

MODEL CHECKING OF BIOCHEMICAL NETWORKS USING PETRI NETS

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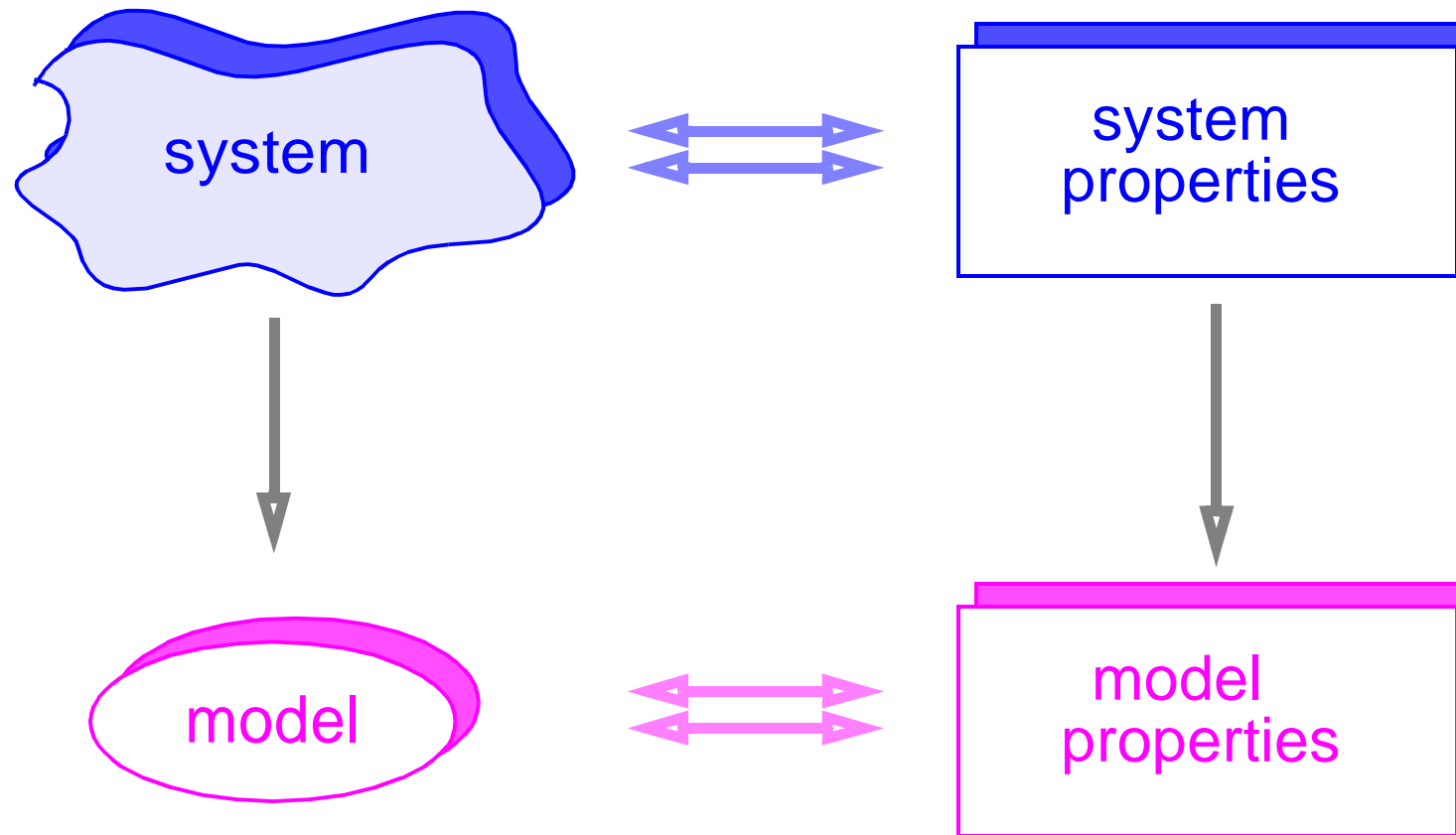
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Cottbus**

