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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 use thresholds or equivalently logical functions to represent the different regulations [1, 2, 3, 4].

Boolean modeling made available some powerful analyses and corresponding insight for gene regulation models. Then, over the years, its use increased even for modelling post-transcriptional mechanisms, supported by the many cases where precise biological data was not sufficiently available to build a detailed quantitative model [5]. This lack of data is more frequent for large and very large models, which led to a steady increase in the size of logical models *à la* Thomas [6]. The main analysis tool for such models is the computation of its fixed and periodic attractors, 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 and for which only simulation was available. However, with the most recent models both being quite large and using rather complex 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-implicant 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

¹<https://github.com/bnediction/mpbn>

30 (up to 100,000 nodes). However, this method is only applicable for *locally-*
31 *monotonic* Boolean networks, whereas the prime implicants based method [7]
32 is applicable for *general* Boolean networks (i.e., including both locally-mono-
33 tonic and non-locally-monotonic ones). In addition, the bioLQM platform
34 also provides another method using Binary Decision Diagrams (BDDs) in
35 <http://colomoto.org/biolqm/doc/tools-trap-space.html>. This method
36 avoids the prime-implicant computation as it characterizes the set of generic
37 trap spaces of a Boolean network by a BDD, then filters this set to get the
38 set of all minimal trap spaces. By this approach, it requires the computation
39 of all solutions, whereas the methods [7, 9] based on Answer Set Program-
40 ming (ASP) can start enumerating them as they are found. Moreover, the
41 main issue with this BDD-based method is that the number of generic trap
42 spaces of a Boolean network may be extremely larger than its number of
43 minimal trap spaces. This issue limits the efficiency of the current BDD-
44 based method. The study [10] highlights the need for non-locally-monotonic
45 Boolean networks in both biological and theoretical aspects. Hence, it is still
46 necessary to develop efficient methods for computing minimal trap spaces of
47 large-scale general Boolean networks.

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

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

68 original model. We then demonstrate its efficiency and compare it to the
69 state-of-the-art methods for computing minimal trap spaces of Boolean net-
70 works on many real-world models from various sources in the literature and
71 on randomly generated models.

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

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

101 2. Preliminaries

102 We shall briefly recall here some preliminaries on Boolean networks re-
103 lated to trap spaces and Petri nets.

104 *2.1. Boolean networks*

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

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

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

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

$$s'(v_i) = f_i(s)$$

121 where s (resp. s') is the state of \mathcal{N} at time t (resp. $t + 1$). Note that for sim-
122 plicity, we write $f_i(s)$ even if $IN(v_i) \subsetneq V$ (i.e., $IN(v_i)$ does not contain some
123 nodes of V). An update scheme of a Boolean network specifies the way that
124 the nodes update their states through time evolution [20]. There are many
125 different update schemes, but the two main types [20] are: *synchronous*,
126 where all the nodes are updated simultaneously, and *fully asynchronous*,
127 where only one node is selected non-deterministically to be updated. Follow-
128 ing the update scheme, the Boolean network transits from a state to another
129 state (possibly identical). This transition is called the *state transition* and
130 denoted by $\rightarrow \subseteq \mathcal{S}_{\mathcal{N}} \times \mathcal{S}_{\mathcal{N}}$. For example, under the synchronous update
131 scheme, we have $x \rightarrow y$ if and only if $y(v_i) = f_i(x), \forall v_i \in V$, whereas under
132 the fully asynchronous update scheme, we have $x \rightarrow y$ if and only if there
133 is a node $v_i \in V$ such that $y(v_i) = f_i(x)$ and $y(v_j) = x(v_j), \forall v_j \in V, j \neq i$.
134 Then the dynamics of \mathcal{N} is captured by the directed graph $(\mathcal{S}_{\mathcal{N}}, \rightarrow)$ called
135 the State Transition Graph (STG).

136 *2.2. Traps spaces*

137 We recall here some definitions from [7] for the introduction of *trap spaces*.
 138 Minimal trap spaces prove to be a very good approximation of the attractors
 139 of a Boolean network under asynchronous update schemes and have become
 140 the *de facto* standard way to analyze models of a few tens of *genes* [21, 22].

141 A non-empty set $T \subseteq \mathcal{S}_{\mathcal{N}}$ is a *trap set* with respect to \rightarrow if for every
 142 $x \in T$ and $y \in \mathcal{S}_{\mathcal{N}}$ with $x \rightarrow y$ it holds that $y \in T$ [7]. An attractor of
 143 \mathcal{N} with respect to \rightarrow can be defined as an inclusion-wise minimal trap set
 144 of $(\mathcal{S}_{\mathcal{N}}, \rightarrow)$. An attractor can be also seen as a terminal strongly connected
 145 component of $(\mathcal{S}_{\mathcal{N}}, \rightarrow)$ [23]. An attractor of size 1 is called a fixed point,
 146 otherwise it is called a cyclic or complex attractor [7].

147 A subspace m of a Boolean network $\mathcal{N} = (V, F)$ is a mapping $m: V \mapsto$
 148 $\mathbb{B} \cup \{\star\}$. $m(v_i) \in \mathbb{B}$ means that the value of v_i is fixed in m and v_i is called
 149 a *fixed* variable. $m(v_i) \in \star$ means that the value of v_i is free in m and v_i is
 150 called a *free* variable. We denote D_m the set of all fixed variables of m . A
 151 subspace m is equivalent to a set of states:

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

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

156 A *trap space* is defined as a subspace that is also a trap set. It is noted
 157 that trap spaces of a Boolean network are independent of the update scheme
 158 of this model [7], we provide in Corollary 3.1 another proof of this. Then, we
 159 define a partial order $<$ on $\mathcal{S}_{\mathcal{N}}^{\star}$ as: $m < m'$ if and only if $\mathcal{S}_{\mathcal{N}}[m] \subseteq \mathcal{S}_{\mathcal{N}}[m']$
 160 and $\mathcal{S}_{\mathcal{N}}[m] \neq \mathcal{S}_{\mathcal{N}}[m']$. Consequently, a trap space m is minimal if and only
 161 if there is no trap space $m' \in \mathcal{S}_{\mathcal{N}}^{\star}$ such that $m' < m$.

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

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

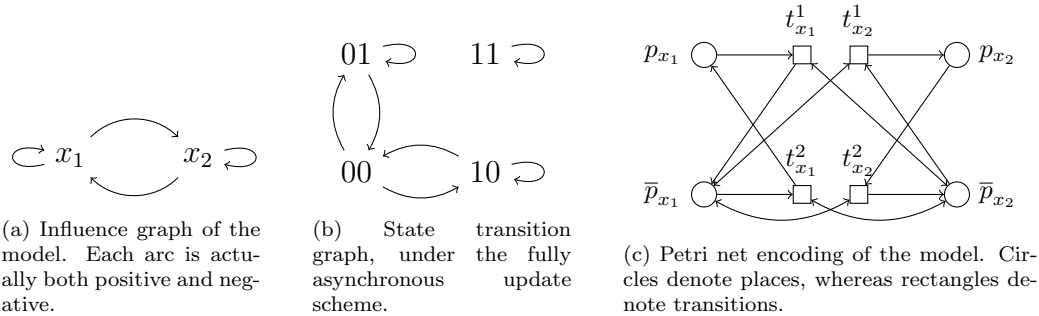


Figure 1: Influence graph, dynamics, and Petri net encoding of the Boolean network of Example 2.1.

171 *2.3. Petri net encoding of Boolean networks*

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

176 A *marking* for a Petri net is a mapping $M : P \mapsto \mathbb{N}$ that assigns a number
 177 of tokens to each place. A place p is *marked* by a marking M if and only
 178 if $M(p) > 0$. We shall write $\text{pred}(x)$ (resp. $\text{succ}(x)$) to represent the set of
 179 vertices that have a (non-zero weighted) arc leading to (resp. coming from)
 180 x . In this work, we consider a class of Petri nets called 1-safe Petri nets
 181 where every place has at most 1 token and all arcs are of weight 1. Note
 182 that in such nets we have $M : P \mapsto \{0, 1\}$, we might therefore represent a
 183 marking by the equivalent set of places containing a token and will use this
 184 notation for simplicity. In this case, weights are implicitly omitted in the
 185 arcs of a Petri net. Then, a transition $t \in T$ is *enabled* at a marking M
 186 and only if $\text{pred}(t) \subseteq M$. A marking M is called a *deadlock* if there are no
 187 enabled transitions at M . The firing of t leads to a new marking M' specified
 188 by $M' = (M \setminus \text{pred}(t)) \cup \text{succ}(t)$. Note that when multiple transitions are
 189 enabled, we need to embed one firing scheme (similar to the update scheme
 190 of a Boolean network) to the Petri net. The classical firing scheme is that
 191 only one of the enabled transition is non-deterministically chosen to fire [12].

192 The link between Boolean networks *à la* Thomas and Petri nets was
 193 originally established in [24] in order to make available formal methods like
 194 model-checking for the analysis of such systems. The basic encoding into 1-
 195 safe (i.e., never more than one token in each place) nets only holds for purely

196 Boolean networks but was later extended to multivalued logical models in
 197 two ways, either in [25] with non 1-safe Petri nets or more recently in [23]
 198 with 1-safe nets but many more places.

199 Since our study is focused on Boolean networks, we briefly recall the origi-
 200 nal encoding here. Its basis is that every node (*gene*) v of the original model
 201 $\mathcal{N} = (V, F)$ is represented by two separate places (p_v and \bar{p}_v), correspond-
 202 ing to its two states, active, and inactive, respectively. Each conjunct of the
 203 logical function that activates the *gene* will lead to a transition t , consuming
 204 the inactive place (i.e., a directional arc from \bar{p}_v to t), producing the active
 205 place (i.e., a directional arc from t to p_v), and with all other literals both
 206 consumed and produced (i.e., a bidirectional arc). Conversely a transition
 207 is added from the active place to the inactive place for each conjunct of the
 208 negation of that function. Let s be a state of the Boolean network and M_s
 209 be its corresponding marking in the encoded Petri net. It holds that $\forall v \in V$,
 210 $s(v) = 0$ if and only if $M_s(\bar{p}_v) = 1$ and $M_s(p_v) = 0$ and $s(v) = 1$ if and only
 211 if $M_s(p_v) = 1$ and $M_s(\bar{p}_v) = 0$. Note also that at any marking M of the Petri
 212 net encoding a Boolean network, it always holds that $M(p_v) + M(\bar{p}_v) = 1$.

