A critical role for induced IgM in the protection against West Nile virus infection

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Motivation: Intervention in a gene regulatory network is used to help avoid undesirable states, such as those associated with a disease. Several types of intervention have been studied in the framework of a probabilistic Boolean network (PBN), which is essentially a finite collection of Boolean networks in which at any discrete time point the gene state vector transitions according to the rules of one of the constituent networks. For an instantaneously random PBN, the governing Boolean network is randomly chosen at each time point. For a context-sensitive PBN, the governing Boolean network remains fixed for an interval of time until a binary random variable determines a switch. The theory of automatic control has been previously applied to find optimal strategies for manipulating external (control) variables that affect the transition probabilities of an instantaneously random PBN to desirably affect its dynamic evolution over a finite time horizon. This paper extends the methods of external control to context-sensitive PBNs.

Results: This paper treats intervention via external control variables in context-sensitive PBNs by extending the results for instantaneously random PBNs in several directions. First, and most importantly, whereas an instantaneously random PBN yields a Markov chain whose state space is composed of gene vectors, each state of the Markov chain corresponding to a context-sensitive PBN is composed of a pair, the current gene vector occupied by the network and the current constituent Boolean network. Second, the analysis is applied to PBNs with perturbation, meaning that random gene perturbation is permitted at each instant with some probability. Third, the (mathematical) influence of genes within the network is used to choose the particular gene with which to intervene. Lastly, PBNs are designed from data using a recently proposed inference procedure that takes steady-state considerations into account. The results are applied to a context-sensitive PBN derived from gene-expression data collected in a study of metastatic melanoma, the intent being to devise a control strategy that reduces the WNT5A gene's action in order to improve survival rates. The results show that disruption of this influence could reduce the chance of a melanoma metastasizing.

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1 INTRODUCTION

A probabilistic Boolean network (PBN) is essentially a discrete collection of Boolean networks in which at any discrete time point, the gene state vector transitions according to the rules of one of the constituent networks (Shmulevich et al., 2002a,b). As originally introduced, the governing Boolean network is randomly chosen at each time point, which means that the probability of updating each gene is randomly chosen at each time step from among several possible rules in accordance with a fixed probability distribution (Shmulevich et al., 2002a). Such PBNs are referred to as instantaneously random PBNs. The intent is to generalize the Boolean model (Kaplan, 1969; Glass and Kauffman, 1973; Kauffman, 1993; Somogyi and Sniegoski, 1996; Huang, 1999) so as to incorporate uncertainty in the functions governing network transitions, whether uncertainty arises from inherent biological considerations or inference from data. In this way, PBNs form a subclass of Markovian genetic regulatory networks. A subsequent modification to the PBN structure allows each gene to randomly change value at each instant with a small perturbation probability \( p \). This insures that all the possible states communicate, thereby resulting in an ergodic Markov chain possessing a steady-state distribution (Shmulevich et al., 2002c).

Switching the constituent Boolean network of a PBN at every instant corresponds to switching the wiring diagram of the network from one time step to the next. While this can help incorporate uncertainty into the original Boolean rule-based paradigm, a model that is more appropriate to the stability of biological systems is achieved by limiting the switching between constituent networks. In such a PBN, the Boolean functions (and their variable sets, known as their predictor sets) remain fixed for an interval of time until the occurrence of some random event, perhaps corresponding to an external stimulus. This random switching is governed by a binary random variable with a typically small probability \( q \) of forcing a switch in constituent Boolean network. Taking the perspective that a switch corresponds to a change in context for the cell, these more general PBNs are referred to as context-sensitive PBNs.

To date, intervention in the context of PBNs has been approached in three ways: (i) resetting the state of an instantaneously random PBN with perturbation to a more desirable initial state and letting the network evolve from there (Shmulevich et al., 2002c); (ii) changing the steady-state (long-run) probability distribution of an instantaneously random PBN with perturbation by minimally...
altered its rule structure (Shmulevich et al., 2002d); and (iii) manipulating external (control) variables that affect the transition probabilities of an instantaneously random PBN (without perturbation) to desirably affect its dynamic evolution over a finite time horizon (Datta et al., 2003, 2004). All of these results have been obtained by exploiting the fact that the dynamic behavior of the PBN can be modeled by a Markov chain, thereby making the PBN amenable to the theory of Markov chains and Markov decision processes. A key difference between instantaneously random and context-sensitive PBNs that affects intervention analysis is that, whereas an instantaneously random PBN forms a Markov chain whose state space is composed of gene vectors, the Markov chain corresponding to a context-sensitive PBN is composed of pairs \((x, f)\), where \(x\) is the current gene vector occupied by the network and \(f\) is the vector of functions defining the current constituent Boolean network.

