PART V
SUMMARY, OUTLOOK
CHALLENGES

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SUMMARY

BIO PETRI NETS, A BIT OF HISTORY

- **Carl Adam Petri, 1962, PhD University of Technology Darmstadt**
  -> *basic ideas introduced*
- **early 1970's**
  -> *first papers contributing to Petri net theory*
- **Petri, 1976**
  -> *application to chemical networks mentioned*
- **early 1980's**
  -> *first monographs on Petri net theory*
- **Reddy, 1993**
  -> *first paper on bio application*
- **late 1990's**
  -> *increasing interest for modelling and analysis of bio networks*

A BIT OF HISTORY

C. A. PETRI, NOVEMBER 2006

A BIT OF HISTORY

SUMMARY

- **representation of bio networks by Petri nets**
  - -> *partial order representation* -> *better comprehension*
  - -> *formal semantics* -> *sound analysis techniques*
  - -> *unifying view* -> *various abstraction levels*

SUMMARY

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

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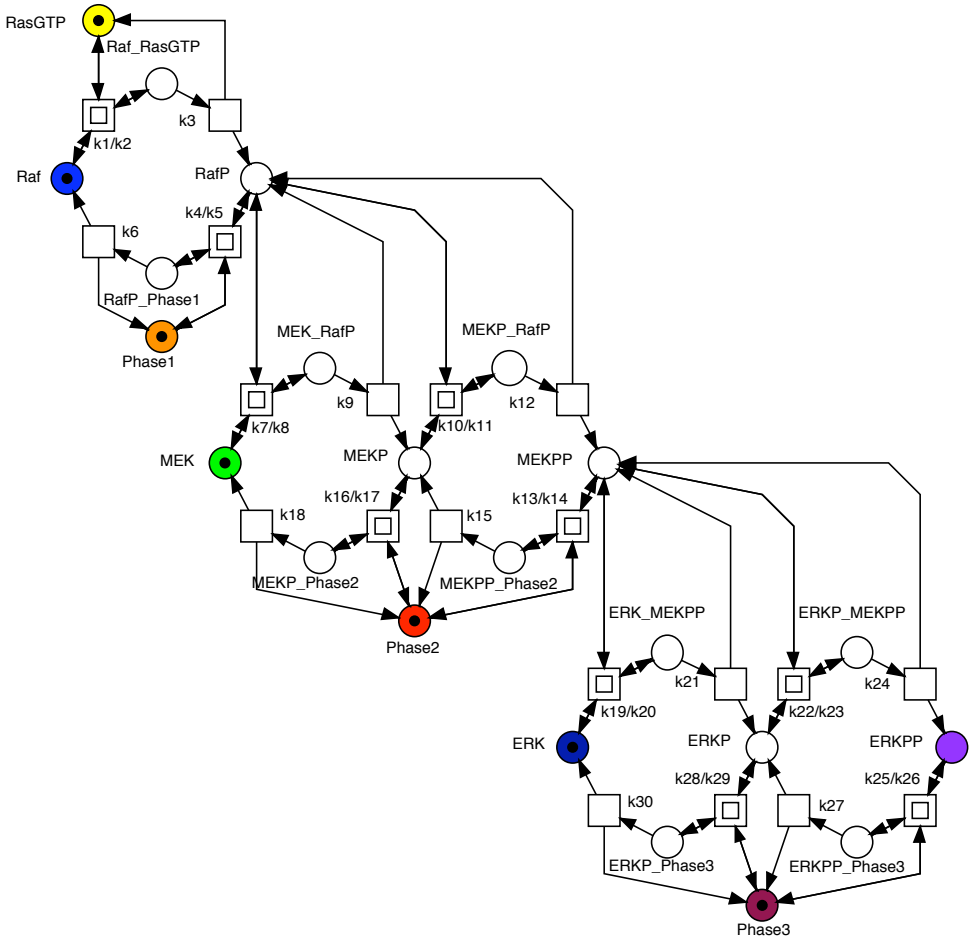
  - -> *qualitative / quantitative behaviour prediction* -> *experiment design, new insights*
- **step-wise model development**
  - -> *qualitative model* -> *discrete Petri nets*
  - -> *discrete quantitative model* -> *stochastic Petri nets*
  - -> *continuous quantitative model* -> *continuous Petri nets = ODEs*

OUTLOOK

CHALLENGES

CHALLENGE 1

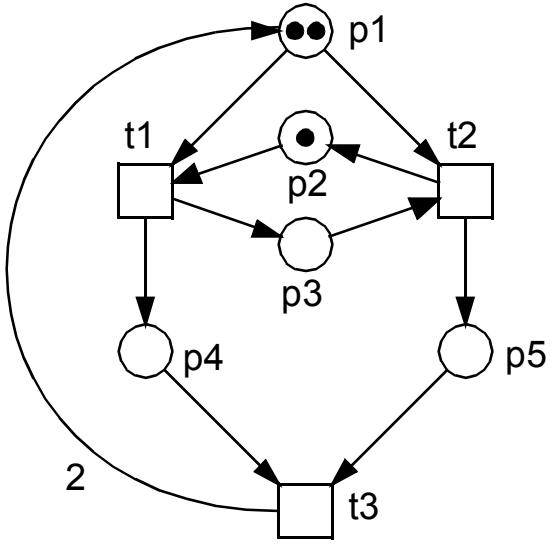
- **discrete models:**
  increasing level number = increasing accuracy

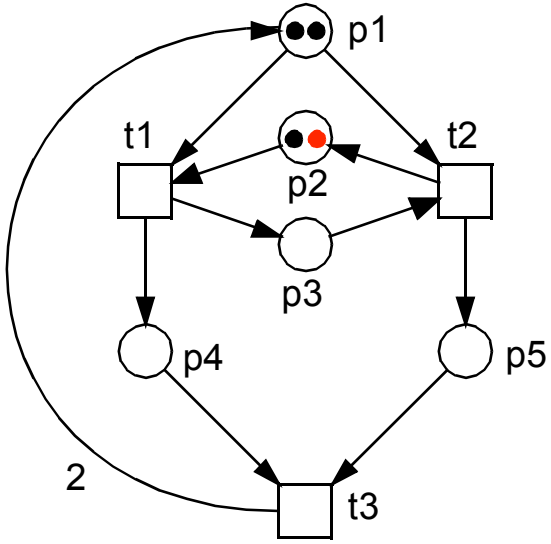


CHALLENGE 1

- **BUT, monotonous liveness holds generally for substructures (EFC) only !**

[STARKE 1990]





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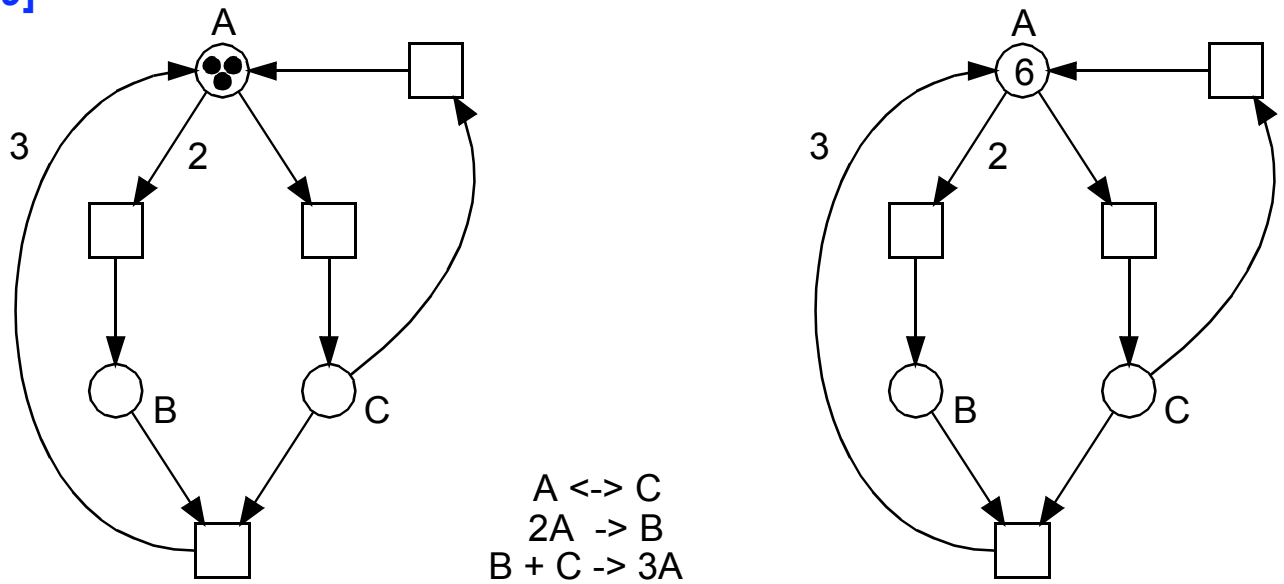
N	Y	Y	Y	Y	N	Y	Y	N	N	N	N	**ES**
DTP	CPI	CTI	SCTI	SB	k-b	1-b	DCF	DSt	DTr	LIV	REV	
N	Y	Y	Y	Y	Y	N	Y	0	N	Y	Y	
							N	**1**	**Y**	**N**	**N**	

