

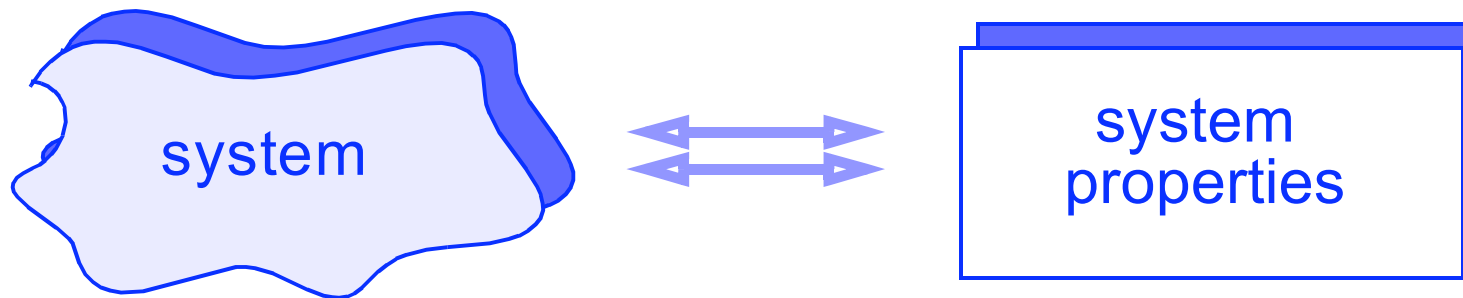
PART I

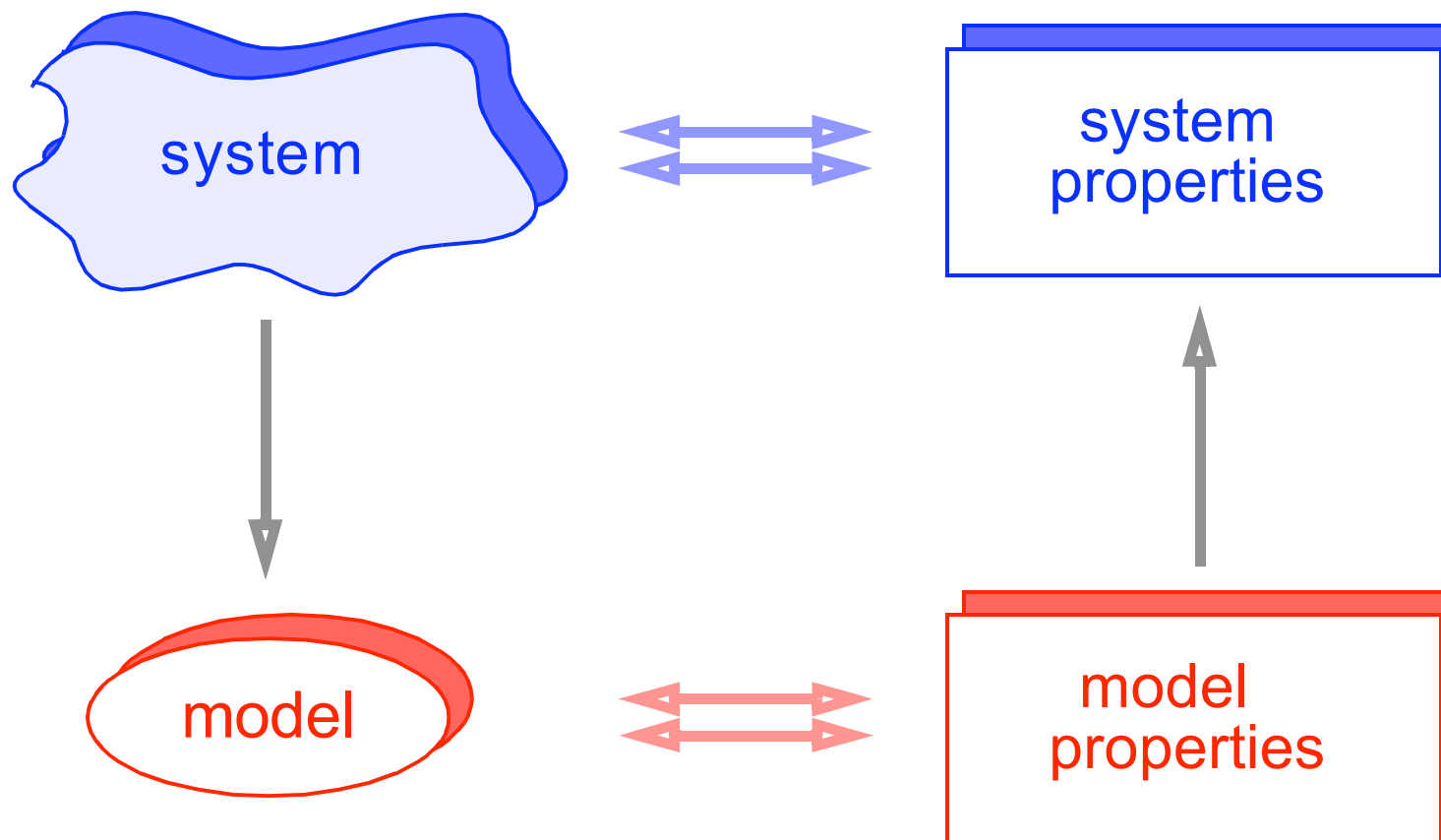
A PETRI NET PERSPECTIVE ON SYSTEMS AND SYNTHETIC BIOLOGY

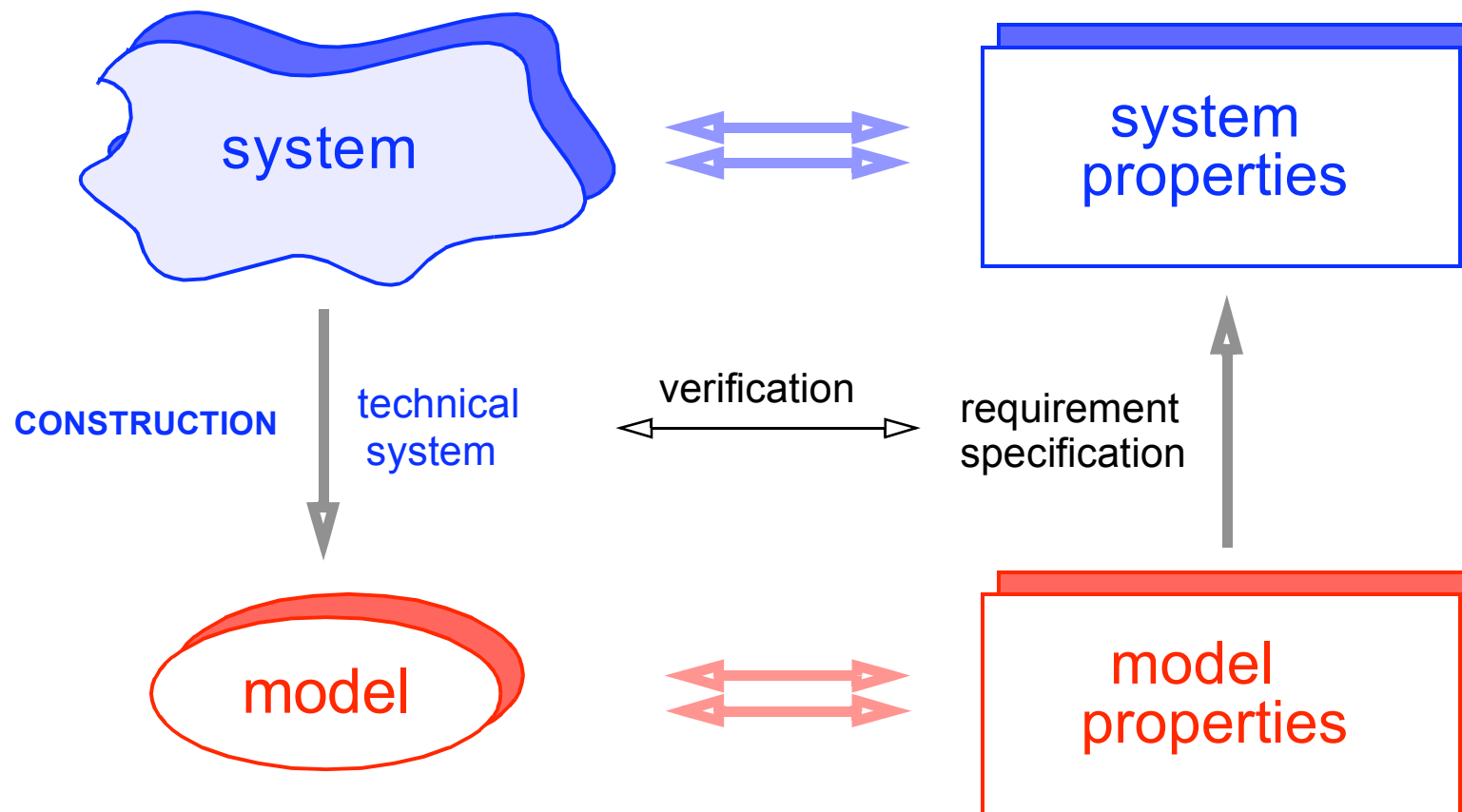
Monika Heiner

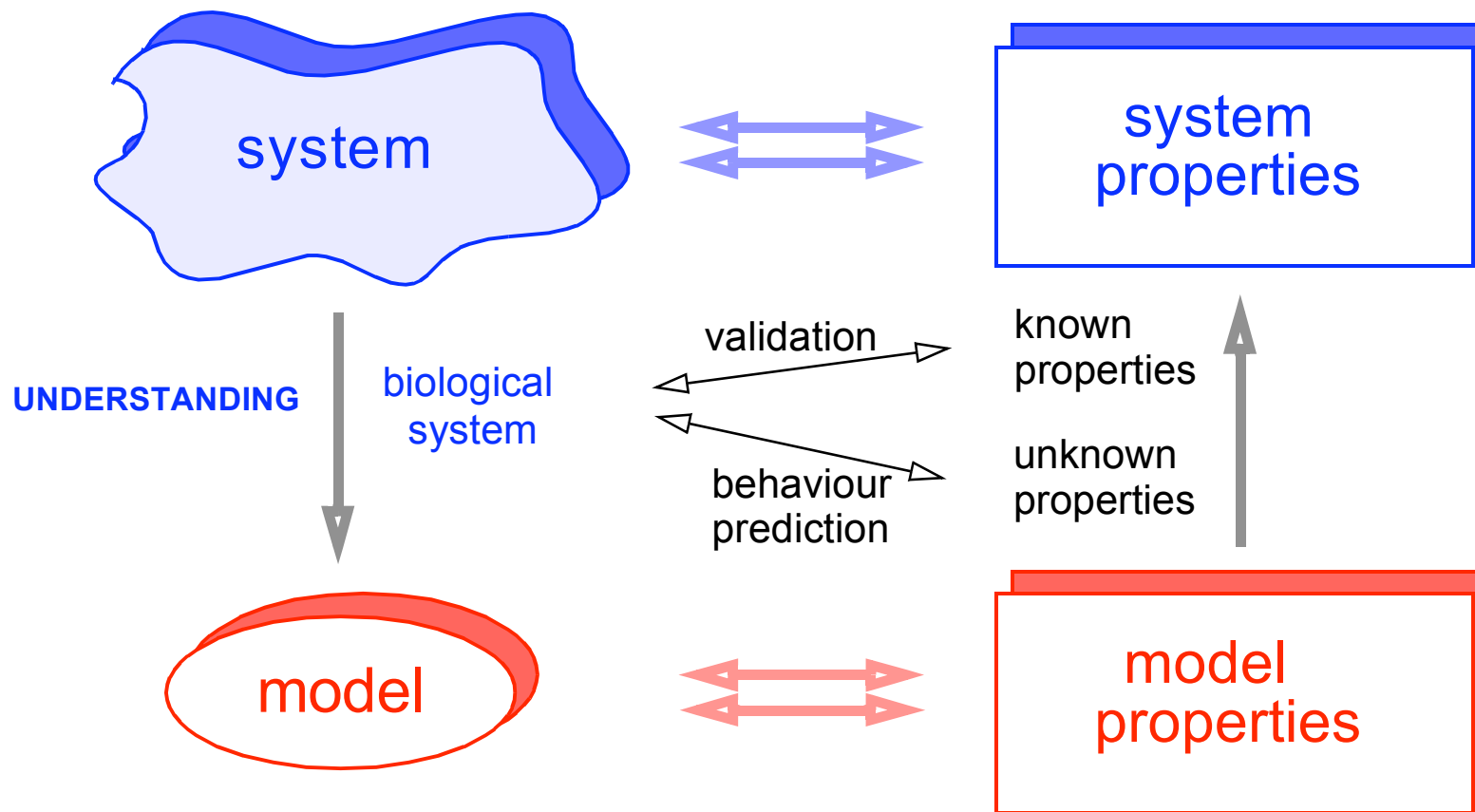
Brandenburg University of Technology Cottbus

Dept. of CS



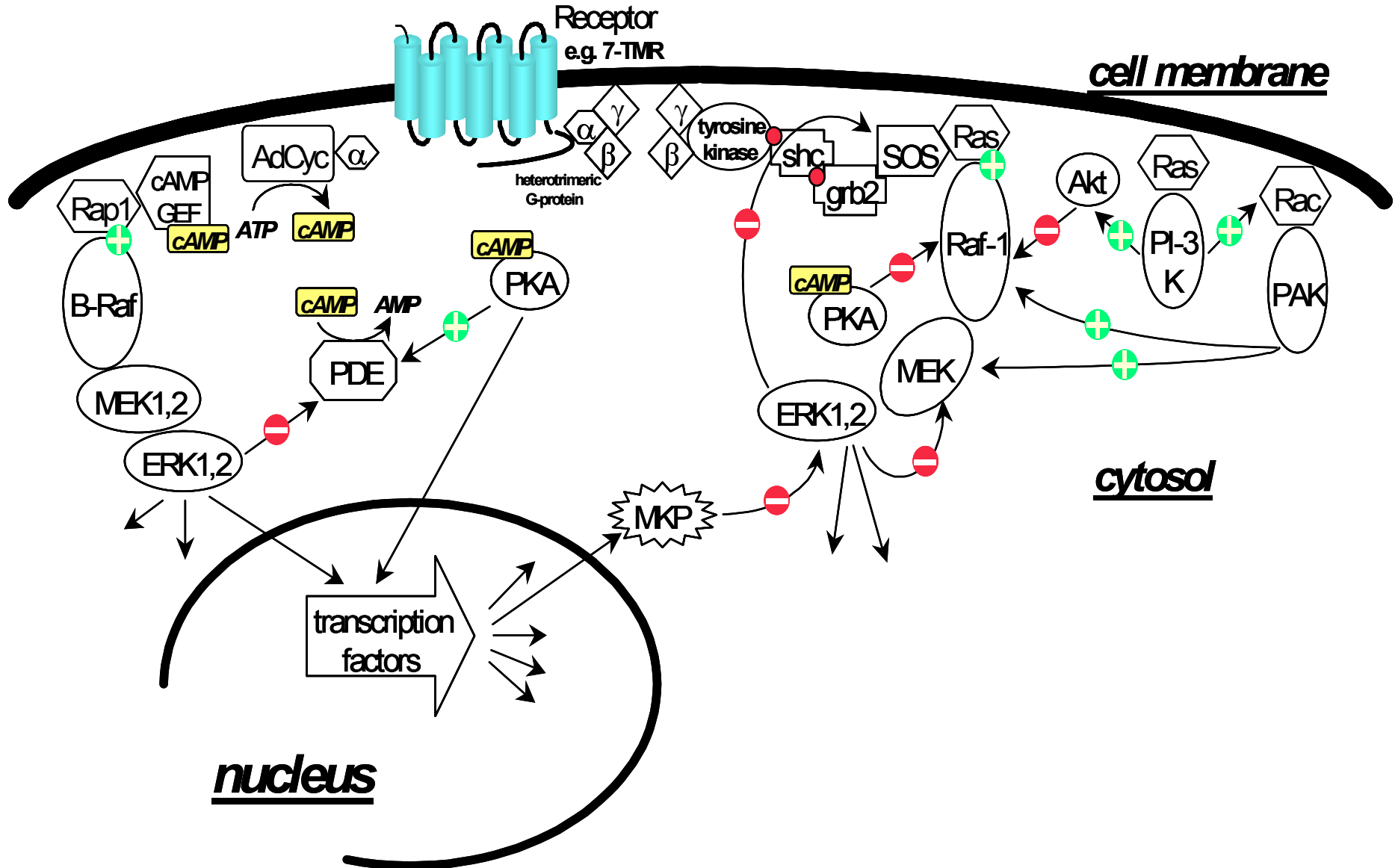


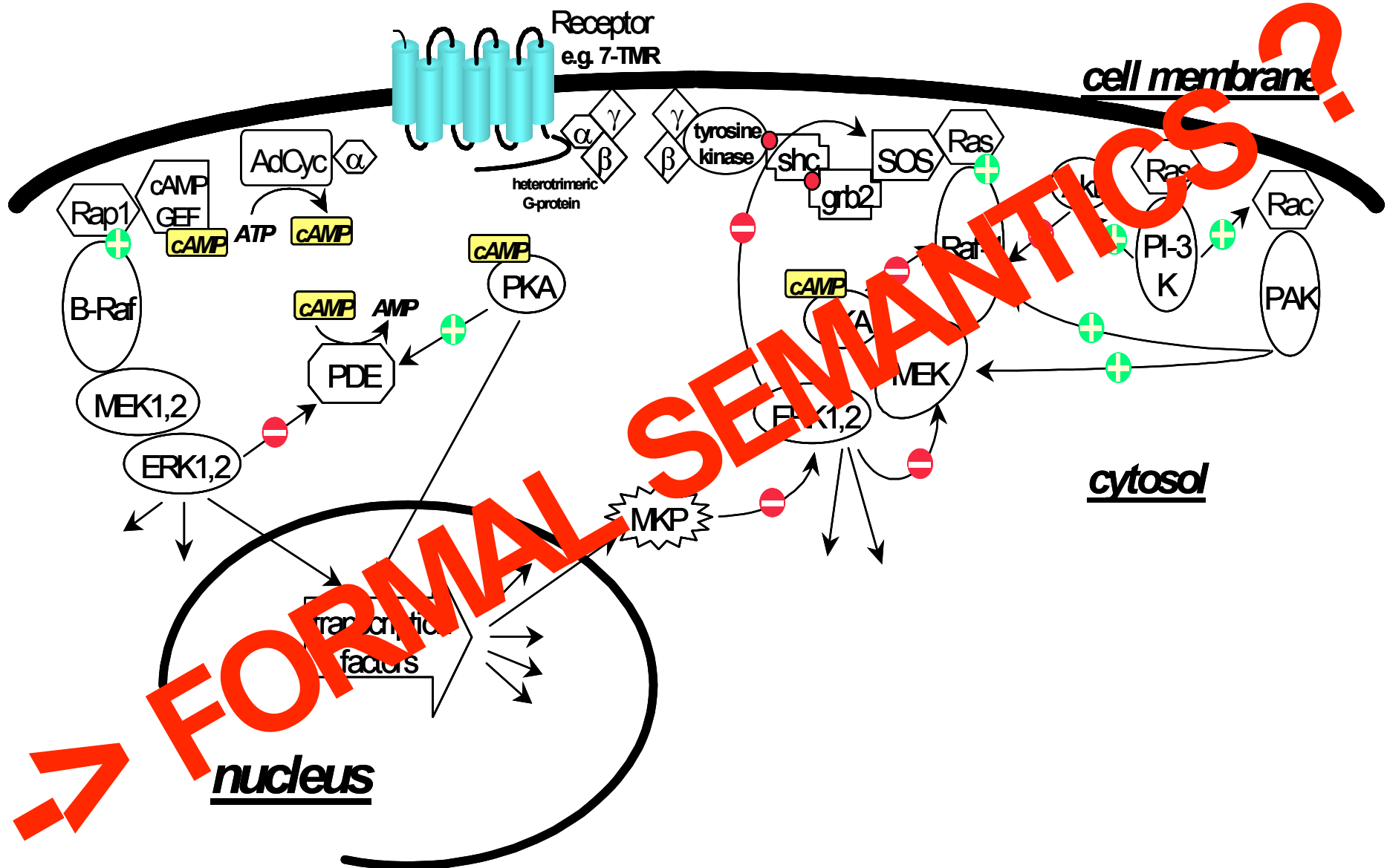




WHAT KIND OF MODEL SHOULD BE USED?