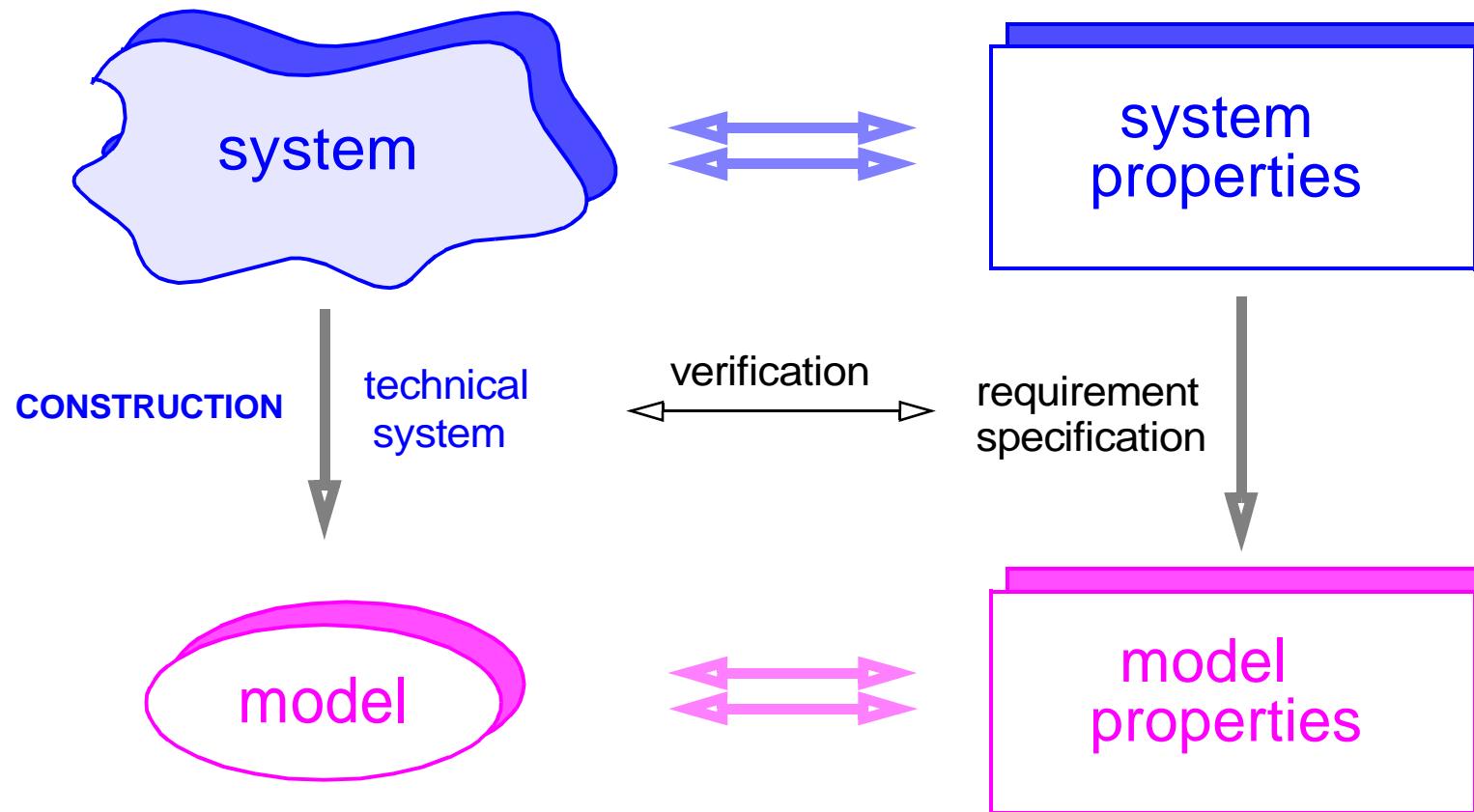
Dep. of CS

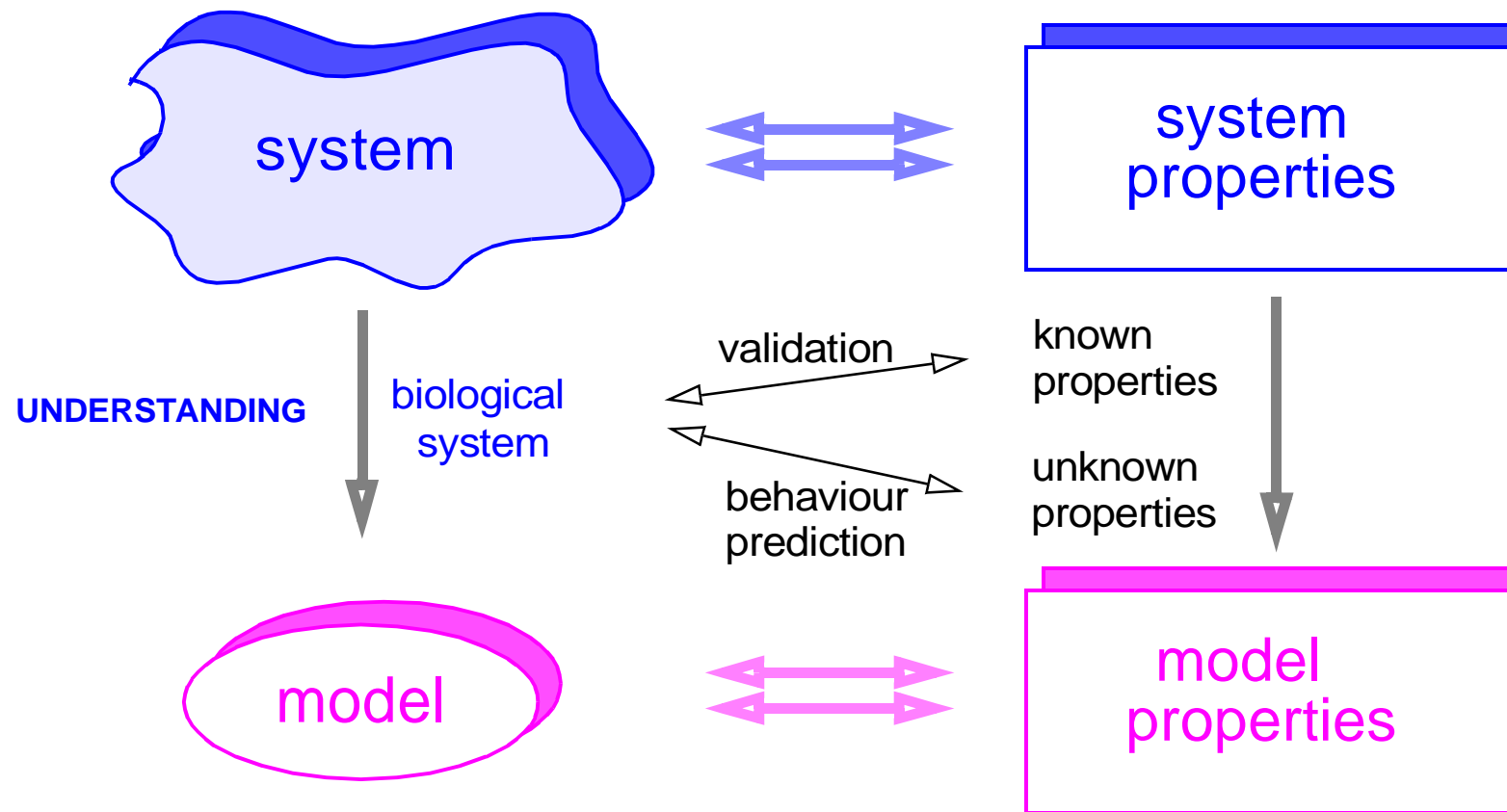
Ina Koch

**Technical University of Applied Sciences
Berlin**

Dep. of Bioinformatics







semantics / time	interleaving	partial order
linear (LTL)	<p style="text-align: center;">traces (no conflict, no concurrency)</p> <p style="text-align: center;">Manna & Pnueli, Kröger, jsp 2001</p> <p style="text-align: center;">DSSZ/LTL</p>	<p style="text-align: center;">runs (no conflict, but concurrency)</p> <p style="text-align: center;">Reisig</p> <p style="text-align: center;">tools: ?</p>
branching (CTL)	<p style="text-align: center;">reachability graph (conflict & concurrency not distinguishable)</p> <p style="text-align: center;">Emmerson, Clarke</p> <p style="text-align: center;">PROD/MARIA, INA, DSSZ/CTL</p>	<p style="text-align: center;">prefix (conflicts & concurrency)</p> <p style="text-align: center;">McMillan, Esparza, pd 2001</p> <p style="text-align: center;">PEP</p>

technique	CTL	LTL
reachability graph	INA	PROD, MARIA
stubborn set reduced reachability graph	LoLA	PROD (LTL\X)
symmetrically reduced reachability graph	LoLA (symmetric formulas)	?
BDD, NDD, ..., xDD	DSSZ-CTL, SMART, DSSZ-CTL2	DSSZ-LTL
Kronecker algebra	[Kemper]	?
prefix	PEP (CTL ₀)	QQ (LTL\X)
process automata	[pd]	?

CTL OPERATORS, INTERLEAVING SEMANTICS

	next f	finally f	globally f	f1 until f2
on all branches	<p>AX</p>	<p>AF</p>	<p>AG</p>	<p>AU</p>
on some branch	<p>EX</p>	<p>EF</p>	<p>EG</p>	<p>EU</p>

