BIOMODEL ENGINEERING
- A PETRI NET PERSPECTIVE -

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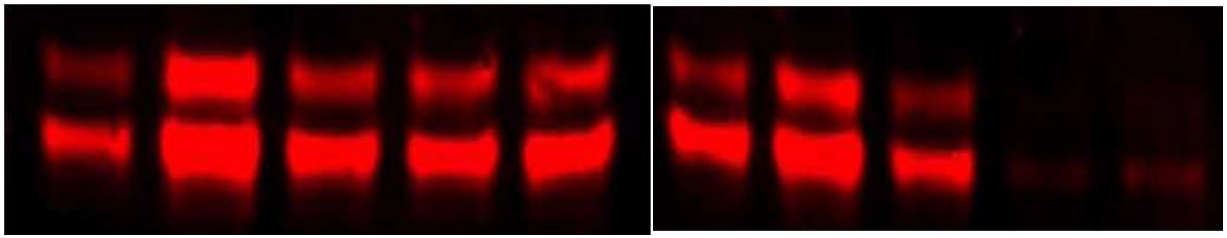
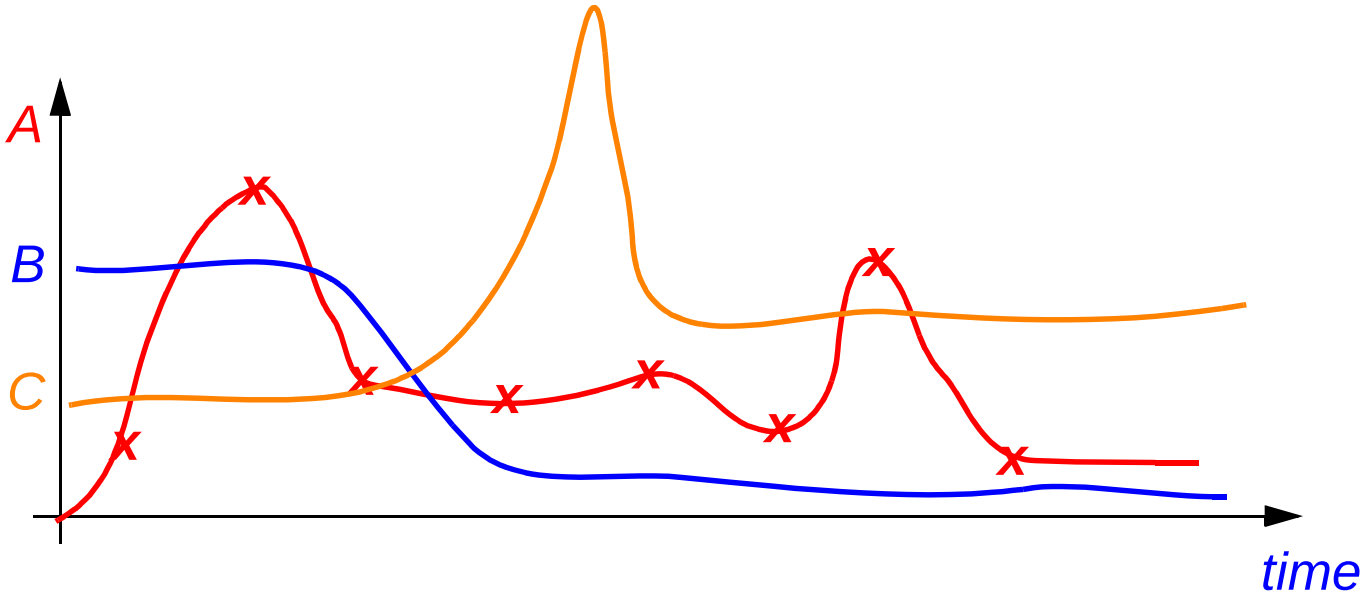
WETLAB EXPERIMENTS - OBSERVED BEHAVIOUR





- **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**

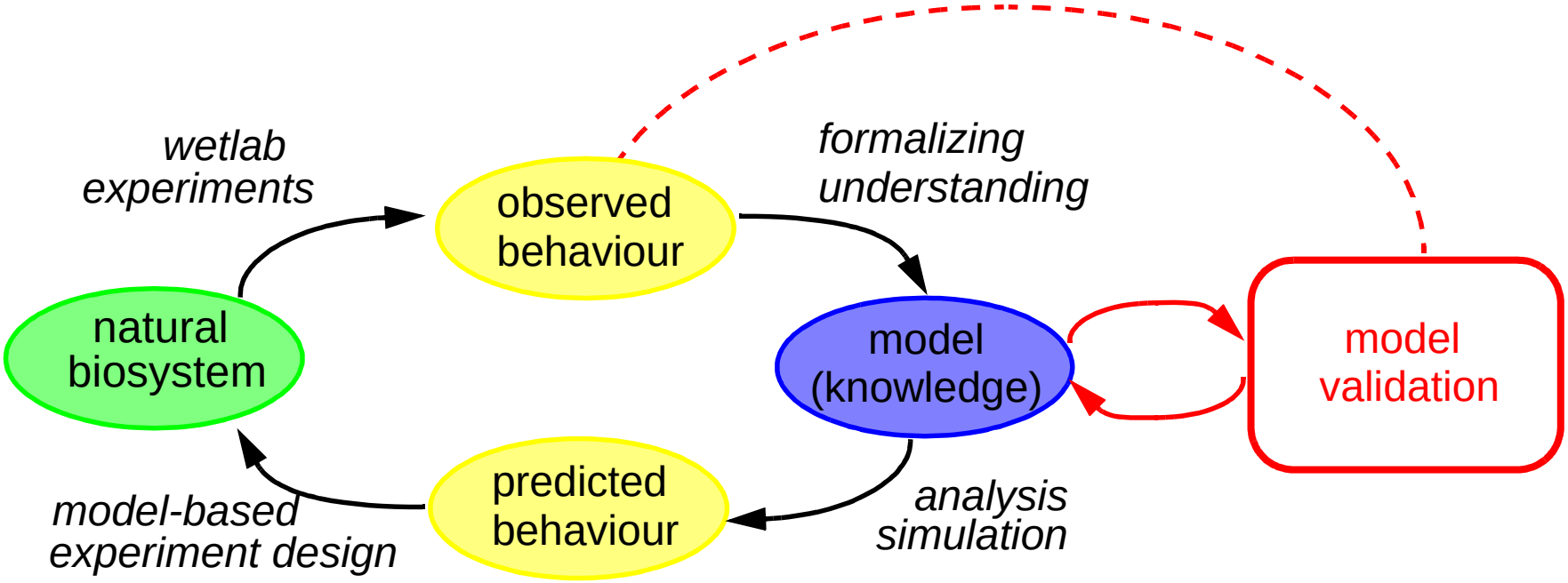
  Protein rises then falls to less than 50% of its peak concentration at 60 minutes.

- **Quantitative**

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

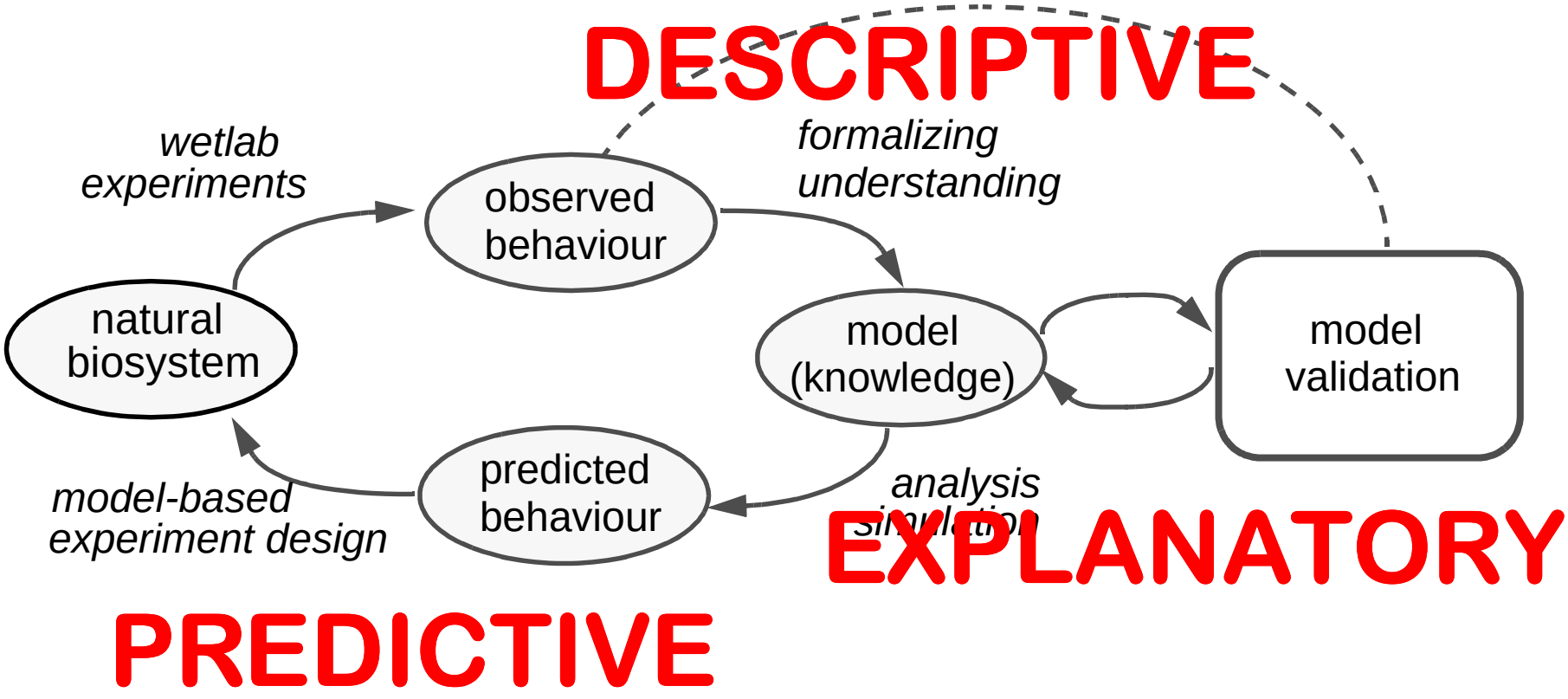
Models explaining these observations ?

MODELLING = FORMAL KNOWLEDGE REPRESENTATION



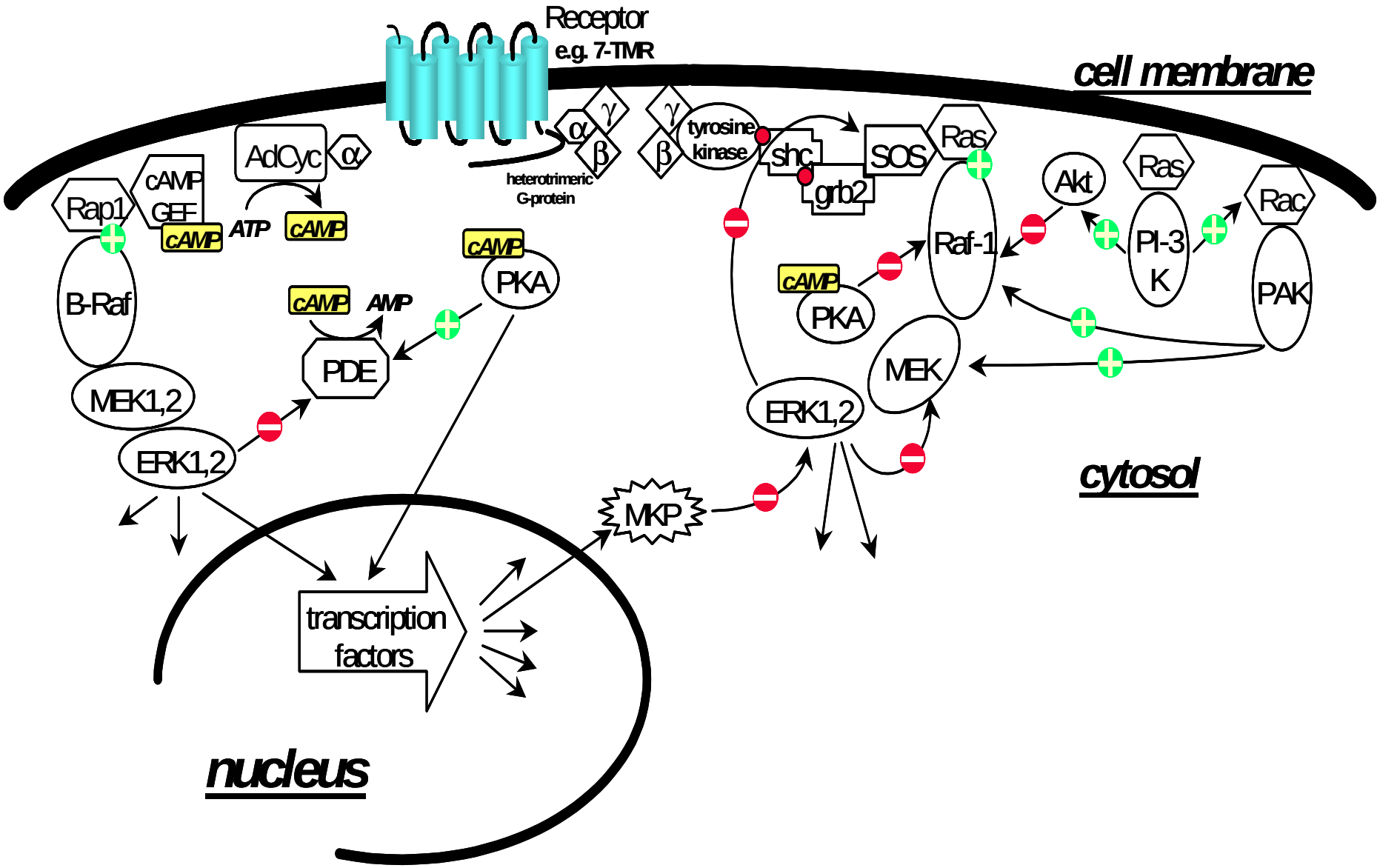
MODEL VALIDATION = CONFIDENCE INCREASE

MODELLING = FORMAL KNOWLEDGE REPRESENTATION

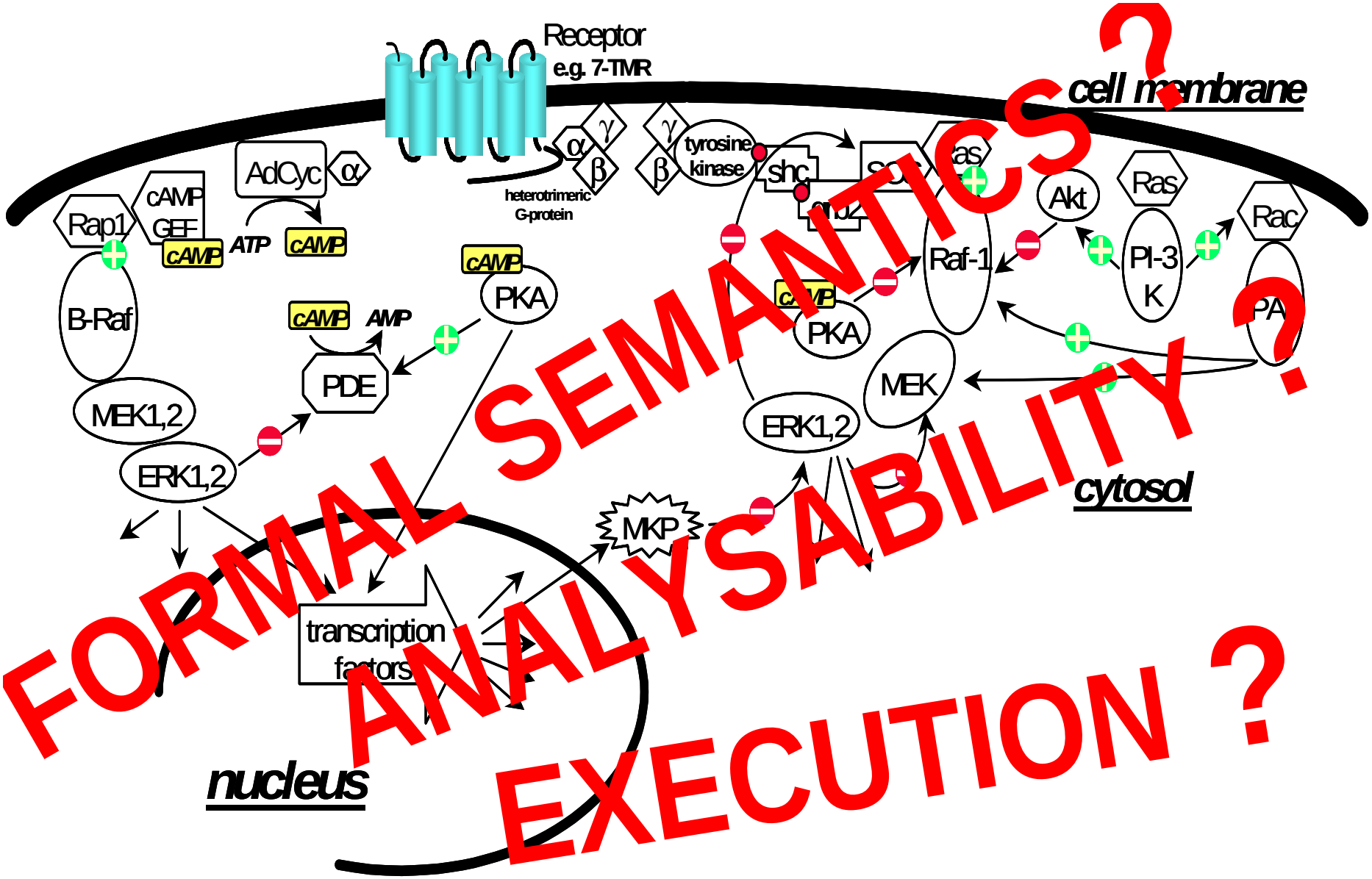


MODEL VALIDATION = CONFIDENCE INCREASE

NETWORK REPRESENTATIONS, EX1



NETWORK REPRESENTATIONS, EX1



NETWORK REPRESENTATIONS, EX2

$$\frac{d\alpha}{dt} = -v_1$$
$$\frac{dSte2}{dt} = -v_2 + v_3 - v_5$$
$$\frac{dSte2_{active}}{dt} = v_2 - v_3 - v_4$$
$$\frac{dSst2_{active}}{dt} = v_{46} - v_{47}$$
$$\frac{dG\alpha\beta\gamma}{dt} = -v_6 + v_9$$
$$\frac{dG\alpha GTP}{dt} = v_6 - v_7 - v_8$$
$$\frac{dG\alpha GDP}{dt} = v_7 + v_8 - v_9$$
$$\frac{dG\beta\gamma}{dt} = v_6 - v_9 - v_{10} + v_{11} + v_{21} + v_{23} + v_{25} + v_{27} + v_{32} - v_{42} + v_{43}$$
$$\frac{dSte5}{dt} = -v_{12} + v_{13} + v_{17} + v_{21} + v_{23} + v_{25} + v_{27} + v_{32}$$
$$\frac{dSte11}{dt} = -v_{12} + v_{13} + v_{17} + v_{21} + v_{23} + v_{25} + v_{27} + v_{32}$$
$$\frac{dSte7}{dt} = -v_{14} + v_{15} + v_{17} + v_{21} + v_{23} + v_{25} + v_{27} + v_{32}$$
$$\frac{dFus3}{dt} = -v_{14} + v_{15} + v_{17} + v_{21} + v_{23} + v_{25} + v_{27} - v_{29} + v_{30} + v_{33}$$
$$\frac{dSte20}{dt} = -v_{18} + v_{19} + v_{21} + v_{23} + v_{25} + v_{27} + v_{32}$$

$$v_1 = \alpha[t] \cdot Bar1_{active}[t] \cdot k_1$$
$$v_2 = Ste2[t] \cdot \alpha[t] \cdot k_2$$
$$v_3 = Ste2_{active}[t] \cdot k_3$$
$$v_4 = Ste2_{active}[t] \cdot k_4$$
$$v_5 = Ste2[t] \cdot k_5$$
$$v_6 = Ste2_{active}[t] \cdot G\alpha\beta\gamma[t] \cdot k_6$$
$$v_7 = G\alpha GTP[t] \cdot k_7$$
$$v_8 = G\alpha GTP[t] \cdot Sst2_{active}[t] \cdot k_8$$
$$v_9 = G\alpha GDP[t] \cdot G\beta\gamma[t] \cdot k_9$$
$$v_{10} = G\beta\gamma[t] \cdot C[t] \cdot k_{10}$$
$$v_{11} = D[t] \cdot k_{11}$$
$$v_{12} = Ste5[t] \cdot Ste11[t] \cdot k_{12}$$
$$v_{13} = A[t] \cdot k_{13}$$
$$v_{14} = Ste7[t] \cdot Fus3[t] \cdot k_{14}$$
$$v_{15} = B[t] \cdot k_{15}$$
$$v_{16} = A[t] \cdot B[t] \cdot k_{16}$$
$$v_{17} = C[t] \cdot k_{17}$$
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$$\frac{d\alpha}{dt} = -v_1$$

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

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

$$\frac{dSte\cdot}{dt} = -v_{\cdot} + v_{\cdot} - v_{\cdot} - v_{23} + v_{25} + v_{27} + v_{32}$$

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

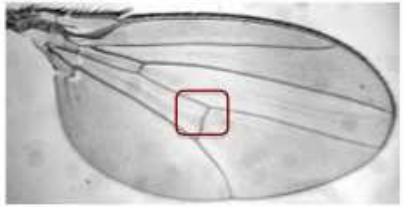
READABILITY ?

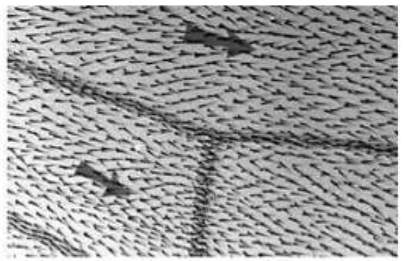
CAUSALITY ?

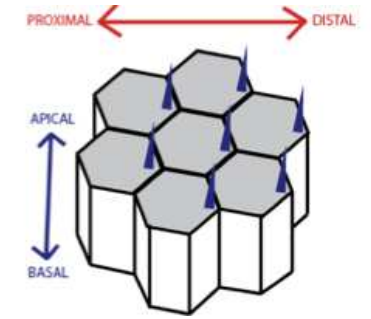
UNIQUE STRUCTURE ?

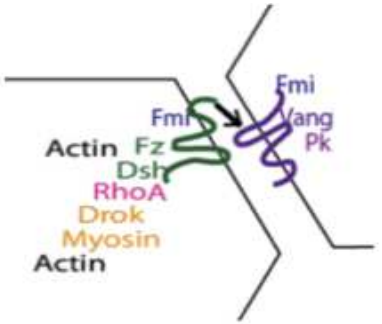
OUTLINE

- **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**
  - -> *open problem: weakly boundedness*









THE PETRI NET FRAMEWORK

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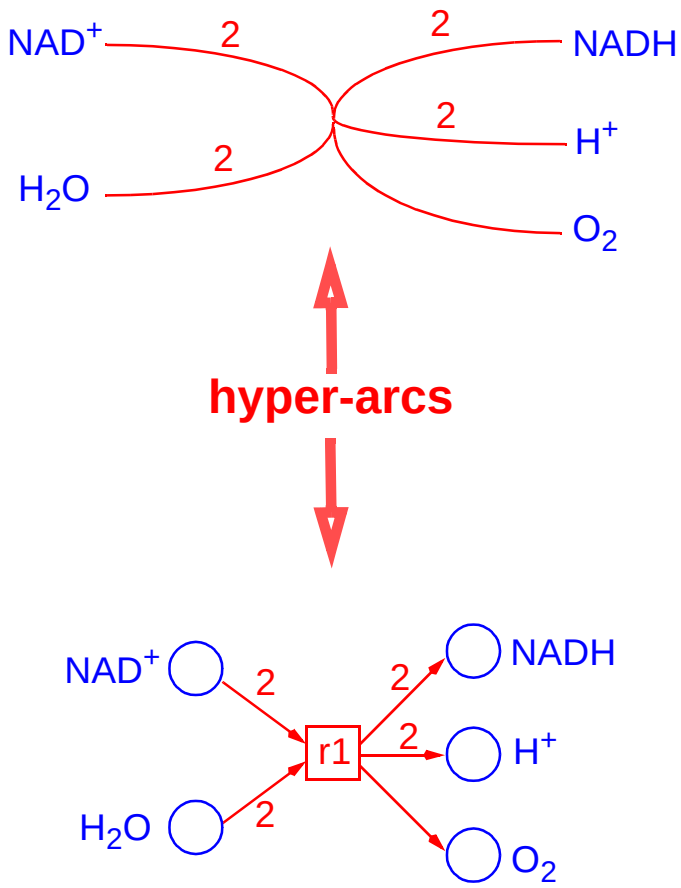
. . .

ARE NETWORKS OF BIOCHEMICAL REACTIONS

. . .

NATURALLY EXPRESSIBLE AS PETRI NETS

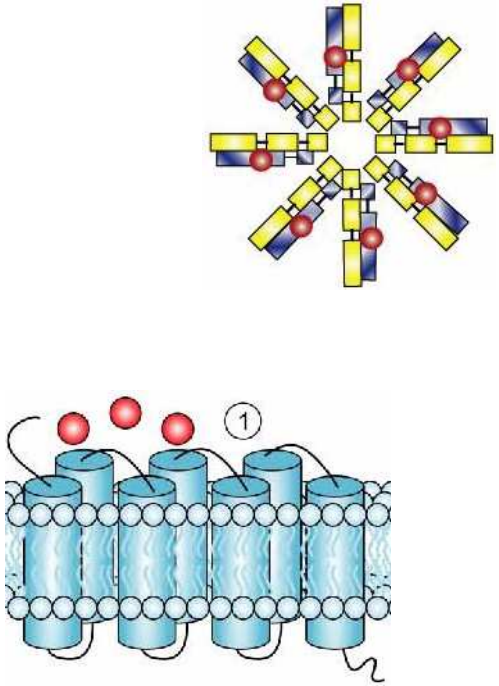
$$2\ NAD^+ + 2\ H_2O \rightarrow 2\ NADH + 2\ H^+ + O_2$$



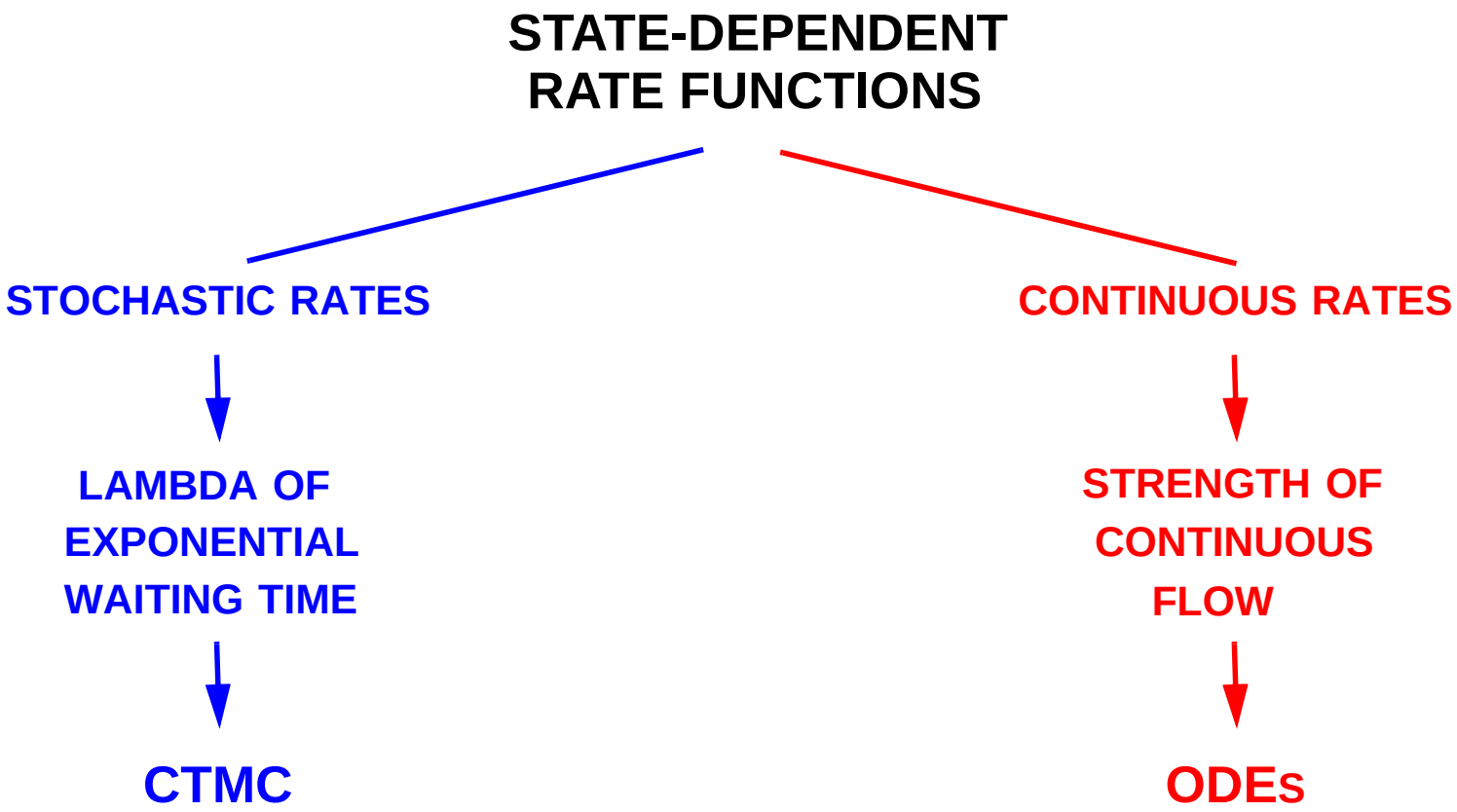
PLACES, TRANSITIONS - SOME BIO INTERPRETATIONS

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

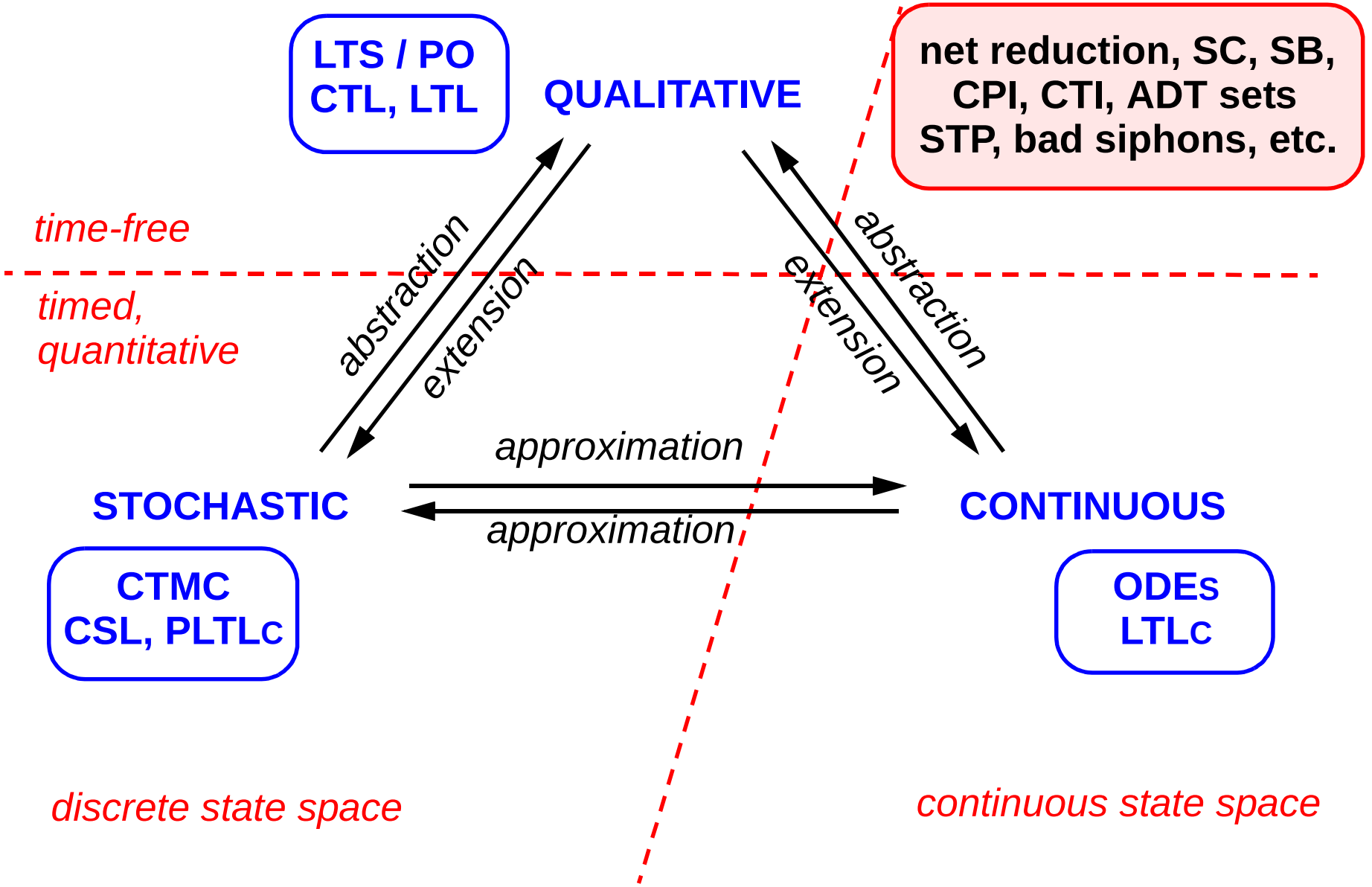
- **transitions -> atomic events**
  - -> *(stoichiometric) chemical reaction*
  - -> *complexation / decomplexation*
  - -> *phosphorylation / dephosphorylation*
  - -> *conformational change*
  - -> *transport step, . . . , etc.*
  - *. . . in different locations*



