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Finding the fixed points of a Boolean network from a positive
feedback vertex set

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Abstract

In the modeling of biological systems by Boolean networks a key problem is finding the set of fixed points of a given network. Some constructed algorithms consider certain structural properties of the interaction graph like those proposed by Akutsu et al. in [3, 56] which consider a feedback vertex set of the graph. However, these methods do not take into account the type of action (activation, inhibition) between its components.

In this paper we propose a new algorithm for finding the set of fixed points of a Boolean network, based on a positive feedback vertex set P of its interaction graph and which works, by applying a sequential update schedule, in time $O(2^{|P|} \cdot n^2)$, where n is the number of components. The theoretical foundation of this algorithm is due a nice characterization, that we give, of the dynamical behavior of the Boolean networks without positive cycles and with a fixed point.

An executable file of FixedPoint algorithm made in Java and some examples of input files are available at: www.inf.udec.cl/~lilian/FPCollector/

1 Introduction

A Boolean network is a system of n interacting Boolean variables, which evolve, in a discrete time, according to a evolution rule and to a predefined updating scheme. Boolean networks have many applications, including computer science, in particular circuit theory, and social systems. In particular, from the seminal works of S. Kauffman [22, 23] and R. Thomas [48, 49], they are extensively used as models of gene networks. In this context, the fixed points of a network are associated to distinct types of cells defined by patterns of gene activity [8, 20, 22]. The problem of finding the steady states or fixed points of a Boolean network is a difficult task. In [2], Akutsu et al. show that deciding if a network has a fixed point is NP-complete, consequently, counting how many fixed points a Boolean network has is #P-complete. For this reason, in the literature, several strategies have been proposed to find fixed points in Boolean networks. Some of them are: Reduction method [50, 52, 54], Representation as polynomial functions [19, 57], SAT-based methods [40, 4, 14, 15, 30, 46, 47], Methods based on Integer Programming [1], Strategic Sampling [56] and Methods based on Minimal Feedback Vertex Sets [3, 56]. For a more detailed description of these and other methods see [51, 16] and references therein.

The structure of a Boolean network is often represented by a digraph, called interaction graph, where vertices are network components, and there is an arc from one component to another when the evolution of the latter depends on the evolution of the former. In some cases, these arcs can have associated a positive or a negative sign if the action associated is of type activation or inhibition respectively.

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Some of the algorithms for finding the fixed points of a Boolean network consider certain characteristics of its interaction graph. In particular, Akutsu et al. in [3, 56] proposed a method consisting in fixing the values of the vertices of a minimal feedback vertex set F and propagating them to the others. In this way the problem of finding the fixed points of a Boolean network of n components is reduced to check $2^{|F|}$ state configurations instead of 2^n , where usually the size of F is less than n . However, this method does not consider the sign of the arcs of the interaction graph.

On the other hand, to our knowledge it does not exist a method to find the fixed points of a Boolean network that take advantage of the fact they are invariant to the update schedule.

In this paper we propose a new strategy to find the fixed points of a Boolean network which consists in fixing the local states of a positive feedback vertex set P of the interaction graph and updating the other local states according to a sequential update schedule constructed from P . In this way we reduce the problem of finding the fixed points of a Boolean network of n components to check $2^{|P|}$ state configurations, where P can be smaller than a feedback vertex set of the network. Thus, the proposed algorithm is quadratic in the size of the network and exponential in the size of P . Consequently, this method can be very efficient, with respect to other methods, in Boolean networks with a small positive feedback vertex set, as for example ones with few positive cycles. A particular case of this latter are the strong inhibition Boolean networks [16].

For the construction of the proposed algorithm we proved first that the dynamical behavior of a Boolean network without positive cycles and with a fixed point is similar to an acyclic Boolean network, i.e. it quickly converges to the fixed point from any initial configuration.

2 Definition and notation

A *Boolean network* (BN) with n components is a discrete dynamical system usually defined by a *global transition function*:

$$f : \{0, 1\}^n \rightarrow \{0, 1\}^n, \quad x \rightarrow f(x) = (f_1(x), \dots, f_n(x)),$$

where each function $f_i : \{0, 1\}^n \rightarrow \{0, 1\}$ associated to the component i is called *local activation function*.

Any vector $x = (x_1, \dots, x_n) \in \{0, 1\}^n$ is called a *state* of the network f with *local state* x_i on each component i . The *dynamics* of f is given by its application on any state of the network. A *steady state or fixed point* of f is any state $x \in \{0, 1\}^n$ such that $f(x) = x$.

We define the *interaction graph* of a BN f with n components, denoted $G(f) = (V, A)$, as the signed directed graph with a sign, +1 or -1, attached to each arc, where V is a finite set of elements called vertices or nodes indexed in the set $[n] := \{1, 2, \dots, n\}$ and A is a collection of ordered pairs of vertices of V , called arcs, such that $\forall u, v \in [n]$:

- $(u, v) \in A$, with sign +1, if $\exists x \in \{0, 1\}^n, x_u = 0, f_v(x) < f_v(x + e_u)$,
- $(u, v) \in A$, with sign -1, if $\exists x \in \{0, 1\}^n, x_u = 0, f_v(x) > f_v(x + e_u)$,

where $e_u \in \{0, 1\}^n$ denotes the binary vector with all entries equal to 0, except for entry u , which equals 1. The vertex set of $G(f)$ is referred to as $V(G(f))$ and its arc set as $A(G(f))$. Note that $G(f)$ can have both a positive and a negative arc from one vertex to another. If $G(f)$ does not have multiple arcs from one vertex to another, then we say that f is a *regulatory Boolean network* (RBN).

A *walk* from a vertex v_0 to a vertex v_l in the interaction graph $G(f)$ is a sequence of vertices and arcs $W = v_0, a_0, v_1, \dots, a_{l-1}, v_l$ of $G(f)$ such that $\forall i \in \{0, \dots, l-1\}, a_i = (v_i, v_{i+1}) \in A(G(f))$. $A(W) = \{a_i : i \in \{0, \dots, l-1\}\}$ is the set of arcs of W . A *path* is a walk without repetition of vertices (except eventually the extreme ones). A *circuit* is a walk without repetition of arcs and closed (i.e. its extreme vertices are equal). A *cycle* is a closed path.

Let $u \in V(G(f))$, we denote the in-degree and out-degree of u by $d^-(u) = |\{v \in V(G(f)) : (v, u) \in A(G(f))\}|$ and $d^+(u) = |\{v \in V(G(f)) : (u, v) \in A(G(f))\}|$, respectively. If $d^-(u) = 0$, we say that u is a *source vertex*. The degree of u is $d(u) = d^-(u) + d^+(u)$. We refer [11] for other basic definitions in digraphs.

The sign of a walk (path, circuit or cycle) is the product of the signs of its arcs. We say that a cycle is a positive cycle, if the sign of the cycle is $+1$, otherwise, we say that is a negative cycle. See Example 1.

A vertex set $F \subseteq V(G(f))$ is a *feedback vertex set* (FVS) of $G(f)$ if $G(f) - F$ is acyclic. F is said to be a *minimal feedback vertex set* of $G(f)$ if F is a FVS of $G(f)$ and there is no other FVS F' such that $F' \subsetneq F$. F is said to be a *minimum feedback vertex set* of $G(f)$ if F is a FVS of $G(f)$ and there is no other FVS set F' such that $|F'| < |F|$.

We denote $\tau(G(f)) = \min \{|F| : F \text{ is a FVS of } G(f)\}$ the *transversal number* of $G(f)$.

$P \subseteq V(G(f))$ is a *positive feedback vertex set* (PFVS) of the signed interaction graph $G(f)$ if $G(f) - P$ is a digraph without positive cycles. The minimum cardinality of a PFVS is denoted by $\tau^+(G(f))$ and called the *positive transversal number* of $G(f)$.

When there is no confusion, for simplicity we denote $\tau(G(f))$ by τ and $\tau^+(G(f))$ by τ^+ .

Remark 1. Since a FVS is a particular PFVS,

$$\tau^+ \leq \tau.$$

Example 1. An example of a BN f and its interaction graph $G(f)$ is shown in Figure 1. Positive arcs are represented by $\xrightarrow{\text{green}}$ and negative arcs by $\xrightarrow{\text{red}}$. Examples of positive cycles are: $C_1 = 4, a_{12}, 5, a_{11}, 4$ and $C_2 = 3, a_4, 2, a_2, 1, a_8, 3$, and examples of negative cycles are: $C_3 = 3, a_6, 2, a_2, 1, a_8, 3$ and $C_4 = 1, a_3, 2, a_2, 1$. Dark vertices are a PFVS of $G(f)$.

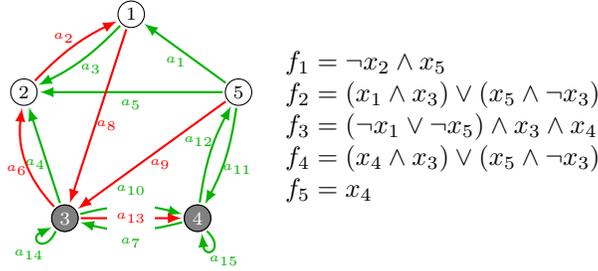


Figure 1: Example of a BN and its interaction graph.

In the sequel, we will refer to the signed cycles of a BN f as the cycles of $G(f)$.

