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SUFFICIENT CONDITIONS FOR THE PRESENCE OF SEVERAL FIXED POINTS OR THE ABSENCE OF FIXED POINT IN BOOLEAN NETWORKS

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RÉSUMÉ :

On prouve que si le graphe d'interaction d'un réseau booléen est sans source et sans circuit négatif (resp. positif) alors il existe plusieurs point fixes (resp. aucun point fixe) dans la dynamique du réseau.

MOTS CLÉS :

Réseau booléen, point fixe, graphe d'interaction, dérivée discrète, circuit positif, circuit négatif, réseau de genes

ABSTRACT:

We prove that if the interaction graph of a boolean network is without source and without negative (resp. positive) circuit, then there are several stables states (resp. no stable state) in the dynamics of the network.

KEY WORDS :

Boolean network, fixed point, interaction graph, discrete derivative, positive circuit, negative circuit, gene network

Sufficient conditions for the presence of several fixed points or the absence of fixed point in boolean networks

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Abstract

We prove that if the interaction graph of a boolean network is without source and without negative (resp. positive) circuit, then there are several stables states (resp. no stable state) in the dynamics of the network.

Key words: Boolean network, fixed point, interaction graph, discrete derivative, positive circuit, negative circuit, gene network.

1 Introduction

We consider a boolean network $F : \{0,1\}^n \to \{0,1\}^n$ and its interaction graph $G(F)$ (the nodes are the variables of the network, and the edges, which are directed and signed, denote the positive and negative interactions present between these variables).

The question we focus on is: *which dynamical properties of the network can be inferred from its interaction graph?* While studying gene networks, the biologist René Thomas stated two general conjectures giving a partial answer to this question [18]. Informally, the first (resp. second) conjecture states that the presence of a positive (resp. negative) circuit in the interaction graph of a network is a *necessary condition* for the presence of several stable states (resp. of sustained oscillations) in the dynamics of the network (the sign of a circuit is the product of the signs of its edges). These conjectures have been recently proved for boolean networks [9, 11, 12] (see [8, 14, 4, 2, 16] for proofs in the continuous case, and [7] for a state of the art).

In this paper, we are interested by converses of these conjectures and thus by *sufficient conditions* for the presence of several stable states or sustained oscillations. As main result, we show that: *if each node of $G(F)$ has a predecessor and if $G(F)$ is without negative (resp. positive) circuit, then F has at least two fixed points (resp. no fixed point).* A weaker statement of this result has previously been proved by Aracena, Demongeot and Goles [1] (in the restrictive context of boolean neural networks).

The boolean versions of the Thomas' conjectures, and the converses proved here, are useful in biology. In the context of gene networks, the first reliable experimental observations are often expressed in terms of interaction graphs [3]. Moreover, boolean models of gene networks are expensively used since the 70's [6, 17], and the presence of several stable states (resp. sustained oscillations) in these networks is related to an important biological phenomena: the cell differentiation process (resp. the homeostatis phenomena) [18, 17, 19].

2 Definitions

In this section, we state the definitions needed to formulate the main result and the boolean versions of the Thomas' conjectures. One of them (the second) will be used to prove the main result.

2.1 Asynchronous state graph and attractors

Let us start with preliminary notations. As usual, $\bar{0} = 1$ and $\bar{1} = 0$. Then, for each point $x = (x_1, \dots, x_n) \in \{0,1\}^n$ and each $i \in \{1, \dots, n\}$, we denote by $\bar{x}^i$ the point of $\{0,1\}^n$ that we obtain by switching the ith component of x:

$$\bar{x}^i = (x_1, \dots, \bar{x}_i, \dots, x_n).$$

Now, consider a boolean network of n variables whose evolution is described by the successive iterations of a map

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

Several iteration modes are possible: parallel, serial, asynchronous, etc. Here, we focus on the asynchronous iterations used by Thomas to model the behavior of gene networks [17, 19]. These iterations are usually visualized by a so called asynchronous state graph:

Definition 1 *The* asynchronous state graph *of F, denoted $\Gamma(F)$, is the directed graph whose set of nodes is $\{0,1\}^n$ and whose set of edges is*

$$\{(x, \bar{x}^i) : x \in \{0,1\}^n,\ i \in \{1, \dots, n\},\ f_i(x) = \bar{x}_i\}.$$

Naturally, the fixed points of F have no successor in $\Gamma(F)$ and correspond to the *stable states* of the system. In the following definition, we extend the notion of stable state to the notion of *attractor*.

