TIME PETRI NETS FOR MODELLING AND ANALYSIS OF BIOCHEMICAL NETWORKS

- *ON THE INFLUENCE OF TIME* -

Monika Heiner

BTU, Computer Science Institute

monika.heiner (at) b-tu.de

OUTLINE

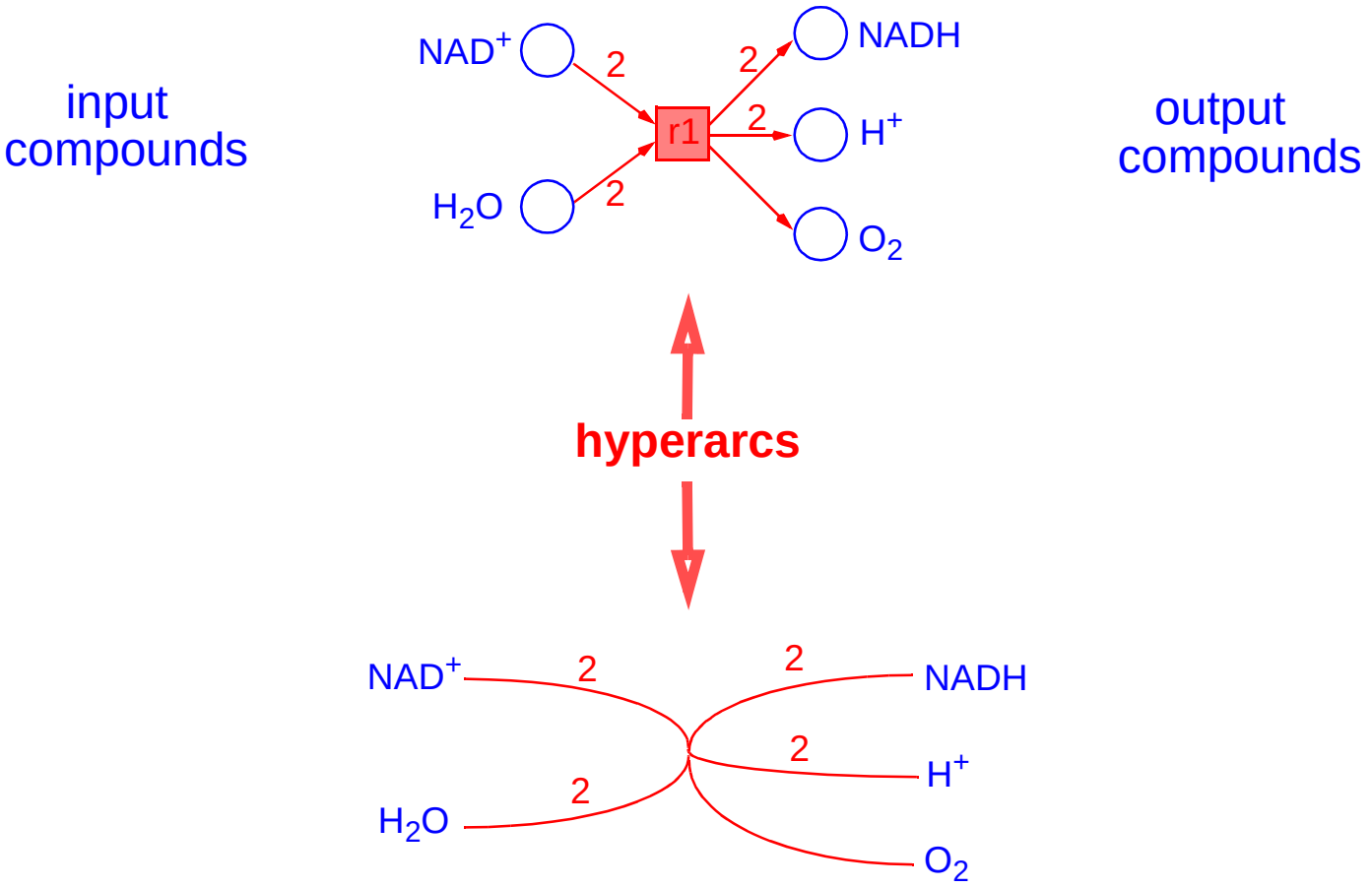
- **Why introduce time ?**
  - -> *more information, less abstraction of reality*
  - -> *may involve boundedness = finite state spaces*
- **How to introduce time ?**
  - -> *qualitative - time - stochastic - continuous - hybrid Petri nets*
  - -> *modelling power : TURING*
  - -> *analysis power : discrete state space construction (if bounded)*
- **How to derive time parameters ?**
  - -> *T-invariants -> steady state behaviour*
- **Two open problems**
  - -> *time-dependent boundedness* -> *weakly bounded*
  - -> *time-dependent liveness* -> *weakly live*

Petri nets

- basics -

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

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



- **metabolic networks**
  signal transduction networks
  gene regulatory networks

- **transitions**
  - -> *(reversible, stoichiometric) chemical reactions,*
  - -> *enzyme-catalysed conversions of metabolites, proteins, . . .*
  - -> *complexations / decomplexations, de- / phosphorylations, . . .*

- **places**
  - -> *(primary, secondary) chemical compounds,*
  - -> *(various states of) proteins, protein complex, genes, . . .*

- **tokens**
  - -> *molecules, moles,*
  - - > *concentration levels, gene expression levels, . . .*
    (e.g., high / low = present / not present, or any finite number)

Time Petri nets

- basics -

How to Introduce Time ?

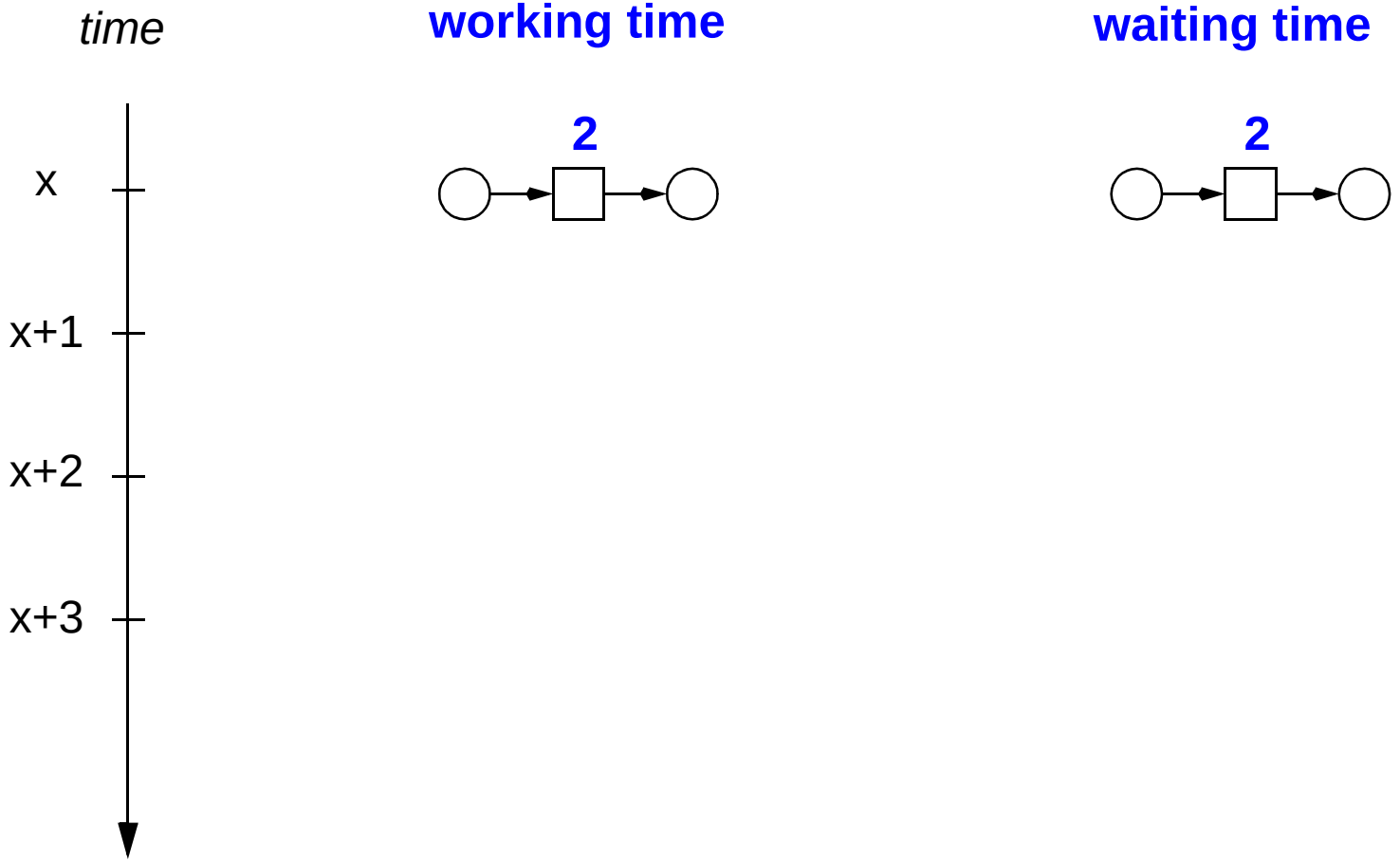
- **which net elements ?**
  -> *places, transitions, arcs, tokens*

