

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-

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

Herein we revise and extend our previous work in [18] as follows. First, more formal definitions are given and the existing proofs are made more detailed. In particular, an updated proof provides another way to prove the independence of trap spaces of a Boolean network on its update scheme, which was originally proved in [7]. Second, we showcase a theoretical application of the connection between trap spaces in Boolean networks and conflict-free siphons in Petri nets. Third, beyond the proposed ASP method implementing the alternative approach [18], we propose several other possible methods for computing minimal trap spaces using Maximum Satisfiability (MaxSAT), Constraint Programming (CP), and Integer Linear Programming (ILP). Fourth, we discuss in detail how to compute several special types of trap spaces in a Boolean network. Besides minimal trap spaces, these special types also play crucial roles in analyzing Boolean networks [19]. Fifth, regarding the implementation, we have developed a new converter that directly reads a `.bnet` file and builds the Petri net encoding, instead of using the PNML conversion of `bioLQM` [18]. Finally, we conduct a more comprehensive benchmark on more real-world models from various sources and randomly generated models to evaluate all the proposed methods (the benchmark conducted in [18] considers only dozens of representative real-world models).

The rest of this paper is organized as follows: Section 2 recalls the basic concepts including Boolean networks, attractors, trap spaces, Petri nets, and siphons. Section 3 presents the main finding, the connection between trap spaces in Boolean networks and siphons in Petri nets. Section 4 presents the alternative approach for computing minimal trap spaces and the four possible methods implementing it. Section 5 shows an important biological case study showing the applicability of the new approach. Section 6 reports the experimental results for evaluating the efficiency of the proposed methods. Finally, Section 7 concludes the paper and draws future work.

2. Preliminaries

We shall briefly recall here some preliminaries on Boolean networks related to trap spaces and Petri nets.

2.1. Boolean networks

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

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

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

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

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

118 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
119 time $t+1$. Note that for simplicity, we write $f_i(v(t))$ even $IN(v_i) \subset V$ (i.e.,
120 $IN(v_i)$ does not contain some nodes of V). An update scheme of a Boolean
121 network specifies the way that the nodes update their states through time
122 evolution [4]. Following the update scheme, the Boolean network transits
123 from a state to another state (possibly identical). This transition is called
124 the *state transition* and denoted by $\rightarrow \subseteq \mathcal{S}_{\mathcal{N}} \times \mathcal{S}_{\mathcal{N}}$. Then the dynamics of \mathcal{N}
125 is captured by the directed graph $(\mathcal{S}_{\mathcal{N}}, \rightarrow)$ called the State Transition Graph
126 (STG). There are two main types of update schemes [4]: synchronous, where
127 all the nodes are update simultaneously, and fully asynchronous, where only
128 one node is nondeterministically selected to be updated.

129 2.2. Traps spaces

130 We recall here some definitions from [7] for the introduction of *trap spaces*.
131 Minimal trap spaces prove to be a very good approximation of the attractors
132 of a Boolean network under asynchronous update schemes and have become
133 the *de facto* standard way to analyze models of a few tens of *genes* [20, 21].

134 An non-empty set $T \subseteq \mathcal{S}_{\mathcal{N}}$ is a trap set with respect to \rightarrow if for every
135 $x \in T$ and $y \in S$ with $x \rightarrow y$ it holds that $y \in T$ [7]. An attractor of \mathcal{N}
136 with respect to \rightarrow can be defined as an inclusion-wise minimal trap set of

137 $(\mathcal{S}_{\mathcal{N}}, \rightarrow)$. An attractor can be also seen as a terminal strongly connected
 138 component of $(\mathcal{S}_{\mathcal{N}}, \rightarrow)$ [22]. An attractor of size 1 is called a fixed point,
 139 otherwise a cyclic attractor [7].

140 A subspace m of a Boolean network $\mathcal{N} = (V, F)$ is a mapping $m: V \mapsto$
 141 $\mathbb{B} \cup \{\star\}$. $m(v_i) \in \mathbb{B}$ means that the value of v_i is fixed in m and v_i is called
 142 a fixed variable. $m(v_i) \in \star$ means that the value of v_i is free in m and v_i is
 143 called a free variable. We denote D_m the set of all fixed variables of m . A
 144 subspace m is equivalent to a set of states:

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

145 For example, $m = \star \star 1$ (for simplicity, we write subspaces likes states)
 146 means that $D_m = \{v_3\}$, $m(v_3) = 1$, and it is equivalent to the set of states
 147 $\{001, 011, 101, 111\}$. We denote $\mathcal{S}_{\mathcal{N}}^* = (\mathbb{B} \cup \{\star\})^n$ the set of all possible
 148 subspaces of \mathcal{N} . Note that $|\mathcal{S}_{\mathcal{N}}^*| = 3^n$ and $\mathcal{S}_{\mathcal{N}} \subset \mathcal{S}_{\mathcal{N}}^*$ [7].

149 A *trap space* is defined as a subspace that is also a trap set. It is noted
 150 that trap spaces of a Boolean network are independent of the update scheme
 151 of this model [7]. Then, we define a partial order $<$ on $\mathcal{S}_{\mathcal{N}}^*$ as: $m < m'$ if and
 152 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
 153 is minimal if and only if there is no trap space $m' \in \mathcal{S}_{\mathcal{N}}^*$ such that $m' < m$.

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

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

164 2.3. Petri net encoding of Boolean networks

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



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

169 A *marking* for a Petri net is a mapping $m : P \mapsto \mathbb{N}$ that assigns a number
170 of tokens to each place. A place p is marked by a marking m if and only if
171 $m(p) > 0$. Marking m can be seen as a subset of P that contains all marked
172 places by m . We shall write $\text{pred}(x)$ (resp. $\text{succ}(x)$) to represent the set of
173 vertices that have a (non-zero weighted) arc leading to (resp. coming from) x .
174 In this work, we consider a class of Petri nets called 1-safe Petri nets where
175 every place has at most 1 token and all arcs are of weight 1. In this case,
176 weights are implicitly omitted in the arcs of a Petri net. Then, a transition
177 $t \in T$ is *enabled* at a marking m if and only if $\text{pred}(t) \subseteq m$. A marking m
178 is called a *deadlock* if there are no enabled transitions at m . The firing of
179 t leads to a new marking m' specified by $m' = (m \setminus \text{pred}(t)) \cup \text{succ}(t)$. Note
180 that when multiple transitions are enabled, we need to embed one firing
181 scheme (similar to the update scheme of a Boolean network) to the Petri
182 net. The classical firing scheme is that only one of the enabled transition is
183 non-deterministically chosen to fire [12].

184 The link between Boolean networks *à la* Thomas and Petri nets was
185 originally established in [23] in order to make available formal methods like
186 model-checking for the analysis of such systems. The basic encoding into 1-
187 safe (i.e., never more than one token in each place) nets only holds for purely
188 Boolean networks but was later extended to multivalued logical models in
189 two ways, either in [24] with non 1-safe Petri nets or more recently in [22]
190 with 1-safe nets but many more places.

