

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

Van-Giang Trinh^a, Belaid Benhamou^a, Sylvain Soliman^{b,*}

^a*LIS, Aix-Marseille University, Marseille, France*

^b*Lifeware team, Inria Saclay center, Palaiseau, France*

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

*Corresponding author.

Email addresses: `trinh.van-giang@lis-lab.fr` (Van-Giang Trinh),
`belaid.benhamou@lis-lab.fr` (Belaid Benhamou), `Sylvain.Soliman@inria.fr`
(Sylvain Soliman)

and randomly generated models.

Keywords:

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

1. Introduction

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

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

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

¹<https://github.com/bnediction/mpbn>

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

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

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

on randomly generated models.

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

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

2. Preliminaries

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

2.1. Boolean networks

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

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

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

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

$$v_i(t+1) = \begin{cases} f_i(v(t)) \\ \text{or} & v_i(t) \end{cases}$$

114 where $v(t)$ is the state of \mathcal{N} at time t . Note that for simplicity, we write
115 $f_i(v(t))$ even if $IN(v_i) \subsetneq V$ (i.e., $IN(v_i)$ does not contain some nodes of
116 V). An update scheme of a Boolean network specifies which nodes update
117 their states, as defined above, through time evolution [4]. Following the
118 update scheme, the Boolean network transits from a state to another state
119 (possibly identical). This transition is called the *state transition* and denoted
120 by $\rightarrow \subseteq \mathcal{S}_{\mathcal{N}} \times \mathcal{S}_{\mathcal{N}}$. Then the dynamics of \mathcal{N} is captured by the directed graph
121 $(\mathcal{S}_{\mathcal{N}}, \rightarrow)$ called the State Transition Graph (STG). There are many different
122 update schemes, but the two main types [4] are: synchronous, where all the
123 nodes are update simultaneously, and fully asynchronous, where only one
124 node is selected non-deterministically to be updated.

125 2.2. Traps spaces

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

130 A non-empty set $T \subseteq \mathcal{S}_{\mathcal{N}}$ is a trap set with respect to \rightarrow if for every
 131 $x \in T$ and $y \in S$ with $x \rightarrow y$ it holds that $y \in T$ [7]. An attractor of \mathcal{N}
 132 with respect to \rightarrow can be defined as an inclusion-wise minimal trap set of
 133 $(\mathcal{S}_{\mathcal{N}}, \rightarrow)$. An attractor can be also seen as a terminal strongly connected
 134 component of $(\mathcal{S}_{\mathcal{N}}, \rightarrow)$ [22]. An attractor of size 1 is called a fixed point,
 135 otherwise it is called a cyclic or complex attractor [7].

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

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

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

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

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

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

154 2.3. Petri net encoding of Boolean networks

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



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

159 A *marking* for a Petri net is a mapping $m : P \mapsto \mathbb{N}$ that assigns a number
 160 of tokens to each place. A place p is marked by a marking m if and only if
 161 $m(p) > 0$. Marking m can be seen as a subset of P that contains all marked
 162 places by m . We shall write $\text{pred}(x)$ (resp. $\text{succ}(x)$) to represent the set of
 163 vertices that have a (non-zero weighted) arc leading to (resp. coming from) x .
 164 In this work, we consider a class of Petri nets called 1-safe Petri nets where
 165 every place has at most 1 token and all arcs are of weight 1. In this case,
 166 weights are implicitly omitted in the arcs of a Petri net. Then, a transition
 167 $t \in T$ is *enabled* at a marking m if and only if $\text{pred}(t) \subseteq m$. A marking m
 168 is called a *deadlock* if there are no enabled transitions at m . The firing of
 169 t leads to a new marking m' specified by $m' = (m \setminus \text{pred}(t)) \cup \text{succ}(t)$. Note
 170 that when multiple transitions are enabled, we need to embed one firing
 171 scheme (similar to the update scheme of a Boolean network) to the Petri
 172 net. The classical firing scheme is that only one of the enabled transition is
 173 non-deterministically chosen to fire [12].

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

181 Since our study is focused on Boolean networks, we briefly recall the origi-
 182 nal encoding here. Its basis is that every node (*gene*) v of the original model
 183 $\mathcal{N} = (V, F)$ is represented by two separate places (p_v and \bar{p}_v), corresponding
 184 to its two states, active, and inactive, respectively. Each conjunct of the
 185 logical function that activates the *gene* will lead to a transition t , consuming

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

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

201 For illustration, let us reconsider the Boolean network shown in Exam-
202 ple 2.1. Figure 1(b) shows the Petri net encoding of this Boolean network.
203 Place p_{x_1} (resp. \bar{p}_{x_1}) in \mathcal{P} represents the activation (resp. the inactivation) of
204 node x_1 in \mathcal{N} . Marking $\{p_{x_1}, \bar{p}_{x_2}\}$ in \mathcal{P} represents state 10 in \mathcal{N} . Transitions
205 $t_{x_1}^1$ and $t_{x_1}^2$ represent the update of node x_1 . Of course, in any marking $t_{x_1}^1$
206 and $t_{x_1}^2$ cannot be both enabled. Then, the fully asynchronous update scheme
207 in \mathcal{N} corresponds to the classical firing scheme in \mathcal{P} where only one of the
208 enabled transitions for a given marking will be fired [12].

209 Note that given a Boolean network in the standard **SBML-Qual** format [26],
210 i.e., the package of SBML v3 [27] for such models, one can easily obtain its
211 Petri net encoding in the Petri Net Markup Language (PNML)² standard
212 using the **bioLQM**³ library. This piece of software extracted from **GINsim** [28]
213 and part of the **CoLoMoTo**⁴ [29] software suite allows for easy conversion
214 between standard formats. It also accepts many other common formats for
215 Boolean networks, notably the **.bnet** files of the BoolNet [30, 20] tools. The
216 conversion is executed as follows:

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

218 Note that transforming a Boolean network defined by its functions into its

²<https://www.pnml.org/>

³<http://www.colomoto.org/biolqm/>

⁴<http://colomoto.org/>

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

233 2.4. Siphons

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

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

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

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

242 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
 243 conventionally $\text{pred}(S) = \text{succ}(S) = \emptyset$. We have an important property on
 244 siphons [34] as follows.

