PART I - TALK 3

INTRODUCTION INTO ADVANCED CONCEPTS - STOCHASTIC/CONTINUOUS PETRI NETS -

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Brandenburg University of Technology Cottbus

THE

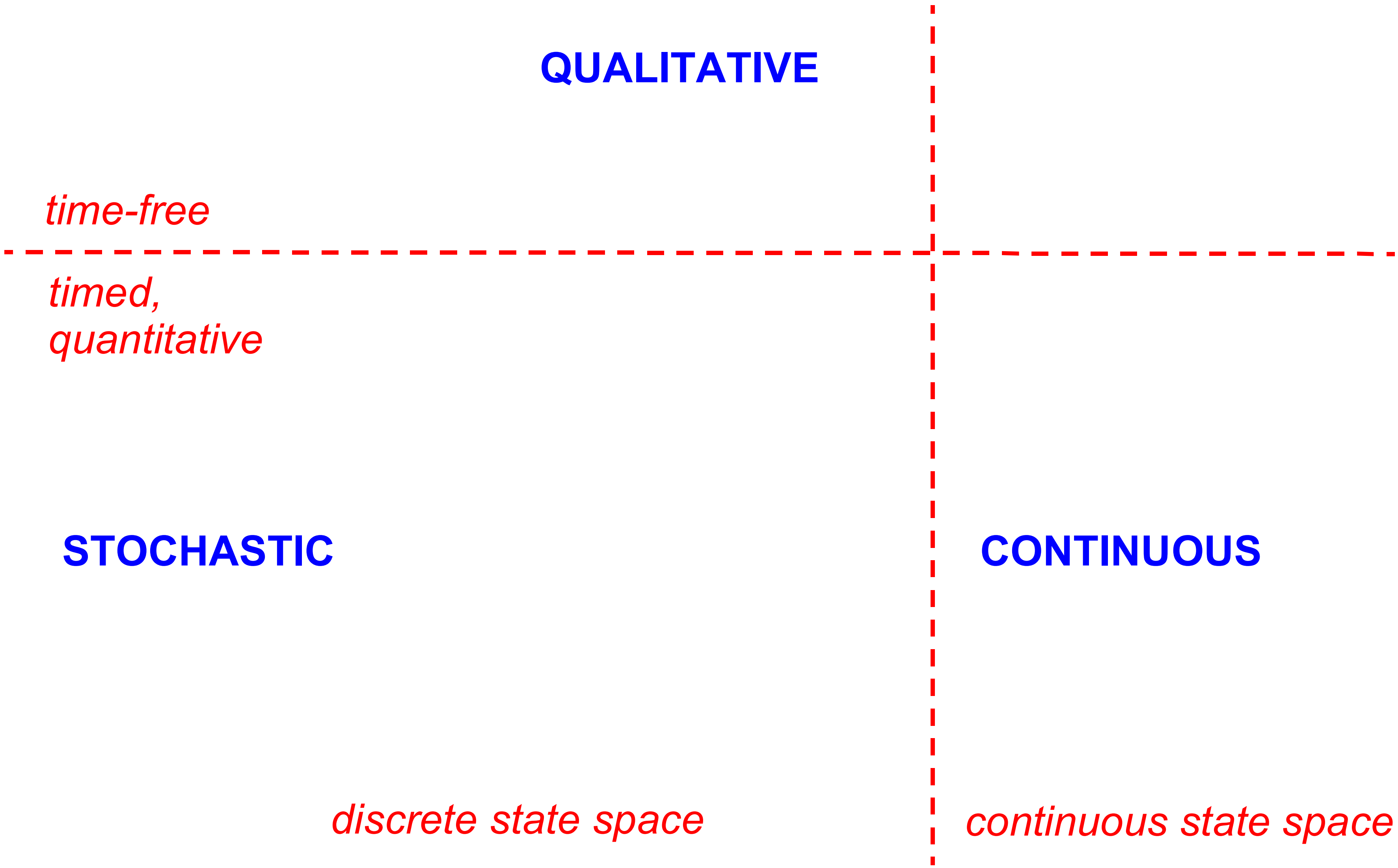
FRAMEWORK

QUALITATIVE

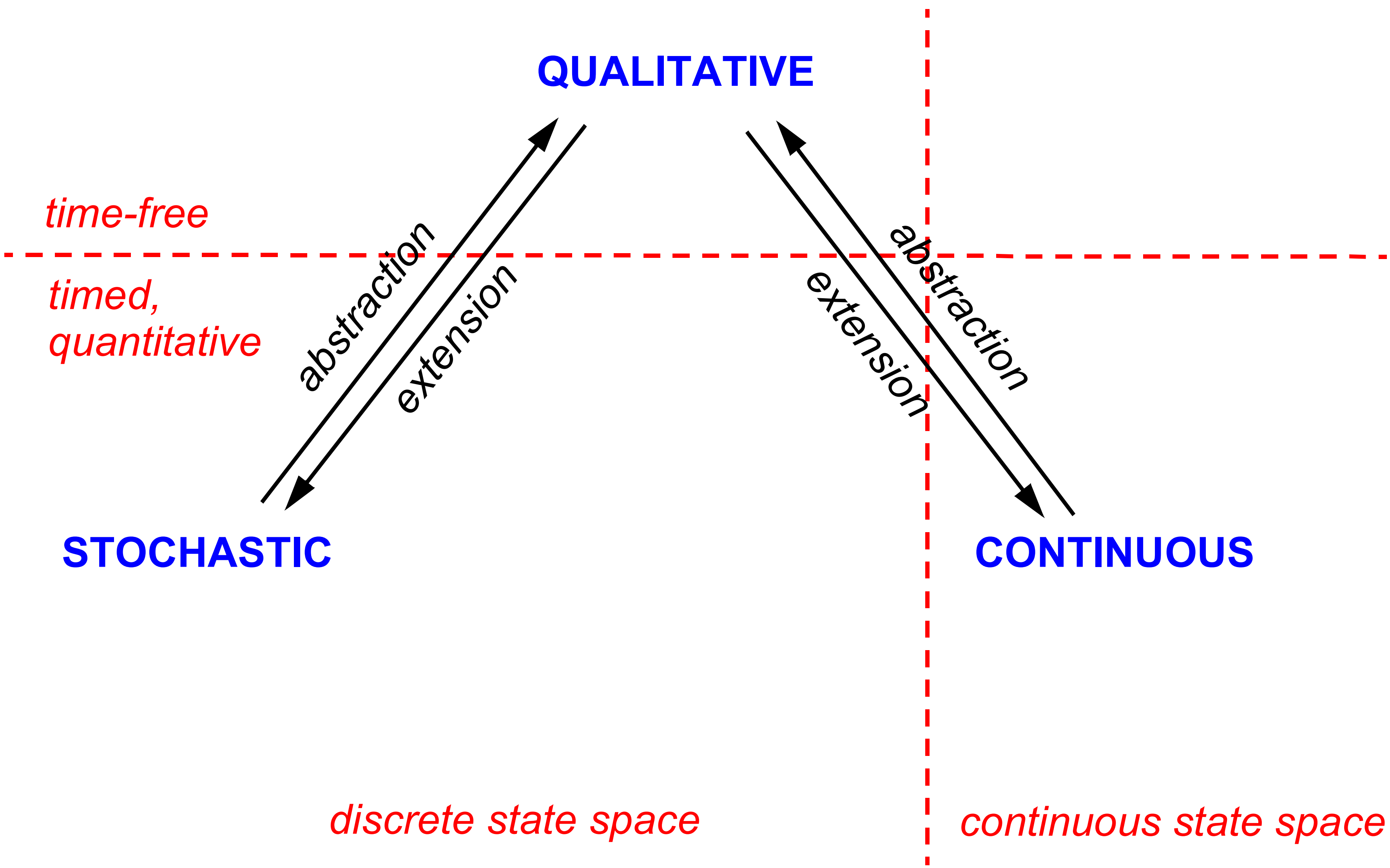
STOCHASTIC

CONTINUOUS

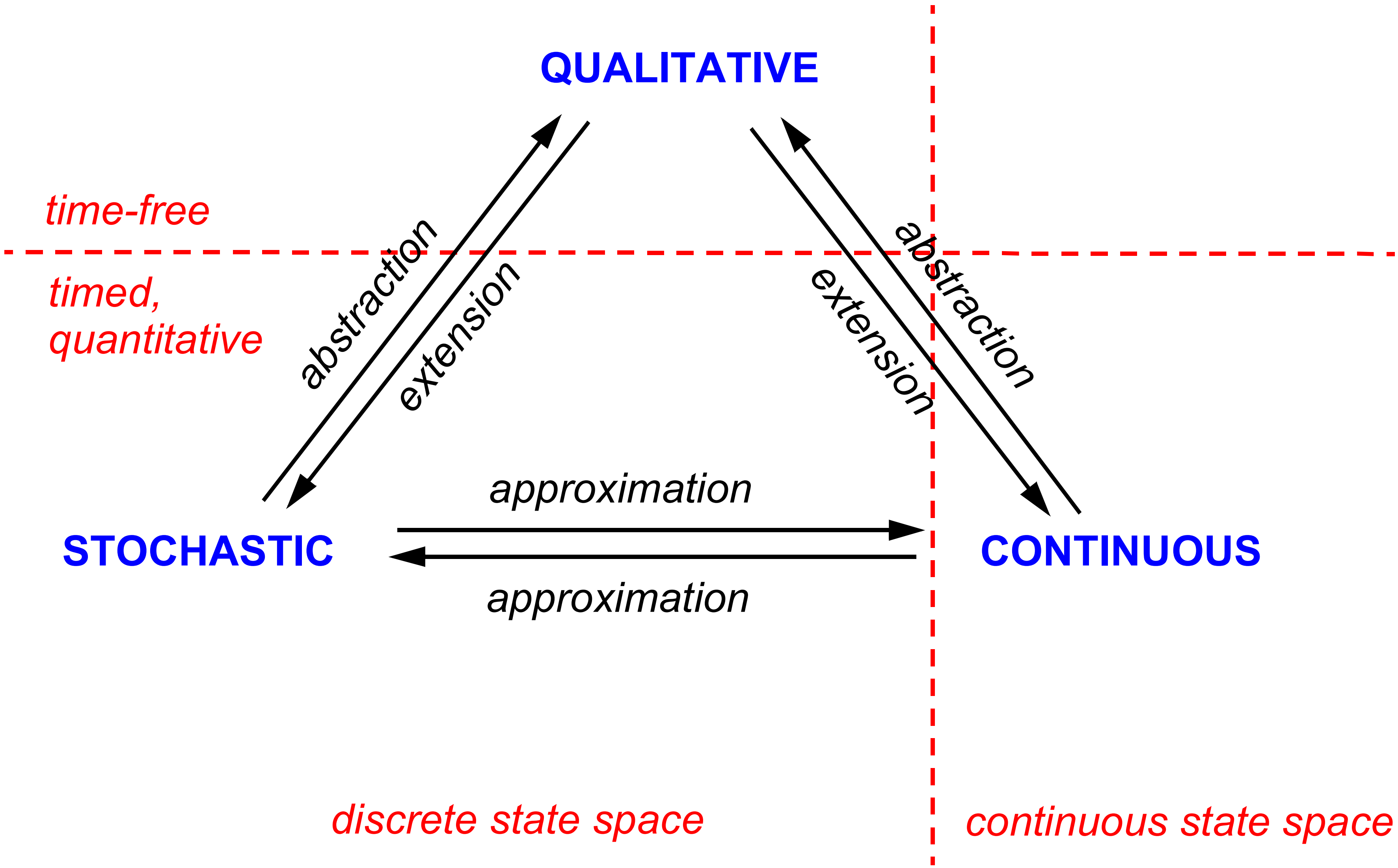
FRAMEWORK

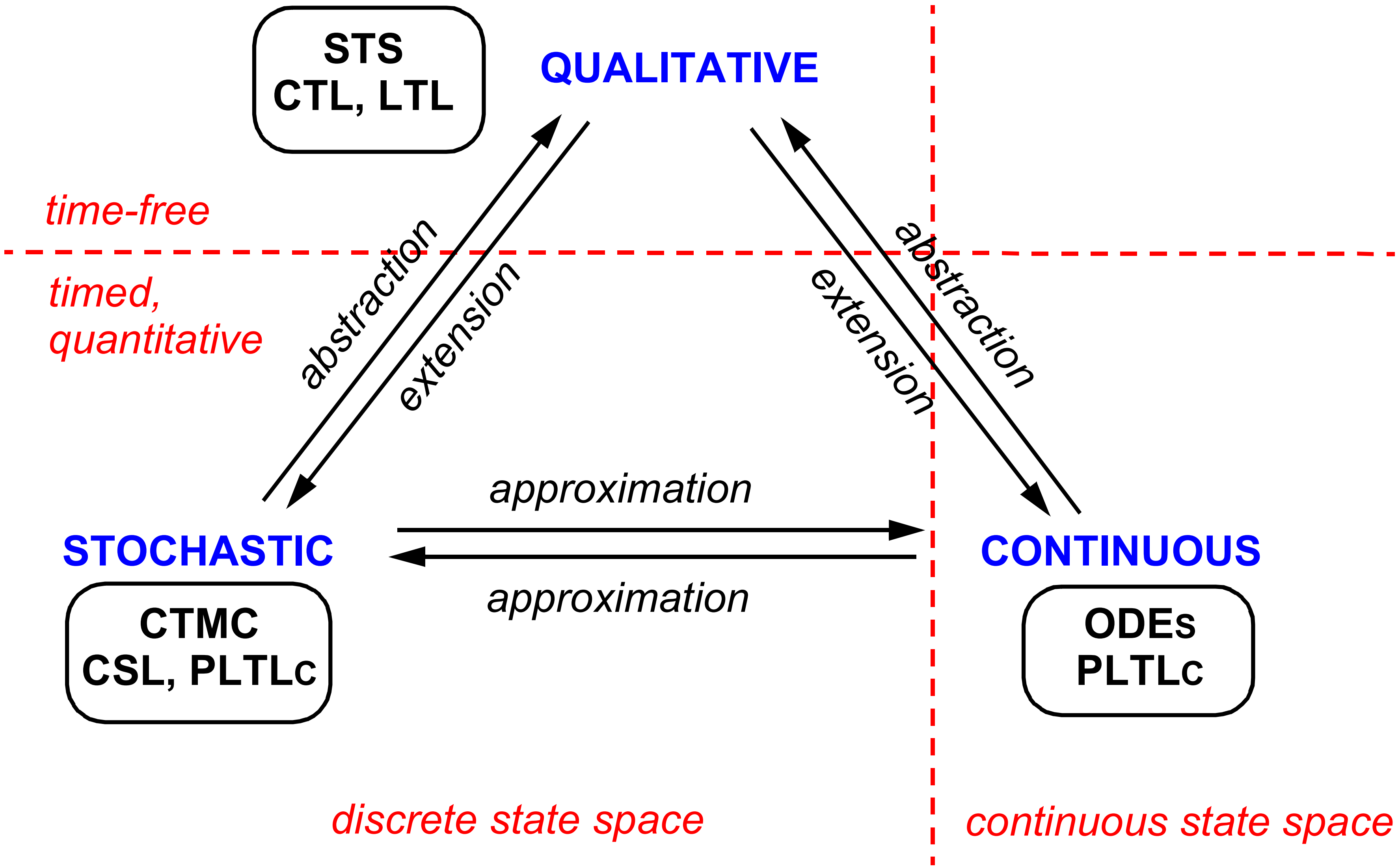

QUALITATIVE
time-free
timed,
quantitative
STOCHASTIC
CONTINUOUS
discrete state space
continuous state space

FRAMEWORK


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

FRAMEWORK


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


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

3 MODELS SHARING STRUCTURE

↓ ↓ ↓

QUANTITATIVE MODEL = QUALITATIVE MODEL

+

RATE FUNCTIONS

(KINETICS)

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

STOCHASTIC PETRI NETS, BASICS

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  -> *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*

