PATHWAY ANALYSIS OF BIOCHEMICAL NETWORKS WITH PETRI NETS

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BASIC NOTIONS

- proper T-invariants -> Pascoletti 1986
- minimal T-invariants -> Lautenbach 1973
- elementary modes -> Schuster 1991
- extreme pathways -> Schilling, Schuster, Palson 1999
- generic pathways -> Bockmayr 2005

MODULAR COMPUTATION

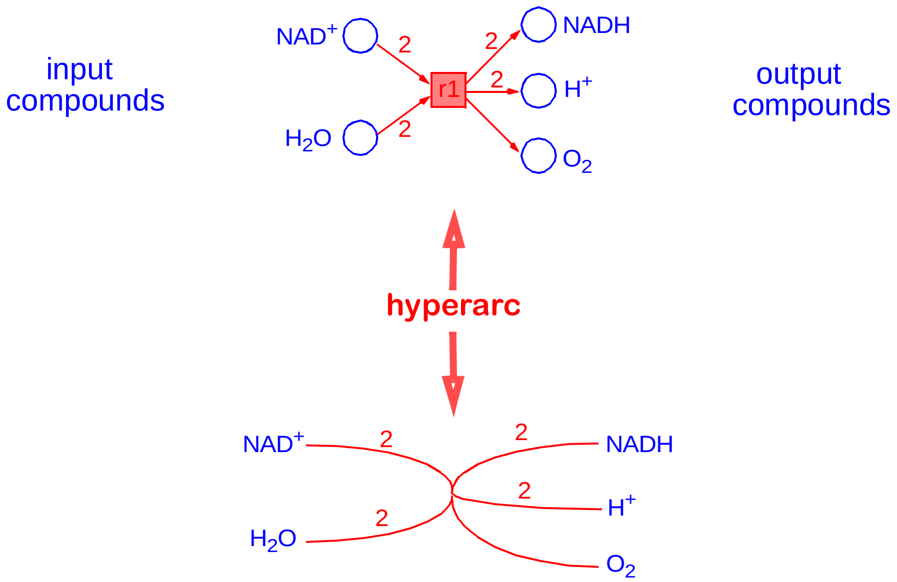
- approach -> Zaitsev 2005
- (preliminary) results -> Lehrack 2006 (to appear)

PETRI NETS - BASICS

PETRI NETS, BASICS - THE STRUCTURE

- **atomic actions -> Petri net transitions -> chemical reactions**

$$2\ NAD^+ + 2\ H_2O \rightarrow 2\ NADH + 2\ H^+ + O_2$$



PETRI NETS, BASICS - THE STRUCTURE

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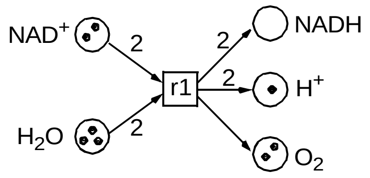
$2\ NAD^+ + 2\ H_2O \rightarrow 2\ NADH + 2\ H^+ + O_2$

input compounds



output compounds

- local conditions -> Petri net places -> chemical compounds
- multiplicities -> Petri net arc weights -> stoichiometric relations
- condition's state -> token(s) in its place -> available amount (e.g. mol)
- system state -> marking -> compounds distribution
- **PN = (P, T, F, m_0), F: (P x T) U (T x P) -> N_0, m_0: P -> N_0**

