact identification of critical point ($\dot{N}_i = 0$) 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, $\vec{X} = [x_1, x_2, \ldots, x_8]^\intercal$, where, $\intercal$ is the transpose of the vector, and $x_i; i = 1, 2, \ldots, 8$ represents the concentrations of the corresponding molecular species such that $\vec{X} = [p53_A, p53_M, Oncogene, RNA_N, RNA_C, MDM2_C, MDM2_N, ARF]^\intercal$. 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

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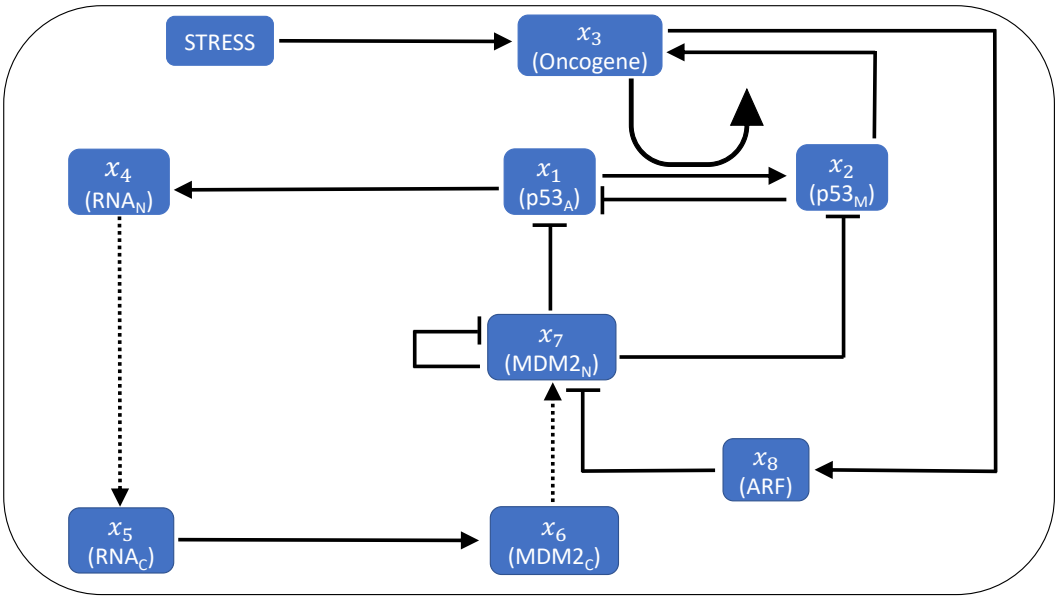

FIG. 1: Interaction network for p53$_A$-p53$_M$-MDM2-ARF-Stress. Dashed arrow shows movement from nucleus to cytoplasm or vice versa, while solid arrow, and bars corresponds to activation, and inhibition on respective node. (Modified network from [35])

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

$$
\begin{aligned}
\frac{dx_1}{dt} &= k_p - \left(k_1 x_7 + d_p + \gamma_{x_1} x_2 + \delta_{x_1} \frac{x_3^{n_1}}{K_1^{n_1} + x_3^{n_1}}\right) x_1 \\
\frac{dx_2}{dt} &= \alpha_{x_2} + \delta_{x_1} \frac{x_3^{n_1}}{K_1^{n_1} + x_3^{n_1}} x_1 - \gamma_{x_2} x_7 x_2 - \delta_{x_2} x_2 \\
\frac{dx_3}{dt} &= \alpha_{x_3} + \beta_{x_3} \frac{S^{n_2}}{K_2^{n_2} + S^{n_2}} + \delta_{x_3} \frac{{x_2}^{n_3}}{K_3^{n_3} + {x_2}^{n_3}} - \gamma_{x_3} x_3 \\
\frac{dx_4}{dt} &= k_m + k_2 \frac{x_1^{1.8}}{k_D^{1.8} + x_1^{1.8}} - k_0 x_4 \\
\frac{dx_5}{dt} &= k_0 x_4 - d_{rc} x_5 \\
\frac{dx_6}{dt} &= k_T x_5 - k_i x_6 \\
\frac{dx_7}{dt} &= k_i x_6 - d_{mn} x_6^2 - k_3 x_7 x_8 \\
\frac{dx_8}{dt} &= k_a + \delta \frac{x_3^{n_4}}{K_4^{n_4} + x_3^{n_4}} x_8 - d_a x_8 - k_3 x_7 x_8
\end{aligned}
$$

