Most Permissive Semantics of Boolean Networks

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(Technical Report)

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Abstract. As shown in [3], the usual update modes of Boolean networks (BNs), including synchronous and (generalized) asynchronous, fail to capture behaviours introduced by multivalued refinements. Thus, update modes do not allow a correct abstract reasoning on dynamics of biological systems, as they may lead to reject valid BN models.

We introduce a new semantics for interpreting BNs which meets with a correct abstraction of any multivalued refinements, with any update mode. This semantics subsumes all the usual updating modes, while enabling new behaviours achievable by more concrete models. Moreover, it appears that classical dynamical analyses of reachability and attractors have a simpler computational complexity:

- reachability can be assessed in a polynomial number of iterations (instead of being PSPACE-complete with update modes);
- attractors are hypercubes, and deciding the existence of attractors with a given upper-bounded dimension is in NP (instead of PSPACE-complete with update modes).

The computation of iterations is in NP in the very general case, and is linear when local functions are monotonic, or with some usual representations of functions of BNs (binary decision diagrams, Petri nets, automata networks, etc.).

In brief, the most permissive semantics of BNs enables a correct abstract reasoning on dynamics of BNs, with a greater tractability than previously introduced update modes.

This technical report lists the main definitions and properties of the most permissive semantics of BNs, and draw some remaining open questions.

1 Boolean networks

The Boolean domain is denoted by $\mathbb{B} \stackrel{\Delta}{=} \{0,1\}$. Given a *configuration* $x \in \mathbb{B}^n$ and $i \in \{1,\dots,n\}$, we denote x_i the i^{th} component of x, so that $x = x_1 \dots x_n$, and $\bar{x}$ the complement of x, i.e., $\forall i \in \{1,\dots,n\}$, $\bar{x}_i = 1 - x_i$. Given two configurations $x, y \in \mathbb{B}^n$, the components that differ are noted $\Delta(x,y) \stackrel{\Delta}{=} \{i \in \{1,\dots,n\} \mid x_i \neq y_i\}$.

Definition 1 (Boolean network). *A Boolean network (BN) of dimension n is a collection of functions $f = \langle f_1, \dots, f_n \rangle$ where $\forall i \in \{1,\dots,n\}, f_i : \mathbb{B}^n \to \mathbb{B}$.*

Given $x \in \mathbb{B}^n$, we write $f(x)$ for $f_1(x) \dots f_n(x)$.

2 The most permissive semantics

2.1 Definition

Definition 2. *Given a finite set M with $\mathbb{B} \subseteq M$, for any $x \in M^n$,*

$$\beta(x) \stackrel{\Delta}{=} \{x' \in \mathbb{B}^n \mid \forall i \in \{1,\dots,n\}, x_i \in \mathbb{B} \Rightarrow x'_i = x_i\} \ .$$

Definition 3. *Given a BN f, the binary irreflexive relation $\xrightarrow[\text{mp}]{f} \subseteq \{0, 01, 10, 1\}^n \times \{0, 01, 10, 1\}^n$ is defined as:*

$$\begin{aligned} x \xrightarrow[\text{mp}]{f} y \stackrel{\Delta}{\iff} & \exists i \in \{1,\dots,n\} : \Delta(x,y) = \{i\} \\ & \wedge (y_i = \bar{b}b \Rightarrow \exists x' \in \beta(x) : b = f_i(x')) \wedge (y_i = b \Rightarrow x_i = \bar{b}b) \end{aligned}$$

where $b \in \mathbb{B}$.
We write $\xrightarrow[\text{mp}]{f}{}^*$ for the transitive closure of $\xrightarrow[\text{mp}]{f}$.

We call $x \xrightarrow[\text{mp}]{f} y$ an *iteration* leading from configuration x to y. The value changes of components induced by this semantics can be described by the automaton in Fig. 1. Notice that an iteration is fully asynchronous as it modifies the value of exactly one component.

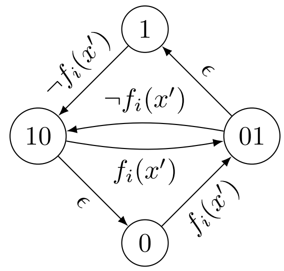

Fig. 1. Automaton of the value change of a component i in the most permissive semantics, following notations of Def. 3. The labels $f_i(x')$ and $\neg f_i(x')$ on edges are the conditions for firing the transitions. ϵ indicates that the transitions can be done without condition.

2.2 Algorithmic aspects

The complexity of computation of $\xrightarrow[\text{mp}]{f}$ iterations which modify a component value to 01 or 10 depends on the structure of the specification of the functions of the BN:

- In the very general case when the functions are specified using propositional logic, the evaluation of such iterations from any configuration $x \in \{0, 01, 10, 1\}^n$ boils down to a Boolean satisfiability (SAT) problem with $|\{i \in \{1, \dots, n\} \mid x_i \notin \mathbb{B}\}|$ variables, therefore is in NP.
- Whenever the functions f_i are (locally) *monotonic* the assessment of satisfiability ($f_i(x') = 1$) and non-satisfiability ($f_i(x') = 0$) is linear.
- The encoding of BNs as *Petri nets* [1,2] or *automata networks* [6] leads to specifying one DNF for satisfiability of f_i ($\exists x' : f_i(x') = 1$), and one DNF for non-satisfiability of f_i ($\exists x' : f_i(x') = 0$). In such a representation, because SAT of DNF is linear, the evaluation of $\xrightarrow[\text{mp}]{f}$ iterations is then linear.
- Whenever the functions are encoded as *binary decision diagrams* (BDDs), the evaluation of $\xrightarrow[\text{mp}]{f}$ iterations is linear.

