A PETRI NET FRAMEWORK FOR SPATIAL AND MULTISCALE MODELLING OF PLANT BIOCHEMISTRY

- A PETRI NET PERSPECTIVE ON SYSTEMS AND SYNTHETIC BIOLOGY -

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OUTLINE

FRAMEWORK

-> *unifying four paradigms:*
QPN - SPN - CPN - HPN

-> *our toolbox:*
Snoopy - Marcie - Charlie - Patty - Strike

COLOURED PETRI NETS -> PDE

-> *Turing patterns (CPN)*

-> *phase variation (SPN)*

-> *planar cell polarity (hierarchical space)*

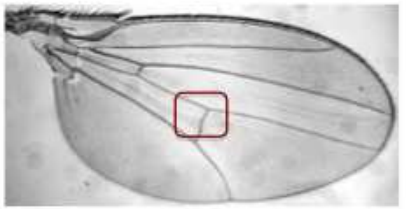
MODELLING BIO PETRI NETS

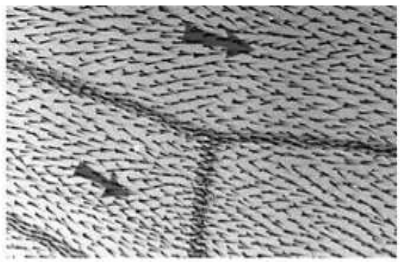
-> *composition from standard components*

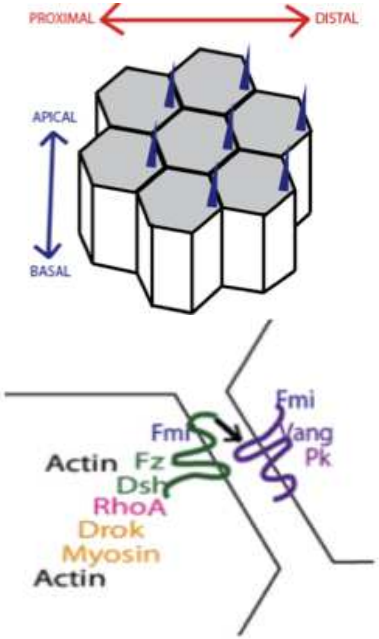
-> *bottom-up (reverse engineering)*

-> *modular modelling*

-> *genome-controlled model generation*







THE PETRI NET FRAMEWORK

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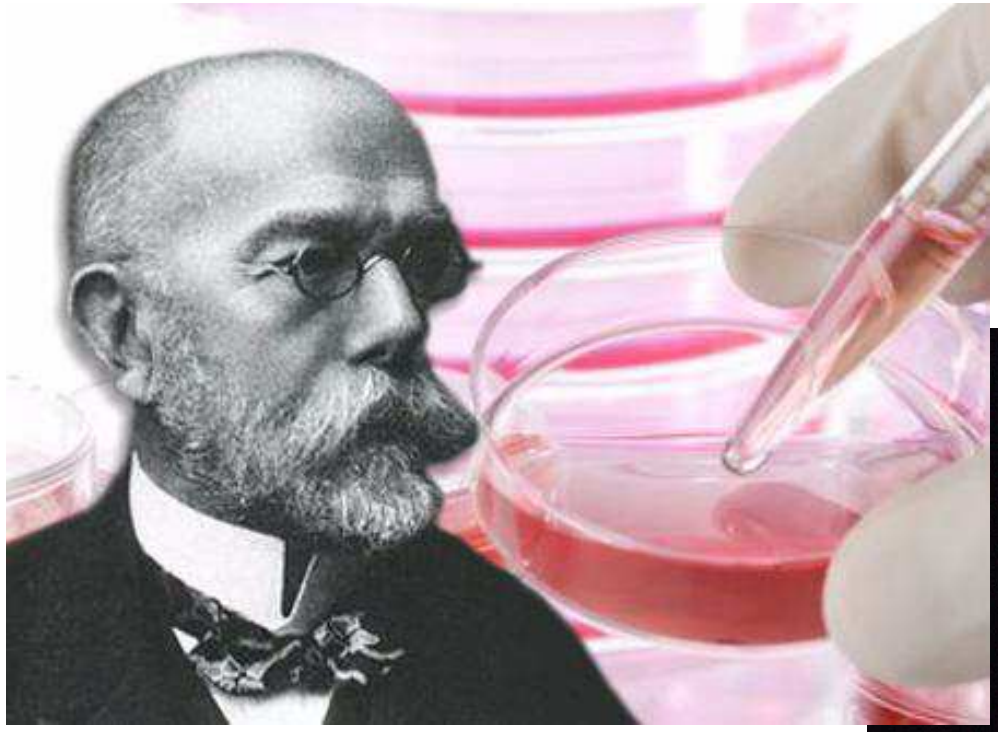
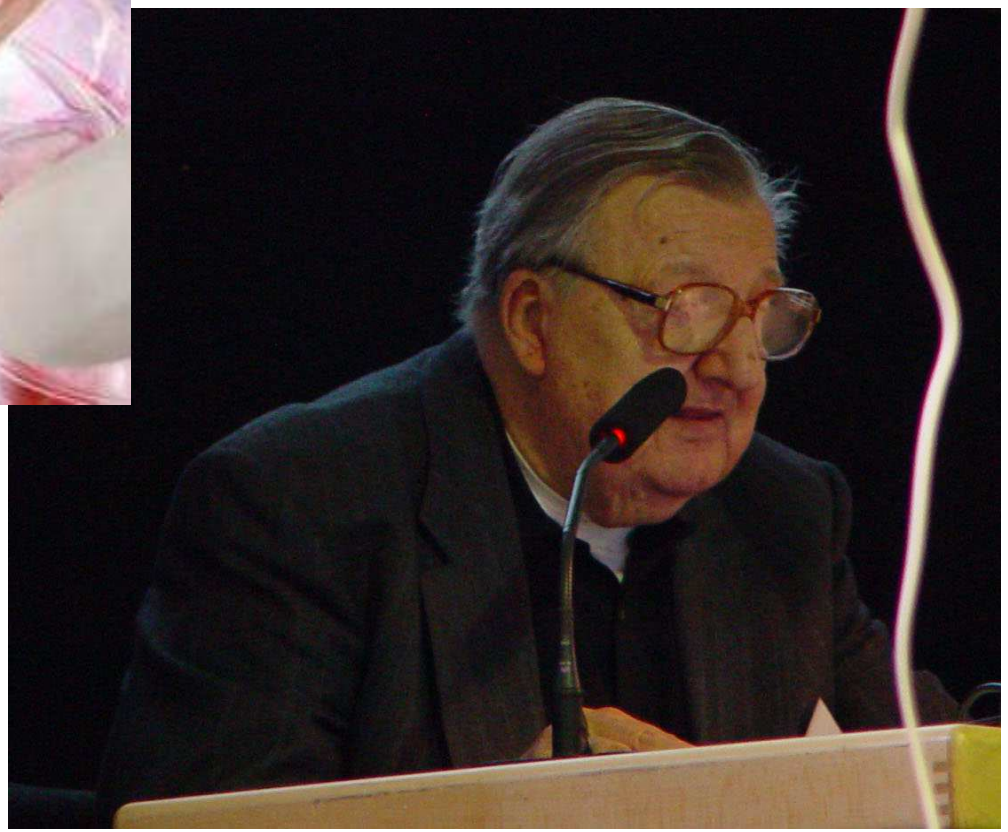
PETRI DISH VS PETRI NET

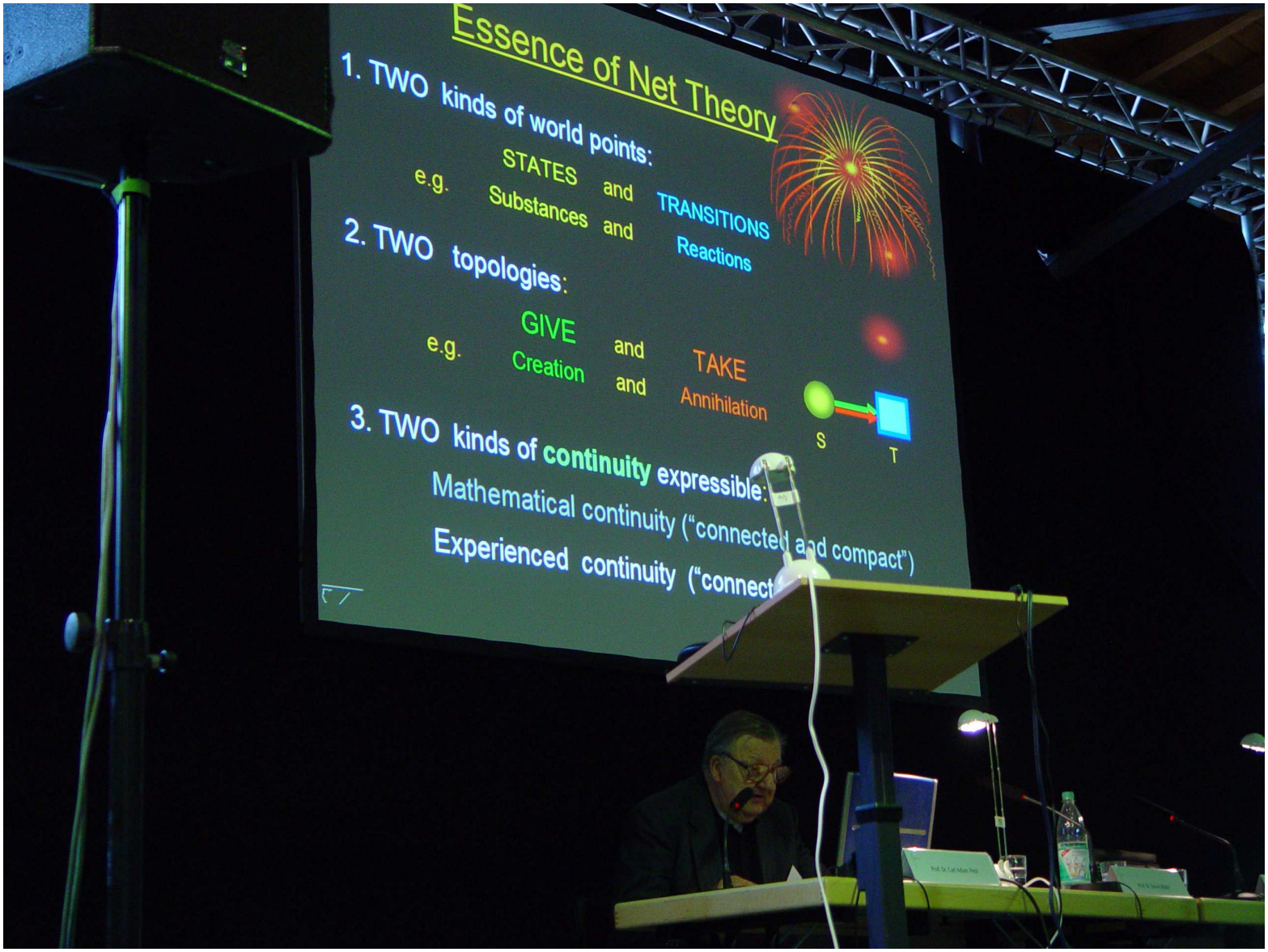


Julius Richard Petri, 1852 - 1921

Carl Adam Petri, 1926 - 2010



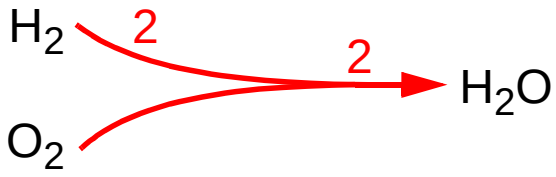
NOVEMBER 2006


Essence of Net Theory
1. TWO kinds of world points:
STATES and TRANSITIONS
e.g. Substances and Reactions
2. TWO topologies:
GIVE and TAKE
e.g. Creation and Annihilation
S
T
3. TWO kinds of continuity expressible:
Mathematical continuity ("connected and compact")
Experienced continuity ("connect

. . .

ARE NETWORKS OF BIOCHEMICAL REACTIONS

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

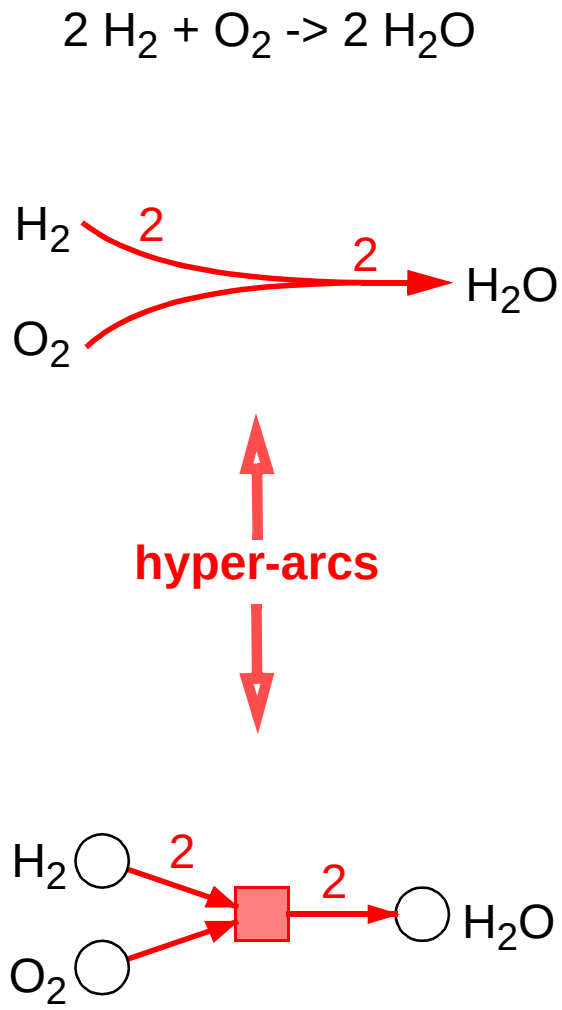


. . .

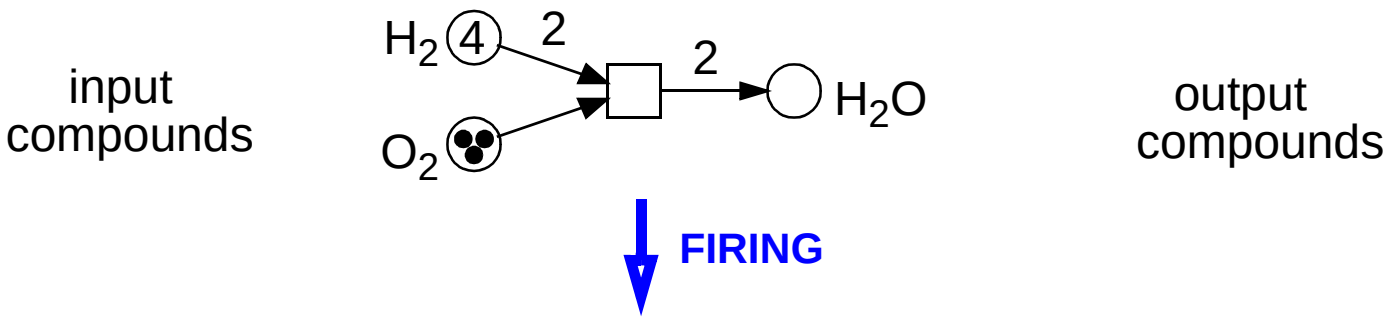
ARE NETWORKS OF BIOCHEMICAL REACTIONS

. . .

