FROM PETRI NETS TO PARTIAL DIFFERENTIAL EQUATIONS AND BEYOND

- BIOMODEL ENGINEERING FOR MULTI-SCALE SYSTEMS BIOLOGY -

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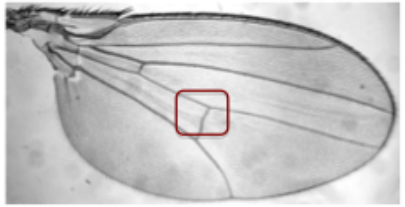
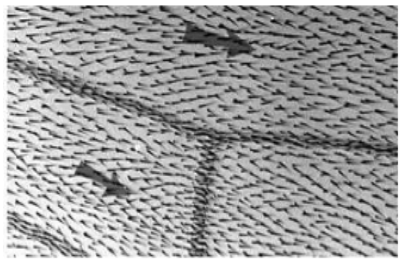
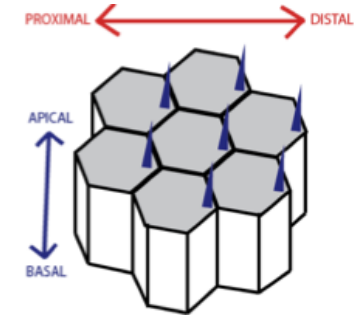
OUTLINE

- **BACKGROUND**
  - -> *modelling, what for ?*
  - -> *how many model types do we need ?*
  - -> *some case studies*
- **FRAMEWORK**
  - -> *unifying paradigms: QPN - SPN - CPN*
- **COLOUR AND MUTLI-SCALE SYSTEM**
  - -> *replication*
  - -> *encoding space*
- **SUMMARY & OUTLOOK**
  - -> *open problems*
  - -> *next steps*

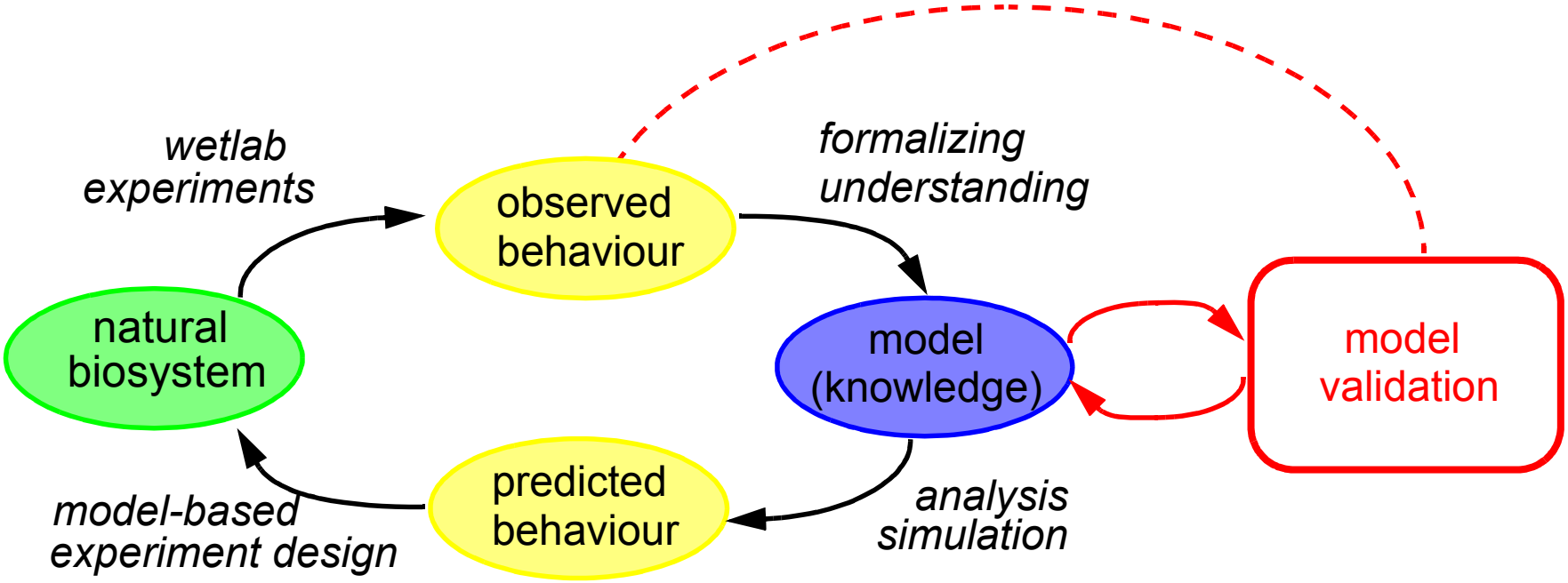






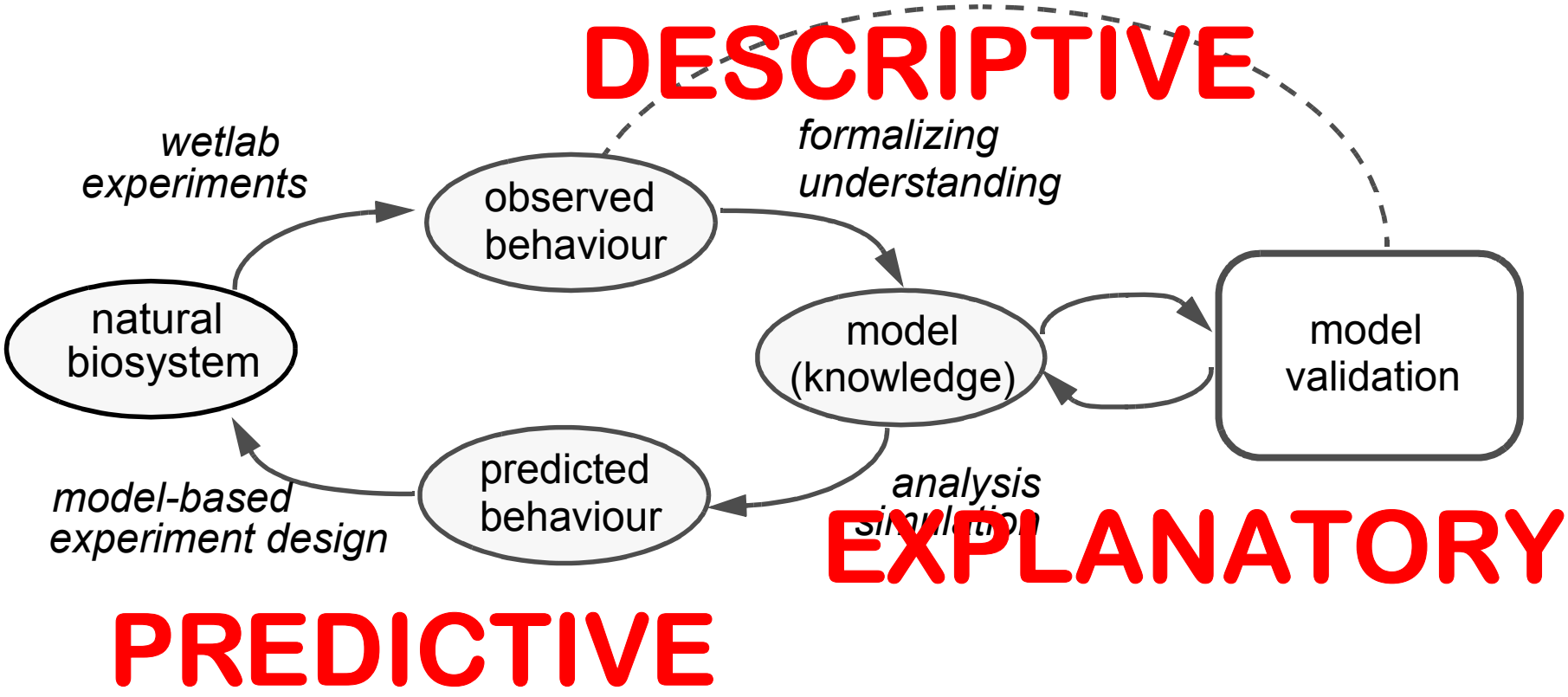
BACKGROUND

MODELLING = FORMAL KNOWLEDGE REPRESENTATION



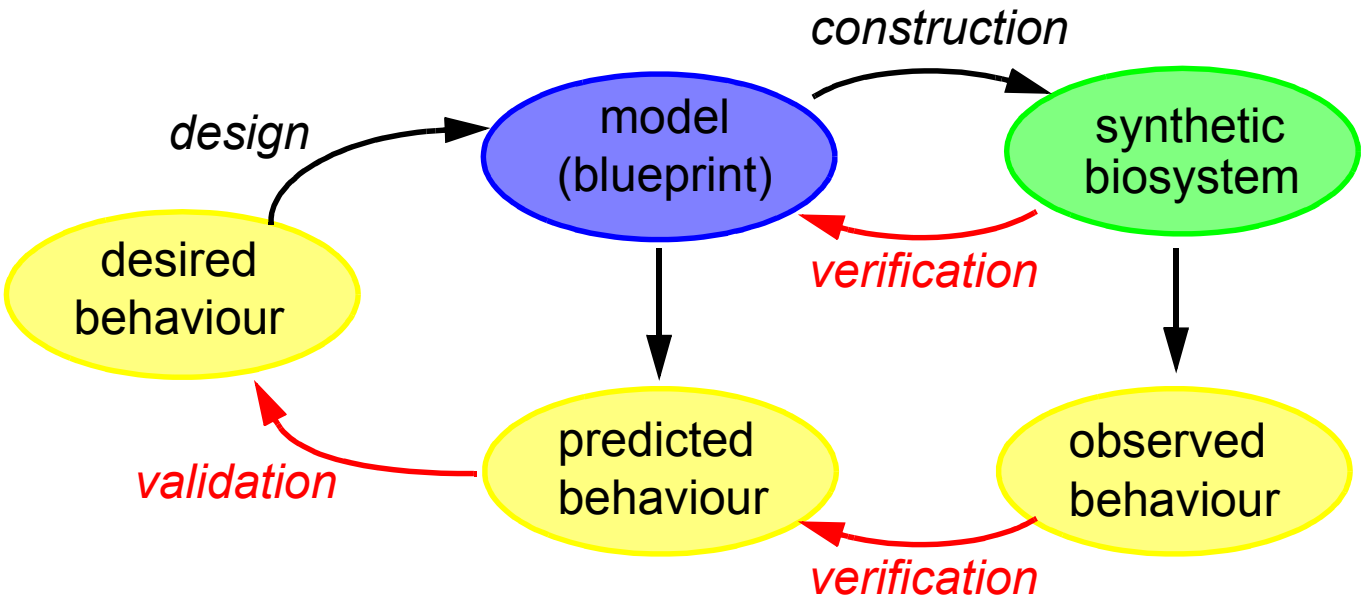
MODEL VALIDATION = CONFIDENCE INCREASE

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?

(BIOCHEMICAL NETWORKS)

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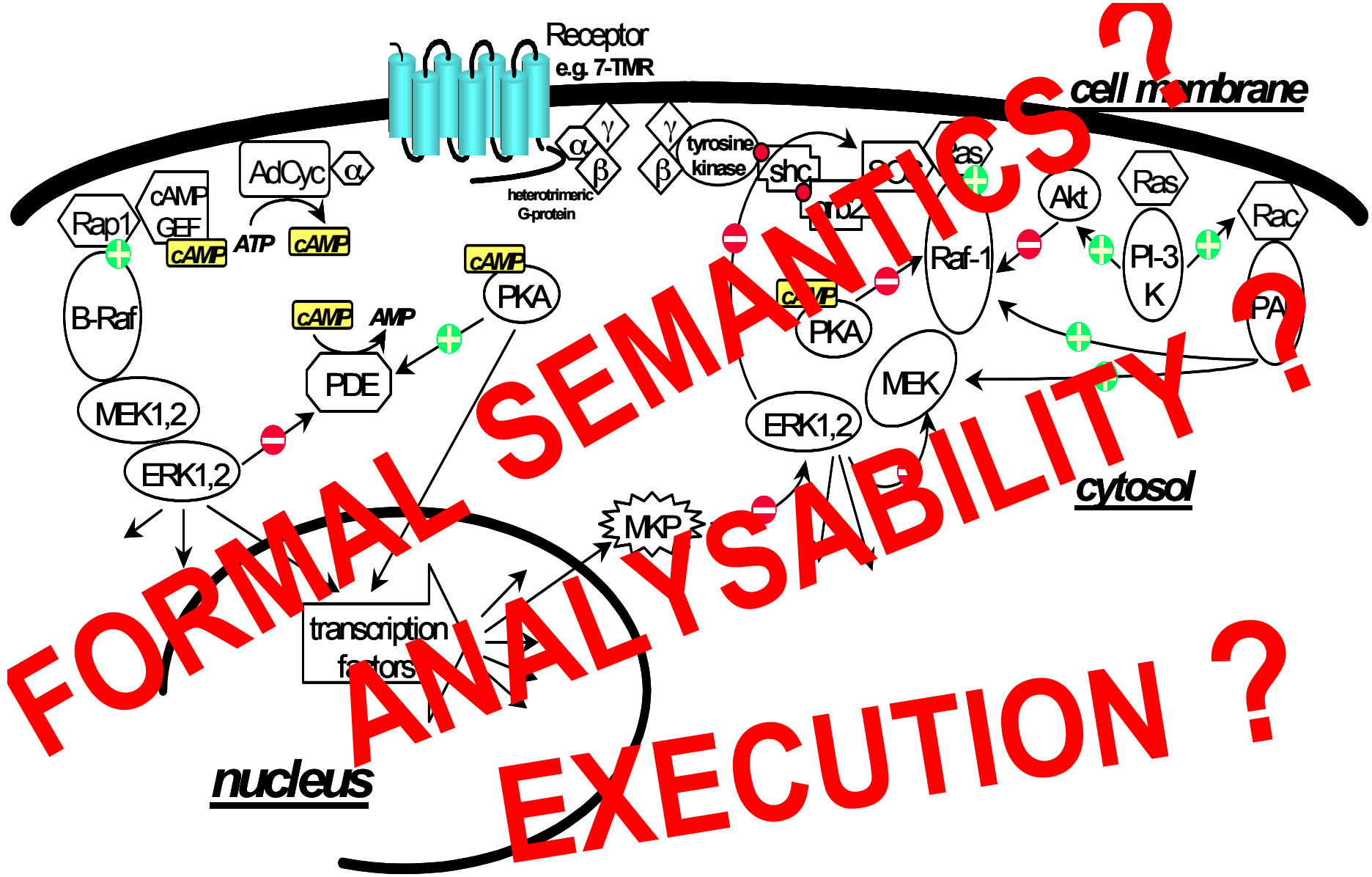

Receptor
e.g. 7-TMR
cell membrane
heterotrimeric
G-protein
tyrosine
kinase
shc
Ras
Rap1
cAMP
GEF
cAMP
ATP
cAMP
AdCyc
B-Raf
MEK1,2
ERK1,2
cAMP
PKA
cAMP
AMP
PDE
PKA
Raf-1
Akt
Ras
PI-3
K
Rac
PA
MEK
ERK1,2
MKP
transcription
factors
nucleus
cytosol
FORMAL SEMANTICS ?
ANALYSABILITY ?
EXECUTION ?

$$\frac{d\alpha}{dt} = -v_1$$

$$\frac{dSte2}{dt} = -v_2 + v_3 - v_5$$

$$\frac{dSte2_{active}}{dt} = v_2 - v_3 - v_4$$

$$\frac{dSst2_{active}}{dt} = v_{46} - v_{47}$$

$$\frac{dG\alpha\beta\gamma}{dt} = -v_6 + v_9$$

$$\frac{dG\alpha GTP}{dt} = v_6 - v_7 - v_8$$

$$\frac{dG\alpha GDP}{dt} = v_7 + v_8 - v_9$$

$$\frac{dG\beta\gamma}{dt} = v_6 - v_9 - v_{\cdot} + v_{\cdot} + v_{21} + v_{23} + v_{25} + v_{27} + v_{32} - v_{42} + v_{43}$$

$$\frac{dSte5}{dt} = -v_{\cdot} + v_{13} + v_{17} + v_{21} + v_{23} + v_{25} + v_{27} + v_{32}$$

$$\frac{d\cdot}{dt} = -v_{\cdot} + v_{13} + v_{17} + v_{21} + v_{\cdot} + v_{25} + v_{27} + v_{32}$$

$$\frac{d\cdot}{dt} = -v_{14} + v_{15} + v_{17} + v_{\cdot} + v_{23} + v_{25} + v_{27} + v_{32}$$

$$\frac{dFus3}{dt} = -v_{14} + v_{15} + v_{17} + v_{21} + v_{23} + v_{25} + v_{27} - v_{29} + v_{30} + v_{\cdot}$$

$$\frac{dSte20}{dt} = -v_{18} + v_{\cdot} + v_{\cdot} + v_{23} + v_{\cdot} + v_{27} + v_{32}$$

$$v_1 = \alpha[t] \cdot Bar1_{active}[t] \cdot k_1$$

$$v_2 = Ste2[t] \cdot \alpha[t] \cdot k_2$$

$$v_3 = Ste2_{active}[t] \cdot k_3$$

$$v_4 = Ste2_{active}[t] \cdot k_4$$

$$v_5 = Ste2[t] \cdot k_5$$

$$v_6 = Ste2_{active}[t] \cdot G\alpha\beta\gamma[t] \cdot k_6$$

$$v_7 = G\alpha GTP[t] \cdot k_7$$

$$v_8 = G\alpha GTP[t] \cdot \cdot st2_{active}[t] \cdot k_8$$

$$v_9 = \cdot G\alpha GDP[t] \cdot G\beta\gamma[t] \cdot k_9$$

$$v_{10} = \cdot G\beta\gamma[t] \cdot C[t] \cdot k_{10}$$

$$v_{11} = D[t] \cdot k_{11}$$

$$v_{12} = Ste5[t] \cdot Ste11[t] \cdot k_{12}$$

$$v_{13} = A[t] \cdot k_{13}$$

$$v_{14} = Ste7[t] \cdot Fus3[t] \cdot k_{14}$$

$$v_{15} = \cdot[t] \cdot k_{15}$$

$$v_{16} = \cdot[t] \cdot B[t] \cdot k_{16}$$

$$v_{17} = C[t] \cdot k_{17}$$

$$v_{18} = D[t] \cdot Ste20[t] \cdot k_{18}$$

READABILITY ?

CAUSALITY ?

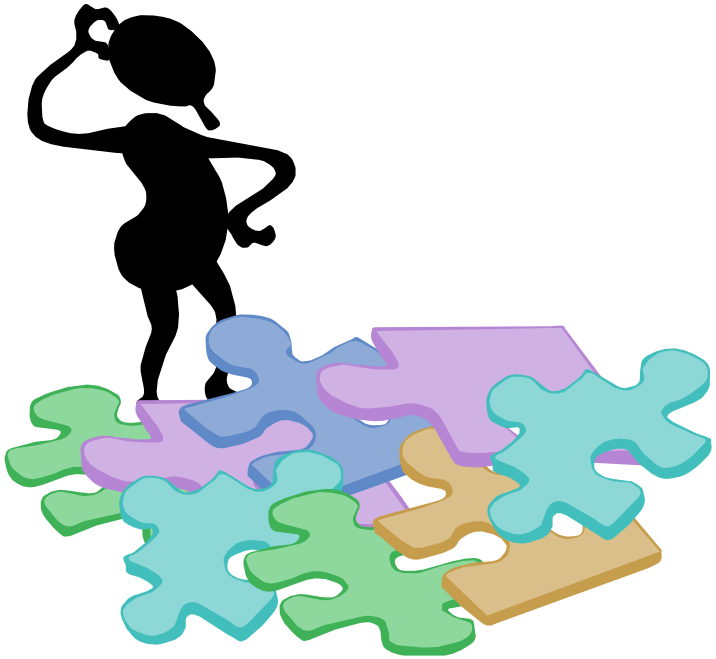
UNIQUE STRUCTURE ?

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 PATCHWORKS FULL OF ASSUMPTIONS

BIO NETWORK REPRESENTATIONS SHOULD BE



- **readable & unambigious**
  -> fault avoidant model construction
- **various abstraction levels**
- **locality - causality - concurrency**
- **compositional**
- **executable**
  -> to experience the model, spec. causality

- **analysable, with unifying power**
  -> formal = mathematical representations
  -> high-level description for various analysis approaches
- **as simple as possible**
  -> how many model types do we need ?

MODELLING = ABSTRACTION

- **hierarchical organisation of components -> model variables**
  genes, molecules, organelles, cells, tissues, organs, organisms
- **functionality of atomic events**
  chemical reactions with/out stoichiometry, conformational change, transport, . . .
- **time**
  qualitative versus quantitative models
- **individual vs population behaviour**
- **(hierarchical) space**
- **observables**
- **shape and volume of components**
- **biosystem development**

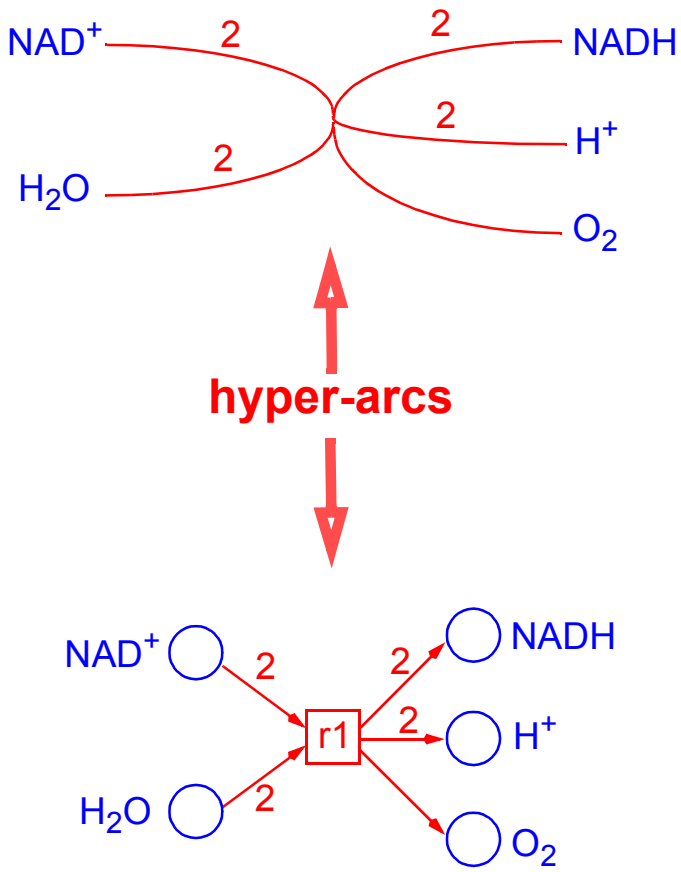
. . .

ARE NETWORKS OF BIOCHEMICAL REACTIONS

. . .

NATURALLY EXPRESSIBLE AS PETRI NETS

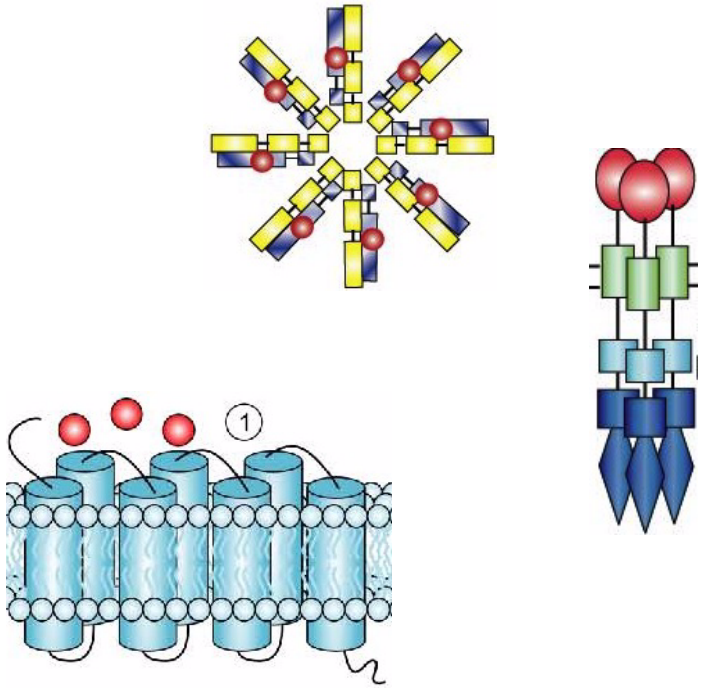
$2\ NAD^+ + 2\ H_2O \rightarrow 2\ NADH + 2\ H^+ + O_2$

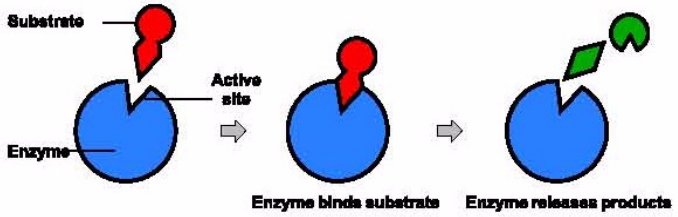


PLACES, TRANSITIONS - SOME BIO INTERPRETATIONS

- **places -> model variables**
  - -> *(bio-) chemical compounds*
  - -> *proteins*
  - -> *protein conformations*
  - -> *complexes*
  - -> *genes, . . . etc.*
  - *. . . in different locations*

- **transitions -> atomic events**
  - -> *(stoichiometric) chemical reaction*
  - -> *complexation / decomplexation*
  - -> *phosphorylation / dephosphorylation*
  - -> *conformational change*
  - -> *transport step, . . . etc.*
  - *. . . in different locations*





BIO PETRI NETS - SOME EXAMPLES

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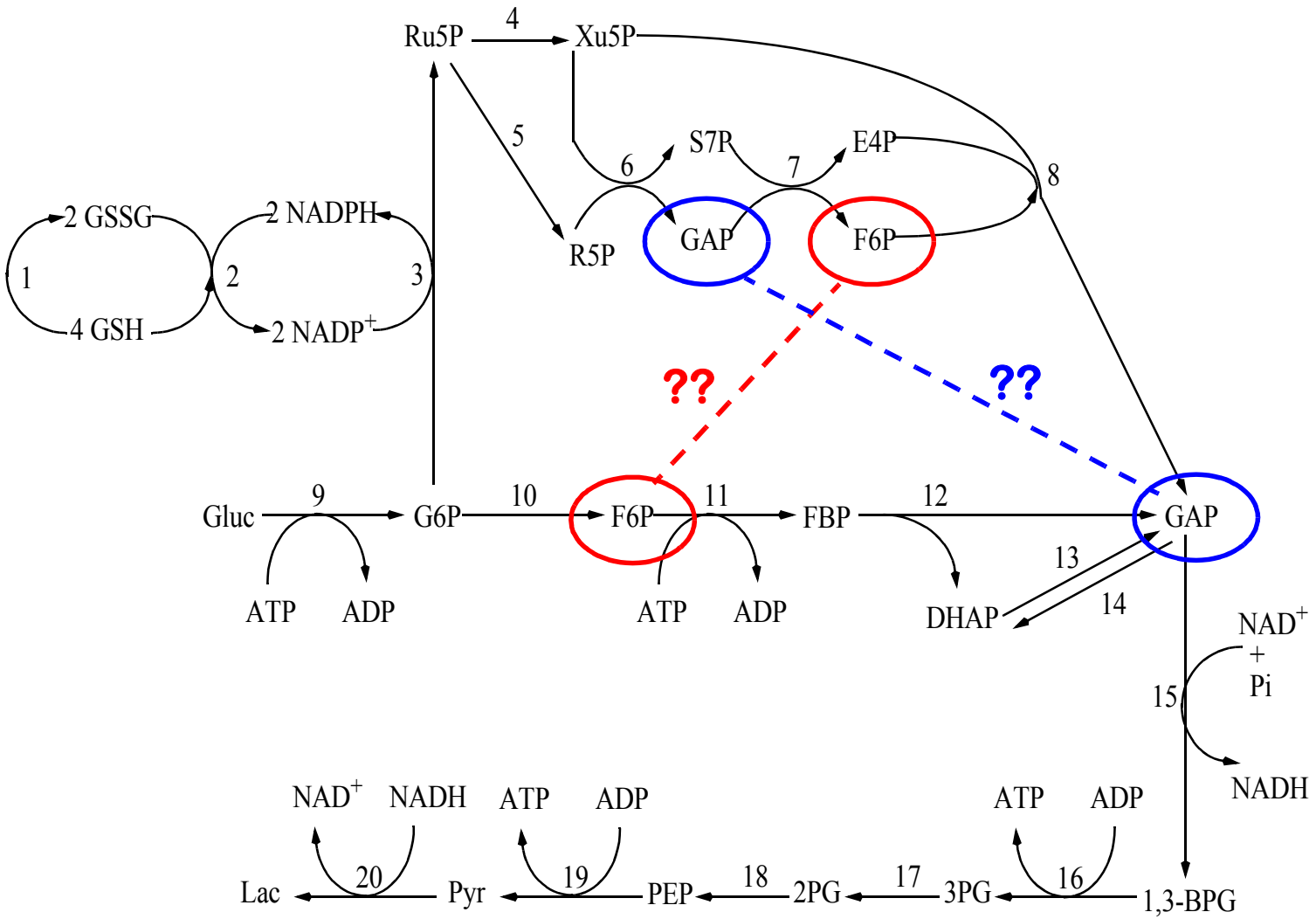
Ex1 - Glycolysis and Pentose Phosphate Pathway

[Reddy 1993]



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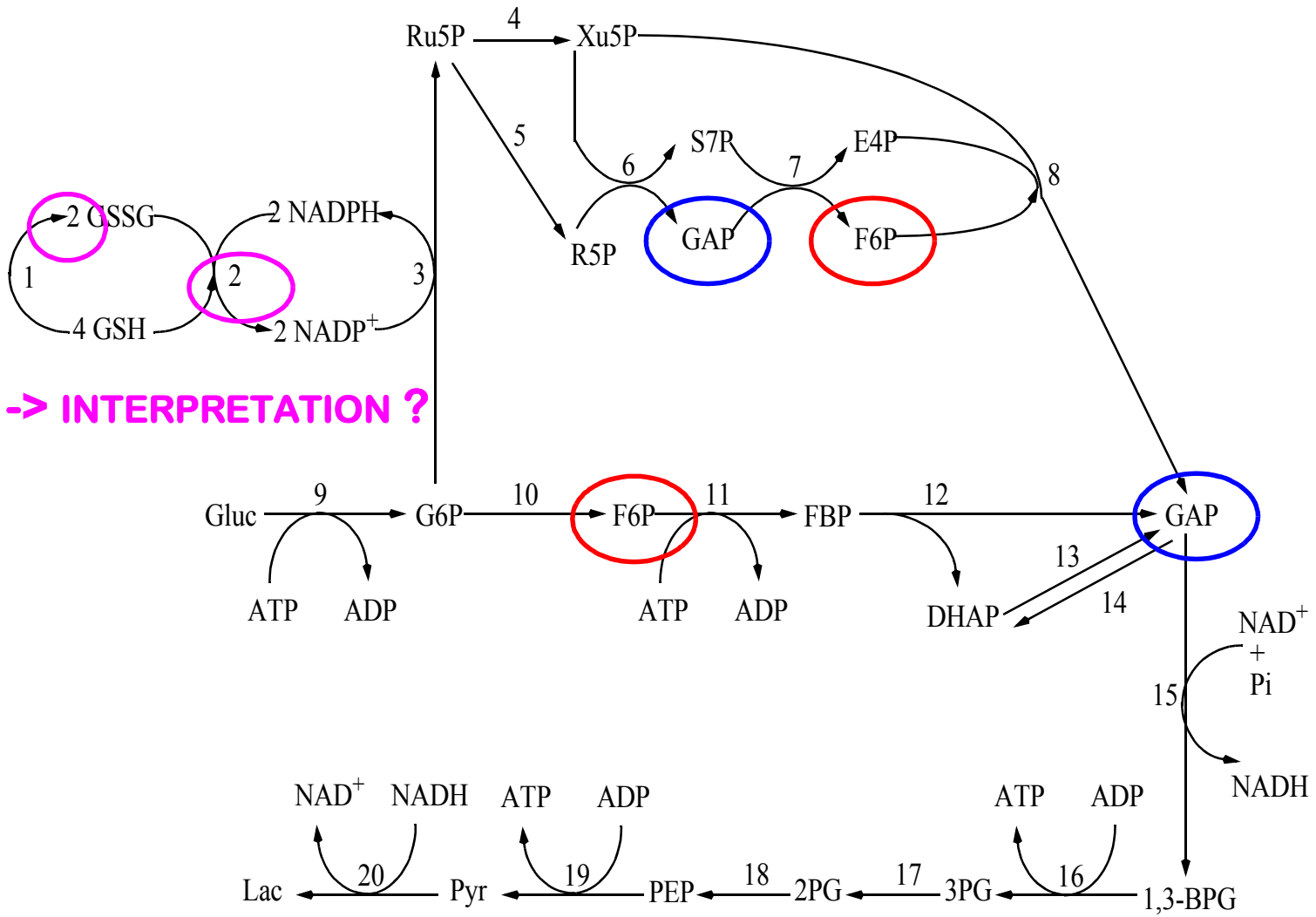