PETRI NETS, BASICS - THE BEHAVIOUR

- atomic actions -> Petri net transitions -> chemical reactions

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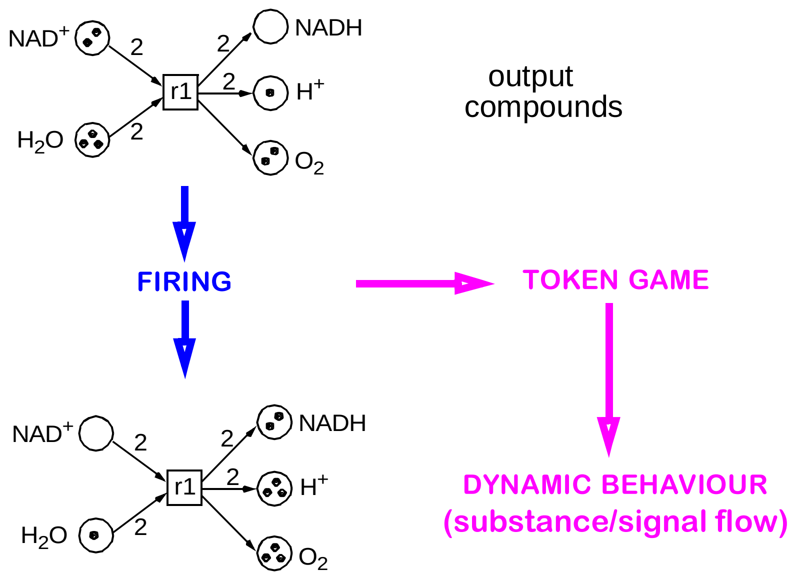
input compounds

output compounds



BIOCHEMICAL PETRI NETS, SUMMARY

- **biochemical networks**
  -> *networks of (abstract) chemical reactions*

- **biochemically interpreted Petri net**
  -> *partial order sequences of chemical reactions (= elementary actions) transforming input into output compounds / signals [respecting the given stoichiometric relations, if any]*
  -> *set of all pathways from the input to the output compounds / signals [respecting the stoichiometric relations, if any]*

- **pathway**
  -> *self-contained partial order sequence of elementary (re-) actions*

INVARIANT ANALYSES

INCIDENCE MATRIX C

- **a representation of the net structure** **=> stoichiometric matrix**

C =

P \ T	t1 . . .	tj	. . . tm
p1			
pi		cij	
: pn		Δtj	

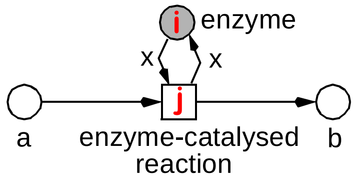
cij = (pi, tj) = F(tj,pi) - F(pi, tj) = Δ tj(pi)

Δtj = Δ tj(*)

- **matrix entry cij:**
  token change in place pi by firing of transition tj

- **matrix column Δtj:**
  vector describing the change of the whole marking by firing of tj

- **side-conditions are neglected**



cij = 0

T-INVARIANTS, BASICS I

- **Lautenbach, 1973**

- **T-invariants** *-> multisets of transitions*
  - *-> integer solutions x of* $Cx = 0, x \neq 0, x \geq 0$
  - *-> Parikh vector*

- **minimal T-invariants**
  - *-> there is no T-invariant with a smaller support* *-> sets of transitions*
  - *-> gcD of all entries is 1*

- **any T-invariant is a non-negative linear combination of minimal ones**
  - *-> multiplication with a positive integer*
  - *-> addition*
  - *-> Division by gcD*

$$kx = \sum_i a_i x_i$$

- **Covered by T-Invariants (CTI)**
  - *-> each transition belongs to a T-invariant*

- **a T-invariant defines a subnet** -> **partial order structure**
  - -> *the T-invariant's transitions (the support),*
    + all their pre- and post-places
    + the arcs in between
  - -> *pre-sets of supports = post-sets of supports*

-> ANALOGUE DEFINITIONS FOR P-INVARIANTS

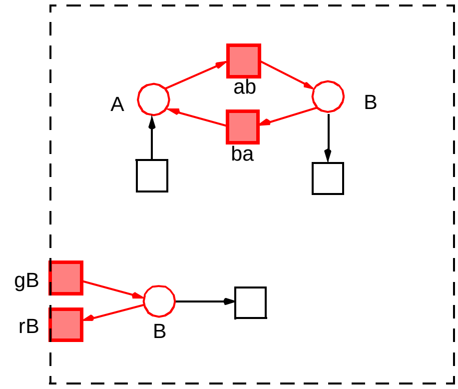
$$yC = 0, y \neq 0, y \geq 0$$

- **T-invariants = (multi-) sets of transitions = Parikh vector**
  - -> *zero effect on marking*
  - -> *reproducing a marking / system state*
- **partially ordered transition sequence** -> **behaviour understanding**
  of transitions occuring one after the other
  - -> *substance / signal flow*
  - -> *signal transduction networks, gene regulatory networks*
- **relative transition firing rates**
  of transitions occuring permanently & concurrently
  - -> *steady state behaviour*
  - -> *metabolic networks*