NATURALLY EXPRESSIBLE AS PETRI NETS

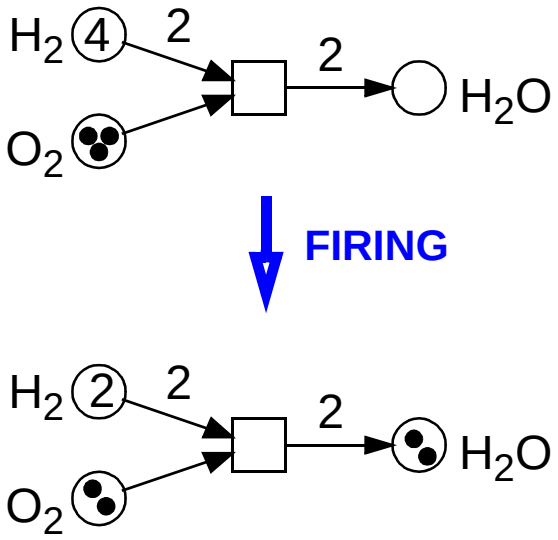


$2\ H_2 + O_2 \rightarrow 2\ H_2O$



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

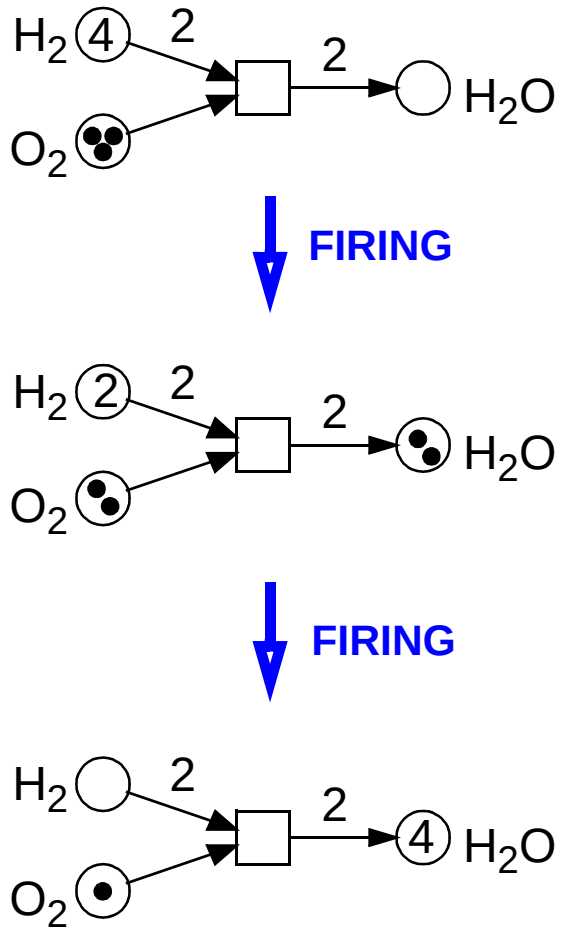
input compounds



output compounds

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

input compounds



output compounds

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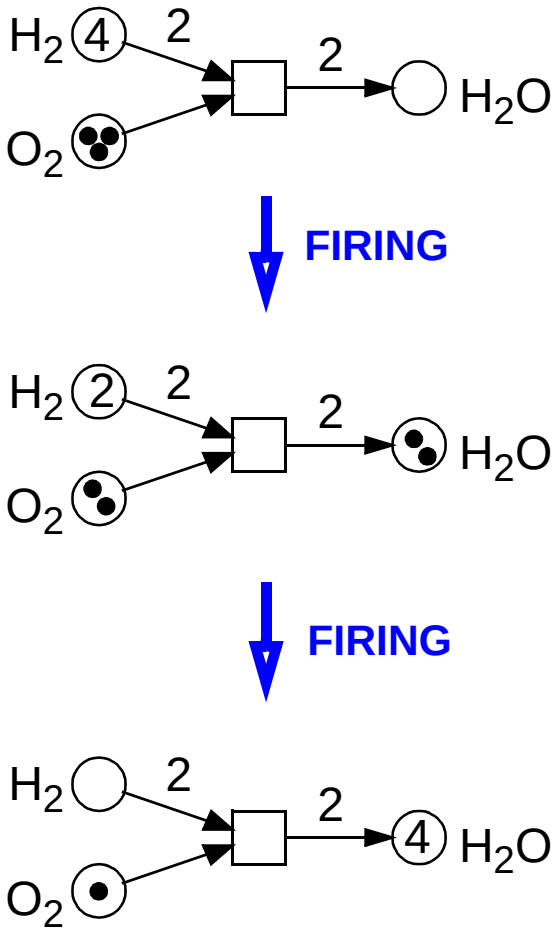


output compounds

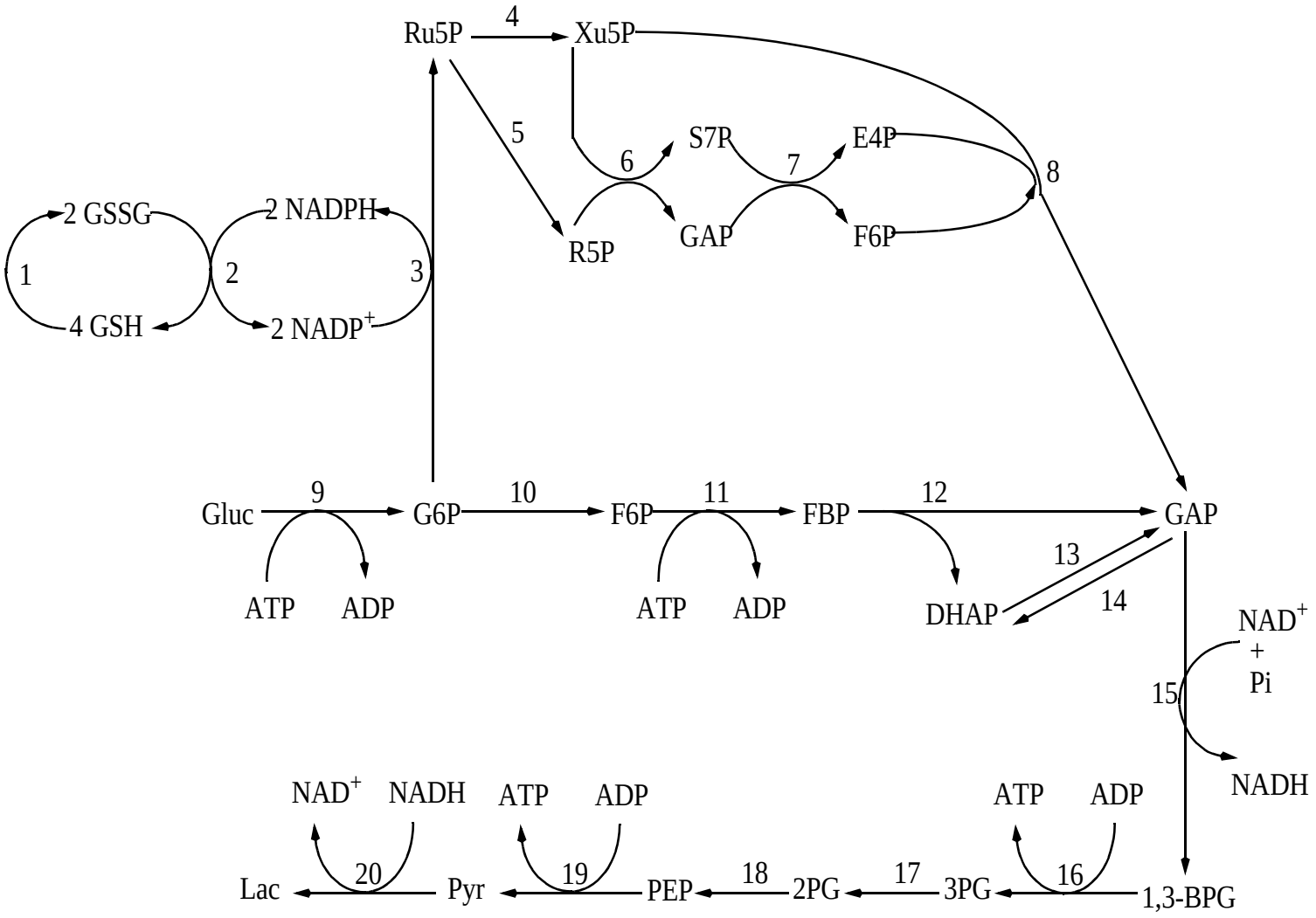
TOKEN GAME

DYNAMIC BEHAVIOUR

(substance/signal flow)

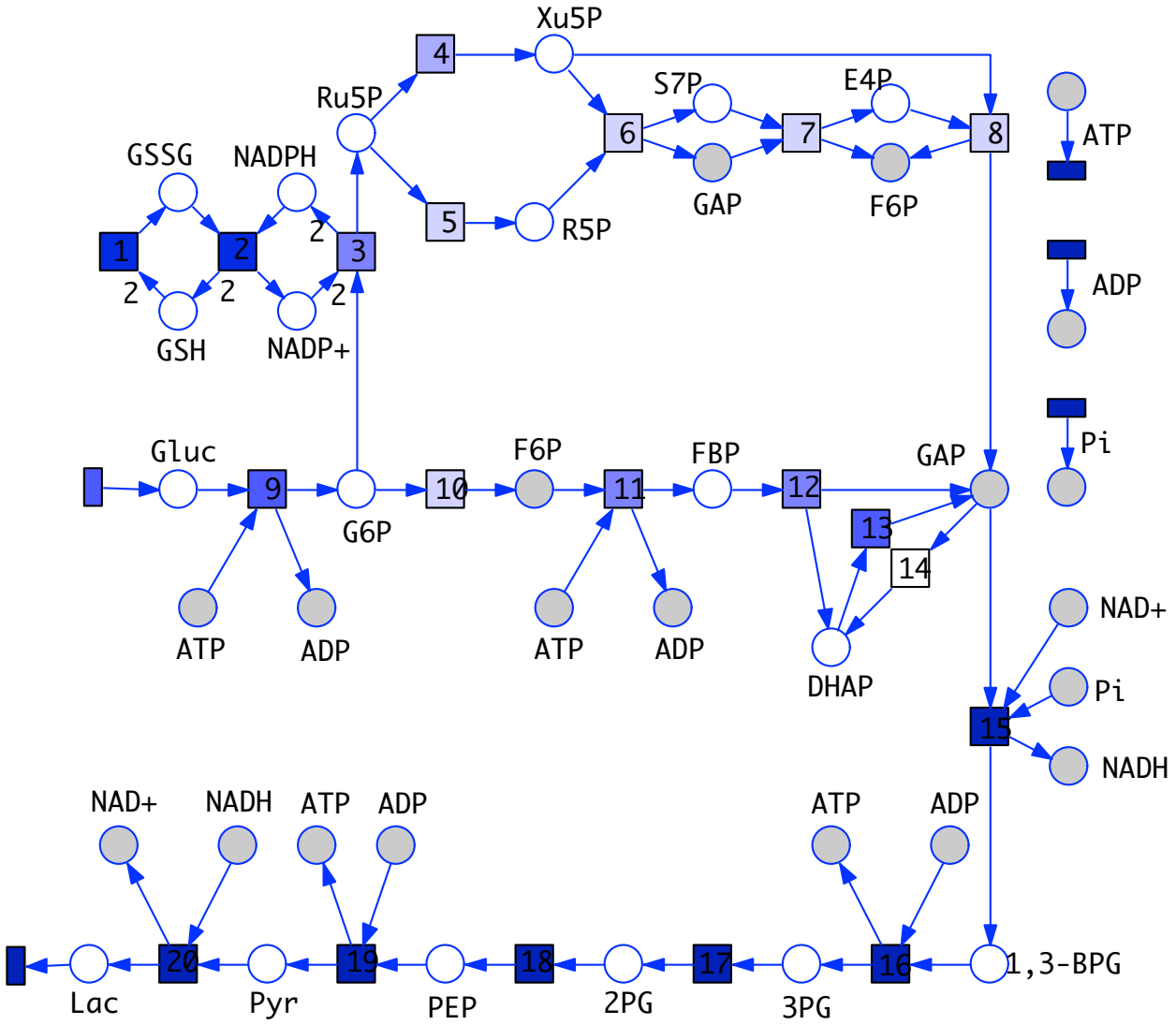
Ex: Glycolysis and Pentose Phosphate Pathway

[Reddy 1993]



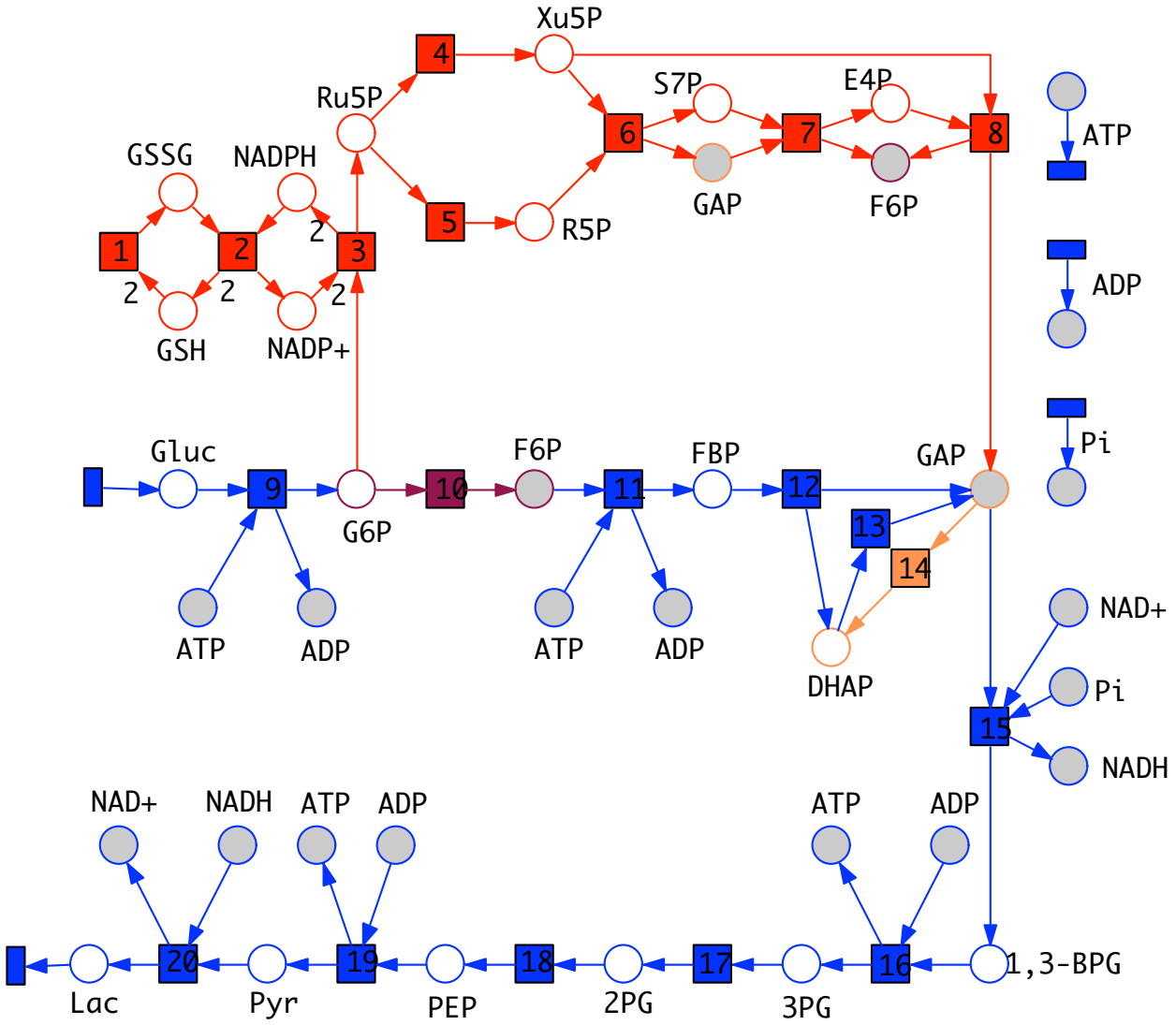
Ex: Glycolysis and Pentose Phosphate Pathway

[Reddy 1993]
[Heiner 1998]