Here, k_p represents the production rate of p53$_A$, k_1 is the rate at which MDM2$_N$ ubiquitinates p5$_A$, d_p is the degradation rate of MDM2$_N$ independent of p53$_A$, γ_{x_1} is the degradation rate due to p53$_M$ inhibition. Further, δ_{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. α_{x_2} is the production rate of p53$_M$ independent from pro-oncogene (which can be ignored), δ_{x_1} is mutational translation rate of p53$_A$ into p53$_M$ due to pro-oncogene mutation. Now, γ_{x_2} is inhibition due to MDM2$_N$ (MDM2$_N$ dependent degradation), and δ_{x_2} shows natural degradation rate of p53$_M$ (which can be ignored). α_{x_3} is the production rate of pro-oncogene (ONCO) independent of stress (which can be ignored), β_{x_3} is the stress dependent activation rate of pro-oncogene (oncogene), n_2 hill coefficient, K_2 is dissociation constant, δ_{x_3} is the mutated p53$_M$ dependent activation rate, n_3 is Hill coefficient, K_3 is the dissociation constant, and γ_{x_3} is the natural degradation rate. k_m represents the production rate of nucleic mRNA, k_2 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 MDM2$_C$, while k_i represents nuclear localization of MDM2$_C$. d_{mn} 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, δ 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

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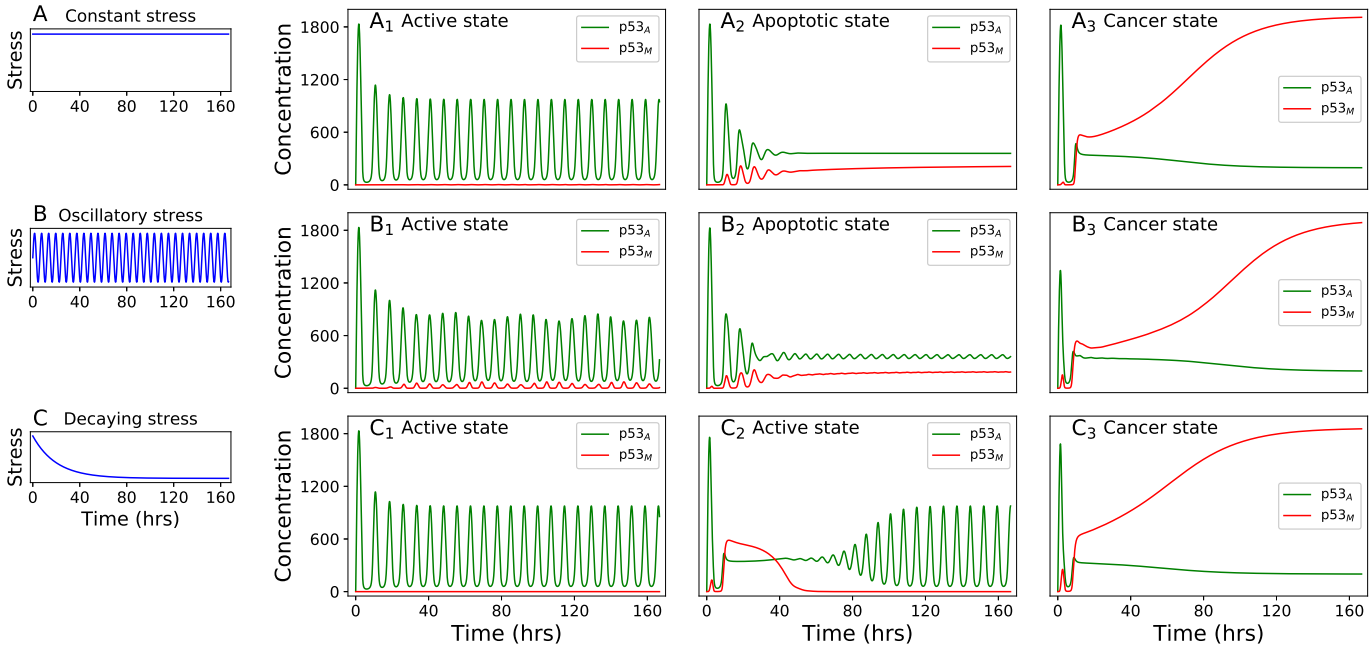

