Controllability of Boolean Control Networks via Perron-Frobenius Theory ⋆

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Abstract

Boolean control networks (BCNs) are recently attracting considerable interest as computational models for genetic and cellular networks. Addressing control-theoretic problems in BCNs may lead to a better understanding of the intrinsic control in biological systems, as well as to developing suitable protocols for manipulating biological systems using exogenous inputs. We introduce two definitions for controllability of a BCN, and show that a necessary and sufficient condition for each form of controllability is that a certain nonnegative matrix is irreducible or primitive, respectively. Our analysis is based on a result that may be of independent interest, namely, a simple algebraic formula for the number of different control sequences that steer a BCN between given initial and final states in a given number of time steps, while avoiding a set of forbidden states.

Key words: Logical systems, reachability, controllability, gene regulating networks, systems biology, nonnegative matrices.

1 Introduction

A Boolean network (BN) is a discrete-time dynamic system with Boolean state-variables. BNs have been studied extensively as models for simple artificial neural networks (see, e.g. Hassoun (1995)), where each neuron realizes a threshold function that attains the values zero or one. BNs have also been used for modeling interactions between simple agents and studying the emergence of social consensus (see, e.g. Green *et al.* (2007)).

BNs are currently attracting considerable interest as models for biological systems. The underlying assumption is that certain biological variables can be approximated as having just two possible levels of operation (i.e., ON and OFF). Kauffman (1969) modeled a gene as a binary device, and studied the behavior of large, randomly constructed nets of these binary genes. He related the behavior of these random nets to various cellular control processes including cell differentiation. The key idea being to view each stable attractor of the BN as representing one possible cell type.

BNs seem especially suitable for modeling genetic regulation networks where the ON (OFF) state corresponds to the transcribed (quiescent) state of the gene. There are several other motivations for using BNs in this context, including the fact that many metabolic and genetic networks demonstrate some form of bi-stability (Huang (2002)). Specific examples of genetic regulation networks modeled using BNs include: the cell cycle regulatory network of the budding yeast (Li *et al.* (2004)); control of the mammalian cell cycle (Faure *et al.* (2006)); the yeast transcriptional network (Kauffman *et al.* (2003)); the network controlling the segment polarity genes in the fly *Drosophila melanogaster* (Albert and Othmer (2003); Chaves *et al.* (2005)); the ABC network determining floral organ cell fate in Arabidopsis (Espinosa-Soto *et al.* (2004); Chaos *et al.* (2006)).

BNs have also been used for modeling various cellular processes. In this context, the two possible logic states may represent the open/closed state of an ion channel, basal/high activity of an enzyme, two possible conformational states of a protein, etc. Examples include a detailed model for the complex cellular signaling network controlling stomatal closure in plants (Li *et al.* (2006)); and a model of the molecular pathway between two neurotransmitter systems, the dopamine and glutamate receptors (Gupta *et al.* (2007)). Szallasi and Liang (1998) discuss the use of BNs in modeling carcinogenesis and for analyzing the effect of therapeutic intervention (see also Kauffman (1971)).

Despite their simplicity, BNs seem to provide an efficient tool for modeling large-scale biological networks (Born-

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holdt (2008)). These models are able to reproduce the main characteristics of the biological dynamics: attractors of the BN correspond to stationary biological states; large attraction basins indicate robustness of the biological state; etc.

Modeling using BNs requires only coarse-grained qualitative information (e.g., an interaction between two genes is either excitatory or inhibitory). Many other models, for example, those based on differential equations, require knowledge of numerous parameter values (e.g., rate constants). For a general exposition on various approaches for modeling gene regulation networks, see Bolouri (2008).

Modeling a biological system involves considerable uncertainty. This is due to the noise and perturbations that affect the biological system, and inaccuracies of the measuring equipment. One approach for tackling this uncertainty is by using *Probabilistic Boolean Networks* (PBNs) (Shmulevich *et al.* (2002b,a)). These may be viewed as a collection of BNs combined with a probabilistic switching rule determining which network is active at each time instant.

BNs with (binary) inputs are referred to as *Boolean Control Networks* (BCNs). For example, a binary input may represent whether a certain medicine is administered or not at each time step. PBNs with inputs were used to design and analyze therapeutic intervention strategies. The idea here is to find a control sequence that steers the network from an undesirable location to a desirable one. For example, from a location corresponding to a diseased state of the biological system to a location corresponding to a healthy state. In the context of PBNs, this type of problems can be cast as stochastic optimal control problems, and solved numerically using dynamic programming (Datta *et al.* (2010); Liu *et al.* (2010)).

