BIOMODEL ENGINEERING
- A PETRI NET PERSPECTIVE -

Monika Heiner

on sabbatical leave from

Brandenburg University of Technology Cottbus

Dept. of CS

OUTLINE

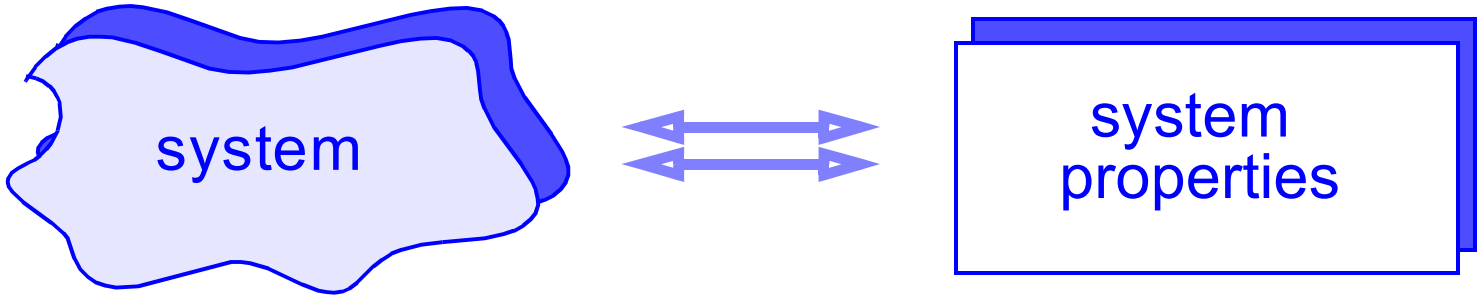
- **BACKGROUND**
  - -> *Petri Nets - a crash course*
  - -> *some case studies*
- **BIOMODEL ENGINEERING**
  - -> *a unifying framework: QPN - SPN - CPN*
  - -> *relation SPN - CPN ?*
- **OUR TOOL BOX**
  - -> *Snoopy*
  - -> *Charlie*
  - -> *Marcie*
- **LATEST NEWS**
  - -> *colored framework*
  - -> *Generalized Hybrid Petri Nets*

OUTLINE

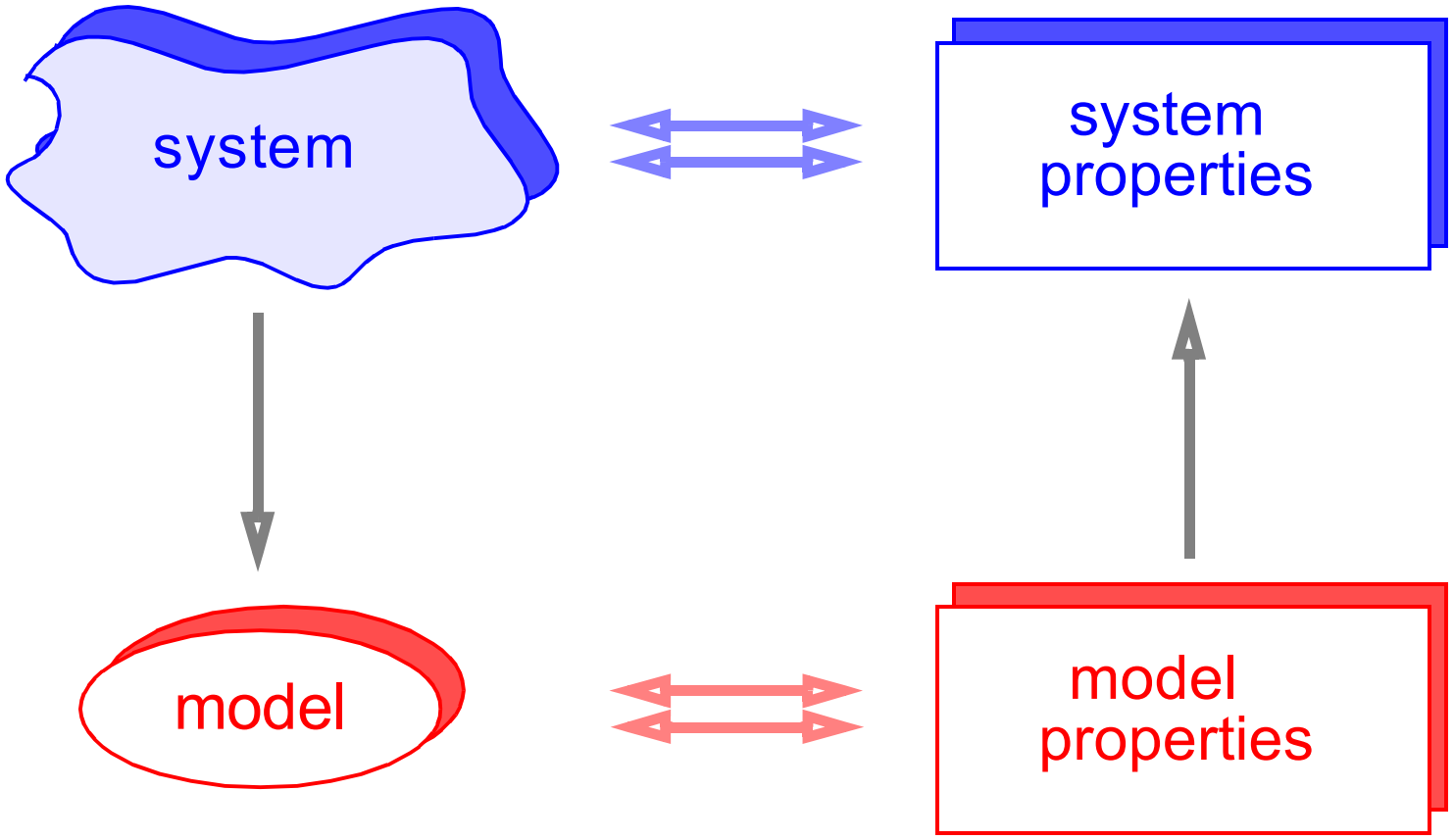
- **BACKGROUND**
  - -> *Petri Nets - a crash course*
  - -> *some case studies*
- **BIOMODEL ENGINEERING**
  - -> *a unifying framework: QPN - SPN - CPN*
  - -> *relation SPN - CPN ?*
- **OUR TOOL BOX**
  - -> *Snoopy*
  - -> *Charlie*
  - -> *Marcie*
- **LATEST NEWS**
  - -> *colored framework*
  - -> *Generalized Hybrid Petri Nets*

-> MANY BUZZWORDS <-

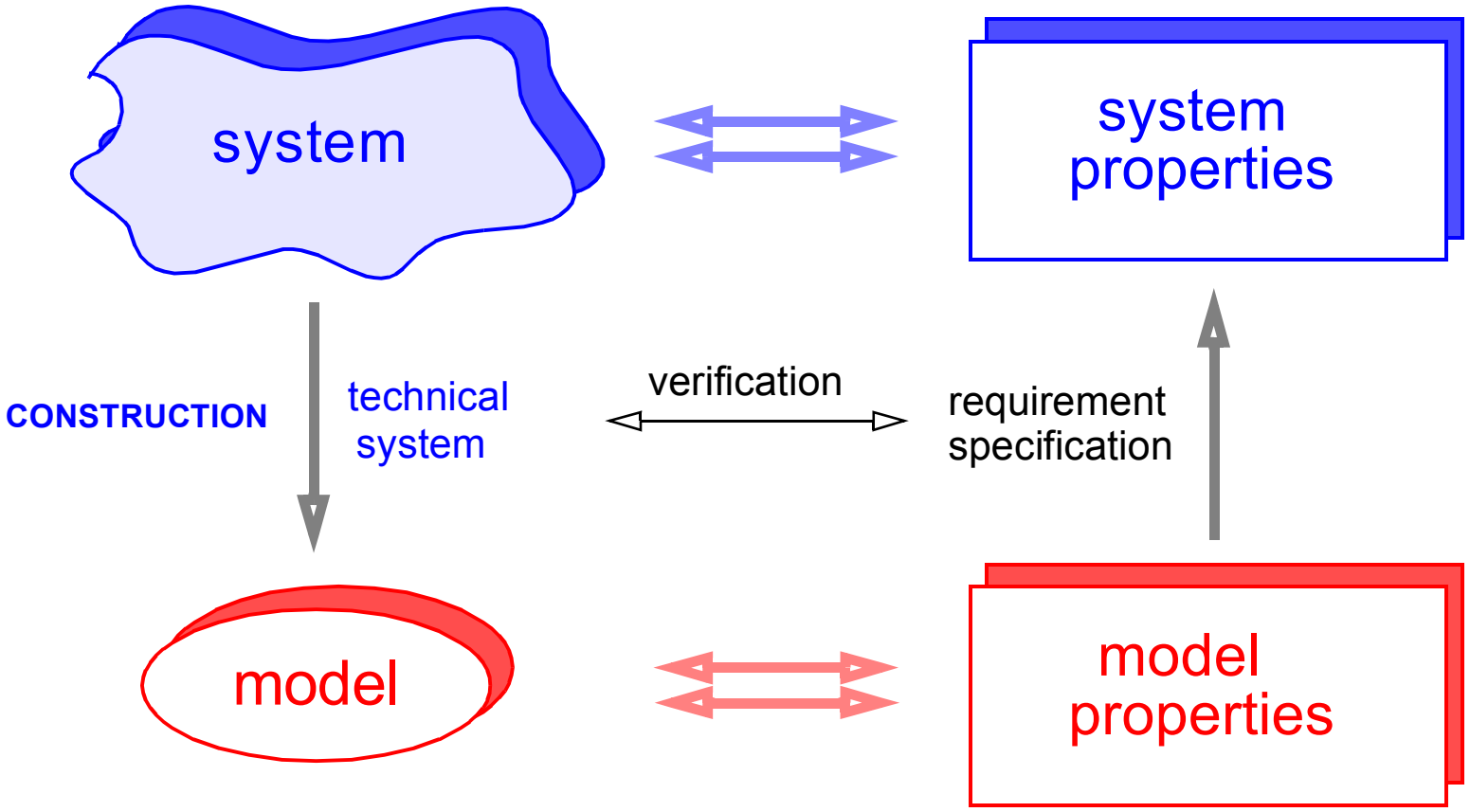
BACKGROUND


system
system
properties

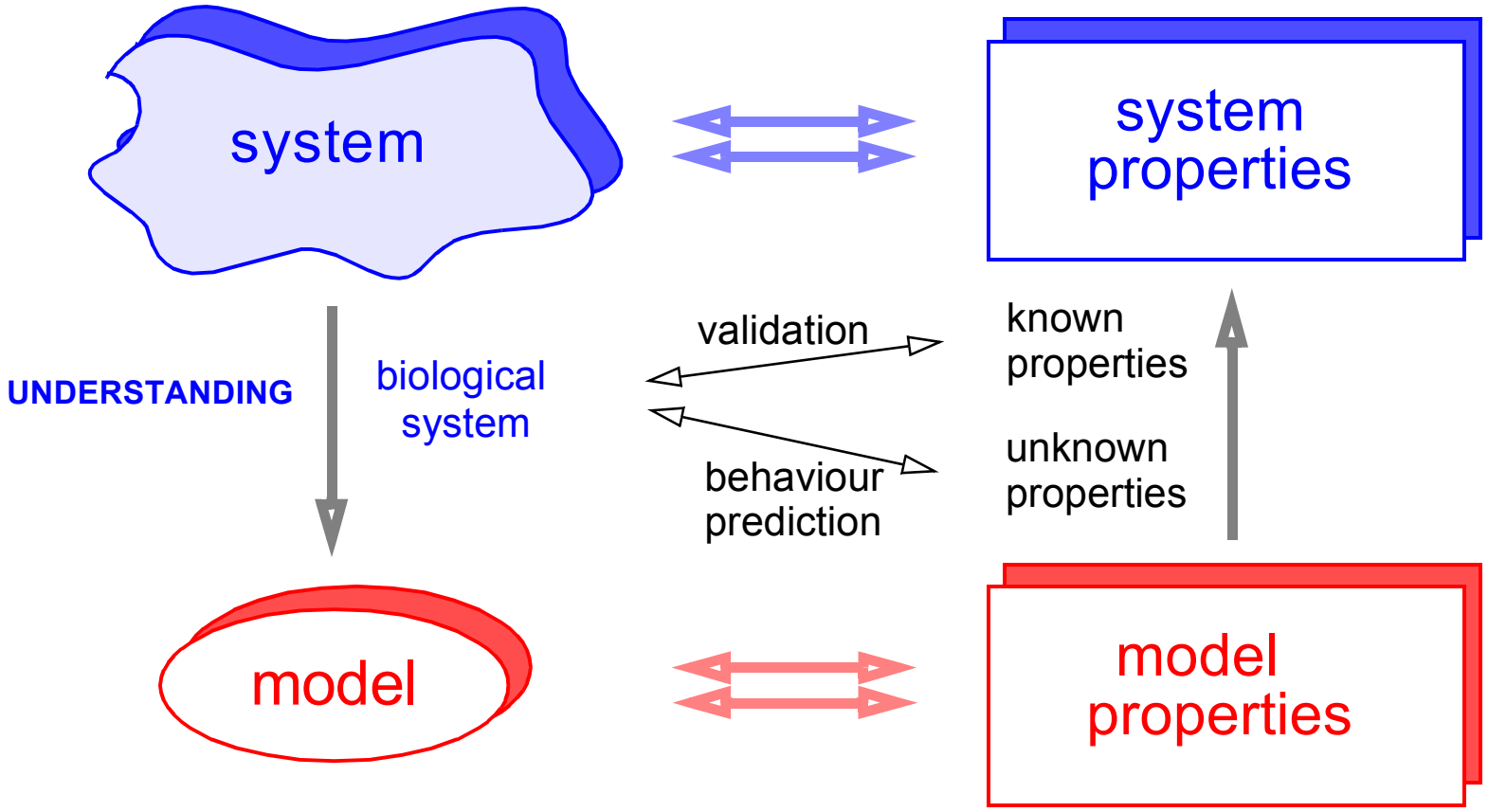
MODEL- BASED SYSTEM ANALYSIS



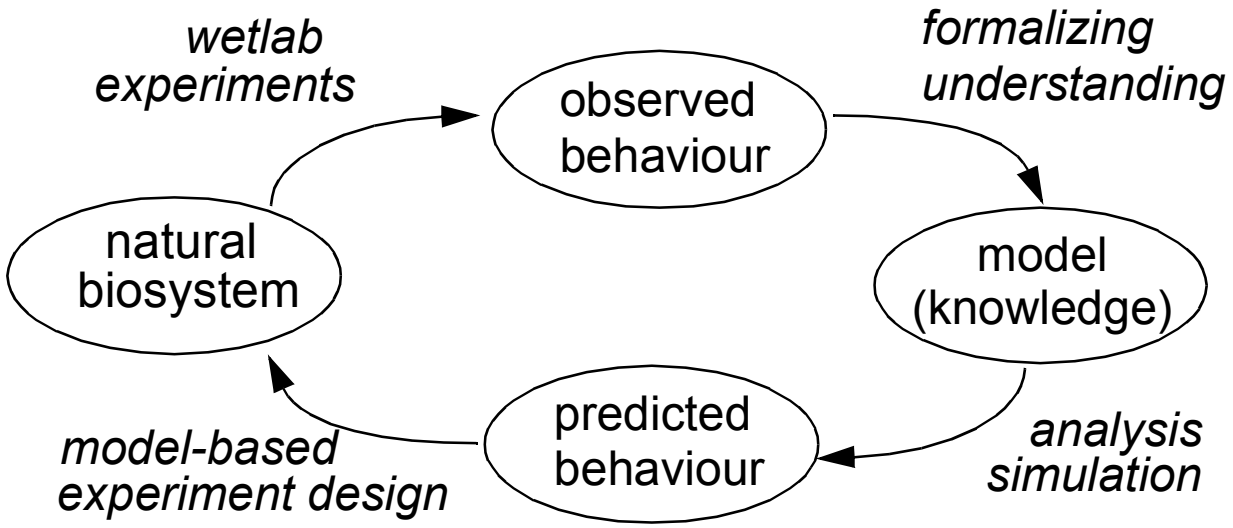
MODEL- BASED SYSTEM ANALYSIS



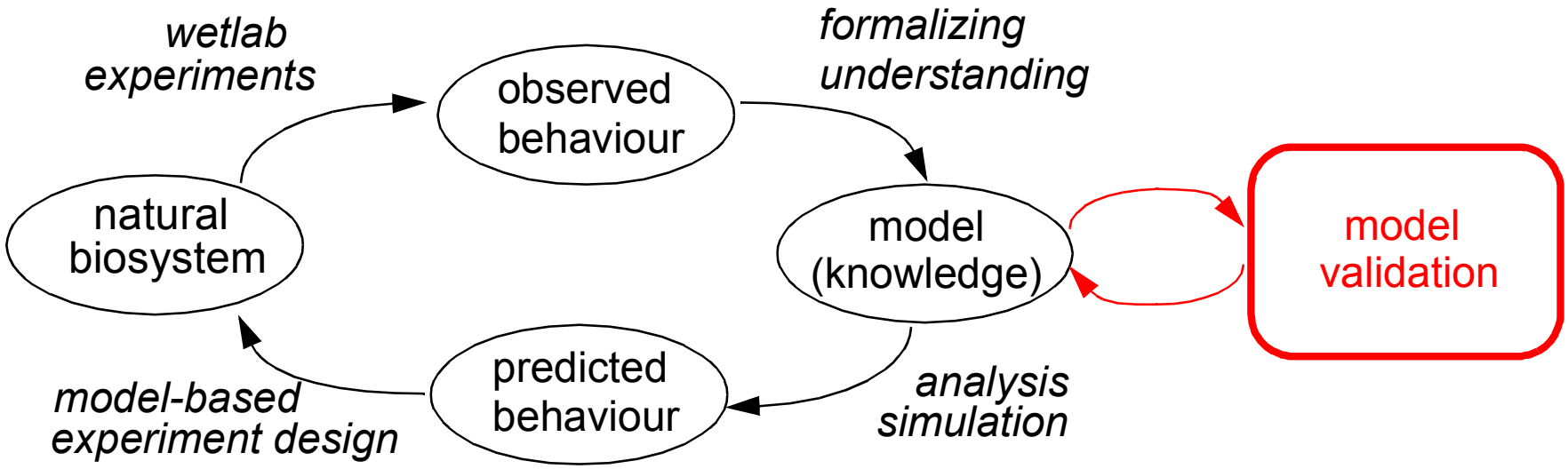
MODEL- BASED SYSTEM ANALYSIS



MODELLING = FORMAL KNOWLEDGE REPRESENTATION

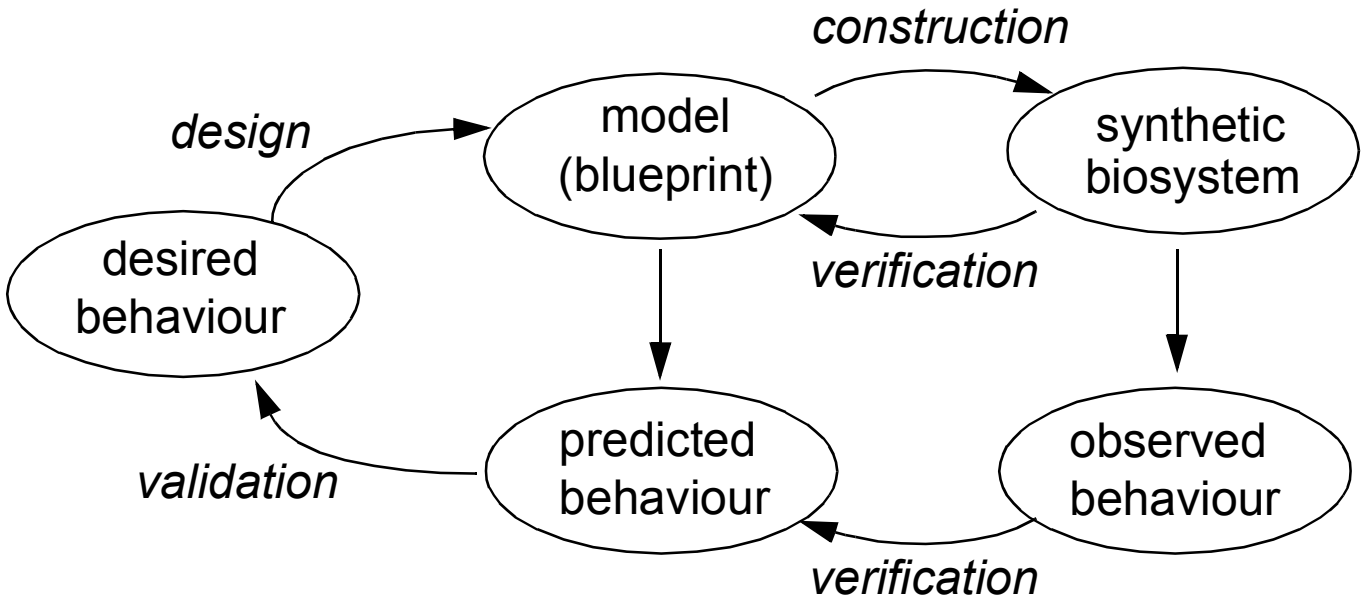


MODELLING = FORMAL KNOWLEDGE REPRESENTATION



MODEL VALIDATION = CONFIDENCE INCREASE

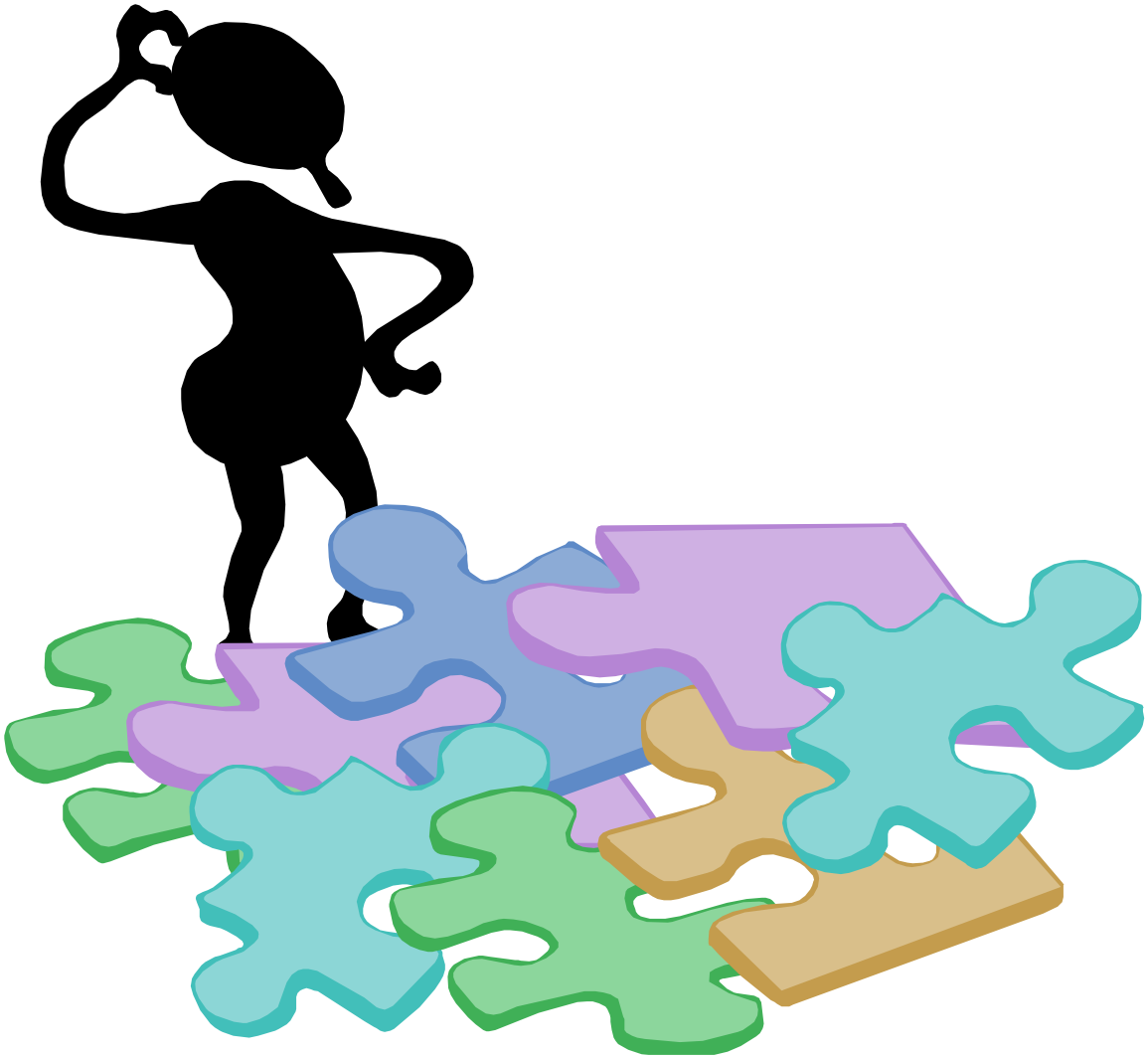
MODELLING = BLUEPRINT FOR SYSTEM CONSTRUCTION



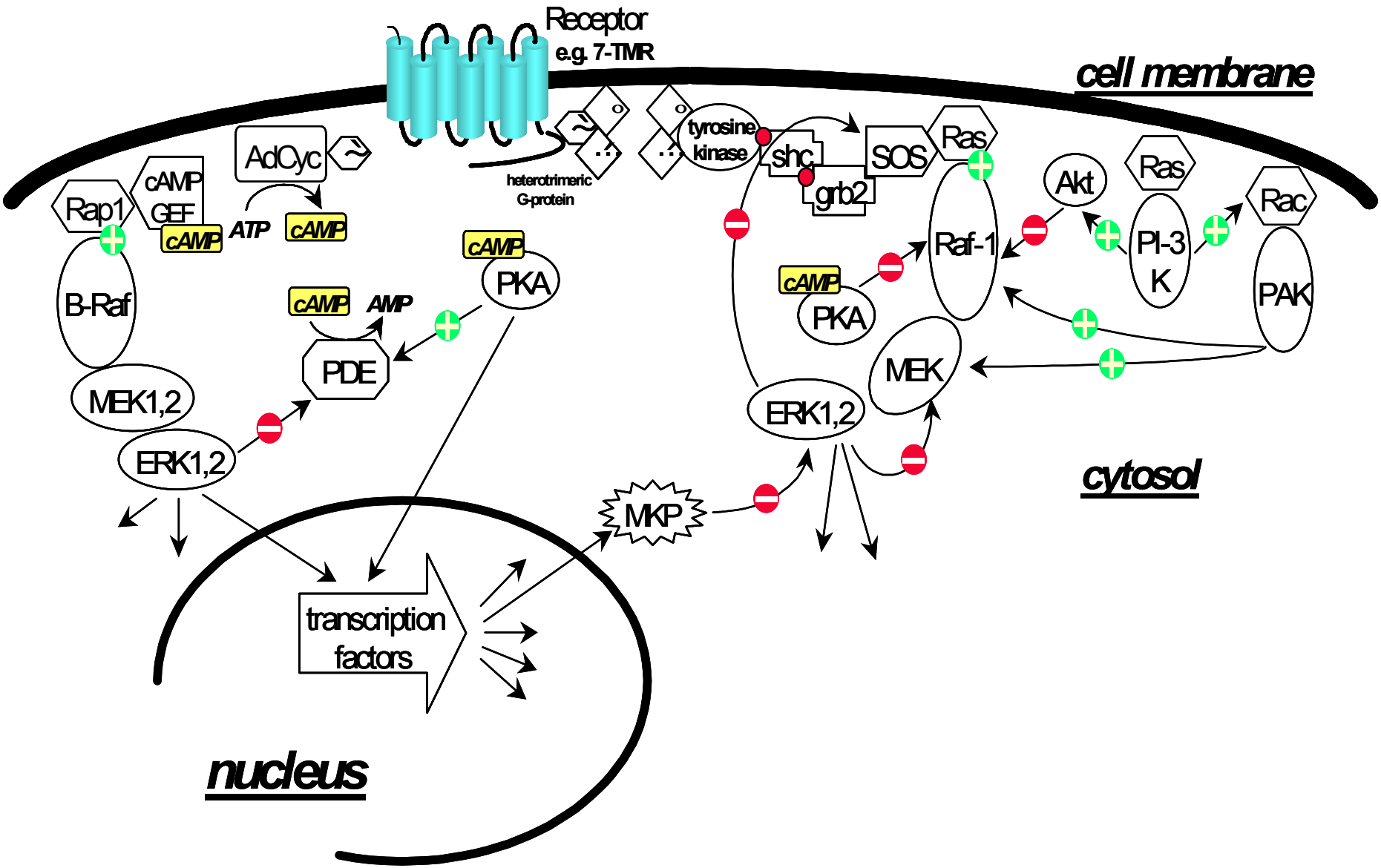
RELIABLE AND ROBUST ENGINEERING REQUIRES VERIFIED MODELS

WHAT KIND OF MODEL SHOULD BE USED?

