Finding minimal siphons and traps as a Constraint satisfaction Problem

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Abstract. Bridging the gap between quantitative and qualitative models, Petri nets (also known as place/transition graphs) have recently emerged as a promising tool for modeling and analysis of biochemical networks. In this paper, we present a method to compute the minimal siphons and traps of a Petri net as a resolution of a CSP. In our case, siphons and traps are purely structural properties that brings us information about the persistence of some molecular species. We present a program that finds minimal siphons and traps containing specific set of places in a Petri net.

1 Introduction

During recent years, Systems Biology has become a rich field of study, trying to encompass the huge amount of heterogeneous information that becomes available thanks to the new high-throughput techniques of biologists, that requires the development of scalable analyzes for detailed models of complex systems.

Some models have been growing bigger and bigger, filled with more and more mechanistic details, especially recently acquired post-transcriptional information, but lacking most of precise kinetic data. Unfortunately, very few analyzes allow to extract information about the dynamics of these models, either because of their size or of the imprecise kinetics. Other models remain of reasonable size, but have an even larger uncertainty about parameter values. For this other kind of model it is also important to be able to provide some dynamical analysis of the system's behavior.

The use of Petri nets to represent biochemical reaction models, by mapping molecular species to places and reactions to transitions, was introduced quite late in [16], together with Petri net concepts and tools new for the analysis of biochemical networks.

In this paper, we consider the Petri net concepts of siphons and traps. These structures have already been considered for the analysis of metabolic networks in [21]. A siphon is a set of places that, once it is unmarked, remains so. A trap is a set of places that, once it is marked, can never loose all its tokens. Siphons can correspond to a set of metabolites that are gradually reduced during starvation whereas traps can correspond to accumulation of metabolites that are produced during the growth of an organism. In this article, after some preliminaries about Petri nets and siphons and traps, we give our CSP model for enumerating minimal siphons and traps containing a given set (possibly empty) in a Petri net.

2 Preliminaries

2.1 Petri Nets

A Petri net graph PN is a weighted bipartite directed graph $PN = (P, T, W)$, where P is a finite set of vertices called places, T is a finite set of vertices (disjoint from P) called transitions and $W : ((P \times T) \cup (T \times P)) \to \mathbf{N}$ represents a set of directed arcs weighted by non-negative integers (the weight zero represents the absence of arc). A marking of a Petri net graph is a mapping $m : P \to \mathbf{N}$ which assigns a number of tokens to each place. A (marked) Petri net is a 4-tuple (P, T, W, m_0) where (P, T, W) is a Petri net graph and m_0 is an initial marking.

The set of predecessors (resp. successors) of a transition $t \in T$ is the set of places ${}^\bullet t = \{p \in P \mid W(p,t) > 0\}$ (resp. $t^\bullet = \{p \in P \mid W(t,p) > 0\}$). Similarly, the set of predecessors (resp. successors) of a place $p \in P$ is the set of transitions ${}^\bullet p = \{t \in T \mid W(t,p) > 0\}$ (resp. $p^\bullet = \{t \in T \mid W(p,t) > 0\}$).

For every markings $m, m' : P \to \mathbf{N}$ and every transition $t \in T$, there is a transition step $m \xrightarrow{t} m'$, if for all $p \in P$, $m(p) \geq W(p,t)$ and $m'(p) = m(p) - W(p,t) + W(t,p)$. This notation extends to sequence of transitions $\sigma = (t_0 \dots t_n)$ by writing $m \xrightarrow{\sigma} m'$ if $m \xrightarrow{t_0} m_1 \xrightarrow{t_1} \dots \xrightarrow{t_{n-1}} m_n \xrightarrow{t_n} m'$ for some markings $m_1, \dots, m_n$.

2.2 Siphons and Traps

Let $PN = (P, T, W)$ be a Petri-net graph.

Definition 1. *A trap is a non-empty set of places $P' \subseteq P$ whose successors are also predecessors: $P'^\bullet \subseteq {}^\bullet P'$.*

A siphon is a non-empty set of places $P' \subseteq P$ whose predecessors are also successors: ${}^\bullet P' \subseteq P'^\bullet$.

It is worth remarking that a siphon in PN is a trap in the dual Petri net graph, obtained by reversing the direction of all arcs in PN.

The following propositions show that traps and siphons provide a structural characterization of some particular dynamical properties on markings.