245 **Proposition 2.1.** *Let S be a siphon of a Petri net (P, T, W) . Then $\text{pred}(S) \subseteq$
 246 $\text{succ}(S)$.*

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

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

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

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

255 Intuitively, a siphon is a set of places that once unmarked remains so.
256 If it is conflict-free then its dual corresponds to a partial-state of the model
257 such that whatever update, the fixed values remain so (since the unmarked
258 places remain unmarked). This is precisely the definition of a trap space and
259 maximality of the siphon is equivalent to as many fixed values as possible,
260 hence minimality of the trap space. For example, the Boolean network given
261 in Example 2.1 has two trap spaces, $m_1 = 11$ and $m_2 = \star\star$. The Petri net
262 encoding of this Boolean network has five generic siphons, $S_1 = \emptyset$, $S_2 =$
263 $\{p_{x_1}, \bar{p}_{x_1}\}$, $S_3 = \{p_{x_2}, \bar{p}_{x_2}\}$, $S_4 = \{\bar{p}_{x_1}, \bar{p}_{x_2}\}$, and $S_5 = \{p_{x_1}, \bar{p}_{x_1}, p_{x_2}, \bar{p}_{x_2}\}$.
264 However, only S_1 and S_4 are conflict-free siphons and correspond to m_2 and
265 m_1 , respectively. Since $S_1 \subset S_4$, S_4 is a maximal siphon corresponding to
266 the minimal trap space m_1 . Hereafter, we formally prove that a (maximal)
267 conflict-free siphon is equivalent to a (minimal) trap space.

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

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

and

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

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

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

274 not a siphon of \mathcal{P} . Then, there is a transition $t \in T$ such that $S \cap \text{succ}(t) \neq \emptyset$
 275 but $S \cap \text{pred}(t) = \emptyset$. This implies that there is a place $p \in S$ such that
 276 $p \in \text{succ}(t)$ but $p \notin \text{pred}(t)$. Let v be the node in \mathcal{N} corresponding to p . By
 277 the characteristics of the encoding [23], there is a directional arc from t to p
 278 and a directional arc from the complementary place of p to t . Without loss
 279 of generality, we assume that $p = p_v$, then there is a directional arc from t
 280 to p_v and a directional arc from \bar{p}_v to t . We follow the following procedure
 281 to find a state $s \in \mathcal{S}_{\mathcal{N}}[m]$ such that $m_s(p') = 1, \forall p' \in \text{pred}(t)$ where m_s is
 282 the corresponding marking in \mathcal{P} of s . For every place $p' \in \text{pred}(t)$, let p'' be
 283 the complementary place of p' and v' be the corresponding node in \mathcal{N} of p'
 284 and p'' . If $p'' \notin S$, then $v' \notin D_m$ and we can always set a Boolean value to
 285 $s(v')$ such that $s \in \mathcal{S}_{\mathcal{N}}[m]$ and $m_s(p') = 1$. If $p'' \in S$, then $v' \in D_m$ and we
 286 set $s(v') = m(v')$. In this case, if $p' = p_v$ then $s(v') = m(v') = 1$ leading to
 287 $m_s(p') = 1$, if $p' = \bar{p}_v$ then $s(v') = m(v') = 0$ leading to $m_s(p') = 1$. For
 288 the remaining nodes of \mathcal{N} , we can always set Boolean values to these nodes
 289 to preserve that $s \in \mathcal{S}_{\mathcal{N}}[m]$. We also have $m_s(p_v) = 0$ by the characteristics
 290 of the encoding [23]. Now, t is enabled at marking m_s . Its firing leads to
 291 a new marking m'_s such that $m'_s(p_v) = 1$ and $m'_s(\bar{p}_v) = 0$. Let s' be the
 292 corresponding state in \mathcal{N} of m'_s . We have $s'(v) = 1$ because $m'_s(p_v) = 1$ and
 293 $m(v) = 0$ because $p_v \in S$. This implies that $s' \notin \mathcal{S}_{\mathcal{N}}[m]$. For any firing
 294 scheme of \mathcal{P} , the firing of t always happens. Since a firing scheme of \mathcal{P} is
 295 equivalent to an update scheme of \mathcal{N} , s can escape from the trap space m
 296 for any update scheme of \mathcal{N} , which contradicts to the property of a trap
 297 space. Hence, S is a siphon of \mathcal{P} . By the definition of a mirror, S is also a
 298 conflict-free one.

299 Second, we show that if S is a conflict-free siphon of \mathcal{P} , then m is a trap
 300 space of \mathcal{N} (**). By the definition of a mirror, m is a subspace of \mathcal{N} . Let
 301 s be an arbitrary state in $\mathcal{S}_{\mathcal{N}}[m]$ and m_s be its corresponding marking in
 302 \mathcal{P} . Assume that there is a place $p \in S$ such that $m_s(p) = 1$. Let v be the
 303 corresponding node in \mathcal{N} of p . Since $p \in S$, $v \in D_m$ and $m(v) = s(v)$. If
 304 $p = p_v$, then $m_s(p_v) = 1$ leading to $m(v) = s(v) = 1$ by the characteristics of
 305 the encoding [23]. By the definition of a mirror, $m(v) = 0$ because $p_v \in S$,
 306 which is a contradiction. It is symmetric for the case that $p = \bar{p}_v$. Hence,
 307 $m_s(p) = 0, \forall p \in S$. In any marking m'_s reachable from m_s regardless of the
 308 firing scheme of \mathcal{P} , we have $m'_s(p) = 0, \forall p \in S$ by the dynamical property on
 309 markings of a siphon [34]. Let s' be the corresponding state in \mathcal{N} of m'_s . For
 310 every node $v \in D_m$, we have all two cases as follows. Case 1: $p_v \in S$, then
 311 $m'_s(p_v) = 0$, thus $s'(v) = 0 = m(v)$. Case 2: $\bar{p}_v \in S$, then $m'_s(\bar{p}_v) = 0$, thus

312 $s'(v) = 1 = m(v)$. Hence, $s'(v) = m(v)$ for every $v \in D_m$. Then, $s' \in \mathcal{S}_{\mathcal{N}}[m]$.
 313 By the definition of a trap space and the arbitrariness of s , m is a trap space
 314 of \mathcal{N} .

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

316 From the proof of Theorem 3.1, we can see that the theorem holds for
 317 any update scheme associated to the Boolean network. Since the Petri net
 318 encoding of a Boolean network is independent of its update scheme and
 319 siphons are a static property of a Petri net, we can imply that trap spaces of a
 320 Boolean network are independent of its update scheme. Note that the original
 321 proof for this property of trap spaces (see Theorem 1 of [7]) only considers
 322 the two popular update schemes (i.e., synchronous and fully asynchronous).
 323 Theorem 3.1 exhibits the very first theoretical application of the connection
 324 between trap spaces of Boolean networks and siphons of Petri nets.