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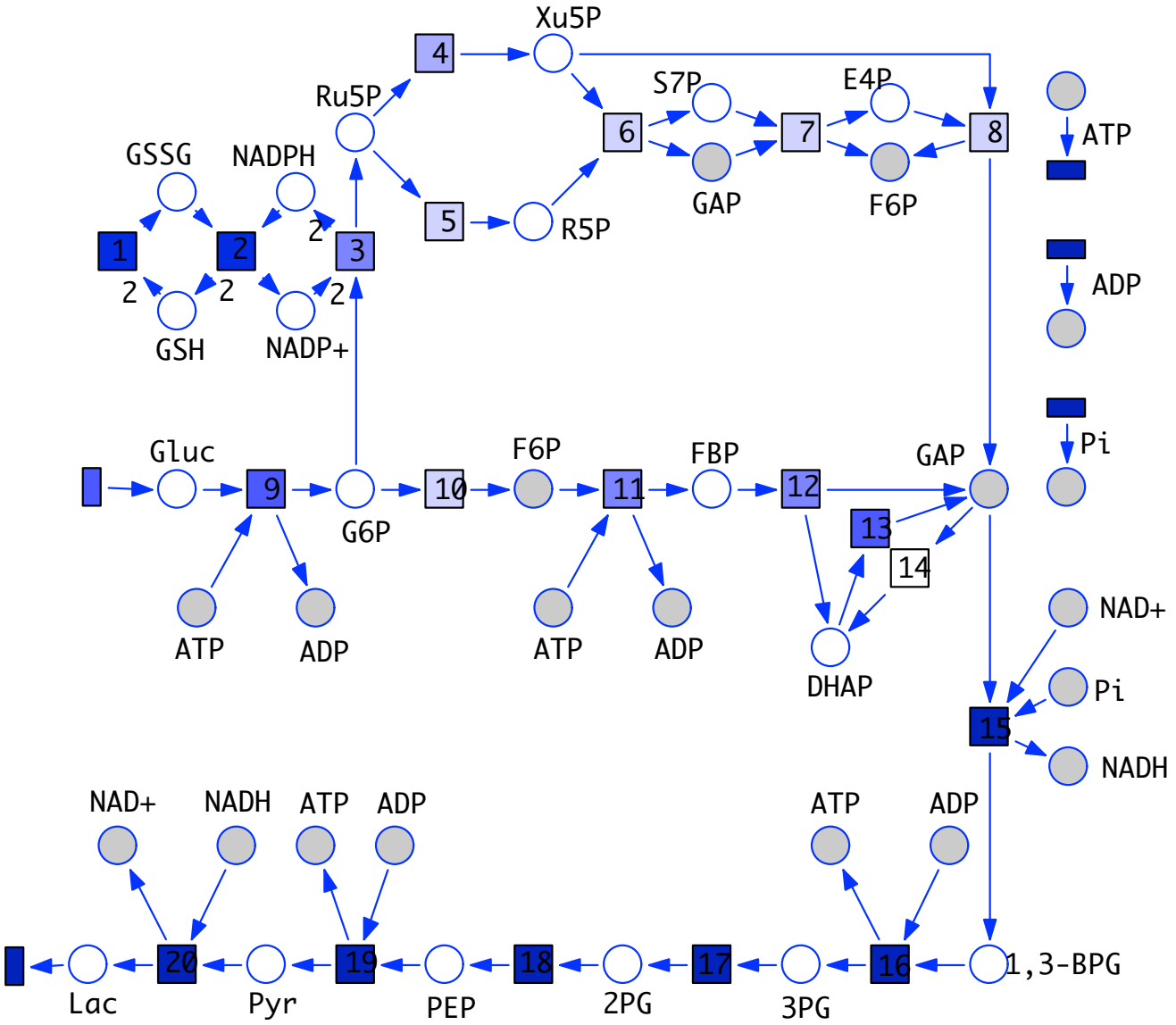


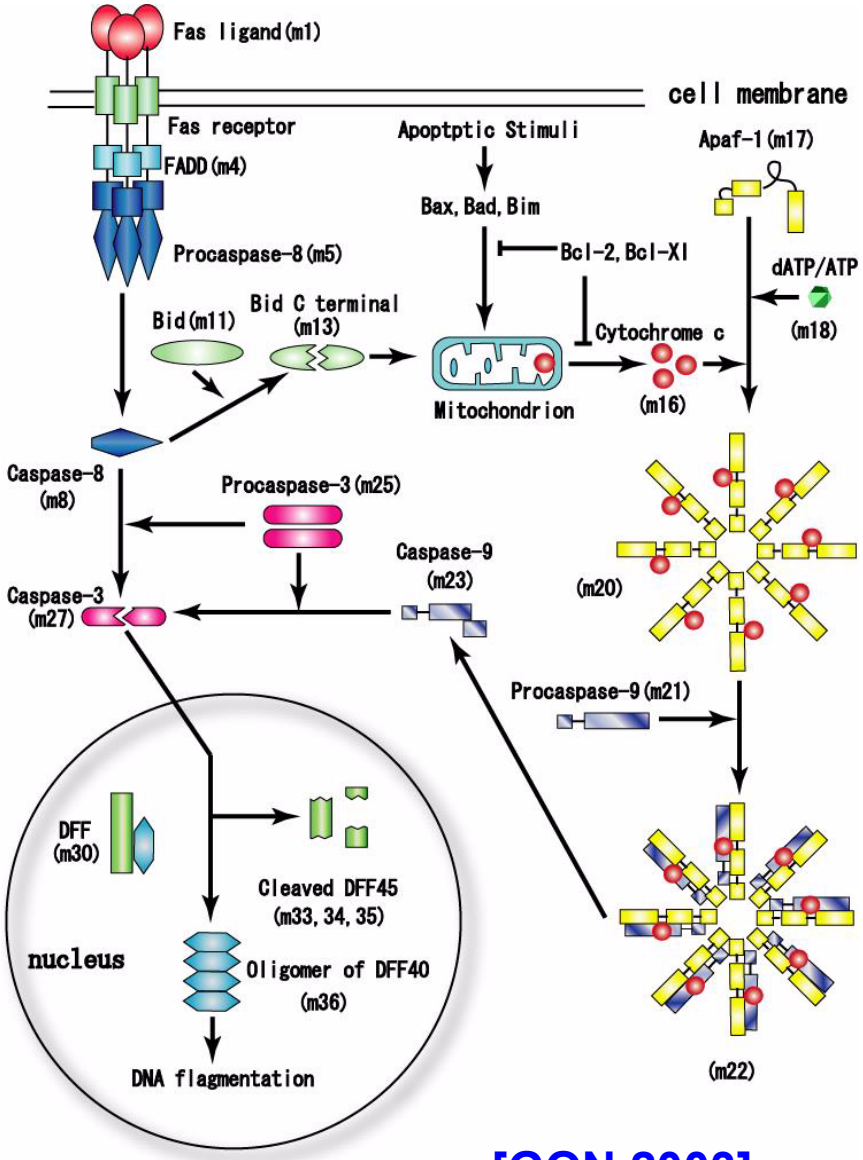
[Reddy 1993]

[Heiner 1998]

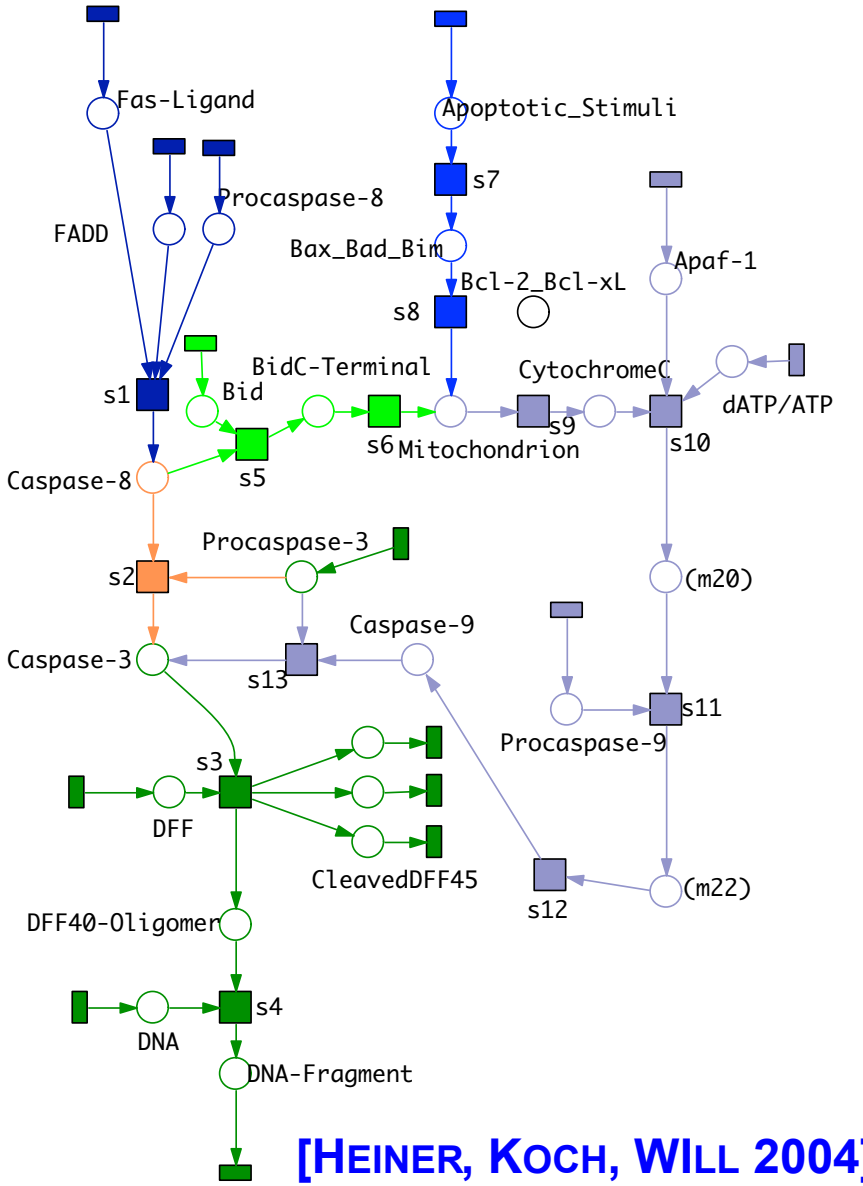
. . .

[Koch, Heiner 2010]

EX2 - APOPTOSIS IN MAMMALIAN CELLS

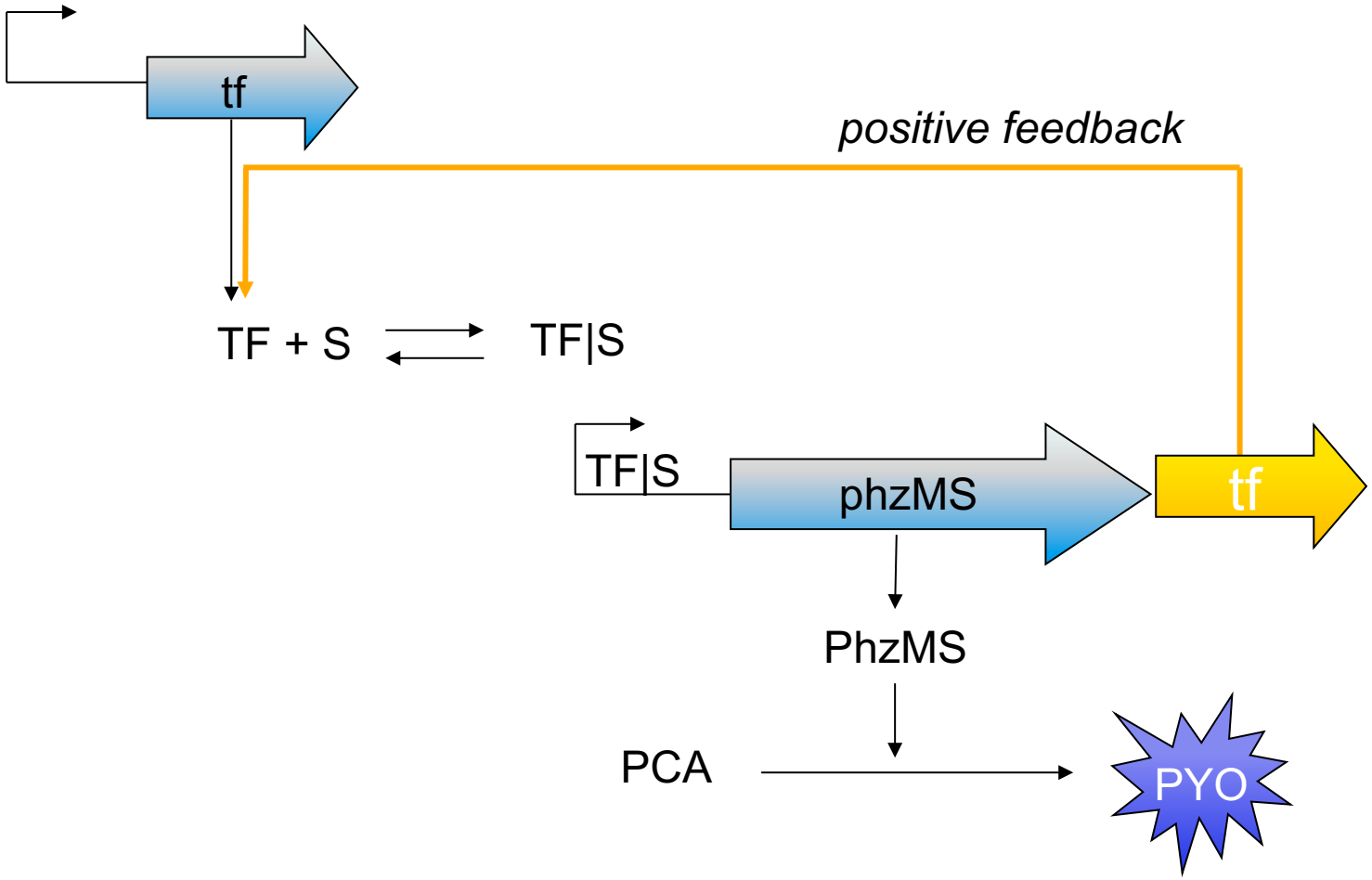


[GON 2003]



[HEINER, KOCH, WILL 2004]

EX3 - BIOSENSOR



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

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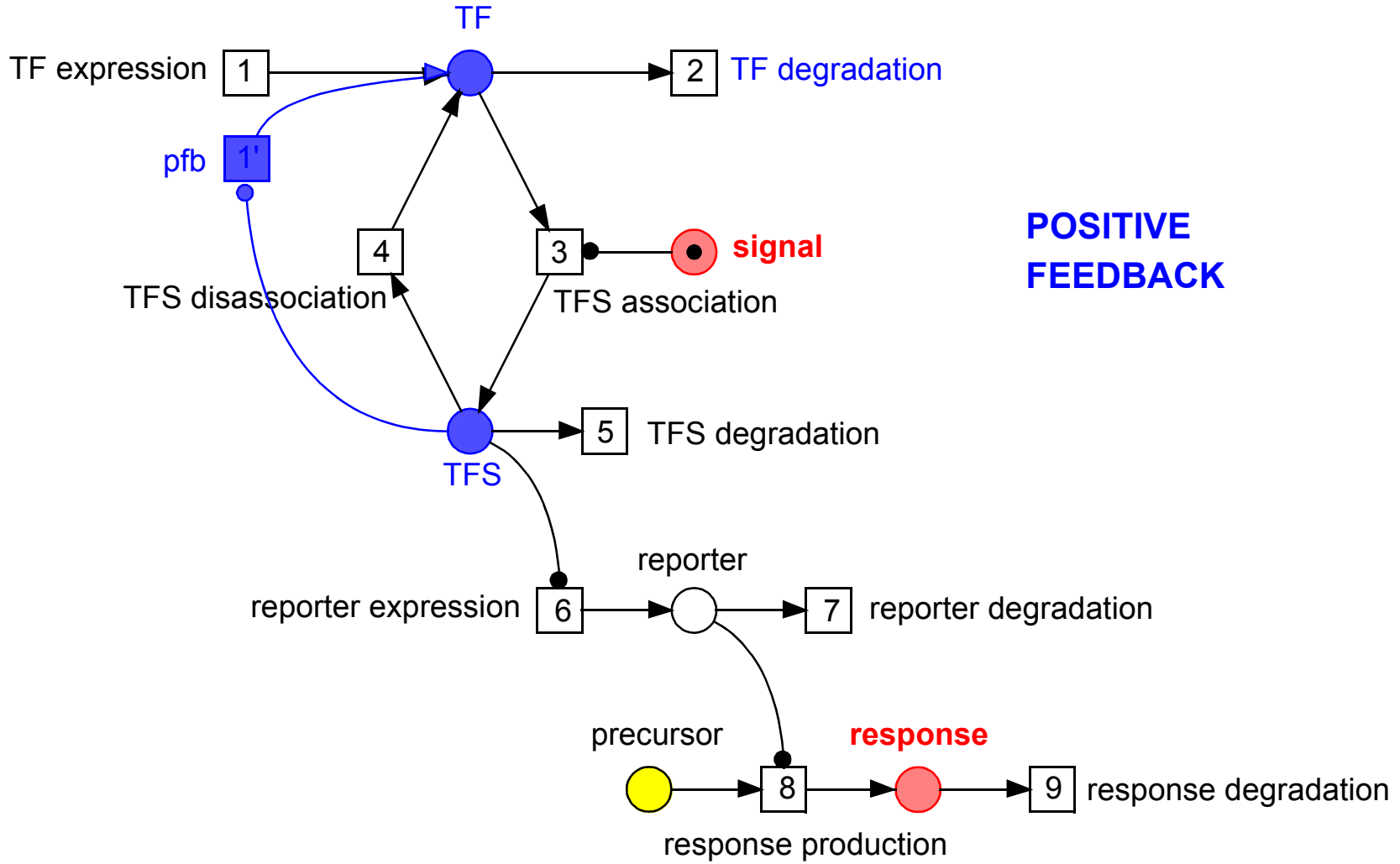
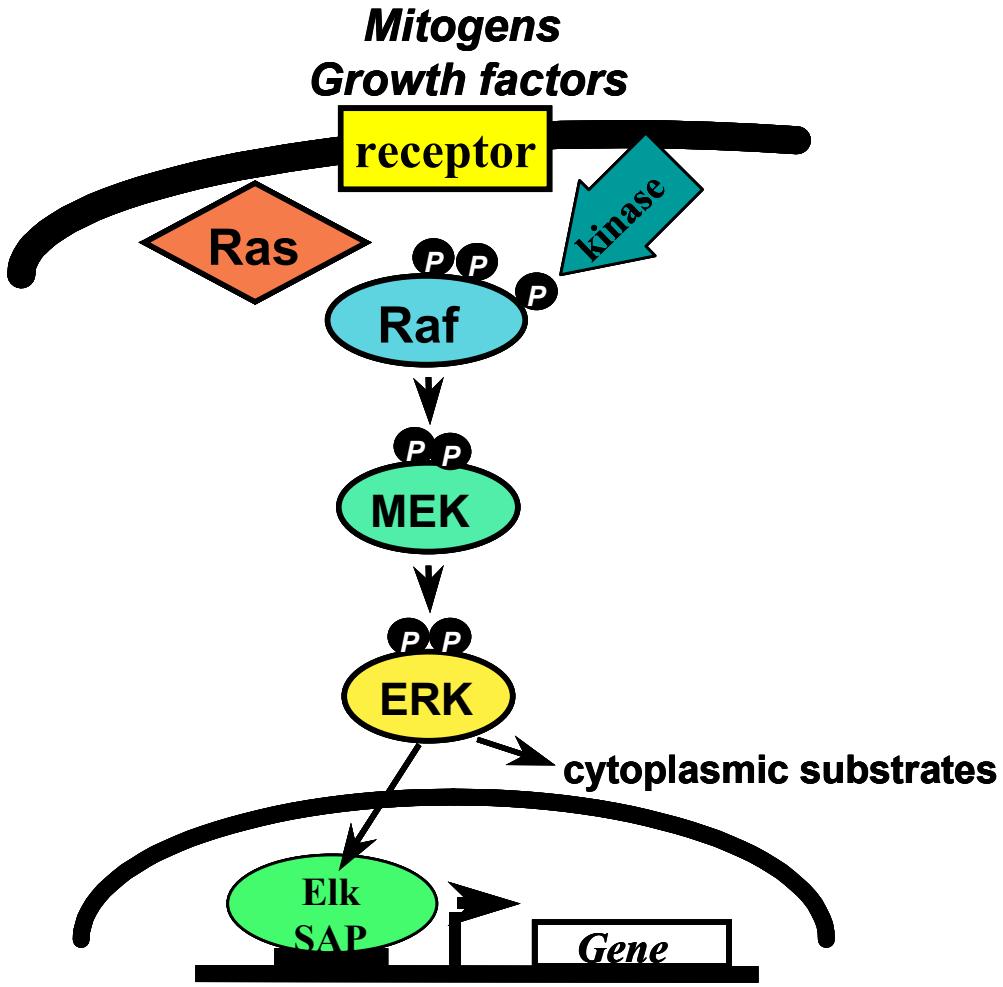
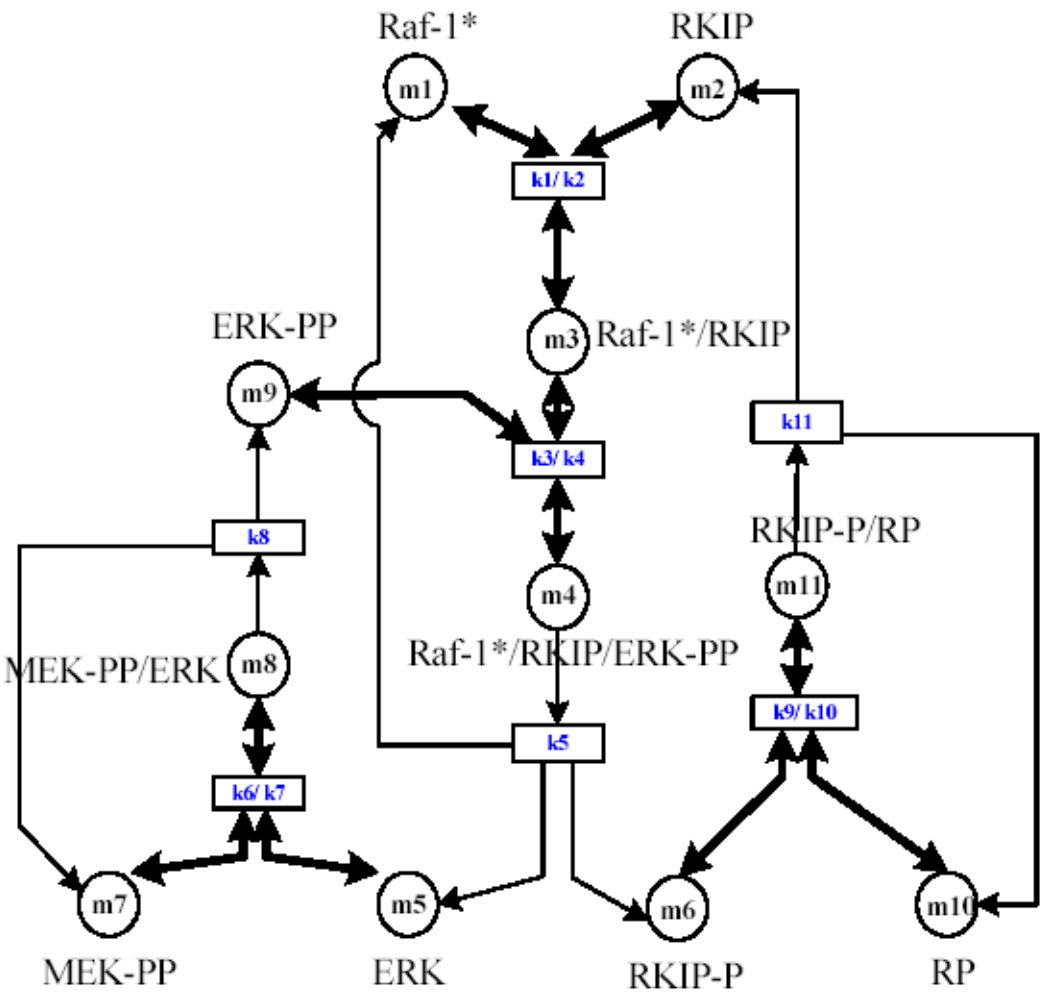


[GILBERT, HEINER, ROSSER, FULTON, GU, TRYBILO 2008]

Ö one pathwayÖ

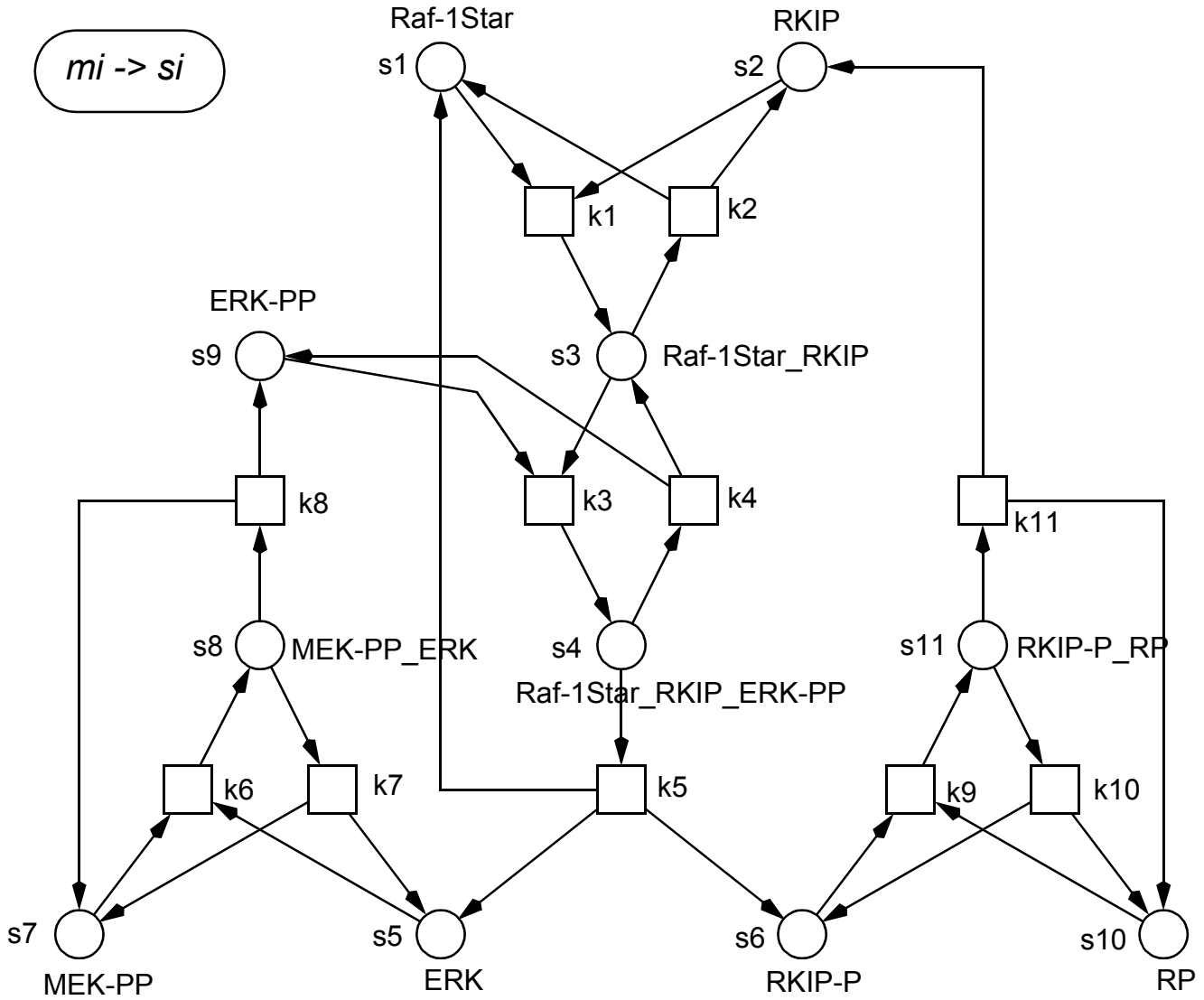


EX4 - RKIP SIGNALLING PATHWAY



[Cho et al. 2003]

