

# External Control in a Special Class of Probabilistic Boolean Networks

Ranadip Pal, Aniruddha Datta, Michael L. Bittner and Edward R. Dougherty

**Abstract**—Instantaneously Random Probabilistic Boolean Networks (PBN's) have been recently introduced as a rule-based paradigm for modeling gene regulatory networks. Furthermore, it has been shown how ideas from optimal control of Markov decision processes can be used to desirably affect the dynamic evolution of the state of such a network. This paper considers the problem of optimal intervention in *context sensitive* PBNs, i.e. PBNs in which the state evolves over one or more time steps as a Boolean network with a fixed set of predictor functions until a random event such as an external stimulus (or a novel context) causes the network to switch to a new Boolean one. In addition, the paper seeks to accommodate random gene perturbations such as one or more gene flippings provided, at a given time step, the state either evolves according to the predictor functions or undergoes random perturbations but both do not occur simultaneously. Another novelty of the results reported in this paper is that the example PBN used for control is derived from steady-state (long run) considerations and the concept of *influence* is used to choose the intervention gene. For a PBN with  $n$  genes and  $k$  possible predictor sets, two possible solutions to the control problem are presented. In the first, the dimension of the state space is artificially increased to  $2^n k$  while in the second, it is shrunk back to  $2^n$ , the usual state dimension encountered in earlier work with instantaneously random PBNs.

## I. INTRODUCTION

*Instantaneously Random* Probabilistic Boolean Networks (PBNs), which form a subclass of Markovian Genetic Regulatory Networks, have been recently introduced as a rule-based paradigm for modeling gene regulatory networks [1], [2]. In these networks, the predictor function for updating each gene is randomly chosen at each time step from among several possible predictor functions in accordance with a fixed probability distribution. In other words, for an instantaneously random PBN, the wiring diagram of the network randomly changes from one time step to the next. This represents one end of the spectrum. At the other end

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of the spectrum are Boolean networks [3] where each gene is associated with a *fixed* Boolean predictor for all time.

For modeling biological reality, perhaps a more appropriate paradigm is provided by the so called *context sensitive* PBNs which represent an intermediate scenario between these two extremes. In such a PBN, the Boolean function and the predictor set for each gene can remain fixed at a specific selection for several time points before another selection takes place, possibly in response to some random event, such as an external stimulus, or a novel context. In this paper, we will study the problem of intervention in context sensitive PBNs.

The problem of intervention using instantaneously random PBNs has been quite well studied in the recent past. Three different approaches have been proposed to date: (i) resetting the state of the PBN, as necessary, to a more desirable initial state and letting the network evolve from there [4]; (ii) changing the steady-state (long run) probability distribution of the network by minimally altering its rule based structure [5]; and (iii) manipulating external (control) variables that affect the transition probabilities of the network and can, therefore, be used to desirably affect its dynamic evolution over a finite time horizon [6], [7]. All of the above results were obtained by exploiting the fact that the dynamic behaviour of an instantaneously random PBN could be modeled using a Markov Chain [1], thereby making them amenable to the theory of Markov Chains and Markov Decision Processes.

In this paper, we significantly extend the results of [6] in several directions. First, instead of an instantaneously random PBN, we consider a context sensitive PBN where at each time step, the state transitions as that of a Boolean network, following which the Boolean network is altered only if a certain random event occurs with a probability  $q$ . In other words, most of the time, the context sensitive PBN evolves as a standard Boolean network until the occurrence of a random event causes a new set of predictors to be randomly chosen for the subsequent evolution. Second, we allow the possibility that each gene may randomly change value with a small perturbation probability  $p$ , thereby ensuring that all the possible states communicate. Third, we use the concept of gene *influence*, introduced in [1], to choose the particular gene with which to intervene and demonstrate that intervening with a higher influence gene results in better performance. Finally, the example PBN used for control is derived from steady-state (long run) considerations which makes the intervention result much more biologically appealing.