191 Since our study is focused on Boolean networks, we briefly recall the origi-
192 nal encoding here. Its basis is that every node (*gene*) v of the original model
193 $\mathcal{N} = (V, F)$ is represented by two separate places (p_v and \bar{p}_v), corresponding
194 to its two states, active, and inactive, respectively. Each conjunct of the
195 logical function that activates the *gene* will lead to a transition t , consuming

the inactive place (i.e., a directional arc from \bar{p}_v to t), producing the active place (i.e., a directional arc from t to p_v), and with all other literals both consumed and produced (i.e., a bidirectional arc). And conversely for the inactivation. Let s be a state of the Boolean network and m_s be its corresponding marking in the encoded Petri net. It holds that $\forall v \in V$, $s(v) = 0$ if 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 at any marking m of the Petri net encoding a Boolean network, it always holds that $m(p_v) + m(\bar{p}_v) = 1$.

The main property of this encoding is that it is completely faithful with respect to the update scheme of the original Boolean network. For each node v of \mathcal{N} , only transitions corresponding to v can change the current marking of p_v or \bar{p}_v . In addition, at any marking at most one of such transitions is enabled because $m(p_v) + m(\bar{p}_v) = 1$ holds. Hence, for any update scheme in \mathcal{N} , we have a corresponding firing scheme in \mathcal{P} , which preserves the equivalence between the dynamics of \mathcal{N} and \mathcal{P} [25].

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

Note that given a Boolean network in the standard SBML-Qual format [26], i.e., the package of SBML v3 [27] for such models, one can easily obtain its Petri net encoding in the Petri Net Markup Language (PNML)² standard using the bioLQM³ library. This piece of software extracted from GINsim [28] and part of the CoLoMoTo⁴ [29] software suite allows for easy conversion between standard formats. It also accepts many other common formats for Boolean networks, notably the .bnet files of the BoolNet [30, 20] 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

²<https://www.pnml.org/>

³<http://www.colomoto.org/biolqm/>

⁴<http://colomoto.org/>

229 Petri net encoding roughly relies on obtaining conditions for the activation
 230 and inactivation of the states. In [23] this took the form of the whole truth
 231 table of the Boolean functions, but as shown in Appendix 1 of [22] comput-
 232 ing Disjunctive Normal Forms (DNF) of each Boolean function is enough.
 233 Though this might appear quite computationally intensive it is important to
 234 remark first that contrary to the prime-implicants case, there is no need to
 235 find *minimal* DNFs. One way to look at this is to consider that this amounts
 236 to a similar approach as that used in [8] but with the encoding of both activa-
 237 tion and inhibition functions as DNFs in order to take into account possible
 238 non-local-monotonicity. This does not change the worst-case-complexity (ob-
 239 taining a single DNF being exponential) but might matter a lot in practice.
 240 As such, we will explore how this transformation, here using BDDs in `bioLQM`
 241 and directly in our tool using the `pyeda`⁵ library, and the one based on the
 242 most-permissive semantics compare in the Section 6 on evaluation.

243 2.4. Siphons

244 Siphons are a static and classical property of Petri nets [11]. Note how-
 245 ever that the use of siphons for the analysis of biological models, though it is
 246 not new, has been mostly relevant to the ODE-based continuous semantics
 247 of Chemical Reaction Networks [31, 32, 33]. We recall here the basic defini-
 248 tion establishing that to produce something in a siphon you must consume
 249 something from the siphon. This corresponds to the idea that a siphon is a
 250 set of places that once unmarked remains unmarked.

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

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

253 *Note that \emptyset is trivially a siphon.*

254 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
 255 conventionally $\text{pred}(S) = \text{succ}(S) = \emptyset$. We have an important property on
 256 siphons [34] as follows.

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

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

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

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

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

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

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

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

282 and

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

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

286 *Proof.* First, we show that if m is a trap space of \mathcal{N} , then S is a conflict-free
287 siphon of \mathcal{P} (*). If $D_m = \emptyset$, then $S = \emptyset$ is trivially a conflict-free siphon of
288 \mathcal{P} . Thus, we consider the case that $D_m \neq \emptyset$ (resp. $S \neq \emptyset$). Assume that S is

289 not a siphon of \mathcal{P} . Then, there is a transition $t \in T$ such that $S \cap \text{succ}(t) \neq \emptyset$
 290 but $S \cap \text{pred}(t) = \emptyset$. This implies that there is a place $p \in S$ such that
 291 $p \in \text{succ}(t)$ but $p \notin \text{pred}(t)$. Let v be the corresponding node in \mathcal{N} of p . By
 292 the characteristics of the encoding [23], there is a directional arc from t to p
 293 and a directional arc from the complementary place of p to t . Without loss
 294 of generality, we assume that $p = p_v$, then there is a directional arc from t
 295 to p_v and a directional arc from \bar{p}_v to t . We follow the following procedure
 296 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
 297 the corresponding marking in \mathcal{P} of s . For every place $p' \in \text{pred}(t)$, let p'' be
 298 the complementary place of p' and v' be the corresponding node in \mathcal{N} of p'
 299 and p'' . If $p'' \notin S$, then $v' \notin D_m$ and we can always set a Boolean value to
 300 $s(v')$ 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
 301 set $s(v') = m(v')$. In this case, if $p' = p_v$ then $s(v') = m(v') = 1$ leading to
 302 $m_s(p') = 1$, if $p' = \bar{p}_v$ then $s(v') = m(v') = 0$ leading to $m_s(p') = 1$. For
 303 the remaining nodes of \mathcal{N} , we can always set Boolean values to these nodes
 304 to preserve that $s \in \mathcal{S}_{\mathcal{N}}[m]$. We also have $m_s(p_v) = 0$ by the characteristics
 305 of the encoding [23]. Now, t is enabled at marking m_s . Its firing leads to
 306 a new marking m'_s such that $m'_s(p_v) = 1$ and $m'_s(\bar{p}_v) = 0$. Let s' be the
 307 corresponding state in \mathcal{N} of m'_s . We have $s'(v) = 1$ because $m'_s(p_v) = 1$ and
 308 $m(v) = 0$ because $p_v \in S$. This implies that $s' \notin \mathcal{S}_{\mathcal{N}}[m]$. For any firing
 309 scheme of \mathcal{P} , the firing of t always happens. Since a firing scheme of \mathcal{P} is
 310 equivalent to an update scheme of \mathcal{N} , s can escape from the trap space m
 311 for any update scheme of \mathcal{N} , which contradicts to the property of a trap
 312 space. Hence, S is a siphon of \mathcal{P} . By the definition of a mirror, S is also a
 313 conflict-free one.

