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# Fixed points and connections between positive and negative cycles in Boolean networks

Adrien Richard

*Laboratoire I3S, CNRS, Université Côte d'Azur & Université Nice Sophia Antipolis, France*

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ABSTRACT

We are interested in the relationships between the number of fixed points in a Boolean network $f : \{0, 1\}^n \to \{0, 1\}^n$ and its interaction graph, which is the arc-signed digraph $G$ on $\{1, \dots, n\}$ that describes the positive and negative influences between the components of the network. A fundamental theorem of Aracena says that if $G$ has no positive (resp. negative) cycle, then $f$ has at most (resp. at least) one fixed point; the sign of a cycle being the product of the signs of its arcs. In this note, we generalize this result by taking into account the influence of connections between positive and negative cycles. In particular, we prove that if every positive (resp. negative) cycle of $G$ has an arc $a$ such that $G \setminus a$ has a non-trivial initial strongly connected component containing the terminal vertex of $a$ and only negative (resp. positive) cycles, then $f$ has at most (resp. at least) one fixed point. This is, up to our knowledge, the first generalization of Aracena's theorem where the conditions are expressed with $G$ only.



## 1. Introduction

A *Boolean network* with $n$ components is a discrete dynamical system usually defined by a global transition function

$$f : \{0, 1\}^n \to \{0, 1\}^n, \qquad x = (x_1, \dots, x_n) \mapsto f(x) = (f_1(x), \dots, f_n(x)).$$

Boolean networks have many applications. In particular, since the seminal papers of McCulloch and Pitts [19], Hopfield [13], Kauffman [14,15] and Thomas [31,33], they are omnipresent in the modeling of neural and gene networks (see [5,18] for reviews). They are also essential tools in information theory, for the network coding problem [1,9].

The structure of a Boolean network $f$ is usually represented via its *interaction graph*, defined below using the following notion of derivative. For every $u, v \in \{1, \dots, n\}$, the *discrete derivative* of $f_v$ with respect to the variable $x_u$ is the function $f_{vu} : \{0, 1\}^n \to \{-1, 0, 1\}$ defined by

$$f_{vu}(x) := f_v(x_1, \dots, x_{u-1}, 1, x_{u+1}, \dots, x_n) - f_v(x_1, \dots, x_{u-1}, 0, x_{u+1}, \dots, x_n).$$

The **interaction graph** of $f$ is the signed digraph $G$ defined as follows: the vertex set is $[n] := \{1, \dots, n\}$ and, for all $u, v \in [n]$, there is a positive (resp. negative) arc from $u$ to $v$ if $f_{vu}(x)$ is positive (resp. negative) for at least one $x \in \{0, 1\}^n$. Note that $G$ can have both a positive and a negative arc from one vertex to another (in that case, the sign of the interaction depends on the state $x$ of the system). In the following, an arc from $u$ to $v$ of sign $\epsilon \in \{+, -\}$ is denoted $(uv, \epsilon)$. Also, cycles are always directed and regarded as subgraphs (no repetition of vertices is allowed). The sign of a cycle is, as usual, defined as the product of the signs of its arcs.

*E-mail address:* richard@unice.fr.

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In many contexts, as in molecular biology, the interaction graph is known — or at least well approximated —, while the actual dynamics described by $f$ is not, and is very difficult to observe [34,18]. A natural question is then the following.

**Question 1.** *What can be said on the dynamics of $f$ according to $G$ only?*

Among the many dynamical properties that can be studied, fixed points are of special interest, since they correspond to stable states and often have a strong meaning. For instance, in the context of gene networks, they correspond to stable patterns of gene expression at the basis of particular biological processes [33,2]. As such, they are arguably the property which has been the most thoroughly studied (see [28] for an introduction to these studies). In particular, many works studied sufficient conditions for the uniqueness or the existence of a fixed point [29,3,21,25,23,24] (such questions have also been widely studied in the continuous setting, see [16] and the references therein).

Here, we are mainly interested in the following two fundamental theorems, suggested by the biologist Thomas [32], and known as the Boolean versions of the first and second Thomas' rules.