213 The main property of this encoding is that it is completely faithful with
 214 respect to the update scheme of the original Boolean network. For each node
 215 v of \mathcal{N} , only transitions corresponding to v can change the current marking
 216 of p_v or \bar{p}_v . In addition, at any marking at most one of such transitions is en-
 217 abled because $M(p_v) + M(\bar{p}_v) = 1$ holds. Hence, for any update scheme in \mathcal{N} ,
 218 we have a corresponding firing scheme in \mathcal{P} , which preserves the equivalence
 219 between the dynamics of \mathcal{N} and \mathcal{P} [26].

220 For illustration, let us reconsider the Boolean network shown in Exam-
 221 ple 2.1. Figure 1(c) shows the Petri net encoding of this Boolean network.
 222 Place p_{x_1} (resp. \bar{p}_{x_1}) in \mathcal{P} represents the activation (resp. the inactivation) of
 223 node x_1 in \mathcal{N} . Marking $\{p_{x_1}, \bar{p}_{x_2}\}$ in \mathcal{P} represents state 10 in \mathcal{N} . Transitions
 224 $t_{x_1}^1$ and $t_{x_1}^2$ represent the update of node x_1 . Of course, in any marking $t_{x_1}^1$
 225 and $t_{x_1}^2$ cannot be both enabled. Then, the fully asynchronous update scheme
 226 in \mathcal{N} corresponds to the classical firing scheme in \mathcal{P} where only one of the
 227 enabled transitions for a given marking will be fired [12].

228 Note that given a Boolean network in the standard SBML-`Qual` format [27],
 229 i.e., the package of SBML v3 [28] for such models, one can easily obtain its
 230 Petri net encoding in the Petri Net Markup Language (PNML)² standard

²<https://www.pnml.org/>

231 using the `bioLQM`³ library. This piece of software extracted from `GINsim` [29]
232 and part of the `CoLoMoTo`⁴ [30] software suite allows for easy conversion
233 between standard formats. It also accepts many other common formats for
234 Boolean networks, notably the `.bnet` files of the `BoolNet` [31, 21] tools. The
235 conversion is executed as follows:

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

237 Note that transforming a Boolean network defined by its functions into its
238 Petri net encoding roughly relies on obtaining conditions for the activation
239 and inactivation of the states. In [24] this took the form of the whole truth
240 table of the Boolean functions, but as shown in Appendix 1 of [23] comput-
241 ing Disjunctive Normal Forms (DNF) of each Boolean function is enough.
242 Though this might appear quite computationally intensive it is important to
243 remark first that contrary to the prime implicants case, there is no need to
244 find *minimal* DNFs. One way to look at this is to consider that this amounts
245 to a similar approach as that used in [8] but with the encoding of both activa-
246 tion and inhibition functions as DNFs in order to take into account possible
247 non-local-monotonicity. This does not change the worst-case-complexity (ob-
248 taining a single DNF being exponential) but might matter a lot in practice.
249 As such, we will explore how this transformation, here using BDDs in `bioLQM`
250 or directly in our tool using the `pyeda`⁵ library, and the one based on the
251 most-permissive semantics compare with each other in Section 6.

252 2.4. Siphons

253 Siphons are a static and classical property of Petri nets [11]. Note how-
254 ever that the use of siphons for the analysis of biological models, though it is
255 not new, has been mostly relevant to the ODE-based continuous semantics
256 of chemical reaction networks [32, 33, 34]. We recall here the basic definition
257 establishing that to produce something in a siphon you must consume some-
258 thing from the siphon. This corresponds to the idea that a siphon is a set of
259 places that once unmarked remains unmarked.

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

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

³<http://www.colomoto.org/biolqm/>

⁴<http://colomoto.org/>

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

262 Note that \emptyset is trivially a siphon.

263 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
 264 conventionally $\text{pred}(S) = \text{succ}(S) = \emptyset$. We have an important property on
 265 siphons [35] as follows.

266 **Proposition 2.1.** *A set S of places is a siphon of a Petri net (P, T, W) if
 267 and only if $\text{pred}(S) \subseteq \text{succ}(S)$.*

268 3. Trap spaces as conflict-free siphons

269 First let us associate subspaces and sets of places in the Petri net encod-
 270 ing.

271 **Definition 3.1.** *Let m be a subspace of Boolean network $\mathcal{N} = (V, F)$. A
 272 mirror of m is a set of places S in the Petri net encoding \mathcal{P} of \mathcal{N} such that:*

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

273 and

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

274 Now, we add a definition related to any set of places of a Petri net en-
 275 coding a Boolean network, and notably a siphon of such a net.

276 **Definition 3.2.** *A set of places of Petri net \mathcal{P} encoding Boolean network
 277 \mathcal{N} is conflict-free if it does not contain any two places corresponding to the
 278 active and inactive states of the same node of \mathcal{N} . Then, a conflict-free siphon
 279 S is said to be maximal if and only if there is no other conflict-free siphon
 280 S' such that $S \subset S'$.*

281 Intuitively, a siphon is a set of places that once unmarked remains so. If
 282 it is conflict-free it is possible to associate a subspace to it, more precisely it
 283 is the *mirror* of a subspace. Since it is a siphon, the fixed values will remain
 284 so whatever update happens, as the unmarked places remain unmarked. The
 285 subspace corresponding to that conflict-free siphon is therefore a trap space,
 286 and the maximality of the siphon is equivalent to the minimality of the trap
 287 space (as many fixed values as possible). For example, the Boolean network
 288 given in Example 2.1 has two trap spaces, $m_1 = 11$ and $m_2 = \star\star$. The
 289 Petri net encoding of this Boolean network has five generic siphons, $S_1 = \emptyset$,
 290 $S_2 = \{p_{x_1}, \bar{p}_{x_1}\}$, $S_3 = \{p_{x_2}, \bar{p}_{x_2}\}$, $S_4 = \{\bar{p}_{x_1}, \bar{p}_{x_2}\}$, and $S_5 = \{p_{x_1}, \bar{p}_{x_1}, p_{x_2}, \bar{p}_{x_2}\}$.

291 However, only S_1 and S_4 are conflict-free siphons and correspond to m_2 and
 292 m_1 , respectively. Since $S_1 \subset S_4$, S_4 is a maximal siphon corresponding to
 293 the minimal trap space m_1 . Hereafter, we formally prove that a (maximal)
 294 conflict-free siphon is equivalent to a (minimal) trap space.

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

298 *Proof.* First, we show that if m is a trap space of \mathcal{N} , then S is a conflict-free
 299 siphon of \mathcal{P} (*).

300 If $D_m = \emptyset$, then $S = \emptyset$ is trivially a conflict-free siphon of \mathcal{P} . Thus,
 301 we consider the case that $D_m \neq \emptyset$ (resp. $S \neq \emptyset$). Assume that S is not a
 302 siphon of \mathcal{P} . Then, there is a transition $t \in T$ such that $S \cap \text{succ}(t) \neq \emptyset$
 303 but $S \cap \text{pred}(t) = \emptyset$. This implies that there is a place $p \in S$ such that
 304 $p \in \text{succ}(t)$ but $p \notin \text{pred}(t)$. Let v be the node in \mathcal{N} corresponding to p . By
 305 the characteristics of the encoding [24], there is a directional arc from t to p
 306 and a directional arc from the complementary place of p to t . Without loss
 307 of generality, we assume that $p = p_v$, then there is a directional arc from t
 308 to p_v and a directional arc from \bar{p}_v to t .

309 We follow the following procedure to find a state $s \in \mathcal{S}_{\mathcal{N}}[m]$ such that
 310 $M_s(p') = 1, \forall p' \in \text{pred}(t)$ where M_s is the corresponding marking in \mathcal{P} of s .
 311 For every place $p' \in \text{pred}(t)$, let p'' be the complementary place of p' and v'
 312 be the corresponding node in \mathcal{N} of p' and p'' .

313 If $p'' \notin S$, then $v' \notin D_m$ and we can always set the Boolean value to $s(v')$
 314 such that $s \in \mathcal{S}_{\mathcal{N}}[m]$ and $M_s(p') = 1$.

315 If $p'' \in S$, then $v' \in D_m$ and we set $s(v') = m(v')$. In this case, if
 316 $p' = p_{v'}$ then $s(v') = m(v') = 1$ leading to $M_s(p') = 1$, if $p' = \bar{p}_{v'}$ then
 317 $s(v') = m(v') = 0$ leading to $M_s(p') = 0$.

318 For the remaining nodes of \mathcal{N} , we can always set Boolean values to these
 319 nodes to preserve that $s \in \mathcal{S}_{\mathcal{N}}[m]$ by applying the same procedure. We also
 320 have $M_s(p_v) = 0$ by the characteristics of the encoding [24] (and Definition
 321 3.1). Now, t is enabled at marking M_s . Its firing leads to a new marking
 322 M'_s such that $M'_s(p_v) = 1$ and $M'_s(\bar{p}_v) = 0$. Let s' be the corresponding state
 323 in \mathcal{N} of M'_s . We have $s'(v) = 1$ because $M'_s(p_v) = 1$ and $m(v) = 0$ because
 324 $p_v \in S$. This implies that $s' \notin \mathcal{S}_{\mathcal{N}}[m]$.

325 For any firing scheme of \mathcal{P} , the firing of t always happens. Since a firing
 326 scheme of \mathcal{P} is equivalent to an update scheme of \mathcal{N} , s can escape from the
 327 trap space m for any update scheme of \mathcal{N} , which contradicts to the property

328 of a trap space. Hence, S is a siphon of \mathcal{P} . By the definition of a mirror, S
 329 is also a conflict-free one.

