BIOCHEMICAL NETWORKS
- A PETRI NET PERSPECTIVE -

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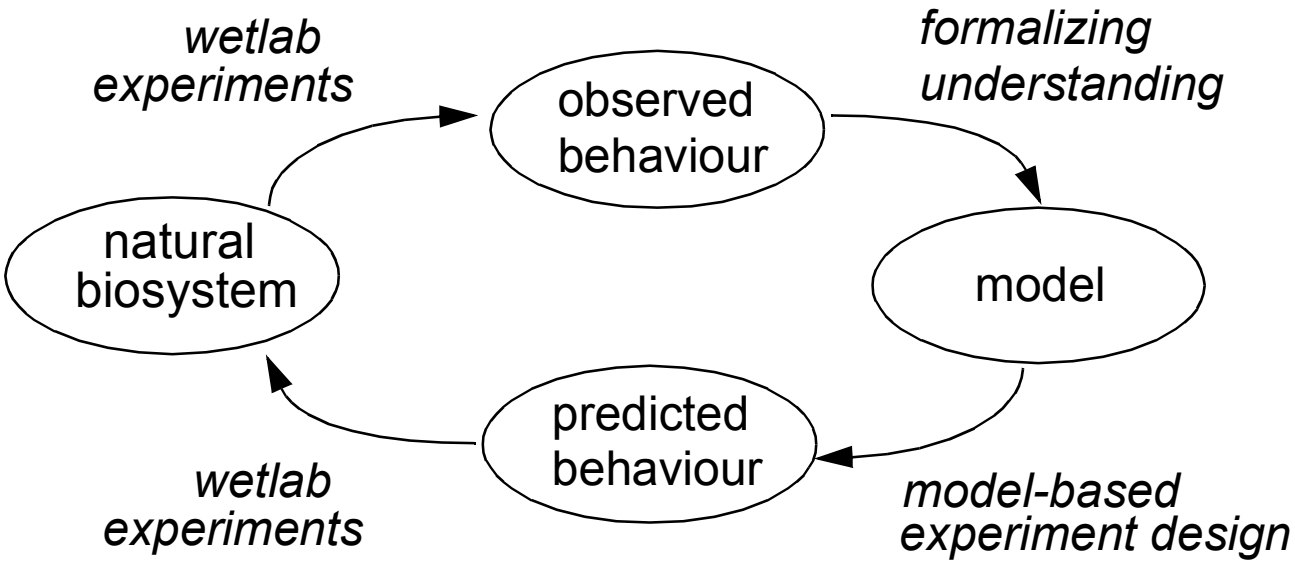
FRAMEWORK: SYSTEMS BIOLOGY

MODELLING = FORMAL KNOWLEDGE REPRESENTATION



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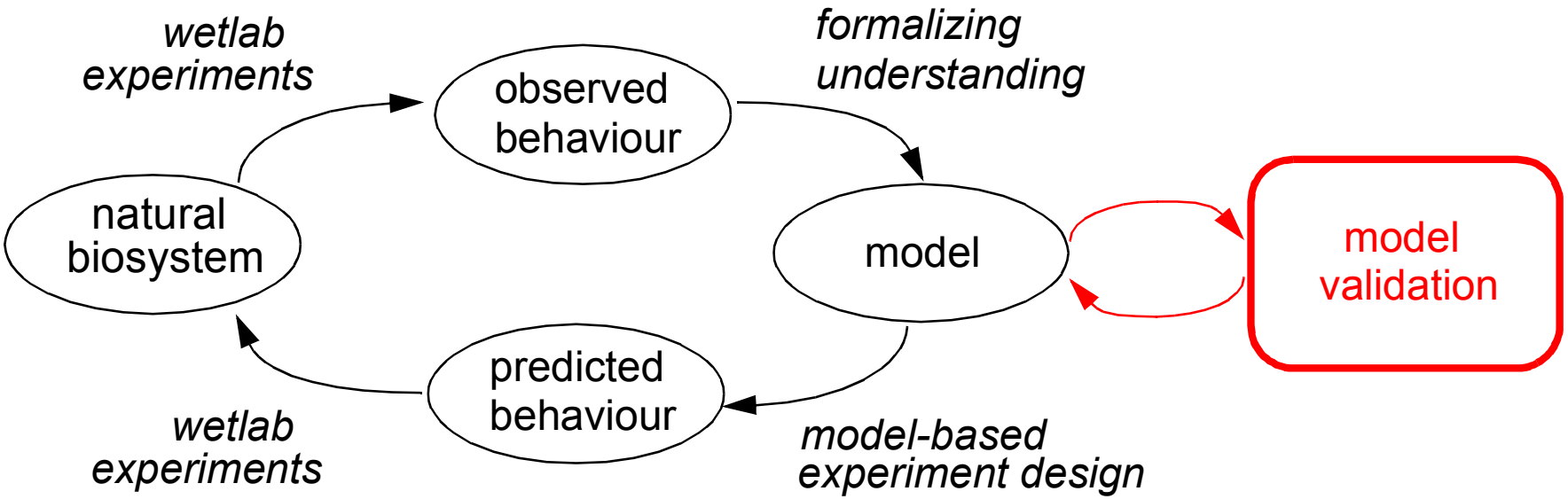
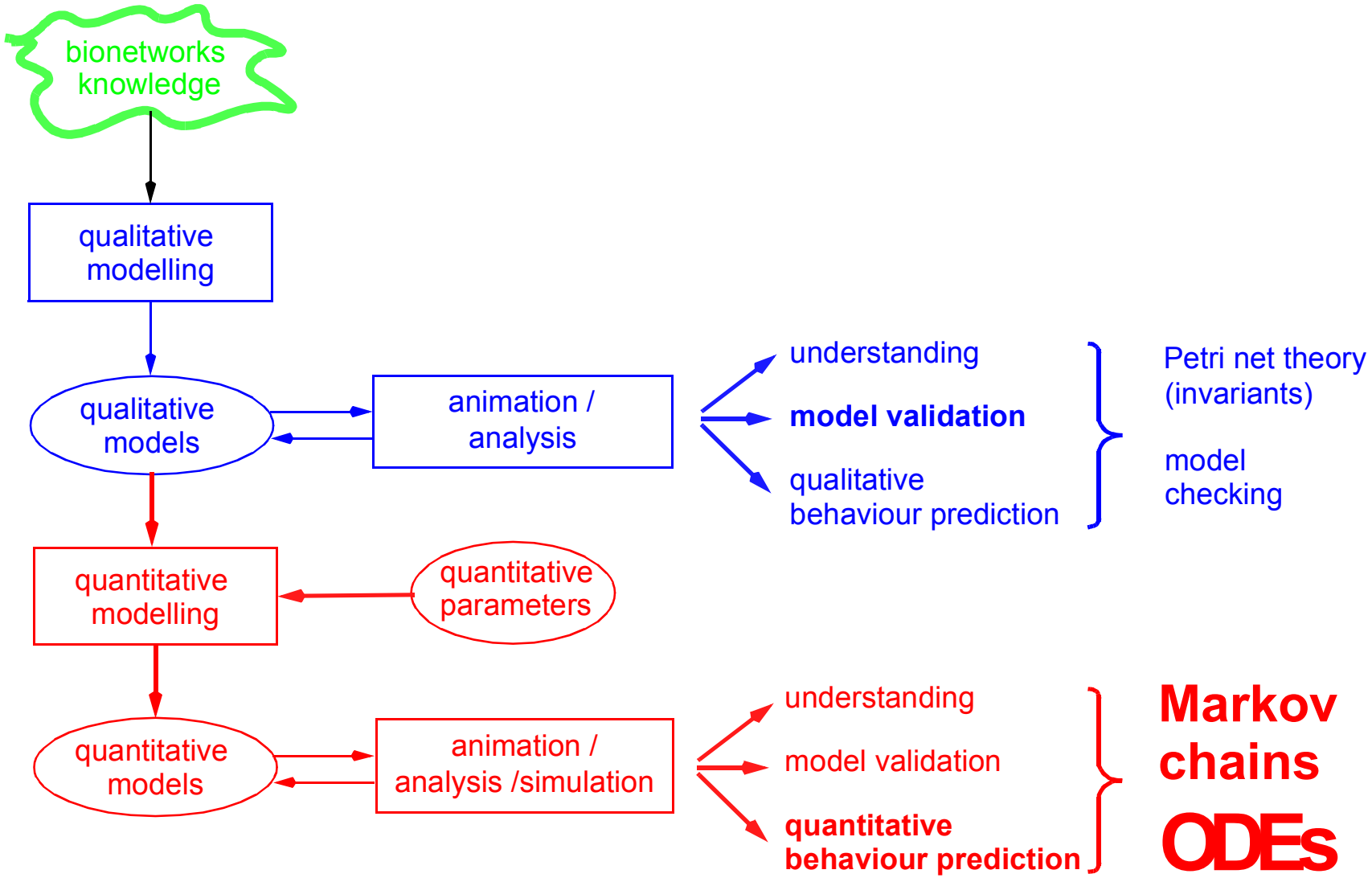
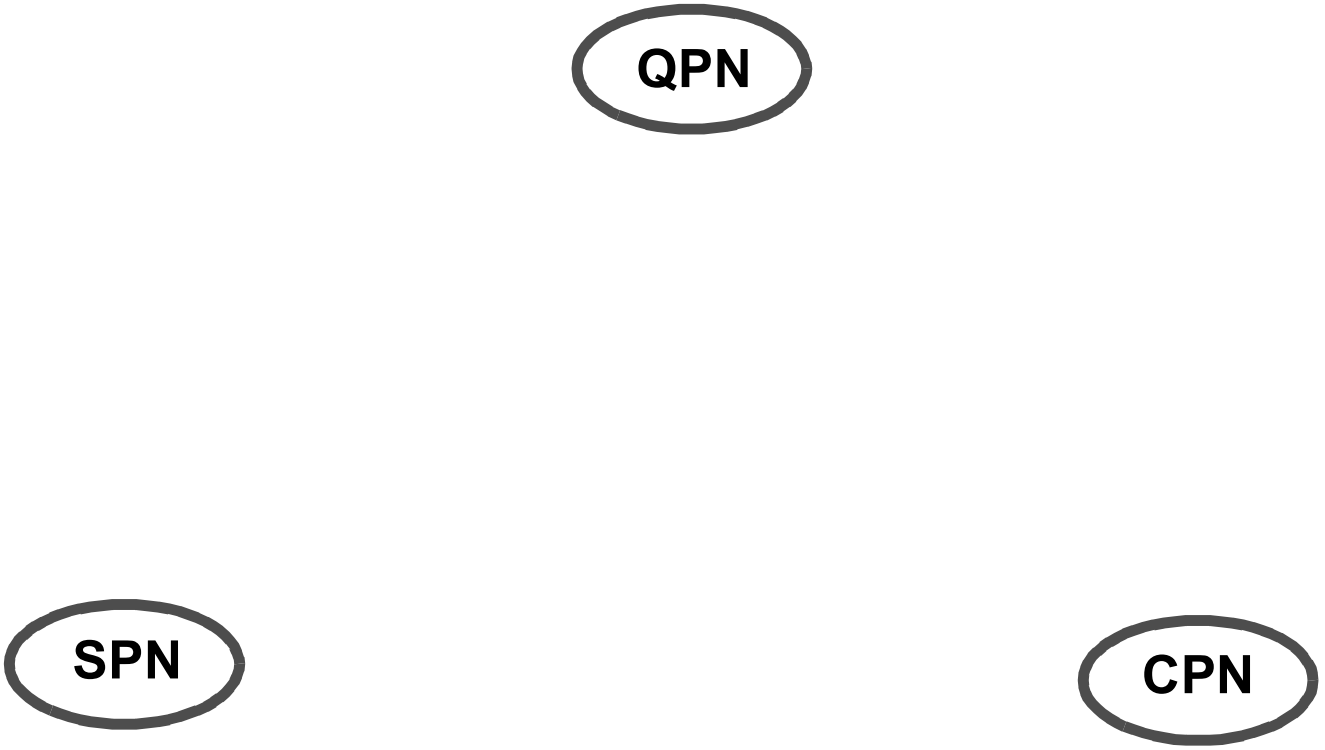


MODEL VALIDATION = CONFIDENCE INCREASE

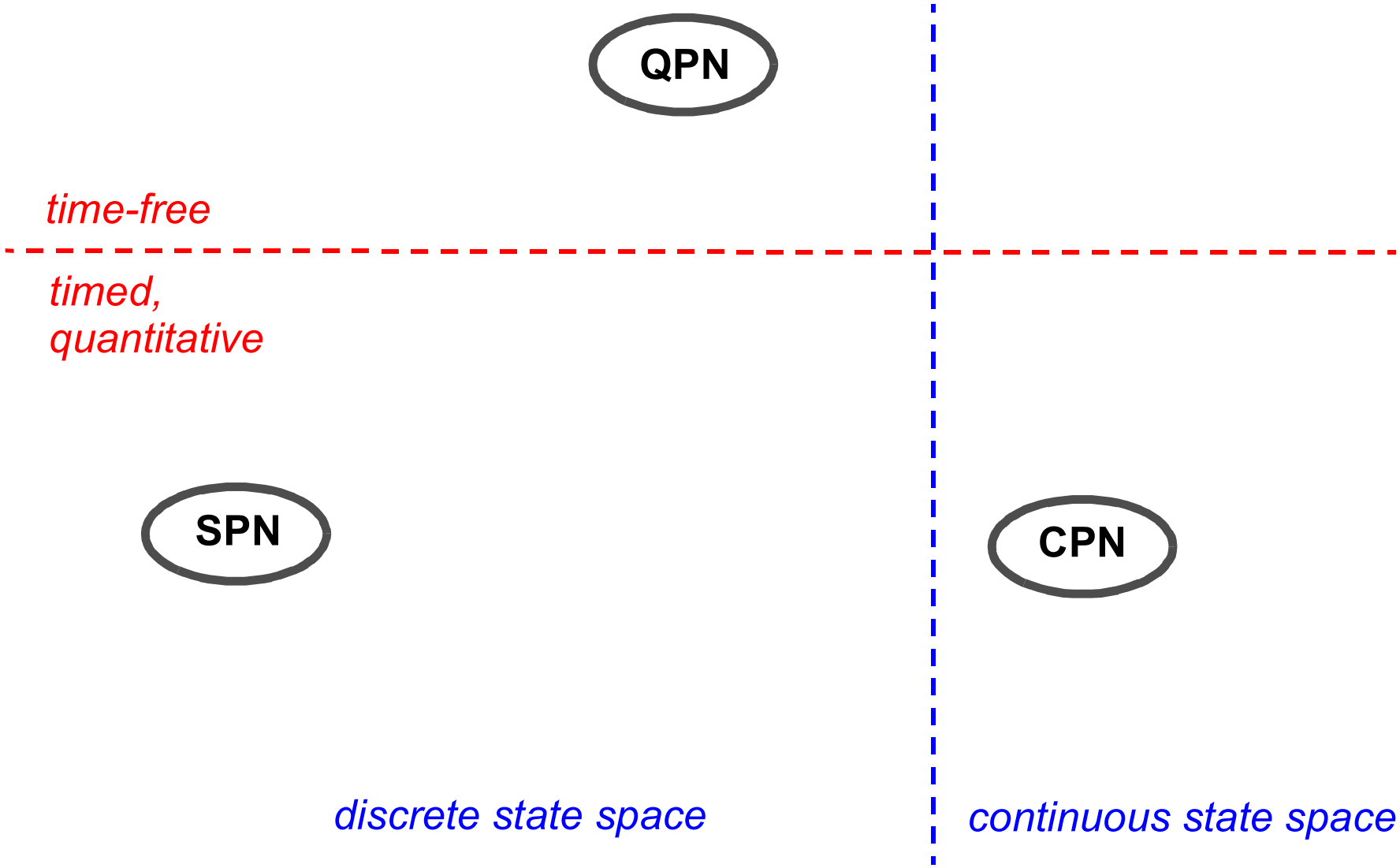
FRAMEWORK


bionetworks knowledge
qualitative modelling
qualitative models
animation / analysis
understanding
model validation
qualitative behaviour prediction
Petri net theory (invariants)
model checking
quantitative modelling
quantitative parameters
quantitative models
animation / analysis /simulation
understanding
model validation
quantitative behaviour prediction
Markov chains
ODEs

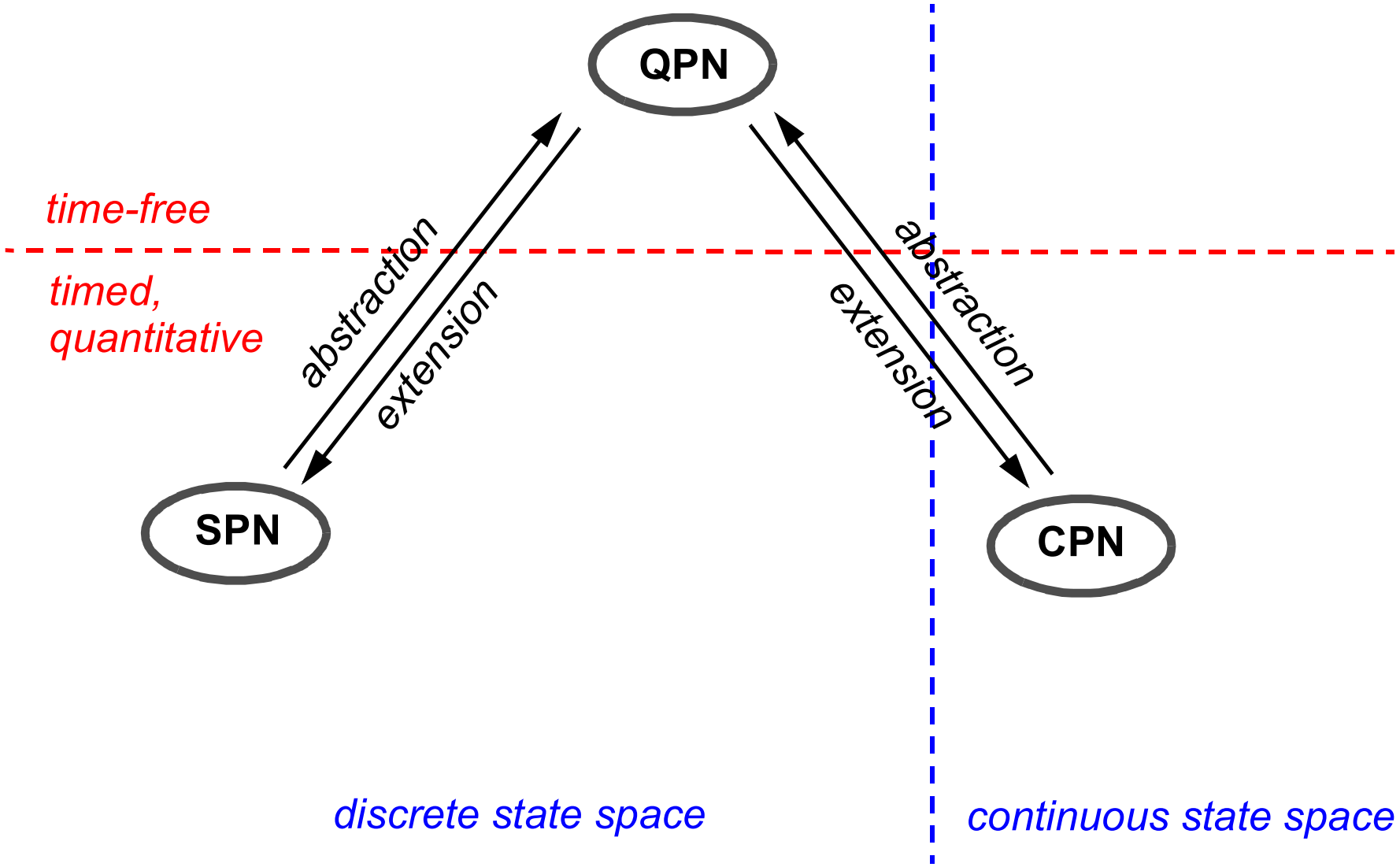
FRAMEWORK



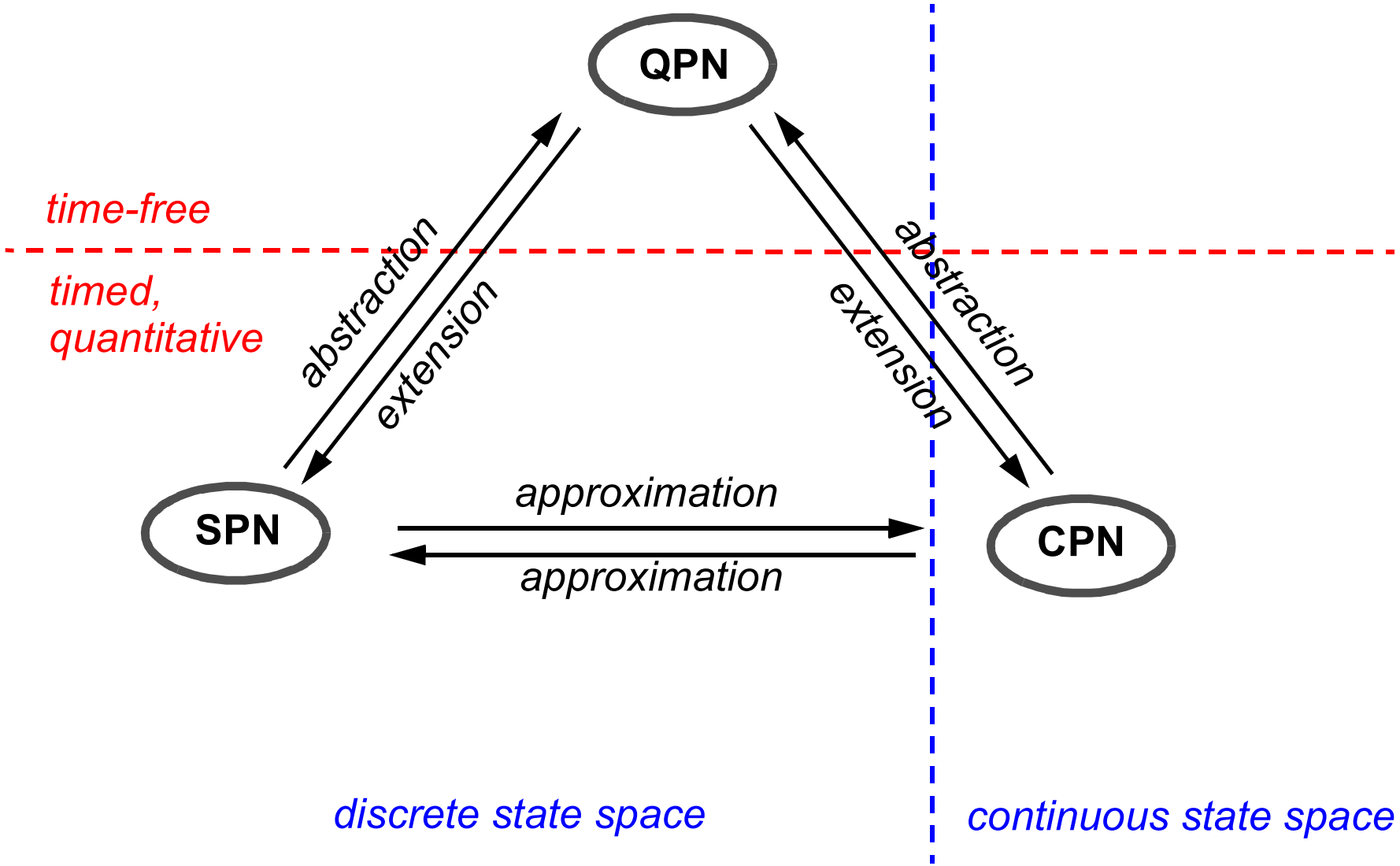
FRAMEWORK


QPN
time-free
timed,
quantitative
SPN
CPN
discrete state space
continuous state space

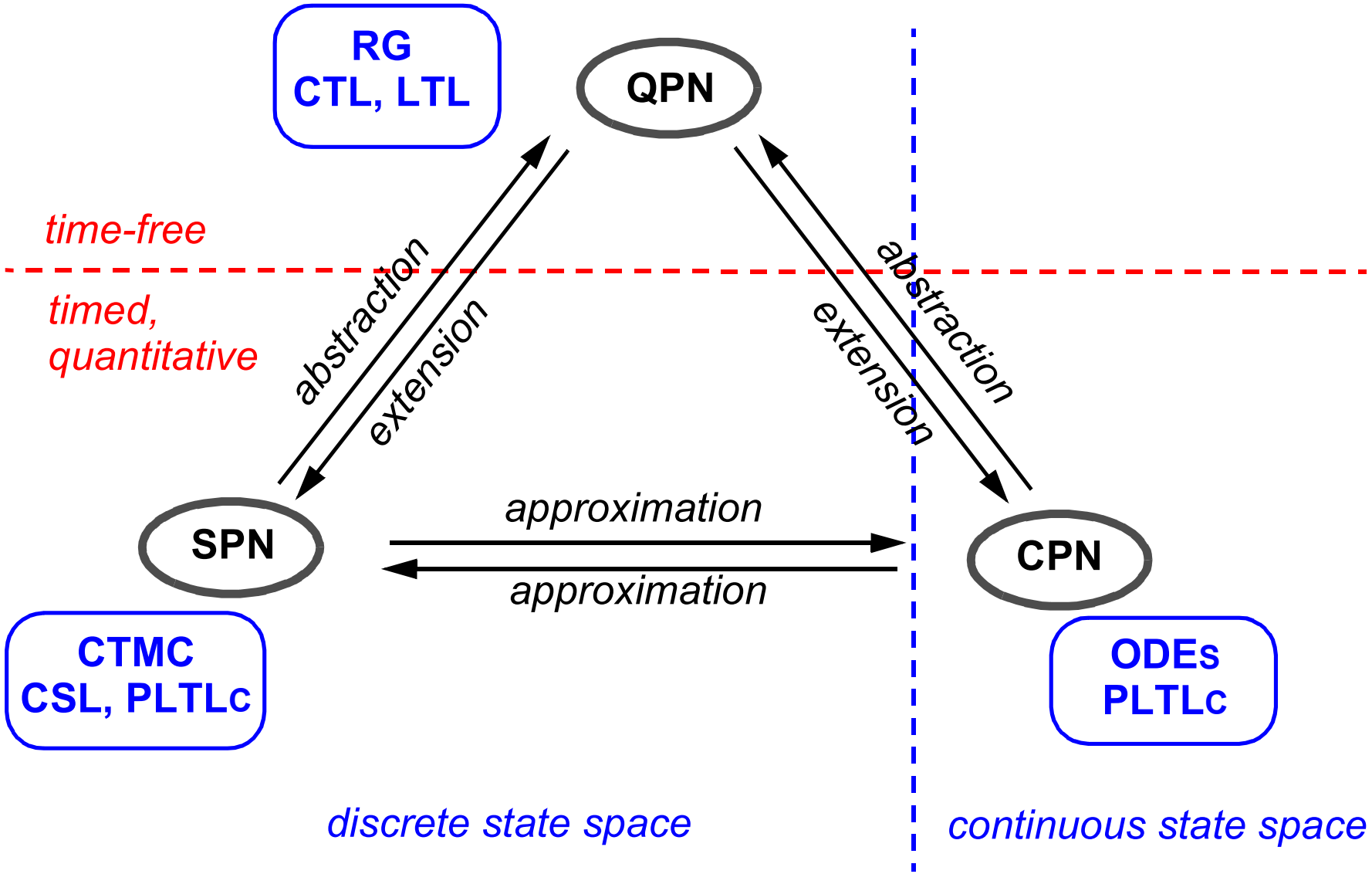
FRAMEWORK


QPN
time-free
timed,
quantitative
abstraction
extension
abstraction
extension
SPN
CPN
discrete state space
continuous state space

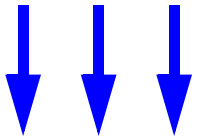
FRAMEWORK


QPN
time-free
timed,
quantitative
abstraction
extension
abstraction
extension
SPN
approximation
approximation
CPN
discrete state space
continuous state space

FRAMEWORK


RG
CTL, LTL
QPN
time-free
timed,
quantitative
abstraction
extension
abstraction
extension
approximation
approximation
SPN
CPN
CTMC
CSL, PLTLc
ODEs
PLTLc
discrete state space
continuous state space