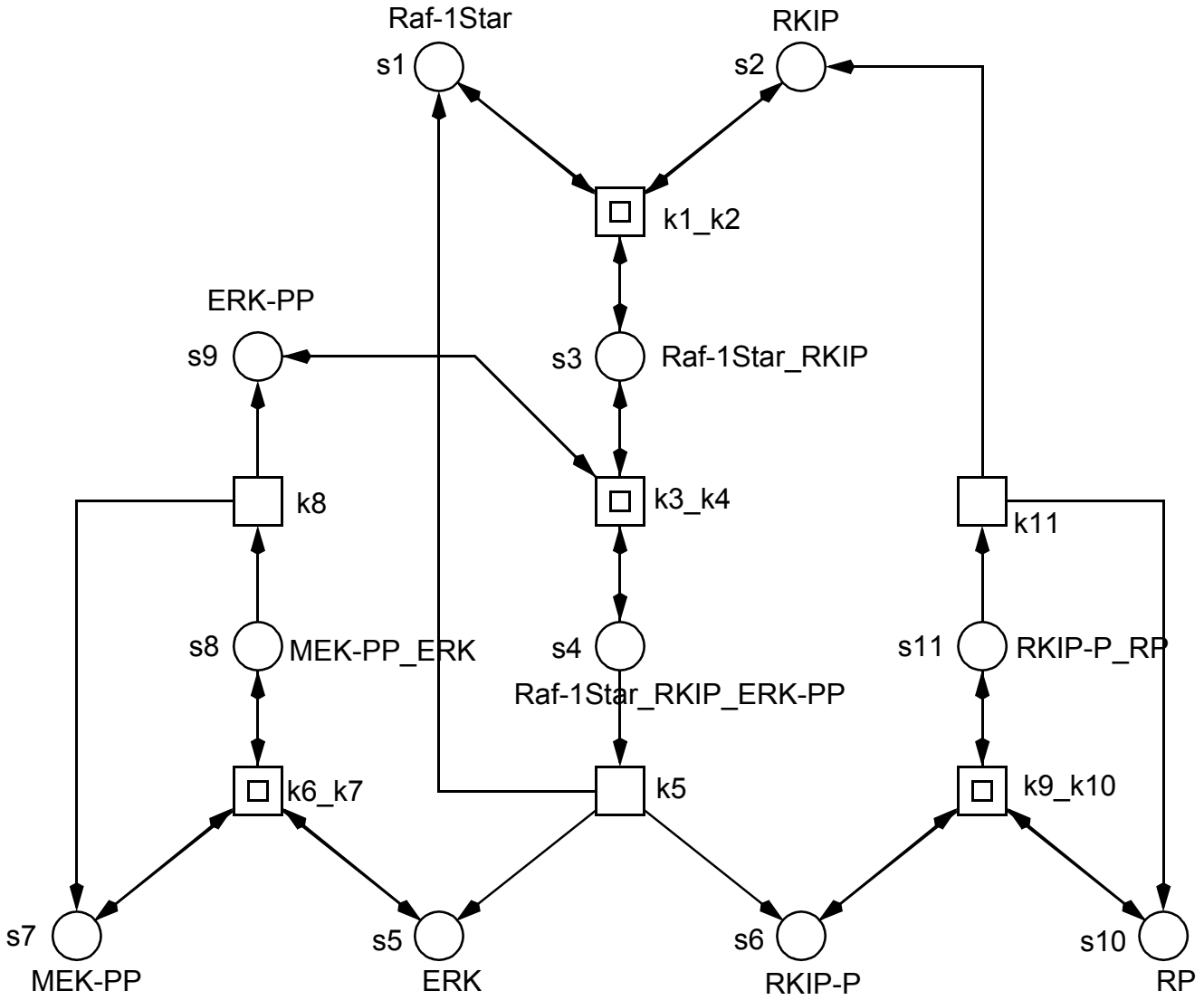
EX4 - RKIP SIGNALLING PATHWAY, PETRI NET



[HEINER, GILBERT 2006]

[HEINER, DONALDSON, GILBERT 2010]

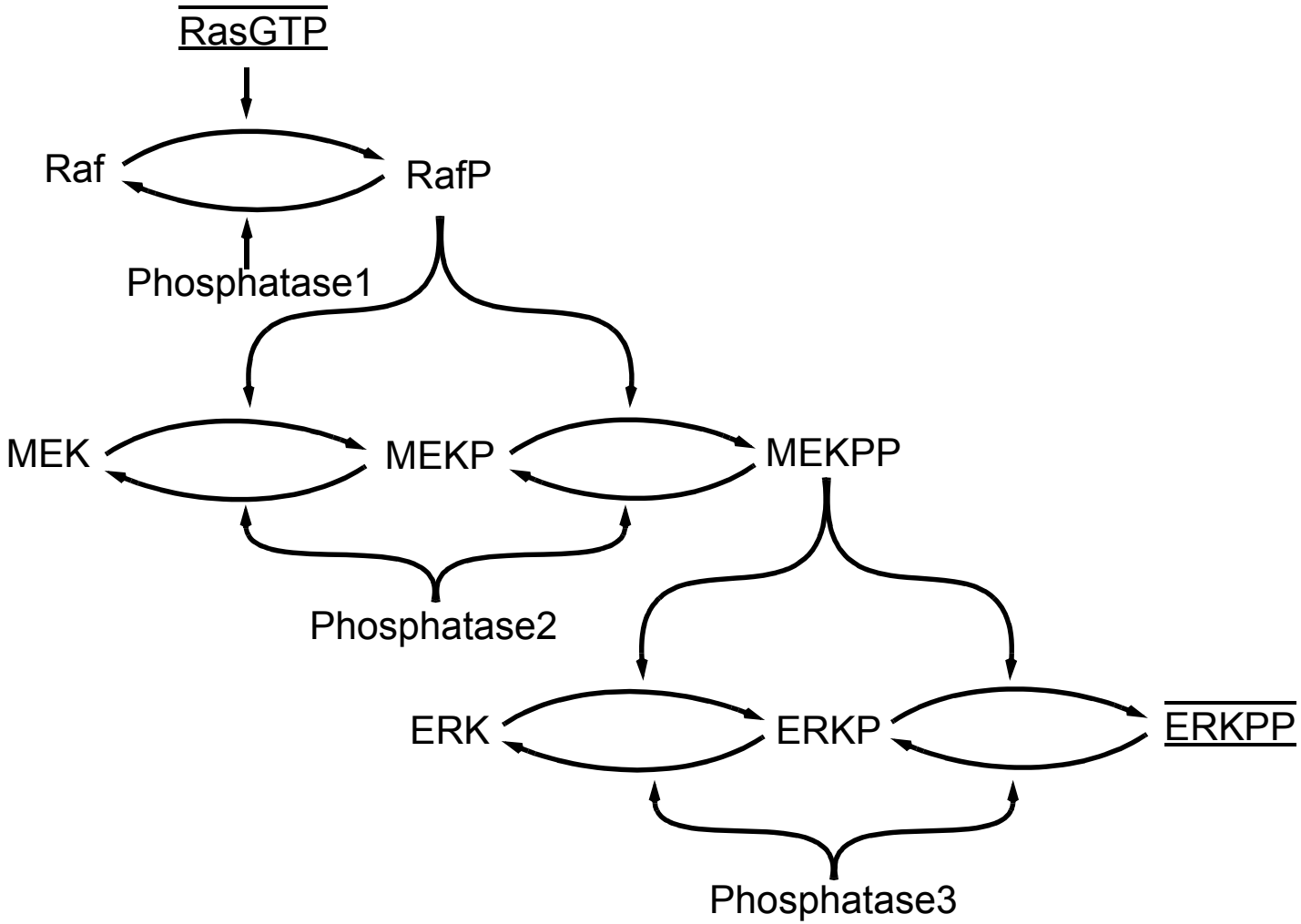
Ex4 - RKIP Signalling Pathway, Hierarchical Petri Net



[Heiner, Gilbert 2006]

[Heiner, Donaldson, Gilbert 2010]

EX5 - SIGNALLING CASCADE



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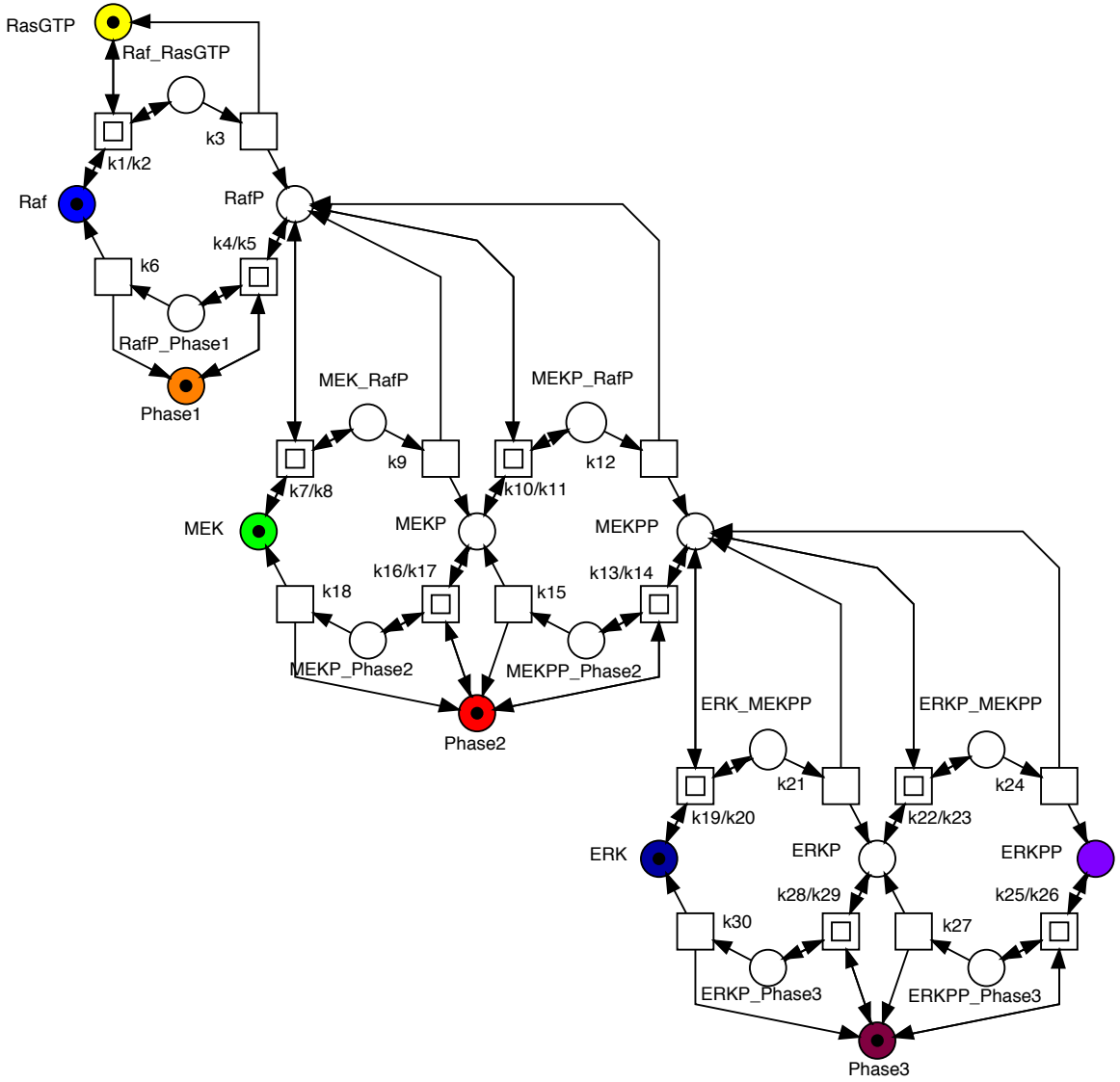
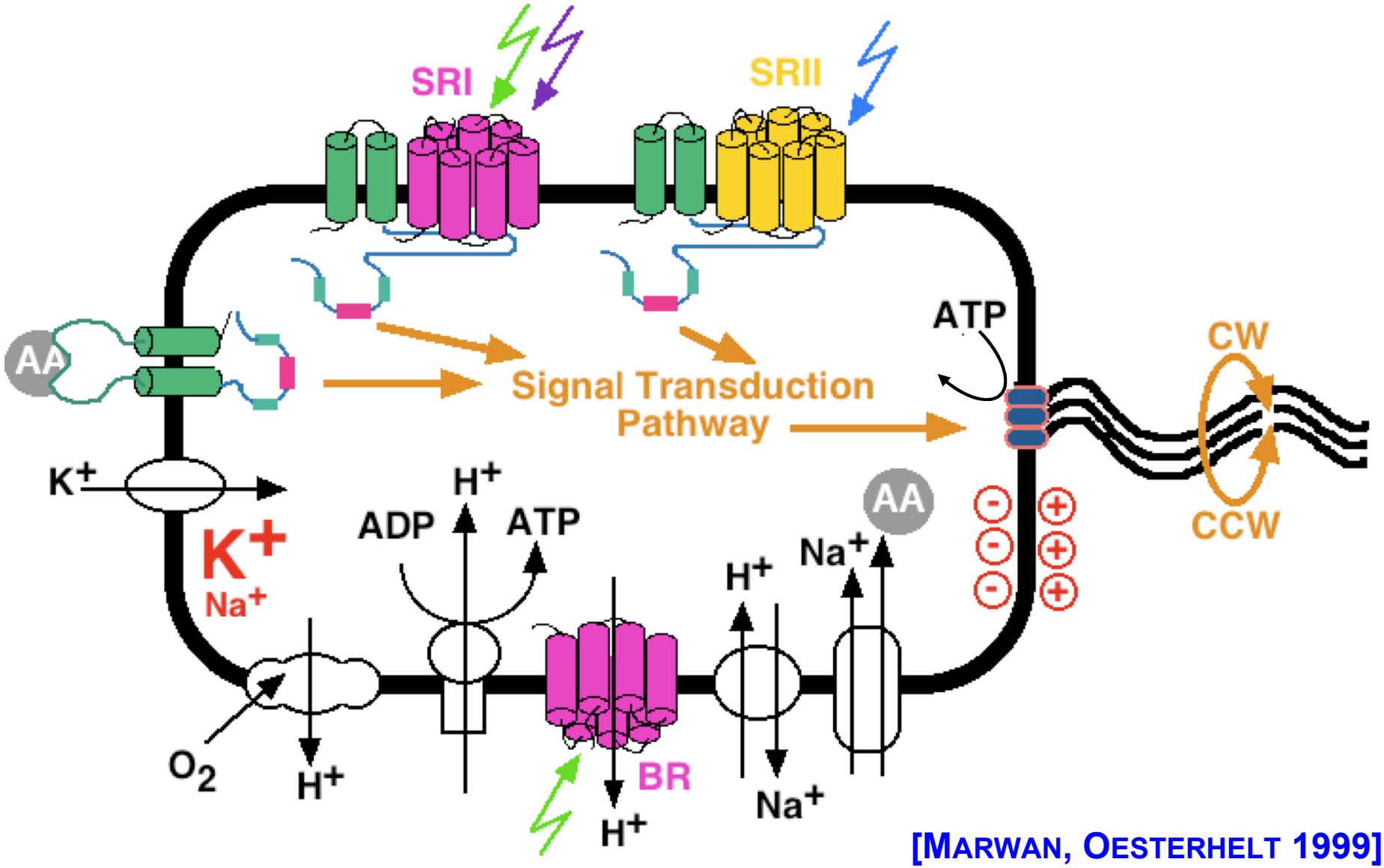


[GILBERT, HEINER, LEHRACK 2007]

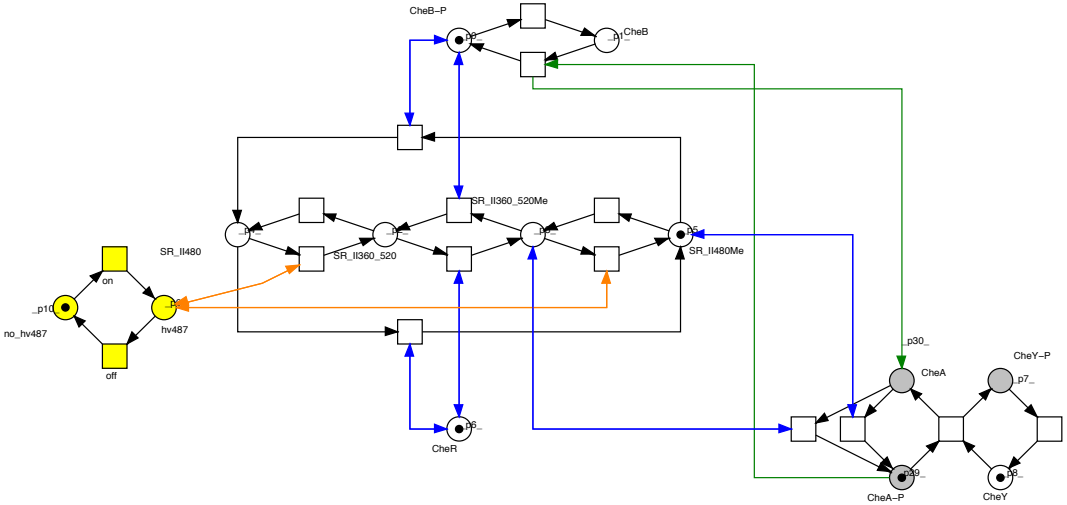
[HEINER, GILBERT, DONALDSON 2008]

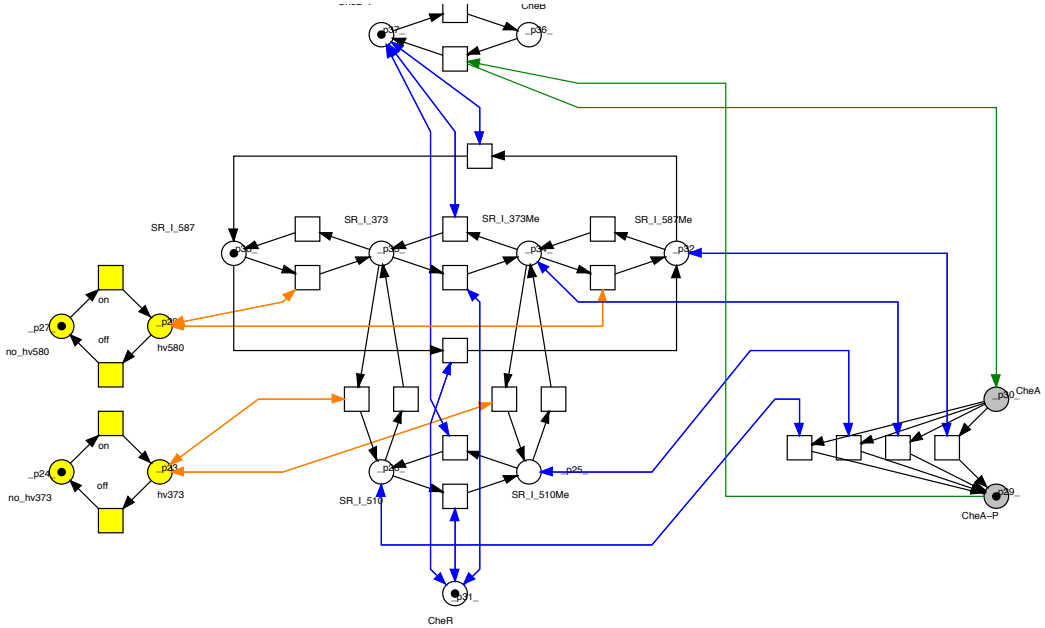
EX6 - HALOBACTERIUM SALINARUM

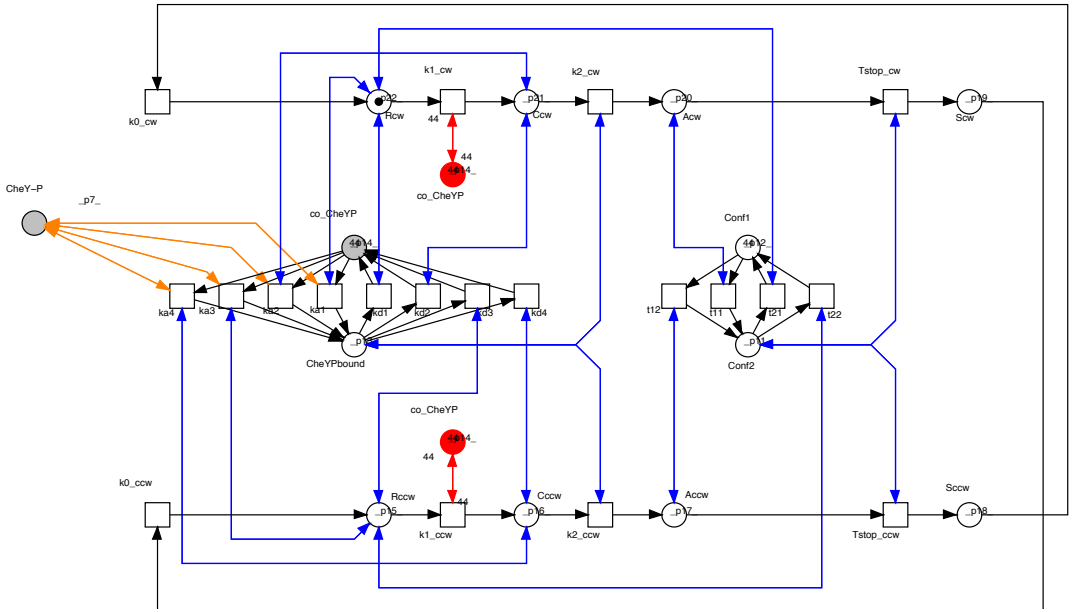


[MARWAN, OESTERHELT 1999]

Ex6 - Halobacterium Salinarum



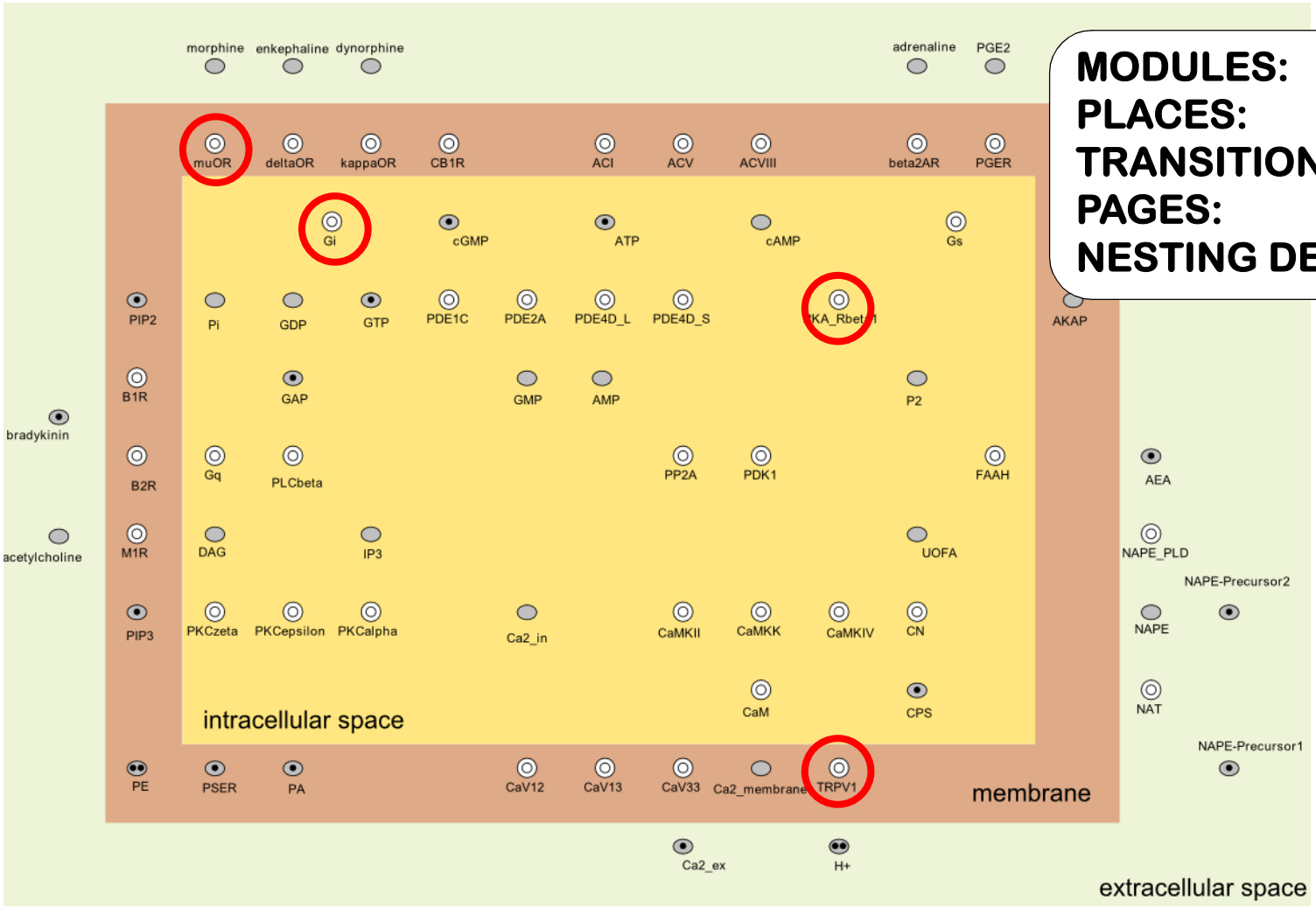




EX7 - PAIN SIGNALLING

[BLÄTKE, MEYER, MARWAN 2011]

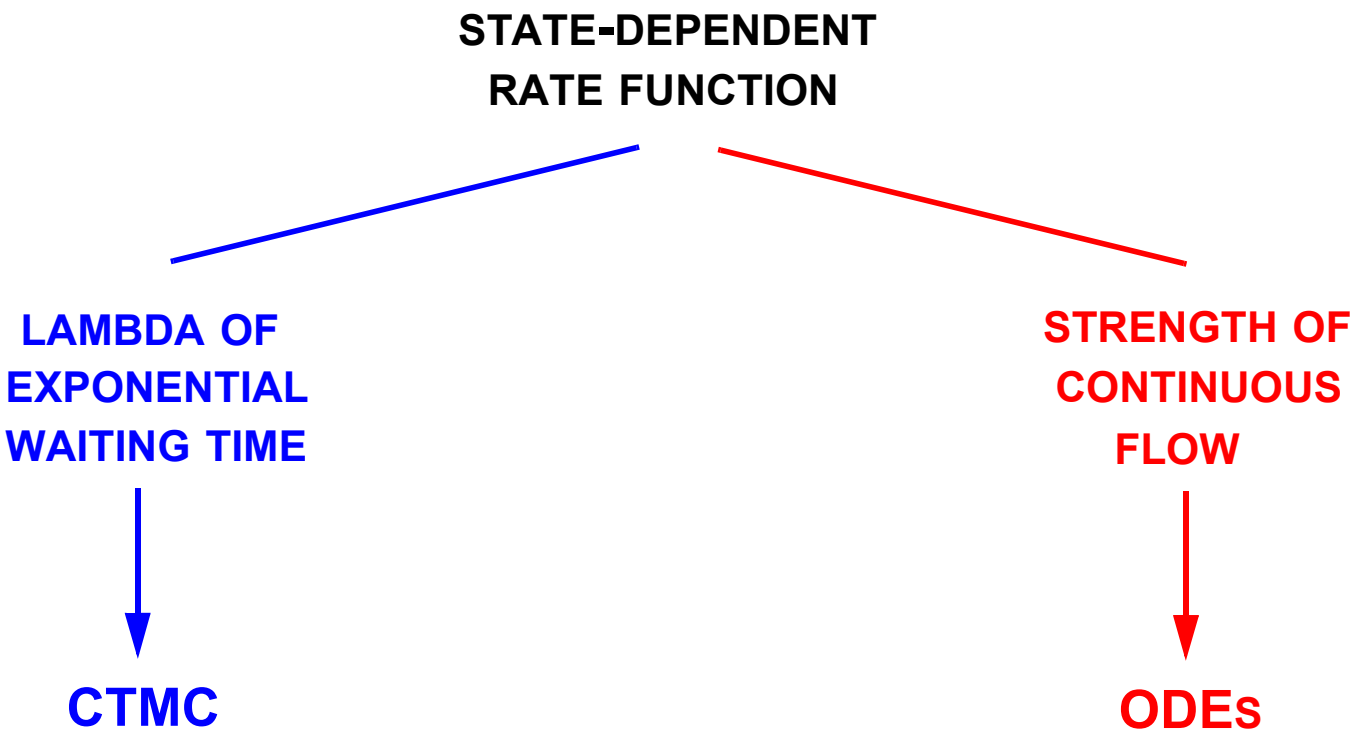
-> A PROTEIN-ORIENTED MODULAR MODELLING CONCEPT



MODULES: 38
PLACES: 713
TRANSITIONS: 775
PAGES: 325
NESTING DEPTH: 4

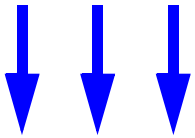
THE FRAMEWORK

CRUCIAL POINT



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

3 MODELS SHARING STRUCTURE

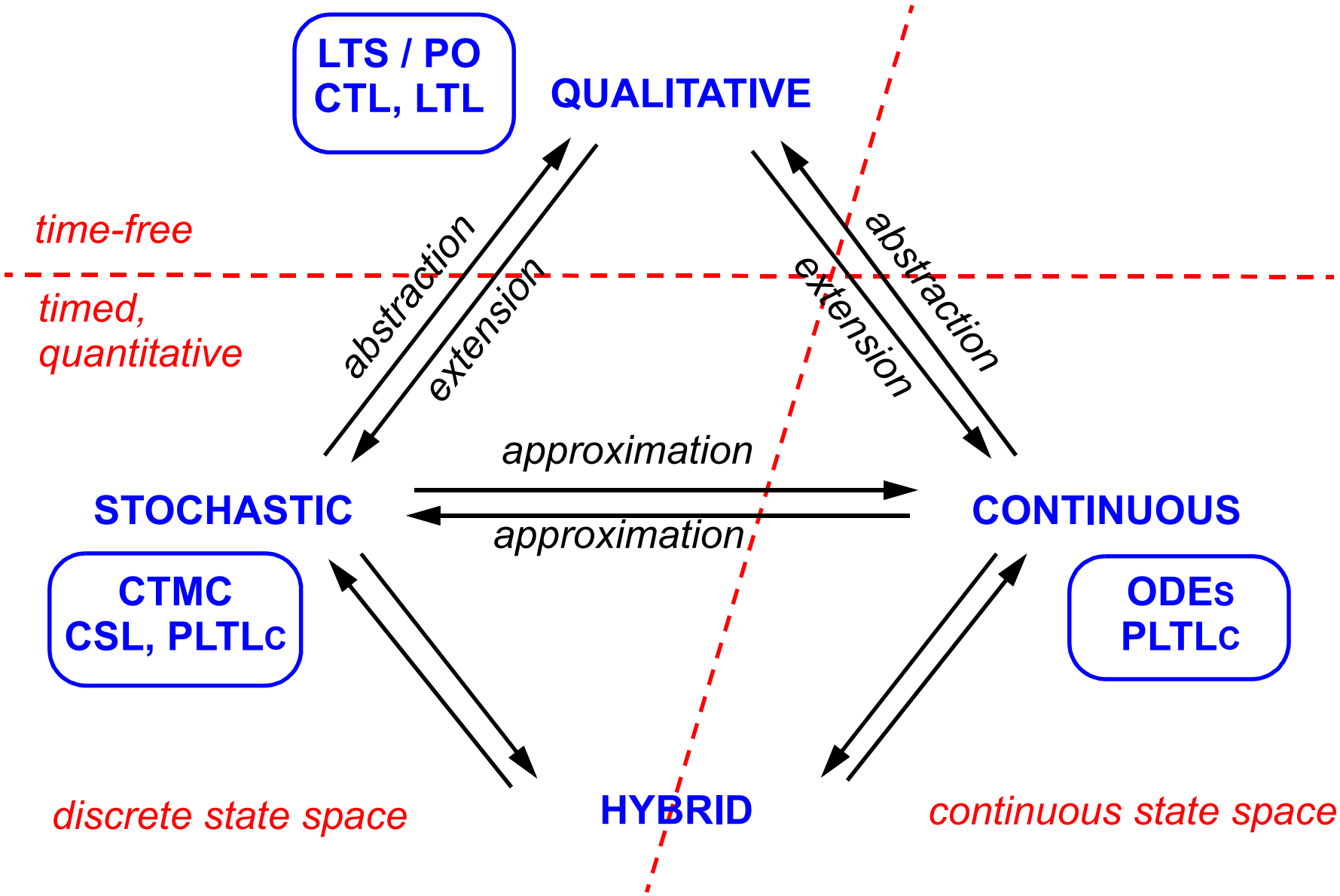


QUANTITATIVE MODEL = QUALITATIVE MODEL

+

RATE FUNCTIONS (KINETICS)

