A Boolean Model for Enumerating Minimal Siphons and Traps in Petri nets

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Chemical Reaction Systems for Systems Biology

BioModels.Net

Repository of chemical reaction systems for systems biology

403 curated models

biggest model:
194 species, 313 reactions

average:
$\sim$ 50 species, $\sim$ 90 reactions

Example: *Michaelis–Menten* enzymatic reactions

Reaction model:

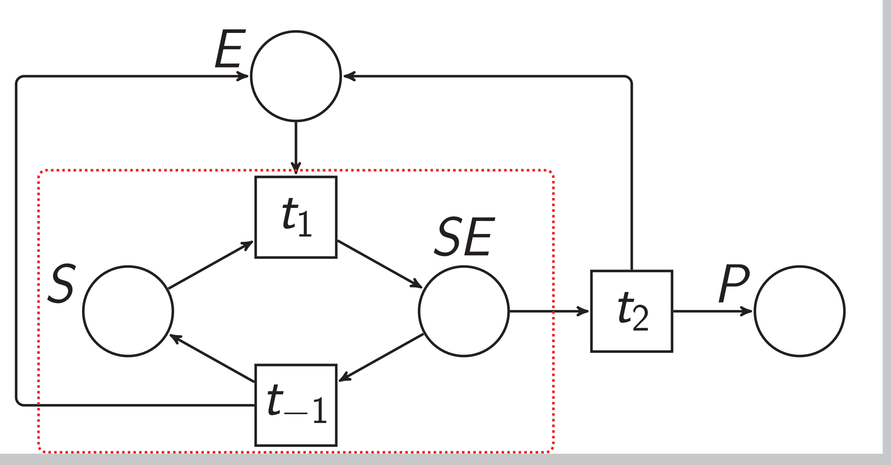
$$S + E \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_3} E + P$$

1913 *Die Kinetik der Invertinwirkung.*
L. Menten, M.I. Michaelis. Biochem.

1962 *Kommunikation mit Automaten.*
Carl Adam Petri. Ph. D. Thesis.

Structural model: Reaction graph

Petri-net
=
reaction graph+discrete dynamics



Siphons in Petri nets

Dynamic Characterization: a subset S of places such that once S is empty, it remains empty

$$\forall p \in S, m_p = 0 \quad \wedge \quad m \to m' \quad \Rightarrow \quad \forall p \in S, m'_p = 0$$

Structural Characterization: S siphon iff $^\bullet S \subseteq S^\bullet$

($^\bullet S$ set of predecessors $\quad S^\bullet$ set of successors)

e.g. in *Michaelis–Menten*: $^\bullet\{S, SE\} = \{t_1, t_{-1}\} \subseteq \{S, SE\}^\bullet = \{t_1, t_{-1}, t_2\}$

Related work: P-invariant, conservation law ODE invariant

2012 *Invariants and Other Structural Properties of Biochemical Models as a Constraint Satisfaction Problem.*
Sylvain Soliman. Algorithms for Molecular Biology.

Useful for liveness analyses in biology

Characterize dead-locks. *e.g.* starch production and accumulation in the potato tubers during growth

2003 *Topological analysis of metabolic networks based on petri net theory.*
I. Zevedei-Oancea and S. Schuster. Silico Biology.

Finding Siphons: a Combinatorial Problem

NP-complete Problems:

- Finding a siphon of cardinality k
  1996 *Finding minimal siphons in general petri nets.*
  S. Tanimoto, M. Yamauchi, and T. Watanabe. IEICE.
- Finding a minimal siphon containing a place p
  1999 *Time complexity analysis of the minimal siphon extraction problem of petri nets.* S. Tanimoto, M. Yamauchi, and T. Watanabe. IEICE.

Nevertheless, our Goal: **Enumerating all minimal siphons!**

State-of-the-art algorithms:

1986 *Generating siphons and traps by petri net representation of logic equations.*
M. Kinuyama and T. Murata. SIG-IECE.

