PART III
PN-BASED STATIC ANALYSIS OF BIOCHEMICAL NETWORKS

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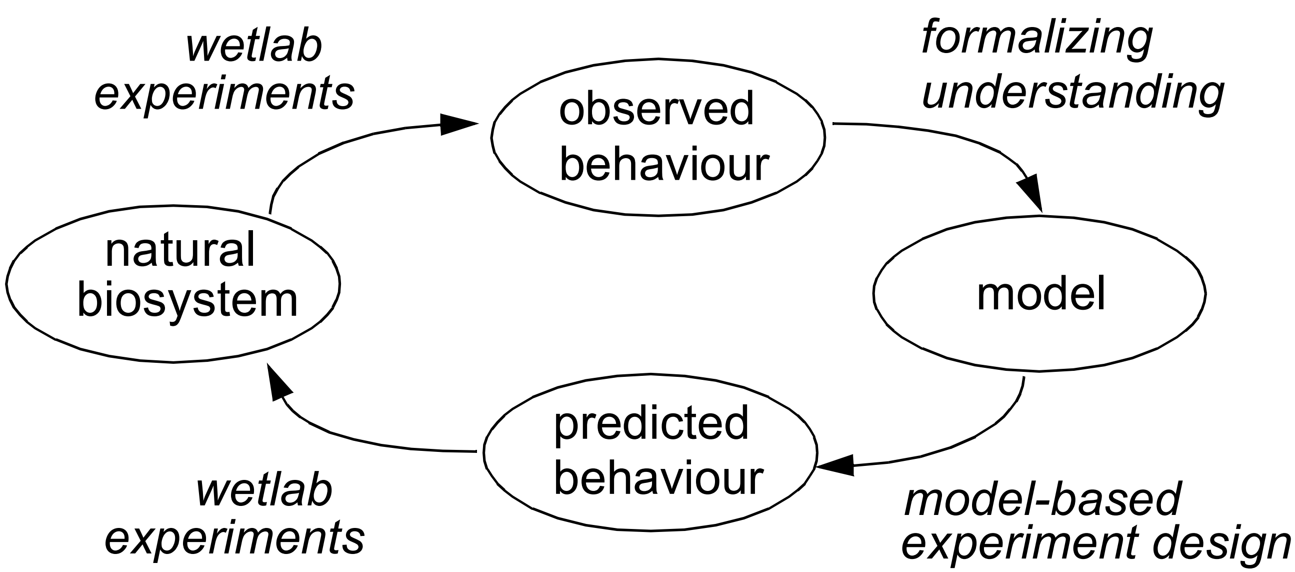
FRAMEWORK: SYSTEMS BIOLOGY

MODELLING = FORMAL KNOWLEDGE REPRESENTATION



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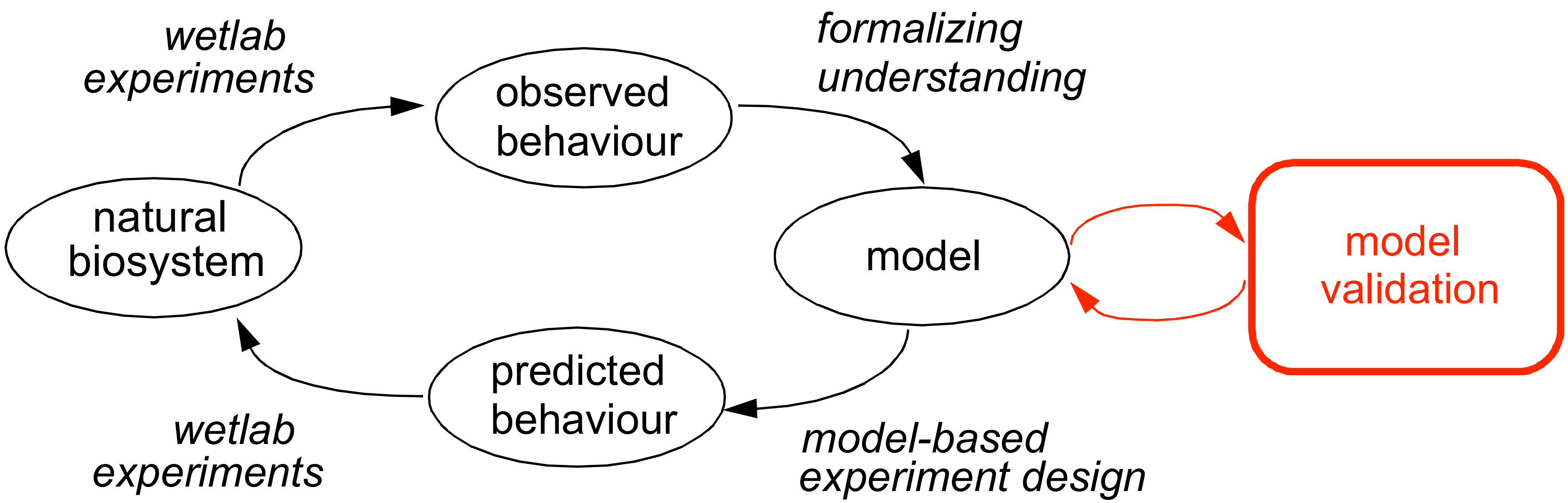


MODEL VALIDATION = CONFIDENCE INCREASE

STATIC ANALYSIS (OF QUALITATIVE PETRI NETS)

- **no (full / partial) state space construction**
  -> works also for unbounded models = infinite state spaces

- **structural analysis**
  -> boundary nodes, . . .
  -> Deadlock Trap Property

- **net reduction**

  } *-> to decide liveness (hopefully)*

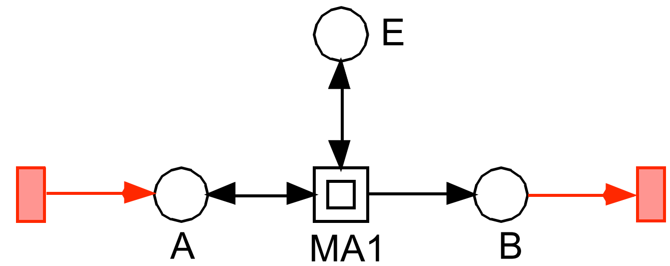
- **invariants**
  -> P-invariants - mass-preserving modules *-> to decide boundedness*
  -> T-invariants - state-repeating modules

- **modularization by T-invariants**
  -> abstract dependent transition sets (ADT-sets) define building blocks

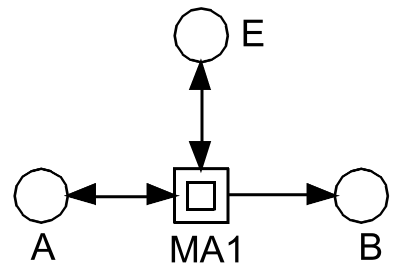
- **core network identification**

STRUCTURAL ANALYSIS, SOME EXAMPLES

- **boundary nodes**
  - -> *input transitions -> not BND*
  - -> *input places -> not LIVE*
  - -> *LIVE & BND -> no boundary nodes*



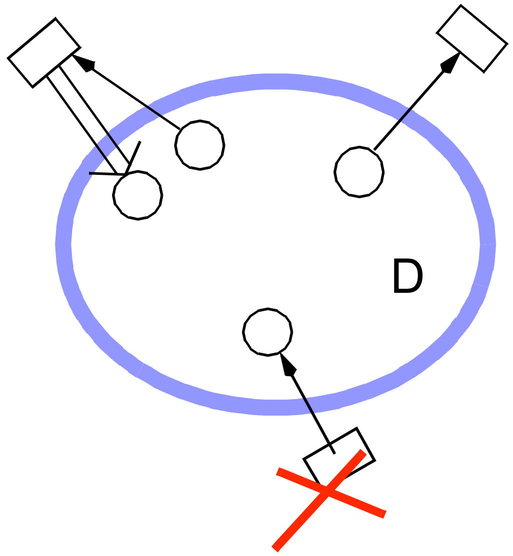
- **conservative -> BND**
  - -> *all transitions preserve token number*



- **Deadlock-Trap Property (DTP)**

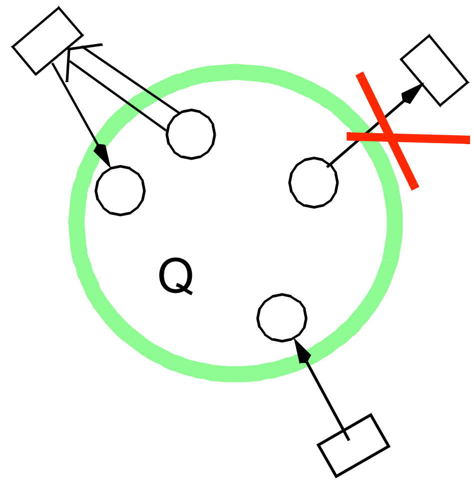
DEADLOCK TRAP PROPERTY (DTP)

Deadlock D
FD ⊆ DF



any transition putting token into the set
also takes token from it:
an empty deadlock will never get marked

Trap Q
QF ⊆ FQ



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DEADLOCK TRAP PROPERTY (DTP)

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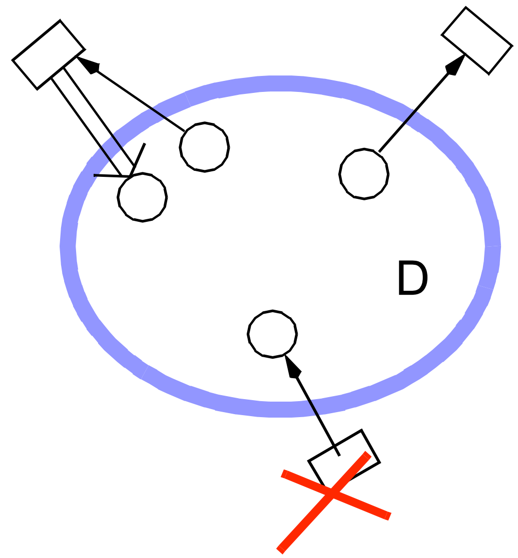
$FD \subseteq DF$



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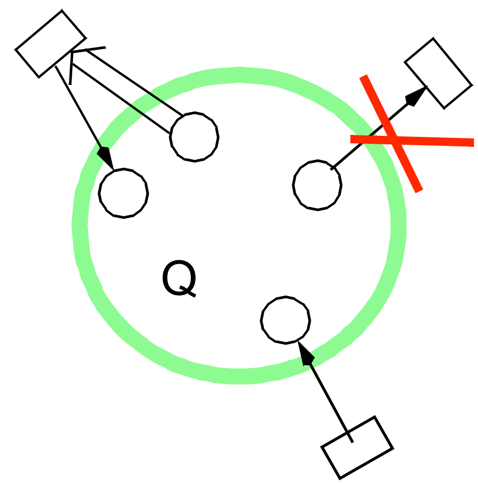
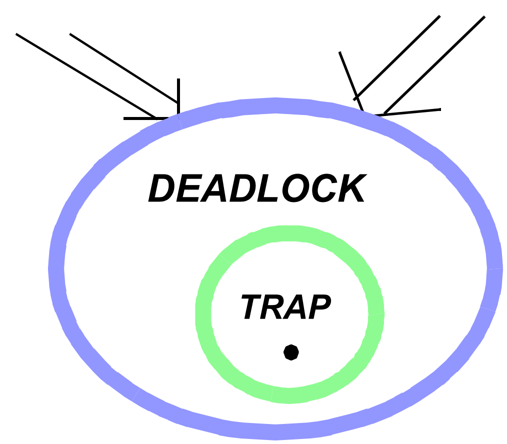
$QF \subseteq FQ$



any transition taking tokens from the set
also puts token into it:
a marked trap will never get empty

DTP: each deadlock contains a (sufficiently) marked trap (at m_0)



DEADLOCK TRAP PROPERTY (DTP)

- allow to decide liveness, sometimes

EFC -> DTP (& HOM & NBM)	*<->*	*live*
ES & DTP (& HOM & NBM)	*->*	*live*
DTP (& HOM & NBM)	*->*	*not DSt*
no (structural) deadlock	*->*	*live*

DEADLOCK TRAP PROPERTY (DTP)

- **allow to decide liveness, sometimes**

EFC -> DTP (& HOM & NBM)	*<->*	*live*
ES & DTP (& HOM & NBM)	*->*	*live*
DTP (& HOM & NBM)	*->*	*not DSt*
no (structural) deadlock	*->*	*live*

- **some examples, where it helps**
  - -> *RKIP pathway (BND): ES & DTP -> live*
  - -> *MAPK cascade (BND): DTP & nES -> no DSt*

  - -> *biosensor (not BND): ES & DTP -> live*
  - -> *apoptosis (not BND): no (structural) deadlock -> live*

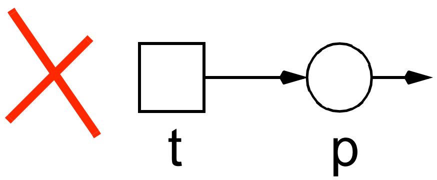
  - -> *lac operon (not BND): DTP & nES -> no DSt*

NET REDUCTION

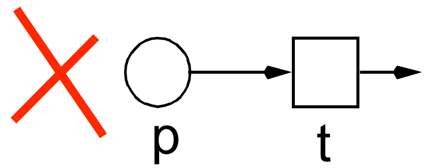
- **downsizing the net structure while preserving some properties**

  -> *liveness, boundedness*

- **example of two simple reduction rules**



t live
p unbounded



t not live
p bounded

-> *input nodes allow net reduction:*
conclude properties -> delete nodes -> conclude properties -> . . .

- **several sets of reduction rules - INA/HUB**

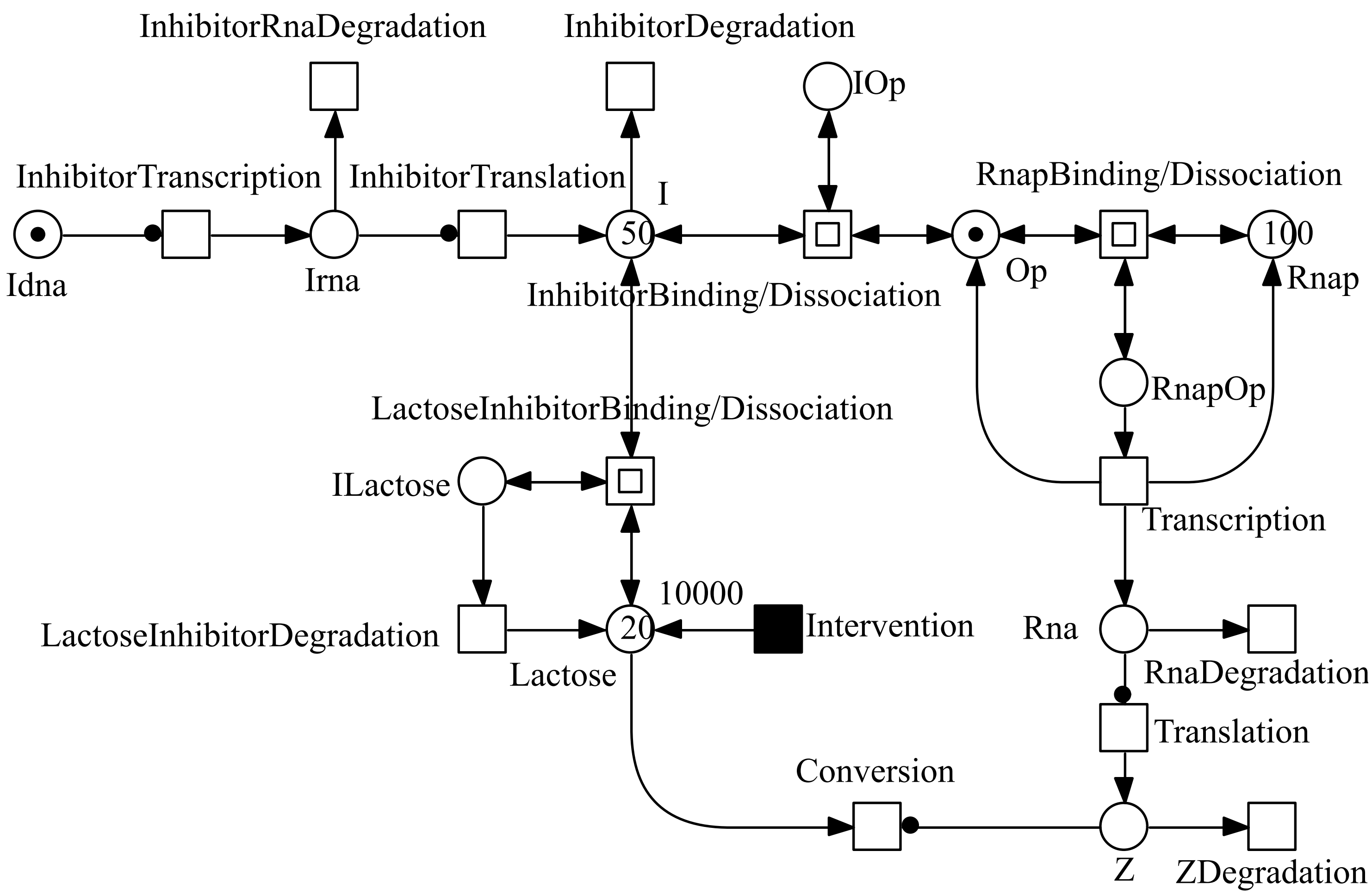
  -> *relatively weak, in general*

  -> *sensitive to the order they are applied*

  -> *however, sometimes they help*

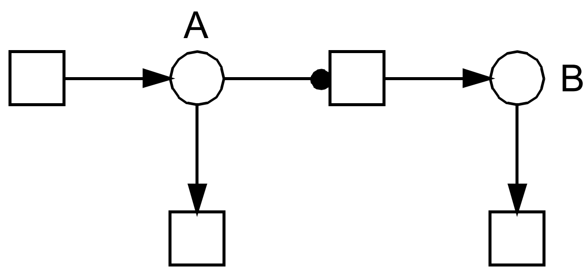
NET REDUCTION, EXAMPLE

- lac operon (Wilkinson 2006)



Net Reduction, Example

- lac operon, reduced by INA/HUB



- liveness becomes obvious

PUR	ORD	HOM	NBM	CSV	SCF	CON	SC	FT0	TF0	FP0	PF0	NC
N	N	Y	Y	N	N	N	N	Y	Y	Y	N	nES
DTP	CPI	CTI	SCTI	SB	k-B	1-B	DCF	DSt	DTr	LIV	RV	
Y	N	Y	-	N	N	N	-	N	-	-	-	

NET INVARIANTS,
A CRASH COURSE

BIO PETRI NETS, EX1

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

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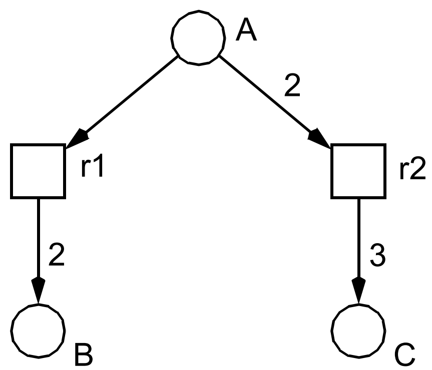
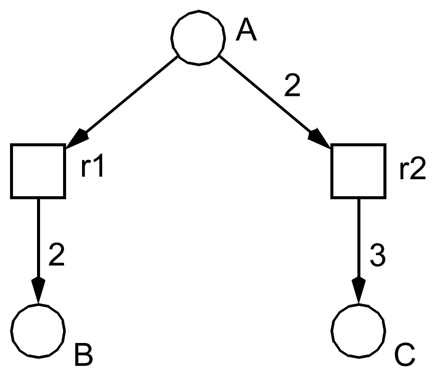
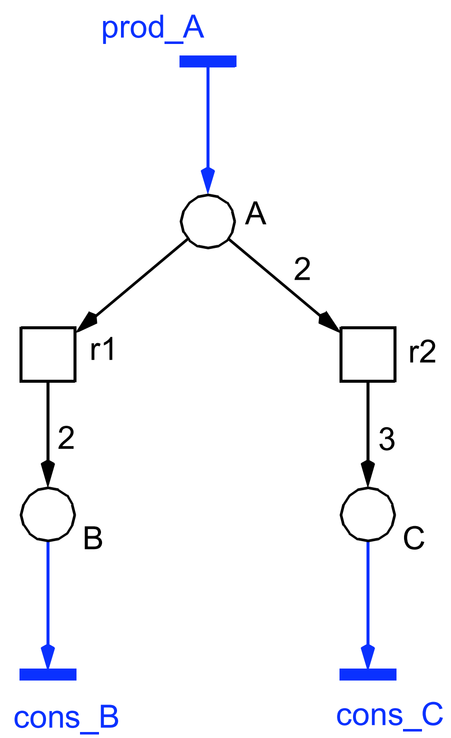


Bio Petri Nets, Ex1

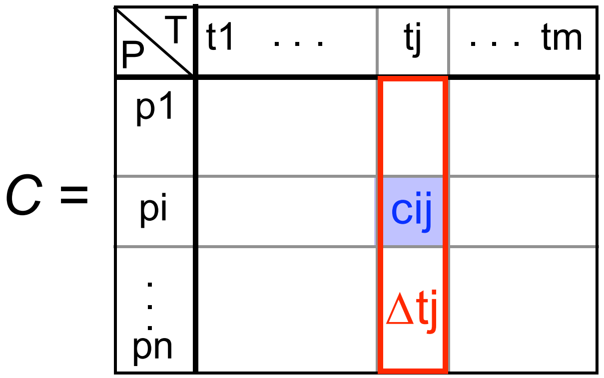
r1: A -> 2 B
r2: 2 A -> 3 C





INCIDENCE MATRIX C

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



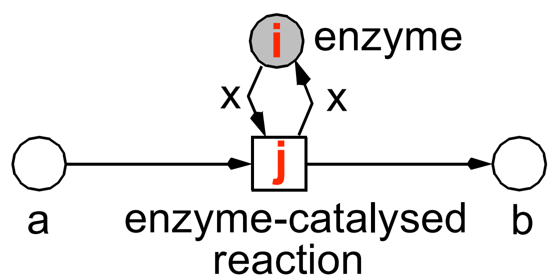
$$cij = (pi, tj) = F(tj,pi) - F(pi, tj) = \Delta\ tj(pi)$$

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

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

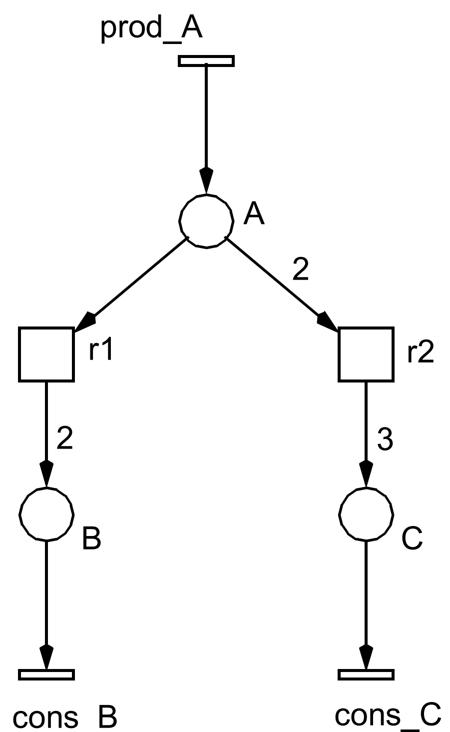
- **matrix column Δtj:**
  vector describing the change of the whole marking by firing of tj