Definition 2 *A* trap domain *of $\Gamma(F)$ is a non-empty subset $A \subseteq X$ such that, for all edges (x, y) of $\Gamma(F)$, if $x \in A$ then $y \in A$. An* attractor *of $\Gamma(F)$ is a smallest trap domain with respect to the inclusion relation. A* cyclic attractor *is an attractor of cardinality ≥ 2.*

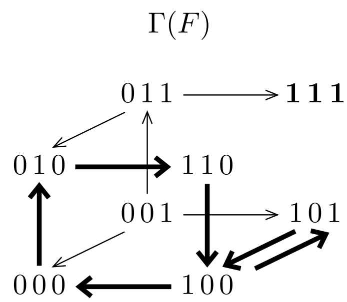
The notion of attractor extends the notion of stable state in the sense that x is a stable state if and only if $\{x\}$ is an attractor. Observe also that attractors perform an attraction in the weak sense that, from each node, there is always a path which leads to one of them. Finally, note that cyclic attractors do not contain stable state. So, when the network is in a cyclic attractor, it necessarily describes, ad infinitum, sustained oscillations.

Example 1 *$n = 3$ and the map $F = (f_1, f_2, f_3) : \{0,1\}^3 \to \{0,1\}^3$ is defined by:*

$$\begin{aligned} f_1(x) &= x_2 + x_3 \\ f_2(x) &= \bar{x}_1 + x_2 x_3 \qquad\qquad (\textit{boolean sum: } 1+1=1) \\ f_2(x) &= x_1(x_2 x_3 + \bar{x}_2 \bar{x}_3) \end{aligned}$$

The table of F and its asynchronous state graph $\Gamma(F)$ are the following:

x	$F(x)$
$(0,0,0)$	$(0,1,0)$
$(0,0,1)$	$(1,1,0)$
$(0,1,0)$	$(1,1,0)$
$(0,1,1)$	$(1,1,0)$
$(1,0,0)$	$(0,0,1)$
$(1,0,1)$	$(1,0,0)$
$(1,1,0)$	$(1,0,0)$
$(1,1,1)$	$(1,1,1)$



So $\Gamma(F)$ contains a stable state (the fixed point $(1,1,1)$) and a cyclic attractor:

$$\{(0,0,0),(0,1,0),(1,1,0),(1,0,0),(1,0,1)\}.$$

2.2 Discrete Jacobian matrix and interaction graph

Let F be a map from $\{0,1\}^n$ into itself. In this section, we attach to F a signed directed graph which describes the structure (or topology) of the network modeled by F. As in [9], this graph is defined from the Jacobian matrix of F.

Definition 3 *The* Jacobian matrix *of F at point $x \in \{0,1\}^n$ is the following $n \times n$ matrix:*

$$F'(x) = (f_{ij}(x)), \qquad f_{ij}(x) = \frac{f_i(\bar{x}^j) - f_i(x)}{\bar{x}_j - x_j} \qquad (i,j = 1,\dots,n).$$

($f_{ij}(x)$ is a discrete analogue of $(\partial f_i / \partial x_j)(x)$.)