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

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

336 Second, we show that if S is a maximal conflict-free siphon of \mathcal{P} , then
 337 m is a minimal trap space of \mathcal{N} (**). Since S is a conflict-free siphon of \mathcal{P} ,
 338 m is a trap space of \mathcal{N} by Theorem 3.1. Assume that m is not minimal.
 339 Then, there is another trap space m' such that $m' < m$. By the definition of
 340 the partial order $<$ on subspaces, $\mathcal{S}_{\mathcal{N}}[m'] \subset \mathcal{S}_{\mathcal{N}}[m]$. Let S' be the mirror of
 341 m' . S' is a conflict-free siphon by Theorem 3.1. Following the definition of
 342 a mirror, $S \subset S'$, which contradicts to the maximality of S . Hence, m is a
 343 minimal trap space of \mathcal{N} .

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

345 We here showcase a theoretical application of the connection between
 346 trap spaces in Boolean networks and conflict-free siphons in Petri nets. We

use it to prove a property of minimal trap spaces, which has surprisingly not been formally proved. Specifically, all minimal trap spaces of a Boolean network are mutually disjoint. This property is important because we can use it to approximate the set of attractors of the Boolean network under any update scheme [7] or to compute exactly the set of complex attractors of the Boolean network under the fully asynchronous update scheme [35]. Note that it would be not difficult to obtain a direct proof on trap spaces for this property, which follows the same structure as the proof on siphons. However, we emphasize here the potential of using the connection between Boolean networks and Petri nets to explore and prove properties of trap spaces in Boolean networks.

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

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

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

A natural computational application of Theorem 3.1 is that we can efficiently decide whether a subspace m is a trap space. In `PyBoolNet` [20], this is checked by using the percolation on the prime-implicants of the Boolean functions. As we have mentioned at the beginning of this article, the computation of prime-implicants is a demanding task for complex Boolean networks,

even is sometimes intractable. Hence, the checking method in [20] shows its limitations. Instead, we can first compute the mirror S_m of m in the Petri net encoding. Then, by Proposition 2.1 and Theorem 3.1, we can check if $\text{pred}(S_m) \subseteq \text{succ}(S_m)$. Note that the Petri net construction is less computationally demanding than the prime-implicant computation because it only requires computing generic (not prime) implicants of the Boolean functions [22]. In addition, the time complexity of the above checking method is quadratic in the number of transitions of the Petri net in worst cases.

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

Note that there are no existing methods specifically designed for computing maximal conflict-free siphons (even maximal siphons) of a Petri net. The reason might be that researchers mainly focus on minimal generic siphons [34] in the field of Petri nets. Hence, we here propose several methods for computing maximal conflict-free siphons of a Petri net. The details of the proposed methods shall be given in the next section.

4. Computation methods

4.1. Characterization

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

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

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

Petri net and has been used with SAT solvers in [16, 17]. To make S to be a conflict-free siphon, we need to add to the system the rule

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

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

410 4.2. Constraint satisfaction problem

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

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

- 415 • $R = P$, i.e., a variable is introduced for each place of \mathcal{P} ,
- 416 • $D(p) = \mathbb{B}$ for all $p \in R$, i.e., the variables are Boolean,
- 417 • $C = \{\neg p_v \vee \neg \bar{p}_v = 1 \mid \forall v \in V\} \wedge \{(p = 1 \rightarrow \bigvee_{p' \in \text{pred}(t)} p' = 1) \mid p \in$
418 $P, t \in \text{pred}(p)\}$.

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

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

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

420 *Proof.* By the former part $\neg p_v \vee \neg \bar{p}_v = 1$ of C , the conflict-freeness is imposed
421 because for any satisfiable valuation r , $r(p_v) = r(\bar{p}_v) = 1$ is impossible for all
422 $v \in V$. As shown in [17], the latter part of C can characterize the set of all
423 generic siphons of \mathcal{P} . Hence, we can conclude the proof.

424 □

425 In [17], the set of all siphons of a given Petri net is characterized by a sim-
426 ilar Boolean CSP except the conflict-freeness constraint. From the encoded
427 CSP, the set of all *minimal* siphons of the Petri net can be enumerated in the
428 set inclusion order. For enumerating siphons in the set inclusion order, the
429 proposed method by [17] uses the technique that labels directly the Boolean
430 variables with increasing value selection (i.e., to test first the absence, then
431 the presence of a place in the candidate solution). The method has two

432 implementations, one uses an iterated SAT procedure and the other uses
 433 Constraint Programming (CP) with backtracking.

434 One natural question is that how to use the CSP-based method for enu-
 435 merating all the maximal conflict-free siphons of a Petri net encoding a
 436 Boolean network? Of course, the set of all conflict-free siphons of the Petri
 437 net can easily be characterized by the CSP model presented in [17] along with
 438 the additional constraint $\neg p_v \vee \neg \bar{p}_v = 1$, for each $v \in V$, which represents
 439 the conflict-freeness. However, the main concern is to enumerate all the
 440 *maximal* ones, which is not trivial to adapt from the CSP-based method.
 441 By Proposition 4.1, the set of all maximal conflict-free siphons of \mathcal{P} can be
 442 enumerated in the (maximality) set inclusion order, by restarting the search
 443 each time a conflict-free siphon S is found, with the following additional con-
 444 straint for disallowing any subset of that conflict-free siphon: $\bigvee_{p \notin S} p = 1$.
 445 For enumerating conflict-free siphons in the set inclusion order, we can use
 446 the same technique as used in [17] but with the opposite setting, i.e., labeling
 447 directly the Boolean variables with decreasing value selection. The correct-
 448 ness of this technique comes from the fact that once S is found, it is the
 449 conflict-free siphon of maximum cardinality among all the remaining feasible
 450 conflict-free siphons. Similar to [17], the newly CSP-based method can also
 451 be implemented with SAT and CP solvers.

452 This method was implemented using the state-of-the-art CP solver Chuffed⁶ [36]
 453 via its MiniZinc [37] interface. Because it is a high-level interface, the
 454 backtrack-and-replay method of [17] was not used but rather the alterna-
 455 tive implementation with two global constraints for lexicographic ordering
 456 (ensuring enumeration of solutions) and iterated non-subset of each already
 457 found solution (for maximality).

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

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

and

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

458 We set a soft clause for each variable of the CSP and then use a “minimal
 459 correction subset” blocking strategy, which will ensure set-inclusion maxi-

⁶<https://github.com/chuffed/chuffed>

460 mality of the solutions. This is what is implemented in `Trappist` using the
 461 `RC2` MaxSAT solver [38] available through the `python-sat` package⁷.