- **what kind of numbers ?**
  -> *real, rationals, integer*

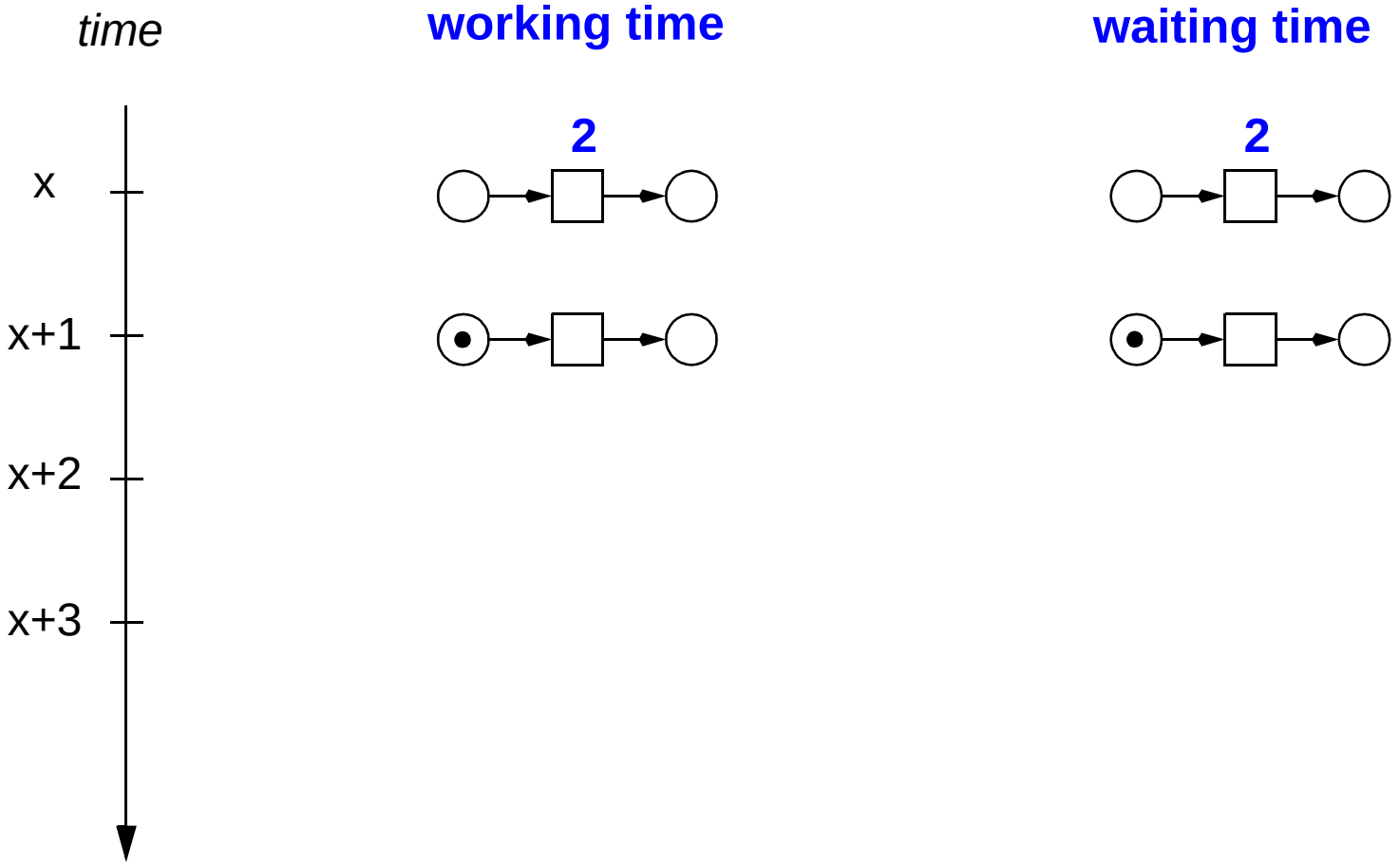
- **value range ?**
  -> *constant* - *Time: $T \rightarrow \mathbf{N_0}$*
  -> *interval* - *Time: $T \rightarrow \mathbf{N_0} \times \mathbf{N_0} \cup \{oo\}$* continuous interval !

- **firing rule** *may $\rightarrow$ must*
  -> *working time* - *transition reacts immediately,*
  (duration) *firing lasts for the specified time*
  -> *waiting time* - *transition reacts after the specified time,*
  (delay) *firing itself does not consume time (-> stochastic Petri nets)*