330 *Second, we show that if S is a conflict-free siphon of \mathcal{P} , then m is a trap*
 331 *space of \mathcal{N} (**).*

332 By the definition of a mirror, m is a subspace of \mathcal{N} . Let s be an arbitrary
 333 state in $\mathcal{S}_{\mathcal{N}}[m]$ and M_s be its corresponding marking in \mathcal{P} . Assume that
 334 there is a place $p \in S$ such that $M_s(p) = 1$. Let v be the corresponding node
 335 in \mathcal{N} of p . Since $p \in S$, $v \in D_m$ and $m(v) = s(v)$. If $p = p_v$, then $M_s(p_v) = 1$
 336 leading to $m(v) = s(v) = 1$ by the characteristics of the encoding [24]. By the
 337 definition of a mirror, $m(v) = 0$ because $p_v \in S$, meaning that $M_s(p_v) = 0$,
 338 which is a contradiction.

339 It is symmetric for the case that $p = \bar{p}_v$. Hence, $M_s(p) = 0, \forall p \in S$. In any
 340 marking M'_s reachable from M_s regardless of the firing scheme of \mathcal{P} , we have
 341 $M'_s(p) = 0, \forall p \in S$ by the dynamical property on markings of a siphon [35].
 342 Let s' be the corresponding state in \mathcal{N} of M'_s . For every node $v \in D_m$,
 343 we have all two cases as follows. Case 1: $p_v \in S$, then $M'_s(p_v) = 0$, thus
 344 $s'(v) = 0 = m(v)$. Case 2: $\bar{p}_v \in S$, then $M'_s(\bar{p}_v) = 0$, thus $s'(v) = 1 = m(v)$.
 345 Hence, $s'(v) = m(v)$ for every $v \in D_m$. Then, $s' \in \mathcal{S}_{\mathcal{N}}[m]$. By the definition
 346 of a trap space and the arbitrariness of s , m is a trap space of \mathcal{N} .

347 From (*) and (**), we can conclude the proof. □

348 Note that this proof gives us as corollary a well-known result on trap
 349 spaces.

350 **Corollary 3.1.** *Trap spaces of a Boolean network are independent of the*
 351 *update scheme.*

352 *Proof.* From the proof of Theorem 3.1, we can see that the theorem holds
 353 for any update scheme associated to the Boolean network. Since the Petri
 354 net encoding of a Boolean network is independent of its update scheme and
 355 siphons are a static property of a Petri net, we get that trap spaces of a
 356 Boolean network are independent of its update scheme. □

357 Note that the original proof for this property of trap spaces (see Theorem
 358 1 of [7]) only considers the two popular update schemes (i.e., synchronous
 359 and fully asynchronous). Theorem 3.1 exhibits the very first theoretical
 360 application of the connection between trap spaces of Boolean networks and
 361 siphons of Petri nets.

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

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

373 Second, we show that if S is a maximal conflict-free siphon of \mathcal{P} , then
 374 m is a minimal trap space of \mathcal{N} (**). Since S is a conflict-free siphon of \mathcal{P} ,
 375 m is a trap space of \mathcal{N} by Theorem 3.1. Assume that m is not minimal.
 376 Then, there is another trap space m' such that $m' < m$. By the definition of
 377 the partial order $<$ on subspaces, $\mathcal{S}_{\mathcal{N}}[m'] \subset \mathcal{S}_{\mathcal{N}}[m]$. Let S' be the mirror of
 378 m' . S' is a conflict-free siphon by Theorem 3.1. Following the definition of
 379 a mirror, $S \subset S'$, which contradicts to the maximality of S . Hence, m is a
 380 minimal trap space of \mathcal{N} .

381 From (*) and (**), we can conclude the proof. □

382 We here showcase a theoretical application of the connection between
 383 trap spaces in Boolean networks and conflict-free siphons in Petri nets. We
 384 use it to prove a property of minimal trap spaces, which has surprisingly
 385 not been formally proved. Specifically, all minimal trap spaces of a Boolean
 386 network are mutually disjoint. This property is important because it can
 387 benefit attractor identification of Boolean networks. Specifically, in [36], the
 388 authors use random walks inside each minimal trap space to obtain approx-
 389 imations for attractors of a Boolean network under the fully asynchronous
 390 update scheme, then they use CTL model checking to verify the quality of
 391 the approximations. In [37], the authors use the set of minimal trap spaces
 392 as a seed to speedup their previous attractor identification method that re-
 393 lies on feedback vertex sets and reachability analysis. The soundness of the
 394 two above approaches comes from the separation of minimal trap spaces.
 395 Note that it would be not difficult to obtain a direct proof on trap spaces
 396 for this property, which follows the same structure as the proof on siphons.
 397 However, we emphasize here the potential of using the connection between

398 Boolean networks and Petri nets to explore and prove properties of trap
 399 spaces in Boolean networks.

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

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

407 Consider two any distinct minimal trap spaces m_1 and m_2 . Assume that
 408 $\mathcal{S}_{\mathcal{N}}[m_1] \cap \mathcal{S}_{\mathcal{N}}[m_2] \neq \emptyset$. Let S_1 and S_2 be the mirrors of m_1 and m_2 , re-
 409 spectively. By Theorem 3.2, S_1 and S_2 are maximal conflict-free siphons
 410 of \mathcal{P} . We have that $S = S_1 \cup S_2$ is also a siphon because of Proposi-
 411 tion 2.1. For every node $v \in V$, assume that $p_v \in S$ and $\bar{p}_v \in S$ hold.
 412 Since S_1 and S_2 are conflict-free, there are all two cases. Case 1: $p_v \in S_1$
 413 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
 414 $m_1(v) \neq m_2(v), m_1(v) \neq \star, m_2(v) \neq \star$, then $\mathcal{S}_{\mathcal{N}}[m_1] \cap \mathcal{S}_{\mathcal{N}}[m_2] = \emptyset$. This is a
 415 contradiction. Hence, for every node $v \in V$, $p_v \in S$ and $\bar{p}_v \in S$ cannot hold
 416 together. Therefore, S is conflict-free. Now, we have that S is a conflict-free
 417 siphon but $S_1 \subset S$ or $S_2 \subset S$ holds because $S_1 \neq S_2$. This contradicts to the
 418 maximality of S_1 and S_2 . Hence, $\mathcal{S}_{\mathcal{N}}[m_1] \cap \mathcal{S}_{\mathcal{N}}[m_2] = \emptyset$ holds.

419 □

420 A natural computational application of Theorem 3.1 is that we can effi-
 421 ciently decide whether a subspace m is a trap space. In PyBoolNet [21], this
 422 is checked by using the percolation on the prime implicants of the Boolean
 423 functions. As we have mentioned at the beginning of this article, the compu-
 424 tation of prime implicants is a demanding task for complex Boolean networks,
 425 even is sometimes intractable. Hence, the checking method in [21] shows its
 426 limitations. Instead, we can first compute the mirror S_m of m in the Petri
 427 net encoding. Then, by Proposition 2.1 and Theorem 3.1, we can check if
 428 $\text{pred}(S_m) \subseteq \text{succ}(S_m)$. Note that the Petri net construction is less com-
 429 putationally demanding than the prime-implicant computation because it
 430 only requires computing generic (not prime) implicants of the Boolean func-
 431 tions [23]. In addition, the worst case time complexity of the above checking
 432 method is quadratic in the number of transitions of the Petri net.

433 Furthermore, by Theorem 3.2, we can reduce the problem of computing
434 all minimal trap spaces of a Boolean network to the problem of computing
435 all maximal conflict-free siphons of its Petri net encoding. Note that in
436 the case of special types of trap spaces (e.g., fixed points), this can be put
437 in regard to special types of siphons in Petri nets. See Subsection 4.5 for
438 more discussions about many special types of trap spaces. It might actually
439 be possible to generalize our result to any 1-safe place-complementary (i.e.,
440 places are defined by pairs such that the markings are complementary) Petri
441 net to define a notion of trap spaces that might be useful for the analysis of
442 Petri nets, but this is out of the scope of the present article. Note also that
443 conversely, investigating static analyses on such 1-safe place-complementary
444 nets might allow for a more efficient computation of their siphons and hence
445 of trap spaces.

446 Note that there are no existing methods specifically designed for comput-
447 ing maximal conflict-free siphons (even maximal generic siphons) of a Petri
448 net. The reason might be that researchers mainly focus on minimal generic
449 siphons [35] in the field of Petri nets. While adapting those methods to ob-
450 tain minimal conflict-free siphons would sometimes be possible, the switch
451 from minimality to maximality is quite a leap. Hence, we here propose sev-
452 eral methods for computing maximal conflict-free siphons of a Petri net. The
453 details of the proposed methods shall be given in the next section.

454 4. Computation methods

455 First, we discuss the complexity of siphon computation in Petri nets.
456 Siphons are a prominent concept in the field of Petri nets, but unfortunately
457 there are very few studies focusing on the complexity aspect. In this field,
458 researchers mainly focus on practical methods for computing minimal generic
459 siphons (also many related types) in general or special Petri nets and the
460 applications of such types to the control of real-world systems modeled by
461 Petri nets [35]. The problem of finding a minimal siphon of a 1-safe Petri
462 net is solvable in polynomial time [38]. Clearly, the problem of finding a
463 siphon of a 1-safe Petri net is also solvable in polynomial time. However, the
464 problem of computing all (minimal) siphons is not easier than the problem
465 of computing a (minimal) siphon but its complexity still not clear. Note
466 that the number of siphons (even minimal siphons) can be exponential in
467 the number of places of the Petri net [35]. Moreover, there is no complexity
468 result for the case of maximal siphons. Regarding the conflict-free siphons,

469 we believe that the polynomial algorithm for computing a minimal generic
470 siphon presented in [38] can be adapted to find a (minimal) conflict-free
471 siphon. This is not in contrast to the NP-hardness of some problems on trap
472 spaces in Boolean networks [39] because in general the number of transitions
473 of the Petri net encoding of a Boolean network can be exponential in the
474 number of nodes of this Boolean network. However, again the complexity of
475 the problem of computing all (minimal/maximal) conflict-free siphons is still
476 open.

477 4.1. Characterization

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

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

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

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

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

490 4.2. Constraint satisfaction problem

491 A Constraint Satisfaction Problem (CSP) is defined by a triple giving
492 its variables, their domains, and the constraints on those variables. The
493 following Boolean CSP directly derives from the above characterization:

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

- 496 • $R = P$, i.e., a variable is introduced for each place of \mathcal{P} ,

- 497 • $D(p) = \mathbb{B}$ for all $p \in R$, i.e., the variables are Boolean,
- 498 • $C = \{\neg p_v \vee \neg \bar{p}_v = 1 \mid \forall v \in V\} \wedge \{(p = 1 \rightarrow \bigvee_{p' \in \text{pred}(t)} p' = 1) \mid p \in$
- 499 $P, t \in \text{pred}(p)\}$.