THREE MODELS SHARING STRUCTURE



QUANTITATIVE MODEL = QUALITATIVE MODEL

+

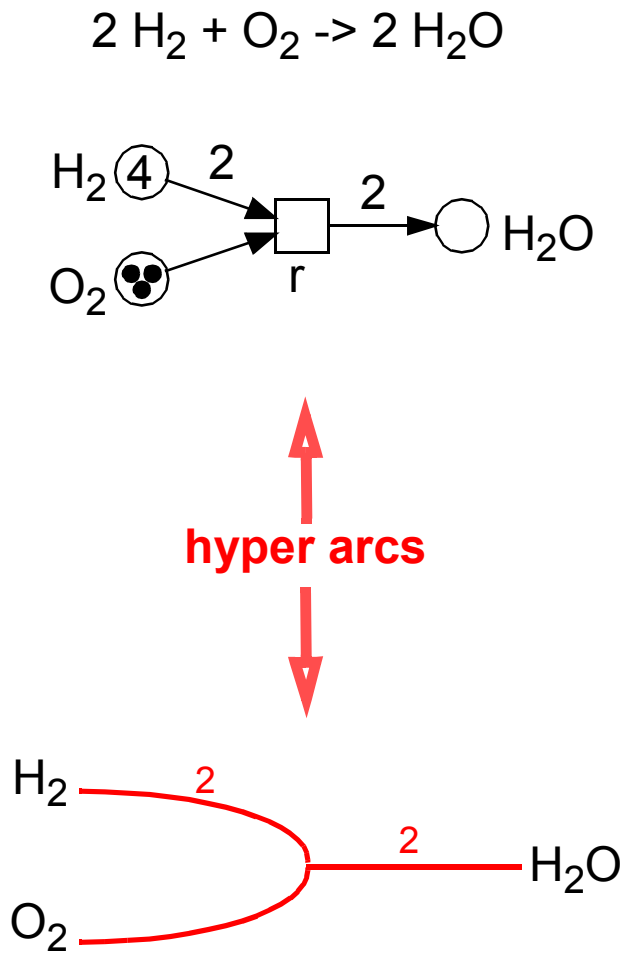
QUANTITATIVE PARAMETERS (KINETICS)

QUALITATIVE PETRI NETS - QPN -

monika.heiner@informatik.tu-cottbus.de

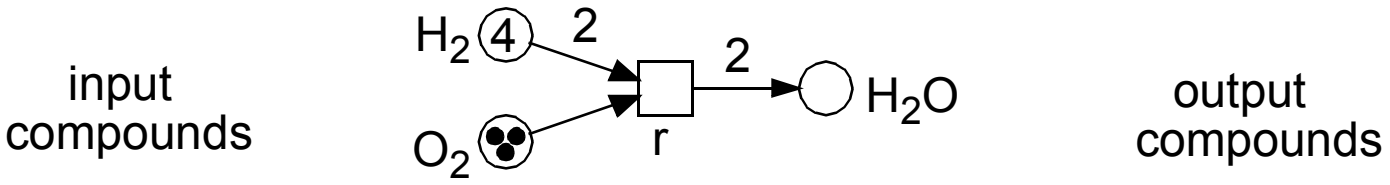
... ARE NETWORKS OF BIOCHEMICAL REACTIONS

... NATURALLY EXPRESSIBLE AS PETRI NETS



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

$$2\ H_2 + O_2 \rightarrow 2\ H_2O$$



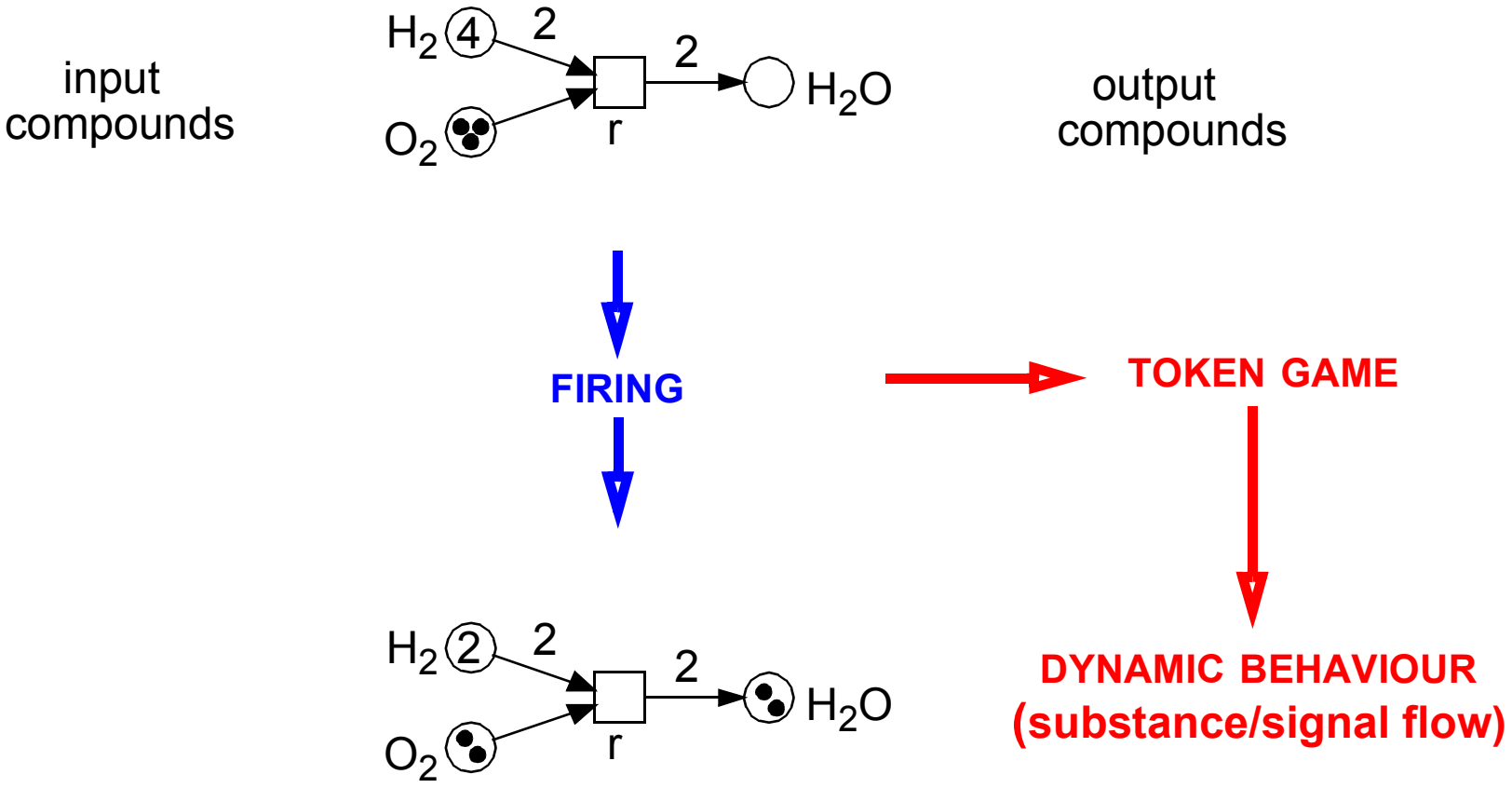
- **local conditions -> Petri net places -> chemical compounds**
- **multiplicities -> Petri net arc weights -> stoichiometric relations**
- **condition's state -> token(s) in its place -> available amount (e.g. mol)**
- **system state -> marking -> compounds distribution**
- **PN = (P, T, F, m_0), F: (P x T) U (T x P) -> N_0, m_0: P -> N_0**

PETRI NETS, BASICS - THE FIRING RULE

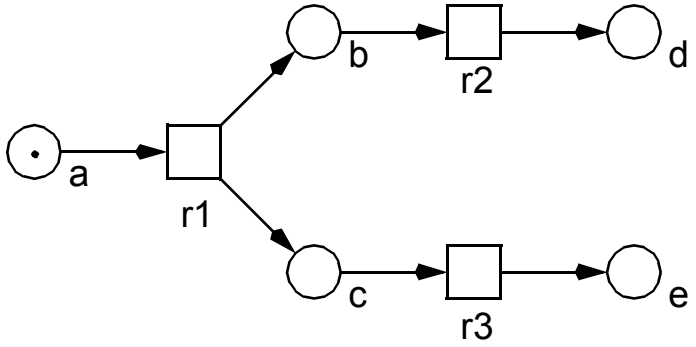
- **an action may happen, if** **-> prerequisite**
  - -> *all preconditions are fulfilled (corresponding to the arc weights);*
- **if an action happens, then** **-> firing behaviour**
  - -> *tokens are removed from all preconditions (corresponding to the arc weights), and*
  - -> *tokens are added to all postconditions (corresponding to the arc weights);*
- **action happens (firing of a transition)** **-> model assumptions**
  - -> *atomic*
  - -> *time-less*

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

$$2\ H_2 + O_2 \rightarrow 2\ H_2O$$



PARTIAL ORDER VERSUS INTERLEAVING SEMANTICS

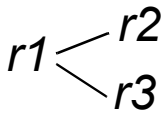


- **possible interleaving runs**
  - -> *r1 - r2 - r3*
  - -> *r1 - r3 - r2*
- **totally ordered runs**

-> **INTERLEAVING SEMANTICS**

all totally ordered runs

- **order between r1 - r2 and r1 - r3**
  - -> *causality* $x < y$ [x-y]
  - -> *dependency*
- **no order between r2 , r3**
  - -> *concurrency* $x \parallel y$
  - -> *independency*
- **partial order run**



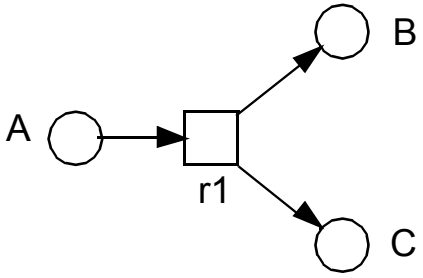
-> **PARTIAL ORDER SEMANTICS**

"true concurrency semantics"

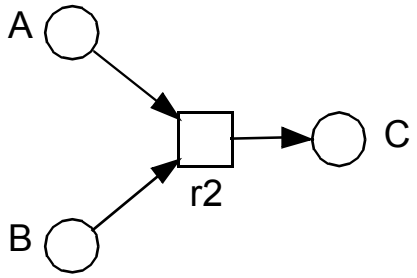
all partially ordered runs

TYPICAL BASIC STRUCTURES I

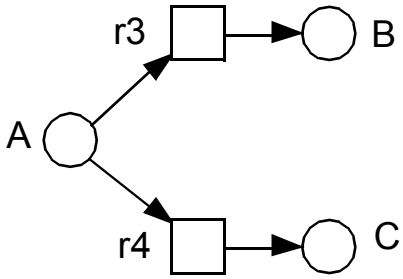
A --> B + C



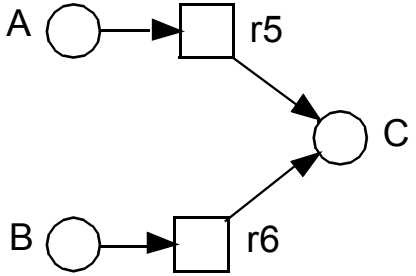
A + B --> C



A --> B,
A --> C

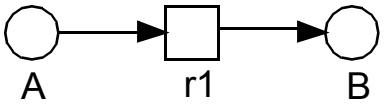


A --> C,
B --> C

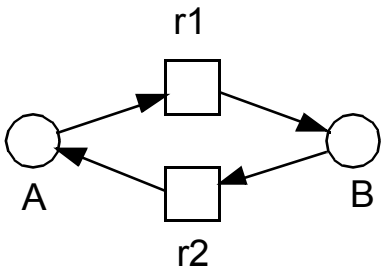


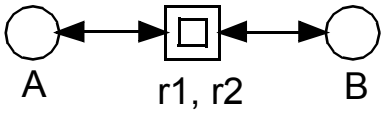
TYPICAL BASIC STRUCTURES II

A --> B

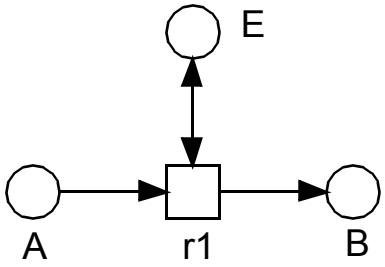


A <--> B

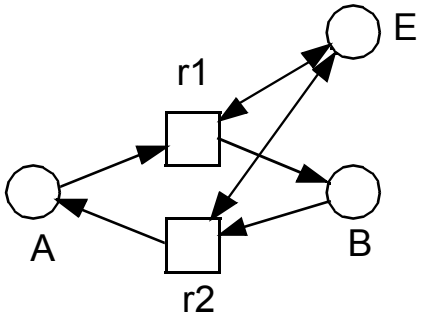


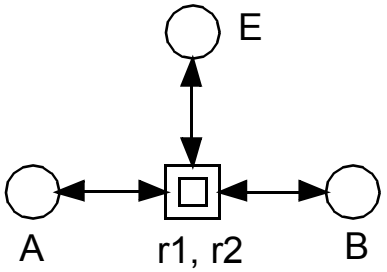


E
A --> B



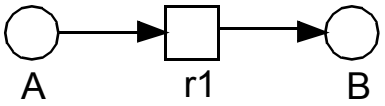
E
A <--> B



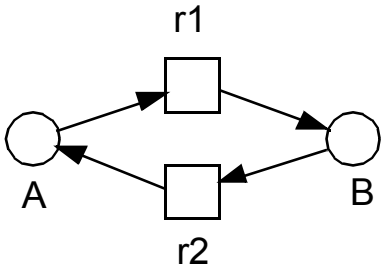


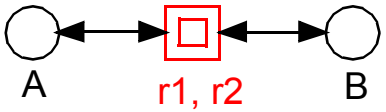
TYPICAL BASIC STRUCTURES II

A --> B

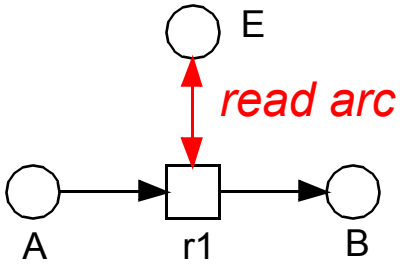


A <--> B

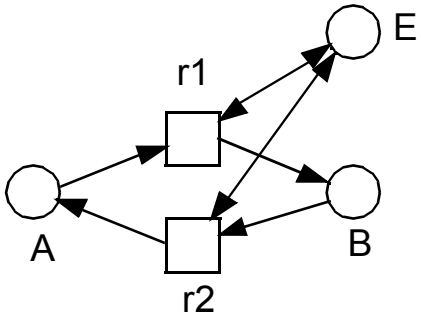


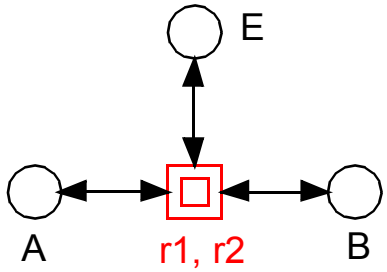


E
A --> B



E
A <--> B

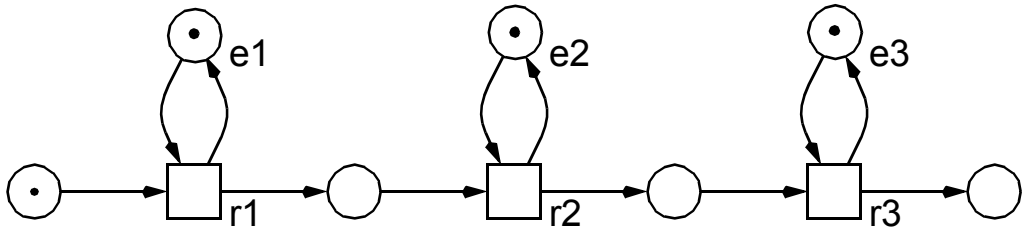




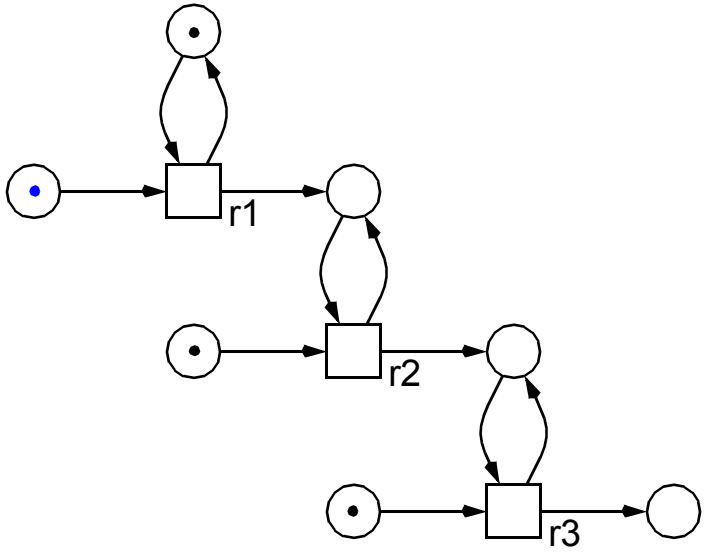
macro transition

TYPICAL BASIC STRUCTURES III

- **metabolic networks**
  -> *substance flows*



- **signal transduction networks**
  -> *signal flows*



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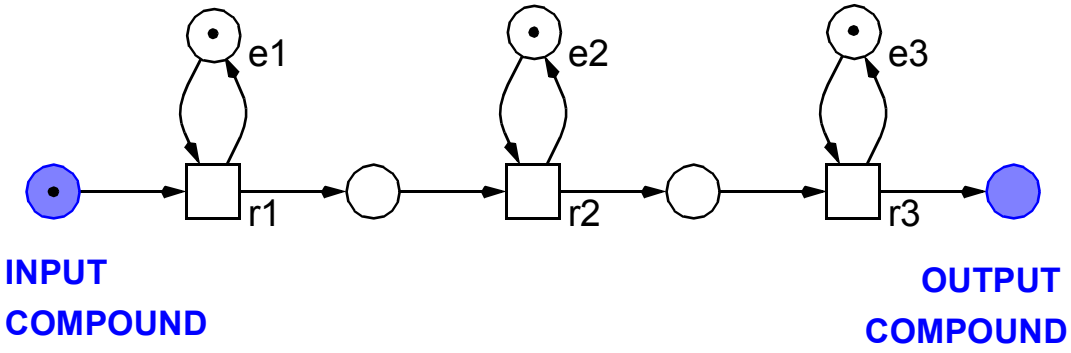

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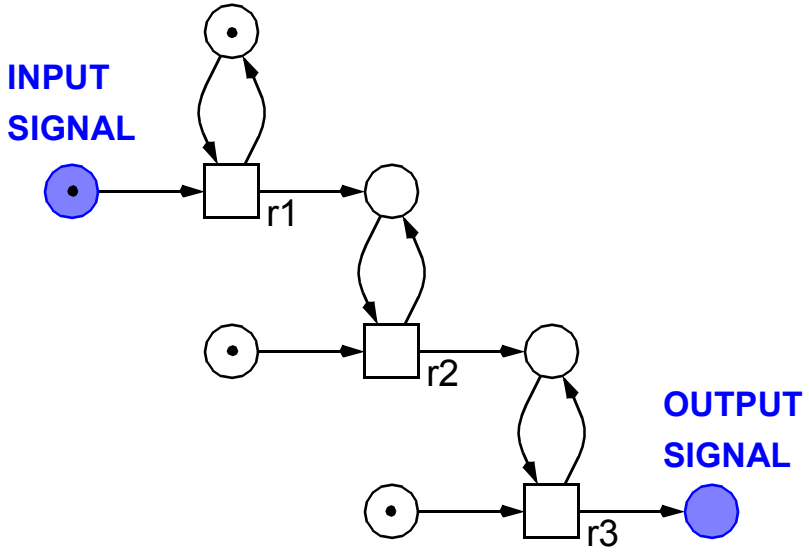

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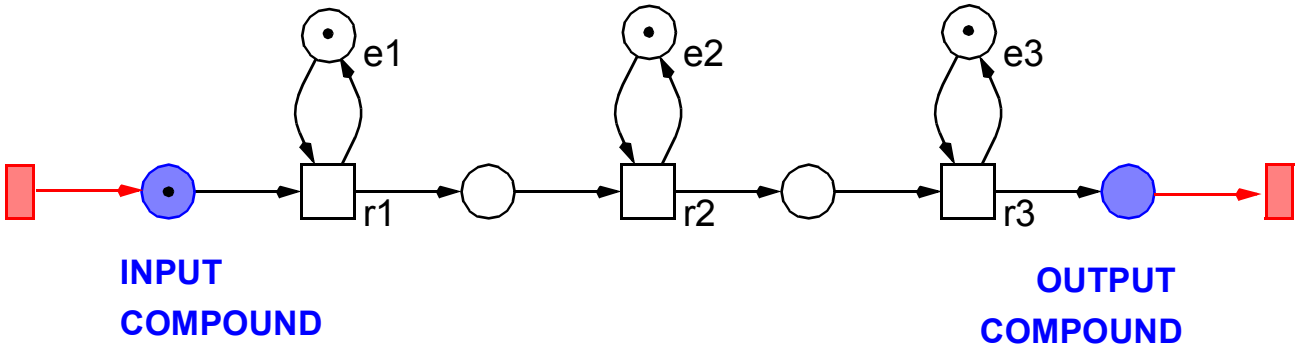

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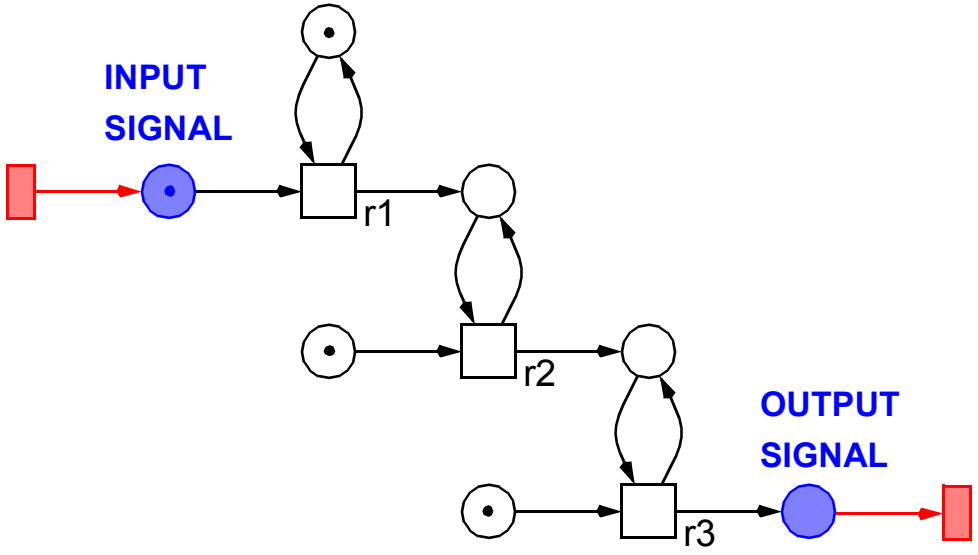
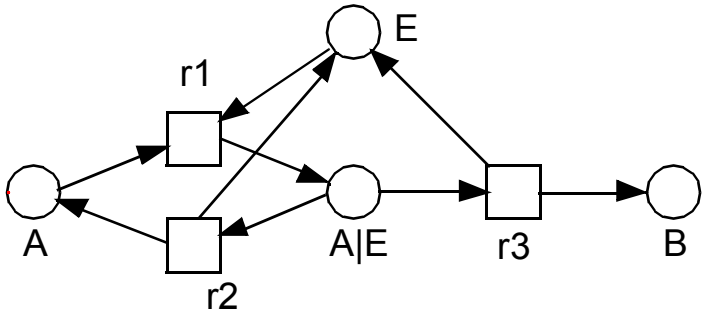


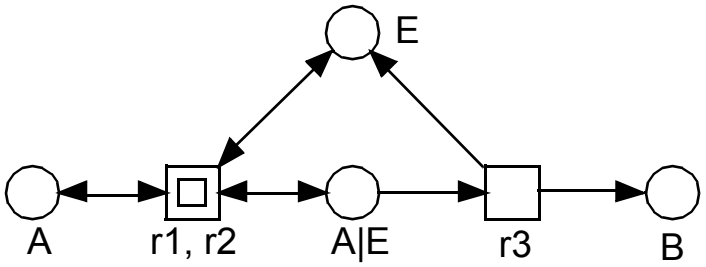
-> OPEN / CLOSED SYSTEMS

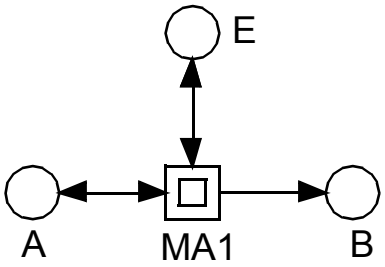
TYPICAL BASIC STRUCTURES IV

E
A <--> A|E --> B

enzymatic reaction,
mass-action approach 1



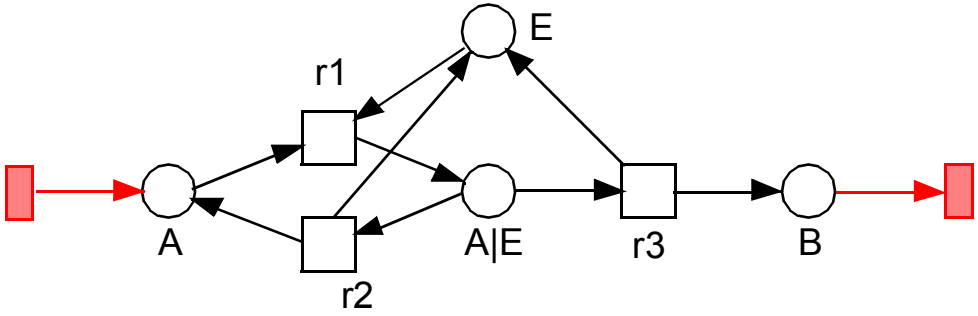


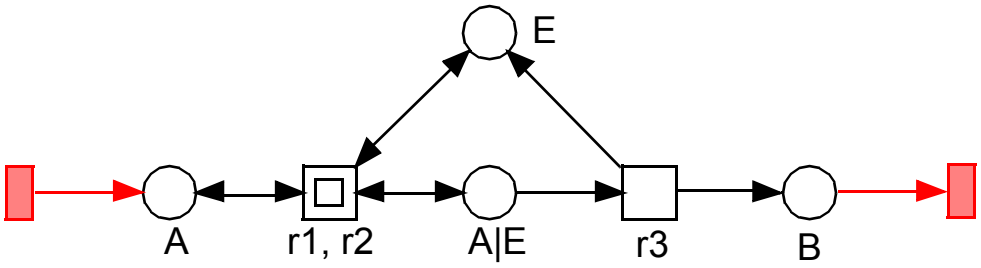


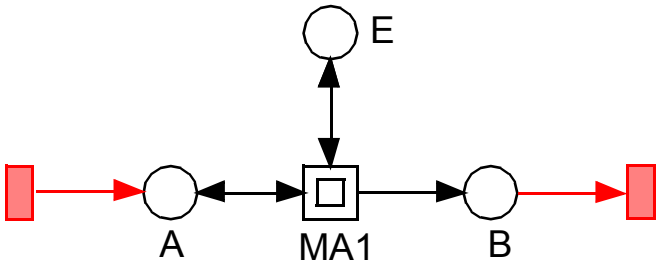
TYPICAL BASIC STRUCTURES IV

E
A <--> A|E --> B

enzymatic reaction,
mass-action approach 1

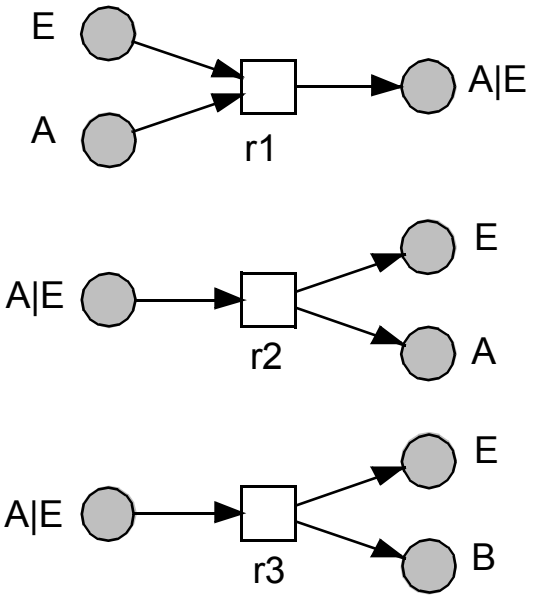






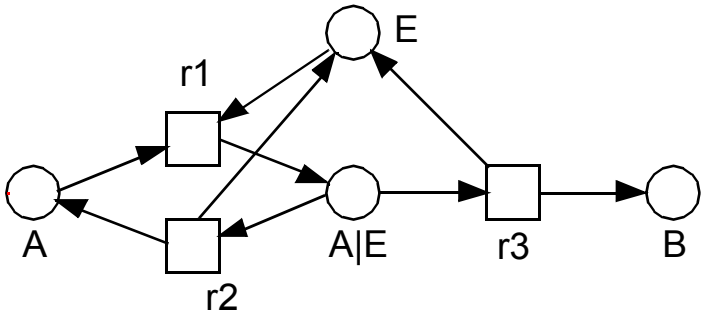
LAYOUT OPTIONS

reaction-centred view

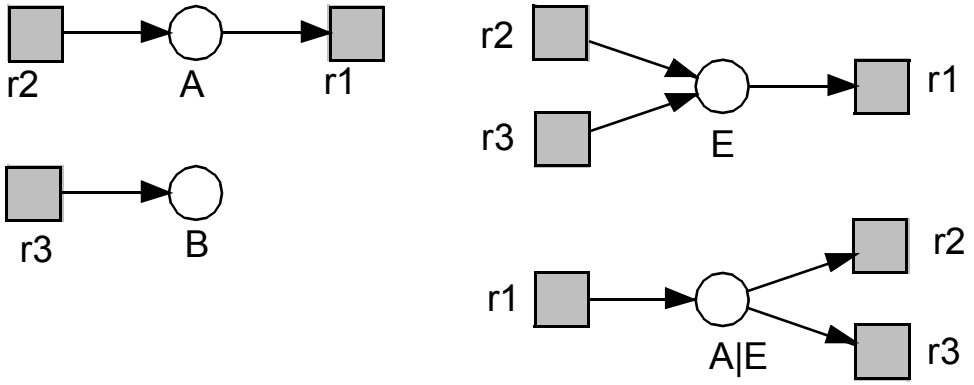


logical nodes (fusion nodes)

