Optimal Finite-Horizon Control for Probabilistic Boolean Networks with Hard Constraints

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Abstract

In this paper, we study optimal control policies for Probabilistic Boolean Networks (PBNs) with hard constraints. Boolean Networks (BNs) and PBNs are useful and effective tools for modelling genetic regulatory networks. A PBN is essentially a collection of BNs driven by a Markov chain process. It is well-known that the control/intervention of a genetic regulatory network is useful for avoiding undesirable states associated with diseases like cancer. Therefore both optimal finite-horizon control and infinite-horizon control policies have been proposed to achieve the purpose. Actually the optimal control problem can be formulated as a probabilistic dynamic programming problem. In many studies, the optimal control problems did not consider the case of hard constraints, i.e., to include a maximum upper bound for the number of controls that can be applied to the PBN. The main objective of this paper is to introduce a new formulation for the optimal finite-horizon control problem with hard constraints. Experimental results are given to demonstrate the efficiency of our proposed formulation.

Keywords: Boolean Networks, Dynamic Programming, Finite-Horizon, Intervention, Markov Chain, Optimal Control, Probabilistic Boolean Networks.

I. INTRODUCTION

An important research issue in systems biology is to understand and model the mechanism in which the cells execute and control a large number of operations

for their normal functions and also the way in which they fail in diseases such as cancer. A lot of mathematical models have been proposed for the former purpose, such as neural networks [19], differential equations [10] and Petri nets [25]. For the captured problem, modelling the genetic regulatory network and inferring its structure by real gene expression data, Boolean Network (BN) and its generalization Probabilistic Boolean Network (PBN) have received much attention. This approach helps one to make efficient and effective predictions of the cellular systems by using computer simulations. BN was first introduced by Kauffman [13]. In a BN, each gene is regarded as a vertex of the network and is then quantized into two levels only (express (0) or not-express (1)) though the idea can be extended to the case of more than two levels. In a BN, the target gene is predicted by several genes through a Boolean function. The genes used to predict a certain gene are called its input genes. If the input genes and the Boolean functions are given, then a BN is said to be defined and it can be considered as a deterministic dynamical system. BN is simple but its dynamics is complex and it is useful in getting insight in the global behavior of a genetic regulatory network [26]. In a BN, attractors play a very important role. Starting with a given state, eventually the BN will enter into a cycle of states called an attractor cycle and will stay there forever [14]. A number of algorithms have been proposed by Akutsu et al. [3], [4] and Zhang et al. [28] for finding attractors.

However, the biological system has its stochastic nature and the microarray data sets used to infer the network structure are usually not accurate because of the experimental noise in the complex measurement process. Thus a deterministic model may not be able to cope with the real situations. In view of this, Akutsu et al. [2] proposed a noisy Boolean network together with an identification algorithm. In their noisy BNs, they relax the requirement of consistency imposed by the Boolean functions. Later Shmulevich *et al.* [20], [21] proposed a PBN that can take the advantage of the rule-based properties of BNs and still be able to cope with the presence of uncertainty. PBNs have been shown to be practical in building a logical representation of cell cycle regulation, see for instance [20], [21]. The dynamics of a PBN can be studied in the context of a standard Markov chain [20], [21]. Therefore the theory of Markov chain process [7] can be applied to analyze the network. It should be noted that the PBNs in [20], [21] are called instantaneously random PBNs. It may not have a unique steady-state probability distribution. To stabilize the network, later random gene perturbations were introduced to the network in [22]. With the random gene perturbation, the system becomes stable in the long-run and has the unique network steady-state probability distribution. Another extension of the instantaneously random PBN is the context-sensitive PBN [16]. The extra feature in a context-sensitive PBN is that at each time step the BN will be changed with

a certain probability. In the computation of the network steady-state probability distribution, the computational cost increases exponentially with respect to the number of genes in the network. To tackle the high dimensionality problem, a multivariate Markov chain model has been developed to approximate a PBN [6]. Other efficient numerical methods such as Markov chain Monte-Carlo (MCMC) method [24], matrix method [27] and approximation method [8] have also been proposed for the computation of the steady-state probability distribution of a PBN.