Daizhan Cheng and his colleagues developed an *algebraic state-space representation* (ASSR) of BCNs. This representation proved quite useful for studying BCNs in a control-theoretic framework. Examples include the analysis of disturbance decoupling (Cheng (2011)), controllability and observability (Cheng and Qi (2009)), realization theory (Cheng *et al.* (2010)), and more (Cheng and Qi (2010a,b); Cheng (2009)). See the recent monograph by Cheng *et al.* (2011) for a detailed presentation.

Let I_j denote the $j \times j$ identity matrix. In the ASSR of a BCN with n state variables, the state vector $x(k)$ is a column of I_{2^n} for any time k. Similarly, the input vector $u(k)$ is a column of I_{2^m}, where m is the number of input variables. In other words, both $x(k)$ and $u(k)$ are *canonical vectors.*

Here we use the ASSR to address the following question. Given states a, b, an integer $k > 0$, and a set of undesirable states C, let $l(k; a, b, C)$ denote the number of different control sequences that steer the BCN from $x(0) = a$ to $x(k) = b$, while avoiding any state in C. We derive a simple algebraic expression for $l(k; a, b, C)$. We introduce two definitions for controllability of a BCN, and use the expression for $l(k; a, b, C)$ and the Perron-Frobenius theory of nonnegative matrices to derive a simple necessary and sufficient condition for each form of controllability.

Some related work includes the following. Akutsu *et al.* (2007) showed that control problems for BCNs are in general NP-hard. Langmead and Jha (2009) noted that for many instances of BCNs control problems can be addressed efficiently using *model checking.* The controllability of BCNs has been addressed in (Cheng and Qi (2009)). An extension to BCNs with time-delays is described in Li and Sun (2011). However, these papers define controllability with respect to a *fixed* initial condition. Our definition, which is motivated by the definition of controllability in linear systems theory, is different and more global in nature. One of the anonymous reviewers of this brief pointed out to us that a formula for $l(k; a, b, \emptyset)$, and its implications for controllability analysis, already appeared in the recent paper by Zhao *et al.* (2010). We further develop these ideas by relating controllability to the Perron-Frobenius theory of nonnegative matrices.

It is not difficult to show that a BCN is a *Boolean switched system* switching between 2^m possible subsystems. Our work is motivated by the variational analysis of continuous-time switched systems (see Margaliot (2006); Margaliot and Branicky (2009); Sharon and Margaliot (2007); Margaliot and Liberzon (2006)). This approach was also extended to analyze discrete-time switched systems (see Barabanov (2005); Monovich and Margaliot (2011a,b) and the references therein). Recently, we considered a Mayer-type optimal control problem for single and multi-input BCNs, and derived a necessary condition for optimality in the form of a maximum principle (Laschov and Margaliot (2011a,b)).

2 Boolean control networks

Let $S = \{\text{True}, \text{False}\}$. A BCN is a discrete-time logical dynamic control system in the form

$$\begin{aligned} x_1(k+1) &= f_1(x_1(k), \dots, x_n(k), u_1(k), \dots, u_m(k)), \\ &\vdots \\ x_n(k+1) &= f_n(x_1(k), \dots, x_n(k), u_1(k), \dots, u_m(k)), \end{aligned} \tag{1}$$

where the state variables x_i and the controls u_i take values in S, and $f_i : S^{n+m} \to S$.

Example 1. *Consider the three-state, one-input BCN*

$$\begin{aligned} x_1(k+1) &= x_2(k), \\ x_2(k+1) &= x_3(k), \\ x_3(k+1) &= u(k) \vee [x_2(k) \wedge x_3(k)]. \end{aligned} \tag{2}$$

■

3 Algebraic representation of BCNs

Control-theoretic problems for BCNs are best addressed in the ASSR (see Cheng *et al.* (2011)). This is based on the *semi-tensor product* (STP) of matrices.

Recall that the *Kronecker product* (see, e.g. (Bernstein, 2005, Ch. 7)) of two matrices $A \in \mathbb{R}^{m\times n}$ and $B \in \mathbb{R}^{p\times q}$ is the $(mp)\times(nq)$ matrix: $A \otimes B = \begin{bmatrix} a_{11}B & \cdots & a_{1n}B \\ \vdots & \ddots & \vdots \\ a_{m1}B & \cdots & a_{mn}B \end{bmatrix}$.

Given two positive integers a, b, let $\operatorname{lcm}(a, b)$ denote the *least common multiple* of a and b, e.g. $\operatorname{lcm}(6, 8) = 24$.

