

Trap spaces of Boolean networks are conflict-free siphons of their Petri net encoding

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Abstract

Boolean network modeling of gene regulation but also of post-transcriptomic systems has proven over the years that it can bring powerful analyses and corresponding insight to the many cases where precise biological data is not sufficiently available to build a detailed quantitative model. Besides simulation, the analysis of such models is mostly based on attractor computation, since those correspond roughly to observable biological *phenotypes*. The recent use of trap spaces made a real breakthrough in that field allowing to consider medium-sized models that used to be out of reach. However, with the continuing increase in model size and complexity of Boolean update functions, the state-of-the-art computation of minimal trap spaces based on *prime-implicants* shows its limits due to the difficulty of the prime-implicant computation.

In this article we explore and prove for the first time a connection between trap spaces of a general Boolean network and siphons of its Petri net encoding. Besides important theoretical applications in studying properties of trap spaces, the connection enables us to propose an alternative approach to compute minimal trap spaces, and hence complex attractors, of a general Boolean network. It replaces the need for prime-implicants by a completely different technique, namely the enumeration of maximal siphons in the Petri net encoding of the original model. We then demonstrate its efficiency and compare it to the state-of-the-art methods on a large collection of real-world

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and randomly generated models.

Keywords:

Logical model, Boolean network, Trap space, Attractor computation, Petri net, Siphon, Systems biology

1. Introduction

From the observation that the transcriptional regulation behaved in a sigmoid step-like way, came the original idea to represent models of gene regulation as discrete event systems. Those Gene Regulation Networks (GRN) use thresholds or equivalently logical functions to represent the different regulations [1, 2, 3, 4].

Boolean net modeling has proven over the years that it can bring powerful analyses and corresponding insight to the many cases where precise biological data is not sufficiently available to build a detailed quantitative model [5], even for modelling post-transcriptional mechanisms. This is even more true for very large models where such data is frequently missing and led to a constant increase in size of logical models *à la* Thomas [6]. Besides simulation, the analysis of such models is mostly based on attractor computation, since those correspond roughly to observable biological *phenotypes*. The recent use of trap spaces [7] made a real breakthrough in that field allowing to consider medium-sized models that used to be out of reach. However, with the continuing increase in model size and complexity of Boolean update functions, the state-of-the-art computation of minimal trap spaces based on *prime-implicants* shows its limits. More specifically, the number of prime implicants of a Boolean function is in general exponential in the number of input nodes of this function [7]. Moreover, the computation of prime implicants is a demanding task, especially for complex Boolean functions.

It is worth noting that the recent method presented in [8] for computing minimal trap spaces avoids the prime-implicants computation by relying on the *most-permissive* semantics of Boolean networks. This method has been implemented in the tool `mpbn`¹ demonstrated in [9] for handling medium-sized models from the literature and very large synthetic models (up to 100,000 nodes). However, this method is only applicable for *locally-monotonic* Boolean networks, whereas the prime-implicants based method [7]

¹<https://github.com/bnediction/mpbn>

30 is applicable for *general* Boolean networks (i.e., including both locally-monotonic
 31 and non-locally-monotonic ones). In addition, the `bioLQM` platform also pro-
 32 vides another method using Binary Decision Diagrams (BDDs) in [http://](http://colomoto.org/biolqm/doc/tools-trapspaces.html)
 33 colomoto.org/biolqm/doc/tools-trapspaces.html. This method avoids
 34 the prime-implicants computation as it characterizes the set of generic trap
 35 spaces of a Boolean network by a BDD, then filters this set to get the set
 36 of all minimal trap spaces. By this approach, it requires the computation
 37 of all solutions, whereas the ASP-based methods [7, 9] can start enumerat-
 38 ing them as they are found. Moreover, the main issue with the BDD-based
 39 method is that the number of generic trap spaces of a Boolean network may
 40 be extremely larger than the number of minimal trap spaces of this Boolean
 41 network. This issue limits the efficiency of the BDD-based method. The
 42 study [10] highlights the need for non-locally-monotonic Boolean networks
 43 in both biological and theoretical aspects. Hence, it is still necessary to
 44 develop efficient methods for computing minimal trap spaces of large-scale
 45 general Boolean networks.

46 Petri nets were introduced in the 60s as simple formalism for describing
 47 and analyzing information-processing systems that are characterized as be-
 48 ing concurrent, asynchronous, non-deterministic and possibly distributed [11,
 49 12]. The use of Petri nets for representing biochemical reaction systems, by
 50 mapping molecular species to places and reactions to transitions, hinted at
 51 already in [11, 12] was used more thoroughly quite late in [13], together with
 52 some Petri net concepts and tools for the analysis of metabolic networks.
 53 Siphons are such a concept, but they have not been used a lot for the study
 54 of biochemical systems [14, 15] even if the practical cost of computing their
 55 minimal/maximal elements appear much more manageable than the theoret-
 56 ical complexity would indicate [16, 17].

57 In this article we explore and prove for the first time a connection be-
 58 tween trap spaces of a general Boolean network and siphons of its Petri net
 59 encoding. Not only having important theoretical applications in studying
 60 properties of trap spaces in Boolean networks, the connection has impor-
 61 tant practical applications in the trap space computation. Specifically, based
 62 on the connection, we propose an alternative approach to compute minimal
 63 trap spaces, and hence complex attractors, of a general Boolean network. It
 64 replaces the need for prime-implicants by a completely different technique,
 65 namely the enumeration of maximal siphons in the Petri net encoding of the
 66 original model. We then demonstrate its efficiency and compare it to the
 67 state-of-the-art methods for computing minimal trap spaces in Boolean net-

68 works on many real-world models from various sources in the literature and
69 randomly generated models.

70 Herein we revise and extend our previous work in [18] as follows. First,
71 more formal definitions are given and the existing proofs are made more de-
72 tailed. In particular, an updated proof provides another way to prove the
73 independence of trap spaces of a Boolean network on its update scheme,
74 which was originally proved in [7]. Second, we showcase a theoretical ap-
75 plication of the connection between trap spaces in Boolean networks and
76 conflict-free siphons in Petri nets. Third, beyond the proposed ASP method
77 implementing the alternative approach [18], we propose several other possi-
78 ble methods for computing minimal trap spaces using Maximum Satisfiability
79 (MaxSAT), Constraint Programming (CP), and Integer Linear Programming
80 (ILP). Fourth, we discuss in detail how to compute several special types of
81 trap spaces in a Boolean network. Fifth, we present the idea for using our
82 Petri net approach to handle the problem of inconsistent and incomplete
83 data in modeling biological systems. Sixth, regarding the implementation,
84 we have developed a new converter that directly reads a `.bnet` file and builds
85 the Petri net encoding, instead of using the PNML conversion of `bioLQM` [18].
86 Finally, we conduct a more comprehensive benchmark on more real-world
87 models from various sources and randomly generated models to evaluate all
88 the proposed methods (the benchmark conducted in [18] considers only real-
89 world models).

90 The rest of this paper is organized as follows: Section 2 recalls the basic
91 concepts including Boolean networks, attractors, trap spaces, Petri nets, and
92 siphons. Section 3 presents the main finding, the connection between trap
93 spaces in Boolean networks and siphons in Petri nets. Section 4 presents
94 the alternative approach for computing minimal trap spaces and the four
95 possible methods implementing it. Section 5 presents the idea to deal with
96 problem of inconsistent and incomplete data. Section 6 shows an important
97 biological case study showing the applicability of the new approach. Section 7
98 reports the experimental results for evaluating the efficiency of the proposed
99 methods. Finally, Section 8 concludes the paper and draws future work.

100 2. Preliminaries

101 We shall briefly recall here some preliminaries on Boolean networks re-
102 lated to trap spaces and Petri nets. **Remove this statement because there**

103 is not sure if the encoded Boolean network preserves the trap spaces of the
 104 original multi-level logical model.

105 2.1. Boolean networks

106 **Definition 2.1.** A Boolean Network (BN) is a pair $\mathcal{N} = (V, F)$ where:

- 107 • $V = \{v_1, \dots, v_n\}$ is the set of nodes. We use v_i to denote both the node
 108 v_i and its associated Boolean variable.
- 109 • $F = \{f_1, \dots, f_n\}$ is the set of update functions. Each function f_i is
 110 associated with node v_i and satisfies $f_i: \mathbb{B}^{|IN(v_i)|} \mapsto \mathbb{B}$ where $\mathbb{B} = \{0, 1\}$
 111 and $IN(v_i)$ denotes the set of input nodes of v_i . Note that a node $v_i \in V$
 112 is called a source node if and only if $f_i = v_i$.

113 A Boolean function is *locally-monotonic* if it can be represented by a
 114 formula in disjunctive normal form in which all occurrences of any given
 115 literal are either negated or non-negated [9]. A Boolean network is said
 116 to be locally-monotonic if all its Boolean functions are locally-monotonic.
 117 Otherwise, this model is said to be non-locally-monotonic.

118 A state $v \in \mathbb{B}^n$ is as a mapping $v: V \mapsto \mathbb{B}$ that assigns either 0 (inactive)
 119 or 1 (active) to each node. We denote the set of all possible states of a
 120 Boolean network \mathcal{N} by $\mathcal{S}_{\mathcal{N}} = \mathbb{B}^n$. At each time step t , node v_i can update
 121 its state by

$$v_i(t+1) = f_i(v(t))$$

122 where $v(t)$ is the state of \mathcal{N} at time t and $v_i(t+1)$ is the state of node v_i at
 123 time $t+1$. Note that for simplicity, we write $f_i(v(t))$ even $IN(v_i) \subset V$ (i.e.,
 124 $IN(v_i)$ does not contain some nodes of V). An update scheme of a Boolean
 125 network specifies the way that the nodes update their states through time
 126 evolution [4]. Following the update scheme, the Boolean network transits
 127 from a state to another state (possibly identical). This transition is called
 128 the *state transition* and denoted by $\rightarrow \subseteq \mathcal{S}_{\mathcal{N}} \times \mathcal{S}_{\mathcal{N}}$. Then the dynamics of \mathcal{N}
 129 is captured by the directed graph $(\mathcal{S}_{\mathcal{N}}, \rightarrow)$ called the State Transition Graph
 130 (STG). There are two main types of update schemes [4]: synchronous, where
 131 all the nodes are update simultaneously, and fully asynchronous, where only
 132 one node is nondeterministically selected to be updated.

2.2. Traps spaces

We recall here some definitions from [7] for the introduction of *trap spaces*. Minimal trap spaces prove to be a very good approximation of the attractors of a Boolean network under asynchronous update schemes and have become the *de facto* standard way to analyze models of a few tens of *genes* [19, 20].