462 4.3. Answer set programming-based method

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

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

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

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

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

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

463 for each $v \in V$. Note that the number of atoms of \mathcal{L} is only $2n$, whereas
 464 the ASP encoding shown in [7] has as many atoms as the number of prime-
 465 implicants of the Boolean network and that number might be exponential in
 466 n . In [8], there is an ASP characterization of trap spaces that does not rely
 467 on minimal DNFs either and thus seems very similar to our ASP encoding.
 468 Remarkably it only requires the DNF for the *activation* part, using the in-
 469 formation that it will only be used for locally-monotonic Boolean networks.
 470 We would therefore expect that, when available, it will have comparable per-
 471 formance on the ASP part (the ASP program would be approximately twice
 472 smaller, though redundancy is not always bad in that field), but can also
 473 avoid combinatorial explosion of the Petri net encoding for some formula

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

474 where the activation DNF is simple but the inhibition is not. Since `mpbn` is
 475 included in our benchmark this will be evaluated in our experiments.

476 Now, a solution (simply an answer set) $A \subseteq \mathcal{A}$ of \mathcal{L} is equivalent to a
 477 conflict-free siphon S of \mathcal{P} , thus a trap space m of \mathcal{N} . The conversion from A
 478 to m is straightforward. If $\mathbf{p-v} \in A$ then $v \in D_m$ and $m(v) = 0$. Conversely,
 479 if $\mathbf{n-v} \in A$ then $v \in D_m$ and $m(v) = 1$. Otherwise, $v \notin D_m$. Comput-
 480 ing multiple answer sets is built into ASP solvers and the solving collection
 481 `POTASSCO` [39] also features the option to find set-inclusion maximal answer
 482 sets with respect to the set of atoms. Naturally, a set-inclusion maximal
 483 answer set of \mathcal{L} is equivalent to a maximal conflict-free siphon of \mathcal{P} , thus a
 484 minimal trap space of \mathcal{N} . By using this built-in option, we can compute all
 485 the set-inclusion maximal answer sets of \mathcal{L} (resp. all the minimal trap spaces
 486 of \mathcal{N}) in one execution.

487 4.4. Integer linear programming-based method

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4.5. Computation of special types of trap spaces

In the field of systems biology, biologists may want to compute more special types of trap spaces beyond minimal trap spaces [20], which also play crucial roles in analysis and control of Boolean networks [21, 19]. We shall show that our proposed methods can be easily adjusted to compute such popular types of trap spaces. We illustrate the adjustments via the ASP-based method (see Subsection 4.3) because ASP is declarative by nature,

⁸<https://github.com/coin-or/Cbc>

515 but these adjustments are completely applicable for other approaches such
 516 as MaxSAT, CP, and ILP.

517 First, the work by [19] uses the concept of *stable motifs* to build the suc-
 518 cession diagram of a Boolean network, a summary of the decisions in the
 519 network dynamics that lead to successively more restrictive nested stable
 520 motifs. The succession diagram is useful for control and decision making
 521 on this Boolean network. In particular, the proposed control methods are
 522 independent to the update scheme. It has been shown that a stable motif of
 523 a Boolean network is equivalent to a maximal trap space of this Boolean net-
 524 work [19]. Hence, it is necessary to develop an efficient method for computing
 525 maximal trap spaces of a Boolean network. We shall show how to adjust the
 526 ASP-method presented in Subsection 4.3 to compute maximal trap spaces.

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

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

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

Second, we consider *fixed points* in Boolean networks. To date, the anal-
 ysis of the fixed points of a Boolean network remains a very useful tool in
 understanding the behavior of complex biological models not only due to the
 fact that in some cases the full computation of complex attractors remains
 intractable, but also because for many biological systems, the expected long-
 term behavior is not cyclic [41]. Furthermore, the fixed point computation is
 also the crucial starting point for several state-of-the-art methods for com-
 puting complex attractors of Boolean networks [35]. Let s be a fixed point of

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

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

530 that ensures that for every conflict-free siphon S , it contains either **p-v** or **n-v**
 531 for every $v \in V$. Equivalently, the trap space corresponding to S is always
 532 a fixed point. Now, the set of answer sets of the encoded ASP is equivalent
 533 to the set of fixed points of \mathcal{N} . In particular, when solving the encoded ASP
 534 using an ASP solver, we do not need to use the built-in option for computing
 535 set-inclusion maximal answer sets. Note that we can also build another ASP
 536 characterizing all fixed points of \mathcal{N} based on the equivalence between a fixed
 537 point of \mathcal{N} and a deadlock of its Petri net encoding [22]. This approach may
 538 give a more compact ASP.

Third, we consider the trap spaces *intersecting* a given subspace m^* of a Boolean network. Such trap spaces are used in the trap space-based control method [21]. A trap space m intersects m^* if and only if $S_{\mathcal{N}}[m] \cap S_{\mathcal{N}}[m^*] \neq \emptyset$. It follows that for every v , if $m^*(v) = 0$ then $m(v) = 0$ or $m(v) = \star$, if $m^*(v) = 1$ then $m(v) = 1$ or $m(v) = \star$. For the former case, we add to \mathcal{L} the ASP rule

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

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

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

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

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

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

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

`n-v.`

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

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

541 where $\{v_{i_1}, \dots, v_{i_k}\}$ is the set of free nodes of m^* . This rule ensures that
 542 $m \neq m^*$. In the case that $m^* = \varepsilon$, we have all maximal trap spaces of the
 543 original Boolean network.

544 5. Motivating example

545 For a few years now we have been collaborating with biologists who build
 546 very large detailed and annotated maps and now wish to analyze the dy-
 547 namics of the corresponding models. One of the main maps studied this way
 548 represents knowledge about the Rheumatoid Arthritis [42], and was the main
 549 motivation for the development of a tool to automatically transform it into
 550 an executable Boolean network [6]. In the supplementary material of the pa-
 551 per, an excerpt of the map, focused around the apoptosis (cell death) module
 552 is transformed into a model of *reasonable* size, namely 180 Boolean variables
 553 (model `F5_RA_apoptosis_executable_module.sbml` of supplementary ma-
 554 terial S3, and model “RA-apoptosis” of Section 6). The study of such model,
 555 though, is a big hurdle. Indeed, as stated in the article about another model
 556 of the same size: “*The size of the CaSQ-inferred MAPK model (181 nodes)*
 557 *made the calculation of stable states a non-realistic endeavour.*”

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

565 However, using a state-of-the-art tool like PyBoolNet [7] on that model
 566 actually fails at the phase of prime-implicant generation. `mpbn` [9] can return
 567 the first 1000 solution within 1.43s, but indeed, it limits the modeling range

of the modelers as it does not permit using non-locally-monotonic Boolean functions. This is also true for the Alzheimer model also mentioned in that same article and originally from [43] (F4 file in the original supplementary material, and “Alzheimer” in Table 2), where `PyBoolNet` also fails at the prime-implicant computation and `mpbn` does not give any answer because this model is actually non-locally-monotonic. The current practice usually revolves then around fixing some source nodes to plausible values and reducing the model accordingly. While this approach makes sense, it relies on potentially arbitrary decisions, and *hides away* critical modelling choices that were actually not part of the original Boolean network or even of the starting map.