Definition 1. *The* STP *of* $A \in \mathbb{R}^{m\times n}$ *and* $B \in \mathbb{R}^{p\times q}$ *is*

$$A \ltimes B = (A \otimes I_{\alpha/n})(B \otimes I_{\alpha/p}),$$

where $\alpha = \operatorname{lcm}(n, p)$.

Remark 1. *Note that* $(A\otimes I_{\alpha/n}) \in \mathbb{R}^{(m\alpha/n)\times\alpha}$ *and* $(B\otimes I_{\alpha/p}) \in \mathbb{R}^{\alpha\times(q\alpha/p)}$, *so* $(A \ltimes B) \in \mathbb{R}^{(m\alpha/n)\times(q\alpha/p)}$.

Remark 2. *If* $n = p$, *then* $A \ltimes B = (A \otimes I_1)(B \otimes I_1) = AB$, *so we recover the standard matrix product. Thus, the STP is a generalization of the standard matrix product that provides a way to multiply two matrices with arbitrary dimensions. Intuitively, this is based on first modifying* A, B *to two matrices* $(A \otimes I_{\alpha/n})$, $(B \otimes I_{\alpha/p})$ *of compatible dimensions, and then calculating their standard matrix product.*

Example 2. *If* $a, b \in \mathbb{R}^2$, *then*

$$\begin{aligned} a \ltimes b &= (a \otimes I_2)(b \otimes I_1) \\ &= \begin{bmatrix} a_1b_1 & a_1b_2 & a_2b_1 & a_2b_2 \end{bmatrix}^T. \end{aligned}$$

■

The STP is associative: $A \ltimes (B \ltimes C) = (A \ltimes B) \ltimes C$, and distributive: $(A + B) \ltimes C = (A \ltimes C) + (B \ltimes C)$ (Cheng and Dong (2003)).

Let e_n^i denote the ith column of I_n. Represent the Boolean values True, False by e_2^1, e_2^2, respectively. Then any Boolean function of n variables $f : S^n \to S$ can be equivalently represented as a mapping $\bar{f} : \{e_2^1, e_2^2\}^n \to \{e_2^1, e_2^2\}$. With some abuse of notation, we identify $\bar{f}$ with f. In other words, from here on a Boolean variable x_i is always a vector in $\{e_2^1, e_2^2\}$.

The STP can be used to provide an ASSR for BCNs.

Theorem 1. *(Cheng and Qi (2010b)) Consider the BCN (1) with* $x_i, u_i \in \{e_2^1, e_2^2\}$. *Denote* $x(k) = x_1(k) \ltimes \cdots \ltimes x_n(k)$ *and* $u(k) = u_1(k) \ltimes \cdots \ltimes u_m(k)$. *There exists a unique matrix* $L \in \{0, 1\}^{2^n\times 2^{n+m}}$ *such that*

$$x(k+1) = L \ltimes u(k) \ltimes x(k). \tag{3}$$

The matrix L *is called the* transition matrix *of the BCN.*

For algorithms that convert between the representations (1) and (3), see Cheng and Qi (2010a, 2009).

Remark 3. *To explain the intuition behind this representation, consider a BCN with* $n = 2$ *and* $m = 1$. *Then* (3) *becomes* $x(k+1) = L \ltimes u_1(k) \ltimes x_1(k) \ltimes x_2(k)$. *To simplify the notation, we omit from here on the dependence on* k. *Let* $x_1 = \begin{bmatrix} p & \bar{p} \end{bmatrix}^T$, $x_2 = \begin{bmatrix} q & \bar{q} \end{bmatrix}^T$, *and* $u_1 = \begin{bmatrix} v & \bar{v} \end{bmatrix}^T$. *Then*

$$u_1 \ltimes x_1 \ltimes x_2 = \begin{bmatrix} vpq & vp\bar{q} & v\bar{p}q & v\bar{p}\bar{q} & \bar{v}pq & \bar{v}p\bar{q} & \bar{v}\bar{p}q & \bar{v}\bar{p}\bar{q} \end{bmatrix}^T.$$

Thus, $u \ltimes x$ *includes all the* possible minterms *of the input and state variables. The equation* $x(k+1) = L \ltimes u(k) \ltimes x(k)$ *amounts to a description of (every minterm of) the next state in terms of the current state and inputs.*

Note that since $u(k) = u_1(k) \ltimes \cdots \ltimes u_m(k)$, with $u_i(k) \in \{e_2^1, e_2^2\}$, $u(k) \in \{e_{2^m}^1, \ldots, e_{2^m}^{2^m}\}$. For example, if $m = 3$, $u_1(k) = e_2^1$, $u_2(k) = e_2^2$, and $u_3(k) = e_2^2$, then $u(k) = e_8^4$.

