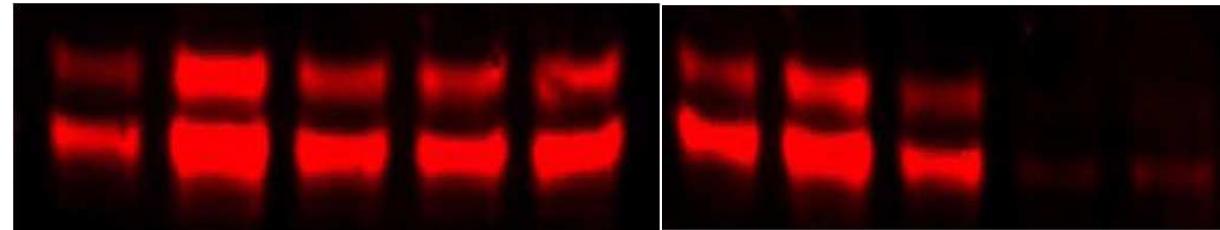
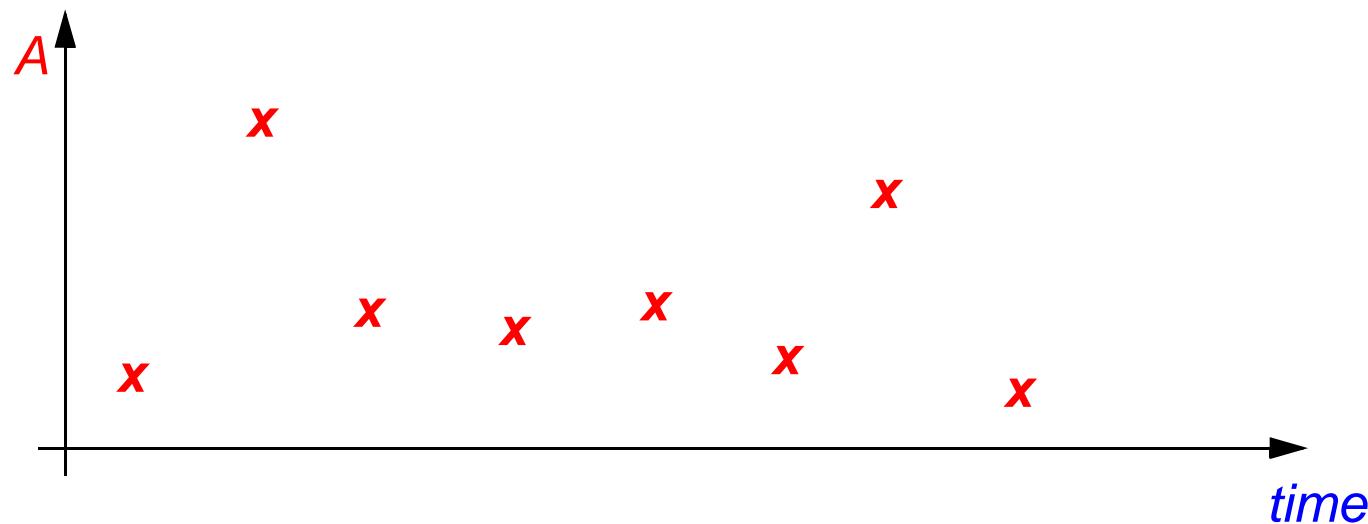
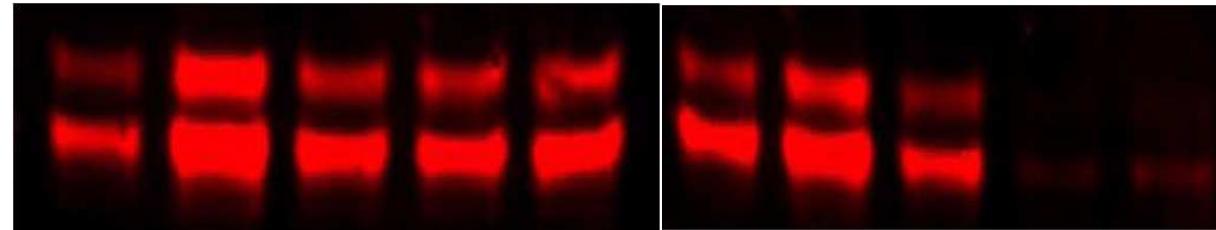


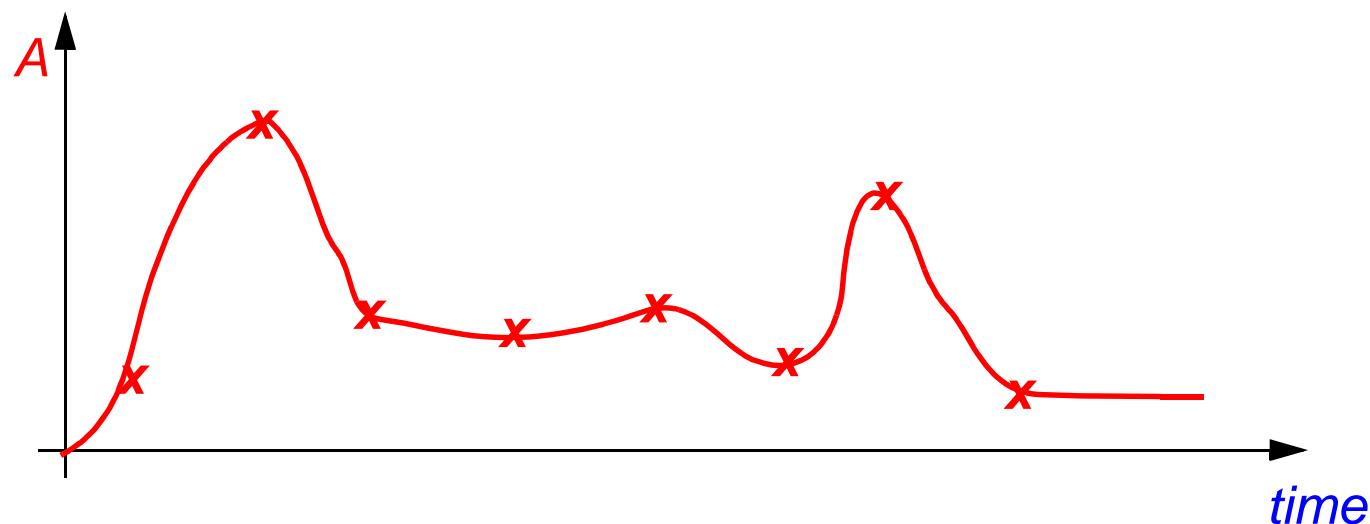
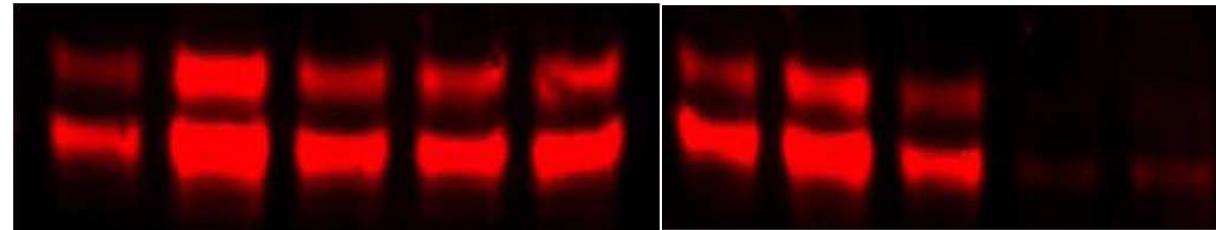
BIOMODEL ENGINEERING - A PETRI NET PERSPECTIVE -

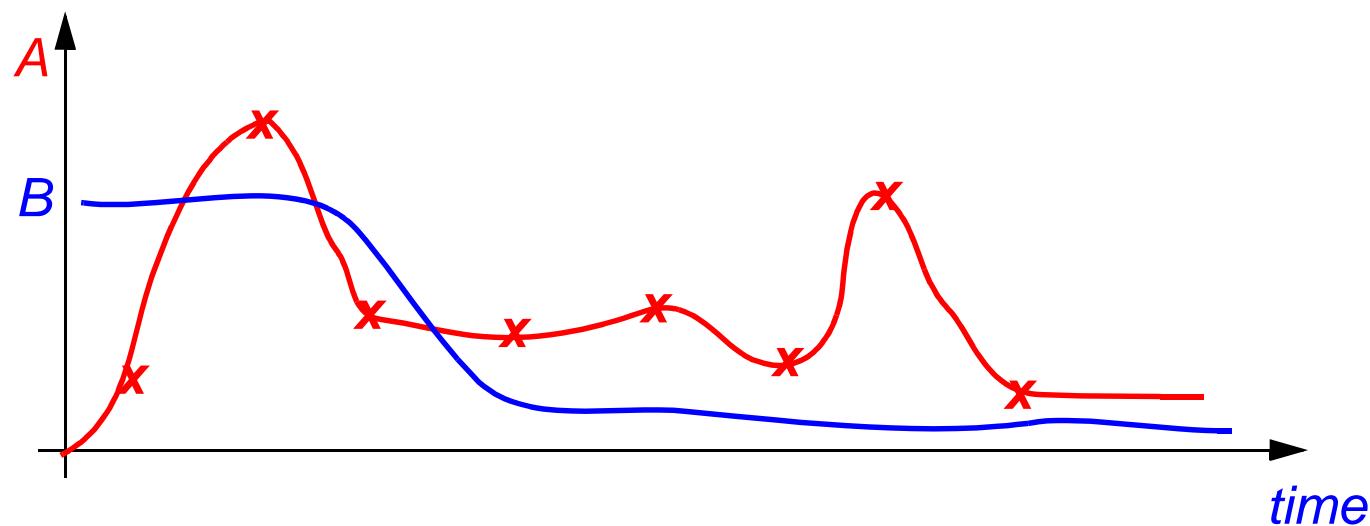
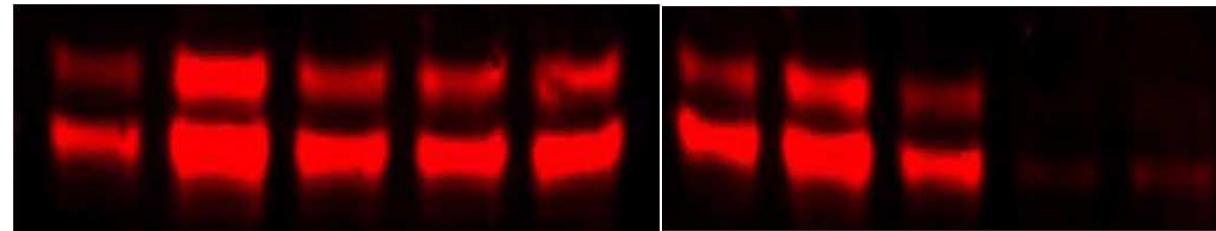
Monika Heiner

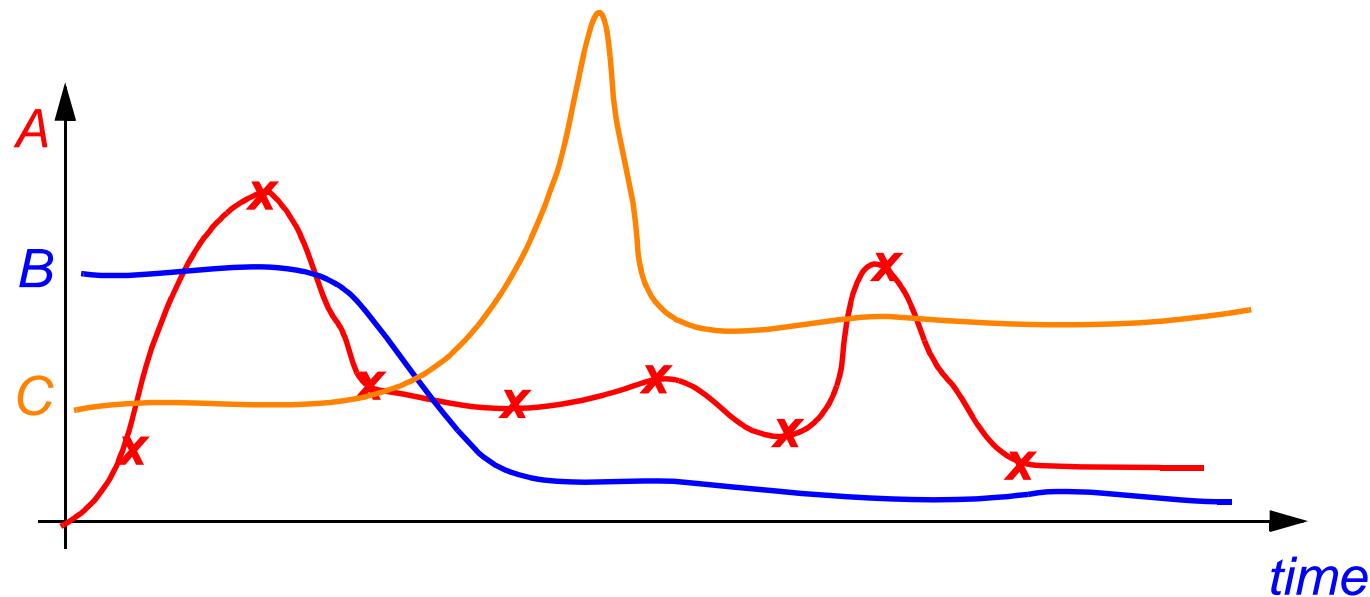
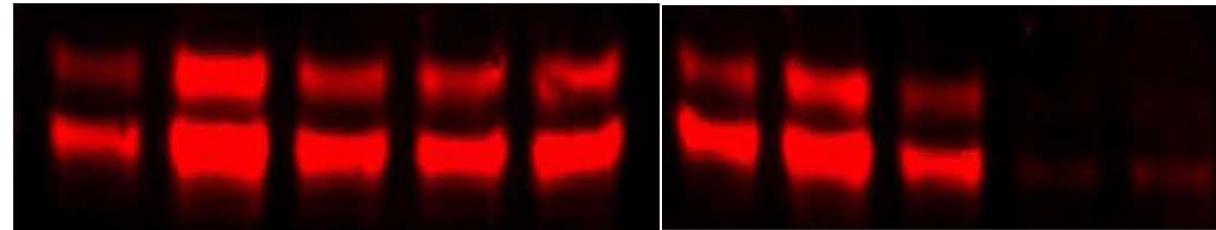
Brandenburg University of Technology
Computer Science Institute









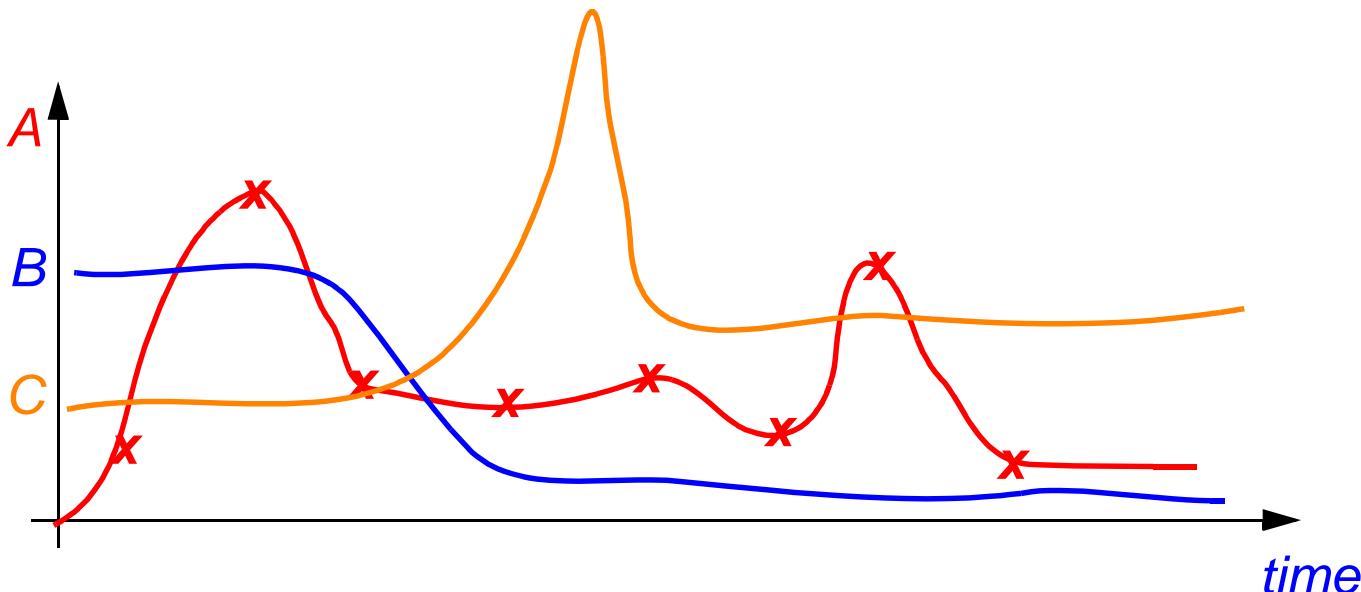


Qualitative

Protein A rises, then falls before rising again.

Protein B starts decreasing after the first peak of A until it reaches its steady state.

Protein C peaks between the two peaks of A.



Qualitative

Protein A rises, then falls before rising again.

Protein B starts decreasing after the first peak of A until it reaches its steady state.

Protein C peaks between the two peaks of A.

Semi-qualitative

Protein rises then falls to less than 50% of its peak concentration.

Semi-quantitative

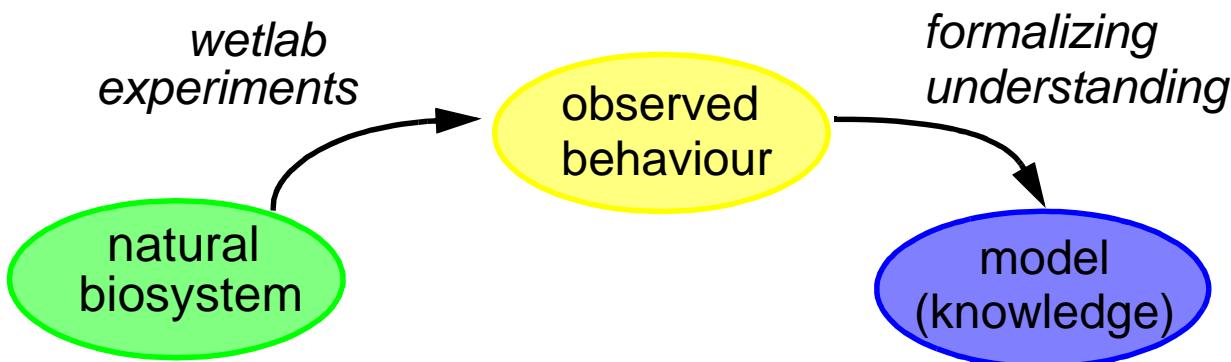
Protein rises then falls to less than 50% of its peak concentration at 60 minutes.

Quantitative

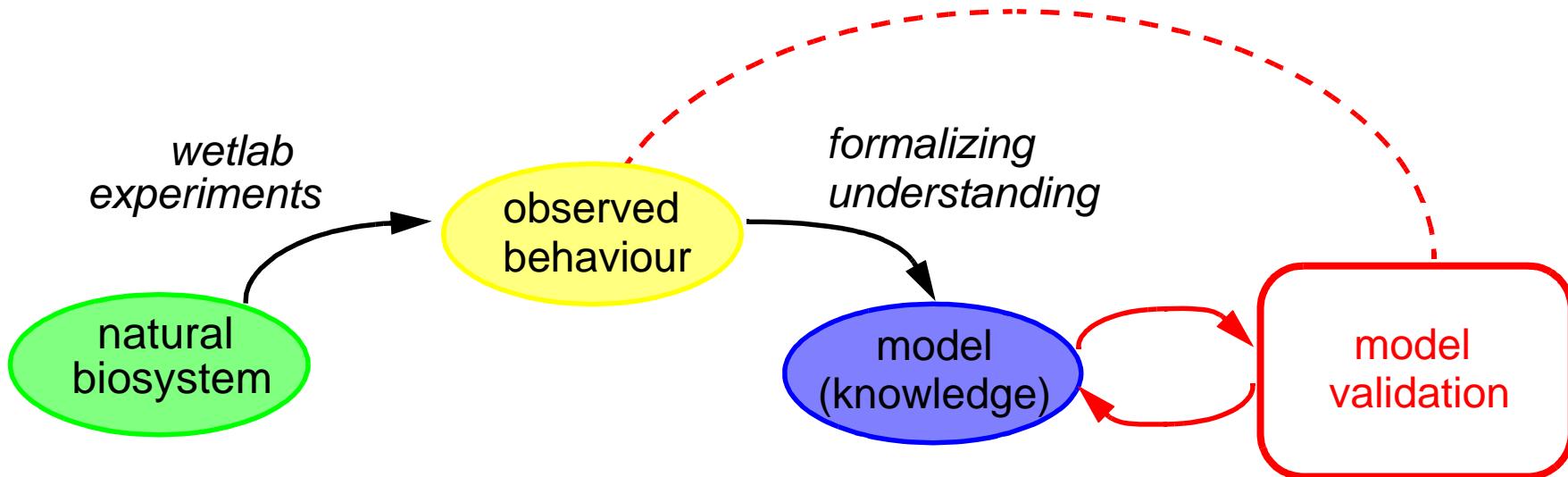
Protein rises then falls to less than 100 microMol at 60 minutes.

Models explaining these observations ?

MODELLING = FORMAL KNOWLEDGE REPRESENTATION

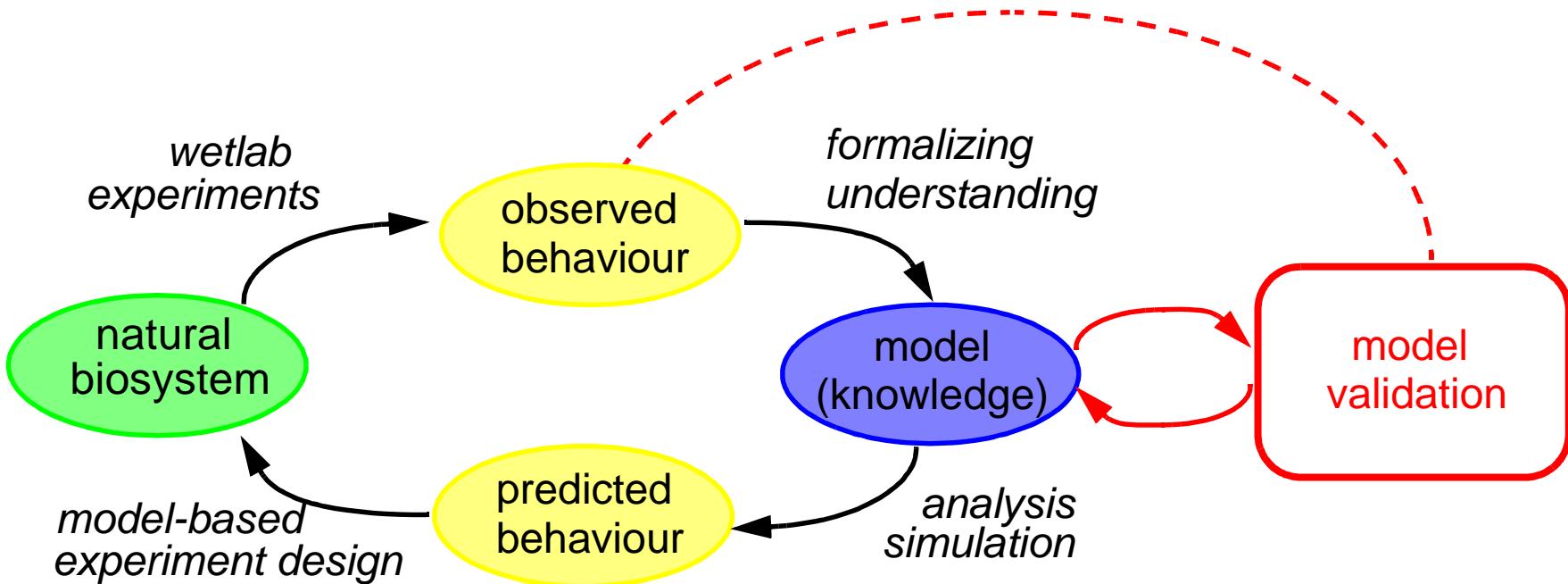


MODELLING = FORMAL KNOWLEDGE REPRESENTATION



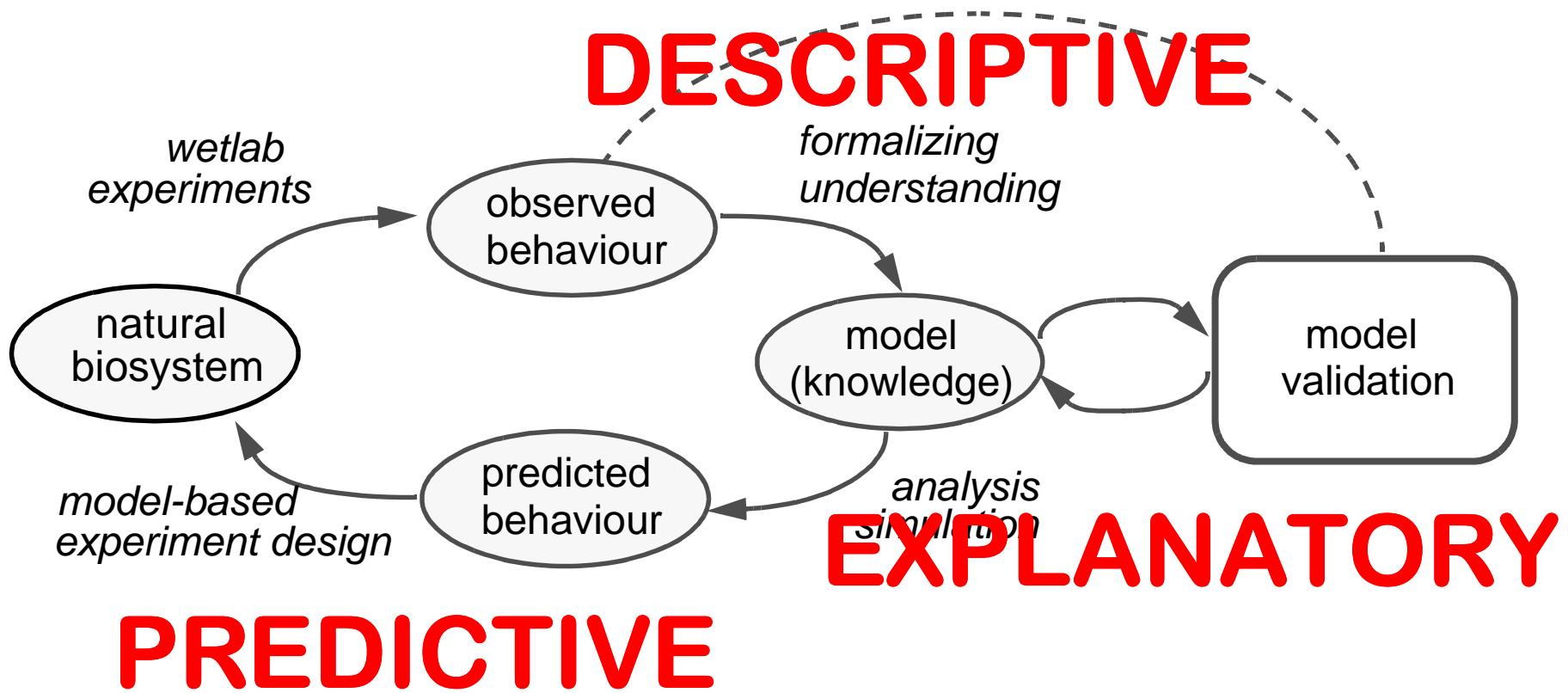
MODEL VALIDATION = CONFIDENCE INCREASE

MODELLING = FORMAL KNOWLEDGE REPRESENTATION



MODEL VALIDATION = CONFIDENCE INCREASE

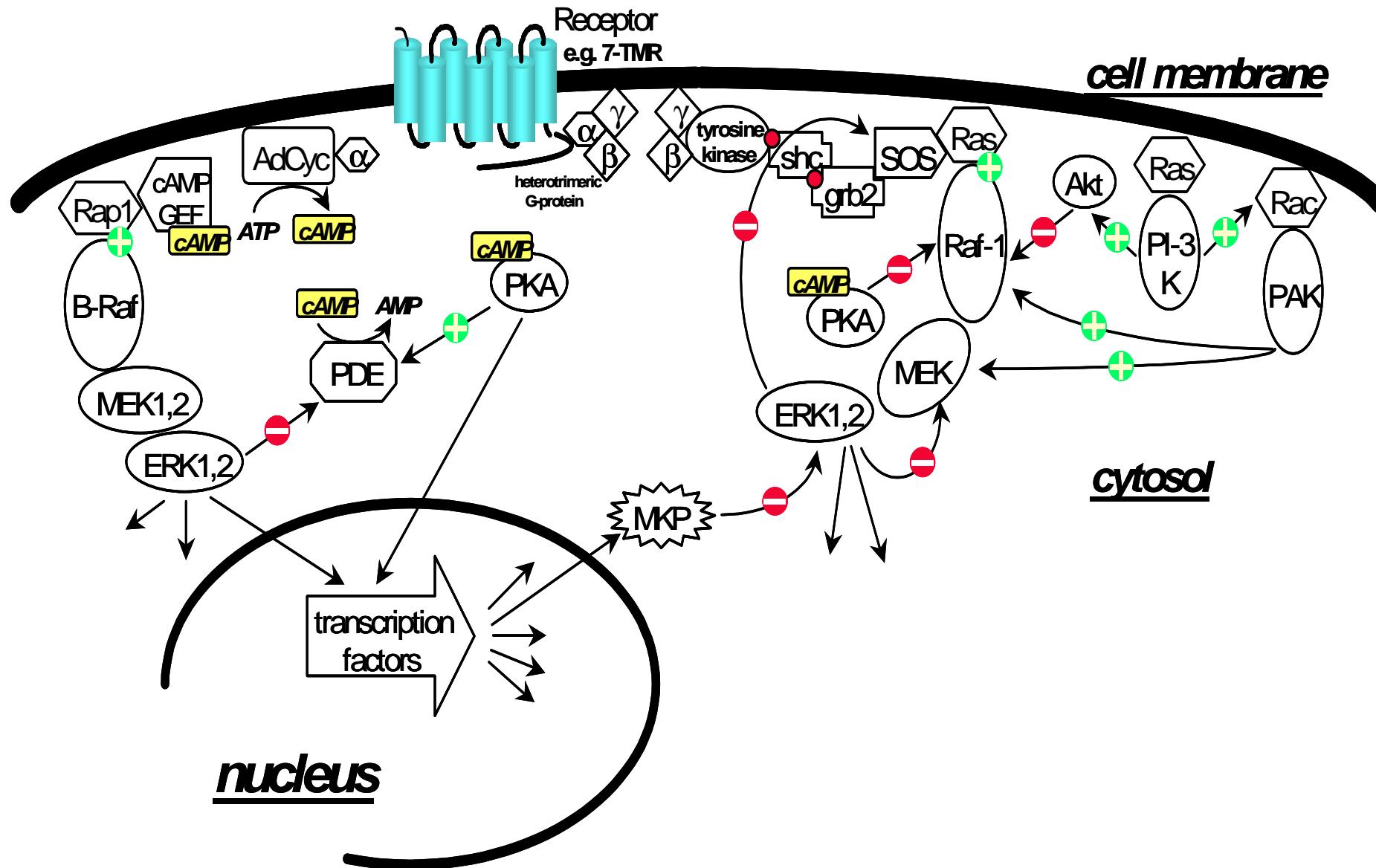
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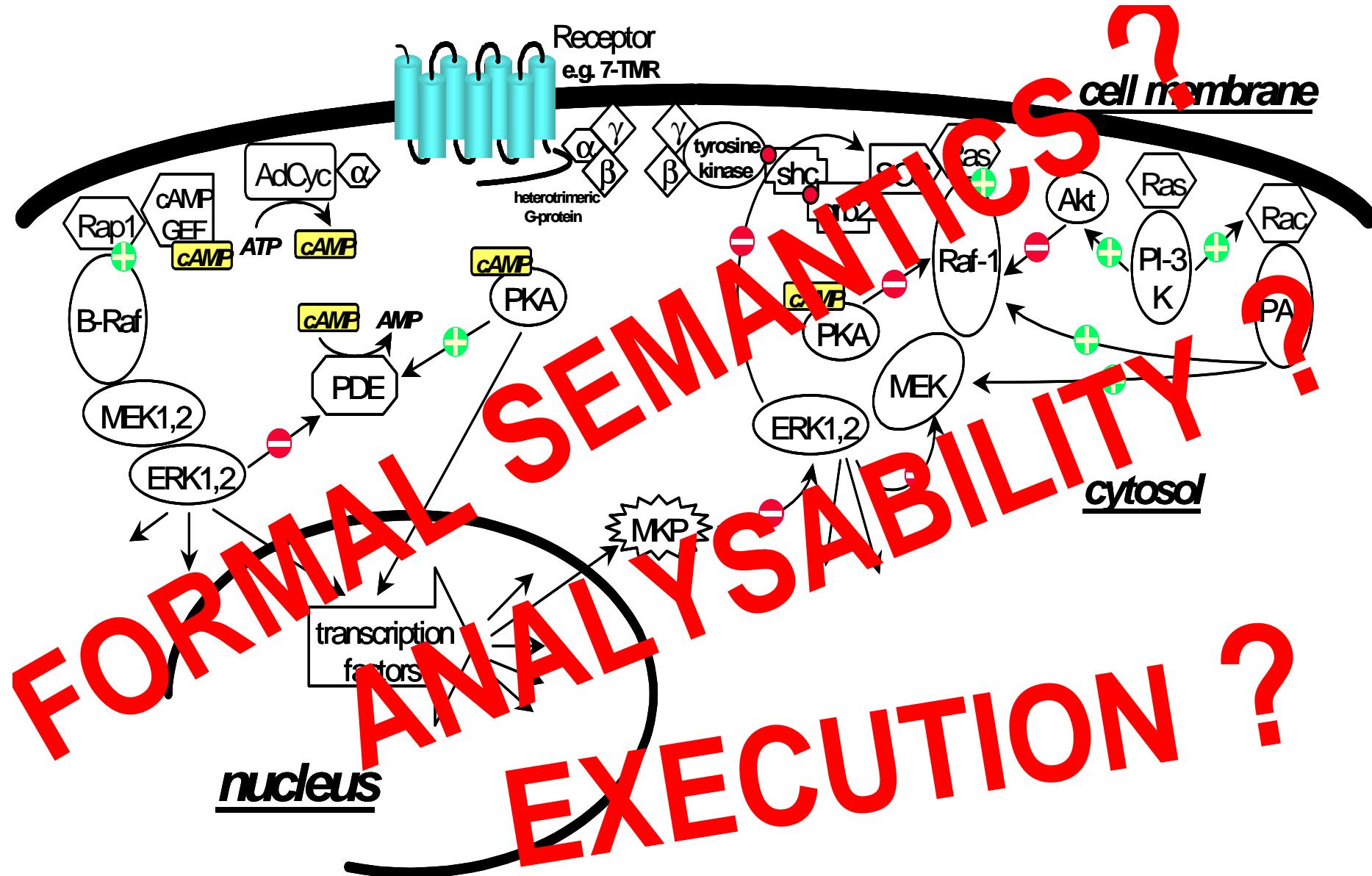