314 Second, we show that if S is a conflict-free siphon of \mathcal{P} , then m is a trap
 315 space of \mathcal{N} (**). By the definition of a mirror, m is a subspace of \mathcal{N} . Let
 316 s be an arbitrary state in $\mathcal{S}_{\mathcal{N}}[m]$ and m_s be its corresponding marking in
 317 \mathcal{P} . Assume that there is a place $p \in S$ such that $m_s(p) = 1$. Let v be the
 318 corresponding node in \mathcal{N} of p . Since $p \in S$, $v \in D_m$ and $m(v) = s(v)$. If
 319 $p = p_v$, then $m_s(p_v) = 1$ leading to $m(v) = s(v) = 1$ by the characteristics of
 320 the encoding [23]. By the definition of a mirror, $m(v) = 0$ because $p_v \in S$,
 321 which is a contradiction. It is symmetric for the case that $p = \bar{p}_v$. Hence,
 322 $m_s(p) = 0, \forall p \in S$. In any marking m'_s reachable from m_s regardless of the
 323 firing scheme of \mathcal{P} , we have $m'_s(p) = 0, \forall p \in S$ by the dynamical property on
 324 markings of a siphon [34]. Let s' be the corresponding state in \mathcal{N} of m'_s . For
 325 every node $v \in D_m$, we have all two cases as follows. Case 1: $p_v \in S$, then
 326 $m'_s(p_v) = 0$, thus $s'(v) = 0 = m(v)$. Case 2: $\bar{p}_v \in S$, then $m'_s(\bar{p}_v) = 0$, thus

327 $s'(v) = 1 = m(v)$. Hence, $s'(v) = m(v)$ for every $v \in D_m$. Then, $s' \in \mathcal{S}_\mathcal{N}[m]$.
 328 By the definition of a trap space and the arbitrariness of s , m is a trap space
 329 of \mathcal{N} .

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

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

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

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

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

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

360 We here showcase a theoretical application of the connection between trap
 361 spaces in Boolean networks and conflict-free siphons in Petri nets. We use it

to prove a property of minimal trap spaces, which has surprisingly not been formally proved. Specifically, all minimal trap spaces of a Boolean network are mutually disjoint. This property is important because we can use it to approximate the set of attractors of the Boolean network under any update scheme [7] or to compute exactly the set of complex attractors of the Boolean network under the fully asynchronous update scheme [35].

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

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

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

A naturally computational application of Theorem 3.1 is that we can efficiently decide whether a subspace m is a trap space. In `PyBoolNet` [20], this is checked by using the percolation on the prime-implicants of the Boolean functions. As we have mentioned at the beginning of this article, the computation of prime-implicants is a demanding task for complex Boolean networks, even is sometimes intractable. Hence, the checking method in [20] shows its limitations. Instead, we can first compute the mirror S_m of m in the Petri net encoding. Then, by Proposition 2.1 and Theorem 3.1, we can check if $\text{pred}(S_m) \subseteq \text{succ}(S_m)$. Note that the Petri net construction is less computationally demanding than the prime-implicant computation because it

only requires computing generic (not prime) implicants of the Boolean functions [22]. 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 [34] 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 $\text{pred}(p)$ must belong to $\text{succ}(S)$. A transition t belongs to $\text{succ}(S)$ if and only if there is at least one place p' in S such that $p' \in \text{pred}(t)$. Hence, for each transition $t \in \text{pred}(p)$, we can state that

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

The system of all the rules of the above form with respect to all pairs (p, t) where $p \in P, t \in T, t \in \text{pred}(p)$ 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.

430 4.2. Constraint satisfaction problem

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

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

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

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

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

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

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

445 □

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

455 One natural question is that how to use the CSP-based method for enu-
456 merating all the maximal conflict-free siphons of a Petri net encoding a
457 Boolean network? Of course, the set of all conflict-free siphons of the Petri
458 net can easily be characterized by the CSP model presented in [17] along with
459 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 [36] via its MiniZinc [37] 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 [38] 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>

490 $\mathbf{n-v}$) to denote place p_v (resp. \bar{p}_v), $\forall v \in V$. The set of all atoms in \mathcal{L} is given
 491 as $\mathcal{A} = \bigcup_{v \in V} \{\mathbf{p-v}, \mathbf{n-v}\}$. For each pair (p, t) where $p \in P, t \in T, t \in \text{pred}(p)$,
 492 we translate the rule (1) into the ASP rule

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

493 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
 494 set of atoms representing places in $\text{pred}(t)$. The rule (2) is translated into
 495 the ASP rule

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

496 for each $v \in V$. This ASP rule guarantees that two places representing
 497 the same node in \mathcal{N} never belong to the same siphon of \mathcal{P} , representing
 498 the conflict-freeness. Naturally, a Herbrand model (see, e.g., [39]) of \mathcal{L} is
 499 equivalent to a conflict-free siphon of \mathcal{P} . To guarantee that a Herbrand
 500 model is also a stable model (an answer set), we need to add to \mathcal{L} the two
 501 choice rules

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

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

515 Now, a solution (simply an answer set) $A \subseteq \mathcal{A}$ of \mathcal{L} is equivalent to a
 516 conflict-free siphon S of \mathcal{P} , thus a trap space m of \mathcal{N} . The conversion from A
 517 to m is straightforward. If $\mathbf{p-v} \in A$ then $v \in D_m$ and $m(v) = 0$. Conversely,
 518 if $\mathbf{n-v} \in A$ then $v \in D_m$ and $m(v) = 1$. Otherwise, $v \notin D_m$. Comput-
 519 ing multiple answer sets is built into ASP solvers and the solving collection
 520 **POTASSCO** [39] also features the option to find set-inclusion maximal answer
 521 sets with respect to the set of atoms. Naturally, a set-inclusion maximal

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

526 4.4. Integer linear programming-based method

527 We first show how an Integer Linear Programming (ILP) \mathcal{I} can define
 528 a set of all conflict-free siphons of the encoded Petri net \mathcal{P} . We introduce
 529 *binary* variable $\mathbf{p-v}$ (resp. $\mathbf{n-v}$) to denote place p_v (resp. \bar{p}_v), $\forall v \in V$. The
 530 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
 531 $p \in P, t \in T, t \in \text{pred}(p)$, we translate the rule (1) into the ILP inequality

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

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

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

535 for each $v \in V$. This inequality forbids both $\mathbf{p-v}$ and $\mathbf{n-p}$ receive the value
 536 1, thus representing the conflict-freeness. Since we only consider feasible
 537 solutions, the objective function is set to $\max \mathbf{p-v}$ for some $v \in V$. Naturally,
 538 a solution I of \mathcal{I} is equivalent to a conflict-free siphon S of \mathcal{P} . The conversion
 539 is that

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

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

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

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

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

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

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

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

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

564 Since we used the MiniZinc framework to interface with the CP solver,
565 it was simple to make the slight modifications described above and use that
566 same interface to call the Coin-OR CBC solver⁸ [40].

567 4.5. Computation of special types of trap spaces

568 In the field of systems biology, biologists may want to compute more spe-
569 cial types of trap spaces beyond minimal trap spaces [20], which also play cru-
570 cial roles in analysis of Boolean networks. We shall show that our proposed
571 methods can be easily adjusted to compute popular types of trap spaces. We
572 illustrate the adjustments via the ASP-based method (see Subsection 4.3),
573 but these adjustments are completely applicable for other approaches such
574 as MaxSAT, CP, and ILP.

575 First, the work by [19] uses the concept of stable motifs to build the suc-
576 cession diagram of a Boolean network, a summary of the decisions in the
577 network dynamics that lead to successively more restrictive nested stable
578 motifs. The succession diagram is useful for control and decision making
579 on this Boolean network. In particular, the proposed control methods are
580 independent to the update scheme. It has been shown that a stable motif of

⁸<https://github.com/coin-or/Cbc>

581 a Boolean network is equivalent to a maximal trap space of this Boolean net-
 582 work [19]. Hence, it is necessary to develop an efficient method for computing
 583 maximal trap spaces of a Boolean network. We shall show how to adjust the
 584 ASP-method presented in Subsection 4.3 to compute maximal trap spaces.

