Automatica 50 (2014) 1272–1278

Contents lists available at ScienceDirect

Automatica

journal homepage: www.elsevier.com/locate/automatica

Brief paper

# State feedback stabilization for probabilistic Boolean networks[☆]

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ARTICLE INFO

*Article history:*
Received 10 April 2013
Received in revised form
11 October 2013
Accepted 29 January 2014
Available online 5 March 2014

*Keywords:*
Boolean logic
Probabilistic Boolean networks
Stabilizability
State feedback

ABSTRACT

A probabilistic Boolean network (PBN) is a discrete-time system composed of a family of Boolean networks (BNs) between which the PBN switches in a stochastic fashion. Studying control-related problems in PBNs may provide new insights into the intrinsic control in biological systems and enable us to develop strategies for manipulating complex biological systems using exogenous inputs. This paper investigates the problem of state feedback stabilization for PBNs. Based on the algebraic representation of logic functions, a necessary and sufficient condition is derived for the existence of a globally stabilizing state feedback controller, and a control design method is proposed when the presented condition holds. It is shown that the controller designed via the proposed procedure can simultaneously stabilize a collection of PBNs that are composed of the same constituent BNs.



## 1. Introduction

A salient problem in systems biology is to understand gene function and the way in which genes interact in an integrative and holistic manner. A number of different genetic regulatory network models have been proposed for this purpose, ranging from Bayesian networks (Friedman, Linial, Nachman, & Pe'er, 2000), neural networks (Smolen, Baxter, & Byrne, 2000), and differential equations (Mestl, Plahte, & Omholt, 1995), to Petri nets (Steggles, Banks, Shaw, & Wipat, 2007), Boolean networks (BNs) (Kauffman, 1993), and probabilistic Boolean networks (PBNs) (Shmulevich, Dougherty, Kim, & Zhang, 2002; Shmulevich, Dougherty, & Zhang, 2002). Among these models, perhaps, the most attention has been given to BN and PBN (an extension from BN). A BN is a deterministic dynamic model, in which gene expression states are quantized to only two levels: on and off (represented as 1 and 0, respectively). The expression state of a gene is functionally related to the expression states of some other genes in the network, using logical rules. Many studies have been done for understanding the dynamic properties of BNs; see, e.g., Cheng (2009); Cheng and Qi (2010a); Cheng and Qi (2010b); Dubrova and Teslenko (2011); Farrow, Heidel, Maloney, and Rogers (2004); Heidel, Maloney, Farrow, and Rogers (2003). Control-related problems in BNs, such as controllability, observability, disturbance decoupling, and optimal control, have also been extensively studied (Cheng, 2011; Cheng & Qi, 2009; Fornasini & Valcher, 2013; Laschov & Margaliot, 2011, 2012; Li & Wang, 2012; Yang, Li, & Chu, 2013; Zhao, Li, & Cheng, 2011; Zhao, Qi, & Cheng, 2010).

A PBN is a stochastic extension of the BN model. It can be considered as a collection of BNs endowed with a probability structure for switching between different constituent BNs. PBNs share the appealing properties of BNs in that they incorporate rule-based dependencies between genes, but are able to cope with uncertainties, both in the data and the model selection (Shmulevich, Dougherty, Kim et al., 2002). Recent efforts in PBN research typically focus on the analysis of dynamic behaviors, such as attractor structures and steady-state distributions (Brun, Dougherty, & Shmulevich, 2005; Ching, Zhang, Ng, & Akutsu, 2007; Hayashida, Tamura, Akutsu, Ching, & Cong, 2009; Pal, 2010; Shmulevich, Gluhovsky, Hashimoto, Dougherty, & Zhang, 2003; Zhang, Ching, Ng, & Akutsu, 2007), and aim to develop methods for finding control strategies for complex biological systems (Ching et al., 2009; Datta, Choudhary, Bittner, & Dougherty, 2003, 2004; Denic, Vasic, Charalambous, & Palanivelu, 2009; Kobayashi & Hiraishi, 2011, 2012; Layek, Datta, Pal, & Dougherty, 2009; Li & Sun, 2011a; Liu, Guo, & Zhou, 2010; Pal, Datta, & Dougherty, 2006, 2008; Tan, Alhajj, & Polat, 2010).

