CPN Workshop`04

Application of Coloured Petri Nets in System Biology

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main aim: **model development of metabolic networks,**

which allows validation techniques

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validation techniques:

T-invariant analysis

- **introduced by Heiner et al. [1]**

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P-invariant analysis

- P-Invariant corresponds to mass conservation law
  ⇨ covering P-invariant necessary ⇨ bounded net
- inconsistencies between reaction & compound formulas detectable

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P-invariant analysis

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- inconsistencies between reaction & compound formulas detectable

model checking

- more detailed prove of properties / conditions
  ⇨ requires finite state space

metabolic network

= set of chemical reactions

r1: A → B r2: B → C

r3:B + u1 → D + u2

- **qualitative modelling / analysis**
  - ⇨ **consider reactions in steady state**
  - ⇨ **live & bounded**

metabolic network

= set of chemical reactions

straightforward

➢ qualitative modelling / analysis

⇨ consider reactions in steady state

⇨ live & bounded

P/T net model

r1: A → B r2: B → C

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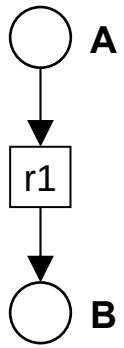

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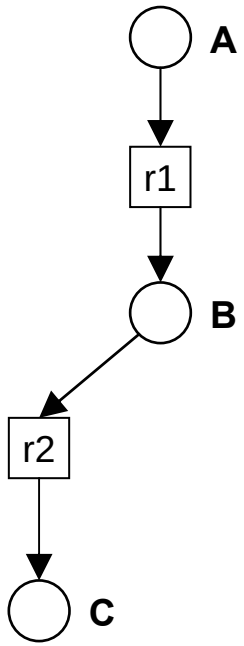

metabolic network

straightforward

= set of chemical reactions

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P/T net model

- **place bordered, called core model**
- **bounded & not live**

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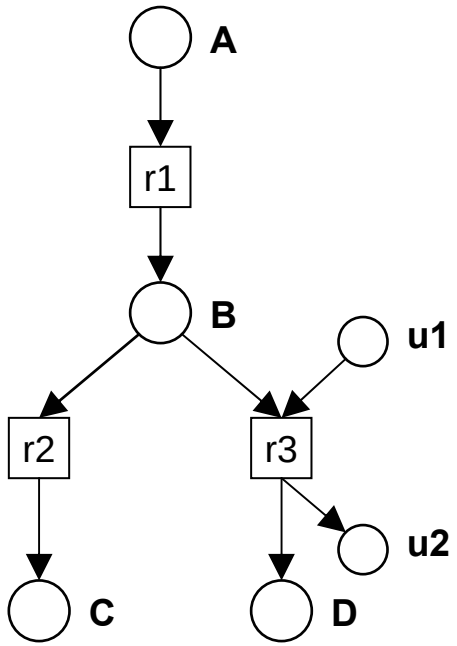

- **A, C, D external metabolites**
- **B internal metabolite**
- **u1, u2 ubiquitous molecules (e. g. ATP, ADP)**

metabolic network

= set of chemical reactions

straightforward

➢qualitative modelling / analysis

⇨ consider reactions in steady state

⇨ live & bounded

P/T net model

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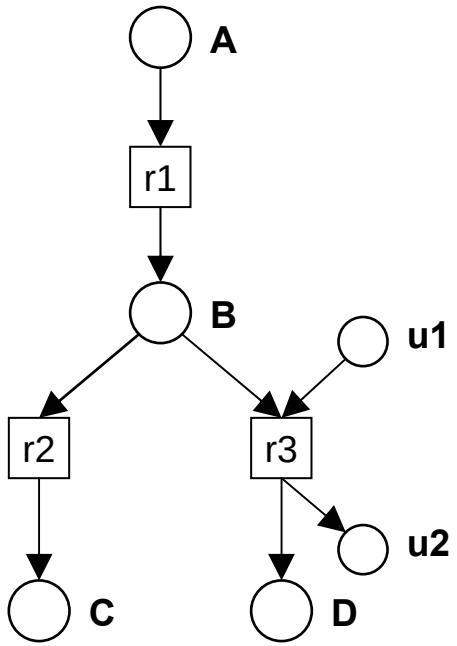