Example 3. *Consider the BCN in Example 1. Here* $n = 3$ *and* $m = 1$, *so* $x(k) = x_1(k) \ltimes x_2(k) \ltimes x_3(k)$. *Applying the algorithm described in Cheng and Qi (2009) yields the transition matrix*

$$L = \begin{bmatrix} e_8^1 & e_8^3 & e_8^5 & e_8^7 & e_8^1 & e_8^3 & e_8^5 & e_8^7 & e_8^1 & e_8^4 & e_8^6 & e_8^8 & e_8^1 & e_8^4 & e_8^6 & e_8^8 \end{bmatrix}, \tag{4}$$

To demonstrate the equivalence of (2) *and* (3), *consider for example the case* $x_1(k) = x_2(k) = x_3(k) = False$, *and* $u(k) = True$. *Then* (2) *yields*

$$x_1(k+1) = x_2(k+1) = False, \quad x_3(k+1) = True. \tag{5}$$

In the ASSR, this corresponds to $x_i(k) = e_2^2$, *and* $u(k) = e_2^1$, *so* $u(k) \ltimes x(k) = e_2^1 \ltimes e_2^2 \ltimes e_2^2 \ltimes e_2^2 = e_{16}^8$, *and*

$$\begin{aligned} x(k+1) &= L \ltimes u(k) \ltimes x(k) \\ &= L e_{16}^8 \\ &= e_8^7. \end{aligned} \tag{6}$$

Writing $x_1(k+1) = \begin{bmatrix} p & \bar{p} \end{bmatrix}^T$, $x_2(k+1) = \begin{bmatrix} v & \bar{v} \end{bmatrix}^T$, *and* $x_3(k+1) = \begin{bmatrix} w & \bar{w} \end{bmatrix}^T$ *yields*

$$x(k+1) = \begin{bmatrix} pvw & pv\bar{w} & p\bar{v}w & p\bar{v}\bar{w} & \bar{p}vw & \bar{p}v\bar{w} & \bar{p}\bar{v}w & \bar{p}\bar{v}\bar{w} \end{bmatrix}^T,$$

so (6) *yields* $\bar{p} = \bar{v} = w = 1$. *Thus,* $x_1(k+1) = e_2^2$, $x_2(k+1) = e_2^2$, $x_3(k+1) = e_2^1$, *and this agrees with* (5). ∎

The next section describes our main results. For a matrix M, $M > 0$ means that every entry of M is positive, and similarly for other inequalities.

4 Main results

Consider the problem of designing a control sequence that steers the BCN between two states, while avoiding certain forbidden states. This seems relevant to biological systems, as some states may correspond to unfavorable or dangerous situations. Fix an arbitrary integer $k > 0$. Let $\mathbb{U}^k$ denote the set of all the sequences $\{u(0), \ldots, u(k-1)\}$, with $u(i) \in \{e_{2^m}^1, \ldots, e_{2^m}^{2^m}\}$. For $a, b \in \{e_{2^n}^1, \ldots, e_{2^n}^{2^n}\}$ and a set of undesirable states C, let $l(k; a, b, C)$ denote the number of different control sequences that steer the BCN (3) from $x(0) = a$ to $x(k) = b$, while avoiding C (i.e. $x(i) \notin C$ for $i = 0, 1, \ldots, k$.). Since (3) is time-invariant, $l(k; a, b, C)$ is the number of different control sequences that steer the BCN from a to b in k time-steps, while avoiding C.

Let $|C|$ denote the cardinality of C. Let 1_r denote the column vector of length r with all entries equal to 1, and let $Q = L \ltimes 1_{2^m}$. By Definition 1, $Q = (L \otimes I_1)(1_{2^m} \otimes I_{2^n})$, so $Q \in \mathbb{R}^{2^n \times 2^n}$. The next result provides a simple algebraic expression for $l(k; a, b, C)$.

Theorem 2. *Suppose that the states in* C *are* $e_{2^n}^{i_1}, \ldots, e_{2^n}^{i_z}$ *where* $z = |C|$. *Let* Q_C *be the matrix obtained from* Q *by substituting zeros in the rows and columns with indexes* $i_1, \ldots, i_z$. *Then*

$$l(k; a, b, C) = b^T (Q_C)^k a. \tag{7}$$

Remark 4. *A similar result for the particular case* $C = \emptyset$ *(i.e.* $Q_C = Q$*) recently appeared in (Zhao* et al. *(2010)).*