T-INVARIANTS, BASIC TYPES IN BIO NETWORKS

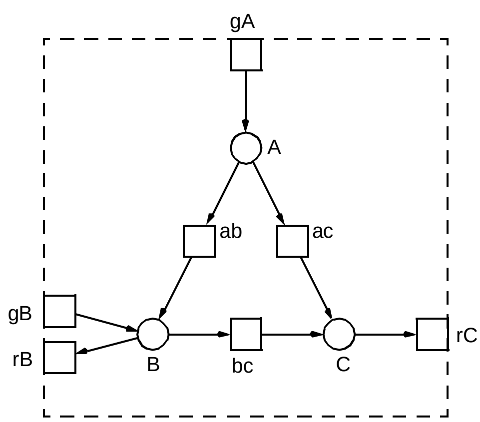
- **trivial minimal T-invariants**
  - -> *reversible reactions*
  - -> *boundary transitions of auxiliary compounds*
- **non-trivial minimal T-invariants**
  - -> *i/o-T-invariants*

    covering boundary transitions of input / output compounds
  - -> *inner cycles*



EXAMPLE, T-INVARIANTS

- substances involved
  - -> *input substance A*
  - -> *output substance C*
  - -> *auxiliary substance B*



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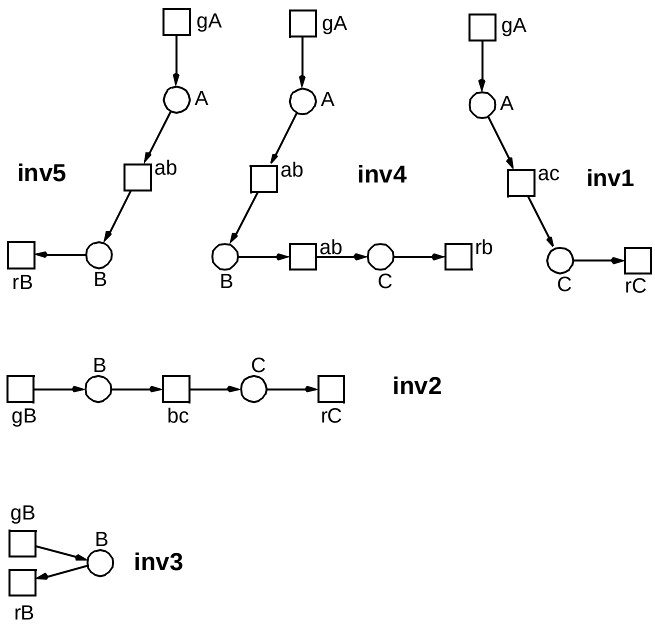
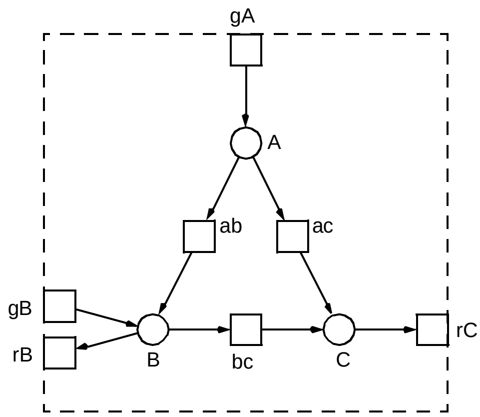


Example, Elementary Modes

- substances involved
  - -> *input substance A*
  - -> *output substance C*
  - -> *auxiliary substance B*