- **side-conditions are neglected**

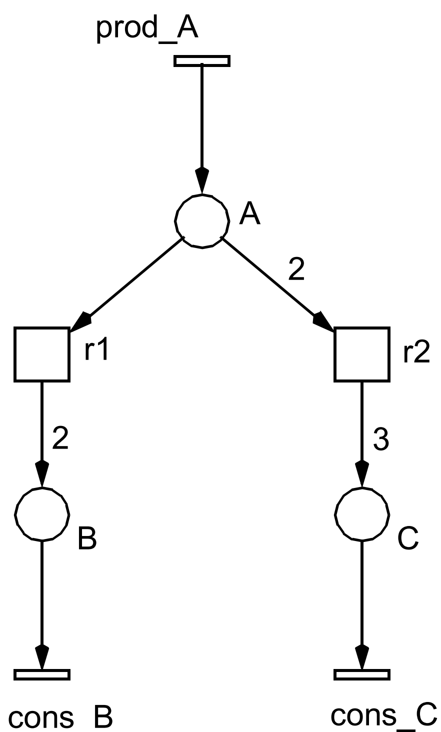


cij = 0

Incidence Matrix C, Ex1

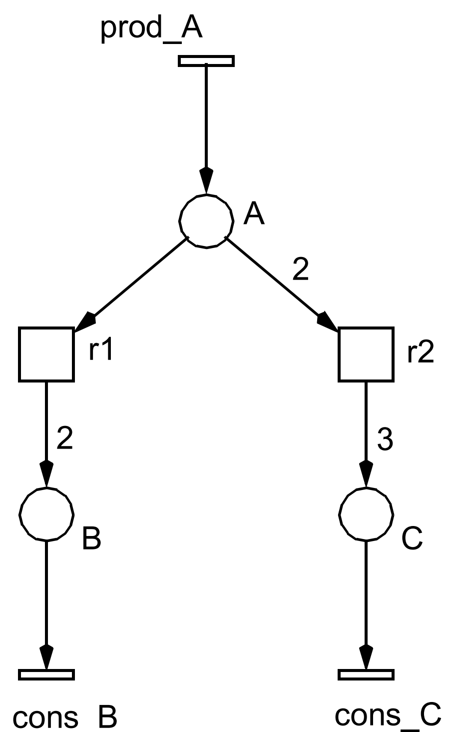


Incidence Matrix C, Ex1



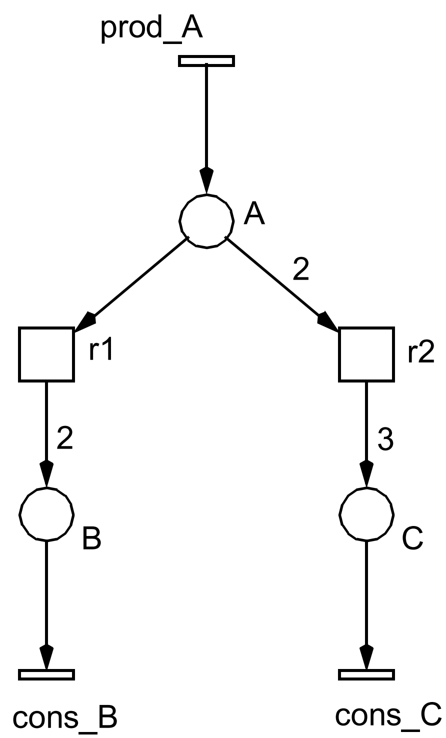
T / P	r1	r2	prod_A	cons_B	cons_C
A					
B					
C					

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**	

T-INVARIANTS, BASICS

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

$$kx = \sum_i a_i x_i$$

- **Covered by T-Invariants (CTI)**
  - -> *each transition belongs to a T-invariant*
  - -> *BND & LIVE => CTI (necessary condition)*

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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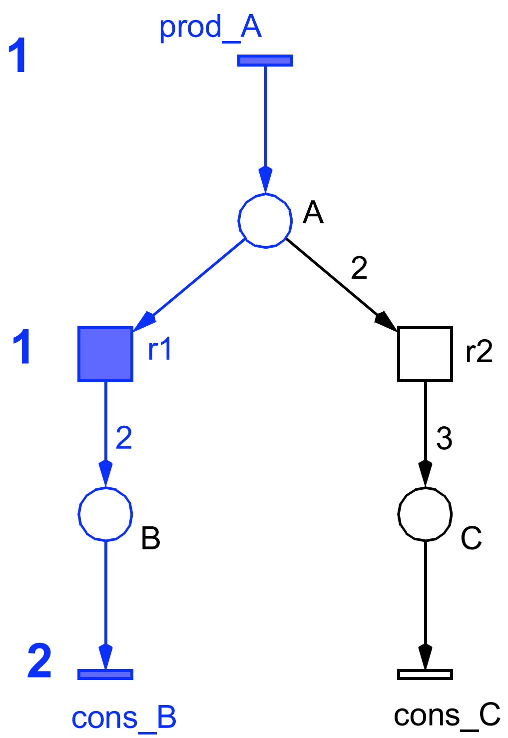
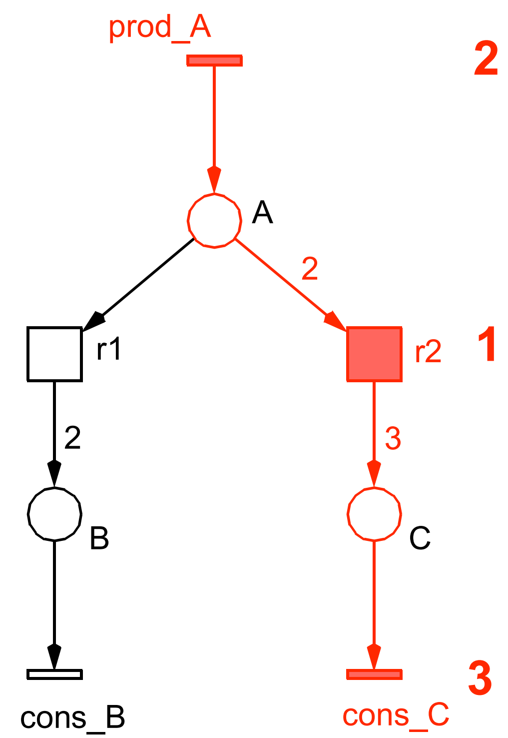


T-INVARIANT 1



T-INVARIANT 2

P-INVARIANTS, BASICS

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  - -> *gcD of all entries is 1*

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

$$ky = \sum_i a_i y_i$$

- **Covered by P-Invariants (CPI)**
  - -> *each place belongs to a P-invariant*
  - -> *CPI => BND (sufficient condition)*

P-INVARIANTS, INTERPRETATION

- **the firing of any transition has no influence on the weighted sum of tokens on the P-invariant's places**

  -> *for all t: the effect of the arcs, removing tokens from a P-invariant's places is equal to the effect of the arcs, adding tokens to a P-invariant's places*

- **set of places with**

  -> *a constant weighted sum of tokens for all markings m reachable from* m_0

  $$ym = ym_0$$

  -> *token / compound preservation,*

  -> *moieties*

  -> *a place belonging to a P-invariant is bounded*

- **a P-invariant defines a subnet**

  -> *the P-invariant's places (the support),*
  + all their pre- and post-transitions
  + the arcs in between

  -> *pre-sets of supports = post-sets of supports* -> **self-contained**

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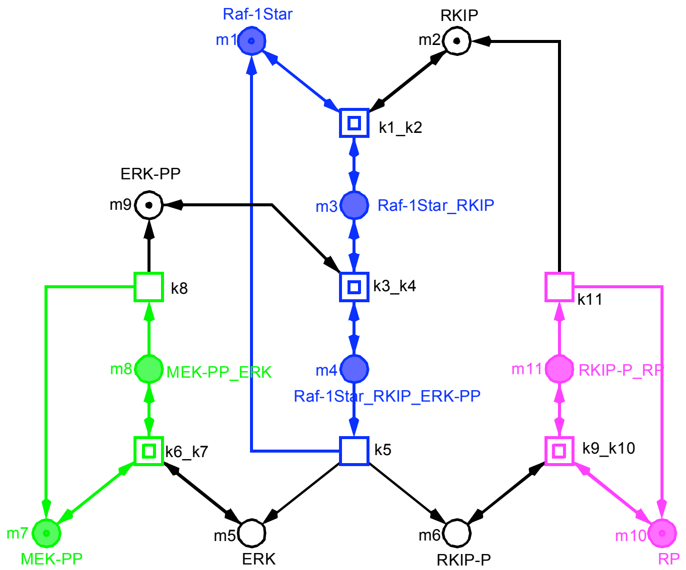
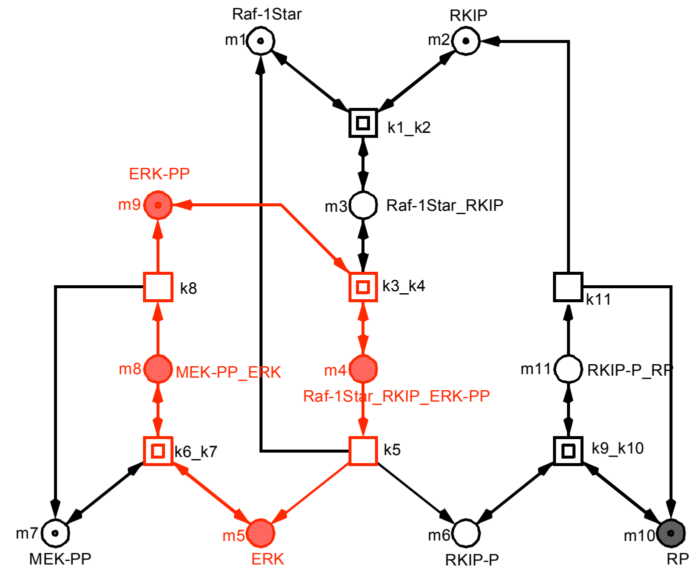
P-Invariants, Ex - RKIP Pathway





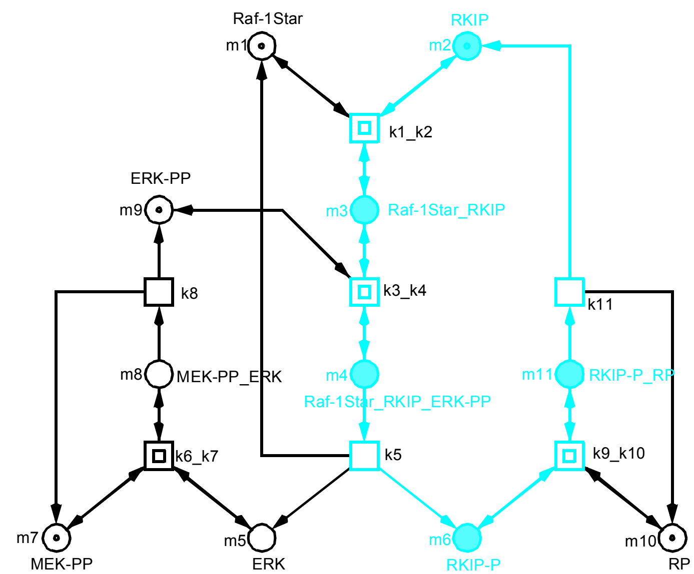
P-INV1: MEK

P-INV2: RAF-1STAR

P-INV3: RP

P-INV4: ERK

P-INV5: RKIP



CONSTRUCTION OF THE INITIAL MARKING

- **each P-invariant gets at least one token**
  - -> *P-invariants are structural deadlocks and traps*
- **in signal transduction networks**
  - -> *exactly 1 token, corresponding to species conservation*
  - -> *token in least active state*
- **all (non-trivial) T-invariants get feasible**
  - -> *to make the net live*
- **minimal marking**
  - -> *minimization of the state space*

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-> UNIQUE INITIAL MARKING <-

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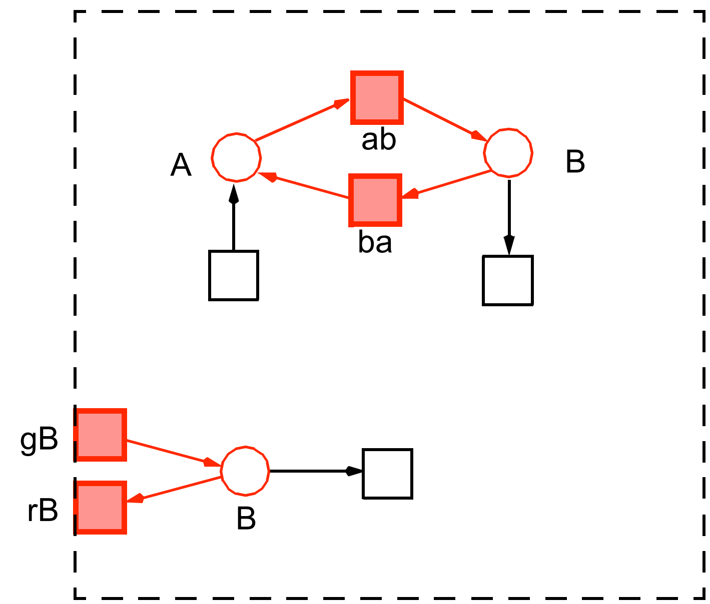
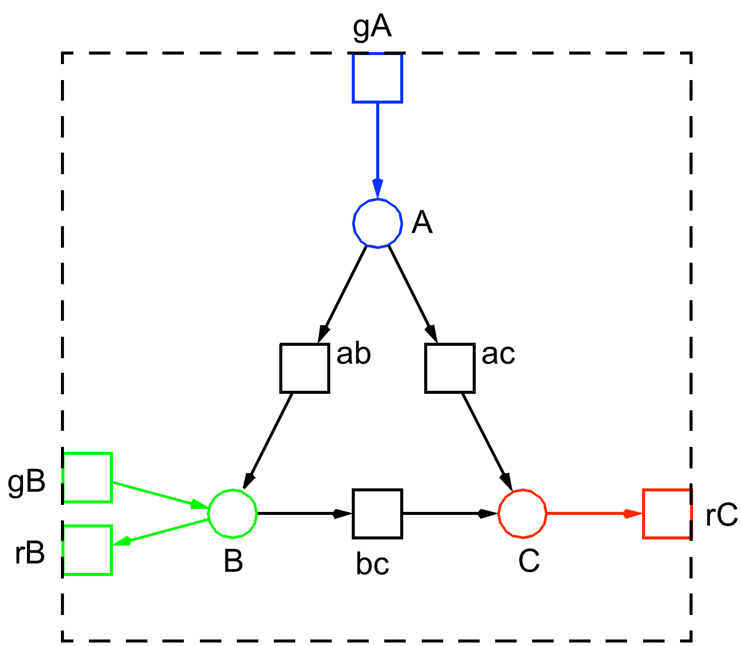
T-INVARIANTS, BASIC TYPES IN BIO NETWORKS

- **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*



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



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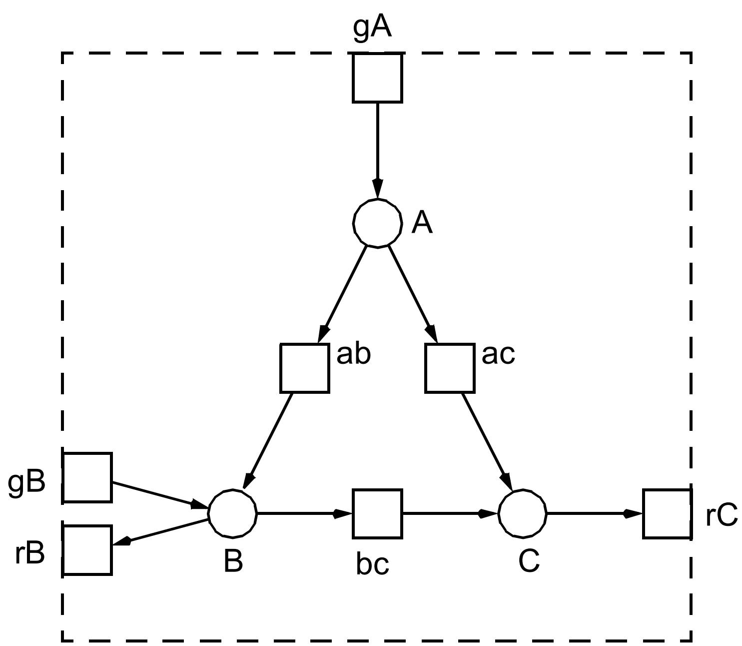
T-INVARIANTS, EX2

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



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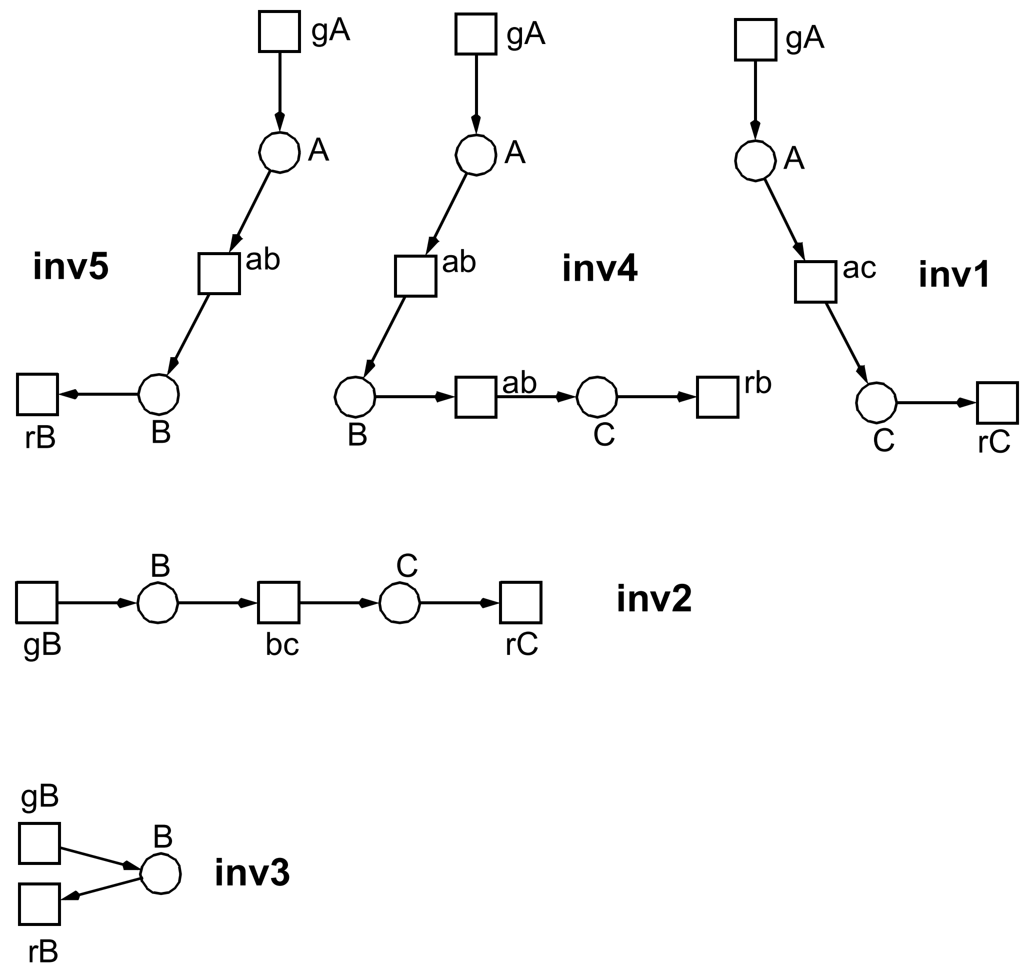

T-INVARIANTS, EX2 - ELEMENTARY MODES

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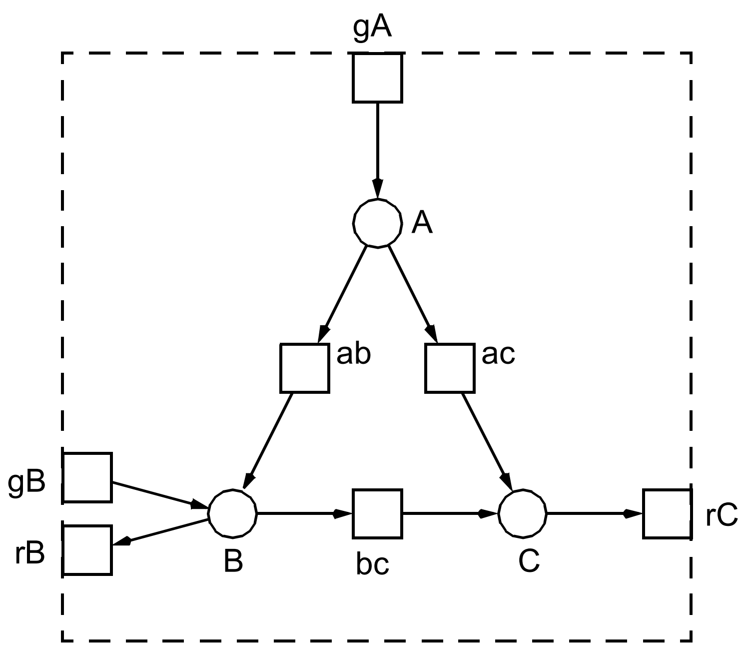

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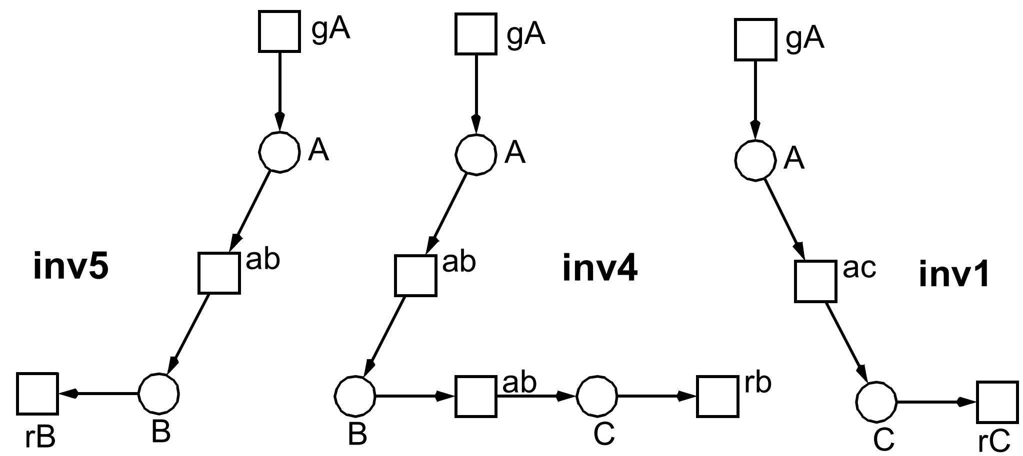

