

BME TUTORIAL - PART 3

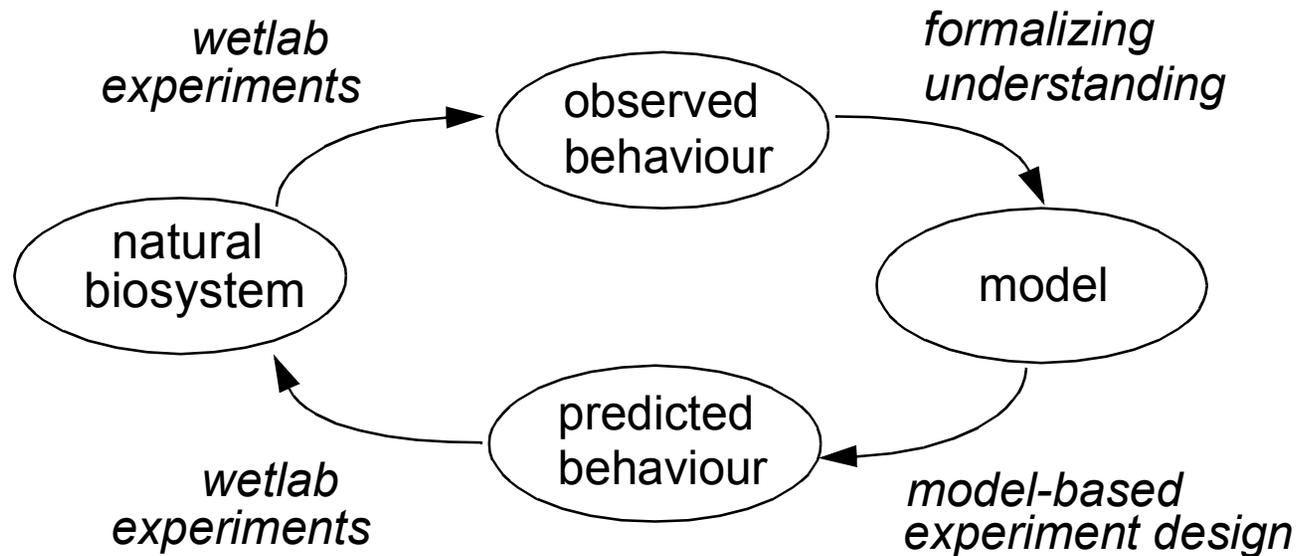
PN-BASED STATIC ANALYSIS OF BIOCHEMICAL NETWORKS

Rainer Breitling, Groningen, NL

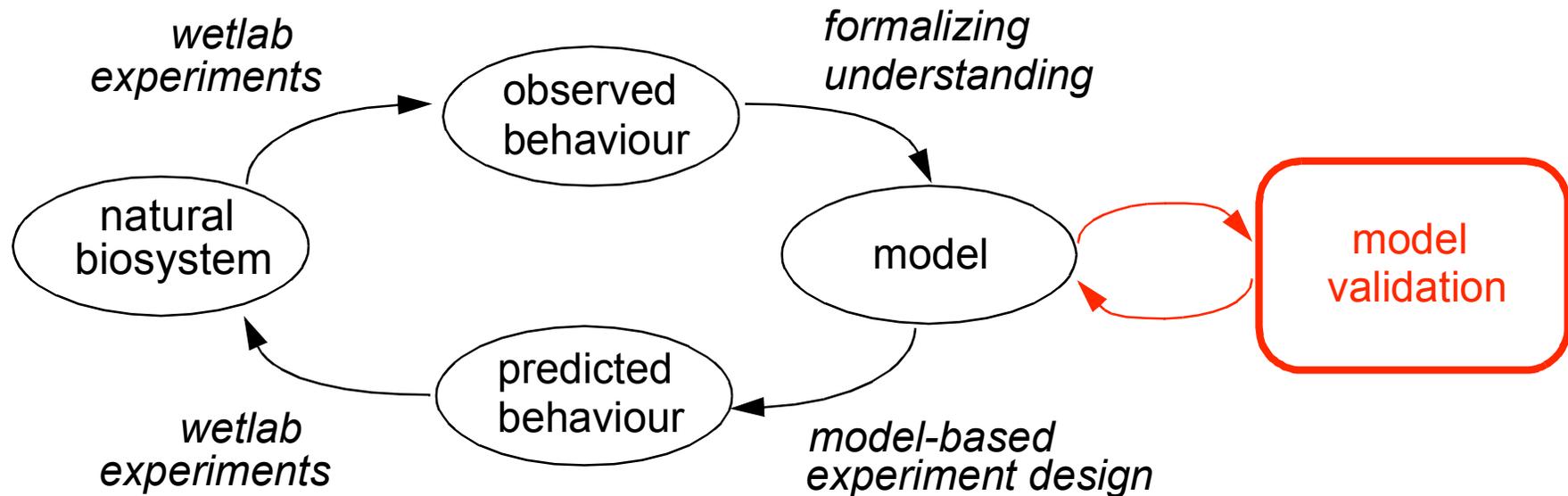
David Gilbert, London, UK

Monika Heiner, Cottbus, DE

MODELLING = FORMAL KNOWLEDGE REPRESENTATION

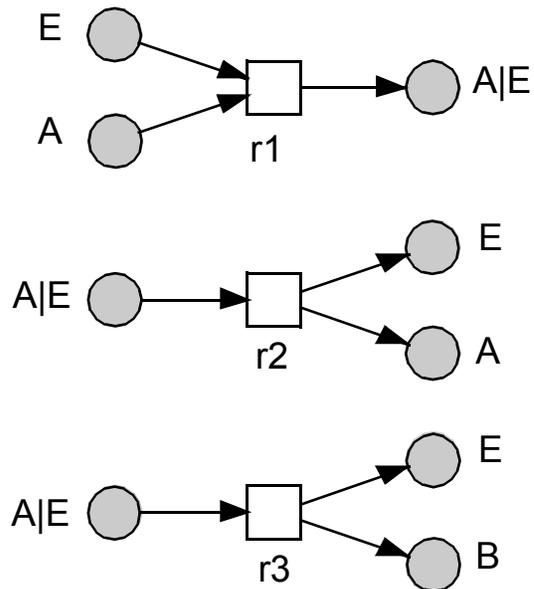


MODELLING = FORMAL KNOWLEDGE REPRESENTATION



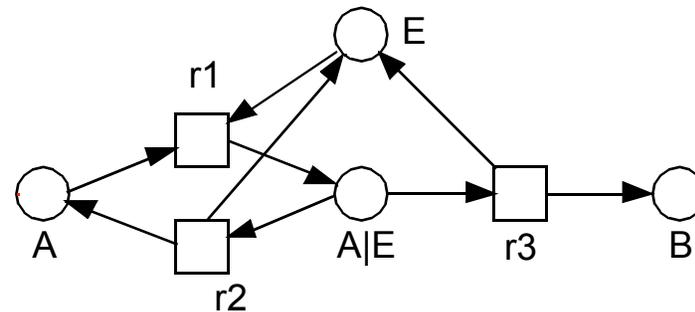
MODEL VALIDATION = CONFIDENCE INCREASE

reaction-centred view

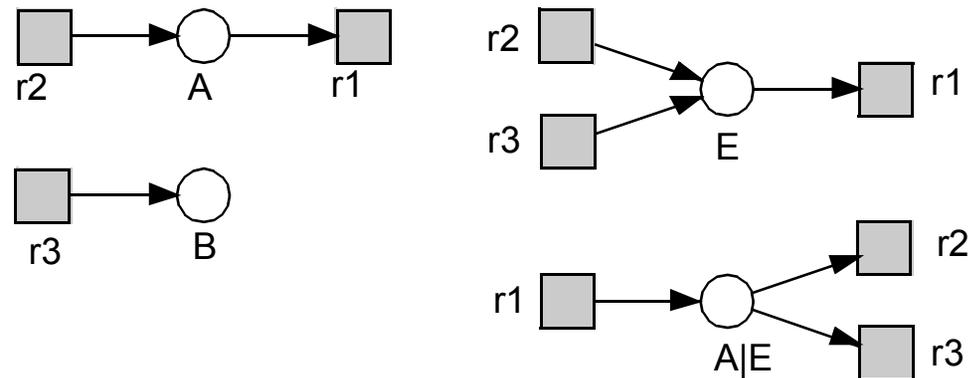


*logical nodes
(fusion nodes)*

process-oriented view



species-centred view



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

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

 - ❑ **net reduction**

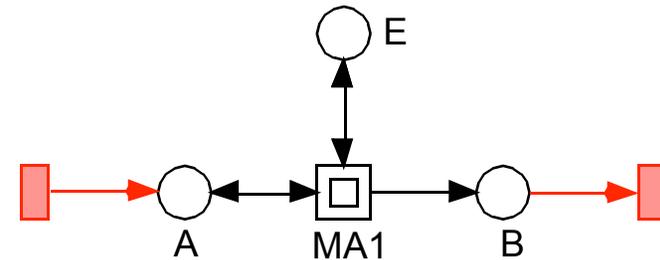
 - ❑ **invariants**
 - > *P-invariants - mass-preserving modules*
 - > *T-invariants - state-repeating modules*

 - ❑ **abstract dependent transition sets (ADT-sets)**
 - > *define building blocks*

 - ❑ **some applications**
- > *to decide liveness (hopefully)*
- > *to decide boundedness*

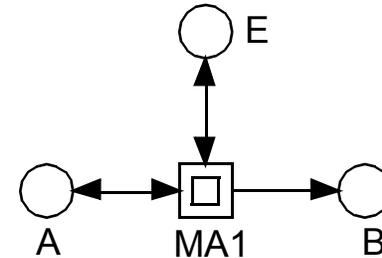
□ boundary nodes

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



□ conservative -> BND

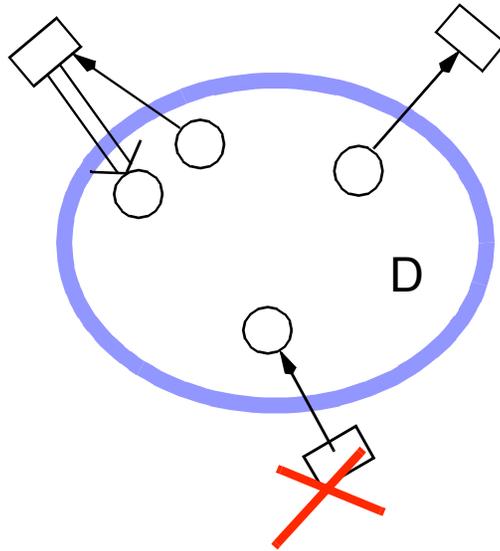
- > *all transitions preserve token number*



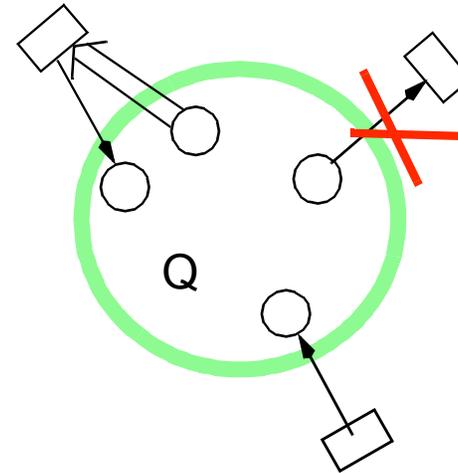
□ Deadlock-Trap Property (DTP)

DEADLOCK TRAP PROPERTY (DTP)

Deadlock D
 $FD \subseteq DF$



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

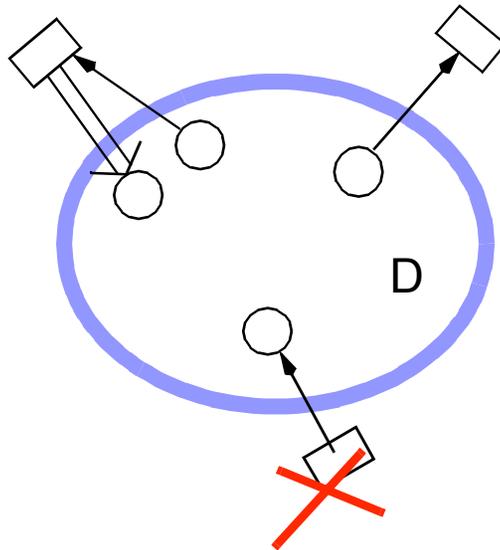


Trap Q
 $QF \subseteq FQ$

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

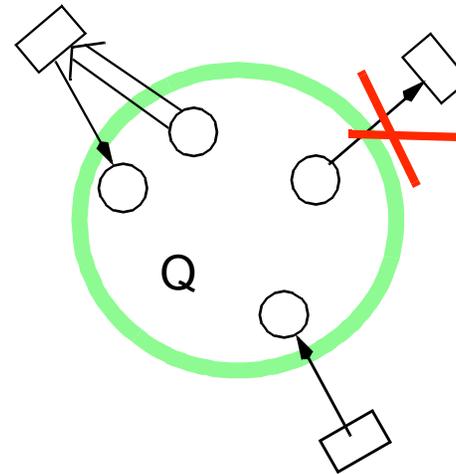
DEADLOCK TRAP PROPERTY (DTP)

Deadlock D
 $FD \subseteq DF$



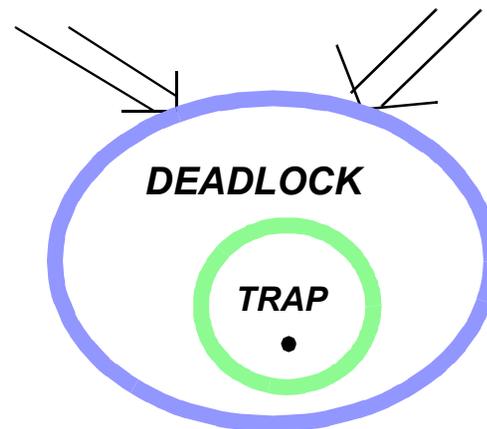
any transition putting token into the set
 also takes token from it:
 an empty deadlock will never get marked

Trap Q
 $QF \subseteq FQ$



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)



- allow to decide liveness, sometimes

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

□ allow to decide liveness, sometimes

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

□ some examples, where it helps

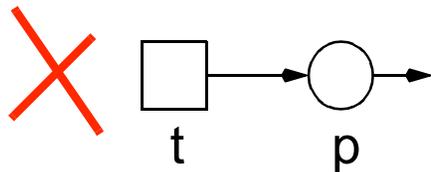
- > RKIP pathway (BND): ES & DTP -> live*
- > MAPK cascade (BND): DTP & nES -> no DSt*

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

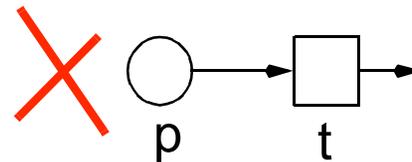
- downsizing the net structure while preserving some properties

-> *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 -> . . .

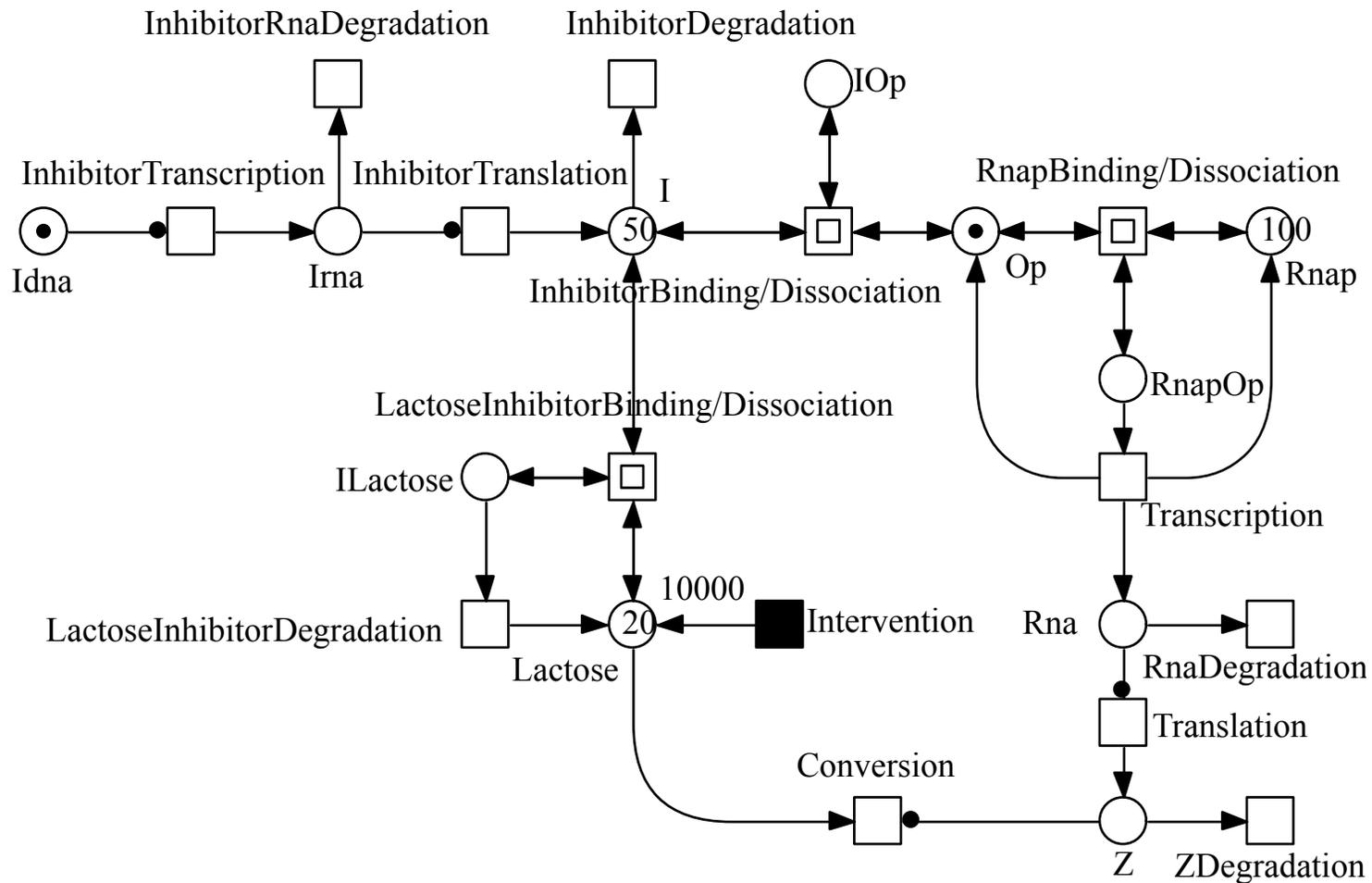
- several sets of reduction rules - **INA/HUB**

-> *relatively weak, in general*

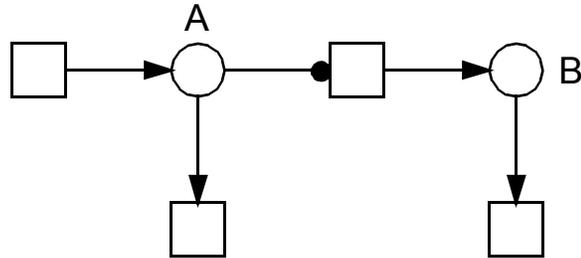
-> *sensitive to the order they are applied*

-> *however, sometimes they help*

❑ lac operon (Wilkinson 2006)



❑ lac operon, reduced by INA/HUB



❑ liveness becomes obvious

PUR	ORD	HOM	NBM	CSV	SCF	CON	SC	FT0	TF0	FPO	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	-	-	-	

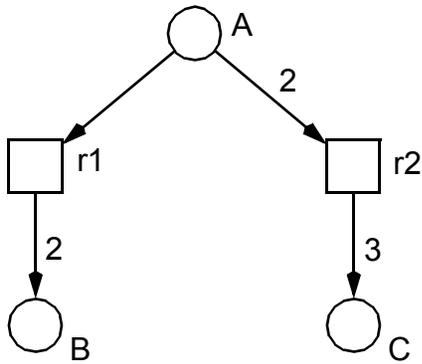
NET INVARIANTS, A CRASH COURSE

$r1: A \rightarrow 2 B$

$r2: 2 A \rightarrow 3 C$

$r1: A \rightarrow 2 B$

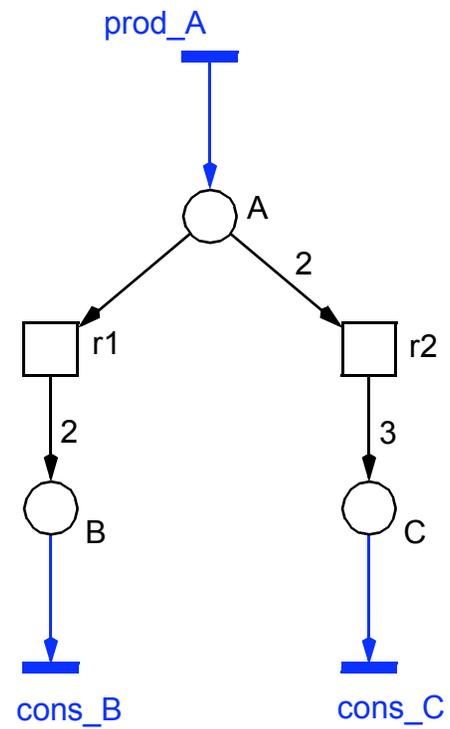
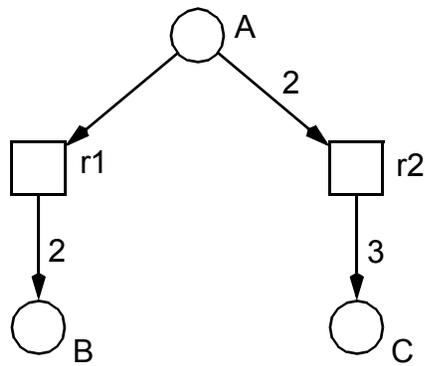
$r2: 2 A \rightarrow 3 C$