☆ This work was supported by the National Natural Science Foundation of China under Grant 61273111 and the National Basic Research Program of China under Grant 2012CB821200. The material in this paper was not presented at any conference. This paper was recommended for publication in revised form by Associate Editor Jan Komenda under the direction of Editor Ian R. Petersen.

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http://dx.doi.org/10.1016/j.automatica.2014.02.034
0005-1098/

The stabilization problem is a basic, yet challenging issue when studying PBNs. The consideration of such a problem could be naturally motivated in the context of gene therapy applications, where one may want to design therapeutic intervention strategies for shifting the state of a diseased network from an undesirable location to a desirable one and maintaining the desirable state afterwards. Also, stabilizability analysis of complex biological systems modeled using PBNs may reveal how the structure and organization of the system contribute to the system stability. In Qi, Cheng, and Hu (2010) and Li and Sun (2011b), the problems of stability and stabilization for PBNs were studied, and some sufficient conditions were found. More recently, by using the state adjacent matrices, Zhao and Cheng (2012, 2014) established a necessary and sufficient condition for stabilizability of PBNs and further extended their result to higher-order probabilistic mix-valued logical networks.

In this paper, following a similar idea as the one used in our recent work (Li, Yang, & Chu, 2013) of designing stabilizing control laws for BNs, we address the problem of constructing globally stabilizing state feedback controllers for PBNs. Using the algebraic representation of logic functions based on the semi-tensor product technique (Cheng, Qi, & Li, 2011), we derive a necessary and sufficient condition for the existence of a globally stabilizing state feedback control law. The main difference between the stabilizability condition and the existing ones is that here the condition is constructive, in that it explicitly constructs the feedback law that achieves global stabilization. This leads to the establishment of a controller design method when global stabilization via state feedback is feasible.

*Notation.* $I_n$ is the $n \times n$ identity matrix. $\delta_n^i$ stands for the $i$th column of $I_n$. $\Delta_n$ stands for the set consisting of the vectors $\delta_n^1, \ldots, \delta_n^n$. $\mathcal{L}_{n\times m}$ denotes the set of all $n \times m$ matrices in which every column has a unique nonzero entry and all nonzero entries are equal to 1. $|S|$ denotes the cardinality of a set $S$. $\otimes$ is the Kronecker product of matrices.

## 2. Preliminaries

### 2.1. Description of PBN and definition of stability

A PBN consists of a set of nodes and a set of logic functions, governing the state transitions of the nodes. Each logic function determines a BN, and the governing BN is randomly chosen at every time step in accordance with a fixed probability distribution. More formally, given a set of logic functions $f_i: \{1, 0\}^n \to \{1, 0\}^n$, $i = 1, 2, \ldots, r$, then the PBN can be modeled as

$$X(t+1) = f(X(t)), \quad t = 0, 1, 2, \ldots, \tag{1}$$

where $X(t)$ denotes the $n$-dimensional state variable at time $t$, taking values in $\{1, 0\}^n$, and the function $f$ is chosen from among $f_1, f_2, \ldots, f_r$ at each time point, with the selection probability $p_i$ of choosing $f_i$.

**Definition 1.** For the PBN (1), a state $X^* \in \{1, 0\}^n$ is said to be globally stable with probability one, if for every $X_0 \in \{1, 0\}^n$ there is a positive integer $N$ such that $P[X(t) = X^* | X(0) = X_0] = 1$ whenever $t \geq N$.

**Remark 1.** The notion of stability for a PBN is a subtle one. If a PBN were to represent a real genetic regulatory system, then stability would indicate whether or not an arbitrary state eventually enters a fixed state, called a singleton attractor, which may be used to characterize a cell's phenotype. Stability is thus related to the concept of convergence and consequently each variant of stochastic convergence (e.g., with probability one, in probability, in mean square, etc.) yields a corresponding definition of stability for PBNs. Currently, the most commonly used definition is that of stability with probability one. This is partly because for practical applications one often desires stability properties as close to deterministic stability as possible; another reason is that some biological systems have been observed to possess an almost sure type of stability (see, e.g., Kozin, 1969).