FIG. 2: The left column show three different form of stress discussed about. In the top row A_1 (normal), A_2 (apoptosis), and A_3 (cancer) display the time course of $p53_A$ (green), and $p53_M$ (red) for constant stress of magnitude 1.00, 1.75, and 2.50 respectively (K_3=1000.0). B_1 (normal), B_2 (apoptosis), and B_3 (cancer) display the time series for averaged oscillatory stress of magnitude 1.00, 1.50, and 2.50 respectively (K_3=1000.0). And C_1 (normal), C_2 (recovery from initial cancer stage), and C_3 (cancer) display the time series for decaying stress of magnitude 1.00, 3.5, and 4.50 respectively (K_3=500.0 and λ=0.05 hrs^{-1}).

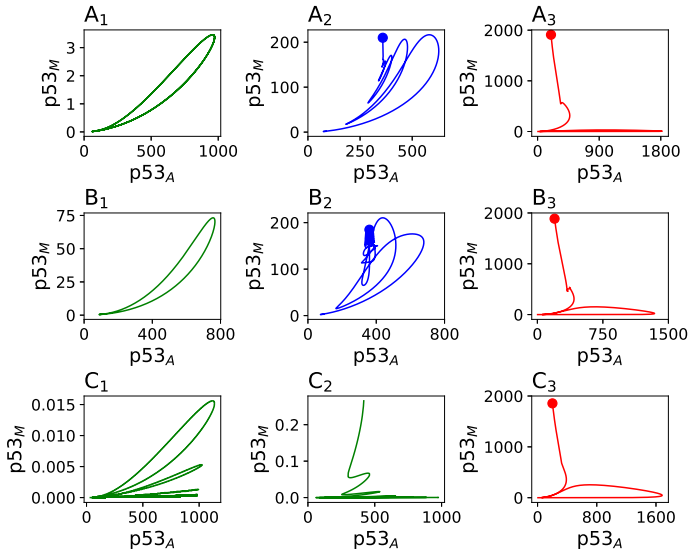

FIG. 3: Dynamics on the phase plane for the time series results in the FIG. 2. Green color indicates active state, blue color apoptotic, and red color cancer state. The dot shows the attractor (end point of the trajectory).

initially there is no mutant p53, and oncogene.

Phase transition driven by Stress

Panels A_1, A_2, and A_3 in FIG. 2 show the time course of $p53_A$ and $p53_M$ 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 ($S = 1$, FIG. 2 panel A_1) both $p53_A$ and $p53_M$ 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 $p53_A$, which dominate those of $p53_M$ 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 $p53_A$ may correspond to the repeated repair efforts of the system to fix damaged DNA.

If the magnitude of the stress signal is significantly high ($I = 1.75$ panel A_2 FIG. 2). The system attempts to repair damaged DNA by generating few pulses (five) of activated p53 (indicated by damped oscillations in $p53_A$ and $p53_M$ 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

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$p53_A > p53_M$. 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 $p53_A$ 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 $p53_A$ still dominates that of $p53_M$ in the cellular dynamics.