NETWORK REPRESENTATIONS, EX1





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

$$\begin{aligned} v_1 &= \alpha[t] \cdot Bar1_{active}[t] \cdot k_1 \\ v_2 &= Ste2[t] \cdot \alpha[t] \cdot k_2 \\ v_3 &= Ste2_{active}[t] \cdot k_3 \\ v_4 &= Ste2_{active}[t] \cdot k_4 \\ v_5 &= Ste2[t] \cdot k_5 \\ v_6 &= Ste2_{active}[t] \cdot G\alpha\beta\gamma[t] \cdot k_6 \\ v_7 &= G\alpha GTP[t] \cdot k_7 \\ v_8 &= G\alpha GTP[t] \cdot Sst2_{active}[t] \cdot k_8 \\ v_9 &= G\alpha GDP[t] \cdot G\beta\gamma[t] \cdot k_9 \\ v_{10} &= G\beta\gamma[t] \cdot C[t] \cdot k_{10} \\ v_{11} &= D[t] \cdot k_{11} \\ v_{12} &= Ste5[t] \cdot Ste11[t] \cdot k_{12} \\ v_{13} &= A[t] \cdot k_{13} \\ v_{14} &= Ste7[t] \cdot Fus3[t] \cdot k_{14} \\ v_{15} &= B[t] \cdot k_{15} \\ v_{16} &= A[t] \cdot B[t] \cdot k_{16} \\ v_{17} &= C[t] \cdot k_{17} \\ v_{18} &= D[t] \cdot Ste20[t] \cdot k_{18} \end{aligned}$$

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READABILITY ?

- ❑ **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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- ❑ **network structure** **-> PROBLEM 3**
 - > *tend to grow fast*
 - > *dense, apparently unstructured*
 - > *hard to read*

-> MODELS ARE FULL OF ASSUMPTIONS <-

readable

-> *fault avoidance*

-> *informal = cartoon-like representations ?*

analysable

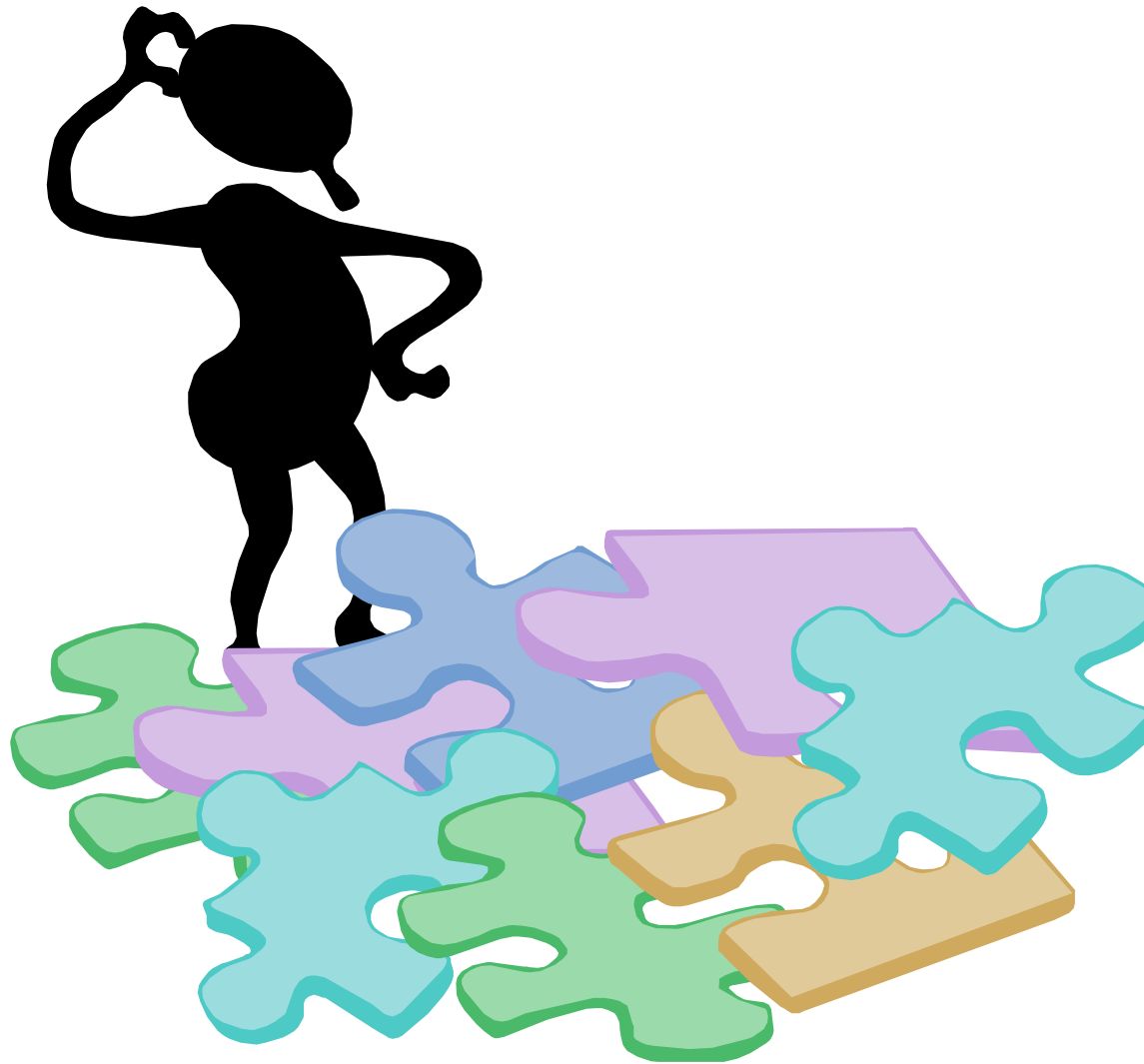
-> *formal = mathematical representations*

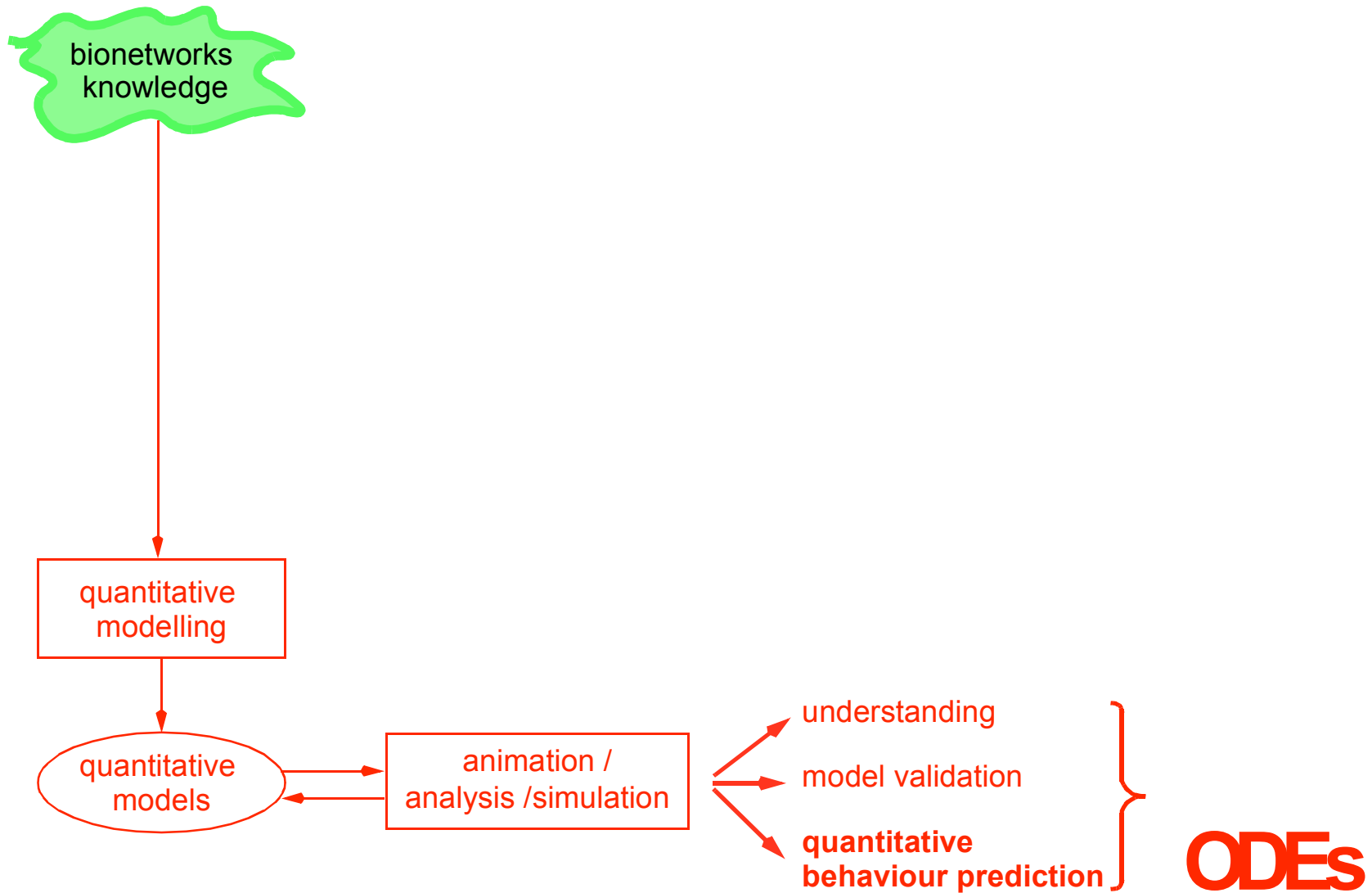
executable

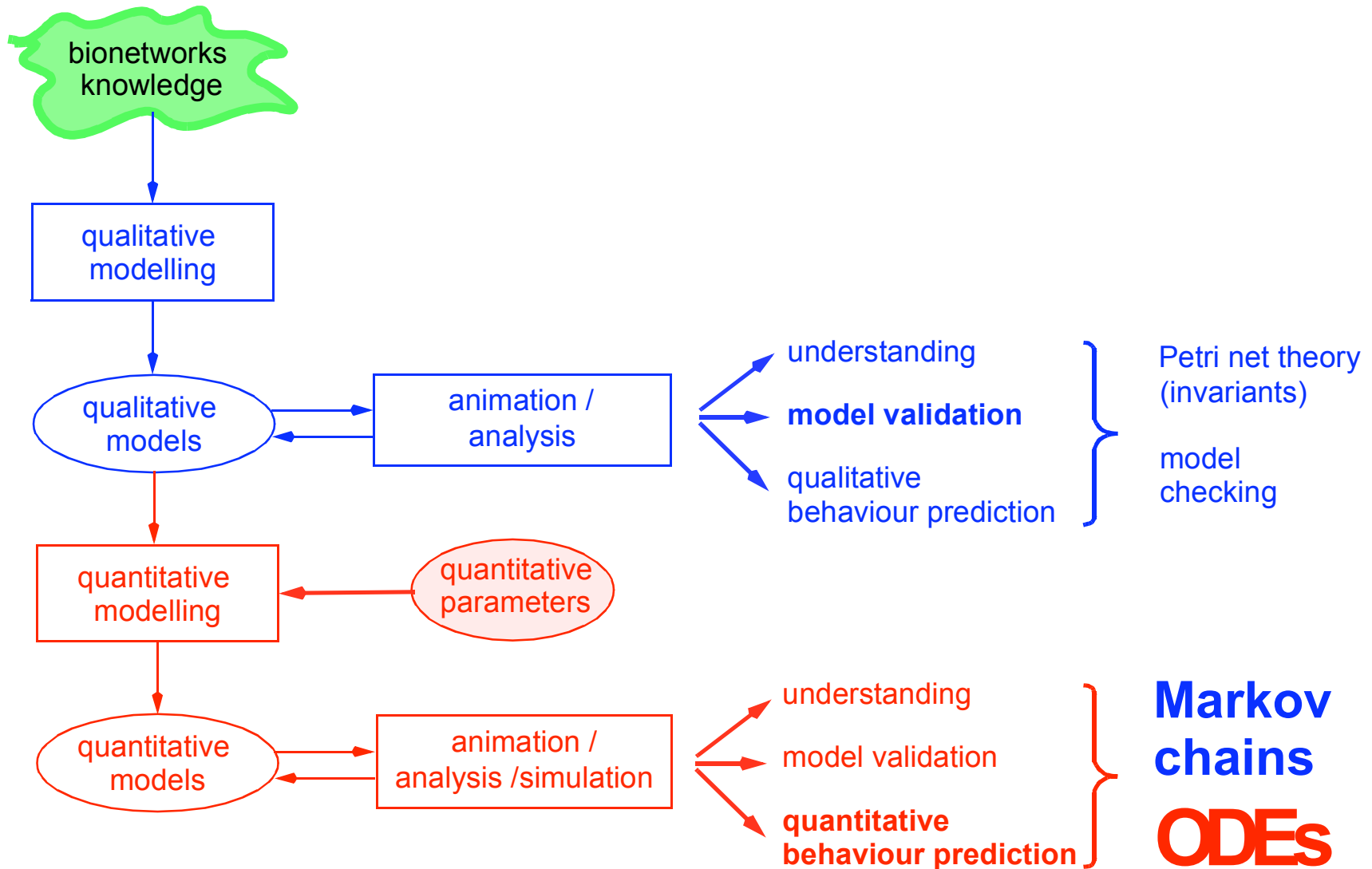
-> *to experience the model*

unifying power

-> *high-level description for various analysis approaches*

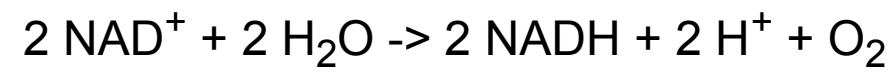


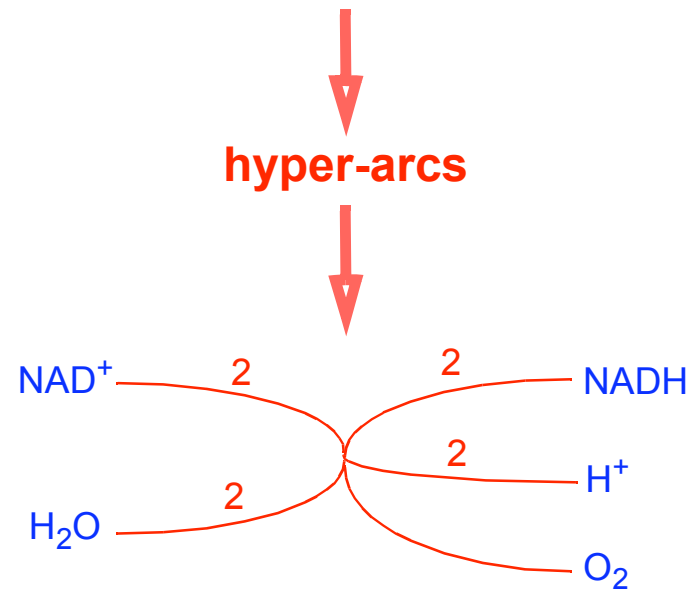
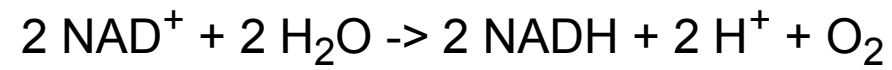


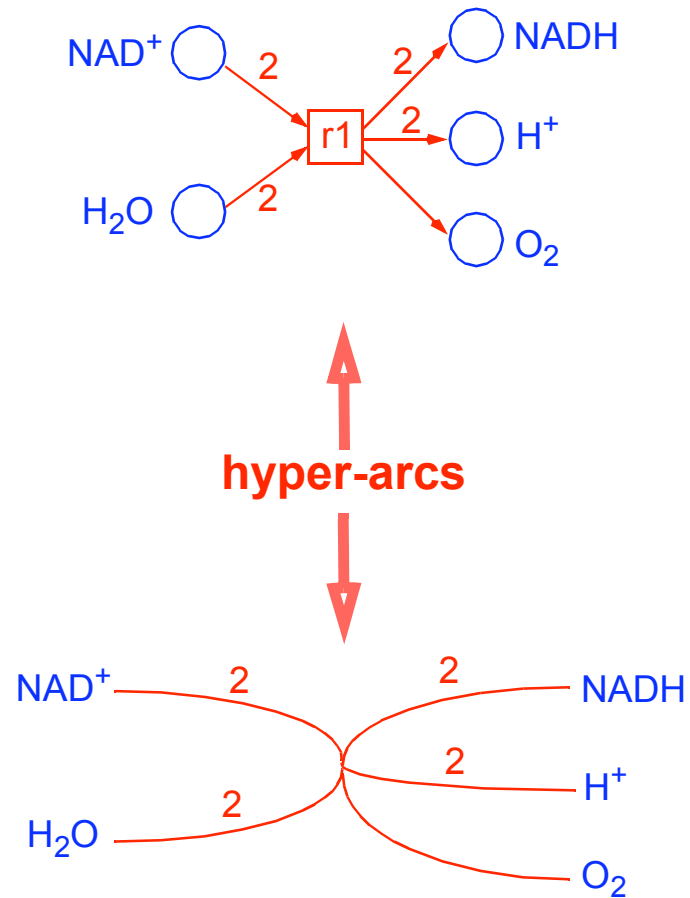
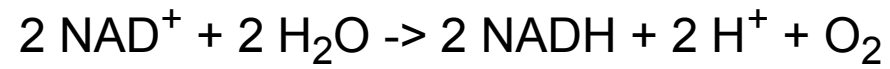


PETRI NETS - AN INFORMAL CRASH COURSE

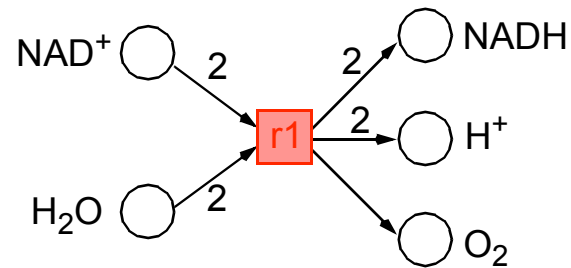
***. . . ARE
NETWORKS OF
(BIO-) CHEMICAL REACTIONS***



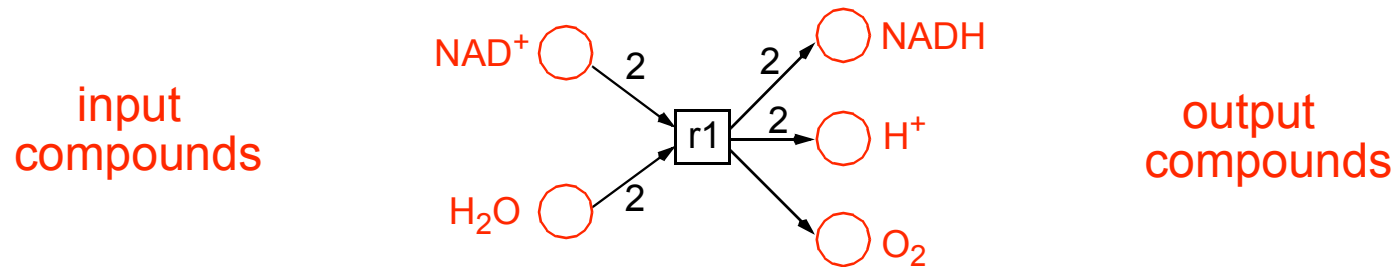
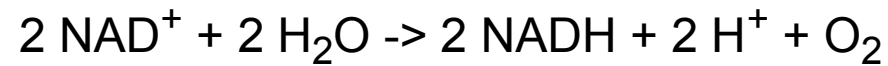




□ **chemical reactions** **-> atomic actions** **-> Petri net transitions**

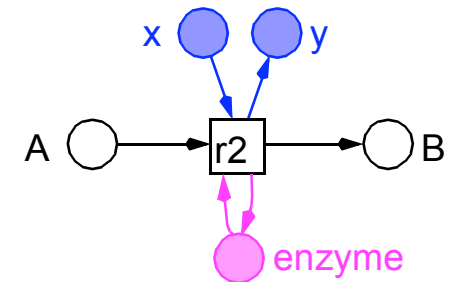


□ **chemical reactions** -> **atomic actions** -> **Petri net transitions**

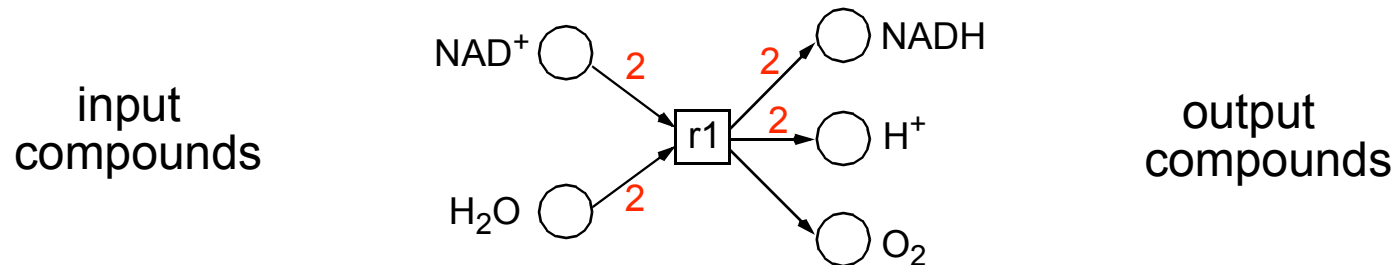
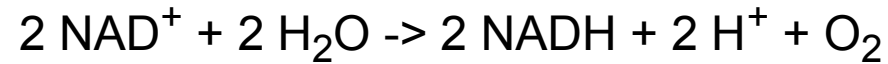


