

Optimal Intervention in Semi-Markov-based Asynchronous Genetic Regulatory Networks

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Abstract—Probabilistic Boolean networks are a class of rule-based models for gene regulatory networks. This class of models is used to design optimal therapeutic intervention strategies. While synchronous probabilistic Boolean networks have been investigated in detail in the literature, no similar endeavor has been completed for asynchronous networks. This paper addresses this issue by introducing an asynchronous extension to probabilistic Boolean networks and by developing intervention methods based on this new model. The proposed framework introduces asynchronism at the level of aggregated genes status. The theory of semi-Markov decision processes is then used to devise effective intervention methods where the objective is to reduce the time duration that the system spends in undesirable states. The necessary timing information for the proposed model can be obtained from sequences of gene-activity profile measurements. This is one of the major advantages of the propose approach.

I. INTRODUCTION

From a translational perspective, the ultimate objective of genetic regulatory network modeling is to put forth a mathematical platform for the design of therapeutic intervention strategies that reduces or eliminates the incidence of undesirable phenotypes, for instance, cancer [1]. To date, regulatory intervention has been studied in the context of probabilistic Boolean networks (PBN) [2]. While synchronous PBNs and their corresponding intervention methods have been investigated in detail [3], there has been no attempt to study their asynchronous counterparts. In this paper, we relax the synchronous assumption and consider intervention in asynchronous networks. We define an asynchronous genetic regulatory network motivated by probabilistic Boolean networks, and study the problem of designing intervention methods based on the proposed asynchronous model. Our approach considers asynchronism relative to the state-space of gene-activity profiles.

The multivariate interactions among the components of a rule-based regulatory network are defined by a *regulatory graph*. From here on, we use the term *gene* loosely to refer to the general biological components, e.g. genes and proteins, involved in a regulatory network. The vertices of a

This work was supported in part by the National Science Foundation (ECS- 0355227, CCF-0514644 & ECCS-0701531), the National Cancer Institute (R01 CA-104620, & CA-90301) and the Translational Genomics Research Institute.

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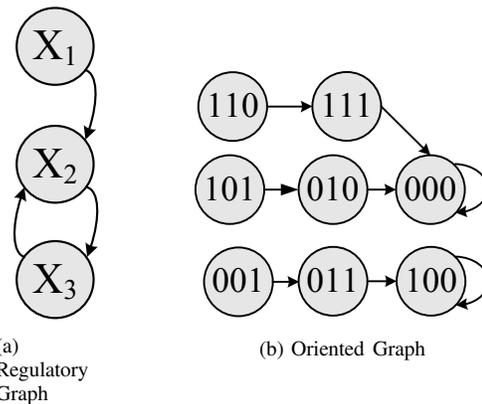


Fig. 1. Presentation of a regulatory graph and its corresponding oriented graph for an arbitrary 3-gene Boolean network.

regulatory graph are the genes or *nodes*. A directed edge starts from a predictor vertex and ends at an influenced vertex. All the vertices directly going into a node are its predictors. A regulatory rule defines the multivariate effects of predictors on the vertex. The node values are selected from a set of possible quantization levels to facilitate the modeling of gene interactions by logical rules. The discrete assumption in rule-based regulatory networks is suitable for many classes of biological systems. Strong evidence suggests that the discrete-state-space models are capable of describing interactions between biological components [4] [5]. Fig. 1a shows the regulatory graph of a hypothetical three-gene network. There is a unidirectional relation between nodes (genes) x_1 and x_2 . The relation between nodes x_2 and x_3 is bidirectional.

To completely specify a class of regulatory networks, we need to adopt an updating scheme. Having the updating scheme, we can translate the dynamical information of the regulatory graph and the regulatory rules into an *oriented graph*. The vertex of an oriented graph is a *logical state*, which is the aggregated values of all the nodes at a given time. An edge traverses from one logical state to another logical state of an oriented graph if a transition can occur in the direction of the edge from one vertex to the other.

