A constraint programming approach to the analysis of Petri nets structural properties and application to biochemical networks

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CONTRAINTES

July 10, 2013

Outline

Differential equations and structure

A classical way to describe and analyse biochemical reaction systems: Differential equations.

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Reaction model

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

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

1913 *Die Kinetik der Invertinwirkung*.
L. Menten, M.I. Michaelis. Biochemistry Zeitung 49.

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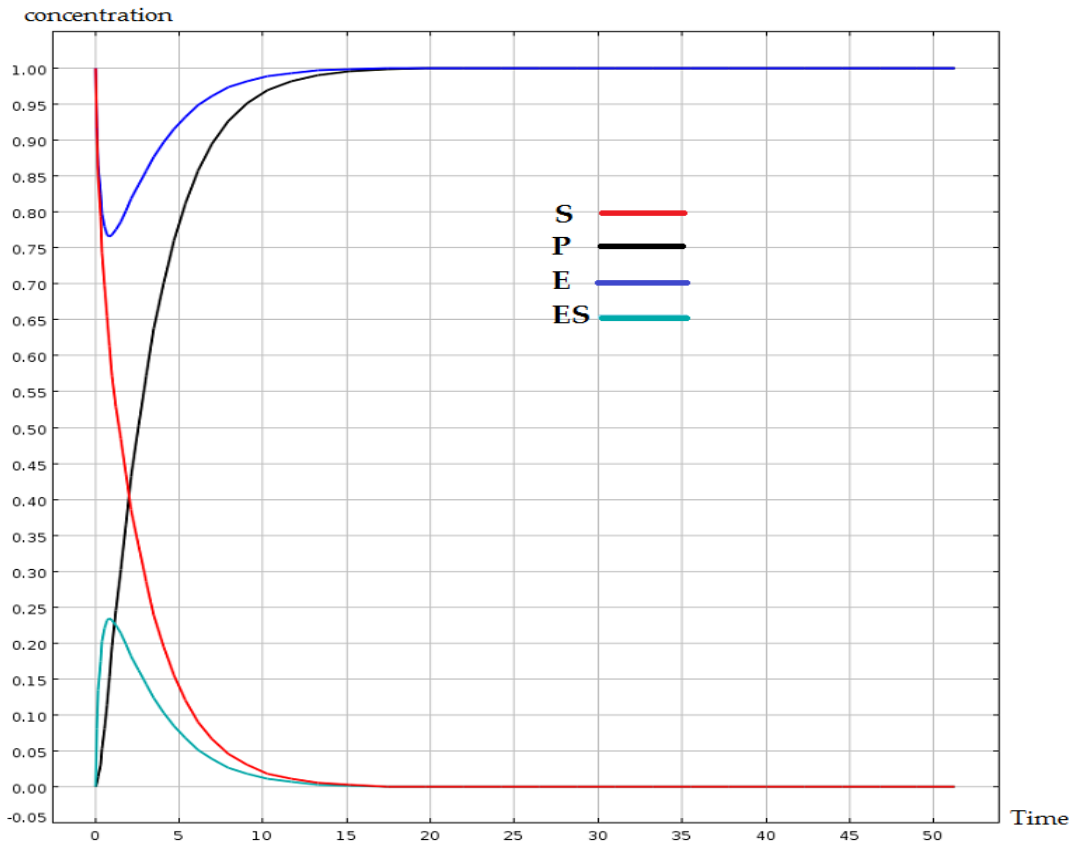

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+

Conservation laws

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

⇓

Equivalent model:

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

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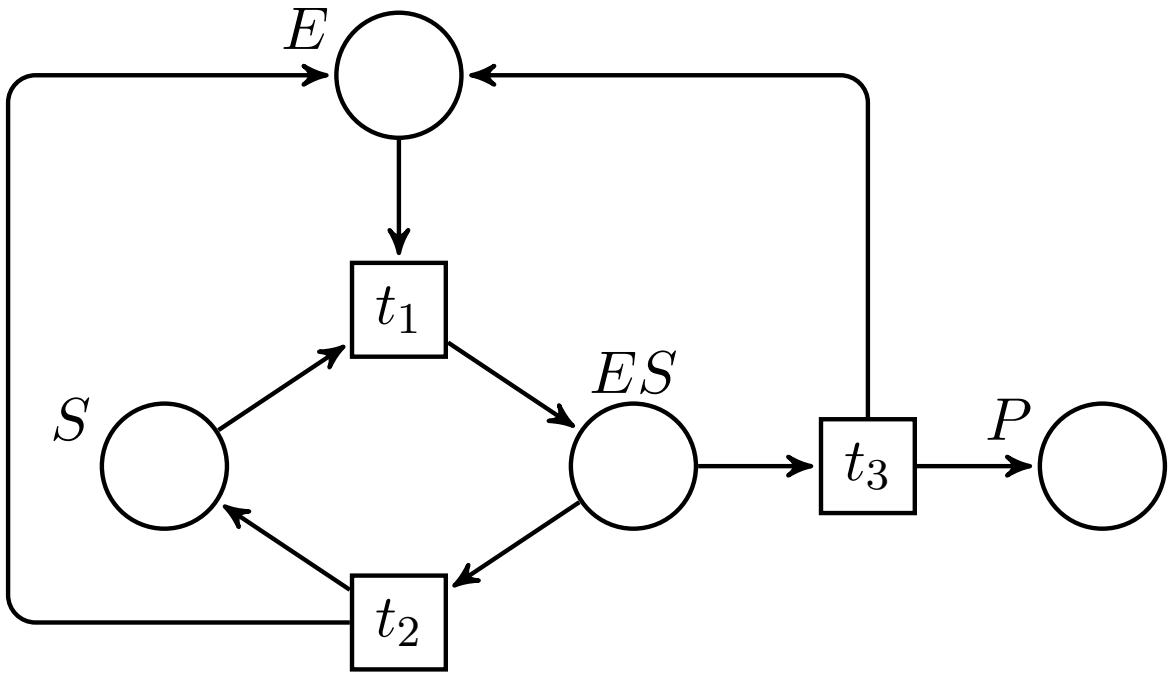
Use of Petri nets structural properties to say something about the system dynamics without knowing the kinetics.

Michaelis–Menten enzymatic reactions

Structural model: Reaction graph



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

Petri-net = reaction graph + discrete dynamics

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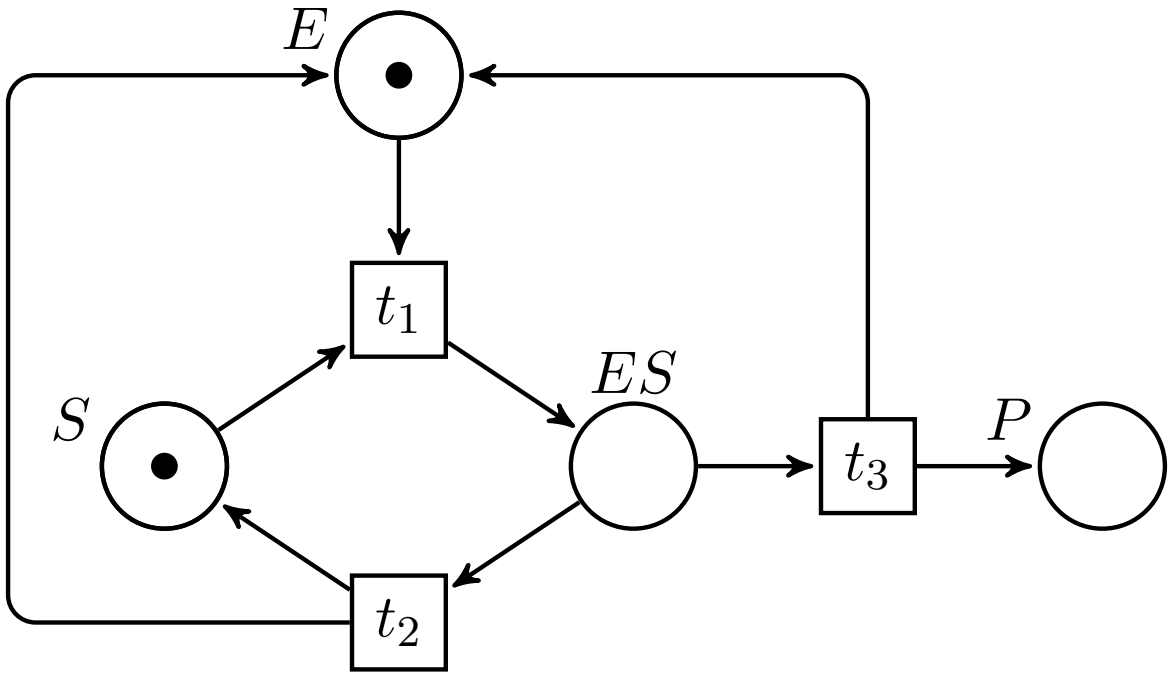

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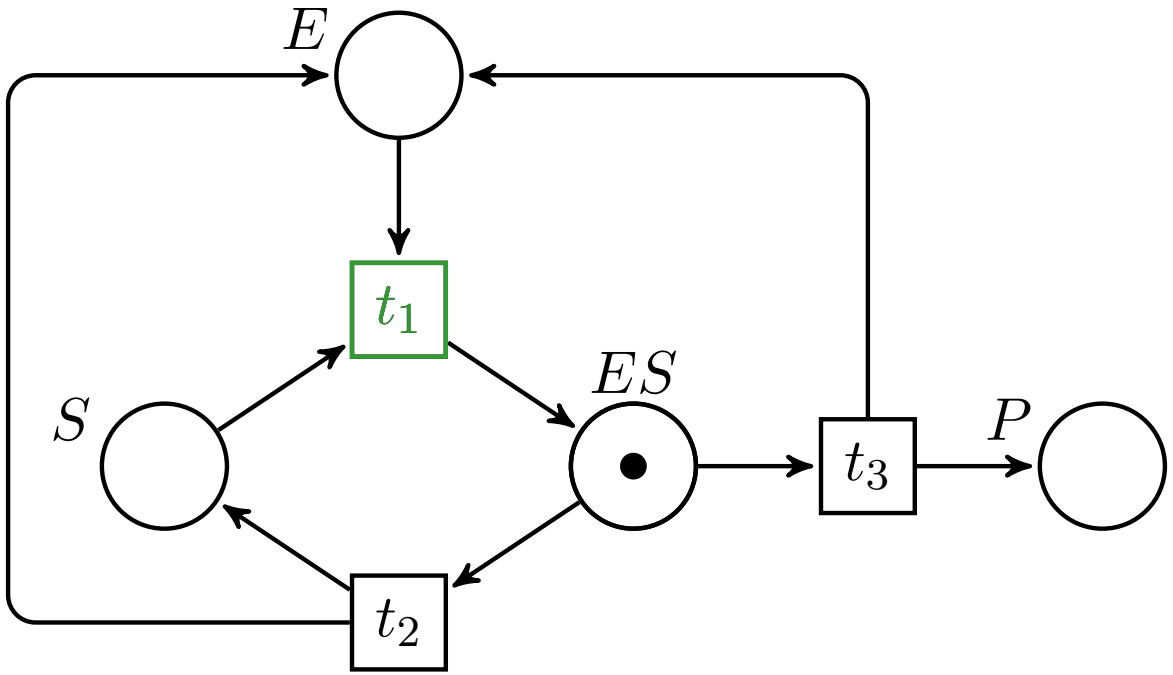

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Siphons and traps

Biological interpretation: A siphon (resp. trap) refers to a non-empty set of chemical species that once none (resp. some) of them is present, they will never be produced (resp. disappear at the same time).

