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

Faten Nabli, François Fages, Thierry Martinez, Sylvain Soliman
EPI Contraintes, Inria Paris-Rocquencourt, France

BioModels.Net
Repository of chemical reaction systems for systems biology

Example: Michaelis– Menten enzymatic reactions
Reaction model:
\[ S + E \xrightarrow{\kappa_1} SE \xrightarrow{\kappa_2} E + P \]
Structural model: Reaction graph
Petri-net

Siphons in Petri nets
Dynamic Characterization: a subset \( S \) of places such that
once \( S \) is empty, it remains empty
\[ \forall p \in S, m_p = 0 \land m \rightarrow m' \Rightarrow \forall p \in S, m_p' = 0 \]
Structural Characterization: \( S \) siphon if \( S \subseteq S^* \)
\( \ast \) set of predecessors \( S^* \) set of successors
\( \ast \) in Michaelis–Menten: \( \ast \{ S, \{ E \} \} = \{ t_1, t_2 \} \subseteq \{ S, \{ E \} \}^* = \{ t_1, t_2, t_3 \} \)
Related work: P-invariant, conservation law ODE invariant
2012 Invariants and Other Structural Properties of Biochemical Models as a Constraint Satisfaction Problem.

Finding Siphons: a Combinatorial Problem
NP-complete Problems:
- Finding a siphon of cardinality \( k \)
- Finding a minimal siphon containing a place \( p \)

State-of-the-art algorithms:
1986 Generating siphons and traps by petri net representation of logic equations.
M. Kinugawa and T. Murata. SIG-IEICE.
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. ICSNS.

Booleans Model of Siphons
variables \( \forall p \) \( X_p = 1 \Rightarrow p \in S \)
constraints \( \forall p \) \( X_p = 1 \Rightarrow \bigwedge_{p \in \Delta p} \bigvee_{p \in S^*} X_p = 1 \)
Finding siphons is reduced to finding Boolean assignments satisfying these formulas.

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

<table>
<thead>
<tr>
<th>database</th>
<th>#models</th>
<th>total time (in ms.)</th>
<th>state-of-the-art algorithm</th>
<th>minSAT</th>
<th>GNU Prolog</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biomodels.net</td>
<td>403</td>
<td>19734</td>
<td>611</td>
<td>195</td>
<td>6</td>
</tr>
<tr>
<td>Petriweb</td>
<td>80</td>
<td>2325</td>
<td>150</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

Kohn’s map of cell cycle
81         28            1   221
BioModel \#175 3042   \infty                  137000 \infty
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 \( O(w) \).

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.


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...