FRAMEWORK 2010



About the Relation Stochastic vs Continuous

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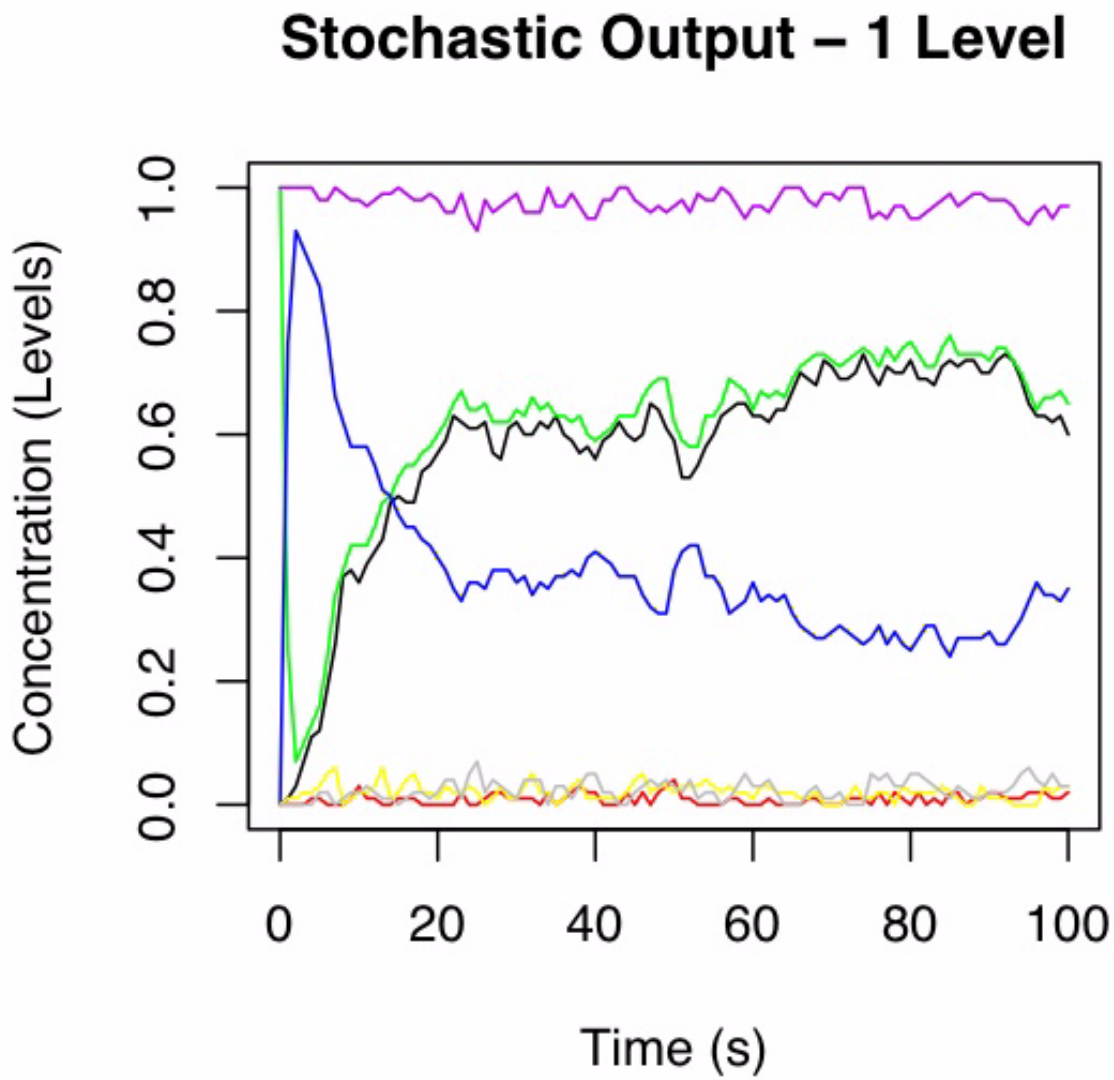
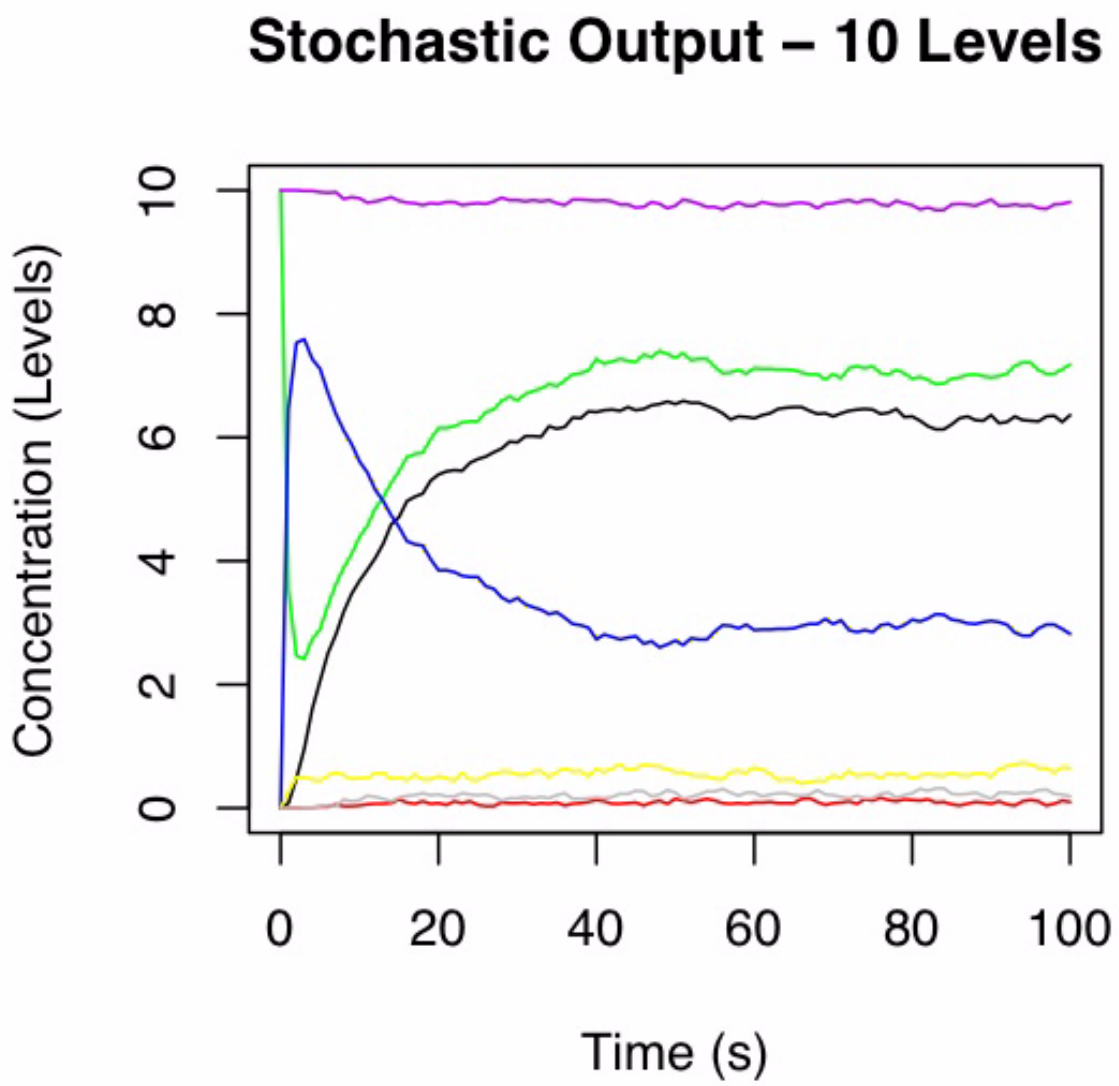
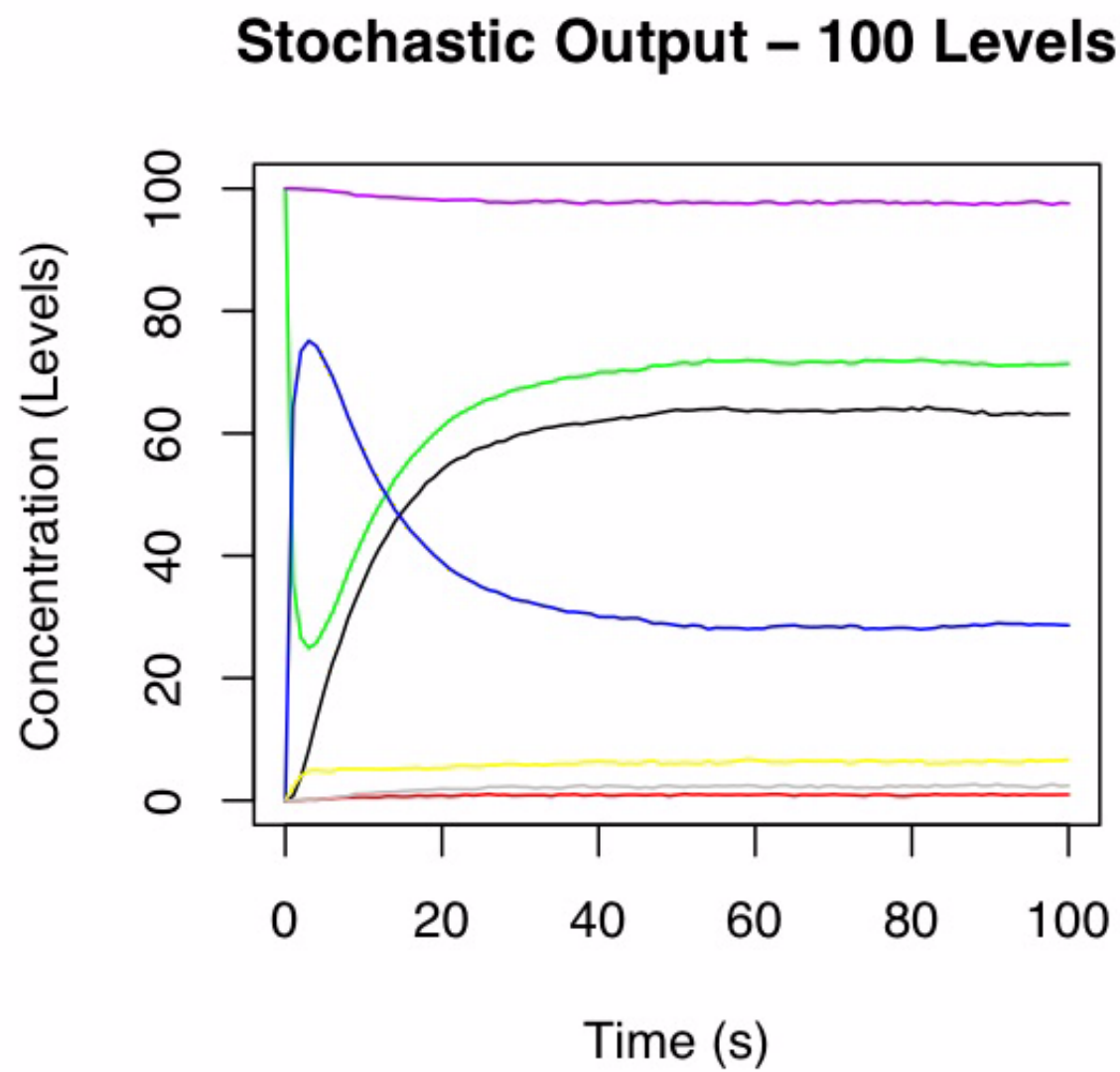
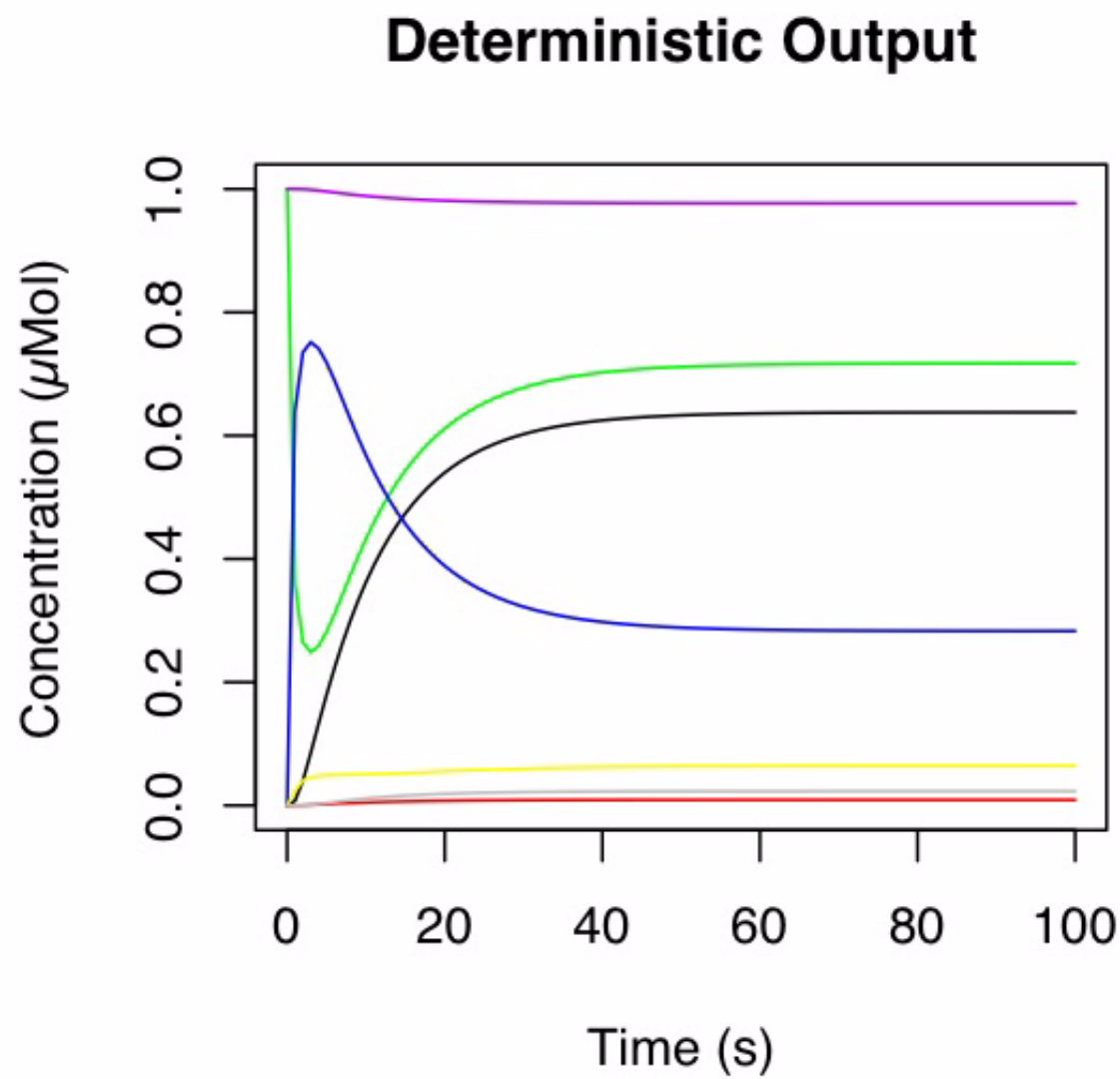

Stochastic Output – 1 Level
Concentration (Levels)
0.0
0.2
0.4
0.6
0.8
1.0
0
20
40
60
80
100
Time (s)


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

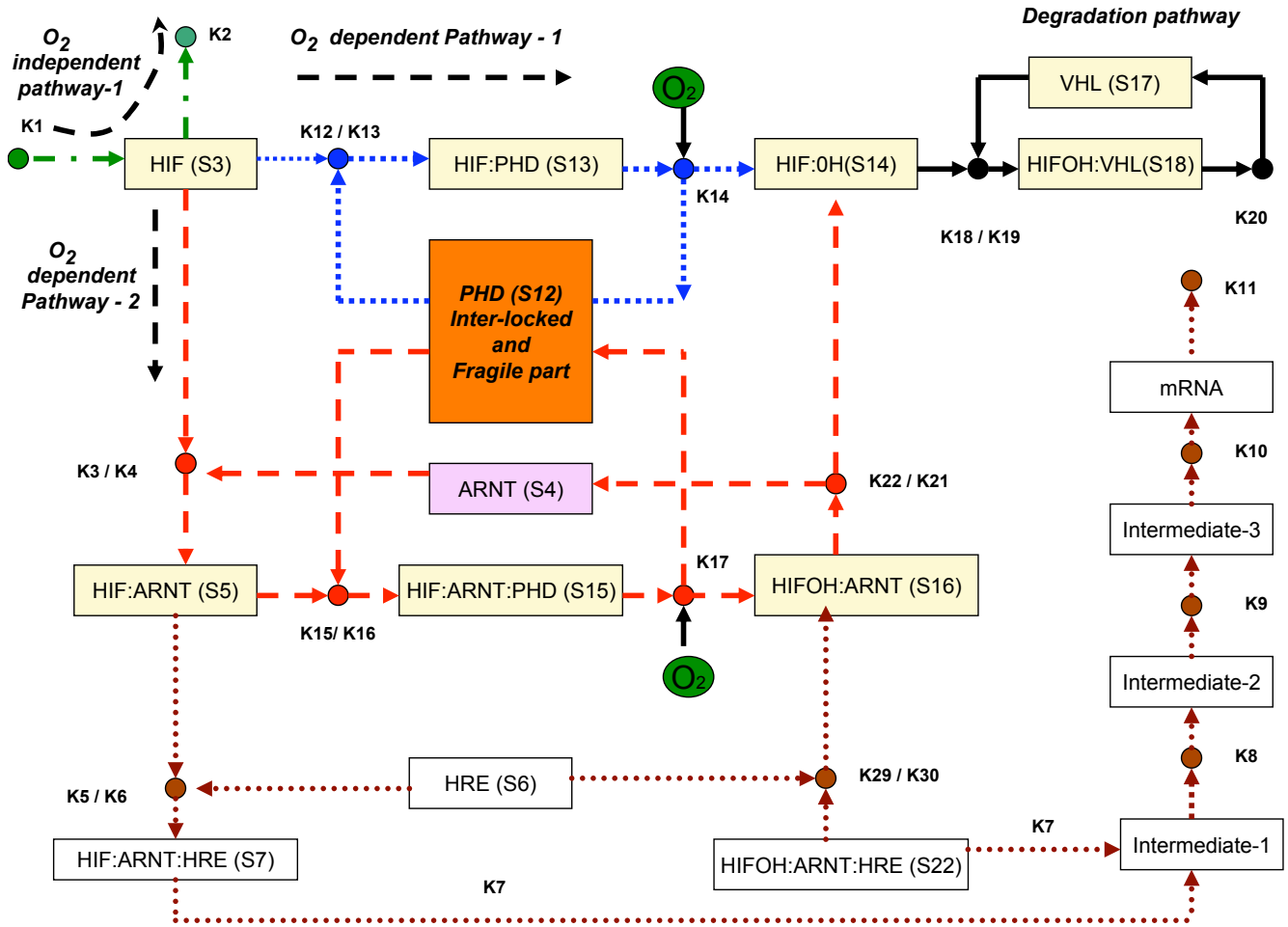

Stochastic Output – 100 Levels
Concentration (Levels)
0
20
40
60
80
100
0
20
40
60
80
100
Time (s)


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

About the Relation Qualitative vs Continuous

EX7 - HYPOXIA

[YU ET AL. 2007]



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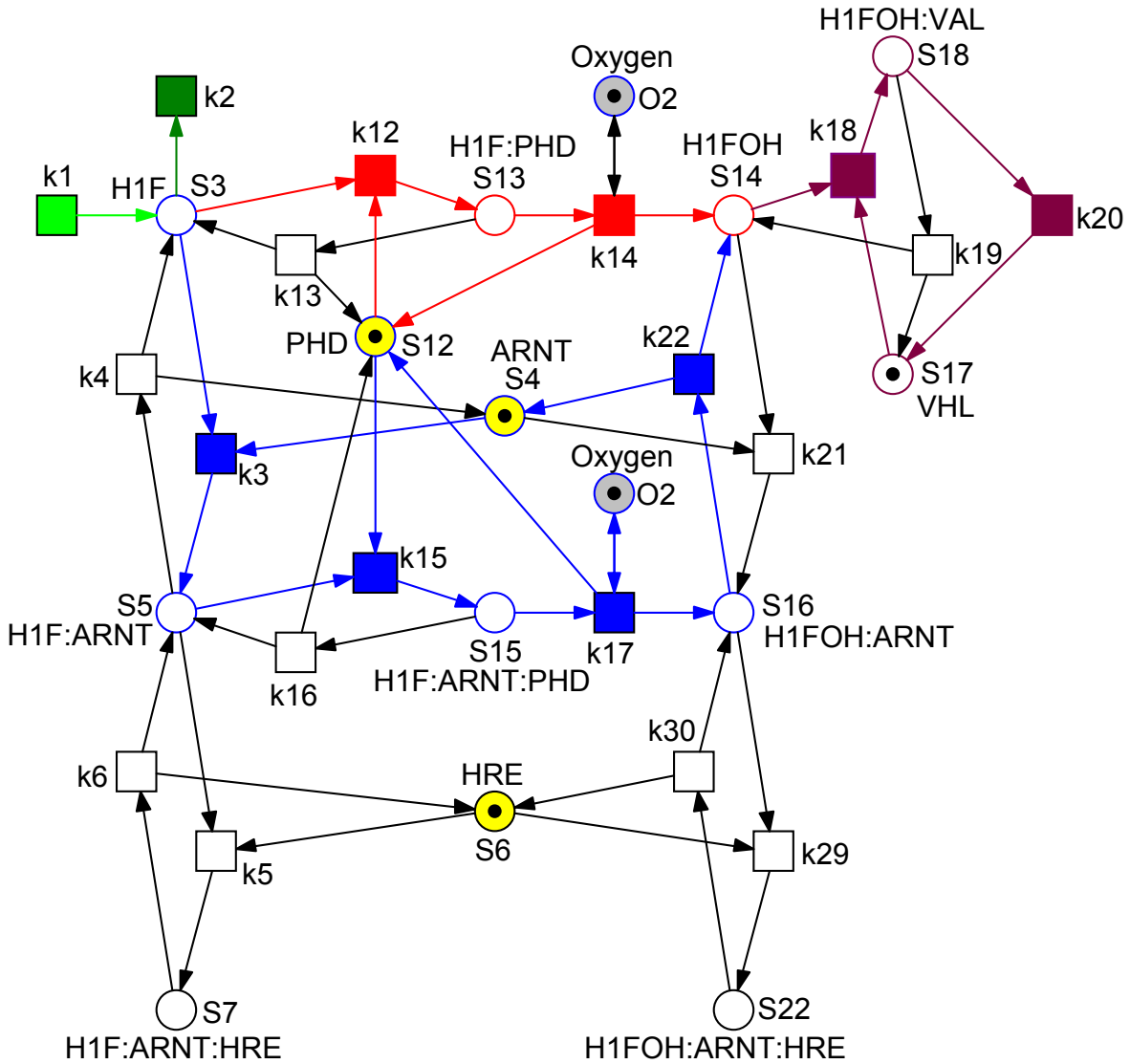
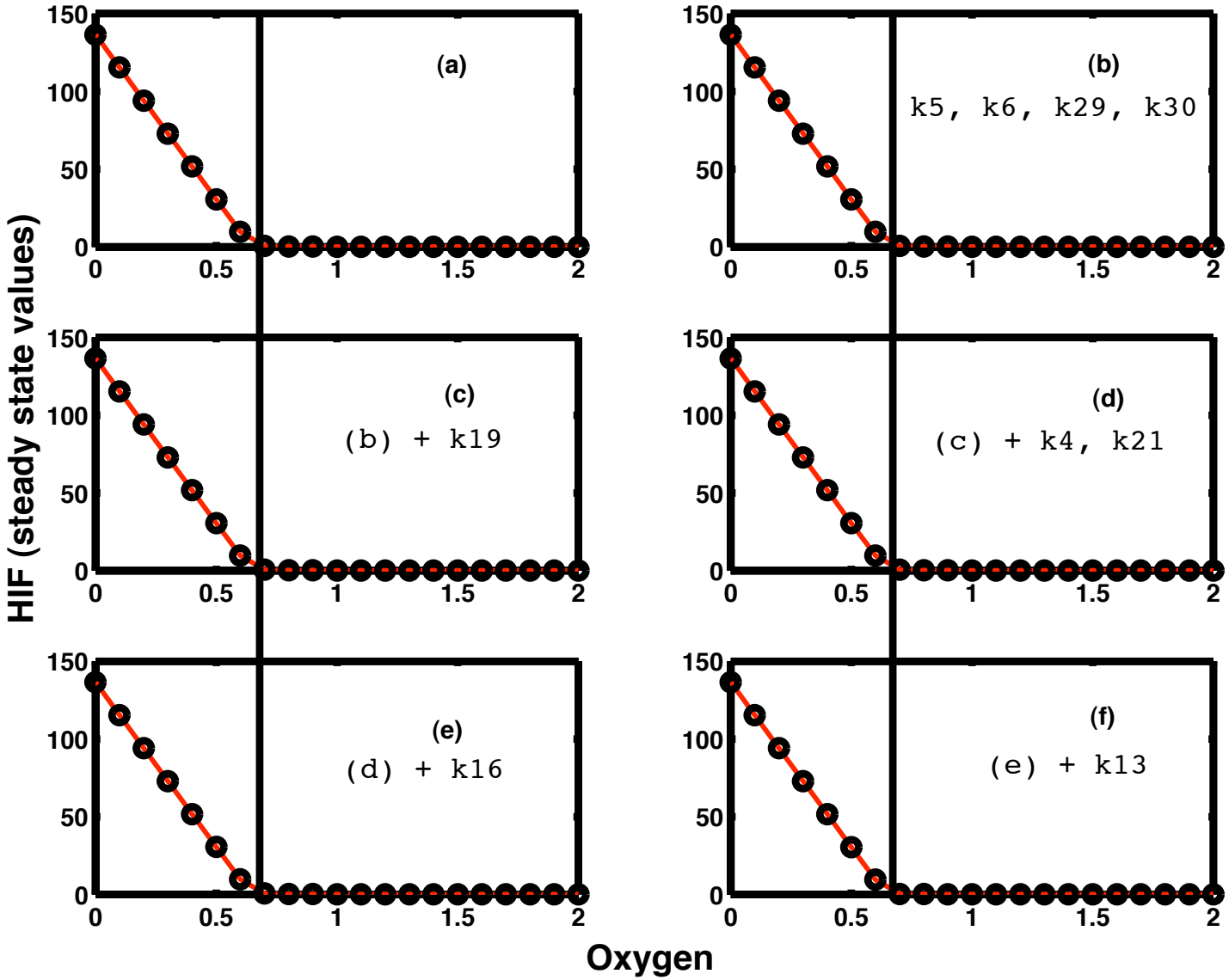
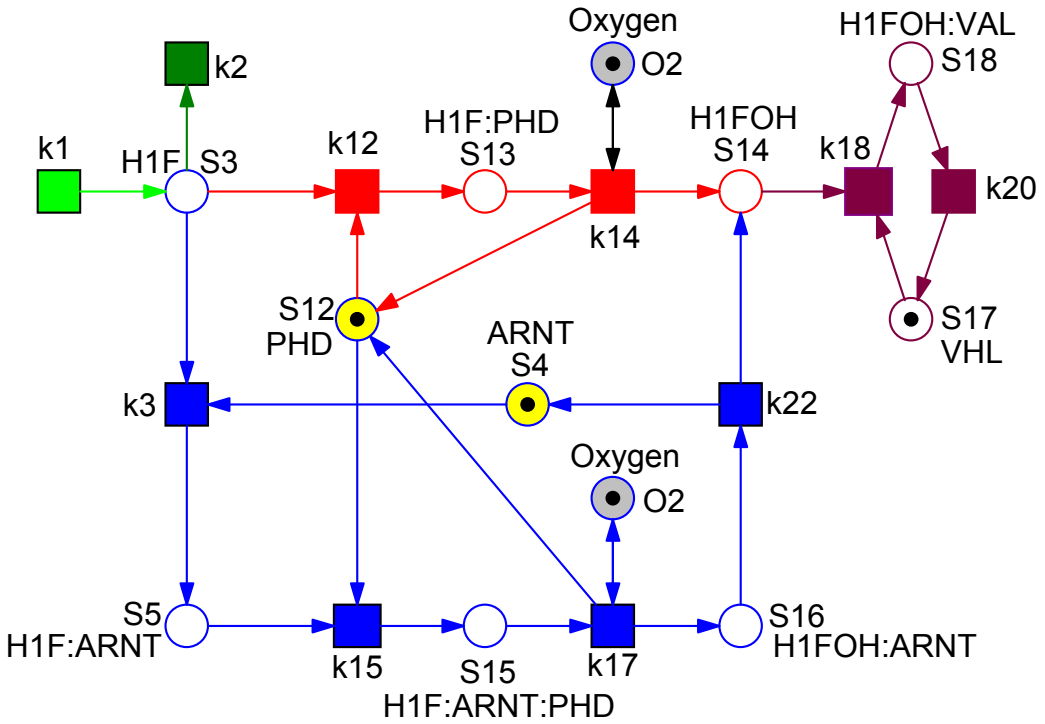
EX7 - HYPOXIA

[HEINER, SRIRAM 2010]

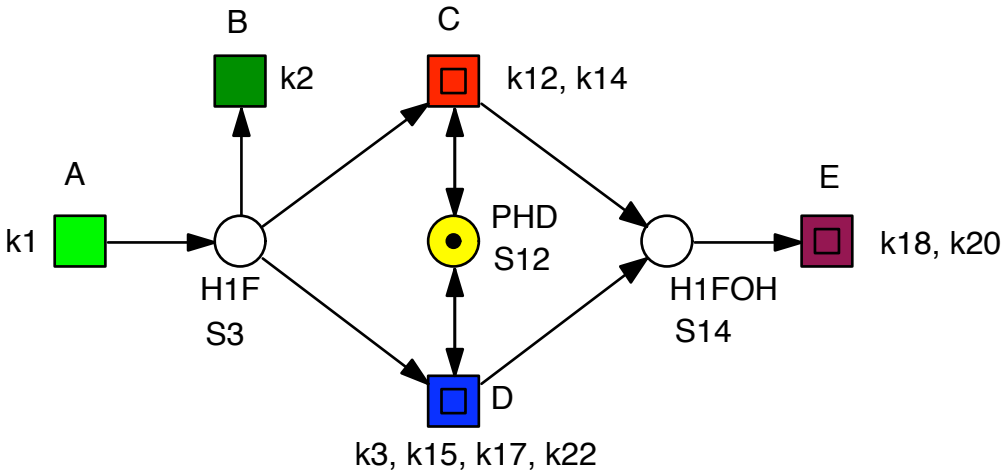



HIF (steady state values)
Oxygen
(a)
(b)
k5, k6, k29, k30
(c)
(b) + k19
(d)
(c) + k4, k21
(e)
(d) + k16
(f)
(e) + k13
150
100
50
0
0
0.5
1
1.5
2