  Indeed, a BDD has a directed acyclic graph structure with at most two terminal nodes among 0 and 1, and where non-terminal nodes refer to components $i \in \{1, \dots, n\}$ and have two successors. Moreover, there is a single root, and any path from the root to a terminal node crosses at most one node referring to each component. Overall, a BDD as the following structure: $\text{BDD} ::= (i, \text{BDD}_0, \text{BDD}_1) \mid 1 \mid 0$, and its evaluation in configuration $x \in \mathbb{B}^n$ is expressed as follows: $\text{eval}(i, \text{BDD}_0, \text{BDD}_1) \stackrel{\Delta}{=} \text{eval}(\text{BDD}_0)$ if $x_i = 0$, $\text{eval}(i, \text{BDD}_0, \text{BDD}_1) \stackrel{\Delta}{=} \text{eval}(\text{BDD}_1)$ if $x_i = 1$, $\text{eval}(1) \stackrel{\Delta}{=} 1$, and $\text{eval}(0) \stackrel{\Delta}{=} 0$.

  This evaluation can be easily extended for assessing iterations from x to change the value of x_j to 01 or 10: $\text{eval}(i, \text{BDD}_0, \text{BDD}_1) \stackrel{\Delta}{=} \text{eval}(\text{BDD}_0) \vee \text{eval}(\text{BDD}_1)$ if $x_i \notin \mathbb{B}$ and $x_j \in \{0, 10\}$ (the iteration to 01 is possible when $\text{eval}(\text{BDD}^j) = 1$, assuming BDD^j is the BDD encoding of f_j); and $\text{eval}(i, \text{BDD}_0, \text{BDD}_1) \stackrel{\Delta}{=} \text{eval}(\text{BDD}_0) \wedge \text{eval}(\text{BDD}_1)$ if $x_i \notin \mathbb{B}$ and $x_j \in \{1, 01\}$ (the iteration to 10 is possible when $\text{eval}(\text{BDD}^j) = 0$).

Iterations modifying component values to 0 or 1 can be computed in constant time.

2.3 Basic properties

Lemma 1. *Given a BN f of dimension n, and any configurations $x, y \in \{0, 01, 10, 1\}^n$ with $x \xrightarrow[\text{mp}]{f} y$ and $\forall j \in \Delta(x, y)$, $y_j \notin \mathbb{B}$, then,*

1. *$\beta(x) \subseteq \beta(y)$, and*
2. *$\forall i \in \{1, \dots, n\}$,*

$$\exists x' \in \beta(x) : f_i(x') \neq x_i \Longrightarrow \exists y' \in \beta(y) : f_i(y') \neq y_i$$

Proof. Property (1) derives from x, y hypothesis and β definition. For property (2), two cases arise: if $i \notin \Delta(x, y)$, $y_i = x_i$, therefore by taking $y' = x'$ we obtain $f_i(y') \neq y_i$; if $i \in \Delta(x, y)$, by hypothesis, $y_i \notin \mathbb{B}$, thus $f_i(x') \neq y_i$. □

Lemma 2. *Given a BN f of dimension n, for any $x \in \{0, 01, 10, 1\}^n$:*

$$x \in \mathbb{B}^n \wedge f(x) = x \Longleftrightarrow \nexists y \in \{0, 01, 10, 1\}^n : x \xrightarrow[\text{mp}]{f} y$$

Lemma 3. *Given a BN f of dimension n, for any $x \in \{0, 01, 10, 1\}^n$,*

$$x \notin \mathbb{B}^n \Longrightarrow \exists y \in \mathbb{B}^n : x \xrightarrow[\text{mp}]{f}{}^{*} y$$

3 A correct abstraction of multivalued refinements

Multivalued networks (MNs) are a generalization of BNs where the components can take values in a finite discrete domain. Let us denote the possible values as $\mathbb{M} \triangleq \{0, \frac{1}{m}, \dots, \frac{m-1}{m}, 1\}$ for some integer m. Without loss of generality, we assume the same domain of values for all the components.

Hence, a *configuration* is now a vector $x \in \mathbb{M}^n$. Given two configurations $x, y \in \mathbb{M}^n$, the components that differ are noted $\Delta(x, y) \triangleq \{i \in \{1, \dots, n\} \mid x_i \neq y_i\}$.

Definition 4 (Multivalued network). *A* multivalued network *(MN) of dimension n over a value range $\mathbb{M} = \{0, \frac{1}{m}, \dots, \frac{m-1}{m}, 1\}$ is a collection of functions $F = \langle F_1, \dots, F_n \rangle$ where $\forall i \in \{1, \dots, n\}, F_i : \mathbb{M}^n \to \{\uparrow, \downarrow, -\}$.*

Definition 5. *Given a multivalued network F, the binary irreflexive relation $\xrightarrow[\text{gen}]{F} \subseteq \mathbb{M}^n \times \mathbb{M}^n$ is defined as:*

$$x \xrightarrow[\text{gen}]{F} y \overset{\Delta}{\iff} x \neq y \wedge \forall i \in \Delta(x, y), F_i(x) \neq -$$
$$\wedge\, y_i = \begin{cases} \min\{0, x_i - \frac{1}{m}\} & \text{if } F_i(x) = \downarrow \\ \max\{1, x_i + \frac{1}{m}\} & \text{if } F_i(x) = \uparrow \end{cases} .$$

We write $\xrightarrow[\text{gen}]{F}{}^*$ for the transitive closure of $\xrightarrow[\text{gen}]{F}$.

We now define a notion of *multivalued refinement* of a BN, which formalizes the intuition that the value changes defined by the multivalued network are compatible with those of the BN.

Definition 6 (Multivalued refinement). *A multivalued network F of dimension n over a value range* $\mathbb{M} = \{0, \frac{1}{m}, \ldots, \frac{m-1}{m}, 1\}$ refines *a BN f of equal dimension n iff for every configuration $x \in \mathbb{M}^n$ and every $i \in \{1, \ldots, n\}$:*

- $F_i(x) = \uparrow \implies \exists x' \in \beta(x) : f_i(x') = 1$
- $F_i(x) = \downarrow \implies \exists x' \in \beta(x) : f_i(x') = 0$

3.1 Most permissive semantics simulates any multivalued refinement with any updating mode

Given $x \in \mathbb{M}^n$,

$$\alpha(x) \overset{\Delta}{=} \{\hat{x} \in \{0, 01, 10, 1\}^n \mid \forall i \in \{1, \ldots, n\}, x_i \in \mathbb{B} \Leftrightarrow \hat{x}_i \in \mathbb{B}\}$$

Theorem 1. *Let f be a BN of dimension n and F a multivalued refinement of f. Then,*

$$\forall x, y \in \mathbb{M}^n, \quad x \xrightarrow[\text{gen}]{F} y \implies \forall \hat{x} \in \alpha(x), \exists \hat{y} \in \alpha(y) : \hat{x} \xrightarrow[\text{mp}]{f}{}^* \hat{y} \ .$$

Proof. Consider any $\hat{x} \in \alpha(x)$.