process-oriented view

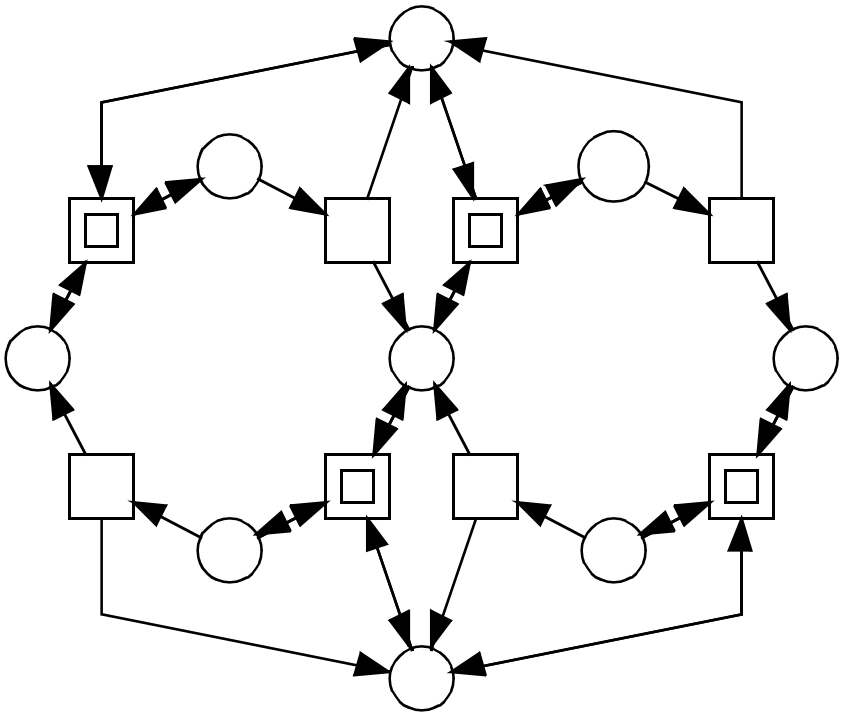


species-centred view



NET COMPOSITION FROM BUILDING BLOCKS

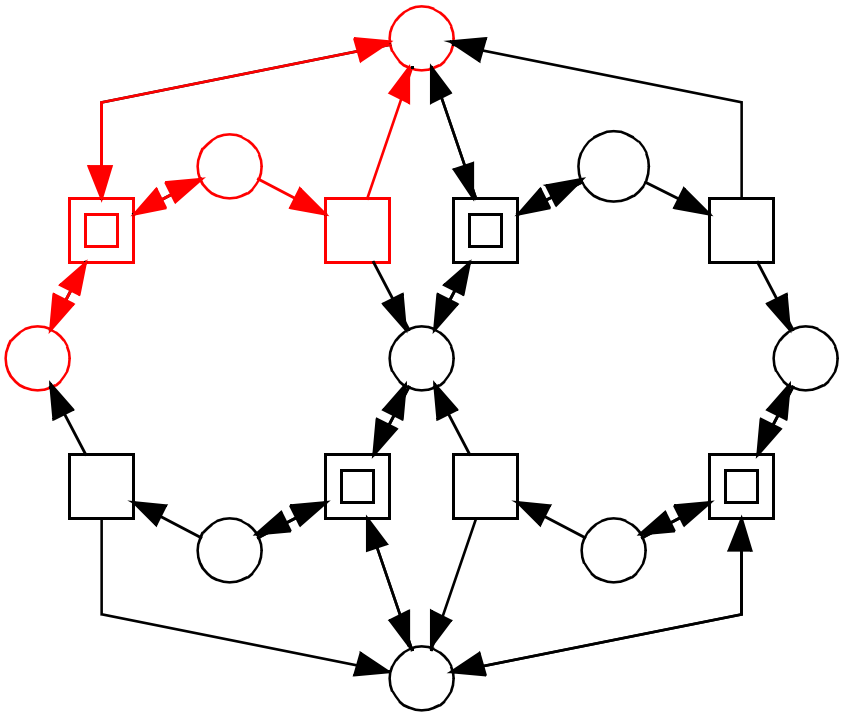
DOUBLE PHOSPHOYLATION / DEPHOSPHORYLATION



NET COMPOSITION FROM BUILDING BLOCKS

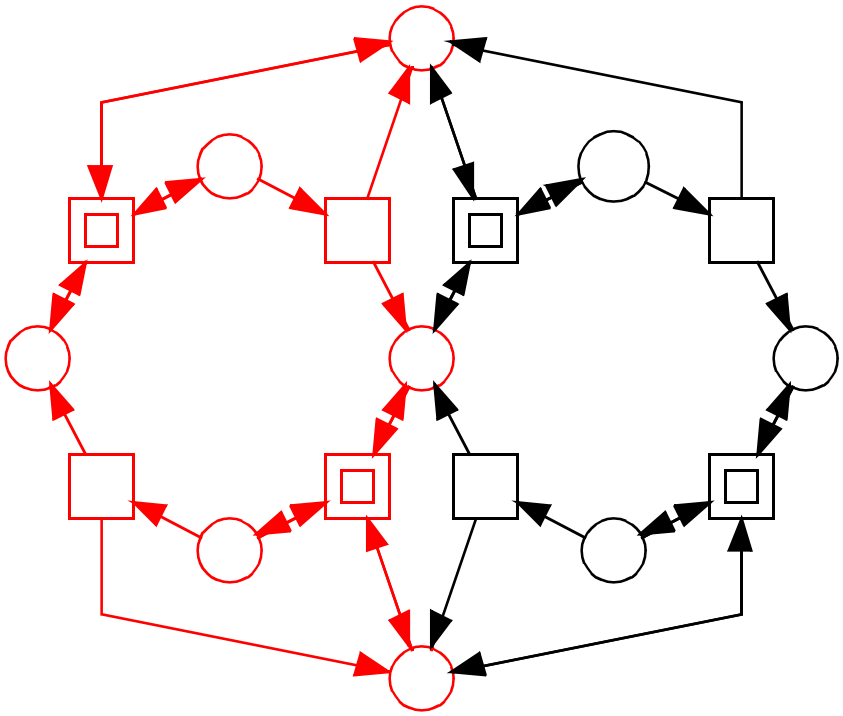
DOUBLE PHOSPHOYLATION / DEPHOSPHORYLATION

SINGLE
MASS-ACTION STEP



NET COMPOSITION FROM BUILDING BLOCKS

DOUBLE PHOSPHOYLATION / DEPHOSPHORYLATION



SINGLE
PHOSPHOYLATION / DEPHOSPHORYLATION

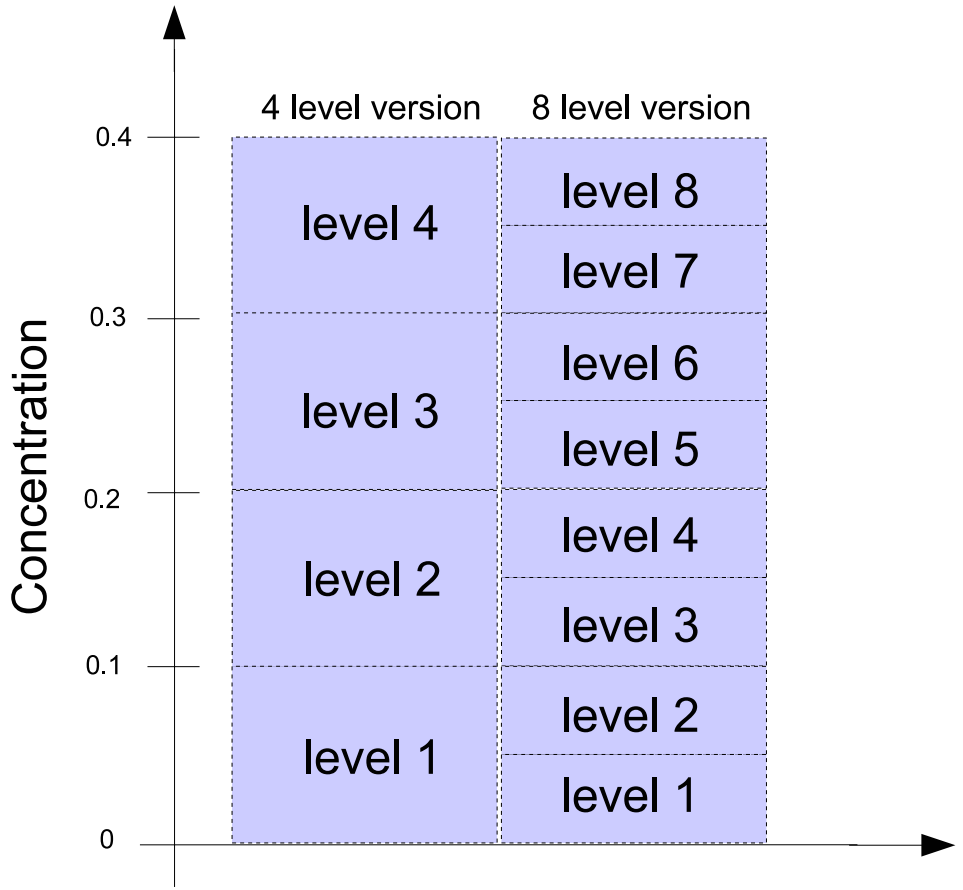
- **metabolic networks**
  signal transduction networks
  gene regulatory networks

- **transitions**
  - -> *(reversible, stoichiometric, enzyme-catalyzed) chemical reactions,*
  - -> *conversions/transport 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, or any finite integer number

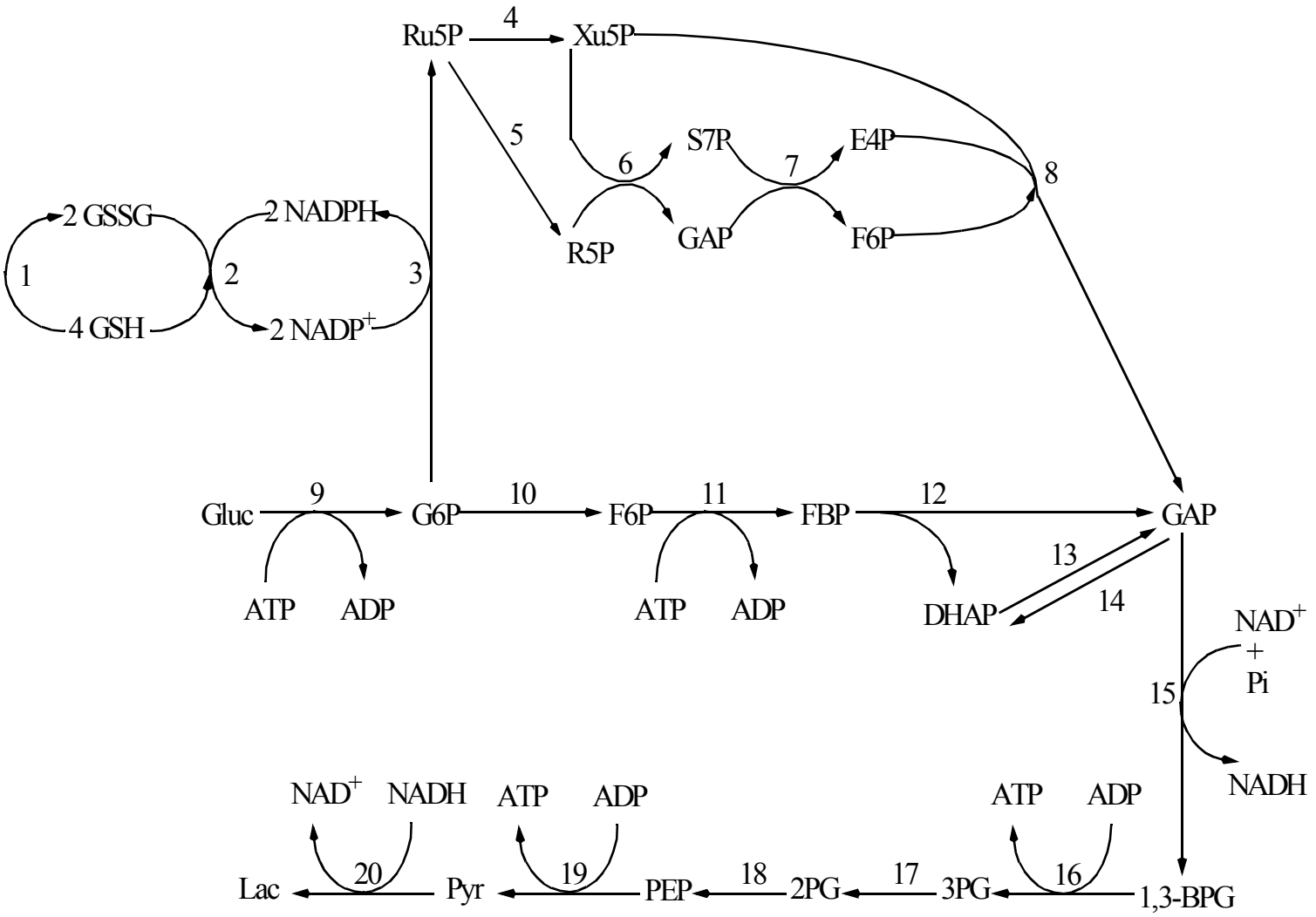
LEVEL CONCEPT



BIO PETRI NETS - SOME EXAMPLES

Ex1 - Glycolysis and Pentose Phosphate Pathway

[Reddy 1993]



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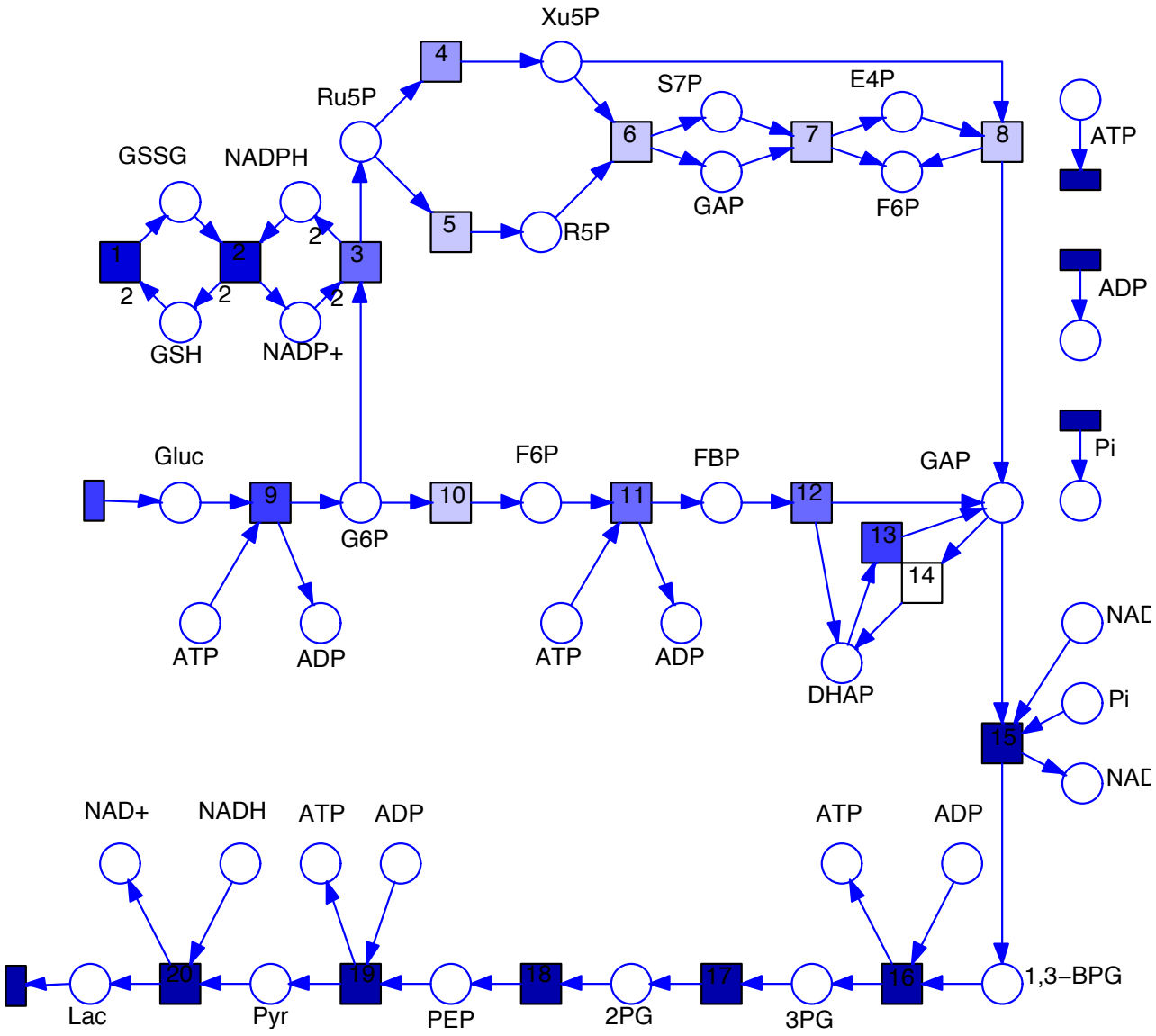
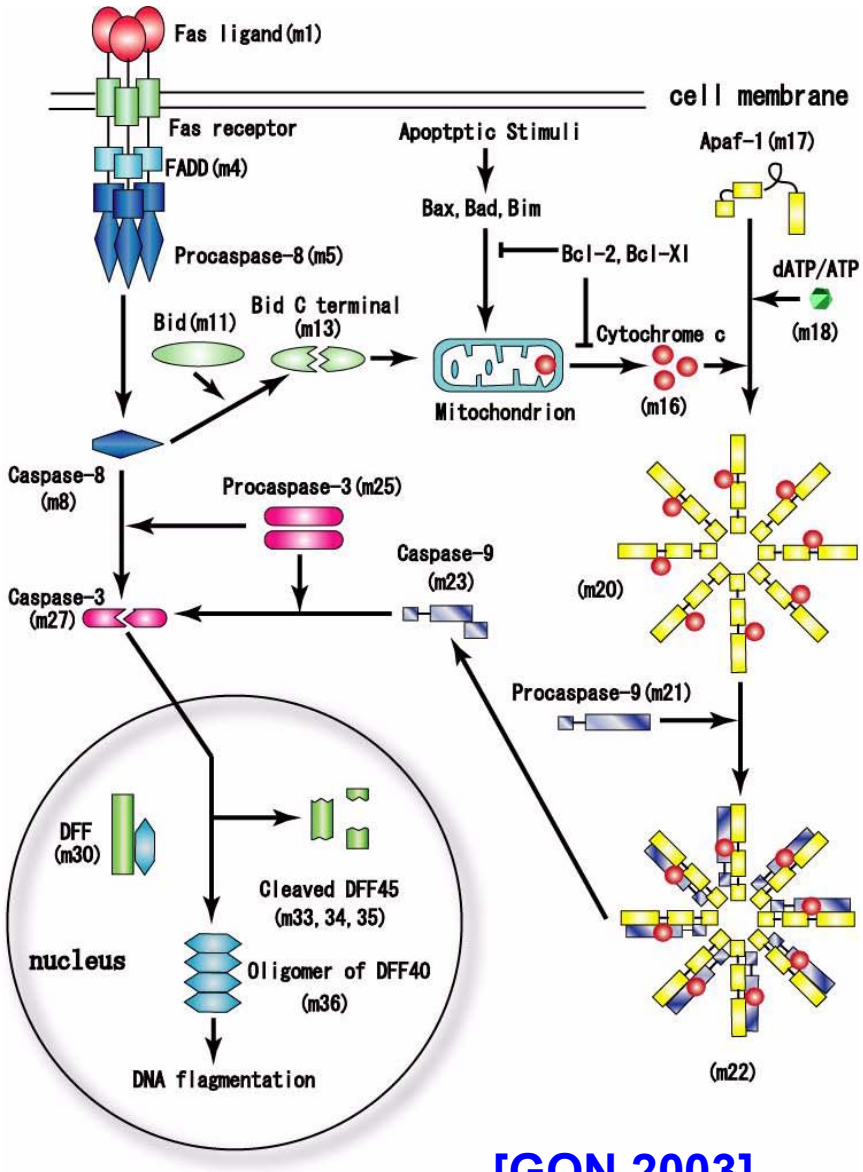
[Reddy 1993]
[Heiner 1998]



EX2: APOPTOSIS IN MAMMALIAN CELLS



[GON 2003]

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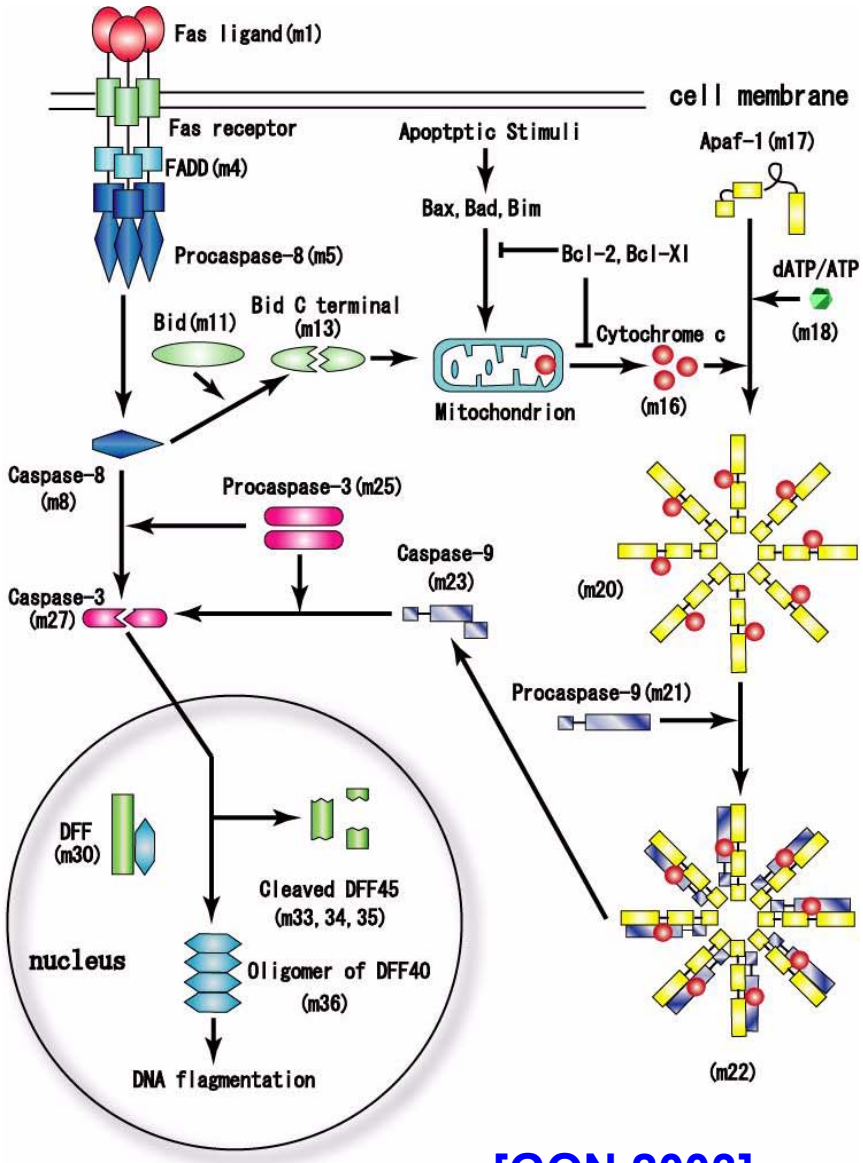
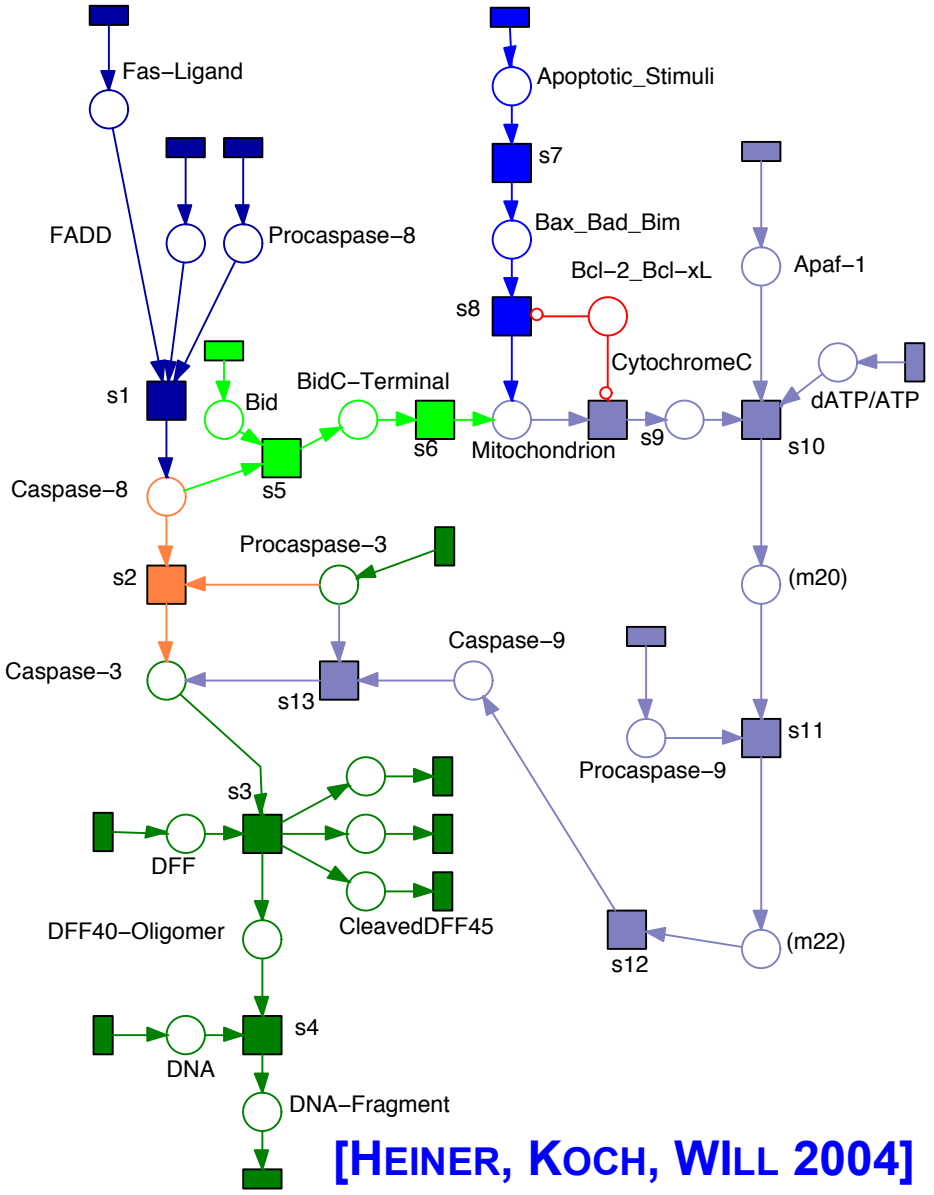


