TIME PETRI NETS FOR MODELLING AND ANALYSIS OF BIOCHEMICAL NETWORKS

- ON THE INFLUENCE OF TIME -

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- **Why introduce time ?**
  - -> *more information, less abstraction of reality*
  - -> *involves boundedness = finite state spaces*

- **What are Time Petri nets ?**
  - -> *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 give steady state behaviour*

- **Two open problems**
  - -> *time-dependent boundedness -> weakly bounded*
  - -> *time-dependent liveness -> weakly live*

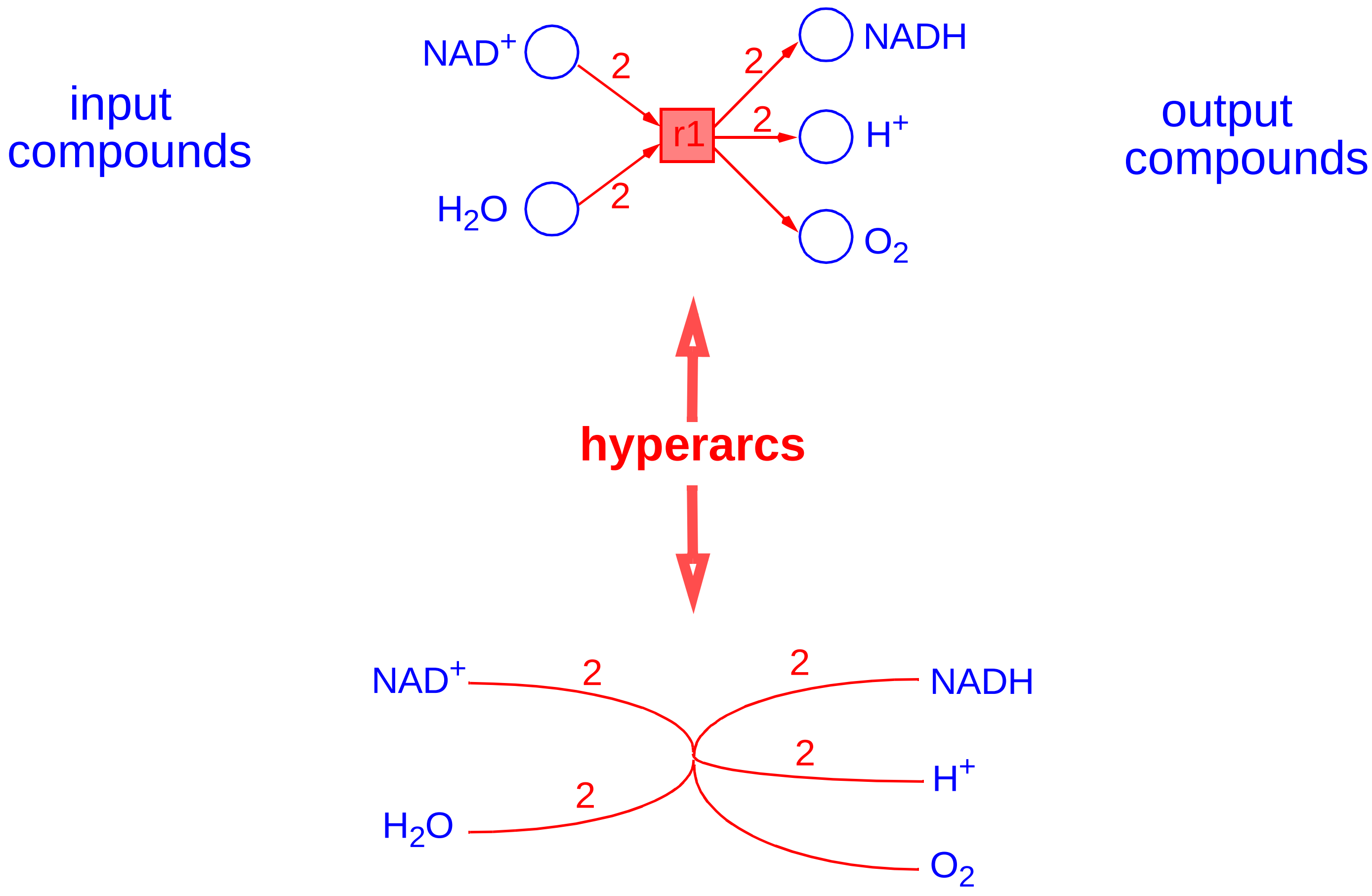
Petri nets

- basics -

PETRI NETS, BASICS - THE STRUCTURE

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

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



PETRI NETS, BASICS - THE STRUCTURE

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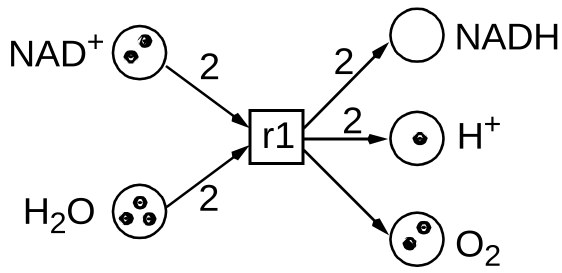
$$2\ NAD^{+} + 2\ H_2O \rightarrow 2\ NADH + 2\ H^{+} + O_2$$

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**

PETRI NETS, BASICS - THE BEHAVIOUR

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input compounds

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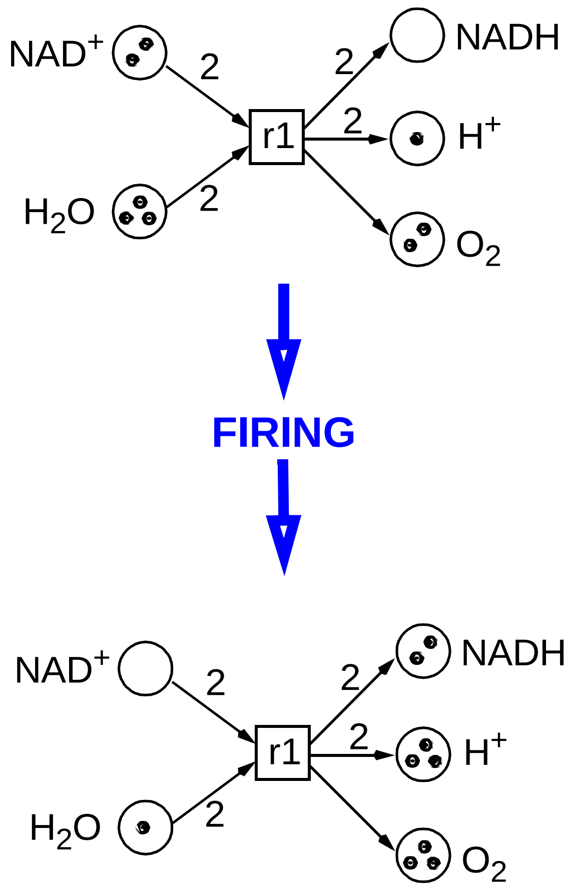

