WHAT CAN PETRI NETS DO 4 MULTISCALE SYSTEMS BIOLOGY ?

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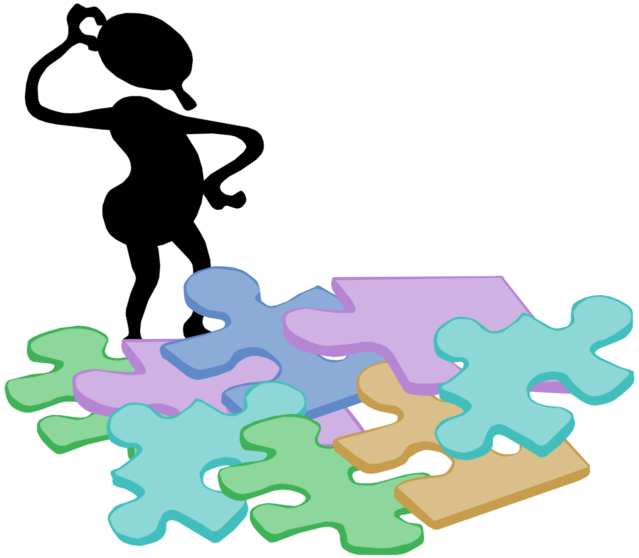
http://www-dssz.informatik.tu-cottbus.de/BME/PetriNets2013

PETRI NETS - THE BIG PROS



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

- **umbrella with unifying power**
  -> *interpretation in qualitative / stochastic / continuous / hybrid paradigms*
- **Petri net theory**
  -> *P/T-invariants, partial order interpretation of T-invariants, conclusions CTI/CPI -> behavioural properties*
  -> *STP, reduction rules, . . .*

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  - *-> STP, reduction rules, . . .*

SEE TUTORIAL PARIS 2009

THE PETRI NET FRAMEWORK

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4 MODELS SHARING STRUCTURE

↓ ↓ ↓

QUANTITATIVE MODEL = QUALITATIVE MODEL

+

RATE FUNCTIONS

(KINETICS)

STATE-DEPENDENT RATE FUNCTIONS

STOCHASTIC RATES

↓

LAMBDA OF EXPONENTIAL WAITING TIME

↓

CTMC

CONTINUOUS RATES

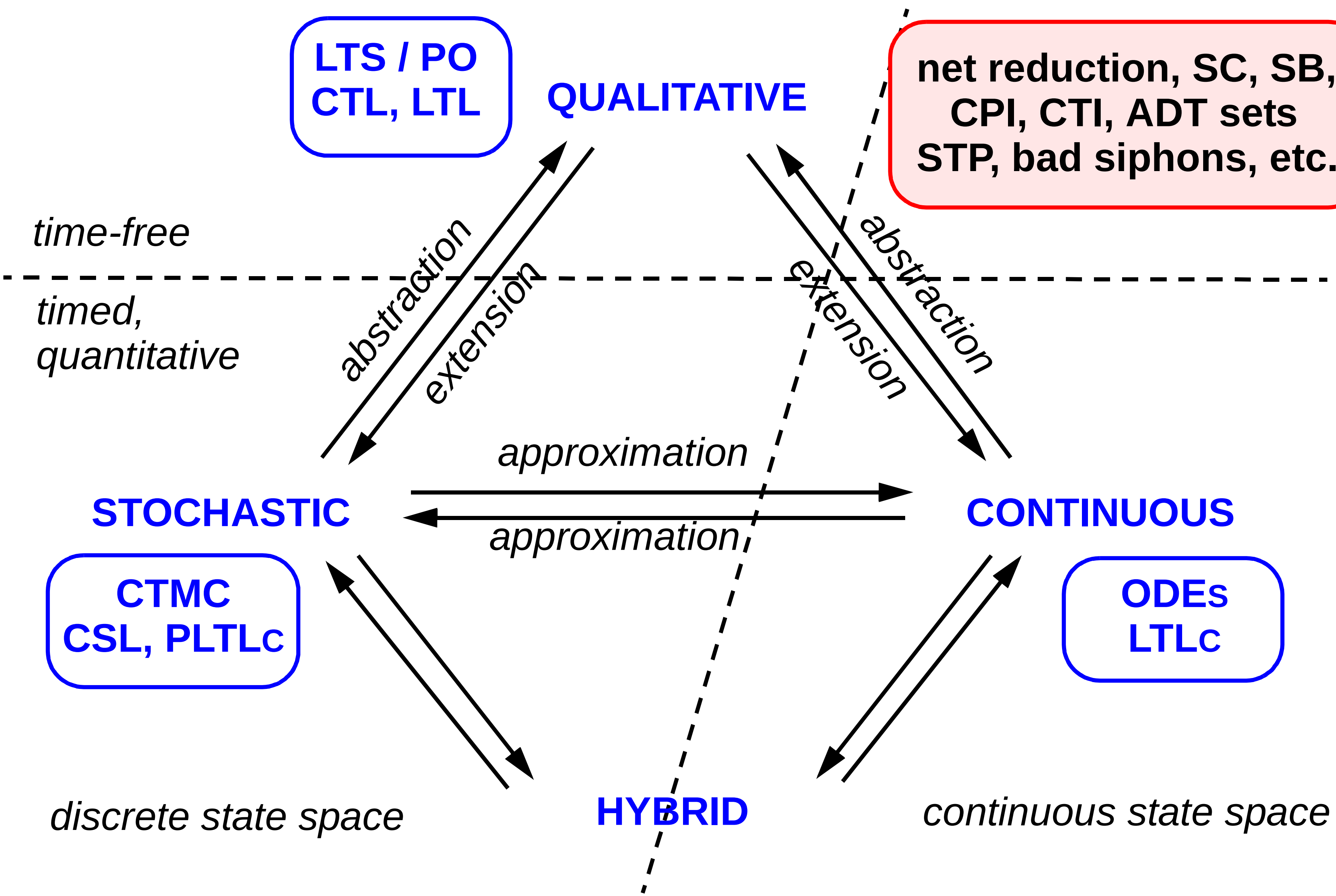
↓

STRENGTH OF CONTINUOUS FLOW

↓

ODEs

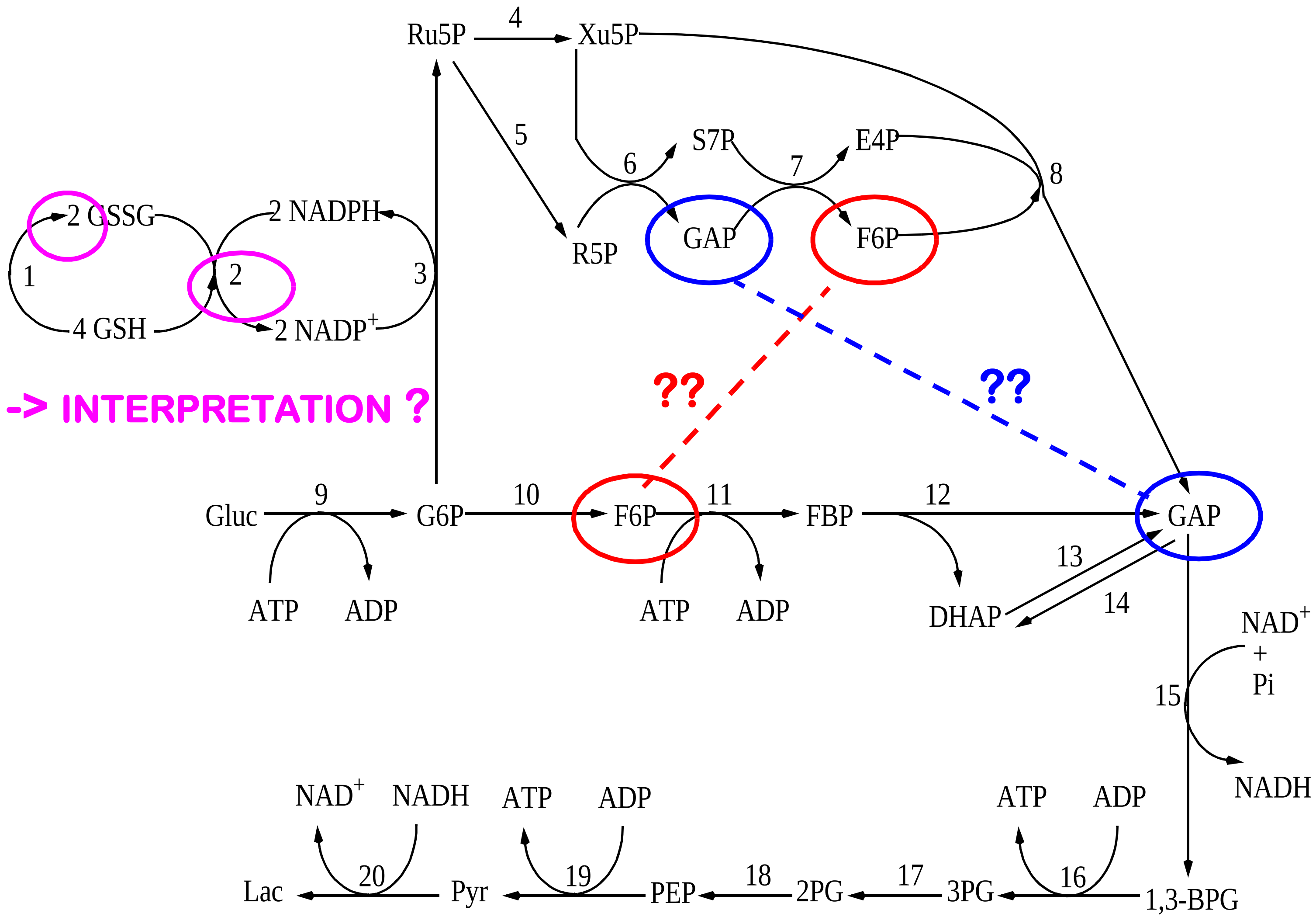
-> supported by, e.g., COPASI, Dizzy, ..., Snoopy


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

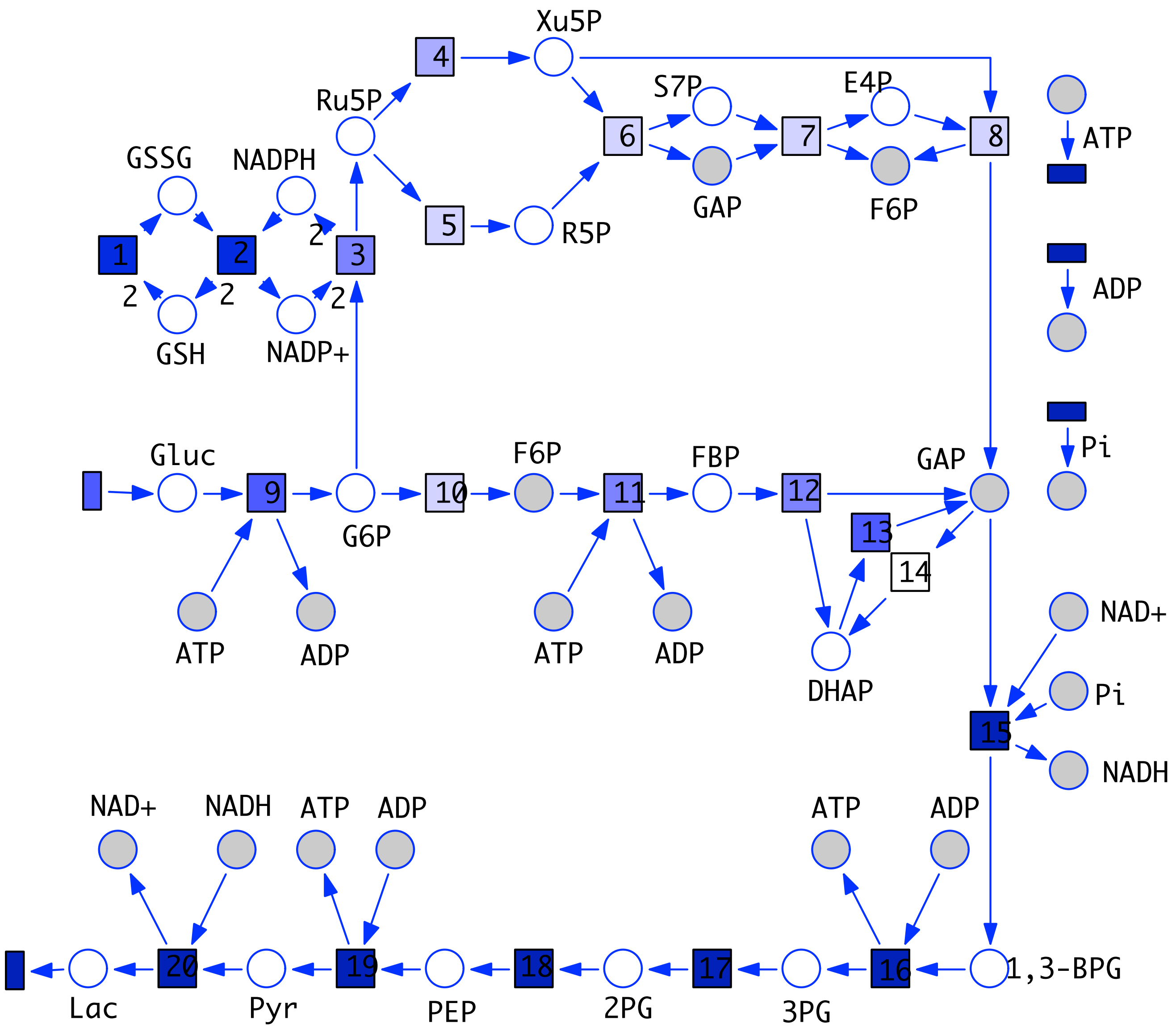
BIO PETRI NETS - SOME EXAMPLES

Ex1 - Glycolysis and Pentose Phosphate Pathway

[Reddy 1993]



Ex1 - Glycolysis and Pentose Phosphate Pathway



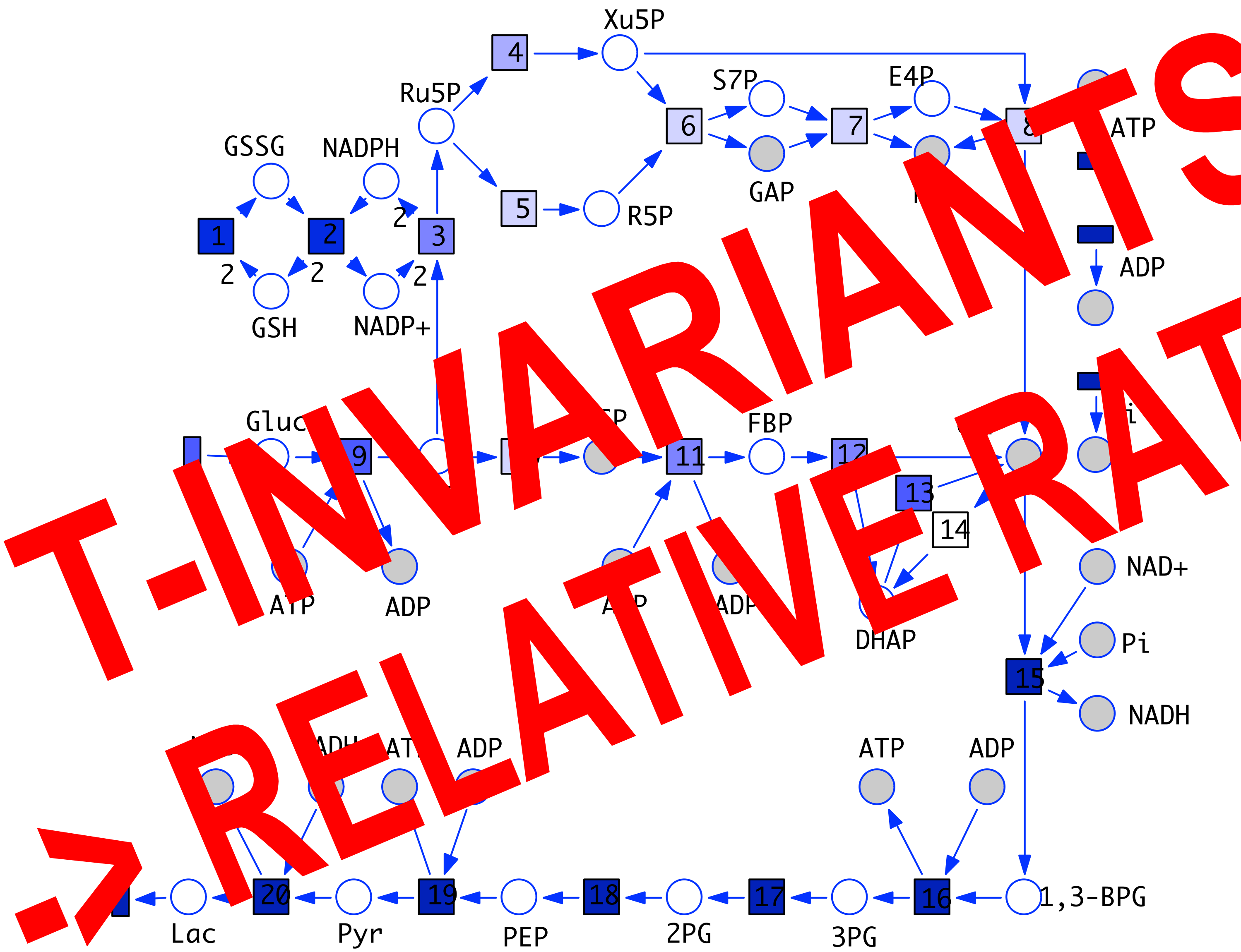
[Reddy 1993]

[Heiner 1998]

. . .

[Koch, Heiner 2010]

Ex1 - Glycolysis and Pentose Phosphate Pathway



[Reddy 1993]

[Heiner 1998]

. . .