Let us first consider the set of components which are in Boolean state in configuration x and differ in configuration y, $I^{\mathbb{B}} \overset{\Delta}{=} \{i \in \Delta(x, y) \mid x_i \in \mathbb{B}\}$.

We prove that for any subset $J \subseteq I^{\mathbb{B}}$, there exists $z \in \{0, 01, 10, 1\}^n$ such that $\hat{x} \xrightarrow[\text{mp}]{f}{}^* z$ with $\Delta(\alpha(x), z) = J$ and $\forall i \in J$, $z_i = x_i \bar{x}_i$. It is trivially true with $J = \emptyset$ and $z = \hat{x}$. Let us assume it is true with $J \subsetneq I^{\mathbb{B}}$ and some $z \in T^n$, and consider $J' = J \cup \{i\}$ with $i \in I^{\mathbb{B}} \setminus J$. By definition of $\xrightarrow[\text{gen}]{F}$, $F_i(x) \in \{\uparrow, \downarrow\}$, and because

F is a refinement of f, $\exists x' \in \beta(x) : f_i(x') \neq x_i$. Because $\beta(x) \subseteq \beta(z)$ (Lemma 1), $x' \in \beta(z)$, therefore $\alpha(x) \xrightarrow[\text{mp}]{f}{}^* z \xrightarrow[\text{mp}]{f} z'$ with $\Delta(z, z') = \{i\}$ and $z'_i = x_i\bar{x}_i$.

Therefore, there exists a configuration $z \in \{0, 01, 10, 1\}^n$ such that $\hat{x} \xrightarrow[\text{mp}]{f}{}^* z$ with $\Delta(\hat{x}, z) = I^{\mathbb{B}}$ and $\forall i \in I^{\mathbb{B}}$, $z_i = x_i\bar{x}_i$; and $\beta(x) \subseteq \beta(z)$.

Then, let us consider the set of components which are in Boolean state in configuration y, $I_{\mathbb{B}} \stackrel{\Delta}{=} \{i \in \Delta(x, y) \mid y_i \in \mathbb{B}\}$. Remark that, by definition of $\xrightarrow[\text{gen}]{F}$, for each component $i \in I_{\mathbb{B}}$, $F_i(x) \in \{\uparrow, \downarrow\}$, and because F is a refinement of f, there exists a configuration $x' \in \beta(x)$ such that $f_i(x') = y_i$.

For each $i \in I_{\mathbb{B}}$, three cases arise: if $i \in I^{\mathbb{B}}$, $z_i = \bar{y}_i y_i$; otherwise, $z_i = \hat{x}_i$ with either $\hat{x}_i = 01$, or $\hat{x}_i = 10$. Thus, $z_i \in \{\bar{y}_i y_i, y_i \bar{y}_i\}$.

By using the same reasoning as for $I^{\mathbb{B}}$, there exists a configuration $w \in \{0, 01, 10, 1\}^n$ such that $\hat{x} \xrightarrow[\text{mp}]{f}{}^* z \xrightarrow[\text{mp}]{f}{}^* w$ where $\Delta(z, w) = \{i \in I_{\mathbb{B}} \mid z_i = y_i \bar{y}_i\}$, with $\forall i \in I_{\mathbb{B}}$, $w_i = \bar{y}_i y_i$, and $\beta(x) \subseteq \beta(w)$.

Finally, let us define $\hat{y}$ such that: (1) $\forall i \in I_{\mathbb{B}}$, $\hat{y}_i \stackrel{\Delta}{=} y_i$; (2) $\forall i \in I^{\mathbb{B}} \setminus I_{\mathbb{B}}$, $\hat{y}_i \stackrel{\Delta}{=} z_i$; (3) $\forall i \in \Delta(x, y) \setminus (I^{\mathbb{B}} \cup I^{\mathbb{B}})$, $\hat{y}_i \stackrel{\Delta}{=} \hat{x}_i$. Notice that $\hat{y} \in \alpha(y)$ and

$$\hat{x} \xrightarrow[\text{mp}]{f}{}^* z \xrightarrow[\text{mp}]{f}{}^* w \xrightarrow[\text{mp}]{f}{}^* \hat{y} \ .$$

□

Remark 1. A BN f is a multivalued refinement of itself with $\mathbb{M} = \mathbb{B}$; therefore a corollary of the above theorem is that the most permissive semantics of BNs weakly simulates the (generalized) asynchronous update mode of BNs.

3.2 Minimality of most permissive semantics

Theorem 2. *Given a BN f of dimension n, $\forall x, y \in \{0, 01, 10, 1\}^n : (x_i = 01 \Rightarrow \exists x' \in \beta(x) : f_i(x') = 1) \wedge (x_i = 10 \Rightarrow \exists x' \in \beta(x) : f_i(x') = 0)$,*

$$x \xrightarrow[\text{mp}]{f} y \Longrightarrow \exists F \text{ refining } f, \check{x}, \check{y} \in \mathbb{M}^n : x \in \alpha(\check{x}), y \in \alpha(\check{y}), \check{x} \xrightarrow[\text{gen}]{F} \check{y} \ .$$

Proof. By definition of $\xrightarrow[\text{mp}]{f}$, $\Delta(x, y) = \{i\}$.