Definition 4 *An* interaction graph *is a finite graph (V, E) where $E \subseteq V \times \{-1,1\} \times V$. An edge $(j,s,i) \in E$ is an edge* from *node j* to *node i of* sign *s.*

Definition 5 *We call* interaction graph of F*, and we denote by $G(F)$, the interaction graph whose set of nodes is $\{1,\dots,n\}$ and which contains a positive (resp. negative) edge from j to i if there exists $x \in \{0,1\}^n$ such that $f_{ij}(x)$ is positive (resp. negative).*

To illustrate this definition, assume that $f_{ij}(x)$ is positive and that $x_j = 0$. Then, $f_i(x) < f_i(\bar{x}^j)$ so we can say that, at state x, an increase of x_j induces an increase of f_i. In other words, j is an activator of i, and we have a positive edge from j to i in $G(F)$.

Remark 1 *There is an edge from j to i if and only if f_i depends on variable x_j. Thus node i has a predecessor if and only if f_i is not constant.*

Definition 6 *A* path *of an interaction graph G is an non-empty sequence of edges*

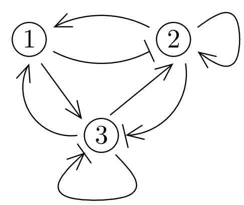
$$(j_1, s_1, i_1), (j_2, s_2, i_2), \ldots, (j_r, s_r, i_r),$$

such that $i_k = j_{k+1}$ for $1 \leq k < r$. Such a path is a path from j_1 to i_r of length r. *It is a* circuit *if $i_r = j_1$ and* elementary *if the nodes j_k are mutually distinct. Finally, its* sign *is the product of the signs s_k.*

Remark 2 *If G has a negative circuit, then G has an elementary negative circuit (this is false for positive circuits, be careful!).*

In the following, *without explicit contra-indication, the considered circuits are always elementary.*

Example 2 *The interaction graph of the map $F : \{0,1\}^3 \to \{0,1\}^3$ of Example 1 is:*



Arrows $\longrightarrow$ and $\longrightarrow\!\!\!\!\mid$ correspond to positive and negative edges respectively. Arrows $\longrightarrow\!\!\mid$ indicate the presence of both a positive and a negative edge from one node to another (these graphical conventions are used throughout the paper). This interaction graph contains 6 *positive circuits* (2 *of length* 1, 2 *of length* 2, *and* 2 *of length* 3) *and* 4 *negative circuits* (1 *of length* 1, 2 *of length* 2, *and* 1 *of length* 3).

3 Thomas' conjectures and main result

We are interested by the following question: which properties on the asynchronous state graph $\Gamma(F)$ (which contains 2^n nodes) can be extract from the rather simple information contained in the interaction graph $G(F)$ (which only contains n nodes)? The following boolean versions of the Thomas' conjectures gives a partial answer to this question.

Theorem 1 (Boolean version of the Thomas' conjectures)
Let F be a map from $\{0,1\}^n$ to itself.

1. *If $G(F)$ has no positive circuit then $\Gamma(F)$ has a unique attractors* [11].

2. *If $G(F)$ has no negative circuit then $\Gamma(F)$ has no cyclic attractor* [12].

This theorem gives necessary (but not sufficient) conditions on $G(F)$ for $\Gamma(F)$ to have several stable states or a cyclic attractor. Our main result gives sufficient (but not necessary) conditions on $G(F)$ for $\Gamma(F)$ to have these properties:

Theorem 2 (Main result)
Let F be a map from $\{0,1\}^n$ to itself, and suppose that each node of $G(F)$ has a predecessor.

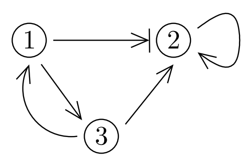
1. If $G(F)$ has no negative circuit then F has at least two fixed points.

2. If $G(F)$ has no positive circuit then F has no fixed point.

(The condition "each node has a predecessor" is rather weak: it means that each component f_i of F is not constant. Note also that this condition implies the presence of at least one circuit in $G(F)$.)