Given $f : \{0, 1\}^n \rightarrow \{0, 1\}^n$ a BN and $u \in [n]$, the *partial evaluation* of f in the local function f_u is the function $f^u : \{0, 1\}^n \rightarrow \{0, 1\}^n$ such that:

$$\forall x \in \{0, 1\}^n, f^u(x) = (x_1, \dots, x_{u-1}, f_u(x), x_{u+1}, \dots, x_n)$$

We define a *sequential schedule* $\pi = (\pi_1, \pi_2, \dots, \pi_n)$ as a permutation of $[n]$. The dynamics of a BN $f : \{0, 1\}^n \rightarrow \{0, 1\}^n$ updated according to π is defined by:

$$\forall x \in \{0, 1\}^n, f^\pi(x) = f^{\pi_n} \circ f^{\pi_{n-1}} \circ \dots \circ f^{\pi_1}(x).$$

To avoid confusion, we use a special notation for self-compositions of f : we denote by $f^{(0)}$ the identity on $\{0, 1\}^n$ and for $k \geq 1$ we set $f^{(k)} = f \circ f^{(k-1)}$. The concatenation of k times the sequential schedule π is denoted π^k . In this way $f^{\pi^k} = (f^\pi)^{(k)}$.

3 Boolean networks without positive cycles

The relationship between the fixed points and the positive and negative cycles in Boolean networks has been greatly studied [6, 9, 10, 34, 35, 36]. In particular, in [6, 34] was proved that every Boolean

network without positive cycles has at most one fixed point and, in addition, if the network has an initial non-trivial strong component, then it has no fixed points. On the other hand, F. Robert studied the Boolean networks without cycles and proved in [37, 38] that these networks have a simple dynamical behavior with a unique attractor, which is a fixed point, and where all initial states quickly converge to it. More precisely, he proved the following theorem.

Theorem (F. Robert). *Let $f : \{0, 1\}^n \rightarrow \{0, 1\}^n$ be a BN such that $G(f)$ is acyclic. Then,*

1. f has a unique fixed point $y \in \{0, 1\}^n$.
2. $\forall x \in \{0, 1\}^n$, $f^{(n)}(x) = y$.
3. $\exists \pi$ a sequential schedule such that $\forall x \in \{0, 1\}^n$, $f^\pi(x) = y$.

In this paper we show that whether a BN without positive cycles has a fixed point, then its dynamical behavior is like a BN without cycles. More precisely, we prove the following theorem.

Theorem 1. *Let $f : \{0, 1\}^n \rightarrow \{0, 1\}^n$ be a BN without positive cycles. Then, the following propositions are equivalent:*

1. f has a unique fixed point $y \in \{0, 1\}^n$.
2. $\forall x \in \{0, 1\}^n$, $f^{(n)}(x) = y$.
3. $\exists \pi$ a sequential schedule such that $\forall x \in \{0, 1\}^n$, $f^\pi(x) = y$.

To proof this result, we need to introduce some definitions and previous results.

Definition 1. Let $f : \{0, 1\}^n \rightarrow \{0, 1\}^n$ be a Boolean network, we denote the following sets (eventually empty):

$$I_1(f) = \{v \in [n] : \exists c \in \{0, 1\}, \forall x \in \{0, 1\}^n, f_v(x) = c\}.$$

In other words, $v \in I_1(f)$ if f_v is constant. For all $v \in I_1(f)$, we denote c_v to the constant value of $f_v(x)$.

Recursively, we define $\forall k \in \mathbb{N}, k \geq 2, I_k(f)$ in the following way:

$$I_k(f) = \{v \in [n] : \exists c \in \{0, 1\}, \forall x \in \{0, 1\}^n, f_v(c_u : u \in I_{k-1}(f); x_u : u \notin I_{k-1}(f)) = c\}.$$

Similarly, $v \in I_k(f)$ if the local activation function associated to the component v with fixed value c_u on input $u \in I_{k-1}(f)$ is a constant function. $\forall v \in I_k(f)$, we denote c_v to the constant value of $f_v(c_u : u \in I_{k-1}(f); x_u : u \notin I_{k-1}(f))$.

From here, if $v \in I_k(f)$, then:

$$\forall t \geq k, \forall x \in \{0, 1\}^n, f_v^{(t)}(x) = c_v.$$

In this case, we say that the component v is *fixed at iteration k of f with value c_v* .

Proposition 1. *The sets $I_k(f)$ have the following properties:*

1. $\forall k \geq 1, I_k(f) \subseteq I_{k+1}(f)$.
2. If $\exists k \in \mathbb{N}, I_k(f) = I_{k+1}(f)$, then $\forall l \in \mathbb{N}, I_k(f) = I_{k+l}(f)$.
3. If $I_1(f) = \emptyset$, then $\forall k \in \mathbb{N}, I_k(f) = \emptyset$.

Proof.

1. By induction on k . First, we prove that $I_1(f) \subseteq I_2(f)$. By definition, $v \in I_1(f)$ if f_v is a constant function. On the other hand, $v \in I_2(f)$ if f_v with fixed value c_u on each input $u \in I_1(f)$ is a constant function. Therefore, $I_1(f) \subseteq I_2(f)$.

Let us suppose that $I_k(f) \subseteq I_{k+1}(f)$. Now, we prove that $I_{k+1}(f) \subseteq I_{k+2}(f)$. Analogously, $v \in I_{k+1}(f)$ if f_v with fixed value c_u on each input $u \in I_k(f)$ is a constant function. On the other hand, $v \in I_{k+2}(f)$ if f_v with fixed value c_u on each input $u \in I_{k+1}(f)$ is a constant function. Since $I_k(f) \subseteq I_{k+1}(f)$, the inclusion $I_{k+1}(f) \subseteq I_{k+2}(f)$ is direct.

2. To prove this, we prove that if $I_k(f) = I_{k+1}(f)$ then $I_{k+1}(f) = I_{k+2}(f)$.

Let us suppose that $I_k(f) = I_{k+1}(f)$. If $I_{k+2}(f) = \emptyset$, by Property 1, $I_{k+1}(f) = \emptyset$. So, let v be a component in $I_{k+2}(f)$, by definition:

$$\exists c \in \{0, 1\}, \forall x \in \{0, 1\}^n, f_v(c_u : u \in I_{k+1}(f); x_u : u \notin I_{k+1}(f)) = c.$$

Since $I_k(f) = I_{k+1}(f)$,

$$\forall x \in \{0, 1\}^n, f_v(c_u : u \in I_k(f); x_u : u \notin I_k(f)) = c.$$

Therefore, $v \in I_{k+1}(f)$. For this reason, $I_{k+2}(f) \subseteq I_{k+1}(f)$ and since $I_{k+1}(f) \subseteq I_{k+2}(f)$, then $I_{k+1}(f) = I_{k+2}(f)$.

3. First, we prove that if $I_1(f) = \emptyset$, then $I_2(f) = \emptyset$.

By contradiction, let us suppose that $I_1(f) = \emptyset$ and $I_2(f) \neq \emptyset$. Let v be a component in $I_2(f)$, then:

$$\exists c \in \{0, 1\}, \forall x \in \{0, 1\}^n, f_v(c_u : u \in I_1(f); x_u : u \notin I_1(f)) = f_v(x) = c.$$

Therefore, by definition, $v \in I_1(f)$ which is a contradiction.

Since $I_1(f) = I_2(f) = \emptyset$, by Property 2, $\forall k \in \mathbb{N}, I_k(f) = \emptyset$.

□

Definition 2. Let $f : \{0, 1\}^n \rightarrow \{0, 1\}^n$ be a Boolean network. We say that f is an *irreducible network after k iterations* or *k -irreducible network* if $I_k(f) = I_{k+1}(f)$. If $I_1(f) = \emptyset$, we say that f is an *irreducible network*.

Definition 3. Let $f : \{0, 1\}^n \rightarrow \{0, 1\}^n$ be a Boolean network and $k \in \mathbb{N}$. We define $f^{I_k} : \{0, 1\}^n \rightarrow \{0, 1\}^n$ the *Boolean network associated to f and $I_k(f)$* by:

$$\forall x \in \{0, 1\}^n, f^{I_k}(x) = f(c_u : u \in I_k(f); x_u : u \notin I_k(f)).$$

Remark 2. Note that if f is an irreducible network, then $f^{I_k}(x) = f(x)$.

Example 2. Figure 2 shows an example of a Boolean network f and the network f^{I_3} , according to Definition 3. Since f_4 and f_5 are the only constant functions, $I_1(f) = \{4, 5\}$ (with $c_4 = 1$ and $c_5 = 0$). On the other hand, $f_1(x_1, x_2, x_3, 1, 0, x_6, x_7) = \overline{x_1} \vee 1 \vee 0 = 1$, hence $1 \in I_2(f)$. Moreover, since there is no other component that satisfies the same condition, $I_2(f) = \{1, 4, 5\}$.

Analogously, $I_3(f) = \{1, 4, 5, 6, 7\}$. In a new iteration, $I_4(f) = I_3(f)$, so f is 3-irreducible.

Remark 3. It is important to remark that $\forall k \in \mathbb{N}$ and for all $f : \{0, 1\}^n \rightarrow \{0, 1\}^n$:

1. $V(G(f^{I_k})) = V(G(f))$.
2. $A(G(f^{I_k})) \subseteq A(G(f))$.
3. If $(u, v) \in A(G(f^{I_k}))$, then the sign of (u, v) is the same in $G(f)$ and $G(f^{I_k})$.

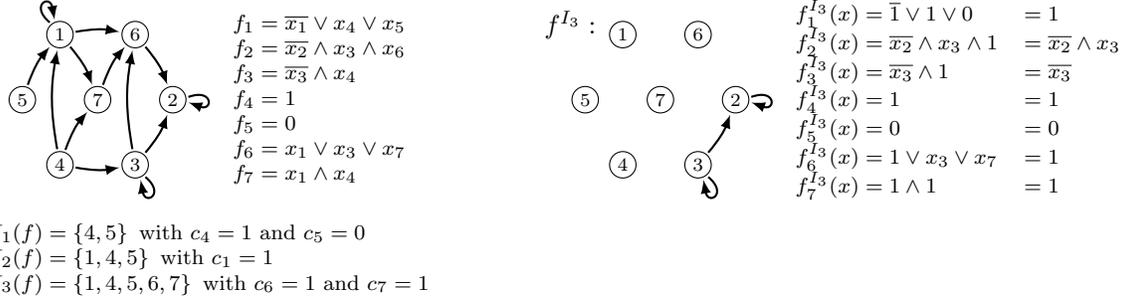


Figure 2: Example of Boolean networks f and f^{I_3} .