PETRI NETS, BASICS - THE BEHAVIOUR

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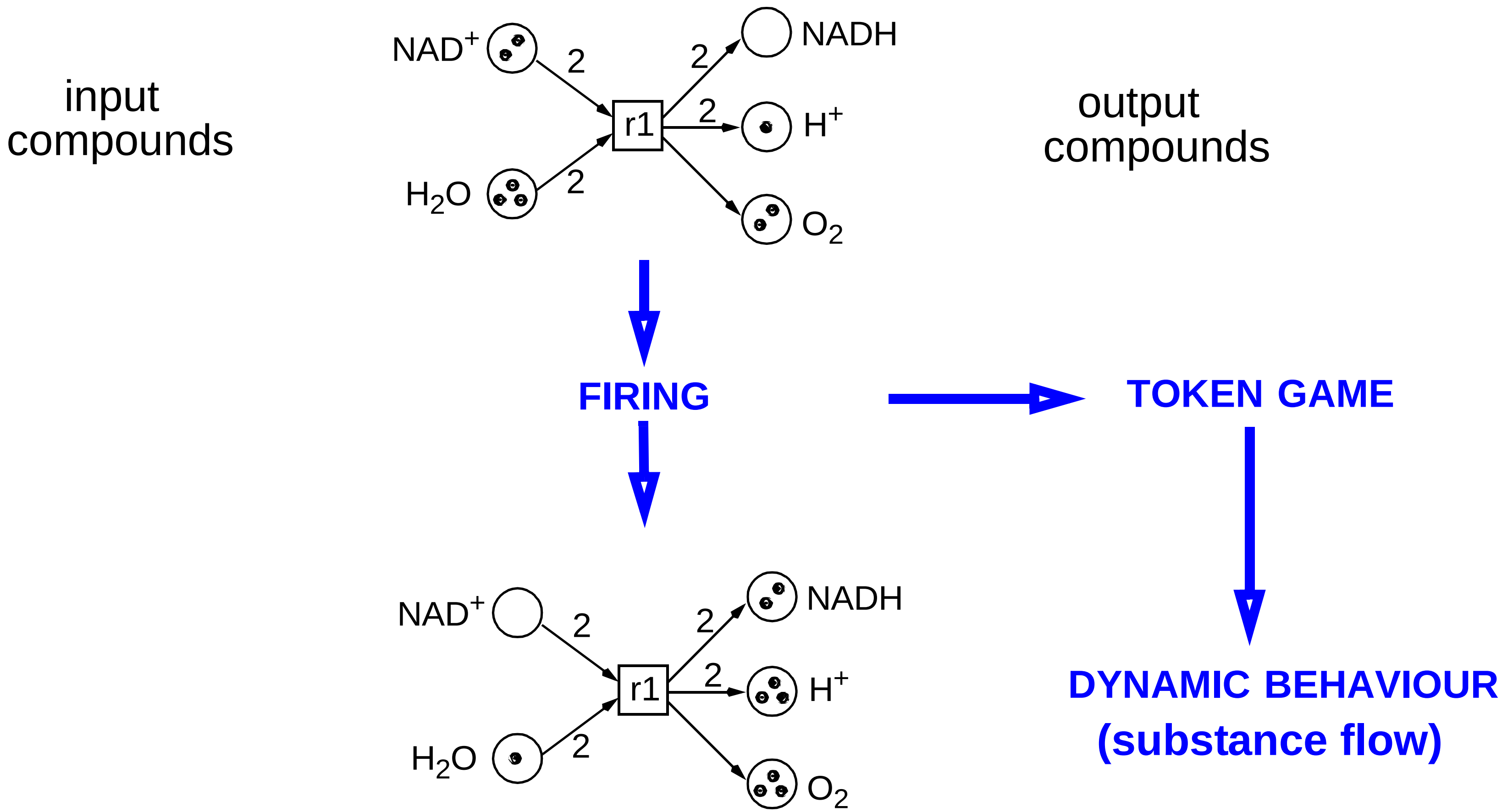

PETRI NETS, BASICS - THE BEHAVIOUR

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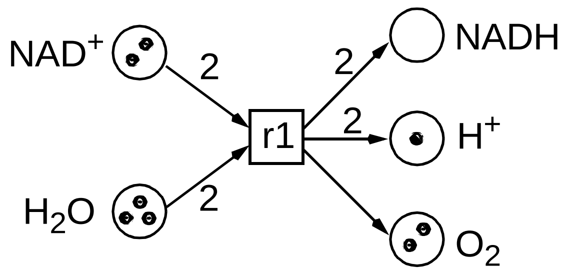
input compounds

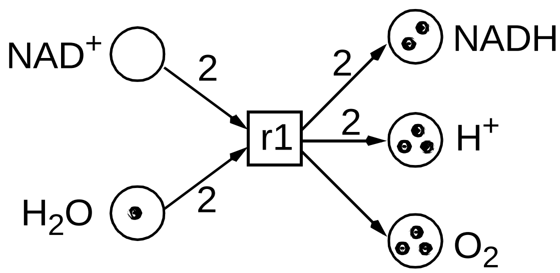


output compounds

FIRING → **TOKEN GAME**

THERE IS NO NOTION OF TIME !

EXHAUSTIVE ANALYSES CONSIDER ALL POSSIBLE TIMING BEHAVIOUR



DYNAMIC BEHAVIOUR (substance flow)

- **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 -

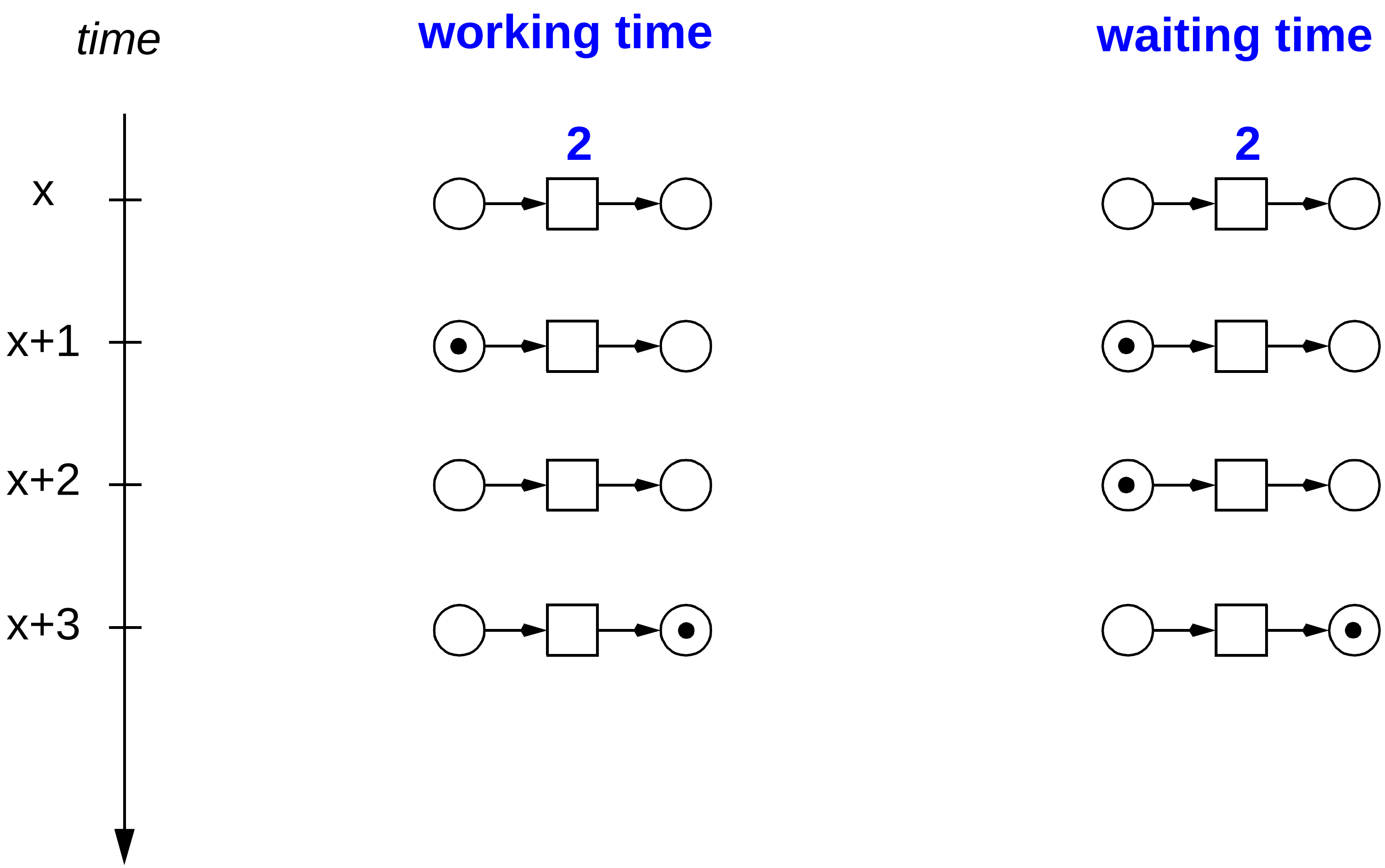
HOW TO INTRODUCE TIME ?