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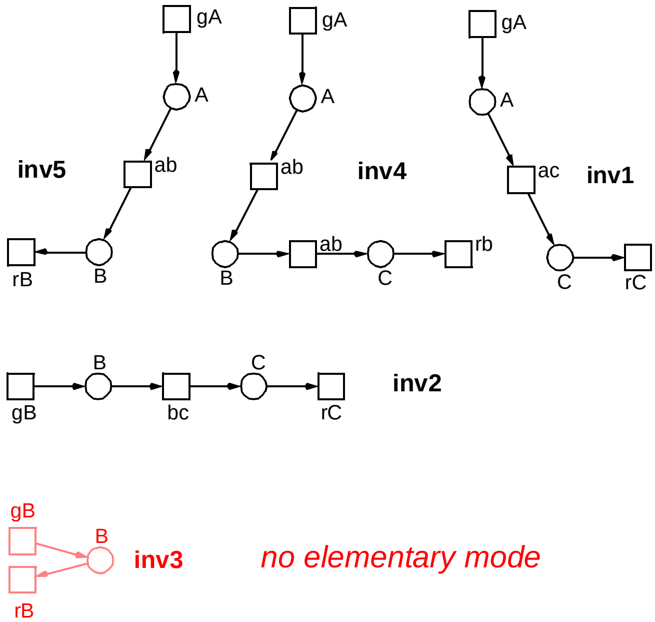
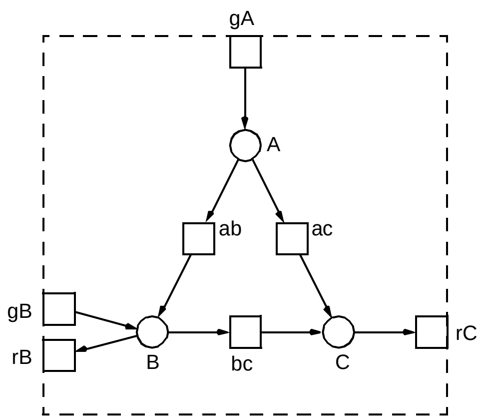


Example, Extreme Pathways

- substances involved
  - -> *input substance A*
  - -> *output substance C*
  - -> *auxiliary substance B*

no extreme pathway



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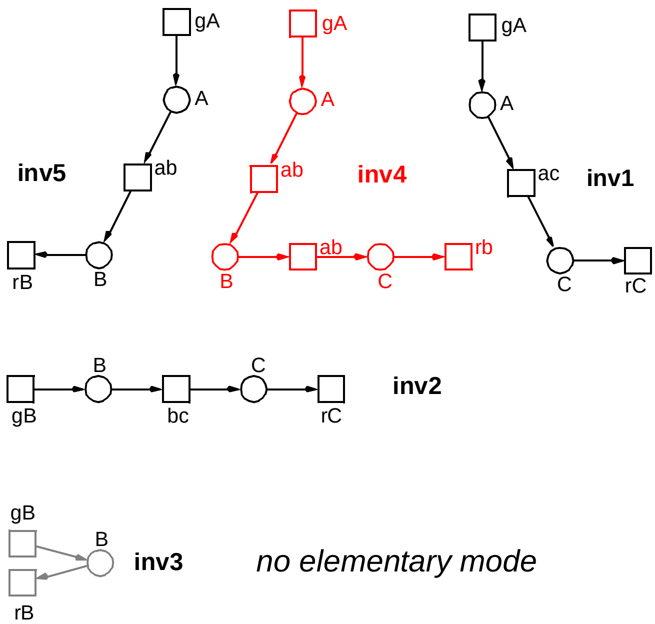

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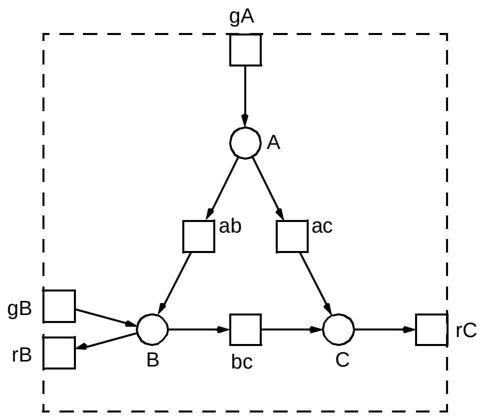