Regarding the final point above, it is appropriate to note that most microarray-based gene-expression studies do not involve controlled time series experimental data; rather, it is assumed that data result from sampling from the steady state. Thus, under the assumption that we are sampling from the steady state, a key criterion for checking the validity of a designed network is that much of its steady-state mass lies in the states observed in the sample. In the Boolean network framework, this signifies a close resemblance between the observed data samples and the attractors of the designed Boolean Networks. We can use the Bayesian Connectivity based approach [9] to construct Probabilistic Boolean Networks with the expectation of generating networks having few, very strong attractors, highly similar to the original observations, mimicing biological state stability and determinism. This approach gives us a number of highly probable Boolean Networks and Bayesian scores for each one of them. These networks can be combined with probabilities proportional to their scores to form a PBN. In this paper, we derive expressions for the state transition probabilities of a PBN formed from a number of such Boolean Networks and devise a strategy to shift the state vector from undesirable states towards more desirable ones using genomic control.

## II. DEFINITIONS, NOTATIONS AND PROBLEM FORMULATION

A *Boolean Network* (BN)  $B = (V, F)$  on  $n$  genes is defined by a set of nodes/genes  $V = \{x_1, \dots, x_n\}$ ,  $x_i \in \{0, 1\}$ ,  $i = 1, \dots, n$ , and a list of Boolean **predictor functions**  $F = (f_1, \dots, f_n)$ ,  $f_i : \{0, 1\}^n \rightarrow \{0, 1\}$ ,  $i = 1, \dots, n$ . Each node  $x_i$  represents the state/expression of the gene  $x_i$ , where  $x_i = 0$  means that the gene  $i$  is OFF and  $x_i = 1$  means that the gene  $i$  is ON. The function  $f_i$  is the **predictor function** for that gene. Updating the states of all of the genes in  $B$  is done synchronously at every time step according to their predictor functions. A *Probabilistic Boolean Network* (PBN) consists of a set of  $n$  genes,  $g_1, g_2, \dots, g_n$ , each taking values in a finite set  $V = \{0, 1\}$ , and a set of vector-valued network functions,  $\mathbf{f}_1, \mathbf{f}_2, \dots, \mathbf{f}_k$ , governing the state transitions of the genes. The choice of which network function  $\mathbf{f}_j$  to apply is governed by a selection procedure. Specifically, at each time point a random decision is made as to whether to switch the network function for the next transition, with the probability  $q$  of a switch being a system parameter. If a decision is made to switch the network function, then a new function is chosen from among  $\mathbf{f}_1, \mathbf{f}_2, \dots, \mathbf{f}_k$ , with the probability of choosing  $\mathbf{f}_j$  being the selection probability  $c_j$ . In other words, each network function  $\mathbf{f}_j$  determines a BN and the PBN behaves as a fixed BN until a random decision (with probability  $q$ ) is made to change the network function according to the probabilities  $c_1, c_2, \dots, c_k$  from among  $\mathbf{f}_1, \mathbf{f}_2, \dots, \mathbf{f}_k$ . The PBN that we have just introduced is called a *context sensitive PBN*, and such a PBN switches between the BNs defined by the network functions according to the switching probability  $q$ . In the special case when  $q = 1$ , i.e. at each time point the network function is switched, the

resulting PBN is called an *instantaneously random PBN* and this is the first class of PBNs to be considered in the literature [1]. For the context sensitive PBNs of this paper, we also assume that at each time point there is a probability  $p$  of any gene changing its value uniformly randomly among the other possible values in  $V$ . Since there are  $n$  genes, the probability of there being a random perturbation at any time point is  $1 - (1 - p)^n$ . The state space  $S$  of the network together with the set of network functions, in conjunction with transitions between the states and network functions, determine a Markov chain. The random perturbation makes the Markov chain ergodic, meaning that it has the possibility of reaching any state from any other state and that it possesses a long-run (steady-state) distribution.