**Theorem 1.** *If $G$ has no positive cycle, then $f$ has at most one fixed point. More generally, if $f$ has two distinct fixed points $x$ and $y$, then $G$ has a positive cycle $C$ such that $x_v \neq y_v$ for every vertex $v$ in $C$.*

**Theorem 2.** *If $G$ has no negative cycle, then $f$ has at least one fixed point.*

The first theorem has been proved by Aracena, see the proof of [3, Theorem 9] and also [4], and a stronger version has been independently proved by Remy, Ruet and Thieffry [21, Theorem 3.2]. The second theorem is an easy application of another result of Aracena [3, Theorem 6].

Two upper bounds on the number of fixed points can be deduced from Theorem 1. Let $\tau^+$ be the minimal number of vertices whose deletion in $G$ leaves a signed digraph without positive cycle. From Theorem 1 we deduce, using arguments reproduced below in the proof of Corollary 1, that *$f$ has at most $2^{\tau^+}$ fixed points* [3, Theorem 9]. For the second bound, two additional definitions are needed. Let $g^+$ be the minimum length of a positive cycle of $G$ (with the convention that $g^+ = \infty$ if $G$ has no positive cycle), and for every integer $d$, let $A(n, d)$ be the maximal size of a subset $X \subseteq \{0, 1\}^n$ such that the Hamming distance between any two distinct elements of $X$ is at least $d$. According to Theorem 1, the Hamming distance between any two distinct fixed points of $f$ is at least $g^+$, and thus we get a second upper bound: *$f$ has at most $A(n, g^+)$ fixed points*. The quantity $A(n, d)$, usually called *maximal size of a binary code of length $n$ with minimal distance $d$*, has been intensively studied in Coding Theory. The well known Gilbert bound and sphere packing bound give the following approximation: $2^n/\sum_{k=0}^{d-1}\binom{n}{k} \leq A(n, d) \leq 2^n/\sum_{k=0}^{D}\binom{n}{k}$ with $D = \lfloor \frac{d-1}{2} \rfloor$. See [10] for other connections with Coding Theory.

All the generalizations of the previous results known so far use additional information on $f$ [21,23] (or consist in enlarging the framework, considering discrete networks instead of Boolean networks and asynchronous attractors instead of fixed points [25,23]). In this note, we establish, up to our knowledge, the first generalizations that only use information on $G$, and which thus contribute directly to Question 1 (these are Theorems 3–5 stated below).

Our approach is the following. The previous results show that positive and negative cycles are key structures to understand the relationships between $G$ and the fixed points of $f$. However, they use information on positive cycles only, or on negative cycles only. It is then natural to think that improvements could be obtained by considering the two kinds of cycles simultaneously. This is what we do here, by highlighting two qualitative phenomena on the influence of connections between positive and negative cycles. These two dual phenomena could be verbally described as follows (we say that two graphs *intersect* if they share a common vertex):

1. *If each positive cycle $C$ of $G$ intersects a negative cycle $C'$, and if $C$ "isolates" $C'$ from the other positive cycles, then $f$ behaves as in the absence of positive cycles: it has at most one fixed point.*
2. *If each negative cycle $C$ of $G$ intersects a positive cycle $C'$, and if $C$ "isolates" $C'$ from the other negative cycles, then $f$ behaves as in the absence of negative cycles: it has at least one fixed point.*

The following three theorems give a support to these phenomena. Theorems 3 and 4 are uniqueness results that generalize (the first assertion in) Theorem 1. Theorem 5 is an existence result that generalizes Theorem 2 and shows, together with Theorem 3, an explicit duality between positive and negative cycles (all the notions involved in these statements are formally defined in the next section).

**Theorem 3.** *If every positive cycle of $G$ has an arc $a = (uv, \epsilon)$ such that $G \setminus a$ has a non-trivial initial strong component containing $v$ and only negative cycles, then $f$ has at most one fixed point.*

**Theorem 4.** *If every positive cycle $C$ of $G$ has a vertex $v$ of in-degree at least two that belongs to no other positive cycle and with only in-neighbors in $C$, then $f$ has at most one fixed point.*

**Theorem 5.** *If every negative cycle of $G$ has an arc $a = (uv, \epsilon)$ such that $G \setminus a$ has a non-trivial initial strong component containing $v$ and only positive cycles, then $f$ has at least one fixed point.*

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