Let us define $\mathbb{M} \stackrel{\Delta}{=} \{0, \frac{1}{3}, \frac{2}{3}, 1\}$ and $\check{x} \in \mathbb{M}^n$ such that $\forall j \in \{1, \dots, n\}$, $x_j \in \mathbb{B} \Rightarrow \check{x}_j \stackrel{\Delta}{=} x_j$ $x_j = 10 \Rightarrow \check{x}_j \stackrel{\Delta}{=} \frac{1}{3}$, $x_j = 01 \Rightarrow \check{x}_j \stackrel{\Delta}{=} \frac{2}{3}$. Remark that $x \in \alpha(\check{x})$.

For any $z \in \mathbb{M}^n$, let us define $\lceil z \rceil \in \mathbb{B}^n$ such that $\forall j \in \{1, \ldots, n\}$, $z_j \in \mathbb{B} \Rightarrow \lceil z \rceil_j \triangleq z_j$ and $z_j \notin \mathbb{B} \Rightarrow \lceil z \rceil_j \triangleq 1$. Remark that $\lceil z \rceil \in \beta(z)$. For $j \in \{1, \ldots, n\}$, $j \neq i$, let us define $\forall z \in \mathbb{M}^n$,

$$F_j(z) \triangleq \begin{cases} \uparrow & \text{if } f_j(\lceil z \rceil) = 1 \\ \downarrow & \text{otherwise.} \end{cases}$$

Remark that F_j is a correct refinement of f_j. A definition of F_i which satisfies the refinement criteria can be done according to the following cases, depending on $x \xrightarrow[\text{mp}]{f} y$:

Case 1: $y_i \in \{01, 1\}$. Necessarily, there exists $x' \in \beta(x) : f_i(x') = 1$, either by $\xrightarrow[\text{mp}]{f}$ definition if $x_i \in \{0, 10\}$, or by hypothesis if $x_i = 01$. Let us define $\theta : \mathbb{M}^n \to \mathbb{B}^n$ such that $\forall z \in \mathbb{M}^n$, $\forall j \in \{1, \ldots, n\}$, $z_j \in \mathbb{B} \Rightarrow \theta(z)_j \triangleq z_j$, and $z_j \notin \mathbb{B} \Rightarrow \theta(z)_j \triangleq x'_j$. Observe that $\theta(z) \in \beta(z)$. Let us then define

$$F_i(z) \triangleq \begin{cases} \uparrow & \text{if } f_i(\theta(z)) = 1 \\ \downarrow & \text{otherwise.} \end{cases}$$

and $\check{x} \in \mathbb{M}^n$ such that $\forall j \in \{1, \ldots, n\}$, $x_j \in \mathbb{B} \Rightarrow \check{x}_j \triangleq x_j$ $x_j = 10 \Rightarrow \check{x}_j \triangleq \frac{1}{3}$, $x_j = 01 \Rightarrow \check{x}_j \triangleq \frac{2}{3}$. Observe that $\theta(\check{x}) = x'$, hence $F_i(\check{x}) = \uparrow$. Moreover, remark that F_i is a refinement of f_i: indeed, if $F_i(z) = \uparrow$ (resp. $\downarrow$), then $\theta(z) \in \beta(z)$ verifies $f_i(\theta(z)) = 1$ (resp. $f_i(\theta(z)) = 0$).

Thus, $\check{x} \xrightarrow[\text{gen}]{F} \check{y}$ with $\Delta(\check{x}, \check{y}) = \{i\}$ and $\check{y}_i = \check{x}_i + \frac{1}{3}$, and $y \in \alpha(\check{y})$.

Case 2: $y_i \in \{10, 0\}$. Necessarily, there exists $x' \in \beta(x) : f_i(x') = 0$, either by $\xrightarrow[\text{mp}]{f}$ definition if $x_i \in \{1, 01\}$, or by hypothesis if $x_i = 10$. Then, $\theta : \mathbb{M}^n \to \mathbb{B}^n$ is defined as in case 1, and let us define

$$F_i(z) \triangleq \begin{cases} \downarrow & \text{if } f_i(\theta(z)) = 0 \\ \uparrow & \text{otherwise.} \end{cases}$$

As in case 1, F_i is a refinement of f_i and $F_i(\check{x}) = \downarrow$. Thus, $\check{x} \xrightarrow[\text{gen}]{F} \check{y}$ with $\Delta(\check{x}, \check{y}) = \{i\}$ and $\check{y}_i = \check{x}_i - \frac{1}{3}$, and $y \in \alpha(\check{y})$. $\square$

3.3 Examples

Example 1. Let us consider the following BN f of dimension 3

$$
\begin{aligned}
f_1(x) &\triangleq \neg x_2 \\
f_2(x) &\triangleq \neg x_1 \\
f_3(x) &\triangleq \neg x_1 \wedge x_2
\end{aligned}
$$

and a 3-level refinement F of it with the following update functions:

$$
\begin{aligned}
F_1(x) &\triangleq \uparrow \text{if } x_2 < 1 \text{ else } \downarrow \\
F_2(x) &\triangleq \uparrow \text{if } x_1 < 1 \text{ else } \downarrow \\
F_3(x) &\triangleq \uparrow \text{if } x_1 \leq \frac{1}{2} \wedge x_2 \geq \frac{1}{2} \text{ else } \downarrow
\end{aligned}
$$

We get $000 \xrightarrow[\text{gen}]{F} 0\tfrac{1}{2}0 \xrightarrow[\text{gen}]{F} \tfrac{1}{2}\tfrac{1}{2}0 \xrightarrow[\text{gen}]{F} \tfrac{1}{2}\tfrac{1}{2}\tfrac{1}{2} \xrightarrow[\text{gen}]{F} \tfrac{1}{2}\tfrac{1}{2}1 \ldots$.

Using (general) asynchronous updating of f from the configuration 000, the following configurations are reachable:

$$
\begin{tikzcd}
010 \arrow[rr, bend left] & 110 \arrow[l] \arrow[d] \arrow[dl] & 011 & 111 \\
000 \arrow[u] \arrow[r] \arrow[ur] & 100 & 001 & 101
\end{tikzcd}
$$

Remark that the configuration 111 is not reachable with f and general asynchronous updates, whereas in the multivalued refinement F, a configuration $\frac{1}{2}\frac{1}{2}1$ is reachable: imagine that a fourth species would activate when x_1, x_2 and x_3 are all $\geq \frac{1}{2}$, then even the generalized asynchronous updating mode would not capture its activation.