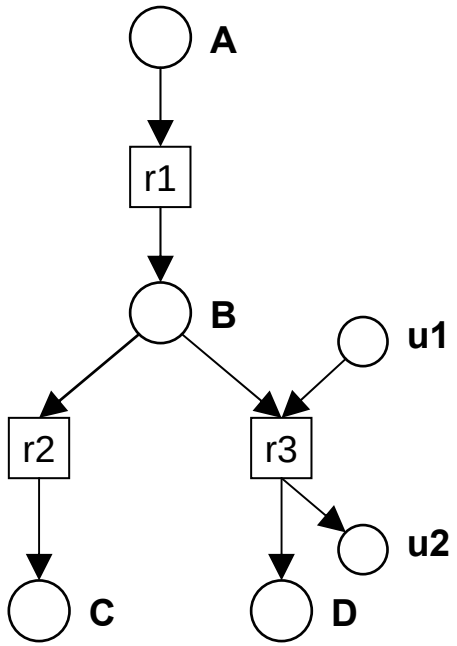
⇨not sufficient for validation techniques

⇨not sufficient for deep understanding of metabolic networks

⇨solution ?

P/T net model (bounded & not live)

- requires environment behaviour
- easiest biochemical behaviour
  - ⇨ supply & removal



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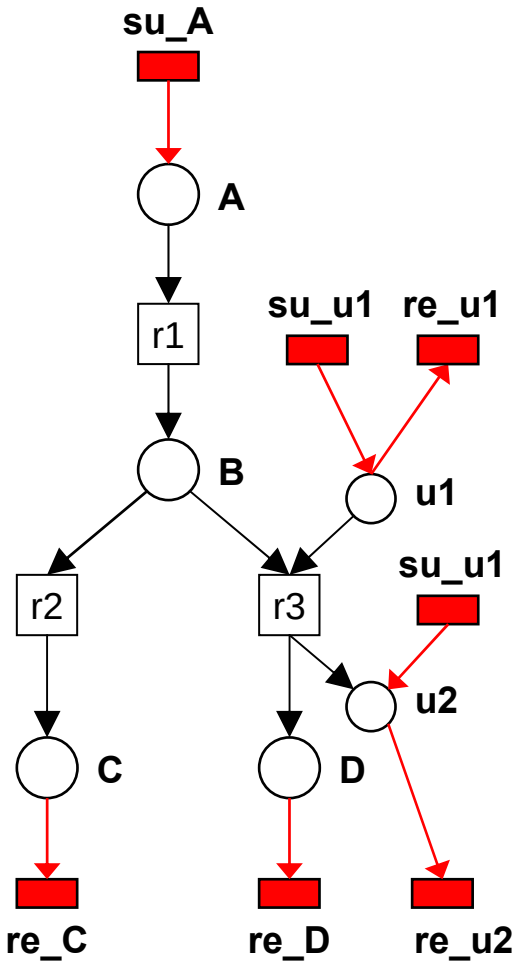
P/T net model with environment type I

- ➢ transition bordered, open system, called system model (I)



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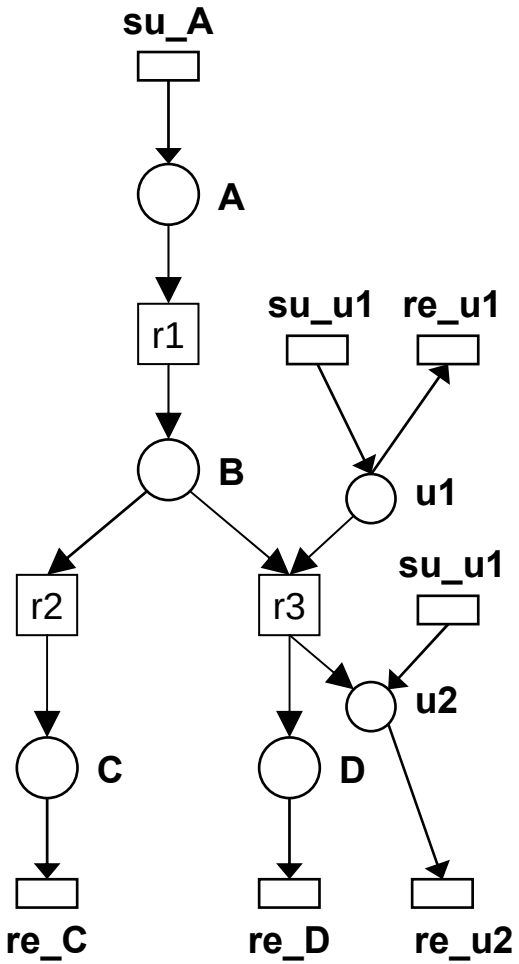
- ➢ unbounded & live & covered by T-invariants (CTI)



