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Negative local feedbacks in Boolean networks

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ABSTRACT

We study the asymptotic dynamical properties of Boolean networks without local negative cycle. While the properties of Boolean networks without local cycle or without local positive cycle are rather well understood, recent literature raises the following two questions about networks without local negative cycle. Do they have at least one fixed point? Should all their attractors be fixed points? The two main results of this paper are negative answers to both questions: we show that and-nets without local negative cycle may have no fixed point, and that Boolean networks without local negative cycle may have antipodal attractive cycles.

1. Introduction

A Boolean network is a map f from $\mathbb{F}_2^n$ to itself, where n is a positive integer and $\mathbb{F}_2$ is the two-element field. We view f as representing the dynamics of n interacting components which can take two values, 0 and 1: at a state $x \in \mathbb{F}_2^n$, the coordinates which can be updated are the integers $i \in \{1, \dots, n\}$ such that $f_i(x) \neq x_i$. Several dynamical systems can therefore be associated to f, depending on the choice of update scheme. In the synchronous dynamics [8,2], all coordinates are updated simultaneously (it is simply the iteration of f), while in the (nondeterministic) asynchronous dynamics [23], one coordinate is updated at a time, if any. Other dynamics are considered in the literature (e.g. random [7]), as well as comparisons between update schemes [4].

Boolean networks have plenty of applications. In particular, they have been extensively used as discrete models of various biological networks, since the early works of McCulloch and Pitts [9], S. Kauffman [7] and R. Thomas [21].

To a Boolean network f, it is possible to associate, for each state x, a directed graph $\mathcal{G}(f)(x)$ representing local influences between components $1, \dots, n$ and defined in a way similar to Jacobian matrices for differentiable maps. Local feedbacks, *i.e.* cycles in these local interaction graphs $\mathcal{G}(f)(x)$, have an impact on fixed points of f: [19] proves that Boolean networks without local cycle have a unique fixed point.

On the other hand, the edges of $\mathcal{G}(f)(x)$ naturally come up with a sign, which is positive in case of a covariant influence and negative otherwise. Intuitively, when applied to the modeling of, e.g., gene regulatory networks, positive and negative signs correspond respectively to activatory and inhibitory effects. It is therefore expected that the dynamics associated with positive and negative cycles (the sign being the product of the signs of the edges) will in general be very different, and the biologist R. Thomas [22,24] proposed rules relating positive cycles to multistationarity (which corresponds to cellular differentiation in the field of gene networks) and negative cycles to sustained oscillations (a form of homeostasis).

In terms of Boolean networks, sustained oscillations can be interpreted either by an attractive cycle (a cycle in the asynchronous dynamics which cannot be escaped), or more generally by a cyclic attractor (a strongly connected component of the asynchronous dynamics which does not consist in a fixed point). Also notice that the absence of fixed point entails a cyclic attractor. Therefore, these rules give rise to the following series of questions:

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$$\begin{aligned} f_1(x) &= (x_2+1)x_3 \\ f_2(x) &= x_3+1 \\ f_3(x) &= (x_1+1)x_2 \end{aligned}$$

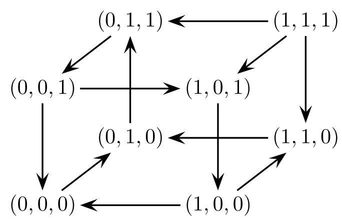

Fig. 1. A map $f : \mathbb{F}_2^3 \to \mathbb{F}_2^3$ and the asynchronous dynamics $\Gamma(f)$ associated to it.

Questions. 1. *Does a network without local positive cycle have at most one fixed point?*
2. *Does a network without local negative cycle have at least one fixed point?*
3. *Does a network with a cyclic attractor have a local negative cycle?*
4. *Does a network with an attractive cycle have a local negative cycle?*

Question 1 is given a positive answer in [13].