[Koch, Heiner 2010]

T-INVARIANTS -> RELATIVE RATES

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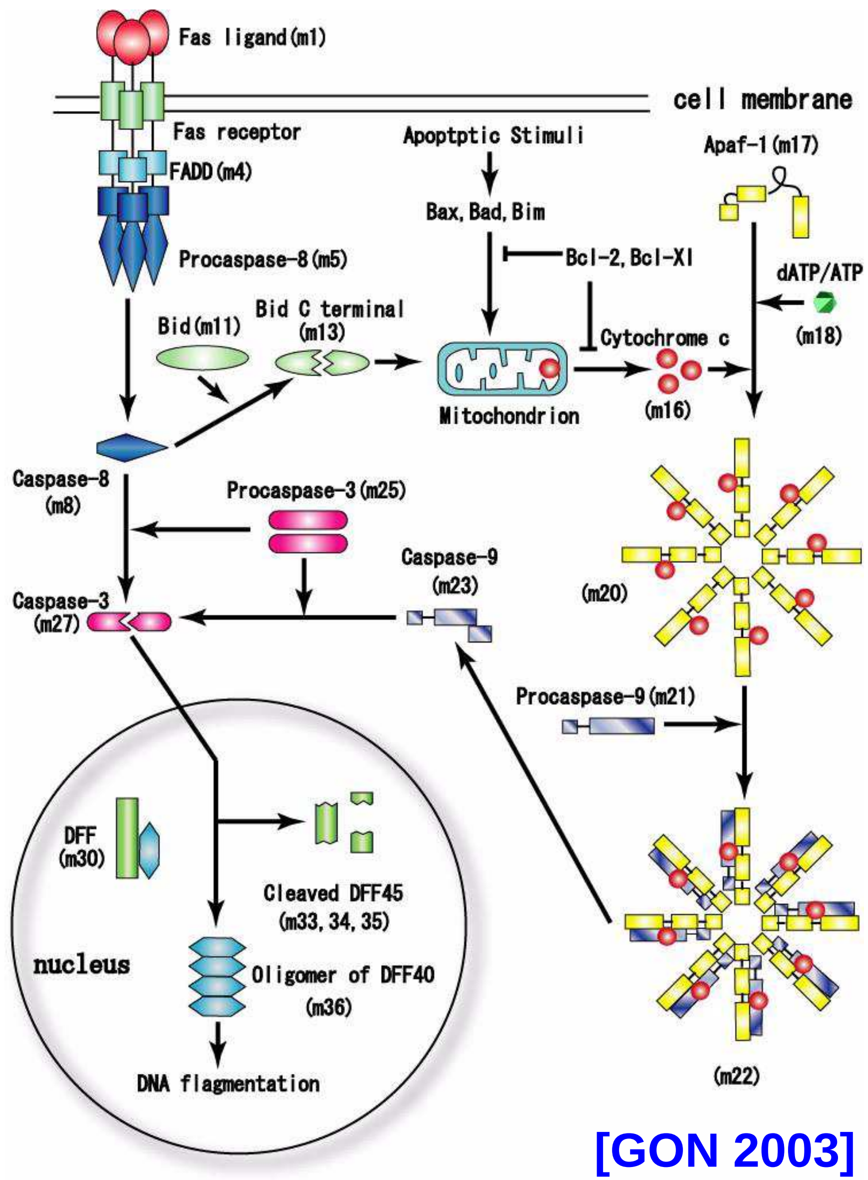
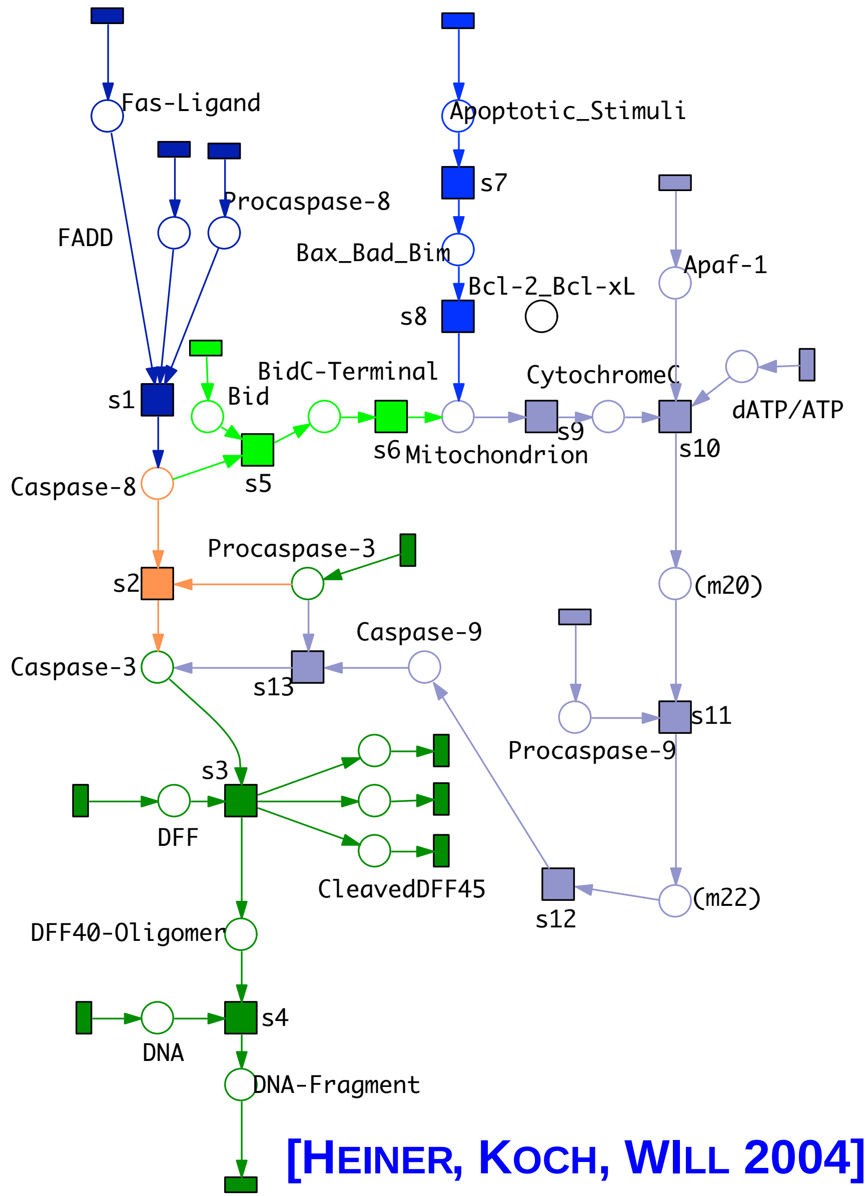
Ex2 - Apoptosis in Mammalian Cells

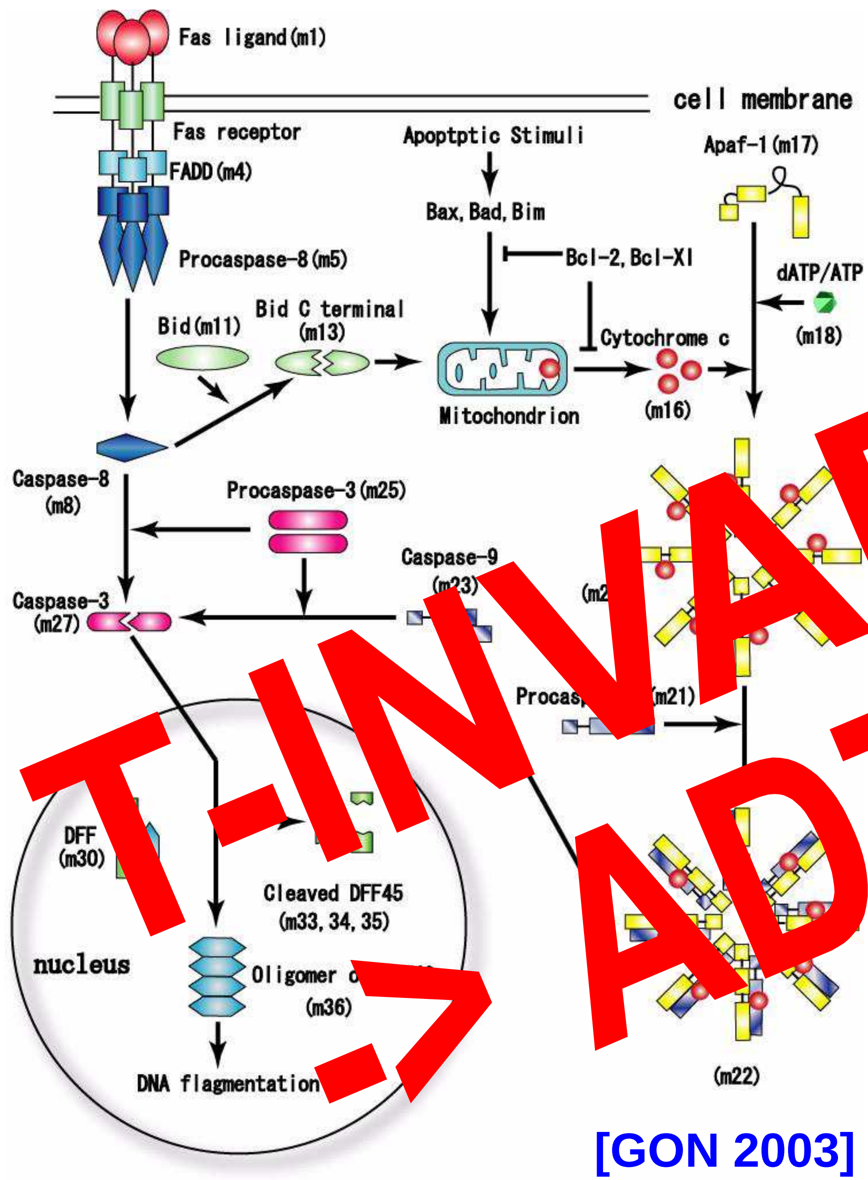


[GON 2003]

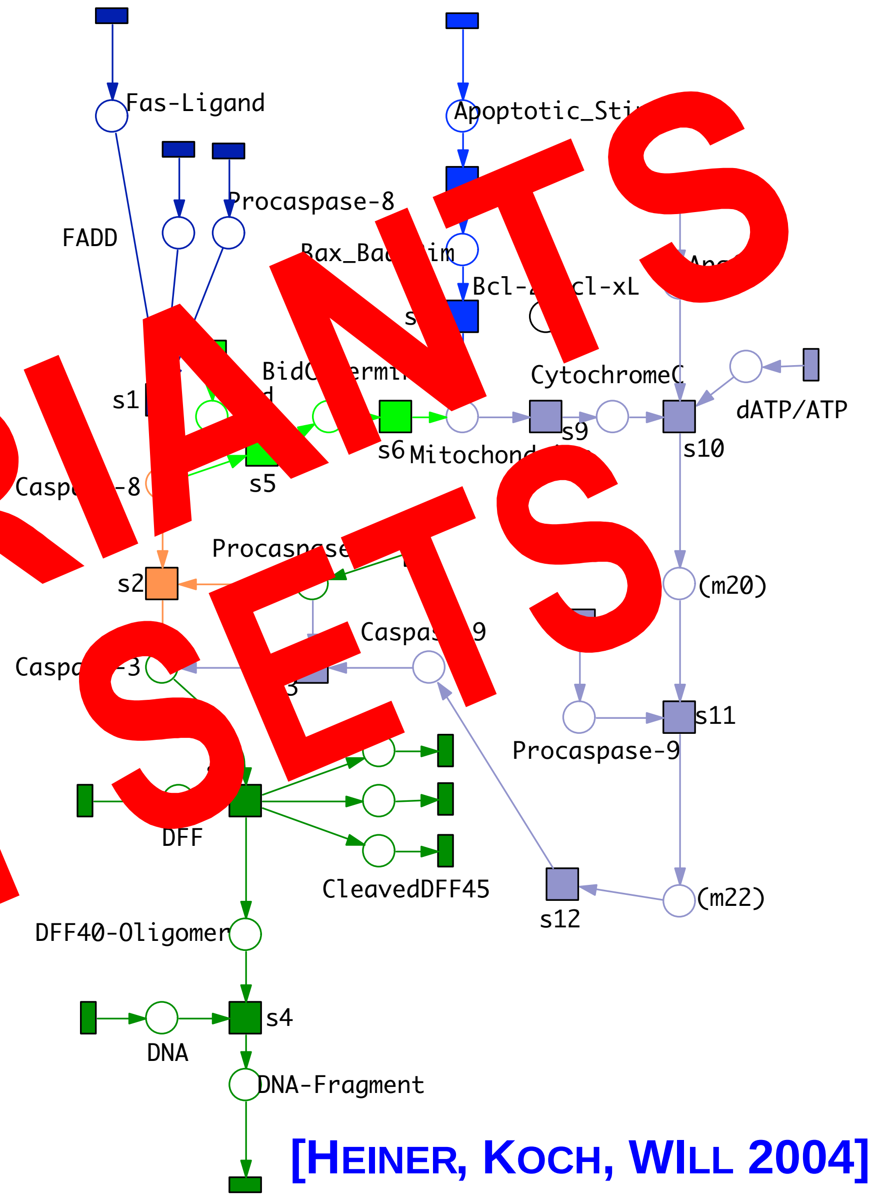


[Heiner, Koch, Will 2004]

Ex2 - Apoptosis in Mammalian Cells



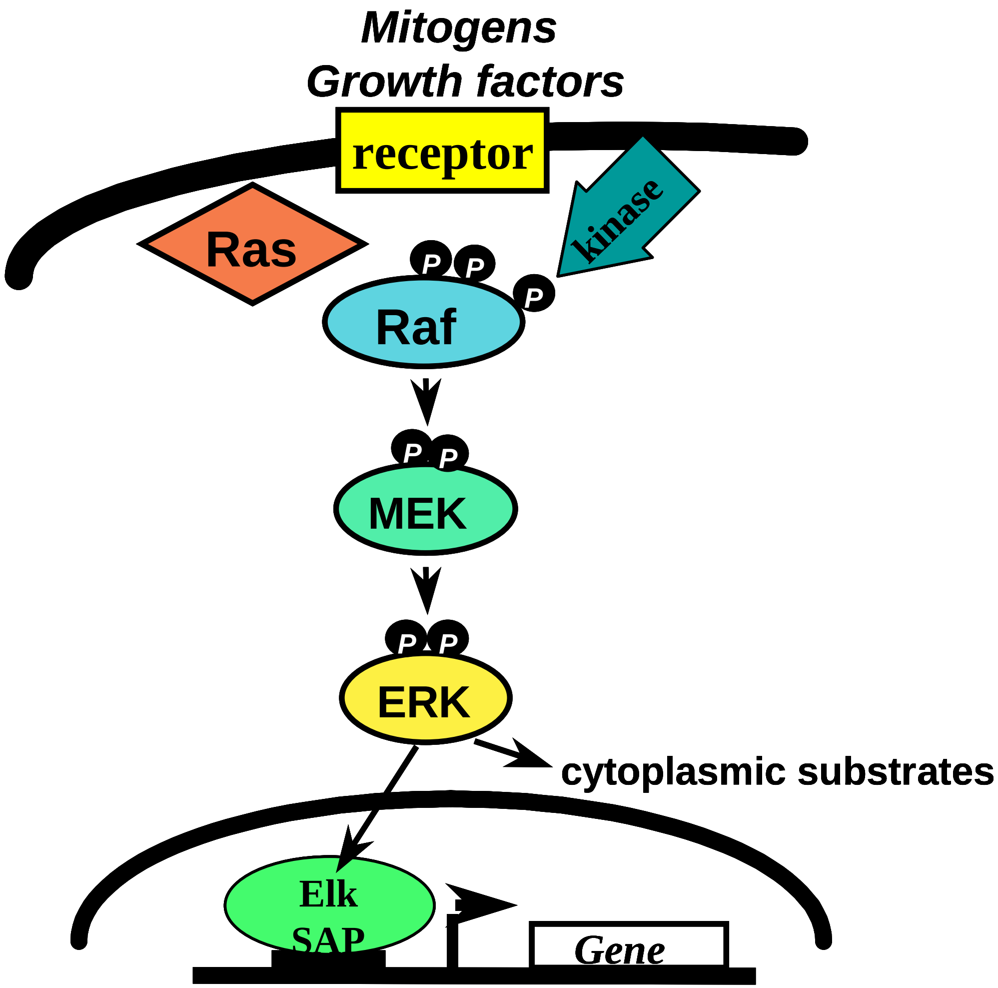
[GON 2003]



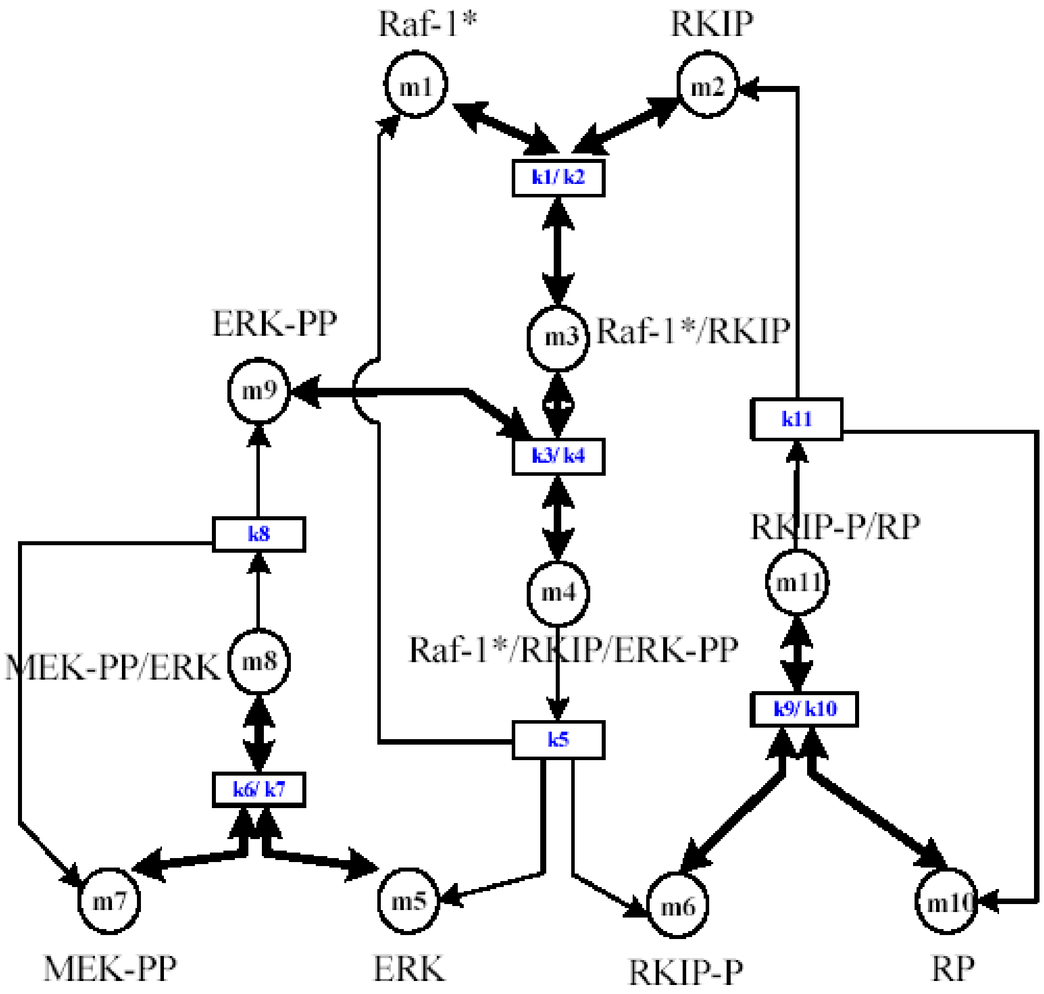
[Heiner, Koch, Will 2004]