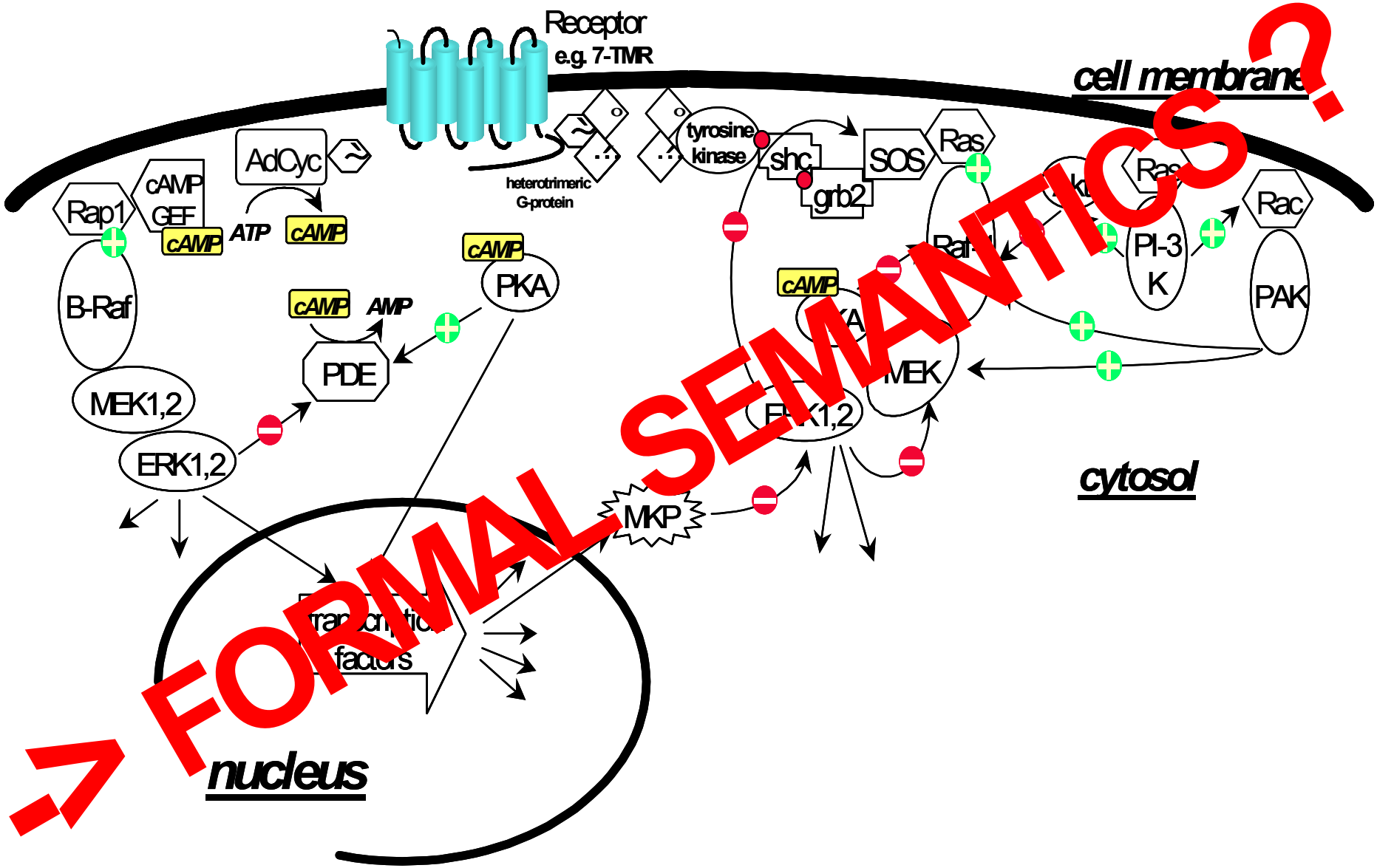
BIO NETWORKS, SOME PROBLEMS



NETWORK REPRESENTATIONS, EX1



NETWORK REPRESENTATIONS, EX1



NETWORK REPRESENTATIONS, EX2

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

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

NETWORK REPRESENTATIONS, EX2

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

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

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*

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*

-> MODELS ARE FULL OF ASSUMPTIONS <-

BIO NETWORK REPRESENTATIONS SHOULD BE

- **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*

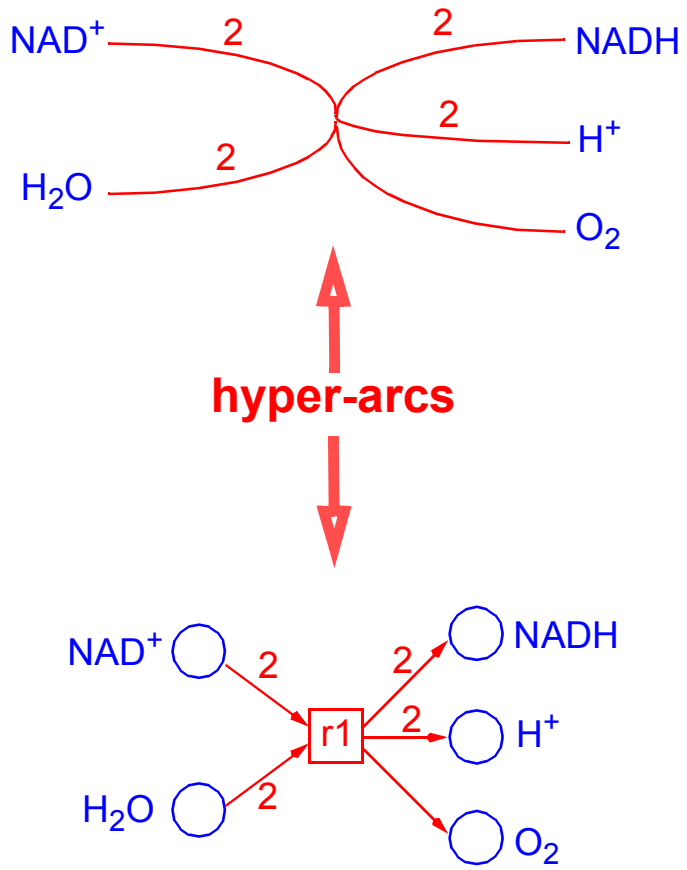
. . .

ARE NETWORKS OF BIOCHEMICAL REACTIONS

. . .

NATURALLY EXPRESSIBLE AS PETRI NETS

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



PETRI NETS
- A CRASH COURSE -

monika.heiner@informatik.tu-cottbus.de

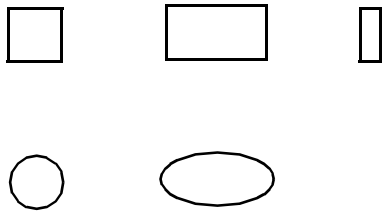
- transitions
  -> active system components

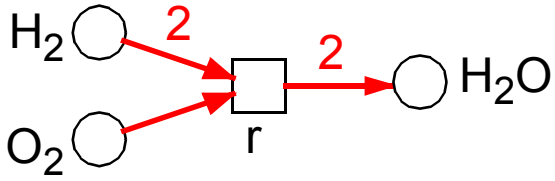
- places
  -> passive system components
  -> local conditions

- transitions
  -> active system components

- places
  -> passive system components
  -> local conditions

- weightes arcs
  -> causality





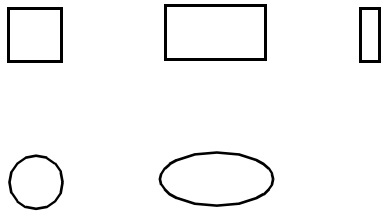
- **transitions**
  -> active system components

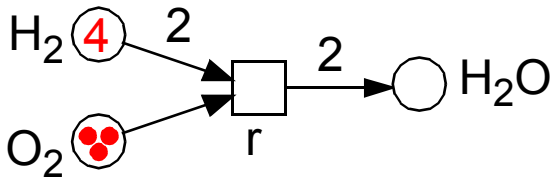
- **places**
  -> passive system components
  -> local conditions

- **weightes arcs**
  -> causality

- **condition's state**
  -> token(s) on its place

- **system state**
  -> marking

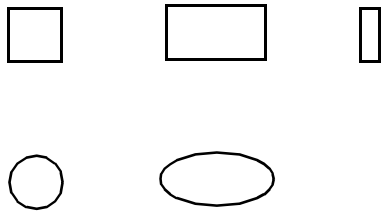




(H_2=4, O_2=3, H_2O=0)

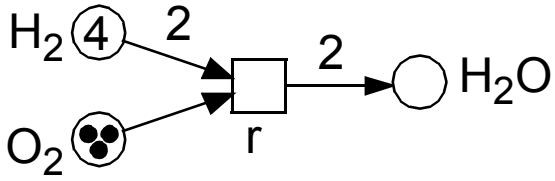
PETRI NETS, BASICS - THE STRUCTURE

- transitions
  -> active system components



- places
  -> passive system components
  -> local conditions

- weightes arcs
  -> causality



- condition's state
  -> token(s) on its place

(H_2=4, O_2=3, H_2O=0)

- system state
  -> marking

- PN = (P, T, F, m_0), F: (P x T) U (T x P) -> N_0, m_0: P -> N_0

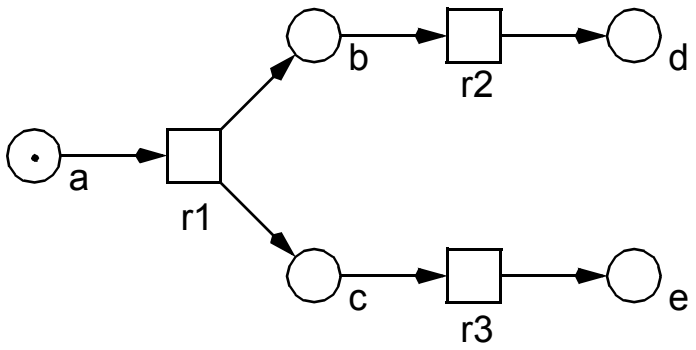
- Petri nets = bipartite directed multigraphs

C. A. PETRI
INTERPRETATIONS OF NET THEORY
GMD, INTERNAL REPORT 75-07, 2ND IMPROVED EDITION 1976

places	transitions
state elements	transitional elements
conditions	events/facts
statements	dependencies
model domains	specifications
chemical compounds	chemical reactions
open one-point sets	closed one-point sets
channels	offices
languages	translators
products	poduction activities

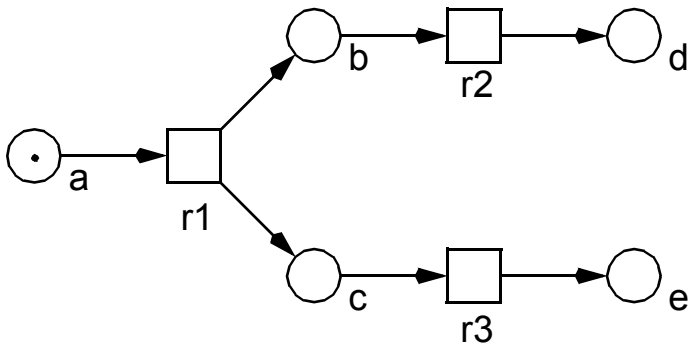
- **an action may happen, if** -> **prerequisite**
  - -> *all preconditions are fulfilled (corresponding to the arc weights);*
- **if an action happens, then** -> **firing behaviour**
  - -> *tokens are removed from all preconditions (corresponding to the arc weights), and*
  - -> *tokens are added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

PARTIAL ORDER VERSUS INTERLEAVING SEMANTICS



- **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 VERSUS INTERLEAVING SEMANTICS

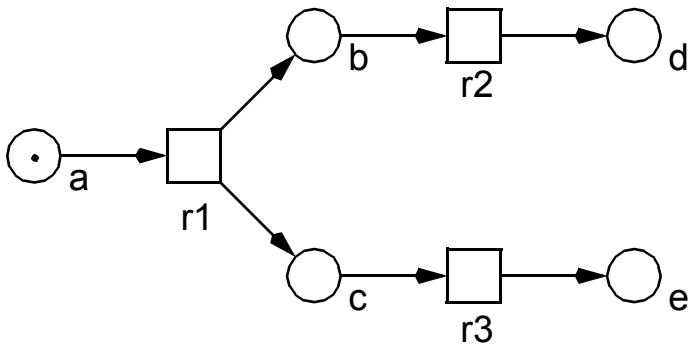


- **order between r1 - r2 and r1 - r3**
  - -> *causality* $x < y$ [x-y]
  - -> *dependency*
- **no order between r2 , r3**
  - -> *concurrency* $x \parallel y$
  - -> *independency*

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

  -> **INTERLEAVING SEMANTICS**
  all totally ordered runs

PARTIAL ORDER VERSUS INTERLEAVING SEMANTICS



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

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

  -> **INTERLEAVING SEMANTICS**
  all totally ordered runs

- **one partial order run**

  r1 < *r2*, *r3*

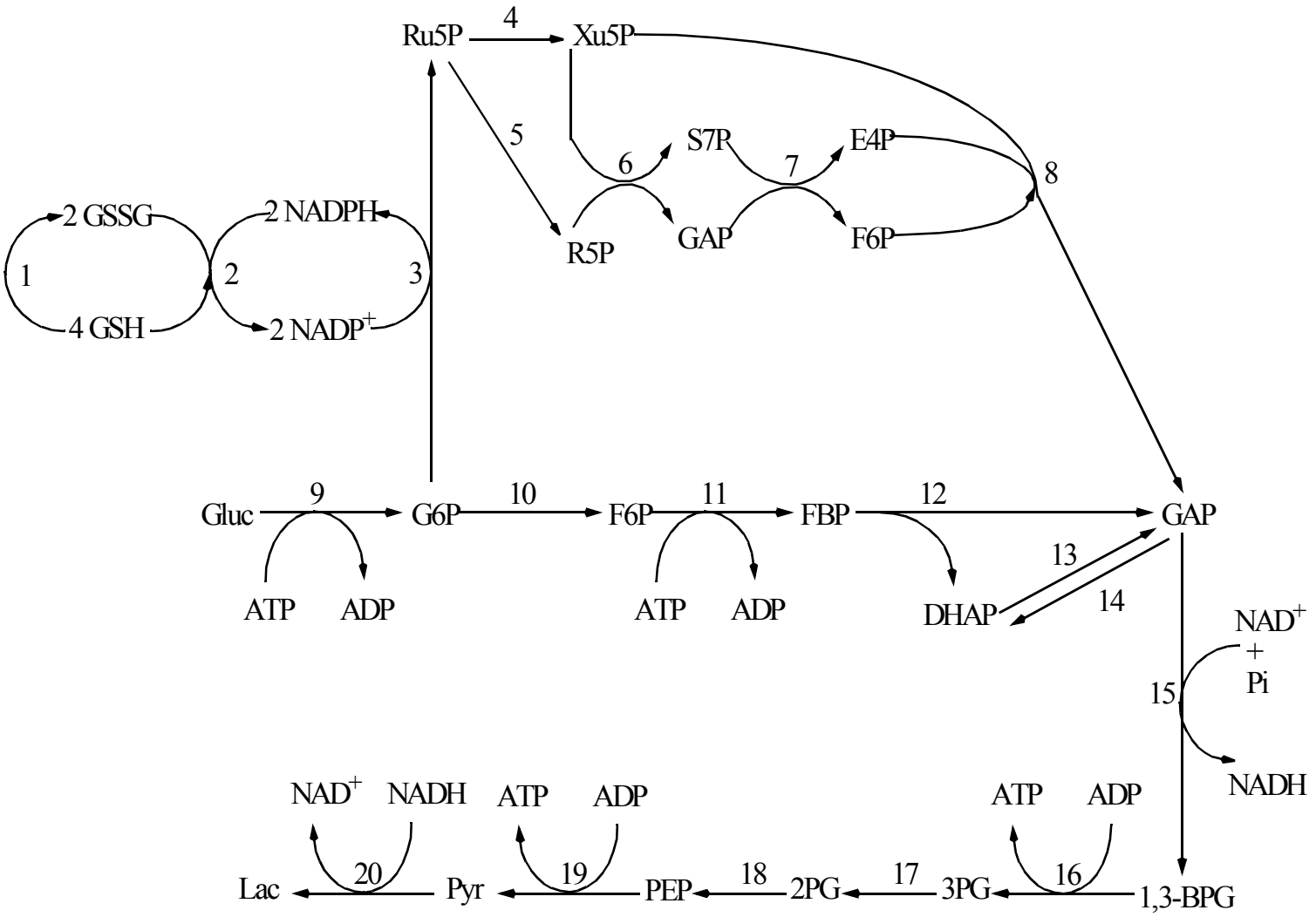
  "true concurrency semantics"

  -> **PARTIAL ORDER SEMANTICS**
  all partially ordered runs

BIO PETRI NETS - SOME EXAMPLES

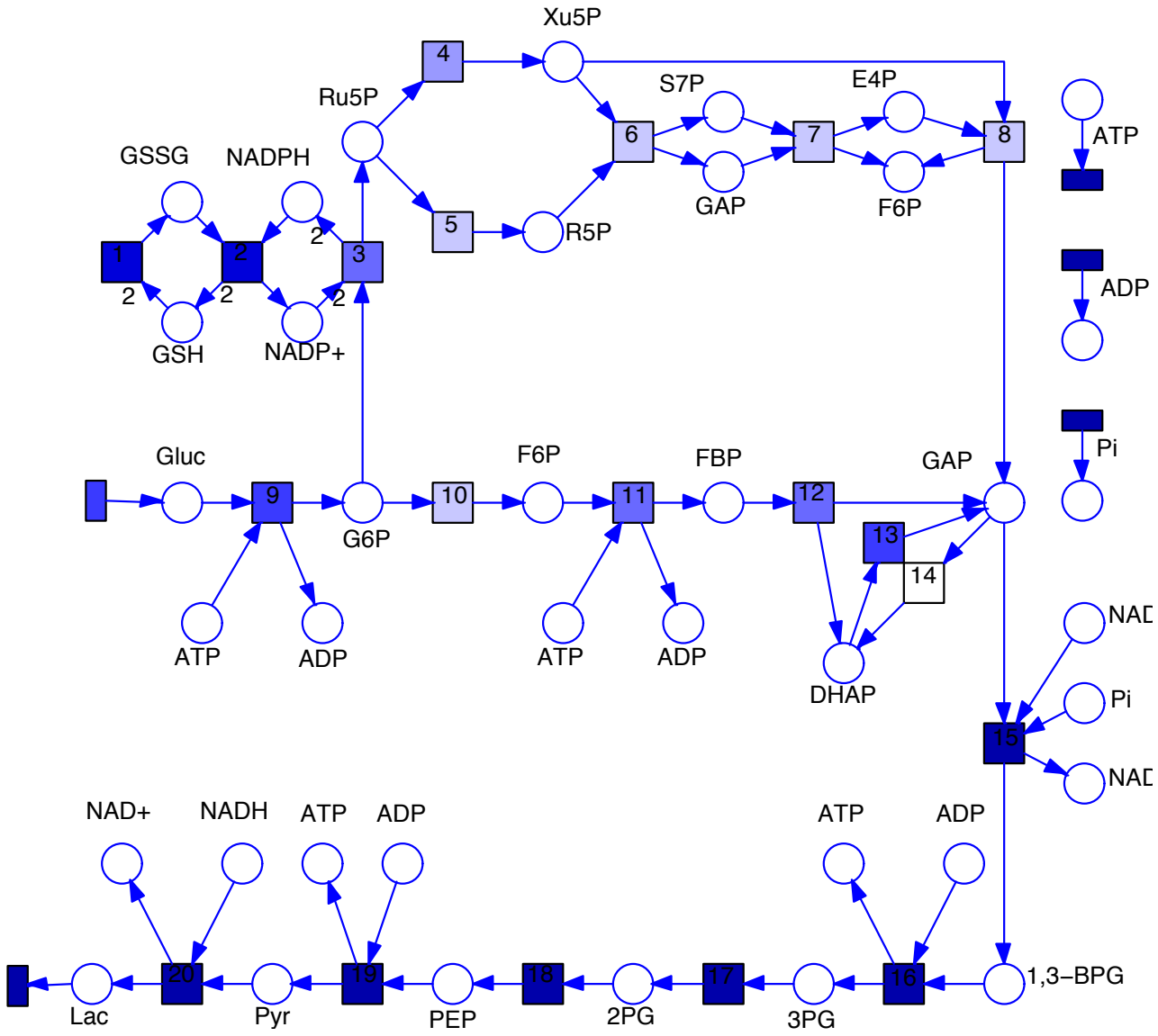
Ex1 - Glycolysis and Pentose Phosphate Pathway

[Reddy 1993]

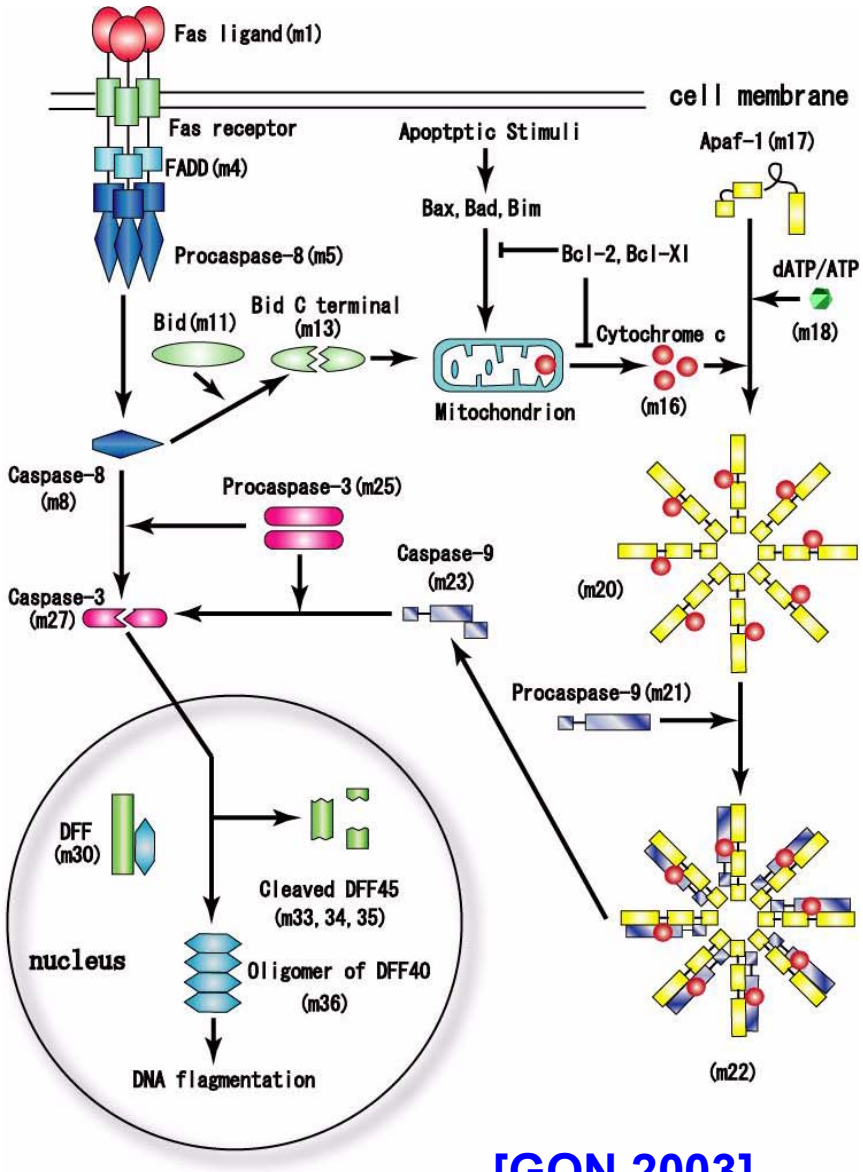


Ex1 - Glycolysis and Pentose Phosphate Pathway

[Reddy 1993]
[Heiner 1998]

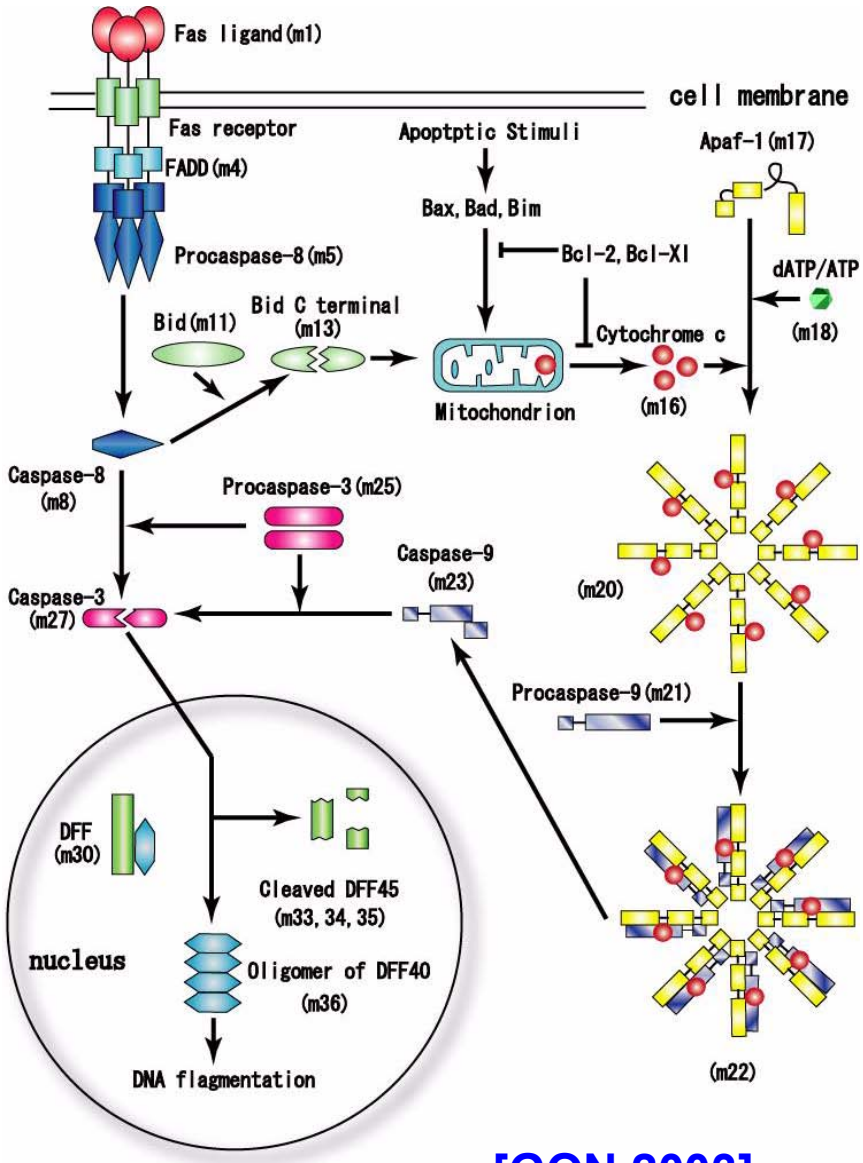


EX2: APOPTOSIS IN MAMMALIAN CELLS

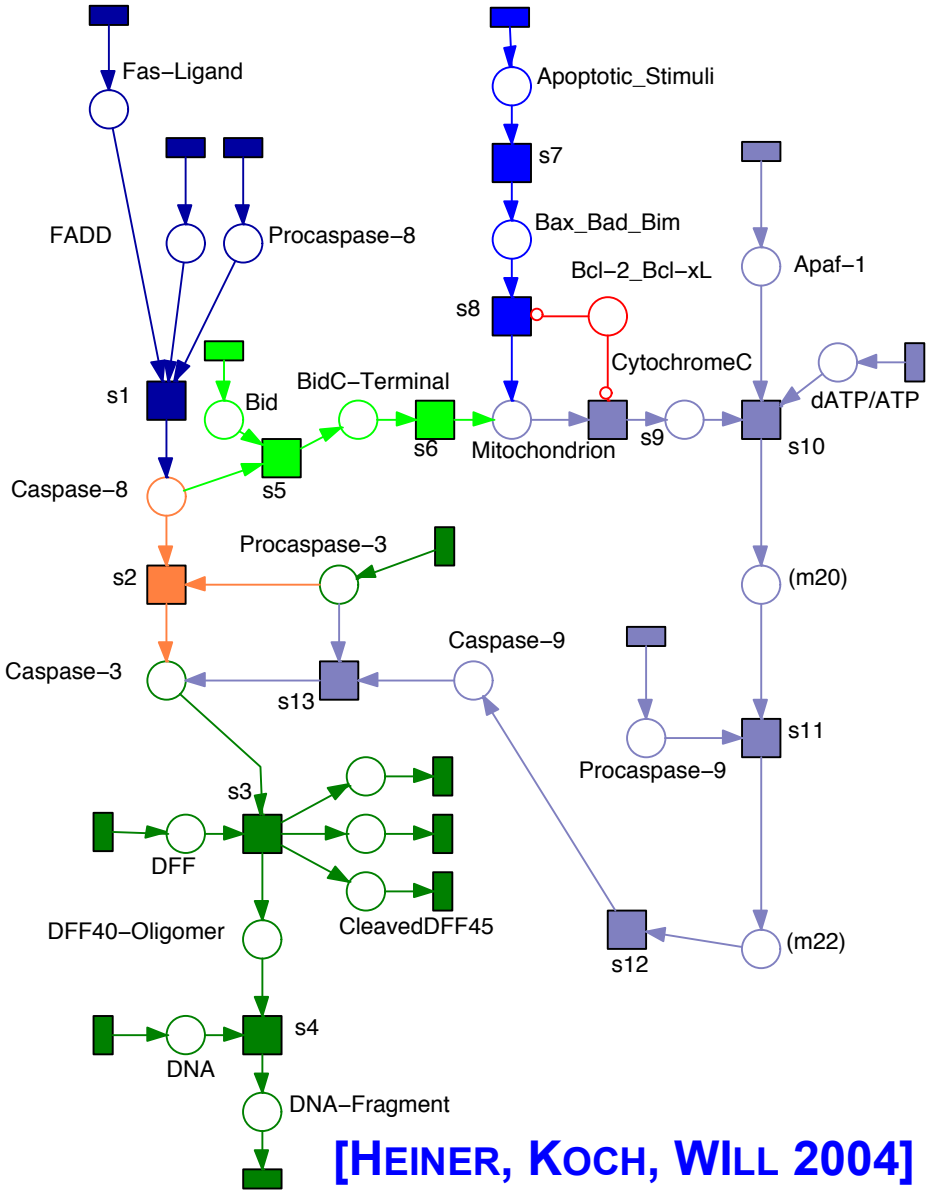


[GON 2003]

EX2: APOPTOSIS IN MAMMALIAN CELLS



[GON 2003]



[HEINER, KOCH, WILL 2004]