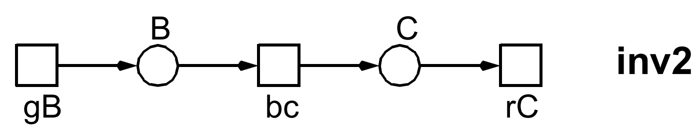

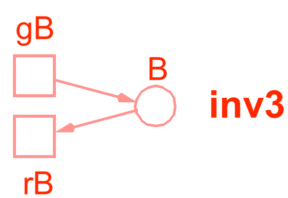

no elementary mode

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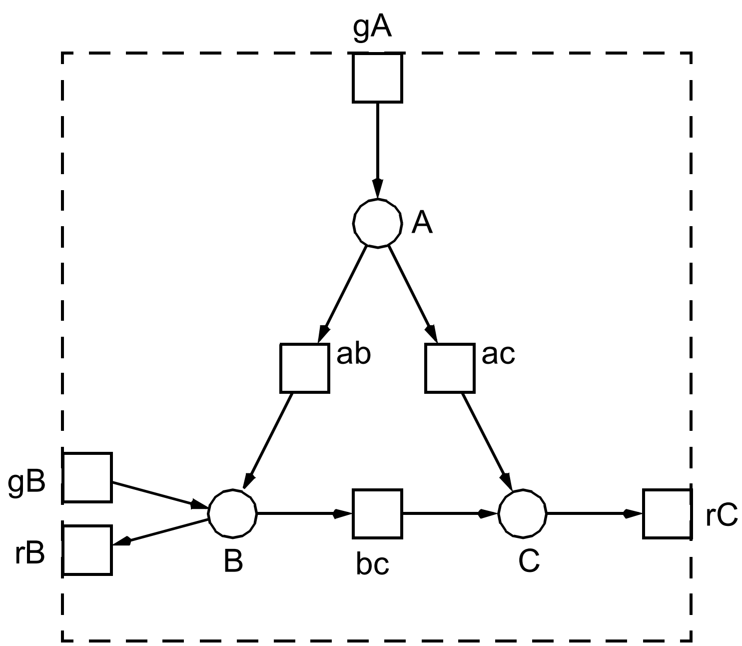

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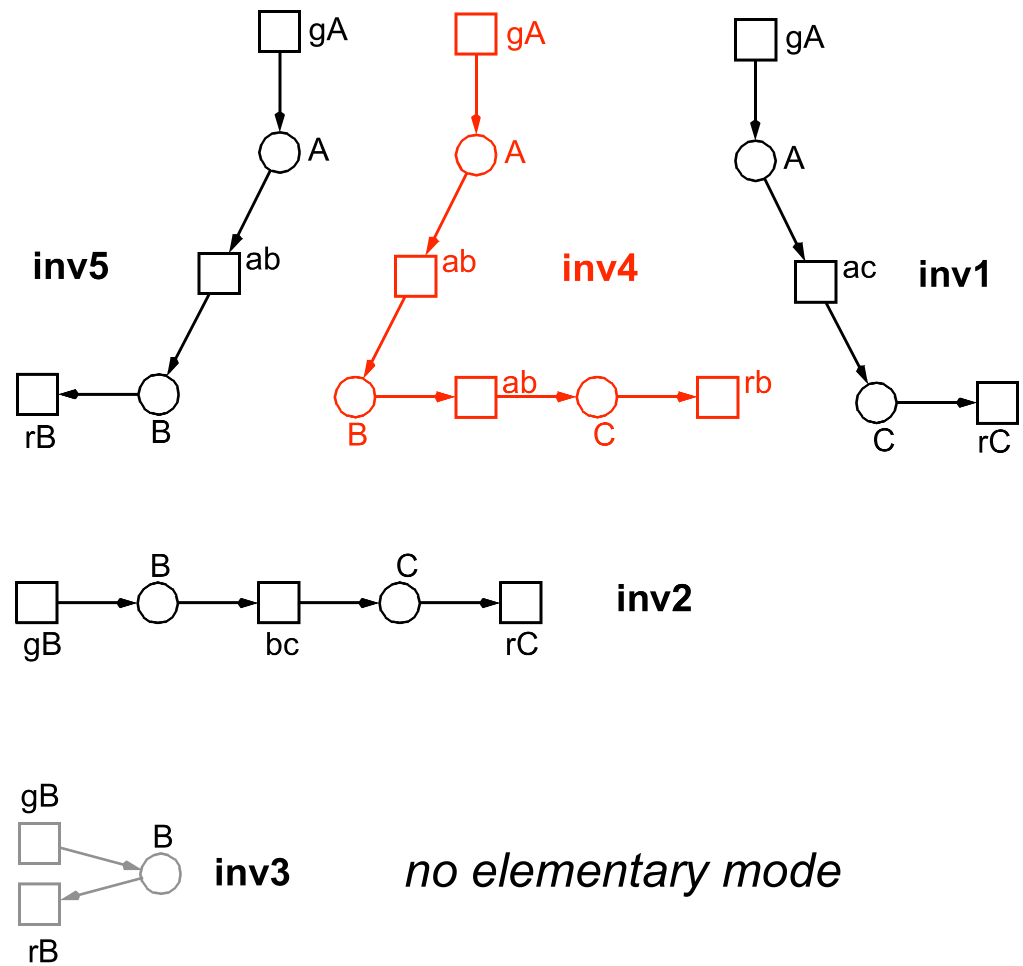
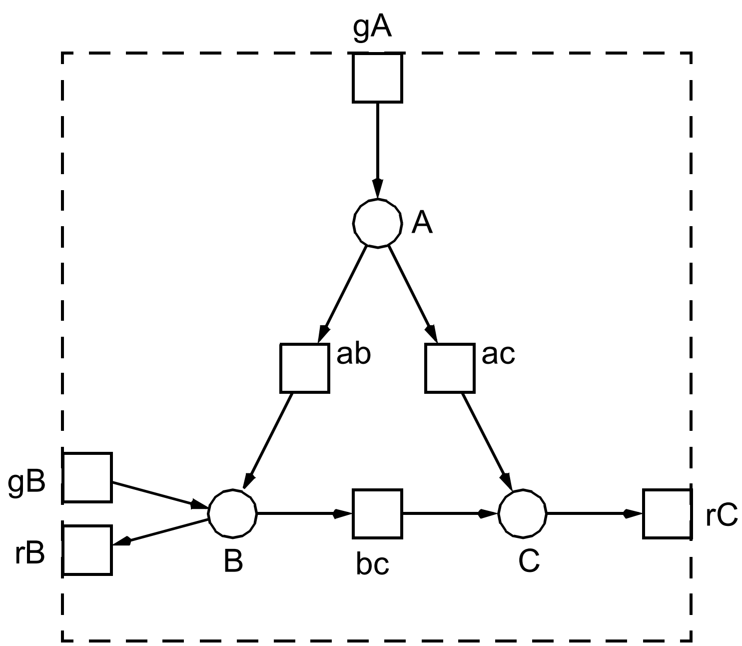
no extreme pathway



no elementary mode

T-INVARIANTS, EX2 - EXTREME PATHWAYS

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



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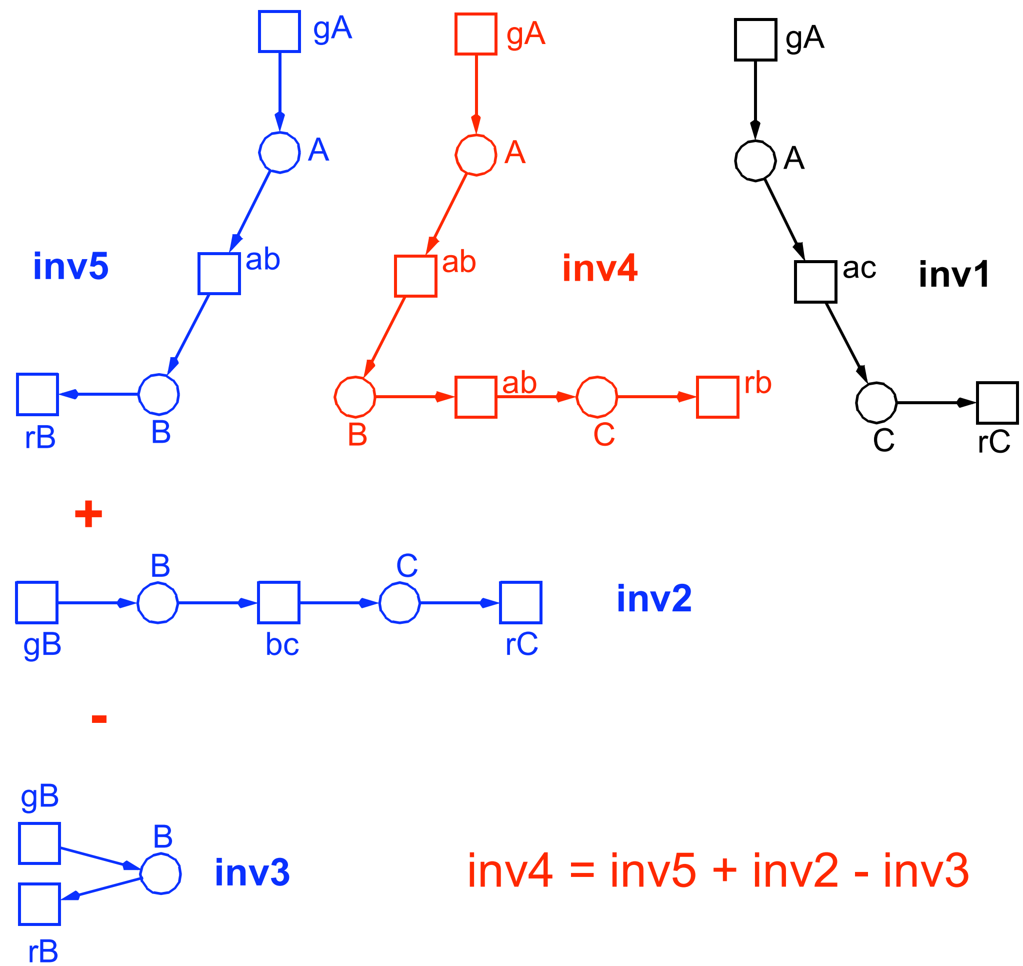
no extreme pathway



inv4 = inv5 + inv2 - inv3

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T-INVARIANTS, EX2, SUMMARY

- **substances involved**
  - -> *input substance A*
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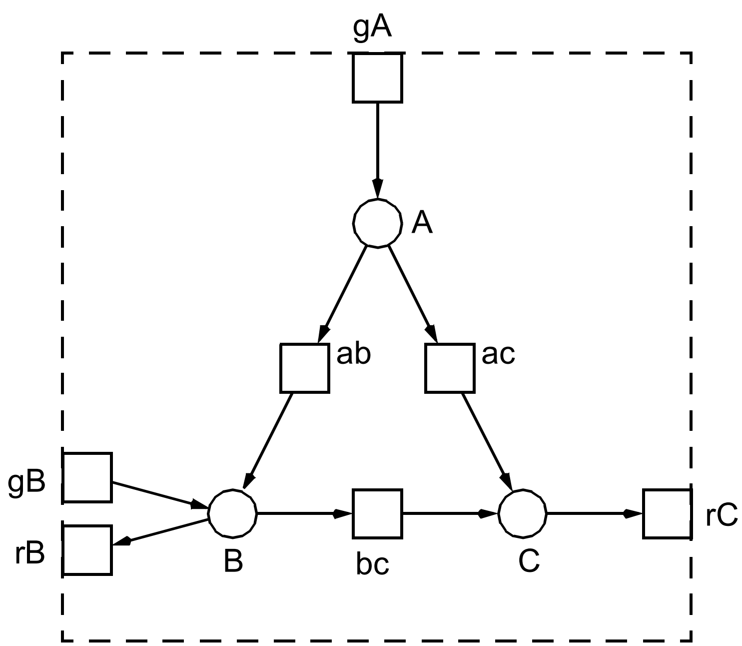

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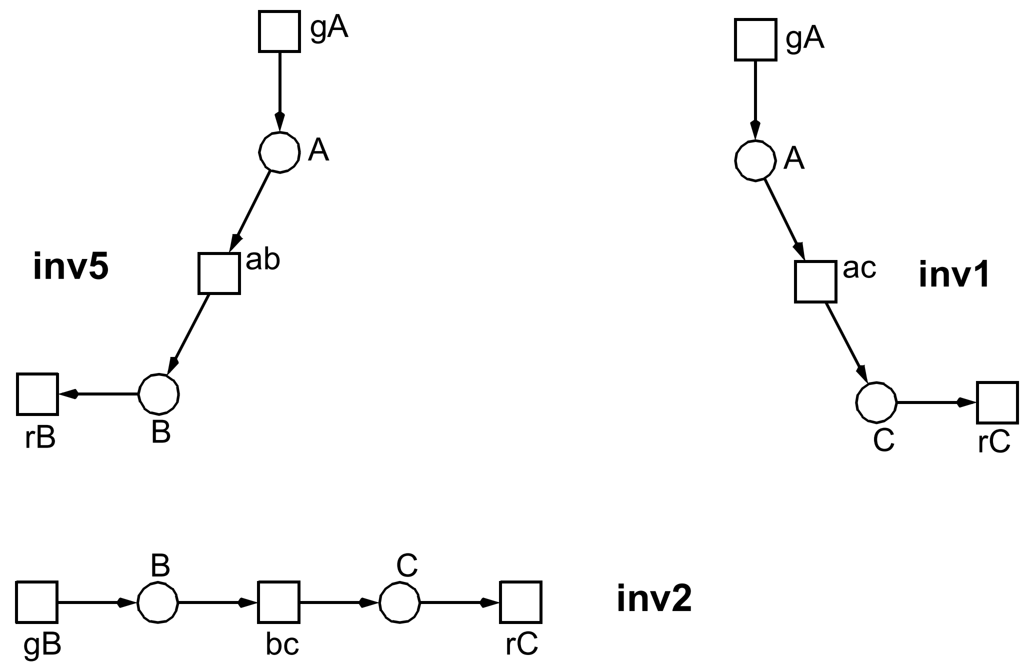
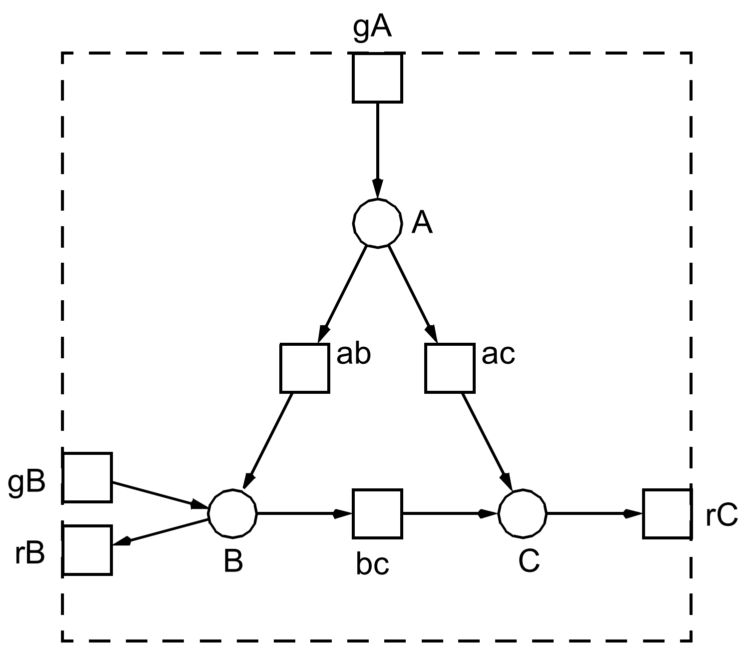
EXTREME PATHWAYS



T-INVARIANTS, EX2, SUMMARY

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



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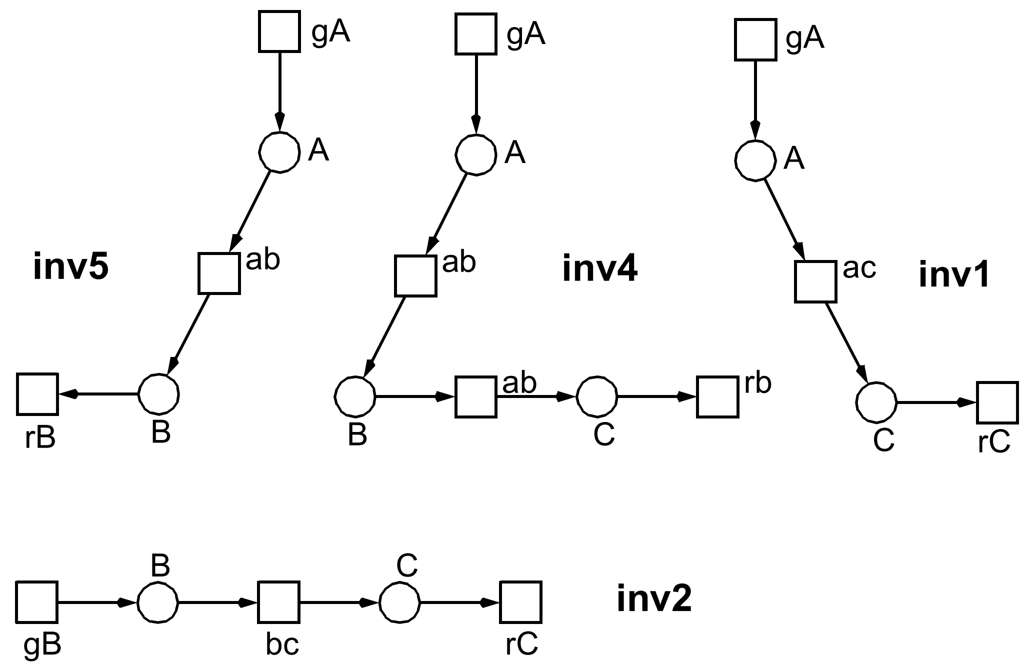
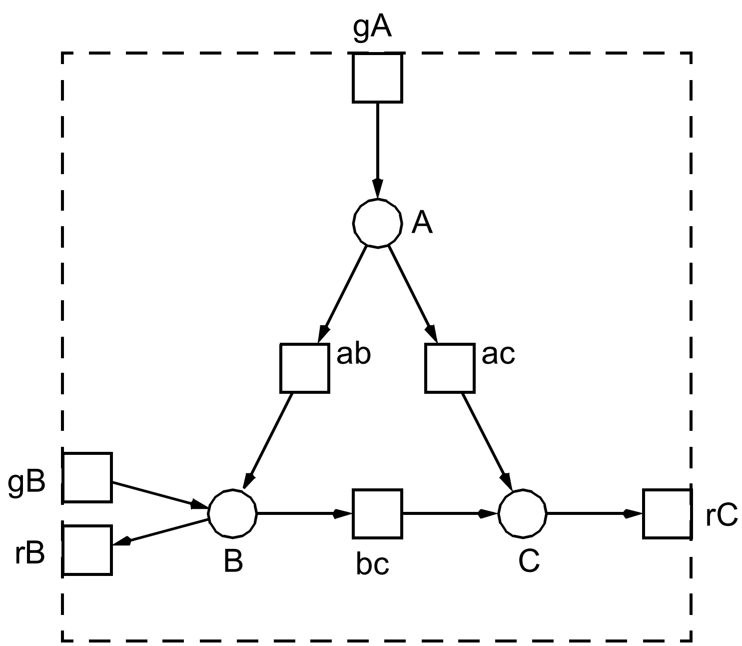
ELEMENTARY MODES



T-INVARIANTS, EX2, SUMMARY

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



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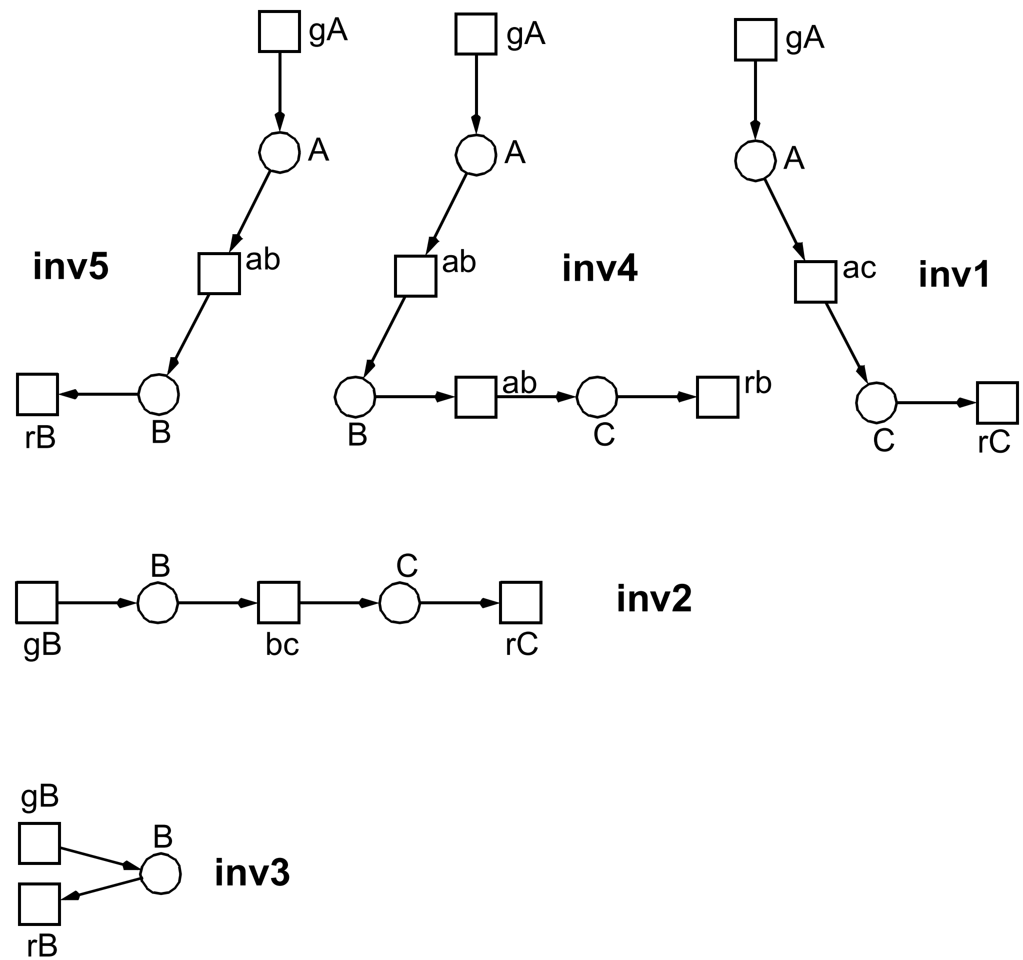
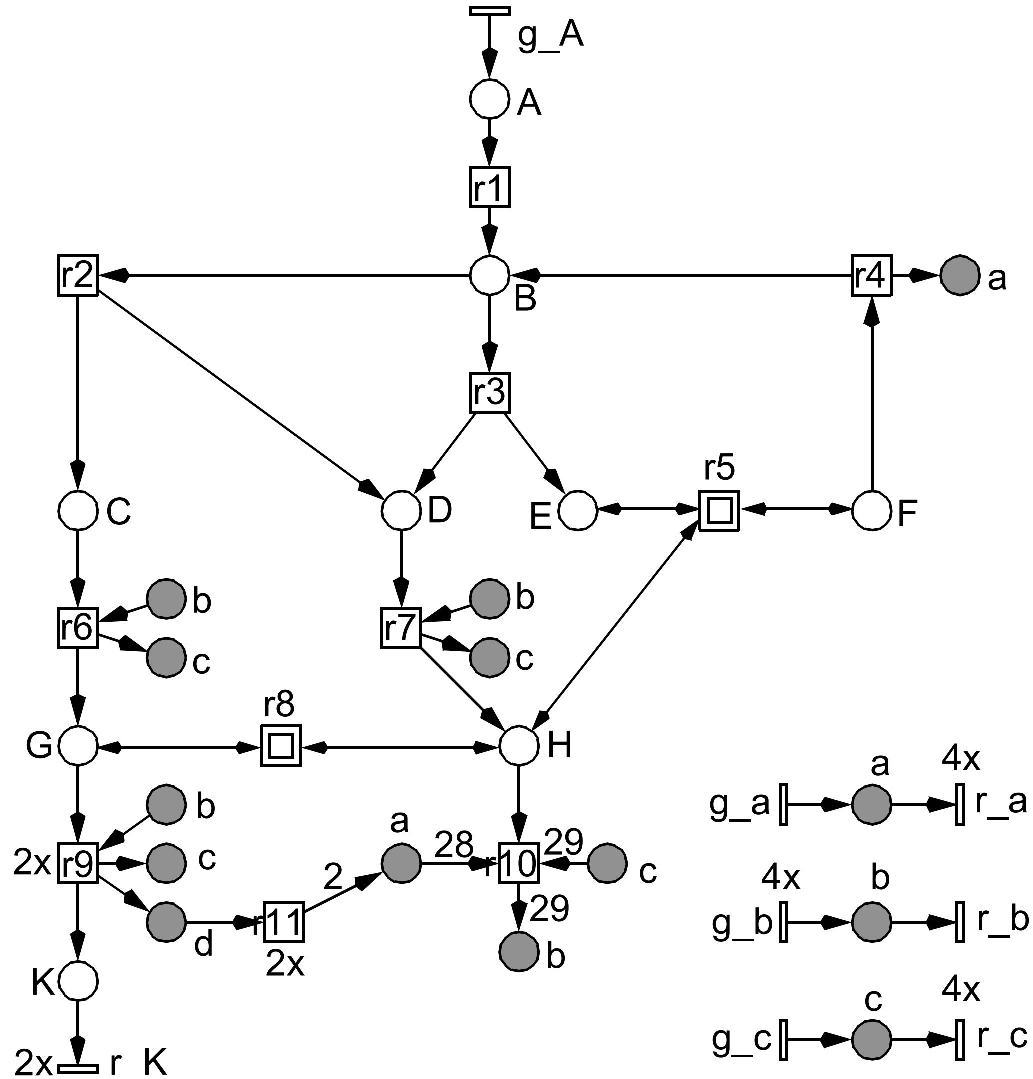
MINIMAL T-INVARIANTS



