MODULARIZATION AND HIERARCHICAL REPRESENTATION OF BIOMOLECULAR NETWORKS WITH PETRI NETS TRANSITION INVARIANTS

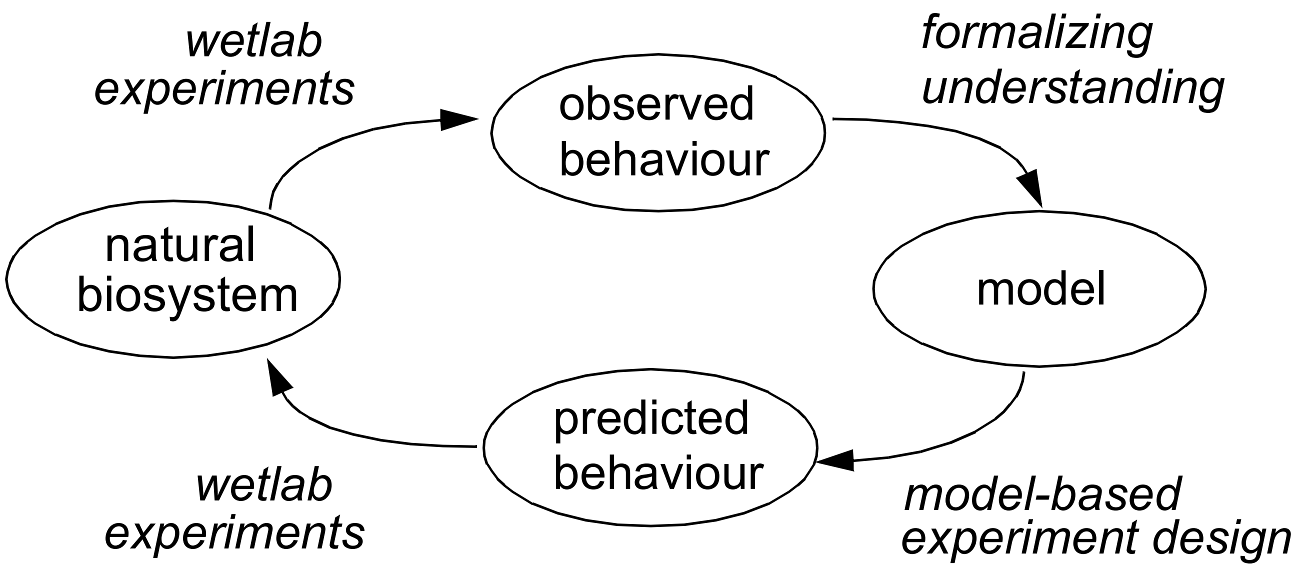
Monika Heiner

Brandenburg University of Technology Cottbus

Dept. of CS

Framework: Systems Biology

MODELLING = FORMAL KNOWLEDGE REPRESENTATION



Framework: Systems Biology

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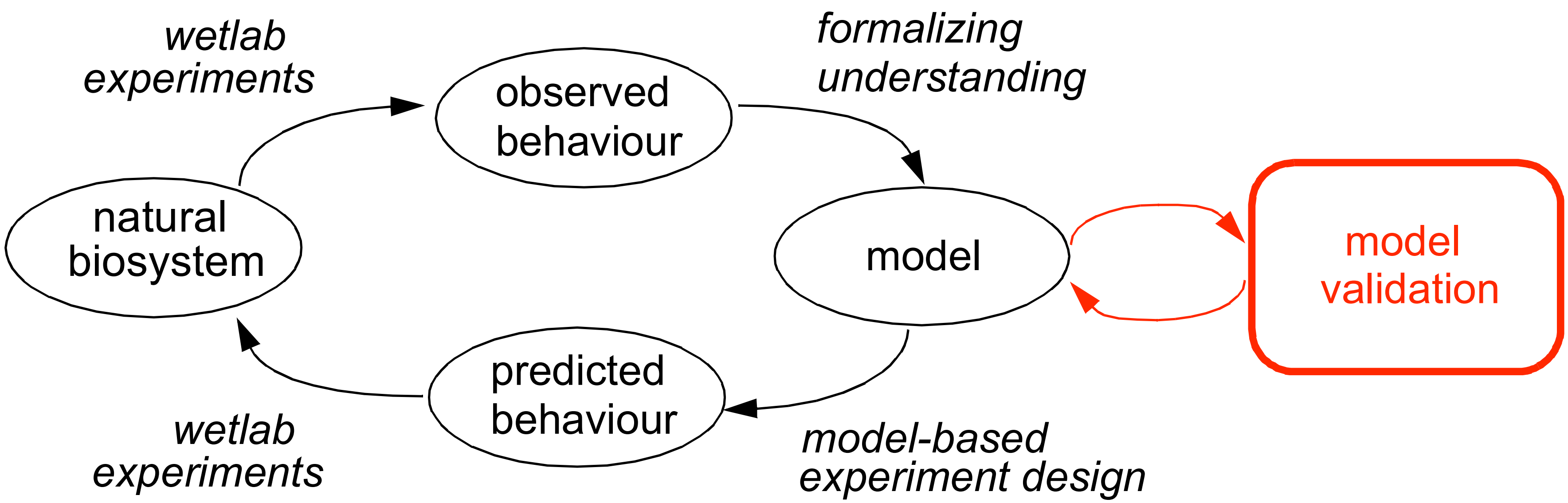

MODEL VALIDATION = CONFIDENCE INCREASE

STRUCTURE OF THE TALK

- **What are biochemically interpreted Petri nets ?**

- **What are T-invariants ?**
  - -> *interpretations*
  - -> *formal definition*

- **Modularization and hierarchical representation using T-invariants**
  - -> *abstract dependent transition sets define logical building blocks*

- **Some applications**
  - -> *glycolysis*
  - -> *apoptosis*
  - -> *hypoxia*
  - -> *potato tuber*

- **Summary**
  - -> *pros & cons*

WHAT ARE BIOCHEMICALLY INTERPRETED PETRI NETS?

Bio Petri Nets, Ex1

r1: A -> 2 B
r2: 2 A -> 3 C

BIO PETRI NETS, EX1

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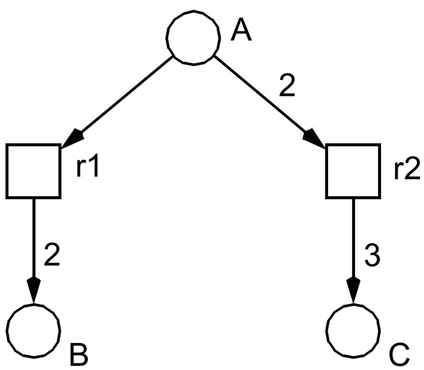

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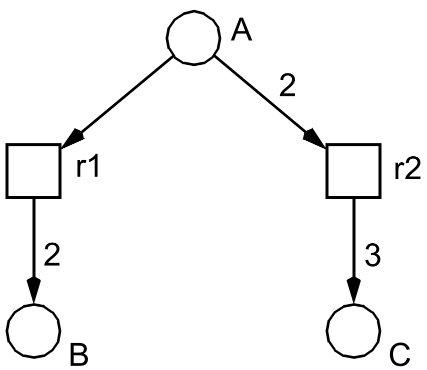
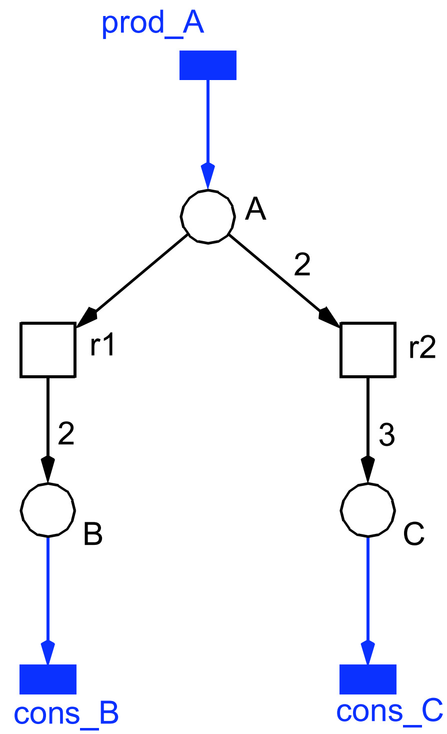




TRANSITION INVARIANTS, A CRASH COURSE

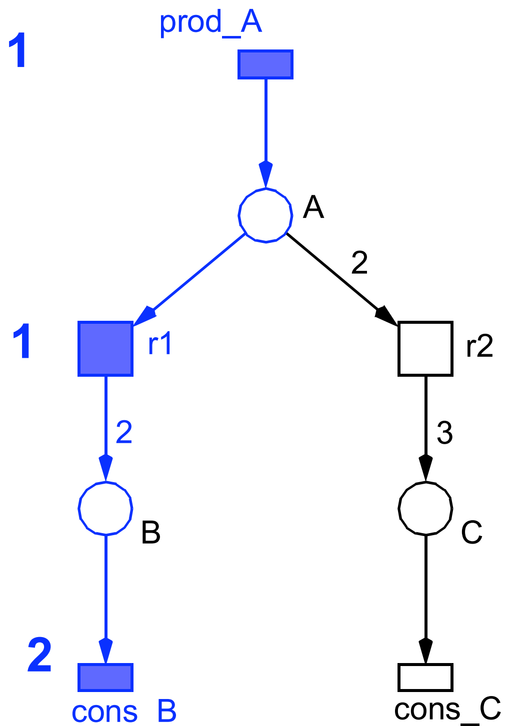
TRANSITION INVARIANTS,
A CRASH COURSE

-> *ELEMENTARY FLUX MODES*

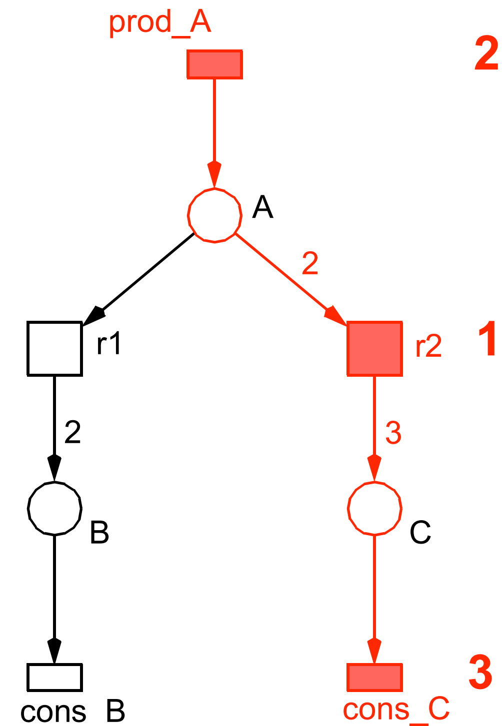
monika.heiner@informatik.tu-cottbus.de

T-INVARIANTS, EX1

r1:   A -> 2 B
r2: 2 A -> 3 C



T-INVARIANT 1



T-INVARIANT 2

INCIDENCE MATRIX C

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

C =

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

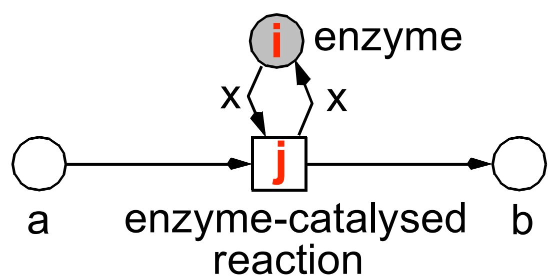
$cij = (pi, tj) = F(tj,pi) - F(pi, tj) = \Delta\ tj(pi)$

$\Delta tj = \Delta\ tj(*)$

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

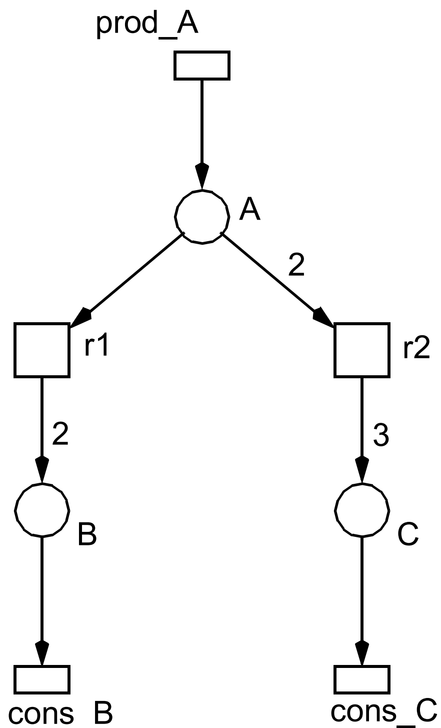
- **matrix column** Δtj**:**
  vector describing the change of the whole marking by firing of tj

- **side-conditions are neglected**

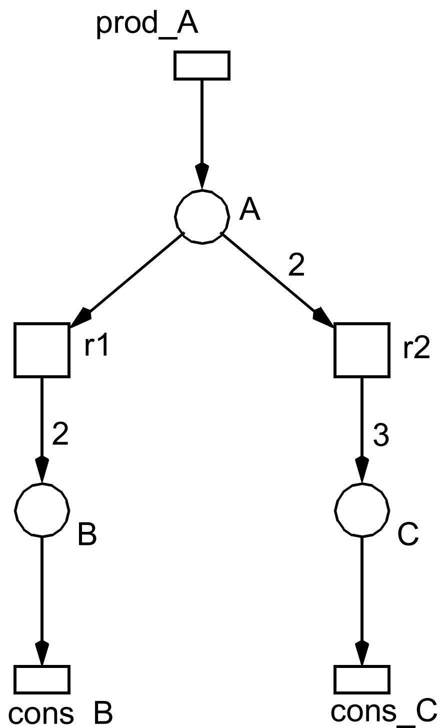


cij = 0

INCIDENCE MATRIX C, EX1

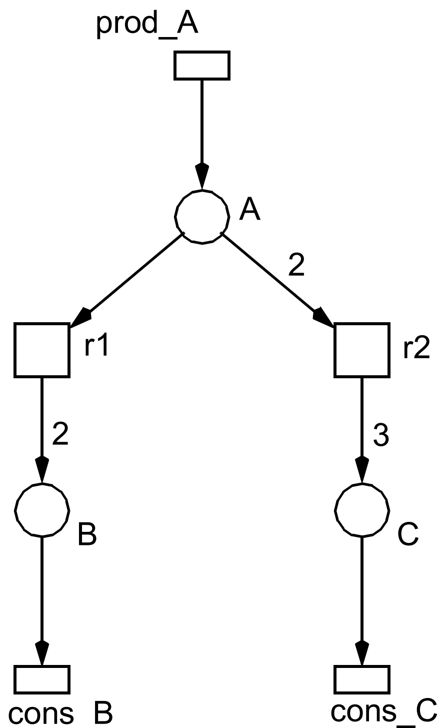


Incidence Matrix C, Ex1



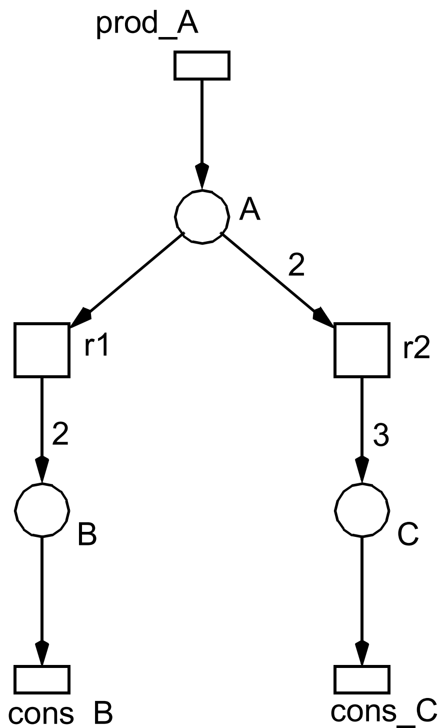
T / P	r1	r2	prod_A	cons_B	cons_C
A					
B					
C					