With the most permissive semantics, we obtain the following possible sequence of iterations of f:

$$
\begin{aligned}
0\,0\,0 \xrightarrow[\text{mp}]{f} 01\,0\,0 \xrightarrow[\text{mp}]{f} 01\,01\,0 \xrightarrow[\text{mp}]{f} 01\,1\,0 \\
\xrightarrow[\text{mp}]{f} 01\,1\,01 \xrightarrow[\text{mp}]{f} 01\,1\,1 \xrightarrow[\text{mp}]{f} 1\,1\,1
\end{aligned}
$$

The configuration 111 is then reachable with the most permissive semantics of f, offering a correct abstraction of F.

Example 2. Let us consider the BN f of dimension 3 defined as follows:

$$f_1(x) \triangleq 1$$
$$f_2(x) \triangleq x_1$$
$$f_3(x) \triangleq x_2 \wedge \neg x_1$$

Starting from configuration 000 the generalized asynchronous mode allows only the following iterations: $000 \xrightarrow[\text{gen}]{f} 100 \xrightarrow[\text{gen}]{f} 110$, where 110 is a fixpoint of f.

Now, let us consider the following 3-level refinement F of the BN f:

$$F_1(x) \triangleq \uparrow$$
$$F_2(x) \triangleq \uparrow \text{ if } x_1 \geq \frac{1}{2} \text{ otherwise } \downarrow$$
$$F_3(x) \triangleq \uparrow \text{ if } x_2 \geq \frac{1}{2} \wedge x_1 \leq \frac{1}{2} \text{ otherwise } \downarrow$$

The following asynchronous iterations are possible from configuration 000: $000 \xrightarrow[\text{gen}]{F} \frac{1}{2}00 \xrightarrow[\text{gen}]{F} \frac{1}{2}\frac{1}{2}0 \xrightarrow[\text{gen}]{F} \frac{1}{2}\frac{1}{2}\frac{1}{2}$. The most permissive semantics of f correctly recovers that the configuration 111 is reachable from 000. Essentially, as in this semantics species can have access to either the before-update or after-update value of other species, species 2 can be activated by reading the after-update value of 1, while species 3 can be activated by reading the before-update value of 1.

$$\begin{aligned} 0\,0\,0 \xrightarrow[\text{mp}]{f} 01\,0\,0 \xrightarrow[\text{mp}]{f} 01\,01\,0 \xrightarrow[\text{mp}]{f} 01\,01\,01 \xrightarrow[\text{mp}]{f} 01\,1\,01 \\ \xrightarrow[\text{mp}]{f} 01\,1\,1 \xrightarrow[\text{mp}]{f} 1\,1\,1 \end{aligned}$$

As in the previous example, let us consider a fourth species activated when x_1, x_2, and x_3 are all greater or equal than $\frac{1}{2}$: such an activation is captured neither by the generalized asynchronous updating nor by the interval semantics of the abstract BN f, whereas it is captured by its most permissive semantics.

4 Complexity of reachability

Definition 7. *The binary relation $\preceq \subseteq \{0, 01, 10, 1\}^n \times \{0, 01, 10, 1\}^n$ is a partial order such that $x \preceq y$ if and only if $\beta(x) \subseteq \beta(y)$.*

Definition 8. *Given a configuration $x \in \mathbb{B}^n$, $\hbar(x)$ is the $\preceq$-smallest configuration $y \in \{0, 01, 10, 1\}^n$ verifying $\forall i \in \{1, \dots, n\}$,*

$$y_i = \begin{cases} x_i\bar{x}_i & \text{if } \exists z \in \beta(y) : x_i \neq f_i(x) \\ x_i & \text{otherwise.} \end{cases}$$

Remark that $\hbar(x)$ always exists and is unique.

Lemma 4. *Given a BN f of dimension n, for any configuration $x \in \mathbb{B}^n$, $x \xrightarrow[\text{mp}]{f}^* \hbar(x)$ and x can reach $\hbar(x)$ in $|\Delta(x, \hbar(x))|$ iterations of $\xrightarrow[\text{mp}]{f}$.*

Proof. From x, performs iterations of the form $x_i \to x_i\bar{x}_i$ until fixpoint (requires $|\Delta(x, \hbar(x))|$ iterations); by Lemma 1 the order does not matter.

Lemma 5. *Given a BN f of dimension n, for any configuration $x \in \mathbb{B}^n$, $\forall y \in \{0, 01, 10, 1\}^n$, $x \xrightarrow[\text{mp}]{f}^* y \implies \beta(y) \subseteq \beta(\hbar(x))$.*

Proof. By induction on the length of the sequence of $\xrightarrow[\text{mp}]{f}$ iterations. If $x = y$, we trivially obtain $\beta(y) \subseteq \beta(\hbar(x))$. Let us assume that the property holds for any configuration $y \in \{0, 01, 10, 1\}^n$ reachable in k iterations. Let us prove that for any $y' \in \{0, 01, 10, 1\}^n$ such that $y \xrightarrow[\text{mp}]{f} y'$, $\beta(y') \subseteq \beta(\hbar(x))$: by definition, there exists a unique $i \in \{1, \dots, n\}$ such that $\Delta(y, y') = \{i\}$. If $y'_i \in \mathbb{B}$, then $y_i \notin \mathbb{B}$, therefore $\beta(y') \subsetneq \beta(y) \subseteq \beta(\hbar(x))$; if $y'_i \notin \mathbb{B} \wedge y_i \notin \mathbb{B}$, then $\beta(y') = \beta(y) \subseteq \beta(\hbar(x))$; finally, if $y'_i \notin \mathbb{B} \wedge y_i \in \mathbb{B}$, then $\exists z \in \beta(y) : f_i(z) \neq y_i$, thus, by induction hypothesis, $z \in \beta(\hbar(x))$ and two cases arise: if $y_i = x_i$, by definition $\hbar(x)_i = x_i\bar{x}_i$, otherwise ($y_i \neq x_i$), because $\beta(y) \subseteq \beta(\hbar(x))$, necessarily $\hbar(x)_i \notin \mathbb{B}$; therefore $\beta(y') \subseteq \beta(\hbar(x))$. □

In particular, for any configurations $x, y \in \mathbb{B}^n$, $x \xrightarrow[\text{mp}]{f}^* y$ only if $y \in \beta(\hbar(x))$.