❑ liveness may also be lost by multiple markings

[BALBO 2009]



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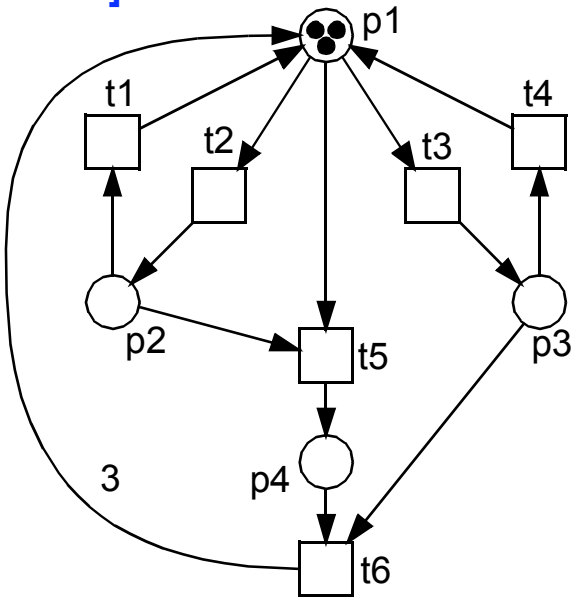
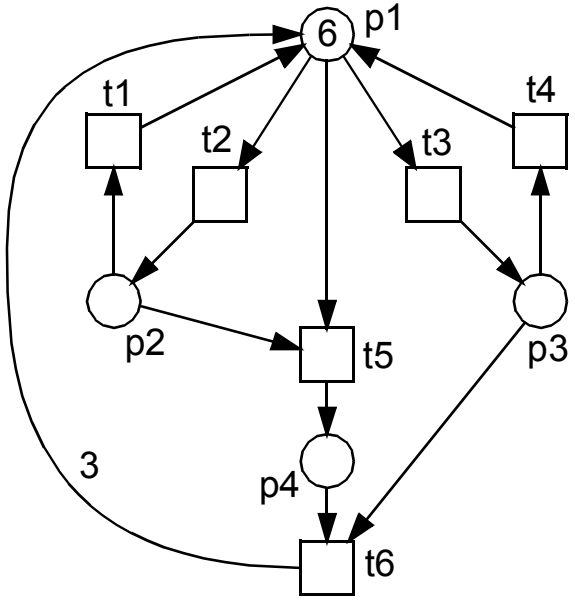
N	Y	N	N	N	N	Y	Y	N	N	N	N	**ES**
DTP	CPI	CTI	SCTI	SB	k-b	1-b	DCF	DSt	DTr	LIV	REV	
N	Y	Y	Y	Y	Y	N	N	0	N	Y	Y	
								1	**Y**	**N**	**N**	

CHALLENGE 1

- liveness may also be lost in homogenous nets

[POPOVA 2010]





ORD	PUR	HOM	NBM	CSV	SCF	CON	SC	FT0	TF0	FP0	PF0	NC
N	Y	Y	Y	N	N	Y	Y	N	N	N	N	nES
DTP	CPI	CTI	SCTI	SB	k-b	1-b	DCF	DSt	DTr	LIV	REV	
N	Y	Y	Y	Y	Y	N	N	0	N	Y	Y	
								1	Y	N	N	

CHALLENGE 2

- **sharing structure = sharing properties**

  BUT, *that's not always the case ! to which extend ?*

  -> *stochastic and continuous behaviour may differ; why ? when ?*

  -> *when holds: continuous behaviour = averaged stochastic behaviour ?*

CHALLENGE 2

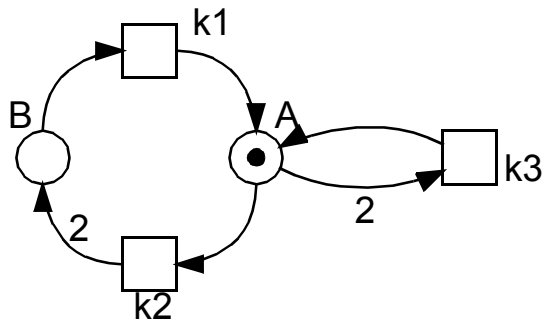
- **sharing structure = sharing properties**

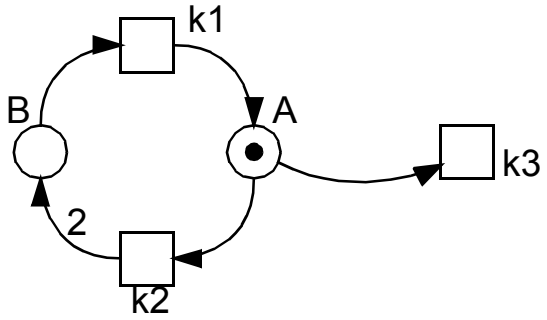
  BUT, *that's not always the case ! to which extend ?*

  -> stochastic and continuous behaviour may differ; why ? when ?

  -> when holds: continuous behaviour = averaged stochastic behaviour ?

- **two continuous Petri nets, generating the same ODEs, but having different discrete behaviour**





PUR	ORD	HOM	NBM	CSV	SCF	CON	SC	FT0	TF0	FP0	PF0	NC
N	N	N	N	N	N	Y	Y	N	N	N	N	FC
DTP	CPI	CTI	SCTI	SB	k-B	1-B	DCF	DSt	DTr	LIV	REV	
Y	N	Y	Y	-	N	N	-	**0**	-	-	-	
N								**1**	**Y**	**N**		

CHALLENGE 3

- **unbounded qualitative model + time = bounded model**
  - -> *stochastic models*
  - -> *continuous models / ODEs*

} *simulation*

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  } *simulation*

- **Should also work for timed Petri nets !**
  - -> *steady state behaviour*

- **What are timed 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*

Time Petri nets

- basics -

How to Introduce Time ?

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

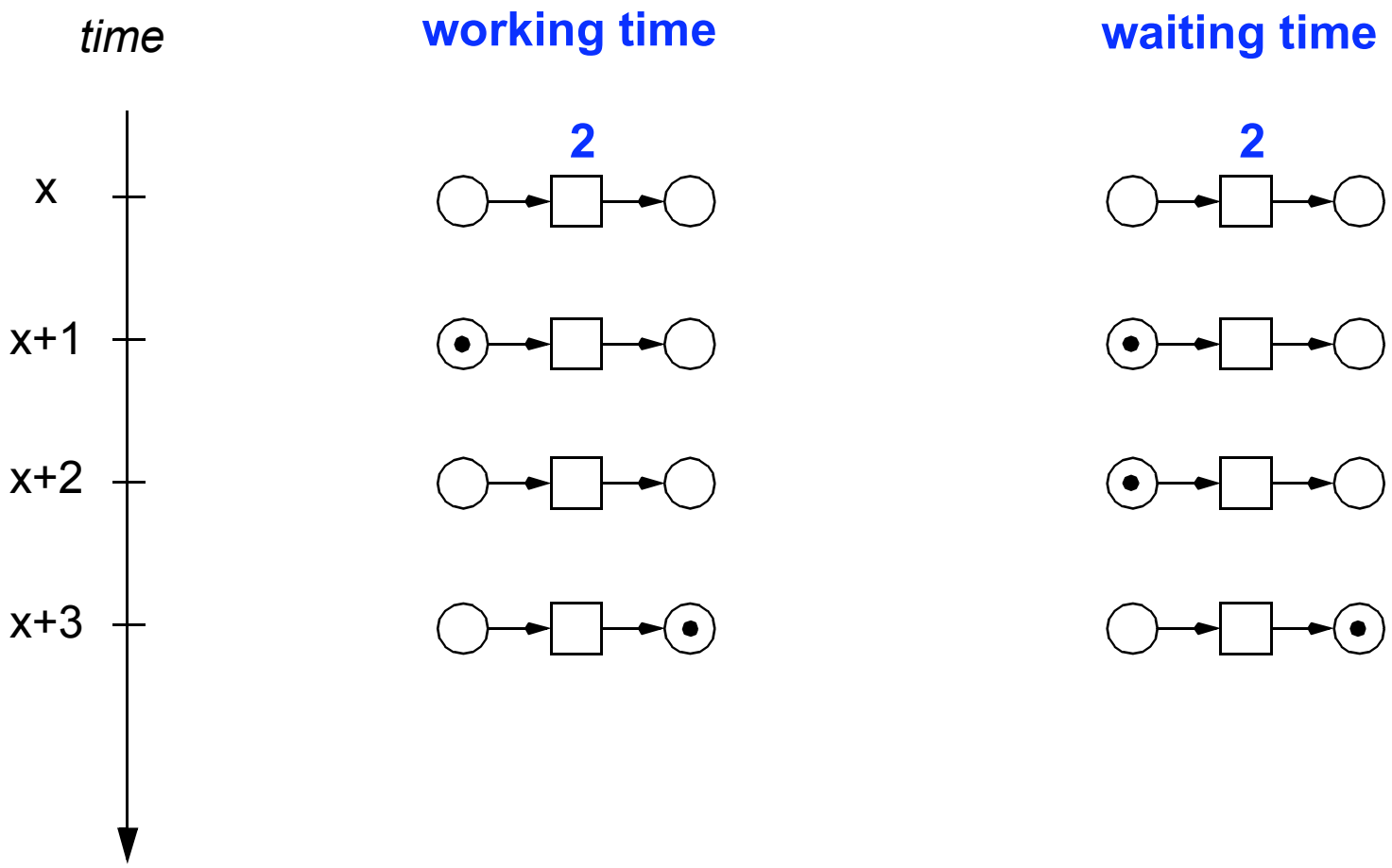
- **what kind of numbers ?**
  -> *real, rationals, integer*