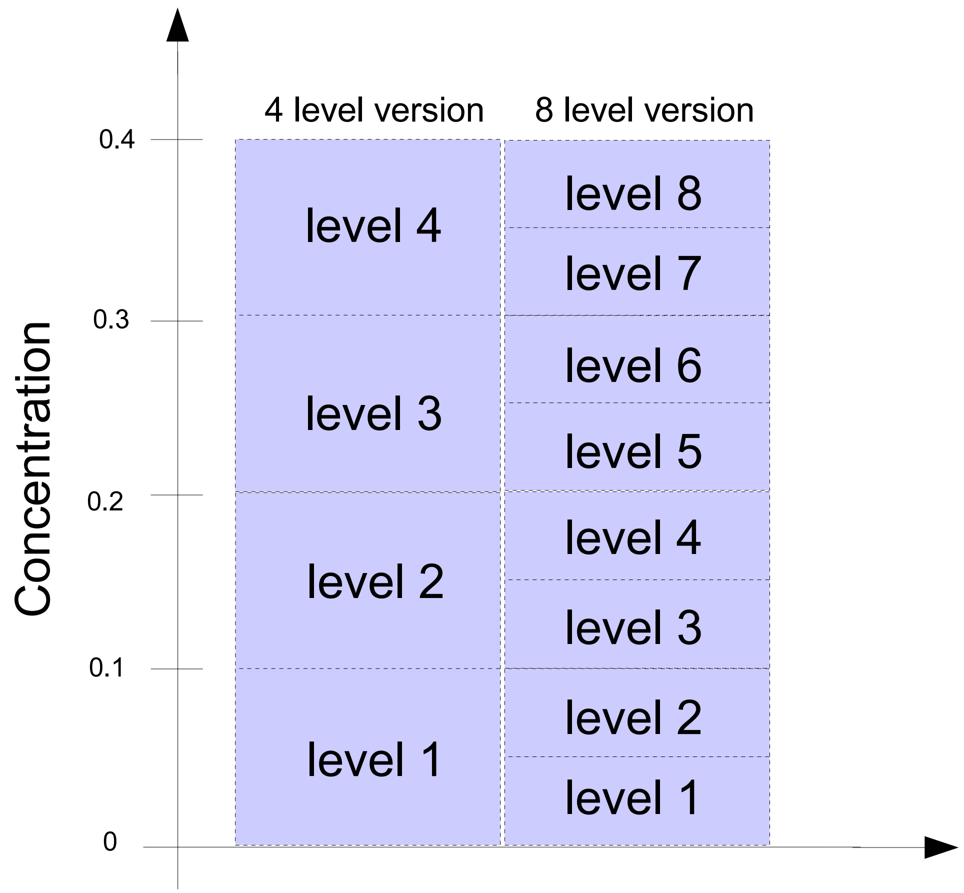
- **mass-action semantics**

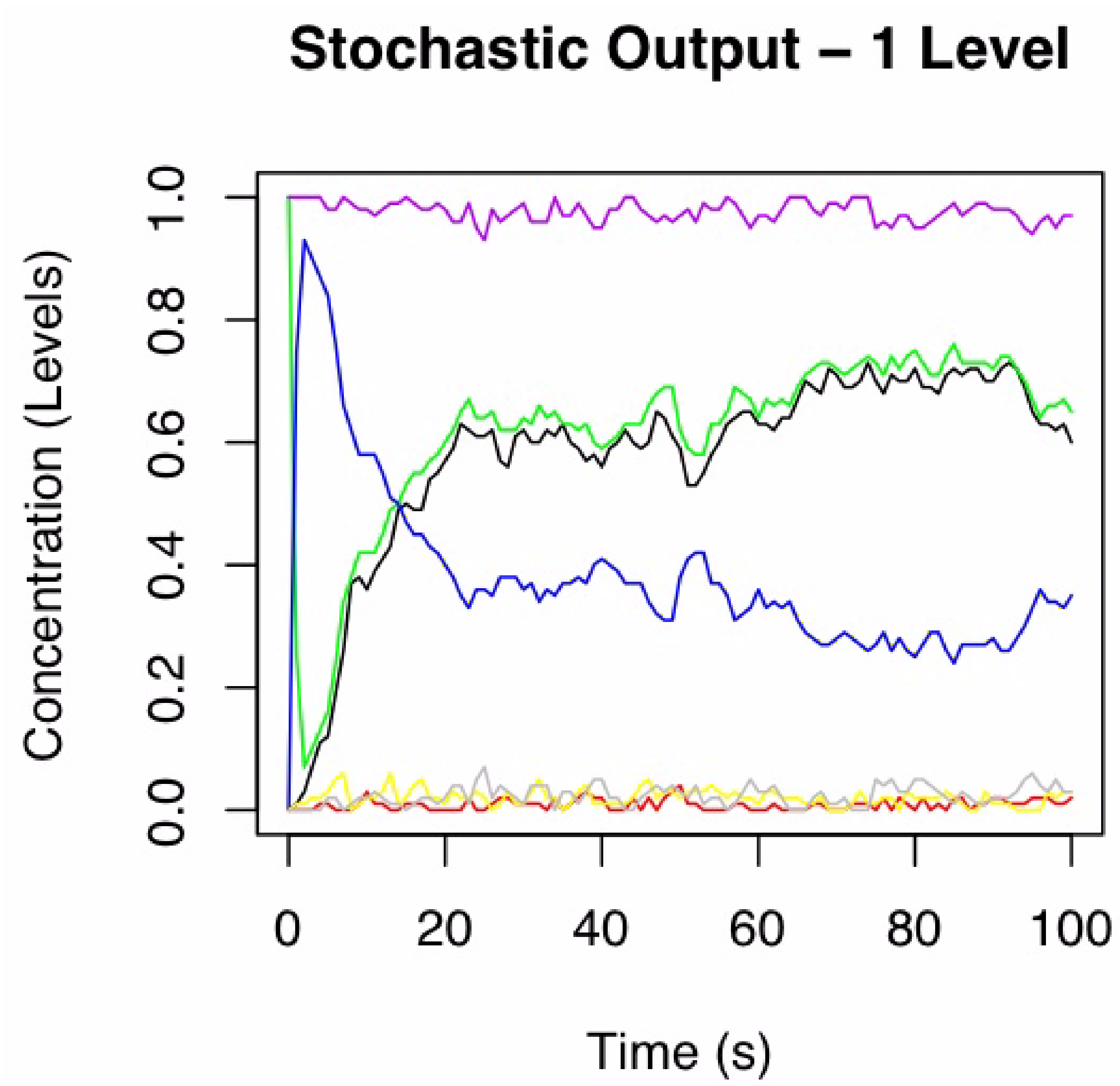
$$h_t := c_t \cdot \prod_{p \in {}^{\bullet}t} \binom{m(p)}{f(p,t)}$$

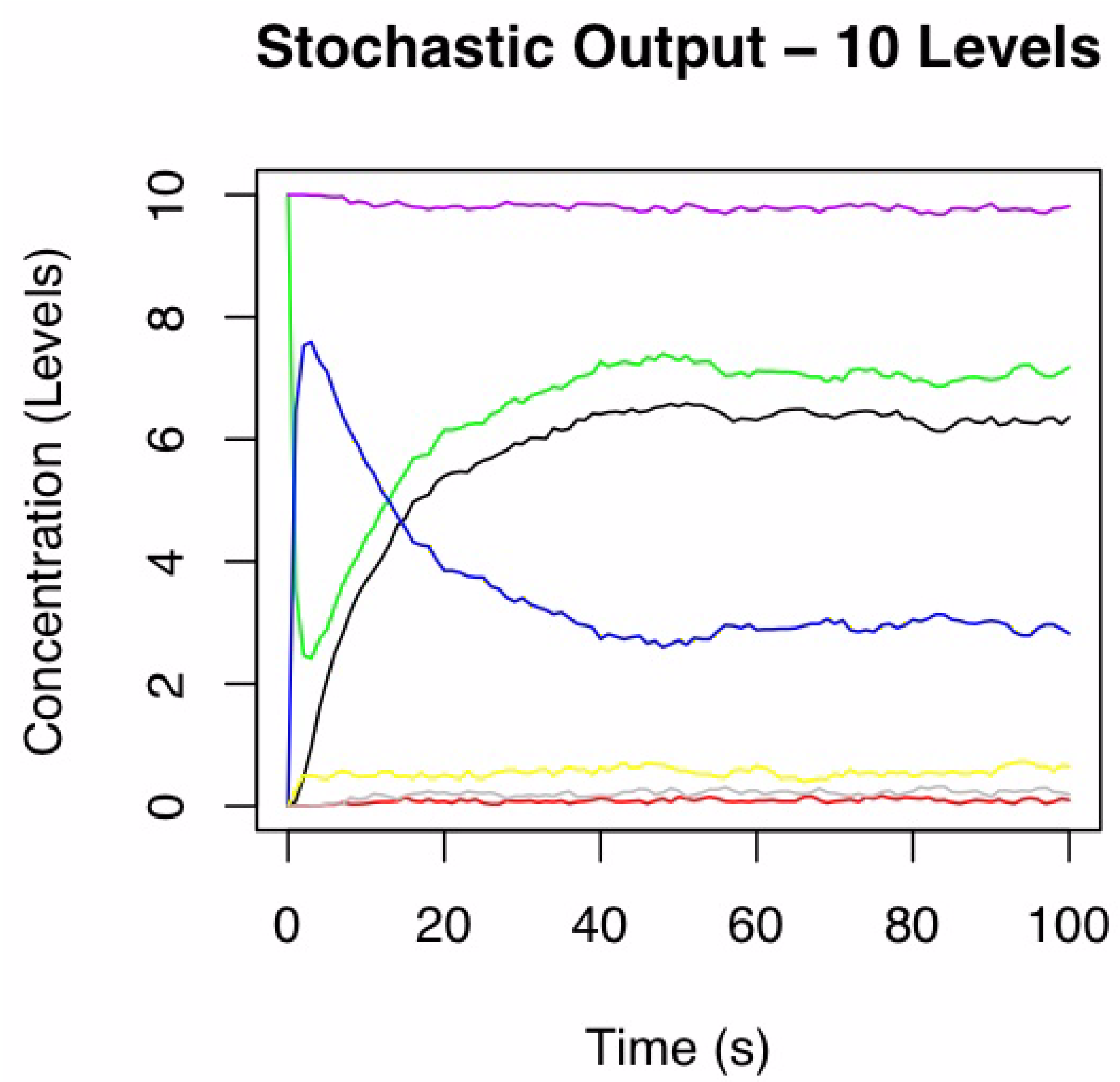
- **level semantics**

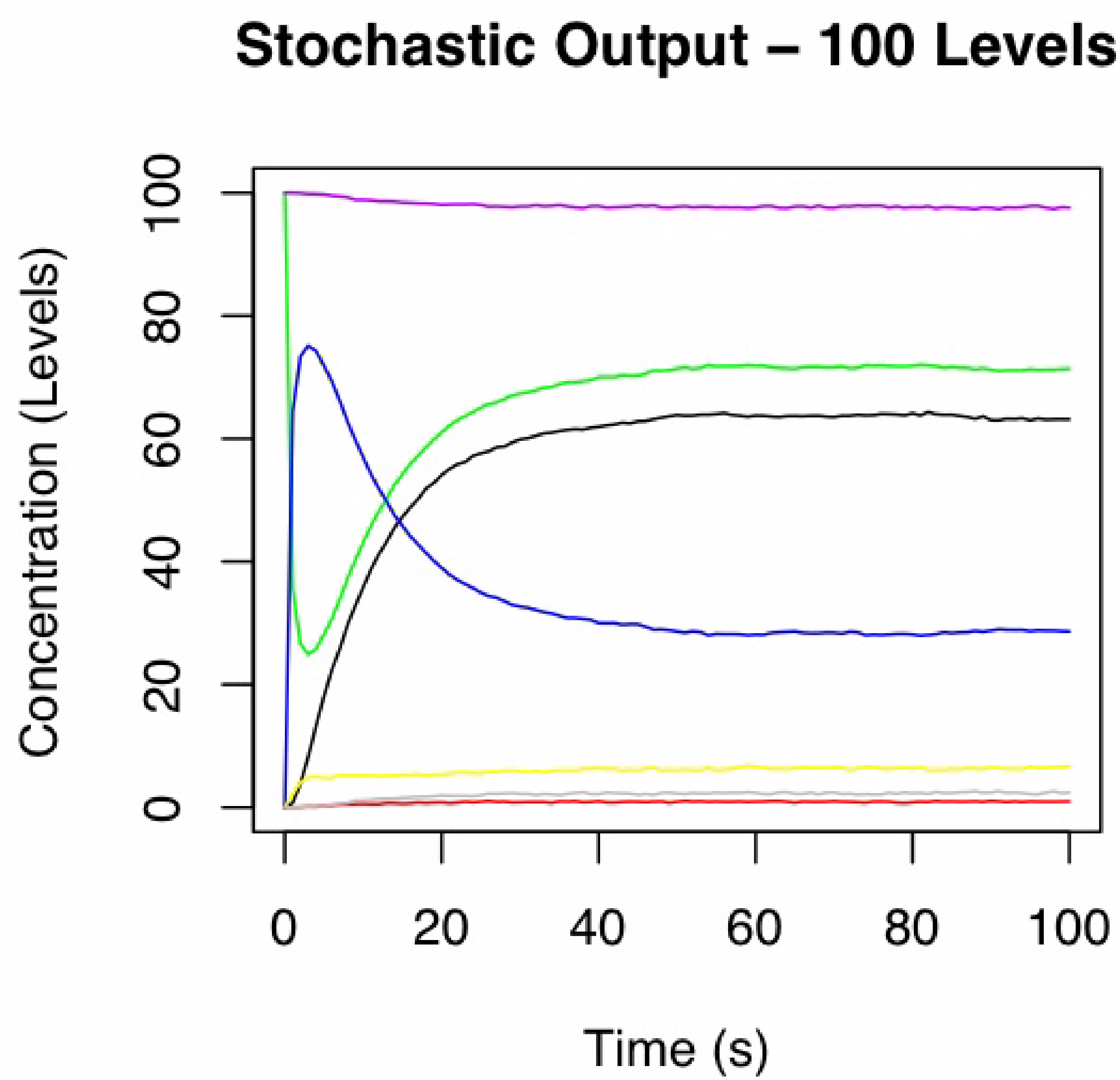
$$h_t := k_t \cdot N \cdot \prod_{p \in {}^{\bullet}t} \left(\frac{m(p)}{N}\right)$$