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

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

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

502 *Proof.* By the former part $\neg p_v \vee \neg \bar{p}_v = 1$ of C , the conflict-freeness is imposed
 503 because for any satisfiable valuation r , $r(p_v) = r(\bar{p}_v) = 1$ is impossible for all
 504 $v \in V$. As shown in [17], the latter part of C can characterize the set of all
 505 generic siphons of \mathcal{P} . Hence, we can conclude the proof. □

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

516 One natural question is that how to use the CSP-based method for enu-
 517 merating all the maximal conflict-free siphons of a Petri net encoding a
 518 Boolean network? Of course, the set of all conflict-free siphons of the Petri
 519 net can easily be characterized by the CSP model presented in [17] along with
 520 the additional constraint $\neg p_v \vee \neg \bar{p}_v = 1$, for each $v \in V$, which represents
 521 the conflict-freeness. However, the main concern is to enumerate all the
 522 *maximal* ones, which is not trivial to adapt from the CSP-based method.
 523 By Proposition 4.1, the set of all maximal conflict-free siphons of \mathcal{P} can be
 524 enumerated in the (maximality) set inclusion order, by restarting the search
 525 each time a conflict-free siphon S is found, with the following additional con-
 526 straint for disallowing any subset of that conflict-free siphon: $\bigvee_{p \notin S} p = 1$.
 527 For enumerating conflict-free siphons in the set inclusion order, we can use
 528 the same technique as used in [17] but with the opposite setting, i.e., labeling

529 directly the Boolean variables with decreasing value selection. The correct-
 530 ness of this technique comes from the fact that once S is found, it is the
 531 conflict-free siphon of maximum cardinality among all the remaining feasible
 532 conflict-free siphons. Similar to [17], the newly CSP-based method can also
 533 be implemented with SAT and CP solvers.

534 This method was implemented using the state-of-the-art CP solver Chuffed⁶
 535 [40] via its MiniZinc [41] interface. Because it is a high-level interface, the
 536 backtrack-and-replay method of [17] was not used but rather the alterna-
 537 tive implementation with two global constraints for lexicographic ordering
 538 (ensuring enumeration of solutions) and iterated non-subset of each already
 539 found solution (for maximality).

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

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

543 and

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

544 We set a soft clause for each variable of the CSP and then use a “minimal cor-
 545 rection subset” blocking strategy, which will ensure set-inclusion maximality
 546 of the solutions. We implement this approach by using the RC2 MaxSAT
 547 solver [42] available through the `python-sat` package⁷.

548 4.3. Answer set programming-based method

549 Another possible method is to translate the characterization shown in
 550 Subsection 4.1 into the ASP \mathcal{L} as follows. We introduce atom `p-v` (resp.
 551 `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
 552 as $\mathcal{A} = \bigcup_{v \in V} \{\text{p-v}, \text{n-v}\}$. For each pair (p, t) where $p \in P, t \in T, t \in \text{pred}(p)$,
 553 we translate the rule (1) into the ASP rule

$$\text{a}_1; \dots ; \text{a}_k :- \text{a}.$$

554 where $\text{a} \in \mathcal{A}$ is the atom representing place p and $\{\text{a}_1, \dots, \text{a}_k\} \subseteq \mathcal{A}$ is the
 555 set of atoms representing places in $\text{pred}(t)$. The rule (2) is translated into

⁶<https://github.com/chuffed/chuffed>

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

556 the ASP rule

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

557 for each $v \in V$. This ASP rule guarantees that two places representing
558 the same node in \mathcal{N} never belong to the same siphon of \mathcal{P} , representing
559 the conflict-freeness. Naturally, a Herbrand model (see, e.g., [43]) of \mathcal{L} is
560 equivalent to a conflict-free siphon of \mathcal{P} . To guarantee that a Herbrand
561 model is also a stable model (an answer set), we need to add to \mathcal{L} the two
562 choice rules

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

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

576 Now, a solution (simply an answer set) $A \subseteq \mathcal{A}$ of \mathcal{L} is equivalent to a
577 conflict-free siphon S of \mathcal{P} , thus a trap space m of \mathcal{N} . The conversion from A
578 to m is straightforward. If $\text{p-v} \in A$ then $v \in D_m$ and $m(v) = 0$. Conversely,
579 if $\text{n-v} \in A$ then $v \in D_m$ and $m(v) = 1$. Otherwise, $v \notin D_m$. Comput-
580 ing multiple answer sets is built into ASP solvers and the solving collection
581 POTASSCO [43] also features the option to find set-inclusion maximal answer
582 sets with respect to the set of atoms. Naturally, a set-inclusion maximal
583 answer set of \mathcal{L} is equivalent to a maximal conflict-free siphon of \mathcal{P} , thus a
584 minimal trap space of \mathcal{N} . By using this built-in option, we can compute all
585 the set-inclusion maximal answer sets of \mathcal{L} (resp. all the minimal trap spaces
586 of \mathcal{N}) in one execution.

587 4.4. Integer linear programming-based method

588 We first show how an Integer Linear Programming (ILP) \mathcal{I} can define
589 a set of all conflict-free siphons of the encoded Petri net \mathcal{P} . We introduce

590 *binary* variable $\mathbf{p-v}$ (resp. $\mathbf{n-v}$) to denote place p_v (resp. \bar{p}_v), $\forall v \in V$. The
 591 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
 592 $p \in P, t \in T, t \in \text{pred}(p)$, we translate the rule (1) into the ILP inequality

$$\mathbf{a} \leq \mathbf{a}_{_1} + \dots + \mathbf{a}_{_k}$$

593 where \mathbf{a} is the binary variable representing place p and $\{\mathbf{a}_{_1}, \dots, \mathbf{a}_{_k}\}$ is
 594 the set of binary variables representing places in $\text{pred}(t)$. The rule (2) is
 595 translated into the ILP inequality

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

596 for each $v \in V$. This inequality forbids both $\mathbf{p-v}$ and $\mathbf{n-p}$ receive the value
 597 1, thus representing the conflict-freeness. Since we only consider feasible
 598 solutions, the objective function is set to $\max \mathbf{p-v}$ for some $v \in V$. Naturally,
 599 a solution I of \mathcal{I} is equivalent to a conflict-free siphon S of \mathcal{P} . The conversion
 600 is that

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

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

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

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

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

608 Now, \mathcal{I} can be solved using a general purpose ILP solver. If it admits any so-
 609 lution I^* , the corresponding conflict-free siphon (say S^*) is maximal. Hence,
 610 it makes sense that it does not need to find any other conflict-free siphon
 611 of the net that is strictly contained in S^* . To do this, we add to \mathcal{I} a new
 612 inequality

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

613 where $\mathbf{a-p}$ is the binary variable presenting place p . Now, we solve \mathcal{I} again to
 614 find a new solution. If a new solution I' exists, then let S' be its corresponding

615 conflict-free siphon. Indeed, abide by the newly added inequality, we have
616 $S' \cap (P \setminus S^*) \neq \emptyset$ because there is some $\mathbf{a-p}$ with $p \in P \setminus S^*$ such that
617 $I'(\mathbf{a-p}) = 1$. This implies that it is impossible that $S' = S^*$ or $S' \subset S^*$.
618 By the objective function, it means that S' is the conflict-free siphon of
619 maximum cardinality among the conflict-free siphons that are not contained
620 in S^* . Hence, S' is also a maximal conflict-free siphon. Again, we add to \mathcal{I}
621 a new inequality with respect to the newly found siphon. The above process
622 is iterated until \mathcal{I} becomes unfeasible, this means that there is no further
623 maximal conflict-free siphon. Thus, all the maximal conflict-free siphons of
624 the Petri net have been found.

625 Since we used the MiniZinc framework to interface with the CP solver, it
626 was simple to make the slight modifications described above and to use that
627 same interface to call the Coin-OR CBC solver⁸ [44].

628 4.5. Computation of special types of trap spaces

629 In the field of systems biology, biologists may want to compute more
630 special types of trap spaces beyond minimal trap spaces [21], which also play
631 crucial roles in analysis and control of Boolean networks [22, 19]. We shall
632 show that our proposed methods can be easily adjusted to compute such
633 popular types of trap spaces. We illustrate the adjustments via the ASP-
634 based method (see Subsection 4.3) because ASP is declarative by nature,
635 but these adjustments are completely applicable for other approaches such
636 as MaxSAT, CP, and ILP.

637 First, the work presented in [19] uses the concept of *stable motifs* to build
638 the succession diagram of a Boolean network, a summary of the decisions in
639 the network dynamics that lead to successively more restrictive nested stable
640 motifs. The succession diagram is useful for control and decision making
641 on this Boolean network. In particular, the proposed control methods are
642 independent to the update scheme. Note that, in [19], the succession dia-
643 gram is also used to identify all attractors of a Boolean network under the
644 fully asynchronous update scheme. It has been shown that a stable motif
645 of a Boolean network is equivalent to a *maximal trap space* of this Boolean
646 network [19]. Indeed, the computation of stable motifs is a bottleneck of
647 the methods proposed in [19]. Hence, it is necessary to develop an efficient
648 method for computing maximal trap spaces of a Boolean network. We shall

⁸<https://github.com/coin-or/Cbc>

649 show how to adjust the ASP-method presented in Subsection 4.3 to compute
 650 maximal trap spaces.