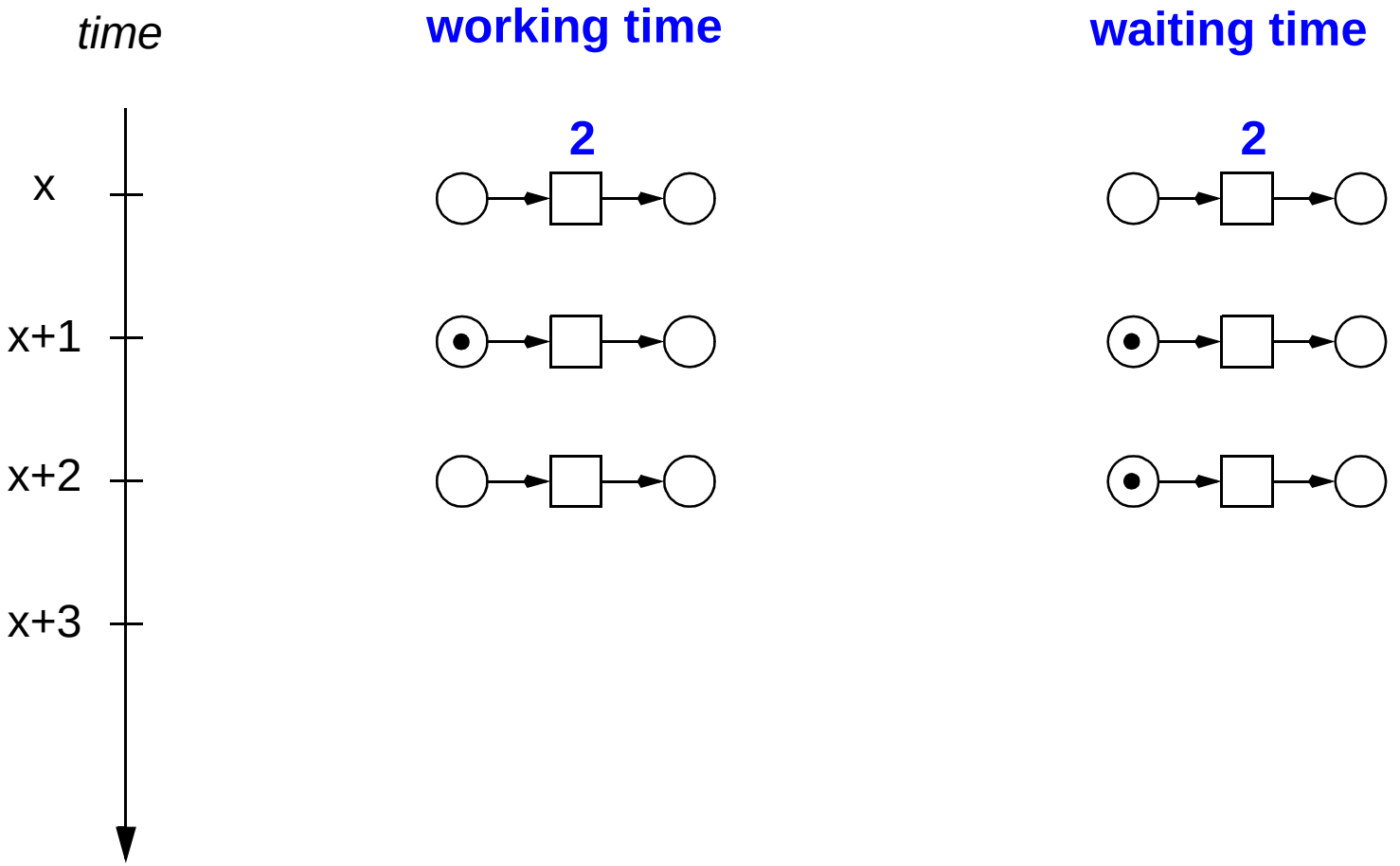
FIRING RULE



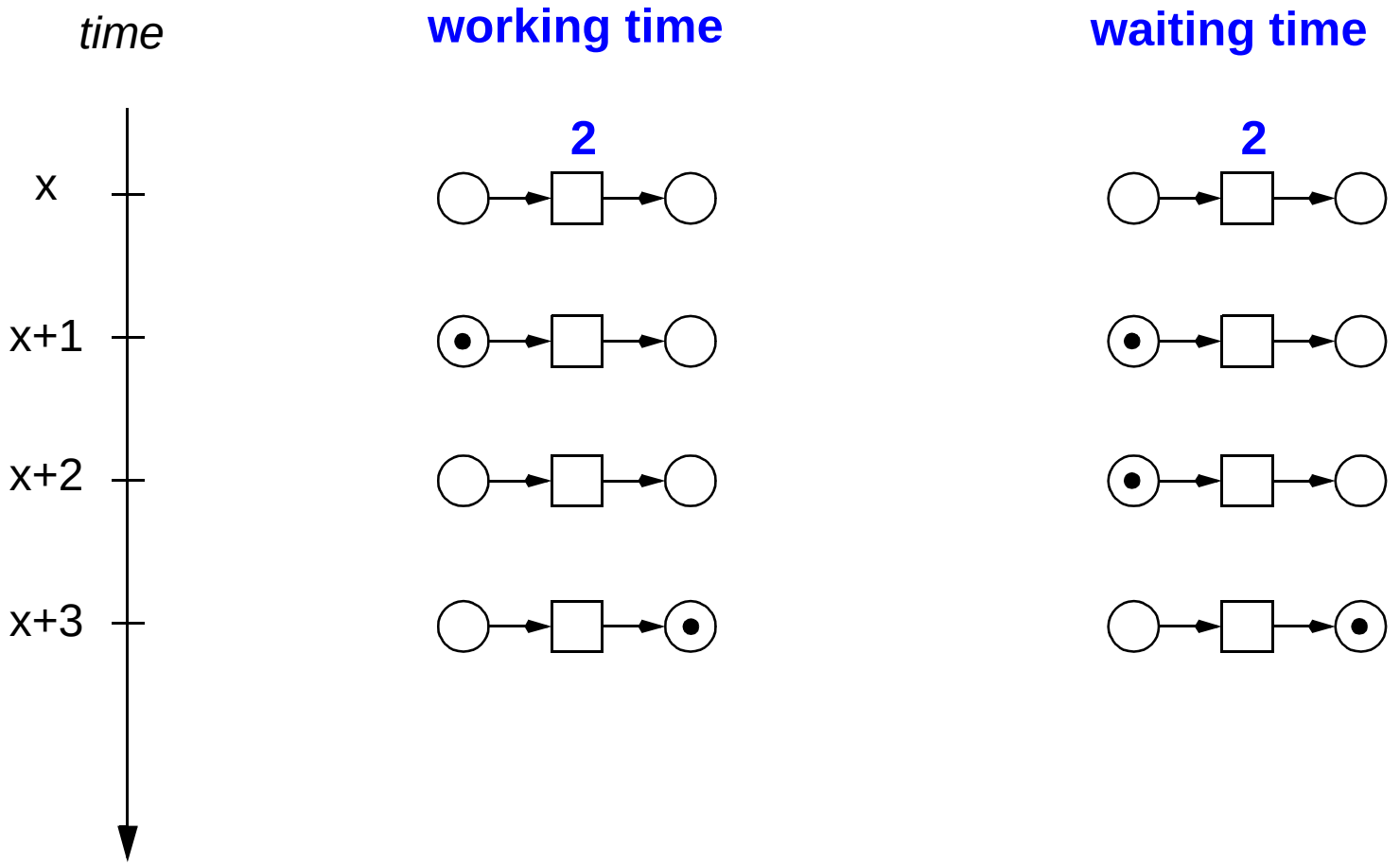
FIRING RULE



FIRING RULE

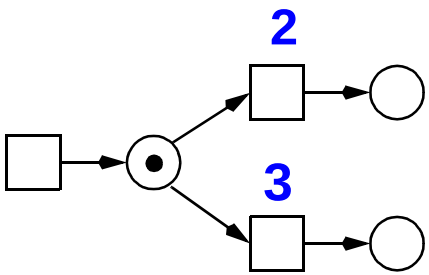


FIRING RULE

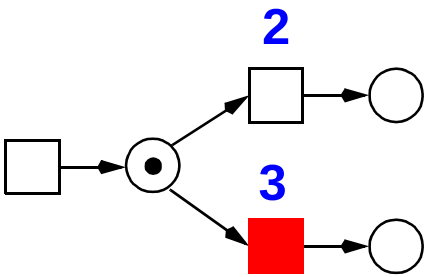


FIRING RULE

working time



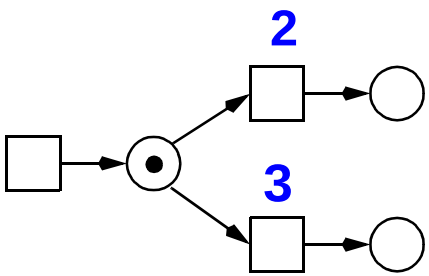
waiting time



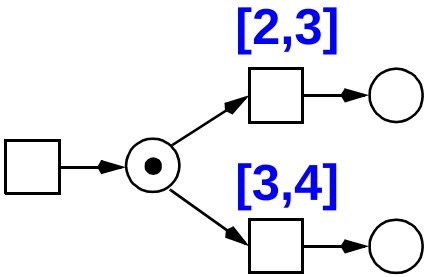
DEAD

FIRING RULE

working time



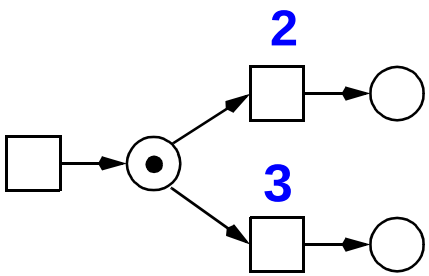
waiting time



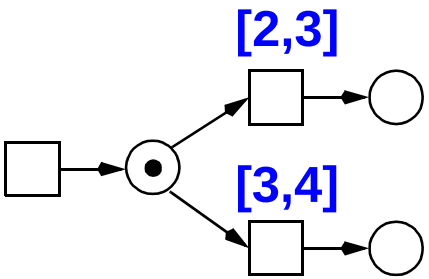
LIVE

FIRING RULE

working time



waiting time



LIVE

TIMED PETRI NET

[Ramchandani 74]

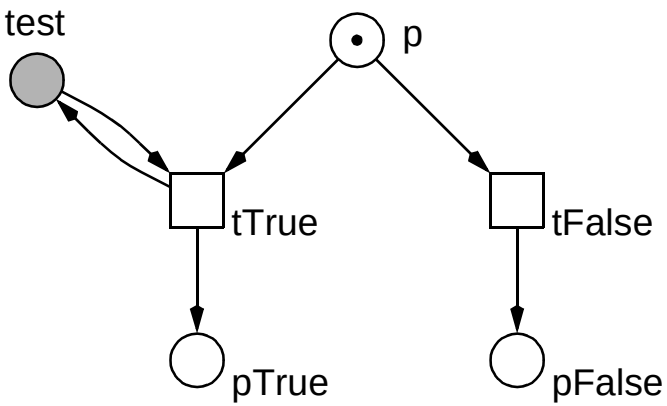
non-preemptive firing

TIME PETRI NET

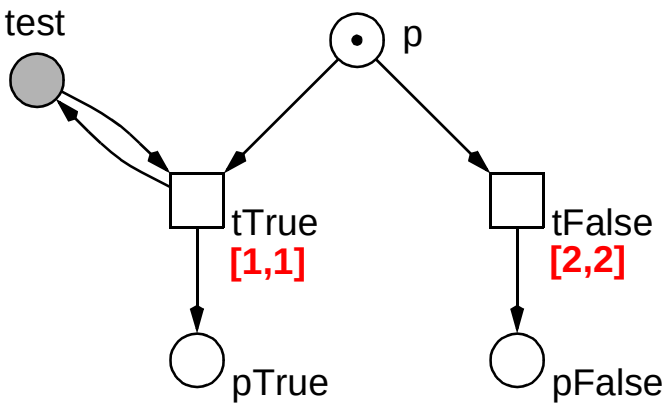
[Merlin 74]

preemptive firing

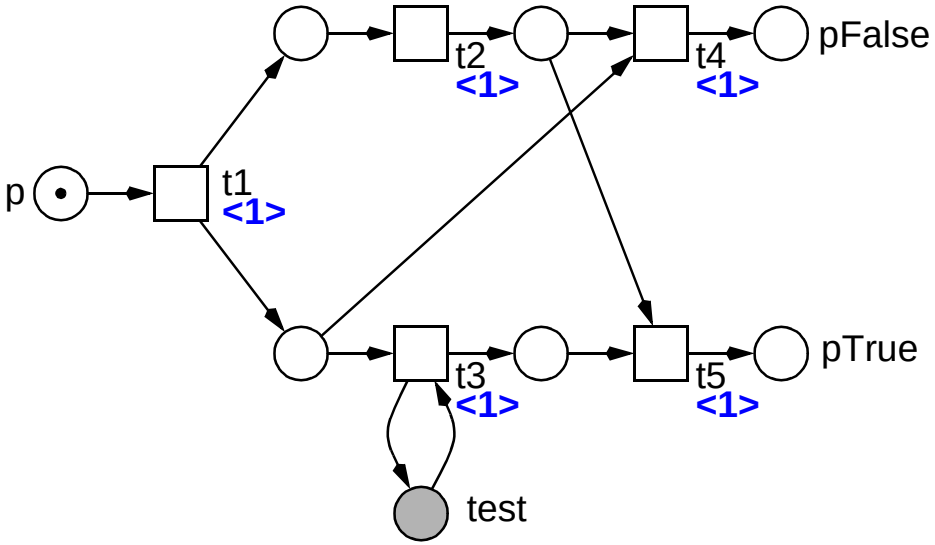
PETRI NET ?