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Dynamical characterisation: A siphon is a non-empty set of places that, once it is unmarked, remains so, whatever the dynamics are.

Structural characterisation: A siphon is a non-empty set of places S such that ${}^\bullet S \subseteq S^\bullet$.

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Structural characterisation: A siphon is a non-empty set of places S such that ${}^\bullet S \subseteq S^\bullet$.
A siphon is minimal if it does not contain any other siphon.

Siphons/Traps and Computation Tree Logic

CTL is used for verifying temporal properties by model checking.

2003 *Symbolic model checking of biochemical networks*.
Nathalie Chabrier and François Fages. CMSB.

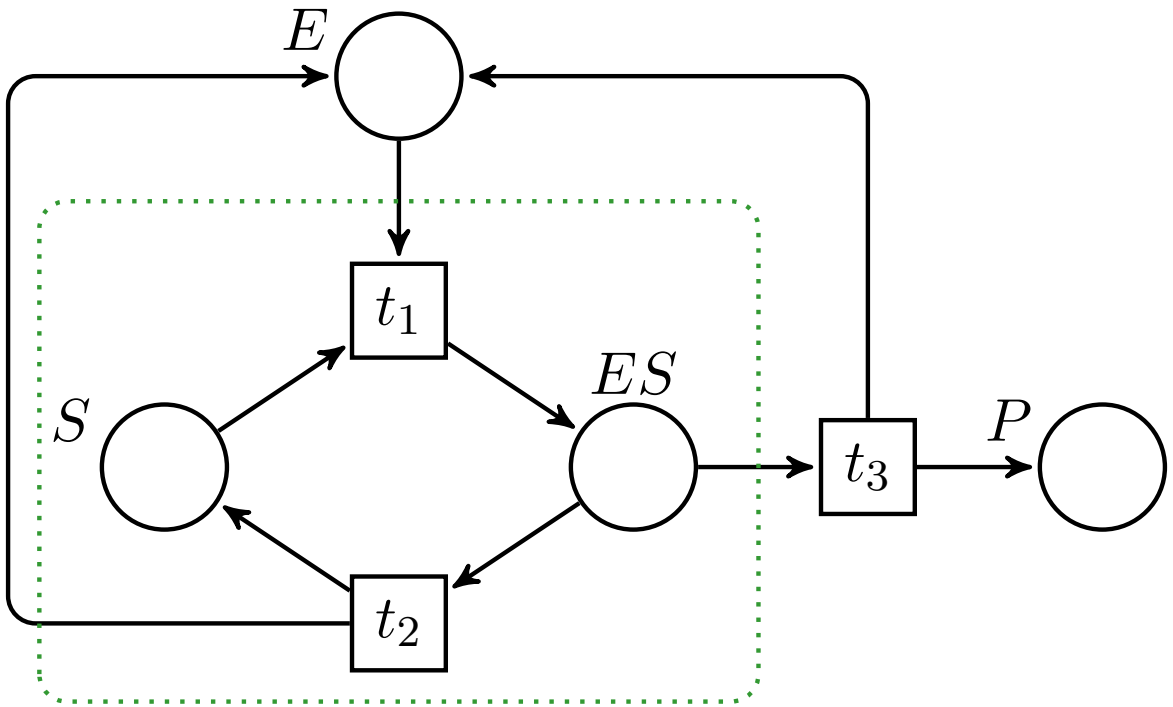
http://contraintes.inria.fr/biocham

Definition. Given a marking m, for any subset $P' \subseteq P$ of places, let $\phi_{P'} = \bigvee_{p \in P'} m_p \geq 1$.

Theorem. The set $P' \subseteq P$ is a trap if and only if for all $s \in \mathbb{N}^P$, $(\mathcal{S}^{PN}, s) \models \phi_{P'} \Rightarrow AG\phi_{P'}$.

Theorem. The set $P' \subseteq P$ is a siphon if and only if for all $s \in \mathbb{N}^P$, $(\mathcal{S}^{PN}, s) \models \neg\phi_{P'} \Rightarrow AG\neg\phi_{P'}$.

Minimal siphon example



$$^\bullet\{S, ES\} = \{t_1, t_2\} \quad \{S, ES\}^\bullet = \{t_1, t_2, t_3\}$$

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

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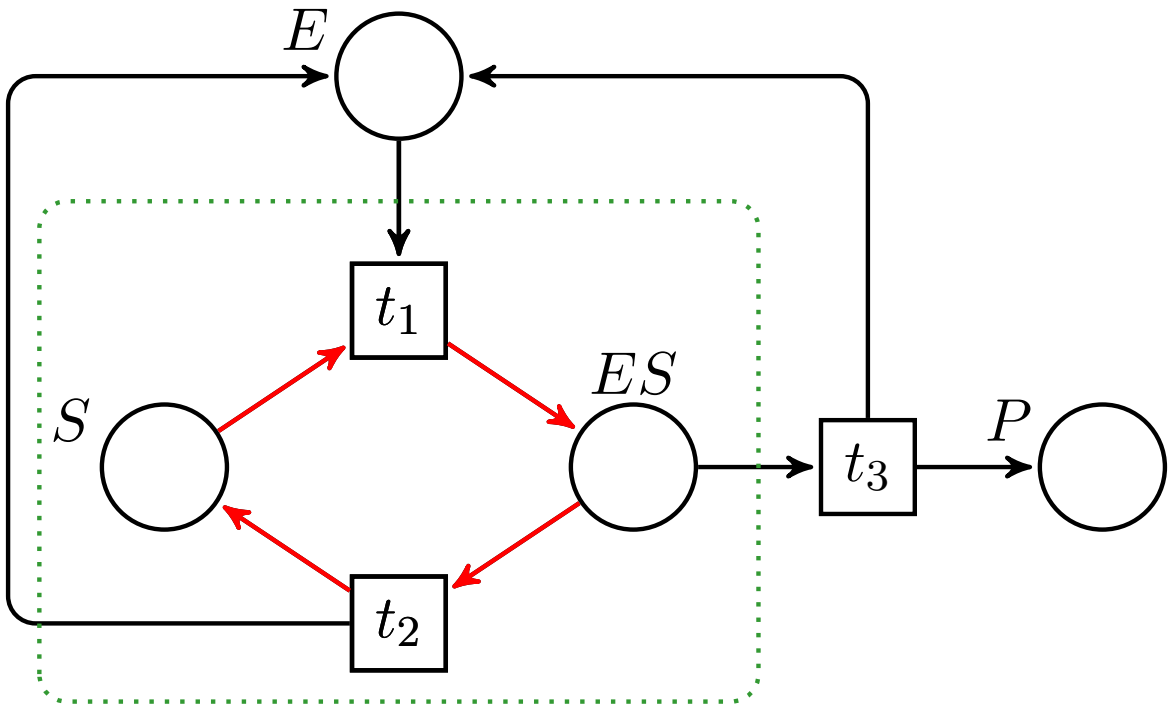

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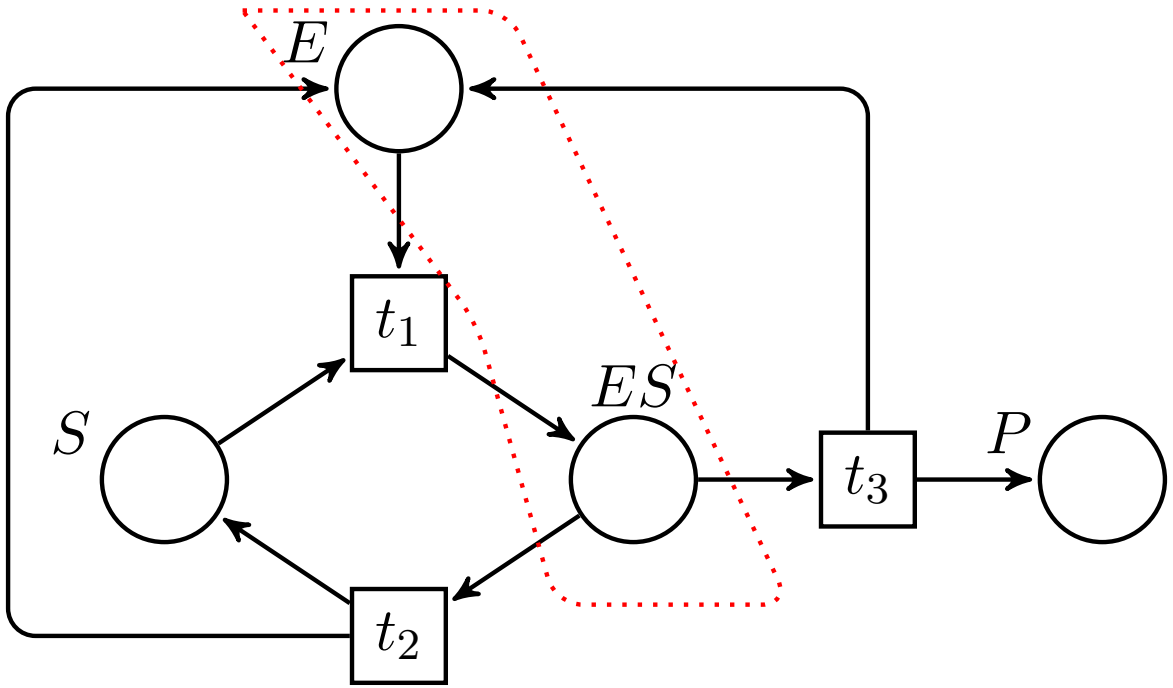

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Siphon-Trap Property (STP)

Definition. The STP holds when every siphon includes a marked trap.

Theorem. An ordinary Petri net in which the STP holds is deadlock-free.

2010 *On the importance of the deadlock trap property for monotonic liveness.*
M. Heiner, C. Mahulea, and M. Silva. In Int. Workshop on Biological Processes and Petri Nets (BioPPN).