T-INVARIANTS, EX3



trivial min. T-invariants (5)

-> CTI

- boundary transitions of auxiliary compounds

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

- reversible reactions

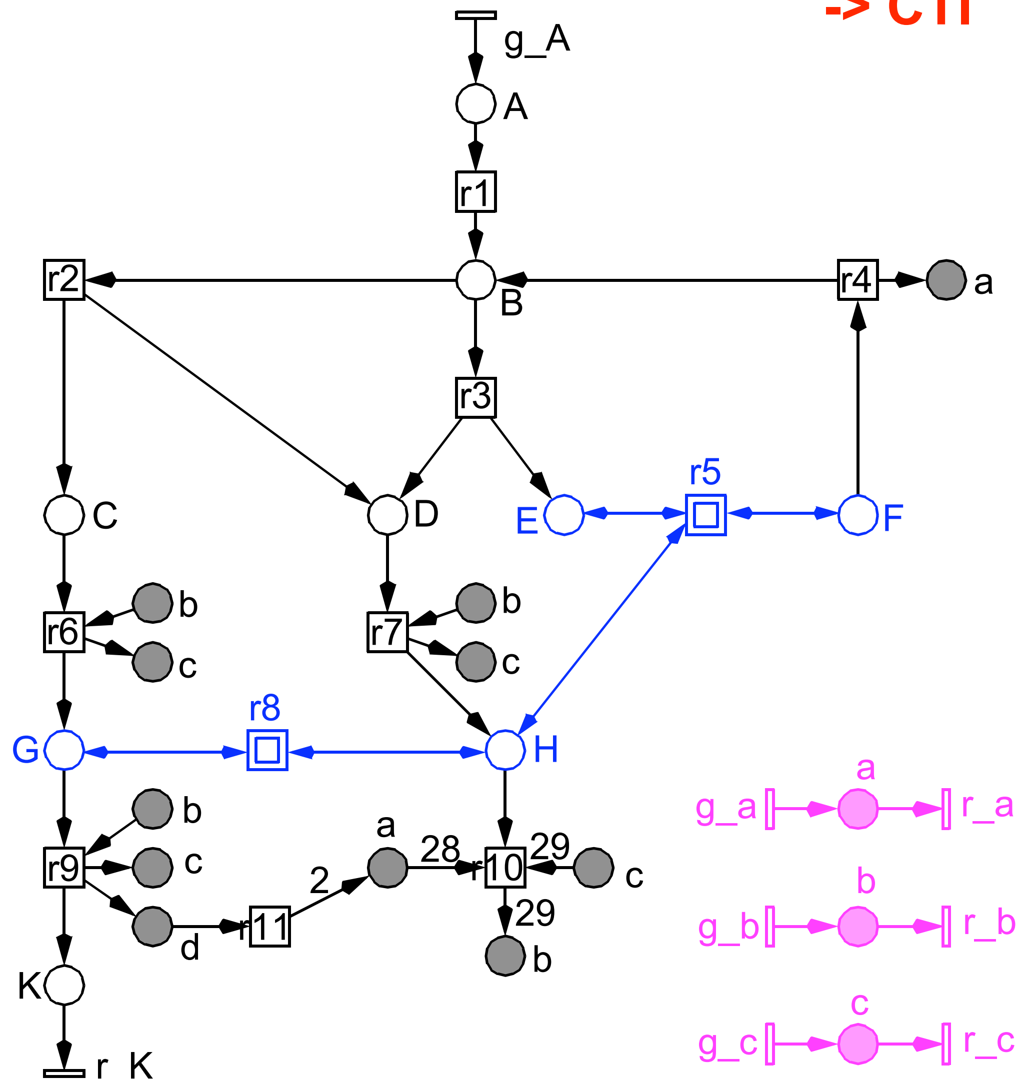
  -> (r5, r5_rev), (r8, r8_rev)

non-trivial min. T-invariants (7)

- covering
  boundary transitions of input / output compounds

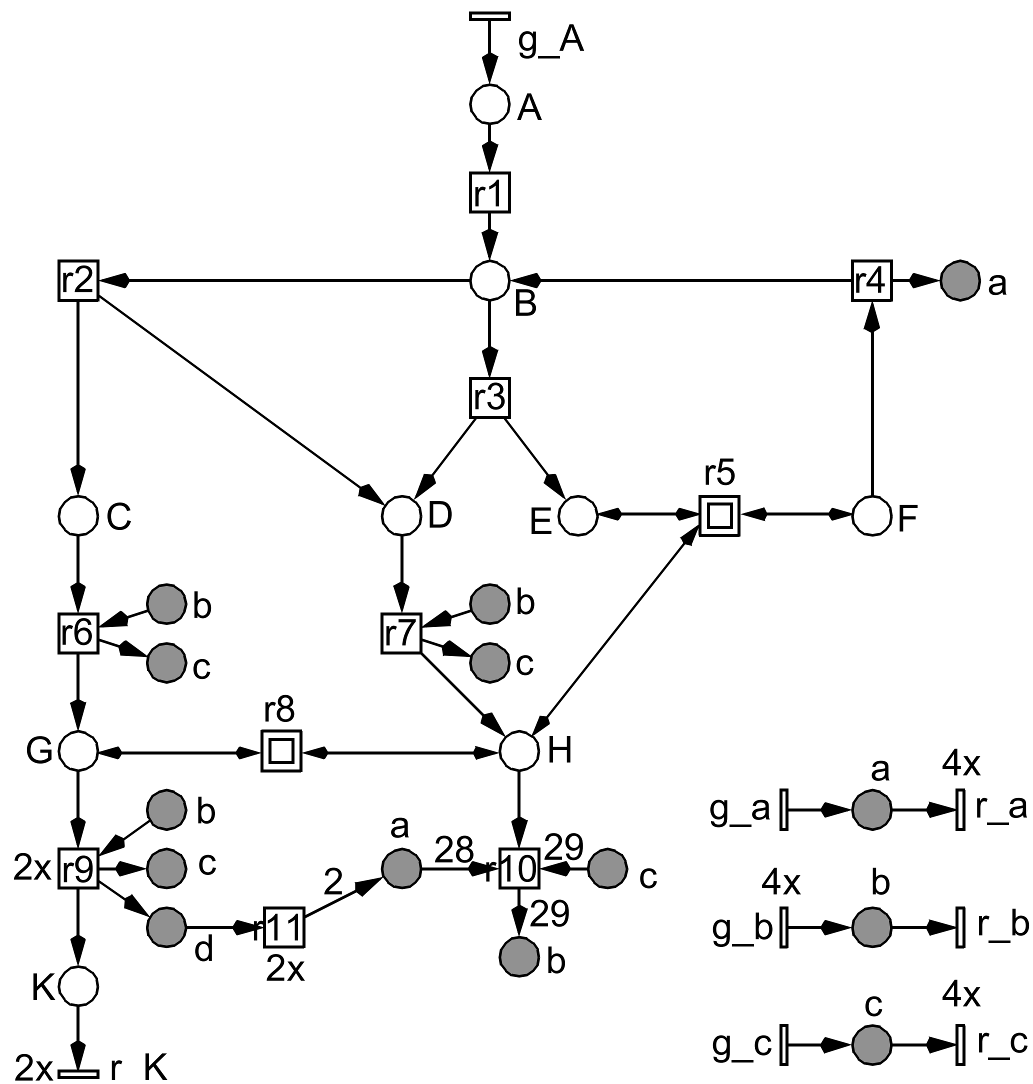
  -> *i/o-T-invariants*

- inner cycles



❑ 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



T-INVARIANTS, EX3

- **i/o-T-invariant, example**

12 | 0.r1 : 1
| 1.r2 : 1,
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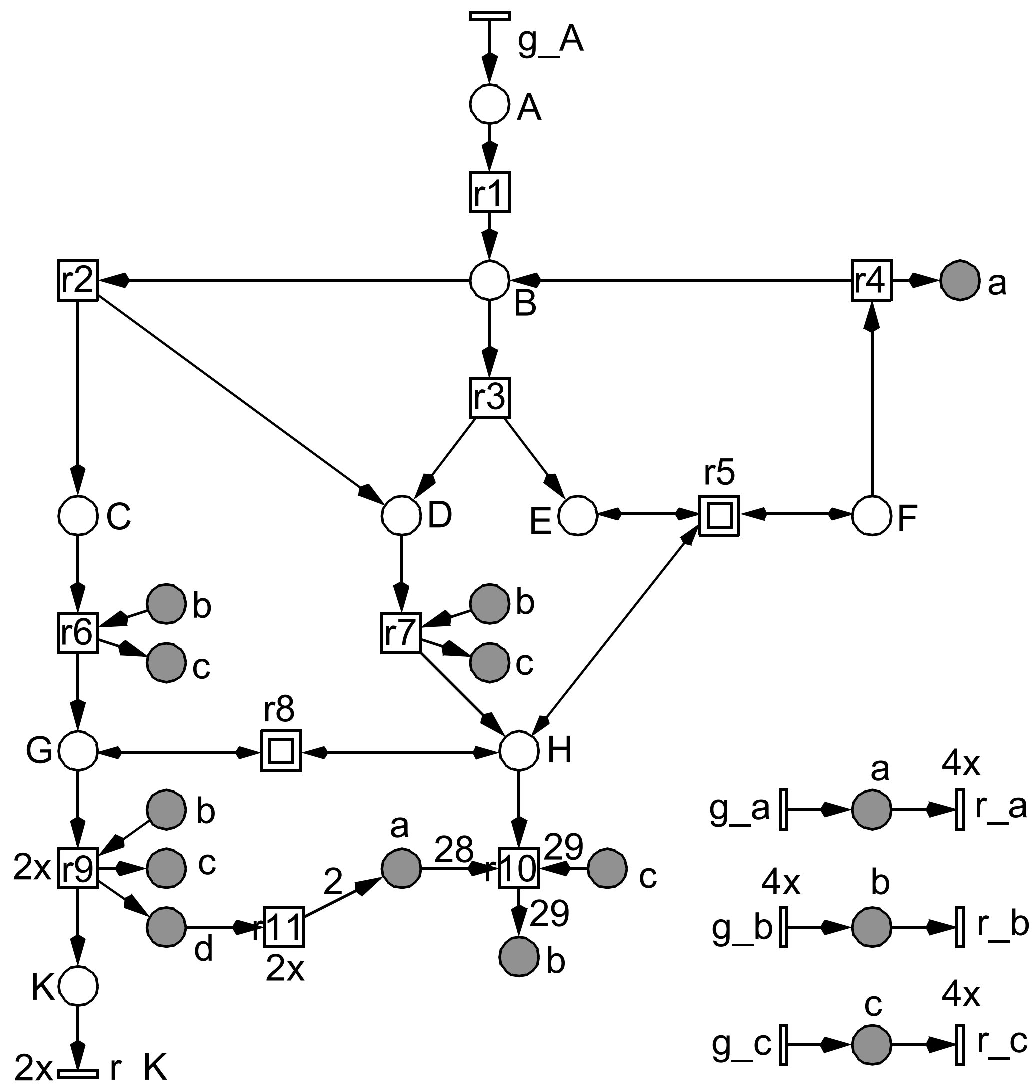
| 20.r_a : 4

- **sum equation**

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



T-INVARIANTS, EX3

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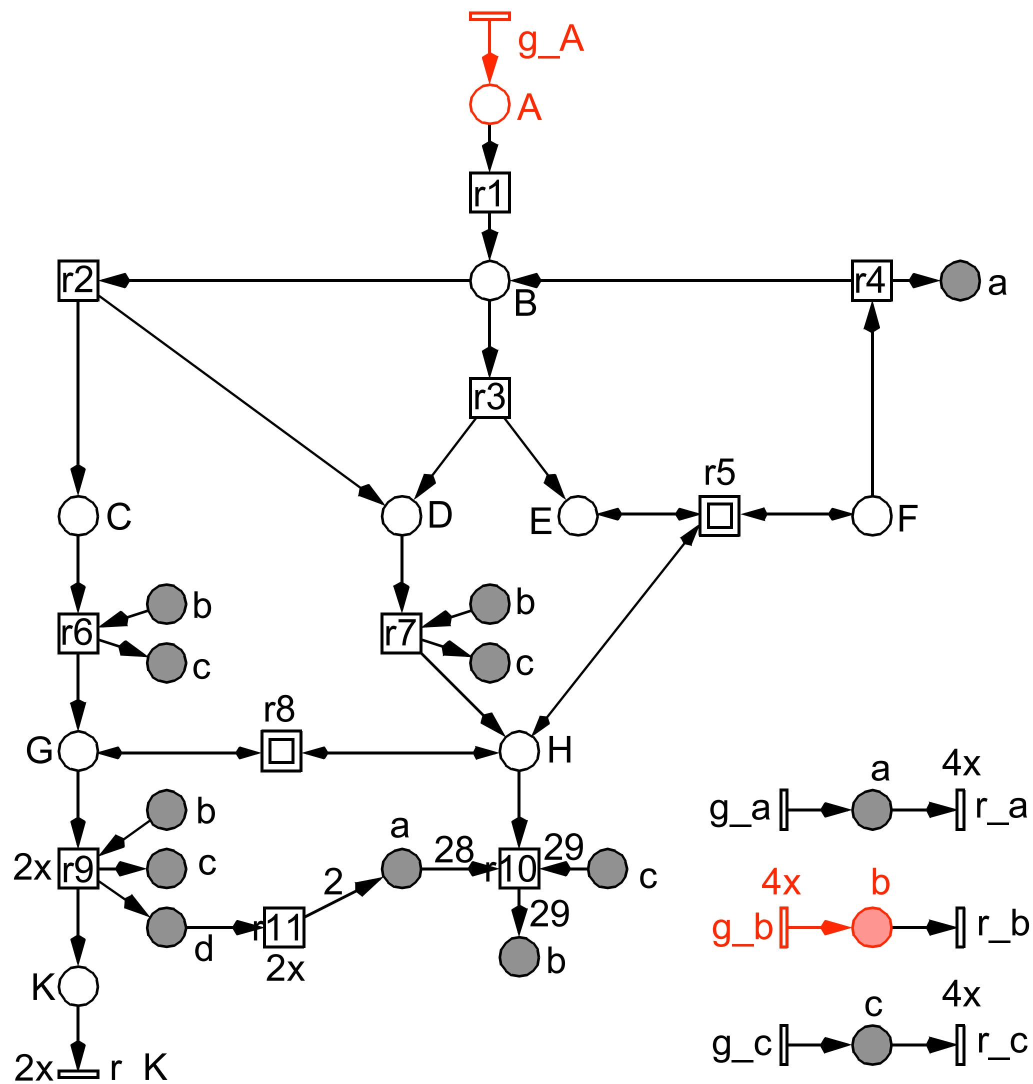

sum equation

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- **i/o-T-invariant, example**

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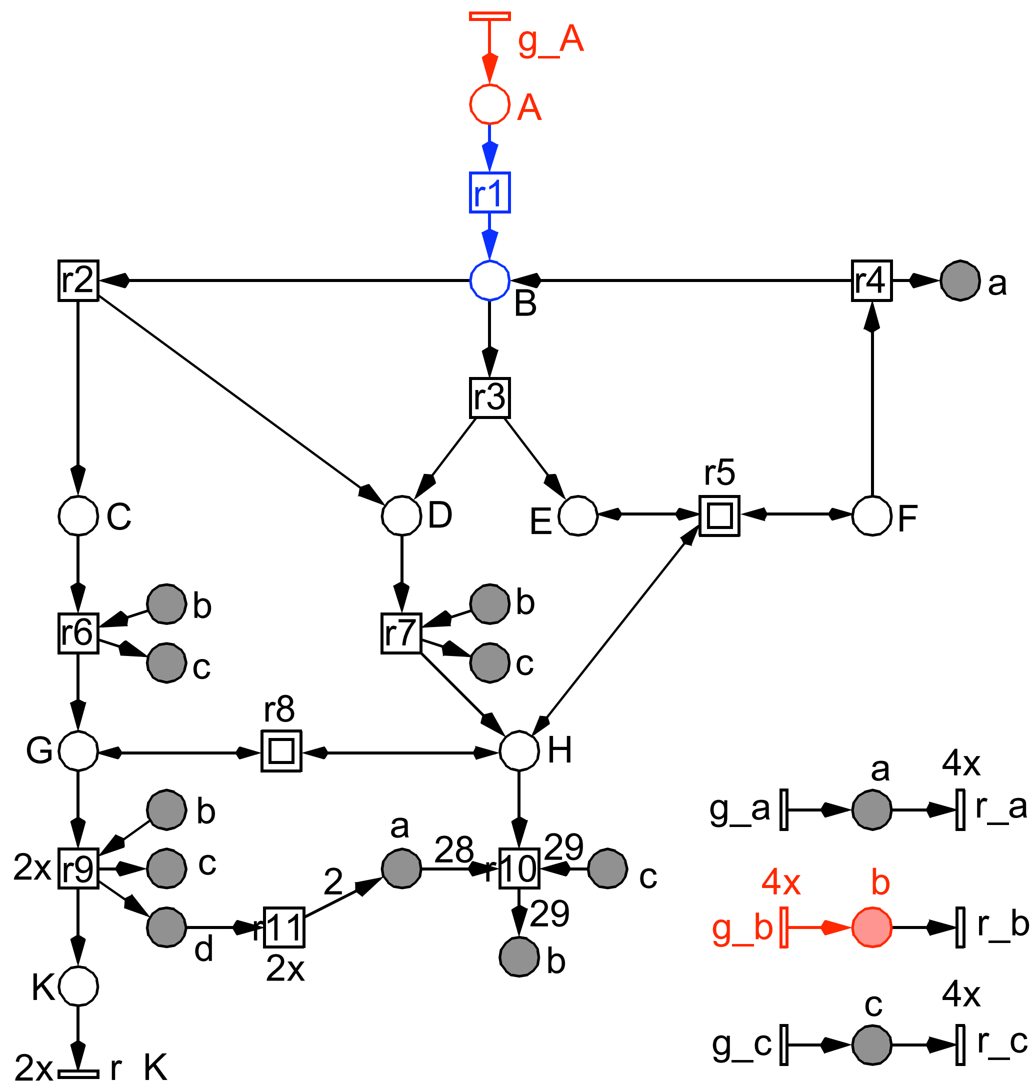

- **sum equation**

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

T-INVARIANTS, EX3

- **i/o-T-invariant, example**

12	0.r1	:	1
	1.r2	:	1,
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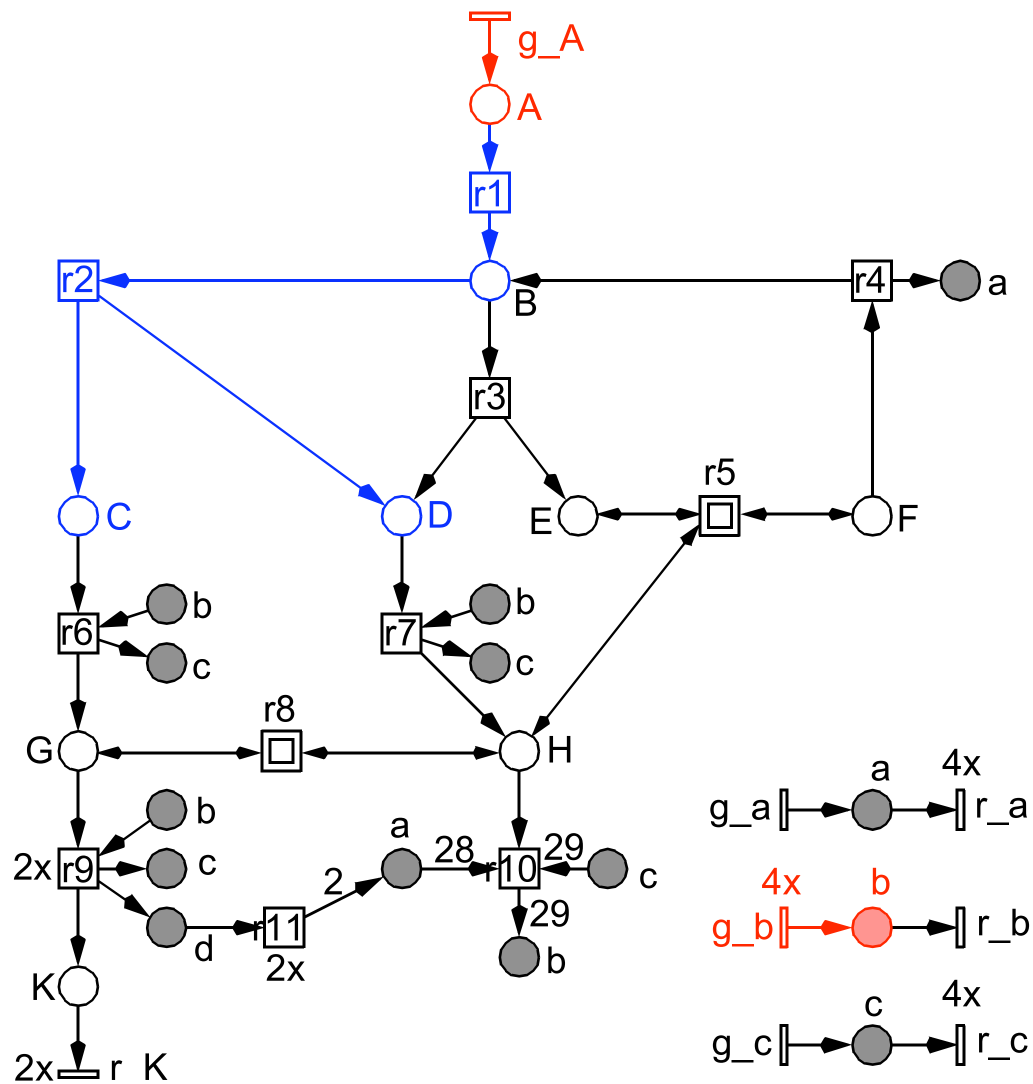
- **sum equation**