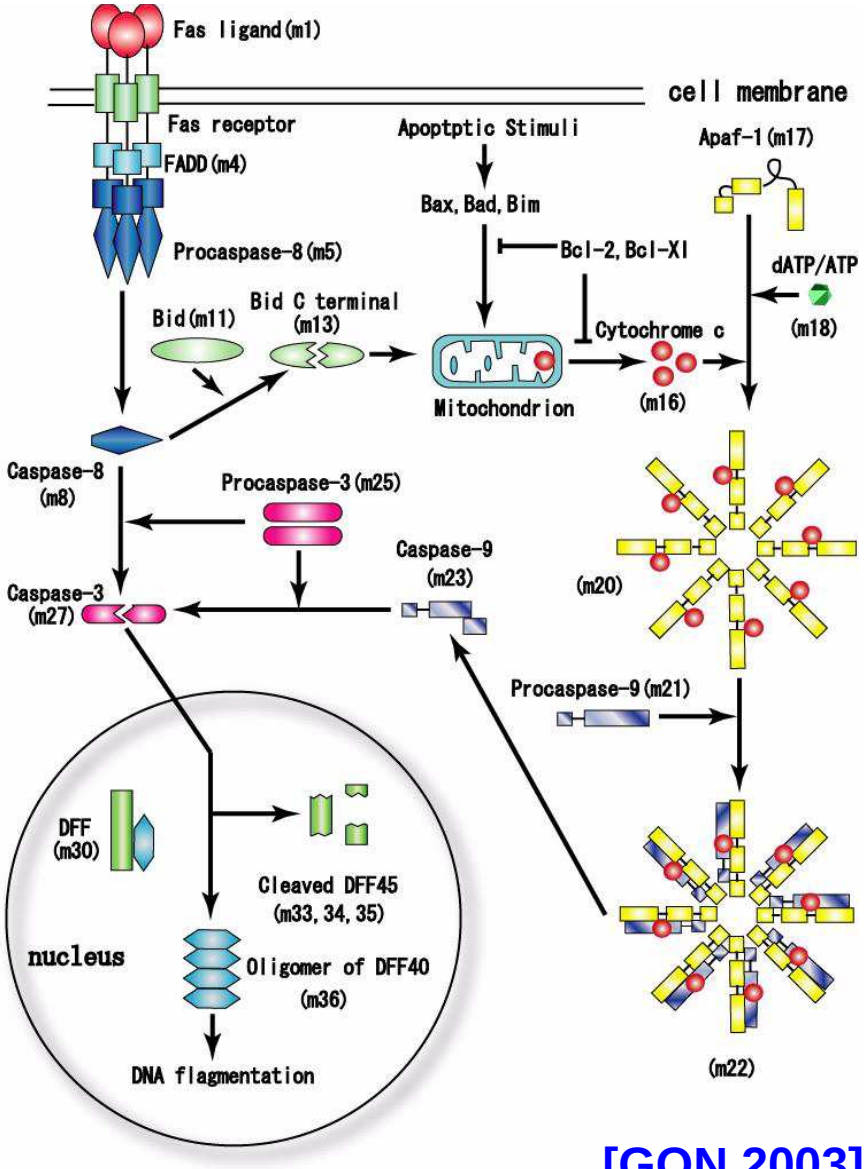


Ex: Glycolysis and Pentose Phosphate Pathway

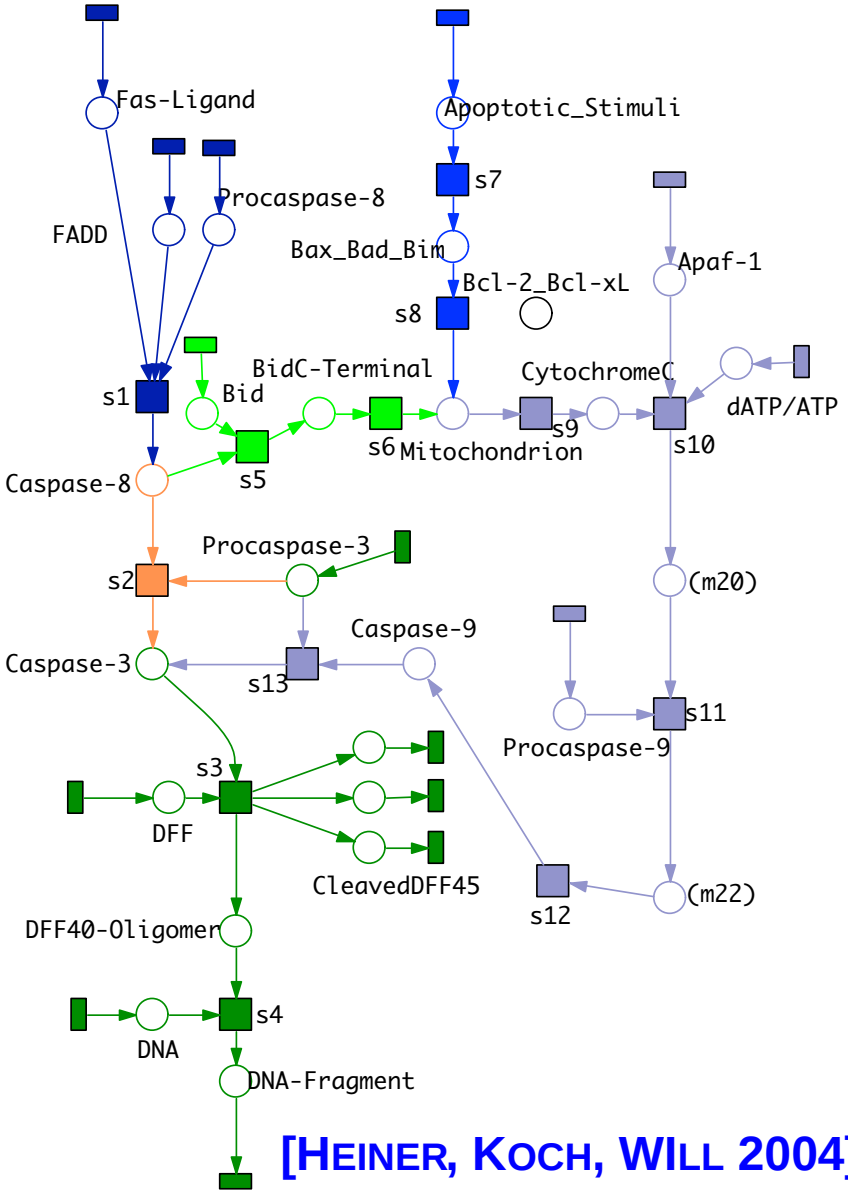
[Reddy 1993]
[Heiner 1998]
[Heiner 2009]



EX: APOPTOSIS IN MAMMALIAN CELLS



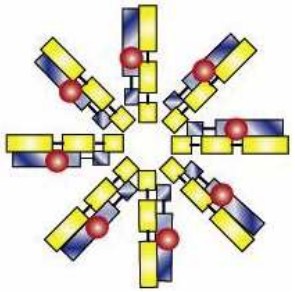
[GON 2003]

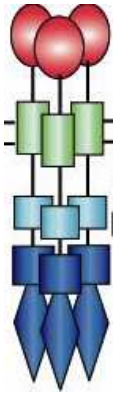


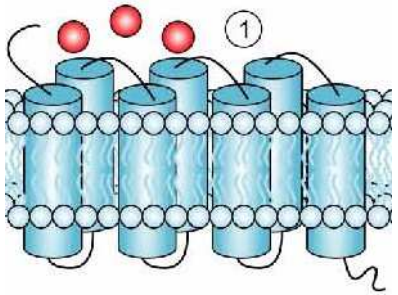
[HEINER, KOCH, WILL 2004]

PLACES, TRANSITIONS - SOME BIO INTERPRETATIONS

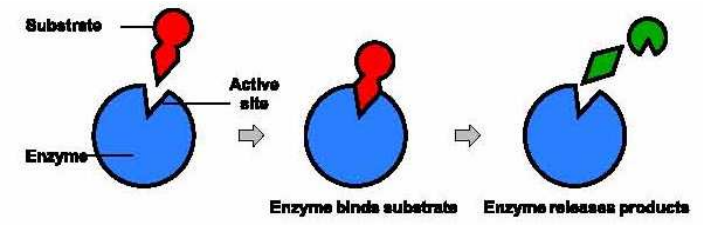
- **places -> model variables**
  - -> *(bio-) chemical compounds*
  - -> *proteins*
  - -> *protein conformations*
  - -> *complexes*
  - -> *genes, . . . , etc.*
  - *. . . in different locations*







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



- **graphics may support communication between professionals not familiar with modelling techniques**

Genomic, Biochemical, and Modeling Analyses of Asparagine Synthetases from Wheat

Hongwei Xu[1,2], Tanya Y. Curtis[2], Stephen J. Powers[3], Sarah Raffan[2], Runhong Gao[1,2], Jianhua Huang[1], Monika Heiner[4], David R. Gilbert[5] and Nigel G. Halford[2]**

[1] Biotechnology Research Institute, Shanghai Academy of Agricultural Sciences, Shanghai, China, [2] Department of Plant Sciences, Rothamsted Research, Harpenden, United Kingdom, [3] Department of Computational and Analytical Sciences, Rothamsted Research, Harpenden, United Kingdom, [4] Department of Computer Science, Brandenburg University of Technology Cottbus-Senftenberg, Cottbus, Germany, [5] Department of Computer Science, College of Engineering, Design and Physical Sciences, Brunel University London, Uxbridge, United Kingdom

Asparagine synthetase activity in cereals has become an important issue wit
discovery that free asparagine concentration determines the potential fo

frontiers in Plant Science

Front. Plant Sci., 15 January 2018
https://doi.org/10.3389/ fpls.2017.02237

EX: WHEAT - FINITE SUPPLY

r1: Gln +ASNe -> ASNe_Gln

r2: ASNe_Gln -> Glu + ASeNH3

r3: ASNe_NH3 + Asp + ATP + Mg2 -> bAsp_AMP_ASNe_NH3 +ATP +Mg2

r4: bAsp_AMP_ASNe_NH3 -> ASNe + Asn + AP

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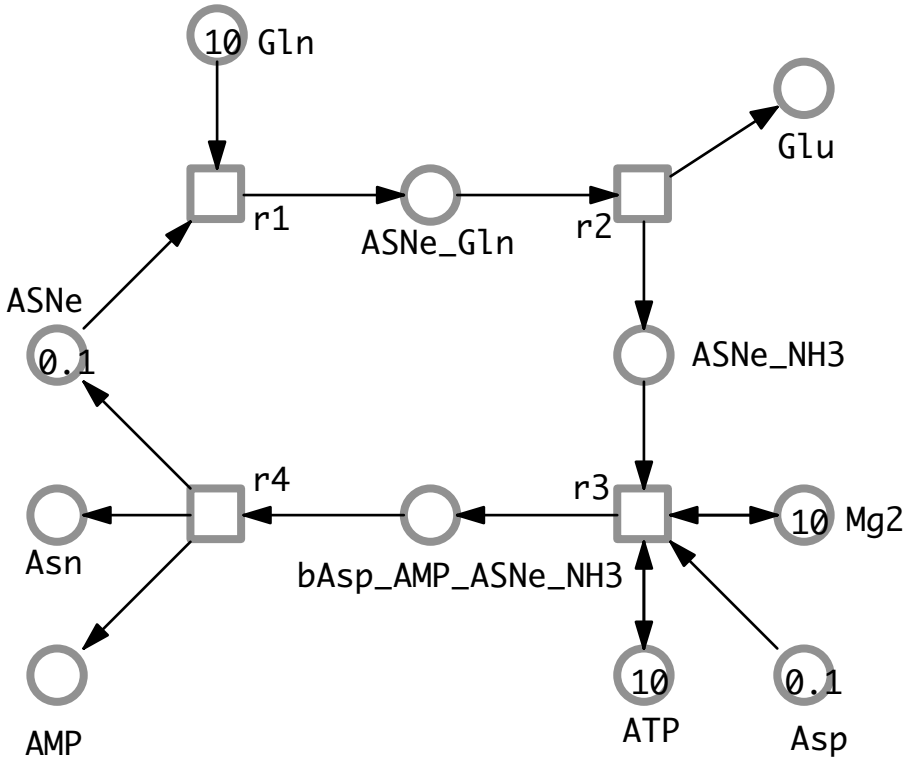

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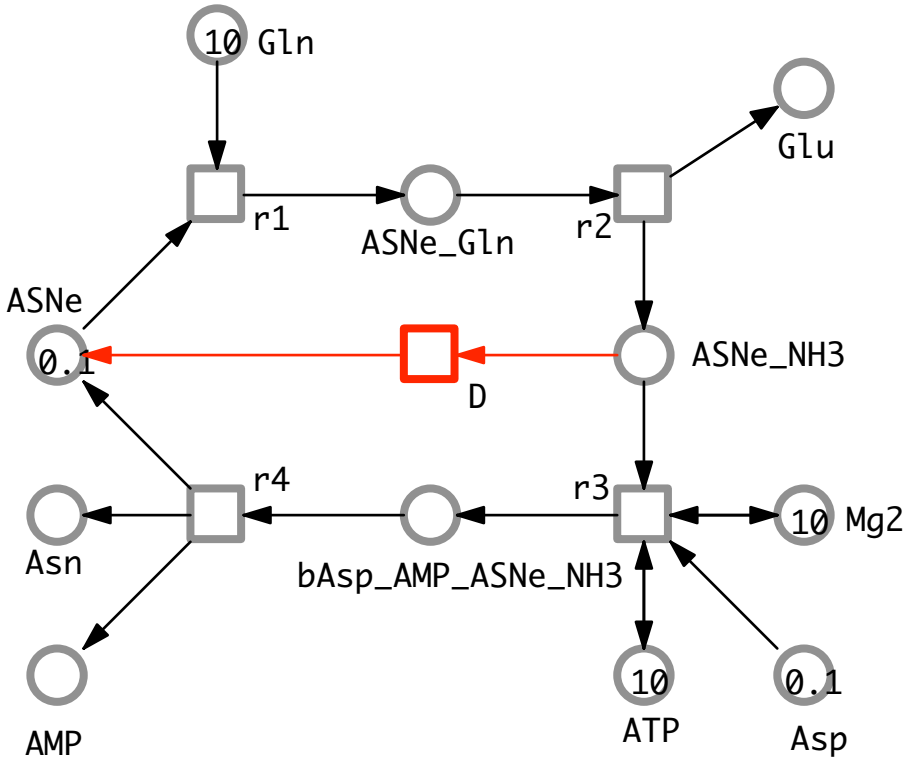