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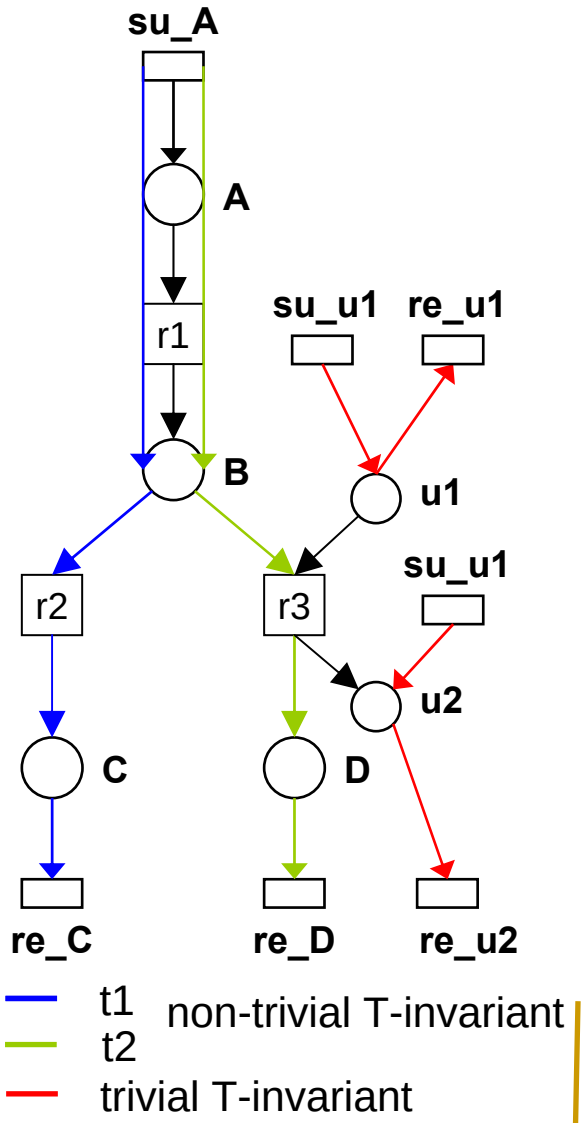
P/T net model with environment type I

- ➢ transition bordered, open system, called system model (I)
- ➢ unbounded & live & covered by T-invariants (CTI)
- ➢ minimal T-invariant
  - =elementary mode (biochemistry)
  - ⇨ deep understanding (pathways)



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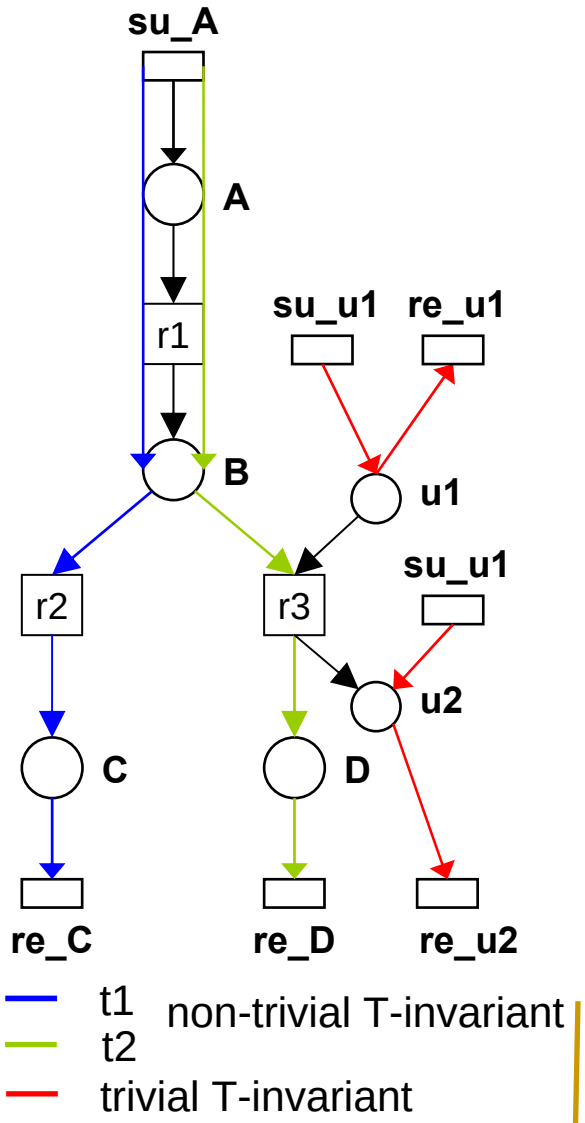
⇨ **P-invariant analysis ?**

