



# Asymptotic stability in probability for Stochastic Boolean Networks<sup>☆</sup>



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## ABSTRACT

In this paper, a new class of Boolean networks, called Stochastic Boolean Networks, is presented. These systems combine some features of the classical deterministic Boolean networks (the state variables admit two operation levels, either 0 or 1) and of Probabilistic Boolean Networks (at each time instant the transition map is selected through a random process), enriching the set of admissible dynamical behaviors, thanks to the set-valued nature of the transition map. Necessary and sufficient Lyapunov conditions are given to guarantee global asymptotic stability (resp., global asymptotic stability in probability) of a given set for a deterministic Boolean network with set-valued transition map (resp., for a Stochastic Boolean Network). A constructive procedure to compute a Lyapunov function (resp., stochastic Lyapunov function) relative to a given set for a deterministic Boolean network with set-valued transition map (resp., Stochastic Boolean Network) is reported.

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## 1. Introduction

The study of the relation between the expression of a gene and the synthesis of a particular biochemical product is one of the most challenging problems in modern molecular biology (Perdew, Vanden Heuvel, & Peters, 2014). In the literature, different frameworks have been proposed to model and analyze this complex relationship, such as: cluster analysis (Eisen, Spellman, Brown, & Botstein, 1998), Bayesian networks (Friedman, Linial, Nachman, & Pe'er, 2000; Yu, Smith, Wang, Hartemink, & Jarvis, 2004), information-theoretic approaches (Margolin et al., 2006), and Ordinary Differential Equations (Bansal, Della Gatta, & Di Bernardo, 2006). Among these analytical models, Boolean networks are receiving growing interest (Grieb et al., 2015; Kaushik & Sahi, 2015).

A Boolean network is a discrete-time nonlinear system described by variables with binary operation levels (Kauffman, 1969). At each time instant, the state of the system is updated by using a logic function of the current variables. In fact, each gene

can have two states: 1, when it is expressed, and 0, when it is not. Similarly, each biochemical product can have two states, 0 or 1, depending on its presence above or below a certain concentration threshold, respectively. This kind of structure can capture the behavior of complex regulatory networks (Albert & Barabási, 2000; Harris, Sawhill, Wuensche, & Kauffman, 2002). In the literature, many different approaches have been proposed to characterize the dynamical behavior of this class of systems. For instance, in Cheng and Qi (2010), a mathematical framework has been proposed to convert a Boolean network into a classical discrete-time, time-invariant system, and it is shown that, by analyzing the transition matrix of such a system, one can identify some features of the Boolean network such as: the number of fixed points, the number of cycles of given length, the transient period for all points to enter the set of attractors, and the basin of attraction for each attractor. On the other hand, in Hinkelmann et al. (2011), an algebraic geometry approach has been proposed to identify attractors. Algebraic geometry techniques have been used also to compute Darboux polynomials (Menini & Tornambe, 2013a) and to design observers for Boolean networks (Menini & Tornambe, 2013b). Even if these systems have been first used to model biological relationships, they are receiving most attention also in other fields such as: financial markets (Caetano & Yoneyama, 2015), electronics (Rosin, 2015), and industrial networks (Easton, Brooks, Georgieva, & Wilkinson, 2008).

One of the most important limitations of classical Boolean networks is their determinism (somehow mitigated in Thomas (1973)

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by the introduction of Boolean networks with asynchronous updates). In Shmulevich, Dougherty, and Zhang (2002b), Probabilistic Boolean Networks (briefly, PBN) have been introduced; they share the appealing structure of Deterministic Boolean Networks, but are also able to cope with uncertainty both in the data and in the model selection. Namely, a PBN is a discrete-time system that shares the structure of a classical Boolean network (i.e., the state variables admit two operation levels), but the transition from a state to another one is governed by a random process. In fact, a PBN involves a set of possible Boolean maps for each state variable and, at each update time, the process of choosing a certain map rather than another is governed by a random process (for further details and the formal definition of a PBN, see Section 2.2). The interest in these systems arises from the advent of gene expression microarrays that yield quantitative and semi-quantitative data on the cell status in a specific condition and time (Bansal, Belcastro, Ambesi-Impiombato, & Di Bernardo, 2007). However, many times, the available data are not sufficient to estimate all the parameters that are present in the system (e.g., when the number of variables involved in the process is higher than the number of available measures, or when some essential variables are unmeasurable). In these cases, it may be preferable to have a probabilistic description of the process being analyzed.