BIO PETRI NETS, EX1

$r1: A \rightarrow 2 B$

$r2: 2 A \rightarrow 3 C$



- a representation of the net structure

=> **stoichiometric matrix**

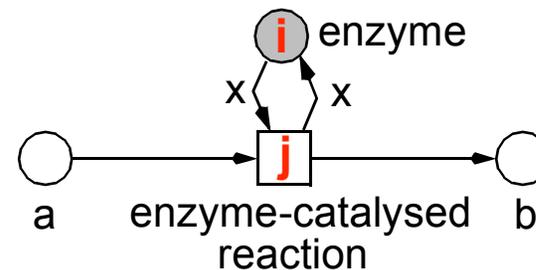
$C =$

P \ T	t1	...	tj	...	tm
p1					
pi			c_{ij}		
⋮			Δt_j		
pn					

$$c_{ij} = (p_i, t_j) = F(t_j, p_i) - F(p_i, t_j) = \Delta t_j(p_i)$$

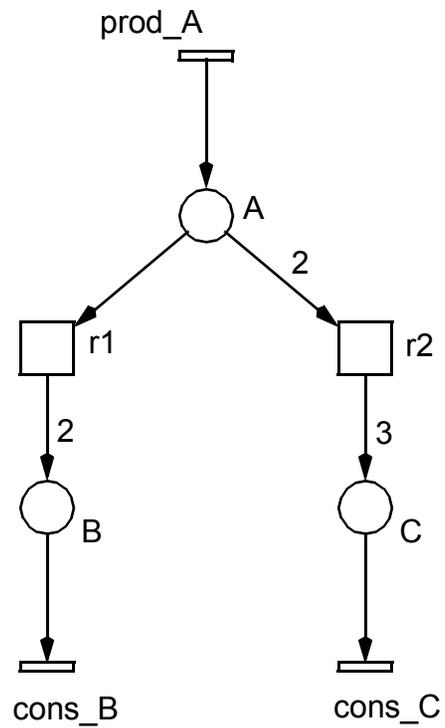
$$\Delta t_j = \Delta t_j^*$$

- matrix entry c_{ij} :
token change in place p_i by firing of transition t_j
- matrix column Δt_j :
vector describing the change of the whole marking by firing of t_j
- side-conditions are neglected

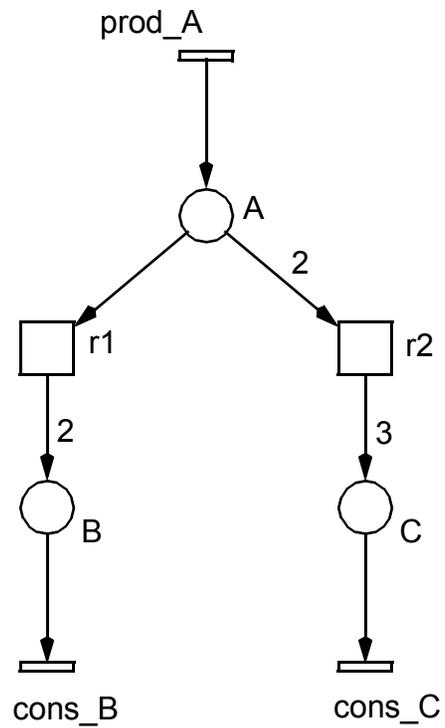


$c_{ij} = 0$

INCIDENCE MATRIX C, EX1

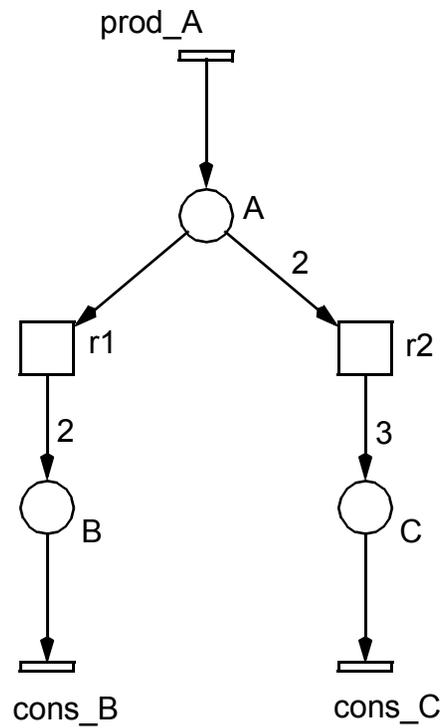


INCIDENCE MATRIX C, EX1



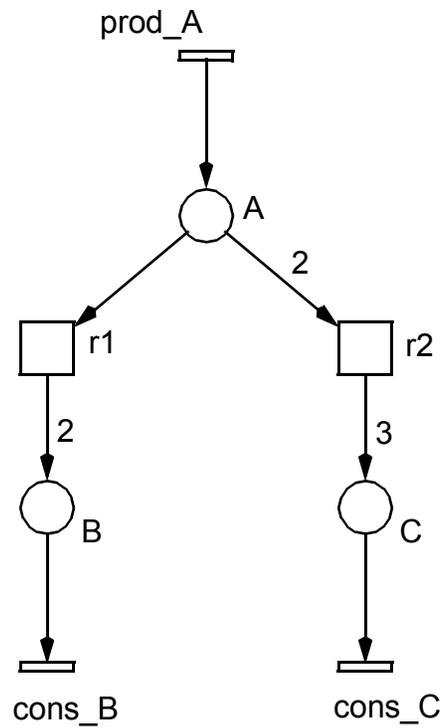
P \ T	r1	r2	prod_A	cons_B	cons_C
A					
B					
C					

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



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

1

1

2

❑ Lautenbach, 1973

❑ T-invariants

-> integer solutions x of $Cx = 0, x \neq 0, x \geq 0$

❑ 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

$$kx = \sum_i a_i x_i$$

❑ Covered by T-Invariants (CTI)

-> each transition belongs to a T-invariant

-> **BND & LIVE => CTI (necessary condition)**

-> **Schuster, 1993**

-> *multisets of transitions*

-> *Parikh vector*

-> *sets of transitions*

- ❑ **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 occurring one after the other
 - > *substance / signal flow*

 2. *relative transition firing rates* **-> steady state behaviour**
of transitions occurring 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*

- **T-invariants = (multi-) sets of transitions = Parikh vector**

 - > *zero effect on marking*

 - > *reproducing a marking / system state*

- **two interpretations**

 - 1. *partially ordered transition sequence*
of transitions occurring one after the other

 - > **behaviour understanding**

 - > *substance / signal flow*

 - 2. *relative transition firing rates*
of transitions occurring permanently & concurrently

 - > **steady state behaviour**

 - > *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*

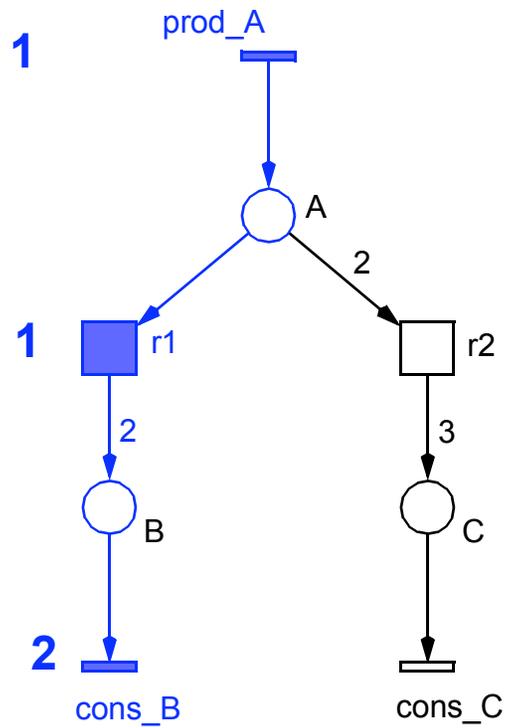
- ❑ **T-invariants = (multi-) sets of transitions = Parikh vector**
 - > *zero effect on marking*
 - > *reproducing a marking / system state*

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

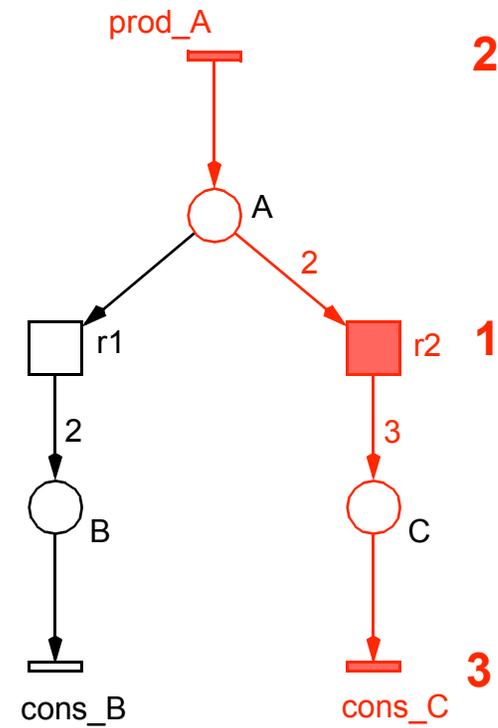
- ❑ **a minimal T-invariant defines a connected subnet**
 - > *the T-invariant's transitions (the support),*
 - + *all their pre- and post-places*
 - + *the arcs in between*
 - > *pre-set of support = post-set of support*

T-INVARIANTS, EX1

$r1: A \rightarrow 2 B$
 $r2: 2 A \rightarrow 3 C$



T-INVARIANT 1



T-INVARIANT 2

❑ Lautenbach, 1973

❑ P-invariants

-> integer solutions y of

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

-> *multisets of places*

❑ minimal P-invariants

-> there is no P-invariant with a smaller support

-> *sets of places*

-> 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)*

- ❑ **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**

- ❑ **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*

- ❑ **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*

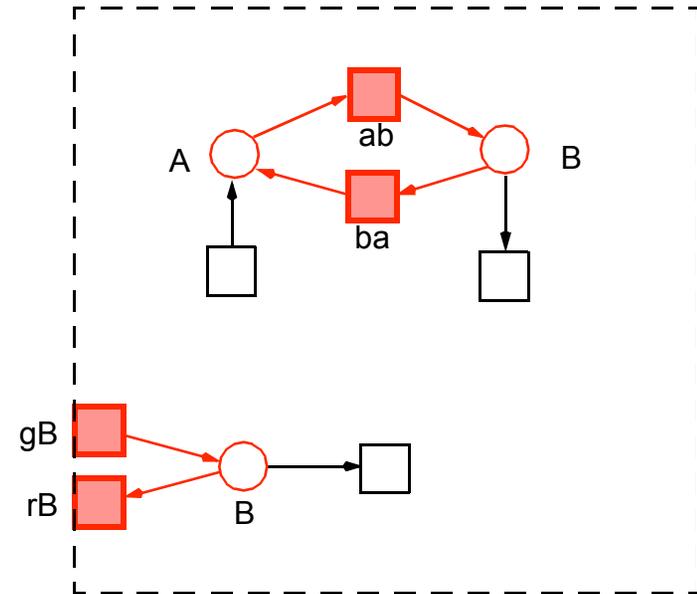
-> UNIQUE INITIAL MARKING <-

□ 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*

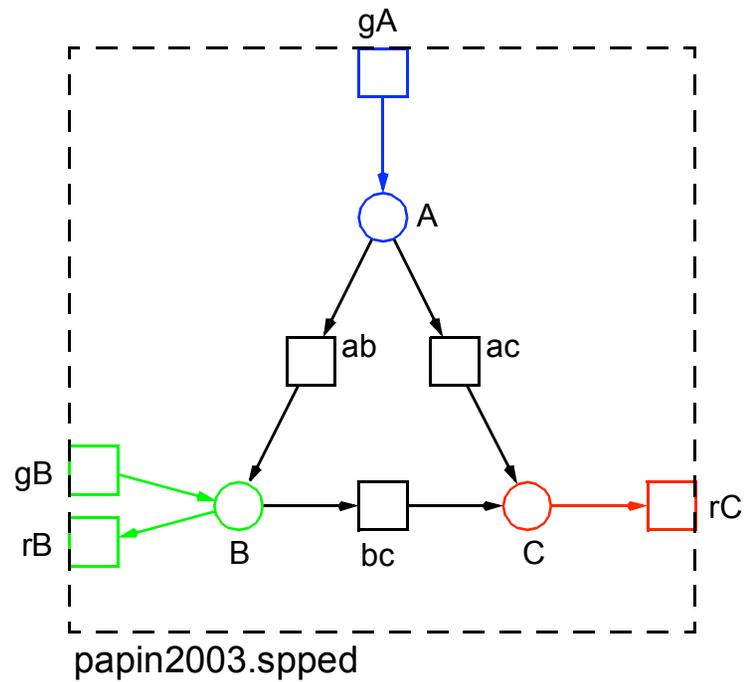


□ substances involved

-> *input substance A*

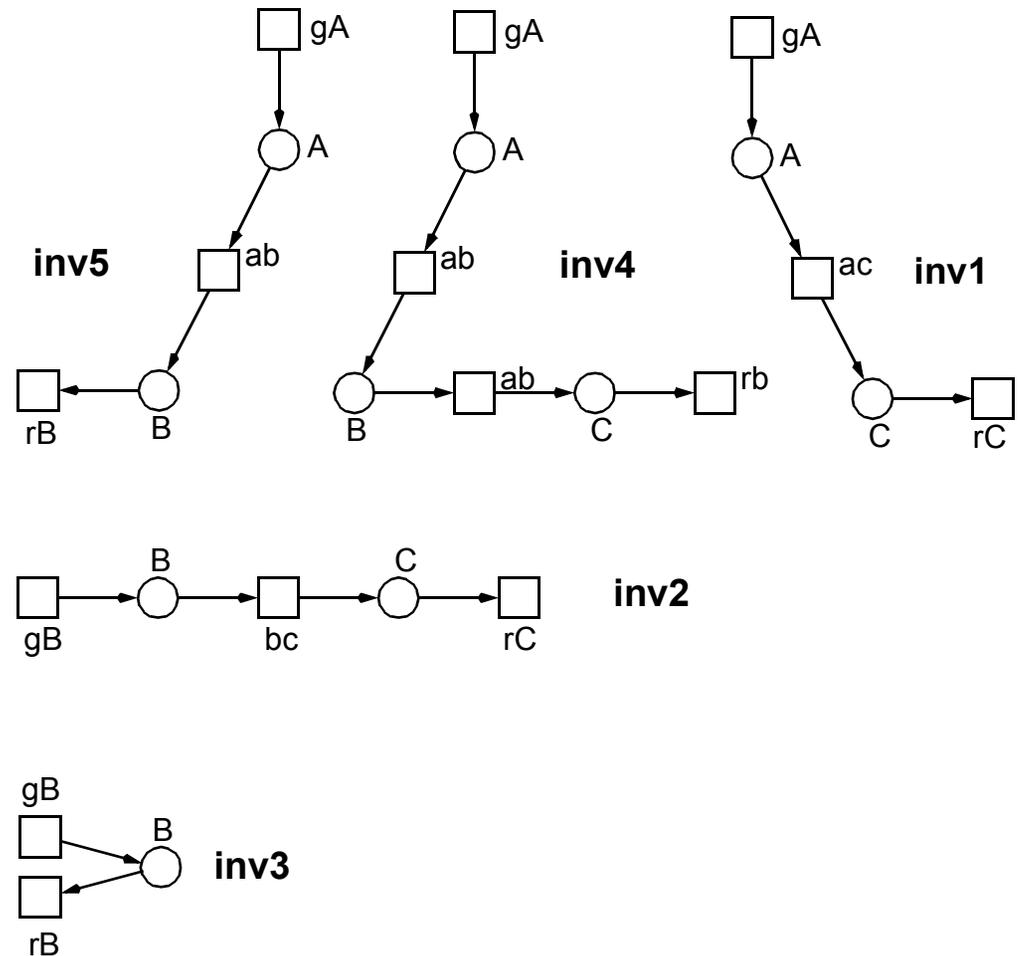
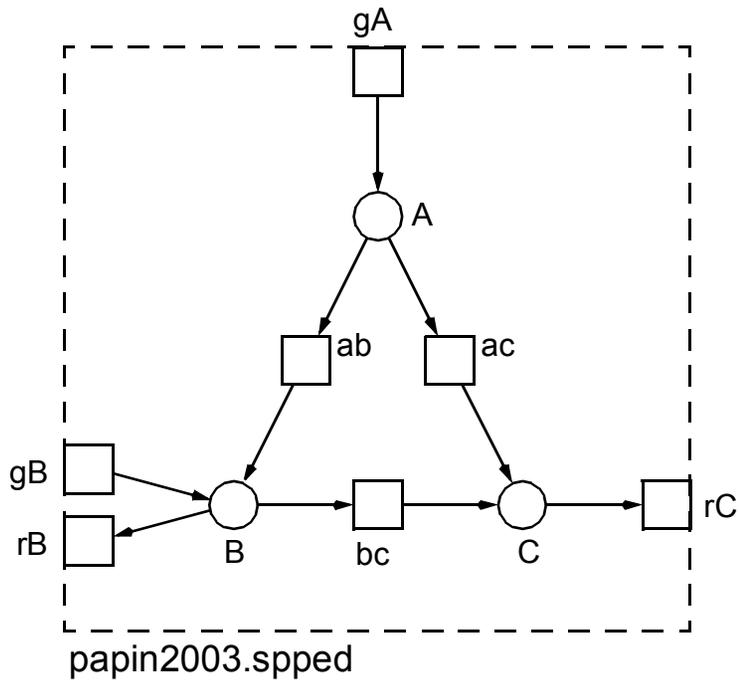
-> *output substance C*

-> *auxiliary substance B*



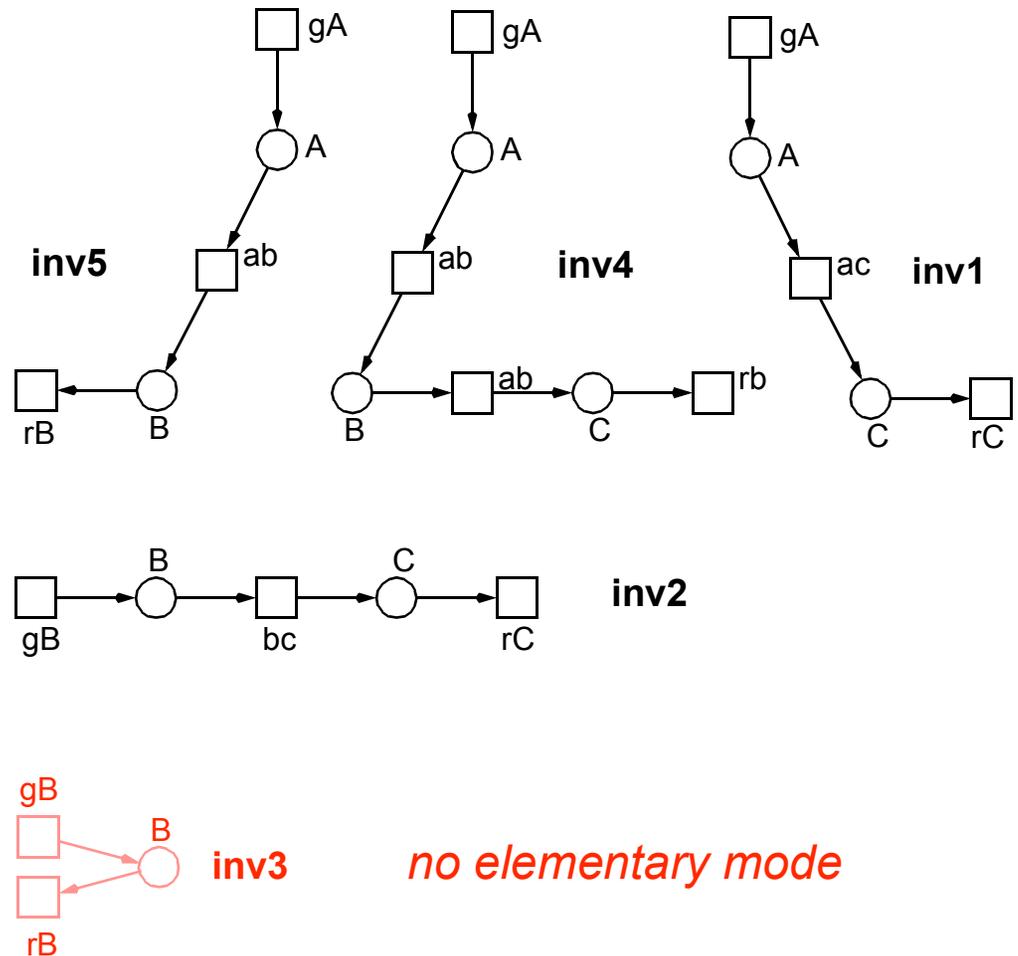
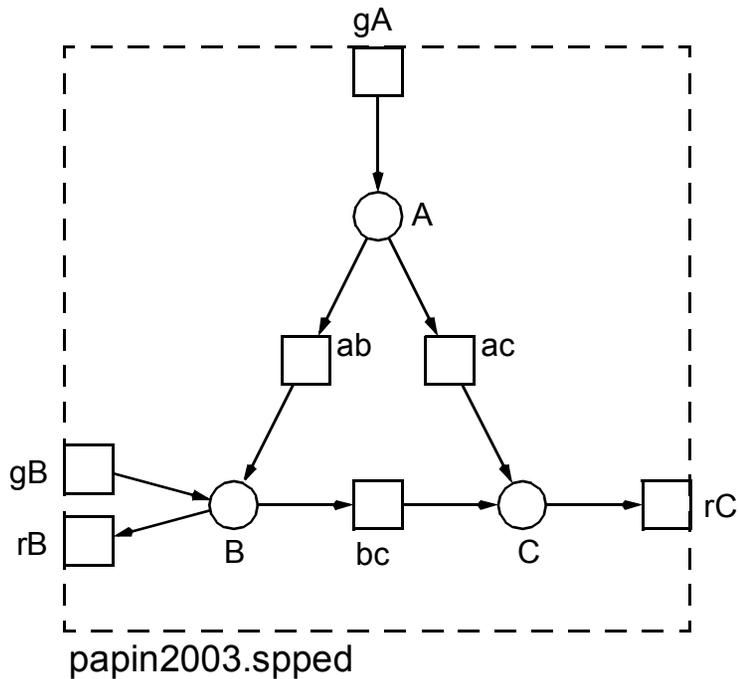
□ substances involved

