MODELLING OF BIOCHEMICAL NETWORKS WITH TIME PETRI NETS

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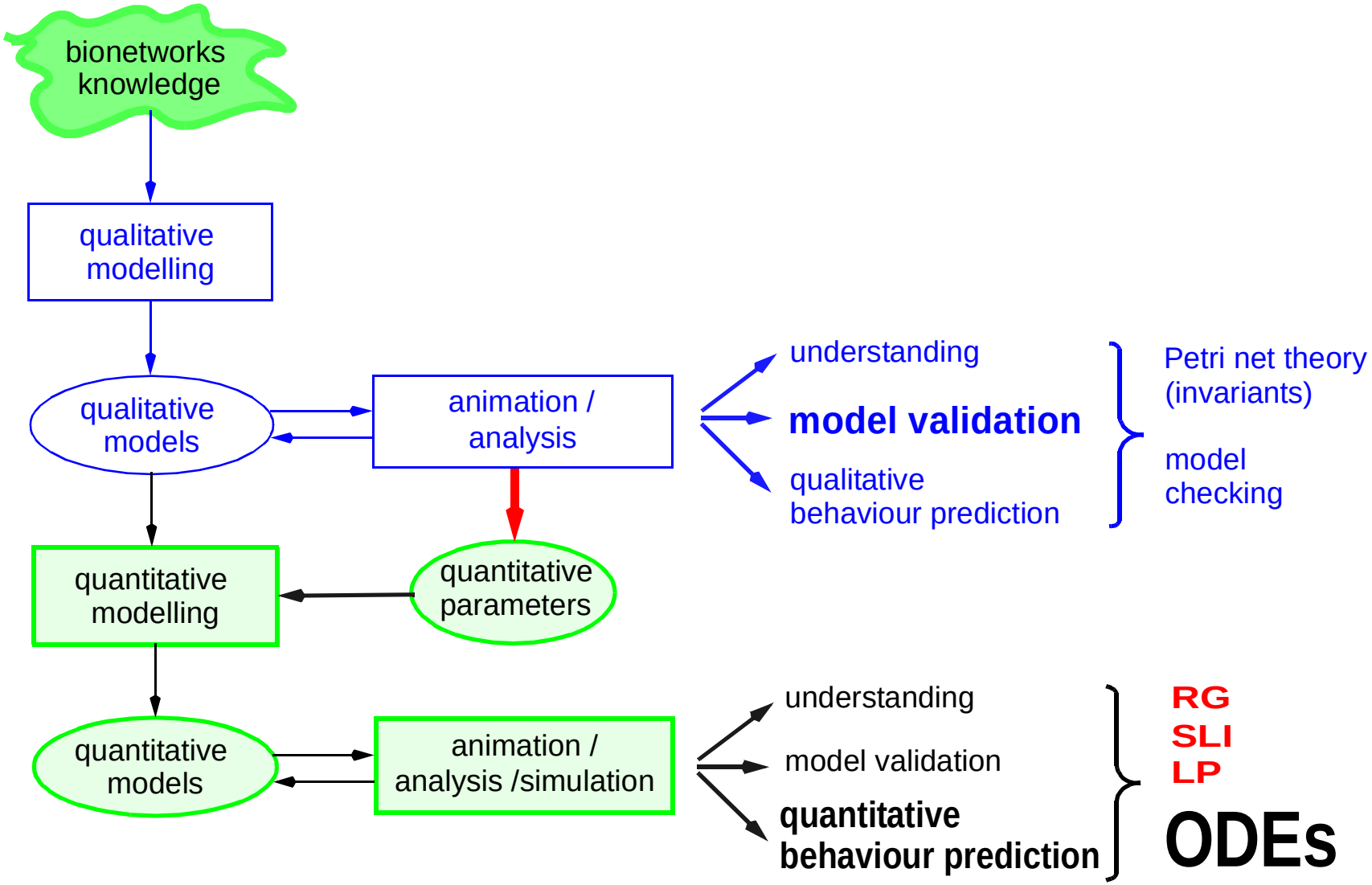
FRAMEWORK


bionetworks knowledge
qualitative modelling
qualitative models
animation / analysis
quantitative modelling
quantitative parameters
quantitative models
animation / analysis /simulation
understanding
model validation
qualitative behaviour prediction
Petri net theory (invariants)
model checking
understanding
model validation
quantitative behaviour prediction
RG
SLI
LP
ODEs

PETRI NETS - BASICS' REFRESH

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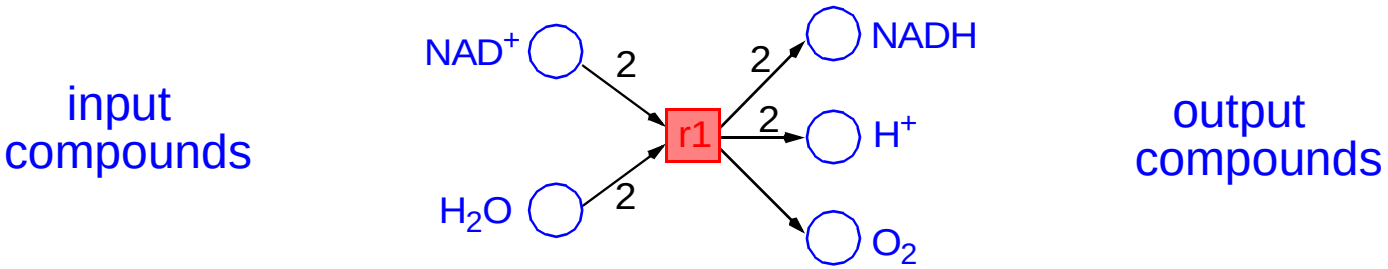
- **atomic actions -> Petri net transitions -> chemical reactions**

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



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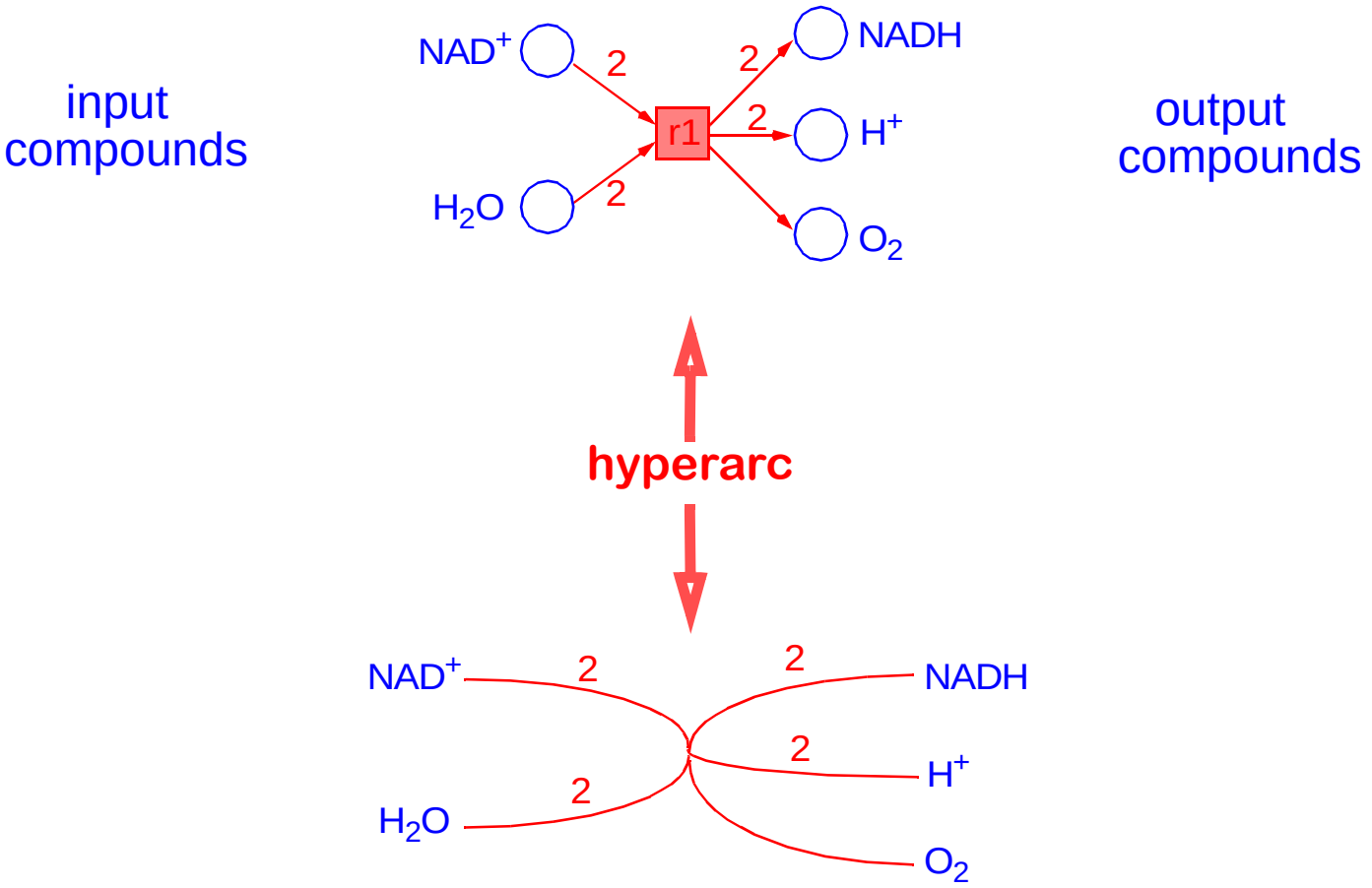

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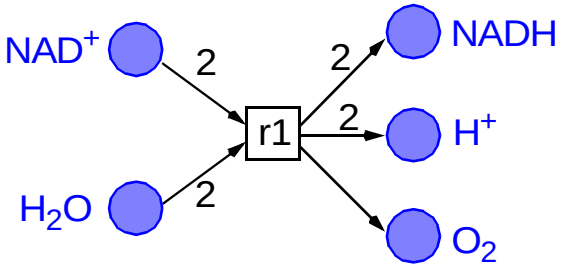
$$2\ NAD^+ + 2\ H_2O \rightarrow 2\ NADH + 2\ H^+ + O_2$$

input compounds

pre-conditions



output compounds

post-conditions

- **local conditions -> Petri net places -> chemical compounds**

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

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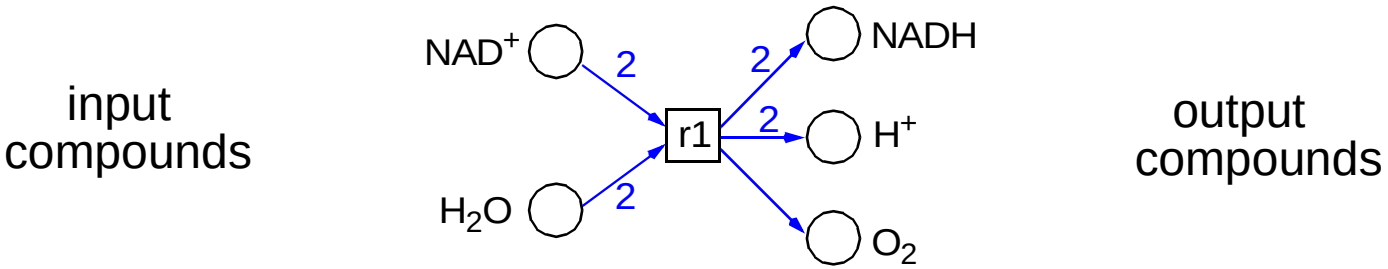

- **local conditions -> Petri net places -> chemical compounds**
- **multiplicities -> Petri net arc weights -> stoichiometric relations**

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

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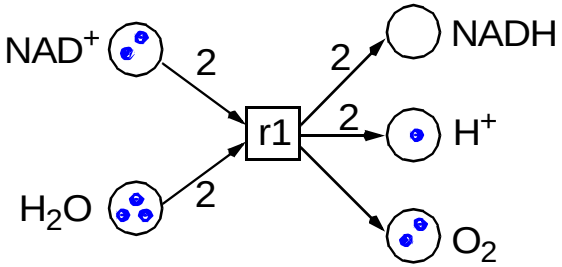
input compounds



output compounds

- **local conditions -> Petri net places -> chemical compounds**
- **multiplicities -> Petri net arc weights -> stoichiometric relations**
- **condition's state -> token(s) in its place -> available amount (e.g. mol)**
- **system state -> marking -> compounds distribution**

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

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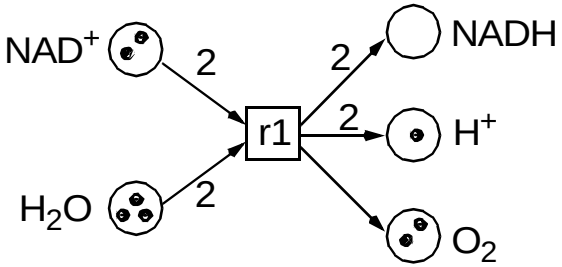
input compounds



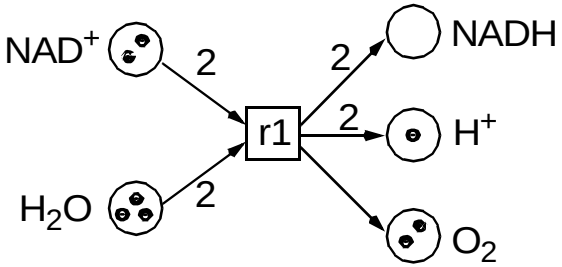
output compounds

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

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

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

input compounds



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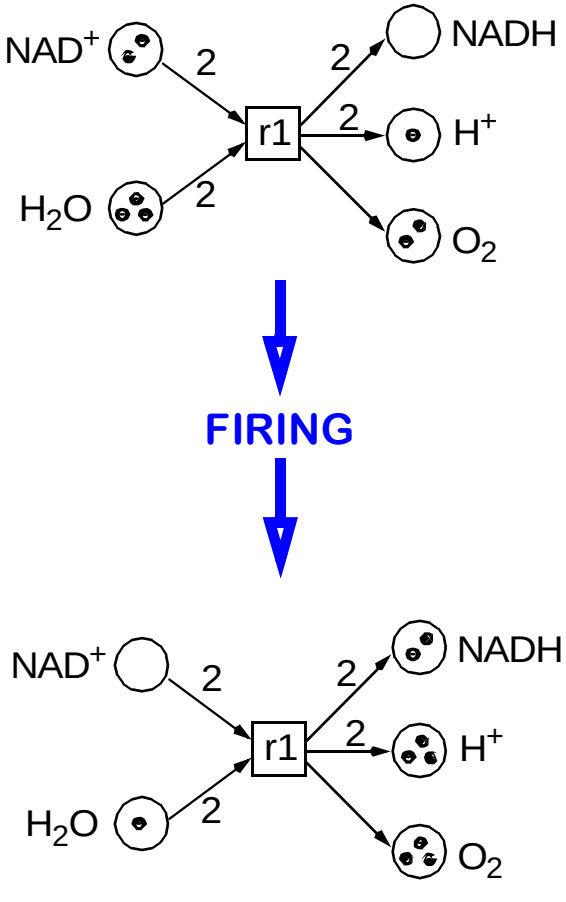