- ❑ ... is a technique for verifying **finite-state** concurrent systems

*Clarke, E. M. Jr.; Grumberg, O.; Peled, D. A.:
Model Checking;
MIT Press 2001*

- ❑ **finite state systems = steady state systems = bounded pn**

- ❑ **model checking of unbounded systems**

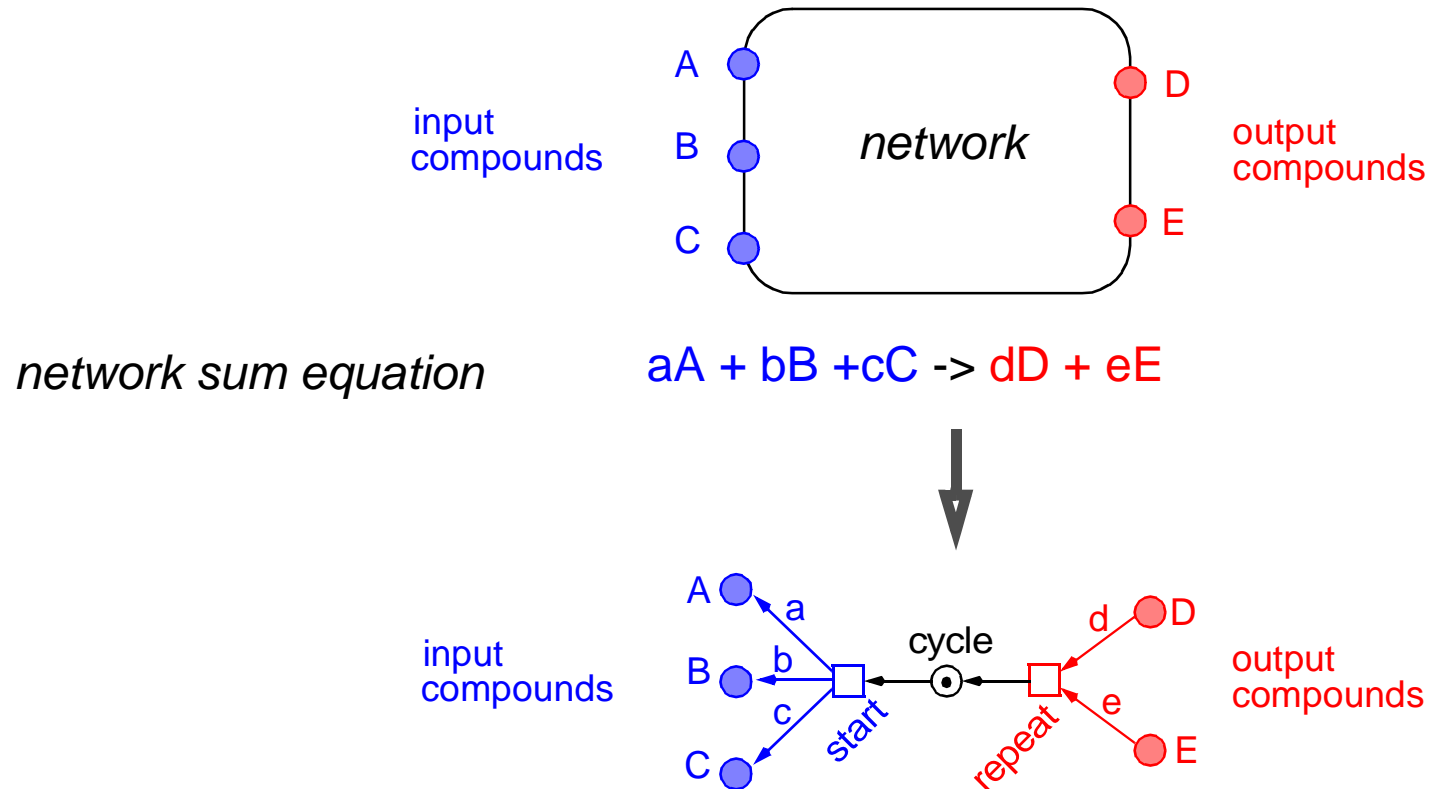
-> CTL *undecidable*

-> LTL *decidable, but no tools (not yet ?)*

-> *unboundedness + inhibitors = undecidability*

- ❑ **how to get bounded bionetworks ?**

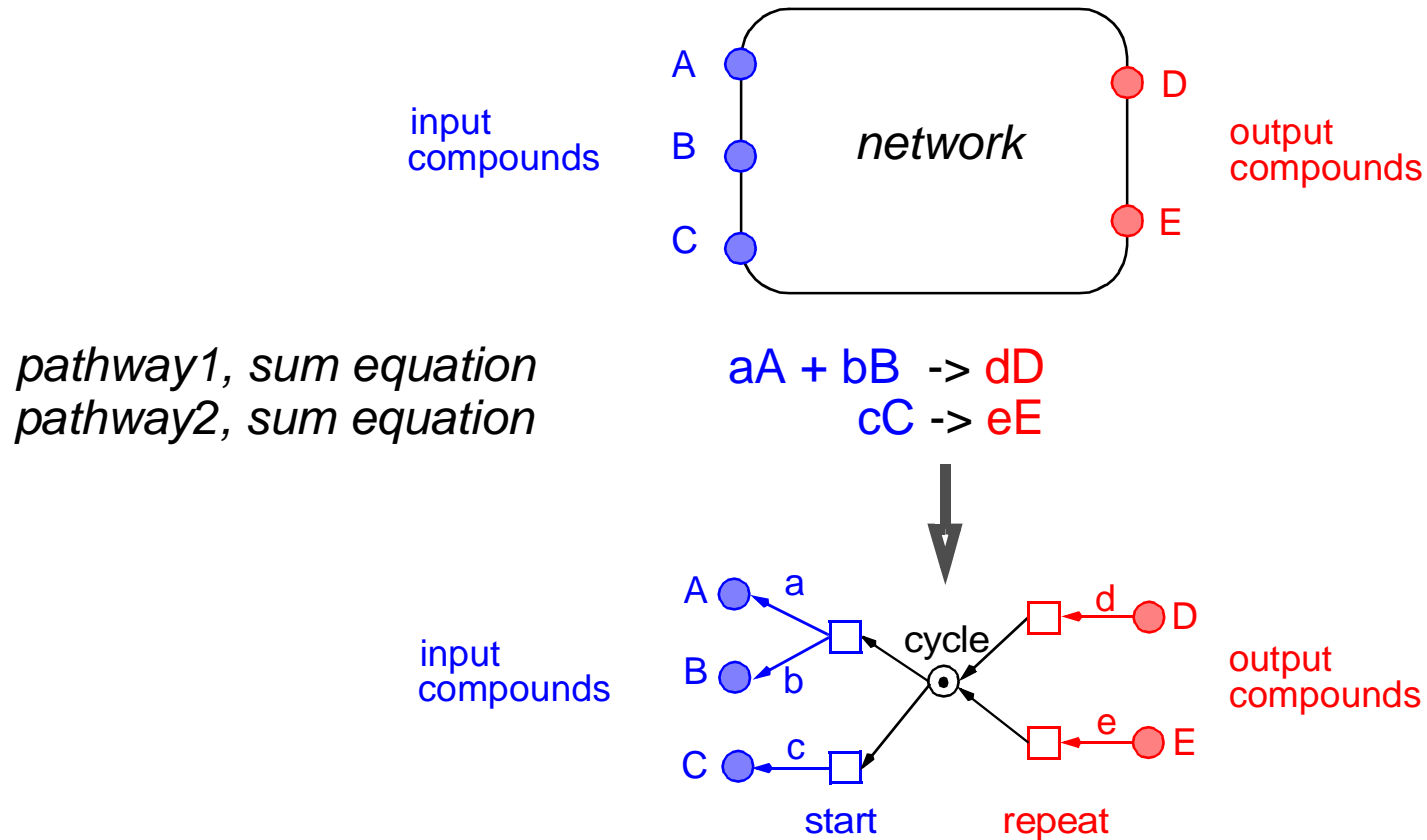
□ additional model component



□ precondition

-> *equal sum equation for all pathways*

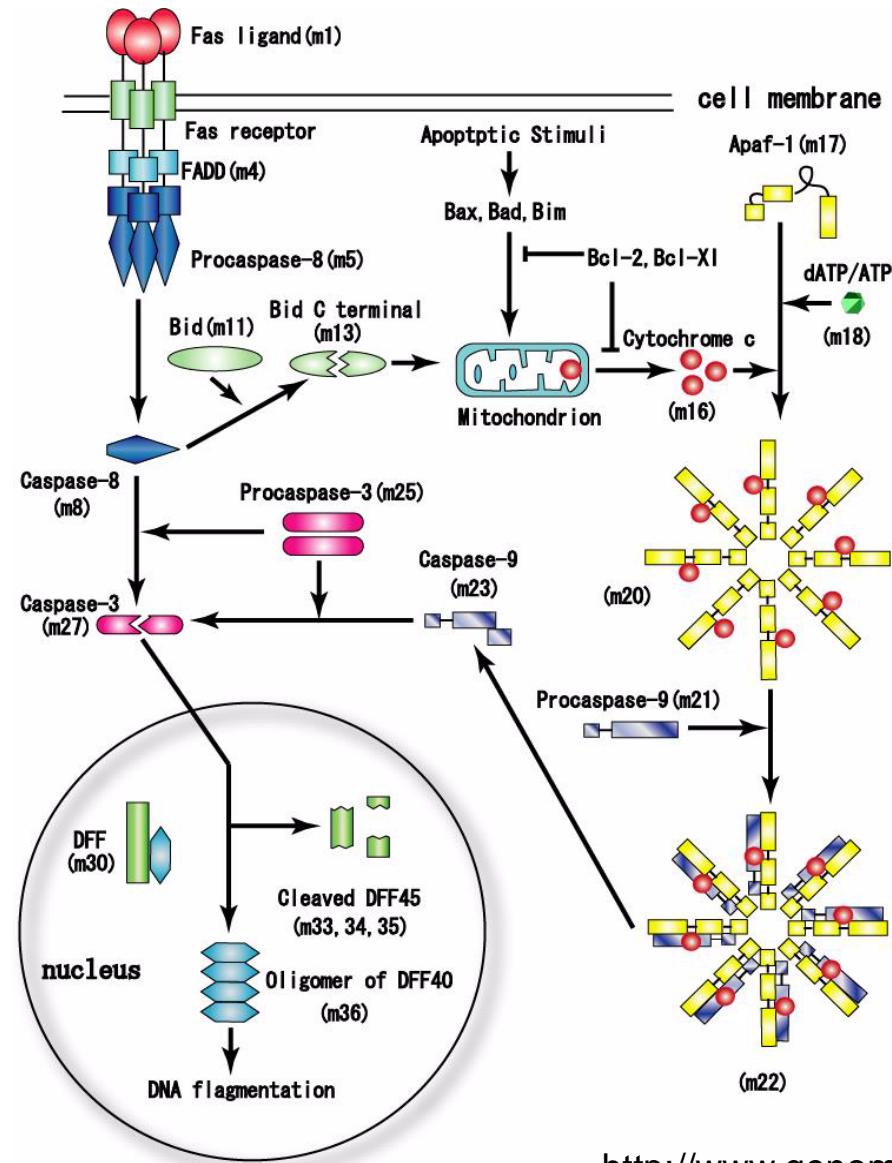
□ additional model component, refinement