T-INVARIANTS -> ADT SETS

…one pathway…

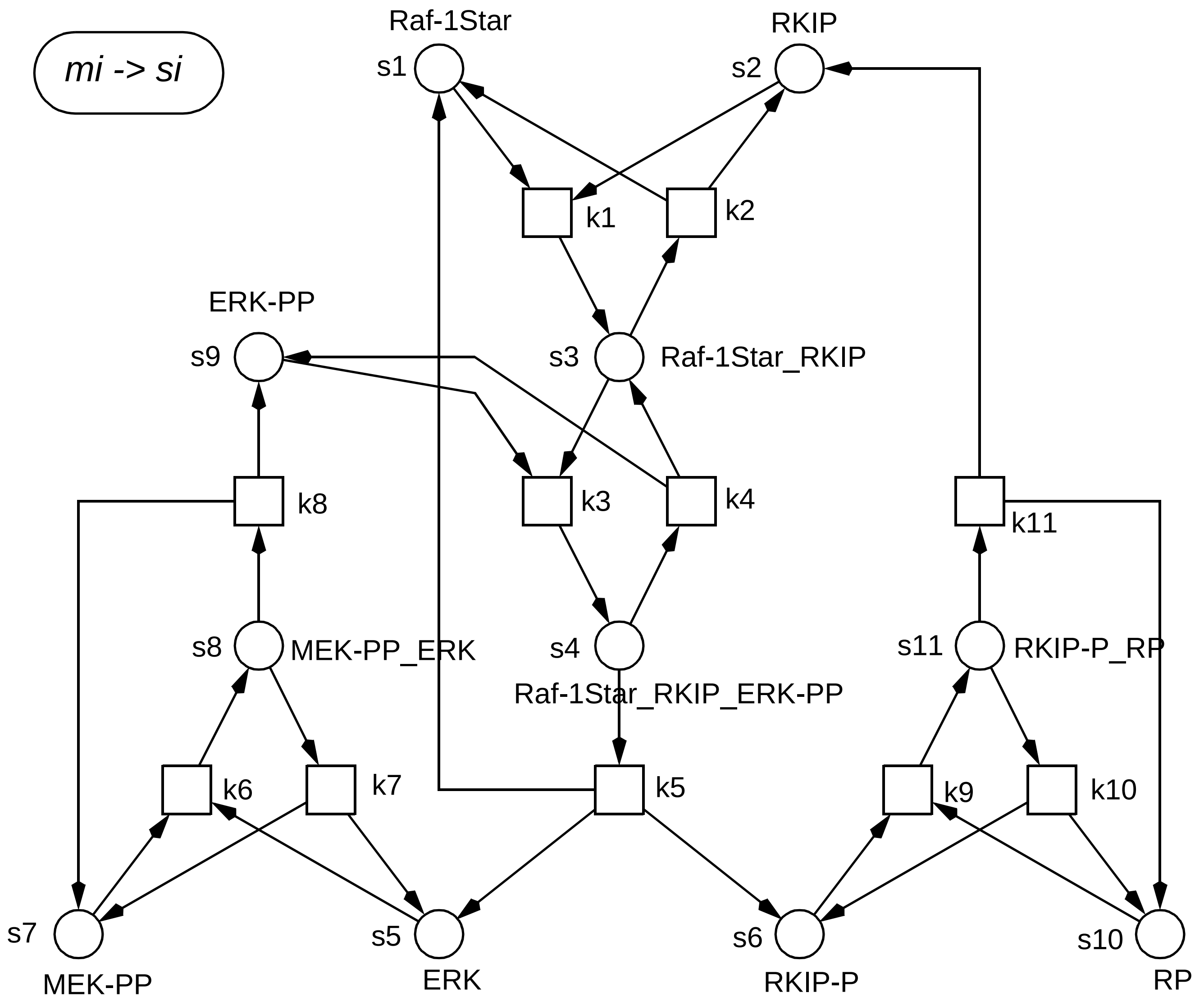

Mitogens
Growth factors
receptor
kinase
Ras
P
P
P
Raf
P
P
MEK
P
P
ERK
cytoplasmic substrates
Elk
SAP
Gene

EX3 - RKIP SIGNALLING PATHWAY



[Cho et al. 2003]

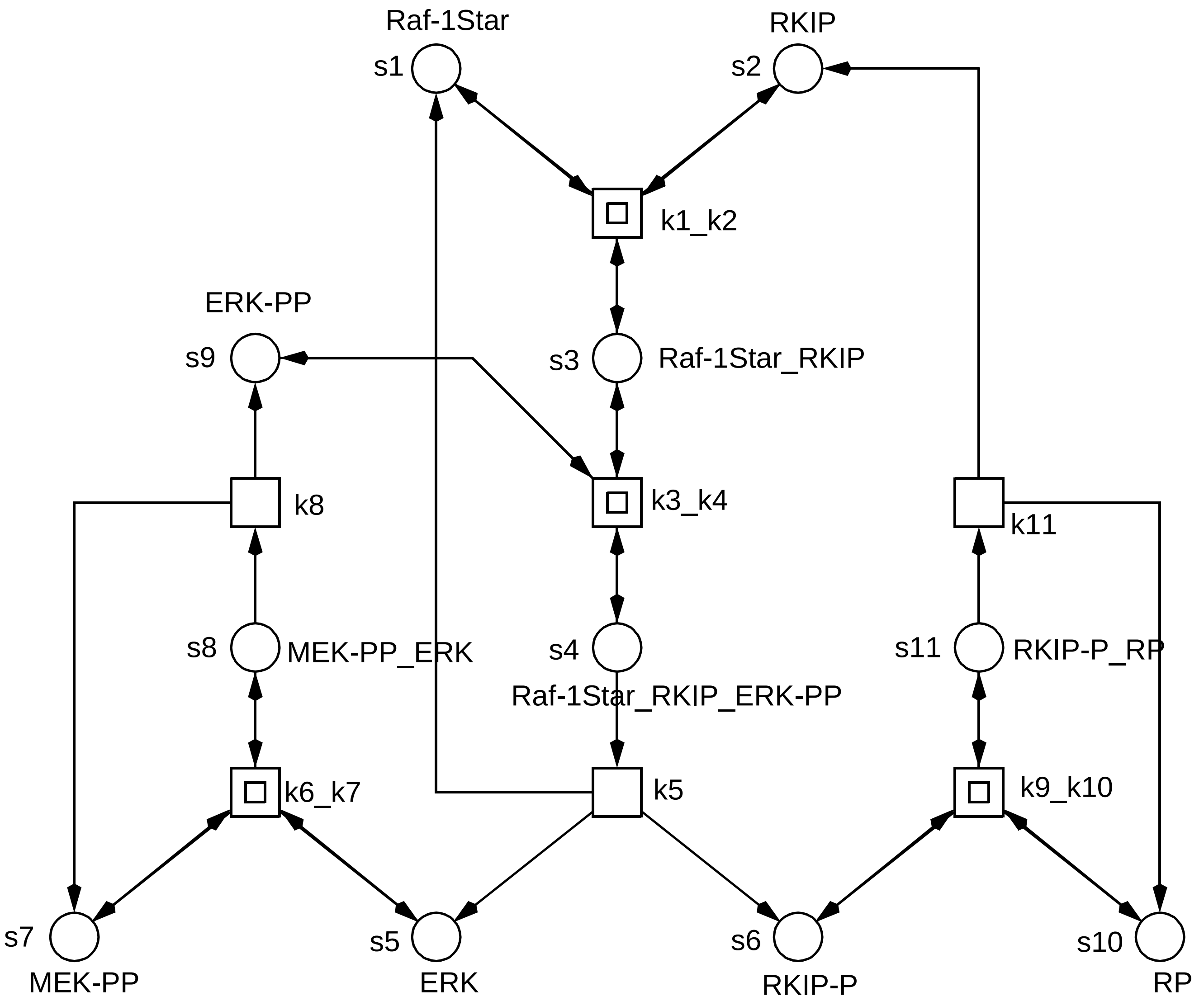
Ex3 - RKIP Signalling Pathway, Petri Net



[Heiner, Gilbert 2006]

[Heiner, Donaldson, Gilbert 2010]

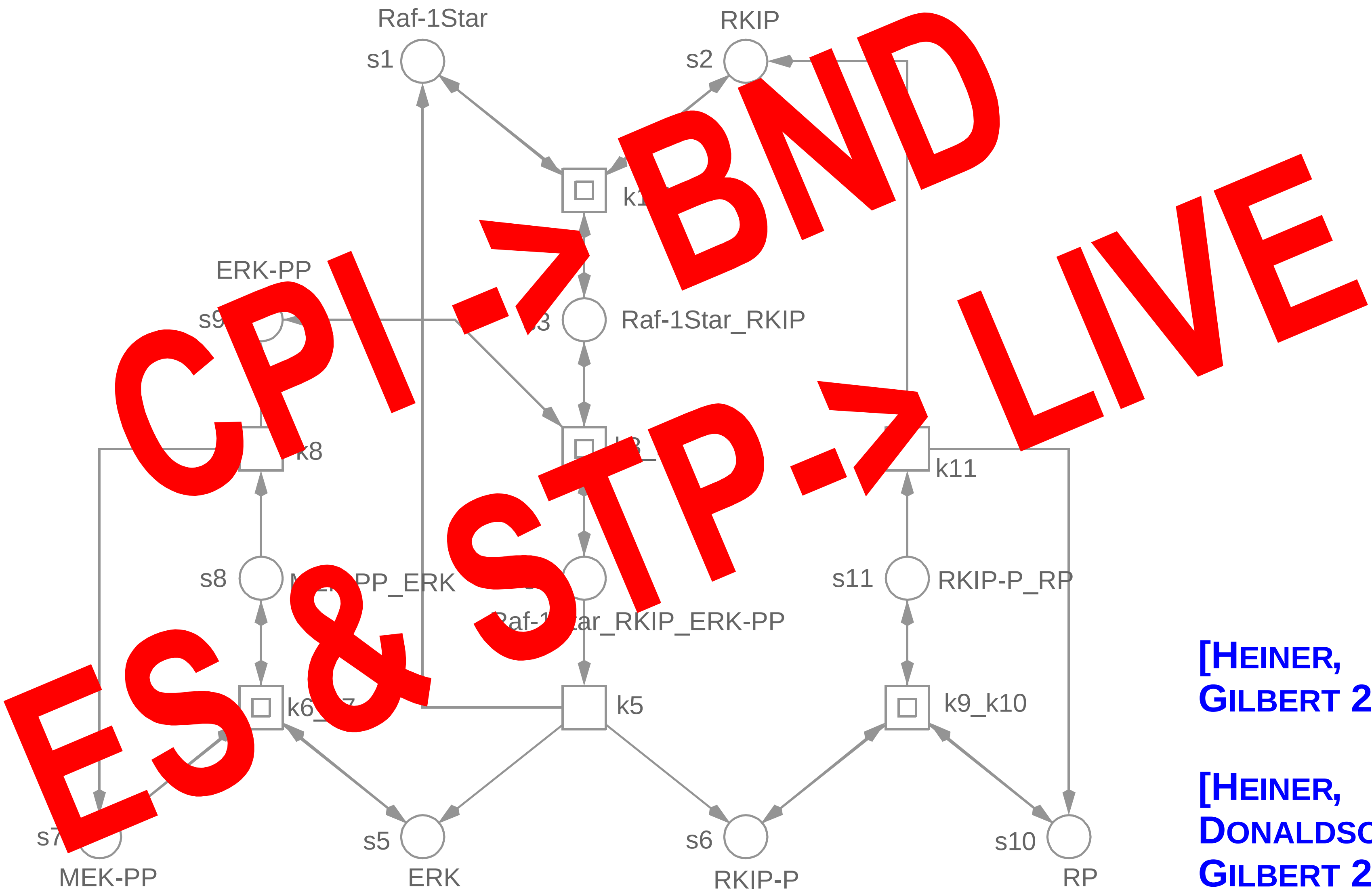
EX3 - RKIP SIGNALLING PATHWAY, HIERARCHICAL PETRI NET



[HEINER, GILBERT 2006]

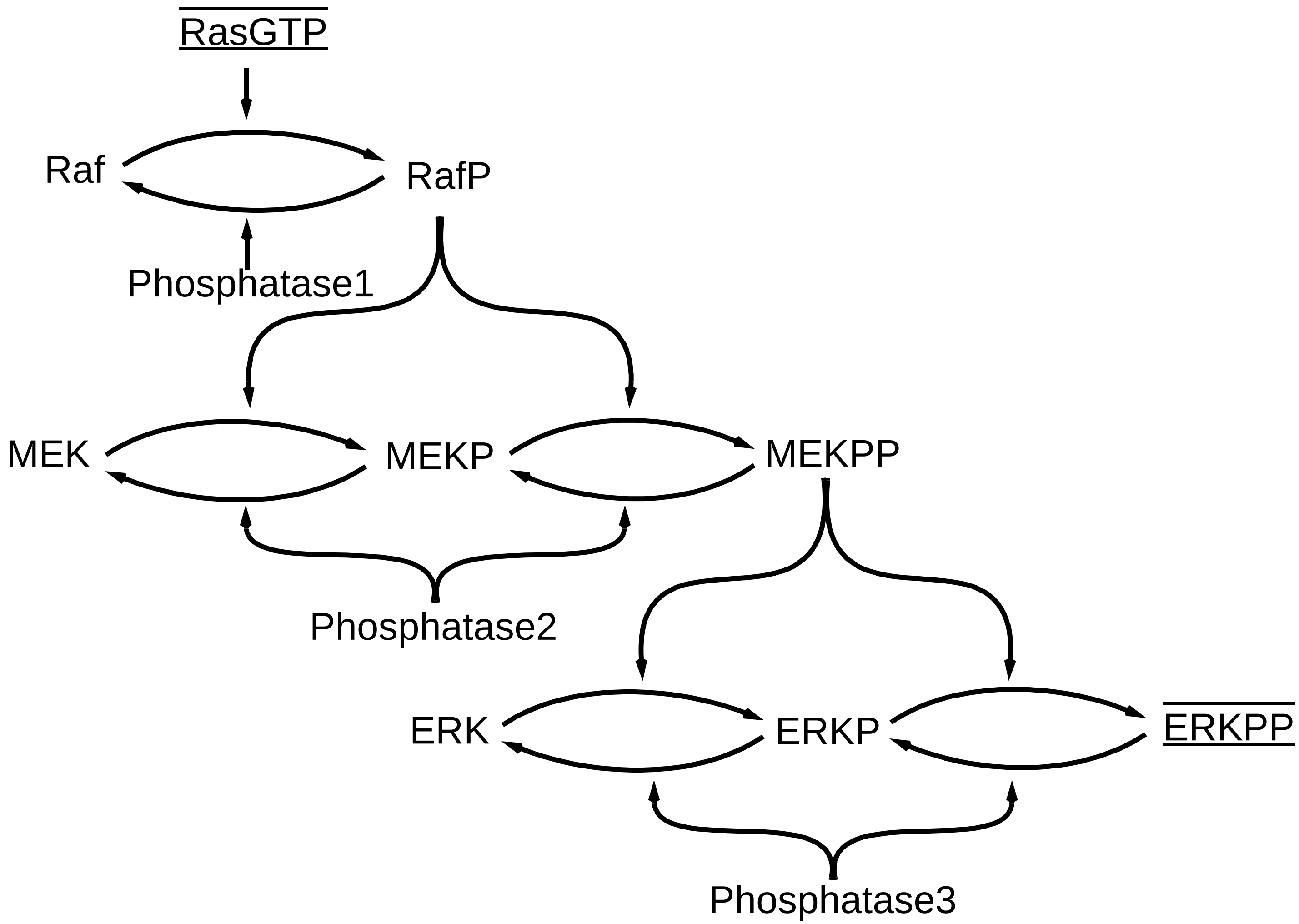
[HEINER, DONALDSON, GILBERT 2010]

EX3 - RKIP SIGNALLING PATHWAY, HIERARCHICAL PETRI NET



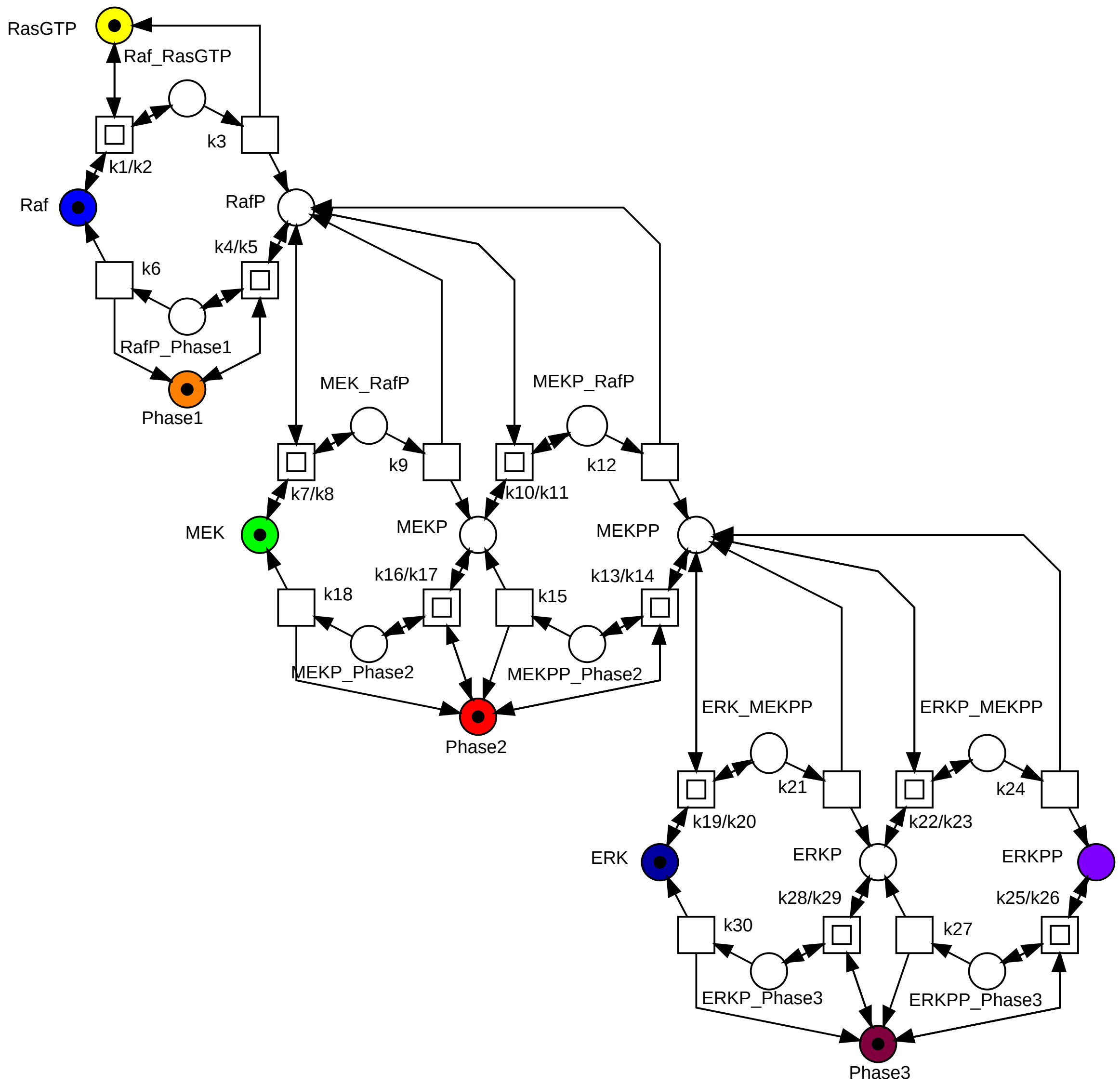
[HEINER, GILBERT 2006]