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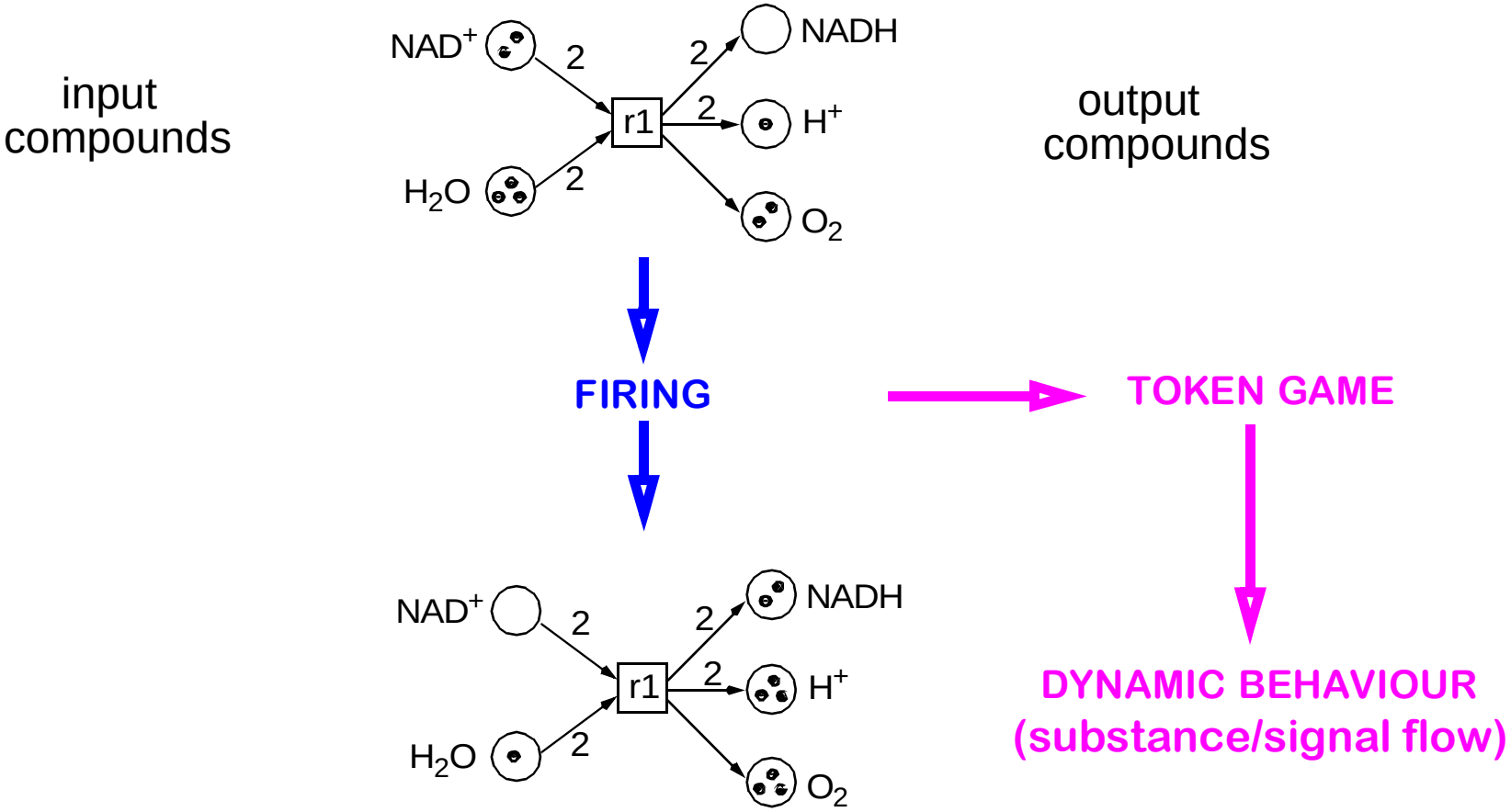
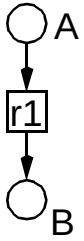


BIO PETRI NETS, EXAMPLE

r1: A -> B

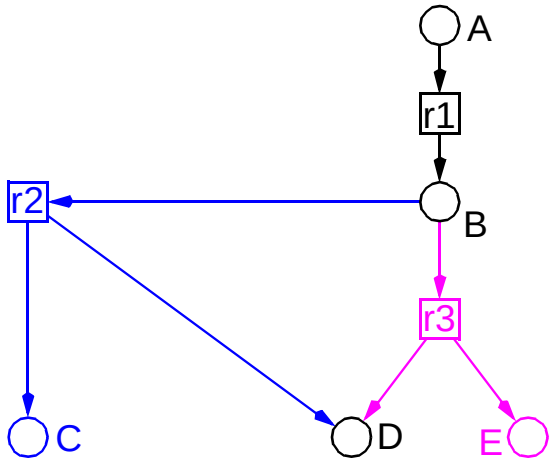


BIO PETRI NETS, EXAMPLE

r1: A -> B

r2: B -> C + D

r3: B -> D + E



-> alternative reactions

BIO PETRI NETS, EXAMPLE

r1: A -> B

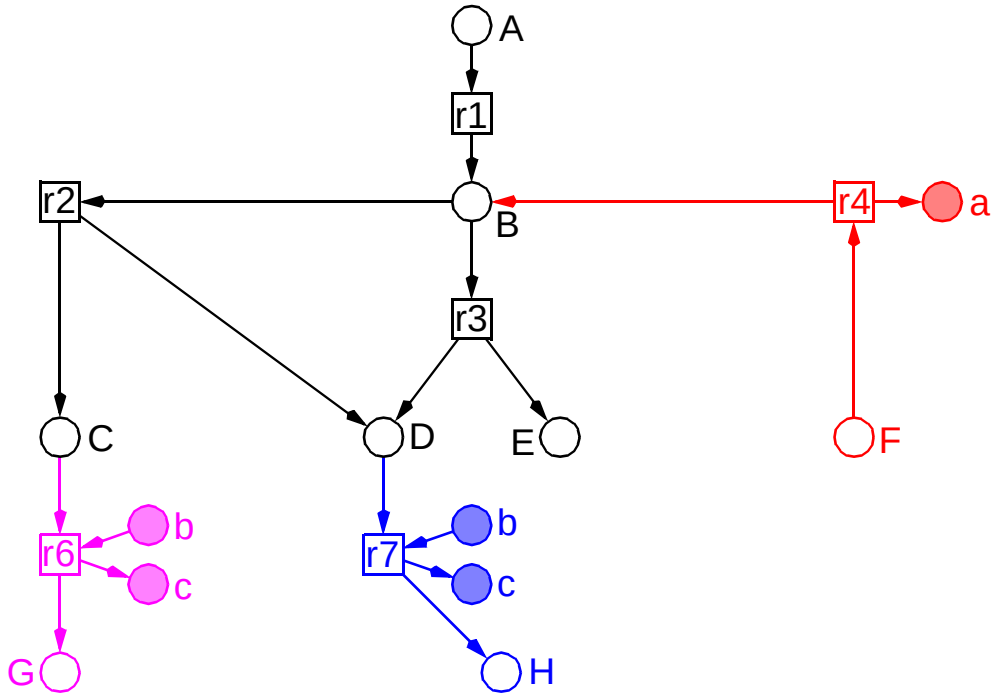
r2: B -> C + D

r3: B -> D + E

r4: F -> B + a

r6: C + b -> G + c

r7: D + b -> H + c



-> concurrent reactions

BIO PETRI NETS, EXAMPLE

r1: A -> B

r2: B -> C + D

r3: B -> D + E

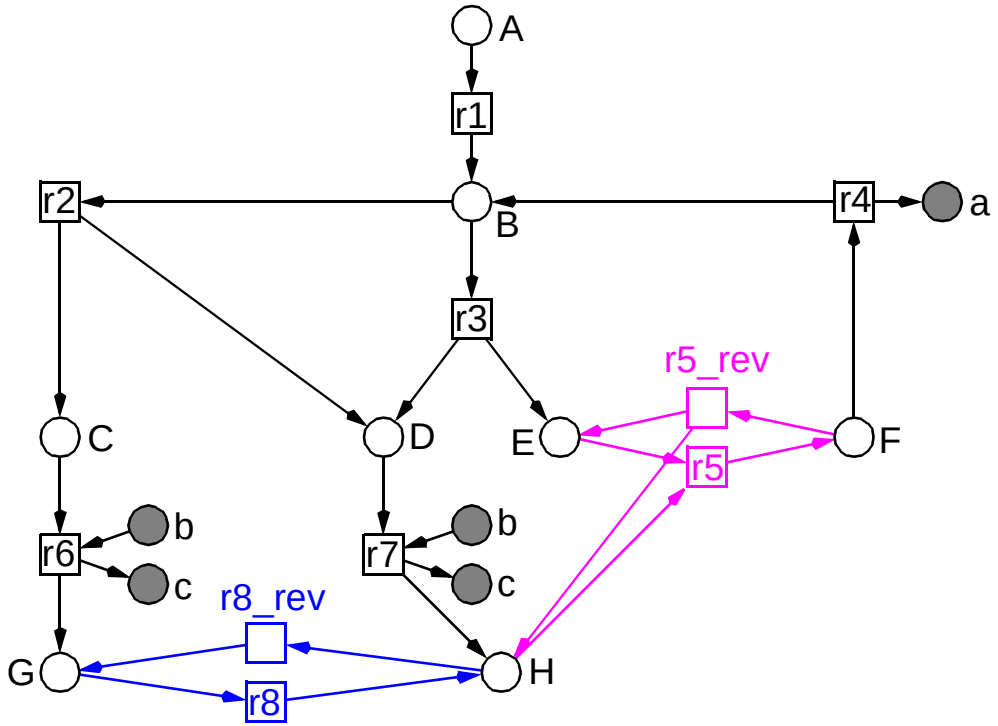
r4: F -> B + a

r5: E + H <-> F

r6: C + b -> G + c

r7: D + b -> H + c

r8: H <-> G



-> reversible reactions

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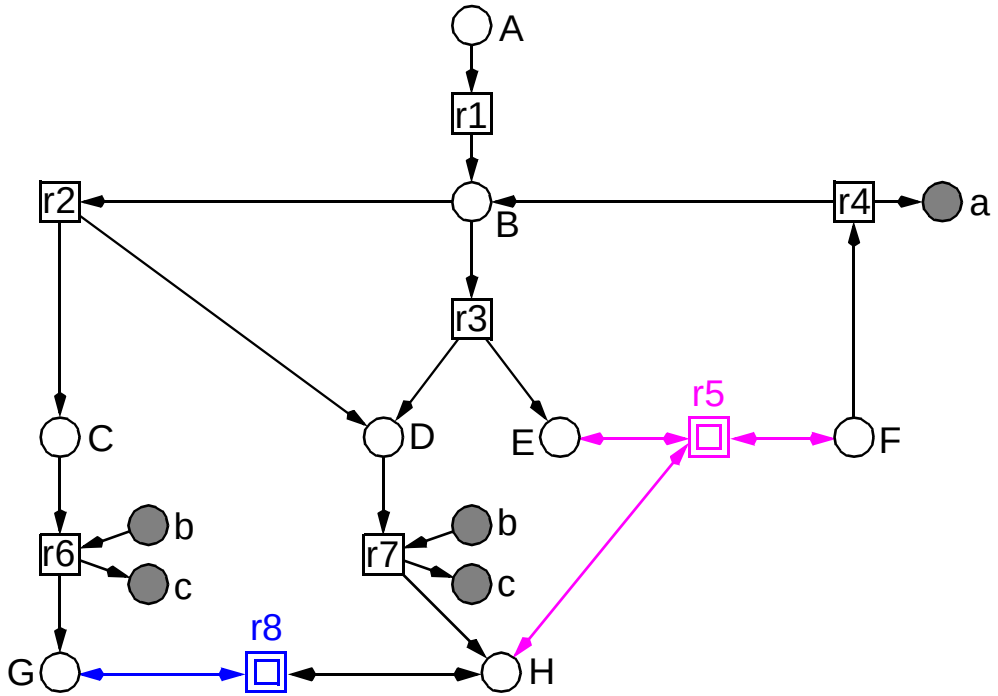