The state vector  $x(t)$  at any time step  $t$  is essentially an  $n$ -digit binary number  $[x_1 x_2 \dots x_n]$  whose decimal equivalent is given by

$$z(t) = \sum_{j=1}^n 2^{n-j} x_j(t). \quad (1)$$

As  $x(t)$  ranges from  $000 \dots 0$  to  $111 \dots 1$ ,  $z(t)$  takes on all values from  $0$  to  $2^n - 1$ . For a context sensitive PBN, the state  $z(t)$  at time  $t$  could be originating from any one of the  $k$  possible networks. In order to keep track of the network emitting a particular state let us redefine the states by incorporating the network number inside the state label. Since we have  $k$  different BNs forming the PBN, the total number of states becomes  $2^n k$  and let us label these states as  $S_0, S_1, \dots, S_{2^n k - 1}$  where for each  $r = 1, 2, \dots, k$ , states  $S_{2^n(r-1)}, S_{2^n(r-1)+1}, \dots, S_{2^n r - 1}$  belong to network  $r$ . Equivalently  $S_{2^n(r-1)+i}$  corresponds to  $z_{r_i}$  where  $z_{r_i}$  is the decimal representation of the  $i$ th state in the network  $r$ . Let the redefined state at time  $t$  be denoted by  $w(t)$ .

## III. COMPUTATION OF TRANSITION PROBABILITIES FOR A CONTEXT SENSITIVE PBN SUBJECT TO RANDOM PERTURBATIONS

In this section, we derive expressions for the transition probabilities in a context sensitive PBN subject to perturbations. To do so, we note that in such a PBN, the following mutually exclusive sequence of events can occur at any time point  $t$

(1) The current network function is applied, the PBN transitions accordingly, and the network function remains the same for the next transition.

(2) The current network function is applied, the PBN transitions accordingly, and a new network function is selected for the next transition.

(3) There is a random perturbation and the network function remains the same for the next transition.

(4) There is a random perturbation and a new network function is selected for the next transition.

Let  $p$  denote the probability that the value of any particular gene undergoes a random perturbation and let us assume that the individual genes perturb independently. In addition, let  $q$  denote the probability that the network

function switches at any given time point. Then we can proceed as follows to determine the transition probability of going from state  $a$  to state  $b$ . There are two possible cases to consider:

**Case 1.**  $[a/2^n]$  and  $[b/2^n]$  are the same (i.e.  $(2^n(r-1)) \leq a, b \leq 2^n r - 1$  for the same  $r$ ). This corresponds to the events (1) and (3) above and the transition probabilities are given by

$$Pr(w(t+1) = b/w(t) = a) = (1-q)(1-p)^n f_{r,a,b} + (1-q)(1-p)^{n-h} p^h s(h) \quad (2)$$

where  $h$  = the Hamming Distance between  $mod(a, 2^n)$  and  $mod(b, 2^n)$ , i.e. the number of genes which differ between the two states ;

$c_i$  = the probability of selecting network  $i$ ;

$mod(x, y)$  = the remainder left over when  $x$  is divided by  $y$ ;

$$f_{r,a,b} = \begin{cases} 1 & \text{if } a \text{ transitions to } b \text{ in 1 step in network } r \\ 0 & \text{otherwise;} \end{cases}$$

$$s(h) = \begin{cases} 0 & \text{if } h = 0 \\ 1 & \text{otherwise.} \end{cases}$$

The first term in Equation 2 corresponds to event (1) above where  $(1-q)$  is the probability that the network selection does not change and  $(1-p)^n$  is the probability that none of the  $n$  genes undergoes a perturbation. Here we have made the assumption that the network selection and random gene perturbation are independent events. The  $f_{r,a,b}$  term is 1 if that particular transition is possible in the  $r$ th Boolean Network. The second term corresponds to event (3) where  $h$  genes have to be perturbed to go from state  $a$  to state  $b$ .