Question 2, which is mentioned for instance in [14], is also a negative counterpart of Question 1, and thus motivated by the above result of [19]. Question 3 is related to the following result: if f has a cyclic attractor, then the global interaction graph $\mathcal{G}(f)$ obtained by taking the union of the local graphs $\mathcal{G}(f)(x)$ has a negative cycle [14]. Several partial results are also known for local negative cycles [15,17], and are recalled in Section 2.4. In the more general discrete case (with more than two values), [14] shows that a network without local negative cycle may have an attractive cycle and no fixed point. A partial positive answer to Question 4 is known for Boolean networks of a special class called and-nets (in which all dependencies are conjunctions): and-nets with a special type of attractive cycle, called antipodal, do have a local negative cycle [18].

Theorem A gives a negative answer to Question 2, and hence to Question 3, even for and-nets. In Section 3, we construct a 12-dimensional and-net with no local negative cycle and no fixed point. The proof relies essentially on a trick for delocalizing cycles by expanding and-nets (Section 3.3). Section 3.5 also mentions a consequence for kernels in graph theory (Theorem A′).

Then Theorem B gives a negative answer to Question 4: in Section 4, we prove that arbitrary Boolean networks without local negative cycle may have (antipodal) attractive cycles. For this construction, we start with a Boolean network with an antipodal attractive cycle, and then modify the neighborhood of this attractive cycle so as to delocalize all negative cycles. The proof that the resulting network has indeed no local negative cycle is simplified by using some isometries of $\mathbb{F}_2^n$ (Sections 4.2 and 4.3). We may remark that the metric structure of $\mathbb{F}_2^n$ was the main ingredient for unsigned cycles and positive cycles too (see [18]), though the proofs were apparently very different.

Section 5 includes remarks on non-expansive Boolean networks, hoopings, invertible Jacobian matrices, and reduction of networks.

2. Definitions and statement of results

Let $\{e^1, \ldots, e^n\}$ denote the canonical basis of the vector space $\mathbb{F}_2^n$, and for each subset I of $\{1, \ldots, n\}$, let $e^I = \sum_{i\in I} e^i$, where the sum is the sum of the field $\mathbb{F}_2$. We may remove some brackets and write $e^{1,2}$ for $e^{\{1,2\}}$ for instance. For $x, y \in \mathbb{F}_2^n$, $d(x, y)$ denotes the Hamming distance, *i.e.* the cardinality of the unique subset $I \subseteq \{1, \ldots, n\}$ such that $x + y = e^I$.

2.1. Boolean networks

A Boolean network is a map $f : \mathbb{F}_2^n \to \mathbb{F}_2^n$. To such a map, it is possible to associate several dynamics with points of $\mathbb{F}_2^n$ as the states.

The *synchronous dynamics* is simply the iteration of f. The *asynchronous dynamics* is the directed graph $\Gamma(f)$ with vertex set $\mathbb{F}_2^n$ and an edge from x to y when for some i, $y = x + e^i$ and $f_i(x) \neq x_i$. It is a nondeterministic dynamics (a state $x \in \mathbb{F}_2^n$ can have 0 or several successors) in which at most one coordinate is updated at a time. The coordinates i such that $f_i(x) \neq x_i$ are those which can be updated in state x, and may therefore naturally be viewed as the *degrees of freedom* of x.

The asynchronous dynamics, illustrated in Fig. 1, can be viewed as a weak form of orientation of the Boolean hypercube $\mathbb{F}_2^n$, in which each undirected edge is replaced by 0,1 or 2 of the possible choices of orientation.

It is easily seen that f can be recovered from $\Gamma(f)$: $f(x) = x + e^I$, where $\{(x, x + e^i), i \in I\}$ is the set of edges leaving x in $\Gamma(f)$.

We shall be essentially interested in asymptotic dynamical properties. Both dynamics agree on fixed points. On the other hand, a *trajectory* will be a path in the asynchronous dynamics $\Gamma(f)$, and an *attractor* a terminal strongly connected component of $\Gamma(f)$. An attractor which is not a singleton (*i.e.* which does not consist in a fixed point) is called a *cyclic attractor*. In particular, a network with no fixed point must have at least one cyclic attractor. In the case of the fixed-point-free network f of Fig. 1, the unique cyclic attractor consists in the subgraph of $\Gamma(f)$ induced by $\mathbb{F}_2^3 \setminus \{(1, 1, 1)\}$.