-> reversible reactions

- hierarchical nodes

BIO PETRI NETS, EXAMPLE

r1: A -> B

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r3: B -> D + E

r4: F -> B + a

r5: E + H <-> F

r6: C + b -> G + c

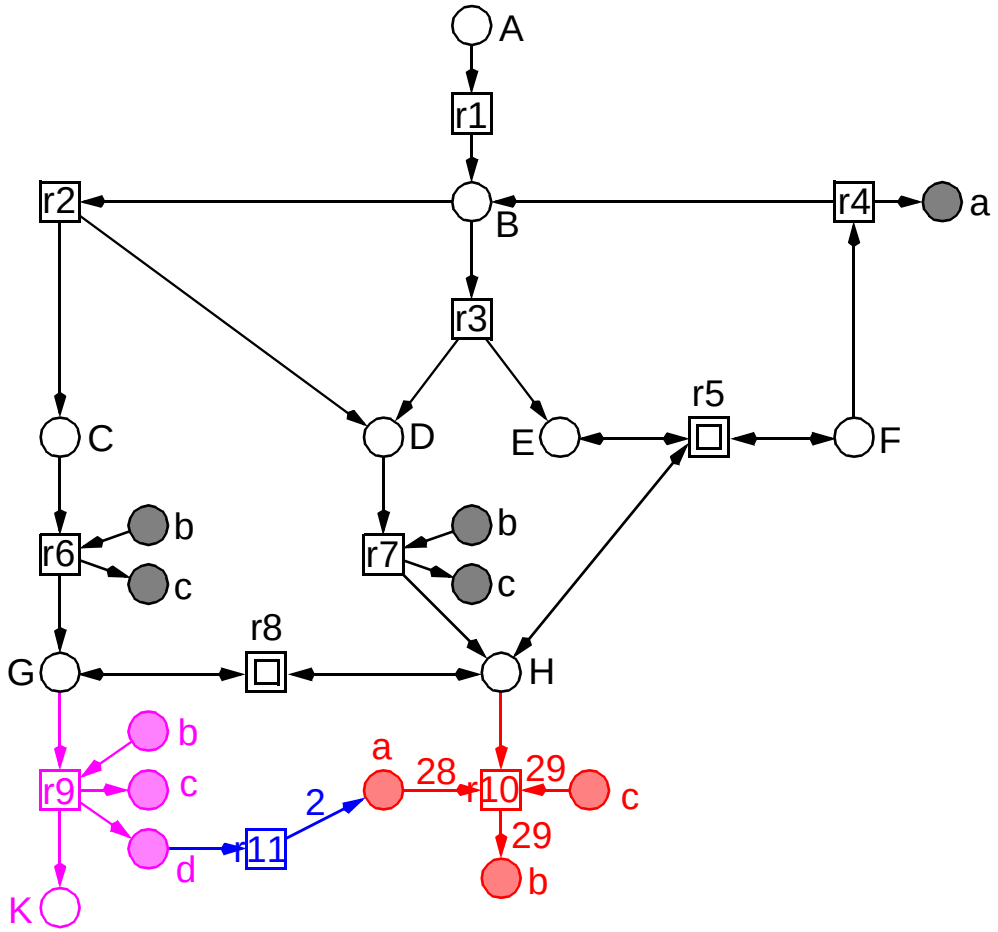
r7: D + b -> H + c

r8: H <-> G

r9: G + b -> K + c + d

r10: H + 28a + 29c -> 29b

r11: d -> 2a



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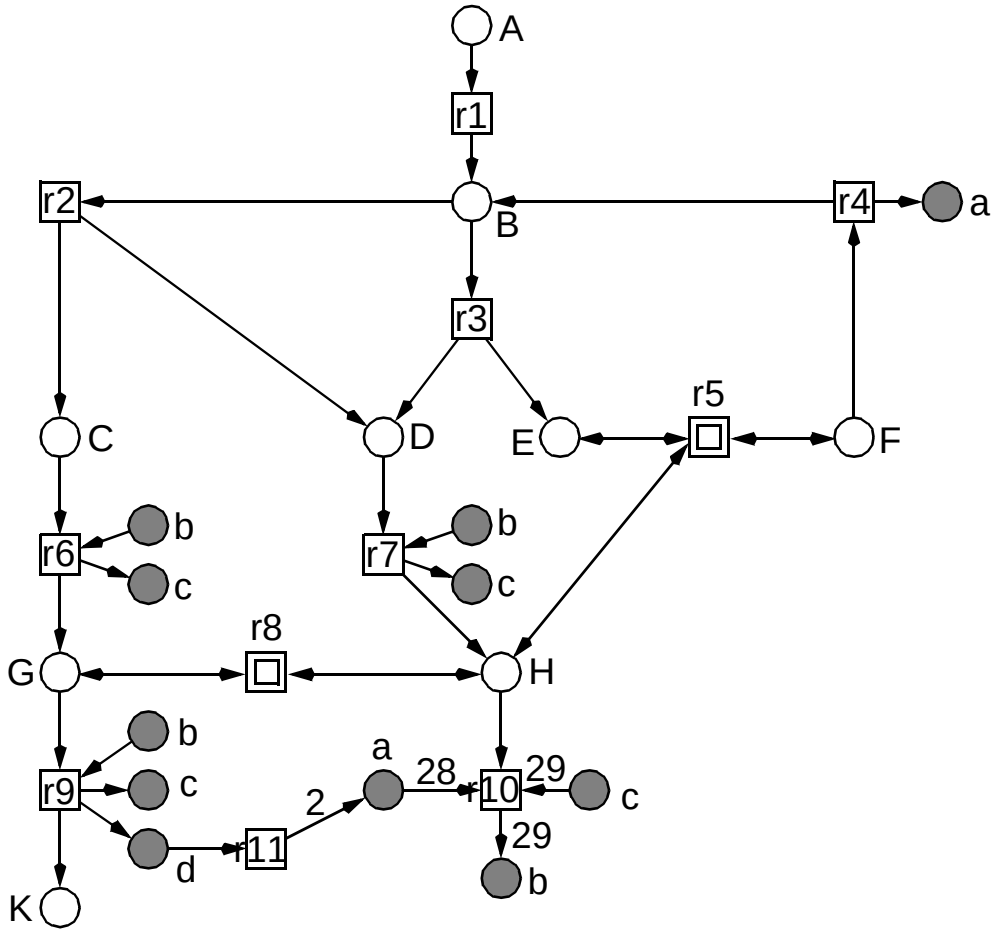

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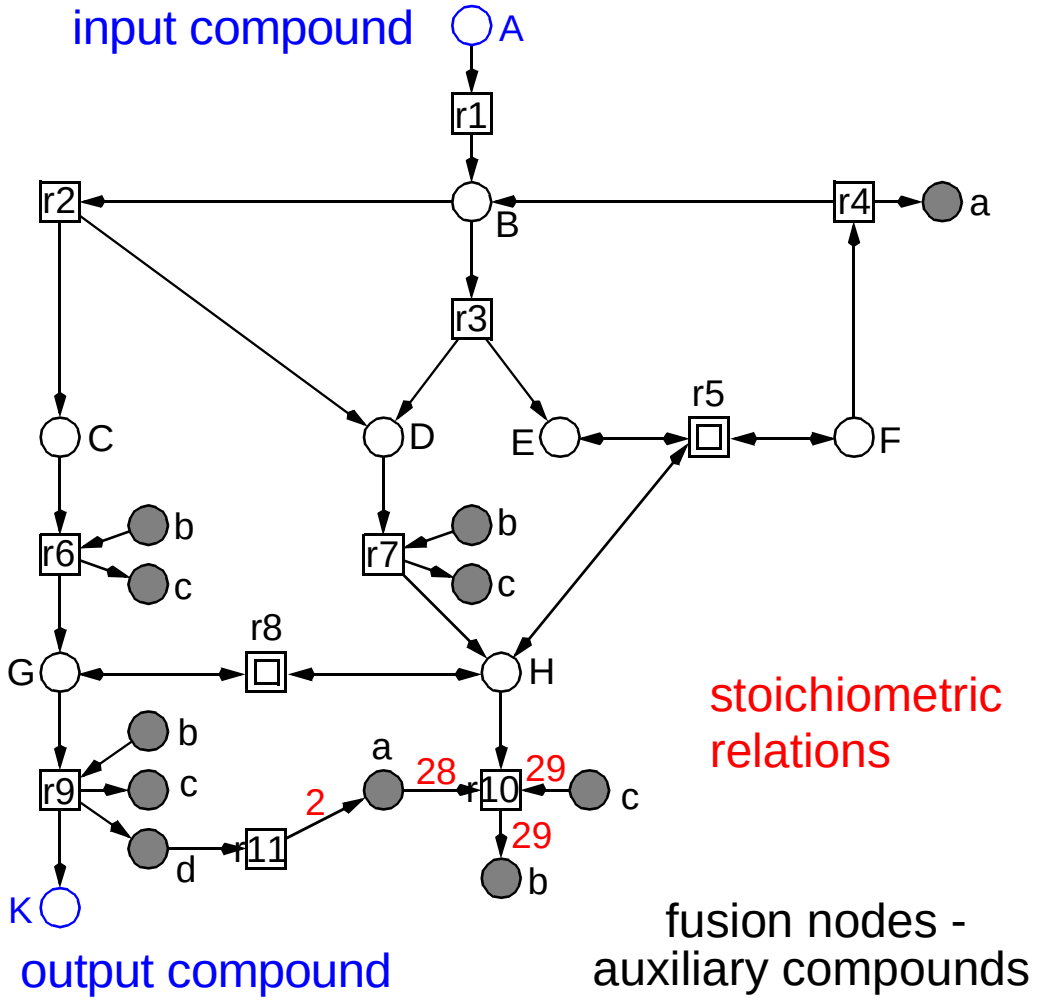
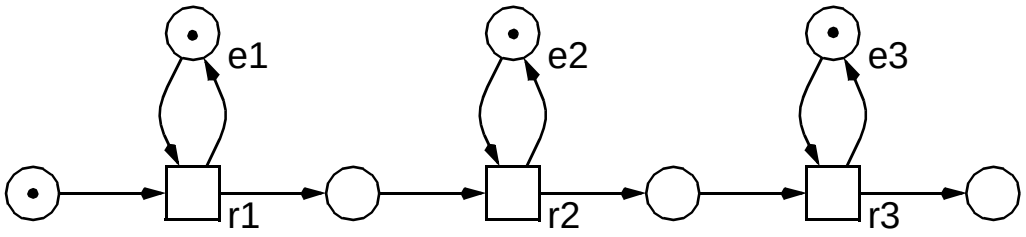


TYPICAL BASIC STRUCTURES

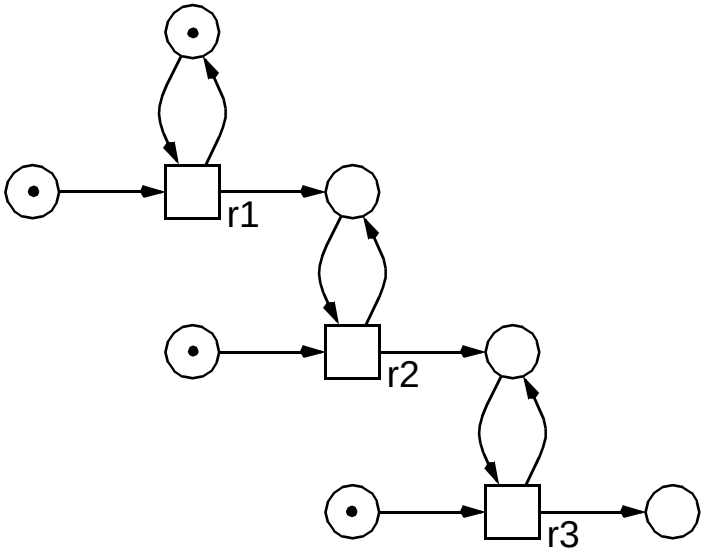
- **metabolic networks**

  -> *substance flows*



- **signal transduction networks**

  -> *signal flows*



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

- **biochemically interpreted Petri net**

  -> *partial order sequences of chemical reactions (= elementary actions)*
  transforming input into output compounds / signals
  [respecting the given stoichiometric relations, if any]

  -> *set of all pathways*
  from the input to the output compounds / signals
  [respecting the stoichiometric relations, if any]

- **pathway**

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

- **typical (structural) properties**

```
INA
ORD HOM NBM PUR CSV SCF CON  SC  Ft0 tF0 Fp0 pF0 MG  SM FC  EFC ES
 N   N   N   Y   N   N   Y   N   N   N   Y   Y   N   N   N   N   N
DTP CPI CTI  B  SB  REV DSt BSt DTr DCF  L   LV L&S
 N   N   N   Y   Y   ?   ?   ?   ?   ?   N   ?   N
```

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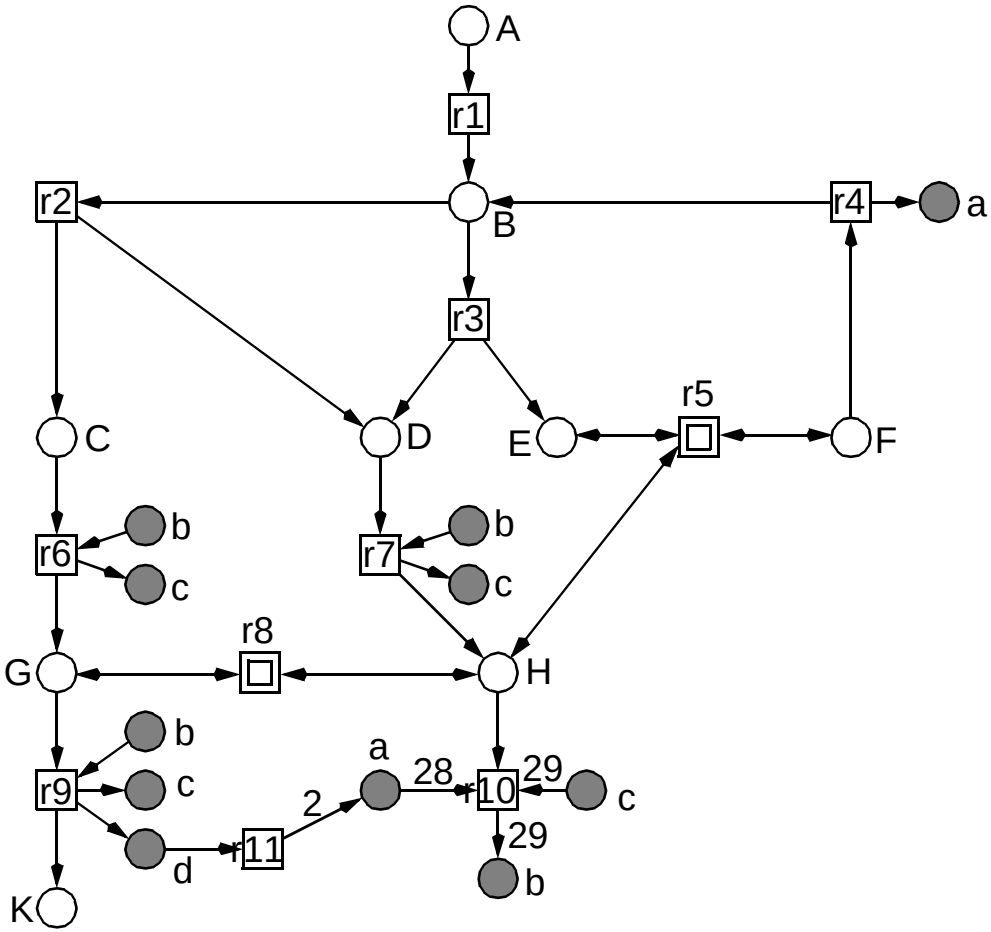
- **typical properties**

INA																		
ORD	HOM	NBM	PUR	CSV	SCF	CON	SC	Ft0	tF0	Fp0	pF0	MG	SM	FC	EFC	ES		
N	N	N	Y	N	N	Y	N	N	N	Y	Y	N	N	N	N	N		
DTP	CPI	CTI	B	SB	REV	DSt	BSt	DTr	DCF	L	LV	L&S						
N	N	N	Y	Y	?	?	?	?	?	N	?	N						