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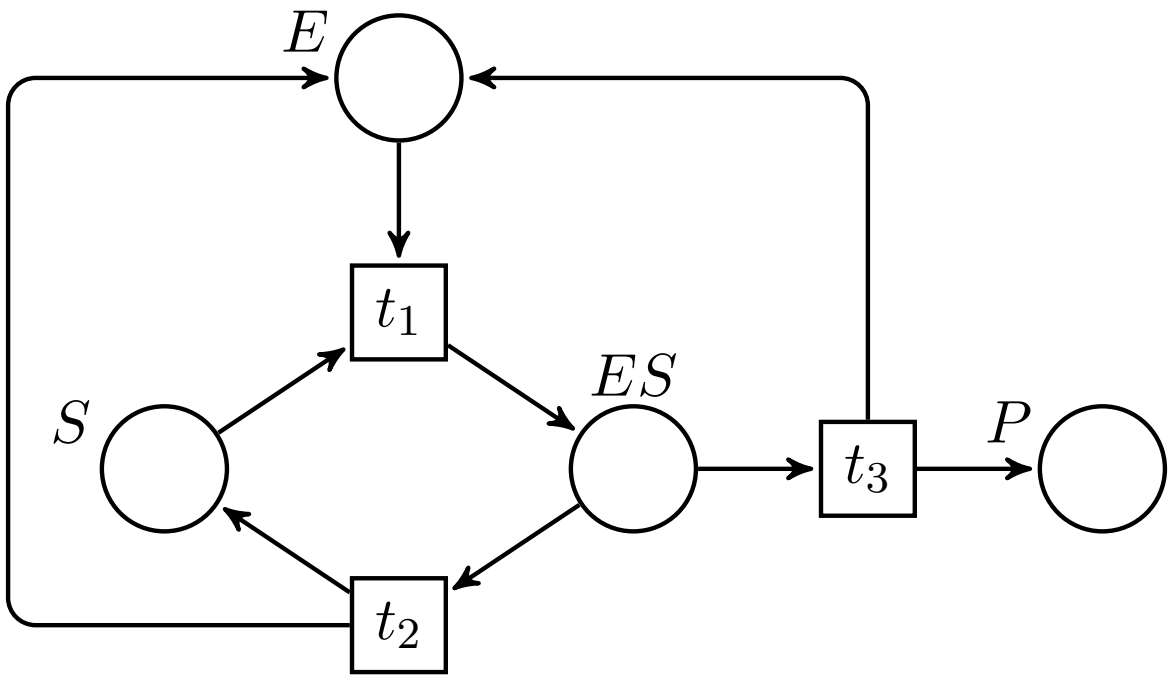
2010 *New Algorithms for Deciding the Siphon-Trap Property.*
O. Oanea, H. Wimmel, and K. Wolf. Petri nets 2010.

P-invariant: Biological interpretation

A P-invariant corresponds to a conservation law.

1993 *Petri net representations in metabolic pathways.* V. N. Reddy, M. L. Mavrovouniotis and M. N. Liebman. ISMB.



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T-invariants: Biological interpretation

Minimal T-invariants correspond to elementary flux modes or reversible reactions.

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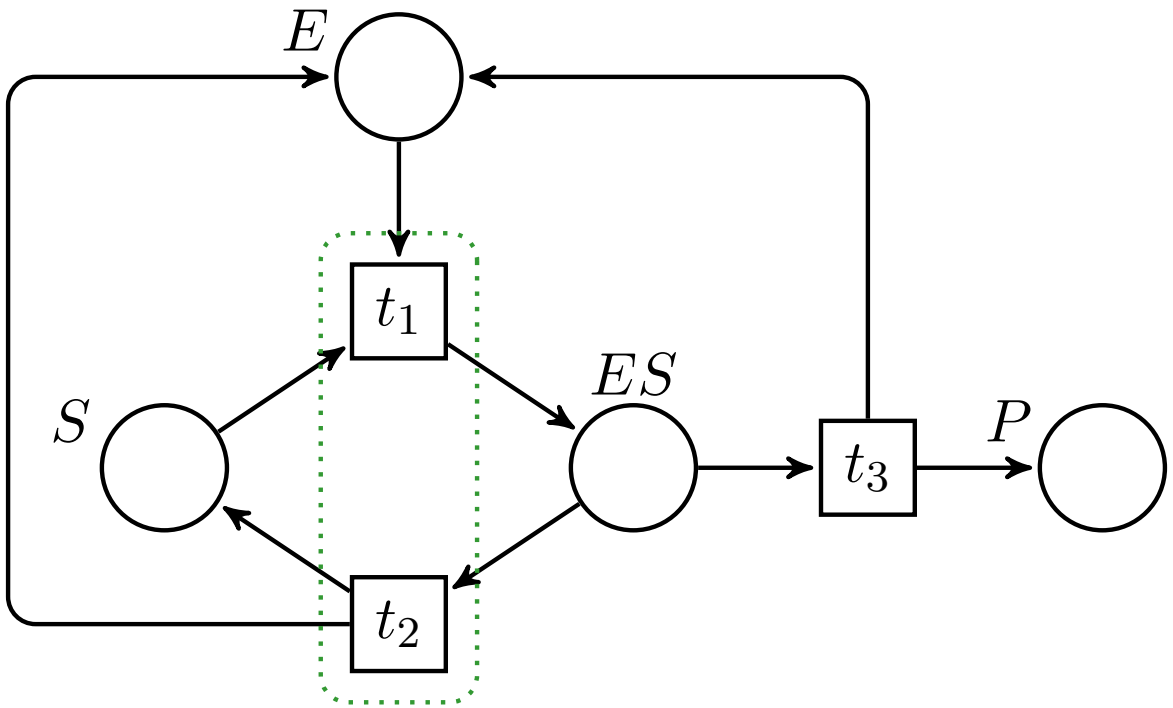

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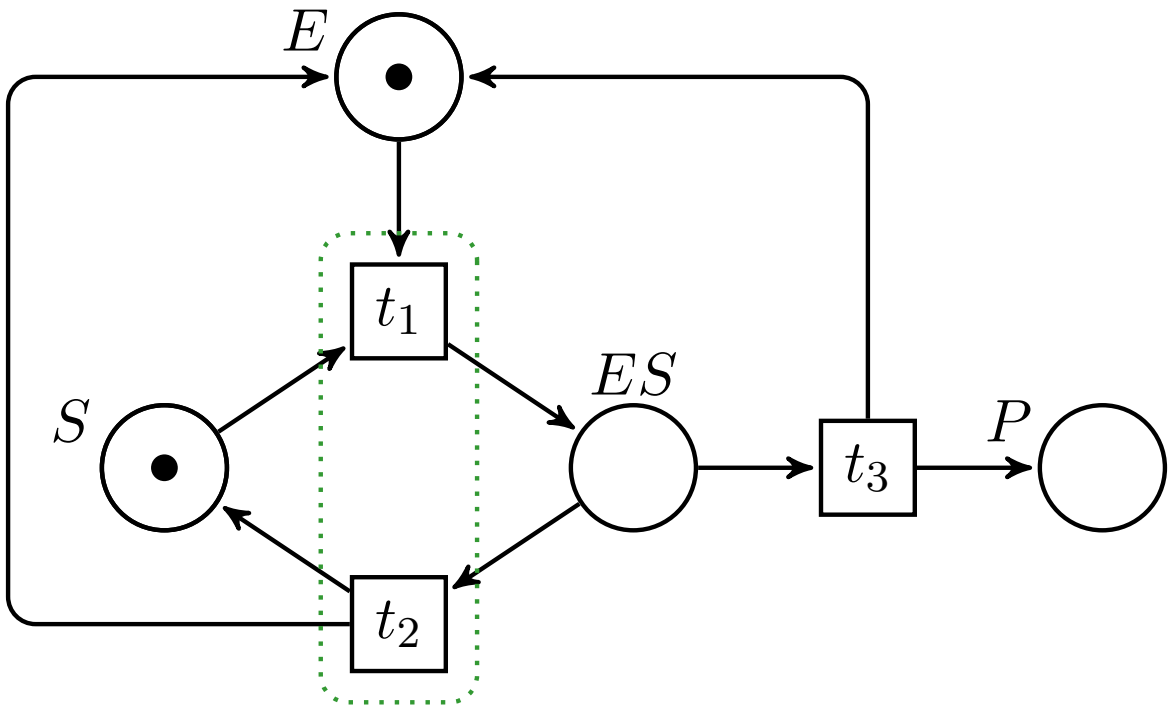

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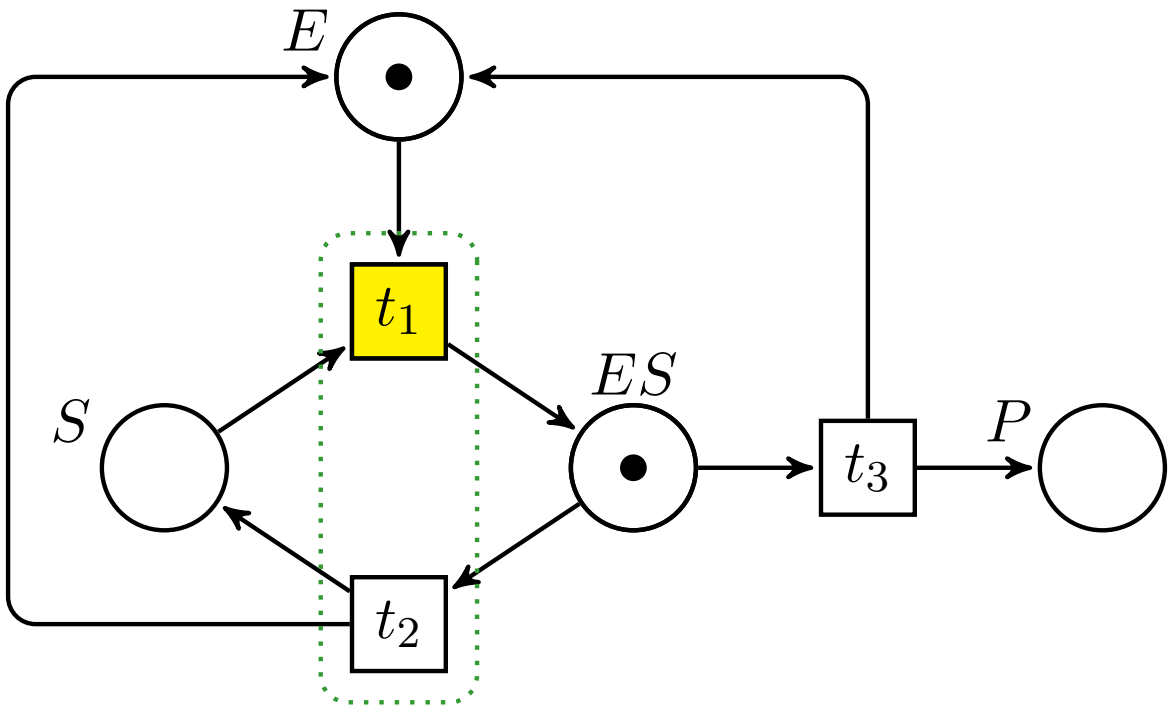