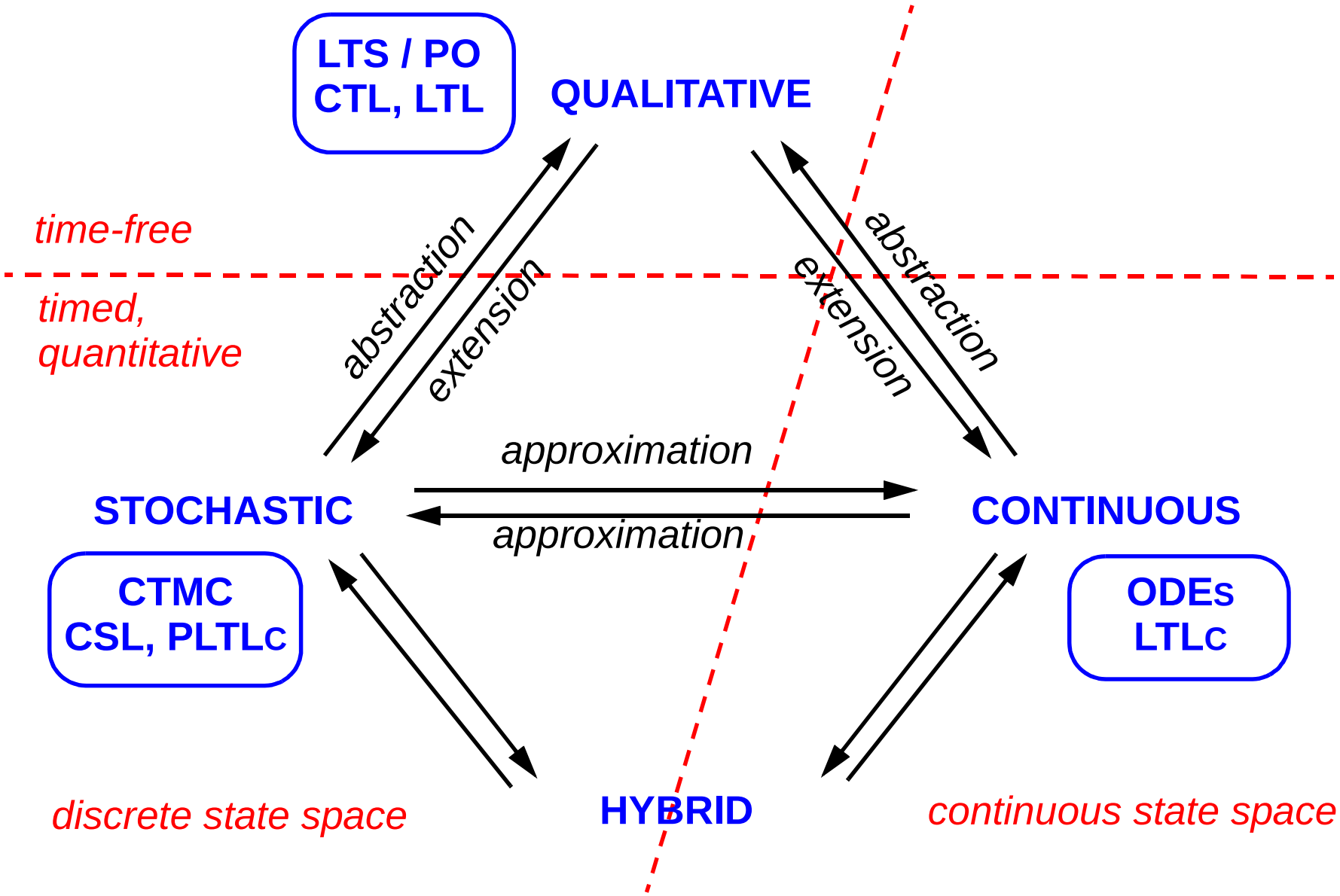
ADDING TIME



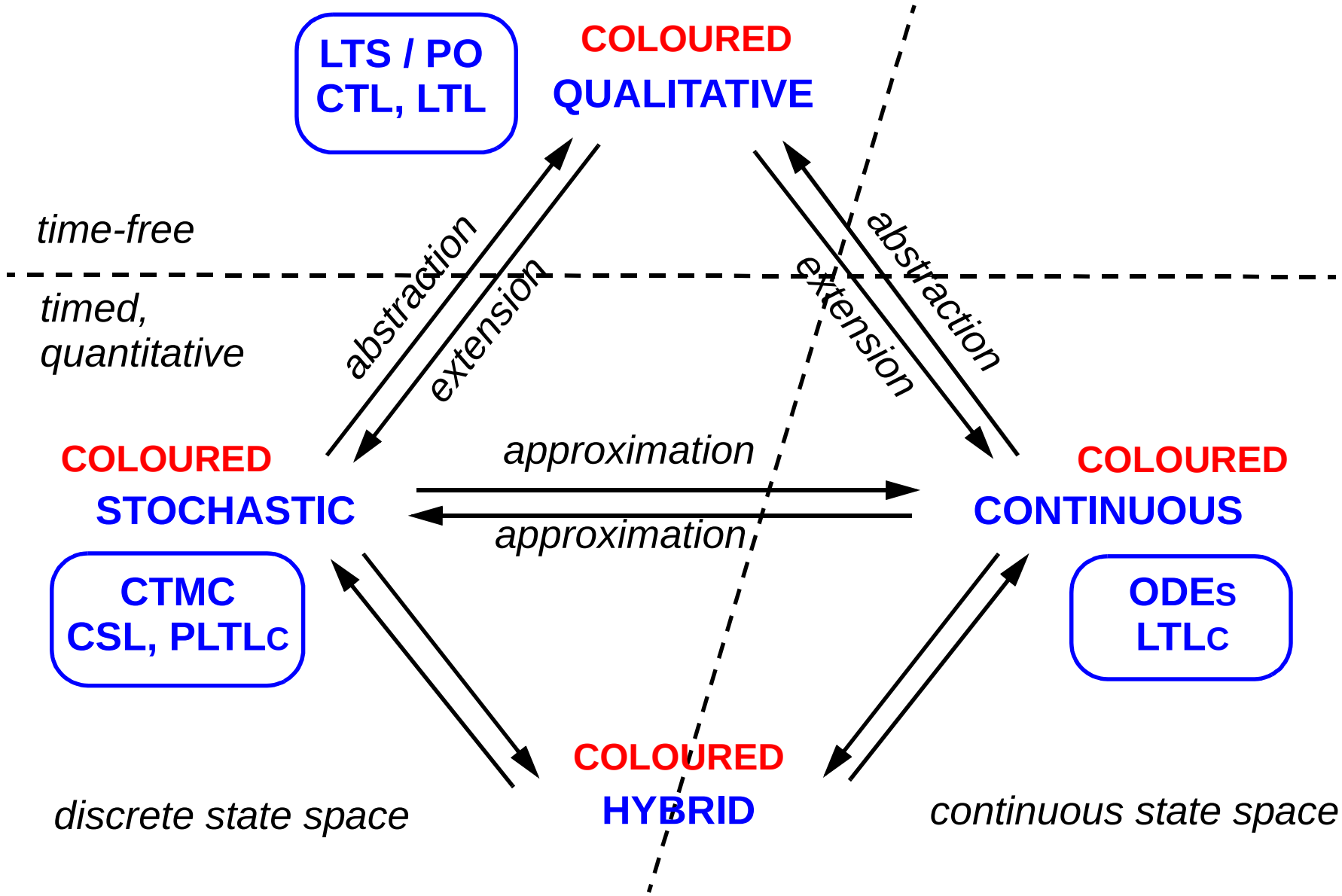
-> supported by, e.g., COPASI, Dizzy, ..., Snoopy


LTS / PO
CTL, LTL
QUALITATIVE
net reduction, SC, SB,
CPI, CTI, ADT sets
STP, bad siphons, etc.
time-free
timed,
quantitative
abstraction
extension
abstraction
extension
approximation
approximation
STOCHASTIC
CONTINUOUS
CTMC
CSL, PLTLc
ODEs
LTLc
discrete state space
continuous state space

FRAMEWORK 2010

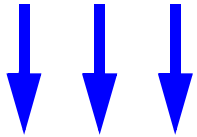


COLOURED FRAMEWORK 2011



4x2

MODELS SHARING STRUCTURE



QUANTITATIVE MODEL = QUALITATIVE MODEL

+

RATE FUNCTIONS (KINETICS)

MODELLING
BIO PETRI NETS

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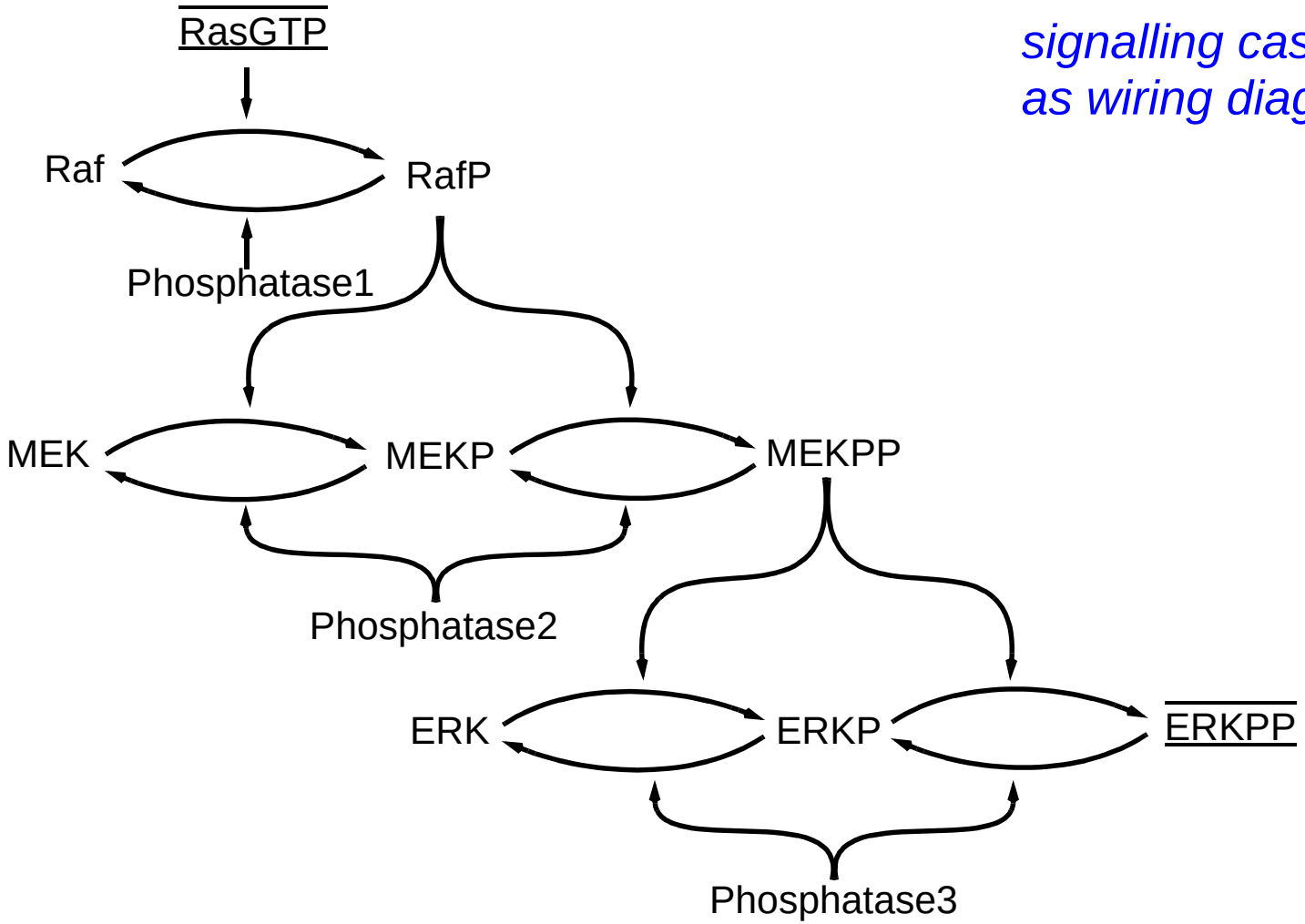
APPROACH 1

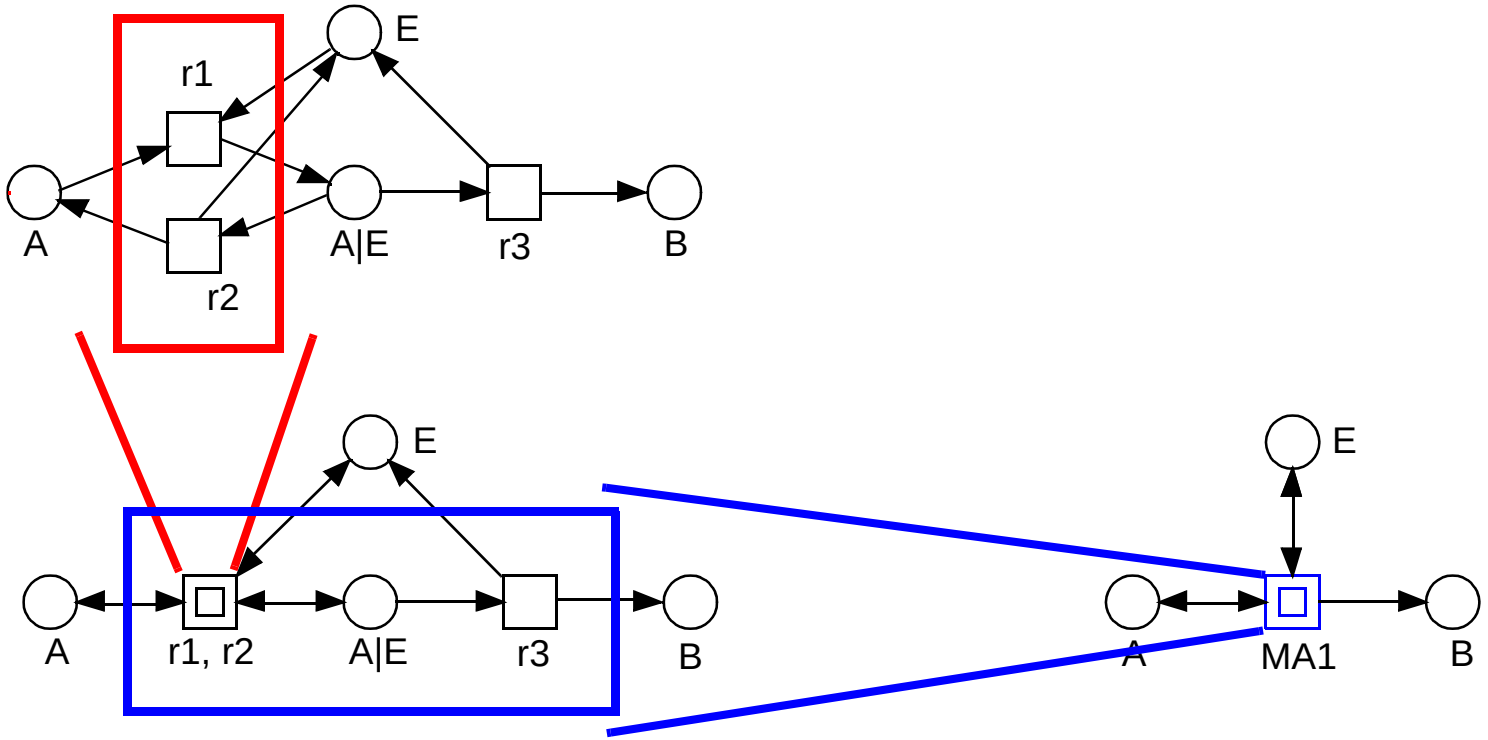
signalling cascade as wiring diagram



BASIC STRUCTURE

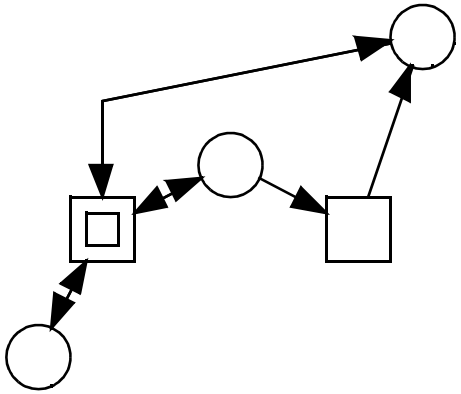
$$A \xleftrightarrow{E} A|E \rightarrow B$$

enzymatic reaction,
mass-action kinetics



NET COMPOSITION FROM BUILDING BLOCKS

SINGLE
MASS-ACTION STEP



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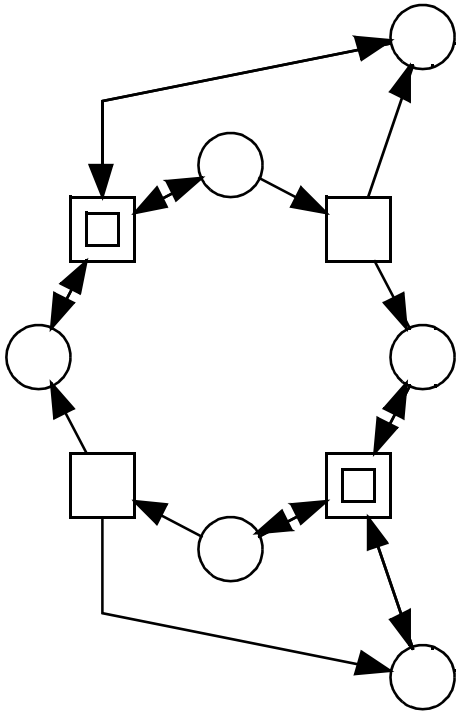
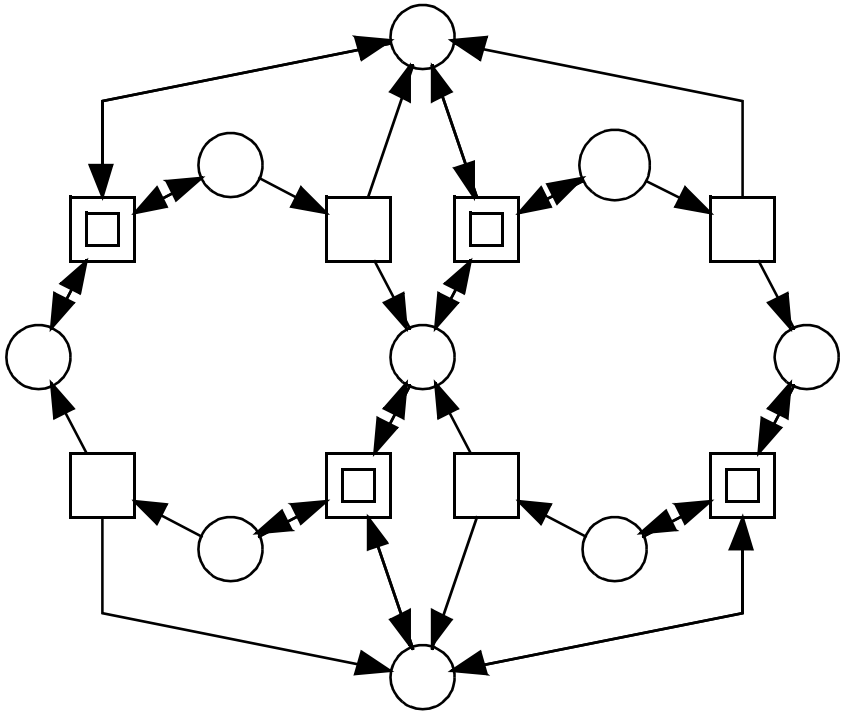
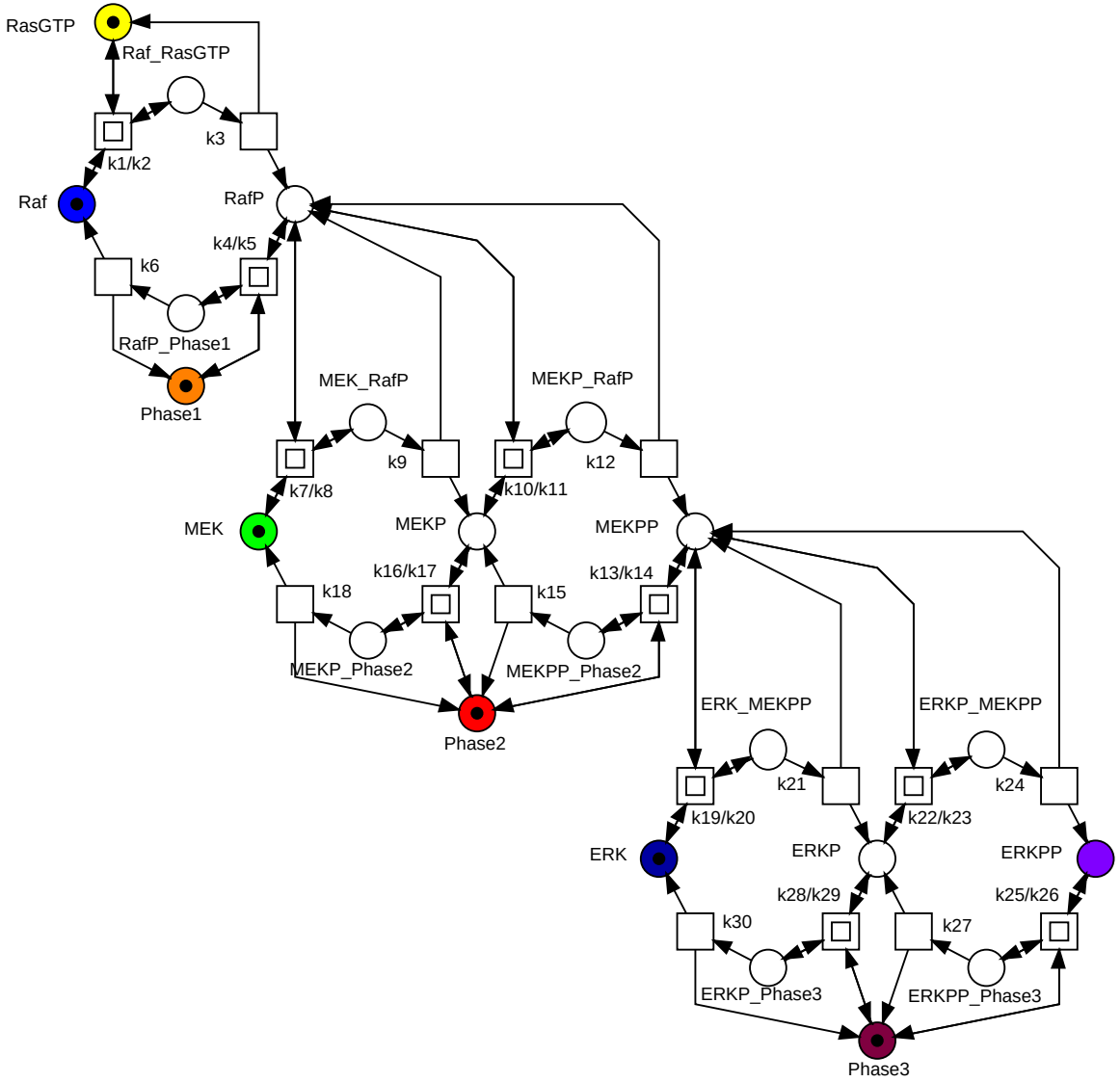


SINGLE
PHOSPHOYLATION / DEPHOSPHORYLATION

DOUBLE PHOSPHOYLATION / DEPHOSPHORYLATION



SIGNALLING CASCADE AS PETRI NET



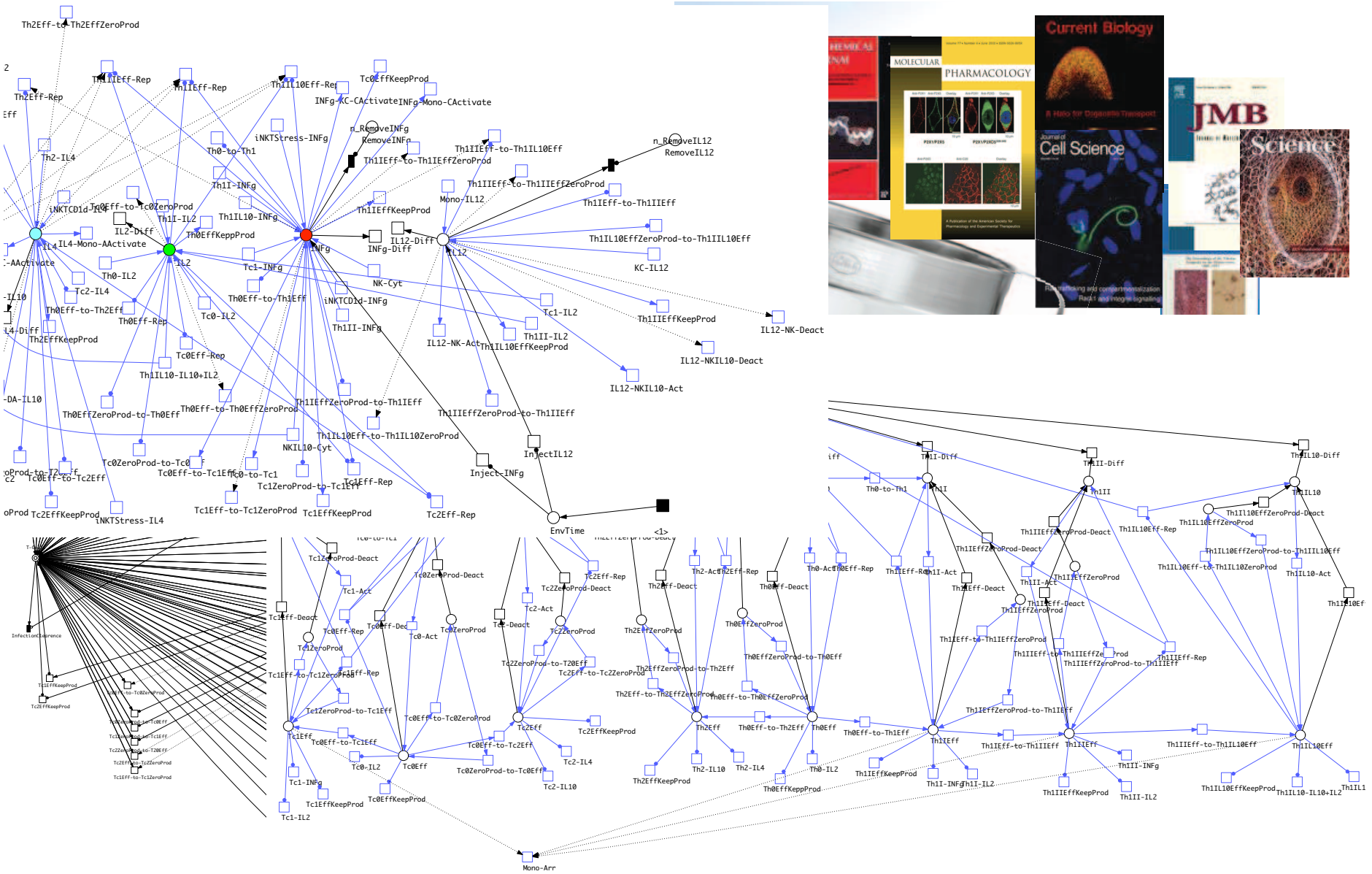
[GILBERT, HEINER, LEHRACK 2007]