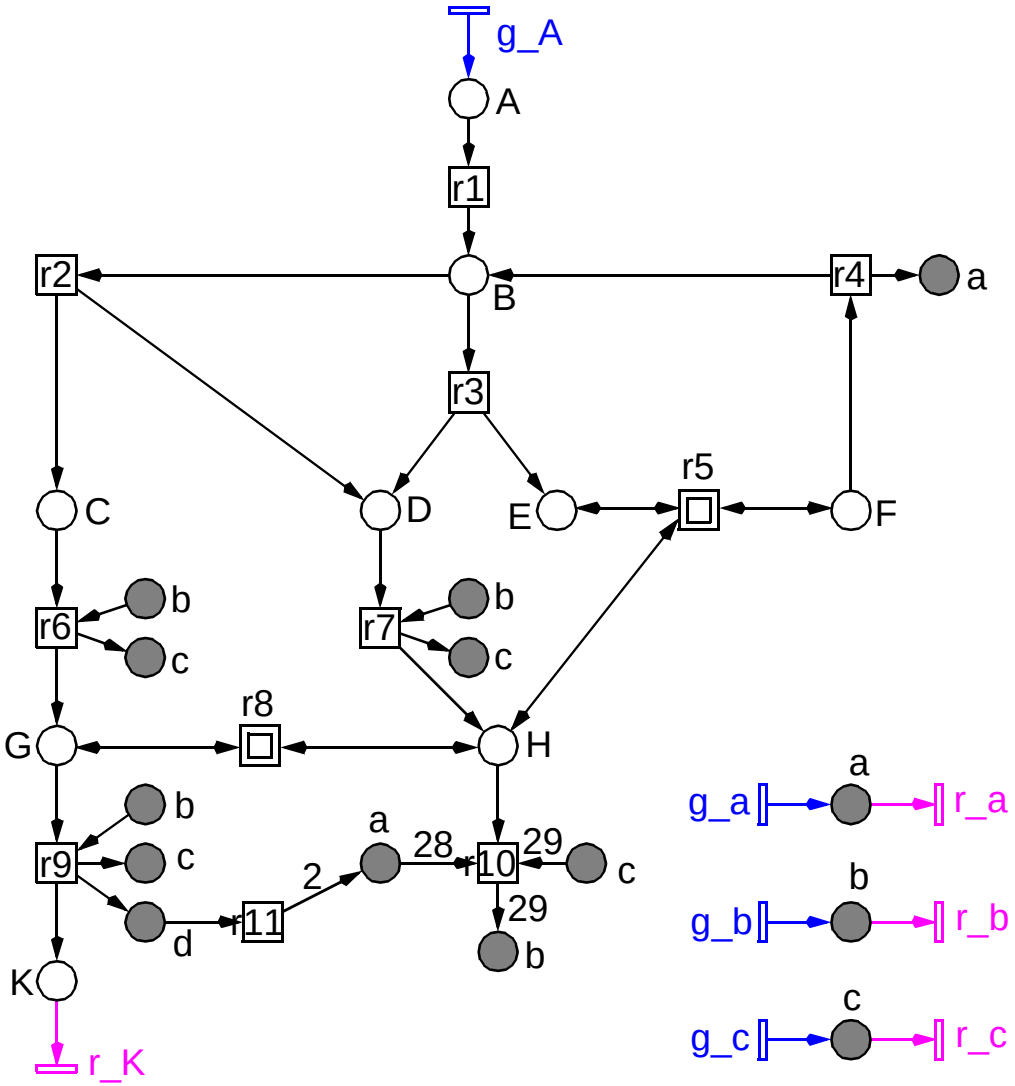
BIO NETWORKS NEED ENVIRONMENT BEHAVIOUR

- **to animate the model**
  - -> *infinite substance flow*
  - -> *deeper insights*
- **to validate the model**
  - -> *consistency criteria*
- **steady flow**
  - -> *input substances*
  - -> *output substances*
- **auxiliary substances**
  - -> *as much as necessary*
- **minimal assumptions**



BIO NETWORK WITH ENVIRONMENT BEHAVIOUR

- **input substances**
  -> *generating pre-transitions*
- **output substances**
  -> *consuming post-transitions*
- **auxiliary substances**
  -> *both*
- **no boundary places, but boundary transitions**
- **transitions without pre-places**
  -> *live*
  -> *all post-places are unbounded*
  -> *all places simultaneously unbounded (?)*



- **typical properties without environment**

INA																	
ORD	HOM	NBM	PUR	CSV	SCF	CON	SC	Ft0	tF0	Fp0	pF0	MG	SM	FC	EFC	ES	
N	N	N	Y	N	N	Y	N	N	N	Y	Y	N	N	N	N	N	
DTP	CPI	CTI	B	SB	REV	DSt	BSt	DTr	DCF	L		LV	L&S				
N	N	N	Y	Y	?	?	?	?	?	N		?	N				

- **typically expected properties with environment**

INA																	
ORD	HOM	NBM	PUR	CSV	SCF	CON	SC	Ft0	tF0	Fp0	pF0	MG	SM	FC	EFC	ES	
N	N	N	Y	N	N	Y	N	Y	Y	N	N	N	N	N	N	N	
DTP	CPI	CTI	B	SB	REV	DSt	BSt	DTr	DCF	L		LV	L&S				
?	N	Y	N	N	y	N	?	n	n	y		y	N				

how to prove ?

UNBOUNDEDNESS - WHAT NEXT ?

BIO NETWORKS, STEADY STATE BEHAVIOUR

- **steady state behaviour**
  - -> *all possible flows preserving a given compounds distribution*
  - -> *elementary modes [Schuster 1993] = minimal T-invariants*

- **consistency criteria -> pathways analysis**
  - -> *CTI*
  - -> *no minimal T-invariant without biological interpretation*
  - -> *no known biological behaviour without corresponding T-invariant*

T-INVARIANTS - BASICS' REFRESH

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INCIDENCE MATRIX C

- a representation of the net structure => stoichiometric matrix

$C =$

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

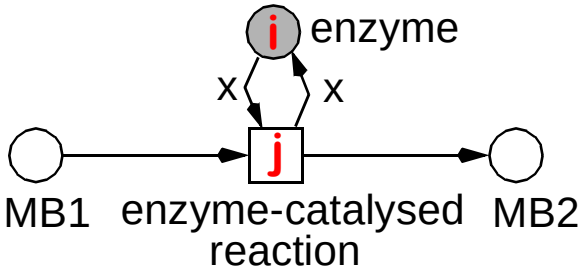
$cij = (pi, tj) = F(tj,pi) - F(pi, tj) = \Delta\, tj(pi)$

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

- 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

T-INVARIANTS, BASICS

- **Lautenbach, 1973**
- **T-invariants**
  - -> *integer solutions x of* $Cx = 0, x \neq 0, x \geq 0$
  - -> *multisets of transitions*
  - -> *Parikh vector*
- **minimal T-invariants**
  - -> *there is no T-invariant with a smaller support*
  - -> *gcD of all entries is 1*
  - -> *sets of transitions*
- **any T-invariant is a non-negative linear combination of minimal ones**
  - -> *multiplication with a positive integer*
  - -> *addition*
  - -> *Division by gcD*

$$kx = \sum_i a_i x_i$$

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

T-INVARIANTS IN BIO NETWORK

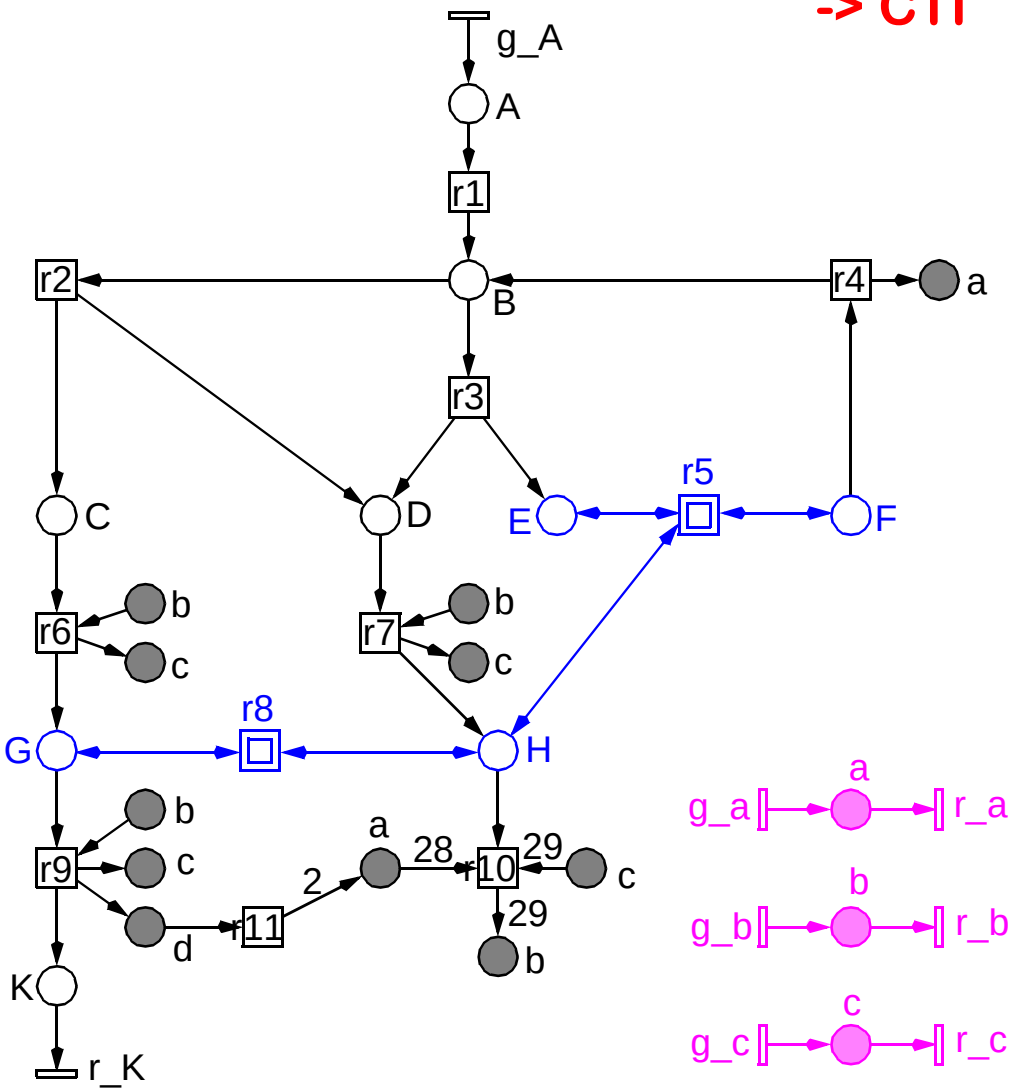
trivial min. T-invariants (5)

-> 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



T-INVARIANTS, INTERPRETATIONS

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

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

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

T-INVARIANTS, FIRST INTERPRETATION

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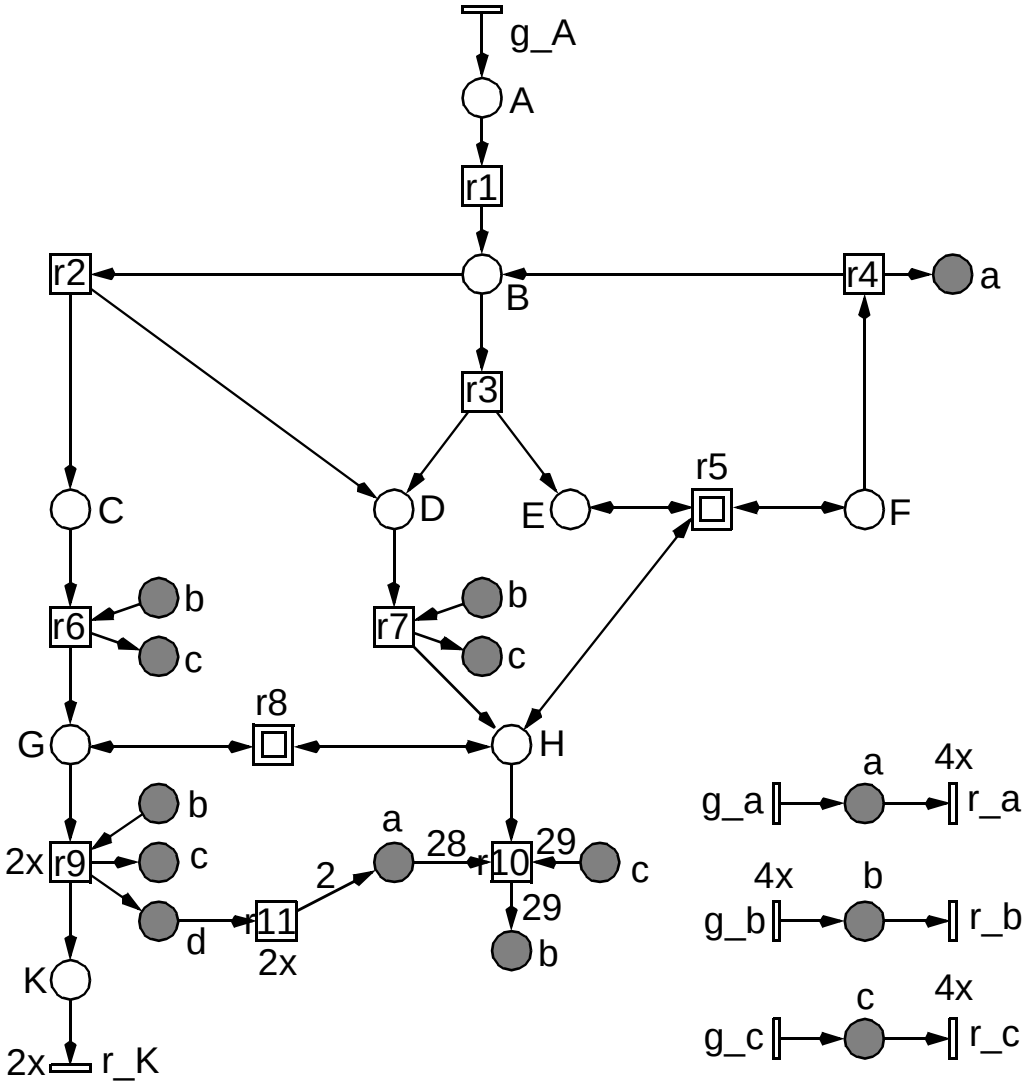
BIO NETWORK, I/O-T-INVARIANT