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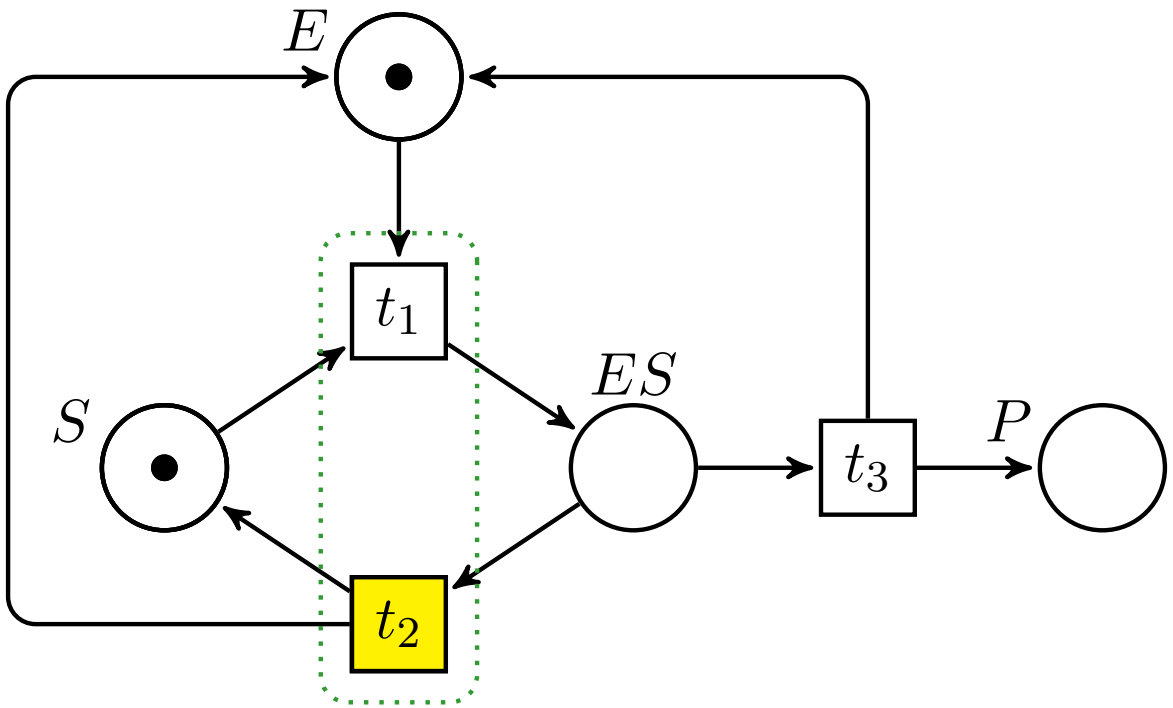

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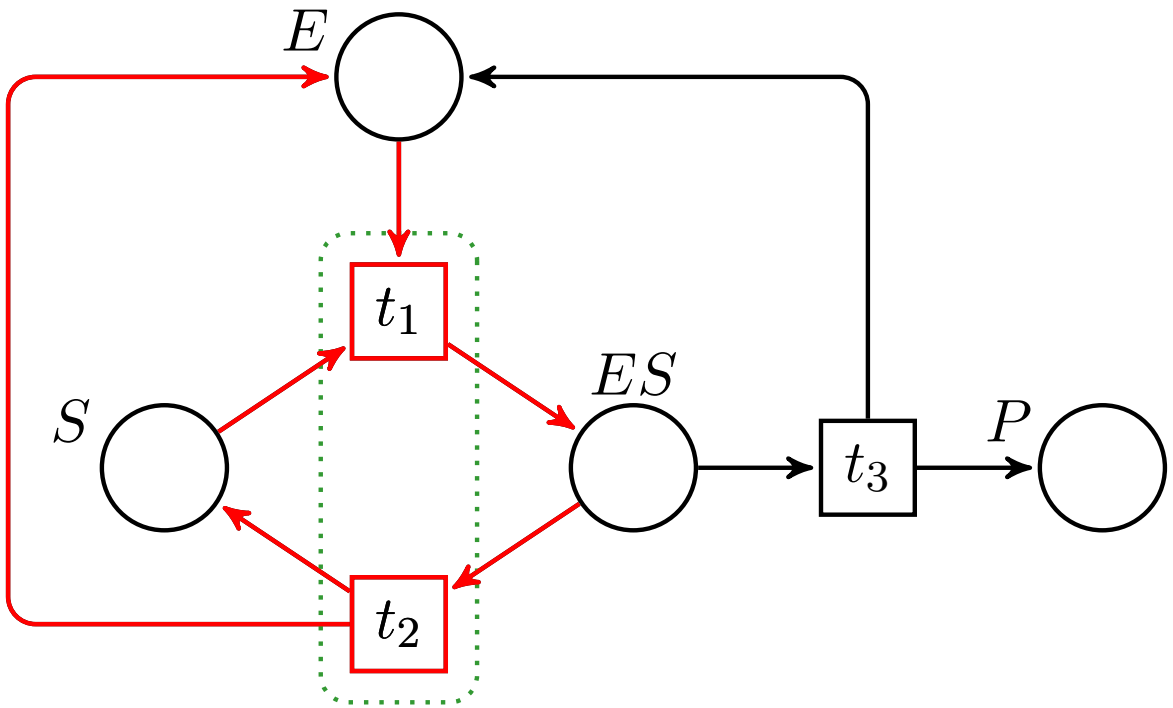

$$t_1 = t_2 = 1 \wedge t_3 = 0$$

Benchmark for evaluation

Database **Biomodels.net** (version March 2012)

404 manually curated quantitative biochemical models.
Average ~ 50 species, ~ 90 reactions.
Biggest model has 194 species, 313 reactions.
Reference publication for each model.

> 2006 *BioModels Database: a free, centralized database of curated, published, quantitative kinetic models of biochemical and cellular systems.*
> le Novère et al. Nucleic Acid Research.

Benchmark for evaluation (2)

Database **Petriweb**

Repository of 80 models modelling real industrial processes.
Average ~ 10 places, ~ 8 transitions.
Biggest model has 68 places, 51 transitions.

2006 *Petriweb: A Repository for Petri Nets*, R. Goud et al. Petri Nets and Other Models of Concurrency - ICATPN.

Complexity

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  1999 *Time complexity analysis of the minimal siphon extraction problem of petri nets.* S. Tanimoto, M. Yamauchi, and T. Watanabe. IEICE.

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- Towards understanding why our techniques are efficient: Linear time complexity on classes of Petri nets of bounded tree-widths.

Boolean model for siphons and traps

Boolean Model of Siphons

variables

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

constraints

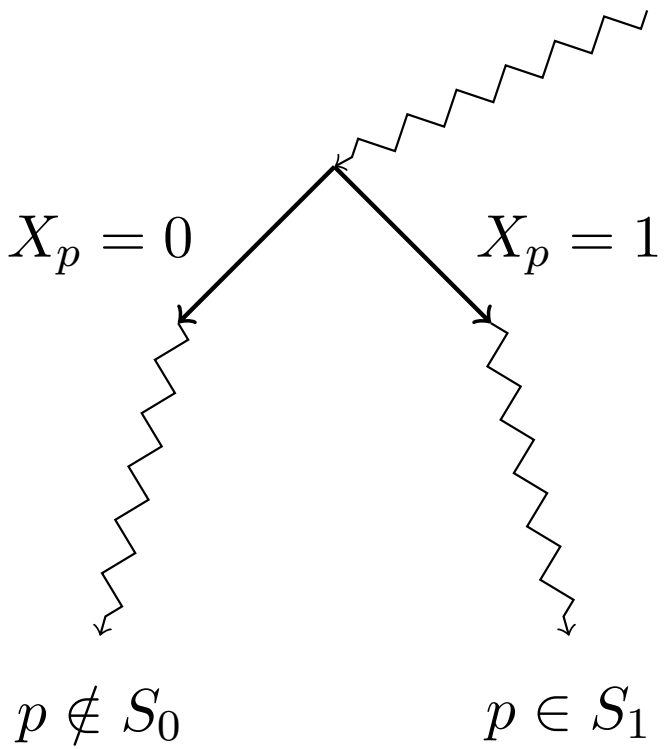
$$(\forall p)\ X_p = 1 \Rightarrow \bigwedge_{t \in {}^\bullet p} \bigvee_{p' \in {}^\bullet t} X_{p'} = 1$$

Finding siphons is reduced to finding

Boolean assignments satisfying these formulas.

Search strategy ensuring minimality

Try absence 0 then presence 1



0 before 1 and S_0 before S_1 in the search tree $\Longrightarrow S_1 \not\subseteq S_0$

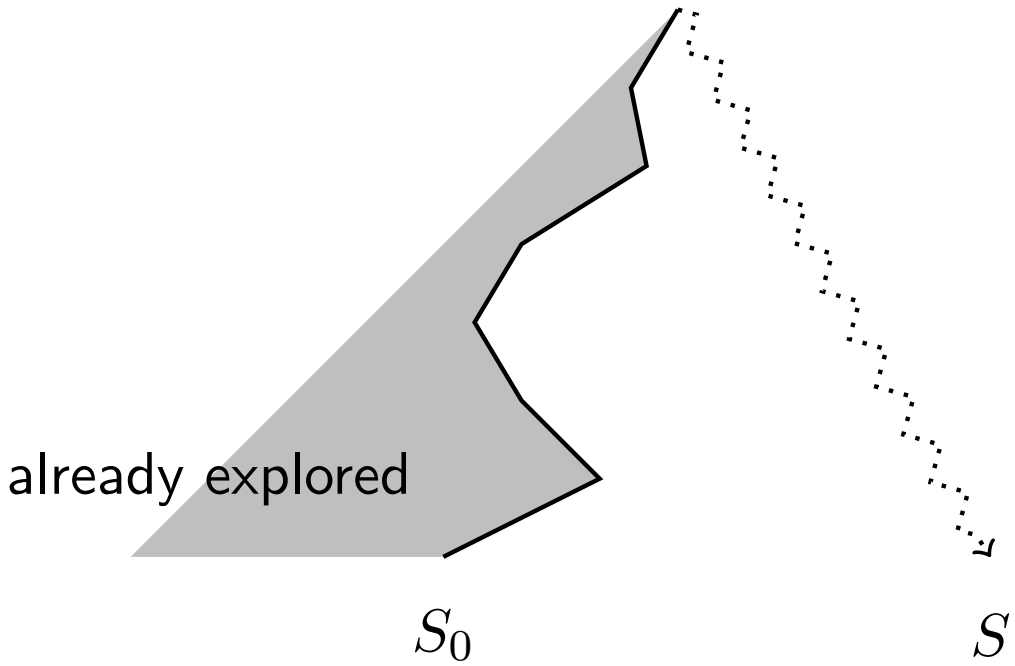
Enumerating all minimal siphons by iteration

Once a (minimal) siphon S is found

1. add the constraint $\bigvee_{p \in S} X_p = 0$
2. restart the search

Optimisation of the search in CLP($\mathcal{B}$)

"Those who cannot remember the past are condemned to repeat it"
George Santayana



2 possible strategies:

add constraint $S \geqslant_{\text{lex}} S_0$
replay search procedure: most efficient!