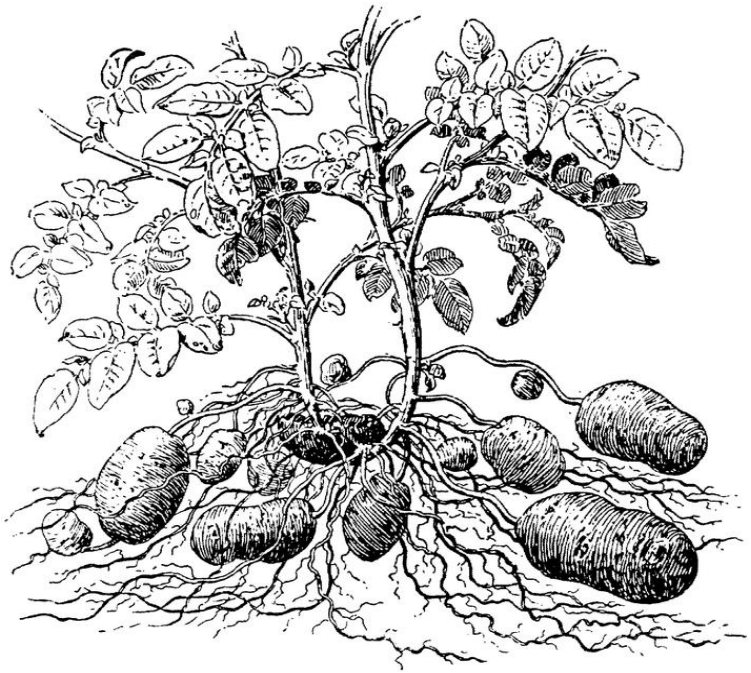
monika.heiner@informatik.tu-cottbus.de

Ex3 - Carbon Metabolism in Potato Tuber

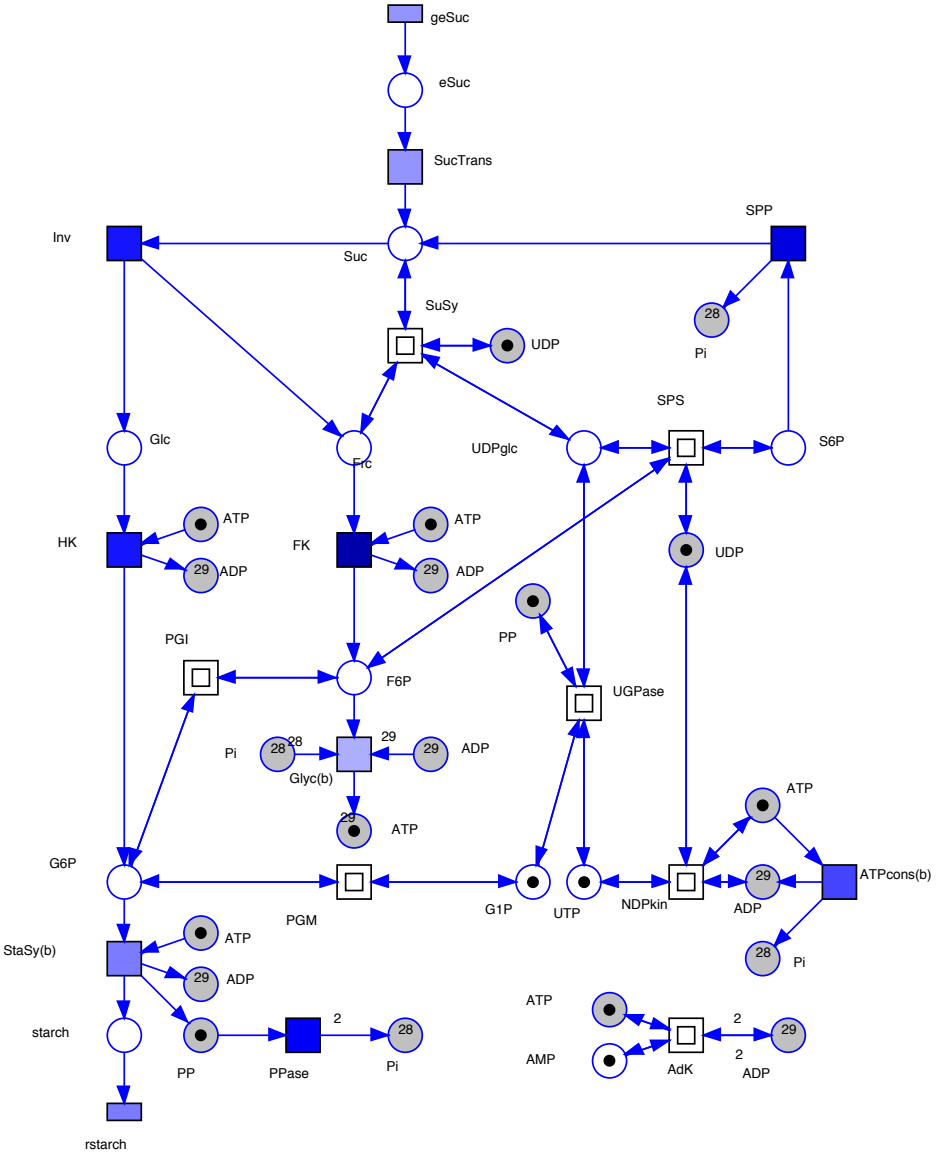
[KOCH, JUNKER, HEINER 2005]

monika.heiner@informatik.tu-cottbus.de

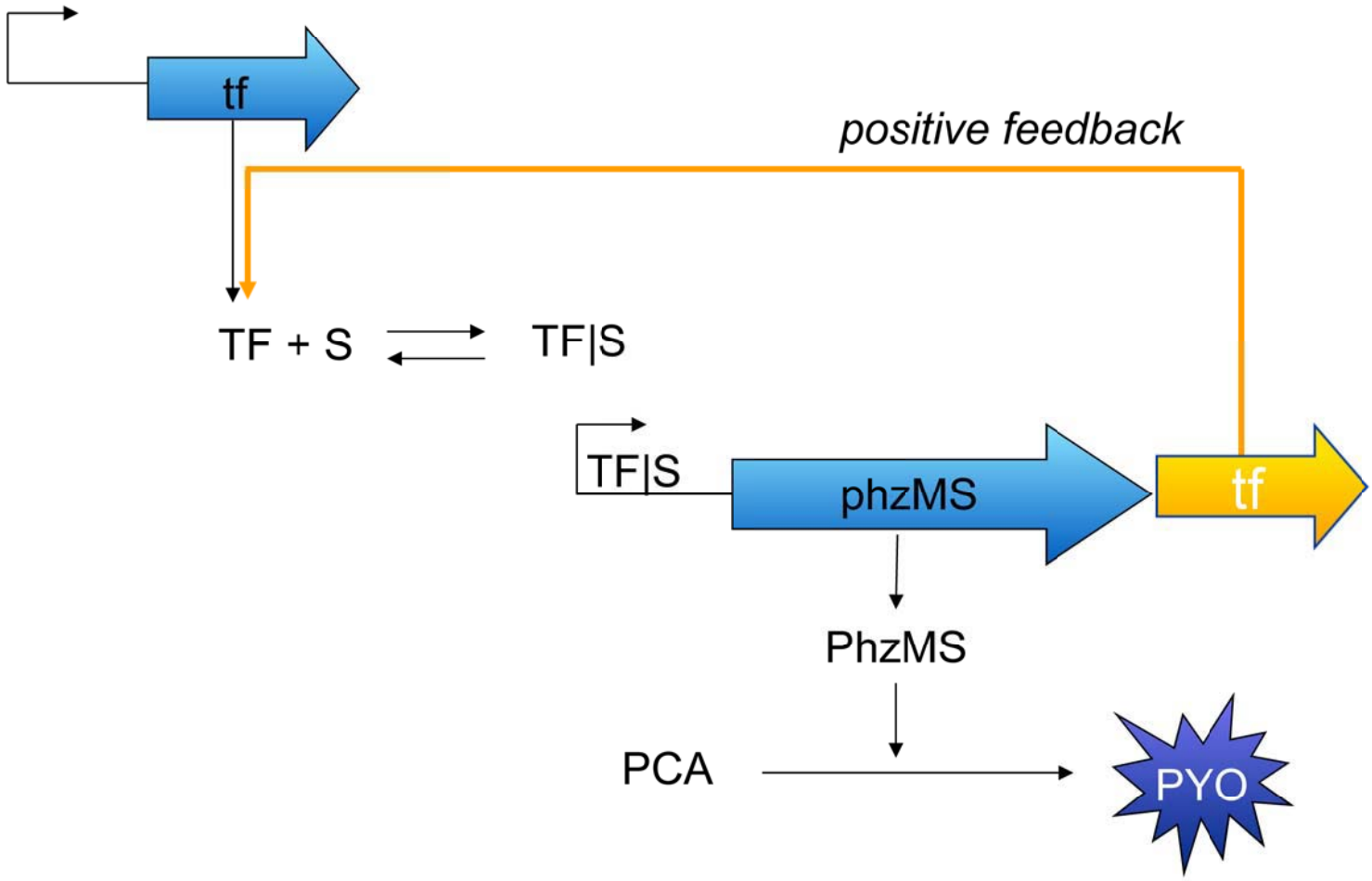
Ex3 - Carbon Metabolism in Potato Tuber



[KOCH, JUNKER, HEINER 2005]

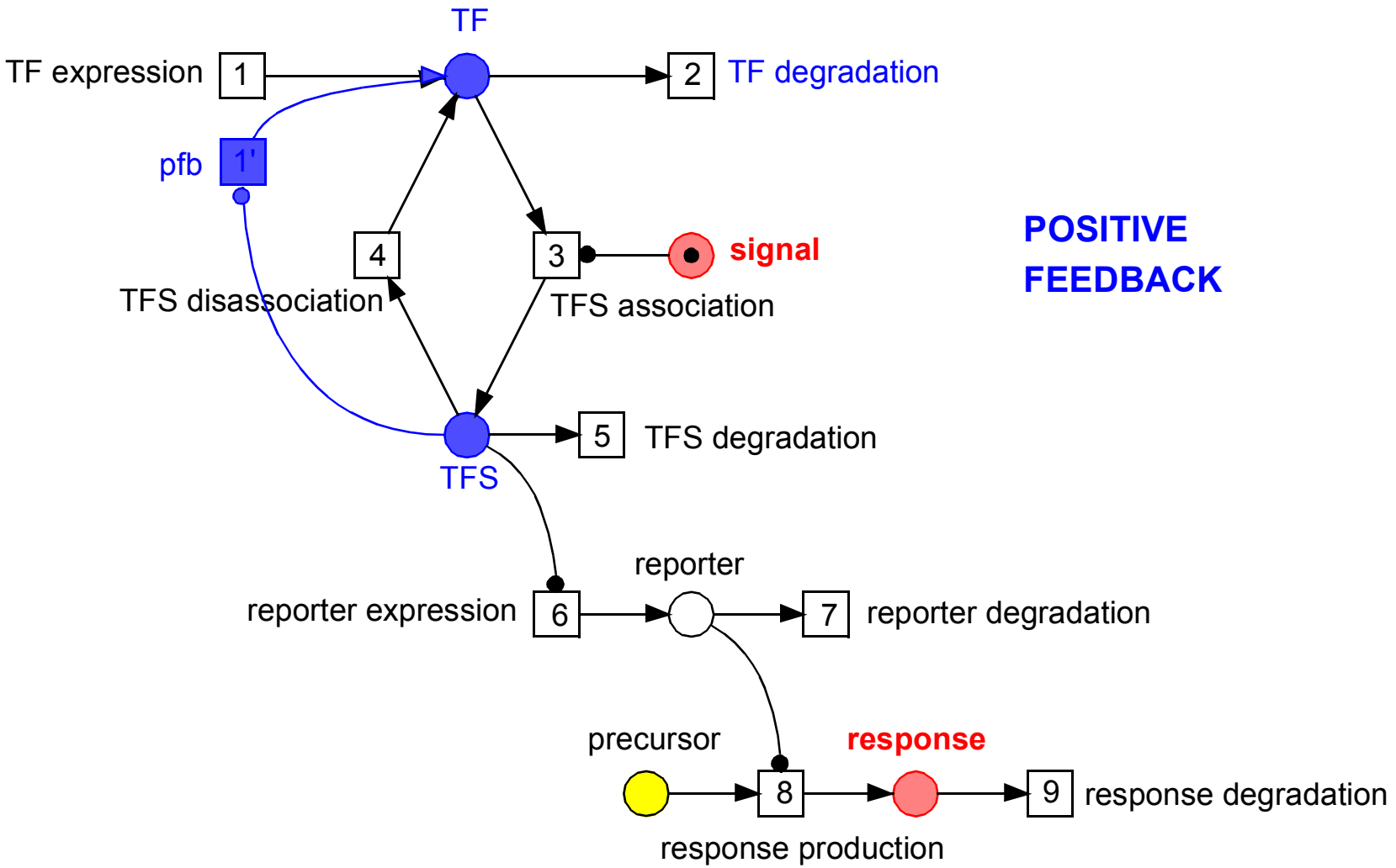


EX4 - BIOSENSOR



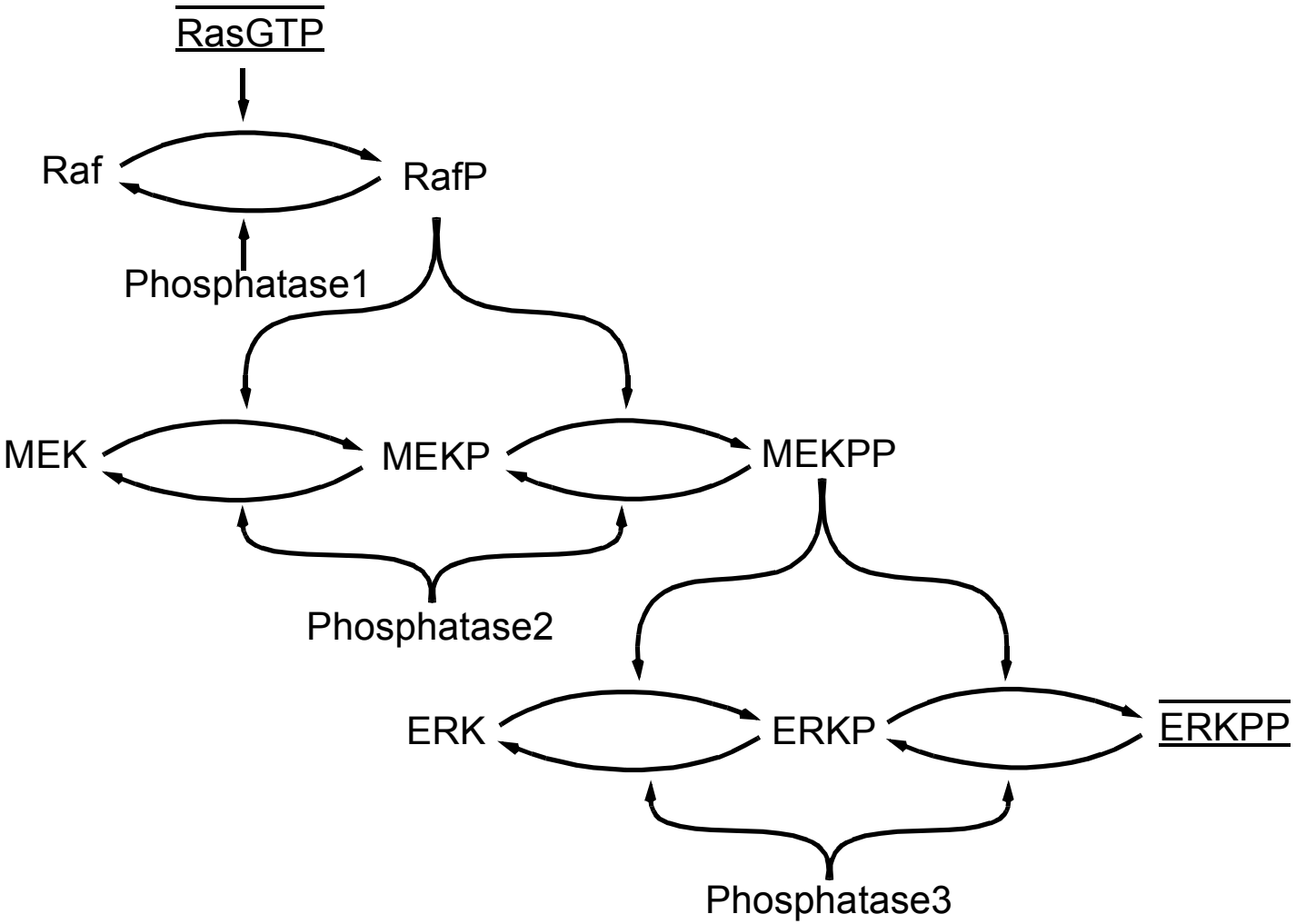
[GILBERT, HEINER, ROSSER, FULTON, GU, TRYBILO 2008]

EX4 - BIOSENSOR

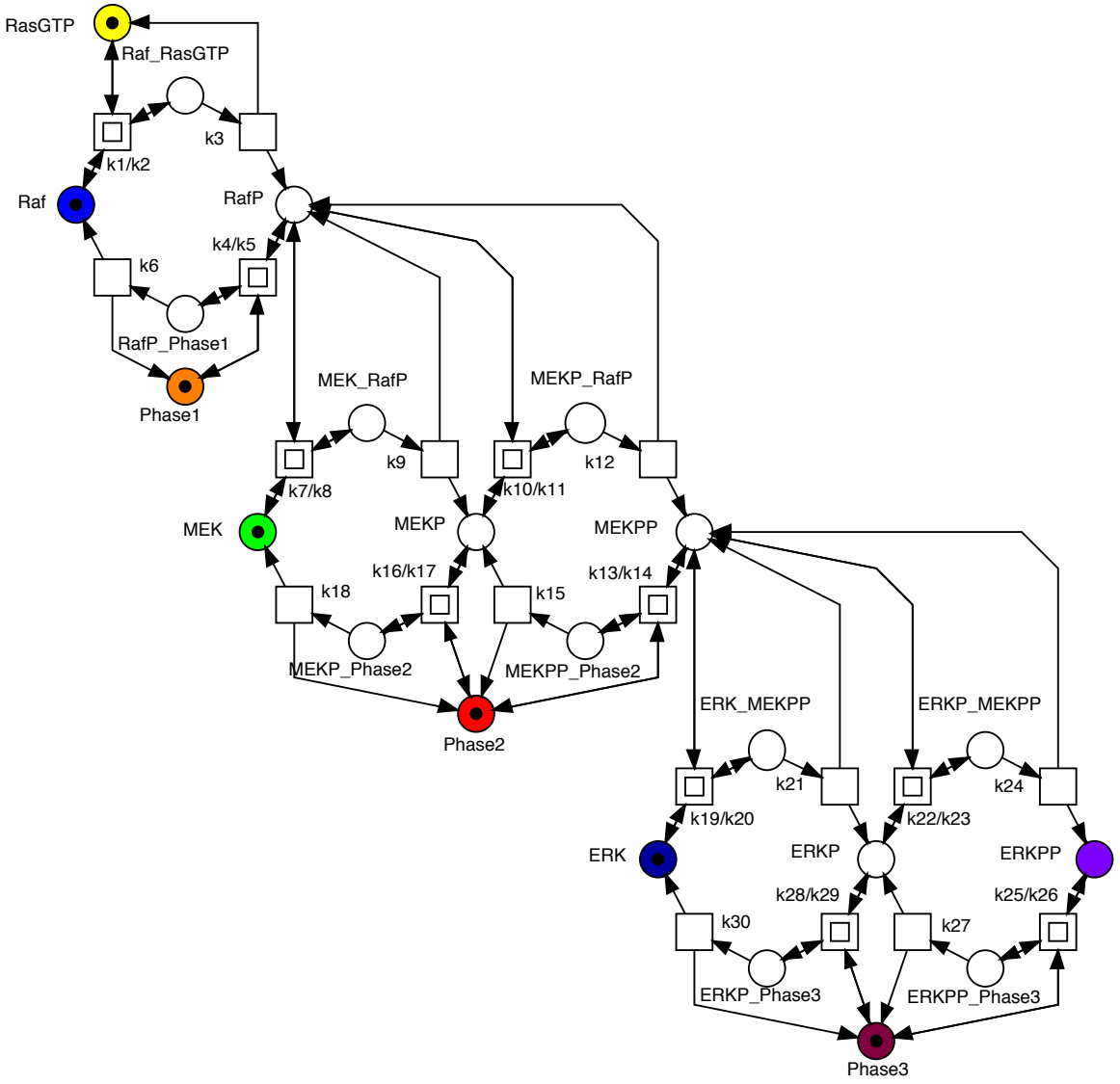


[GILBERT, HEINER, ROSSER, FULTON, GU, TRYBILO 2008]

EX5 - SIGNALLING CASCADE



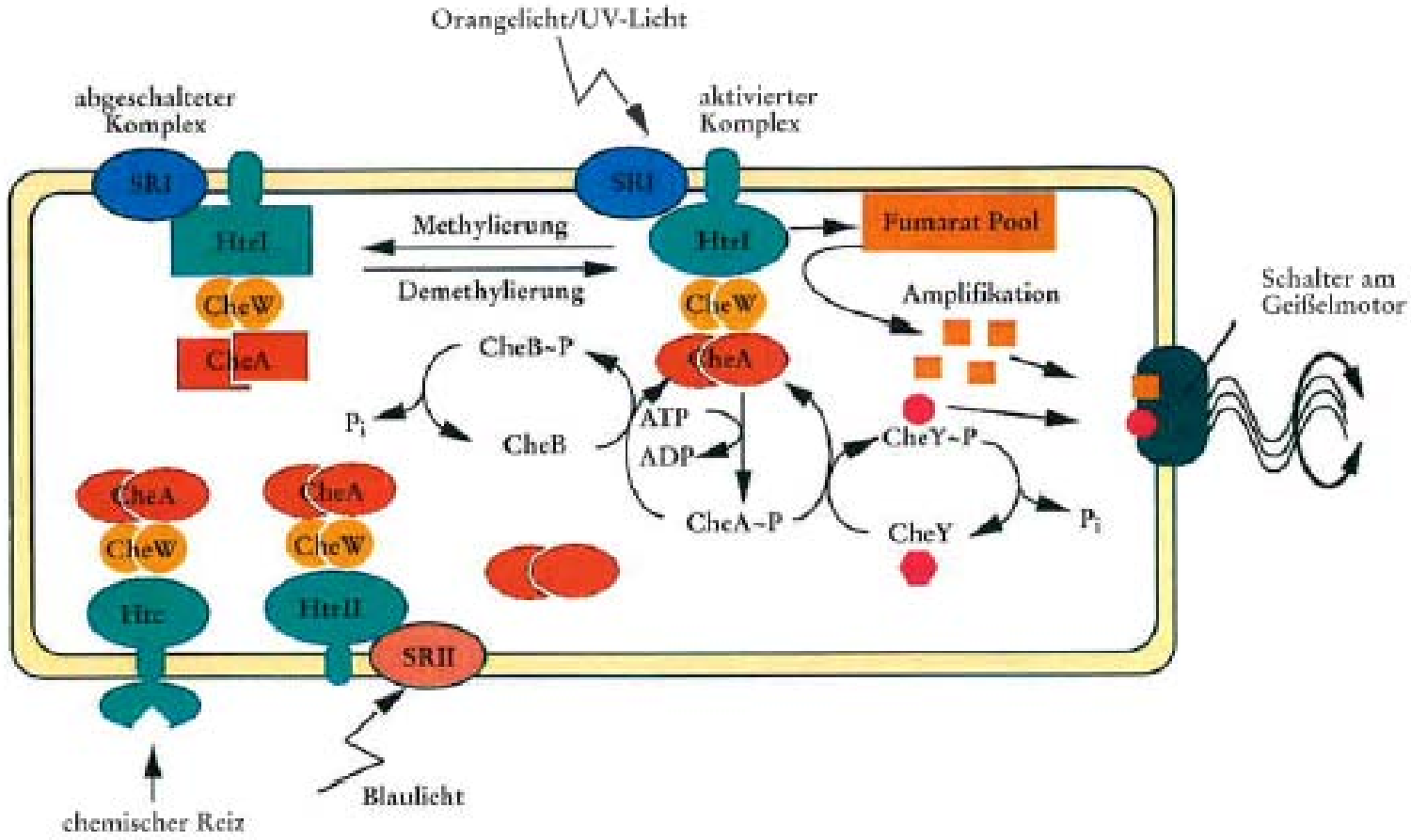
EX5 - SIGNALLING CASCADE



[GILBERT, HEINER, LEHRACK 2007]

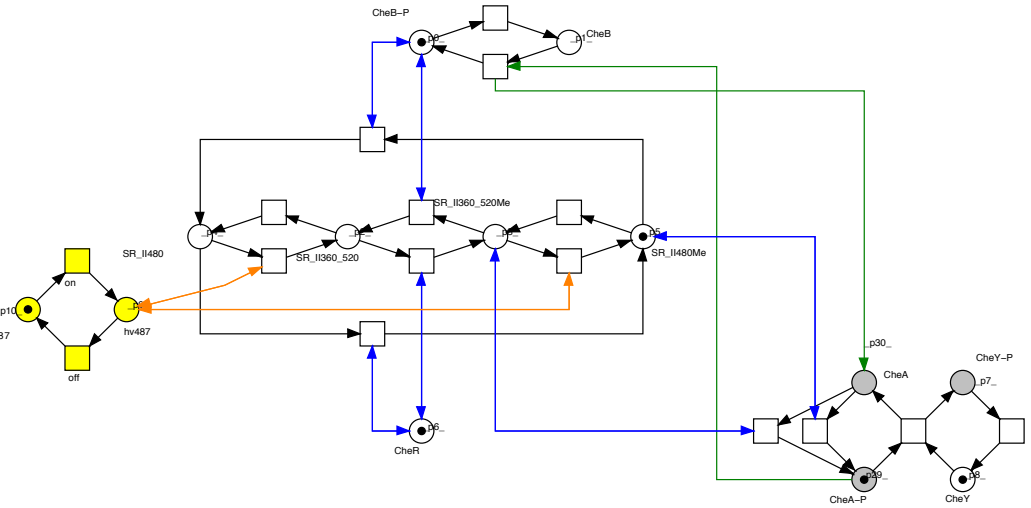
[HEINER, GILBERT, DONALDSON 2008]

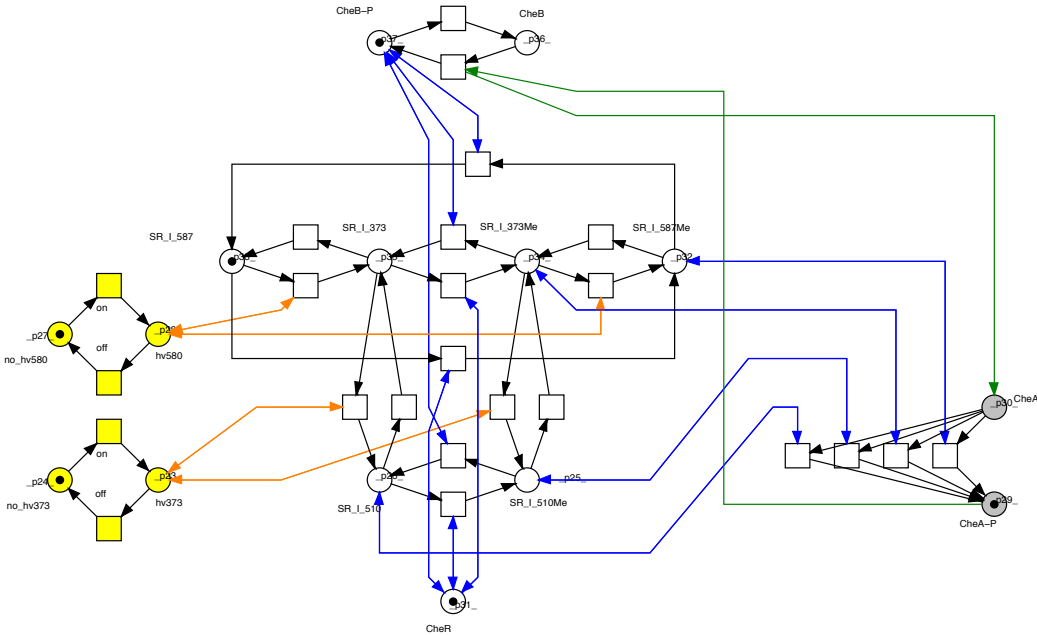
EX6 - SWITCH CYCLE HALOBACTERIUM SALINARUM

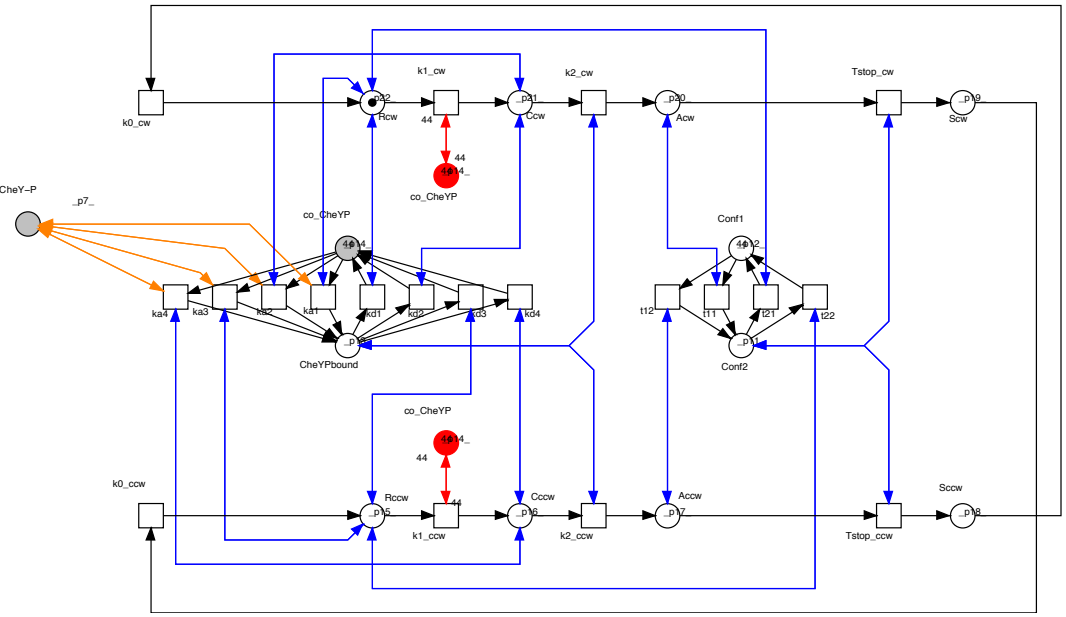


[MARWAN, OESTERHELT 1999]