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

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

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

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

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

608 that ensures that for every conflict-free siphon S , it contains either **p-v** or **n-v**
 609 for every $v \in V$. Equivalently, the trap space corresponding to S is always
 610 a fixed point. Now, the set of answer sets of the encoded ASP is equivalent
 611 to the set of fixed points of \mathcal{N} . In particular, when solving the encoded ASP
 612 using an ASP solver, we do not need to use the built-in option for computing
 613 set-inclusion maximal answer sets. Note that we can also build another ASP

614 characterizing all fixed points of \mathcal{N} based on the equivalence between a fixed
 615 point of \mathcal{N} and a deadlock of its Petri net encoding [22]. This approach may
 616 give a more compact ASP.

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

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

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

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

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

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

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

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

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

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

$$\text{ p-v_i1; n-v_i1; \dots; p-v_ik; n-v_ik.}$$

635 where $\{v_{i_1}, \dots, v_{i_k}\}$ is the set of free nodes of m^* . This rule ensures that
 636 $m \neq m^*$. In the case that $m^* = \varepsilon$, we have all maximal trap spaces of the
 637 original Boolean network.

638 5. Motivating example

639 For a few years now we have been collaborating with biologists who build
 640 very large detailed and annotated maps and now wish to analyze the dy-
 641 namics of the corresponding models. One of the main maps studied this way

642 represents knowledge about the Rheumatoid Arthritis [41], and was the main
643 motivation for the development of a tool to automatically transform it into
644 an executable Boolean network [6]. In the supplementary material of the pa-
645 per, an excerpt of the map, focused around the apoptosis (cell death) module
646 is transformed into a model of *reasonable* size, namely 180 Boolean variables
647 (model `F5_RA_apoptosis_executable_module.sbml` of supplementary ma-
648 terial S3, and model “RA-apoptosis” of Section 6). The study of such model,
649 though, is a big hurdle. Indeed, as stated in the article about another model
650 of the same size: *“The size of the CaSQ-inferred MAPK model (181 nodes)*
651 *made the calculation of stable states a non-realistic endeavour.”*

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

659 However, using a state-of-the-art tool like `PyBoolNet` [7] on that model
660 actually fails at the phase of prime-implicant generation. `mpbn` [9] can return
661 the first 1000 solution within 1.43s, but indeed, it limits the modeling range
662 of the modelers as it does not permit using non-locally-monotonic Boolean
663 functions. This is also true for the Alzheimer model also mentioned in that
664 same article and originally from [42] (F4 file in the original supplementary
665 material, and “Alzheimer” in Table 2), where `PyBoolNet` also fails at the
666 prime-implicant computation and `mpbn` does not give any answer because
667 this model is actually non-locally-monotonic. The current practice usually
668 revolves then around fixing some source nodes to plausible values and re-
669 ducing the model accordingly. While this approach makes sense, it relies
670 on potentially arbitrary decisions, and *hides away* critical modelling choices
671 that were actually not part of the original Boolean network or even of the
672 starting map.

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

679 6. Evaluation

680 To evaluate the performance of the newly proposed methods (imple-
 681 mented as a Python package named **Trappist**) and the state-of-the-art meth-
 682 ods (**bioLQM**⁹, **PyBoolNet** [7, 20], and **mpbn** [9]), we compared them on both
 683 **PyBoolNet**’s own model repository and many real-world models from various
 684 sources in the literature. It is worth noting that **mpbn** [9] only handles locally-
 685 monotonic models, whereas the other methods can handle general models.
 686 To obtain a more comprehensive comparison, we also used random models
 687 generated by a third-party software (i.e., **BoolNet** R package [30]). As ex-
 688 plained in Section 5, in our benchmarks, we only searched for the first 1000
 689 minimal trap spaces for each model. It is worth noting that unlike existing
 690 analysis shown in the literature, we did not fix specific values for source nodes
 691 in all the considered models.

692 To solve the ASP problems, we used the same ASP solver **Clingo** [39] and
 693 the same configuration as that used in **PyBoolNet** [7, 20] and **mpbn** [9]. Specif-
 694 ically, we used the configuration `-heuristic=Domain -enum-mod=domRec`
 695 `-dom-mod=3` (subset maximality, equivalent to the deprecated `--dom-pref=32`
 696 `--heuristic=domain --dom-mod=7` used by **PyBoolNet**). We ran all the
 697 benchmarks on a machine whose environment is CPU: Intel® Core™ i9-
 698 11950H 2.60GHz \times 16, 16 GB DDR4 RAM, Ubuntu 20.04.5 LTS. Finally,
 699 we set a time limit of three minutes for each model.

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

703 6.1. *PyBoolNet* repository

704 Table 1 shows the experimental results on the models from the official
 705 **PyBoolNet** repository¹⁰. Column n denotes the number of nodes of each
 706 model. Column $|M|$ denotes the number of minimal trap spaces and for
 707 each method is given the computation time in seconds, asking only for the
 708 first 1000 minimal trap spaces. In the case of **bioLQM**, “N/A” means that the
 709 number of all minimal trap spaces of the model is larger than 1000 and we did
 710 not recorded the running time of **bioLQM** because it always requires to com-
 711 pute all minimal trap spaces. A number in bold indicates a ratio greater than

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

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

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).

717 As shown in Table 1, for most of the models of the `PyBoolNet` repository,
 718 the results are comparable with all minimal trap spaces found very fast. For
 719 3 of the 29 models, `mpbn` did not give any answer because these models are
 720 locally-monotonic.

721 6.2. *BBM repository*

722 Currently, a research group has made a great effort for building a collec-
 723 tion (called **BBM**) of real-world Boolean models from various sources used in
 724 systems biology. It aims to be a comprehensive collection suitable for bench-
 725 marking and testing new tools and methods. **BBM** consists of 211 models (24
 726 out of them are non-locally-monotonic), peaking at 321 nodes, 1100 regula-
 727 tions among the nodes, and 133 source nodes, respectively. It is released and
 728 maintained at <https://github.com/sybila/biodivine-boolean-models>.
 729 We here tested all the compared methods on this model repository.

730 Figure 2 (above) shows cumulative numbers of the **BBM** models that have
 731 less than 1000 minimal trap spaces solved by the competing methods with
 732 respect to enumerating the first 1000 minimal trap spaces. The number of
 733 such models is 134 (per all 211 models), and 15 of them are non-locally-
 734 monotonic. We can first see that ...

735 Figure 2 (below) shows cumulative numbers of the **BBM** models solved by
 736 the competing methods (except `bioLQM`) with respect to enumerating the
 737 first 1000 minimal trap spaces. ...

