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Relations between gene regulatory networks and cell dynamics in Boolean models

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ABSTRACT

An asynchronous Boolean dynamics to some extent represents the joint evolution of a system of Boolean-discretized variables. In a biological context, these kinds of objects are used to model the evolution of the gene expression levels. With such a dynamics, one can associate a (genetic) regulatory graph summarizing the influence of each variable on the others. The first of Thomas's rules, formally proved in particular in the asynchronous Boolean framework, states that the presence of several stationary states in a dynamics arises only if the corresponding regulatory graph contains a positive feedback loop.

In the present work, we first give a necessary condition for the presence of a single stationary state in a dynamics and next derive a necessary condition for multistationarity which is slightly stronger than that required in the first of Thomas's rules. Next, we reverse the approach and study the properties of dynamics corresponding to a particular class of regulatory graphs, that are made up of several circuits sharing a common component. We prove that the corresponding dynamics contains at most two stationary states and give more specific results for when the regulatory graphs contain less than two positive (resp. negative) circuits. Moreover, we show that the behavior of a dynamics cannot be predicted if its regulatory graph contains both at least two positive circuits and two negative circuits (all sharing a common component). In particular, it may contain zero, one or two stationary states.

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1. Introduction

A living cell is sometimes modeled as a system of variables containing the quantitative levels of its components (essentially genes/proteins). On assuming that such a system is isolated, the joint dynamics of this set of variables just results from the mutual influences between its components. The regulatory graph of the system is a representation of these mutual influences, in the sense that it contains an edge from one component to another if the first component influences the level of the second one under some conditions. This edge is signed according to the direction of the influence (activation or repression) [1].

Relating regulatory graph properties with dynamics behaviors of the system is then a challenging problem which has been investigated in several frameworks. Among these, two general types can be distinguished, depending on the continuous or discrete nature of the variables [3,10]. In the first case, the dynamics of the system satisfies a differential equation of the form $\dot{x} = F(x)$, where x is the real-valued vector of the gene expression levels (see for instance [13]). The discrete representation that we are working with can be seen as a state space discretization of such a continuous model. This discretized dynamics is summarized by the so-called asynchronous dynamical graph [7], in which there is an edge

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between two discretized states if a trajectory of the continuous dynamics successively crosses the two subsets associated with these states.

Among the famous examples of relations between the dynamical behavior of the system and its regulatory graph are Thomas's rules [15] which can be stated as follows:

1. a necessary condition for multistability (i.e. the existence of several stationary states in the dynamics) is the existence of a positive circuit in the regulatory graph,
2. a necessary condition for the existence of an attractive cycle in the dynamics is the existence of a negative circuit.

From a biological point of view, the first rule corresponds to a basic case of cell differentiation, while the second one fits homeostasis or periodic behavior. These rules have been proved in several frameworks: piecewise linear [12], continuous [4,11,13] and discrete [2,8,7] dynamical systems.

In the present work, we deal with the same Boolean formalism as in [7]. We first give a necessary condition for the existence of a single stationary state and then we derive a necessary condition for the existence of several stationary states in the dynamics. This last condition turns out to be slightly stronger than that stated in the first of Thomas's rules. Next, we investigate what a regulatory graph can say about the stationary states of a corresponding dynamics. For when its regulatory graph is a simple circuit, it has been shown in [6] that the stationary states of a corresponding dynamics are completely determined. More specifically, if the regulatory graph is a positive circuit, there are two stationary states, while there is no stationary state when the regulatory graph is a negative circuit. We consider here the wider class of regulatory graphs combining several circuits through a common component. A first result is that the corresponding dynamics contains at most two stationary states. More specific results are given in the case of regulatory graphs containing less than two positive (resp. negative) circuits. Moreover, we show that the behavior of a dynamics cannot be predicted if its regulatory graph contains both at least two positive circuits and two negative circuits. In particular, it may contain zero, one or two stationary states.