2003 *Some results on the computation of minimal siphons in petri nets.*
R. Cordone, L. Ferrarini, and L. Piroddi. IEEE DC.

2005 *Enumeration algorithms for minimal siphons in petri nets based on place constraints.* R. Cordone, L. Ferrarini, and L. Piroddi. IEEE TSC.

2012 *Computation of all minimal siphons in Petri nets.*
S.G. Wang, Y. Li, C.Y. Wang, M.C. Zhou. ICNSC.

Boolean Model of Siphons

variables $\quad (\forall p)\ X_p = 1 \Leftrightarrow p \in S$

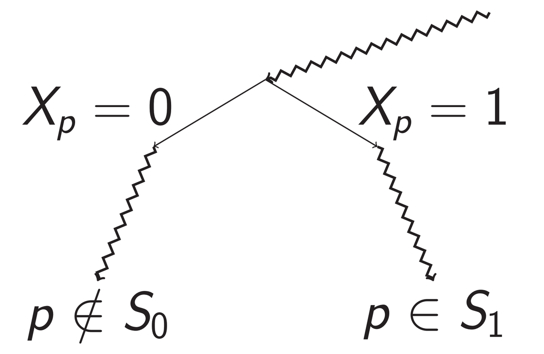
constraints $\quad (\forall p) X_p = 1 \Rightarrow \bigwedge_{t \in {}^\bullet p} \bigvee_{p' \in {}^\bullet t} X_{p'} = 1$

Finding siphons is reduced to finding Boolean assignments satisfying these formulas.

Search strategy

- Find **minimal siphons** first

Value selection strategy: **first 0 then 1**



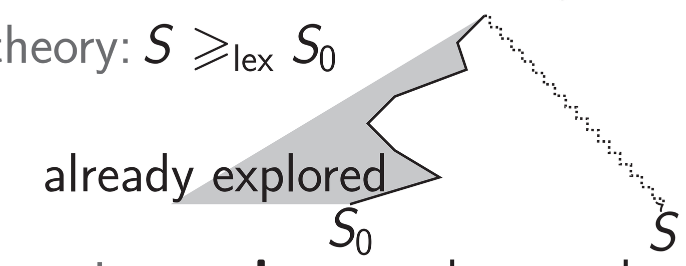
S_1 right of S_0 in search tree $\Longrightarrow S_1 \not\subseteq S_0$

- **All siphons**: Branch & Bound

After having found a siphon S_0 is found

1. add the constraint $\bigvee_{p \in S_0} X_p = 0$
2. **restart** the search **efficiently**:

In theory: $S \geqslant_{\text{lex}} S_0$



In practice: **replay** search procedure

Resolution with SAT and CLP($\mathcal{B}$)

database	#models	total time (in ms.) state-of-the-art algorithm	miniSAT	GNU Prolog
Biomodels.net	403	19734	611	195
Petriweb	80	2325	156	6

model	# siphons	state-of-the-art algorithm	miniSAT	GNU Prolog
Kohn's map of cell cycle	81	28	1	221
Biomodel #175	3042	∞	137000	∞
Biomodel #205	32	21	1	34
Biomodel #239	64	2980	1	22

- CP in GNU Prolog as good as miniSAT.
- Amazingly fast resolution on some large instances!

Bounded tree-widths (extension of the paper)

Lemma. If a Petri-net has a tree-width w, then the associated Boolean model has tree-width $\mathbf{O}(w)$.

Proof. The tree decomposition of the Petri-net maps to a tree decomposition of the associated Boolean model of proportional width. □

Theorem. The following problems

- finding siphon of cardinality k
- finding minimal siphon containing a place p

are **polynomial** for Petri-nets of **fixed tree-width**.

Proof. 2000. *A Comparison of Structural CSP Decomposition Methods.* Gottlob, Leone, Scarcello. Artificial Intelligence. □

Biomodels generally have **small tree-width**.

Modeling leads to understanding

- Boolean model outperforms state-of-the-art algorithms.
- "Real life" instances may have characteristics that NP-complete proofs ignore: bounded tree-width, regularity...

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