[HEINER, DONALDSON, GILBERT 2010]



RasGTP
Raf
RafP
Phosphatase1
MEK
MEKP
MEKPP
Phosphatase2
ERK
ERKP
ERKPP
Phosphatase3

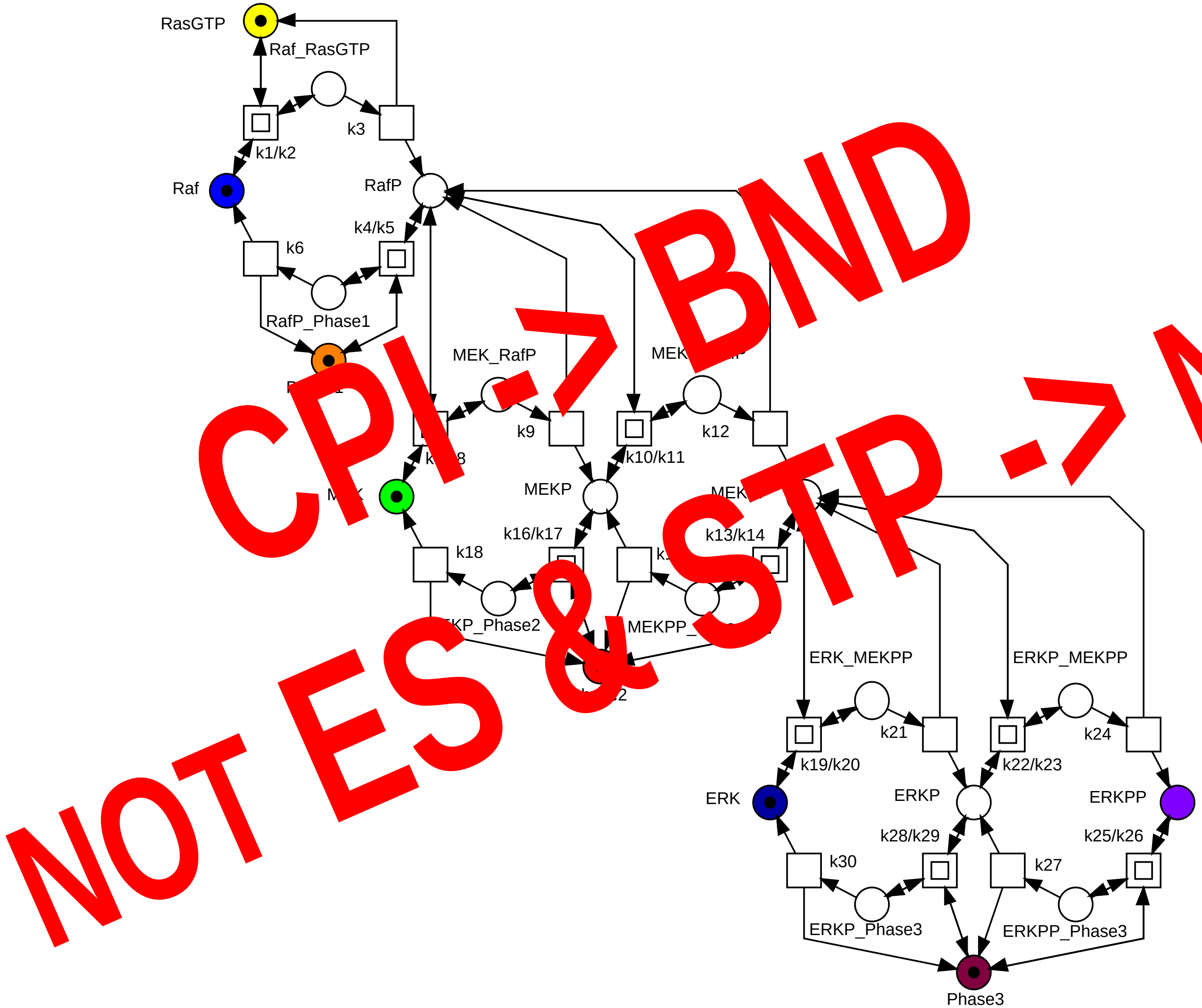
EX4 - SIGNALLING CASCADE



[GILBERT, HEINER, LEHRACK 2007]

[HEINER, GILBERT, DONALDSON 2008]

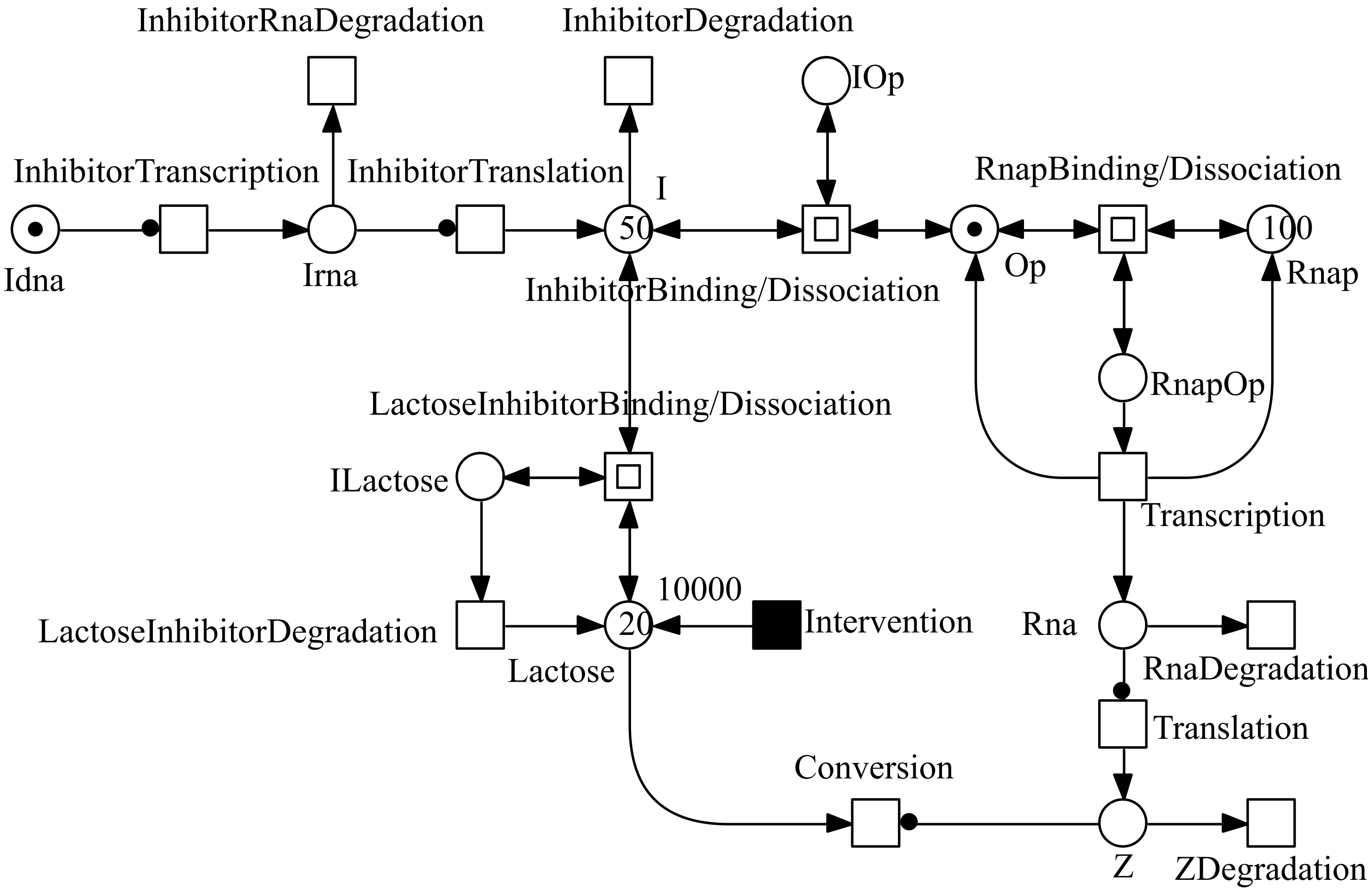
Ex4 - Signalling Cascade



[Gilbert, Heiner, Lehrack 2007]

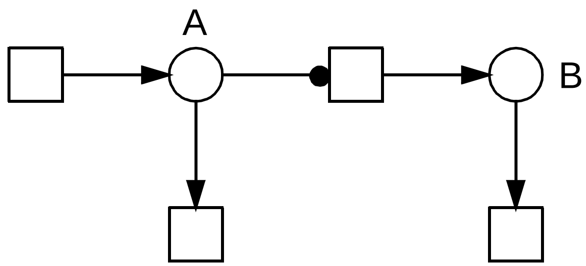
[Heiner, Gilbert, Donaldson 2008]

Ex5 - Lac Operon



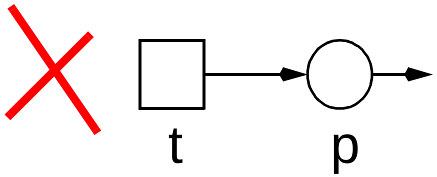
[Wilkinson 2006]

- **reduced net structure while preserving liveness & boundedness**

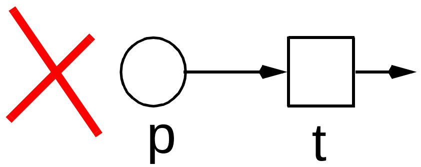


liveness becomes obvious

- **example of two simple reduction rules**



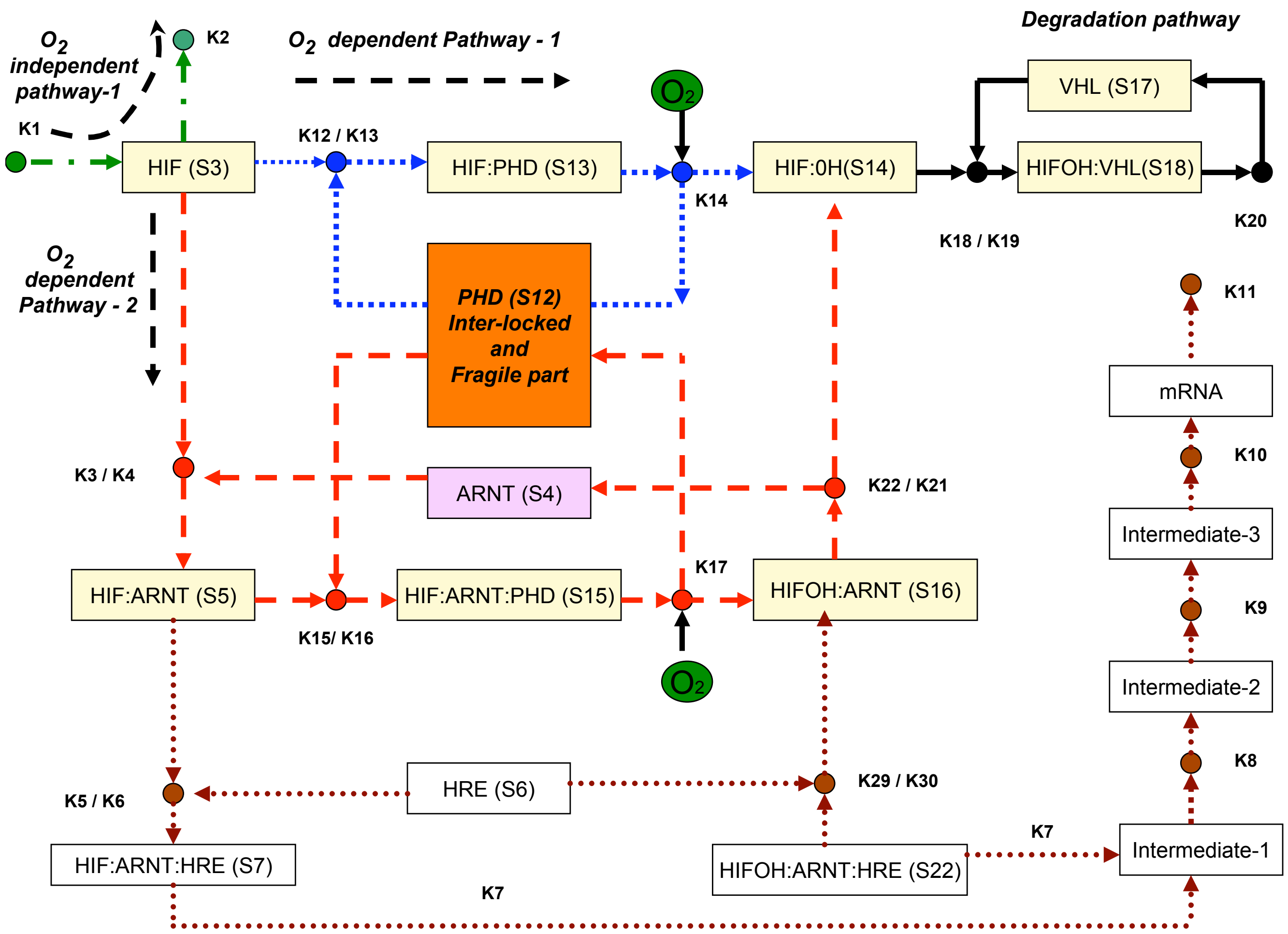
t live
p unbounded



t not live
p bounded

ABOUT THE RELATION
QUALITATIVE VS CONTINUOUS

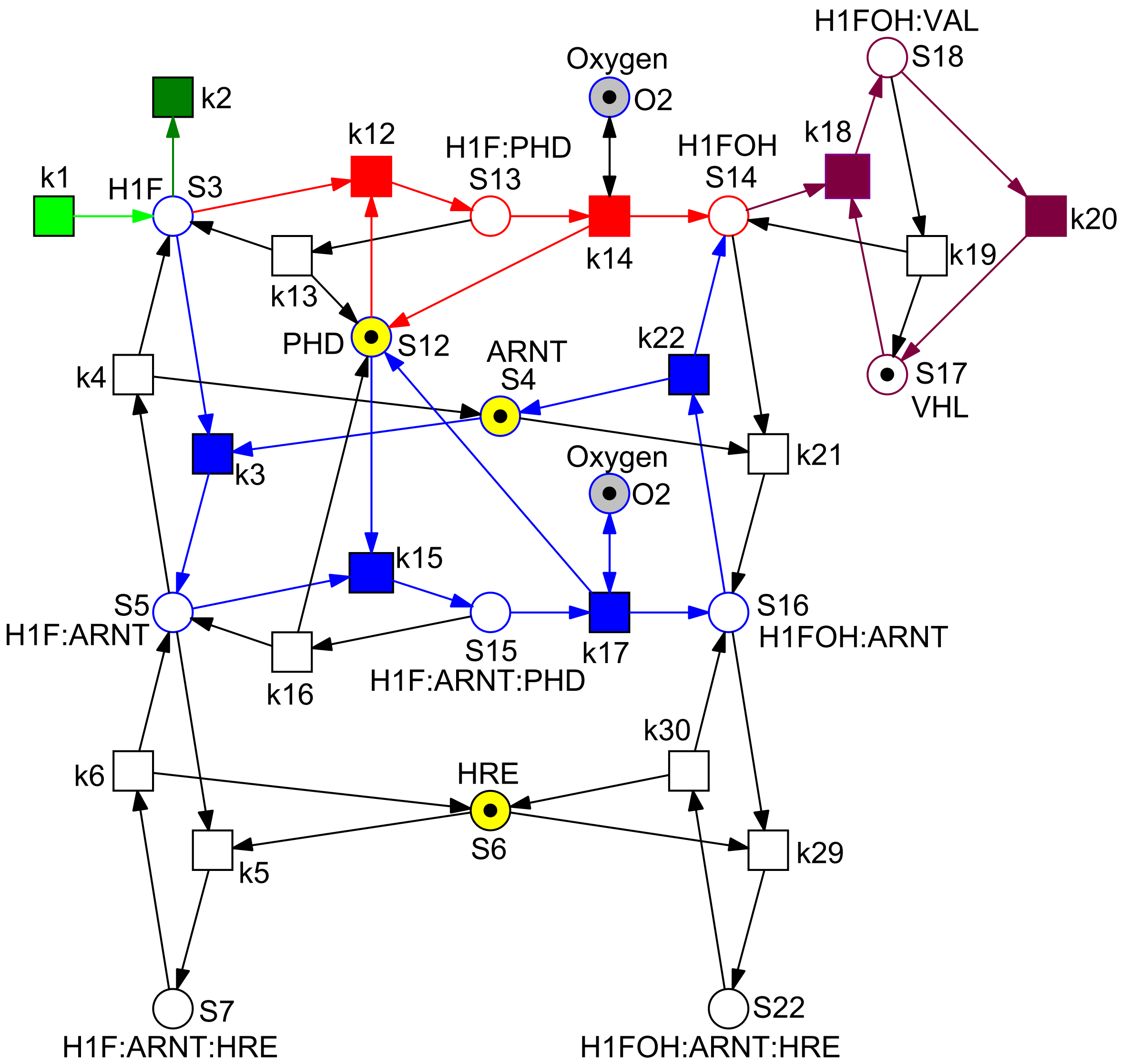
[YU ET AL. 2007]