Example: Michaelis-Menten enzymatic reaction

Boolean variables

e, s, es and p

initial clauses

$$e \vee s \vee es \vee p$$
$$\neg es \vee e \vee s$$
$$\neg s \vee es$$
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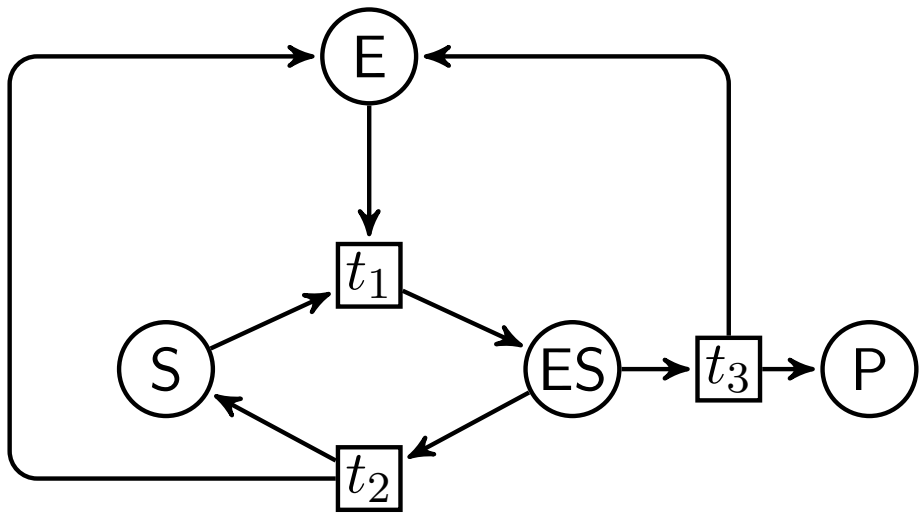


Example: Michaelis-Menten enzymatic reaction

Boolean variables

$$e,\ s,\ es \text{ and } p$$

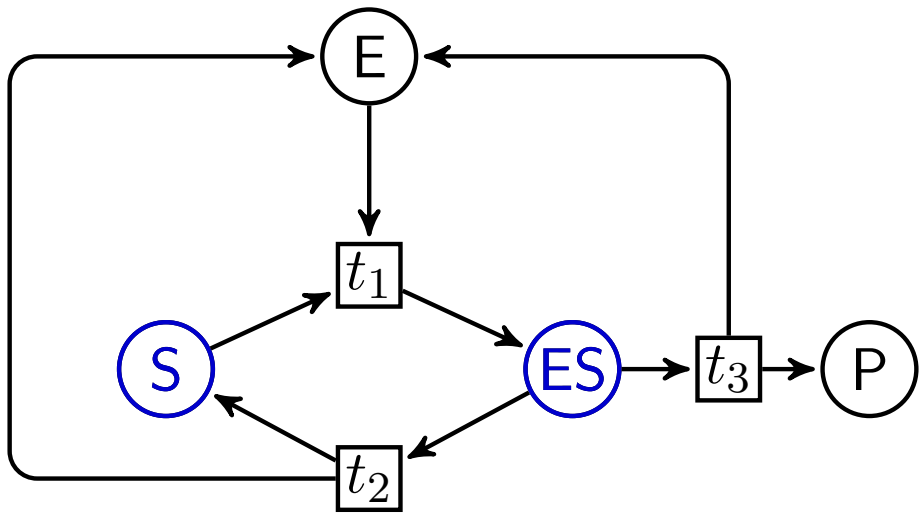
assignment

$$s = es = 1 \wedge e = p = 0$$

$\Rightarrow \{S, ES\}$ is a minimal siphon.

minimality constraint:

$$\neg s \vee \neg es$$



Example: Michaelis-Menten enzymatic reaction

Boolean variables

$$e,\ s,\ es \text{ and } p$$

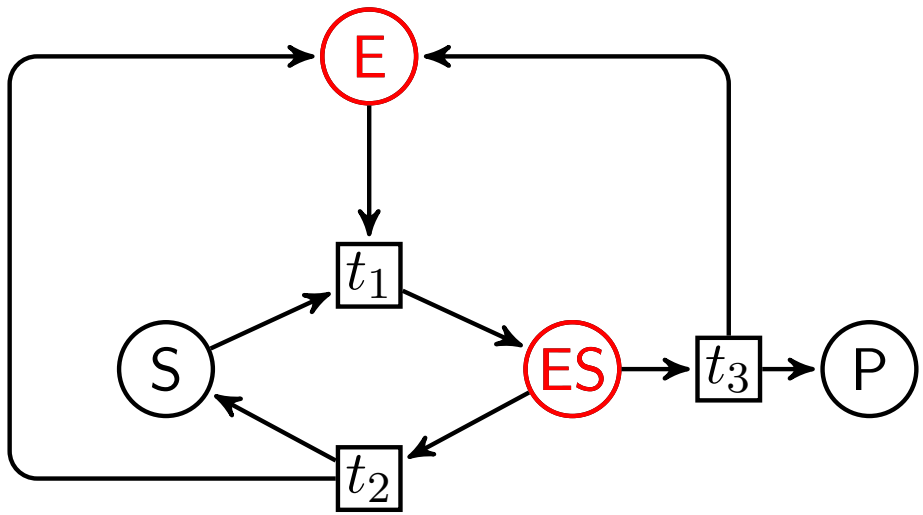
second iteration. assignment:

$$e = es = 1 \wedge s = p = 0$$

$\Rightarrow$ $\{E, ES\}$ is also a minimal siphon.

minimality constraint:

$$\neg e \vee \neg es$$

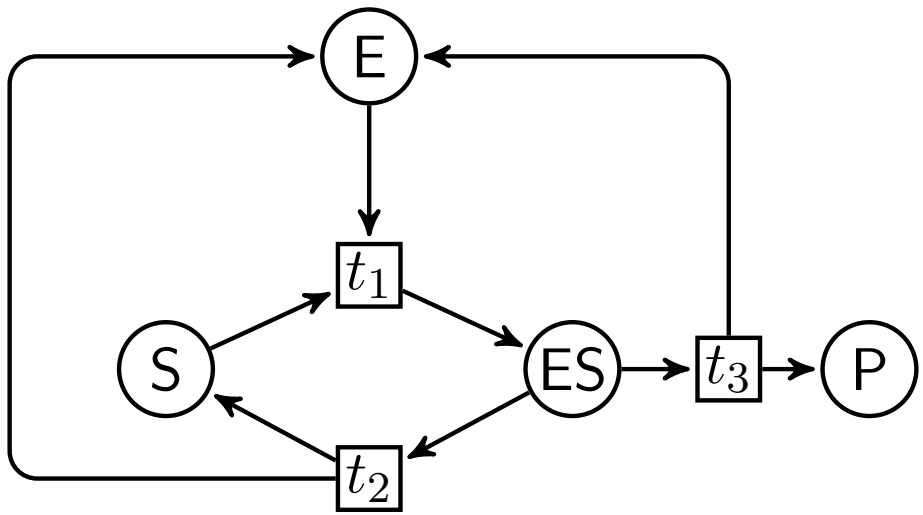


Example: Michaelis-Menten enzymatic reaction

Boolean variables

e, s, es and p

No more variable assignment.
2 minimal siphons: $\{S, ES\}$ and $\{E, ES\}$.



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5	2	0.03	0.05
10	10	0.28	0.07
15	60	5.45	0.39
20	302	303.47	6.84

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

2013 *Computation of Minimal Siphons in Petri Nets by Using Binary Decision Diagrams* Y. Chen, G. Liu. ACM-TECS

Enumerating minimal siphons with SAT and CLP($\mathcal{B}$)

database	#models	#P,#T (avg)	#P+#T (max)	#siphons (avg)	total time (in ms.) algo. 2005	mini SAT	GNU-Prolog
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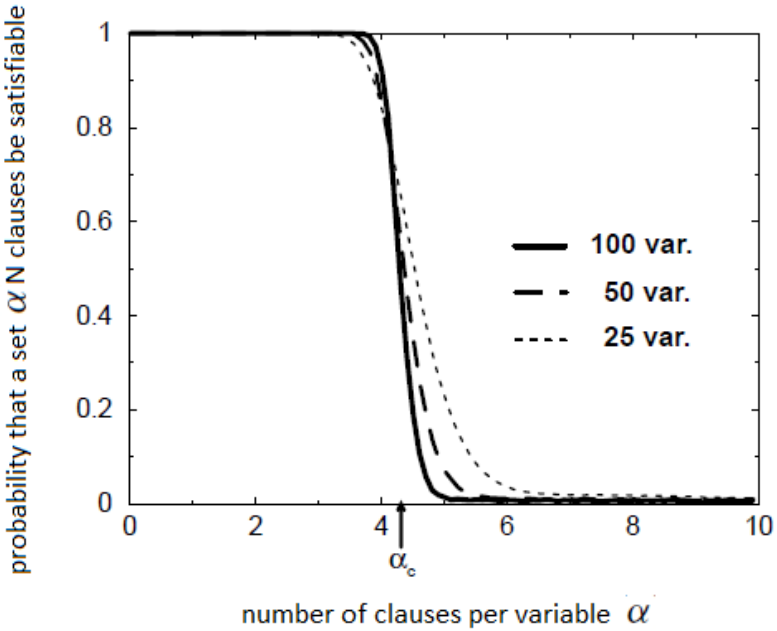
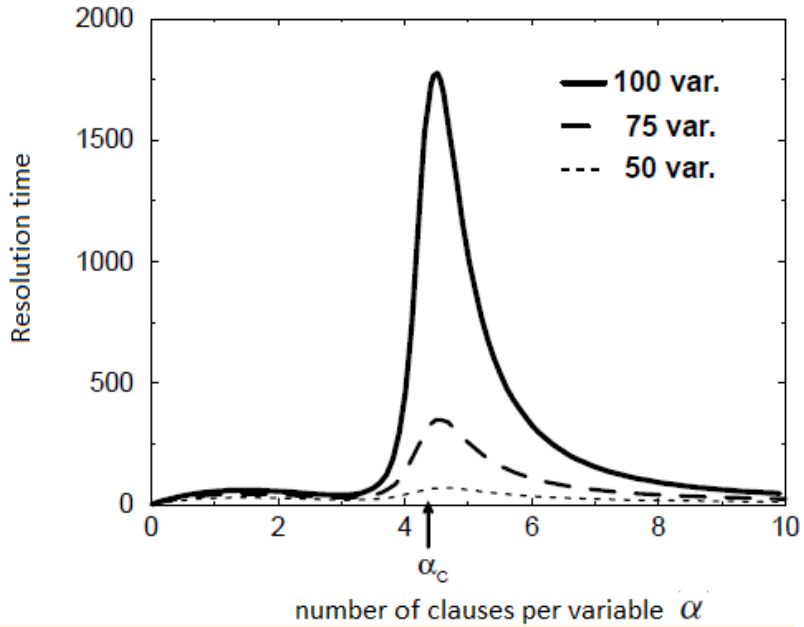
but why are we so efficient?