INCIDENCE MATRIX C, EX1



P \ T	r1	r2	prod_A	cons_B	cons_C
A	-1	-2	1		
B	2			-1	
C		3			-1

INCIDENCE MATRIX C, EX1



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C		3			-1
	1		**1**	**2**	

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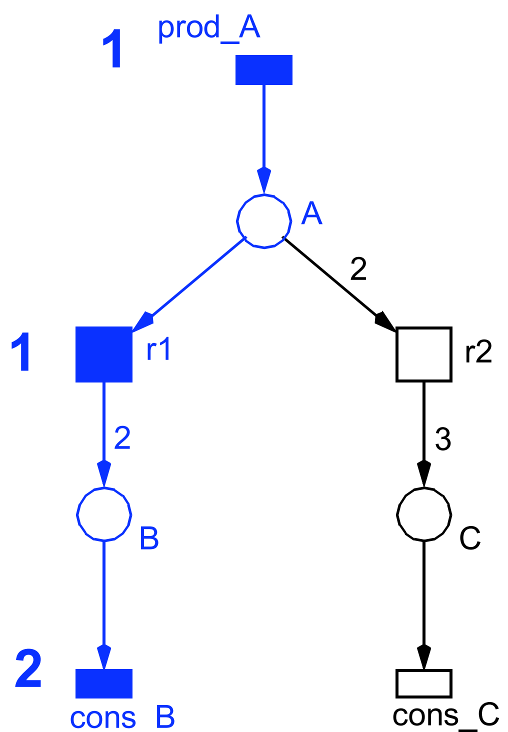

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	1		1	2	

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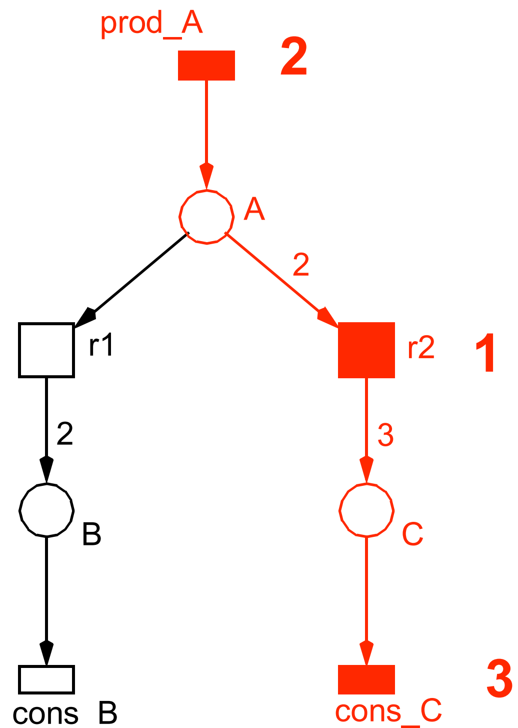

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		1	2		3

T-INVARIANTS, BASICS

- **Lautenbach, 1973** -> **Schuster, 1993**

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

- **support of a T-invariant x -> supp(x)** -> *set of transitions*
  - -> *set of transitions involved, i.e.* $x(i) \neq 0$

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

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

$$kx = \sum_i a_i x_i$$

T-INVARIANTS, INTERPRETATIONS

- **T-invariants = (multi-) sets of transitions = Parikh vector**
  - -> *zero effect on marking*
  - -> *reproducing a marking / system state*

- **two interpretations**
  1. *partially ordered transition sequence* **-> behaviour understanding**
     of transitions occuring one after the other
     - -> *substance / signal flow*
  2. *relative transition firing rates* **-> steady state behaviour**
     of transitions occuring permanently & concurrently
     - -> *steady state behaviour*

- **a minimal T-invariant defines a connected subnet**
  - -> *the T-invariant's transitions (the support),*
    + all their pre- and post-places
    + the arcs in between
  - -> *pre-set of support = post-set of support*

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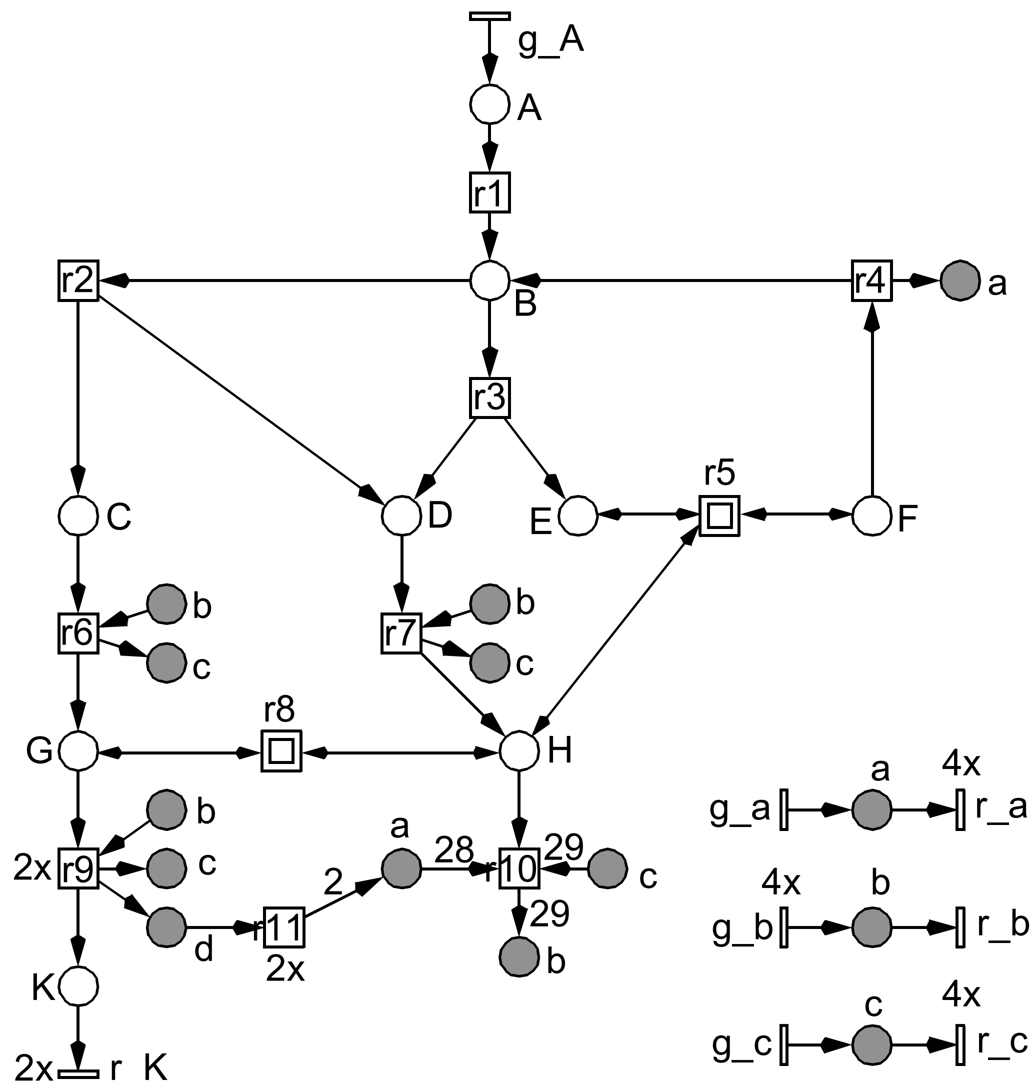
T-INVARIANTS, EX2



T-INVARIANTS, EX2

trivial min. T-invariants (5)

- **boundary transitions of auxiliary compounds**

  -> (g_a, r_a), (g_b, r_b), (g_c, r_c)

- **reversible reactions**

  -> (r5, r5_rev), (r8, r8_rev)

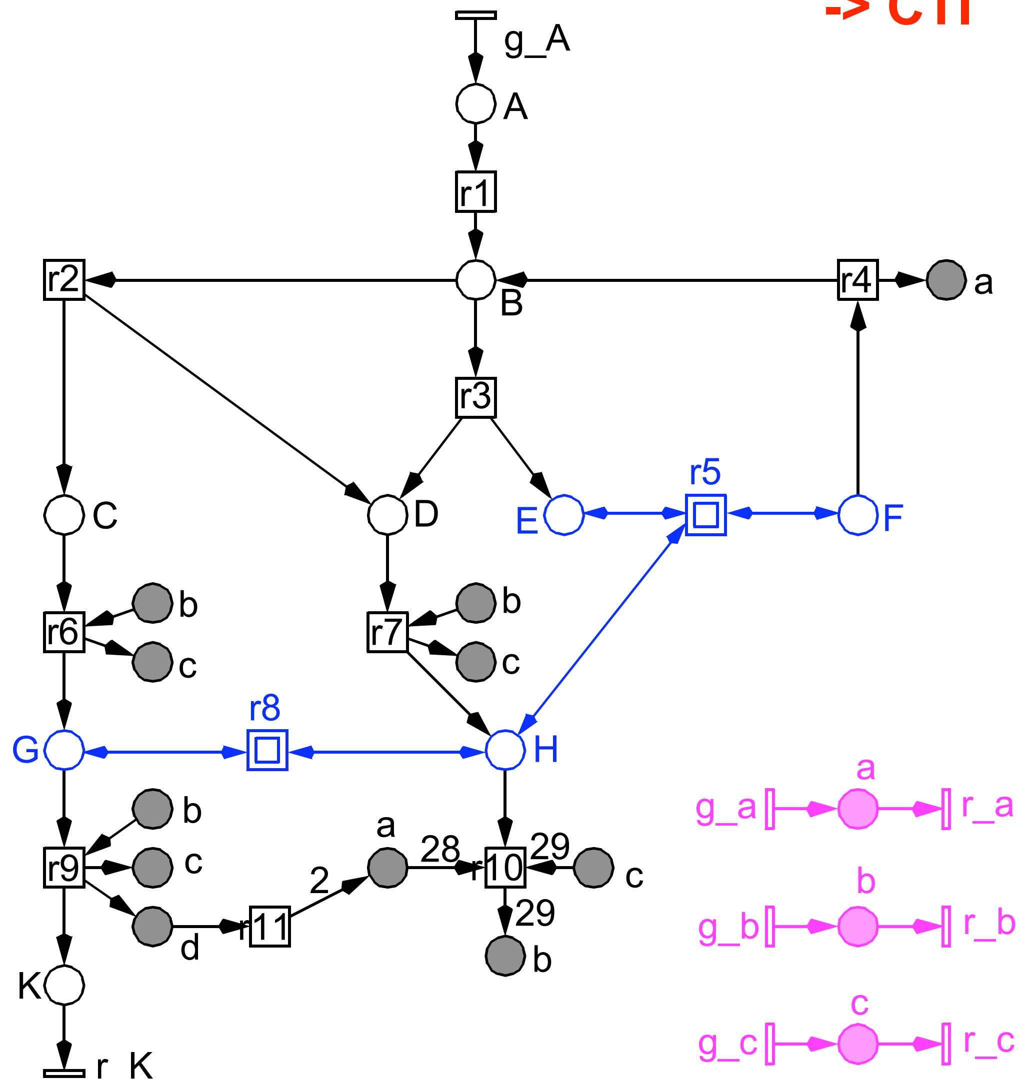
non-trivial min. T-invariants (7)

- **covering boundary transitions of input / output compounds**

  -> i/o-T-invariants

- **inner cycles**

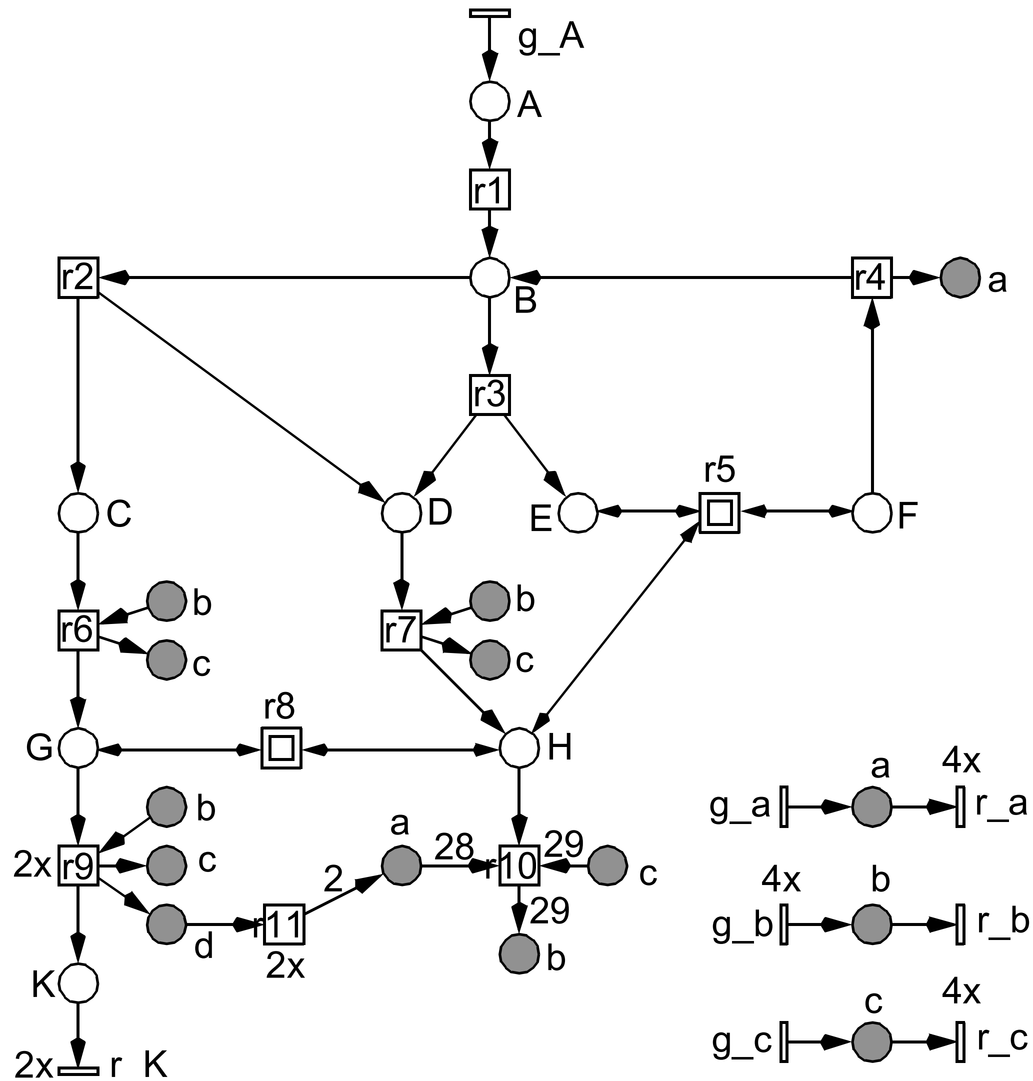
-> CTI



T-INVARIANTS, EX2

- i/o-T-invariant, example

12 | 0.r1 : 1
| 1.r2 : 1,
| 3.r8_rev : 1,
| 4.r6 : 1,
| 5.r7 : 1,
| 9.r9 : 2,
| 12.r11 : 2,
| 13.g_A : 1,
| 14.r_K : 2,
| 15.g_b : 4,
| 18.r_c : 4,
| 20.r_a : 4



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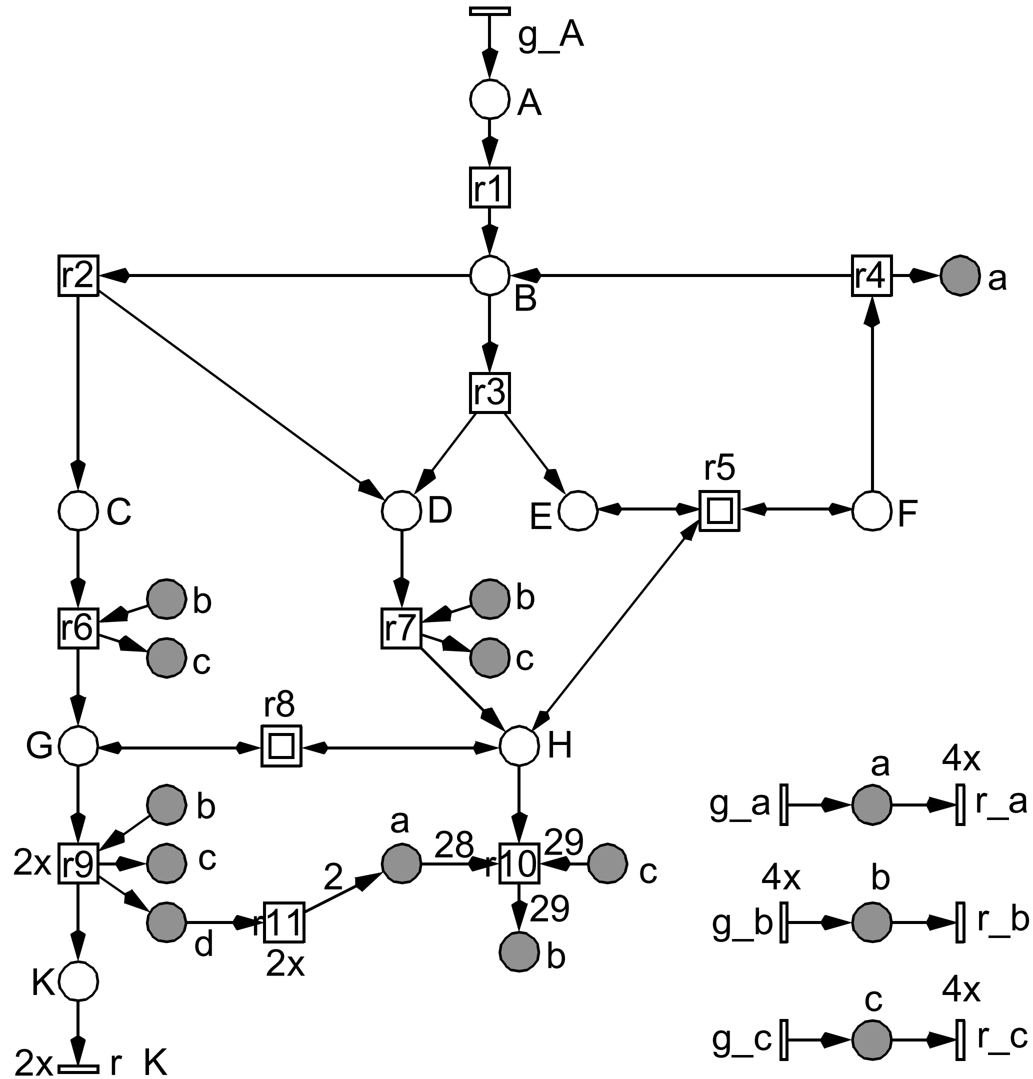
- **sum equation**