- **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



BIO NETWORK, I/O-T-INVARIANT

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| *12.r11* : *2,*
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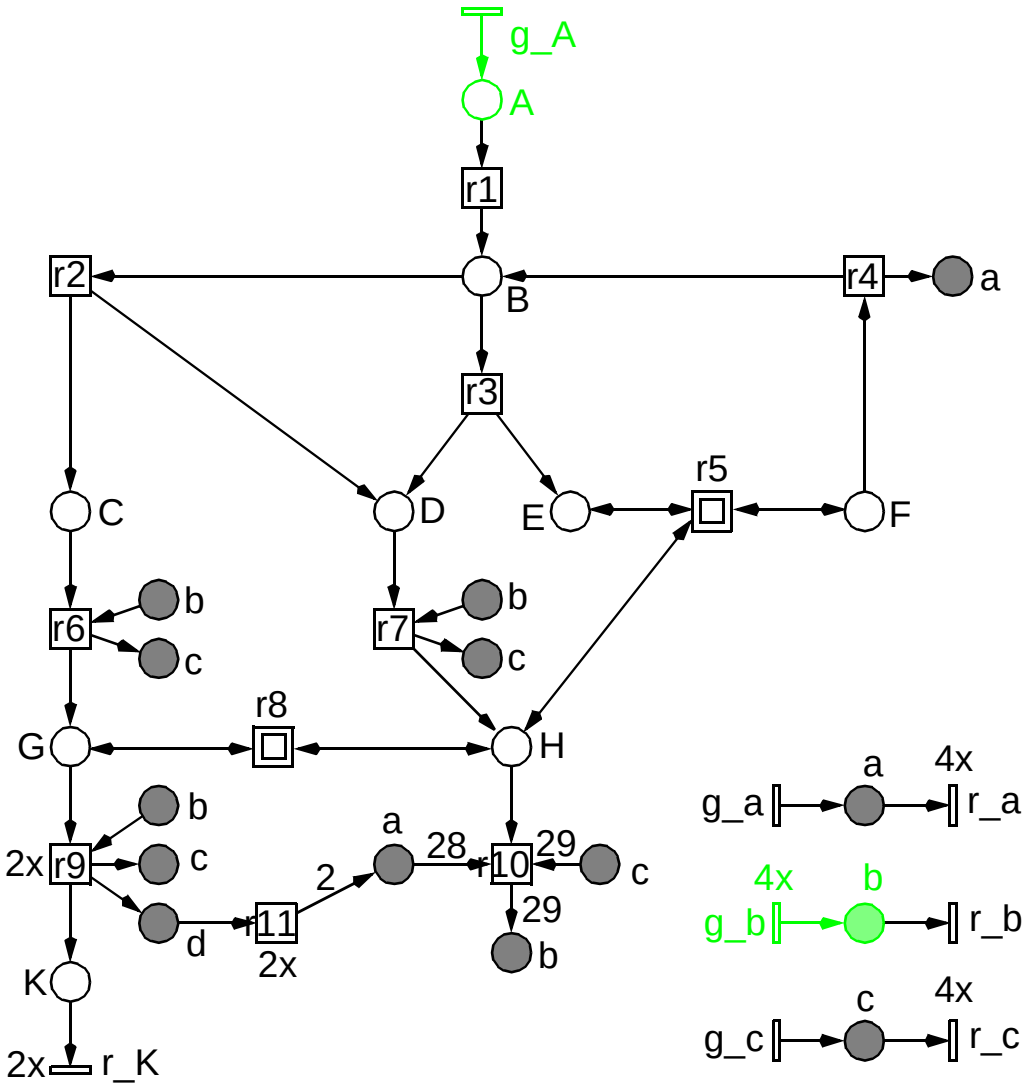

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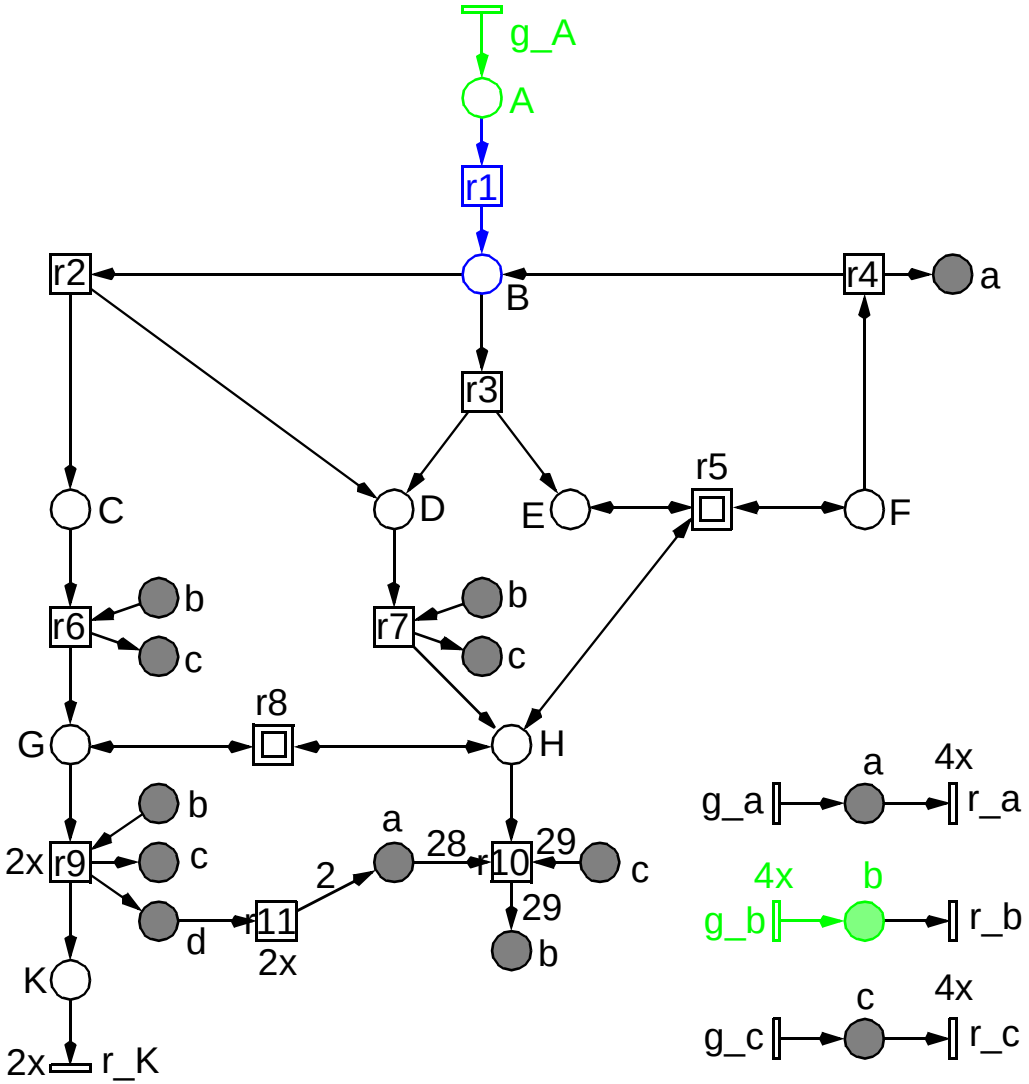

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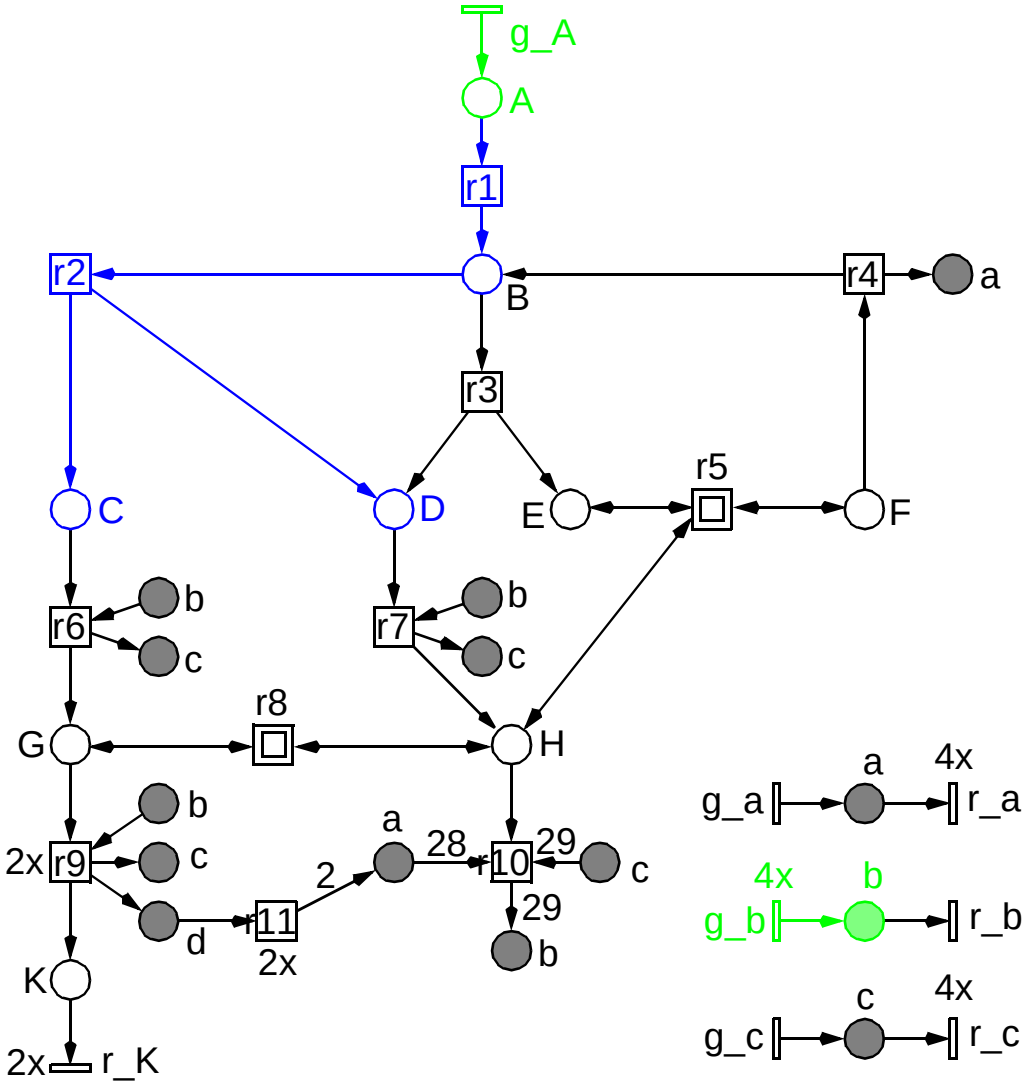

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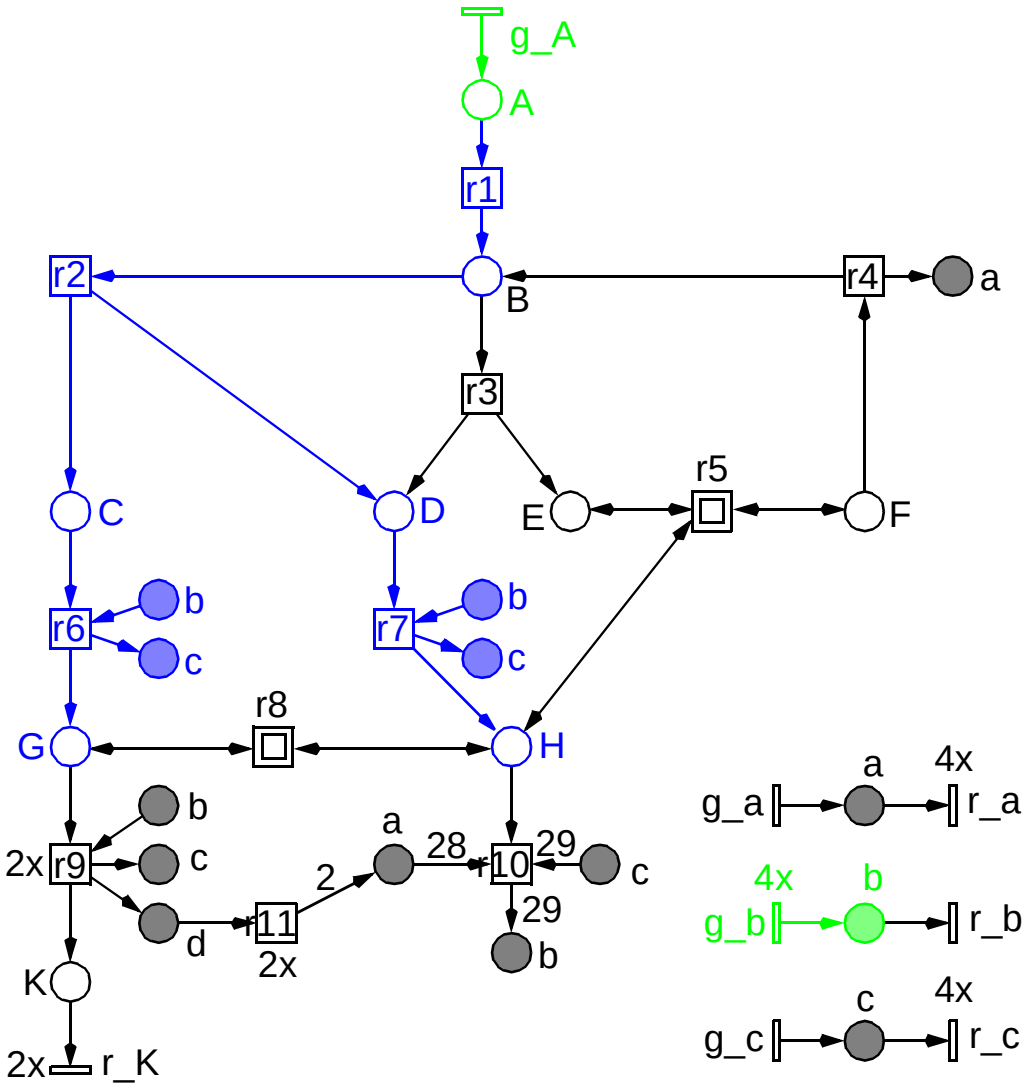
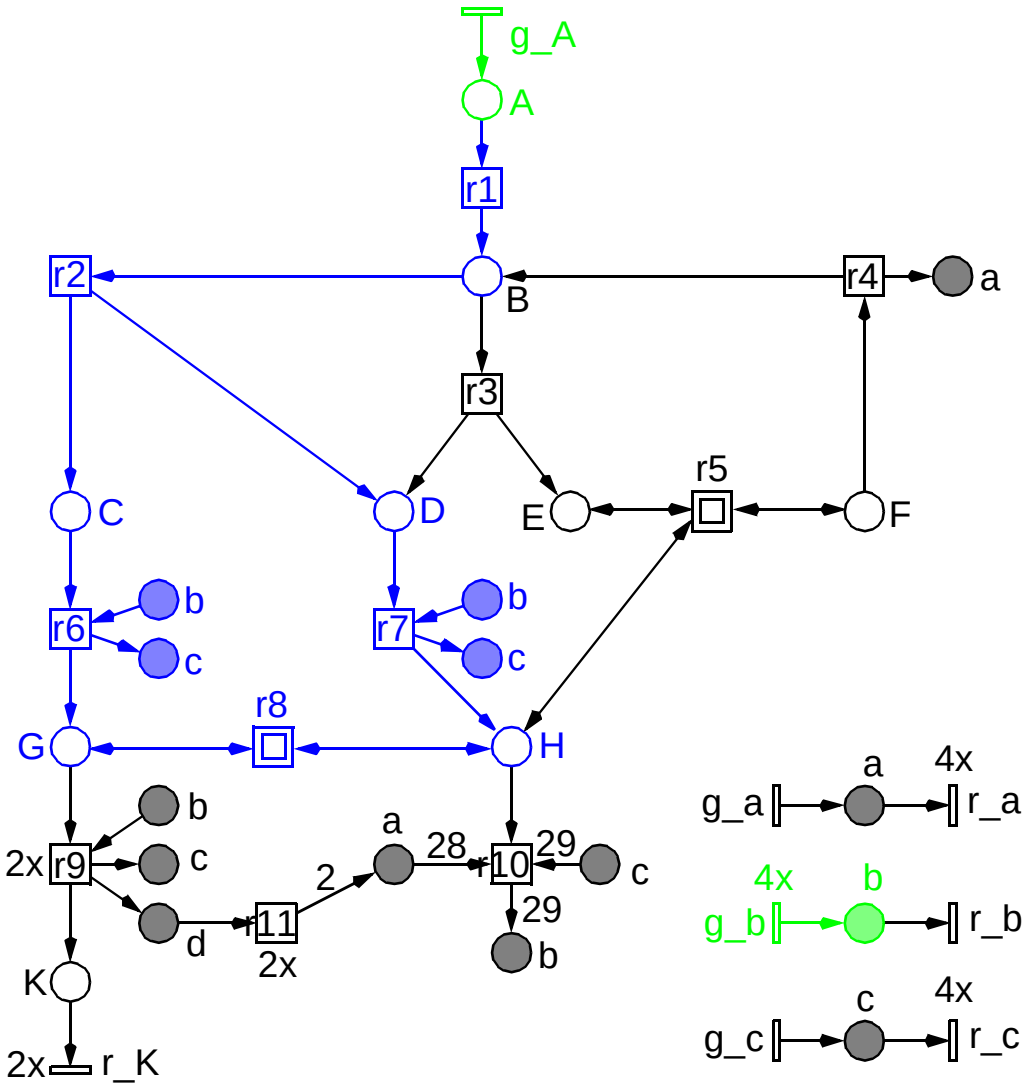
| 14.r_K : 2,
| 15.g_b : 4,
| 18.r_c : 4,
| 20.r_a : 4



