ABSTRACT

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Title of the Thesis: Understanding biological networks to identify regulatory points under perturbation
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In the era of high throughput approaches, cell signalling research has made significant advances in interdisciplinary fields. However, treatment approaches that target important molecules have yet to perform up to their expected promises for most common malignancies. Incomplete understanding brought on by single-pathway targeted techniques is one of the main challenges. Signal transduction is not linear, and they involve molecular cross-talks. To address these cross-talks, we must consider the system as a complicated network of interconnecting components. This shift from the conventional paradigm of focusing on a specific pathway to a broader strategy will help develop innovative treatments. The current thesis combined a systems biology approach with mathematical modelling (based on ordinary and stochastic differential equations) to comprehend the intricate mechanisms underlying cell signalling networks globally. The presence of densely coupled modules controlling cellular processes makes signalling networks complicated. These signalling systems must be sensitive enough to capture the variations in the input stimuli. At the same time, they must be robust enough to execute their cellular activities. The inclusion of inherent noise adds more complicity to these input-output relations and is much more challenging to comprehend. We have considered the more compact functional subunits known as network motifs to help uncover this complexity. The motif organisation affects the network's sensitivity, robustness, and trade-off in a signalling network. This thesis focused on developing new mathematical models and tools. With the help of mathematical models, we have created analytical formulas that can classify and rank motifs according to their sensitivity to random perturbations.

Bistability, the simultaneous existence of two outputs for a single input, emerged from a pilot study of two frequently observed two-node motifs. The inherent randomness of the signalling network disrupts emerged bistability. These complex phenomenons are extremely important to explain the intricate cellular signalling systems of cancer, diabetes and autoimmunity. The emergence of bistability and the effect of randomness on it demands an in-depth study of the association of network motifs and the input-output relation under random perturbation. To get a global view of the association, we have considered all possible two-node network motifs that can construct any biological network. The study reveals the significance of network motifs in maintaining cell signalling in a noisy environment and provides a methodology for screening potential drug targets. The dependency of the input-output relation on motif structure was applied to design a quantitative scoring formula to identify critical nodes in a protein-protein interaction network. Potential drug targets from cancer networks were identified using the tool and were validated by existing databases. The study reveals that potential drug targets also can be identified using a mathematical tool based on the emergence of bistability in the motif structures. Through hysteretic switching, signalling systems maintain robust signals in noisy conditions, which can also be used to identify drug targets. Existing techniques to identify drug targets are dependent on the data structure. They are mainly based on centrality and differentia. Differential networks compare different networks to identify therapeutic targets that heavily rely on data, whereas centrality-based methods identify targets using centrality measures. Targeting these central positions helps to disintegrate the networks but has detrimental side effects. Our study overcomes these drawbacks by proposing methods to identify prospective drug targets independent of the data and network structure. The significance of bistability and randomness was further explored through two biological processes. The emergence of bistability was observed in the tumour necrosis factor (TNF) signalling network in T regulatory cells that helps in the decision-making processes. The complex behaviour of cell survival and death of T regulatory cells was explained through bistable switching. The model demonstrates that the primary contributor to cell death is the elevated TNF concentration and increased c-Jun N-terminal kinase (JNK) phosphorylation. The results suggest that cell death can be controlled by reducing the TNF concentration. The bistable region can be reduced by intrinsic randomness, thus affecting the cell's normal functioning. Calcium signalling in diabetic cardiomyocytes was studied to investigate the significance of randomness in the complex case of diabetic cardiomyopathy. Altered calcium oscillation is a major contributor to the insulin-resistant cardiomyocytes that mimic the diabetes condition. The study proposed several strategies to restore the physiological calcium oscillations, which signify normal functioning. Early oscillation was observed when we incorporated the random translocation of the GLUT4 into the plasma membrane that controls glucose uptake, facilitating the restoration mechanisms.

Overall, the early part of the thesis was devoted to developing novel methods and tools to identify regulatory points of complex biological networks based on the association of network motifs and signal-noise relationships. Mathematical tools were constructed by exploring the emergence of bistability and the presence of intrinsic randomness in the system. Unlike existing methods, these methods are independent of data and network structures that can be used to identify potential drug targets. In the later part, we further explore the significance of noise in various biological processes through mathematical models. The significance of bistability in decision-making processes was captured by studying a small-scale kinetic model of TNF signalling. The random translocation of GLUT4 in diabetic cardiomyocytes was studied to comprehend the importance of randomness in the cell signalling system. The study reveals that randomness facilitates the restoration mechanism of physiological calcium oscillations.

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