An non-empty set $T \subseteq \mathcal{S}_{\mathcal{N}}$ is a trap set with respect to \rightarrow if for every $x \in T$ and $y \in S$ with $x \rightarrow y$ it holds that $y \in T$ [7]. An attractor of \mathcal{N} with respect to \rightarrow can be defined as an inclusion-wise minimal trap set of $(\mathcal{S}_{\mathcal{N}}, \rightarrow)$. An attractor can be also seen as a terminal strongly connected component of $(\mathcal{S}_{\mathcal{N}}, \rightarrow)$ [21]. An attractor of size 1 is called a fixed point, otherwise a cyclic attractor [7].

A subspace m of a Boolean network $\mathcal{N} = (V, F)$ is a mapping $m: V \mapsto \mathbb{B} \cup \{\star\}$. $m(v_i) \in \mathbb{B}$ means that the value of v_i is fixed in m and v_i is called a fixed variable. $m(v_i) \in \star$ means that the value of v_i is free in m and v_i is called a free variable. We denote D_m the set of all fixed variables of m . A subspace m is equivalent to a set of states:

$$\mathcal{S}_{\mathcal{N}}[m] := \{s \in \mathcal{S}_{\mathcal{N}} \mid \forall v \in D_m: s(v) = m(v)\}.$$

For example, $m = \star \star 1$ (for simplicity, we write subspaces likes states) means that $D_m = \{v_3\}$, $m(v_3) = 1$, and it is equivalent to the set of states $\{001, 011, 101, 111\}$. We denote $\mathcal{S}_{\mathcal{N}}^* = (\mathbb{B} \cup \{\star\})^n$ the set of all possible subspaces of \mathcal{N} . Note that $|\mathcal{S}_{\mathcal{N}}^*| = 3^n$ and $\mathcal{S}_{\mathcal{N}} \subset \mathcal{S}_{\mathcal{N}}^*$ [7].

A *trap space* is defined as a subspace that is also a trap set. It is noted that trap spaces of a Boolean network are independent of the update scheme of this model [7]. Then, we define a partial order $<$ on $\mathcal{S}_{\mathcal{N}}^*$ as: $m < m'$ if and only if $\mathcal{S}_{\mathcal{N}}[m] \subseteq \mathcal{S}_{\mathcal{N}}[m']$ and $\mathcal{S}_{\mathcal{N}}[m] \neq \mathcal{S}_{\mathcal{N}}[m']$. Consequently, a trap space m is minimal if and only if there is no trap space $m' \in \mathcal{S}_{\mathcal{N}}^*$ such that $m' < m$.

For example, let us consider the Boolean network shown in Example 2.1. Figure 1(a) shows the dynamics of this model under the fully asynchronous update (i.e., only one node is nondeterministically selected in order to be updated at each time step). The model has all two trap spaces, $m_1 = 11$ and $m_2 = \star\star$. Since $m_1 < m_2$, m_1 is a minimal trap space of the Boolean network.

Example 2.1. We give a Boolean network $\mathcal{N} = (V, F)$, where $V = (x_1, x_2)$ and $F = (f_1, f_2)$ with $f_1 = (x_1 \wedge x_2) \vee (\neg x_1 \wedge \neg x_2)$, $f_2 = (x_1 \wedge x_2) \vee (\neg x_1 \wedge \neg x_2)$. Herein, \wedge , \vee , and \neg denote the conjunction, disjunction, and negation logical operators, respectively.



Figure 1: Dynamics and encoding of the Boolean network of Example 2.1.

2.3. Petri net encoding of Boolean networks

Definition 2.2. A Petri net is a weighted bipartite directed graph (P, T, W) , where P is a non-empty finite set of vertices called places, T is a non-empty finite set of vertices called transitions, $P \cap T = \emptyset$, and $W : (P \times T) \cup (T \times P) \mapsto \mathbb{N}$ is a weight function attached to the arcs.

A marking for a Petri net is a mapping $m : P \mapsto \mathbb{N}$ that assigns a number of tokens to each place. A place p is marked by a marking m if and only if $m(p) > 0$. Marking m can be seen as a subset of P that contains all marked places by m . We shall write $\text{pred}(x)$ (resp. $\text{succ}(x)$) to represent the set of vertices that have a (non-zero weighted) arc leading to (resp. coming from) x . In this work, we consider a class of Petri nets called 1-safe Petri nets where every place has at most 1 token and all arcs are of weight 1. In this case, weights are implicitly omitted in the arcs of a Petri net. Then, a transition $t \in T$ is *enabled* at a marking m if and only if $\text{pred}(t) \subseteq m$. A marking m is called a *deadlock* if there are no enabled transitions at m . The firing of t leads to a new marking m' specified by $m' = (m \setminus \text{pred}(t)) \cup \text{succ}(t)$. Note that when multiple transitions are enabled, we need to embed one firing scheme (similar to the update scheme of a Boolean network) to the Petri net. The classical firing scheme is that only one of the enabled transition is non-deterministically chosen to fire [12].

The link between Boolean networks *à la* Thomas and Petri nets was originally established in [22] in order to make available formal methods like model-checking for the analysis of such systems. The basic encoding into 1-safe (i.e., never more than one token in each place) nets only holds for purely Boolean networks but was later extended to multivalued logical models in two ways, either in [23] with non 1-safe Petri nets or more recently in [21] with 1-safe nets but many more places.

195 Since our study is focused on Boolean networks, we briefly recall the orig-
 196 inal encoding here. Its basis is that every node (*gene*) v of the original model
 197 $\mathcal{N} = (V, F)$ is represented by two separate places (p_v and \bar{p}_v), corresponding
 198 to its two states, active, and inactive, respectively. Each conjunct of the
 199 logical function that activates the *gene* will lead to a transition t , consuming
 200 the inactive place (i.e., a directional arc from \bar{p}_v to t), producing the active
 201 place (i.e., a directional arc from t to p_v), and with all other literals both
 202 consumed and produced (i.e., a bidirectional arc). And conversely for the
 203 inactivation. Let s be a state of the Boolean network and m_s be its corre-
 204 sponding marking in the encoded Petri net. It holds that $\forall v \in V, s(v) = 0$ if
 205 and only if $m_s(\bar{p}_v) = 1$ and $s(v) = 1$ if and only if $m_s(p_v) = 1$. Note also that
 206 at any marking m of the Petri net encoding a Boolean network, it always
 207 holds that $m(p_v) + m(\bar{p}_v) = 1$.

208 The main property of this encoding is that it is completely faithful with
 209 respect to the update scheme of the original Boolean network. For each node
 210 v of \mathcal{N} , only transitions corresponding to v can change the current marking
 211 of p_v or \bar{p}_v . In addition, at any marking at most one of such transitions is en-
 212 abled because $m(p_v) + m(\bar{p}_v) = 1$ holds. Hence, for any update scheme in \mathcal{N} ,
 213 we have a corresponding firing scheme in \mathcal{P} , which preserves the equivalence
 214 between the dynamics of \mathcal{N} and \mathcal{P} [24].

215 For illustration, let us reconsider the Boolean network shown in Exam-
 216 ple 2.1. Figure 1(b) shows the Petri net encoding of this Boolean network.
 217 Place p_{x_1} (resp. \bar{p}_{x_1}) in \mathcal{P} represents the activation (resp. the inactivation) of
 218 node x_1 in \mathcal{N} . Marking $\{p_{x_1}, \bar{p}_{x_2}\}$ in \mathcal{P} represents state 10 in \mathcal{N} . Transitions
 219 $t_{x_1}^1$ and $t_{x_1}^2$ represent the update of node x_1 . Of course, in any marking $t_{x_1}^1$
 220 and $t_{x_1}^2$ cannot be both enabled. Then, the fully asynchronous update scheme
 221 in \mathcal{N} corresponds to the classical firing scheme in \mathcal{P} where only one of the
 222 enabled transitions for a given marking will be fired [12].

223 Note that given a Boolean network in the standard **SBML-Qual** format [25],
 224 i.e., the package of SBML v3 [26] for such models, one can easily obtain its
 225 Petri net encoding in the Petri Net Markup Language (PNML)² standard
 226 using the **bioLQM**³ library. This piece of software extracted from **GINsim** [27]
 227 and part of the **CoLoMoTo**⁴ [28] software suite allows for easy conversion

²<https://www.pnml.org/>

³<http://www.colomoto.org/biolqm/>

⁴<http://colomoto.org/>

between standard formats. It also accepts many other common formats for Boolean networks, notably the `.bnet` files of the BoolNet [29, 19] tools. The conversion is executed as follows:

```
java -jar GINsim.jar -lqm <input.{sbml,bnet,zginml,...}> <output.pnml>
```

Note that transforming a Boolean network defined by its functions into its Petri net encoding roughly relies on obtaining conditions for the activation and inactivation of the states. In [22] this took the form of the whole truth table of the Boolean functions, but as shown in Appendix 1 of [21] computing Disjunctive Normal Forms (DNF) of each Boolean function is enough. Though this might appear quite computationally intensive it is important to remark first that contrary to the prime-implicants case, there is no need to find *minimal* DNFs. One way to look at this is to consider that this amounts to a similar approach as that used in [8] but with the encoding of both activation and inhibition functions as DNFs in order to take into account possible non-local-monotonicity. This does not change the worst-case-complexity (obtaining a single DNF being exponential) but might matter a lot in practice. As such, we will explore how this transformation, here using BDDs in `bioLQM` and directly in our tool using the `pyeda`⁵ library, and the one based on the most-permissive semantics compare in the Section 7 on evaluation.

2.4. Siphons

Siphons are a static and classical property of Petri nets [11]. Note however that the use of siphons for the analysis of biological models, though it is not new, has been mostly relevant to the ODE-based continuous semantics of Chemical Reaction Networks [30, 31, 32]. We recall here the basic definition establishing that to produce something in a siphon you must consume something from the siphon. This corresponds to the idea that a siphon is a set of places that once unmarked remains unmarked.

Definition 2.3. A siphon of a Petri net (P, T, W) is a set of places S such that:

$$\forall t \in T, S \cap \text{succ}(t) \neq \emptyset \Rightarrow S \cap \text{pred}(t) \neq \emptyset.$$

Note that \emptyset is trivially a siphon.

Let $\text{pred}(S) := \bigcup_{s \in S} \text{pred}(s)$ and $\text{succ}(S) := \bigcup_{s \in S} \text{succ}(s)$. If $S = \emptyset$, then conventionally $\text{pred}(S) = \text{succ}(S) = \emptyset$. We have an important property on siphons [33] as follows.