For the “RA-apoptosis” model, using the ASP-based method presented in Section 4.3, it is possible to obtain the first 1000 minimal trap spaces (including ones that contain more than one state) within 0.19s, which is much quicker than `mpbn`. The needed time for the “Alzheimer” model is 0.79s. Unfortunately since this method was not available at the time, the analysis of the model remained very high-level and qualitative, instead of being able to use the rich information of computed minimal trap spaces.

6. Evaluation

To evaluate the performance of the newly proposed methods (implemented as a Python package named `Trappist` and available on the Python package index⁹) and the state-of-the-art methods (`bioLQM`¹⁰, `PyBoolNet` [7, 20], and `mpbn` [9]), we compared them on both `PyBoolNet`’s own model repository and many real-world models from various sources in the literature. To our knowledge, these models are a highly representative sample of Boolean models currently available. It is worth noting that `mpbn` [9] only handles locally-monotonic models, whereas the other methods can handle general models. To obtain a more comprehensive comparison, we also used random models generated by a third-party software `BoolNet` R package [30]. As explained in Section 5, in our benchmarks, we only searched for the first 1000 minimal trap spaces for each model. It is worth noting that unlike existing analysis shown in the literature, we did not fix specific values for source nodes in all the considered models.

⁹<https://pypi.org/project/trappist/>

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

601 To solve the ASP problems, we used the same ASP solver `Clingo` [39] and
602 the same configuration as that used in `PyBoolNet` [7, 20] and `mpbn` [9]. Specif-
603 ically, we used the configuration `-heuristic=Domain -enum-mod=domRec`
604 `-dom-mod=3` (subset maximality, equivalent to the deprecated `--dom-pref=32`
605 `--heuristic=domain --dom-mod=7` used by `PyBoolNet`). We ran all the
606 benchmarks on a machine whose environment is CPU: Intel® Core™ i9-
607 11950H 2.60GHz \times 16, 16 GB DDR4 RAM, Ubuntu 20.04.5 LTS. Finally,
608 we set a time limit of three minutes for each model.

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

613 6.1. *PyBoolNet* repository

614 Table 1 shows the experimental results on the models from the official
615 `PyBoolNet` repository¹¹. Column n denotes the number of nodes of each
616 model. Column $|M|$ denotes the number of minimal trap spaces and for
617 each method is given the computation time in seconds, asking only for the
618 first 1000 minimal trap spaces. “DNF” means that the method did not
619 finish the computation within the time limit of three minutes. In the case
620 of `bioLQM`, “N/A” means that the number of all minimal trap spaces of the
621 model is larger than 1000 and we did not recorded the running time of `bioLQM`
622 because it always requires to compute all minimal trap spaces. A number
623 in bold indicates a ratio greater than three compared to the best result.
624 “NM” indicates a non-locally-monotonic model. There are four variants of
625 `Trappist`: `SAT` (i.e., `Trappist-MaxSAT`, the MaxSAT-based method shown
626 in Subsection 4.2), `CP` (i.e., `Trappist-CP`, the CP-based method shown in
627 Subsection 4.2), `ILP` (i.e., `Trappist-ILP`, the ILP-based method shown in
628 Subsection 4.4), and `ASP` (i.e., `Trappist-ASP`, the ASP-based method shown
629 in Subsection 4.3).

630 We first analyze the results of the four variants of `Trappist`. We can
631 see that `Trappist-MaxSAT` and `Trappist-ASP` are comparable in most mod-
632 els, but `Trappist-ASP` is much faster for the `jaoude_thdiff` and `selvaggio_empt`
633 models where the number of minimal trap spaces is greater than 1000. The
634 latter can be explained by the fact that `Trappist-MaxSAT` follows an iter-

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

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

model	n	$ M $	LQM	PBN	mpbn	Trappist			
						SAT	CP	ILP	ASP
1 arellano_rootstem	9	4	0.13	0.01	0.00	0.00	0.97	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	DNF	DNF	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	DNF	DNF	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_tlgl	60	156	0.60	0.09	0.09	0.07	37.26	DNF	0.04
29 zhang_tlgl_v2	60	258	0.64	0.04	0.08	0.11	69.95	DNF	0.04

635 active approach, i.e., it restarts the search with a new constraint each time
 636 a solution is found (see Subsection 4.2). This iterative approach may be
 637 less efficient than the way ASP solvers use to enumerate multiple solutions
 638 (answer sets), which is an advantage of ASP solvers [39]. Hence, when
 639 the number of solutions increases, the inferiority of Trappist-MaxSAT com-
 640 pared to Trappist-ASP will be exhibited more clearly. The two remain-

ing variants, **Trappist-CP** and **Trappist-ILP**, are much less efficient than **Trappist-MaxSAT** and **Trappist-ASP** in every model, even are more than three orders of magnitude slower in some models. The first reason for their bad performance is that they are also iterative methods like **Trappist-MaxSAT**, thus they are not efficient for "enumeration" problems. Upon closer inspection, for the Boolean CSP characterizing conflict-free siphons, CP seems to be something that is a "less-efficient-SAT", handling mostly Boolean constraints and making little use of the global constraints only added for the iterative part. For ILP, it may be even worse, since the problem is purely Boolean (no real or integer numbers whatsoever). This is confirmed by the observation that for some quite large models (e.g., the `grieco_mapk`, `zhang_tlg1`, and `zhang_tlg1.v2` models), **Trappist-ILP** is much slower than **Trappist-CP**. Note that the inferiority of ILP compared to ASP with respect to the trap space enumeration has been reported in [7]. Hereafter, we shall compare the best variant of **Trappist** (i.e., **Trappist-ASP**) with other methods.

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

6.2. *BBM repository*

Currently, a research group has made a great effort for building a collection (called **BBM**) of real-world Boolean models from various sources used in systems biology. It aims to be a comprehensive collection suitable for benchmarking and testing new tools and methods. **BBM** consists of 211 models (24 out of them are non-locally-monotonic), peaking at 321 nodes, 1100 regulations among the nodes, and 133 source nodes, respectively. It is released and

677 maintained at <https://github.com/sybila/biodivine-boolean-models>.
678 We here tested all the compared methods on this model repository.

