Intervention in genetic disease using signal processing

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Discovering an optimal way to alter the logic of a gene regulatory network provides the most effective means of lessening the long-term likelihood of cells entering pathological states.

Transcriptional signaling (cellular activity related to protein production) plays a major role in genomics. It seems only natural, then, that signal processing should figure largely in understanding gene regulatory effects and their relationship to changes at both the genotypic (internally coded) and phenotypic (outwardly observed) levels. Gene regulatory networks describe the manner in which cells execute and control normal function and how abnormal function results from a breakdown in regulation. Accordingly, gene network models are central to translational genomics, whose aim is to develop therapies based on the disruption or mitigation of aberrant gene function contributing to the pathology of a disease. Engineering therapeutic tools involves synthesizing dynamic networks, analyzing these networks to characterize gene regulation, and developing intervention strategies to modify dynamic behavior.

Gene regulatory networks modeled as discrete dynamic systems (Markov chains) generally follow two basic approaches: external control and structural intervention. For the most part, we and others have considered the problem in the context of gene-logic (rule)-based Boolean networks, whose probabilistic and transitional structures are modeled as a Markov chain.

External control generally involves changing the value of a control gene, which means altering its protein product. We have taken this approach in the framework of infinite-horizon stationary external control, in which the control action is based on an objective function that rewards beneficial gene activity. The control policy for the function is determined through dynamic programming and by using greedy algorithms that circumvent the computational impediments of such programming. The salient goal is to alter the steady-state distribution of the network to lessen the likelihood of it being in undesirable states, for instance, metastatic states in cancer.

Structural intervention involves a one-time change of the structure (wiring) of the network to beneficially alter its long-term behavior (steady state). Given a class of potential structural changes, the challenge is to find the intervention that results in an optimal alteration of the steady-state distribution. For rule-based networks, transitions are determined by regulatory rules among the genes, and a structural intervention results from perturbing one of the rules. Two issues are involved: characterizing the effects of a rule perturbation, and determining the optimal perturbation(s) to achieve a desirable alteration in the steady-state distribution (one in which the steady-state mass is moved in the direction of desirable states and away from undesirable ones).

To find an optimal structural intervention, we need to determine the long-run effect of perturbations to one or more regulatory rules. Following perturbation, the original transition matrix $P$ and steady-state distribution $\pi$ are changed to $P_a$ and $\pi_a$, respectively. The key issue is to apply matrix methods to represent the altered steady-state distribution, $\pi_a$, in terms of $\pi$ and $P$ so that an optimal perturbation can be determined directly from them. It is first accomplished for a rank-one perturbation to $P$. The results for this special case are then extended to...
arbitrary types of perturbations to enable computation of the steady-state distributions of arbitrarily perturbed Markov chains in an iterative fashion. A key point for understanding network dynamics is that perturbation theory can be used to characterize the long-term sensitivity of a gene network to structural interventions, and that this sensitivity is related to the inference and controllability of the network.8

We consider a gene regulatory network developed from data collected in a study of metastatic melanoma in which the abundance of messenger RNA for the gene WNT5A was found to be a highly discriminating difference between cells with properties typically associated with high versus low metastatic competence.9 This suggests intervention to alter the contribution of the WNT5A gene’s action to reduce the chance of a melanoma metastasizing, a desirable outcome. Our network contains seven genes: WNT5A, pirin, S100P, RET1, MART1, HADHB, and STC2 (detailed description published elsewhere7). Figure 1 shows the steady-state distribution of the network, along with the probability masses for the undesirable (WNT5A upregulated) and desirable (WNT5A downregulated) states. The goal is to reduce the probability of undesirable states while at the same time not introducing probability mass for states possessing negligible probability in the original network because such states represent unknown phenotypes. Using the Markov-chain perturbation theory, we deduced an optimal structural change to the regulatory network based on these criteria that alters the regulation of RET1. Figure 2 shows the resulting steady-state distribution.

In summary, we have briefly outlined the structural intervention problem and shown how classical signal-processing methods can be used to characterize it and determine an optimal strategy for proceeding. As when moving from any abstract mathematical characterization to practice, numerous issues must be addressed. In this case, there are three major areas of concern: model specificity, computational complexity, and physical implementation. We are addressing these questions in a variety of ways, including design of robust intervention strategies that perform well in the presence of model uncertainty, approximation of optimality, network reduction through lossy compression, and model adjustment to better fit practical physical conditions.10

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References