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

- **firing rule** ***may → 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)*

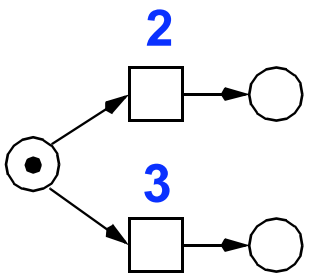
- **single server semantics**
  -> *transitions do not fire self-concurrently*

FIRING RULE

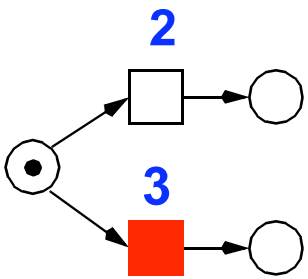


FIRING RULE

working time



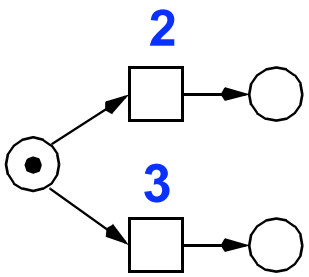
waiting time



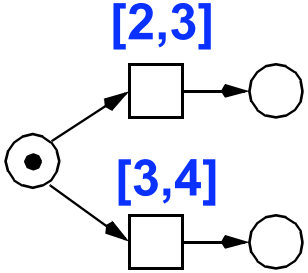
DEAD

FIRING RULE

working time



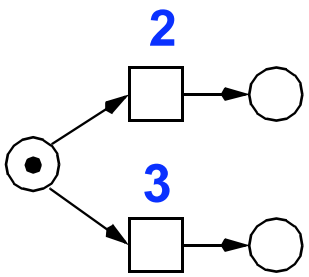
waiting time



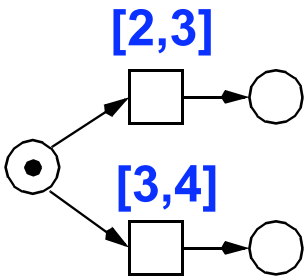
LIVE

FIRING RULE

working time



waiting time



LIVE

TIMED PETRI NET

[Ramchandani 74]

non-preemptive firing

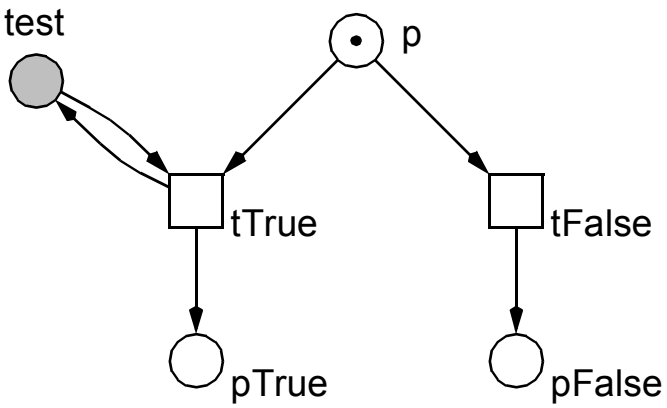
TIME PETRI NET

[Merlin 74]

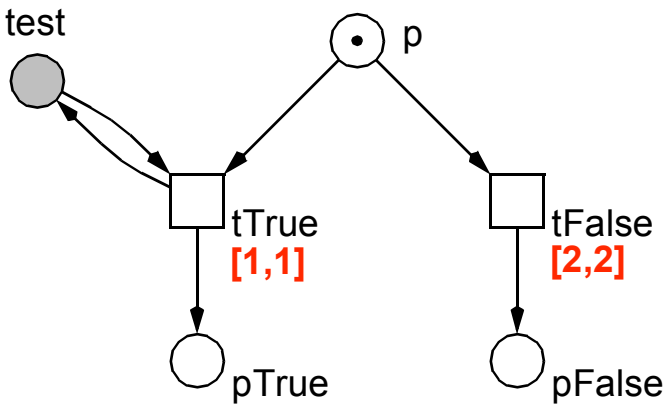
preemptive firing

ZERO TEST FOR TURING POWER

PETRI NET ?