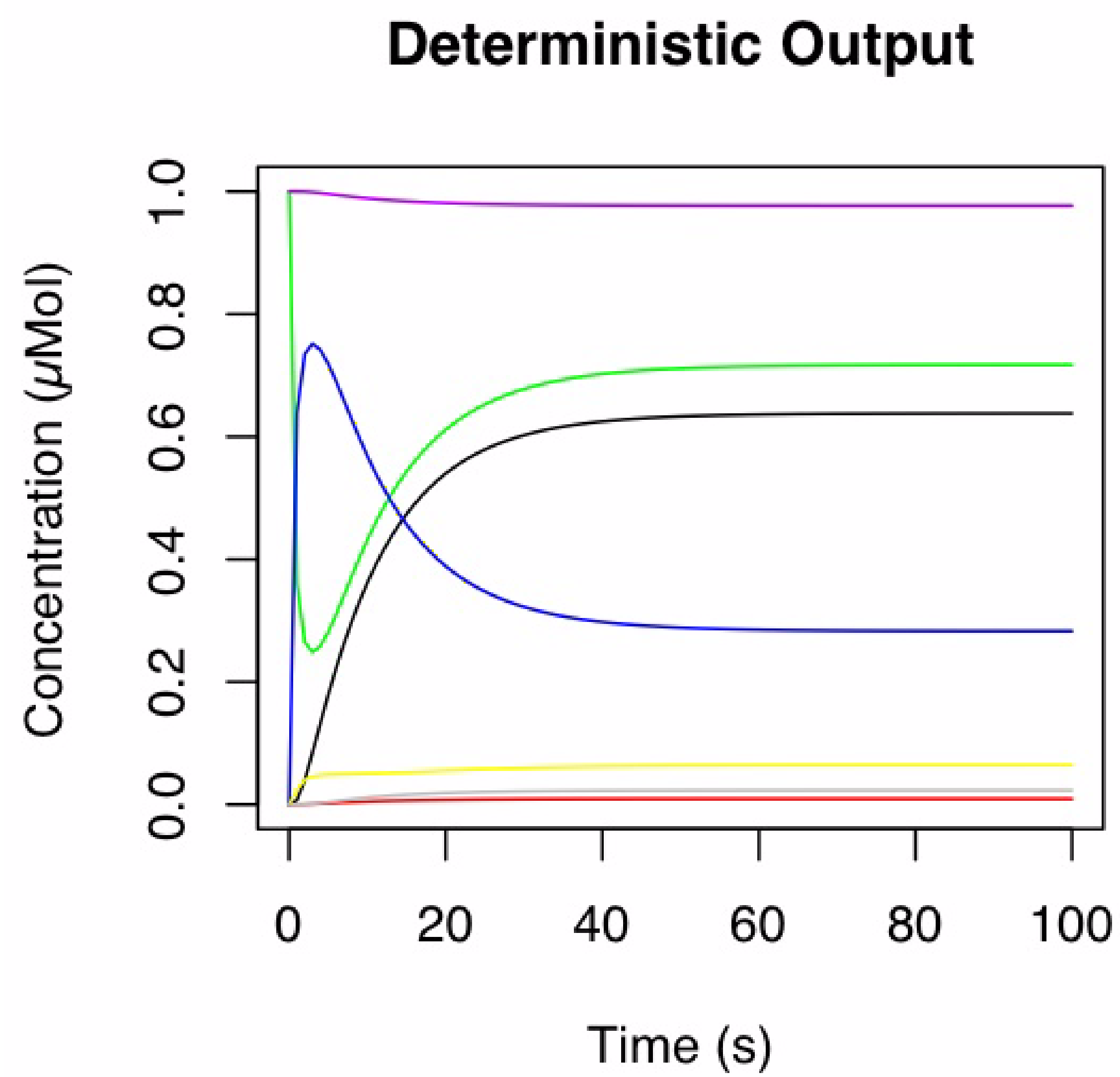
LEVEL CONCEPT




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
Time (s)
0
20
40
60
80
100


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

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*

CONTINUOUS PETRI NETS, BASICS

- **transitions fire continuously**

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  -> *any arithmetic function including*
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- **real-valued tokens**

  -> *concentrations*

- **semantics: set of Ordinary Differential Equations (ODEs)**

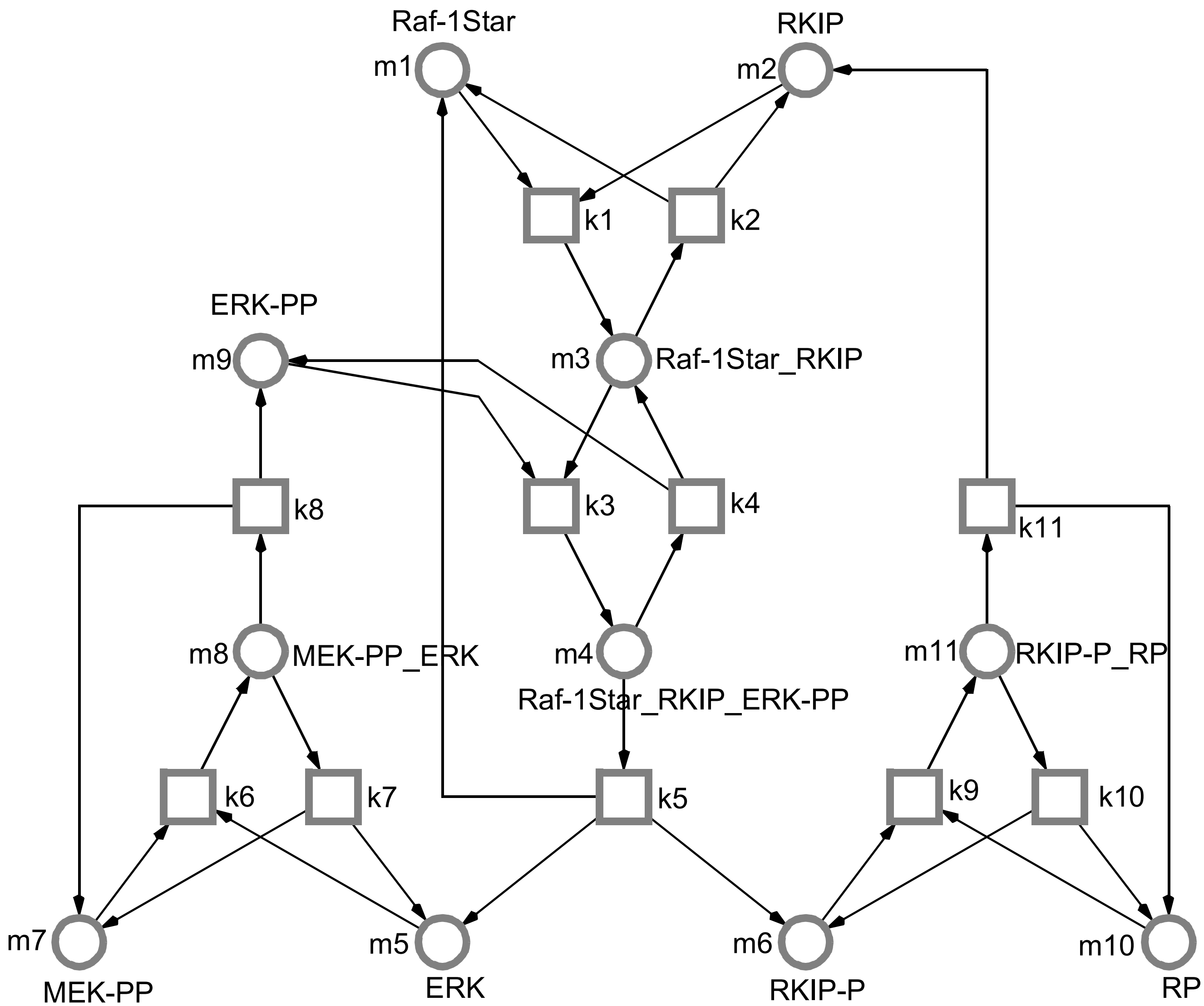
  -> *uniquely defined, but not vice versa*