Theorem 2 has been proved by Aracena Demongeot and Goles [1] under additional assumptions. The map F is supposed to be a Hopfield's boolean neural network [5] (this implies that $G(F)$ cannot have both a positive and a negative edge from one node to another) and, more importantly, a rather stronger hypothesis is used to arrive to the conclusion of the first point: it is the absence of a negative circuit in the *undirected* version of $G(F)$, that is, in the interaction graph which contains a positive (resp. negative) edge from j to i if $G(F)$ contains a positive (resp. negative) edge from j to i *or* from i to j.

Example 3 *Consider the following interaction graph:*



Each node has a predecessor and there is no negative circuit (but its undirected version contains negative circuits, $1 \longrightarrow 3 \longrightarrow 2 \longrightarrow\!\!| \ 1$ for instance). According to Theorem 2, all the maps from $\{0,1\}^3$ to itself whose interaction graph is the one above have at least two fixed points. There exists in fact (exactly) two maps with such an interaction graph: the maps F and H defined, with the boolean sum $(1+1=1)$, by:

$$\begin{cases} f_1(x) = x_3 \\ f_2(x) = x_2x_1 + x_3\bar{x}_1 \\ f_3(x) = x_1 \end{cases} \quad \text{and} \quad \begin{cases} h_1(x) = x_3 \\ h_2(x) = x_3x_1 + x_2\bar{x}_1 \\ h_3(x) = x_1 \end{cases}$$

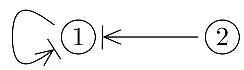
The fixed points of F are $(0,0,0)$, $(0,1,0)$ and $(1,1,1)$. Those of H are $(0,0,0)$, $(1,0,1)$ and $(1,1,1)$. So F and H have indeed more than two fixed points.

The following two examples show that the conditions for the presence of several fixed points or the absence of fixed point given by Theorem 2 are not necessary.

Example 4 *$n=2$. The map F and its interaction graph $G(F)$ are the following:*

x	$F(x)$
$(0,0)$	$(0,0)$
$(0,1)$	$(1,0)$
$(1,0)$	$(1,0)$
$(1,1)$	$(0,0)$

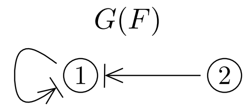
$G(F)$



F has two fixed points, but $G(F)$ has a node without predecessor and a negative circuit.

Example 5 $n = 2$. *The map F and the resulting interaction graph $G(F)$ are the following:*

x	$F(x)$
$(0,0)$	$(1,0)$
$(0,1)$	$(0,0)$
$(1,0)$	$(0,0)$
$(1,1)$	$(1,0)$



F has no fixed point, but $G(F)$ has a node without predecessor and a positive circuit.

4 Proof of Theorem 2

Let us state few additional notations. If (j, s, i) is an edge of a interaction graph G, we abusively write $(j, s, i) \in G$. Then, we set:

$$\tilde{0} = -1 \qquad \text{and} \qquad \tilde{1} = 1.$$

The following lemma (obvious for boolean neural networks [1]) play a crucial role in the proof of both points of Theorem 2. See Figure 1 for an illustration.

Lemma 1 *Let*

$$F : \{0,1\}^n \to \{0,1\}^n, \quad x \in \{0,1\}^n, \quad i \in \{1, \dots, n\} \quad \textit{and} \quad a \in \{0,1\}.$$

If f_i is not constant and if, for all edges $(j, s, i) \in G(F)$, we have $\tilde{a} = s \cdot \tilde{x}_j$, then $f_i(x) = a$.

Proof −Suppose that the conditions of the lemma are satisfied and suppose that $a = 1$ (the demonstration is similar when $a = 0$). We first prove that

$$\forall y \in \{0,1\}^n, \qquad f_i(y) \leq f_i(x). \tag{1}$$

We reason by induction on the *Hamming distance* between x and y, that is, on the number $d(x, y)$ of $j \in \{1, \dots, n\}$ such that $x_j \neq y_j$. If $d(x, y) = 0$ then it is obvious that $f_i(y) \leq f_i(x)$. Otherwise, we suppose that $f_i(z) \leq f_i(x)$ for all z such that $d(x, z) < d(x, y)$ and we suppose, by contradiction, that $f_i(x) < f_i(y)$. Since $d(x, y) > 0$, there exists $j \in \{1, \dots, n\}$ such that $x_j \neq y_j$. Hence $d(x, \bar{y}^j) < d(x, y)$ and so, by hypothesis,