[GON 2003]



[HEINER, KOCH, WILL 2004]

Ex3 - Carbon Metabolism in Potato Tuber

[KOCH, JUNKER, HEINER 2005]

monika.heiner@informatik.tu-cottbus.de

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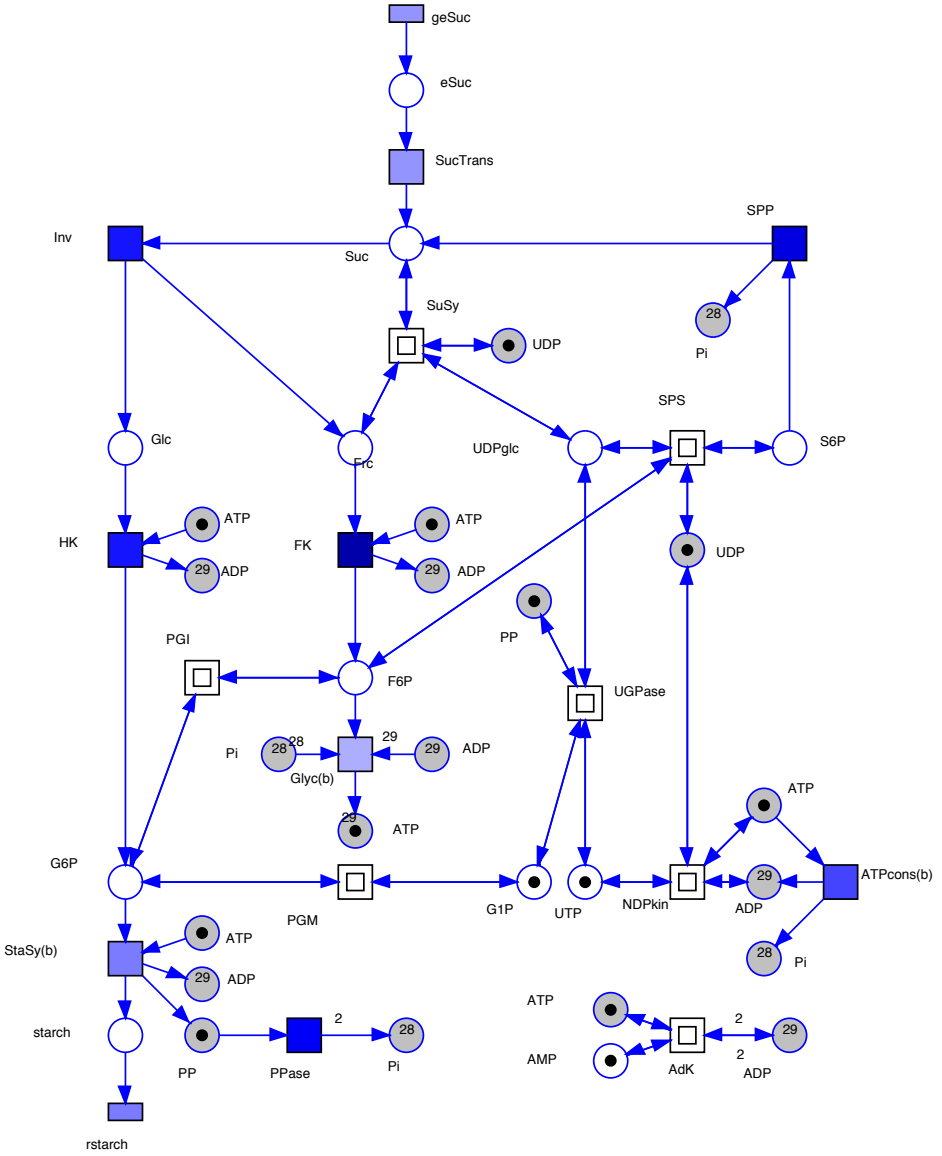
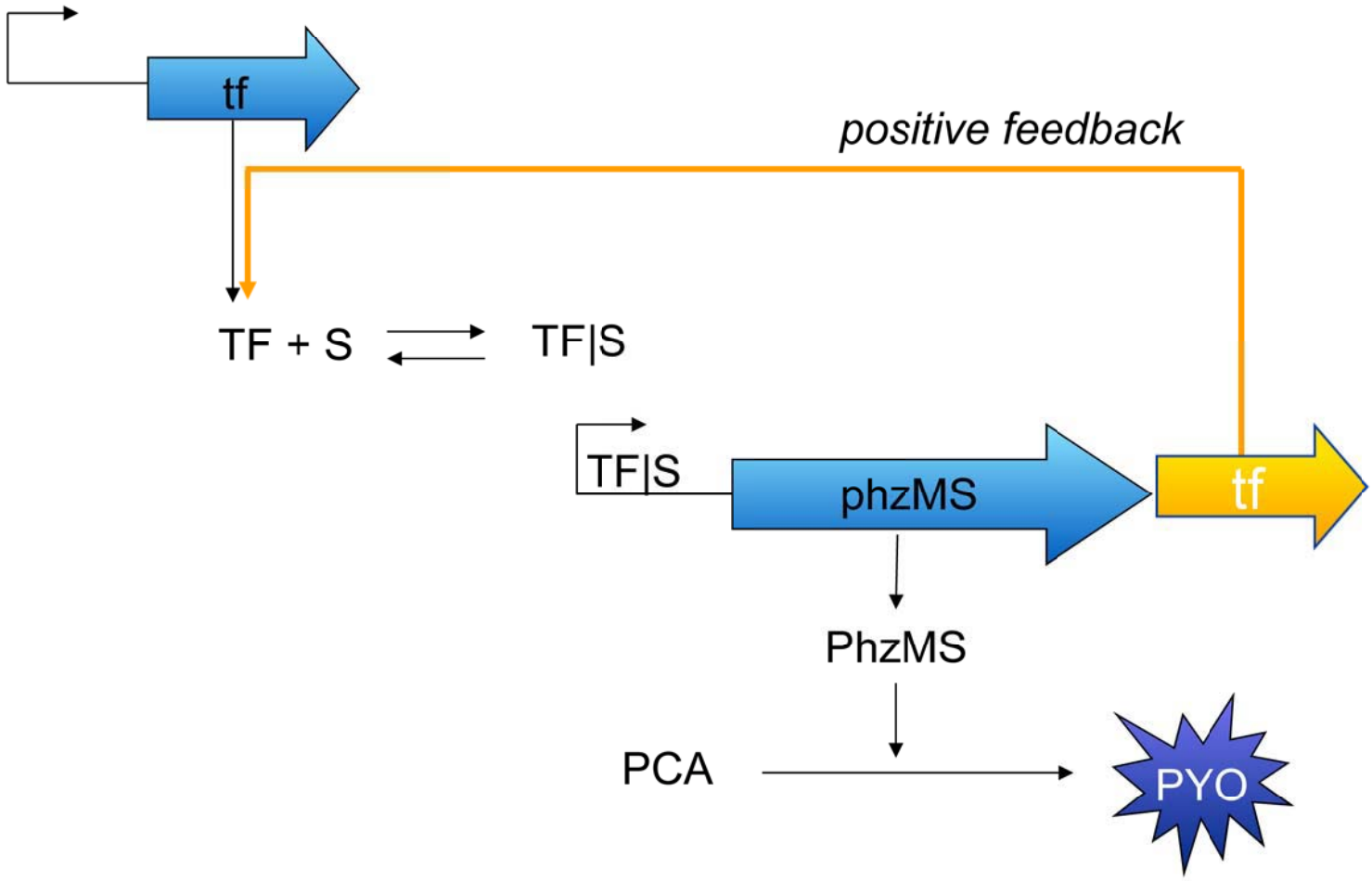


EX4 - BIOSENSOR



[GILBERT, HEINER, ROSSER, FULTON, GU, TRYBILO 2008]

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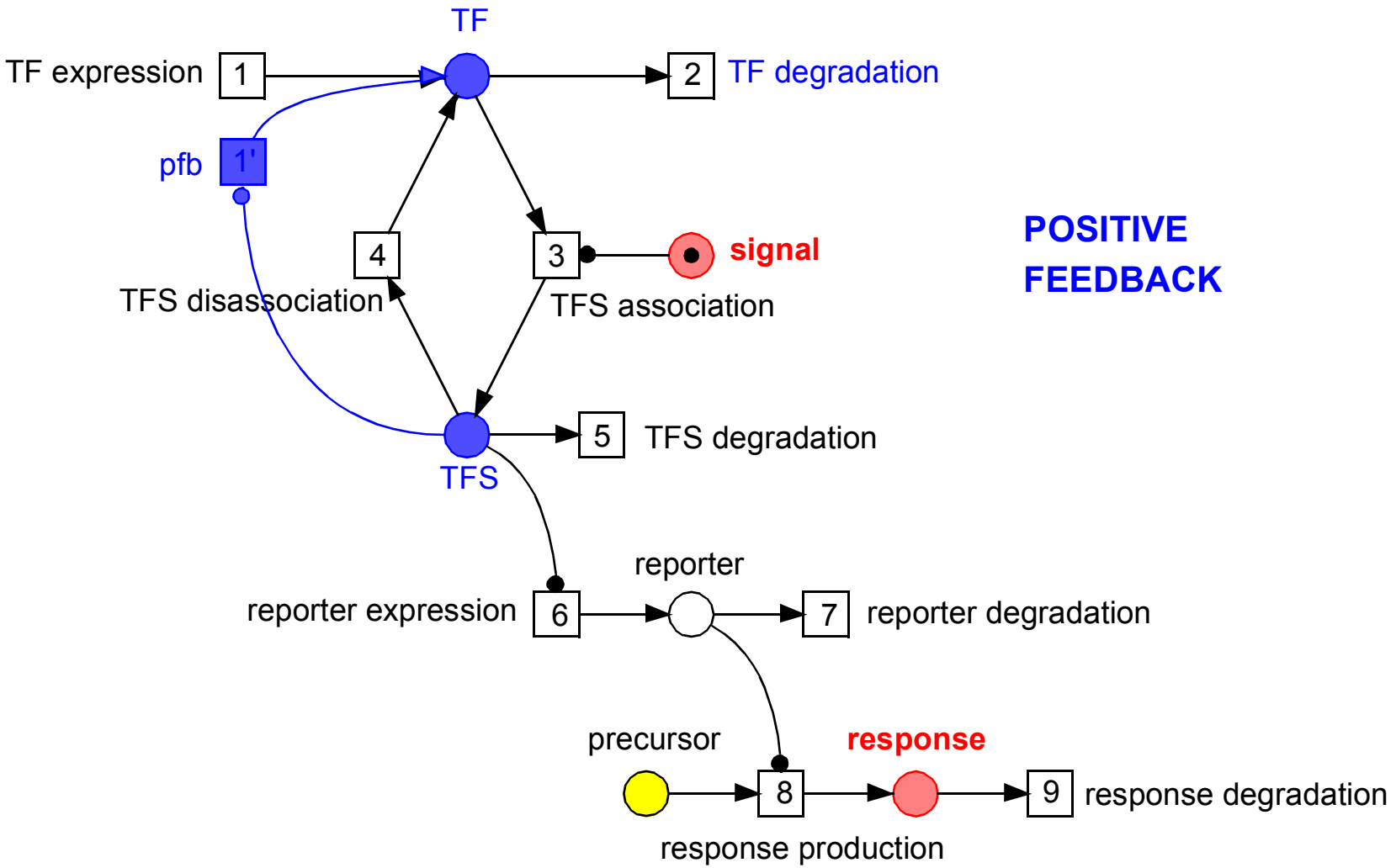
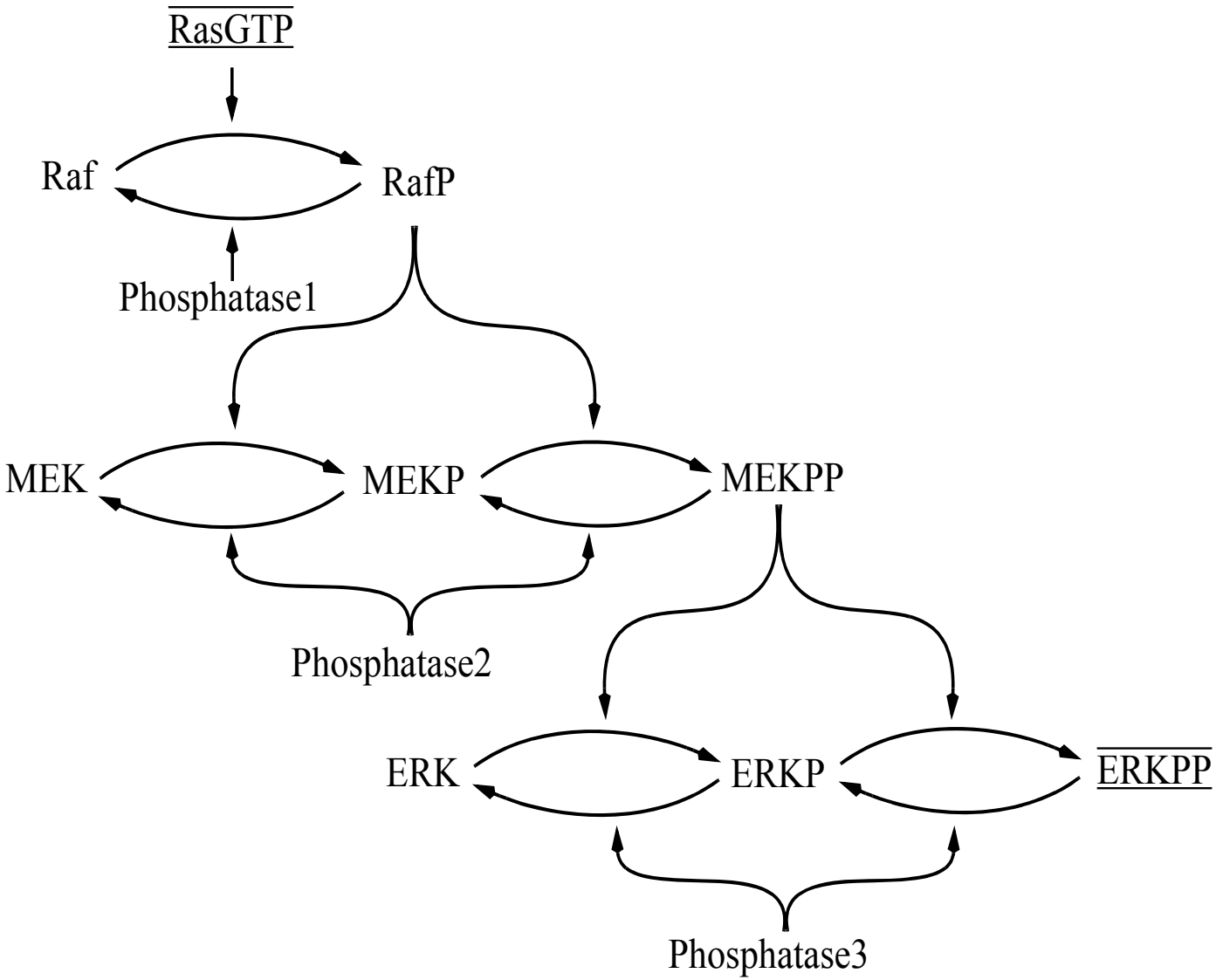


[GILBERT, HEINER, ROSSER, FULTON, GU, TRYBILO 2008]

EX5 - SIGNALLING CASCADE



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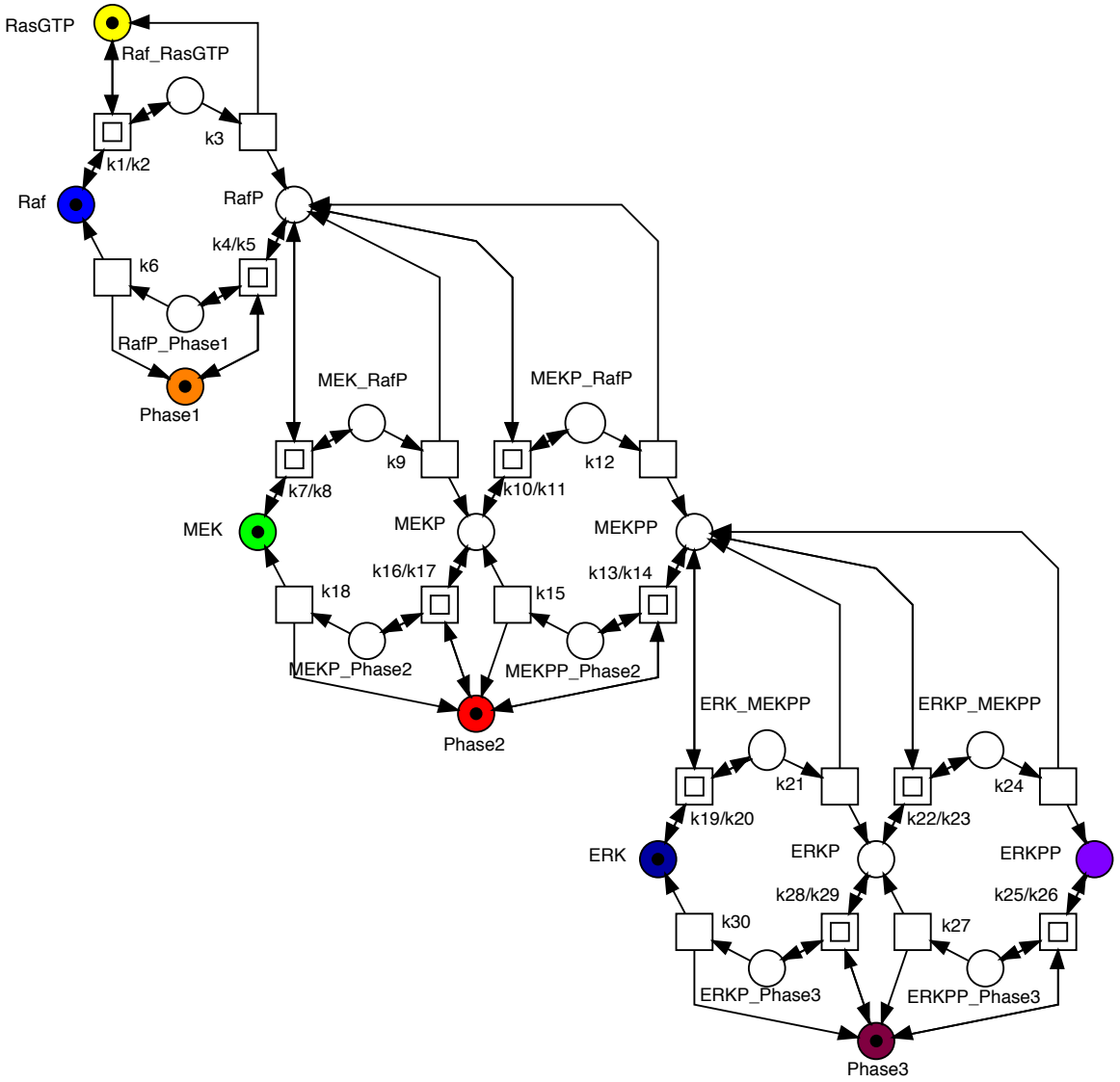
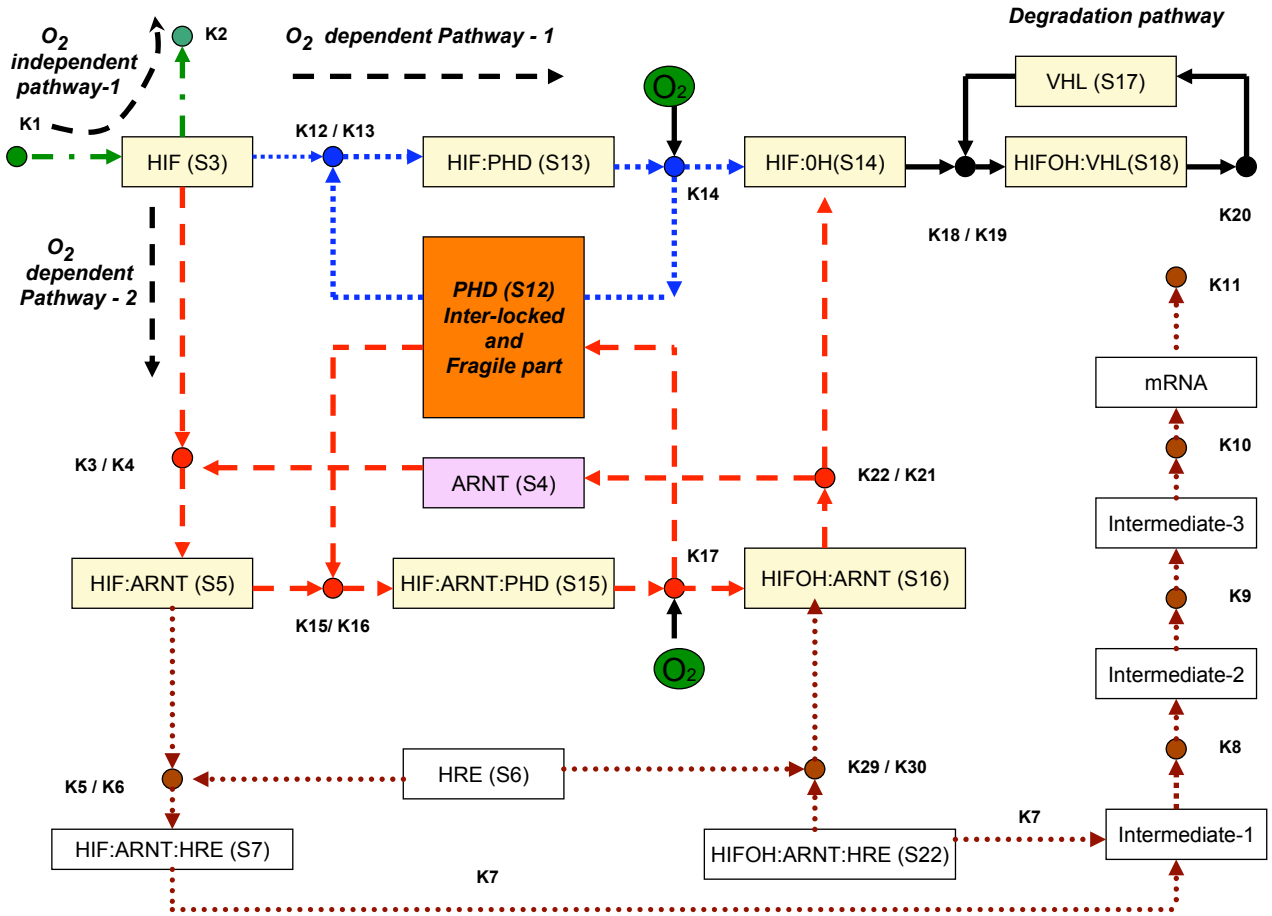


[GILBERT, HEINER, LEHRACK 2007]

[HEINER, GILBERT, DONALDSON 2008]

EX6 - HYPOXIA



[YU ET AL. 2007]

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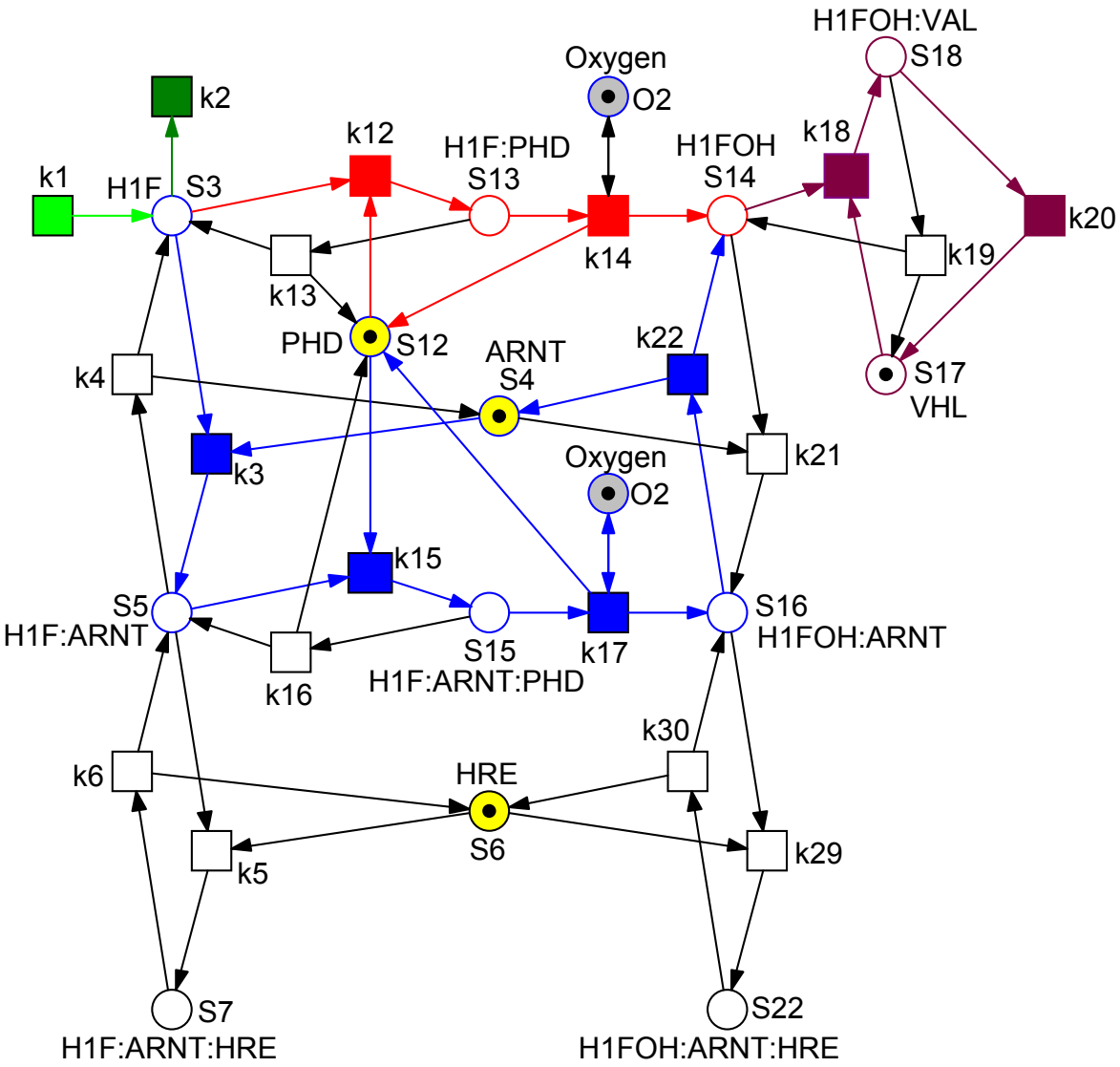

[HEINER, SRIRAM 2010]