Proposition 1. *[15] For every subset $P' \subseteq P$ of places, P' is a trap if and only if for any marking $m \in \mathbf{N}^P$ with $m_p \geq 1$ for some place $p \in P'$, and any marking $m' \in \mathbf{N}^P$ such that $m \xrightarrow{\sigma} m'$ for some sequence σ of transitions, there exists a place $p' \in P'$ such that $m'_{p'} \geq 1$.*

Proposition 2. *[15] For every subset $P' \subseteq P$ of places, P' is a siphon if and only if for any marking $m \in \mathbf{N}^P$ with $m_p = 0$ for all $p \in P'$, and any marking $m' \in \mathbf{N}^P$ such that $m \xrightarrow{\sigma} m'$ for some sequence σ of transitions, we have $m'_{p'} = 0$ for all $p' \in P'$.*

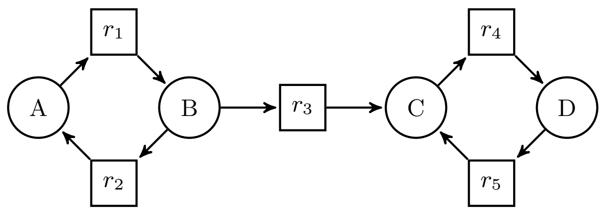

Fig. 1. Petri net graph of Example 1.

Example 1. In the Petri-net graph depicted in Figure 1, $\{A, B\}$ is a minimal siphon: $^\bullet\{A, B\} = \{r_1, r_2\} \subset \{A, B\}^\bullet = \{r_1, r_2, r_3\}$. $\{C, D\}$ is a minimal trap: $\{C, D\}^\bullet = \{r_4, r_5\} \subset {}^\bullet\{C, D\} = \{r_3, r_4, r_5\}$.

2.3 Minimality

A trap (resp. siphon) is minimal if it does not contain any other trap (resp. siphon). One reason to consider minimal siphons is that they provide a sufficient condition for the non-existence of deadlocks. It has been shown indeed that in a deadlocked Petri net (i.e. where no transition can fire) all unmarked places form a siphon [3]. Accordingly, the siphon-based approach for deadlocks detection checks if the net contains a proper siphon (a siphon is proper if its predecessors set is strictly included in its successors set) that can become unmarked by some firing sequence. A proper siphon does not become unmarked if it contains an initially marked trap. If such a siphon is identified, the initial marking is modified by the firing sequence and the check continues for the remaining siphons until a deadlock is identified, or until no further progress can be done. Considering only the set of minimal siphons is enough because if any siphon becomes unmarked during the analysis, then at least one of the minimal siphons must be unmarked.

Other links with behavioral properties of liveness are summarized in [8].

3 Complexity and Algorithms

3.1 Complexity

The problem of computing the set of minimal siphons of a given Petri net is EXPSPACE since there can be an exponential number of such structures. This is the case in the model given in the following example and depicted in Figure 3.1.

Example 2. The following model has 2^n minimal siphons and 2^n minimal traps, each including either Ai or Bi for all i but not both of them: A1 +B1 =>A2 +B2 A2 +B2 =>A3 +B3, . . . , An +Bn =>A1 +B1.

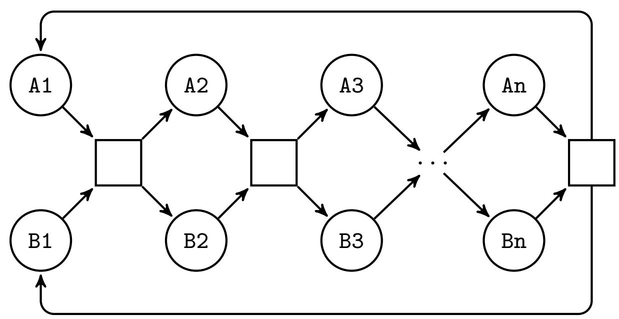

Fig. 2. Petri net representation of the model of Example 2.

Moreover, the decision problem of the existence of a minimal siphon containing a given place is NP-complete [19]. On the other hand, deciding whether a Petri net contains a siphon or a trap and exhibiting one if it exists is polynomial [6].

3.2 Constraint Programming Algorithm

In the literature, many algorithms have been proposed to compute minimal siphons and traps of Petri nets. Since a siphon in a Petri net N is a trap of the dual net N', it is enough to focus on siphons, the traps are obtained by duality. Some algorithms are based on inequalities [14], logic equations [9,13], or algebraic approaches [11]. More recent methods were presented in [19,20,6]. In this section we present a constraint satisfaction algorithm for solving this problem with a good practical efficiency.

The search for siphons can be viewed as a Constraint Satisfaction Problem (CSP), in a similar manner to what has been done in mixed integer linear programming in [5] or in constraint logic programming for P- and T-invariants in [18]. For a Petri net of n places and m transitions, a siphon S is a set of places whose predecessors are also successors. S can be represented with a vector $\boldsymbol{V}$ of $\{0,1\}^n$ such that for all $i \in \{1,2,..,n\}$, $V_i = 1$ if and only if $p_i \in S$.