BIO NETWORK, I/O-T-INVARIANT

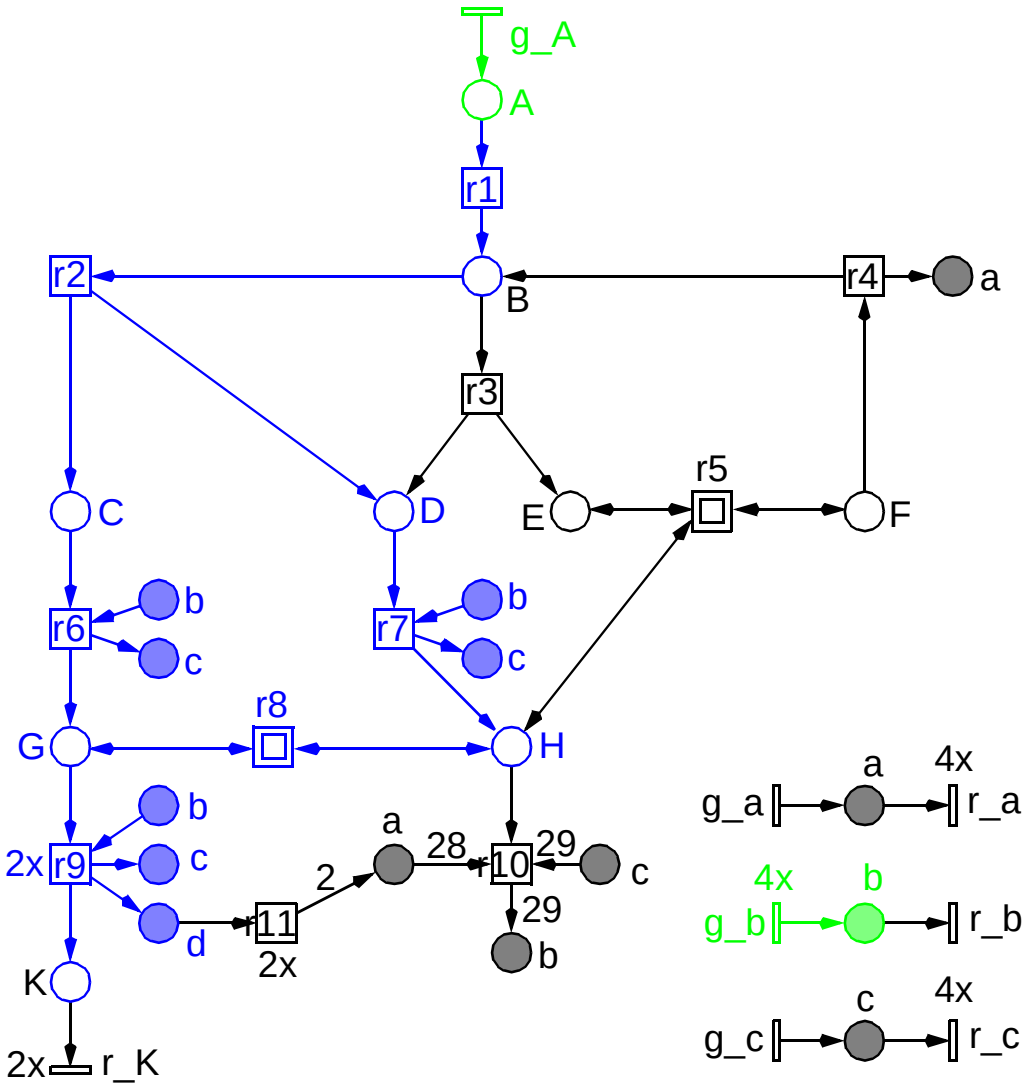
- **i/o-T-invariant, example**

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



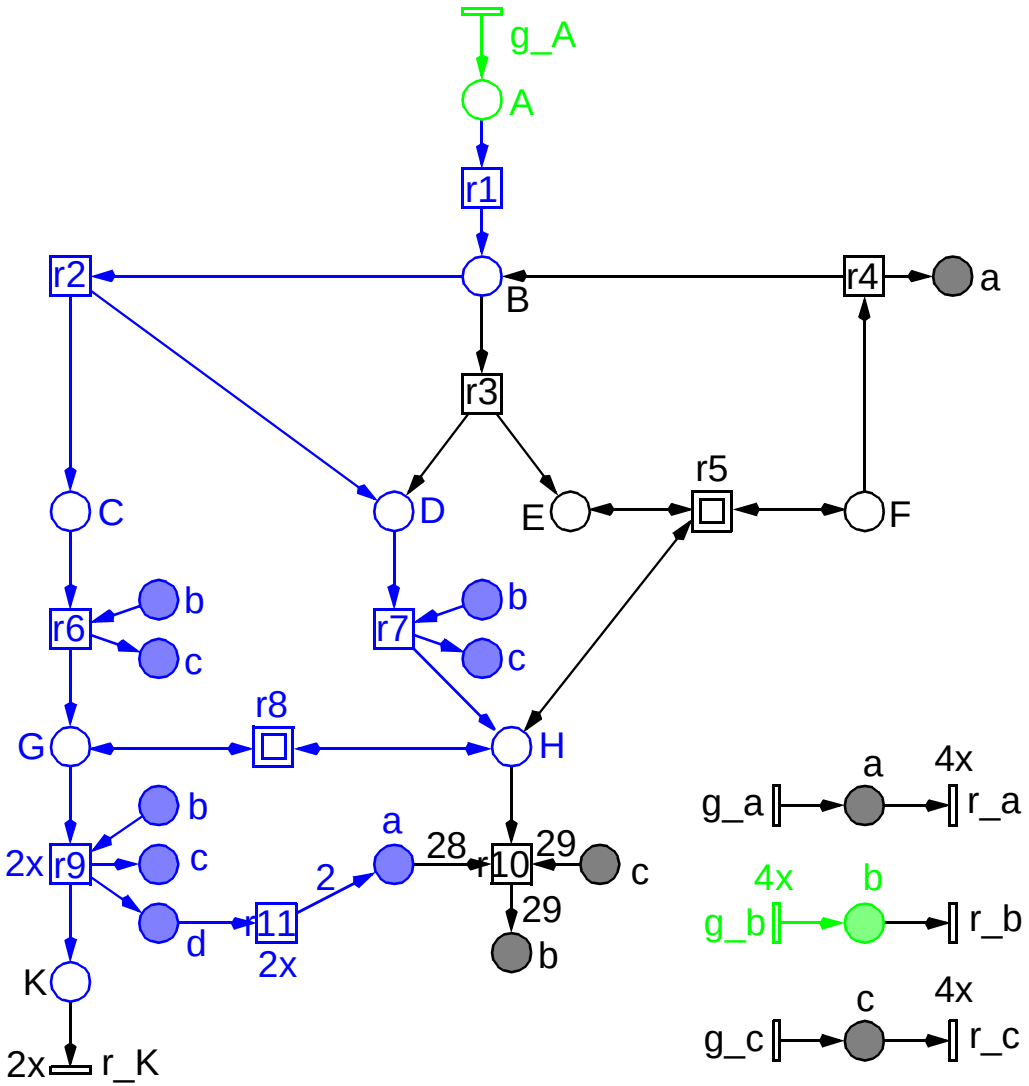
- **i/o-T-invariant, example**

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



- **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*



BIO NETWORK, I/O-T-INVARIANT

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

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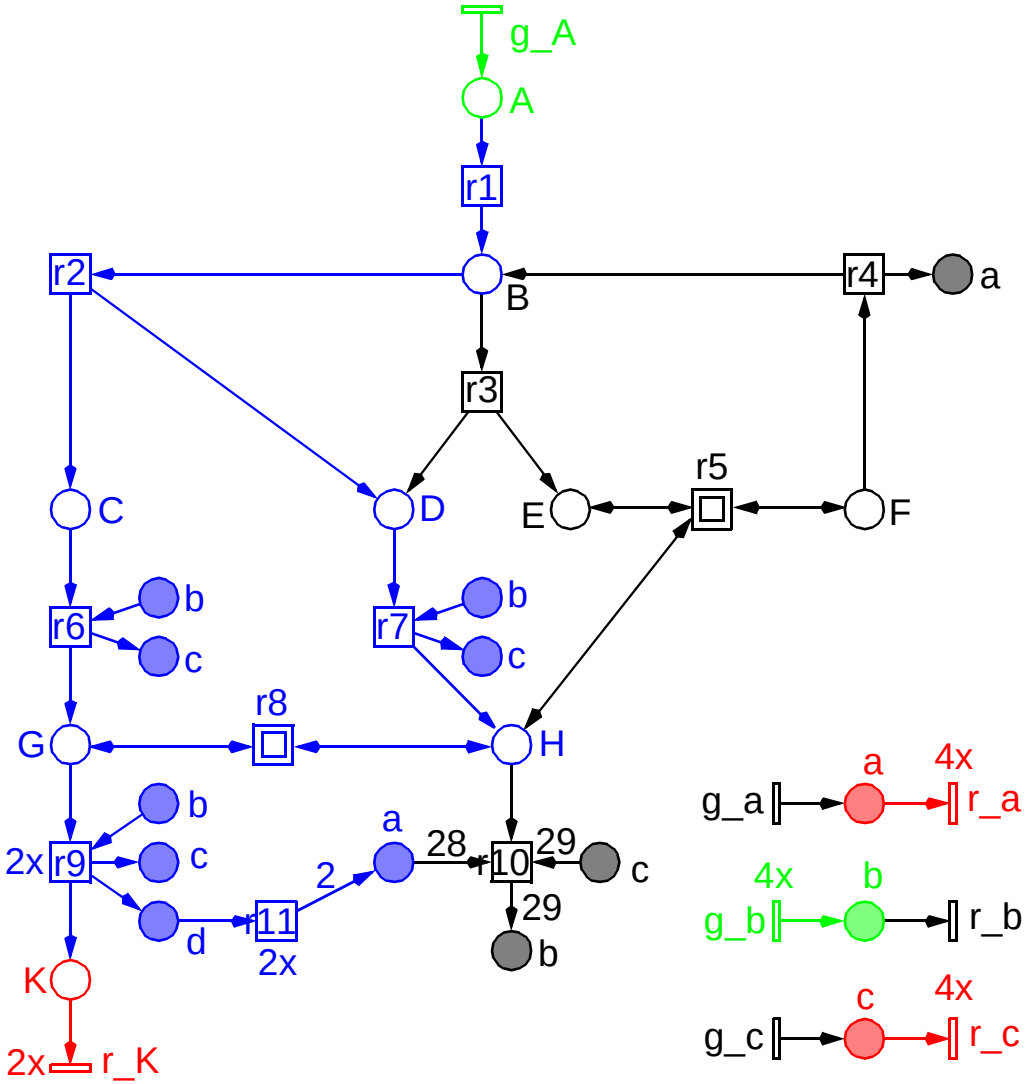
| *1.r2* : *1,*
| *3.r8_rev* : *1,*
| *4.r6* : *1,*
| *5.r7* : *1,*
| *9.r9* : *2,*
| *12.r11* : *2,*
| *13.g_A* : *1,*
| *14.r_K* : *2,*
| *15.g_b* : *4,*
| *18.r_c* : *4,*
| *20.r_a* : *4*