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

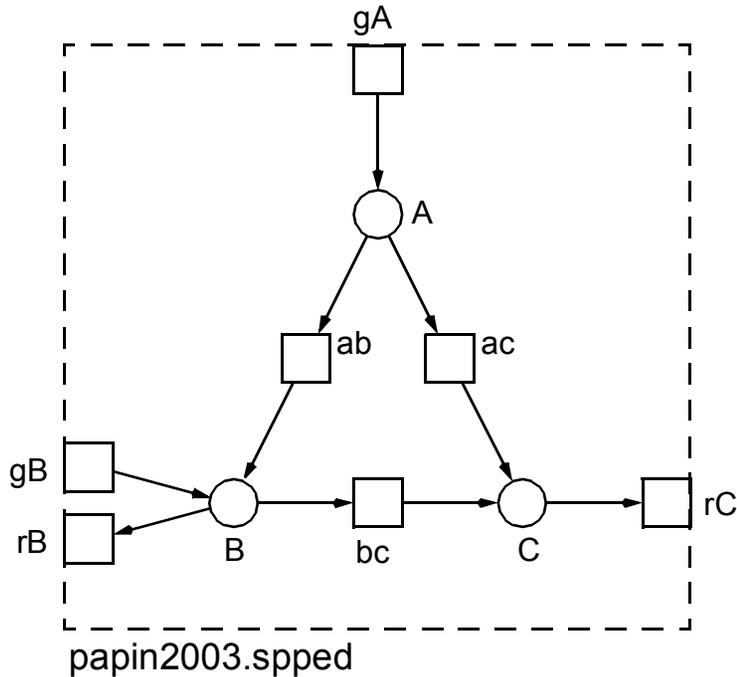


□ substances involved

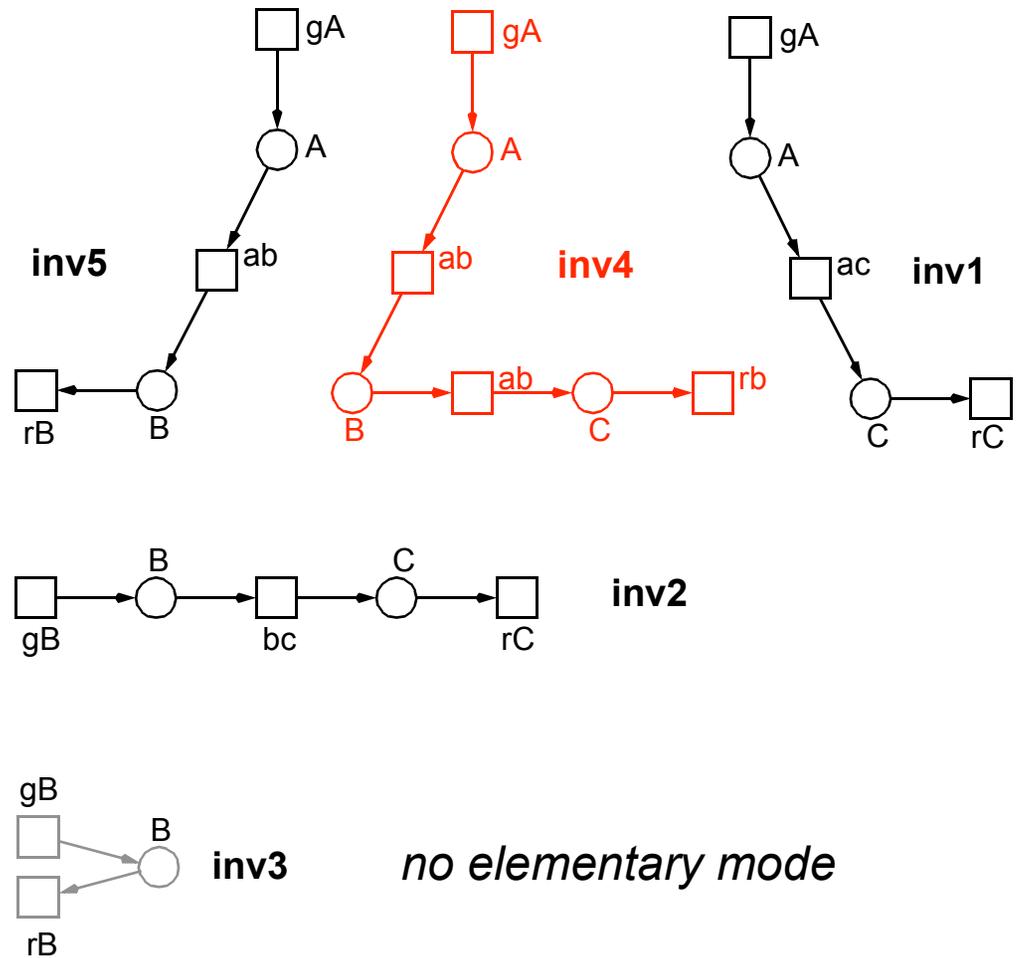
- > *input substance A*
- > *output substance C*
- > *auxiliary substance B*



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

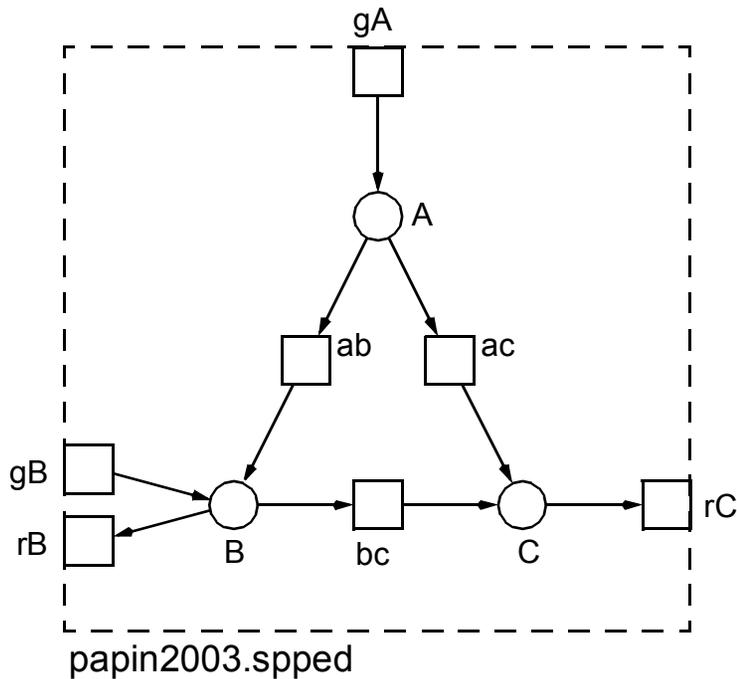


no extreme pathway

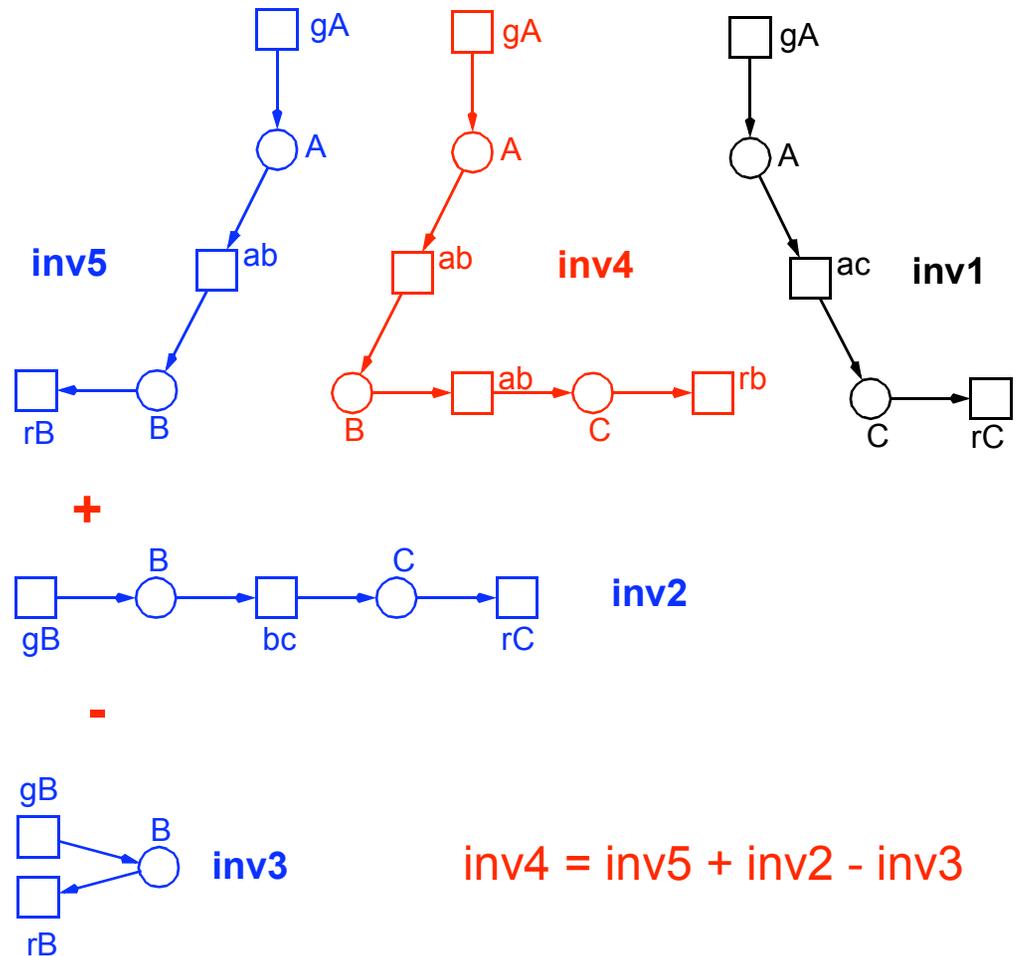


□ substances involved

- > input substance A
- > output substance C
- > auxiliary substance B



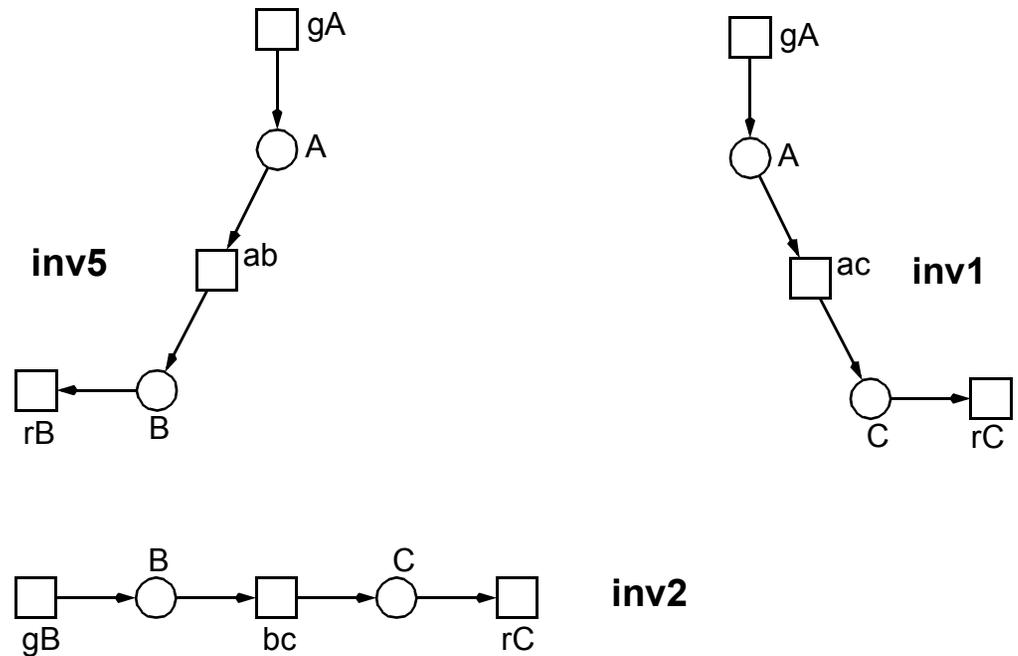
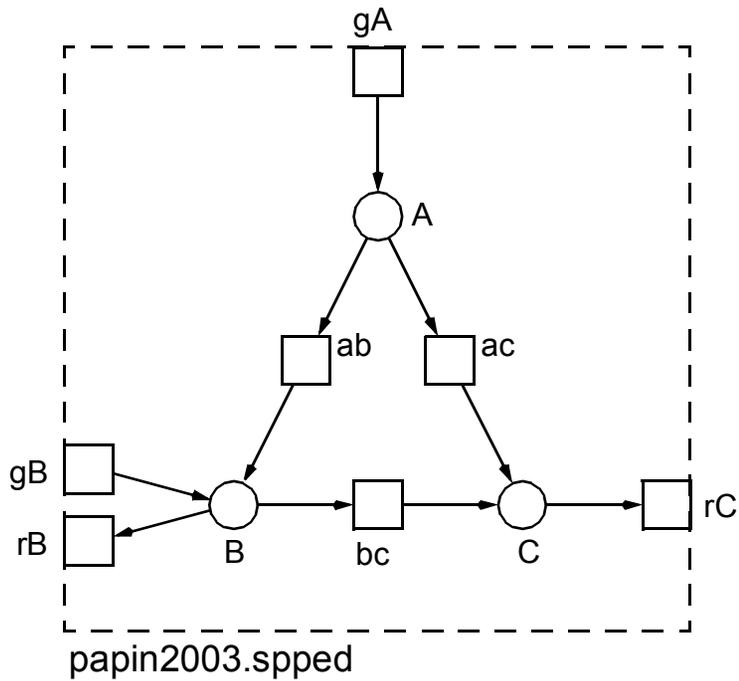
no extreme pathway



□ substances involved

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

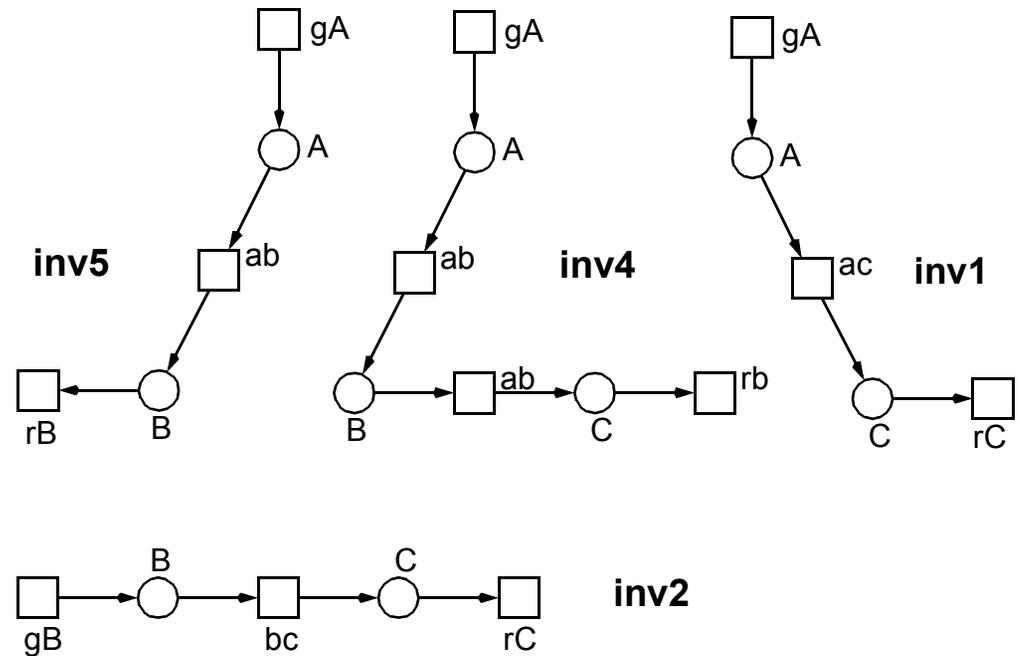
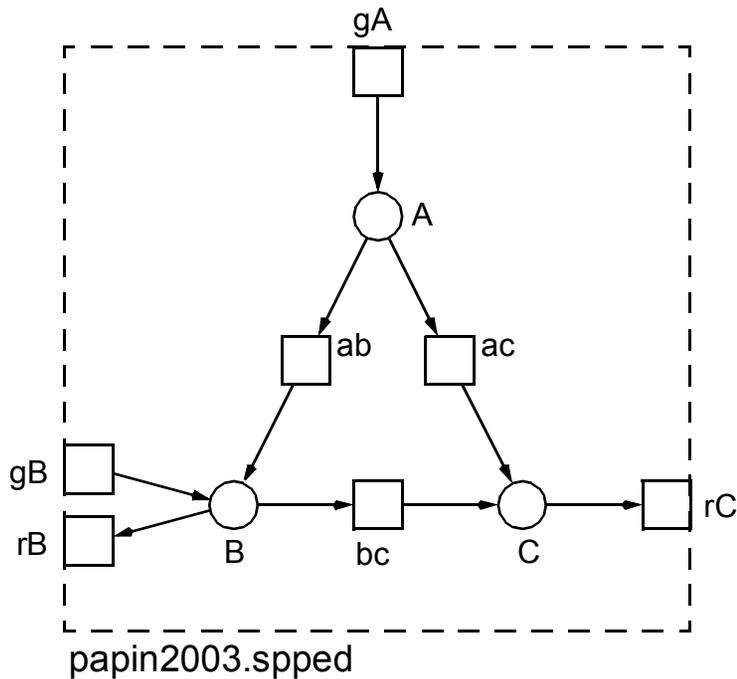
EXTREME PATHWAYS