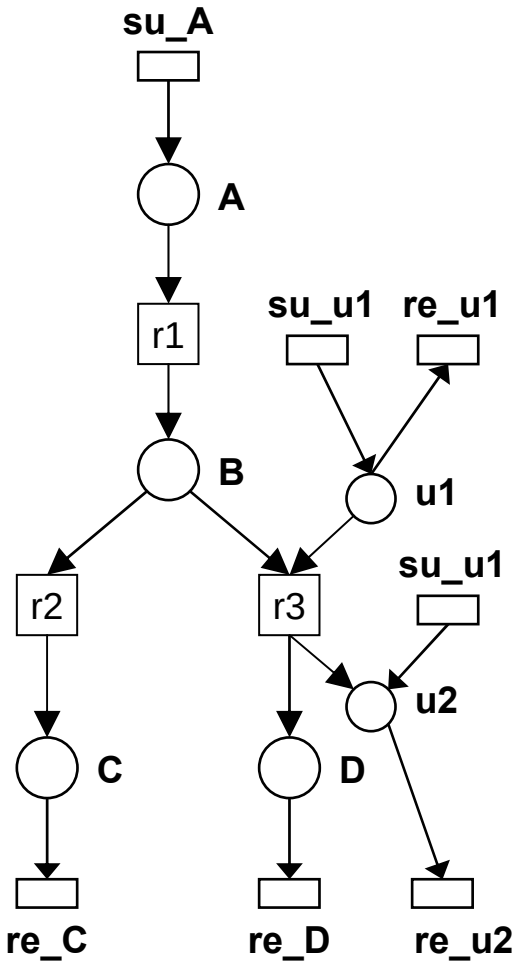
⇨ **model checking ?**



P/T net model with environment type I

CPN model with environment type II

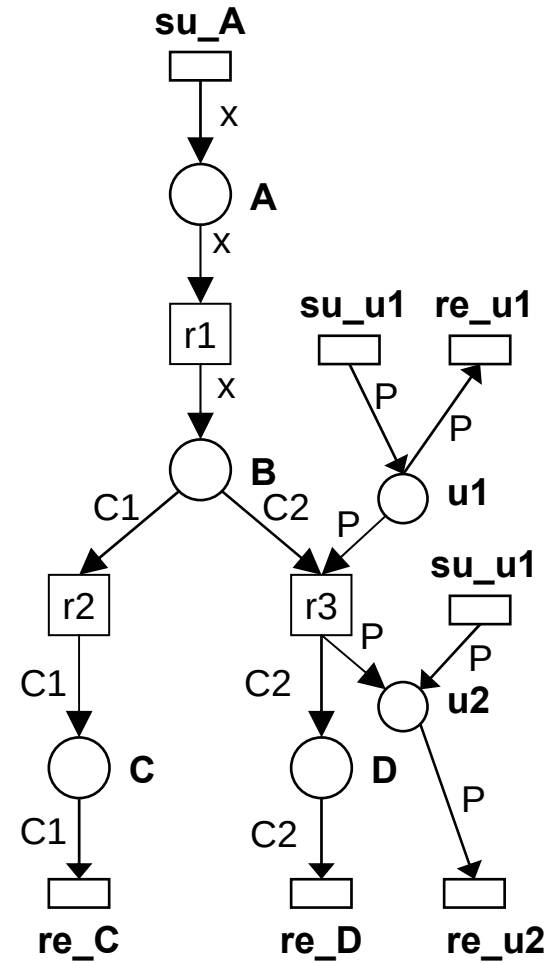
- closed system,
  called system model (II)