□ precondition

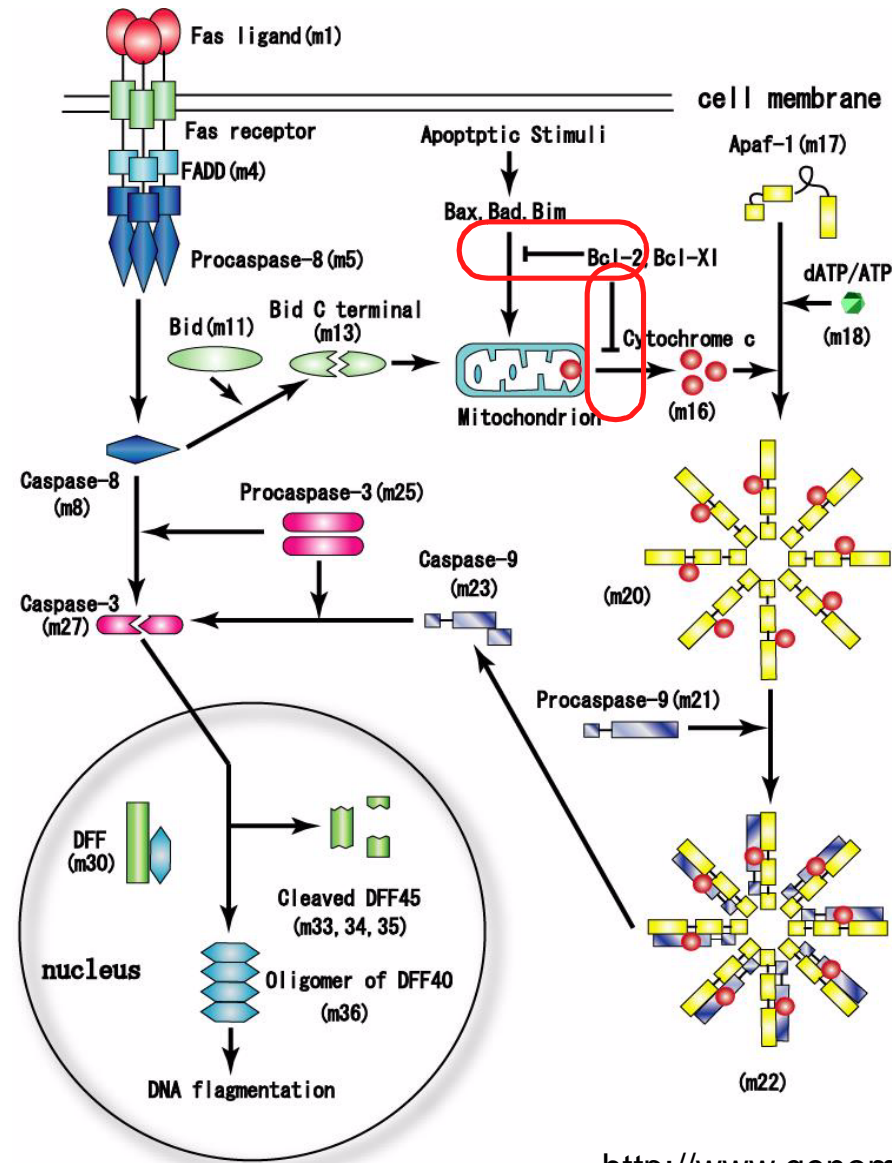
-> *controlled conflicts between pathways with unequal sum equations*

- example - apoptosis
-> *Matsuno et al.*
- signal-transduction pathway



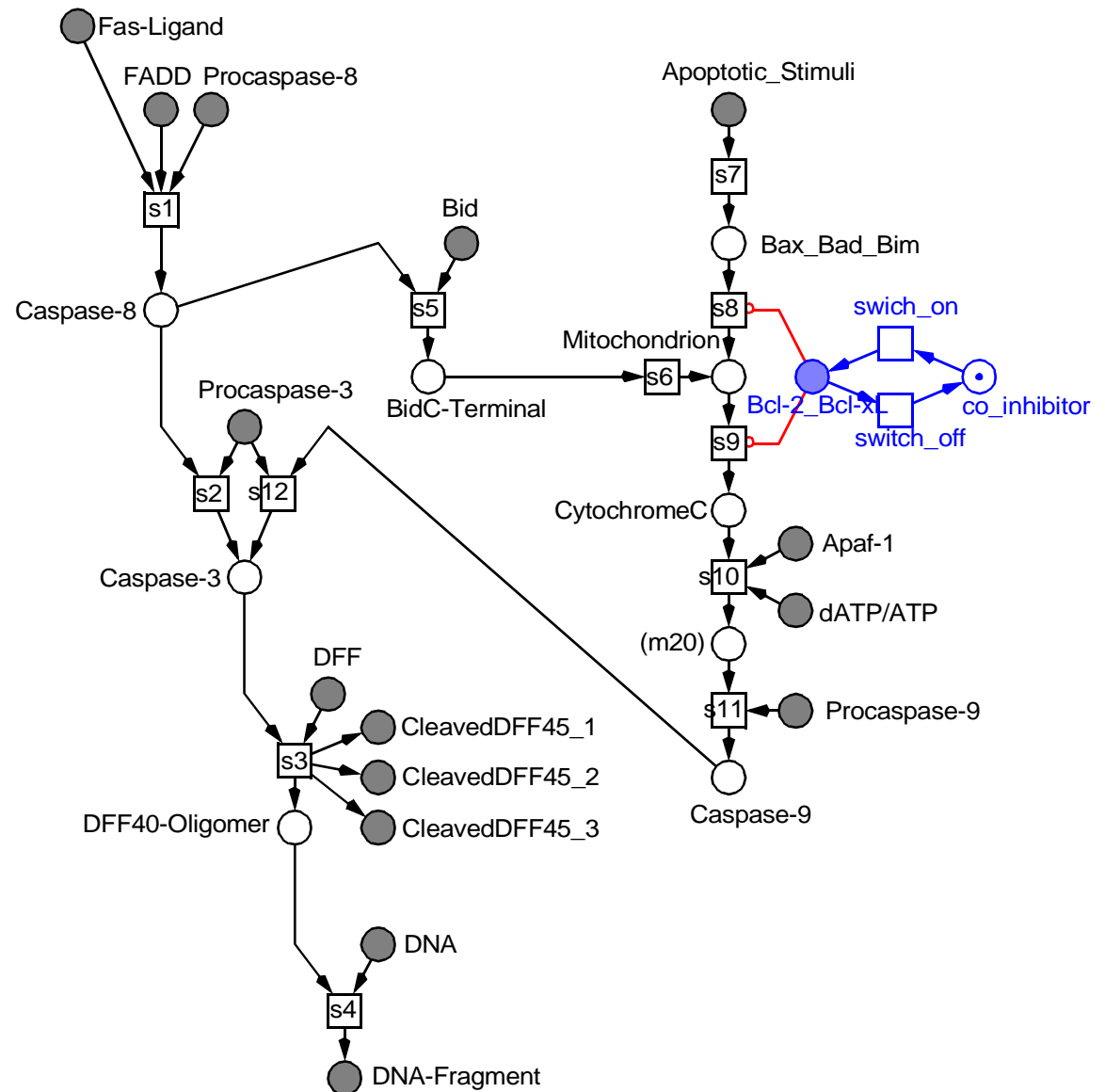
<http://www.genomicObject.net>

- example - apoptosis
-> *Matsuno et al.*
- signal-transduction pathway
- inhibitor arcs