MODEL VALIDATION = CONFIDENCE INCREASE

NETWORK REPRESENTATIONS, Ex1

PN & BioModel Engineering





NETWORK REPRESENTATIONS, Ex2

PN & BioModel Engineering

$$\frac{d\alpha}{dt} = -v_1$$

$$\frac{dSte2}{dt} = -v_2 + v_3 - v_5$$

$$\frac{dSte2_{active}}{dt} = v_2 - v_3 - v_4$$

$$\frac{dSst2_{active}}{dt} = v_{46} - v_{47}$$

$$\frac{dG\alpha\beta\gamma}{dt} = -v_6 + v_9$$

$$\frac{dG\alpha GTP}{dt} = v_6 - v_7 - v_8$$

$$\frac{dG\alpha GDP}{dt} = v_7 + v_8 - v_9$$

$$\begin{aligned} \frac{dG\beta\gamma}{dt} = & v_6 - v_9 - v_{10} + v_{11} + v_{21} + v_{23} + v_{25} + v_{27} + v_{32} \\ & - v_{42} + v_{43} \end{aligned}$$

$$\frac{dSte5}{dt} = -v_{12} + v_{13} + v_{17} + v_{21} + v_{23} + v_{25} + v_{27} + v_{32}$$

$$\frac{dSte11}{dt} = -v_{12} + v_{13} + v_{17} + v_{21} + v_{23} + v_{25} + v_{27} + v_{32}$$

$$\frac{dSte7}{dt} = -v_{14} + v_{15} + v_{17} + v_{21} + v_{23} + v_{25} + v_{27} + v_{32}$$

$$\begin{aligned} \frac{dFus3}{dt} = & -v_{14} + v_{15} + v_{17} + v_{21} + v_{23} + v_{25} + v_{27} - v_{29} \\ & + v_{30} + v_{33} \end{aligned}$$

$$\frac{dSte20}{dt} = -v_{18} + v_{19} + v_{21} + v_{23} + v_{25} + v_{27} + v_{32}$$

$$v_1 = \alpha[t] \cdot Bar1_{active}[t] \cdot k_1$$

$$v_2 = Ste2[t] \cdot \alpha[t] \cdot k_2$$

$$v_3 = Ste2_{active}[t] \cdot k_3$$

$$v_4 = Ste2_{active}[t] \cdot k_4$$

$$v_5 = Ste2[t] \cdot k_5$$

$$v_6 = Ste2_{active}[t] \cdot G\alpha\beta\gamma[t] \cdot k_6$$

$$v_7 = G\alpha GTP[t] \cdot k_7$$

$$v_8 = G\alpha GTP[t] \cdot Sst2_{active}[t] \cdot k_8$$

$$v_9 = G\alpha GDP[t] \cdot G\beta\gamma[t] \cdot k_9$$

$$v_{10} = G\beta\gamma[t] \cdot C[t] \cdot k_{10}$$

$$v_{11} = D[t] \cdot k_{11}$$

$$v_{12} = Ste5[t] \cdot Ste11[t] \cdot k_{12}$$

$$v_{13} = A[t] \cdot k_{13}$$

$$v_{14} = Ste7[t] \cdot Fus3[t] \cdot k_{14}$$

$$v_{15} = B[t] \cdot k_{15}$$

$$v_{16} = A[t] \cdot B[t] \cdot k_{16}$$

$$v_{17} = C[t] \cdot k_{17}$$

$$v_{18} = D[t] \cdot Ste20[t] \cdot k_{18}$$

$$\begin{aligned}
 \frac{d\alpha}{dt} &= -v_1 \\
 \frac{d\text{Ste2}}{dt} &= -v_2 + v_3 - v_5 \\
 \frac{d\text{Ste2}_{\text{active}}}{dt} &= v_2 - v_3 - v_4 \\
 \frac{d\text{Sst2}_{\text{active}}}{dt} &= v_{46} - v_{47} \\
 \frac{d\text{G}\alpha\beta\gamma}{dt} &= -v_6 + v_9 \\
 \frac{d\text{G}\alpha\text{GTP}}{dt} &= v_6 - v_7 - v_8 \\
 \frac{d\text{G}\alpha\text{GDP}}{dt} &= v_7 + v_8 - v_9 \\
 \frac{d\text{G}\beta\gamma}{dt} &= v_6 - v_9 - v_{10} + v_{11} + v_{21} + v_{23} + v_{25} + v_{27} + v_{32} \\
 &\quad - v_{42} + v_{43} \\
 \frac{d\text{Ste5}}{dt} &= -v_{12} + v_{13} + v_{17} + v_{21} + v_{23} + v_{25} + v_{27} + v_{32} \\
 \frac{d\text{Ste7}}{dt} &= -v_{12} + v_{13} + v_{17} + v_{21} + v_{22} + v_{25} + v_{27} + v_{32} \\
 \frac{d\text{Fus3}}{dt} &= -v_{14} + v_{15} + v_{17} + v_{21} + v_{23} + v_{25} + v_{27} + v_{32} \\
 \frac{d\text{Ste20}}{dt} &= -v_{18} + v_{19} - v_{20} + v_{23} + v_{25} + v_{27} + v_{32}
 \end{aligned}$$

READABILITY?

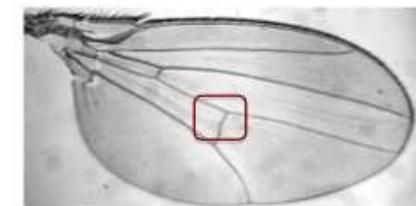
CAUSALITY?

UNIQUE STRUCTURE?

$$\begin{aligned}
 v_1 &= \alpha[t] \cdot \text{Bar1}_{\text{active}}[t] \cdot k_1 \\
 v_2 &= \text{Ste2}[t] \cdot \alpha[t] \cdot k_2 \\
 v_3 &= \text{Ste2}_{\text{active}}[t] \cdot k_3 \\
 v_4 &= \text{Ste2}_{\text{active}}[t] \cdot k_4 \\
 v_5 &= \text{Ste2}[t] \cdot k_5 \\
 v_6 &= \text{Ste2}_{\text{active}}[t] \cdot \text{G}\alpha\beta\gamma[t] \cdot k_6 \\
 v_7 &= \text{G}\alpha\text{GTP}[t] \cdot k_7 \\
 v_8 &= \text{G}\alpha\text{GTP}[t] \cdot \text{Sst2}_{\text{active}}[t] \cdot k_8 \\
 v_9 &= \text{G}\alpha\text{GDP}[t] \cdot \text{G}\beta\gamma[t] \cdot k_9 \\
 v_{10} &= \text{G}\beta\gamma[t] \cdot \text{C}[t] \cdot k_{10} \\
 v_{11} &= \text{C}[t] \cdot k_{11} \\
 v_{12} &= \text{Ste5}[t] \cdot \text{Ste11}[t] \cdot k_{12} \\
 v_{13} &= \text{A}[t] \cdot k_{13} \\
 v_{14} &= \text{Ste7}[t] \cdot \text{Fus3}[t] \cdot k_{14} \\
 v_{15} &= \text{B}[t] \cdot k_{15} \\
 v_{16} &= \text{A}[t] \cdot \text{B}[t] \cdot k_{16} \\
 v_{17} &= \text{C}[t] \cdot k_{17} \\
 v_{18} &= \text{D}[t] \cdot \text{Ste20}[t] \cdot k_{18}
 \end{aligned}$$

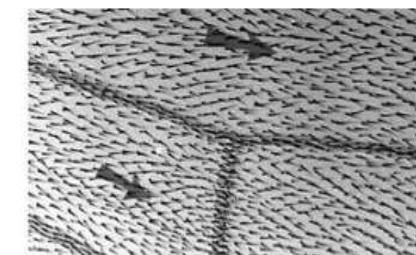
□ FRAMEWORK

- > *unifying four paradigms: QPN - SPN - CPN - HPN*
- > *structural analysis by T-invariants*



□ ABSTRACT-DEPENDENT TRANSITION SETS

- > *modularisation*
- > *hierarchical representation (coarsening)*
- > *network structuring*
- > *identification of fragile nodes*

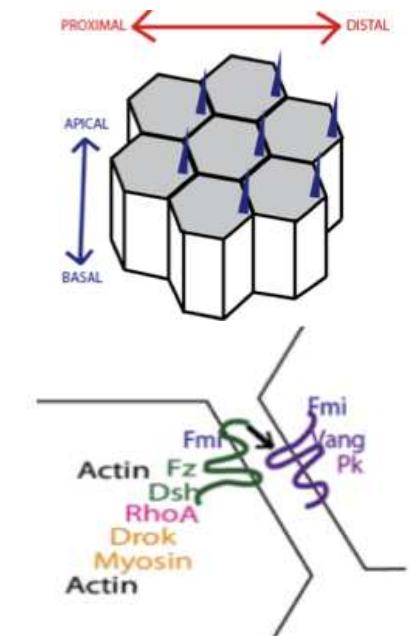


□ STEADY STATE INTERPRETATION

- > *core network identification*

□ SUMMARY & OUTLOOK

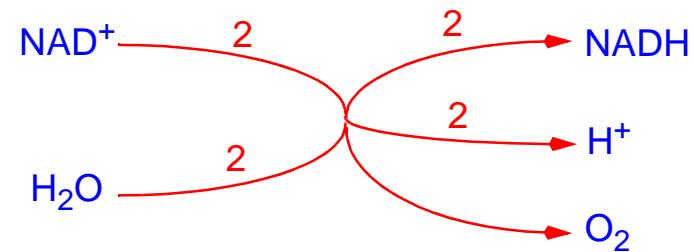
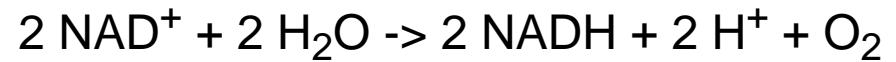
- > *our tool box*



THE PETRI NET FRAMEWORK

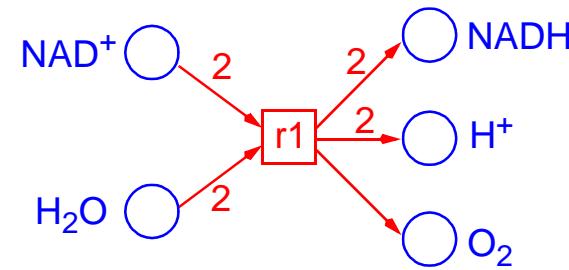
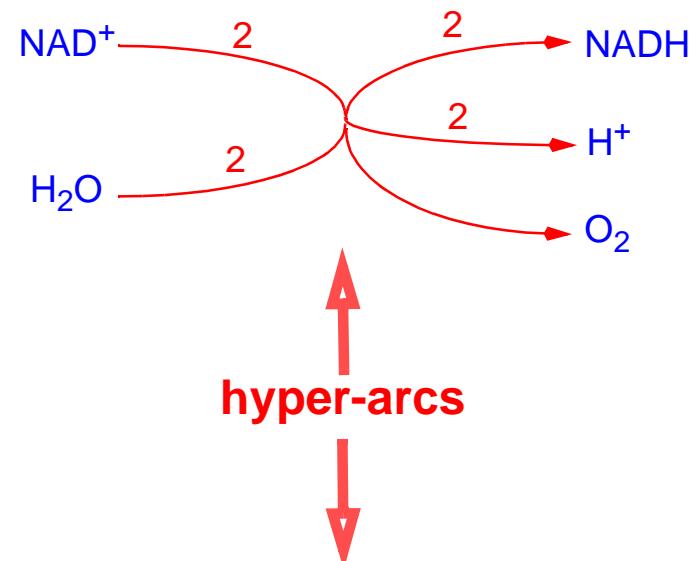
• • •

ARE NETWORKS OF BIOCHEMICAL REACTIONS



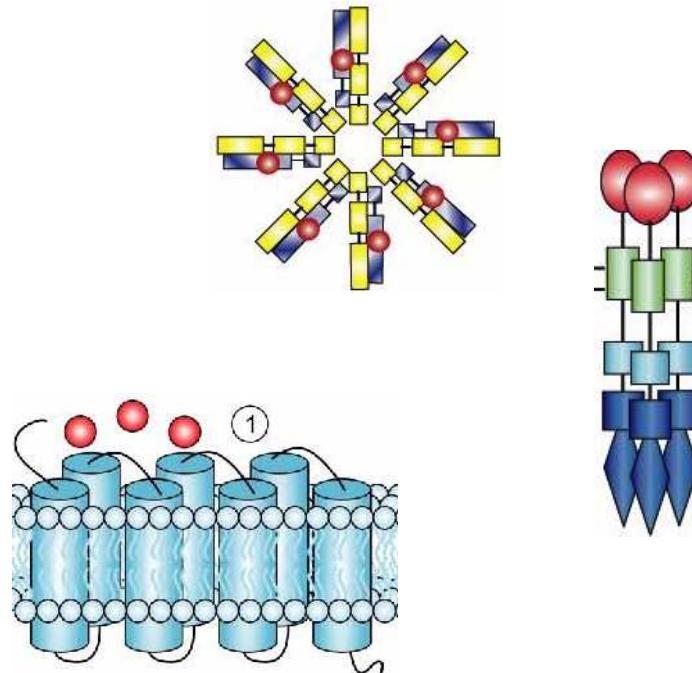
**ARE NETWORKS
OF BIOCHEMICAL
REACTIONS**

**NATURALLY
EXPRESSIBLE AS
PETRI NETS**



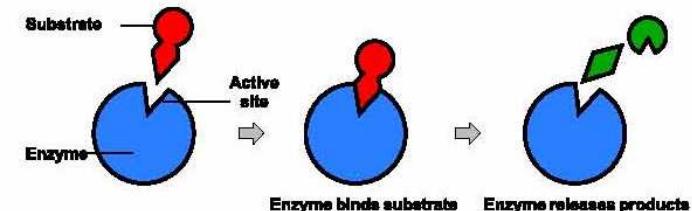
□ places → model variables

- > (bio-) chemical compounds
- > proteins
- > protein conformations
- > complexes
- > genes, . . . , etc.
- ... in different locations*

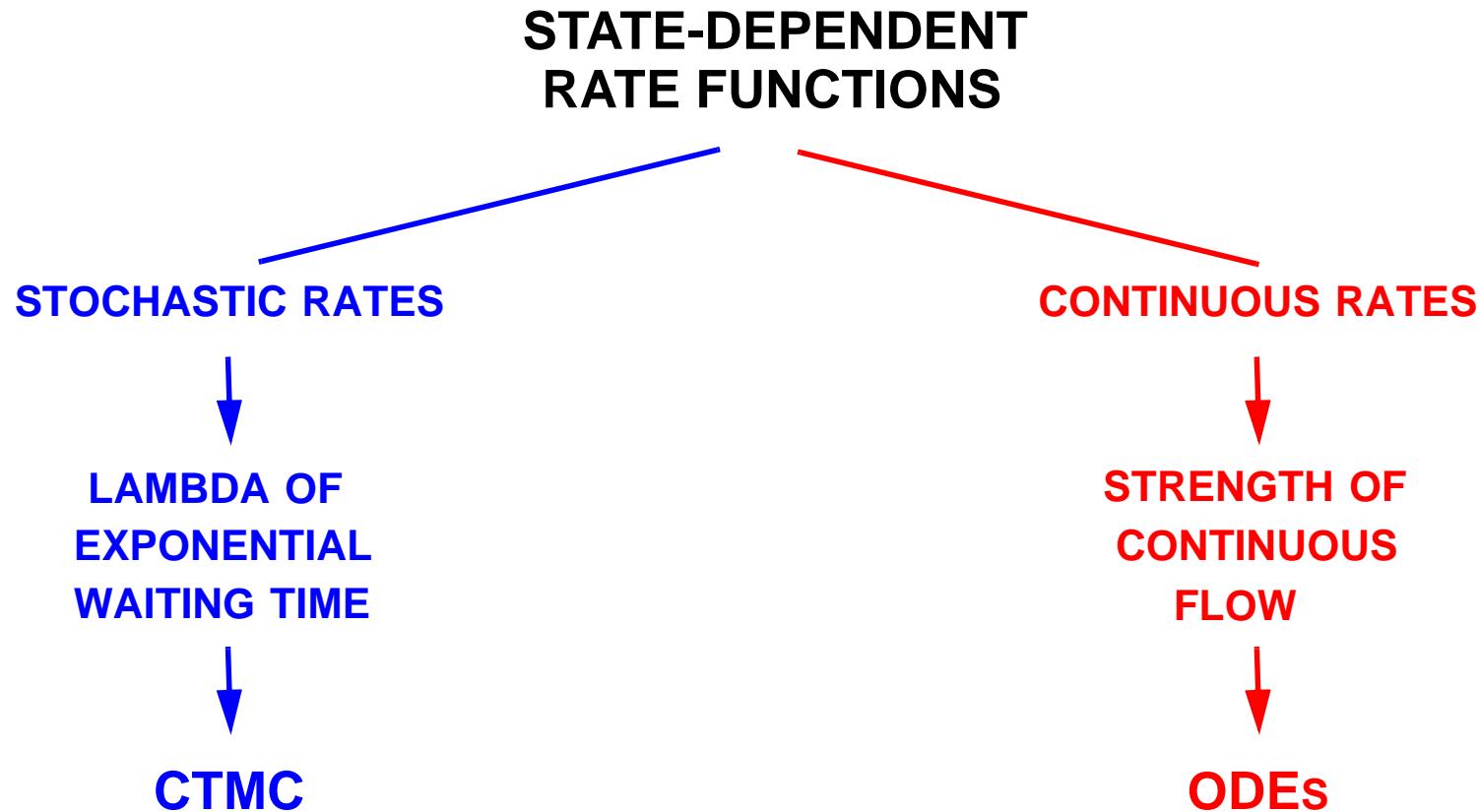


□ transitions → atomic events

- > (stoichiometric) chemical reaction
- > complexation / decomplexation
- > phosphorylation / dephosphorylation
- > conformational change
- > transport step, . . . , etc.
- ... in different locations*



STATE-DEPENDENT RATE FUNCTIONS

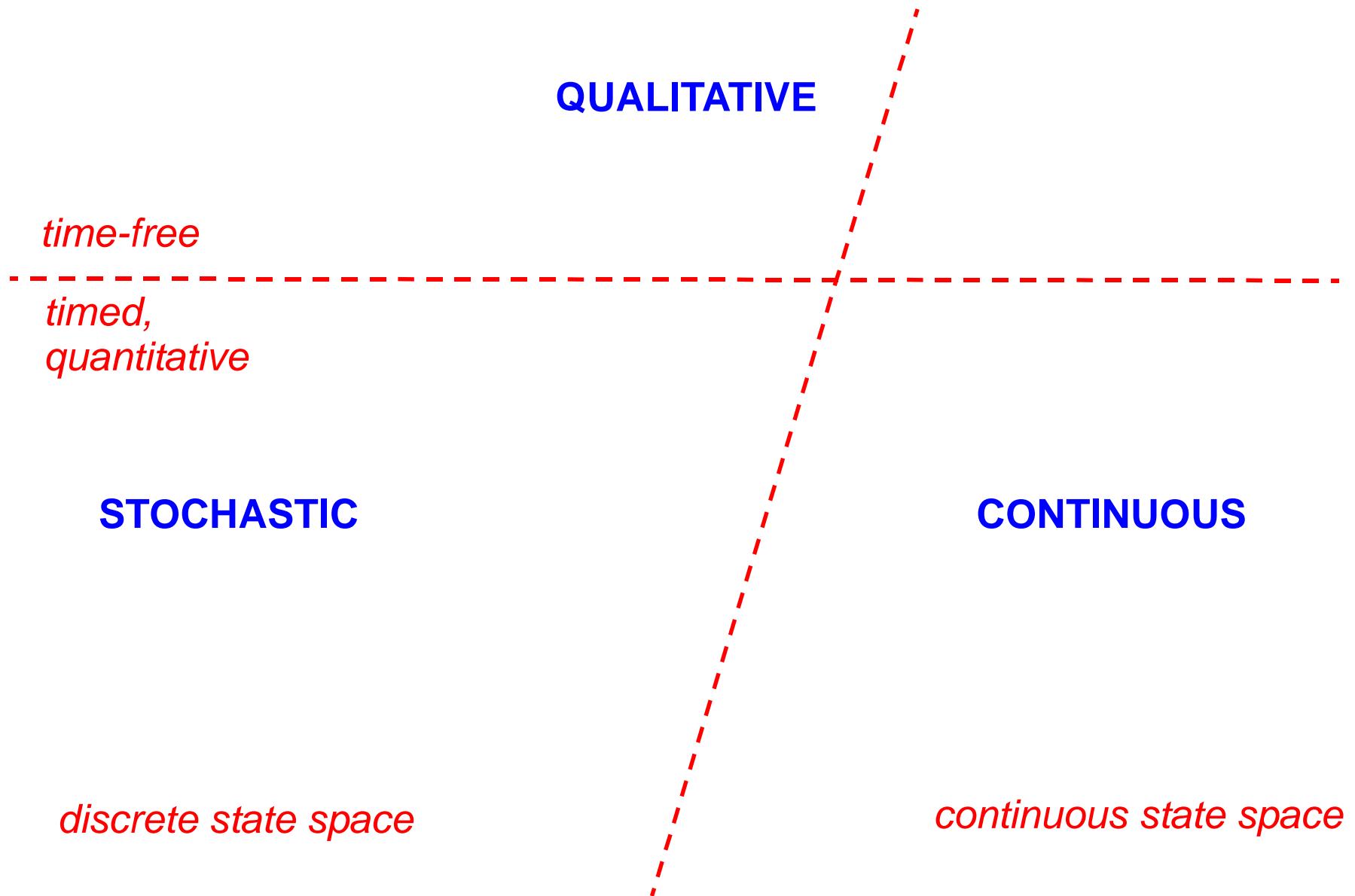


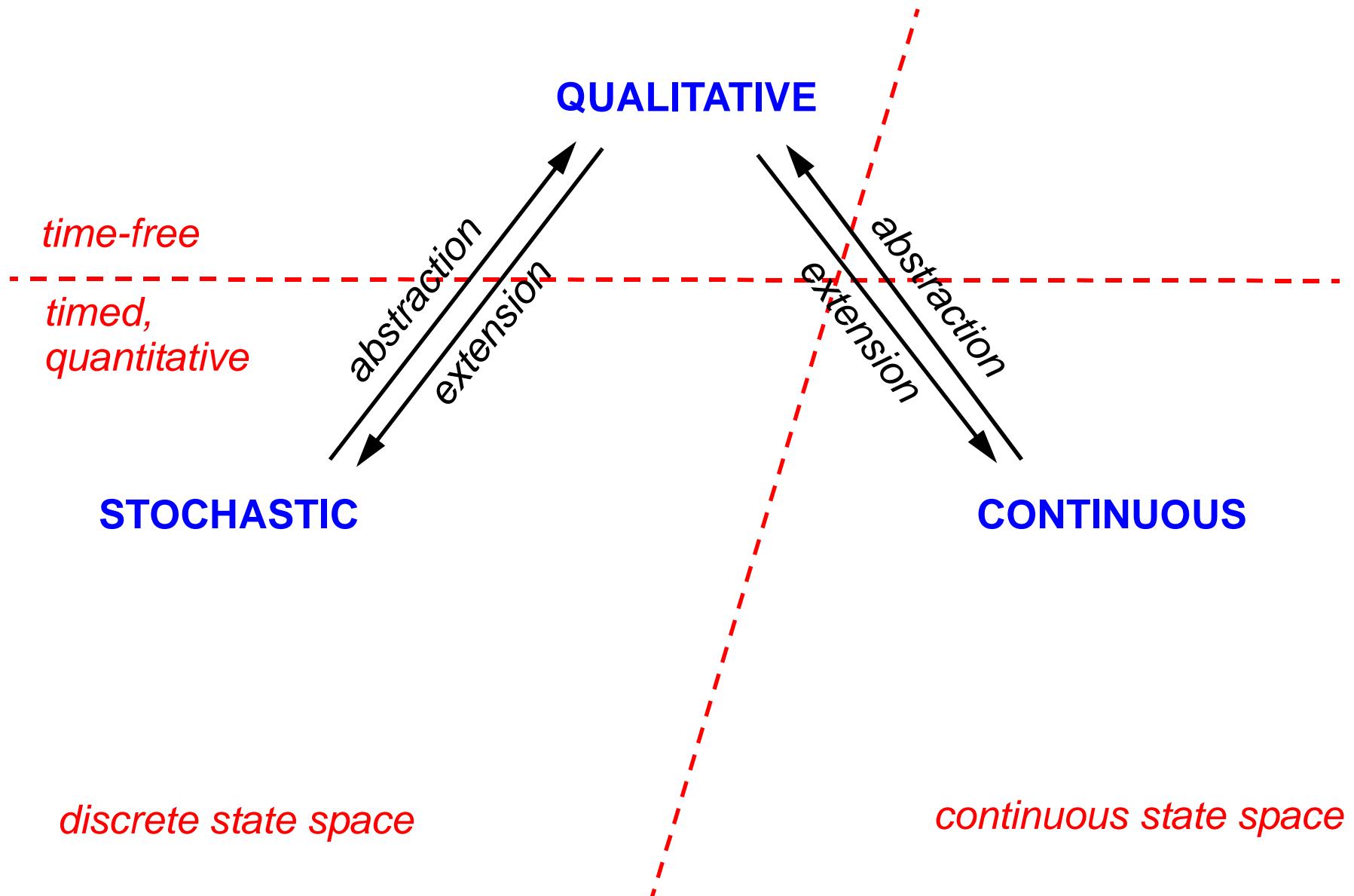
-> supported by, e.g., COPASI, Dizzy, ..., Snoopy

