Supplementary Information

Cancer dynamics: Identification of states for therapeutic intervention

Amit Jangid[1,2], Md Zubbair Malik[1*], Ram Ramaswamy[2*] and R.K. Brojen Singh[1*]
[1*] *School of Computational and Integrative Sciences, Jawaharlal Nehru University, New Delhi 110067, India.*
[2] *Department of Chemistry, Indian Institute of Technology Delhi, New Delhi 110016, India.*

Minimal regulatory network

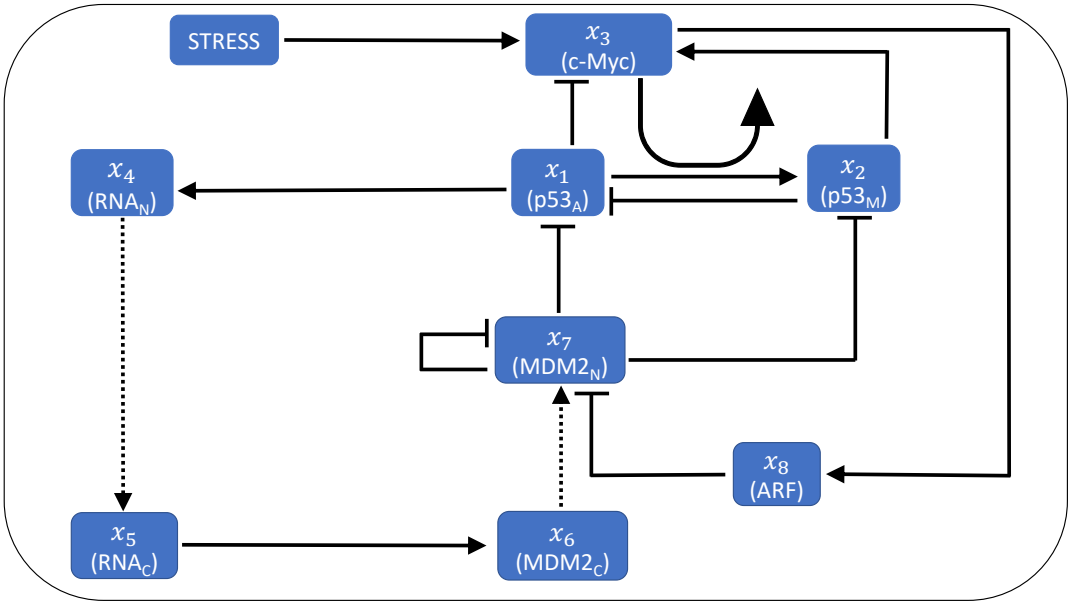

FIG. 1: Interaction network for $p53_A$-$p53_M$-MDM2-ARF-Stress. Modified network from [1] where $p53_A$ inhibits activation of c-Myc [2] [3]. c-Myc pro-oncogene induces the expression of $p53_M$ from $p53_A$ due to de-ragulation in c-Myc [4]. Dashed arrow shows movement from nucleus to cytoplasm or vice versa, while solid arrow, and bars corresponds to activation, and inhibition on respective node.

*Electronic address: zubbairmalik@jnu.ac.in, ramaswamy@iitd.ac.in, brojen@jnu.ac.in