[HEINER, GILBERT, DONALDSON 2008]

APPROACH 2


Current Biology
MOLECULAR
PHARMACOLOGY
Journal of
Cell Science
JMB
Science
Literature

APPROACH 2



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BIO NETWORKS, SOME PROBLEMS

- **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*

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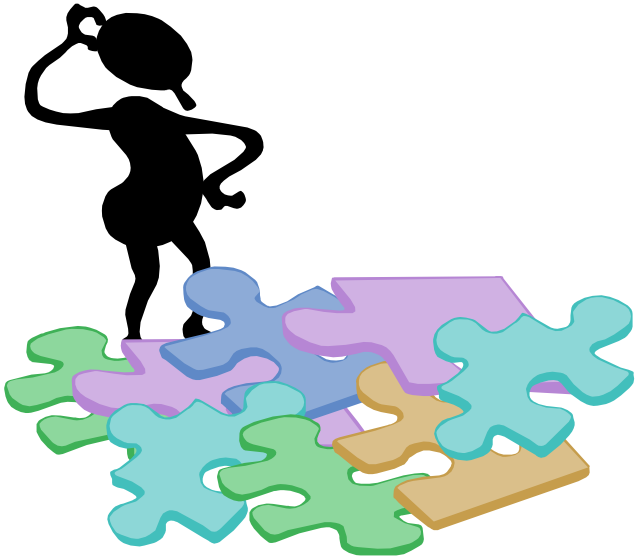
MODELS ARE PATCHWORKS FULL OF ASSUMPTIONS

PETRI NETS - THE BIG PROS



- **readable & unambigious**
  -> fault avoidant model construction
- **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

- **a representation of the net structure** **=> stoichiometric matrix**

$C =$

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

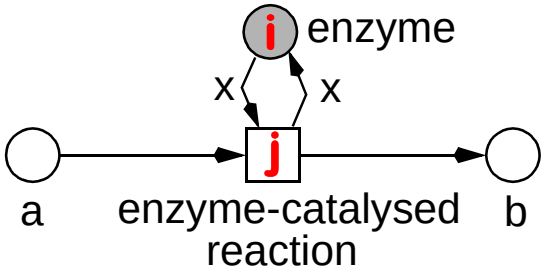
$cij = (pi, tj) = F(tj,pi) - F(pi, tj) = \Delta\, tj(pi)$

$\Delta tj = \Delta\, tj(*)$

- **matrix entry cij:**
  token change in place pi by firing of transition tj

- **matrix column Δtj:**
  vector describing the change of the whole marking by firing of tj

- **side-conditions are neglected**



cij = 0

T-INVARIANTS, BASICS

- **Lautenbach, 1973** -> **Schuster, 1993**
- **T-invariant x** -> *multiset of transitions*
  -> *integer solution of* $Cx = 0, x \neq 0, x \geq 0$
- **support of a T-invariant x -> supp(x)** -> *set of transitions*
  -> *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 occuring one after the other
     -> *substance / signal flow*
  2. *relative transition firing rates* **-> steady state behaviour**
     of transitions occuring 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*

T-INVARIANTS, INTERPRETATIONS

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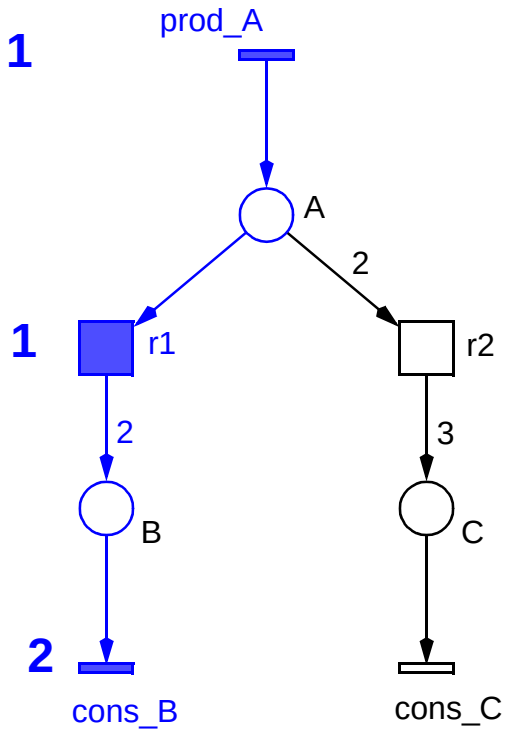
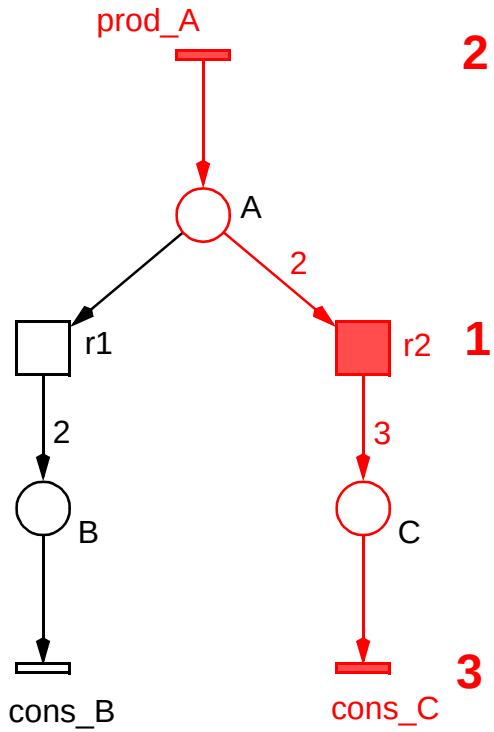
T- INVARIANTS, EX

r1: A -> 2 B
r2: 2 A -> 3 C



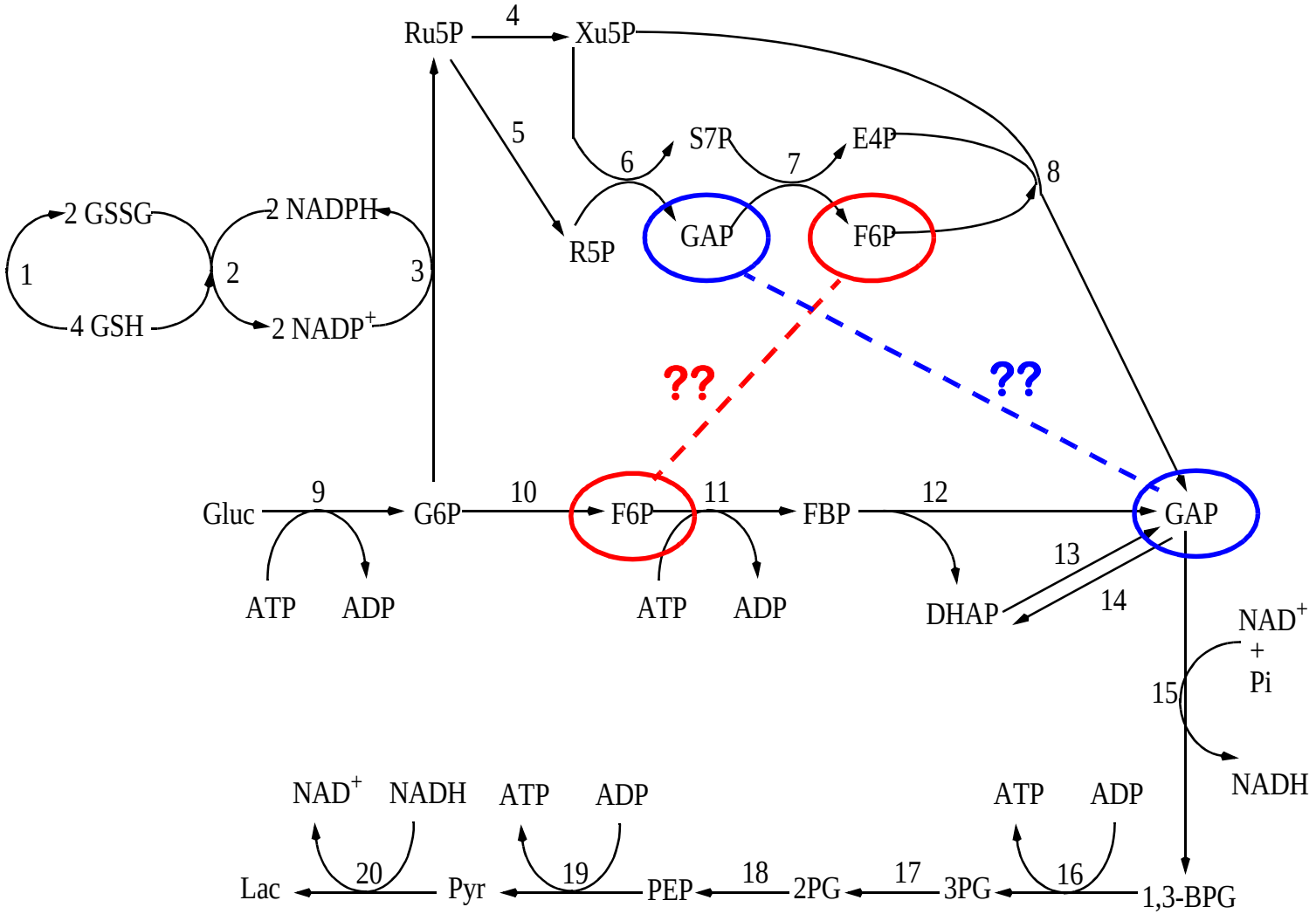
T-INVARIANT 1



T-INVARIANT 2

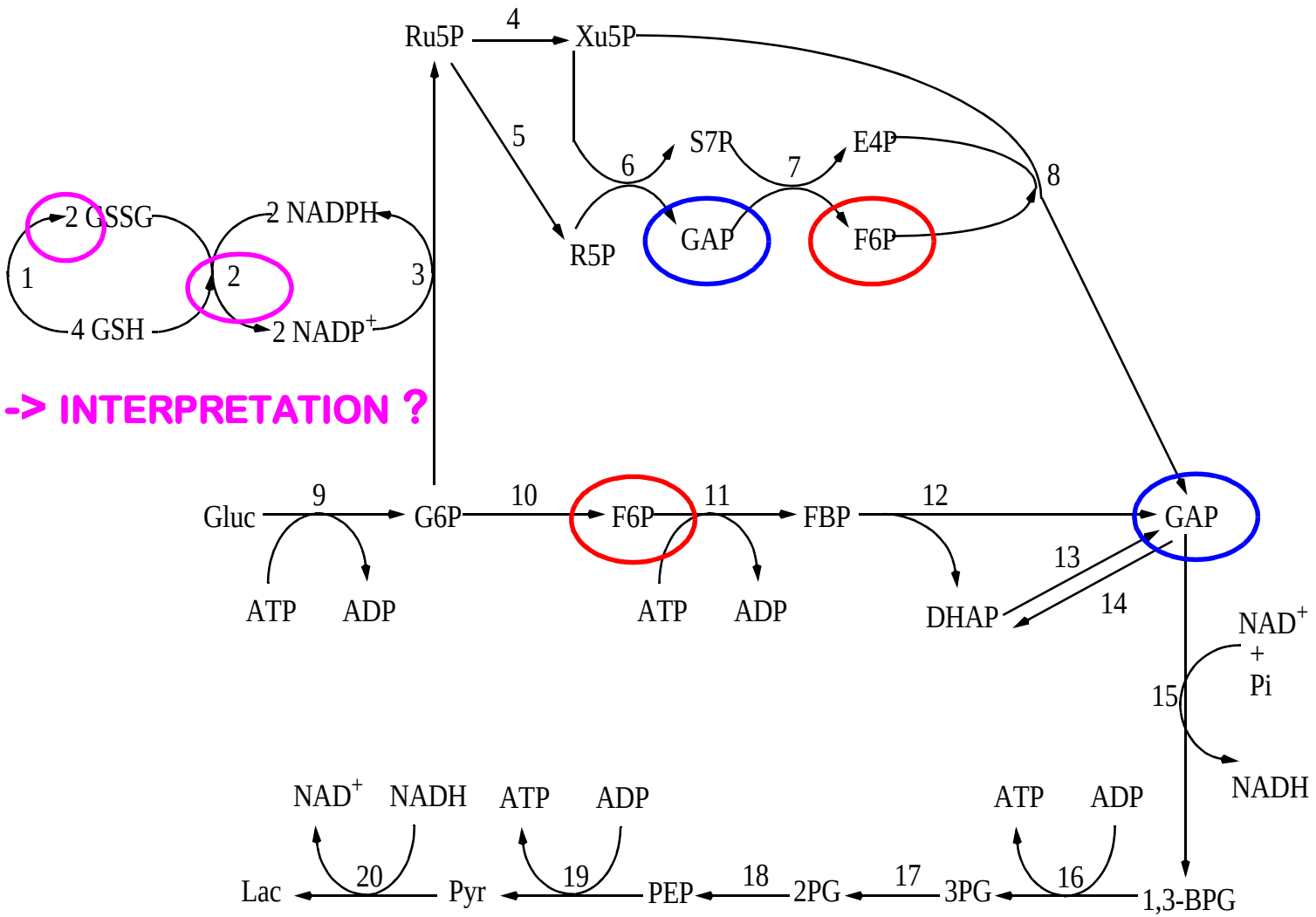
Ex1 - Glycolysis and Pentose Phosphate Pathway

[Reddy 1993]



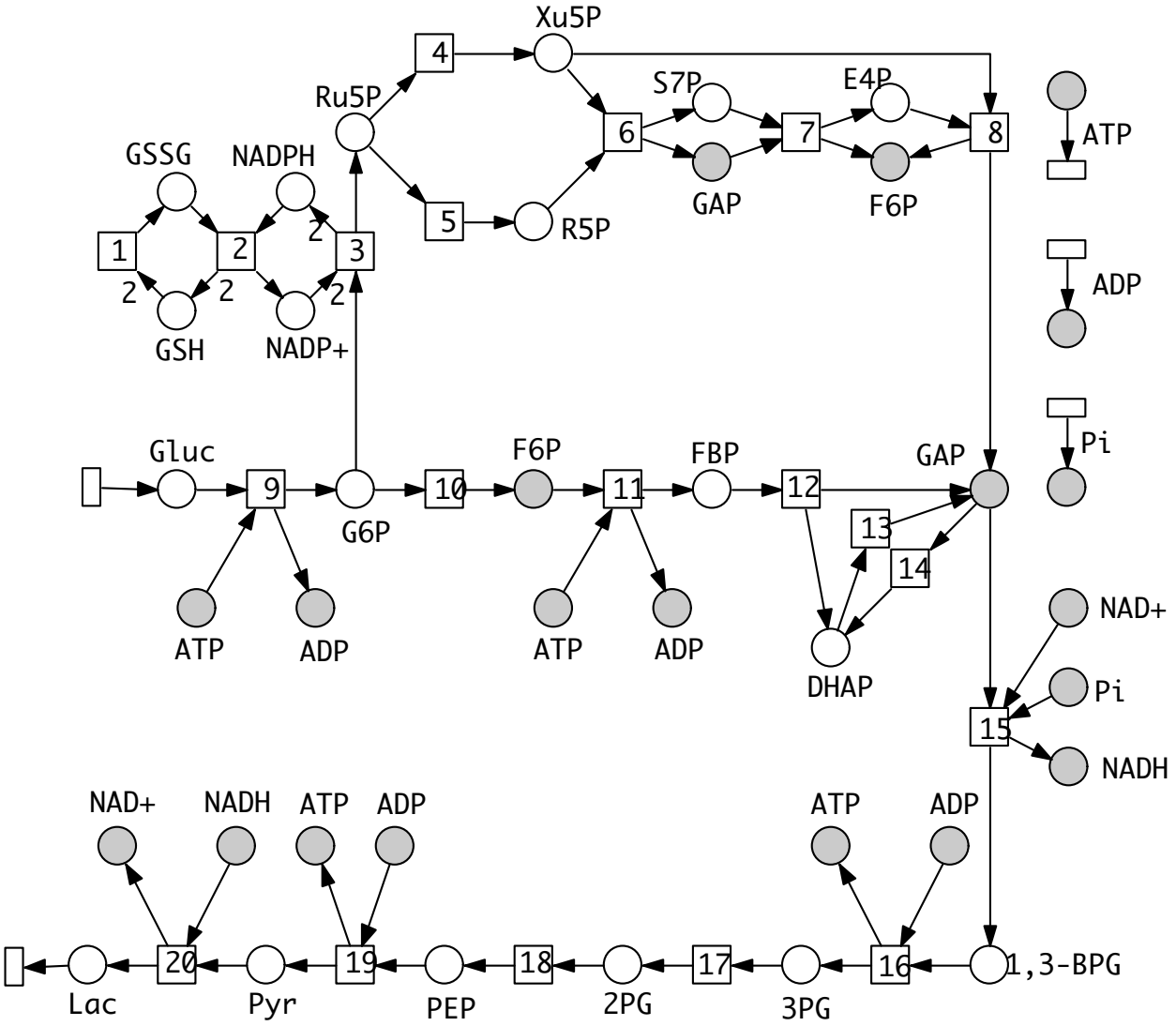
Ex1 - Glycolysis and Pentose Phosphate Pathway

[Reddy 1993]



Ex1 - Glycolysis and Pentose Phosphate Pathway

[Reddy 1993]
[Heiner 1998]



Ex1 - Glycolysis and Pentose Phosphate Pathway

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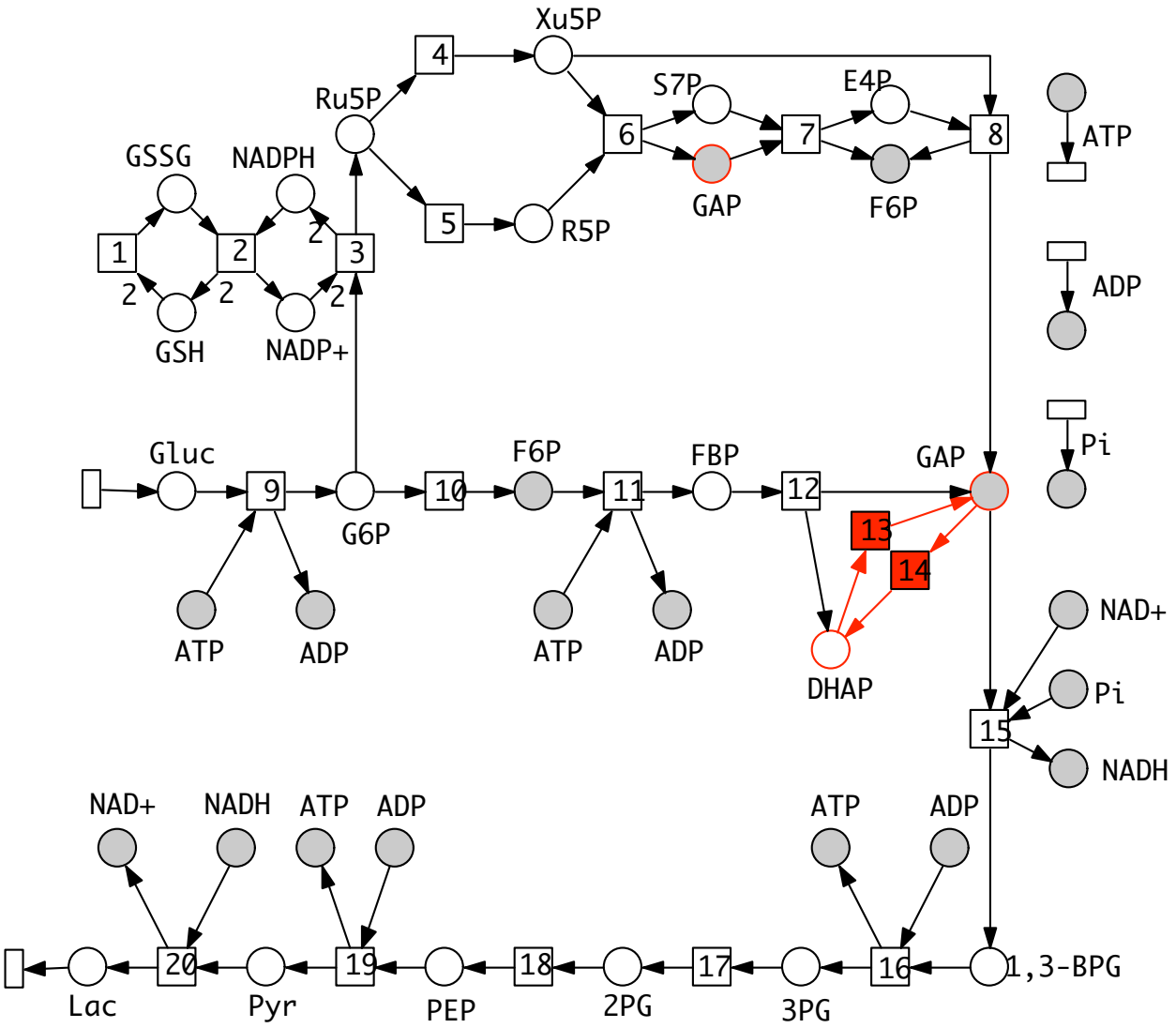

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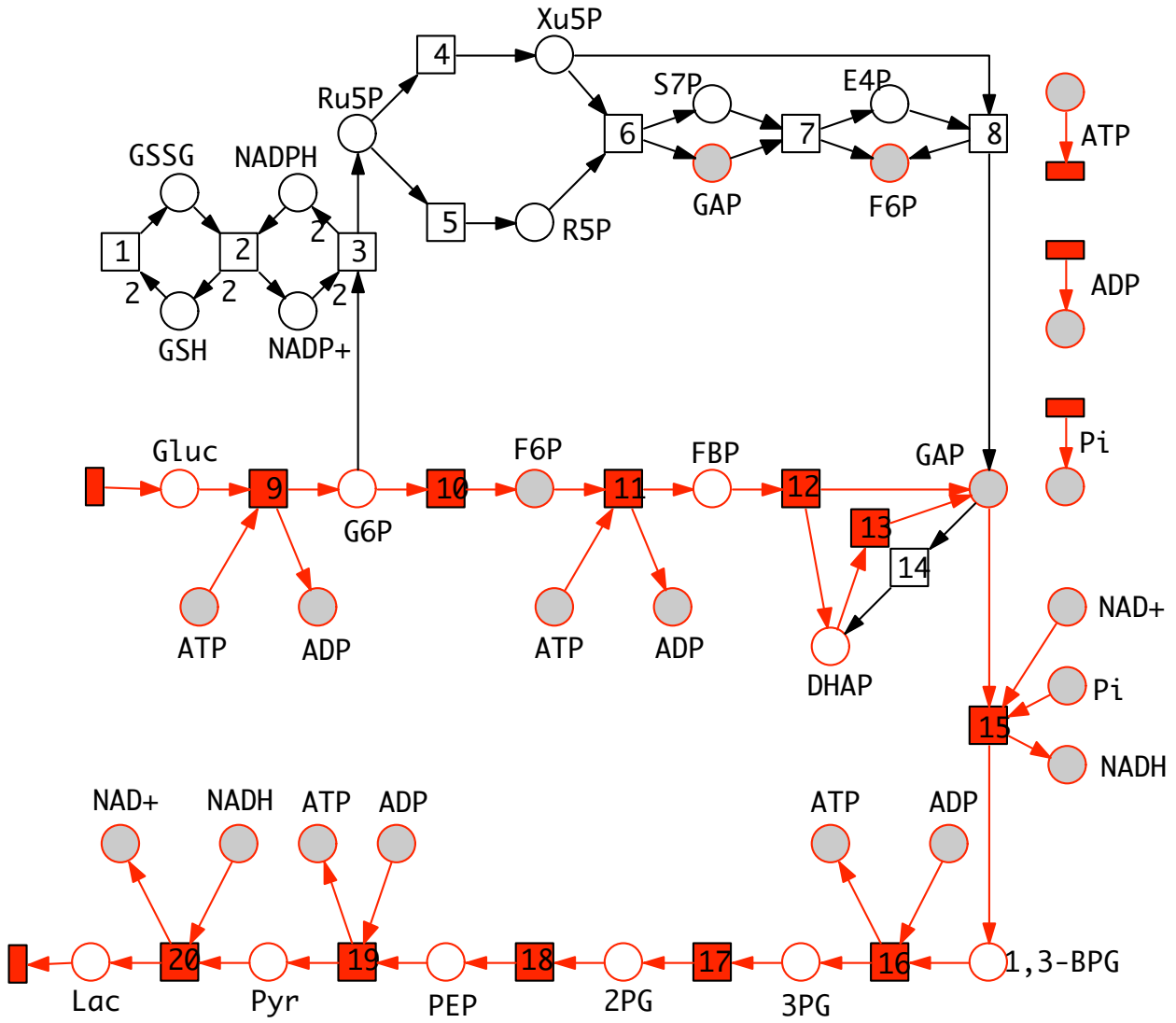

Ex1 - Glycolysis and Pentose Phosphate Pathway

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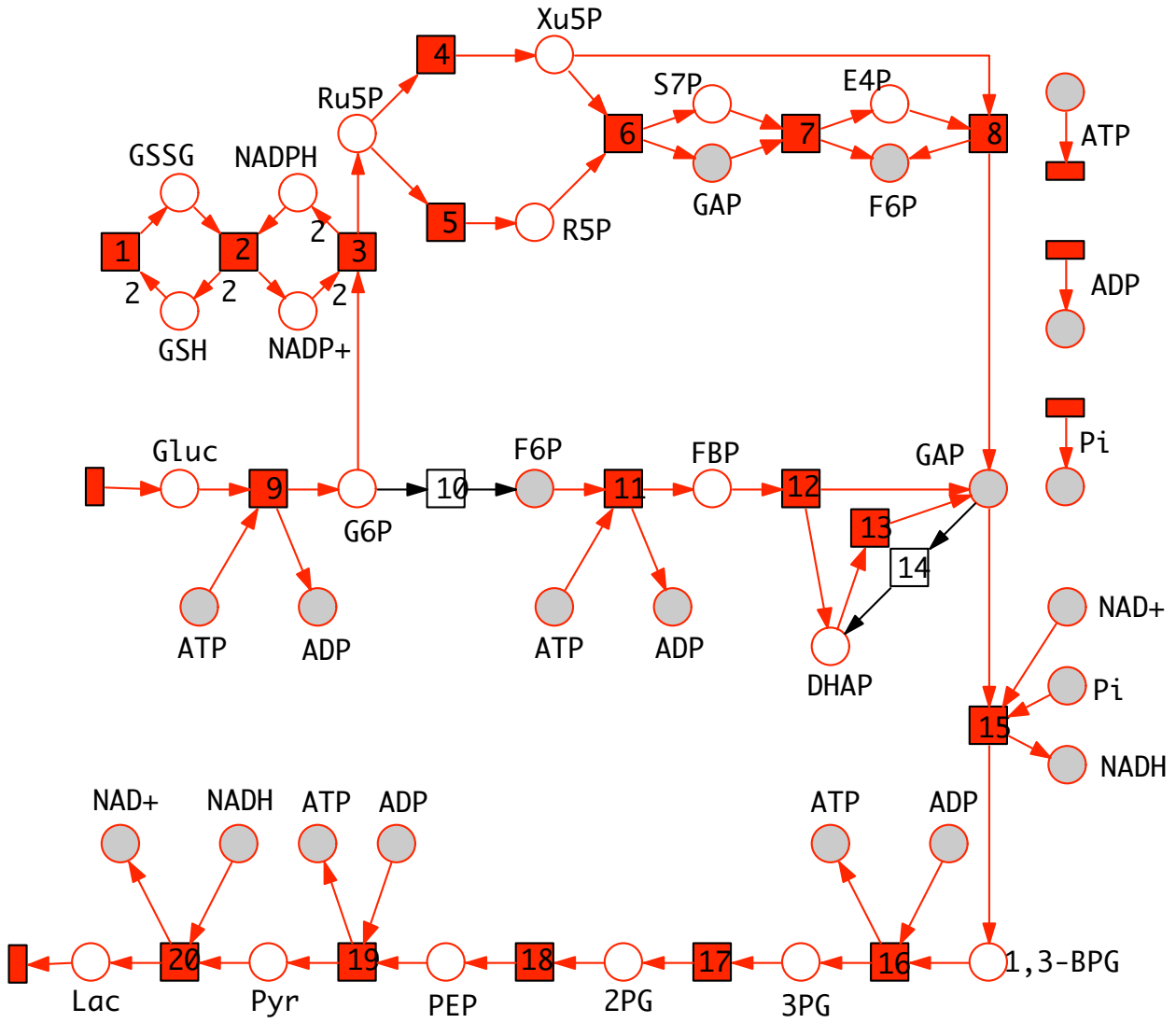