WAITING TIME



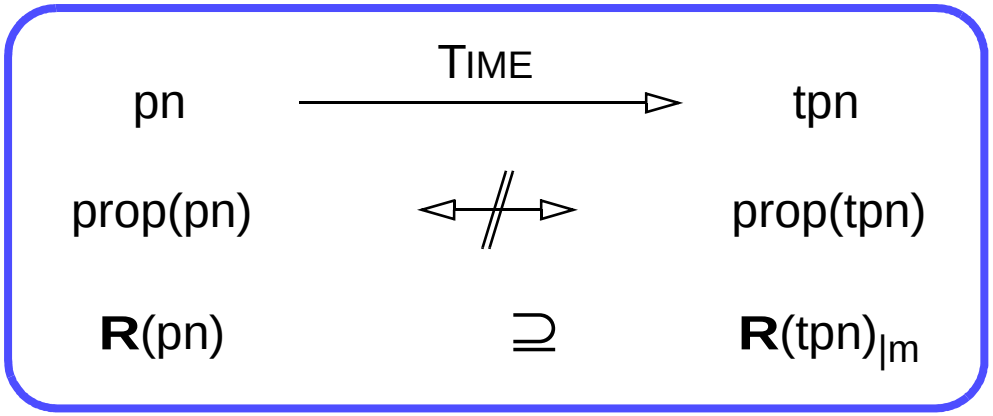
WORKING TIME



False: t1, t2, t4
True: t1, t2+t3, t5

KNOWN FACTS

- **time may restrict the behaviour**



- **time may influence qualitative properties**

TIME-INSENSITIVE PROPERTIES

BND (pn) -> BND (tpn)

not DSt (pn) -> not DSt (tpn)

DTr (pn) -> DTr (tpn)

TIME-SENSITIVE PROPERTIES

not BND (pn) -> BND (tpn)

DSt (pn) -> not DSt (tpn)

LIVE (pn) -> not LIVE (tpn)

not LIVE (pn) -> LIVE (pn)

KNOWN FACTS

- **TIME-INDEPENDENT LIVENESS**

  -> net structures, remaining live under any timing

- **persistent (dynamically conflict free) nets**

- **working time**

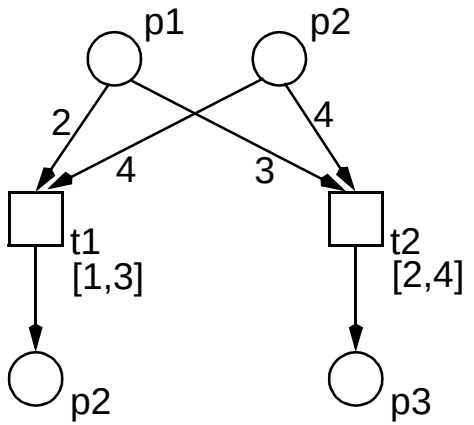
  -> *(homogeneous) ES nets, Starke 1990*

- **waiting time**

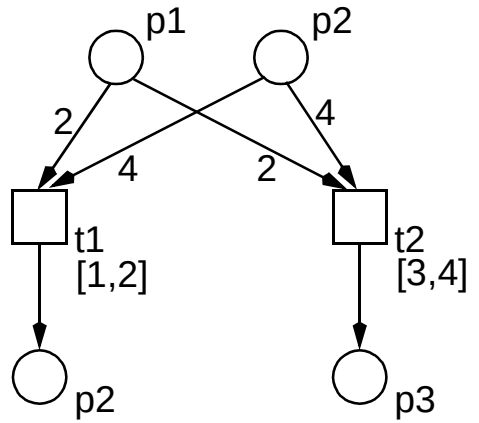
  -> *well-formed BFC nets, Popova 1994*

  -> *well-formed ES nets, Popova 2010*

  -> *well-formed =*
  homogeneous &
  timely homogeneous &
  no purely immediate transitions



not homogeneous



not timely homogeneous

Problem 1:

time-dependent boundedness

TIME-DEPENDENT BOUNDEDNESS

- **given: time-free Petri net**
  - -> *unbounded*
  - -> *live (supposed to be)*
- **wanted: corresponding time-dependent Petri net**
  - -> *(weakly) bounded*
  - -> *(still) live*
- **T-invariants**

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 entries is 1*
- **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)** -> **consistency criterion**
  - -> *each transition belongs to a T-invariant*
  - -> *BND & LIVE => CTI*

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*
     of transitions occuring permanently & concurrently
     -> *steady state behaviour*

- **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*

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*
     of transitions occuring permanently & concurrently
     -> steady state behaviour

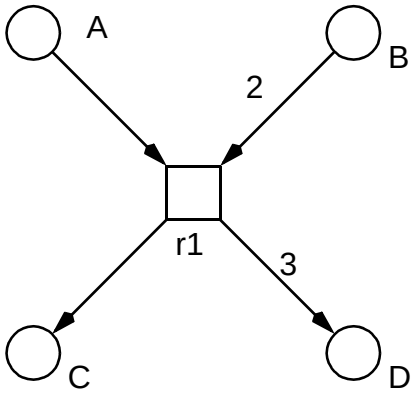
- **a T-invariant defines a subnet** **-> partial order structure**
  - -> *the T-invariant's transitions (the support),*
    + all their pre- and post-places
    + the arcs in between
  - -> *pre-sets of supports = post-sets of supports*

TIME-DEPENDENT BOUNDEDNESS

- **given: time-free Petri net**
  - -> *unbounded*
  - -> *live (supposed to be)*
- **wanted: corresponding time-dependent Petri net**
  - -> *(weakly) bounded*
  - -> *(still) live*
- **T-invariants -> relative transition firing rates**
  - -> *may be implemented by transition firing duration (constant / interval)*
- **claim**
  - -> *transformation preserves all possible behaviour (= minimal T-invariants)*
- **guess**
  - -> *transformation reflects the steady state, so the model should become bounded*

TRANSFORMATION, EX1

A + 2 B -> C + 3 D

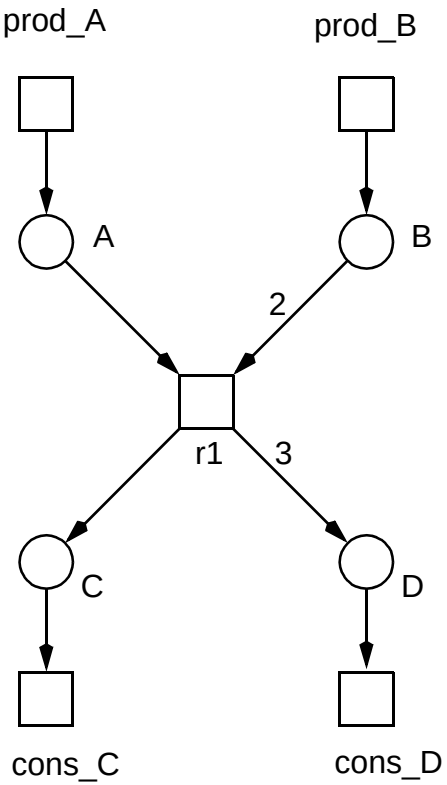


-> properties as time-free net

```
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   N   Y   N
```