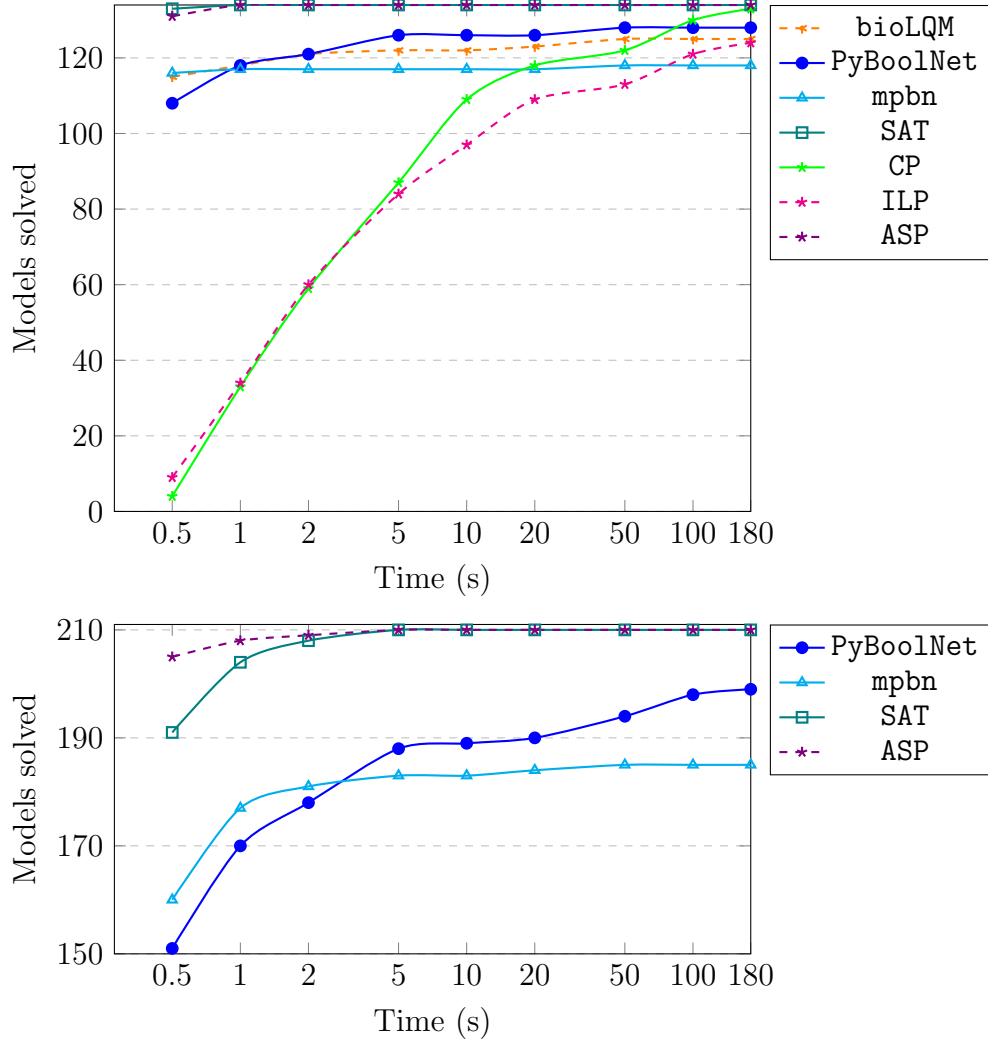


Figure 2: Cumulative numbers of the BBM models that have less than 1000 minimal trap spaces (upper panel) and BBM models solved by the compared methods with respect to enumerating the first 1000 minimal trap spaces (lower panel).

679 Figure 2 (upper panel) shows cumulative numbers of the BBM models that
680 have less than 1000 minimal trap spaces solved by the compared methods
681 with respect to enumerating the first 1000 minimal trap spaces. The number
682 of such models is 134 (per all 211 models), and 15 of them are non-locally-

monotonic. This model set allows us to fairly consider `bioLQM` for comparison, since `bioLQM` always requires to compute all minimal trap spaces. We can first see that `Trappist-ASP` and `Trappist-MaxSAT` are still the two best methods as they can handle every model within 1s as well as they always can handle more models than all the remaining methods on every time limit. Second, `Trappist-CP` is better than `Trappist-ILP`, which is consistent with their comparison shown in the previous subsection. Third, one notable remark is that for the time limit of 100s or 180s, `Trappist-CP` can handle more models than all `bioLQM`, `PyBoolNet`, and `mpbn`. This remark shows that even with a not best implementation, our alternative approach is still better than the state-of-the-art methods on a certain set of real-world models. This is supported by the fact that our alternative approach avoids the need for computing prime implicants (as opposed to `PyBoolNet`) and can handle non-locally-monotonic Boolean networks (as opposed to `mpbn`).

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

6.3. Selected models

We used a set of real-world Boolean networks lying in various scales collected from numerous bibliographic sources in the literature. Most of these models are quite big (in size), complex (i.e., having high average in-degree, which is related to the number of prime-implicants), and have never been fully analyzed. Note that these models are not included in the `PyBoolNet` and `BBM` repositories. We then applied `bioLQM`, `PyBoolNet`, `mpbn`, and the four variants of `Trappist` to computing minimal trap spaces of these real-world models. Table 2 shows the obtained experimental results. A number in bold indicates a ratio greater than or equal to 10 compared to the best

720 result. The remaining notations are similar to those in Table 1. Hereafter, we
721 analyze in detail the results with respect to minimal trap space computation.

Table 2: Timing comparisons (in seconds) between **bioLQM** (LQM), **PyBoolNet** (PBN), **mpbn** and the four variants of **Trappist** on selected models from the literature.