□ substances involved

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

ELEMENTARY MODES

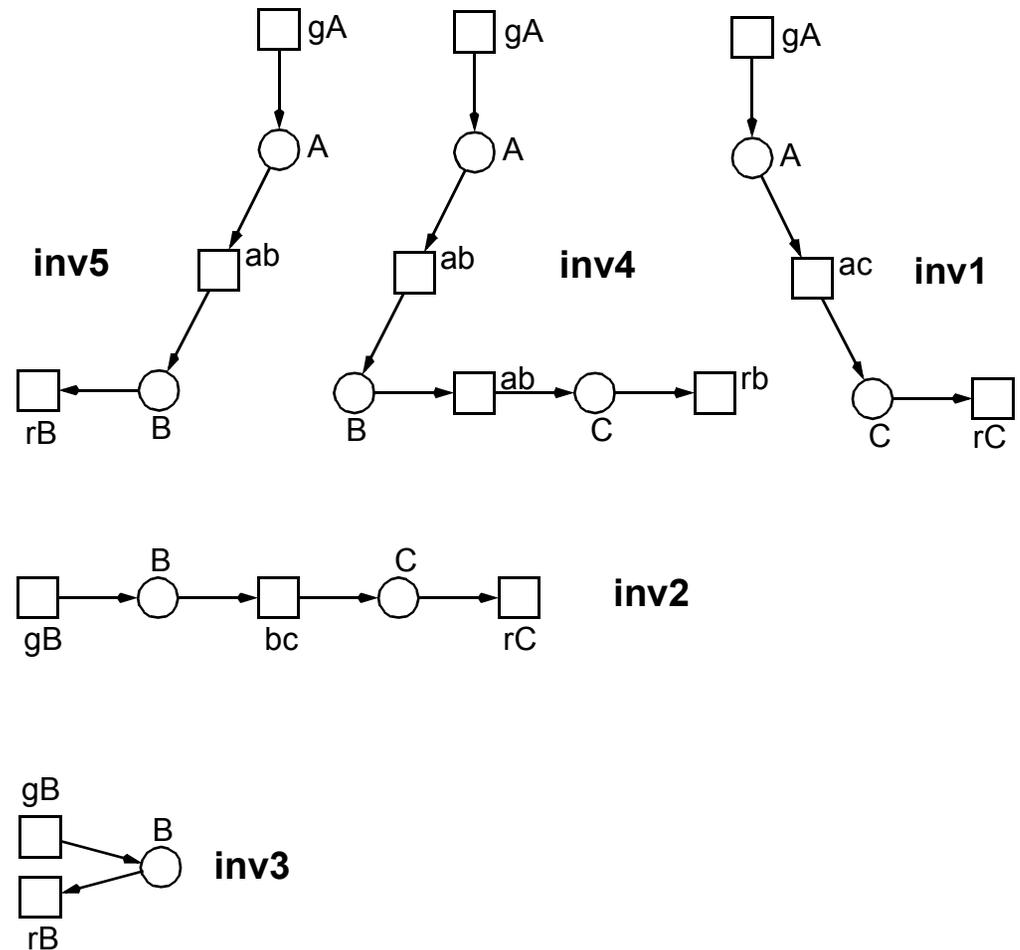
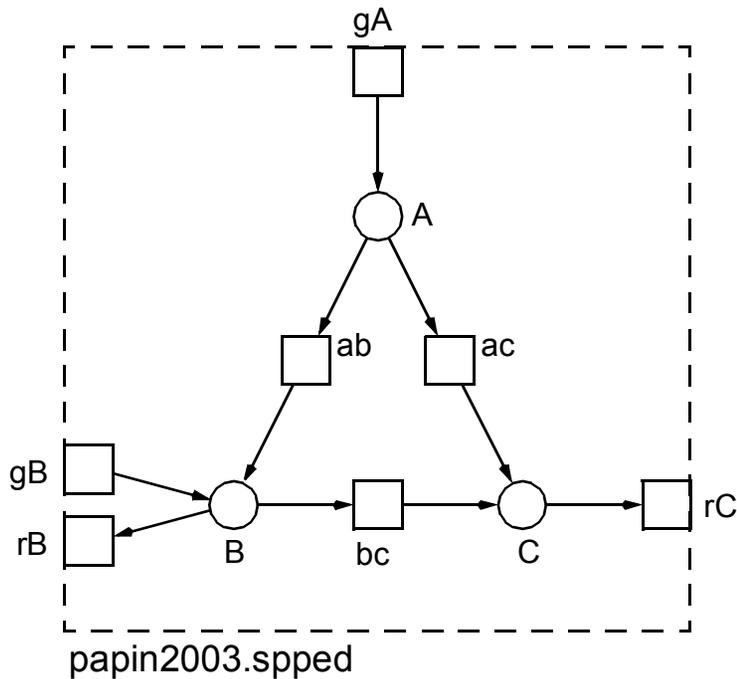


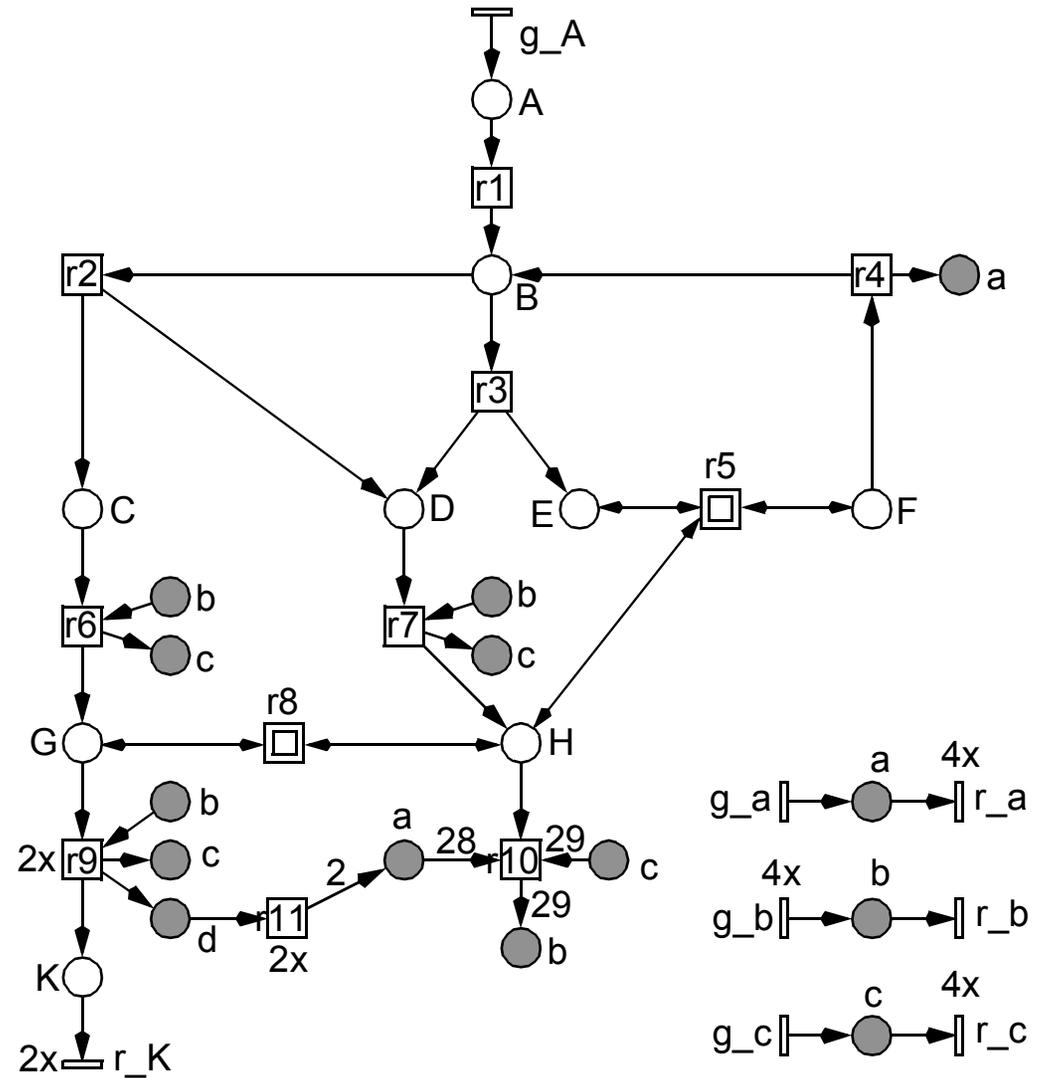
T-INVARIANTS, Ex2, SUMMARY

□ substances involved

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

MINIMAL T-INVARIANTS





trivial min. T-invariants (5)

- boundary transitions of auxiliary compounds

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

- reversible reactions

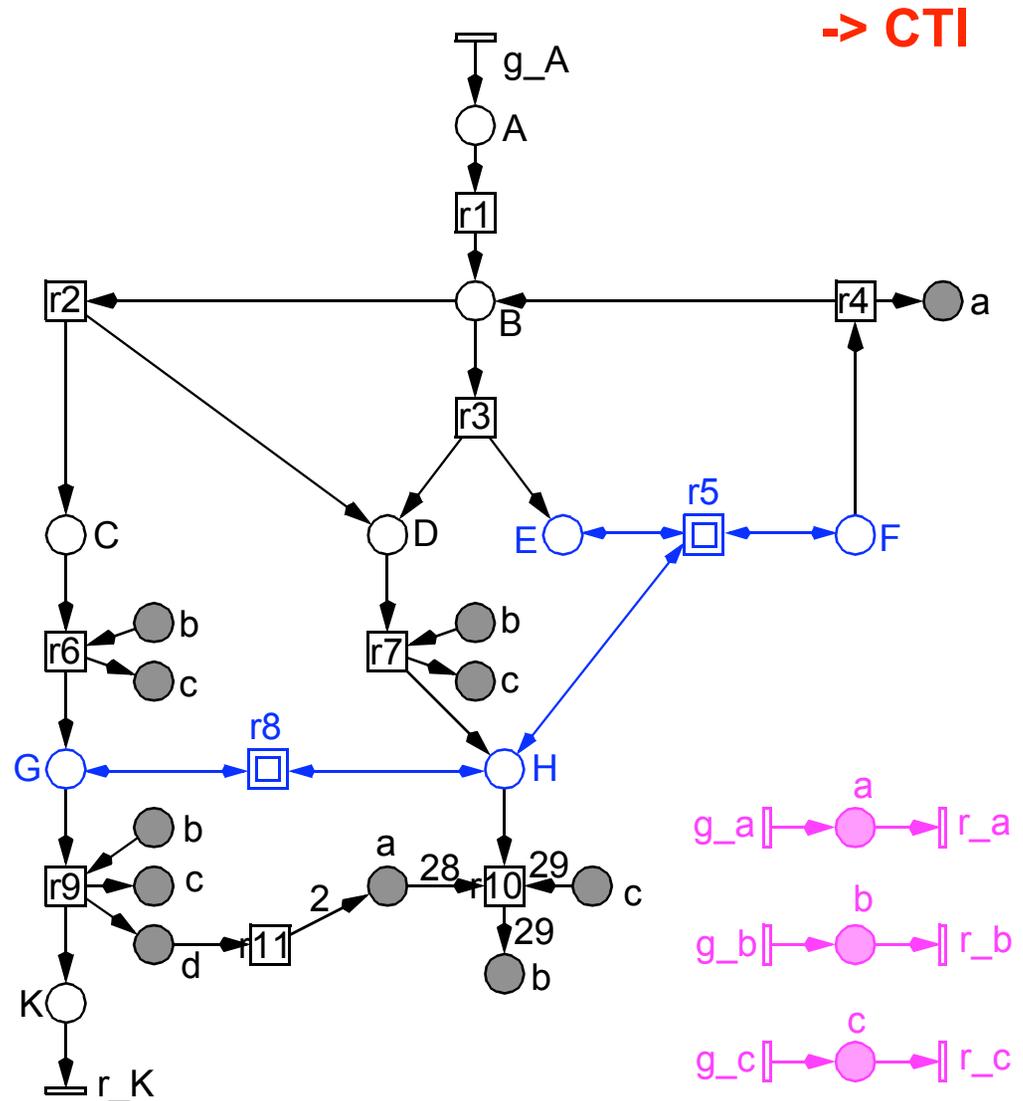
-> $(r5, r5_{rev}), (r8, r8_{rev})$

non-trivial min. T-invariants (7)

- covering boundary transitions of input / output compounds

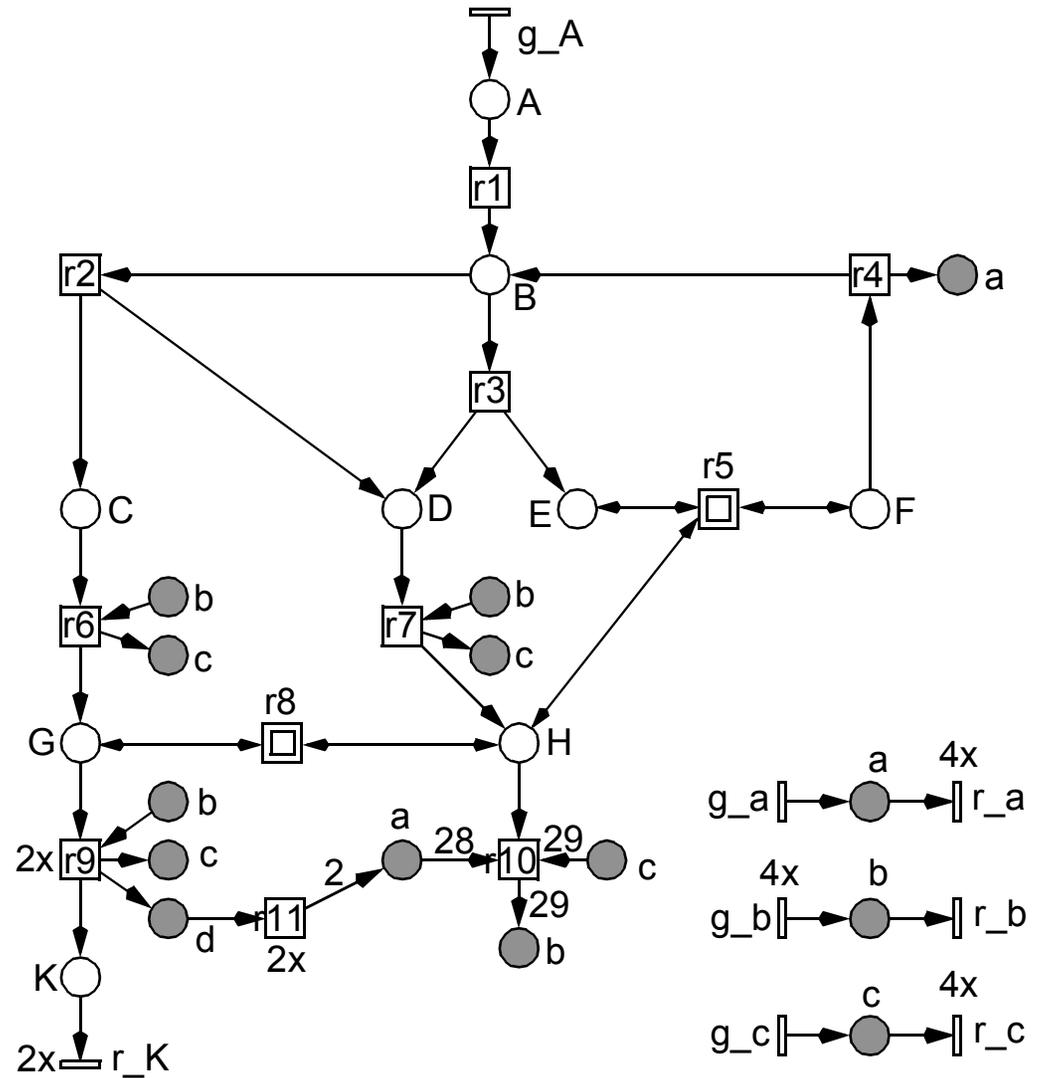
-> *i/o-T-invariants*

- inner cycles



□ i/o-T-invariant, example

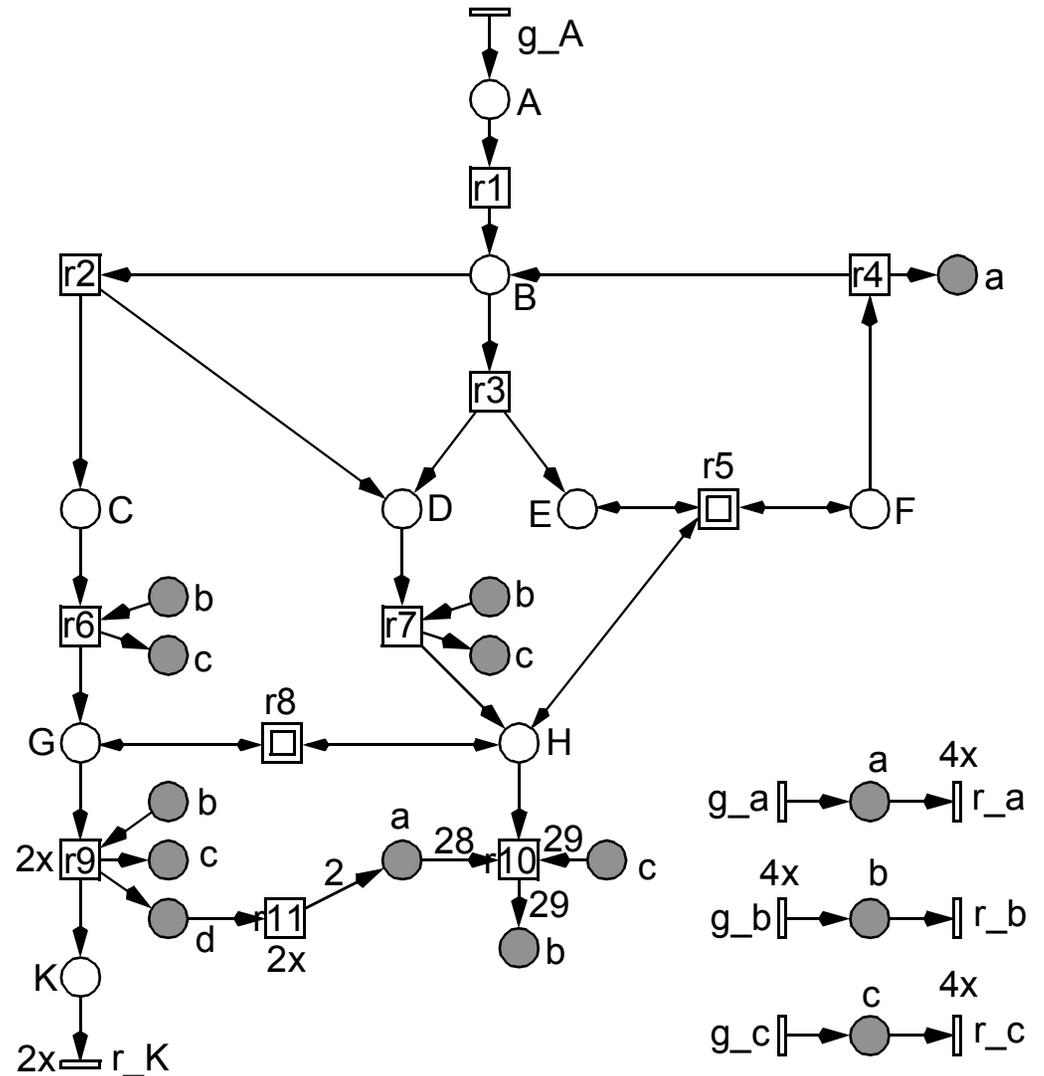
12		0.r1	:	1
		1.r2	:	1,
		3.r8_rev	:	1,
		4.r6	:	1,
		5.r7	:	1,
		9.r9	:	2,
		12.r11	:	2,
		13.g_A	:	1,
		14.r_K	:	2,
		15.g_b	:	4,
		18.r_c	:	4,
		20.r_a	:	4