- **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 !

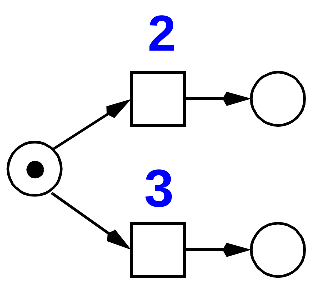
- **firing rule** *may* $\rightarrow$ *must*
  -> *working time* - *transition reacts immediately, firing lasts for the specified time*
  -> *waiting time* - *transition reacts after the specified time, firing itself does not consume time(-> stochastic Petri nets)*



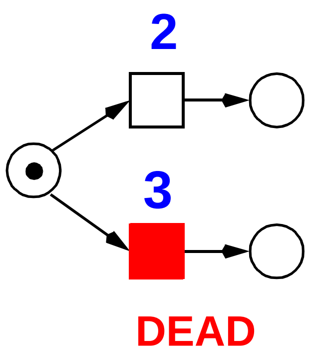
time
working time
waiting time
2
2
x
x+1
x+2
x+3

FIRING RULE

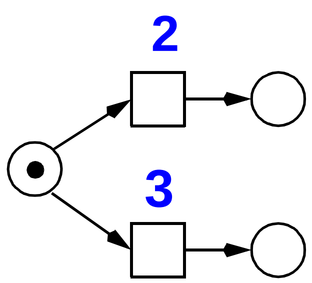
working time



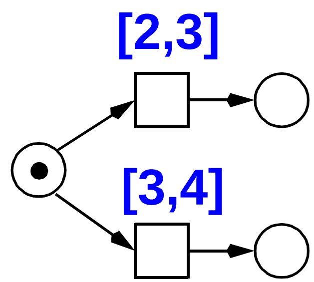
waiting time



working time



waiting time



LIVE

TIMED PETRI NET

[Ramchandani 74]

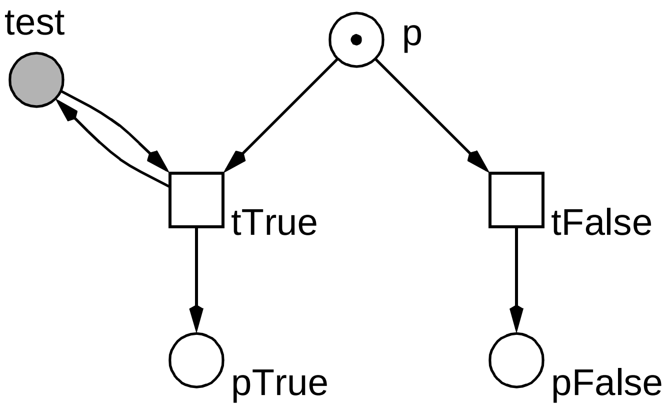
non-preemptive firing

TIME PETRI NET

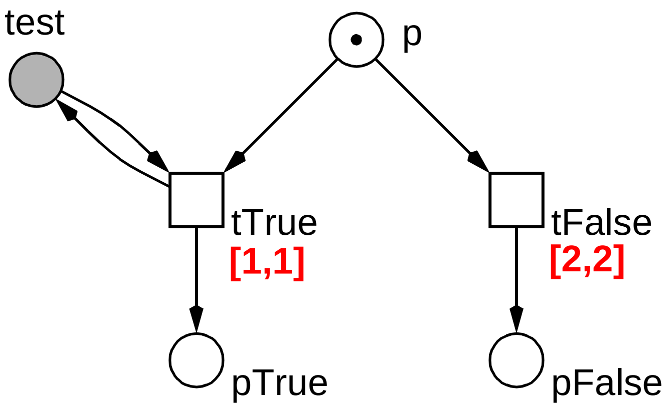
[Merlin 74]

preemptive firing

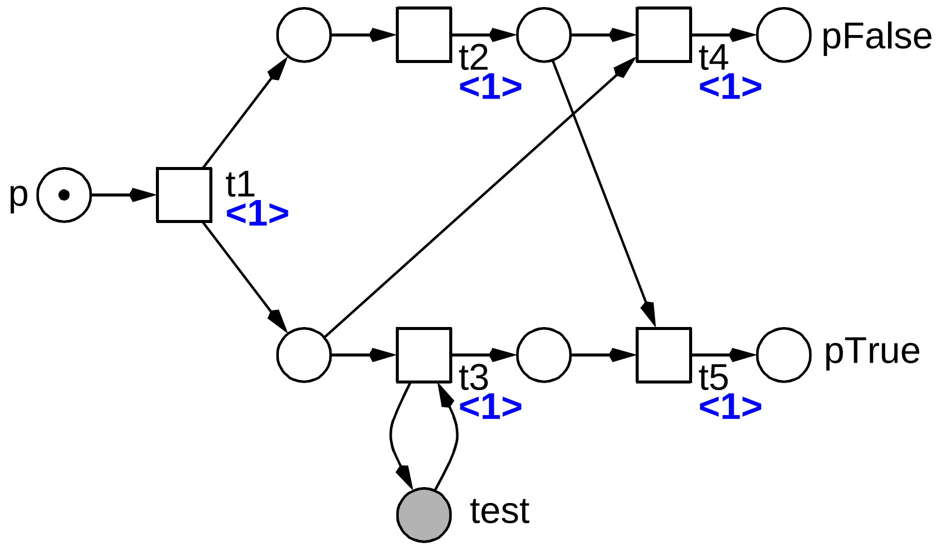
PETRI NET ?



WAITING TIME



WORKING TIME



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

- **time may restrict the behaviour**

	TIME	
pn	$\longrightarrow$	tpn
prop(pn)	$\not\Leftrightarrow$	prop(tpn)
RG (pn)	$\supseteq$	**RG** $(tpn)_{\vert m}$

- **time may influence qualitative properties**

TIME-INSENSITIVE PROPERTIES

BND (pn) -> BND (tpn)

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

DTr_{m0} (pn) -> DTr_{m0} (tpn)

TIME-SENSITIVE PROPERTIES

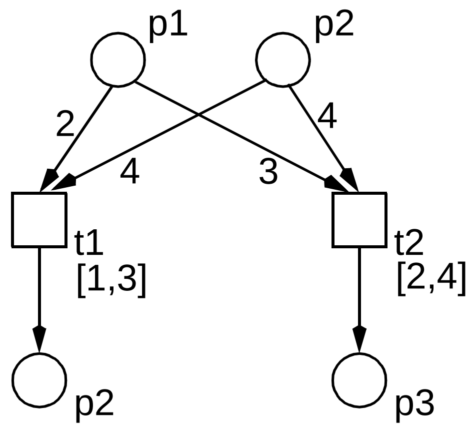
not BND (pn) -> BND (tpn)