$$f_i(\bar{y}^j) \leq f_i(x) < f_i(y).$$

If $y_j = 1$ then $\bar{y}_j - y_j = -1$ thus $f_{ij}(y) > 0$ and we deduce that $(j, 1, i)$ is an edge of $G(F)$. Consequently, $\tilde{a} = \tilde{x}_j$ so $x_j = 1 = y_j$, a contradiction. If $y_j = 0$ we similarly arrive to a contradiction. So (1) is proved and we deduce that if, $f_i(x) = 0$, then $f_i = \text{cst} = 0$. Since $f_i \neq \text{cst}$, we deduce that $f_i(x) = 1$. □

4.1 First point

We now prove the first point of Theorem 2. Let us say that an interaction graph G is *strongly connected* if, for all distinct nodes i, j, it contains a path from j to i.

Lemma 2 *If G is a strongly connected interaction graph without negative circuit, then all the paths from a given node to another given node have the same sign.*

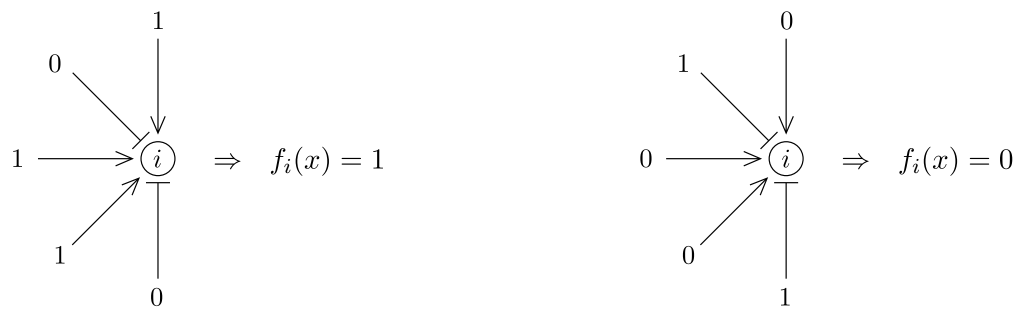


Figure 1: Illustration of Lemma 1.

Proof –Suppose that the conditions of the lemma are satisfied but that there exists both a positive and a negative path from node j to node i, denoted by P^+ and P^- respectively. Since G is strongly connected, there exists a path Q from i to j. If Q is positive (resp. negative) then the concatenation of P^- (resp. P^+) and Q forms a negative circuit which is not necessarily elementary. We deduce from Remark 2 that G has an elementary negative circuit, a contradiction. □

For each $x \in \{0,1\}^n$, set $\bar{x} = (\bar{x}_1, \dots, \bar{x}_n)$. Using arguments found in [1], we prove the

Lemma 3 *Let F be a map from $\{0,1\}^n$ to itself. If F is not constant, if $G(F)$ is strongly connected, and if $G(F)$ has no negative circuit, then F has at least two fixed points. More precisely, there exists $x \in \{0,1\}^n$ such that x and $\bar{x}$ are fixed points of F.*

Proof –Suppose that the conditions of the lemma are satisfied. We first show that:

$$\textit{Each node of } G(F) \textit{ has a predecessor.} \tag{2}$$

Indeed, suppose that there exists a node i without predecessor. If there exists a node $j \neq i$ then there is no path from j to i so $G(F)$ is not strongly connected. We deduce that $n = 1$. Hence, $G(F)$ has no edge so $F = \text{cst}$, a contradiction.