4. y is a fixed point of f if and only if y is a fixed point of f^{I_k} and $\forall v \in I_k(f), c_v = y_v$.

Remark 4. Let $f : \{0, 1\}^n \rightarrow \{0, 1\}^n$ be a Boolean network such that $I_k(f) = I_{k+1}(f) \neq \emptyset$. Then, $G(f^{I_k})$ has the following properties:

1. $\forall u \in I_k(f), d_{G(f^{I_k})}^+(u) = 0$.
2. If there exists a non-trivial strong component, then there is an initial non-trivial strong component.

In [6, 34] was proved the following theorem, known as the Thomas's first rule:

Theorem (Thomas's first rule). Let $f : \{0, 1\}^n \rightarrow \{0, 1\}^n$ a BN without positive cycles. Then, f has at most one fixed point.

A direct corollary from previous theorem is that if f is a BN without positive cycles such that has an initial non-trivial strong component, then f has no fixed points [6].

From theorem Thomas's first rule we can state the following result.

Lemma 1. Let $f : \{0, 1\}^n \rightarrow \{0, 1\}^n$ be a RBN without positive cycles. f has a unique fixed point if and only if there exists $k \in \{1, \dots, n\}$ such that $\emptyset \neq I_1(f) \subset I_2(f) \subset \dots \subset I_k(f) = [n]$.

Proof. (\Rightarrow) Let us suppose that f has a unique fixed point $y \in \{0, 1\}^n$, we prove that $\forall k \in \{1, \dots, n\}, |I_k| \geq k$. Since f does not have any positive cycle, by theorem Thomas's first rule all initial strong components of $G(f)$ are trivial, hence there exists a vertex $v_1 \in [n]$ whose local activation function is constant. Then, $v_1 \in I_1(f)$ and $|I_1(f)| \geq 1$.

By contradiction, let us suppose that $\exists l \in \{2, \dots, n\}$ such that $|I_l| < l$. So, by Property 1 of Proposition 1:

$$\exists k \leq (n-1), I_k(f) = I_{k+1}(f) \neq [n].$$

In this case, $\forall v \notin I_k(f), \exists u \notin I_k(f)$, such that f_v depends on x_u , i.e., $\forall v \notin I_k(f), \exists u \notin I_k(f), (u, v) \in A(f^{I_k})$.

Then, the in-degree of all vertices in $[n] \setminus I_k(f)$ is greater than 0, hence there exists a non-trivial strong component of $G(f^{I_k})$ induced by the vertices in $[n] \setminus I_k(f)$. Since $\forall u \in I_k(f), d_{G(f^{I_k})}^+(u) = 0$, there exists an initial non-trivial strong component in $G(f^{I_k})$ and thus f^{I_k} has no fixed points. Hence, by Remark 3.4) f has no fixed points, which is a contradiction.

Therefore, if $k \leq (n-1)$, then $I_k(f) \subsetneq I_{k+1}(f)$ or $I_k(f) = [n]$.

(\Leftarrow) If $I_n(f) = [n], \forall v \in [n], \forall t \geq n, \forall x \in \{0, 1\}^n, f_v^{(t)}(x) = c_v$. Then, f has a fixed point and, because f does not have any positive cycles, this fixed point is unique. □

Now we give the proof of Theorem 1.

Proof of Theorem 1. The proof of (2) \Rightarrow (1) and (3) \Rightarrow (1) are straightforward, so we prove that (1) \Rightarrow (2) and (1) \Rightarrow (3).

Both proofs are very similar, so we give the proof for (1) \Rightarrow (2).

First, notice that $\{I_1, I_2 \setminus I_1, \dots, I_k \setminus I_{k-1}\}$ is a partition of $[n]$, we define an order of the vertices $\pi = (\pi_1, \dots, \pi_n)$ such that:

$$\pi_i \in (I_j \setminus I_{j-1}) \wedge \pi_{i'} \in (I_{j'} \setminus I_{j'-1}) \wedge j < j' \implies i < i'.$$

Now we prove by induction that $\forall i \in \{1 \dots, k\}, \forall t \geq k, f_{\pi_i}^{(t)}(x) = y_{\pi_i}$.

If $k = 1$, $\pi_1 \in I_1(f)$, then f_{π_1} is a constant function and therefore $\forall t \geq 1, f_{\pi_1}^{(t)}(x) = y_{\pi_1}$.

Let us suppose that $\forall i \in \{1 \dots, k\}, \forall t \geq k, f_{\pi_i}^{(t)}(x) = y_{\pi_i}$.

Now we need to prove that $\forall t \geq k + 1, f_{\pi_{k+1}}^{(t)}(x) = y_{\pi_{k+1}}$.

$$f_{\pi_{k+1}}^{(t)}(x) = f_{\pi_{k+1}}(f^{(t-1)}(x)).$$

Since $t \geq k + 1, t - 1 \geq k$, then by hypothesis of induction:

$$f_{\pi_{k+1}}^{(t)}(x) = f_{\pi_{k+1}}(y_{\pi_i} : i \leq k; \tilde{x}_{\pi_i} : i > k).$$

By definition of π , if $\pi_{k+1} \in I_j \setminus I_{j-1}$ then $I_{j-1} \subseteq \{\pi_1, \dots, \pi_k\}$, therefore, by definition of I_j :

$$f_{\pi_{k+1}}^{(t)}(x) = y_{\pi_{k+1}}.$$

The proof for (1) \Rightarrow (3) works the same way to prove that $\forall i \in \{1, \dots, k\}, f_{\pi_i}^{(\pi_1, \dots, \pi_k)}(x) = f_{\pi_i}((f^{\pi_{k-1}} \circ \dots \circ f^{\pi_1})(x)) = y_{\pi_i}$. \square

A difference between BNs with acyclic interaction graphs and BNs without positive cycles is that, in the first case, the sequential schedule referred in F. Robert's theorem depends only on the interaction graph and not on the function. This latter is not true in the case of BNs without positive cycles as shown in Example 3.

Example 3. Let $f : \{0, 1\}^3 \rightarrow \{0, 1\}^3$ be a BN with interaction graph shown in Figure 3 and $\pi = (1, 2, 3)$ a sequential schedule. If we choose the functions:

$$f_1(x) = 1, \quad f_2(x) = \neg x_1 \wedge x_3, \quad f_3(x) = x_1 \wedge \neg x_2,$$

then $y = (1, 0, 1)$ is a fixed point of f and $\forall x \in \{0, 1\}^3, f^\pi(x) = y$. On the contrary, if we choose the functions:

$$f_1(x) = 1, \quad f_2(x) = \neg x_1 \vee x_3, \quad f_3(x) = x_1 \vee \neg x_2,$$

$y' = (1, 1, 1)$ is a fixed point of f , but $f^\pi(1, 1, 0) = (1, 0, 1) \neq y'$. In this case, if we choose $\pi' = (1, 3, 2)$, then $\forall x \in \{0, 1\}^3, f^{\pi'}(x) = y'$.

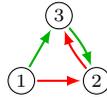


Figure 3: Interaction graph of a network without positive cycles.

On the other hand, as consequence of Theorem 1 the following corollary shows us that the problem of the existence of a fixed point in a BN without positive cycles can be solved in polynomial time.

Corollary 1. *Determining whether a BN $f : \{0, 1\}^n \rightarrow \{0, 1\}^n$ without positive cycles has a fixed point can be done through $n + 1$ applications of f on any state of the network.*

Proof. If y is a fixed point of f , then $\forall x \in \{0, 1\}^n, f^{(n)}(x) = y$. Hence, it suffices to check for some state x (for example, $x = \vec{0} := (0, 0, \dots, 0)$), if $f^{(n)}(x)$ is a fixed point of the network. In other words, if $f^{(n)}(x) = f^{(n+1)}(x)$, then $f^{(n)}(x)$ is a fixed point of f . Otherwise, f has no fixed points. \square

4 Methods

4.1 Algorithm to detect the fixed points in Boolean networks from a PFVS

In [6] was proved that for every RBN f there is an injection between its fixed points and the local states of a PFVS of its interaction graph $G(f)$, allowing to conclude that the maximum number of fixed points of a RBN f is $2^{\tau^+(G(f))}$. A simple exercise shows that this result is also valid in general Boolean networks [36]. In this way, we develop an algorithm that considers all the possible states of a given PFVS and efficiently verifies, by application of f , which of them produces a fixed point for the network. This is achieved thanks to the dynamical behavior of a BN without positive cycles described in Theorem 1. Previously, we give some definitions and results.

Definition 4. Let $f : \{0, 1\}^n \rightarrow \{0, 1\}^n$ be a BN, P a PFVS of $G(f)$ and $a : P \rightarrow \{0, 1\}$ a function, which can be represented by a vector $a \in \{0, 1\}^{|P|}$. We define the Boolean network $fa : \{0, 1\}^n \rightarrow \{0, 1\}^n$ as follows:

$$\forall v \in [n], \forall x \in \{0, 1\}^n, fa_v(x) = \begin{cases} a(v) & \text{if } v \in P, \\ f_v(x) & \text{if } v \notin P. \end{cases}$$

Example 4. Figure 4 shows an example of a BN f and a BN fa , where $a(1) = a(3) = 0$ and $a(2) = 1$, according to Definition 4. Dark gray vertices represent P .