In this paper, a new class of Boolean networks, called Stochastic Boolean Networks (briefly, SBN), is presented. This kind of system admits state variables with binary operation levels as classical Boolean networks and the transition from a state to the following one is governed by a stochastic process as in PBNs. The difference between these systems and PBNs is that, at each time instant and for each outcome of the random process, the map from the current state to the subsequent one need not be single-valued, but can be set-valued. The advantage of this feature is that, when the number of possible states is too large for precise estimation or when some essential variables are either not measurable or unknown, it is not necessary to restrict the number of considered values to an essential set that defines a function. In fact, a whole branch of behaviors can be encoded by a single SBN. Moreover, the structure of SBNs allows to cope with biological dynamical models having non-unique solutions (Conte, Federici, & Zbilut, 2004; Kaitala & Heino, 1996; Kaitala, Ylikarjula, & Heino, 2000; Upadhyay, 2003). Two motivating examples are given in Section 2.

## 2. Notation and preliminaries

Let  $\mathbb{Z}$  and  $\mathbb{R}$  denote the set of integers and real numbers, respectively. Given  $k \in \mathbb{Z}$ , let  $\mathbb{Z}_{\geq k} := \{z \in \mathbb{Z} : z \geq k\}$ ,  $\mathbb{R}_{\geq k} := \{r \in \mathbb{R} : r \geq k\}$ , and  $\mathbb{Z}_{< k} := \{z \in \mathbb{Z}_{\geq 0} : z < k\}$ . A function  $\alpha : \mathbb{R}_{\geq 0} \rightarrow \mathbb{R}_{\geq 0}$  is of class  $\mathcal{K}$ , denoted  $\alpha \in \mathcal{K}$ , if it is continuous, strictly increasing and  $\alpha(0) = 0$ . A function  $\alpha : \mathbb{R}_{\geq 0} \rightarrow \mathbb{R}_{\geq 0}$  is of class  $\mathcal{K}_{\infty}$ , denoted  $\alpha \in \mathcal{K}_{\infty}$ , if  $\alpha \in \mathcal{K}$  and it is unbounded. Let  $(\mathbb{K}, \mathfrak{d})$  be a metric space. Since  $\mathfrak{d}$  is a metric for  $\mathbb{K}$ , the concept of convergence is well defined. Namely, a sequence  $\{x^v\}_{v=0}^{\infty}$  is said to converge to  $x$ , denoted  $x^v \rightarrow x$ , if for every  $\varepsilon > 0$  there exists  $N \in \mathbb{Z}_{\geq 0}$  such that  $v \geq N$  implies  $\mathfrak{d}(x^v, x) \leq \varepsilon$ . A set-valued mapping  $S : \mathbb{K} \rightrightarrows \mathbb{K}$  is a left-total relation assigning to each element  $x \in \mathbb{K}$  a set  $S(x) \subset \mathbb{K}$ . A set-valued mapping  $S : \mathbb{K} \rightrightarrows \mathbb{K}$  is *outer semicontinuous* at  $\bar{x} \in \mathbb{K}$  if  $\limsup_{x \rightarrow \bar{x}} S(x) \subset S(\bar{x})$ , where  $\limsup_{x \rightarrow \bar{x}} S(x) := \{y \in \mathbb{K} : \exists x^v \rightarrow \bar{x}, \exists y^v \rightarrow y, \text{ with } y^v \in S(x^v)\}$ . A mapping  $S : \mathbb{K} \rightrightarrows \mathbb{K}$  is *locally bounded* if, for each bounded set  $K \subset \mathbb{K}$ ,  $S(K) := \bigcup_{x \in K} S(x)$  is bounded. A mapping  $S : \mathbb{K}_1 \rightrightarrows \mathbb{K}_2$  is *measurable* if, for every open set  $\mathcal{O} \subset \mathbb{K}_2$ , the set  $S^{-1}(\mathcal{O}) := \{y \in \mathbb{K}_1 : S(y) \cap \mathcal{O} \neq \emptyset\}$  is measurable. Given  $\mathcal{A} \subset \mathbb{K}$ , a continuous function  $\varrho : \mathbb{K} \rightarrow \mathbb{R}_{\geq 0}$  is of class  $\mathcal{PD}(\mathcal{A})$ , denoted  $\varrho \in \mathcal{PD}(\mathcal{A})$ , if  $\varrho(x) = 0$ , for all  $x \in \mathcal{A}$  and  $\varrho(x) > 0$ , for all  $x \in \mathbb{K} \setminus \mathcal{A}$ . Given a finite set  $\Psi \subset \mathbb{K}$ , the symbol  $\mathcal{P}(\Psi)$  denotes the *power set* of  $\Psi$ , i.e., the set of all the subsets of  $\Psi$ . The symbols  $\neg, \vee, \wedge$ , and  $\oplus$  represent the entry wise logical “not”, “or”, “and”, and “exclusive or” operators, respectively. The symbol  $(\cdot)^+$  denotes the next value.