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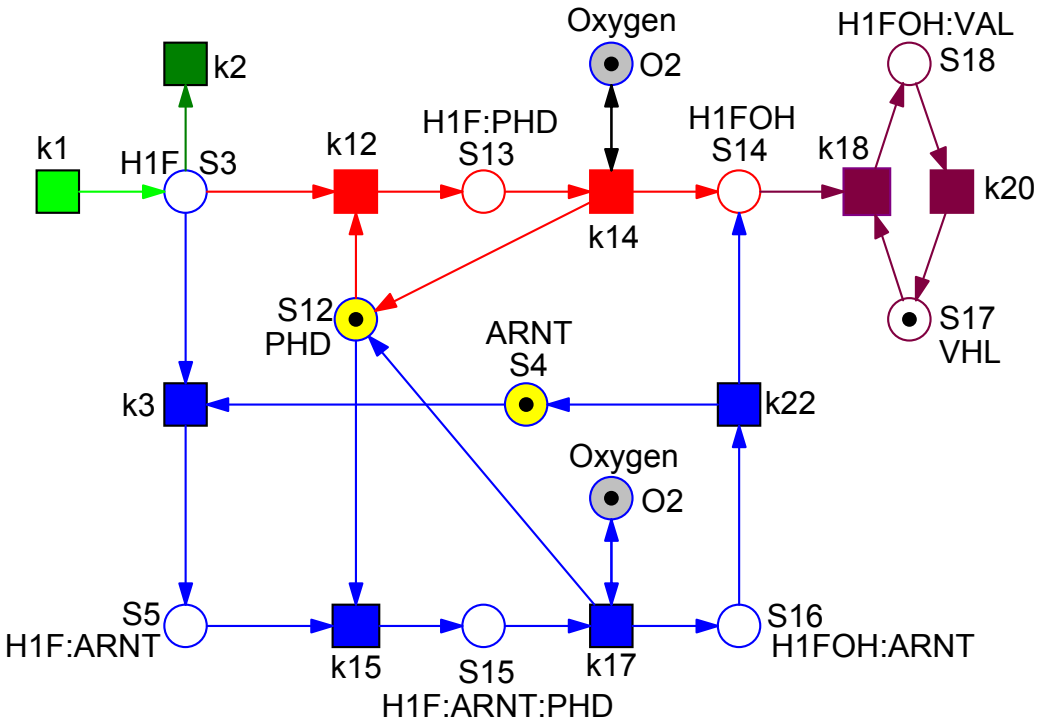

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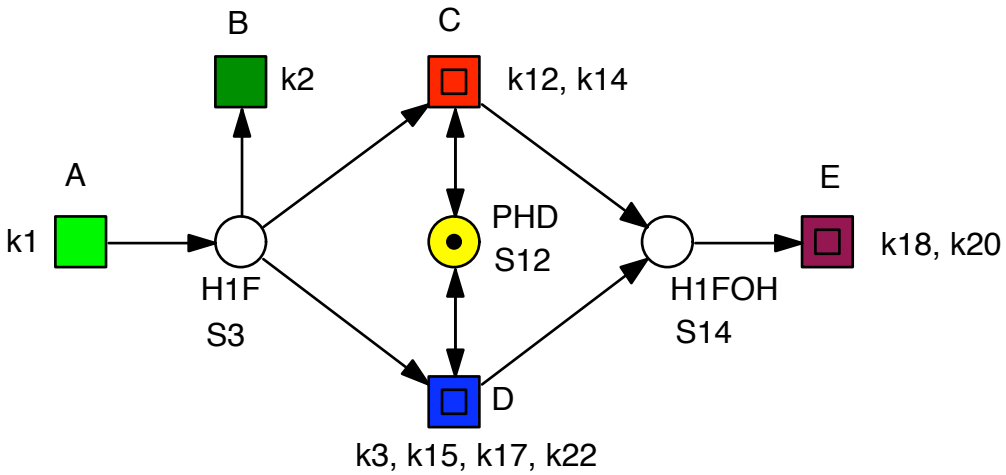
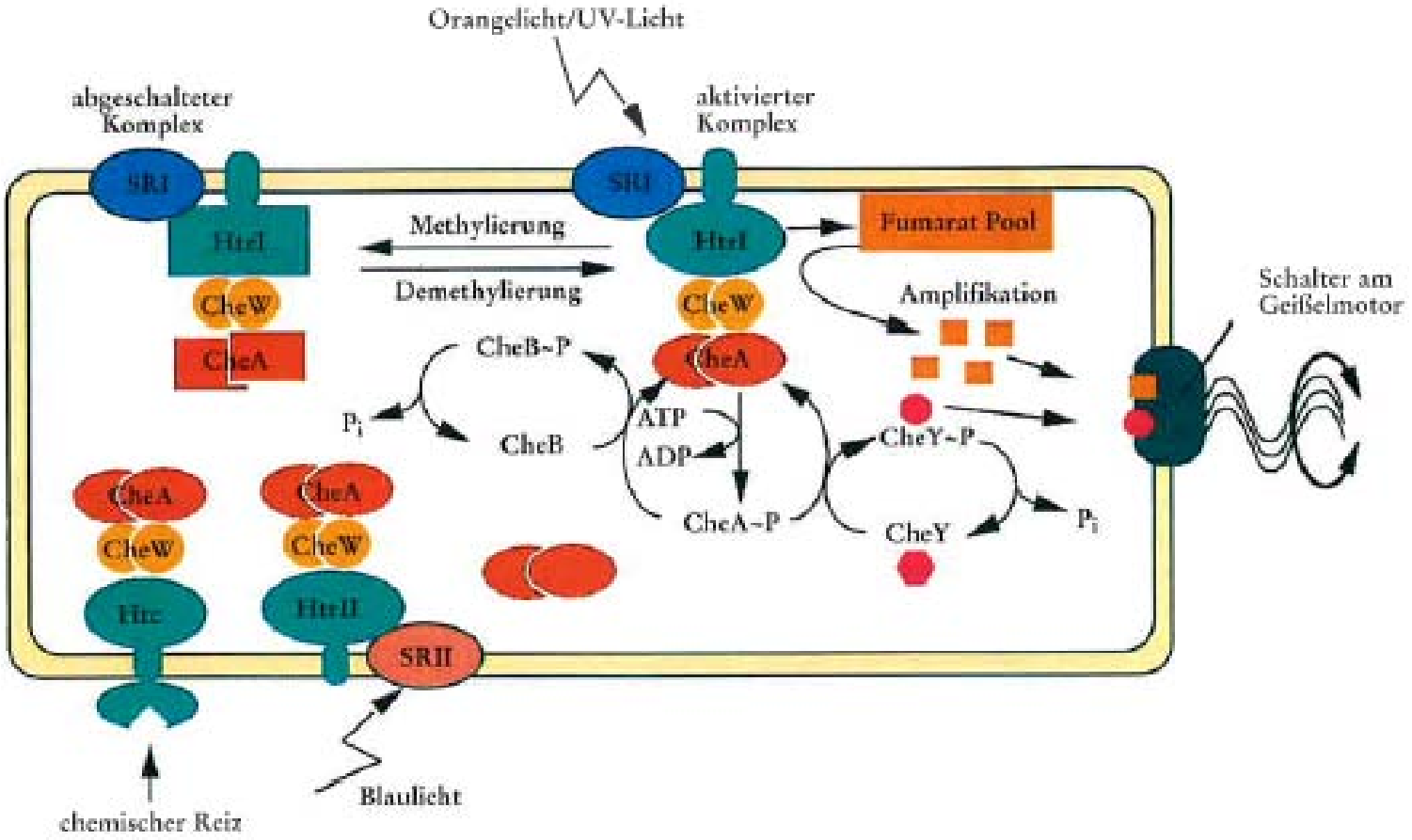


[HEINER, SRIRAM 2010]

EX7 - SWITCH CYCLE HALOBACTERIUM SALINARUM



[MARWAN, OESTERHELT 1999]

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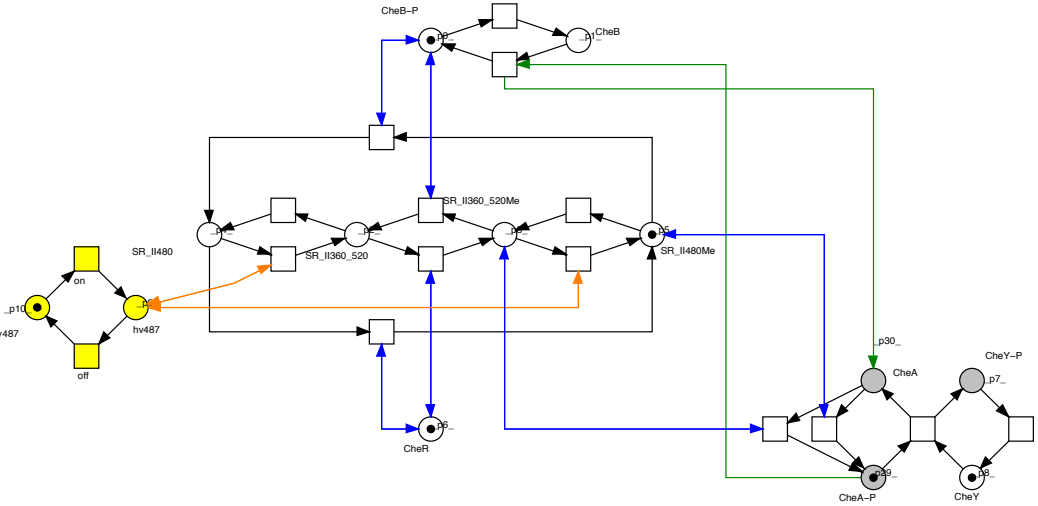

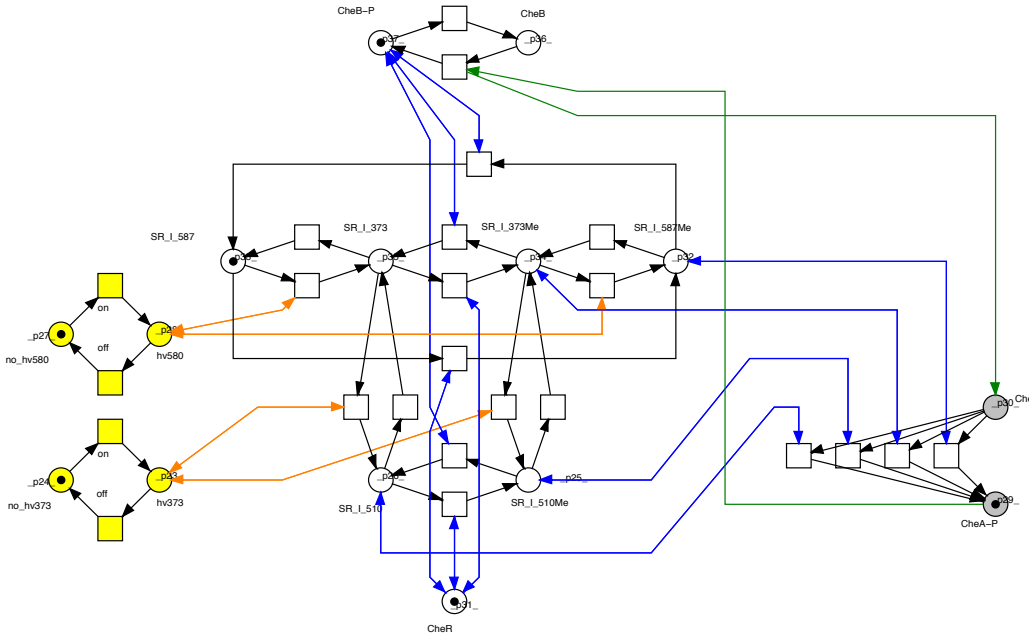

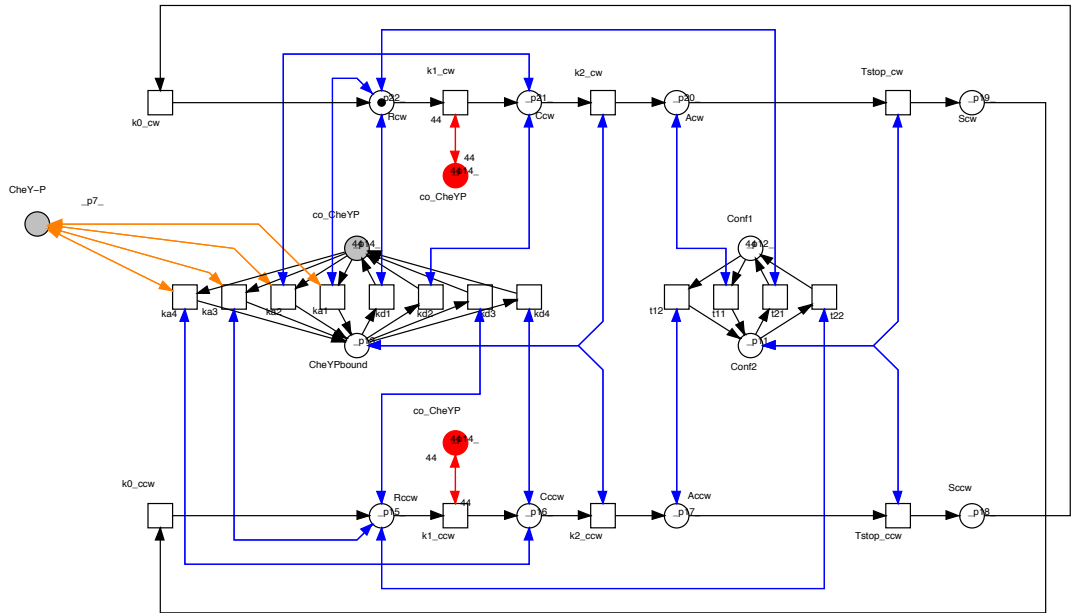

QUALITATIVE ANALYSES

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- **How many tokens can reside at most in a given place ?**

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GENERAL BEHAVIOURAL PROPERTIES

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SPECIAL BEHAVIOURAL PROPERTIES

- **. . . and many more -> temporal logics** -> *CTL / LTL - CSL / PLTL*

ANALYSIS TECHNIQUES

- **static analyses** -> **no state space construction**
- **dynamic analyses** -> **total/ partial state space construction**

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  - -> *structural properties (graph theory, combinatorics), e.g. DTP*
  - -> *P / T - invariants (linear algebra)*
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  - -> *P / T - invariants (linear algebra)*
- **dynamic analyses** **-> total/ partial state space construction**

-> *analysis of general behavioural system properties,*

e.g. boundedness, liveness, reversibility, . . .

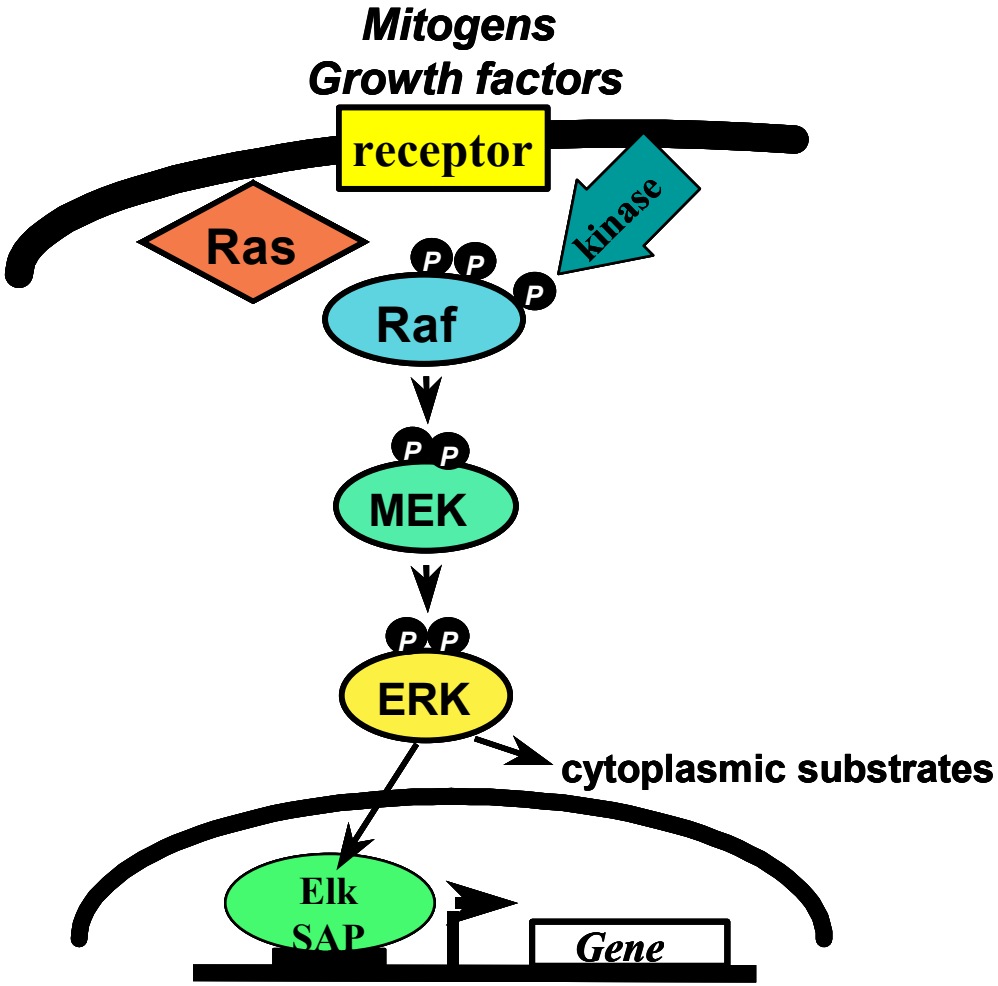
-> *model checking of special behavioural system properties,*

e.g. reachability of a given (sub-) system state (with constaints),
reproducability of a given (sub-) system state (with constraints)

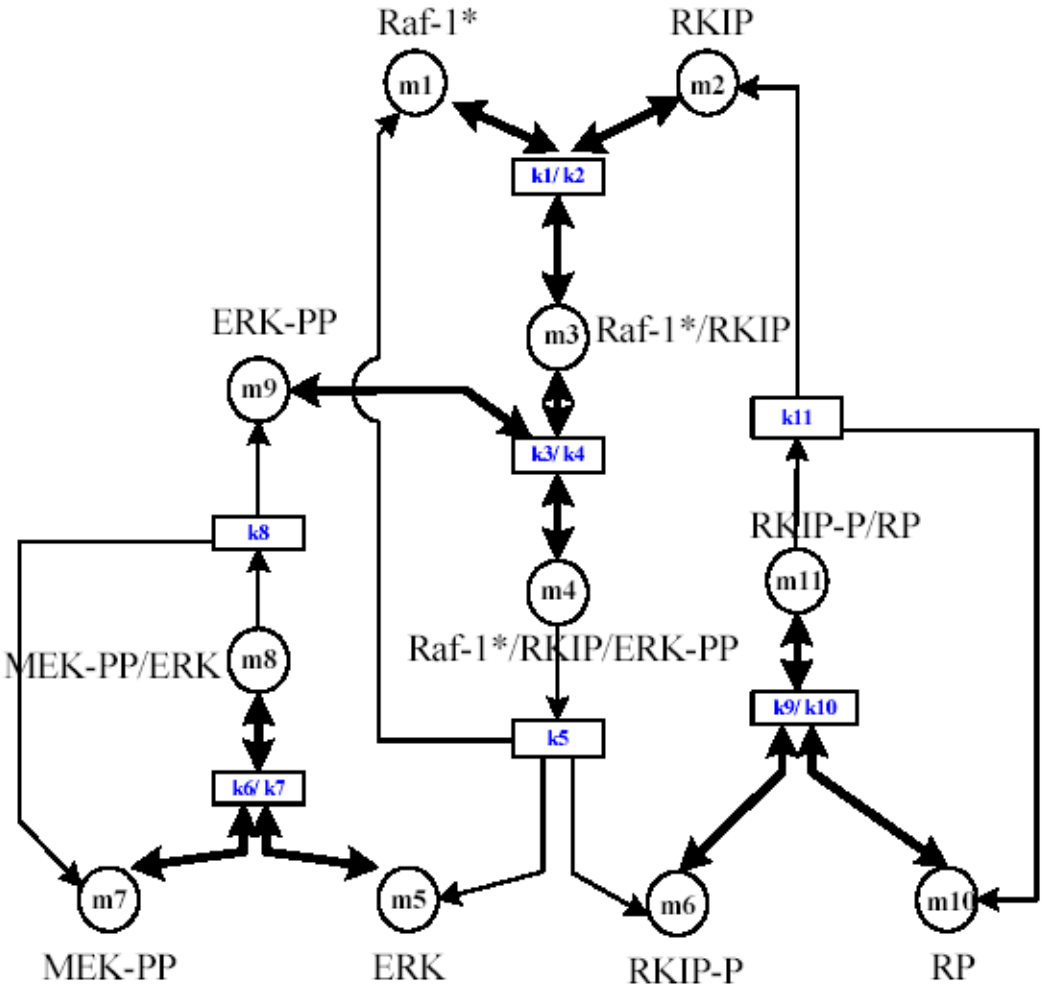
expressed in temporal logics (CTL / LTL),
-> *very flexible, powerful query language*

A CASE STUDY

…one pathway…


Mitogens
Growth factors
receptor
Ras
kinase
P P
P
Raf
P P
MEK
P P
ERK
cytoplasmic substrates
Elk
SAP
Gene

THE RKIP PATHWAY



[Cho et al., CMSB 2003]

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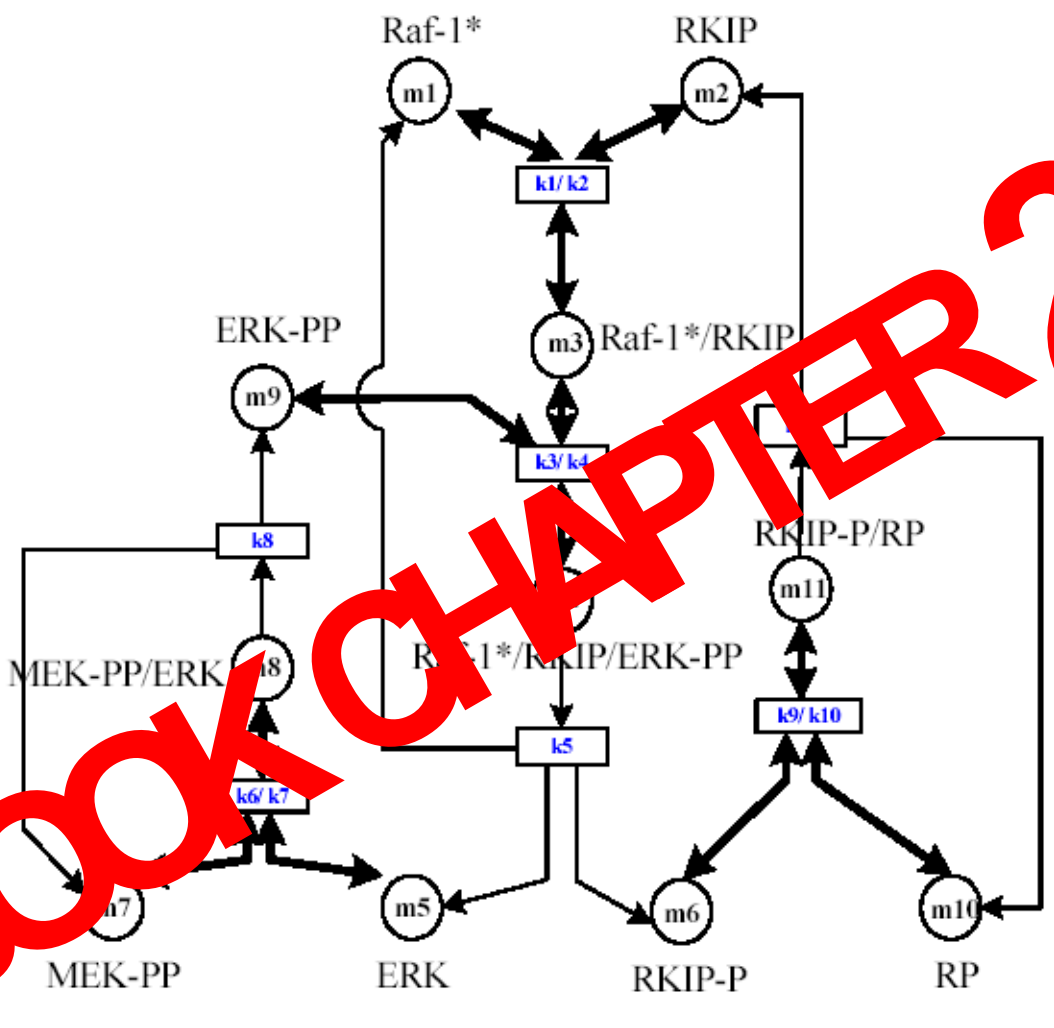

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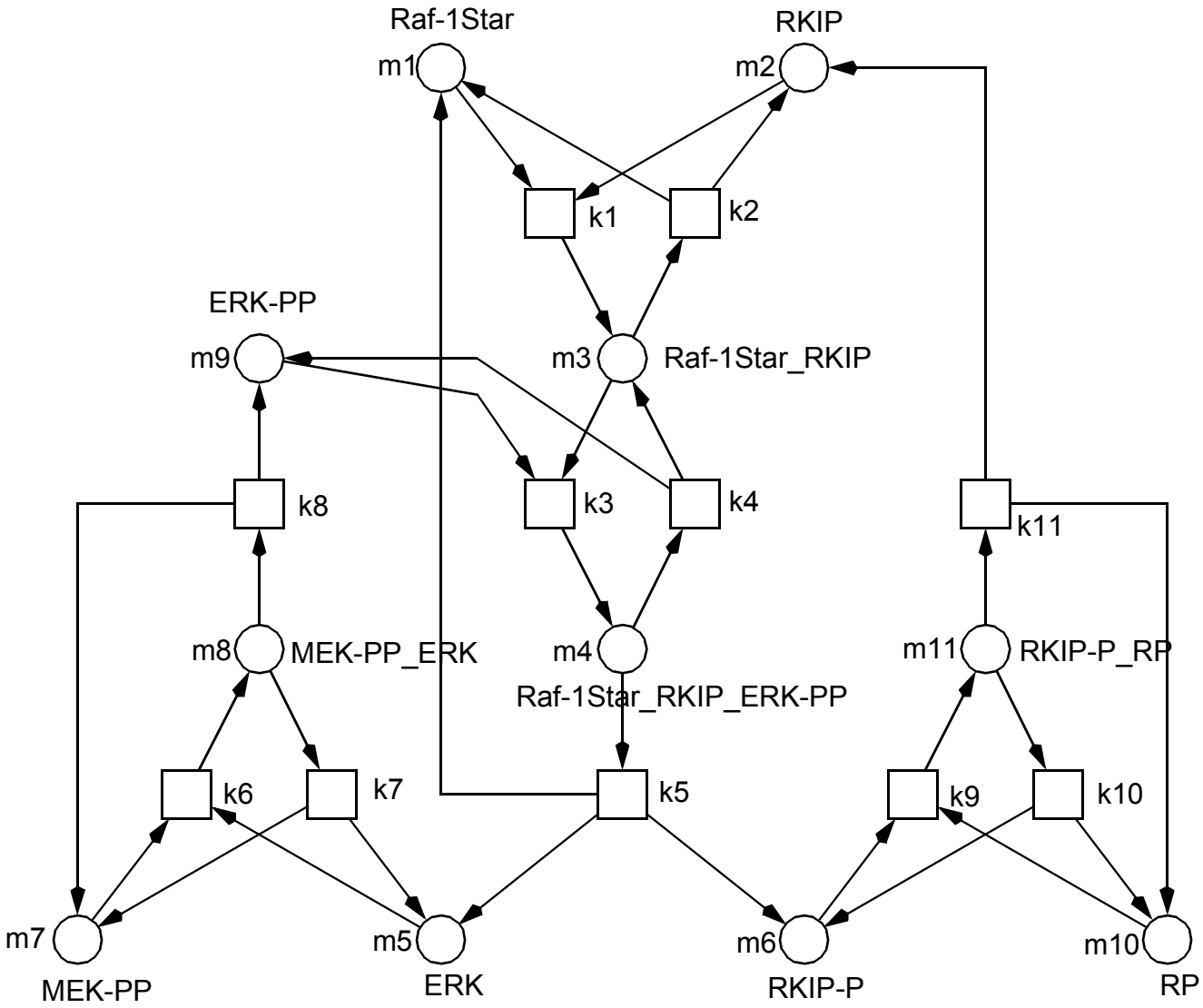
THE RKIP PATHWAY, PETRI NET