The paper is organized as follows. In Section 2, we introduce basic definitions and notation, and formally present how regulatory graphs are associated with the dynamics. Section 3 is devoted to stationarity phenomena. Namely, we study conditions under which a (unique) stationary state may occur, give a stronger necessary condition for multistationarity and discuss unreachability. In Section 4, we first study the behavior of a component influenced by several regulators, then apply these results to dynamics associated with a class of graphs called flower-graphs, which can be seen as the simplest regulatory graphs containing several circuits. Then, we introduce two transformations over asynchronous dynamics which preserve both the number of stationary states and the essential features of the corresponding regulatory graphs. These transformations are next used to transpose the results obtained on flower-graphs onto the general class of graphs made up of several circuits, all sharing a same component (called hub-graphs). We give a brief conclusion in the last section.

2. Definitions and notation

The negation of a binary variable $a \in \{0, 1\}$ is denoted as $\overline{a}$ and is defined by $\overline{0} = 1$ and $\overline{1} = 0$. We put $\#A$ for the cardinality of a finite set A.

In what follows, Ω denotes a finite set of elements called *components* (*genes* in biological applications). The elements of $\{0, 1\}^{\Omega}$ are called *configurations* of Ω. One can think of Ω as a set of random variables taking values in $\{0, 1\}$ and of a configuration as a realization of this set of variables.

Let $\Gamma \subset \Omega$ and $x \in \{0, 1\}^{\Omega}$. We put $\overline{x}^{\Gamma}$ for the element of $\{0, 1\}^{\Omega}$ defined by

$$(\overline{x}^{\Gamma})_{\beta} = \begin{cases} \overline{x_{\beta}} & \text{if } \beta \in \Gamma \\ x_{\beta} & \text{otherwise.} \end{cases}$$

Given a component $\alpha \in \Omega$, the symbols $\overline{x}^{\alpha}$ and $\overline{x}$ stand for $\overline{x}^{\{\alpha\}}$ and $\overline{x}^{\Omega}$ respectively.

Let x and y be two configurations. We denote by $\Delta(x, y)$ the subset of components differentiating x and y: $\Delta(x, y) = \{\alpha \in \Omega \mid x_{\alpha} \neq y_{\alpha}\}$. Basically, we have both $x = \overline{y}^{\Delta(x,y)}$ and $y = \overline{x}^{\Delta(x,y)}$.

2.1. Asynchronous Boolean dynamics

An *asynchronous Boolean dynamics* is a directed graph represented by a pair $\langle \Omega, \mathcal{E} \rangle$, where Ω is a finite set of components and $\mathcal{E}$ is the edge set. The vertex set of $\langle \Omega, \mathcal{E} \rangle$ is $\{0, 1\}^{\Omega}$. The set $\mathcal{E}$ is assumed to be a subset of $\{(x, \overline{x}^{\alpha}) \mid x \in \{0, 1\}^{\Omega}$ and $\alpha \in \Omega\}$. In other words, two configurations connected by an edge only differ by one component (the so-called asynchronous character).

In [7], the authors introduce a Boolean function $f_{\langle \Omega, \mathcal{E} \rangle}$ from $\{0, 1\}^{\Omega}$ to $\{0, 1\}^{\Omega}$ which fully summarizes the asynchronous Boolean dynamics $\langle \Omega, \mathcal{E} \rangle$: for all $x \in \{0, 1\}^{\Omega}$ and all $\alpha \in \Omega$, $f_{\langle \Omega, \mathcal{E} \rangle}(x)$ is defined by $[f_{\langle \Omega, \mathcal{E} \rangle}(x)]_{\alpha} = \overline{x_{\alpha}}$ if $(x, \overline{x}^{\alpha}) \in \mathcal{E}$ and by $[f_{\langle \Omega, \mathcal{E} \rangle}(x)]_{\alpha} = x_{\alpha}$ otherwise.

A configuration x is said to be *stationary* (resp. *unreachable*) in $\langle \Omega, \mathcal{E} \rangle$ if there is no component $\alpha \in \Omega$ such that $(x, \overline{x}^{\alpha}) \in \mathcal{E}$ (resp. $(\overline{x}^{\alpha}, x) \in \mathcal{E}$).

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