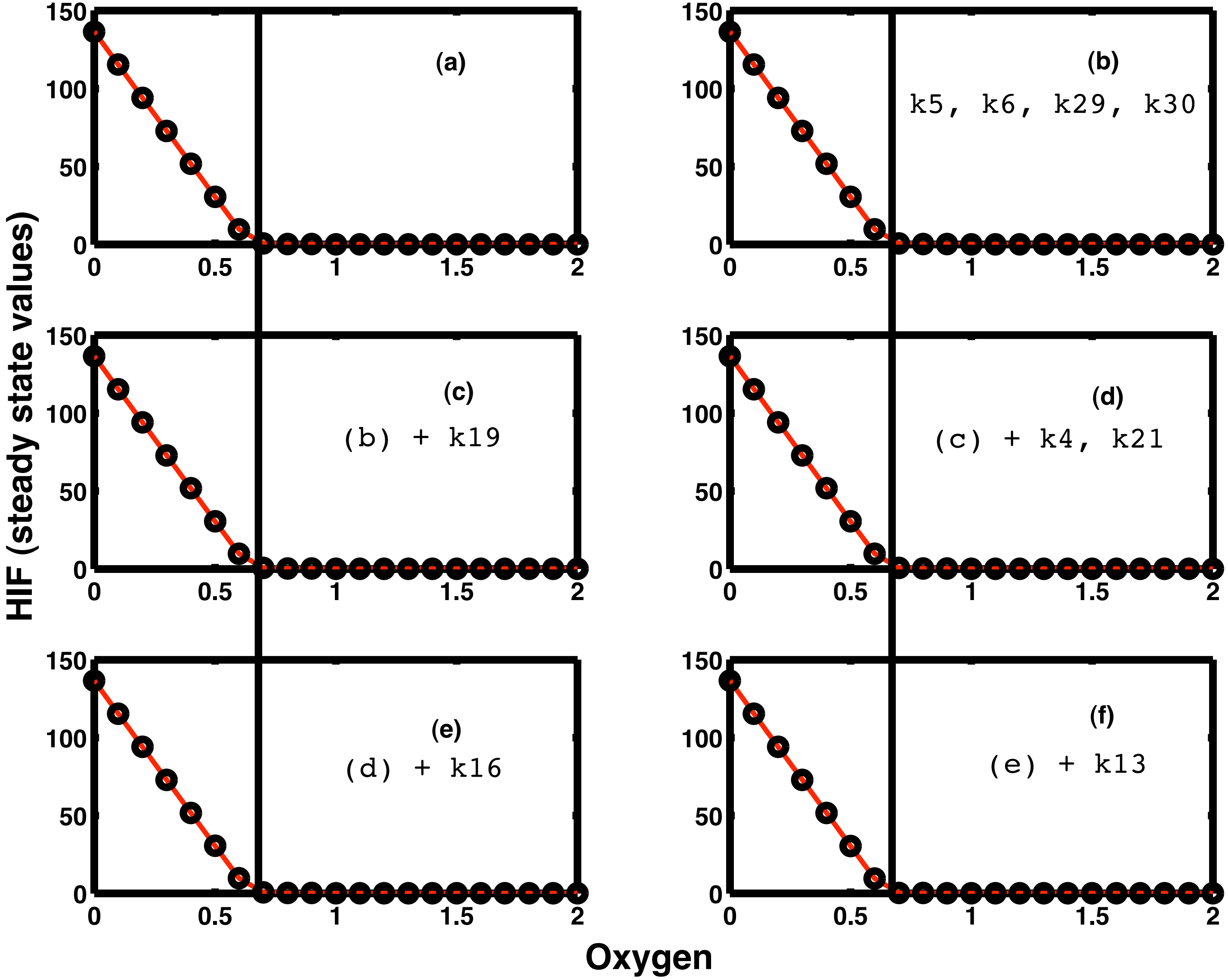
O_2 independent pathway-1
K1
K2
O_2 dependent Pathway - 1
Degradation pathway
O_2
VHL (S17)
HIF (S3)
K12 / K13
HIF:PHD (S13)
HIF:0H(S14)
HIFOH:VHL(S18)
K14
K18 / K19
K20
O_2 dependent Pathway - 2
PHD (S12) Inter-locked and Fragile part
K11
mRNA
K10
K3 / K4
ARNT (S4)
K22 / K21
Intermediate-3
K17
HIF:ARNT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

EX8 - HYPOXIA

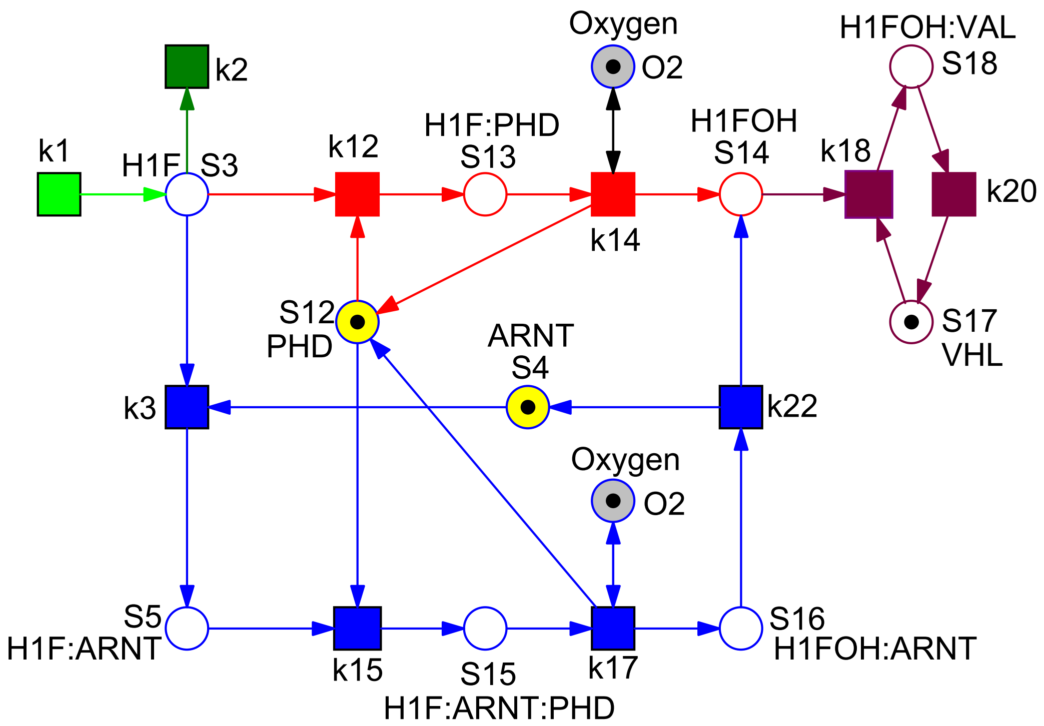
[HEINER, SRIRAM 2010]



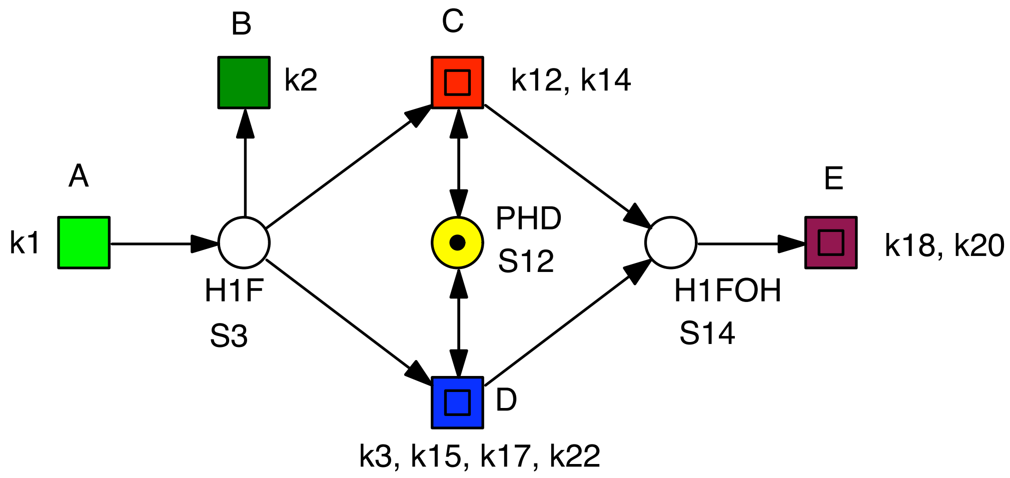
Ex8 - Hypoxia

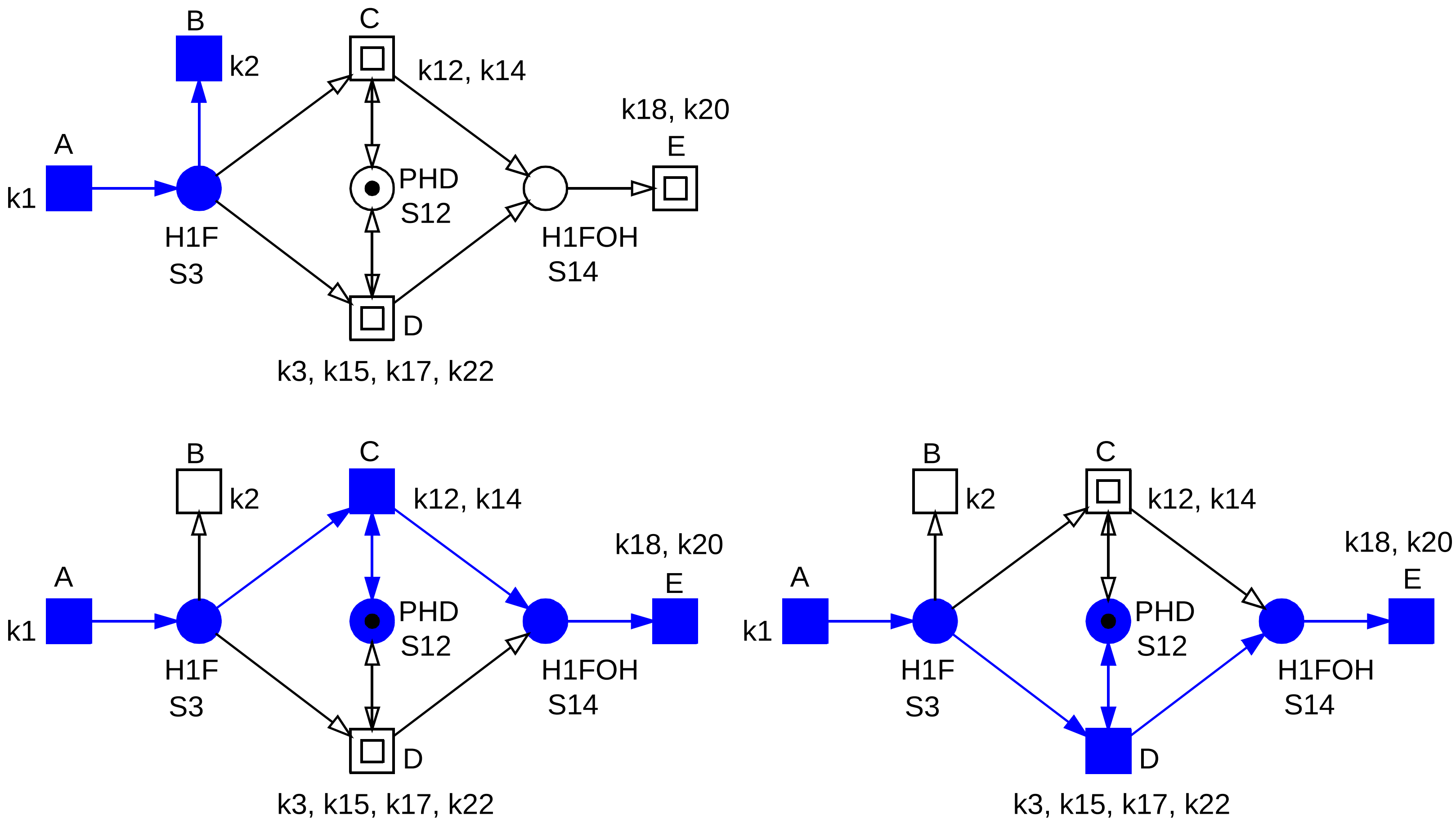

(a)
(b)
k5, k6, k29, k30
(c)
(b) + k19
(d)
(c) + k4, k21
(e)
(d) + k16
(f)
(e) + k13
HIF (steady state values)
Oxygen
0
50
100
150
0.5
1
1.5
2

Ex8 - Hypoxia

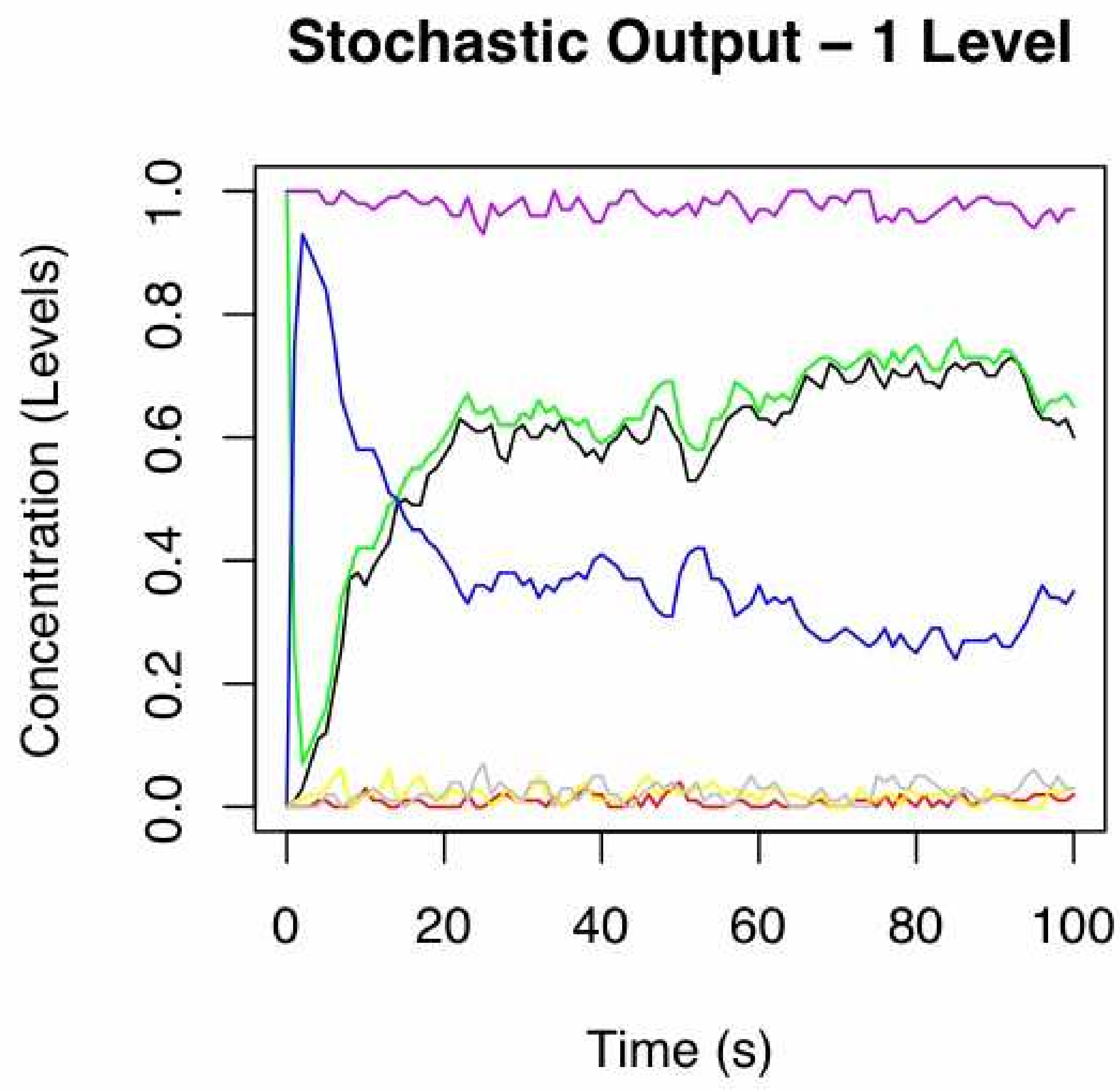

Oxygen
O2
H1FOH:VAL
S18
k2
H1F:PHD
S13
H1FOH
S14
k1
H1F
S3
k12
k18
k20
k14
S12
PHD
ARNT
S4
S17
VHL
k3
k22
Oxygen
O2
S5
H1F:ARNT
k15
S15
H1F:ARNT:PHD
k17
S16
H1FOH:ARNT