In this paper we consider intervention via external control variables in context-sensitive PBNs. This involves significant extension of the results in Datta et al. (2003) in several directions. First, constituent network switching only occurs with probability \(q\) at each time instant. Second, there is random gene perturbation at each instant with probability \(p\). Third, we use the concept of gene influence, introduced in Shmulevich et al. (2002a), to choose the particular gene with which to intervene and demonstrate that intervening with a higher influence gene results in better performance. Finally, when applying the control theory, the designed PBN is derived from steady-state considerations, which makes the intervention strategy more biologically appealing.

Regarding the final point, we 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. Under this assumption, 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 points and the attractors of the designed Boolean network. Here we use the Bayesian connectivity-based approach (Zhou et al., 2004) to construct Boolean networks with the expectation of generating networks having a few very strong attractors (thereby reflecting biological stability) that are highly similar to the data. This approach yields a number of highly probable Boolean networks and Bayesian scores for each of them. These networks are 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.

2 DEFINITIONS

A Boolean network (BN) \(B = (V, F)\) on \(n\) genes is defined by a set of nodes/genes \(V = \{x_1, \ldots, x_n\}, x_i \in \{0, 1\}, i = 1, \ldots, n\), and a list \(F = \{f_1, \ldots, f_n\}\) of Boolean functions, \(f_i : \{0, 1\}^n \rightarrow \{0, 1\}, i = 1, \ldots, n\). Each node \(x_i\) represents the state/expression of the gene \(x_i\), where \(x_i = 0\) means that gene \(i\) is OFF and \(x_i = 1\) means that gene \(i\) is ON. The function \(f_i\) is called the predictor function for gene \(i\). Updating the states of all 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 nodes/genes \(V = \{x_1, \ldots, x_n\}, x_i \in \{0, 1\}, i = 1, \ldots, n\), and a set of vector-valued network functions, \(f_1, f_2, \ldots, f_n\), governing the state transitions of the genes, each network function being of the form \(f_i = (f_{i1}, f_{i2}, \ldots, f_{in})\), where \(f_{ij} : \{0, 1\}^n \rightarrow \{0, 1\}, i = 1, \ldots, n\). The choice of which network function \(f_i\) 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 \(f_1, f_2, \ldots, f_n\), with the probability of choosing \(f_i\) being the selection probability \(c_i\). In other words, each network function \(f_i\) 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 \(c_1, c_2, \ldots, c_n\) from among \(f_1, f_2, \ldots, f_n\). The PBN just described is called a context-sensitive PBN. In the special case when \(q = 1\), the network function is switched at every time point and the PBN is called an instantaneously random PBN. We consider context-sensitive PBNs with perturbation, meaning that at each time point there is a probability \(p\) of any gene changing its value uniformly randomly. 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, determines 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 steady-state distribution.

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

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

As \(x(t)\) ranges from \(000\ldots0\) to \(111\ldots1\), \(z(t)\) 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. 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 we label these states as \(S_0, S_1, \ldots, S_{2^n k-1}\), where for each \(r = 1, 2, \ldots, k\), states \(S_{2^r t - 1}, S_{2^r t - 1} + 1, \ldots, S_{2^r t - 1}\) belong to network \(r\). Equivalently \(S_{2^r t - 1} + i\) corresponds to \(z_r\), where \(z_r\) is the decimal representation of the \(r\)th state in the network \(r\). Let the redefined state at time \(t\) be denoted by \(w(t)\).

3 TRANSITION PROBABILITIES

In this section, we derive expressions for the transition probabilities in a context-sensitive PBN subject to perturbations by recognizing that the following mutually exclusive 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.

Assuming that the individual genes perturb independently, and letting $\text{mod}(v, w)$ denote the remainder left over when $v$ is divided by $w$, we consider two cases for determining the transition probability of going from state $a$ to state $b$:

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

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

(2)

where $h$ is the Hamming Distance between $\text{mod}(a, 2^n)$ and $\text{mod}(b, 2^n)$, i.e. the number of genes which differ between the two states,

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

and

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

The first term in Equation (2) corresponds to event (1) above, where $1 - q$ is the probability that the network selection does not change, $(1 - p)^n$ is the probability that none of the $n$ genes undergo a perturbation, we assume that network selection and random gene perturbation are independent events, and $f_{r,a,b} = 1$ 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 $r_1 \neq r_2$. This corresponds to events (2) and (4) above and the transition probabilities are given by