TRANSFORMATION, EX1

A + 2 B -> C + 3 D

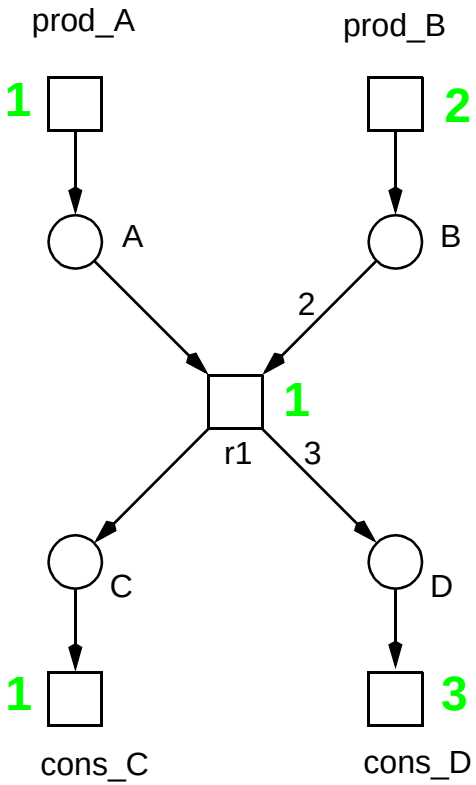


-> properties as time-free net

```
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

A + 2 B -> C + 3 D



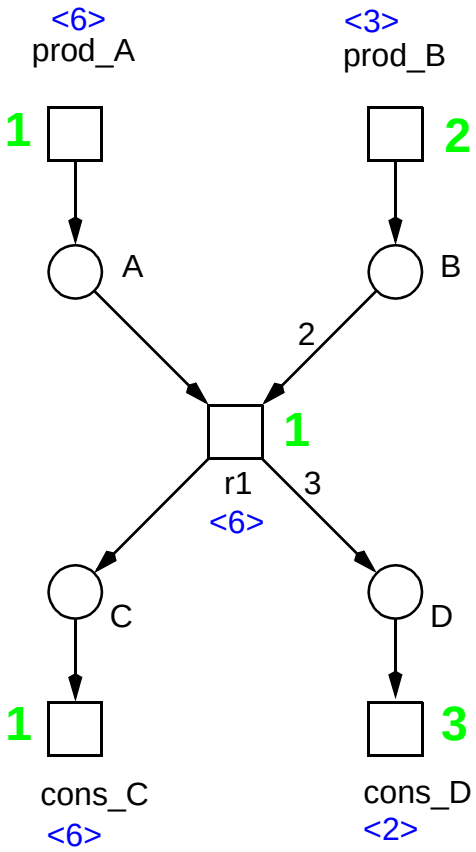
T-INVARIANT

-> properties as time-free 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

A + 2 B -> C + 3 D



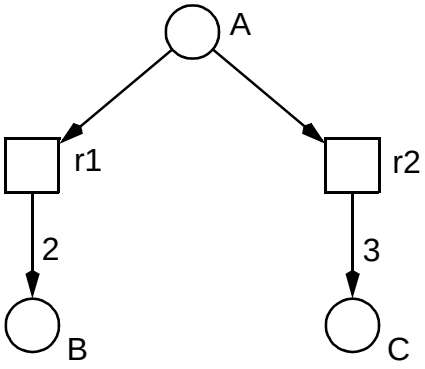
T-INVARIANT

-> 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

A ->2 B, A -> 3 C

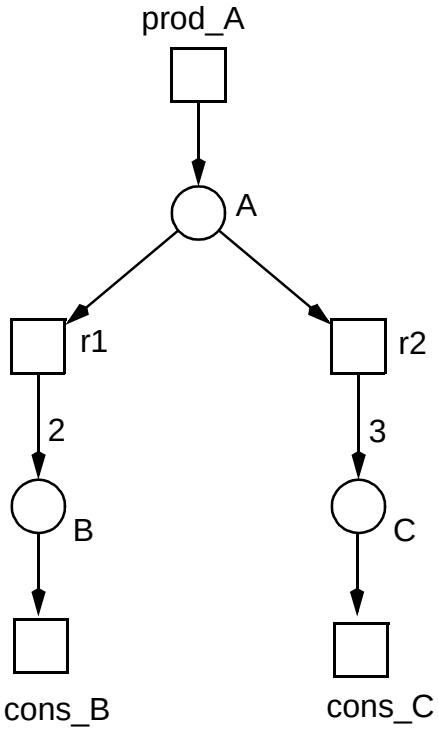


-> properties as time-free net

```
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   N   N   Y   N
```

TRANSFORMATION, EX2

A ->2 B, A -> 3 C

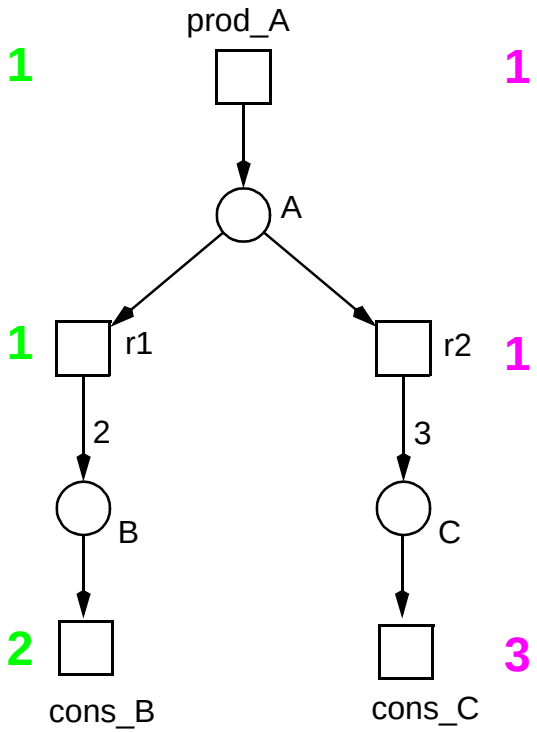


-> properties as time-free net