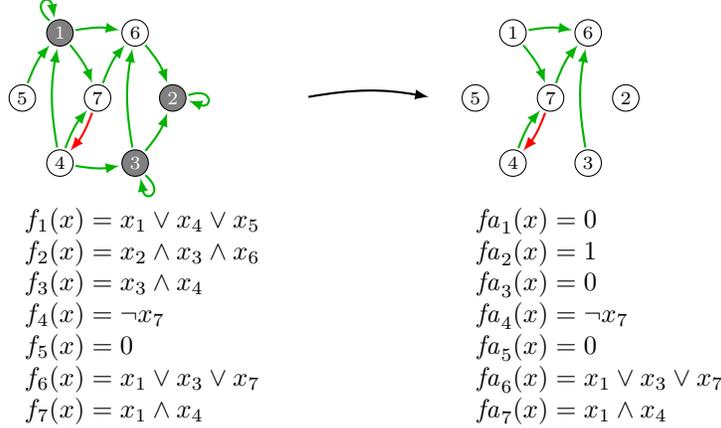


Figure 4: A Boolean network f and a *network without positive cycles* fa .

Note that $G(fa) = G(f) - \{(u, v) \in A(G(f)) : v \in P\}$. Hence, fa is a BN without positive cycles. As a direct result, we have the following proposition.

Proposition 2. Let $f : \{0, 1\}^n \rightarrow \{0, 1\}^n$ be a BN, $P \neq \emptyset$ a PFVS of $G(f)$ and $a : P \rightarrow \{0, 1\}$ a function. $x \in \{0, 1\}^n$ is a fixed point of f such that $\forall v \in P, x_v = a(v)$ if and only if:

1. x is a fixed point of fa ,
2. $\forall v \in P, f_v(x) = a(v)$.

Proof. (\Rightarrow) Let $x \in \{0, 1\}^n$ be a fixed point of f such that $\forall v \in P, x_v = a(v)$, then, as x is a fixed point of f , then $\forall v, f_v(x) = x_v$. Hence, by Definition 4, if $v \notin P, fa_v(x) = f_v(x) = x_v$, and if $v \in P, fa_v(x) = a(v) = x_v$. Therefore, $\forall v, fa_v(x) = x_v$, thus, x is a fixed point of fa and, by hypothesis, condition (2) also holds.

(\Leftarrow) If $x \in \{0, 1\}^n$ is a fixed point of fa , then $\forall v, fa_v(x) = x_v$. Hence, by Definition 4, if $v \notin P, x_v = fa_v(x) = f_v(x)$.

Moreover, If $\forall v \in P, x_v = fa_v(x) = a(v) = f_v(x)$.

Therefore, $\forall v, x_v = f_v(x)$, then, x is a fixed point of f and $\forall v \in P, x_v = a(v)$. \square

In this way, we use Proposition 2 to define Algorithm 1, which finds the fixed points of a given BN.

Proposition 3. *Given $f : \{0, 1\}^n \rightarrow \{0, 1\}^n$ be a BN and P a PFVS of $G(f)$, Algorithm 1 finds the set of fixed points of f in time $O(n^2 2^{|P|})$.*

Proof. The correctness of the algorithm is direct from Proposition 2 and Corollary 1. In particular, if $P \neq \emptyset$, the instruction $x \leftarrow fa^{(n)}(\vec{0})$ obtains a fixed point candidate (after n executions of fa , for some $a \in \{0, 1\}^{|P|}$) that is checked in the next line according to Proposition 2. Otherwise, i.e. f has no positive cycles, $x \leftarrow f^{(n)}(\vec{0})$ obtains a fixed point candidate (after n executions of f) that is checked in the next line according to Corollary 1. Finally, the total number of operations, corresponding mainly to the applications of the local activation functions, in the worst case is $O(n^2 2^{|P|})$. \square

Algorithm 1: BasicFixedPoint

Input: f a BN with n components and P a PFVS of $G(f)$.

Output: S the set of fixed points of f .

$S \leftarrow \emptyset$;

if $P \neq \emptyset$ **then**

foreach $a \in \{0, 1\}^{|P|}$ **do**

$x \leftarrow fa^{(n)}(\vec{0})$;

if $(fa(x) = x) \wedge (\forall u \in P, f_u(x) = a(u))$ **then**

$S \leftarrow S \cup \{x\}$;

else

$x \leftarrow f^{(n)}(\vec{0})$;

if $(f(x) = x)$ **then** $S \leftarrow \{x\}$;

return S

In order to make the Algorithm 1 faster, and following the ideas introduced in [7], we use a sequential update schedule that allows a faster convergence to the fixed points when they exist. By Theorem 1, the BNs without positive cycles has a sequential update schedule such that they convergence to the only fixed point, when there exists, in only one step. However, determining such a schedule can be as difficult as finding the fixed points of the network, because it depends on the value of each local activation functions as shown in Example 3. We propose to use a sequential update schedule which depends only on the interaction graph structure of input network. More precisely, given a FVS F and a PFVS P contained in it, we determine in polynomial time a sequential scheme such that the global activation function applied with this schedule in each iteration fixes at least the value of one vertex in $F \setminus P$ (in the case that this is possible), then the network is updated once more to fix the remaining vertices. Thus, the number of applications in the new algorithm is reduced from n to $|F| - |P| + 1$.

Definition 5. Given $f : \{0, 1\}^n \rightarrow \{0, 1\}^n$ a BN, F a FVS of $G(f)$ and $P \subseteq F$ a PFVS of $G(f)$, We say that a permutation $\pi = (\pi_1, \pi_2, \dots, \pi_n)$ on the set $[n]$ is an *order compatible with F and P* if it satisfies the following properties:

- $\forall \pi_i \in (F - P), \forall \pi_j \notin (F - P), i > j$.

- $\forall \pi_i \in P, \forall \pi_j \notin P, i < j$.
- $\forall \pi_i, \pi_j \notin F, (\pi_i, \pi_j) \in A(G(f)) \implies i < j$.

Example 5. Figure 5 shows examples of orders compatible with F and P . Dark gray vertices represent the PFVS P and light gray vertices represent $F \setminus P$.

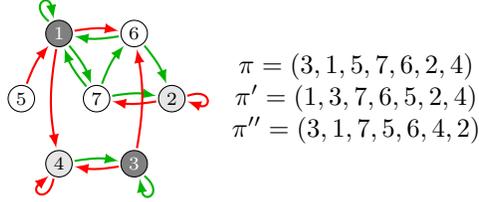


Figure 5: A digraph $G(f)$ and orders compatible with F and P . Set P is denoted for dark gray vertices and set F for light gray vertices.

Proposition 4. Let $f : \{0, 1\}^n \rightarrow \{0, 1\}^n$ be a BN, such that the interaction graph $G(f)$ does not have positive cycles, F be a FVS of $G(f)$, π be an order compatible with F and $y \in \{0, 1\}^n$. y is the unique fixed point of f if and only if $\forall x \in \{0, 1\}^n, (f^\pi)^{\langle |F|+1 \rangle}(x) = y$.

Proof. (\implies) Let us suppose that $y \in \{0, 1\}^n$ is the unique fixed point of f . Without loss of generality, let us suppose that $\pi = (1, 2, \dots, n)$. Then, by Theorem 1, there exist $I_1(f) \subsetneq I_2(f) \subsetneq \dots \subsetneq I_{k-1}(f) \subsetneq I_k(f) = [n]$ such that:

$$\forall j \in \{1, \dots, k\}, \forall v \in I_j(f), \forall t \geq j, \forall x \in \{0, 1\}^n, f_v^{(t)}(x) = y_v.$$

Now, we prove that by iterating f according to the order π , the n vertices fix their value in m iterations (with $m \leq |F| + 1$).

To perform this, let us consider the following sequence of indices o_i defined as follows:

$$o_1 = \min \{j \in \{1, \dots, k\} : (I_j(f) \cap F) \neq \emptyset\},$$

$$\forall p \geq 2, o_p = \min \{j > o_{p-1} : ((I_j(f) \setminus I_{j-1}(f)) \cap F) \neq \emptyset \vee (j = k)\}.$$

Notice that $o_1 < o_2 < \dots < o_m = k$ and $m \leq |F| + 1$.

We prove that $\forall i \in \{1, \dots, m\}, \forall u \in I_{o_i}, \forall t \geq i, \forall x \in \{0, 1\}^n, (f^\pi)_u^{(t)}(x) = y_u$.