⁵<https://pyeda.readthedocs.io/en/latest/>

261 **Proposition 2.1.** *Let S be a siphon of a Petri net (P, T, W) . Then $\text{pred}(S) \subseteq$*
 262 *$\text{succ}(S)$.*

263 3. Minimal trap spaces as maximal conflict-free siphons

264 First, we add a definition related to any set of places of a Petri net
 265 encoding a Boolean network, and notably a siphon of such a net.

266 **Definition 3.1.** *A set of places of Petri net \mathcal{P} encoding Boolean network*
 267 *\mathcal{N} is conflict-free if it does not contain any two places corresponding to the*
 268 *active and inactive states of the same node of \mathcal{N} . Then, a conflict-free siphon*
 269 *S is said to be maximal if and only if there is no other conflict-free siphon*
 270 *S' such that $S \subset S'$.*

271 Intuitively, a siphon is a set of places that once unmarked remains so.
 272 If it is conflict-free then its dual corresponds to a partial-state of the model
 273 such that whatever update, the fixed values remain so (since the unmarked
 274 places remain unmarked). This is precisely the definition of a trap space and
 275 maximality of the siphon is equivalent to as many fixed values as possible,
 276 hence minimality of the trap space. For example, the Boolean network given
 277 in Example 2.1 has two trap spaces, $m_1 = 11$ and $m_2 = \star\star$. The Petri net
 278 encoding of this Boolean network has five generic siphons, $S_1 = \emptyset$, $S_2 =$
 279 $\{p_{x_1}, \bar{p}_{x_1}\}$, $S_3 = \{p_{x_2}, \bar{p}_{x_2}\}$, $S_4 = \{\bar{p}_{x_1}, \bar{p}_{x_2}\}$, and $S_5 = \{p_{x_1}, \bar{p}_{x_1}, p_{x_2}, \bar{p}_{x_2}\}$.
 280 However, only S_1 and S_4 are conflict-free siphons and correspond to m_2 and
 281 m_1 , respectively. Since $S_1 \subset S_4$, S_4 is a maximal siphon corresponding to
 282 the minimal trap space m_1 . Hereafter, we formally prove that a (maximal)
 283 conflict-free siphon is equivalent to a (minimal) trap space.

284 **Definition 3.2.** *Let m be a subspace of Boolean network $\mathcal{N} = (V, F)$. A*
 285 *mirror of m is a set of places S in the Petri net encoding \mathcal{P} of \mathcal{N} such that:*

$$\forall v \in D_m, m(v) = 0 \Leftrightarrow p_v \in S, m(v) = 1 \Leftrightarrow \bar{p}_v \in S$$

286 and

$$\forall v \in V \setminus D_m, p_v \notin S, \bar{p}_v \notin S.$$

287 **Theorem 3.1.** *Let $\mathcal{N} = (V, F)$ be a Boolean network and \mathcal{P} be its Petri net*
 288 *encoding. A subspace m is a trap space of \mathcal{N} if and only if its mirror S is a*
 289 *conflict-free siphon of \mathcal{P} .*

290 *Proof.* First, we show that if m is a trap space of \mathcal{N} , then S is a conflict-free
 291 siphon of \mathcal{P} (*). If $D_m = \emptyset$, then $S = \emptyset$ is trivially a conflict-free siphon of
 292 \mathcal{P} . Thus, we consider the case that $D_m \neq \emptyset$ (resp. $S \neq \emptyset$). Assume that S
 293 is not a siphon of \mathcal{P} . Then, there is a transition $t \in T$ such that $S \cap \text{succ}(t) \neq \emptyset$
 294 but $S \cap \text{pred}(t) = \emptyset$. This implies that there is a place $p \in S$ such that
 295 $p \in \text{succ}(t)$ but $p \notin \text{pred}(t)$. Let v be the corresponding node in \mathcal{N} of p . By
 296 the characteristics of the encoding [22], there is a directional arc from t to p
 297 and a directional arc from the complementary place of p to t . Without loss
 298 of generality, we assume that $p = p_v$, then there is a directional arc from t
 299 to p_v and a directional arc from \bar{p}_v to t . We follow the following procedure
 300 to find a state $s \in \mathcal{S}_{\mathcal{N}}[m]$ such that $m_s(p') = 1, \forall p' \in \text{pred}(t)$ where m_s is
 301 the corresponding marking in \mathcal{P} of s . For every place $p' \in \text{pred}(t)$, let p'' be
 302 the complementary place of p' and v' be the corresponding node in \mathcal{N} of p'
 303 and p'' . If $p'' \notin S$, then $v' \notin D_m$ and we can always set a Boolean value to
 304 $s(v')$ such that $s \in \mathcal{S}_{\mathcal{N}}[m]$ and $m_s(p') = 1$. If $p'' \in S$, then $v' \in D_m$ and we
 305 set $s(v') = m(v')$. In this case, if $p' = p_v$ then $s(v') = m(v') = 1$ leading to
 306 $m_s(p') = 1$, if $p' = \bar{p}_v$ then $s(v') = m(v') = 0$ leading to $m_s(p') = 1$. For
 307 the remaining nodes of \mathcal{N} , we can always set Boolean values to these nodes
 308 to preserve that $s \in \mathcal{S}_{\mathcal{N}}[m]$. We also have $m_s(p_v) = 0$ by the characteristics
 309 of the encoding [22]. Now, t is enabled at marking m_s . Its firing leads to
 310 a new marking m'_s such that $m'_s(p_v) = 1$ and $m'_s(\bar{p}_v) = 0$. Let s' be the
 311 corresponding state in \mathcal{N} of m'_s . We have $s'(v) = 1$ because $m'_s(p_v) = 1$ and
 312 $m(v) = 0$ because $p_v \in S$. This implies that $s' \notin \mathcal{S}_{\mathcal{N}}[m]$. For any firing
 313 scheme of \mathcal{P} , the firing of t always happens. Since a firing scheme of \mathcal{P}
 314 is equivalent to an update scheme of \mathcal{N} , s can escape from the trap space m
 315 for any update scheme of \mathcal{N} , which contradicts to the property of a trap
 316 space. Hence, S is a siphon of \mathcal{P} . By the definition of a mirror, S is also a
 317 conflict-free one.

318 Second, we show that if S is a conflict-free siphon of \mathcal{P} , then m is a trap
 319 space of \mathcal{N} (**). By the definition of a mirror, m is a subspace of \mathcal{N} . Let
 320 s be an arbitrary state in $\mathcal{S}_{\mathcal{N}}[m]$ and m_s be its corresponding marking in
 321 \mathcal{P} . Assume that there is a place $p \in S$ such that $m_s(p) = 1$. Let v be the
 322 corresponding node in \mathcal{N} of p . Since $p \in S$, $v \in D_m$ and $m(v) = s(v)$. If
 323 $p = p_v$, then $m_s(p_v) = 1$ leading to $m(v) = s(v) = 1$ by the characteristics of
 324 the encoding [22]. By the definition of a mirror, $m(v) = 0$ because $p_v \in S$,
 325 which is a contradiction. It is symmetric for the case that $p = \bar{p}_v$. Hence,
 326 $m_s(p) = 0, \forall p \in S$. In any marking m'_s reachable from m_s regardless of the
 327 firing scheme of \mathcal{P} , we have $m'_s(p) = 0, \forall p \in S$ by the dynamical property on

328 markings of a siphon [33]. Let s' be the corresponding state in \mathcal{N} of m'_s . For
 329 every node $v \in D_m$, we have all two cases as follows. Case 1: $p_v \in S$, then
 330 $m'_s(p_v) = 0$, thus $s'(v) = 0 = m(v)$. Case 2: $\bar{p}_v \in S$, then $m'_s(\bar{p}_v) = 0$, thus
 331 $s'(v) = 1 = m(v)$. Hence, $s'(v) = m(v)$ for every $v \in D_m$. Then, $s' \in \mathcal{S}_{\mathcal{N}}[m]$.
 332 By the definition of a trap space and the arbitrariness of s , m is a trap space
 333 of \mathcal{N} .

334 From (*) and (**), we can conclude the proof. \square

335 From the proof of Theorem 3.1, we can see that this theorem still holds
 336 for any update scheme of the Boolean network. Since the Petri net encoding
 337 of a Boolean network is independent of its update scheme and siphons are
 338 a static property of a Petri net, we can imply that trap spaces of a Boolean
 339 network are independent of its update scheme. Note that the original proof
 340 for this property of trap spaces (see Theorem 1 of [7]) only considers the two
 341 popular update schemes (i.e., synchronous and fully asynchronous). This
 342 exhibits the very first theoretical application of the connection between trap
 343 spaces of Boolean networks and siphons of Petri nets.

344 **Theorem 3.2.** *Let \mathcal{N} be a Boolean network and \mathcal{P} be its Petri net encoding.*
 345 *A subspace m is a minimal trap space of \mathcal{N} if and only if its mirror S is a*
 346 *maximal conflict-free siphon of \mathcal{P} .*

347 *Proof.* First, we show that if m is a minimal trap space of \mathcal{N} , then S is
 348 a maximal conflict-free siphon of \mathcal{P} (*). Since m is a trap space of \mathcal{N} ,
 349 S is a conflict-free siphon of \mathcal{P} by Theorem 3.1. Assume that S is not
 350 maximal. Then, there is another conflict-free siphon S' such that $S \subset S'$.
 351 By Theorem 3.1, there is a trap space m' corresponding to S' . Following the
 352 definition of a mirror, $D_m \subset D_{m'}$ and $m(v) = m'(v), \forall v \in D_m$. It follows
 353 that $\mathcal{S}_{\mathcal{N}}[m'] \subset \mathcal{S}_{\mathcal{N}}[m]$, thus $m' < m$. This contradicts to the minimality of
 354 m . Hence, S is a maximal conflict-free siphon of \mathcal{P} .

355 Second, we show that if S is a maximal conflict-free siphon of \mathcal{P} , then
 356 m is a minimal trap space of \mathcal{N} (**). Since S is a conflict-free siphon of \mathcal{P} ,
 357 m is a trap space of \mathcal{N} by Theorem 3.1. Assume that m is not minimal.
 358 Then, there is another trap space m' such that $m' < m$. By the definition of
 359 the partial order $<$ on subspaces, $\mathcal{S}_{\mathcal{N}}[m'] \subset \mathcal{S}_{\mathcal{N}}[m]$. Let S' be the mirror of
 360 m' . S' is a conflict-free siphon by Theorem 3.1. Following the definition of
 361 a mirror, $S \subset S'$, which contradicts to the maximality of S . Hence, m is a
 362 minimal trap space of \mathcal{N} .