The choice of the updating scheme plays a crucial rule in the dynamical behavior of the network. For instance, Fig. 1b shows the oriented graph corresponding to the regulatory graph in Fig. 1a. According to this oriented graph, whenever the aggregate value of the three nodes in the network is $(x_1 = 1, x_2 = 1, x_3 = 1)$ and if all the nodes update synchronously, then the next logical state is $(x_1 = 0, x_2 =$

0, $x_3 = 0$). A regulatory graph is a static representation of interactions among biological components, whereas an oriented graph shows the dynamics of the interactions among these components. We can practically observe timing information related to the dynamical representation of biological component interactions, that is, timing relative to the oriented graph.

Synchronous abstractions are used under the implicit assumption that asynchronous updating will not unduly alter system properties central to the application of interest [6]. Clearly, some properties will be altered [7]–[9]. On the other hand, from a biological perspective, interactions among genes causing transcription, translation, and degeneration occur over a wide range of time-scales. Hence, relaxing the synchronous abstraction is arguably the next logical step in the design of genetic regulatory networks.

These observations instigate examining intervention strategies in asynchronous models. Since adopting the asynchronous assumption alters the time progression of regulatory models, we cannot readily apply existing intervention techniques designed for synchronous networks. Alternative approaches to influence network dynamics in asynchronous models are needed.

To date, asynchronism in the context of Boolean networks has been introduced by updating each node based on its period. Assuming asynchronism at the node level for Boolean networks has practical and theoretical impediments that may prevent independent node updating to serve as a basis for designing effective therapeutic intervention strategies [10], [11]. In particular, the delay and the updating order of a given gene are only observable with respect to the activity levels of other genes and proteins involved in the regulation process. Thus, it is impractical to study the alteration of one specific gene over time, while keeping the levels of all other genes in the model constant. Practically, we can measure the aggregated values of all the genes (logical states) at each observation instant. The inter-transition interval between two logical states can then be modeled by a random variable. In [10] and [11], experimentally validated Boolean rules are considered. Under a synchronous assumption, the oriented graphs can accurately determine the phenotypic behavior of the underlying biological processes. However, these studies suggest that asynchronously updating the nodes when utilizing the same Boolean rules generates very complex pathways which possess many incompatible and unrealistic phenotypes. Although not mentioned explicitly in [10] and [11], it appears that asynchronously updating the nodes changes the global behavior of regulatory networks by changing their oriented graphs.

The results of [10] and [11] indicate that rule-based regulatory models should maintain the topology of the oriented graph generated by experimentally validated predictor rules, as if the genes are coupled. In other words, regulatory models should accurately translate the logical relationships, i.e. the regulatory graph, governing the interactions of nodes into the oriented graph specifying the dynamics of the model. Moreover, they should enable the analysis of the temporal

behavior of biological systems. Since our objective is to alter the long-run behavior of biological systems via effective intervention strategies, our regulatory models should not only possess the previous two attributes, but these models should also be inferable from the empirical data.

In this paper, we propose an asynchronous regulatory network model, termed *semi-Markov asynchronous regulatory networks* (SM-ARN). In the SM-ARN, the asynchronism is at the logical state. In this model, the empirically measurable timing information of biological systems is incorporated into the model. This timing information determines the typical time delay between transitions from one logical state to another. Since the order of updating nodes and their relative time delays depend on the levels of other regulatory components, estimating the updating time of each gene in isolation, and independent of the values of other genes, is highly problematic, if not impossible. Time-course data enable the estimation of inter-transition times between logical states, not the updating time of each node. It is then natural to introduce asynchronism at the logical-state level.

An SM-ARN is specified with two sets of information. The first set determines the rule-based multivariate interactions between genes. Considering simultaneous updating, we can specify the oriented graph of the model based on this information. In other words, the first set of information specifies a PBN, which is generated from a given set of Boolean functions for updating each gene. The generated oriented graph guarantees the predictability of the rule-based topology. The second set of information consists of the distributions of inter-transition intervals between any two logical states that are directly connected. These values can be empirically inferred from time-course data.

To design optimal intervention strategies based on the SM-ARN model, we apply results from the theory of semi-Markov decision processes (SMDP). Appropriately formulating the problem of intervention in the SM-ARN model, we devise an optimal control policy that minimizes the time that the system spends in undesirable states.