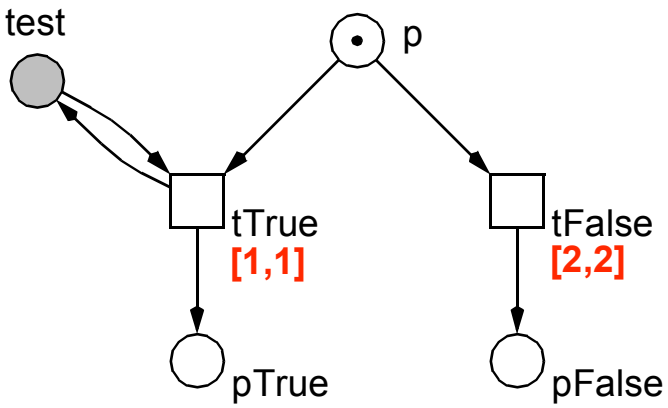


WAITING TIME

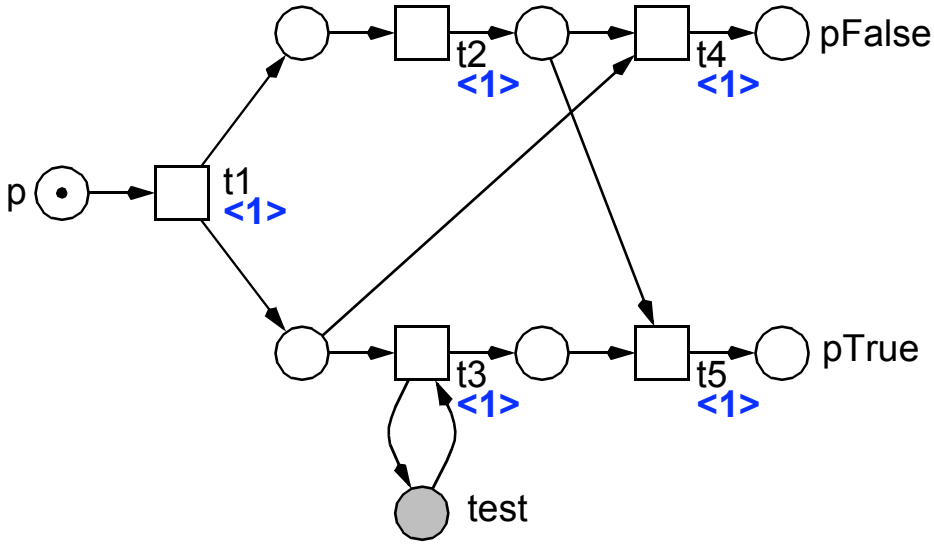


ZERO TEST FOR TURING POWER

WAITING TIME

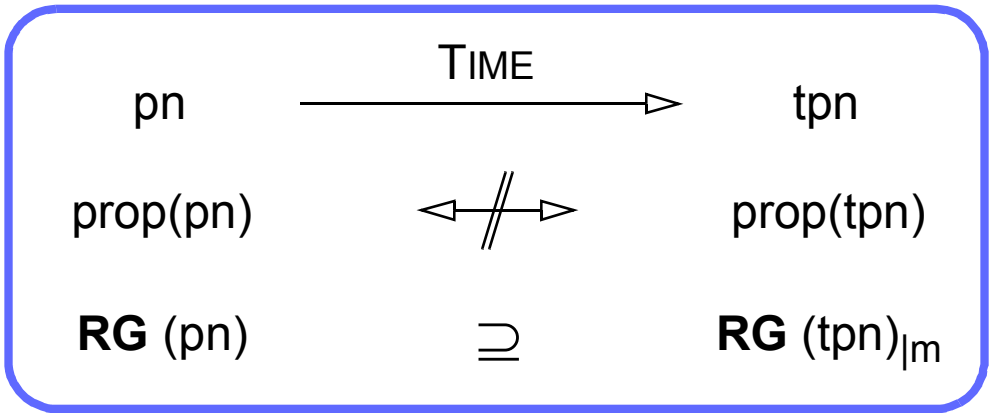


WORKING TIME



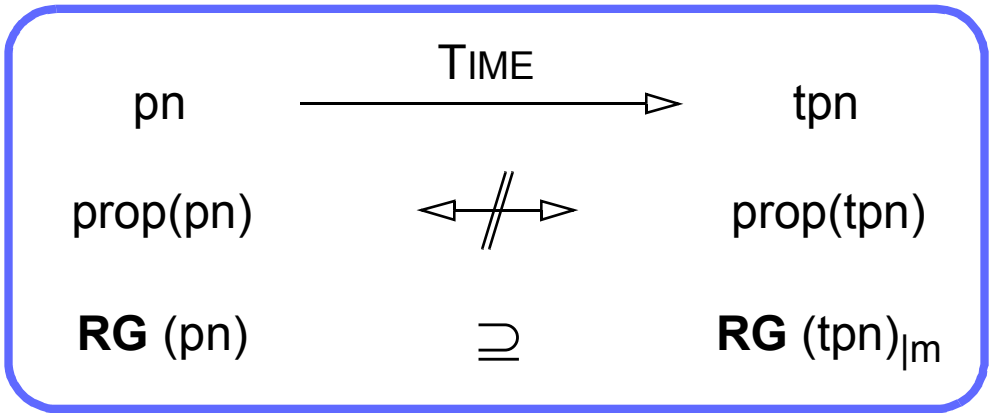
False: t1, t2, t4
True: t1, t2+t3, t5

- **time may restrict the behaviour**



KNOWN FACTS

- **time may restrict the behaviour**

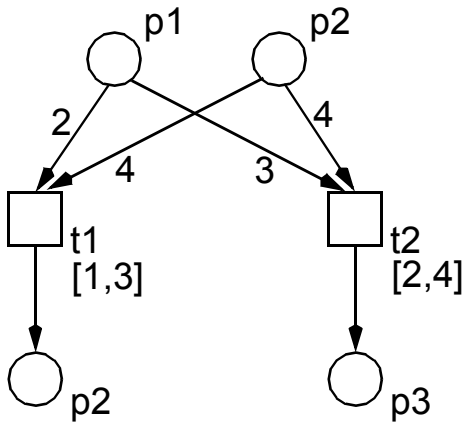


- **time may influence qualitative properties**

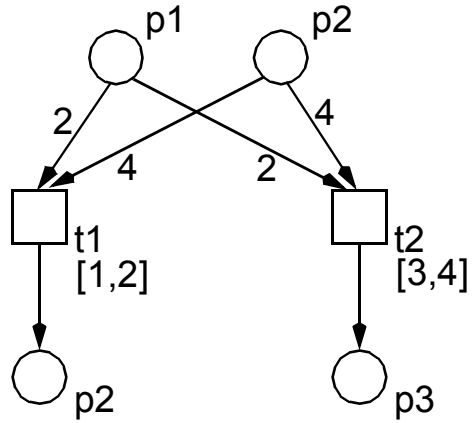
TIME-INSENSITIVE PROPERTIES	TIME-SENSITIVE PROPERTIES
BND (pn) -> BND (tpn)	not BND (pn) -> BND (tpn)
not DSt (pn) -> not DSt (tpn)	DSt (pn) -> not DSt (tpn)
DTr (pn) -> DTr (tpn)	not DTr (pn) -> DTr (tpn)
not REV(pn) -> not REV(tpn)	REV(pn) -> not REV(tpn)

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

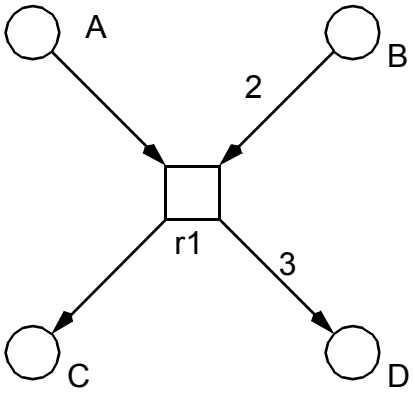
How to derive time parameters

T-INVARIANTS

- **T-invariants** **-> *multisets of transitions***
  - -> *integer solutions x of* $Cx = 0, x \neq 0, x \geq 0$ -> *Parikh vector*
- **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*

TRANSFORMATION, EX1

A + 2 B -> C + 3 D

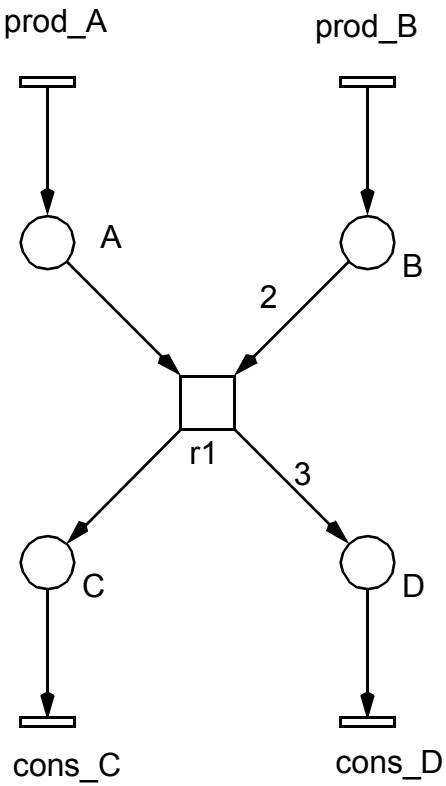


-> properties as time-free net

```
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



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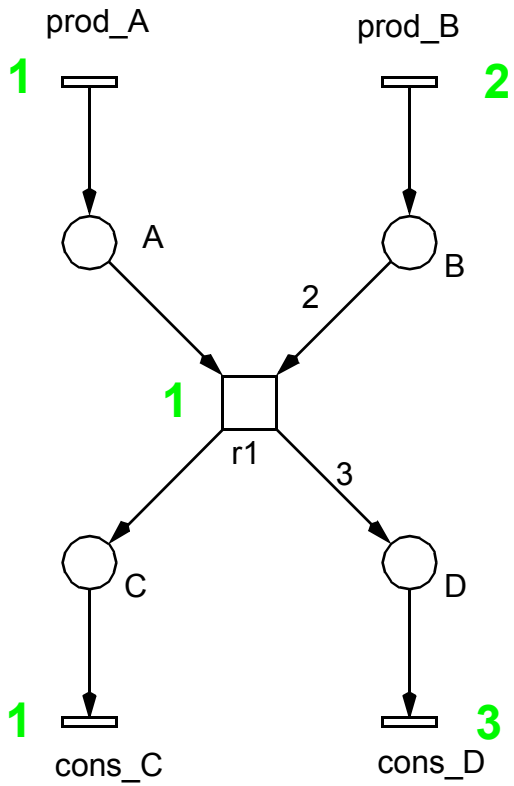
```
INA
ORD HOM NBM PUR CSV SCF CON SC  Ft0 tF0 Fp0 pF0 MG  SM  FC  EFC ES
 N   Y   N   Y   N   Y   Y   N   Y   Y   N   N   Y   N   Y   Y   Y
CPI CTI  B  SB  REV DSt BSt DTr DCF  L   LV L&S
 N   Y   N   N   Y   N   ?   N   Y   Y   Y   N
```

TRANSFORMATION, EX1

A + 2 B -> C + 3 D



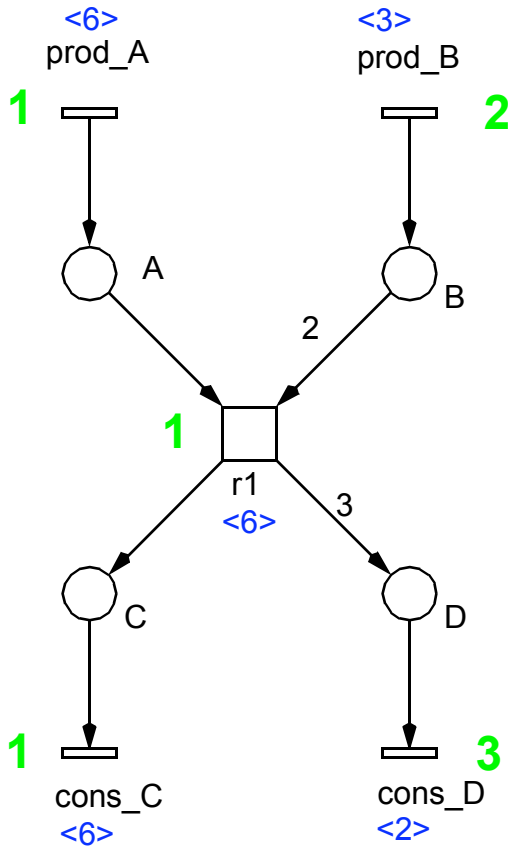
T-INVARIANT

-> 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



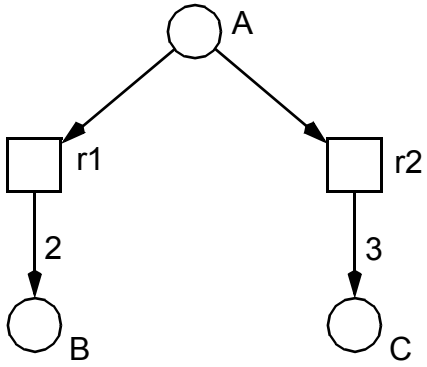
T-INVARIANT

-> 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

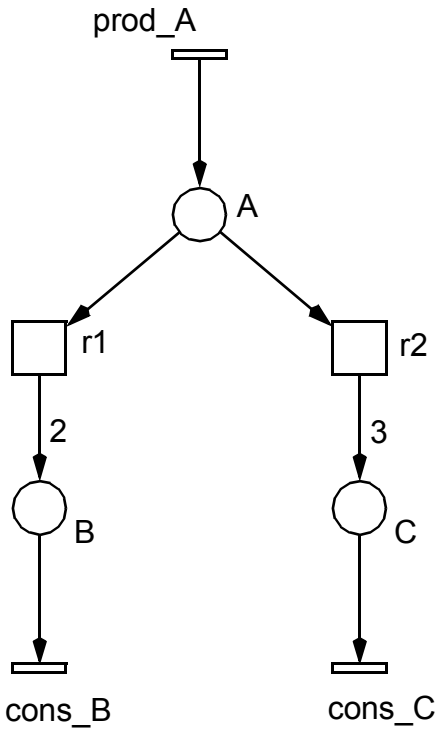


-> properties as time-free net