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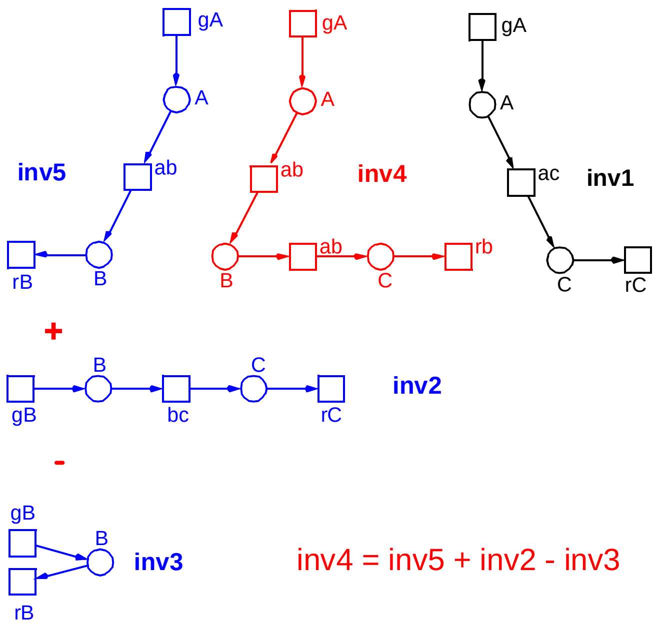
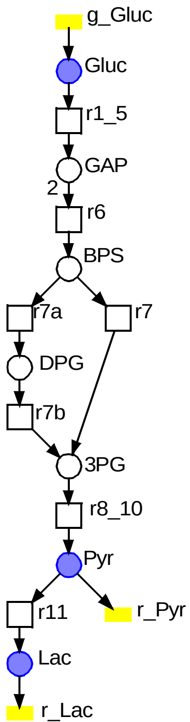


inv4 = inv5 + inv2 - inv3

Elementary T-Invariants / Hilbert Basis



four minimal T-invariants

1. Gluc -> r7 -> 2 Pyr
2. Gluc -> r7 -> 2 Lac
3. Gluc -> r7a, r7b -> 2 Pry
4. Gluc -> r7a, r7b -> 2 Lac

Gluc -> [r7 / r7a, r7b] -> [2 Lac / 2 Pyr]

$$kx = \sum_i a_i x_i$$

five additional T-invariants

inv5 = (inv1 + inv3) / 2
inv6 = (inv2 + inv4) / 2

inv7 = (inv1 + inv2) / 2
inv8 = (inv3 + inv4) / 2

inv9 = (inv1 + inv2 + inv3 + inv4) / 4

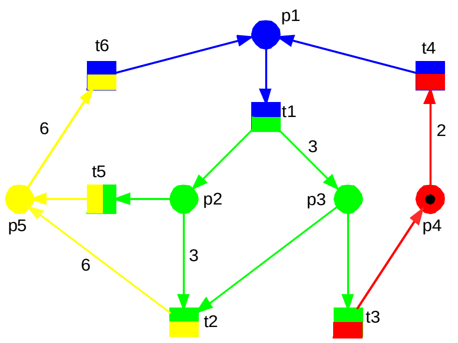
Gluc -> [r7 / r7a, r7b] -> [1 Lac / 1 Pyr]

$$x = \sum_i a_i x_i$$

MODULAR COMPUTATION

BASIC IDEA

- **decomposition into subnets**
- **for each subnet: computation of (local) invariants**
- **computation of interface invariants**
- **calculation of system invariants**
  - -> *by composition of subnet invariants*
  - -> *guided by interface invariants*



subnet -
transition-bordered conflict cluster C,
defined by its places

all postplaces of input transitions belong to C
all preplaces of output transitions belong to C

each interface transition has at most
- one input subnet
- one output subnet

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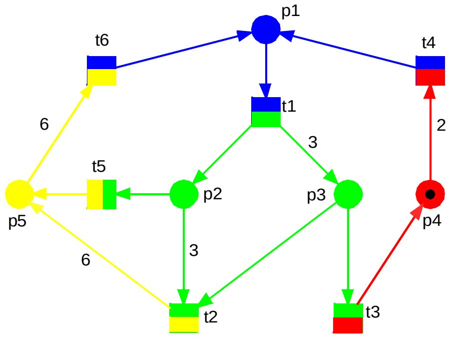