  -> *typically non-linear*

- **simulation (numerical integration)**

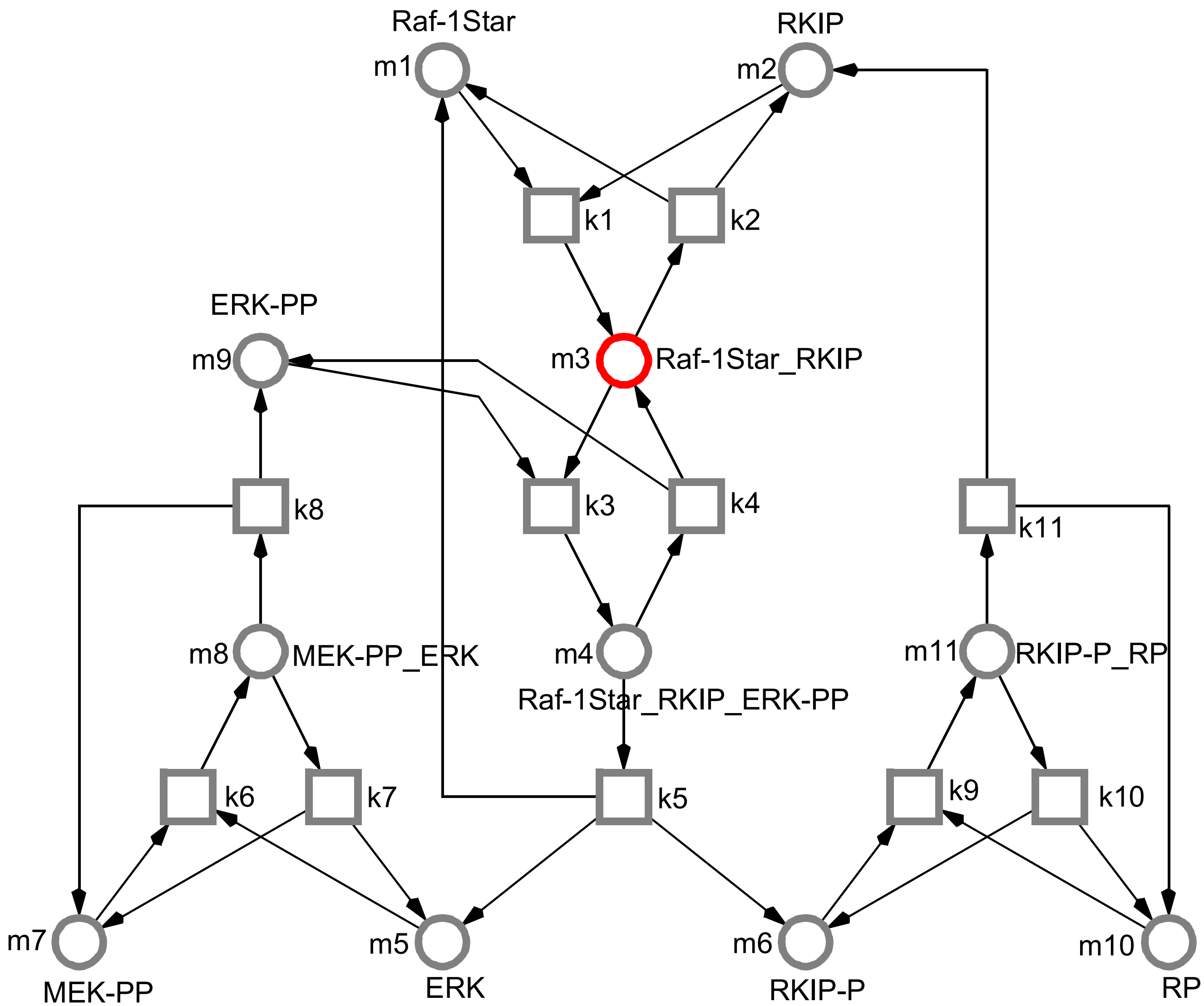
  -> *stiff/unstiff solvers*

CONTINUOUS PETRI NET DEFINES ODES



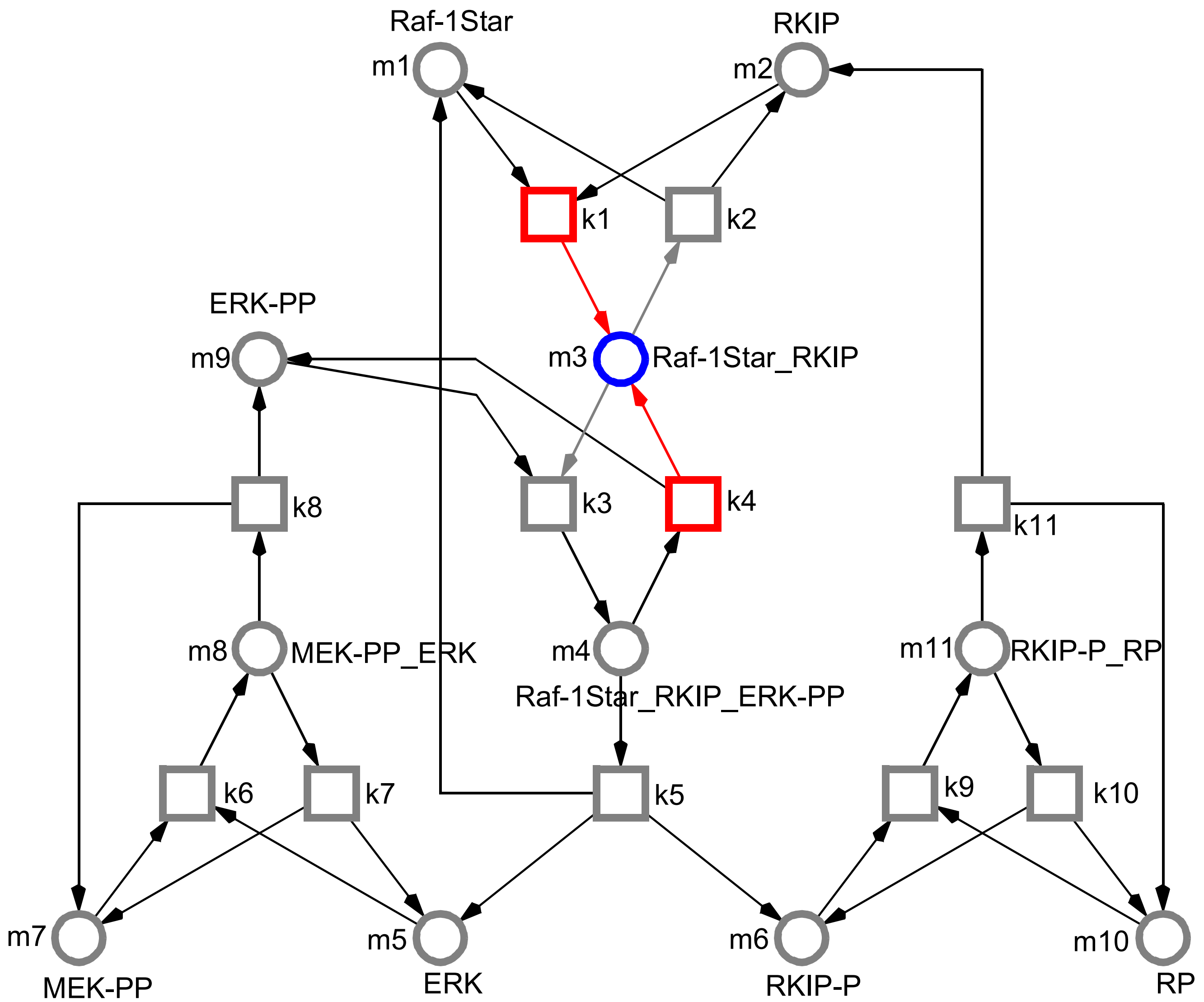
Continuous Petri Net Defines ODEs

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



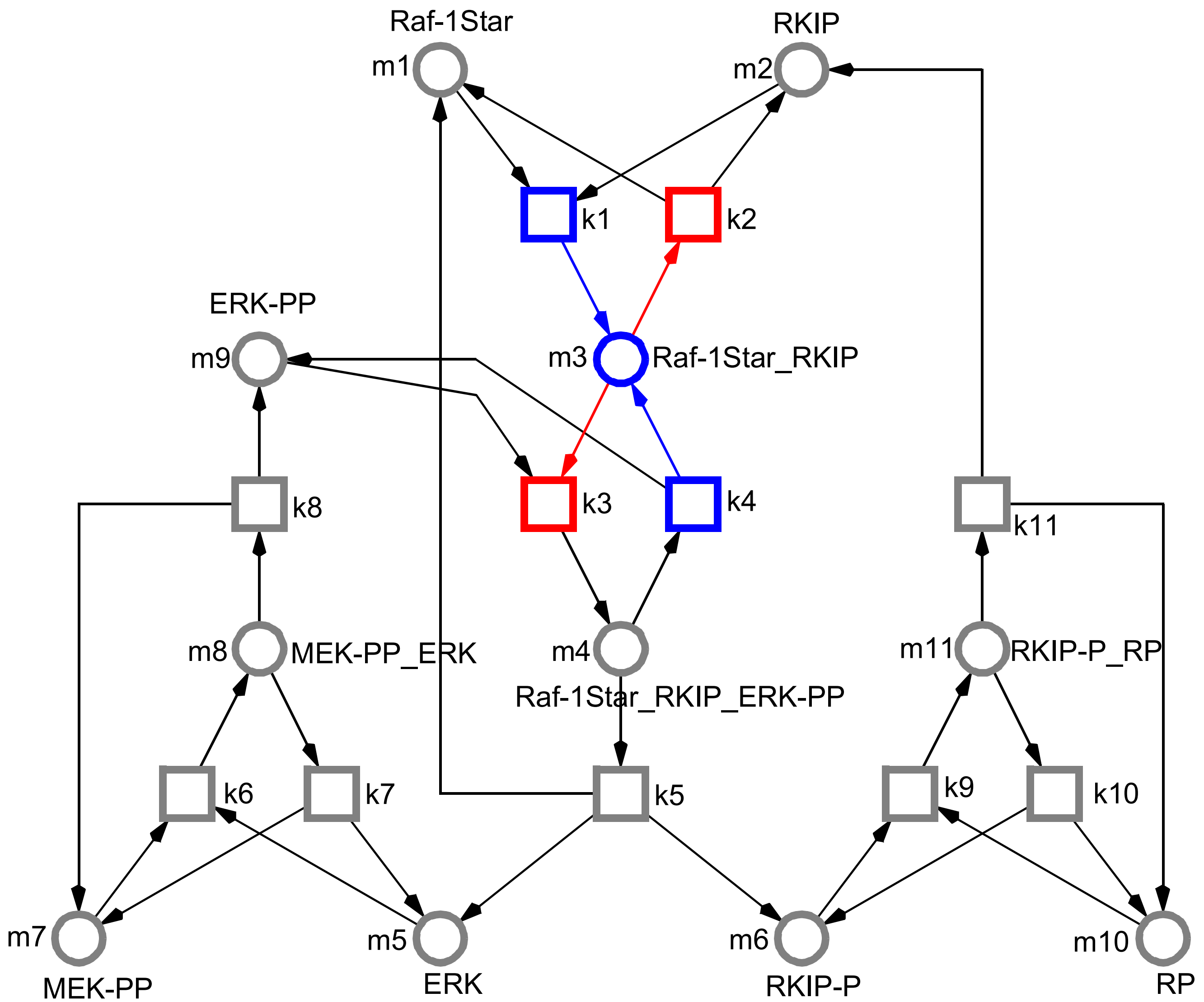
Continuous Petri Net Defines ODEs

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



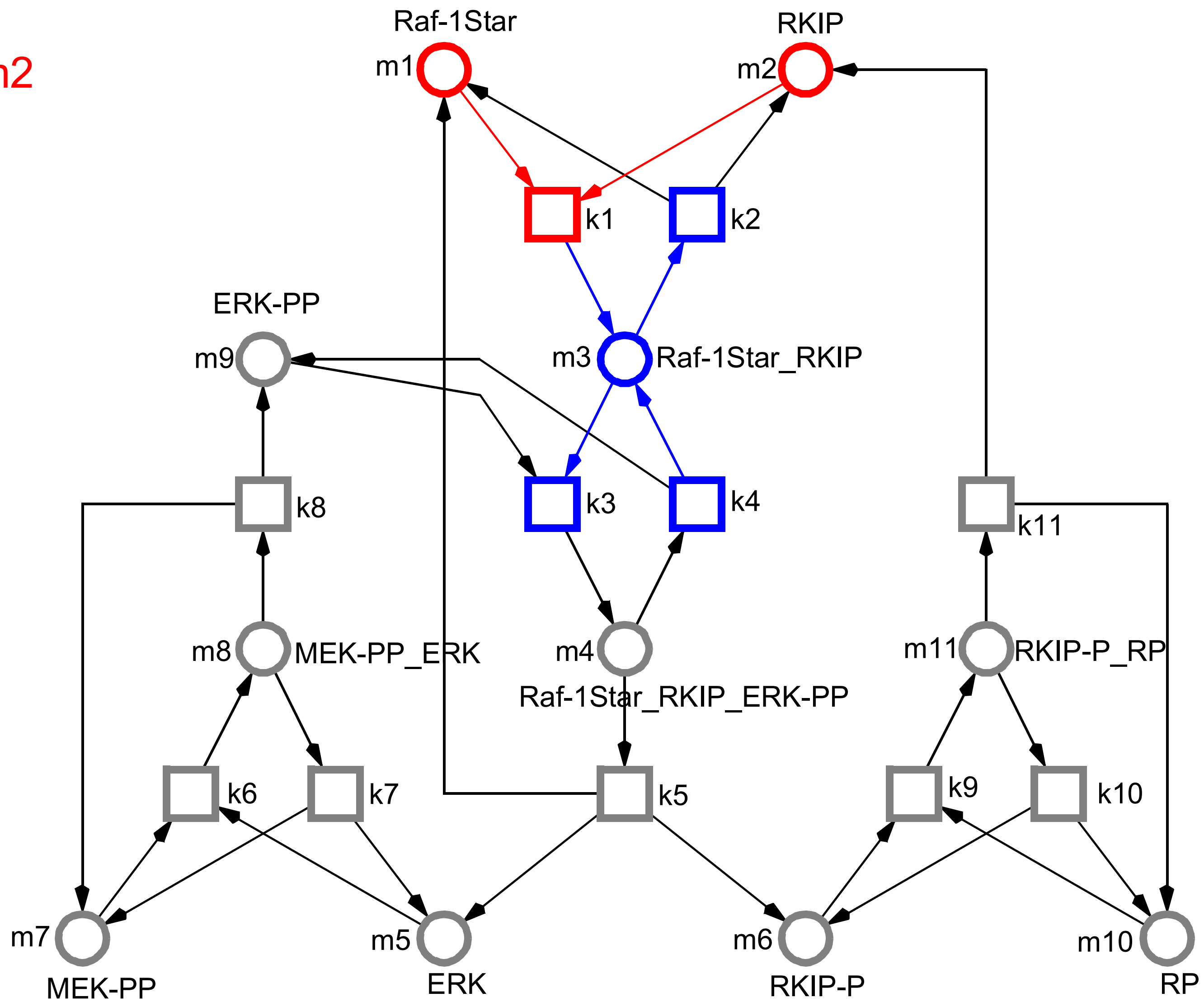
Continuous Petri Net Defines ODEs

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



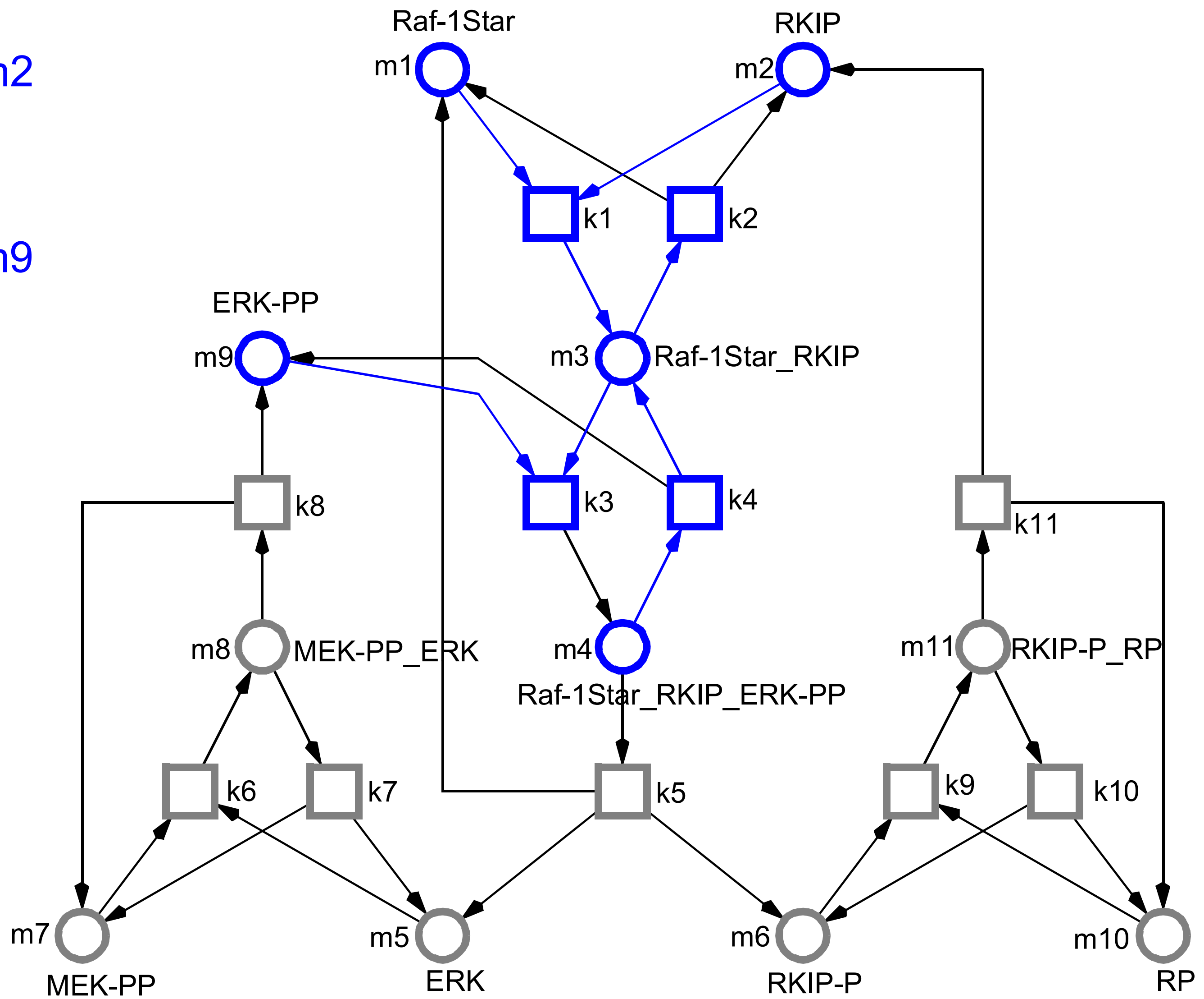
Continuous Petri Net Defines ODEs

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

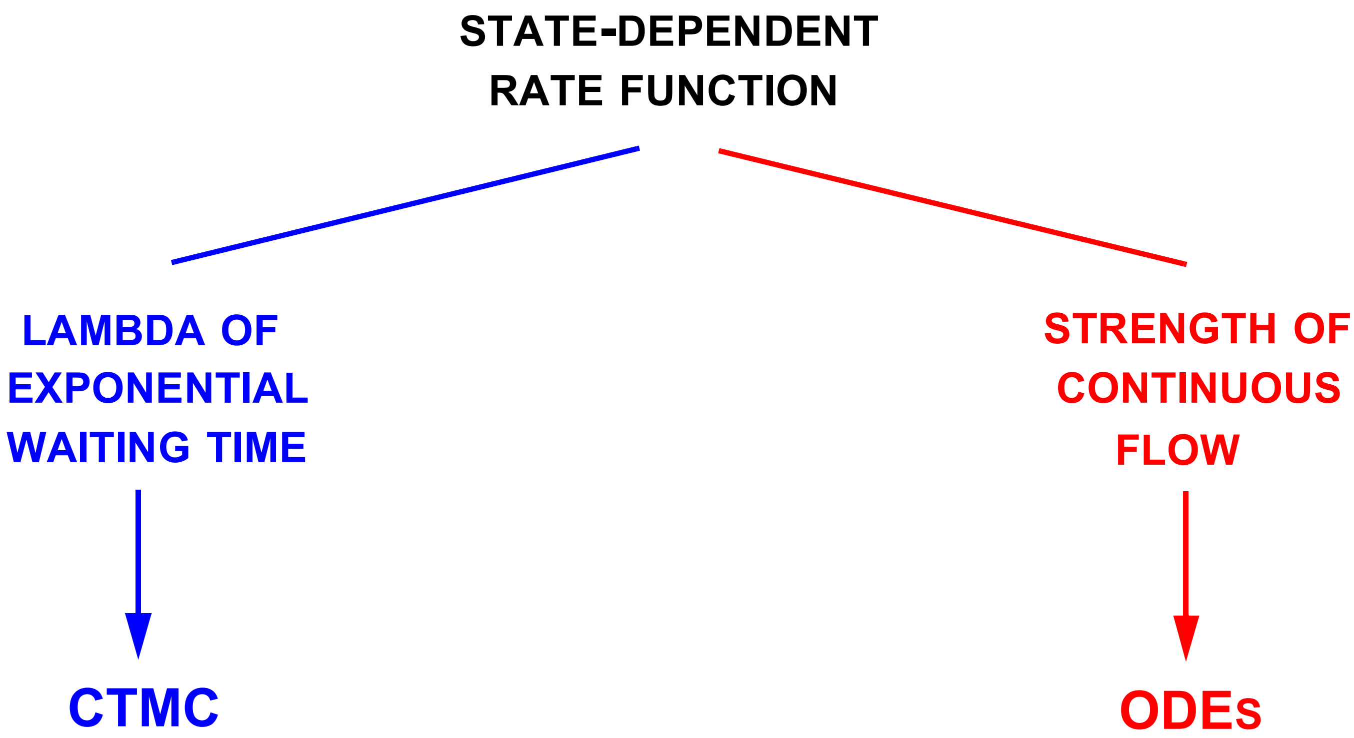


Continuous Petri Net Defines ODEs

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



CRUCIAL POINT

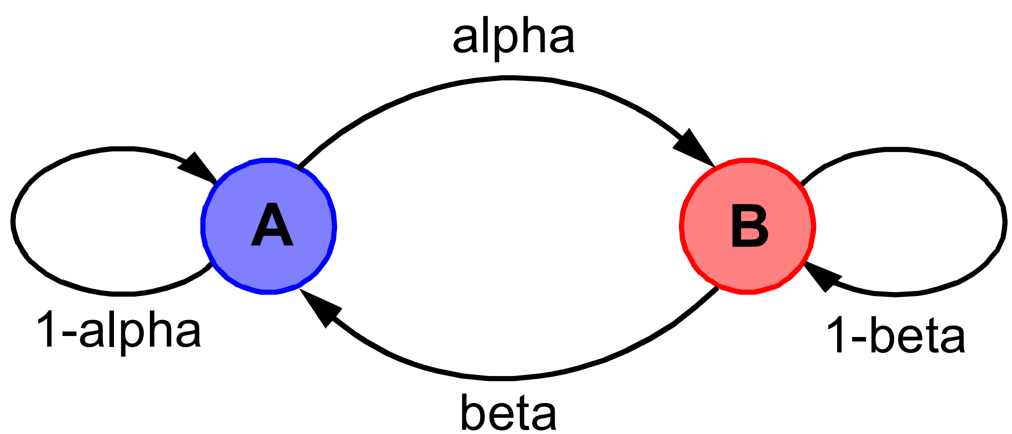


-> supported by, e.g., COPASI, Dizzy, ..., Snoopy

CASE STUDY -
MULTICELL COLONIES

MULTICELL COLONY, BASIC MODEL

- **two cell types: phenotype A and B**
- **cell divide**
  - -> *cell division may involve mutation of the offspring*
  - -> *parent cell keeps its phenotype*