738 6.3. *Selected models*

739 We used a set of real-world Boolean networks lying in various scales col-
 740 lected from numerous bibliographic sources in the literature. Most of these
 741 models are quite big (in size), complex (i.e., having high average in-degree,
 742 which is related to the number of prime-implicants), and have never been
 743 fully analyzed. Note that these models are not included in the `PyBoolNet`
 744 and **BBM** repositories. We then applied `bioLQM`, `PyBoolNet`, `mpbn`, and the
 745 four variants of **Trappist** to computing minimal trap spaces of these real-
 746 world models. Table 2 shows the obtained experimental results. “DNF”
 747 means that the method did not finish the computation (stopping at the first
 748 1000 minimal trap spaces) within the time limit of three minutes. A number
 749 in bold indicates a ratio greater than or equal to 10 compared to the best
 750 result. The remaining notations are similar to those in Table 1. Hereafter, we
 751 analyze in detail the results with respect to minimal trap space computation.

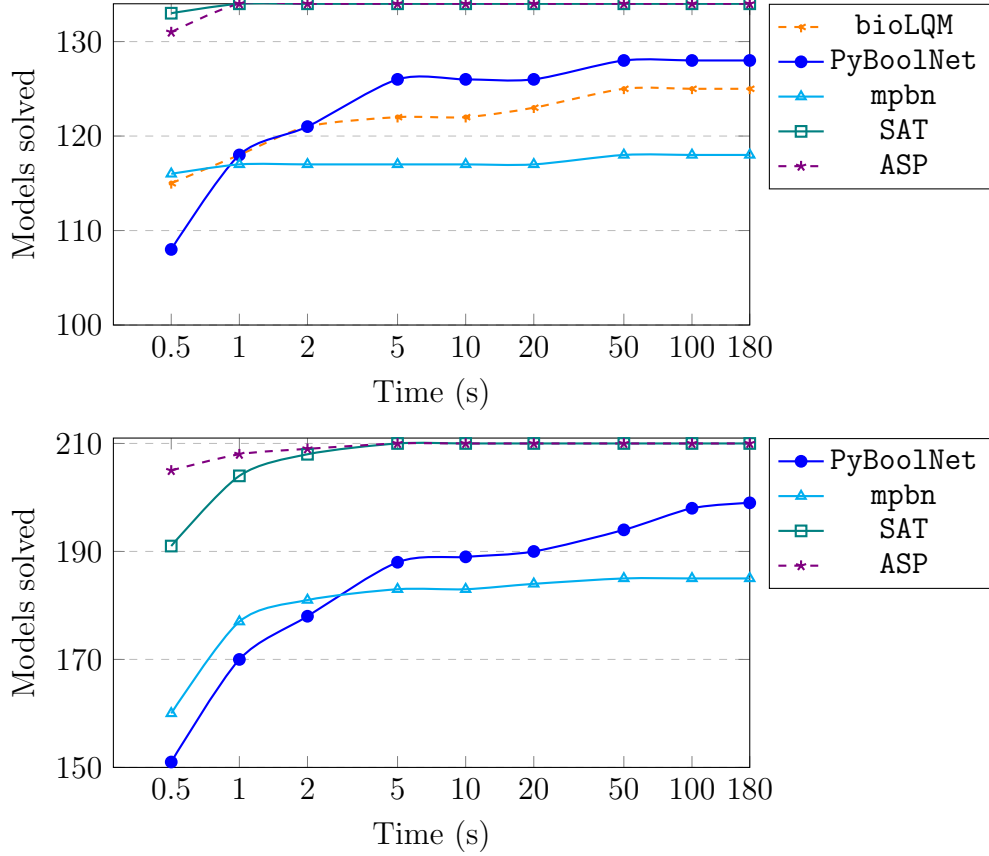


Figure 2: Cumulative numbers of the BBM models that have less than 1000 minimal trap spaces (above) and BBM models (below) solved by the competing methods with respect to enumerating the first 1000 minimal trap spaces.

752 The first observation is that for 11 of the 32 models (more than 34%),
753 **mpbn** did not give any answer because these models as not locally-monotonic.
754 For 22 of the 32 models where **mpbn** returned the answers, **mpbn** and **Trappist**
755 are comparable in computation time, though surprisingly **mpbn** appears quite
756 slower on average than the best variant of **Trappist**. In particular, for the
757 Rho-GTPases model, **mpbn** is 577 \times slower than the best variant of **Trappist**.
758 However, since **mpbn** can handle only locally-monotonic models and **Trappist**
759 can handle general models, it is difficult to further compare between them.
760 Hence, we focus on only comparisons among **bioLQM**, **PyBoolNet**, and **Trappist**
761 in the following observations.

Table 2: 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 [43]	10	4	0.10	0.04	NM	0.01	-	-	0.02
2 Arabidopsis.thaliana [43]	15	8	0.10	0.06	NM	0.01	-	-	0.02
3 p53_high_dna [43]	16	1	0.38	1.76	NM	0.08	-	-	0.14
4 p53_low_dna [43]	16	1	0.41	1.76	NM	0.07	-	-	0.14
5 FT-GRN [44]	23	32	DNF	DNF	NM	0.03	-	-	0.19
6 DNA_damage [43]	26	16	0.24	0.33	NM	0.02	-	-	0.05
7 Rho-GTPases [43]	33	2	0.17	0.57	40.39	0.07	-	-	0.11
8 Pluripotency [45]	36	440	DNF	DNF	NM	0.16	-	-	0.28
9 Pluripotent [43]	36	276	0.37	0.43	NM	0.07	-	-	0.06
10 Pancreatic_Cancer [43]	43	1000+	N/A	0.11	0.36	0.17	-	-	0.06
11 Drosophila [46]	52	128	0.33	0.05	0.07	0.06	-	-	0.05
12 Cacace_TdevModel [47]	61	28	1.29	5.67	NM	0.06	-	-	0.08
13 hedgehog [43]	65	1000+	N/A	DNF	0.50	0.34	-	-	0.33
14 EMT [19]	69	268	39.22	1.01	0.20	0.12	-	-	0.05
15 Bcell [48]	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 [49]	92	1000+	N/A	107.57	0.76	0.56	-	-	0.16
18 Adhesion_CIP [50]	121	78	56.81	4.25	0.23	0.17	-	-	0.19
19 EMT_Mech [51]	136	82	DNF	14.01	0.27	0.20	-	-	0.25
20 macrophage [43]	136	1000+	N/A	0.54	1.09	0.84	-	-	0.27
21 angiogenesis [43]	141	1000+	N/A	0.16	1.07	1.06	-	-	0.16
22 angiofull [52]	142	1000+	N/A	0.17	1.06	0.88	-	-	0.23
23 EMT_Mech_TGFbeta [51]	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 [53]	202	1000+	N/A	1.13	1.47	1.43	-	-	0.31
27 T-cell-co-receptor [43]	206	1000+	N/A	DNF	1.52	2.26	-	-	0.35
28 TcellCheckPoint [54]	218	1000+	N/A	4.99	NM	1.96	-	-	0.28
29 Mycobacterium [43]	317	1000+	N/A	0.42	2.36	4.91	-	-	0.44
30 Leishmania [43]	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

6.4. 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

766 studying the dynamics of Boolean networks [1, 7, 19]. For each network size,
767 50 instances were generated using the `generateRandomNKNetwork` function.
768 In total, we have 350 random models. We then applied the compared methods
769 to these models and recorded the running time of each method for each model.
770 It is worth noting that N-K models usually have small numbers of minimal
771 trap spaces [7]. Hence, we searched for all solutions in each model, which
772 makes the comparison to `bioLQM` more comprehensive. In addition, each
773 node has only three input nodes, i.e., the number of prime-implicants of the
774 associated Boolean function is small. Hence, `PyBoolNet` always passed the
775 phase of computing prime-implicants in every model even within 1s, which
776 enables us to compare the ASP encoding of `PyBoolNet` and that of `Trappist`.