While the mechanism of a genetic network can be studied and understood by using a PBN, it is an ultimate goal of the systems biologists to design therapy and strategy for the intervention of the network dynamics, in particular, in the case of diseases like cancer. We note that although a PBN allows uncertainty in the inter-gene relations, actually it evolves according to some fixed state transition probabilities. Therefore there is no internal control to drive this evolution to some desirable states or to avoid some undesirable states. Genetic intervention has been proposed to facilitate a PBN to evolve to some targeted desirable state. Shmulevich et al. [22], [23] have studied two approaches for genetic intervention. In the first approach, they influence the network by toggling the state of a particular gene from on to off [22]. But this approach can only affect the behavior of the system for a while as the system dynamics still depends on the network itself. Another approach is to apply the structural intervention to change the network steady state [23]. But still this approach constitutes only transient intervention. To achieve relatively more permanent effect of intervention, optimal control theory (finite-horizon and infinite-horizon) finds its application. In [9], an optimal control formulation for gene intervention problem has been formulated as a minimization problem with some costs. The costs are defined as the cost of applying the control inputs in some particular states. Of course relatively higher terminal costs are assigned to those undesirable states. But the costs have to be decided by the biologists or clinicians and can be subjective. Since the system is stochastic in nature, the cost is given by its expectation. Thus the optimal control policy is the one which minimizes the overall expected cost and is obtained by using the theory of probabilistic dynamic programming [17]. Here we would like to remark that the number of possible states in the network increases exponentially with respect to the number of genes n and therefore the computational cost for solving the optimal control problem can be enormous even for moderate n. Take for example of a BN, it has been shown that finding a control strategy for BN to the desired global state is NP-hard [4]. Therefore the problem of solving optimal control in a PBN is challenging and approximate methods should be considered. Recently an approximate finite-horizon optimal control has been introduced in [15] and a heuristic method based on Q-learning algorithm for approximating

the optimal infinite-horizon control policy has been proposed in [12]. However, all the optimal control formulations did not consider the case of hard constraints [1], i.e., to include a maximum upper bound for the number of controls that can be applied to the PBN. Here we will introduce a new formulation for the optimal finite-horizon control problem with hard constraints [5]. The new formulation can be applied to both perturbed and context-sensitive PBNs though we only discuss examples of instantaneously random PBNs. On one hand, during the treatment of one patient, the cost of the operation conducted may be expensive. On the other hand, it may be impractical to apply many operations to the patient due to the organism quality of their body, as in chemotherapy. Apart from the hard constraints, the followings are two more features of our optimal control model. First, our formulation does not need to define any control cost or terminal cost. The only constraint is the maximum number of controls that one can apply to the network. Second, the control policy is not state dependent. However, we remark that our formulation here can be modified to include both the control costs and the state dependent control policies.

The paper is organized in the following sequel. In Section two, we give a probabilistic dynamic programming formulation for our optimal finite-horizon control problem. In Section three, numerical examples are given to demonstrate the efficiency of our proposed optimal control formulation. Finally, concluding remarks are given to address further research issues in Section four.

II. The Optimal Finite-Horizon Control Problem

In this section, we give a mathematical formulation for the optimal control problem based on the principle of dynamic programming. Here the problem can be considered as a discrete time control problem. Beginning with an initial probability distribution $\mathbf{v}_0$ the PBN (or the Markov chain) evolves according to two possible transition probability matrices P_0 and P_1. Without any external control, we assume that the PBN evolves according to a fixed transition probability matrix P_0. When a control is applied to the network, the PBN will then evolve according to another transition probability matrix P_1 (with more favorable steady states or a BN) but it will return back to P_0 again when no more control is applied to the network. We remark that one can have more than one type of control, i.e., more than one transition probability matrix P_1 to choose in each time step. But for simplicity of discussion, we assume that there is only one possible control here. We then suppose that the maximum number of controls that can be applied to the network during the finite investigation period T (finite-horizon) is K where $K \leq T$ and which can be determined under the guidance of a doctor or a biologist. The objective here is to find an optimal control policy such that state of the network is close to a target state vector $\mathbf{z}$. The vector $\mathbf{z}$