BIO NETWORK, I/O-T-INVARIANT

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

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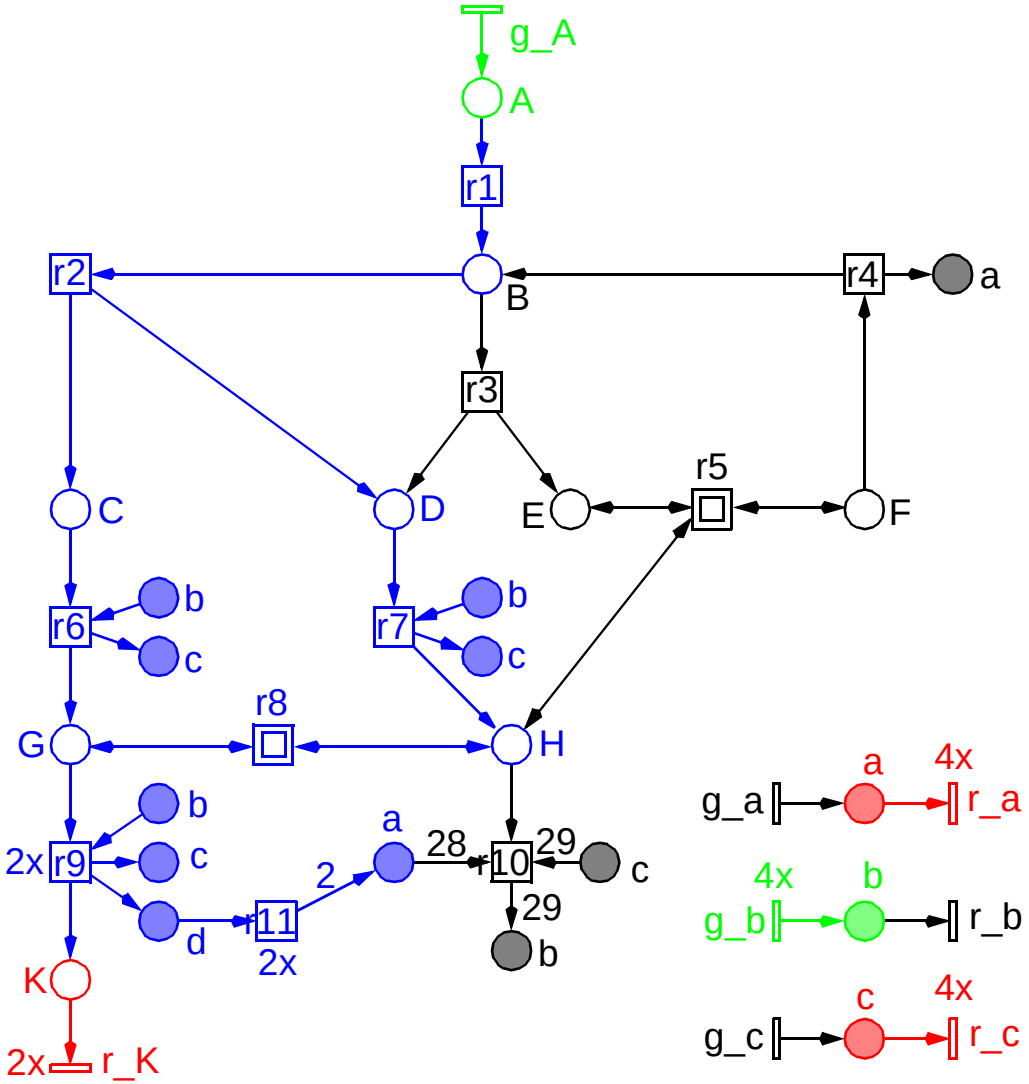
| *4.r6* : *1,*
| *5.r7* : *1,*
| *9.r9* : *2,*
| *12.r11* : *2,*
| *13.g_A* : *1,*
| *14.r_K* : *2,*
| *15.g_b* : *4,*
| *18.r_c* : *4,*
| *20.r_a* : *4*

- **sum equation**

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



T-INVARIANTS, SECOND INTERPRETATION

T-INVARIANTS, SECOND INTERPRETATION

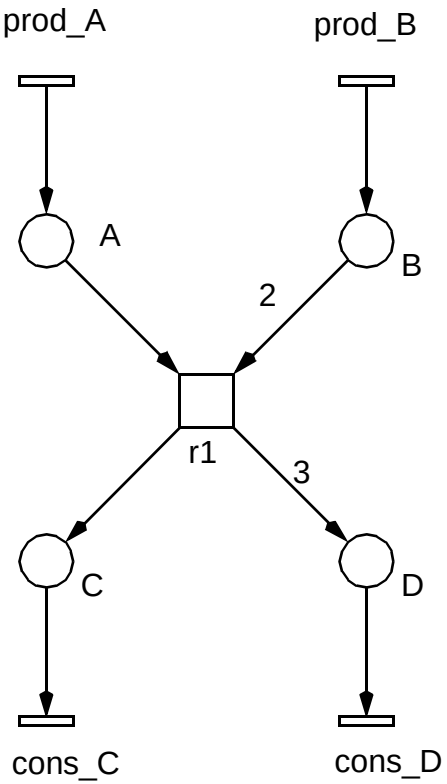
- **Parikh vector**
  -> *relative transition firing rates of transitions occuring permanently & concurrently*

- **relative transition firing rates**
  -> *may be implemented by transition firing times*
    - *constant*
    - *interval*

- **quantitative model**
  -> *qualitative model + firing times reflecting the firing rates*
  -> *time-dependent model*

- **claim**
  -> *transformation preserves all possible behaviour (= minimal T-invariants)*

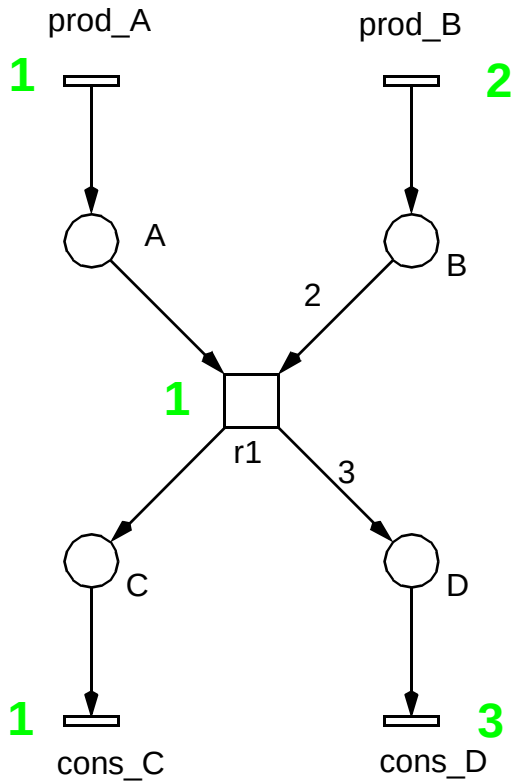
TRANSFORMATION, EX1



-> properties as time-less net

```
INA
ORD HOM NBM PUR CSV SCF CON SC  Ft0 tF0 Fp0 pF0 MG  SM  FC  EFC ES
 N   Y   N   Y   N   Y   Y   N   Y   Y   N   N   Y   N   Y   Y   Y
CPI CTI  B  SB  REV DSt BSt DTr DCF  L   LV L&S
 N   Y   N   N   Y   N   ?   N   Y   Y   Y   N
```

TRANSFORMATION, EX1

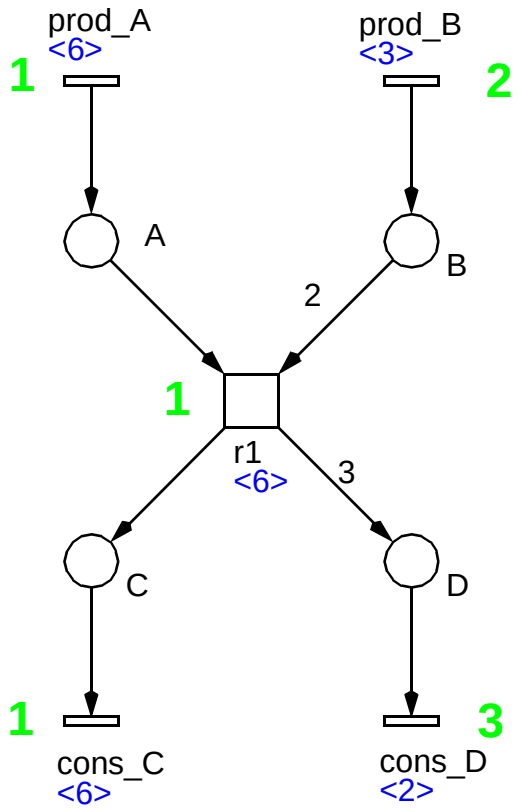


T-INVARIANT

-> properties as time-less net

```
INA
ORD HOM NBM PUR CSV SCF CON SC  Ft0 tF0 Fp0 pF0 MG  SM  FC  EFC ES
 N   Y   N   Y   N   Y   Y   N   Y   Y   N   N   Y   N   Y   Y   Y
CPI CTI  B  SB  REV DSt BSt DTr DCF  L   LV L&S
 N   Y   N   N   Y   N   ?   N   Y   Y   Y   N
```

TRANSFORMATION, EX1

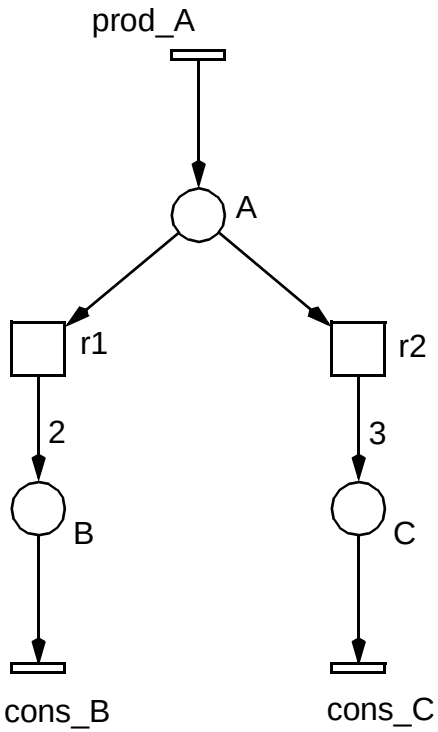


T-INVARIANT

-> properties as time net

```
INA
ORD HOM NBM PUR CSV SCF CON SC  Ft0 tF0 Fp0 pF0 MG  SM  FC  EFC ES
 N   Y   N   Y   N   Y   Y   N   Y   Y   N   N   Y   N   Y   Y   Y
CPI CTI  B  SB  REV DSt BSt DTr DCF  L   LV L&S
 N   Y   Y   N   N   N   ?   N   Y   Y   Y   N
```

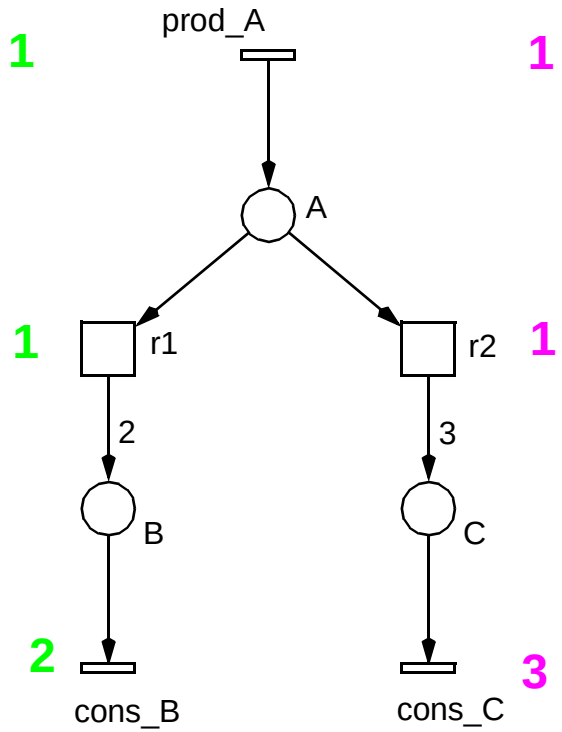
TRANSFORMATION, EX2



-> properties as time-less net

```
INA
ORD HOM NBM PUR CSV SCF CON SC  Ft0 tF0 Fp0 pF0 MG  SM  FC  EFC ES
 N   Y   N   Y   N   Y   Y   N   Y   Y   N   N   Y   N   Y   Y   Y
CPI CTI  B  SB  REV DSt BSt DTr DCF  L   LV L&S
 N   Y   N   N   Y   N   ?   N   N   Y   Y   N
```

TRANSFORMATION, EX2



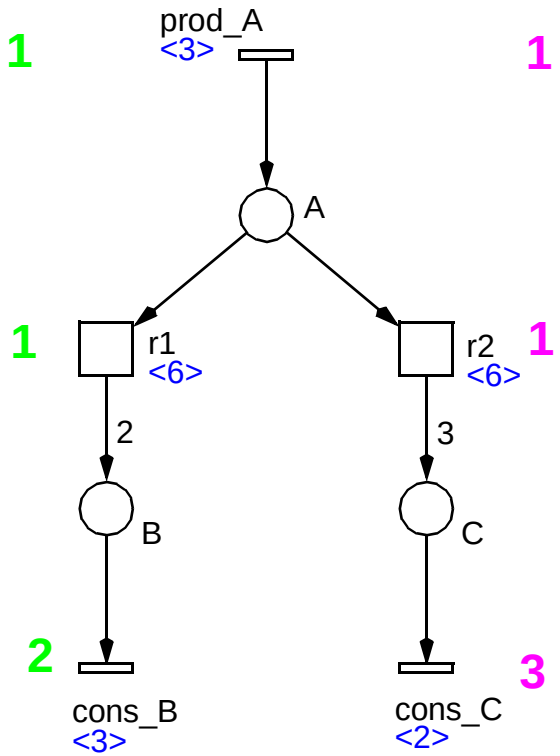
T-INVARIANT 1

T-INVARIANT 2

-> properties as time-less net

```
INA
ORD HOM NBM PUR CSV SCF CON SC  Ft0 tF0 Fp0 pF0 MG  SM  FC  EFC ES
 N   Y   N   Y   N   Y   Y   N   Y   Y   N   N   Y   N   Y   Y   Y
CPI CTI  B  SB  REV DSt BSt DTr DCF  L   LV L&S
 N   Y   N   N   Y   N   ?   N   N   Y   Y   N
```

TRANSFORMATION, EX2



T-INVARIANT 1

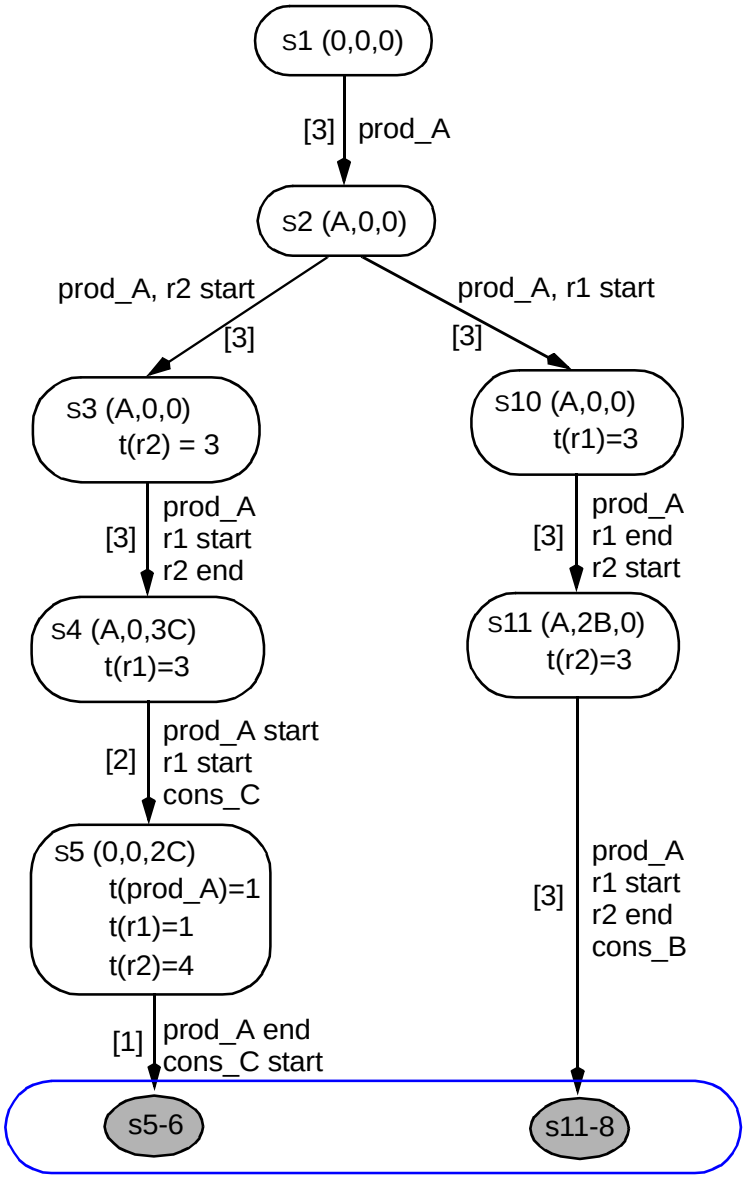
T-INVARIANT 2

-> properties as time net

```
INA
ORD HOM NBM PUR CSV SCF CON SC  Ft0 tF0 Fp0 pF0 MG  SM  FC  EFC ES
 N   Y   N   Y   N   Y   Y   N   Y   Y   N   N   Y   N   Y   Y   Y
CPI CTI  B  SB  REV DSt BSt DTr DCF  L   LV L&S
 N   Y   Y   N   N   N   ?   N   Y   Y   Y   N
```