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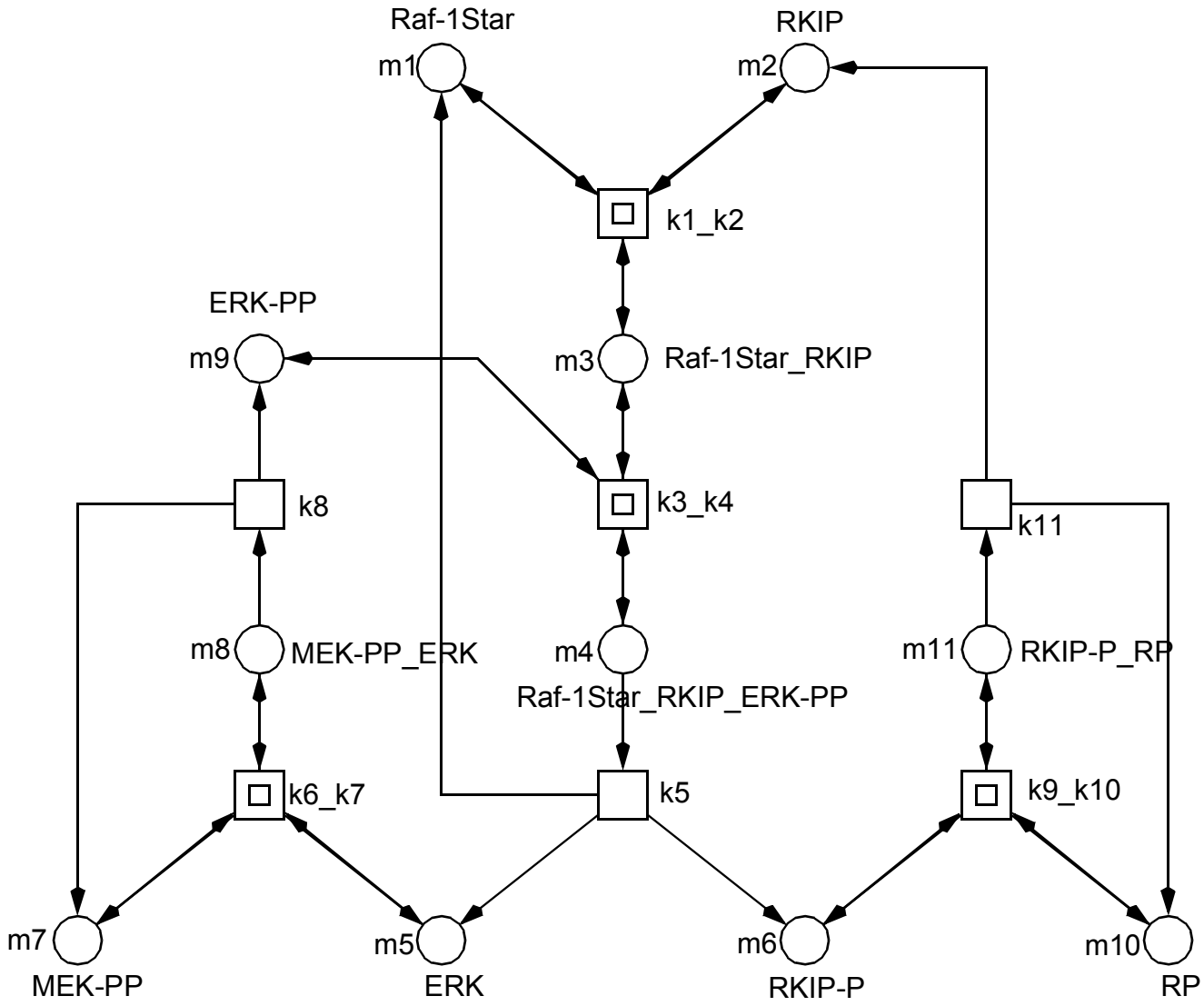
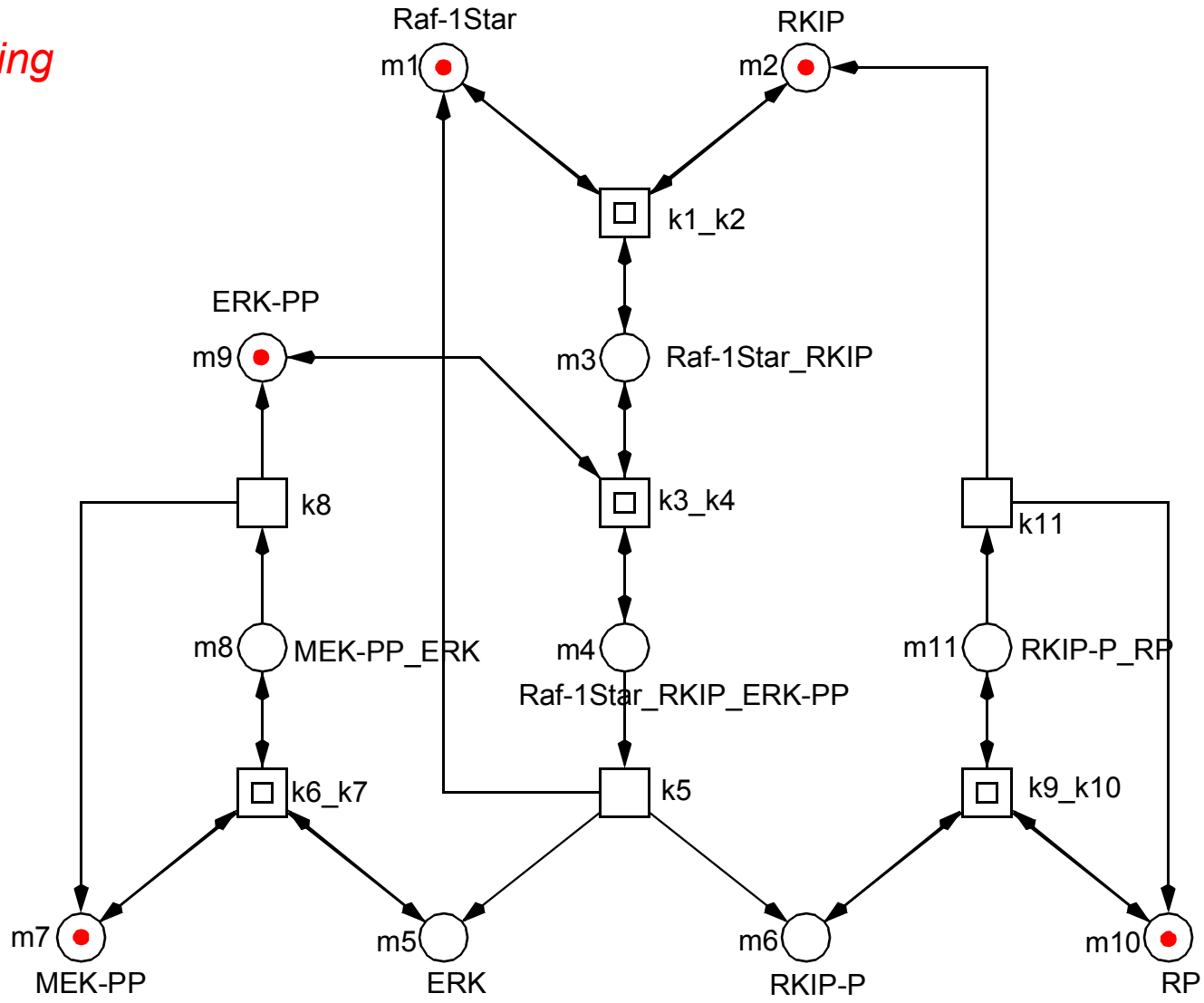


THE RKIP PATHWAY, HIERARCHICAL PETRI NET

initial marking



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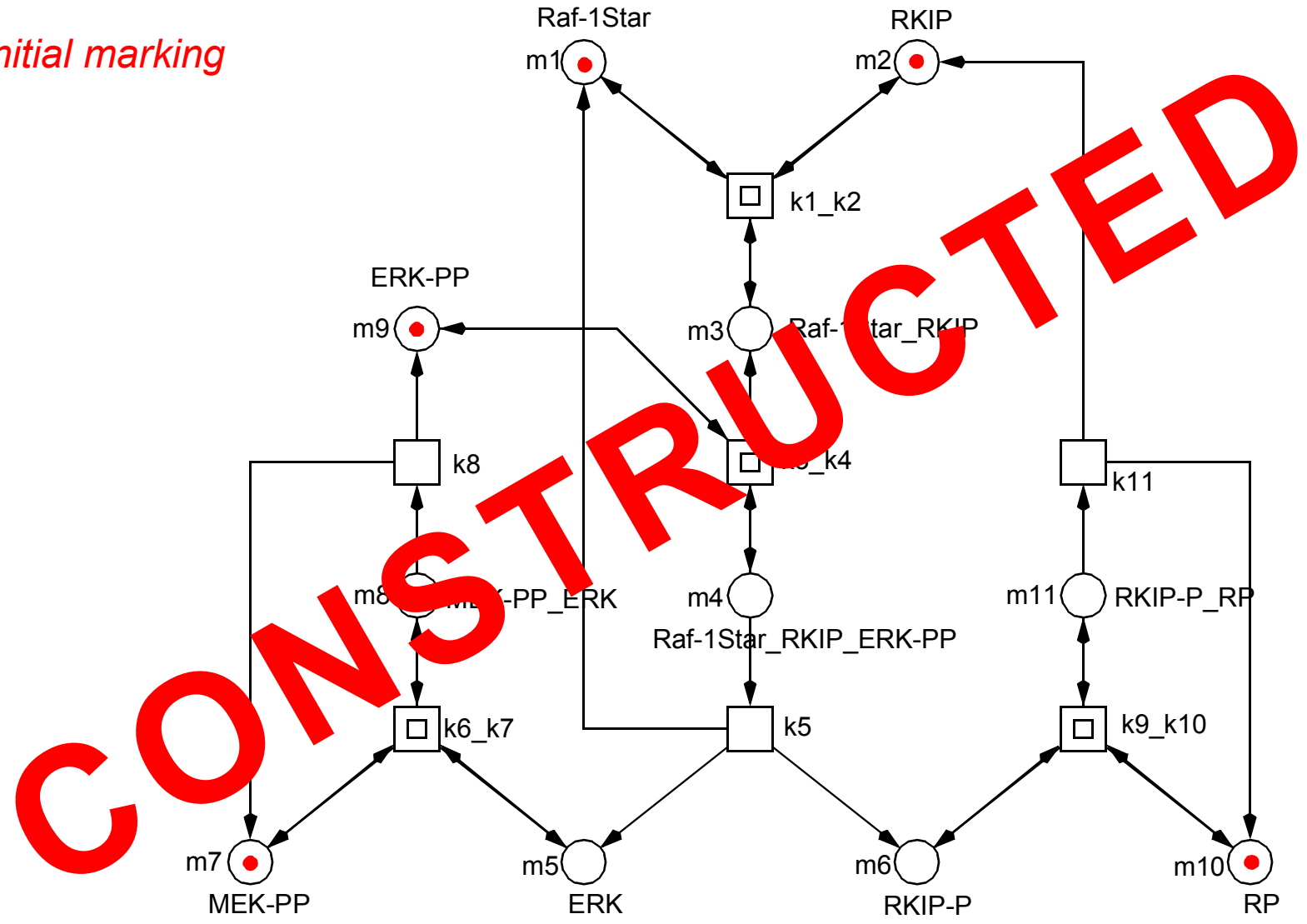

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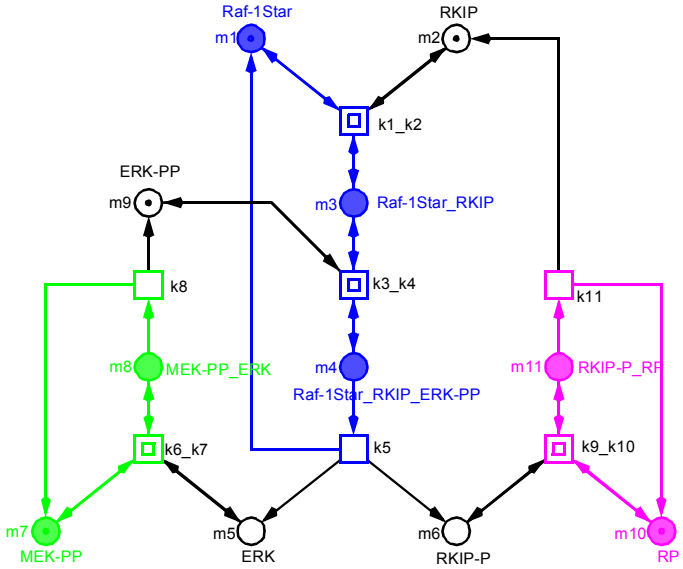
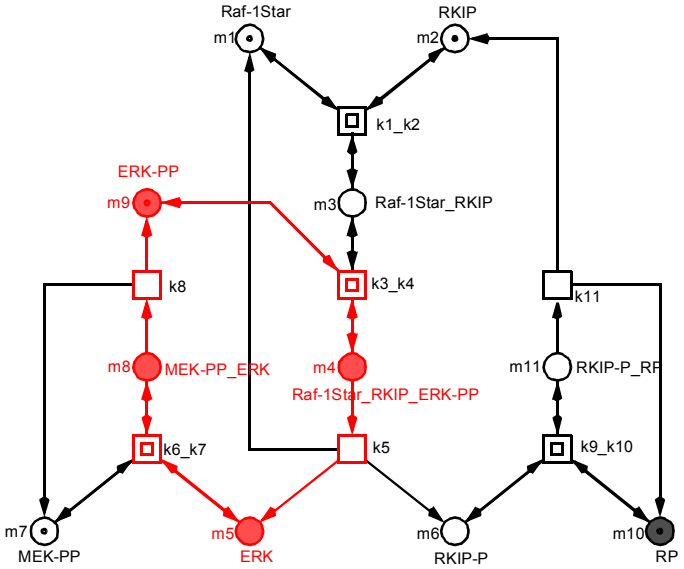
THE RKIP PATHWAY, P-INVARIANTS





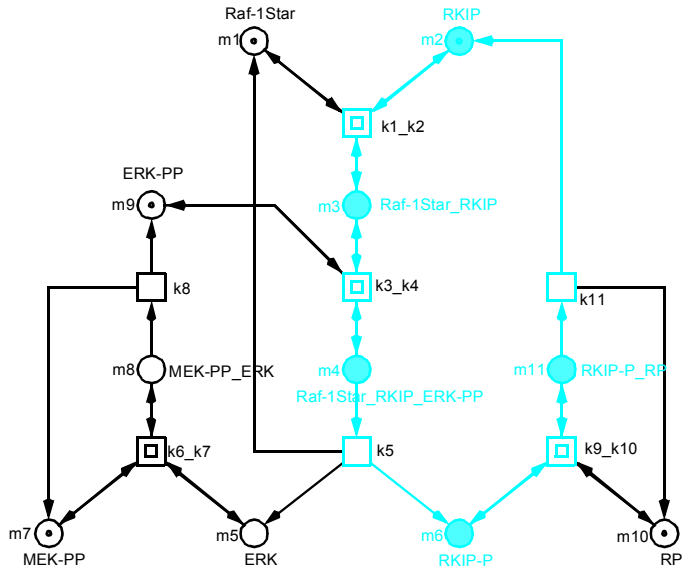
P-INV1: MEK

P-INV2: RAF-1STAR

P-INV3: RP

P-INV4: ERK

P-INV5: RKIP



CONSTRUCTION OF THE INITIAL MARKING

- **each P-invariant gets at least one token**
  -> *P-invariants are structural deadlocks and traps*

- **in signal transduction**
  -> *exactly 1 token, corresponding to species conservation*
  -> *token in least active state*

- **all (non-trivial) T-invariants get realizable**
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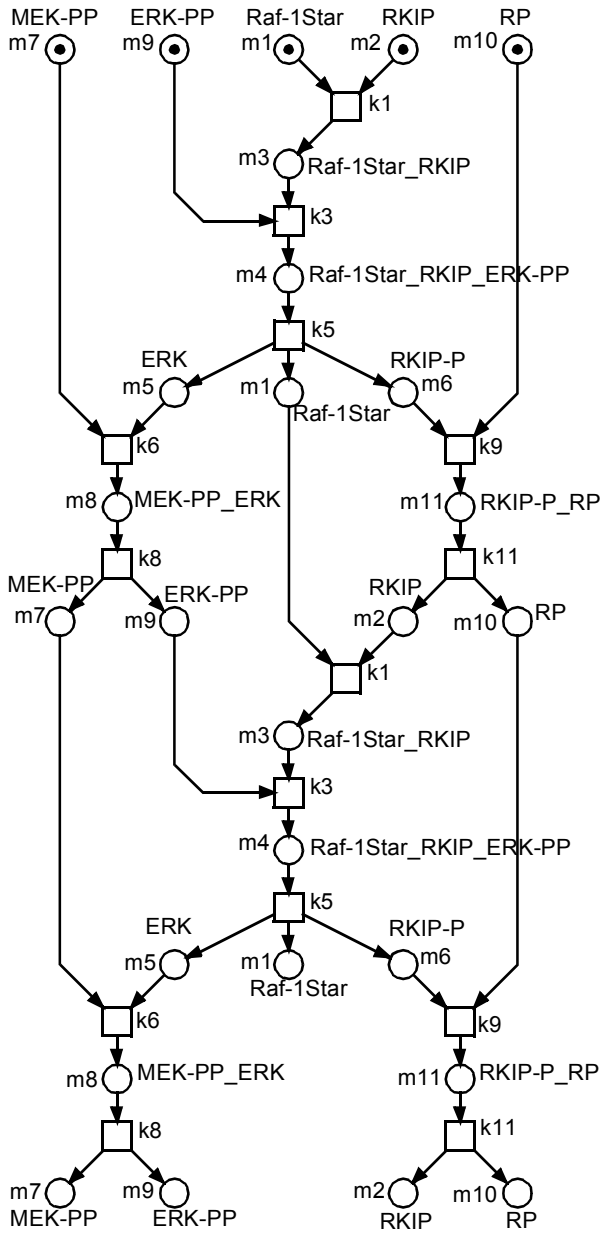
-> UNIQUE INITIAL MARKING <-

NON-TRIVIAL T-INVARIANT, RUN

- **realizability check under the constructed marking**
- **T-invariant's unfolding to describe its behaviour**
  - -> *partial order structure*
- **labelled condition / event net**
  - -> *events (boxes)*
    - transition occurences
  - -> *conditions (circles)*
    - involved compounds
- **occurrence net**
  - -> *acyclic*
  - -> *no backward branching conditions*
  - -> *infinite*



MODEL CHECKING, EXAMPLES

- **property 1**

  Is a given (sub-) marking (system state) reachable ?

  *EF (ERK * RP);*

- **property 2**

  Liveness of transition k8 ?

  AG EF (MEK-PP_ERK);

- **property 3**

  Is it possible to produce ERK-PP neither creating nor using MEK-PP ?

  E (! MEK-PP U ERK-PP);

- **property 4**

  Is there cyclic behaviour w.r.t. the presence / absence of RKIP ?

  *EG ((RKIP -> EF (! RKIP)) * (! RKIP -> EF (RKIP)));*

QUALITATIVE ANALYSIS RESULTS, SUMMARY

- **structural decisions of behavioural properties** **-> static analysis**
  - -> *CPI* -> *BND*
  - -> *ES & DTP* -> *LIVE*
- **CPI & CTI**
  - -> *all minimal T-invariant / P-invariants enjoy biological interpretation*
  - -> *non-trivial T-invariant -> partial order description of the essential behaviour*
- **reachability graph** **-> dynamic analysis**
  - -> *finite* -> *BND*
  - -> *the only SCC contains all transitions* -> *LIVE*
  - -> *one Strongly Connected Component (SCC)* -> *REV*
- **model checking** **-> requires professional understanding**
  - -> *all expected properties are valid*

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-> VALIDATED QUALITATIVE MODEL

- **validation criterion 1**
  - -> *all expected structural properties hold*
  - -> *all expected general behavioural properties hold*
- **validation criterion 2**
  - -> *CTI*
  - -> *no minimal T-invariant without biological interpretation*
  - -> *no known biological behaviour without corresponding T-invariant*
- **validation criterion 3**
  - -> *CPI*
  - -> *no minimal P-invariant without biological interpretation (?)*
- **validation criterion 4**
  - -> *all expected special behavioural properties hold*
  - -> *temporal-logic properties -> TRUE*

NOW WE ARE READY FOR SOPHISTICATED QUANTITATIVE ANALYSES !

STOCHASTIC PETRI NETS
- SPN *(XSPN)* -

STOCHASTIC PETRI NETS, BASICS

- **transitions get a stochastic waiting time**
  - -> *exponential distribution with parameter lambda*
- **state-dependent lambda defined by rate function**
  - -> *any arithmetic function including*
    the transition's pre-places as integer variables and
    user-defined real-valued parameters
  - -> *modifier arcs*
  - -> *popular kinetics:*
    mass-action semantics, level semantics
- **semantics: Continuous Time Markov Chain (CTMC)**
  - -> *reachability graph + state transition rates*
- **analysis**
  - -> *standard Markov analysis techniques: transient, steady state*
  - -> *stochastic simulation algorithms (SSA), e.g. Gillespie's SSA*