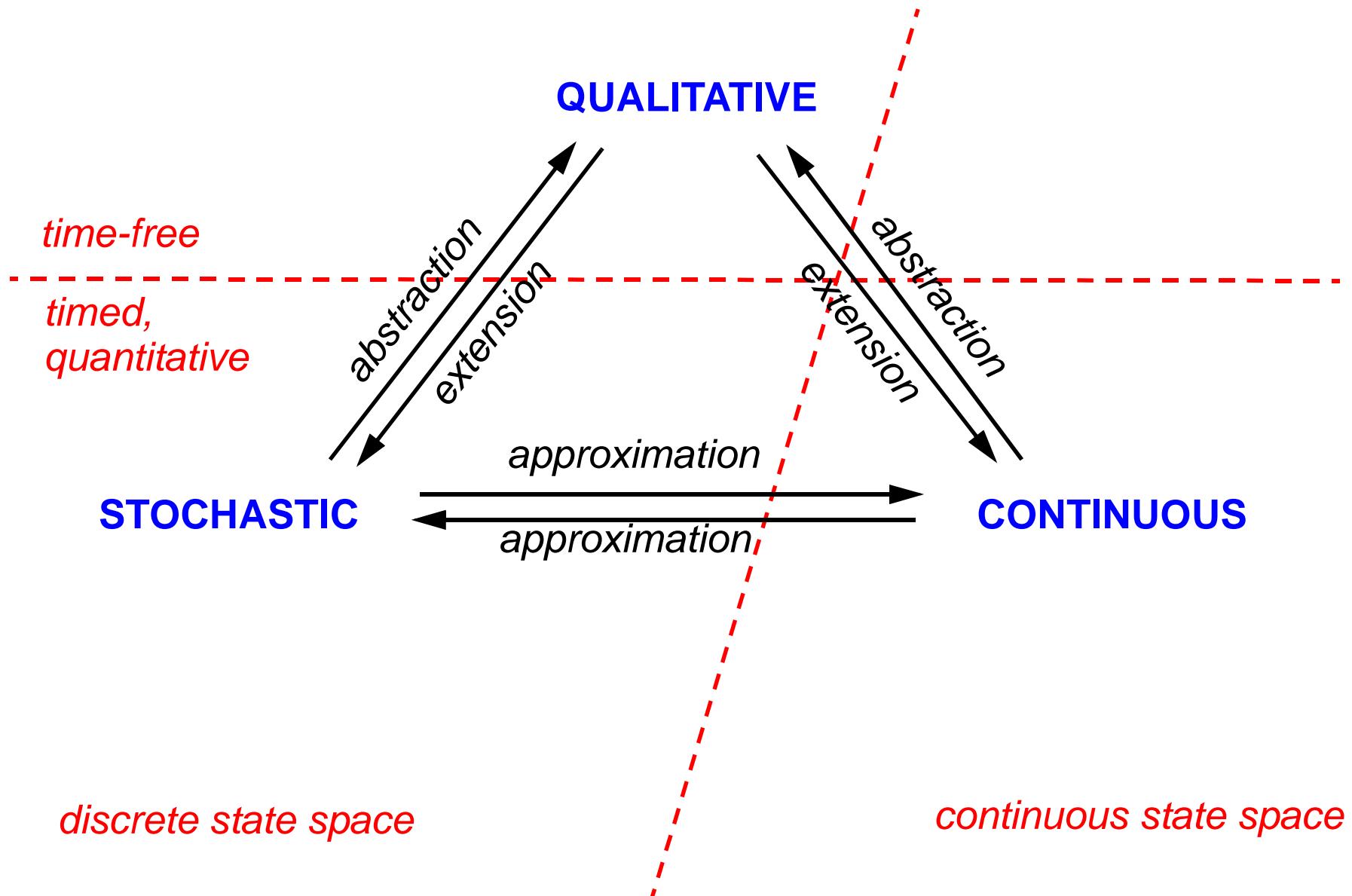
QUALITATIVE

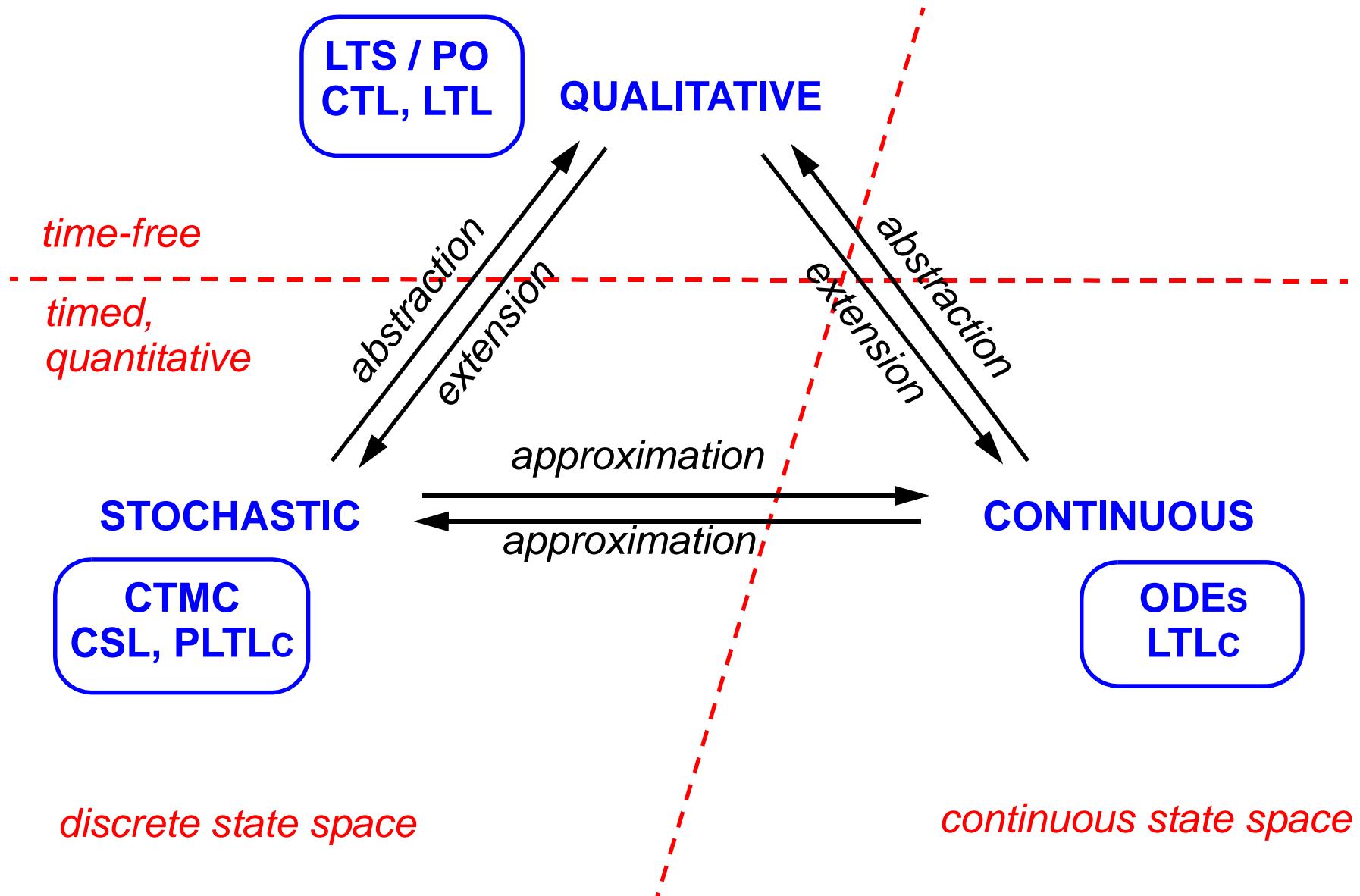
STOCHASTIC

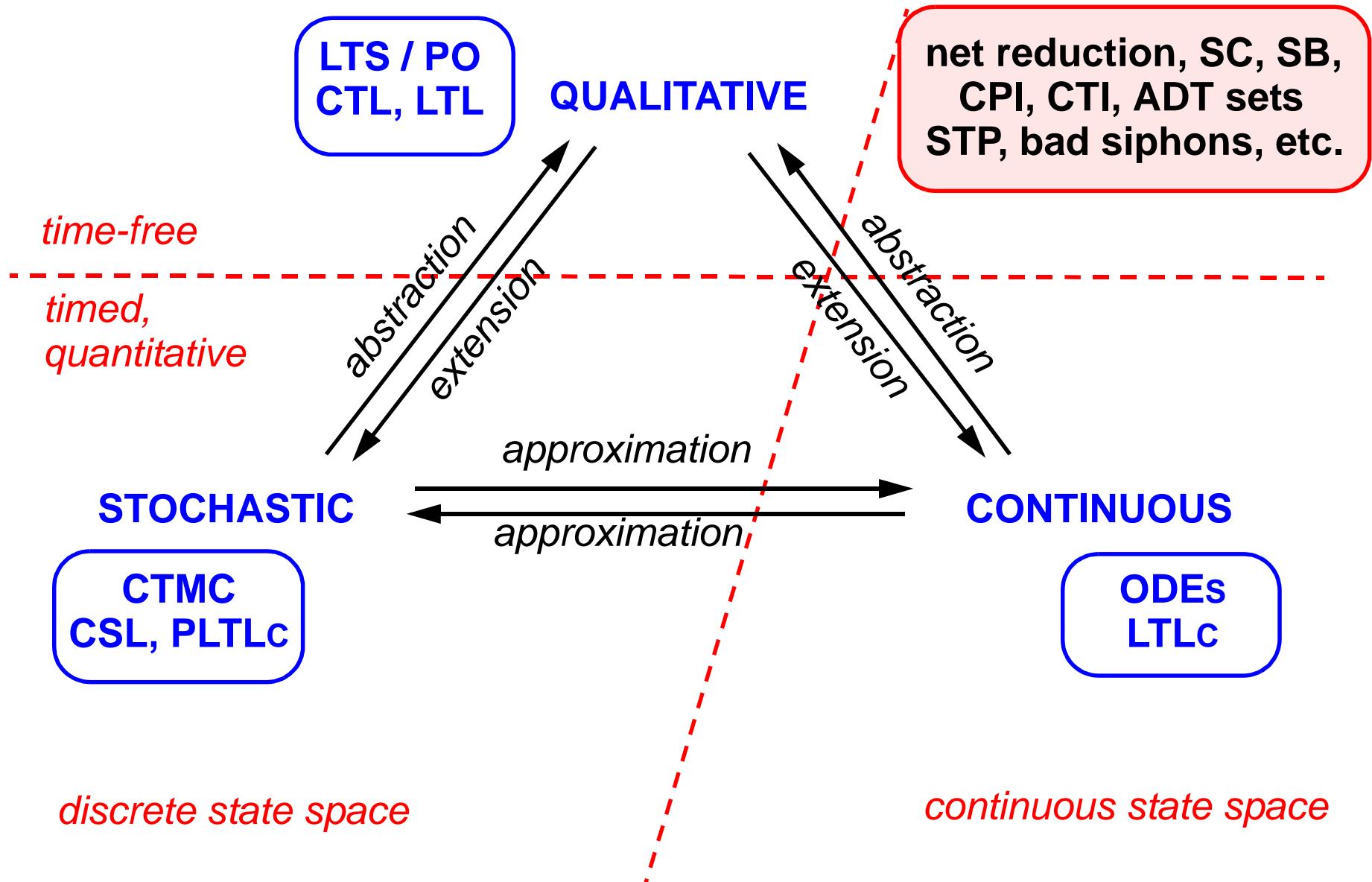
CONTINUOUS

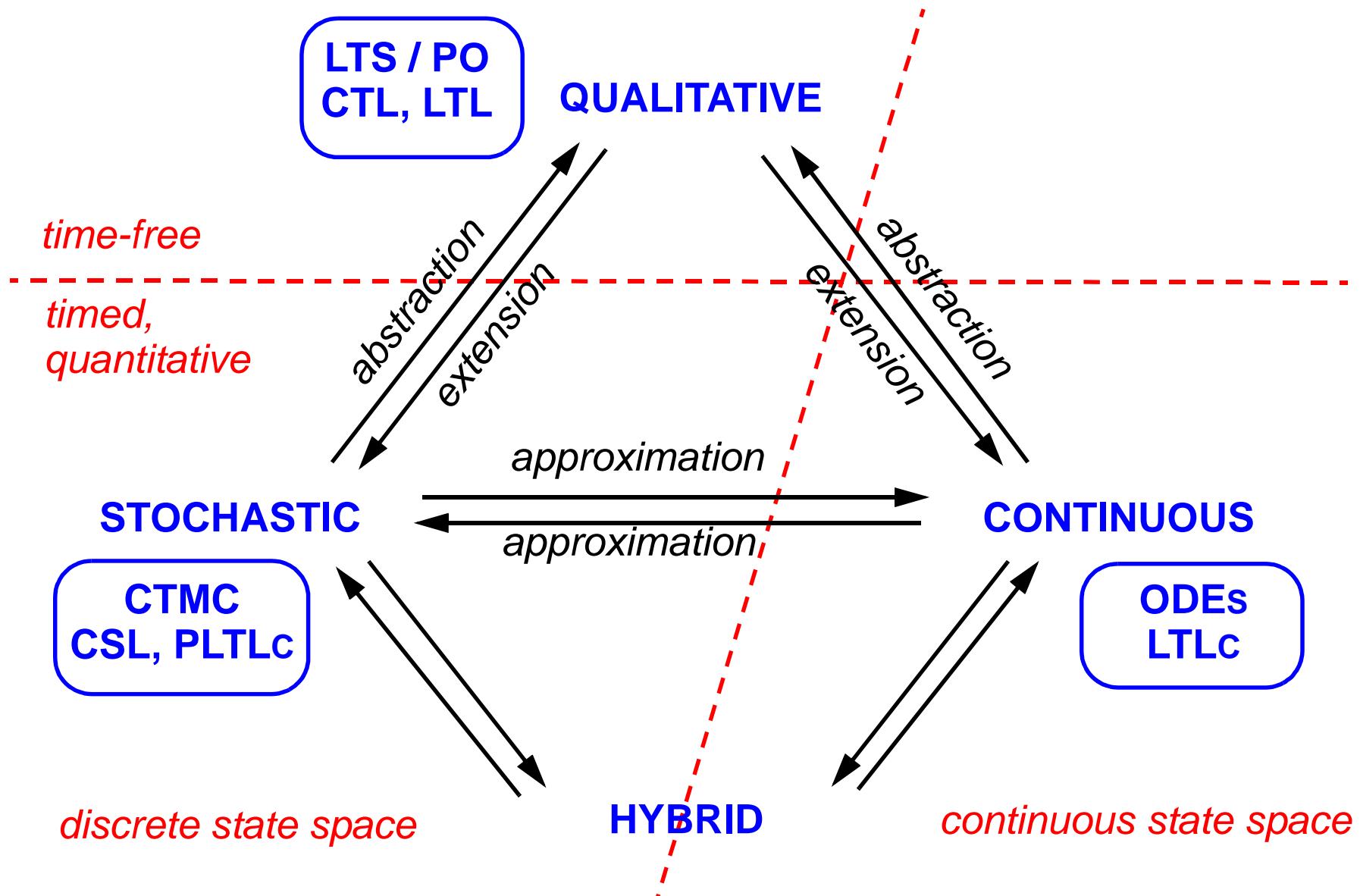


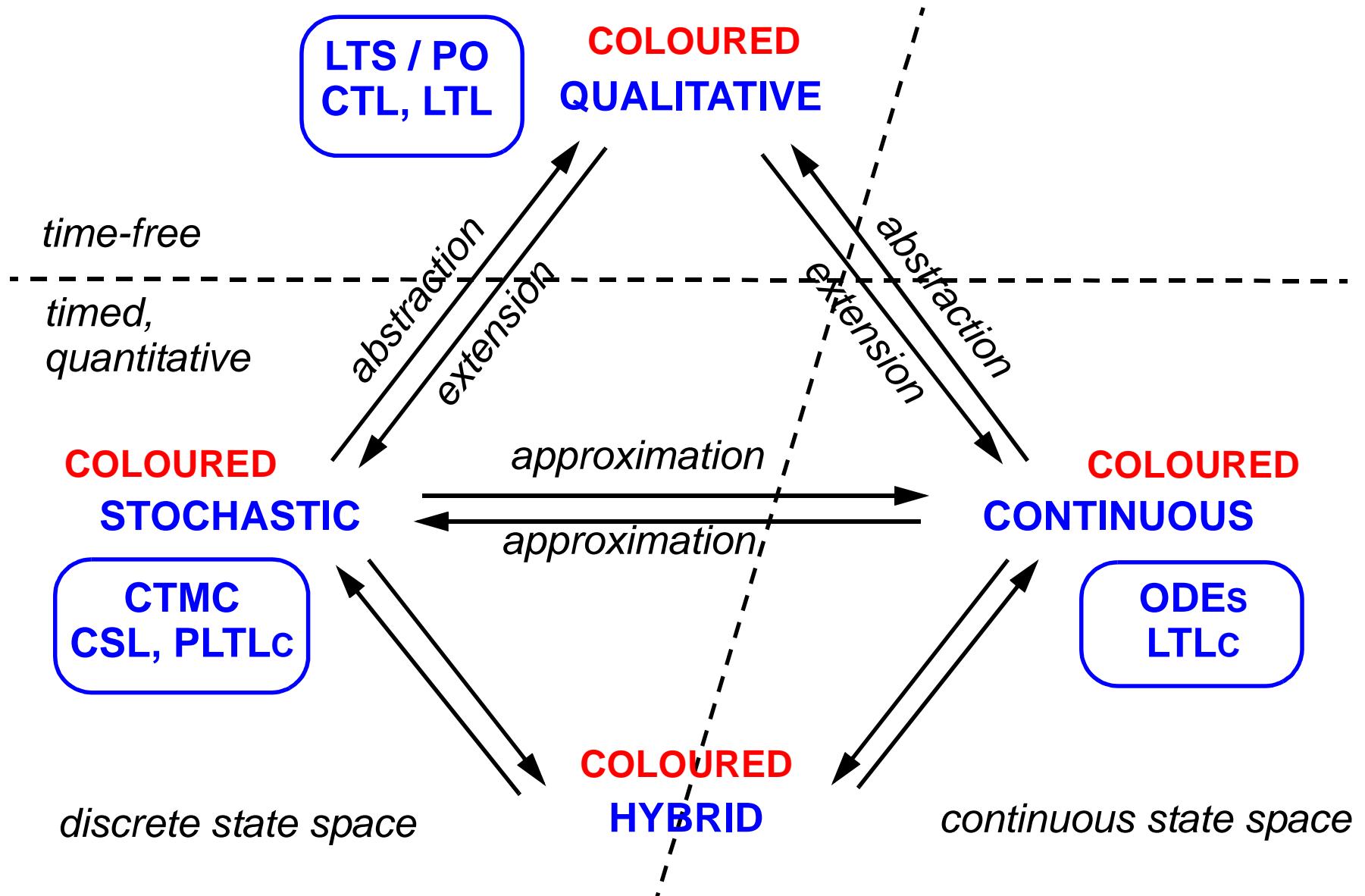






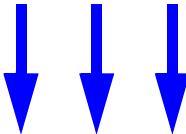






4x2

MODELS SHARING STRUCTURE

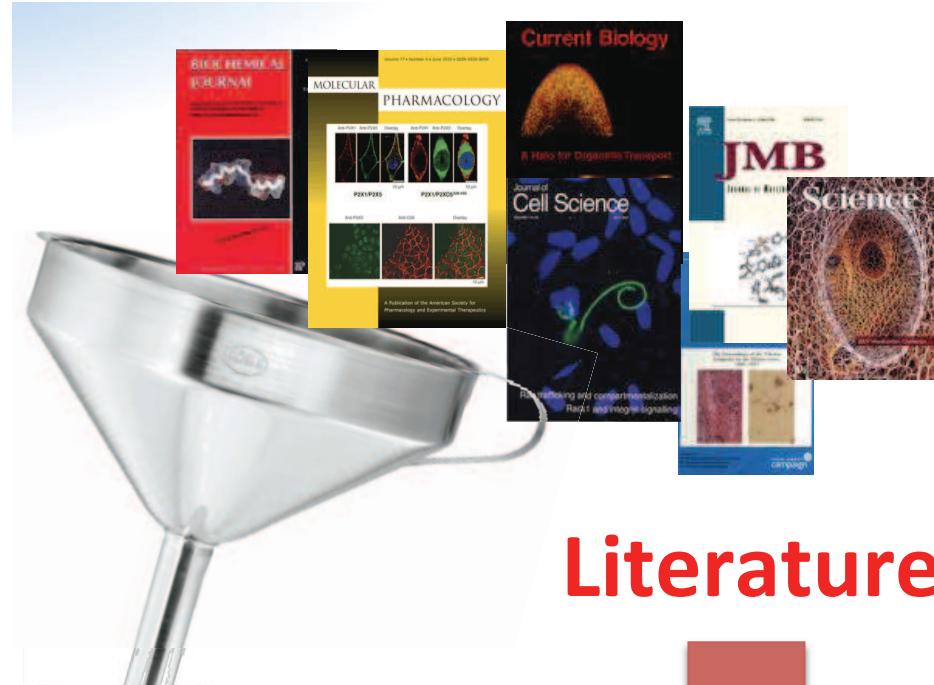


QUANTITATIVE MODEL = QUALITATIVE MODEL

+

**RATE FUNCTIONS
(KINETICS)**

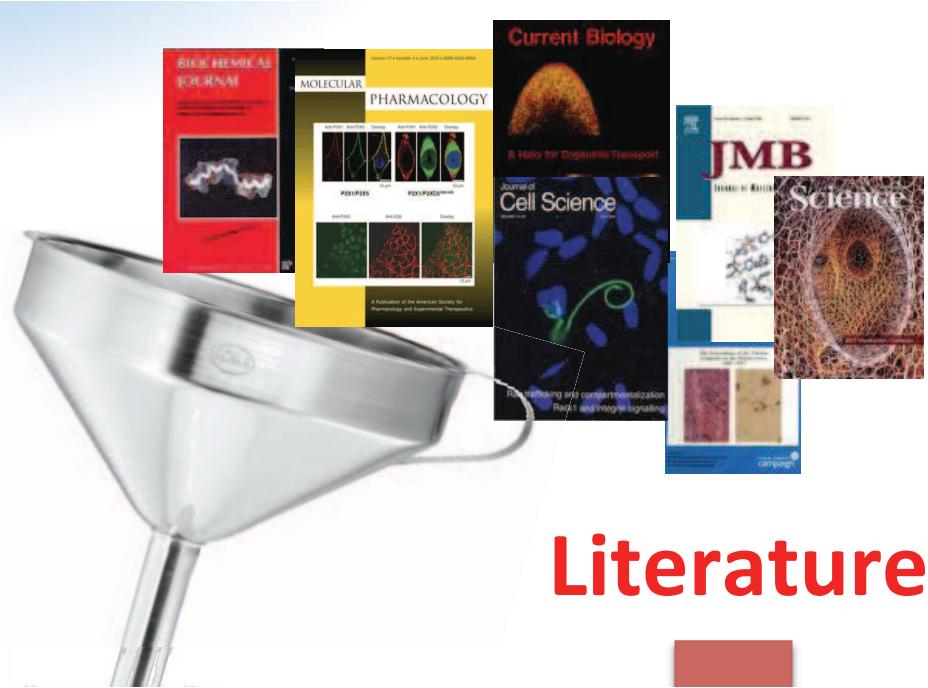
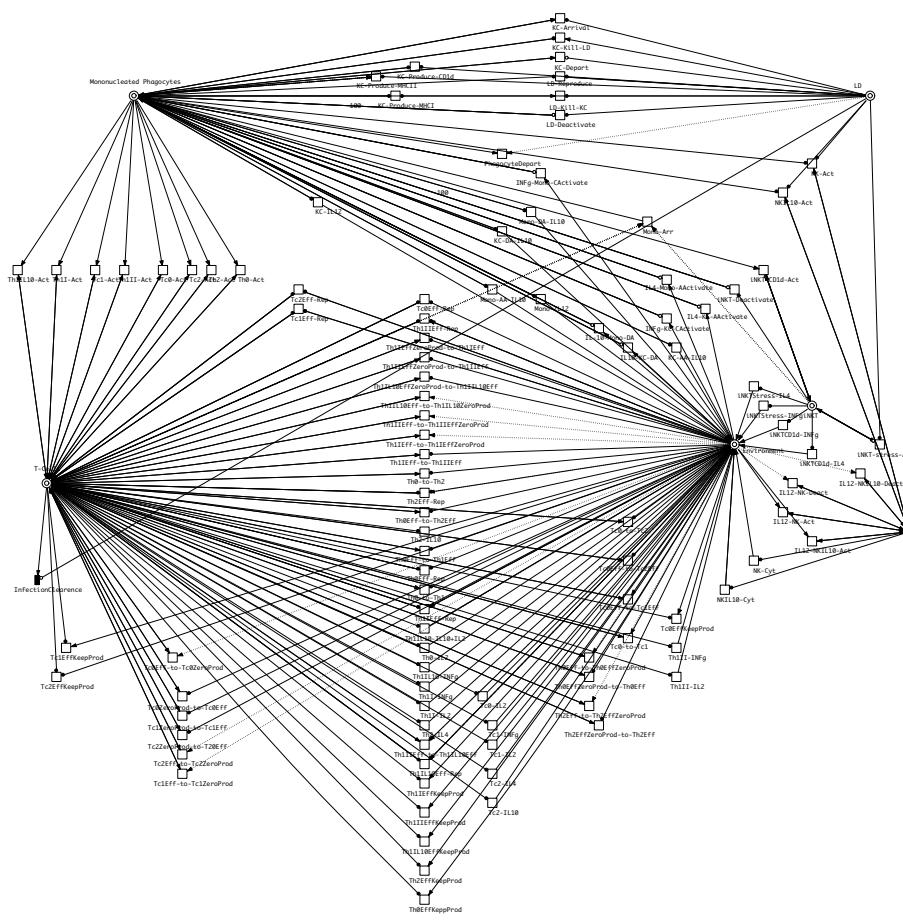
MODELLING Bio PETRI NETS



Literature

FROM LITERATURE TO MODELS

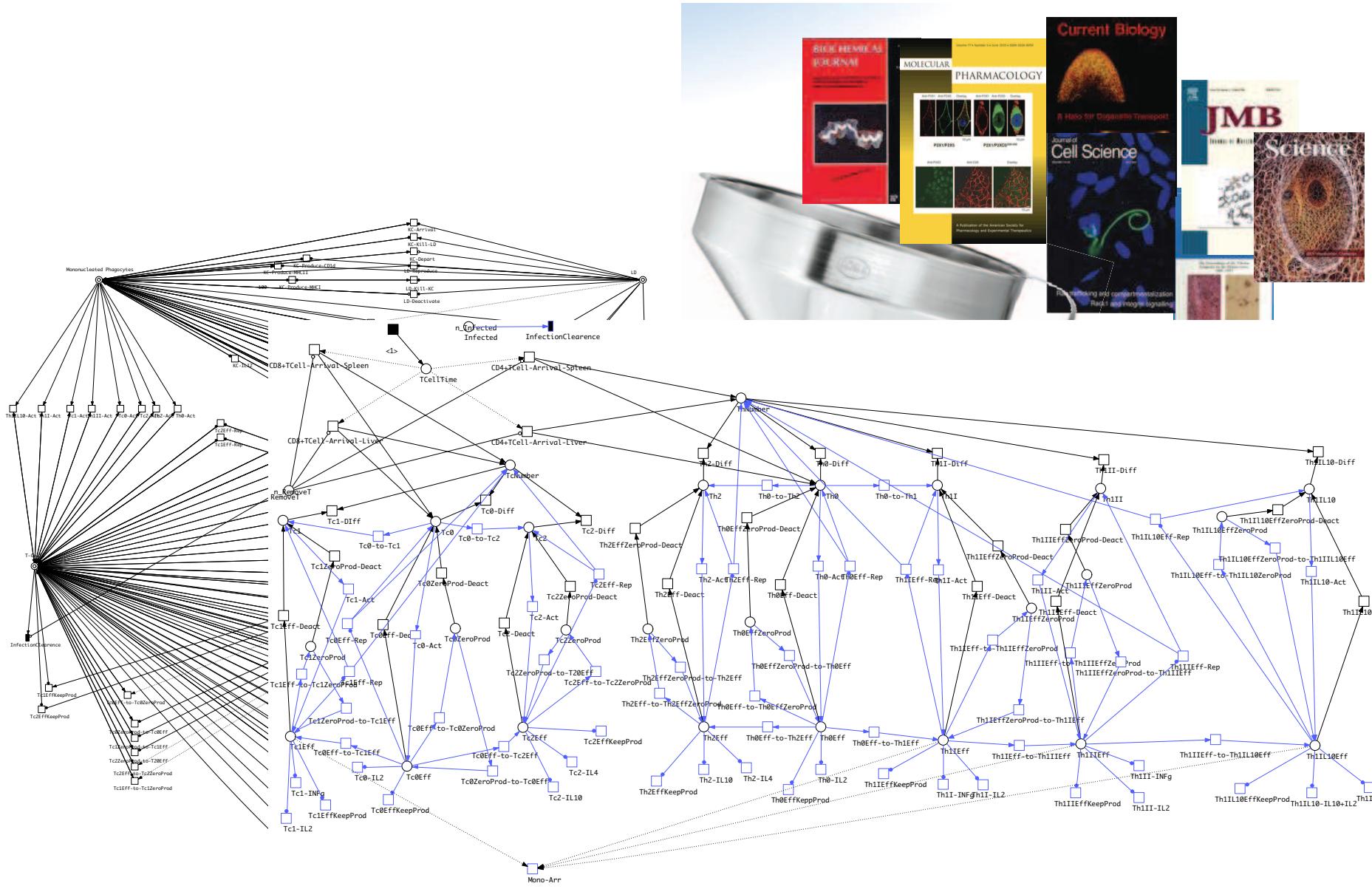
PN & BioModel Engineering



Literature

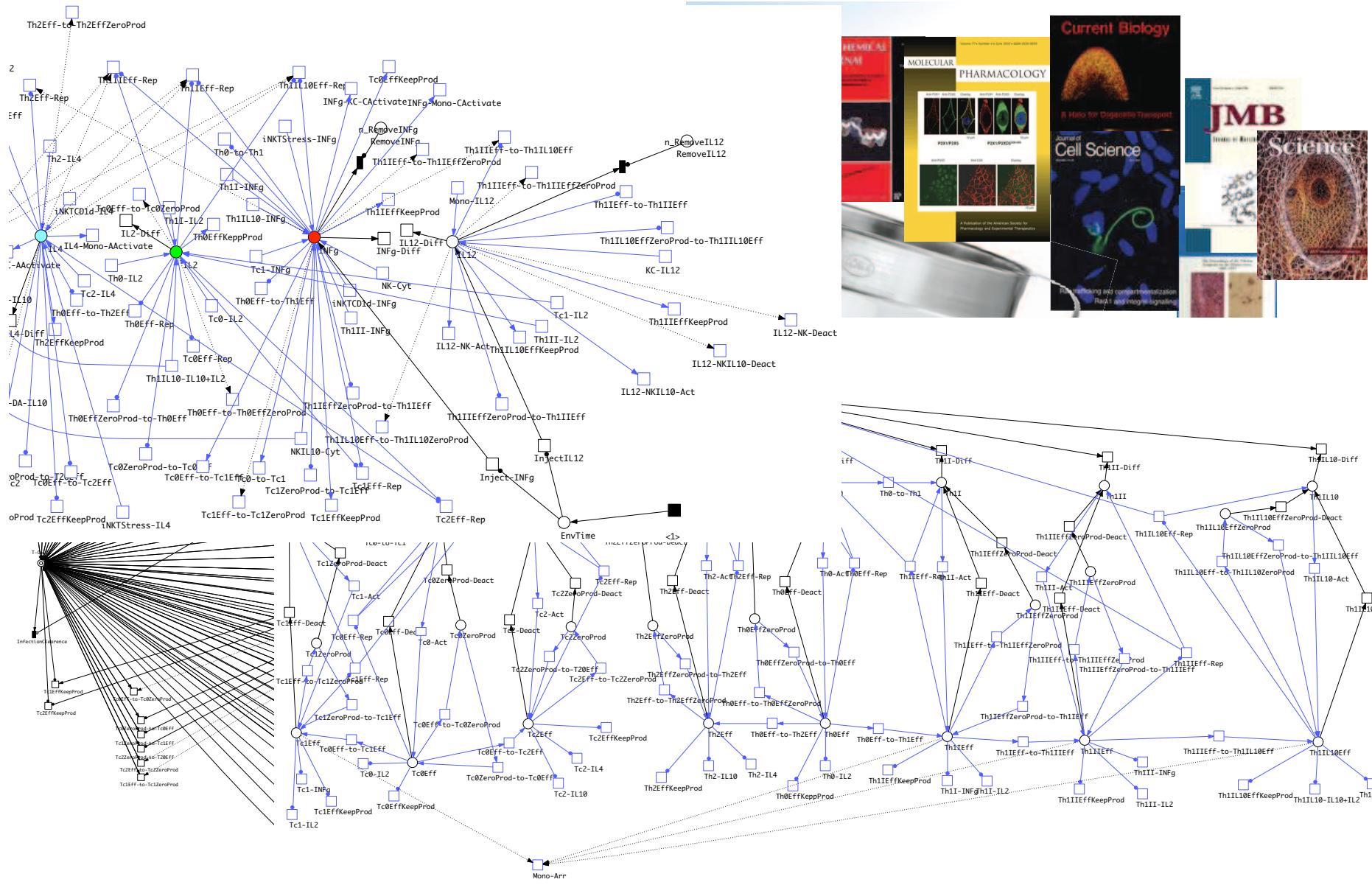
FROM LITERATURE TO MODELS

PN & BioModel Engineering



FROM LITERATURE TO MODELS

PN & BioModel Engineering



knowledge

-> **PROBLEM 1**

- > *uncertain*
- > *growing, changing*
- > *distributed over independent data bases, papers, journals, . . .*

various, mostly ambiguous representations

-> **PROBLEM 2**

- > *verbose descriptions*
- > *diverse graphical representations*
- > *contradictory and / or fuzzy statements*

network structure

-> **PROBLEM 3**

- > *tend to grow fast*
- > *dense, apparently unstructured*
- > *hard to read*

- knowledge

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-> **PROBLEM 2**

- network structure

- > *tend to grow fast*
- > *dense, apparently unstructured*
- > *hard to read*

-> **PROBLEM 3**

**MODELS ARE
PATCHWORKS
FULL OF ASSUMPTIONS**





- **readable & unambiguous**
-> *fault avoidant model construction*
- **locality - causality - concurrency**
- **compositional, hierarchical notations**
-> *logical and macro nodes*
- **executable**
-> *to experience the model, spec. causality*