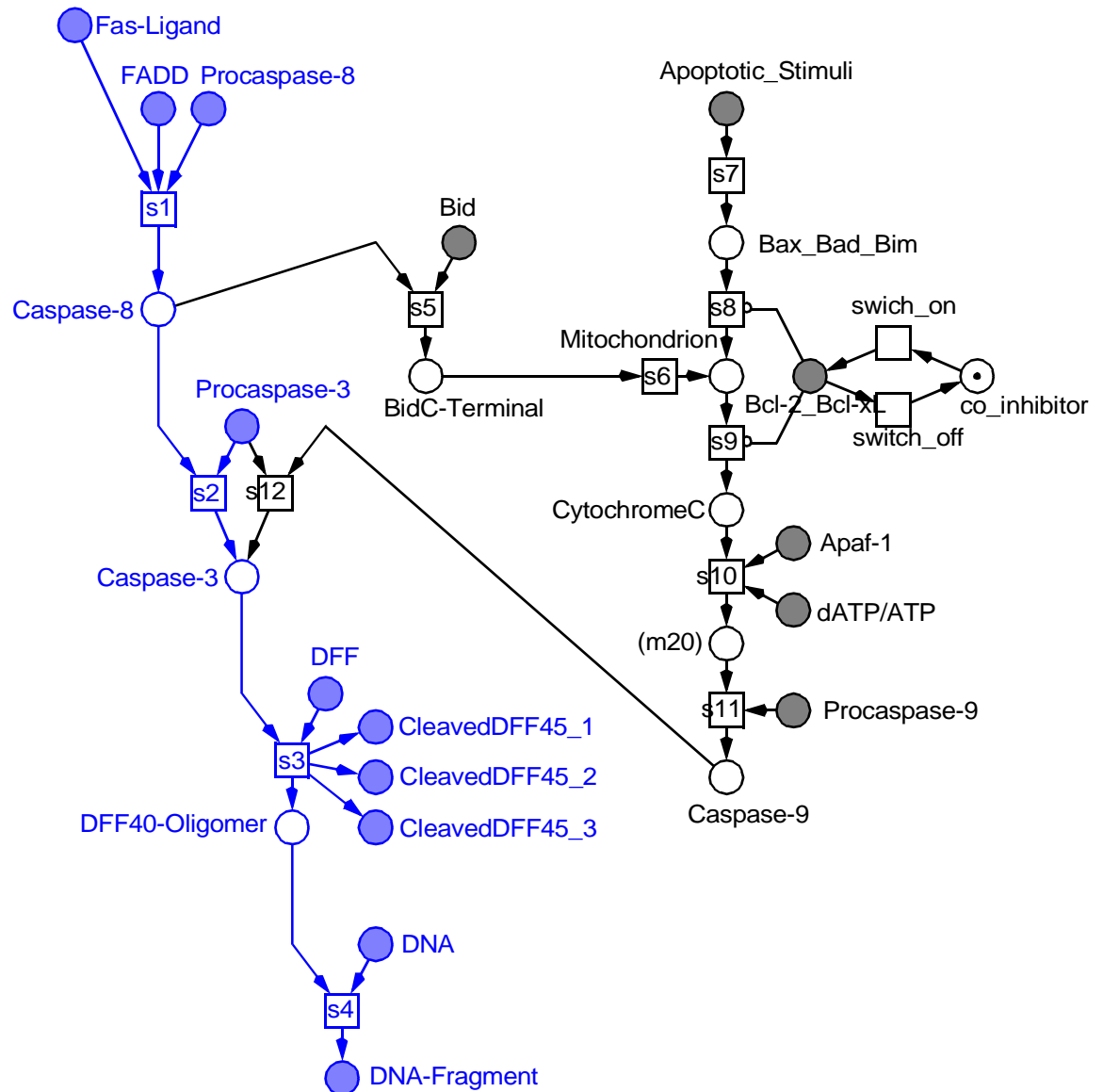


<http://www.genomicObject.net>

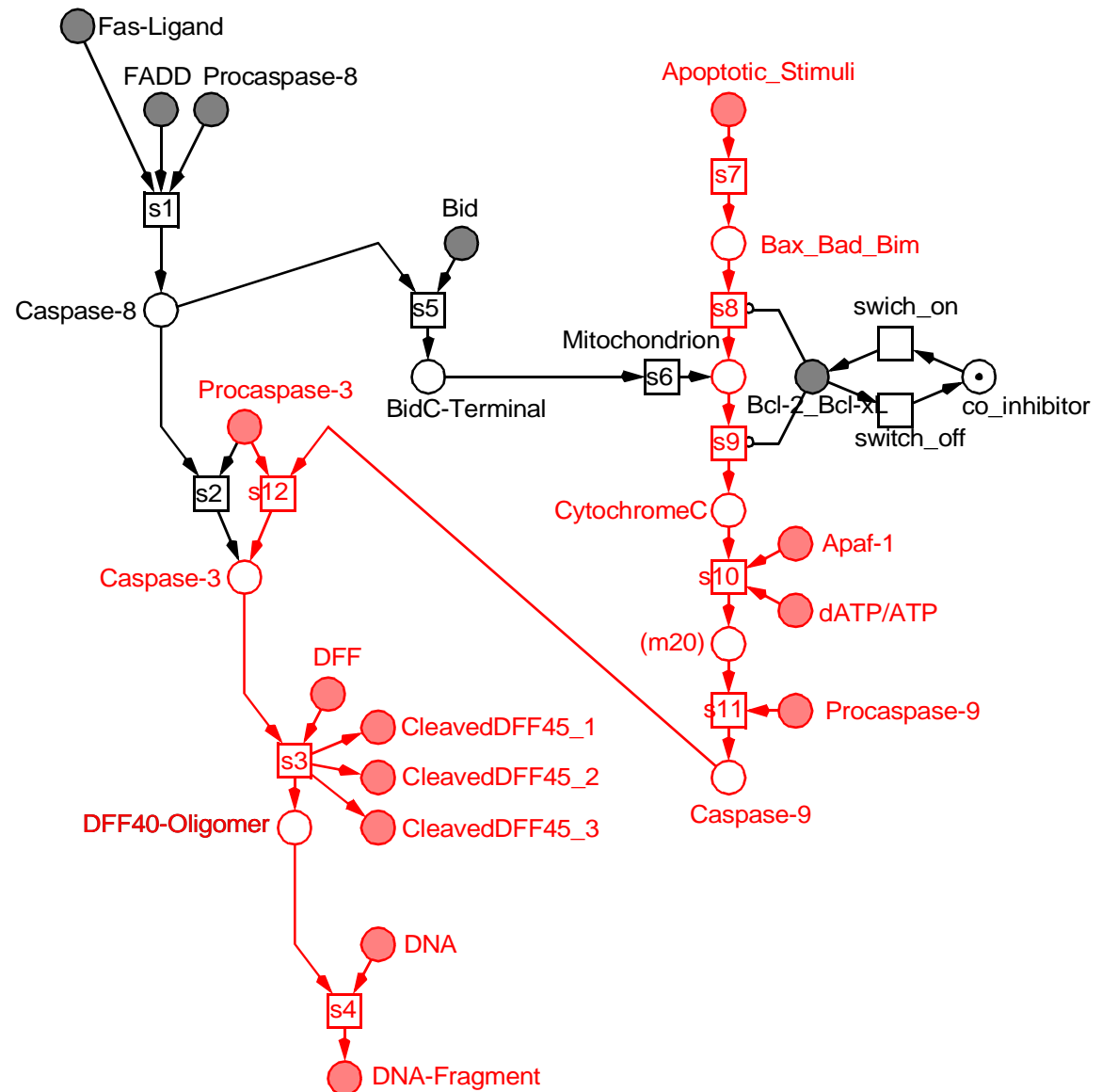
- example - apoptosis
- network model
- inhibitor arcs
- three pathways = min. T-invariants



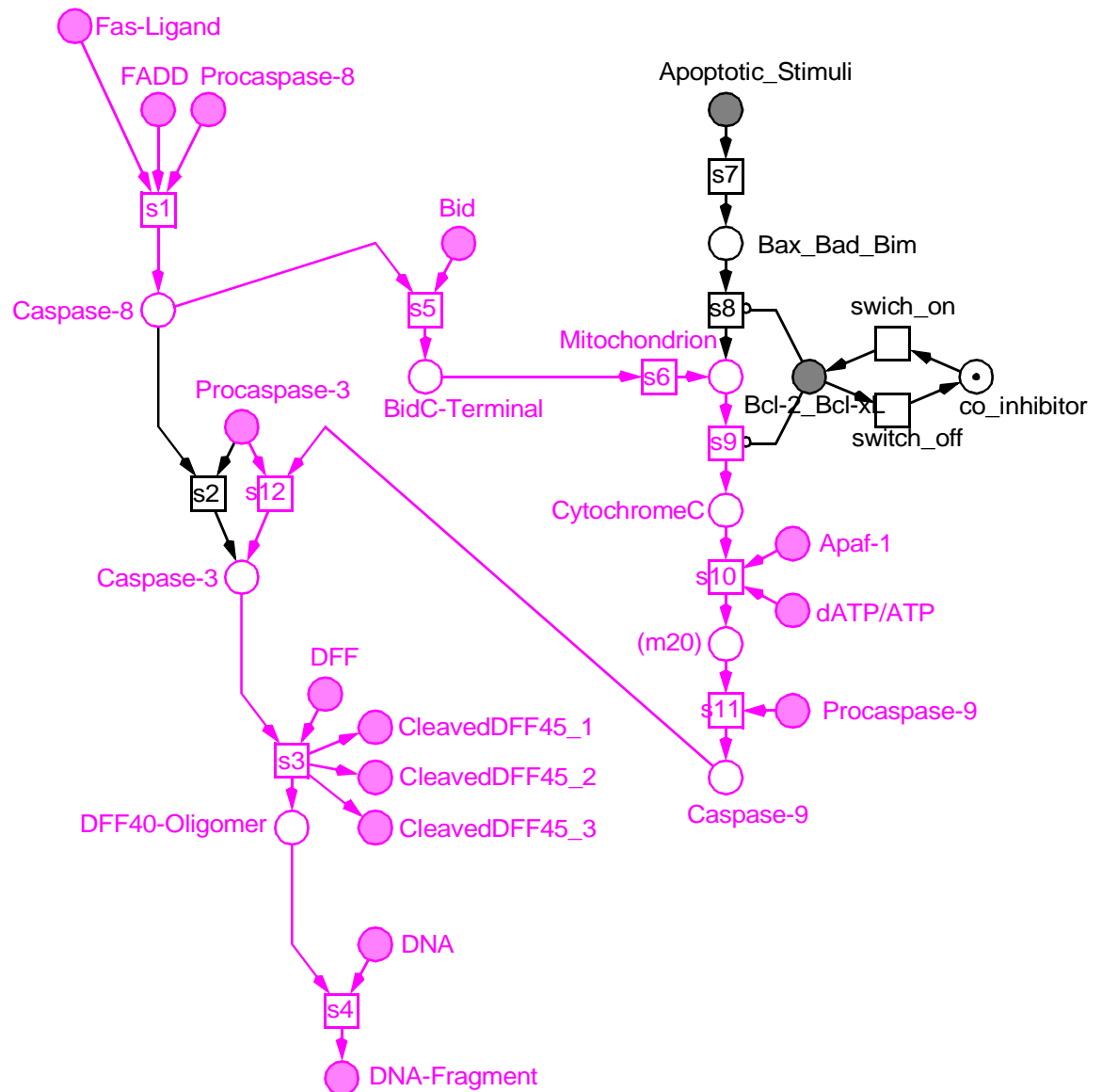
- example - apoptosis
- network model
- environment, style 1
 - > three pathways
 - = min. T-invariants
- T-invariant 1
 - > Fas-induced
 - > 'death-receptor' pathway