model	n	$ M $	LQM	PBN	mpbn	Trappist			
						SAT	CP	ILP	ASP
1 metastatic [44]	10	4	0.10	0.04	NM	0.01	1.15	0.89	0.02
2 Arabidopsis.thaliana [44]	15	8	0.10	0.06	NM	0.01	2.06	1.83	0.02
3 p53_high_dna [44]	16	1	0.38	1.76	NM	0.08	0.53	0.43	0.14
4 p53_low_dna [44]	16	1	0.41	1.76	NM	0.07	0.58	0.48	0.14
5 FT-GRN [45]	23	32	DNF	DNF	NM	0.03	8.41	12.38	0.19
6 DNA_damage [44]	26	16	0.24	0.33	NM	0.02	3.91	5.33	0.05
7 Rho-GTPases [44]	33	2	0.17	0.57	40.39	0.07	0.74	0.56	0.11
8 Pluripotency [46]	36	440	DNF	DNF	NM	0.16	138.92	DNF	0.28
9 Pluripotent [44]	36	276	0.37	0.43	NM	0.07	72.40	DNF	0.06
10 Pancreatic.Cancer [44]	43	1000+	N/A	0.11	0.36	0.17	DNF	DNF	0.06
11 Drosophila [47]	52	128	0.33	0.05	0.07	0.06	32.66	126.22	0.05
12 Cacace_TdevModel [48]	61	28	1.29	5.67	NM	0.06	7.51	23.15	0.08
13 hedgehog [44]	65	1000+	N/A	DNF	0.50	0.34	DNF	DNF	0.33
14 EMT [19]	69	268	39.22	1.01	0.20	0.12	75.81	DNF	0.05
15 Bcell [49]	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	DNF	DNF	0.15
17 Corral_ThIL17diff [41]	92	1000+	N/A	107.57	0.76	0.56	DNF	DNF	0.16
18 Adhesion_CIP [50]	121	78	56.81	4.25	0.23	0.17	25.20	DNF	0.19
19 EMT_Mech [51]	136	82	DNF	14.01	0.27	0.20	27.55	DNF	0.25
20 macrophage [44]	136	1000+	N/A	0.54	1.09	0.84	DNF	DNF	0.27
21 angiogenesis [44]	141	1000+	N/A	0.16	1.07	1.06	DNF	DNF	0.16
22 angiofull [52]	142	1000+	N/A	0.17	1.06	0.88	DNF	DNF	0.23
23 EMT_Mech_TGFBeta [51]	150	492	DNF	11.28	0.78	0.69	DNF	DNF	0.35
24 RA_apoptosis [6]	180	1000+	N/A	DNF	1.43	1.55	DNF	DNF	0.19
25 MAPK [6]	181	1000+	N/A	13.58	1.76	1.51	DNF	DNF	0.27
26 Snf1-pathway [53]	202	1000+	N/A	1.13	1.47	1.43	DNF	DNF	0.31
27 T-cell-co-receptor [44]	206	1000+	N/A	DNF	1.52	2.26	DNF	DNF	0.35
28 TcellCheckPoint [54]	218	1000+	N/A	4.99	NM	1.96	DNF	DNF	0.28
29 Mycobacterium [44]	317	1000+	N/A	0.42	2.36	4.91	DNF	DNF	0.44
30 Leishmania [44]	342	1000+	N/A	DNF	2.56	5.62	DNF	DNF	0.46
31 Cholocystokinin [6]	383	1000+	N/A	0.36	2.99	4.81	DNF	DNF	0.37
32 Alzheimer [6]	762	1000+	N/A	DNF	NM	18.21	DNF	DNF	0.79

722 First, we obtained some observations on the four variants of **Trappist**
723 consistent with the observations obtained in the previous subsections. More
724 specifically, **Trappist-ASP** is still the best variant with a running time below
725 one second for every model, and followed by **Trappist-MaxSAT**. In particular,

726 the difference in running time between **Trappist-ASP** and **Trappist-MaxSAT**
727 is bigger for larger models or models with more than 1000 minimal trap
728 spaces. **Trappist-CP** and **Trappist-ILP** still have a much worse perfor-
729 mance, with **Trappist-CP** better than **Trappist-ILP**. They still can handle
730 no model with more than 1000 minimal trap spaces. However, **Trappist-CP**
731 or **Trappist-ILP** can handle the FT-GRN and Pluripotency models, whereas
732 all **bioLQM**, **PyBoolNet**, and **mpbn** cannot.

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

739 Third, for 11 of the 32 models (more than 34%), **mpbn** did not give any
740 answer because these models are non-locally-monotonic. For 21 of the 32 mod-
741 els where **mpbn** returned the answers, **mpbn** and **Trappist-ASP** are roughly
742 comparable in computation time, but **mpbn** appears quite slower on aver-
743 age. In particular, for the Rho-GTPases model, **mpbn** is $577\times$ slower than
744 **Trappist-ASP**. This observation along with the comparisons between **mpbn**
745 and **Trappist-ASP** in the previous subsections are quite surprising because
746 the ASP encoding of **mpbn** only requires the DNF for the activation part of a
747 Boolean function, whereas that of **Trappist-ASP** requires both the activation
748 and inhibition parts (see Subsection 4.3). However, the reason may lie on the
749 differences in the ASP encoding characteristics of the two methods and the
750 fact that **mpbn** needs to spend time checking the locally-monotonicity of each
751 Boolean function in a Boolean network. We expect that **mpbn** may outper-
752 form **Trappist** for a certain set of models, but not for the set of real-world
753 models considered in this article.

754 Fourth, regarding the comparison of the ASP-based methods (i.e., **PyBoolNet**,
755 **mpbn**, and **Trappist-ASP**), we note that for all the models where **PyBoolNet**
756 did not finish before the time limit, the timeout occurred during the compu-
757 tation of the prime-implicants. Hence, not even a single minimal trap space
758 was output by that method. For all the remaining models, once **PyBoolNet**
759 went through the prime-implicant phase, its ASP solving phase quickly re-
760 turned the first 1000 minimal trap spaces, all under one second. Hence,
761 with the experimental results shown in this subsection as well as the two
762 previous subsections, the practical differences between the ASP encoding of
763 **Trappist-ASP** and that of **PyBoolNet** are not distinctly exposed. The fact

764 that our new ASP encoding is guaranteed to be linear in the number of nodes
 765 of the original model (see Subsection 4.3) does not seem to be crucial here,
 766 however a much deeper analysis of those cases shall be shown in the next
 767 subsection.

768 6.4. Randomly generated models

769 We randomly generated a set of N-K models [1] with network size n in the
 770 set $\{100, 150, 200, 250, 300, 350, 400\}$ and in-degree $K = 3$ (i.e., each node
 771 has exactly three input nodes). We chose N-K models because they are a
 772 useful tool for studying the dynamics of Boolean networks [1, 7, 19]. For each
 773 network size, 50 instances were generated using the `generateRandomNKNetwork`
 774 function. In total, we have 350 random models. We then applied the com-
 775 pared methods to these models and recorded the running time of each method
 776 for each model. It is worth noting that N-K models usually have small
 777 numbers of minimal trap spaces [7]. Hence, we searched for all solutions
 778 in each model, which makes the comparison to `bioLQM` more comprehen-
 779 sive. In addition, each node has only three input nodes, i.e., the number
 780 of prime-implicants of the associated Boolean function is small. Hence,
 781 `PyBoolNet` always passed the phase of computing prime-implicants in ev-
 782 ery model even within one second, which enables us to compare the ASP
 783 encoding of `PyBoolNet` and that of `Trappist-ASP`.