Proof. By induction on k. Consider the case $k = 1$. Let $s = l(1; a, b, C)$. If $a \in C$ or $b \in C$, then clearly $s = 0$. Since in Q_C either the row corresponding to b or the column corresponding to a is zero, $b^T Q_C a = 0$. So in this case, $l(1; a, b, C) = b^T Q_C a$. Now suppose that $a \notin C$ and $b \notin C$. Let $w^1, \ldots, w^s$ be the different control sequences steering (3) from $x(0) = a$ to $x(1) = b$, i.e.

$$b = L \ltimes w^i(0) \ltimes a, \quad i \in \{1, \ldots, s\}. \tag{8}$$

Since each control value is a column of I_{2^m}, there exist $t = 2^m - s$ different control sequences $v^j \in \mathbb{U}^1$ such that

$$b \neq L \ltimes v^j(0) \ltimes a, \quad j \in \{1, \ldots, t\}. \tag{9}$$

Note that the term on the right-hand side of this inequality must be a column of I_{2^n}. Therefore, multiplying (8) and (9) from the left by b^T yields

$$\begin{aligned} 1 &= b^T L \ltimes w^i(0) \ltimes a, && i \in \{1, \ldots, s\}, \\ 0 &= b^T L \ltimes v^j(0) \ltimes a, && j \in \{1, \ldots, t\}. \end{aligned}$$

Since each of the control values is a different column of I_{2^m}, summing up this set of $s+t = 2^m$ equations yields

$$s = b^T \ltimes L \ltimes 1_{2^m} \ltimes a = b^T Q a.$$

We conclude that when $a \notin C$ and $b \notin C$, $l(1; a, b, C) = b^T Q a$. Since in this case $b^T Q a = b^T Q_C a$, $l(1; a, b, C) = b^T Q_C a$. This proves (7) for $k = 1$. For the induction step, consider

$$\begin{aligned} b^T (Q_C)^{k+1} a &= (e_{2^n}^j)^T (Q_C)^{k+1} e_{2^n}^i \\ &= ((Q_C)^k Q_C)_{ji} \\ &= \sum_{p=1}^{2^n} ((Q_C)^k)_{jp} (Q_C)_{pi} \\ &= \sum_{p=1}^{2^n} (e_{2^n}^j)^T ((Q_C)^k) e_{2^n}^p (e_{2^n}^p)^T Q_C e_{2^n}^i. \end{aligned}$$

Applying the induction hypothesis yields $b^T (Q_C)^{k+1} a = \sum_{p=1}^{2^n} l(k; e_{2^n}^p, b, C) l(1; a, e_{2^n}^p, C)$. This is the sum, over all possible states p, of the product of (1) the number of control sequences that steer from a to $e_{2^n}^p$ in one time step (while avoiding C); and (2) the number of control sequences that steer from $e_{2^n}^p$ to b in k time steps (while avoiding C). But this is just the number of control sequences that steer from a to b in $k+1$ time steps (while avoiding C). □

Example 4. *Consider the three-state, one-input BCN in Example 1, with* $x_i(0) = False$. *Fig. 1 depicts the possible trajectories of this BCN up to time* $k = 3$. *Each node corresponds to a possible value of* $x(i)$ *at time* $i \in \{0, 1, 2, 3\}$. *Here* $n = 3$, $m = 1$, L *is given by* (4), *and* $x(0) = e_8^8$. *A calculation yields*

$$\begin{aligned} Q = \big[&2e_8^1 \;\; e_8^3 + e_8^4 \;\; e_8^5 + e_8^6 \;\; e_8^7 + e_8^8 \;\; 2e_8^1 \;\; e_8^3 + e_8^4 \\ &e_8^5 + e_8^6 \;\; e_8^7 + e_8^8 \big], \end{aligned} \tag{10}$$

so

$$\begin{aligned} b^T Q a = &2b_1(a_1 + a_5) + b_3(a_2 + a_6) + b_4(a_2 + a_6) \\ &+ b_5(a_3 + a_7) + b_6(a_3 + a_7) + b_7(a_4 + a_8) + b_8(a_4 + a_8). \end{aligned}$$

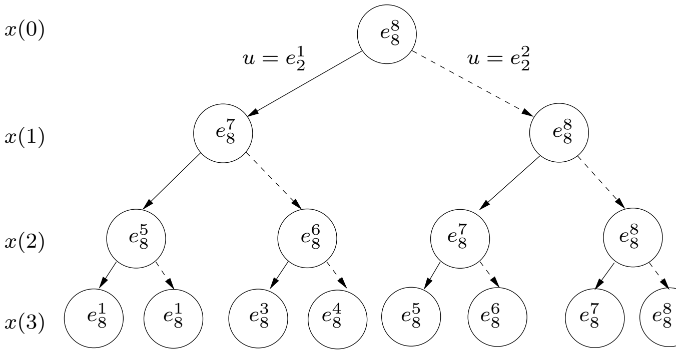

Fig. 1. Trajectories of the BCN. Each node depicts the value of $x(i)$ for either $u(i-1) = e_2^1$ (solid line) or $u(i-1) = e_2^2$ (dashed line).