□ **chemical compounds** -> **Petri net places**

- | | |
|---|---------------------------------|
| - <i>primary compounds</i> | - <i>metabolites</i> |
| - <i>auxiliary compounds, ubiquitous -> fusion nodes</i> | - <i>e. g. electron carrier</i> |
| - <i>catalyzing compounds</i> | - <i>enzymes</i> |

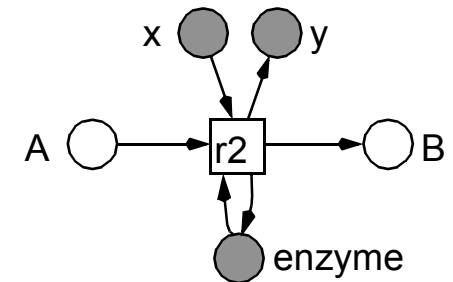


□ **chemical reactions** → **atomic actions** → **Petri net transitions**



□ **chemical compounds** → **Petri net places**

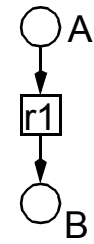
- | | |
|--|--------------------------|
| - primary compounds | - metabolites |
| - auxiliary compounds, ubiquitous → fusion nodes | - e. g. electron carrier |
| - catalyzing compounds | - enzymes |



□ **stoichiometric relations** → **Petri net arc multiplicities**

□ **compounds distribution** → **marking**

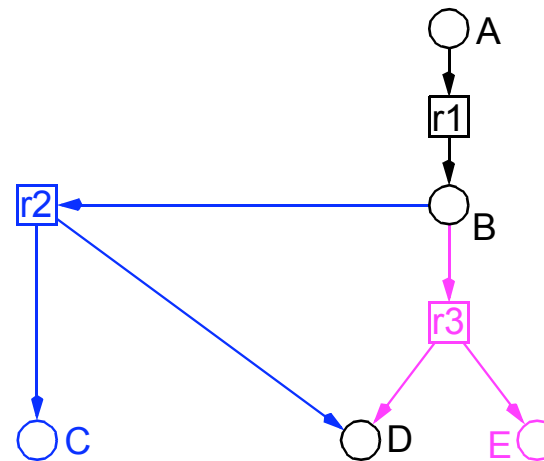
r1: A -> B



r1: $A \rightarrow B$

r2: $B \rightarrow C + D$

r3: $B \rightarrow D + E$



-> alternative reactions

r1: $A \rightarrow B$

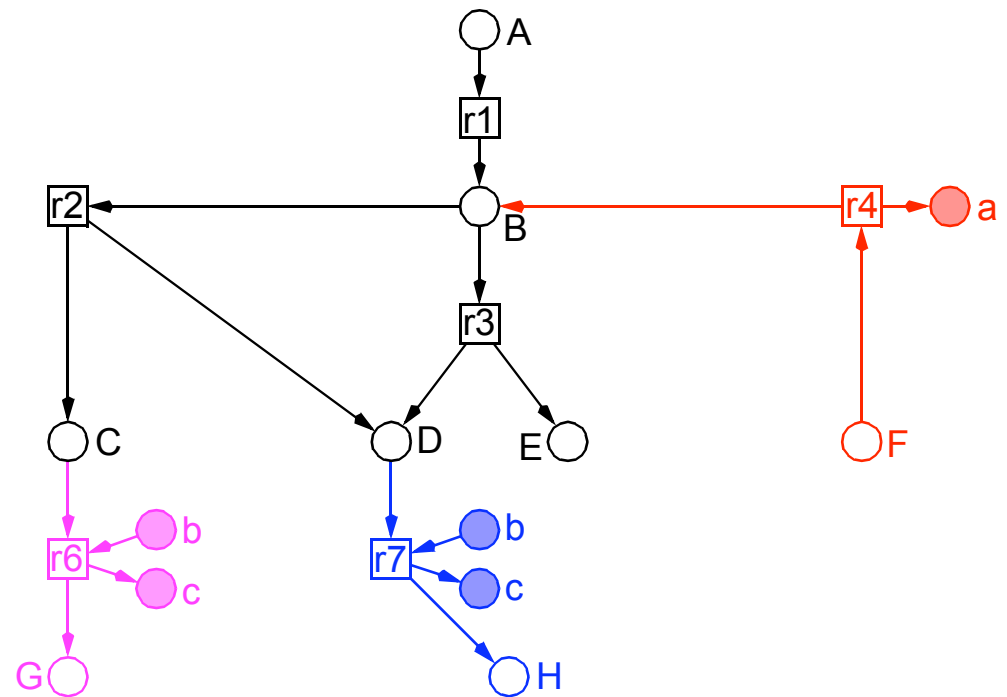
r2: $B \rightarrow C + D$

r3: $B \rightarrow D + E$

r4: $F \rightarrow B + a$

r6: $C + b \rightarrow G + c$

r7: $D + b \rightarrow H + c$



-> concurrent reactions

r1: $A \rightarrow B$

r2: $B \rightarrow C + D$

r3: $B \rightarrow D + E$

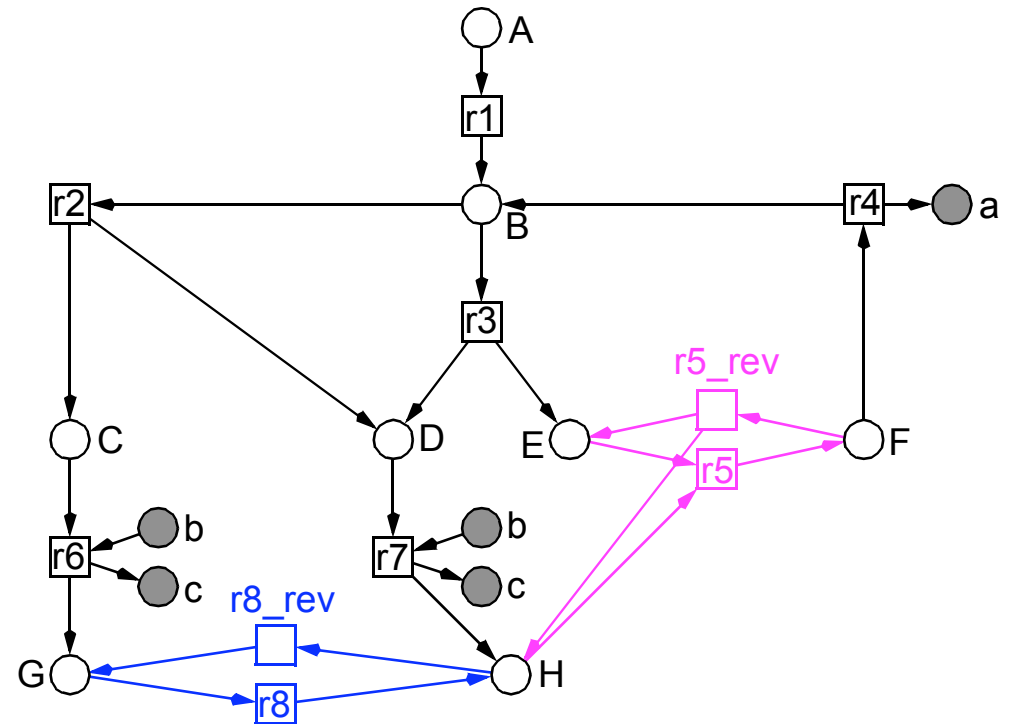
r4: $F \rightarrow B + a$

r5: $E + H \leftrightarrow F$

r6: $C + b \rightarrow G + c$

r7: $D + b \rightarrow H + c$

r8: $H \leftrightarrow G$



-> reversible reactions

r1: $A \rightarrow B$

r2: $B \rightarrow C + D$

r3: $B \rightarrow D + E$

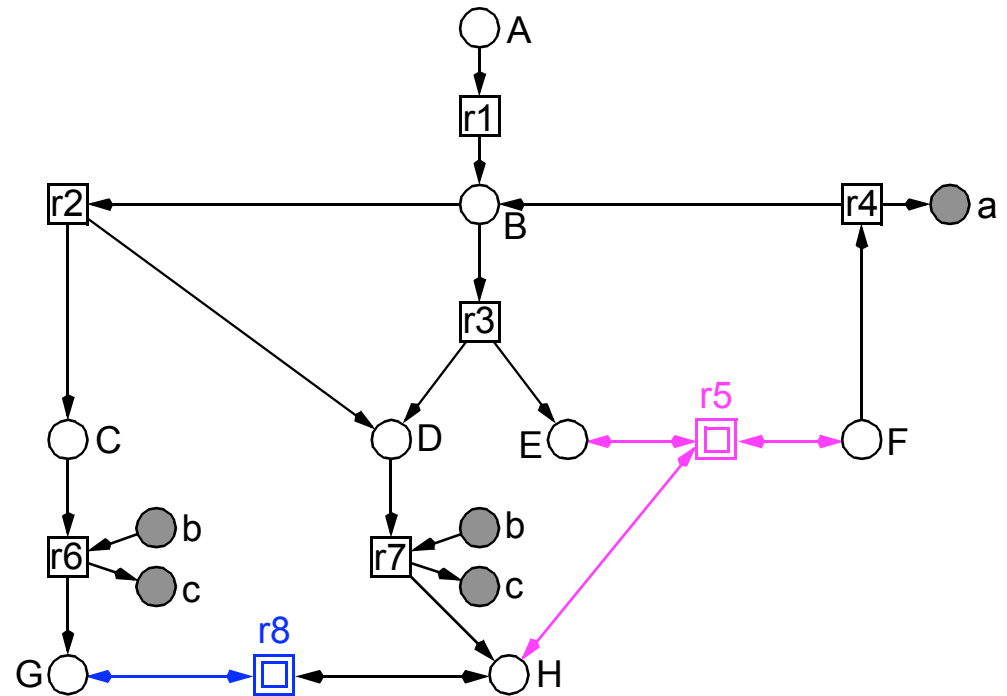
r4: $F \rightarrow B + a$

r5: $E + H \leftrightarrow F$

r6: $C + b \rightarrow G + c$

r7: $D + b \rightarrow H + c$

r8: $H \leftrightarrow G$



*-> reversible reactions
- hierarchical nodes*

r1: $A \rightarrow B$

r2: $B \rightarrow C + D$

r3: $B \rightarrow D + E$

r4: $F \rightarrow B + a$

r5: $E + H \leftrightarrow F$

r6: $C + b \rightarrow G + c$

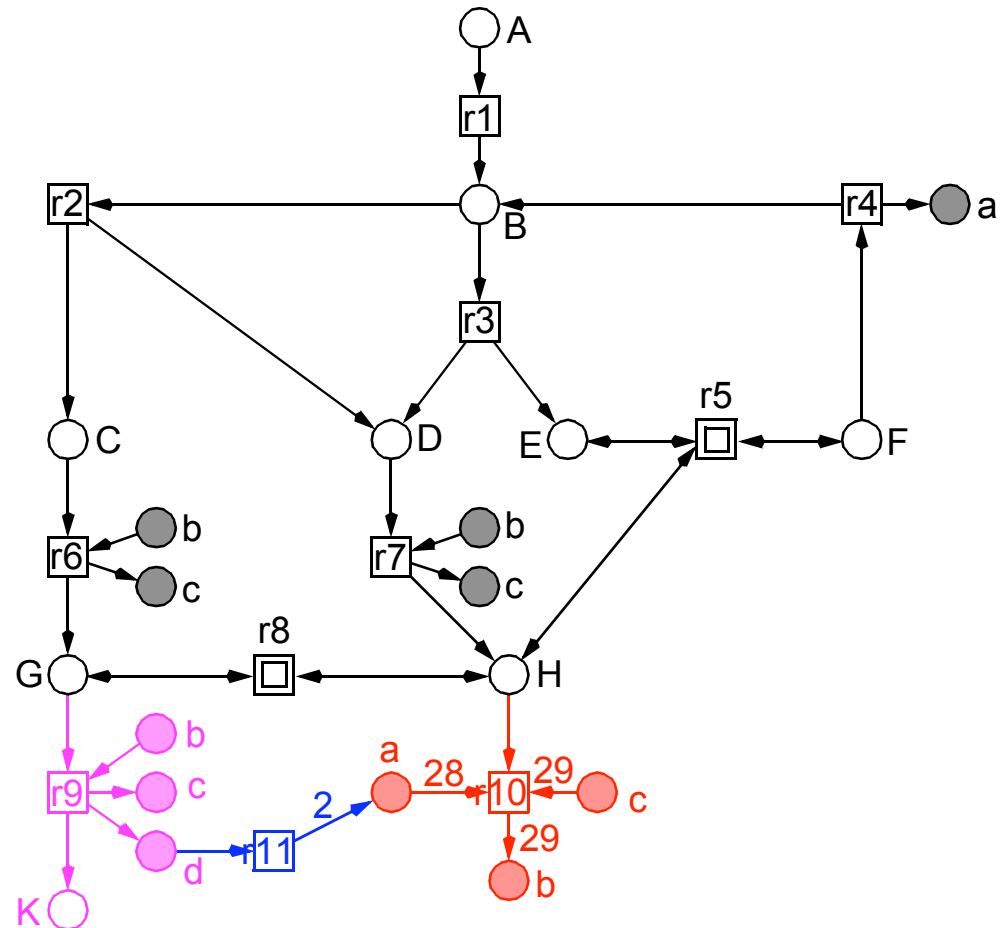
r7: $D + b \rightarrow H + c$

r8: $H \leftrightarrow G$

r9: $G + b \rightarrow K + c + d$

r10: $H + 28a + 29c \rightarrow 29b$

r11: $d \rightarrow 2a$



r1: $A \rightarrow B$

r2: $B \rightarrow C + D$

r3: $B \rightarrow D + E$

r4: $F \rightarrow B + a$

r5: $E + H \leftrightarrow F$

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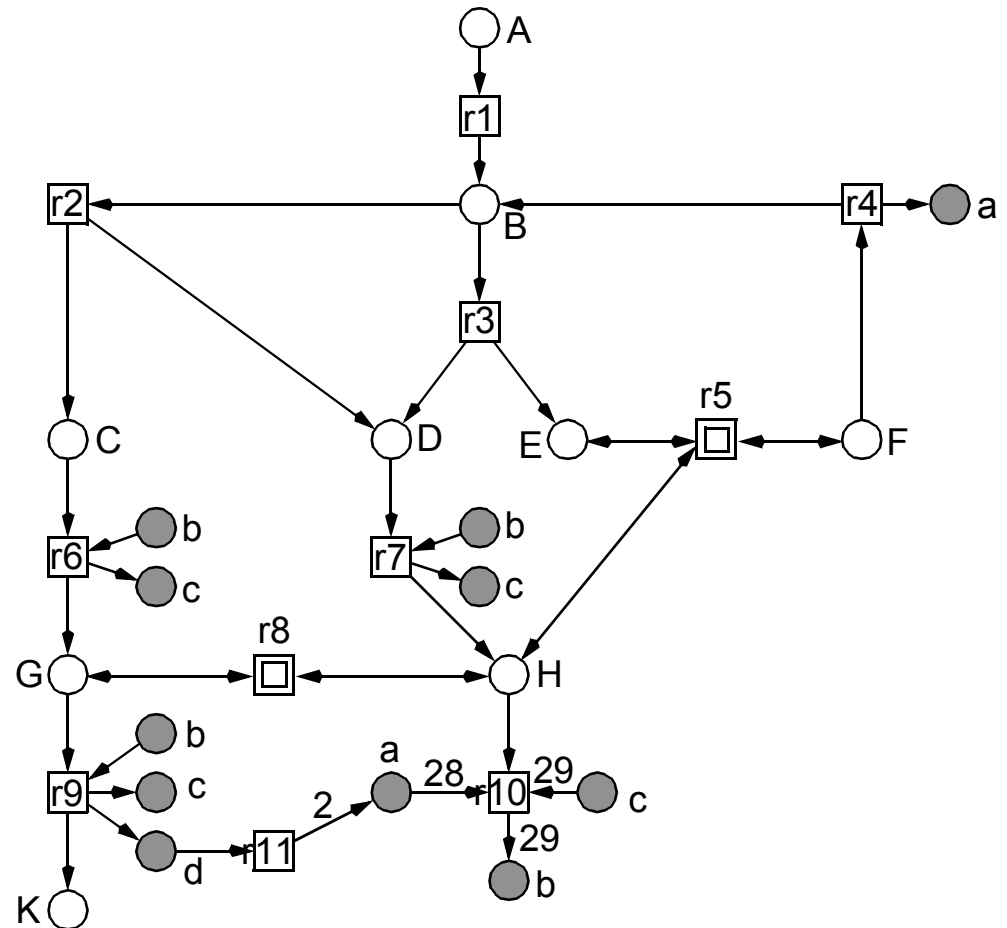
r7: $D + b \rightarrow H + c$