□ 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

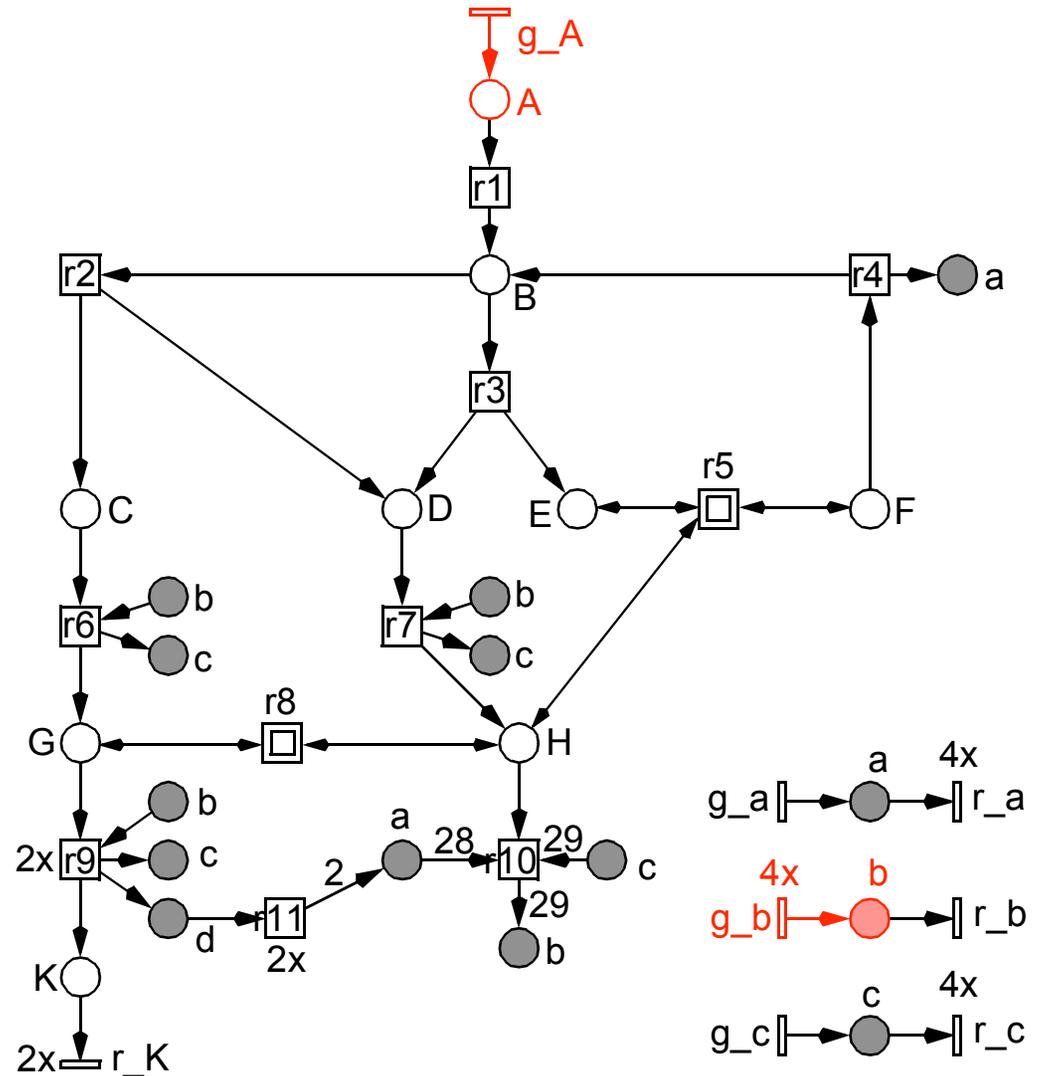
□ sum equation



□ 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

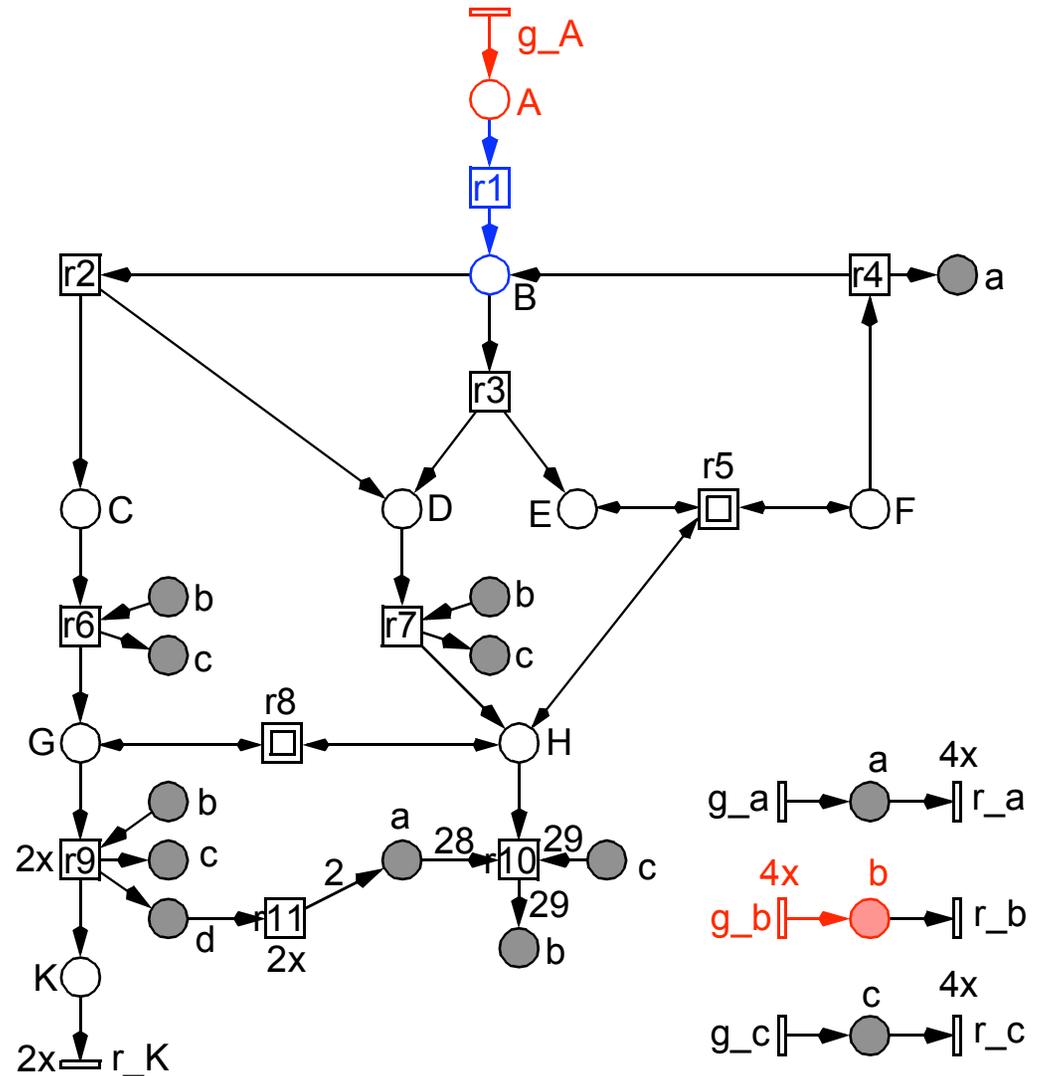
□ sum equation



□ i/o-T-invariant, example

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

□ sum equation

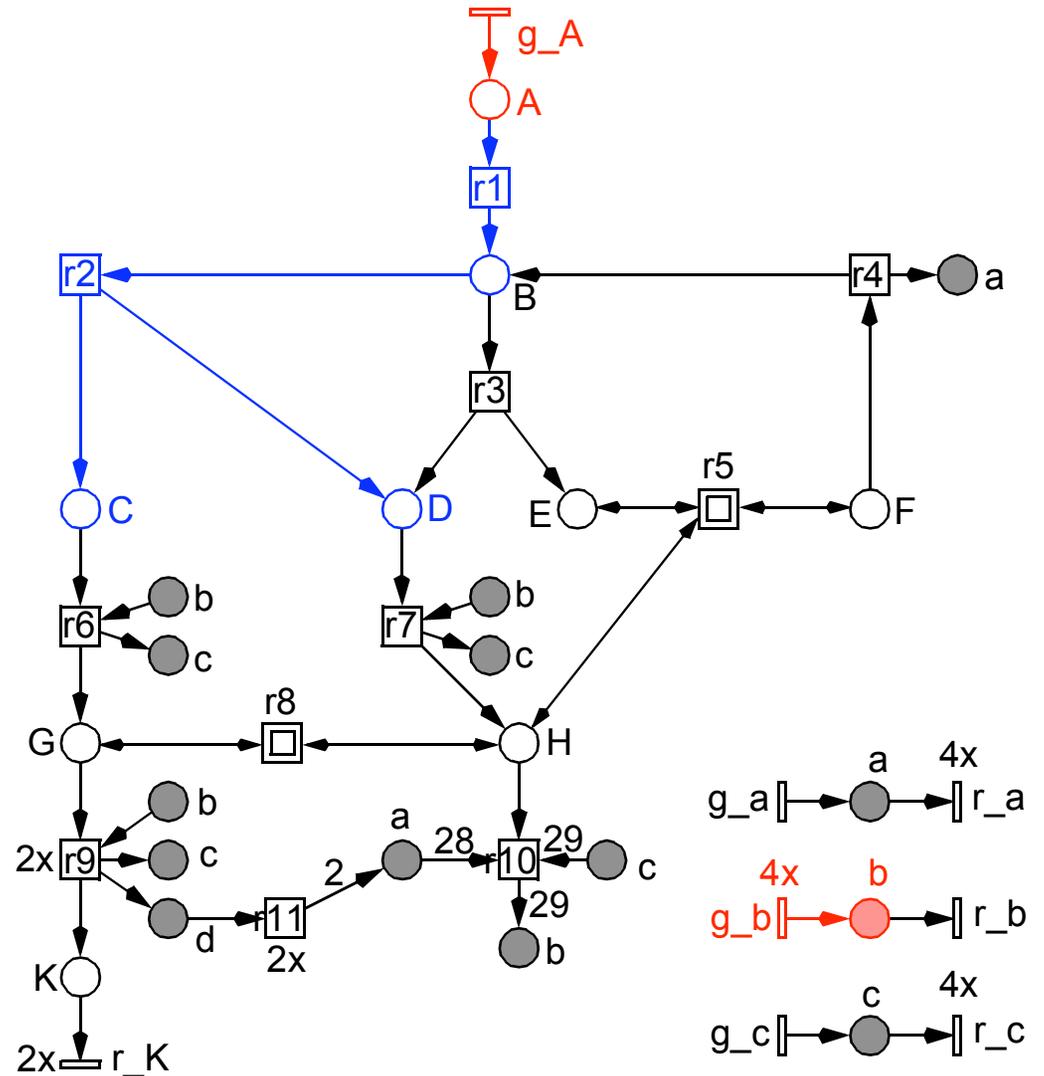


□ i/o-T-invariant, example

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

□ sum equation

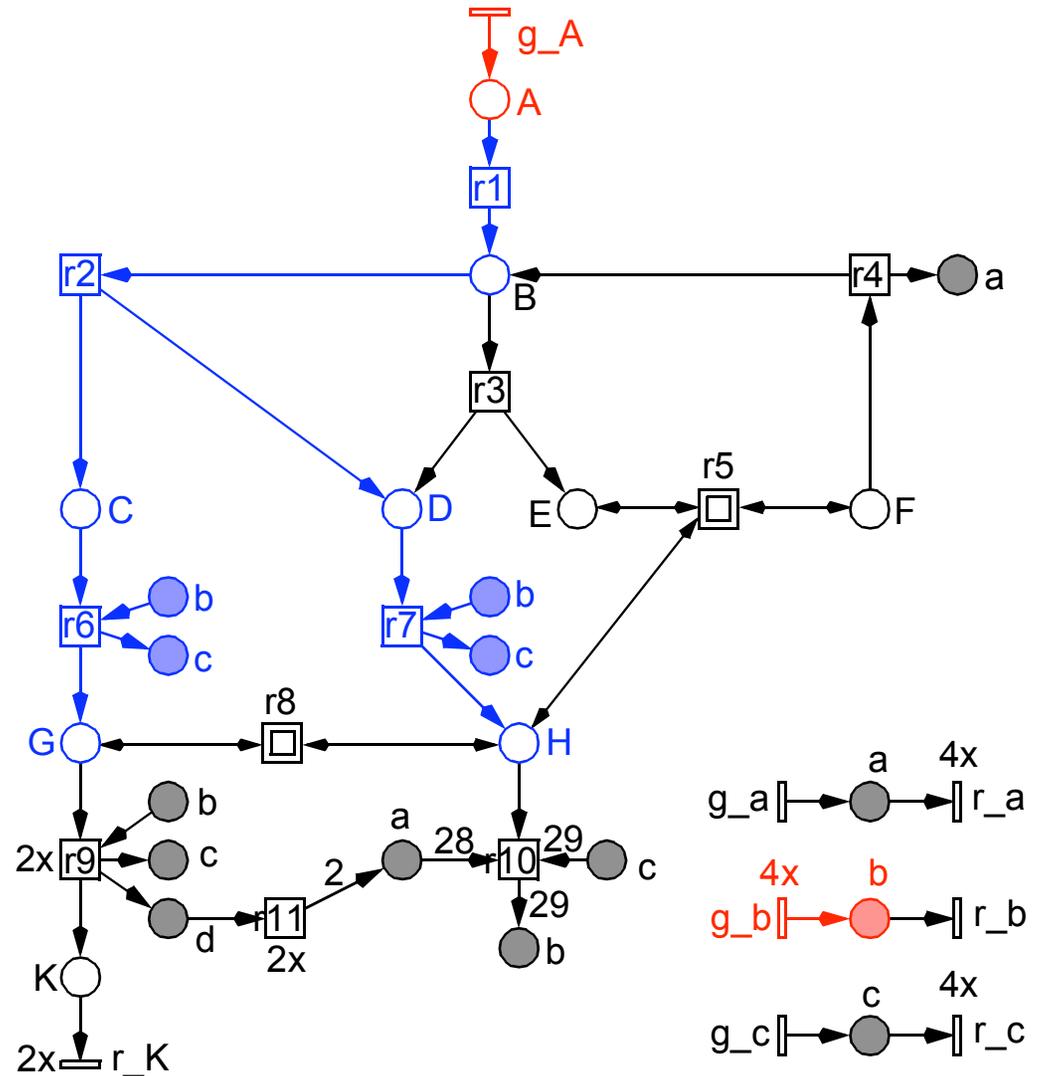
$$A + 4b \rightarrow 2K + 4a + 4c$$



□ i/o-T-invariant, example

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

□ sum equation

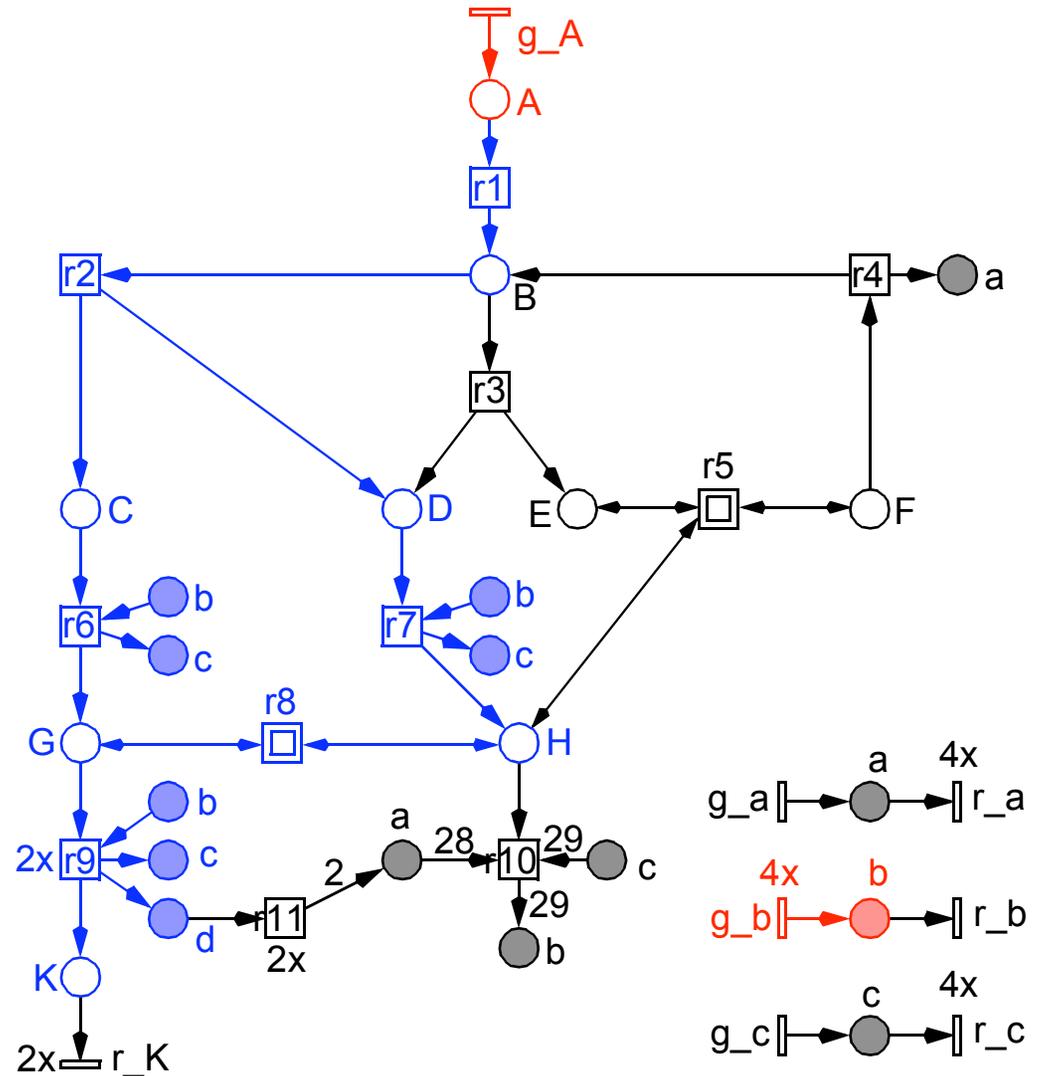


□ i/o-T-invariant, example

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

□ sum equation

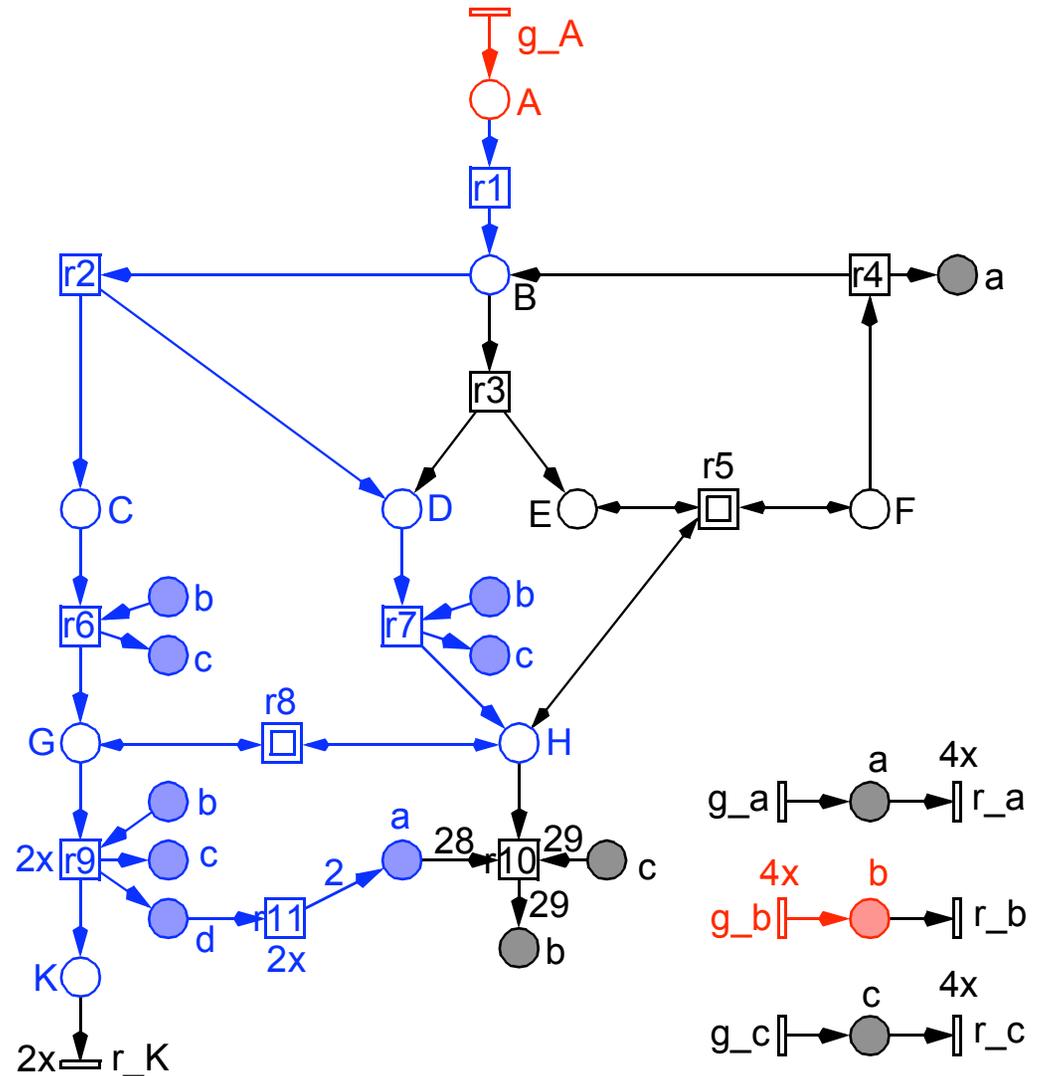
$$A + 4b \rightarrow 2K + 4a + 4c$$



□ i/o-T-invariant, example

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

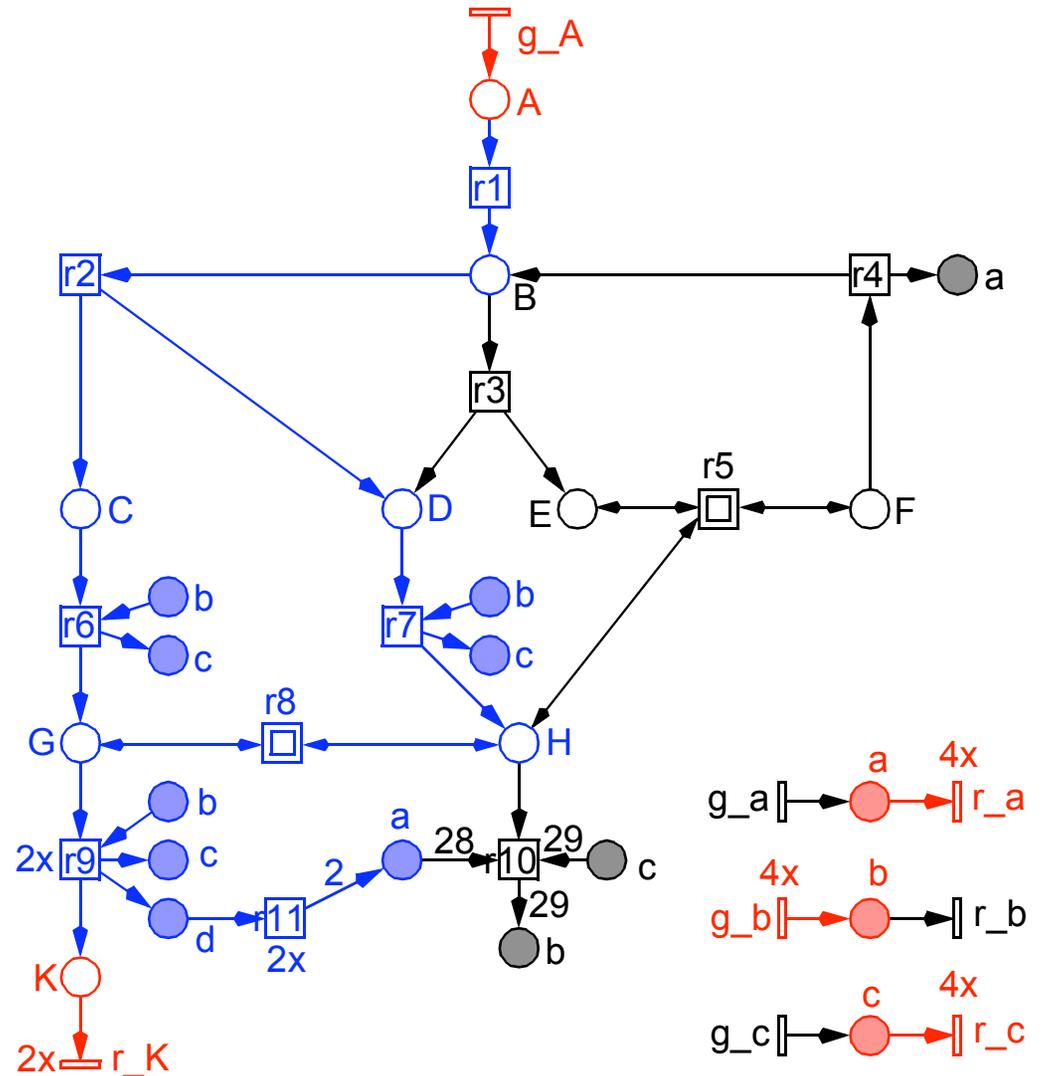
□ sum equation



□ i/o-T-invariant, example

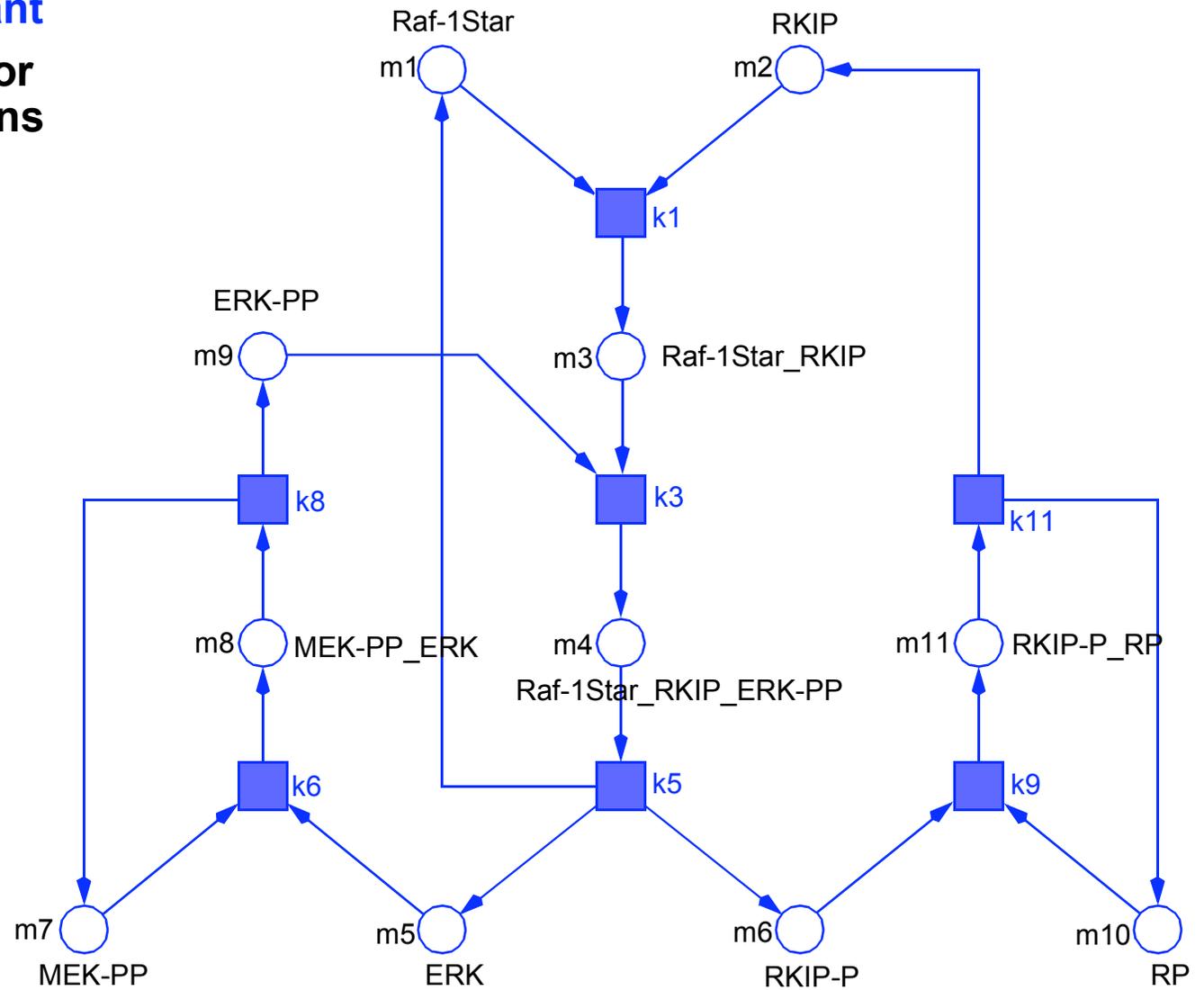
12		0.r1	:	1
		1.r2	:	1,
		3.r8_rev	:	1,
		4.r6	:	1,
		5.r7	:	1,
		9.r9	:	2,
		12.r11	:	2,