The SM-ARN model is introduced in Section II. Having the objective of reducing the time that the regulatory network spends in undesirable states, we derive optimal intervention strategies for exponentially distributed inter-transition time distributions in section III. As a numerical study, we apply the SM-ARN intervention method to control a regulatory model of the mammalian cell-cycle in Section IV.

II. SEMI-MARKOV ASYNCHRONOUS REGULATORY NETWORKS

Similar to synchronous PBNs, in a SM-ARN, node values are quantized to a finite number of levels. A SM-ARN consists of a sequence $V = \{x_i\}_{i=1}^n$, of n nodes, where $x_i \in \{0, 1, \dots, d-1\}$. In the framework of gene regulation, each x_i represents the expression value of a gene selected from d possible quantization levels. It is common to mix terminology by referring to x_i as the i th gene. The gene-activity profile (GAP) is an n -tuple $\mathbf{x}(t) = (x_1(t), \dots, x_n(t))$ giving the expression values of the genes at time t , where $\mathbf{x}(t) \in$

$\{0, \dots, d-1\}^n$ [4]. There is a natural bijection between the GAP, $\mathbf{x}(t)$, and the decimal number $z(t)$ taking values in $\mathcal{W} = \{0, \dots, d^n - 1\}$. We define the states of an SM-ARN as the gene-activity profiles of the nodes in V . The decimal representation of a GAP facilitates the visualization of the intervention in a SM-ARN. At each time $t \in \mathbb{R}^+$, the state $z(t)$ of the SM-ARN is selected from the set of all possible states \mathcal{W} .

Considering two consecutive epoch times t_k and t_{k+1} per Fig. 2, the state of the SM-ARN for all the times $t_k \leq t < t_{k+1}$ is $z(t_k) = i$. At t_{k+1} , the model enters a new state $z(t_{k+1}) = j$. If τ_{k+1} is the time spent in state i prior to transition to state j , then we have $\tau_{k+1} = t_{k+1} - t_k$. In the SM-ARN model, this inter-transition interval is modeled with a non-negative random variable with probability distribution

$$P_{ij}(\tau) = P(\tau_{k+1} \leq \tau | z(t_k) = i, z(t_{k+1}) = j). \quad (1)$$

According to (1), the probability distribution of sojourn time in the current state i prior to transition to the successive state j could depend on both states. We require the inter-transition interval distributions, $P_{ij}(\tau)$, for any two directly connected states as one of the two sets of information needed to define an SM-ARN. Time-course data can provide the information leading to these distributions.

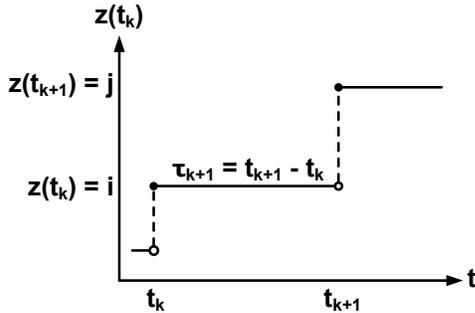


Fig. 2. A schematic of transition in SM-ARN with two consecutive epoch times t_k and t_{k+1} . The inter-transition interval, τ_{k+1} , is the sojourn time in state i prior to the transition to state j .

Borrowing the methodology proposed in [2], we proceed to define the *embedded-PBN* of an SM-ARN. The embedded-PBN of an SM-ARN models the probabilistic rule-based connections of gene interactions and constitutes the other set of information required for specification of an SM-ARN. The embedded-PBN specifies the oriented graph of the SM-ARN based on the predictors of the genes. The oriented graph of an SM-ARN is a directed graph whose vertices are the states of the SM-ARN in \mathcal{W} , and for which there is an edge between any two directly connected states. The weight of each edge is the transition probability between two vertices connected by that edge.