**Case 2.**  $(2^n(r_1 - 1)) \leq a \leq 2^n r_1 - 1$  and  $(2^n(r_2 - 1)) \leq b \leq 2^n r_2 - 1$  where  $r_1$  and  $r_2$  are different. This corresponds to events (2) and (4) above and the transition probabilities are given by

$$Pr(w(t+1) = b/w(t) = a) = q \frac{c_{r_2}}{\sum_{i=1, i \neq r_1}^k c_i} (1-p)^n f_{r_1, a, b} + q \frac{c_{r_2}}{\sum_{i=1, i \neq r_1}^k c_i} (1-p)^{n-h} p^h s(h). \quad (3)$$

Define

$$g(a, b) = \begin{cases} 1 & \text{if } [a/2^n] - [b/2^n] = 0 \\ 0 & \text{otherwise.} \end{cases}$$

Then a unified transition probability expression encompassing the two cases considered is given by

$$Pr(w(t+1) = b/w(t) = a) = [(1-q)(1-p)^n f_{r,a,b} + (1-q)(1-p)^{n-h} p^h s(h)] g(a, b) + [q \frac{c_{r_2}}{\sum_{i=1, i \neq r_1}^k c_i} (1-p)^n f_{r_1, a, b} + q \frac{c_{r_2}}{\sum_{i=1, i \neq r_1}^k c_i} (1-p)^{n-h} p^h s(h)] (1 - g(a, b)). \quad (4)$$

By letting  $a$  and  $b$  range over all integers from 0 to  $2^k - 1$  and using Equation (4), we can determine all the entries of the  $2^k \times 2^k$  matrix of transition probabilities.

From a practical point of view, it may not be possible to detect the Boolean Network from which the current gene activity profile is being emitted. In most cases, we will be having knowledge of only the states of the individual genes. To handle such situations, we can proceed as follows to derive an expression for the transition probability from state  $s_2$  to state  $s_1$  where these states run from 0 to  $2^n - 1$  and reflect only the expression status of the  $n$  gene state vector. Clearly,

$$\begin{aligned} Pr[z(t+1) = s_1/z(t) = s_2] &= \sum_{i=1}^k Pr[z(t+1) = s_1, s_2 \text{ belongs to network } i / z(t) = s_2] \\ &= \sum_{i=1}^k Pr[z(t+1) = s_1/z(t) = s_2, s_2 \text{ belongs to network } i]. Pr[s_2 \text{ belongs to network } i] \\ &= \sum_{i=1}^k Pr[z(t+1) = s_1/w(t) = s_2 + 2^n(i-1)]. c_i \\ &= \sum_{i=1}^k \sum_{j=1}^k c_i. Pr[w(t+1) = s_1 + 2^n(j-1) / w(t) = s_2 + 2^n(i-1)] \quad (5) \end{aligned}$$

where  $s_1$  and  $s_2$  run from 0 to  $2^n - 1$ . Note that here the state  $s_1$  is equivalent to the distinct states  $s_1, s_1 + 2^n, \dots, s_1 + (k-1)2^n$  in the previous  $2^k$  formulation. Similarly  $s_2$  here is equivalent to  $s_2, s_2 + 2^n, \dots, s_2 + (k-1)2^n$  in the earlier formulation. By letting  $s_1$  and  $s_2$  range from 0 to  $2^n - 1$  and using Equation (5), we can derive the  $2^n \times 2^n$  transition probability matrix  $A$  corresponding to the context sensitive PBN.

#### IV. CONTROL IN CONTEXT SENSITIVE PBNs

In this section, we consider the problem of external control in a context sensitive PBN. Towards this end, suppose that a probabilistic Boolean network with  $n$  genes has  $m$  control inputs  $u_1, u_2, \dots, u_m$ , each of which can take on only the binary values zero or one. Then at any given time step  $t$ , the row vector  $u(t) \triangleq [u_1(t), u_2(t), \dots, u_m(t)]$  describes the complete status of all the control inputs. Clearly,  $u(t)$  can take on all binary values from  $[0, 0, \dots, 0]$  to  $[1, 1, \dots, 1]$ .