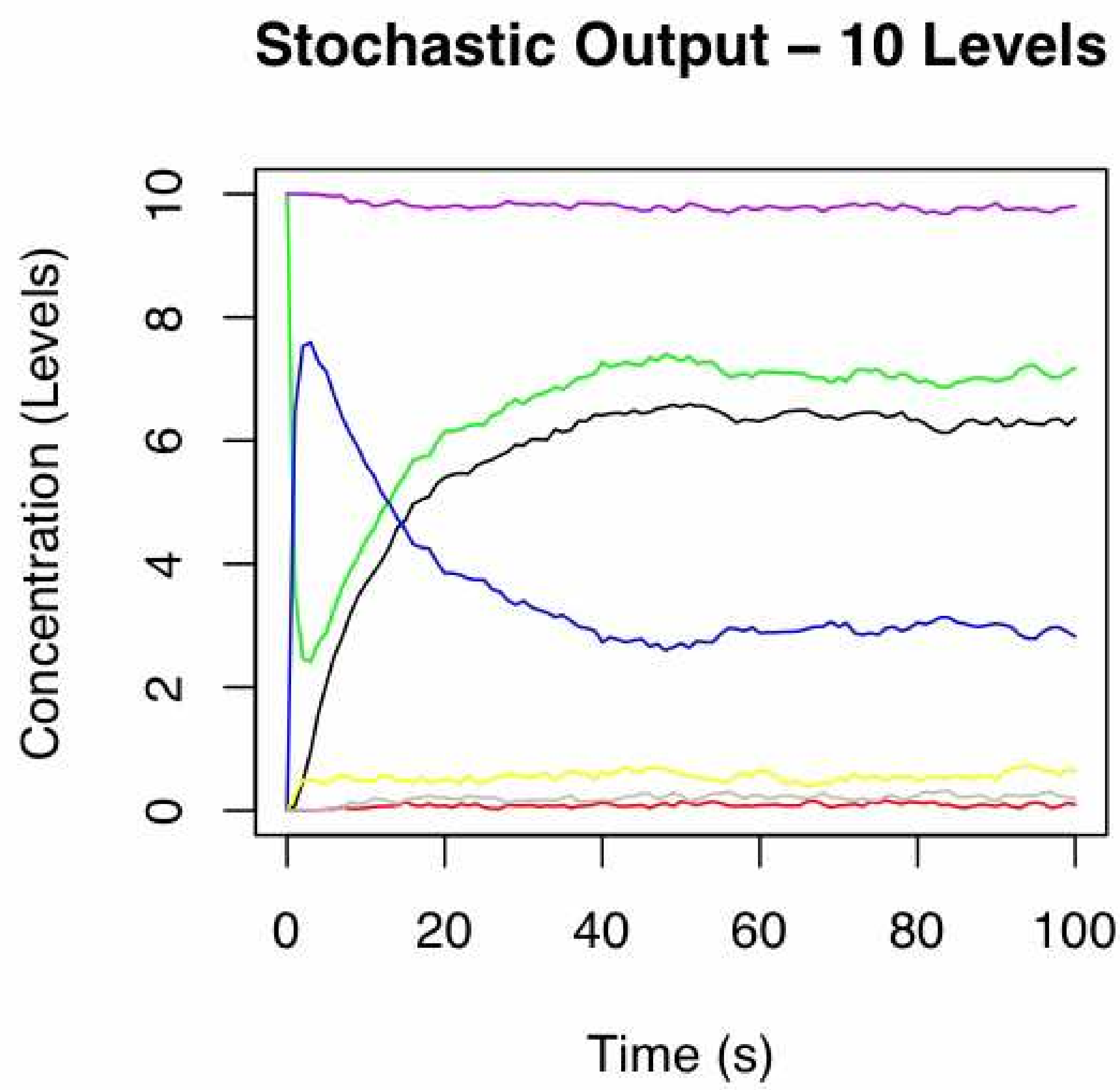
Ex8 - Hypoxia

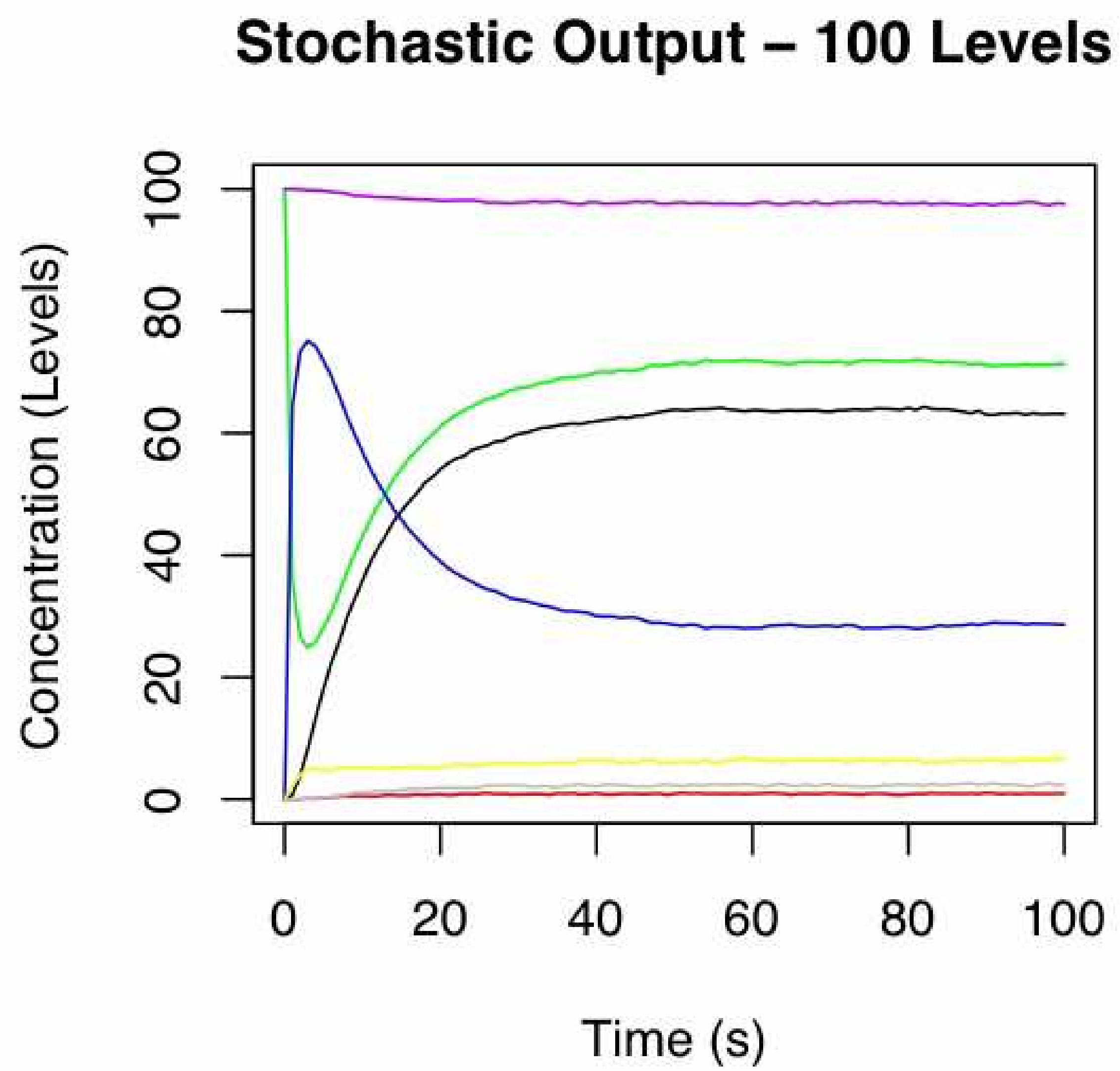

B
C
k2
k12, k14
A
E
k1
PHD
S12
k18, k20
H1F
H1FOH
S3
S14
D
k3, k15, k17, k22

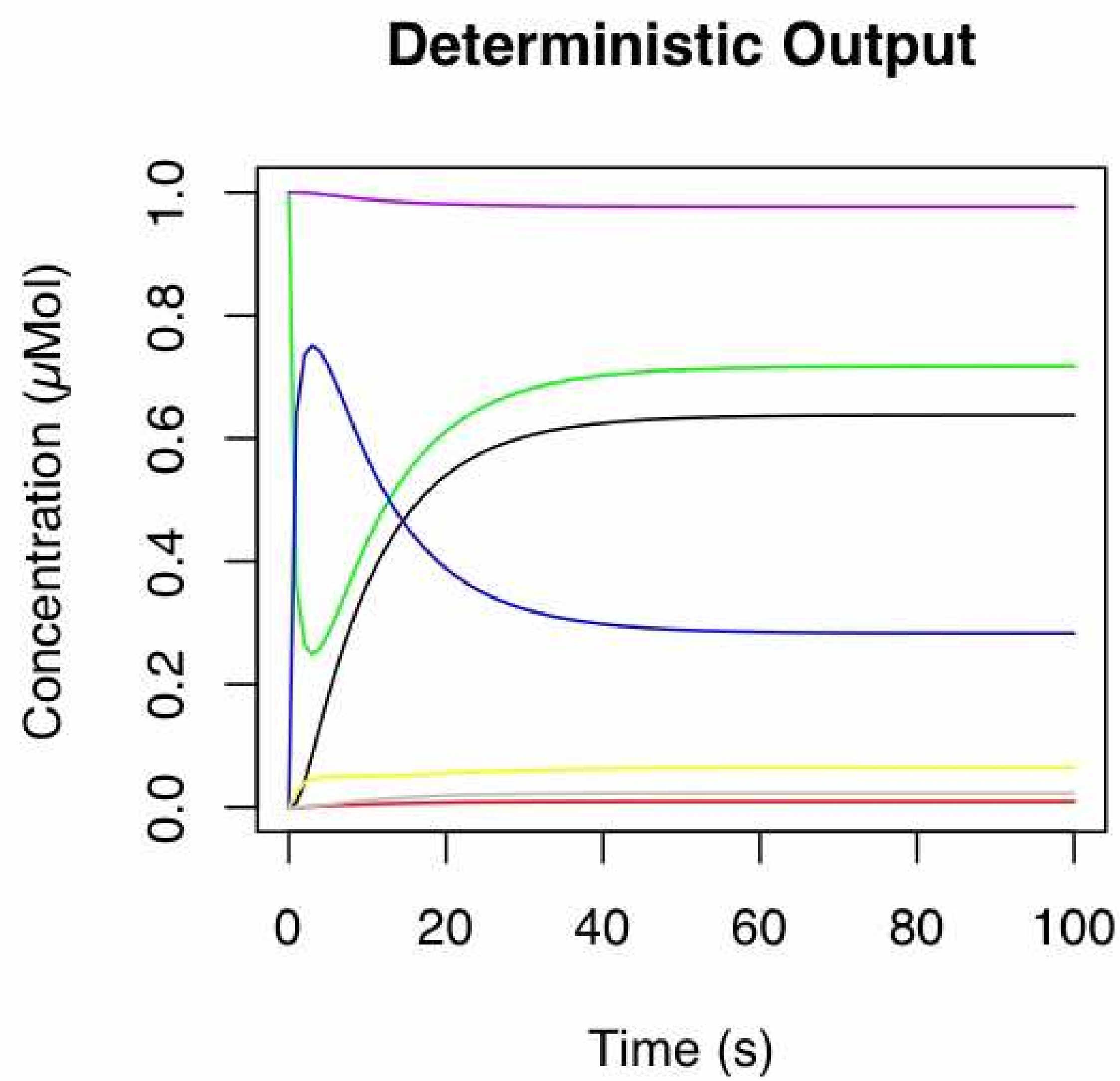

B
C
k2
k12, k14
k18, k20
A
E
k1
PHD
S12
H1F
S3
H1FOH
S14
D
k3, k15, k17, k22
B
C
k2
k12, k14
k18, k20
A
E
k1
PHD
S12
H1F
S3
H1FOH
S14
D
k3, k15, k17, k22
B
C
k2
k12, k14
k18, k20
A
E
k1
PHD
S12
H1F
S3
H1FOH
S14
D
k3, k15, k17, k22

ABOUT THE RELATION STOCHASTIC VS CONTINUOUS


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)

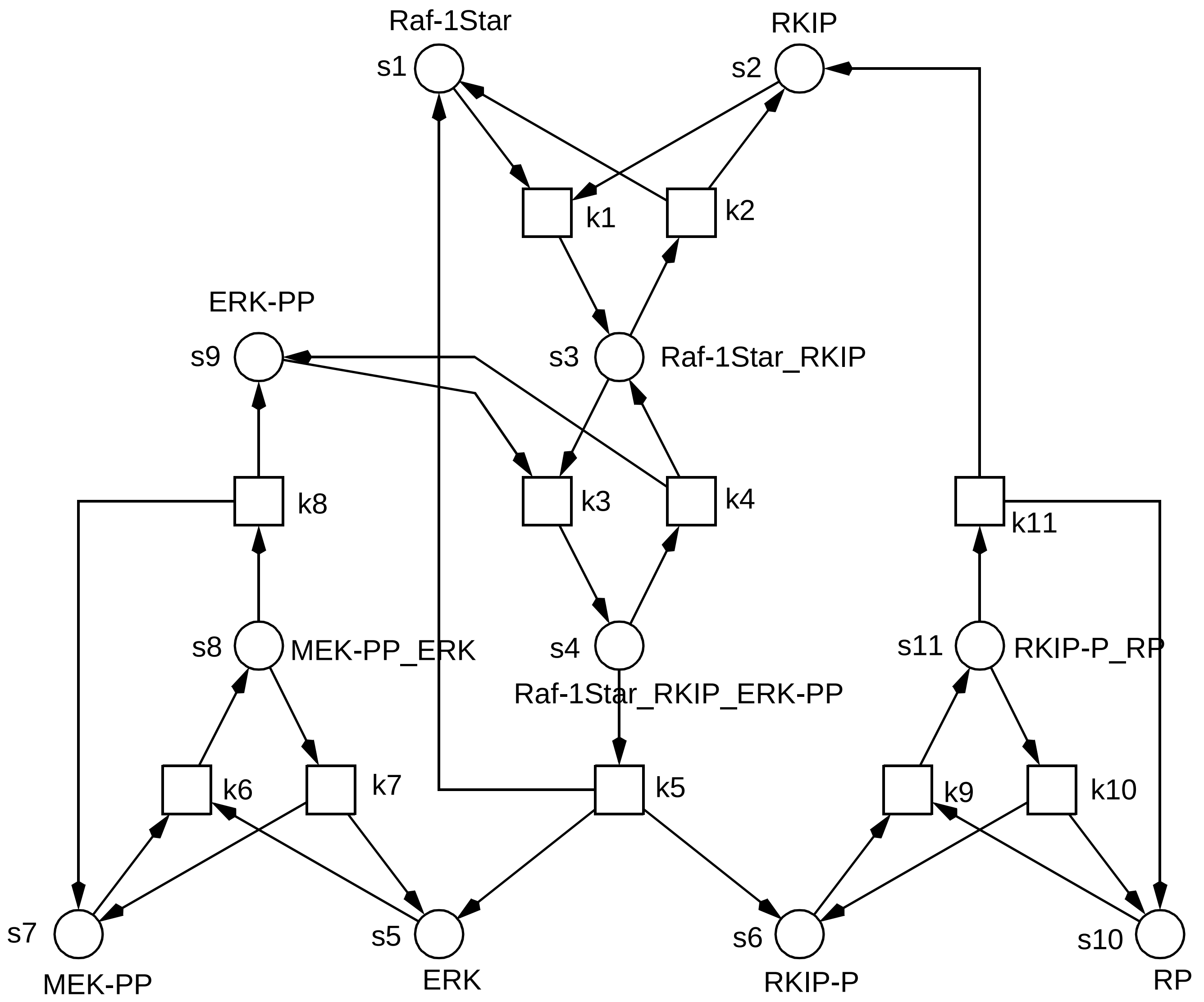

Stochastic Output – 10 Levels
Concentration (Levels)
0
2
4
6
8
10
0
20
40
60
80
100
Time (s)


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



Deterministic Output
Concentration (μMol)
0.0
0.2
0.4
0.6
0.8
1.0
0
20
40
60
80
100
Time (s)

EX4 - RKIP SIGNALLING PATHWAY, PETRI NET

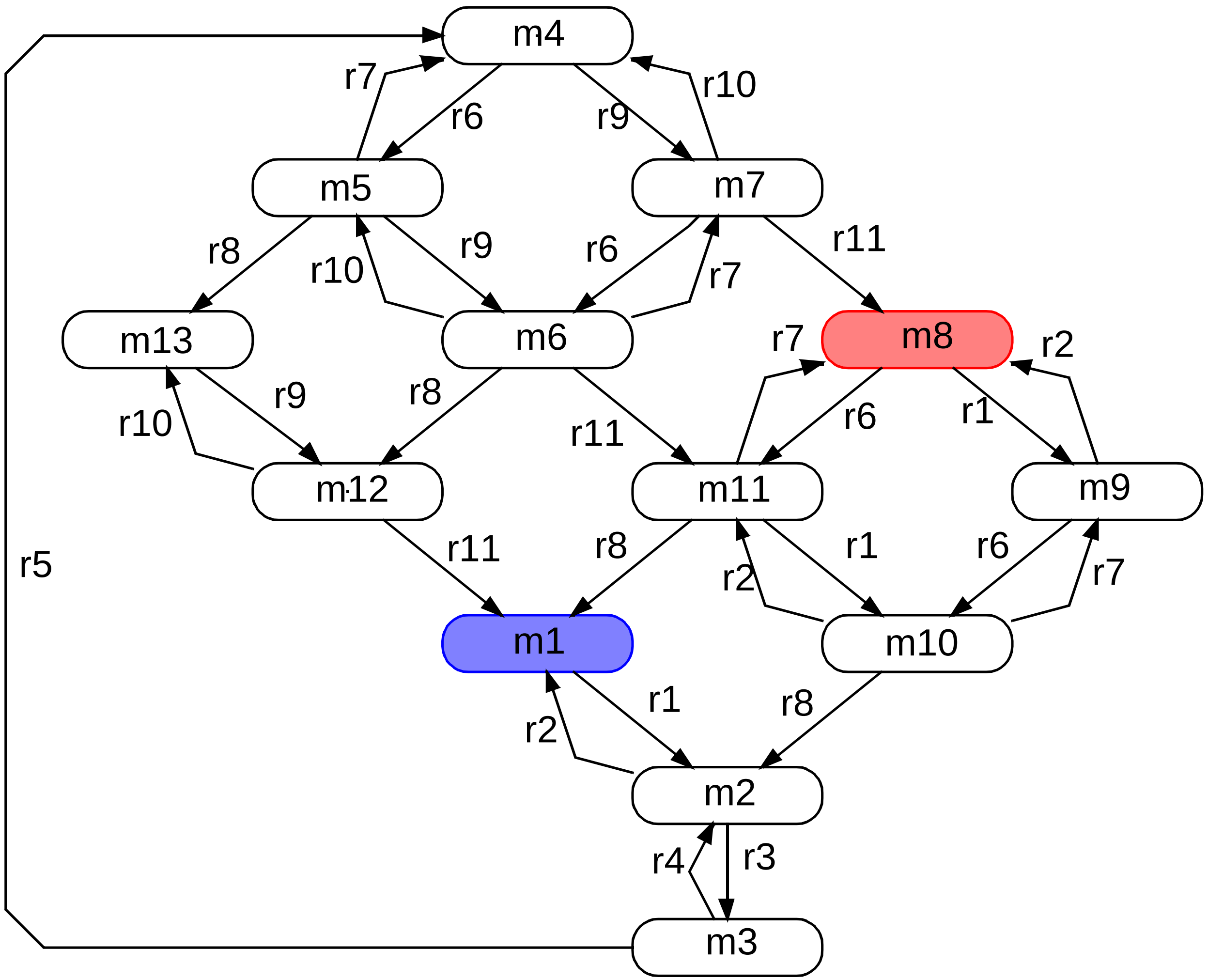


[HEINER, GILBERT 2006]

[HEINER, DONALDSON, GILBERT 2010]

Ex4 - RKIP, Reachability Graph (STS)