In the third phase $p53_A$ and $p53_M$ dynamics, for hight stress ($S = 2.5$), are different from earlier two phases (panel A_3 FIG. 2). In this phase, $p53_M$ concentration grows rapidly, and is high compared to $p53_A$ in the normal phase, indicating uncontrolled behavior of $p53_M$. 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 $p53_A$, and low $p53_M$) and *cancer* ($p53_M$ concentration rapidly increasing behavior, and low concentration of $p53_A$ 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 B_1, B_2 and B_3 FIG. 2 respectively). We observed three distinct dynamical phases, active, apoptosis, and cancer phase (panels B_1, B_2 and B_3 FIG. 2 respectively), which are qualitatively similar to the constant stress case (panels A_1, A_2 and A_3 FIG. 2 respectively). However, the behavior of $p53_A$ and $p53_M$ in FIG. 2 panel B_2 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 $p53_M$ 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 C_1, C_2 and C_3 FIG. 2 show the time course of $p53_A$, and $p53_M$ for the magnitude $I = 1.0, 3.5, 4.5$. For $I = 1.0$, we observed active state with sustain oscillations (panel C_1 FIG. 2). Increasing the stress ($I = 3.5$), the dynamics shows that first, the stress provides a shock to the system allowing $p53_A$ moves to amplitude death [59] ($A_{p53_A} \rightarrow$ constant) for small interval of time $T_{ps} \rightarrow$ [9.8-37] hrs, whereas $p53_M$ concentration is suddenly increased dominating $p53_A$ concentration during T_{ps}. Since $p53_M$ dominates over $p53_A$ during T_{ps}, 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 ($T_{ps} \rightarrow$ finite and $A_{p53_A} \rightarrow$ constant), the active state of the system is collapsed, and $p53_M$ becomes uncontrollable, and if $T_{ps} \rightarrow \infty$, 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, $p53_A$ attains its sustain oscillation state by suppressing $p53_M$ concentration level, and then the system repairs damaged DNA. Significantly high dose of the stress signal triggers higher expression of mutated p53 protein than 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 A_1, B_1, C_1, and C_2), blue color apoptotic (panel A_2, and B_2), and red color cancer state (panel A_3, B_3, and C_3). 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 $p53_A$ and $p53_M$ in the regulating pathway. We consider microscopic dissociation parameter K_3, 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 $P53_A$, and $p53_M$ as a function of magnitude of stress (I) for three different values of $K_3 = 1000, 500, 100$. The system's behavior and transition of the states can be studied from steady state behavior (FIG. 4). For oscillatory behavior of $p53_A$ and $p53_M$, 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 $p53_A$, and $p53_M$ were taken at time 166.66 hrs (end point of trajectory).

We observed different phases/states (FIG. 4 panels A_1, A_2 and A_3) in the dynamics of $p53_A$ and $p53_M$ driven by constant stress for three different values of $K_3 = 1000, 500, 100$. For small I values ($I\langle 1.19$), the criteria for this was as average value of $p53_A$ reduces by 5% to its maximum averaged value in the case of without stress, both $p53_A$ and $p53_M$ exhibit oscillatory behavior (FIG. 4 panel A_1, $K_3 = 1000$) with the concentration of $p53_M$ maintained at minimum level as compared to that of $p53_A$. This phase may be considered as active phase of the cellular system, where, $p53_A$ 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 x_1 and x_2 is almost constant ($\Delta x_{12} \rightarrow constant$). Increasing the strength of the stress I ($I \rightarrow [1.19 - 2.04]$), we get that Δx_{12} becomes variable where, $p53_A > p53_M$ and A_{p53_A}, $A_{p53_M} \rightarrow constant$ exhibits amplitude death (cell programmed death) scenario in both $p53_A$ and $p53_M$ 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, $p53_A$ activates apoptogenic genes favoring to program cell death. It can also be observed that the concentration levels of both $p53_A$ and $p53_M$ are converged to a *critical* level x_c as $I \rightarrow I_c = 2.04$, which is termed as *critical point* (FIG. 4 panel A_1). This *critical point* can be defined such as: $\lim_{I \rightarrow I_c} \Delta x_{12} \rightarrow 0$ and $x_1, x_2 \rightarrow x_c$. Slight increase in I ($I > I_c = 2.04$) triggers slow dominance of $p53_M$ over $p53_A$, 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, $p53_M$ is found to rapidly increased, while $p53_A$ is decreased significantly low, indicating $p53_A$ can no longer control $p53_M$ signal such that Δx_{12} 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 $K_3 = 500$, we observe similar behavior in $p53_A$ and $p53_M$ dynamics (FIG. 4 panel A_2), but *critical point* can be obtained at smaller value of magnitude of stress signal, $I_c = 1.79$ and range of apoptotic