One can equivalently represent the control input status using the decimal number

$$v(t) = \sum_{i=1}^m 2^{m-i} u_i(t). \quad (6)$$

As  $u(t)$  takes on binary values from  $[0, 0, \dots, 0]$  to  $[1, 1, \dots, 1]$ , the variable  $v(t)$  ranges from 0 to  $2^m - 1$ . We can equivalently use  $v(t)$  as an indicator of the complete control input status of the probabilistic Boolean network at time step  $t$ .

If a control action is applied, then the transition probability expressions will change. Suppose that our control action consists of forcibly altering the value of a single

gene (say the gene at position  $g$ ) from 0 to 1 or from 1 to 0. Thus,  $m = 1$  here. Then the new transition probabilities with control (Prc1) are given by

$$\begin{aligned} \text{Prc1}(w(t+1) = b/w(t) = a) = \\ \text{Pr}(w(t+1) = b/w(t) = a + 2^{n-g})\text{func}(a) + \\ \text{Pr}(w(t+1) = b/w(t) = a - 2^{n-g})(1 - \text{func}(a)) \end{aligned} \quad (7)$$

where  $\text{func}(a) = \begin{cases} 1 & \text{if state of gene } g \text{ is 0 for } a \\ 0 & \text{if state of gene } g \text{ is 1 for } a \end{cases}$  and the transition probabilities  $\text{Pr}$  without control are given by Equation (4).

Here  $a$  and  $b$  range over 0 through  $2^n - 1$ . As before we can reduce the dimension of the state space by replacing the  $w$ 's in (7) by  $z$ 's and using Equation (5) to determine the transition probabilities without the control action:

$$\begin{aligned} \text{Prc1}(z(t+1) = b/z(t) = a) = \\ \text{Pr}(z(t+1) = b/z(t) = a + 2^{n-g})\text{func}(a) + \\ \text{Pr}(z(t+1) = b/z(t) = a - 2^{n-g})(1 - \text{func}(a)). \end{aligned} \quad (8)$$

By letting  $a$  and  $b$  vary over 0 to  $2^n - 1$  and making use of (8), we can determine the  $2^n \times 2^n$  matrix  $A(v(t))$  of control-dependent transition probabilities.

In the rest of this section, we formulate and solve the control problem assuming  $2^n$  states and the availability of full state information. The same development can be carried out for the  $2^{nk}$  state formulation if we simultaneously have the gene state information and the network labels. As shown in [6], the one-step evolution of the probability distribution vector in the case of a PBN containing  $2^n$  states with control inputs takes place according to the equation:

$$pd(t+1) = pd(t)A(v(t)) \quad (9)$$

where  $pd(t)$  is the  $2^n$  dimensional state probability distribution vector and  $A(v(t))$  is the  $2^n \times 2^n$  matrix of control-dependent transition probabilities determined using (8).

Since the transition probability matrix here is a function of the control input  $v(t)$ , the evolution of the probability distribution vector of the PBN with control, now depends not only on the initial distribution vector but also on the values of the control input at different time steps. Furthermore, intuitively it appears that it may be possible to make the states of the network evolve in a desirable fashion by appropriately choosing the control input at each time step.

These ideas were formalized in [6] to arrive at the following finite horizon optimization problem, Given an initial state  $z_0$ ,

$$\min_{\mu_0, \mu_1, \dots, \mu_{M-1}} E \left[ \sum_{t=0}^{M-1} C_t(z_t, \mu_t(z_t)) + C_M(z_M) \right] \quad (10)$$

subject to

$$\text{Pr}(z(t+1) = j | z(t) = i, v(t)) \text{ given by equation (8),}$$

where

- $M$  represents the treatment/intervention window;
- $\mu_t : [0, 1, 2, \dots, 2^n - 1] \rightarrow [0, 1, 2, \dots, 2^m - 1]$ ,  $t = 0, 1, 2, \dots, M-1$  are functions mapping the state space into the control space;
- $C_t(z_t, v_t)$  is the one step cost of applying the control  $v_t$  at state  $z_t$ ;
- and  $C_M(z_M)$  is the terminal cost associated with the state  $z_M$ .