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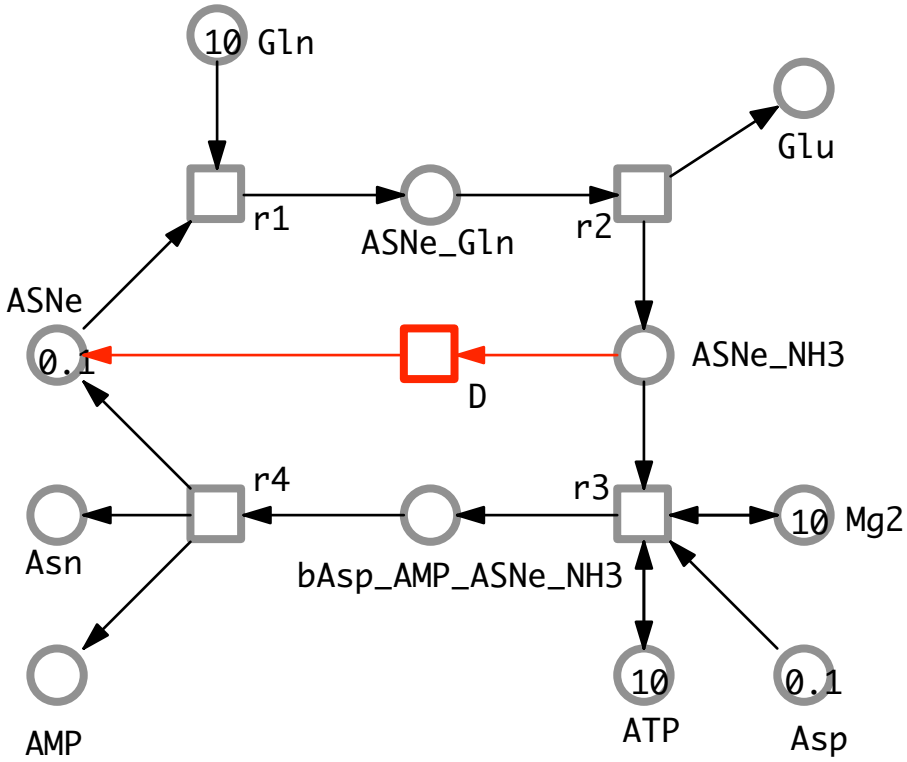
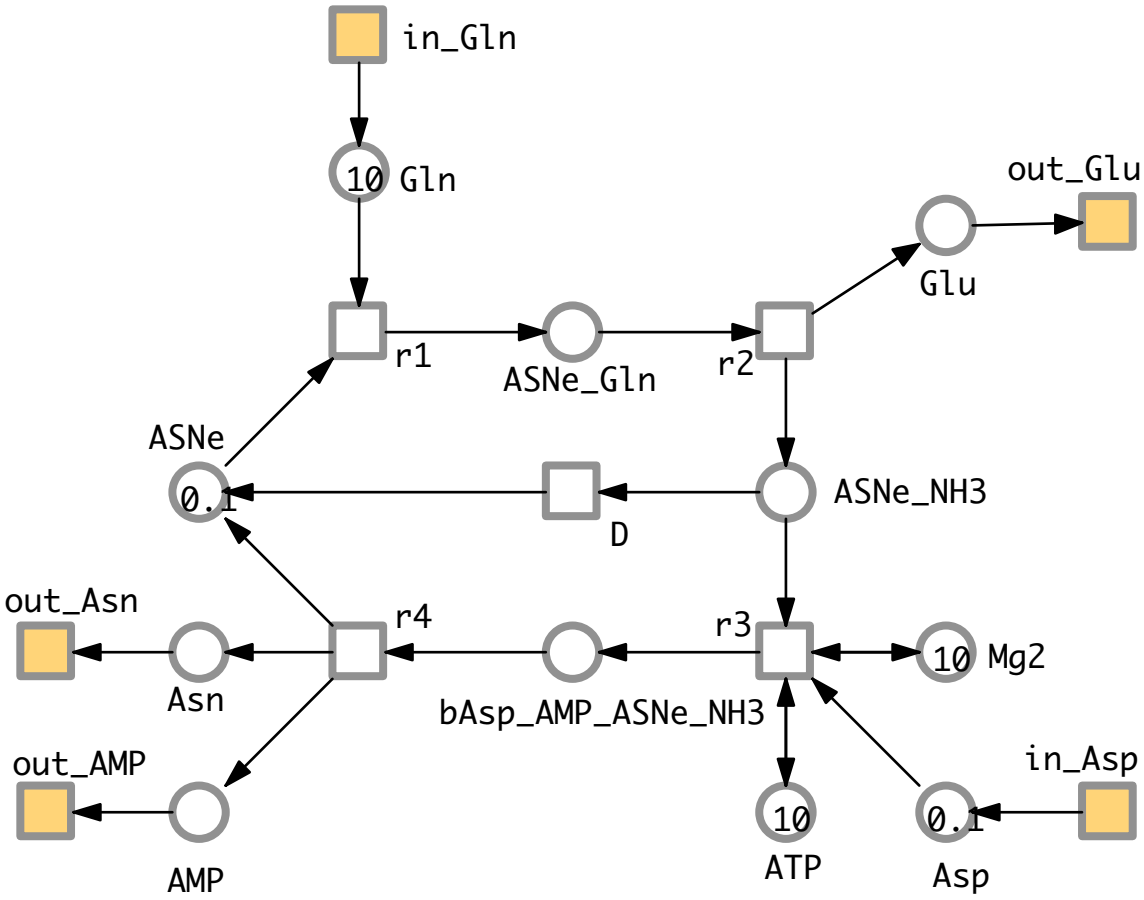
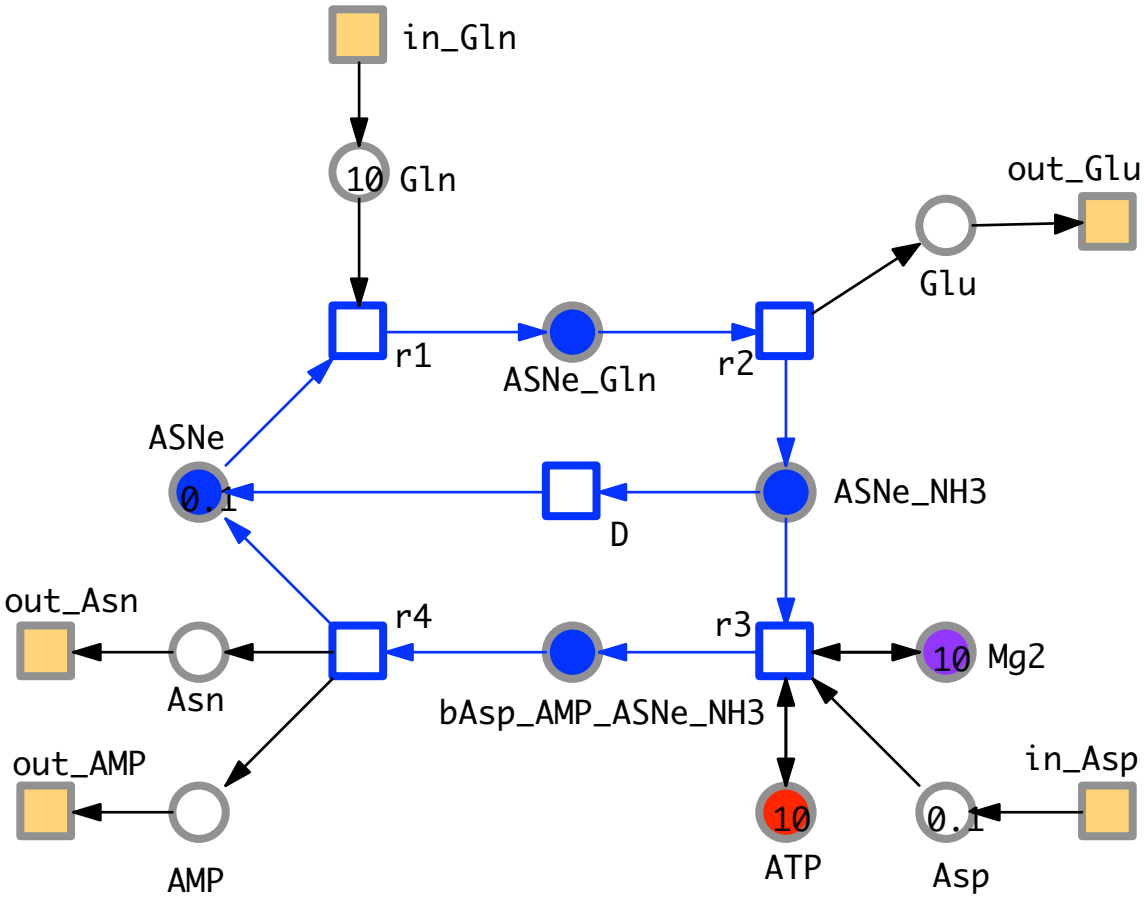