651 We first provide the definition of maximal trap spaces. Let ε be the special
 652 trap space of \mathcal{N} where all the nodes are free. Of course, ε corresponds to the
 653 special conflict-free siphon \emptyset . A trap space m is called maximal if $m \neq \varepsilon$ and
 654 there is no other trap space m' such that $m' \neq \varepsilon$ and $m < m'$. Analogously,
 655 a conflict-free siphon S is called minimal if $S \neq \emptyset$ and there is no other
 656 trap space S' such that $S' \neq \emptyset$ and $S' \subset S$. By using the reasoning similar
 657 to the proof of Theorem 3.2, we can easily conclude that a maximal trap
 658 space of \mathcal{N} is equivalent to a minimal conflict-free siphon of its encoded
 659 Petri net \mathcal{P} . Let \mathcal{L} be the ASP characterizing all conflict-free siphons of \mathcal{P}
 660 (see Subsection 4.3). Naturally, we need to exclude \emptyset from the solution space
 661 of \mathcal{L} (equivalently exclude ε from the set of trap spaces). To do this, we add
 662 to \mathcal{L} the ASP rule

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

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

666 Second, we consider *fixed points* in Boolean networks. To date, the anal-
 667 ysis of the fixed points of a Boolean network remains a very useful tool in
 668 understanding the behavior of complex biological models not only due to the
 669 fact that in some cases the full computation of complex attractors remains
 670 intractable, but also because for many biological systems, the expected long-
 671 term behavior is not cyclic [45]. Furthermore, the fixed point computation is
 672 also the crucial starting point for several state-of-the-art methods for com-
 673 puting complex attractors of Boolean networks [37]. Let s be a fixed point of
 674 a Boolean network \mathcal{N} . We have a subspace m corresponding to s as follows:
 675 $\forall v \in V, m(v) = s(v)$, i.e., all nodes are fixed in m . Clearly, s is a trap set
 676 of \mathcal{N} regardless of the update scheme. Hence, m is a trap space of \mathcal{N} . In
 677 addition, since $|S_{\mathcal{N}}[m]| = 1$, m is also a minimal trap space. To compute all
 678 fixed points of \mathcal{N} , we can add more constraints to the encoded ASP charac-
 679 terizing all conflict-free siphons (equivalently trap spaces). For every $v \in V$,
 680 we add to the encoded ASP the rule

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

681 that ensures that for every conflict-free siphon S , it contains either p-v or n-v
 682 for every $v \in V$. Equivalently, the trap space corresponding to S is always

683 a fixed point. Now, the set of answer sets of the encoded ASP is equivalent
 684 to the set of fixed points of \mathcal{N} . In particular, when solving the encoded ASP
 685 using an ASP solver, we do not need to use the built-in option for computing
 686 set-inclusion maximal answer sets. Note that we can also build another ASP
 687 characterizing all fixed points of \mathcal{N} based on the equivalence between a fixed
 688 point of \mathcal{N} and a deadlock of its Petri net encoding [23]. This approach may
 689 give a more compact ASP.

690 Third, we consider the trap spaces *intersecting* a given subspace m^* of
 691 a Boolean network. Such trap spaces (along with minimal trap spaces) are
 692 used in the phenotype control method [22]. This method uses the prime
 693 implicant-based method [7, 21] to compute trap spaces, which has been shown
 694 inefficient. Hence, having a more efficient method for computing such trap
 695 spaces can push the barrier previously existing in this control method. A
 696 trap space m intersects m^* if and only if $S_{\mathcal{N}}[m] \cap S_{\mathcal{N}}[m^*] \neq \emptyset$. It follows
 697 that for every v , if $m^*(v) = 0$ then $m(v) = 0$ or $m(v) = \star$, if $m^*(v) = 1$ then
 698 $m(v) = 1$ or $m(v) = \star$. For the former case, we add to \mathcal{L} the ASP rule

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

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

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

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

703 Finally, we consider the trap spaces that are *inside* a given subspace m^*
 704 of a Boolean network. Such trap spaces are used in the iterative procedure
 705 of building the succession diagram of a Boolean network [19], which is hier-
 706 archical. We first adjust \mathcal{L} to characterize all such trap spaces. A trap space
 707 m is inside m^* if and only if $m(v) = m^*(v)$ for every $v \in D_{m^*}$. If $m^*(v) = 0$,
 708 we add to \mathcal{L} the ASP rule

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

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

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

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

713 rule

`p-v_i1;n-v_i1;...;p-v_ik;n-v_ik.`

714 where $\{v_{i_1}, \dots, v_{i_k}\}$ is the set of free nodes of m^* . This rule ensures that
715 $m \neq m^*$. In the case that $m^* = \varepsilon$, we have all maximal trap spaces of the
716 original Boolean network.

717 5. Motivating example

718 For a few years now we have been collaborating with biologists who build
719 very large detailed and annotated maps and now wish to analyze the dy-
720 namics of the corresponding models. One of the main maps studied this way
721 represents knowledge about the Rheumatoid Arthritis [46], and was the main
722 motivation for the development of a tool to automatically transform it into
723 an executable Boolean network [6]. In the supplementary material of the pa-
724 per, an excerpt of the map, focused around the apoptosis (cell death) module
725 is transformed into a model of *reasonable* size, namely 180 Boolean variables
726 (model `F5_RA_apoptosis_executable_module.sbml` of supplementary ma-
727 terial S3, and model “RA_apoptosis” of Subsection 6.3). The study of such
728 model, though, is a big hurdle. Indeed, as stated in the article about another
729 model of the same size: “*The size of the CaSQ-inferred MAPK model (181*
730 *nodes) made the calculation of stable states a non-realistic endeavour.*”

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

738 However, using a state-of-the-art tool like `PyBoolNet` [7] on that model
739 unfortunately fails at the phase of prime-implicant generation. `mpbn` [9] can
740 return the first 1000 solutions within 1.43s, but indeed, it limits the model-
741 ing range of the modelers as it does not permit using non-locally-monotonic
742 Boolean functions. This is also true for the Alzheimer model also mentioned
743 in that same article and originally from [47] (F4 file in the original supple-
744 mentary material, and “Alzheimer” in Table 2), where `PyBoolNet` also fails
745 at the prime-implicant computation and `mpbn` does not give any answer be-
746 cause this model is actually non-locally-monotonic. The current practice

747 usually revolves then around fixing some source nodes to plausible values
748 and reducing the model accordingly. While this approach makes sense, it
749 relies on potentially arbitrary decisions, and *hides away* critical modelling
750 choices that were clearly not part of the original Boolean network or even of
751 the starting map.

752 For the “RA_apoptosis” model, using the ASP-based method presented
753 in Subsection 4.3, it is now possible to obtain the first 1000 minimal trap
754 spaces (including ones that contain more than one state) within 0.19s, which
755 is much quicker than `mpbn`. The needed time for the “Alzheimer” model is
756 0.79s.

757 6. Evaluation

758 To evaluate the performance of the newly proposed methods (imple-
759 mented as a Python package named `Trappist` and available on the Python
760 package index⁹) and the state-of-the-art methods (`bioLQM`¹⁰, `PyBoolNet` [7,
761 21], and `mpbn` [9]), we compared them on both `PyBoolNet`’s own model repos-
762 itory and many real-world models from various sources in the literature. To
763 our knowledge, these models are a highly representative sample of Boolean
764 models currently available. It is worth noting that `mpbn` [9] only handles
765 locally-monotonic models, whereas the other methods can handle general
766 models. To obtain a more comprehensive comparison, we also used random
767 models generated by a third-party software `BoolNet R` package [31]. As ex-
768 plained in Section 5, in our benchmarks, we only searched for the first 1000
769 minimal trap spaces for each model. It is worth noting that unlike existing
770 analysis shown in the literature, we did not fix specific values for source nodes
771 in all the considered models.

772 To solve the ASP problems, we used the same ASP solver `Clingo` [43] and
773 the same configuration as that used in `PyBoolNet` [7, 21] and `mpbn` [9]. Specif-
774 ically, we used the configuration `-heuristic=Domain -enum-mod=domRec`
775 `-dom-mod=3` (subset maximality, equivalent to the deprecated `--dom-pref=32`
776 `--heuristic=domain --dom-mod=7` used by `PyBoolNet`). We ran all the
777 benchmarks on a machine whose environment is CPU: Intel® Core™ i9-
778 11950H 2.60GHz × 16, 16 GB DDR4 RAM, Ubuntu 20.04.5 LTS. Finally,
779 we set a time limit of three minutes for each model.

⁹<https://pypi.org/project/trappist/>

¹⁰<http://colomoto.org/biolqm/doc/tools-trap-space.html>

780 All the models and some Jupyter notebooks realizing the benchmarks
781 (and named TCS-Benchmark-<...>.ipynb) can be found at <https://github.com/soli/trap-spaces-as-siphons/>. These can be run on a Docker image
782 in the cloud by clicking the “Binder” button.

784 *6.1. 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	0.97	0.96	0.01
2 calzone_cellfate	28	27	0.12	0.02	0.01	0.01	5.59	6.03	0.01
3 dahlhaus_neuroplastoma	23	32	0.11	0.03	0.01	0.01	6.56	6.99	0.01
4 davidich_yeast	10	12	0.11	0.02	0.01	0.01	2.56	2.21	0.01
5 dinwoodie.life	15	7	0.11	0.01	0.00	0.01	1.68	1.39	0.01
6 dinwoodie.stomatal	13	1	0.10	0.01	0.00	0.00	0.39	0.29	0.01
7 faure_cellcycle	10	2	0.11	0.02	0.01	0.01	0.58	0.46	0.01
8 grieco_mapk	53	18	0.19	0.03	0.02	0.03	3.93	10.46	0.02
9 irons_yeast	18	1	0.12	0.03	0.01	0.01	0.37	0.39	0.02
10 jaoude_thdiff	103	1000+	N/A	0.85	0.45	0.56	NF	NF	0.09
11 klamt_tcr	40	8	0.11	0.01	0.01	0.01	1.98	1.22	0.02
12 krumsiek_myeloid	11	6	0.10	0.01	0.00	0.00	1.48	1.26	0.01
13 multivalued	13	4	0.10	0.01	0.00	0.00	0.93	0.86	0.01
14 n12c5	11	5	0.11	17.83	0.01	0.01	1.21	1.10	0.01
15 n3s1c1a	2	2	0.10	0.01	0.00	0.00	0.63	0.49	0.01
16 n3s1c1b	2	2	0.09	0.02	0.00	0.00	0.56	0.49	0.01
17 n5s3	4	3	0.10	0.02	NM	0.00	0.74	0.69	0.01
18 n6s1c2	5	3	0.10	0.02	0.00	0.00	0.91	0.59	0.01
19 n7s3	6	3	0.11	0.02	0.00	0.00	0.79	0.68	0.01
20 raf	3	2	0.10	0.01	0.00	0.00	0.55	0.39	0.01
21 randomnet_n15k3	15	3	0.10	0.02	NM	0.01	0.77	0.67	0.01
22 randomnet_n7k3	7	10	0.10	0.01	NM	0.00	2.07	1.46	0.01
23 remy_tumorigenesis	34	25	0.15	0.94	0.02	0.02	5.98	7.98	0.02
24 saadatpour_guardcell	13	1	0.10	0.06	0.00	0.00	0.53	0.45	0.02
25 selvaggio.emt	56	1000+	N/A	0.48	0.28	0.28	NF	NF	0.09
26 tournier_apoptosis	12	3	0.10	0.01	0.00	0.00	0.74	0.75	0.01
27 xiao_wnt5a	7	4	0.10	0.01	0.00	0.00	1.00	0.89	0.01
28 zhang_tlg1	60	156	0.60	0.09	0.09	0.07	37.26	NF	0.04
29 zhang_tlg1.v2	60	258	0.64	0.04	0.08	0.11	69.95	NF	0.04