Ex1 - Glycolysis and Pentose Phosphate Pathway

[Reddy 1993]
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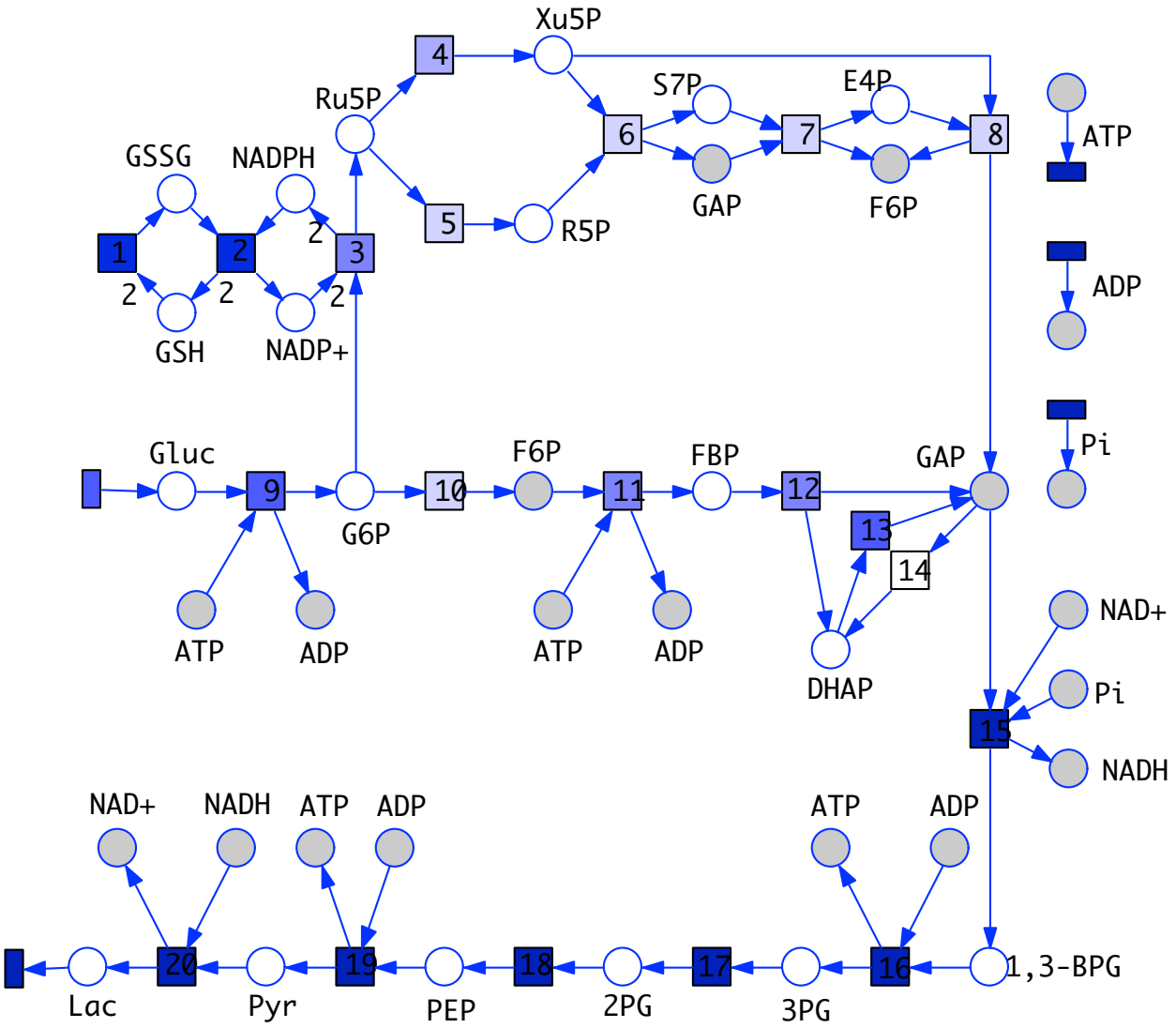
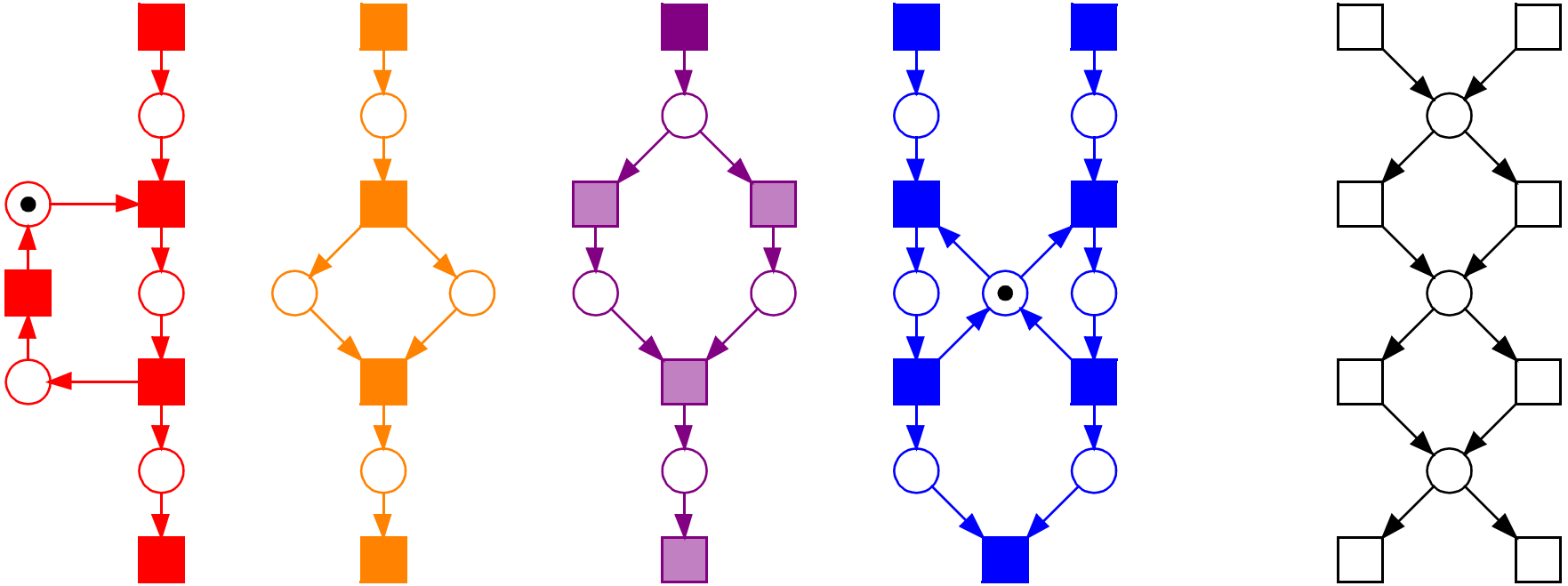


- **T-invariants may contain any structure**



- **minmal T-invariants generally overlap**

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

MODULARIZATION BY T-INVARIANTS

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ABSTRACT DEPENDENT TRANSITION SETS (ADT-SETS)

- **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 $\mathbf{x}$, i.e.

$$\forall(x \in X) \; : \; supp(x)(i) \; = \; supp(x)(j)$$

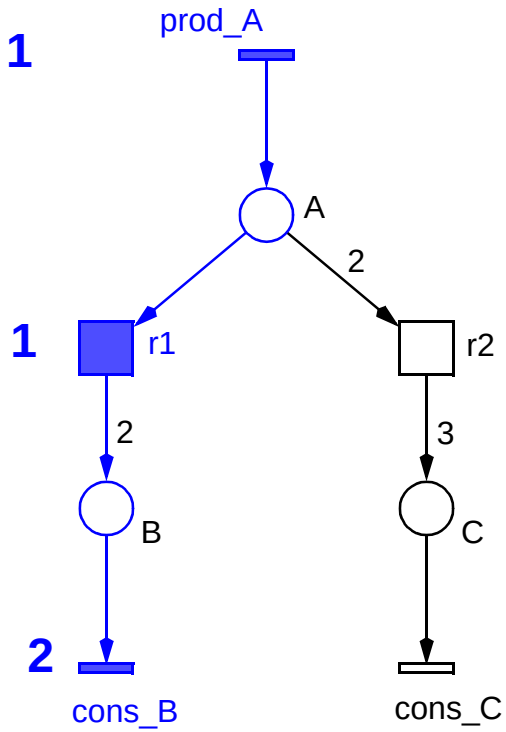
- **equivalence relation in the transition set, leading to a partition of T**
  - -> *reflexive*
  - -> *symmetric*
  - -> *transitive*

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

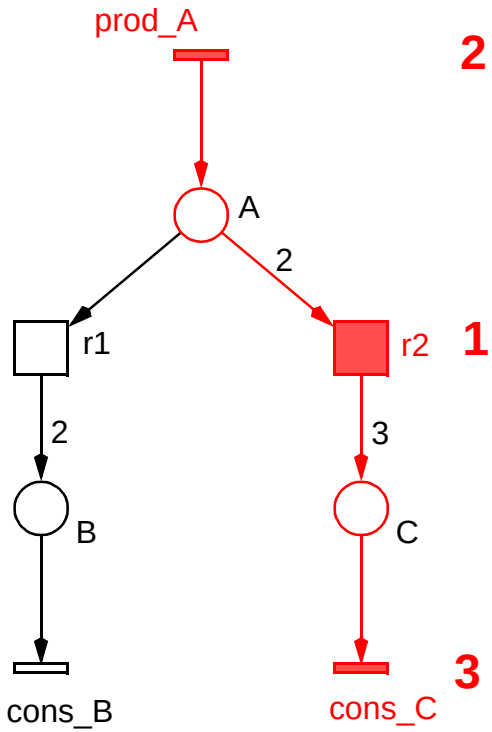
$$\forall(x \in X) \mathbf{:} \; A \subseteq supp(x) \vee A \cap supp(x) \; = \; \varnothing$$

ADT-SETS, EX1

r1: A -> 2 B
r2: 2 A -> 3 C



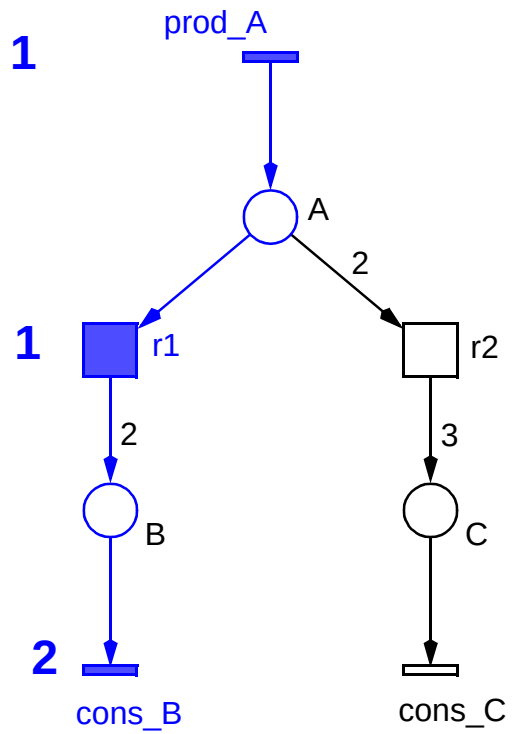
T-INVARIANT 1



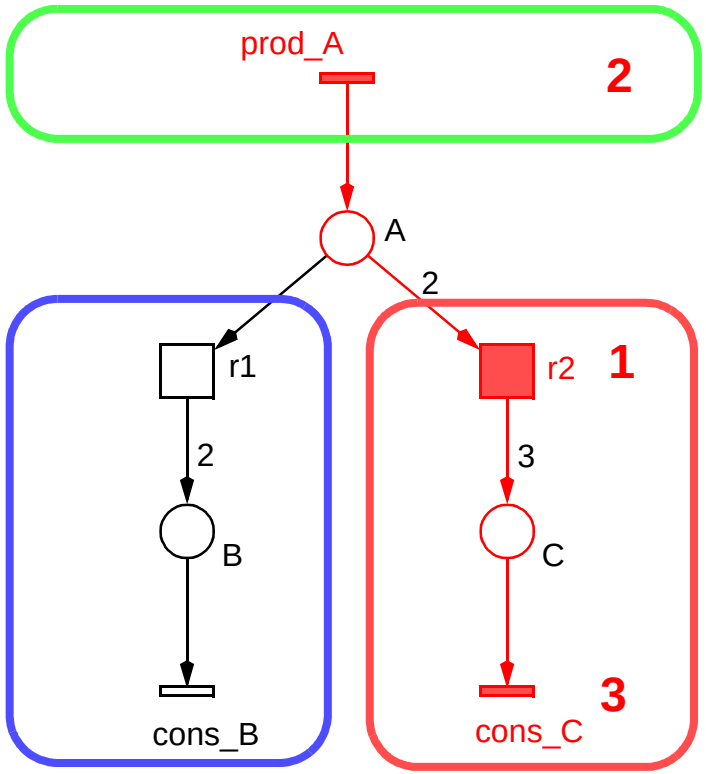
T-INVARIANT 2

ADT-SETS, EX1

r1: A -> 2 B
r2: 2 A -> 3 C



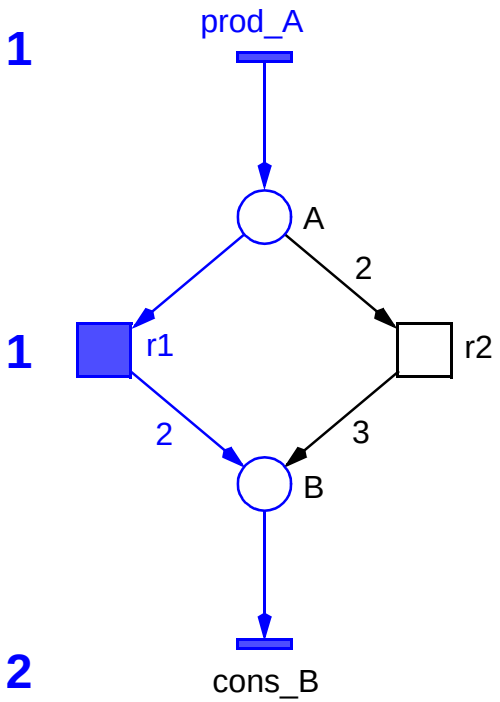
T-INVARIANT 1



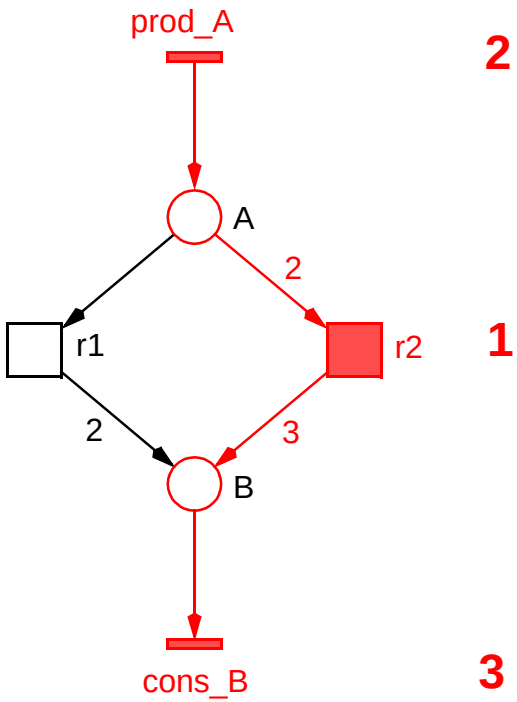
T-INVARIANT 2

AADT-SETS, EX2

r1: A -> 2 B
r2: 2 A -> 3 B



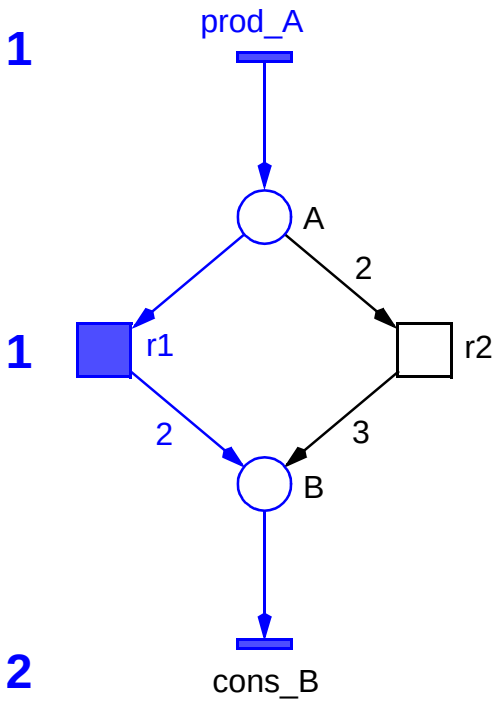
T-INVARIANT 1



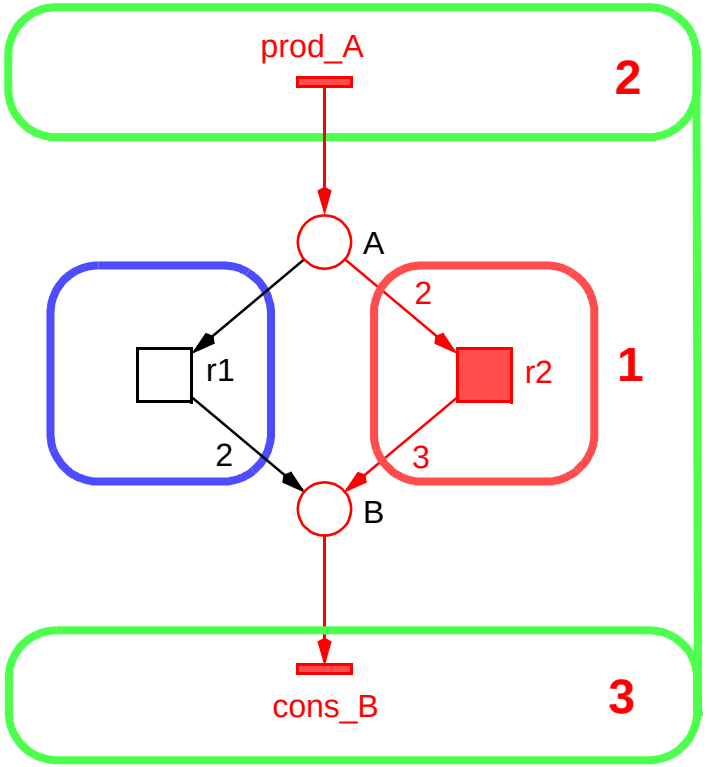
T-INVARIANT 2

ADT-SETS, EX2

r1: A -> 2 B
r2: 2 A -> 3 B



T-INVARIANT 1



T-INVARIANT 2

ADT-SETS, INTERPRETATION

- **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*

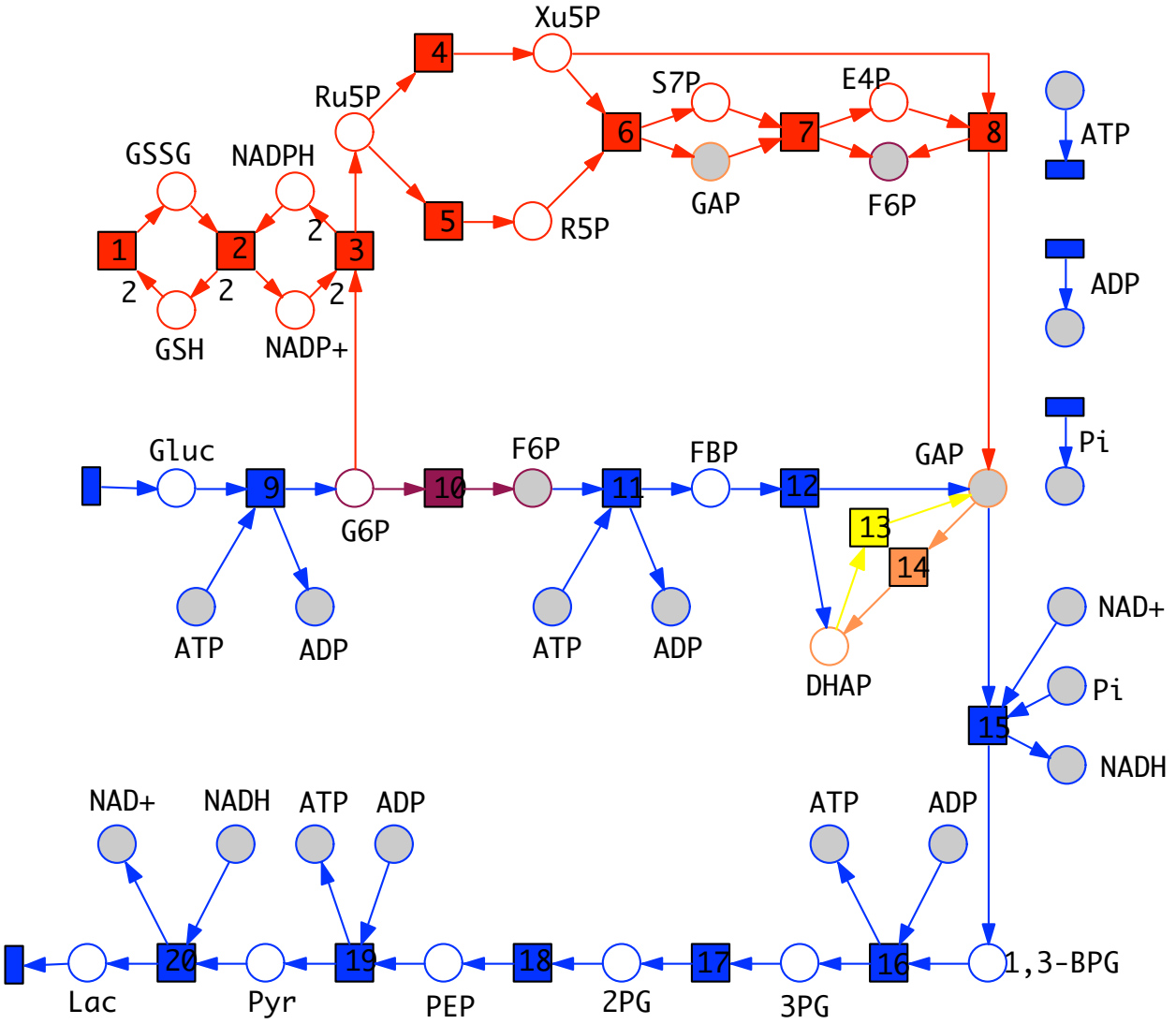
} *not necessarily maximal ADT-sets*

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

ADT-SETS, APPLICATION

- **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



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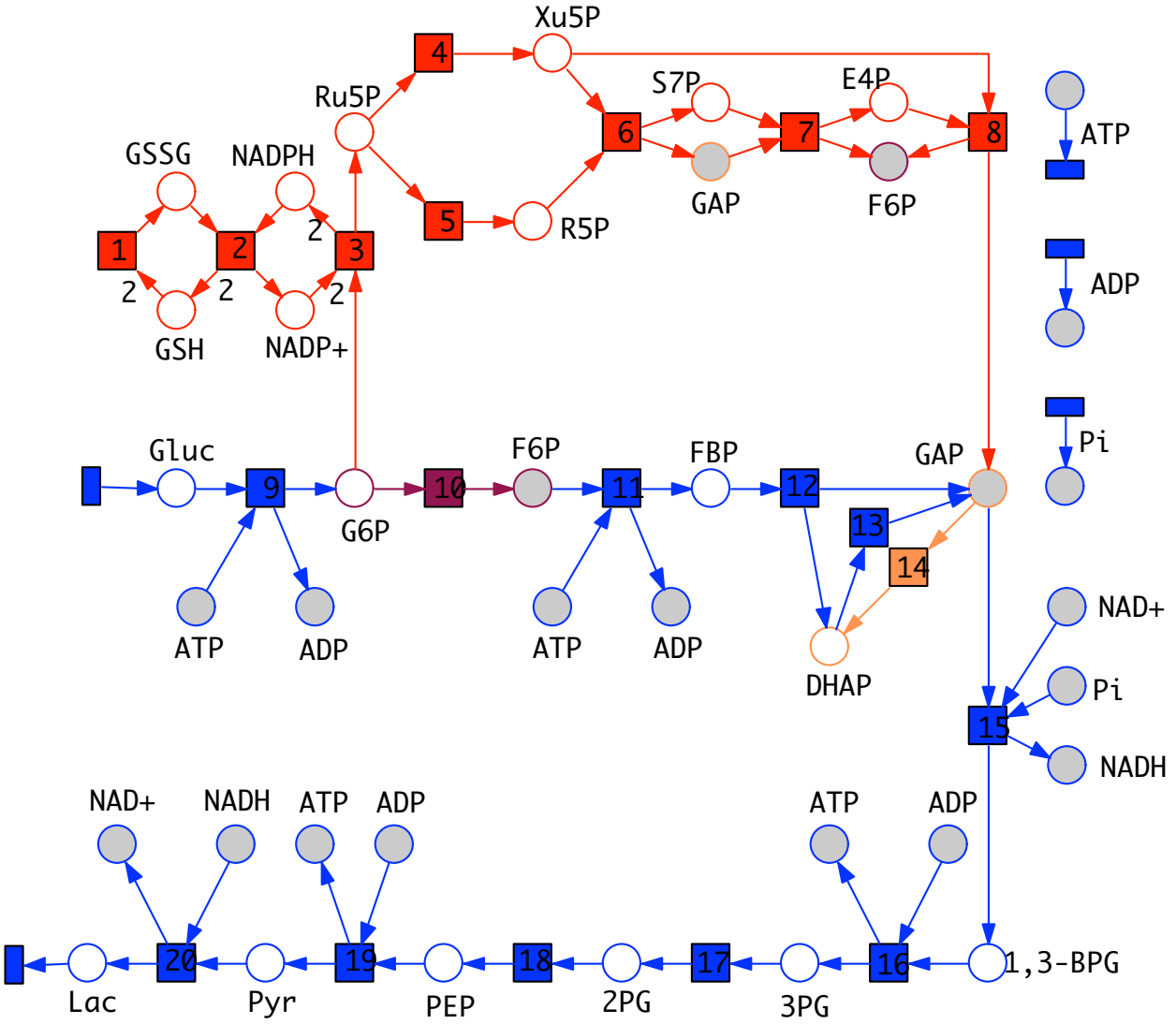

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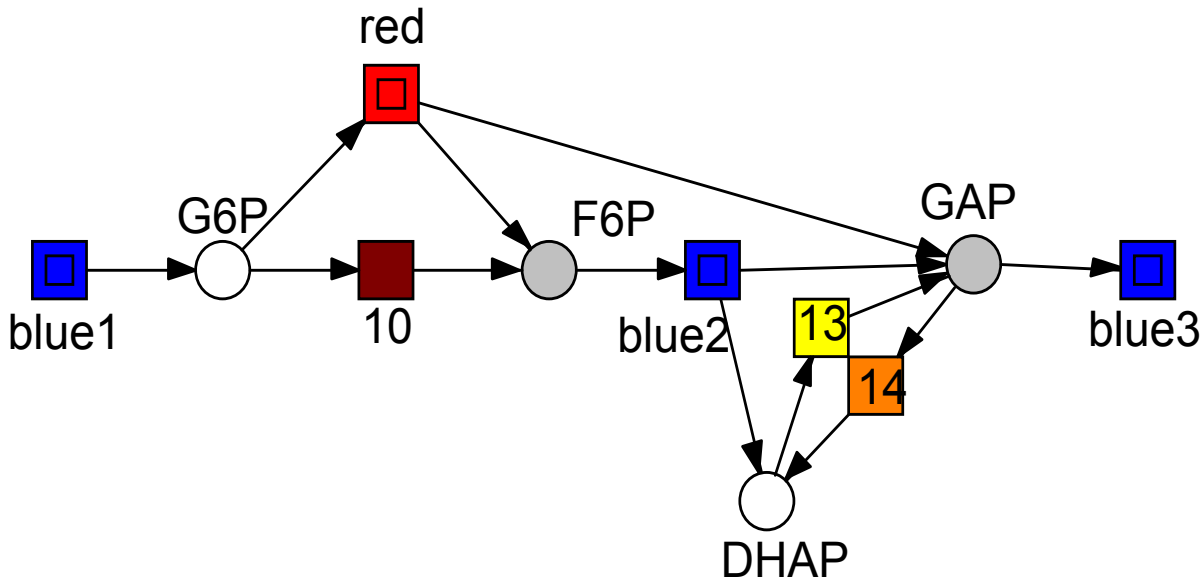
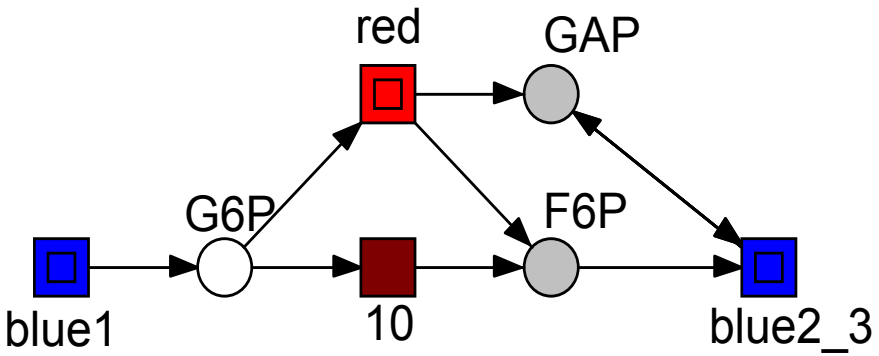
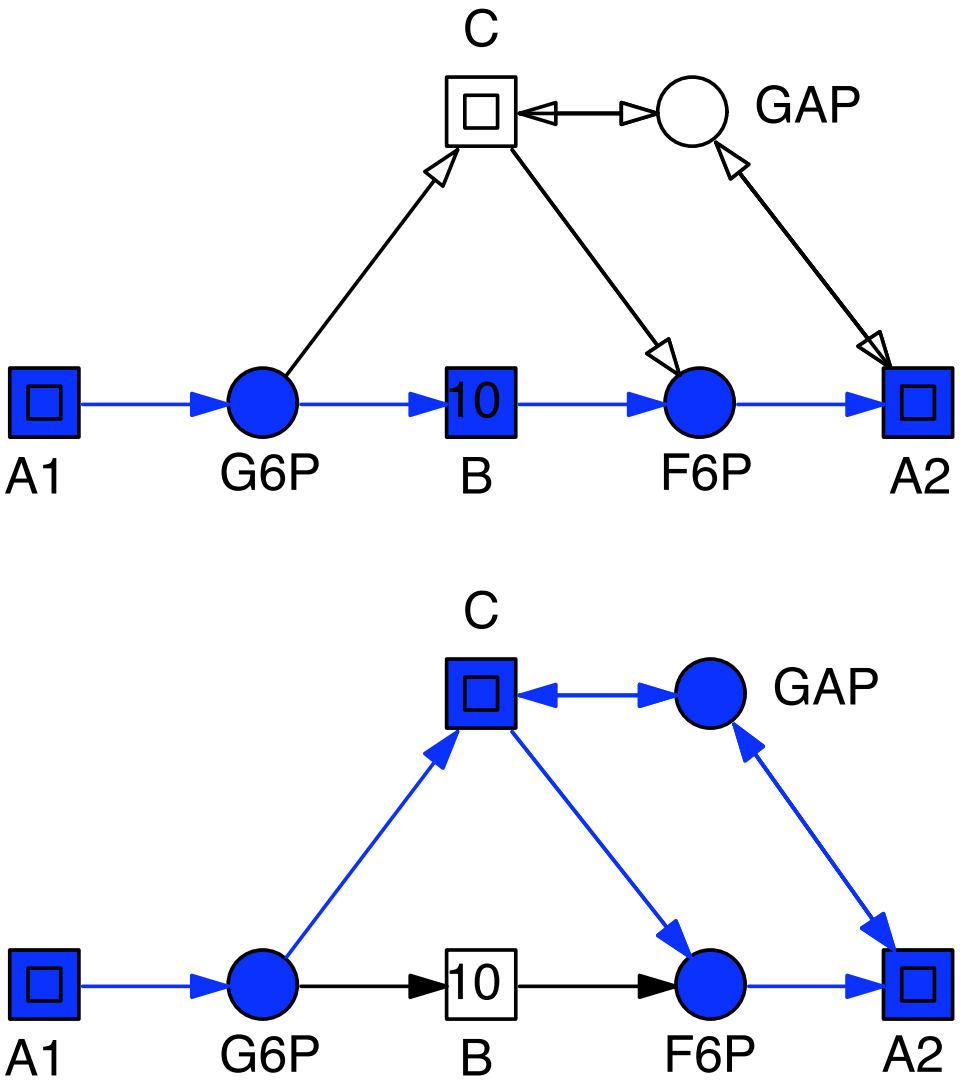
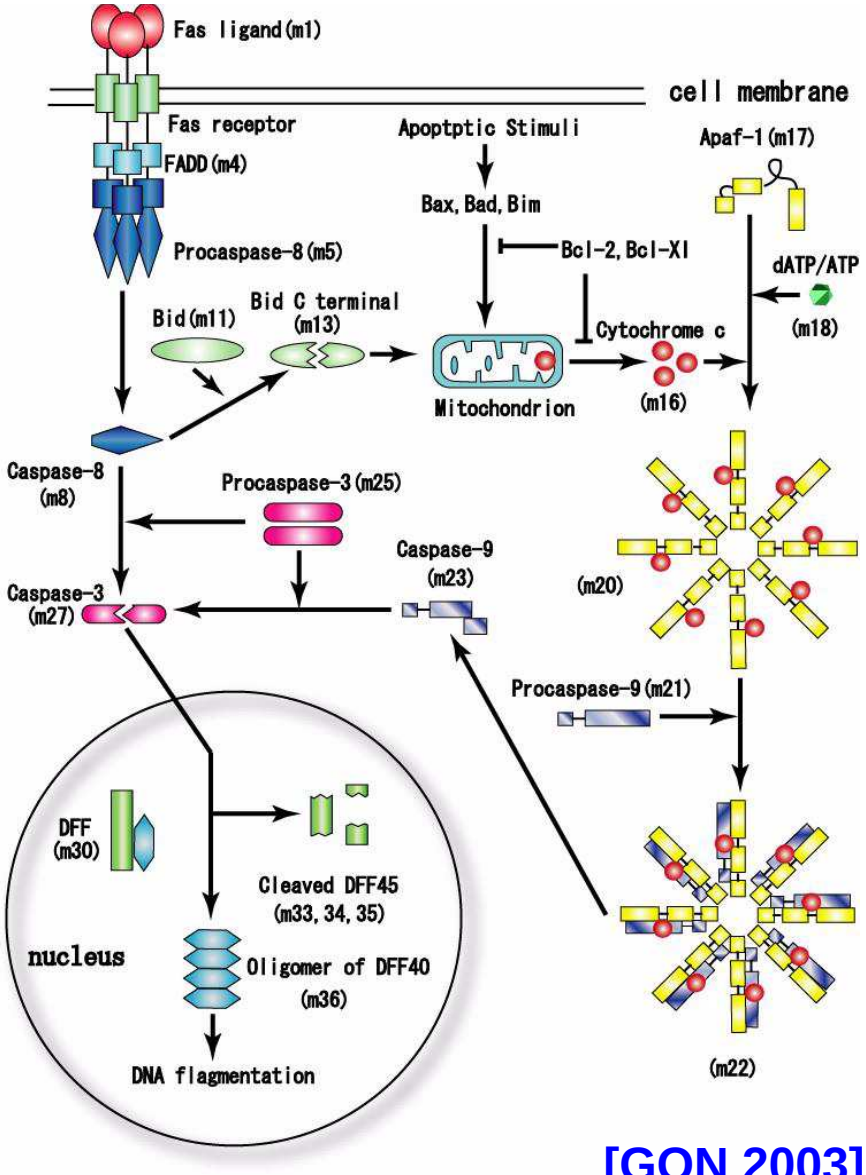




