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Stability structures of conjunctive Boolean networks ☆

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ABSTRACT

A Boolean network is a finite dynamical system, whose variables take values from a binary set. The value update rule for each variable is a Boolean function, depending on a selected subset of variables. Boolean networks have been widely used in modeling gene regulatory networks. We focus in this paper on a special class of Boolean networks, termed as *conjunctive Boolean networks*. A Boolean network is *conjunctive* if the associated value update rule is comprised of only AND operations. It is known that any trajectory of a finite dynamical system will enter a periodic orbit. We characterize in this paper all periodic orbits of a conjunctive Boolean network whose underlying graph is strongly connected. In particular, we establish a bijection between the set of periodic orbits and the set of binary necklaces of a certain length. We further investigate the stability of a periodic orbit. Specifically, we perturb a state in the periodic orbit by changing the value of a single entry of the state. The trajectory, with the perturbed state being the initial condition, will enter another (possibly the same) periodic orbit in finite time steps. We then provide a complete characterization of all such transitions from one periodic orbit to another. In particular, we construct a digraph, with the vertices being the periodic orbits, and the (directed) edges representing the transitions among the orbits. We call such a digraph the stability structure of the conjunctive Boolean network.

1. Introduction

Finite dynamical systems are discrete-time dynamical systems with finite state spaces. They have a long and successful history of being used in biological networks (Funahashi & Nakamura, 1993), epidemic networks (Khanafer, Başar, & Gharesifard, 2014), social networks (Etesami & Başar, 2016), and engineering control systems (Imer, Yüksel, & Başar, 2006). In this paper, we focus on a special class of finite dynamical systems, called Boolean networks (or Boolean automata networks (Noual, Regnault, & Sené, 2013)). Boolean networks are finite dynamical systems whose variables are of Boolean type, usually labeled as "1" and "0". The Boolean function, also known as the value update rule, for each variable depends on a selected subset of the variables.

Boolean networks have been widely used in systems biology and (mathematical) computational biology. This line of research began with Boolean network representations of molecular networks (Kauffman, 1969a), and was later generalized to the so-called logical models (Thomas & D'Ari, 1990). Since then there have been some studies of various classes of Boolean functions which are particularly suited to the logical expression of gene regulation (Kauffman, 1969b; Raeymaekers, 2002; Thomas, 1973). Evidence has been provided in Sontag, Veliz-Cuba, Laubenbacher, and Jarrah (2008) that biochemical networks are "close to monotone". Roughly speaking, a Boolean network is monotonic if its Boolean function has the property that the output value of the function for each variable is non-decreasing if the number of "1"s in the inputs increases. Monotonic Boolean networks have been studied both theoretically (Jarrah, Laubenbacher, & Veliz-Cuba, 2010; Melliti, Regnault, Richard, & Sené, 2013; Noual, 2012; Noual, Regnault, & Sené, 2012; Remy, Mossé, Chaouiya, & Thieffry, 2003) and in applications (Georgescu et al., 2008; Mendoza, Thieffry, & Alvarez-Buylla, 1999). Also, there have been studies of Boolean networks with other types of Boolean functions: For example, Boolean networks whose Boolean functions are monomials were studied in Colón-Reyes, Jarrah, Laubenbacher, and Sturmfels (2006); Colón-Reyes, Laubenbacher, and Pareigis (2005); Park and Gao (2012). The work by Veliz-Cuba and Laubenbacher (2010) considers the dynamics of the systems where the Boolean functions are comprised of semilattice operators, i.e., operators that are commutative, associative, and idempotent. Boolean networks whose Boolean functions are comprised of only XOR operations were investigated in Alcolei, Perrot, and Sené (2015), and whose Boolean functions are comprised of AND and NOT operations were

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studied in Veliz-Cuba, Aguilar, and Laubenbacher (2015); Veliz-Cuba et al. (2012).

A special class of Boolean functions, of particular interest to us here, is the so-called nested canalyzing functions. This class of functions was introduced in Kauffman (1993), and often used to model genetic networks (Harris, Sawhill, Wuensche, & Kauffman, 2002; Kauffman, Peterson, Samuelsson, & Troein, 2003, 2004). Roughly speaking, a canalyzing function is such that if an input of the function holds a certain value, called the "canalyzing value", then the output value of the function is uniquely determined regardless of the other values of the inputs (Jarrah, Raposa, & Laubenbacher, 2007). The majority of Boolean functions that appear in the literature on Boolean networks are nested canalyzing functions. Among the nested canalyzing functions, there are two simple but important classes: A function in the first class is comprised of only AND operations, with "0" the canalyzing value, while a function in the second class is comprised of only OR operations, with "1" the canalyzing value. The corresponding Boolean networks are said to be *conjunctive* and *disjunctive*, respectively (Goles & Noual, 2012; Jarrah et al., 2010). Note that there is a natural isomorphism between the class of conjunctive Boolean networks and the class of disjunctive Boolean network: indeed, if f (resp. g) is a function on n Boolean variables $x_1, \dots, x_n$, comprised of only AND (resp. OR) operations, then $f(x_1, \dots, x_n) = \neg g(\neg x_1, \dots, \neg x_n)$, where "$\neg$" is the negation operator, i.e., $\neg 0 = 1$ and $\neg 1 = 0$. It thus suffices to consider only conjunctive Boolean networks. We note here that a conjunctive Boolean network is monotonic.