P/T net model with environment type I

construction

- colour the model to avoid dynamic conflicts (dead markings)
  ⇨ two variants



CPN model with environment type II

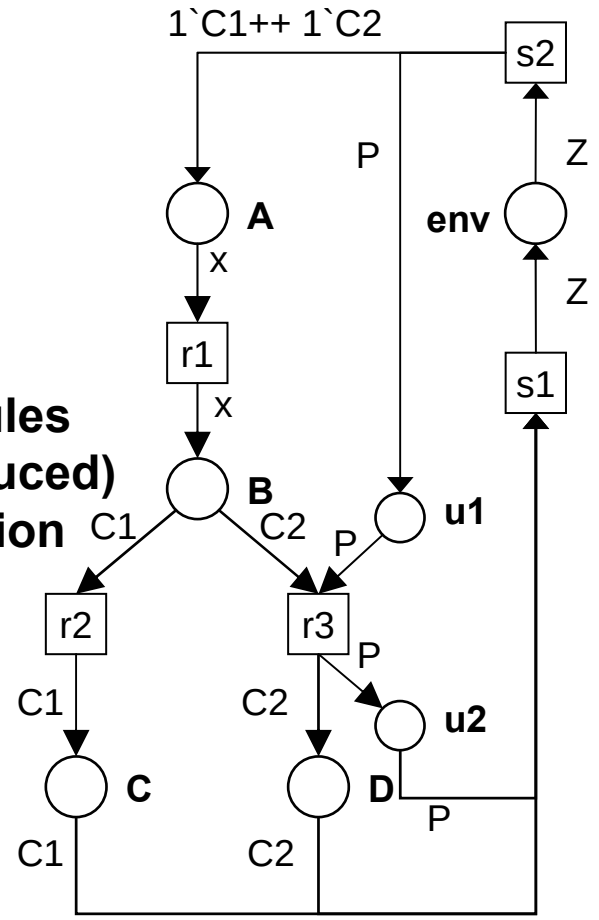
- closed system, called system model (II)

```
color CS = C1 | C2 | P;
color X = subset CS with [C1, C2];
var x:X;
```

P/T net model with environment type I

construction

- colour the model to avoid dynamic conflicts (dead markings)
  - ⇨ two variants
- transform environment behaviour
  - ⇨ limit amount of suppliable molecules
  - ⇨ supply (remove) consumed (produced) molecules by a start (stop) transition



CPN model with environment type II

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color CS = C1 | C2 | P | Z;
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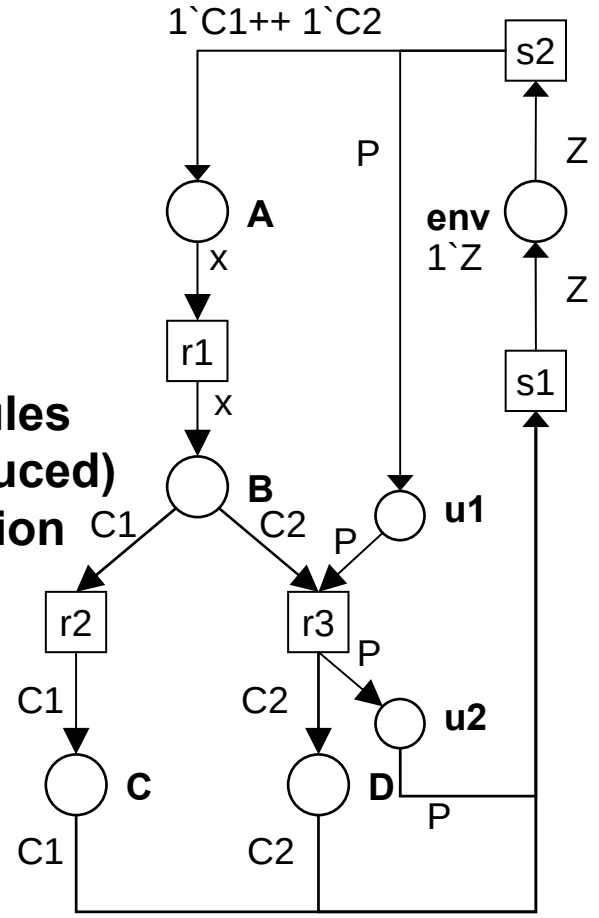
- simple initial marking