3-SAT phase transition

$$\alpha = \frac{\#\text{clauses}}{\#\text{variables}}$$

Phase transition for satisfiability at $\alpha \simeq 4.26$



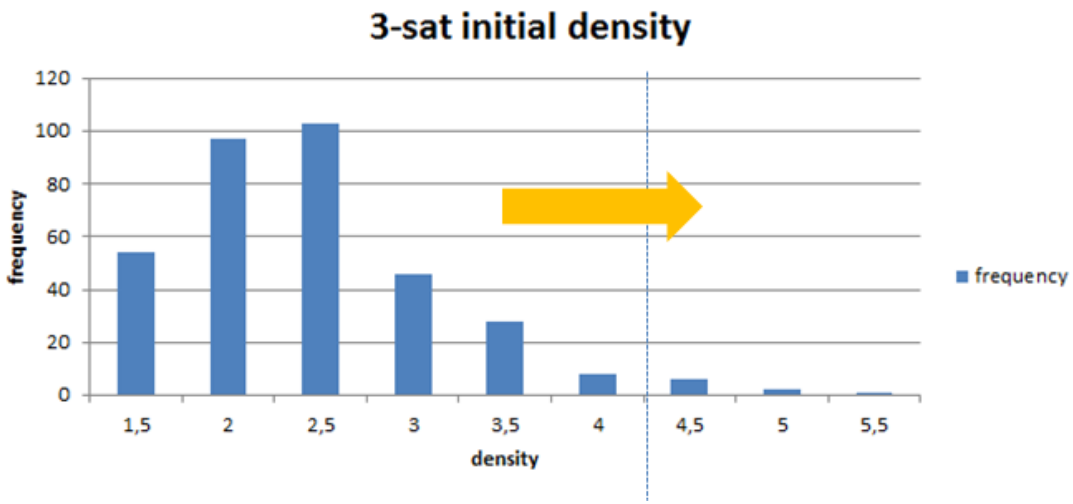


1996 *Generating Hard Satisfiability Problems.* B. Selman, D. Mitchell and H. Levesque. Artificial Intelligence.

Initial density $\geq$ 4.2 ?

$$\text{initial density}_{\text{3-SAT}} = \frac{\sum_{t \in T} \mid t^{\bullet} \mid +1+\mu}{\mid \text{places} \mid +\mu} \text{ where}$$

$$\mu = \sum_{t \in T} \max(0, \mid {}^{\bullet}t \mid -2)$$



3-SAT initial density of BIOMD175=2.39

The density grows during enumeration: potentially hard problems.

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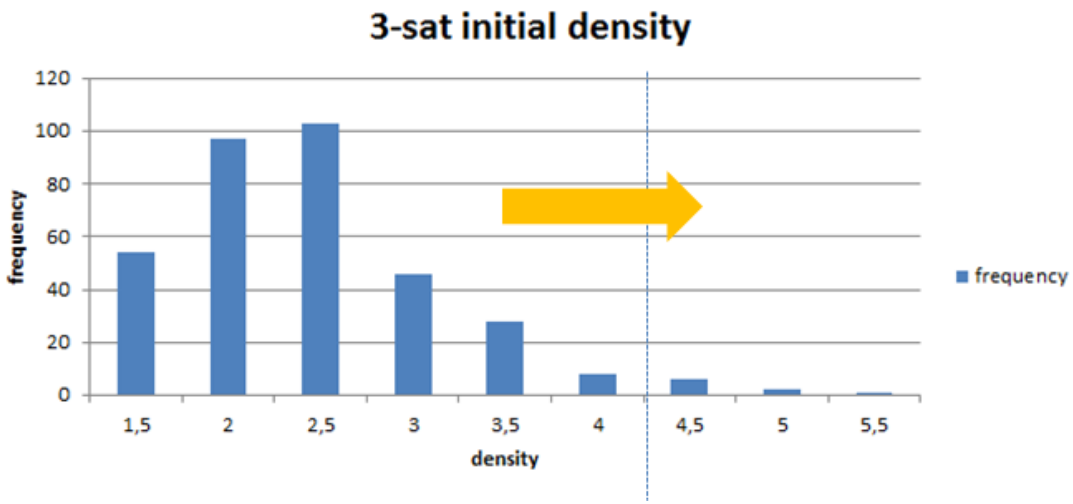

3-SAT initial density of BIOMD175=2.39

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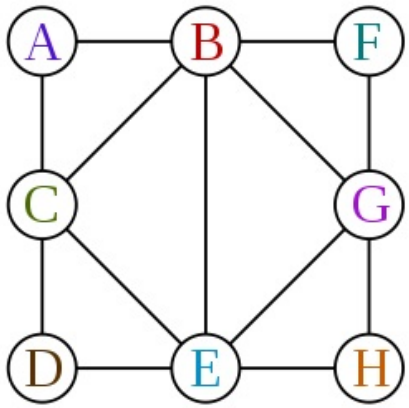
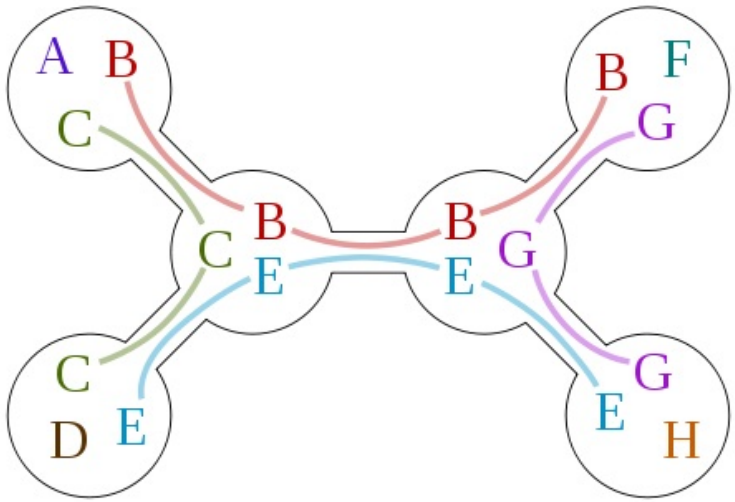
Not sufficient to explain good performances.

Tree-width of non-oriented graph

Tree-decomposition of a graph:

1. Each graph vertex is associated with at least one tree node.





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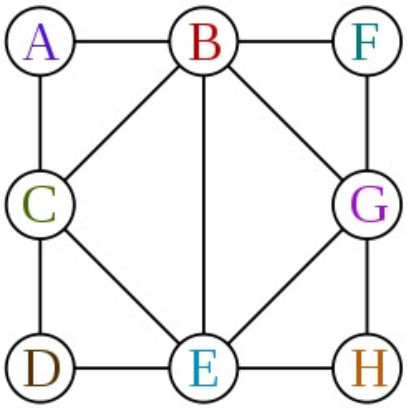

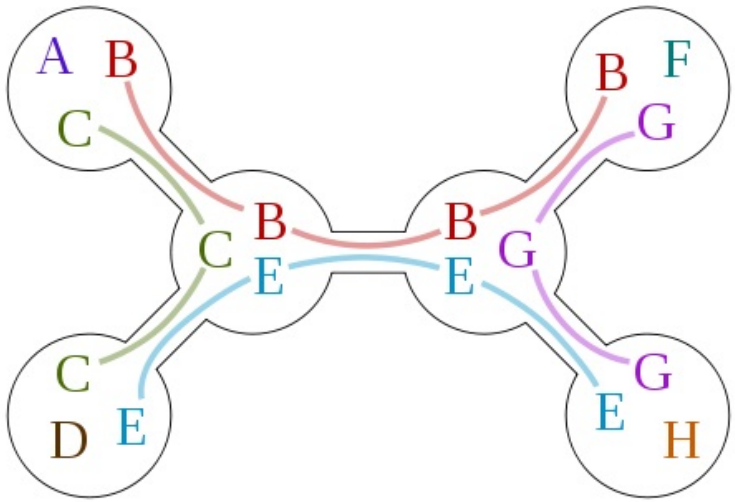

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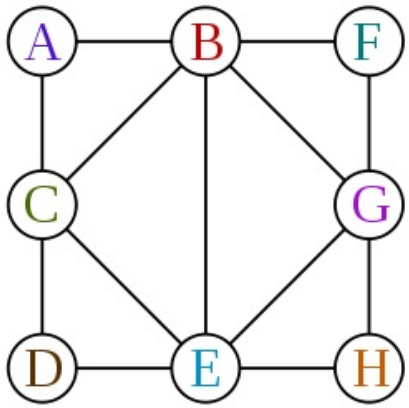