```
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

A ->2 B, A -> 3 C



T-INVARIANT1

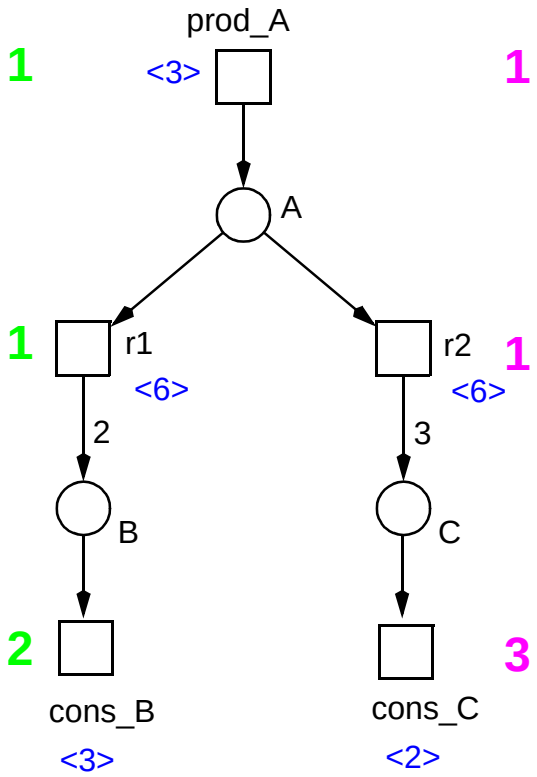
T-INVARIANT2

-> properties as time-free 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

A ->2 B, A -> 3 C



T-INVARIANT1

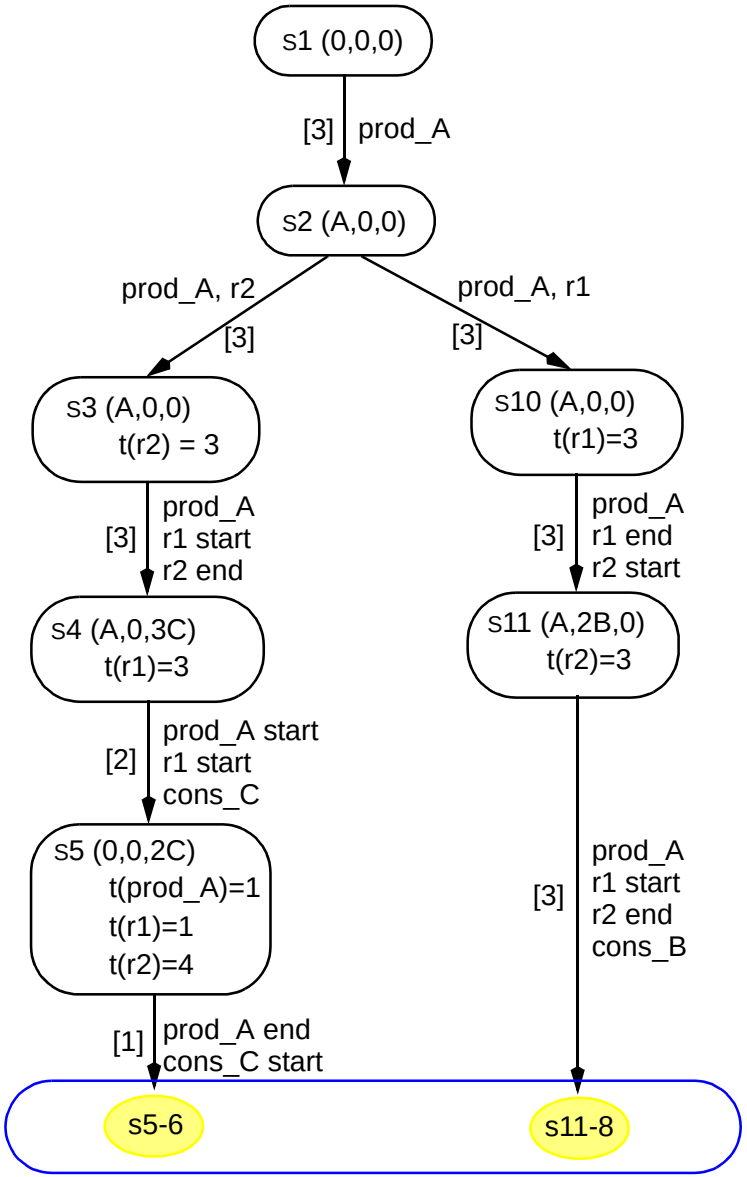
T-INVARIANT2

-> 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   N   Y   Y   N
```

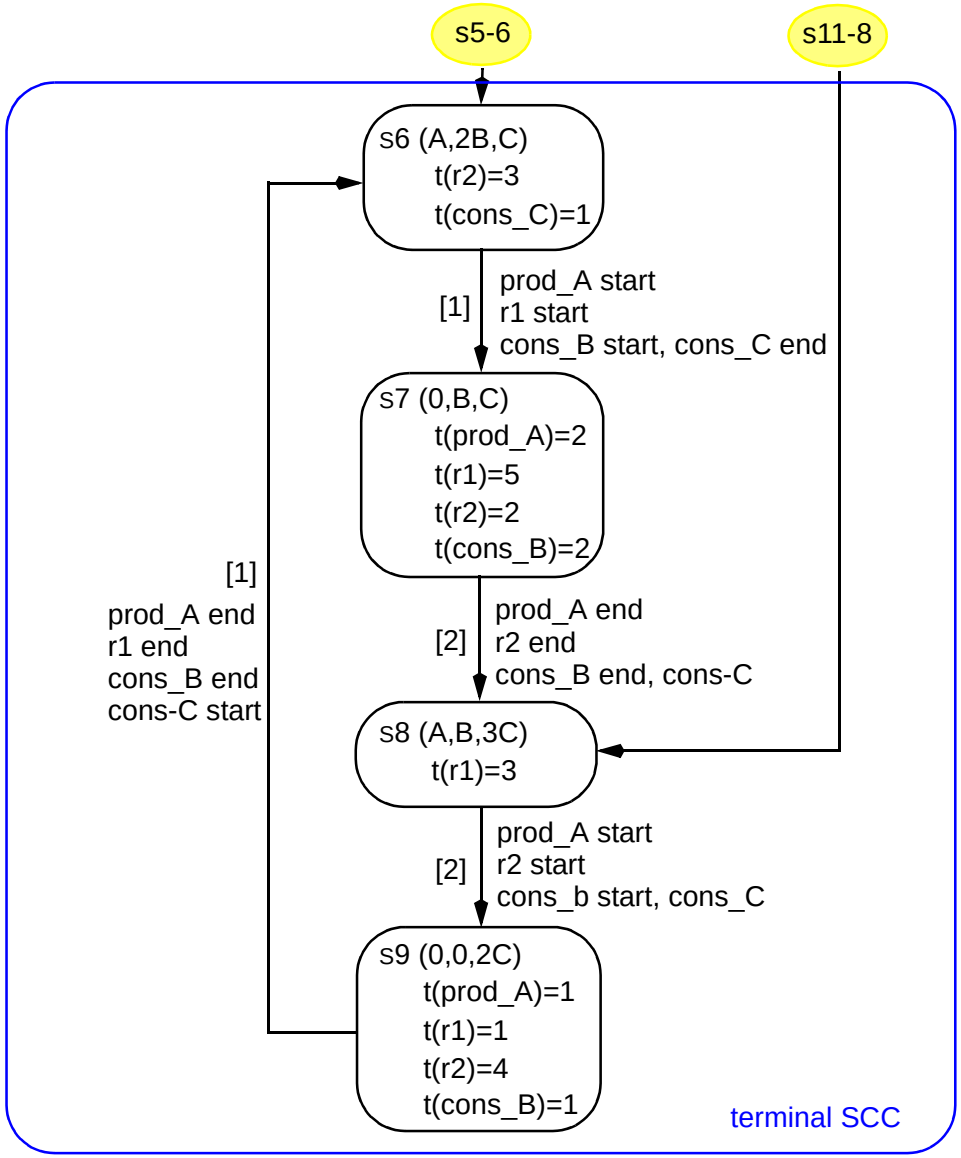
RG(EX2), PART 1

- **transient state**



RG(EX2), PART 2

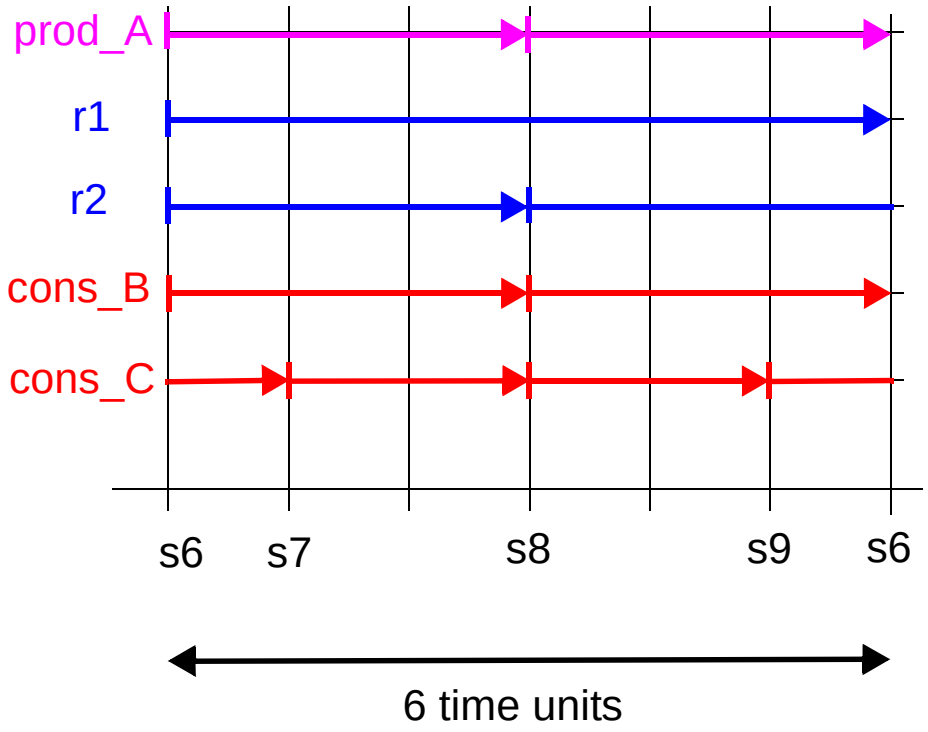
- **steady state**



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**

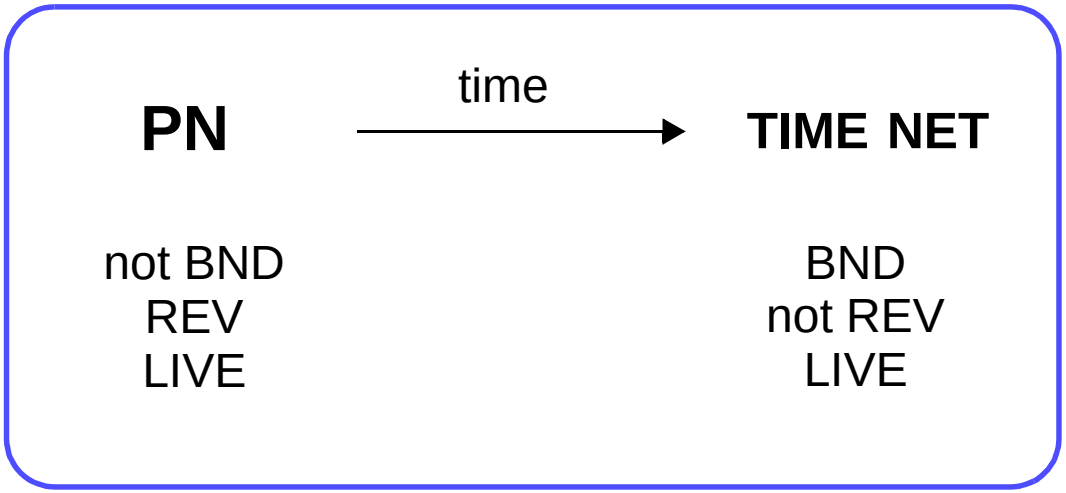


EX1+ EX2, SUMMARY

- CTI,
  but not CPI

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

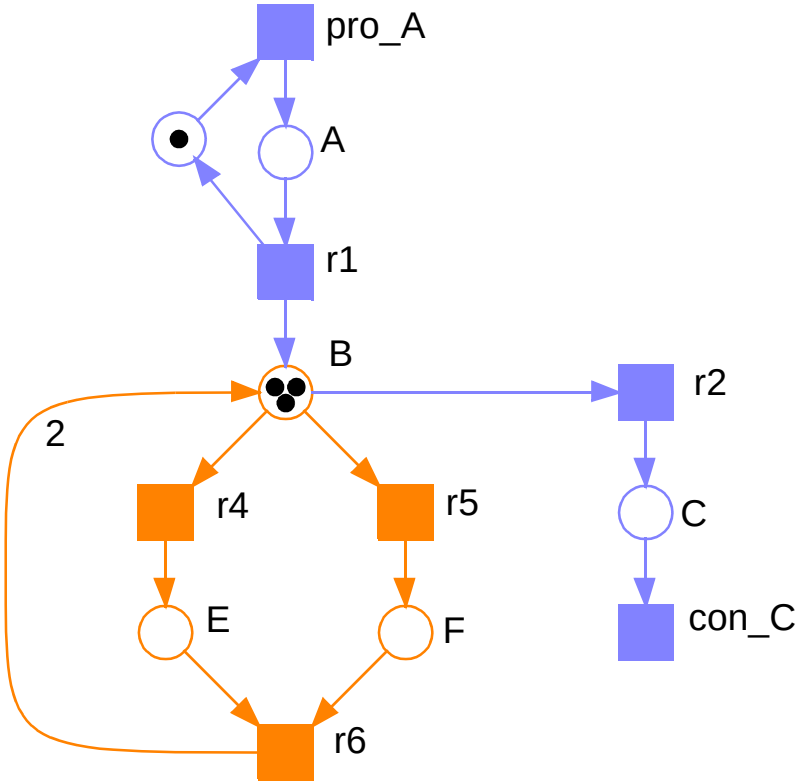
- steady state behaviour
  - -> *terminal scc*
  - -> *here, BND*
  - -> *here, DCF*

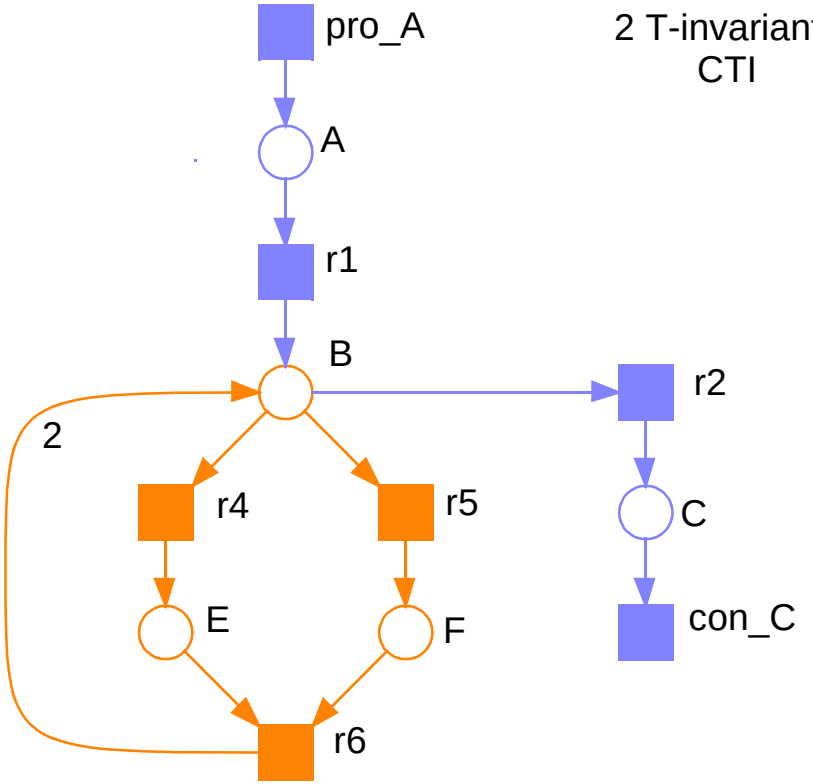


However,