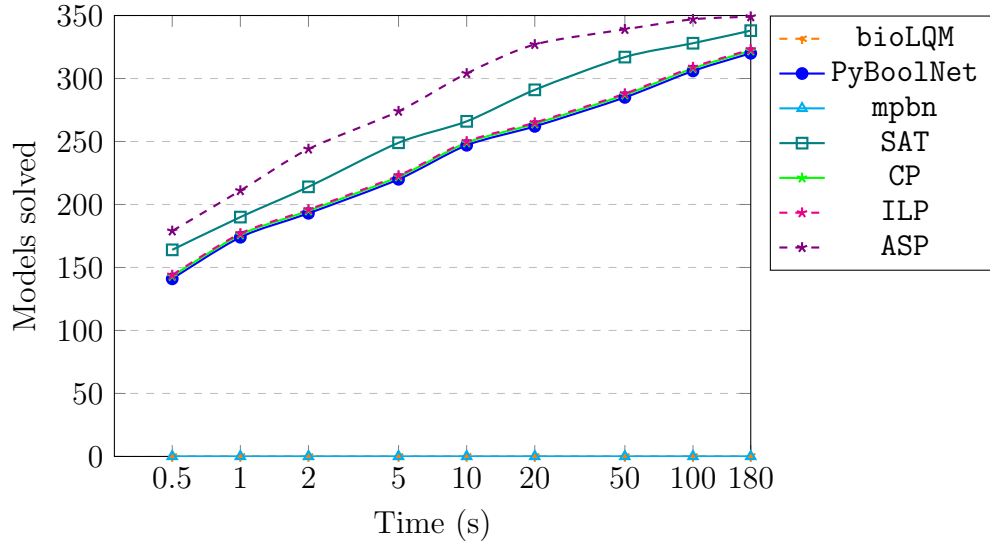


Figure 3: Cumulative numbers of random models solved by the competing methods with respect to enumerating all the minimal trap spaces.

777 Figure 3 shows cumulative numbers of random models solved by the com-
778 peting methods with respect to enumerating all the minimal trap spaces.
779 The number of succeeded models within three minutes for each method is
780 as follows: `bioLQM` (0), `PyBoolNet` (320), `mpbn` (0), `Trappist-maxSAT` (338),
781 `Trappist-CP` (0), `Trappist-ILP` (0), `Trappist-ASP` (349). We can see that
782 `Trappist-ASP` is the method that could handle the most number of mod-
783 els. Note that none of the other methods could handle the model failed
784 by `Trappist-ASP`. Upon closer inspection, we obtained several observations

785 consistent with those obtained for real-world models as follows.

786 First, **mpbn** did not be able to handle any model because all the models
787 are non-locally-monotonic. Recall that a Boolean network is non-locally-
788 monotonic if only one of its Boolean functions is non-locally-monotonic.
789 Hence, it is apparent that all the randomly generated models are non-locally-
790 monotonic because of the number of nodes is large ($n \geq 100$). This observa-
791 tion confirms the limit on the applicable model class of **mpbn**.

792 Second, surprisingly **bioLQM** could not handle any model. One of the
793 reason may be that the BDD characterizing all trap spaces is too large, and
794 its computation is slow. In addition, having too many generic trap spaces
795 before the filtering process may be also a reason. It is apparent because the
796 network size is large ($n \geq 100$) and the Boolean functions are not simple.

797 Third, ...

798 Finally, ...

799 7. Conclusion

800 In this article we have explored and proved for the first time the equiva-
801 lence between (minimal) trap spaces of a general Boolean network and (max-
802 imal) conflict-free siphons of its Petri net encoding. We have shown several
803 important applications of this finding to studying properties of trap spaces
804 in Boolean networks. As an important practical application of the equiva-
805 lence, we have proposed a new approach for the computation of minimal trap
806 spaces in Boolean networks, based on the enumeration of maximal conflict-
807 free siphons of Petri nets. We have also proposed the four possible methods
808 using MaxSAT, CP, ILP, and ASP for implementing the new approach. The
809 proposed methods have been evaluated on many real-world models from the
810 literature as well as randomly generated models. The experimental results
811 show that the new approach vastly outperforms all the state-of-the-art meth-
812 ods in terms of general Boolean networks and is comparable to the **mpbn**
813 method even better in average in terms of locally-monotonic Boolean net-
814 works. We believe that this opens up the way to a much better analysis
815 of large Boolean networks, which is needed with the advent of automatic
816 model-generation pipelines [55].

817 Although the experimental results show the superiority of our approach
818 to **mpbn** in general, we however note that there is a model in the **BBM** repos-
819 itory (with identifier 122) where all the four proposed methods for the new

820 approach did not manage to finish the Petri net conversion before the time-
 821 out, whereas `mpbn` can still handle this model. The model is not very large
 822 but its Boolean functions are rather complicated. This points to the fact that
 823 our current choice of using a BDD-based translation to obtain that Petri net
 824 encoding, though it provides a small/efficient ASP might be too costly to
 825 handle the complex models. In such a case, a more *naive* encoding might
 826 provide a much larger ASP program, with many redundant rules, but eas-
 827 ier/faster to obtain. The evaluation of the feasibility of such strategy, and
 828 of its impact on smaller instances, remains to be done. Recognizing that
 829 a model is locally-monotonic and applying in that specific case dedicated
 830 strategies as those of `mpbn` might also be a partial solution.

831 It is worth noting that there may be possibly other methods for comput-
 832 ing minimal/maximal conflict-free siphons in Petri nets, like the methods for
 833 generic siphon computation in the field of Petri nets (see [34] for a survey
 834 about these methods). Although these approaches do not directly support
 835 the minimal/maximal conflict-free siphon computation now, we plan to in-
 836 vestigate them in the future. They could replace our proposed methods if
 837 they give significantly better performance. However, the current methods
 838 appear to already perform very well even on the biggest models we have
 839 considered.

840 Finally, we think that the links between Petri nets and Boolean networks
 841 that we stumbled upon in this method might have deeper roots. Exploring
 842 those connections might lead both to interesting topics of research for Petri
 843 nets, like a notion of trap-spaces, and for Boolean networks. We also believe
 844 that the connection between trap spaces of Boolean networks and siphons
 845 of Petri nets can be a very useful tool for exploring and proving more new
 846 properties of trap spaces in Boolean networks, as we have used it to success-
 847 fully prove the separation of minimal trap spaces. Diving into this direction
 848 is one of our future work.

849 References

- 850 [1] L. Glass, S. A. Kauffman, The logical analysis of continuous, non-linear
 851 biochemical control networks, J. Theor. Biol. 39 (1973) 103–129.
- 852 [2] R. Thomas, Boolean formalisation of genetic control circuits, J. Theor.
 853 Biol. 42 (1973) 565–583.
- 854 [3] R. Thomas, R. d’Ari, Biological feedback, CRC press, 1990.