Lemma 6. *Given a BN f of dimension n and any configurations $x, y \in \mathbb{B}^n$, if $x \xrightarrow[\text{mp}]{f}^* y$, then there exists a sequence of at most $3n$ iterations of $\xrightarrow[\text{mp}]{f}$ from x to y. Moreover, this sequence first consists of at most n and at least $|\Delta(x, y)|$ iterations of the form $x_i \to x_i\bar{x}_i$, then at most n iterations of the form $y_i\bar{y}_i \to \bar{y}_i y_i$, and then at most n iterations of the form $\bar{y}_i y_i \to y_i$.*

Proof. Let us consider any sequence of iterations $x \xrightarrow[\text{mp}]{f} w^1 \xrightarrow[\text{mp}]{f} \cdots w^k \xrightarrow[\text{mp}]{f} y$. Let us define the set of components which went through the state $x_i\bar{x}_i$ during this sequence of iterations, $\hat{I} \triangleq \{i \in \{1, \dots, n\} \mid \exists j \in \{1, \dots, k\}, w^j = x_i\bar{x}_i\ \}$.

There exists $\hat{z} \in \{0, 01, 10, 1\}^n$ with $\Delta(x, \hat{z}) = \hat{I}$ and $\forall i \in \hat{I}$, $\hat{z}_i = x_i\bar{x}_i$, such that $x \xrightarrow[\text{mp}]{f}^* \hat{z}$ in $|\hat{I}|$ iterations. Indeed, for each $i \in \hat{I}$, let us write $j(i) \triangleq \min\{1, \dots, k \mid w^j = x_i\bar{x}_i\}$, and $\{j^1, \dots, j^{|\hat{I}|}\} = \{j(i) \mid i \in \hat{I}\}$ with

$j^1 < \dots < j^{|\hat{I}|}$. Necessarily, for each $i \in \hat{I}$, $\exists z \in \beta(w^{j(i)-1}) : f_i(z) = \bar{x}_i$, identifying w^0 with x. First, remark that $j^1 = 1$, hence $x \xrightarrow[\text{mp}]{f} z^1$ with $\Delta(x, z^1) = \Delta(w^{j^1-1}, w^{j^1}) = \{i^1\}$ and $z^1_{i^1} = w^{j^1}_{i^1}$. Then, remark that $\beta(w^{j^2}) \subseteq \beta(z^1)$, hence, $z^1 \xrightarrow[\text{mp}]{f} z^2$ with $\Delta(z^1, z^2) = \Delta(w^{j^2-1}, w^{2^1}) = \{i^2\}$ and $z^2_{i^2} = w^{j^2}_{i^2}$. By induction, we obtain $x \xrightarrow[\text{mp}]{f}{}^* \hat{z}$.

Now, let us consider the subset of components which are equal in x and y, $\bar{I} \triangleq \{i \in \hat{I} \mid x_i = y_i\}$.

There exists $\check{z} \in \{0, 01, 10, 1\}^n$ with $\Delta(\hat{z}, \check{z}) = \bar{I}$ and $\forall i \in \{1, \dots, n\}$, either $\check{z}_i = y_i$ or $\check{z}_i = \bar{y}_i y_i$ such that $\hat{z} \xrightarrow[\text{mp}]{f}{}^* \check{z}$ in $|\bar{I}|$ iterations. Indeed, for any $i \in \bar{I}$, $\hat{z}_i = x_i\bar{x}_i = y_i\bar{y}_i$ and there exists $j' \in \{1, \dots, k\}$ with $w^{j'}_i = \hat{z}_i$. Then, necessarily, there exists $j \in \{j', \dots, k-1\}$ with $w^j_i = \hat{z}_i$ and $w^{j+1}_i = \bar{y}_i y_i$, thus, $\exists z \in \beta(w^j) : f_i(z) = y_i$. Then, remark that $\forall j \in \{1, \dots, k\}$, $\beta(w^j) \subseteq \beta(\hat{z})$: from $\hat{z}$ one can update the components $i \in \bar{I}$ from $y_i\bar{y}_i$ to $\bar{y}_i y_i$, in any order (Lemma 1).

Finally, we remark that $\check{z} \xrightarrow[\text{mp}]{f}{}^* y$ in $|\hat{I}|$ iterations.

In summary, $x \xrightarrow[\text{mp}]{f}{}^* \hat{z} \xrightarrow[\text{mp}]{f}{}^* \check{z} \xrightarrow[\text{mp}]{f}{}^* y$ in $|\hat{I}| + |\bar{I}| + |\hat{I}| \leq 3n$ iterations. □

Theorem 3. *Given a BN f of dimension n and any configurations $x, y \in \mathbb{B}^n$, deciding if $x \xrightarrow[\text{mp}]{f}{}^* y$ requires computing at most $\frac{n(n-1)}{2}$ iterations of $\xrightarrow[\text{mp}]{f}$.*

Proof. Let us consider the following procedure with $L \subseteq \{1, \dots, n\}$, initially with $L = \emptyset$:

1. From x, apply only iterations of the form $x_i \to x_i\bar{x}_i$ to components $i \in \{1, \dots, n\} \setminus L$. Let us denote by $\hat{z}^L \in \{0, 01, 10, 1\}^n$ the (unique) reached configuration.
2. If $y \notin \beta(\hat{z}^L)$, then y is not reachable from x.
3. Otherwise, let us consider the components that cannot reach their value in y from $\hat{z}^L$, $\bar{I}^L \triangleq \{i \in \{1, \dots, n\} \mid \hat{z}^L_i = y_i\bar{y}_i \wedge \nexists z \in \beta(\hat{z}^L), f_i(z) = y_i\ \}$:
   (a) If $\bar{I}^L = \emptyset$, then $\hat{z}^L \xrightarrow[\text{mp}]{f}{}^* y$.
   (b) Otherwise, repeat the procedure with $L := L \cup \bar{I}^L$.