can be an unit vector (a desirable state) or a probability distribution (a weighted average of desirable states). To facilitate our discussion, we first define the following state probability distribution vectors $\mathbf{v}(i_k i_{k-1} \dots i_1) = P_{i_k} \cdots P_{i_1} \mathbf{v}_0$ to represent all the possible network state probability distribution vectors up to time k. Here $i_1, \dots, i_k \in \{0,1\}$ and $\sum_{j=1}^{k} i_j \leq K$ and $i_k i_{k-1} \dots i_1$ is a Boolean string of size k. We then define $U(k) = \{\mathbf{v}(i_k i_{k-1} \dots i_1) : i_1, \dots, i_k \in \{0,1\} \text{ and } \sum_{j=1}^{k} i_j \leq K\}$ to be the set containing all the possible state probability vectors up to time k. We note that one can conduct a forward calculation to compute all the state vectors in the sets $U(1), U(2), \dots, U(T)$ recursively. Beginning with $\mathbf{v}_0$, we have $\mathbf{v}(0) = P_0 \mathbf{v}_0$ and $\mathbf{v}(1) = P_1 \mathbf{v}_0$ and therefore $U(1) = \{\mathbf{v}(0), \mathbf{v}(1)\} = \{P_0 \mathbf{v}_0, P_1 \mathbf{v}_0\}$. We then compute $\mathbf{v}(00) = P_0 \mathbf{v}(0)$, $\mathbf{v}(10) = P_1 \mathbf{v}(0)$, $\mathbf{v}(01) = P_0 \mathbf{v}(1)$, $\mathbf{v}(11) = P_1 \mathbf{v}(1)$ and we have $U(2) = \{\mathbf{v}(00), \mathbf{v}(01), \mathbf{v}(10), \mathbf{v}(11)\} = \{P_0 P_0 \mathbf{v}_0, P_1 P_0 \mathbf{v}_0, P_0 P_1 \mathbf{v}_0, P_1 P_1 \mathbf{v}_0\}$ Recursively one can compute $U(3), \dots, U(T)$. Here the main computational cost is the matrix-vector multiplication and the cost is $O(2^{2n})$ where n is the number of genes in the network. However, we don't need to compute and store all the 2^T vectors as some state probability distribution actually does not exist because the maximum number of controls is K. In fact, the total number of vectors involved is

$$\sum_{j=0}^{K} \frac{T!}{j!(T-j)!}.$$

For example if $K = 1$, the complexity of the above algorithm is $O(T 2^{2n})$.

There are at least two possible formulations for our optimal control problem. The first one is to minimize the terminal distance with the target vector $\mathbf{z}$, i.e.,

$$\min_{\mathbf{v}(i_T i_{T-1} \dots i_1) \in U(T)} ||\mathbf{v}(i_T i_{T-1} \dots i_1) - \mathbf{z}||_2. \tag{1}$$

The second one is to minimize the overall average of the distances of the state vectors $\mathbf{v}(i_t \dots i_1)$ $(t = 1, 2, \dots, T)$ to the target vector $\mathbf{z}$, i.e.,

$$\min_{\mathbf{v}(i_T i_{T-1} \dots i_1) \in U(T)} \frac{1}{T} \sum_{t=1}^{T} ||\mathbf{v}(i_t \dots i_1) - \mathbf{z}||_2. \tag{2}$$

For the first optimal control problem (1), once we compute all the feasible state vectors $U(T)$, we can then compute the minimum of the following: $\min\{||\mathbf{v}(i_T i_{T-1} \dots i_1) - \mathbf{z}||_2\}$. The optimal control policy can be found accordingly. For the second optimal control formulation (2), we have to define the following cost function $D(\mathbf{v}(\mathbf{w}_t), t, k),\ 1 \leq t \leq T,\ 0 \leq k \leq K$ as the minimum total distance to the terminal time T when beginning with state distribution vector $\mathbf{v}(\mathbf{w}_t)$ at time t and that the number of controls used is k. Here $\mathbf{w}_t$ is

a Boolean string of length t. To reduce the duplication in the calculation of distances, we consider the following dynamic programming formulation ([1]):

$$\begin{array}{ll} D(\mathbf{v}(\mathbf{w}_{t-1}), t-1, k) & = \min\{||\mathbf{v}(0\mathbf{w}_{t-1}) - \mathbf{z}||_2 + D(\mathbf{v}(0\mathbf{w}_{t-1}), t, k), \\ & \quad ||\mathbf{v}(1\mathbf{w}_{t-1}) - \mathbf{z}||_2 + D(\mathbf{v}(1\mathbf{w}_{t-1}), t, k+1)\}. \end{array} \quad (3)$$