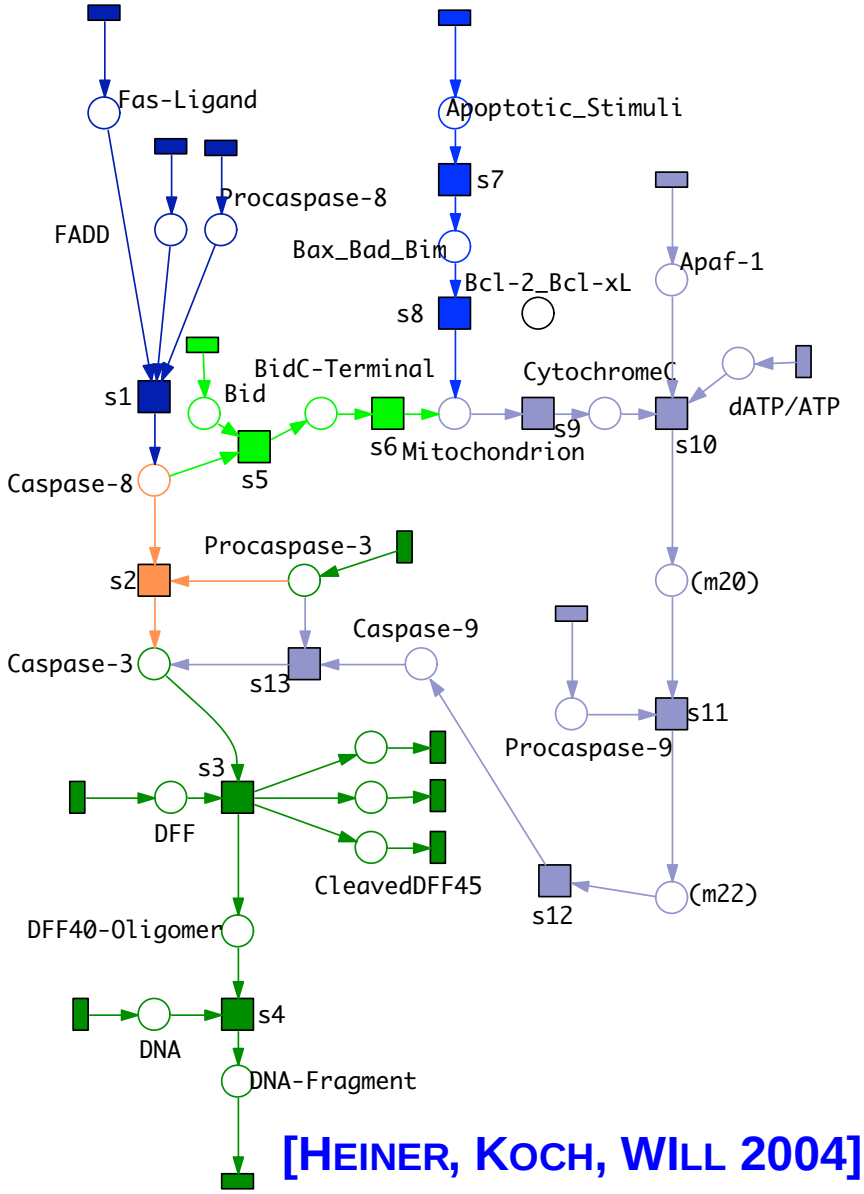
Ex1 - Glycolysis and Pentose Phosphate Pathway



EX2 - APOPTOSIS IN MAMMALIAN CELLS

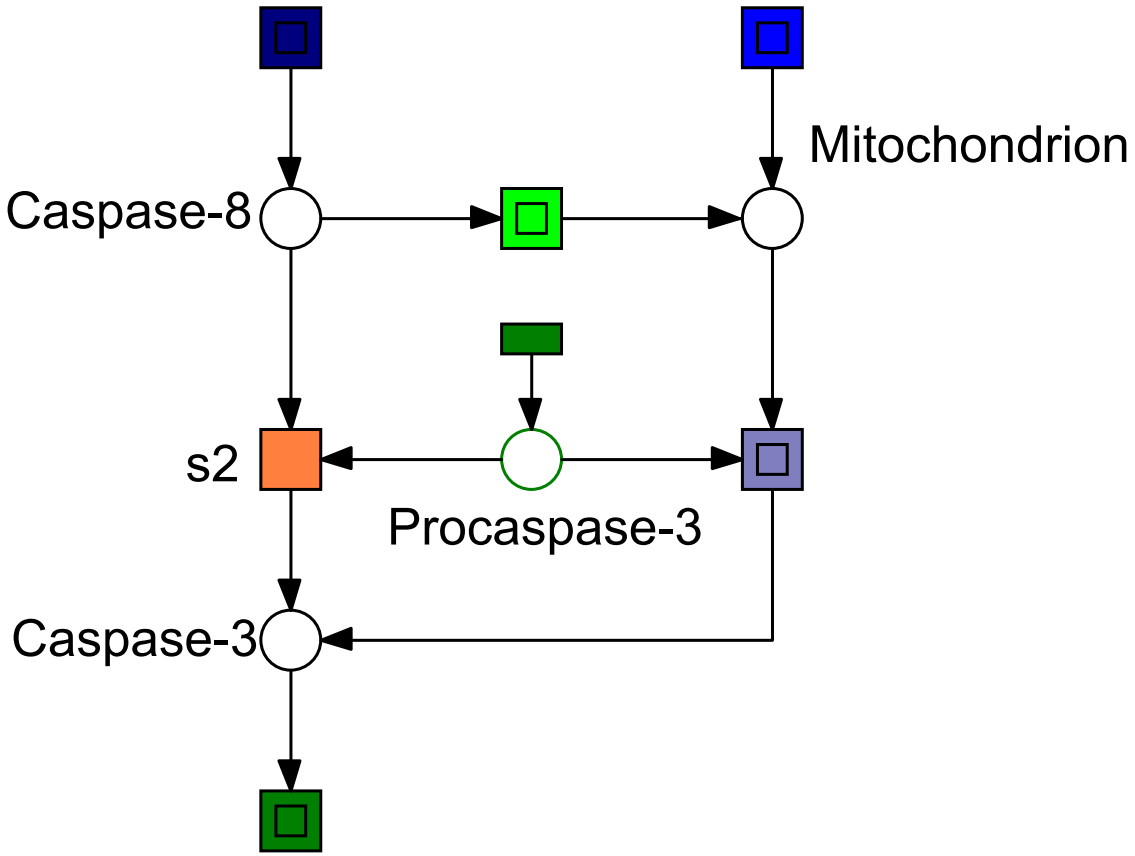


[GON 2003]

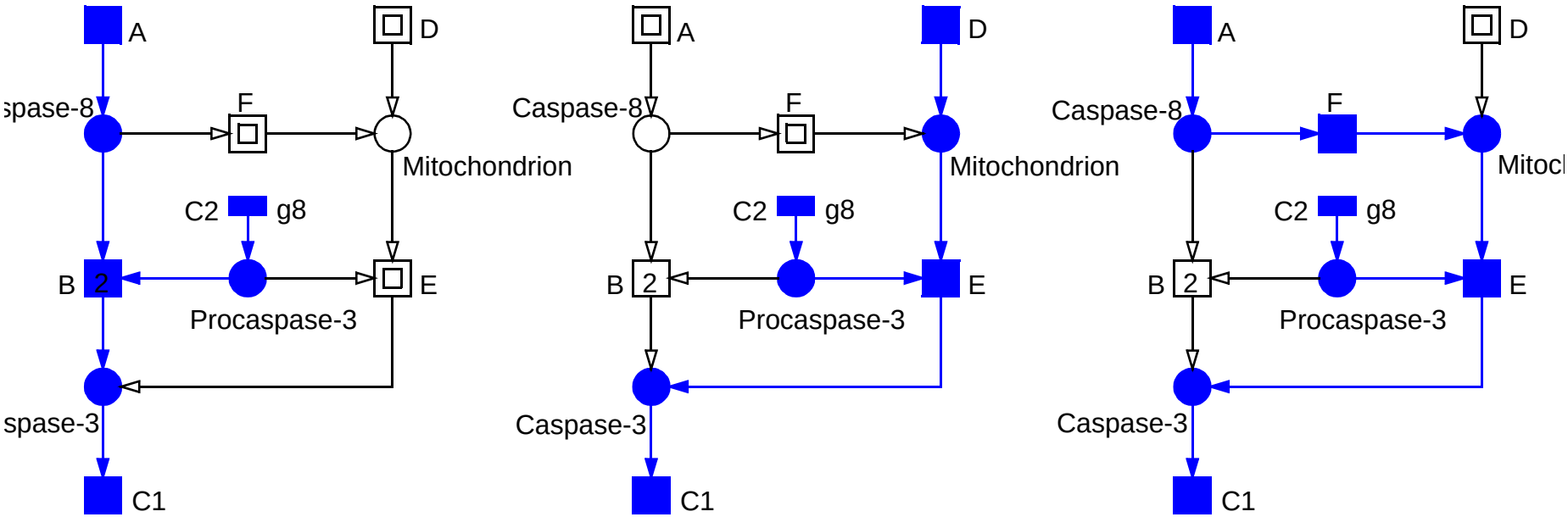


[HEINER, KOCH, WILL 2004]

EX2: APOPTOSIS IN MAMMALIAN CELLS



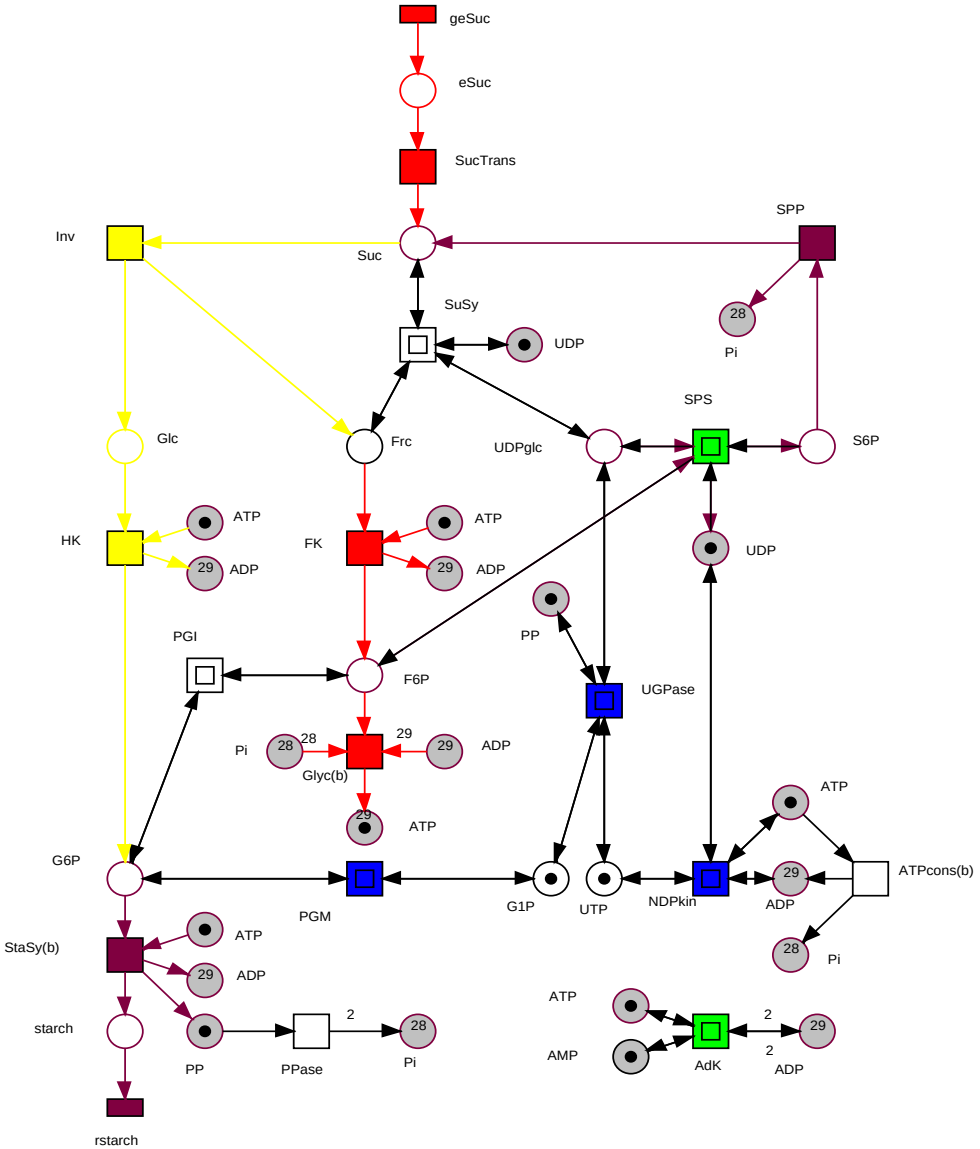
EX2: APOPTOSIS IN MAMMALIAN CELLS



Ex3 - Carbon Metabolism in Potato Tuber

[Koch; Junker; Heiner 2005]

ADT-sets without trivial T-invariants



About the Relation Qualitative vs Continuous

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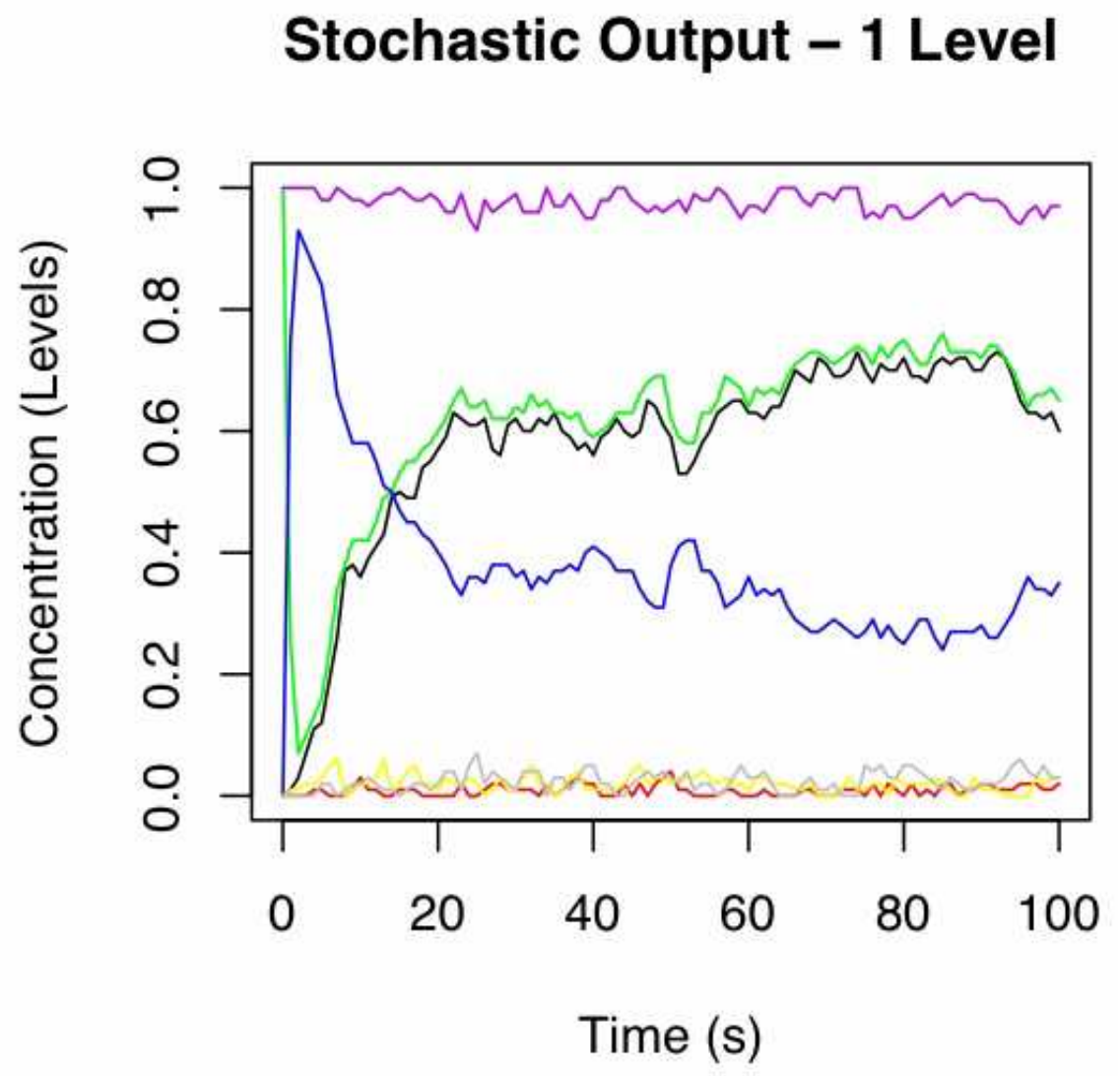
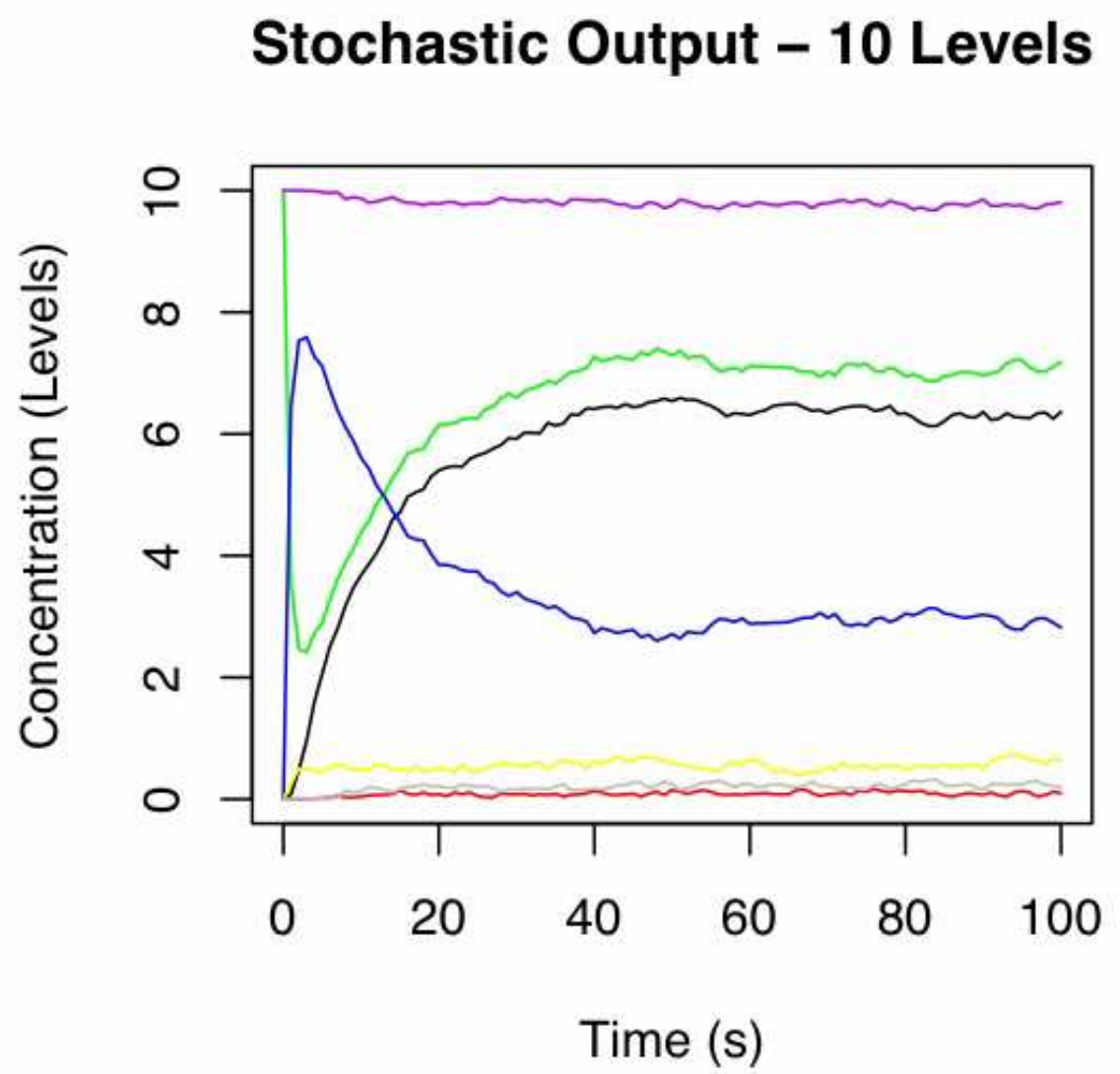
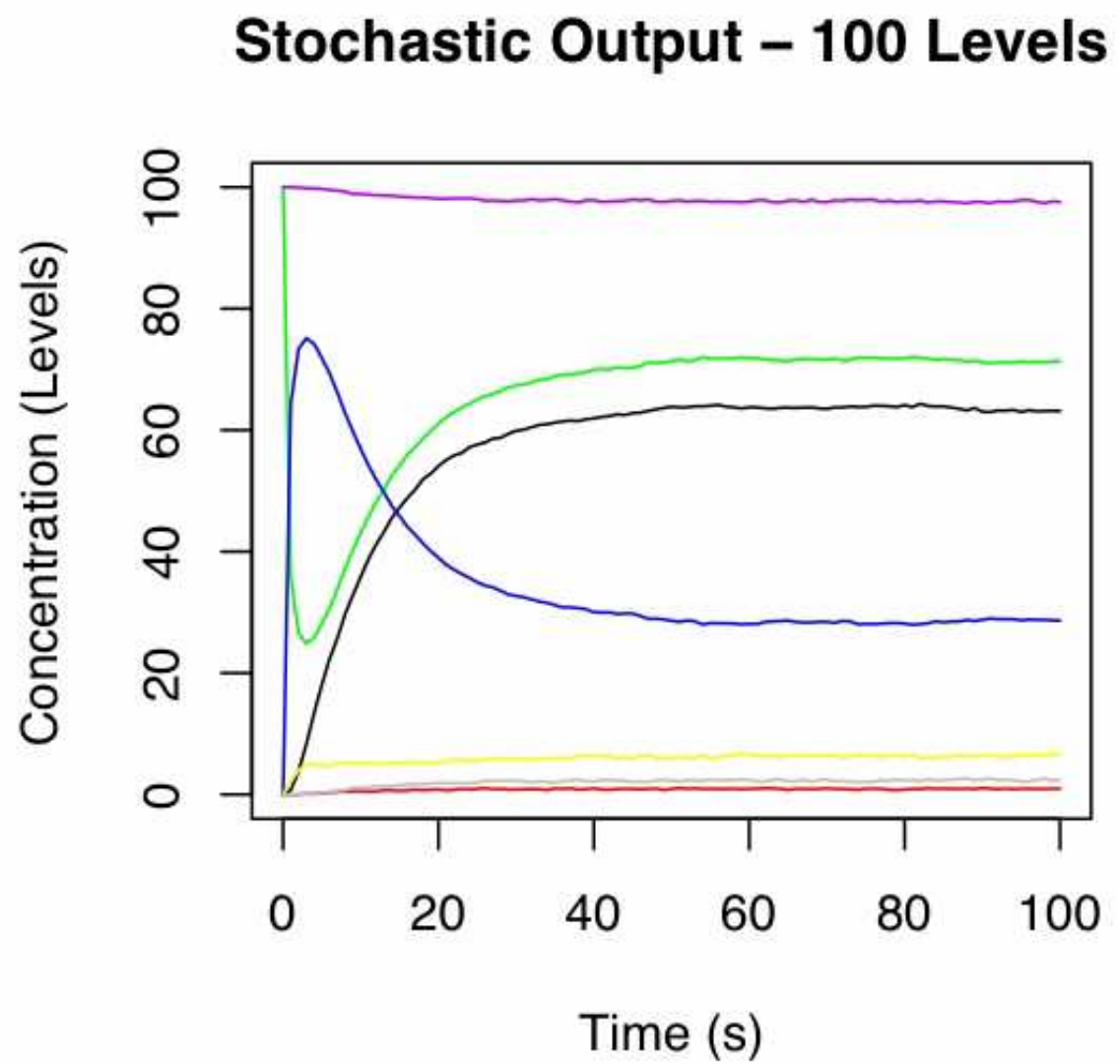
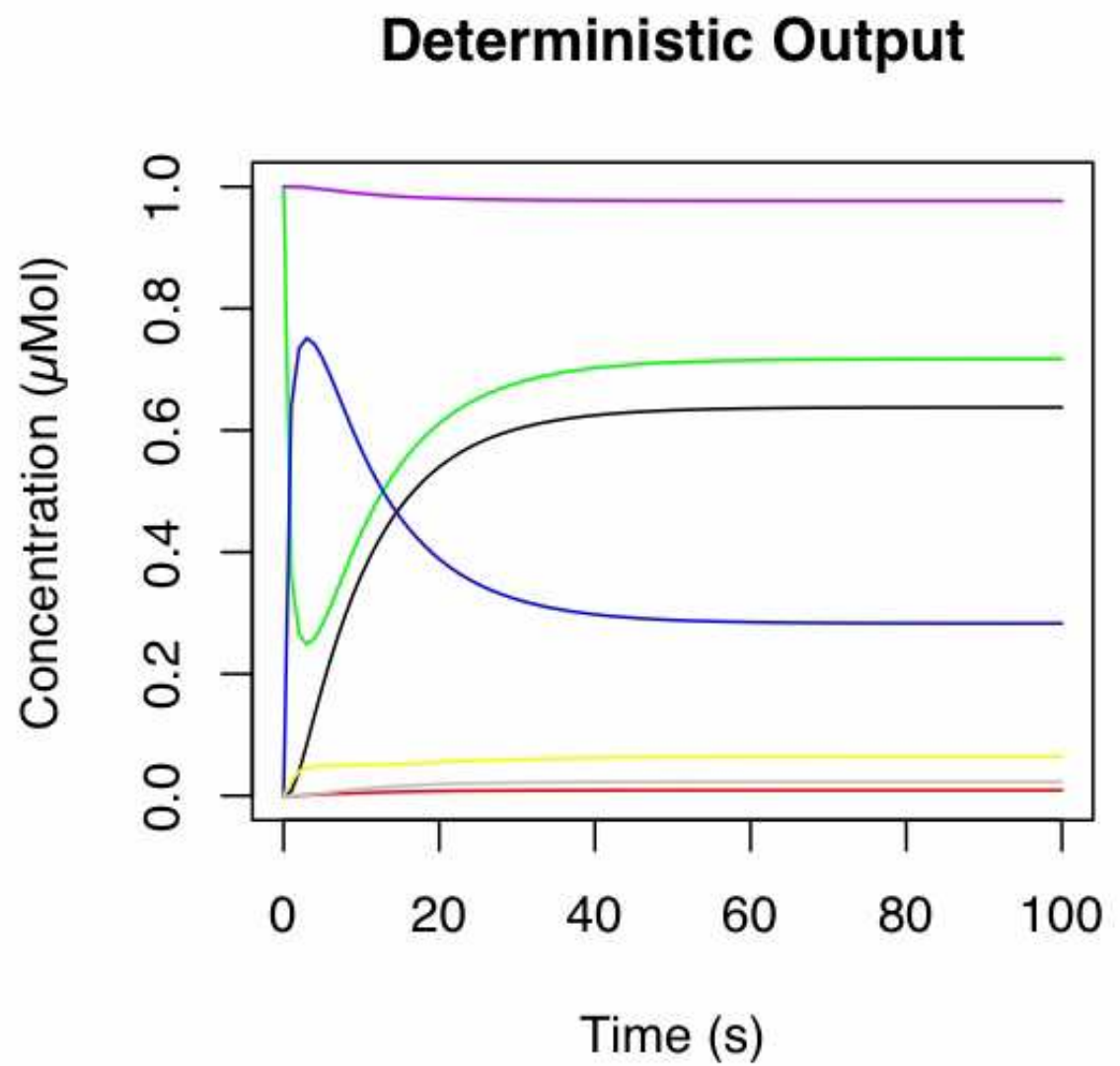