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



T-INVARIANTS, EX3

- **i/o-T-invariant, example**

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  | 1.r2 : 1,
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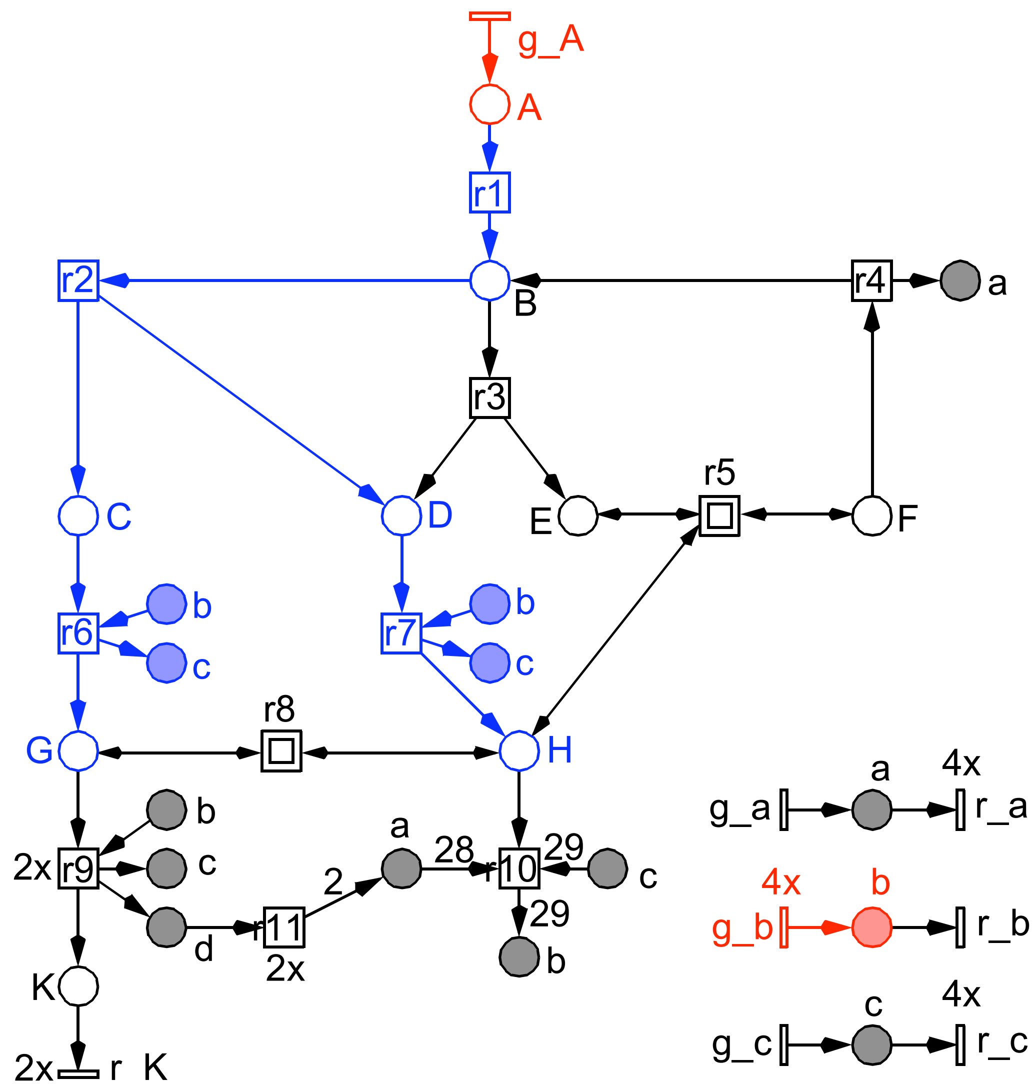
- **sum equation**

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



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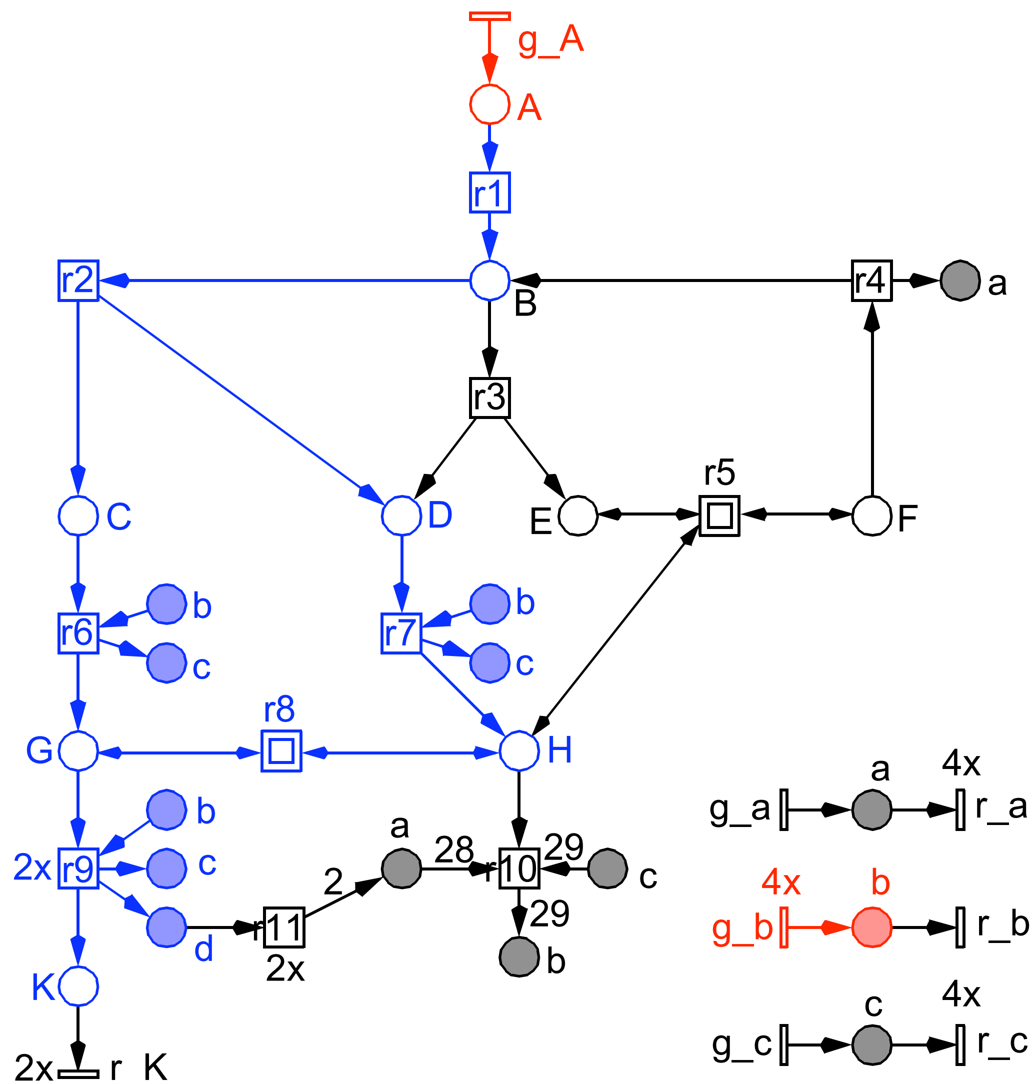
- **sum equation**

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



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- **sum equation**

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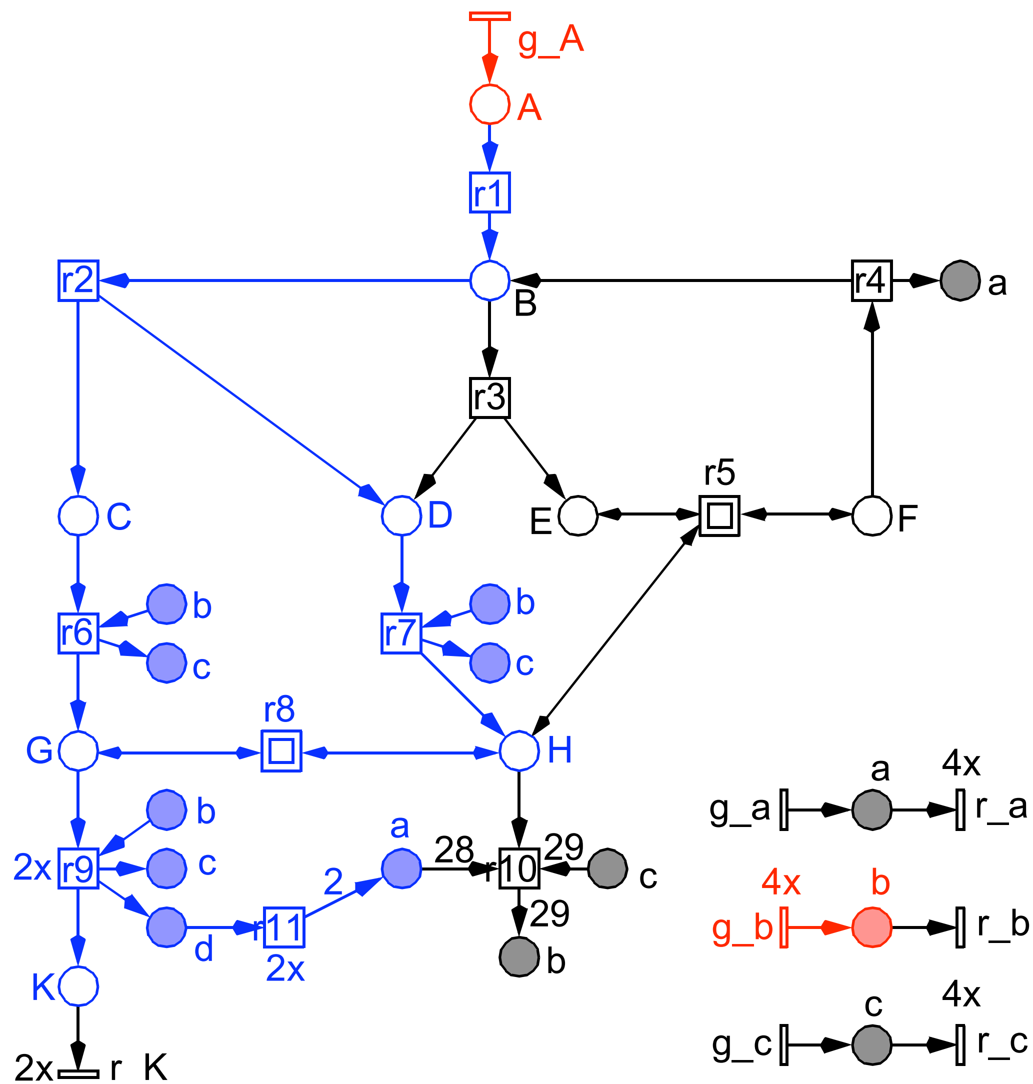

- **i/o-T-invariant, example**

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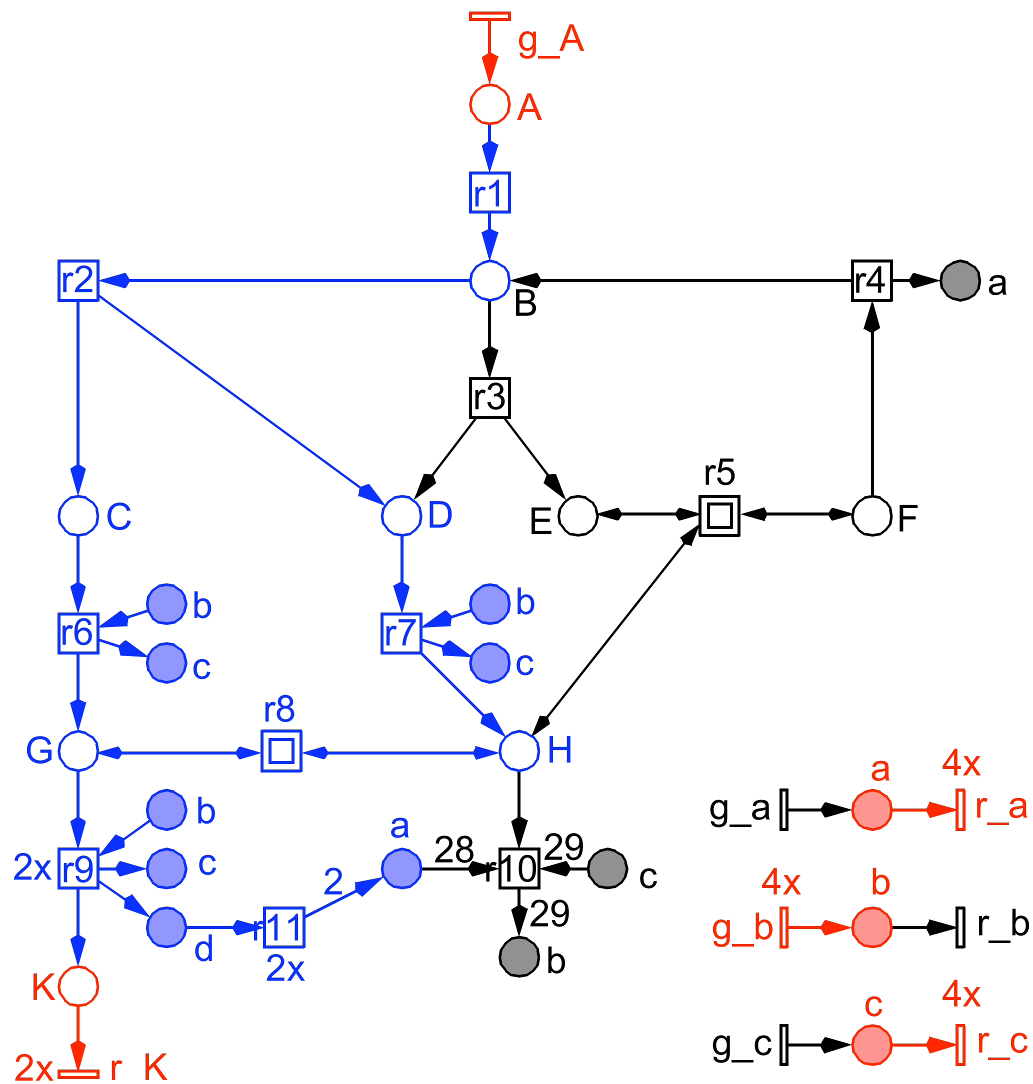
- **sum equation**

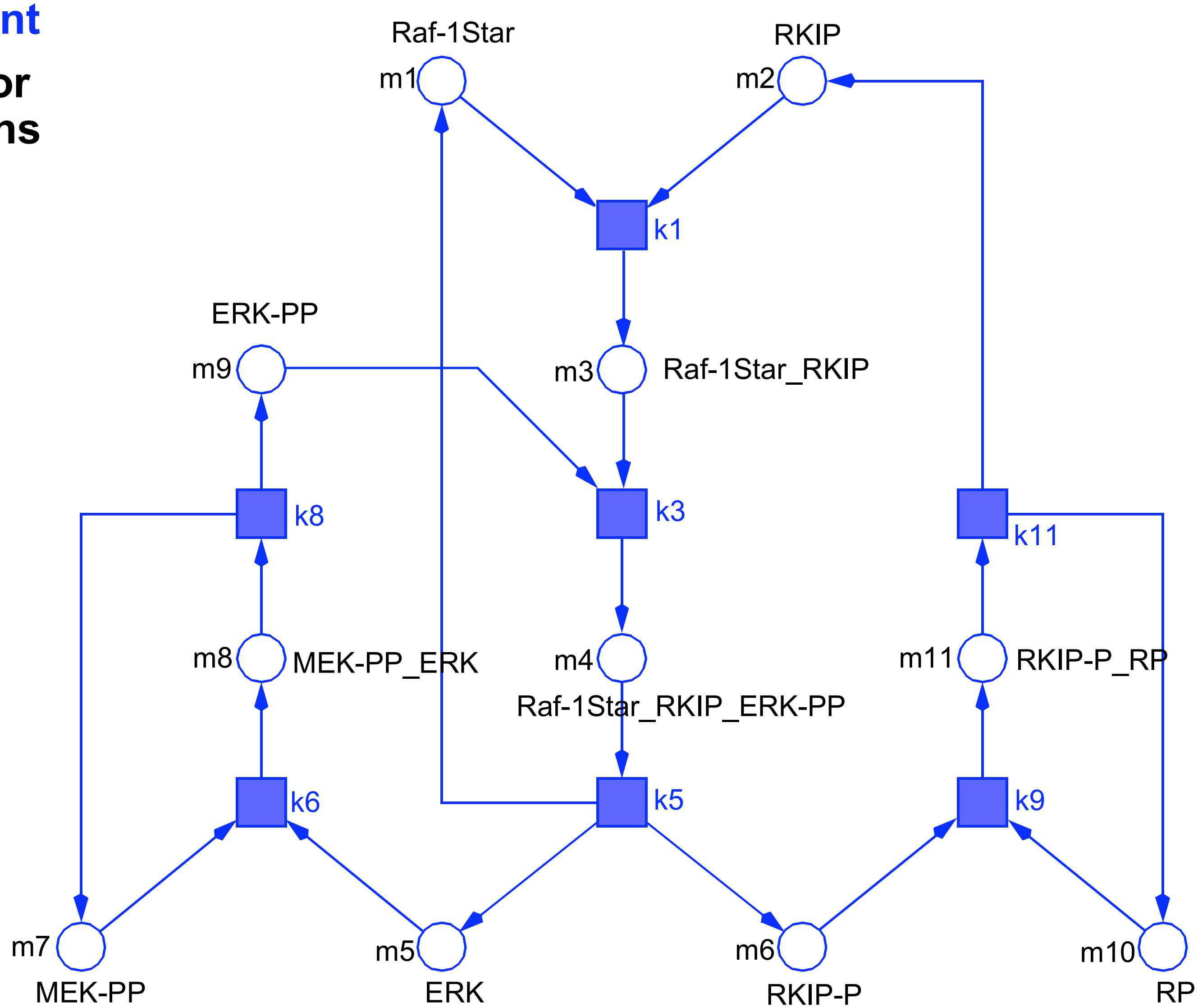
A + 4b -> 2K +4a + 4c



T-INVARIANT, EX4: THE RKIP PATHWAY

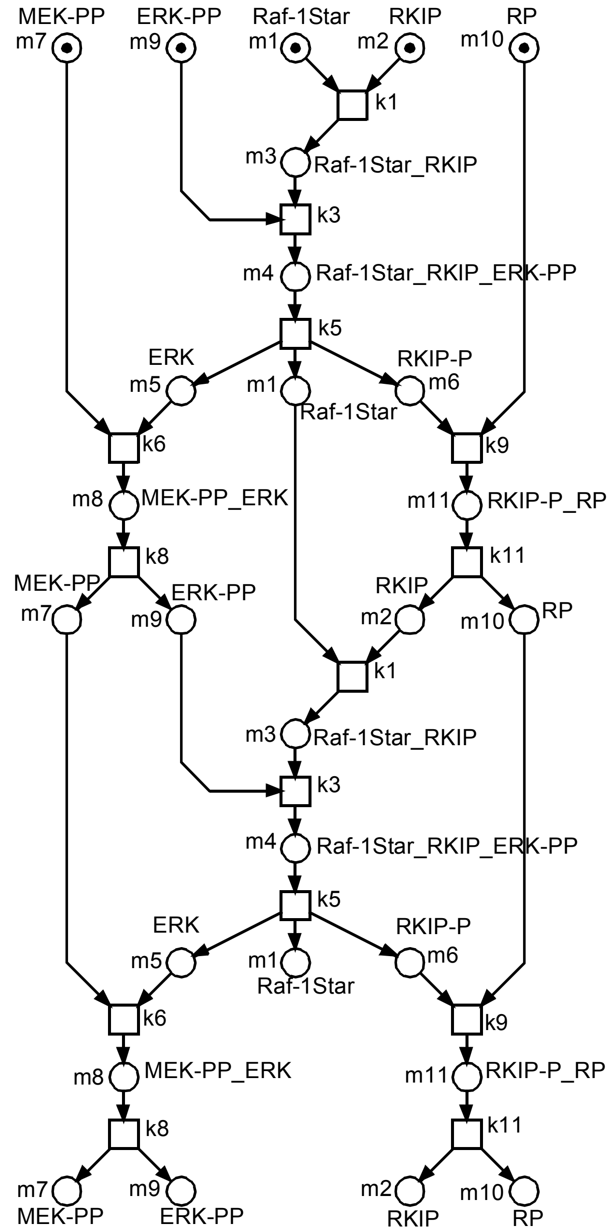
-> non-trivial T-invariant

+ four trivial ones for reversible reactions

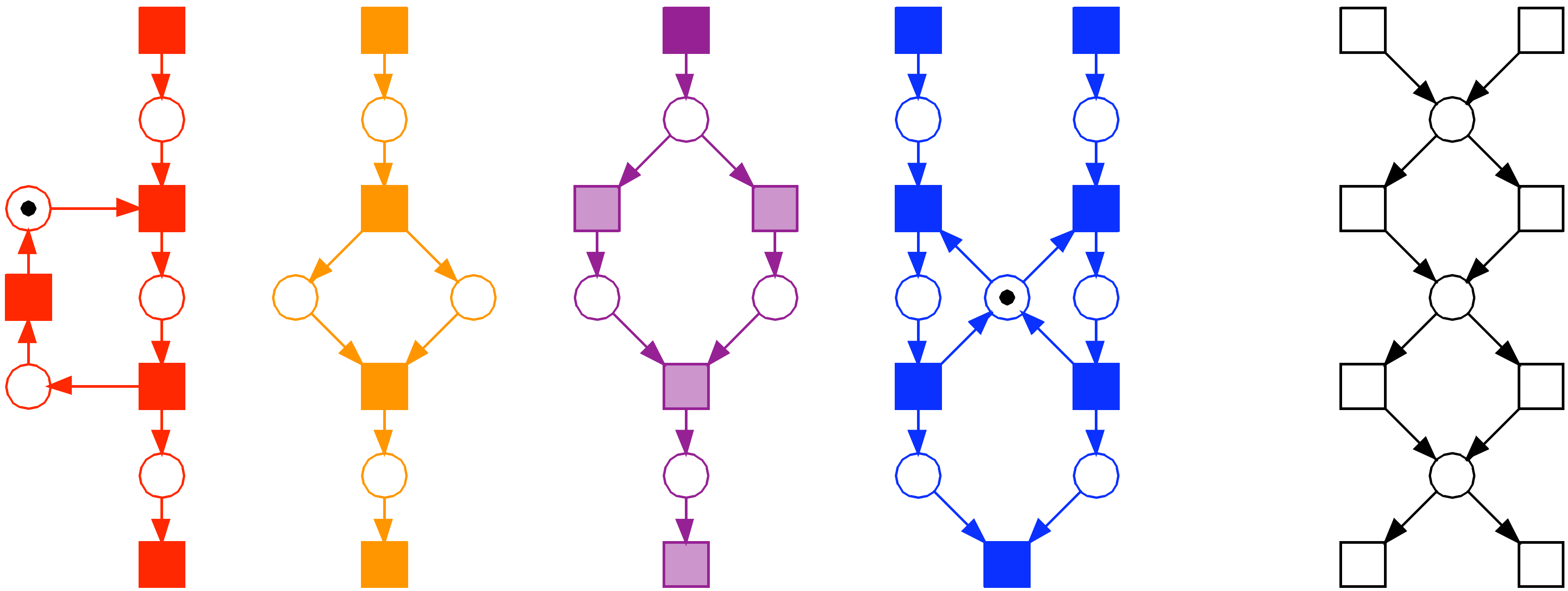


NON-TRIVIAL T-INVARIANT, RUN

- **realizability check under the constructed marking**
- **T-invariant's unfolding to describe its behaviour**
  -> **partial order structure**
- **labelled condition / event net**
  -> *events (boxes)*
  - transition occurences
  -> *conditions (circles)*
  - involved compounds
- **occurrence net**
  -> *acyclic*
  -> *no backward branching conditions*
  -> *infinite*



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



- **T-invariants generally overlap**

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

- **likewise for P-invariants**

MODULARIZATION BY T-INVARIANTS

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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.