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



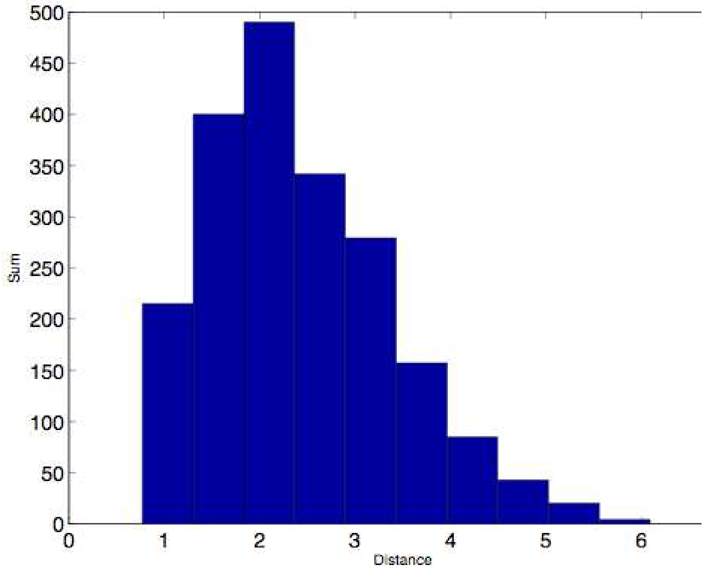
EX4 - RKIP, QUANTITATIVE ANALYSIS

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

Cho et al

Biochemist

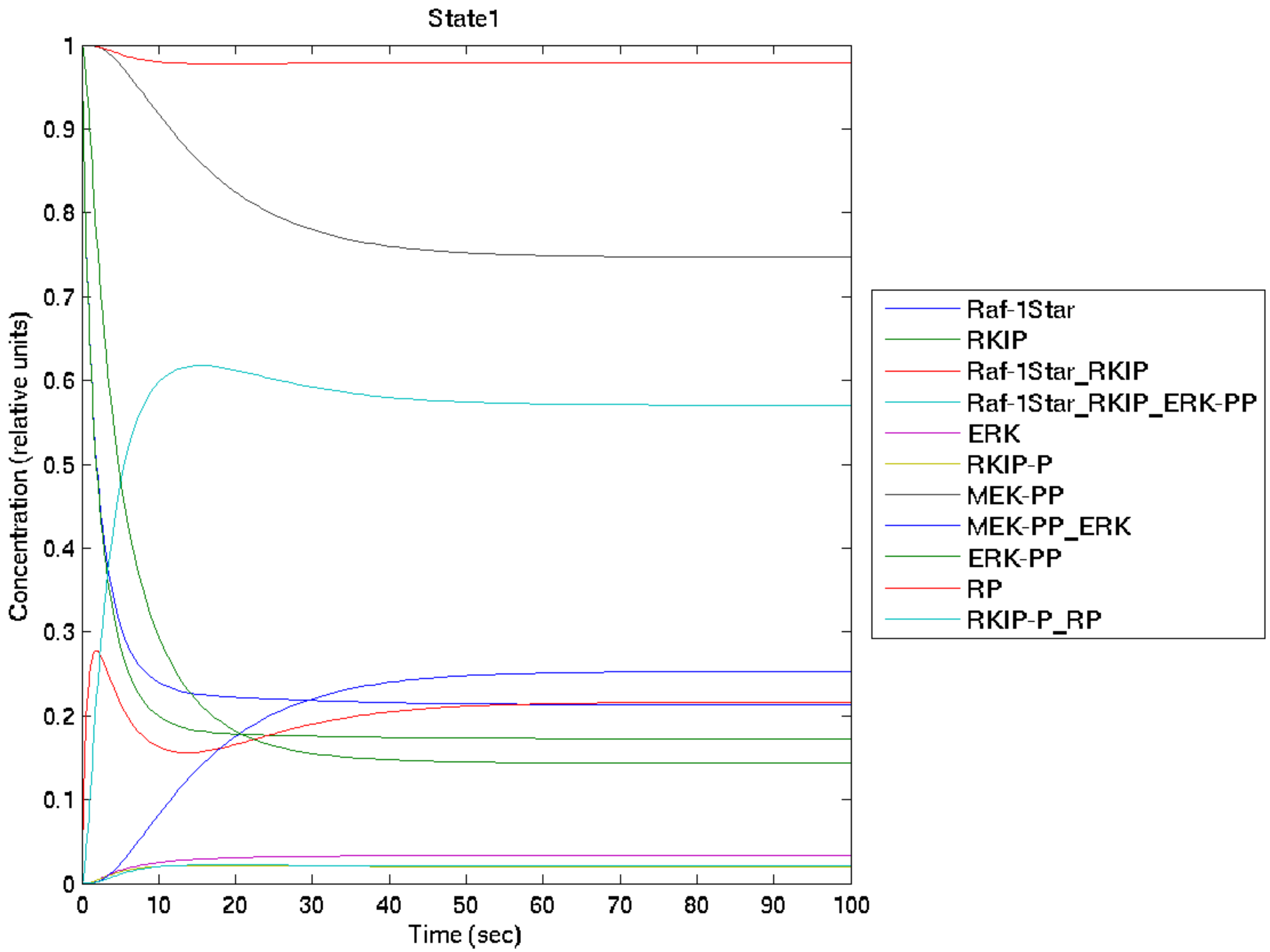
13 good state configurations



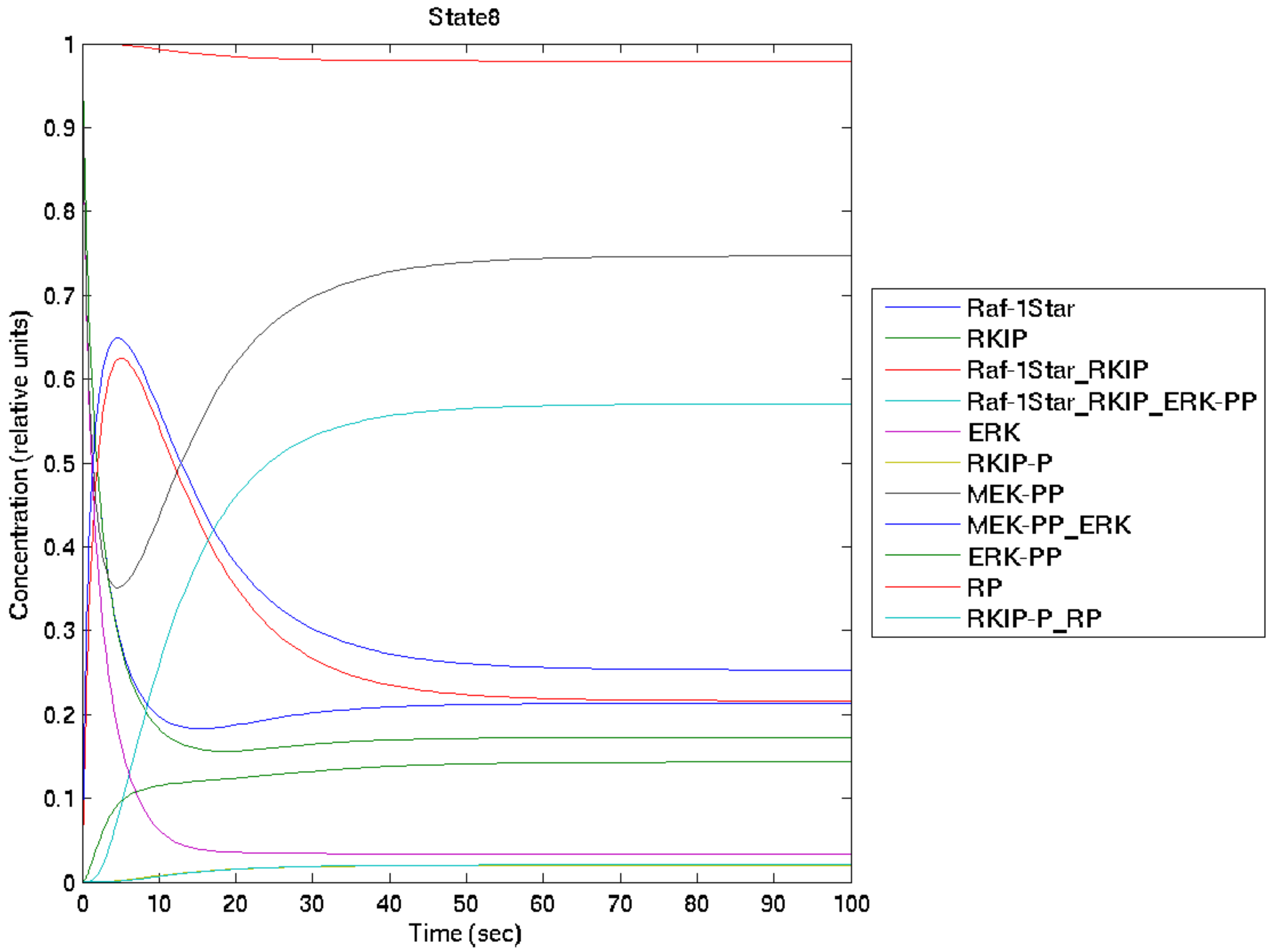
Distribution of `bad' steady states as euclidean distances from the `good' final steady state

the bad ones

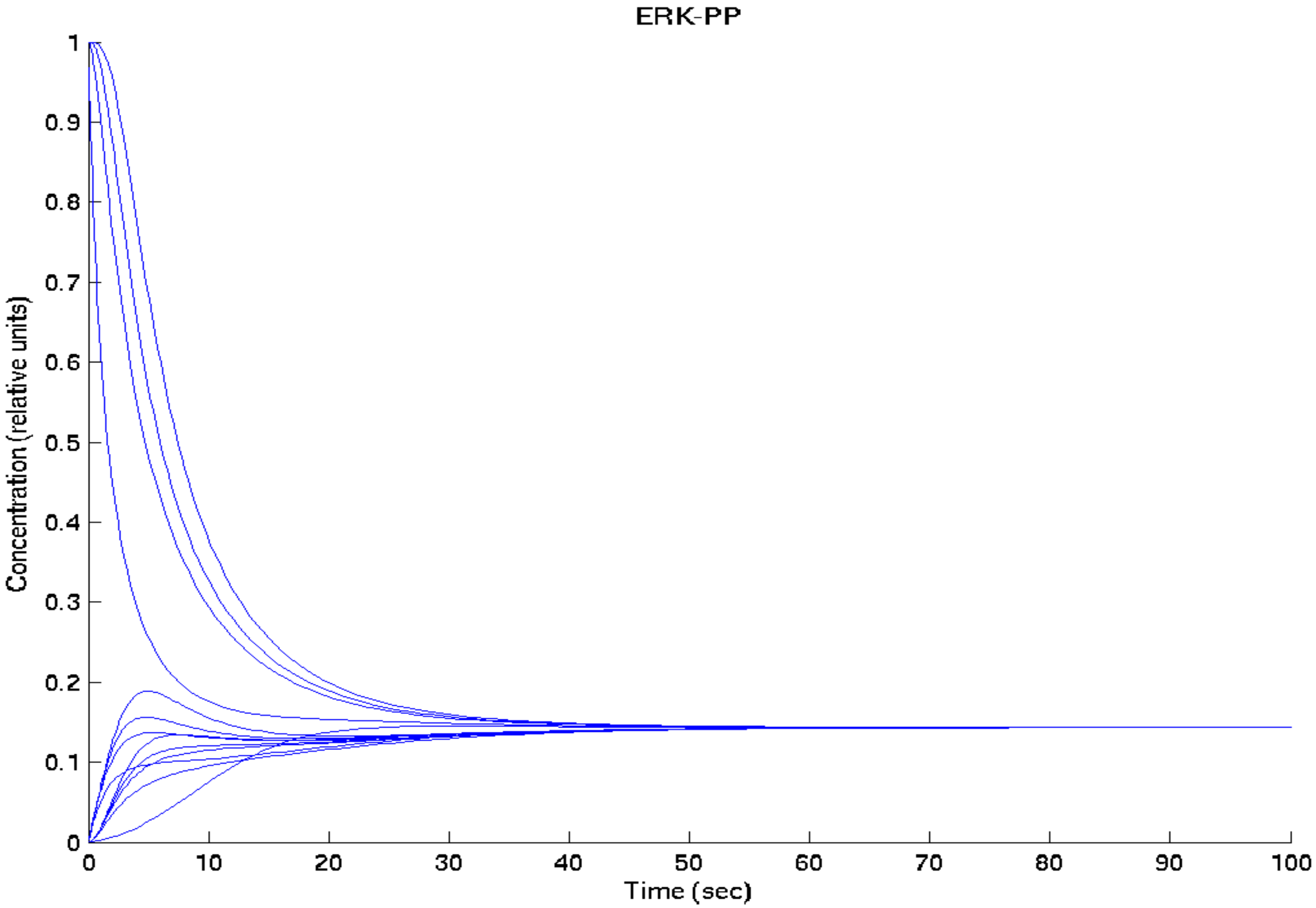
Ex4 - RKIP, Quantitative Analysis



Ex4 - RKIP, Quantitative Analysis



Ex4 - RKIP, Quantitative Analysis



BUT,

TRANSITION SPN -> CPN

MAY COME WITH

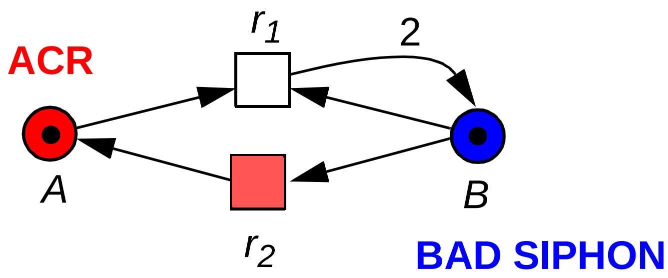
COUNTERINTUITIVE EFFECTS.

- **ACR: steady state value of variable (place) does not depend on total mass, only on kinetic constants** *-> [SHINAR, FEINBERG 2010]*

- **simple example** **mass-action kinetics**

  r_1: $A + B \to 2B$ $v_1(r_1) = k_1AB$

  r_2: $B \to A$ $v_2(r_2) = k_2B$



- **ODEs**

  $dA/dt = v_2 - v_1 = k_2B - k_1AB$

  $dB/dt = v_1 - v_2 = k_1AB - k_2B$

CPI: $m_0(A) + m_0(B) = total$

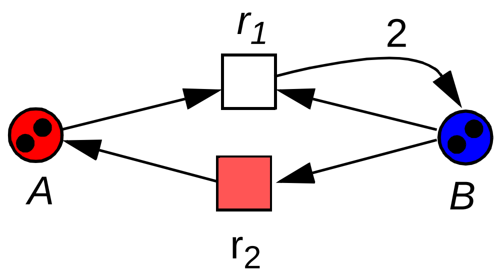
- **steady state**

  $dA/dt = k_2B - k_1AB = 0$

  $dB/dt = k_1AB - k_2B = 0$

  -> $steady\_state(A) = k_2/k_1$

  $steady\_state(B) = total - k_2/k_1$



SUMMARY

- **representation of bio networks by Petri nets**
  - -> *partial order representation* -> *better comprehension*
  - -> *formal semantics* -> *sound analysis techniques*
  - -> *unifying view*
- **purposes**
  - -> *animation* -> *to experience the model*
  - -> *model validation against consistency criteria* -> *to increase confidence*
  - -> *qualitative / quantitative behaviour prediction* -> *experiment design, new insights*
- **step-wise model development**
  - -> *qualitative model* -> *discrete Petri nets*
  - -> *discrete quantitative model* -> *stochastic Petri nets*
  - -> *continuous quantitative model* -> *continuous Petri nets = ODEs, hybrid models*
  - -> *locality and space* -> *coloured Petri nets*

APPENDIX

- **transitions r_i get a stochastic waiting time**
  - -> *exponential distribution with parameter lambda*
- **state-dependent lambda defined by rate function $v_i(r_i)$**
  - -> *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*

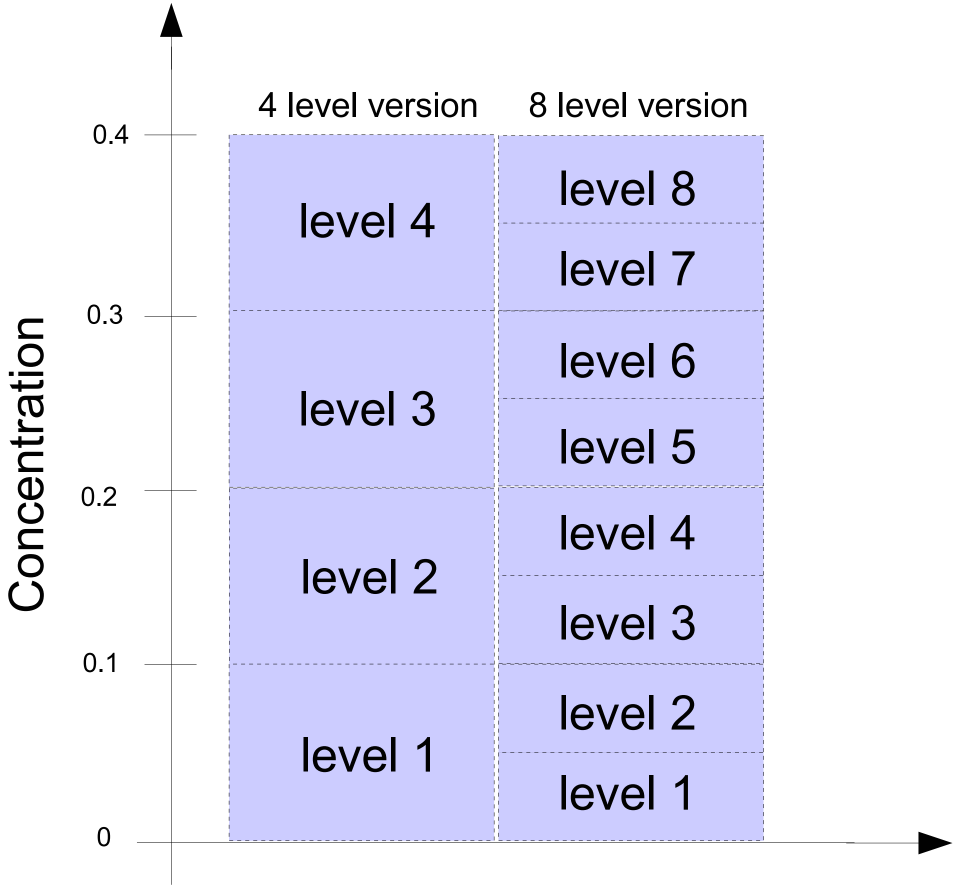
- **mass-action semantics**

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

- **level semantics**

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

LEVEL CONCEPT



CONTINUOUS PETRI NETS, BASICS

- **transitions r_i fire continuously**

- **rate functions $v_i(r_i)$**

  -> *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* -> [SOLIMAN, HEINER 2010]

