Decision making of p53 network: an example of kinetic control in biological decision-making

Zhiyuan Li[a,b], Ming Ni[a,b], Jikun Li[a,b], Yuping Zhang[a,c], Qi Ouyang[a,b,1], and Chao Tang[a,b,d,1]

***Short Abstract* — many stress-response network, like the p53 DNA damage response pathway, can initiate distinctive responses according to different levels of external signal. We use Ordinary Differential Equations to analyze the information processing of the p53 network and propose that integration and time-differential of the p53 time-course controls the pro-death and pro-life module respectively. Oscillatory behavior of p53 appears in intermediate level of damage and maximizes the tendency towards repair and survival, without compromising the cell's potential of apoptosis. More general rules of this kind of stress-response network can also be derived mathematically.**

***Keywords* — Dynamic control, p53, stress response network, ODE**

I. Background

P53, the tumor suppressor protein involving in both pro-life and pro-death pathways, is a typical decision making protein that initiates distinctive cellular responses according to different environment clues. In response to DNA damage, elevated p53 determines cell fate by damage intensity: repairable damage prefers repair and survive, while severe damage leads to death [1]. The p53-mediated stress responses are extensively investigated [2], yet the overall decision-making strategy remains unclear.

Another mystery associated with the p53 network is the functional significance of p53 oscillation. Since 2000, oscillatory behavior of p53 after DNA damage has been found [2]. It is speculated that this oscillation may have certain functional roles in cell fate decision. However, despite these efforts it remains unclear whether and how the p53 oscillation plays any role in coordinating the stress response and/or in the cell-fate decision-making. [3]

II. Purpose

we aim to address the following questions: (1) whether and how the p53 network uses different information to regulate the pro-life module and the pro-death module; (2) what is the overall strategy of this decision making, and (3) what is the role of the p53 oscillation in this process; (4) are there general strategies in similar decision-making networks.

Author affiliation: [a]Center for Theoretical Biology, [b]The State Key Laboratory for Artificial Microstructures and Mesoscopic Physics, School of Physics and [c]School of Mathematics, Peking University, Beijing 100871, China; [d]Department of Bioengineering and Therapeutic Sciences, University of California, San Francisco,

III. Method

Based on the large amounts of literature on p53 pathway, we first build a network of p53-mediated response to DNA damage, and then translate the network into Ordinary Differential Equations. Logical-rule analysis is also taken to explore the general principle of decision-making networks.

IV. Conclusion

Analysis of this system suggests that distinct information of the nuclear p53 concentration is used to regulate the modules of cell cycle arrest and apoptosis: While the cell cycle arrest is determined by the instantaneous or peak values of the nuclear p53, the initiation of apoptosis depends on the time integration of the nuclear p53 level. This strategy gives the cell a time window -- the length of which is roughly inversely proportional to the stress level -- to recover from the stress before taking the death fate. Oscillation appears in intermediate level of damage, and because of the strategy above, it promotes cell survival. Furthermore, by logical-rule analysis, we show several rules for decision-making networks with similar structure of that in p53: (1) different information inputs to sub-modules are required for correct cell-fate choice; (2) under certain kinds of input information, the oscillatory behavior of controlling protein maximizes the preference towards one sub-module over anther, without affecting the cell's ability to choose the opposite fate in another circumstance. The existence of oscillation and steady states under different signal levels is required for optimal decision-making.

V. References

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