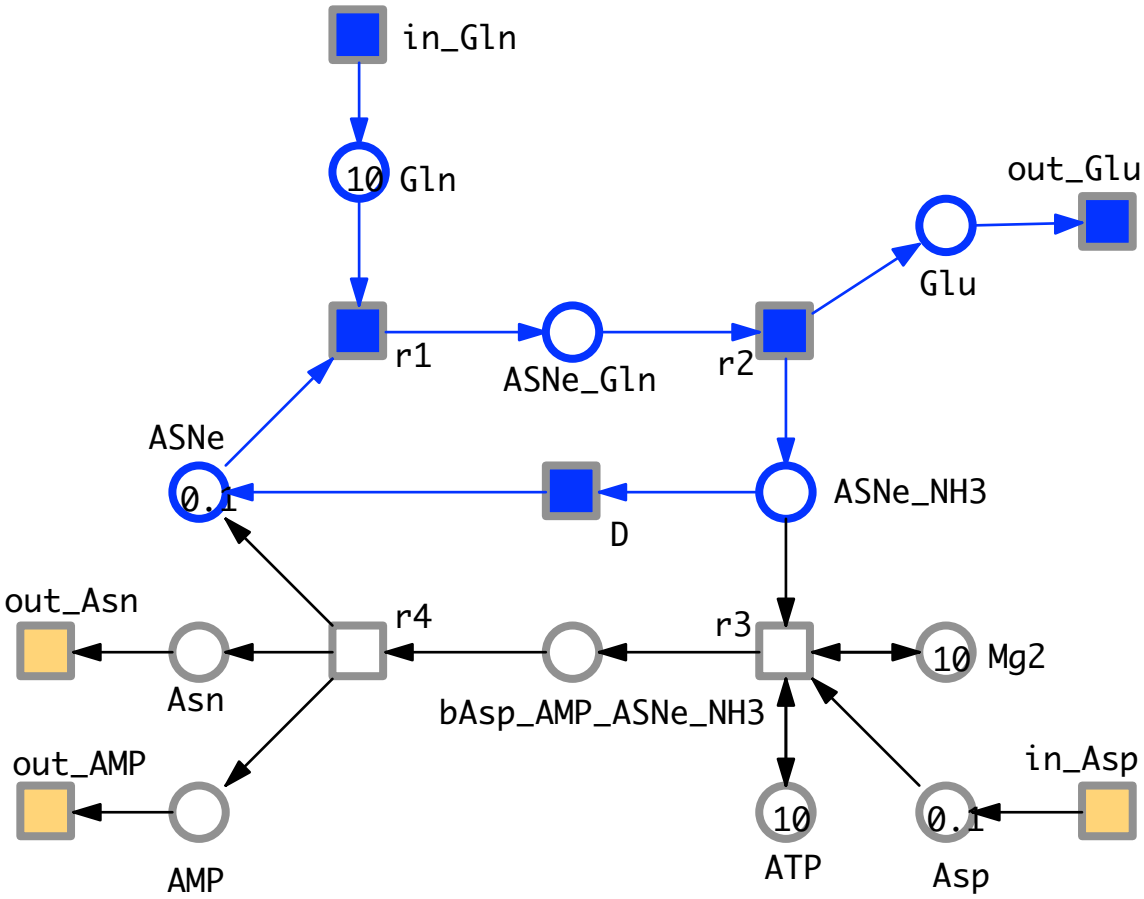
EX: WHEAT - INFINITE FLOW



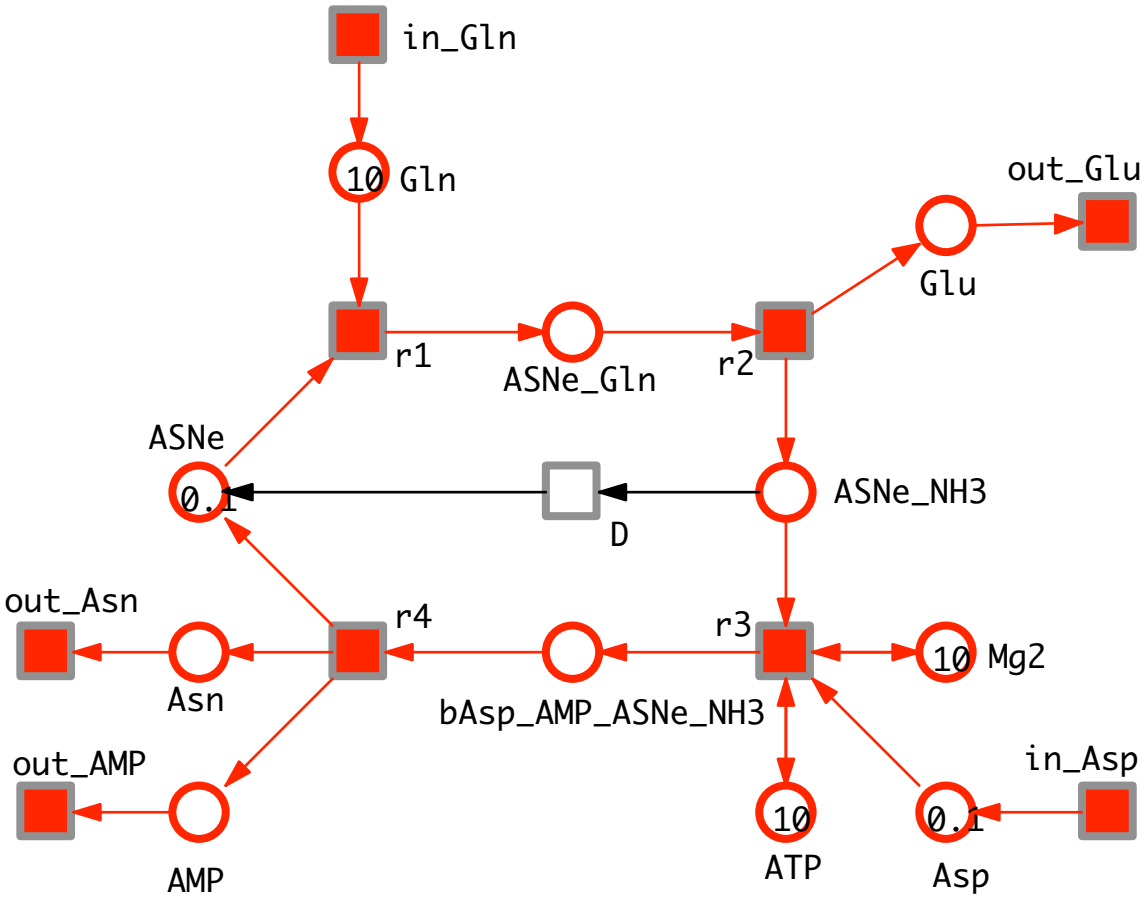
EX: WHEAT - THREE P-INVARIANTS



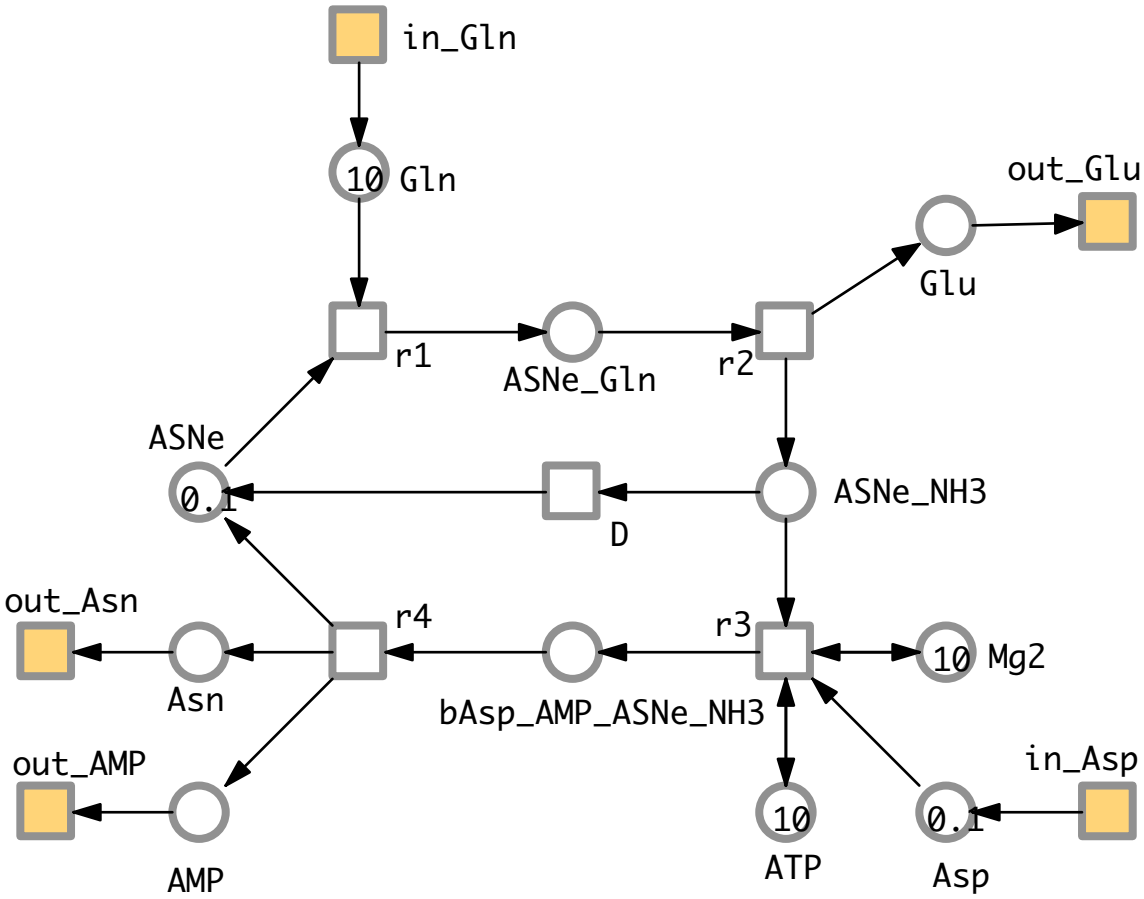
EX: WHEAT - T-INVARIANT 1



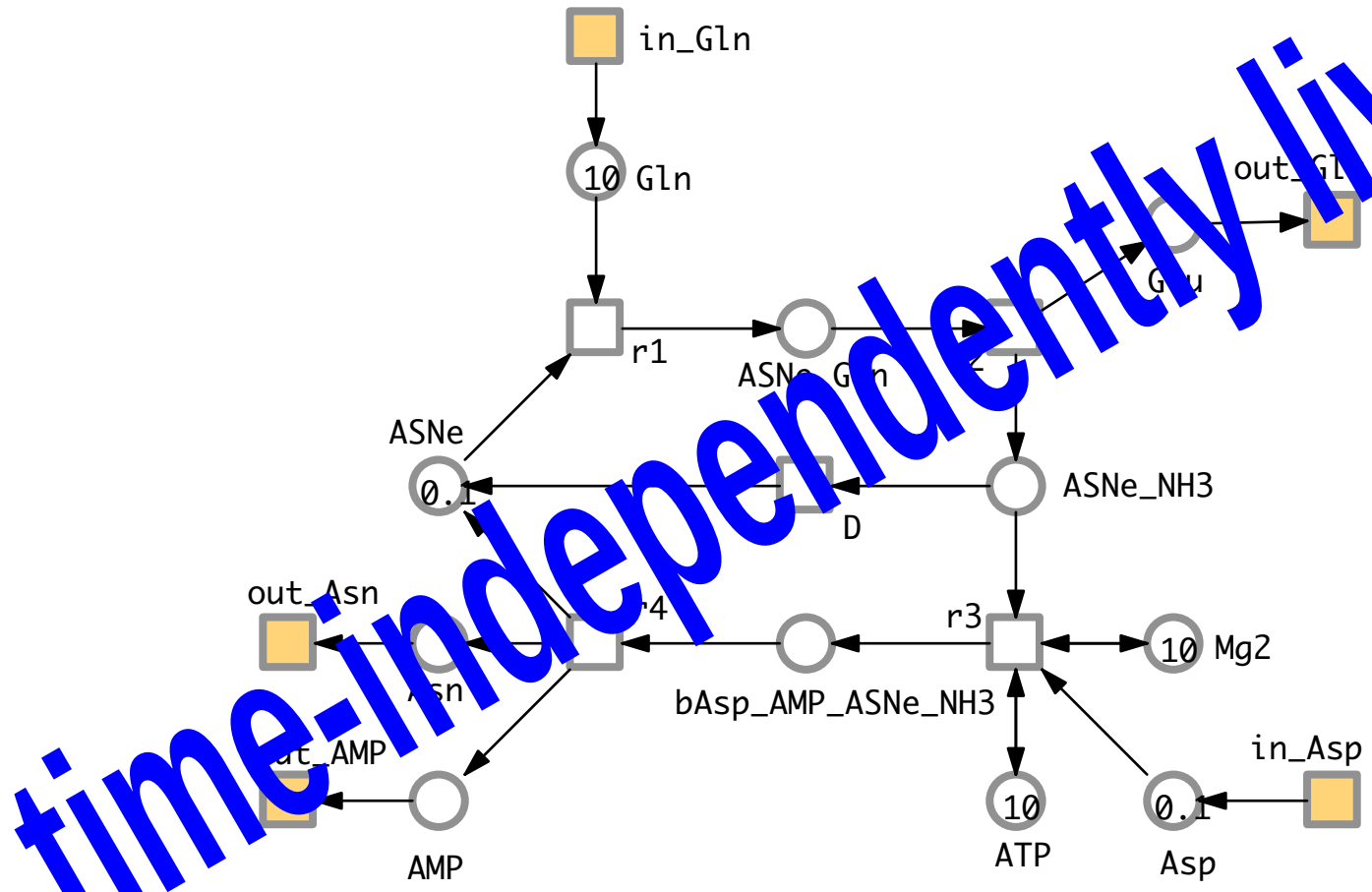
EX: WHEAT - T-INVARIANT 2



STP & ES -> LIVE


in_Gln
10 Gln
out_Glu
Glu
r1
ASNe_Gln
r2
ASNe
0.1
D
ASNe_NH3
out_Asn
r4
r3
10 Mg2
Asn
bAsp_AMP_ASNe_NH3
out_AMP
in_Asp
10
ATP
0.1
Asp
AMP

STP & ES -> LIVE


in_Gln
10 Gln
r1
ASNe
0.1
D
ASNe_NH3
out_Asn
r3
10 Mg2
bAsp_AMP_ASNe_NH3
in_Asp
AMP
10
ATP
0.1
Asp
time-independently live

. . . AND THEN THERE WAS TIME

Canary Wharf, 20/08/2011

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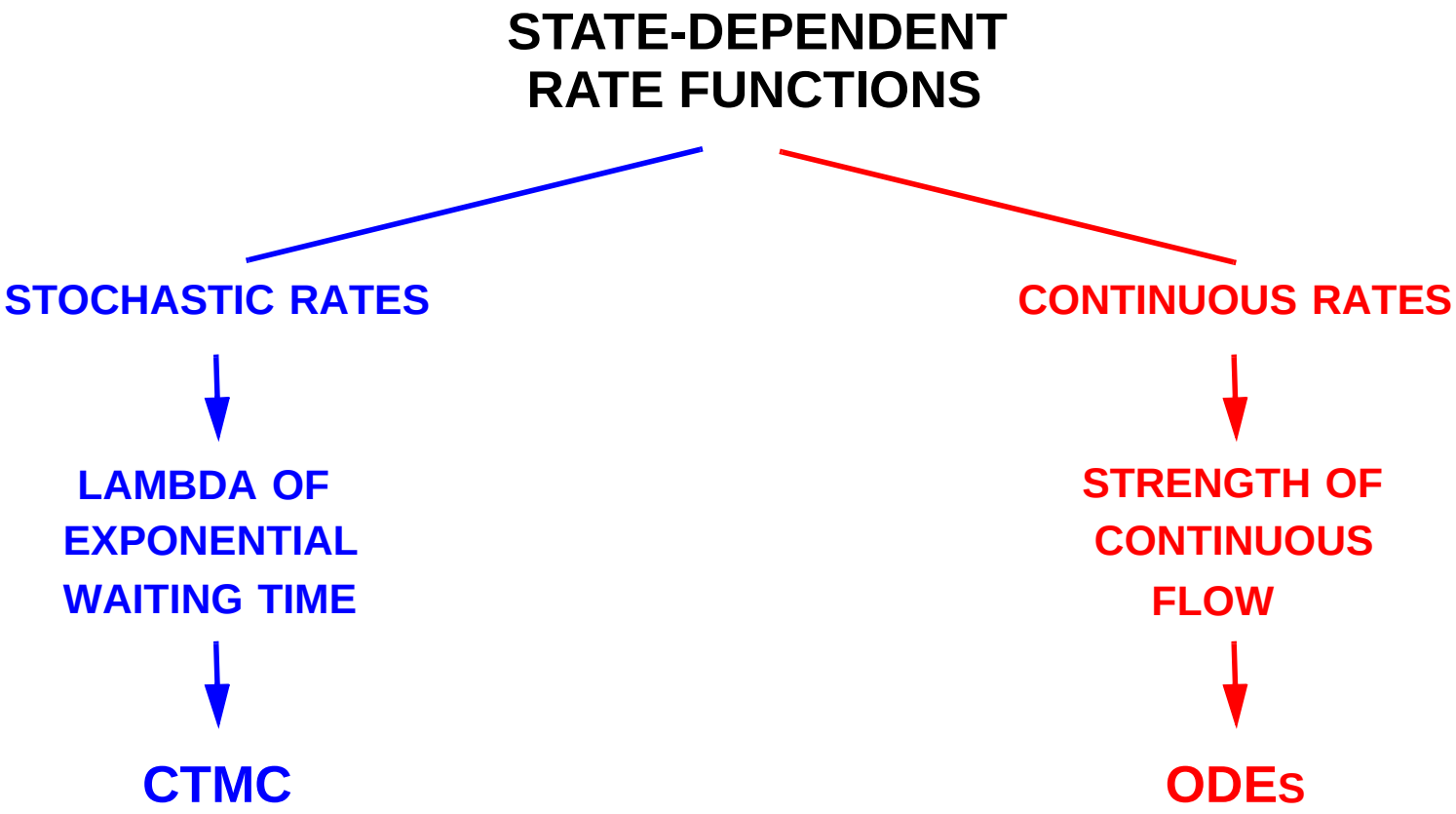
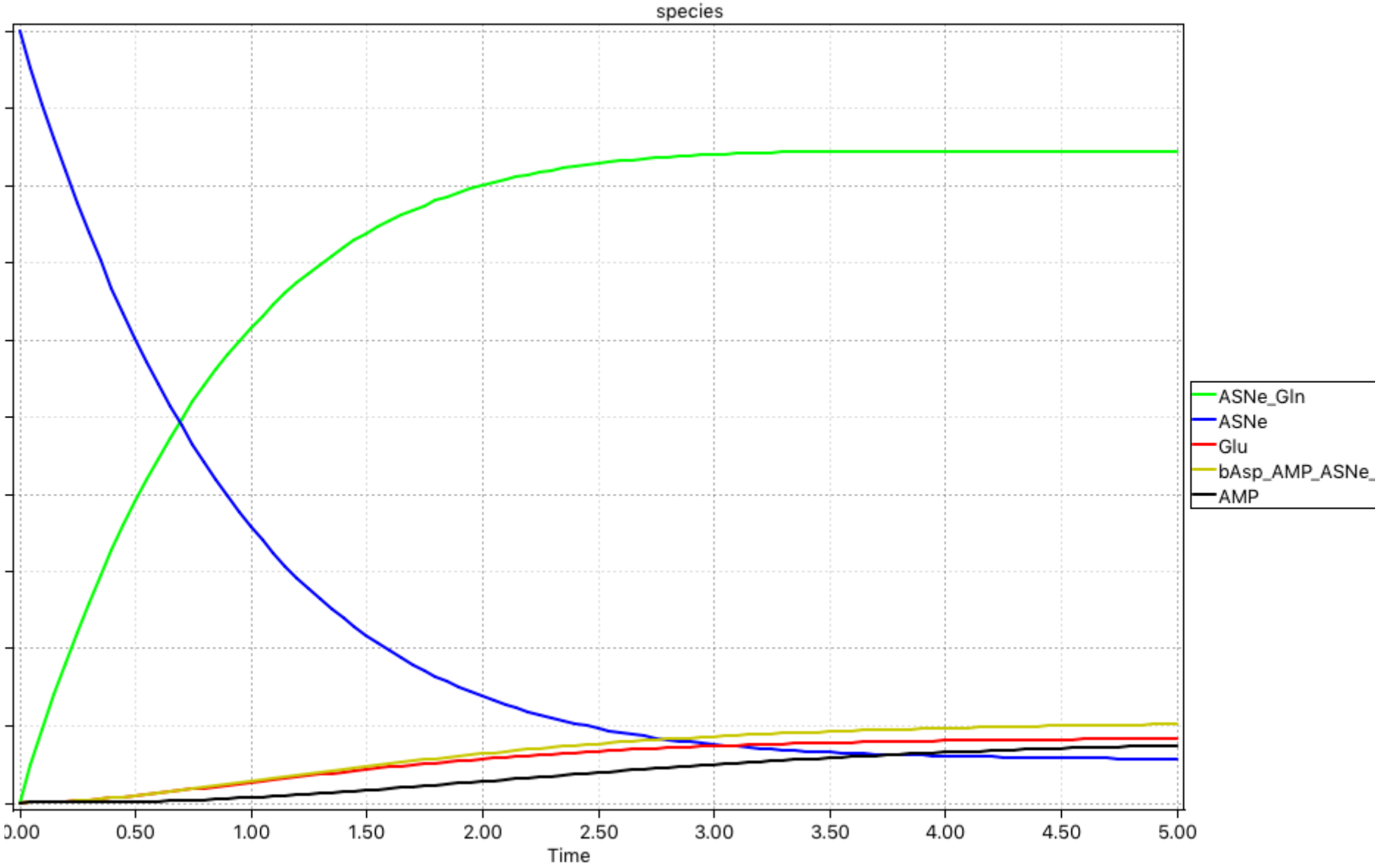
STATE-DEPENDENT RATE FUNCTIONS

ADDING TIME TO TRANSITIONS / REACTIONS



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

EX: WHEAT - DETERMINISTIC RUN (ODES)