- readable & unambiguous**
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- locality - causality - concurrency**
- compositional, hierarchical notations**
-> *logical and macro nodes*
- executable**
-> *to experience the model, spec. causality*
- umbrella with unifying power**
-> *interpretation in qualitative / stochastic / continuous / hybrid paradigms*
- Petri net theory -> model validation**
-> *P/T-invariants, partial order interpretation of T-invariants, conclusions CTI/CPI -> behavioural properties*
-> *STP, reduction rules, . . .*

T- INVARIANTS

(ELEMENTARY MODES)

(EXTREME PATHWAYS)

(GENERIC PATHWAYS)

INCIDENCE MATRIX C

PN & BioModel Engineering

- a representation of the net structure

=> stoichiometric matrix

P \ T	t1	...	tj	...	tm
p1					
pi			cij		
:			Δt_j		
pn					

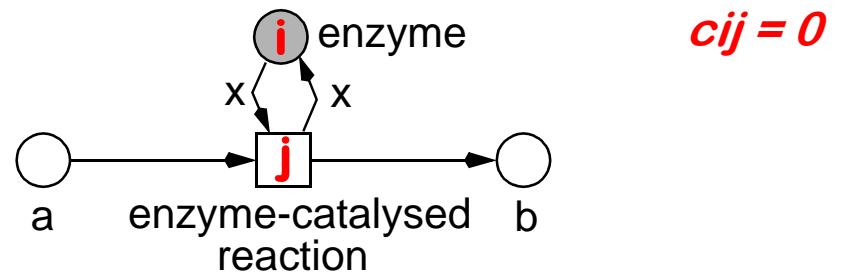
$$c_{ij} = (p_i, t_j) = F(t_j, p_i) - F(p_i, t_j) = \Delta t_j(p_i)$$

$$\Delta t_j = \Delta t_j(*)$$

- matrix entry c_{ij} :
token change in place p_i by firing of transition t_j

- matrix column Δt_j :
vector describing the change of the whole marking by firing of t_j

- side-conditions are neglected



- Lautenbach, 1973
- T-invariant x
 - > integer solution of $Cx = 0, x \neq 0, x \geq 0$
- support of a T-invariant x -> $\text{supp}(x)$
 - > set of transitions involved, i.e. $x(i) \neq 0$
- minimal T-invariants
 - > there is no T-invariant with a smaller support
 - > 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

$$kx = \sum_i a_i x_i$$

- 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 occurring one after the other
-> substance / signal flow
2. *relative transition firing rates* **-> steady state behaviour**
of transitions occurring permanently & concurrently
-> steady state behaviour

- a minimal T-invariant defines a connected subnet

- > the T-invariant's transitions (the support),
+ all their pre- and post-places
+ the arcs in between
- > pre-set of support = post-set of support

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-> steady state behaviour

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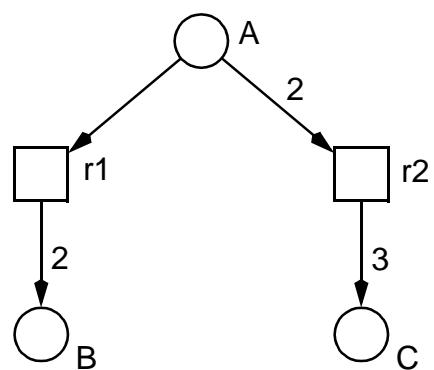
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$r1: A \rightarrow 2 B$

$r2: 2 A \rightarrow 3 C$

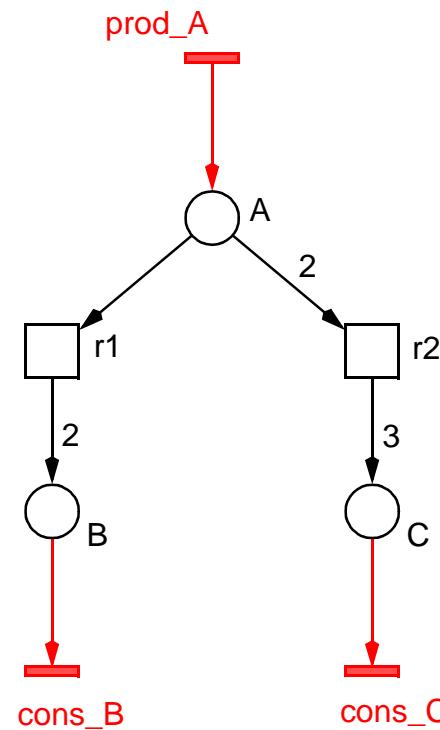
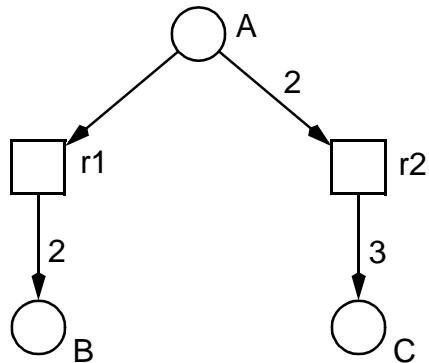
$r1: A \rightarrow 2 B$

$r2: 2 A \rightarrow 3 C$



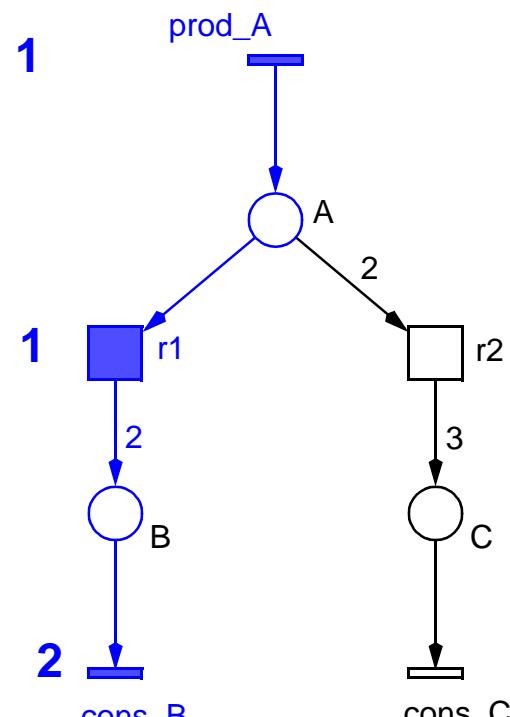
$r1: A \rightarrow 2 B$

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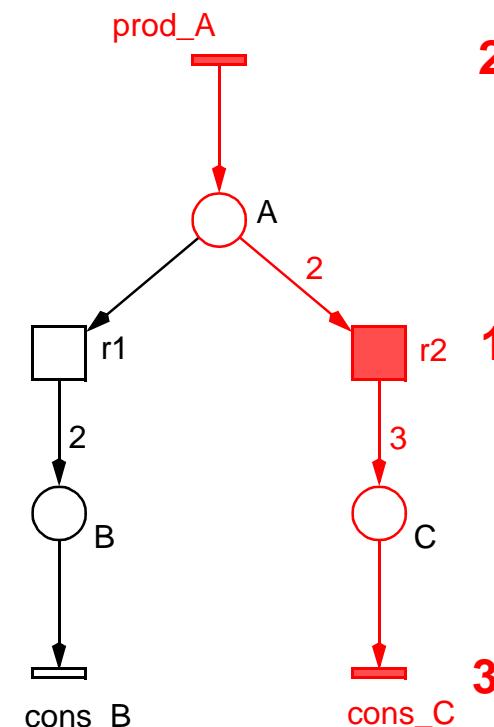


$r1: A \rightarrow 2 B$

$r2: 2 A \rightarrow 3 C$



T-INVARIANT 1

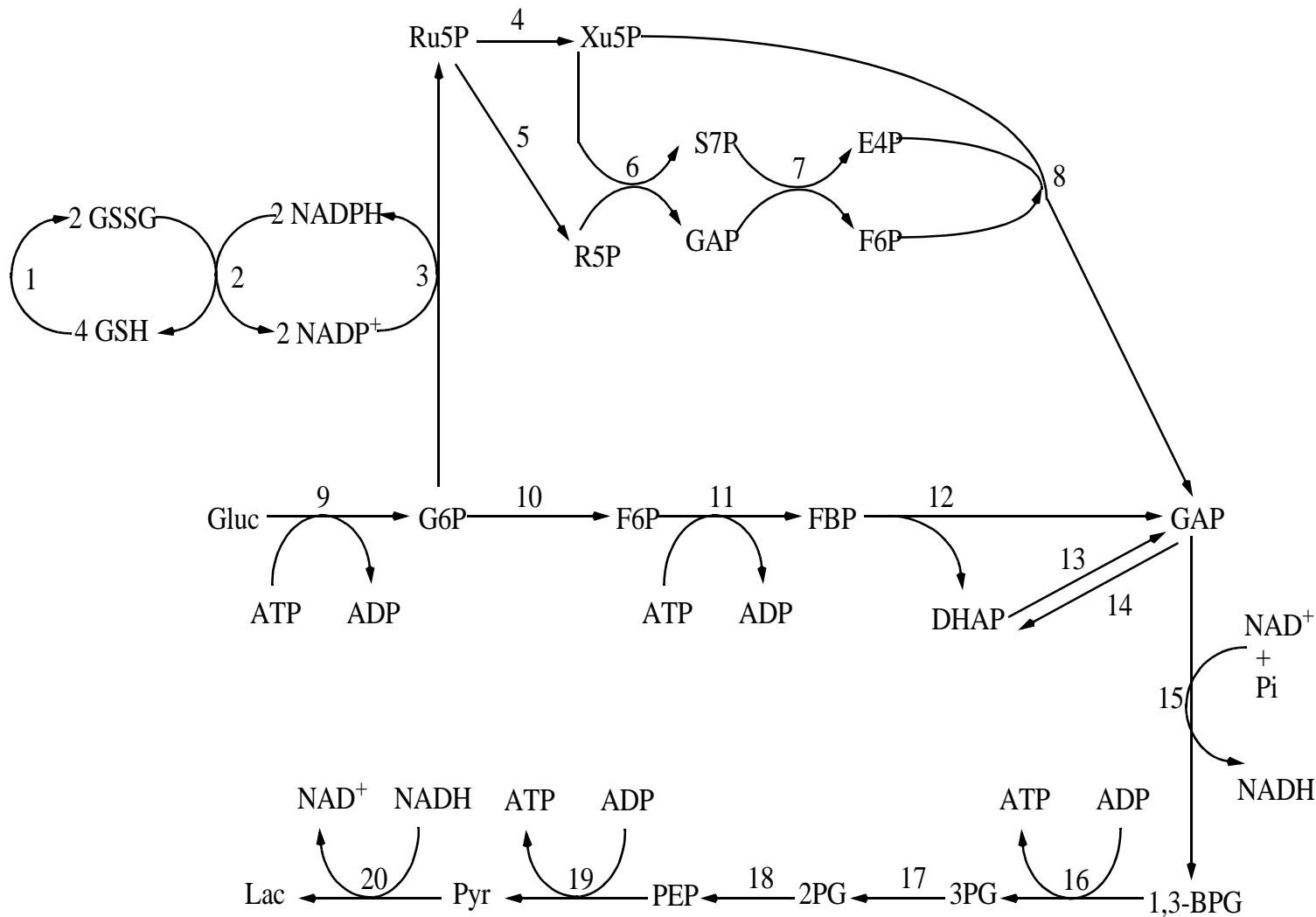


T-INVARIANT 2

Ex1 - Glycolysis and Pentose Phosphate Pathway

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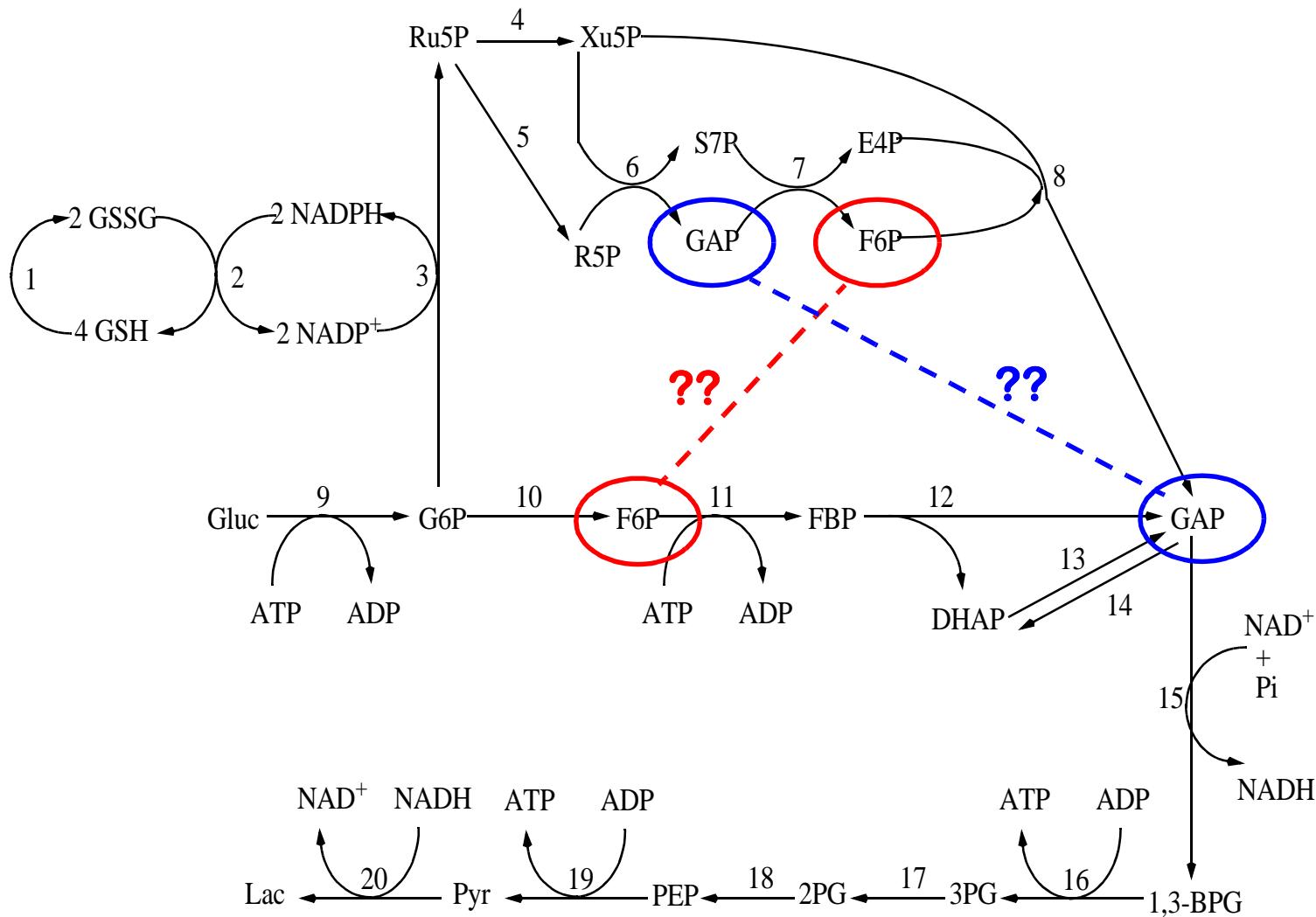
[Reddy 1993]



Ex1 - Glycolysis and Pentose Phosphate Pathway

PN & BioModel Engineering

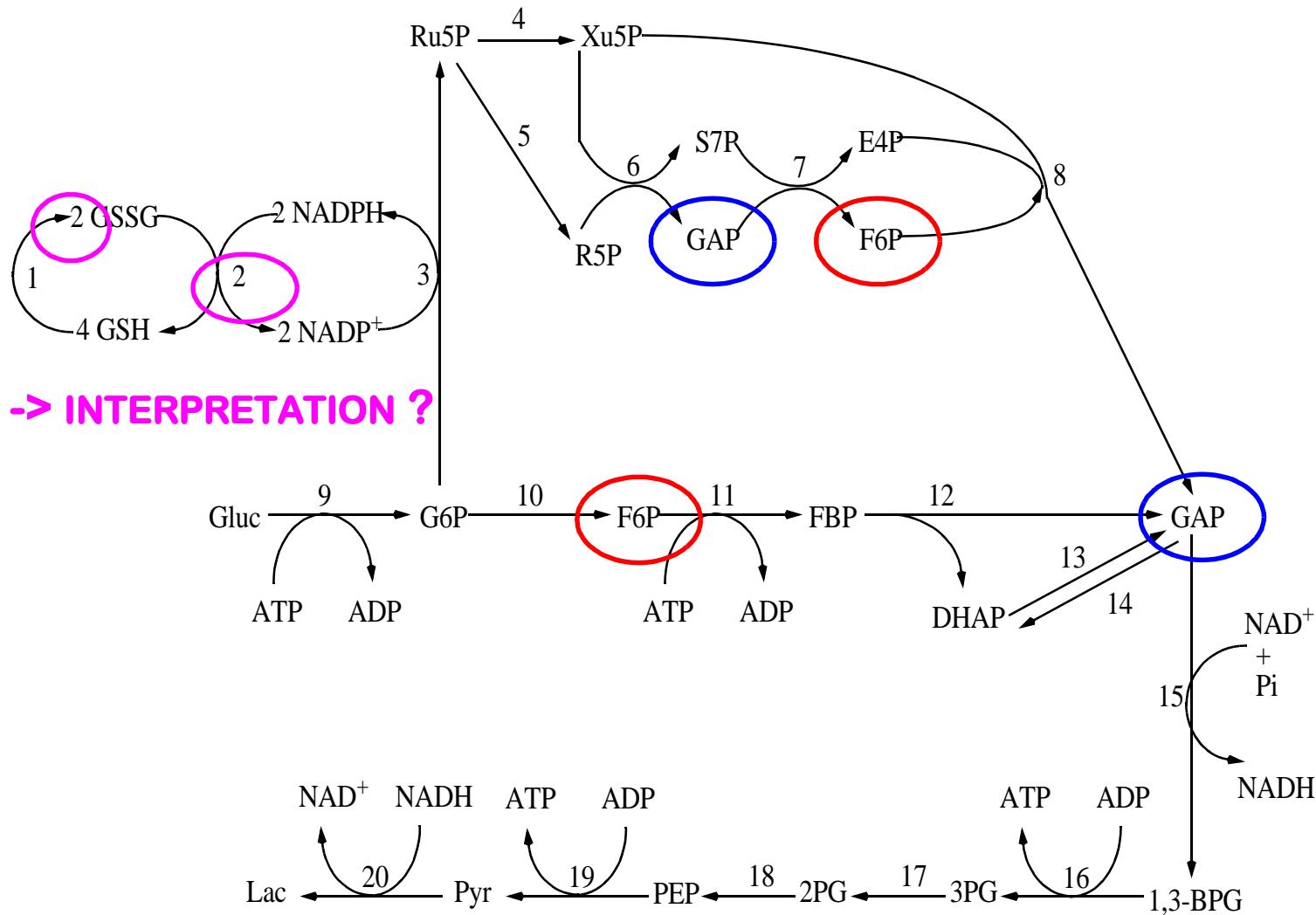
[Reddy 1993]



Ex1 - Glycolysis and Pentose Phosphate Pathway

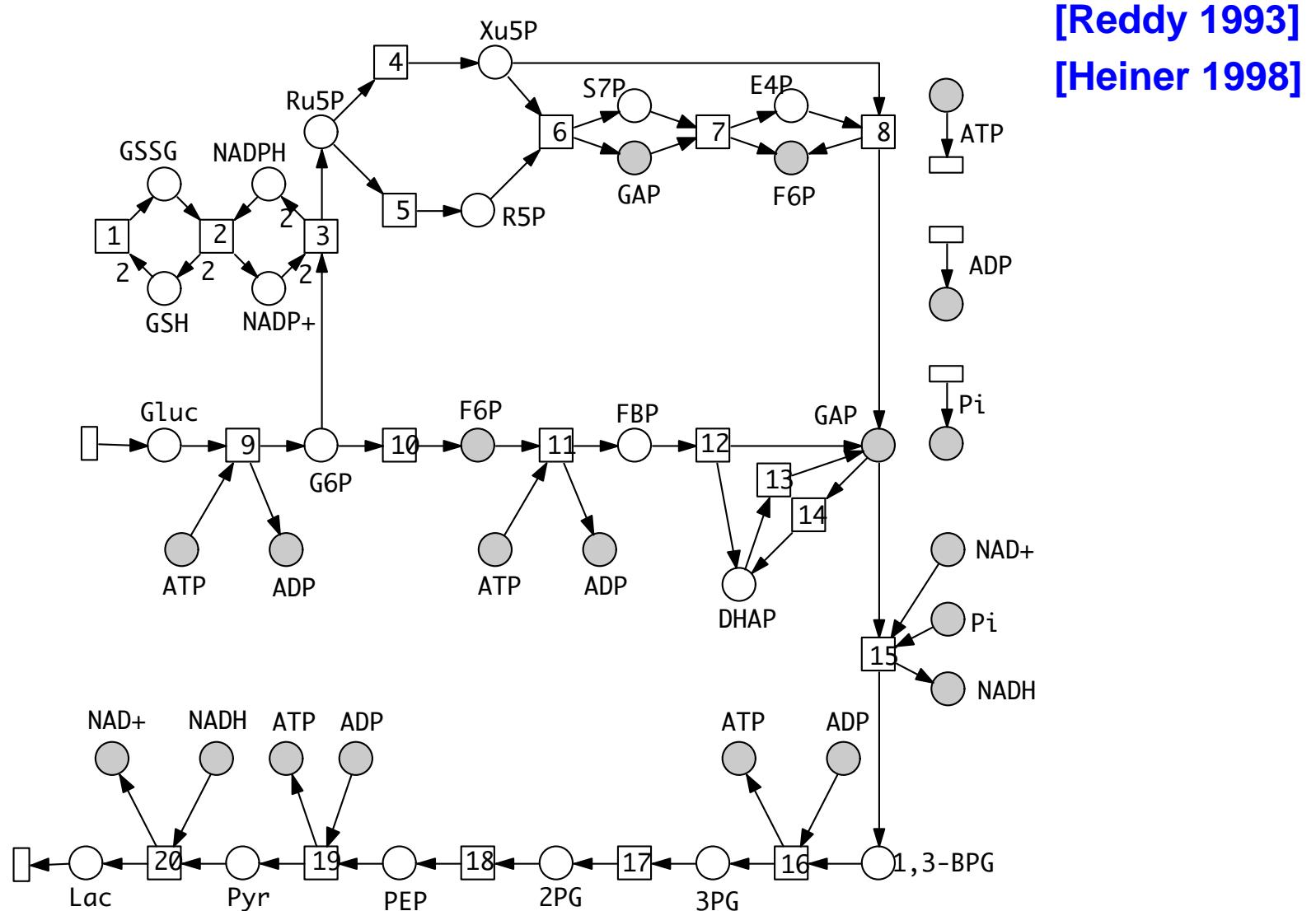
PN & BioModel Engineering

[Reddy 1993]



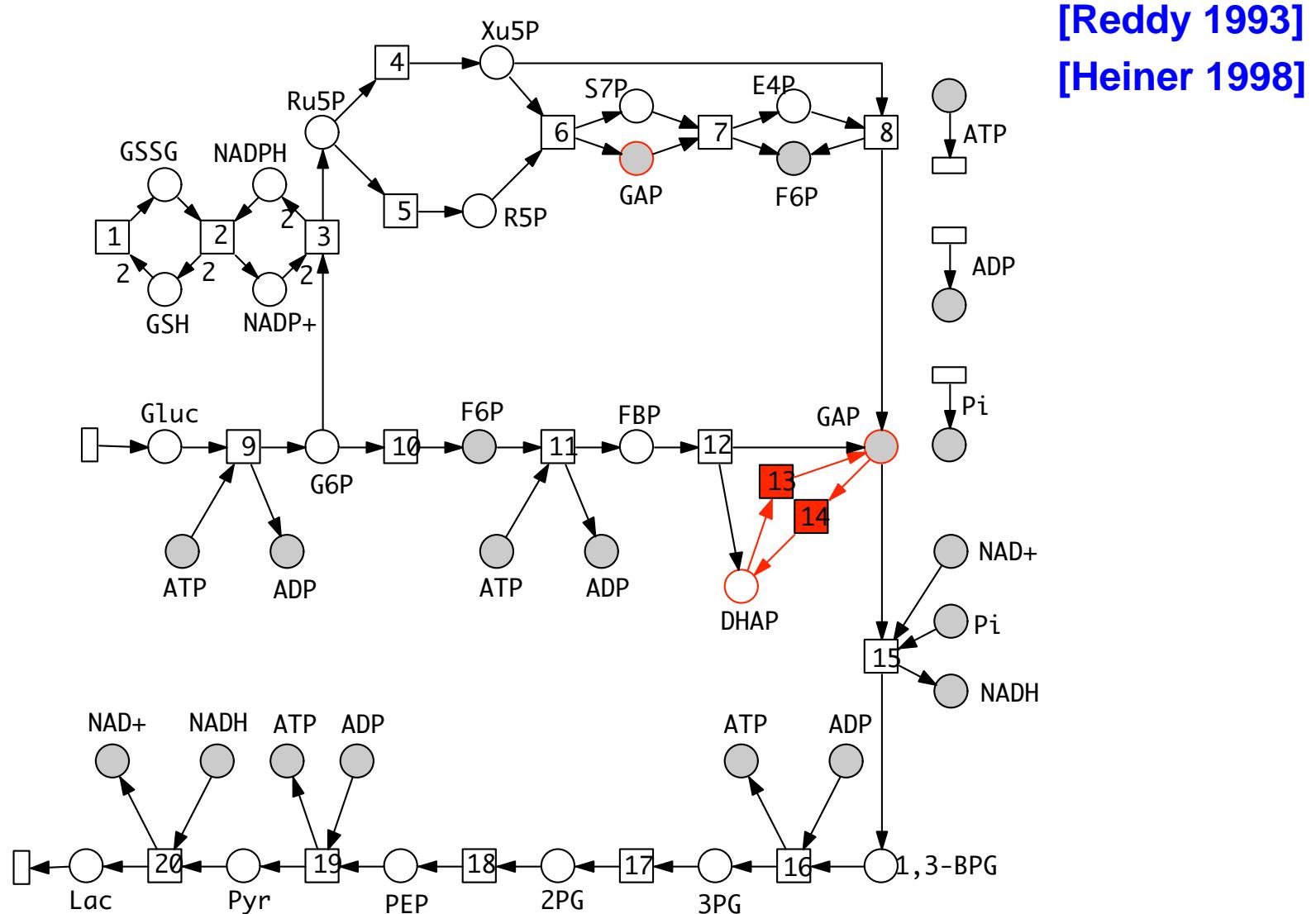
Ex1 - Glycolysis and Pentose Phosphate Pathway