Stochastic Output – 1 Level
Concentration (Levels)
0.0
0.2
0.4
0.6
0.8
1.0
0
20
40
60
80
100
Time (s)

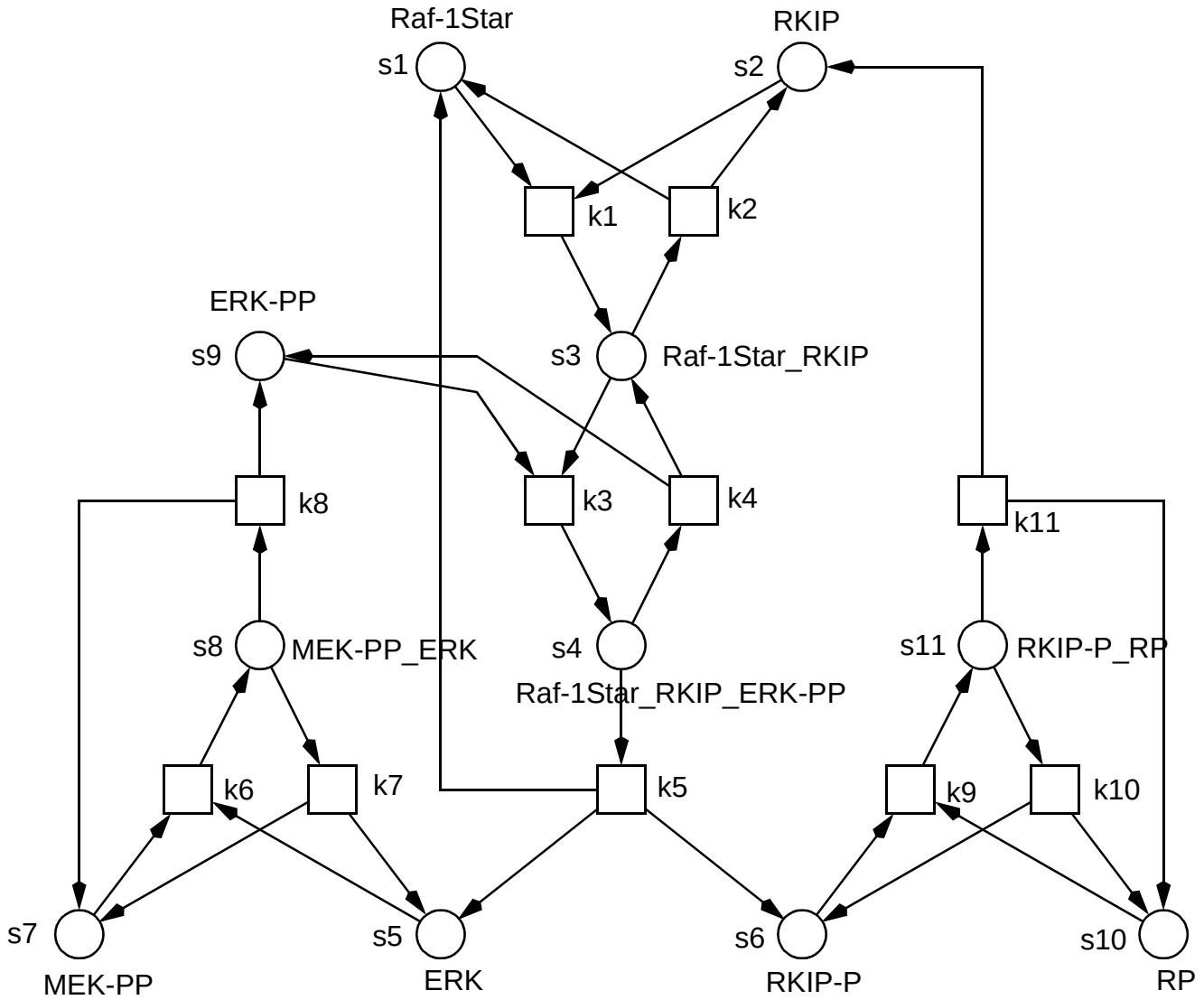

Stochastic Output – 10 Levels
Concentration (Levels)
0
2
4
6
8
10
0
20
40
60
80
100
Time (s)


Stochastic Output – 100 Levels
Concentration (Levels)
0
20
40
60
80
100
0
20
40
60
80
100
Time (s)

DETERMINISTIC SIMULATION



EX4 - RKIP SIGNALLING PATHWAY, PETRI NET

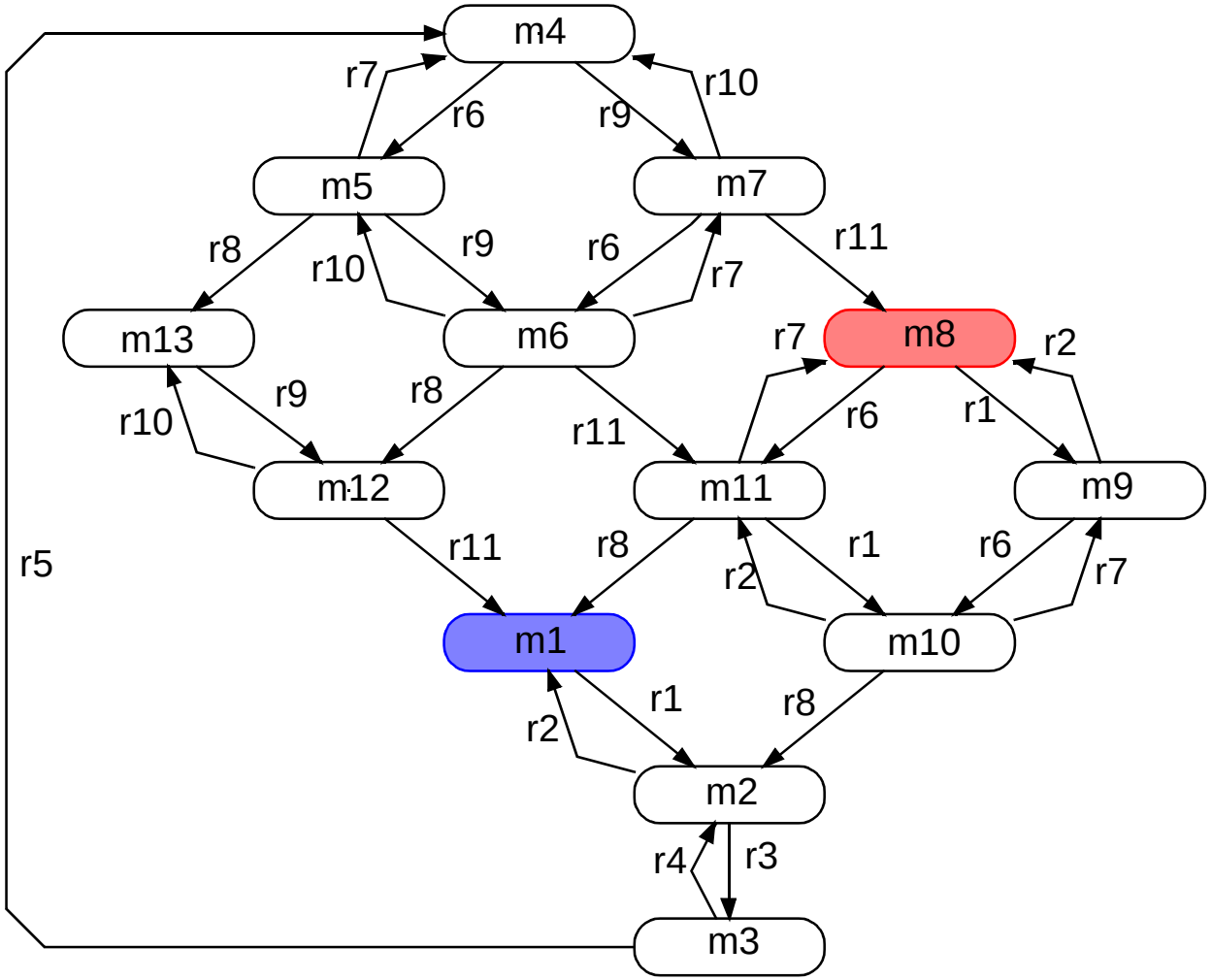


[HEINER, GILBERT 2006]

[HEINER, DONALDSON, GILBERT 2010]

EX4 - RKIP, REACHABILITY GRAPH (STS)

- simple algorithm
- nodes : system states
- arcs : the (single) firing transition
- single step firing rule

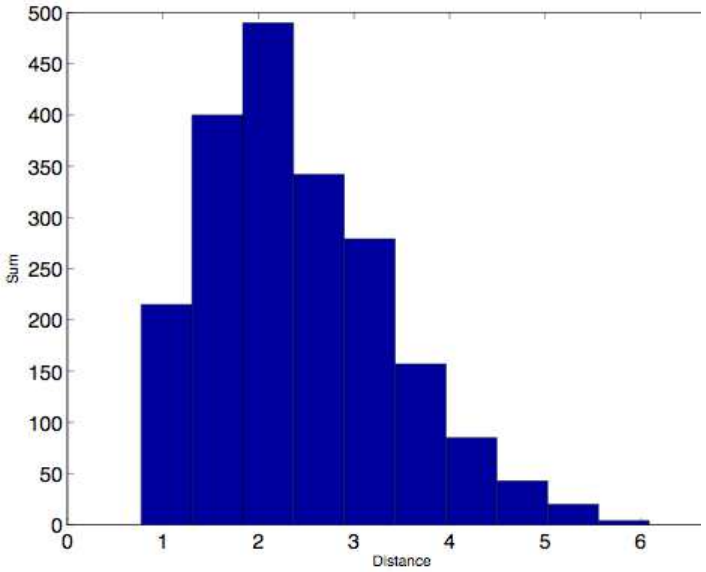


EX4 - RKIP, QUANTITATIVE ANALYSIS

Species	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12	S13
Raf-1*	1	0	0	1	1	1	1	1	0	0	1	1	1
RKIP	1	0	0	0	0	0	0	1	0	0	1	0	0
Raf-1*_RKIP	0	1	0	0	0	0	0	0	1	1	0	0	0
Raf-1*_RKIP_ERK-PP	0	0	1	0	0	0	0	0	0	0	0	0	0
ERK	0	0	0	1	0	0	1	1	1	0	0	0	0
RKIP-P	0	0	0	1	1	0	0	0	0	0	0	0	1
MEK-PP	1	1	1	1	0	0	1	1	1	0	0	1	1
MEK-PP_ERK	0	0	0	0	1	1	0	0	0	1	1	0	0
ERK-PP	1	1	0	0	0	0	0	0	0	0	0	1	1
RP	1	1	1	1	1	0	0	1	1	1	1	0	1
RKIP-P_RP	0	0	0	0	0	1	1	0	0	0	0	1	0

Cho et al

Biochemist

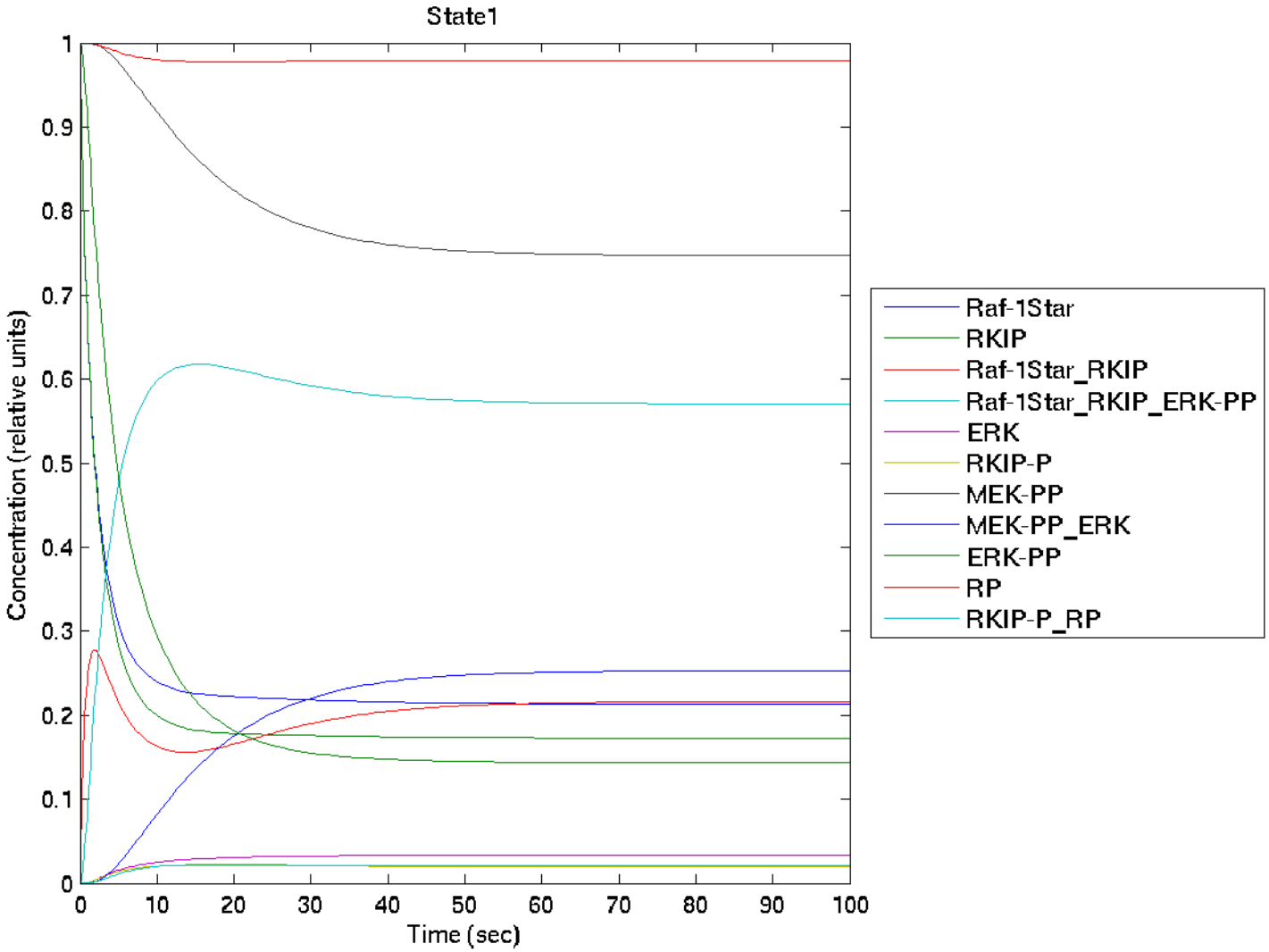


Distribution of `bad' steady states as euclidean distances from the `good' final steady state

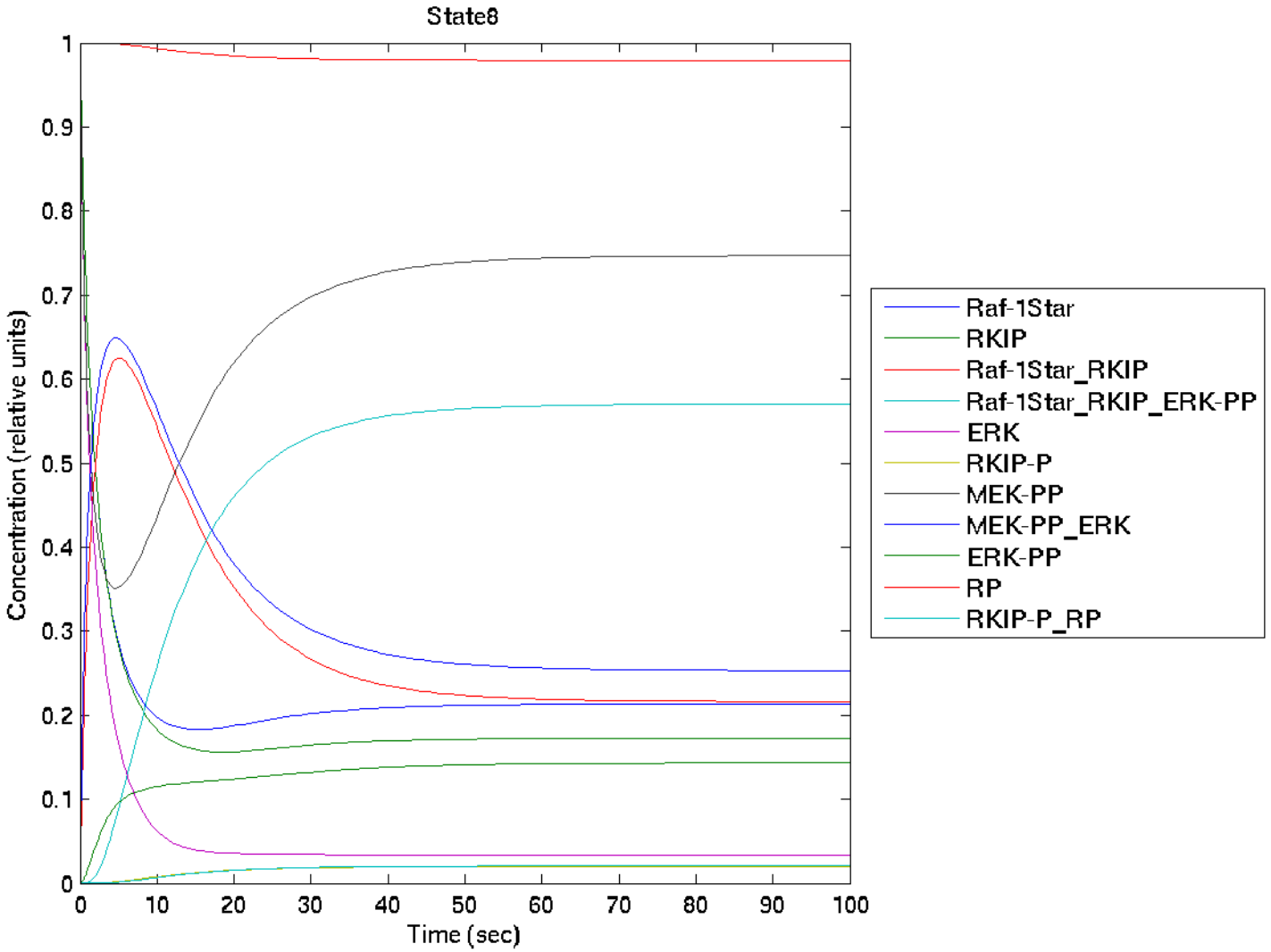
13 good state configurations

the bad ones

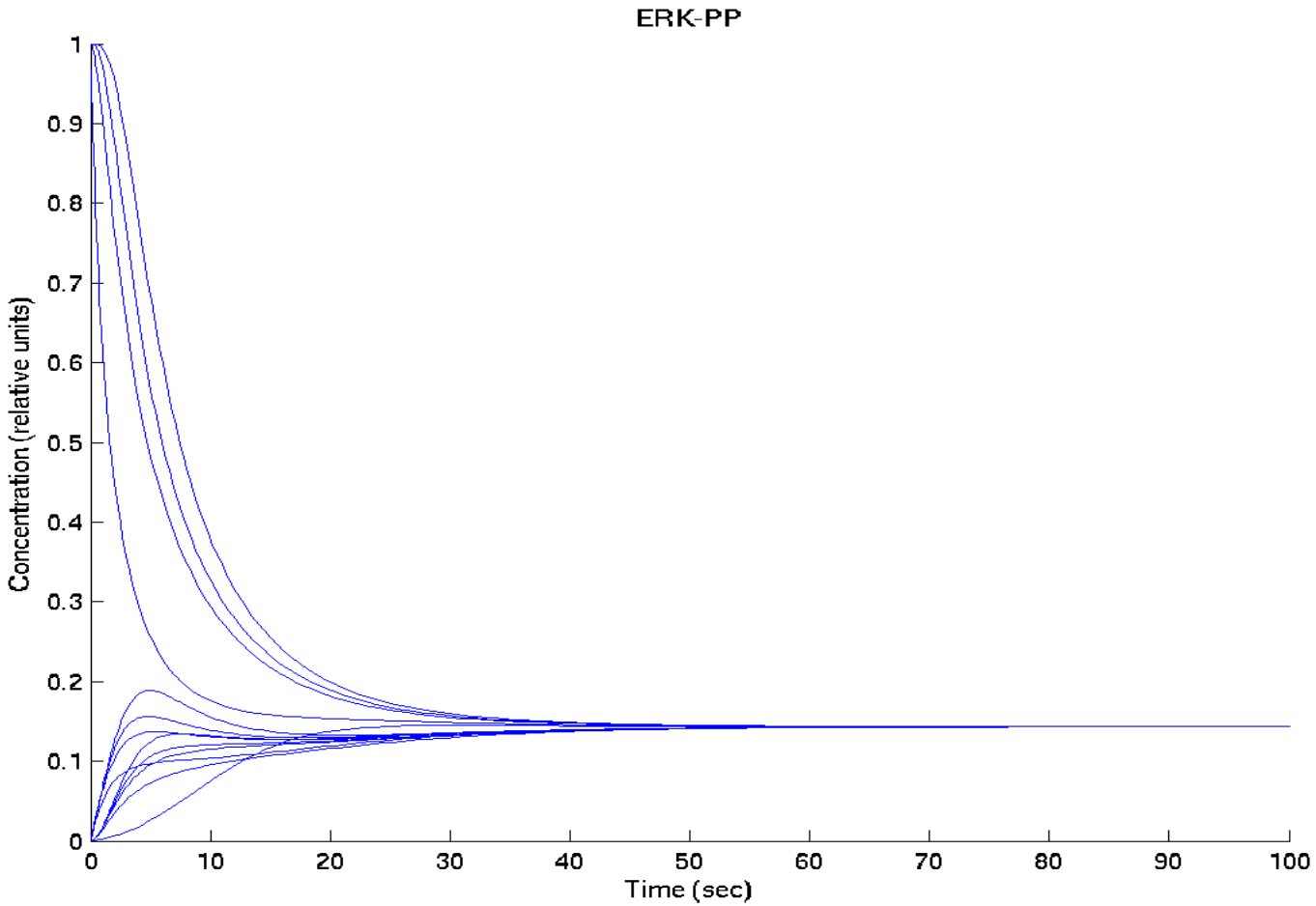
EX4 - RKIP, QUANTITATIVE ANALYSIS



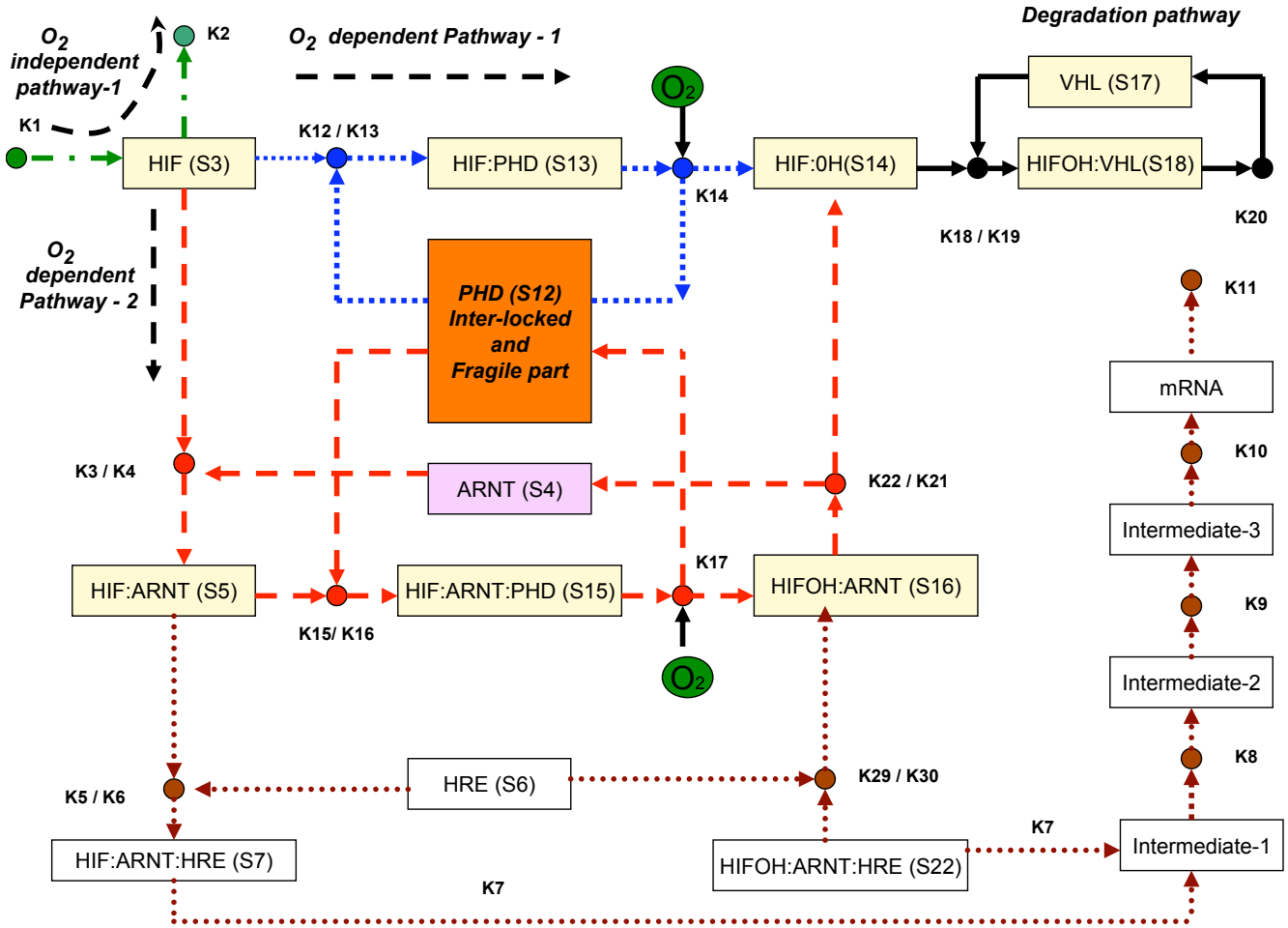
EX4 - RKIP, QUANTITATIVE ANALYSIS



EX4 - RKIP, QUANTITATIVE ANALYSIS

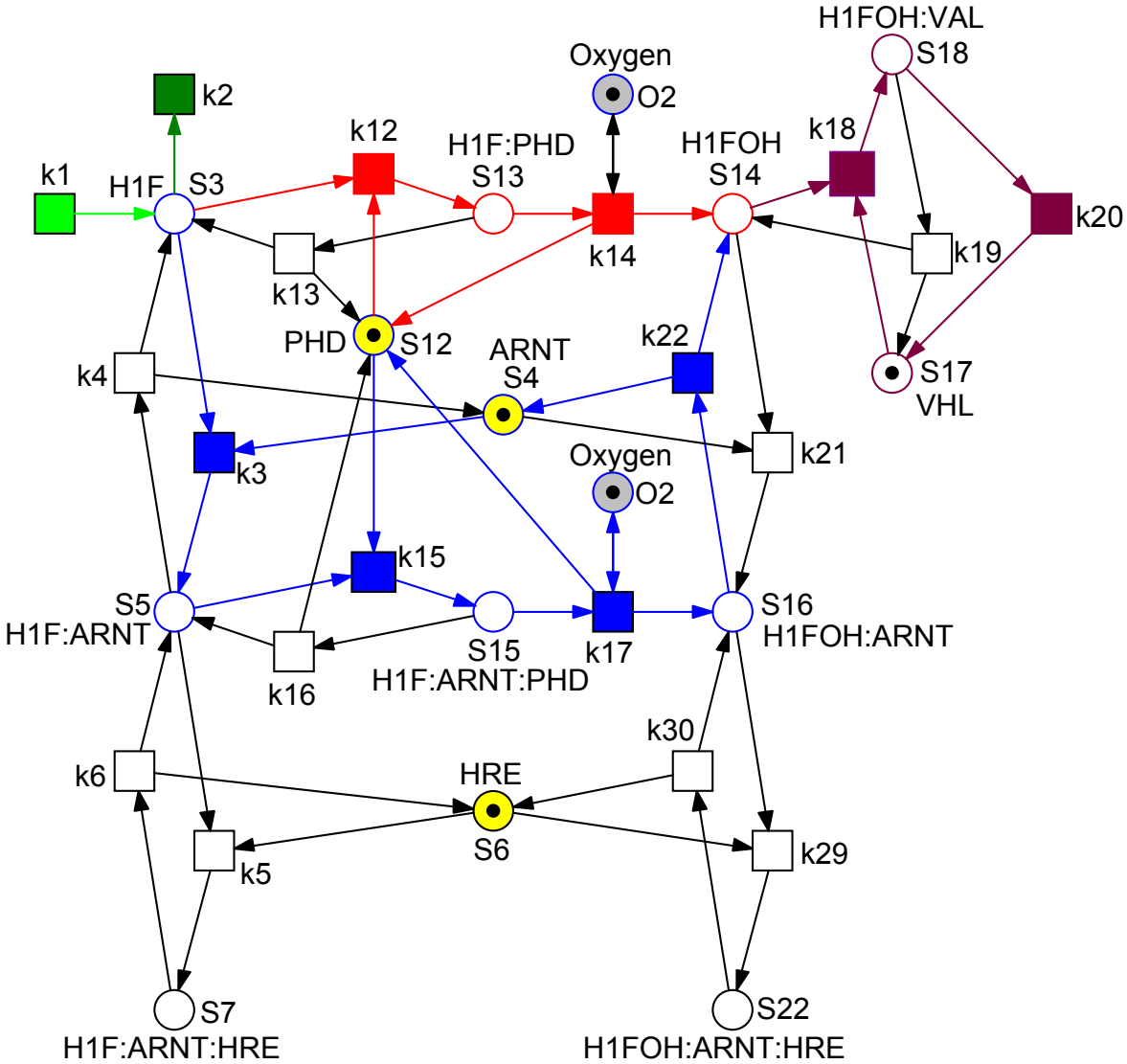


[YU ET AL. 2007]