```
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

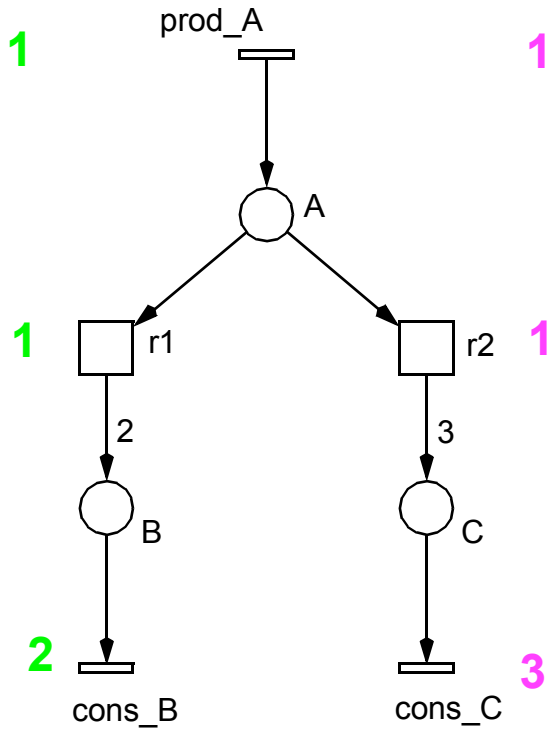


-> properties as time-free net

```
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

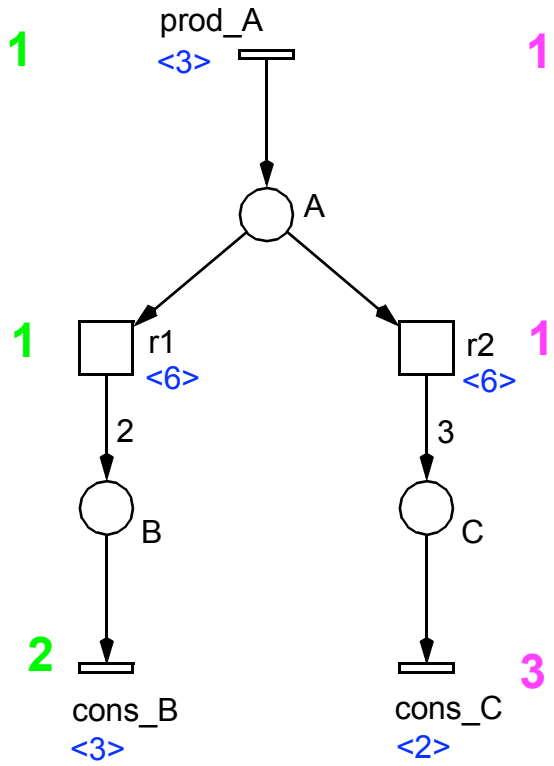
T-INVARIANT2

-> 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

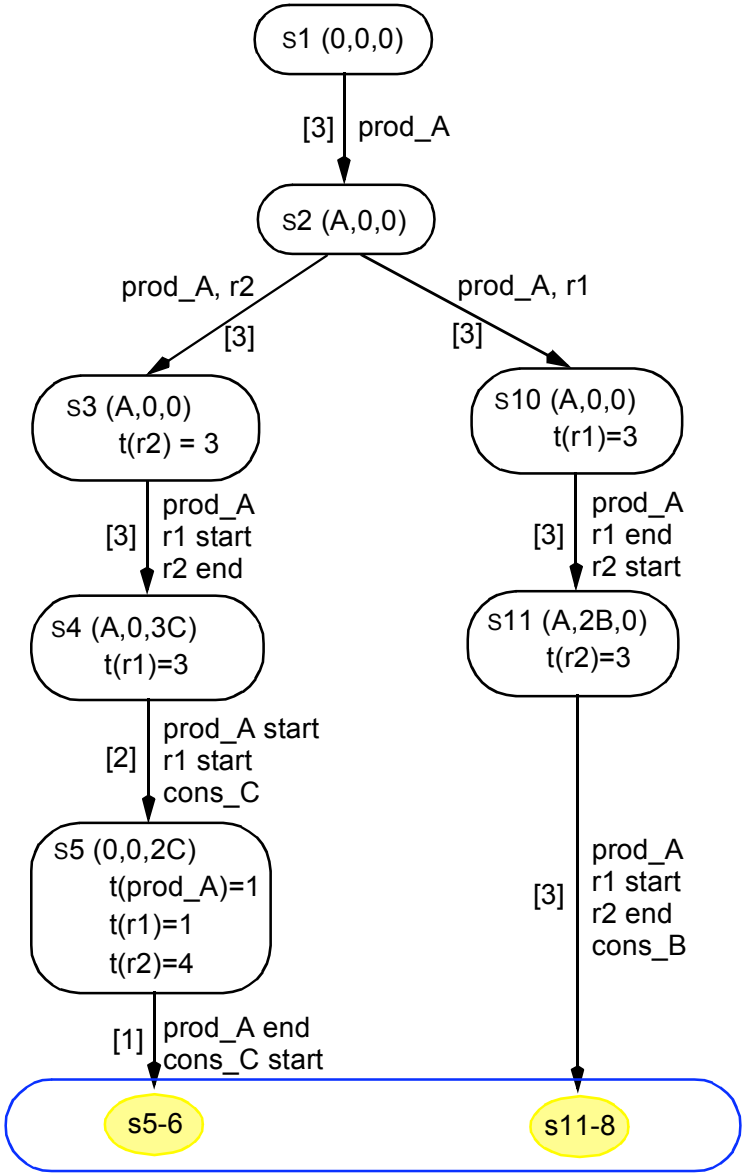
T-INVARIANT2

-> 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   Y   Y   Y   N
```