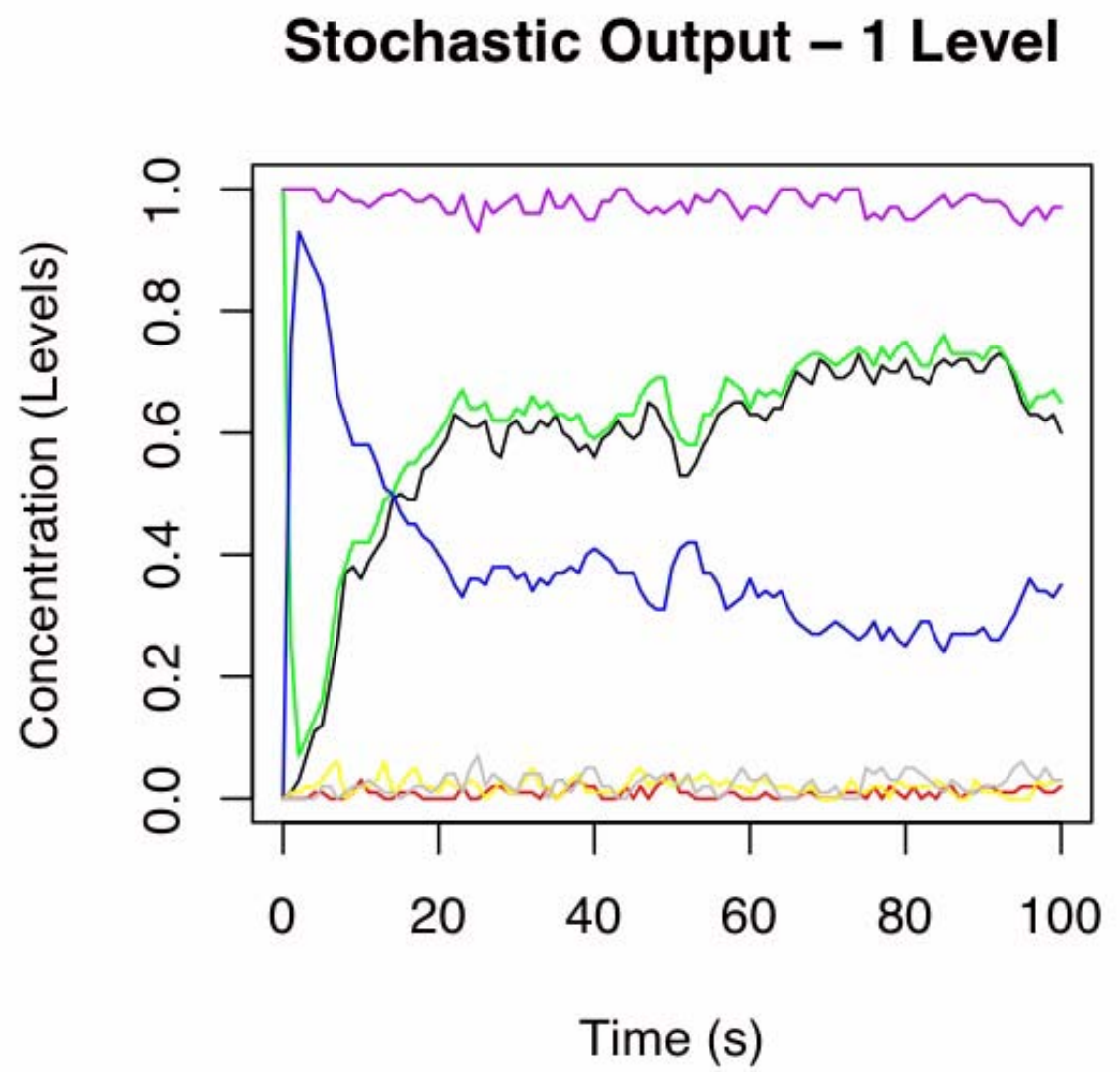
RATE FUNCTIONS

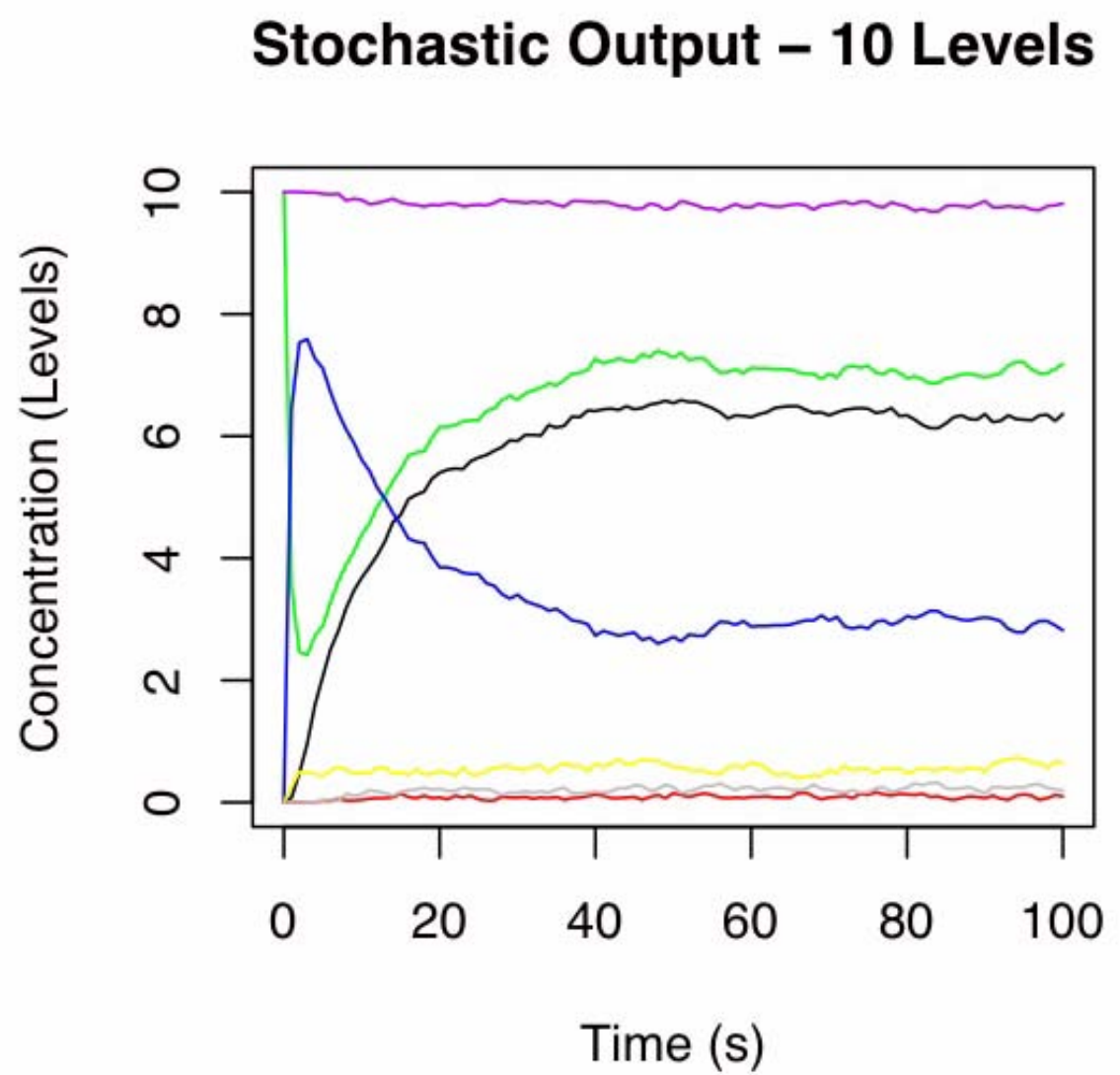
- *molecules semantics*

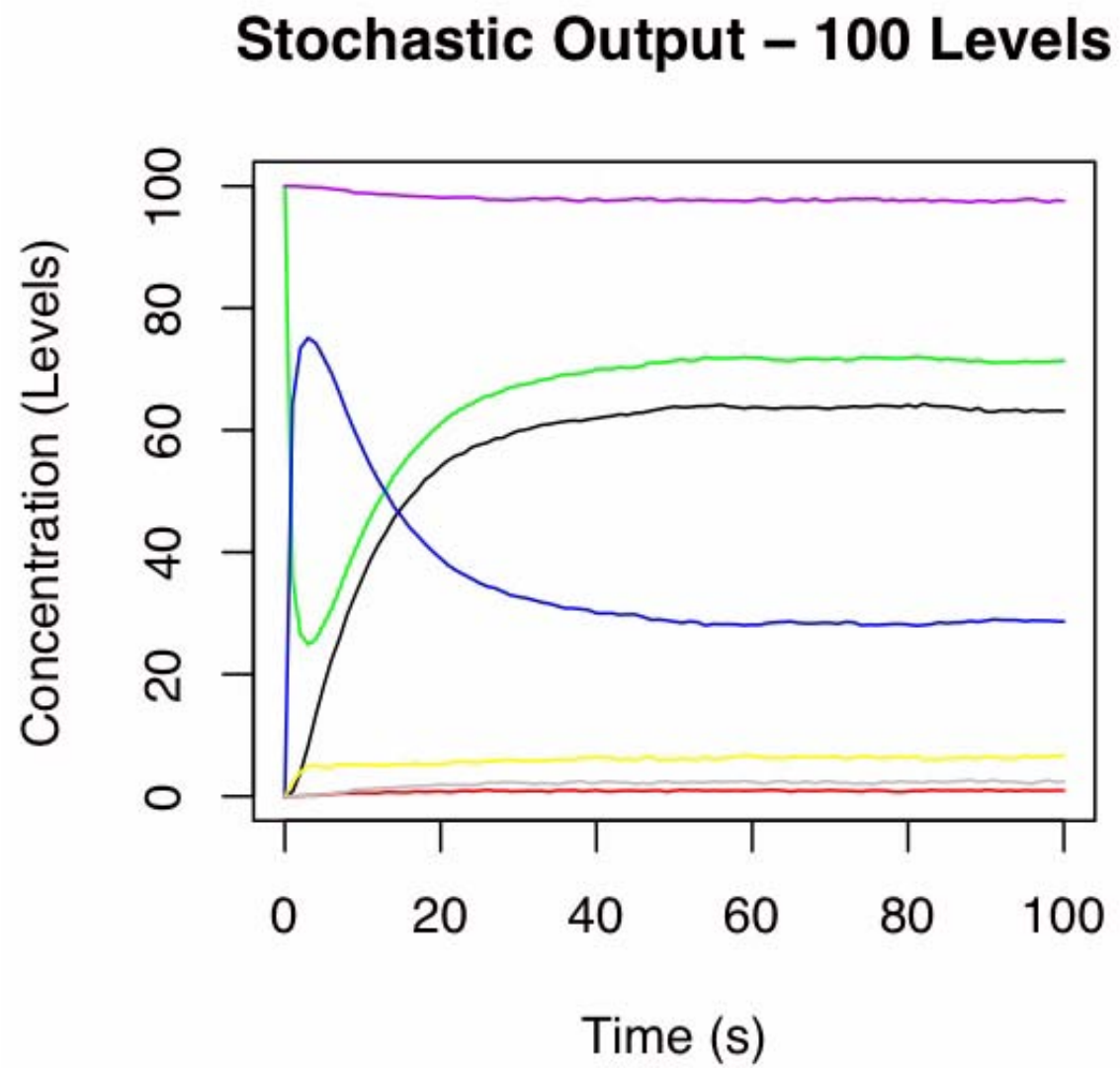
$$h_t := c_t \cdot \prod_{p \in {}^\bullet t} \binom{m(p)}{f(p,t)}$$

- *concentration levels semantics*

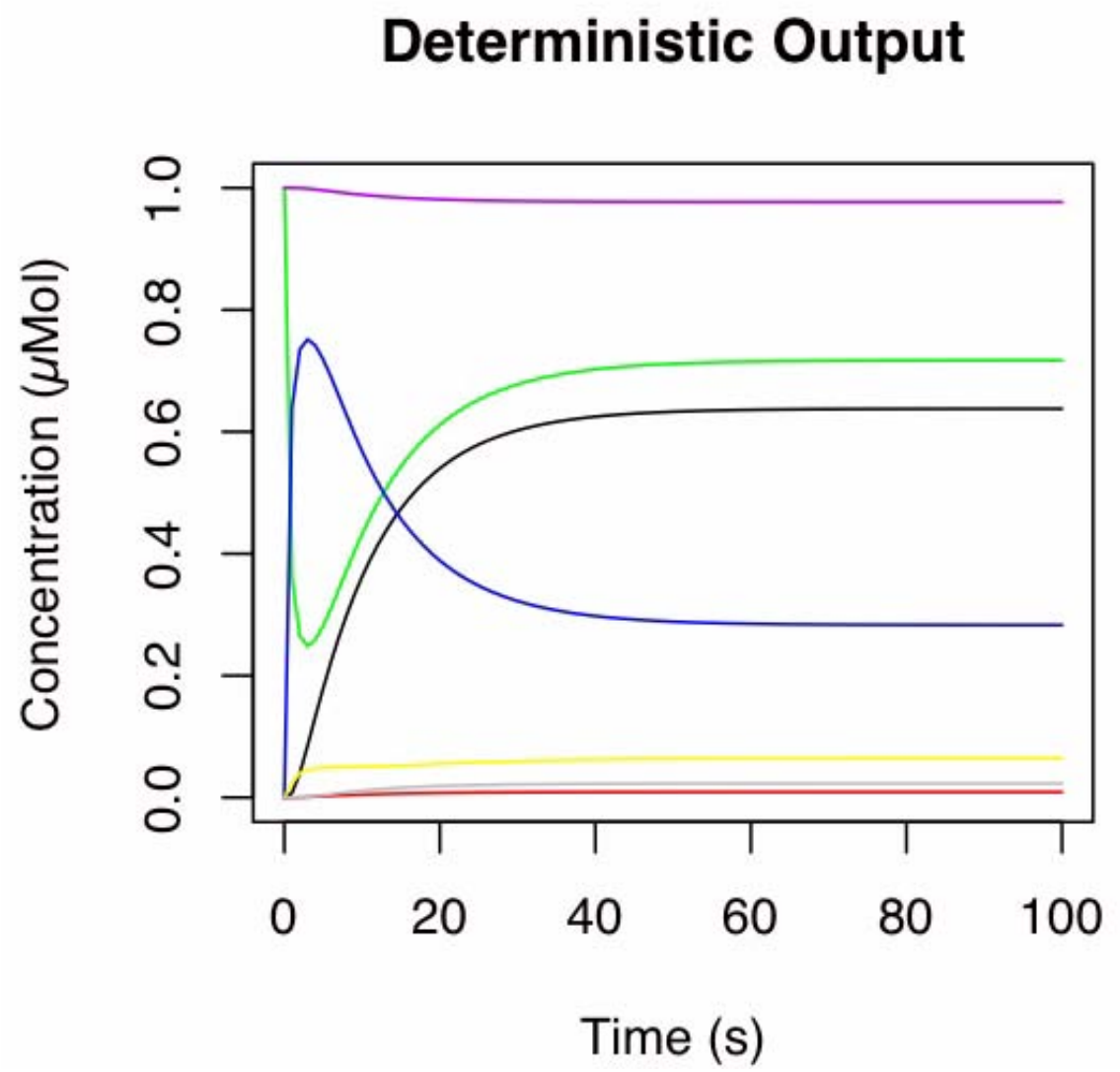
$$h_t := k_t \cdot N \cdot \prod_{p \in {}^\bullet t} \left(\frac{m(p)}{N}\right)$$


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

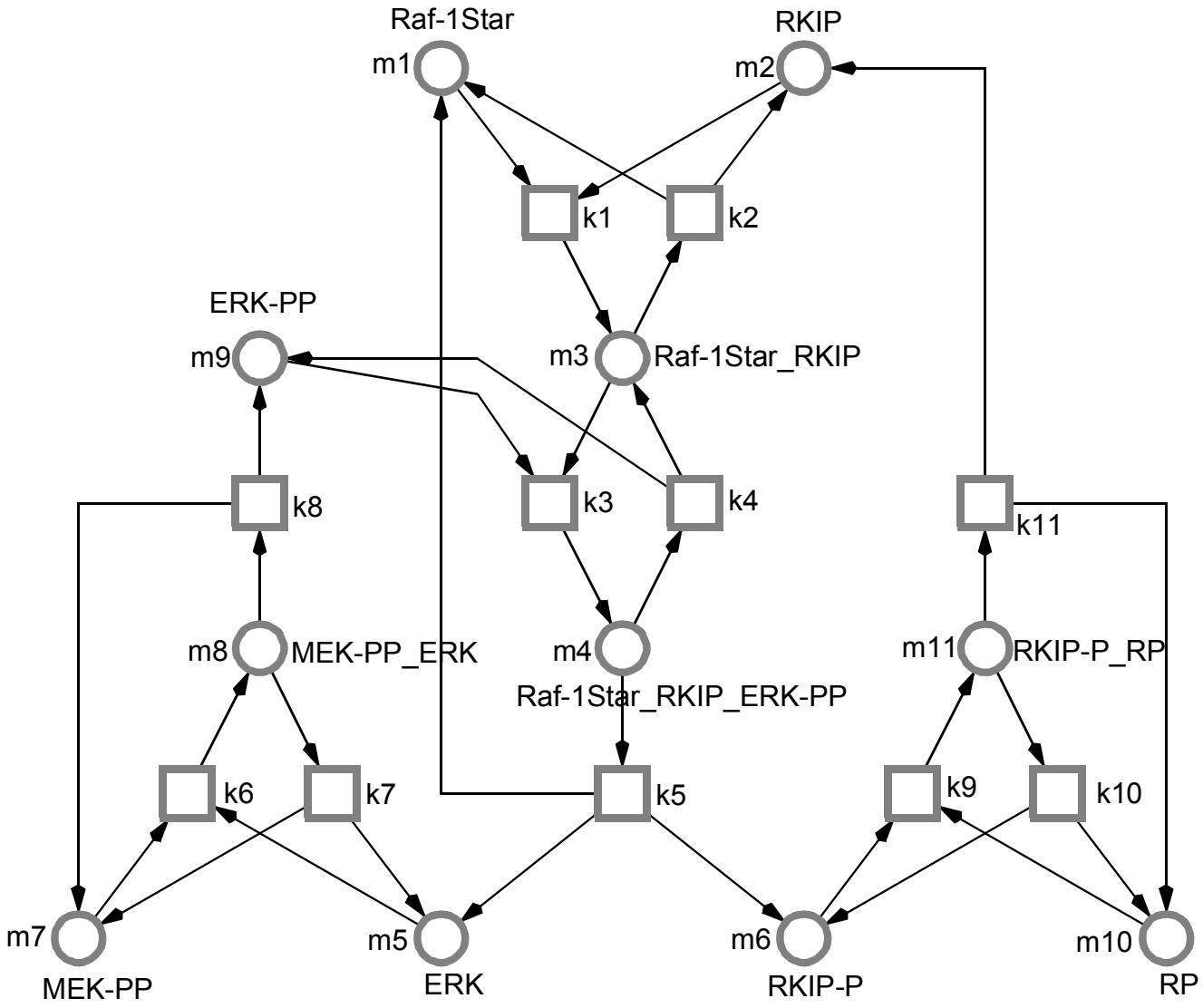


CONTINUOUS PETRI NETS - CPN -

CONTINUOUS PETRI NETS, BASICS

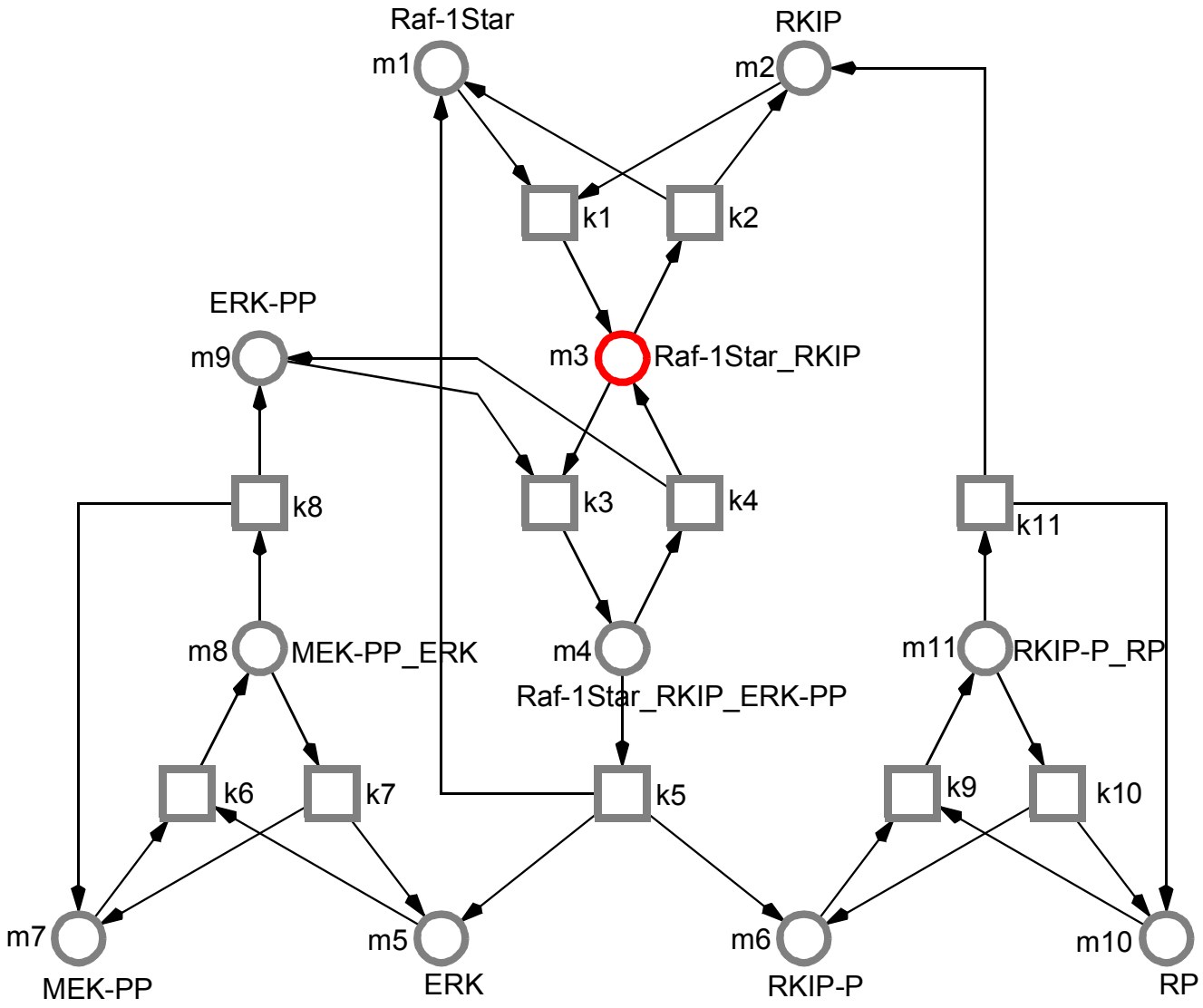
- **transitions fire continuously**
- **rate functions**
  - -> *any arithmetic function including the transition's pre-places as real-valued variables and user-defined real-valued parameters*
- **real-valued tokens**
  - -> *concentrations*
- **semantics: set of Ordinary Differential Equations (ODEs)**
  - -> *uniquely defined, but not vice versa*
  - -> *typically non-linear*
- **simulation (numerical integration)**
  - -> *stiff/unstiff solvers*