Let $\{\mathbf{f}_l\}_{l=1}^N$ be the set of N realizations of the embedded-PBN. If the genes are coupled, then at each simultaneous updating instant, one of the N possible realizations of the embedded-PBN is selected. Each vector-valued function \mathbf{f}_l has the form $\mathbf{f}_l = (f_{l1}, \dots, f_{ln})$. Each function f_{li} :

$\{0, \dots, d-1\}^n \rightarrow \{0, \dots, d-1\}$ denotes the predictor of gene i , when the realization l is selected. At each simultaneous updating instant a decision is made whether to switch the context of the network. The switching probability q is a system parameter. If at a particular updating instant, it is decided that the realization of the network should not be switched, then the embedded-PBN behaves as a fixed Boolean network and simultaneously updates the values of all the genes according to their current predictors. If it is decided that the network should be switched, then a realization of the embedded-PBN is randomly selected according to a selection distribution $\{r_l\}_{l=1}^N$. After selecting the vector-valued function \mathbf{f}_l , the values of the genes are updated according to the predictors determined by \mathbf{f}_l . We assume that the probability of selecting the i th realization, r_i , of the embedded-PBN is known [2]. In addition, we allow perturbations in the embedded-PBN, whereby each gene may change its value with a small probability p at each updating instant.

The graph specifying the relationships among the GAPs of an embedded-PBN, defined as above, can be represented as a Markov chain [2]. On the other hand, the graph of the relationships among the GAPs specified by the embedded-PBN is the regulatory graph of the SM-ARN. Originating from a state $z(t_k) = i$, the successor state $z(t_{k+1}) = j$ is selected randomly within the set \mathcal{W} according to the transition probability p_{ij} defined by regulatory graph of the SM-ARN:

$$p_{ij} = P(z(t_{k+1}) = j | z(t_k) = i), \quad \text{for all } i, j \in \mathcal{W}. \quad (2)$$

In other words, the oriented graph of an SM-ARN is the same as its regulatory graph. However, the update of states in the oriented graph of an SM-ARN occurs on various time-scales according to inter-transition interval distributions. We note that, the oriented graph of the SM-ARN defined by the embedded-PBN maintains the topology of the oriented graph generated by the experimentally validated predictors of genes.

Gene perturbation ensures that all the states of the SM-ARN communicate in the oriented graph. Hence, the fraction of time that the SM-ARN spends in each state in the long run is unambiguous and can be computed numerically using standard techniques [12].

III. STOCHASTIC CONTROL OF AN SM-ARN

Now that the dynamical behavior of a SM-ARN is described by a semi-Markov process, the theory of semi-Markov decision processes (SMDP) can be utilized to find an optimal sequence of interventions. Reducing the time that the regulatory network spends in undesirable states in the long run is the objective of the intervention problem. We suppose that the SM-ARN has a binary control input $u(t)$ taking values in $\mathcal{C} = \{0, 1\}$. Originating from state i , the successor state j is selected randomly within the set \mathcal{W} according to the transition probability $p_{ij}(u)$:

$$p_{ij}(u) \triangleq P(z(t_{k+1}) = j | z(t_k) = i, u(t_k) = u), \quad (3)$$

for all i and j in \mathcal{W} and for all u in \mathcal{C} . Moreover, the inter-transition interval distribution is also a function of the control u :

$$P_{ij}(\tau, u) \triangleq P(\tau_{k+1} \leq \tau | z(t_k) = i, z(t_{k+1}) = j, u(t_k) = u), \quad (4)$$

for all states i and j in \mathcal{W} , and all controls u in \mathcal{C} . We associate a rate of reward $r(z(t), u(t))$ for sojourning in state $z(t)$ per unit of time while the control is $u(t)$. Considering consecutive epoch times t_k and t_{k+1} , the rate of reward $r(z(t), u(t))$ is constant for all $t_k \leq t < t_{k+1}$. It is equal to $r(i, u)$, whenever $z(t_k) = i$ and $u(t_k) = u$. The rate of reward of undesirable states is lower than those for desirable states. In practice, the rates of reward have to capture the relative preferences for the different states. A state in which metastatic biological components are active is considered to be undesirable. We also consider the cost of applying a control action, which reduces the rate of reward of each state.

To devise a stationary intervention policy, we consider the discounted reward formulation. The discounting factor per unit of time, $\lambda \in (0, 1)$, insures the convergence of the expected total reward over the long run [13]. Including a discounting factor in the expected total reward signifies that the incurred reward at a later time is less significant than the incurred reward at an earlier time. In the case of cancer therapy, the discounting factor attempts to capture the fact that obtaining treatment earlier is better than postponing treatment to a later stage.