By contradiction, let us suppose that:

$$\exists i \in \{1, \dots, m\}, \exists u \in I_{o_i}, \exists t \geq i, \exists x \in \{0, 1\}^n, (f^\pi)_u^{(t)}(x) \neq y_u.$$

Let:

$$i_* = \min \left\{ i \in \{1, \dots, m\} : \exists u \in I_{o_i}, \exists t \geq i, \exists x \in \{0, 1\}^n, (f^\pi)_u^{(t)}(x) \neq y_u \right\} \text{ and}$$

$$l_* = \min \left\{ l \leq o_{i_*} : \exists u \in I_l, \exists t \geq i_*, \exists x \in \{0, 1\}^n, (f^\pi)_u^{(t)}(x) \neq y_u \right\}.$$

Let $u_* \in I_{l_*} \setminus I_{l_*-1}$ be such that $\exists t \geq i_*, \exists x \in \{0, 1\}^n, (f^\pi)_{u_*}^{(t)}(x) \neq y_{u_*}$. Then, by Definition 1, $\forall t \geq i_*, \forall x \in \{0, 1\}^n$:

$$(f^\pi)_{u_*}^{(t)}(x) = f_{u_*}^\pi((f^\pi)^{\langle t-1 \rangle}(x))$$

$$= f_{u_*}((f^\pi)_i^{(t)}(x) : i < u_*; (f^\pi)_i^{\langle t-1 \rangle} : i \geq u_*).$$

Notice that $l_* > 1$, then:

$$(f^\pi)_{u_*}^{(t)}(x) = f_{u_*}((f^\pi)_v^{(t)}(x) : v < u_* \wedge v \in I_{l_*-1}; (f^\pi)_v^{(t)}(x) : v < u_* \wedge v \notin I_{l_*-1}; \\ (f^\pi)_v^{(t-1)}(x) : v \geq u_* \wedge v \in I_{l_*-1}; (f^\pi)_v^{(t-1)}(x) : v \geq u_* \wedge v \notin I_{l_*-1}).$$

By definition of l_* , if $v \in I_{l_*-1}$, then $(f^\pi)_v^{(t)}(x) = y_v$. Moreover, If $v \geq u_*$, then $v \in F$ and, therefore, if $v \in F$ and $v \in I_{l_*-1}$, then $v \in I_{o(i_*-1)}$ and, thus, if $v \geq u_*$ and $v \in I_{l_*-1}$, then $(f^\pi)_v^{(t-1)}(x) = y_v$. Also, if $i_* = 1$, then $\forall l \leq o_1, F \cap I_{l-1} = \emptyset$:

$$(f^\pi)_{u_*}^{(t)}(x) = f_{u_*}(y_v : v < u_* \wedge v \in I_{l_*-1}; (f^\pi)_v^{(t)}(x) : v < u_* \wedge v \notin I_{l_*-1}; \\ y_v : v \geq u_* \wedge v \in I_{l_*-1}; (f^\pi)_v^{(t-1)} : v \geq u_* \wedge v \notin I_{l_*-1}) \\ = f_{u_*}(y_v : v \in I_{l_*-1}; (f^\pi)_v^{(t)}(x) : v < u_* \wedge v \notin I_{l_*-1}; \\ (f^\pi)_v^{(t-1)}(x) : v \geq u_* \wedge v \notin I_{l_*-1}).$$

By Definition 1, $\forall t \geq i_*, \forall x \in \{0, 1\}^n$, $(f^\pi)_{u_*}^{(t)}(x) = y_{u_*}$, which is a contradiction.

Therefore, in at most m iterations of f^π , all vertices in $I_{o_m}(f) = I_k(f)$ are fixed.

(\Leftarrow) Let us suppose that $\forall x \in \{0, 1\}^n$, $(f^\pi)^{\langle |F|+1 \rangle}(x) = y$, then:

$$f^\pi(y) = f^\pi((f^\pi)^{\langle |F|+1 \rangle}(x)) = (f^\pi)^{\langle |F|+2 \rangle}(x) = (f^\pi)^{\langle |F|+1 \rangle}(f^\pi(x)) = y.$$

Since $f^\pi(y) = y$, then, y is a fixed point of f . □

Theorem 2. Let F be a FVS of $G(f)$ and $P \subseteq F$ a PFVS of $G(f)$, Algorithm 2 finds the set of fixed points of f in time $O((|F| - |P| + 1)n2^{|P|})$.

Proof. As the Algorithm 1, the correctness of this algorithm is based on the fact that its execution demonstrates each of the necessary conditions according to the Proposition 2. The difference is that the way to find the fixed point of fa (for some $a \in \{0, 1\}^{|P|}$) is done according to Proposition 4, i.e. instead of executing n times fa , fa^π is executed $|F| - |P| + 1$ times. For this reason, the complexity of this algorithm is $O((|F| - |P| + 1)n2^{|P|})$. □

Algorithm 2: FixedPoint

Input: f a BN with n components, F a FVS of $G(f)$, $P \subseteq F$ a PFVS of $G(f)$, π an order compatible with F and P .

Output: S the set of fixed points of f .

$m \leftarrow |F| - |P|$;

$S \leftarrow \emptyset$;

if $P \neq \emptyset$ **then**

foreach $a \in \{0, 1\}^{|P|}$ **do**

$x \leftarrow (fa^\pi)^{\langle m+1 \rangle}(\vec{0})$;

if $(fa(x) = x) \wedge (\forall u \in P, f_u(x) = a(u))$ **then**

$S \leftarrow S \cup \{x\}$;

else

$x \leftarrow (f^\pi)^{\langle m+1 \rangle}(\vec{0})$;

if $(f(x) = x)$ **then** $S \leftarrow S \cup \{x\}$;

return S

4.2 Building a PFVS

FixedPoint algorithm requires as input a FVS F and a PFVS $P \subseteq F$ of the interaction graph of a Boolean network. It is known that the problems of finding a minimum FVS and a minimum PFVS in a signed digraph are both NP-complete [21, 32]. In this section we propose an polynomial algorithm that allows to find a PFVS (not necessarily minimal) and a minimal FVS containing it.

Let $G(f)$ be the signed interaction graph of a BN f with n components. Given (v_1, v_2, \dots, v_n) an order over $V(G(f))$, Algorithm 3 classifies the vertices of $G(f)$ in the following sets:

- P : A set of vertices that is a PFVS of $G(f)$.
- O : A set of vertices such that $P \cup O$ is a minimal FVS of $G(f)$.
- R : The rest of the vertices of $G(f)$.

In addition, the algorithm considers the following auxiliary sets:

- Y : A set of vertices that covers some circuit.
- U : The vertices that have not yet been assigned to any set.

The operation of the algorithm is as follows:

First, we classify vertices with positive loop directly into P . Subsequently, the negative loops are removed from the arcs of $G(f)$.

Then, the first phase begins. All vertices that are not in P or R , are incorporated in U to be visited. Then, the first vertex in U (according to the input order) is incorporated into R (i.e., it is discarded from the PFVS) and if this vertex originally had a negative loop, it is incorporated into O (since that vertex has to be part of the FVS). Subsequently, for each vertex $v \in U \cup Y$, G'' (the subdigraph induced by $R \cup \{v\}$) is calculated, where, if G'' has a circuit, v is removed from U and from Y (since v covers some circuit in $G(f)$), and then, if G'' has a positive circuit, v is incorporated in P (since v is the only unclassified vertex of the positive circuit of G''), and otherwise, v is incorporated into Y (since it covers some circuit, but no positive circuit is known, to add v to P). Once U is empty, the first phase is terminated.

If at the end of the first phase, there are vertices that are neither in P nor in R (for example, they are in Y), a second phase begins. The only difference of this phase (and subsequent ones) with respect to the first phase, is that if a vertex is sent to R it is automatically sent to O (since this phase, all unclassified vertices cover some circuit, but being discarded, it means that they do not cover any positive circuit, so they are part of the FVS).

If at the end of the second phase some unclassified vertices remain, a third phase begins under the same conditions of the second phase, and so on.

Notice that, the constructed PFVS is not minimal, since a vertex can be included in P because it covers a positive circuit (not necessarily a positive cycle), but the FVS is minimal, because the algorithm works looking for cycles in $G(f) - P - O$, in this way, once we add a vertex to $P \cup O$ every cycle covered for this vertex it is eliminated of $G(f) - P - O$, so the only reason because a vertex is included in $P \cup O$ is that there exists a cycle that is not covered for another vertex in $P \cup O$, therefore $P \cup O$ is a minimal FVS.

The following algorithm is the way we implement the force-subroutine. A vertex $v \in V(G(f))$ is an *ancestor* of a vertex u if $v \in R$ and exists a path P_{vu} from v to u such that $\forall w \in P_{vu}, w \in R$. The set of ancestors of u is denoted by $\text{Anc}(u)$. A vertex $v \in V(G(f))$ is a *descendant* of a vertex u if $v \in U \cup Y$ and exists a path P_{vu} such that $\forall w \in V(P_{vu}), w \neq u$ implies $w \in R$. The set of descendants of u is denoted by $\text{Dec}(u)$. The sets $\text{Bef}(u)$ and $\text{aft}(u)$ contain the elements related to u (the last vertex added to R) that can form a circuit. If there is an arc that goes from a vertex $a \in \text{Aft}(u)$ to a vertex $b \in \text{Bef}(u)$, it means that there is a circuit formed by:

- The path from b to u ,

Algorithm 3: PFVS

Input: The signed interaction graph $G(f)$ of a BN f with n components and (v_1, v_2, \dots, v_n) an ordered sequence of $V(G(f))$.

Output: A PFVS P of $G(f)$, and a FVS F of $G(f)$ such that $P \subseteq F$.

```
// Initialization
 $V^\oplus \leftarrow \{u \in V(G(f)) : (u, u) \text{ is a positive arc of } G(f)\};$ 
 $V^\ominus \leftarrow \{u \in V(G(f)) : (u, u) \text{ is a negative arc of } G(f)\};$ 
 $G' \leftarrow G(f) - \{(u, u) \in A(G(f)) : u \in V^\ominus\};$ 
 $P \leftarrow V^\oplus; O \leftarrow \emptyset; R \leftarrow \emptyset;$ 
phase  $\leftarrow 1;$ 
while  $(P \cup R) \neq V(G(f))$  do
   $U \leftarrow V(G(f)) \setminus (P \cup R);$ 
   $Y \leftarrow \emptyset;$ 
  while  $U \neq \emptyset$  do
     $u \leftarrow$  vertex in  $U$  with lowest index;
     $U \leftarrow U \setminus \{u\}; R \leftarrow R \cup \{u\};$ 
    if  $(\text{phase} > 1) \vee (u \in V^\ominus)$  then  $O \leftarrow O \cup \{u\};$ 
    // Force-subroutine
    foreach  $v \in U \cup Y$  do
       $G'' \leftarrow G'[R \cup \{v\}];$ 
      if  $G''$  has a circuit then
         $U \leftarrow U \setminus \{v\}; Y \leftarrow Y \setminus \{v\};$ 
        if  $G''$  has a positive circuit then  $P \leftarrow P \cup \{v\};$ 
        else  $Y \leftarrow Y \cup \{v\};$ 
      // end Force-subroutine
    phase  $\leftarrow$  phase + 1;
   $F \leftarrow P \cup O;$ 
return  $P$  and  $F$ 
```

- The path from u to a and
- The arc from a to b .