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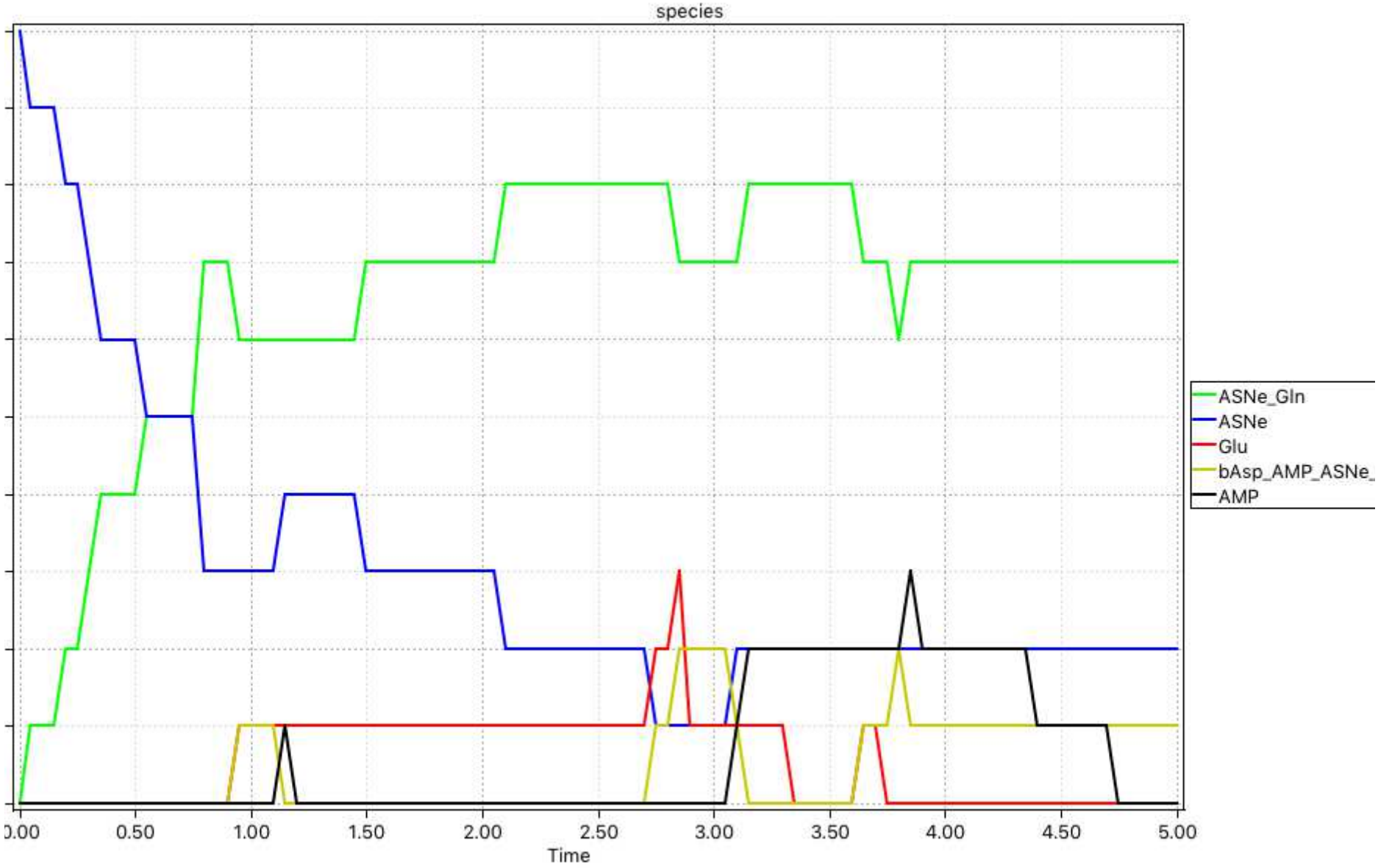
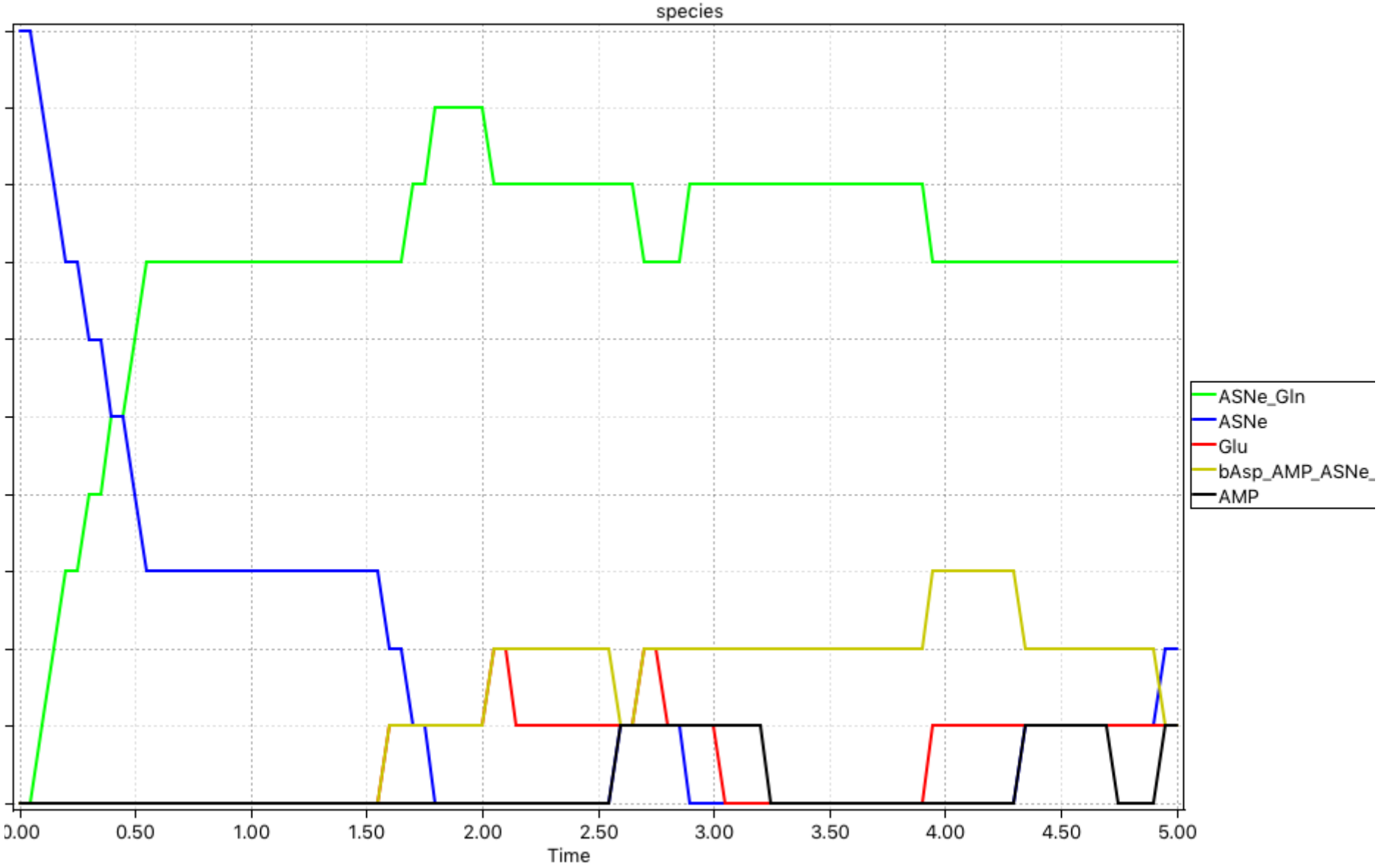
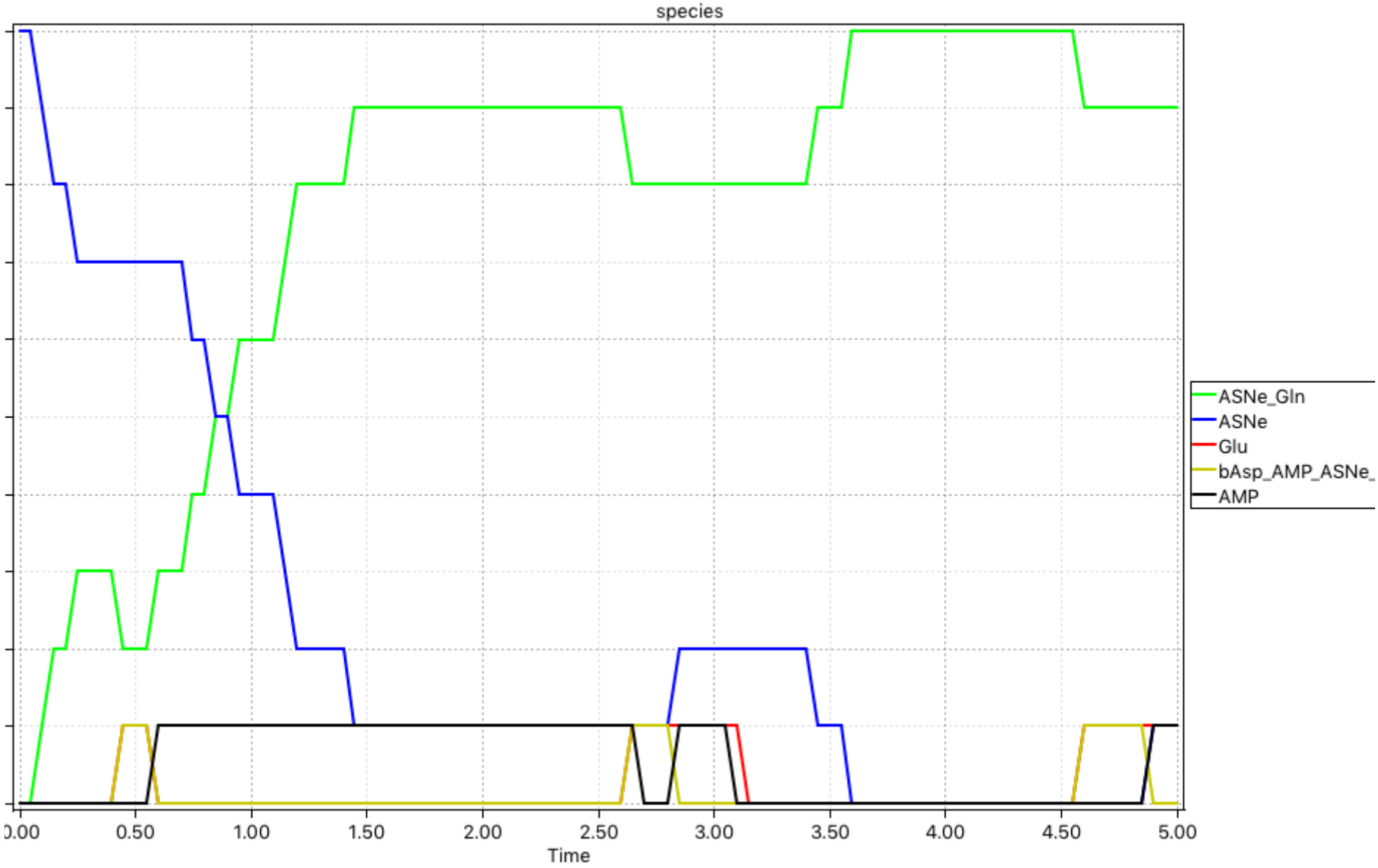
EX: WHEAT - STOCHASTIC RUNS - 10 A



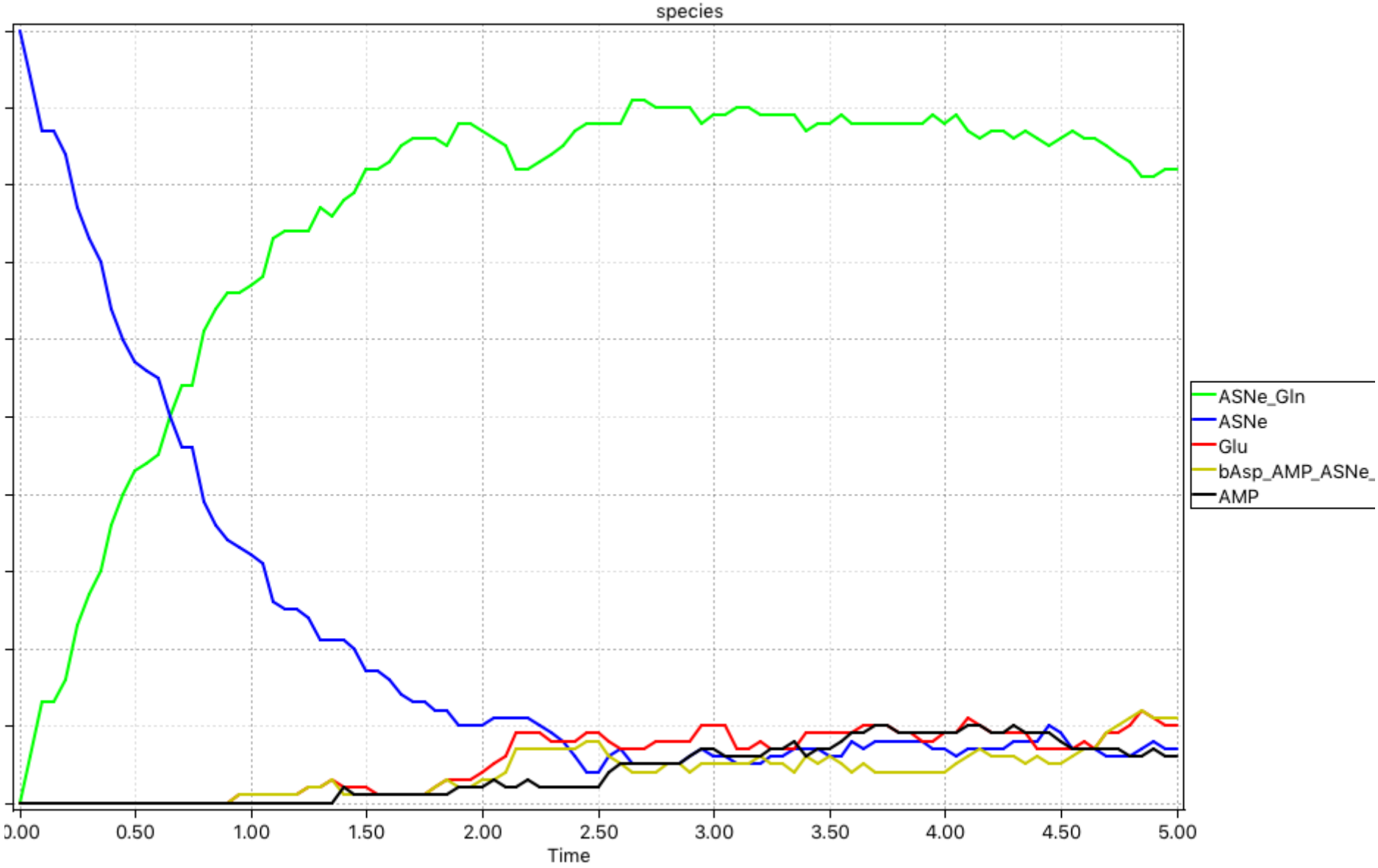
EX: WHEAT - STOCHASTIC RUNS - 10 B



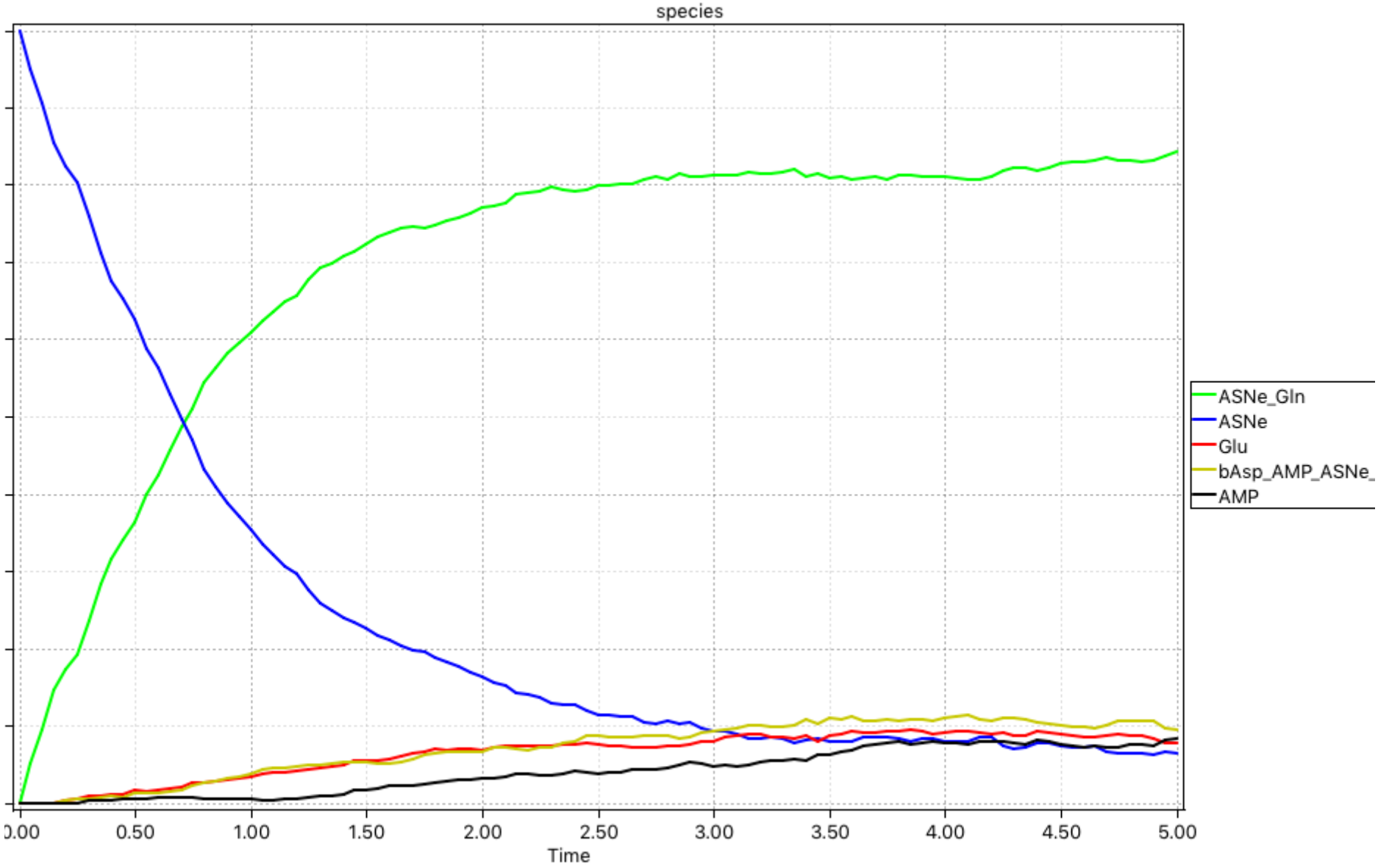
EX: WHEAT - STOCHASTIC RUNS - 10 C



EX: WHEAT - STOCHASTIC RUNS - 100



EX: WHEAT - STOCHASTIC RUNS - 1,000



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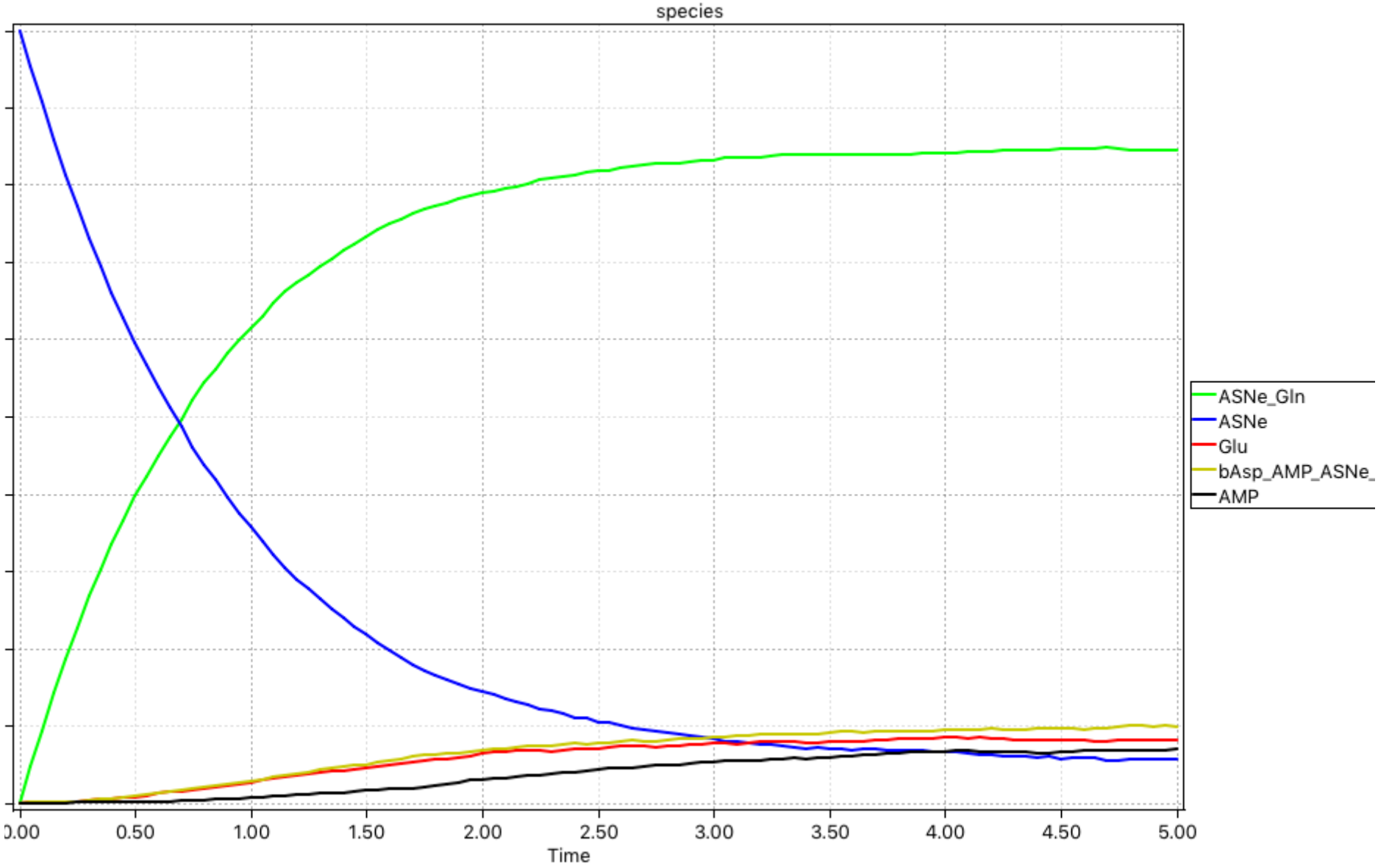
EX: WHEAT - STOCHASTIC RUNS - 10,000