Among all admissible policies Π , the SMDP methodology finds a policy $\pi = \{\mu_0, \mu_1, \dots\}$, where $\mu_t : \mathcal{W} \rightarrow \mathcal{C}$ is the decision rule at time t , that maximizes the expected total discounted reward. The infinite-horizon expected total discounted reward, given the policy π and the initial state i , is

$$J_\pi(i) = \lim_{M \rightarrow \infty} E \left\{ \int_0^{t_M} e^{-\lambda t} r(z(t), \mu(z(t))) dt \right\}, \quad (5)$$

where t_M is the M -th epoch time. We seek a policy π^* that maximizes the value function for each state i . An optimal control policy is a solution of the SMDP with discounted reward:

$$\pi^*(i) = \arg \max_{\pi \in \Pi} J_\pi(i), \quad \forall i \in \mathcal{S}. \quad (6)$$

Intervention using the policy π^* increases the time spent in desirable states determined through appropriate assignment of rate of rewards $r(z(t), u(t))$ to each state-control pair $(z(t), u(t))$.

The amount of data observed from a biological system is usually limited. Instead of using the data to estimate an arbitrary inter-transition interval distribution, we can postulate a class of parametric distributions whose members can be defined by a small number parameters, e.g. the expected value. Here, we assume that the distribution of the inter-transition interval follows an exponential distribution. If all the inter-transition intervals of state i are exponentially distributed, then the sojourn time of state i possesses an

exponential distribution:

$$P_i(\tau, u) = 1 - e^{-\nu_i(u)\tau} \quad \tau \geq 0. \quad (7)$$

In (7), $\nu_i(u)$ is the rate of transition from state i whenever the control has value u . Practically, the rates $\nu_i(u)$ are bounded for all states i in \mathcal{W} , and all controls u in \mathcal{C} . Assuming that the inter-transition interval is exponentially distributed, we use ‘‘uniformization’’ to find a solution to the optimization problem in (6). Due to lack of space, we skip the details and refer to [13] for treatment of the uniformization method.

IV. CONTROL OF A MAMMALIAN CELL CYCLE RELATED NETWORK

Faure *et al.* recently proposed a Boolean model for the mammalian cell cycle [10]. In this section, we design a SM-ARN that is a probabilistic version of this Boolean model. We construct a SM-ARN that postulates the cell-cycles with mutated phenotype. The proposed intervention method is then applied to hinder the cell growth in the absence of growth factors.

The authors of [10] have been able to quantitatively reproduce the main known features of the wild-type biological system, as well as the consequences of several types of mutations. The regulatory graph for the wild-type mammalian cell-cycle network, as it is presented in [10], is shown in Fig.3.

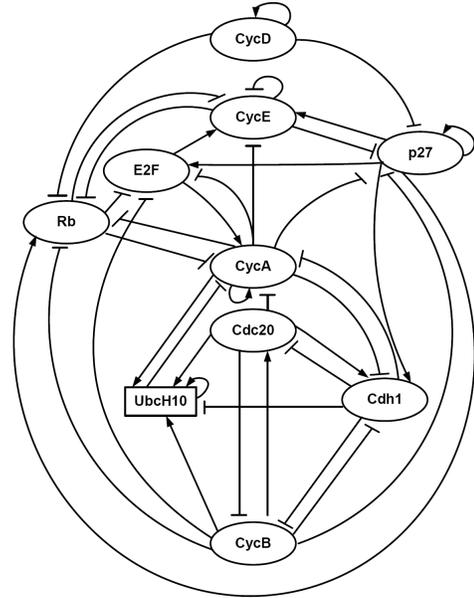


Fig. 3. Logical regulatory graph for the mammalian cell cycle network as it was presented in [10]. Each node represents the activity of a key regulatory element. Blunt arrows stand for inhibitory effects, normal arrows for activations.

The cell cycle involves a succession of molecular events leading to the reproduction of the genome of a cell and its division into two daughter cells. Mammalian cell division is tightly controlled. In a growing mammal, the cell division should coordinate with the overall growth of the organism. This coordination is controlled via extra-cellular signals.

These signals indicate whether a cell should divide or remain in a resting state. The positive signals, or growth factors, elicit the activation of Cyclin D (CycD) in the cell.