It is quite natural to see this as a CSP on n Boolean variables. The siphon constraint can be formulated as $\forall i, V_i = 1 \Rightarrow (\forall t \in T, t \in {}^\bullet p_i \Rightarrow t \in (\cup_{V_j=1}\{p_j\})^\bullet)$. This constraint is equivalent to $\forall i, V_i = 1 \Rightarrow {}^\bullet p_i \subseteq (\bigcup_{V_j=1}\{p_j\})^\bullet$ which can be written again as $\forall i, V_i = 1 \Rightarrow \bigwedge_{t \in {}^\bullet p_i}(\bigvee_{p_j \in t^\bullet} V_j = 1)$. Under this later form, the constraint is a Boolean constraint that can be directly processed in a constraint programming system.

To exclude the case of the empty set, we add the constraint $\bigvee_i V_i = 1$.

To ensure minimality, variable values are enumerated by trying sets of smallest cardinality first. A branch and bound procedure is wrapped around this enumeration, maintaining a set $\mathcal{M}$ of minimal siphons: after finding a new minimal siphon, the constraint that the next solution should not have its support bigger than any vector already present in $\mathcal{M}$ is added. In other words, a vector $\boldsymbol{V}$ is minimal in the set $\mathcal{M}$ if $\forall m \in \mathcal{M}, \exists i, V_i = 0 \wedge m_i = 1$.

In a post-processing phase, the set of minimal siphons can be filtered to only keep minimal siphons that contain a given set of places, in order to solve the above mentioned NP-complete problem.

These constraints and search strategy constitute a constraint satisfaction algorithm which has been implemented in GNU PROLOG [7], a Prolog compiler with constraint solving over finite domains facilities. The program can be used to either enumerate minimal siphons and traps containing a given set of places (possibly empty), check whether a set of places is a siphon or a trap.

4 Evaluation

Compared to the mixed integer linear model [5], our CSP seems to compare favorably on random instances given in that article. In this section, we evaluate its performance on systems biology models.

The MAPK signal transduction cascade [12] is a well studied system that appears in lots of organisms and is very important for regulating cell division. The following table shows the minimal siphons of this model.

MAPK, MAPKMEKpp, MAPKp, MAPKpMAPKPH, MAPKpMEKpp,MAPKpp, MAPKppMAPKPH
MAPKMEKpp, MAPKpMEKpp, MEK, MEKp, MEKpMEKPH, MEKpp, MEKppMEKPH, MEKpRAFp, MEKRAFp
MAPKPH, MAPKpMAPKPH, MAPKppMAPKPH
MEKPH, MEKpMEKPH, MEKppMEKPH
MEKpRAFp, MEKRAFp, RAF, RAFp, RAFpRAFPH, RAFRAFK
RAFK, RAFRAFK
RAFPH, RAFpRAFPH

Table 1. Minimal siphons of the MAPK cascade model of [12]

The proposed implementation appears to scale up quite well also on bigger models. In particular, on the largest interaction maps of the cell cycle control we have, the performance figures are as follows:

– Schoeberl's model of the MAP kinase cascade activated by surface and internalized EGF receptors [17] contains 100 places and 242 transitions.13 minimal siphons and 15 minimal traps are computed in almost 20 ms [1].
– Calzone et al. E2F/Rb [1] has 408 places and 534 transitions. Its 74 minimal siphons and 250 minimal traps are computed in about 2000 seconds and less than 5 seconds respectively.
– Khon's map [10,2] has 509 places and 775 transitions. Its 81 minimal siphons and 297 minimal traps are both computed in around 10 seconds.

5 Conclusion

Siphons and traps define meaningful pools of compounds that display a specific behavior during the dynamical evolution of a biochemical system.

We have described a constraint satisfaction algorithm for computing siphons and traps and evaluated its scalability on almost biggest biochemical models available in the Biomodels repository [2].

The idea of applying constraint based methods to classical problems of the Petri-net community is not new, but seems currently mostly applied to the model-checking. We argue that structural problems can also benefit from the know-how developed for finite domain CP solving. The CSP model of minimal siphons and traps computation extends naturally to the previous model for P- and T-invariants search as a CSP [18].

In a parallel work, we have shown that siphons and traps entail a family of particular stability properties which can be characterized by a fragment of CTL [4] over infinite state structures. This fragment of Boolean CTL formulas can thus be verified efficiently thanks these structural properties.

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[1] computation time on a PC with an intel Core2 Quad processor 2.8GHz and 8Go of memory.
[2] dated January 2011

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