  A + 4b -> 2K +4a + 4c



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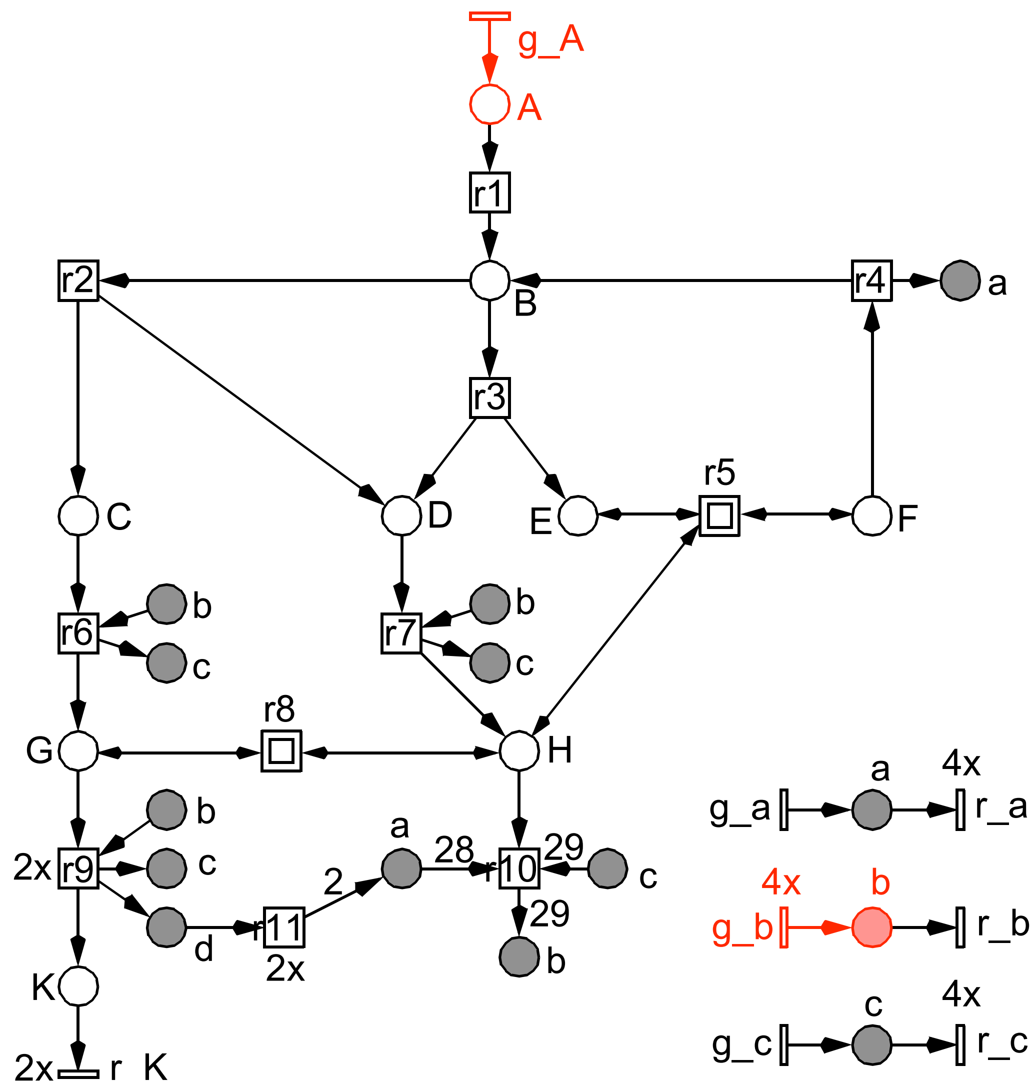

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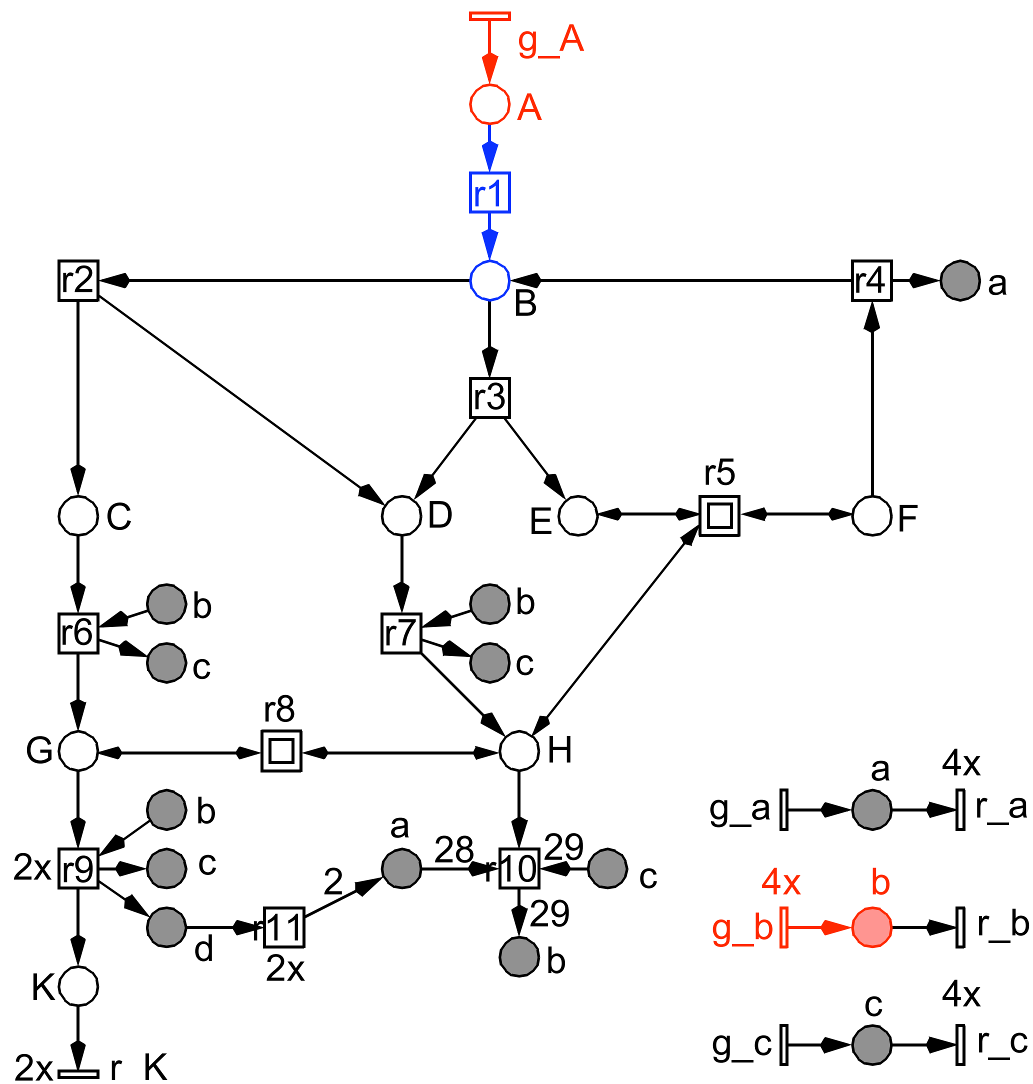

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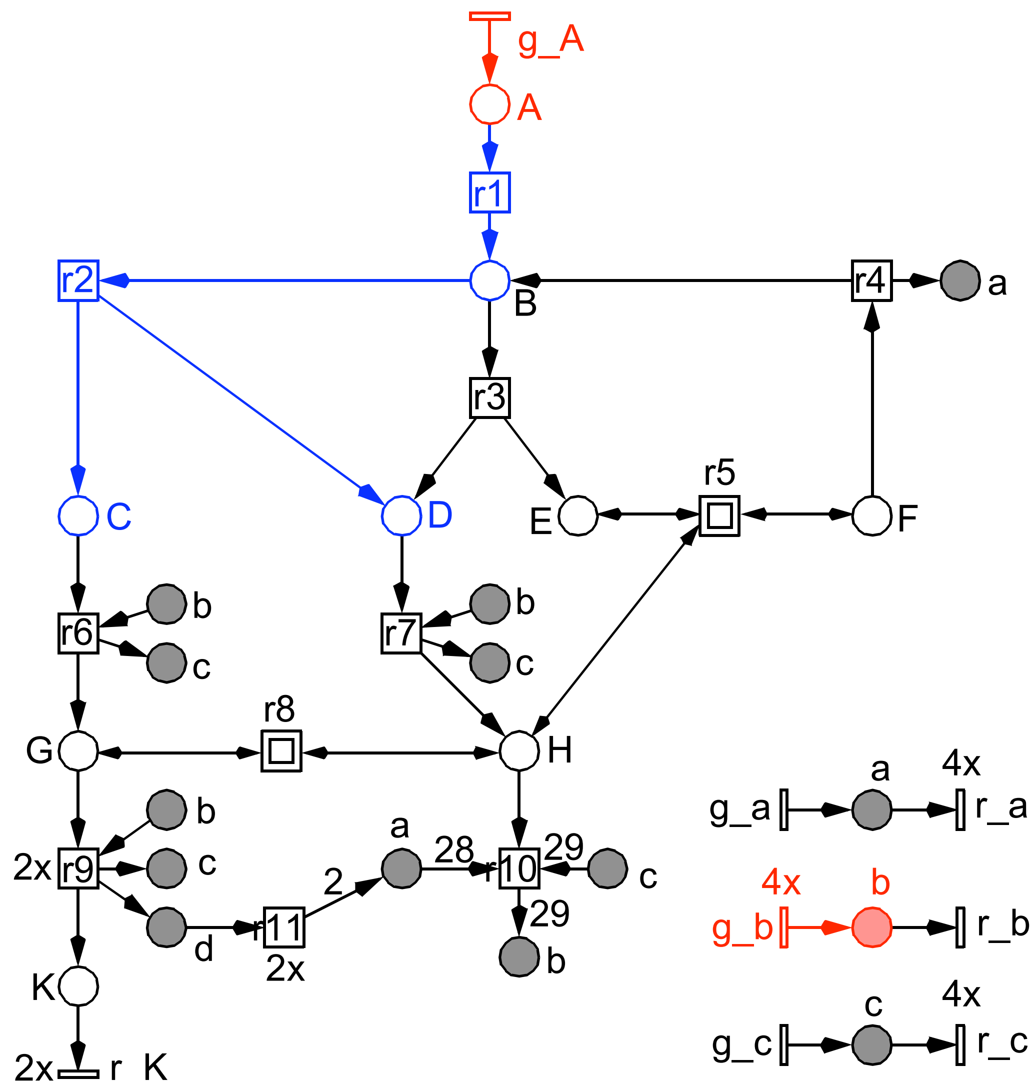

- **sum equation**

$A + 4b \rightarrow 2K + 4a + 4c$

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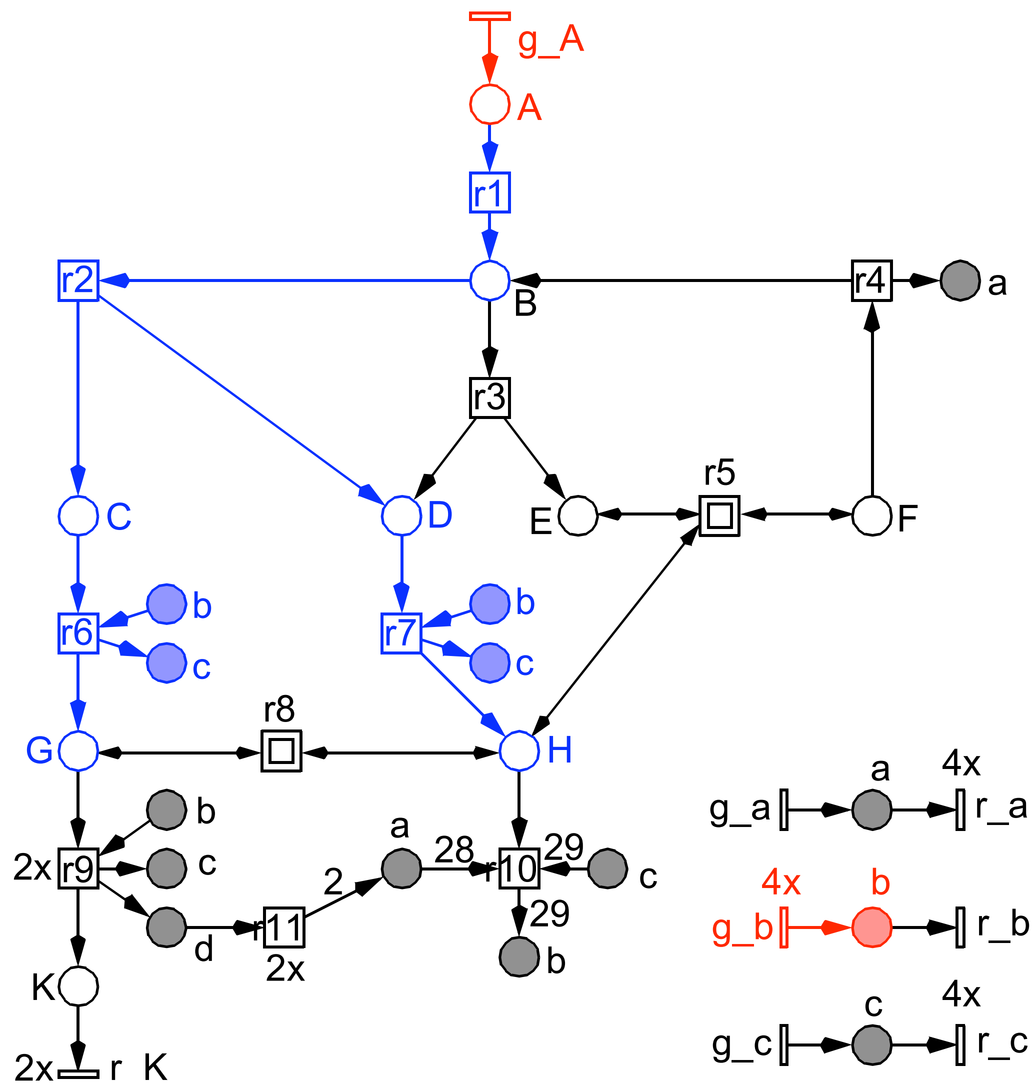