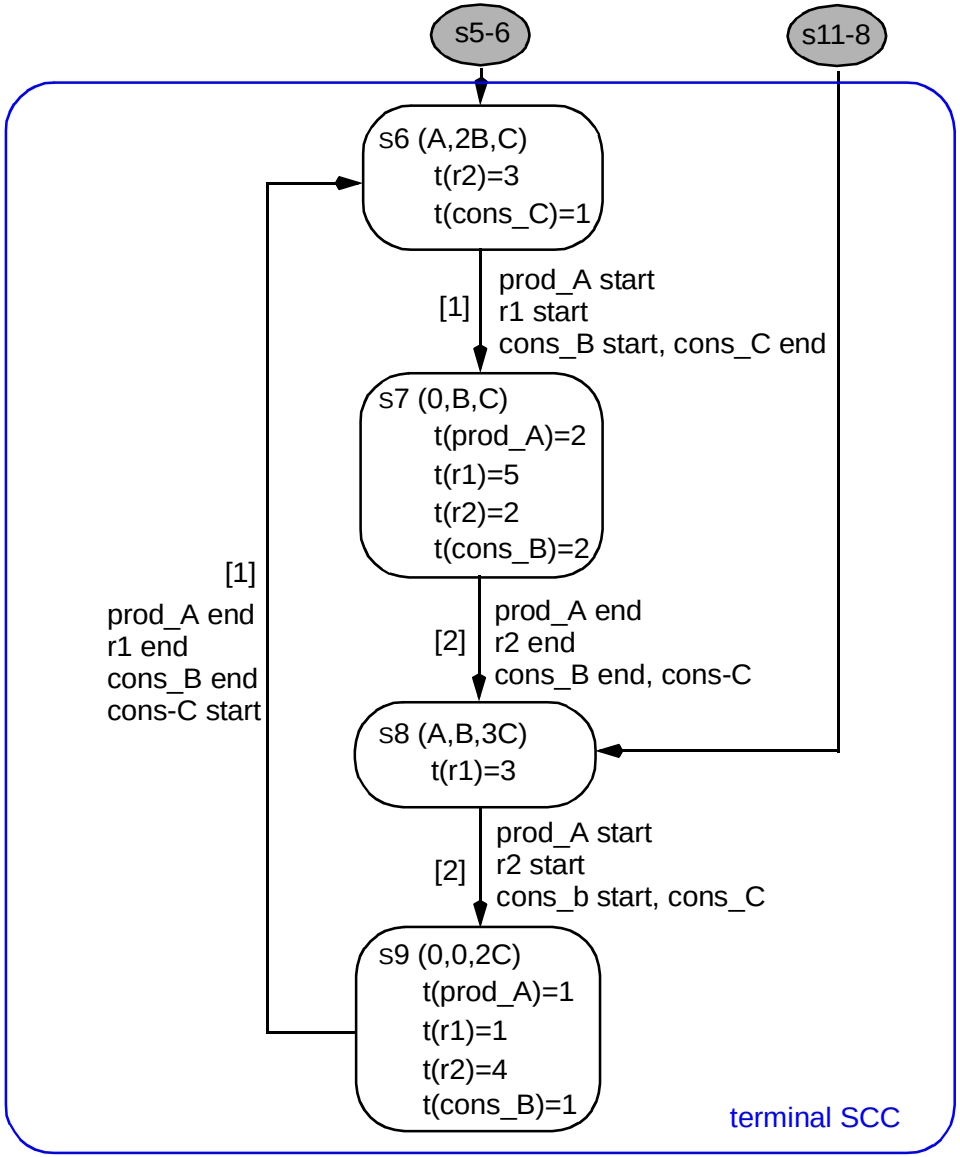
RG(Ex2), Part 1

- transient state



RG(Ex2), Part 2

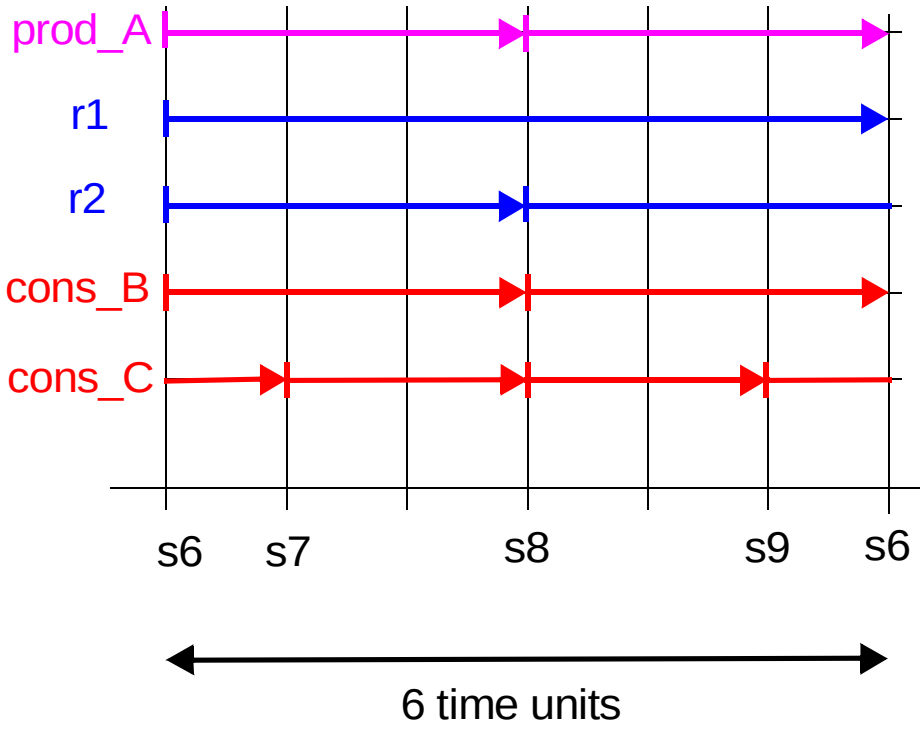
- steady state



RG(Ex2), Terminal SCC

- **contains all transitions**
  - -> *always running*
  - -> *start / end at different time points*
- **contains all minimal T-invariants**
- **timing diagram**
- **relative transition firing rates**

prod_A	**:**	**1**	**+**		**1**
r1	**:**	**1**	**r2**	**:**	**1**
cons_B	**:**	**2**	**cons_C**	**:**	**3**

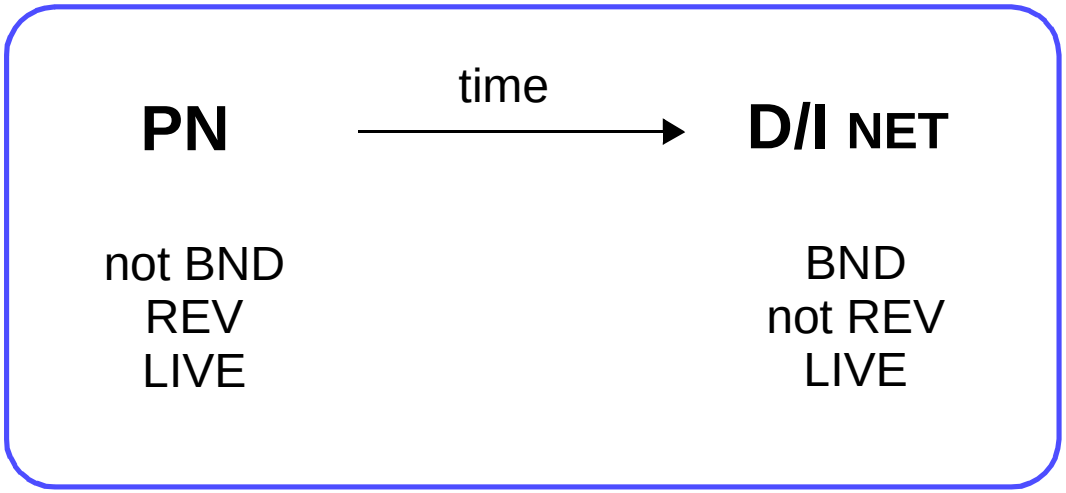


EX1+ EX2, SUMMARY

- CTI,
  but not CPI

- transient state
  - -> *initial behaviour to reach steady state*
  - -> *not REV*
  - -> *generally, not DCF*

- steady state behaviour
  - -> *terminal scc*
  - -> *here, BND*
  - -> *here, DCF*



BUT, WHAT DO WE DO

- if the timed model is bounded,
  but the reachability graph does not fit into memory ?

- if the timed model is (still) unbounded ?

QUANTITATIVE ANALYSIS, QUESTIONS

interval time Petri net

$I: T \to \mathbf{Q_0}^+ \times \mathbf{Q_0}^+$ and for each $t \in T$ holds $a_t \leq b_t$, where $I(t) = (a_t, b_t)$

initial marking / state

finite transition word w

$w \in T^*$

LOUCHKA POPOVA, HUB

w is time-dependent realizable / not realizable

min/max time length of w

which time windows guarantee realizability

QUANTITATIVE ANALYSIS, METHOD I

interval time Petri net

$I: T \to \mathbf{Q_0}^+ \times \mathbf{Q_0}^+$ and for each $t \in T$ holds
$a_t \leq b_t$, where $I(t) = (a_t, b_t)$

initial marking / state

finite transition word w $\quad w \in T^*$

(SLI)

$$b_1 \leq a_{11}x_1 + \ldots + a_{1n}x_n \leq c_1$$
$$\ldots$$
$$b_m \leq a_{m1}x_1 + \ldots + a_{mn}x_n \leq c_m$$
$$a_{ij} \in \{0, 1\}, b_i \in \mathbf{N}, c_i \in \mathbf{N}$$
$$\forall i \forall s \forall k (1 \leq i \leq n \wedge 1 \leq s \leq k \leq m \wedge$$
$$a_{is} = a_{ik} = 1 \to \forall j (s \leq j \leq k \to a_{ij} = 1))$$

if there is an $\boldsymbol{R}$ solution,
then there is an $\boldsymbol{N}$ solution.

w is time-dependent realizable / not realizable

QUANTITATIVE ANALYSIS, METHOD I

interval time Petri net

$I: T \to \boldsymbol{Q_0}^+ \times \boldsymbol{Q_0}^+$ and for each $t \in T$ holds
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initial marking / state

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$$\forall i \forall s \forall k (1 \le i \le n \wedge 1 \le s \le k \le m \wedge$$
$$a_{is} = a_{ik} = 1 \to \forall j (s \le j \le k \to a_{ij} = 1))$$

polynomial time

if there is an $\boldsymbol{R}$ solution,
then there is an $\boldsymbol{N}$ solution.

linear time

w is time-dependent realizable / not realizable

QUANTITATIVE ANALYSIS, METHOD II

interval time Petri net

$I: T \to \mathbf{Q_0}^+ \times \mathbf{Q_0}^+$ and for each $t \in T$ holds
$a_t \leq b_t$, where $I(t) = (a_t, b_t)$

initial marking / state

finite transition word w $\quad w \in T^*$

(LP)

$$min / max\ x_1 + ... + x_n$$

$$\begin{cases} b_1 \leq a_{11}x_1 + ... + a_{1n}x_n \leq c_1 \\ ... \\ b_m \leq a_{m1}x_1 + ... + a_{mn}x_n \leq c_m \\ a_{ij} \in \{0, 1\}, b_i \in \mathbf{N}, c_i \in \mathbf{N} \\ \forall i \forall s \forall k (1 \leq i \leq n \wedge 1 \leq s \leq k \leq m \wedge \\ a_{is} = a_{ik} = 1 \to \forall j (s \leq j \leq k \to a_{ij} = 1)) \end{cases}$$

if there is a solution,
then it is an $\mathbf{N}$ solution.

w is time-dependent realizable / not realizable

min/max time length of w

monika.heiner@informatik.tu-cottbus.de

QUANTITATIVE ANALYSIS, METHOD II

interval time Petri net

$I: T \to \mathbf{Q_0}^+ \times \mathbf{Q_0}^+$ and for each $t \in T$ holds
$a_t \leq b_t$, where $I(t) = (a_t, b_t)$

initial marking / state

finite transition word w $\quad w \in T^*$

$$\text{(LP)} \quad \begin{cases} \min / \max\ x_1 + \ldots + x_n \\ b_1 \leq a_{11}x_1 + \ldots + a_{1n}x_n \leq c_1 \\ \ldots \\ b_m \leq a_{m1}x_1 + \ldots + a_{mn}x_n \leq c_m \\ a_{ij} \in \{0, 1\},\ b_i \in \mathbf{N},\ c_i \in \mathbf{N} \\ \forall i \forall s \forall k (1 \leq i \leq n \wedge 1 \leq s \leq k \leq m \wedge \\ a_{is} = a_{ik} = 1 \to \forall j (s \leq j \leq k \to a_{ij} = 1)) \end{cases}$$

polynomial time

if there is a solution,
then it is an $\boldsymbol{N}$ solution.

w is time-dependent realizable / not realizable

min/max time length of w

SUMMARY

- **representation of bionetworks by Petri nets**
  - -> *partial order representation*
  - -> *formal semantics* -> *various sound analysis techniques*
  - -> *unifying view*

- **purposes**
  - -> *animation* -> *to experience the model*
  - -> *model validation against consistency criteria* -> *to increase confidence*
  - -> *qualitative / quantitative behaviour prediction* -> *new insights*

- **two-step model development**
  - -> *qualitative model* -> *discrete Petri nets*
  - -> *quantitative model* -> *timed Petri nets, continuous Petri nets*

- **many challenging questions for analysis techniques**
  - -> *qualitative as well as quantitative ones*

THANKS !

Popova-Zeugmann, L.; Heiner, M.; Koch, I.:
Time Petri Nets for Modelling and Analysis of Biochemical Networks;
Fundamenta Informaticae 67 (2005) 149–162