### 2.1. The Galois field $\mathbb{F}_2$

Let  $\mathbb{F}_2 := \{0, 1\}$  denote the *Galois field of order 2* (Lidl & Niederreiter, 1994). The set of all the  $n$ -dimensional vectors whose entries are in  $\mathbb{F}_2$  is denoted  $\mathbb{F}_2^n$ . Note that each vector in  $\mathbb{F}_2^n$  is essentially an  $n$ -bit digital number  $[x_1 \ x_2 \ \cdots \ x_n]^T$ , whose decimal equivalent is given by  $\pi_n : \mathbb{F}_2^n \rightarrow \mathbb{Z}_{\geq 0}$ ,  $\pi_n(x) = \sum_{i=1}^n 2^{i-1} \psi^{-1}(x_i)$ , where  $\psi^{-1} : \mathbb{F}_2 \rightarrow \{0, 1\} \subset \mathbb{Z}$  maps each  $x \in \mathbb{F}_2$  to the corresponding integer value in  $\{0, 1\} \subset \mathbb{Z}$ . In the following,  $\pi_n^{-1}$  denotes the inverse map of  $\pi_n$ . Let a point  $y \in \mathbb{F}_2^n$  be given. For each  $x \in \mathbb{F}_2^n$ , the *distance between  $x$  and  $y$*  is  $\mathfrak{d}(x, y) : \mathbb{F}_2^n \times \mathbb{F}_2^n \rightarrow \mathbb{Z}_{\geq 0}$ ,  $\mathfrak{d}(x, y) := \sum_{i=1}^n \psi^{-1}(x_i \oplus y_i)$ , where  $x_i, y_i \in \mathbb{F}_2$ , because  $x, y \in \mathbb{F}_2^n$ . The distance  $\mathfrak{d}$  is usually known in coding theory as *Hamming distance* (Hamming, 1950), when applied to strings of equal length. On the other hand, letting  $\mathcal{A} \subset \mathbb{F}_2^n$ , the *distance between  $x$  and  $\mathcal{A}$*  is  $|x|_{\mathcal{A}} := \min_{y \in \mathcal{A}} \mathfrak{d}(x, y)$ . The following lemma, whose proof is well known (Bourbaki, 1998), states that the function  $\mathfrak{d}$  is a metric on  $\mathbb{F}_2^n$  and hence the definitions given at the beginning of this section apply to such a field, when the distance  $\mathfrak{d}$  is used as a metric.