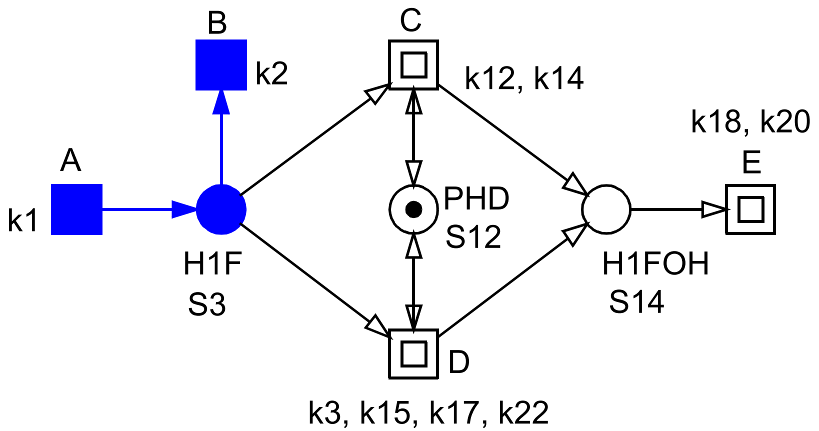
EX7 - HYPOXIA

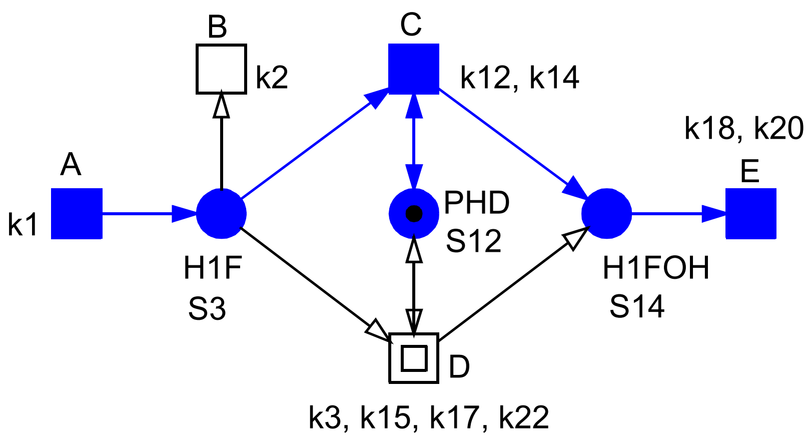

Oxygen
O2
H1FOH:VAL
S18
k2
k1
H1F
S3
k12
H1F:PHD
S13
H1FOH
S14
k18
k20
k14
S12
PHD
S17
VHL
ARNT
S4
k3
k22
Oxygen
O2
S5
H1F:ARNT
k15
S15
H1F:ARNT:PHD
k17
S16
H1FOH:ARNT

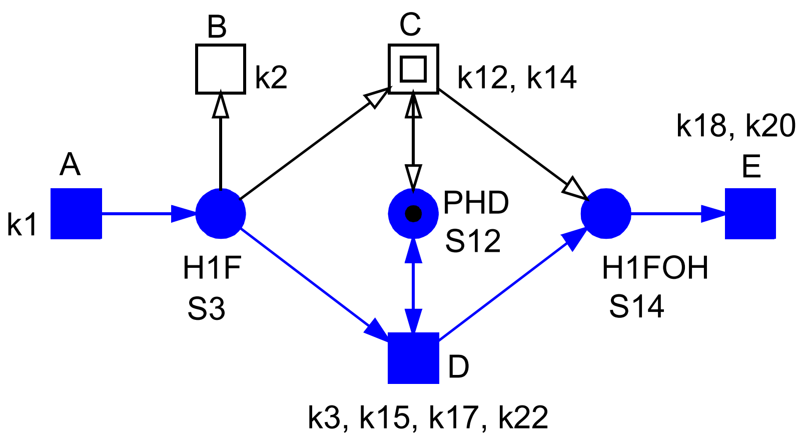
EX7 - HYPOXIA

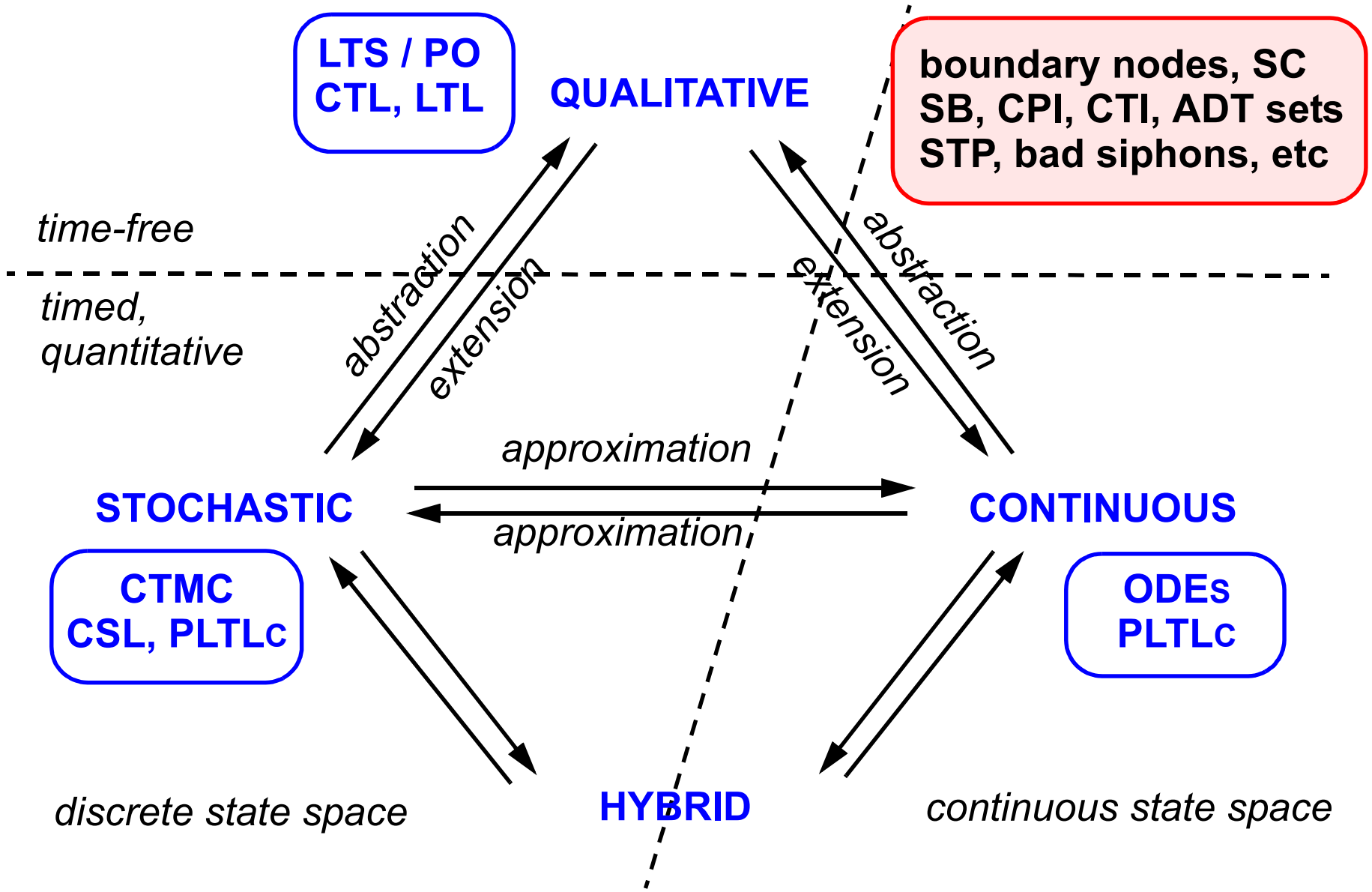

B
C
k2
k12, k14
A
E
k1
PHD
S12
k18, k20
H1F
S3
H1FOH
S14
D
k3, k15, k17, k22

Ex7 - Hypoxia


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


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


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

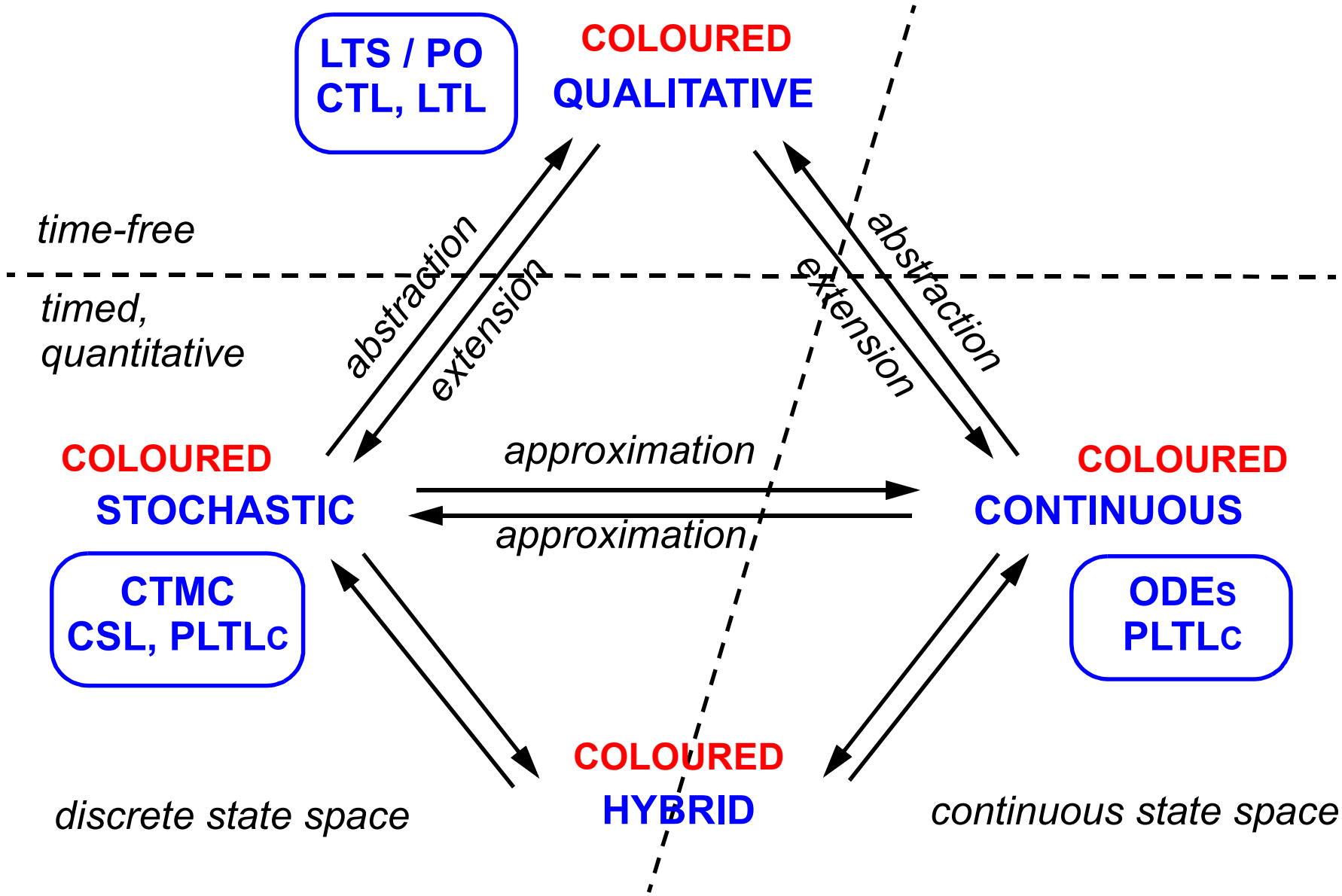

LTS / PO
CTL, LTL
QUALITATIVE
boundary nodes, SC
SB, CPI, CTI, ADT sets
STP, bad siphons, etc
time-free
timed,
quantitative
abstraction
extension
abstraction
extension
approximation
approximation
STOCHASTIC
CONTINUOUS
CTMC
CSL, PLTLc
ODEs
PLTLc
discrete state space
HYBRID
continuous state space

. . . AND THEN THERE WAS COLOUR

Kew Gardens, 24/04/2011

monika.heiner@tu-cottbus.de

COLOURED FRAMEWORK 2011

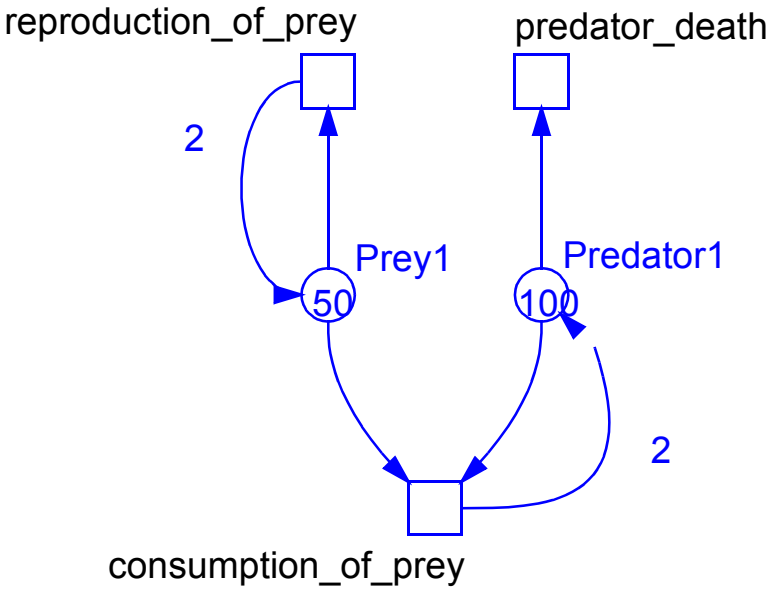


COLOUR -

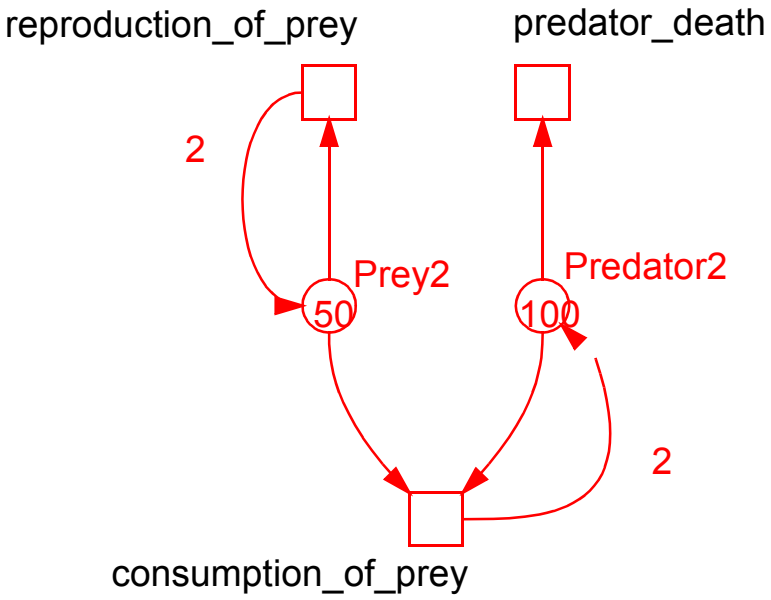
WHAT FOR ?

EX1: PREY - PREDATOR

sub-system1



sub-system2



EX1: PREY - PREDATOR

- **definitions**

  colourset *CS = 1-2;*

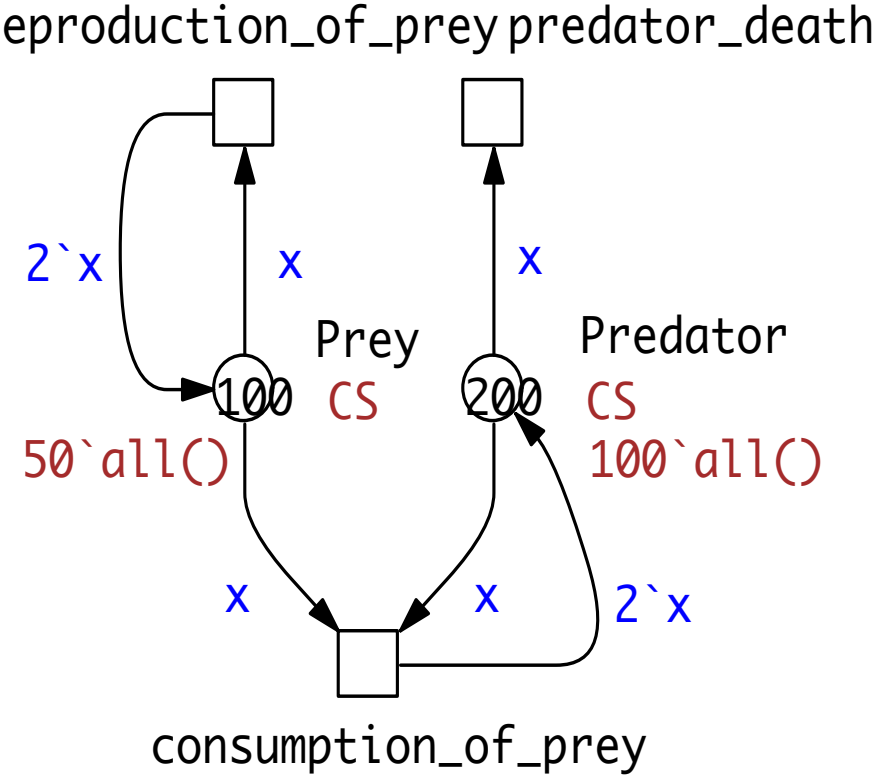
  var *x : CS;*

- **better:**

  const *SIZE = 2;*

  colourset *CS = 1-SIZE;*

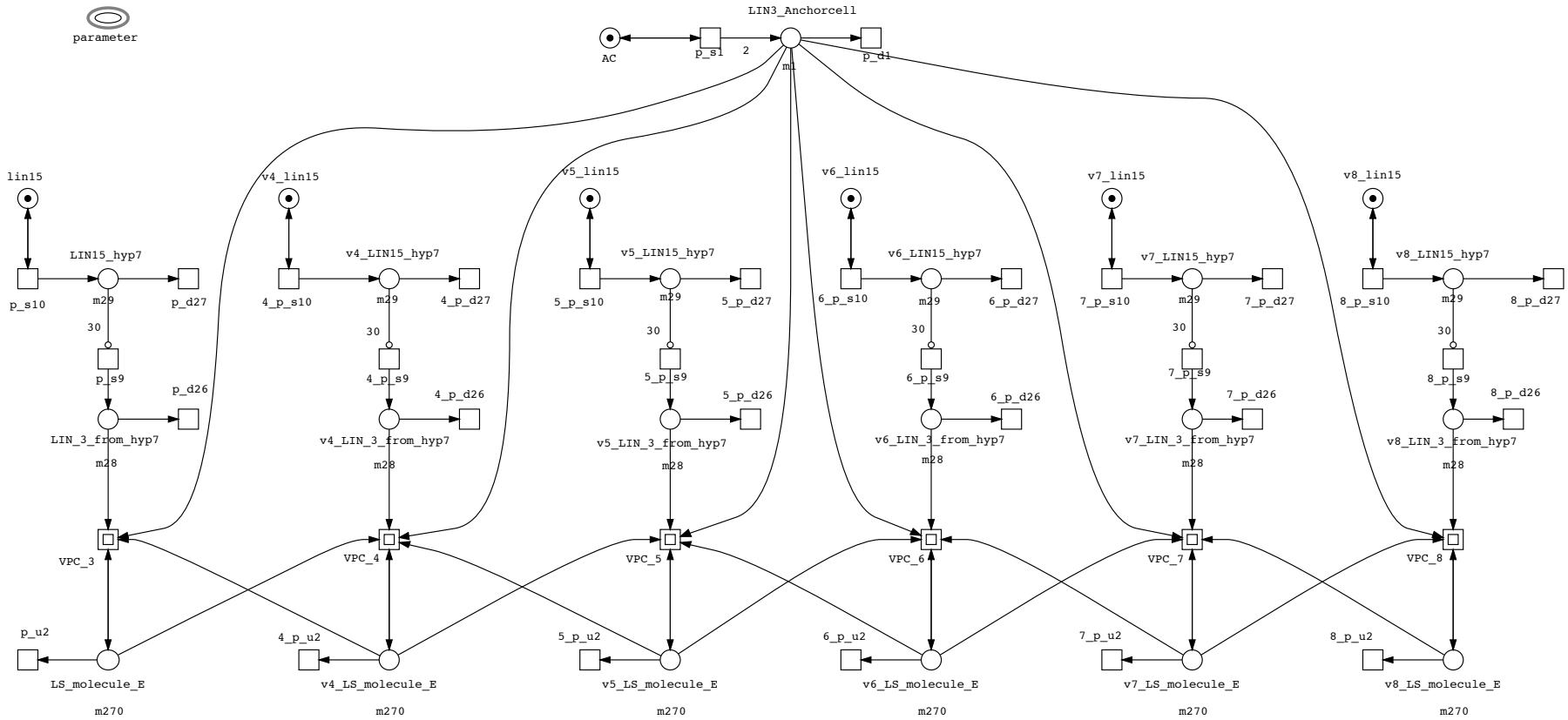
  var *x : CS;*



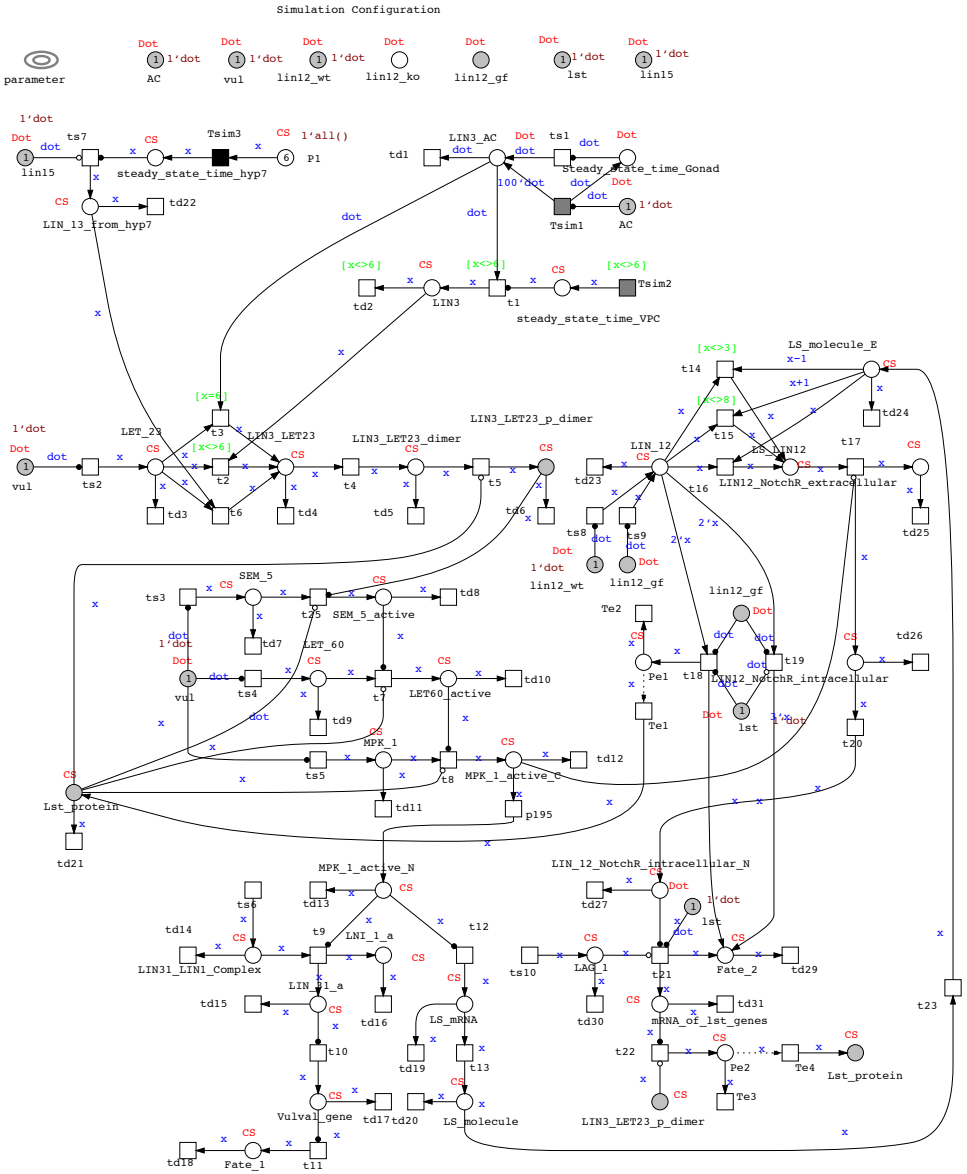
- **changing SIZE adapts the model to various scenarious**

EX2 - C. ELEGANS

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

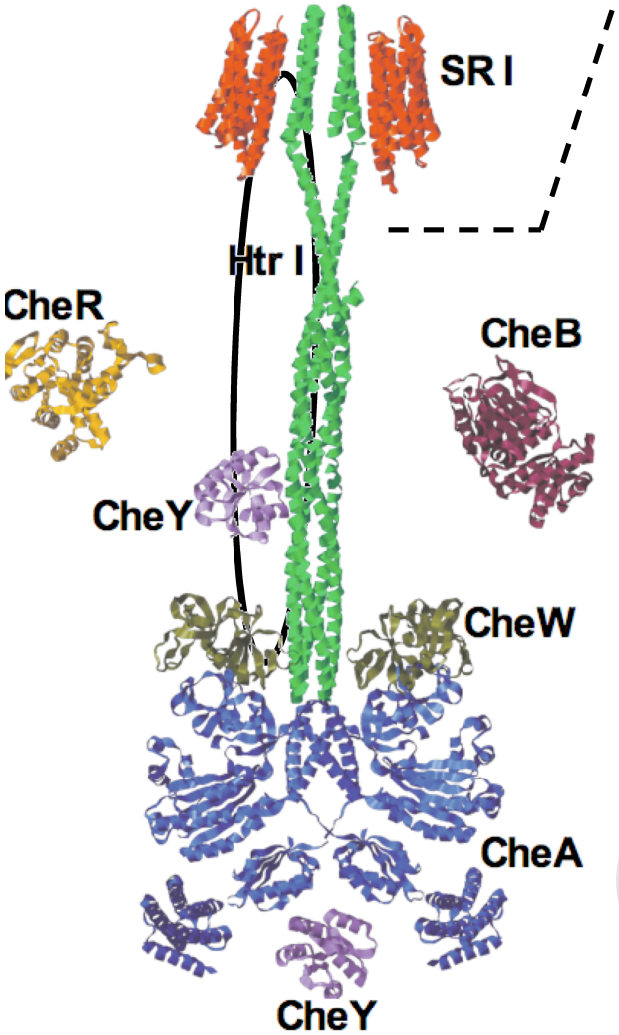


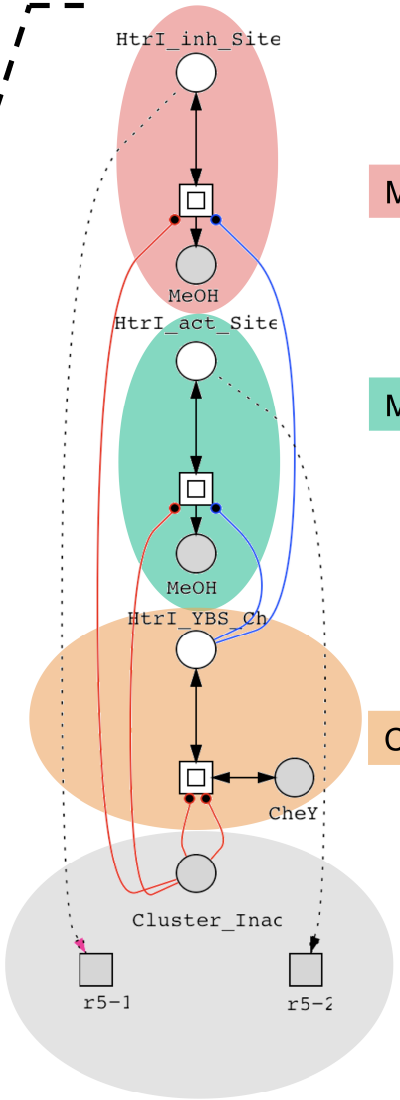
Ex2 - C. Elegans



EX3 - HALOBACTERIUM SALINARUM

[MARWAN 2010]

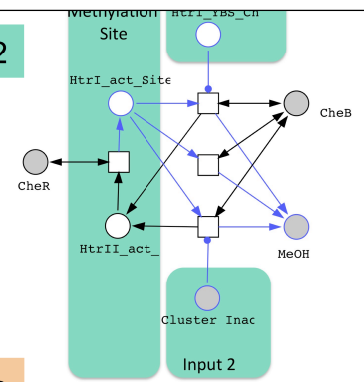




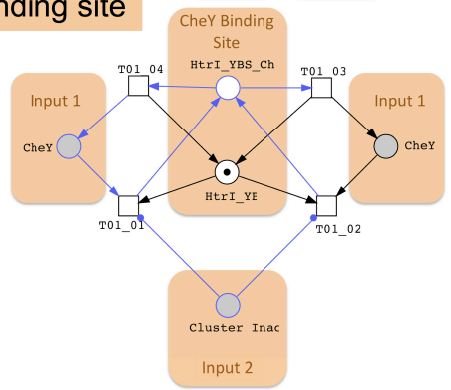
Methylat

cluster type 1/2:	400/850
PLACES:	12,426
TRANSITIONS:	16,577
unfolding:	6 sec
stoch. simulation:	10-15h