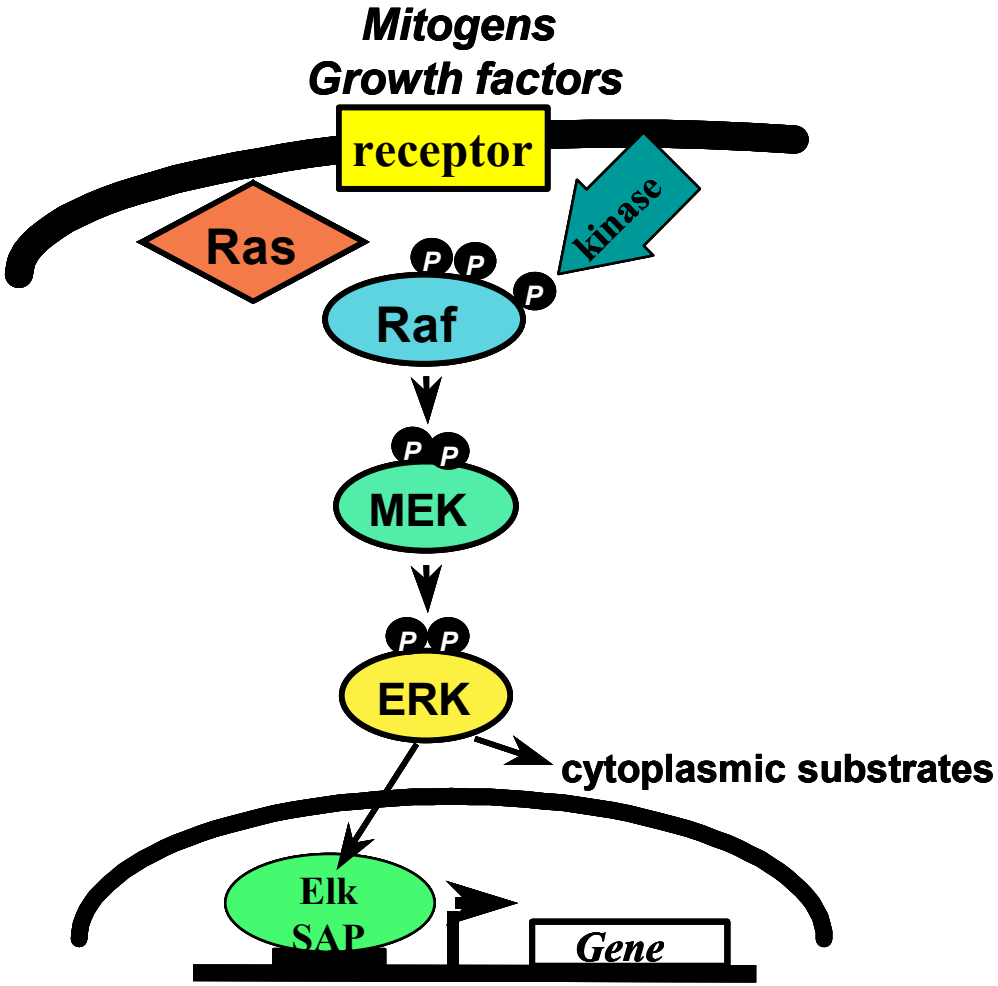
EX6 - SWITCH CYCLE HALOBACTERIUM SALINARUM



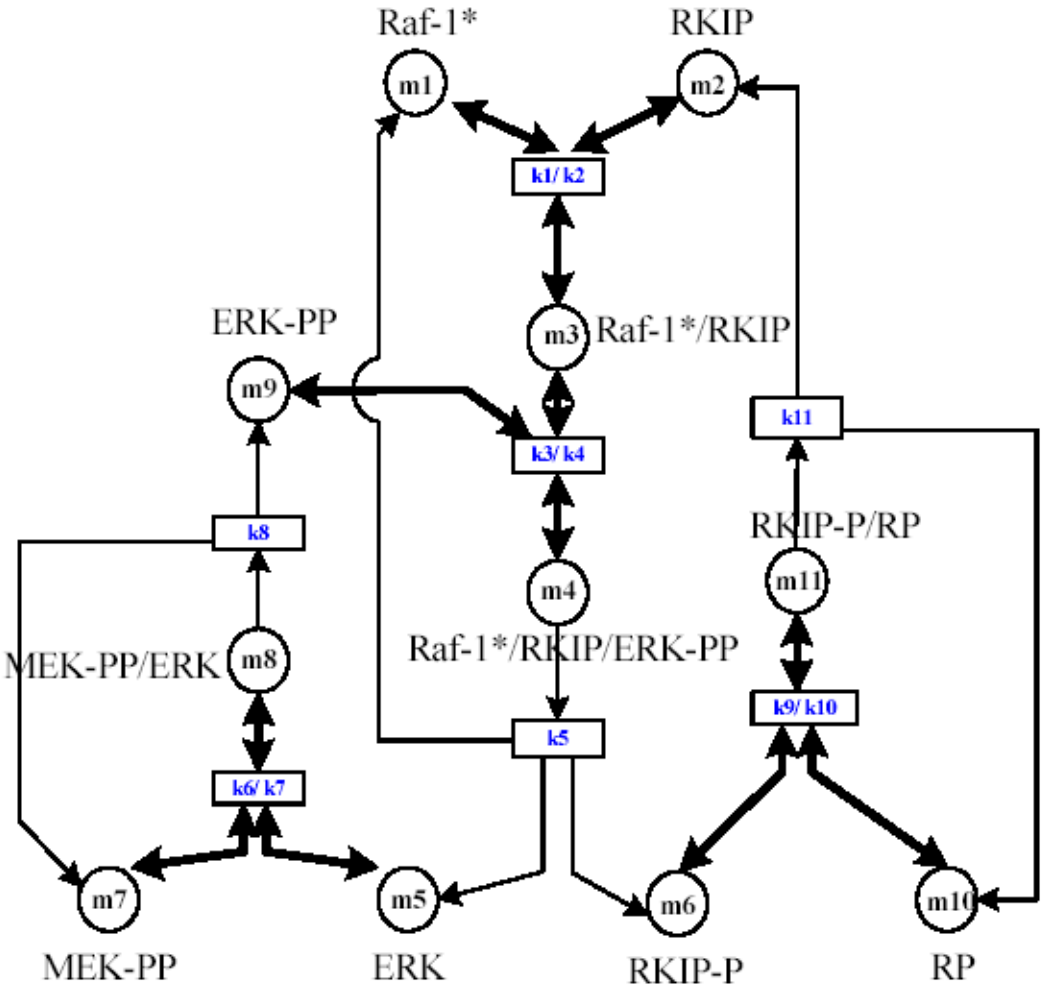




…one pathway…

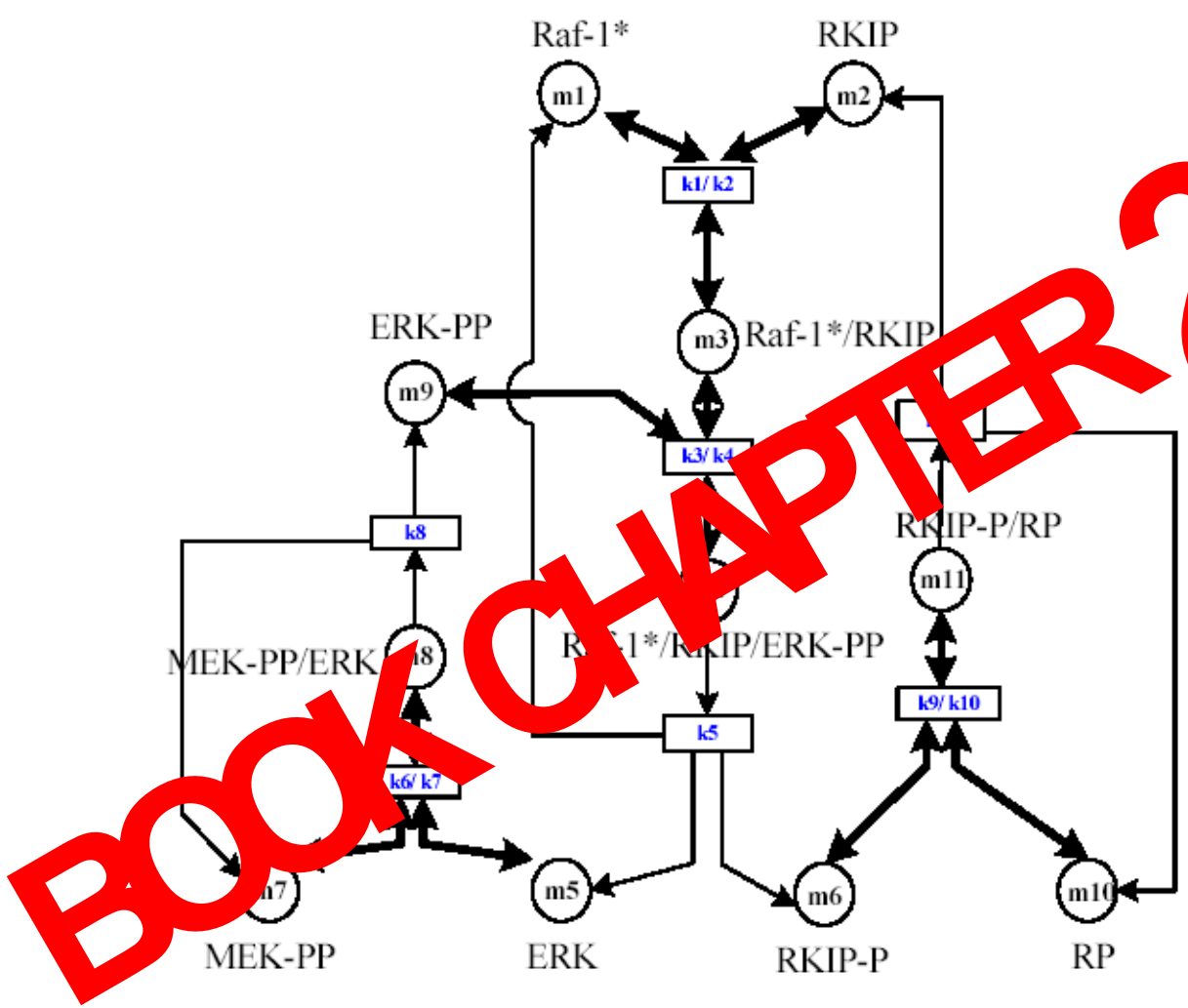

Mitogens
Growth factors
receptor
Ras
kinase
P P
P
Raf
P P
MEK
P P
ERK
cytoplasmic substrates
Elk
SAP
Gene

EX7 - RKIP SIGNALLING PATHWAY



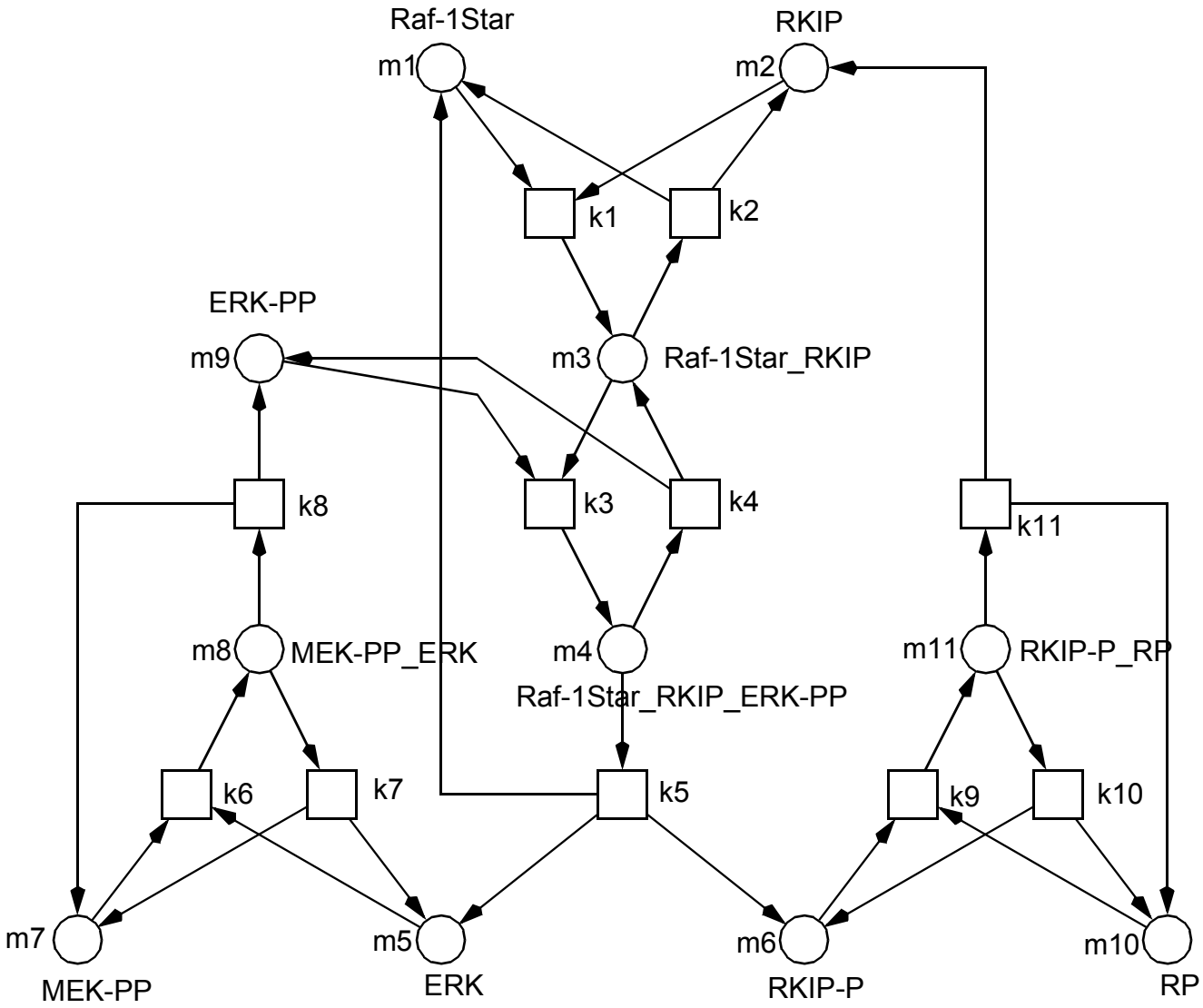
[Cho et al., CMSB 2003]

EX7 - RKIP SIGNALLING PATHWAY

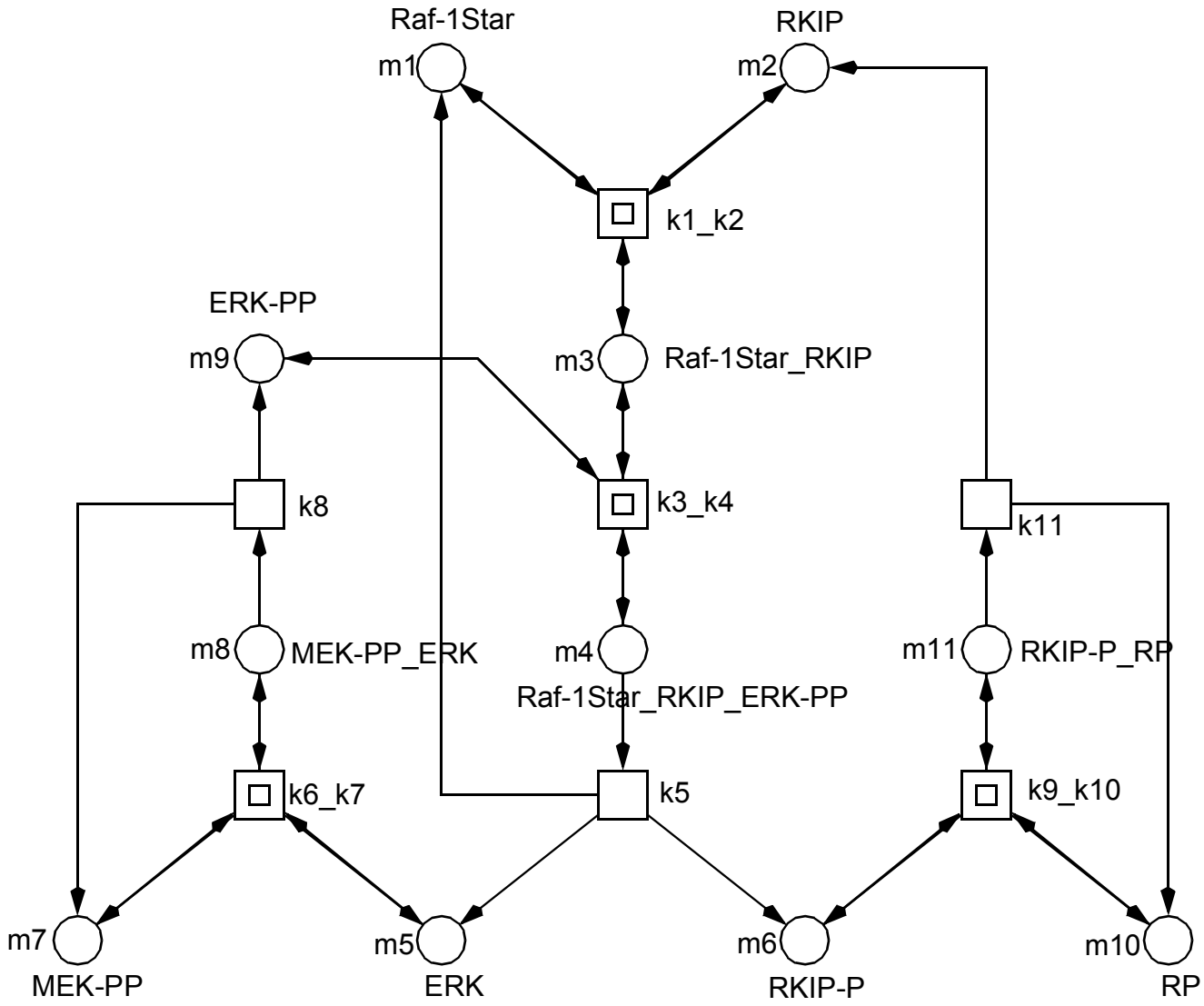


[Cho et al., CMSB 2003]

EX7 - RKIP SIGNALLING PATHWAY, PETRI NET



EX7 - RKIP SIGNALLING PATHWAY, HIERARCHICAL PETRI NET



monika.heiner@informatik.tu-cottbus.de

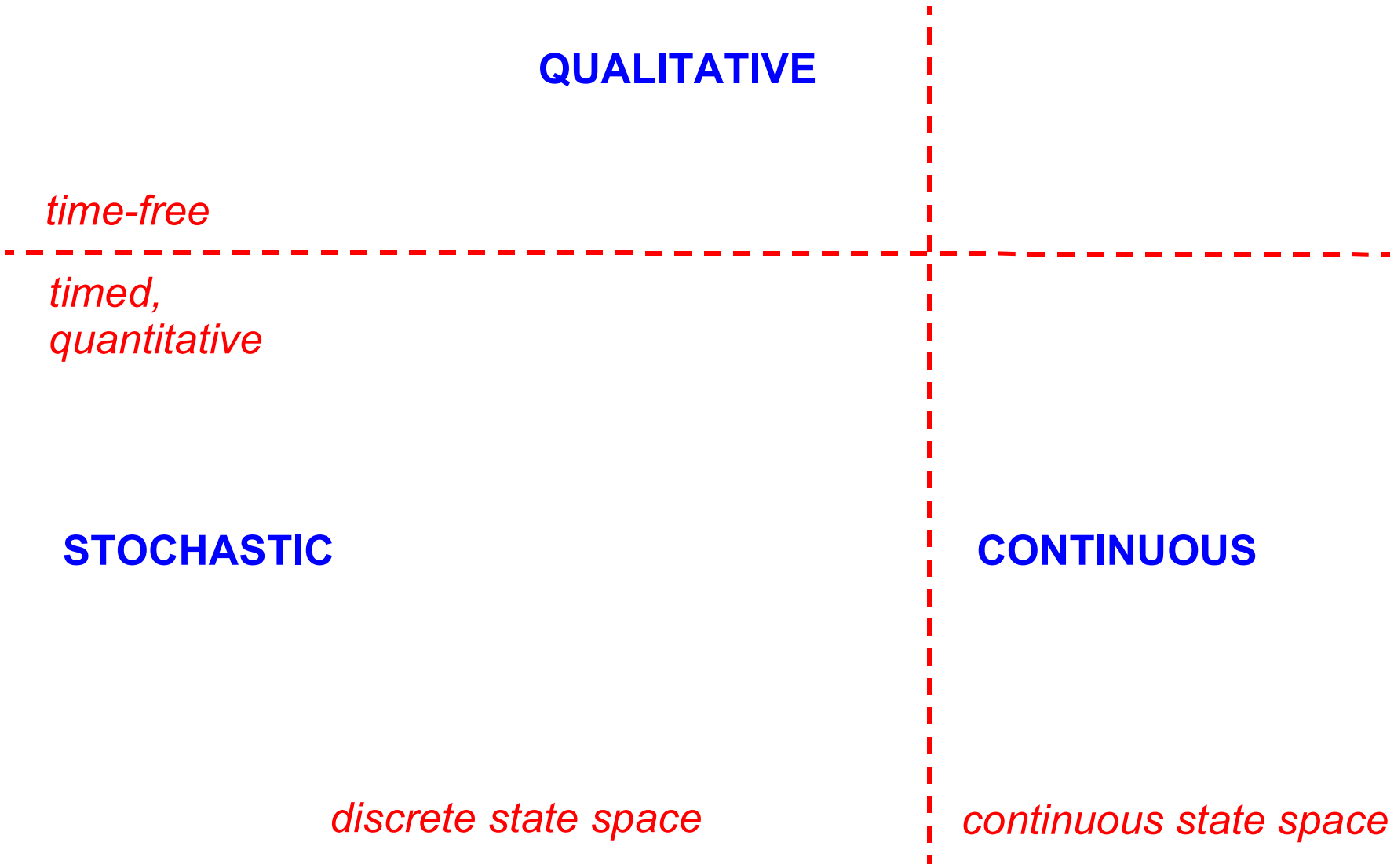
THE FRAMEWORK

QUALITATIVE

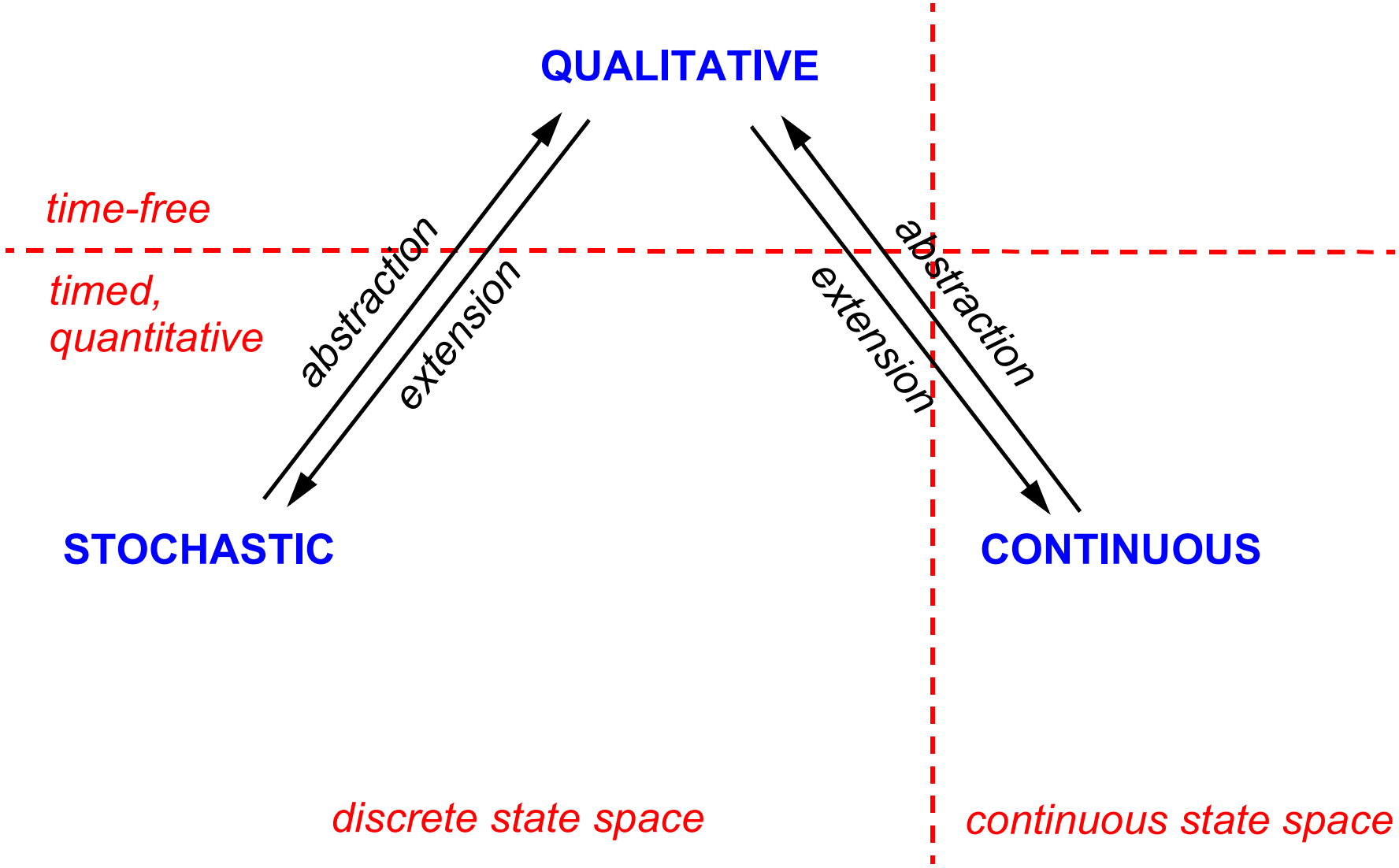
STOCHASTIC

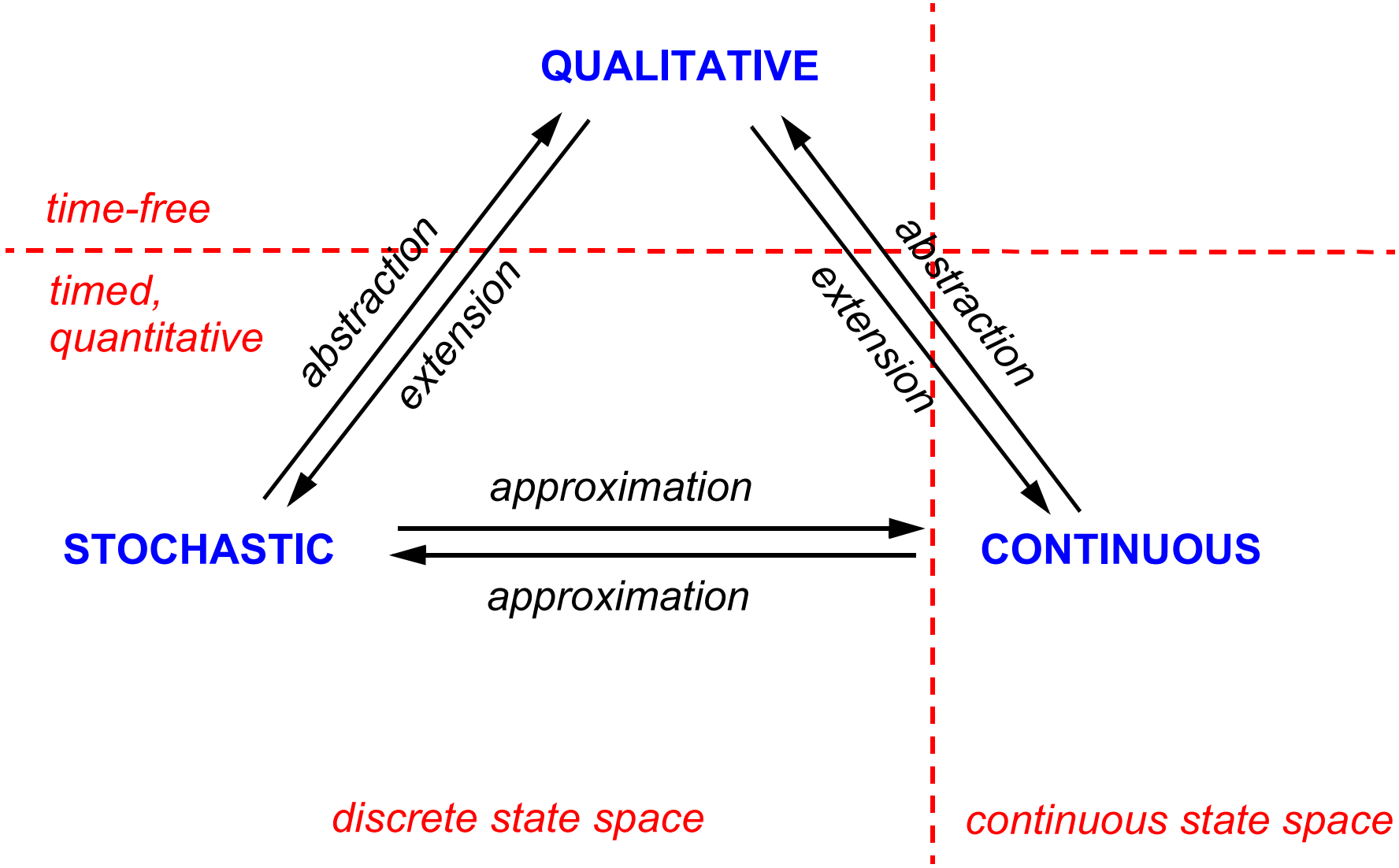
CONTINUOUS

FRAMEWORK

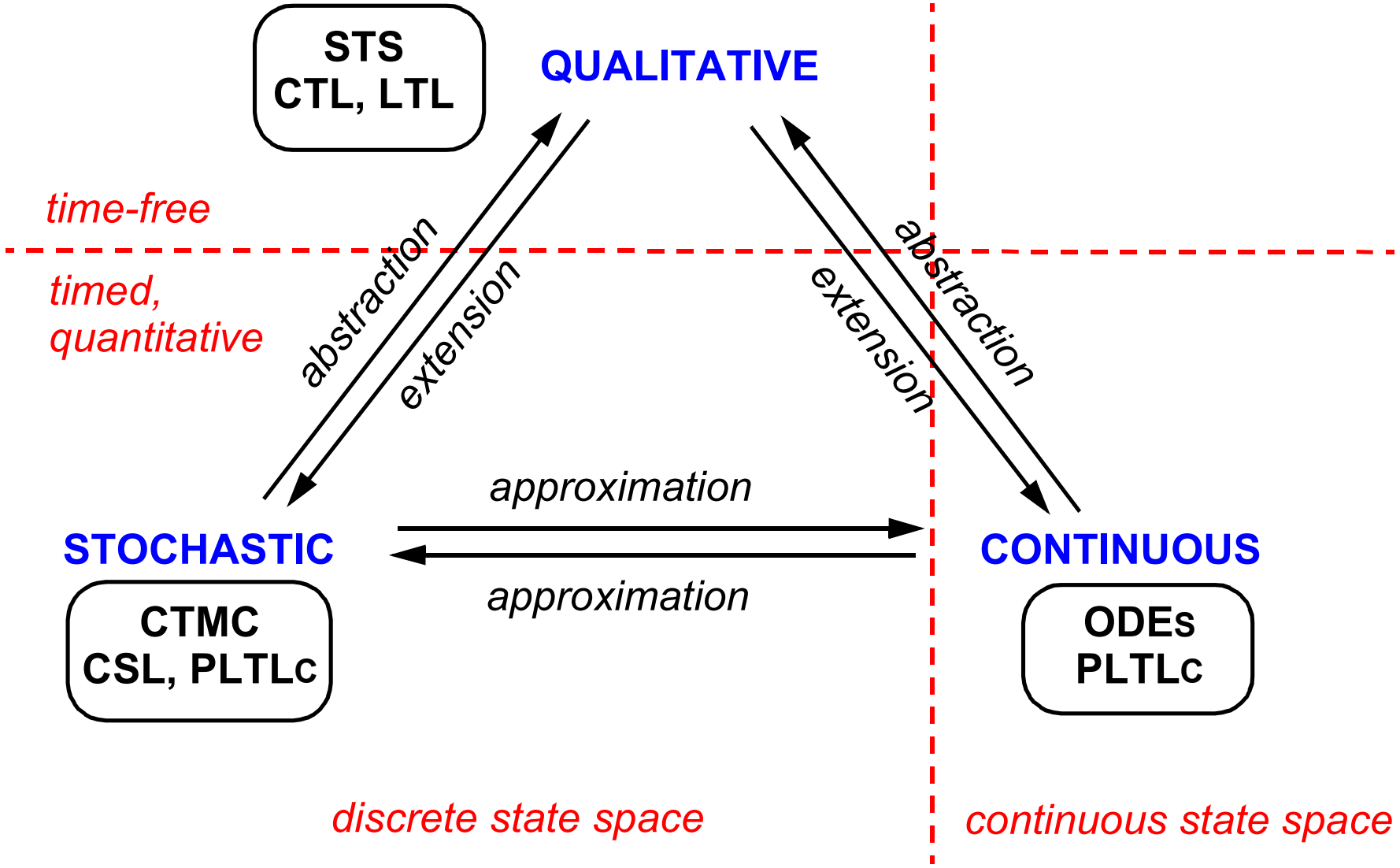

QUALITATIVE
time-free
timed,
quantitative
STOCHASTIC
CONTINUOUS
discrete state space
continuous state space