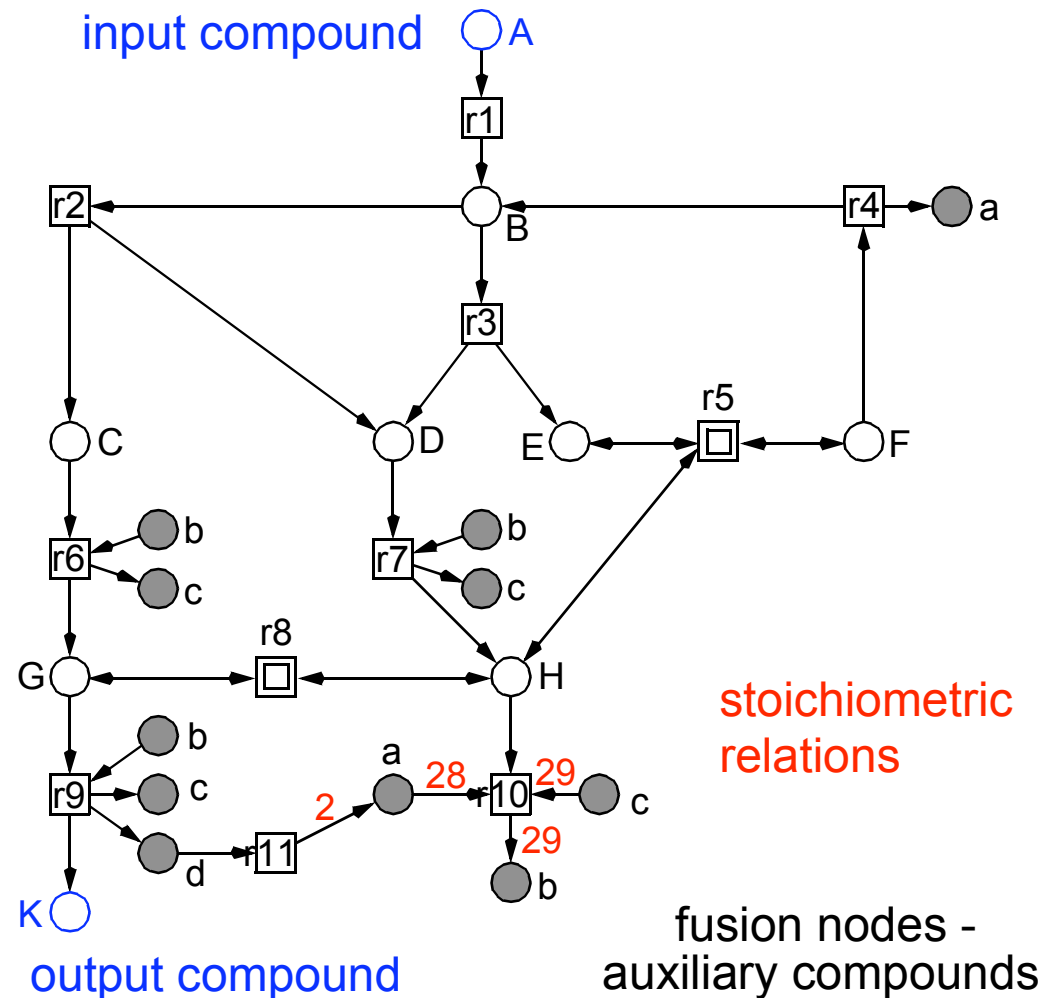
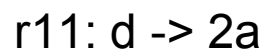
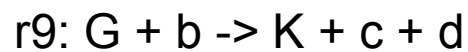
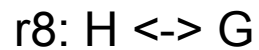
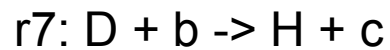
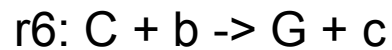
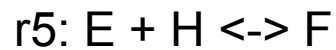
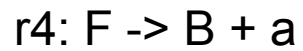
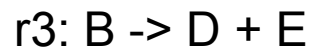
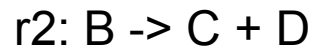
r8: $H \leftrightarrow G$

r9: $G + b \rightarrow K + c + d$

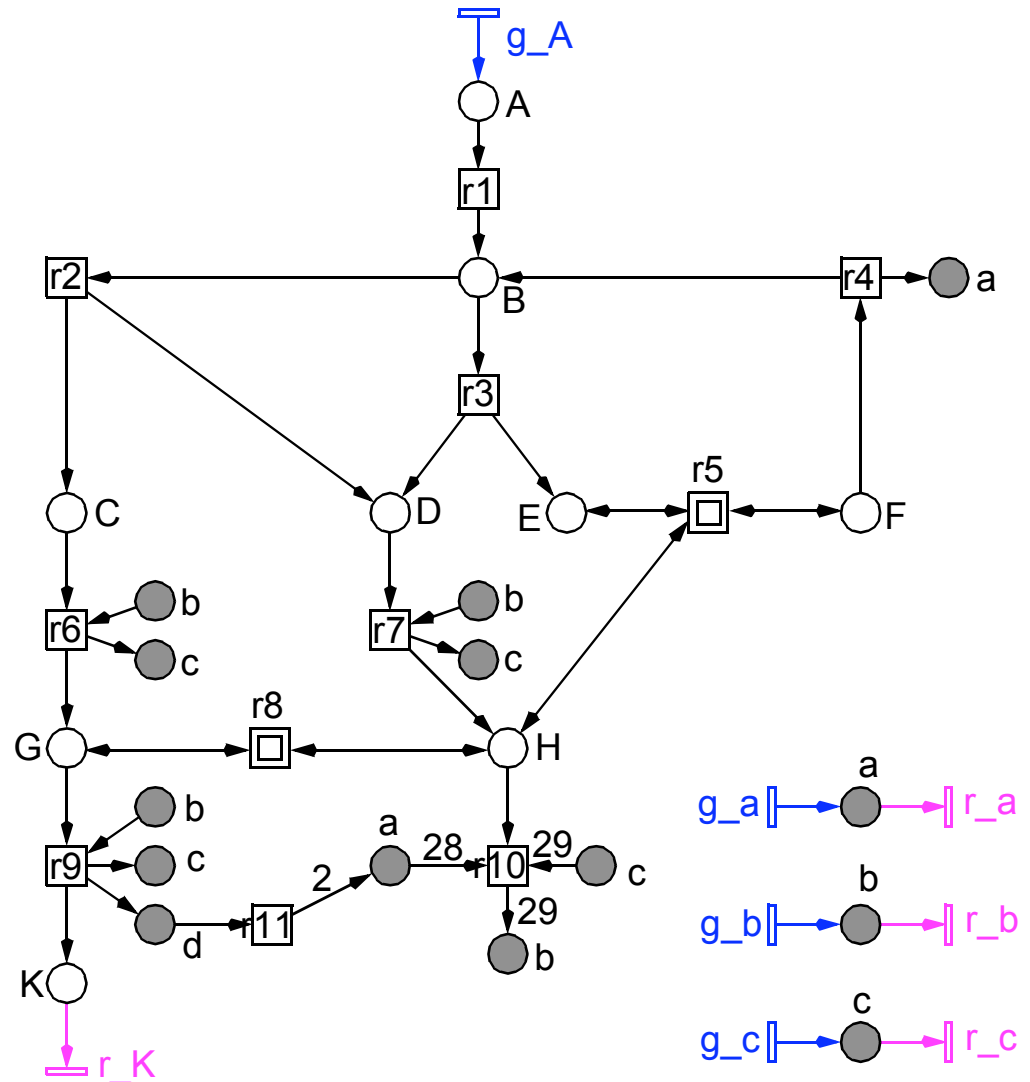
r10: $H + 28a + 29c \rightarrow 29b$

r11: $d \rightarrow 2a$





- ❑ **input substances**
-> *generating pre-transitions*
- ❑ **output substances**
-> *consuming post-transitions*
- ❑ **auxiliary substances**
-> *both*
- ❑ **no boundary places, but boundary transitions**
- ❑ **transitions without pre-places**
-> *live*
-> *all post-places are unbounded*
- ❑ **steady state behaviour**
-> *empty marking reproduction*



❑ biochemical networks

-> *networks of (abstract) chemical reactions*

❑ biochemically interpreted Petri net

-> *partial order sequences* of chemical reactions (= elementary actions) transforming input into output compounds / signals

[respecting the given stoichiometric relations, if any]

-> set of all *pathways* (*self-contained partial order sequence*) from the input to the output compounds / signals

[respecting the stoichiometric relations, if any]

❑ typical properties

INA

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

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

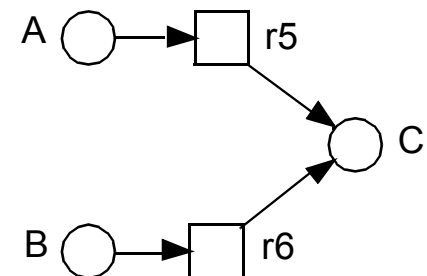
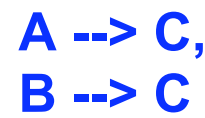
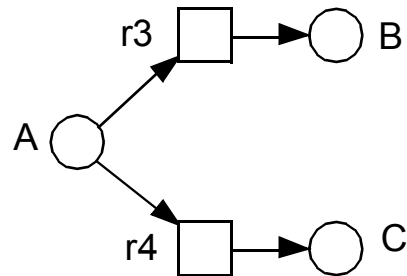
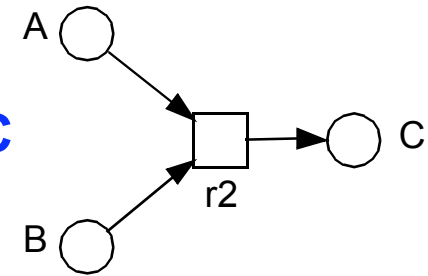
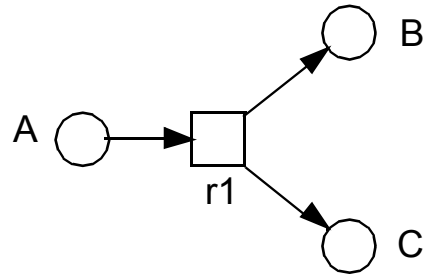
CLAIMS

- ❑ **metabolic networks**
 - signal transduction networks**
 - gene regulatory networks**

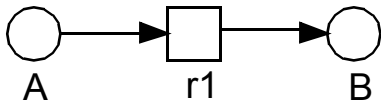
- ❑ **transitions**
 - > *(reversible, stoichiometric) chemical reactions,*
 - > *enzyme-catalyzed conversions of metabolites, proteins, . . .*
 - > *complexations/decomplexations, de-/phosphorylations, . . .*

- ❑ **places**
 - > *(primary, secondary) chemical compounds,*
 - > *(various states of) proteins, protein complex, genes, . . .*

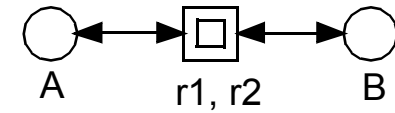
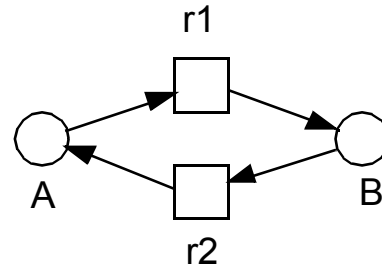
- ❑ **tokens**
 - > *molecules, moles,*
 - > *concentration levels, gene expression levels, . . .*
(e.g., high/low = present/not present)



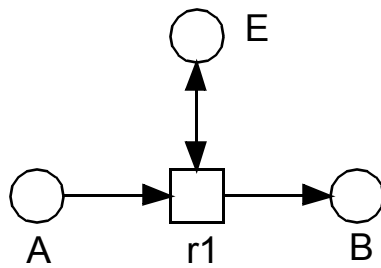
A \dashrightarrow B



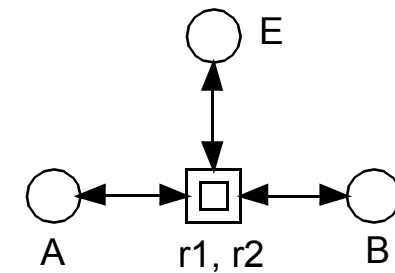
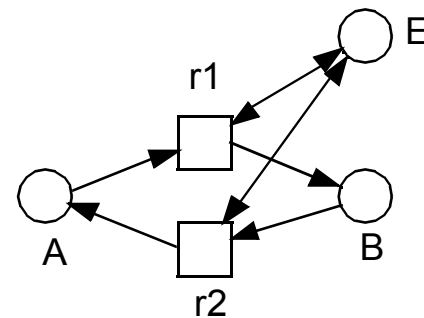
A \leftrightarrow B



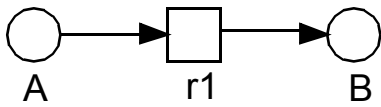
A $\overset{E}{\dashrightarrow}$ B



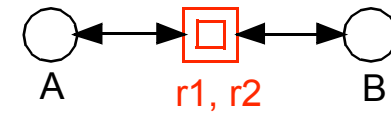
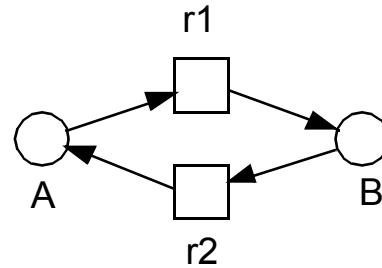
A $\overset{E}{\leftrightarrow}$ B



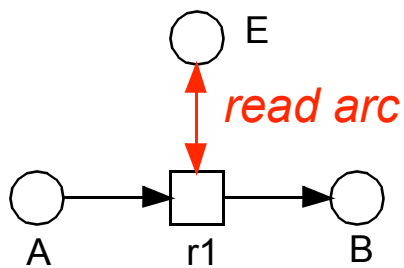
A \dashrightarrow B



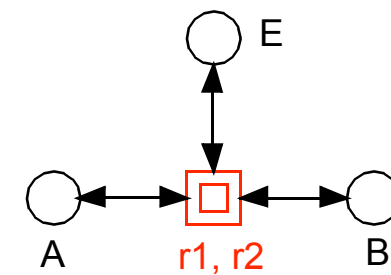
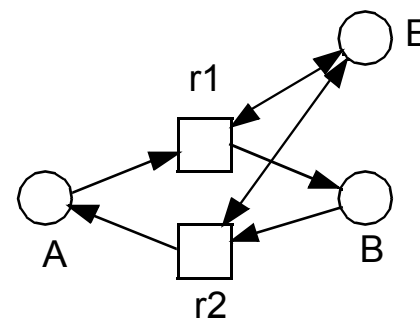
A \leftrightarrow B



A \xrightarrow{E} B



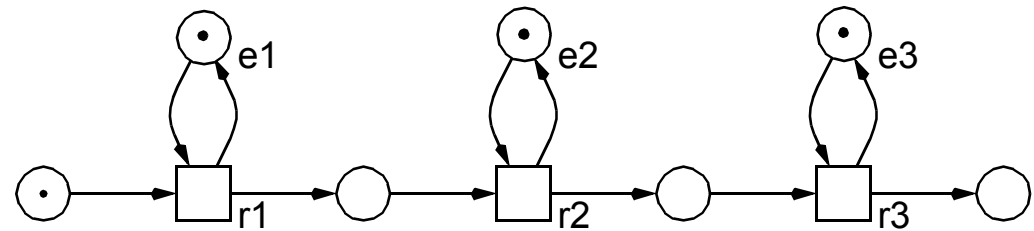
A \xleftrightarrow{E} B



macro transition

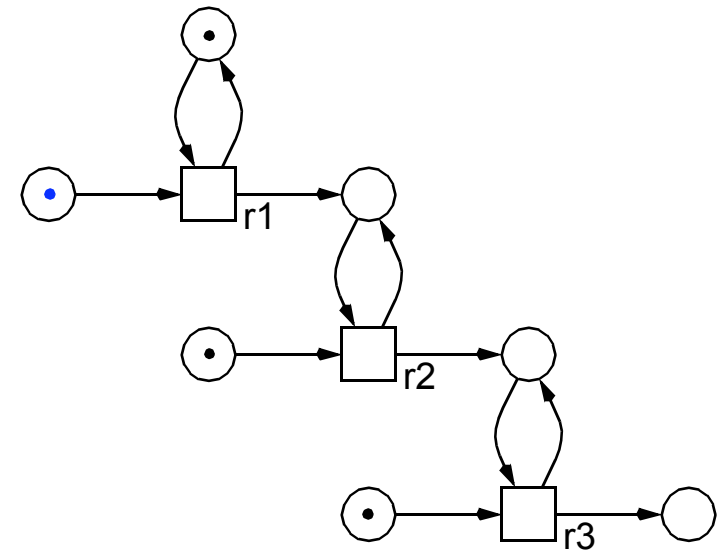
□ metabolic networks

-> *substance flows*



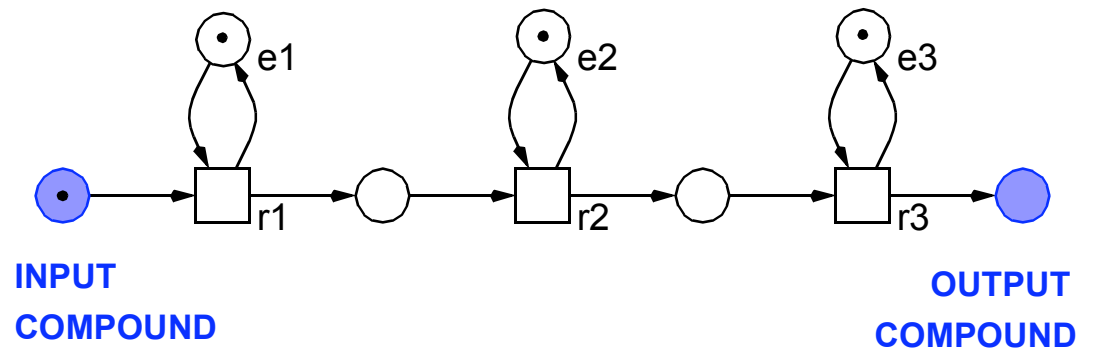
□ signal transduction networks

-> *signal flows*



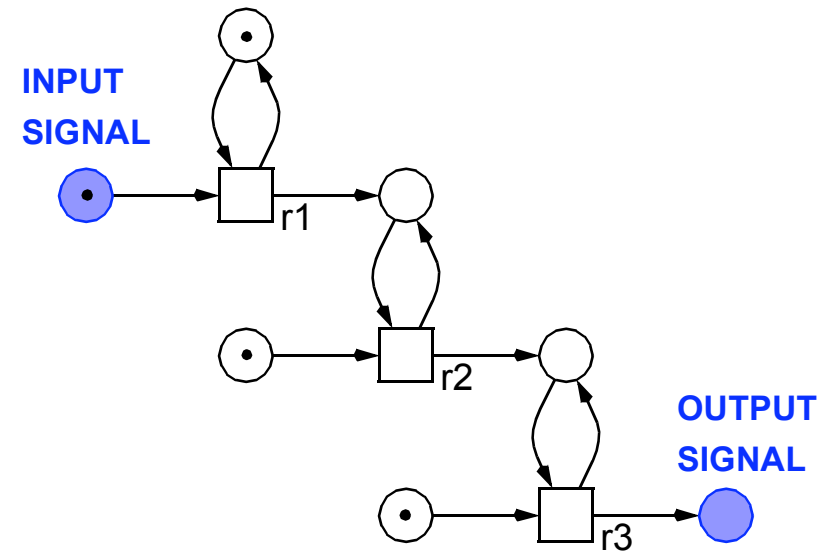
metabolic networks

-> *substance flows*



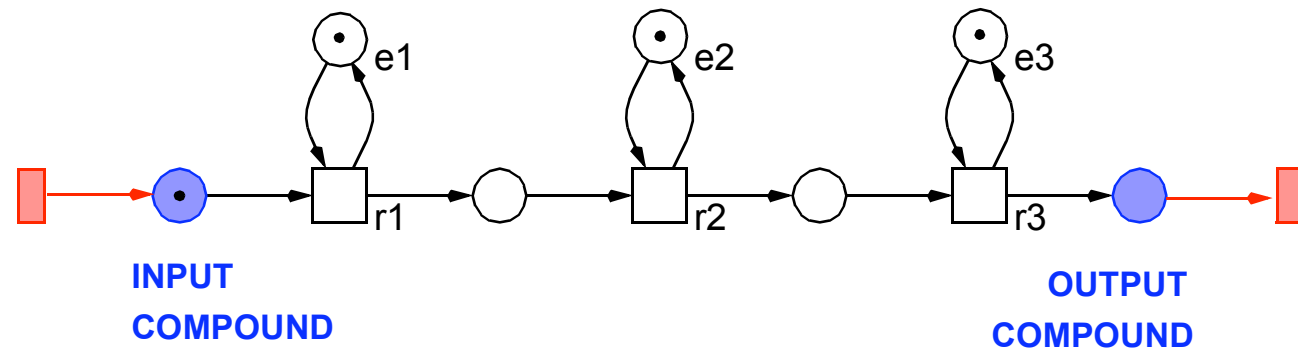
signal transduction networks

-> *signal flows*



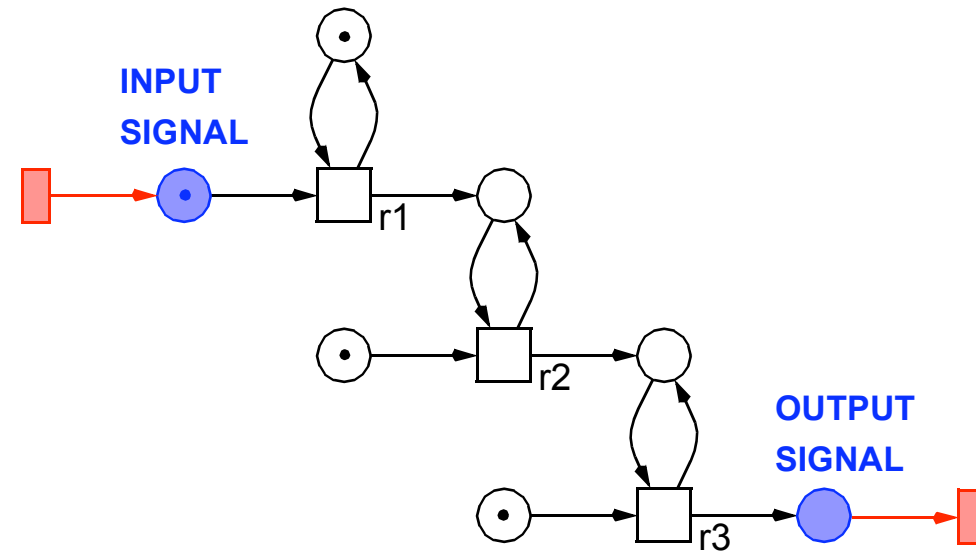
metabolic networks

-> *substance flows*



signal transduction networks

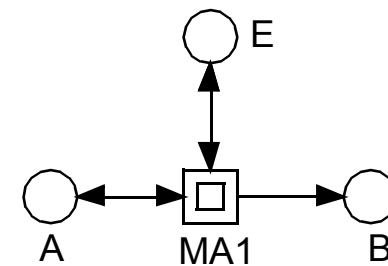
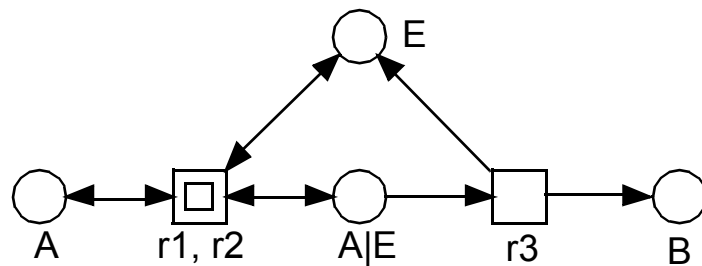
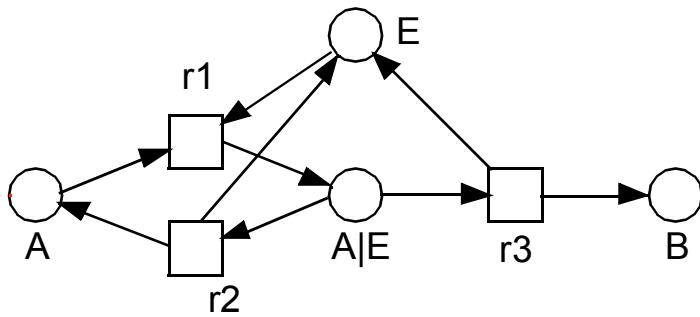
-> *signal flows*