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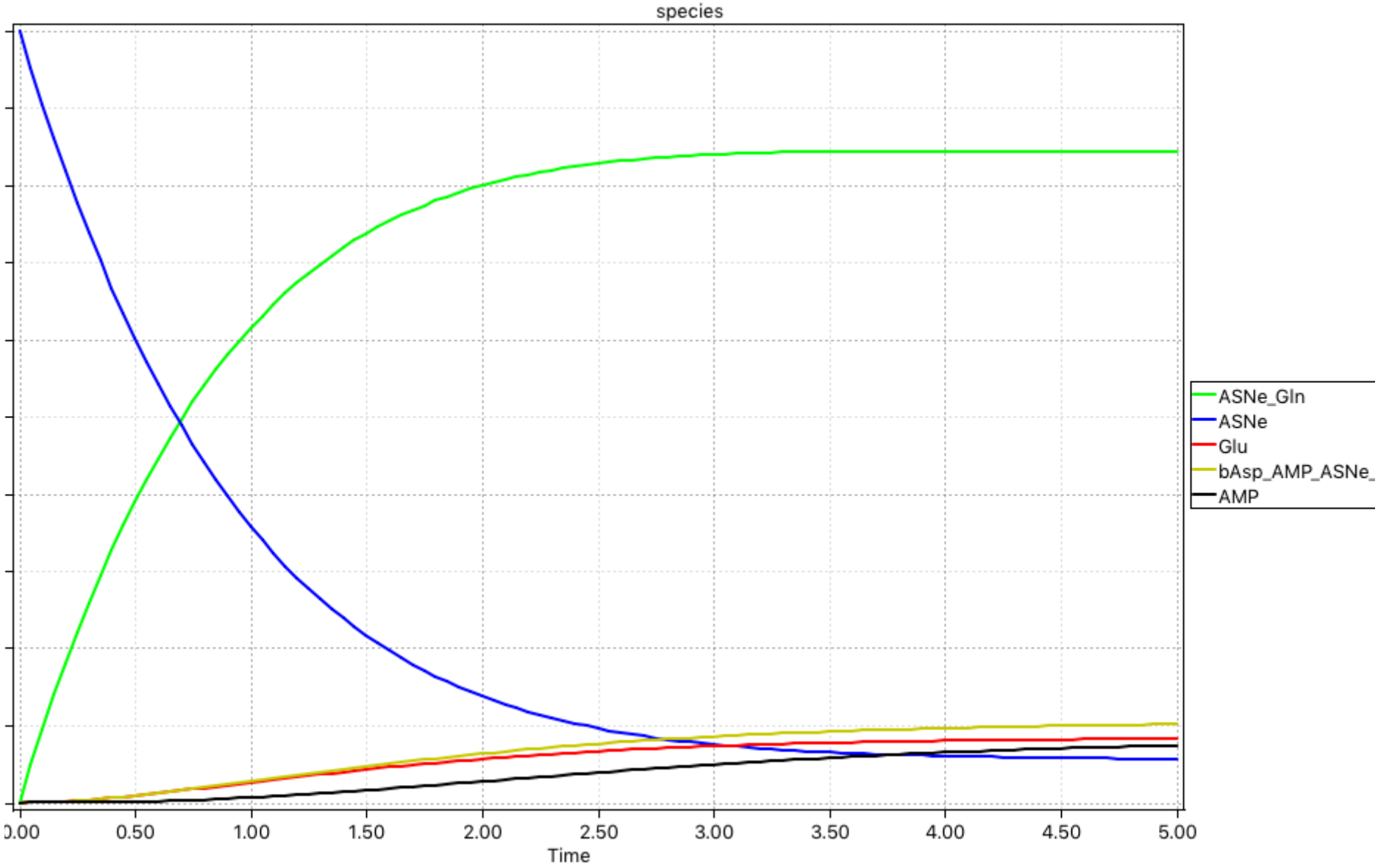
EX: WHEAT - DETERMINISTIC RUN (ODES)



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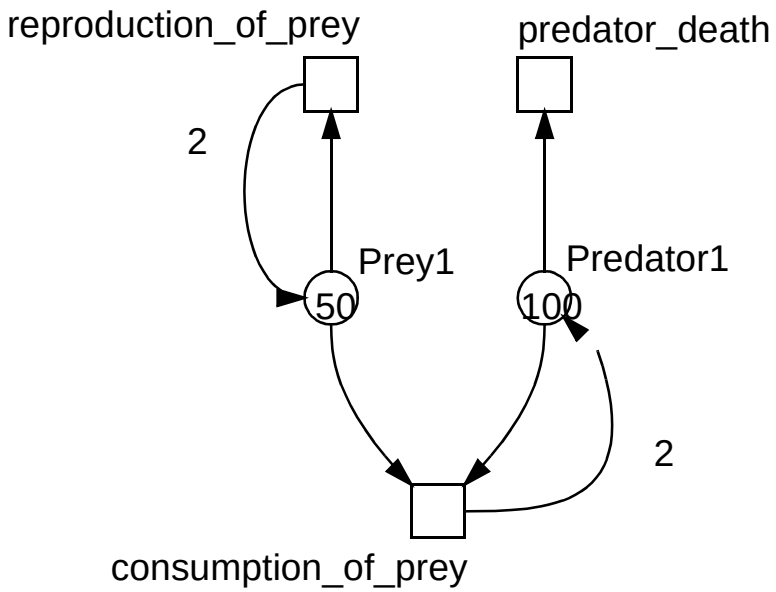
. . . AND THEN THERE WAS COLOUR

Kew Gardens, 24/04/2011

monika.heiner@b-tu.de

EX: PREY - PREDATOR



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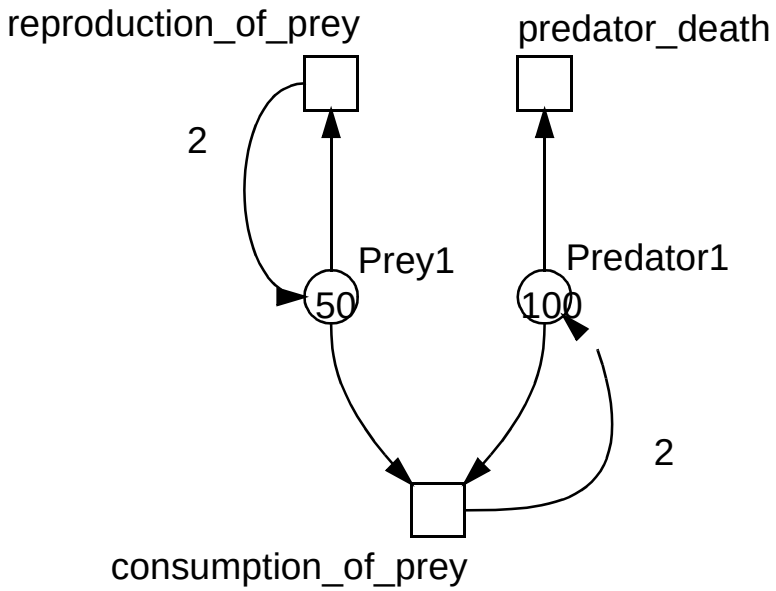
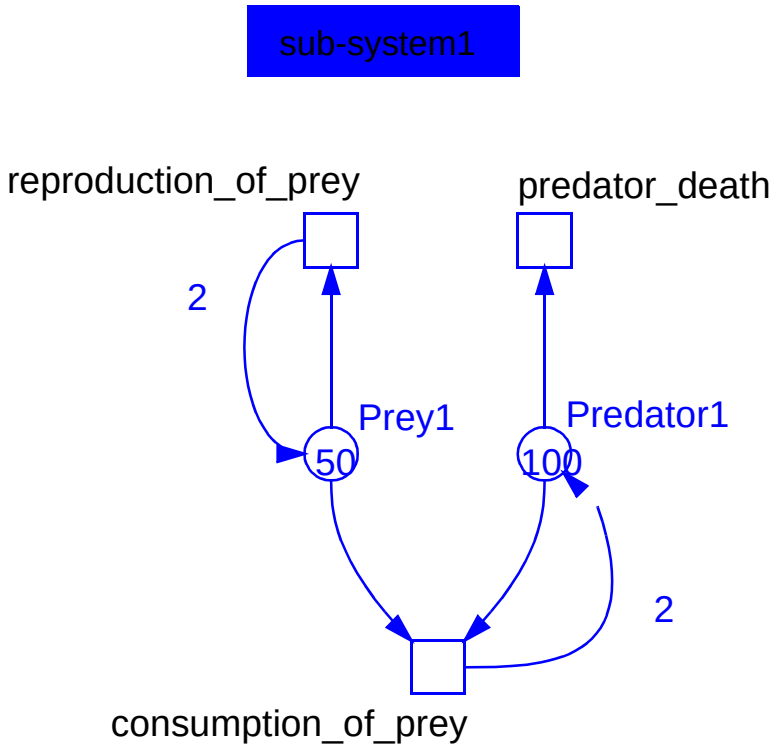
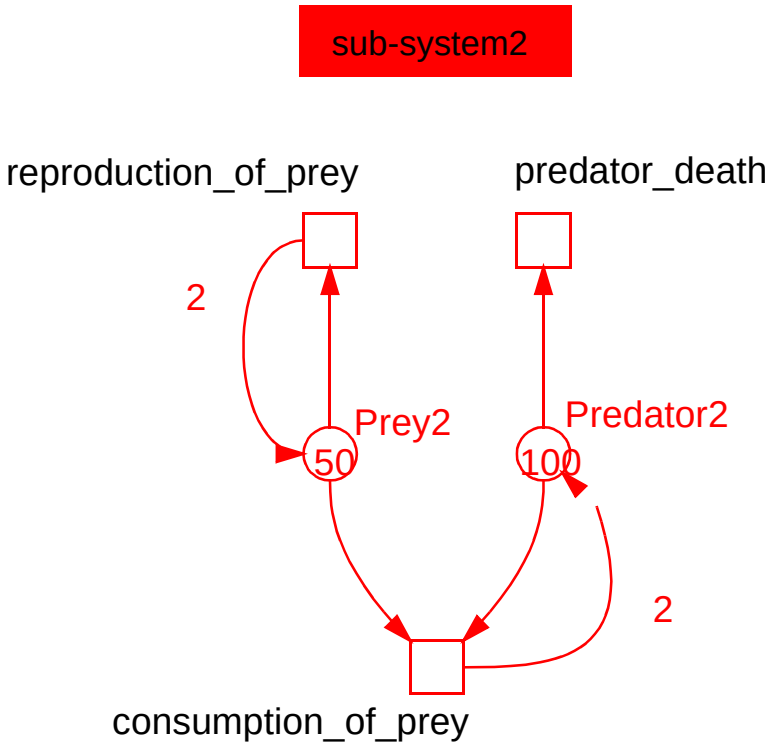


EX: PREY - PREDATOR





EX: PREY - PREDATOR

- **definitions**

  colourset *CS = 1-2;*

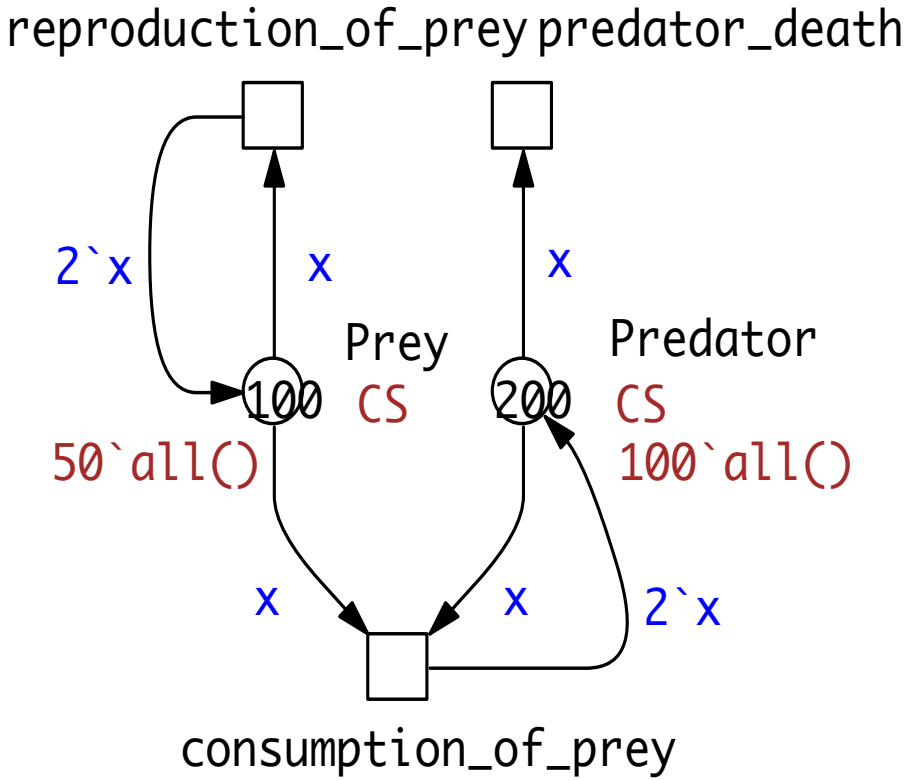
  var *x : CS;*

- **better:**

  const *SIZE = 2;*

  colourset *CS = 1-SIZE;*

  var *x : CS;*



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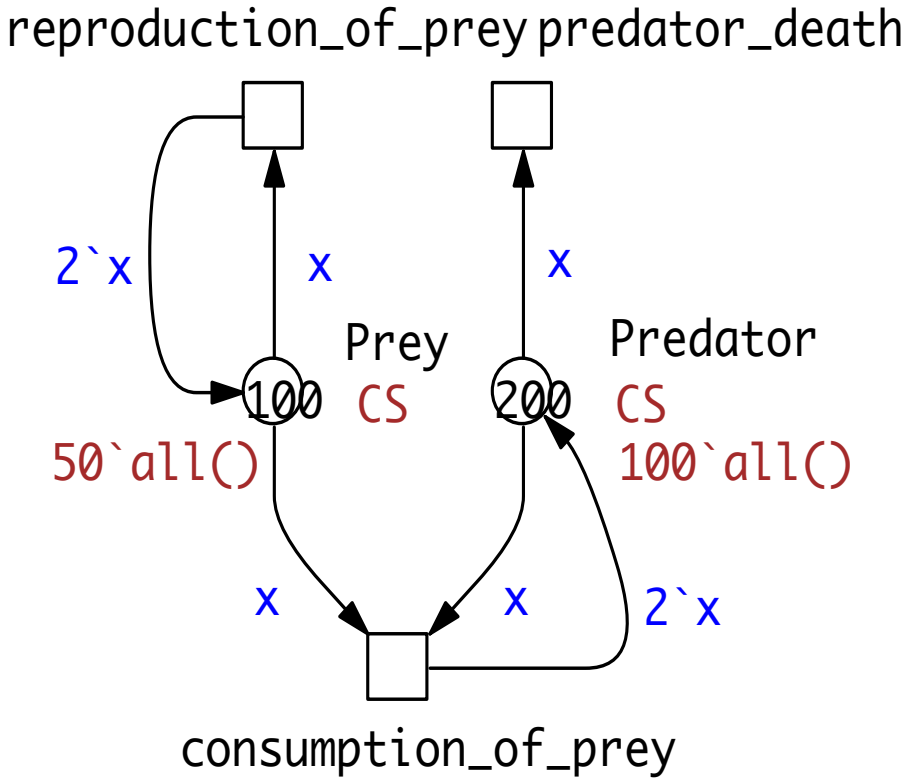
  colourset *CS = 1-SIZE;*

  var *x : CS;*



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

COLOURING SPACE

.