Mathematical framework of the model system

$$
\begin{aligned}
\frac{dx_1}{dt} &= k_p - \left(k_1 x_7 + d_p + \gamma_{x_1} x_2 + \delta_{x_1} \frac{x_3^{n_1}}{K_1^{n_1} + x_3^{n_1}} \right) x_1 \\
\frac{dx_2}{dt} &= \alpha_{x_2} + \delta_{x_1} \frac{x_3^{n_1}}{K_1^{n_1} + x_3^{n_1}} x_1 - \gamma_{x_2} x_7 x_2 - \delta_{x_2} x_2 \\
\frac{dx_3}{dt} &= \alpha_{x_3} + \beta_{x_3} \frac{S^{n_2}}{K_2^{n_2} + S^{n_2}} + \delta_{x_3} \frac{{x_2}^{n_3}}{K_3^{n_3} + {x_2}^{n_3}} - \gamma_{x_3} x_3 - \omega_{x_3} x_3 x_1 \\
\frac{dx_4}{dt} &= k_m + k_2 \frac{x_1^{1.8}}{k_D^{1.8} + x_1^{1.8}} - k_0 x_4 \\
\frac{dx_5}{dt} &= k_0 x_4 - d_{rc} x_5 \\
\frac{dx_6}{dt} &= k_T x_5 - k_i x_6 \\
\frac{dx_7}{dt} &= k_i x_6 - d_{mn} x_6^2 - k_3 x_7 x_8 \\
\frac{dx_8}{dt} &= k_a + \delta \frac{x_3^{n_4}}{K_4^{n_4} + x_3^{n_4}} x_8 - d_a x_8 - k_3 x_7 x_8
\end{aligned} \tag{1}
$$

Here, x_3 is c-Myc oncogene, and ω_{x_3} is the parameter which represents activated p53 dependent decay rate in c-Myc. $\omega_{x_3} = 9.963 \times 10^{-8}$, and rest of all the parameter are the same as in table 1 in main text. See the main text for the detail of the equations. Red term in coupled differential equation shows the inhibition in c-Myc by $\mathrm{p53_A}$.