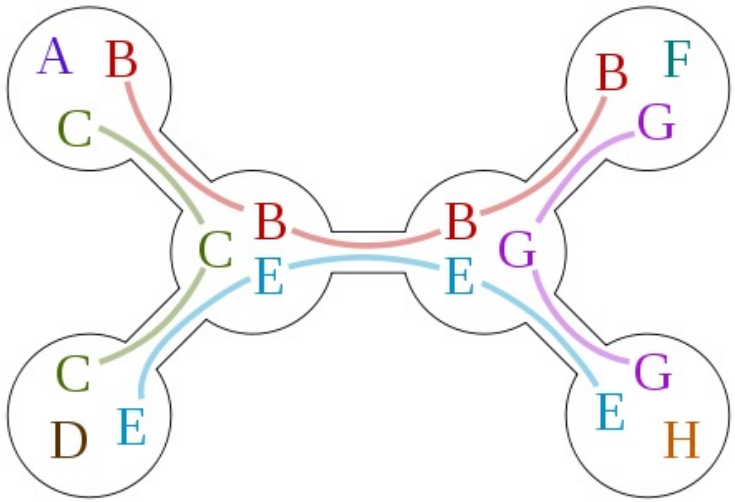

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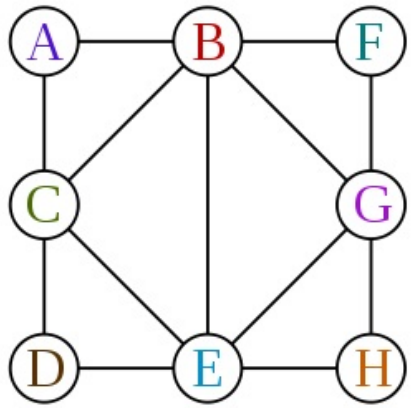

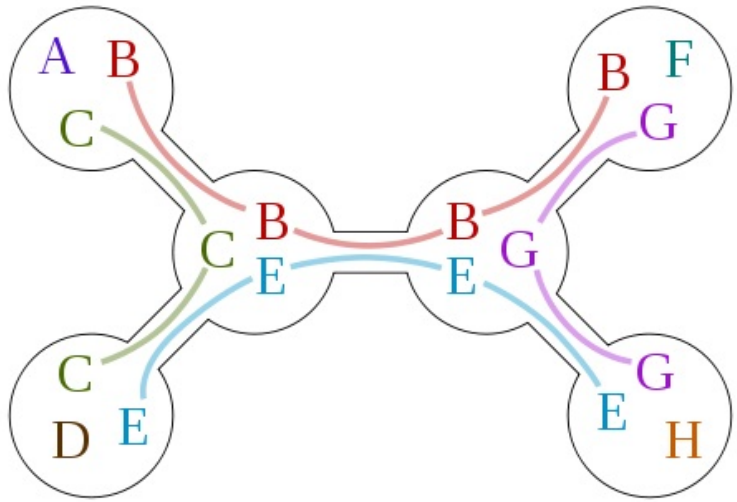

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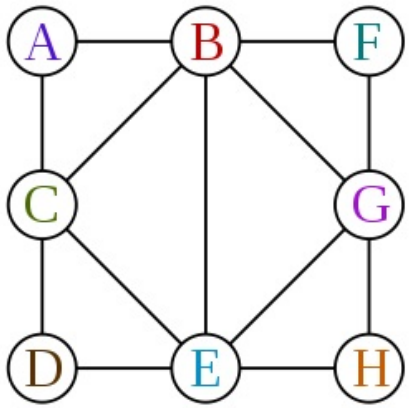
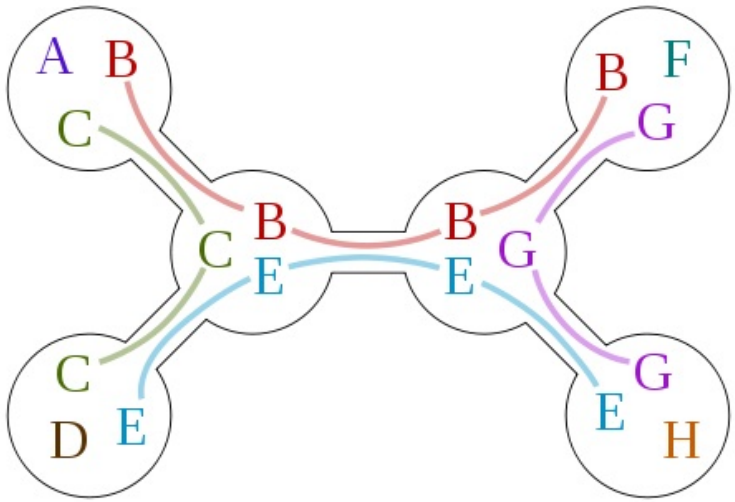
The tree-width of a graph is the minimum width among all its possible tree-decompositions.





Bounded tree-widths

Theorem. Deciding the existence of a minimal siphon containing a given set of places Q can be done in linear time for Petri-nets of bounded tree-width.

Proof. Definable in Monadic Second Order logic $\Longrightarrow$ Recognizable in linear time.

1990 *Definable monadic second-order logic of graphs I. Recognizable sets of Finite Graphs.* Bruno Courcelle. Information and Computation.

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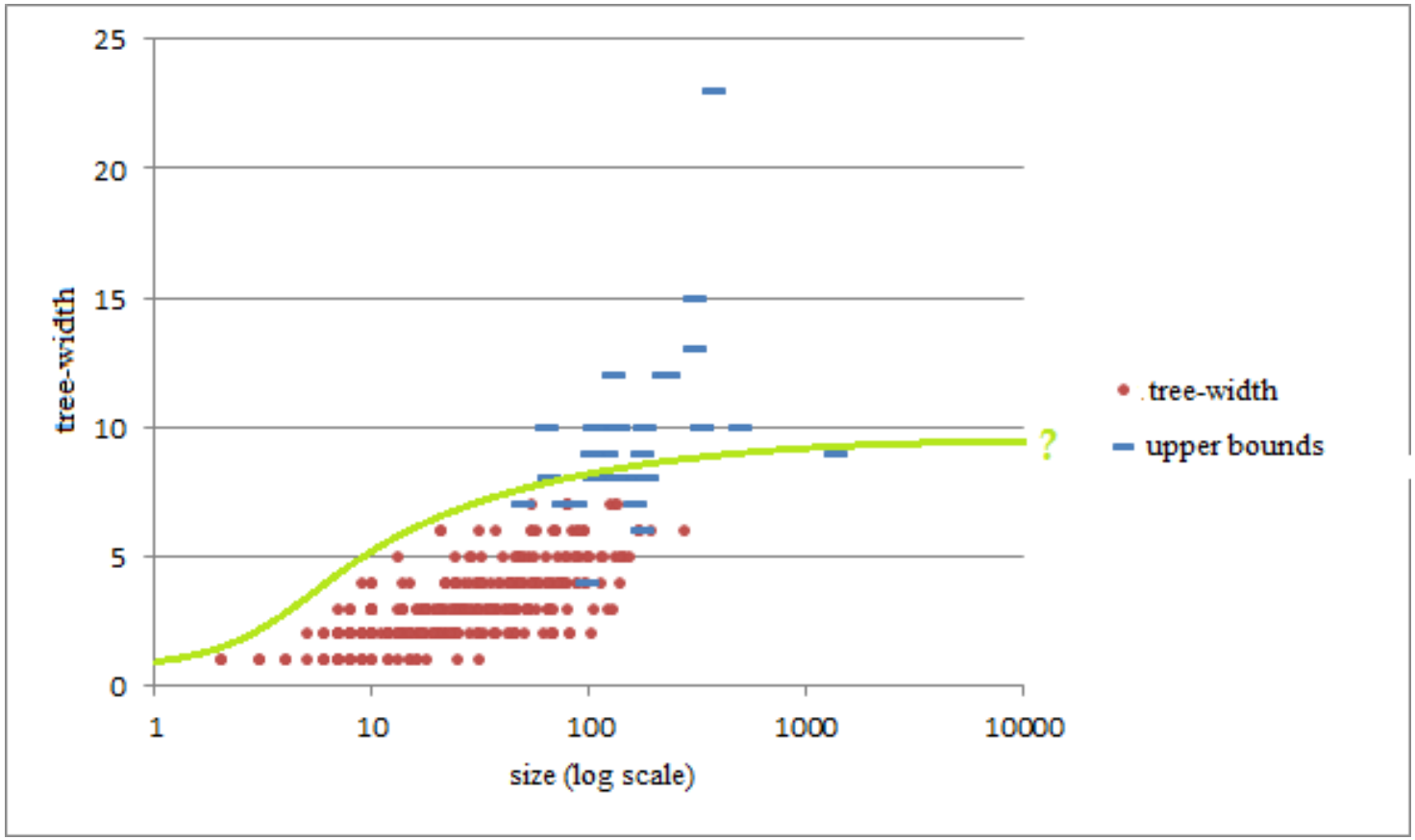
Biochemicals networks seem to have a **bounded** tree-width



Biomodels.net tree-width as a function of the size (places and transitions) of the Petri net Computed tree-width ≤ 10

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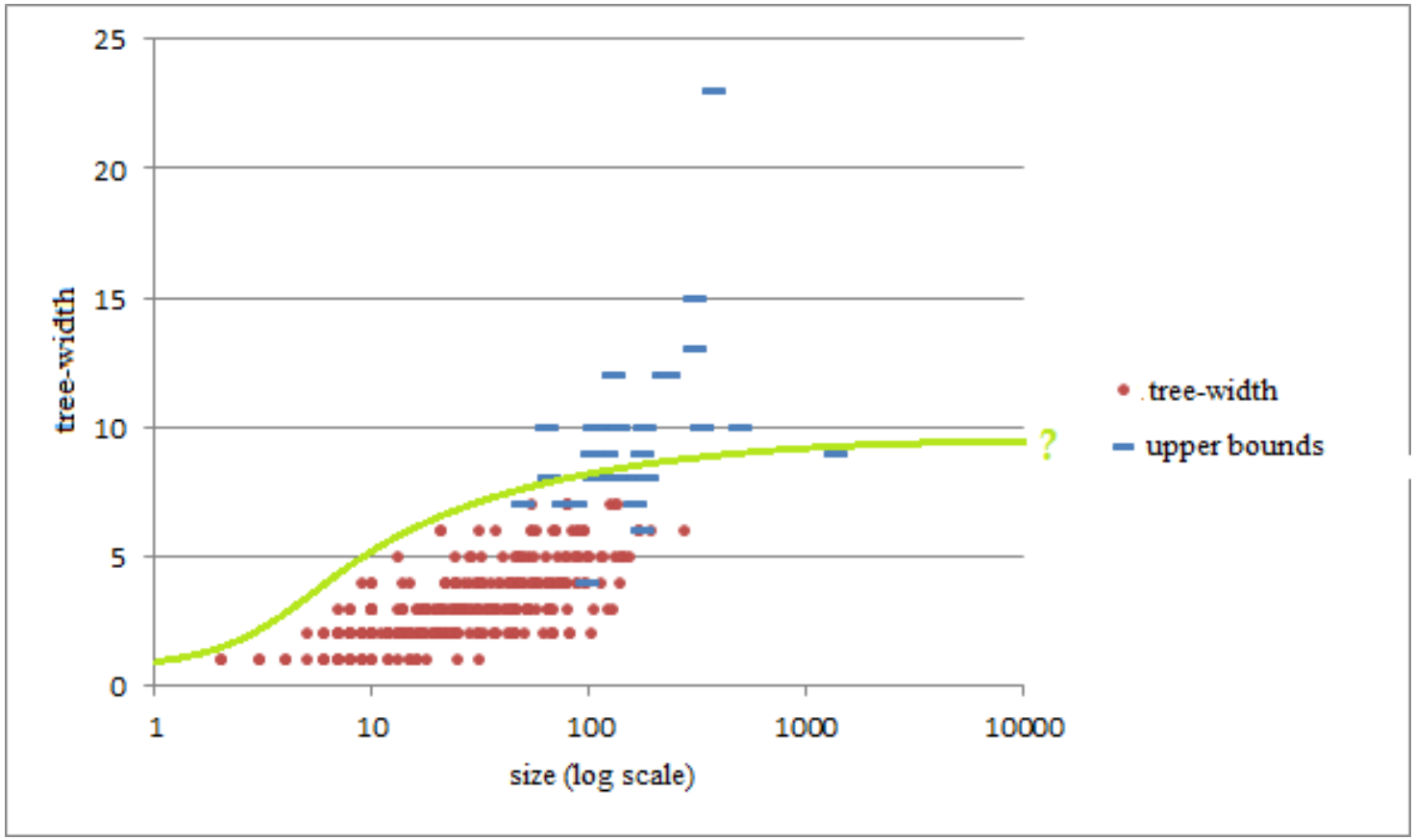