PN & BioModel Engineering



Ex1 - Glycolysis and Pentose Phosphate Pathway

PN & BioModel Engineering

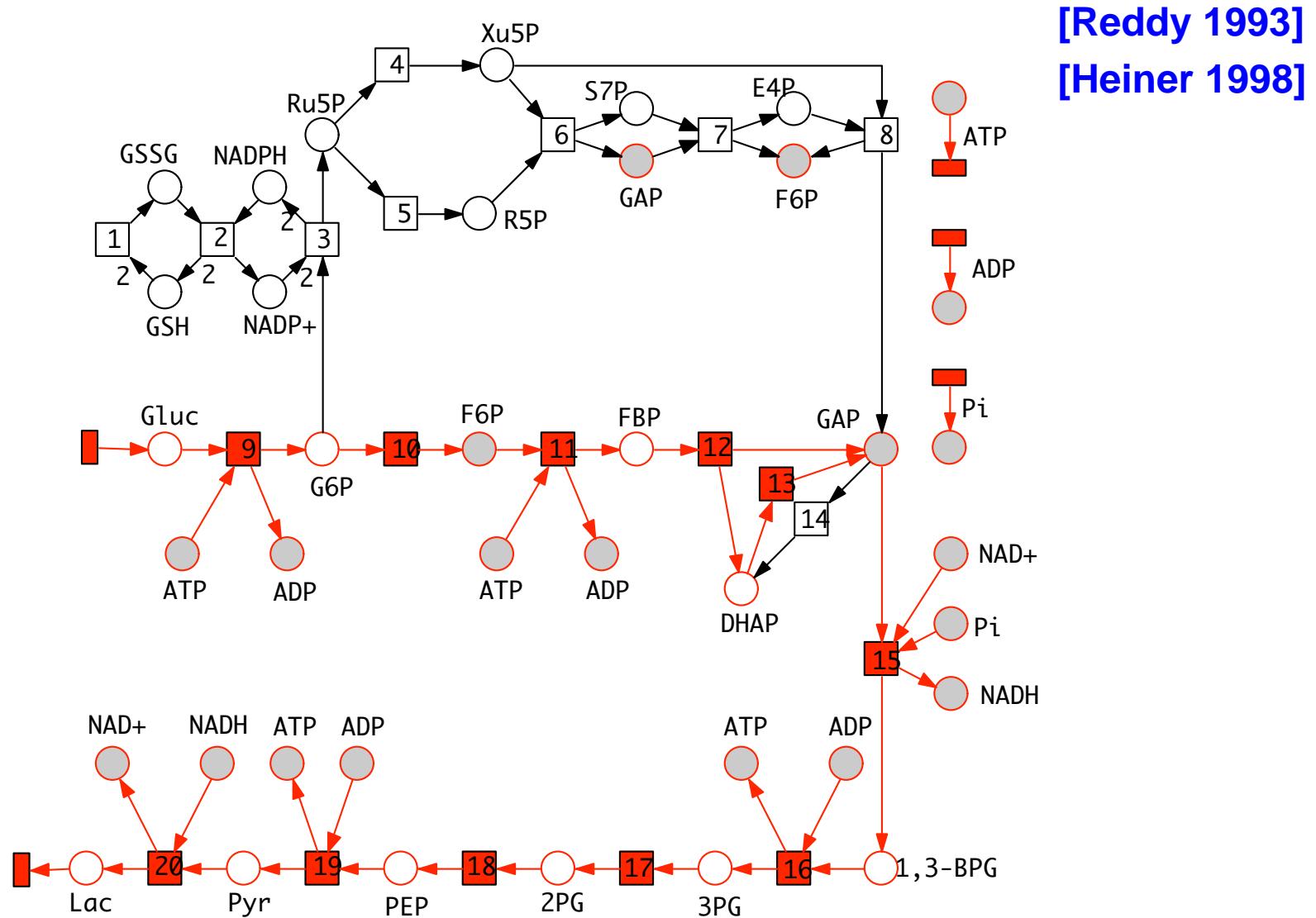


[Reddy 1993]

[Heiner 1998]

Ex1 - Glycolysis and Pentose Phosphate Pathway

PN & BioModel Engineering

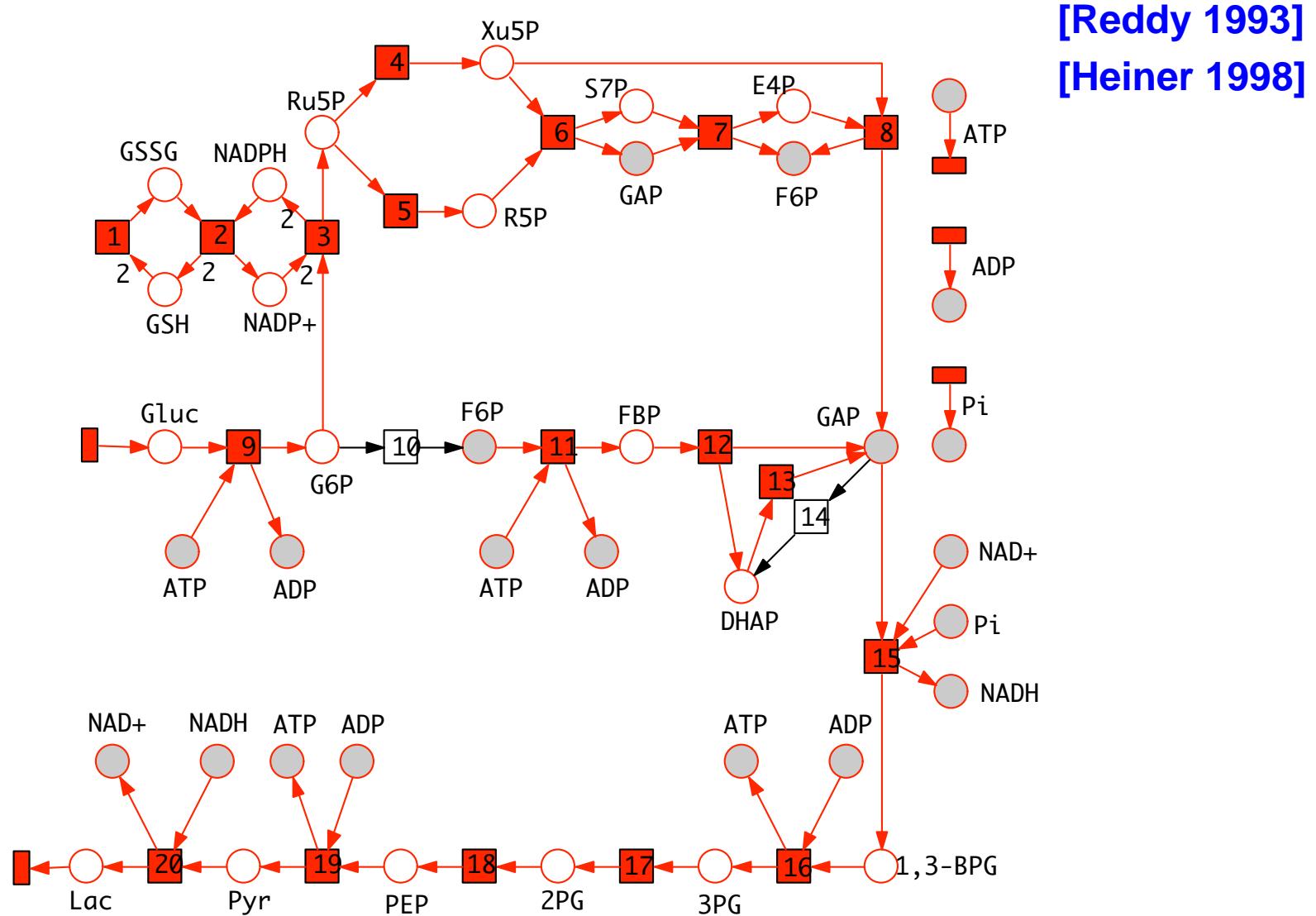


[Reddy 1993]

[Heiner 1998]

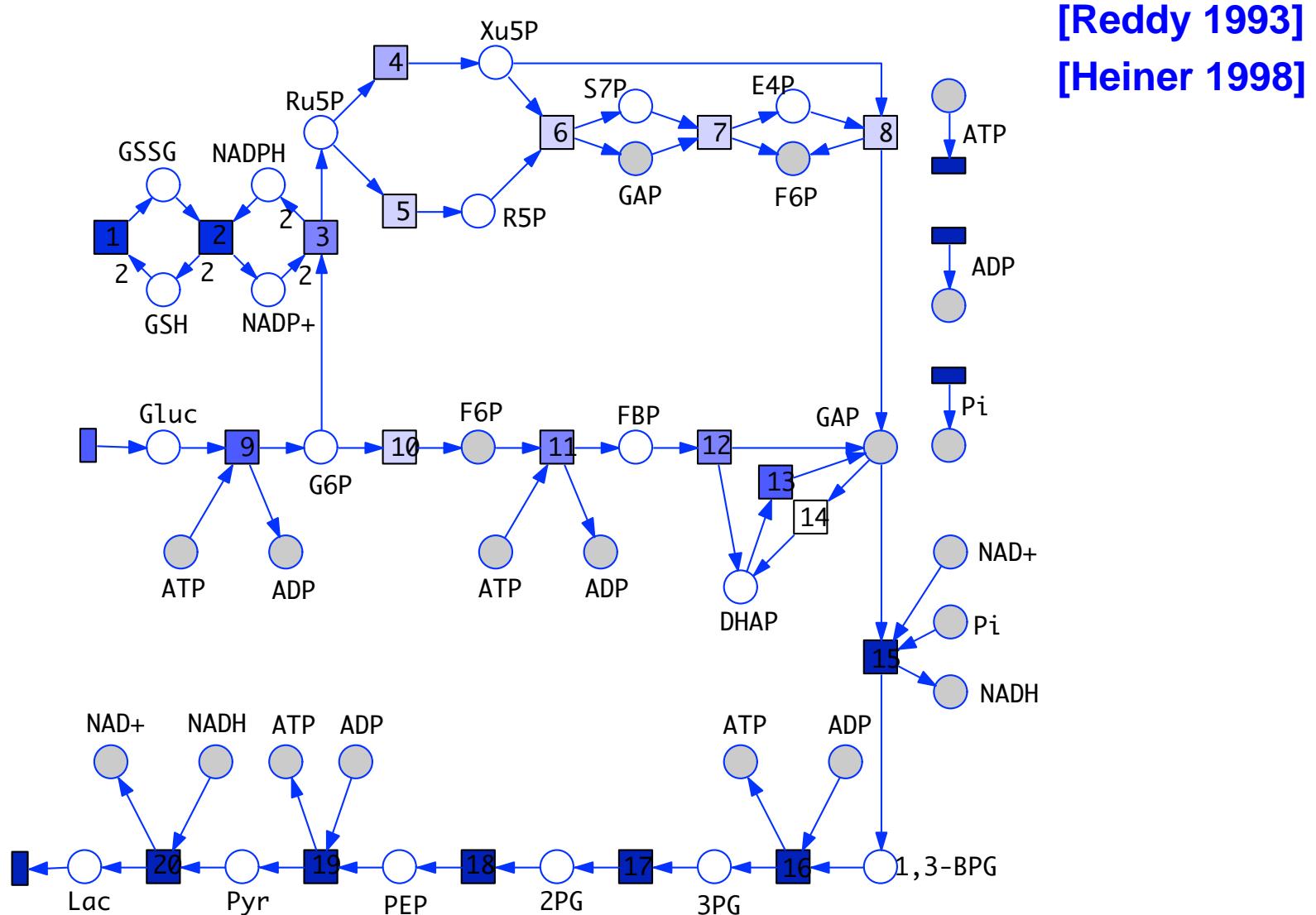
Ex1 - Glycolysis and Pentose Phosphate Pathway

PN & BioModel Engineering

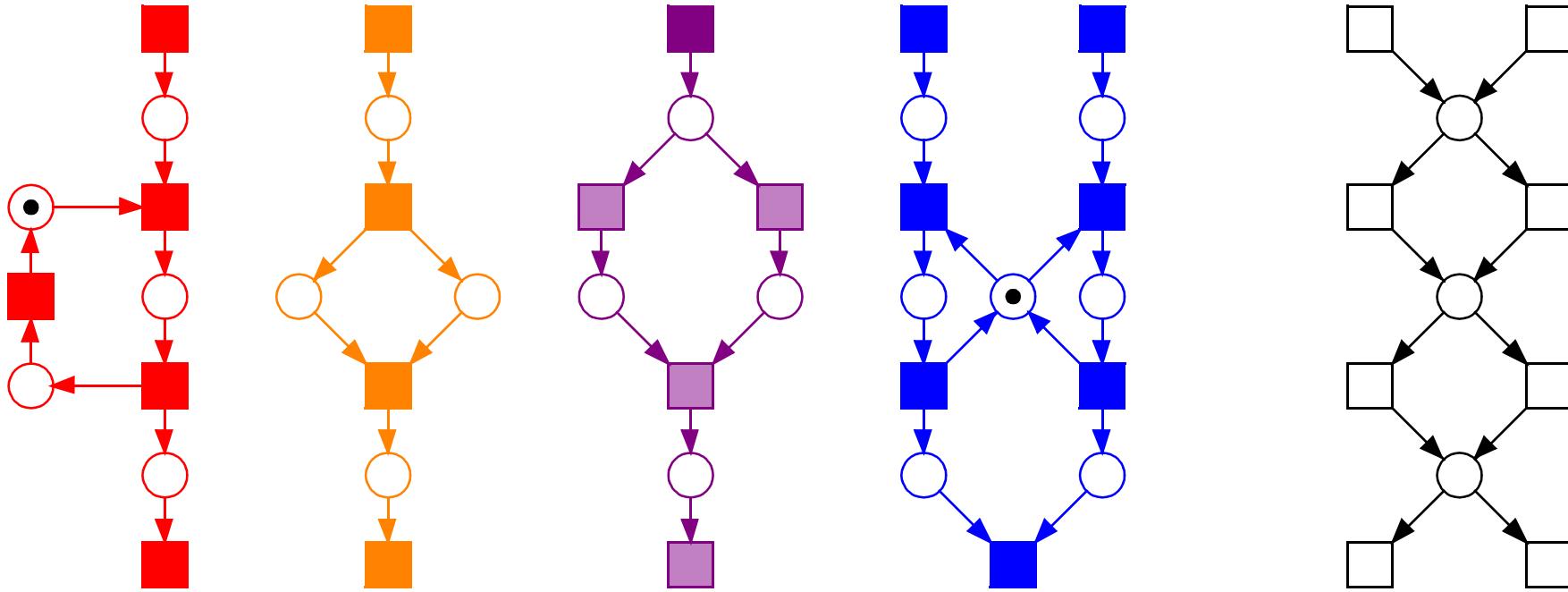


Ex1 - Glycolysis and Pentose Phosphate Pathway

PN & BioModel Engineering



- T-invariants may contain any structure



- minimal T-invariants generally overlap
-> combinatorial effect brings explosion in the number of min. T-invariants (2^4)

MODULARIZATION BY T-INVARIANTS

- Let X denote the set of all (non-trivial) minimal T-invariants x of a given PN.

- **dependency relation**

*Two transitions i, j depend on each other,
if they always appear together in all minimal T-invariants x , i.e.*

$$\forall(x \in X) : \text{supp}(x)(i) = \text{supp}(x)(j)$$

- **equivalence relation** in the transition set, leading to a partition of T

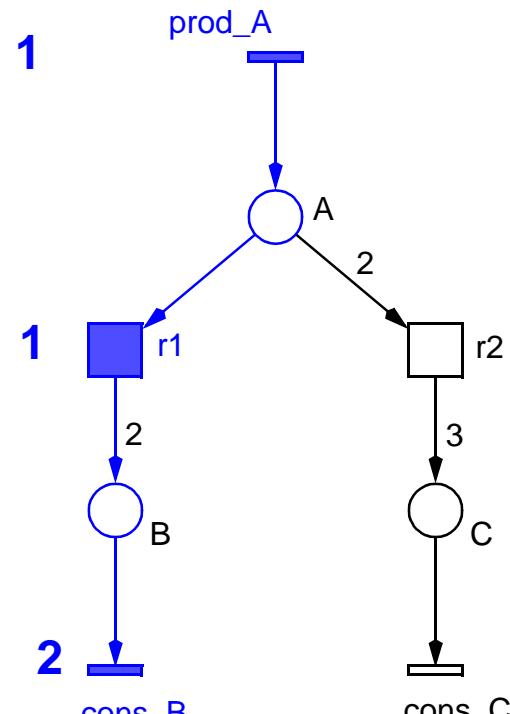
- > *reflexive*
- > *symmetric*
- > *transitive*

- **the equivalence classes** A represent maximal ADT-sets

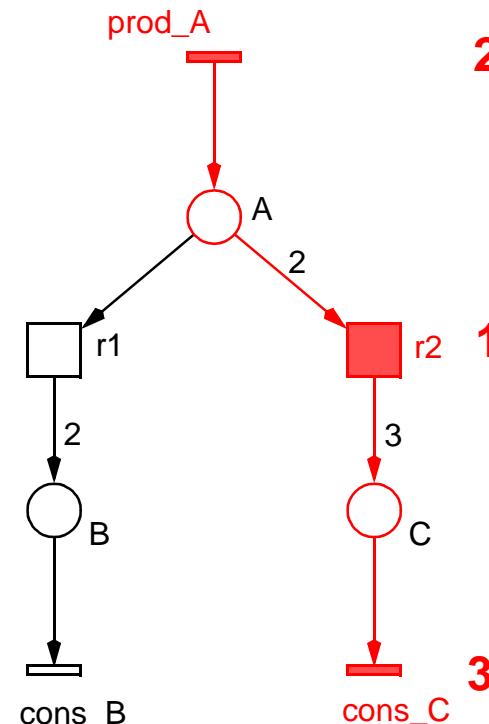
$$\forall(x \in X) : A \subseteq \text{supp}(x) \vee A \cap \text{supp}(x) = \emptyset$$

$r1: A \rightarrow 2 B$

$r2: 2 A \rightarrow 3 C$



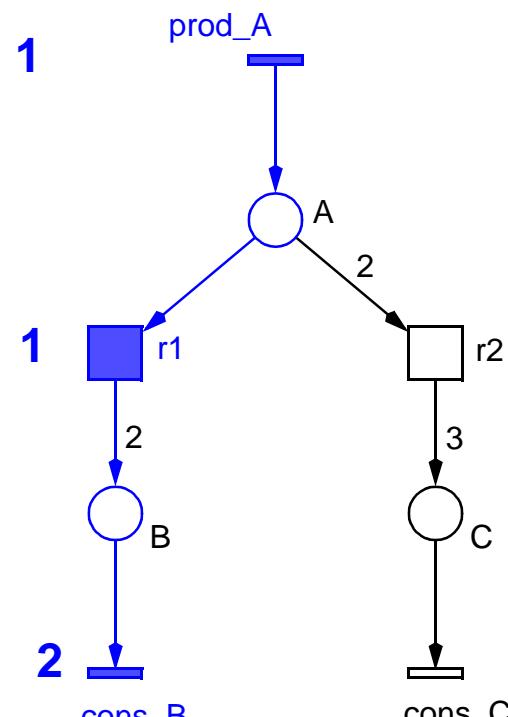
T-INVARIANT 1



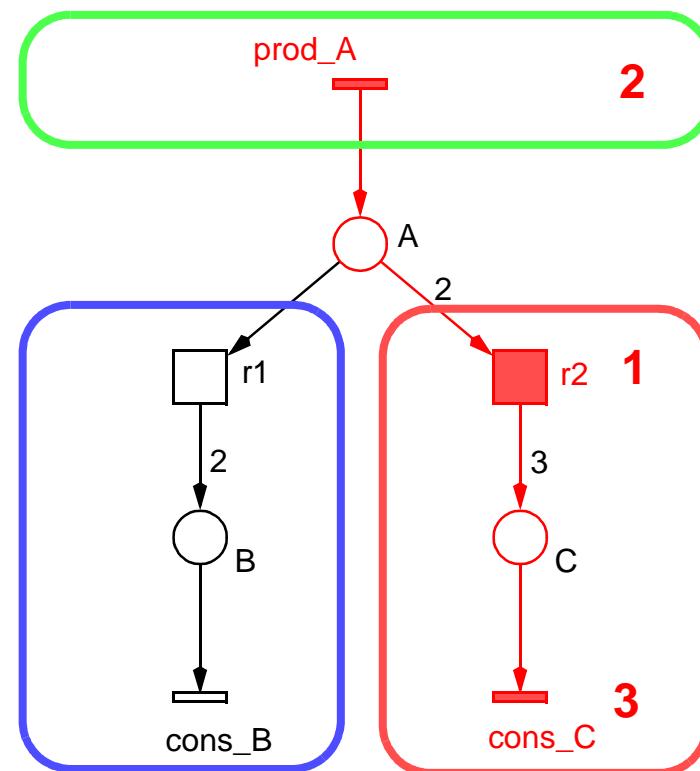
T-INVARIANT 2

$r1: A \rightarrow 2 B$

$r2: 2 A \rightarrow 3 C$



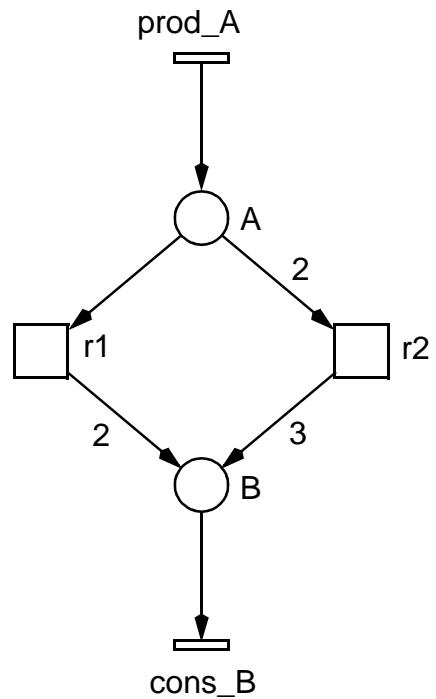
T-INVARIANT 1



T-INVARIANT 2

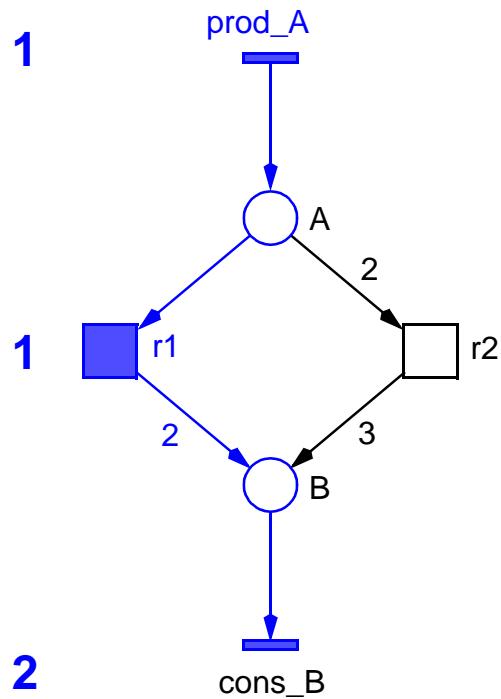
$r1: A \rightarrow 2 B$

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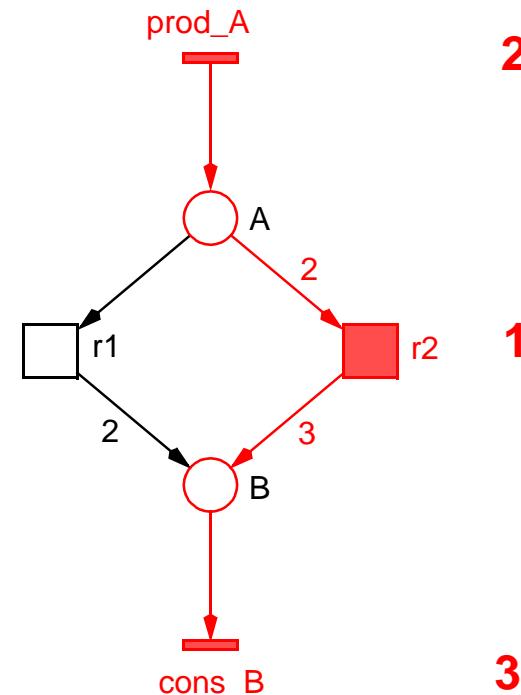


$r1: A \rightarrow 2 B$

$r2: 2 A \rightarrow 3 B$



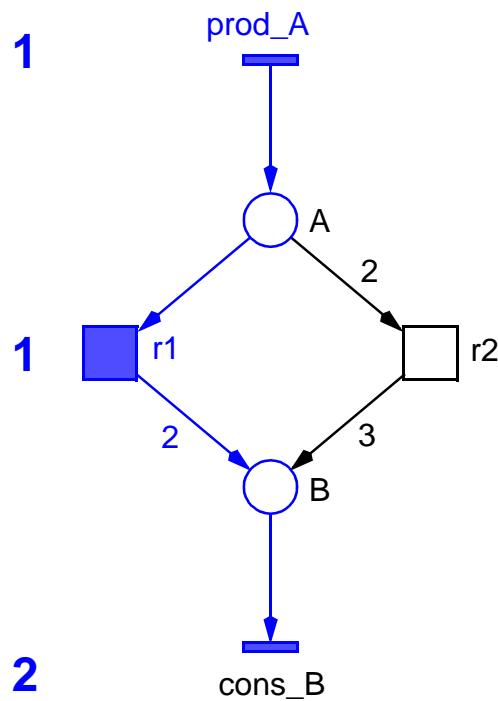
T-INVARIANT 1



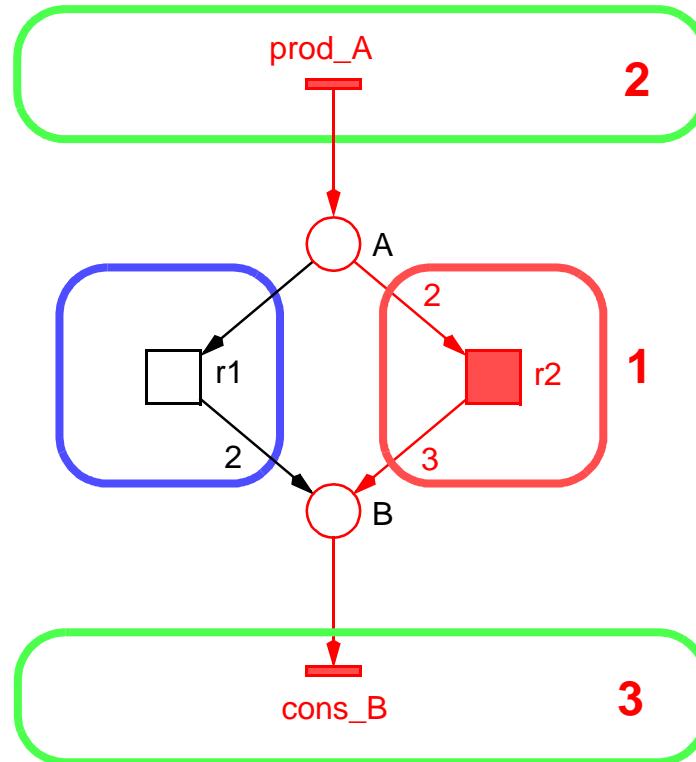
T-INVARIANT 2

$r1: A \rightarrow 2 B$

$r2: 2 A \rightarrow 3 B$



T-INVARIANT 1



T-INVARIANT 2

□ maximal ADT-sets

- > *disjunctive subnets*
- > *not necessarily connected*

minimal T-invariants

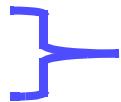
- > *overlapping subnets*
- > *connected*

□ interpretation

- > *structural decomposition into rather small subnets*
- > *smallest biologically meaningful functional units*
- > *building blocks*

□ variations

- > *with / without trivial T-invariants*
- > *whole / partial set of T-invariants*



not necessarily maximal ADT-sets

□ classification of all transitions based on the T-invariants' support

- maximal ADT-sets

- > *not necessarily connected*

- further decomposition into connected ADT-sets

- > *possibly according to primary compounds, only,
i.e. neglecting connections by auxiliary compounds*
 - > *non-maximal ADT-sets*

- coarse network structure, definition

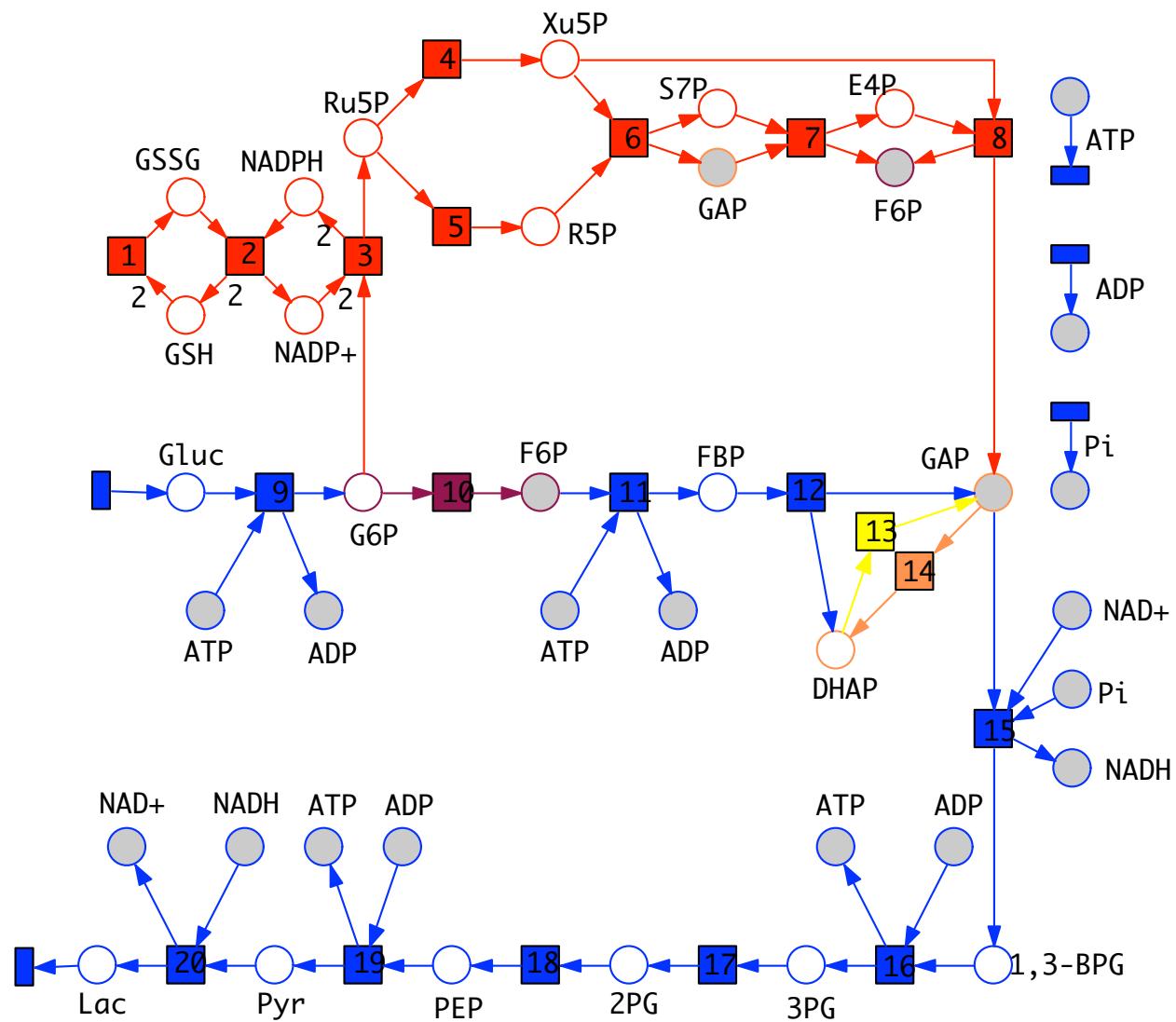
- > *macro transitions* - *abstract from connected ADT-sets*
 - > *places* - *interface between functional units*
 - > *(minimal) path* - *(minimal) T-invariant*

- coarse network structure, what for?