785 Table 1 shows the experimental results on the models from the official
786 PyBoolNet repository¹¹. Column n denotes the number of nodes of each
787 model. Column $|M|$ denotes the number of minimal trap spaces and for
788 each method is given the computation time in seconds, asking only for the
789 first 1000 minimal trap spaces. “NF” means that the method did not fin-
790 ish the computation within the time limit of three minutes. In the case of
791 bioLQM, “N/A” means that the number of all minimal trap spaces of the
792 model is larger than 1000 and we did not record the running time of bioLQM
793 because it always requires to compute all minimal trap spaces. A number
794 in bold indicates a ratio greater than three compared to the best result.
795 “NM” indicates a non-locally-monotonic model. There are four variants of
796 Trappist: SAT (i.e., Trappist-MaxSAT, the MaxSAT-based method shown
797 in Subsection 4.2), CP (i.e., Trappist-CP, the CP-based method shown in
798 Subsection 4.2), ILP (i.e., Trappist-ILP, the ILP-based method shown in
799 Subsection 4.4), and ASP (i.e., Trappist-ASP, the ASP-based method shown
800 in Subsection 4.3).

801 We first analyze the results of the four variants of Trappist. We can
802 see that Trappist-MaxSAT and Trappist-ASP are comparable in most mod-
803 els, but Trappist-ASP is much faster for the jaoude_thdiff and selvaggio_empt
804 models where the number of minimal trap spaces is greater than 1000. The
805 latter can be explained by the fact that Trappist-MaxSAT follows an iter-
806 ative approach, i.e., it restarts the search with a new constraint each time
807 a solution is found (see Subsection 4.2). This iterative approach may be
808 less efficient than the way ASP solvers use to enumerate multiple solutions
809 (answer sets), which is an advantage of ASP solvers [43]. Hence, when
810 the number of solutions increases, the inferiority of Trappist-MaxSAT com-
811 pared to Trappist-ASP will be exhibited more clearly. The two remain-
812 ing variants, Trappist-CP and Trappist-ILP, are much less efficient than
813 Trappist-MaxSAT and Trappist-ASP in every model, even are more than
814 three orders of magnitude slower in some models. The first reason for their
815 bad performance is that they are also iterative methods like Trappist-MaxSAT,
816 thus they are not efficient for “enumeration” problems. Upon closer inspec-
817 tion, for the Boolean CSP characterizing conflict-free siphons, CP seems to be
818 something that is a “less-efficient-SAT”, handling mostly Boolean constraints
819 and making little use of the global constraints only added for the iterative

¹¹<https://github.com/hklarner/pyboolnet/tree/master/pyboolnet/repository>

820 part. For ILP, it may be even worse, since the problem is purely Boolean
821 (no real or integer numbers whatsoever). This is confirmed by the obser-
822 vation that for some quite large models (e.g., the grieco_mapk, zhang_tlg1,
823 and zhang_tlg1.v2 models), **Trappist-ILP** is much slower than **Trappist-CP**.
824 Note that the inferiority of ILP compared to ASP with respect to the trap
825 space enumeration has been reported in [7]. Hereafter, we shall compare the
826 best variant of **Trappist** (i.e., **Trappist-ASP**) with other methods.

827 As shown in Table 1, for most of the models of the **PyBoolNet** repos-
828 itory, the results are comparable with all minimal trap spaces found very
829 fast. However upon closer inspection, we can see some notable differences.
830 First, **Trappist-ASP** is far more efficient than **bioLQM** in every model with
831 speedups between $5\times$ and $16\times$. Second, for small models, **PyBoolNet** and
832 **mpbn** are comparable to **Trappist-ASP**. However, on every model that was
833 a bit challenging for **PyBoolNet** or **mpbn**, **Trappist-ASP** is far more efficient
834 with speedups between $3\times$ and $5\times$ for the case of **mpbn**, and between $5\times$ and
835 $1783\times$ for the case of **PyBoolNet**. In particular, the second best variant of
836 **Trappist** (i.e., **Trappist-MaxSAT**) is even far more efficient than **bioLQM** and
837 **PyBoolNet**, and is comparable to **mpbn** on every model. It is worth noting
838 that for 3 of the 29 models, **mpbn** did not give any answer because these mod-
839 els are non-locally-monotonic but all the other methods did, which confirms
840 the limit of **mpbn** on the applicable class of models.

841 6.2. *BBM repository*

842 The research group behind the **BBM** repository [48] has recently undertaken
843 considerable effort for building a collection of real-world Boolean models from
844 various sources used in systems biology. It aims to be a comprehensive col-
845 lection suitable for benchmarking and testing new tools and methods. **BBM**
846 consists of 211 models (24 out of them are non-locally-monotonic), peaking
847 at 321 nodes, 1100 regulations among the nodes, and 133 source nodes, re-
848 spectively. It is released and maintained at [https://github.com/sybila/
849 biodivine-boolean-models](https://github.com/sybila/biodivine-boolean-models). We here tested all the compared methods on
850 this model repository.

851 Figure 2 (upper panel) shows cumulative numbers of the **BBM** models that
852 have less than 1000 minimal trap spaces solved by the compared methods
853 with respect to enumerating the first 1000 minimal trap spaces. The number
854 of such models is 134 (per all 211 models), and 15 of them are non-locally-
855 monotonic. This model set allows us to fairly consider **bioLQM** for comparison,
856 since **bioLQM** always requires to compute all minimal trap spaces. We can

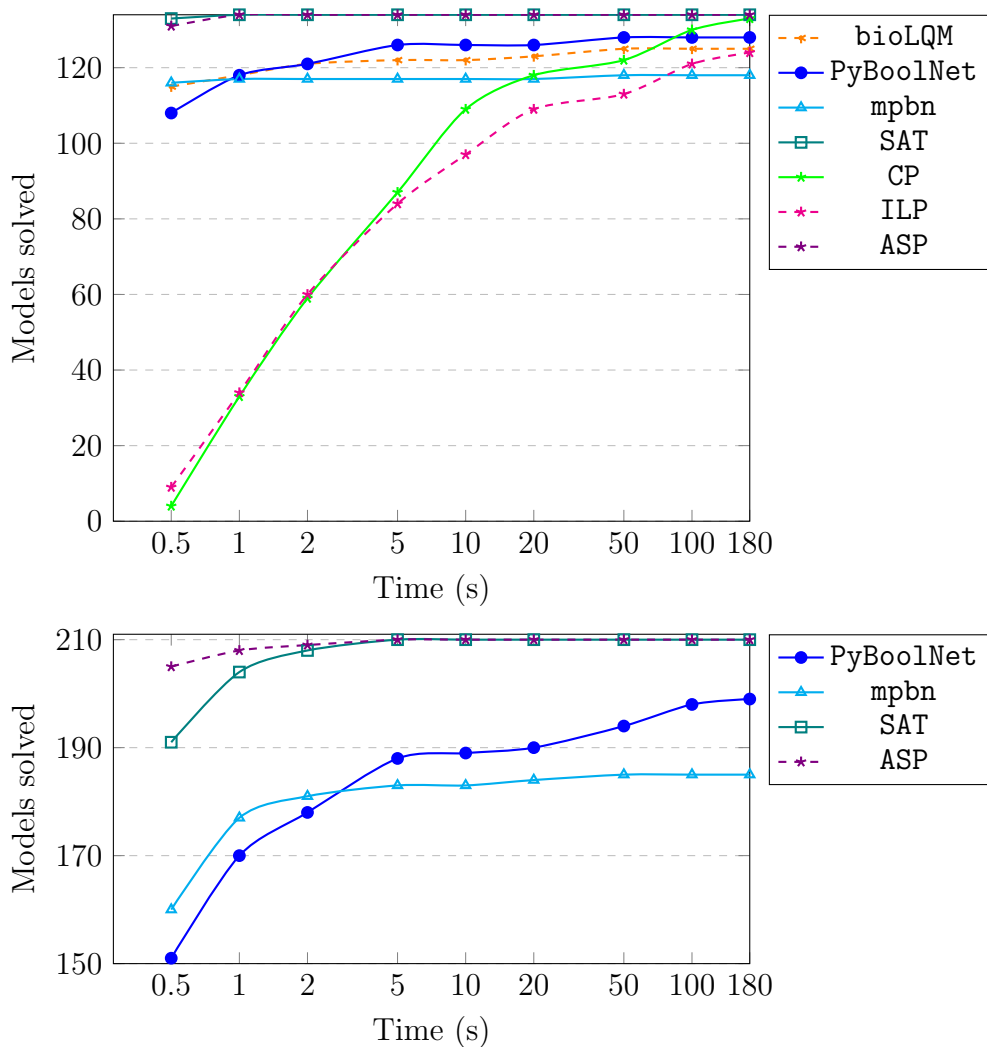


Figure 2: Cumulative numbers of the BBM models that have less than 1000 minimal trap spaces (upper panel) and BBM models solved by the compared methods with respect to enumerating the first 1000 minimal trap spaces (lower panel).