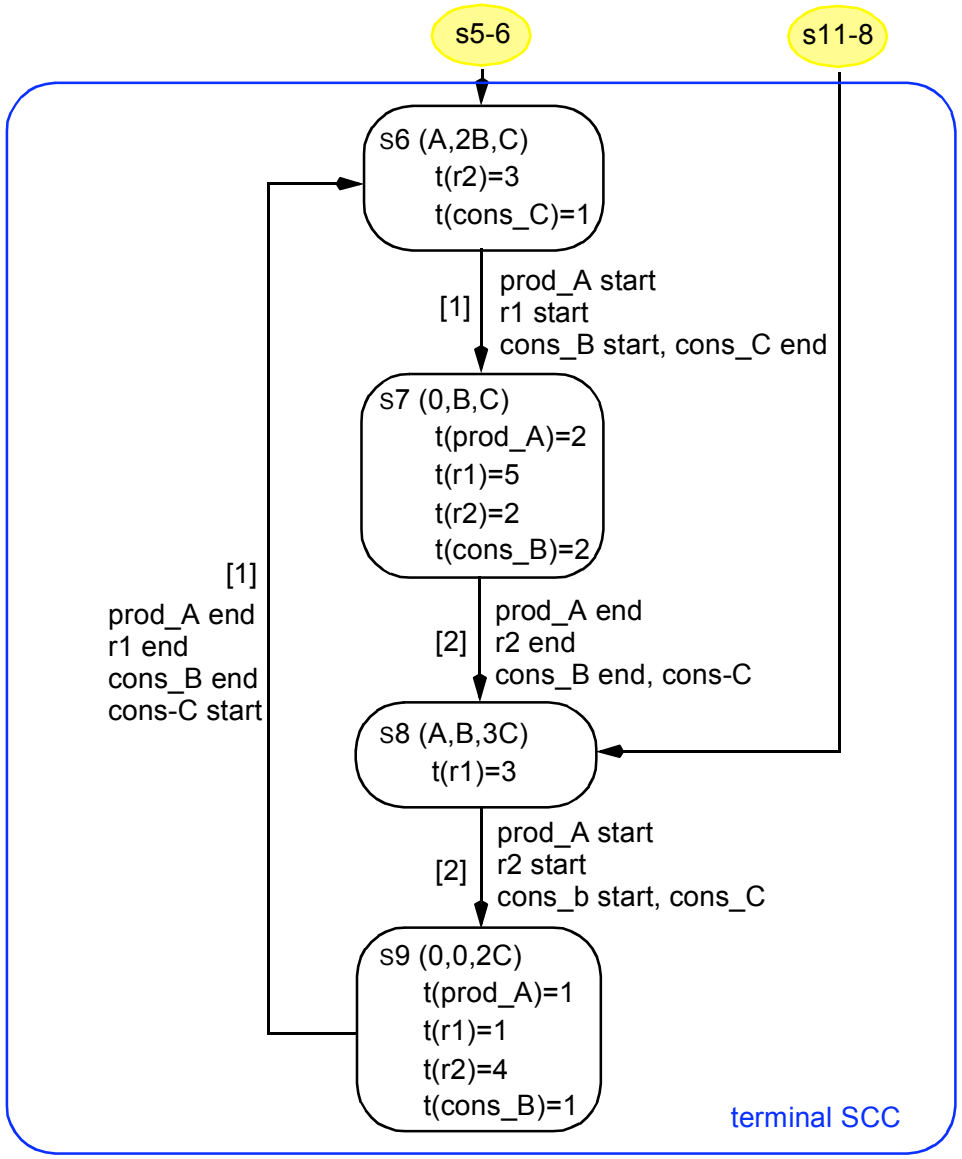
RG(Ex2), Part 1

- transient state



RG(Ex2), Part 2

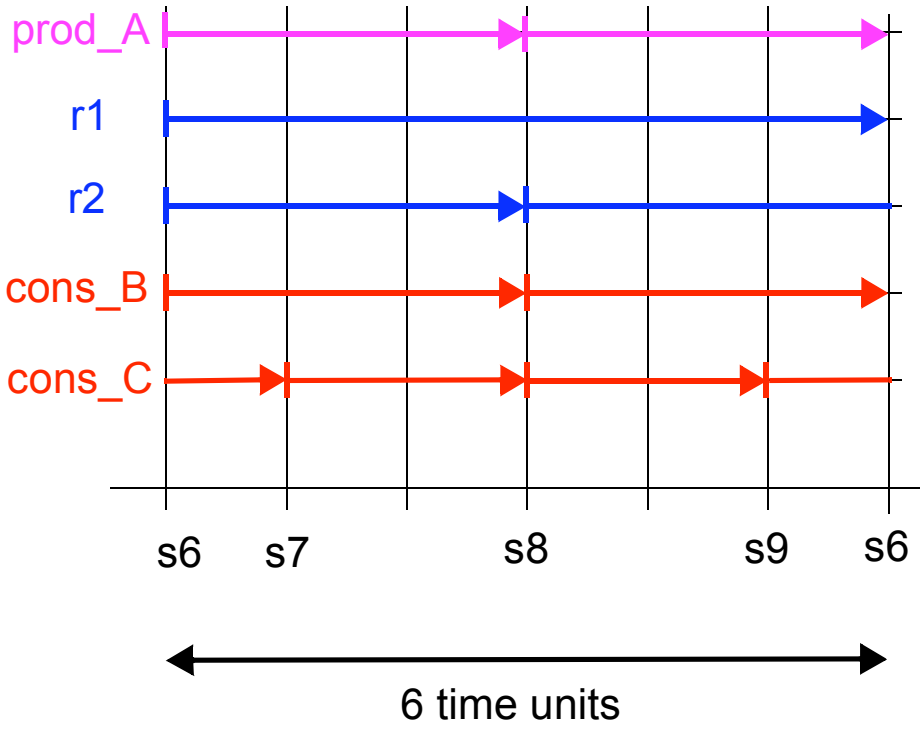
- steady state



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**

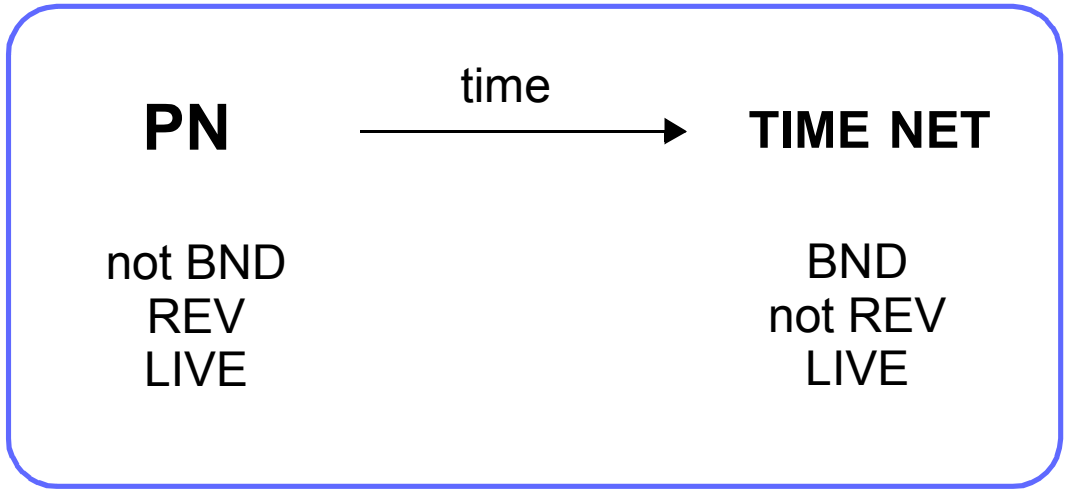


Ex1+ Ex2, Summary

- **CTI,**
  but not CPI

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

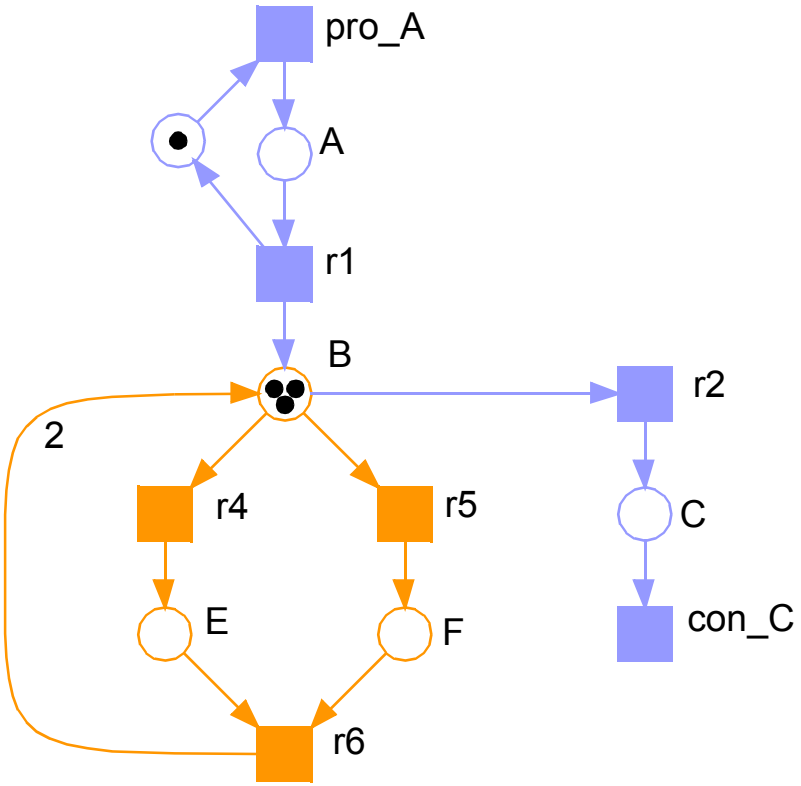
- **steady state behaviour**
  - -> *terminal scc*
  - -> *here, BND*
  - -> *here, DCF*