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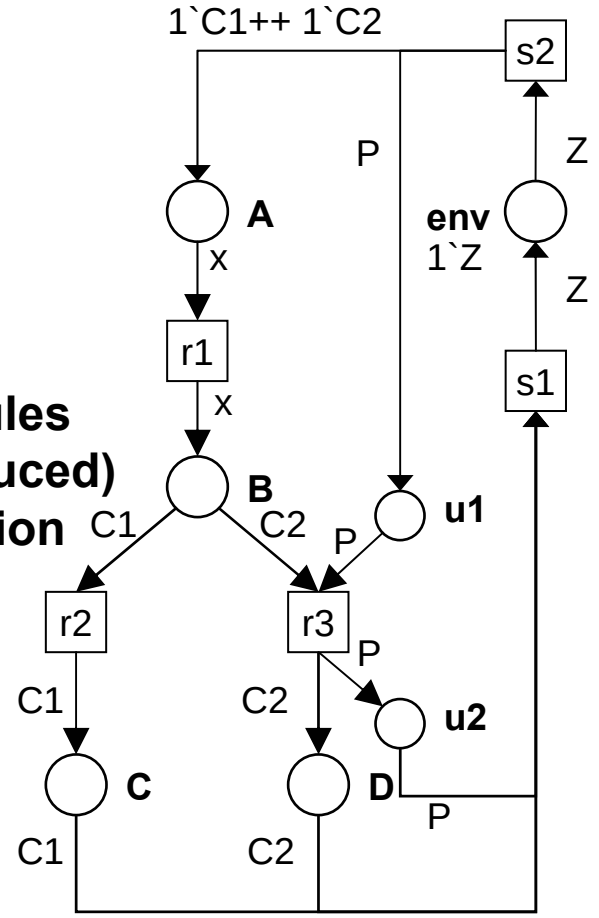

CPN model with environment type II

- closed system, called system model (II)
- bounded & live & CTI & covered by P-invariants (CPI)
- only small subset of CPN used

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color CS = C1 | C2 | P | Z;
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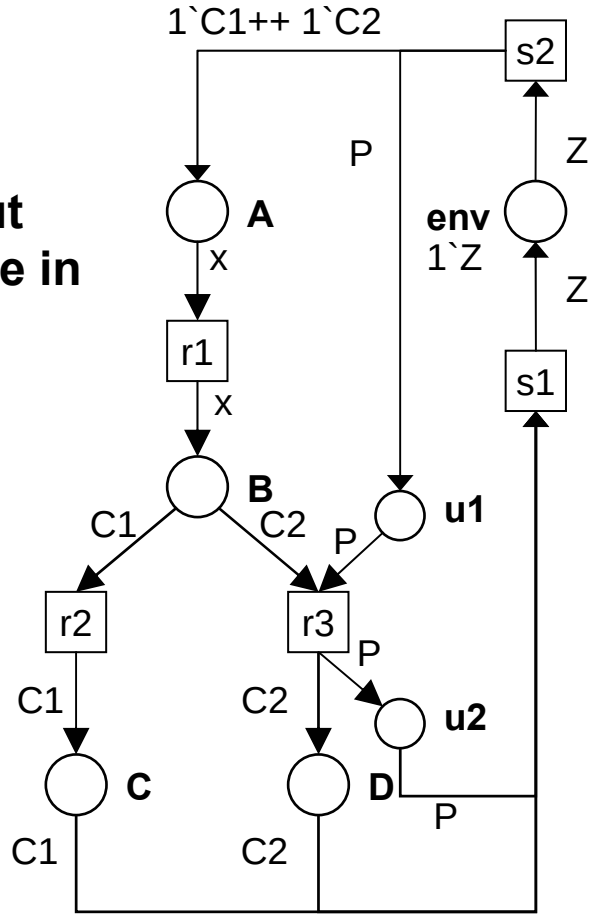
P/T net model with environment type I

behavioural equivalence

- **Each realizable T-invariant of the unbounded system model (I) without border transitions must be realizable in the bounded system model (II).**