In particular, $b^T Q e_8^8 = b_7 + b_8$, and $b^T Q e_8^5 = 2b_1$. Thm. 2 implies that $l(1; e_8^8, e_8^i, \emptyset)$ is equal to one [zero] if $i \in \{7, 8\}$ [otherwise]. Also, $l(1; e_8^5, e_8^i, \emptyset)$ is equal to two [zero] if $i = 1$ [otherwise]. This agrees with the trajectories depicted in Fig. 1.

A calculation yields $b^T Q^3 e_8^8 = b^T \begin{bmatrix} 2 & 0 & 1 & 1 & 1 & 1 & 1 & 1 \end{bmatrix}^T$, so $l(3; e_8^8, e_8^i, \emptyset)$ equals two for $i = 1$; zero for $i = 2$; and one, otherwise. Again, this agrees with Fig. 1.

Now suppose that $C = \{e_8^7\}$, i.e. e_8^7 is an undesirable state. Q_C is obtained from Q by substituting zeros in row 7 and column 7, i. e.

$$Q_C = \begin{bmatrix} 2e_8^1 & e_8^3 + e_8^4 & e_8^5 + e_8^6 & e_8^8 & 2e_8^1 & e_8^3 + e_8^4 & 0_8 & e_8^8 \end{bmatrix},$$

where 0_8 denotes a column vector of 8 zeros. Then $(e_8^i)^T Q_C^3 e_8^8$ is 1 for $i = 8$ and zero, otherwise, so the number of control sequences steering $x(0) = e_8^8$ to $x(3) = e_8^i$, while avoiding e_8^7, is one for $i = 8$ and zero, otherwise. This agrees with the trajectories depicted in Fig. 1. ■

For $C = \emptyset$, $Q_C = Q$ and the interpretation of Q_C^k in Thm. 2 implies the following.

Corollary 1. *For any $k > 0$, the sum of the elements in any column of Q^k is 2^{mk}.*

Proof. The sum of the elements in column i of Q^k is $\sum_{j=1}^{2^n} (e_{2^n}^j)^T Q^k e_{2^n}^i$. By Thm. 2 this is the number of different control sequences steering $x(0) = e_{2^n}^i$ to some vector in $\{e_{2^n}^1, \dots, e_{2^n}^{2^n}\}$ in k time steps. But this is just the total number of different control sequences of length k, i.e. 2^{mk}. □

Thm. 2 has important applications for the controllability of BCNs.

Definition 2. *Given a set of undesirable states C (that may be empty), we say that the BCN* (3) *is* controllable *if for* any $a, b \in \left(\{e_{2^n}^1, \dots, e_{2^n}^{2^n}\} \setminus C\right)$ *there exist $k \geq 0$ and a control $u \in \mathbb{U}^k$ that steers the BCN from $x(0) = a$ to $x(k) = b$, while avoiding C.*

Note that k here may depend on a, b. It is clear that controllability implies that for any a and b, $k(a, b) \leq 2^n$, since the total number of different states is 2^n.

We use the Perron-Frobenius theory of nonnegative matrices to derive a necessary and sufficient condition for controllability. We recall the following definitions (see e.g. (Horn and Johnson, 1985, Ch. 8)).

Definition 3. *A matrix $M \in \mathbb{R}^{n \times n}$, with $n \geq 2$, is said to be* reducible *if there exists a permutation matrix $P \in \{0, 1\}^{n \times n}$, and an integer r with $1 \leq r \leq n-1$ such that*

$$P^T M P = \begin{bmatrix} B & C \\ 0 & D \end{bmatrix}, \tag{11}$$

where $B \in \mathbb{R}^{r \times r}$, $D \in \mathbb{R}^{(n-r) \times (n-r)}$, $C \in \mathbb{R}^{r \times (n-r)}$ and $0 \in \mathbb{R}^{(n-r) \times r}$ is a zero matrix. A matrix is said to be irreducible *if it is not reducible.*

Theorem 3. *(Berman and Plemmons, 1987, Ch. 2) Suppose that $A \in \mathbb{R}^{n \times n}$ is nonnegative. Then A is irreducible if and only if for any $i, j \in \{1, \dots, n\}$ there exists an integer $k \geq 1$ such that $(A^k)_{ij} > 0$.*

Let $\tilde{Q}_C$ denote the matrix obtained from Q by *deleting* the rows and columns with indexes $i_1, \dots, i_z$. Note that $\tilde{Q}_C \in \mathbb{R}^{q \times q}$, with $q = 2^n - |C|$. Arguing as in the proof of Thm. 2 and using Thm. 3 yields the following result.