-> **OPEN / CLOSED SYSTEMS**

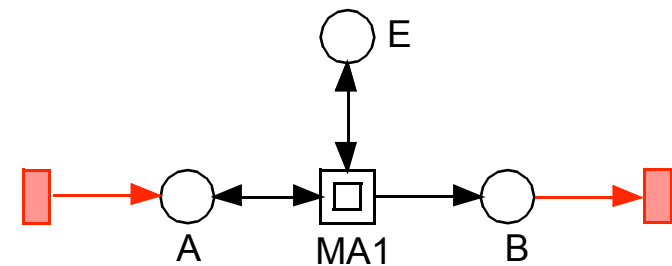
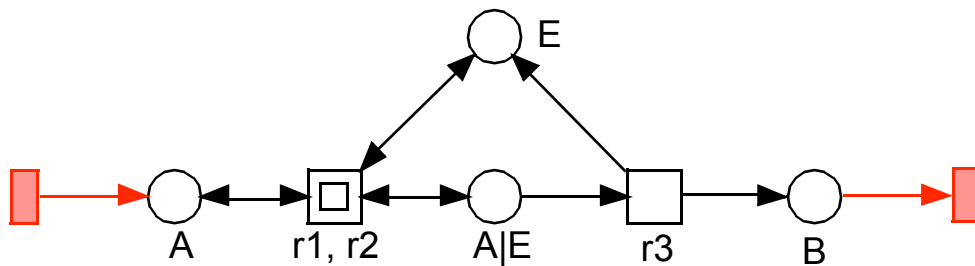
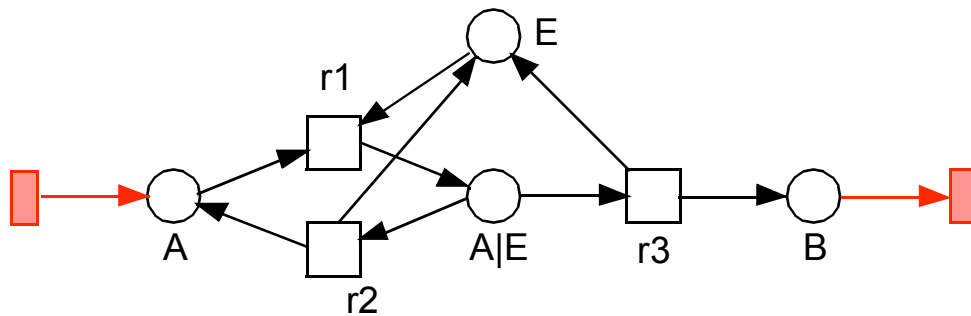


*enzymatic reaction,
mass-action approach 1*

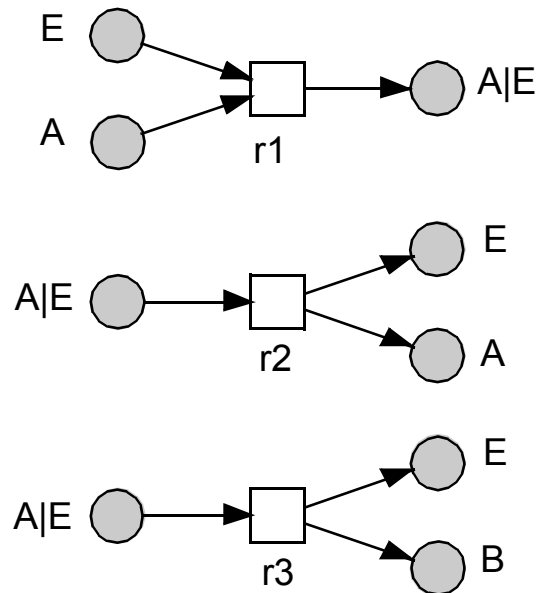




*enzymatic reaction,
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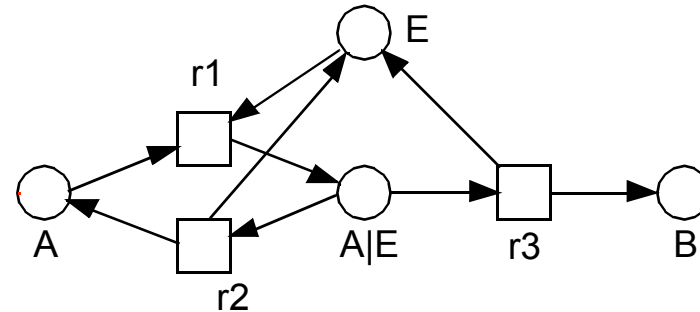


reaction-centred view

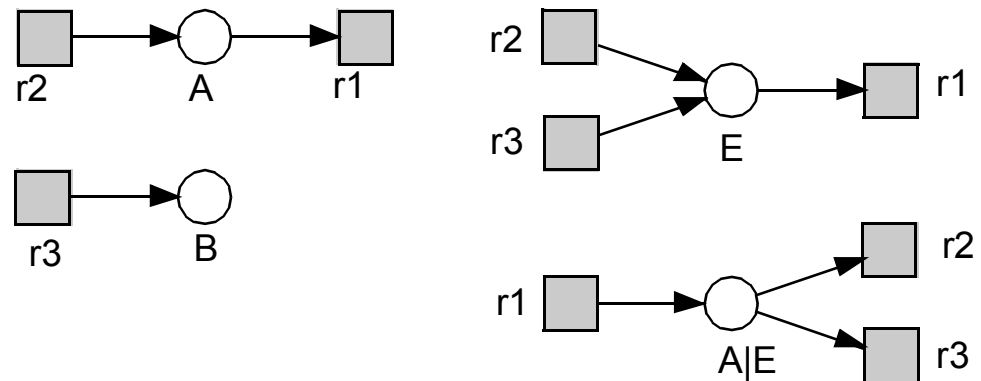


*logical nodes
(fusion nodes)*

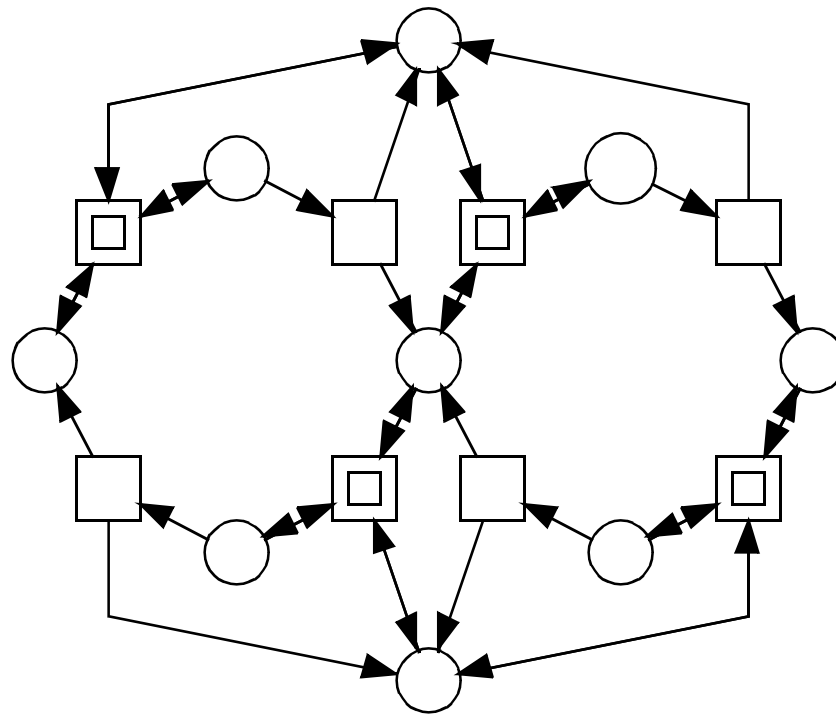
process-oriented view



species-centred view

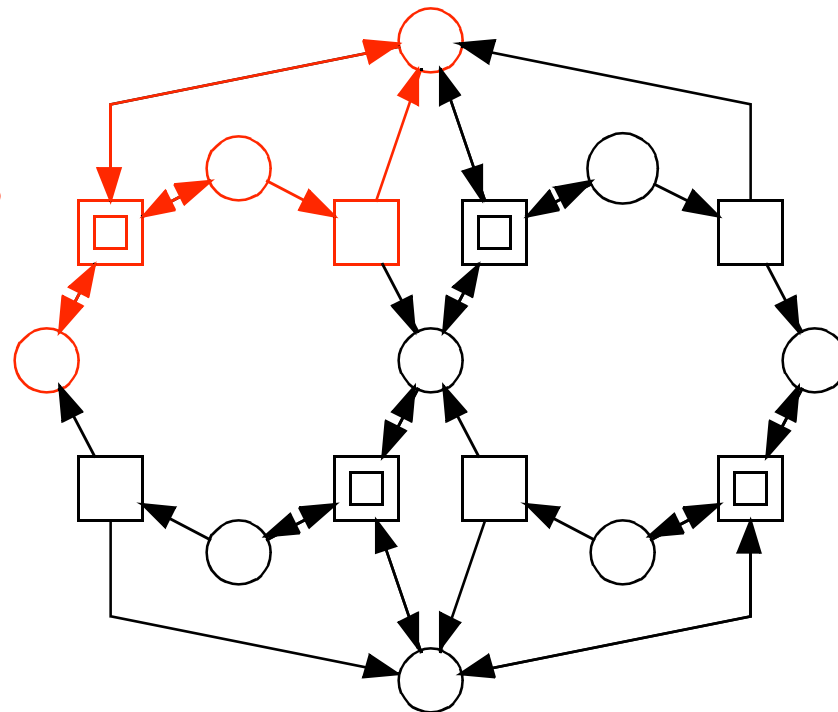


DOUBLE PHOSPHORYLATION/DEPHOSPHORYLATION

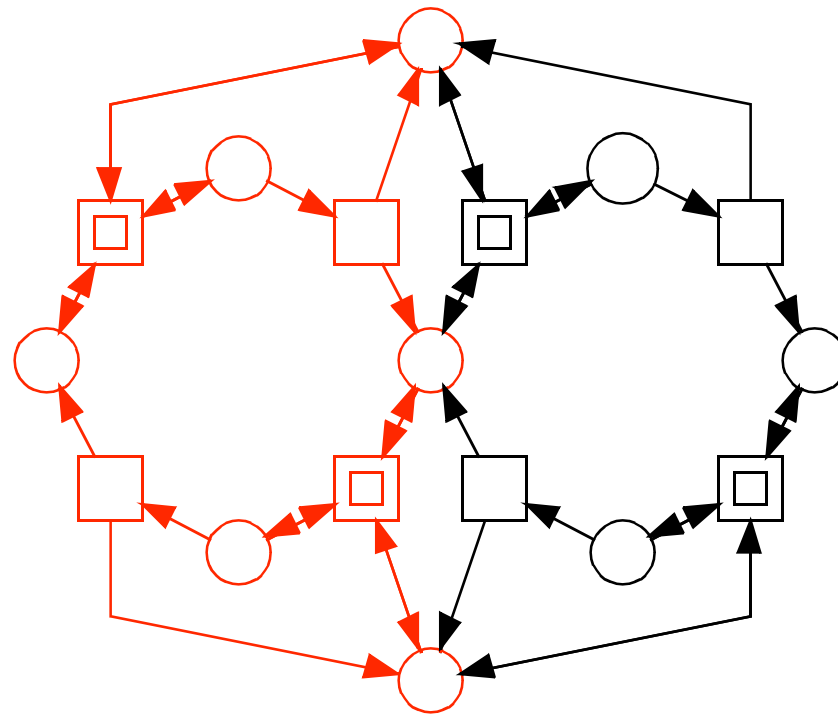


DOUBLE PHOSPHORYLATION/DEPHOSPHORYLATION

SINGLE
MASS-ACTION STEP



DOUBLE PHOSPHOYLATION / DEPHOSPHORYLATION

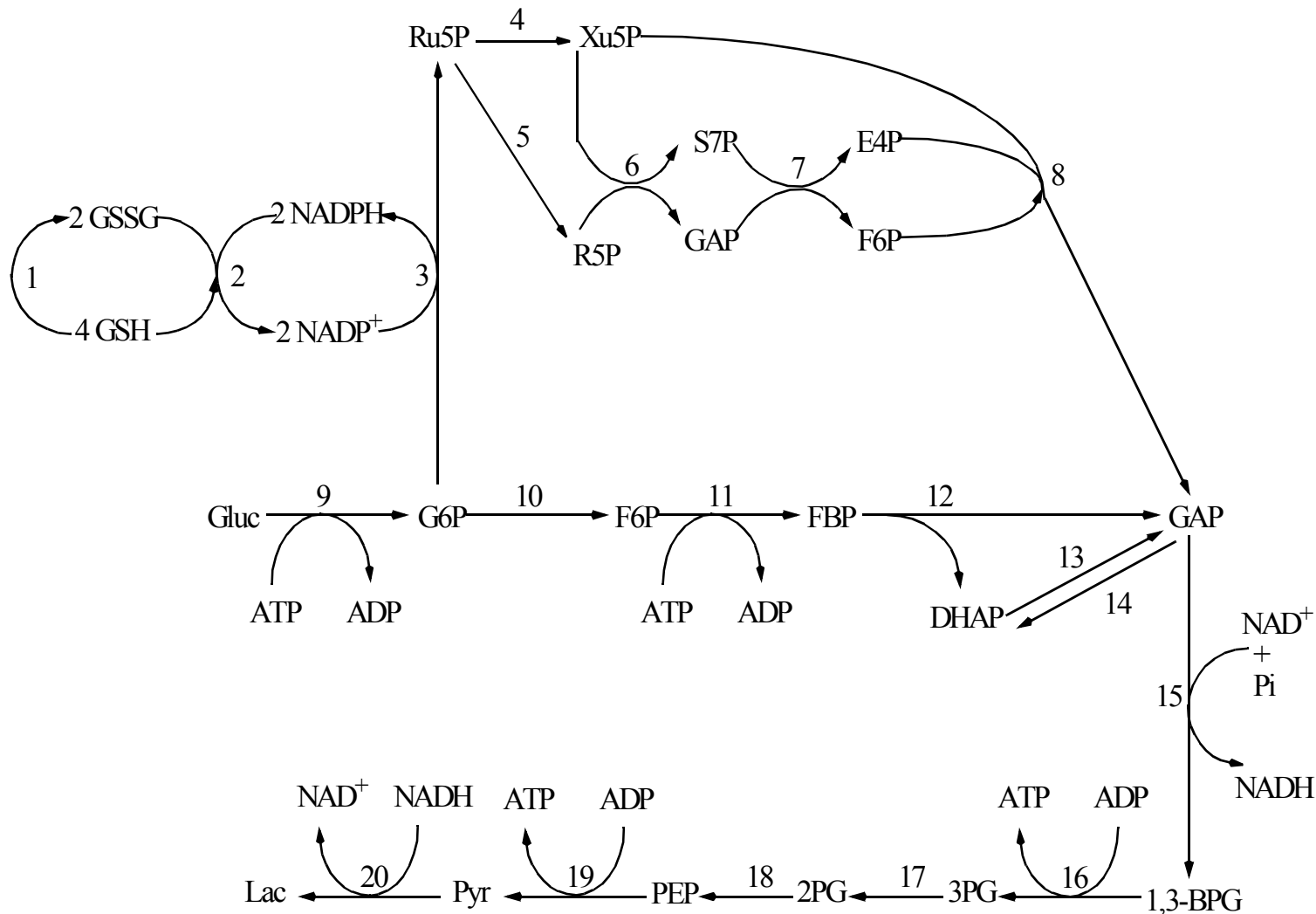


*SINGLE
PHOSPHOYLATION / DEPHOSPHORYLATION*

BIO PETRI NETS - SOME EXAMPLES

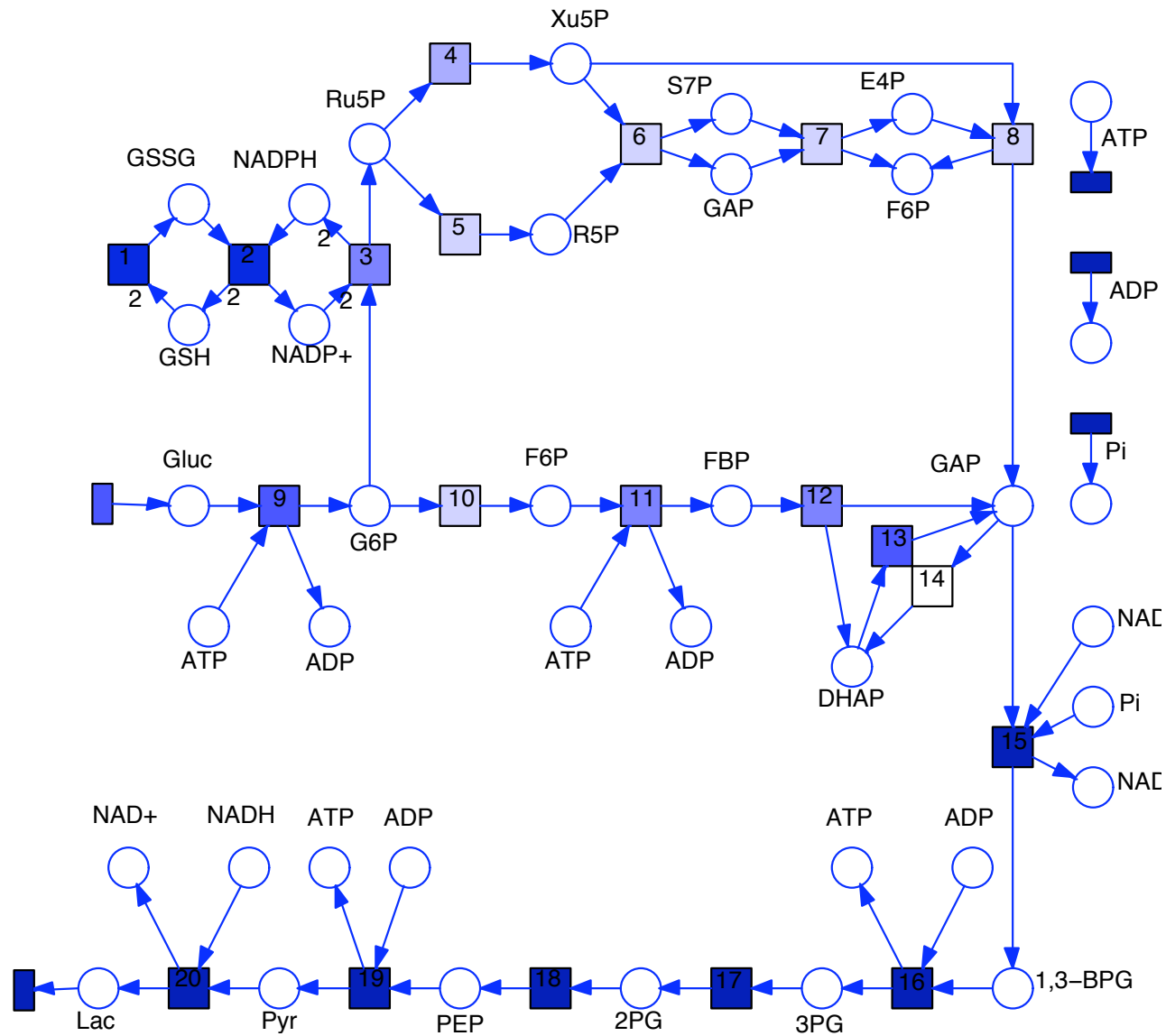
Ex1 - Glycolysis and Pentose Phosphate Pathway

[Reddy 1993]



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[Reddy 1993]