Multicell Colony, Basic Model

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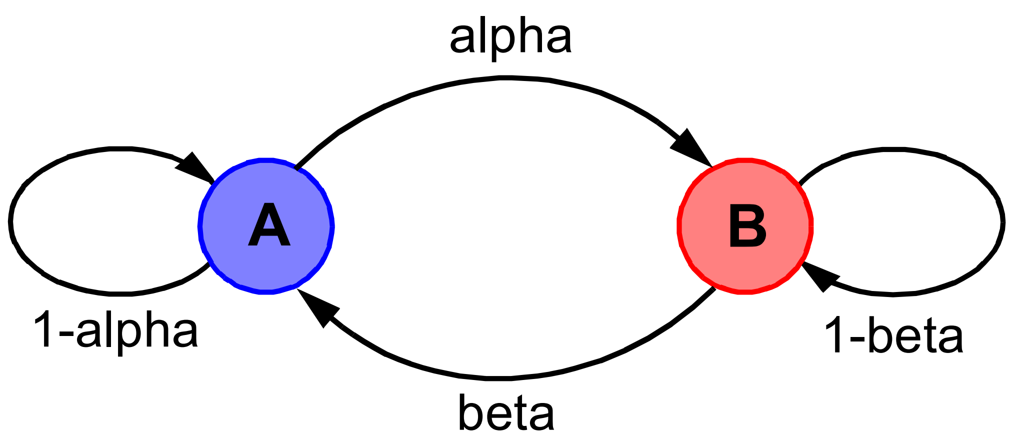
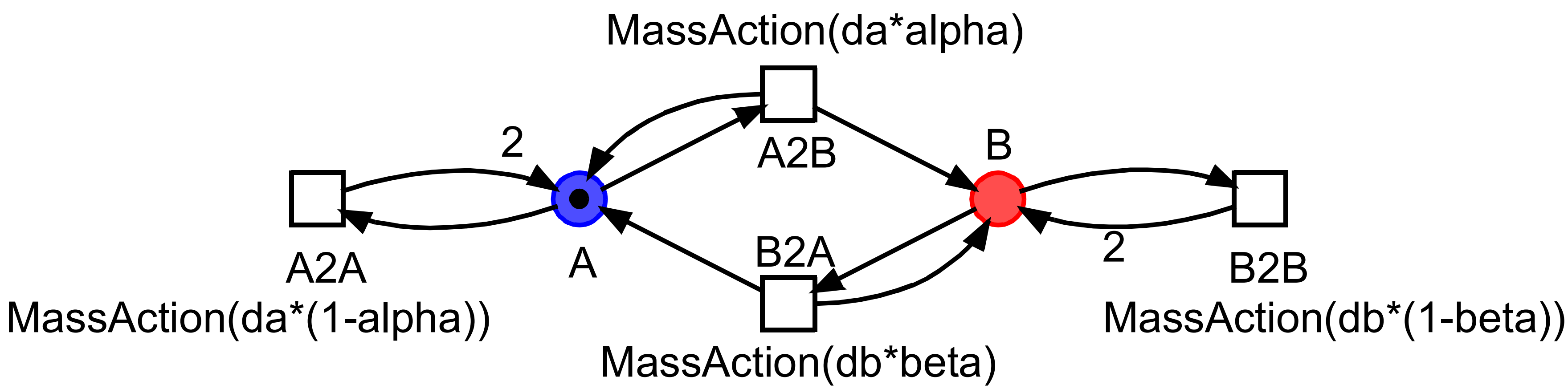
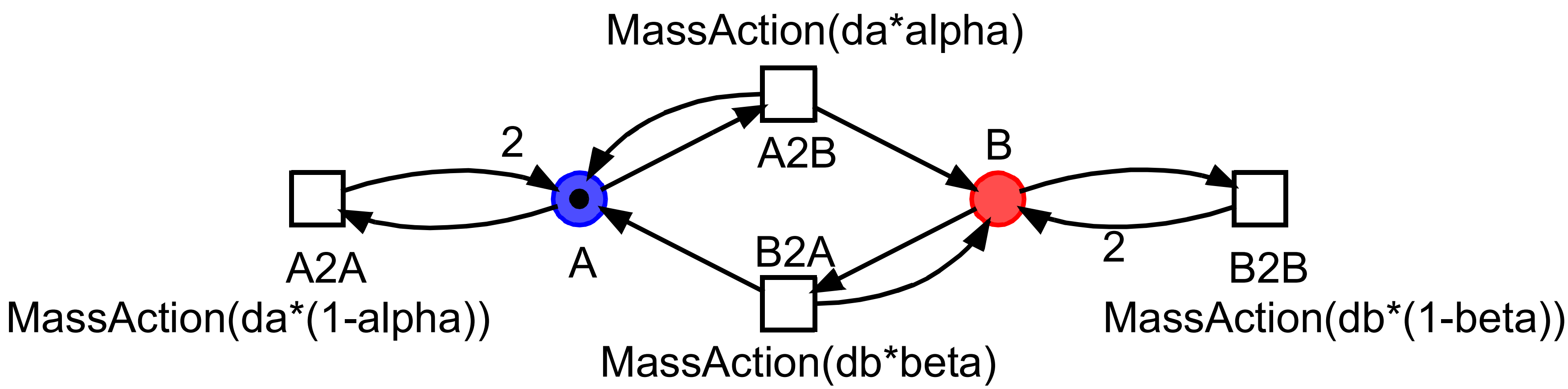


- **model parameters**
  - -> *alpha = beta - mutation rates*
  - -> *da, db - fitness of A, B*
  - -> *da/db - relative fitness*
- **output**
  - -> *total number of bacteria*
  - -> *proportion of A = A / (A + B)*
  - -> *proportion of B = B / (A + B)*

MULTICELL COLONIES, PETRI NET 1



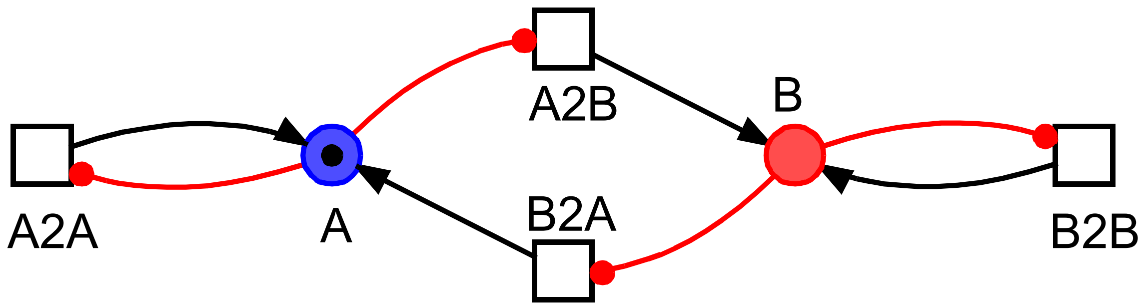
MULTICELL COLONIES, PETRI NET 1



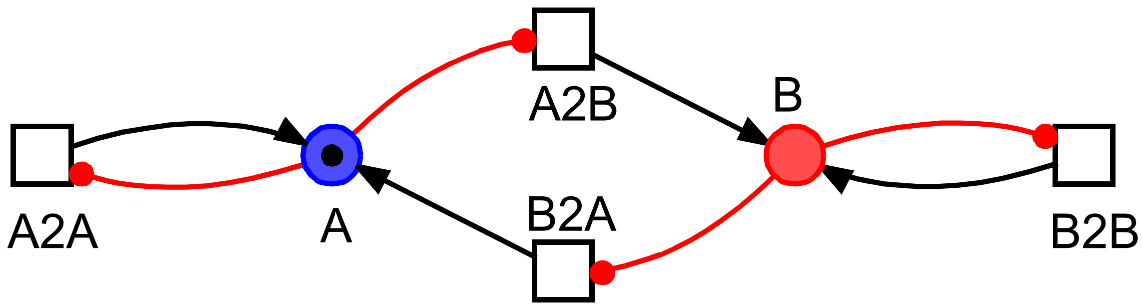
$$dA/dt = da * (1 - alpha) * A + db * beta * B$$

$$dB/dt = db * (1 - beta) * B \quad + da * alpha * A$$

MULTICELL COLONIES, PETRI NET 2



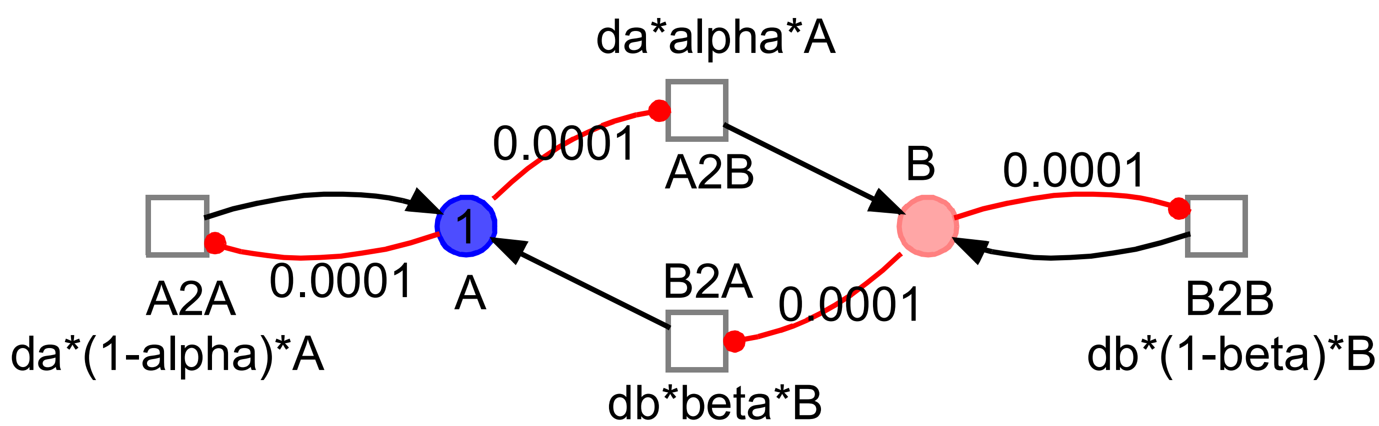
Multicell Colonies, Petri Net 2



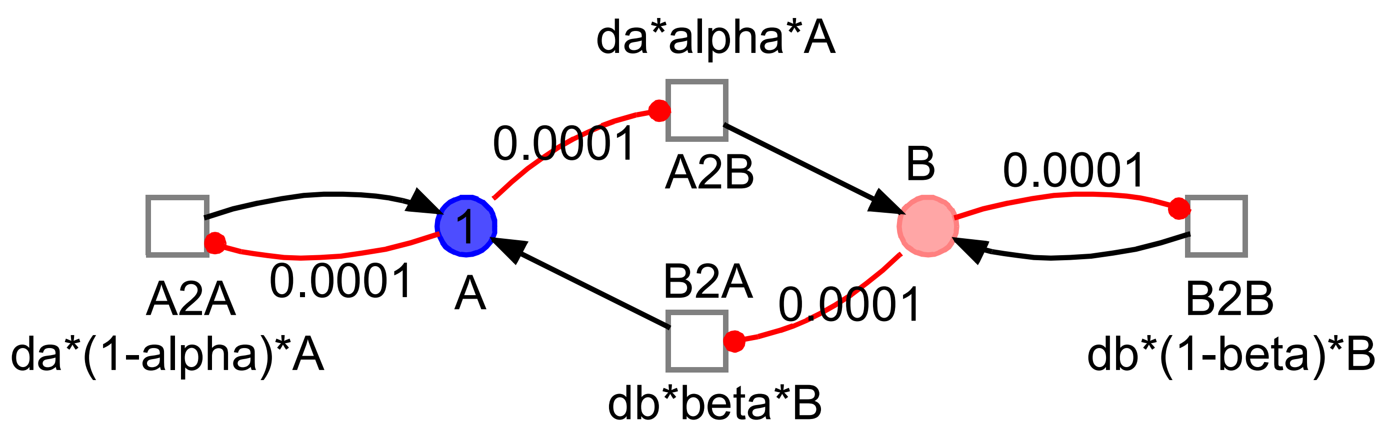
dA/dt = da * (1 - alpha) * A * read(1,A)
+ db * beta * B * read(1,B)

dB/dt = db * (1 - beta) * B * read(1,B)
+ da * alpha * A * read(1,A)