The key genes in this model are CycD, retinoblastoma (Rb), and p27. Rb is a tumor-suppressor gene. This gene is expressed in the absence of the cyclins, which inhibit the Rb by phosphorylation. Whenever p27 is present, Rb can also be expressed even in the presence of CycE or CycA. Gene p27 is active in the absence of the cyclins. Whenever p27 is present, it blocks the action of CycE or CycA. Hence, it stops the cell cycle.

The preceding explanation represents the wild-type cell-cycle model. We assume p27 is mutated and its logical rule is always zero (OFF). This mutation is listed in [10] as one of many possible mutations in the cell cycle network. In this cancerous scenario, p27 can never be activated. This mutation introduces a situation where both CycD and Rb may be inactive. As a result, in this mutated phenotype, the cell cycles in the absence of any growth factor. In summary, when p27 is mutated we consider the logical states in which both Rb and CycD are down-regulated as *undesirable states*.

The Boolean functions corresponding to the cancerous scenario are derived to construct the embedded-PBN of the cell-cycle's SM-ARN. The defined embedded-PBN maintains the topology of the oriented graph generated by these Boolean functions. To this end, we assume that the extracellular signal to the cell-cycle model is a latent variable. The growth factor is not part of the cell and its value is determined by the surrounding cells. The expression of CycD changes independently of the cell's content and reflects the state of the growth factor. Depending on the expression status of CycD, we obtain two constituent Boolean networks for the embedded-PBN. The first constituent Boolean network is determined from the Boolean functions defined in Fig. 3 when the value of CycD is equal to zero. Similarly, the second constituent Boolean network is determined by setting the variable of CycD to one. To completely define the embedded-PBN, the switching probability, the perturbation probability, and the probability of selecting each constituent Boolean network have to be specified. We assume that these are known.

The SM-ARN for the cell-cycle consists of nine genes: CycD, Rb, E2F, CycE, CycA, Cdc20, Cdh1, UbcH10, and CycB. The above order of genes is used in the binary representation of the logical states, with CycD as the most significant bit and CycB as the least significant bit. This order of genes in the logical states facilitates the presentation of our results and does not affect the computed control policy.

We also have to specify the inter-transition interval distributions between the logical states to fully define the cell-cycle's SM-ARN. Although such information is likely to become available from time-course data in the near future, it is not available today. Here, we simply assume that all inter-transition intervals between logical states are exponentially distributed. If $\tau(i, j)$ is the sojourn time in logical state i before transition to state j , then we need the rate of the transition from state i to state j to specify its distribution.

We use the gene-expression data to determine the probability p_{ij} of the transition from state i to state j in the embedded-PBN. We assume that the rate of the transition from state i to state j is assigned such that

$$P\{\tau(i, j) < \min_{\substack{k=1, \dots, |S| \\ k \neq j}} \tau(i, k)\} = p_{ij}. \quad (8)$$

In other words, the probability of the first transition out of state i to state j is equal to the transition probability p_{ij} . The left side of equation (8) can be determined for exponentially distributed sojourn times.

Avoiding the logical states with simultaneously down-regulated CycD and Rb as our objective, we apply the intervention method described in Section III to the constructed SM-ARN. If the control is high, $u = 1$, then the state of the control gene is reversed; if $u = 0$, then the state of the control gene remains unchanged. The control gene can be any one of the the genes in the model except CycD.

We assume that the reward of the logical states with down-regulated Rb and CycD is lower than those for the states in which these two genes are not simultaneously down-regulated. We also consider the cost of applying a control action, which reduces the reward of each logical state. We postulate the following rate-of-reward function:

$$r(i, u) = \begin{cases} 6, & \text{if } u = 0 \text{ and } (CycD, Rb) \neq (0, 0) \text{ in } i \\ 1, & \text{if } u = 0 \text{ and } (CycD, Rb) = (0, 0) \text{ in } i \\ 5, & \text{if } u = 1 \text{ and } (CycD, Rb) \neq (0, 0) \text{ in } i \\ 0, & \text{if } u = 1 \text{ and } (CycD, Rb) = (0, 0) \text{ in } i. \end{cases} \quad (9)$$

We select an arbitrary rate of reward; however, the reward and control cost are selected so that applying the control to prevent the undesirable logical states is preferable in comparison to not applying control and remaining in an undesirable state. In practice, the reward values have to capture the benefits and costs of the intervention and the relative preference of the states. They have to be set in consultation with physicians relying on their clinical judgement.