Ex2 - Carbon Metabolism in Potato Tuber

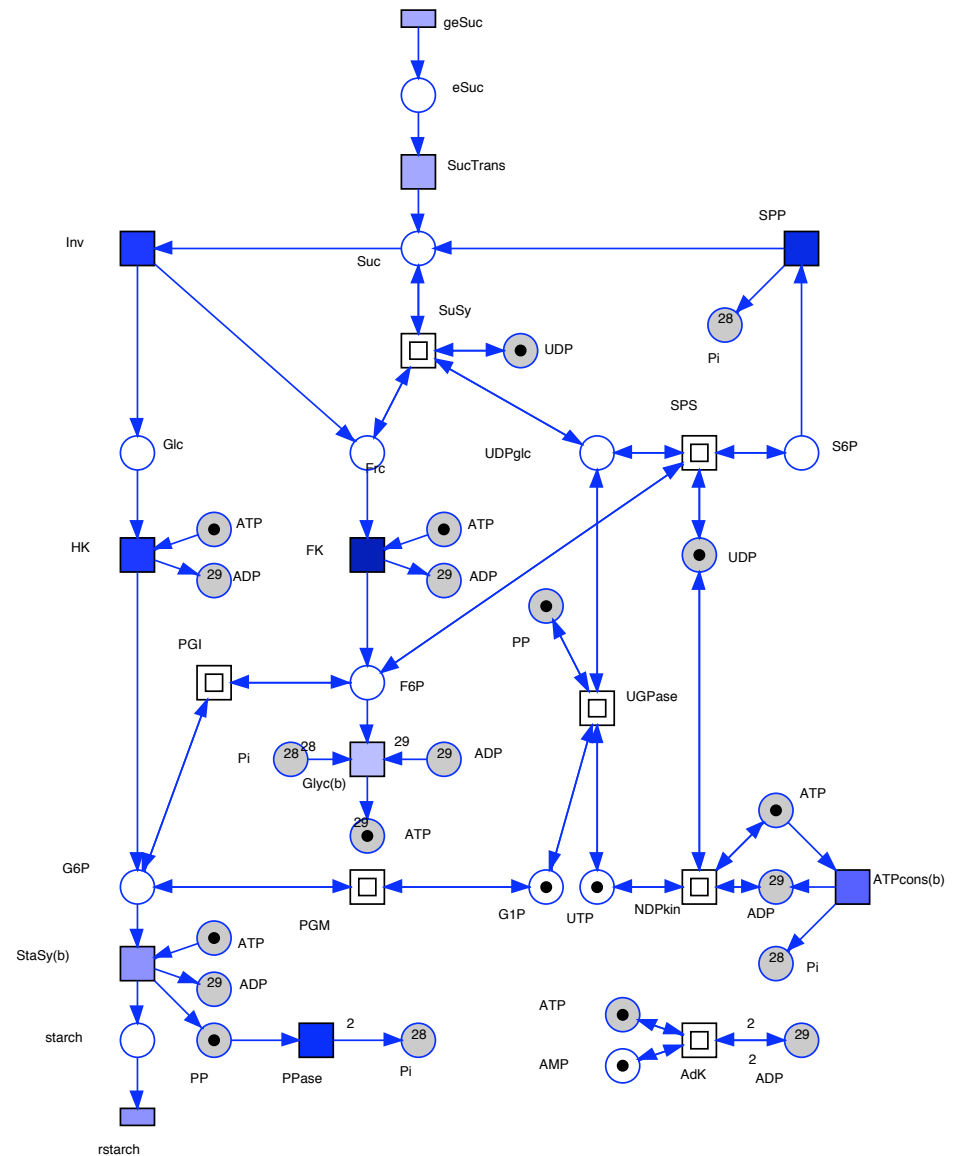


[KOCH; JUNKER; HEINER 2005]

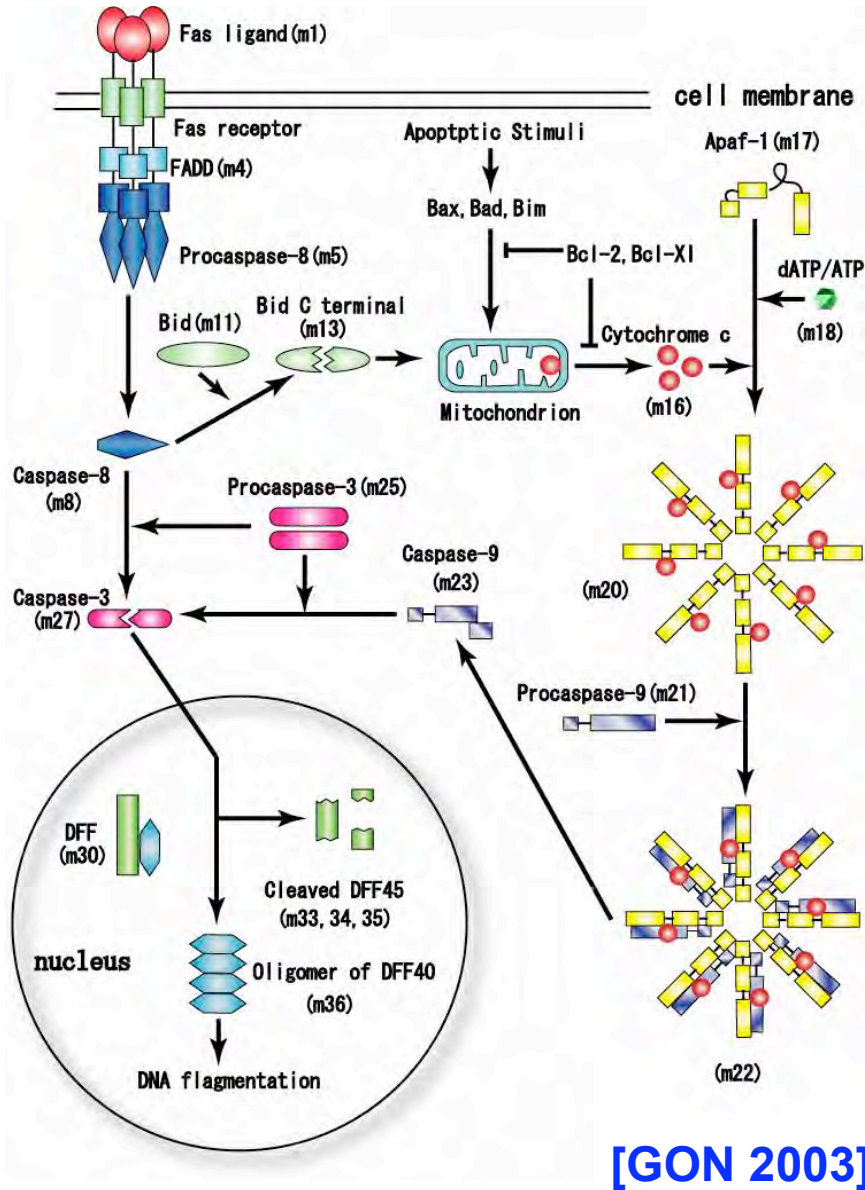
Ex2 - Carbon Metabolism in Potato Tuber



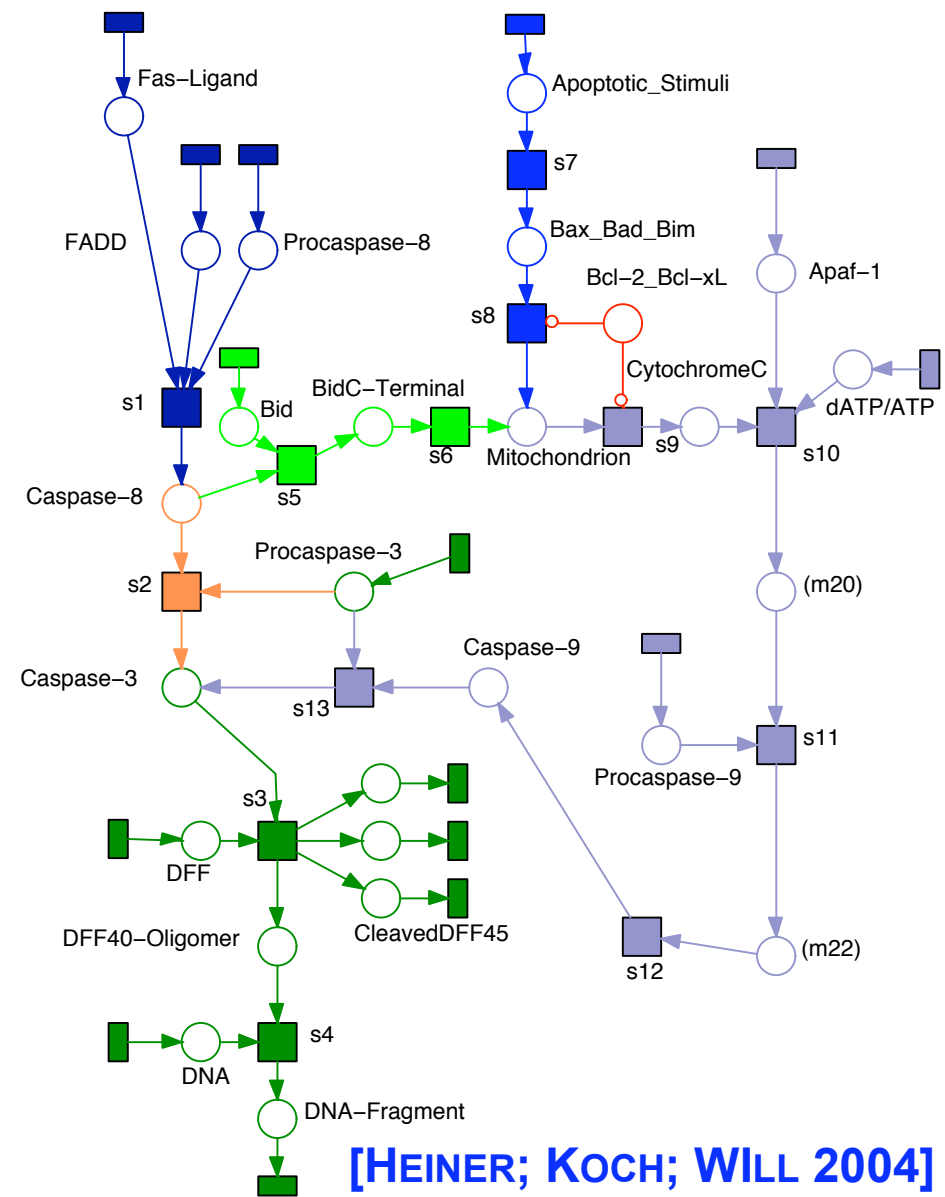
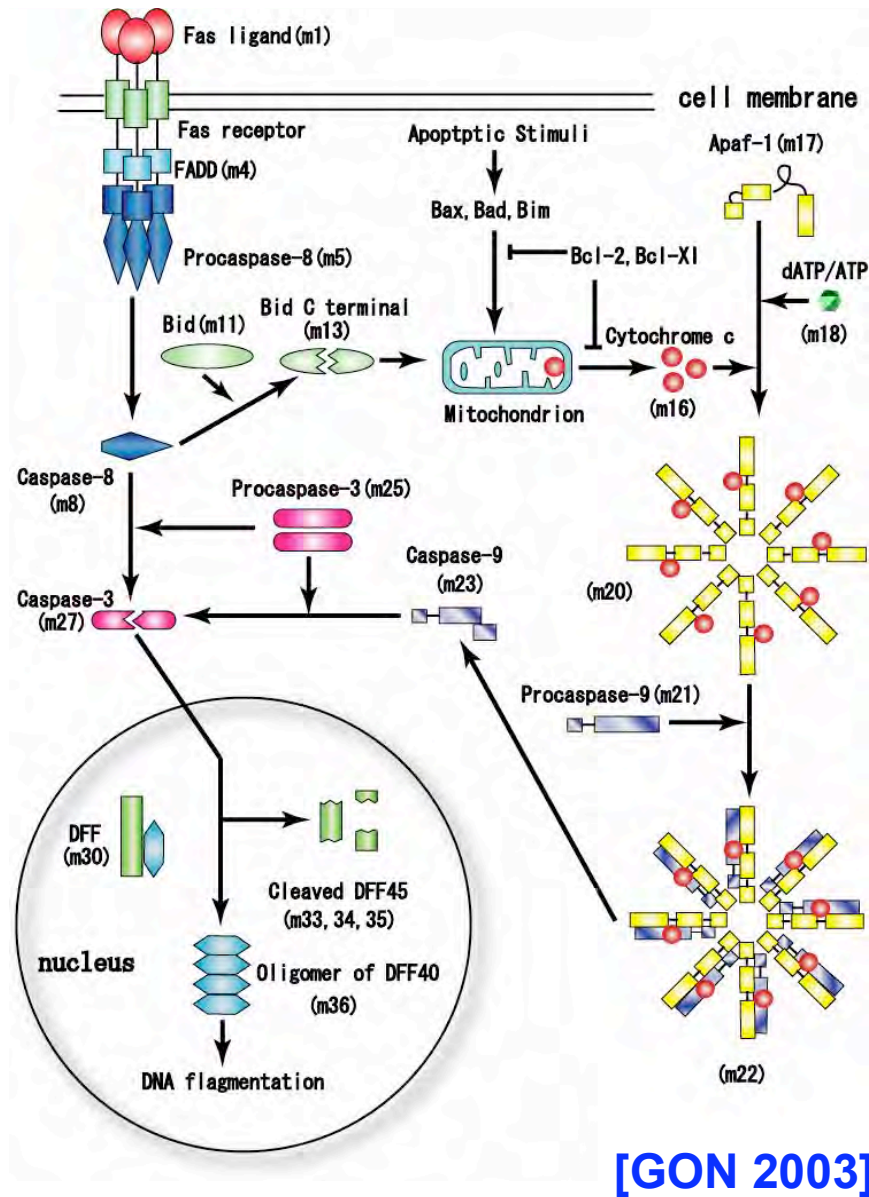
[KOCH; JUNKER; HEINER 2005]



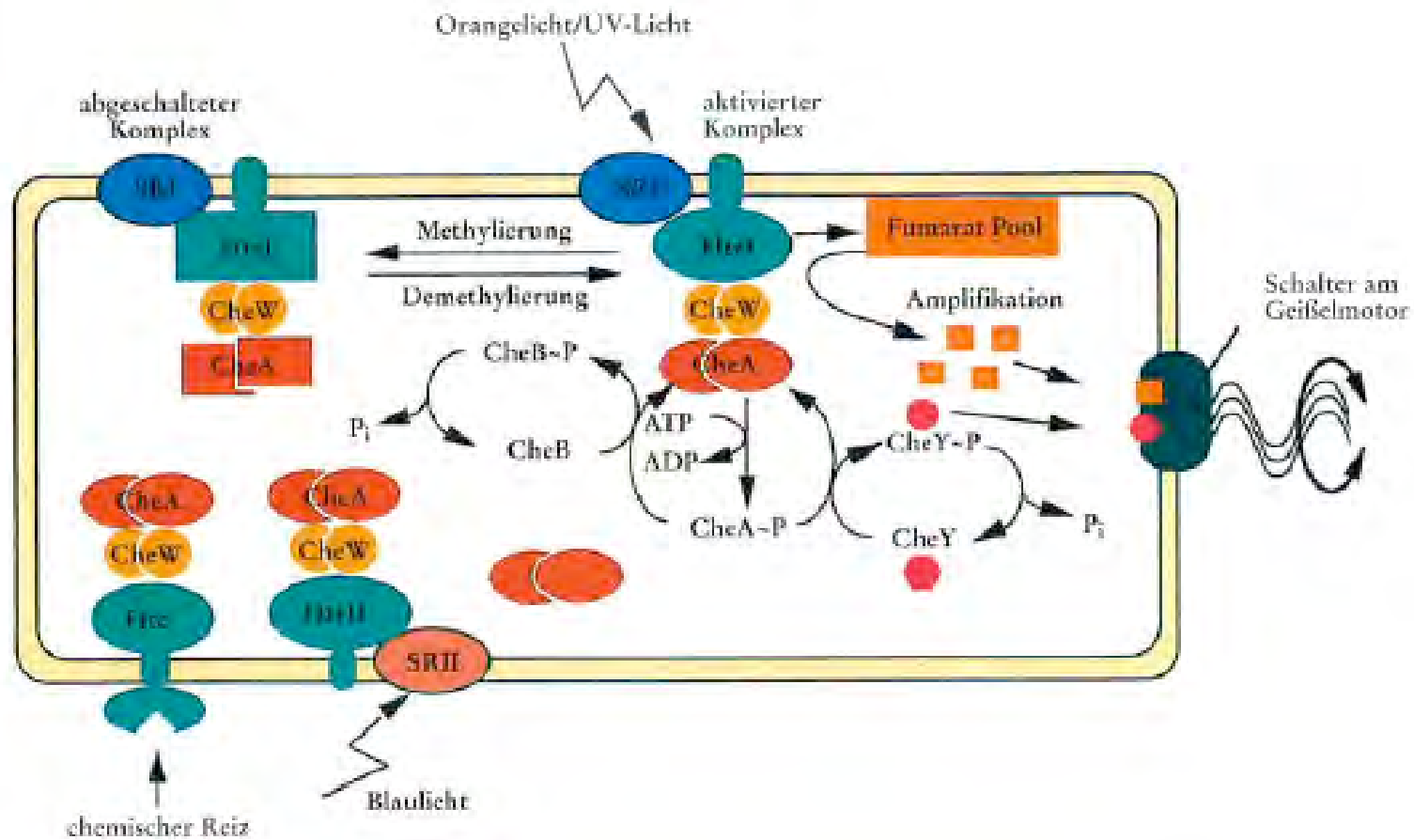
EX3: APOPTOSIS IN MAMMALIAN CELLS



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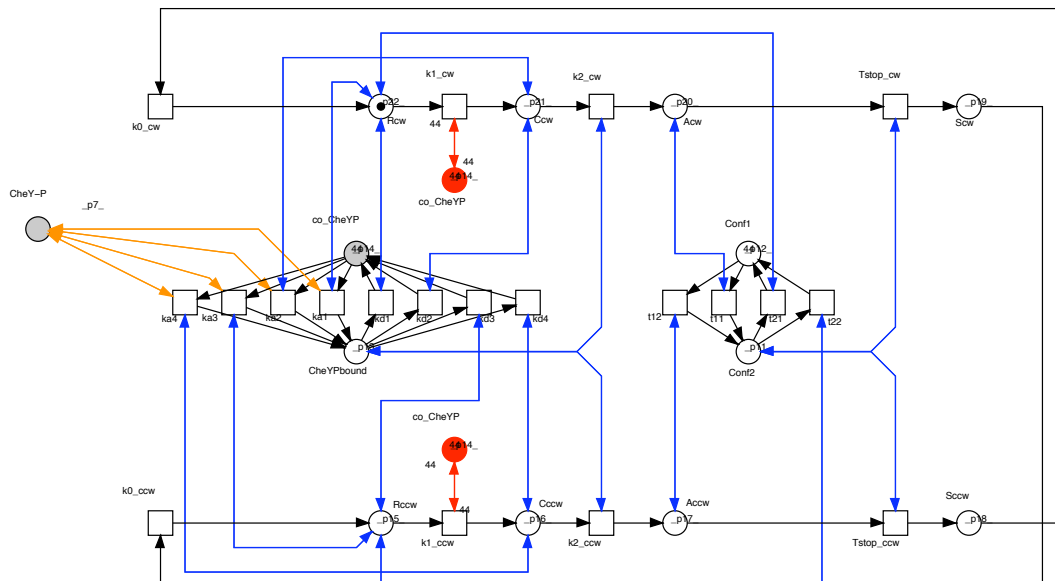
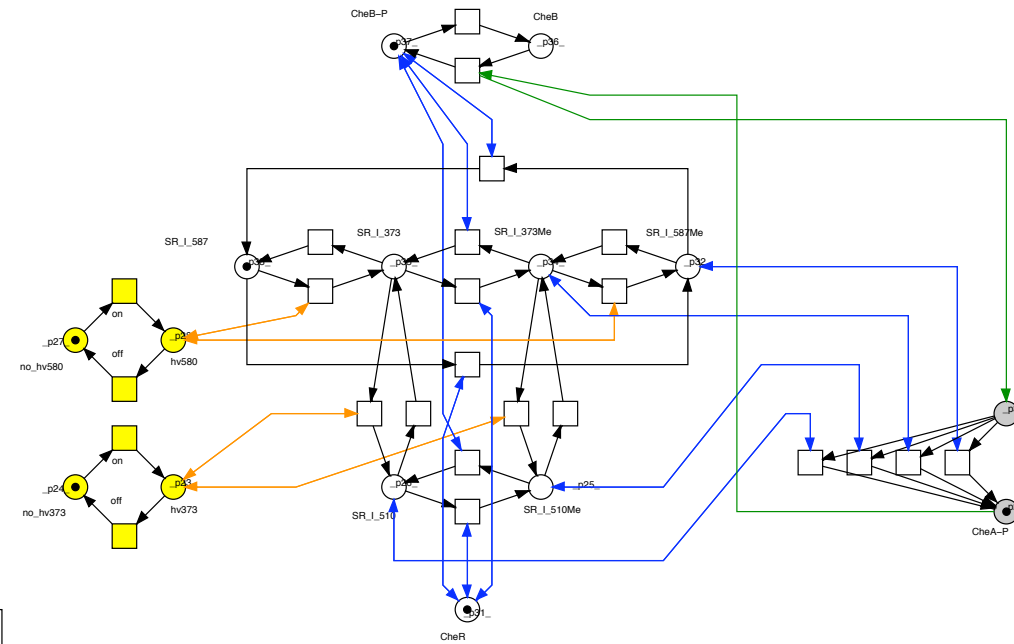
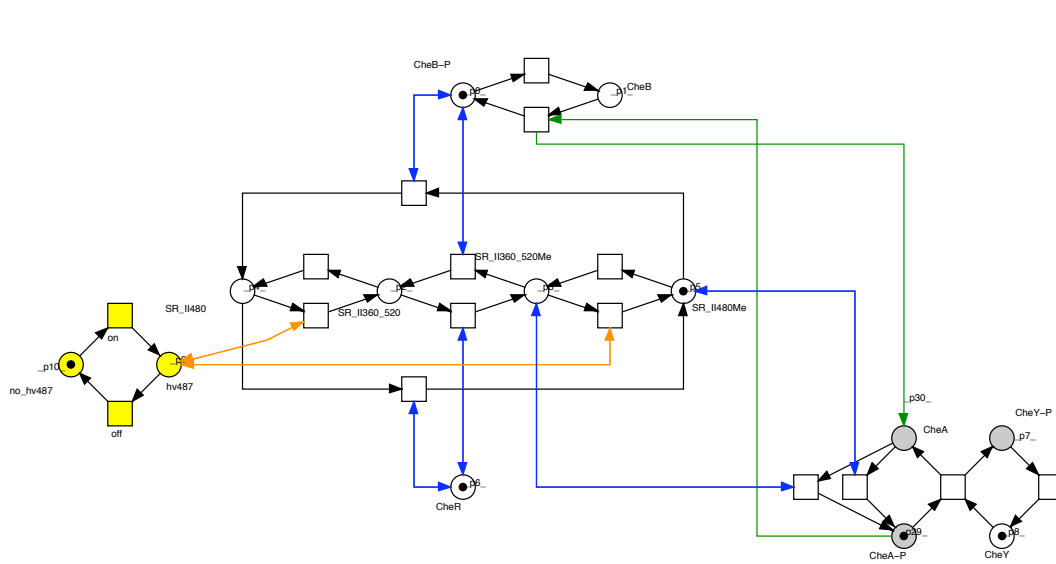