### 2.2. Algebraic representation of logic functions

Representing a logic function in an algebraic form is quite useful when studying logic-based problems. This is based on the semi-tensor product of matrices.

**Definition 2** (*Cheng et al., 2011*)**.** Let $A \in \mathbb{R}^{n_1\times m_1}$ and $B \in \mathbb{R}^{n_2\times m_2}$. The semi-tensor product of $A$ and $B$ is

$$A \ltimes B = (A \otimes I_{l/m_1})(B \otimes I_{l/n_2}),$$

where $l$ is the least common multiple of $m_1$ and $n_2$.

**Remark 2.** If $m_1 = n_2$, then $A \ltimes B = AB$, so we may view the semi-tensor product as an extension of the standard matrix product. Notice that if $a \in \Delta_{n_1}$ and $b \in \Delta_{n_2}$ then $a \ltimes b \in \Delta_{n_1 n_2}$. Various properties of the semi-tensor product are discussed in Cheng et al. (2011). For our purposes, it is sufficient to note that the semi-tensor product is associative: $(A \ltimes B) \ltimes C = A \ltimes (B \ltimes C)$, and distributive: $A \ltimes (B+C) = (A\ltimes B)+(A\ltimes C)$ and $(A+B)\ltimes C = (A\ltimes C)+(B\ltimes C)$.

Now represent the Boolean values 1 and 0 by the canonical vectors $\delta_2^1$ and $\delta_2^2$, respectively. Then any logic function $g$ of $\{1, 0\}^q$ into $\{1, 0\}^p$ can be equivalently represented as a mapping $\bar{g}$ of $(\Delta_2)^q$ into $(\Delta_2)^p$. With some abuse of notation, we will identify $\bar{g}$ with $g$. In other words, from here on a Boolean variable is always a vector in $\Delta_2$. We have the following result.

**Lemma 1** (*Cheng et al., 2011*)**.** *Suppose that $g$ maps $(\Delta_2)^q$ into $(\Delta_2)^p$, $X = (x_1, \ldots, x_q) \in (\Delta_2)^q$, and $Y = (y_1, \ldots, y_p) = g(X)$. Then there exists a unique matrix $G \in \mathcal{L}_{2^p\times 2^q}$ such that*

$$y_1 \ltimes \cdots \ltimes y_p = G \ltimes x_1 \ltimes \cdots \ltimes x_q. \tag{2}$$

Since, for every positive integer $k$, the mapping from $(\Delta_2)^k$ to $\Delta_{2^k}$ sending $(x_1, \ldots, x_k)$ to $x_1 \ltimes \cdots \ltimes x_k$ is bijective (Cheng et al., 2011), (2) provides an algebraic representation of the logic function $g$. The matrix $G$ is called the structure matrix of $g$. Specific algorithms for calculating the structure matrix from a logic function, and vice versa, can be found in Cheng et al. (2011).

## 3. State feedback controller

Let $f_1, f_2, \ldots, f_r$ be logic functions of $(\Delta_2)^n \times (\Delta_2)^m$ into $(\Delta_2)^n$. Consider the following PBN

$$X(t+1) = f(X(t), U(t)), \quad t = 0, 1, 2, \ldots, \tag{3}$$

where $X(t)$ and $U(t)$ denote the $n$-dimensional state variable and the $m$-dimensional input at time $t$, taking values in $(\Delta_2)^n$ and $(\Delta_2)^m$, respectively, and $f$ is chosen from among $f_1, f_2, \ldots, f_r$ at every time step, with the probability $p_i > 0$ of choosing $f_i$. Then the relation $\sum_{i=1}^r p_i = 1$ must be satisfied.

It is worth noting that, for every $X_1 \in (\Delta_2)^n$, $X_2 \in (\Delta_2)^n$, and $U \in (\Delta_2)^m$, the conditional probabilities

$$P[X(t+1) = X_2 | X(t) = X_1, U(t) = U], \quad t = 0, 1, 2, \ldots,$$

are independent of $t$. Thus, in this sense, the PBN (3) represents a stationary discrete-time dynamic system.

In this paper, we shall deal with a state feedback stabilization problem for the PBN (3). More precisely, we are concerned with