The sign of this circuit will determine how the vertex a is classified (If the circuit is positive, a is added to P . If the circuit is negative, a is added to Y).

The sets $\text{Anc}(u)$, $\text{Dec}(u)$, $\text{Bef}(u)$ and $\text{Aft}(u)$ contain elements of the form (v, σ) , where v is a vertex, and σ is a sign (+1 or -1). Let x be an element of any of these sets, we will denote $v(x)$ to the vertex associated with the element x , and we will denote $\sigma(x)$ to the sign associated with the element x .

4.2.1 Heuristics for the order of the vertices

Different orders of the vertices as input of PFVS algorithm can generate different PFVS as outputs, so it may be necessary to define some heuristics to choose an appropriate order of the vertices. In this paper we use random order and Min-order defined as follows:

- Min-order: the vertices are ordered according:
 1. Their degrees, from lowest to highest.
 2. If two or more vertices have equal degree then by in-degree, from lowest to highest.

Figure 6 shows an example Min-order.

Algorithm 4: Force-subroutine

```
// During initialization
foreach  $v \in V(G(f))$  do
   $\text{Anc}(v) \leftarrow \emptyset; \text{Dec}(v) \leftarrow \emptyset;$ 
// Force-subroutine, ‘ $u$ ’ is the selected vertex in PFVS-Algorithm
 $\text{Bef}(u) \leftarrow \text{Anc}(u) \cup \{(u, +1)\};$ 
 $\text{Aft}(u) \leftarrow \emptyset;$ 
foreach  $v \in N^+(u)$  do
  if  $v \in U$  then  $\text{Aft}(u) \leftarrow \text{Aft}(u) \cup \{(v, \sigma(u, v))\};$ 
  else  $\text{Aft}(u) \leftarrow \text{Aft}(u) \cup \text{Dec}(v);$ 
foreach  $(a, b) \in \text{Aft}(u) \times \text{Bef}(u)$  do
  if  $(v(a), v(b)) \in A(G)$  then
     $U \leftarrow U \setminus \{a\};$ 
     $\sigma \leftarrow \sigma(a) \cdot \sigma(b) \cdot \sigma(v(a), v(b));$ 
    if  $\sigma = +$  then  $P \leftarrow P \cup \{d\};$ 
    else
       $Y \leftarrow Y \cup \{d\};$ 
       $\text{Dec}(b) \leftarrow \text{Dec}(b) \cup \{(a, \sigma_d \cdot \sigma_a)\};$ 
       $\text{Anc}(a) \leftarrow \text{Anc}(a) \cup \{(b, \sigma_d \cdot \sigma_a)\};$ 
  else
     $\text{Dec}(b) \leftarrow \text{Dec}(b) \cup \{(a, \sigma_d \cdot \sigma_a)\};$ 
     $\text{Anc}(a) \leftarrow \text{Anc}(a) \cup \{(b, \sigma_d \cdot \sigma_a)\};$ 
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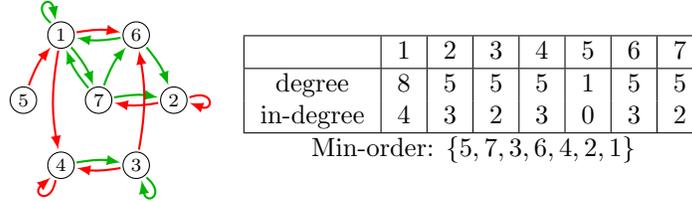


Figure 6: A signed interaction graph $G(f)$ and the order of its vertices according to the Min-order.

5 Results

We first tested the running time of FixedPoint algorithm in random BNs with a fixed transversal number τ and with different numbers of components n and positive transversal numbers τ^+ . The tested networks were constructed in such a way that a minimum FVS and a minimum PFVS were both known a priori, i.e. we did not use PFVS algorithm in these cases. The average times obtained in milliseconds with one hundred networks tested in each case, are shown in Figures 7 to 9. We can see that the time performance of FixedPoint algorithm grows exponentially with the value of τ^+ and polynomially with the size of the network.

The results of PFVS algorithm using different heuristic to chose the order of the vertices are presented in Figure 10. We can see that running time of the algorithm depends mainly on the size of the network and not on the sizes of the positive feedback vertex sets. Besides, in random networks as well as in networks from the literature described in Table 1 the performance of the min-order heuristic is better than the random one.

On the other hand, the correctness and time performance of FixedPoint algorithm and PFVS algorithm were also tested with networks from the literature where the sets of fixed points obtained

Time performance of FixedPoint algorithm
for different network sizes ($\tau = 15$)

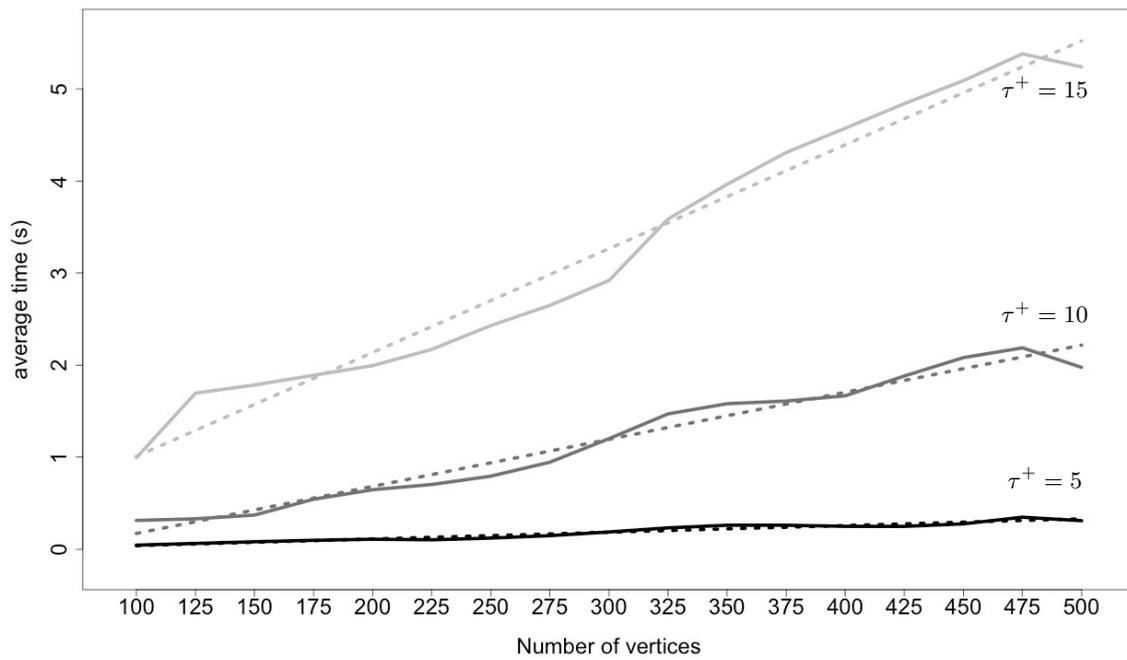


Figure 7: Results of FixedPoint algorithm .

Time performance of FixedPoint algorithm
for different PFVS sizes ($\tau = 15$)

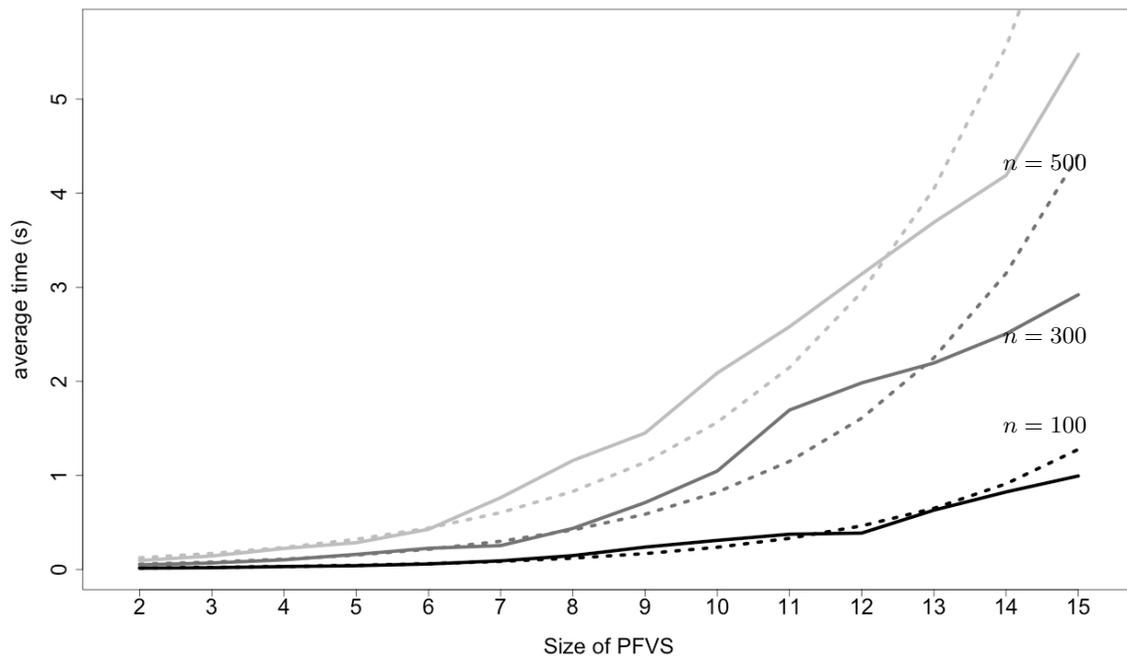


Figure 8: Results of FixedPoint algorithm .

**Time performance of FixedPoint algorithm
for different PFVS sizes ($n = 300, \tau = 30$)**

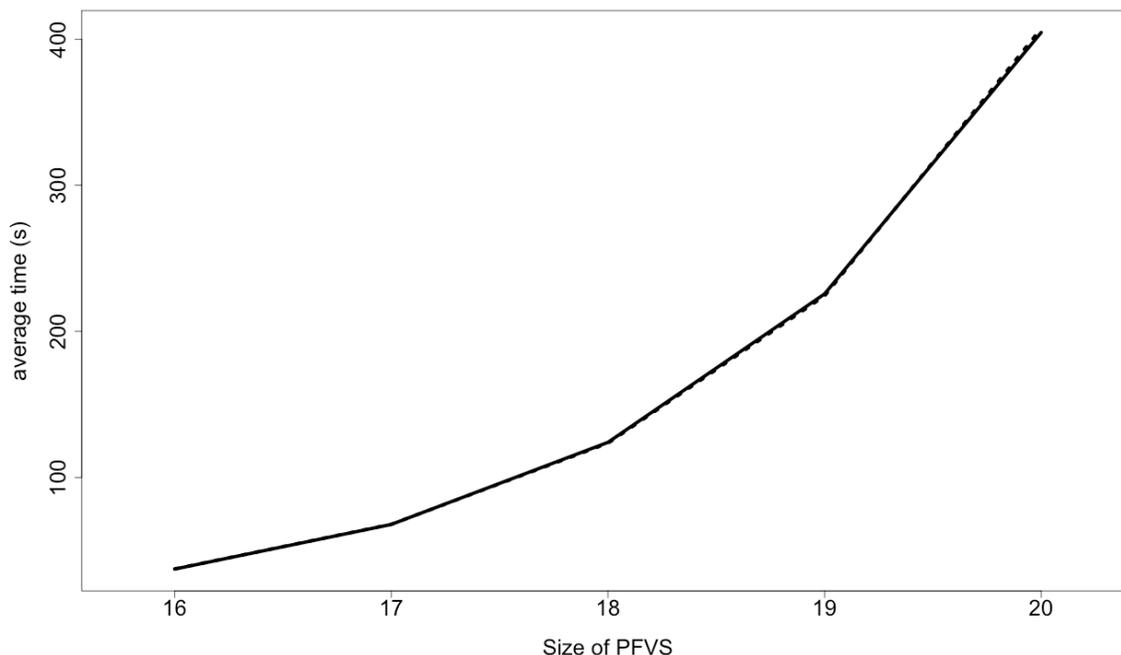


Figure 9: Results of FixedPoint algorithm .

coincides with those published. The results of these tests, shown in Table 1, were obtained with a PC 3.60GHz Intel Core i7 processor with 16GB of RAM and can be directly checked with the implementation FixedPointsCollector located at www.inf.udec.cl/~lilian/FPCollector/. We can observe that the running times obtained in these networks are short, probably due to the small size of their positive feedback vertex sets. The latter is also observed in another family of published networks, which are shown in Table 2, where the times obtained (using the same PC) are shorter than those obtained by the Veliz-Cuba algorithm in [51] for networks with a small τ^+ , however the same does not occur when τ^+ is large.