For $i = 1, \dots, n$, let P_i be an elementary path from 1 to i (according to (2) and the strongly connectivity of $G(F)$, such a path exists). Then, consider the point $x \in \{0,1\}^n$ such that $\tilde{x}_i$ is the sign of P_i $(i = 1, \dots, n)$. We show that,

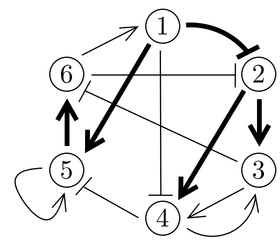
$$\forall (j, s, i) \in G(F), \qquad \tilde{x}_i = s \cdot \tilde{x}_j. \tag{3}$$

Let (j, s, i) be an edge of $G(F)$. Then, the concatenation of P_j and (j, s, i) forms a path from 1 to i of sign $\tilde{x}_j \cdot s$. According to the previous lemma, this path and P_i have the same sign, i.e., $\tilde{x}_i = s \cdot \tilde{x}_j$. So (3) is proved, and it follows that, for $y = \bar{x}$, we have:

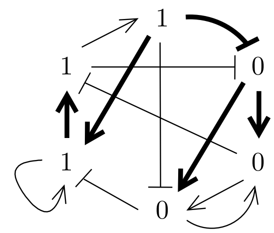
$$\forall (j, s, i) \in G(F), \qquad \tilde{y}_i = s \cdot \tilde{y}_j. \tag{4}$$

We then deduce from (2), (3), (4) and Lemma 1, that x and y are fixed points of F. □

Remark 3 *The proof gives a very efficient way to compute, from the interaction graph of the network, the opposite fixed points x and $\bar{x}$. It is sufficient to build a spanning tree of the interaction graph and to compute the sign of the paths starting from the root. For instance, consider the following strongly connected interaction graph which has no negative circuit:*



Put the first variable in state 1, *and put the other variables i in state* 1 (*resp.* 0) *when, in the highlighted spanning tree of root* 1, *the path from* 1 *to i is positive* (*resp. negative*)*:*



According to the previous proof, the point $x = (1, 0, 0, 0, 1, 1)$ defined in this way, and the opposite point $\bar{x} = (0, 1, 1, 1, 0, 0)$, are fixed points of any map F whose interaction graph is the one above (*there are* 648 *maps with this interaction graph*). *This property can be "graphically verified" using the previous figure and Figure 1.*

Let G be an interaction graph, let V be the set of nodes of G, and let $\sim$ be the equivalence relation on V defined by $i \sim j$ if $i = j$ or if there exists a path from i to j and a path from j to i. Equivalence classes of $\sim$ are called *strongly connected components* of G. It is easy to see that there exists a strongly connected component I without *input edge*, i.e., such that there is no $(j, s, i) \in G$ with $j \notin I$ and $i \in I$. (Indeed, if each component has an input edge, we can build a circuit whose nodes belong to distinct components, a contradiction.)

Lemma 4 *Let F be a map from $\{0,1\}^n$ to itself such that each node of $G(F)$ has a predecessor. If $G(F)$ has no negative circuit then $\Gamma(F)$ has at least two attractors.*

Proof –Suppose that the conditions of the lemma are satisfied, and let I be a strongly connected component of $G(F)$ without input edge. Without loss of generality, suppose that

$$I = \{1, \dots, m\}.$$

If $m = n$ then $G(F)$ is strongly connected. So, according to the previous lemma, F has two fixed points and it follows that $\Gamma(F)$ has two attractors. So suppose that $m < n$ and let us (abusively) denote by 0 the $(n - m)$-tuple whose all components are zero.