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P/T net model with environment type I

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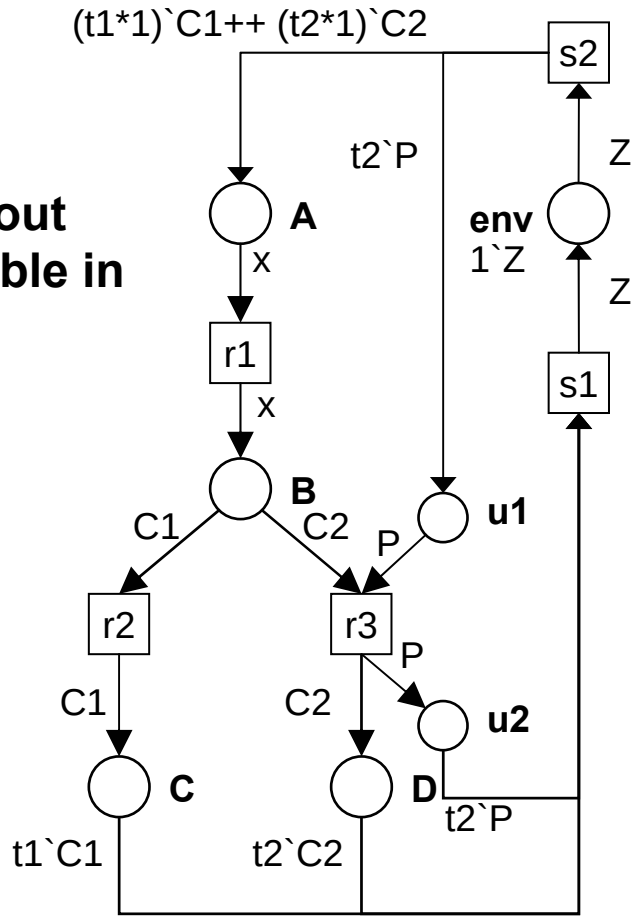
- **Each realizable T-invariant of the unbounded system model (I) without border transitions must be realizable in the bounded system model (II).**
- **normally fusion of T-invariants**
- **selection parameter** (t1 and t2)

CPN model with environment type II

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color CS = C1 | C2 | P | Z;
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P/T net model with environment type I

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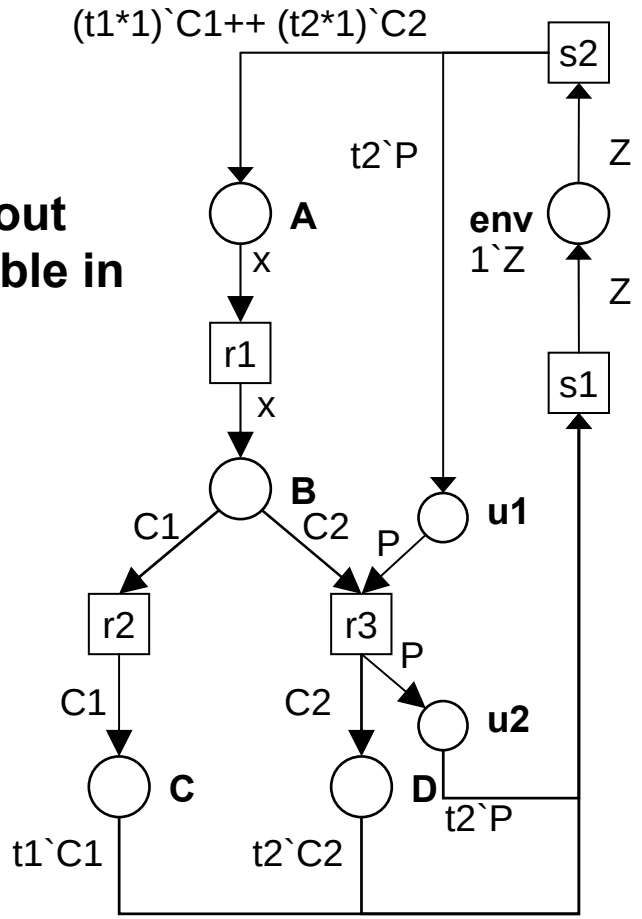