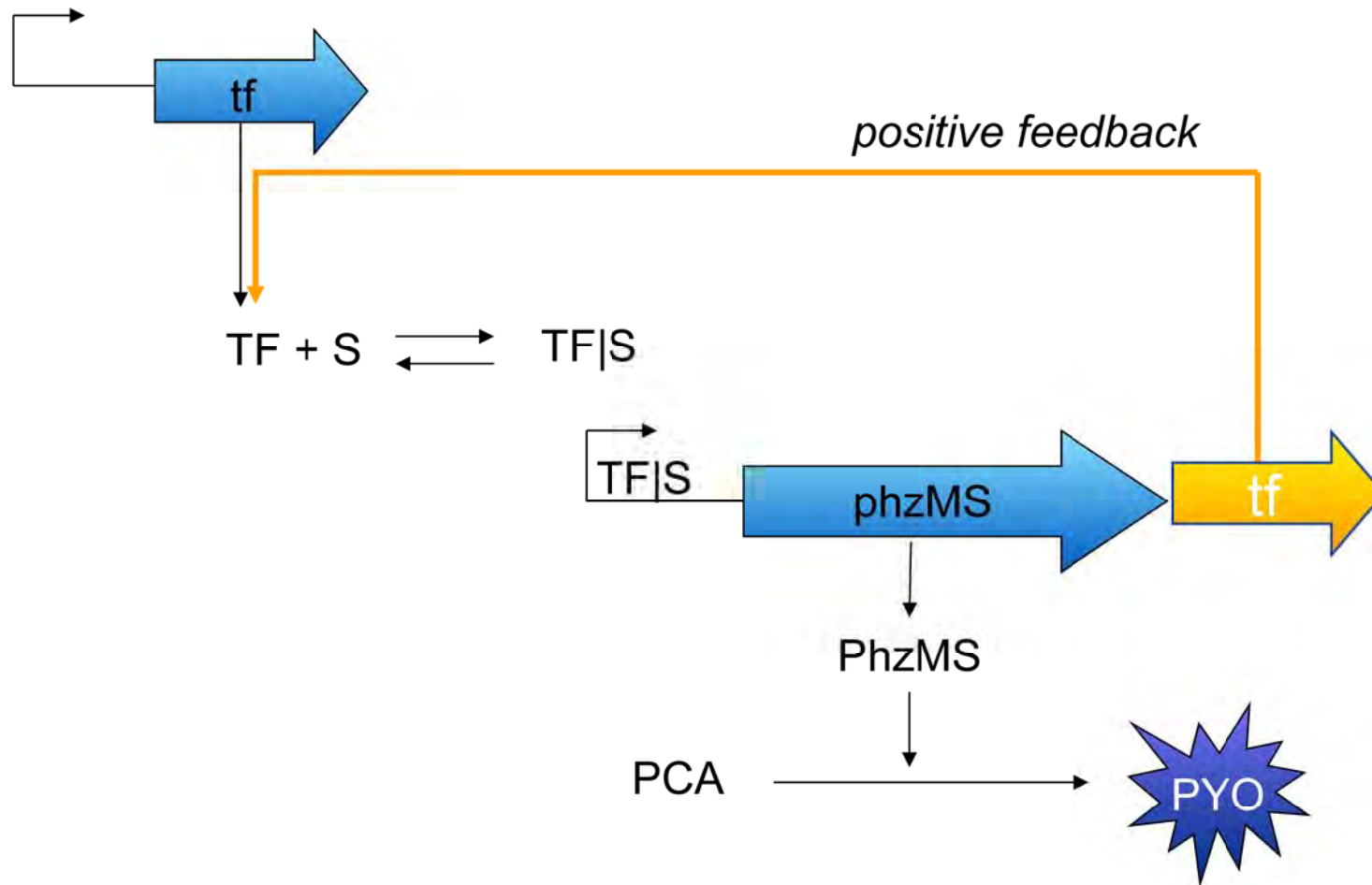
EX4 - SWITCH CYCLE HALOBACTERIUM SALINARUM

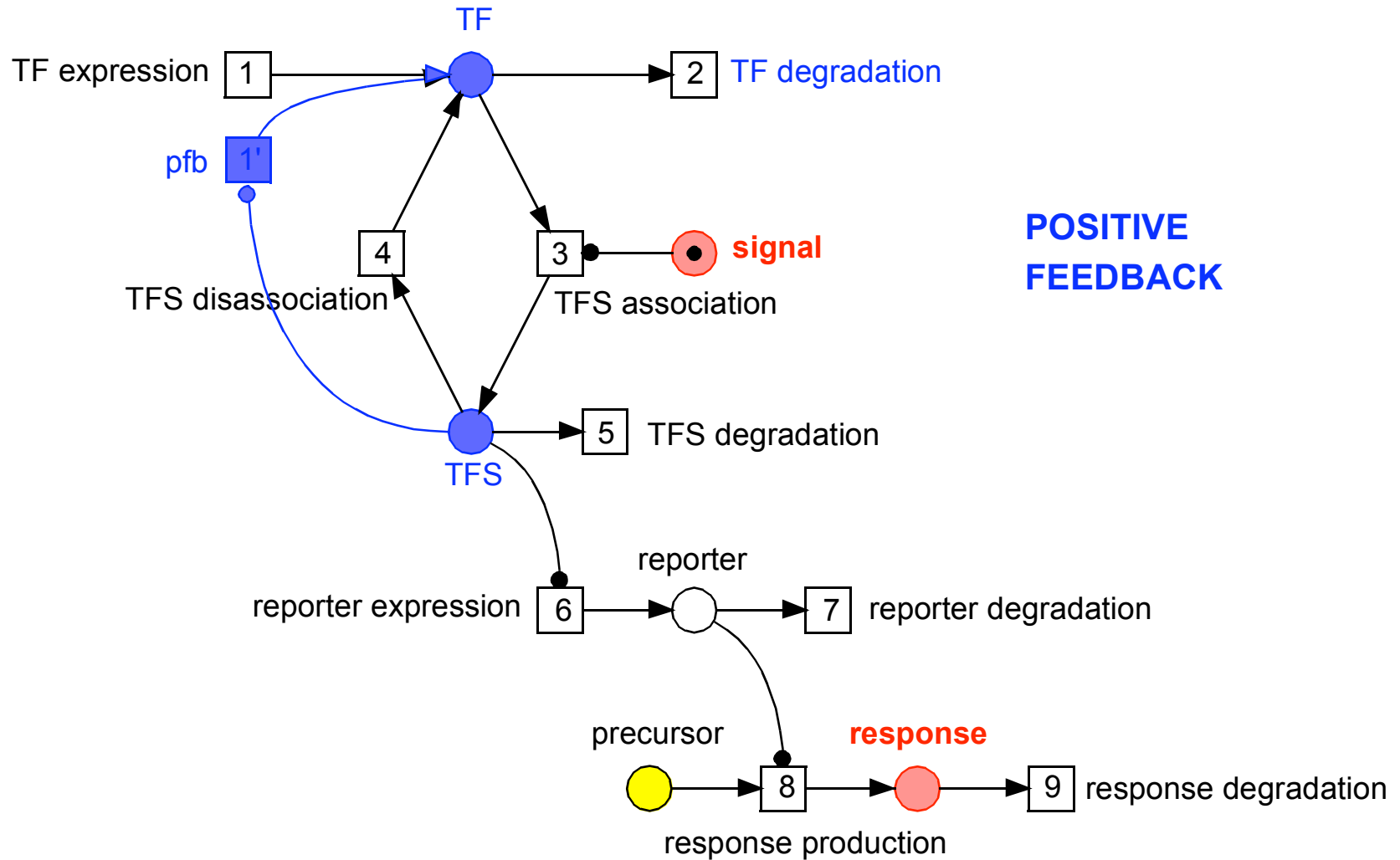


[Marwan; Oesterhelt 1999]

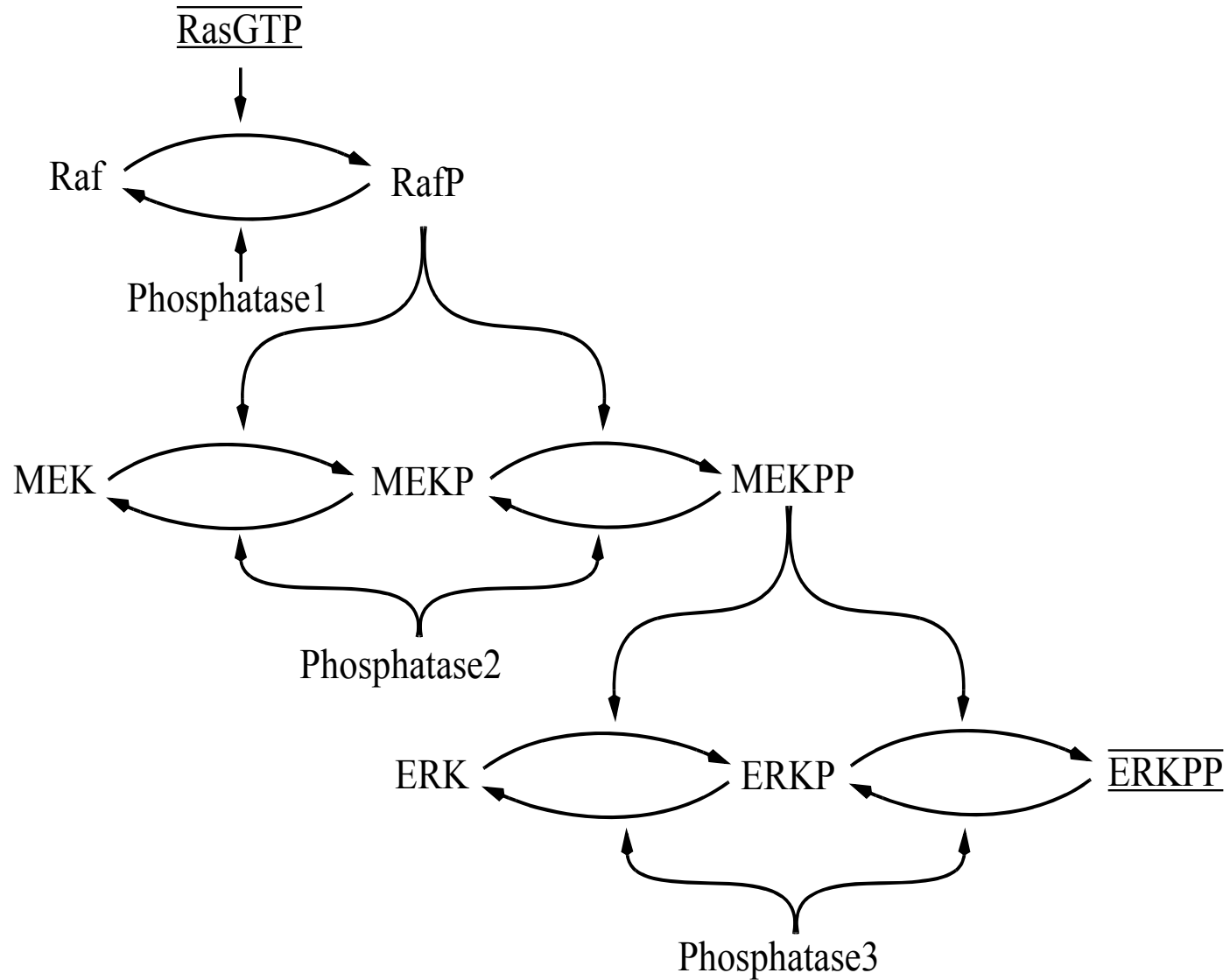
Ex4 - SWITCH CYCLE HALOBACTERIUM SALINARUM