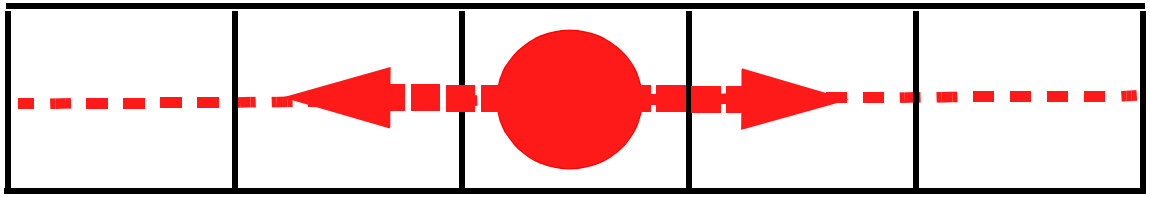
Methylation site 2

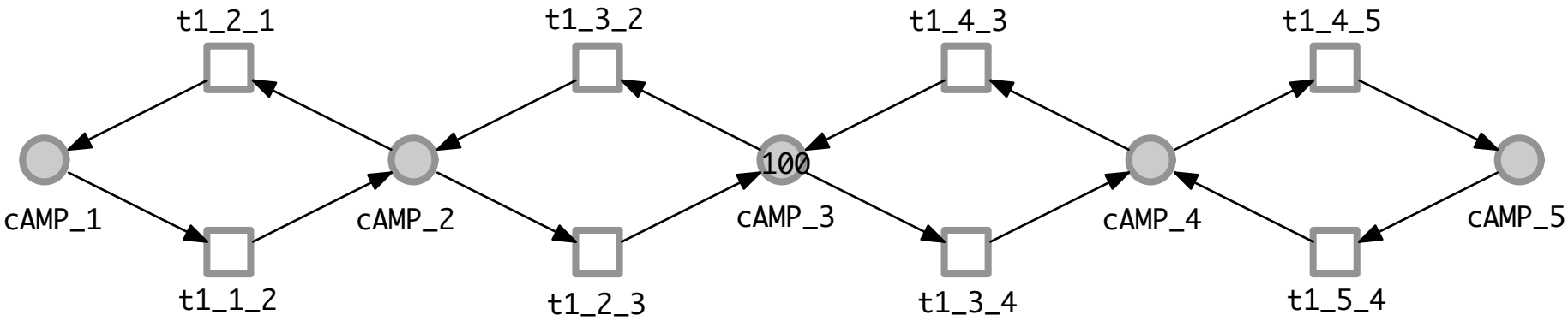


CheY binding site



EX4: DIFFUSION - 1D



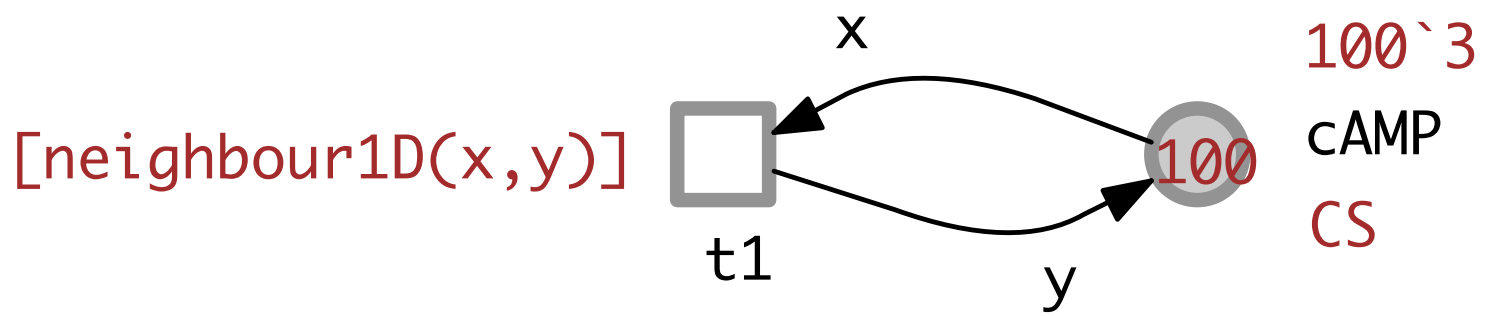


EX4: DIFFUSION - 1D

definitions

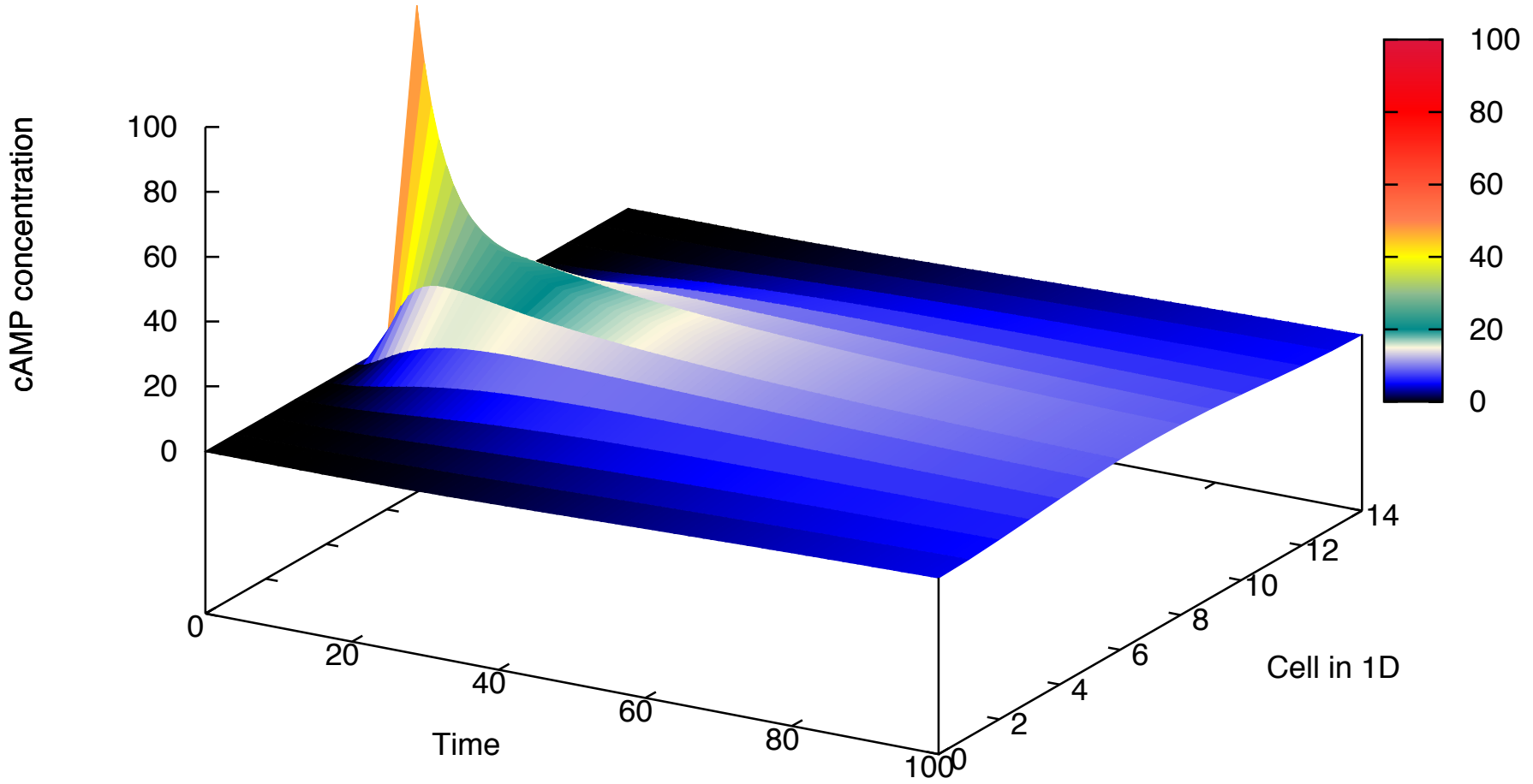
```
const D1 = 5;              // grid size
colorset CS = 1-D1;        // grid positions
var x,y : CS;

function neighbour1D (CS x,a) bool:
  // a is neighbour of x
  ( a=x-1 | a=x+1)  & (1<=a) & (a<=D1);
```



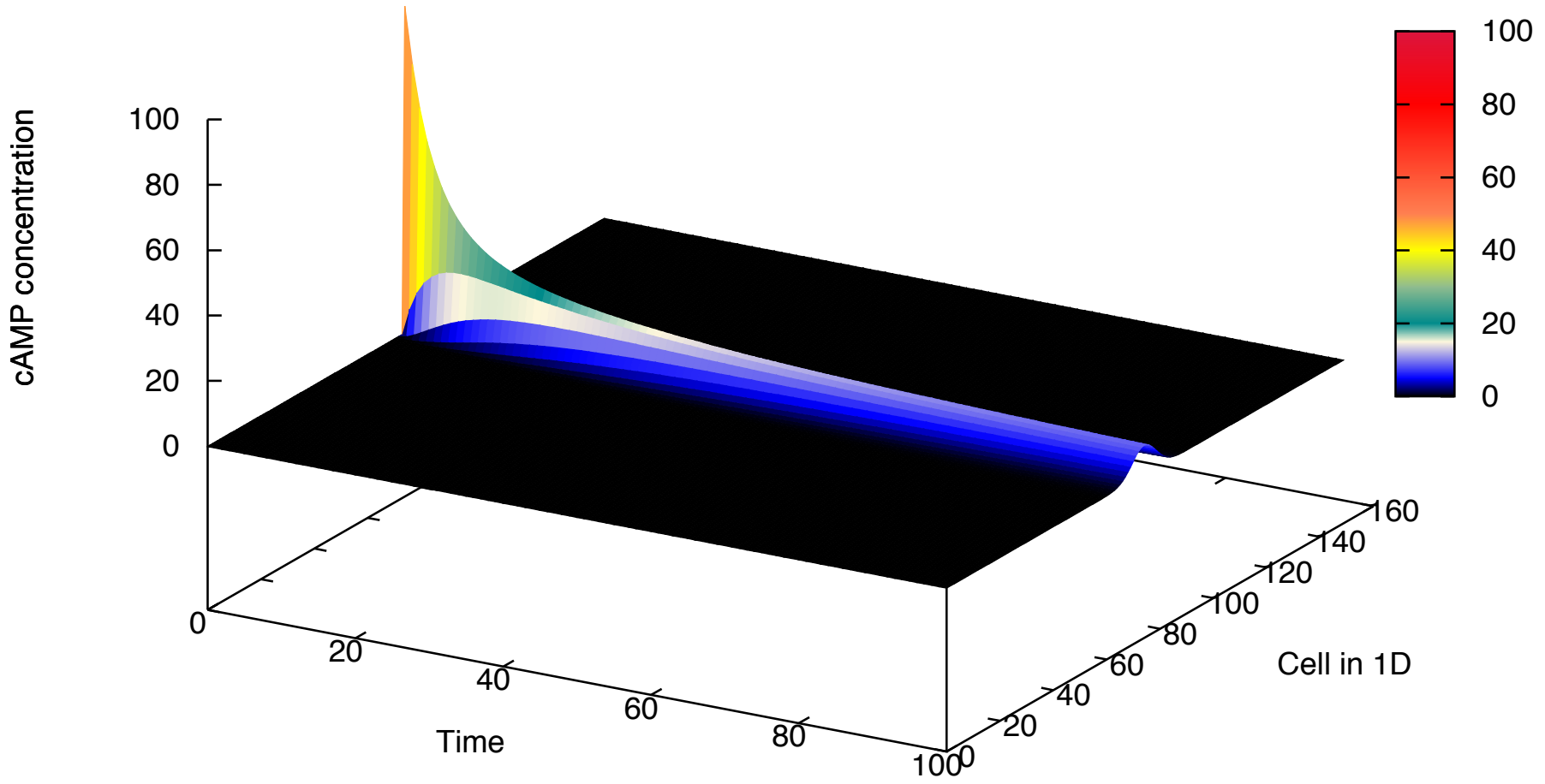
$$
\begin{aligned}
\frac{dc_1}{dt} &= k \cdot c_2 - k \cdot c_1 \\
\frac{dc_2}{dt} &= k \cdot c_1 + k \cdot c_3 - 2 \cdot k \cdot c_2 \\
\frac{dc_3}{dt} &= k \cdot c_2 + k \cdot c_4 - 2 \cdot k \cdot c_3 \\
\frac{dc_4}{dt} &= k \cdot c_3 + k \cdot c_5 - 2 \cdot k \cdot c_4 \\
\frac{dc_5}{dt} &= k \cdot c_4 - k \cdot c_5
\end{aligned}
$$

EX4: DIFFUSION - 1D



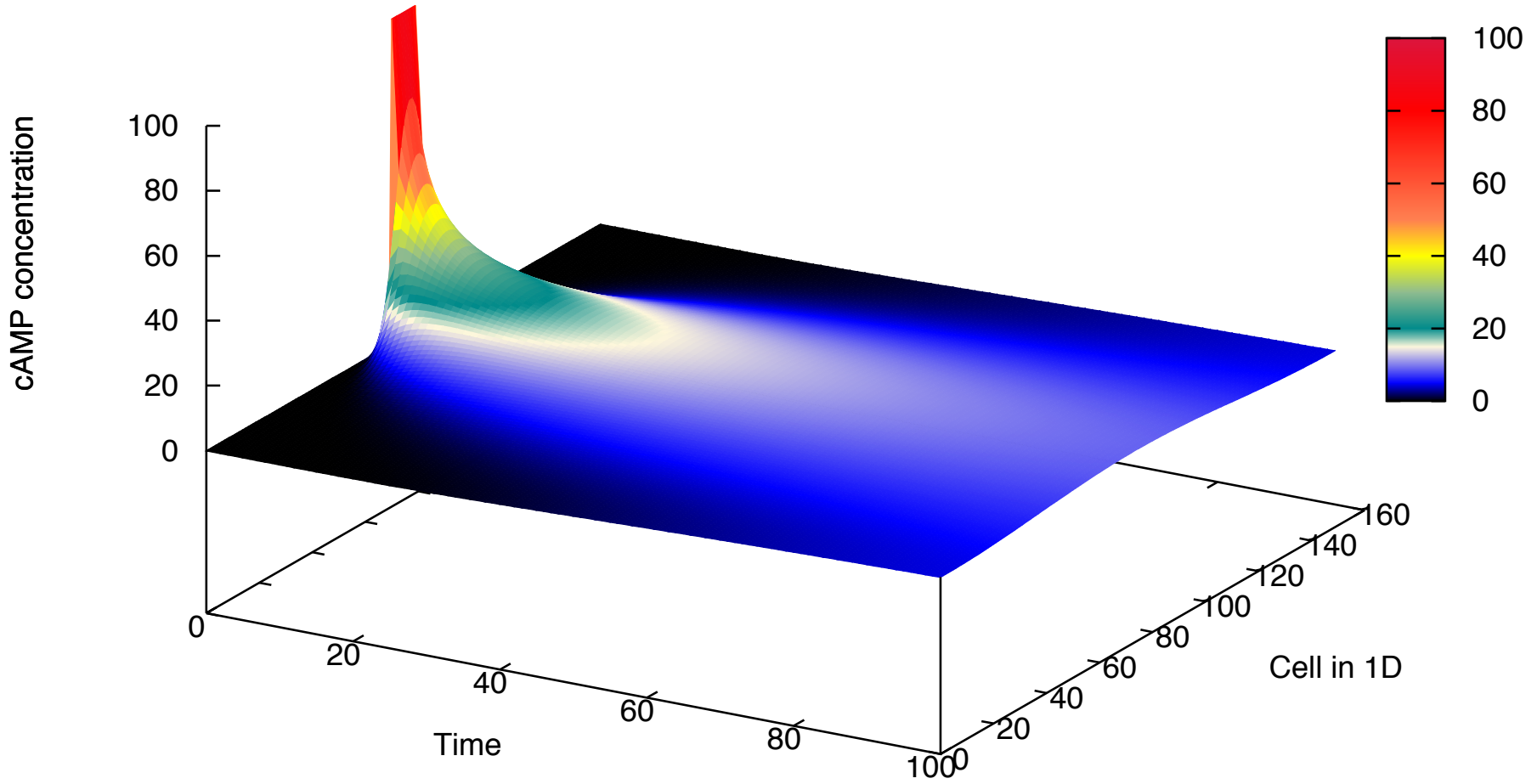
15 GRID POSITIONS

EX4: DIFFUSION - 1D



150 GRID POSITIONS, NO SCALING

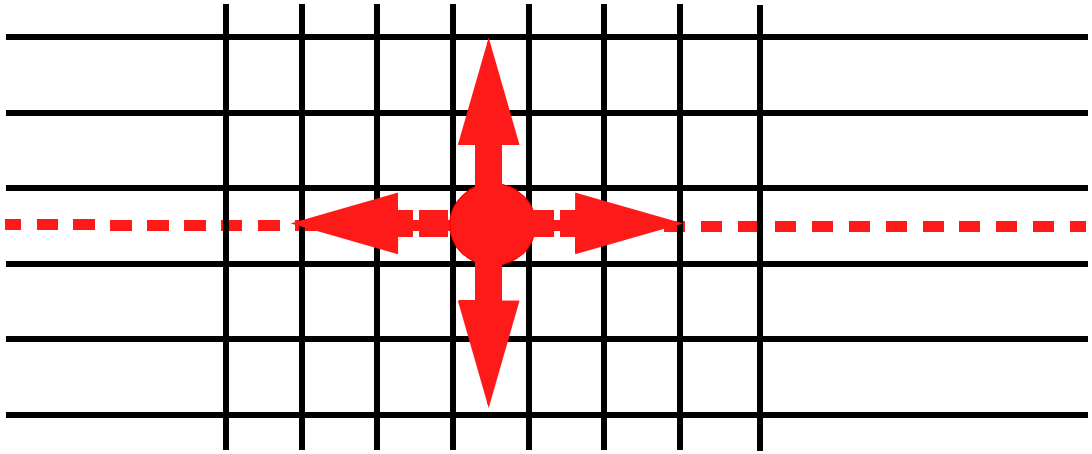
EX4: DIFFUSION - 1D



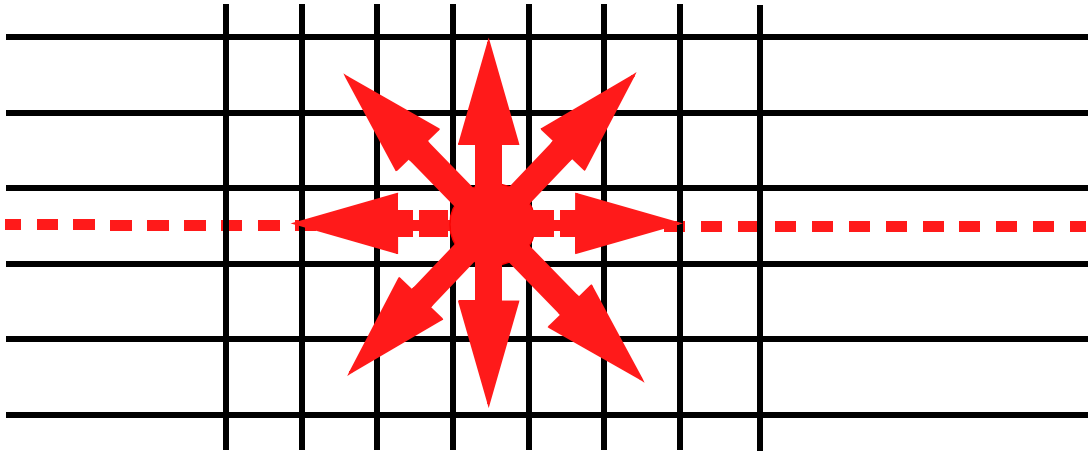
150 GRID POSITIONS, SCALING OF INITIAL MARKING AND RATES

EX4: DIFFUSION - 2D4 NEIGHBOURHOOD

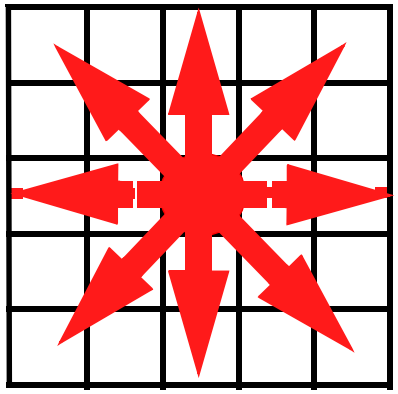
SCHEME



SCHEME



SCHEME



definitions

```
const D1 = 5;                    // grid size first dimension
const D2 = 5;                    // grid size second dimension

colorset CD1 = 1-D1;             // row index
colorset CD2 = 1-D2;             // column index
colorset Grid2D = CD1 x CD2;     // 2D grid

var x, a : CD1;
var y, b : CD2;
```

EX4: DIFFUSION - 2D4 NEIGHBOURHOOD

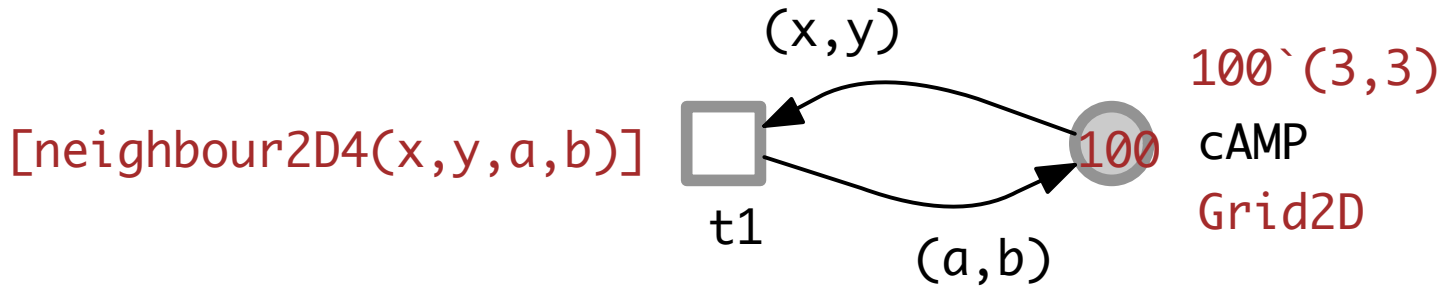
four neighbours

function *neighbour2D4 (CD1 x, CD2 y, CD1 a, CD2 b)* ***bool****:*

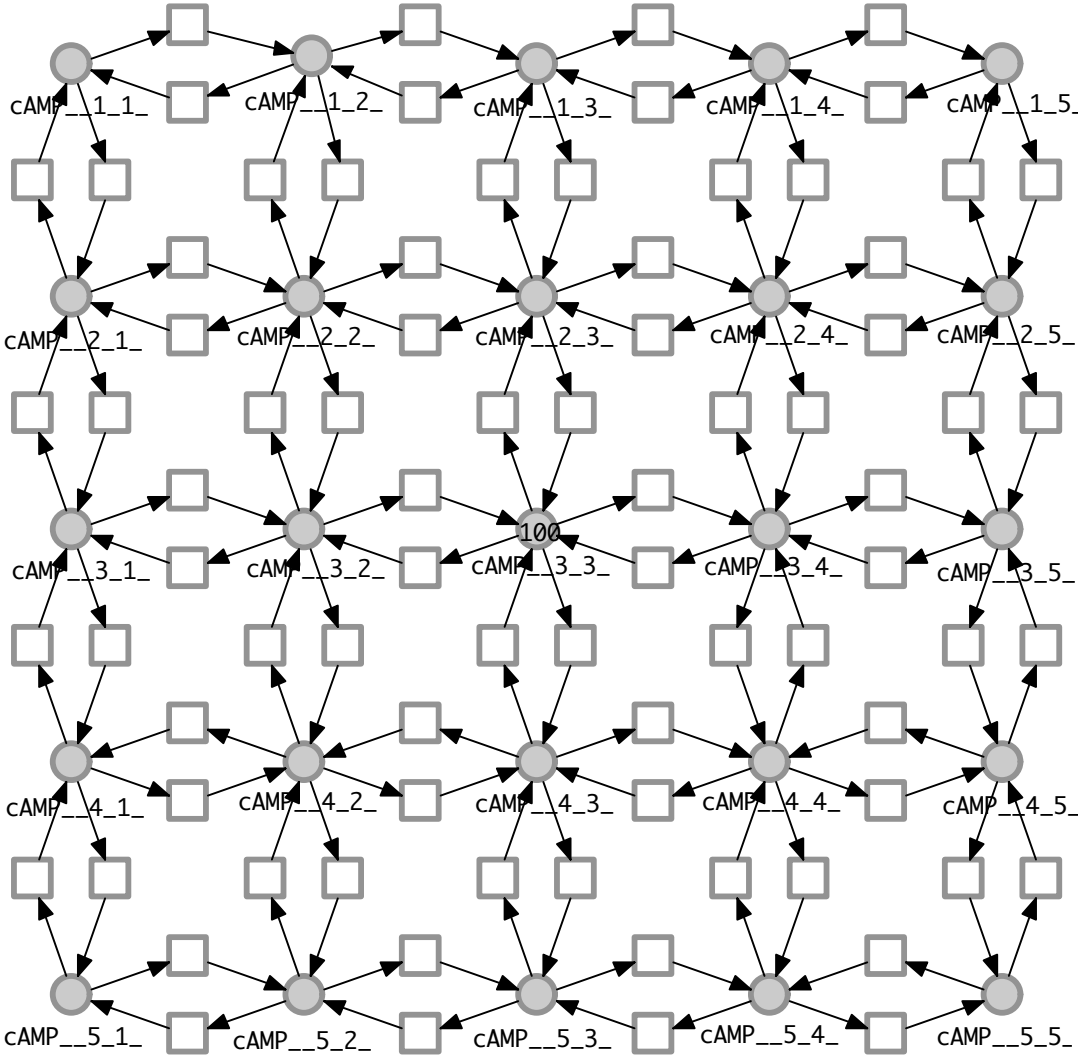
// (a,b) is one of the up to four neighbours of (x,y)

(a=x & b=y-1) | (a=x & b=y+1)

| (b=y & a=x-1) | (b=y & a=x+1);



EX4: DIFFUSION - 2D4 NEIGHBOURHOOD



eight neighbours

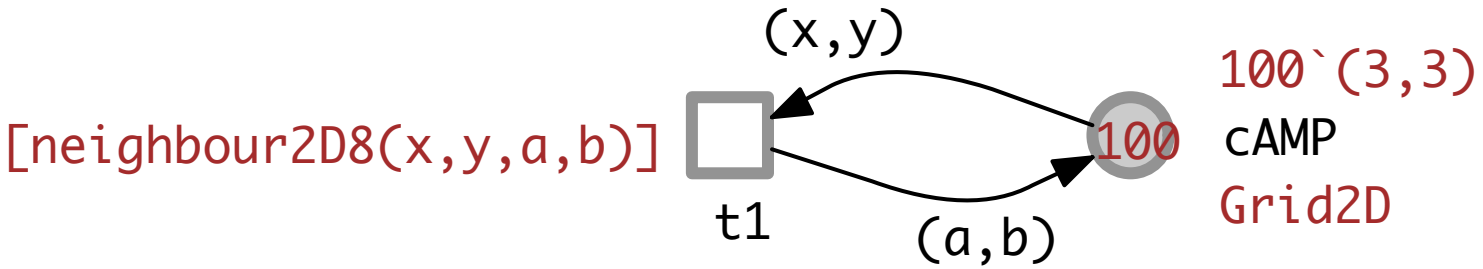
function *neighbour2D8 (CD1 x, CD2 y, CD1 a, CD2 b)* ***bool****:*

// (a,b) is one of the up to eight neighbours of (x,y)

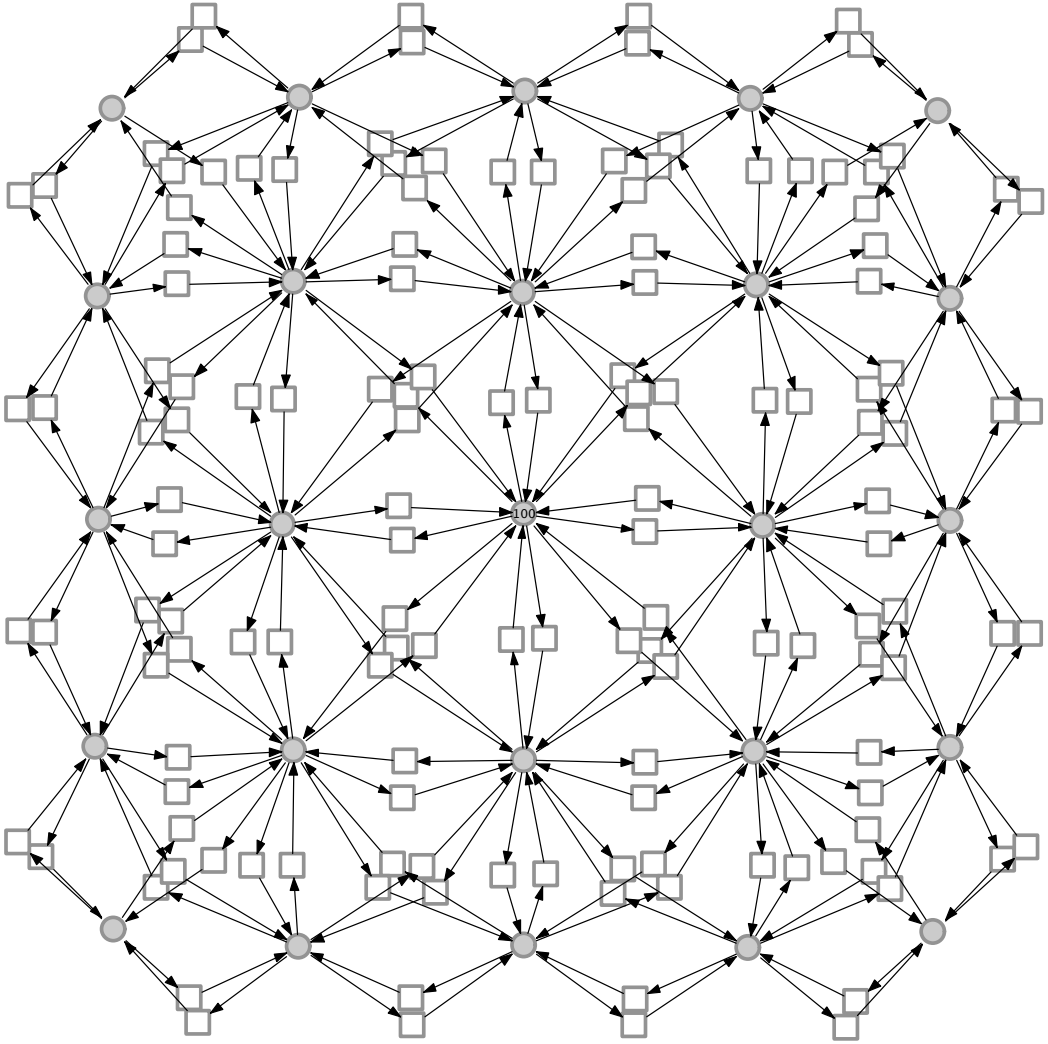
(a=x-1 | a=x | a=x+1) & (b = y-1 | b=y | b=y+1)

& (!(a=x & b=y))

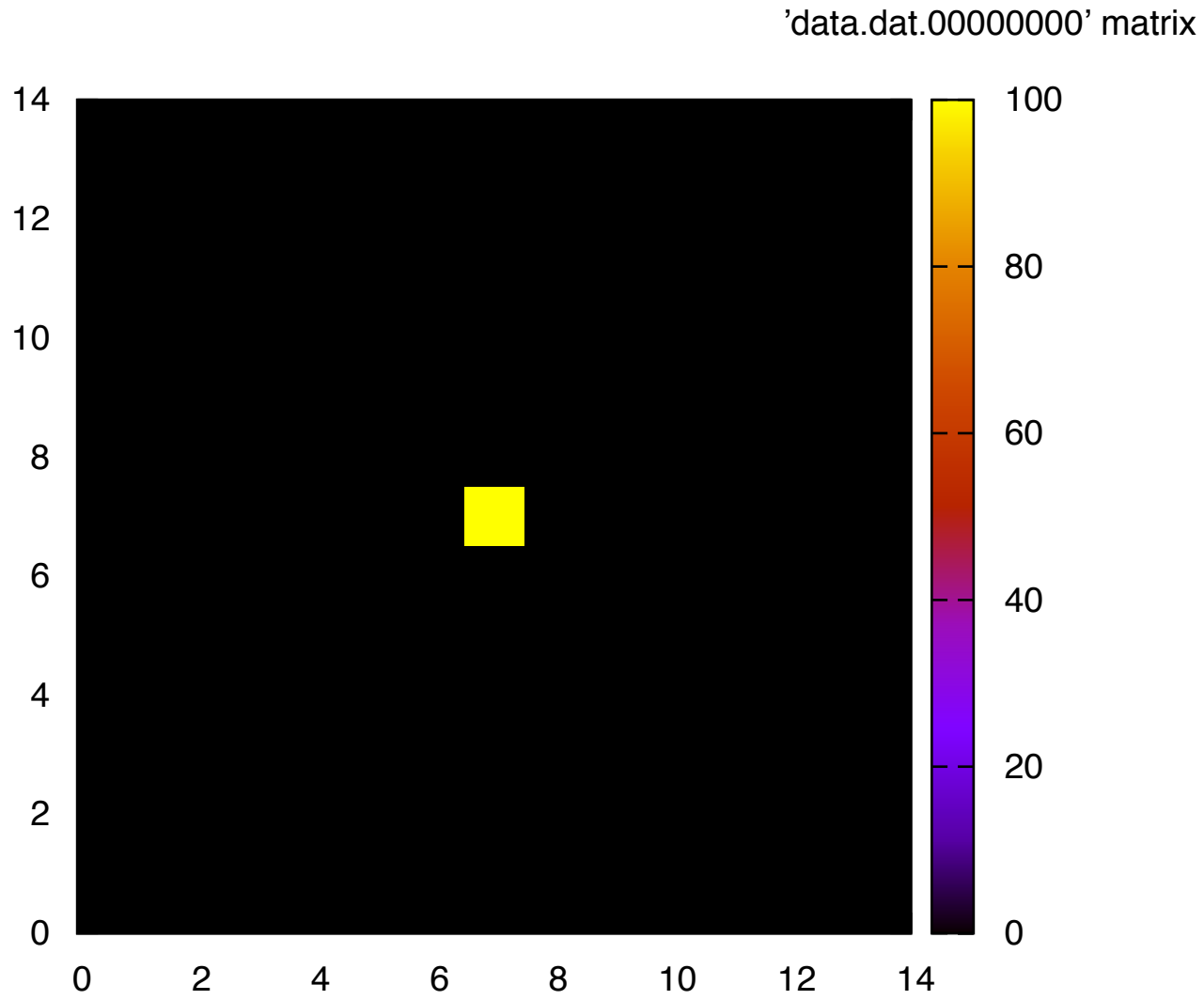
& (1<=a & a<=D1) & (1<=b & b<=D2);