DSt (pn) -> not DSt (tpn)

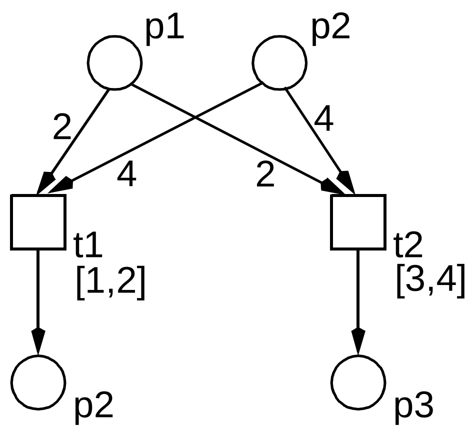
live (pn) -> not live (tpn)

KNOWN FACTS, TIME-INDEPENDENT LIVENESS

- **net structures, remaining live under any timing**
  - -> *persistent (dynamically conflict free) nets*
- **working time**
  - -> *ES*
- **waiting time**
  - -> *earliest firing time of all transitions is zero*
  - -> *latest firing time of all transitions is infinite*
  - -> *well-formed EFC*
  - -> *well-formed behaviourally free choice, i.e.,*
    t1 # t2: AG (enabled (t1) ⇔ enabled (t2))
  - -> *well-formed ES (?!)*
  - -> *well-formed =*
    homogeneous &
    timely homogeneous &
    no purely immediate transitions



not homogeneous



not timely homogeneous

Problem 1:

time-dependent boundedness

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*

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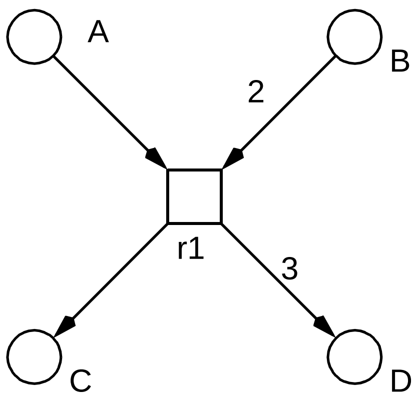
TIME-DEPENDENT BOUNDEDNESS

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

A + 2 B -> C + 3 D



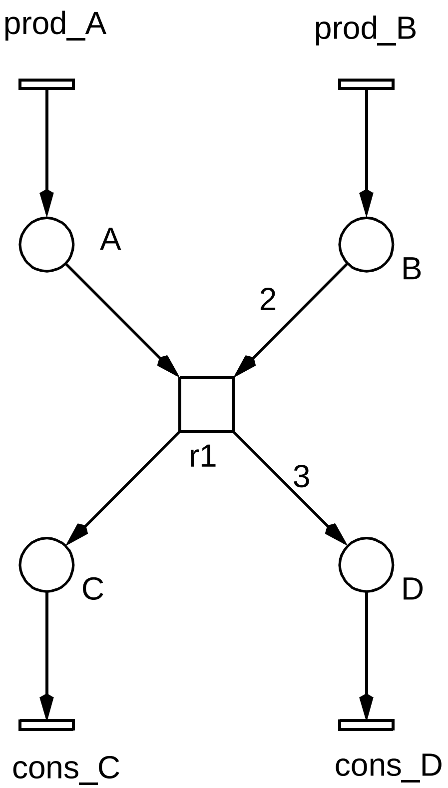
-> properties as time-free net

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

A + 2 B -> C + 3 D



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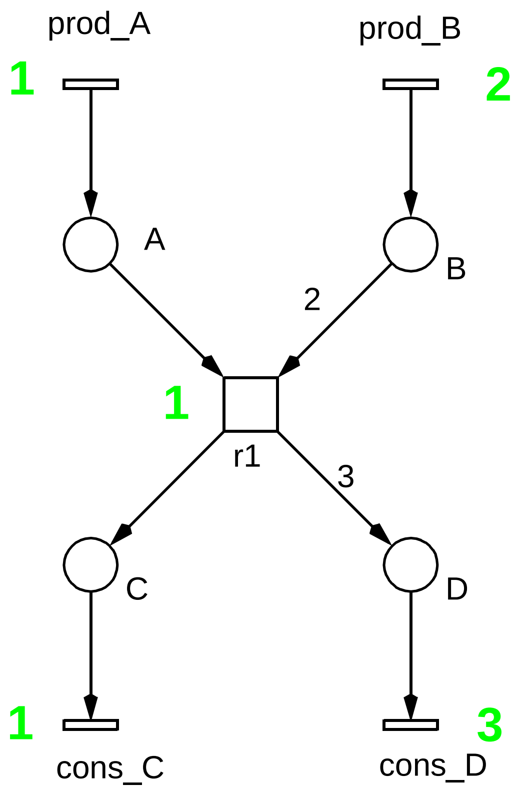
N	Y	N	Y	N	Y	Y	N	Y	Y	N	N	Y	N	Y	Y	Y