CONTINUOUS PETRI NET DEFINES ODES



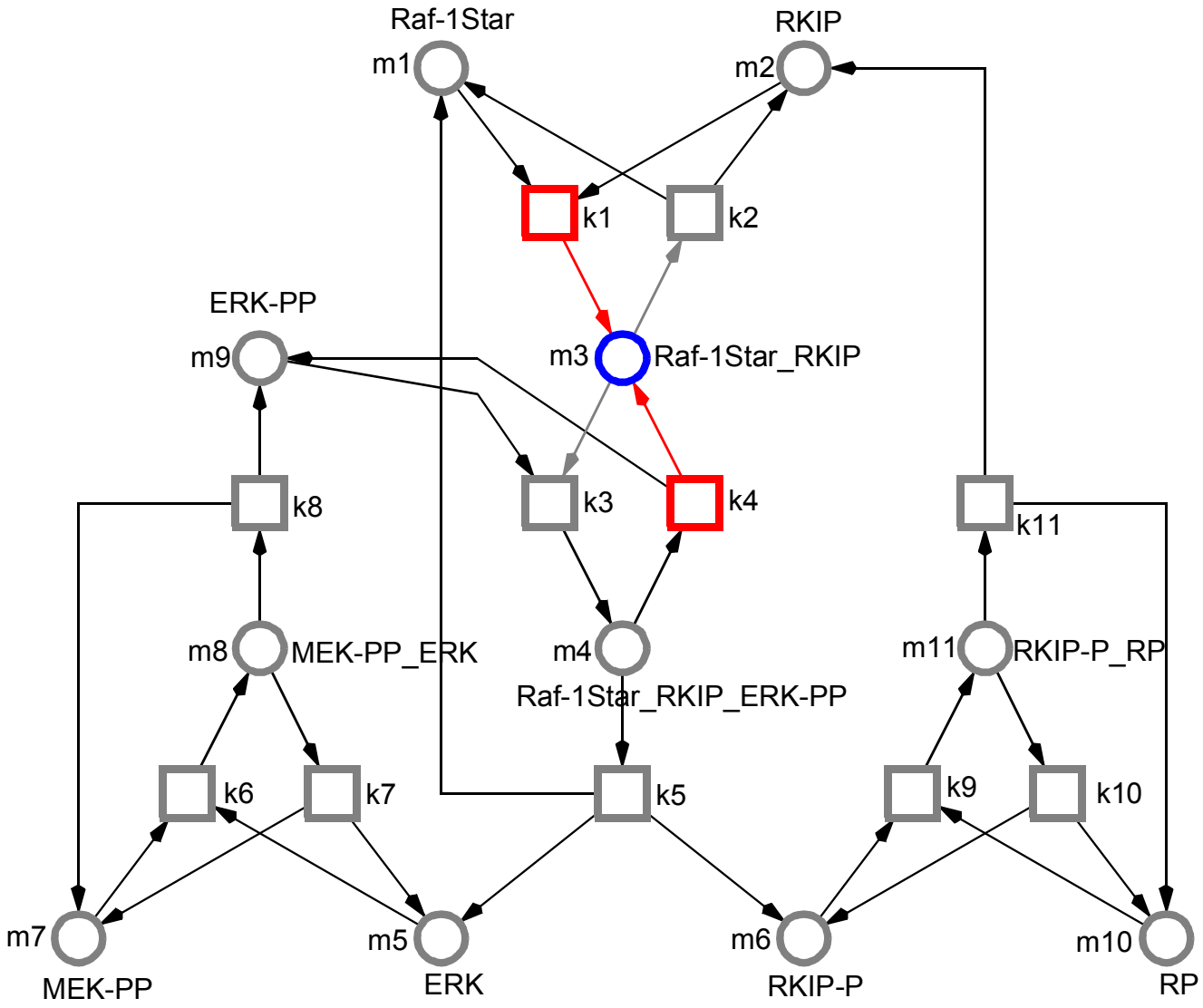
CONTINUOUS PETRI NET DEFINES ODES

$$\frac{dm3}{dt} =$$



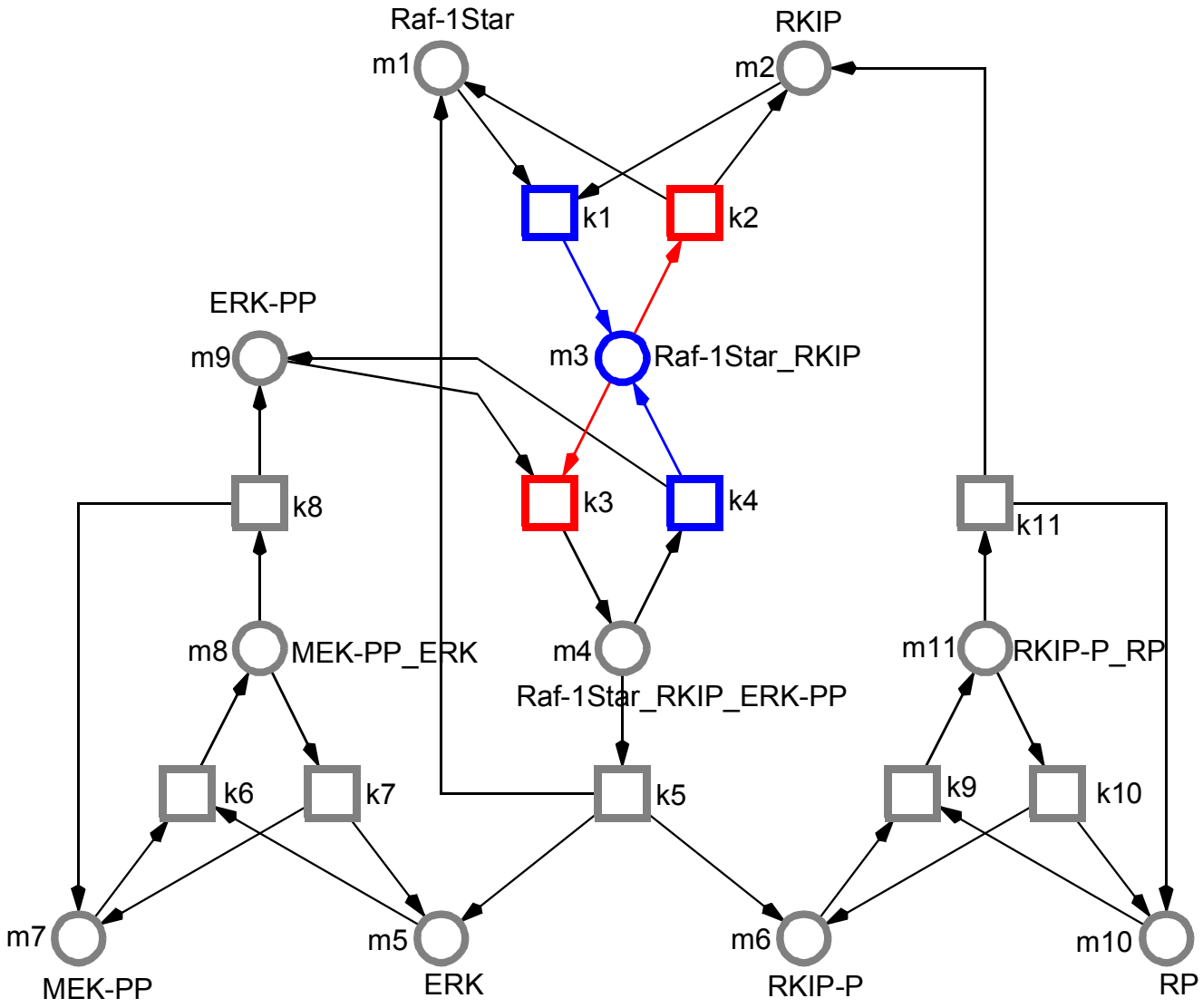
CONTINUOUS PETRI NET DEFINES ODES

$$\frac{dm3}{dt} = + r1 + r4$$



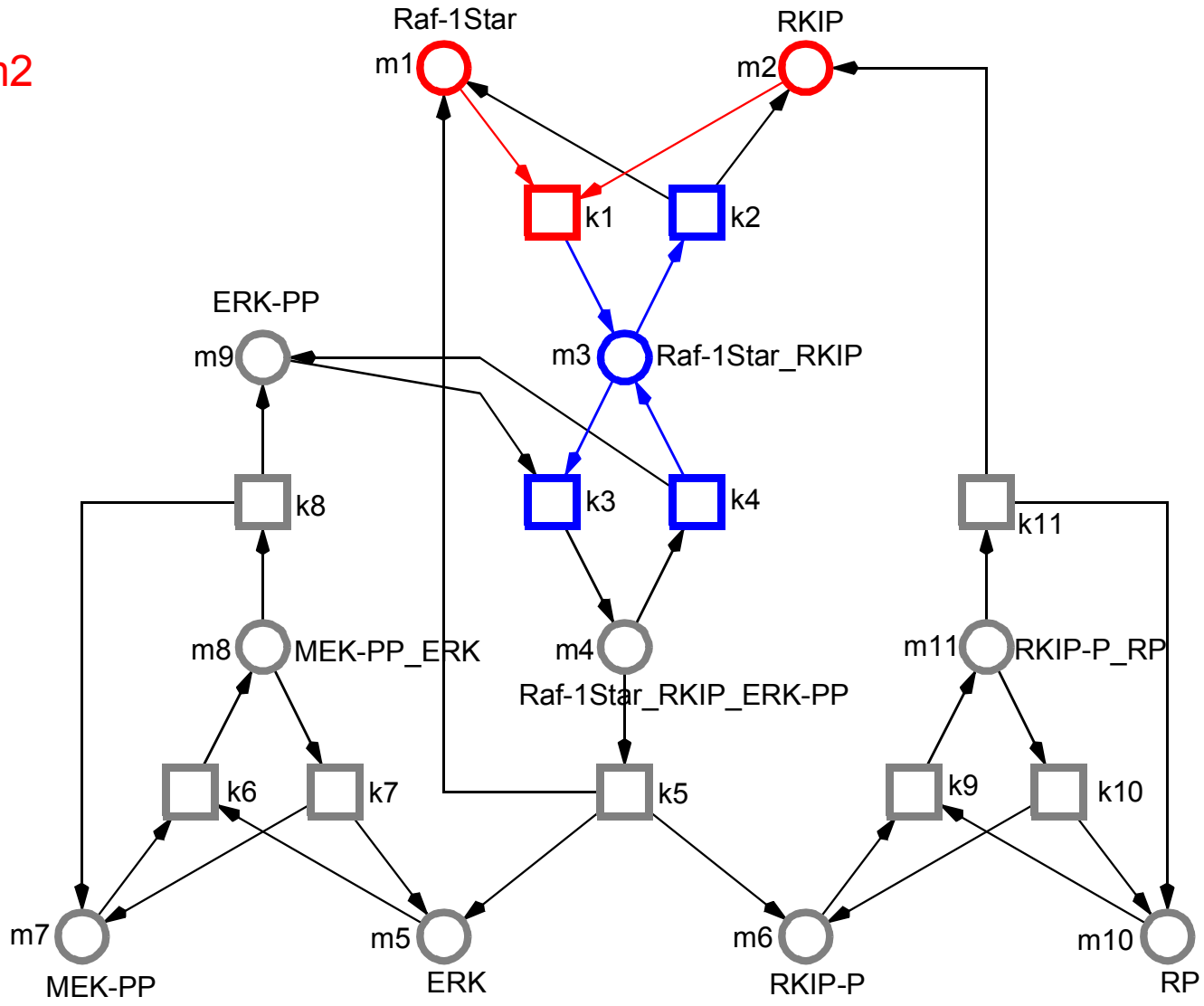
CONTINUOUS PETRI NET DEFINES ODES

$$\frac{dm3}{dt} = + r1 + r4 - r2 - r3$$



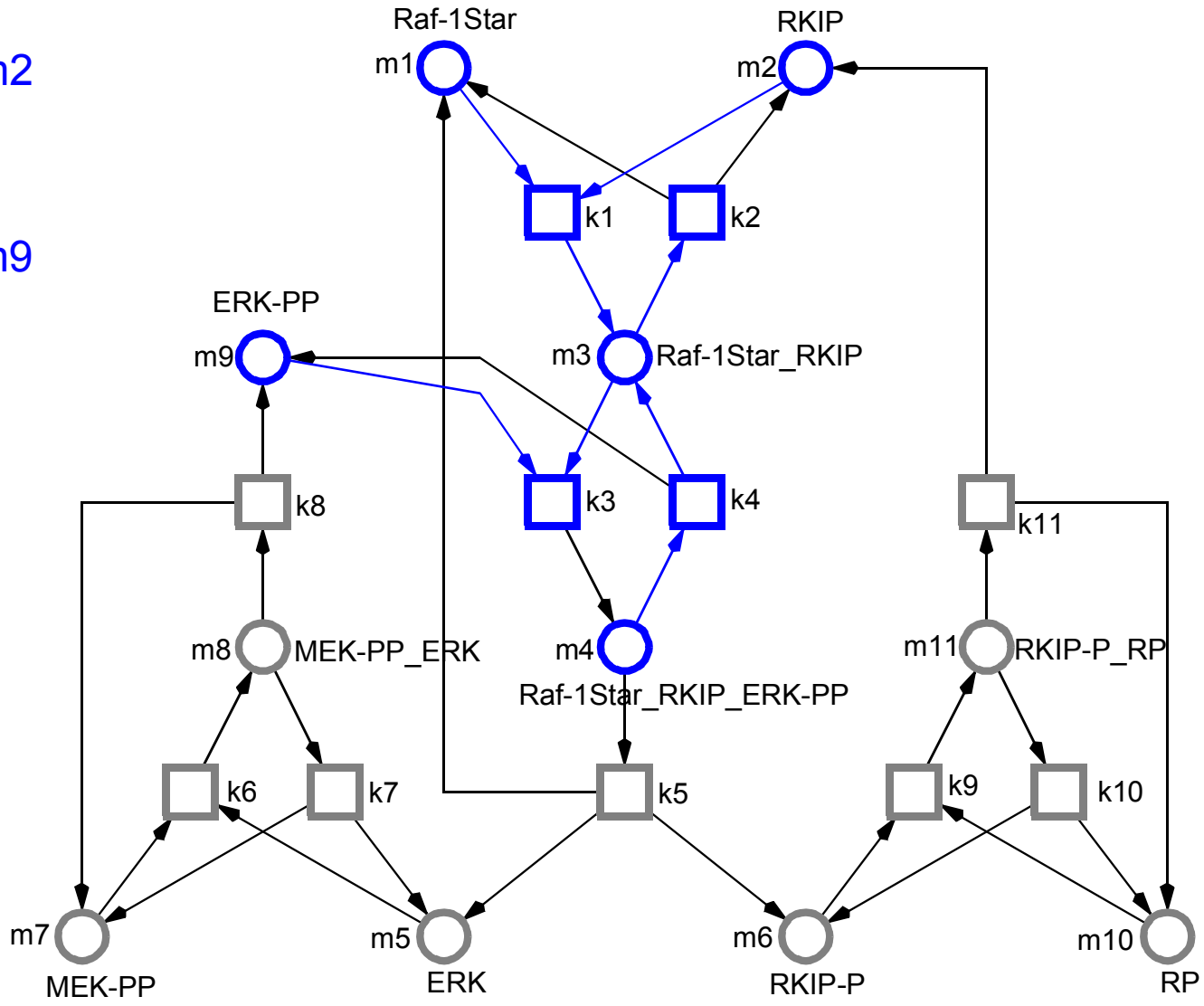
CONTINUOUS PETRI NET DEFINES ODES

$$\frac{dm3}{dt} = + k1 * m1 * m2 + r4 - r2 - r3$$



CONTINUOUS PETRI NET DEFINES ODES

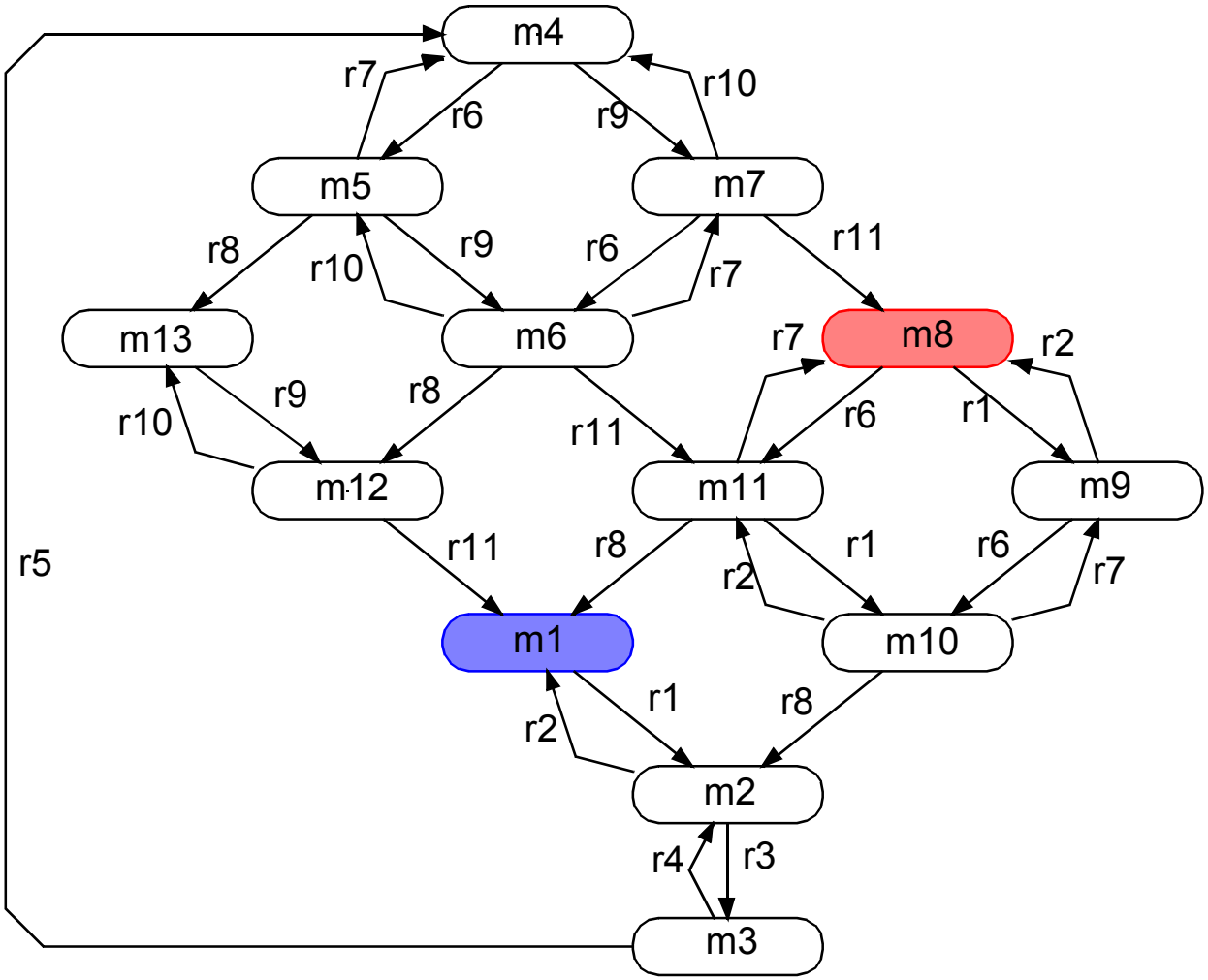
$$\frac{dm3}{dt} = + k1 * m1 * m2 + k4 * m4 - k2 * m3 - k3 * m3 * m9$$



THE QUALITATIVE MODEL BECOMES THE STRUCTURED DESCRIPTION OF THE QUANTITATIVE MODEL !

REACHABILITY GRAPH CONSTRUCTION

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

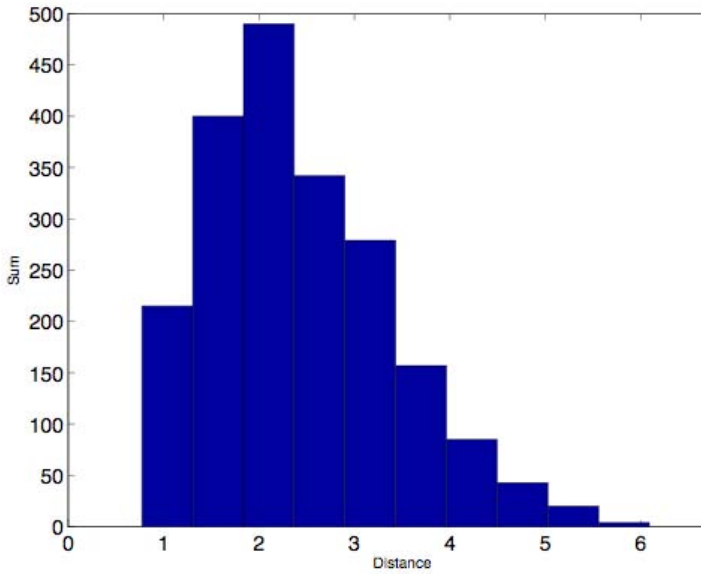


QUANTITATIVE ANALYSIS

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

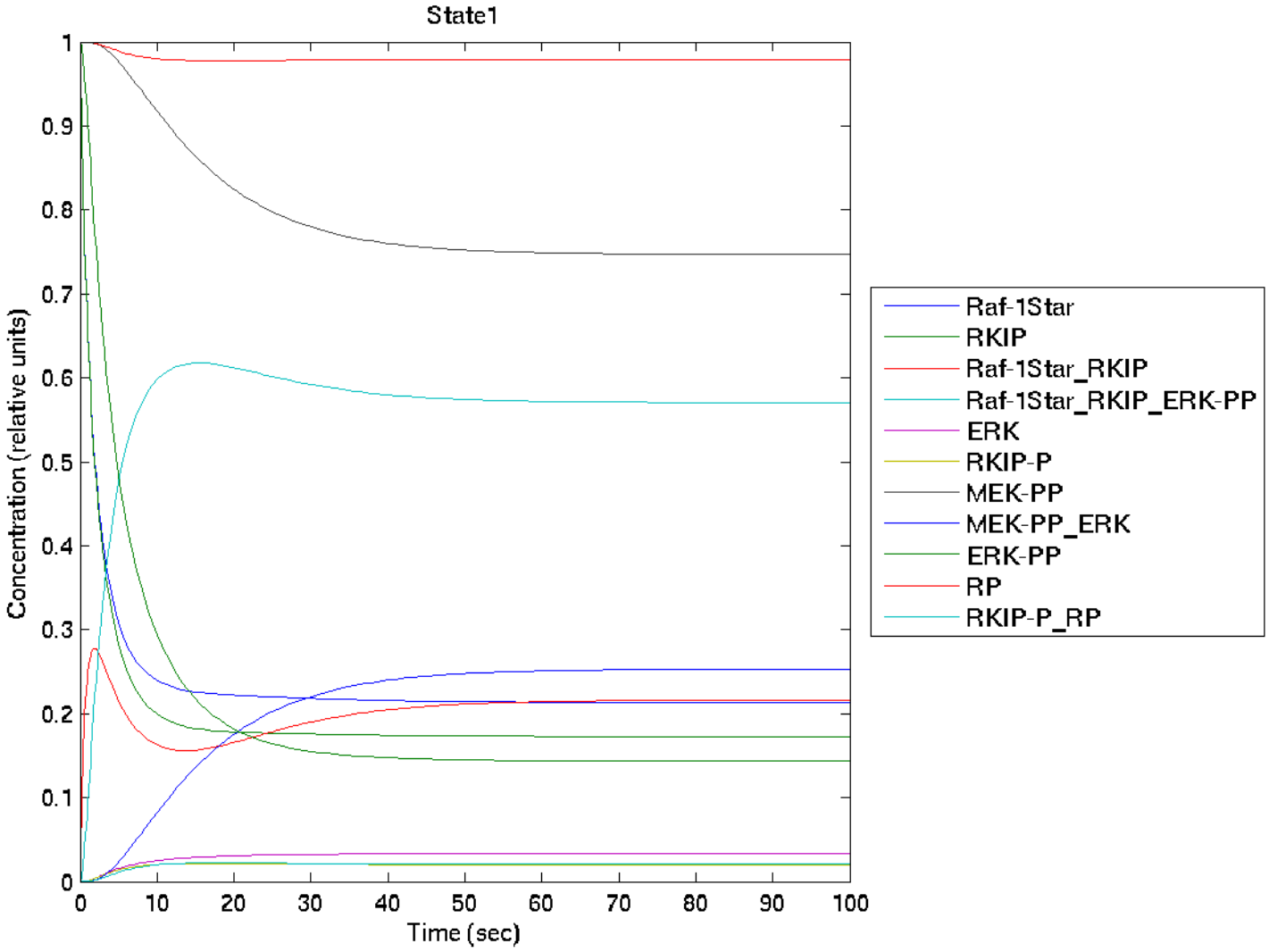


Distribution of `bad' steady states as euclidean distances from the `good' final steady state

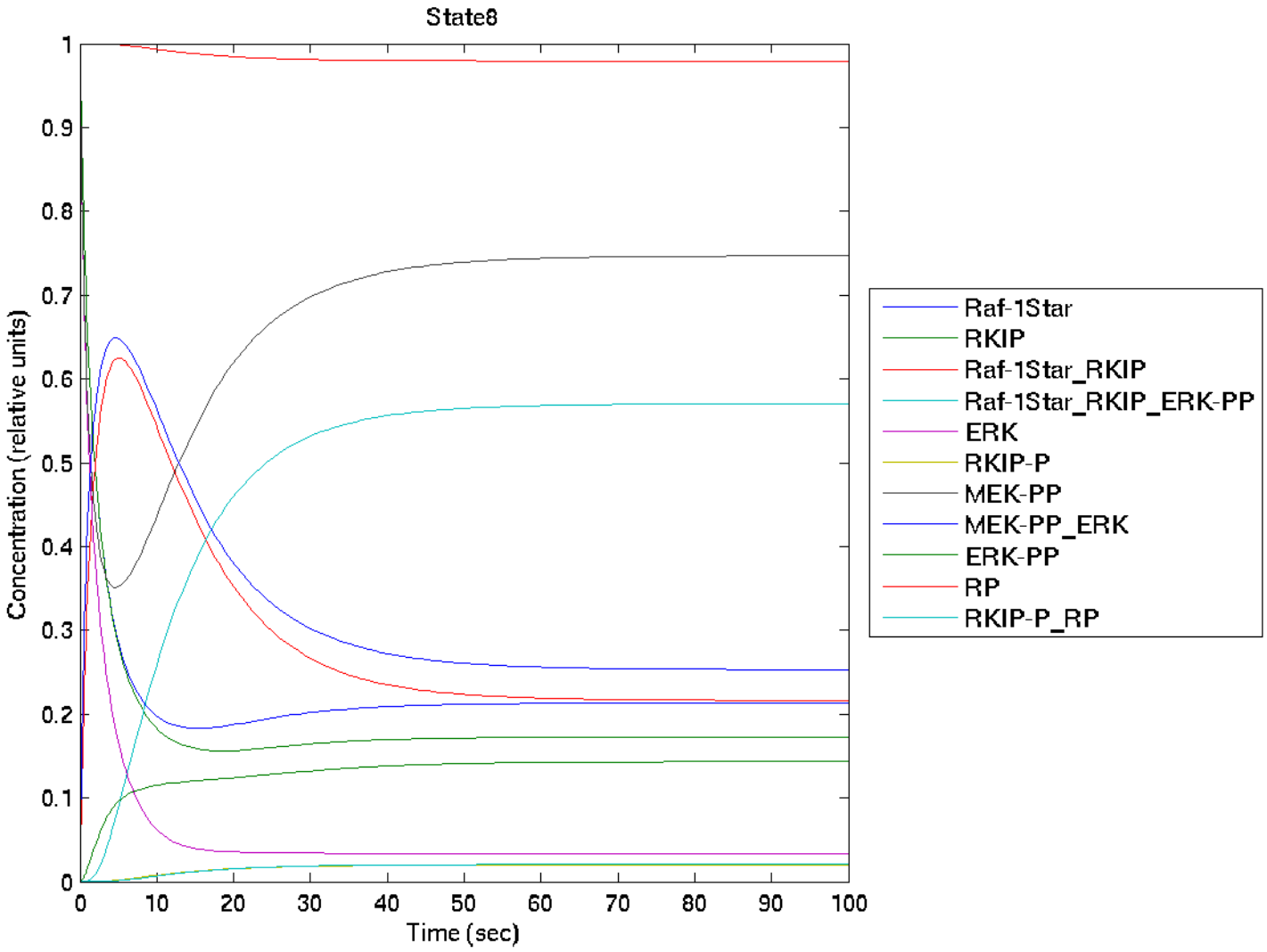
13 “good” state configurations

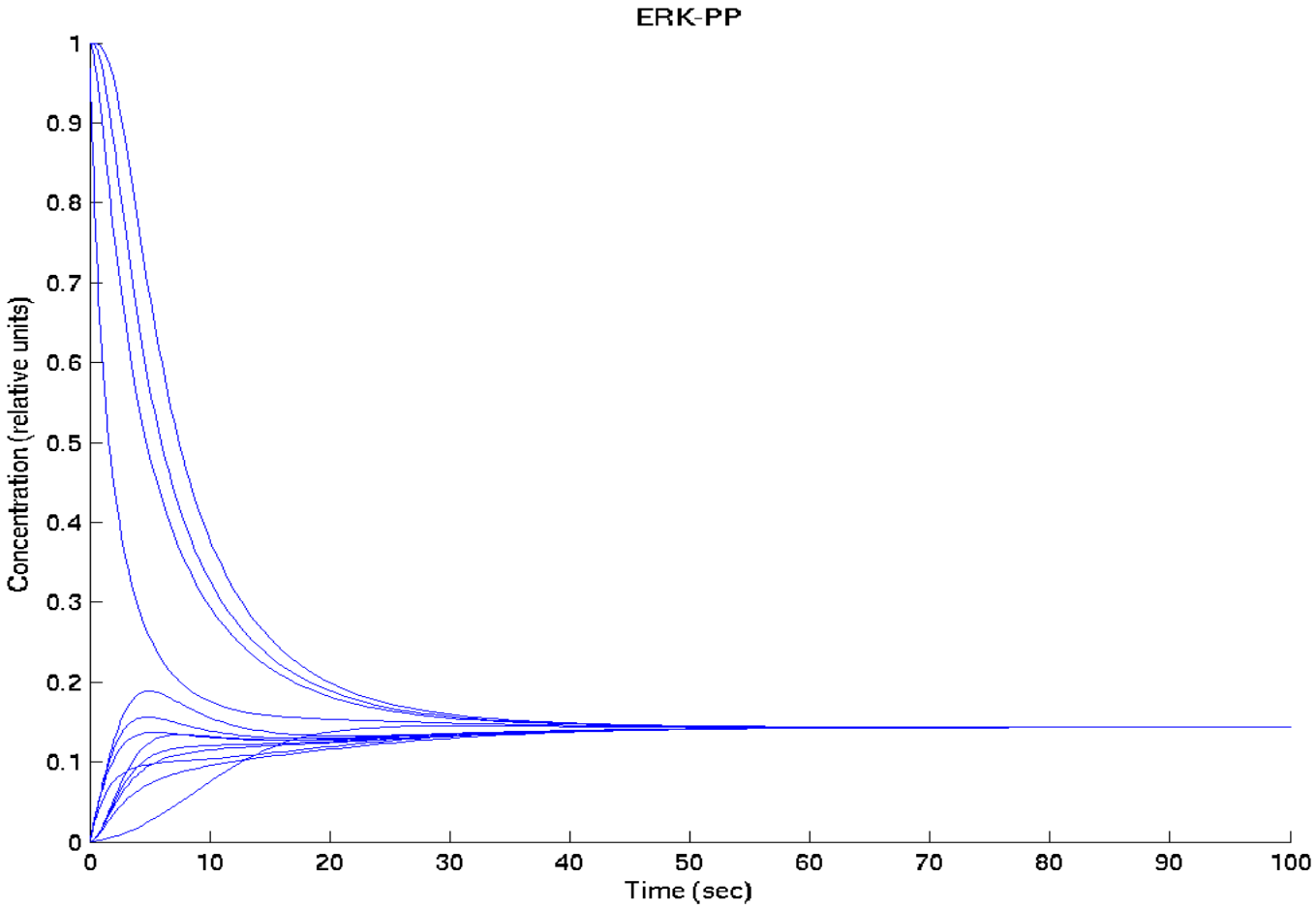
the “bad” ones

QUANTITATIVE ANALYSIS



QUANTITATIVE ANALYSIS




ERK-PP
Concentration (relative units)
Time (sec)
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
10
20
30
40
50
60
70
80
90
100

SUMMARY

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

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

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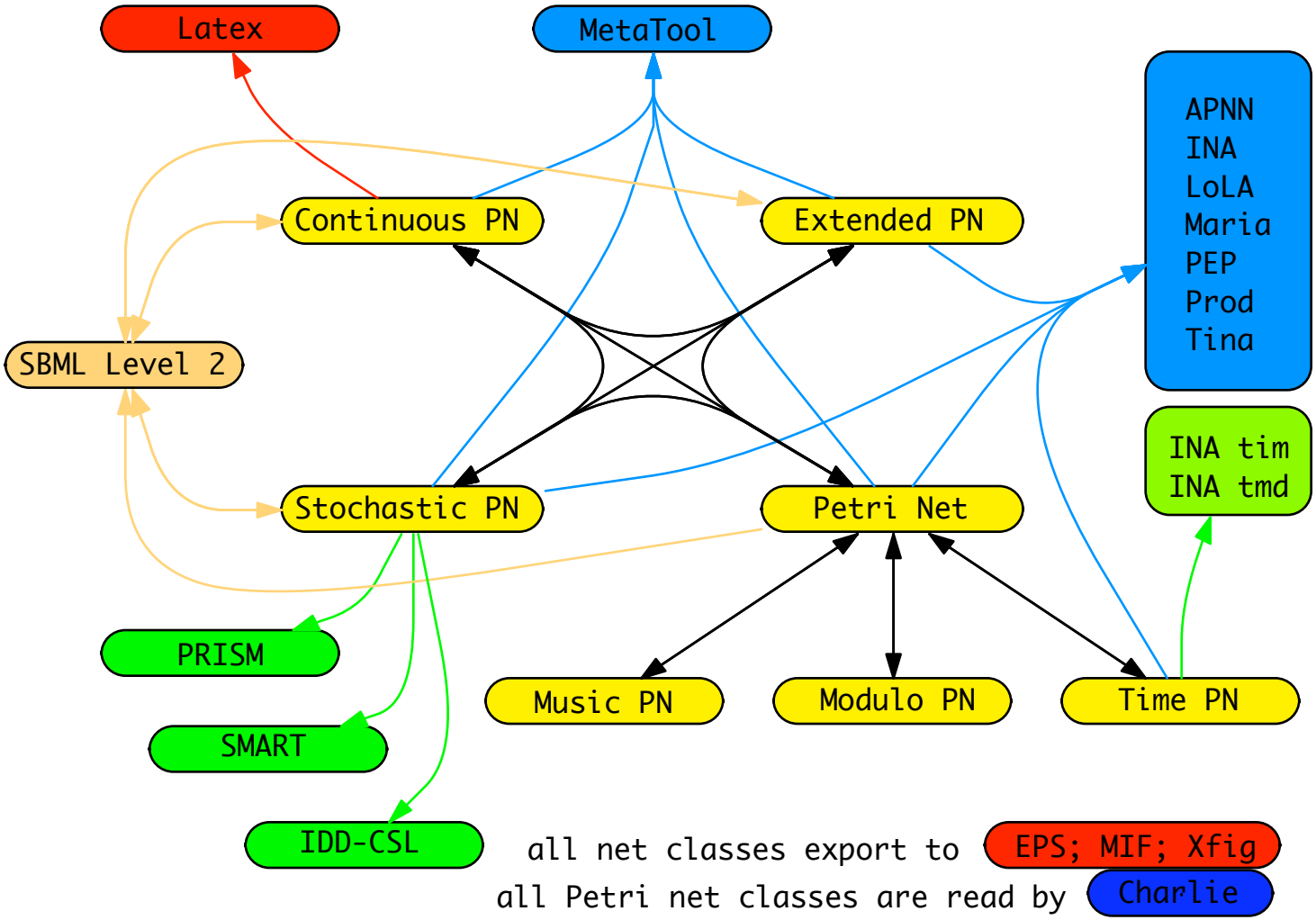
  - -> *qualitative / quantitative behaviour prediction* -> *experiment design, new insights*
- **step-wise model development**
  - -> *qualitative model* -> *discrete Petri nets*
  - -> *discrete quantitative model* -> *stochastic Petri nets*
  - -> *continuous quantitative model* -> *continuous Petri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

TOOLKIT - SNOOPY'S EXPORT FEATURES



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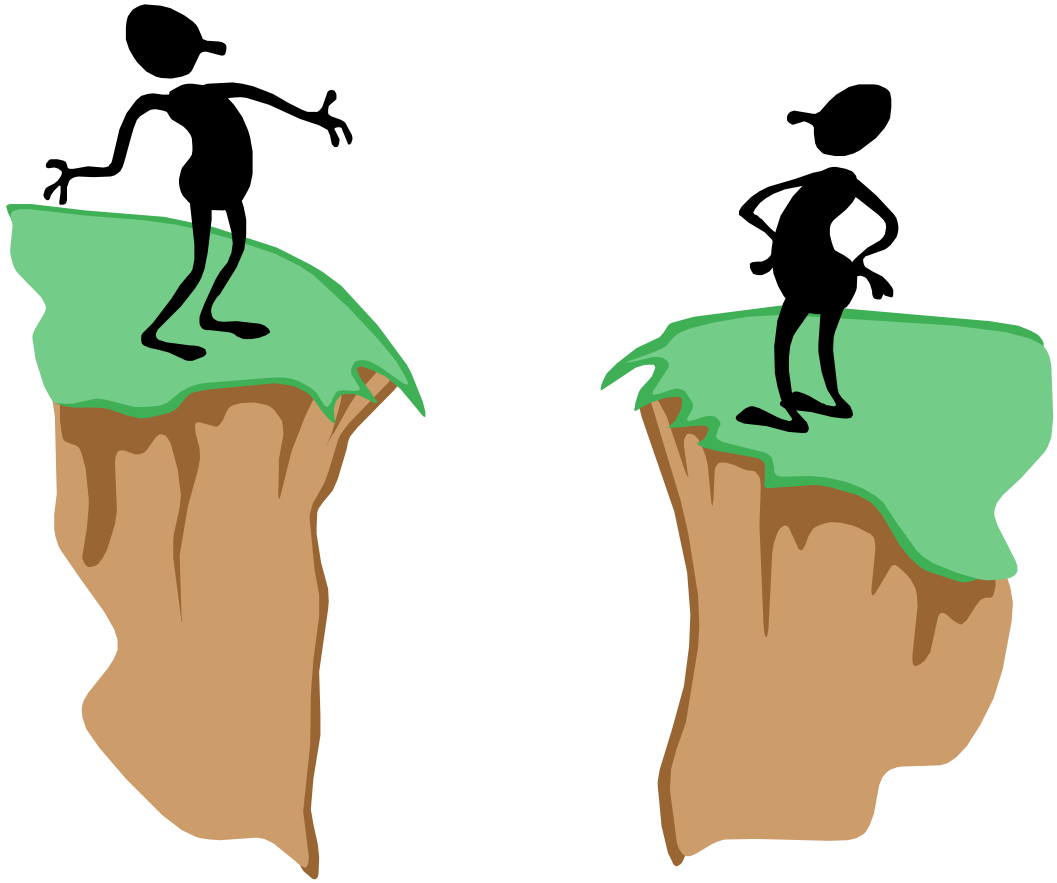
OUTLOOK



THANKS !

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