Biomodels.net tree-width as a function of the size (places and transitions) of the Petri net Computed tree-width ≤ 10

Does not explain our good performance but suggests that the problem is tractable.

Siphon-Trap Property (STP) in MSO

Theorem. Deciding the STP in linear time for Petri nets of bounded tree-width.

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$\textsc{stp}$:

$$\begin{aligned}&\forall S(\textsc{siphon}(S) \Rightarrow\\ &\exists S'(\forall v(S'(v) \Rightarrow S(v)) \wedge \textsc{trap}(S')\\ &\wedge \exists v(S'(v) \wedge \mathsf{marked}(v))))\end{aligned}$$

Finite domain model for T-/P-invariants

Minimal T-invariants

Dynamical characterisation: Multi-set of transitions whose weighted firing produces any initial marking.

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A T-invariant is minimal if its support is not the support of any other T-invariant, and the greatest common divisor of all entries is 1.

CSP model for P/T-invariants

A Petri net with n places and m transitions

variables

m Finite Domains variables.

constraints

n (linear) equality constraints

$$\forall 1 \leq i \leq n,\ Pre_i \cdot V = Post_i \cdot V$$

Finding (some) T-invariants is reduced to finding integer assignments satisfying these formulas.

Enumerating all minimal T-invariants

CSP model for an invariant V:

$$\forall 1 \leq i \leq n,\ Pre_i \cdot V = Post_i \cdot V \wedge V \cdot \mathbf{1} > 0$$

repeat

find a solution, enumerating from low to high

add the solution to the basis

remove non-minimal T-invariants from the basis if there are any

post the new constraint

$$\forall B \in \mathcal{B} \prod_{B_i \neq 0} V_i = 0$$

until no solution found

Experimental results: minimal T-invariants enumeration

Using GNU-Prolog solver:

404 models of Biomodels.net

- 6 models include non-integer stoichiometry
- 22 models could not be solved within 10 min
- 376 models: all minimal T-invariants of each model are enumerated in less than 10 seconds

80 models of Petriweb

- all instances in less than 1 second

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T-invariants and Steady states

$R = \{R_1, R_2, ..., R_m\}$ reactions, $X = \{X_1, X_2, .., X_n\}$ species.

$$R_j\colon \sum_{i=1}^{n} Pre_{ij} X_i \stackrel{e_j}{\Rightarrow} \sum_{i=1}^{n} Post_{ij} X_i \qquad Pre_{ij} \text{ and } Post_{ij} \text{ positive integers}$$

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R_j: $\sum_{i=1}^{n} Pre_{ij} X_i \stackrel{e_j}{\Rightarrow} \sum_{i=1}^{n} Post_{ij} X_i$ Pre_{ij} and $Post_{ij}$ positive integers

Finding a steady state amounts to solving:

$$\forall X_i \in X, \frac{dX_i}{dt} = 0$$

equivalent to:

$$I \cdot E(X) = 0 \text{ where } E = (e_1, \ldots, e_m).$$

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➡Let $V = \sum \alpha_j V'_j$. (V'_j is a minimal T-invariants, $\alpha_j \in \mathbb{R}^+$) Solving

$E(X) = V$ will lead to steady states of the original system.

Solving E(X)=V for computing steady states

Given (V) a linear combination of minimal T-invariants:

For support:

Restriction to General Mass Action

➟Gauss Elimination on log-linearised equations

For null entries of V:

Restriction to multiplicative kinetics

$e_j(X) = 0 \Leftrightarrow \exists i, Pre_{ij} > 0 \wedge X_i = 0$

➟simple enumeration

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Solve (1) to compute steady states:

$$(1) \begin{cases} (a) & k_j \prod_{i=1}^{n} X_i^{Pre_{ij}} = V_j & j \in support(V) \\ (b) & \exists i, Pre_{ij} > 0 \wedge X_i = 0 & j \notin support(V) \end{cases}$$

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2000 *Biochemical systems analysis of genome-wide expression data.*
E. O. Voit and T. Radivoyevitch. Bioinformatics.

Heuristic enumeration of steady states

Infinity of T-invariants $\Rightarrow$ Restriction to specific combinations of minimal invariants.

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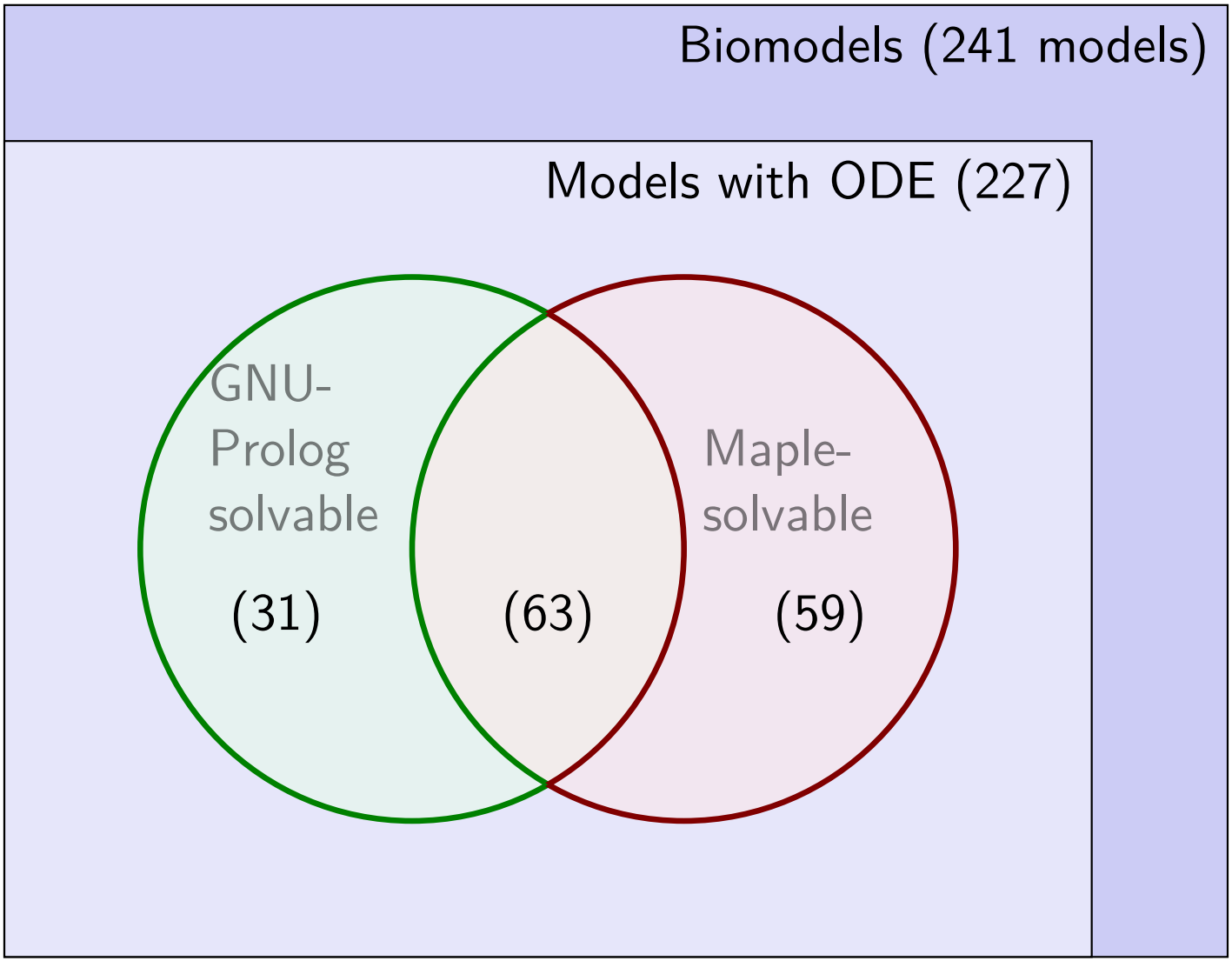
Look for minimal T-invariants;
For minimal T-invariant combinations (starting with 0 or 1 invariant), try to solve the system (1)
if (b) is not satisfiable **then**
  add another minimal T-invariant (heuristic)
else
  try to add all other minimal T-invariants and stop if (a) is unsatisfiable
end if

Other choices

- We can apply this approach to any T-invariant (even not minimal).
- The method does not need all minimal T-invariants.
- The computational cost of trying to compute steady states is low, compared to the T-invariant computation.

Steady states computation

Analytical solutions computed in less than 2 min:



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- Constraint programming over finite domain can be successfully applied to Petri nets structural problems.
- GNU-Prolog and miniSAT solvers outperform state-of-the-art algorithms for enumerating minimal siphons.
- Surprisingly good performance on real-size practical models.
- Linear-time complexity result for Petri nets with bounded tree-width.

Perspectives

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- Provide a generic tool for the verification of graphs structural properties having a biological meaning, with an underlying CLP engine. (e.g. model reduction as sub-graph epimorphism)
- Identify parameters for certain structural properties computation that ensure no performance issues.
- Understand the links between structural properties of graphs and the practical complexity of solving NP-hard problems on them.