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

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

$$\forall x \in X: A \subseteq supp(x) \vee A \cap supp(x) = \emptyset$$

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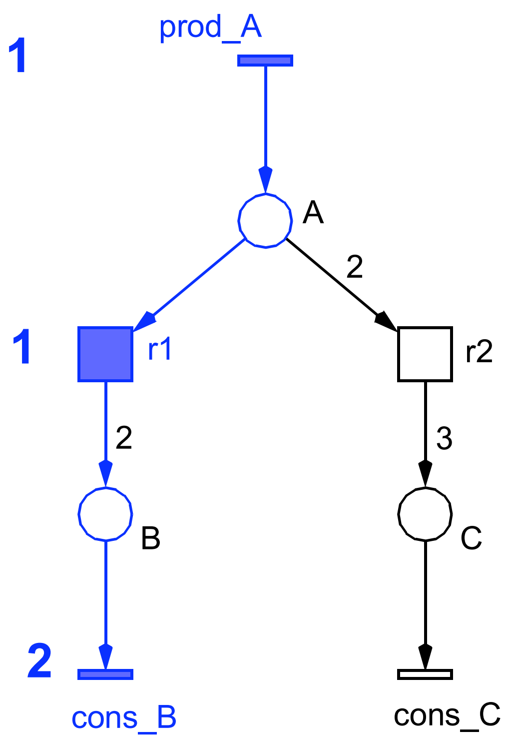
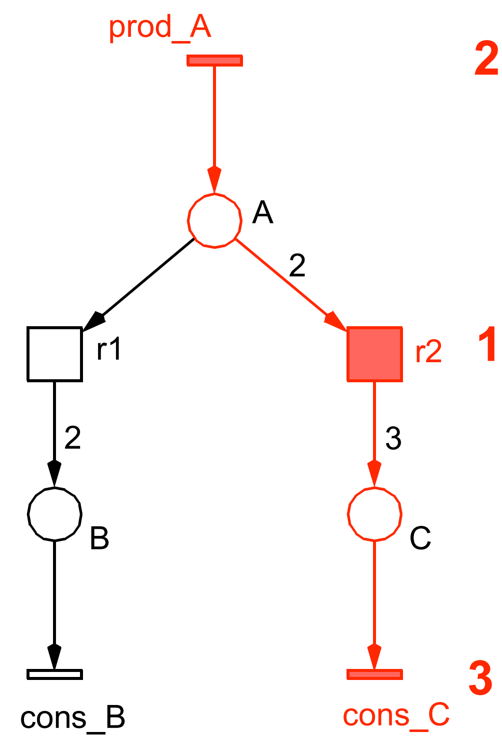
ADT-SETS, EX1

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



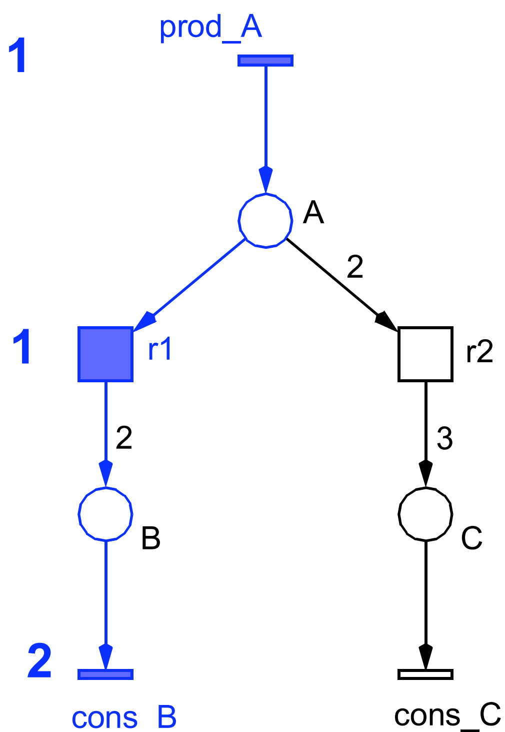
T-INVARIANT 1



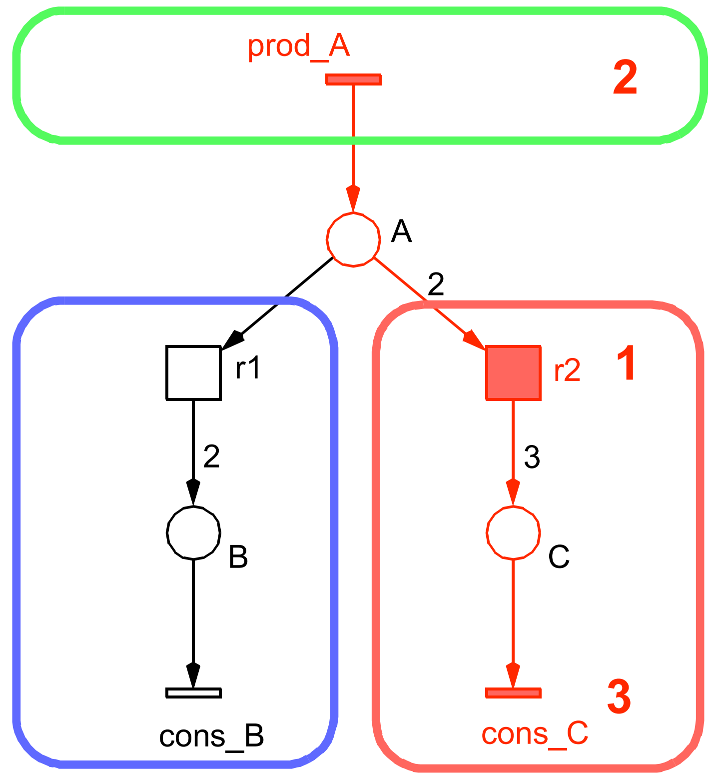
T-INVARIANT 2

ADT-SETS, EX1

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



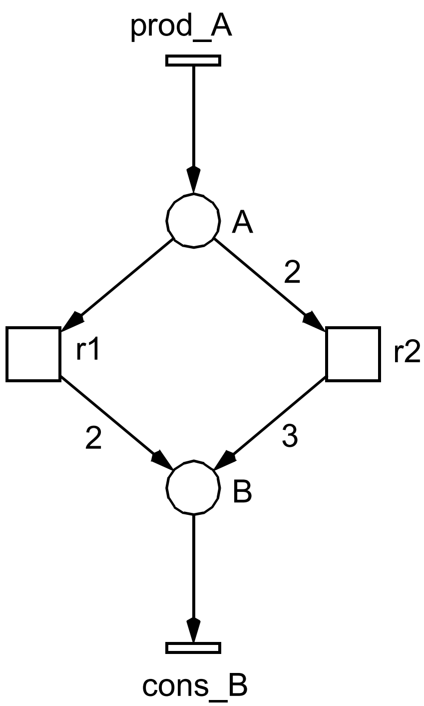
T-INVARIANT 1



T-INVARIANT 2

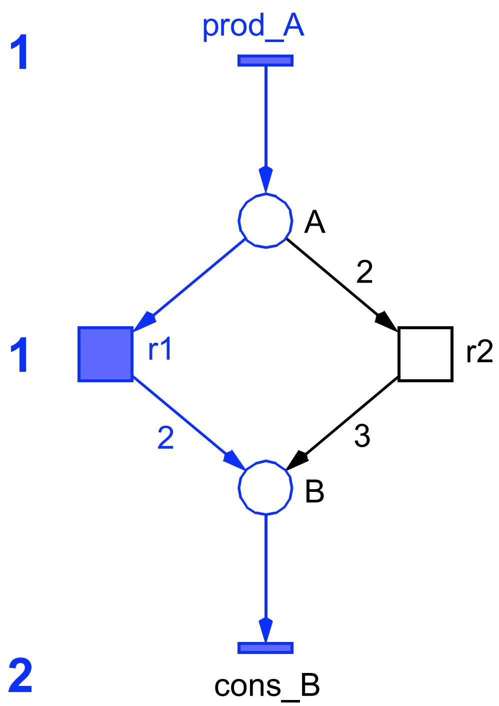
ADT-SETS, EX2

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

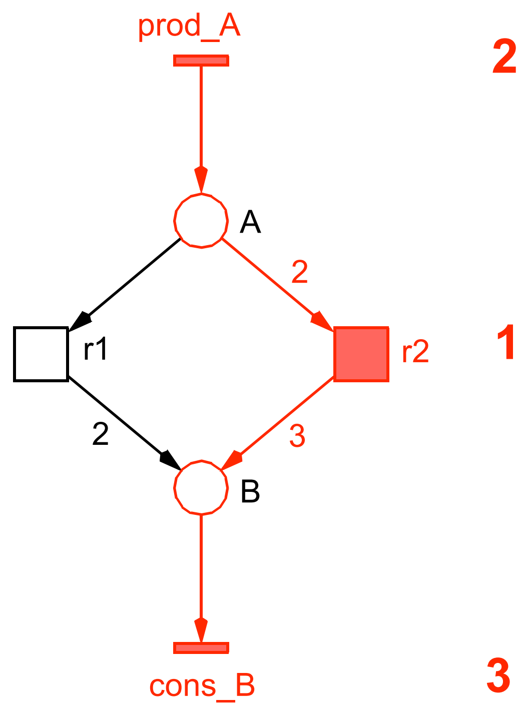


ADT-SETS, EX2

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



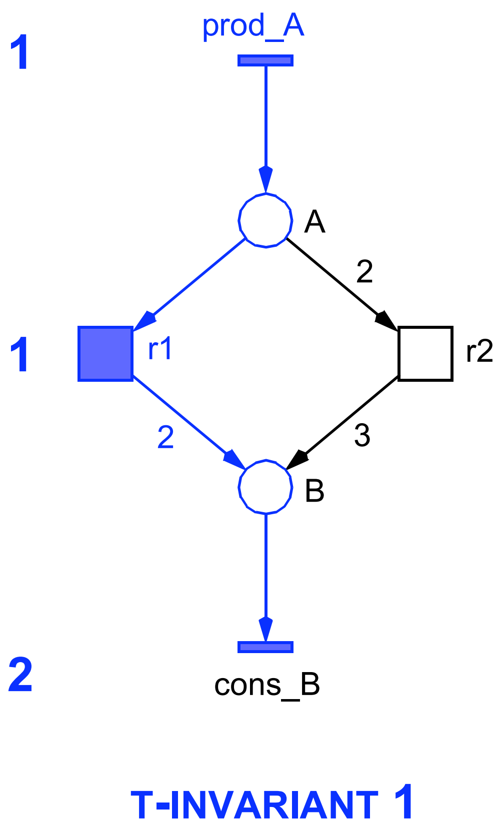
T-INVARIANT 1

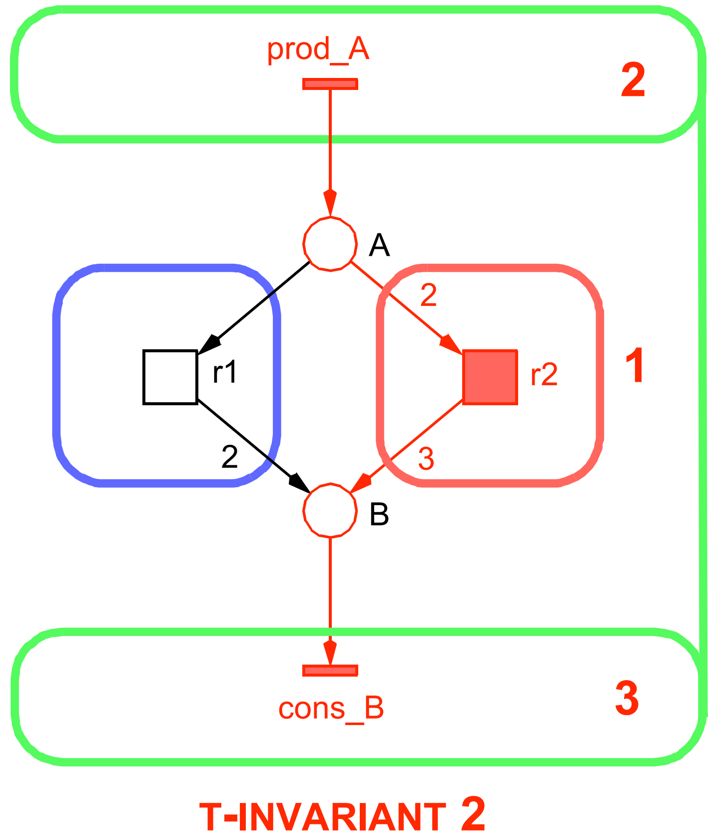


T-INVARIANT 2

ADT-SETS, EX2

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





ADT-SETS, INTERPRETATION

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

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

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

- **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**

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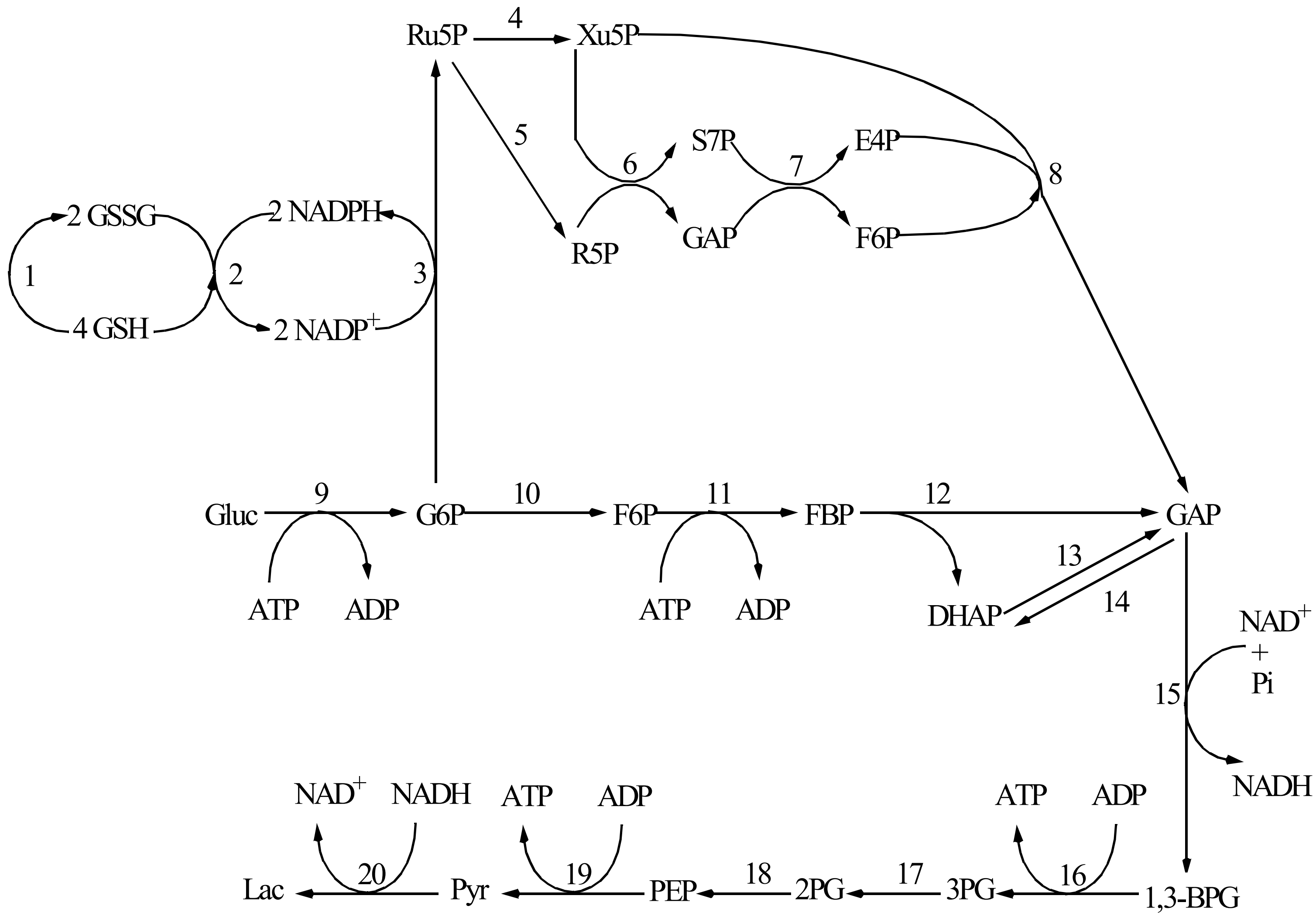
ADT-SETS, APPLICATIONS

- **maximal ADT-sets**
  - -> *not necessarily connected*
- **further 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 functional units*
- **coarse network structure, what for?**
  - -> *set of T-invariants gets structured*
  - -> *better understanding of the net behaviour*

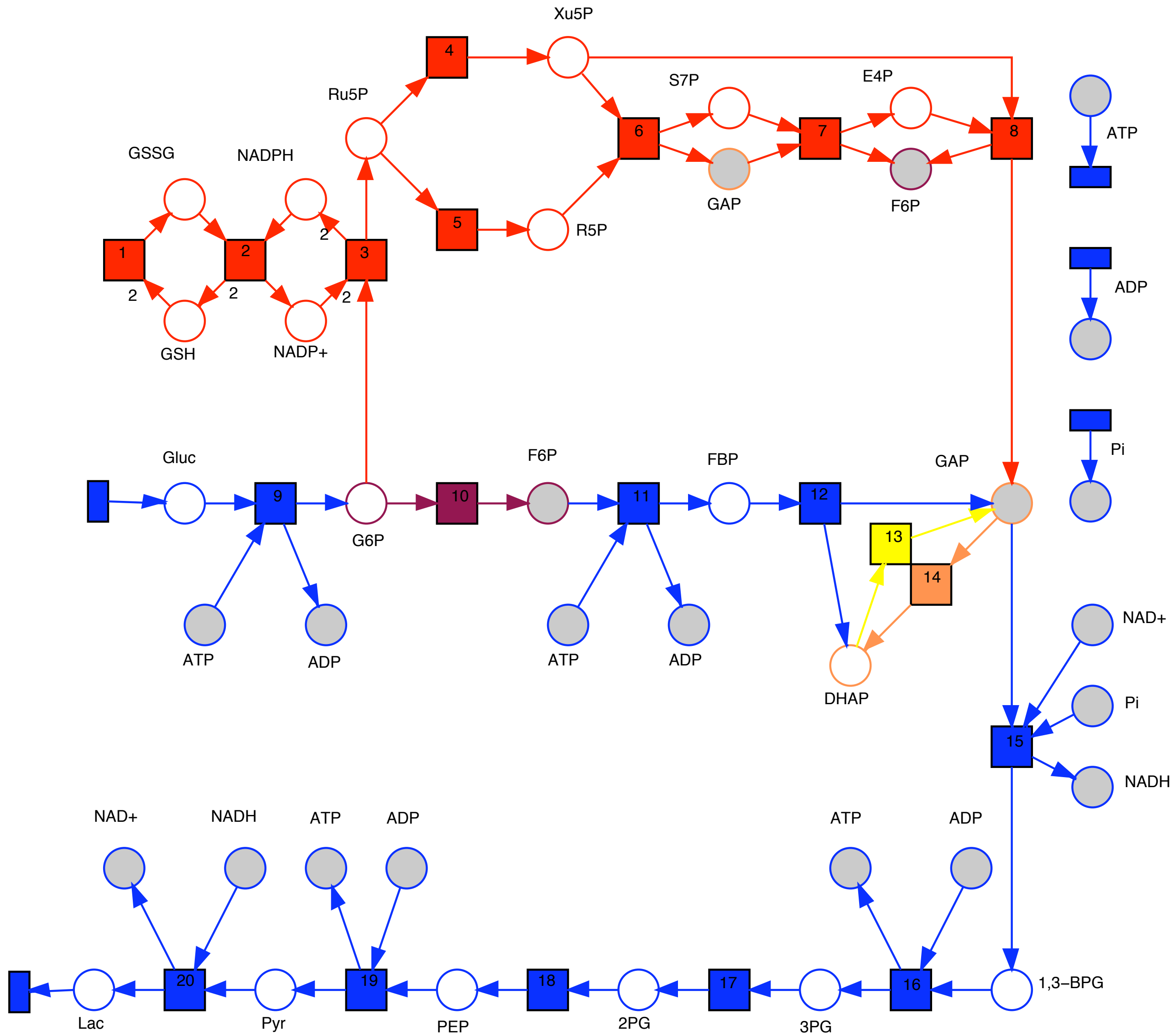
BIO PETRI NETS, SOME EXAMPLES

Ex1 - Glycolysis and Pentose Phosphate Pathway

[Reddy 1993]



Ex1 - Glycolysis and Pentose Phosphate Pathway



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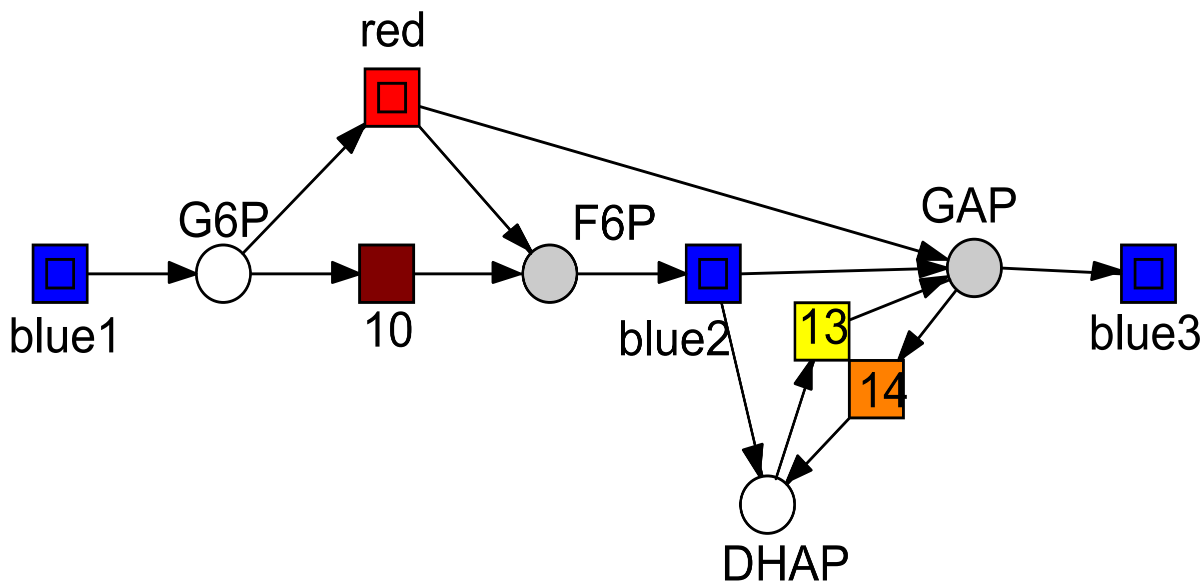