		13.g_A	:	1,
		14.r_K	:	2,
		15.g_b	:	4,
		18.r_c	:	4,
		20.r_a	:	4

□ sum equation



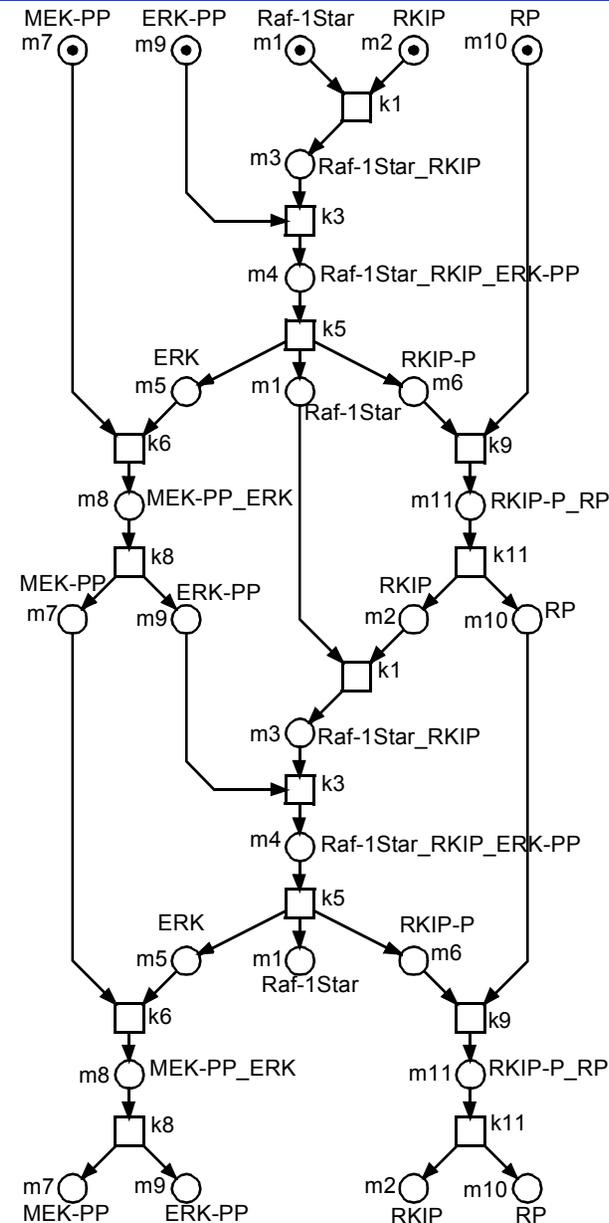
T-INVARIANT, EX4: THE RKIP PATHWAY

-> non-trivial T-invariant
+ four trivial ones for reversible reactions

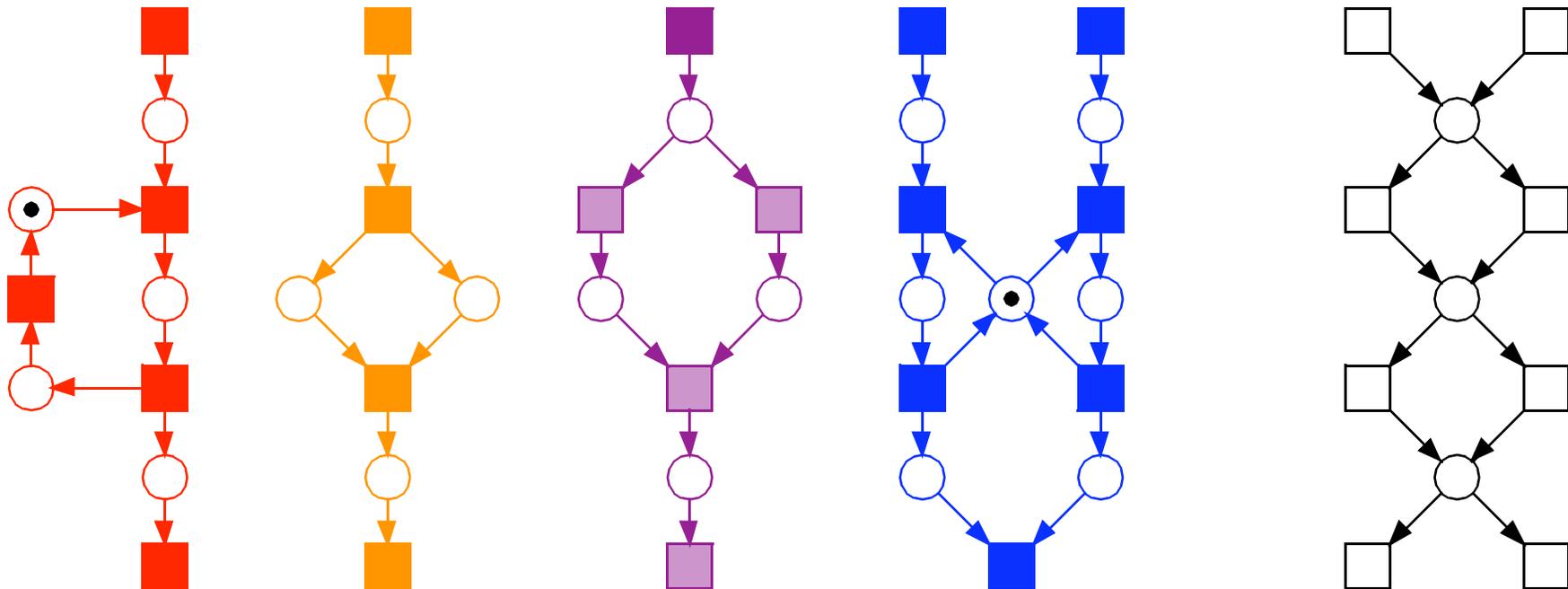


NON-TRIVIAL T-INVARIANT, RUN

- ❑ realizability check under the constructed marking
- ❑ T-invariant's unfolding to describe its behaviour
 - > partial order structure
- ❑ labelled condition / event net
 - > events (boxes)
 - transition occurrences
 - > 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

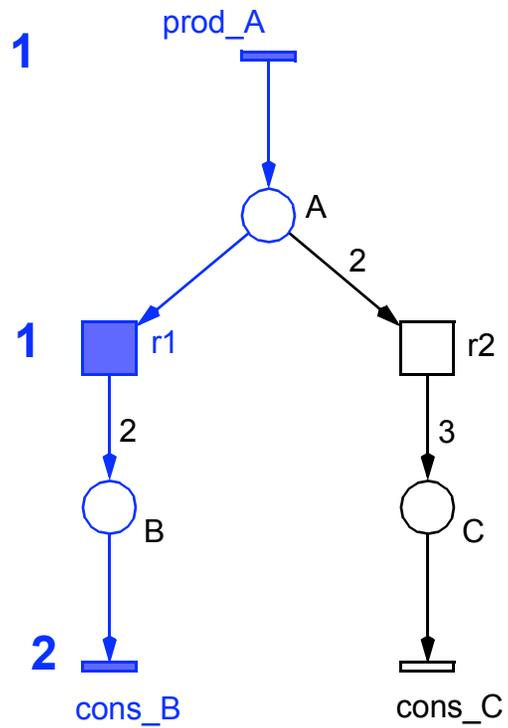
- Let X denote a set of (all / non-trivial) minimal t-invariants x of a given PN.
- **dependency relation:**
Two transitions i, j depend on each other,
if they always appear together in all minimal T-invariants x , i.e.

$$\forall x \in X: i \in \text{supp}(x) \Leftrightarrow j \in \text{supp}(x)$$

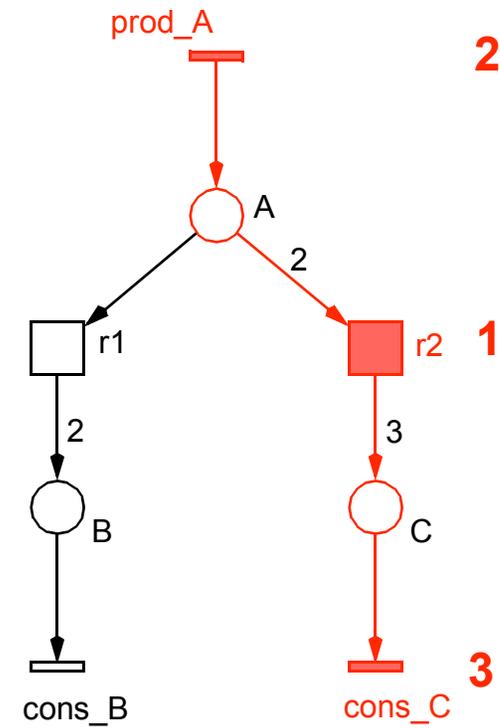
- **equivalence relation** in the transition set, leading to a partition of T
 - > *reflexive*
 - > *symmetric*
 - > *transitive*
- the **equivalence classes** A represent **maximal ADT-sets**

