Control of biological networks and multi-drug combinatorial therapies (C. Piermarocchi, Michigan State University)

In medicine, a new pharmacological approach involves the use of combinatorial therapies [1], in which different drugs are simultaneously used to control different pathways associated with a cellular function. The transfer of information inside a cell is a complex phenomenon, including transcription and its control by transcription factors, translation, and molecular modifications. All these processes contribute to a wireless *signal transduction network* regulating the cell [2]. A variety of different mathematical approaches have been developed to model biological signaling networks, ranging from Boolean models [3] to non-linear differential equations [4].

Our research focuses on the general properties of perturbations that can control the state of a complex biological signaling network. This provides hints on how to design and discover combinatorial therapies that could be more effective in curing complex diseases. For instance, we have investigated the control of the human apoptosis (cell death) signaling network [5]. We have built a model for a heterogeneous population of cells, characterized by a signaling network with identical topology, but having different link strengths. This model has allowed us to address the issue of selectivity, i.e. a control that must occur with minimal response in non-target cells exposed to treatment. Some important remaining questions are related on the minimal requirements for controllability in systems with incomplete knowledge of the networks. Some rigorous results on this issue have been recently obtained in the linear case [6], but the extension to include important nonlinear features in biology, such as multi-stability, remains a challenge.

An exciting development involves the integration of modeling, biological data, and *in-vitro* high-throughput screening. Control of cellular function depends typically on bipartite networks, in which one class of node (the controller) acts on the other class (the target). Examples include transcription factors targeting genes, microRNAs targeting mRNA transcripts, and protein kinases targeting phosphorylated protein substrates. In these bipartite networks each controller has many targets, and the targets themselves are under the influence of many controlling molecules. Certain properties of these bipartite networks seem universal across systems and species, suggesting the existence of universal control strategies in biology [7]. This information can be used to guide high throughput in-vitro searches of drugs to discover therapies that have *biomimetic* properties, i.e. have a controller-to-target network structure similar to the ones found in nature.

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