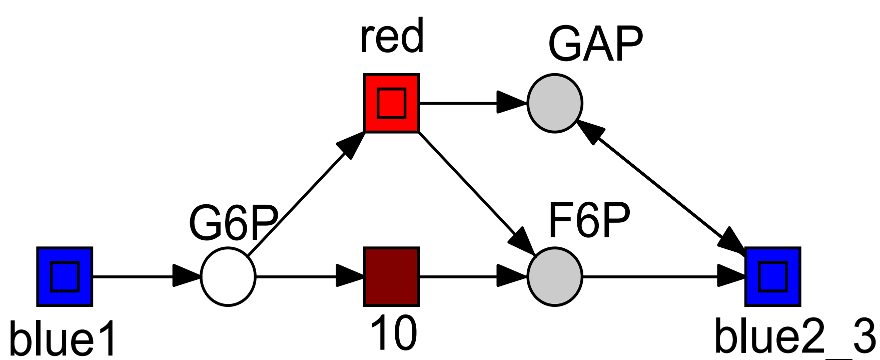

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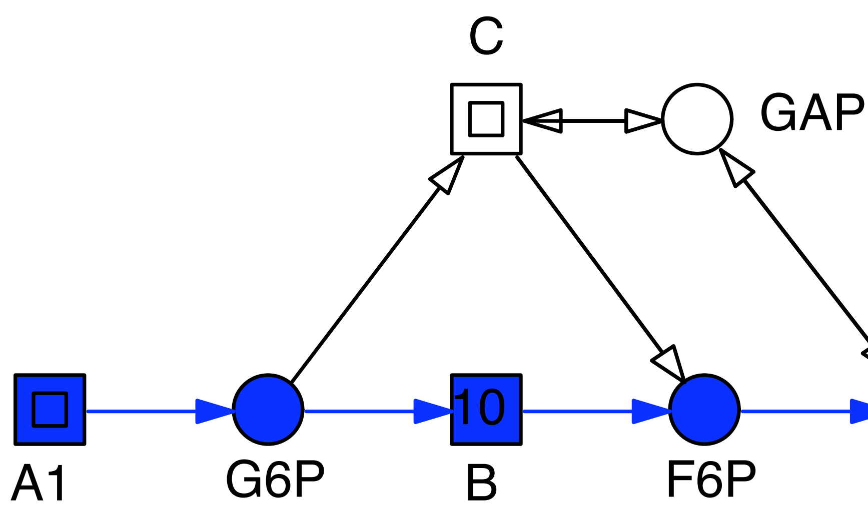
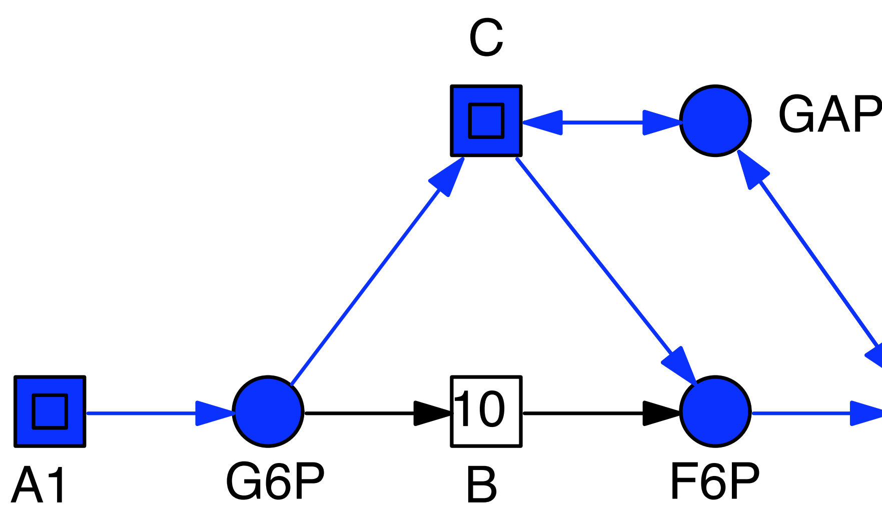
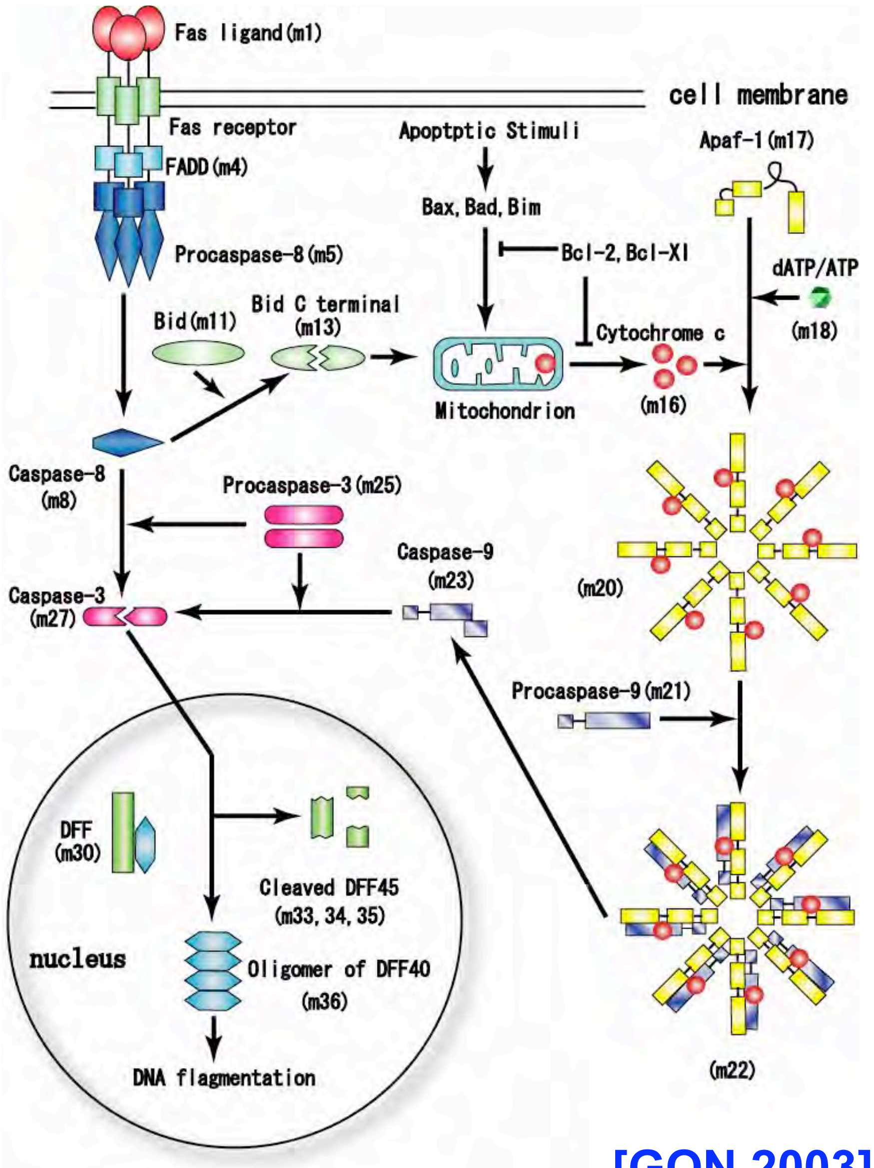


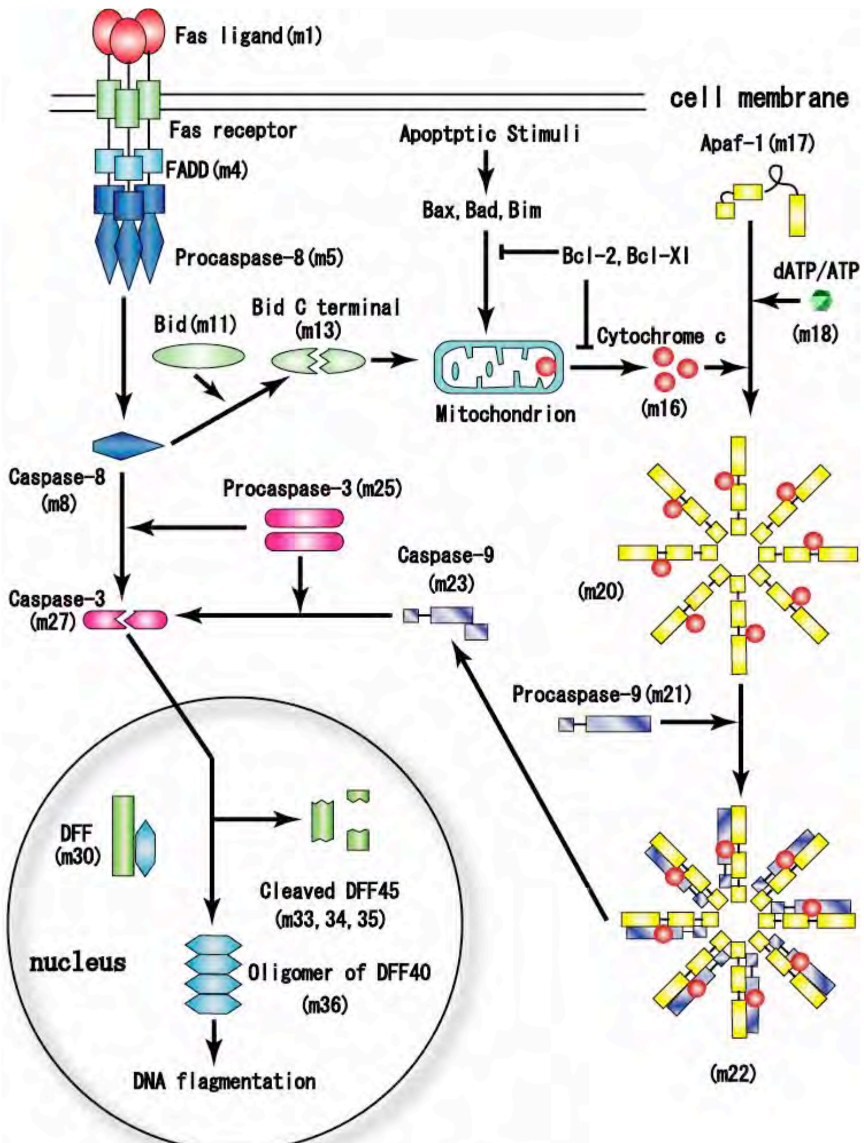


EX2: APOPTOSIS IN MAMMALIAN CELLS

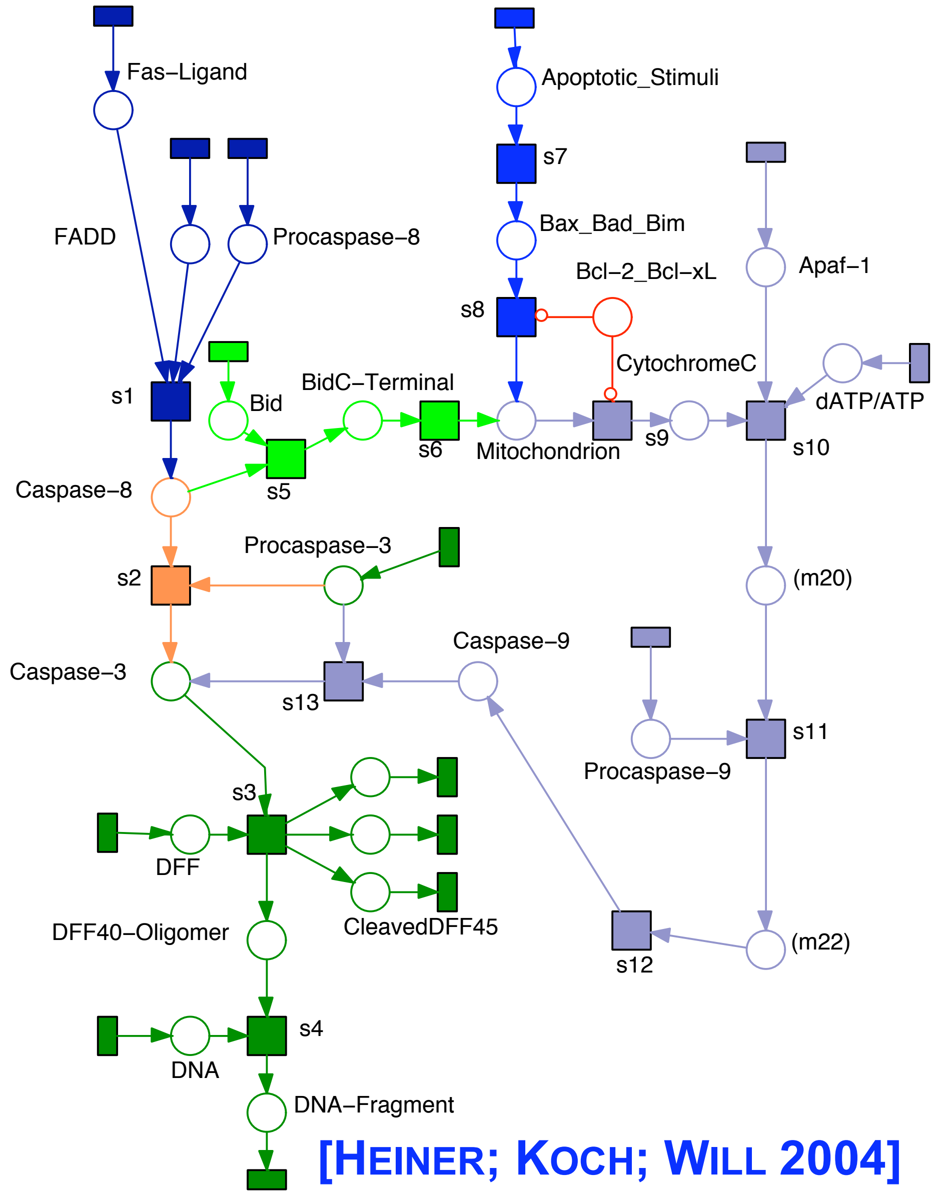


[GON 2003]

Ex2: Apoptosis in Mammalian Cells

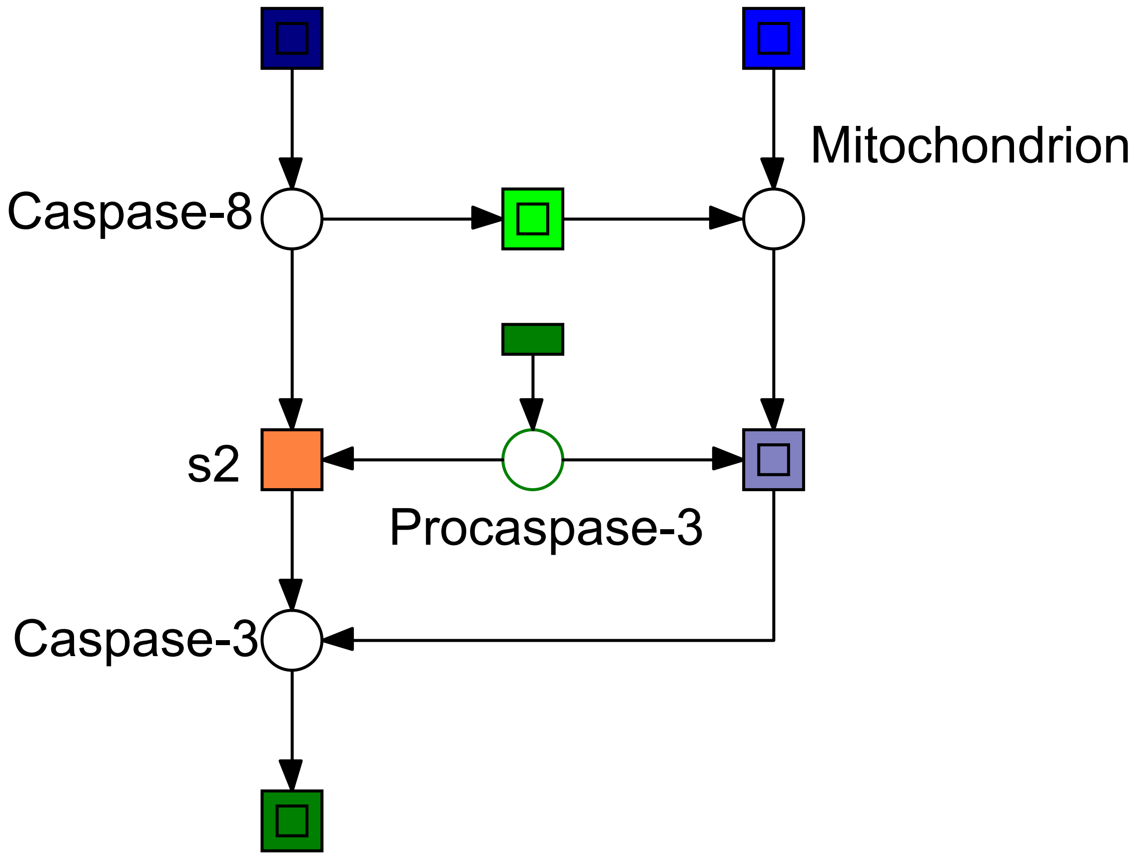


[GON 2003]

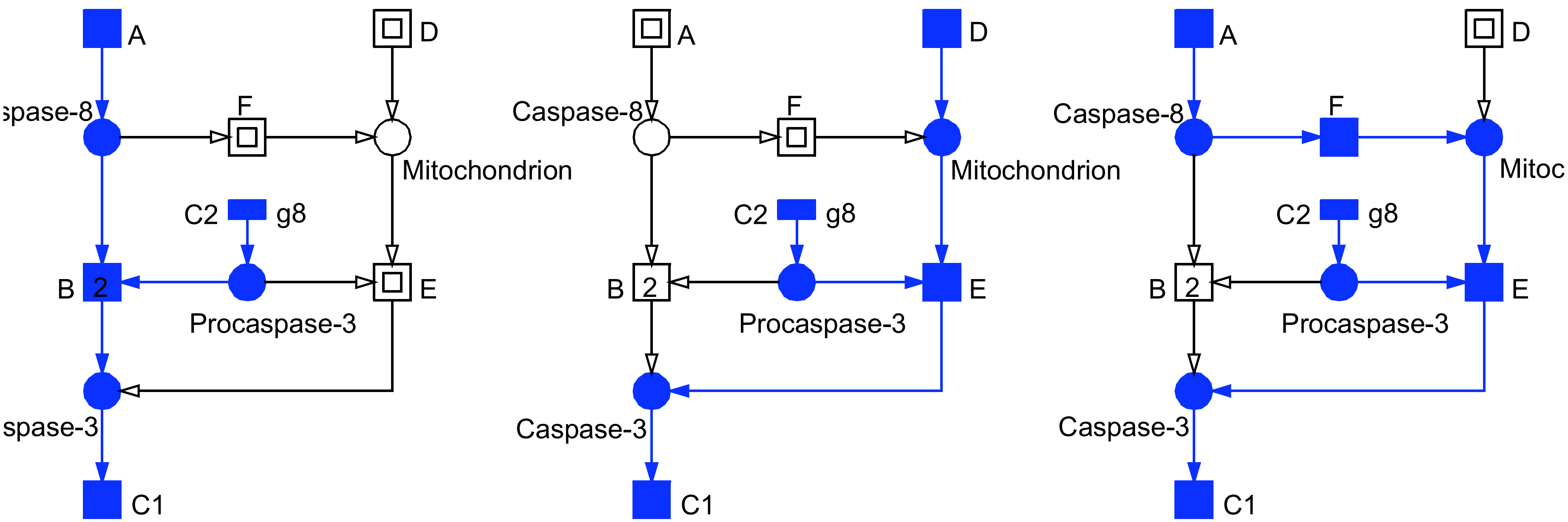


[Heiner; Koch; Will 2004]

Ex2: Apoptosis in Mammalian Cells



Ex2: Apoptosis in Mammalian Cells



Ex3 - Carbon Metabolism in Potato Tuber

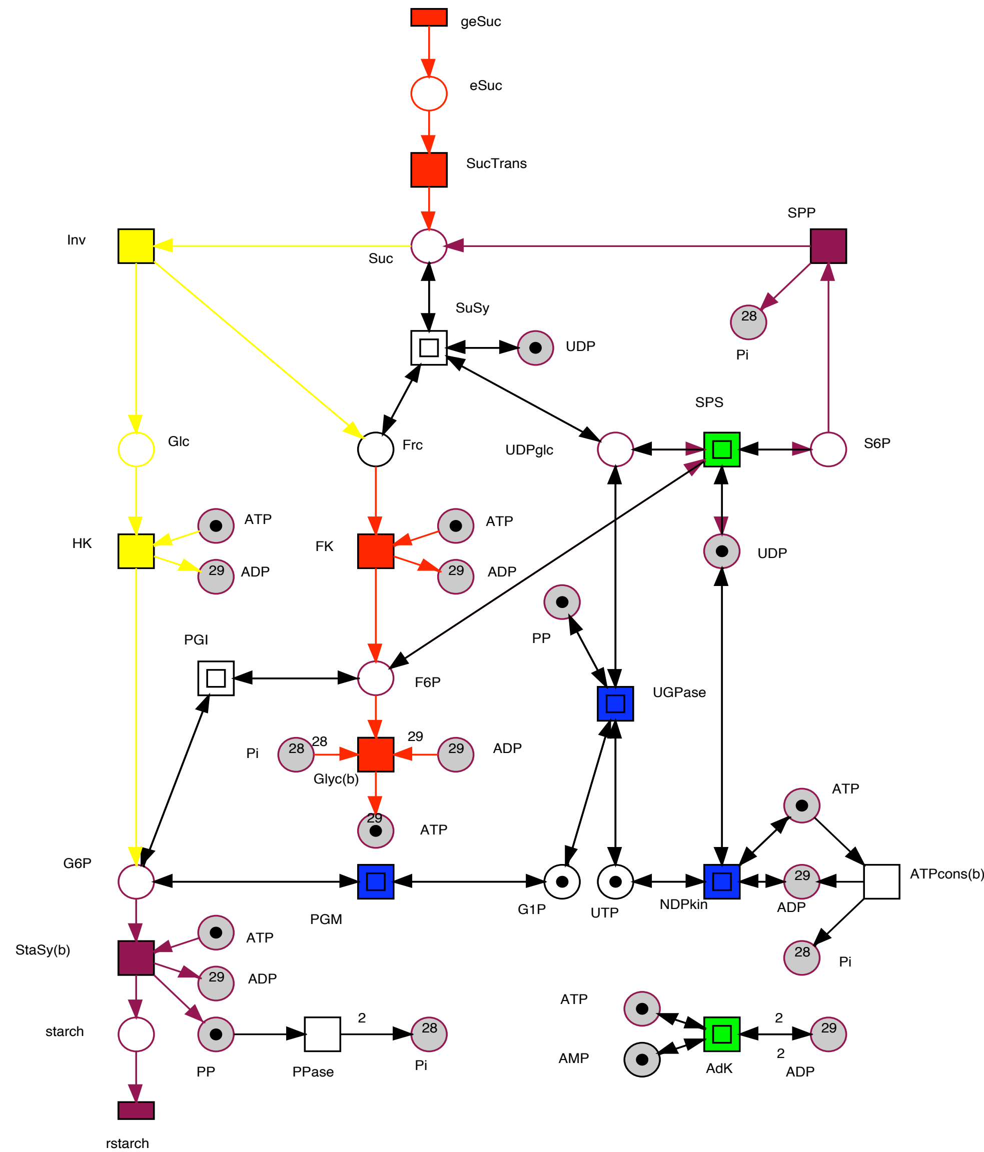
[KOCH; JUNKER; HEINER 2005]

ADT-sets without trivial T-invariants

Ex3 - Carbon Metabolism in Potato Tuber

[KOCH; JUNKER; HEINER 2005]