- > *set of T-invariants gets structured*
 - > *better understanding of the net behaviour*

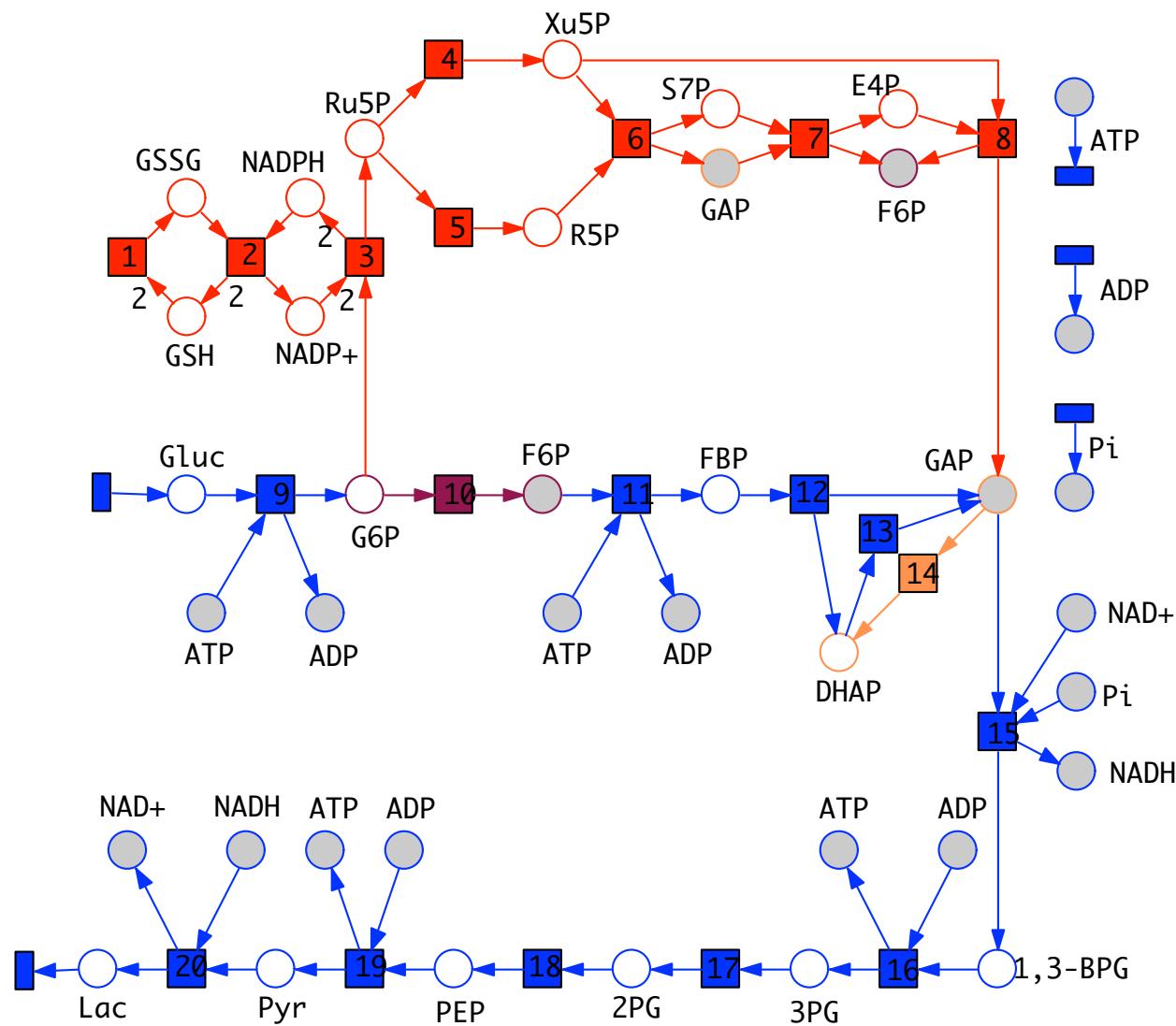
Ex1 - Glycolysis and Pentose Phosphate Pathway

PN & BioModel Engineering



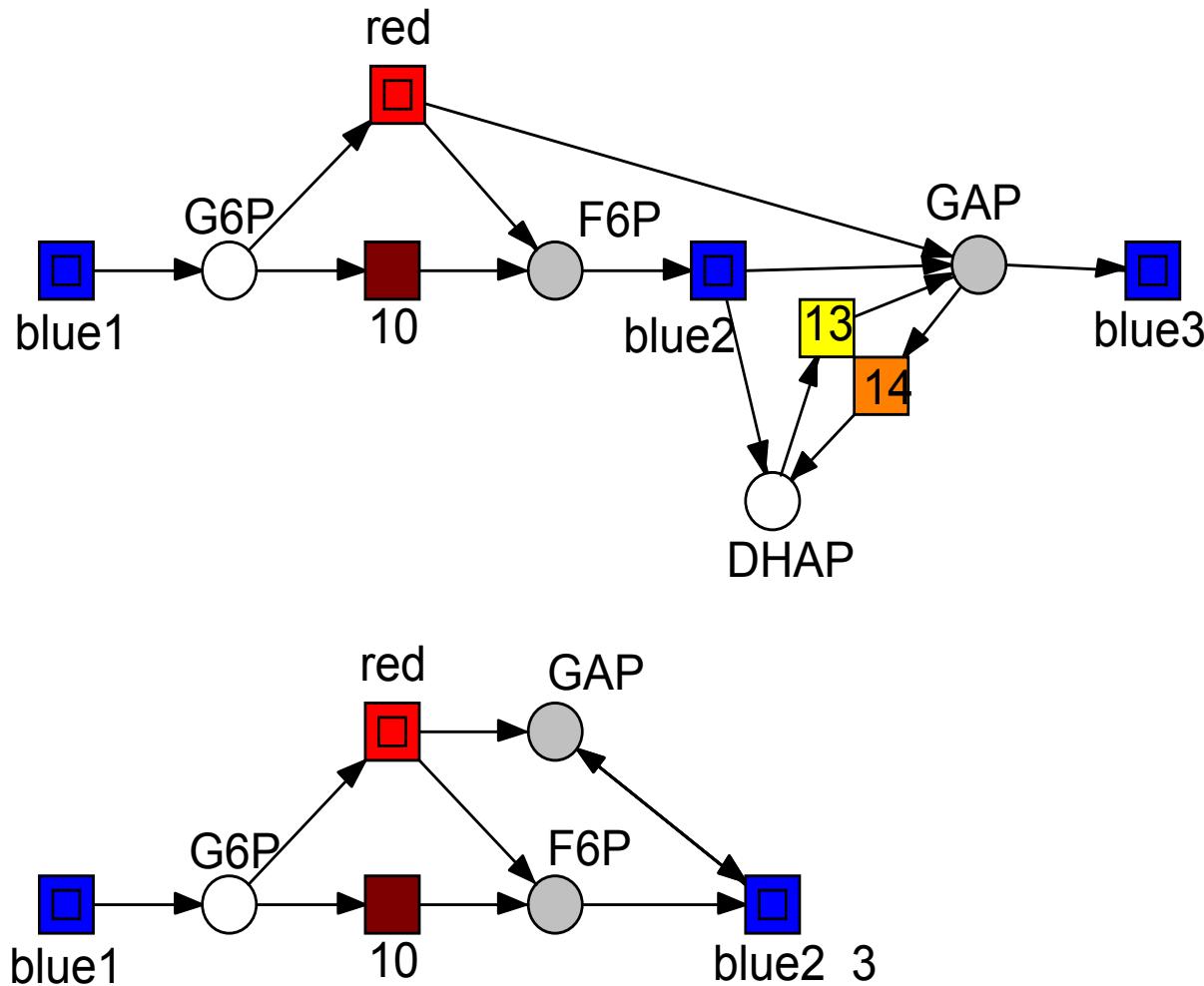
Ex1 - Glycolysis and Pentose Phosphate Pathway

PN & BioModel Engineering



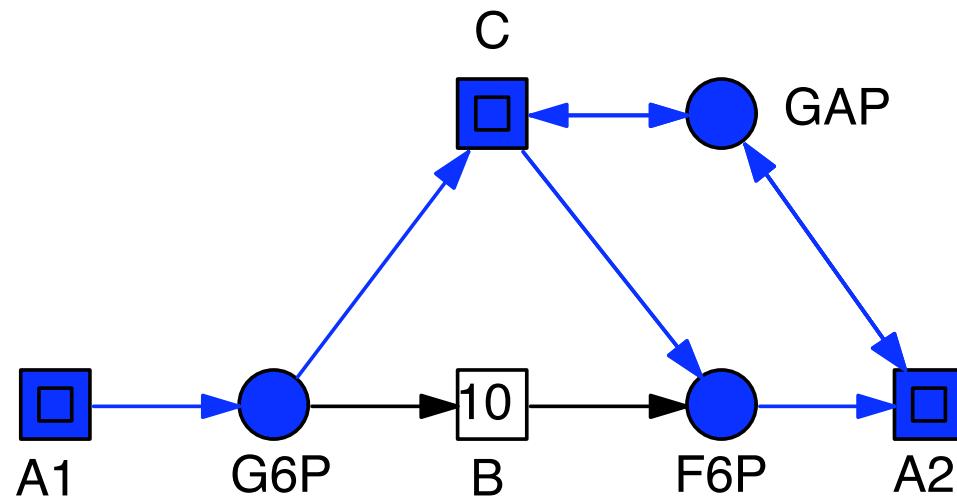
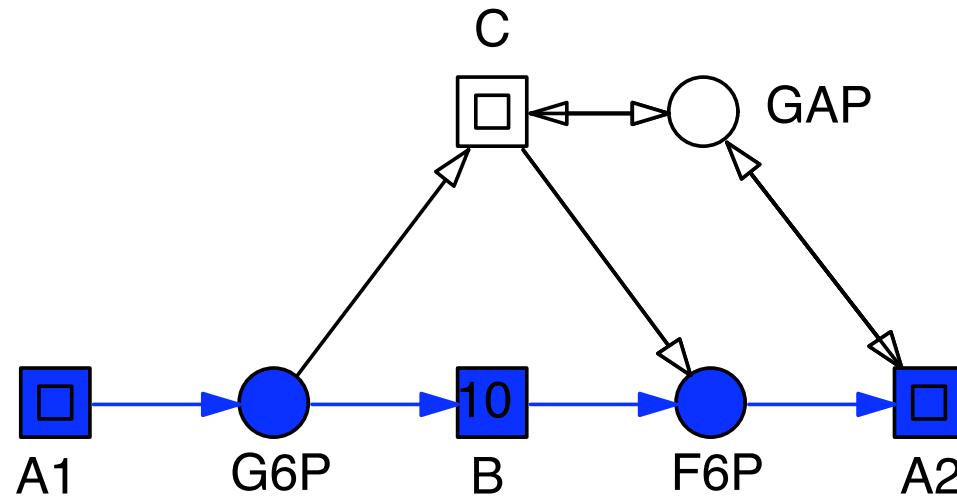
Ex1 - Glycolysis and Pentose Phosphate Pathway

PN & BioModel Engineering



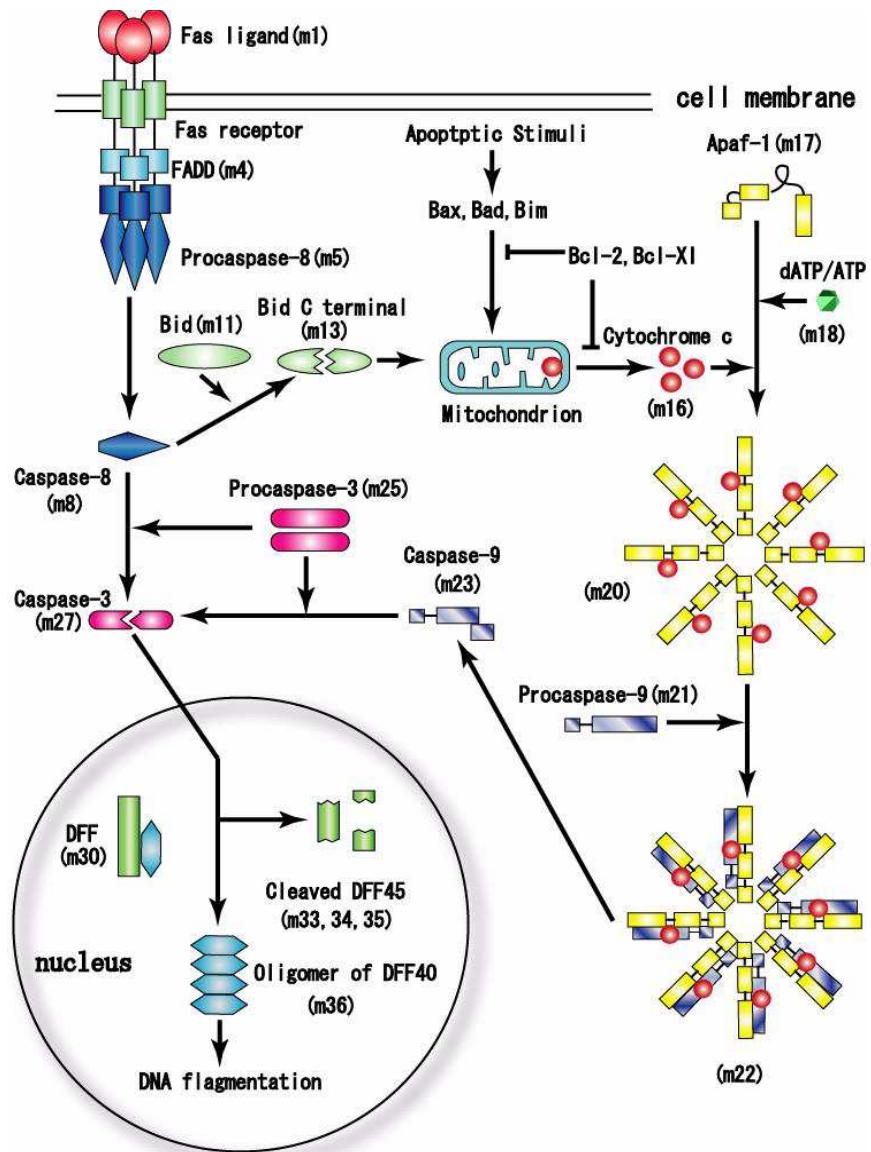
Ex1 - Glycolysis and Pentose Phosphate Pathway

PN & BioModel Engineering



Ex2 - APOPTOSIS IN MAMMALIAN CELLS

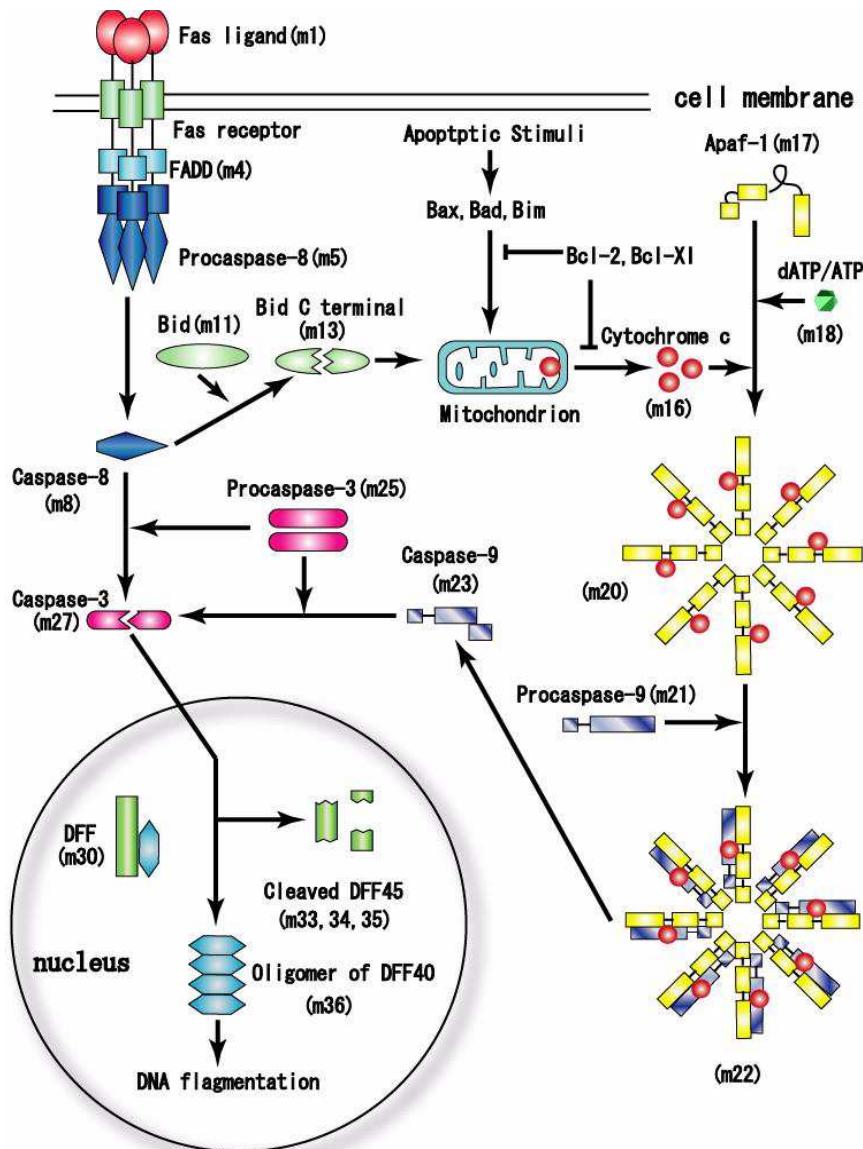
PN & BioModel Engineering



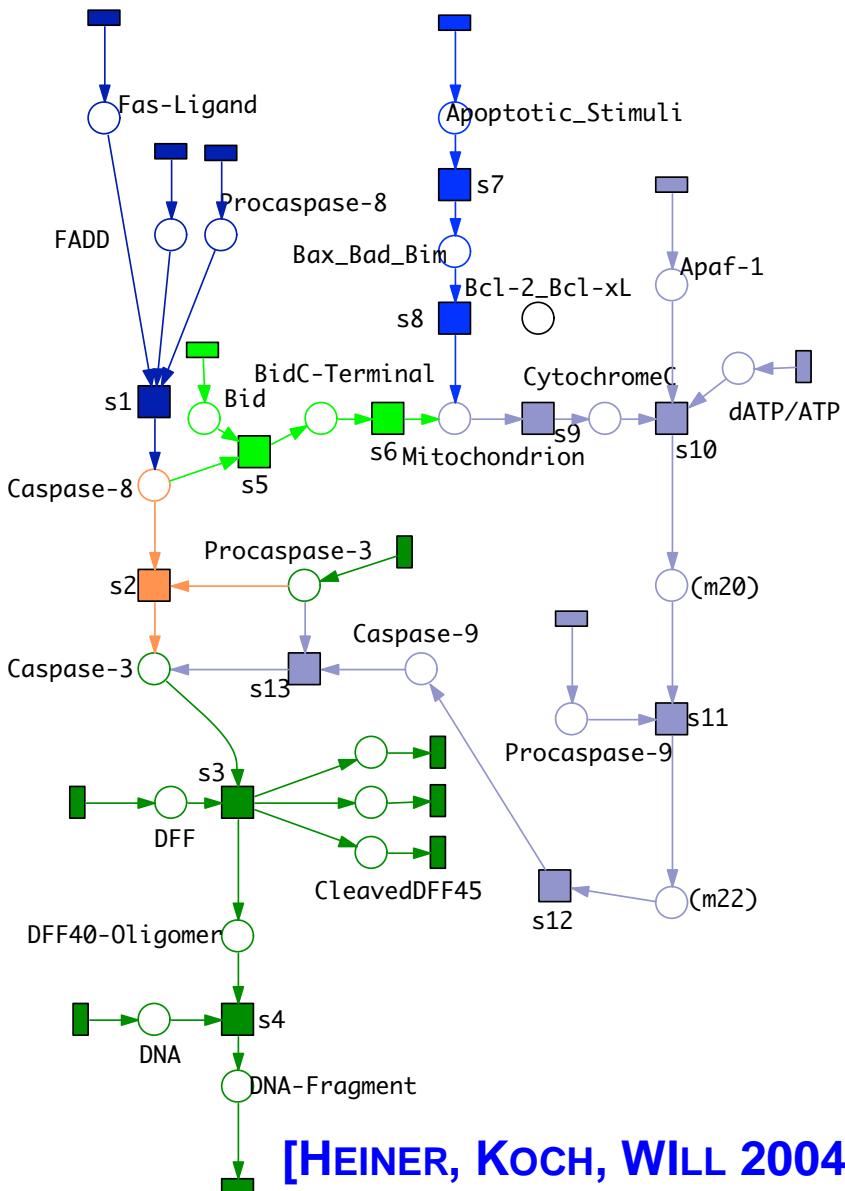
[GON 2003]

Ex2 - APOPTOSIS IN MAMMALIAN CELLS

PN & BioModel Engineering



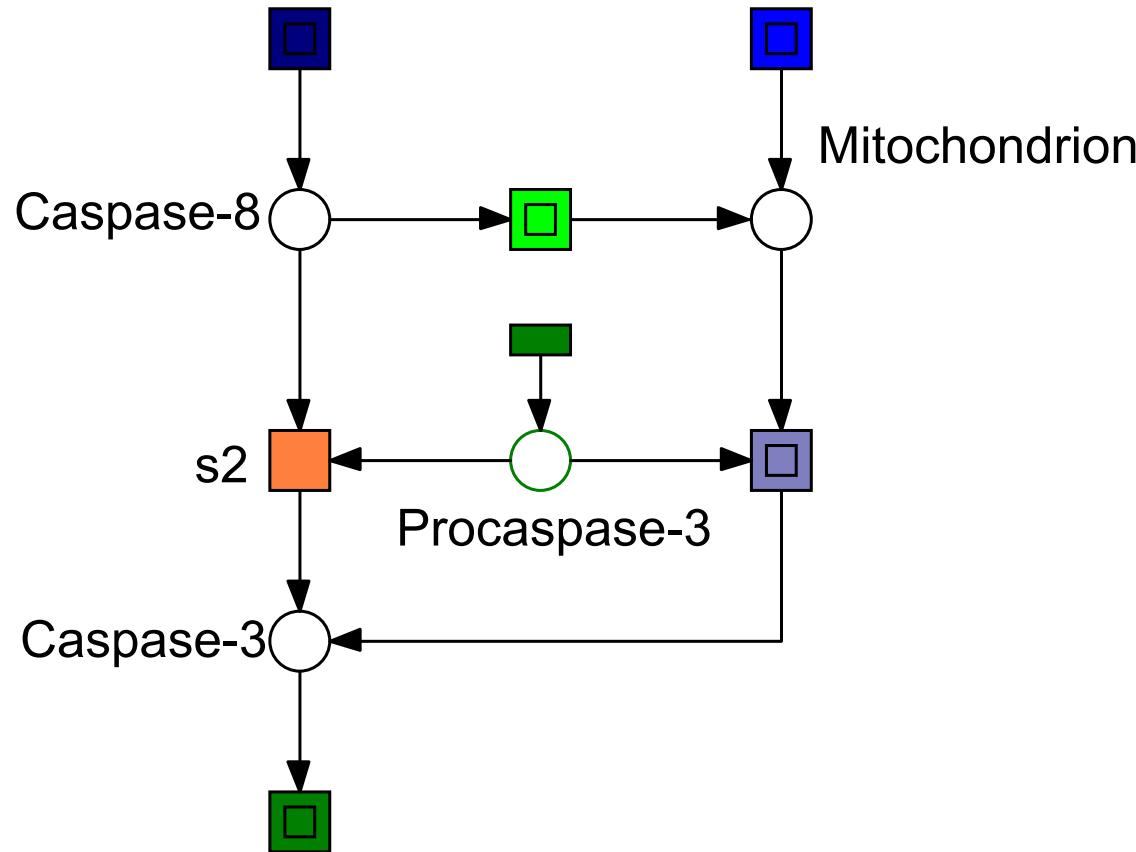
[GON 2003]



[HEINER, KOCH, WILL 2004]

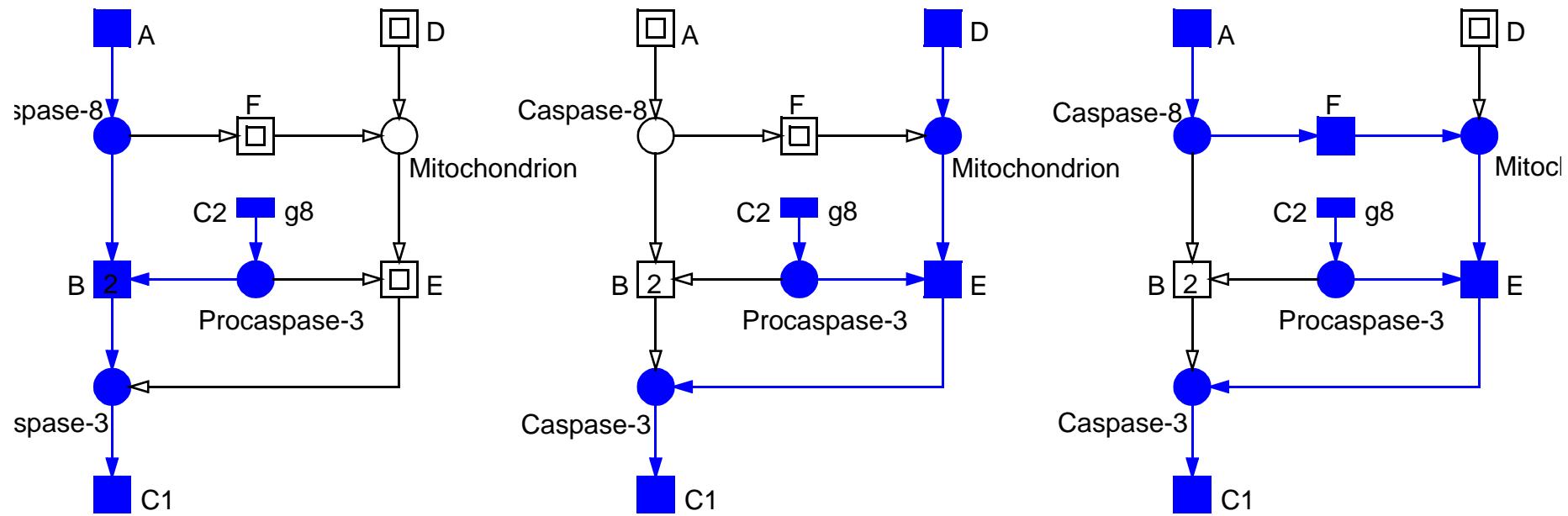
Ex2: APOPTOSIS IN MAMMALIAN CELLS

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Ex2: APOPTOSIS IN MAMMALIAN CELLS

PN & BioModel Engineering



Ex3 - Carbon Metabolism in Potato Tuber

PN & BioModel Engineering



[Koch, JUNKER, HEINER 2005]

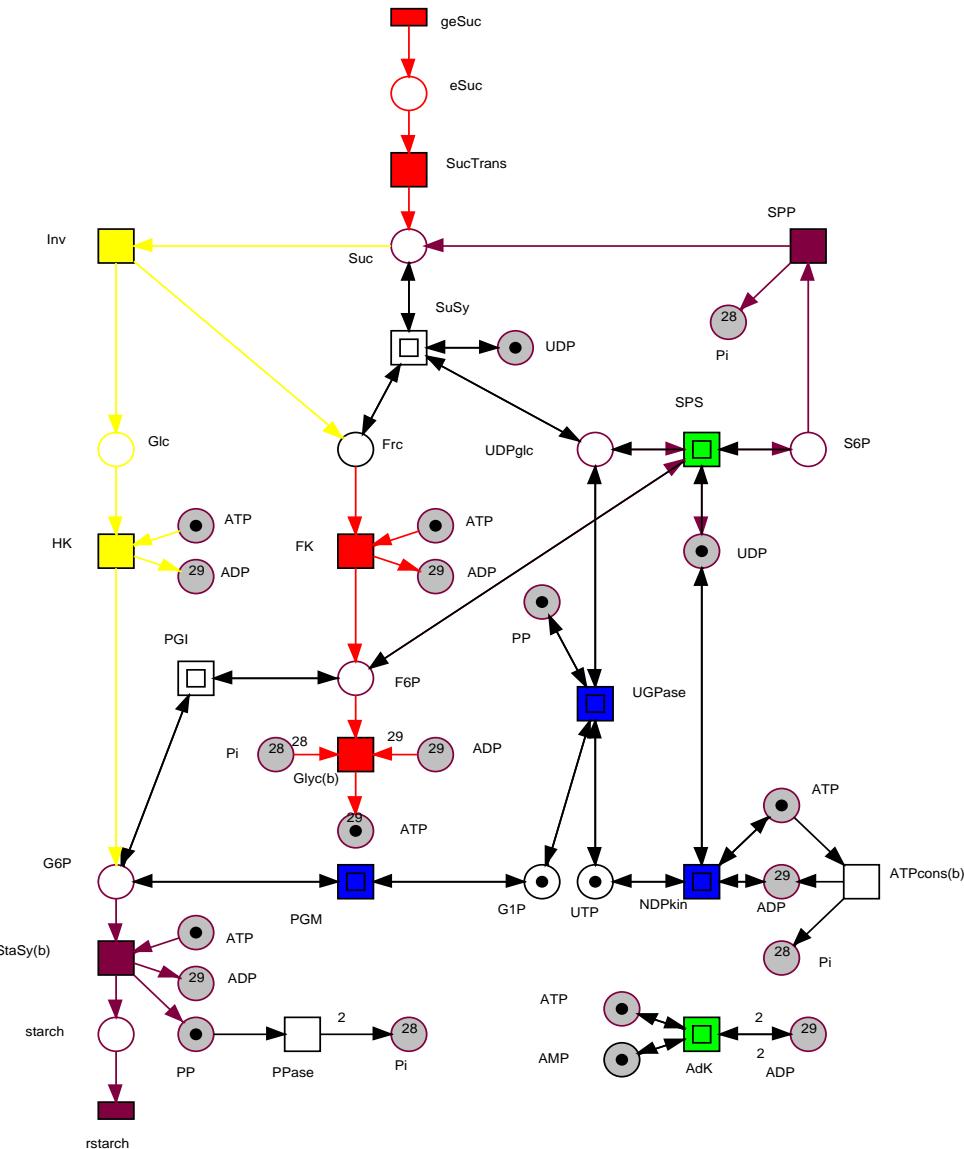
Ex3 - Carbon Metabolism in Potato Tuber

PN & BioModel Engineering



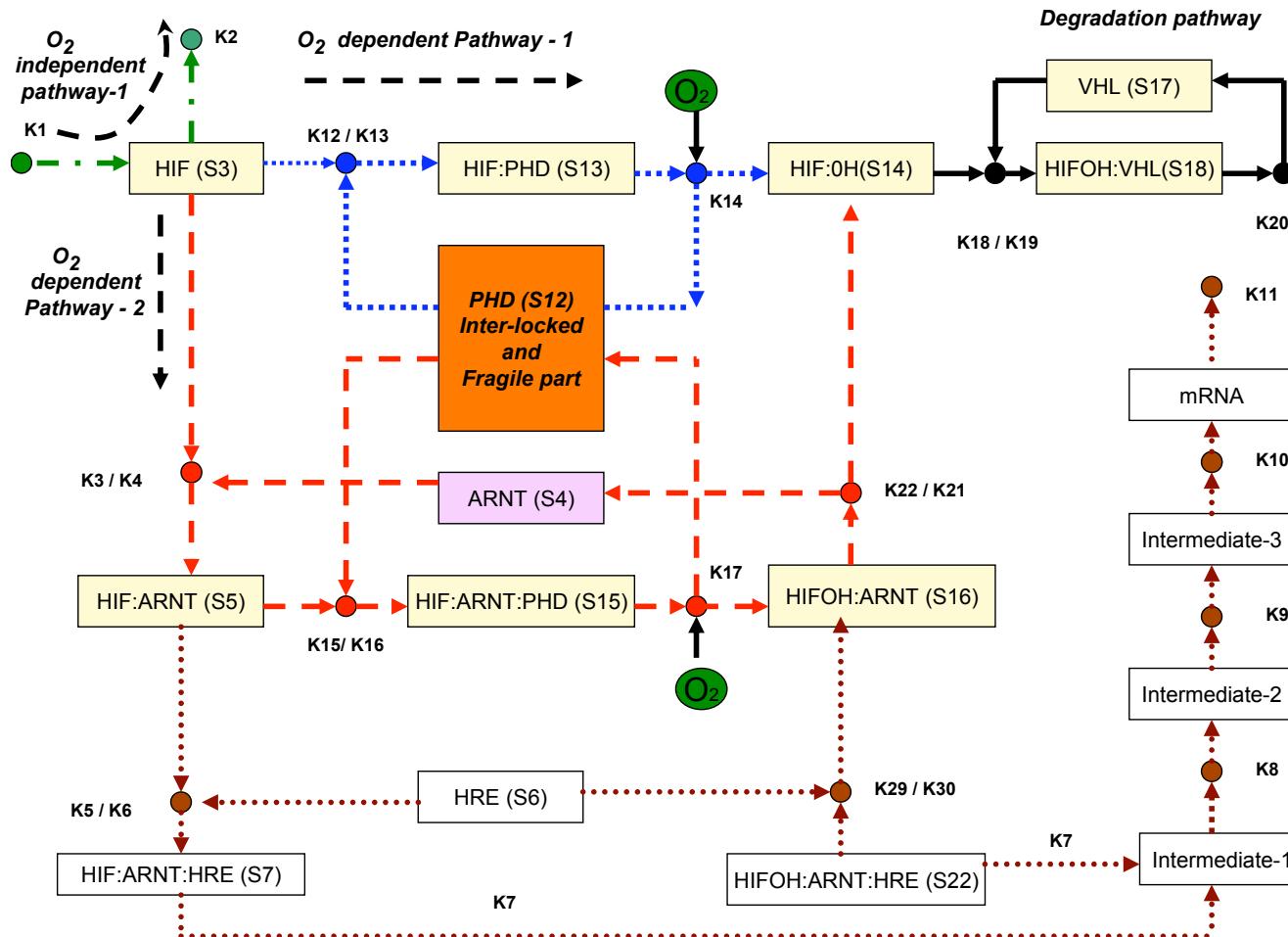
[Koch, JUNKER, HEINER 2005]