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

$r1: A \rightarrow 2 B$
 $r2: 2 A \rightarrow 3 C$

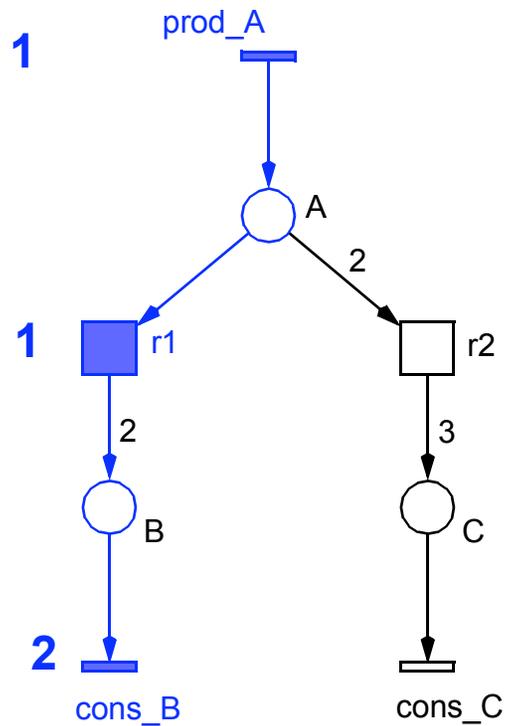


T-INVARIANT 1

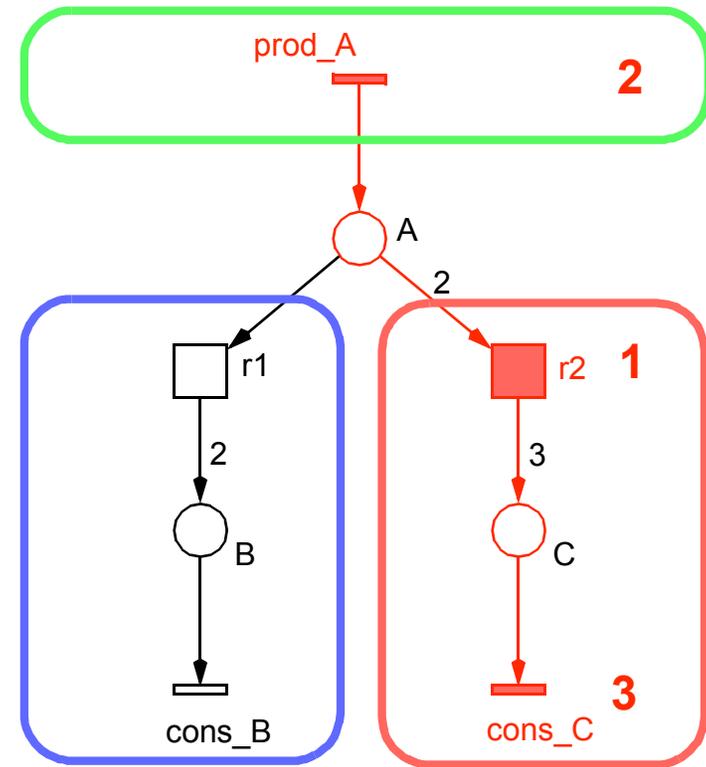


T-INVARIANT 2

$r1: A \rightarrow 2 B$
 $r2: 2 A \rightarrow 3 C$



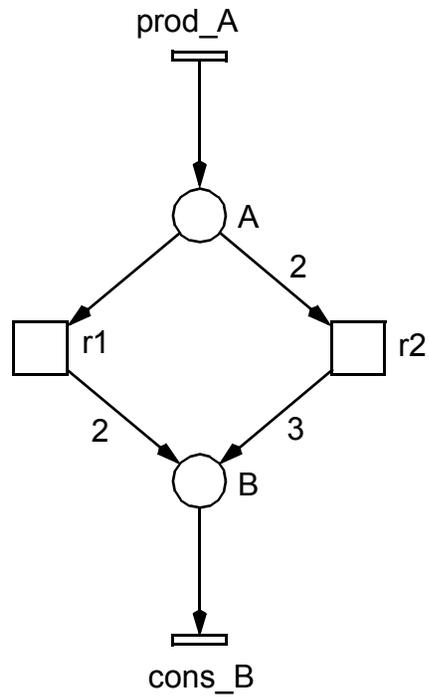
T-INVARIANT 1



T-INVARIANT 2

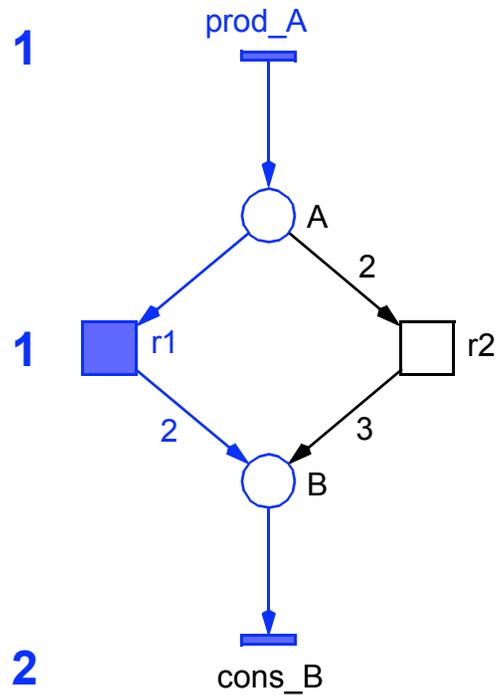
$r1: A \rightarrow 2 B$

$r2: 2 A \rightarrow 3 B$

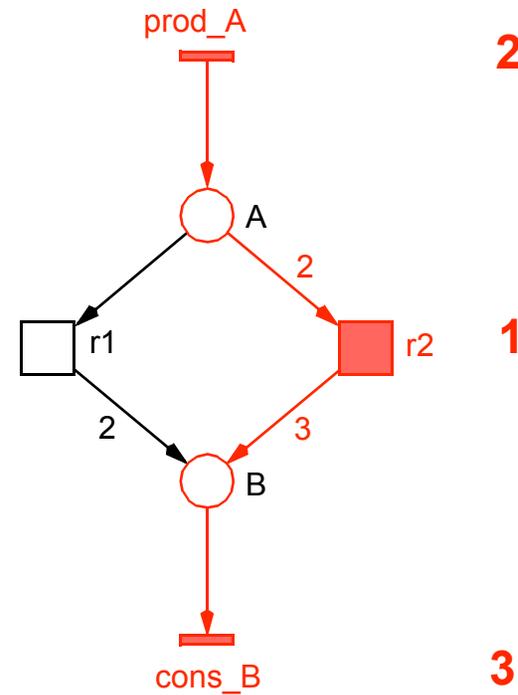


$r1: A \rightarrow 2 B$

$r2: 2 A \rightarrow 3 B$



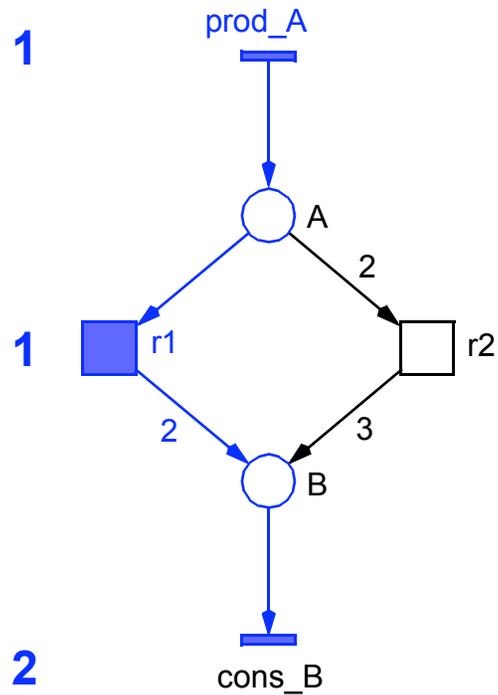
T-INVARIANT 1



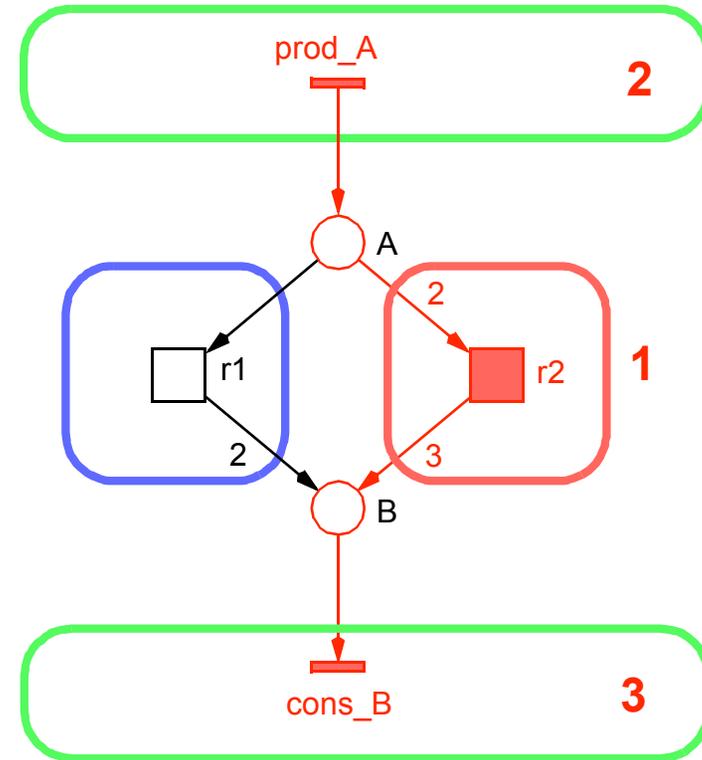
T-INVARIANT 2

$r1: A \rightarrow 2 B$

$r2: 2 A \rightarrow 3 B$



T-INVARIANT 1



T-INVARIANT 2

❑ 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

❑ **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?**

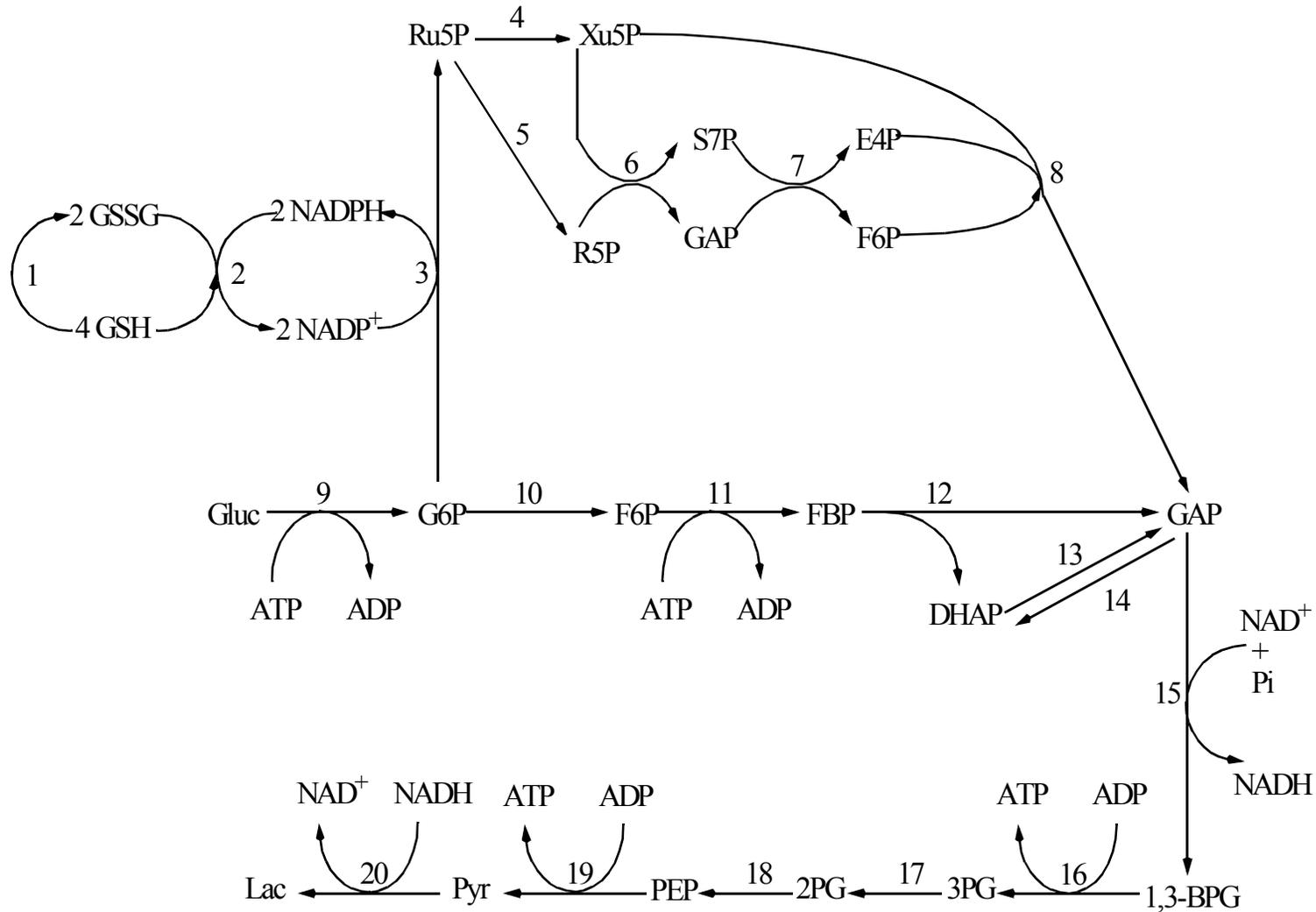
-> *set of T-invariants gets structured*

-> *better understanding of the net behaviour*

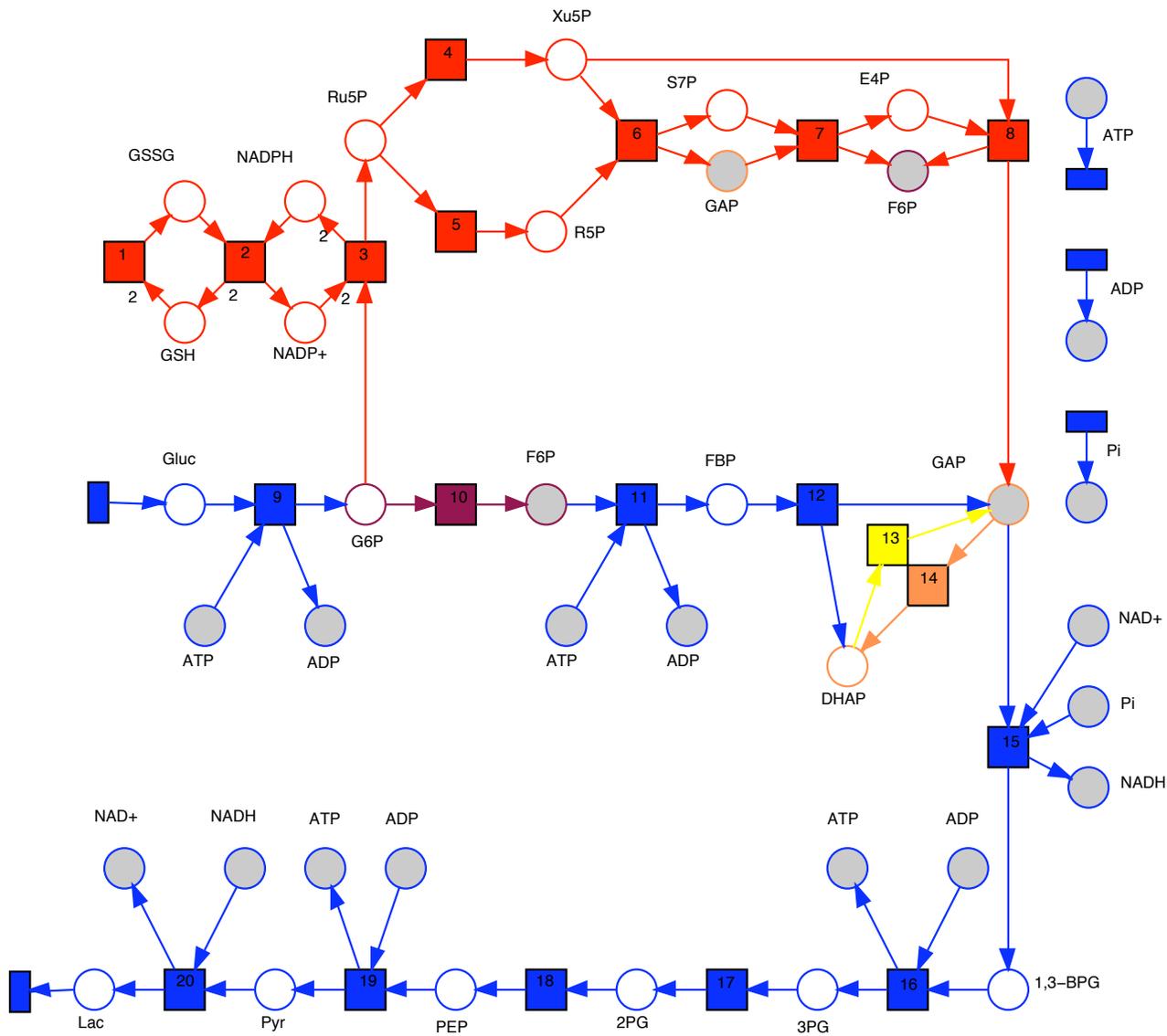
BIO PETRI NETS, SOME EXAMPLES

Ex1 - Glycolysis and Pentose Phosphate Pathway

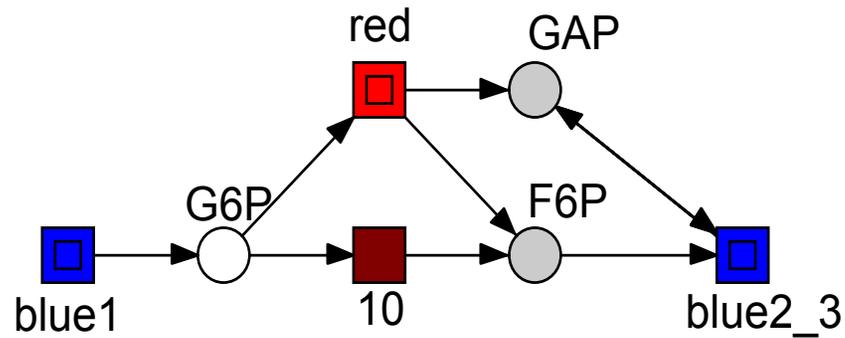
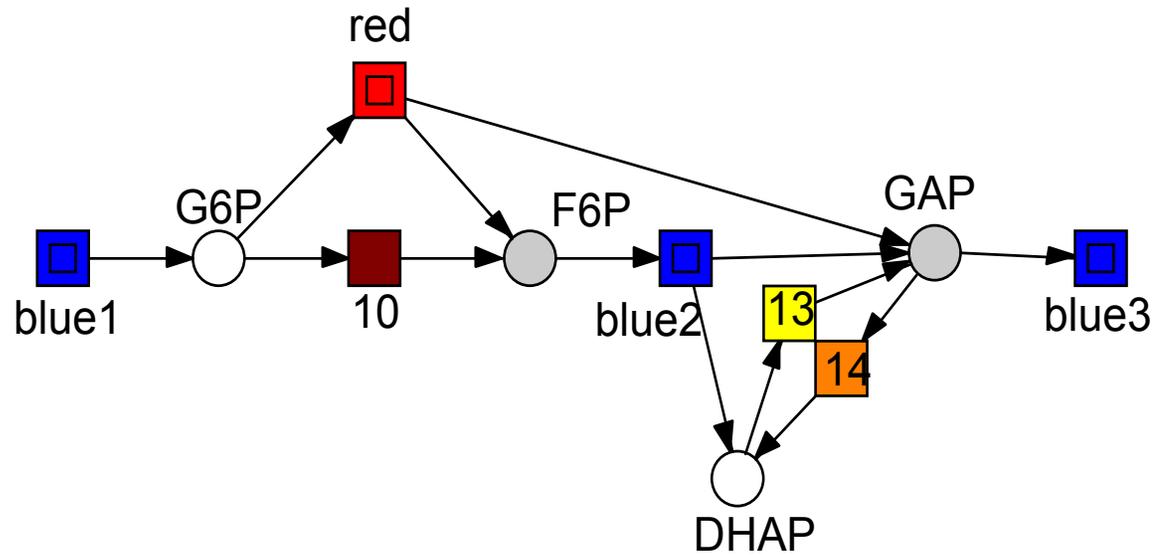
[Reddy 1993]



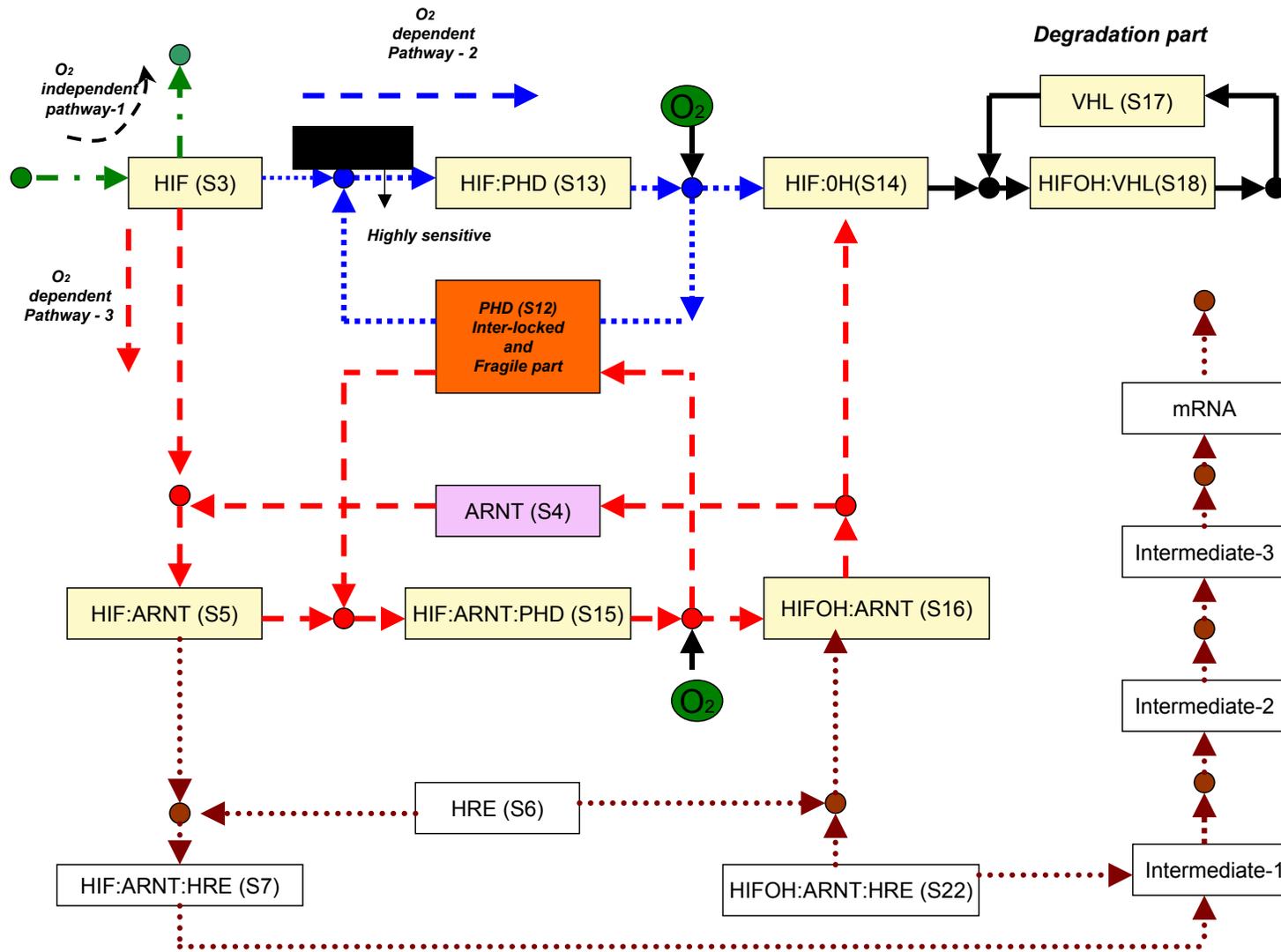
Ex1 - Glycolysis and Pentose Phosphate Pathway



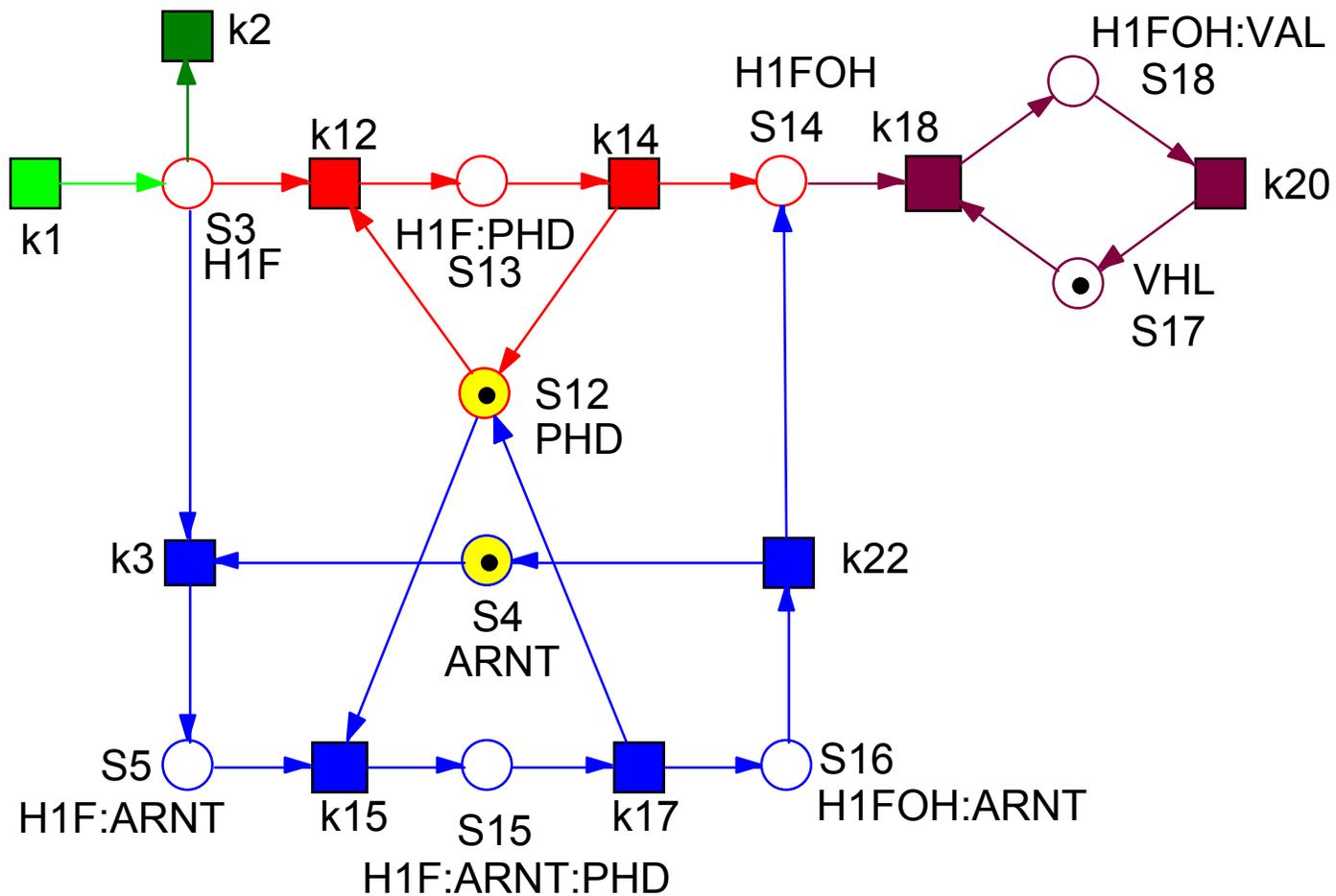
Ex1 - Glycolysis and Pentose Phosphate Pathway