363 From (*) and (**), we can conclude the proof. \square

364 We here showcase a theoretical application of the connection between trap
 365 spaces in Boolean networks and conflict-free siphons in Petri nets. We use it
 366 to prove a property of minimal trap spaces, which has surprisingly not been
 367 formally proved. Specifically, all minimal trap spaces of a Boolean network
 368 are mutually disjoint. This property is important because we can use it to
 369 approximate the set of attractors of the Boolean network [7].

370 **Theorem 3.3.** *Let $\mathcal{N} = (V, F)$ be a Boolean network. For any two distinct*
 371 *minimal trap spaces m_1 and m_2 of \mathcal{N} , we have that $\mathcal{S}_{\mathcal{N}}[m_1] \cap \mathcal{S}_{\mathcal{N}}[m_2] = \emptyset$.*

372 *Proof.* Let \mathcal{P} be the Petri net encoding of \mathcal{N} . If \mathcal{N} has only one minimal
 373 trap space, then the theorem trivially holds. Note that by Theorem 3.2,
 374 \mathcal{N} always has at least one minimal trap space because \mathcal{P} has at least one
 375 maximal conflict-free siphon. Hence, we consider the case that \mathcal{N} has at least
 376 two minimal trap spaces.

377 Consider two any distinct minimal trap spaces m_1 and m_2 . Assume that
 378 $\mathcal{S}_{\mathcal{N}}[m_1] \cap \mathcal{S}_{\mathcal{N}}[m_2] \neq \emptyset$. Let S_1 and S_2 be the mirrors of m_1 and m_2 , re-
 379 spectively. By Theorem 3.2, S_1 and S_2 are maximal conflict-free siphons
 380 of \mathcal{P} . We have that $S = S_1 \cup S_2$ is also a siphon because of Proposi-
 381 tion 2.1. For every node $v \in V$, assume that $p_v \in S$ and $\bar{p}_v \in S$ hold.
 382 Since S_1 and S_2 are conflict-free, there are all two cases. Case 1: $p_v \in S_1$
 383 and $\bar{p}_v \in S_2$. Case 2: $p_v \in S_2$ and $\bar{p}_v \in S_1$. These two cases lead to
 384 $m_1(v) \neq m_2(v)$, $m_1(v) \neq \star$, $m_2(v) \neq \star$, then $\mathcal{S}_{\mathcal{N}}[m_1] \cap \mathcal{S}_{\mathcal{N}}[m_2] = \emptyset$. This is a
 385 contradiction. Hence, for every node $v \in V$, $p_v \in S$ and $\bar{p}_v \in S$ cannot hold
 386 together. Therefore, S is conflict-free. Now, we have that S is a conflict-free
 387 siphon but $S_1 \subset S$ or $S_2 \subset S$ holds because $S_1 \neq S_2$. This contradicts to the
 388 maximality of S_1 and S_2 . Hence, $\mathcal{S}_{\mathcal{N}}[m_1] \cap \mathcal{S}_{\mathcal{N}}[m_2] = \emptyset$ holds.

389 \square

390 One naturally computational application of Theorem 3.1 is that we can ef-
 391 ficiently decide whether a subspace m is a trap space. In PyBoolNet [19], this
 392 is checked by using the percolation on the prime-implicants of the Boolean
 393 functions. As we have mentioned at the beginning of this article, the compu-
 394 tation of prime-implicants is a demanding task for complex Boolean networks,
 395 even is sometimes intractable. Hence, the checking method in [19] shows its
 396 limitations. Instead, we can first compute the mirror S_m of m in the Petri
 397 net encoding. Then, by Proposition 2.1 and Theorem 3.1, we can check if
 398 $\text{pred}(S_m) \subseteq \text{succ}(S_m)$. Note that the Petri net construction is less com-
 399 putationally demanding than the prime-implicant computation because it

only requires computing generic (not prime) implicants of the Boolean functions [21]. In addition, the time complexity of the above checking method is quadratic in the number of transitions of the Petri net in worst cases.

Furthermore, by Theorem 3.2, we can reduce the problem of computing all minimal trap spaces of a Boolean network to the problem of computing all maximal conflict-free siphons of its Petri net encoding. Note that in the case of special types of trap spaces (e.g., fixed points), this can be put in regard to special types of siphons in Petri nets. See Subsection 4.5 for more discussions about many special types of trap spaces. It might actually be possible to generalize our result to any 1-safe place-complementary Petri net to define a notion of trap spaces that might be useful for the analysis of Petri nets, but this is out of the scope of this present article.

It is noted that there are no existing methods specifically designed for computing maximal conflict-free siphons (even maximal siphons) of a Petri net. The reason might be that researchers mainly focus on minimal generic siphons [33] in the field of Petri nets. Hence, we here propose several methods for computing maximal conflict-free siphons of a Petri net. The details of the proposed methods shall be given in the next section.

4. Computation methods

4.1. Characterization

First, we show the characterization of all conflict-free siphons of the encoded Petri net $\mathcal{P} = (P, T, W)$. Suppose that S is a generic siphon of \mathcal{P} . If a place p should belong to S , then by Proposition 2.1 all the transitions in $pred(p)$ must belong to $succ(S)$. A transition t belongs to $succ(S)$ if and only if there is at least one place p' in S such that $p' \in pred(t)$. Hence, for each transition $t \in pred(p)$, we can state that

$$p \in S \Rightarrow \bigvee_{p' \in pred(t)} p' \in S. \quad (1)$$

The system of all the rules of the above form with respect to all pairs (p, t) where $p \in P, t \in T, t \in pred(p)$ fully characterizes all generic siphons of a Petri net and has been used with SAT solvers in [16, 17]. To make S to be a conflict-free siphon, we need to add to the system the rule

$$p_v \in S \Rightarrow \bar{p}_v \notin S \wedge \bar{p}_v \in S \Rightarrow p_v \notin S \quad (2)$$

for each node $v \in V$. By definition, the final system fully characterizes all conflict-free siphons of the encoded Petri net.

432 4.2. Constraint satisfaction problem

433 The following Boolean Constraint Satisfaction Problem (CSP) directly
434 derives from the above characterization:

435 **Definition 4.1.** *Given a Petri net $\mathcal{P} = (P, T, W)$ encoding a Boolean net-*
436 *work $\mathcal{N} = (V, F)$. The CSP $\mathcal{C}(\mathcal{P})$ is the triple (R, D, C) where*

- 437 • $R = P$, i.e., a variable is introduced for each place of \mathcal{P} ,
- 438 • $D(p) = \mathbb{B}$ for all $p \in R$, i.e., the variables are Boolean,
- 439 • $C = \{\neg p_v \vee \neg \bar{p}_v = 1 \mid \forall v \in V\} \wedge \{(p = 1 \rightarrow \bigvee_{p' \in \text{pred}(t)} p' = 1) \mid p \in$
440 $P, t \in \text{pred}(p)\}$.

441 **Proposition 4.1.** $\mathcal{C}(\mathcal{P})$ is satisfied by a valuation r if and only if

$$\{p \in P \mid r(p) = 1\}$$

442 is a conflict-free siphon of \mathcal{P} .

443 *Proof.* By the former part $\neg p_v \vee \neg \bar{p}_v = 1$ of C , the conflict-freeness is imposed
444 because for any satisfiable valuation r , $r(p_v) = r(\bar{p}_v) = 1$ is impossible for all
445 $v \in V$. As shown in [17], the latter part of C can characterize the set of all
446 generic siphons of \mathcal{P} . Hence, we can conclude the proof. □

448 In [17], the set of all siphons of a given Petri net is characterized by a sim-
449 ilar Boolean CSP except the conflict-freeness constraint. From the encoded
450 CSP, the set of all *minimal* siphons of the Petri net can be enumerated in the
451 set inclusion order. For enumerating siphons in the set inclusion order, the
452 proposed method by [17] uses the technique that labels directly the Boolean
453 variables with increasing value selection (i.e., to test first the absence, then
454 the presence of a place in the candidate solution). The method has two
455 implementations, one uses an iterated SAT procedure and the other uses
456 Constraint Programming (CP) with backtracking.

457 One natural question is that how to use the CSP-based method for enu-
458 merating all the maximal conflict-free siphons of a Petri net encoding a
459 Boolean network? Of course, the set of all conflict-free siphons of the Petri
460 net can easily be characterized by the CSP model presented in [17] along with
461 the additional constraint $\neg p_v \vee \neg \bar{p}_v = 1$, for each $v \in V$, which represents

the conflict-freeness. However, the main concern is to enumerate all the *maximal* ones, which is not trivial to adapt from the CSP-based method. By Proposition 4.1, the set of all maximal conflict-free siphons of \mathcal{P} can be enumerated in the (maximality) set inclusion order, by restarting the search each time a conflict-free siphon S is found, with the following additional constraint for disallowing any subset of that conflict-free siphon: $\bigvee_{p \notin S} p = 1$. For enumerating conflict-free siphons in the set inclusion order, we can use the same technique as used in [17] but with the opposite setting, i.e., labeling directly the Boolean variables with decreasing value selection. The correctness of this technique comes from the fact that once S is found, it is the conflict-free siphon of maximum cardinality among all the remaining feasible conflict-free siphons. Similar to [17], the newly CSP-based method can also be implemented with SAT and CP solvers.

This method was implemented using the state-of-the-art CP solver Chuffed⁶ [34] via its MiniZinc [35] interface. Because it is a high-level interface, the backtrack-and-replay method of [17] was not used but rather the alternative implementation with two global constraints for lexicographic ordering (ensuring enumeration of solutions) and iterated non-subset of each already found solution (for maximality).

For the SAT-based method, however a more direct method is to use a MaxSAT solver. We construct a MaxSAT problem with the following hard clauses:

$$(\neg p_v \vee \neg \bar{p}_v), \forall v \in V$$

and

$$(\neg p \vee \bigvee_{p' \in \text{pred}(t)} p'), \forall p \in P, \forall t \in \text{pred}(p).$$

We set a soft clause for each variable of the CSP and then use a “minimal correction subset” blocking strategy, which will ensure set-inclusion maximality of the solutions. This is what is implemented in **Trappist** using the RC2 MaxSAT solver [36] available through the **python-sat** package⁷.

4.3. Answer set programming-based method

Another possible method is to translate the characterization shown in Subsection 4.1 into the ASP \mathcal{L} as follows. We introduce atom **p-v** (resp.