- 855 [4] R. Thomas, Regulatory networks seen as asynchronous automata: a
856 logical description, *J. Theor. Biol.* 153 (1991) 1–23.
- 857 [5] R.-S. Wang, A. Saadatpour, R. Albert, Boolean modeling in systems
858 biology: an overview of methodology and applications, *Phys. Biol.* 9
859 (2012) 055001.
- 860 [6] S. S. Aghamiri, V. Singh, A. Naldi, T. Helikar, S. Soliman, A. Niarakis,
861 J. Xu, Automated inference of Boolean models from molecular interac-
862 tion maps using CaSQ, *Bioinform.* 36 (2020) 4473–4482.
- 863 [7] H. Klarner, A. Bockmayr, H. Siebert, Computing maximal and minimal
864 trap spaces of Boolean networks, *Nat. Comput.* 14 (2015) 535–544.
- 865 [8] S. Chevalier, C. Froidevaux, L. Paulevé, A. Y. Zinovyev, Synthesis of
866 Boolean networks from biological dynamical constraints using answer-
867 set programming, in: *International Conference on Tools with Artificial*
868 *Intelligence*, IEEE, 2019, pp. 34–41.
- 869 [9] L. Paulevé, J. Kolčák, T. Chatain, S. Haar, Reconciling qualitative,
870 abstract, and scalable modeling of biological networks, *Nat. Commun.*
871 11 (2020) 1–7.
- 872 [10] M. Noual, D. Regnault, S. Sené, About non-monotony in Boolean au-
873 tomata networks, *Theor. Comput. Sci.* 504 (2013) 12–25.
- 874 [11] J. L. Peterson, *Petri net theory and the modeling of systems*, Prentice
875 Hall PTR, 1981.
- 876 [12] T. Murata, Petri nets: Properties, analysis and applications, *Proc.*
877 *IEEE* 77 (1989) 541–580.
- 878 [13] V. N. Reddy, M. L. Mavrovouniotis, M. N. Liebman, Petri net rep-
879 resentations in metabolic pathways, in: *International Conference on*
880 *Intelligent Systems for Molecular Biology*, AAAI, 1993, pp. 328–336.
- 881 [14] I. Zevedei-Oancea, S. Schuster, Topological analysis of metabolic net-
882 works based on Petri net theory, *Silico Biol.* 3 (2003) 323–345.
- 883 [15] M. A. Blätke, M. Heiner, W. Marwan, Biomodel engineering with Petri
884 nets, in: *Algebraic and Discrete Mathematical Methods for Modern*
885 *Biology*, Elsevier, 2015, pp. 141–192.

- 886 [16] O. Oanea, H. Wimmel, K. Wolf, New algorithms for deciding the siphon-
887 trap property, in: International Conference on Applications and Theory
888 of Petri Nets, Springer, 2010, pp. 267–286.
- 889 [17] F. Nabli, T. Martinez, F. Fages, S. Soliman, On enumerating mini-
890 mal siphons in Petri nets using CLP and SAT solvers: theoretical and
891 practical complexity, *Constraints An Int. J.* 21 (2016) 251–276.
- 892 [18] V. Trinh, B. Benhamou, K. Hiraishi, S. Soliman, Minimal trap spaces of
893 logical models are maximal siphons of their Petri net encoding, in: In-
894 ternational Conference on Computational Methods in Systems Biology,
895 Springer, 2022, pp. 158–176.
- 896 [19] J. C. Rozum, J. G. T. Zañudo, X. Gan, D. Deritei, R. Albert, Parity
897 and time reversal elucidate both decision-making in empirical models
898 and attractor scaling in critical Boolean networks, *Sci. Adv.* 7 (2021)
899 eabf8124.
- 900 [20] H. Klarner, A. Streck, H. Siebert, PyBoolNet: a python package for the
901 generation, analysis and visualization of Boolean networks, *Bioinform.*
902 33 (2017) 770–772.
- 903 [21] L. C. Fontanals, E. Tonello, H. Siebert, Control strategy identification
904 via trap spaces in Boolean networks, in: International Conference on
905 Computational Methods in Systems Biology, Springer, 2020, pp. 159–
906 175.
- 907 [22] T. Chatain, S. Haar, L. Jezequel, L. Paulevé, S. Schwoon, Characteriza-
908 tion of reachable attractors using Petri net unfoldings, in: International
909 Conference on Computational Methods in Systems Biology, Springer,
910 2014, pp. 129–142.
- 911 [23] C. Chaouiya, E. Remy, P. Ruet, D. Thieffry, Qualitative modelling of
912 genetic networks: From logical regulatory graphs to standard Petri nets,
913 in: International Conference on Applications and Theory of Petri Nets,
914 Springer, 2004, pp. 137–156.
- 915 [24] C. Chaouiya, A. Naldi, E. Remy, D. Thieffry, Petri net representation of
916 multi-valued logical regulatory graphs, *Nat. Comput.* 10 (2011) 727–750.

- 917 [25] T. Chatain, S. Haar, J. Kolcák, L. Paulevé, A. Thakkar, Concurrency
918 in Boolean networks, *Nat. Comput.* 19 (2020) 91–109.
- 919 [26] C. Chaouiya, D. Bérenguier, S. M. Keating, A. Naldi, et al., SBML
920 qualitative models: a model representation format and infrastructure to
921 foster interactions between qualitative modelling formalisms and tools,
922 *BMC Syst. Biol.* 7 (2013) 1–15.
- 923 [27] S. M. Keating, D. Waltemath, M. König, F. Zhang, et al., SBML Level
924 3: an extensible format for the exchange and reuse of biological models,
925 *Mol. Syst. Biol.* 16 (2020) e9110.
- 926 [28] C. Chaouiya, A. Naldi, D. Thieffry, Logical modelling of gene regulatory
927 networks with GINsim, in: *Bacterial Molecular Networks*, Springer,
928 2012, pp. 463–479.
- 929 [29] A. Naldi, P. T. Monteiro, C. Müssel, C. for Logical Models, Tools,
930 H. A. Kestler, D. Thieffry, I. Xenarios, J. Saez-Rodriguez, T. Helikar,
931 C. Chaouiya, Cooperative development of logical modelling standards
932 and tools with CoLoMoTo, *Bioinform.* 31 (2015) 1154–1159.
- 933 [30] C. Müssel, M. Hopfensitz, H. A. Kestler, BoolNet - an R package for
934 generation, reconstruction and analysis of Boolean networks, *Bioinform.*
935 26 (2010) 1378–1380.
- 936 [31] D. Angeli, P. D. Leenheer, E. Sontag, A Petri net approach to persistence
937 analysis in chemical reaction networks, in: *Biology and Control Theory:
938 Current Challenges*, Springer, 2007, pp. 181–216.
- 939 [32] D. Angeli, P. D. Leenheer, E. D. Sontag, Persistence results for chemical
940 reaction networks with time-dependent kinetics and no global conserva-
941 tion laws, *SIAM J. Appl. Math.* 71 (2011) 128–146.
- 942 [33] E. Degrand, F. Fages, S. Soliman, Graphical conditions for rate inde-
943 pendence in chemical reaction networks, in: *International Conference on
944 Computational Methods in Systems Biology*, Springer, 2020, pp. 61–78.
- 945 [34] G. Liu, K. Barkaoui, A survey of siphons in Petri nets, *Inf. Sci.* 363
946 (2016) 198–220.

