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Ph.D. thesis title : Computational Study of Complex p53 Signaling Network

Abstract

The thesis gives a detailed account of the various important signaling molecular species interacting with p53 either directly or indirectly in the complex information processing mechanisms in normal/stress systems. Some of these works provide an important link among the p53 pathway with other important pathways such as GSK3-β, Wnt, Notch etc. while some provides stress to the cell i.e. ROS. The behavior of complex cross-talks of these important interacting pathways are reflected in the dynamics of p53 through five distinct dynamical states of the system dynamics. The characteristics and properties of some of the important behaviors of the system are studied using various time series analysis techniques, such as visibility graph, information theoretical analysis and multifractal analysis. Moreover, properties and nature of the complex cancer networks (breast and ovarian cancer) constructed from the experimentally verified genes, and using well known human databases and related resources.

One important work present in this thesis is stress driven dynamics of Notch-Wnt-p53 cross-talk is subjected to a few possible dynamical states governed by simple fractal rules, and allowed to decide its own fate by choosing one of these states which are contributed from long range correlation with varied fluctuations due to active molecular interaction. The topological properties of the networks corresponding to these dynamical states have hierarchical features with assortive structure. The stress signal driven by Nutlin and modulated by mediator GSK3 acts as anti-apoptotic signal in this system, whereas, the stress signal driven by Axin2 and modulated by GSK3 behaves as anti-apoptotic for a certain range of Axin2 and GSK3 interaction, and beyond which the signal acts as favour-apoptotic signal. However, this stress system prefers to stay in active dynamical state whose

counterpart complex network is closest to hierarchical topology with exhibited roles of few interacting hubs.

This study may highlight the switching mechanism at different dynamical states of p53 corresponds to various cellular states. These studies show that the introduction of stress in the p53 regulatory network allows to switch the stabilized p53 state to oscillatory dynamics via DNA damage and further excess stress may lead to apoptosis. Stress induced in p53 signalling network by stress inducing molecules (Nutlin, Axin2, SMAR1, HDAC1 etc. in this case), which are involved in stress p53 dynamics, drives the system at various dynamical states defined by different fractal laws, and the system switch to these dynamical states depending on the amount of stress induced. This stress system prefers to stay in an active dynamical state which has simple fractal rule subjected to the optimal fluctuations available due to active molecular interaction driven by stress. However, the system still associates a group of few hubs (assortive topology), but not in dependent manner (absence of these hubs do not cause system's breakdown), for better signal processing and system regulation. Then this stress signal is propagated throughout the pathways, and found to inherit all the properties of the propagator pathway to the receiver pathways may be with slight modifications in them. This excellent co-ordination in cross-talk helps the system to save it from one directional apoptosis (once the system falls in this phase, it can never come back to normal situation) by regulating available active molecular interaction. This regulating mechanism could be different depending on the type of stress induced in the system. It may also open up new understanding on perturbation in the network which affect in local stability to global stability in network will give deep insight in how natural networks self-organized subject to the perturbations in the network.

This study will also help in cancer studies (breast, ovarian cancer), and since these networks are generally self-organized, one needs to have rigorous investigation on the proper identification of important key regulators of these networks to understand the mechanism of diseases and prevention, diagnosis and clinical trials and personalized medicine.