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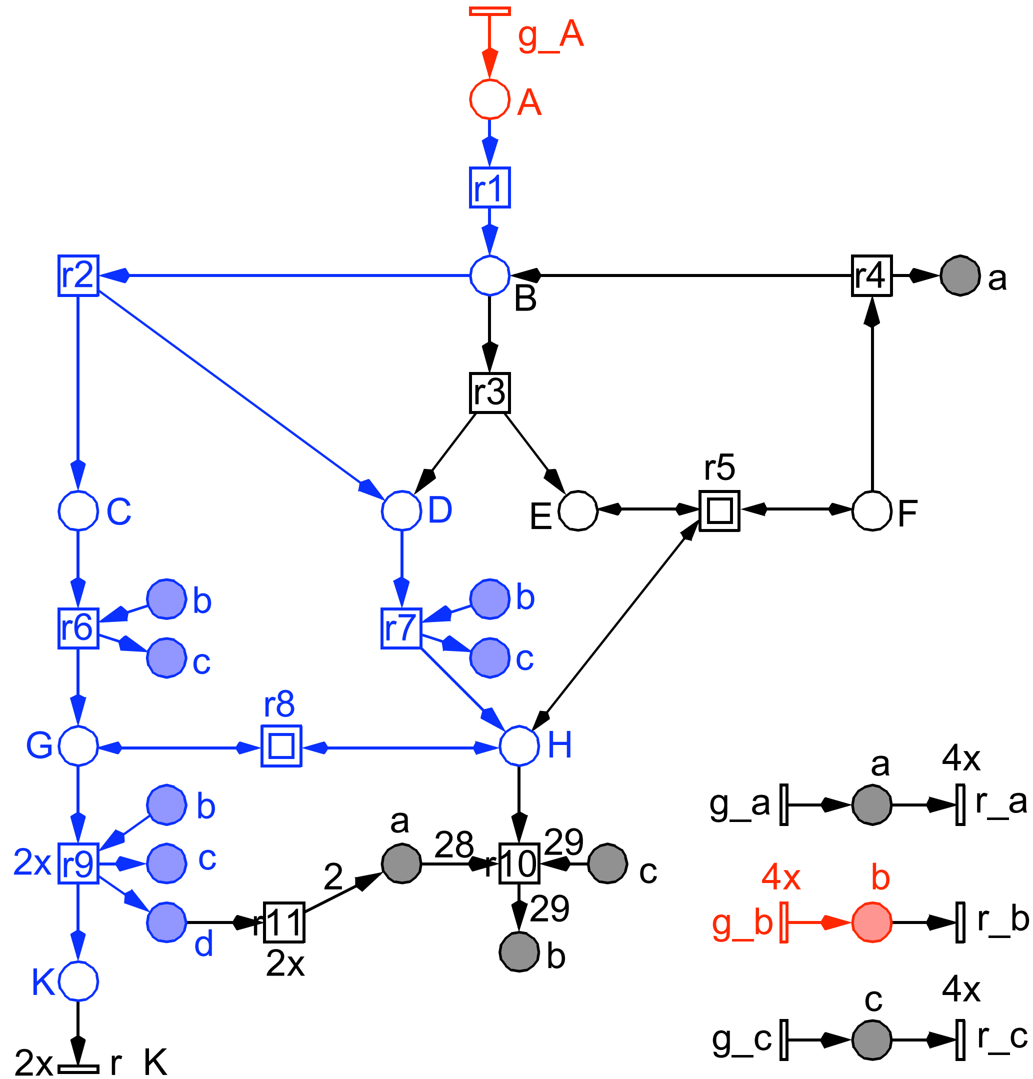

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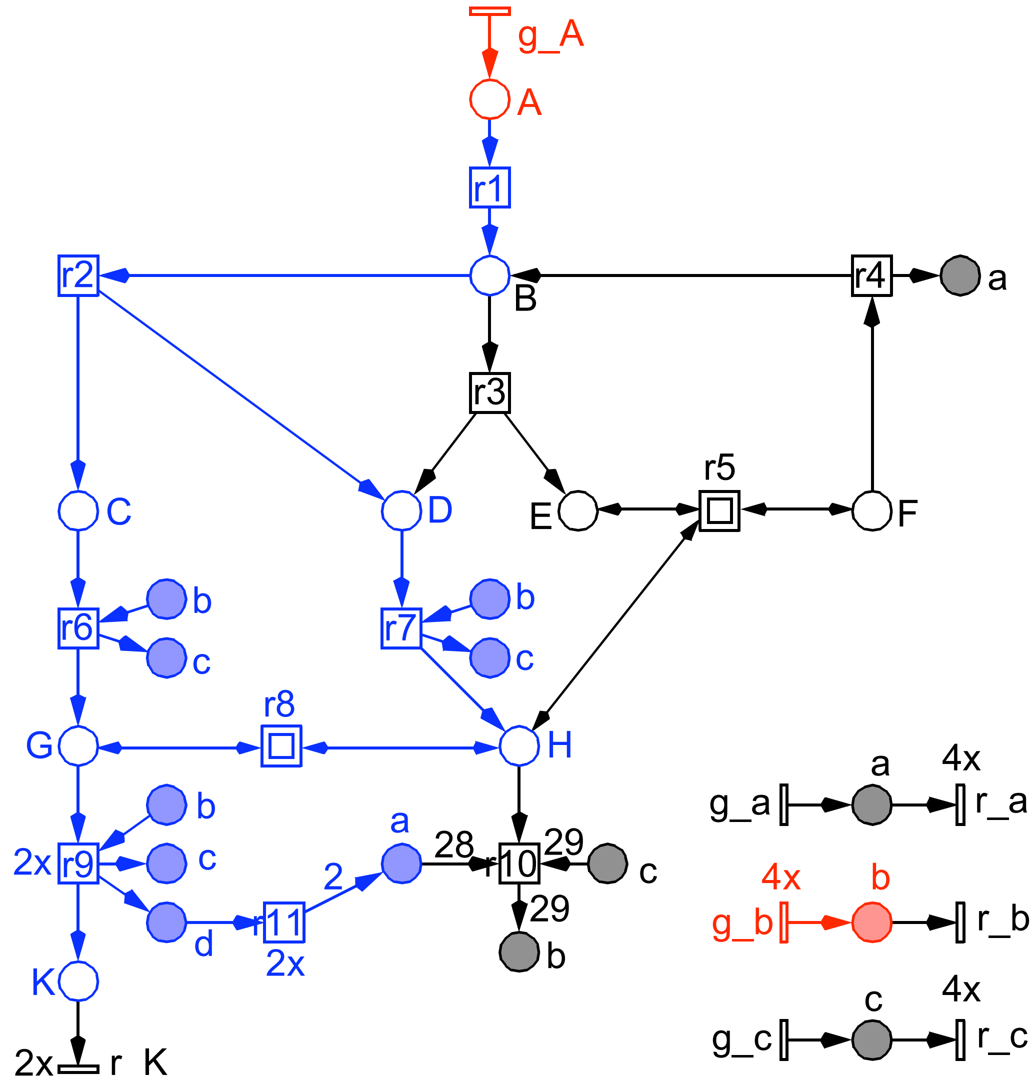

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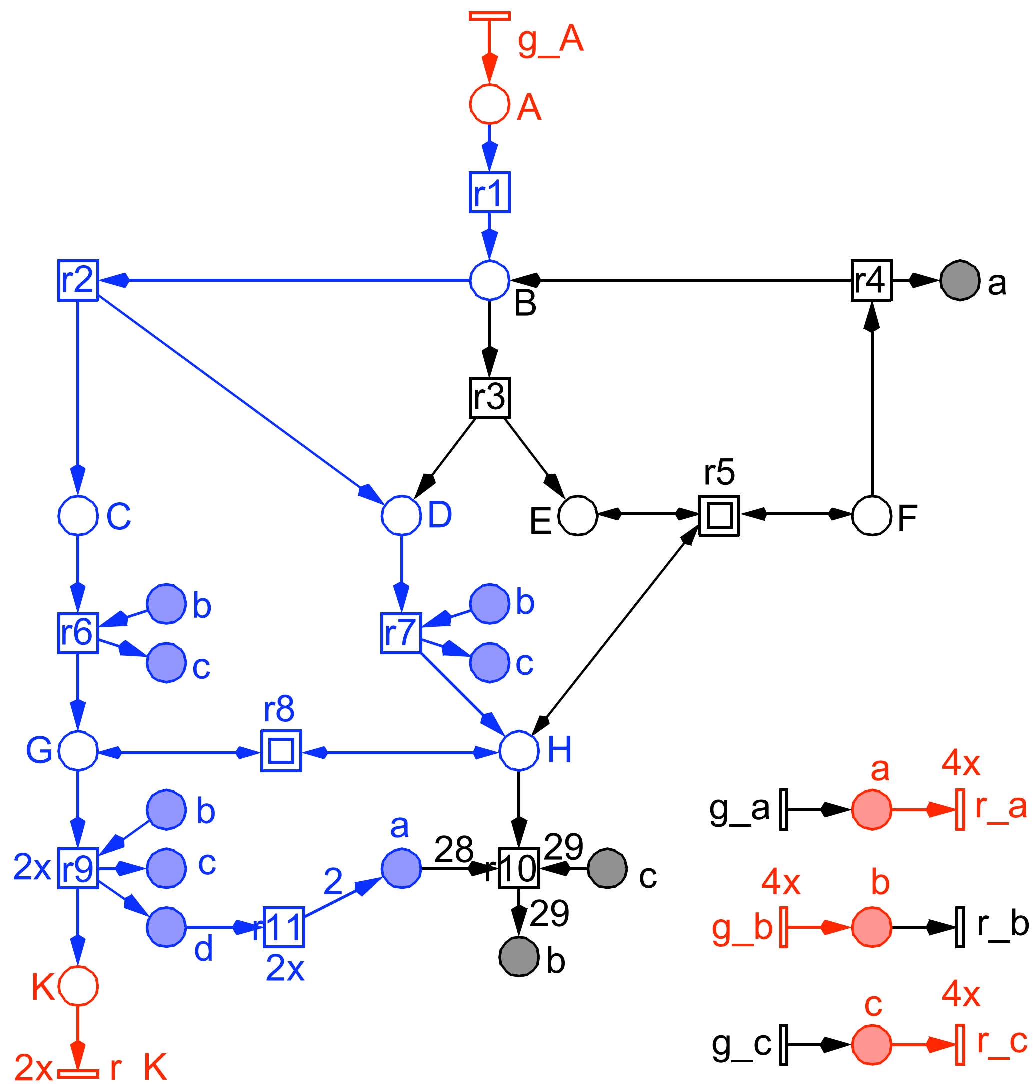
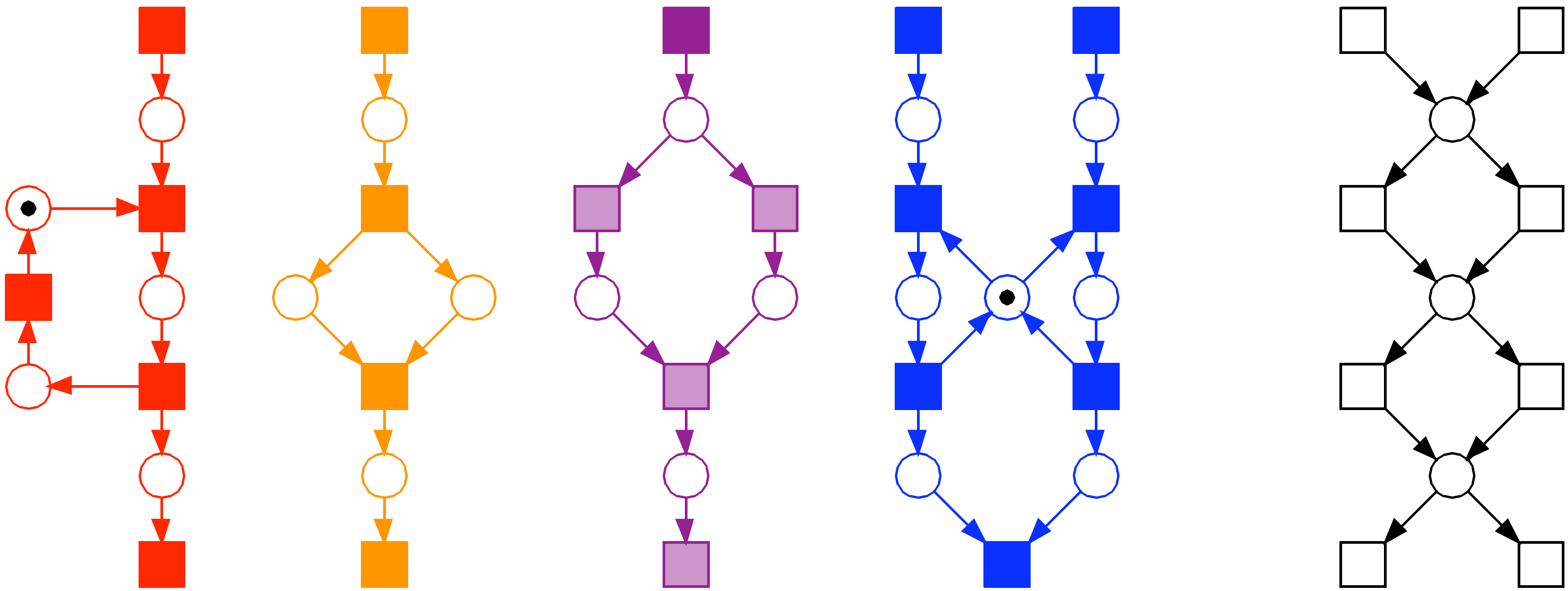


- **T-invariants may contain any structure**



- **T-invariants generally overlap**

  -> combinatorial effect brings explosion in the number of min. T-invariants **(2^4)**

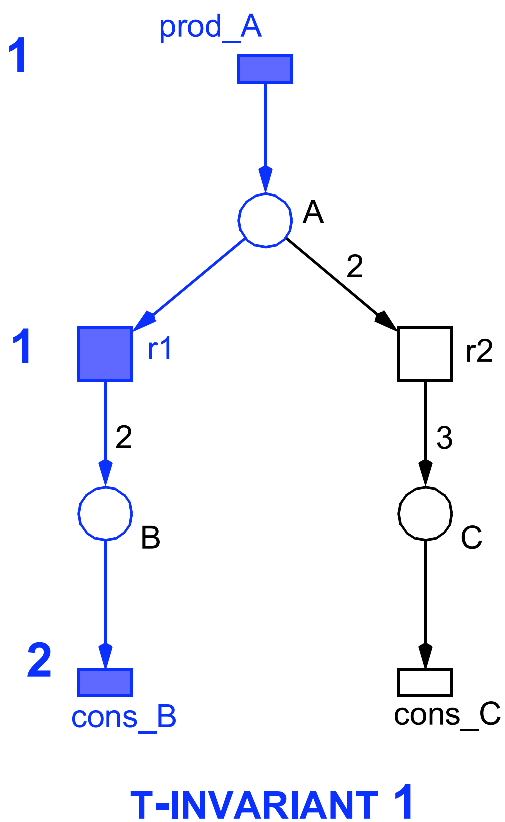
MODULARIZATION AND HIERARCHICAL REPRESENTATION USING T-INVARIANTS

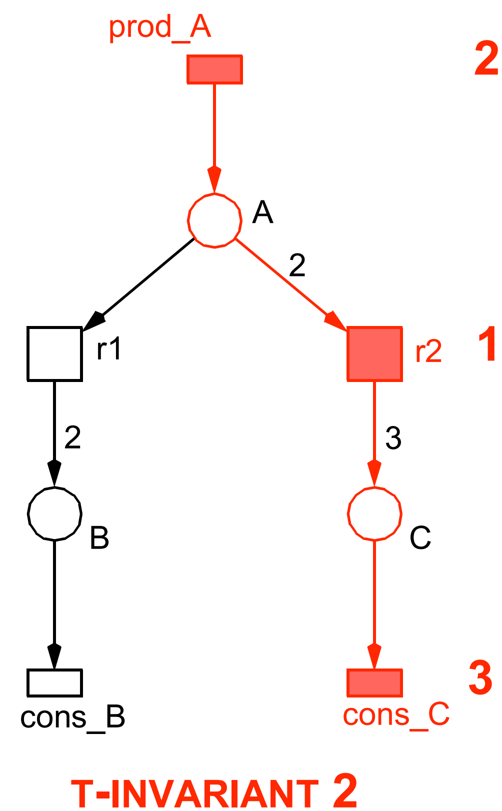
MODULARIZATION AND HIERARCHICAL REPRESENTATION USING T-INVARIANTS

-> ABSTRACT DEPENDENT TRANSITION SETS (ADT-SETS)