FRAMEWORK

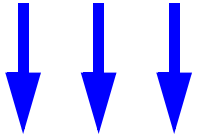

QUALITATIVE
time-free
timed,
quantitative
abstraction
extension
abstraction
extension
STOCHASTIC
CONTINUOUS
discrete state space
continuous state space


QUALITATIVE
time-free
timed,
quantitative
abstraction
extension
extension
abstraction
approximation
STOCHASTIC
CONTINUOUS
approximation
discrete state space
continuous state space

FRAMEWORK


STS
CTL, LTL
QUALITATIVE
time-free
timed,
quantitative
abstraction
extension
abstraction
extension
approximation
approximation
STOCHASTIC
CONTINUOUS
CTMC
CSL, PLTLc
ODEs
PLTLc
discrete state space
continuous state space

THREE MODELS SHARING STRUCTURE



QUANTITATIVE MODEL = QUALITATIVE MODEL

+

QUANTITATIVE PARAMETERS (KINETICS)

- **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*

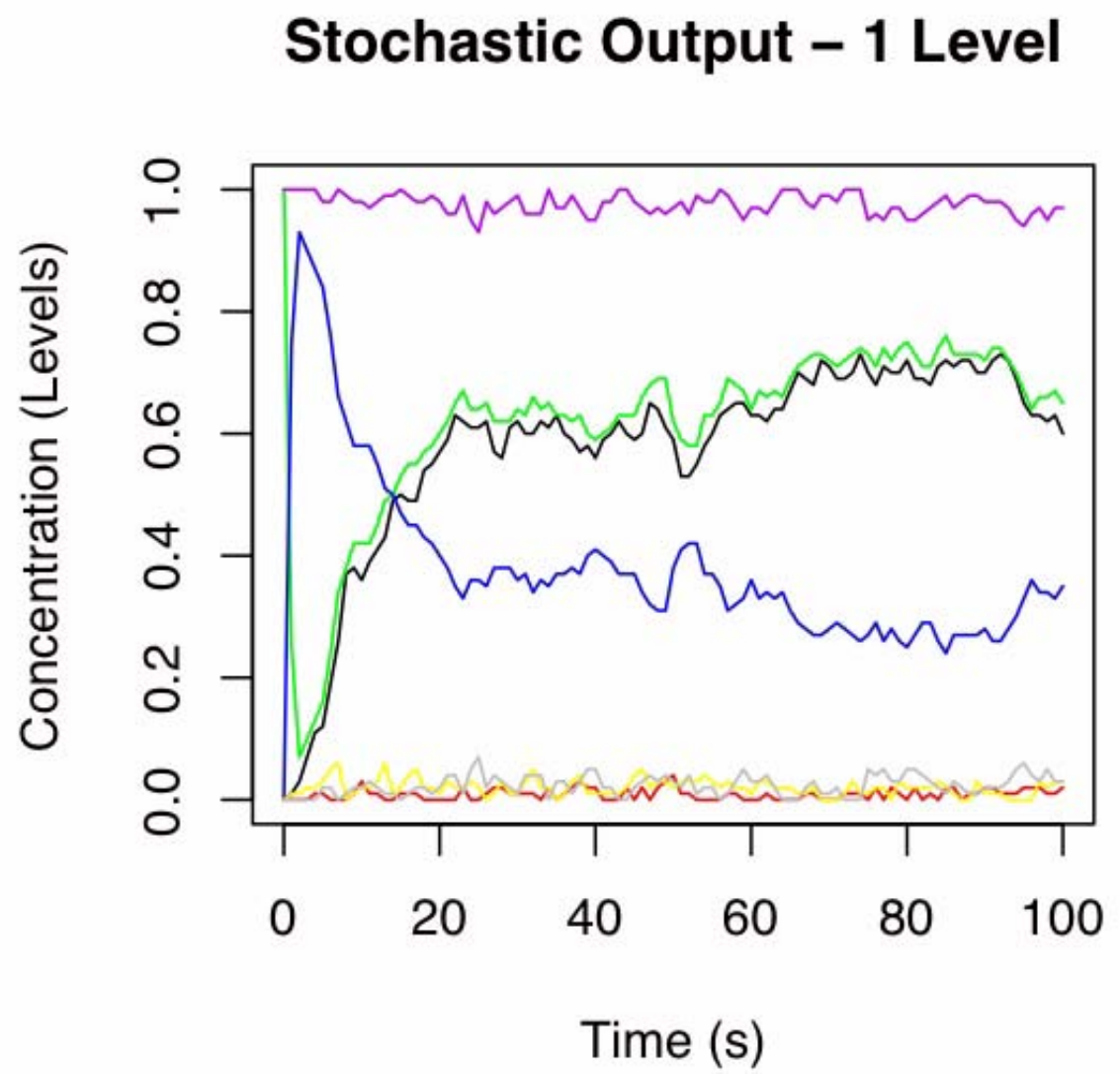
RATE FUNCTIONS

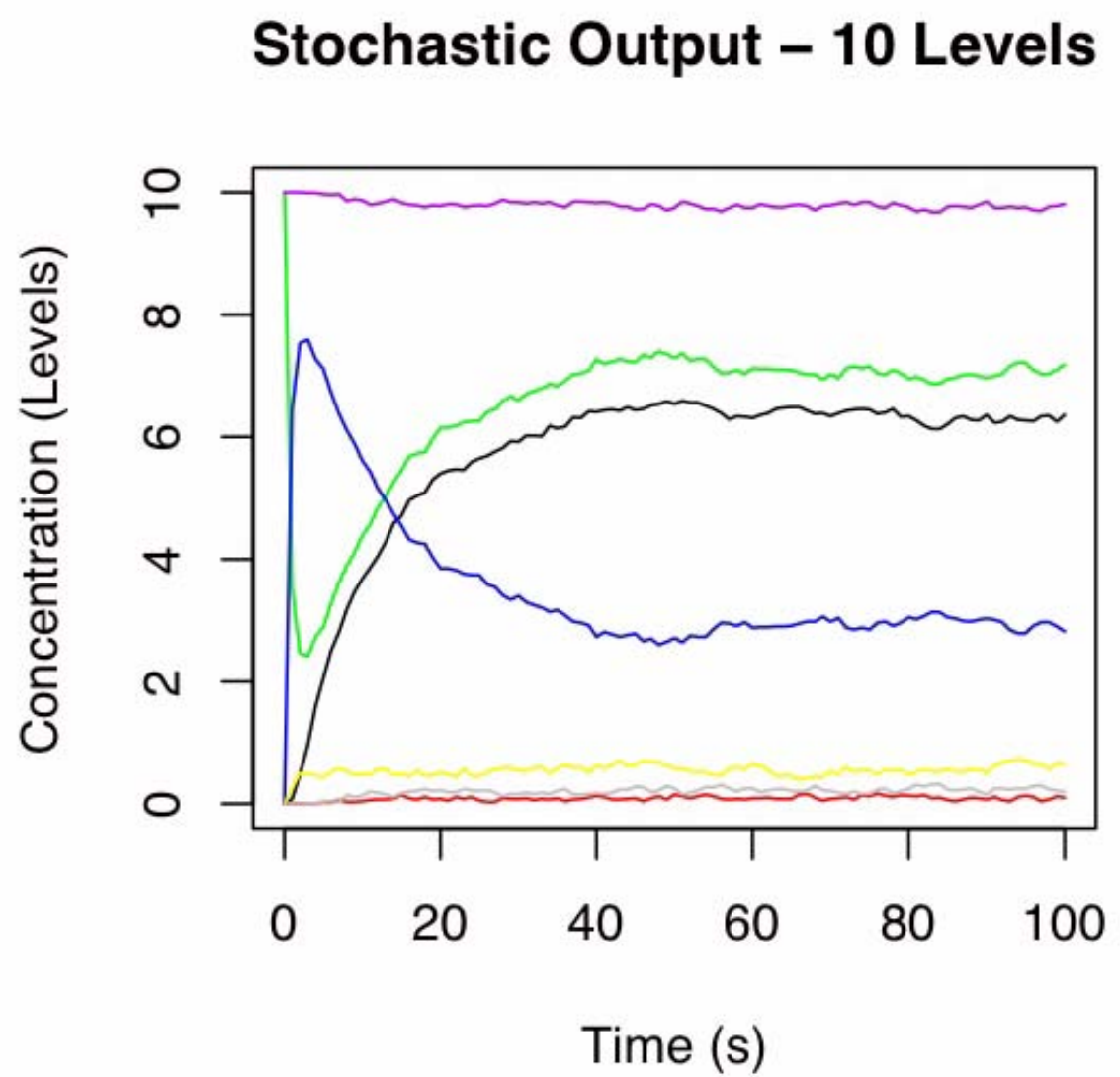
- *molecules semantics*

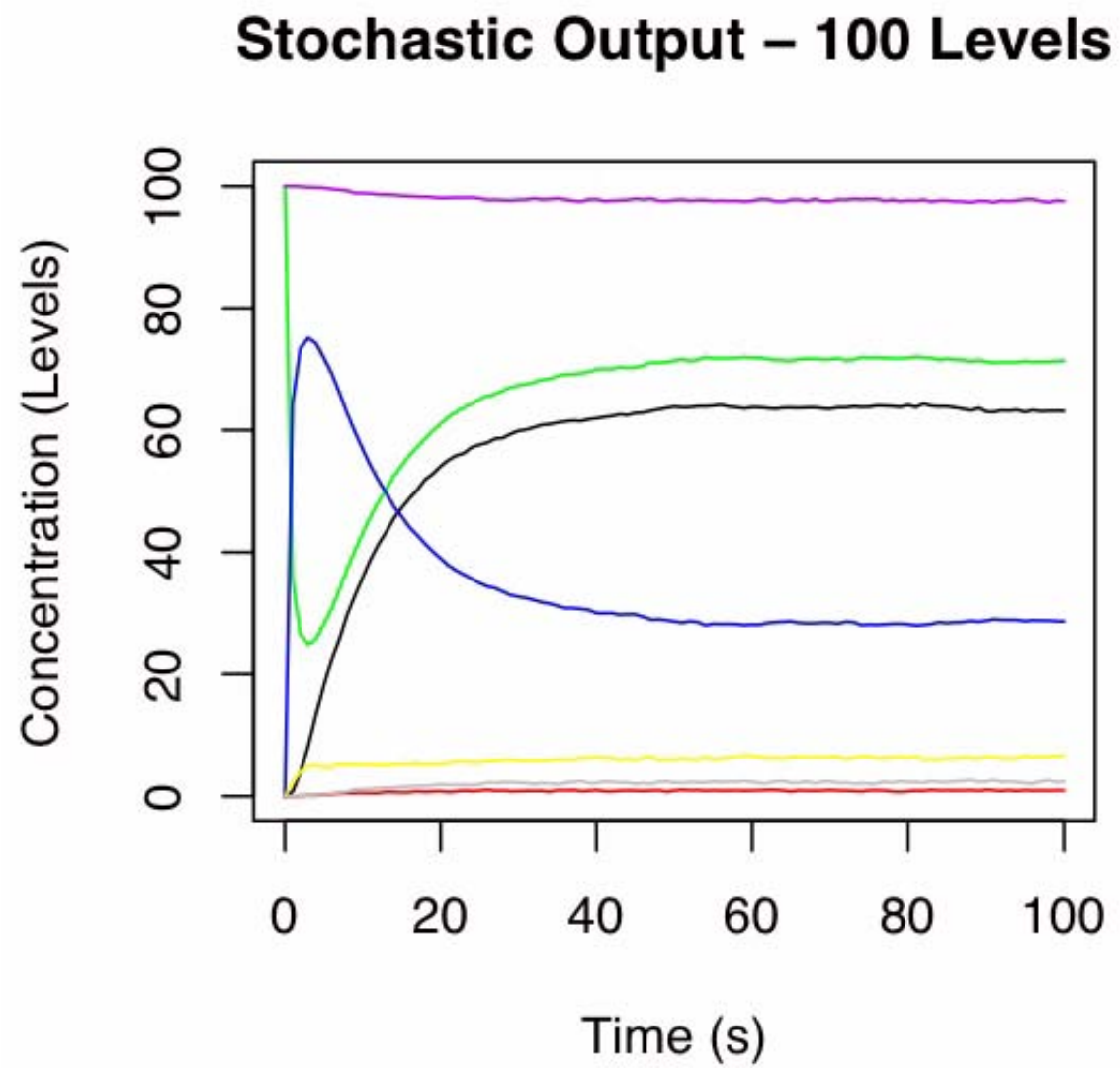
$$h_t := c_t \cdot \prod_{p \in {}^\bullet t} \binom{m(p)}{f(p,t)}$$

- *concentration levels semantics*

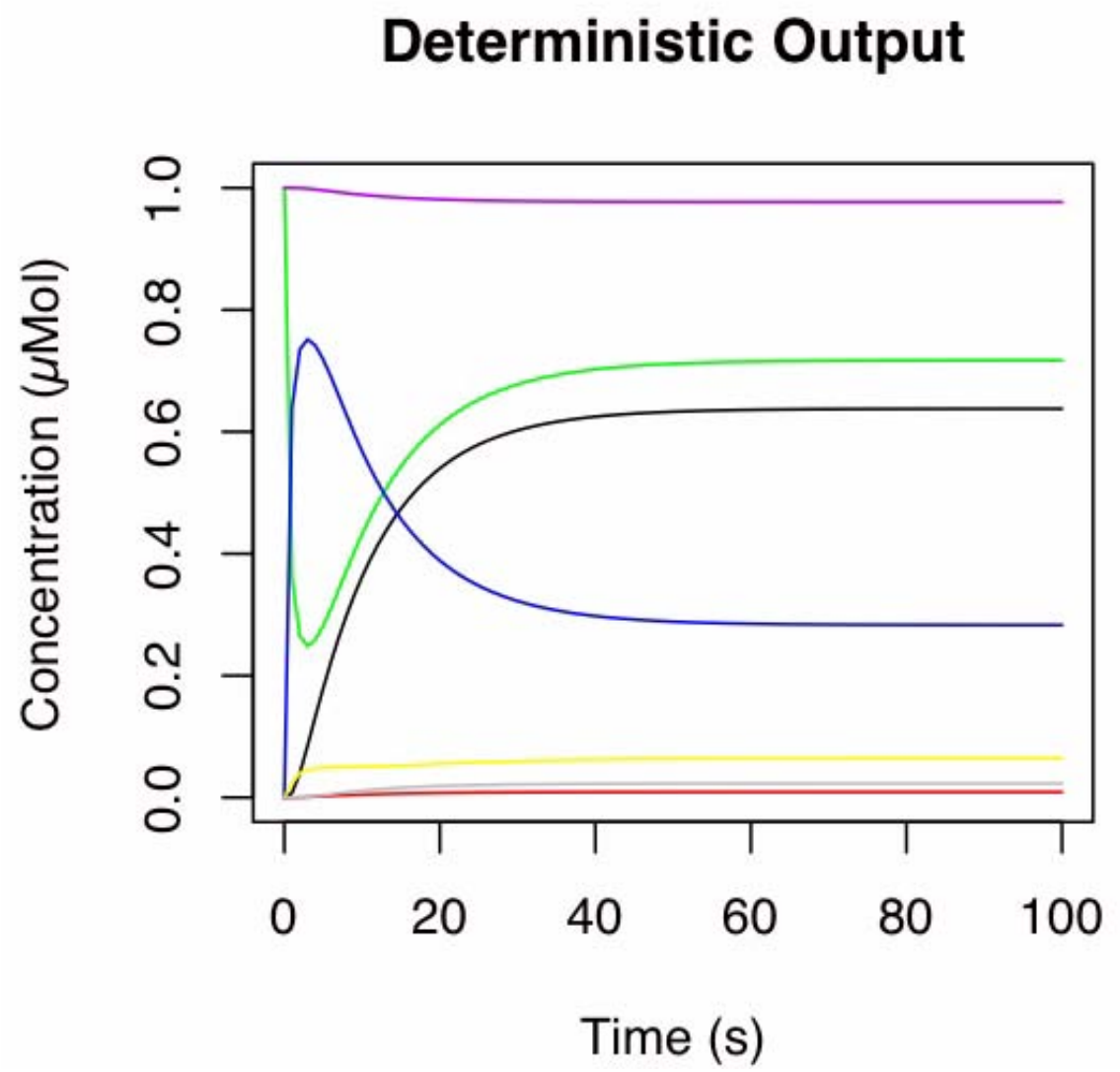
$$h_t := k_t \cdot N \cdot \prod_{p \in {}^\bullet t} \left(\frac{m(p)}{N}\right)$$


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)

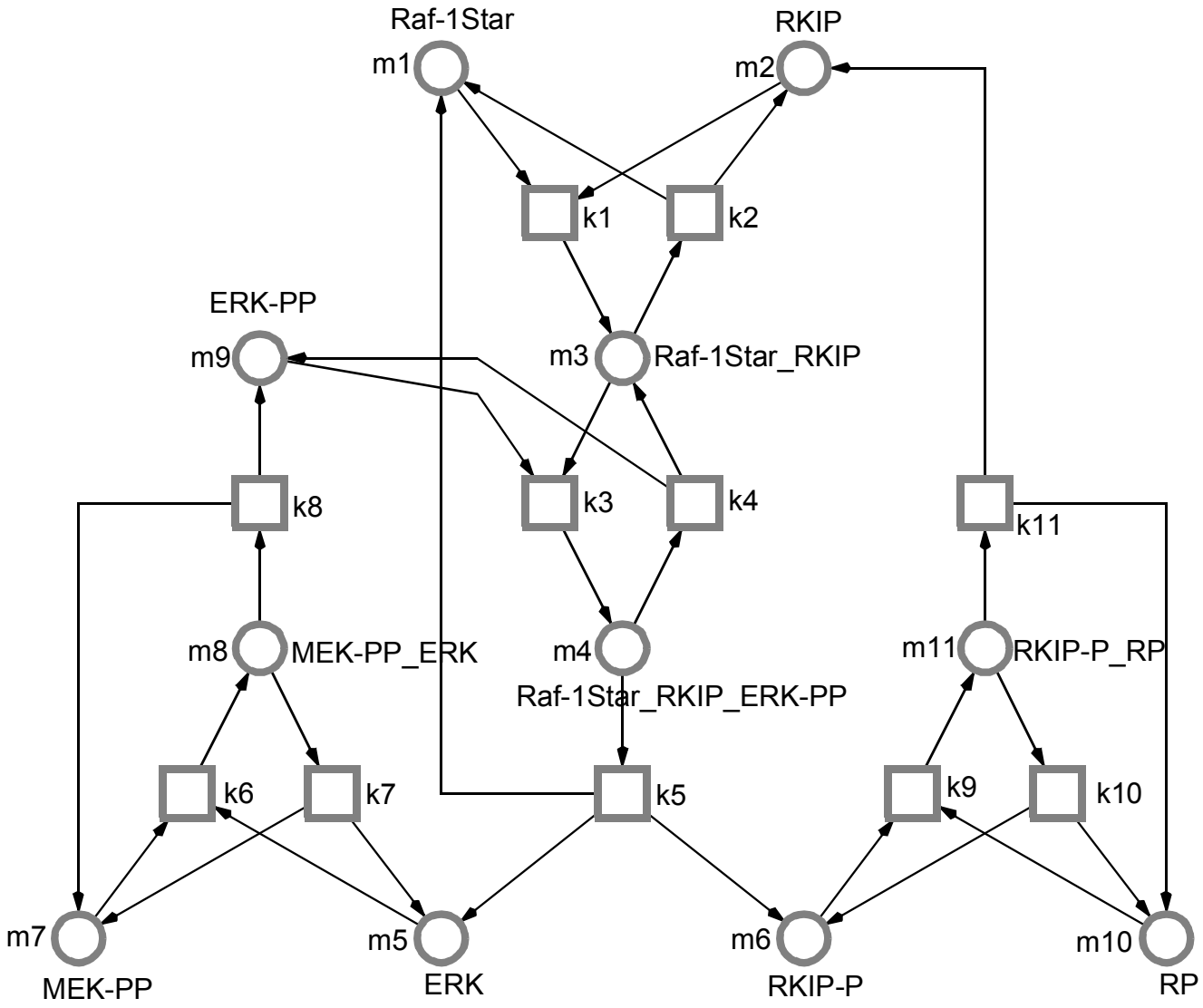

Stochastic Output – 100 Levels
Concentration (Levels)
0
20
40
60
80
100
0
20
40
60
80
100
Time (s)

DETERMINISTIC SIMULATION



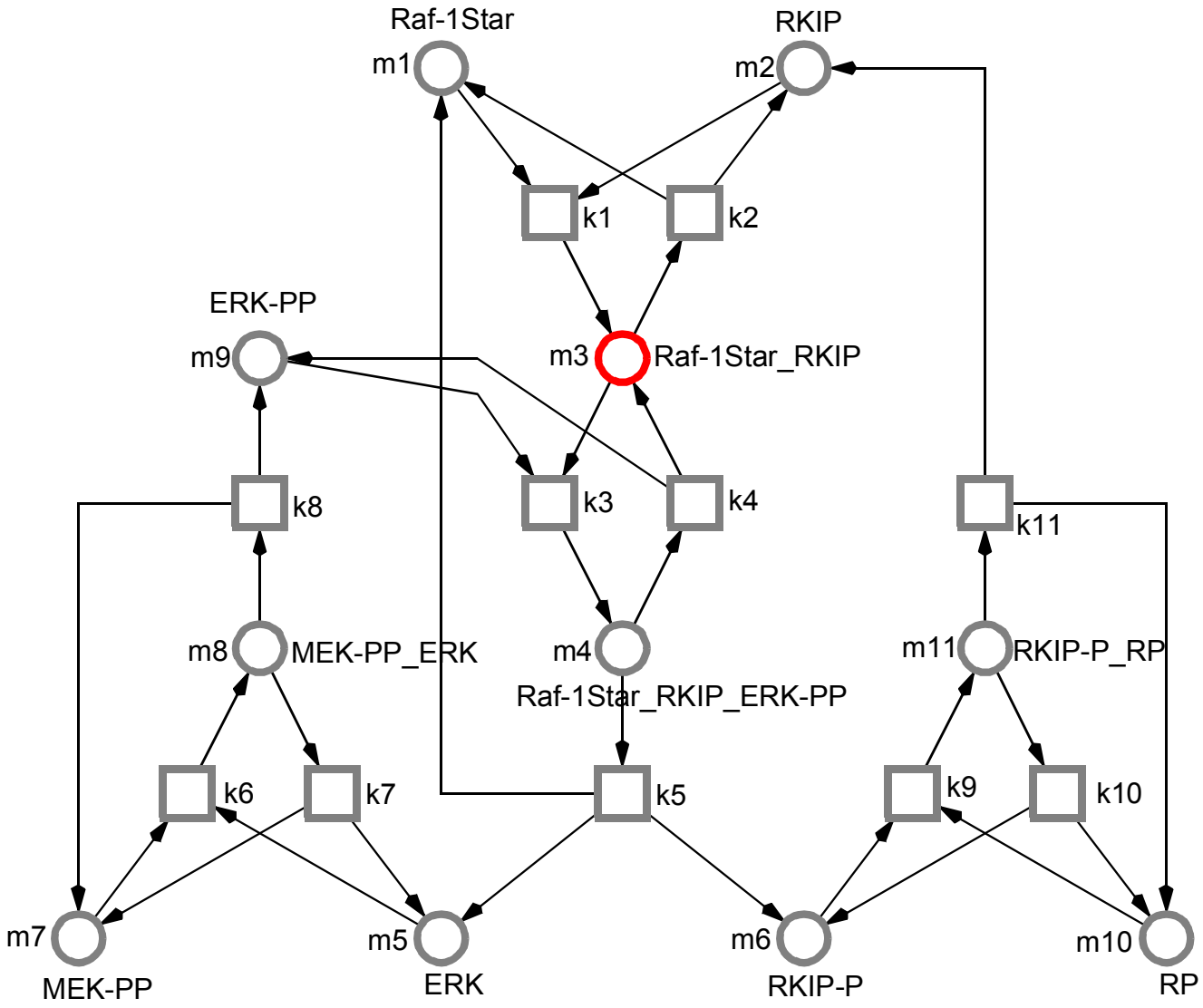
- **transitions fire continuously**
- **rate functions**
  - -> *any arithmetic function including*
    the transition's pre-places as real-valued variables and
    user-defined real-valued parameters
- **real-valued tokens**
  - -> *concentrations*
- **semantics: set of Ordinary Differential Equations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

