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

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

Wednesday 10 October, CP'2012

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BioModels.Net

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

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

"Compilation" in an ODE model

$$\begin{aligned} dS/dt &= -k_1 \times S \times E + k_2 \times ES \\ dP/dt &= k_3 \times ES \\ dE/dt &= -k_1 \times S \times E + (k_2 + k_3) \times ES \\ dES/dt &= k_1 \times S \times E - (k_2 + k_3) \times ES \end{aligned}$$

Conservation laws:

$E + ES = \text{cte}$

$P + S + ES = \text{cte}$

Reduced model:

$dS/dt = k2 \times ES - k1 \times E \times S$

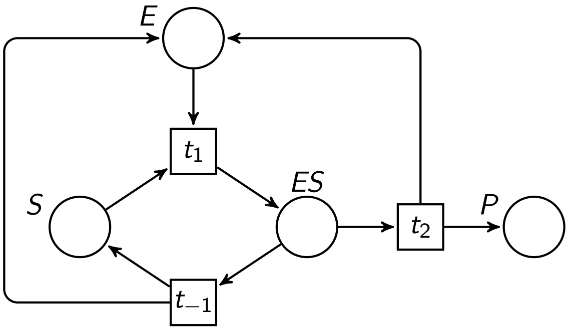
$dES/dt = k1 \times E \times S - (k2 + k3) \times ES$

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

Michaelis–Menten enzymatic reactions

Structural model: Reaction graph

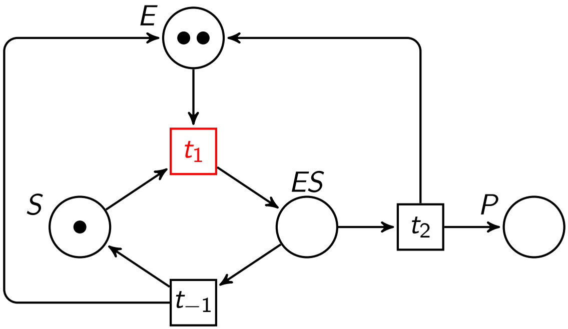
Petri-net = reaction graph + discrete dynamics



$$S + E \rightleftharpoons ES \longrightarrow E + P$$

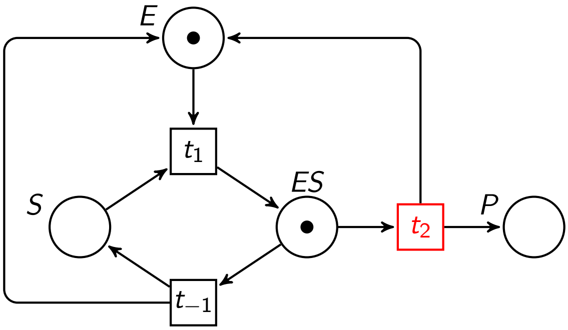
1962 *Kommunikation mit Automaten.* Carl Adam Petri. Ph. D. Thesis. University of Bonn.

Petri-net Discrete Dynamics



1993 *Petri net representations in metabolic pathways.*
V. N. Reddy, M. L. Mavrovouniotis, M. N. Liebman.
Intelligent Systems for Molecular Biology.

Petri-net Discrete Dynamics



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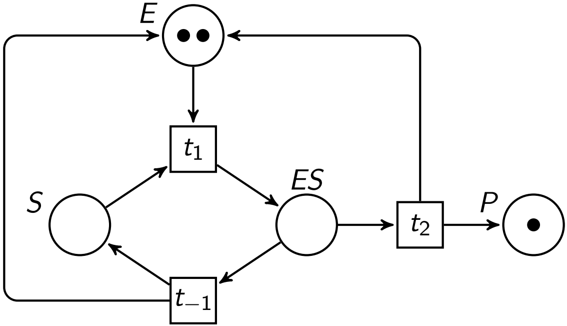