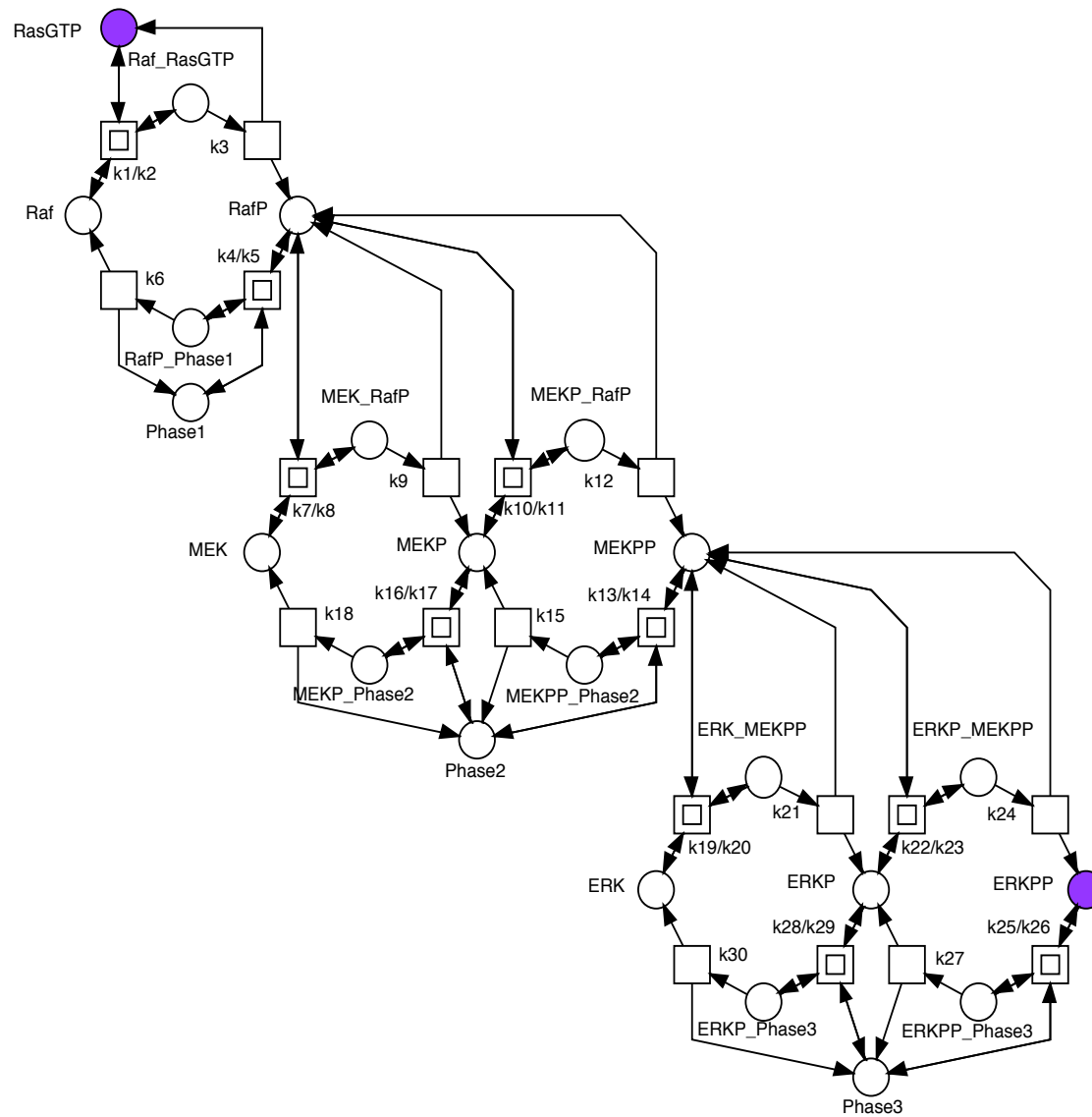




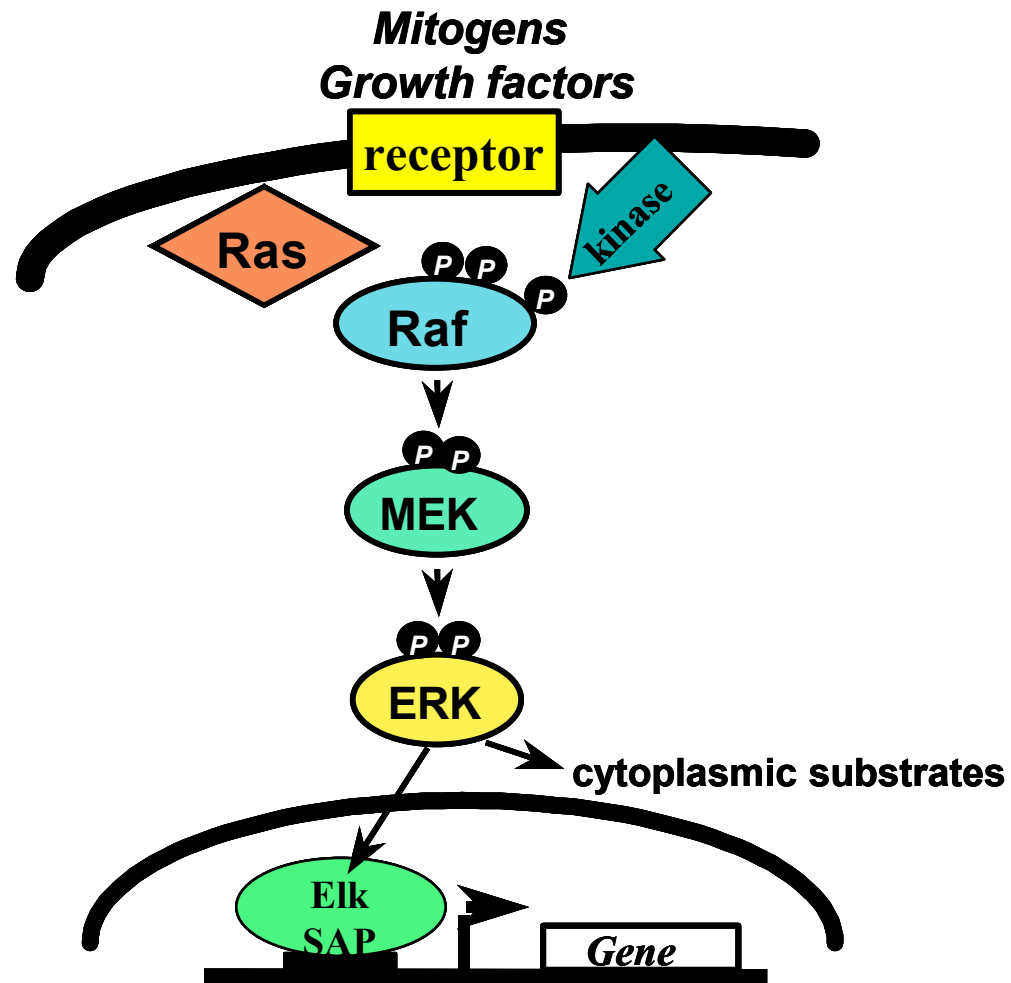
EX6 - SIGNALLING CASCADE



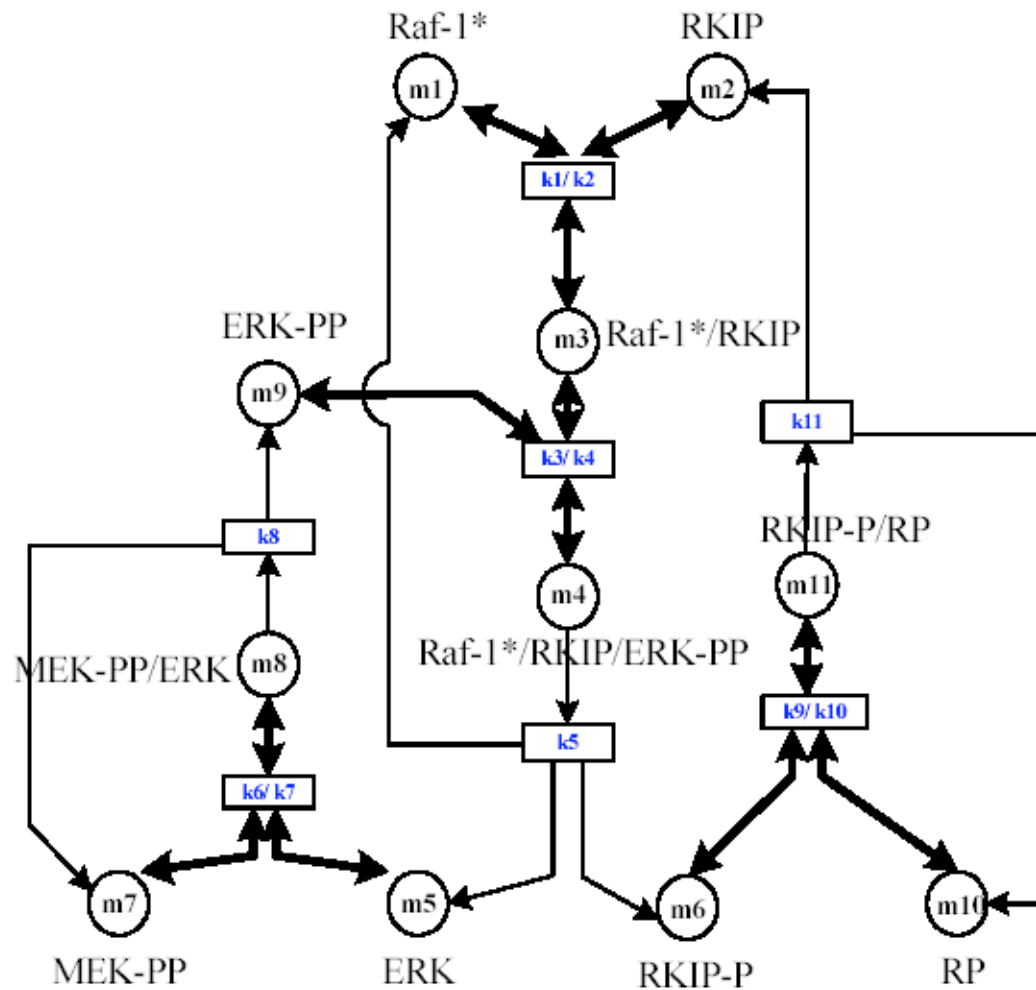
EX6 - SIGNALLING CASCADE



...one pathway...

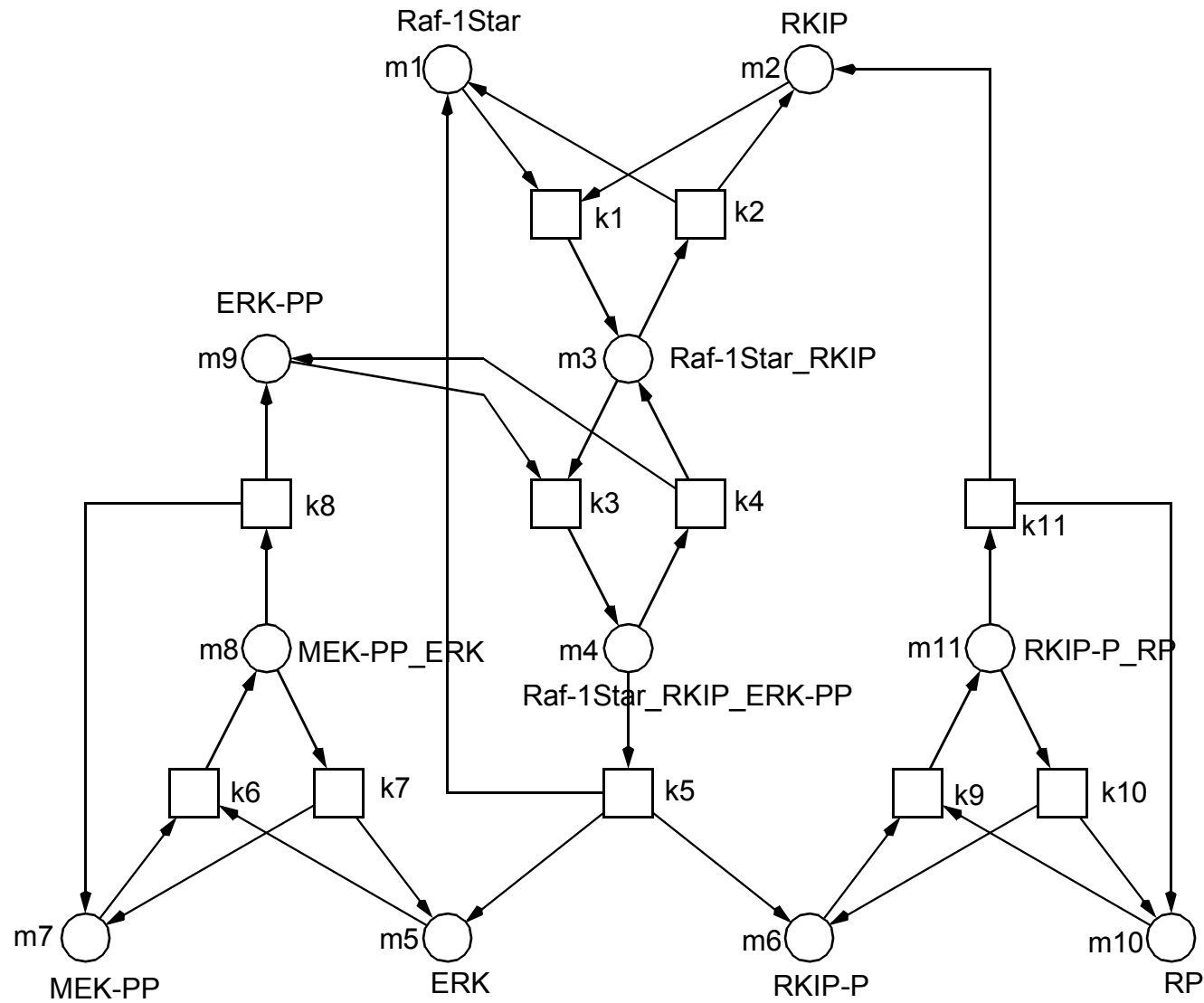


EX7 - RKIP PATHWAY

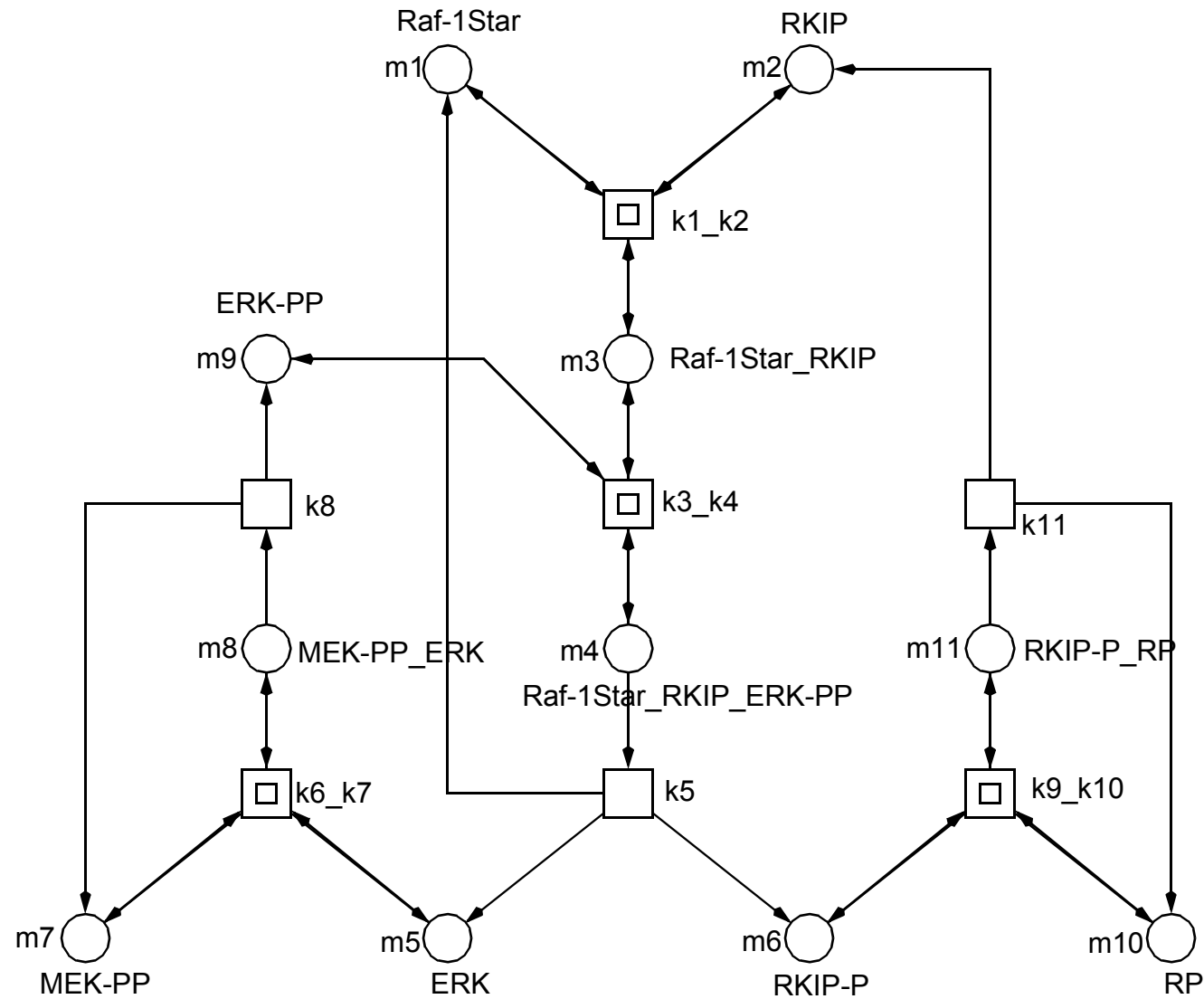


[Cho et al.,
CMSB 2003]

EX7 - RKIP PATHWAY, PETRI NET



EX7 - RKIP PATHWAY, HIERARCHICAL PETRI NET



□ representation of bionetworks by Petri nets

-> *partial order representation*

-> *formal semantics*

-> *unifying view*

-> *better comprehension*

-> *sound analysis techniques*

❑ representation of bionetworks by Petri nets

- > *partial order representation*
- > *formal semantics*
- > *unifying view*

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- > *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*

❑ representation of bionetworks by Petri nets

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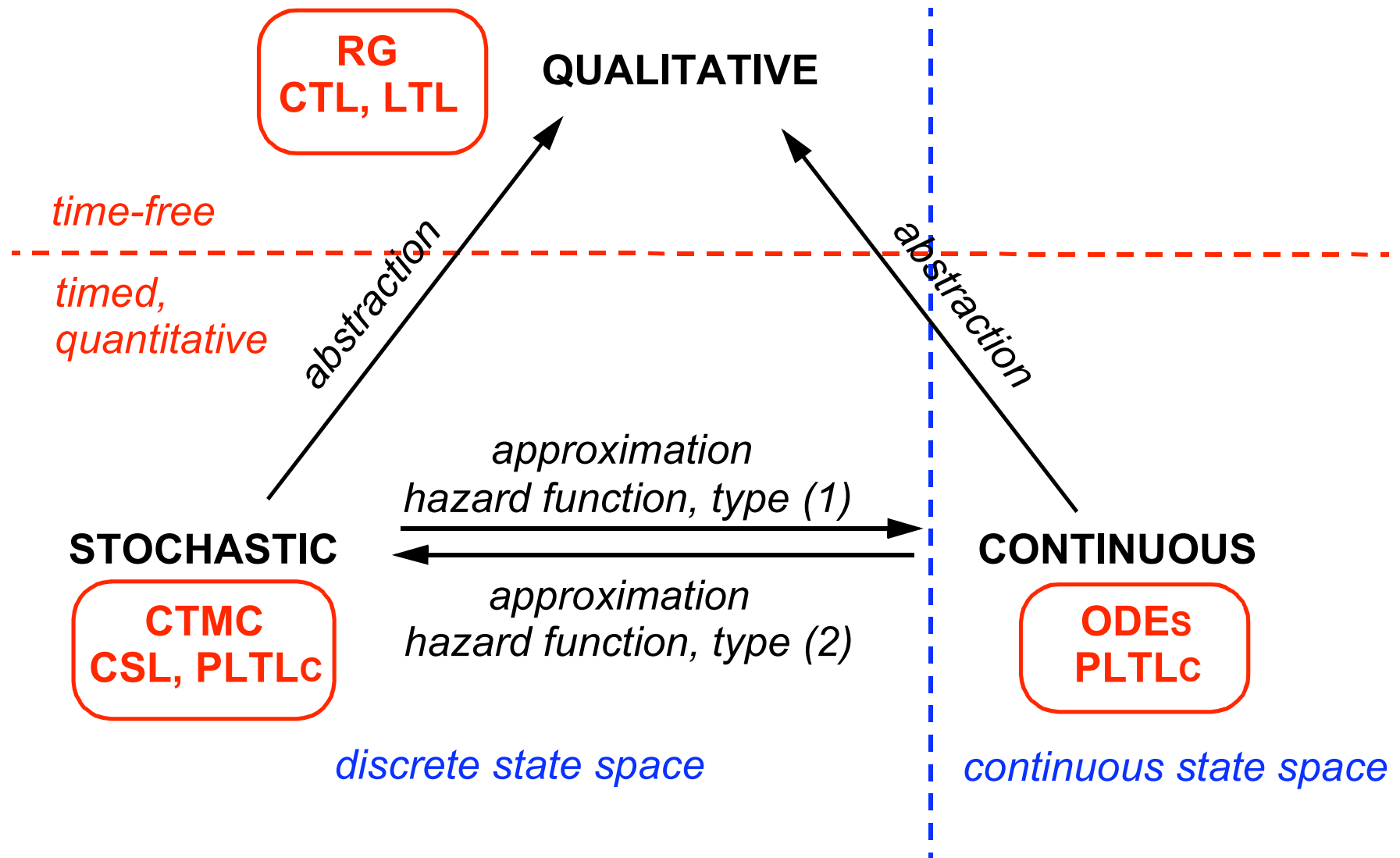
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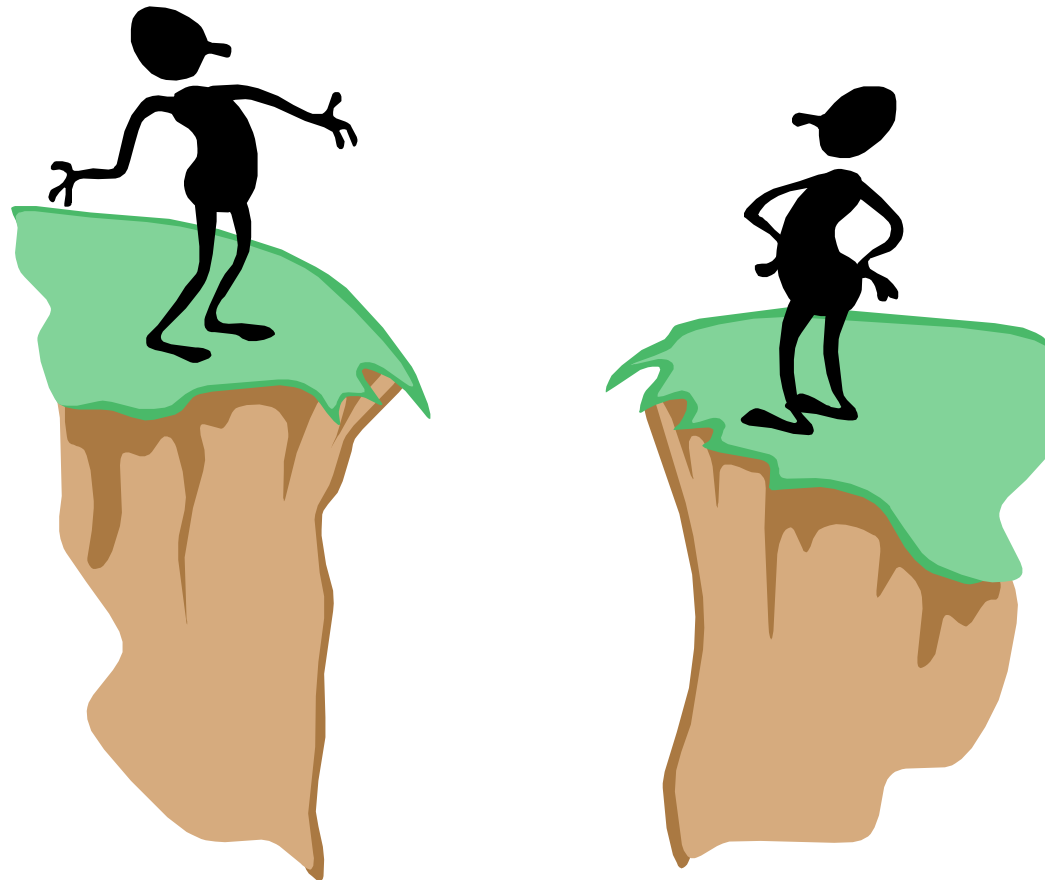
❑ step-wise model development

- > *qualitative model*
- > *discrete quantitative model*
- > *continuous quantitative model*

- > *discrete Petri nets*
- > *stochastic Petri nets*
- > *continuous Petri nets = ODEs*



- ❑ M Heiner; R Donaldson; D Gilbert:
Petri Nets for Systems Biology; MS Iyengar (ed.): Symbolic Systems Biology: Theory and Methods, Jones & Bartlett Publishers, LLC, in Press.
- ❑ M Heiner, S Lehrack, D Gilbert, W Marwan:
Extended Stochastic Petri Nets for Model-based Design of Wetlab Experiments;
Trans. on Computational Systems Biology XI, Springer LNBI 5750, pp. 138-163, 2009.
- ❑ R Breitling, D Gilbert, M Heiner, R Orton:
A structured approach for the engineering of biochemical network models, illustrated for signalling pathways; Briefings in Bioinformatics, September 2008; 9: 404 - 421.
- ❑ D Gilbert, M Heiner, S Rosser, R Fulton, X Gu, M Trybilo:
A Case Study in Model-driven Synthetic Biology; IFIP WCC 2008, BICC 2008, Milano, Sept. 2008, Springer Boston, IFIP, Vol . 268, pp. 163-175, 2008.
- ❑ M Heiner, D Gilbert, R Donaldson:
Petri Nets for Systems and Synthetic Biology; M Bernardo, P Degano, and G Zavattaro (eds.): SFM 2008, Springer LNCS 5016, pp. 215–264, 2008.



THANKS !

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