ADT-sets without trivial T-invariants

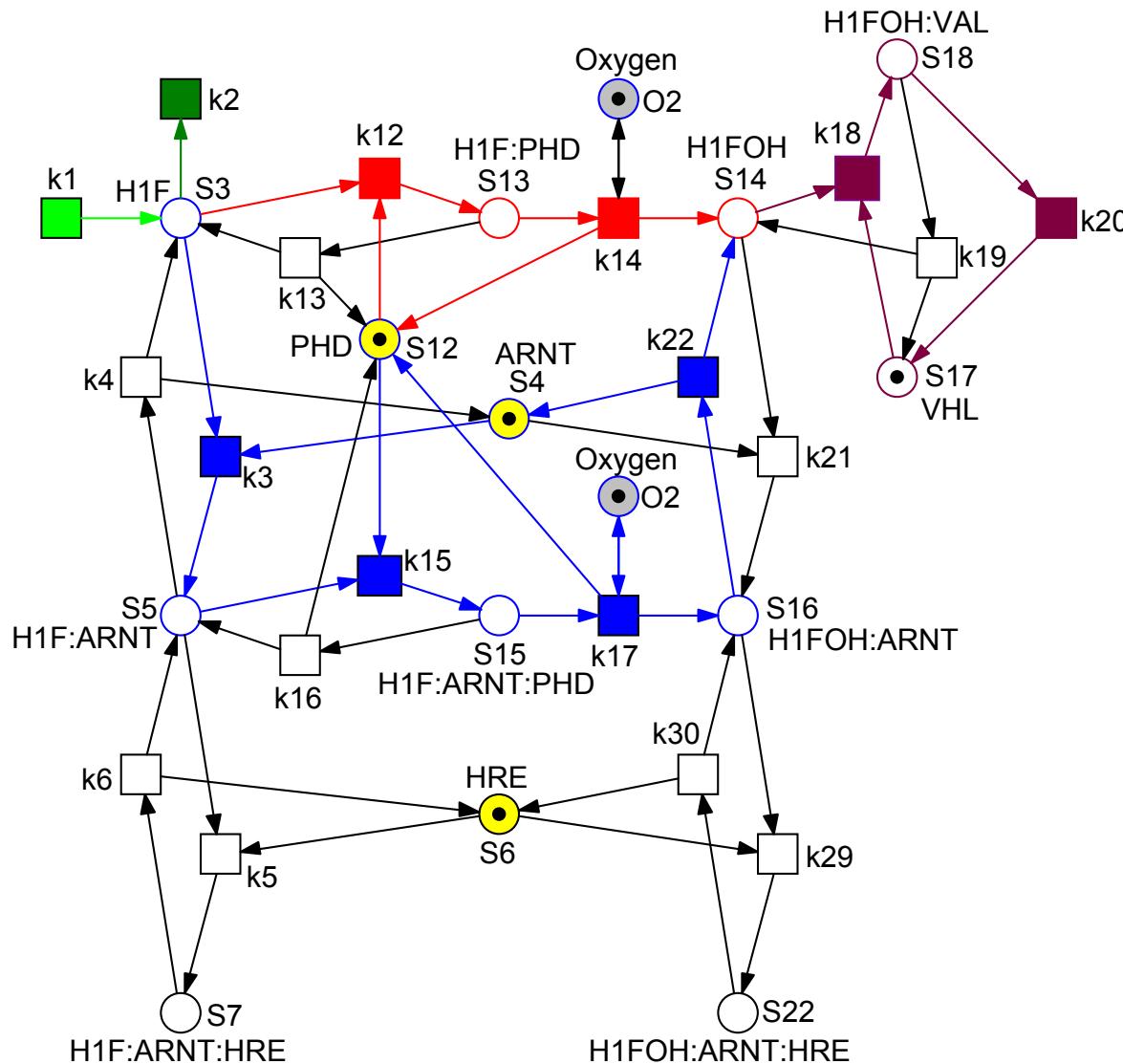


ABOUT THE RELATION QUALITATIVE VS CONTINUOUS

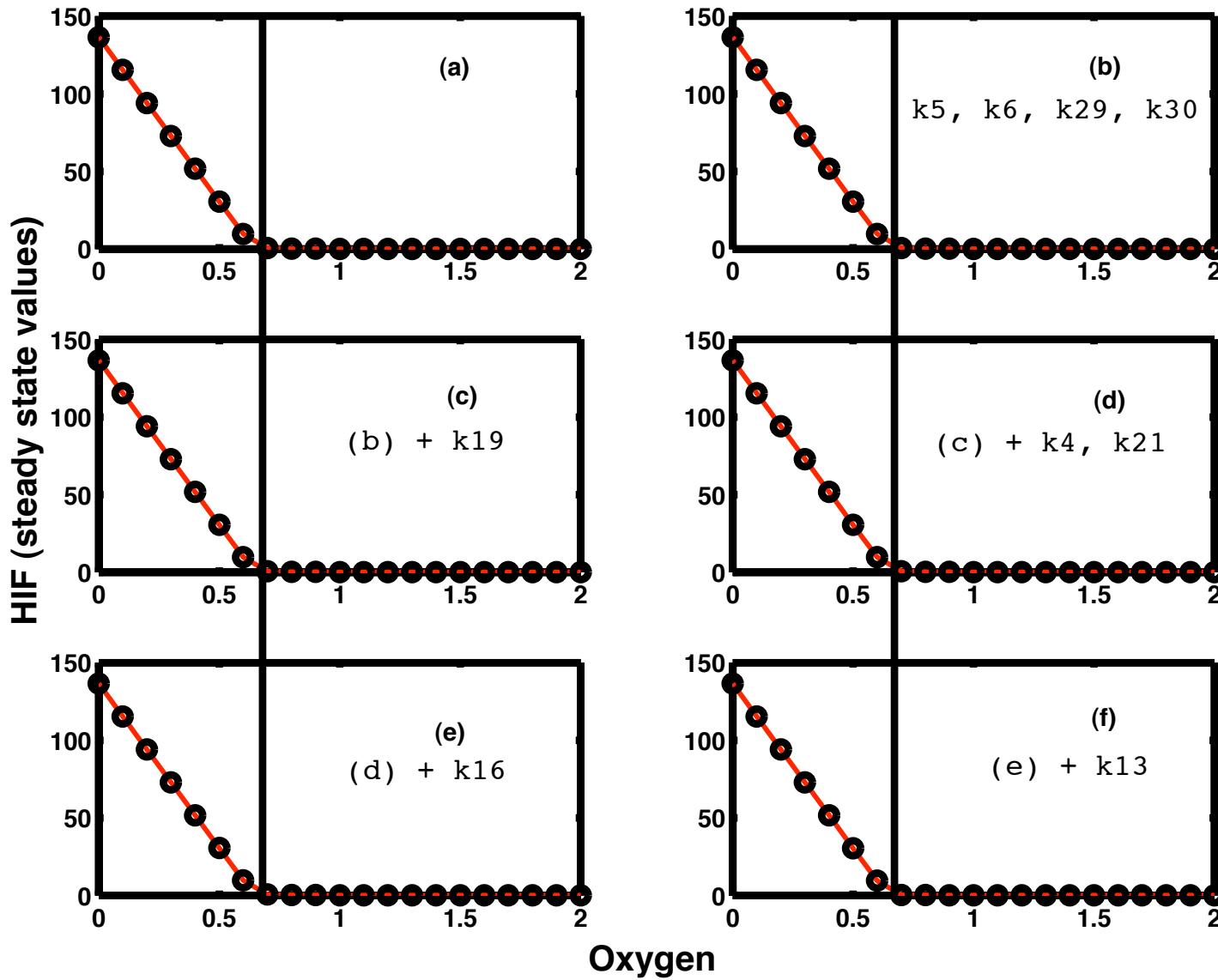
[YU ET AL. 2007]



[HEINER,
SRIRAM 2010]

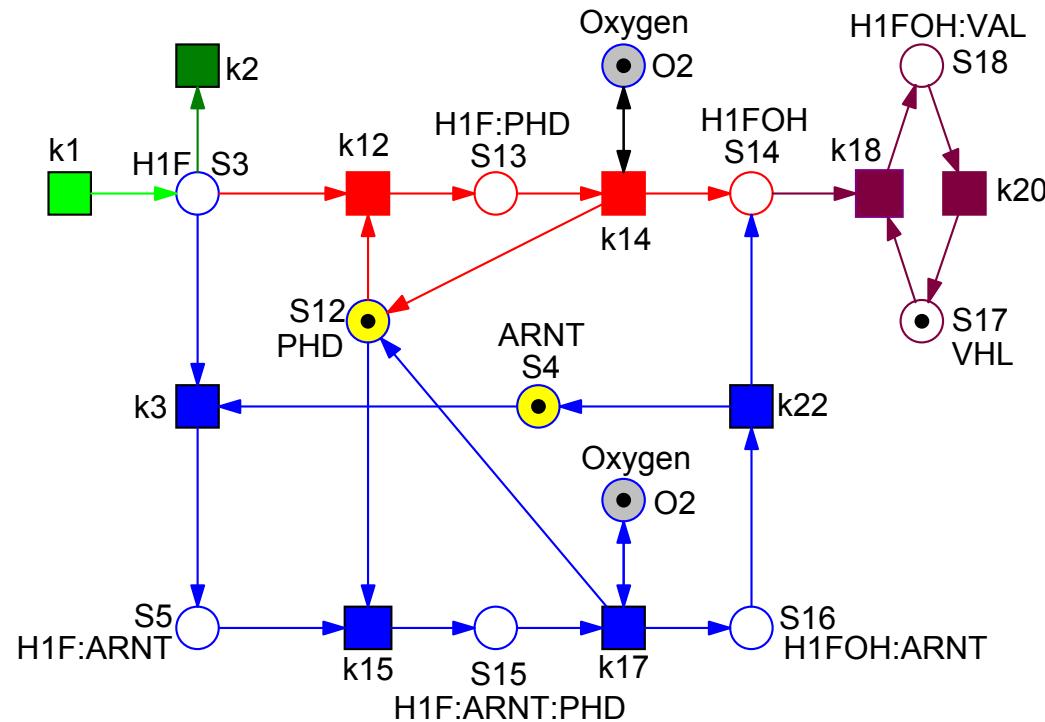


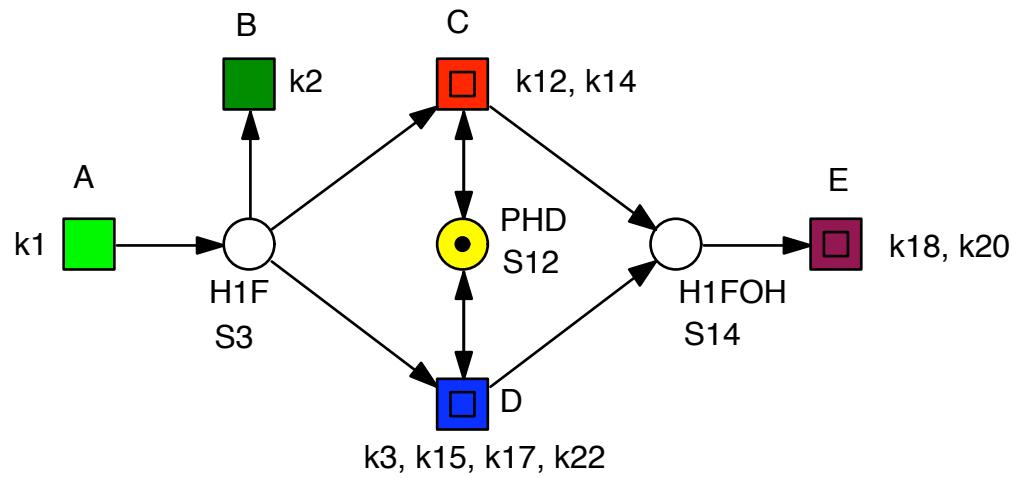
Ex4 - HYPOXIA



Ex4 - HYPOXIA

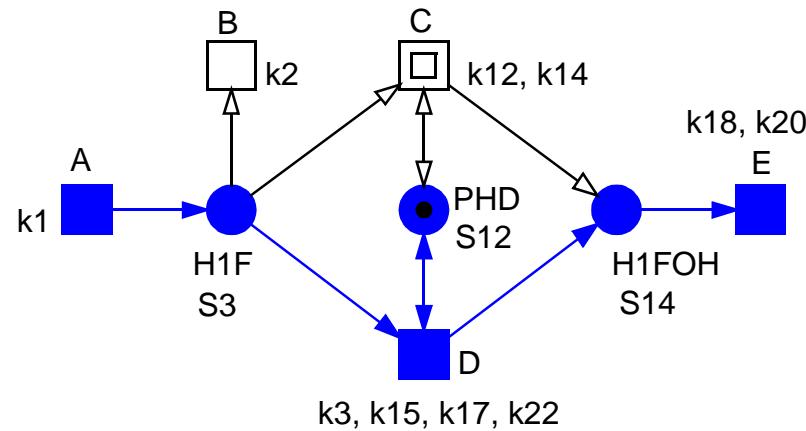
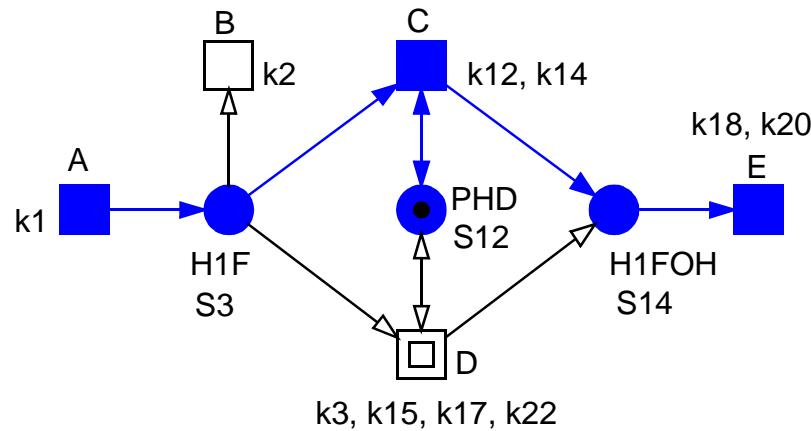
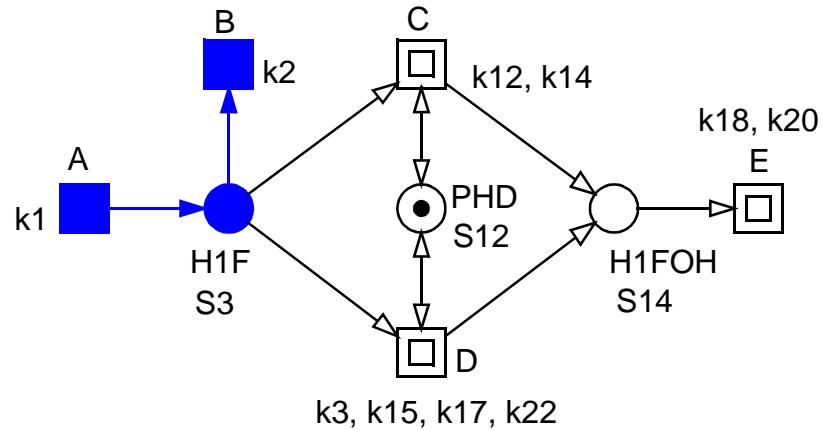
PN & BioModel Engineering





Ex4 - HYPOXIA

PN & BioModel Engineering



SUMMARY & OUTLOOK

□ SNOOPY

- > *modelling and animation/simulation of hierarchical graphs,*
e.g. (extended) fault trees,
various Petri net classes, e.g. PN, XPN, SPN, XSPN, CPN, TPN,
...,
free style graphs

□ CHARLIE

- > PN, XPN, Time/Timed Petri nets (TPN)
- > mostly standard analysis techniques of Petri net theory

□ MARCIE

- > PN, XPN, SPN, XSPN, SRN
- > *symbolic and simulative model checking*

□ Patty

- > *animation via web browser*

SNOOPY

-> *modelling and animation/simulation of hierarchical graphs,*

e.g. (extended) fault trees,

various Petri net class



XPN, SPN, XSPN, CPN, TPN,

....

free style graphs

GRAKEL

-> PN, XPN, Time/Timed Petri nets (TPN)

-> mostly standard analysis techniques of Petri net theory

MARCIE

-> PN, KPN, SPN, XSPN, SRN

-> symbolic and simulative model checking

Patty

-> animation via web browser

SBML import/export

**EXPORT TO MATLAB AND
MANY OTHER TOOLS**

□ representation of bio networks by Petri nets

- > *partial order representation*
- > *formal semantics*
- > *unifying view*
- > *better comprehension*
- > *sound analysis techniques*

□ purposes

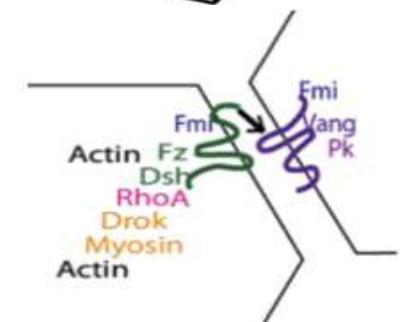
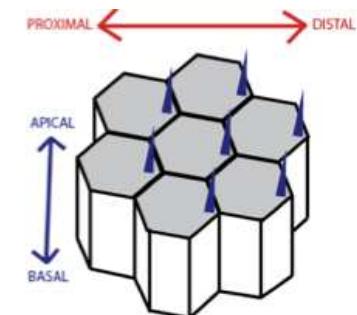
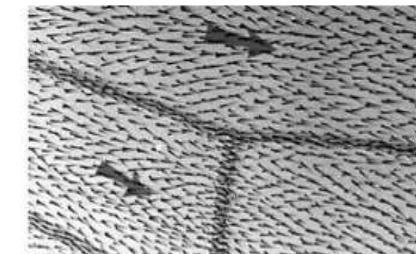
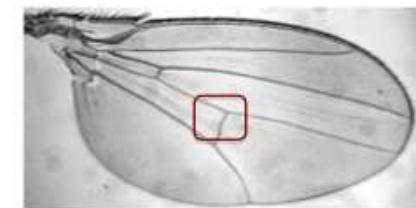
- > *animation*
- > *model validation against consistency criteria*
- > *qualitative / quantitative behaviour prediction*
- > *to experience the model*
- > *to increase confidence*
- > *experiment design, new insights*

□ step-wise model development

- > *qualitative model*
- > *discrete quantitative model*
- > *continuous quantitative model*
- > *locality and space*
- > *discrete Petri nets*
- > *stochastic Petri nets*
- > *continuous Petri nets = ODEs, hybrid models*
- > *coloured Petri nets*

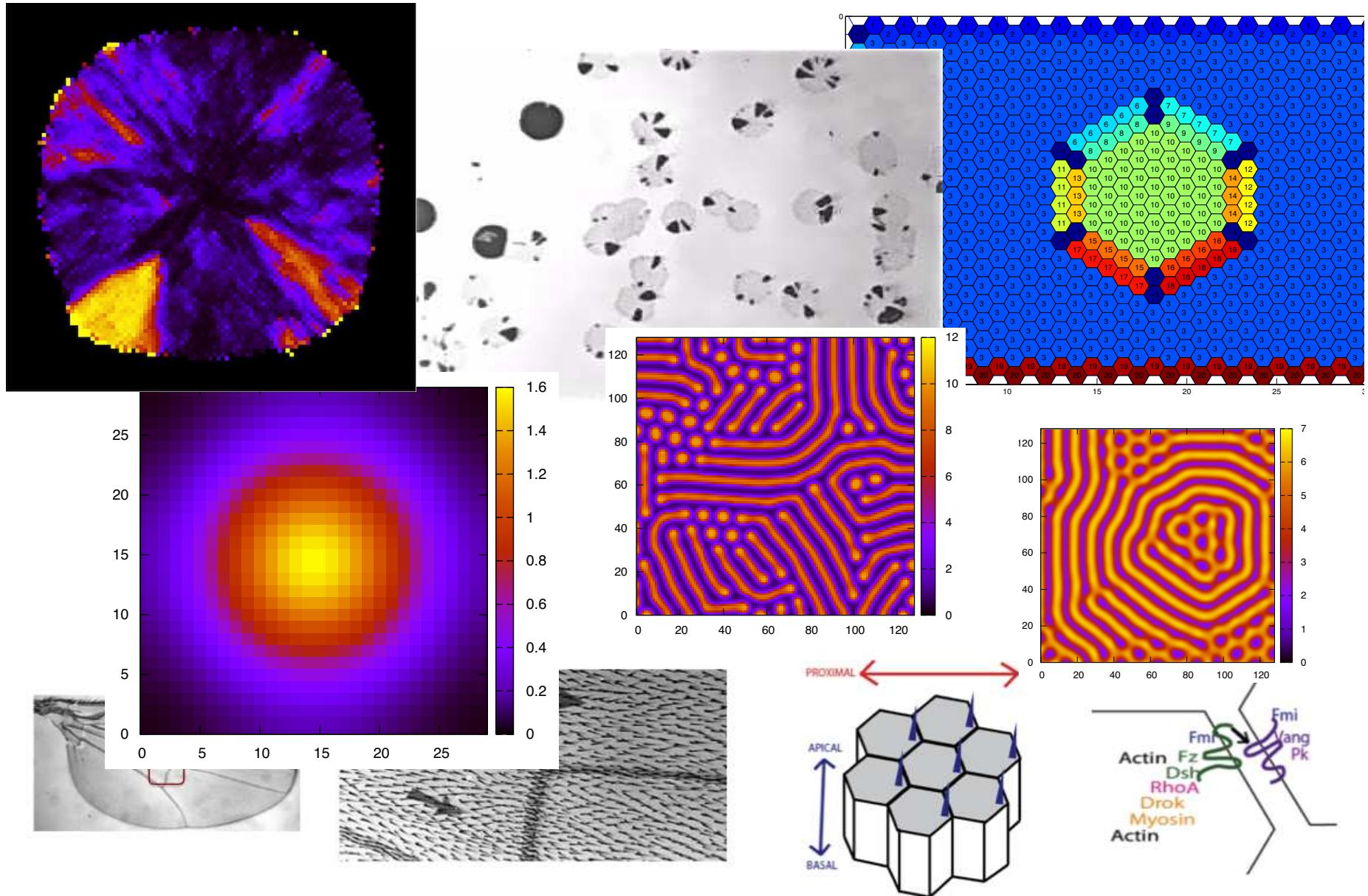
- efficient simulation of very large Petri nets
 - > stochastic
 - > continuous
 - > hybrid
- (hierarchical) space
- shape and volume of components
- hierarchical organisation of components
- observables
- biosystem development

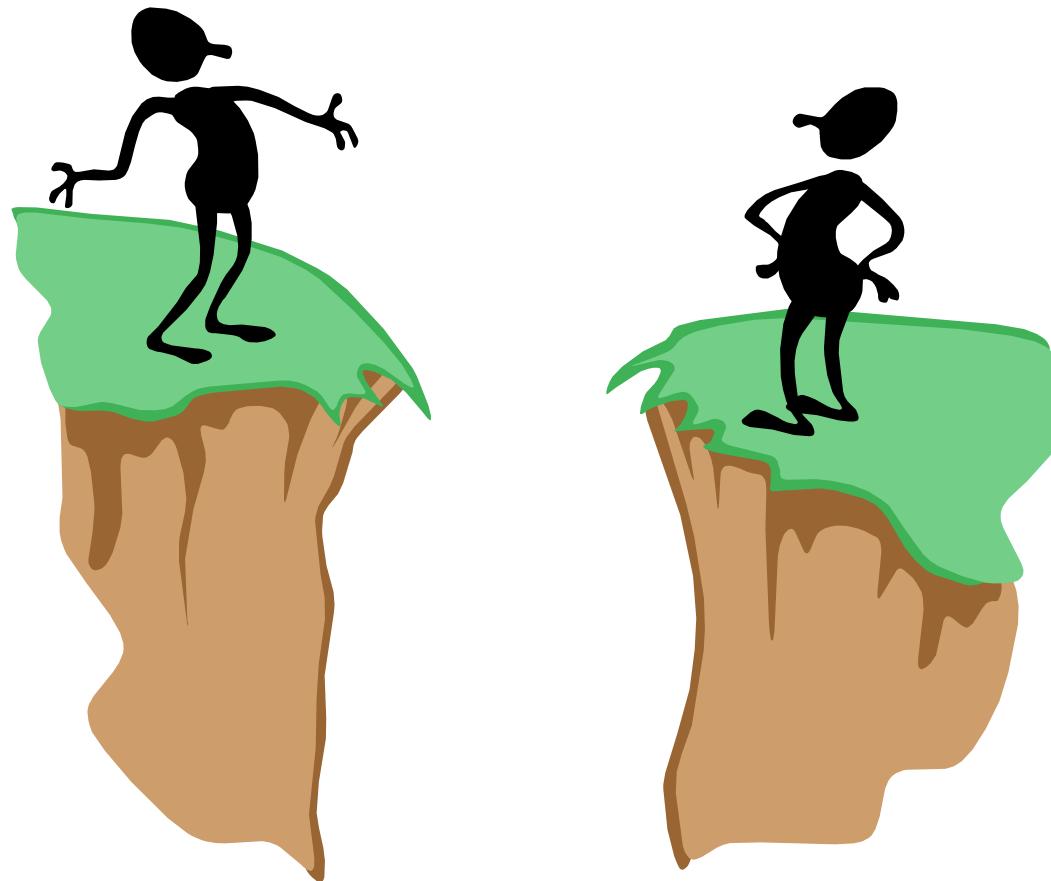
MULTISCALE CHALLENGES



PROCESSES OVER TIME AND SPACE

PN & BioModel Engineering





THANKS !