⁶<https://github.com/chuffed/chuffed>

⁷<https://pysathq.github.io/docs/html/api/examples/rc2.html>

492 $\mathbf{n-v}$) to denote place p_v (resp. \bar{p}_v), $\forall v \in V$. The set of all atoms in \mathcal{L} is given
 493 as $\mathcal{A} = \bigcup_{v \in V} \{\mathbf{p-v}, \mathbf{n-v}\}$. For each pair (p, t) where $p \in P, t \in T, t \in \text{pred}(p)$,
 494 we translate the rule (1) into the ASP rule

$$\mathbf{a_1}; \dots ; \mathbf{a_k} :- \mathbf{a}.$$

495 where $\mathbf{a} \in \mathcal{A}$ is the atom representing place p and $\{\mathbf{a_1}, \dots, \mathbf{a_k}\} \subseteq \mathcal{A}$ is the
 496 set of atoms representing places in $\text{pred}(t)$. The rule (2) is translated into
 497 the ASP rule

$$:- \mathbf{p-v}, \mathbf{n-v}.$$

498 for each $v \in V$. This ASP rule guarantees that two places representing
 499 the same node in \mathcal{N} never belong to the same siphon of \mathcal{P} , representing
 500 the conflict-freeness. Naturally, a Herbrand model (see, e.g., [37]) of \mathcal{L} is
 501 equivalent to a conflict-free siphon of \mathcal{P} . To guarantee that a Herbrand
 502 model is also a stable model (an answer set), we need to add to \mathcal{L} the two
 503 choice rules

$$\{\mathbf{p-v}\}. \{\mathbf{n-v}\}.$$

504 for each $v \in V$. Note that the number of atoms of \mathcal{L} is only $2n$, whereas
 505 the ASP encoding shown in [7] has as many atoms as the number of prime-
 506 implicants of the Boolean network and that number might be exponential in
 507 n . In [8], there is an ASP characterization of trap spaces that does not rely
 508 on minimal DNFs either and thus seems very similar to our ASP encoding.
 509 Remarkably it only requires the DNF for the *activation* part, using the in-
 510 formation that it will only be used for locally-monotonic Boolean networks.
 511 We would therefore expect that, when available, it will have comparable per-
 512 formance on the ASP part (the ASP program would be approximately twice
 513 smaller, though redundancy is not always bad in that field), but can also
 514 avoid combinatorial explosion of the Petri net encoding for some formula
 515 where the activation DNF is simple but the inhibition is not. Since **mpbn** is
 516 included in our benchmark this will be evaluated in our experiments.

517 Now, a solution (simply an answer set) $A \subseteq \mathcal{A}$ of \mathcal{L} is equivalent to a
 518 conflict-free siphon S of \mathcal{P} , thus a trap space m of \mathcal{N} . The conversion from A
 519 to m is straightforward. If $\mathbf{p-v} \in A$ then $v \in D_m$ and $m(v) = 0$. Conversely,
 520 if $\mathbf{n-v} \in A$ then $v \in D_m$ and $m(v) = 1$. Otherwise, $v \notin D_m$. Comput-
 521 ing multiple answer sets is built into ASP solvers and the solving collection
 522 **POTASSCO** [37] also features the option to find set-inclusion maximal answer
 523 sets with respect to the set of atoms. Naturally, a set-inclusion maximal

answer set of \mathcal{L} is equivalent to a maximal conflict-free siphon of \mathcal{P} , thus a minimal trap space of \mathcal{N} . By using this built-in option, we can compute all the set-inclusion maximal answer sets of \mathcal{L} (resp. all the minimal trap spaces of \mathcal{N}) in one execution.

4.4. Integer linear programming-based method

We first show how an Integer Linear Programming (ILP) \mathcal{I} can define a set of all conflict-free siphons of the encoded Petri net \mathcal{P} . We introduce binary variable $\mathbf{p-v}$ (resp. $\mathbf{n-v}$) to denote place p_v (resp. \bar{p}_v), $\forall v \in V$. The set of all binary variables in \mathcal{I} is $\bigcup_{v \in V} \{\mathbf{p-v}, \mathbf{n-v}\}$. For each pair (p, t) where $p \in P, t \in T, t \in \text{pred}(p)$, we translate the rule (1) into the ILP inequality

$$\mathbf{a} \leq \mathbf{a_1} + \dots + \mathbf{a_k}$$

where \mathbf{a} is the binary variable representing place p and $\{\mathbf{a_1}, \dots, \mathbf{a_k}\}$ is the set of binary variable representing places in $\text{pred}(t)$. The rule (2) is translated into the ILP inequality

$$\mathbf{p-v} + \mathbf{n-v} \leq 1$$

for each $v \in V$. This inequality forbids both $\mathbf{p-v}$ and $\mathbf{n-p}$ receive the value 1, thus representing the conflict-freeness. Since we only consider feasible solutions, the objective function is set to $\max \mathbf{p-v}$ for some $v \in V$. Naturally, a solution I of \mathcal{I} is equivalent to a conflict-free siphon S of \mathcal{P} . The conversion is that

$$S = \{p \in P \mid I(\mathbf{a-p}) = 1\}$$

where $\mathbf{a-p}$ is the binary variable presenting place p .

We can see the similarity between \mathcal{I} and the encoded ASP shown in the previous subsection. However, due to the nature of solutions of an ILP, it is hard to compute all the set-inclusion maximal solutions of \mathcal{I} in one execution of an ILP solver. Hence, we propose an iterative approach as follows.

The conflict-free siphon of maximum cardinality is of course maximal. Therefore, we impose the following objective function:

$$\max \sum_{v \in V} (\mathbf{p-v} + \mathbf{n-v}).$$

Now, \mathcal{I} can be solved using a general purpose ILP solver. If it admits any solution I^* , the corresponding conflict-free siphon (say S^*) is maximal. Hence, it makes sense that it does not need to find any other conflict-free siphon

552 of the net that is strictly contained in S^* . To do this, we add to \mathcal{I} a new
 553 inequality

$$1 \leq \sum_{p \in P \setminus S^*} \mathbf{a-p}$$

554 where $\mathbf{a-p}$ is the binary variable presenting place p . Now, we solve \mathcal{I} again to
 555 find a new solution. If a new solution I' exists, then let S' be its corresponding
 556 conflict-free siphon. Indeed, abide by the newly added inequality, we have
 557 $S' \cap (P \setminus S^*) \neq \emptyset$ because there is some $\mathbf{a-p}$ with $p \in P \setminus S^*$ such that
 558 $I'(\mathbf{a-p}) = 1$. This implies that it is impossible that $S' = S^*$ or $S' \subset S^*$.
 559 By the objective function, it means that S' is the conflict-free siphon of
 560 maximum cardinality among the conflict-free siphons that are not contained
 561 in S^* . Hence, S' is also a maximal conflict-free siphon. Again, we add to \mathcal{I}
 562 a new inequality with respect to the newly found siphon. The above process
 563 is iterated until \mathcal{I} becomes unfeasible, this means that there is no further
 564 maximal conflict-free siphon. Thus, all the maximal conflict-free siphons of
 565 the Petri net have been found.

566 Since we used the MiniZinc framework to interface with the CP solver,
 567 it was simple to make the slight modifications described above and use that
 568 same interface to call the Coin-OR CBC solver⁸ [38].

569 4.5. Computation of special types of trap spaces

570 In the field of systems biology, biologists may want to compute more
 571 special types of trap spaces beyond minimal trap spaces [19]. We shall show
 572 that our proposed methods can be easily adjusted to compute popular types
 573 of trap spaces. We illustrate the adjustments via the ASP-based method (see
 574 Subsection 4.3), but these adjustments are completely applicable for other
 575 approaches such as MaxSAT, CP, and ILP.

576 First, the work by [39] uses the concept of stable motifs to build the suc-
 577 cession diagram of a Boolean network, a summary of the decisions in the
 578 network dynamics that lead to successively more restrictive nested stable
 579 motifs. The succession diagram is useful for control and decision making
 580 on this Boolean network. In particular, the proposed control methods are
 581 independent to the update scheme. It has been shown that a stable motif of
 582 a Boolean network is equivalent to a maximal trap space of this Boolean net-
 583 work [39]. Hence, it is necessary to develop an efficient method for computing

⁸<https://github.com/coin-or/Cbc>

584 maximal trap spaces of a Boolean network. We shall show how to adjust the
 585 ASP-method presented in Subsection 4.3 to compute maximal trap spaces.

586 We first provide the definition of maximal trap spaces. Let ε be the special
 587 trap space of \mathcal{N} where all the nodes are free. Of course, ε corresponds to the
 588 special conflict-free siphon \emptyset . A trap space m is called maximal if $m \neq \varepsilon$ and
 589 there is no other trap space m' such that $m' \neq \varepsilon$ and $m < m'$. Analogously,
 590 a conflict-free siphon S is called minimal if $S \neq \emptyset$ and there is no other
 591 trap space S' such that $S' \neq \emptyset$ and $S' \subset S$. By using the reasoning similar
 592 to the proof of Theorem 3.2, we can easily conclude that a maximal trap
 593 space of \mathcal{N} is equivalent to a minimal conflict-free siphon of its encoded
 594 Petri net \mathcal{P} . Let \mathcal{L} be the ASP characterizing all conflict-free siphons of \mathcal{P}
 595 (see Subsection 4.3). Naturally, we need to exclude \emptyset from the solution space
 596 of \mathcal{L} (equivalently exclude ε from the set of trap spaces). To do this, we add
 597 to \mathcal{L} the ASP rule

$$\text{p-v}_1; \text{n-v}_1; \dots; \text{p-v}_n; \text{n-v}_n.$$

598 that ensures that every answer set of \mathcal{L} cannot be empty. Then a set-inclusion
 599 minimal answer set of \mathcal{L} is equivalent to a minimal conflict-free siphon of \mathcal{P} ,
 600 thus a maximal trap space of \mathcal{N} .

601 Second, we consider fixed points in Boolean networks. Let s be a fixed
 602 point of a Boolean network \mathcal{N} . We have a subspace m corresponding to s
 603 as follows: $\forall v \in V, m(v) = s(v)$, i.e., all nodes are fixed in m . Clearly, s is
 604 a trap set of \mathcal{N} regardless of the update scheme. Hence, m is a trap space
 605 of \mathcal{N} . In addition, since $|S_{\mathcal{N}}[m]| = 1$, m is also a minimal trap space. To
 606 compute all fixed points of \mathcal{N} , we can add more constraints to the encoded
 607 ASP characterizing all conflict-free siphons (equivalently trap spaces). For
 608 every $v \in V$, we add to the encoded ASP the rule

$$\text{p-v}; \text{n-v}.$$

609 that ensures that for every conflict-free siphon S , it contains either p-v or n-v
 610 for every $v \in V$. Equivalently, the trap space corresponding to S is always
 611 a fixed point. Now, the set of answer sets of the encoded ASP is equivalent
 612 to the set of fixed points of \mathcal{N} . In particular, when solving the encoded ASP
 613 using an ASP solver, we do not need to use the built-in option for computing
 614 set-inclusion maximal answer sets. Note that we can also build another ASP
 615 characterizing all fixed points of \mathcal{N} based on the equivalence between a fixed
 616 point of \mathcal{N} and a deadlock of its Petri net encoding [21]. This approach may
 617 give a more compact ASP.