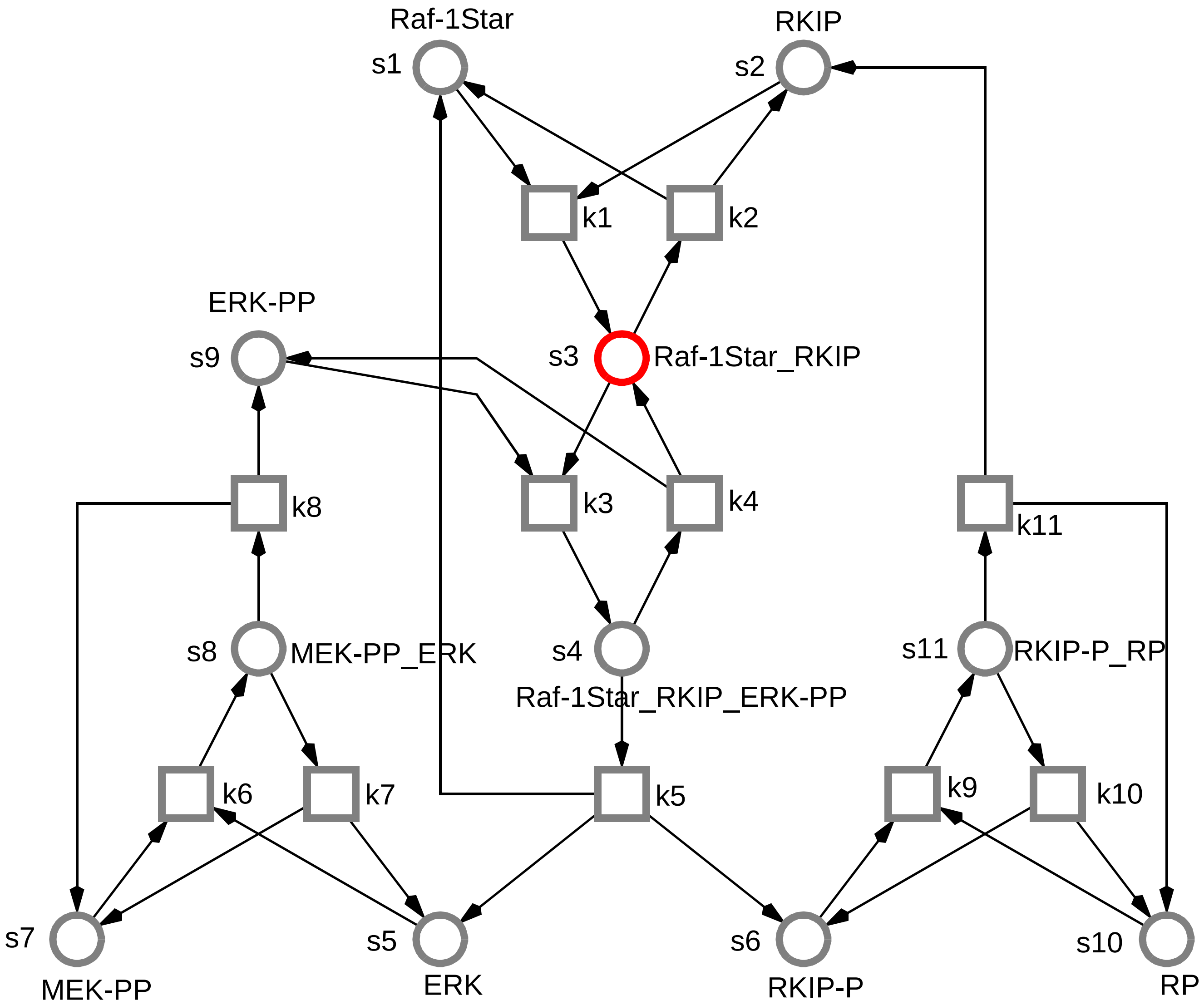
  -> *typically non-linear*

- **simulation (numerical integration)**

  -> *stiff / unstiff solvers*

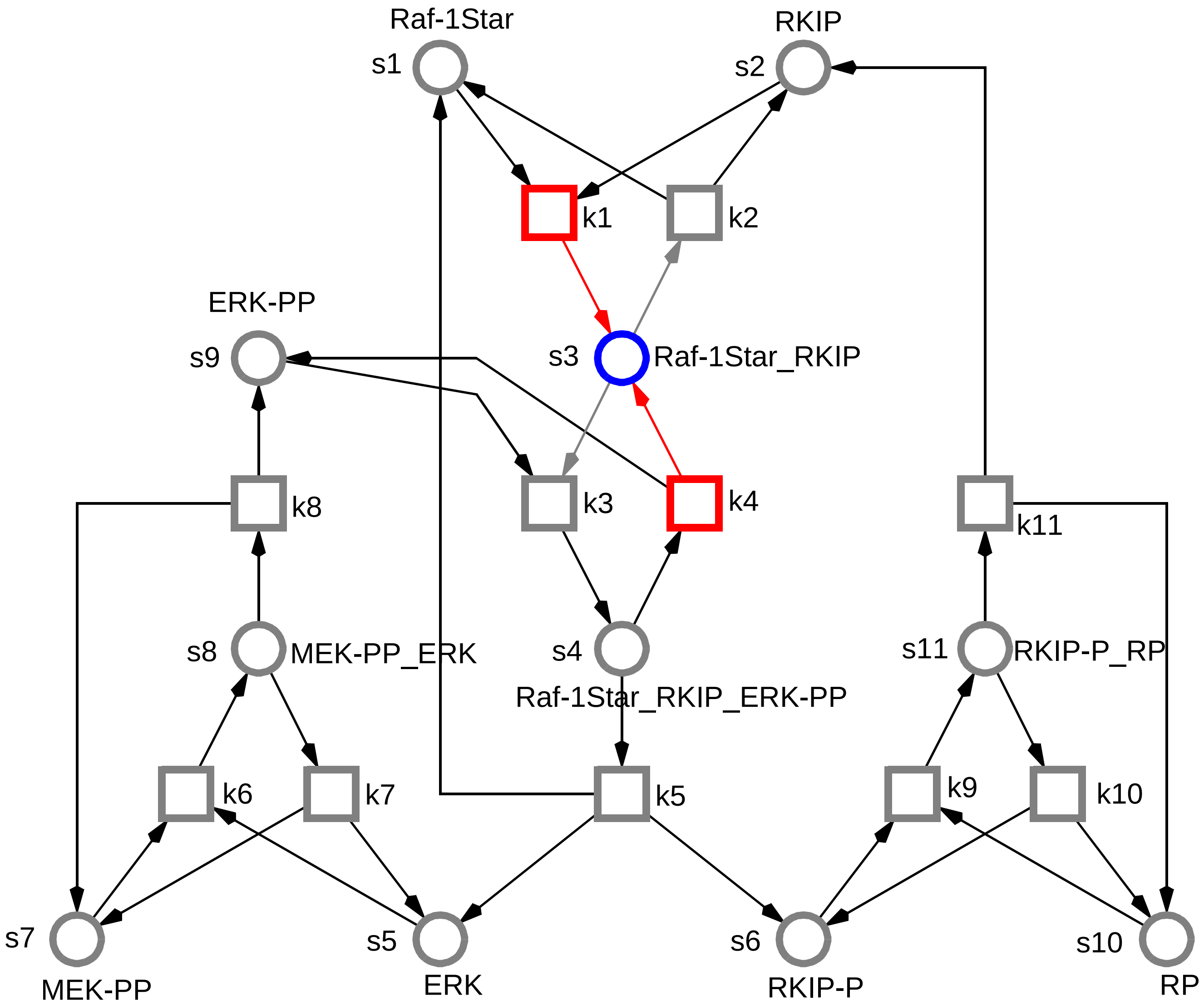
CContinuous Petri Net Defines ODEs

$$\frac{ds3}{dt} =$$



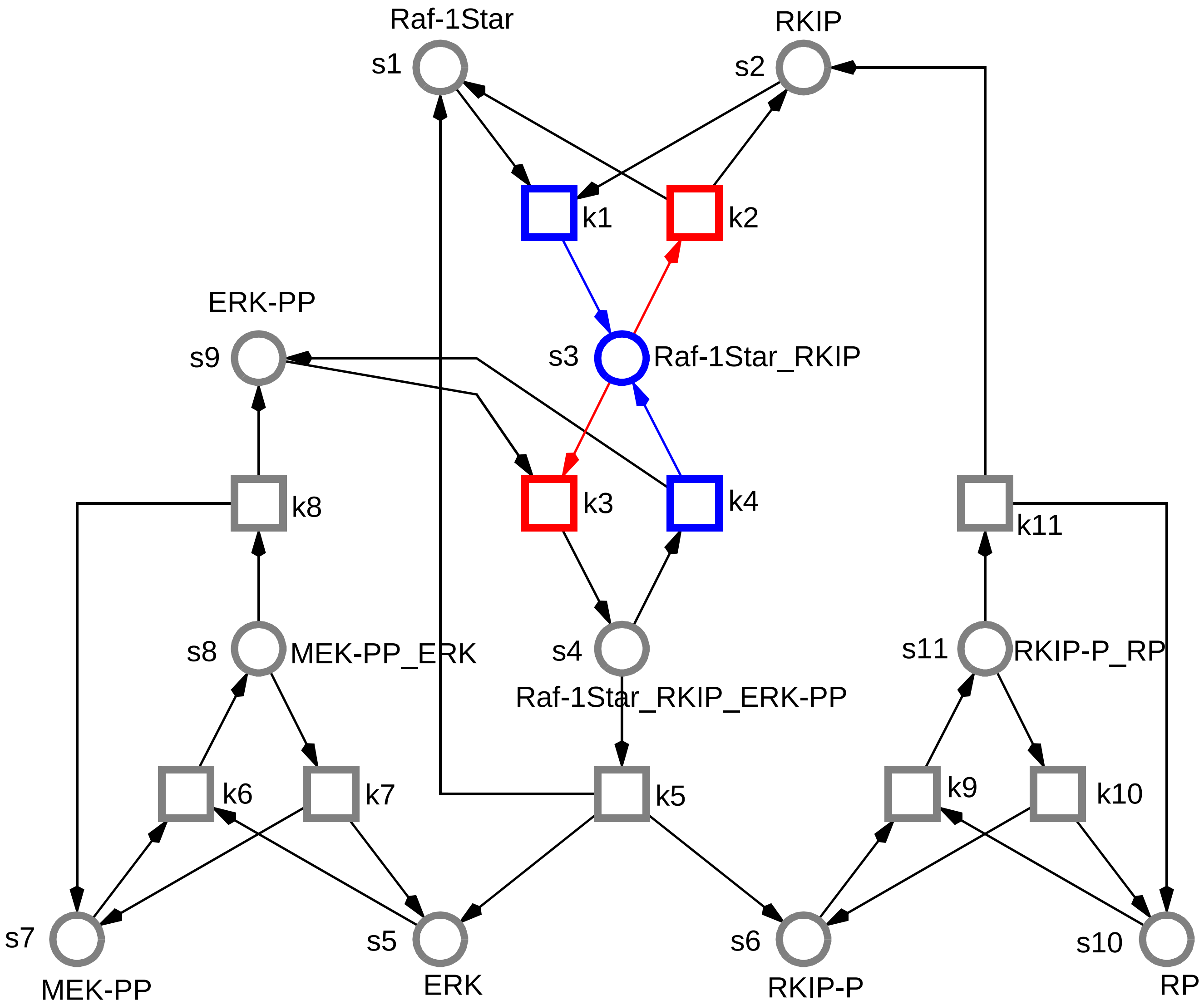
CONTINUOUS PETRI NET DEFINES ODES

$$\frac{ds3}{dt} = + v1 + v4$$



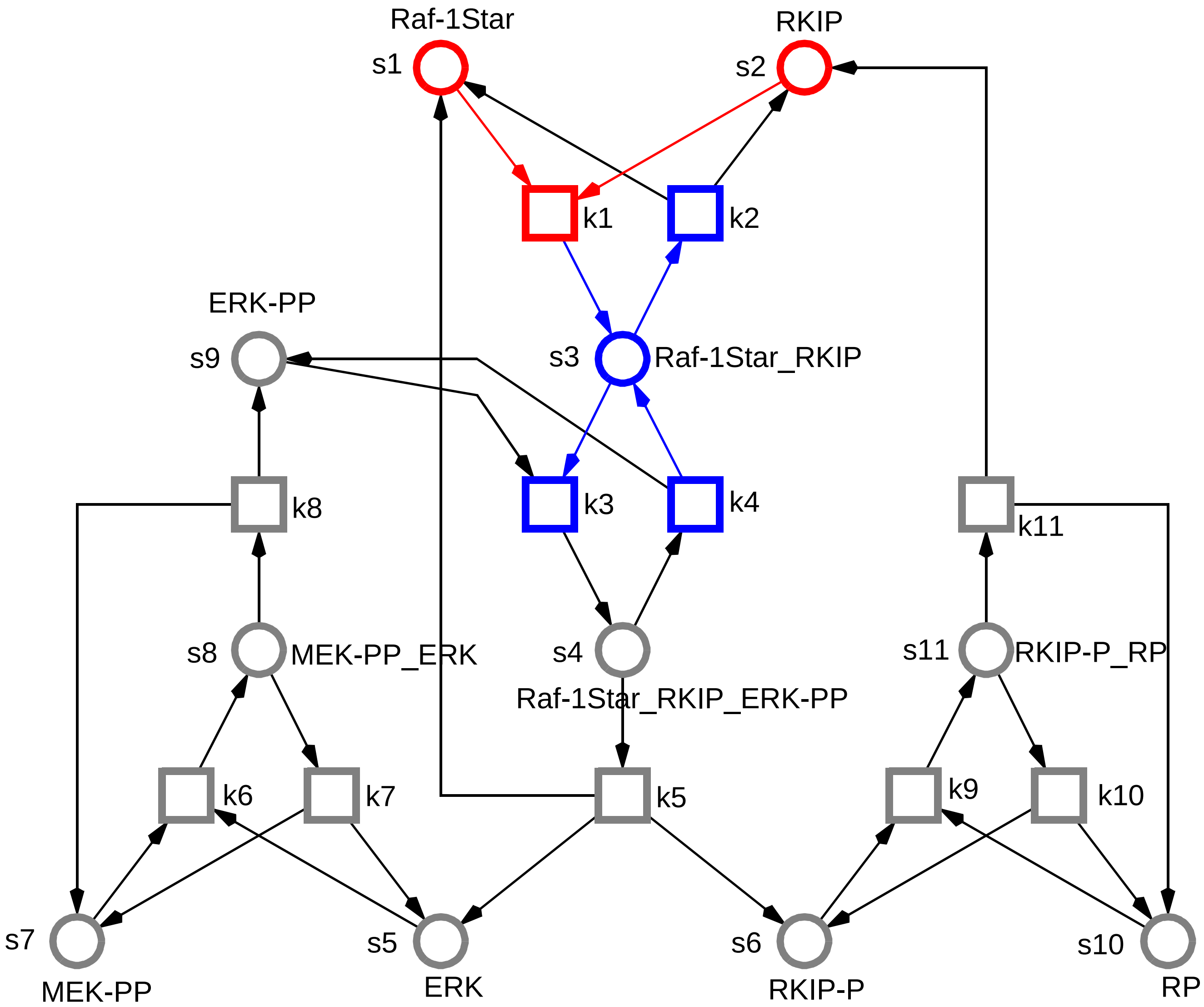
Continuous Petri Net Defines ODEs

$$\frac{ds3}{dt} = +v1 + v4 - v2 - v3$$



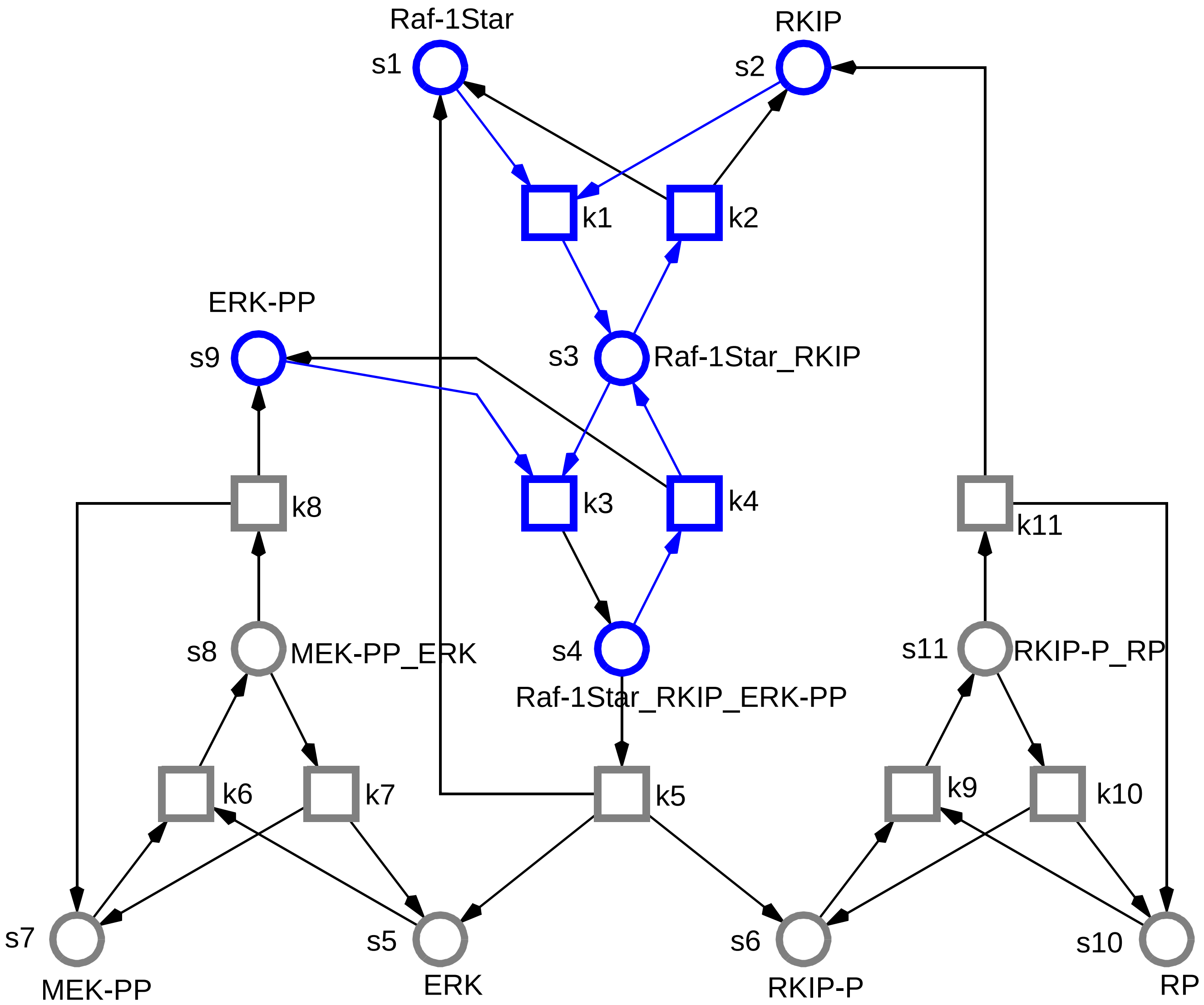
CONTINUOUS PETRI NET DEFINES ODES

$$\frac{ds3}{dt} = + k1 * s1 * s2 + v4 - v2 - v3$$



Continuous Petri Net Defines ODEs

$$\frac{ds3}{dt} = + k1 * s1 * s2 + k4 * s4 - k2 * s3 - k3 * s3 * s9$$



- GHPN = XSPN + CPN

[HERAJY, HEINER 2010]

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

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

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