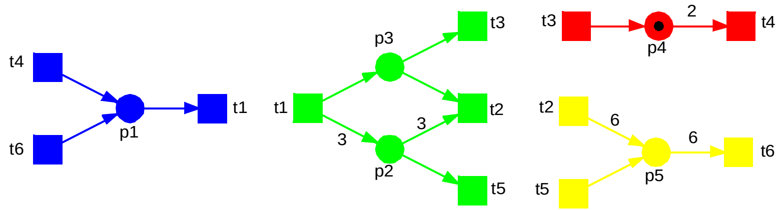

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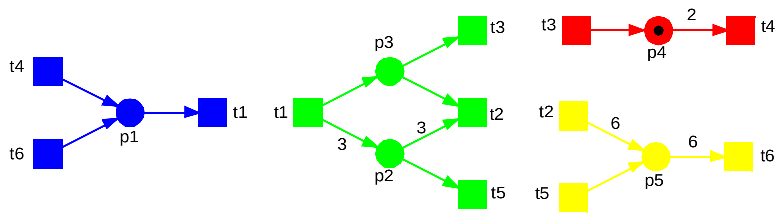
x2 = (t6, t1)

x3 = (t1, t2)
x4 = (t1, t3, 3 t5)

x5 = (2 t3, t4)

x6 = (t2, t6)
x7 = (6 t5, t6)



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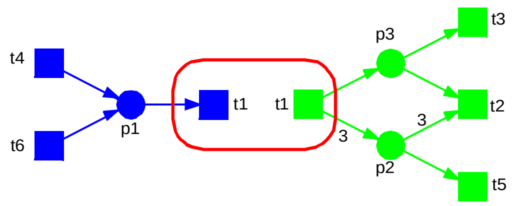
t1: x1 + x2 = x3 + x4



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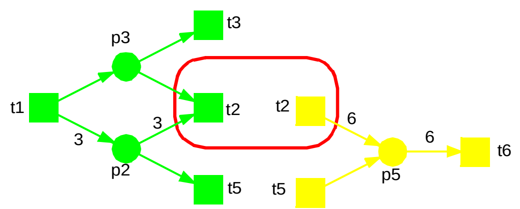
t1: x1 + x2 = x3 + x4
t2: x3 = x6



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t1: x1 + x2 = x3 + x4
t2: x3 = x6
t3: x4 = 2 x5
t4: x5 = x1
t5: 3 x4 = 6 x7
t6: x6 + x7 = x2

→ (x2, x3, x6)
(x1, x2, 2 x4, x5, x7)

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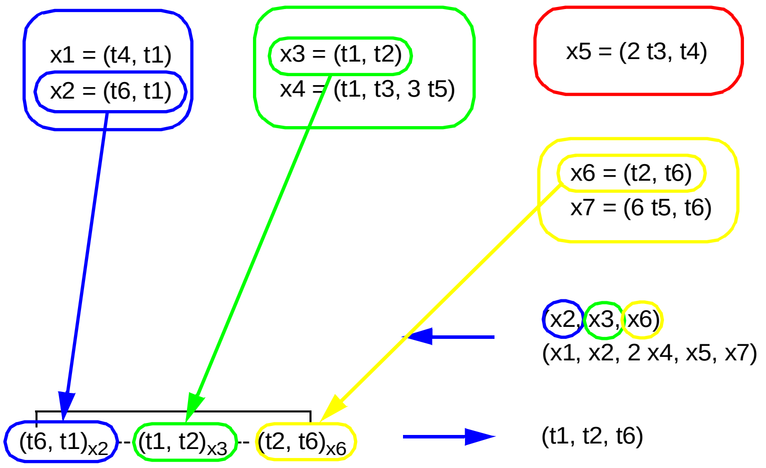

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(x2, x3, x6)
(x1, x2, 2 x4, x5, x7)

$(t6, t1)_{x2}$ -- $(t1, t2)_{x3}$ -- $(t2, t6)_{x6}$ → (t1, t2, t6)

$2\begin{pmatrix} t1, & t3 \\ & 3\ t5 \end{pmatrix}_{x4}$ -- $(2\ t3, t4)_{x5}$ -- $(t4, t1)_{x1}$ -- $(6\ t5, t6)_{x7}$ -- $(t6, t1)_{x2}$ → (2 t1, 2 t3, t4, 6 t5, t6)

(Preliminary) Summary

Assumption

- the solution of many small systems is less time/space consuming than the solution of a single larger one

Major (known) drawback

- the computation of system invariants does not only produce minimal invariants

Case studies

- -> excel file

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THANKS !

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