**Time performance of PFVS algorithm
for different network sizes ($\tau = 15, \tau^+ = 5$)**

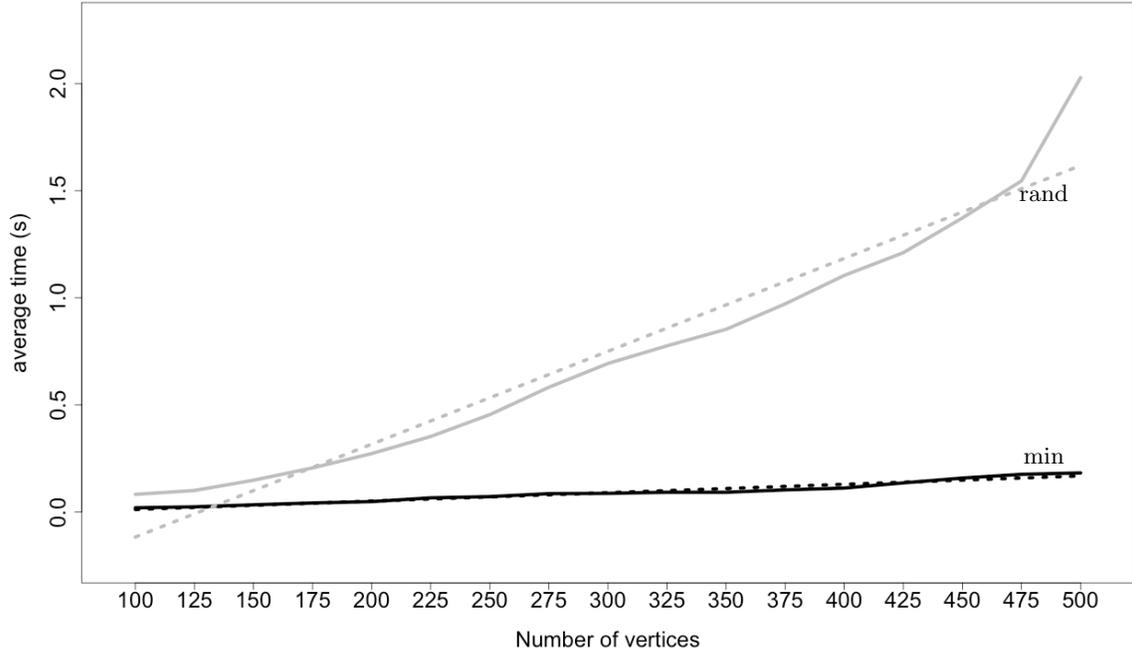


Figure 10: Results of PFVS algorithm .

Table 1: Performance of FixedPoint algorithm in real networks.

Network	n	FP	$ P $	T(min)	T(rand)
Cancer cell [53]	8	5	4	6.952	8.248
Cancer backbone [53]	8	12	5	7.019	7.321
Budding yeast [27]	11	7	6	5.963	7.036
Fission yeast [13]	10	12	4	8.980	9.416
Arabidopsis Thaliana [44]	13	10	7	8.938	8.919
T-helper cell [31]	23	3	3	7.407	13.512
T-cell receptor [25]	40	1	1	12.782	29.895
HGF [45]	66	2	3	17.286	61.969
Apostosis model 1 [26]	12	2	2	6.923	8.181
Apostosis model 2 [26]	12	4	2	6.870	9.170
Apostosis model 3 [26]	3	4	2	5.143	6.174
Drosophila melanogaster [5]	60	10	9	19.140	64.565
Ventral spinal cord [28]	8	5	4	6.751	7.126

$|P|$ is the size the PFVS obtained with min-order.

T(min) and T(rand) correspond to the time in milliseconds of the PFVS-Alg.+FP-Alg. using Min-order and random-order (in this case, its considered the execution of $n/2$ random permutations to choose the smallest PFVS), respectively.

Table 2: Time Performance Comparison

Network	n	$ P $	Veliz-Cuba		Our algorithm	
			mean	stdev.	mean	stdev.
HGF Signaling in Keratinocytes [45]	68	3	2.347	0.299	0.451	0.079
T Cell Receptor Signaling [42]	101	1	2.355	0.337	0.347	0.054
Signaling in Macrophage Activation [33]	321	3	2.406	0.298	0.464	0.044
Yeast Apoptosis [24]	73	3	2.370	0.429	0.378	0.042
Influenza A Virus Replication Cycle [29]	131	12	3.599	0.897	0.407	0.044
T-LGL Survival network (v. 2011) [41]	60	10	3.152	0.786	0.580	0.041
T-LGL Survival network (v. 2008) [55]	61	10	1.790	1.181	0.409	0.044
EGFR & ErbB Signaling [43]	104	2	1.185	0.910	0.356	0.041
Signal Transduction in Fibroblasts [18]	139	39	23,19*	98.42	DNF	DNF
ErbB (1-4) Receptor Signaling [17]	247	42	4186*	12284	DNF	DNF

$|P|$ is the size the PFVS obtained with min-order. Times presented in seconds.

*Times obtained from [51]. DNF: Tests that did not finish within 3 days

6 Discussion

In the modeling of biological systems by Boolean networks usually the interaction graph of the network is known as well as the type of interaction between their components (activation, inhibition). In this way, it seems natural to use this information to determine the fixed points of a network. In this paper, we have constructed FixedPoint algorithm to find the set of fixed points of a Boolean network based mainly on the structure of the positive cycles of its interaction graph and to a lesser extent on the size of the network. This can be considered an improvement to the results obtained by Akutsu et al. in [3], since the set of states to test is smaller and, in the case that $\tau = \tau^+$, our algorithm works the same way. The theoretical foundation of the algorithm is given by Theorem 1, which provides a nice characterization of the dynamical behavior of Boolean networks without positive cycles and with a fixed point.

The efficiency of FixedPoint algorithm depends mainly on the size of the input PFVS. Due to this, it is important to have a PFVS as close to the minimum as possible. In this sense, it is clear that PFVS algorithm can be improved. One improvement could be done implementing an efficient algorithm to decide the existence of a positive cycle in a signed digraph. This latter problem, which is equivalent to the existence of an even cycle in a digraph [32], is a surprisingly difficult problem and whose algorithmic complexity was unknown for a long time. Although Robertson, Seymour and Thomas finally proved that this decision problem can be solved in polynomial time [39], the implementation of such algorithm is not easy to do which makes it one of our future challenges. Another way to improve PFVS algorithm is the possibility of building a fixed-parameter tractable algorithm to determine a PFVS of minimum size, i.e. an algorithm whose complexity depends mainly on this size and not on the size of the interaction graph. It is known that this type of algorithm exists to solve the minimum FVS problem in digraphs [12]. However, it is an open problem, at our knowledge, in the case of minimum PFVS in signed digraphs.