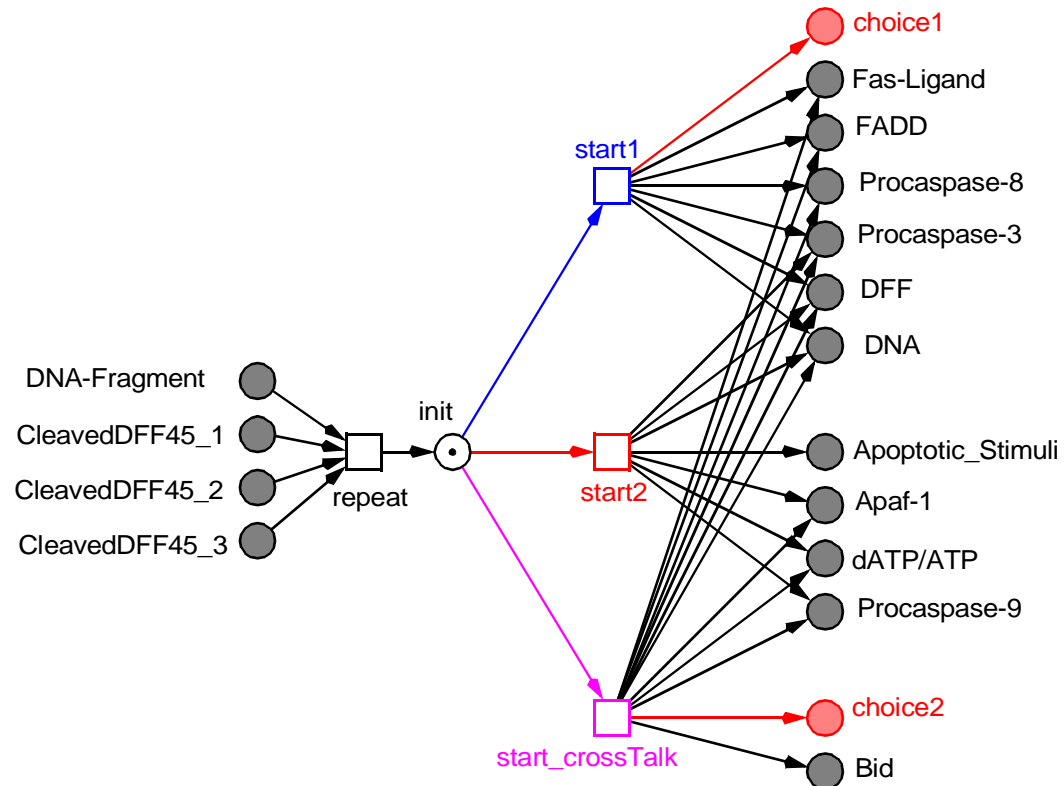
- example - apoptosis
- network model
- environment, style 1
 - > three pathways
 - = min. T-invariants
- T-invariant 2
 - > apoptotic-stimuli-induced
 - > 'mitochondrial' pathway



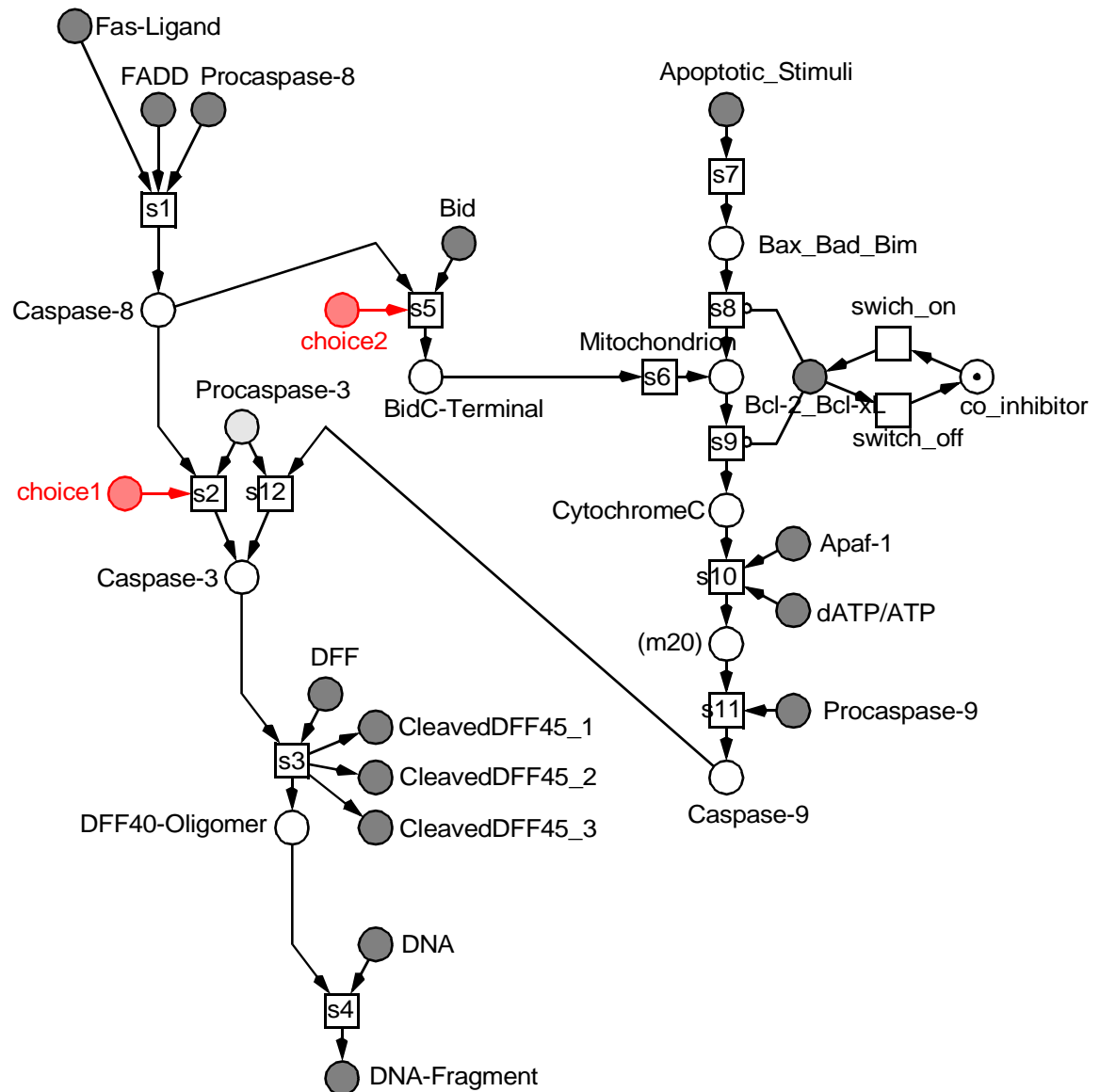
- example - apoptosis
- network model
- environment, style 1
 - > three pathways
 - = min. T-invariants
- T-invariant 3
 - > 'cross-talk by Bid' pathway



- example - apoptosis
- environment model
- pathway 1 / 3
 - > overlap at the beginning
 - > then branch
 - > controlled by places *choice1 / choice2*
- all pathways share the same ending
 - > only one repeat transition



- example - apoptosis
- network model, adapted
- system model
 - > network model
 - > environment model
- system model
 - > 1-bounded
 - > live
- ready for model checking



□ property 1

if inhibitor substance *Bcl_2_Bcl_xL* is present,
then the progress of the cross-talk pathway is stopped at *Mitochondrion*

$AG (Bcl_2_Bcl_xL * Mitochondrion \rightarrow AX (Mitochondrion));$

□ property 2

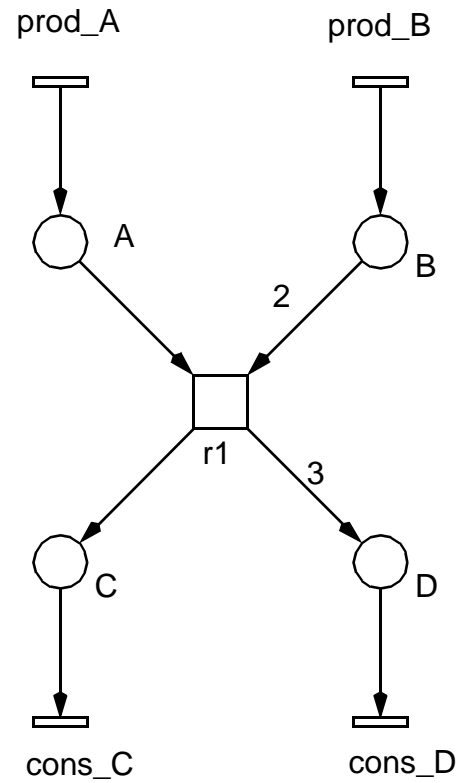
if inhibitor substance *Bcl_2_Bcl_xL* is present,
then the progress of the cross-talk pathway is stopped at *Mitochondrion*
until the inhibitor substance disappears