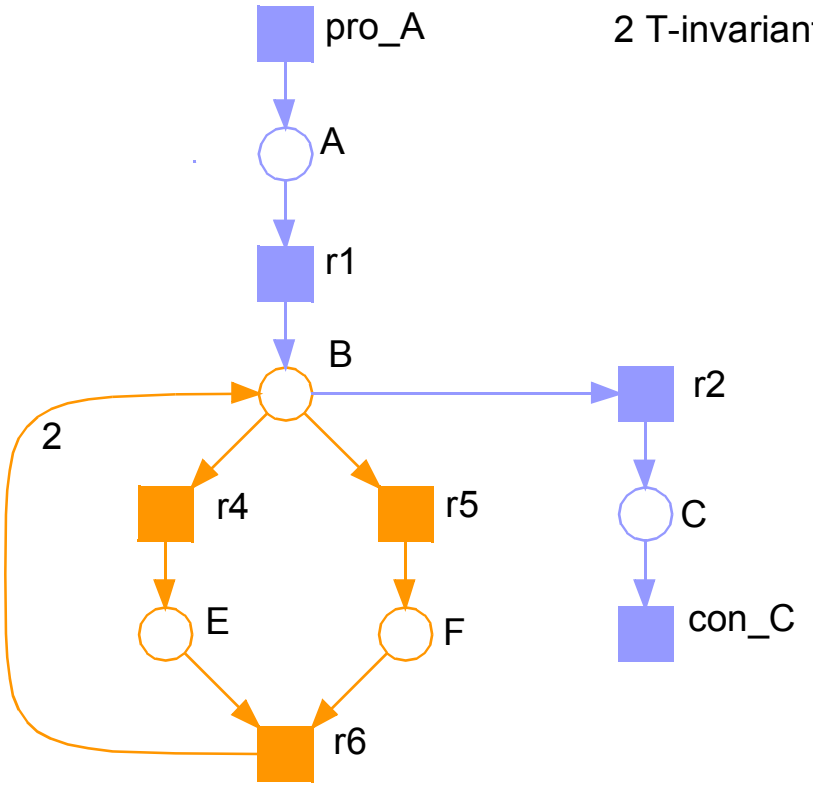


However,
this does not always work !

COUNTEREXAMPLE 1

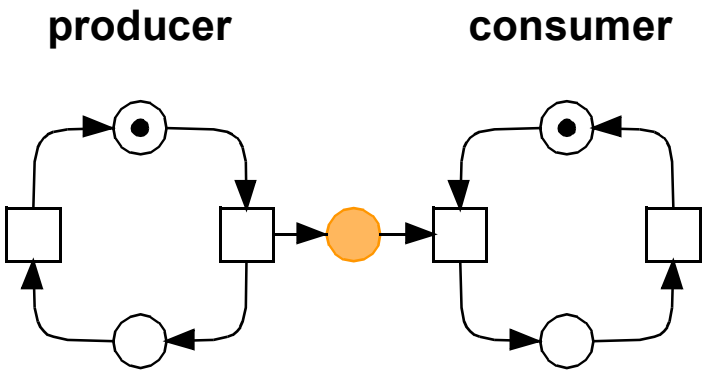
1-working time for all transitions;
FC, there are no deadlocks, traps, p-invariants, besides the pseudo-P-invariant (A , co_A);