In future work it would be important to explore methods to reduce the size of a network that conserve τ^+ . Also, since the efficiency of the FixedPoint algorithm depends on the size of a input PFVS, it is important to study the relationship between τ^+ and other parameters of the interaction graph of a Boolean network such as: minimum and maximum in-degree, out-degree and degree distributions.

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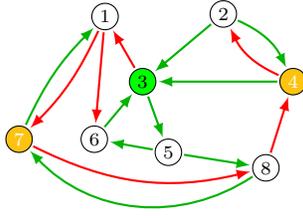
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A Example of the algorithms

Example 6. Figures 11 and 12 show the operation of the FixedPoint-Algorithm with a Boolean network with $\tau^+ = 1$ and $\tau = 3$. Note that in the tables in steps 3 and 5, the purple cells represent the components that are fixed according to Definition 1

1. Given the following network, where $\{3, 4, 7\}$ is a FVS and $\{3\}$ is a PFVS:



$$\begin{aligned} f_1 &= \overline{x_3} \vee x_7 \\ f_2 &= \overline{x_4} \\ f_3 &= (x_2 \wedge x_4) \vee (x_2 \wedge x_6) \vee (x_4 \wedge x_6) \\ f_4 &= x_2 \vee \overline{x_8} \\ f_5 &= x_3 \\ f_6 &= \overline{x_1} \vee x_5 \\ f_7 &= \overline{x_1} \vee x_8 \\ f_8 &= x_5 \wedge \overline{x_7} \end{aligned}$$

2. We choose an order compatible with the FVS and PFVS selected.
In this case, we choose $\pi = (3, 1, 2, 5, 6, 8, 4, 7)$.

3. If $a(3) = 0$, the execution of $(fa)^\pi$ would be the following:

		x_1	x_2	x_3	x_4	x_5	x_6	x_7	x_8
$(fa)^\pi$	3	0	0	0	0	0	0	0	0
	1	1	0	0	0	0	0	0	0
	2	1	1	0	0	0	0	0	0
	5	1	1	0	0	0	0	0	0
	6	1	1	0	0	0	0	0	0
	8	1	1	0	0	0	0	0	0
	4	1	1	0	1	0	0	0	0
	7	1	1	0	1	0	0	0	0
$((fa)^\pi)^2$	3	1	1	0	1	0	0	0	0
	1	1	1	0	1	0	0	0	0
	2	1	0	0	1	0	0	0	0
	5	1	0	0	1	0	0	0	0
	6	1	0	0	1	0	0	0	0
	8	1	0	0	1	0	0	0	0
	4	1	0	0	1	0	0	0	0
	7	1	0	0	1	0	0	0	0
$((fa)^\pi)^3$	3	1	0	0	1	0	0	0	0
	1	1	0	0	1	0	0	0	0
	2	1	0	0	1	0	0	0	0
	5	1	0	0	1	0	0	0	0
	6	1	0	0	1	0	0	0	0
	8	1	0	0	1	0	0	0	0
	4	1	0	0	1	0	0	0	0
	7	1	0	0	1	0	0	0	0

4. Since $(fa)(10010000) = 10010000$ and $f_3(1001000) = 0 = a(3)$, then 1001000 is a fixed point of f

Figure 11: Example of $(fa)^\pi$ execution.

Example 7. Figures 13 and 14 show the operation of the PFVS-Algorithm. Green vertices represent vertices in P , red vertices represent vertices in $R \setminus O$, yellow vertices represent vertices in Y , orange vertices represent vertices in R and O and white vertices represent vertices in U .

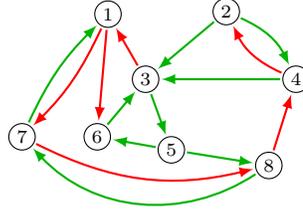
5. If $a(3) = 1$, the execution of $(fa)^\pi$ would be the following:

		x_1	x_2	x_3	x_4	x_5	x_6	x_7	x_8
$(fa)^\pi$	3	0	0	1	0	0	0	0	0
	1	0	0	1	0	0	0	0	0
	2	0	1	1	0	0	0	0	0
	5	0	1	1	0	1	0	0	0
	6	0	1	1	0	1	1	0	0
	8	0	1	1	0	1	1	0	1
	4	0	1	1	1	1	1	0	1
	7	0	1	1	1	1	1	1	1
$((fa)^\pi)^2$	3	0	1	1	1	1	1	1	1
	1	1	1	1	1	1	1	1	1
	2	1	0	1	1	1	1	1	1
	5	1	0	1	1	1	1	1	1
	6	1	0	1	1	1	1	1	1
	8	1	0	1	1	1	1	1	0
	4	1	0	1	1	1	1	1	0
	7	1	0	1	1	1	1	0	0
$((fa)^\pi)^3$	3	1	0	1	1	1	1	0	0
	1	0	0	1	1	1	1	0	0
	2	0	0	1	1	1	1	0	0
	5	0	0	1	1	1	1	0	0
	6	0	0	1	1	1	1	0	0
	8	0	0	1	1	1	1	0	1
	4	0	0	1	0	1	1	0	1
	7	0	0	1	0	1	1	1	1

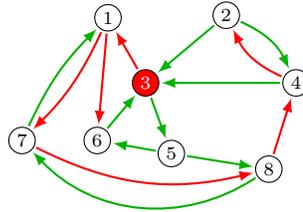
6. Since $(fa)(00101111) = 11101110$, does not exist fixed point of f such that $f_3(x) = 1$

Figure 12: Example of $(fa)^\pi$ execution (continuation).

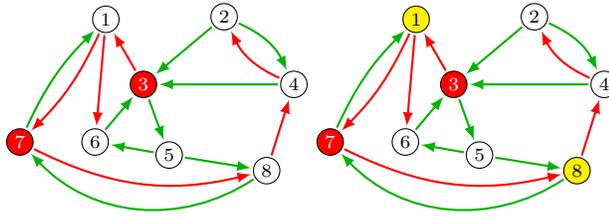
1. Given a labeled digraph and an order over its vertices $(3, 7, 2, 5, 1, 4, 8, 6)$. All vertices are added to U .



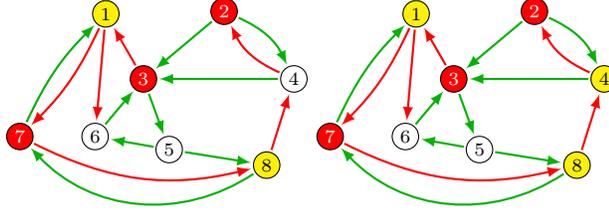
2. The vertex in U with lower index (the vertex 3) is discarded from PFVS (added to R). Since $\forall v \in U \cup Y$, the subgraph induced by $R \cup \{v\}$ has no circuits, a new vertex is selected.



3. The next vertex (7) is discarded from PFVS. Since the subgraph induced by $R \cup \{1\}$ has a negative circuit, (1) is added to Y . Similarly, (8) is added to Y .



4. The next vertex (2) is discarded from PFVS. (4) is added to Y .



5. The next vertex (5) is discarded from PFVS. Since the subgraph induced by $R \cup \{6\}$ has a positive circuit, (6) is included in the PFVS (added to G). Since U is empty, the first step is finished.

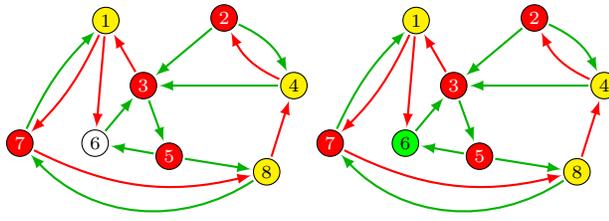
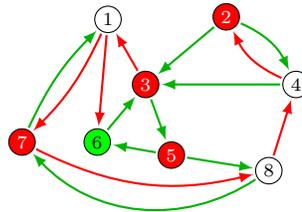
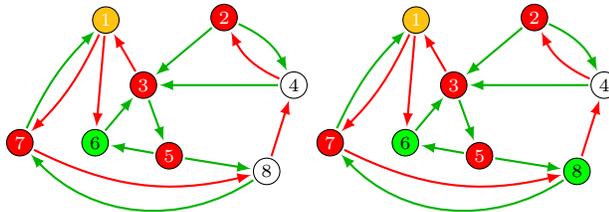


Figure 13: Example of PFVS Algorithm (First step).

6. For the second step (and following), all vertices in Y are added to U .



7. The vertex in U with lower index (1) is discarded from the PFVS (added to R and O). Since the subgraph induced by $R \cup \{8\}$ has a positive circuit $(1, 7, 8, 7, 1)$, (8) is included in the PFVS.



8. The next vertex (4) is discarded from PFVS. Since U is empty, the second step is finished. Since no vertex in Y , the algorithm ends.

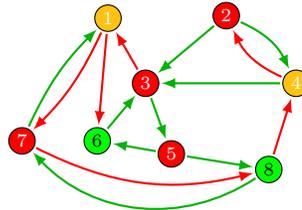


Figure 14: Example of PFVS Algorithm (Second step).

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