$AG (Bcl_2_Bcl_xL * Mitochondrion \rightarrow A (Mitochondrion \ U \ ! \ Bcl_2_Bcl_xL));$

□ property 3

if inhibitor substance *Bcl_2_Bcl_xL* is not present,
then the progress of the cross-talk pathway is not stopped at *Mitochondrion*

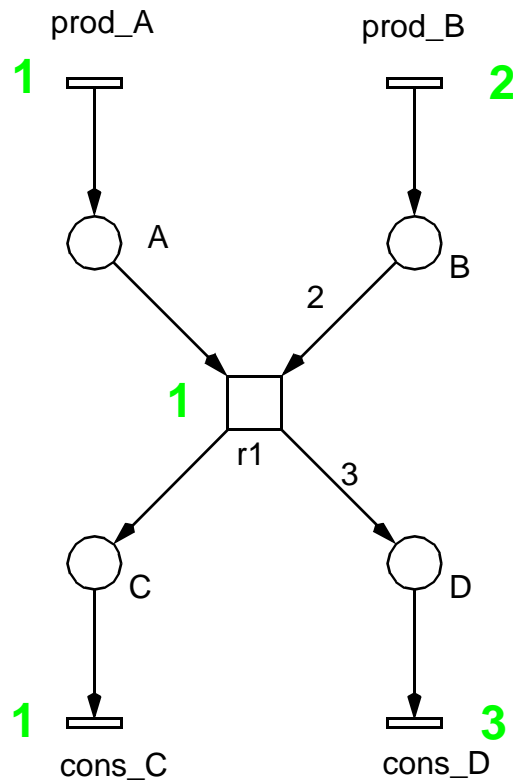
$AG (!Bcl_2_Bcl_xL * Mitochondrion \rightarrow EX (CytochromeC));$