Remark that this procedure can be iterated at most n times, each of them computing $n - |L|$ iterations. Its correctness can be demonstrated as follows.

By Lemma 6, $x \xrightarrow[\text{mp}]{f}{}^* y$ if and only if there exists $L \subseteq \{1, \dots, n\}$ such that $y \in \beta(\hat{z}^L)$ and $\bar{I}^L = \emptyset$. Notice that there is a unique $\subseteq$-minimal L^* verifying $y \in \beta(\hat{z}^{L^*})$ and $\bar{I}^{L^*} = \emptyset$: if L^1 and L^2 verify these properties, then so does $L^1 \cap L^2$.

Let us denote by $L^0, \dots, L^m$ the successive values of L at the beginning of each iteration of the procedure ($L^0 = \emptyset$). We prove that $L^* = L^m$. Let us admit that $L^k \subseteq L^*$ with $k < m$. By construction, $\beta(\hat{z}^{L^*}) \subseteq \beta(\hat{z}^{L^k})$.

Let us assume there exists $i \in \bar{I}^{L^k}$ and $i \notin L^*$. Then, $\hat{z}^{L^*} = \hat{z}^{L^k} = y_i\bar{y}_i$, and there exists $z \in \beta(\hat{z}^{L^*})$ with $f_i(z) = y_i$, which is a contradiction. $\square$

Therefore, in the general case, reachability is NP.

Remark that if $f(y) = y$, and more generally, if y belongs to an attractor (Def. 9), the procedure is executed only once, i.e., at most n iterations are computed.

5 Complexity of attractors

Definition 9. *Given a BN f of dimension n, an* attractor *of $\xrightarrow[\text{mp}]{f}$ is a non-empty set of configurations $A \subseteq \mathbb{B}^n$ such that $\forall x, y \in A, x \xrightarrow[\text{mp}]{f}{}^* y$, and $\forall z \in \mathbb{B}^n, x \xrightarrow[\text{mp}]{f}{}^* z \Rightarrow z \in A$.*

Remark: for any $z \in \mathbb{B}^n$ such that $f(z) = z$, $\{z\}$ is an attractor of $\xrightarrow[\text{mp}]{f}$.

Lemma 7. *Given a BN f of dimension n, if $A \subseteq \mathbb{B}^n$ is an attractor of $\xrightarrow[\text{mp}]{f}$, then there exists $z \in \{0, \frac{1}{2}, 1\}^n$ such that $\beta(z) = A$. The attractor A is then said of dimension $|\{i \in \{1, \dots, n\} \mid z_i \notin \mathbb{B}\}|$.*

Proof. Given two configurations $x, y \in A$ with $\Delta(x, y) \supseteq \{i, j\}$, $i \neq j$, let us prove that necessarily, there exists $w \in A$ with $\Delta(y, w) = \{i\}$ (hence $w_i = x_i$) and $w' \in A$ with $\Delta(y, w') = \{j\}$ (hence $w'_j = x_j$). Indeed, $x, y \in A \Rightarrow x \xrightarrow[\text{mp}]{f}{}^* y \wedge y \xrightarrow[\text{mp}]{f}{}^* x$. Therefore, there exists $\hat{y} \in \{0, 01, 10, 1\}^n$ such that $x \xrightarrow[\text{mp}]{f}{}^* \hat{y}$, and $\forall k \in \{1, \dots, n\}$, $\hat{y}_k \in \{y_k, \bar{y}_k y_k\}$, and $y \in \beta(\hat{y})$. Let us focus on the $\preceq$-largest $\hat{y}$ verifying these conditions. Necessarily, $\hat{y}_i \notin \mathbb{B}$ and $\hat{y}_j \notin \mathbb{B}$. Because $y \in \beta(\hat{y})$, $\hat{y} \xrightarrow[\text{mp}]{f}{}^* x$, thus $\exists z', z'' \in \beta(\hat{y}) : f_i(z') = x_i \wedge f_j(z'') = x_j$. Hence, $\hat{y} \xrightarrow[\text{mp}]{f} \hat{y}^i$ and $\hat{y} \xrightarrow[\text{mp}]{f} \hat{y}^j$ with $\Delta(\hat{y}, \hat{y}^i) = \{i\}$ and $\hat{y}^i_i = \bar{x}_i x_i$, and $\Delta(\hat{y}, \hat{y}^j) = \{j\}$ and $\hat{y}^j_j = \bar{x}_j x_j$. Thus, $\hat{y}^i \xrightarrow[\text{mp}]{f}{}^* w'$ and $\hat{y}^j \xrightarrow[\text{mp}]{f}{}^* w$. Therefore, with $z \in \{0, \frac{1}{2}, 1\}^n$ such that $\Delta(y, z) = \{i, j\}$ and $z_i = z_j = \frac{1}{2}$, we obtain $\beta(z) \subseteq A$.

Now, let us assume there exists no $z \in \{0, \frac{1}{2}, 1\}^n$ such that $\beta(z) = A$. Then, let us consider the $\preceq$-largest z so that $\beta(z) \subsetneq A$, and $x \in A \setminus \beta(z)$. Necessarily, $\exists i \in \{1, \dots, n\}$ such that $z_i \in \mathbb{B}$ and $x_i \neq z_i$. Two cases arise: (1) if $\forall j \in \{1, \dots, n\}$, $j \neq i$, $z_j = x_j$, then $z' \in \{0, \frac{1}{2}, 1\}^n$ with $\Delta(z, z') = \{j\}$ and $z_j = \frac{1}{2}$ verifies $\beta(z') \subseteq A$ which contradicts the hypothesis; (2) otherwise, $\exists j \in \{1, \dots, n\}$, $j \neq i$, such that $x_j \neq z_j$ and either $z_j \notin \mathbb{B}$ or $z_j \in \mathbb{B}$. Thus, $\exists y \in \beta(z)$ with $\{i, j\} \subseteq \Delta(x, y)$, hence $z' \in \{0, \frac{1}{2}, 1\}^n$ with $\Delta(z, z') = \{i, j\}$ and $z_i = z_j = \frac{1}{2}$ verifies $\beta(z') \subseteq A$ which contradicts the hypothesis. $\square$