Results

Oncogenic regulation of normal and cancer dynamics

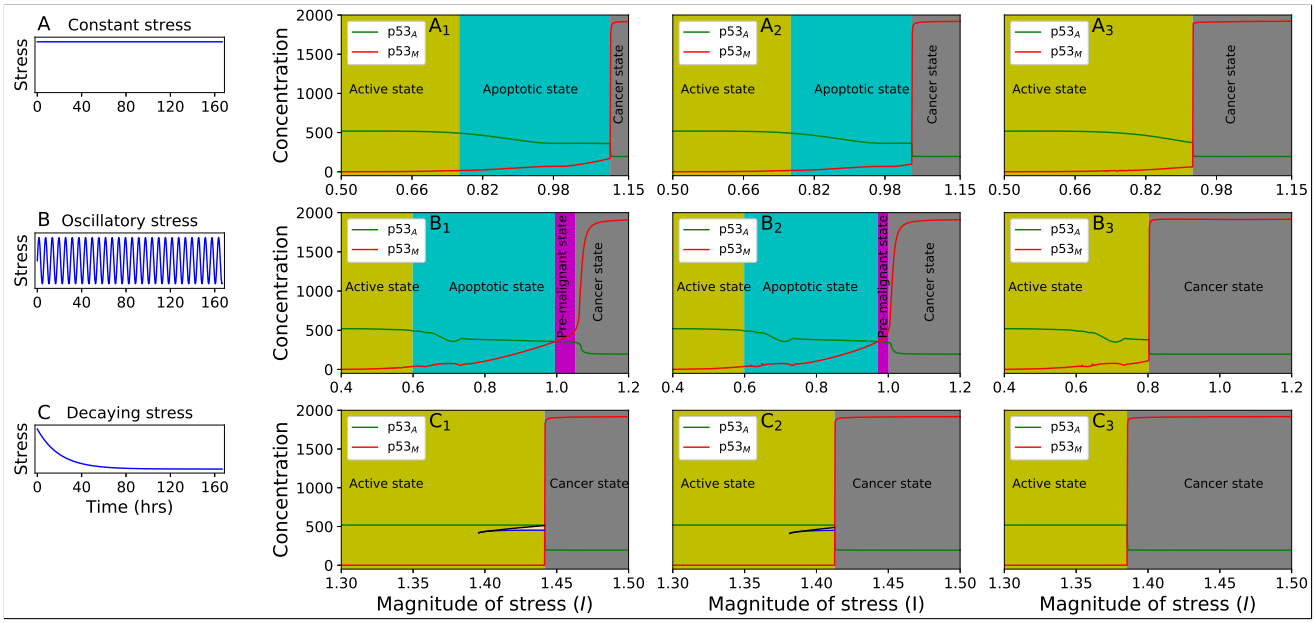

FIG. 2: The left column show three different form of stress discussed about. A_1, A_2, and A_3 display the steady state behaviour against magnitude of stress for different K_3 values 1000.0, 750.0, and 400.0 respectively driven with constant stress. B_1, B_2, and B_3 display the steady state behaviour against magnitude of stress for different K_3 values 2000.0, 1400.0, and 800.0 respectively driven with oscillatory stress. C_1, C_2, and C_3 display the steady state behaviour against amplitude for different K_3 values 700.0, 650.0, and 600.0 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. In constant stress case we did not observe pre-malignant regime.

Phase transition, key to therapeutic intervention and cancer recovery phase

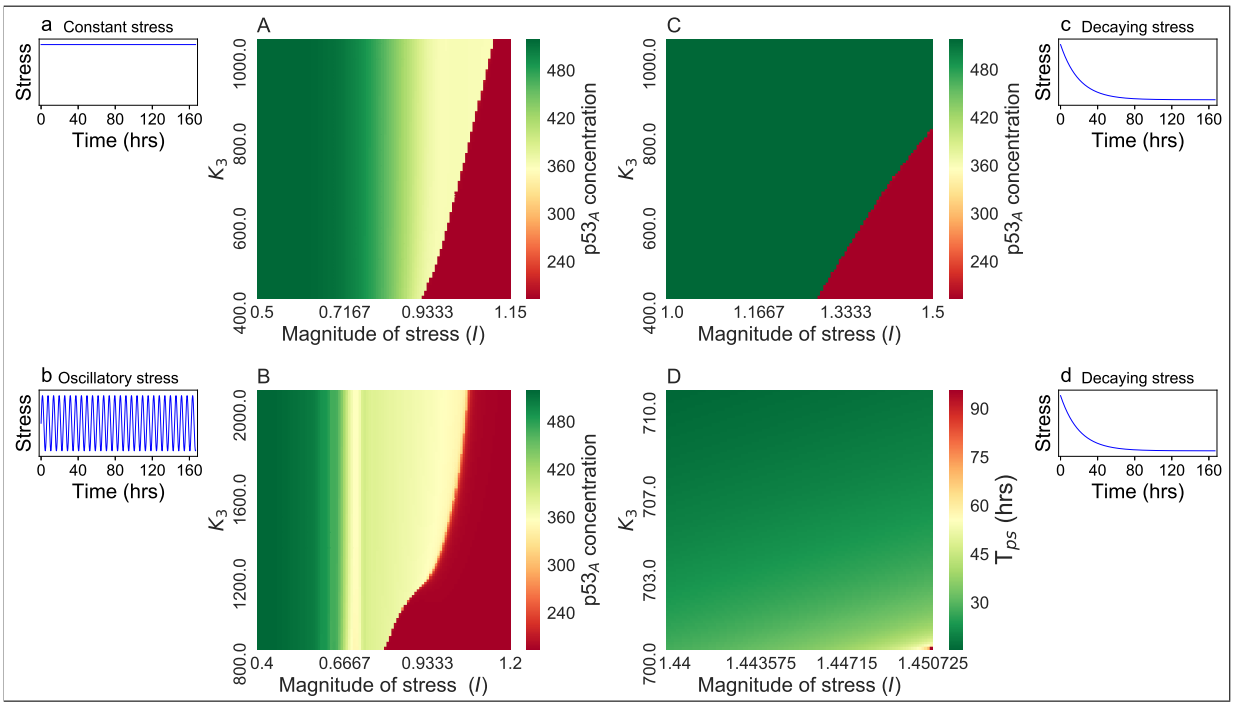

FIG. 3: A, B, and C show the two parameter (*Magnitude of stress* (I), K_3) steady state behavior of the system driven by different stress a, b, and c respectively. D shows two parameter cancer recovery behaviour of the system (*magnitude of stress*, and K_3) driven with decaying stress. On the heap map (panel A, B, and C) green, yellow, and red region indicate active, apoptotic, and cancer phase respectively.

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