CPI	CTI	B	SB	REV	DSt	BSt	DTr	DCF	L	LV	L&S
N	Y	N	N	Y	N	?	N	Y	Y	Y	N

A + 2 B -> C + 3 D



T-INVARIANT

-> properties as time-free net

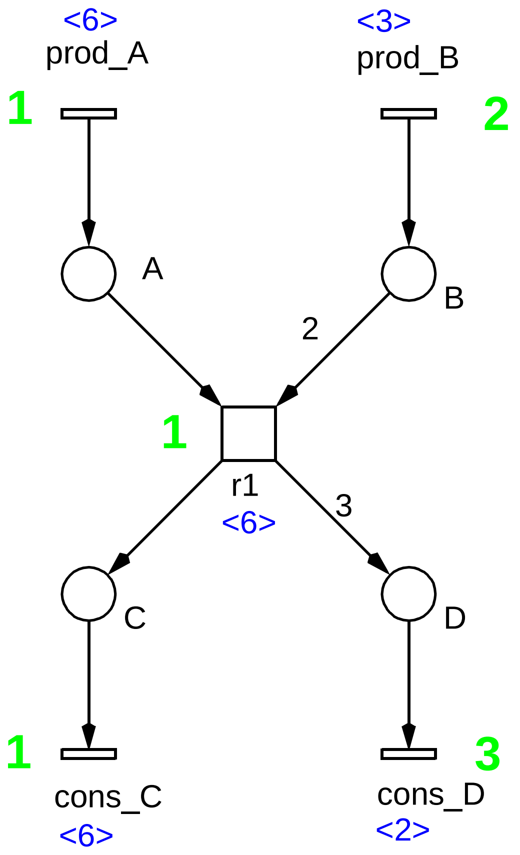
INA

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

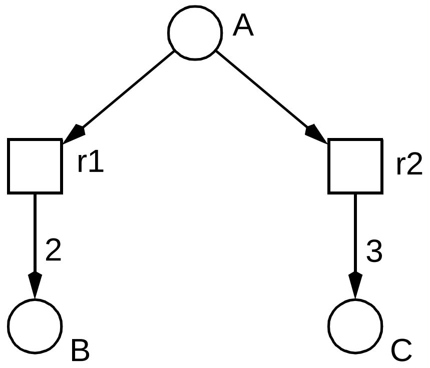
-> properties as time net

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

A ->2 B, A -> 3 C



-> properties as time-free net

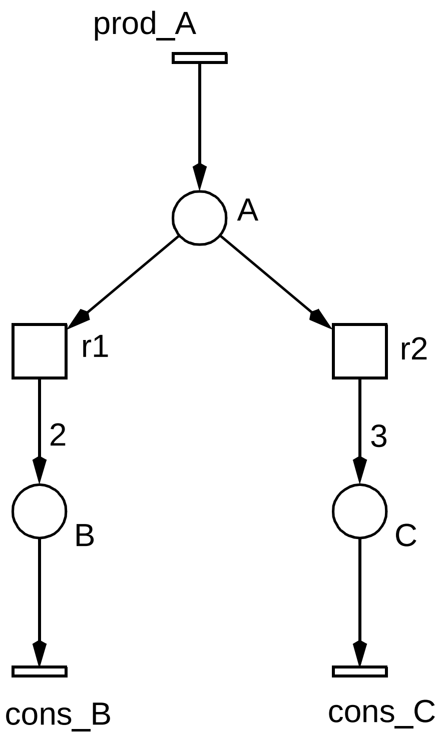
INA

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

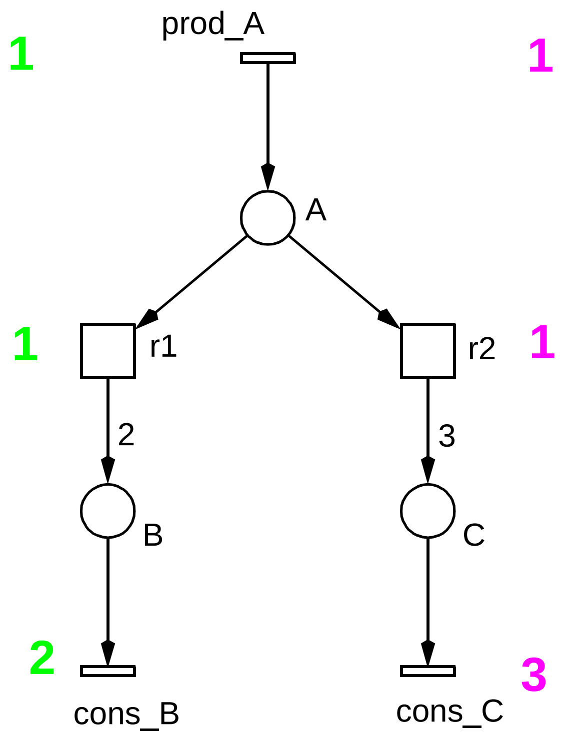
INA

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

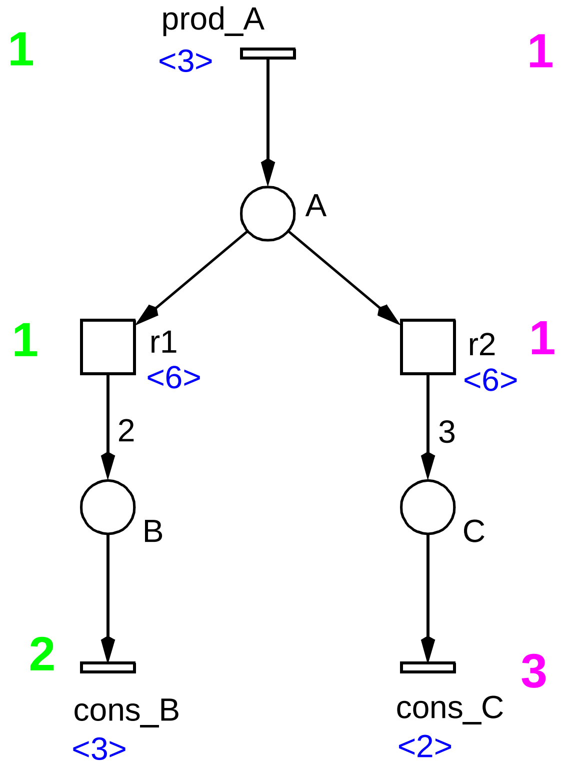