ADT-SETS, EX1

r1: A -> 2 B
r2: 2 A -> 3 C





ADT-sets, Ex1

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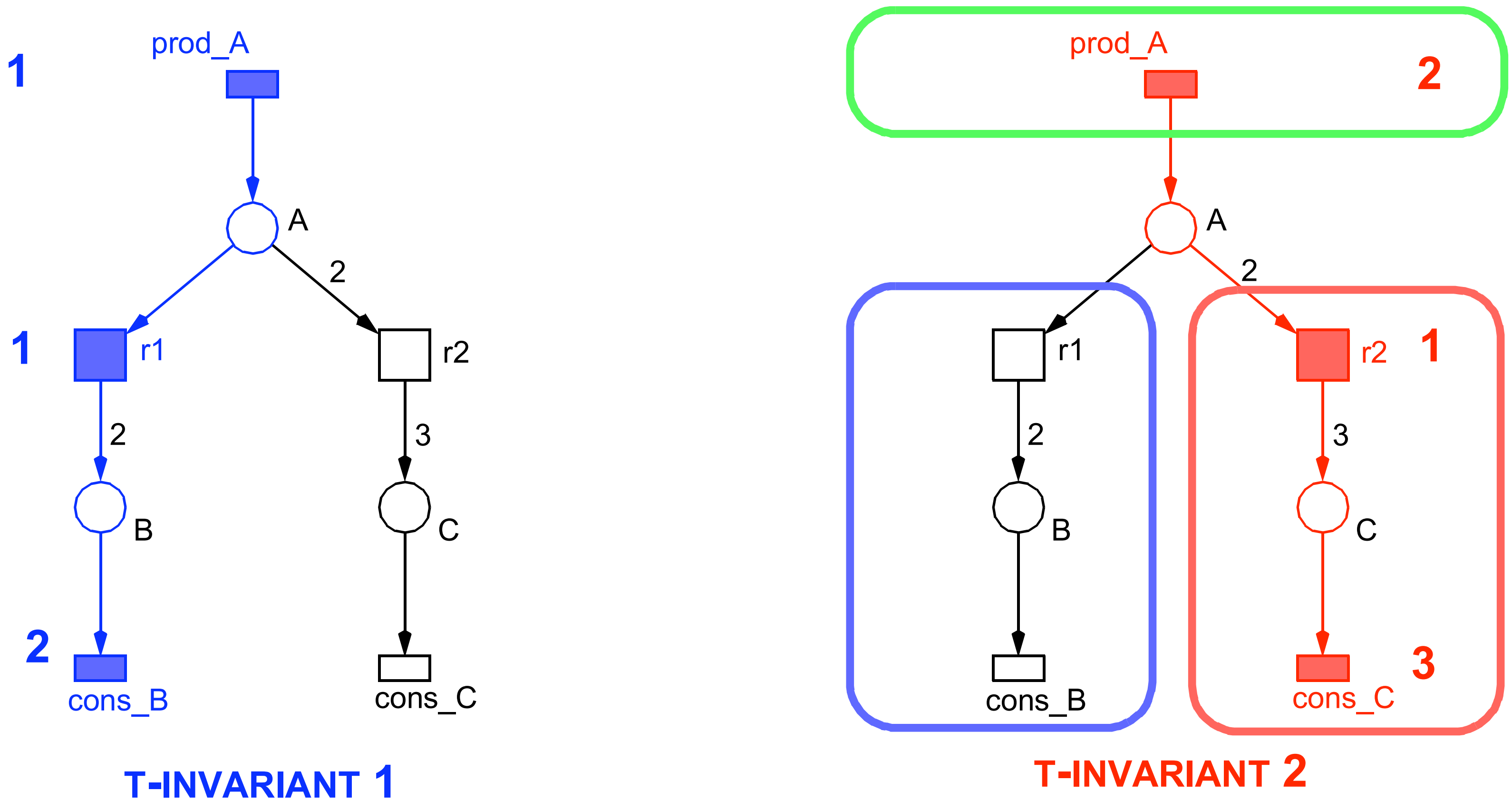


ABSTRACT DEPENDENT TRANSITION SETS (ADT-SETS)

- **Let X denote a set of (all / non-trivial) minimal T-invariants x of a given PN.**
- **dependency relation:**
  Two transitions i, j depend on each other,
  if they always appear together in all minimal T-invariants x, i.e.

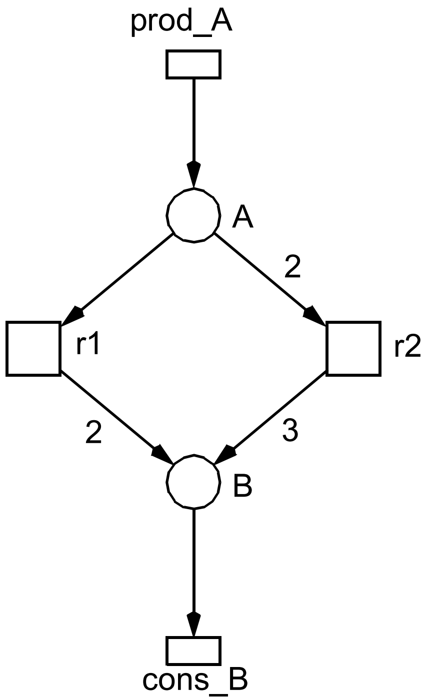
$$\forall x \in X\colon\ i \in supp(x) \Leftrightarrow j \in supp(x)$$

- **equivalence relation in the transition set, leading to a partition of T**
  -> *reflexive*
  -> *symmetric*
  -> *transitive*
- **the equivalence classes A represent maximal ADT-sets**

$$\forall x \in X\colon A \subseteq supp(x) \vee A \cap supp(x) = \varnothing$$

ADT-SETS, EX2

r1:   A -> 2 B
r2: 2 A -> 3 B



ADT-SETS, EX2

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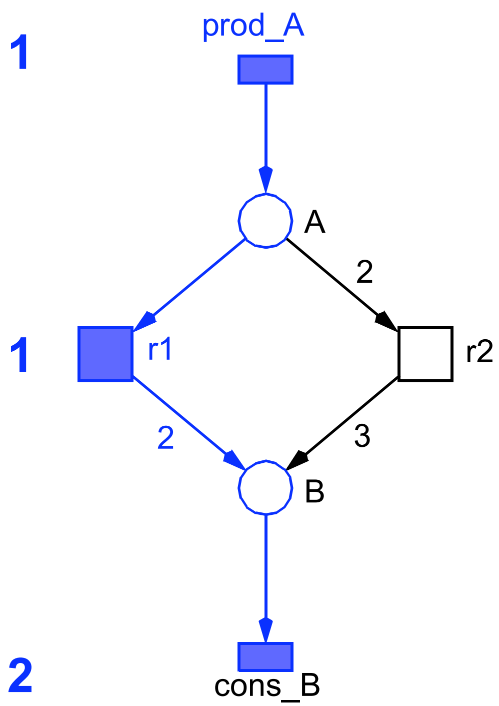
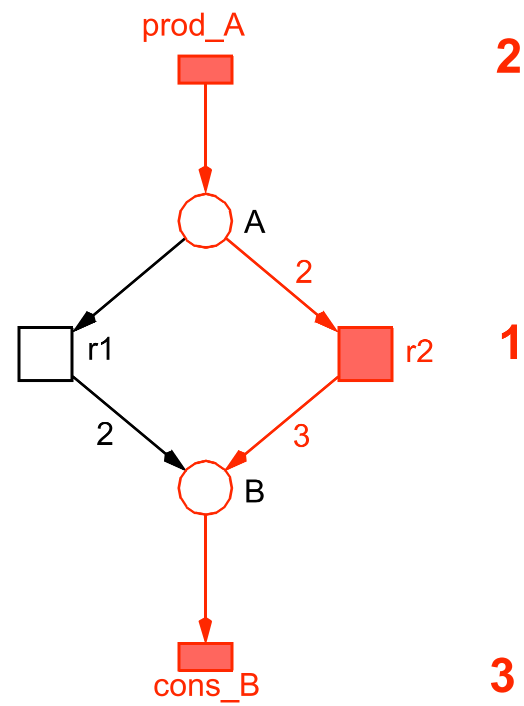


T-INVARIANT 1



T-INVARIANT 2

ADT-sets, Ex2

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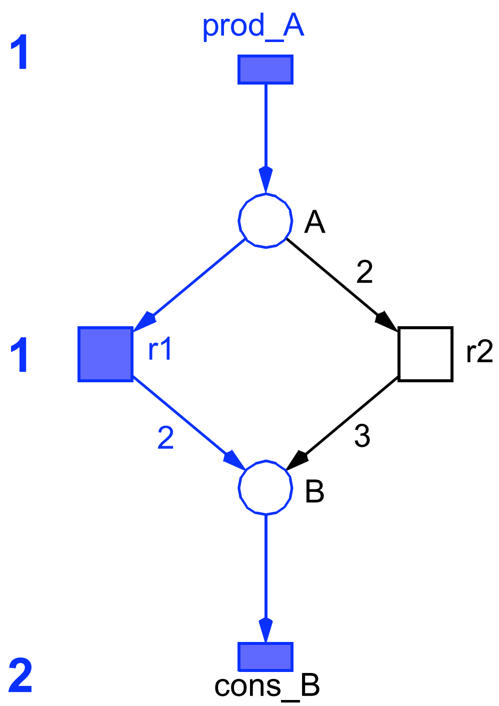

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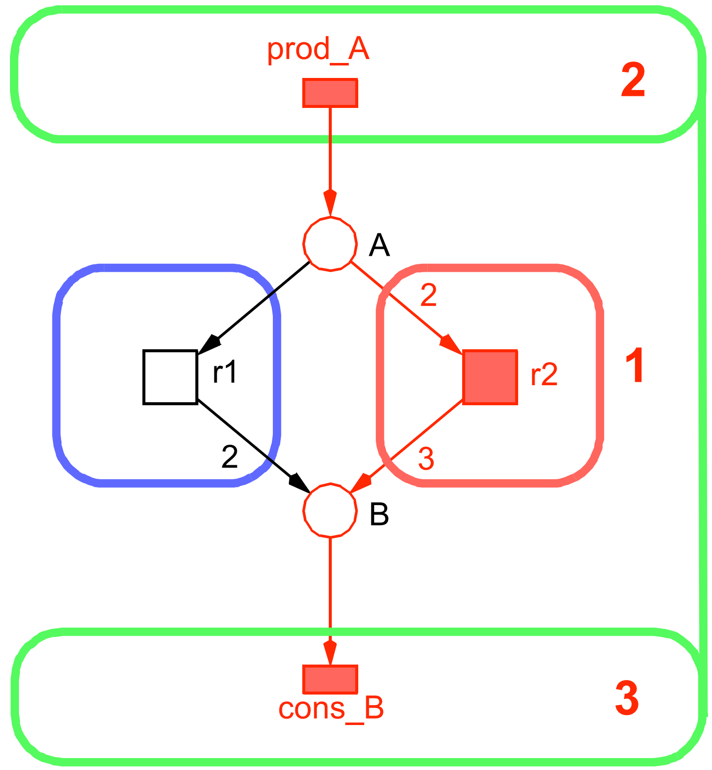


T-INVARIANT 2

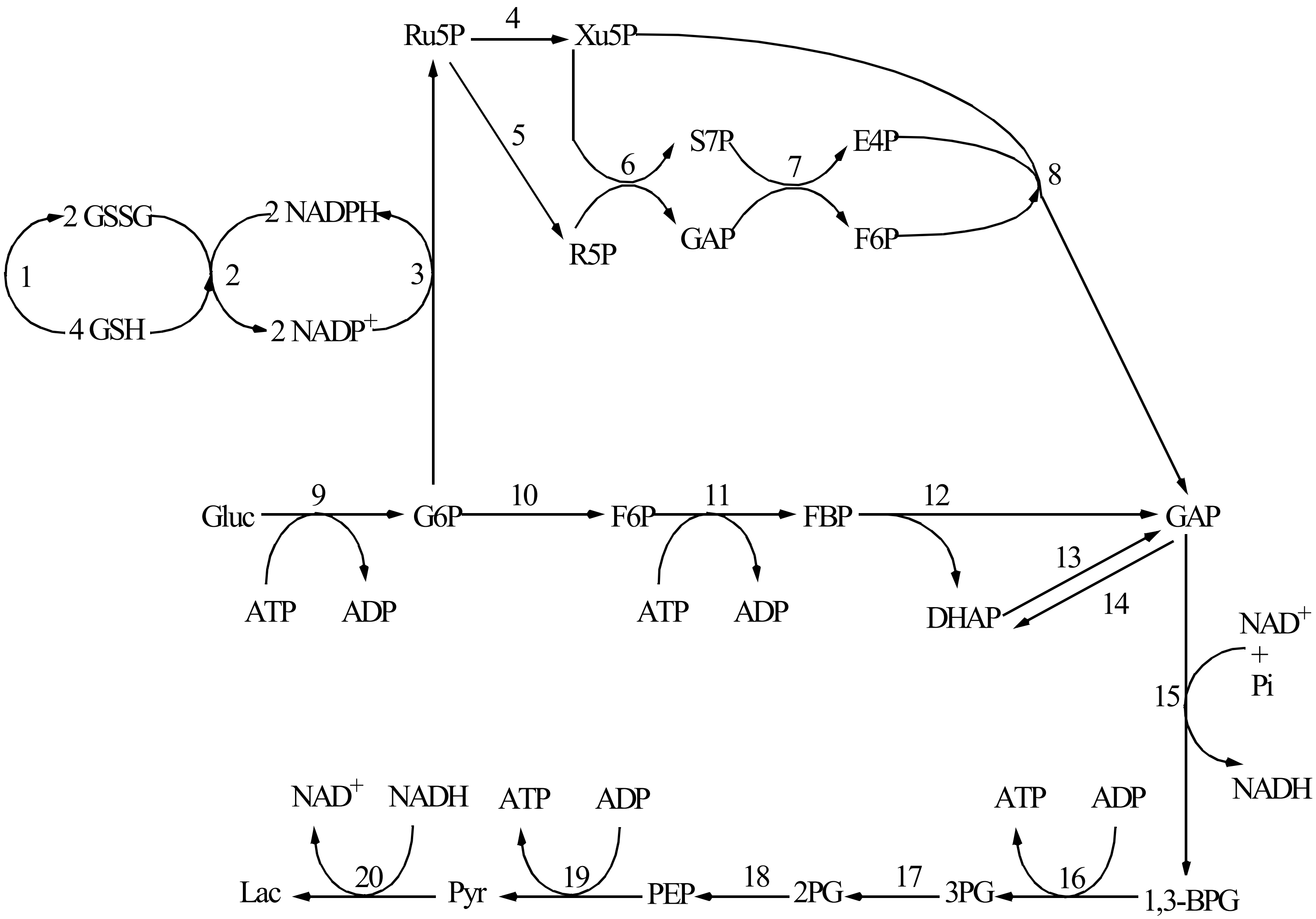
ADT-SETS, APPLICATIONS

- **maximal ADT-sets**
  - -> *not necessarily connected*
- **decomposition into connected ADT-sets**
  - -> *possibly according to primary compounds, only,*
    i.e. neglecting connections by auxiliary compounds
  - -> *non-maximal ADT-sets*
- **coarse network structure, definition**
  - -> *macro transitions* - *abstract from connected ADT-sets*
  - -> *places* - *interface between connected ADT-sets*
- **coarse network structure, what for?**
  - -> *set of T-invariants gets structured*
  - -> *better understanding of the net behaviour*

BIO PETRI NETS,
SOME EXAMPLES

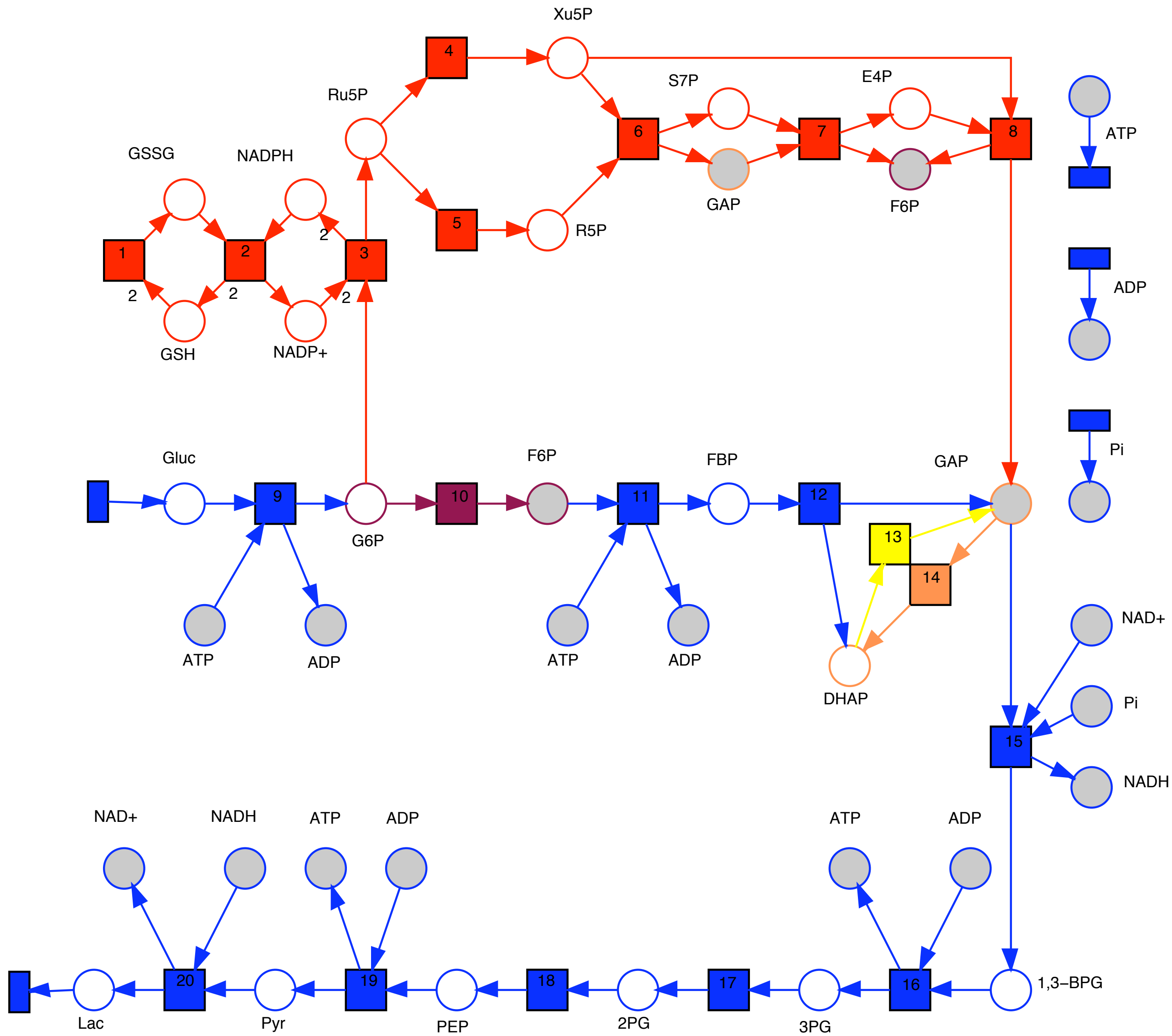
Ex1 - Glycolysis and Pentose Phosphate Pathway