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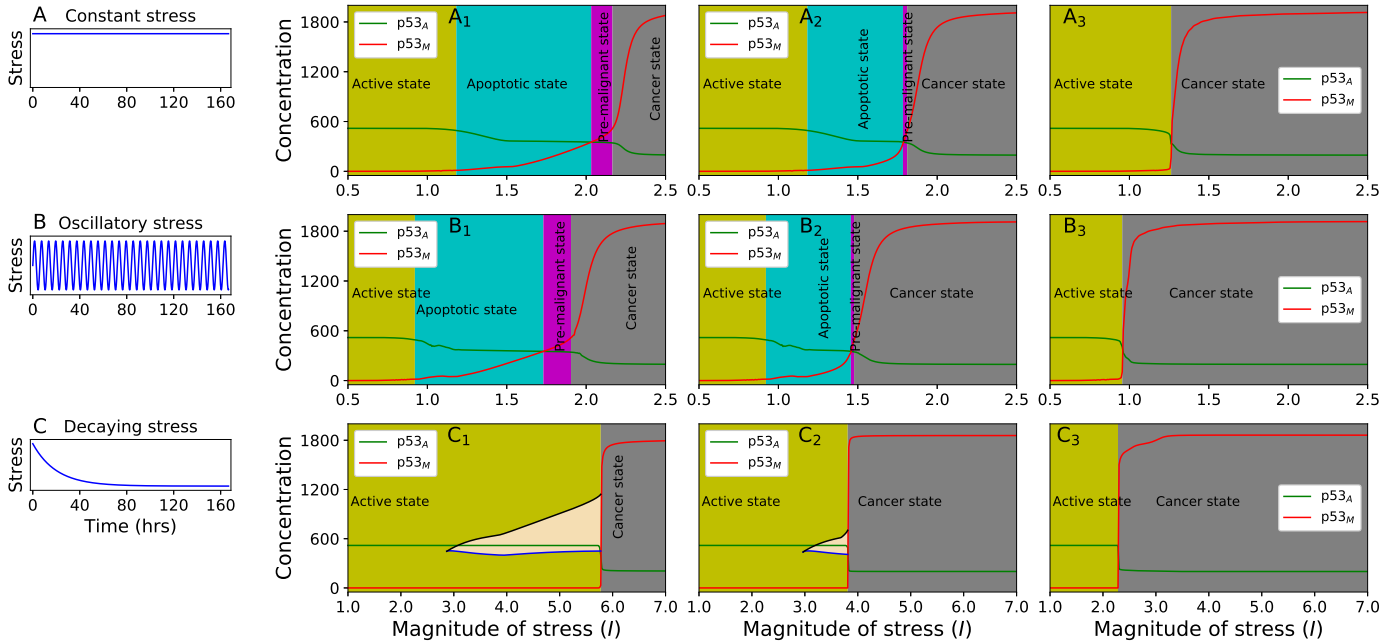

FIG. 4: The left column show three different form of stress discussed about. A_1, A_2, and A_3 display the steady state behaviour against magnitude of stress for different K_3 values 1000.0, 500.0, and 100.0 respectively driven with constant stress. B_1, B_2, and B_3 display the steady state behaviour against magnitude of stress for different K_3 values 1000.0, 500.0, and 100.0 respectively driven with oscillatory stress. C_1, C_2, and C_3 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 C_1, and C_2 (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 A_1). For comparatively small value of dissociation parameter $K_3 = 100$, $\Delta I_{ms} \approx 0$ and $\Delta I_{cs} \to large$ (FIG. 4 panel A_3). 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 ($\Delta x_{12} \to constant$) 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 A_1, A_2, and A_3 FIG. 2).

In case of periodic stress, and for same values of $K_3 = 1000, 500, 100$ (FIG. 4 panels B_1, B_2 and B_3), 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 C_1, C_2 and C_3). We have also observed that there are two critical points, x_{c_1} and x_{c_2} ($x_{c_2} > x_{c_1}$) in the range $\Delta I = I_{c_2} - I_{c_1}$ (wheat region, FIG. 4 panels C_1 and C_2). In this range ΔI, $p53_M$ dominates over $p53_A$ 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 $I \in [I_{c_1}, I_{c_2}]$, where, $I_{c_2} = 5.80$ for $K_3 = 1000$ and $I_{c_2} = 3.83$ 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 $I \in [I_{c_1}, I_{c_2}]$, there is a possibility of repairing damaged DNA. For lower value of K_3 parameter ($K_3 = 100$), if $I > I_{c_2}$ the two critical points become single $I_{c_1} = I_{c_2} > I_c$, and the active state directly jumps to cancer state ($T_{ps} \to \infty$) via I_c (FIG. 4 panels C_3). 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 state 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 A_1, A_2, A_3, and A_4 are the time course at different point on the heat map (FIG. 5 A).