As discussed in [6], the consideration of such an optimization problem could be naturally motivated in the context of cancer treatment applications where one must choose between a number of alternative treatments to be applied over a finite horizon of time. Once input from biologists/clinicians has been used to select an appropriate cost function and an appropriate treatment window, the control problem is essentially reduced to that of controlling a Markov Chain over a finite horizon.

The dynamic programming solution to (10) is given by [8], [6]:

$$J_M(z_M) = C_M(z_M) \quad (11)$$

$$J_t(z_t) = \min_{v_t \in \{0, 1, \dots, 2^m - 1\}} \left[ C_t(z_t, v_t) + \sum_{j=0}^{2^n - 1} \text{Pr}(z_t/j, v_t) \cdot J_{t+1}(j) \right] \quad t = 0, 1, \dots, M-1. \quad (12)$$

Furthermore, if  $v_t^* = \mu_t^*(z_t)$  minimizes the right hand side of (12) for each  $z_t$  and  $t$ , the control law  $\pi^* = \{\mu_0^*, \mu_1^*, \dots, \mu_{M-1}^*\}$  is optimal.

*Remark 1: Note that the optimal control problem (10) and its solution (11), (12) are from a very general setting. However, in our case, the class of allowable controls is severely constrained since our control action consists of forcibly altering the expression status of only one single gene. This is dictated primarily by the kind of interventions that are biologically feasible at the current time.*

## V. SELECTING THE GENE USED TO ACHIEVE THE CONTROL

Given a particular target gene, there may be several genes that are good predictors for it. Among a set of predictors for a particular gene, some of them may have more impact on the value of the target gene than the others. For instance, in many cancer studies it has been shown that p53 has a much more profound effect on the cell cycle regulator gene WAF1/p21 than other predictors of WAF1 like AP2, BRCA1 [10]. In view of this, one can define ([1]) the *influence* of the variable  $x_j$  on the Boolean function  $f$ . To do so, let  $D$  be the probability mass distribution over the states of a Boolean network and let  $\frac{\partial f(x)}{\partial x_j}$  be the partial derivative of the Boolean function  $f$  with respect to the argument  $x_j$  [1].

$$\text{Then } I_j(f) = E_D \left[ \frac{\partial f(x)}{\partial x_j} \right]$$

$= \Pr\{\frac{\partial f(x)}{\partial x_j} = 1\} = \Pr\{f(x) \neq f(x^{(j)})\}$  where  $x^{(j)}$  is the same as  $x$  except that the  $j$ th component is toggled. In this paper, we will assume that the distribution  $D$  is uniform.

The main idea behind the influence definition is to quantify the amount by which the gene  $x_j$  affects the value of the function  $f$ . If the value of the function  $f$  changes on toggling the value of gene  $x_j$  for most gene activity profiles  $x$ , then the influence of the  $j$ th gene on  $f$  is high. For the case of PBNs, let  $F_i$  be the set of predictors for gene  $x_i$  with corresponding probabilities  $c_1^{(i)}, \dots, c_{l(i)}^{(i)}$ . Let  $I_k(f_j^{(i)})$  be the influence of variable  $x_k$  on the predictor  $f_j^{(i)}$ , then the influence of gene  $x_k$  on gene  $x_i$  is given by [1]

$$I_k(x_i) = \sum_{j=1}^{l(i)} I_k(f_j^{(i)}) \cdot c_j^{(i)}$$

We can use the *influence* of genes to select the control gene. As an example, say we have drugs  $d_1, d_2, \dots, d_r$  which can affect genes  $g_1, g_2, \dots, g_r$  respectively. Biological and economic considerations may constrain us to use only one drug at a time. Then we can use the gene which has the highest influence on the target gene  $g_r$ . The influence can be directly calculated from the PBN as given by the previous formula or it can be approximated from the observed gene activity profiles. The hope is that by selecting a gene with high influence as the control gene, we will be able to carry out a more cost-effective intervention. The simulation results presented in the next section show that such an expectation is met.