Consider the map H from $\{0,1\}^m$ to itself defined by:

$$\forall x \in \{0,1\}^m, \qquad h_i(x) = f_i(x_1, \dots, x_m, 0) \qquad (i = 1, \dots, m).$$

Since, I has no input edge, for all $i \in I$, f_i only depends on the variables x_j such that $j \in I$. It means that, for all $x \in \{0,1\}^n$,

$$f_i(x) = f_i(x_1, \dots, x_m, 0) = h_i(x_1, \dots, x_m) \qquad (i = 1, \dots, m)$$

and thus that

$$f_{ij}(x) = f_{ij}(x_1, \dots, x_m, 0) = h_{ij}(x_1, \dots, x_m) \qquad (i, j = 1, \dots, m).$$

Hence, the set of edges of $G(H)$ is the set of edges $(j, s, i) \in G(F)$ such that $i, j \in I$. It is then clear that $G(H)$ is strongly connected and without negative circuit. Furthermore, since $f_1 \neq \text{cst}$, we have $h_1 \neq \text{cst}$ and so $H \neq \text{cst}$.

Hence, following Lemma 3, H has at least two fixed points, say α and β. Let

$$A = \{x \in \{0,1\}^n : (x_1, \dots, x_m) = \alpha\},$$

and let us show that A is a trap domain of $\Gamma(F)$. Suppose that (x, y) is an edge of $\Gamma(F)$ with $x \in A$, and let i be the index of $\{1, \dots, n\}$ such that $y = \bar{x}^i$ and $f_i(x) = \bar{x}_i$. Since if $i \in I$ we have

$$f_i(x) = f_i(x_1, \dots, x_m, 0) = h_i(x_1, \dots, x_m) = h_i(\alpha) = \alpha_i = x_i,$$

we deduce that $i \notin I$. Thus

$$(y_1, \dots, y_m) = (x_1, \dots, x_m) = \alpha,$$

that is, $y \in A$. Consequently, A is a trap domain of $\Gamma(F)$. So, by definition, A contains (at least) one attractor. We show similarly that

$$B = \{x \in \{0,1\}^n : (x_1, \dots, x_m) = \beta\}$$

contains an attractor. Since $\alpha \neq \beta$, A and B are disjointed, and we deduce that $\Gamma(F)$ has two attractors. □

We are now in position to conclude. Suppose that each node of $G(F)$ has a predecessor and that $G(F)$ has no negative circuit. According to the previous lemma, $G(F)$ has two attractors, and according to (the second point of) Theorem 1, these attractors are not cyclic. So $\Gamma(F)$ has two attractors of cardinality 1, i.e., F has two fixed points.

4.2 Second point

The proof of the second point follows the reasoning used by *Aracena et al* in [1, Theorem 2]. Let F be a map from $\{0,1\}^n$ to itself such that each node of $G(F)$ has a predecessor and such that $G(F)$ has no positive circuit. By contradiction, suppose, that x is a fixed point of F. Let $y = \bar{x}$ and let i be any element of $\{1, \dots, n\}$. We have $f_i(x) = x_i \neq y_i$ and, since i has a predecessor in $G(F)$, $f_i \neq \text{cst}$. So, following Lemma 1, there exists an edge (j, s, i)

in $G(f)$ such that $\tilde{y}_i \neq s \cdot \tilde{x}_j$ and thus such that $s = \tilde{x}_j \cdot \tilde{x}_i$. We can thus construct, in this way, a circuit

$$(j_1, s_1, i_1), (j_2, s_2, i_2), \ldots, (j_r, s_r, i_r)$$

where $s_k = \tilde{x}_{j_k} \cdot \tilde{x}_{i_k}$ for $k = 1, \ldots, r$. By setting $j_{r+1} = j_1$, the sign of this circuit is

$$\prod_{k=1}^{r} s_k = \prod_{k=1}^{r} \tilde{x}_{j_k} \tilde{x}_{i_k} = \prod_{k=1}^{r} \tilde{x}_{j_k} \tilde{x}_{j_{k+1}} = \prod_{k=1}^{r} \tilde{x}_{j_k} \tilde{x}_{j_k} > 0,$$

a contradiction.

