Graph-Theoretic Topological Control of Biological Genetic Networks

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Abstract— **The control of biological genetic networks is an important problem. If the system is abstracted into a graph, then the affect of drugs, pharmaceuticals, and gene therapy can be abstracted as changing the topology of the graph. We consider the control objective of removing the stable oscillations of the genetic network. This control is done using several theorems relating the topology of the network to the dynamics of the system. These theorems suggest that the controller should remove all the negative feedback in the networks. We prove that the problem of minimizing the edges and vertices to remove, in order to remove negative feedback, is NP-hard. In light of this result, a heuristic algorithm to solve this graph problem is presented. The algorithm is applied to several genetic networks, and it is shown that the heuristic gives reasonable results. Additionally, we consider the p53 network and show that the algorithm gives biologically relevant results.**

I. Introduction

The problem of control of biological genetic networks is an important one. The chief applications of such control are medical in nature. For instance, the problem of deciding which components (e.g. protein or mRNA) of a network to target pharmaceuticals in order to treat a condition is such an application.

Unfortunately, biological genetic networks contain features that make it difficult to do traditional control. Measuring the states of a system for the purposes of feedback control can be prohibitively difficult or even not feasible with current technologies. Moreover, such genetic networks do not typically have inputs that can be changed to do control. In light of these difficulties, we proposed a new framework in [1] for doing the topological control for such networks. A related line of research that has been developed concurrently is [2].

In our framework, we abstract the affect of drugs, pharmaceuticals, and gene therapy to having a graph theoretic interpretation. It is common for biologists to abstract genetic networks, which are dynamical systems, to a signed, directed graph which qualitatively describes the influence of a state on another state. This graph is often referred to as a promotion-inhibition network. Using a quasi-steady-state approximation, we were able to show that drugs and pharmaceuticals can be interpreted as modifying the signed, directed graph by removing vertices or edges of the graph [1].

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A. Topological Control

If we interpret pharmaceuticals as modifying a graph, then we can try to do control by intelligently modifying the topology of the genetic networks. The topology of a network will remain modified only in the presence of the pharmaceutical: As soon as the pharmaceutical degrades, the topology of the network will return to an unmodified nature, and the system will go back to being uncontrolled. The control that we choose also depends on having correct knowledge of the genetic network.

We can do the topological control by using theorems that relate the topology of the network to the dynamical behavior of the network. A big class of results concerns monotone systems [3], [4], [5], systems with no undirected, negative cycles within the graph of the network. These systems do not have any stable oscillations, and all trajectories converge to equilibrium points. A related class of results concerns systems with no directed, negative cycles within the graph of the network. If the graph is also strongly connected, then all trajectories of the system converge to equilibrium points and there are no stable oscillations [6]. Similar results are found in [7], [8], [9], [10]. These results can be extended to prove that all systems with no directed, negative cycles have the same behavior. The particular case of piecewise-affine hybrid systems with no self-inhibition was proved in [11], [12], and the more general case of arbitrary smooth vector fields was proved in [4].

Directed, negative cycles correspond to our intuitive notion of negative feedback in a system. Undirected, negative cycles, which are a superset of directed, negative cycles, do not always match the intuitive notion of negative feedback. We do the control by removing the negative feedback of the system, which removes the oscillations of the system. This is the goal of the current paper: How can we remove the negative feedback of the system, so that the system trajectories do not have stable oscillations and converge to equilibrium points? The goal is: What should we design pharmaceuticals to target, so that the concentrations in the genetic network converge to equilibria?

This is a crude level of control, but we will provide a biological example of the p53 pathway – which is implicated in cancer – that shows that it can generate useful controllers. This type of control is related to the work in [13], [14]; however, the difference is that removing undirected, negative cycles is a more restrictive condition, because negative feedback is a subset of undirected, negative cycles.

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