ADT-sets without trivial T-invariants



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 --

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

CORE NETWORK IDENTIFICATION

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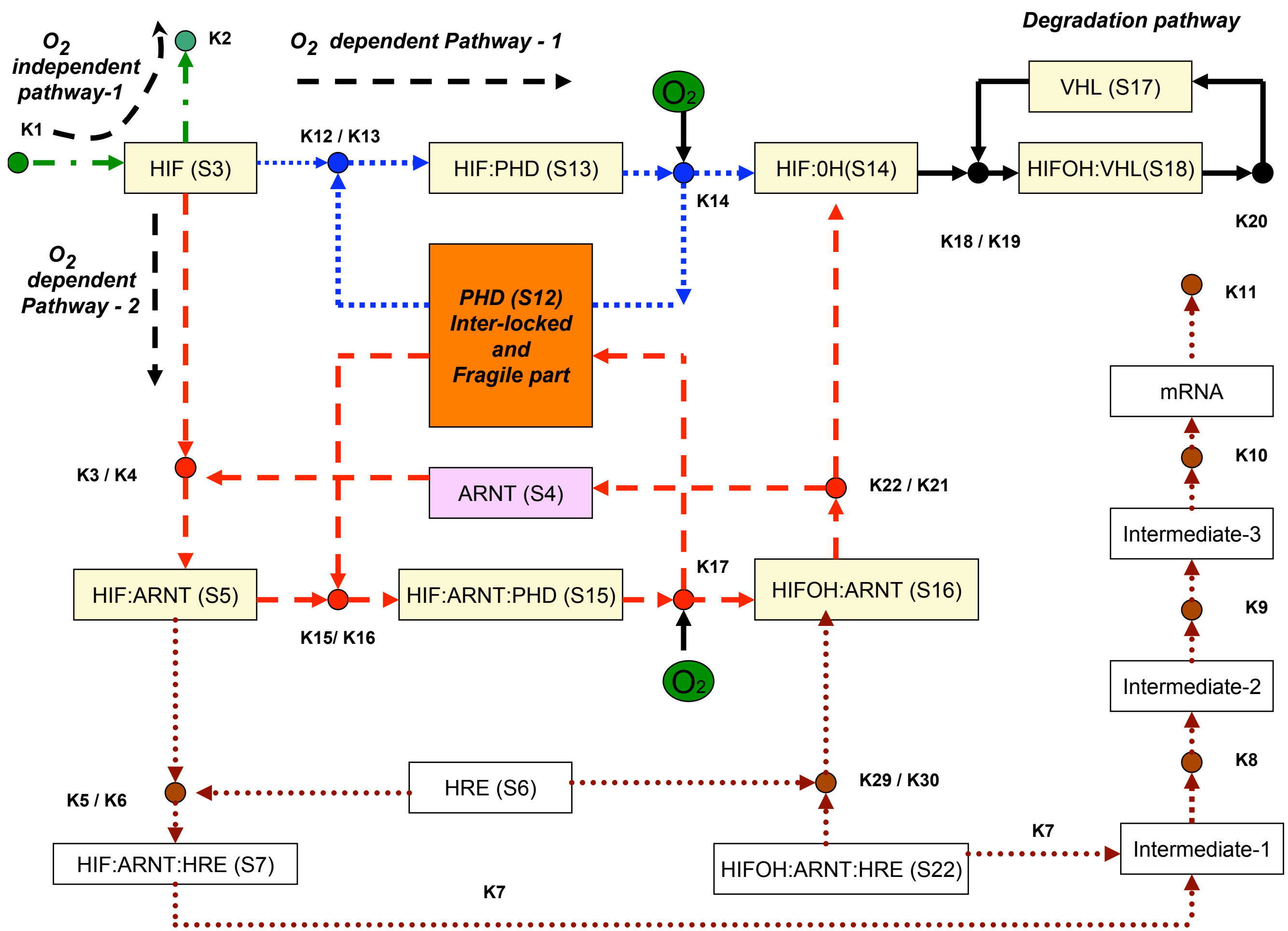
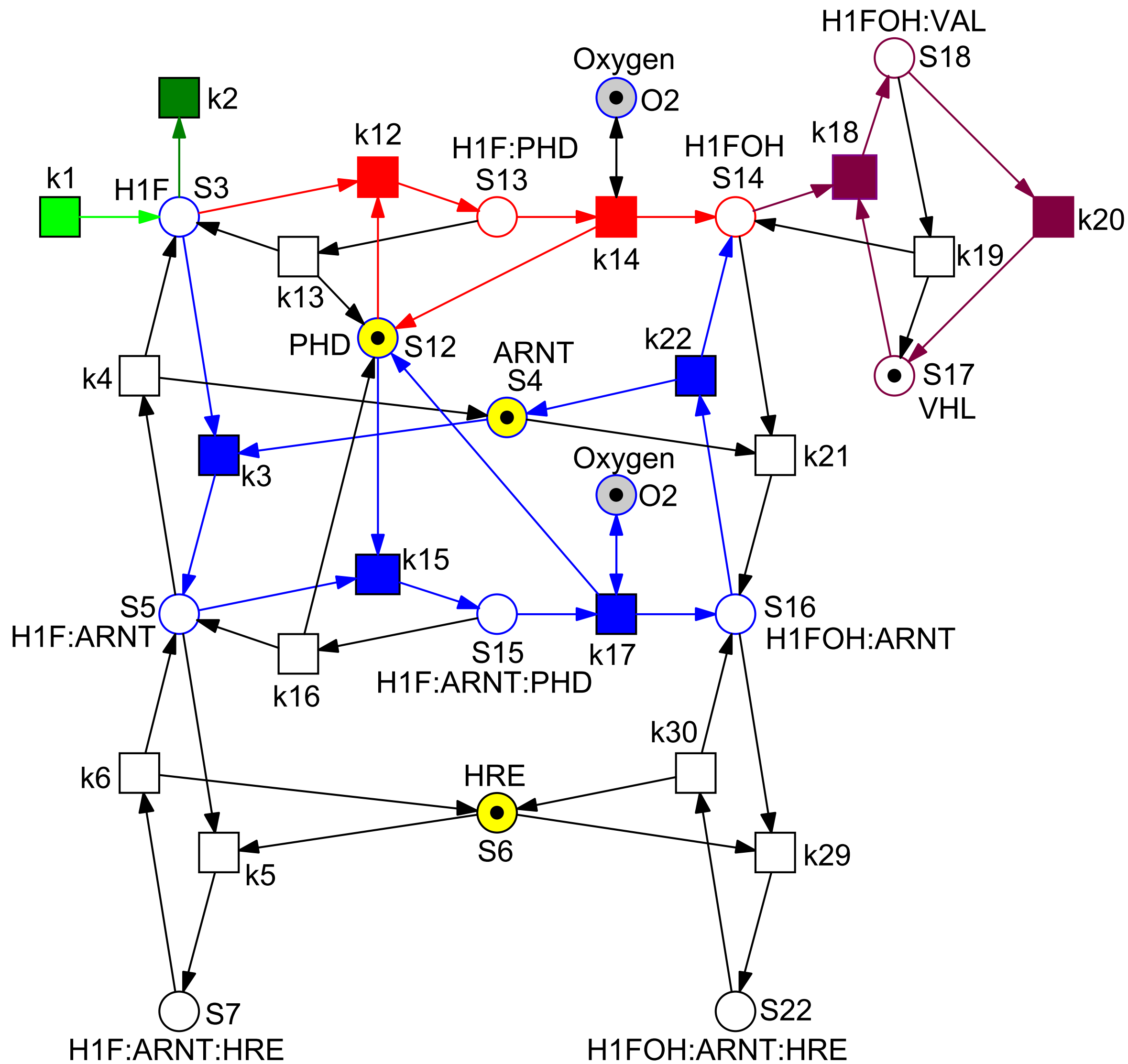
Ex - Hypoxia

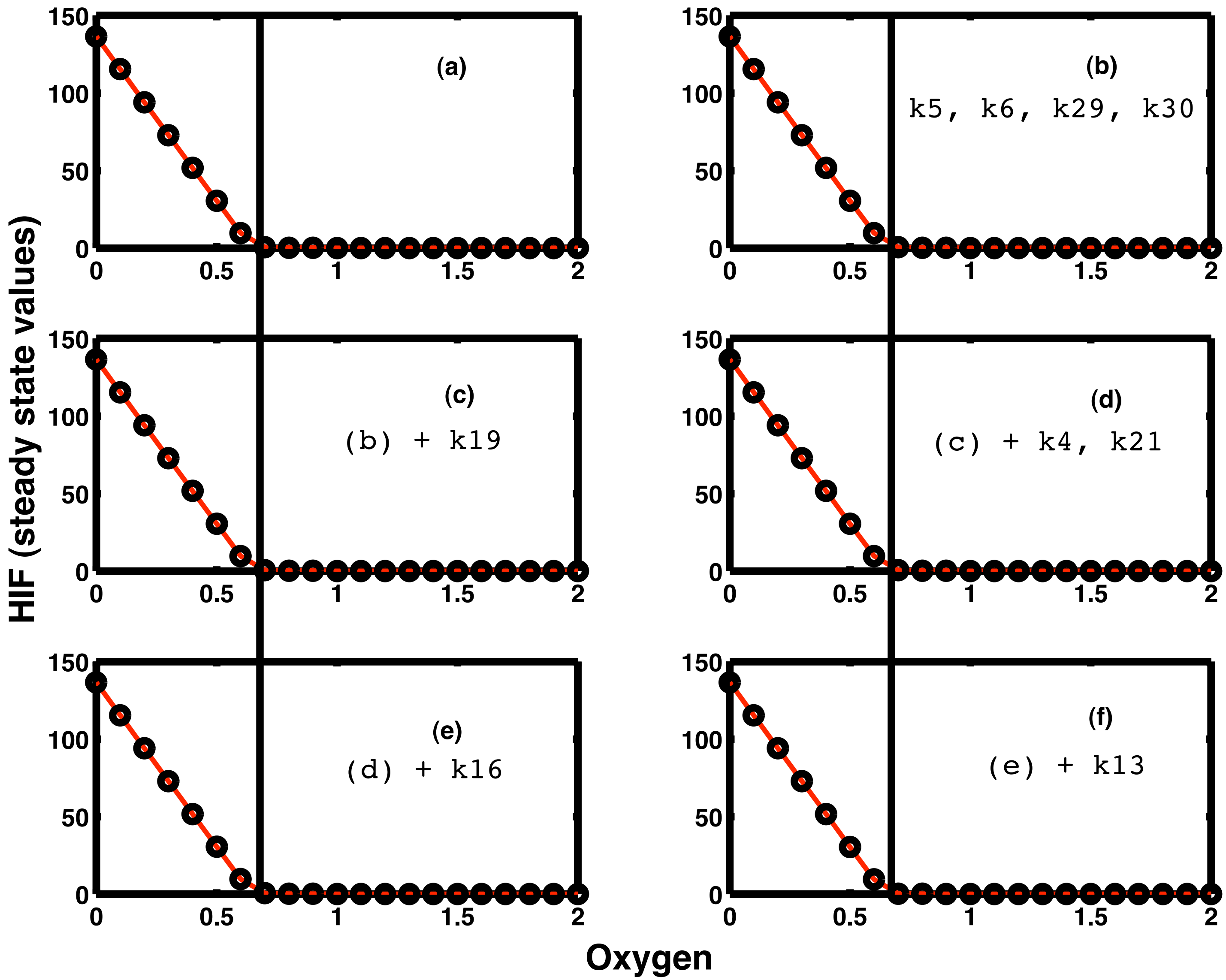
[Yu et al. 2007]



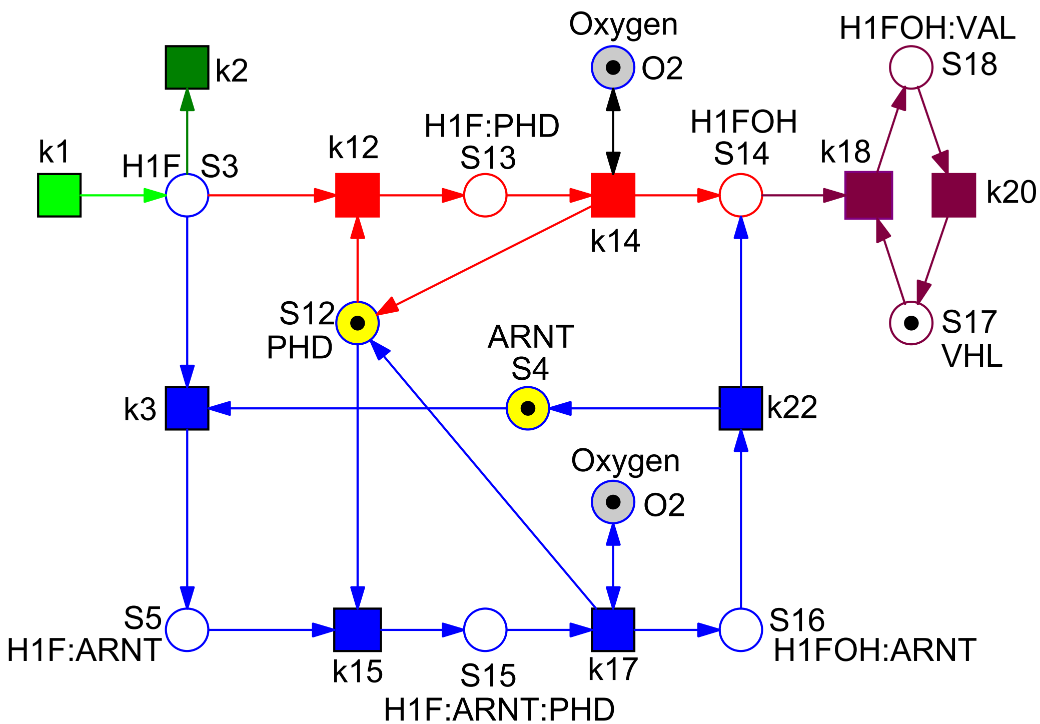
Ex - Hypoxia


H1FOH:VAL
S18
Oxygen
O2
k2
k12
H1F:PHD
S13
H1FOH
S14
k18
k1
H1F
S3
k14
k20
k13
k19
PHD
S12
ARNT
S4
k22
S17
VHL
k4
k3
k21
Oxygen
O2
k15
S5
H1F:ARNT
S15
H1F:ARNT:PHD
k17
S16
H1FOH:ARNT
k16
k30
k6
HRE
S6
k5
k29
S7
H1F:ARNT:HRE
S22
H1FOH:ARNT:HRE

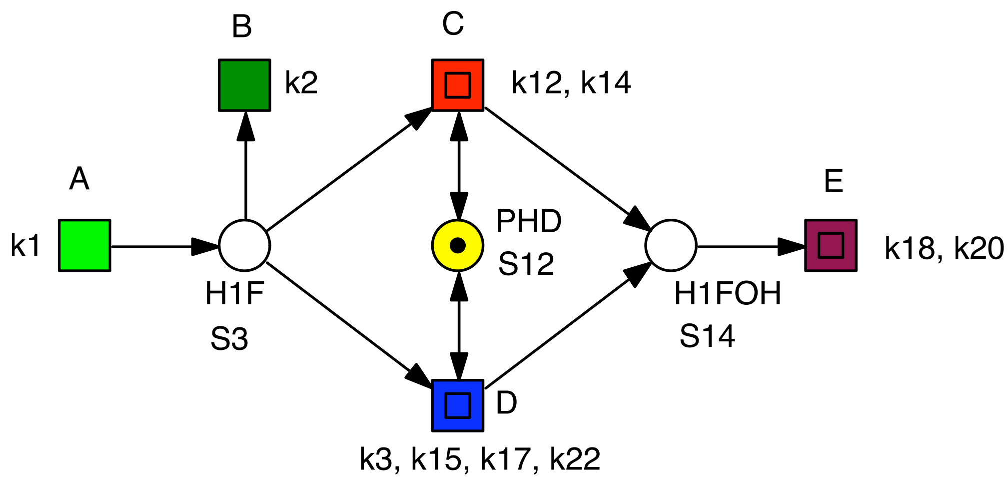
Ex - Hypoxia


(a)
(b)
k5, k6, k29, k30
(c)
(b) + k19
(d)
(c) + k4, k21
(e)
(d) + k16
(f)
(e) + k13
HIF (steady state values)
Oxygen
0
50
100
150
0
0.5
1
1.5
2

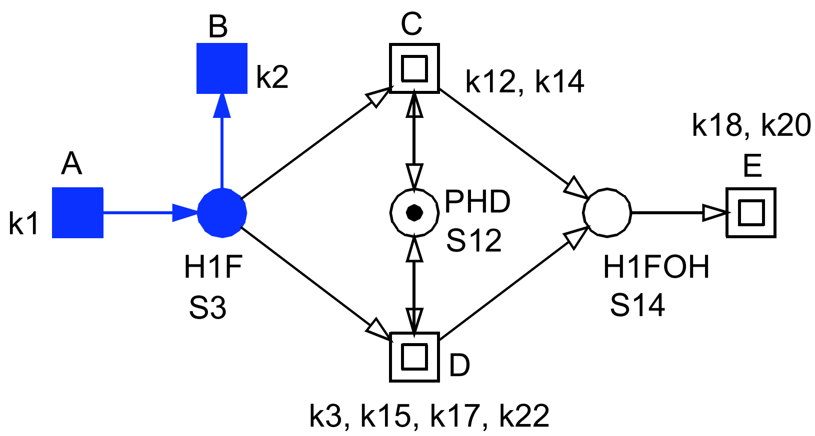
Ex - Hypoxia

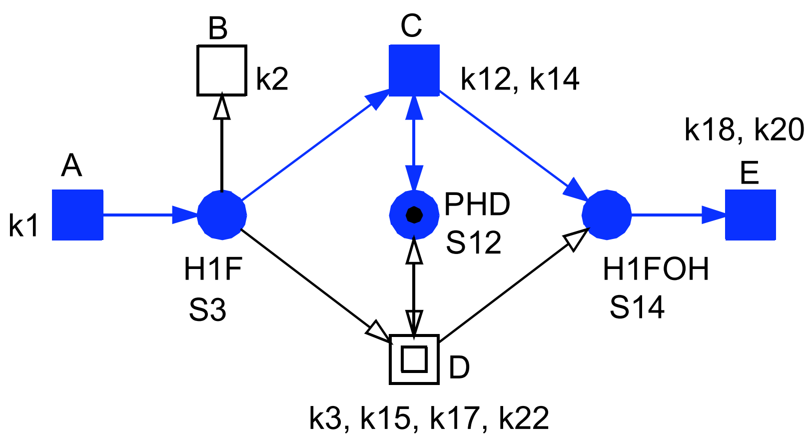

Oxygen
O2
H1FOH:VAL
S18
k2
k1
H1F
S3
k12
H1F:PHD
S13
H1FOH
S14
k18
k20
k14
S12
PHD
ARNT
S4
S17
VHL
k3
k22
Oxygen
O2
S5
H1F:ARNT
k15
S15
H1F:ARNT:PHD
k17
S16
H1FOH:ARNT

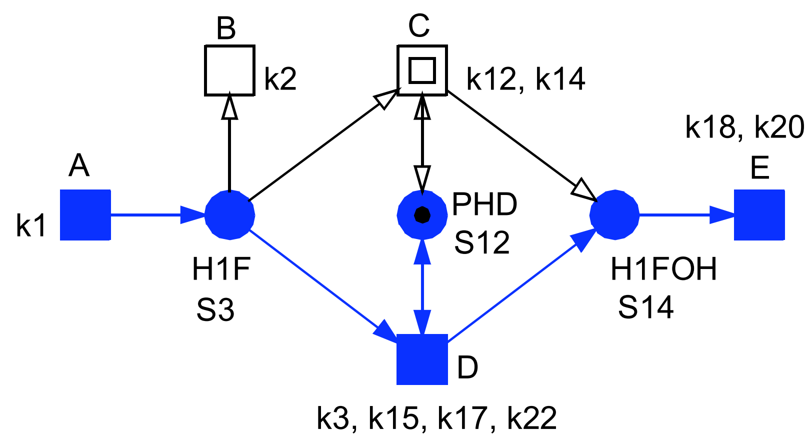
Ex - Hypoxia


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

Ex - Hypoxia


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


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


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

Static Analysis, Summary

- **subnetwork identification**
  - -> *P-invariants: token-preserving modules (mass conservation)*
  - -> *T-invariants: state-repeating modules (elementary modes)*
- **network validation**
  - -> *CPI (if closed model), CTI*
  - -> *no minimal P/T-invariant without biological interpretation*
  - -> *no known mass conservation without corresponding P-invariant*
  - -> *no known biological behaviour without corresponding T-invariant*
- **construction of initial marking**
- **sometimes decision of liveness**
- **choice of stochastic analysis techniques**
  - -> *bounded - analysis techniques, esp. analytic model checking*
  - -> *unbounded - simulation techniques, esp. simulative model checking*

REFERENCES

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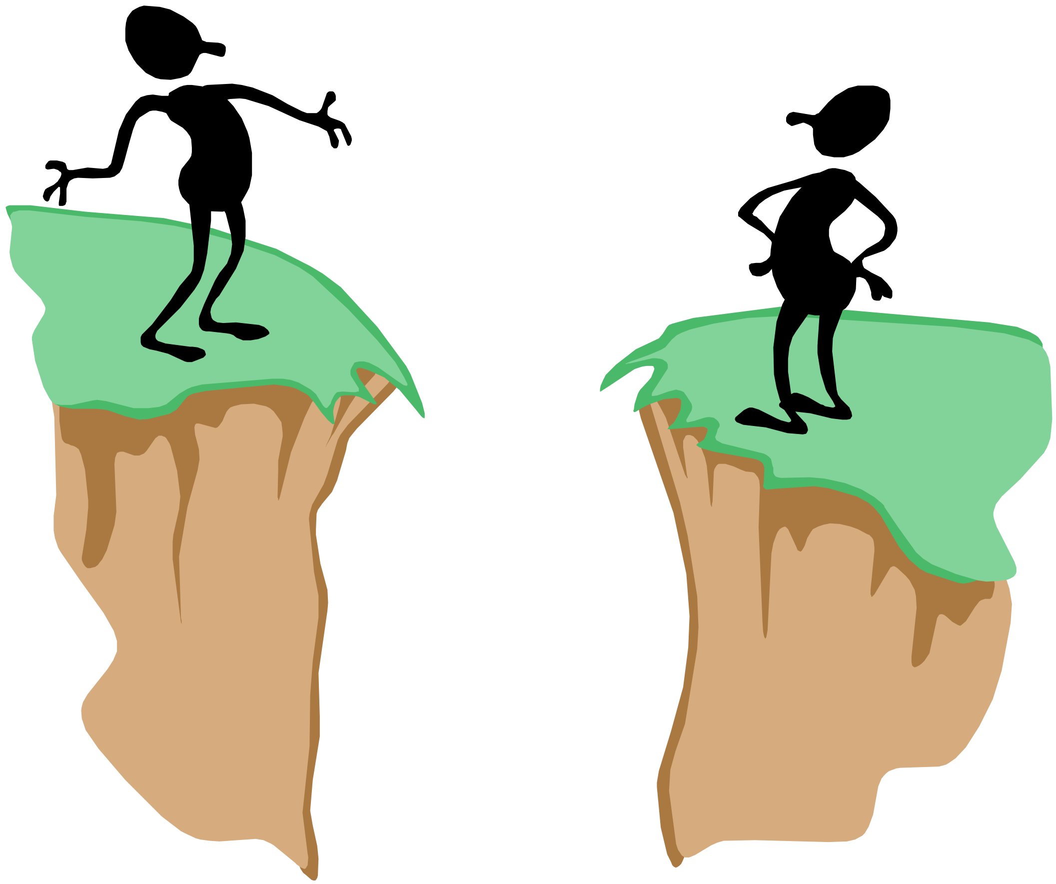
  PLoS ONE 5(1): e8600, doi:10.1371/journal.pone.0008600, January 2010.

THANKS !



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