MULTICELL COLONIES, PETRI NET 3



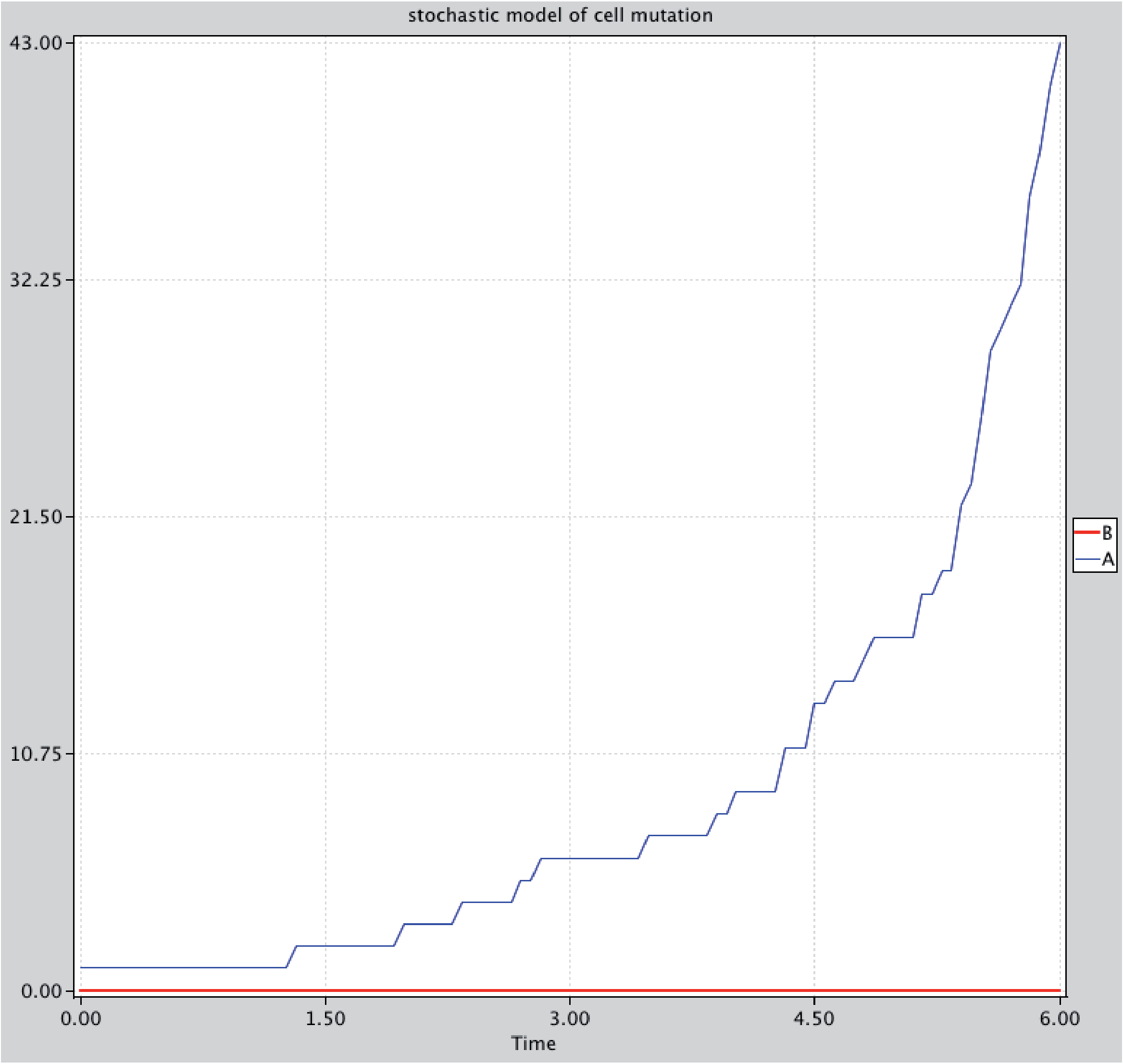
MULTICELL COLONIES, PETRI NET 3



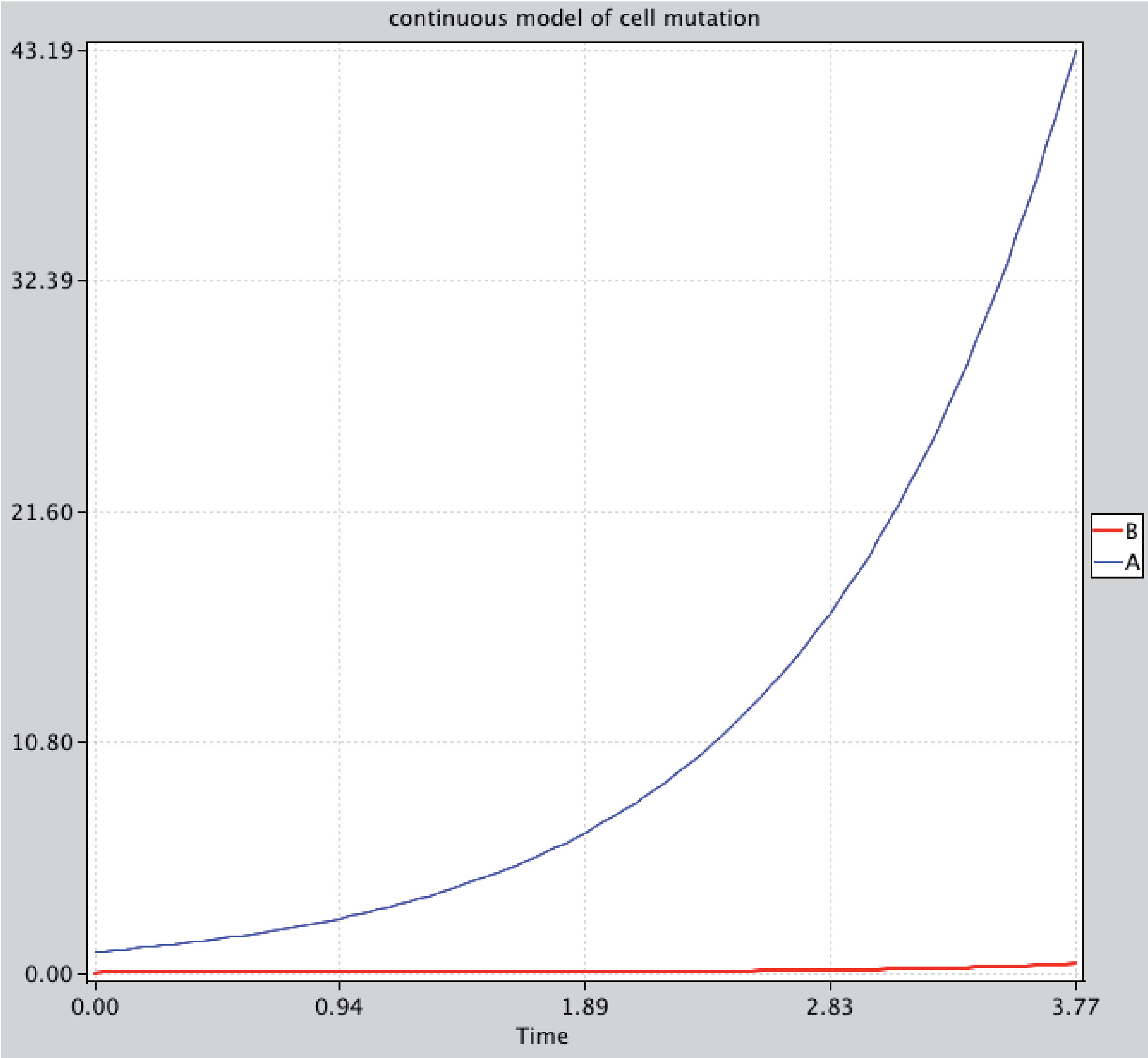
$$\frac{dA}{dt} = da \cdot (1 - alpha) \cdot A \cdot read(0.0001, A) + db \cdot beta \cdot B \cdot read(0.0001, B)$$

$$\frac{dB}{dt} = db \cdot (1 - beta) \cdot B \cdot read(0.0001, B) + da \cdot alpha \cdot A \cdot read(0.0001, A)$$

MULTICELL COLONY, STOCHASTIC PLOT



Multicell Colony, Stochastic Plot



- **cellDivision0a.spcontped**

  -> *take a look on the unreduced ODEs and simulate them*

- **cellDivision0a.spcontped**

  -> *take a look on the reduced ODEs and simulate them*

- **cellDivision0b.spcontped**

  -> *take a look on the ODEs and simulate them*

- **cellDivision0c.spcontped**

  -> *take a look on the ODEs and simulate them*

  -> *repeat with varied parameters and different read arc weights;*

MAIN LESSON LEARNT:

NEVER BLINDLY TRUST NUMERICAL SIMULATION RESULTS.

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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  - -> *animation* -> *to experience the model*
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  - -> *qualitative / quantitative behaviour prediction* -> *experiment design, new insights*

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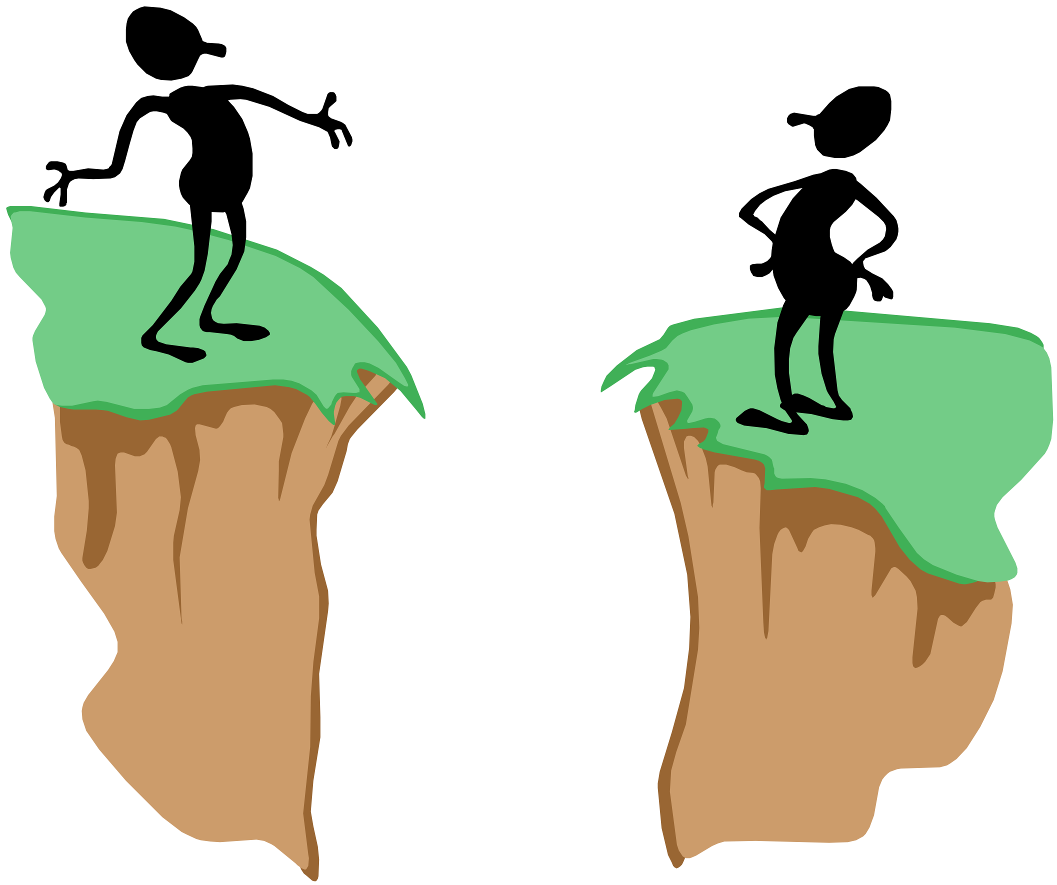
  - -> *qualitative / quantitative behaviour prediction* -> *experiment design, new insights*
- **step-wise model development**
  - -> *qualitative model* -> *discrete Petri nets*
  - -> *discrete quantitative model* -> *stochastic Petri nets*
  - -> *continuous quantitative model* -> *continuous Petri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



THANKS !

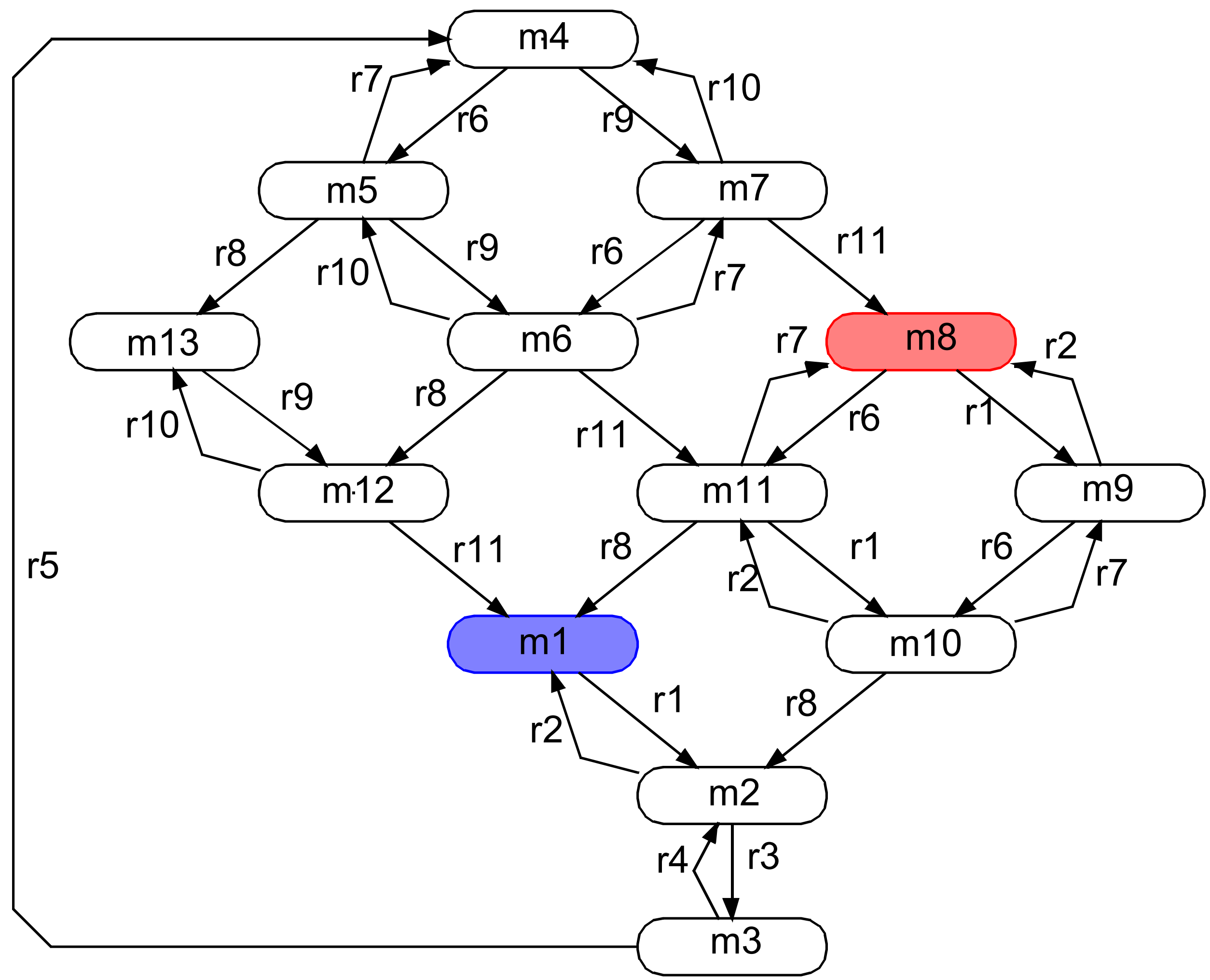
HHTP://WWW-DSSZ.INFORMATIK.TU-COTTBUS.DE

SUPPLEMENT:

ABOUT THE RELATION SPN - CPN

Ex1 - RKIP, Reachability Graph (STS)