this does not always work !

COUNTEREXAMPLE 1

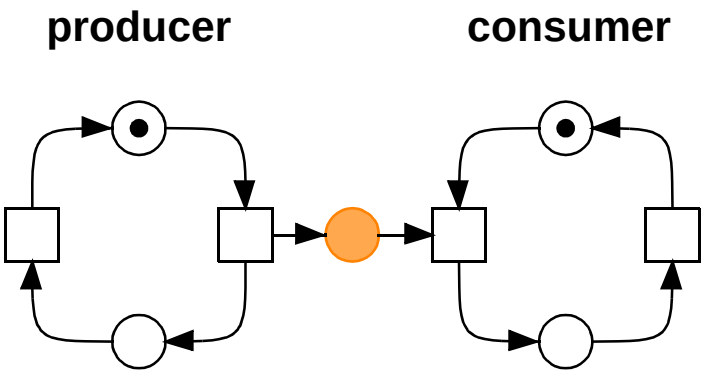
1-working time for all transitions;
FC, there are no deadlocks, traps, P-invariants, besides the pseudo-P-invariant (A , co_A);

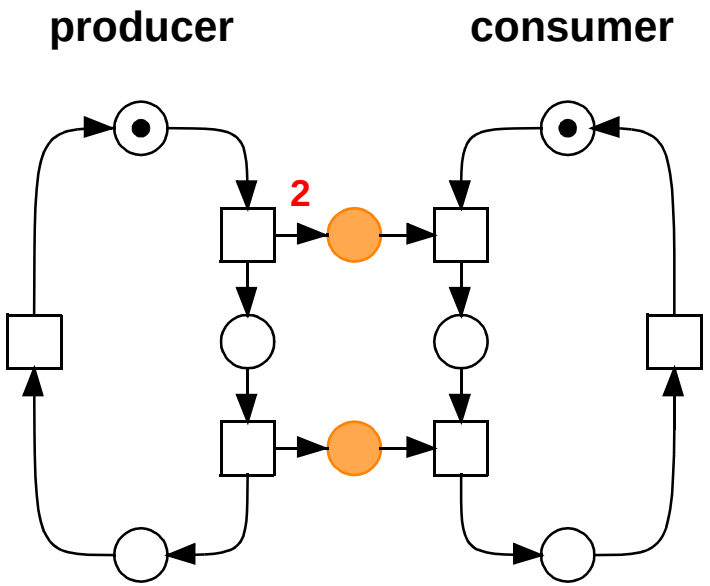




wBND & LIVE for the given initial marking

COUNTEREXAMPLE 2





weakly bounded (CTI)

not weakly bounded (not CTI, sur-T-invariant)

[DESEL 2006], WEAKLY BOUNDED PETRI NETS; AWPN '06

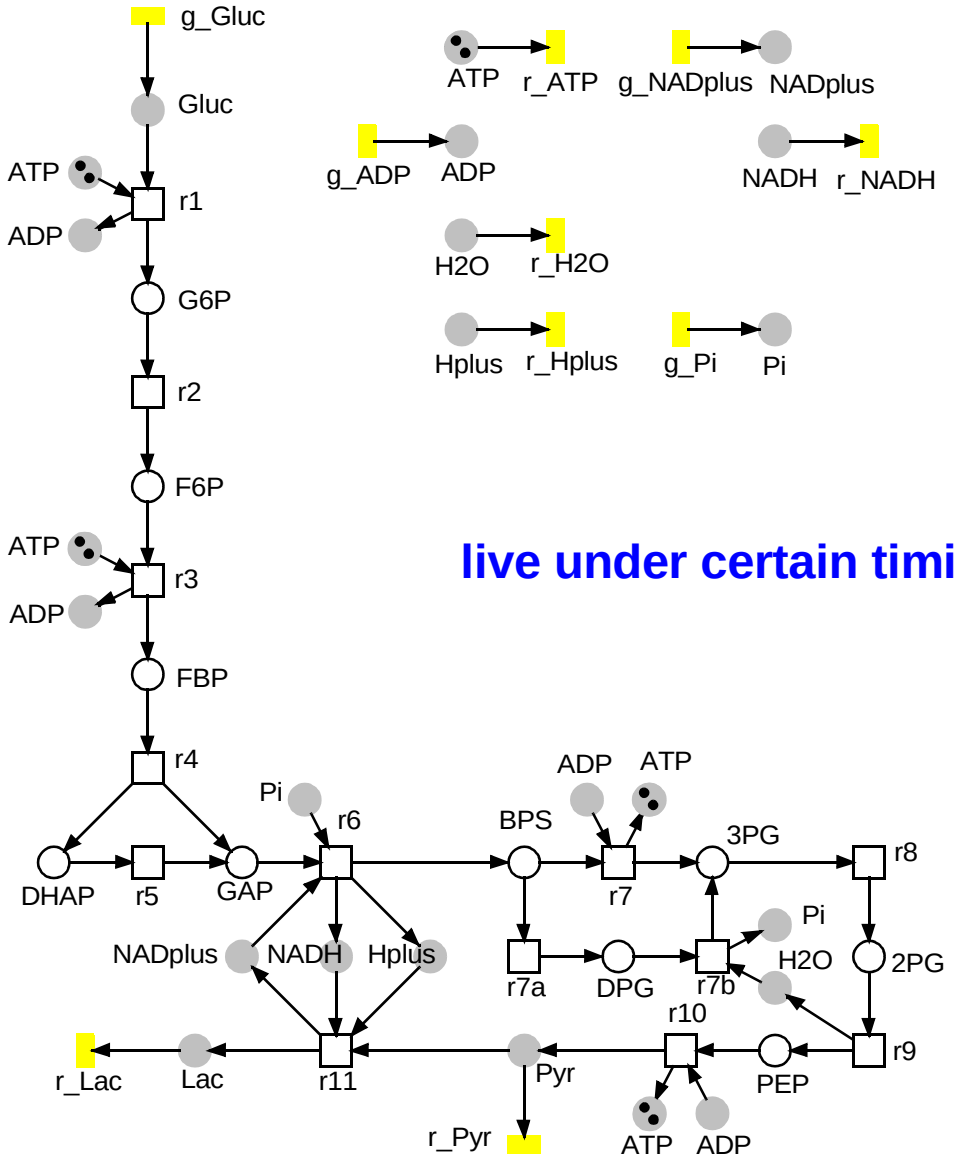
TIME-DEPENDENT BOUNDEDNESS

- **given: time-free Petri net**
  - -> *unbounded*
  - -> *live (supposed to be)*
- **wanted: corresponding time-dependent Petri net**
  - -> *(weakly) bounded*
  - -> *(still) live*
- **questions**
  - -> *for which structures does it work / does it not work ?*
  - -> *are there sufficient / necessary conditions ?*
  - -> *which time intervals make the net bounded ?*
  - -> *which time intervals preserve a transition sequence's realizability ?*