Similar behavior was observed in the patterns of two parametre space in case of periodic stress (FIG. 5 panel B). The panels B_1, B_2, B_3, and B_4 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

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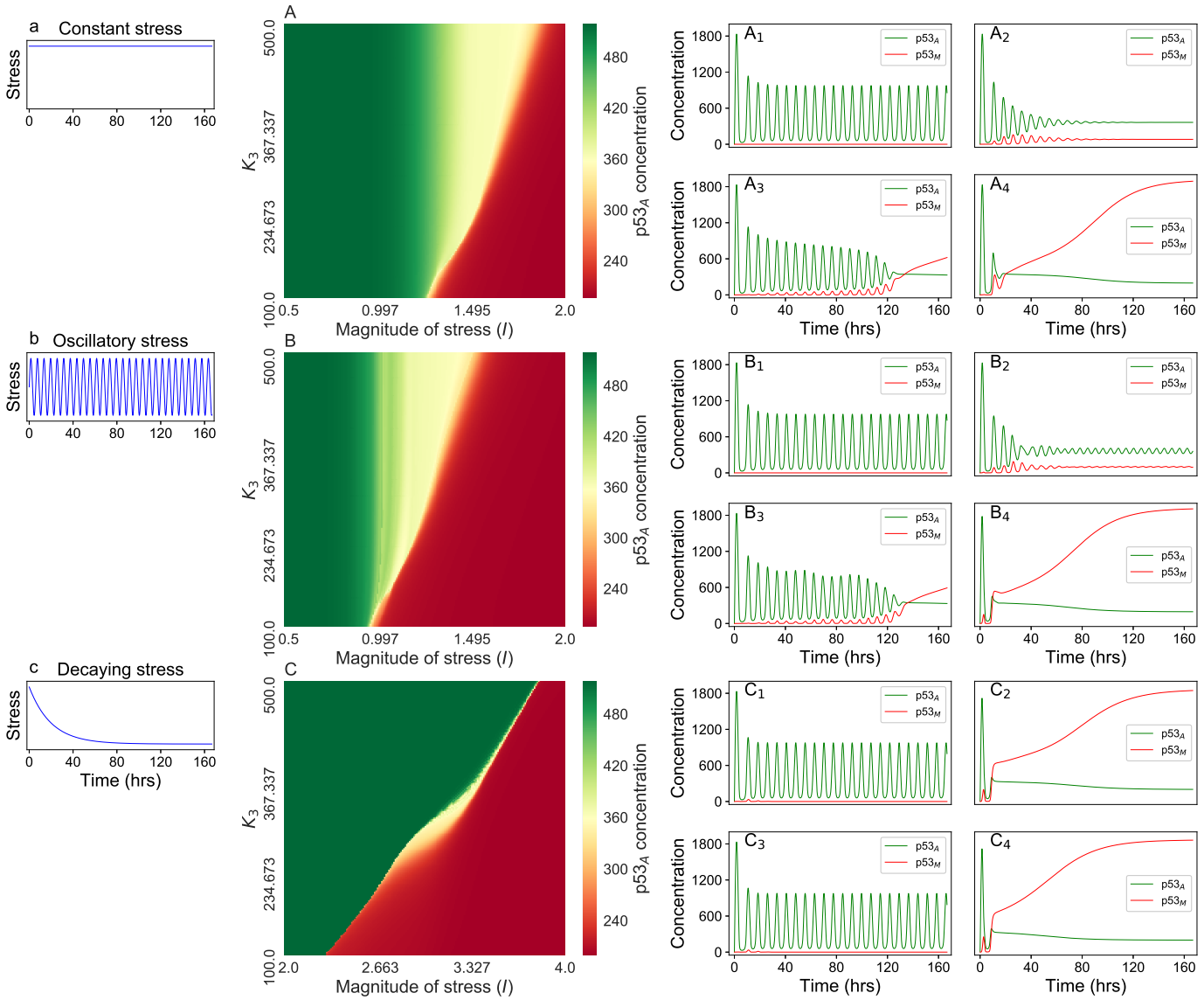

FIG. 5: The left column show three different form of stress discussed about. Second column (A, B, and C) show two parameter steady state behavior of the system for three different form of driven stress (a, b, and c) respectively. A_1, A_2, A_3, and A_4 correspond to the time course of $p53_A$ (green), and $p53_M$ (red) for the parameter set (0.5,500.0), (1.6, 500.0), (1.27, 100.0), and (2.0, 200.0) respectively on the heat map A. B_1, B_2, B_3, and B_4 correspond to the time course for the parameter set (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_1, C_2, C_3, and C_4 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), and K_3 respectively. Green, yellow, and red region indicate active, apoptotic, and cancer phase respectively on the heap map (A, B, and C).

different phase transition than constant stress.