5 Conclusion

We have establish sufficient conditions on the interaction graph of a boolean network for the presence of several fixed points or the absence of fixed point in the dynamics of the network. The considered interaction graph $G(F)$ gives a very coarse information about the dynamics of the system. Our aim is now to establish more subtle sufficient conditions by considering the *local* interactions graphs of the system, i.e., the interactions graphs $G(F)(x)$ defined in each point x as follow: $G(F)(x)$ has a positive (resp. negative) edge from j to i if $f_{ij}(x)$ is positive (resp. negative). Let us remark that, thanks to this notion of local interaction graphs, the following strong boolean version of the first Thomas' conjecture has been proved [9, 11]: if $G(F)(x)$ has no positive circuit for all $x \in \{0,1\}^n$, then F has at most one fixed point. Note also that local sufficient conditions for the multistationarity or the presence of oscillations have been discussed in [15, 10]. Among several other directions of research, we also would like to establish sufficient conditions the presence of at least k attractors ($1 < k < 2^n$). In other words, we would like to express, from the interaction graph, a lower bound on the number of attractors. The tools used in [1, 13] to establish upper bounds on the number of attractors may be useful to achieve this goal.

References

[1] Aracena, J., J. Demongeot and E. Goles, *Positive and negative circuits in discrete neural networks*, IEEE Transactions of Neural Networks **15** (2004), 77-83.

[2] Cinquin, O. and J. Demongeot, *Roles of positive and negative feedback in biological systems*, C.R.Biol. **325** (2002), 1085-1095.

[3] de Jong, H., *Modeling and simulation of genetic regulatory systems: a literature review*, Journal of Computational Biology **9** (2002), 67-103.

[4] Gouzé, J. L., *Positive and negative circuits in dynamical systems*, Journal of Biological Systems **6** (1998), 11-15.

[5] Hopfield, J., *Neural networks and physical systems with emergent collective computational abilities*, Proc. Nat. Acad. Sci. **79** (1982), 2554-2558.

[6] Kauffman, S. A., *Metabolic stability and epigenesis in randomly constructed genetic nets*, J. Theor. Biol. **22** (1969), 437-469.

[7] Kaufman, M., C. Soulé and R. Thomas, *A new necessary condition on interaction graphs for multistationarity,* J. Theor. Biol. **248** (2007), 675-685.

[8] Plathe, E., T. Mestl and S.W. Omholt, *Feedback loops, stability and multistationarity in dynamical systems*, Journal of Biological Systems **3** (1995), 569-577.

[9] Remy, É, P. Ruet and D. Thieffry, *Graphics requirement for multistability and attractive cycles in a boolean dynamical framework*, Advances in Applied Mathematics (2008), to appear.

[10] Remy, É, and P. Ruet, *From minimal signed circuit to the dynamics of Boolean regulatory networks*, Bioinformatics (2008), to appear.

[11] Richard, A. and J.-P. Comet, *Necessary conditions for multistationarity in discrete dynamical systems*, Discrete Applied Mathematics (2007)???.

[12] Richard, A., *On the link between negative circuits and sustained oscillations in discrete genetic regulatory networks*, in JOBIM 2007 (10-12 July 2007, France), 213-218.

[13] Richard, A., *Positive circuits and maximal number of fixed points in discrete dynamical systems*, Technical report, University of Nice-Sophia Antipolis (2008).

[14] Snoussi, E. H., *Necessary conditions for multistationarity and stable periodicity*, Journal of Biological Systems **6** (1998), 3-9.

[15] Snoussi, E. H. and R. Thomas, *Logical identification of all steady states : the concept of feedback loop caracteristic states*, Bull. Math. Biol. **55** (1993), 973-991.

[16] Soulé, C., *Graphical requirements for multistationarity*, ComPlexUs **1** (2003), 123-133.

[17] Thomas, R., *Boolean formalization of genetic control circuits*, J. Theor. Biol. **42** (1973), 563-585.

[18] Thomas, R., *On the relation between the logical structure of systems and their ability to generate multiple steady states and sustained oscillations*, Series in Synergetics **9**, Springer (1981), 180-193.

[19] Thomas, R. and R. d'Ari, "Biological Feedback", CRC Press (1990).