-> 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					

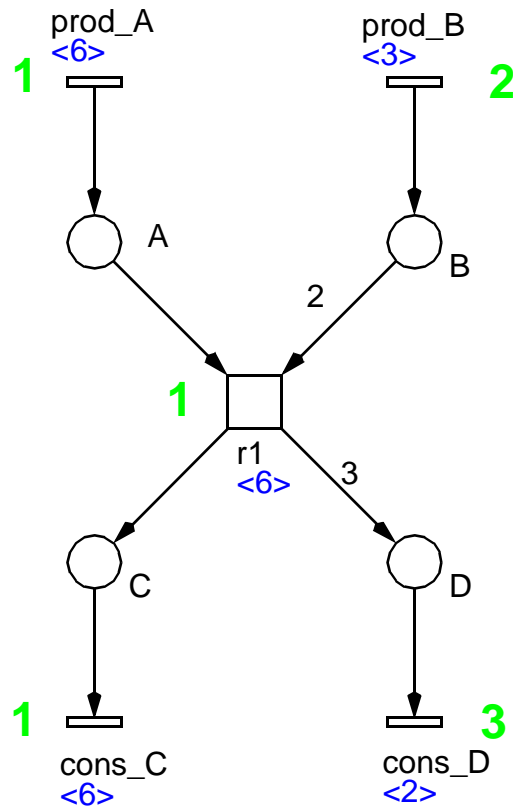


T-INVARIANTE

-> 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					



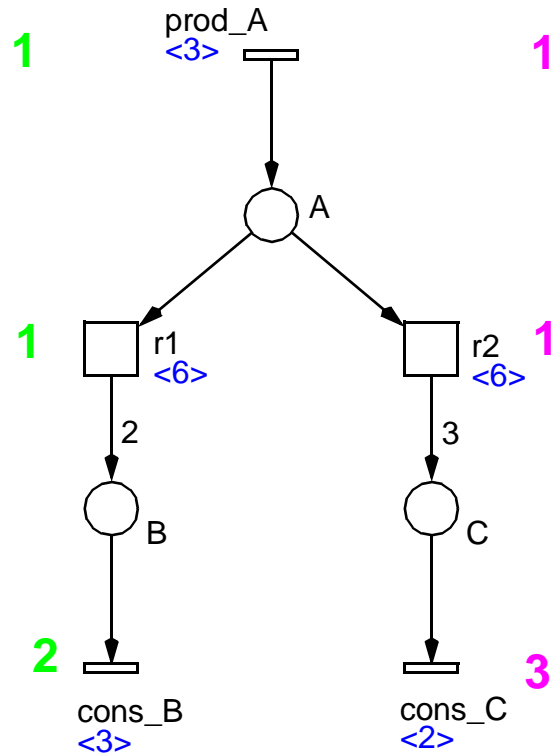
T-INVARIANTE

-> properties as duration 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					

size (RG (d-net)) = 8 nodes



T-INVARIANTE1
T-INVARIANTE2

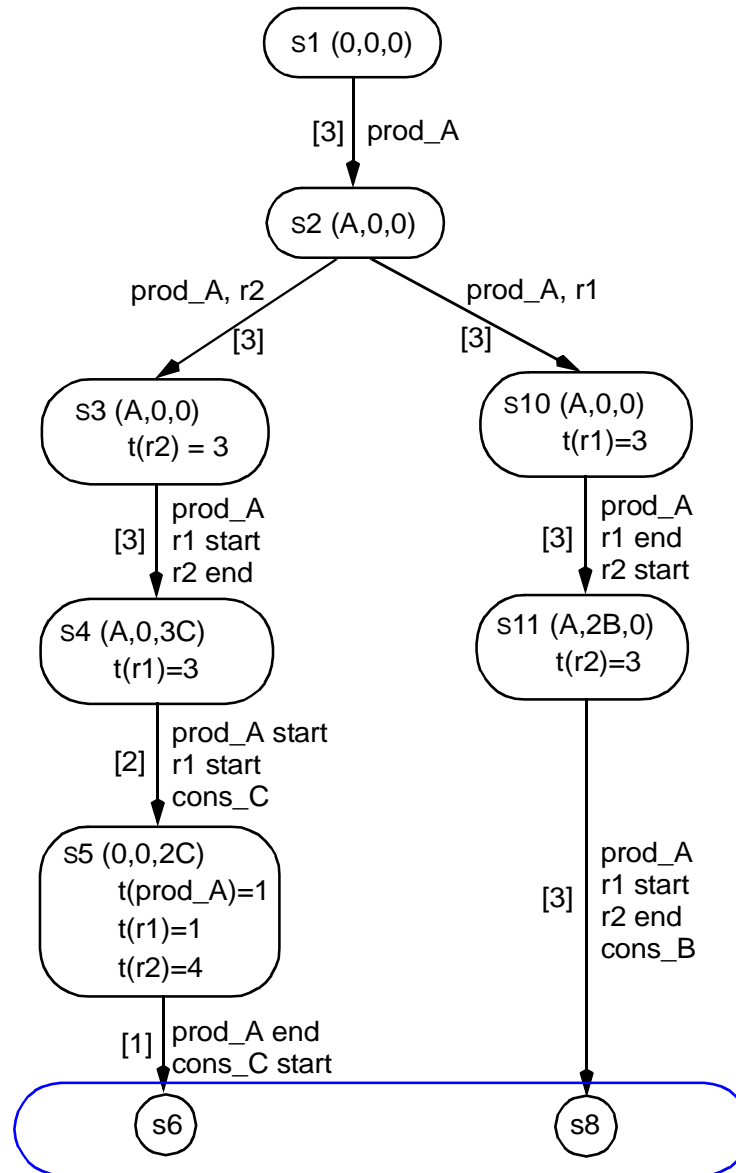
-> properties as duration net

INA

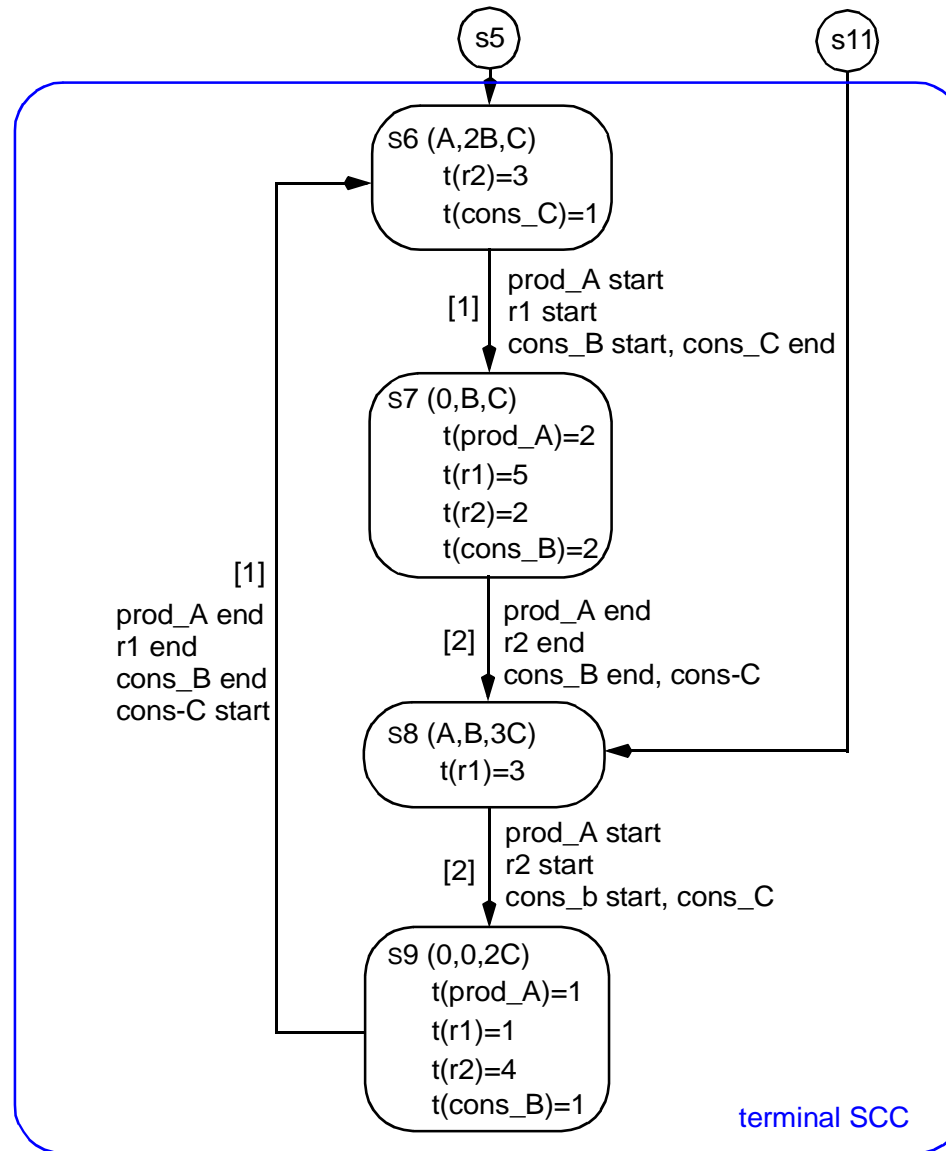
ORD	HOM	NBM	PUR	CSV	SCF	CON	SC	Ft0	tF0	Fp0	pF0	MG	SM	FC	EFC	ES
N	Y	N	Y	N	Y	Y	N	Y	Y	N	N	Y	N	Y	Y	Y
CPI	CTI	B	SB	REV	DSt	BSt	DTr	DCF	L	LV	L&S					
N	Y	Y	N	N	N	?	N	Y	Y	Y	N					

size (RG (d-net)) = 11 nodes

□ transient state



□ steady state



EX2, TERMINAL SCC

- contains all transitions

 - > *always running*

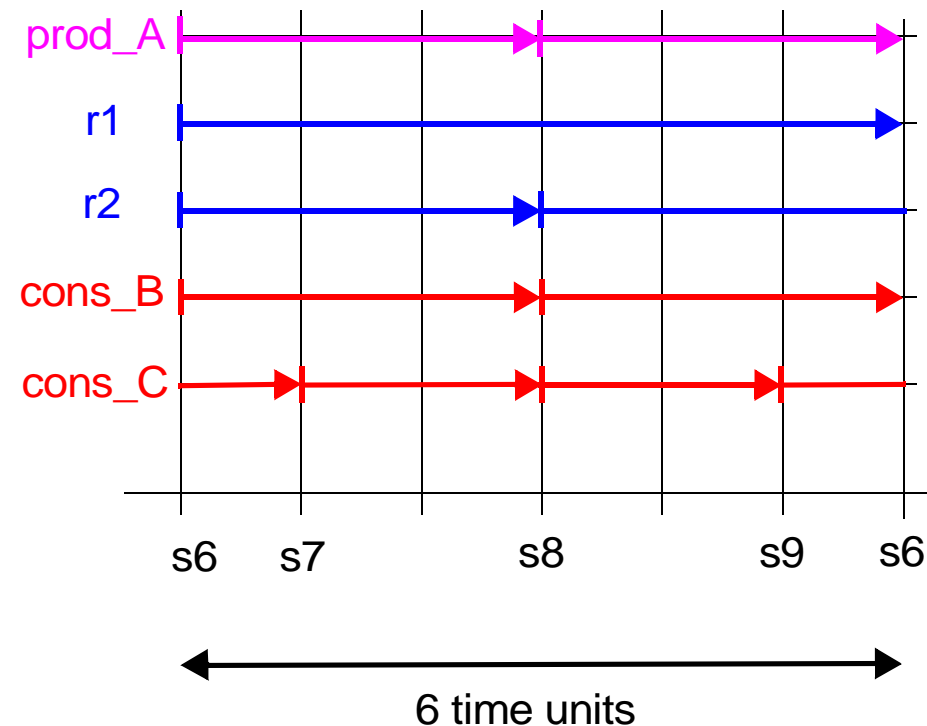
 - > *start / end at different time points*

- contains all minimal t-invariants

- relative transition firing rates

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

- timing diagram

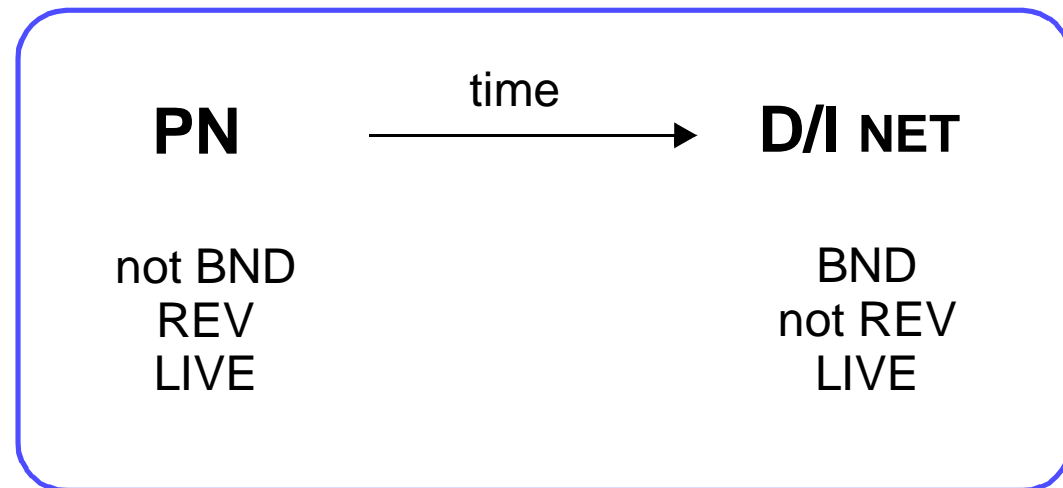


APPROACH 2, SUMMARY

- ❑ CTI,
but not CPI

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

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



❑ validation criterion 1

-> *CTI*

-> *no minimal T-invariant without biological interpretation*

-> *no known biological behaviour without corresponding T-invariant*

❑ validation criterion 2

-> *P-invariants - groups of compounds with conservation property*

-> *no minimal P-invariant without biological interpretation*

❑ validation criterion 3

-> *CPI*

-> *all expected temporal-logic properties -> TRUE*

- ❑ **extensions**
 - > *read arcs*
 - > *inhibitor arcs !?*

- ❑ **efficient computation of minimal invariants**
 - > *exponential complexity*
 - > *compositional / step-wise refinement approach ?*

- ❑ **analysis of bounded, but not safe non-ordinary nets with inhibitor arcs**
 - > *huge state spaces, beyond exponential growth (?)*
 - > *smaller, bounded version of case study 2 $\geq 10^{10}$ states (IDD-based mc tool)*

- ❑ **analysis of unbounded nets**
 - > *besides T-invariant analysis ?*

- ❑ **model checking**
 - > *relevant properties ?*

- ❑ **representation of bionetworks by Petri nets**
 - > *unifying view*
 - > *animation*
 - > *model validation against consistency criteria*
 - > *qualitative/quantitative behaviour prediction*

- ❑ **steady state behaviour**
 - > *qualitative model*
 - > *quantitative model*

- ❑ **many challenging questions for analysis techniques**

THANKS !