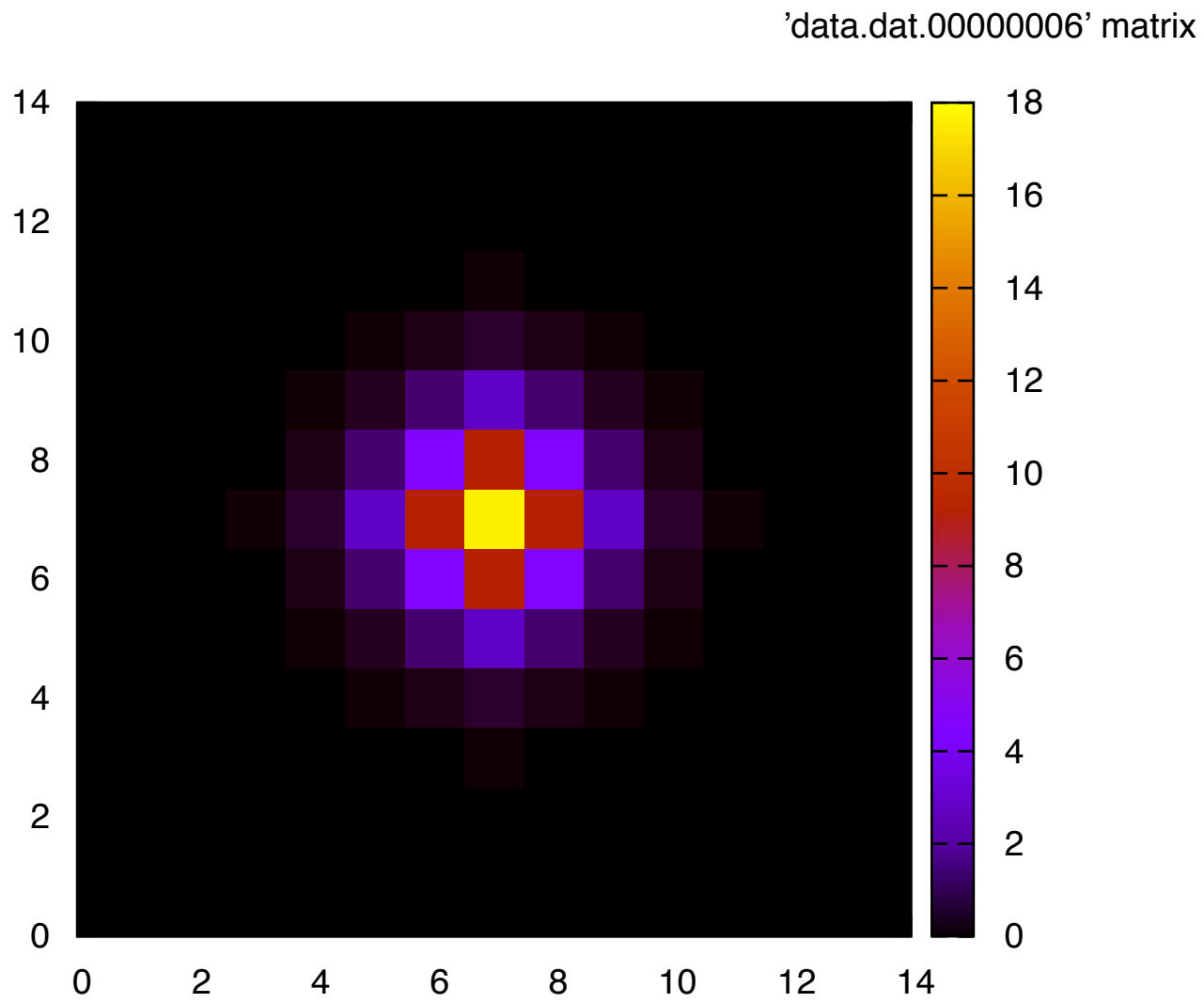
EX4: DIFFUSION - 2D8 NEIGHBOURHOOD



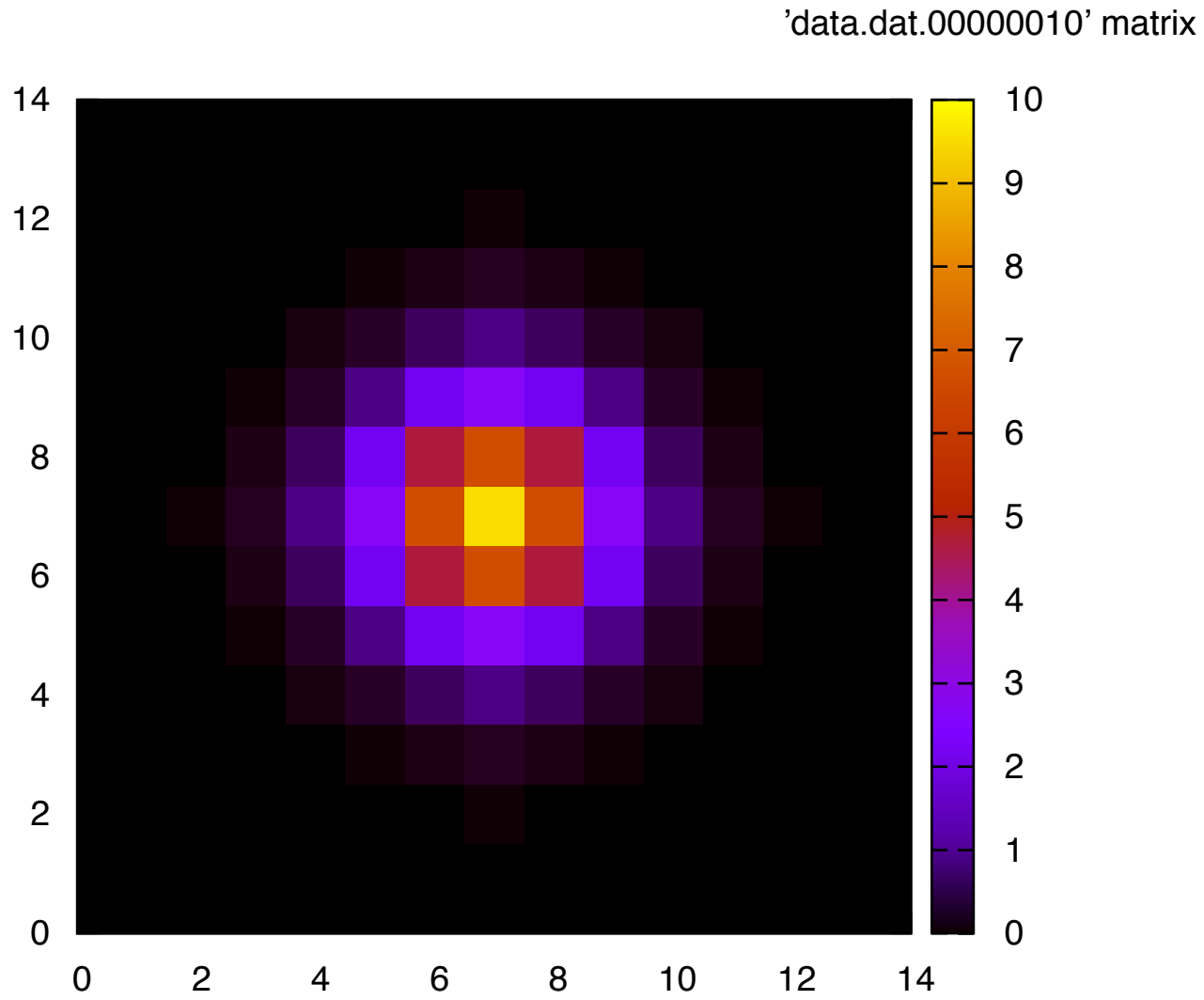
EX4: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15



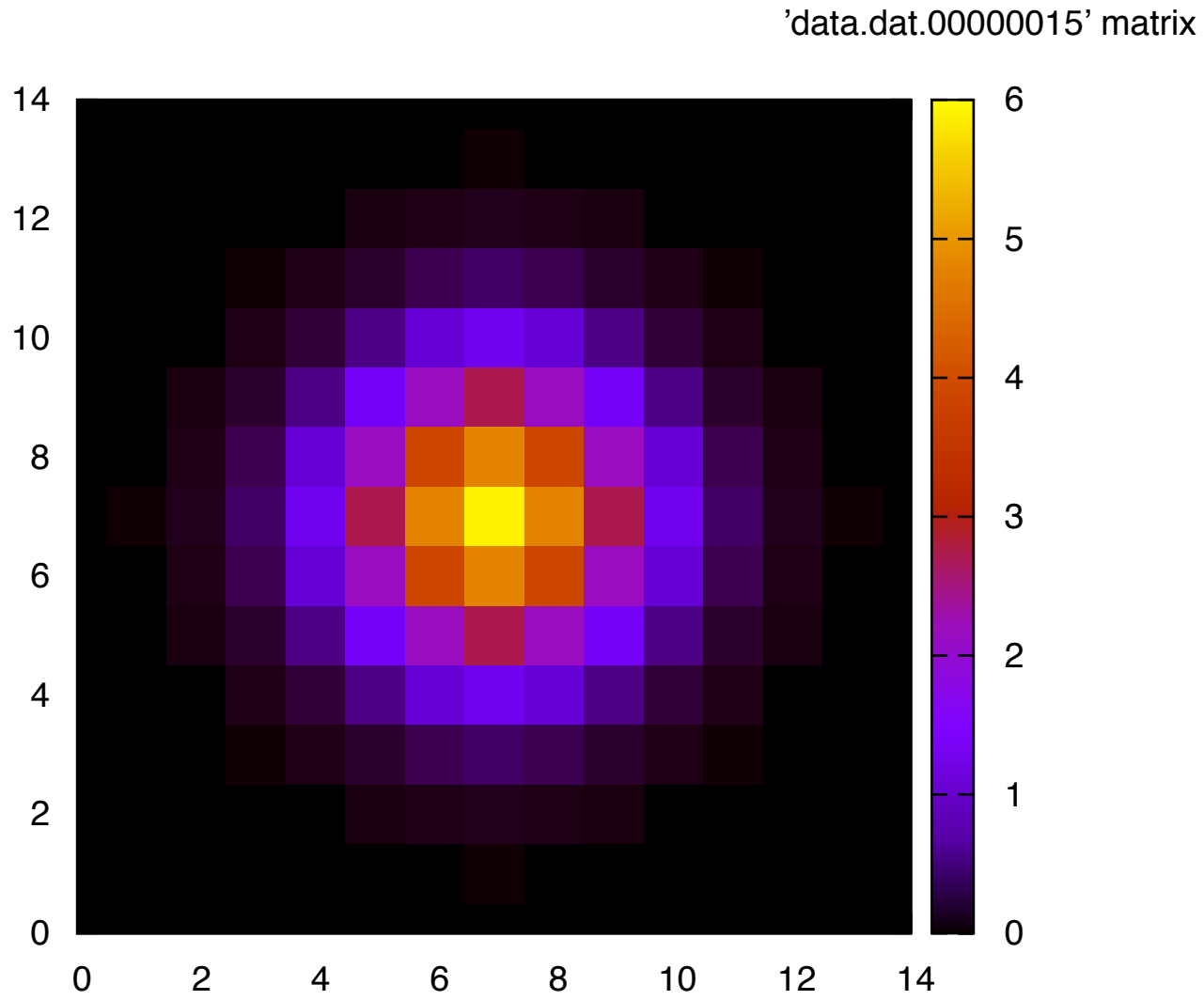
EX4: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15



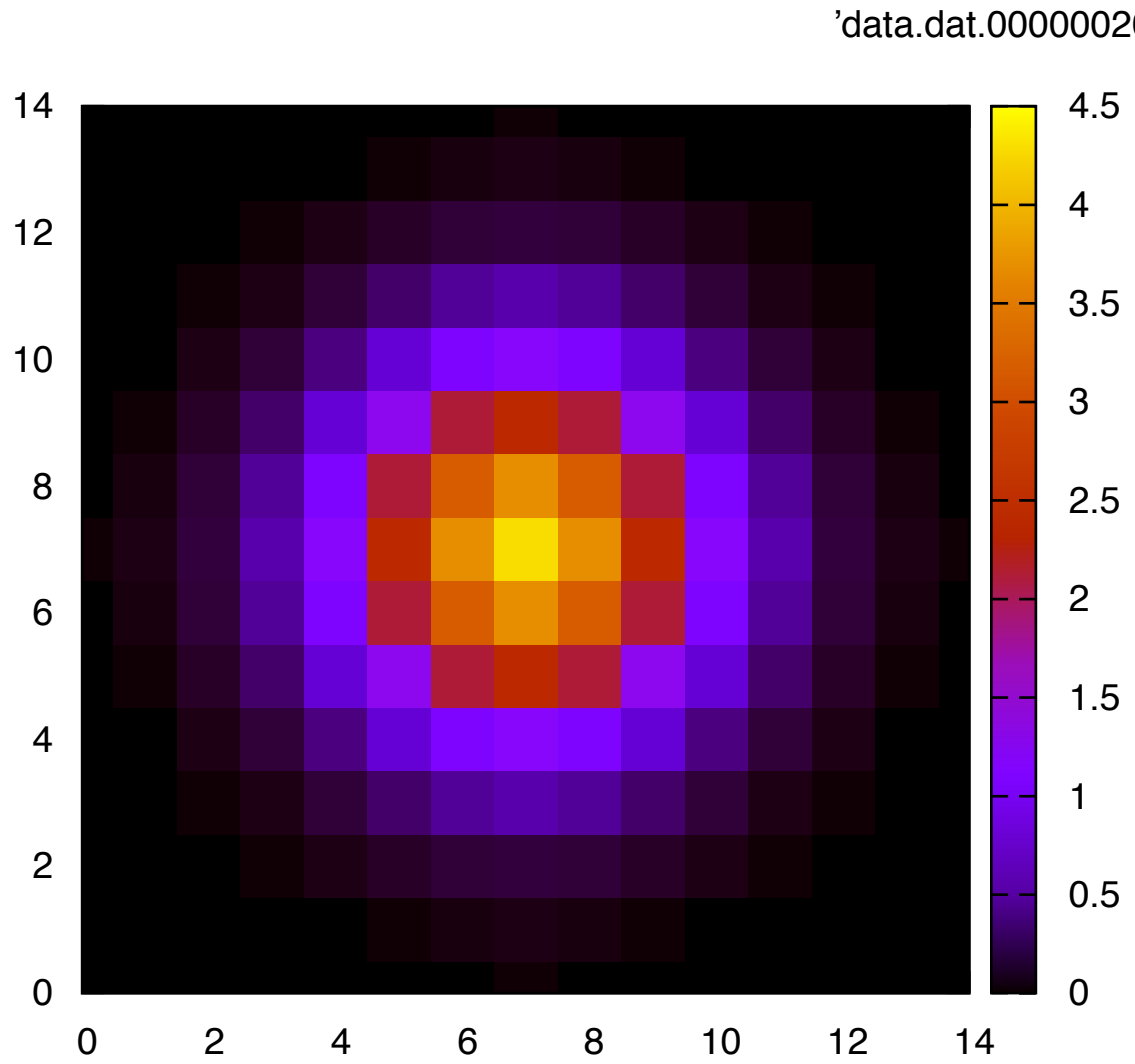
EX4: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15



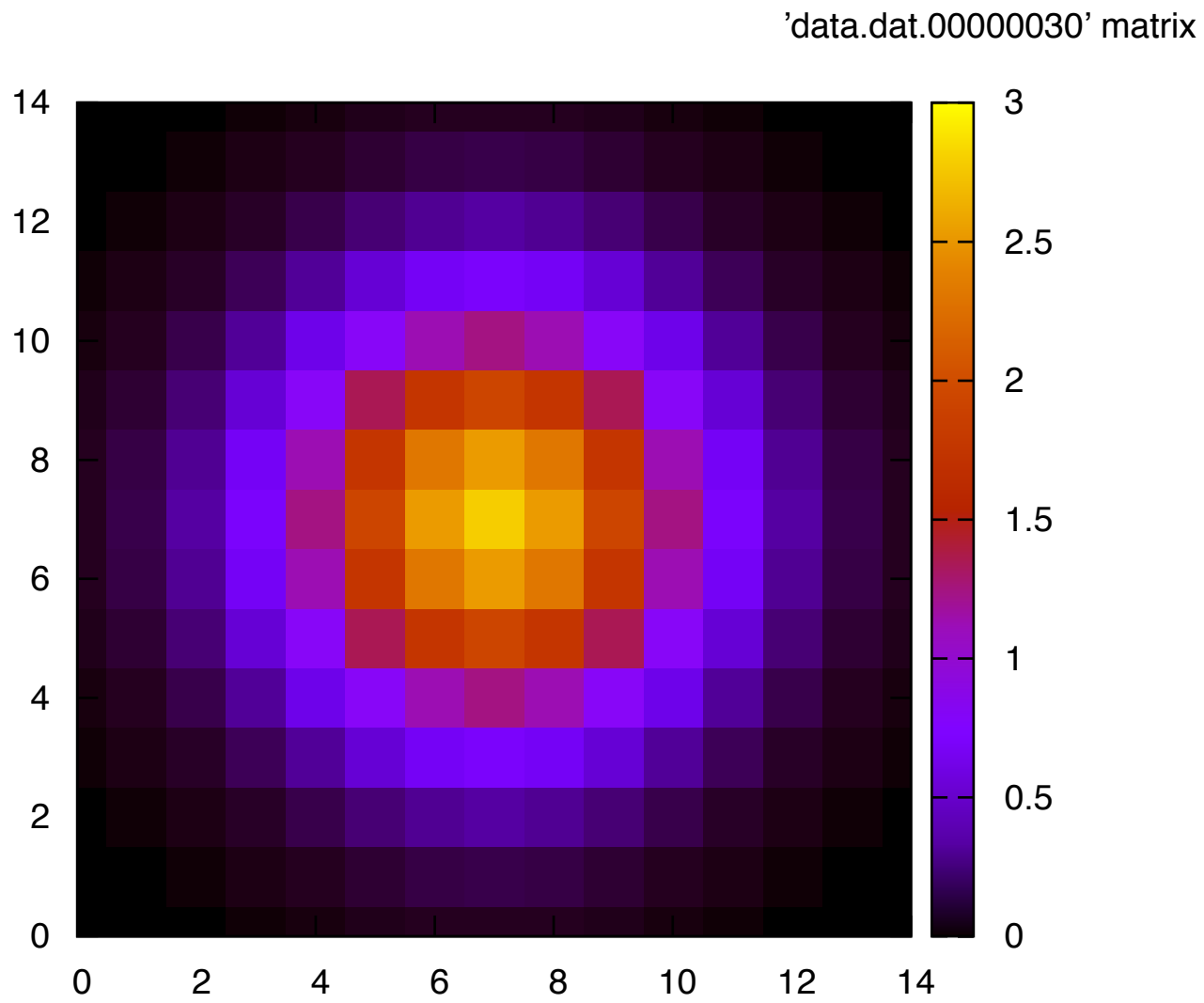
EX4: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15



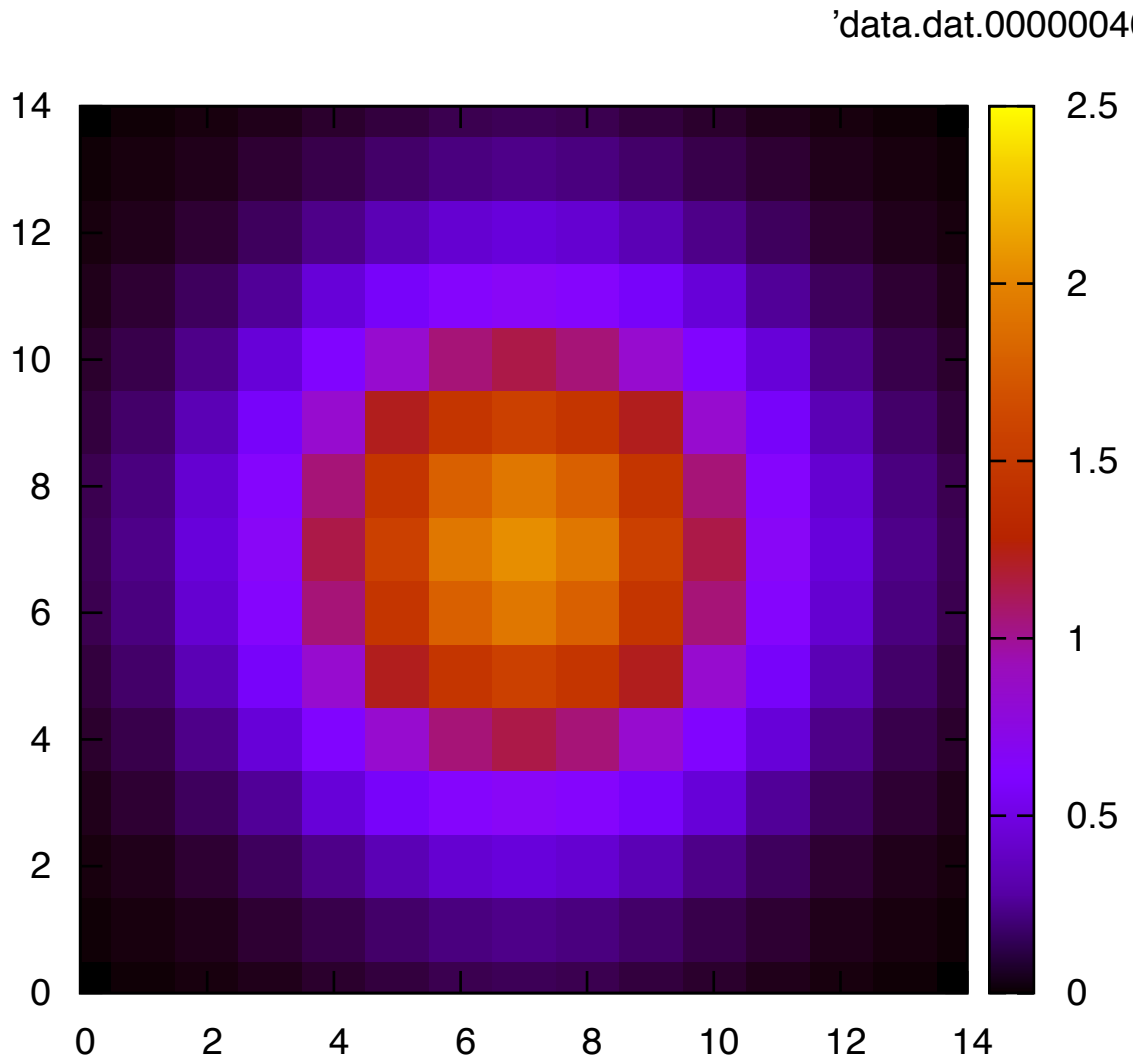
EX4: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15



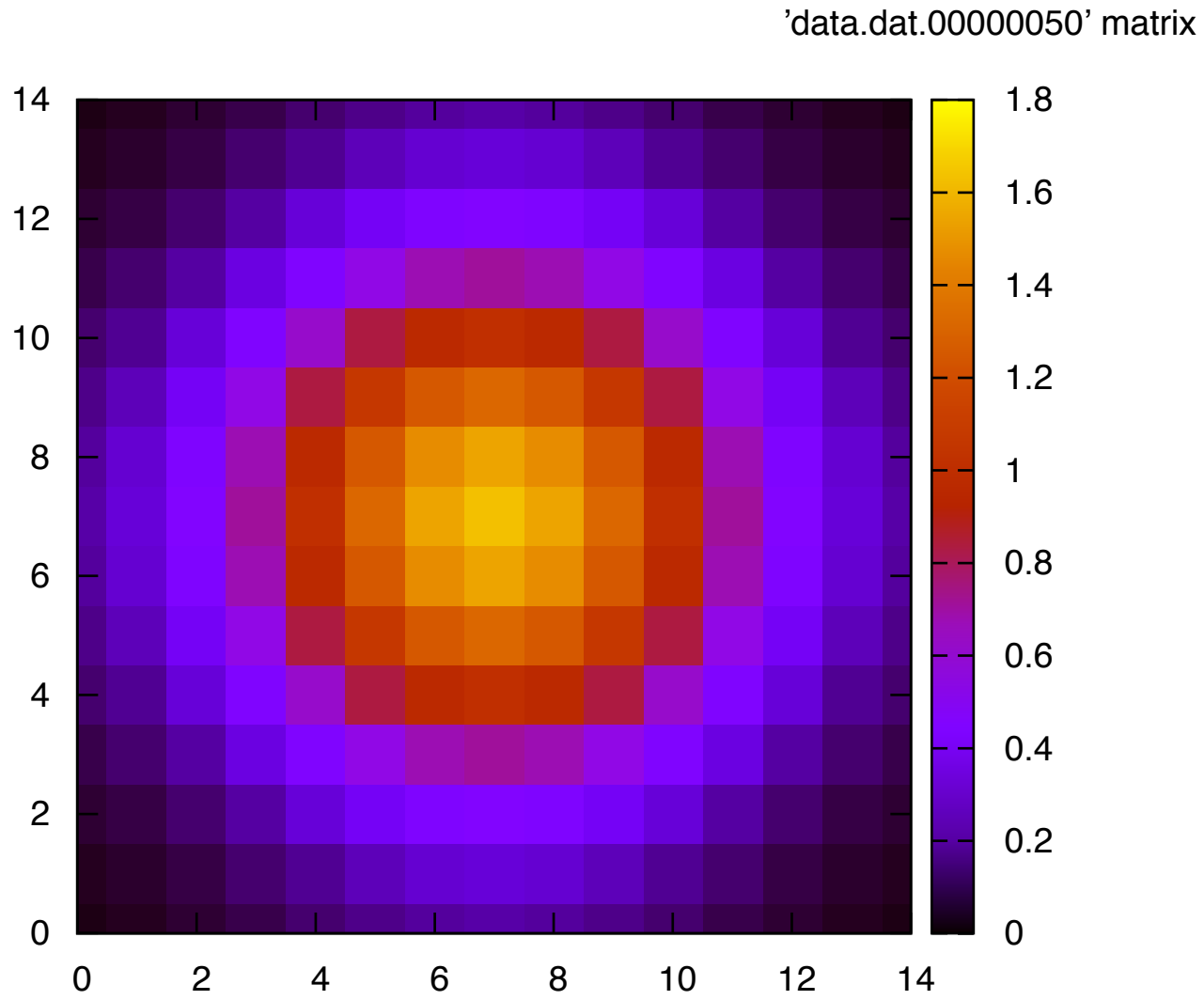
EX4: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15



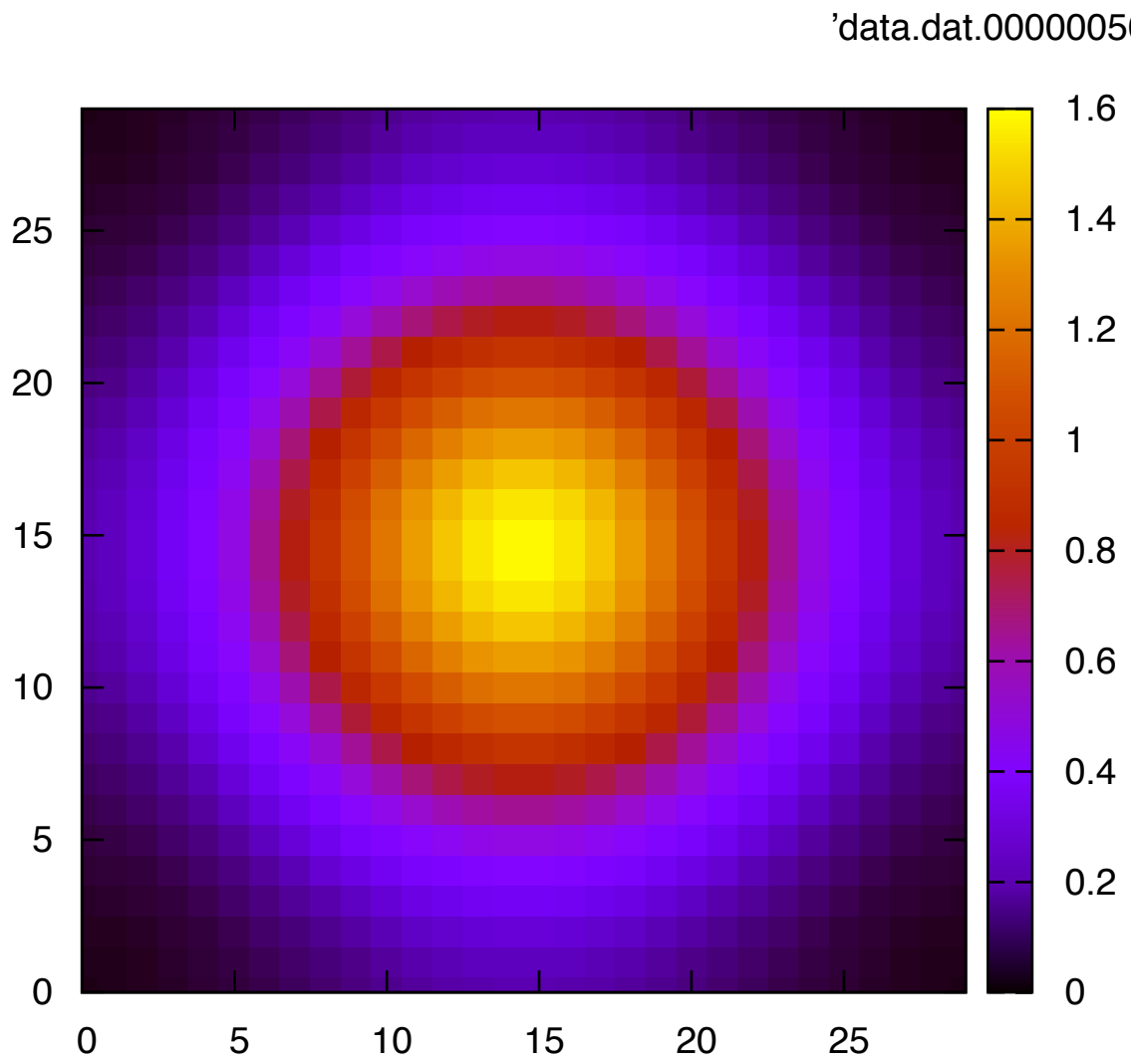
EX4: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15