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

(3)

If we 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 is given by

$$Pr(w(t + 1) = b|w(t) = a) = [(1 - q)(1 - p)^n f_{r,a,b} + (1 - q)(1 - p)^{n-h} p^h s(h)]g(a, b)$$

$$\times \left[ q \frac{c_{r_2}}{\sum_{i=1,j \neq r_1} c_i} (1 - p)^n f_{r_1,a,b} + q \frac{c_{r_2}}{\sum_{i=1,j \neq r_1} c_i} (1 - p)^{n-h} p^h s(h) \right] \times [1 - g(a, b)].$$

(4)

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

In practice, it will likely be impossible to detect the Boolean network from which the current gene activity profile is being emitted. In most cases, we will only have knowledge of the states of the genes. To handle such situations, we can 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 network vector:

$$Pr[z(t + 1) = s_1|z(t) = s_2] = \sum_{i=1}^k Pr[z(t + 1) = s_1, s_2 \text{ belongs to network } i|z(t) = s_2]$$

$$= \sum_{i=1}^k Pr[z(t + 1) = s_1|z(t) = s_2, s_2 \text{ belongs to network } i]$$

$$= \sum_{i=1}^k \sum_{j=1} c_i \cdot Pr[w(t + 1) = s_1 + 2^n (j - 1)|w(t)]$$

$$= s_2 + 2^n (j - 1)]$$

(5)

where $s_1$ and $s_2$ run from 0 to $2^n - 1$. Note that here state $s_1$ is equivalent to the distinct states $s_1, s_1 + 2^n, \ldots, s_1 + (k - 1)2^n$ in the previous $2^n k$ formulation. Similarly $s_2$ here is equivalent to $s_2, s_2 + 2^n, \ldots, s_2 + (k - 1)2^n$ 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.

### 4 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 PBN with $n$ genes has $m$ control inputs, $u_1, u_2, \ldots, u_m$, each of which can take on only the binary values 0 or 1. Then at any time $t$, the row vector $u(t) = [u_1(t), u_2(t), \ldots, u_m(t)]$ describes the complete...
status of all the control inputs. $u(t)$ can take on all binary values from $[0,0,\ldots,0]$ to $[1,1,\ldots,1]$. One can equivalently represent the control input status using the decimal number

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

As $u(t)$ takes on binary values from $[0,0,\ldots,0]$ to $[1,1,\ldots,1]$, 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 PBN at time $t$.

If a control action is applied, then the transition probability expressions will change. Suppose that our control action consists of forcibly altering the expression of a single gene, $g$, from 0 to 1 or from 1 to 0. Thus, $m = 1$ here. Then the new transition probabilities with control, denoted by $Pr_c$, are given by

$$Pr_c(w(t + 1) = b|w(t) = a) = \Pr(w(t) = a + 2^{a-b})func(a) + \Pr(w(t) = a - 2^{a-b})(1 - func(a)).$$ \hfill (7)

where

$$func(a) = \begin{cases} 1, & \text{if state of gene } g \text{ is 0 for } a, \\ 0, & \text{if state of gene } g \text{ is 1 for } a, \end{cases}$$

and the transition probabilities, $Pr$, without control are given by Equation (4).

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

$$Pr(z(t + 1) = a|z(t) = a) = \Pr(z(t) = a + 2^{a-b})func(a) + \Pr(z(t) = a - 2^{a-b})(1 - func(a)).$$ \hfill (8)

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

In the rest of this section, we formulate and solve the control problem assuming $2^m$ states and the availability of full state information. The same development can be carried out for the $2^m k$ state formulation if we simultaneously have the gene state information and the network labels. As shown in Datta et al. (2003), the one-step evolution of the probability distribution vector in the case of a PBN containing $2^m$ states with control inputs takes place according to the equation:

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

where $pd(t)$ is the $2^m$ dimensional state probability distribution vector and $A(v(t))$ is the $2^m \times 2^m$ matrix of control-dependent transition probabilities determined by Equation (8). Since the transition probability matrix 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 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 have been formalized in Datta et al. (2003) to arrive at the following finite horizon optimization problem. Given an initial state $z_0$,

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

subject to $Pr(z(t + 1) = j|z(t) = i, v(t))$, given by Equation (8), where

- $M$ represents the treatment/intervention window;
- $\mu_t : [0,1,2,\ldots,2^m - 1] \rightarrow [0,1,2,\ldots,2^m - 1]$,
- $t = 0, 1, 2, \ldots, M - 1$ 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 $z_t$;
- $CM(z_M)$ is the terminal cost associated with the state $z_M$.