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 paramaters such as (*magnitude of stress*, and K_3), (*magnitude of stress*, and K_4), and (*magnitude of stress*, and λ) (FIG. 6). In this case, we observed two critical points $T_{c_1} > 0$ and $T_{c_2} > 0$

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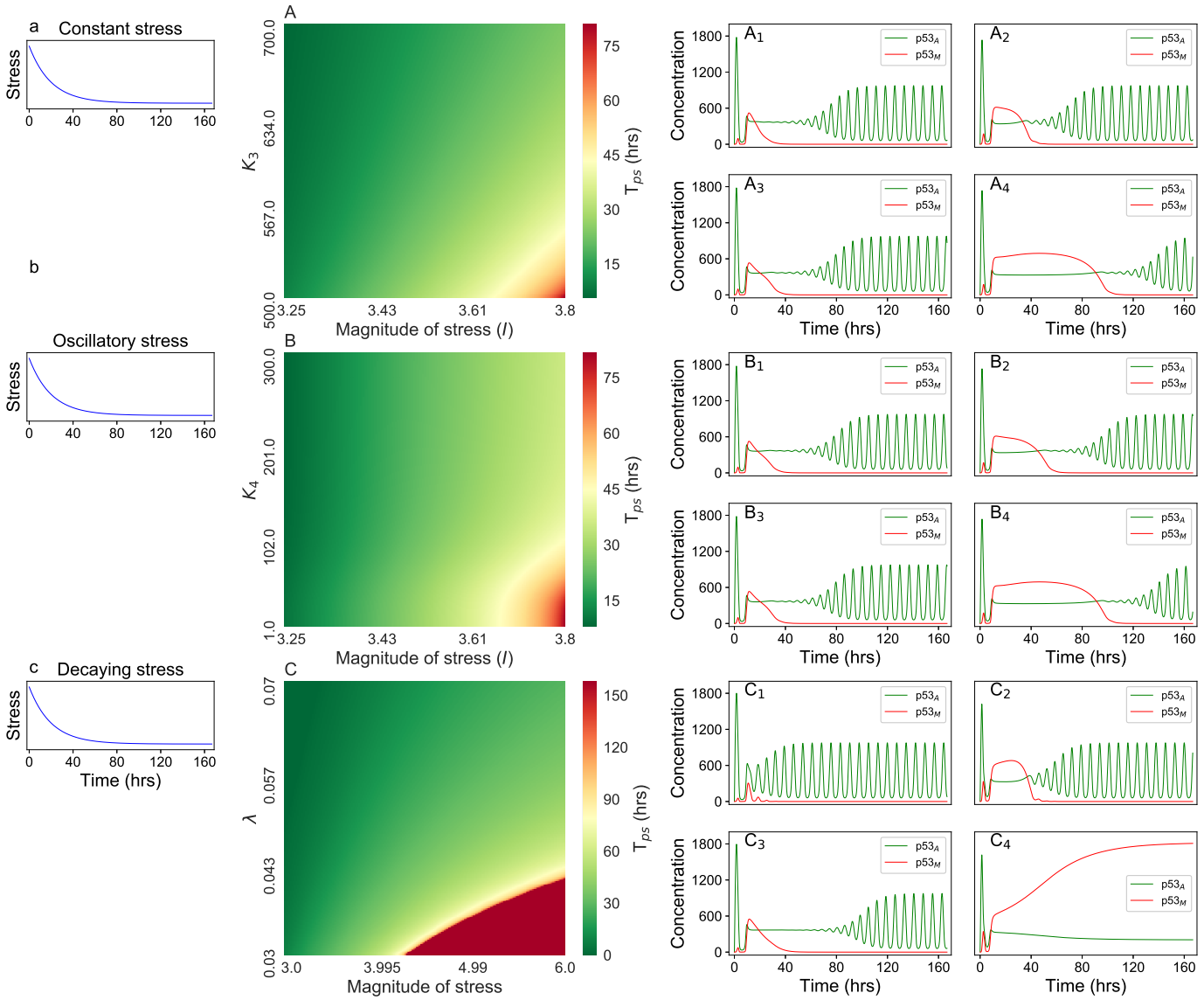