CONTINUOUS PETRI NET DEFINES ODES



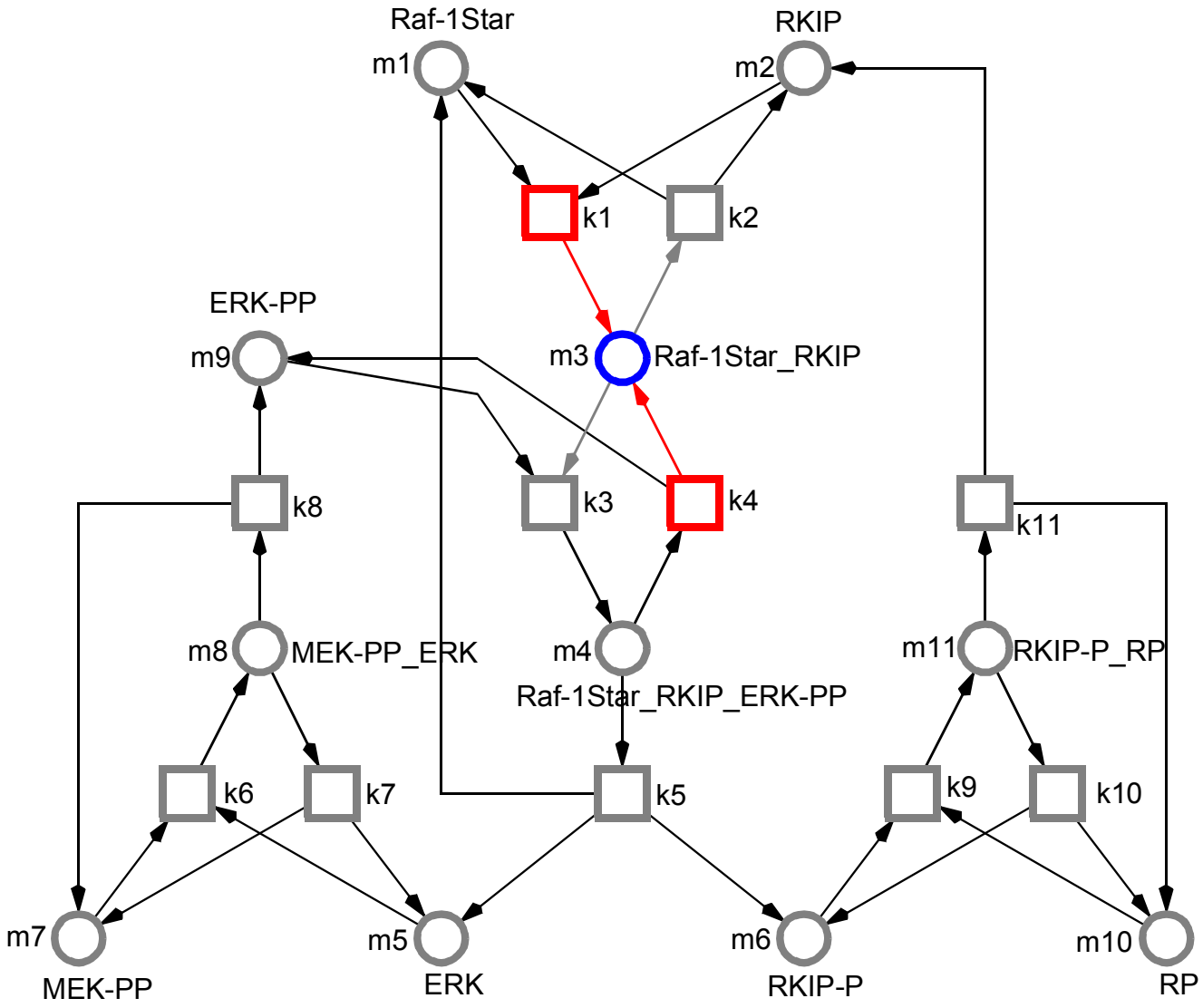
CONTINUOUS PETRI NET DEFINES ODES

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



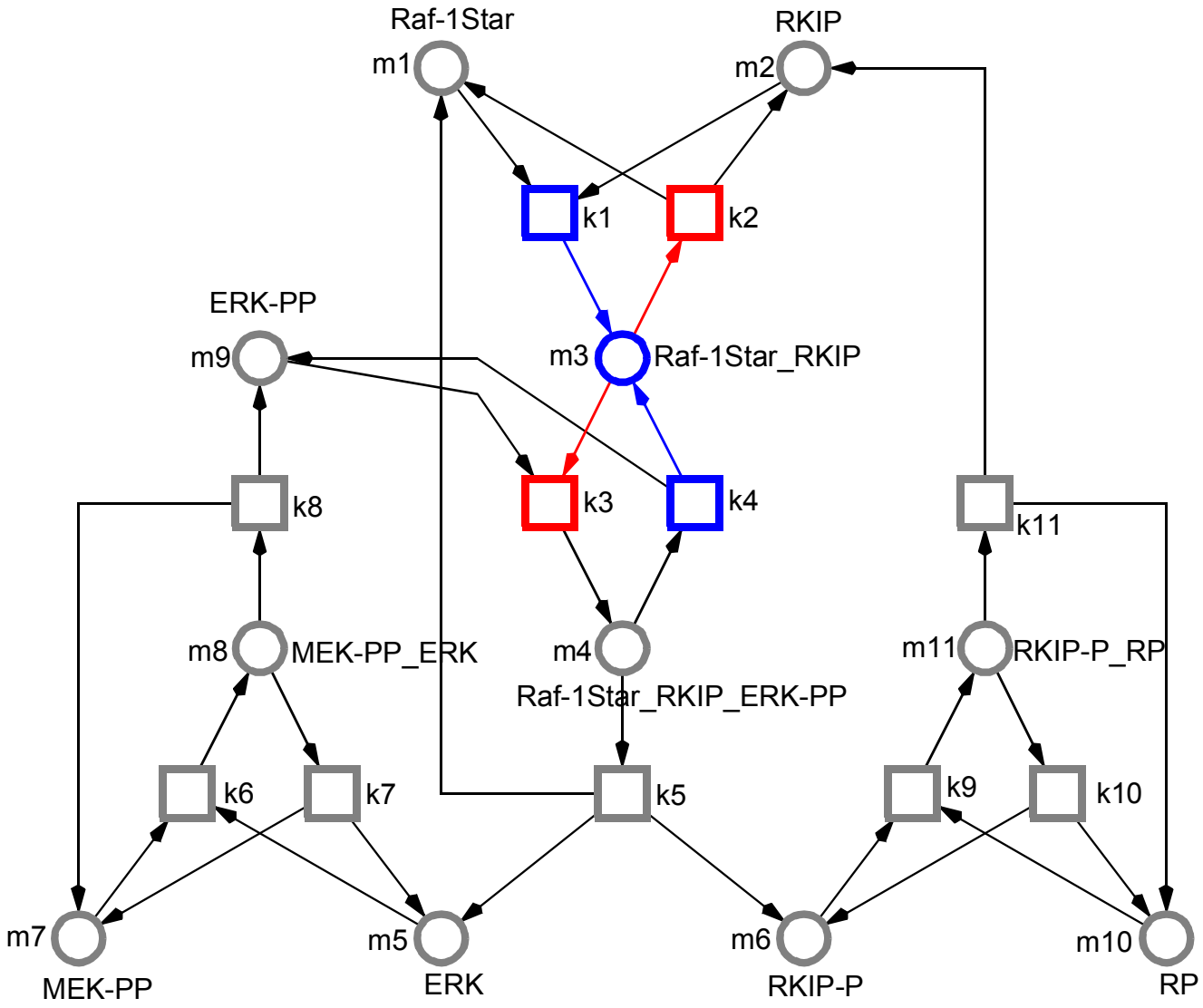
CONTINUOUS PETRI NET DEFINES ODES

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



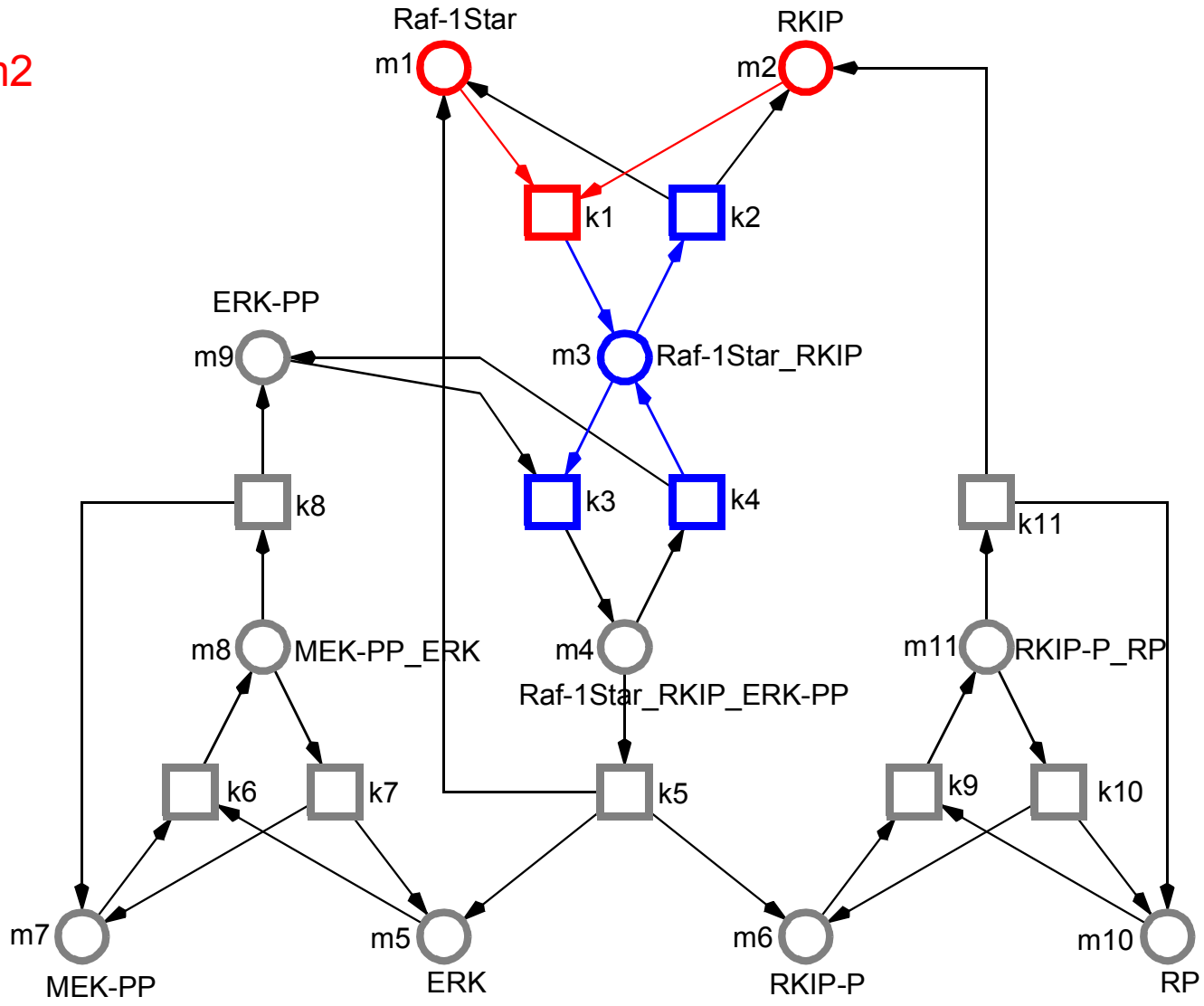
CONTINUOUS PETRI NET DEFINES ODES

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



CONTINUOUS PETRI NET DEFINES ODES

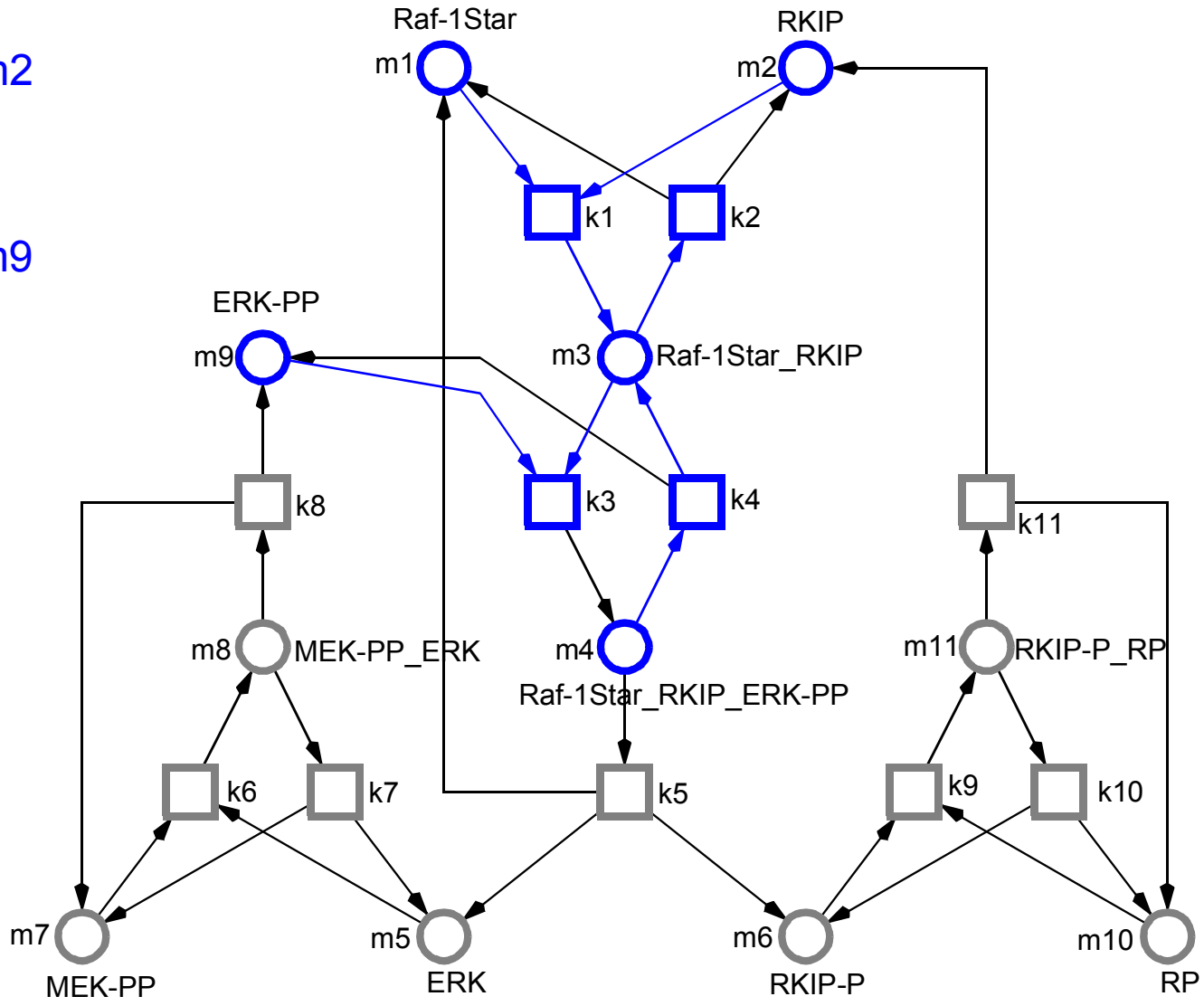
$$\frac{dm3}{dt} = + k1 * m1 * m2 + r4 - r2 - r3$$



monika.heiner@informatik.tu-cottbus.de

CONTINUOUS PETRI NET DEFINES ODES

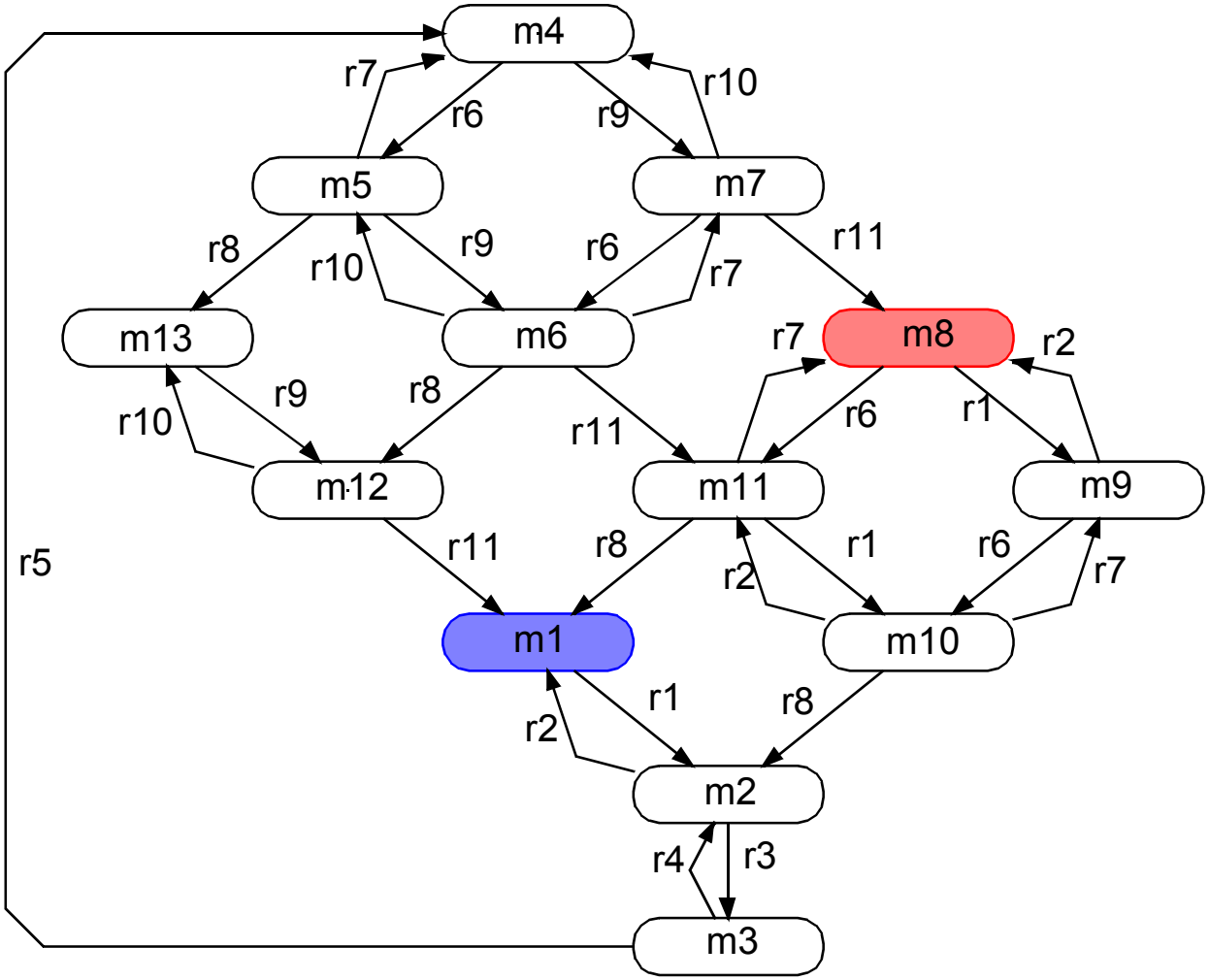
$$\frac{dm3}{dt} = + k1 * m1 * m2 + k4 * m4 - k2 * m3 - k3 * m3 * m9$$



About the Relation SPN - CPN

EX1 - RKIP, REACHABILITY GRAPH (STS)

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

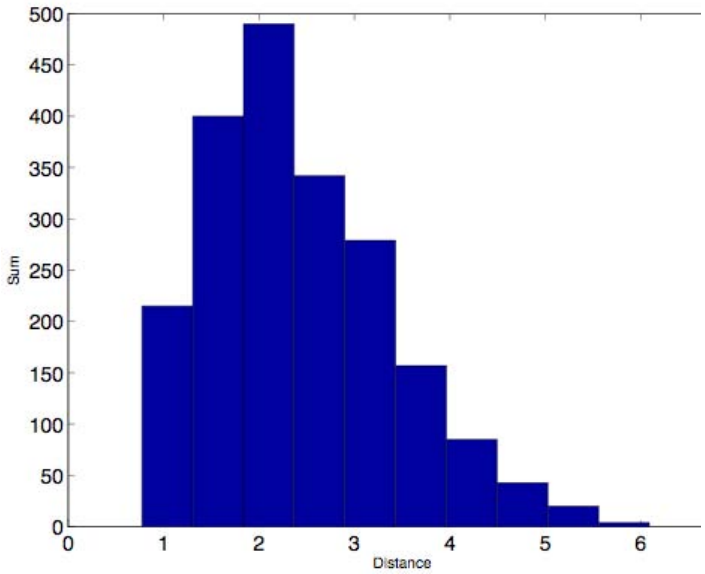


EX1 - RKIP, QUANTITATIVE ANALYSIS

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

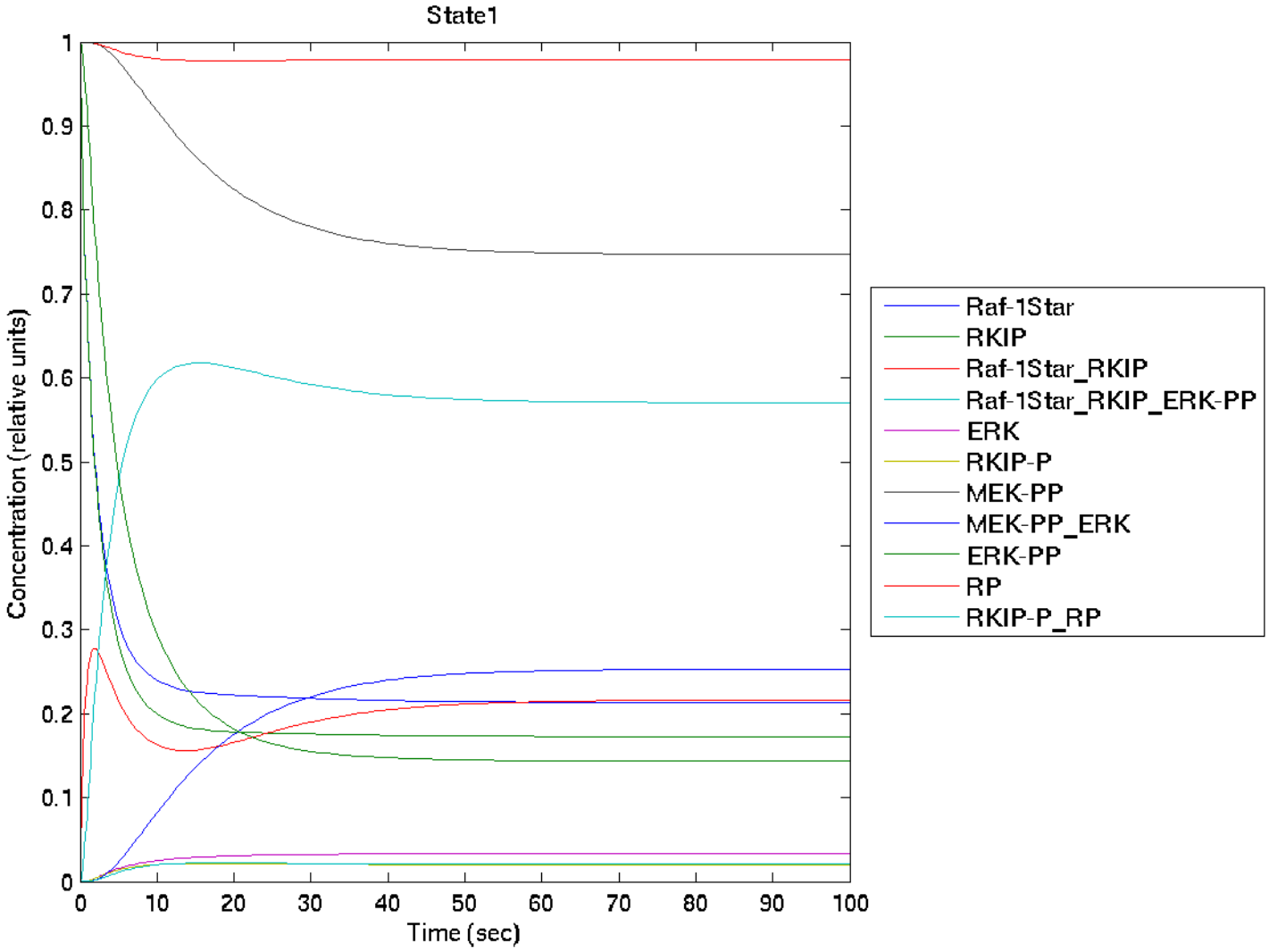


Distribution of `bad' steady states as euclidean distances from the `good' final steady state