Theorem 4. *Given a BN f of dimension n, deciding if there exists an attractor of $\xrightarrow[\text{mp}]{f}$ of dimension at most $k < n$ is in NP.*

Proof. By Lemma 7, there exists an attractor of $\xrightarrow[\text{mp}]{f}$ of dimension at most k if and only if there exists $z \in \{0, \frac{1}{2}, 1\}^n$ such that $|\{i \in \{1, \dots, n\} \mid z_i \notin \mathbb{B}\}| \leq k$ and $\forall i \in \{1, \dots, n\} : z_i \in \mathbb{B}, \nexists y \in \beta(z) : z_i \neq f_i(z)$, which can be decided by checking the possibility of at most n iterations of $\xrightarrow[\text{mp}]{f}$. $\square$

Following Theorem 4, the attractors can be enumerated from dimension 0 (fixpoints) to $n-1$, by excluding supersets of previously identified attractors. If no attractor of dimension at most $n-1$ is found, the only attractor is $\mathbb{B}^n$.

6 Discussion

The usual updating modes on Boolean networks (BNs), ranging from the synchronous to (generalized) asynchronous, can hinder a correct qualitative reasoning on dynamics of networks. As illustrated with some biologically relevant examples, an analysis of dynamics at the Boolean level can lead to falsely conclude on the impossibility of some behaviours: when adding information to the model, like detailing the interaction thresholds, states that where not reachable with the Boolean analysis turn to be actually reachable in a multivalued refinement of the model. This is a strong limitation of the current Boolean approaches, especially when applied to the automatic inference of model according to time series (reachability) data: valid models may be incorrectly rejected.

The most permissive semantics of BNs introduced in this report aims at enabling a correct abstract Boolean reasoning on the dynamics of networks: any refinement of the model with any updating mode will only remove behaviours (transitions). Therefore, the most permissive semantics of BNs results in an over-approximation of behaviours achievable by the modeled network.

Another limitation of usual updating modes of BNs is their high computational complexity to assess dynamical features such as reachability and attractor properties, which are both PSPACE-complete problems, thus hampering their tractability on large networks.

We demonstrated that the dynamical analysis of BNs with the most permissive semantics has a lower computational complexity: reachability properties can be assessed with a polynomial (quadratic) number of iterations, whereas attractor identification is in NP. Whereas in general the computation of iterations of the most permissive semantics is NP-complete (leading to reachability and attractors in NP), their computation is actually linear when BNs are locally monotonic, a common hypothesis in systems biology, or when they are represented with Petri nets or binary decisions diagrams. Therefore, the tractability of most permissive semantics can be expected to be of several orders of magnitude higher than with the classical update modes.

Interestingly, the characterization of reachability and attractors with the most permissive semantics matches with prior introduced approximations for BNs: the reachability analysis in most permissive semantics is very close to the *meta-state* semantics of [5] which was introduced as an over-approximation of reachability in BNs with (generalized) asynchronous update. Moreover, it appears that the attractors of the most permissive semantics match with the *minimal trap spaces* [4] of BNs, which are then used to over-approximate attractors in BNs with asynchronous update (which can be different from hypercubes).

Dynamics of BNs with usual updating modes is often represented with state transition graphs, where nodes are the Boolean configurations (states), and edges represent the possible iterations (transitions). Such an object is less relevant with the most permissive semantics as there would be a direct transition from a configuration to each of the configurations reachable from it. The complexity results on reachability also suggests that computing such a structure is not efficient, as there is no need for an exponential enumeration of configurations. Alternatively, hierarchies of trap spaces (hypercubes), as described in [4] constitutes a more promising structure to visualize the attractor basins and undergoing differentiation processes.

A remaining open question is on the existence of alternative semantics being abstractions of any multivalued refinements while generating fewer iterations than the most permissive semantics introduced here, and possibly with the same complexity advantage. Also, we provided here no proof of NP-hardness for the attractor identification within the most permissive semantics.

References

1. C. Chaouiya, A. Naldi, E. Remy, and D. Thieffry. Petri net representation of multi-valued logical regulatory graphs. *Natural Computing*, 10(2):727–750, 2011. doi:10.1007/s11047-010-9178-0.
2. T. Chatain, S. Haar, L. Jezequel, L. Paulevé, and S. Schwoon. Characterization of reachable attractors using Petri net unfoldings. In *Computational Methods in Systems Biology*, volume 8859 of *Lecture Notes in Computer Science*, pages 129–142. Springer, 2014. doi:10.1007/978-3-319-12982-2_10.
3. T. Chatain, S. Haar, and L. Paulevé. Boolean Networks: Beyond Generalized Asynchronicity. In J. M. Baetens and M. Kutrib, editors, *Cellular Automata and Discrete Complex Systems (AUTOMATA 2018)*, volume 10875 of *Lecture Notes in Computer Science*, pages 29–42, Cham, 2018. Springer. doi:10.1007/978-3-319-92675-9_3.
4. H. Klarner, A. Bockmayr, and H. Siebert. Computing maximal and minimal trap spaces of boolean networks. *Natural Computing*, 14(4):535–544, 2015. doi:10.1007/s11047-015-9520-7.
5. M. Ostrowski, L. Paulevé, T. Schaub, A. Siegel, and C. Guziolowski. Boolean network identification from perturbation time series data combining dynamics abstraction and logic programming. *Biosystems*, 149:139 – 153, 2016. doi:10.1016/j.biosystems.2016.07.009.

6. L. Paulevé. Reduction of Qualitative Models of Biological Networks for Transient Dynamics Analysis. *IEEE/ACM Transactions on Computational Biology and Bioinformatics*, 15(4):1167–1179, 2018. doi:10.1109/TCBB.2017.2749225.