[HTTP://WWW-DSSZ.INFORMATIK.TU-COTTBUS.DE](http://www-dssz.informatik.tu-cottbus.de)

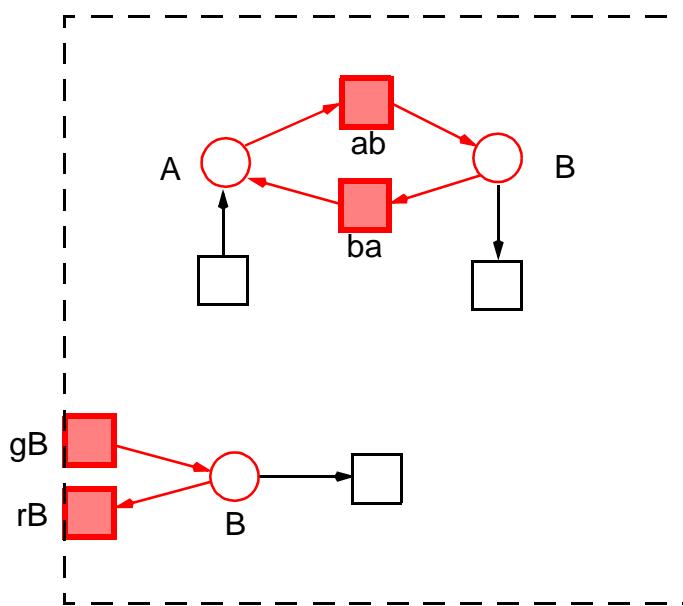
APPENDIX

- **trivial minimal T-invariants**

- > *reversible reactions*
- > *boundary transitions of auxiliary compounds*

- **non-trivial minimal T-invariants**

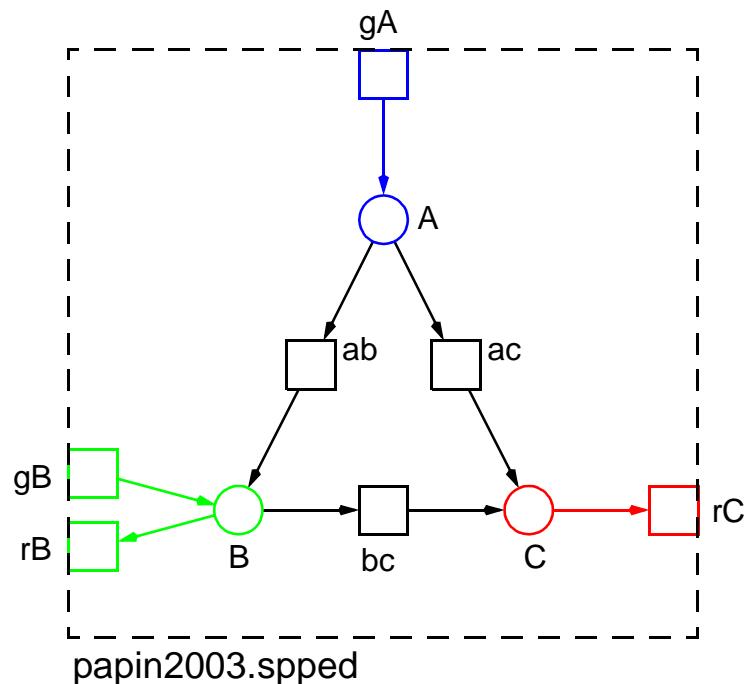
- > *i/o-T-invariants*
covering boundary transitions of input / output compounds
- > *inner cycles*



EXAMPLE

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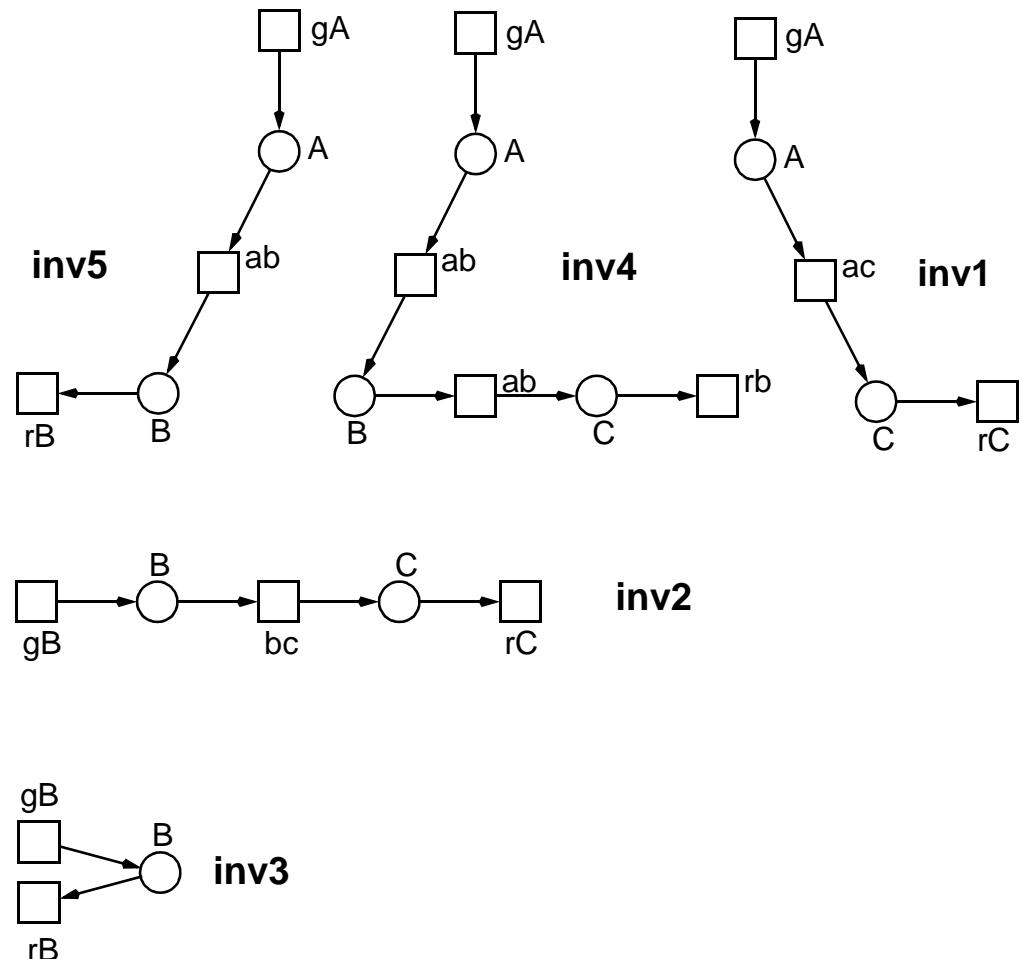
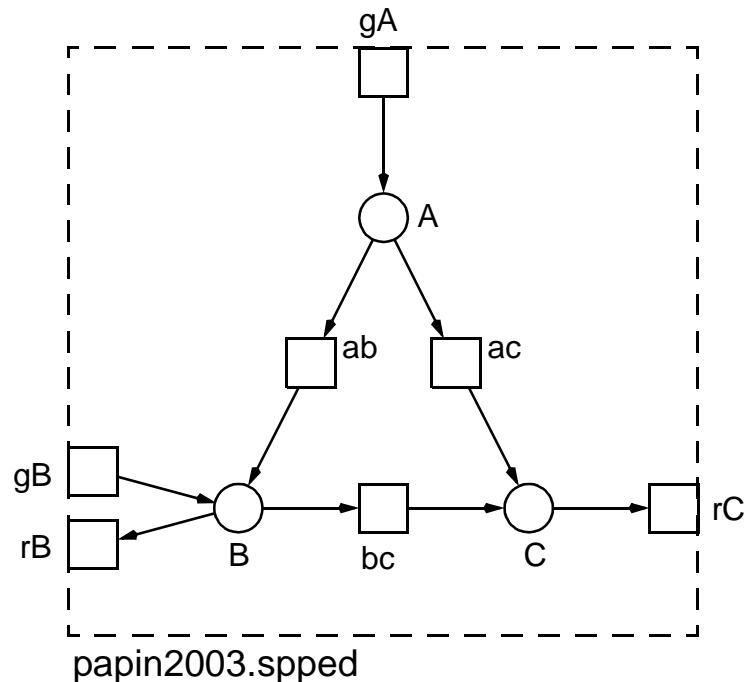
- substances involved
 - > *input substance A*
 - > *output substance C*
 - > *auxiliary substance B*



EXAMPLE, T-INVARIANTS

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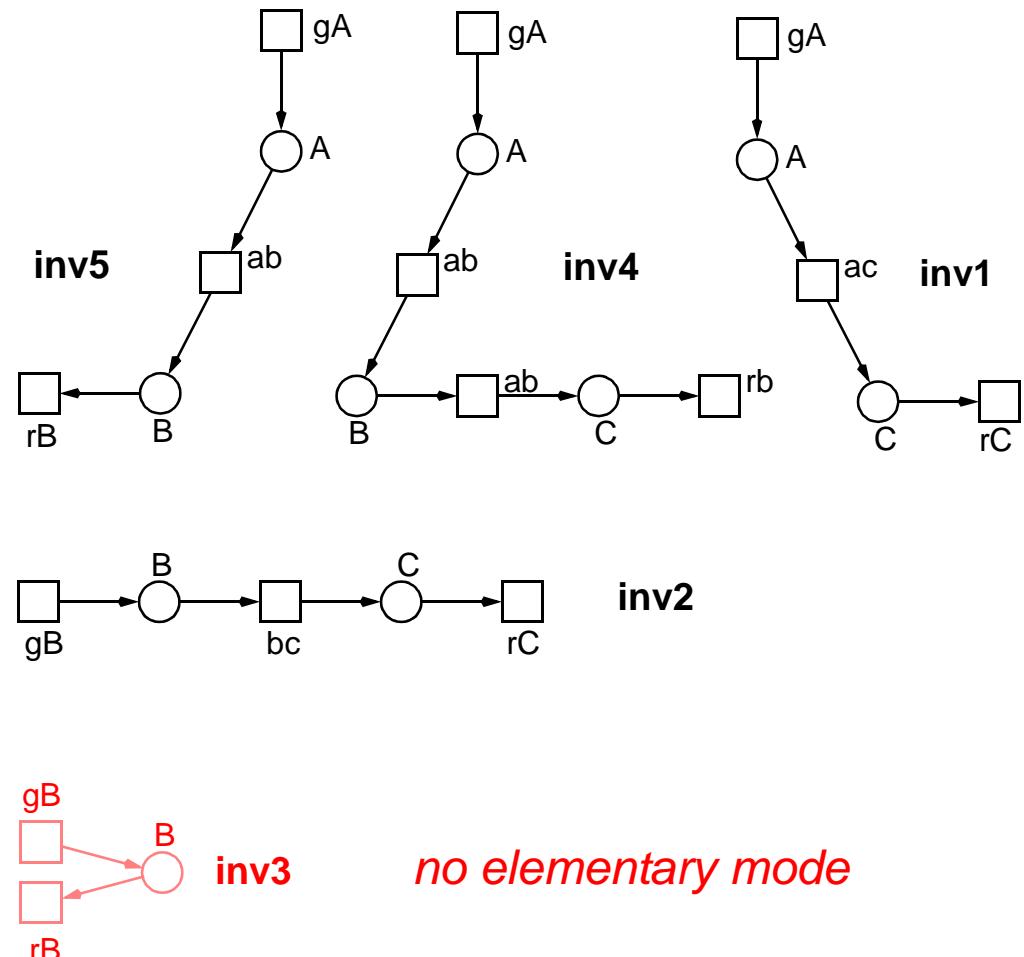
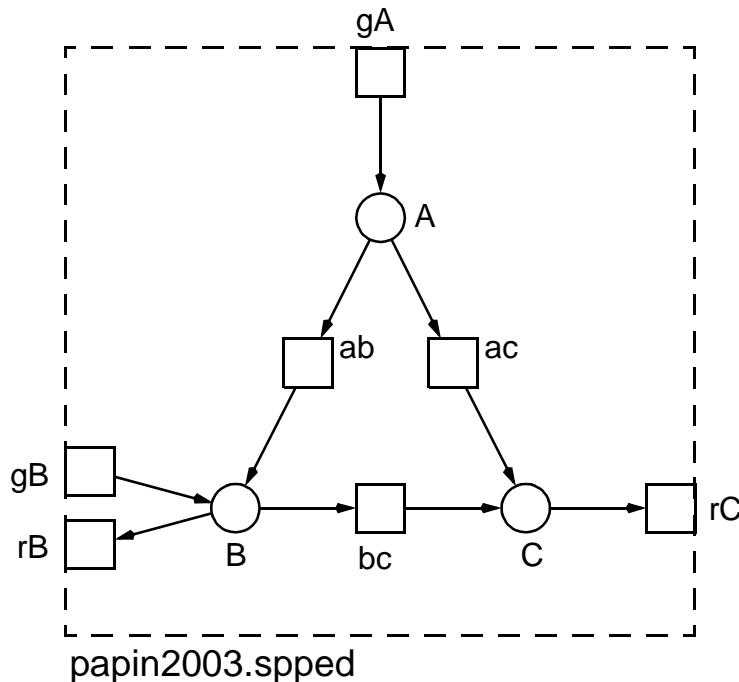
- substances involved
 - > *input substance A*
 - > *output substance C*
 - > *auxiliary substance B*



EXAMPLE, ELEMENTARY MODES

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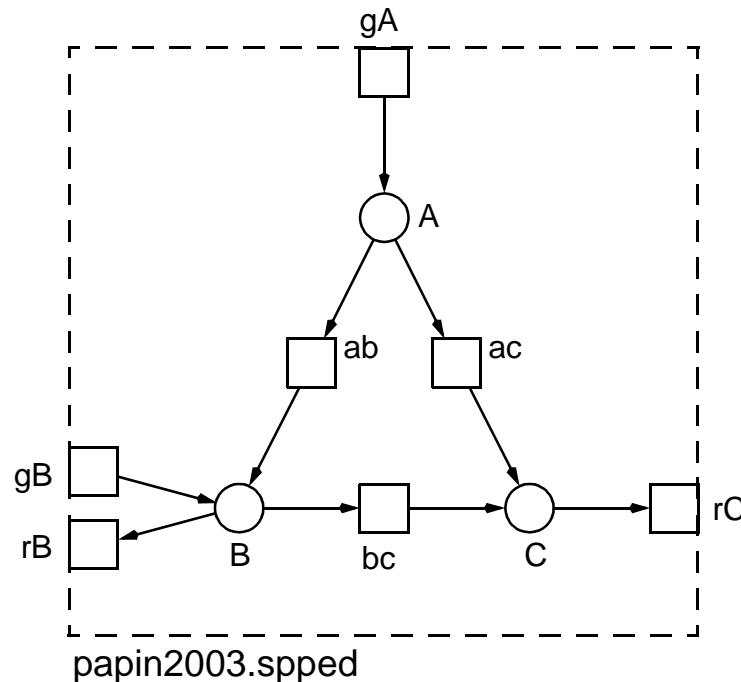
- substances involved
 - > *input substance A*
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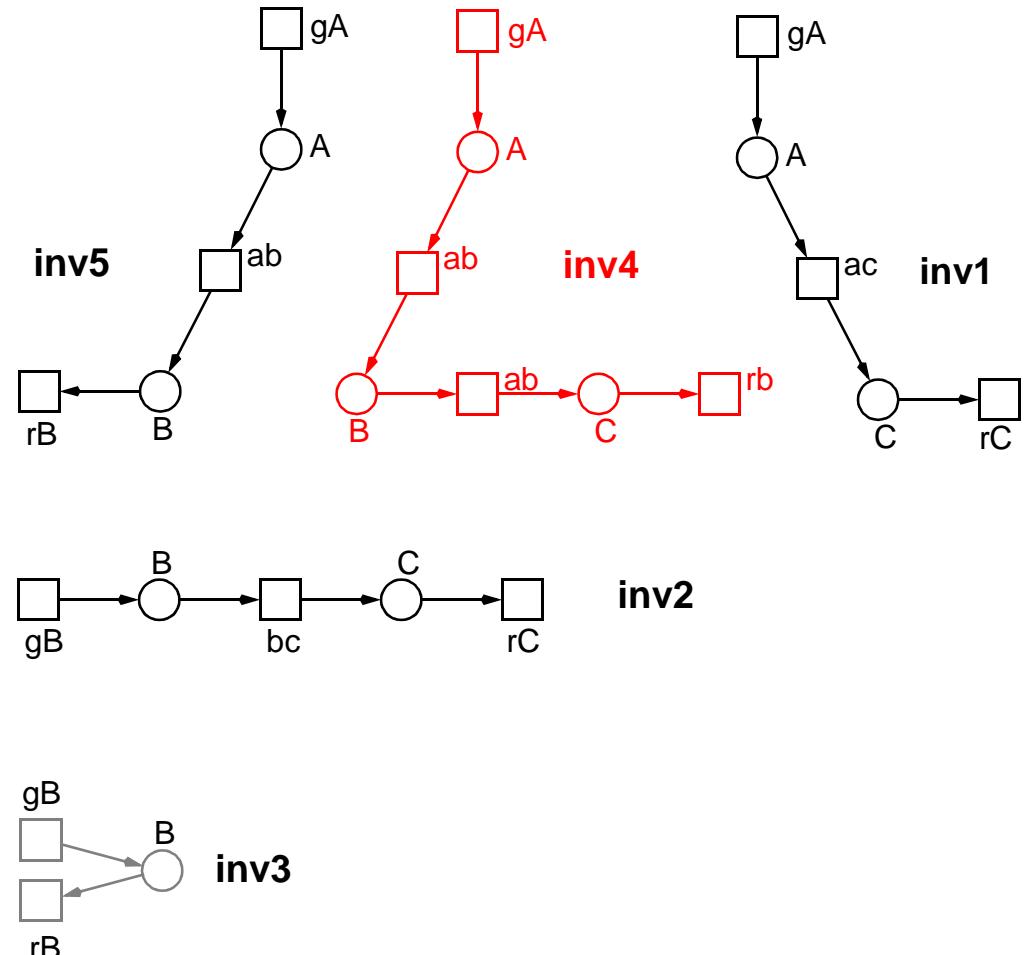
EXAMPLE, EXTREME PATHWAYS

PN & BioModel Engineering

- substances involved
 - > *input substance A*
 - > *output substance C*
 - > *auxiliary substance B*



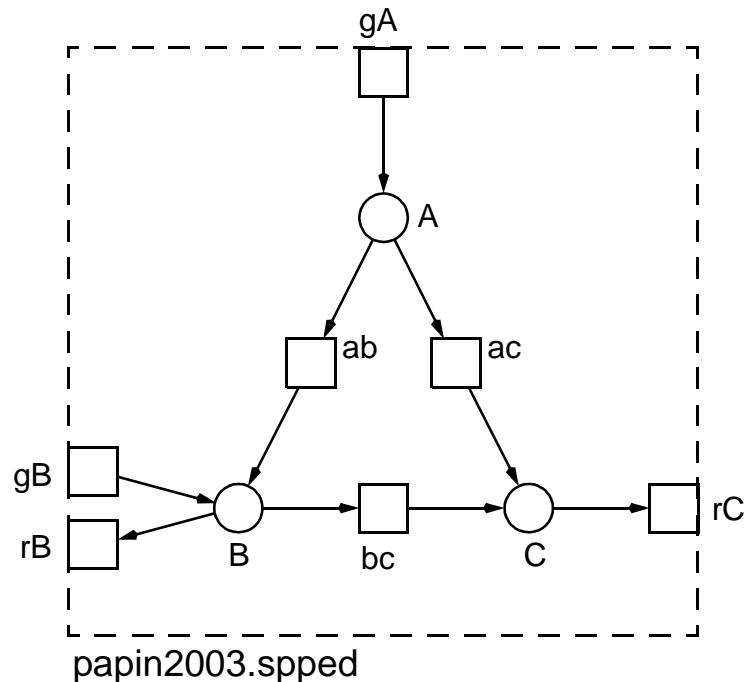
no extreme pathway



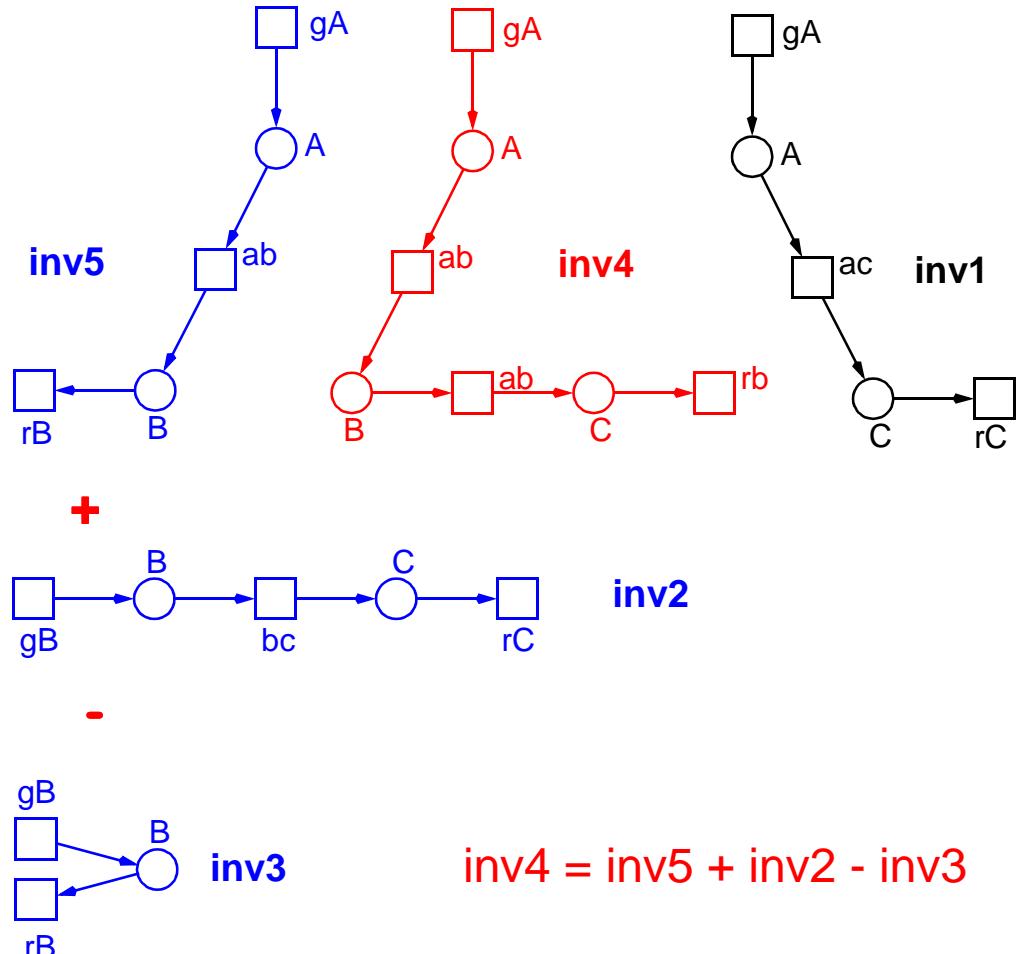
EXAMPLE, EXTREME PATHWAYS

PN & BioModel Engineering

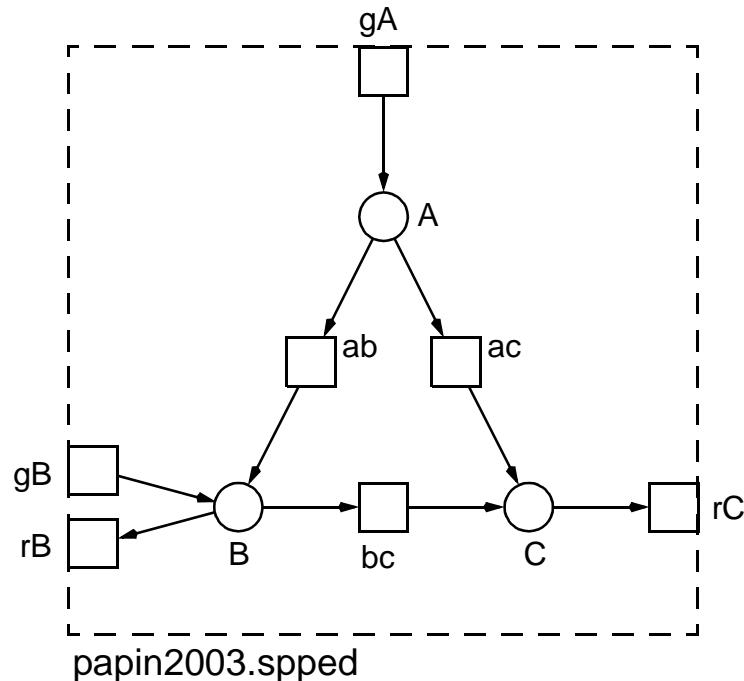
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 - > *output substance C*
 - > *auxiliary substance B*



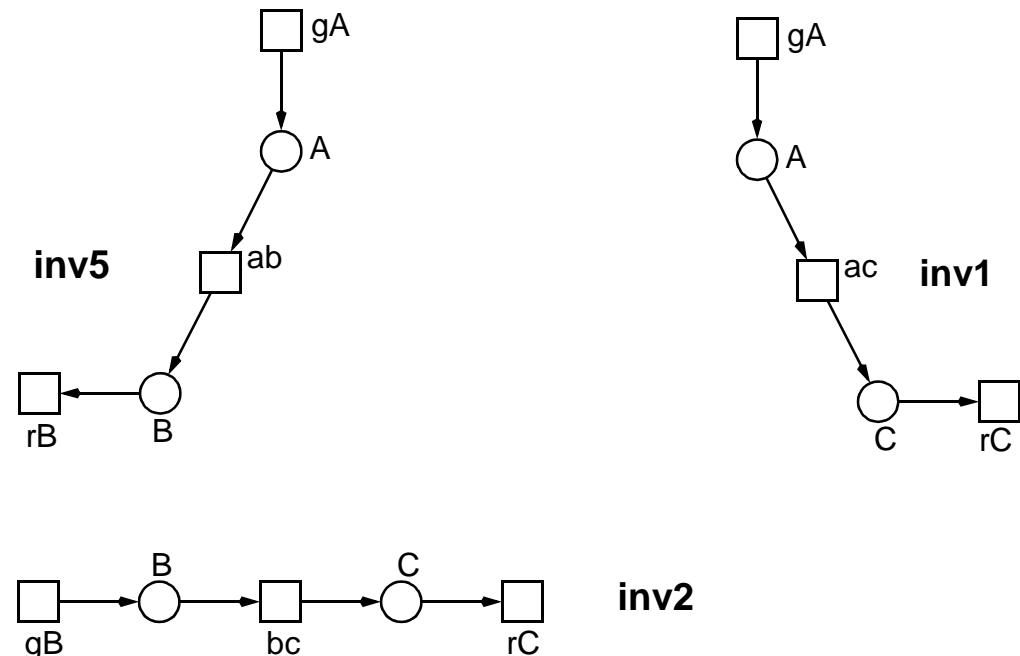
no extreme pathway



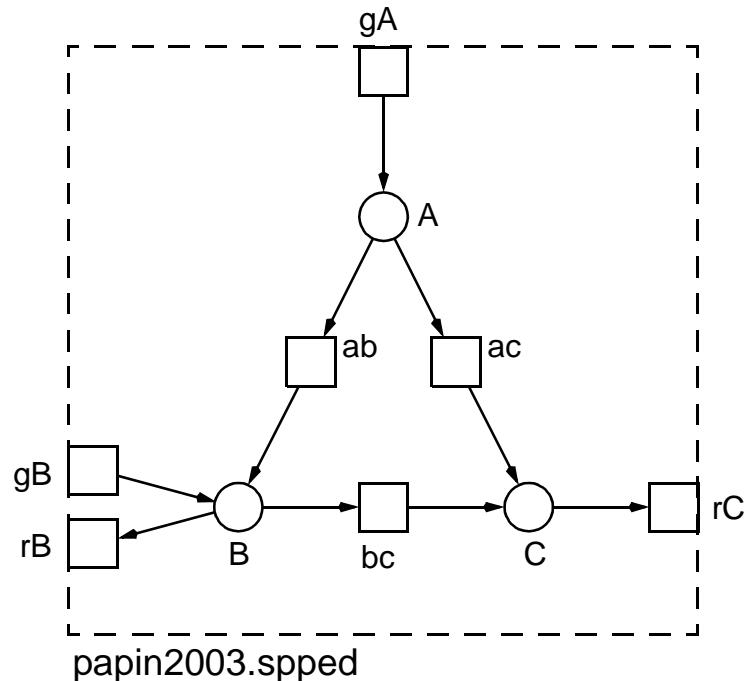
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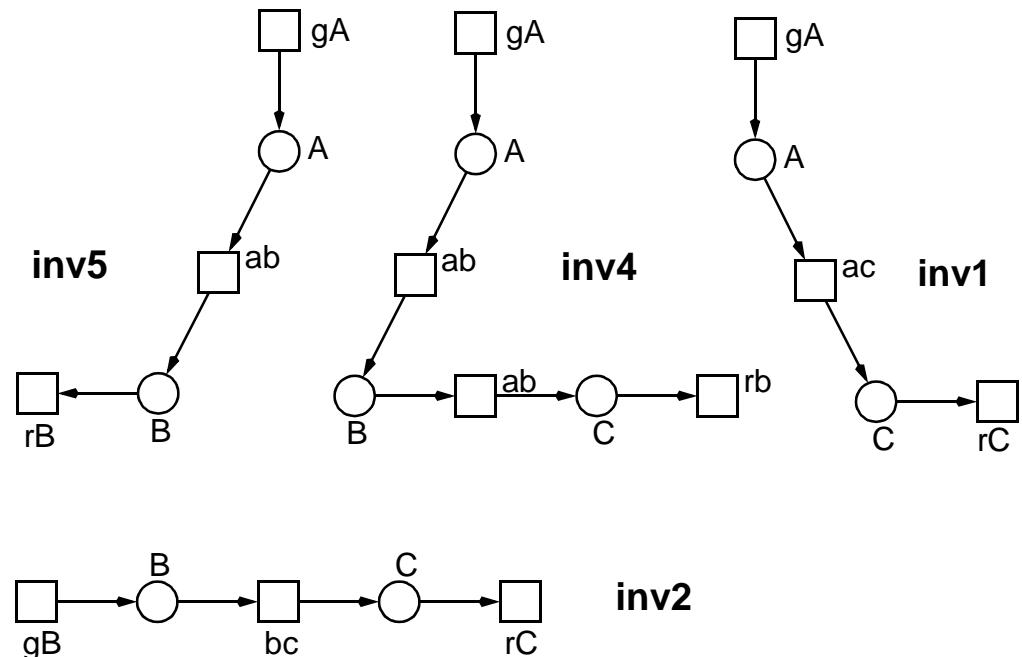
EXTREME PATHWAYS



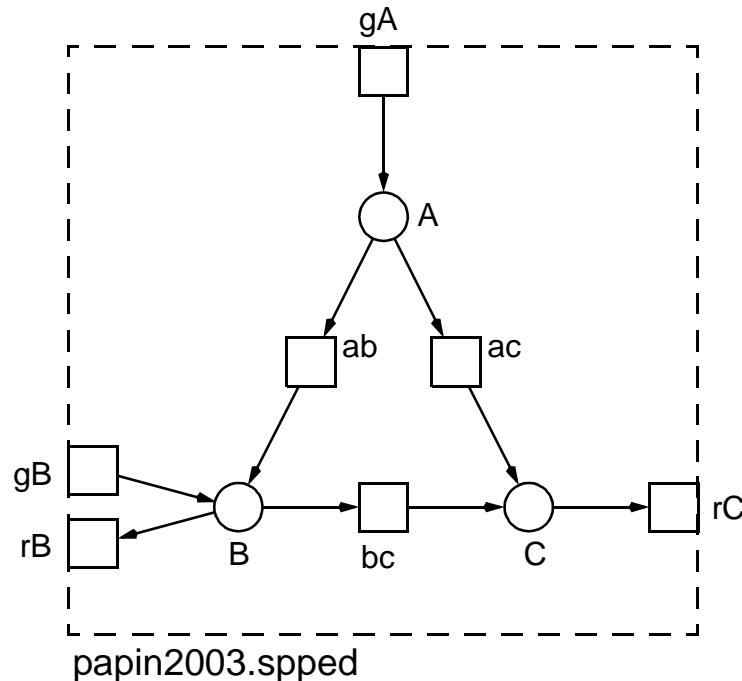
- substances involved
 - > *input substance A*
 - > *output substance C*
 - > *auxiliary substance B*



ELEMENTARY MODES



- substances involved
 - > *input substance A*
 - > *output substance C*
 - > *auxiliary substance B*



MINIMAL T-INVARIANTS