## VI. EXAMPLE USING GENE EXPRESSION DATA

In this section, we apply the results of this paper to a context sensitive PBN derived from gene expression data collected in a study of metastatic melanoma [11]. In this expression profiling study, the abundance of mRNA for the gene WNT5A was found to be highly discriminating between cells with properties typically associated with high metastatic competence versus those with low metastatic competence. These findings were validated and expanded in a second study [12] in which experimentally increasing the levels of the Wnt5a protein secreted by a melanoma cell line via genetic engineering methods directly altered the metastatic competence of that cell as measured by the standard in vitro assays for metastasis. Furthermore, it was found that an intervention that blocked the Wnt5a protein from activating its receptor, the use of an antibody that binds Wnt5a protein, could substantially reduce Wnt5a's ability to induce a metastatic phenotype. This suggests that a reasonable control strategy would be to use an intervention that reduces the WNT5A gene's action in affecting biological regulation, since the available data suggests that disruption of this influence could reduce the chance of a melanoma metastasizing, a desirable outcome. Instantaneously random PBNs derived from the same expression data have been used in [6], [7] for demonstrating earlier intervention strategies.

Here, we consider a 7 gene network containing the genes WNT5a, pirin, S100P, RET1, MART1, HADHB and STC2. To obtain the PBN, we used the Bayesian connectivity based

approach of [9] to construct a number of highly probable boolean networks which were then combined in the ratio of their Bayesian scores. One of the generated networks with high score is shown in Figure 1 where the states are labeled from 0 to 127 (i.e.  $2^7 - 1$ ). The figures for the other three BNs used to generate the PBN is available at <http://gsp.tamu.edu/Publications/Control/figures.htm>. The networks are derived from the steady state gene expression data and the attractor states and the level sets are clearly shown. Furthermore, observe that in each of these networks, the state enters an attractor cycle in a small number of steps (at most nine). This is consistent with current biological thought.

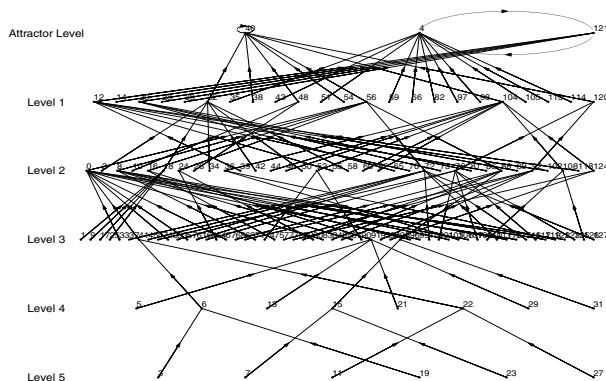


Fig. 1. Network 2

Next, the control strategy of the last section was applied to this network with Pirin chosen as the control gene and  $p = q = 0.01$ . Figure 2 shows the expected cost for a finite horizon problem of length 5 originating from each of the 128 states. In these simulations, the problem formulation for  $2^n$  states was used. The cost of control was assumed to be 0.5 and the states were assigned a terminal penalty of 5 if WNT5a was 1 and 0 if WNT5a was 0. The control objective, of course, was to try and down-regulate the WNT5a gene. From Figure 2, it is clear that the expected cost with control is much lower than that without control, which is intuitively appealing. If the length of the control horizon is increased, Figure 3 shows that all the initial states start yielding almost the same expected cost. This may be due to the fact that the maximum level of the BNs forming the PBN is 9 and the Markov chain is also ergodic. If, on the other hand, the  $2^n * k$  formulation is used, the expected costs for different initial states become almost equal after a larger number of time steps (data not shown). This is possibly due to the fact that no averaging is used in that formulation.