INA

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

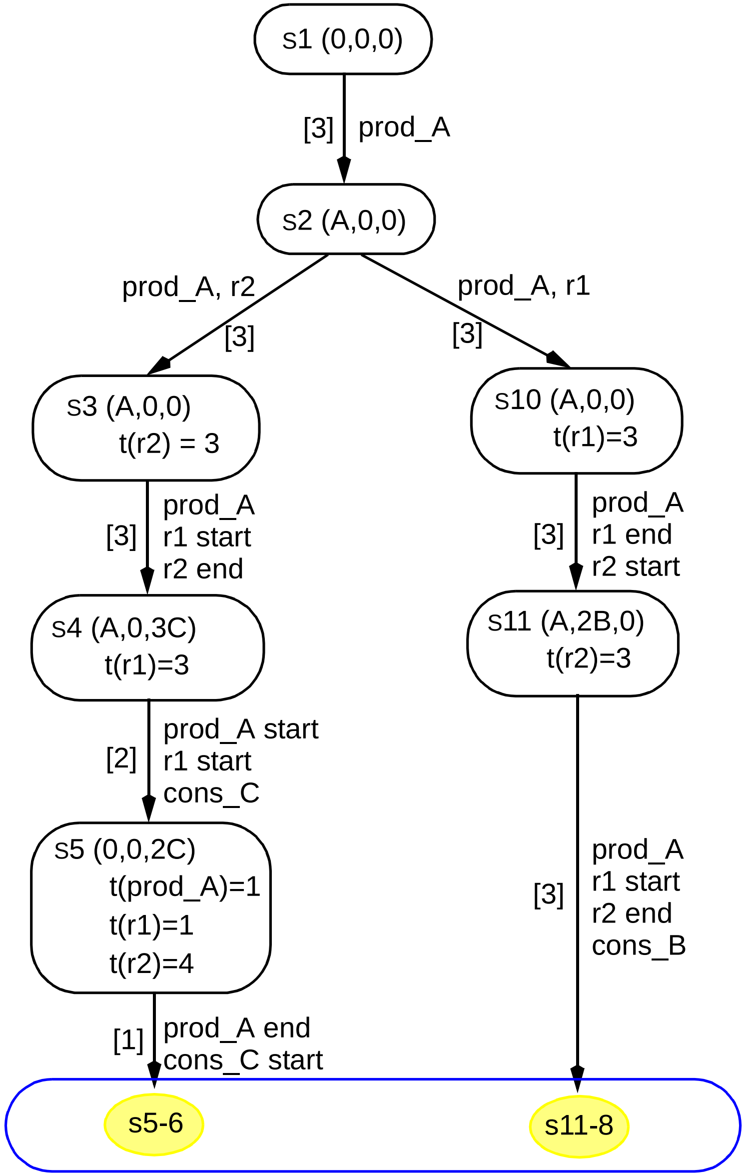
INA

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	Y	Y	Y	N

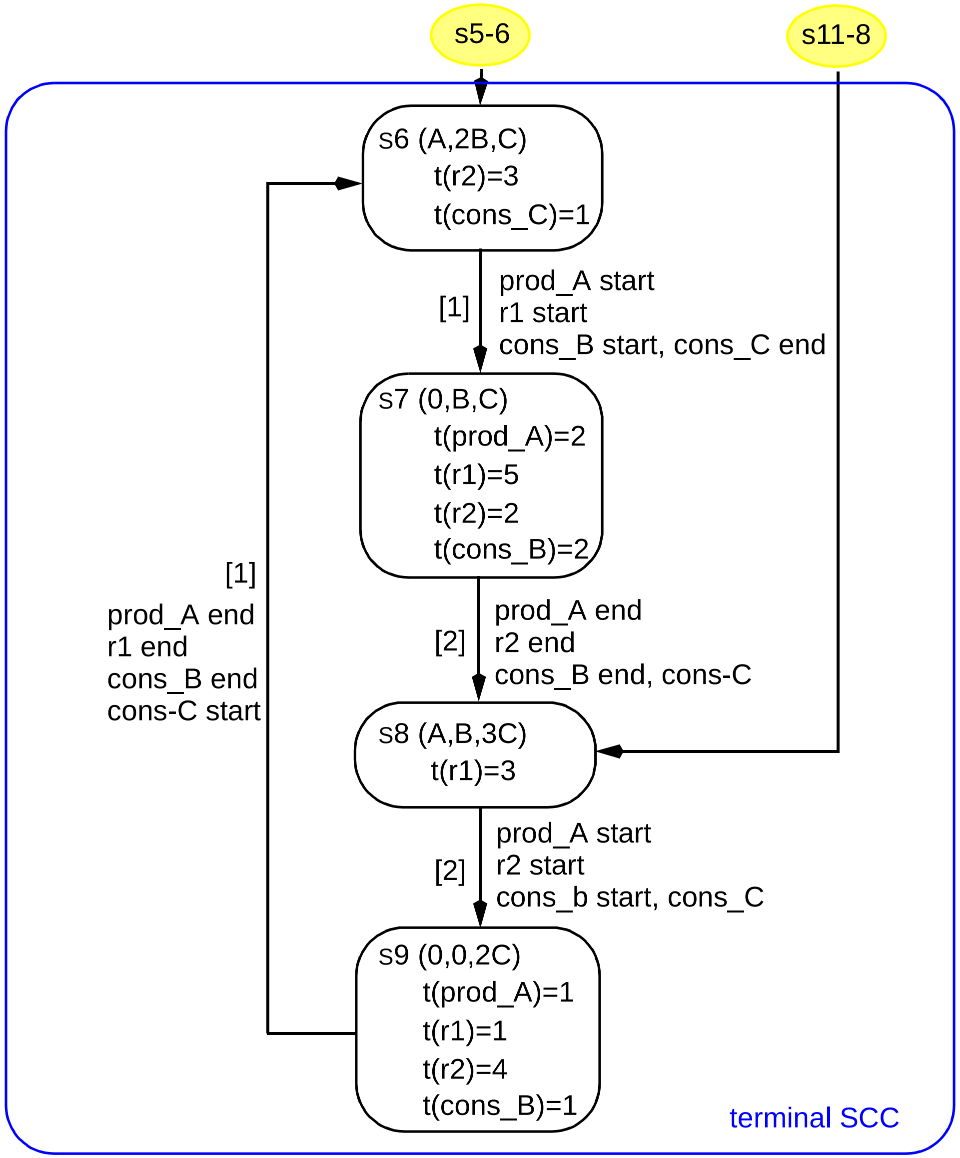
RG(Ex2), Part 1

- transient state



RG(Ex2), Part 2

- steady state



RG(Ex2), Terminal SCC

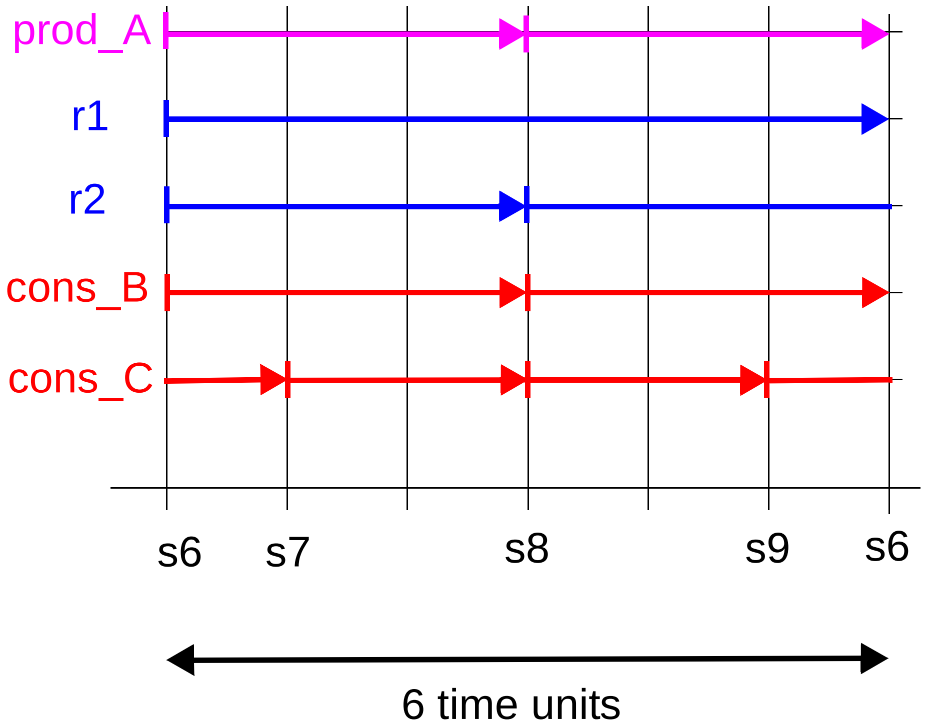
- **contains all transitions**
  - -> *always running*
  - -> *start / end*
    at different time points

- **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*

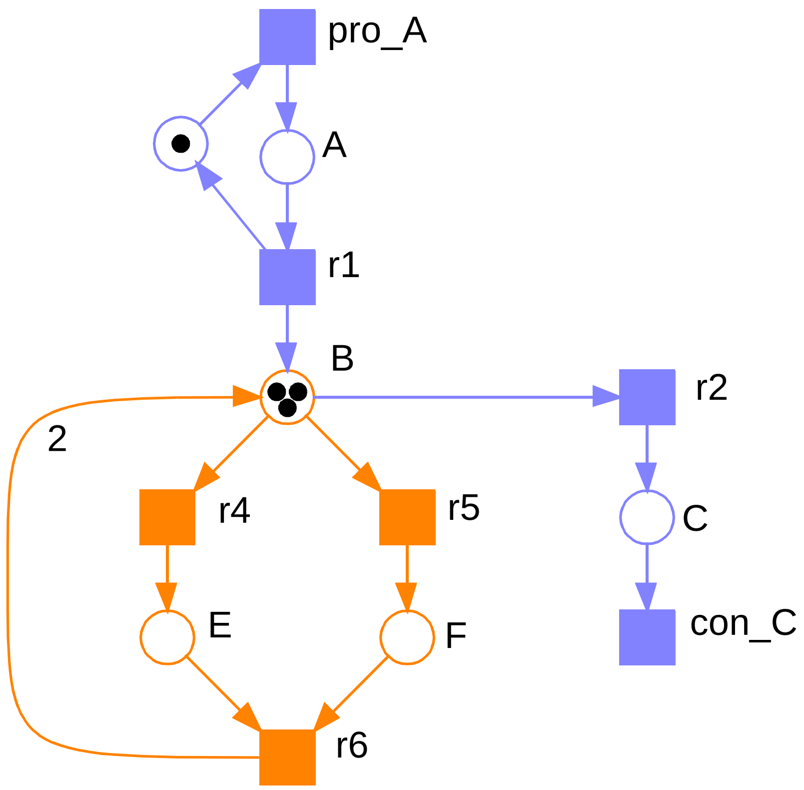
- steady state behaviour
  - -> *terminal scc*
  - -> *here, BND*
  - -> *here, DCF*