Theorem 4. *The BCN* (3) *is controllable if and only if $\tilde{Q}_C$ is irreducible.*

Note that we cannot use the matrix Q_C here. Indeed, if $C \neq \emptyset$, then Q_C includes at least one row and one column of zeros so it is always reducible. This is reasonable, as clearly there is no control steering the system to one of the states in C. The use of $\tilde{Q}_C$ overcomes this problem.

Example 5. *Consider the BCN in Example 4. Suppose that $C = \{e_8^7\}$. $\tilde{Q}_C$ is obtained from Q by deleting the seventh row and the seventh column, i. e.*

$$\tilde{Q}_C = \begin{bmatrix} 2e_7^1 & e_7^3 + e_7^4 & e_7^5 + e_7^6 & e_7^7 & 2e_7^1 & e_7^3 + e_7^4 & e_7^7 \end{bmatrix}.$$

It is well-known that a nonnegative matrix $A \in \mathbb{R}^{n \times n}$ is irreducible if and only if $(I_n + A)^{n-1} > 0$ (Berman and Plemmons, 1987, Ch. 1). Since $(I_7 + \tilde{Q}_C)^6$ includes zero entries, $\tilde{Q}_C$ is reducible, and we conclude that the BCN is not controllable for $C = \{e_8^7\}$. Indeed, Fig. 1 shows that in this case there is no control steering e_8^8 to any state $b \neq e_8^8$. ■

Recall that if a linear control system of dimension n is controllable, then any initial condition can be steered to any final condition in n time-steps (Kailath (1980)). This motivates the following stronger notion of controllability.

Definition 4. *Given a set of undesirable states C (that may be empty), we say that the BCN* (3) *is k* fixed-time controllable *if for* any $a, b \in \left(\{e_{2^n}^1, \dots, e_{2^n}^{2^n}\} \setminus C\right)$ *there* *exists a control $u \in \mathbb{U}^k$ that steers the BCN from $x(0) = a$ to $x(k) = b$, while avoiding C.*

To motivate this definition, consider a biological system composed of several identical parts, each part modeled using the same BCN. For example, the biological system is a multi-cellular organism, and the identical BCNs model the cell-cycle. We may be interested in applying a control to every part of the system in order to *synchronize* all the parts, say, steering all the parts to the same desired state b at the *same* final time. If the BCN is k fixed-time controllable, then this can be done, as there exists a control sequence $u^i \in \mathbb{U}^k$ that steers part number i from its (arbitrary) initial state $x^i(0)$ to b in exactly k time-steps.

Arguing as in the proof of Thm. 2 yields the following result.

Theorem 5. *The BCN (3) is k fixed-time controllable if and only if $(\tilde{Q}_C)^k > 0$.*

Again, we use known results from the Perron-Frobenius theory to derive a necessary and sufficient condition for k fixed-time controllability.

Theorem 6. *(Horn and Johnson, 1985, Ch. 8) A nonnegative matrix $A \in \mathbb{R}^{n\times n}$ is called* primitive *if there exists an integer $j \geq 1$ such that $A^j > 0$. In this case, the smallest such j is called the* index of primitivity *of A, denoted $\gamma(A)$. If A is primitive, then $\gamma(A) \leq n^2 - 2n + 2$.*

Let $q = 2^n - |C|$. Combining Thm. 6 with Thm. 5 and recalling that $\tilde{Q}_C \in \mathbb{R}^{q\times q}$ yields the following result.

Corollary 2. *If the matrix $\tilde{Q}_C$ is primitive, then*

$$\gamma(\tilde{Q}_C) \leq q^2 - 2q + 2 \tag{12}$$

and the BCN (3) is $\gamma(\tilde{Q}_C)$ fixed-time controllable. If $\tilde{Q}_C$ is not primitive, then the BCN is not k fixed-time controllable for any k.

The link between k fixed-time controllability and primitivity of $\tilde{Q}_C$ implies the following result.