Next we studied the relationship between the influence of a control gene and its effectiveness in carrying out the intervention. The influences of the other six genes on wnt5a are as follows: pirin=1; s100p=0.75; ret1=0; mart1=0; hadhb=1; stc2=1. The influence was calculated from the influences of those genes in the individual boolean networks (here four in number), assuming equal probab-

ities for each network. These influence values ( $GIn$ ) are tabulated along side the control genes (C Gene) in Table I. The perturbation probability  $p$  was not taken into account for influence calculations as it had a very low value here. If the starting GAP is  $pirin=0$ ;  $s100p=0$ ;  $ret1=0$ ;  $mart1=0$ ;  $hadhb=1$ ;  $stc2=0$ ;  $wnt5a=1$  then the expected costs for finite horizon control problems of lengths (len) 5 and 30 are shown in Table I. Here  $Ec1$  represents the expected cost when the  $2^n$  state formulation is used and  $Ec2$  represents the expected cost when the  $2^{nk}$  state formulation is used, the suffix  $wc$  denotes with control and the suffix  $woc$  denotes without control. The table shows that the expected cost is much lower (0.35, 0.39) when high influence genes  $pirin$ ,  $hadhb$  are used as compared to the expected cost (0.56) obtained when a low influence gene  $mart1$  is used to control the network.

## VII. CONCLUSIONS

In this paper, we have extended our earlier results on intervention in instantaneously random PBNs to the domain of context sensitive PBNs. This is a significant extension as the latter class of networks is probably a much closer approximation to modeling biological reality. In addition,

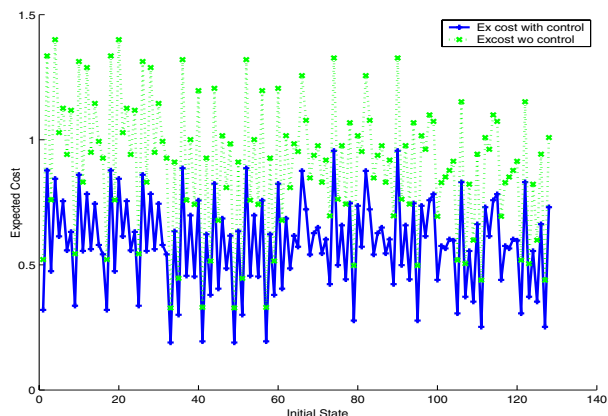


Fig. 2. Expected Cost for a Finite Horizon Problem of Length 5 Originating from the Different Initial States

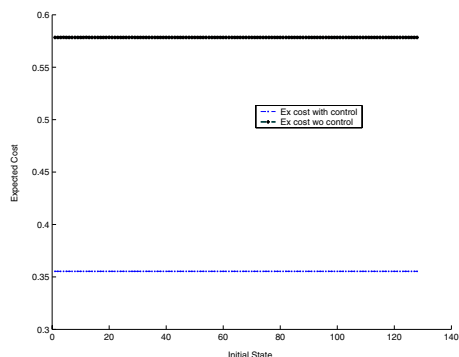


Fig. 3. Expected Cost for a Finite Horizon Problem of Length 30 Originating from the Different Initial States

C Gene	$GIn$	Len	$Ec1wc$	$Ec1woc$	$Ec2wc$	$Ec2woc$
pirin	1	30	.355352	.5784	.566017	.949586
mart1	0	30	.568611	.5784	.743938	.949586
hadhb	1	30	.398291	.5784	.300602	.949586
stc2	1	30	.413105	.5784	.569817	.949586
pirin	1	5	.652455	.974544	.396288	.61994
mart1	0	5	.963684	.974544	.53374	.61994
hadhb	1	5	.762097	.974544	.304567	.61994
stc2	1	5	.830185	.974544	.398155	.61994

TABLE I  
EXPECTED COST TABLE

we have allowed random gene perturbations in our problem formulation. The results show that even with the new formulation, the expected cost with control is much lower than that without control. In addition, we have shown that we can achieve a much better control outcome if a gene with high influence is selected as the control gene.

## VIII. ACKNOWLEDGMENTS

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