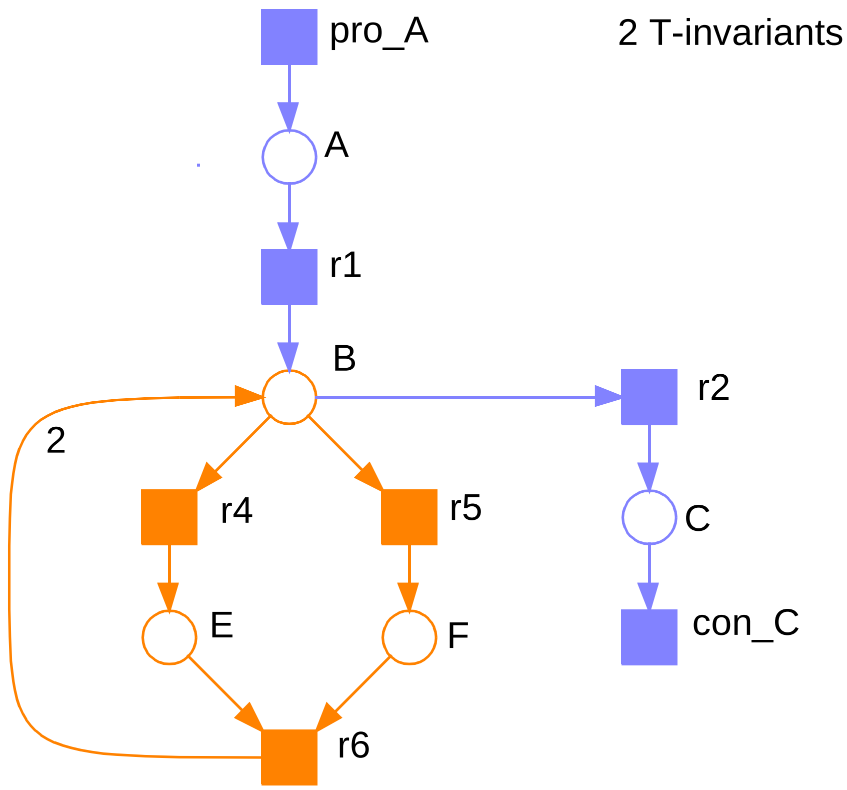
PN	—— time ——>	**TIME NET**
not BND REV LIVE		BND not REV LIVE

However,
this does not always work !

COUNTEREXAMPLE 1

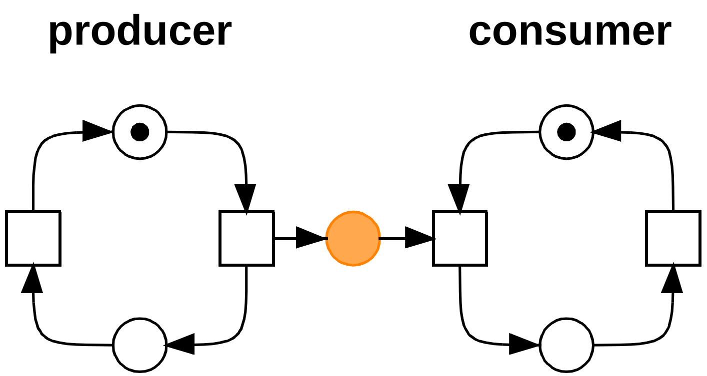
1-working time for all transitions;
FC, there are no deadlocks, traps, p-invariants, besides the pseudo-P-invariant (A , co_A);



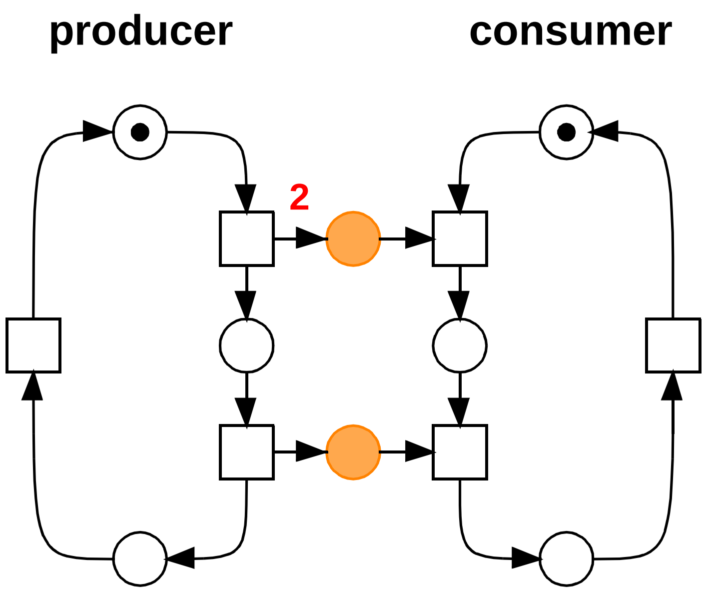


wBND & LIVE for the given initial marking

COUNTEREXAMPLE 2



weakly bounded



not weakly bounded

[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*

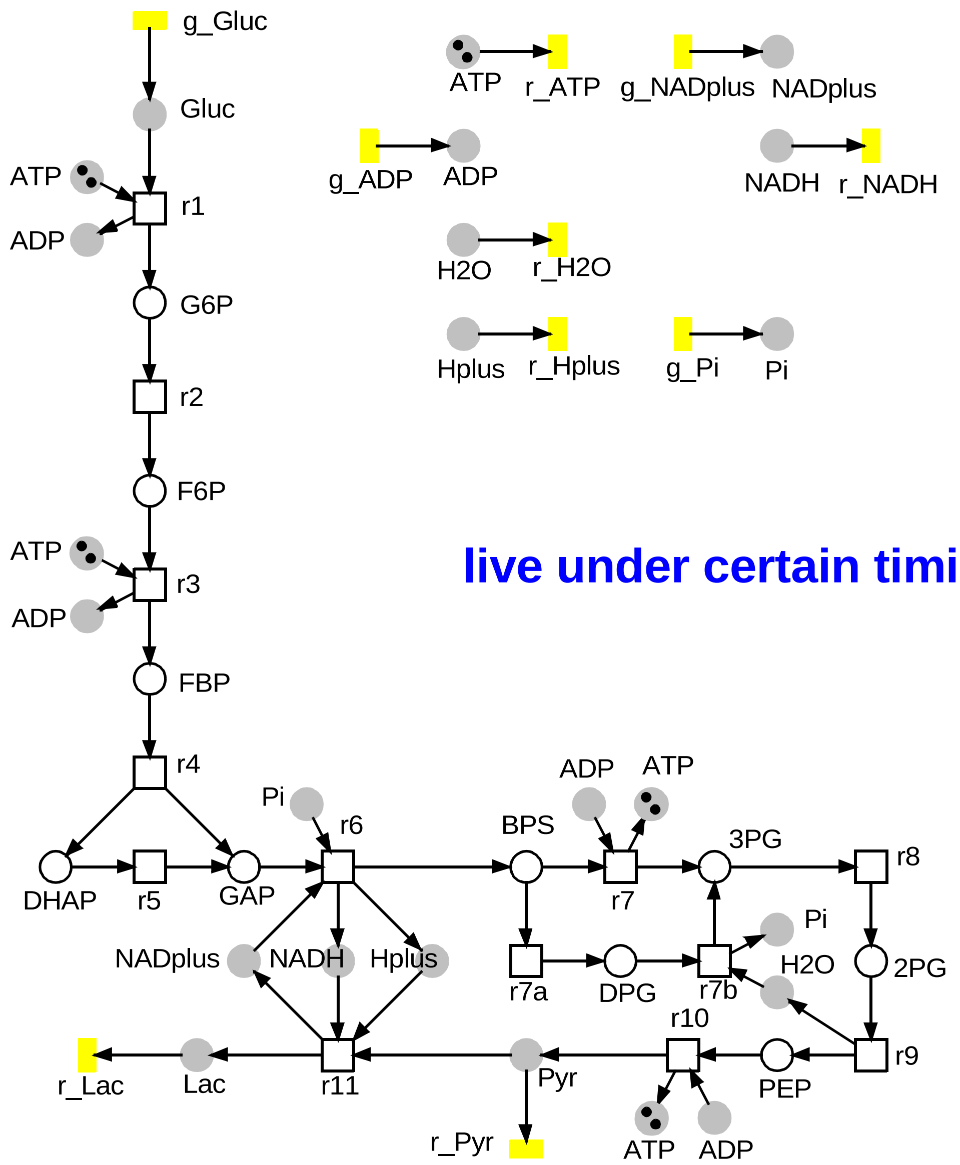
- **questions**
  - -> *for which structures does it work / does it not work ?*
  - -> *are there sufficient / necessary conditions ?*
  - -> *which time intervals make the net bounded ?*
  - -> *which time intervals preserve a transition sequence's realizability ?*