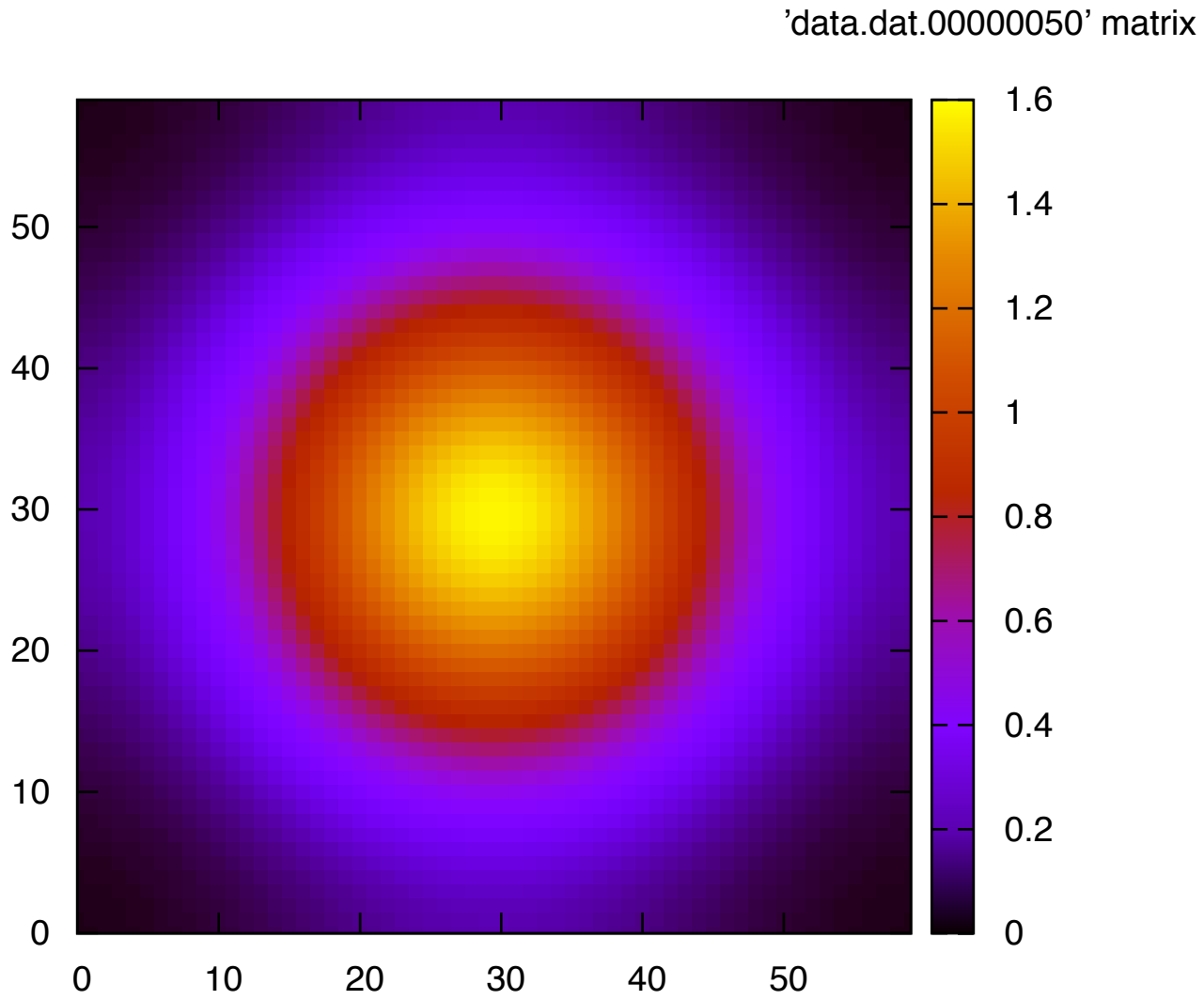
EX4: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15



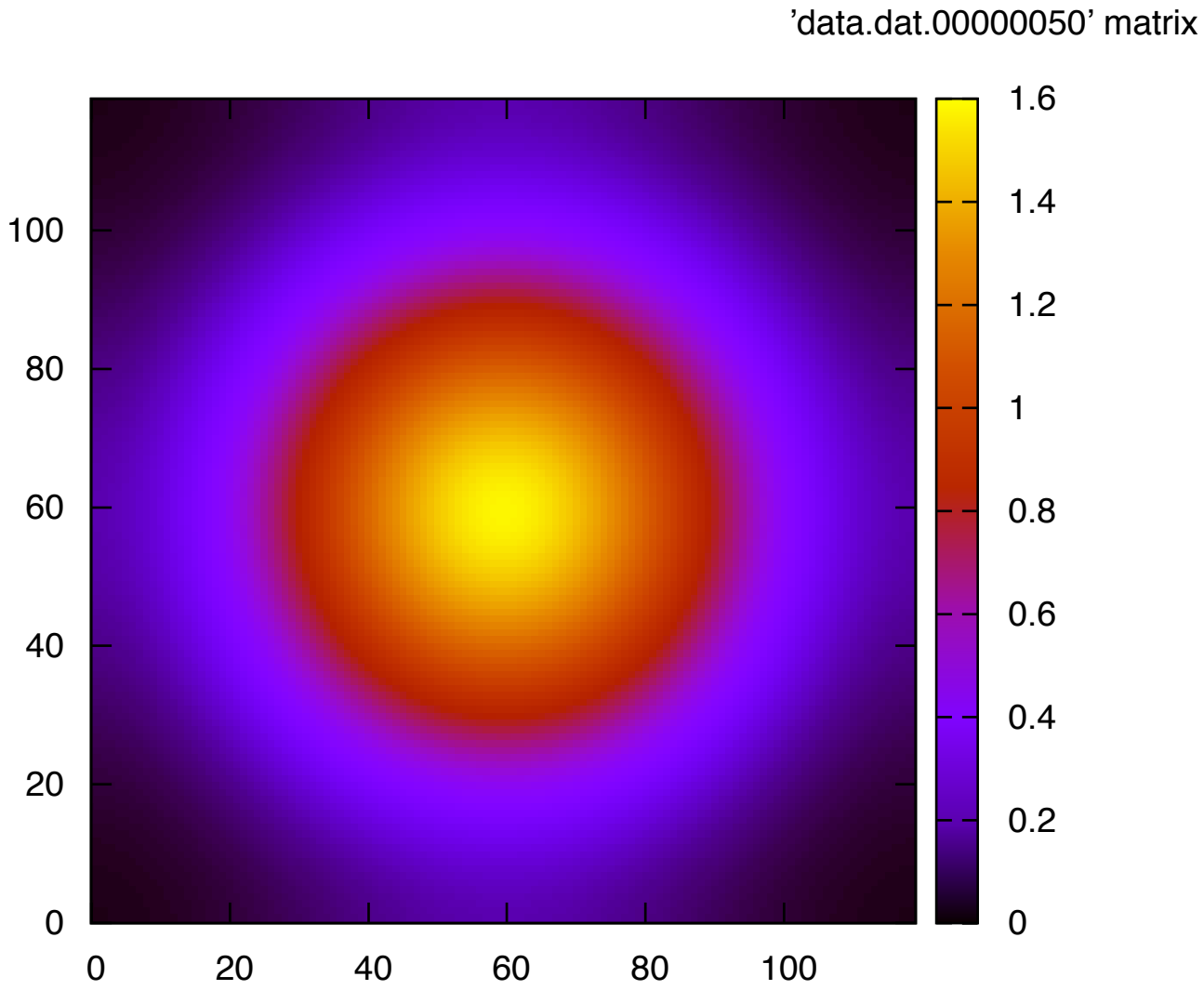
EX4: DIFFUSION - 2D4 NEIGHBOURHOOD, 30X30



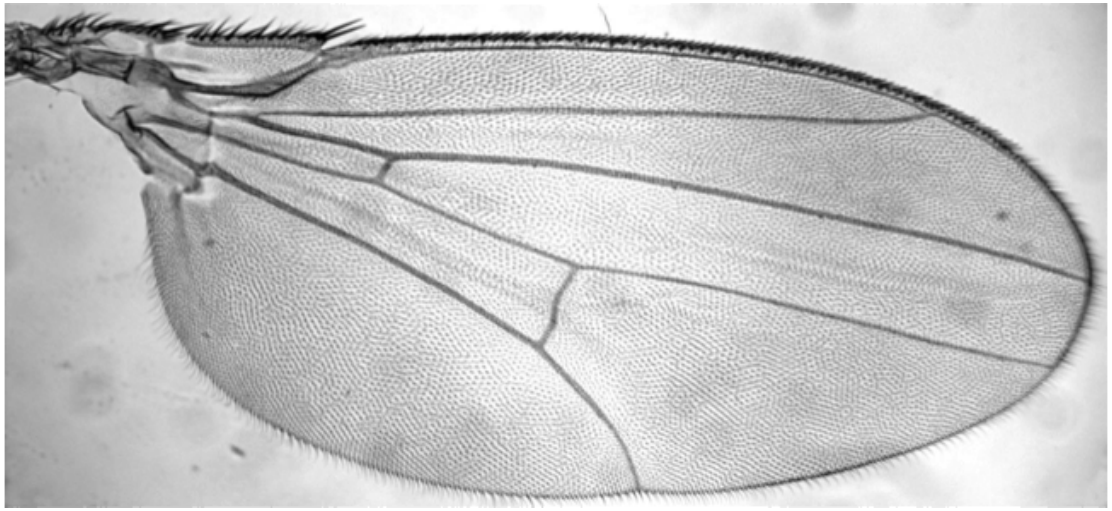
EX4: DIFFUSION - 2D4 NEIGHBOURHOOD, 60X60

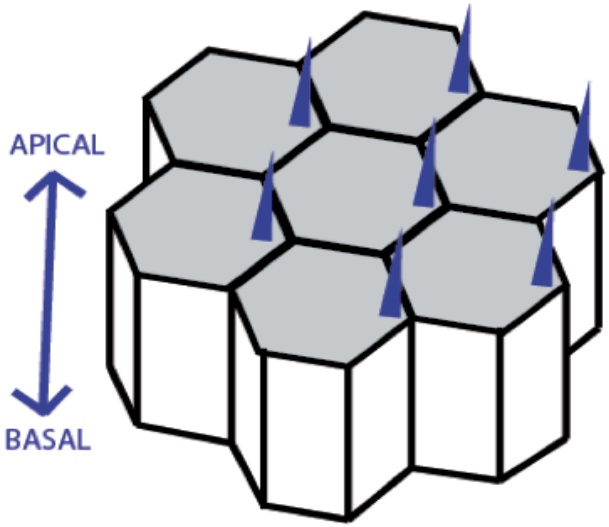


EX4: DIFFUSION - 2D4 NEIGHBOURHOOD, 120X120



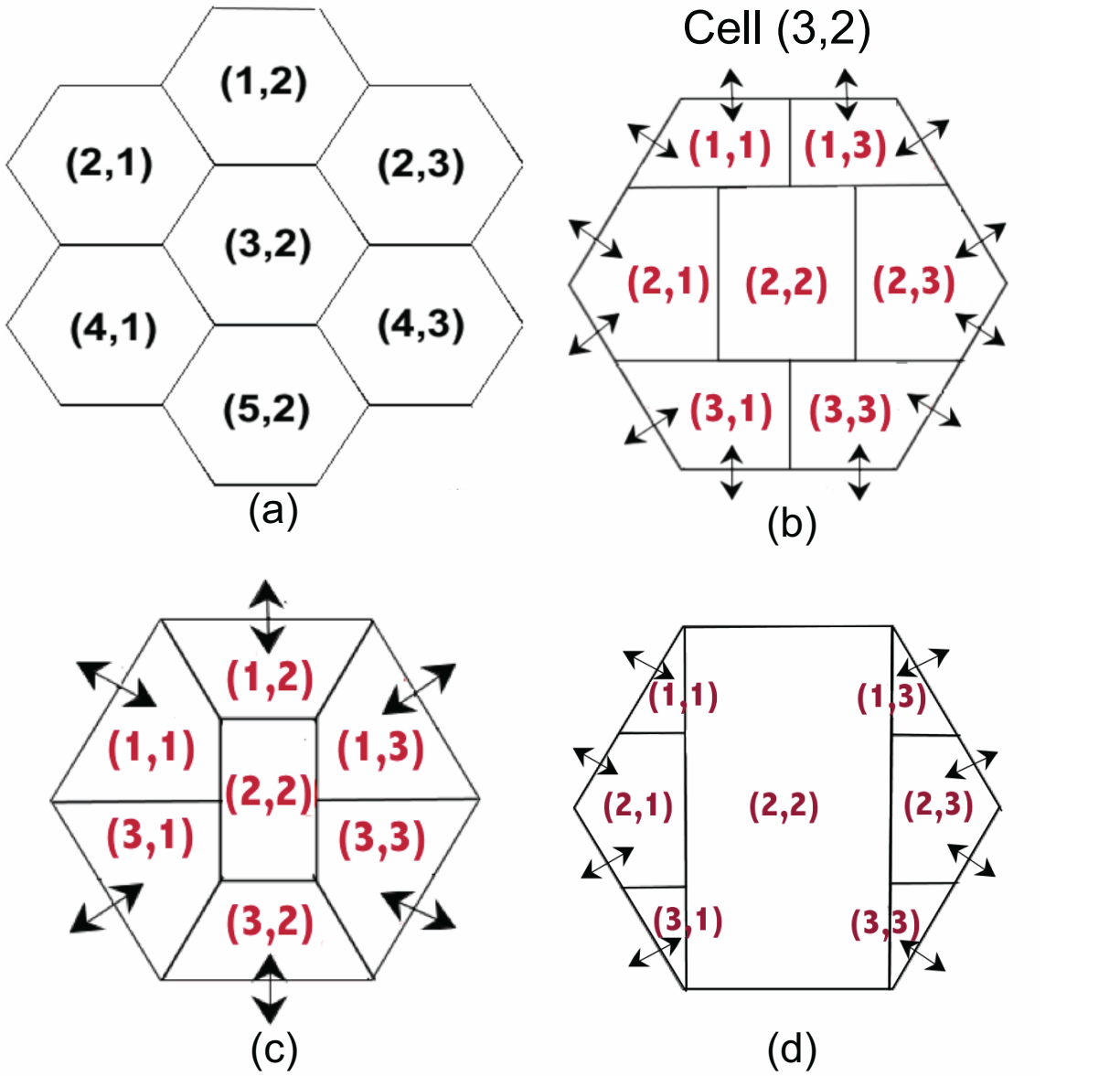
EX5 - PLANAR CELL POLARITY



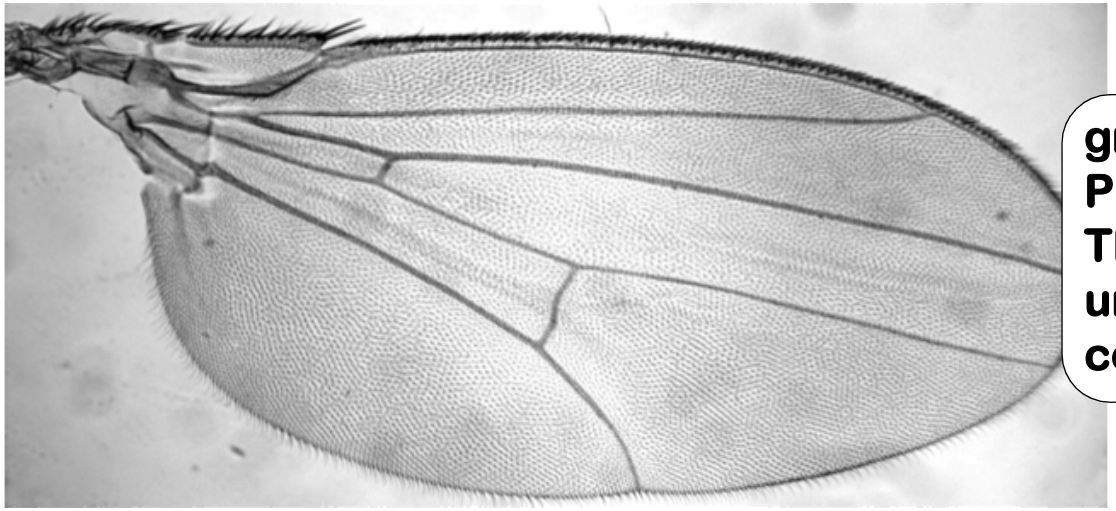


[BIOPPN 2011]
[CMSB 2011]

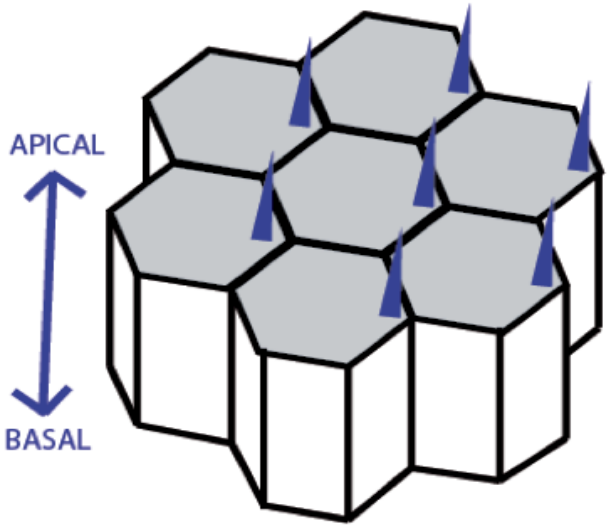
monika.heiner@tu-cottbus.de


(1,2)
(2,1)
(2,3)
(3,2)
(4,1)
(4,3)
(5,2)
(a)
Cell (3,2)
(1,1)
(1,3)
(2,1)
(2,2)
(2,3)
(3,1)
(3,3)
(b)
(1,2)
(1,1)
(1,3)
(2,2)
(3,1)
(3,3)
(3,2)
(c)
(1,1)
(1,3)
(2,1)
(2,2)
(2,3)
(3,1)
(3,3)
(d)

EX5 - PLANAR CELL POLARITY

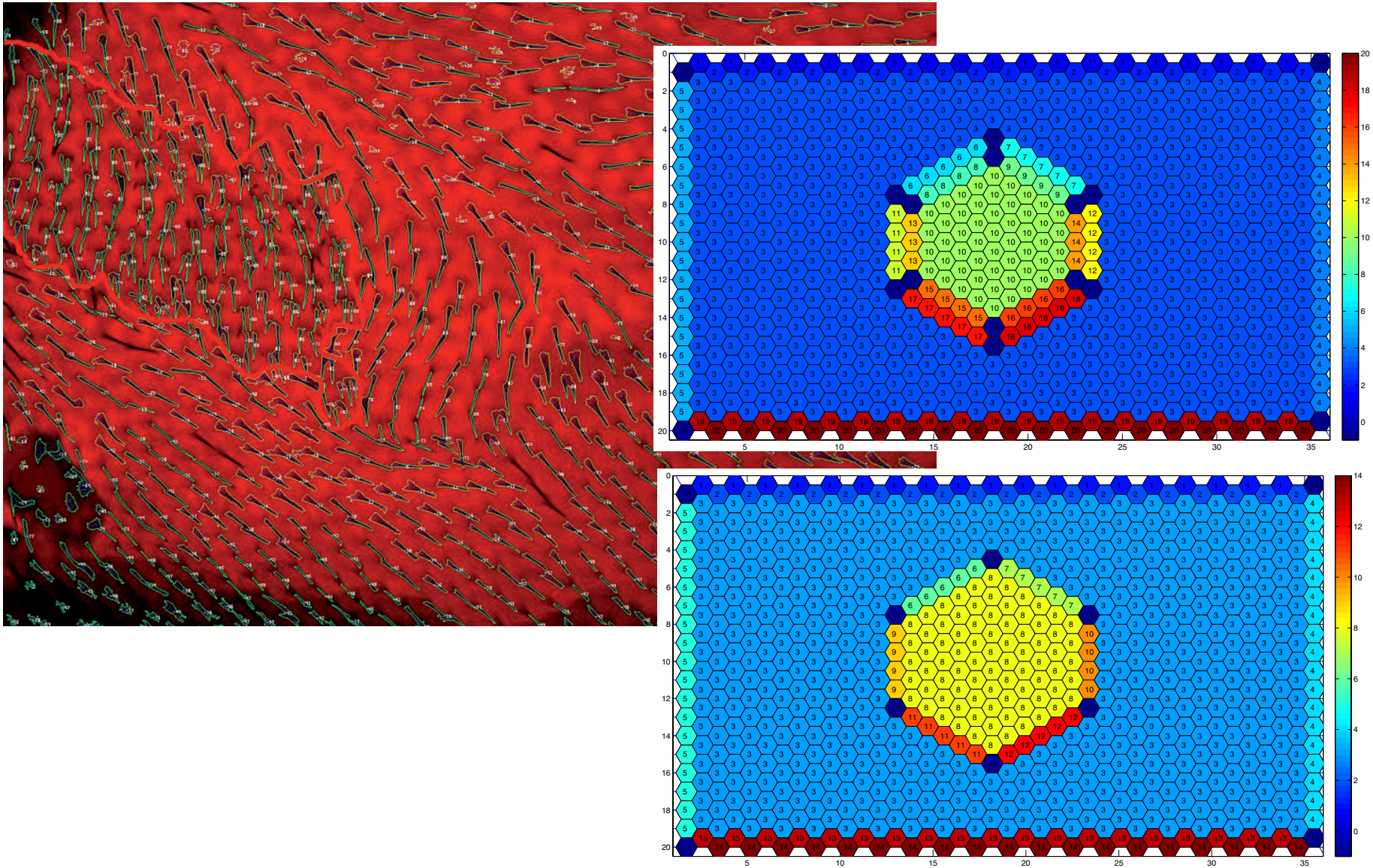


grid size:	40 x 40
PLACES:	164,000
TRANSITIONS:	229,686
unfolding:	2 min
cont. simulation:	2 h



[BIOPPN 2011]
[CMSB 2011]

EX5 - PLANAR CELL POLARITY



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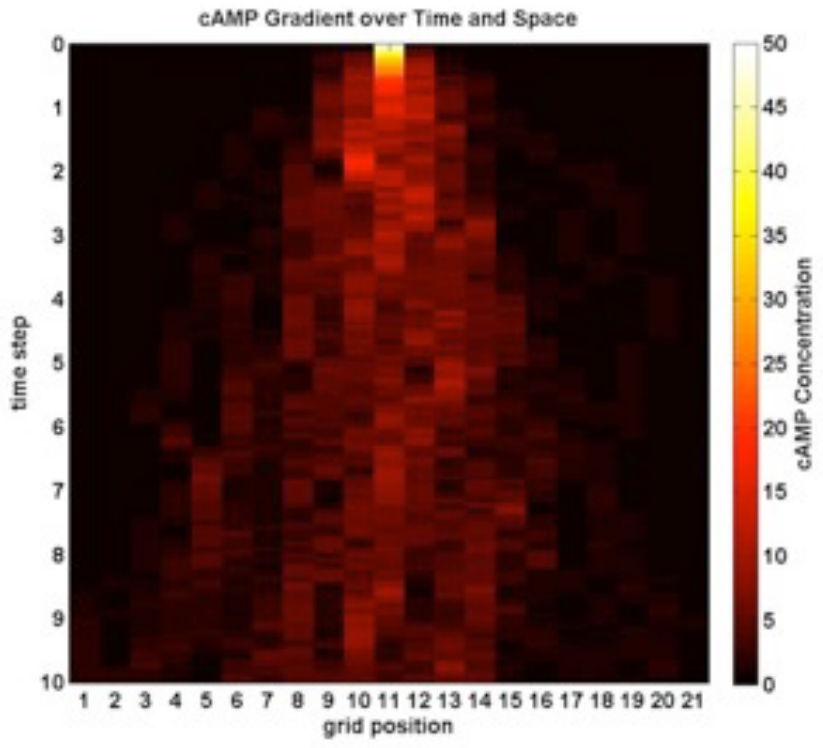
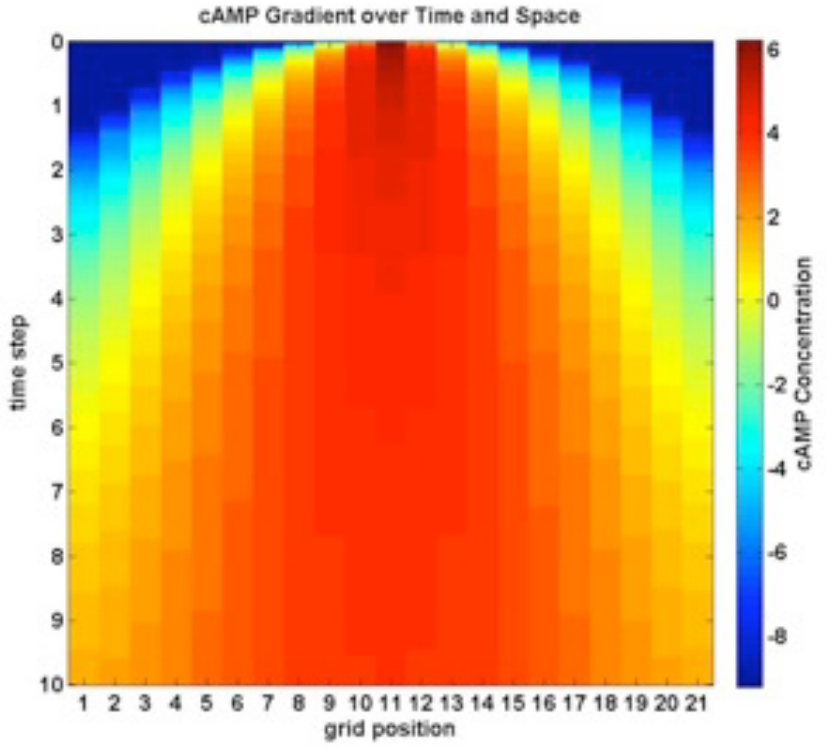
EX6 - MOBILITY / MOTILITY

-> GRADIENTS





[DAGSTUHL 2011]

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

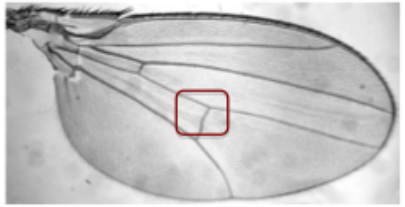
SUMMARY & OUTLOOK

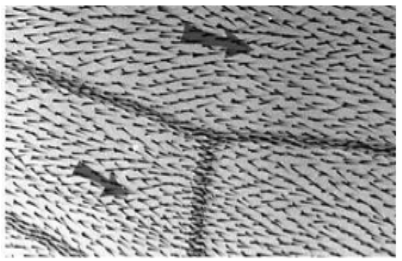
MODELLING = ABSTRACTION

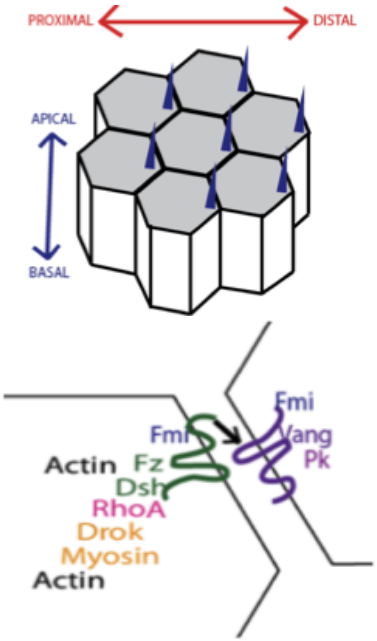
- **hierarchical organisation of components -> model variables**
  genes, molecules, organelles, cells, tissues, organs, organisms
- **functionality of atomic events**
  chemical reactions with/out stoichiometry, conformational change, transport, . . .
- **time**
  qualitative versus quantitative models
- **individual vs population behaviour**
- **(hierarchical) space**
- **observables**
- **shape and volume of components**
- **biosystem development**

MULTI-SCALE CHALLENGES

- ❑ **repetition** *... of components*
- ❑ **variation**
- ❑ **spacial organisation**
- ❑ **hierarchical organisation**
- ❑ **communication**
- ❑ **mobility / motility**
- ❑ **replication / deletion**
- ❑ **pattern formation**
- ❑ **differentiation**
- ❑ **semi-regular/irregular/dynamic organisation**





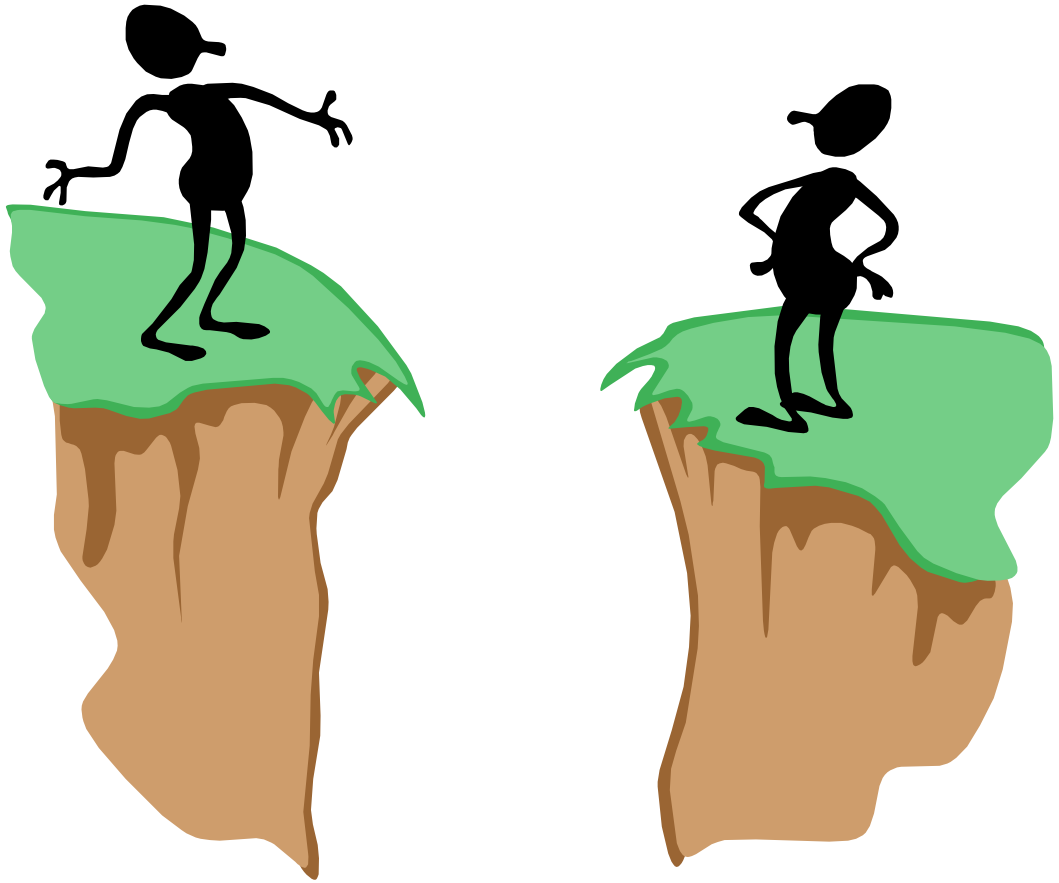


modification over time may include

- addition/subtraction of model components
- rewiring yielding new structures
- parameter modification (e.g. triggered by mutation)
- model translocation (model passing, nets in nets)
- reorganizing the hierarchical structure, adding, removing levels

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*



THANKS !

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