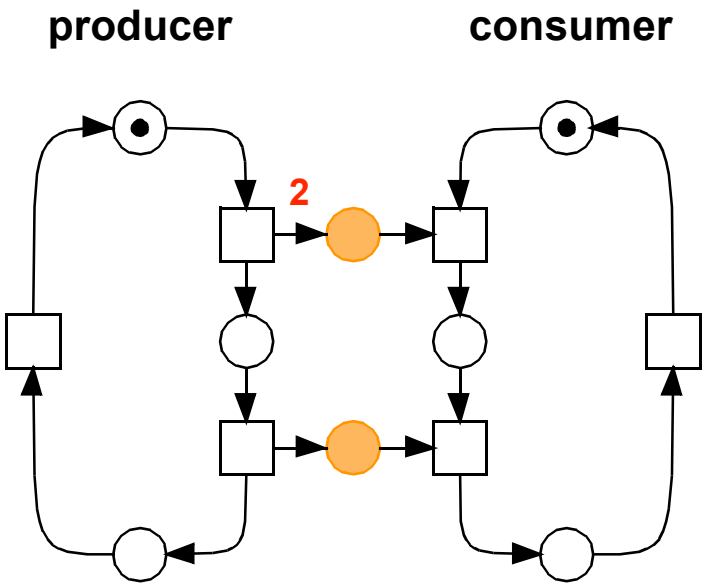


wBND & LIVE for the given initial marking

COUNTEREXAMPLE 2



weakly bounded



not weakly bounded

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

CHALLENGE 3 - TIME-DEPENDENT BOUNDEDNESS

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

CHALLENGE 3 - TIME-DEPENDENT BOUNDEDNESS

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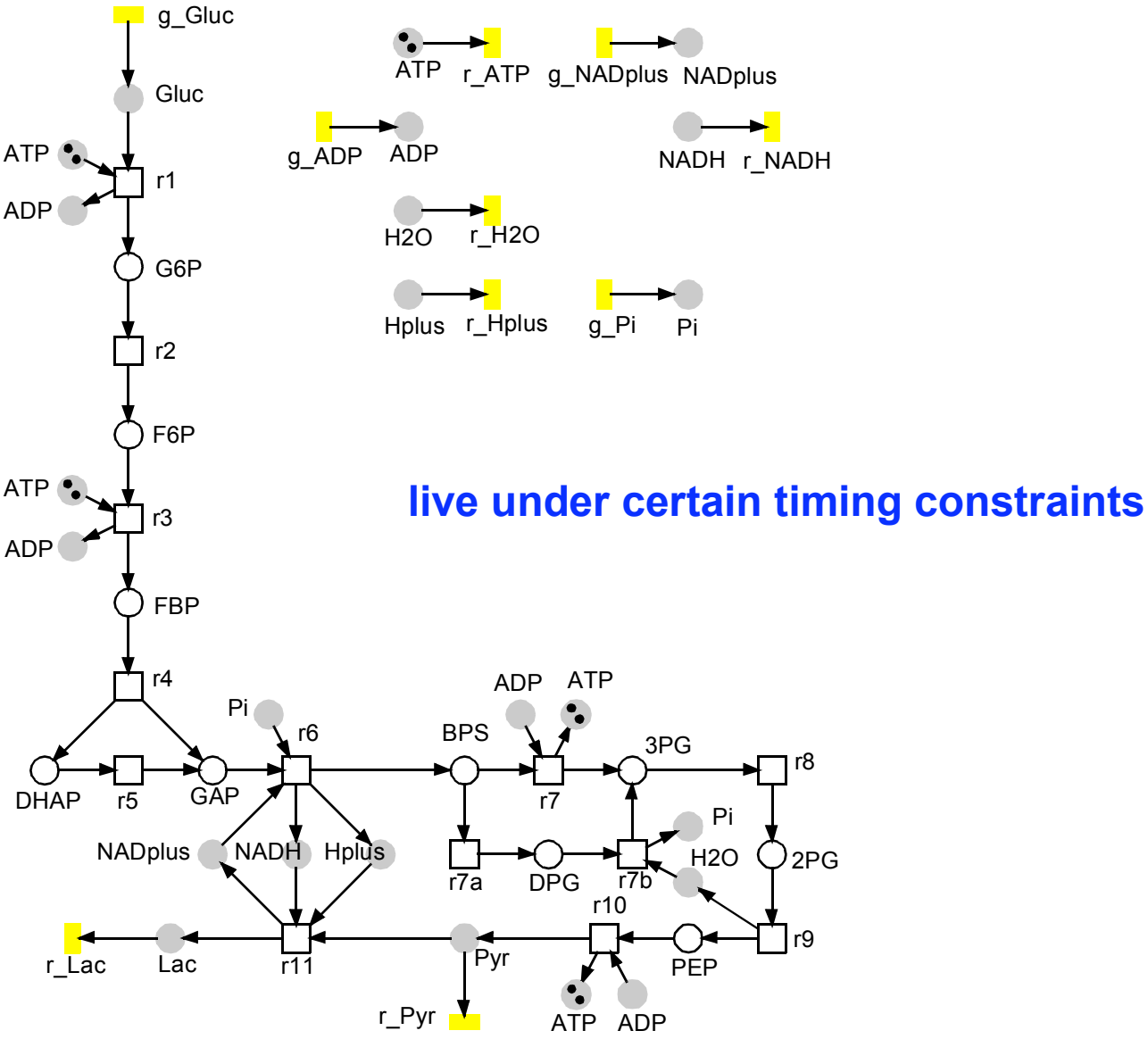
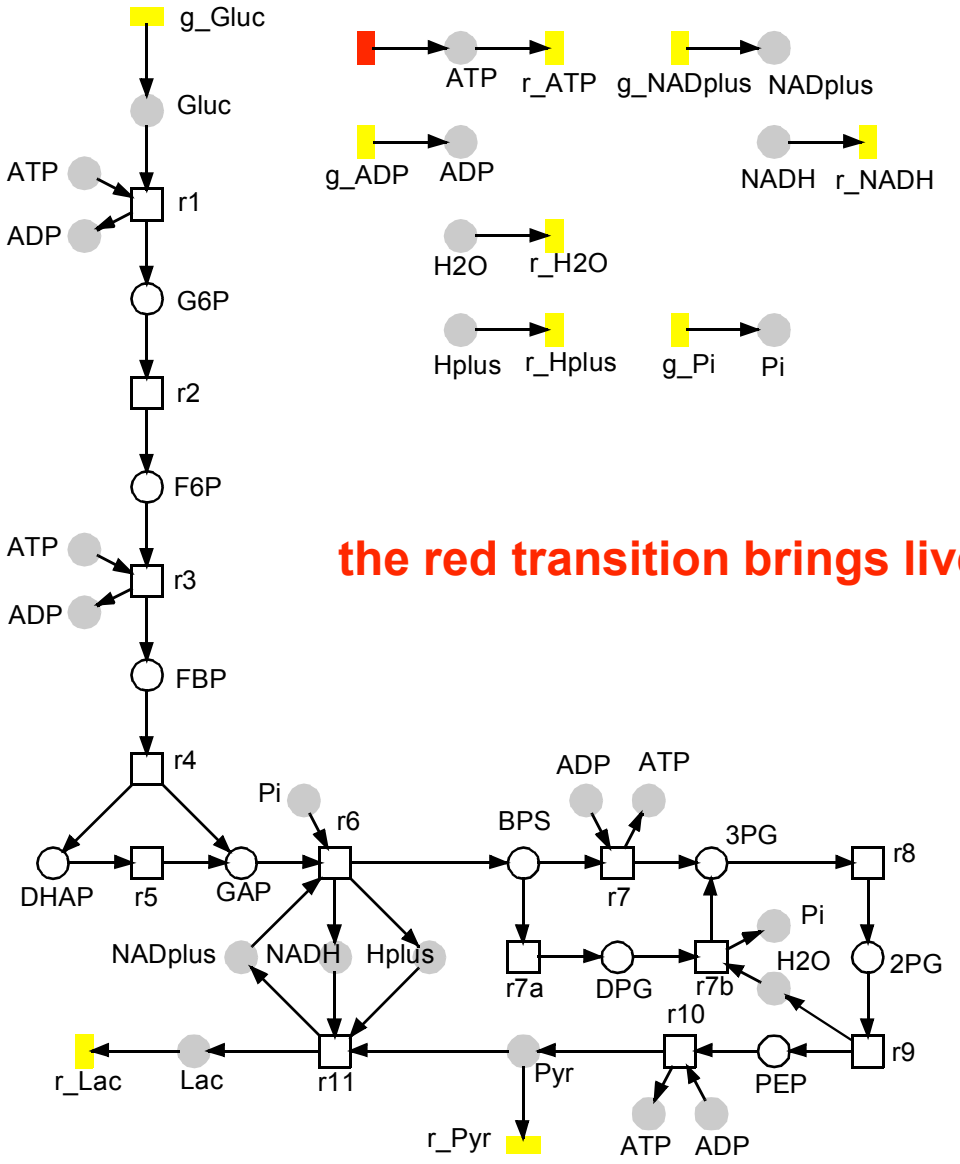
  - -> *unbounded*
  - -> *live (supposed to be)*
- **wanted: corresponding time-dependent Petri net**
  - -> *(weakly) bounded*
  - -> *(still) live*
- **questions**
  - -> *for which structures does it work / does it not work ?*
  - -> *are there sufficient / necessary conditions ?*
  - -> *which time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

CHALLENGE 4 - TIME-DEPENDENT LIVENESS



live under certain timing constraints

CHALLENGE 4 - TIME-DEPENDENT LIVENESS



the red transition brings liveness under any timing

CHALLENGE 4 - TIME-DEPENDENT LIVENESS

- **given: time-free Petri net**

  -> *non-live*

- **question**

  -> *under which conditions are there time restrictions, making this Petri net live ?*

CHALLENGES, SUMMARY

- **increasing level number = increasing accuracy**

  BUT, *monotonous liveness holds generally for substructures only !*

- **sharing structure = sharing properties**

  BUT, *that's not always the case ! to which extend ?*

  -> *when holds: continuous behaviour = averaged stochastic behaviour ?*

- **unbounded qualitative model + time = bounded model**

  BUT, *that's not always the case !*

  -> *(structural) criteria for time-dependent boundedness ?*

- **non-live qualitative model + time = live model**

  BUT, *how to do it in general the case ?*

  -> *(structural) criteria for time-dependent liveness ?*

FURTHER READING

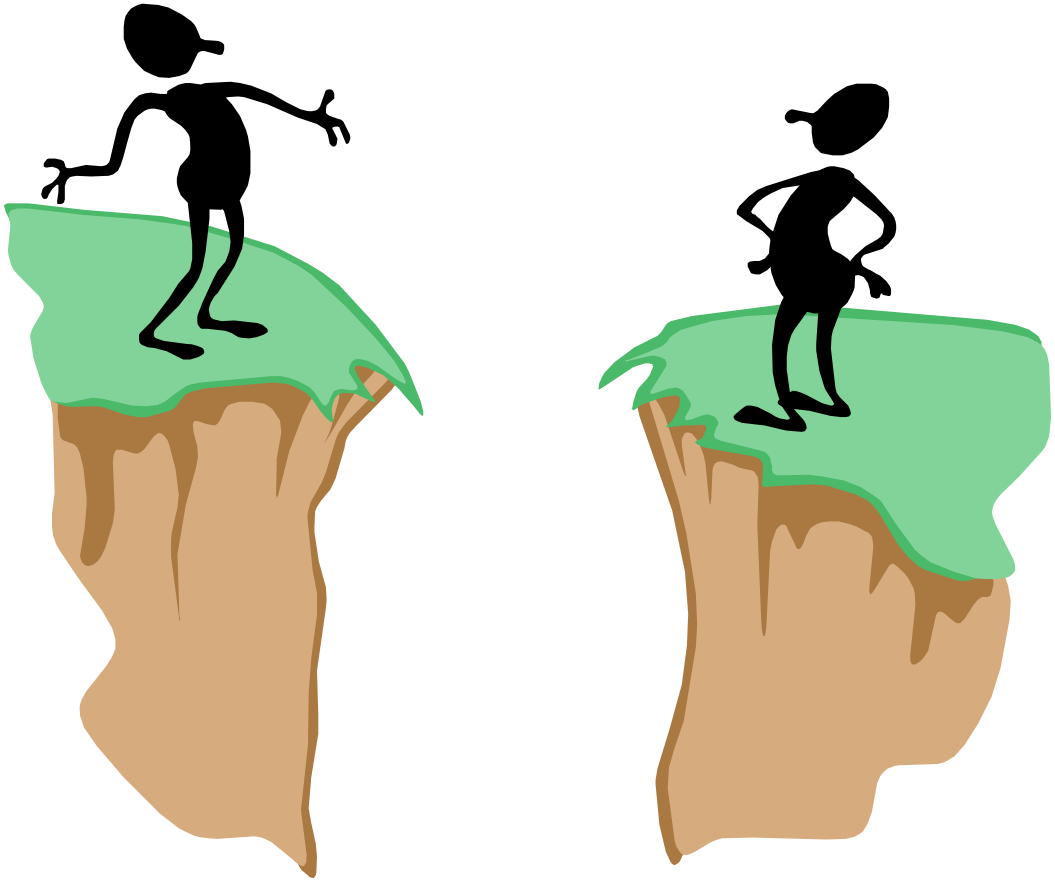
- D Gilbert, R Breitling, M Heiner, R Donaldson:
  An Introduction to BioModel Engineering, Illustrated for Signal Transduction Pathways;
  Proc. WMC 2008, Springer LNCS 5391, pp. 13-28, 2009.

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

- R Breitling, D Gilbert, M Heiner, R Orton:
  A structured approach for the engineering of biochemical network models, illustrated for signalling pathways;
  Briefings in Bioinformatics, September 2008; 9: 404 - 421.

- **Your paper to one or the other of the challenges ?**

THANKS !



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