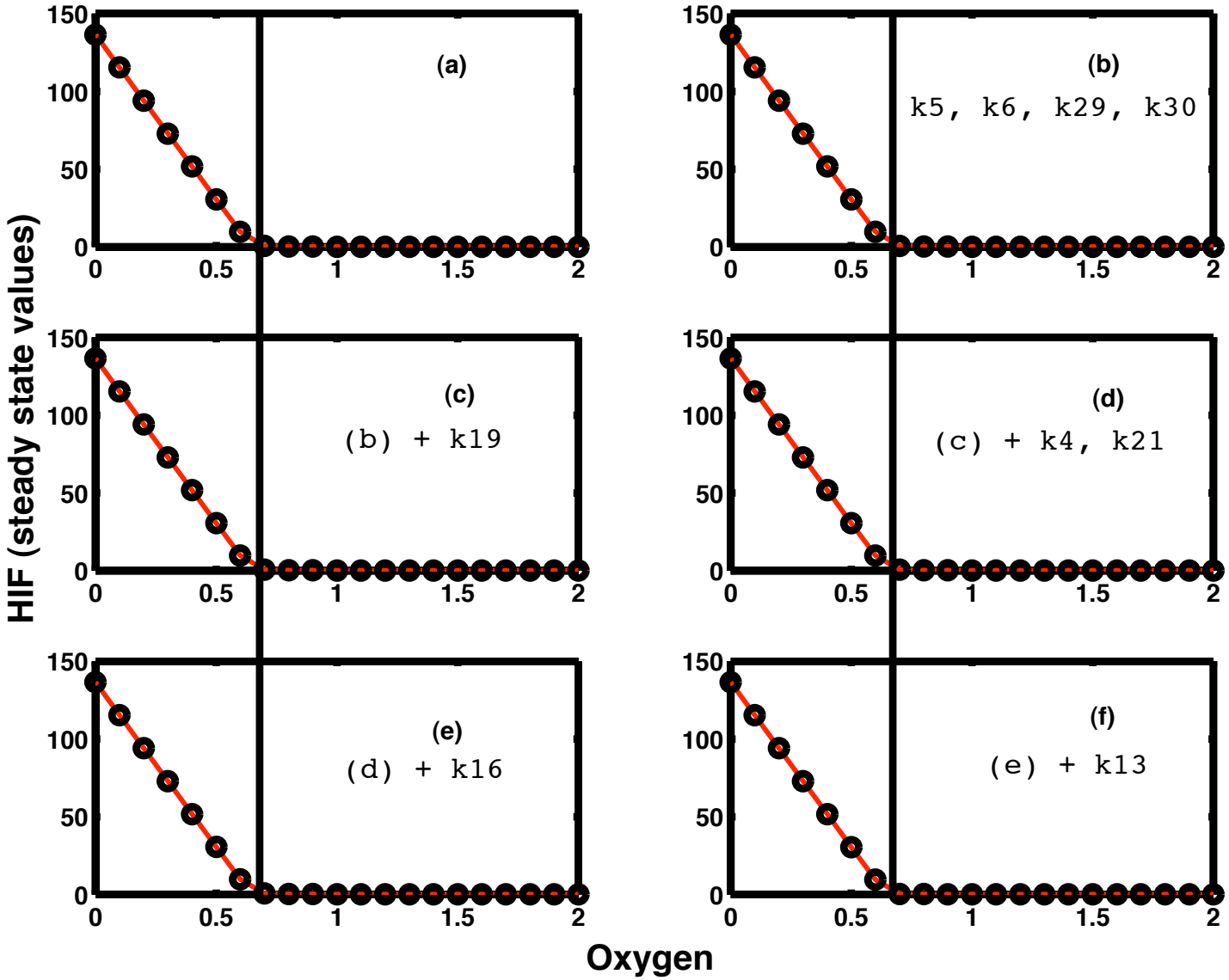

Degradation pathway
O_2 independent pathway-1
K2
O_2 dependent Pathway - 1
K1
HIF (S3)
K12 / K13
HIF:PHD (S13)
O_2
K14
HIF:0H(S14)
VHL (S17)
HIFOH:VHL(S18)
K20
K18 / K19
O_2 dependent Pathway - 2
PHD (S12) Inter-locked and Fragile part
K11
mRNA
K10
K3 / K4
ARNT (S4)
K22 / K21
Intermediate-3
K17
HIF:ARNT (S5)
HIF:ARNT:PHD (S15)
HIFOH:ARNT (S16)
K9
K15/ K16
O_2
Intermediate-2
K8
HRE (S6)
K29 / K30
K5 / K6
K7
HIF:ARNT:HRE (S7)
HIFOH:ARNT:HRE (S22)
Intermediate-1
K7

EX5 - HYPOXIA

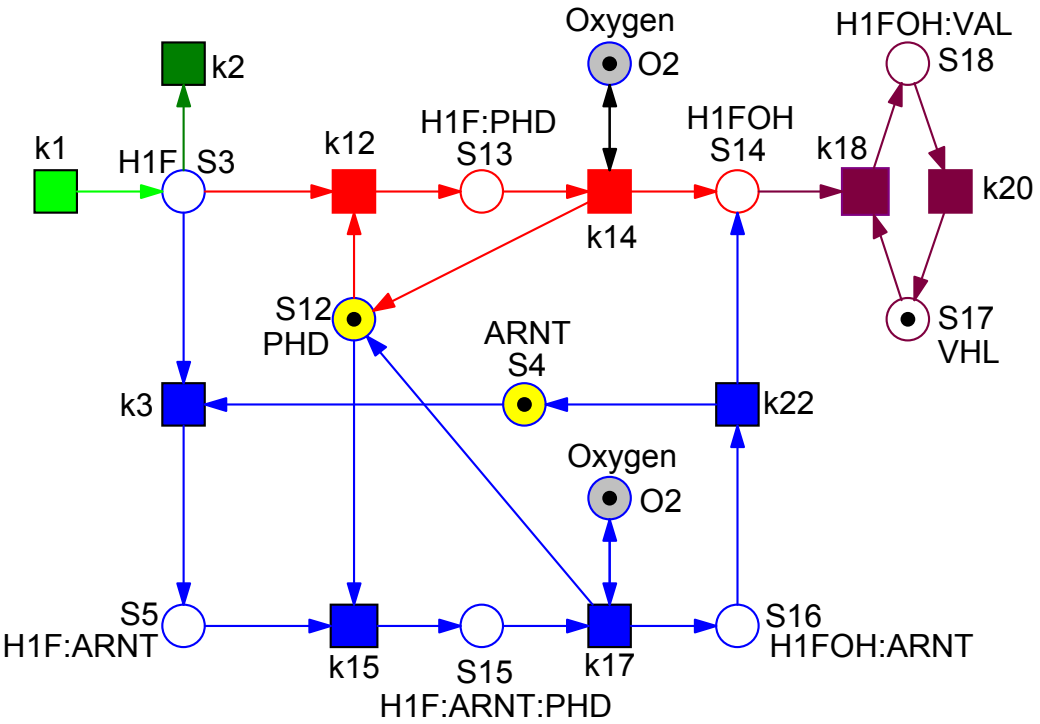
[HEINER, SRIRAM 2010]



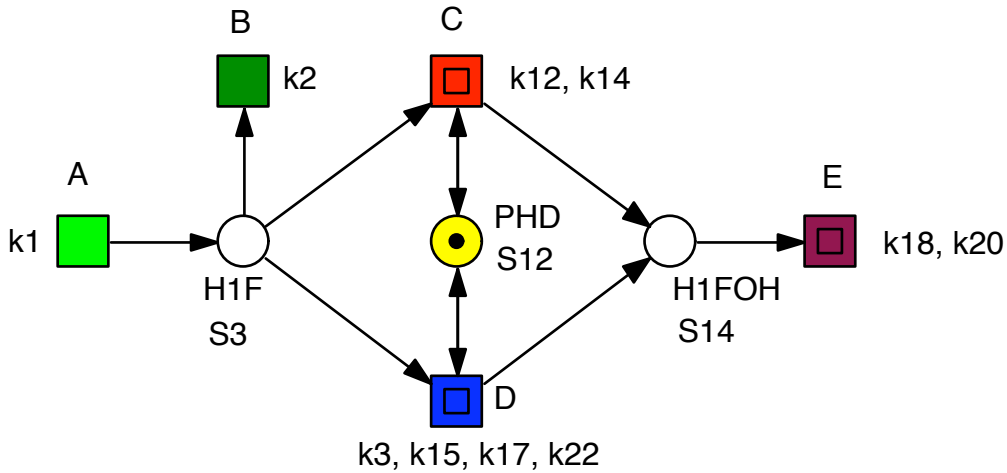
EX5 - HYPOXIA


HIF (steady state values)
Oxygen
(a)
(b)
k5, k6, k29, k30
(c)
(b) + k19
(d)
(c) + k4, k21
(e)
(d) + k16
(f)
(e) + k13
150
100
50
0
0
0.5
1
1.5
2

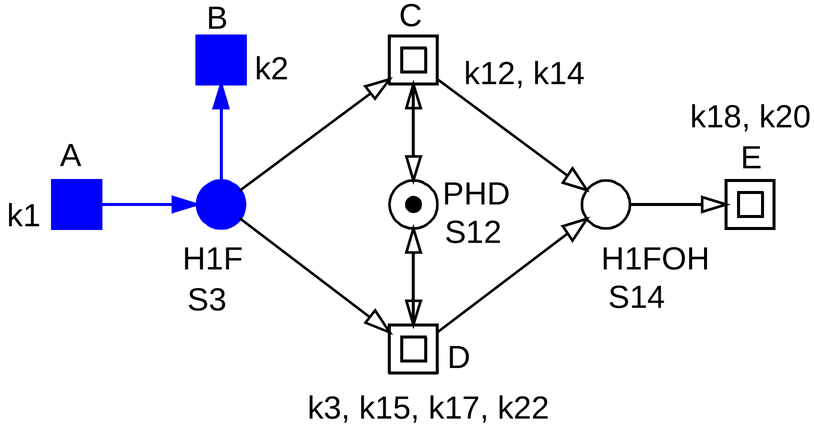
EX5 - HYPOXIA

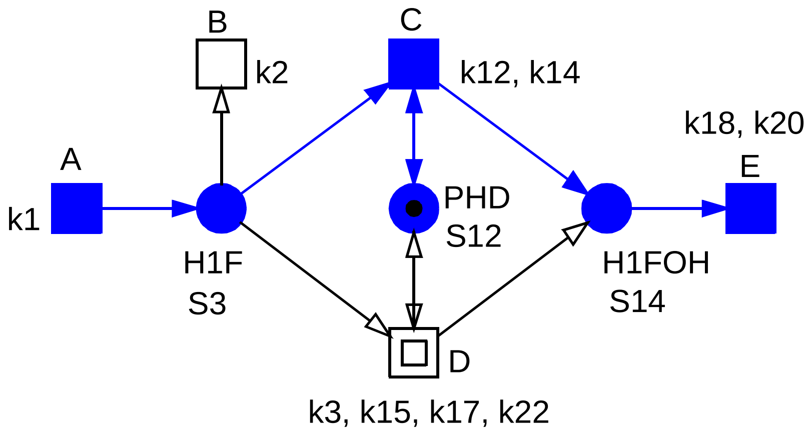

Oxygen
O2
H1FOH:VAL
S18
k2
k1
H1F
S3
k12
H1F:PHD
S13
H1FOH
S14
k18
k20
k14
S12
PHD
S17
VHL
ARNT
S4
k3
k22
Oxygen
O2
S5
H1F:ARNT
S16
H1FOH:ARNT
k15
S15
H1F:ARNT:PHD
k17

EX5 - HYPOXIA


B
C
k2
k12, k14
A
E
k1
PHD
S12
k18, k20
H1F
S3
H1FOH
S14
D
k3, k15, k17, k22

Ex5 - Hypoxia


B
C
k2
k12, k14
k18, k20
A
E
k1
PHD
S12
H1F
S3
H1FOH
S14
D
k3, k15, k17, k22


B
C
k2
k12, k14
k18, k20
A
E
k1
PHD
S12
H1F
S3
H1FOH
S14
D
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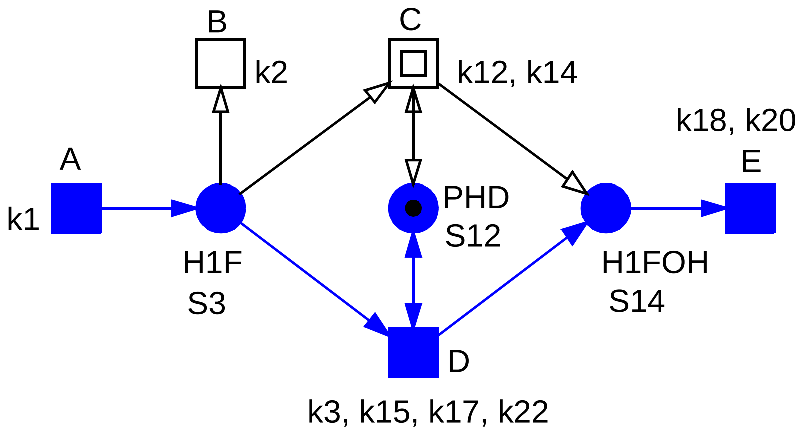
B
C
k2
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k18, k20
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E
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S12
H1F
S3
H1FOH
S14
D
k3, k15, k17, k22

Open Problem - Time-dependent Boundedness

monika.heiner@tu-cottbus.de

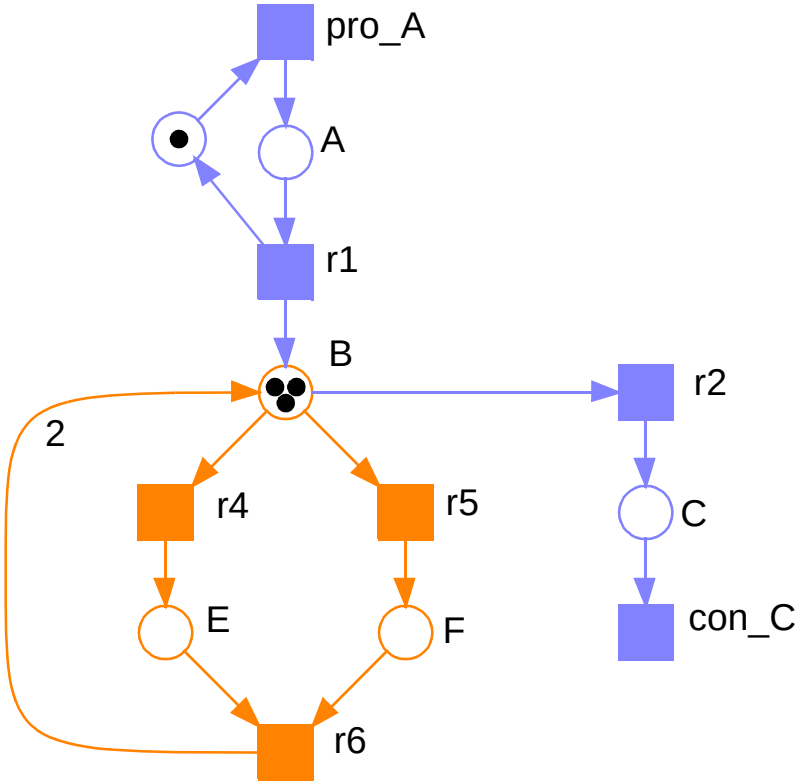
TIME-DEPENDENT BOUNDEDNESS

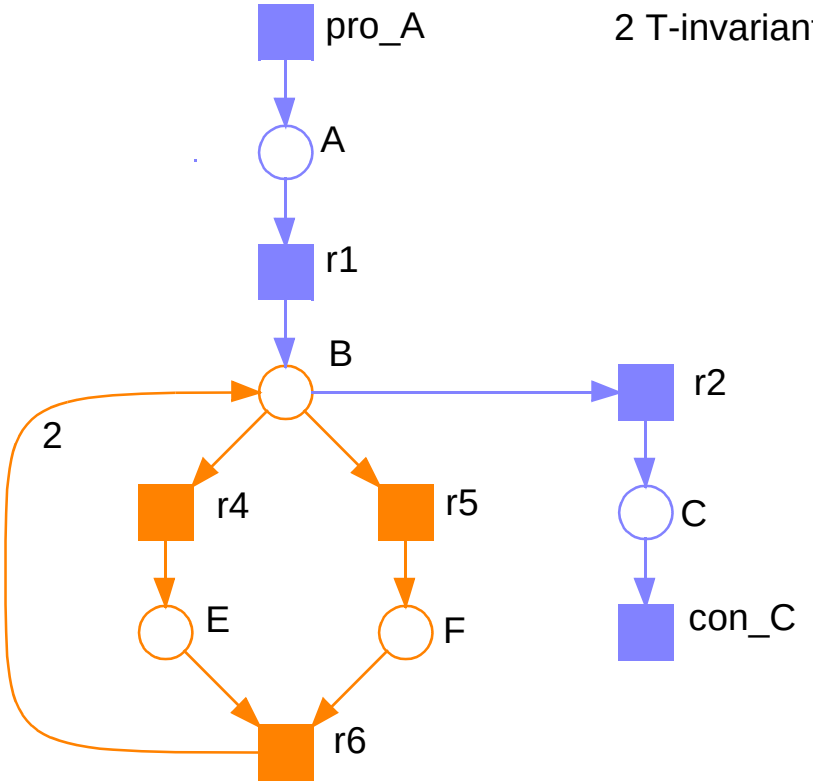
- **given: time-free Petri net**
  - -> *unbounded*
  - -> *live (supposed to be)*
- **wanted: corresponding time-dependent Petri net**
  - -> *(weakly) bounded*
  - -> *(still) live*
- **relative transition firing rates**
  - -> *may be implemented by transition firing duration (constant / interval)*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

However,
this does not always work !

COUNTEREXAMPLE 1

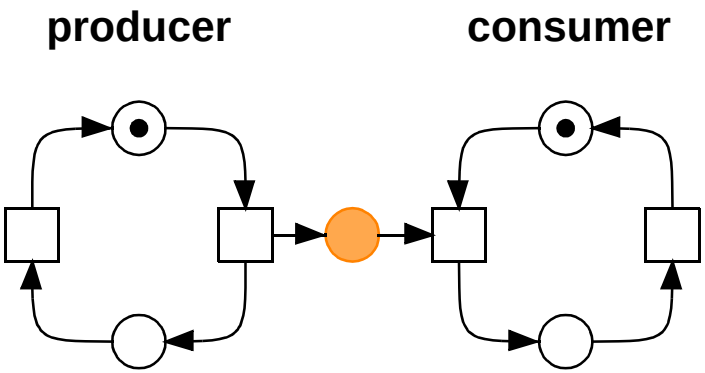
1-working time for all transitions;
FC, there are no deadlocks, traps, p-invariants, besides the pseudo-P-invariant (A , co_A);



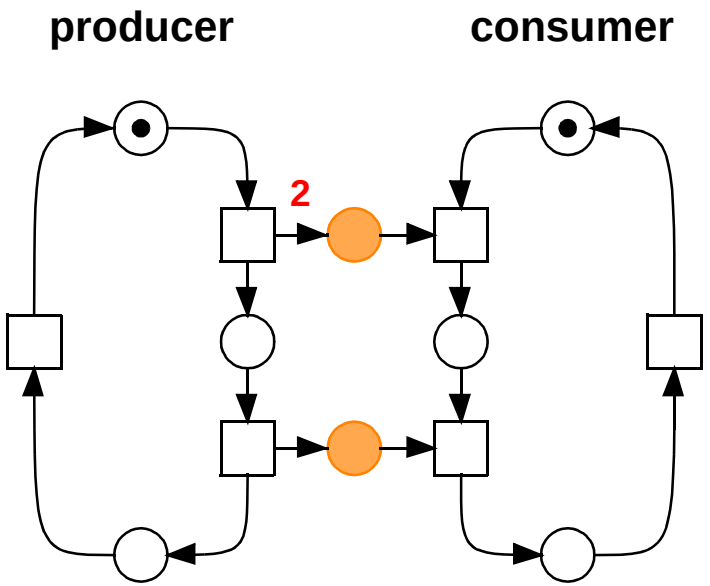


wBND & LIVE for the given initial marking

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 !?**

SUMMARY & OUTLOOK

OUR TOOL BOX

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

- **CHARLIE**
  - -> *QPN, XQPN, Time/Timed Petri nets (TPN)*
  - -> *mostly standard analysis techniques of Petri net theory*

- **MARCIE**
  - -> *XQPN, SPN, XSPN, SRN*
  - -> *symbolic and simulative model checking*

- **Patty**
  - -> *animation via web browser*

OUR TOOL BOX

- **SNOOPY**
  - -> *modelling and animation/simulation of hierarchical graphs,*
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  - -> *symbolic and simulative model checking*
- **Patty**
  - -> *animation via web browser*

SBML import/export

EXPORT TO MATAB AND

MANY OTHER TOOLS

SUMMARY

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

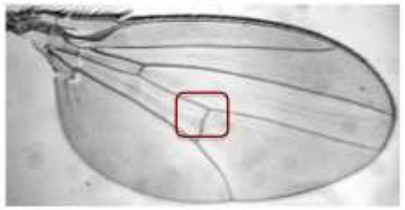
- **purposes**
  - -> *animation* -> *to experience the model*
  - -> *model validation against consistency criteria* -> *to increase confidence*
  - -> *qualitative / quantitative behaviour prediction* -> *experiment design, new insights*

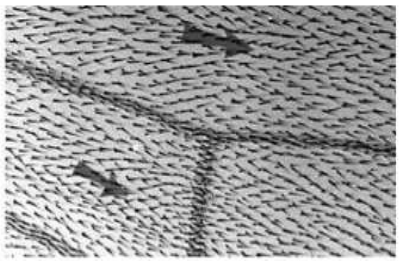
- **step-wise model development**
  - -> *qualitative model* -> *discrete Petri nets*
  - -> *discrete quantitative model* -> *stochastic Petri nets*
  - -> *continuous quantitative model* -> *continuous Petri nets = ODEs, hybrid models*
  - -> *locality and space* -> *coloured Petri nets*

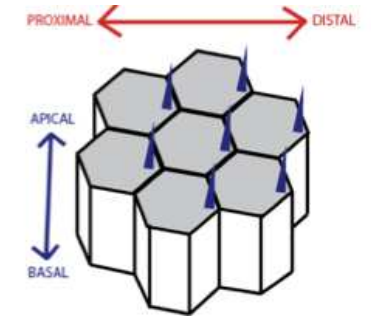
OUTLOOK

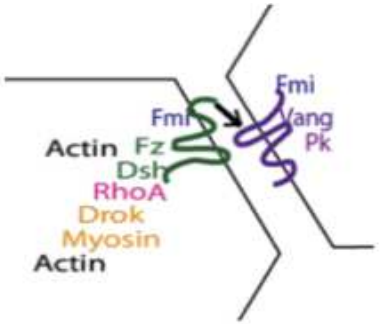
- **efficient simulation of very large Petri nets**
  - -> *stochastic*
  - -> *continuous*
  - -> *hybrid*
- **(hierarchical) space**
- **shape and volume of components**
- **hierarchical organisation of components**
- **observables**
- **biosystem development**

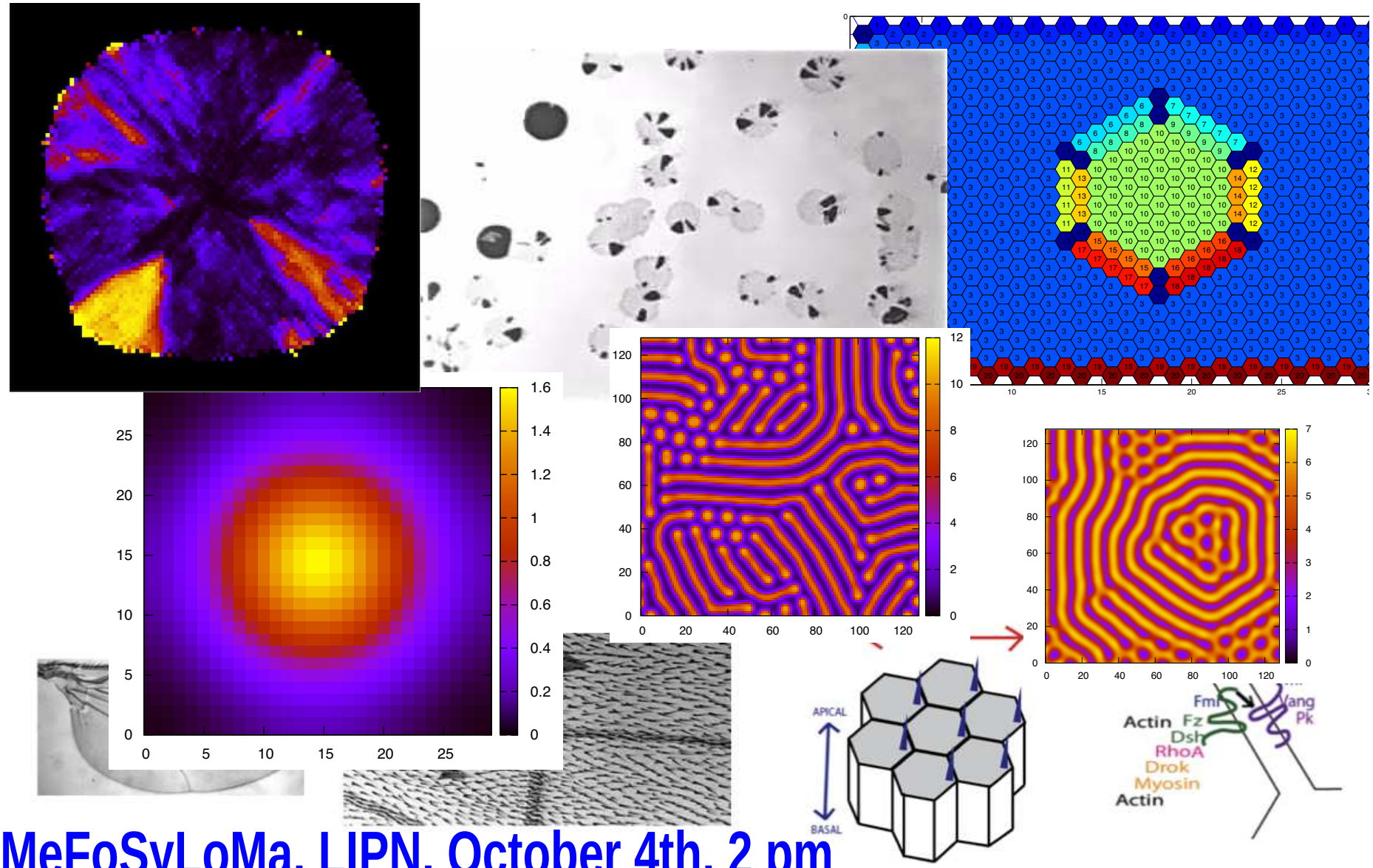
MULTISCALE CHALLENGES







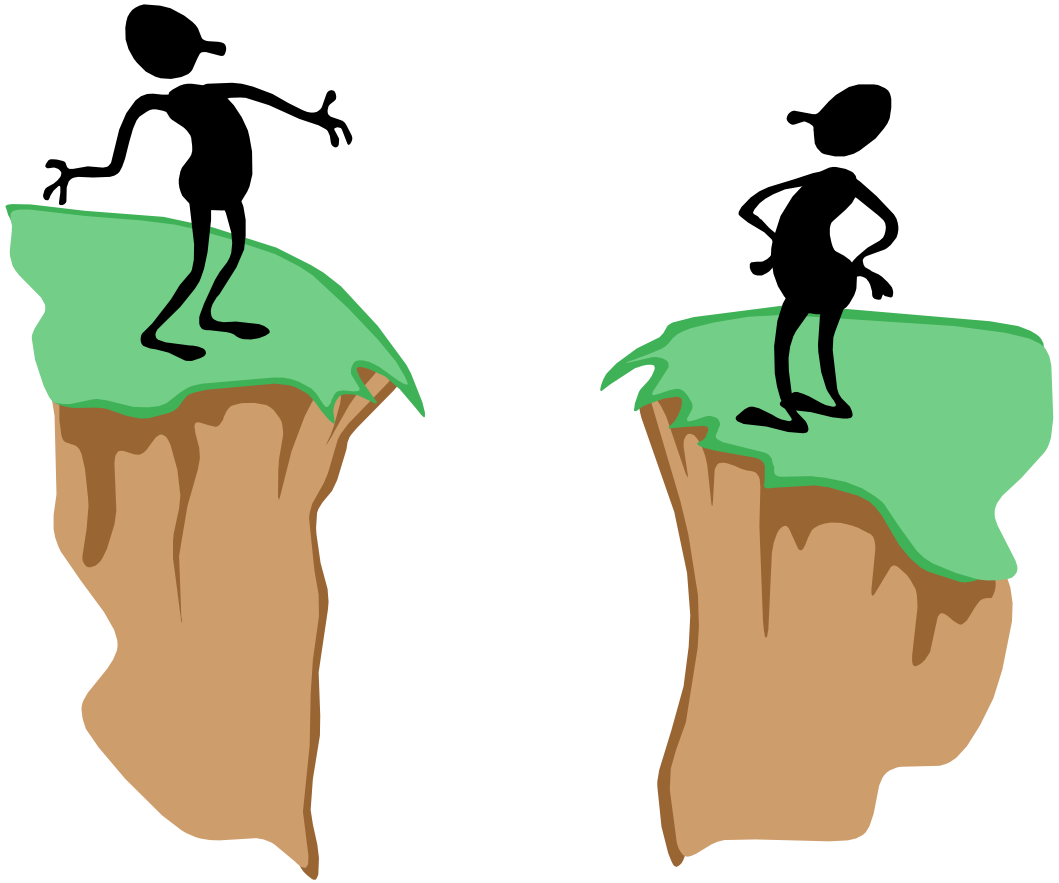




MeFoSyLoMa, LIPN, October 4th, 2 pm

monika.heiner@tu-cottbus.de

OUTLOOK



THANKS !