[Reddy 1993]



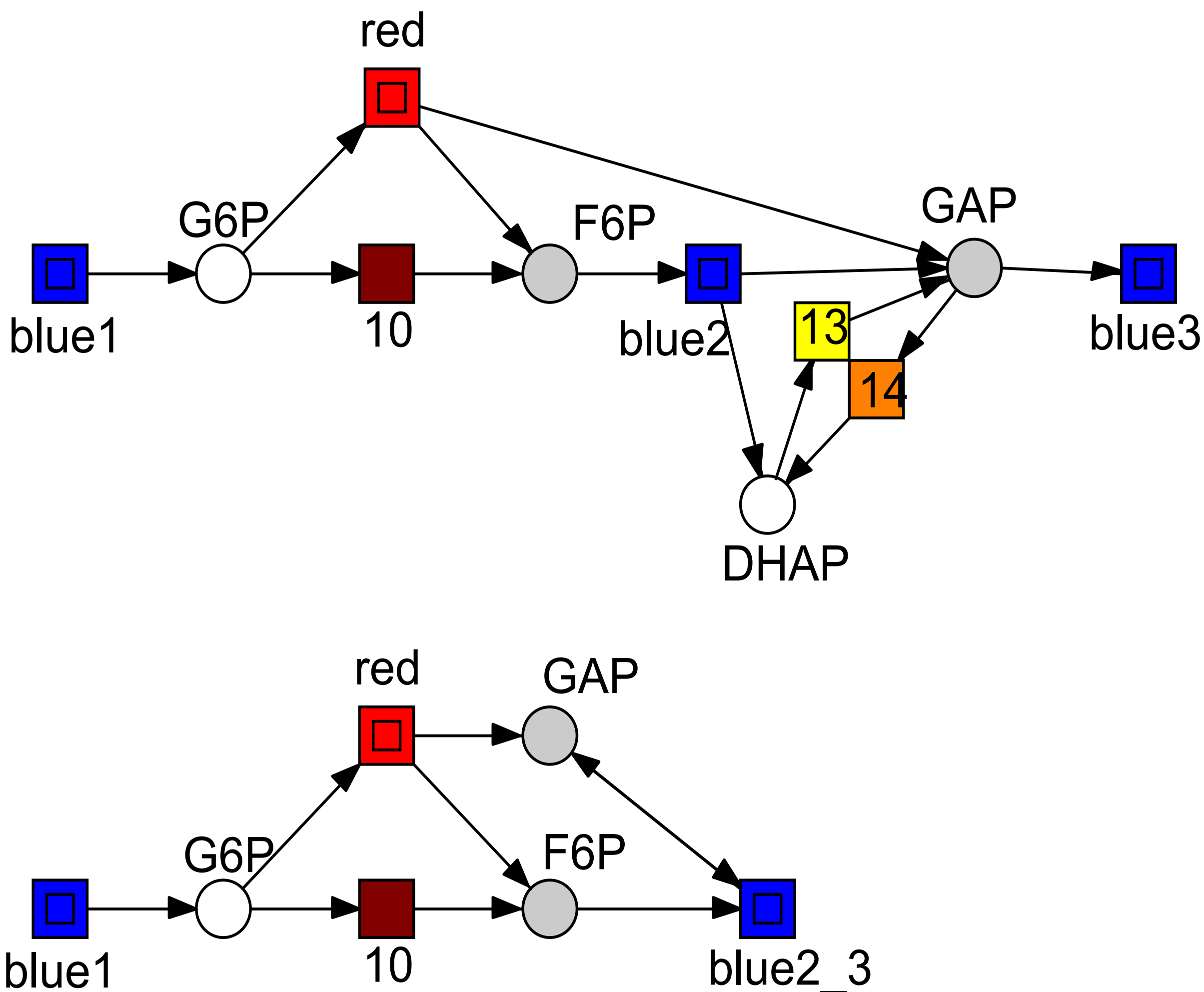
Ex1 - Glycolysis and Pentose Phosphate Pathway

[HEINER 1998]

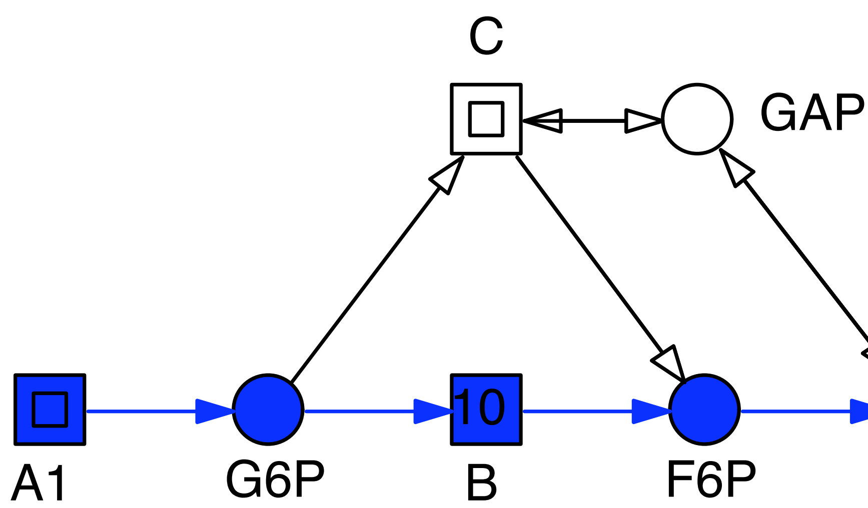


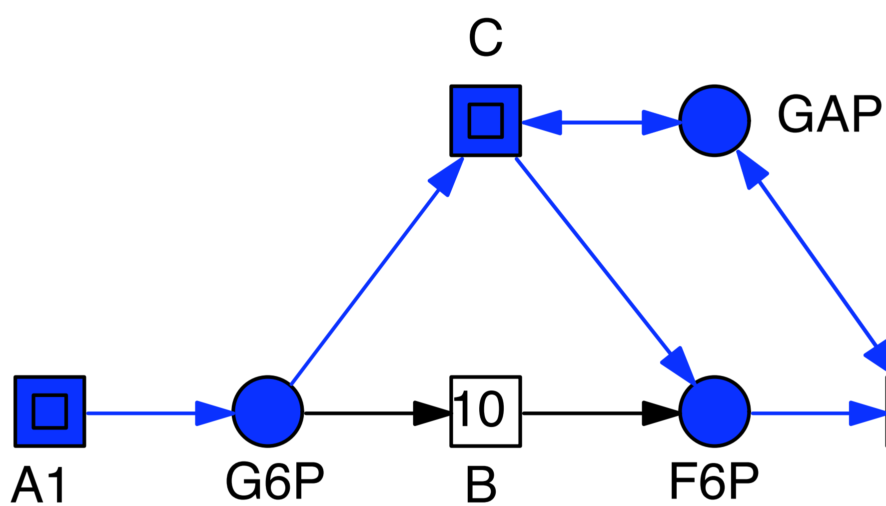
monika.heiner@informatik.tu-cottbus.de

Ex1 - Glycolysis and Pentose Phosphate Pathway

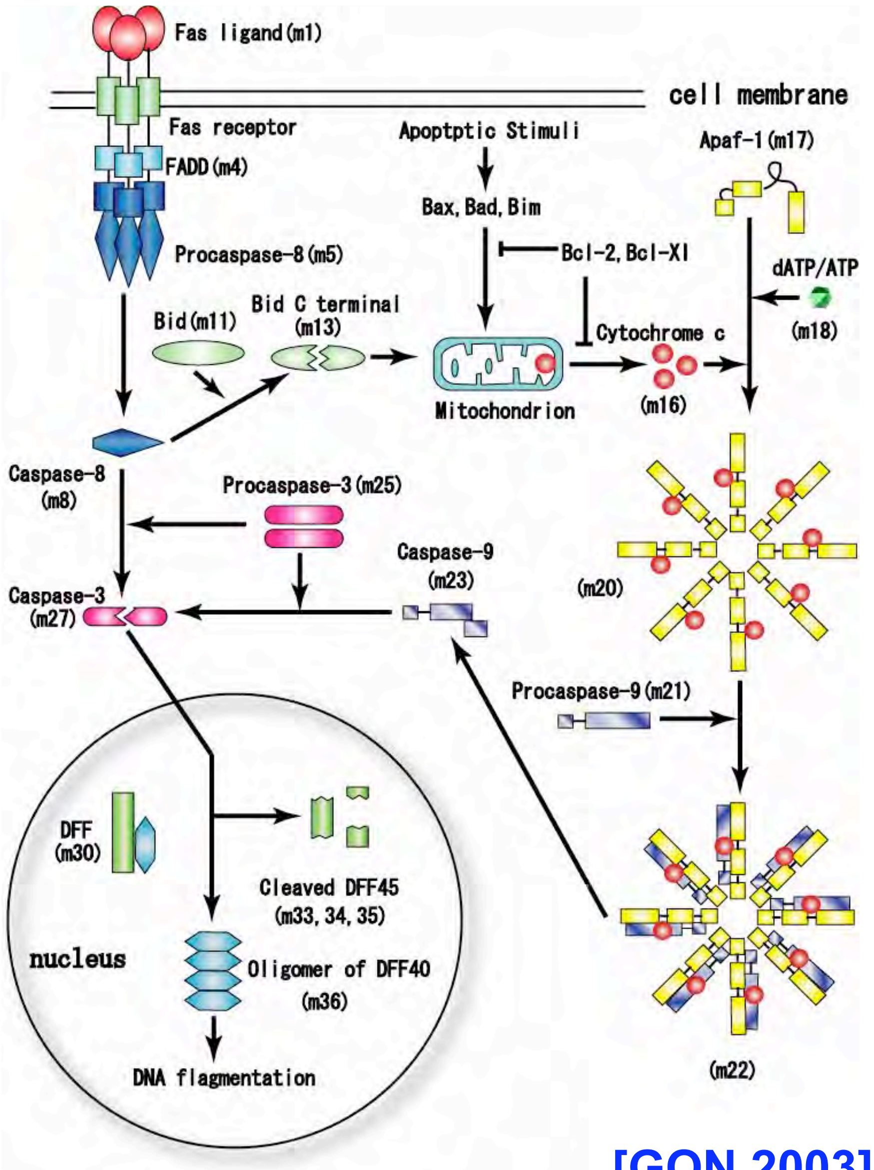


Ex1 - Glycolysis and Pentose Phosphate Pathway



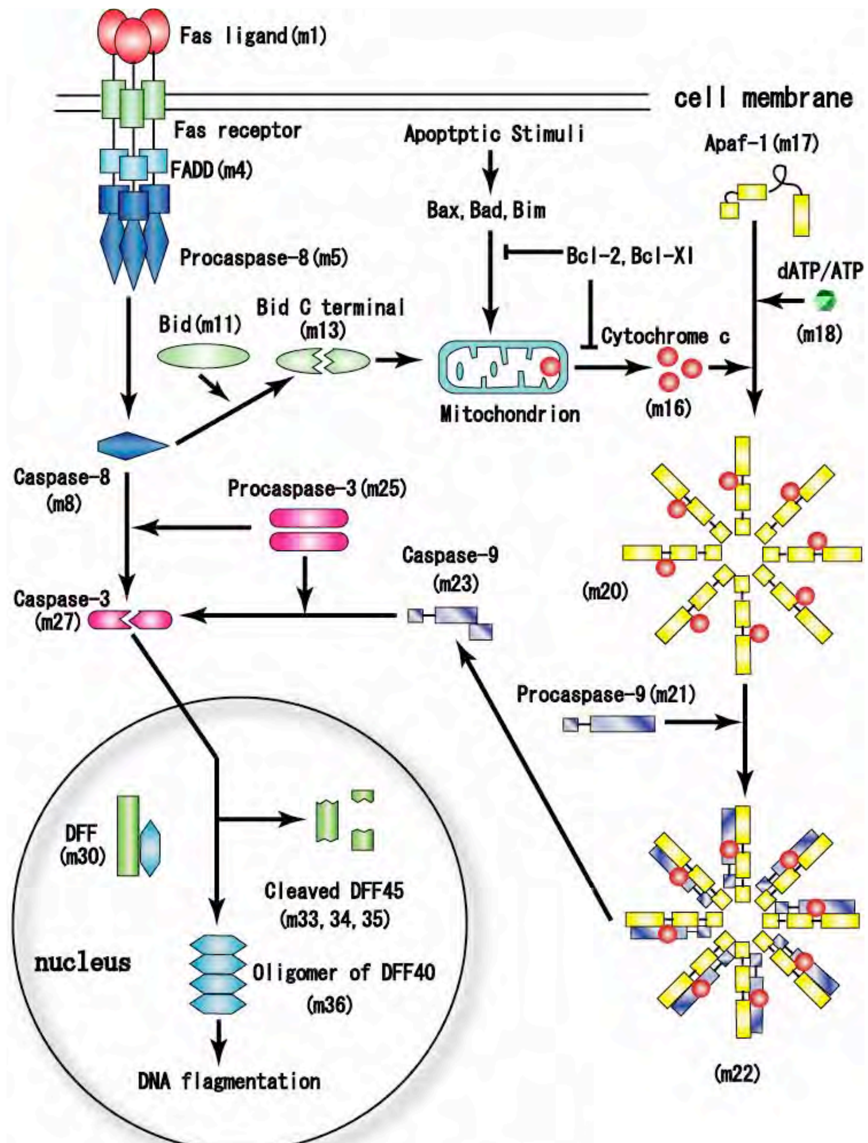


EX2: APOPTOSIS IN MAMMALIAN CELLS

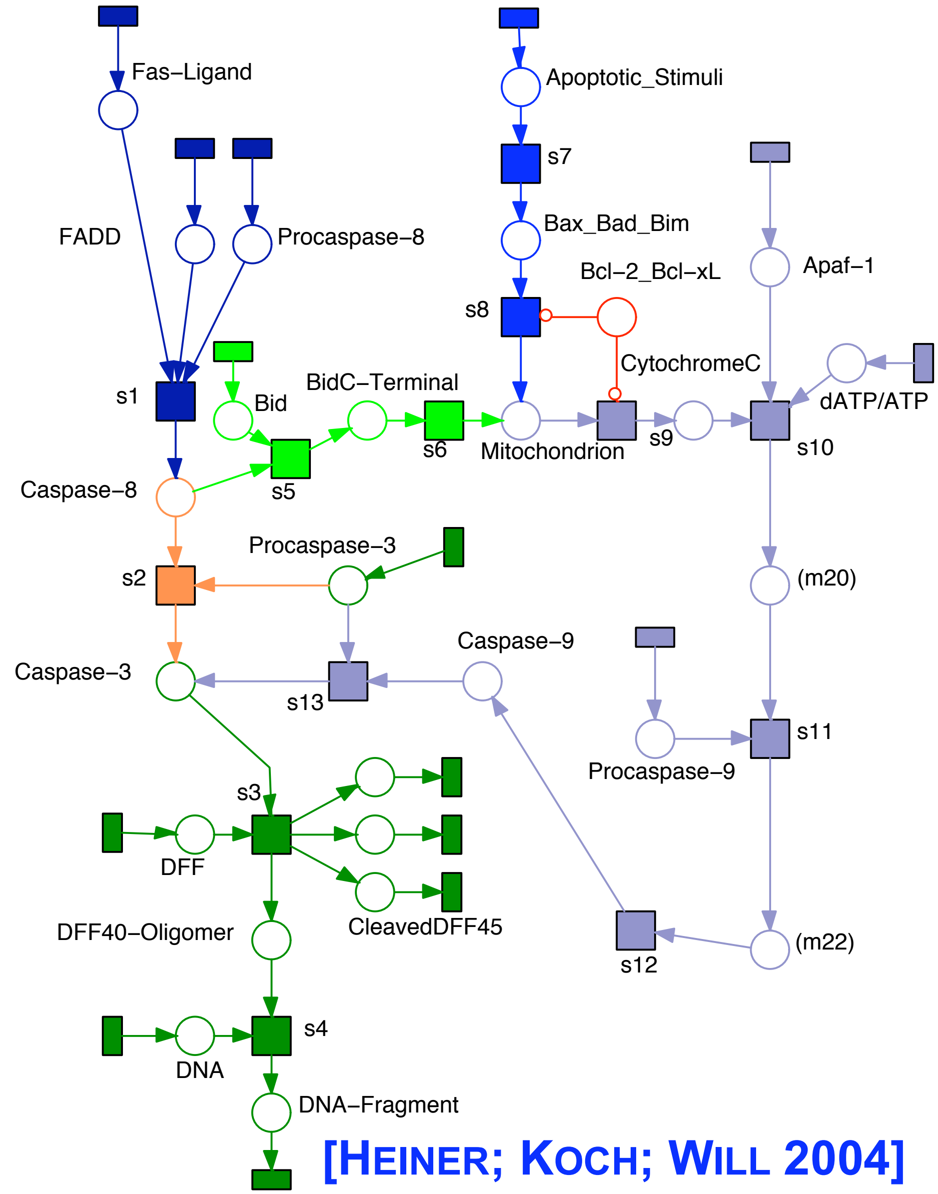


[GON 2003]

