Plenary 7

Direct the Fate of a Bio Complex System with an Engineering Optimization Scheme

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A complex system is composed of a large number of interacting building blocks/ elements which self organize, generating emerging properties that are usually not directly linked to those of the individual building elements. Cell is the most fundamental biological system and yet is a complex system.

In each living cell, the interactions among the bio molecules, proteins and nucleic acids intrinsically serve as the foundation of the extensive networks of signal and regulatory pathways. Emergent cellular functionalities are derived from the self-organization of these pathways, but can not be easily related to individual bio-molecular interactions. It becomes obvious that exploring and understanding the cell functions based on the bottom-up reductionist approach present significant challenges due to the sheer magnitude of pathway processes and pathway crosstalk. Furthermore, we frequently intend to direct cellular phenotypic and genotypic outcomes toward a desired state with a key example being the application of pharmacological agents to treat diseased cells in medicine. In other words, the drug application is an expedition to manipulate the cell fate by stimulating a far from understanding network.

Rather than laboriously mapping out the detailed cascade of signaling pathways from the bottom up, we take a top-down approach by employing a feedback system control (FSC) scheme to bypass the challenges associated with simultaneously considering multiple cellular regulatory pathways in cellular complex systems. In addition, we have harnessed these control schemes to rationally design combinatorial drug therapy modalities to direct the cellular system output with improved efficacy and low toxicity. This imposes another challenge which pertains to the large parameter space. For example, 6 drugs with 10 concentrations each would result in 1,000,000 potential search trials. With the feedback system optimization approach, we have demonstrated that only tens of searches instead of 1,000,000 cases are needed to identify the optimized drug cocktail.