784 Figure 3 shows cumulative numbers of random models solved by the com-
 785 pared methods with respect to enumerating all the minimal trap spaces. The
 786 number of succeeded models within three minutes for each method is: `bioLQM`
 787 (0), `PyBoolNet` (320), `mpbn` (0), `Trappist-maxSAT` (338), `Trappist-CP` (226),
 788 `Trappist-ILP` (39), `Trappist-ASP` (349). We can see that `Trappist-ASP` is
 789 the only method that can handle every model, but one. Note that none of
 790 the other methods can handle that only model failed by `Trappist-ASP`. We
 791 also obtained some observations consistent with those obtained for real-world
 792 models. More specifically, `Trappist-MaxSAT` is still the second best method
 793 and `Trappist-CP` is better than `Trappist-ILP`. Upon closer inspection, we
 794 obtained several notable observations as follows.

795 First, `mpbn` was not able to handle any model because all the models
 796 are non-locally-monotonic. Recall that a Boolean network is non-locally-
 797 monotonic if only one of its Boolean functions is non-locally-monotonic.
 798 Hence, it is apparent that all this type of randomly generated models are
 799 non-locally-monotonic because of the number of nodes is large ($n \geq 100$).
 800 This observation confirms a limit on the applicable model class of `mpbn`.

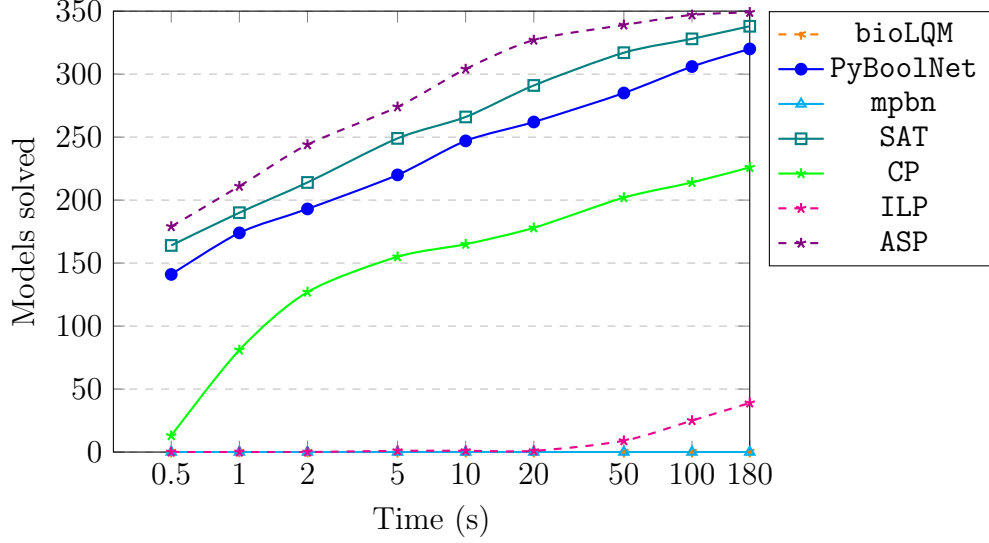


Figure 3: Cumulative numbers of random models solved by the compared methods with respect to enumerating all the minimal trap spaces.

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

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

6.5. Experimental summary

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

819 Among the four variants of the alternative approach, **Trappist-ASP** is the
820 best method as it vastly outperforms all the other variants. The second best
821 one is **Trappist-MaxSAT**. The two remaining variants (i.e., **Trappist-CP** and
822 **Trappist-ILP**) give bad performance for most models. However, for certain
823 cases, they are still better than all state-of-the-art methods (i.e., **bioLQM**,
824 **PyBoolNet**, and **mpbn**). This is evidence for the advantages of an alternative
825 approach compared to what preexisted.

826 Regarding general Boolean networks, **Trappist-ASP** (even **Trappist-MaxSAT**)
827 is far more efficient than both **bioLQM** and **PyBoolNet**. The speedups of
828 **Trappist-ASP** or **Trappist-MaxSAT** are large, even between one and three
829 orders of magnitude for most models. In addition, the experimental results
830 also confirm that the ASP encoding of **Trappist-ASP** is much more efficient
831 than that of **PyBoolNet**.

832 Regarding locally-monotonic Boolean networks, the performance of **mpbn**
833 is roughly comparable to that of **Trappist-ASP** or **Trappist-MaxSAT**. How-
834 ever, **mpbn** is quite slower than **Trappist-ASP** on average. This shows the
835 practical advantage of **Trappist-ASP** compared to **mpbn**, though its ASP
836 encoding may be more complex than that of **mpbn** in theory.

837 7. Conclusion

838 In this article we have explored and proved for the first time the equiva-
839 lence between (minimal) trap spaces of a general Boolean network and (max-
840 imal) conflict-free siphons of its Petri net encoding. We have shown sev-
841 eral useful applications of this finding to studying properties of trap spaces
842 in Boolean networks. As an important practical application of the equiva-
843 lence, we have proposed a new approach for the computation of minimal trap
844 spaces in Boolean networks, based on the enumeration of maximal conflict-
845 free siphons of Petri nets. We have also proposed the four possible methods
846 using MaxSAT, CP, ILP, and ASP for implementing the new approach. In
847 particular, we have shown how to adjust our approach to compute several
848 specific types of trap spaces (e.g., maximal trap spaces, fixed points), which
849 besides minimal trap spaces also play crucial roles in the analysis and con-
850 trol of Boolean networks. The proposed methods for the minimal trap space
851 computation have been evaluated on many real-world models from the liter-
852 ature as well as randomly generated models. The experimental results show
853 that the new approach vastly outperforms all the state-of-the-art methods
854 in terms of general Boolean networks and is comparable to the **mpbn** method

855 even much better on average in terms of locally-monotonic Boolean net-
856 works. We believe that this opens up the way to a much better analysis
857 of large Boolean networks, which is needed with the advent of automatic
858 model-generation pipelines [55].

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

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

882 Finally, we think that the links between Petri nets and Boolean networks
883 that we stumbled upon in this method might have deeper roots. Exploring
884 those connections might lead both to interesting topics of research for Petri
885 nets, like a notion of trap-spaces, and for Boolean networks. We also believe
886 that the connection between trap spaces of Boolean networks and siphons
887 of Petri nets can be a very useful tool for exploring and proving more new
888 properties of trap spaces in Boolean networks, as we have used it to success-
889 fully prove the independence of trap spaces to the update scheme and the
890 separation of minimal trap spaces. Diving into this direction is promising
891 and one of our future work.

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