618 Third, we consider the trap spaces intersecting a given subspace m^* of
 619 a Boolean network. A trap space m intersects m^* if and only if $S_{\mathcal{N}}[m] \cap$
 620 $S_{\mathcal{N}}[m^*] \neq \emptyset$. It follows that for every v , if $m^*(v) = 0$ then $m(v) = 0$ or
 621 $m(v) = \star$, if $m^*(v) = 1$ then $m(v) = 1$ or $m(v) = \star$. For the former case, we
 622 add to \mathcal{L} the ASP rule

$$:- \text{ n-v.}$$

623 that ensures that $m(v)$ cannot be 1. For the latter case, we add to \mathcal{L} the
 624 ASP rule

$$:- \text{ p-v.}$$

625 that ensures that $m(v)$ cannot be 0. Now \mathcal{L} characterizes all trap spaces that
 626 intersect m^* .

627 Finally, we consider the trap spaces that are inside a given subspace m^*
 628 of a Boolean network. We first adjust \mathcal{L} to characterize all such trap spaces.
 629 A trap space m is inside m^* if and only if $m(v) = m^*(v)$ for every $v \in D_{m^*}$.
 630 If $m^*(v) = 0$, we add to \mathcal{L} the ASP rule

$$\text{ p-v.}$$

631 that ensures that $m(v) = 0$. If $m^*(v) = 1$, we add to \mathcal{L} the ASP rule

$$\text{ n-v.}$$

632 that ensures that $m(v) = 1$. It is noted that if we want to compute maximal
 633 trap spaces inside m^* , we need to exclude the conflict-free siphon correspond-
 634 ing m^* from the solution space. Specifically, we need to add to \mathcal{L} the ASP
 635 rule

$$\text{ p-v}_{i1}; \text{ n-v}_{i1}; \dots; \text{ p-v}_{ik}; \text{ n-v}_{ik}.$$

636 where $\{v_{i1}, \dots, v_{ik}\}$ is the set of free nodes of m^* . This rule ensures that
 637 $m \neq m^*$. In the case that $m^* = \varepsilon$, we have all maximal trap spaces of the
 638 original Boolean network.

639 5. Inconsistent and incomplete data

640 So far we have assumed that we are always able to derive complete and
 641 consistent truth tables (i.e., Boolean functions) that correctly capture the
 642 behavior of each node in a Boolean network. However, in practice it is rarely
 643 the case that a Boolean network of a biological system is fully understood

and indeed, this is one important reason for modeling such networks. The data provided may be incomplete in the sense that information is missing about what happens in certain states, or it may be inconsistent in that we have conflicting information. The result is that the behavior of some nodes under certain conditions may be non-deterministic [40].

Non-deterministic behavior is problematic for Boolean networks with the synchronous update scheme, which are unable to represent the possibility of more than one next state. It can be addressed by using Boolean networks with asynchronous update schemes because of their non-determinism. However, multiple update functions may be considered for each node, which is problematic for existing analysis methods in Boolean networks. For example, if the truth table of a node have k unknown-output rows, then this node may have 2^k possible Boolean functions and the analysis methods such as `PyBoolNet` and `mpbn` need to consider 2^k possible Boolean networks due to they require complete Boolean functions for their underlying processing. Moreover, one interesting question maybe raised from systems biologists is if there is a common behavioral property (e.g., minimal trap space, fixed point, attractor) among all possible combinations. To answer this question, the existing analysis methods maybe need to consider 2^k possible Boolean networks as well.

We shall show how our Petri net approach presented the previous section can handle the problem of inconsistent and incomplete data. The idea is to build the Petri net encoding of the Boolean network from its partial truth tables. More specifically, for each unknown-output row in the truth table of a node, we create two conflicting transitions representing the two possible outputs (i.e., 0 or 1). For the remaining rows, we create transitions as usual following the Petri net encoding [21]. Because of the non-deterministic choice mechanisms of Petri nets, the new Petri net is still equivalent in dynamics to the incomplete Boolean network. One notable advantage of the connection between trap spaces of a Boolean network and conflict-free siphons of its Petri net encoding is that it still holds if the Petri net encoding changes (e.g., more or less transitions) but still maintain the equivalence in dynamics to the Boolean network. Hence, the minimal trap spaces of the incomplete Boolean network can be computed by computing maximal conflict-free siphons of the resulting Petri net. As a consequence, we can easily answer the question on common behavioral property.

Example 5.1. Consider an incomplete Boolean network $\mathcal{N} = (V, F)$ (men-

tioned in [40]), where $V = (g_1, g_2, g_3)$ and $F = (f_1, f_2, f_3)$ with $f_1 = g_2, f_3 = \neg g_1$. Herein, f_2 is an incomplete function and the partial truth table is as follows.

g_1	g_3	g_2
0	0	0
0	1	0
1	0	?
1	1	1

We have two possible update functions for g_2 : $f_2 = g_1 \wedge g_3$ for the case that $? = 0$ and $f_2 = g_1$ for the case that $? = 1$. Accordingly, we have two possible Boolean networks. The first one has one minimal trap space: 001. The second one has two minimal trap spaces: 001 and 110. Both have a common minimal trap space: 001. The asynchronous dynamics of the incomplete Boolean network is shown in Figure 2a. The resulting Petri net following our idea is given in Figure 2b. Herein, $t_{g_2}^3$ and $t_{g_2}^4$ are the two conflicting transitions representing the unknown-output row. This Petri net has only one maximal conflict-free siphon $\{p_{g_1}, p_{g_2}, \bar{p}_{g_3}\}$ corresponding to the common minimal trap space 001.

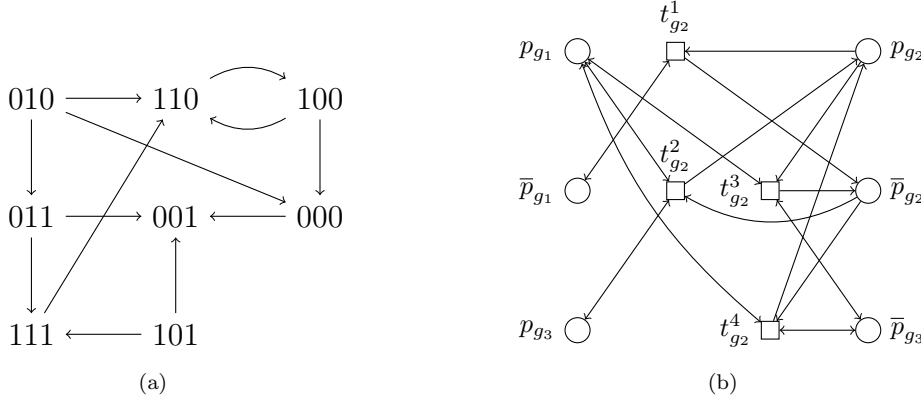


Figure 2: Asynchronous dynamics (self arcs are omitted for simplicity) and new Petri net encoding (the transitions corresponding to g_1 and g_3 are omitted for simplicity) of the incomplete Boolean network of Example 5.1.

In summary, we can still perform meaningful analysis on the resulting Petri net. Note that the new Petri net may have more transitions, however

697 the number of additional transitions is only $O(2k)$ where k is the number
 698 of unknown-output rows in the truth tables. This is actually a significant
 699 advantage, since we do not need to consider 2^k possible Boolean networks. It
 700 is worth noting that the approach proposed in [40] is only shown to deal with
 701 the case that $k = 1$, thus it is not clear how this approach can handle the
 702 case that $k > 1$. Moreover, in the context of Boolean models construction
 703 of biological systems from prior knowledge and experimental data, the work
 704 by [41] also deals with some kind of uncertainty. It uses ASP to represent all
 705 possible Boolean networks possessing the same given property, where each
 706 solution of this ASP is equivalent to a distinct Boolean network. Then it
 707 samples through that solution space with heuristics to select *diverse* Boolean
 708 networks, and proceed further simulations or analysis on every individual
 709 Boolean network. Compared to our Petri net approach presented above,
 710 it still requires to consider multiple Boolean networks as well as it is only
 711 applicable for locally-monotonic Boolean networks [41].

712 To this end, as more data becomes available for the underlying biological
 713 system, the Petri net model can be refined to reduce the amount of non-
 714 determinism (i.e., the number of conflicting transitions) it contains. Specif-
 715 ically, if we know the output for an unknown-output row of a node, we can
 716 remove one of the two conflicting transitions corresponding to this unknown-
 717 output row. Hence, Petri nets provide an interesting means of documenting
 718 the development of knowledge for a biological system, and our Petri net-based
 719 approach can be more useful in the model refinement loop.

720 6. Motivating example

721 For a few years now we have been collaborating with biologists who build
 722 very large detailed and annotated maps and now wish to analyze the dy-
 723 namics of the corresponding models. One of the main maps studied this way
 724 represents knowledge about the Rheumatoïd Arthritis [42], and was the main
 725 motivation for the development of a tool to automatically transform it into
 726 an executable Boolean network [6]. In the supplementary material of the pa-
 727 per, an excerpt of the map, focused around the apoptosis (cell death) module
 728 is transformed into a model of *reasonable* size, namely 180 Boolean variables
 729 (model `F5_RA_apoptosis_executable_module.sbml` of supplementary ma-
 730 terial S3, and model “RA-apoptosis” of Section 7). The study of such model,
 731 though, is a big hurdle. Indeed, as stated in the article about another model

732 of the same size: “*The size of the CaSQ-inferred MAPK model (181 nodes)*
733 *made the calculation of stable states a non-realistic endeavour.*”

734 In practice, even if there is a huge number of attractors in such a model,
735 obtaining a sample of those can reveal very useful to invalidate the model and
736 lead to further refinement. In particular, it provides a feature-rich alternative
737 to random simulations for this type of very non-deterministic model. Being
738 able to detect that there are inconsistencies with published experimental data
739 in some of the first 1000 attractors, for instance, can lead to a much quicker
740 Systems Biology loop: model, invalidate, refine.