Ex2: Apoptosis in Mammalian Cells

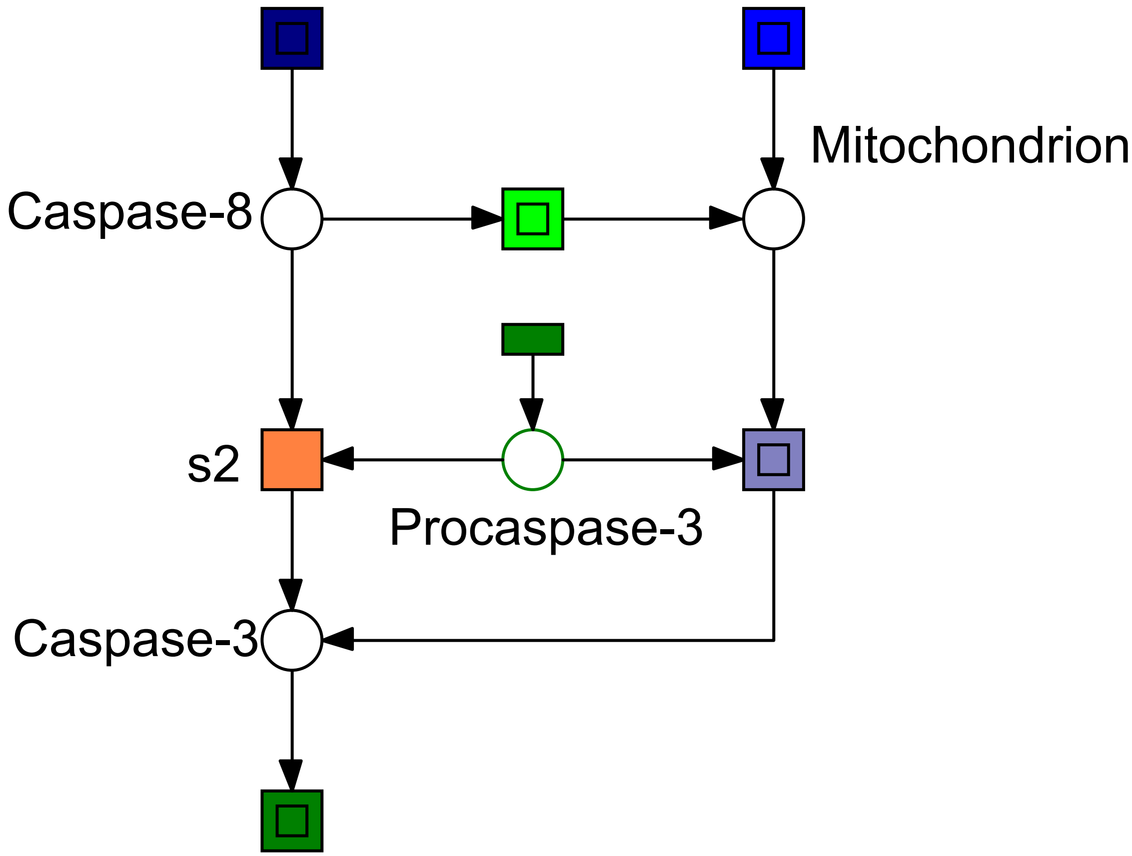


[GON 2003]

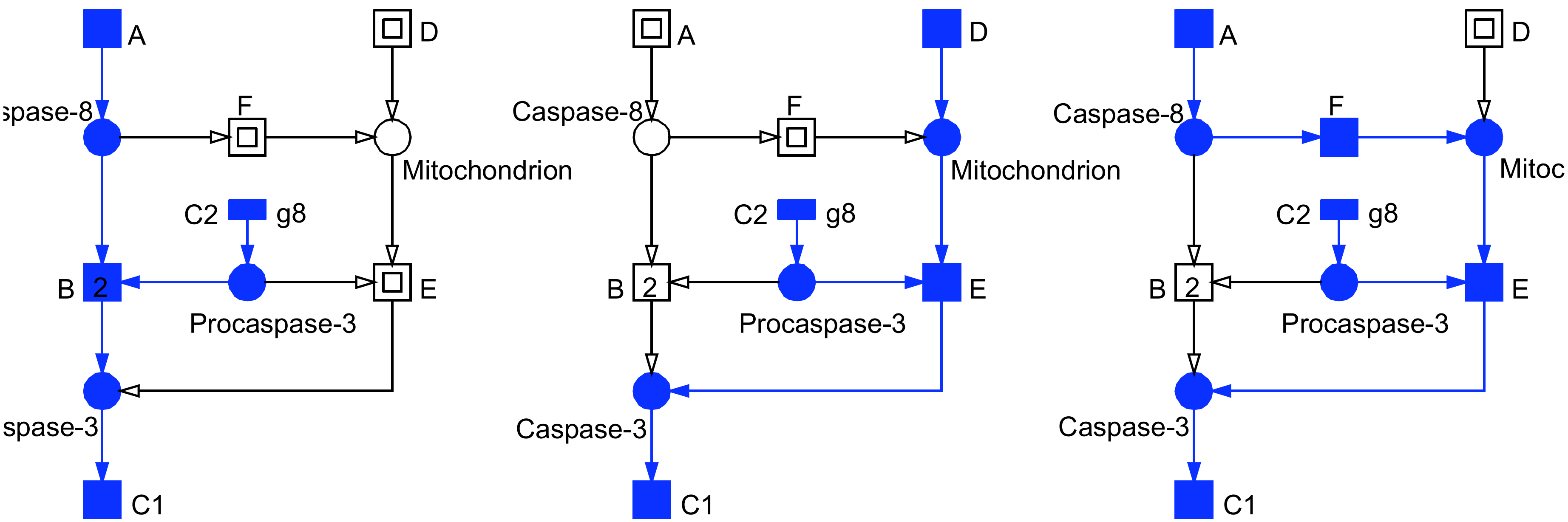


[Heiner; Koch; Will 2004]

Ex2: Apoptosis in Mammalian Cells

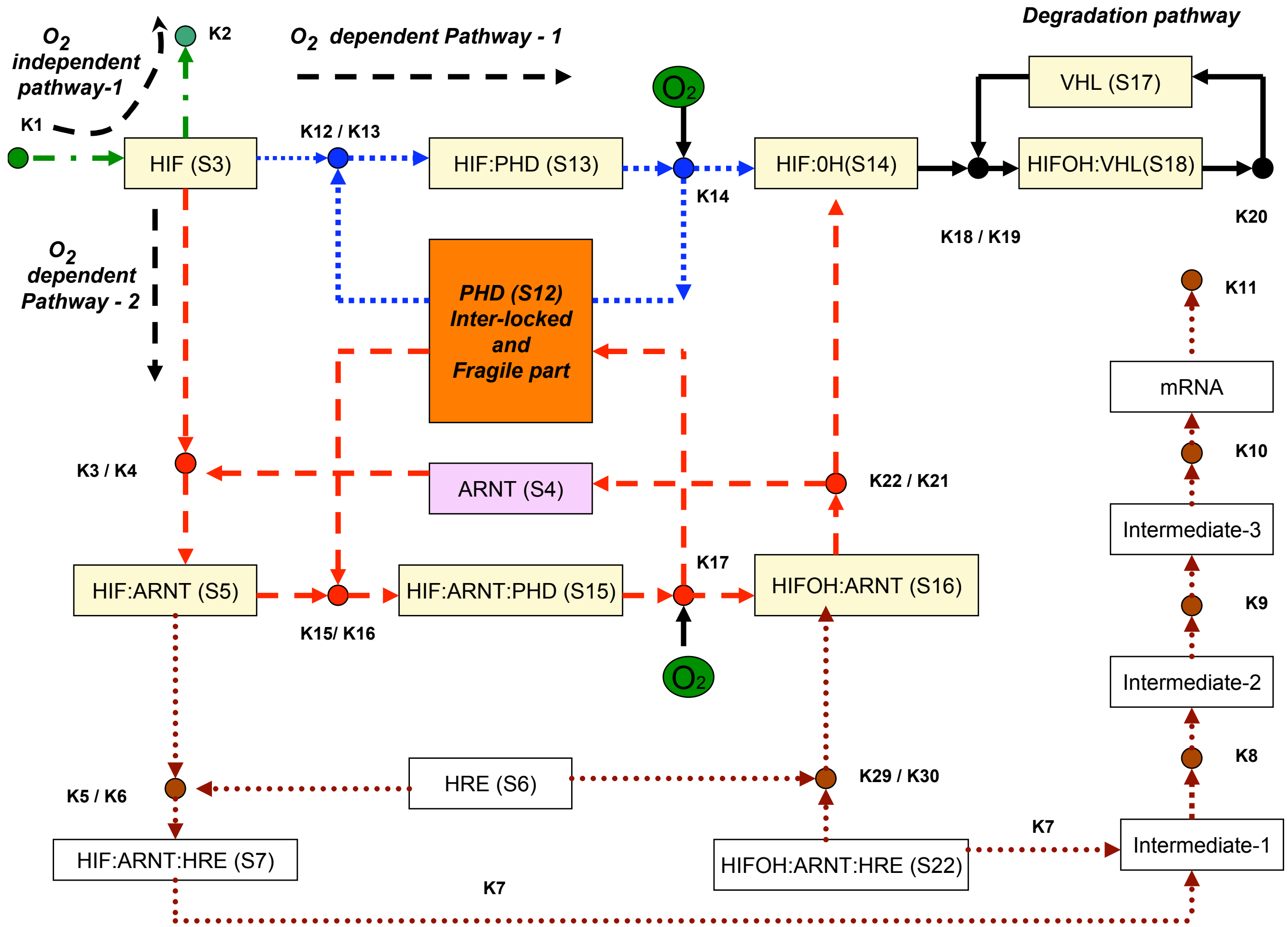


Ex2: Apoptosis in Mammalian Cells



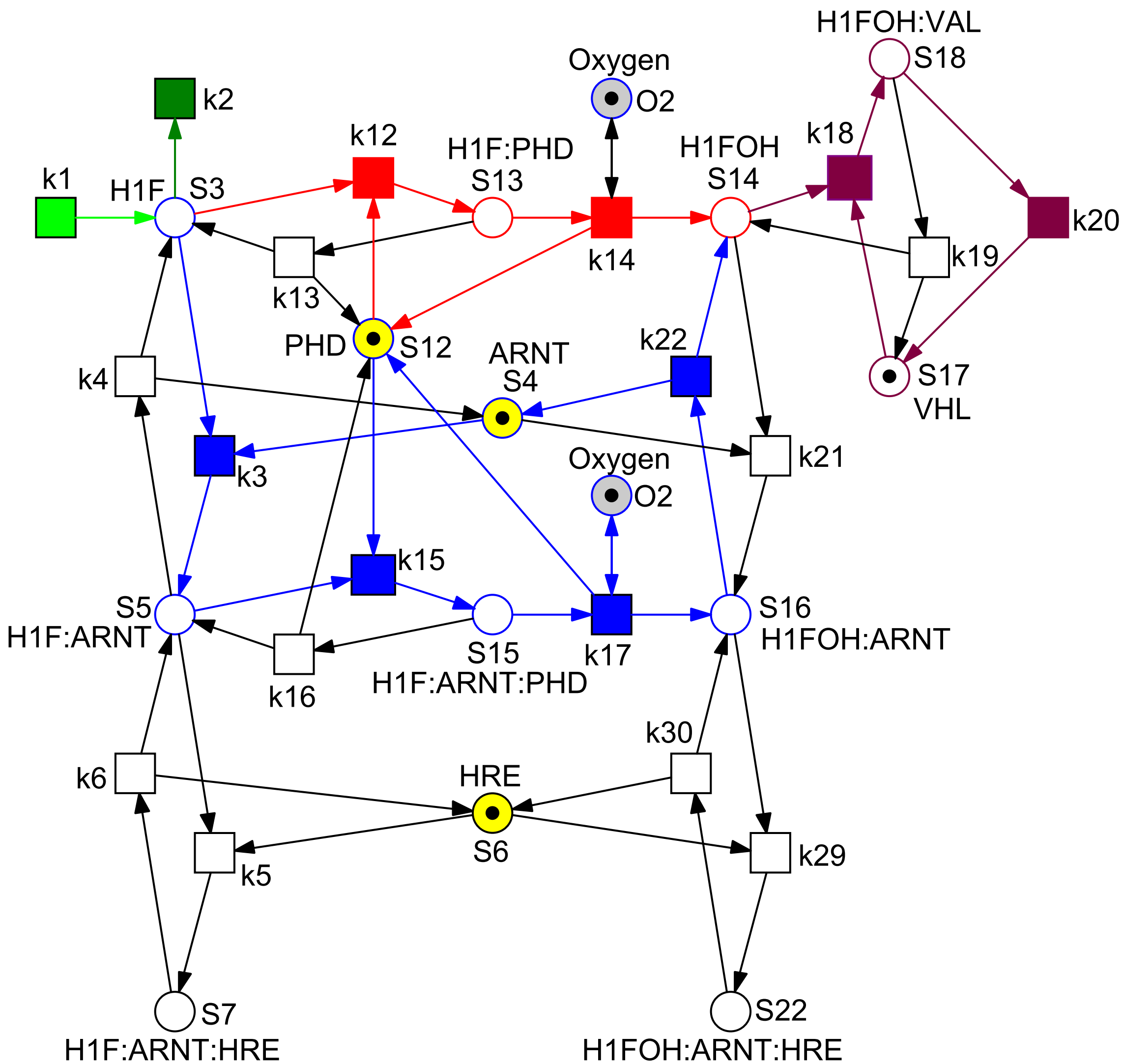
Ex3 - Hypoxia

[Yu et al. 2007]

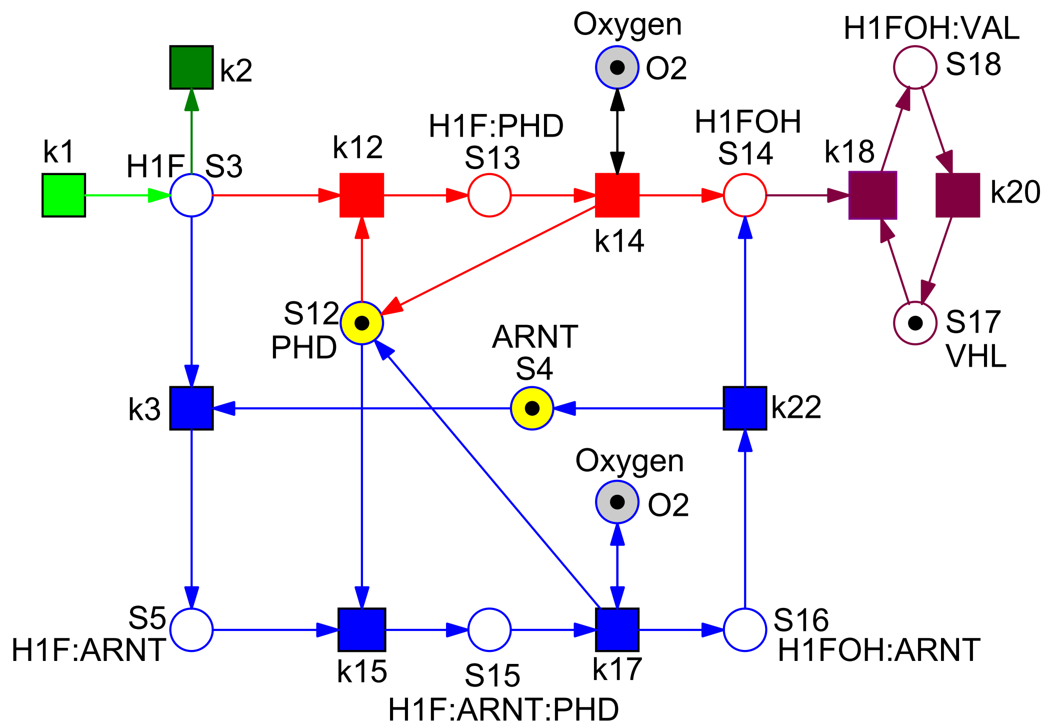


Ex3 - Hypoxia

[Heiner; Sriram 2010]