Since a Boolean network is a finite dynamical system, for any initial condition, the trajectory generated by the system will enter a periodic orbit (also known as a limit cycle) in finite time steps (see, for example, Colón-Reyes et al., 2005). A question that comes up naturally is how the dynamical system behaves if a "perturbation" occurs in a state of a periodic orbit—meaning that one (and only one) of the variables fails to follow the update rule for the next time step (a precise definition is given in Section 4.2). The trajectory, with the perturbed state as its initial condition, will then enter another periodic orbit (possibly return to the original orbit). One of the questions addressed in this work is thus to characterize all possible transitions among the periodic orbits upon the occurrence of a perturbation.

A complete characterization of these transitions among the periodic orbits is given in Theorem 2, which captures the stability structure of a conjunctive Boolean network. The analysis of Theorem 2 relies on a representation of periodic orbits, which identifies the orbits with the so-called binary necklaces (a definition is given in Section 2.2). In particular, we show that there is a bijection between the set of periodic orbits and the set of binary necklaces of a certain length. To establish this bijection, we introduce in Section 3 a new approach for analyzing the system behavior of a conjunctive Boolean network: Roughly speaking, we decompose the original Boolean network into several components. For each of the components, there corresponds an induced dynamics. We then relate in Theorem 1 the original dynamic to these induced dynamics and establish several necessary and sufficient conditions for a state to be in a periodic orbit. This new approach may be of independent interest as it can be applied to other types of Boolean networks as well.

The rest of the paper is organized as follows. In Section 2, we first provide some basic definitions and notations for directed graphs and the binary necklace. We then introduce the class of conjunctive Boolean networks in precise terms. Some preliminary results on such networks are also given. In Section 3, we introduce the new approach as mentioned above. A detailed organization will be given at the beginning of that section. Then, in Section 4, we characterize all possible transitions among periodic orbits. Moreover, we associate each transition with a positive real number, termed as transition weight, which can be understood as the likelihood of the occurrence of the transition. We provide conclusions and outlooks in Section 5. The paper ends with Appendices which contains proofs of some technical results.

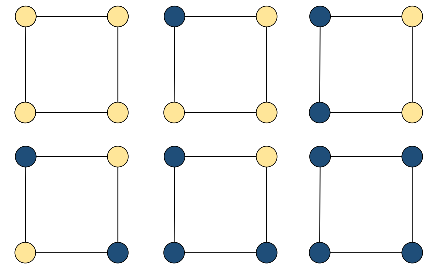

Fig. 1. All binary necklaces of length 4. If the bead is plotted in dark blue (resp. light yellow), then it holds value "1" (resp, "0"). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2. Preliminaries

2.1. Directed graph

We introduce here some useful notation associated with a directed graph (or simply digraph). Let $D = (V, E)$ be a directed graph. We denote by v_iv_j an edge from v_i to v_j in D. We say that v_i is an *in-neighbor* of v_j and v_j is an *out-neighbor* of v_i. The sets of in-neighbors and out-neighbors of vertex v_i are denoted by $\mathcal{N}_{\text{in}}(v_i)$ and $\mathcal{N}_{\text{out}}(v_i)$, respectively. The *in-degree* and *out-degree* of vertex v_i are defined as $|\mathcal{N}_{\text{in}}(v_i)|$ and $|\mathcal{N}_{\text{out}}(v_i)|$, respectively.

Let v_i and v_j be two vertices of D. A *walk* from v_i to v_j, denoted by w_{ij}, is a sequence $v_{i_0}v_{i_2}\cdots v_{i_m}$ (with $v_{i_0} = v_i$ and $v_{i_m} = v_j$) in which $v_{i_k}v_{i_{k+1}}$ is an edge of D for all $k \in \{0, 1, \dots, m-1\}$. A walk is said to be a *path* if all the vertices in the walk are pairwise distinct. A *closed walk* is a walk w_{ij} such that the starting vertex and ending vertex are the same, i.e., $v_i = v_j$. A walk is said to be a *cycle* if there is no repetition of vertices in the walk other than the repetition of the starting- and ending-vertex. The *length* of a path/cycle/walk is defined to be the number of edges in that path/cycle/walk.

A *strongly connected graph* is a directed graph such that for any two distinct vertices v_i and v_j in the graph, there is a path from v_i to v_j. A *cycle digraph* is a directed graph that consists of a single cycle.

2.2. Binary necklace

A **binary necklace** of length p is an equivalence class of p-character strings over the binary set $\mathbb{F}_2 = \{0, 1\}$, taking all rotations (circular shifts) as equivalent. For example, in the case of $p = 4$, there are six different binary necklaces, as illustrated in Fig. 1. A *necklace with fixed density* is a necklace in which the number of zeros (and hence, ones) is fixed. The **order** of a necklace is the cardinality of the corresponding equivalence class, and it is always a divisor of p. An *aperiodic necklace* (see, for example, Varadarajan & Wehrhahn, 1990) is a necklace of order p, i.e., no two distinct rotations of a necklace from such a class are equal. Thus, an aperiodic necklace cannot be partitioned into more than one sub-strings which have the same alphabet pattern. For example, a necklace of 1010 (row 2, column 1 in Fig. 1) can be partitioned into two substrings 10 and 10 which have the same alphabet pattern, and thus is not aperiodic. A necklace of 1000 (row 1, column 2 in Fig. 1) cannot be partitioned into more than one sub-strings with the same alphabet pattern, and is aperiodic.

2.3. Conjunctive Boolean network

Let $\mathbb{F}_2 = \{0, 1\}$ be the finite field with two elements. The two elements "0" and "1" can, for example, represent the "off" status