857 first see that **Trappist-ASP** and **Trappist-MaxSAT** are still the two best
 858 methods as they can handle every model within 1s and always can handle
 859 more models than all the remaining methods on every time limit. Second,
 860 **Trappist-CP** is better than **Trappist-ILP**, which is consistent with their
 861 comparison shown in the previous subsection. Third, one notable remark is
 862 that for the time limit of 100s or 180s, **Trappist-CP** can handle more models

863 than all `bioLQM`, `PyBoolNet`, and `mpbn`. This remark shows that even without
864 focusing on the optimization of our implementation, our alternative approach
865 is still better than the state-of-the-art methods on a certain set of real-world
866 models. This is supported by the fact that our alternative approach avoids
867 the need for computing prime implicants (as opposed to `PyBoolNet`) and can
868 handle non-locally-monotonic Boolean networks (as opposed to `mpbn`).

869 Figure 2 (lower panel) shows cumulative numbers of the `BBM` models solved
870 by the compared methods (except `bioLQM`, `Trappist-CP`, and `Trappist-ILP`)
871 with respect to enumerating the first 1000 minimal trap spaces. We omit
872 the results of `Trappist-CP` and `Trappist-ILP` because they can handle
873 no model with more than 1000 minimal trap spaces. Again, we can see
874 that `Trappist-ASP` and `Trappist-MaxSAT` are the two best methods as they
875 can handle every but one model within 5s. They also always handle many
876 more models than both `PyBoolNet` and `mpbn` on every time limit. Note that
877 with the time limit of 0.5s, `Trappist-ASP` can handle 14 more models than
878 `Trappist-MaxSAT`, which is opposed to the case of models with less than
879 1000 minimal trap spaces (see Figure 2 (upper panel)). This observation
880 confirms the disadvantage of `Trappist-MaxSAT` compared to `Trappist-ASP`
881 for the case of many minimal trap spaces.

882 6.3. Selected models

883 We used a set of real-world Boolean networks lying in various scales col-
884 lected from numerous bibliographic sources in the literature. Most of these
885 models are quite big (in size), complex (i.e., having high average in-degree,
886 which is related to the number of prime implicants), and have never been
887 fully analyzed. Note that these models are not included in the `PyBoolNet`
888 and `BBM` repositories. We then applied `bioLQM`, `PyBoolNet`, `mpbn`, and the
889 four variants of `Trappist` to computing minimal trap spaces of these real-
890 world models. Table 2 shows the obtained experimental results. A number
891 in bold indicates a ratio greater than or equal to 10 compared to the best
892 result. The remaining notations are similar to those in Table 1. Hereafter, we
893 analyze in detail the results with respect to minimal trap space computation.

894 First, we obtained some observations on the four variants of `Trappist`
895 consistent with the observations obtained in the previous subsections. More
896 specifically, `Trappist-ASP` is still the best variant with a running time below
897 one second for every model, and followed by `Trappist-MaxSAT`. In particular,
898 the difference in running time between `Trappist-ASP` and `Trappist-MaxSAT`
899 is bigger for larger models or models with more than 1000 minimal trap

Table 2: Timing comparisons (in seconds) between bioLQM (LQM), PyBoolNet (PBN), mpbn and the four variants of Trappist on selected models from the literature. The models are sorted by size with a horizontal rule inserted to split at 100 and 200 nodes, as in [18]

model	n	$ M $	LQM	PBN	mpbn	Trappist			
						SAT	CP	ILP	ASP
1 metastatic [49]	10	4	0.10	0.04	NM	0.01	1.15	0.89	0.02
2 Arabidopsis_thaliana [49]	15	8	0.10	0.06	NM	0.01	2.06	1.83	0.02
3 p53_high_dna [49]	16	1	0.38	1.76	NM	0.08	0.53	0.43	0.14
4 p53_low_dna [49]	16	1	0.41	1.76	NM	0.07	0.58	0.48	0.14
5 FT-GRN [50]	23	32	NF	NF	NM	0.03	8.41	12.38	0.19
6 DNA_damage [49]	26	16	0.24	0.33	NM	0.02	3.91	5.33	0.05
7 Rho-GTPases [49]	33	2	0.17	0.57	40.39	0.07	0.74	0.56	0.11
8 Pluripotency [51]	36	440	NF	NF	NM	0.16	138.92	NF	0.28
9 Pluripotent [49]	36	276	0.37	0.43	NM	0.07	72.40	NF	0.06
10 Pancreatic.Cancer [49]	43	1000+	N/A	0.11	0.36	0.17	NF	NF	0.06
11 Drosophila [52]	52	128	0.33	0.05	0.07	0.06	32.66	126.22	0.05
12 Cacace_TdevModel [53]	61	28	1.29	5.67	NM	0.06	7.51	23.15	0.08
13 hedgehog [49]	65	1000+	N/A	NF	0.50	0.34	NF	NF	0.33
14 EMT [19]	69	268	39.22	1.01	0.20	0.12	75.81	NF	0.05
15 Bcell [54]	73	72	0.23	0.04	0.08	0.06	18.95	81.85	0.05
16 mast_cell [6]	73	1000+	N/A	0.09	0.55	0.37	NF	NF	0.15
17 Corral_ThIL17diff [45]	92	1000+	N/A	107.57	0.76	0.56	NF	NF	0.16
18 Adhesion_CIP [55]	121	78	56.81	4.25	0.23	0.17	25.20	NF	0.19
19 EMT_Mech [56]	136	82	NF	14.01	0.27	0.20	27.55	NF	0.25
20 macrophage [49]	136	1000+	N/A	0.54	1.09	0.84	NF	NF	0.27
21 angiogenesis [49]	141	1000+	N/A	0.16	1.07	1.06	NF	NF	0.16
22 angiofull [57]	142	1000+	N/A	0.17	1.06	0.88	NF	NF	0.23
23 EMT_Mech_TGFbeta [56]	150	492	NF	11.28	0.78	0.69	NF	NF	0.35
24 RA_apoptosis [6]	180	1000+	N/A	NF	1.43	1.55	NF	NF	0.19
25 MAPK [6]	181	1000+	N/A	13.58	1.76	1.51	NF	NF	0.27
26 Snf1-pathway [58]	202	1000+	N/A	1.13	1.47	1.43	NF	NF	0.31
27 T-cell-co-receptor [49]	206	1000+	N/A	NF	1.52	2.26	NF	NF	0.35
28 TcellCheckPoint [59]	218	1000+	N/A	4.99	NM	1.96	NF	NF	0.28
29 Mycobacterium [49]	317	1000+	N/A	0.42	2.36	4.91	NF	NF	0.44
30 Leishmania [49]	342	1000+	N/A	NF	2.56	5.62	NF	NF	0.46
31 Cholocystokinin [6]	383	1000+	N/A	0.36	2.99	4.81	NF	NF	0.37
32 Alzheimer [6]	762	1000+	N/A	NF	NM	18.21	NF	NF	0.79

900 spaces. Trappist-CP and Trappist-ILP still have a much worse perfor-
901 mance, with Trappist-CP better than Trappist-ILP. They still can handle
902 no model with more than 1000 minimal trap spaces. However, Trappist-CP
903 or Trappist-ILP can handle the FT-GRN and Pluripotency models, whereas
904 all bioLQM, PyBoolNet, and mpbn cannot.

905 Second, **Trappist-ASP** (even **Trappist-MaxSAT**) is far more efficient than
906 both **bioLQM** and **PyBoolNet** on every model where the comparison is possi-
907 ble. For most models, the speedups of **Trappist-ASP** compared to **bioLQM**
908 and **PyBoolNet** are between one and three orders of magnitude. This again
909 confirms the superiority of **Trappist-ASP** compared to the other methods
910 that can handle general Boolean networks.

911 Third, for 11 of the 32 models (more than 34%), **mpbn** did not give any an-
912 swer because these models are non-locally-monotonic. For 21 of the 32 mod-
913 els where **mpbn** returned the answers, **mpbn** and **Trappist-ASP** are roughly
914 comparable in computation time, but **mpbn** appears quite slower on aver-
915 age. In particular, for the Rho-GTPases model, **mpbn** is $577\times$ slower than
916 **Trappist-ASP**. This observation along with the comparisons between **mpbn**
917 and **Trappist-ASP** in the previous subsections are quite surprising because
918 the ASP encoding of **mpbn** only requires the DNF for the activation part of a
919 Boolean function, whereas that of **Trappist-ASP** requires both the activation
920 and inhibition parts (see Subsection 4.3). However, the reason may lie on the
921 differences in the ASP encoding characteristics of the two methods and the
922 fact that **mpbn** needs to spend time checking the local-monotonicity of each
923 Boolean function in a Boolean network. We expect that **mpbn** may outper-
924 form **Trappist** for a certain set of models, but not for the set of real-world
925 models considered in this article.

926 Fourth, regarding the comparison of the ASP-based methods (i.e.,
927 **PyBoolNet**, **mpbn**, and **Trappist-ASP**), we note that for all the models where
928 **PyBoolNet** did not finish before the time limit, the timeout occurred during
929 the computation of the prime implicants. Hence, not even a single minimal
930 trap space was output by that method. For all the remaining models, once
931 **PyBoolNet** went through the prime-implicant phase, its ASP solving phase
932 quickly returned the first 1000 minimal trap spaces, all under one second.
933 Hence, with the experimental results shown in this subsection as well as the
934 two previous subsections, the practical differences between the ASP encod-
935 ing of **Trappist-ASP** and that of **PyBoolNet** are not distinctly exposed. The
936 fact that our new ASP encoding is guaranteed to be linear in the number of
937 nodes of the original model (see Subsection 4.3) does not seem to be crucial
938 here, however a much deeper analysis of those cases shall be shown in the
939 next subsection.

940 *6.4. Randomly generated models*

941 We randomly generated a set of N-K models [1] with network size n in the
 942 set $\{100, 150, 200, 250, 300, 350, 400\}$ and in-degree $K = 3$ (i.e., each node
 943 has exactly three input nodes). We chose N-K models because they are a
 944 useful tool for studying the dynamics of Boolean networks [1, 7, 19]. For each
 945 network size, 50 instances were generated using the `generateRandomNKNetwork`
 946 function. In total, we have 350 random models. We then applied the compared
 947 methods to these models and recorded the running time of each method
 948 for each model. It is worth noting that N-K models usually have small numbers
 949 of minimal trap spaces [7]. Hence, we searched for all solutions in each
 950 model, which makes the comparison to `bioLQM` more comprehensive. In addition,
 951 each node has only three input nodes, leading to a small number of prime
 952 implicants of the associated Boolean function. Hence, `PyBoolNet` always
 953 passed the phase of computing prime implicants in every model even within
 954 one second, which enables us to compare the ASP encoding of `PyBoolNet`
 955 and that of `Trappist-ASP`.