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



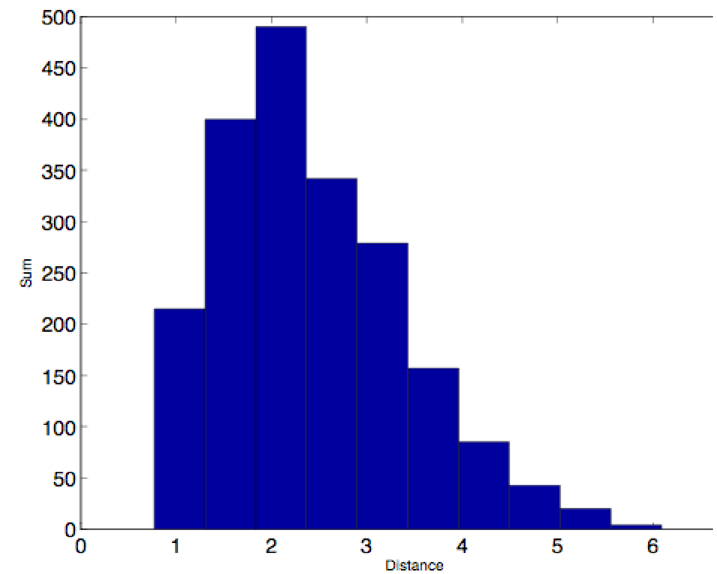
Ex1 - RKIP, Quantitative Analysis

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

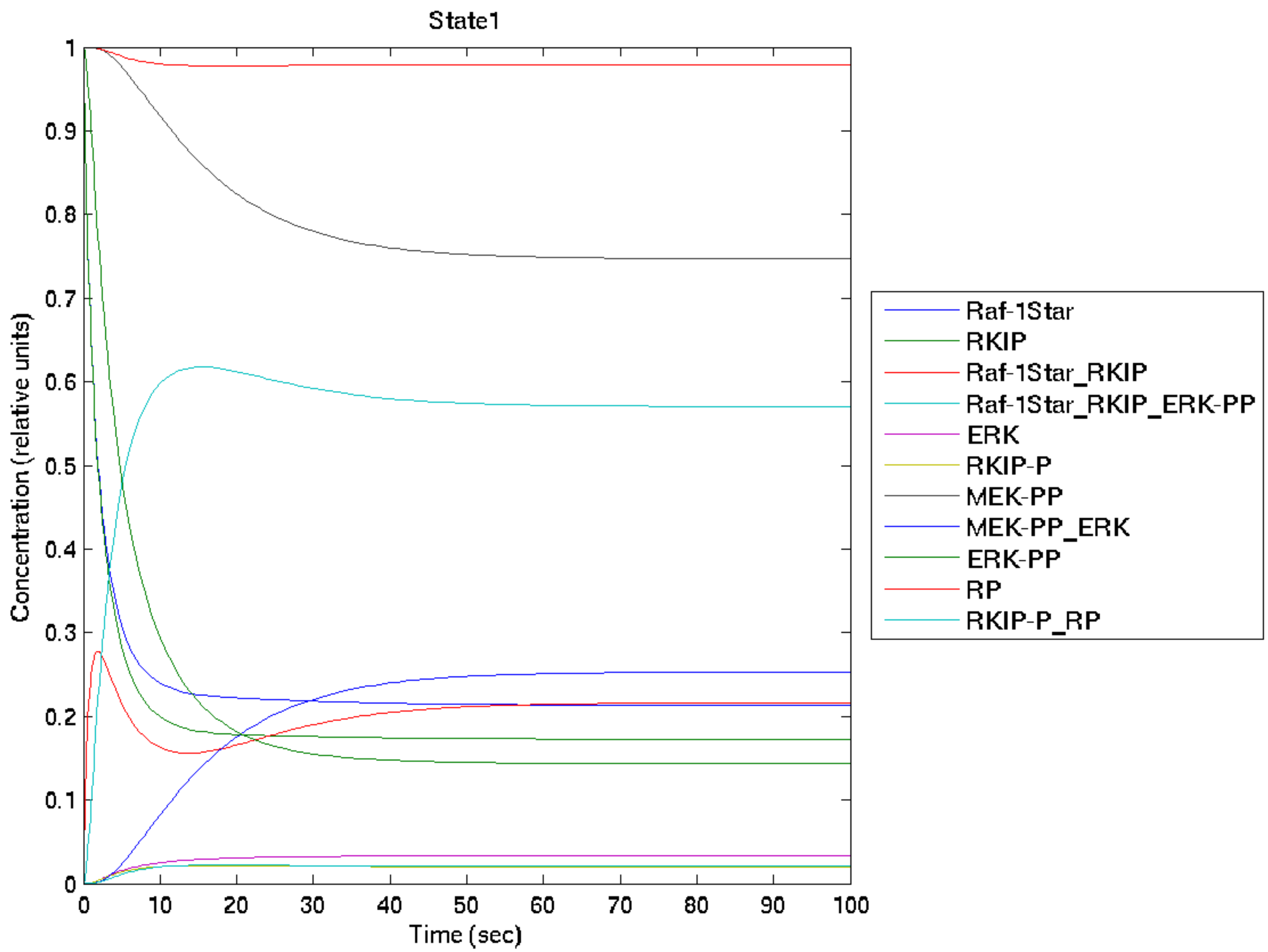
13 "good" state configurations



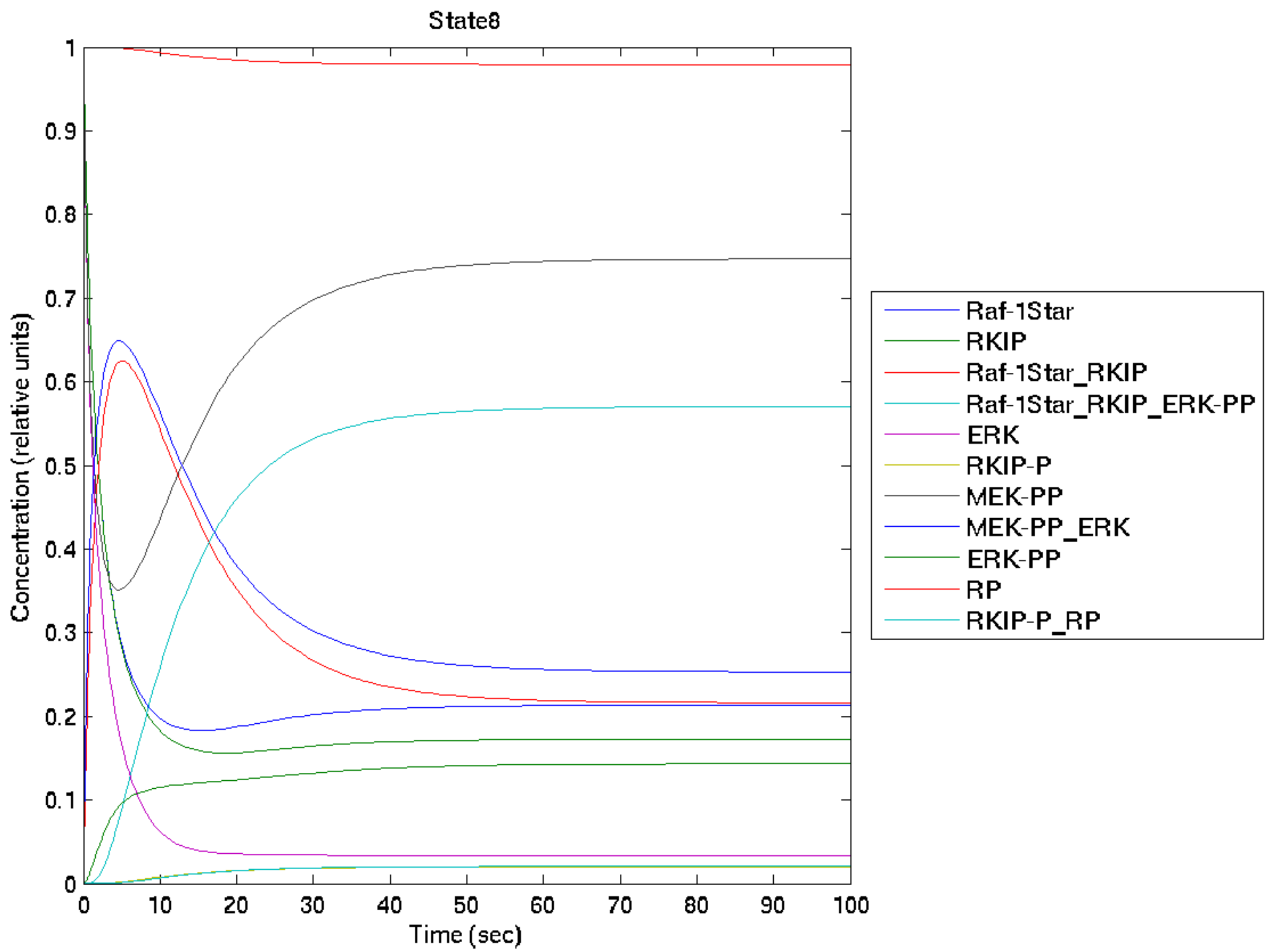
Distribution of `bad' steady states as euclidean distances from the `good' final steady state

the "bad" ones

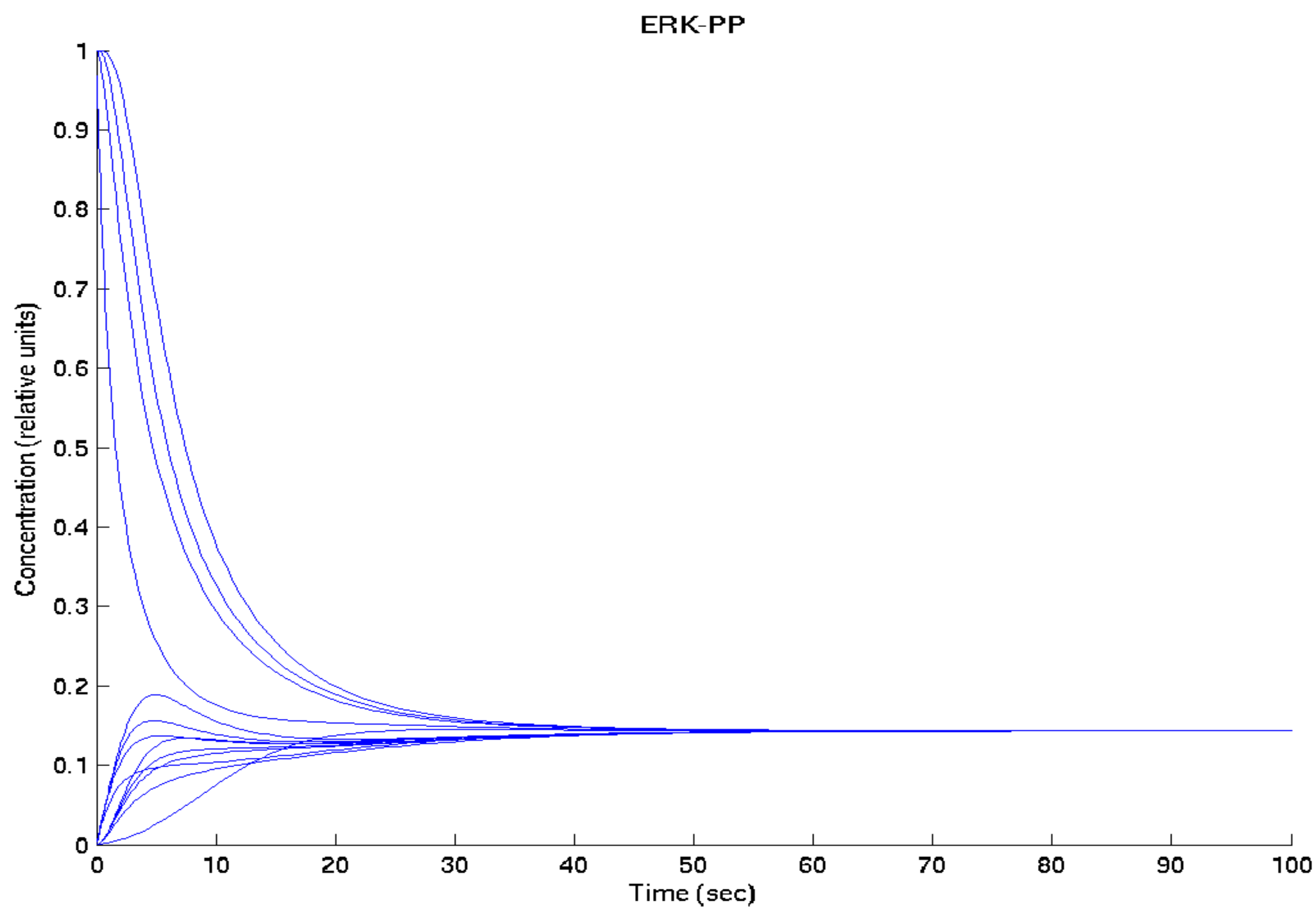
Ex1 - RKIP, Quantitative Analysis



Ex1 - RKIP, Quantitative Analysis

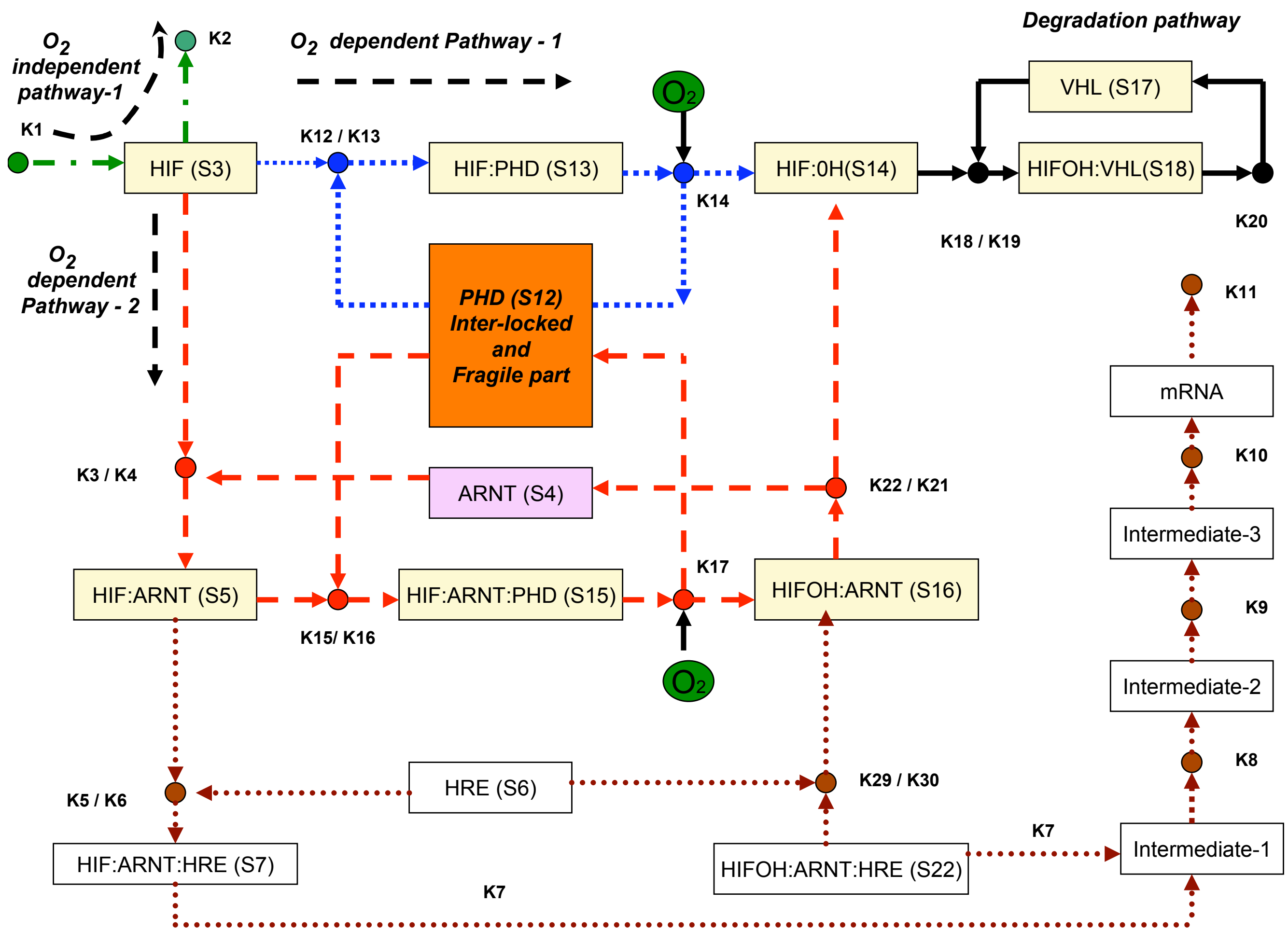


Ex1 - RKIP, Quantitative Analysis



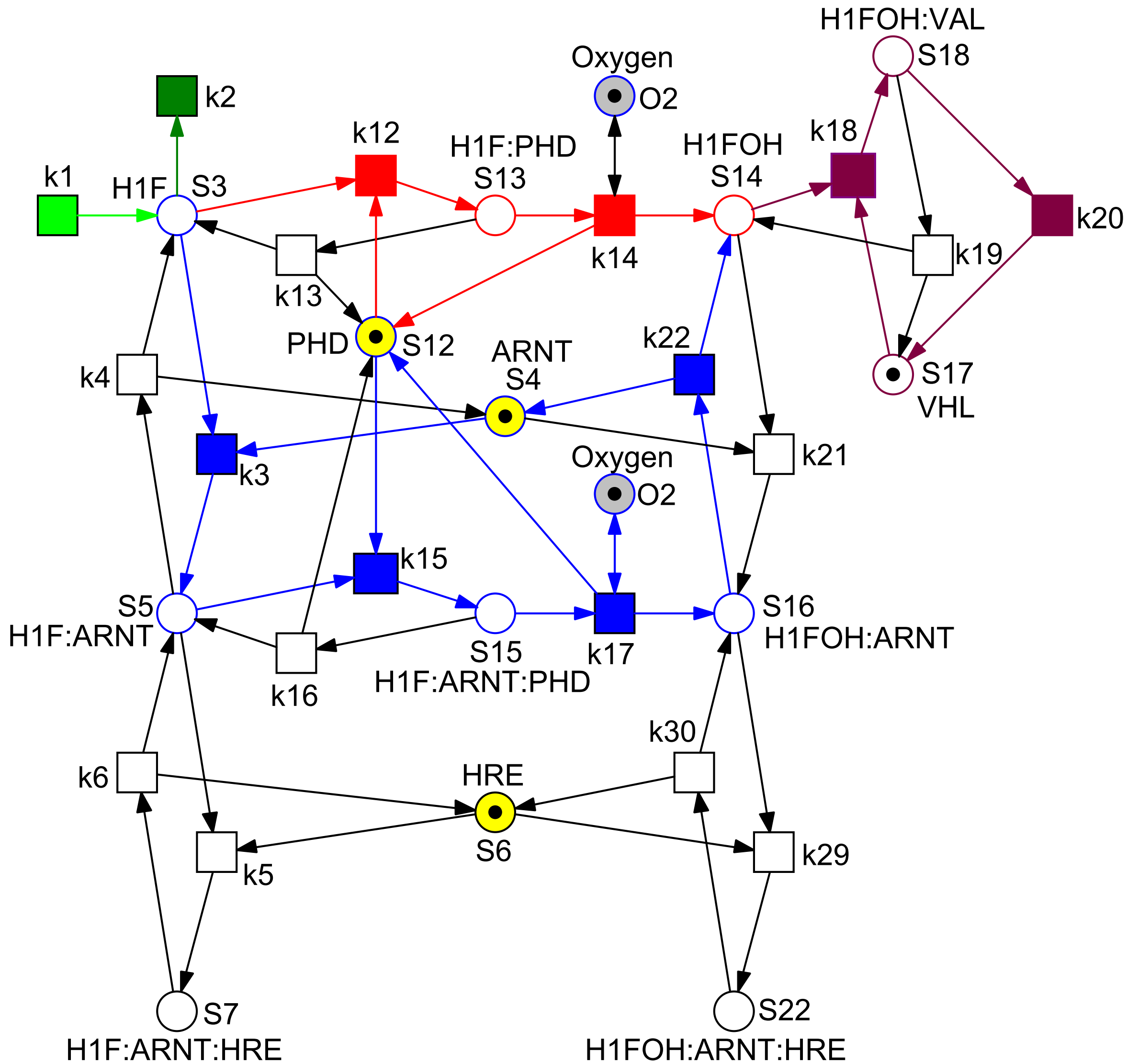
Ex2 - Hypoxia

[Yu et al. 2007]