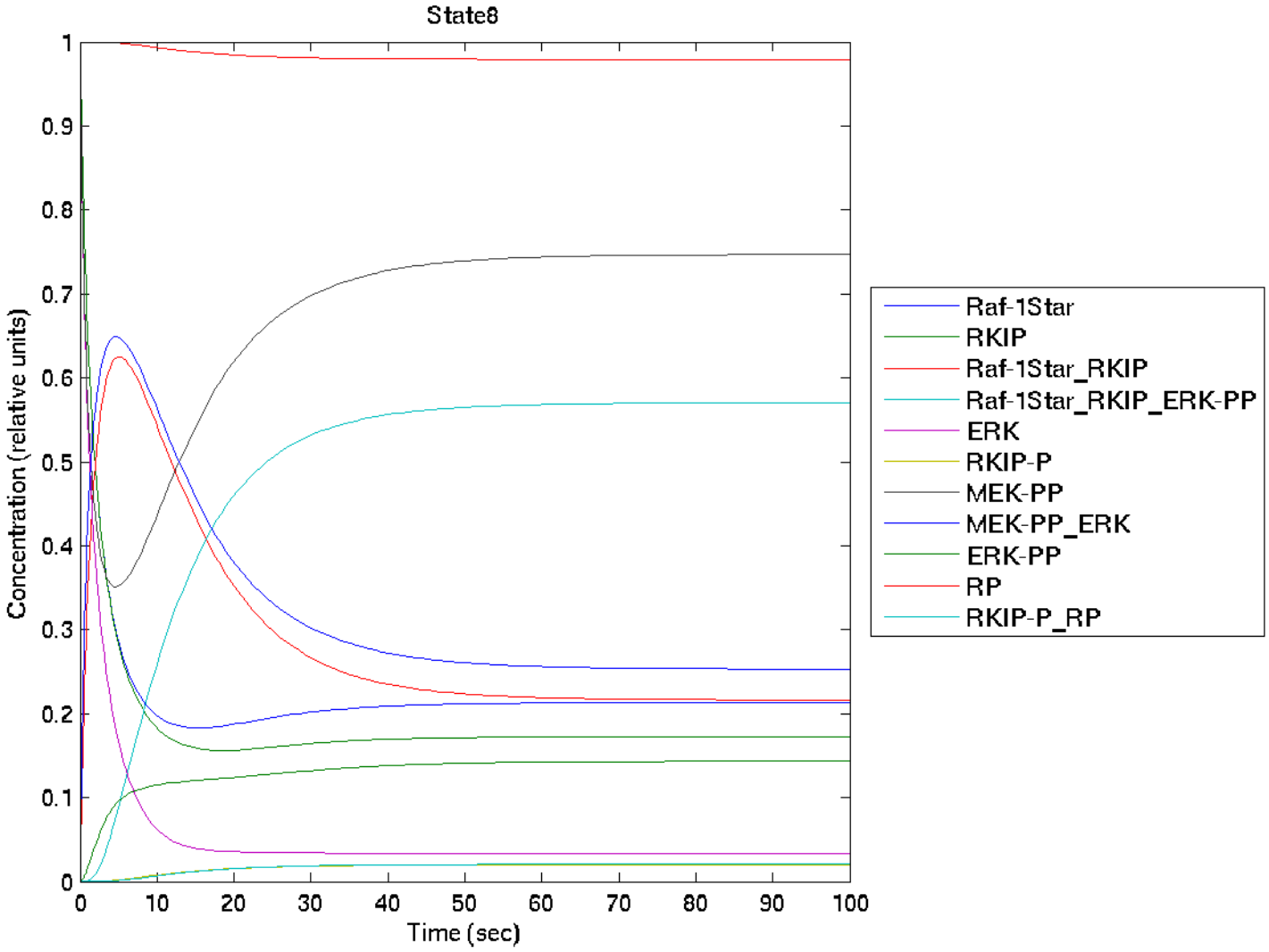
13 “good” state configurations

the “bad” ones

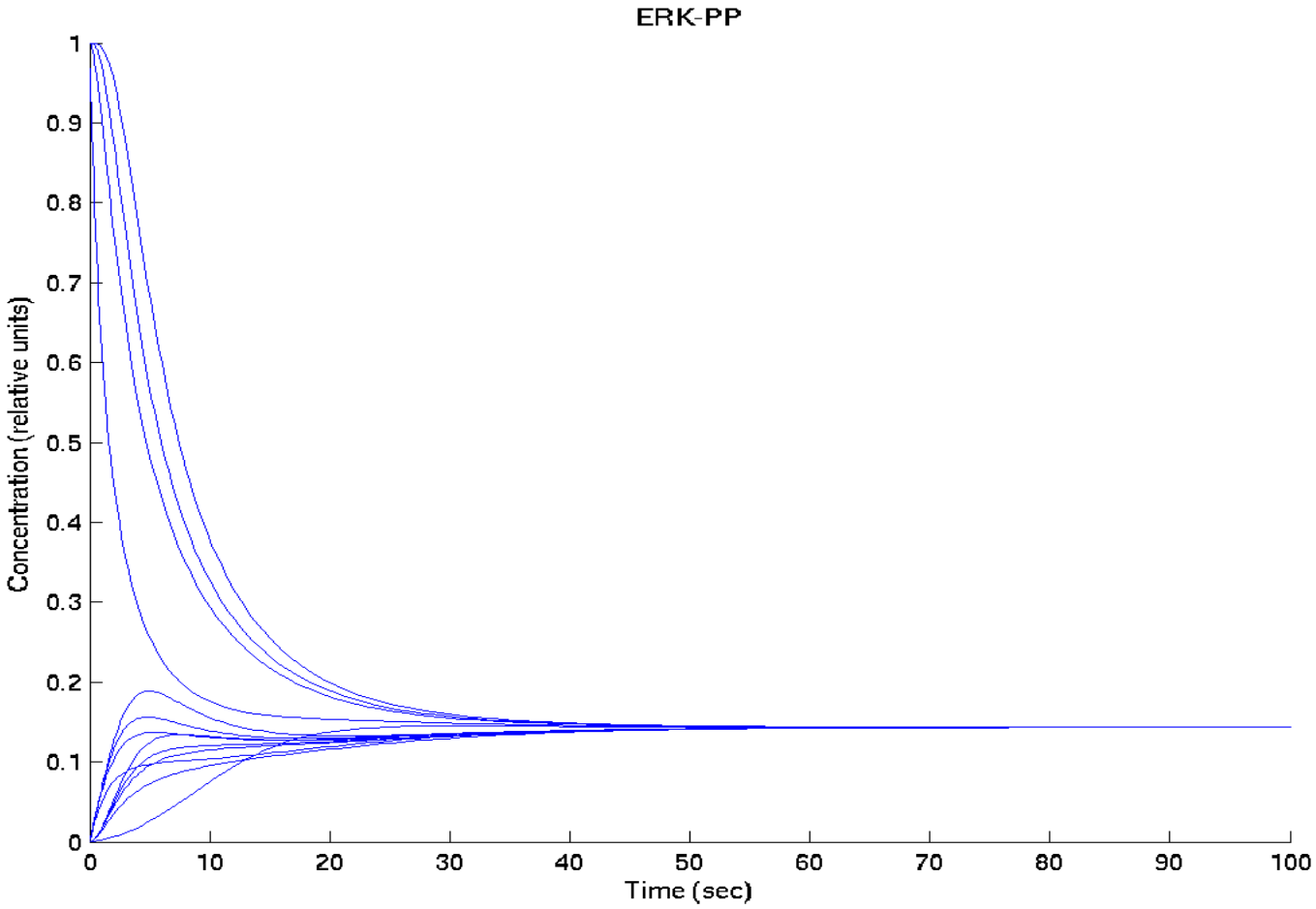
EX1 - RKIP, QUANTITATIVE ANALYSIS



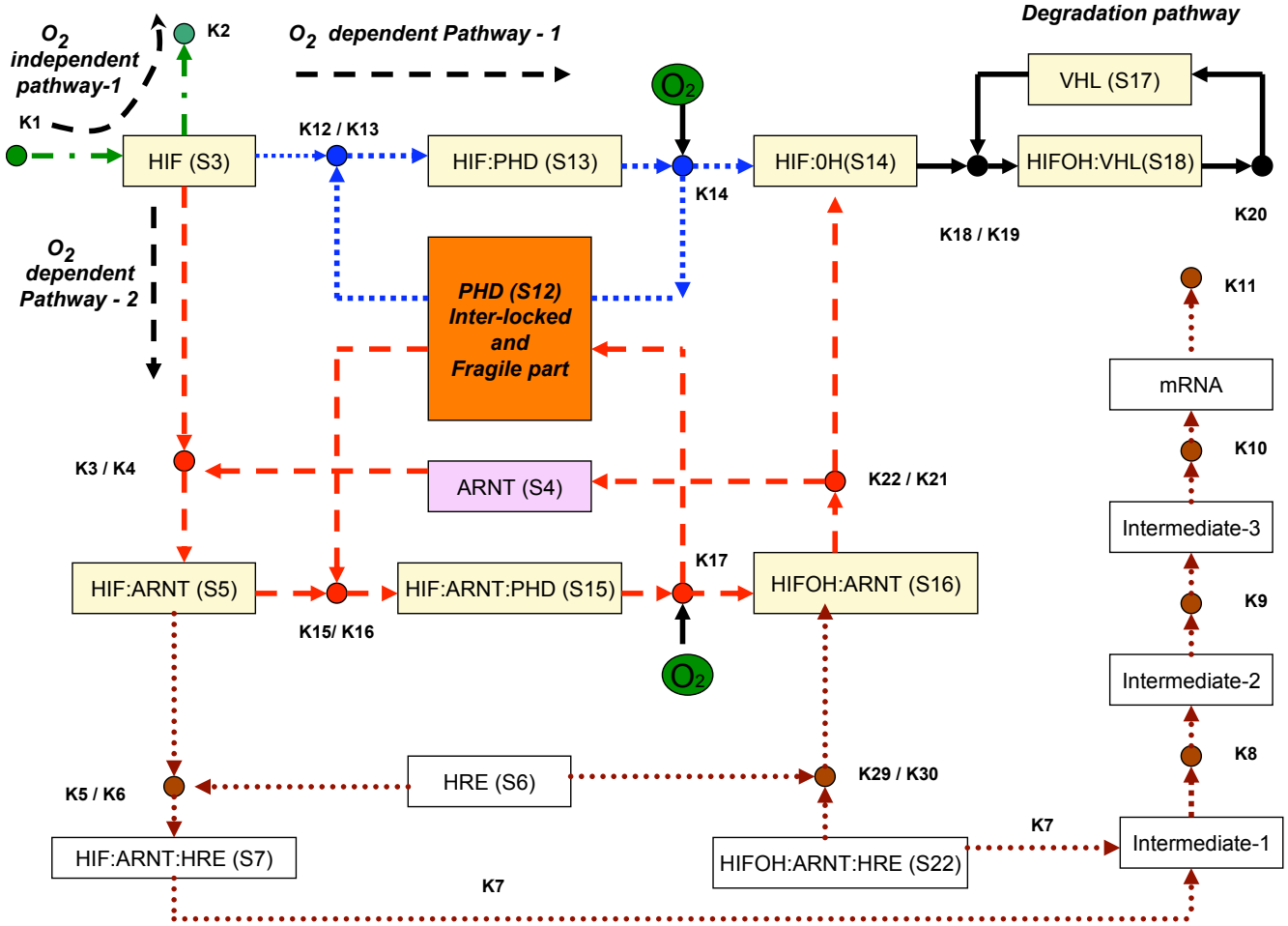
EX1 - RKIP, QUANTITATIVE ANALYSIS



EX1 - RKIP, QUANTITATIVE ANALYSIS

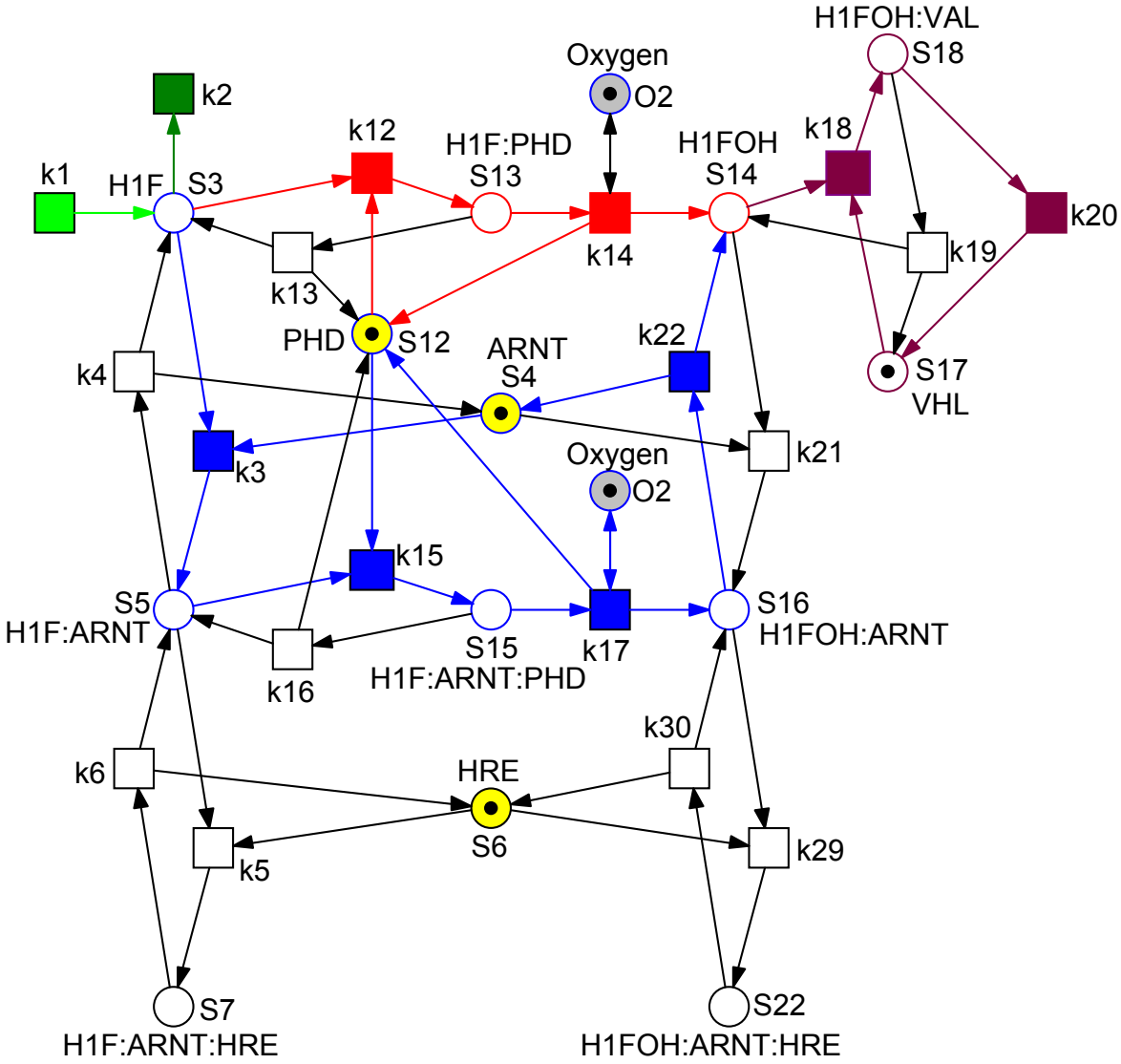


[YU ET AL. 2007]


O_2 independent pathway-1
K1
K2
O_2 dependent Pathway - 1
Degradation pathway
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
Intermediate-3
K3 / K4
ARNT (S4)
K22 / K21
K9
Intermediate-2
HIF:ARNT (S5)
K15/ K16
HIF:ARNT:PHD (S15)
K17
HIFOH:ARNT (S16)
O_2
K8
HRE (S6)
K29 / K30
K5 / K6
K7
Intermediate-1
HIF:ARNT:HRE (S7)
HIFOH:ARNT:HRE (S22)
K7

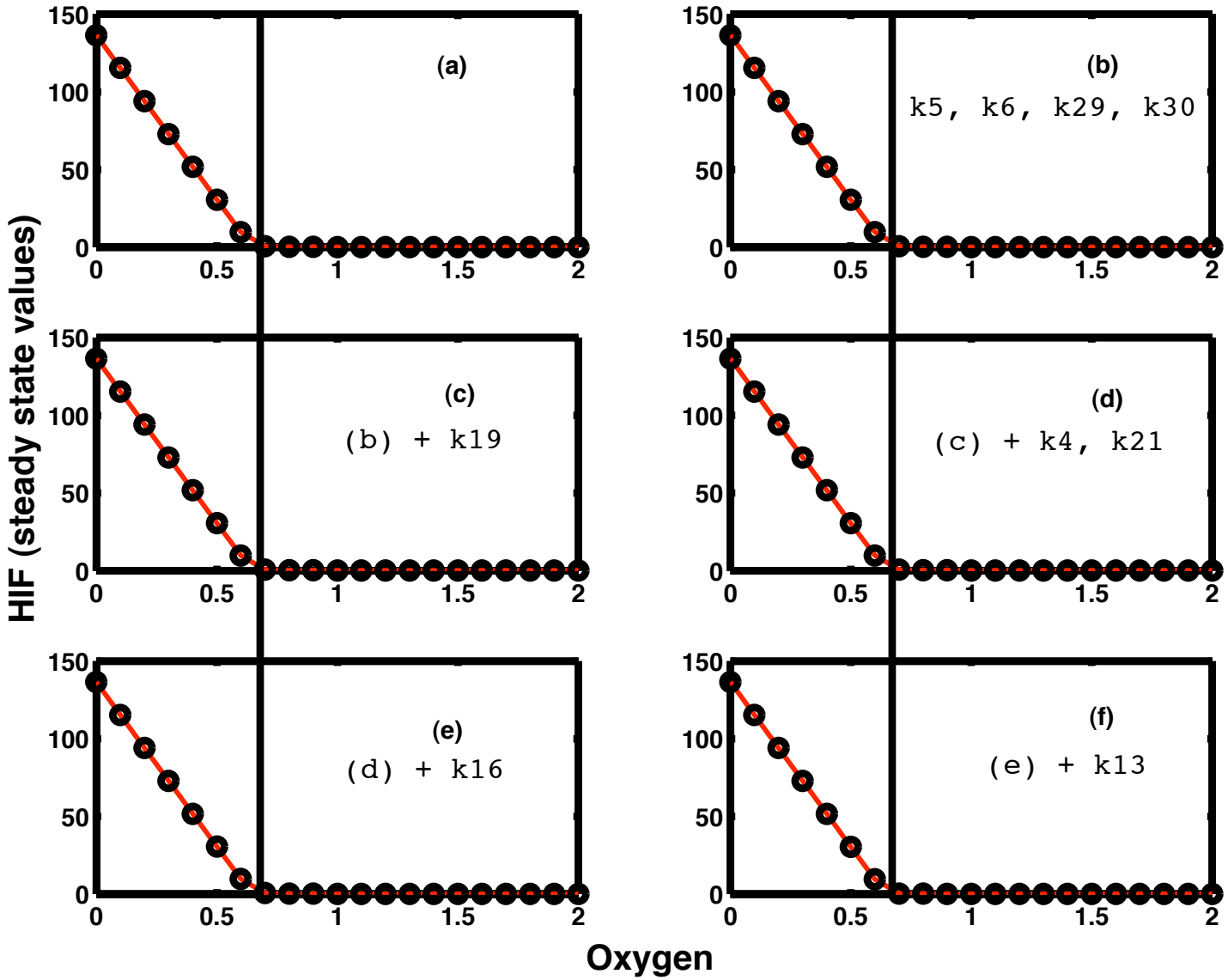
EX2 - HYPOXIA

[HEINER; SRIRAM 2010]

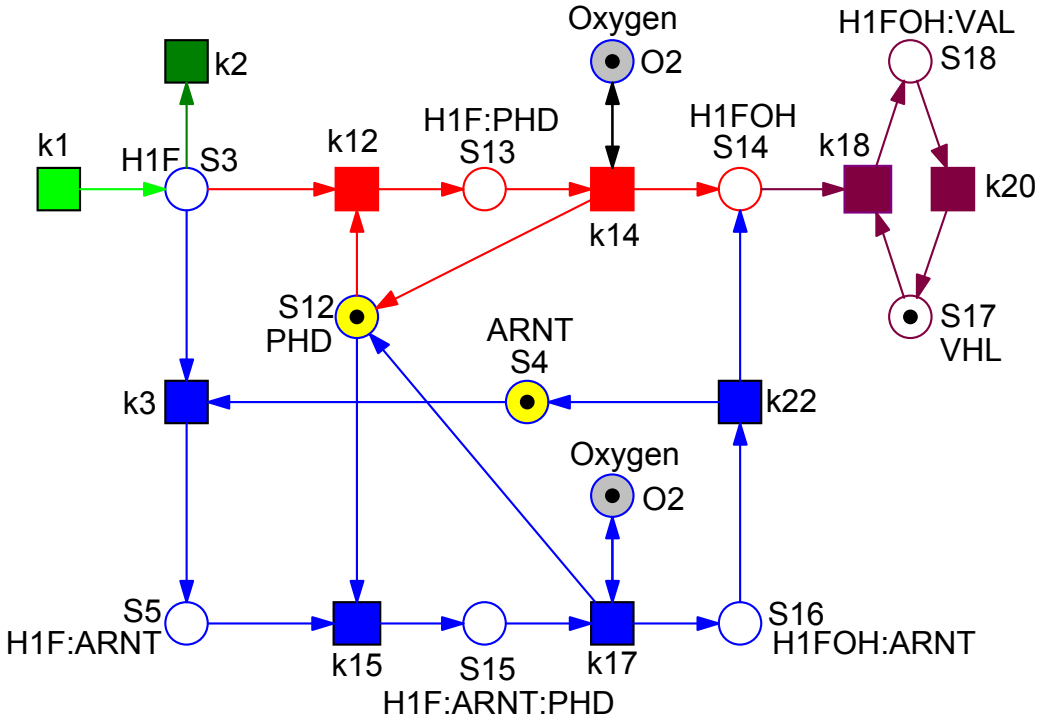


monika.heiner@informatik.tu-cottbus.de

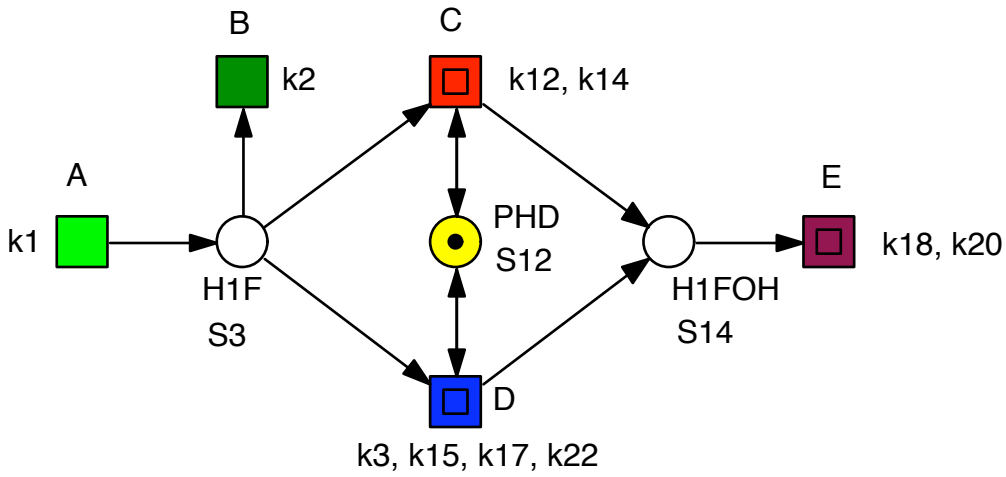
EX2 - HYPOXIA


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

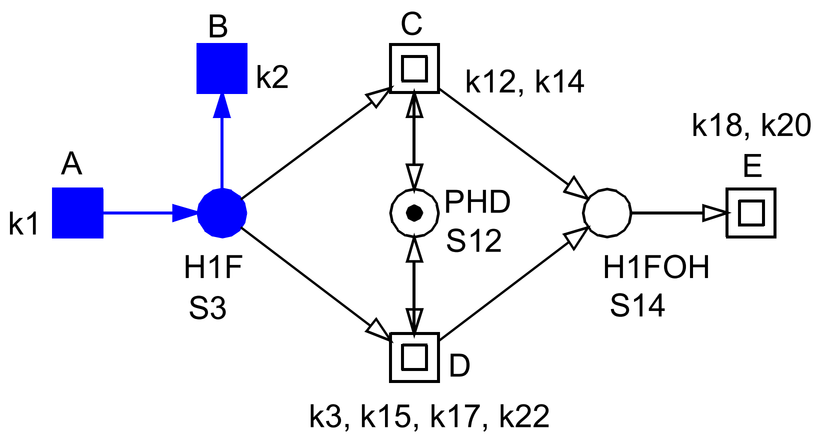
EX2 - HYPOXIA

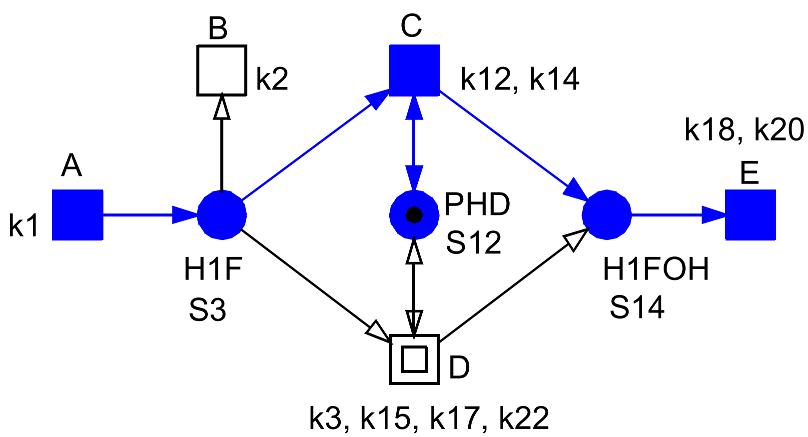

Oxygen
O2
H1FOH:VAL
S18
k2
k1
H1F
S3
k12
H1F:PHD
S13
H1FOH
S14
k18
k20
k14
S12
PHD
S17
VHL
ARNT
S4
k3
k22
Oxygen
O2
S5
H1F:ARNT
S16
H1FOH:ARNT
k15
S15
H1F:ARNT:PHD
k17

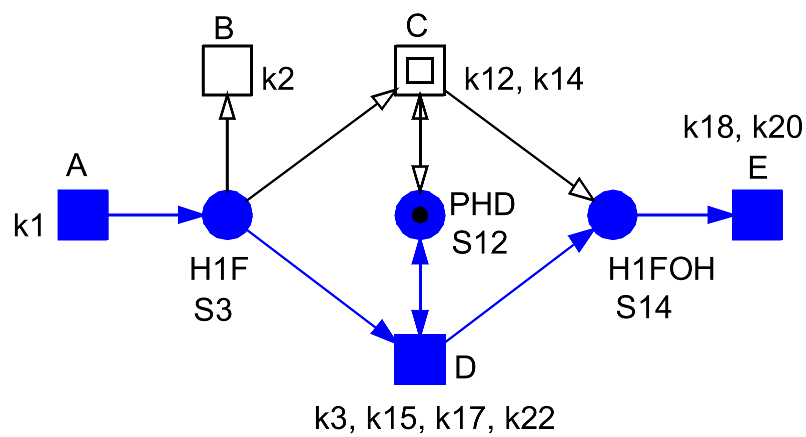
EX2 - HYPOXIA


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

Ex2 - Hypoxia


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


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


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

BUT,

THERE ARE MANY EXAMPLES WHERE THE TRANSITION SPN -> CPN COMES WITH COUNTERINTUITIVE EFFECTS.

OUR TOOL BOX

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*
  - -> *symbolic and simulative model checking*

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

- **history**
  - -> *predecessor: Petri Net Editor PED, 1992 - 2004*
  - -> *initial implementation concepts 1997*
  - -> *core implementation 2004*
  - -> *many Master Theses*

- **platform-independent**
  - -> *implementation in C++*
  - -> *wxWidgets (http://www.wxwidgets.org)*

- **supported operating systems**
  - -> *MAC OS X*
  - -> *Windows*
  - -> *Linux (selected distributions)*

- **now about 120,000 lines of code (without running extensions)**

-> *standard analysis techniques of Petri net theory -> QPN*

-> *inspired by INA*

- **structural analysis**
  - -> *net classes: SM, SG, FC, EFS, ES*
  - -> *siphon/trap property, rank theorem*

- **analysis based on incidence matrix**
  - -> *structural boundedness test*
  - -> *place/transition invariants*
  - -> *Abstract Dependent Transition sets (ADT sets)*

- **reachability/coverability graph**
  - -> *explicite model checking ->RG of XQPN*

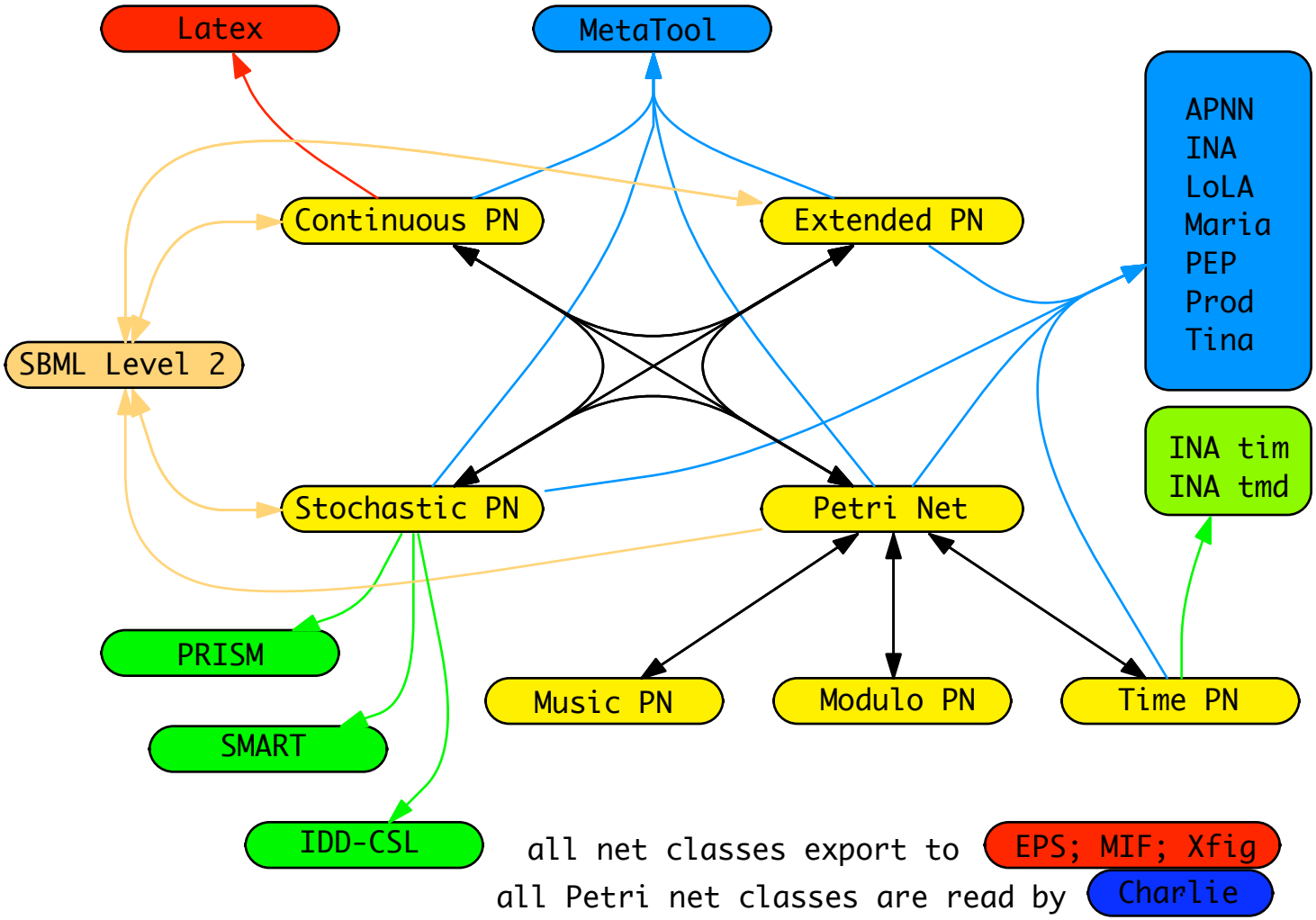
- **structural reduction**

- **Java thread programming with GUI**

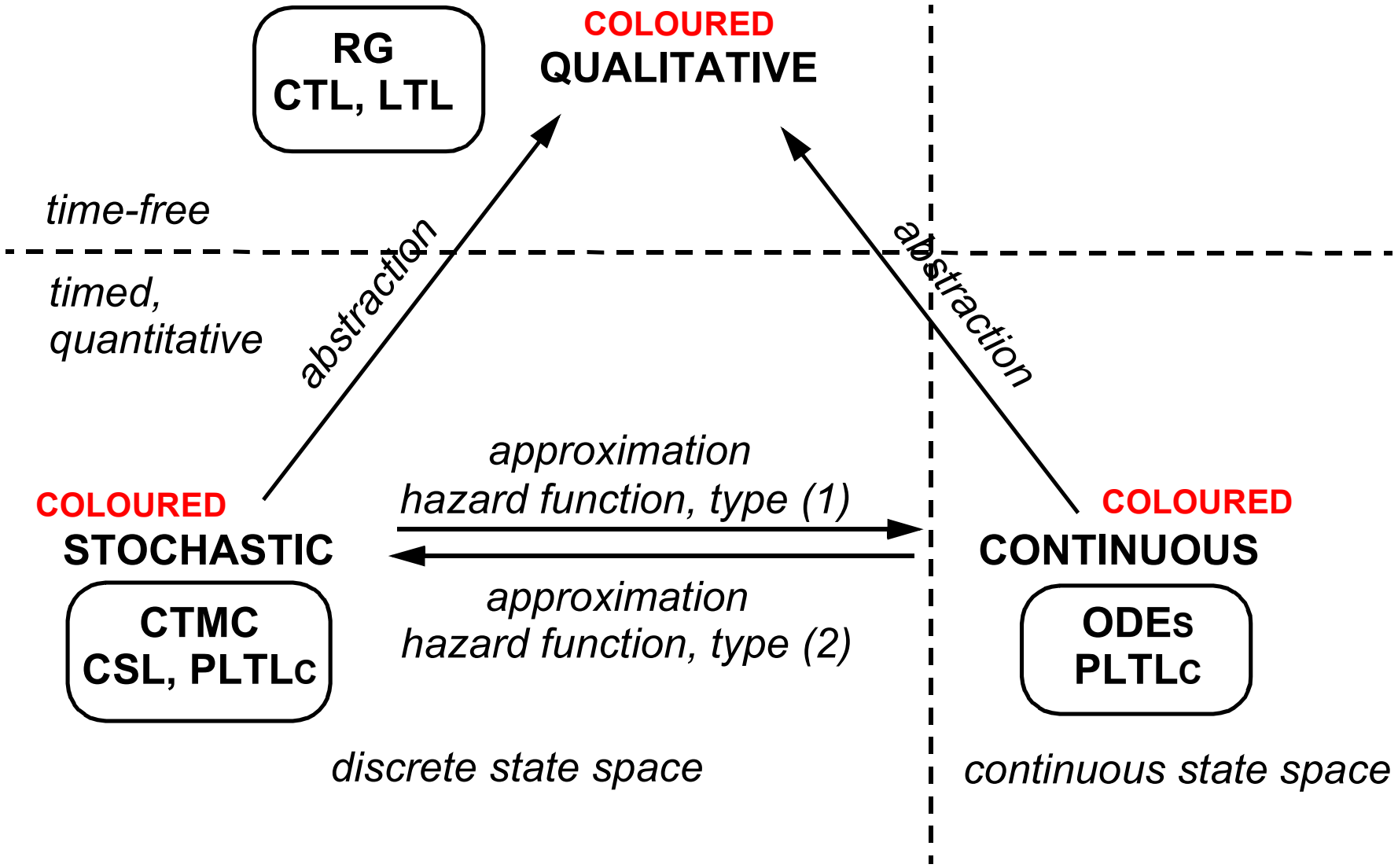
MARCIE

- **Model checking And Reachability analysis done effiCIEntly**
  - -> *symbolic state space analysis (strongly connected components)*
    - -> *Interval Decision Diagrams*
  - -> *model checking of XQPN, SPN, XSPN*
- **XQPN: symbolic CTL model checking**
- **SPN: symbolic CSL model checking**
  - -> *"matrix free" transient and steady state analysis*
  - -> *parallelized*
  - -> *full CSL model checking + rewards*
- **XSPN: simulative PLTL model checking**
  - -> *distributed*
  - -> *in-line/ off-line traces*
- **command line tool, written in C++**

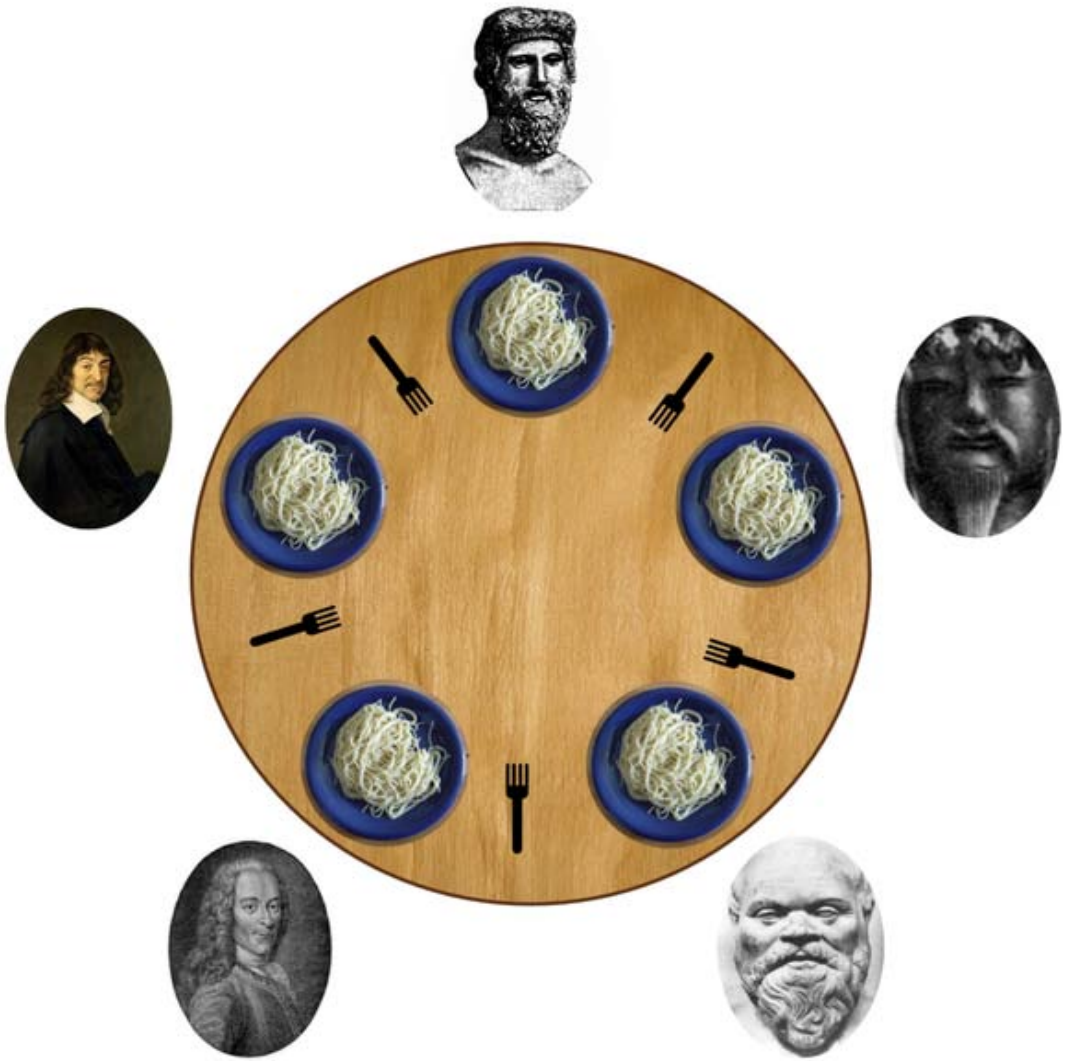
SNOOPY'S EXPORT FEATURES



LATEST NEWS


RG
CTL, LTL
COLOURED
QUALITATIVE
time-free
timed,
quantitative
abstraction
abstraction
approximation
hazard function, type (1)
approximation
hazard function, type (2)
COLOURED
STOCHASTIC
CTMC
CSL, PLTLc
COLOURED
CONTINUOUS
ODEs
PLTLc
discrete state space
continuous state space