- **consistency criterion for (steady state) bio networks !?**

Problem 2:

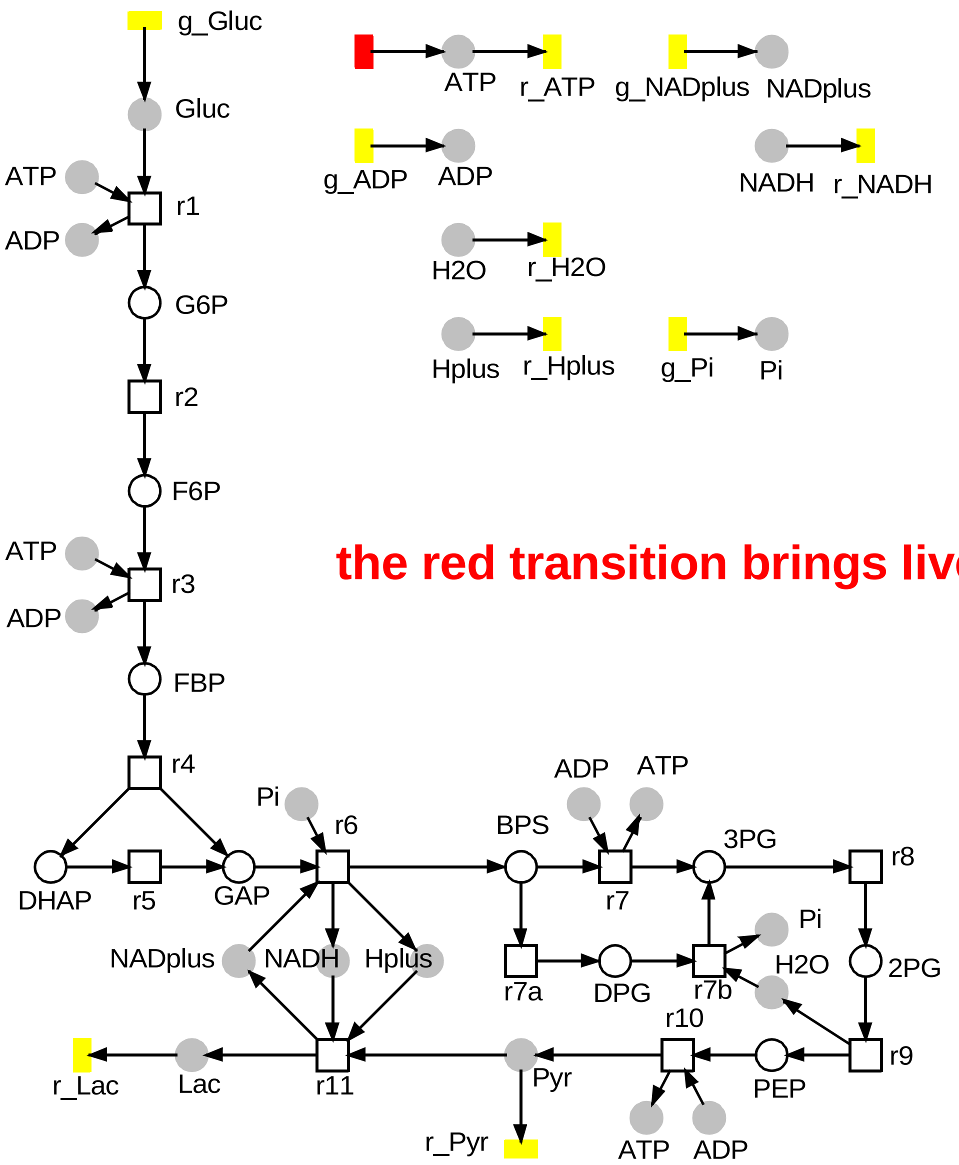
time-dependent liveness

EXAMPLE - GLYCOLYSIS



live under certain timing constraints

EXAMPLE - GLYCOLYSIS

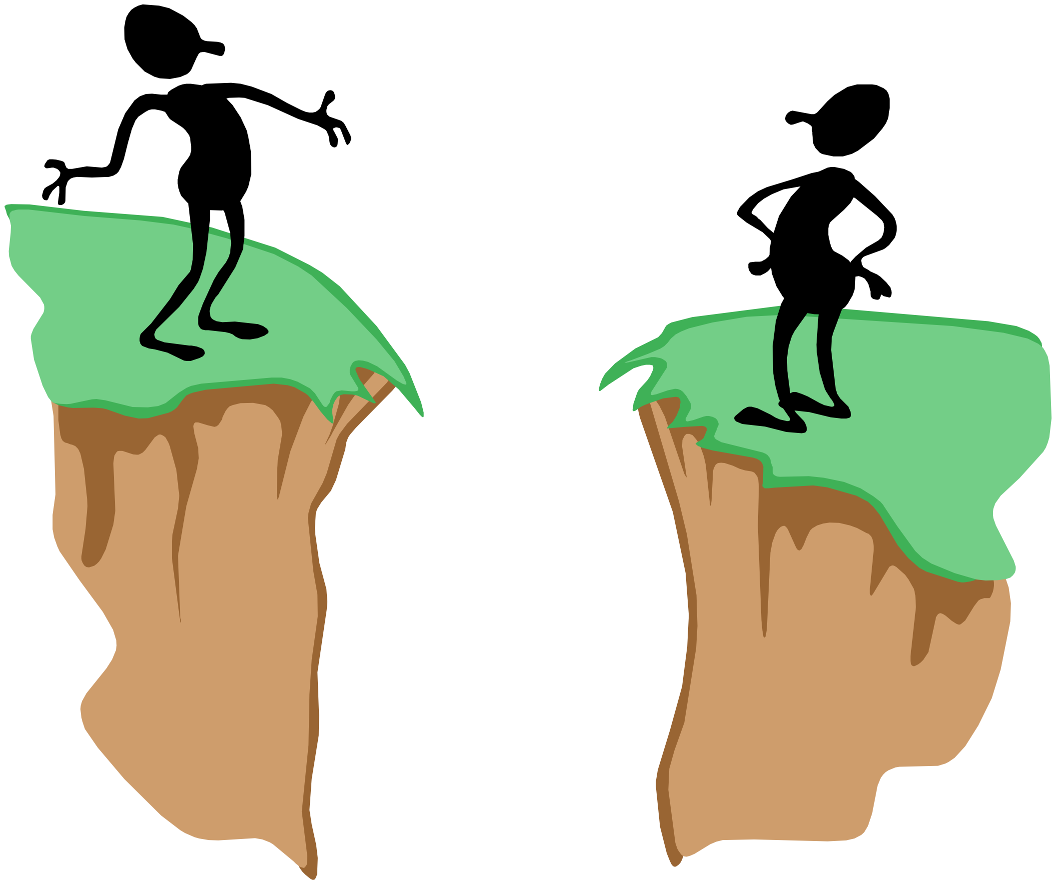


the red transition brings liveness under any timing

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 --



Thanks !

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