Here $0\mathbf{w}_{t-1}$ and $1\mathbf{w}_{t-1}$ are Boolean strings of size t. The first term in the right-hand-side of (3) is the cost (distance) when no control is applied at time t while the second term is the cost when a control is applied. The optimal control policy can be obtained during the process of solving (3). To solve our optimal control problem: $\min_{0\le k\le K}\{D(\mathbf{v}_0, 0, k)\}$ we need the following boundary conditions: $D(\mathbf{v}(\mathbf{w}_t), t, K+1) = \infty \quad \text{for all } \mathbf{w}_t \text{ and } t \text{ and for } k = 0, 1, \ldots, K,$

$$D(\mathbf{v}(\mathbf{w}_T), T, k) = ||\mathbf{v}(\mathbf{w}_T) - \mathbf{z}||_2 \quad \text{for} \quad \mathbf{w}_T = i_T \ldots i_1 \quad \text{and} \quad \sum_{j=1}^{T} i_j \le K.$$

Finally, we remark that the formulations are still valid when $||.||_2$ is replaced by other vector norms such as $||.||_1$ or $||.||_\infty$.

III. Experimental Results

In this section, we apply the optimal control to a eight-gene network [15]. We assume that there are two Boolean functions $f_1^{(i)}$ and $f_2^{(i)}$ associated with each gene i. Moreover, all the Boolean functions and their variables are generated randomly as in [15]. Here we assume the control when applied to the network will suppress gene 1, i.e., gene 1 is not expressed. We further assume that the transition probability matrix when a control is applied is given by

$$P_1 = \begin{pmatrix} 0 & 0 \\ I & I \end{pmatrix}$$

where $\mathbf{0}$ and I are the 2^7-by-2^7 zero matrix and the identity matrix respectively.

In the numerical experiment, we assume that the initial state vector of the network is the uniform distribution vector $\mathbf{v}_0 = \frac{1}{2^8}(1, 1, \ldots, 1)^T$. The target vector is $\mathbf{z} = \frac{1}{2^7}(\mathbf{0}, \mathbf{1})^T$ where $\mathbf{0}$ and $\mathbf{1}$ are the 1×2^7 zero vector and the 1×2^7 vector of all ones respectively. Again we assume that the total time T to be 12 and we try several different maximum number of controls $K = 1, 2, 3, 4, 5$. Tables I and II report the numerical results. It took 10.7 seconds to generate the transition probability matrix P_0. The computational time for solving for optimal policy in all cases is less then 4 seconds. In Tables I and II, we observed that we should apply as many controls as possible up to the maximum constraints for both formulations (1) and (2). According to the formulation (2), the controls should be conducted as soon as possible (the optimal policy is to apply the controls at the beginning of the period).

TABLE I
THE EXAMPLE OF EIGHT-GENE NETWORK (OBJECTIVE FUNCTION (1) IS USED)

K	1	2	3	4	5
Control time point	(7)	(9,11)	(7,9,11)	(3,7,9,11)	(2,5,7,9,11)
Optimal value	0.1585	0.1454	0.1309	0.1297	0.1272

TABLE II
THE EXAMPLE OF EIGHT-GENE NETWORK (OBJECTIVE FUNCTION (2) IS USED)

K	1	2	3	4	5
Control time point	(1)	(1,2)	(1,2,3)	(1,2,3,4)	(1,2,3,4,5)
Optimal value	0.1459	0.1327	0.1194	0.1061	0.0929

IV. CONCLUDING REMARKS

In this paper, we introduce a new optimal finite-horizon control formulation for PBNs with hard constraints. The new formulation can be applied to both perturbed and context-sensitive PBNs though we only test it with the instantaneously random PBNs. We remark again that our proposed optimal control method can be extended easily to the case of more than two control policies. The followings are our future research issues. First, we will extend our formulation for PBNs to the case of optimal infinite-horizon control based on the results in [1], [5]. Second, we will extend the approximation method in [8] to our control problem. Finally, we will conduct more numerical experiments to bigger size networks.

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