As discussed in Datta et al. (2003), the consideration of such an optimization problem can 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 Equation (10) is given by (Bertsekas, 1976; Datta et al., 2003):

$$JM(z_M) = CM(z_M),$$ \hfill (11)

$$J_t(z_t) = \min_{v_t \in \{0,1,\ldots,2^m-1\}} \left[ C_t(z_t, v_t) + \sum_{j=0}^{2^m-1} Pr(z_{t+1} = j|z_t, v_t) \cdot J_{t+1}(j) \right],$$ \hfill (12)

If $v^*_t = \mu^*_t(z_t)$ minimizes the right-hand side of Equation (12) for each $z_t$ and $t$, then the control law $\pi^* = \{v^*_0, v^*_1, \ldots, v^*_M\}$ is optimal.

The optimal control problem [Equation (10)] and its solution [Equations (11) and (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 a single gene. This limited control objective is dictated primarily by limitations on the kind of interventions that appear to be within the realm of biological possibility.

### 5 SELECTING THE CONTROL GENE

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 others. For instance, in cancer studies it has been shown that p53 has a more profound effect on the cell cycle regulator gene WAF1/p21 than other predictors of WAF1, such as AP2 or BRCA1 (Gartel and
Suppose we have treatments d that affect 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 disruption of this influence could reduce the chance of a melanoma metastasizing, a desirable outcome. Instantaneously random disruption of this influence could reduce the chance of a melanoma metastasizing, a desirable outcome. Instantaneously random disruption of this influence could reduce the chance of a melanoma metastasizing, a desirable outcome. Instantaneously random disruption of this influence could reduce the chance of a melanoma metastasizing, a desirable outcome. Instantaneously random disruption of this influence could reduce the chance of a melanoma metastasizing, a desirable outcome. Instantaneously random disruption of this influence could reduce the chance of a melanoma metastasizing, a desirable outcome. Instantaneously random disruption of this influence could reduce the chance of a melanoma metastasizing, a desirable outcome. Instantaneously random disruption of this influence could reduce the chance of a melanoma metastasizing, a desirable outcome. Instantaneously random disruption of this influence could reduce the chance of a melanoma metastasizing, a desirable outcome.
initial states start yielding almost the same expected cost. This may be due to the fact that the maximum level of the constituent networks is 9 and the Markov chain is ergodic. If, on the other hand, the $2^n k$ formulation is used, then 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 consider 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,
is pirin because it has a very low value. If the starting gene activity profile
\( p \) is taken into account for the influence calculations, the expected cost is much lower (0.35 and 0.39) when the high-influence genes pirin and HADHB are used, as compared to the expected cost (0.56) obtained when the low-influence gene MART1 is used to control the network.

\[
\begin{array}{|c|c|c|c|c|c|}
\hline
\text{CG} & \text{GI} & \text{Ln} & \text{Ec}1\text{wc} & \text{Ec}1\text{woc} & \text{Ec}2\text{wc} & \text{Ec}2\text{woc} \\
\hline
\text{pirin} & 1 & 30 & 0.355352 & 0.5784 & 0.566017 & 0.949586 \\
\text{mart1} & 0 & 30 & 0.568611 & 0.5784 & 0.743938 & 0.949586 \\
\text{hadhb} & 1 & 30 & 0.398291 & 0.5784 & 0.300602 & 0.949586 \\
\text{stc2} & 1 & 30 & 0.413105 & 0.5784 & 0.569817 & 0.949586 \\
\text{pirin} & 1 & 5 & 0.652455 & 0.974544 & 0.396288 & 0.61994 \\
\text{mart1} & 0 & 5 & 0.963684 & 0.974544 & 0.533740 & 0.61994 \\
\text{hadhb} & 1 & 5 & 0.762097 & 0.974544 & 0.304567 & 0.61994 \\
\text{stc2} & 1 & 5 & 0.830185 & 0.974544 & 0.398155 & 0.61994 \\
\hline
\end{array}
\]

7 CONCLUSION

This paper extends earlier results on intervention in instantaneously random PBNs without perturbation to context-sensitive PBNs with perturbation. The extension is significant because the latter class more closely models small biological subnetworks whose logical behavior is affected by conditions outside the genes represented in the model network. The results show that the expected cost with control is much lower than without control. In addition, the results indicate that we can achieve a much better control outcome if a gene with high influence is selected as the control gene.

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