- 947 [35] V. Trinh, K. Hiraishi, B. Benhamou, Computing attractors of large-scale
948 asynchronous Boolean networks using minimal trap spaces, in: ACM
949 International Conference on Bioinformatics, Computational Biology and
950 Health Informatics, ACM, 2022, pp. 13:1–13:10.
- 951 [36] E. Demirović, G. Chu, P. J. Stuckey, Solution-based phase saving for
952 CP: A value-selection heuristic to simulate local search behavior in com-
953 plete solvers, in: International Conference on Principles and Practice of
954 Constraint Programming, Springer, 2018, pp. 99–108.
- 955 [37] N. Nethercote, P. J. Stuckey, R. Becket, S. Brand, G. J. Duck, G. Tack,
956 MiniZinc: Towards a standard CP modelling language, in: Interna-
957 tional Conference on Principles and Practice of Constraint Program-
958 ming, Springer, 2007, pp. 529–543.
- 959 [38] A. Ignatiev, A. Morgado, J. Marques-Silva, RC2: an efficient MaxSAT
960 solver, *J. Satisf. Boolean Model. Comput.* 11 (2019) 53–64.
- 961 [39] M. Gebser, B. Kaufmann, R. Kaminski, M. Ostrowski, T. Schaub,
962 M. Schneider, Potassco: The Potsdam answer set solving collection,
963 *AI Commun.* 24 (2011) 107–124.
- 964 [40] J. Forrest, T. Ralphs, H. G. Santos, S. Vigerske, J. Forrest, L. Hafer,
965 B. Kristjansson, jpfasano, EdwinStraver, M. Lubin, rlougee, jp-
966 goncall, Jan-Willem, h-i gassmann, S. Brito, Cristina, M. Saltz-
967 man, tosttost, B. Pitrus, F. MATSUSHIMA, to st, coin-or/Cbc: Re-
968 lease releases/2.10.8, 2022. URL: [https://doi.org/10.5281/zenodo.](https://doi.org/10.5281/zenodo.6522795)
969 [6522795](https://doi.org/10.5281/zenodo.6522795).
- 970 [41] V. Singh, M. Ostaszewski, G. D. Kalliolias, G. Chiocchia, R. Olasso,
971 E. Petit-Teixeira, T. Helikar, A. Niarakis, Computational systems bi-
972 ology approach for the study of rheumatoid arthritis: from a molecular
973 map to a dynamical model, *Genom. Comput. Biol.* 4 (2018) 100050.
- 974 [42] S. Ogishima, S. Mizuno, M. Kikuchi, A. Miyashita, R. Kuwano,
975 H. Tanaka, J. Nakaya, AlzPathway, an updated map of curated sig-
976 naling pathways: towards deciphering Alzheimer’s disease pathogenesis,
977 in: *Systems Biology of Alzheimer’s Disease*, Springer, 2016, pp. 423–432.

978 [43] C. Kadelka, T.-M. Butrie, E. Hilton, J. Kinseth, H. Serdarevic, A meta-
979 analysis of Boolean network models reveals design principles of gene
980 regulatory networks, arXiv preprint arXiv:2009.01216 (2020).

981 [44] E. C. Chávez-Hernández, S. Quiroz, B. García-Ponce, E. R. Álvarez-
982 Buylla, The flowering transition pathways converge into a complex gene
983 regulatory network that underlies the phase changes of the shoot apical
984 meristem in *Arabidopsis thaliana*, *Front. Plant Sci.* 13 (2022) 852047.

985 [45] A. Yachie-Kinoshita, K. Onishi, J. Ostblom, M. A. Langley, E. Posfai,
986 J. Rossant, P. W. Zandstra, Modeling signaling-dependent pluripotency
987 with Boolean logic to predict cell fate transitions, *Mol. Syst. Biol.* 14
988 (2018) e7952.

989 [46] M. R. Vega, Analyzing toys models of *Arabidopsis* and *Drosophila* us-
990 ing Z3 SMT-LIB, in: *Independent Component Analyses, Compressive*
991 *Sampling, Wavelets, Neural Net, Biosystems, and Nanoengineering XII*,
992 volume 9118, SPIE, 2014, pp. 240–254.

993 [47] E. Cacace, S. Collombet, D. Thieffry, Logical modeling of cell fate
994 specification—Application to T cell commitment, in: *Current Topics in*
995 *Developmental Biology*, Elsevier, 2020, pp. 205–238.

996 [48] P. Dutta, L. Ma, Y. Ali, P. M. Sloom, J. Zheng, Boolean network model-
997 ing of B-cell apoptosis and insulin resistance in type 2 diabetes mellitus,
998 *BMC Syst. Biol.* 13 (2019) 1–12.

999 [49] K. F. Corral-Jara, C. Chauvin, W. Abou-Jaoudé, M. Grandclaude,
1000 A. Naldi, V. Soumelis, D. Thieffry, Interplay between SMAD2 and
1001 STAT5A is a critical determinant of IL-17A/IL-17F differential expres-
1002 sion, *Mol. Biomed.* 2 (2021) 1–16.

1003 [50] E. Guberman, H. Sherief, E. R. Regan, Boolean model of anchorage
1004 dependence and contact inhibition points to coordinated inhibition but
1005 semi-independent induction of proliferation and migration, *Comput.*
1006 *Struct. Biotechnol. J.* 18 (2020) 2145–2165.

1007 [51] E. Sullivan, M. Harris, A. Bhatnagar, E. Guberman, I. Zonfa, E. R. Re-
1008 gan, Boolean modeling of mechanosensitive Epithelial to Mesenchymal
1009 Transition and its reversal, *bioRxiv* (2022).

- 1010 [52] N. Weinstein, L. Mendoza, I. Gitler, J. Klapp, A network model to
 1011 explore the effect of the micro-environment on endothelial cell behavior
 1012 during angiogenesis, *Front. Physiol.* 8 (2017) 960.
- 1013 [53] T. Lubitz, N. Welkenhuysen, S. Shashkova, L. Bendrioua, S. Hohmann,
 1014 E. Klipp, M. Krantz, Network reconstruction and validation of the
 1015 Snf1/AMPK pathway in baker’s yeast based on a comprehensive litera-
 1016 ture review, *npj Syst. Biol. Appl.* 1 (2015) 1–10.
- 1017 [54] C. Hernandez, M. Thomas-Chollier, A. Naldi, D. Thieffry, Computa-
 1018 tional verification of large logical models—Application to the prediction
 1019 of T cell response to checkpoint inhibitors, *Front. Physiol.* 11 (2020)
 1020 558606.
- 1021 [55] M. Ostaszewski, A. Niarakis, A. Mazein, I. Kuperstein, R. Phair,
 1022 A. Orta-Resendiz, V. Singh, S. S. Aghamiri, M. L. Acencio, E. Glaab,
 1023 et al., COVID19 Disease Map, a computational knowledge repository of
 1024 virus–host interaction mechanisms, *Mol. Syst. Biol.* 17 (2021) e10387.