Assuming the preceding rate-of-reward function, we compute a control policy for the SM-ARN of the cell cycle. Fig. 4 depicts the fraction of time that the SM-ARN spends in each logical state when there is no intervention. Per Fig. 4, the aggregated fraction of time that the cell-cycle model spends in the logical states with simultaneously down-regulated CycD and Rb is 49%.

From the Fig. 5, it is clear that after intervention using Rb, the fraction of time that the model spends in the logical states is significantly altered. Directly using Rb as the control gene, we can reduce the fraction of time that the model spends in the undesirable states to less than 2%. Fig. 5 depicts the fraction of time that the SM-ARN spends in each logical state when the intervention is applied using Rb. If the direct control of Rb is not feasible, then one can use E2F as the control gene. In this case the system spends slightly more time in the undesirable states, but still less than 4.5%. For all practical purposes, the difference between the

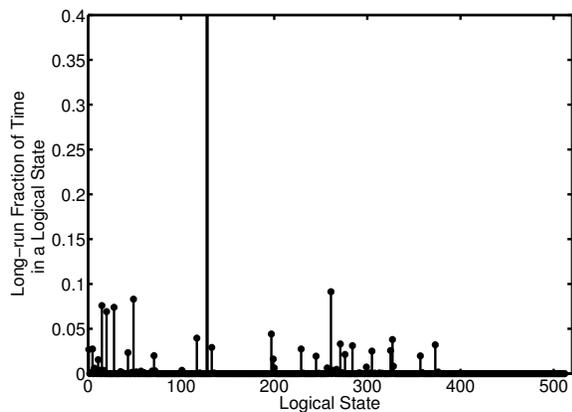


Fig. 4. The fraction of time that the SM-ARN of mammalian cell cycle spends in each logical state prior to intervention. The vertical line separates the undesirable logical states from the desirable logical states.

performance achieved using either of these two control genes is insignificant.

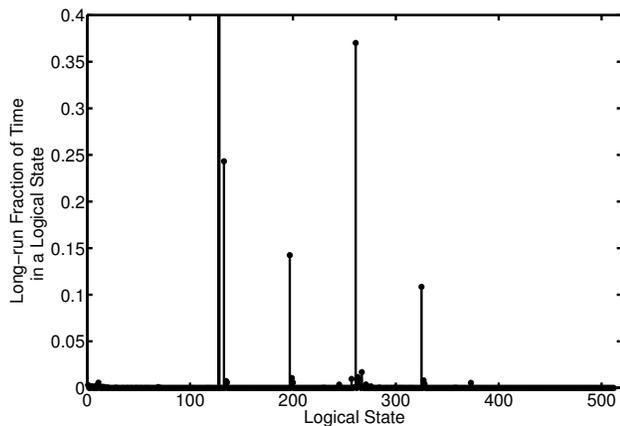


Fig. 5. The fraction of time that the SM-ARN of mammalian cell cycle spends in logical states after intervention using Rb as the control gene. The vertical line separates the undesirable logical states from the desirable logical states.

V. CONCLUSION

In this work, we proposed an asynchronous regulatory network model with discrete state space. We formulated the optimal intervention strategies for this class of regulatory networks. Since asynchronism at the node level has practical limitations, we introduced the SM-ARN model, in which the asynchronism is at the logical-state level. Empirically measurable timing information of biological systems can be directly incorporated into the SM-ARN model to determine the time-delay distributions between transitions from one logical state to another logical state. We modeled the dynamics of a mutated mammalian cell-cycle regulatory network using the SM-ARN. The proposed intervention method for the SM-ARN was then used to design a strategy to influence the dynamics of the constructed SM-ARN. The goal of the intervention was to reduce the long-run likelihood of the cell growth in the absence of growth factors. The presented

numerical studies indicate that our intervention method effectively alters the dynamics of the cell-cycle model.

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