741 However, using a state-of-the-art tool like PyBoolNet [7] on that model
742 actually fails at the phase of prime-implicant generation. mpbn [9] can return
743 the first 1000 solution within 1.43s, but indeed, it limits the modeling range
744 of the modelers as it does not permit using non-locally-monotonic Boolean
745 functions. This is also true for the Alzheimer model also mentioned in that
746 same article and originally from [43] (F4 file in the original supplementary
747 material, and “Alzheimer” in Table 3), where PyBoolNet also fails at the
748 prime-implicant computation and mpbn does not give any answer because
749 this model is actually non-locally-monotonic. The current practice usually
750 revolves then around fixing some source nodes to plausible values and re-
751 ducing the model accordingly. While this approach makes sense, it relies
752 on potentially arbitrary decisions, and *hides away* critical modelling choices
753 that were actually not part of the original Boolean network or even of the
754 starting map.

755 Using the ASP-based method presented in Section 4.3, it is possible to
756 obtain the first 1000 minimal trap spaces (including ones that contain more
757 than one state) within 0.19s, which is much quicker than mpbn. Unfortu-
758 nately since this was not available at the time, the analysis of the model
759 remained very high-level and qualitative, instead of being able to use the
760 rich information of computed minimal trap spaces.

761 7. Evaluation

762 To evaluate the performance of the newly proposed methods (imple-
763 mented as a Python package named Trappist) and the state-of-the-art meth-
764 ods (bioLQM⁹, PyBoolNet [7, 19], and mpbn [9]), we compared them on both

⁹<http://colomoto.org/biolqm/doc/tools-trap-space.html>

PyBoolNet’s own model repository and many real-world models from various sources in the literature. It is worth noting that `mpbn` [9] only handles locally-monotonic models, whereas the other methods can handle general models. To obtain a more comprehensive comparison, we also used random models generated by a third-party software (i.e., `BoolNet` R package [29]). As explained in Section 6, in our benchmarks, we only searched for the first 1000 minimal trap spaces for each model. It is worth noting that unlike existing analysis shown in the literature, we did not fix specific values for source nodes in all the considered models.

To solve the ASP problems, we used the same ASP solver `Clingo` [37] and the same configuration as that used in `PyBoolNet` [7, 19] and `mpbn` [9]. Specifically, we used the configuration `-heuristic=Domain -enum-mod=domRec -dom-mod=3` (subset maximality, equivalent to the deprecated `--dom-pref=32 --heuristic=domain --dom-mod=7` used by `PyBoolNet`). We ran all the benchmarks on a machine whose environment is CPU: Intel® Core™ i9-11950H 2.60GHz \times 16, 16 GB DDR4 RAM, Ubuntu 20.04.5 LTS. Finally, we set a time limit of three minutes for each model.

All the models and a Jupyter notebook realizing the benchmarks can be found at <https://github.com/soli/trap-spaces-as-siphons>. These can be run on a Docker image in the cloud by clicking the “Binder” button.

7.1. *PyBoolNet* repository

Table 1 shows the experimental results on the models from the official `PyBoolNet` repository¹⁰. Column n denotes the number of nodes of each model. Column $|M|$ denotes the number of minimal trap spaces and for each method is given the computation time in seconds, asking only for the first 1000 trap spaces. In the case of `bioLQM`, “N/A” means that the number of all minimal trap spaces of the model is larger than 1000 and we did not recorded the running time of `bioLQM` because it always requires to compute all minimal trap spaces. A number in bold indicates a ratio greater than three compared to the best result. “NM” indicates a non-locally-monotonic model. There are four variants of `Trappist`: SAT (i.e., the MaxSAT-based method shown in Subsection 4.2), CP (i.e., the CP-based method shown in Subsection 4.2), ILP (i.e., the ILP-based method shown in Subsection 4.4), and ASP (i.e., the ASP-based method shown in Subsection 4.3).

¹⁰<https://github.com/hklarner/pyboolnet/tree/master/pyboolnet/repository>

Table 1: Timing comparisons (in seconds) between **bioLQM** (LQM), **PyBoolNet** (PBN), **mpbn** and the four variants of **Trappist** on the **PyBoolNet** repository.

model	n	$ M $	LQM	PBN	mpbn	Trappist			
						SAT	CP	ILP	ASP
1 arellano_rootstem	9	4	0.13	0.01	0.00	0.00	-	-	0.01
2 calzone_cellfate	28	27	0.12	0.02	0.01	0.01	-	-	0.01
3 dahlhaus_neuroplastoma	23	32	0.11	0.03	0.01	0.01	-	-	0.01
4 davidich_yeast	10	12	0.11	0.02	0.01	0.01	-	-	0.01
5 dinwoodie_life	15	7	0.11	0.01	0.00	0.01	-	-	0.01
6 dinwoodie_stomatal	13	1	0.10	0.01	0.00	0.00	-	-	0.01
7 faure_cellcycle	10	2	0.11	0.02	0.01	0.01	-	-	0.01
8 grieco_mapk	53	18	0.19	0.03	0.02	0.03	-	-	0.02
9 irons_yeast	18	1	0.12	0.03	0.01	0.01	-	-	0.02
10 jaoude_thdiff	103	> 1000	N/A	0.85	0.45	0.56	-	-	0.09
11 klamt_tcr	40	8	0.11	0.01	0.01	0.01	-	-	0.02
12 krumsiek_myeloid	11	6	0.10	0.01	0.00	0.00	-	-	0.01
13 multivalued	13	4	0.10	0.01	0.00	0.00	-	-	0.01
14 n12c5	11	5	0.11	17.83	0.01	0.01	-	-	0.01
15 n3s1c1a	2	2	0.10	0.01	0.00	0.00	-	-	0.01
16 n3s1c1b	2	2	0.09	0.02	0.00	0.00	-	-	0.01
17 n5s3	4	3	0.10	0.02	NM	0.00	-	-	0.01
18 n6s1c2	5	3	0.10	0.02	0.00	0.00	-	-	0.01
19 n7s3	6	3	0.11	0.02	0.00	0.00	-	-	0.01
20 raf	3	2	0.10	0.01	0.00	0.00	-	-	0.01
21 randomnet_n15k3	15	3	0.10	0.02	NM	0.01	-	-	0.01
22 randomnet_n7k3	7	10	0.10	0.01	NM	0.00	-	-	0.01
23 remy_tumorigenesis	34	25	0.15	0.94	0.02	0.02	-	-	0.02
24 saadatpour_guardcell	13	1	0.10	0.06	0.00	0.00	-	-	0.02
25 selvaggio_emt	56	> 1000	N/A	0.48	0.28	0.28	-	-	0.09
26 tournier_apoptosis	12	3	0.10	0.01	0.00	0.00	-	-	0.01
27 xiao_wnt5a	7	4	0.10	0.01	0.00	0.00	-	-	0.01
28 zhang_tlg1	60	156	0.60	0.09	0.09	0.07	-	-	0.04
29 zhang_tlg1_v2	60	258	0.64	0.04	0.08	0.11	-	-	0.04

As shown in Table 1, for most of the models of the **PyBoolNet** repository, the results are comparable with all minimal trap spaces found very fast. For 5 of the 29 models, **mpbn** did not give any answer because it recognized these models as not locally-monotonic. Note that on some very small models, **Trappist** is sometimes slower than **PyBoolNet** and/or **mpbn**, but still significantly under one second. On the contrary, on every model that was a

805 bit challenging for PyBoolNet or mpbn, the new method is far more efficient
 806 with speedups between one and two orders of magnitude.

807 7.2. *BBM repository*

808 Currently, a research group has made a great effort for building a col-
 809 lection (called **BBM**) of real-world Boolean models from various sources used
 810 in systems biology. It aims to be a comprehensive collection suitable for
 811 benchmarking and testing new tools and methods. It is released and main-
 812 tained at <https://github.com/sybila/biodivine-boolean-models>. We
 813 here tested all the compared methods on this model repository.

Table 2: Results on the real-world models from the BBM repository.

Method	# failures	avg-lqm (s)	avg-mono (s)	avg-all (s)
bioLQM	9 (134)	12.87	N/A	N/A
PyBoolNet	12	8.87	11.00	13.59
mpbn	2 (187)	N/A	2.31	N/A
Trappist-MaxSAT	1	0.03	1.09	1.01
Trappist-CP	-	-	-	-
Trappist-ILP	-	-	-	-
Trappist-ASP	1	0.05	1.02	0.93

814 Table 2 shows the experimental results on the 211 real-world models from
 815 the **BBM** repository. Column 2 expresses the numbers of failures (i.e., did not
 816 finish the computation within a time limit of three minutes) of each method.
 817 For the case of **bioLQM**, we only considered the models that have at most
 818 1000 minimal trap spaces. The number of such models is 134 (per all 211
 819 models) and is denoted inside the parentheses. For the case of **mpbn**, we
 820 only considered the models that are locally-monotonic. The number of such
 821 models is 187 (per all 211 models) and is denoted inside the parentheses.
 822 Columns 3-5 express the average running time (in seconds) of each method for
 823 the models having at most 1000 minimal trap spaces, the locally-monotonic
 824 models, and all the models, respectively. Note that when computing the
 825 average running time, if the running time exceeds 180s, it is considered as
 826 180s. From the results shown in Table 2, we reported several observations as
 827 follows.

7.3. Selected models

We used a set of real-world Boolean networks lying in various scales collected from numerous bibliographic sources. Most of these models are quite big (in size), complex (i.e., having high average in-degree, which is related to the number of prime-implicants) and have never been fully analyzed. Note that these models are not included in the **PyBoolNet** and **BBM** repositories. We then applied **bioLQM**, **PyBoolNet**, **mpbn**, and the four variants of **Trappist** to computing minimal trap spaces of these real-world models. Table 3 shows the obtained experimental results. “DNF” means that the method did not finish the computation (stopping at the first 1000 minimal trap spaces) within the timeout of two minutes. A number in bold indicates a ratio greater than or equal to 10 compared to the best result. The remaining notations are similar to those in Table 1. Hereafter, we analyze in detail the results with respect to minimal trap space computation.

The first observation is that for 26 of the 33 models (more than 78%), **mpbn** did not give any answer because it recognized that these models as not locally-monotonic. For 6 of the 33 models where **mpbn** returned the answers, **mpbn** and **Trappist** are comparable in computation time, though surprisingly **mpbn** appears a bit slower on average. Note however that **mpbn** was the only tool to provide a solution for the SN-5 model, thus confirming that if the activation function is in the right form, not having to compute the inactivation function’s disjunctive normal form can render a difficult problem tractable. However, since **mbpn** can handle only locally-monotonic models and **Trappist** can handle general models, it is difficult to further compare between them. Hence, we focus on only comparisons between **PyBoolNet** and **Trappist** in the following observations.