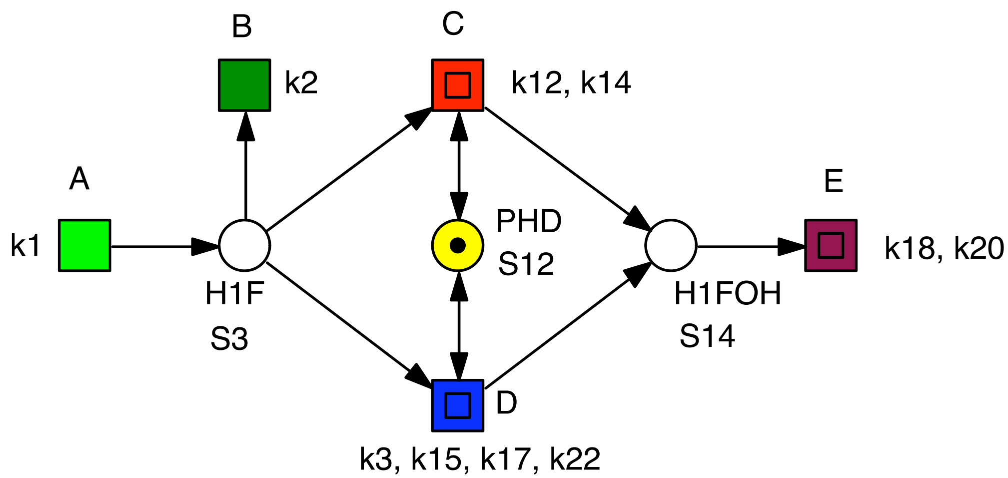


Ex3 - Hypoxia



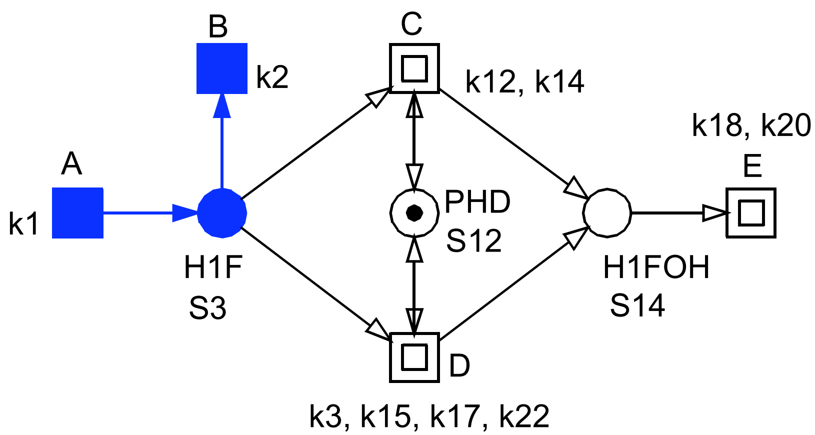
Oxygen
O2
H1FOH:VAL
S18
k2
k1
H1F
S3
k12
H1F:PHD
S13
H1FOH
S14
k18
k20
k14
S12
PHD
ARNT
S4
S17
VHL
k3
k22
Oxygen
O2
S5
H1F:ARNT
k15
S15
H1F:ARNT:PHD
k17
S16
H1FOH:ARNT

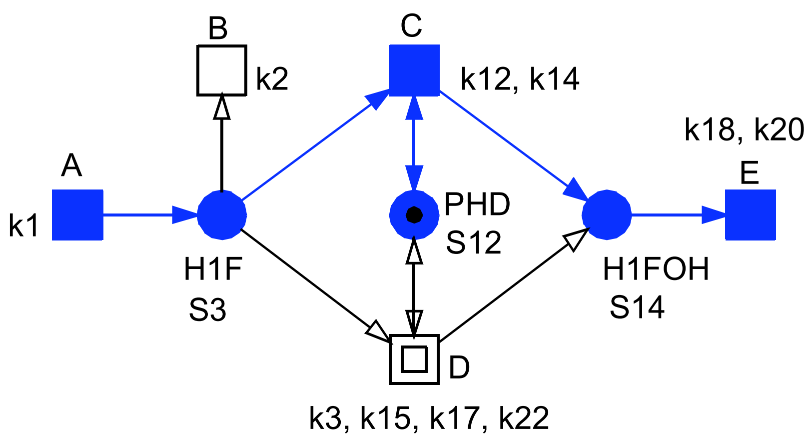
Ex3 - Hypoxia



B
C
k2
k12, k14
A
E
PHD
k1
S12
k18, k20
H1F
H1FOH
S3
S14
D
k3, k15, k17, k22

EX3 - HYPOXIA


B
C
k2
k12, k14
k18, k20
A
E
k1
PHD
S12
H1F
S3
H1FOH
S14
D
k3, k15, k17, k22


B
C
k2
k12, k14
k18, k20
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E
k1
PHD
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H1FOH
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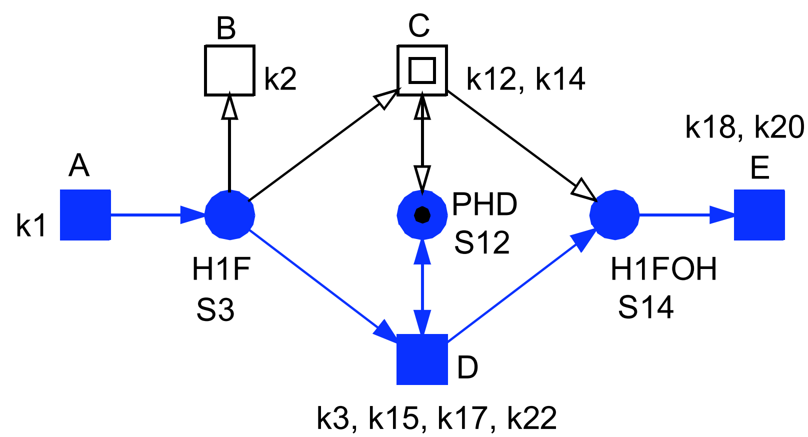
D
k3, k15, k17, k22


B
C
k2
k12, k14
k18, k20
A
E
k1
PHD
S12
H1F
S3
H1FOH
S14
D
k3, k15, k17, k22

Ex4 - Carbon Metabolism in Potato Tuber

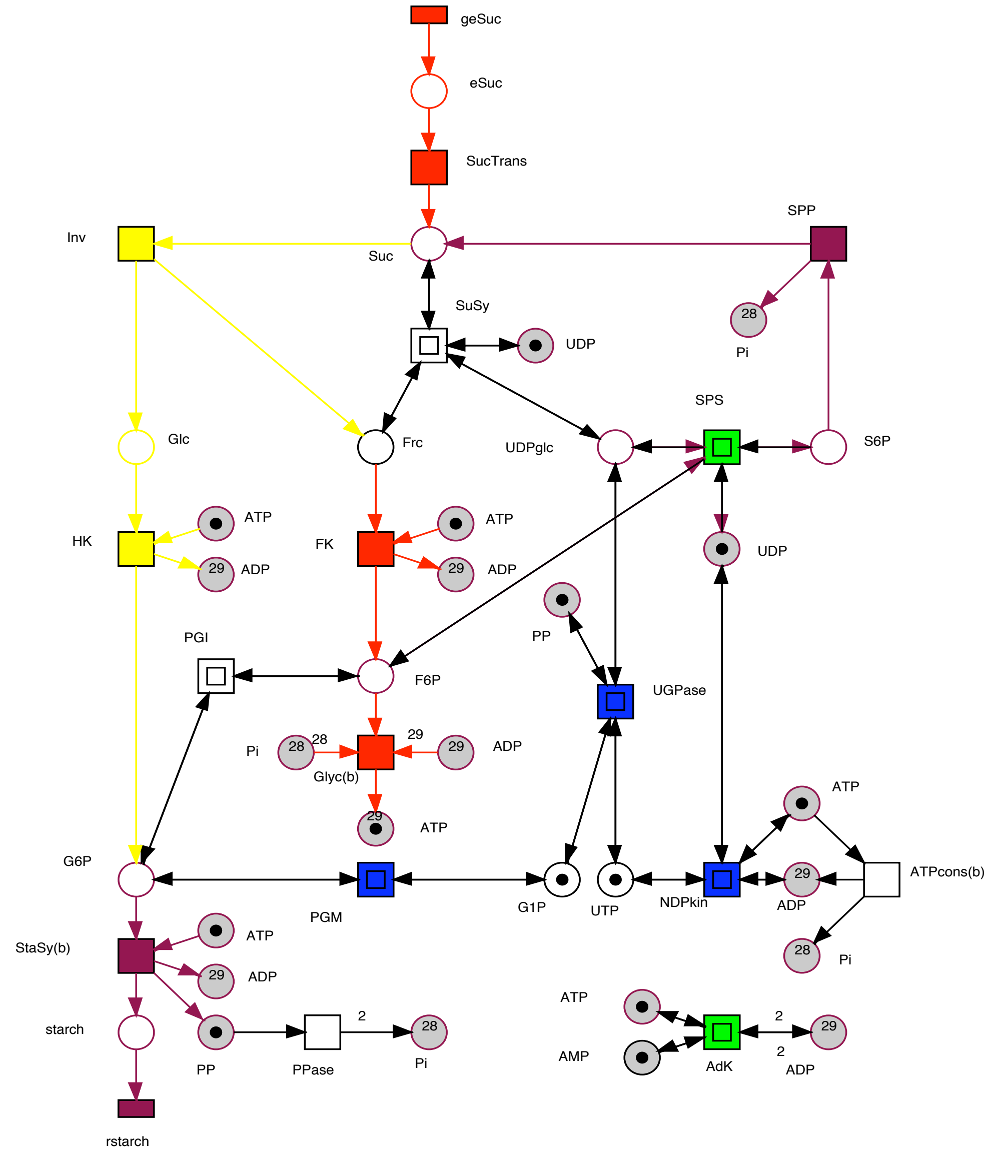
[KOCH; JUNKER; HEINER 2005]

ADT-sets without trivial T-invariants

Ex4 - Carbon Metabolism in Potato Tuber

[KOCH; JUNKER; HEINER 2005]

ADT-sets without trivial T-invariants



monika.heiner@informatik.tu-cottbus.de

SUMMARY

ADT-SETS, Technicalities

- **minimal T-invariants**
  -> *overlapping subnets*
  -> *connected*

- **maximal ADT-sets**
  -> *disjunctive subnets*
  -> *not necessarily connected*

connected ADT-sets
-> *disjunctive and connected subnets*

- **variations**
  -> *with / without trivial T-invariants*
  -> *whole / partial set of T-invariants*
  } *not necessarily maximal ADT-sets*

- **classification of all transitions based on the T-invariants' support**

- **interpretation**
  -> *structural decomposition into rather small subnets*
  -> *smallest biologically meaningful functional units*
  -> *building blocks*

ADT-SETS, Interpretations

- **"promote hierarchical thinking & unbiased modularization"**

- **structured representation of invariants**
  -> *may contribute to a better understandability*

- **coarse network structure identifies sensitive net parts**
  -> *the knock-off of interface places affects several ADT-sets*

- **efficient design of wetlab experiments**
  -> *minimal sets of observation points providing coverage of the whole network (one for each ADT-set)*

- **support of dedicated layout algorithms**

"can include non-obvious groups of reactions and differ from groupings of reactions based on a visual inspection of the network topology"
(Papin, Reed, Palsson 2004)

ADT-SETS, SUMMARY

- **PROS**
  - -> *algorithmically defined*
  - -> *static analysis technique (state space not constructed), works also for unbounded models*

- **CONS**
  - -> *may be computational expensive*
  - -> *to avoid computation of all (T-) invariants:*

$$Cx = 0, x \neq 0, x \geq 0, \quad x(i) = 0, x(j) \neq 0, \forall i, j \in T$$

-- ESPECIALLY HELPFUL FOR ANALYZING BIO PETRI NETS --

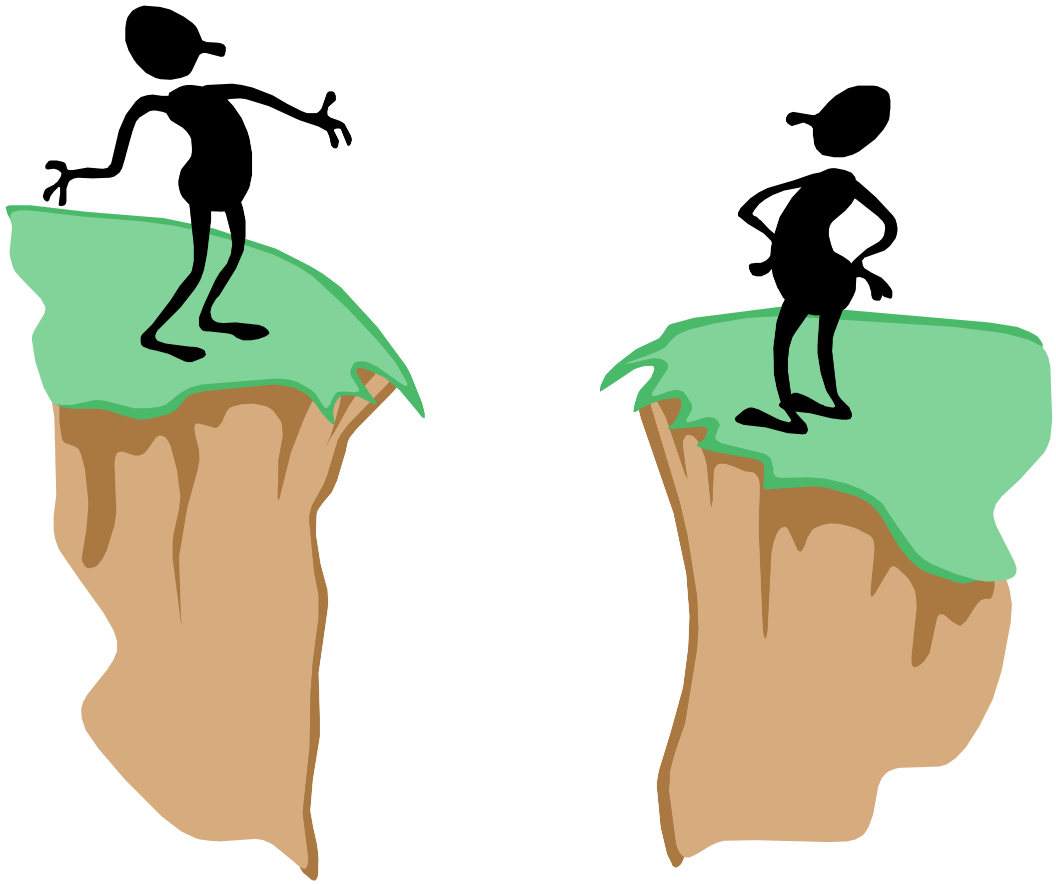
REFERENCES

- **related work**
  - -> *partially correlated reaction sets (Papin, Reed, Palsson 2004)*
  - -> *Flux coupling analysis (Burgard 2004)*
  - -> *MCT-sets (Sackmann, Heiner, Koch 2006)*
  - -> *(A)DT-sets (Winder 2006)*
  - *. . .*
  - -> *probably some more*

- M Heiner:
  Understanding Network Behaviour by Structured Representations of Transition Invariants - A Petri Net Perspective on Systems and Synthetic Biology;
  in A Condon, D Harel, JN Kok, A Salomaa, E Winfree (eds.): Algorithmic Bioproc-esses; Chapter 19, Springer, July 2009.

- M Heiner, K Sriram:
  Structural Analysis to Determine the Core of Hypoxia Response Network;
  PLoS ONE 5(1): e8600, doi:10.1371/journal.pone.0008600, January 2010.

THANKS !



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