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

Faten Nabli, François Fages, Thierry Martinez, and Sylvain Soliman (PhD thesis)

INRIA

Wednesday 10 October, CP’2012
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Repository of chemical reaction systems for systems biology

406 curated models

biggest model has 194 species, 313 reactions

average $\sim$ 50 species, $\sim$ 90 reactions
Michaelis–Menten enzymatic reactions

Reaction model

\[ S + E \xrightleftharpoons[k_2]{k_1} ES \xrightarrow{k_3} E + P \]

“Compilation” in an ODE model

\[
\begin{align*}
\frac{dS}{dt} &= -k_1 \times S \times E + k_2 \times ES \\
\frac{dP}{dt} &= k_3 \times ES \\
\frac{dE}{dt} &= -k_1 \times S \times E + (k_2 + k_3) \times ES \\
\frac{dES}{dt} &= k_1 \times S \times E - (k_2 + k_3) \times ES \\
\end{align*}
\]

Conservation laws:
\[
E + ES = cte
\]
\[
P + S + ES = cte
\]

Reduced model:
\[
\begin{align*}
\frac{dS}{dt} &= k_2 \times ES - k_1 \times E \times S \\
\frac{dES}{dt} &= k_1 \times E \times S - (k_2 + k_3) \times ES
\end{align*}
\]

1913 *Die Kinetik der Invertinwirkung.*
Michaelis–Menten enzymatic reactions

Structural model: Reaction graph

Petri-net = reaction graph + discrete dynamics

\[
S + E \rightleftharpoons ES \rightarrow E + P
\]

Petri-net Discrete Dynamics

Petri-net Discrete Dynamics

1993  *Petri net representations in metabolic pathways.*  
Intelligent Systems for Molecular Biology.
Petri-net Discrete Dynamics

Petri-net Discrete Dynamics

Related work  P-invariant: conservation law ODE invariant

Related work P-invariant: conservation law ODE invariant

2012 *Invariants and Other Structural Properties of Biochemical Models as a Constraint Satisfaction Problem.*
Petri-net Discrete Dynamics

Petri net representations in metabolic pathways.
Intelligent Systems for Molecular Biology.

Related work P-invariant: conservation law ODE invariant

Invariants and Other Structural Properties of Biochemical Models as a Constraint Satisfaction Problem.
Siphons: Structural Characterization

• $S$ set of predecessors  
  $S^*$ set of successors

\[
\{S, ES\} = \{t_1, t_{-1}\} \quad \{S, ES\}^* = \{t_1, t_{-1}, t_2\}
\]

$S$ siphon  iff  $\bullet S \subseteq S^*$
Dynamic Characterization of Siphons

a subset $S$ of places such that
once $S$ is empty, it remains empty

$$\forall p \in S, m_p = 0 \land m \rightarrow m' \Rightarrow \forall p \in S, m'_p = 0$$

classify dead-locks:
useful for liveness analyses in biology

e.g. starch production and accumulation
    in the potato tubers during growth

2003 Topological analysis of metabolic networks based on petri net theory.
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*
ICNSC.
Boolean Model of Siphons

variables

\[(\forall p) \ X_p = 1 \iff p \in S\]

constraints

\[(\forall p) \ X_p = 1 \Rightarrow \bigwedge_{t \in \bullet p} \bigvee_{p' \in \bullet t} X_{p'} = 1\]

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

2002  *Characterization of minimal and basis siphons with predicate logic and binary programming.*
R. Cordone, L. Ferrarini, and L. Piroddi. IEEE CACSD.

Resolution of a *Mixed Integer Programming* model

slower than the state-of-the-art algorithm

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

<table>
<thead>
<tr>
<th>PN size</th>
<th>#minimal siphons (avg)</th>
<th>total time (in s.) MIP model</th>
<th>total time (in s.) dedicated algorithm</th>
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### Resolution with SAT and CLP(\(B\))

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

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but why are we so efficient?
Encoding of SAT

1999 Time complexity analysis of the minimal siphon extraction problem of petri nets. S. Tanimoto, M. Yamauchi, and T. Watanabe. IEICE.
Bounded tree-widths (extension)

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.

Proof. Fixed tree-width CSP $\implies$ polynomial-time resolution.

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

Biomodels generally have small tree-width.
Conclusion

- The Boolean model outperforms state-of-the-art algorithms.
- CP in GNU Prolog as good as miniSAT. (provided a well-chosen strategy: replay branch&bound)
- Fast resolution on some large instances of an NP-complete problem!
- “Real life” instances may have characteristics that NP-complete proofs ignore: bounded tree-width, regularity...
- Beyond solving, modeling leads to understanding.
Thank you for your attention!
Let’s go for questions.