**Lemma 1.** *The pair  $(\mathbb{F}_2^n, \mathfrak{d})$  constitutes a metric space.*

Since the pair  $(\mathbb{F}_2^n, \mathfrak{d})$  is a metric space, it is possible to define the *open ball of radius  $r > 0$  about  $x \in \mathbb{F}_2^n$*  as  $\mathbb{B}(x, r) = \{y \in \mathbb{F}_2^n : \mathfrak{d}(y, x) < r\}$ . A set  $\mathcal{A} \subset \mathbb{F}_2^n$  is *open* if, for every  $x \in \mathcal{A}$ ,  $\exists r > 0$  such that  $\mathbb{B}(x, r) \subset \mathcal{A}$ . A set  $\mathcal{A} \subset \mathbb{F}_2^n$  is *closed* if  $\mathbb{F}_2^n \setminus \mathcal{A}$  is open. For any set  $\mathcal{A}$  and  $\varepsilon > 0$ , let  $\mathcal{A} + \mathbb{B}(0, \varepsilon) = \{x \in \mathbb{F}_2^n : |x|_{\mathcal{A}} < \varepsilon\}$ . Next lemma characterizes the topology of the metric space  $(\mathbb{F}_2^n, \mathfrak{d})$ .

**Lemma 2.** *Each set  $\mathcal{A} \subset \mathbb{F}_2^n$  is both open and closed.*

**Proof.** By Lemma 1,  $(\mathbb{F}_2^n, \mathfrak{d})$  constitutes a metric space. Hence, the open ball  $\mathbb{B}(x, r)$  is well defined. Consider the set  $\mathcal{A}_i = \{\bar{x}\}$ , with  $\bar{x} \in \mathbb{F}_2^n$ . The set  $\mathcal{A}_i$  is open because  $\mathbb{B}(\bar{x}, 1) \subset \mathcal{A}_i$ . Hence, since every set  $\mathcal{A} \subset \mathbb{F}_2^n$  is such that  $\mathcal{A} = \bigcup_{i \in I} \mathcal{A}_i$ , for some finite  $I$ ,  $\mathcal{A}$  is open (Bourbaki, 1998, Section 2.6, Section 2.7). Consider now  $\mathcal{B}_i := \mathbb{F}_2^n \setminus \mathcal{A}_i$ . The set  $\mathcal{B}_i$  is closed, because it is the complement of an open set. Since every set  $\mathcal{A}_i = \bigcap_{i \in I} \mathcal{B}_i$  for some finite  $I$ , the set  $\mathcal{A}_i$  is closed. Therefore, since each set  $\mathcal{A} = \bigcup_{i \in I} \mathcal{A}_i$ , for some finite  $I$ , and the union of finitely many closed sets is closed, the set  $\mathcal{A}$  is closed.  $\square$

### 2.2. Classes of Boolean networks

A map  $g : \mathbb{F}_2^n \rightarrow \mathbb{F}_2^\ell$  is called *Boolean* and can be defined by assigning to each of the  $2^n$  elements of  $\mathbb{F}_2^n$  one of the  $2^\ell$  elements of  $\mathbb{F}_2^\ell$ . A *Deterministic Boolean Network* (briefly, *DBN*) is a discrete-time system of the form

$$x^+ = g(x) \quad (1)$$

where  $x \in \mathbb{F}_2^n$  and  $g : \mathbb{F}_2^n \rightarrow \mathbb{F}_2^n$  is a Boolean map.

In order to deal with non-unique solutions (see the subsequent Examples 1 and 2), the concept of DBN can be extended through the notion of Boolean network with set-valued transition map, written formally as

$$x^+ \in G(x), \quad (2)$$

with  $G : \mathbb{F}_2^n \rightrightarrows \mathbb{F}_2^n$  having nonempty values for every  $x \in \mathbb{F}_2^n$ .

The following lemma states that the number of dynamical behaviors modeled by a Boolean network is bounded.

**Lemma 3.** *Let  $M := 2^n$  and  $N := (2^M - 1)^M$ . There exist  $M^M$  different  $g : \mathbb{F}_2^n \rightarrow \mathbb{F}_2^n$  and  $N$  different  $G : \mathbb{F}_2^n \rightrightarrows \mathbb{F}_2^n$  such that  $G(x)$  is nonempty for each  $x \in \mathbb{F}_2^n$ .*

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