- **consistency criterion for (steady state) bio networks !?**

Problem 2:

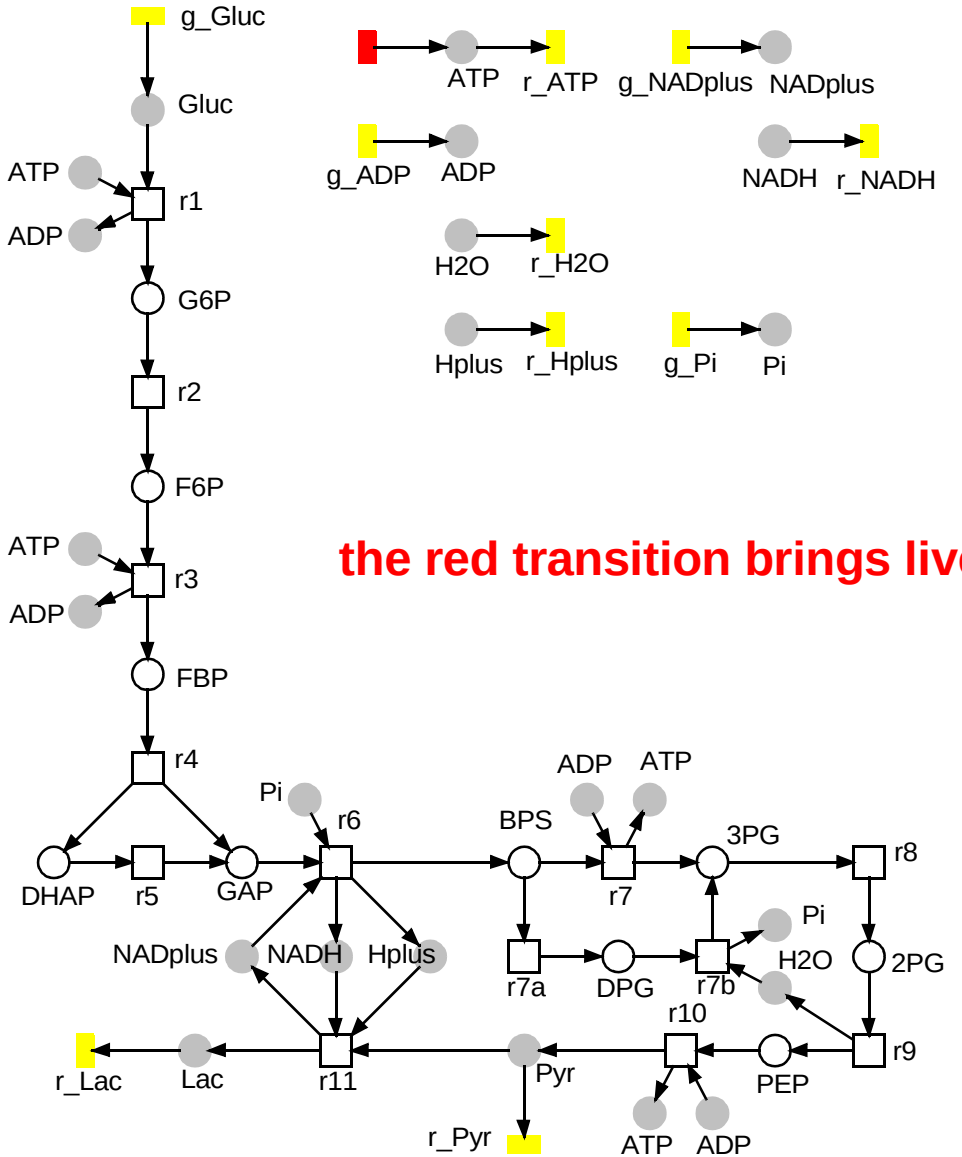
time-dependent liveness

EXAMPLE - GLYCOLYSIS



live under certain timing constraints

EXAMPLE - GLYCOLYSIS



the red transition brings liveness under any timing

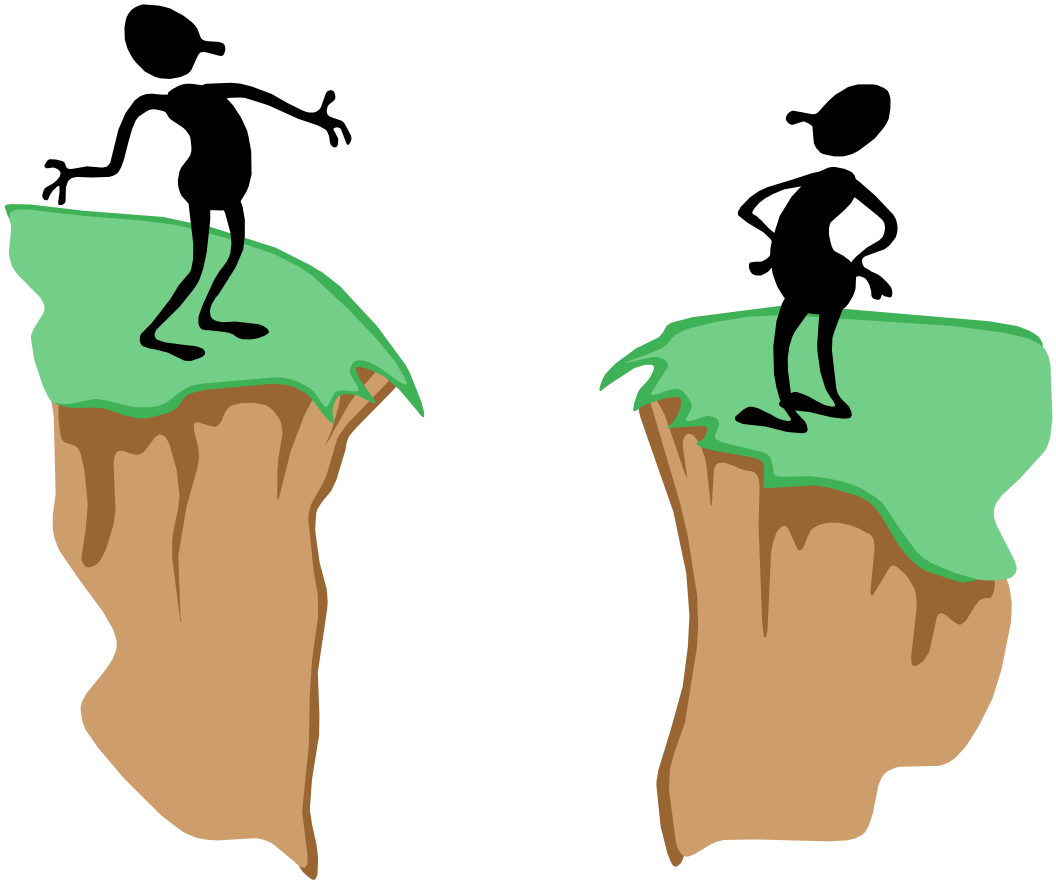
SUMMARY, TWO OPEN PROBLEMS

- **problem 1: time-dependent boundedness**
  - -> *given:* *unbounded and live time-free Petri net*
  - -> *question:* *under which conditions are there time restrictions, making this Petri net (weakly) bounded, while preserving liveness ?*

- **problem 2: time-dependent liveness**
  - -> *given:* *non-live time-free Petri net*
  - -> *question:* *under which conditions are there time restrictions, making this Petri net live ?*

-- especially helpful for analyzing bio Petri nets --

OUTLOOK



Thanks !

hhttp://www-dssz.informatik.tu-cottbus.de