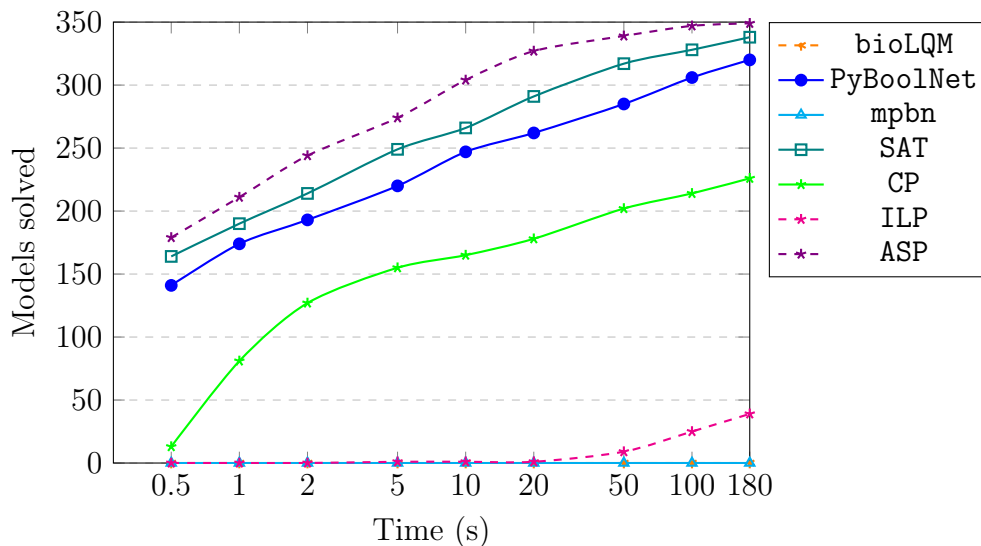


Figure 3: Cumulative numbers of random models solved by the compared methods with respect to enumerating all the minimal trap spaces.

956 Figure 3 shows cumulative numbers of random models solved by the compared
 957 methods with respect to enumerating all the minimal trap spaces. The
 958 number of succeeded models within three minutes for each method is: `bioLQM`

959 (0), PyBoolNet (320), mpbn (0), Trappist-maxSAT (338), Trappist-CP (226),
960 Trappist-ILP (39), Trappist-ASP (349). We can see that Trappist-ASP is
961 the only method that can handle every model, but one. Note that none of
962 the other methods can handle that only model failed by Trappist-ASP. We
963 also obtained some observations consistent with those obtained for real-world
964 models. More specifically, Trappist-MaxSAT is still the second best method
965 and Trappist-CP is better than Trappist-ILP. Upon closer inspection, we
966 obtained several notable observations as follows.

967 First, mpbn was not able to handle any model because all the models
968 are non-locally-monotonic. Recall that a Boolean network is non-locally-
969 monotonic if only one of its Boolean functions is non-locally-monotonic.
970 Hence, it is apparent that all these types of randomly generated models are
971 non-locally-monotonic because of the number of nodes is large ($n \geq 100$).
972 This observation confirms a limit on the applicable model class of mpbn.

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

978 Third, for every time limit, Trappist-ASP can always handle many more
979 models than PyBoolNet, ranging from 29 to 65 more models. Since the
980 time for the phase of computing prime implicants of PyBoolNet is negligible
981 in every model, most of the running time of PyBoolNet was spent for its
982 ASP solving phase. Hence, we can easily see that the ASP encoding of
983 Trappist-ASP is much better than that of PyBoolNet. This observation
984 is consistent with the theoretical comparison in the ASP encoding between
985 Trappist-ASP and PyBoolNet mentioned in Subsection 4.3.

986 6.5. Experimental summary

987 We have tested our alternative approach on many Boolean network mod-
988 els of various sizes and types (e.g., real-world models, randomly generated
989 models) on existing and newly created benchmarks. This indicates the high
990 coverage and comprehensiveness of the experiments.

991 Among the four variants of the alternative approach, Trappist-ASP is the
992 best method as it vastly outperforms all the other variants. The second best
993 one is Trappist-MaxSAT. The two remaining variants (i.e., Trappist-CP and
994 Trappist-ILP) give bad performance for most models. However, for certain
995 cases, they are still better than all state-of-the-art methods (i.e., bioLQM,

996 PyBoolNet, and mpbn). This is evidence for the advantages of an alternative
997 approach compared to what preexisted.

998 Regarding general Boolean networks, Trappist-ASP (even Trappist-
999 MaxSAT) is far more efficient than both bioLQM and PyBoolNet. The speedups
1000 of Trappist-ASP or Trappist-MaxSAT are large, even between one and three
1001 orders of magnitude for most models. In addition, the experimental results
1002 also confirm that the ASP encoding of Trappist-ASP is much more efficient
1003 than that of PyBoolNet.

1004 Regarding locally-monotonic Boolean networks, the performance of mpbn
1005 is roughly comparable to that of Trappist-ASP or Trappist-MaxSAT. How-
1006 ever, mpbn is quite slower than Trappist-ASP on average. This shows the
1007 practical advantage of Trappist-ASP compared to mpbn, though its ASP
1008 encoding may be more complex than that of mpbn in theory.

1009 7. Conclusion

1010 In this article we have explored and proved for the first time the equiva-
1011 lence between (minimal) trap spaces of a general Boolean network and (max-
1012 imal) conflict-free siphons of its Petri net encoding. We have shown sev-
1013 eral useful applications of this finding to studying properties of trap spaces
1014 in Boolean networks. As an important practical application of the equiva-
1015 lence, we have proposed a new approach for the computation of minimal trap
1016 spaces in Boolean networks, based on the enumeration of maximal conflict-
1017 free siphons of Petri nets. We have also proposed four possible methods
1018 using MaxSAT, CP, ILP, and ASP for implementing the new approach. In
1019 particular, we have shown how to adjust our approach to compute several
1020 specific types of trap spaces (e.g., maximal trap spaces, fixed points), which
1021 besides minimal trap spaces also play crucial roles in the analysis and con-
1022 trol of Boolean networks. The proposed methods for the minimal trap space
1023 computation have been evaluated on many real-world models from the liter-
1024 ature as well as randomly generated models. The experimental results show
1025 that the new approach vastly outperforms all the state-of-the-art methods
1026 in terms of general Boolean networks and is comparable to the mpbn method
1027 even much better on average in terms of locally-monotonic Boolean net-
1028 works. We believe that this opens up the way to a much better analysis
1029 of large Boolean networks, which is needed with the advent of automatic
1030 model-generation pipelines [60].

1031 Although the experimental results show the superiority of our approach
1032 to `mpbn` in general, we however note that there is a model in the `BBM` repos-
1033 itory (with identifier 122) where all the four proposed methods for the new
1034 approach did not manage to finish the Petri net conversion before the time-
1035 out, whereas `mpbn` can still handle this model. The model is not very large
1036 but its Boolean functions are rather complicated. This points to the fact that
1037 our current choice of using a BDD-based translation to obtain that Petri net
1038 encoding, though it provides a small/efficient ASP might be too costly to
1039 handle the complex models. In such a case, a more *naive* encoding might
1040 provide a much larger ASP program, with many redundant rules, but eas-
1041 ier/faster to obtain. The evaluation of the feasibility of such strategy, and
1042 of its impact on smaller instances, remains to be done. Recognizing that
1043 a model is locally-monotonic and applying in that specific case dedicated
1044 strategies as those of `mpbn` might also be a partial solution.

1045 Another direction to speed up our approach in the side of Boolean net-
1046 works is to apply reduction techniques to the original Boolean network. Many
1047 reduction techniques on Boolean networks [61, 62] have been proposed and
1048 some of them fully preserve attractors of a Boolean network under the fully
1049 asynchronous update scheme. In particular, a reduction technique on elim-
1050 ination of negatively auto-regulated nodes with respect to asynchronous at-
1051 tractors has recently been proposed [62]. However, there are two major issues
1052 needed to be considered. First, the question of whether these reduction tech-
1053 niques fully preserve minimal trap spaces of a Boolean network is still open.
1054 Second, although these reduction techniques can reduce the number of nodes,
1055 they can also increase the complexity of Boolean update functions [61], which
1056 is also an important factor for the performance of computation methods. It
1057 raises the question of whether they really simplify the computational burden
1058 of trap space computation. We will deeply investigate the two issues. Fur-
1059 thermore, we believe that the connection between trap spaces and siphons
1060 can be a very useful tool for addressing the first issue.

1061 It is worth noting that there may be possibly other methods for comput-
1062 ing minimal/maximal conflict-free siphons in Petri nets, like the methods for
1063 generic siphon computation in the field of Petri nets (see [35] for a survey
1064 about these methods). Although these approaches do not directly support
1065 the minimal/maximal conflict-free siphon computation now, we plan to in-
1066 vestigate them in the future. In particular, several approaches based on
1067 the network structure at the Petri net level (e.g., the decomposition ap-
1068 proaches [63, 64] for identifying minimal generic siphons) can be adapted

1069 to help the identification of minimal conflict-free siphons. Making use of
1070 the specific structure (1-safe, place-complementary) might also reveal new
1071 techniques to be considered. It is potentially possible because in the field of
1072 Petri nets, most of the methods for identifying minimal generic siphons focus
1073 on various net classes with special structures [35]. The above potential ap-
1074 proaches could replace our proposed methods if they give significantly better
1075 performance. However, the current methods appear to already perform very
1076 well even on the biggest models we have considered.

1077 Finally, we think that the links between Petri nets and Boolean networks
1078 that we stumbled upon in this article might have deeper roots. Exploring
1079 those connections might lead both to interesting topics of research for Petri
1080 nets, like a notion of trap-spaces, and for Boolean networks. We also believe
1081 that the connection between trap spaces of Boolean networks and siphons
1082 of Petri nets can be a very useful tool for exploring and proving more new
1083 properties of trap spaces in Boolean networks, as we have used it to success-
1084 fully prove the independence of trap spaces to the update scheme and the
1085 separation of minimal trap spaces. Diving into this direction is promising
1086 and one of our future work.

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