FIG. 6: The left column show decaying stress. Second column, A, B, and C, show two parameter cancer recovery behavior for the parameter set (*magnitude of stress*, K_3), (*magnitude of stress*, K_4), and (*magnitude of stress*, λ) respectively driven with same decaying stress. A_1, A_2, A_3, and A_4 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), (6.0,0.07), (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, $T_{ps} \to \infty$, $T_{c_1} \to T_{c_2} \to T_c$ 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 $T_{c_1} \to constant(same)$, 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: $\lim_{(K_3 \leq K_3^c, I \geq I^c)} T_{ps} \to \infty$, $T_{c_1} \to T_{c_2} \to T_c$ 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, λ) 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.

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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 ($p53_M \rangle p53_A$). 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.

Acknowledgments

AJ (21/06/2015(i)EU-V) is financially supported by University Grants Commission of India, New Delhi, India. MZM is financially supported by Department of Health and Research, Ministry of Health and Family Welfare, Government of India (File No. R.12014/01/2018-HR, FTS No. 3146887). RR is financially supported by JC Bose Fellowship, Department of Science and Technology, India. RKBS acknowledges UPE-II (101) for providing financial support.

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.

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TABLE I: Table 1 Parameters descriptions, and parameter values

S. No.	Parameter	Value	Description	References
1.	k_P	0.5 proteins/s	[$p53_A$] production	[35]
2.	k_1	9.963×10^{-6}	[$MDM2_N$] dependent [$p53_A$] decay	[35]
3.	d_P	1.925×10^{-5}	[$p53_A$] decay	[35]
4.	γ_{x_1}	9.963×10^{-7}	[$p53_M$] dependent [$p53_A$] decay	Estimated
5.	δ_{x_1}	4.963×10^{-6}	[GENE] dependent [$p53_A$] decay	Estimated
6.	K_1	50	Cooperative coefficient	Estimated
7.	n_1	4	Hill coefficient	Estimated
8.	α_{x_2}	1.5×10^{-7} proteins/s	[$p53_M$] production	Estimated
9.	γ_{x_2}	9.963×10^{-6}	[$MDM2_N$] dependent [$p53_M$] decay	Estimated
10.	δ_{x_2}	1.925×10^{-5}	[$p53_M$] decay	Estimated
11.	α_{x_3}	1.5×10^{-7}	[GENE] production	Estimated
12.	β_{x_3}	5.5×10^{-3}	Stress dependent maximum [GENE] activation rate	Estimated
13.	K_2	3	Cooperative coefficient	Estimated
14.	n_2	3	Hill coefficient	Estimated
15.	δ_{x_3}	2.0635×10^{-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.	γ_{x_3}	1.925×10^{-5}	[GENE] decay	Estimated
19.	k_m	1.5×10^{-3}	[RNA_N] production	[35]
20.	k_2	1.5×10^{-2}	[$p53_A$] dependent maximum [RNA_N] activation rate	[35]
21.	k_D	740.0	Cooperative coefficient	[35]
22.	k_0	8.0×10^{-4}	[RNA_N] decay and [RNA_C] production	[35]
23.	d_{rc}	1.444×10^{-4}	[RNA_C] decay	[35]
24.	k_T	1.66×10^{-2}	[$MDM2_C$] production	[35]
25.	k_i	9.0×10^{-4}	[$MDM2_C$] decay and [$MDM2_N$] production	[35]
26.	d_{mn}	1.66×10^{-7}	[$MDM2_N$] decay	[35]
27.	k_3	9.963×10^{-6}	[ARF] dependent [$MDM2_N$] decay	[35]
28.	k_a	0.5 proteins/s	[ARF] production	[35]
29.	K_4	10	Cooperative coefficient for ARF	Estimated
30.	n_4	3	Hill coefficient	Estimated
31.	δ	3.5×10^{-4}	[ARF] activation rate due to stress	Estimated
32.	d_a	3.209×10^{-5}	[ARF] decay	[35]
33.	k_3	9.963×10^{-6}	[$MDM2_N$] dependent [ARF] decay	[35]