The second observation is that the proposed method vastly outperforms **PyBoolNet** in computational time, on each and every model, and sometimes with orders of magnitude of difference (e.g., for most models in the 100–1000 nodes size range). Note that for all the cases where **PyBoolNet** did not manage to finish before the timeout, as marked by “DNF” in Table 3, the timeout occurred during the computation of the prime-implicants. Hence, not even a single minimal trap space was output by that method. The computational advantage is therefore immediately a practical advantage since on the one hand the state-of-the-art method did not allow any analysis whatsoever of the models, and on the other hand the proposed method could provide, very often under one second, the first thousand minimal trap spaces. For modellers having a critical look at a model and in a *model, invalidate, refine* loop

Table 3: Timing comparisons (in seconds) between **bioLQM** (LQM), **PyBoolNet** (PBN), **mpbn** and the four variants of **Trappist** on selected models from the literature.

model	n	$ M $	LQM	PBN	mpbn	Trappist			
						SAT	CP	ILP	ASP
1 metastatic [44]	10	4	0.10	0.04	NM	0.01	-	-	0.02
2 Arabidopsis_thaliana [44]	15	8	0.10	0.06	NM	0.01	-	-	0.02
3 p53_high_dna [44]	16	1	0.38	1.76	NM	0.08	-	-	0.14
4 p53_low_dna [44]	16	1	0.41	1.76	NM	0.07	-	-	0.14
5 FT-GRN [45]	23	32	DNF	DNF	NM	0.03	-	-	0.19
6 DNA_damage [44]	26	16	0.24	0.33	NM	0.02	-	-	0.05
7 Rho-GTPases [44]	33	2	0.17	0.57	40.39	0.07	-	-	0.11
8 Pluripotency [46]	36	440	DNF	DNF	NM	0.16	-	-	0.28
9 Pluripotent [44]	36	276	0.37	0.43	NM	0.07	-	-	0.06
10 Pancreatic_Cancer [44]	43	> 1000	N/A	0.11	0.36	0.17	-	-	0.06
11 Drosophila [47]	52	128	0.33	0.05	0.07	0.06	-	-	0.05
12 Cacace_TdevModel [48]	61	28	1.29	5.67	NM	0.06	-	-	0.08
13 hedgehog [44]	65	> 1000	N/A	DNF	0.50	0.34	-	-	0.33
14 EMT [39]	69	268	39.22	1.01	0.20	0.12	-	-	0.05
15 Bcell [49]	73	72	0.23	0.04	0.08	0.06	-	-	0.05
16 mast_cell [6]	73	> 1000	N/A	0.09	0.55	0.37	-	-	0.15
17 Corral_ThIL17diff [50]	92	> 1000	N/A	107.57	0.76	0.56	-	-	0.16
18 Adhesion_CIP [51]	121	78	56.81	4.25	0.23	0.17	-	-	0.19
19 EMT_Mech [52]	136	82	DNF	14.01	0.27	0.20	-	-	0.25
20 macrophage [44]	136	> 1000	N/A	0.54	1.09	0.84	-	-	0.27
21 angiogenesis [44]	141	> 1000	N/A	0.16	1.07	1.06	-	-	0.16
22 angiofull [53]	142	> 1000	N/A	0.17	1.06	0.88	-	-	0.23
23 EMT_Mech_TGFbeta [52]	150	492	DNF	11.28	0.78	0.69	-	-	0.35
24 RA_apoptosis [6]	180	> 1000	N/A	DNF	1.43	1.55	-	-	0.19
25 MAPK [6]	181	> 1000	N/A	13.58	1.76	1.51	-	-	0.27
26 Snf1-pathway [54]	202	> 1000	N/A	1.13	1.47	1.43	-	-	0.31
27 T-cell-co-receptor [44]	206	> 1000	N/A	DNF	1.52	2.26	-	-	0.35
28 TcellCheckPoint [55]	218	> 1000	N/A	4.99	NM	1.96	-	-	0.28
29 Mycobacterium [44]	317	> 1000	N/A	0.42	2.36	4.91	-	-	0.44
30 Leishmania [44]	342	> 1000	N/A	DNF	2.56	5.62	-	-	0.46
31 Cholocystokinin [6]	383	> 1000	N/A	0.36	2.99	4.81	-	-	0.37
32 Alzheimer [6]	762	> 1000	N/A	DNF	NM	18.21	-	-	0.79

866 this means a huge difference in the models that are amenable to study.

867 Note that even with a very restricted time-limit of two minutes, it was
868 possible with the proposed technique to find *all* minimal trap spaces of small
869 models (roughly under 130 nodes, i.e., considered as quite big up to now).
870 Though it might seem impractical to handle tens of thousands of such pos-

sible complex attractors in a manual way, i.e., to compare them to specific experimental conditions and corresponding data, we hope that an automatic analysis of such attractors might become possible with systematic verification methods, not unlike that described in [55]. Since the ASP code is declarative by nature, it is also possible to add to it supplementary constraints coming from the modeler in case one is looking for specific attractors. Finally, sampling from the ASP-generated solutions as is done in [41] would allow for a different type of exploration.

The third observation is that for all the models where **PyBoolNet** finished before the timeout, once **PyBoolNet** went through the prime-implicant phase, its ASP solving phase quickly returned the first 1000 minimal trap spaces, all under one second. For these models, the ASP solving phase of the proposed method also took very short time, all under one second. Hence, with the experimental results shown in this paper, the practical differences between our ASP encoding and that of **PyBoolNet** are not distinctly exposed. The fact that our new ASP encoding is guaranteed to be linear in the number of nodes of the original model does not seem to be crucial here, however a much deeper analysis of those cases remains to be done.

Note that though enumerating the extremal siphons of a Petri net is exponential (see [17] for instance) this is apparently not the bottleneck of the proposed method, showing once again that networks obtained from biochemical models do have a specific structure.

7.4. Randomly generated models

We randomly generated a set of N-K models [1] with network size n in the set $\{100, 150, 200, 250, 300, 350, 400\}$ and $K = 3$ (i.e., each node has exactly three input nodes). We chose N-K models because they are a useful tool for studying the dynamics of Boolean networks [1, 7]. For each network size, 50 instances were generated using the **generateRandomNKNetwork** function. In total, we have 350 random models. We then applied the compared methods to these models and recorded the numbers of failures (i.e., failed to obtain the result within a time limit of three minutes) as well as the average running time (inside the parentheses) in each method for each network size n . It is worth noting that N-K models usually have small numbers of minimal trap spaces [7]. Hence, we searched for all solutions in each model, which makes the comparison to **bioLQM** more comprehensive. In addition, each node has only three input nodes, i.e., the number of prime-implicants of the associated Boolean function is small. Hence, **PyBoolNet** always passed the phase of

908 computing prime-implicants in every model even within 1s, which enables us
 909 to compare the ASP encoding of **PyBoolNet** and that of **Trappist**.

Table 4: Results on N-K models.

n	LQM	mpbn	PBN	Trappist			
				SAT	CP	ILP	ASP
100	50 (> 180)	50 (N/A)	0 (0.07)	0 (0.05)	- ()	- ()	0 (0.09)
150	50 (> 180)	50 (N/A)	0 (0.14)	0 (0.10)	- ()	- ()	0 (0.14)
200	50 (> 180)	50 (N/A)	0 (0.43)	0 (0.25)	- ()	- ()	0 (0.24)
250	50 (> 180)	50 (N/A)	0 (1.92)	0 (1.04)	- ()	- ()	0 (0.56)
300	50 (> 180)	50 (N/A)	0 (9.68)	0 (4.46)	- ()	- ()	0 (1.83)
350	50 (> 180)	50 (N/A)	1 (46.54)	0 (20.09)	- ()	- ()	0 (6.10)
400	50 (> 180)	50 (N/A)	29 (144.09)	12 (90.36)	- ()	- ()	1 (33.01)

910 Table 4 shows the experimental results on N-K models. Column n de-
 911 notes the network size. Columns LQM and PBN show the results of **bioLQM** and
 912 **PyBoolNet**, respectively. For each method, the number outside the parenthe-
 913 ses indicates the number of failures, whereas the number inside the paren-
 914 theses indicates the average running time (in seconds). Note that when
 915 computing the average running time, if the running time exceeds 180s, it
 916 is considered as 180s. From these results, we obtained several observations
 917 consistent with those obtained for real-world models.

918 TODO: ...
 919 First, ...
 920 Second, ...
 921 Third, ...
 922 Finally, ...

923 8. Conclusion

924 In this article we have explored and proved for the first time the equiva-
 925 lence between (minimal) trap spaces of a general Boolean network and (max-
 926 imal) conflict-free siphons of its Petri net encoding. We have shown several
 927 important applications of this finding to studying properties of trap spaces
 928 in Boolean networks. As an important practical application of the equiva-
 929 lence, we have proposed a new approach for the computation of minimal trap

spaces of Boolean networks, based on the enumeration of maximal conflict-free siphons of Petri nets. We have also proposed the four possible methods using MaxSAT, CP, ILP, and ASP for implementing the new approach. The proposed methods have been evaluated on many real-world models from the literature and randomly generated models. The experimental results show that the new approach vastly outperforms all the state-of-the-art methods in terms of general Boolean networks and is comparable to the `mpbn` method even better in average in term of locally-monotonic Boolean networks. We believe that this opens up the way to a much better analysis of large Boolean networks, which is needed with the advent of automatic model-generation pipelines [56].

Although the experimental results show the superiority of our approach to `mpbn` in general, we however note that there is a model in the `BBM` repository (with identifier 122) where all the four proposed methods for the new approach did not manage to finish the Petri net conversion before the timeout, whereas `mpbn` can still handle this model. The model is not very large but its Boolean functions are rather complicated. This points to the fact that our current choice of using a BDD-based translation to obtain that Petri net encoding, though it provides a small/efficient ASP might be too costly to handle the complex models. In such a case, a more *naive* encoding might provide a much larger ASP program, with many redundant rules, but easier/faster to obtain. The evaluation of the feasibility of such strategy, and of its impact on smaller instances, remains to be done. Recognizing that a model is locally-monotonic and applying in that specific case dedicated strategies as those of `mpbn` might also be a partial solution.

It is worth noting that there may be possibly other methods for computing minimal/maximal conflict-free siphons in Petri nets, like the methods for generic siphon computation in the field of Petri nets (see [33] for a survey about these methods). Although these approaches do not directly support the minimal/maximal conflict-free siphon computation now, we plan to investigate them in the future. They could replace our proposed methods if they give significantly better performance. However, the current methods appear to already perform very well even on the biggest models we have considered.

Finally, we think that the links between Petri nets and Boolean networks that we stumbled upon in this method might have deeper roots. Exploring those connections might lead both to interesting topics of research for Petri nets, like a notion of trap-spaces, and for Boolean networks.

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