Corollary 3. *If a BCN is k fixed-time controllable, then it is p fixed-time controllable for any $p \geq k$.*

Proof. k fixed-time controllability implies that $\tilde{Q}_C^k > 0$. Assume that there exist i, j such that $(\tilde{Q}_C^{k+1})_{ij} = 0$. Thus, the multiplication of row i of $\tilde{Q}_C^k$ and column j of $\tilde{Q}_C$ is zero. Since $\tilde{Q}_C^k > 0$ and $\tilde{Q}_C \geq 0$, this implies that every entry in column j of $\tilde{Q}_C$ is zero. But then clearly $\tilde{Q}_C^k$ cannot be positive. This contradiction shows that $\tilde{Q}_C^k > 0$ implies that $\tilde{Q}_C^{k+1} > 0$. □

The bound (12) cannot be improved in general. However, under additional assumptions on A it is possible to derive tighter bounds for $\gamma(A)$ (see e.g. (Berman and Plemmons, 1987, Ch. 2)).

Example 6. *For $C = \emptyset$, consider the controllability of the three-state, one-input BCN*

$$\begin{aligned} x_1(k+1) =& [\bar{x}_1(k) \wedge \bar{x}_2(k) \wedge \bar{x}_3(k)] \vee [x_1(k) \wedge x_3(k)] \\ & \vee [x_1(k) \wedge x_2(k)], \\ x_2(k+1) =& [\bar{x}_2(k) \wedge \bar{x}_3(k)] \vee [x_2(k) \wedge x_3(k)], \\ x_3(k+1) =& [x_2(k) \wedge \bar{x}_3(k)] \vee [\bar{x}_2(k) \wedge \bar{x}_3(k) \wedge [u(k) \vee x_1(k)]]. \end{aligned} \tag{13}$$

The ASSR is given by $n = 3$, $m = 1$, and

$$L = \begin{bmatrix} e_8^2 & e_8^3 & e_8^4 & e_8^5 & e_8^6 & e_8^7 & e_8^8 & e_8^1 & e_8^2 & e_8^3 & e_8^4 & e_8^5 & e_8^6 & e_8^7 & e_8^8 & e_8^2 \end{bmatrix},$$

and $Q = L \ltimes \begin{bmatrix} 1 & 1 \end{bmatrix}^T$ yields

$$Q = \begin{bmatrix} 2e_8^2 & 2e_8^3 & 2e_8^4 & 2e_8^5 & 2e_8^6 & 2e_8^7 & 2e_8^8 & e_8^1 + e_8^2 \end{bmatrix}.$$

A calculation yields $Q^i \not> 0$, $i \in \{1, \dots, 49\}$, and $Q^{50} > 0$, so the BCN is k fixed-time controllable for any $k \geq 50$, but not for any $k < 50$. Note that in this case the bound in (12) is $\gamma(Q) \leq 2^6 - 2^4 + 2 = 50$.

Fig. 2 depicts the trajectories of this BCN. Let $s(k; a)$ denote the number of different states that are reachable at time k starting from $x(0) = a$. It is easy to see from Fig. 2 that $s(k; e_8^1) = 1$ for $k \in \{1, \dots, 7\}$, $s(k; e_8^1) = 2$ for $k \in \{8, \dots, 14\}$, and so on. Therefore, $s(k; e_8^1) = 8$ if and only if $k \geq 50$. In other words, 50 is the minimal value such that starting from $x(0) = e_8^1$, any state can be reached at time k. ■

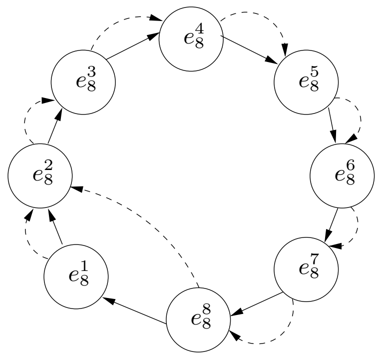

Fig. 2. Trajectories of the BCN in Example 6. A solid [dashed] line denotes the transition corresponding to $u(k) = e_2^1$ [$u(k) = e_2^2$].

5 Conclusion

Controllability analysis in biological systems modeled using BCNs may reveal how the structure and organization of the system guarantee the property of controllability. Also, when the controls represent inputs that may be manipulated from the outside world (e.g. the administration of a drug), then controllability analysis is of course a preliminary step to control synthesis.

Using Cheng's ASSR, we derived a simple formula for the number of different control sequences that steer a BCN between two given states in a given number of time-steps, while avoiding a set of forbidden states. We used this to derive a necessary and sufficient condition for two forms of controllability in terms of known results from the Perron-Frobenius theory.

Perron-Frobenius theory and graph-theoretic arguments play an important role in the analysis of discrete-time positive switched systems (see e.g. Fornasini and Valcher (2011) and the references therein). We believe that combining ideas from these fields with the special, canonical structure of BCNs may lead to further progress in the control-theoretic analysis of BCNs.

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