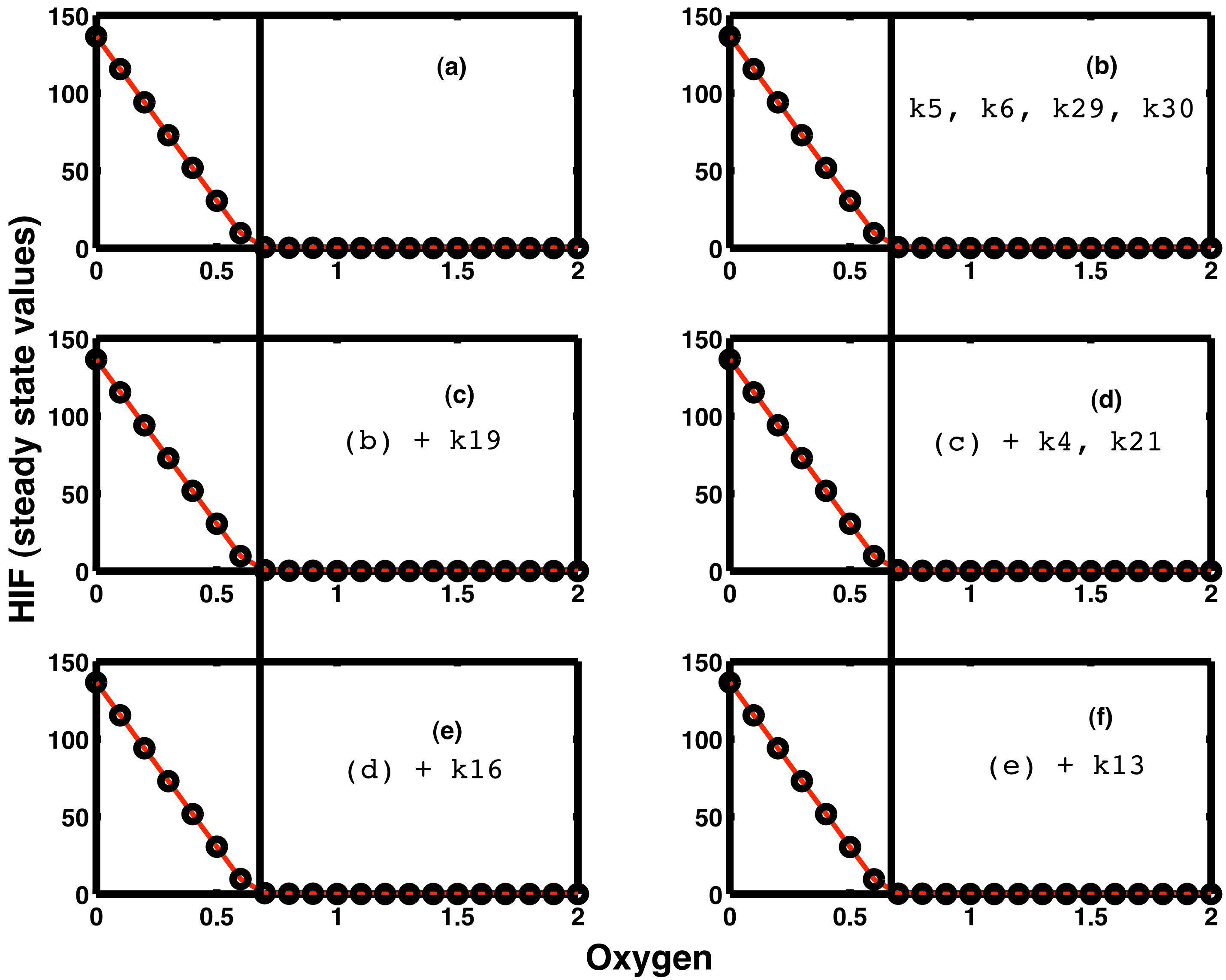


Ex2 - Hypoxia

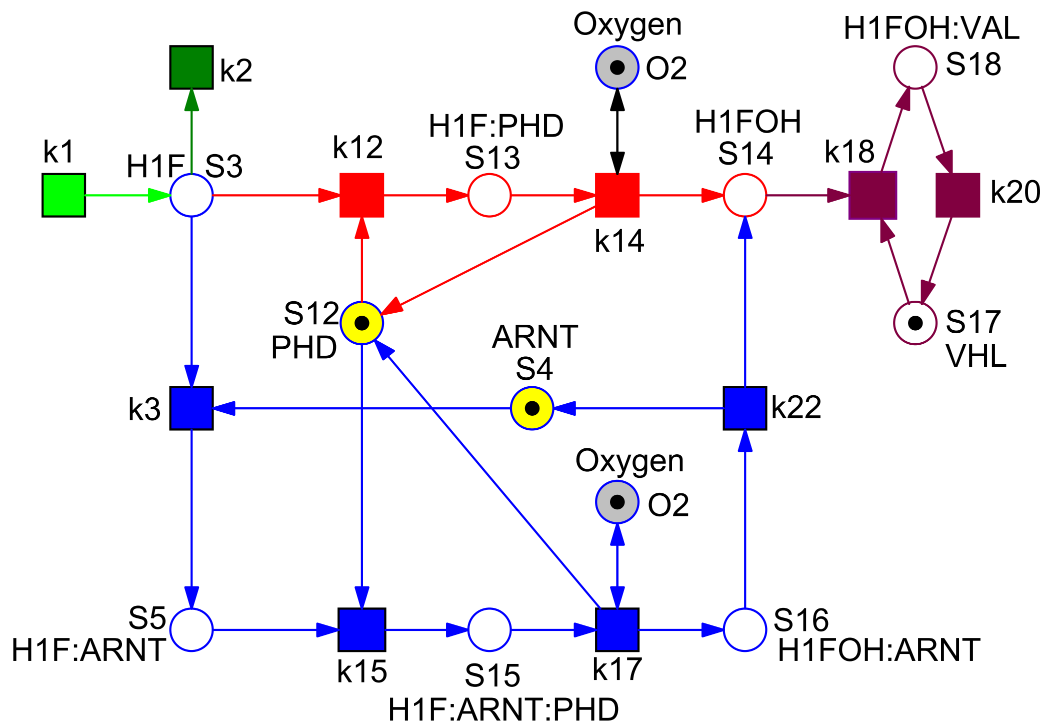
[Heiner; Sriram 2010]



Ex2 - Hypoxia

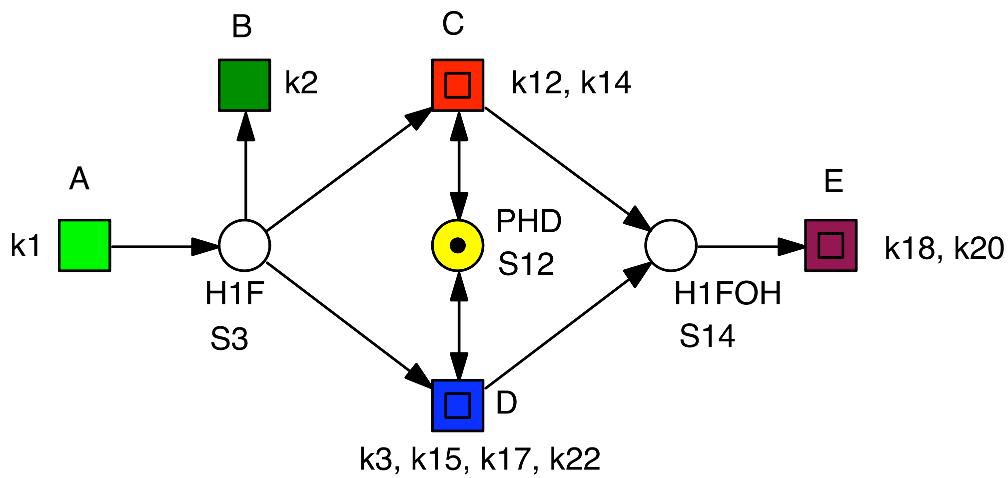

150
100
50
0
0
0.5
1
1.5
2
(a)
(b)
k5, k6, k29, k30
(c)
(b) + k19
(d)
(c) + k4, k21
(e)
(d) + k16
(f)
(e) + k13
HIF (steady state values)
Oxygen

Ex2 - Hypoxia



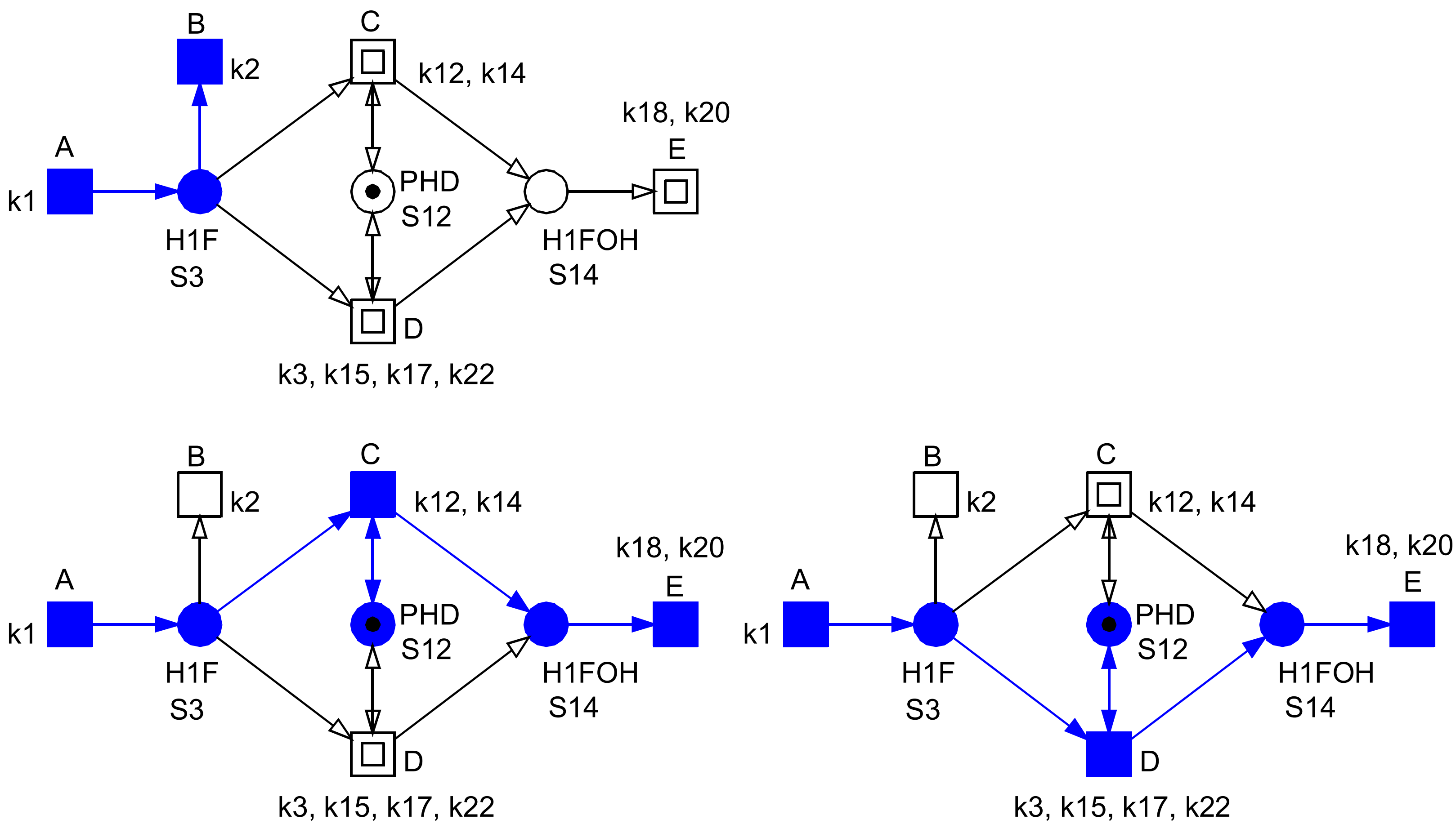
k2
k1
H1F
S3
k12
H1F:PHD
S13
Oxygen
O2
H1FOH
S14
k14
H1FOH:VAL
S18
k18
k20
S17
VHL
S12
PHD
ARNT
S4
k3
k22
Oxygen
O2
S5
H1F:ARNT
k15
S15
H1F:ARNT:PHD
k17
S16
H1FOH:ARNT

Ex2 - Hypoxia



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

Ex2 - Hypoxia


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

ABSOLUT CONCENTRATION ROBUSTNESS (ACR)

- **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 -> 2B $v_1(r_1) = k_1AB$

  r_2: B -> A $v_2(r_2) = k_2B$

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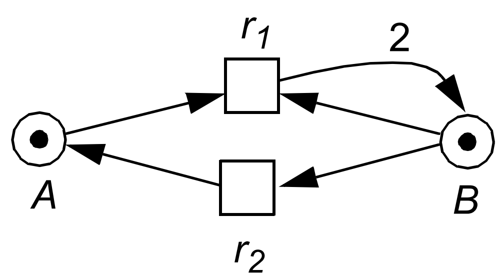

ABSOLUT CONCENTRATION ROBUSTNESS (ACR)

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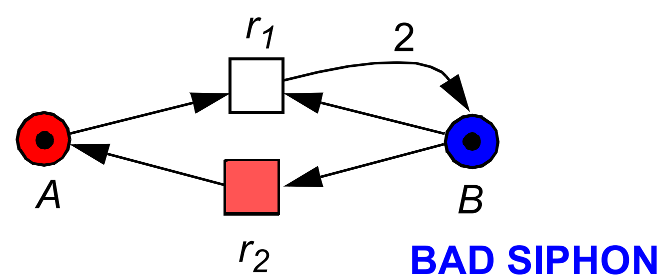

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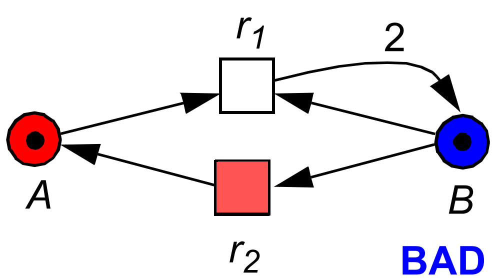

- **ODEs**

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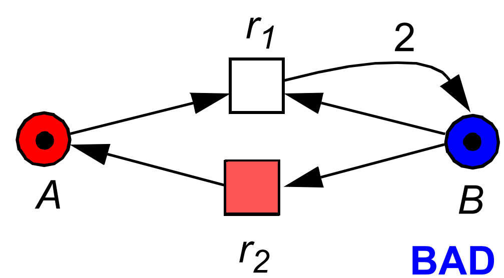

BAD SIPHON

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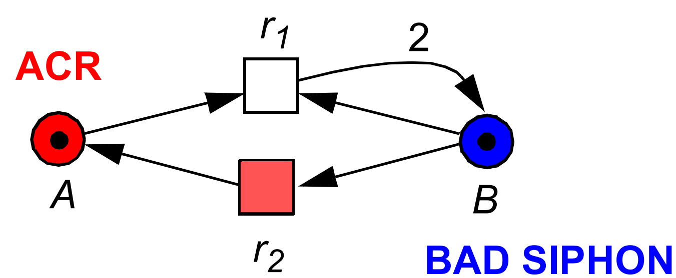

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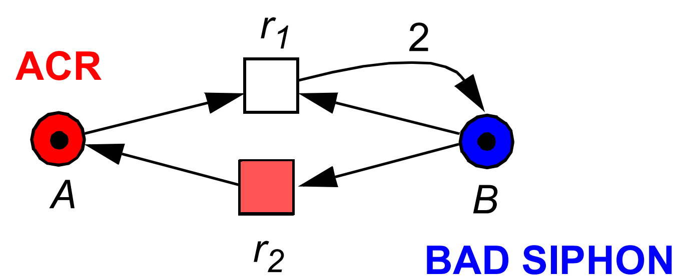

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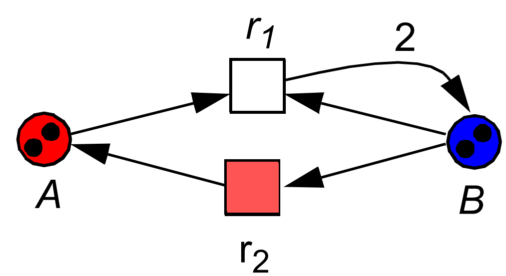

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