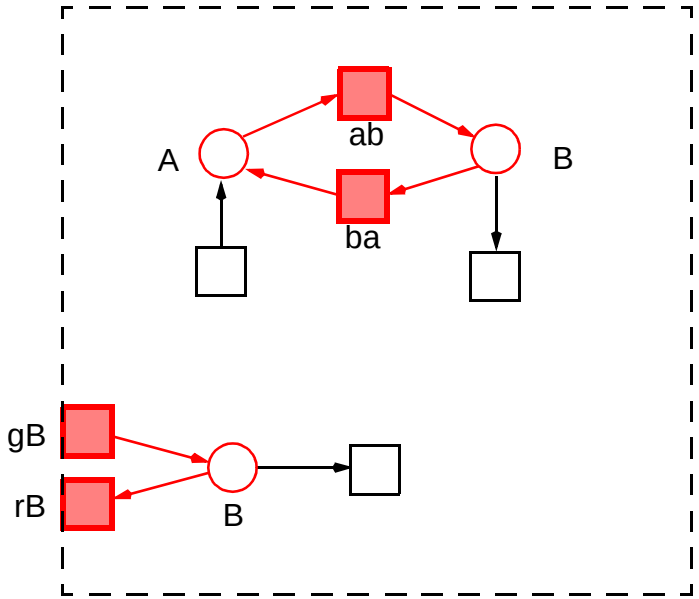
HHTP://WWW-DSSZ.INFORMATIK.TU-COTTBUS.DE

APPENDIX

- **trivial minimal T-invariants**
  - -> *reversible reactions*
  - -> *boundary transitions of auxiliary compounds*

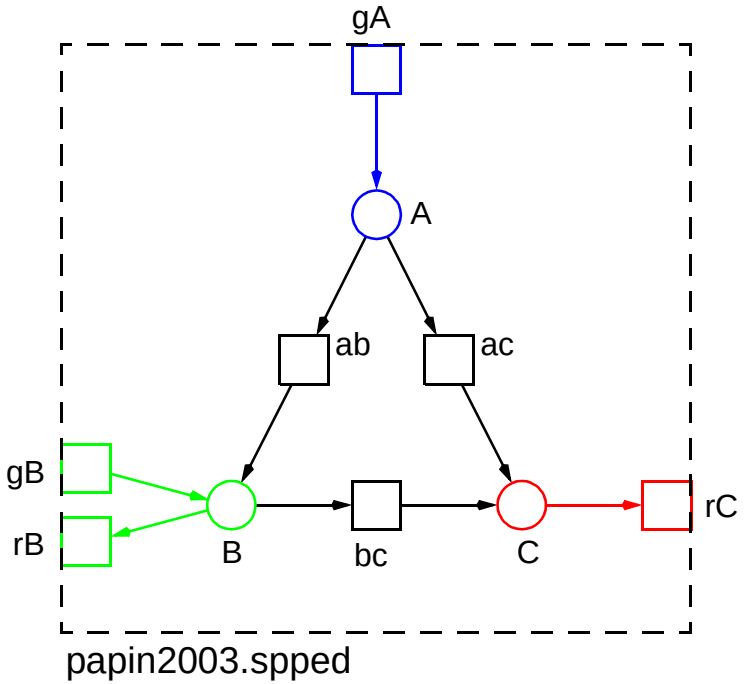
- **non-trivial minimal T-invariants**
  - -> *i/o-T-invariants*

    covering boundary transitions of input / output compounds
  - -> *inner cycles*



EXAMPLE

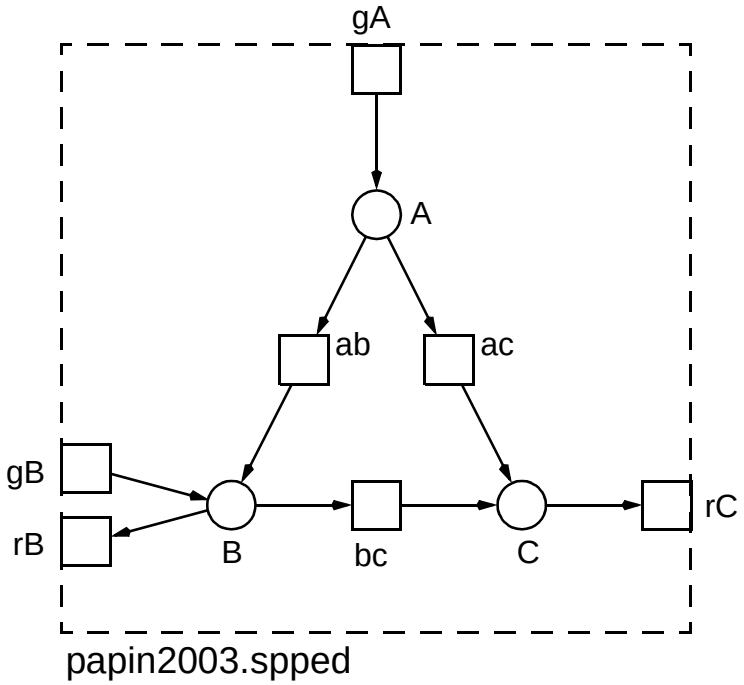
- substances involved
  - -> *input substance A*
  - -> *output substance C*
  - -> *auxiliary substance B*



papin2003.spped

EXAMPLE, T-INVARIANTS

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



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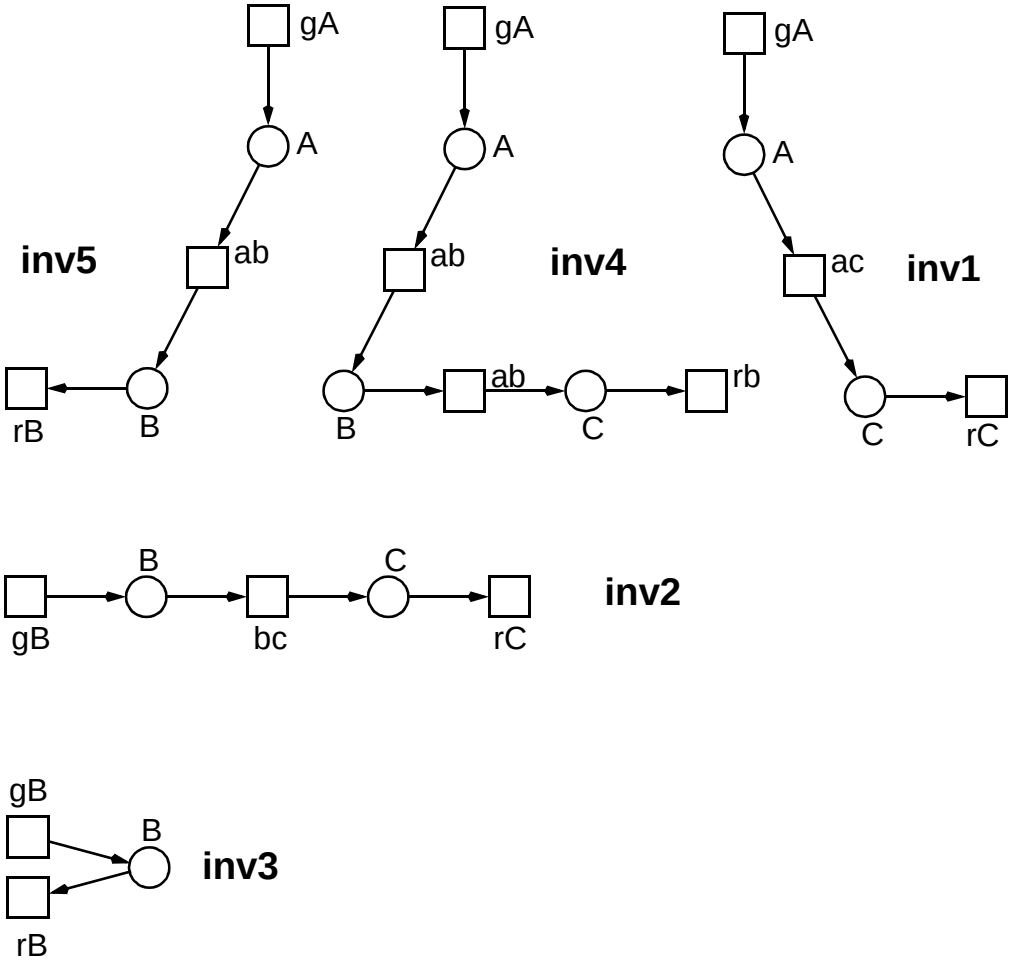
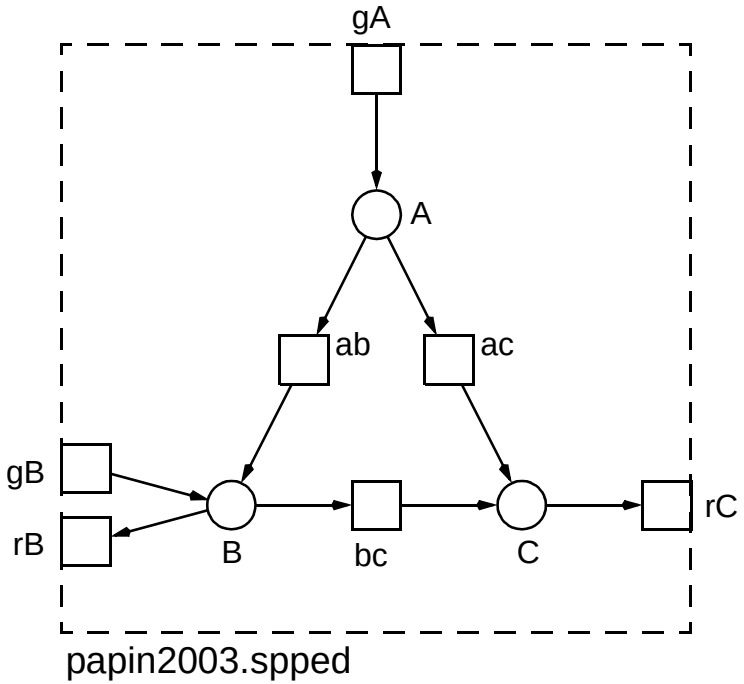


EXAMPLE, ELEMENTARY MODES

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



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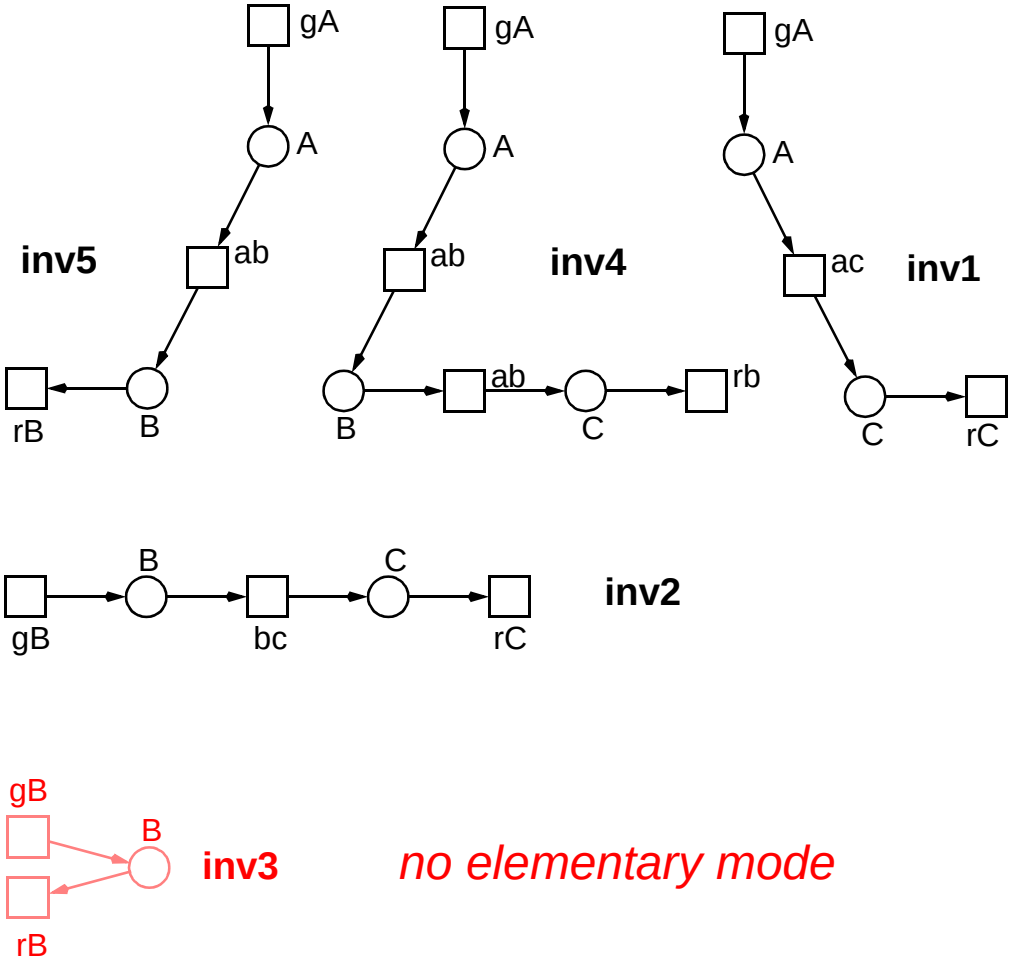
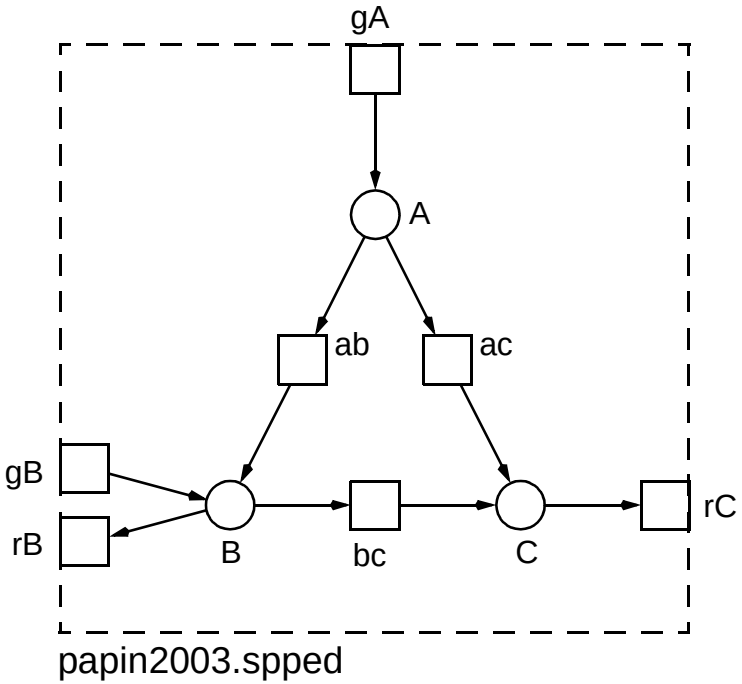


no elementary mode

EXAMPLE, EXTREME PATHWAYS

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



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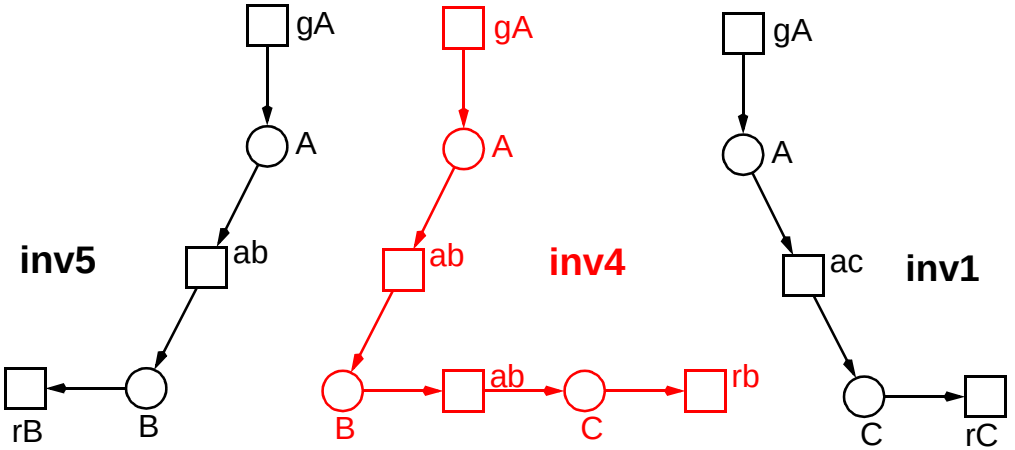
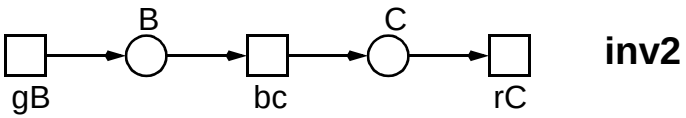
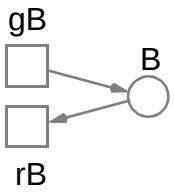
no extreme pathway







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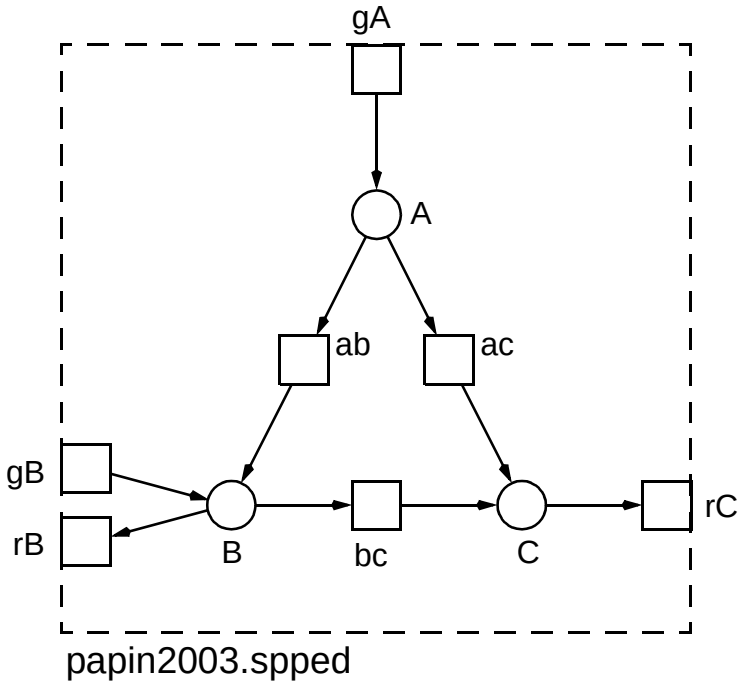

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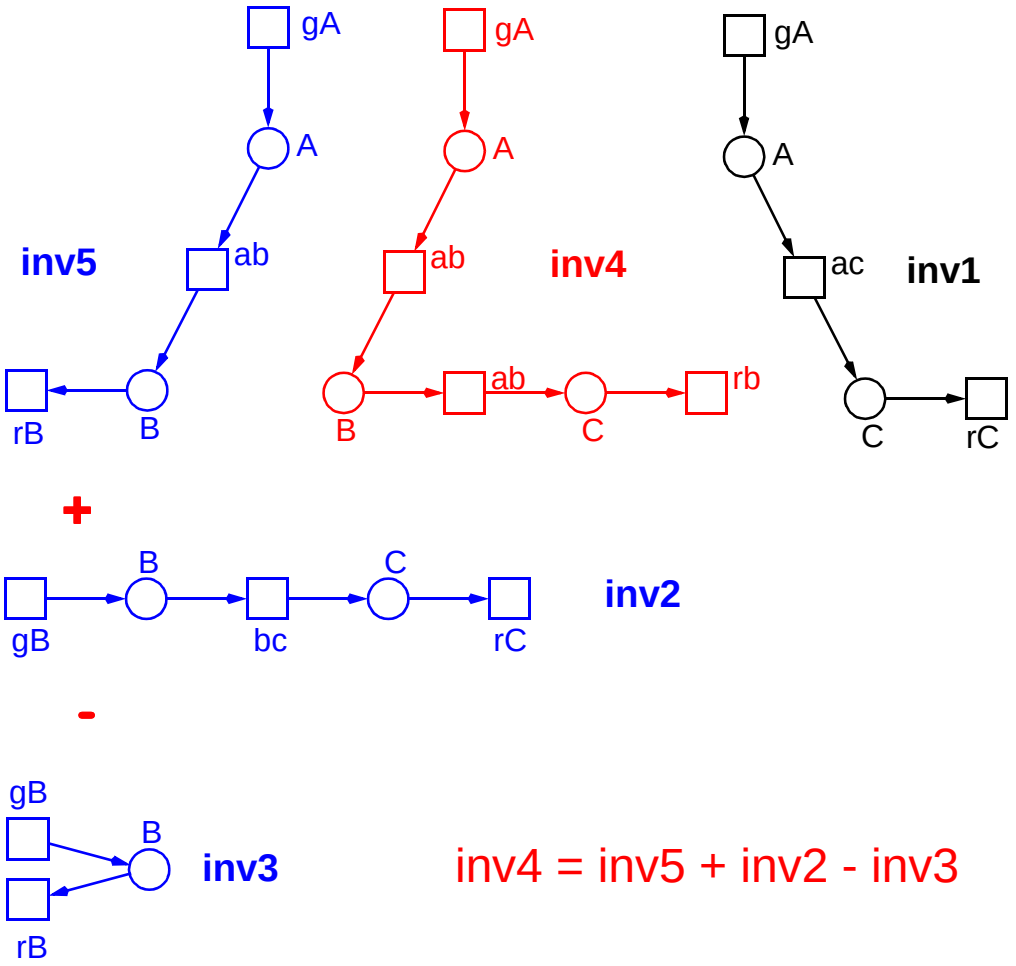
no extreme pathway



inv4 = inv5 + inv2 - inv3

- substances involved
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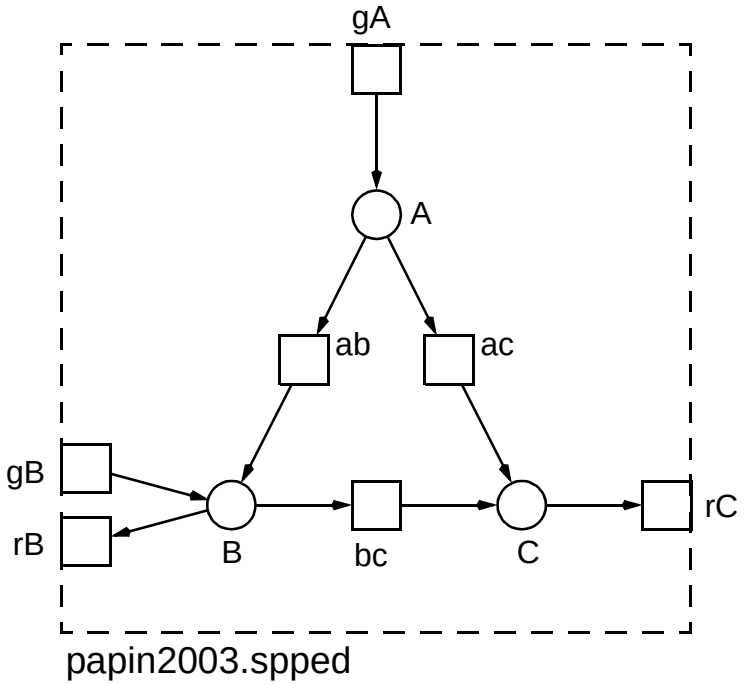

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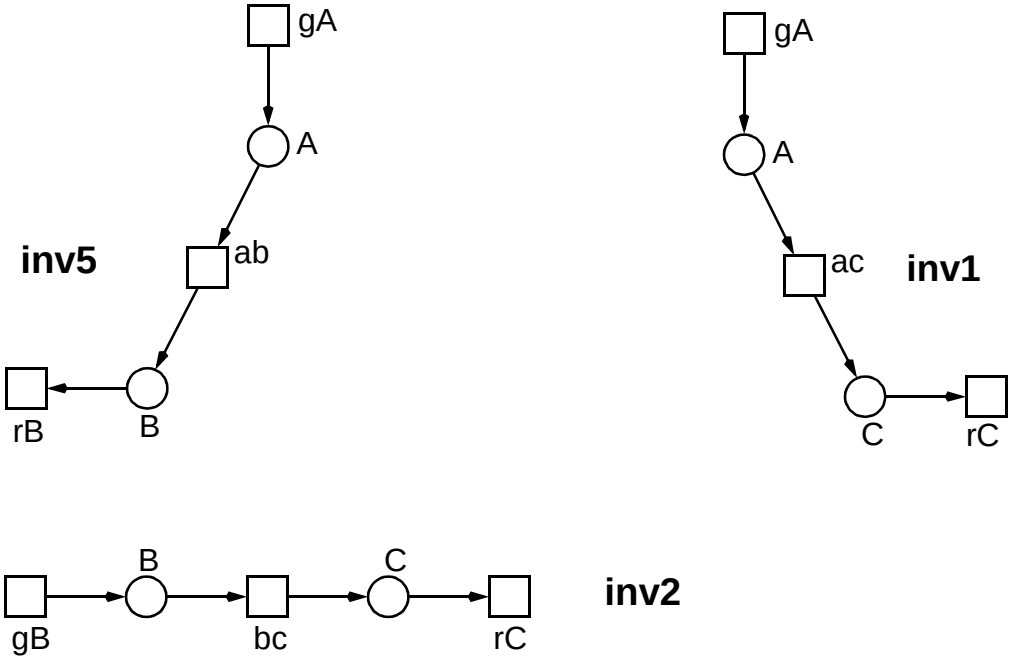
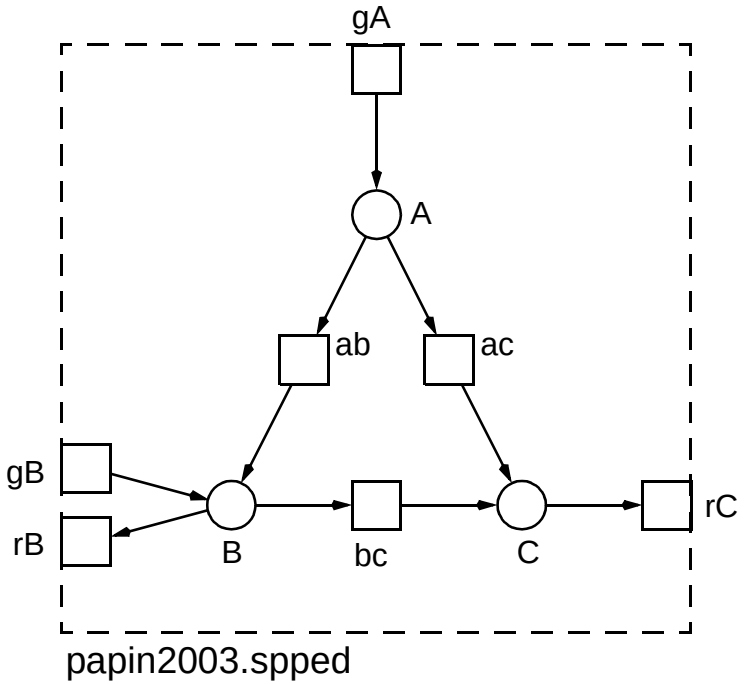
EXTREME PATHWAYS



EXAMPLE, SUMMARY

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



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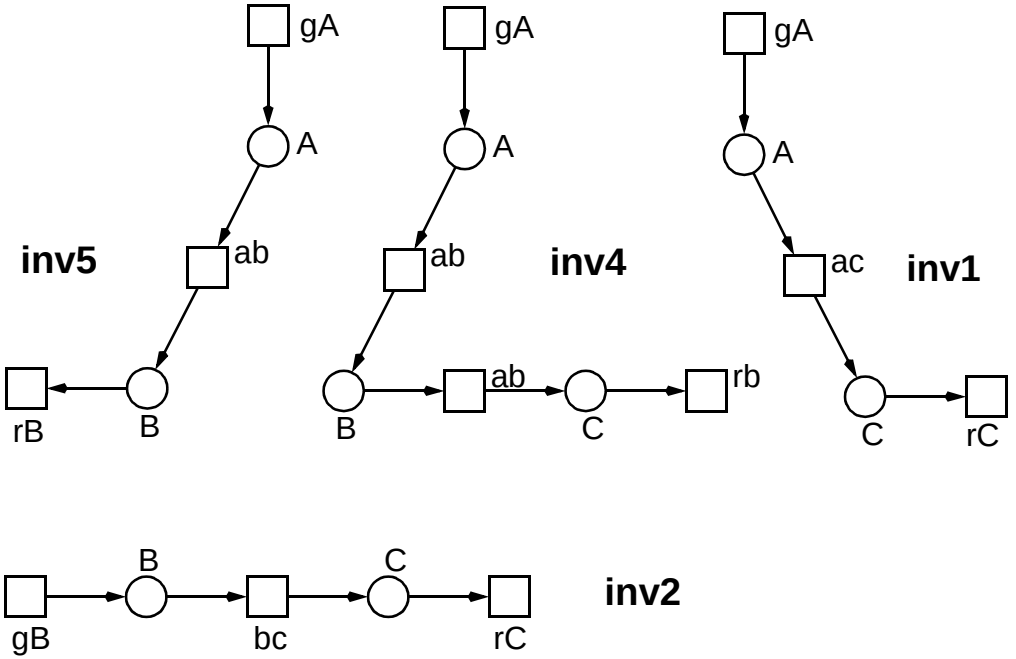
ELEMENTARY MODES



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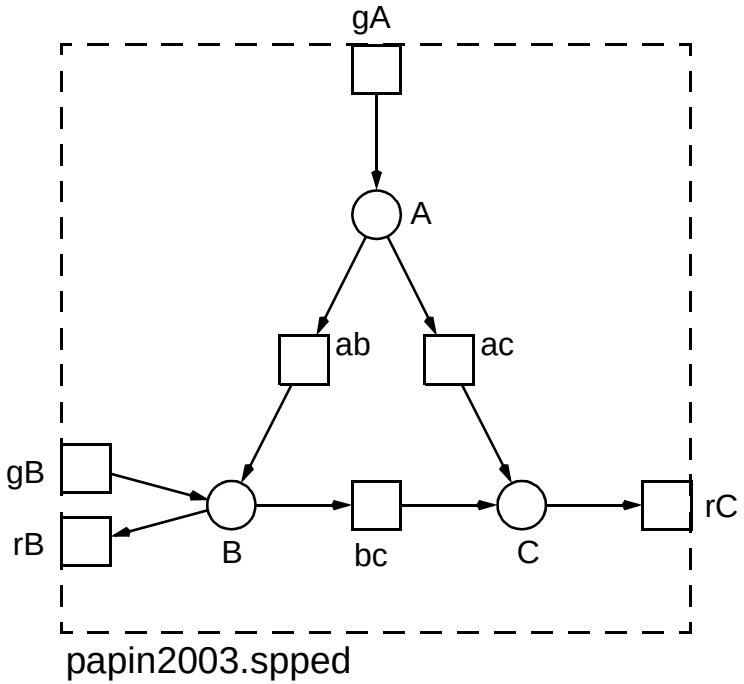

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MINIMAL T-INVARIANTS