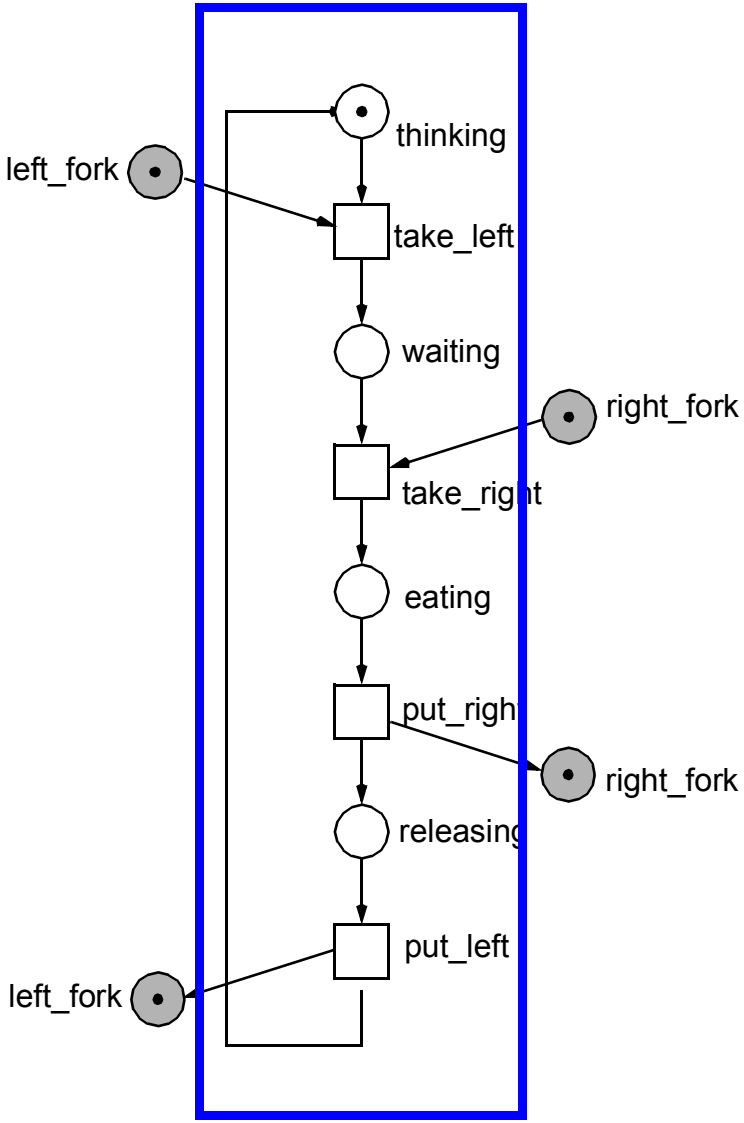
COLOURED PETRI NETS, EXAMPLE

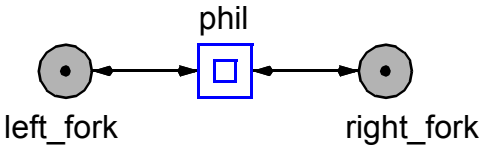


http://en.wikipedia.org/wiki/Dining_philosophers_problem

COLOURED PETRI NETS, EXAMPLE

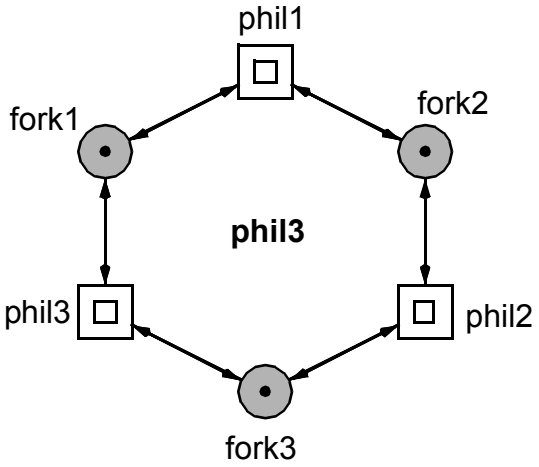
PHILOSOPHER PATTERN

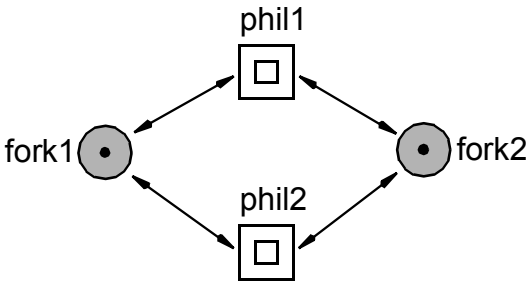


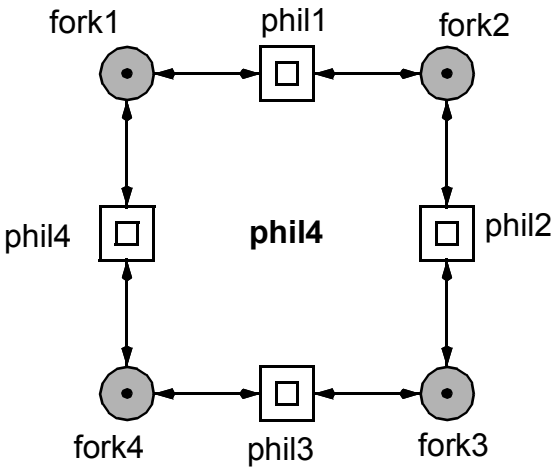


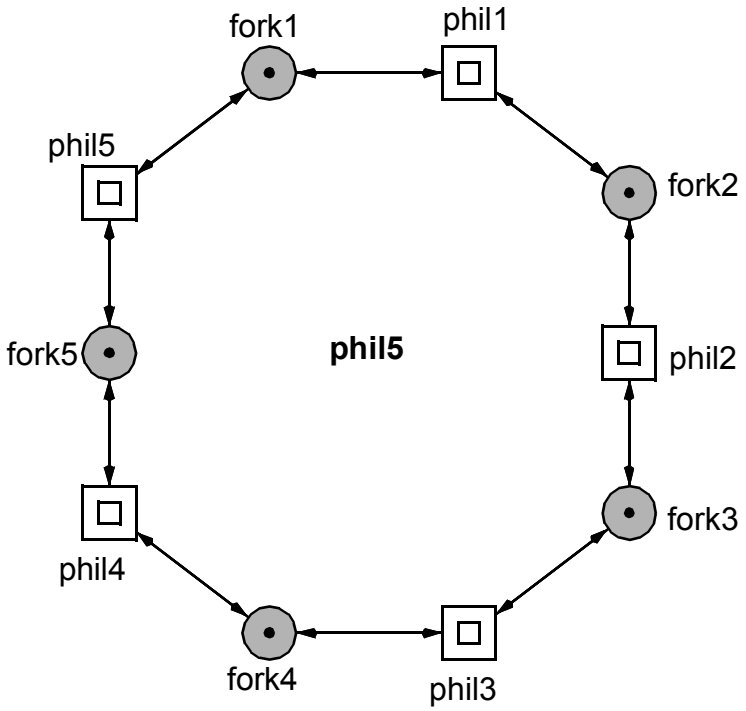
COLOURED PETRI NETS, EXAMPLE

SYSTEMS OF PHILOSOPHERS

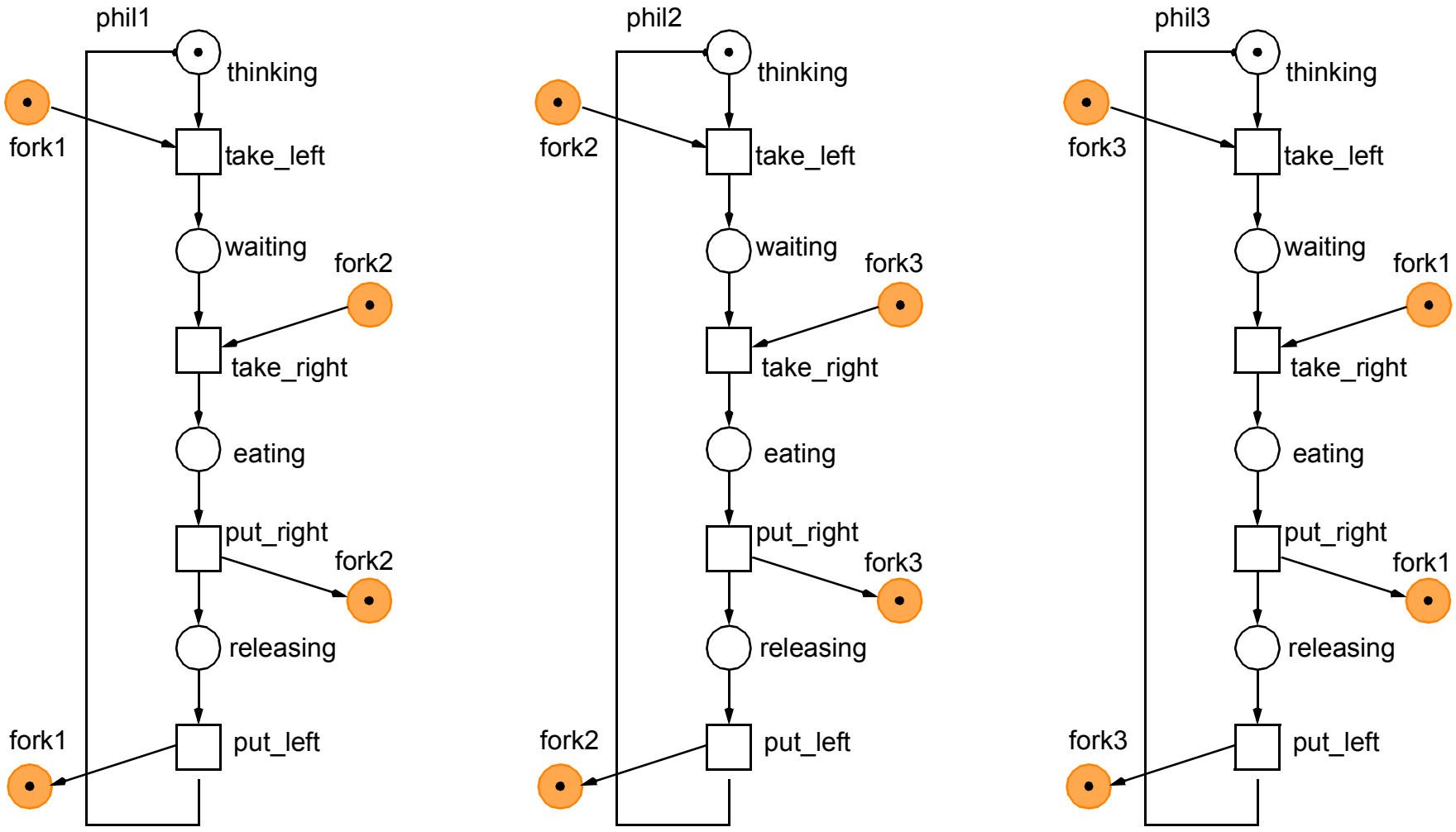




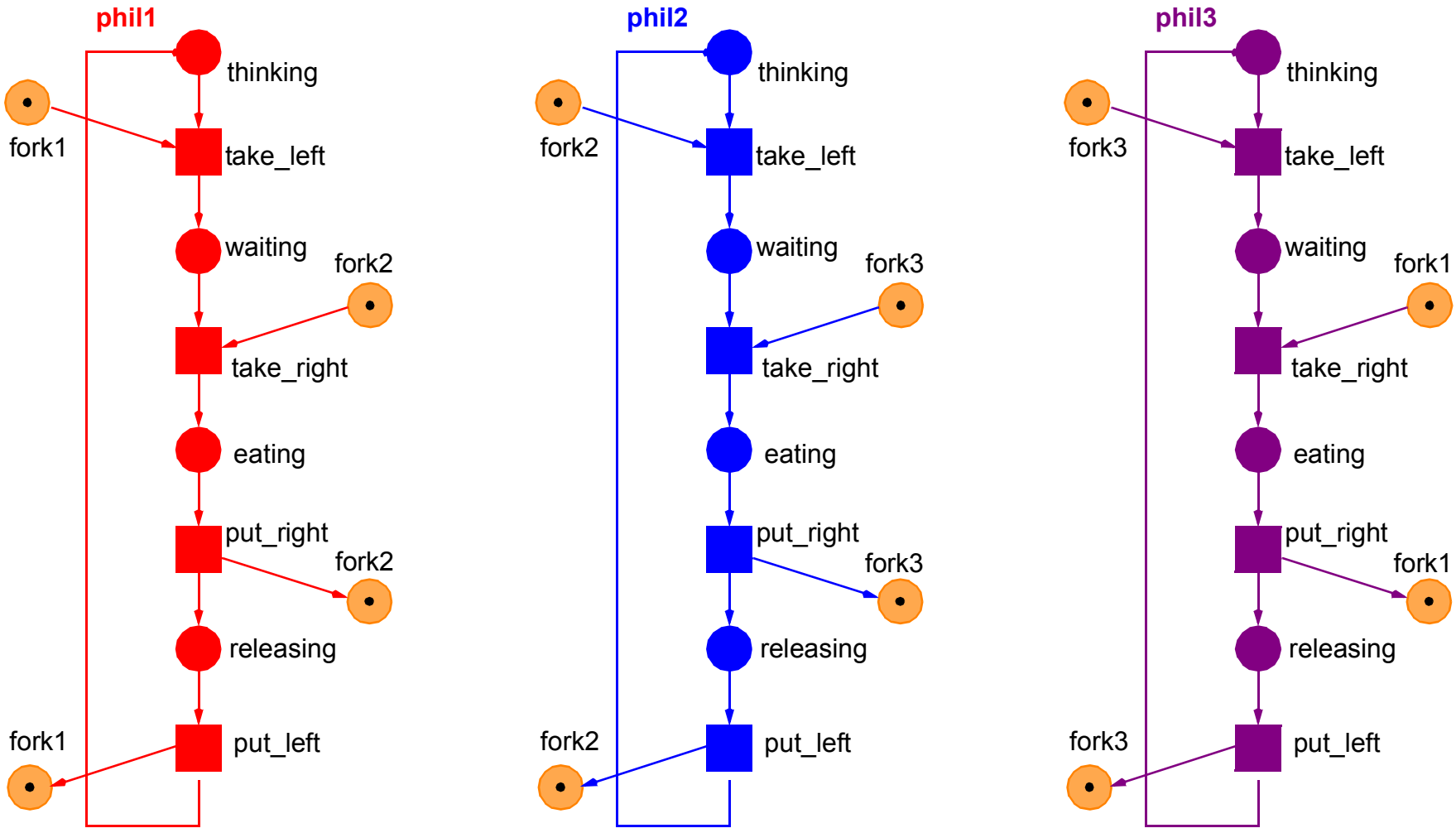




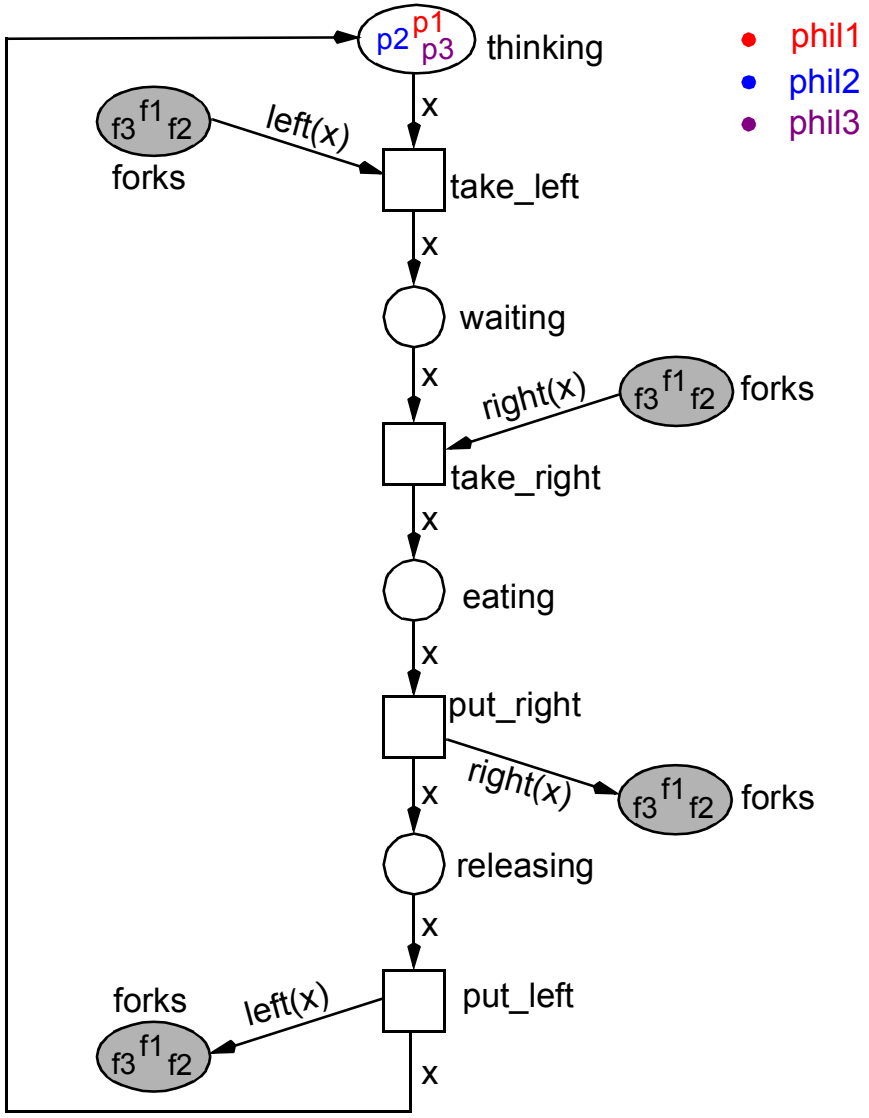
COLOURED PETRI NETS, EXAMPLE



COLOURED PETRI NETS, EXAMPLE



COLOURED PETRI NETS, EXAMPLE



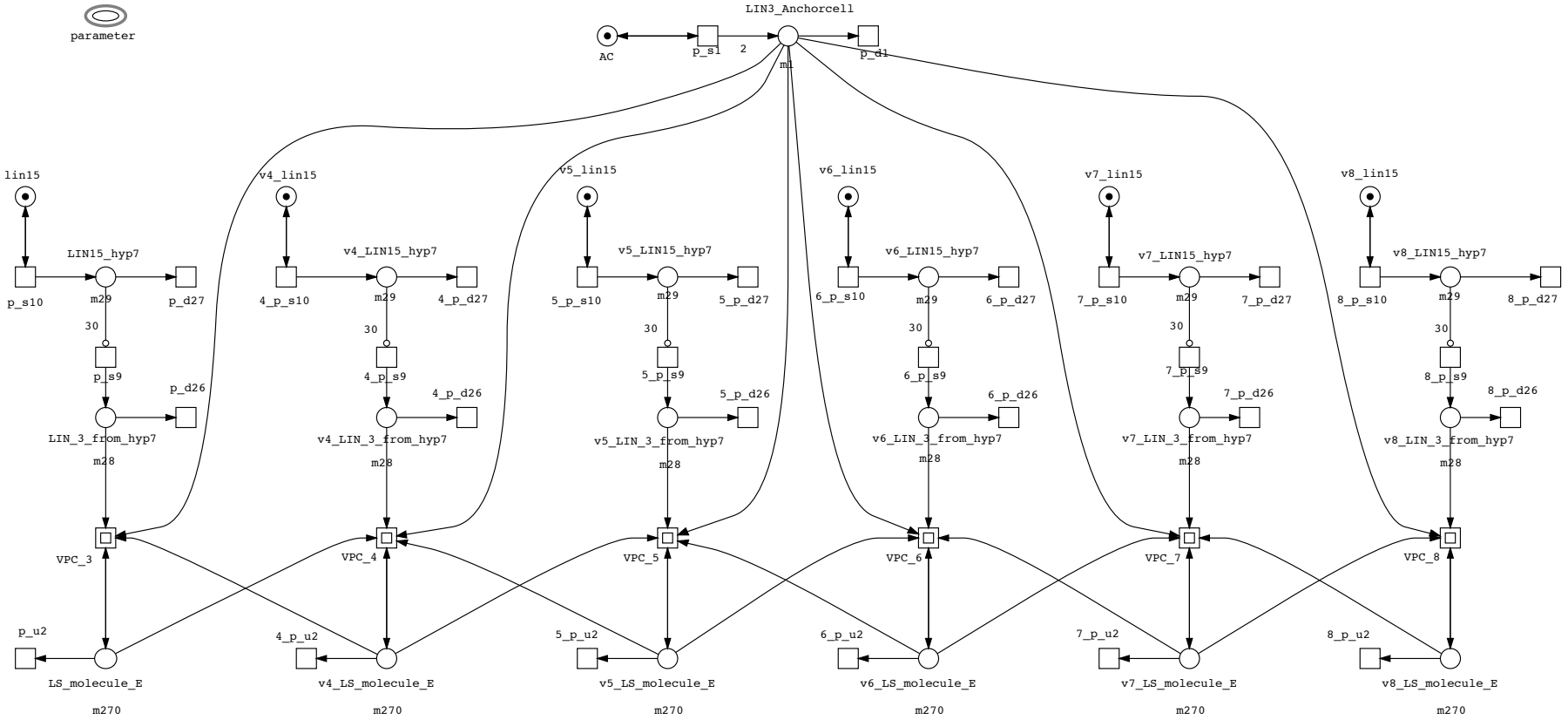
- phil1
- phil2
- phil3

```
const N = 3     // number of phils

colour_set Phils  = p{1 .. N}
colour_set Forks = f{1 .. N}

colour_set(thinking) = Phils
. . .
colour_set(releasing) = Phils

colour_set(forks) = Forks

var x : Phils

left(x) = x
right(x) = (x mod n) + 1
```

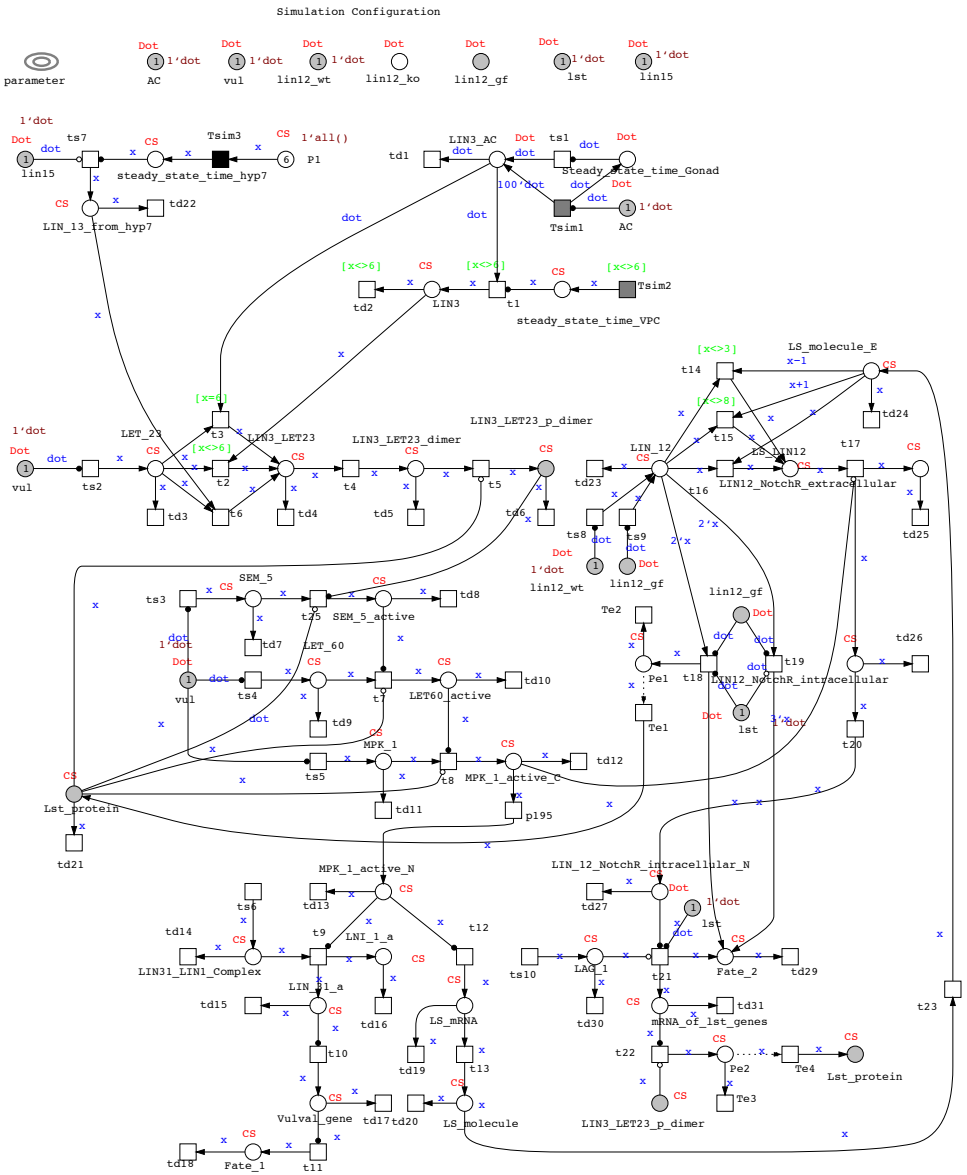
- **get multiple copies of patterns**
  - -> *Halo model, new order of net sizes*
- **differentiate between submodels within a master net**
  - -> *T-invariants*
  - -> *generated models in conformance with wet-lab data*
  - -> *mutants*
  - -> *algorithmic folding*
- **encode locality**
  - -> *Ca channel models*
  - -> *cell tissue + communication between cells*
  - -> *motility, gradients, . . .*
- **dynamic membrane systems**
- **. . .**

EX - C. ELEGANCE

[LI ET AL. 2009]
[BONZANNI ET AL. 2009]



EX - C. ELEGANCE



GENERALIZED HYBRID PETRI NETS (GHPN)

- **Extended Generalized Stochastic Petri Nets (XSPN)**
  - -> *discrete places*
  - -> *discrete transitions: stochastic, immediate, deterministically delayed, scheduled*
  - -> *special arcs: read, inhibitor, equal, reset*

- **Continuous Petri Nets (CPN)**
  - -> *continuous places*
  - -> *continuous transitions*
  - -> *special arcs: read, inhibitor*

- **GHPN = XSPN + CPN**

- **hybrid simulation engine**
  - -> *static partitioning*
  - -> *dynamic partitioning*

SUMMARY

SUMMARY

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

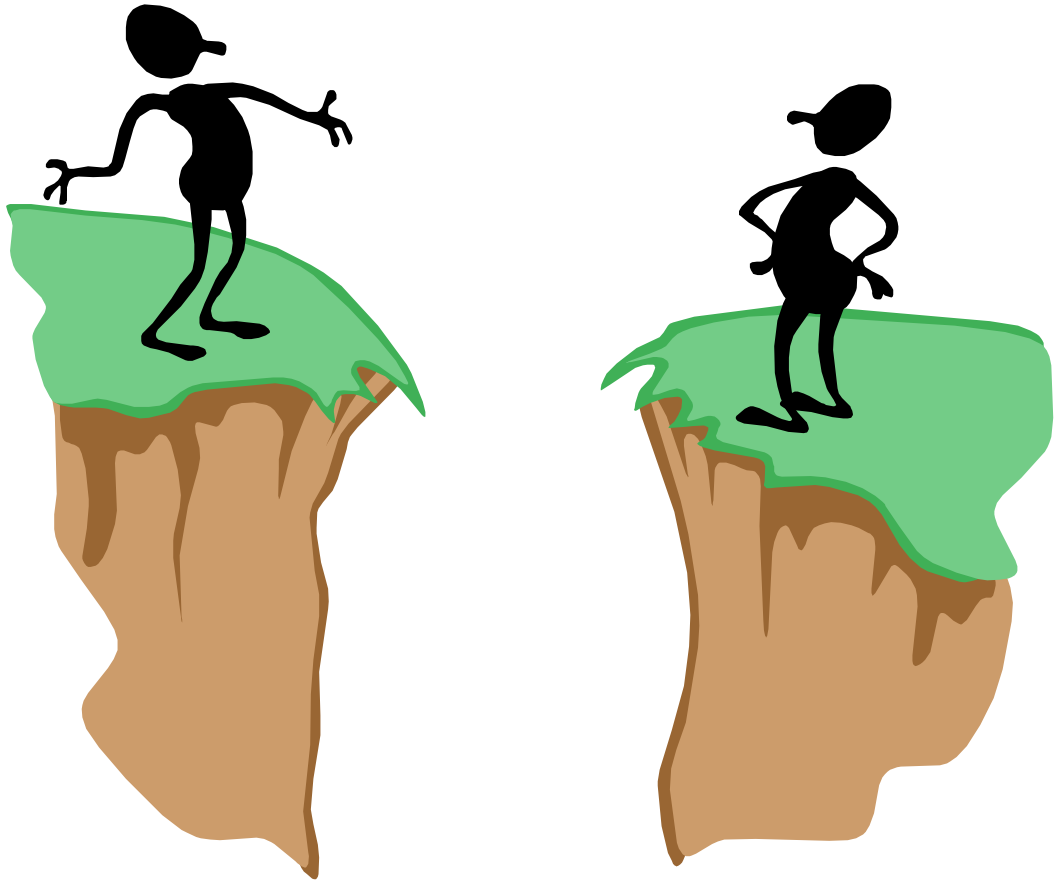
SUMMARY

- **representation of bionetworks 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*

SUMMARY

- **representation of bionetworks 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*

OUTLOOK



THANKS !

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