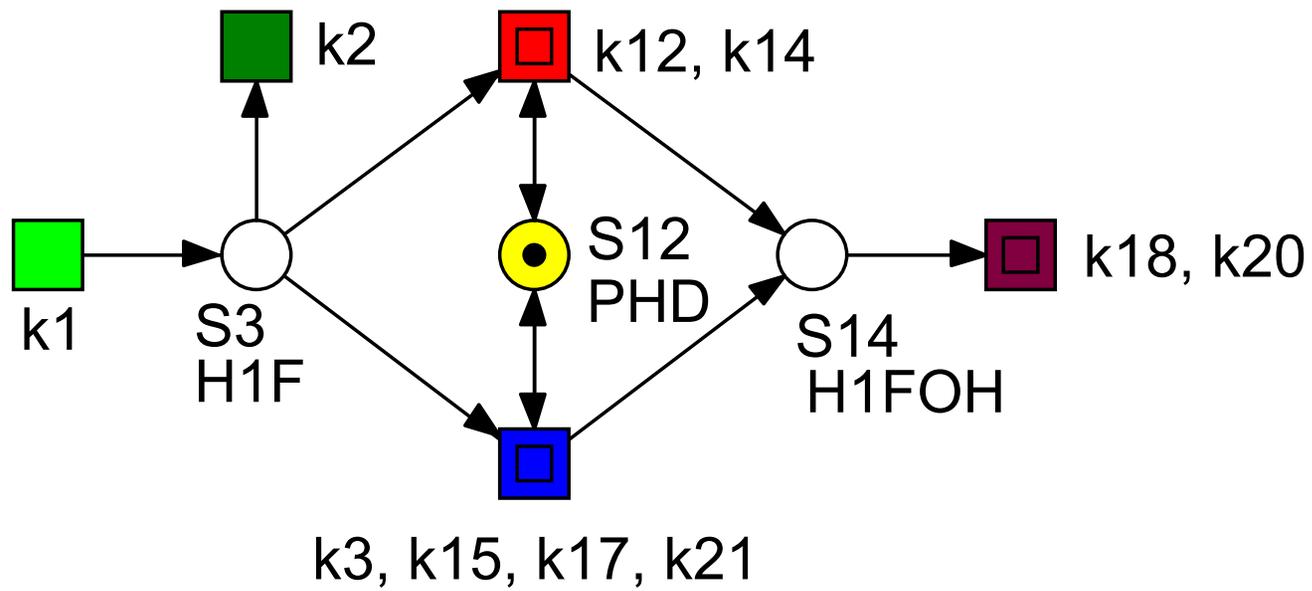


[YU ET AL. 2007]

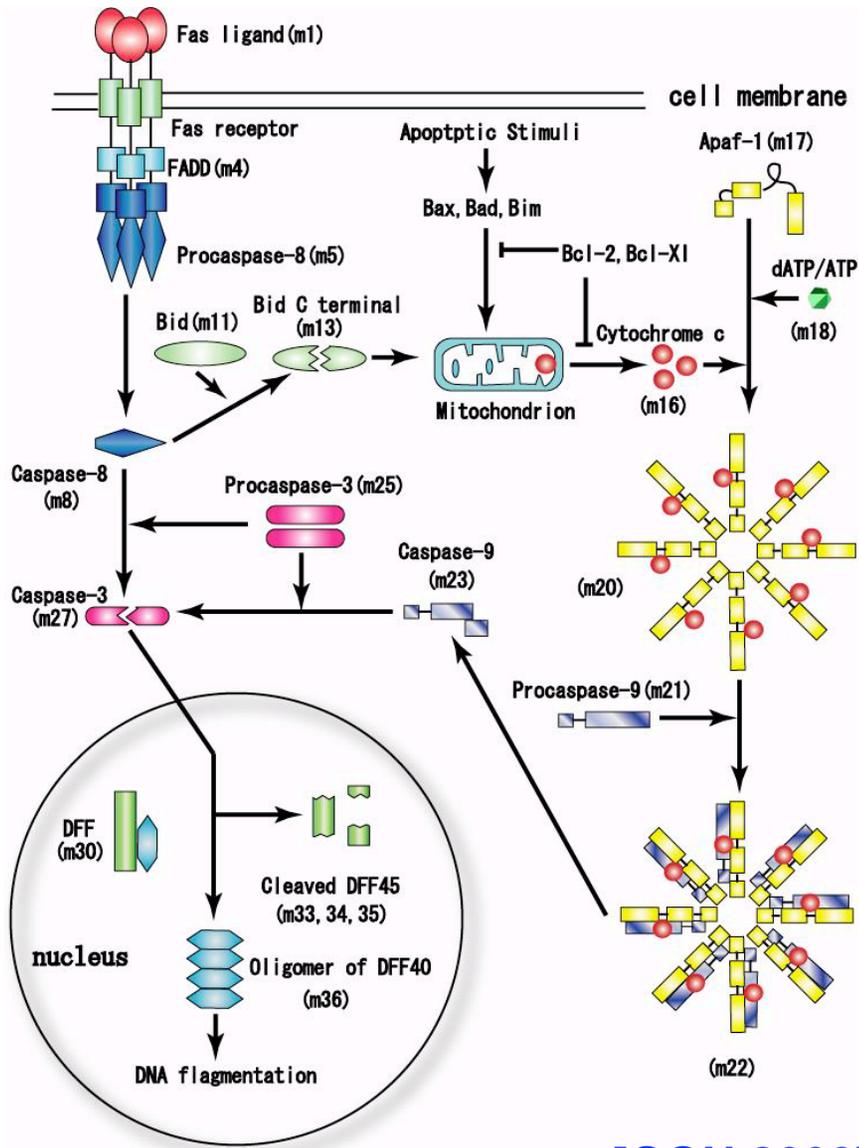


Ex2 - HYPOXIA



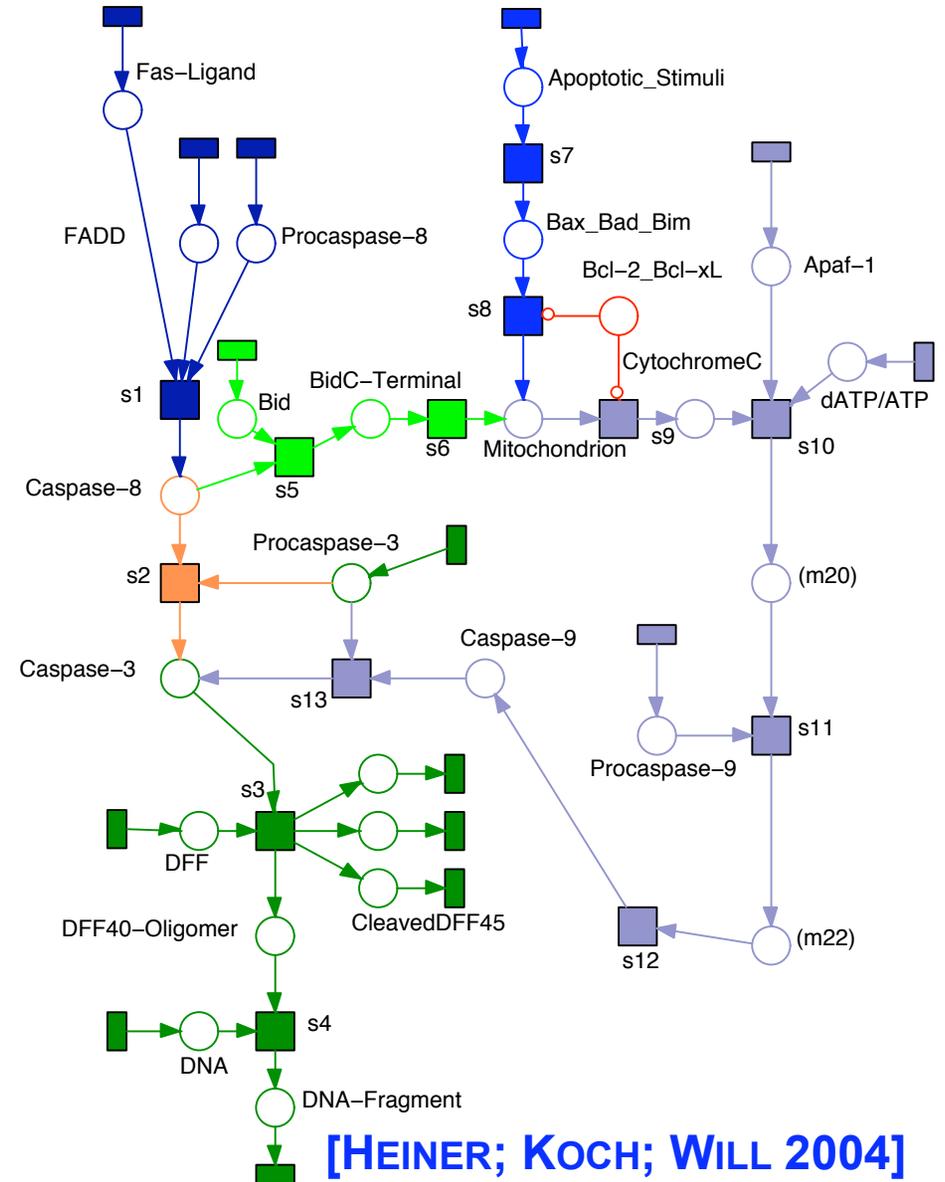
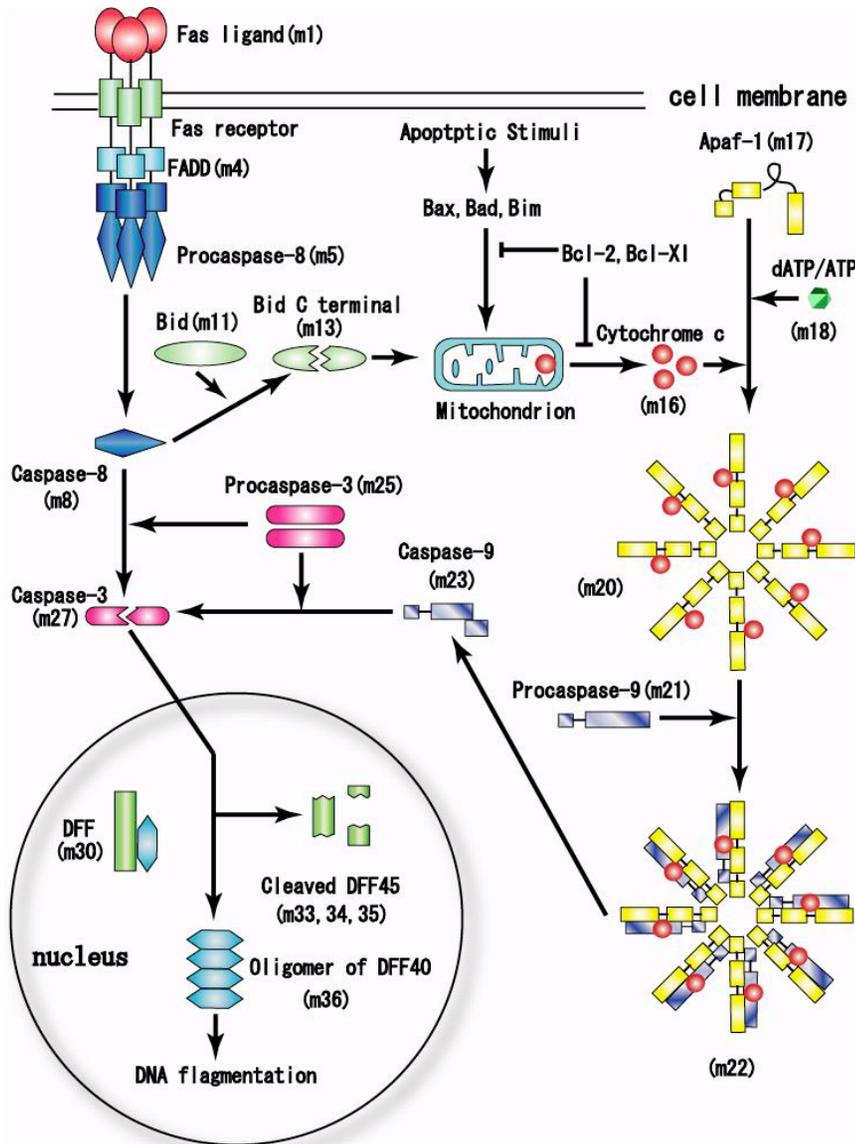


EX3: APOPTOSIS IN MAMMALIAN CELLS

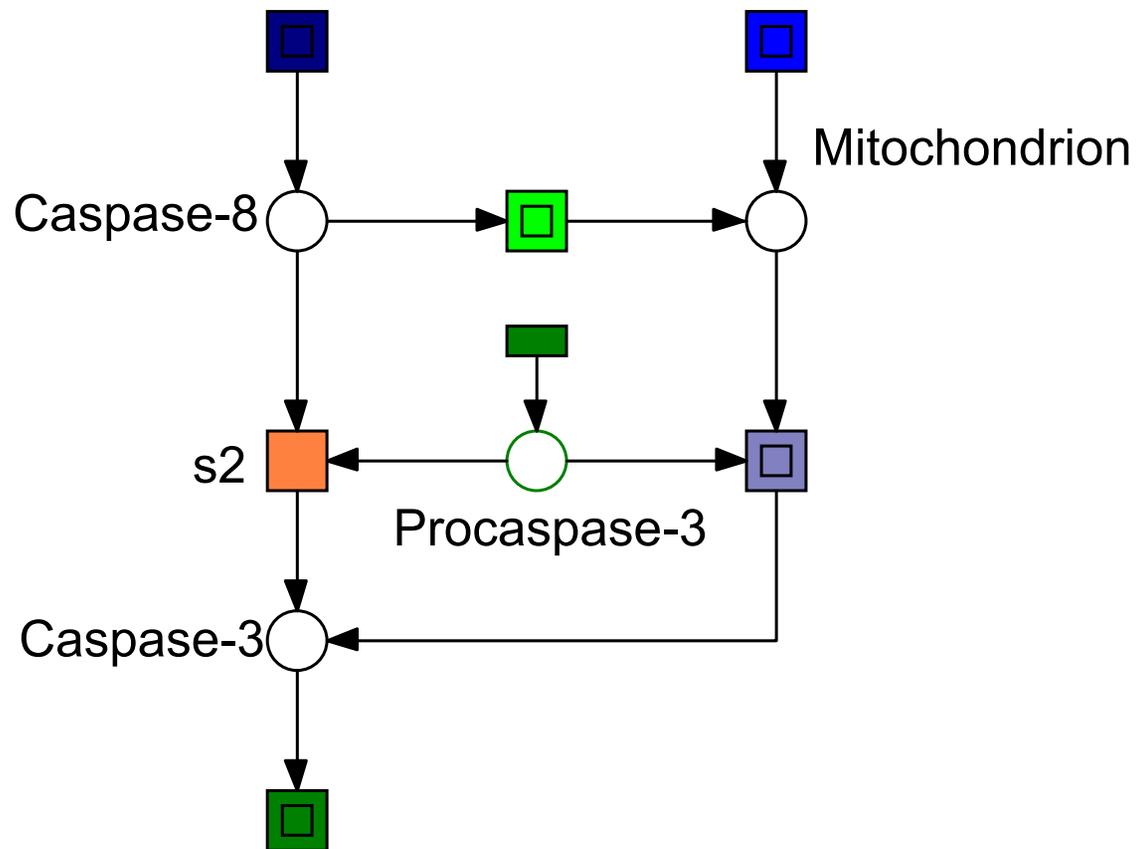


[GON 2003]

EX3: APOPTOSIS IN MAMMALIAN CELLS



EX3: APOPTOSIS IN MAMMALIAN CELLS



Ex4 - Carbon Metabolism in Potato Tuber



[KOCH; JUNKER; HEINER 2005]

ADT-sets without trivial T-invariants

- ❑ **“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)*

❑ 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)*

❑ **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**

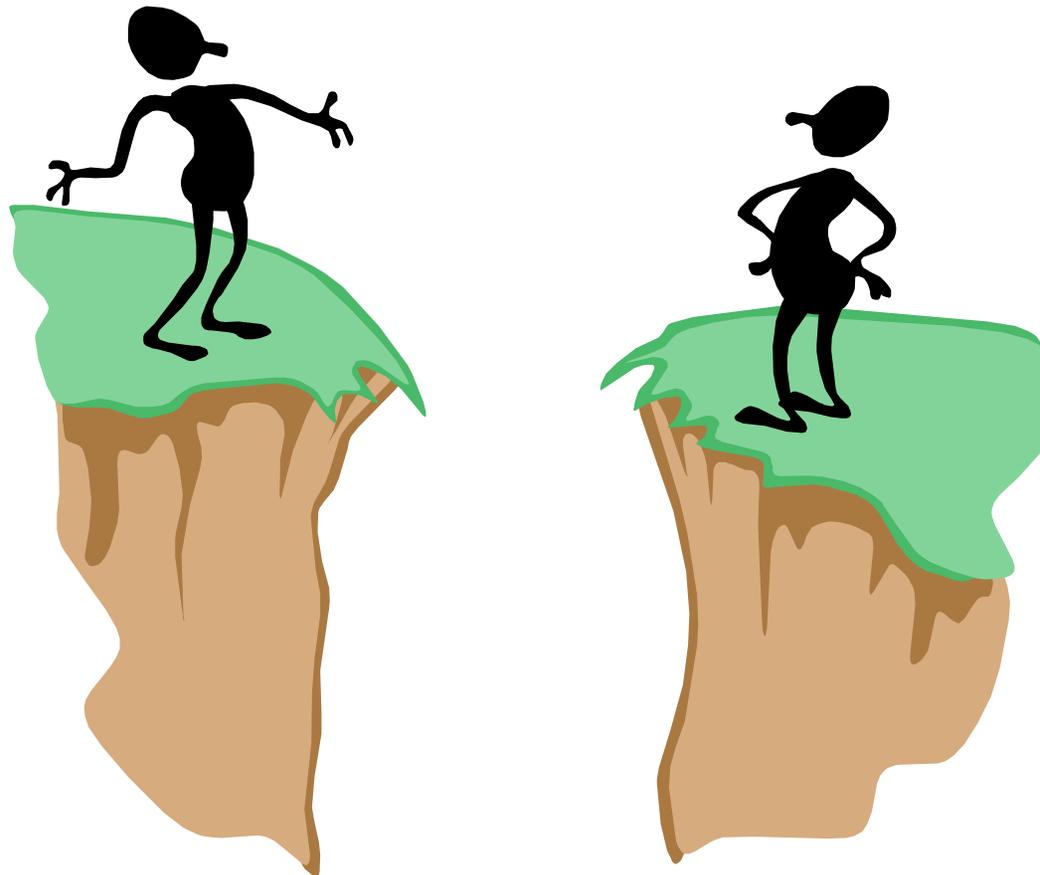
- > *bounded* - *analysis techniques, esp. analytic model checking*
- > *unbounded* - *simulation techniques, esp. simulative model checking*

- ❑ M Heiner, D Gilbert, R Donaldson:
Petri Nets for Systems and Synthetic Biology;
in SFM 2008, Springer LNCS 5016, pp. 215-264, 2008.

- ❑ M Heiner:
Understanding Network Behaviour by Structured Representations of Transition Invariants - A Petri Net Perspective on Systems and Synthetic Biology;
in Algorithmic Bioprocesses; Chapter 19, Springer, July 2009.

THANKS !

PN & Systems Biology



[HTTP://WWW-DSSZ.INFORMATIK.TU-COTTBUS.DE/BME/PETRINET2009](http://www-dssz.informatik.tu-cottbus.de/BME/PETRINET2009)