CPN model with environment type II

- **CTI & CPI**
  - ⇨ **prove using effect / defect calculation²**
- **bounded & live**
  - ⇨ **prove using Occ/ Scc graph calculation**

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CPN model with environment type II

- CTI & CPI
  - ⇨ prove using effect / defect calculation
    - ⇨ multiplying PxT-incidence matrix C with transformation vectors

effect

C*x = z; x .. substitution vector (T-vector),
z .. effect of x = P-vector, which denotes marking differences for each place

z = 0 ⇨ x is T-invariant

substitution ⇨ binding element
e. g. r1: x <- (1`C1),(1`C2)

CPN model with environment type II

- ➢CTI & CPI
  - ⇨ prove using effect / defect calculation
    - ⇨ multiplying PxT-incidence matrix C with transformation vectors

effect - example

	r1	r2	r3	s1	s2
A	-x				C1+ C2
B	x	-C1	-C2		
C		C1		-C1	
D			C2	-C2	
u1			-P		P
u2			P	-P	
env				Z	-Z

incidence matrix C

*

r1: x <- (1`C1),(1`C2)
r2: _ <- (1`_)
r3: _ <- (1`_)
s1: _ <- (1`_)
s2: _ <- (1`_)

substitution vector

= 0

⇨ **T-invariant**

⇨ **CTI**

* replaces variables by expressions in token colours

CPN model with environment type II

- ➢CTI & CPI
  - ⇨ prove using effect / defect calculation
    - ⇨ multiplying PxT-incidence matrix C with transformation vectors

defect

$C^T * y = w$; y .. distribution vector (P-vector),
w .. defect of y = T-vector, which denotes marking differences caused by each transition

w = 0 ⇨ y is P-invariant

sensible biochemical distributions
e. g. Glucose $C_6H_{12}O_6$ ⇨ Gluc: -> 6`C + 12`H + 6`O

CPN model with environment type II

- ➢ **CTI & CPI**
- ⇨ **prove using effect / defect calculation**
  - ⇨ **multiplying PxT-incidence matrix C with transformation vectors**

defect - example

	A	B	C	D	u1	u2	env
r1	-x	x					
r2		-C1	C1				
r3		-C2		C2	-P	P	
s1			-C1	-C2		-P	Z
s2	C1+ C2				P		-Z

transposed incidence matrix C

*

A: C1,C2,x -> (1`C1),(1`C2), (1`C1 + 1`C2)
B: C1,C2,x -> (1`C1),(1`C2), (1`C1 + 1`C2)
C: C1 -> 1`C1
D: C2 -> 1`C2
u1: P -> 1`P
u2: P -> 1`P
env: Z -> 1`C1 + 1`C2 + 1`P

= 0

* transforms elements of colour set D into linear combination of elements of set E

distribution vector (imagined)

⇨ **P-invariant**

⇨ **CPI**

CPN model with environment type II

- bounded & live
  - ⇨ prove using Occ/ Scc graph calculation
- artificial example CPN model (not shown)

	places	transitions	token colours	T-invariants	Occ graph	
					nodes	arcs
variant I	10	10	5	4	92.177	513.047
variant II			8		274.187	1.707.422

- case study: extended glycolysis
  - ⇨ 33 places, 21 transitions and 40 T-invariants
  - ⇨ Occ graph calculation not completed (limited resources)

Summary

- **method to construct behavioural equivalent system model (II) from system model (I) using coloured Petri nets**
  ⇨ validation possible
- **verification of P- and T- invariants for subset of coloured Petri nets**
- **conditions to prove with model checking? ⇨ biochemists**

References

[1] HEINER, M. ; KOCH, I.: Petri Net Based Model Validation in Systems Biology. In: *LNCS* Bd. 3099, Springer, 2004, S. 216–237

[2] VOSS, K. ; HEINER, M. ; KOCH, I.: Steady state analysis of metabolic pathways using Petri nets. *In Silico Biol.* 3 (2003), Nr. 3, S. 367–387