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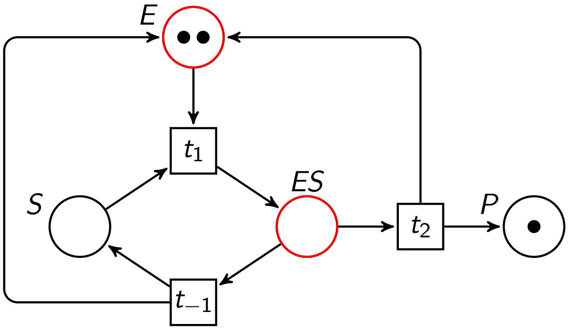
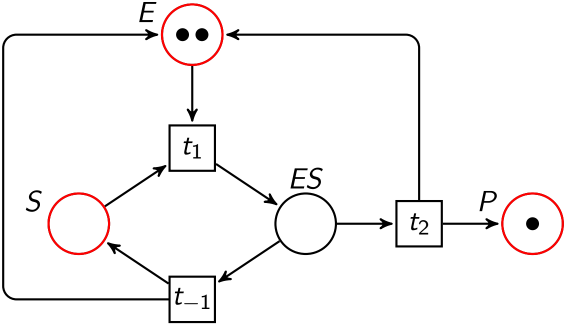


Related work P-invariant: conservation law ODE invariant

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

Petri-net Discrete Dynamics



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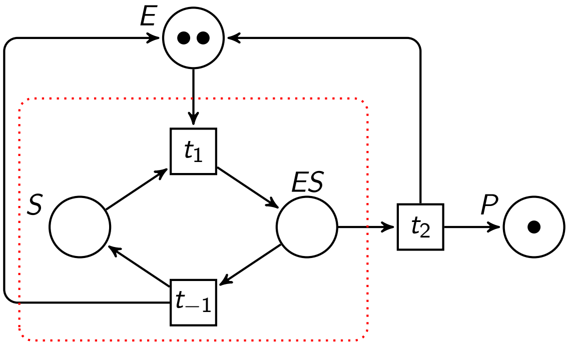
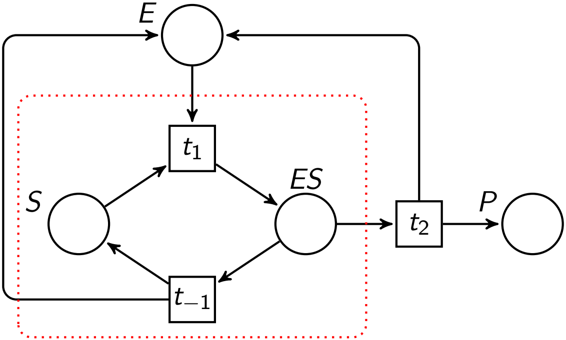


Siphons: Structural Characterization

${}^\bullet S$ set of predecessors $\quad S^\bullet$ set of successors



${}^\bullet\{S, ES\} = \{t_1, t_{-1}\} \quad \{S, ES\}^\bullet = \{t_1, t_{-1}, t_2\}$

S siphon iff ${}^\bullet S \subseteq S^\bullet$

Dynamic Characterization of Siphons

a subset S of places such that

once S is empty, it remains empty

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

characterize 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.*
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

$$(\forall p)\ X_p = 1 \iff p \in S$$

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.

PN size	#minimal siphons (avg)	total time (in s.)	
		MIP model	dedicated algorithm
5	2	0.03	0.05
10	10	0.28	0.07
15	60	5.45	0.39
20	302	303.47	6.84

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

database	#models	total time (in s.)		
		dedicated algorithm	miniSAT	GNU Prolog
Petriweb	80	2325	156	6
Biomodels.net	403	19734	611	195

model	# siphons	dedicated 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

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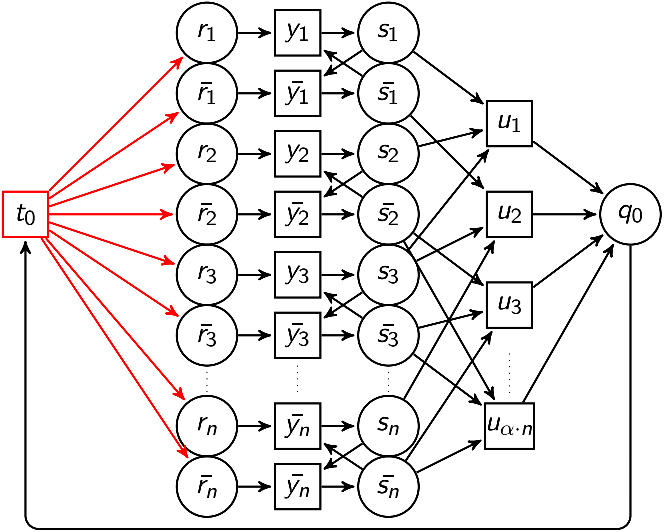
but why are we so effficient?

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 $\mathbf{O}(w)$.

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. Fixed tree-width CSP $\Longrightarrow$ 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.