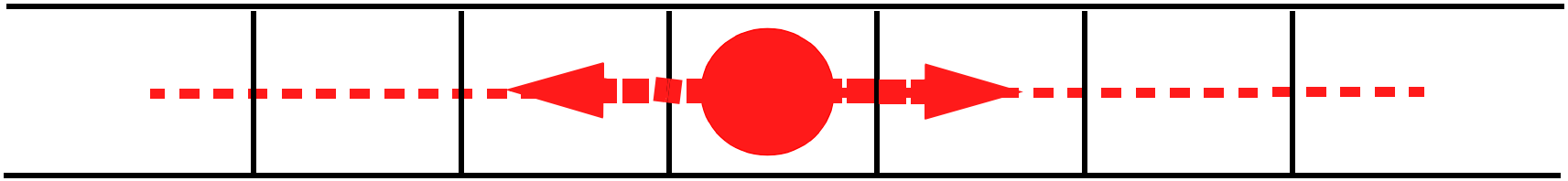
EXAMPLE 1:

DIFFUSION IN SPACE

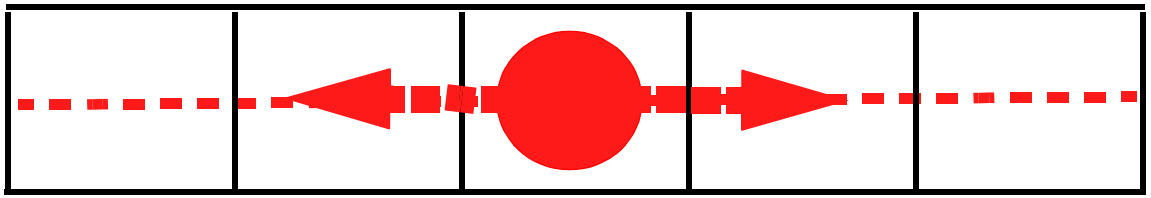
Heiner, Gilbert, Liu, Saunders:
Colouring Space - A Coloured Framework for Spatial Modelling in Systems Biology;
Proc. PETRI NETS 2013, LNCS 7927, 2013.

Richmond, 13/09/2011

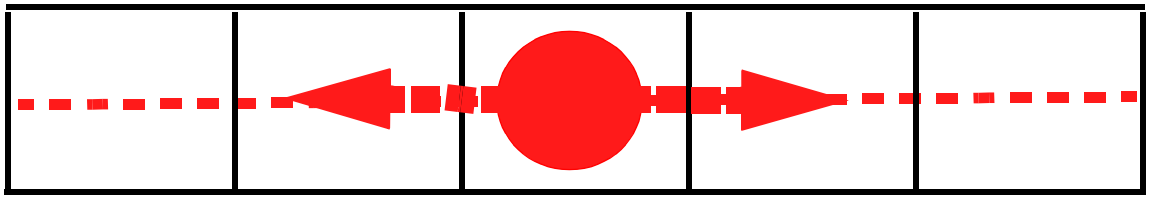
EX1: DIFFUSION - 1D

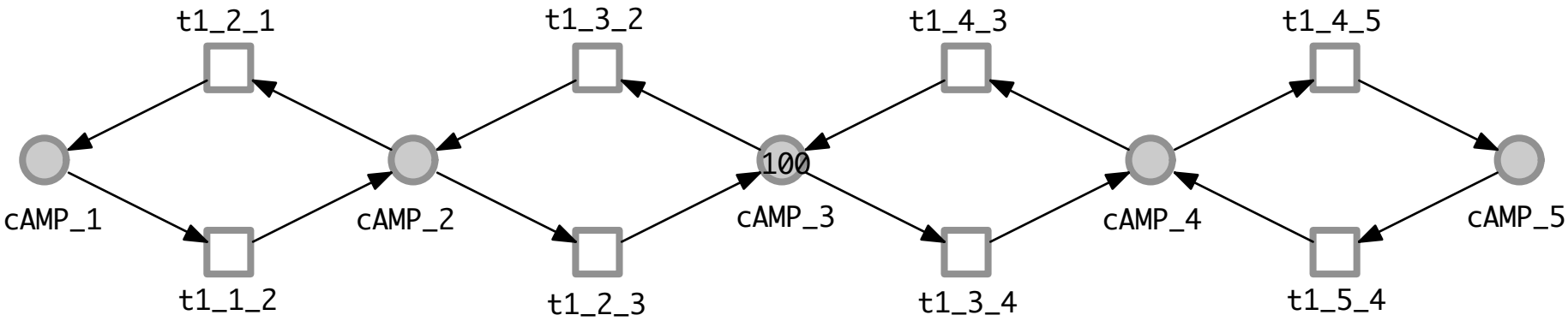


EX1: DIFFUSION - 1D



EX1: DIFFUSION - 1D





EX1: DIFFUSION - 1D

- **definitions**

```
const D1 = 5;                // grid size
const MIDDLE = D1/2;
colorset Grid1D = 1-D1; // grid positions
var x,y : Grid1D;
```

EX1: DIFFUSION - 1D

- **definitions**

```
const D1 = 5;                // grid size
const MIDDLE = D1/2;
colorset Grid1D = 1-D1; // grid positions
var x,y : Grid1D;

function neighbour1D (Grid1D x,a) bool:
  // a is neighbour of x
  ( a=x-1 | a=x+1)  & (1<=a) & (a<=D1);
```

EX1: DIFFUSION - 1D

definitions

```
const D1 = 5;                // grid size
const MIDDLE = D1/2;
colorset Grid1D = 1-D1; // grid positions
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```
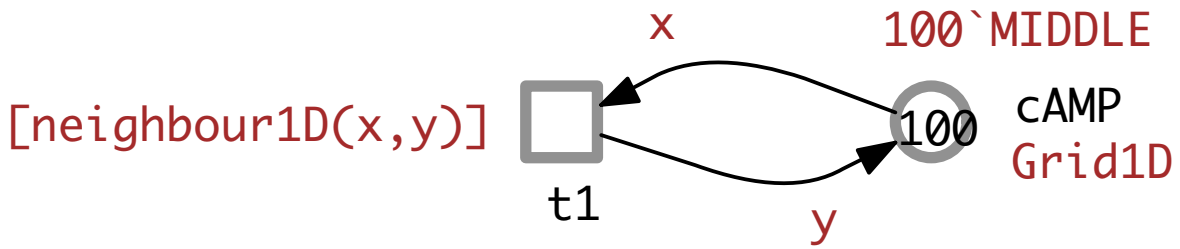
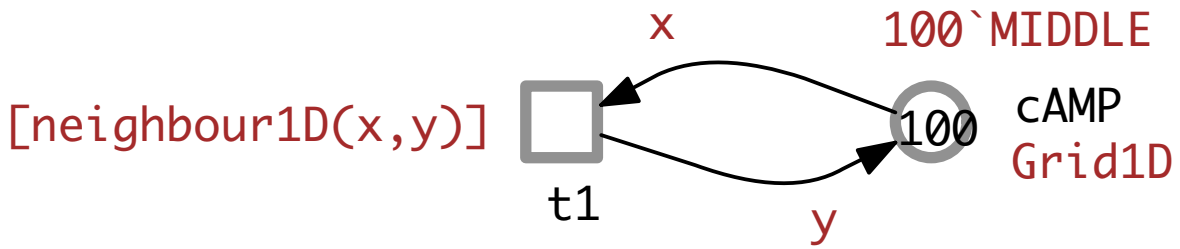



EX1: DIFFUSION - 1D

- **definitions**

```
const D1 = 5;                // grid size
const MIDDLE = D1/2;
colorset Grid1D = 1-D1; // grid positions
var x,y : Grid1D;

function neighbour1D (Grid1D x,a) bool:
  // a is neighbour of x
  ( a=x-1 | a=x+1)  & (1<=a) & (a<=D1);
```

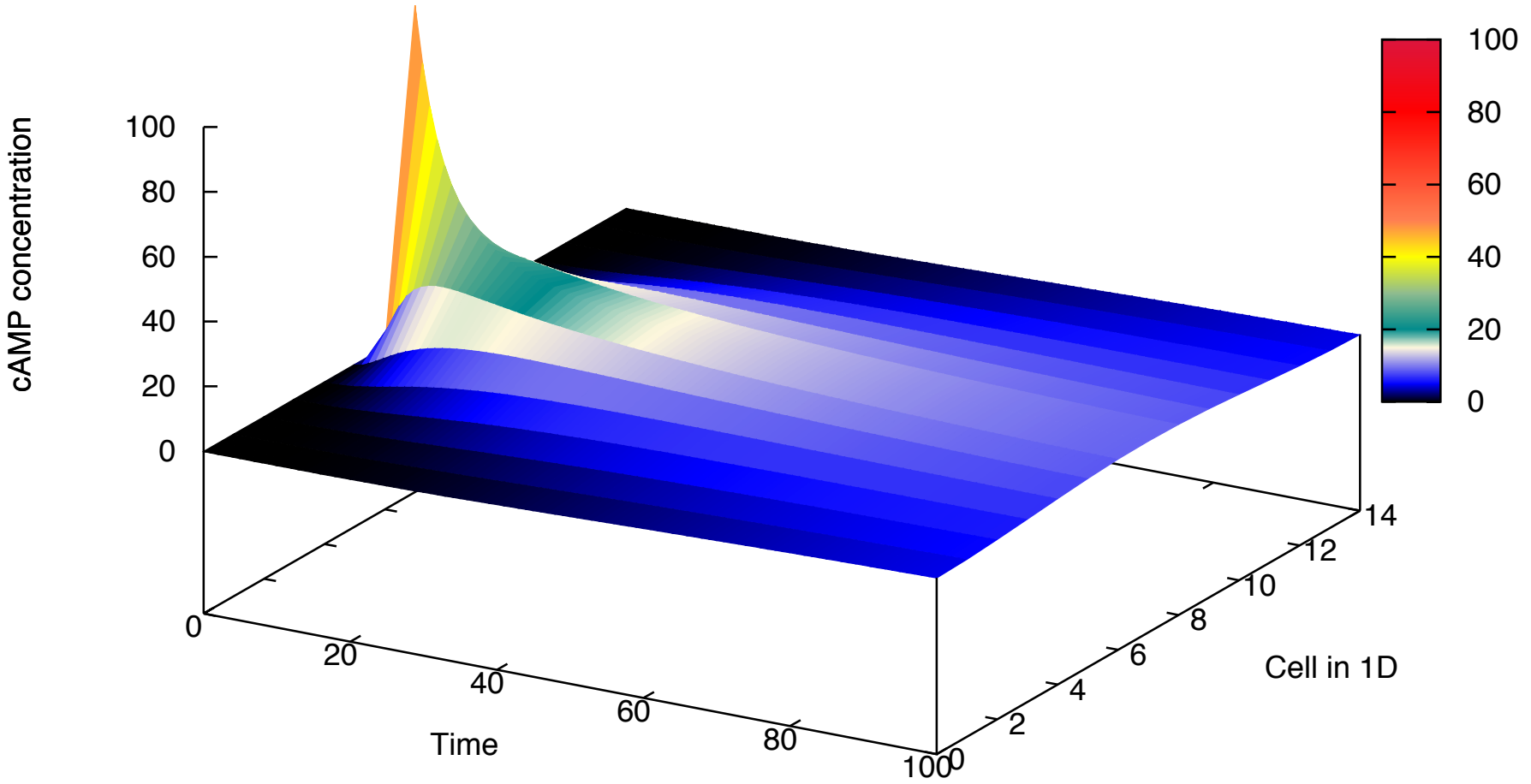


- **movement = changing colour**

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

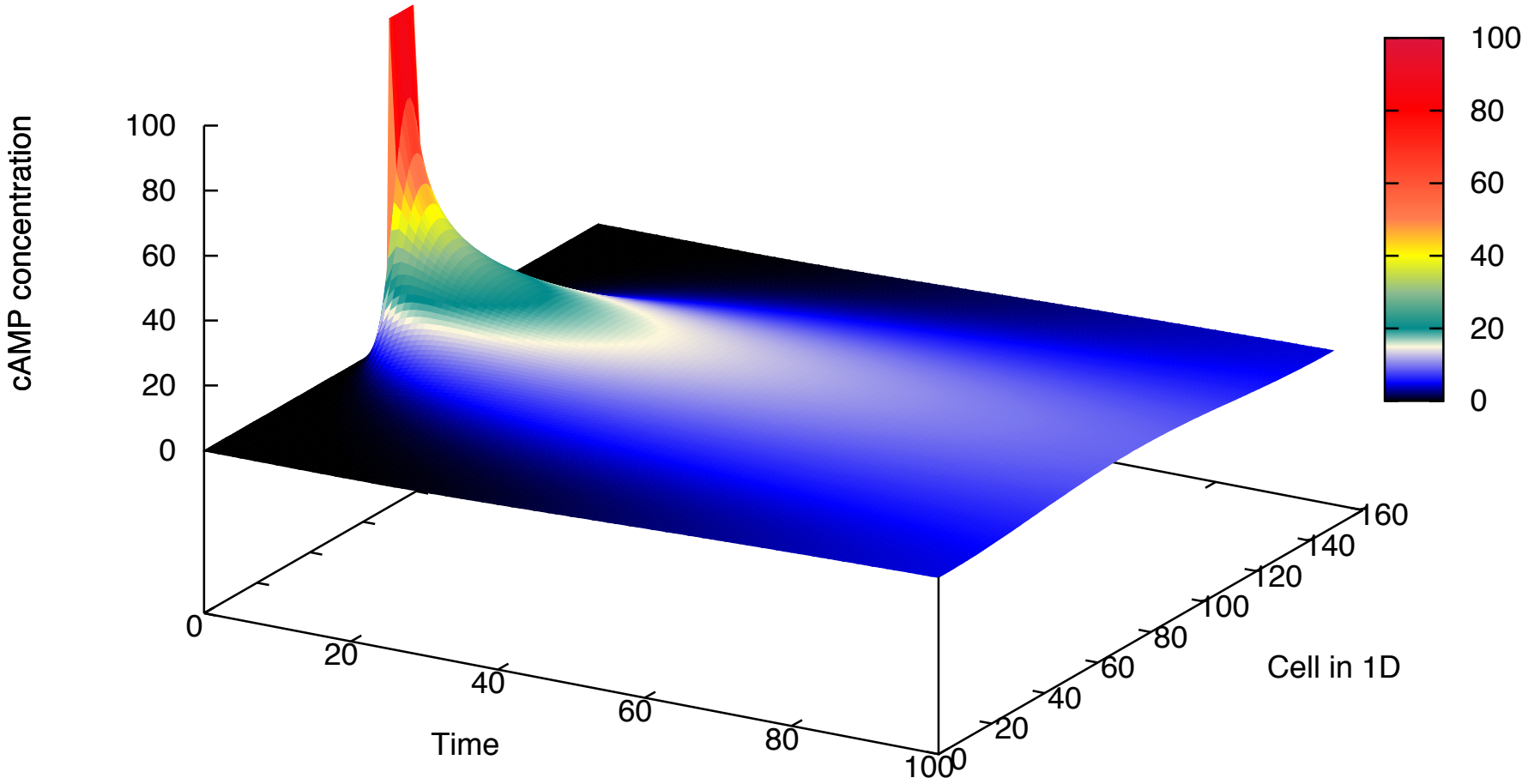
with c_i := cAMP_i

EX1: DIFFUSION - 1D



15 GRID POSITIONS

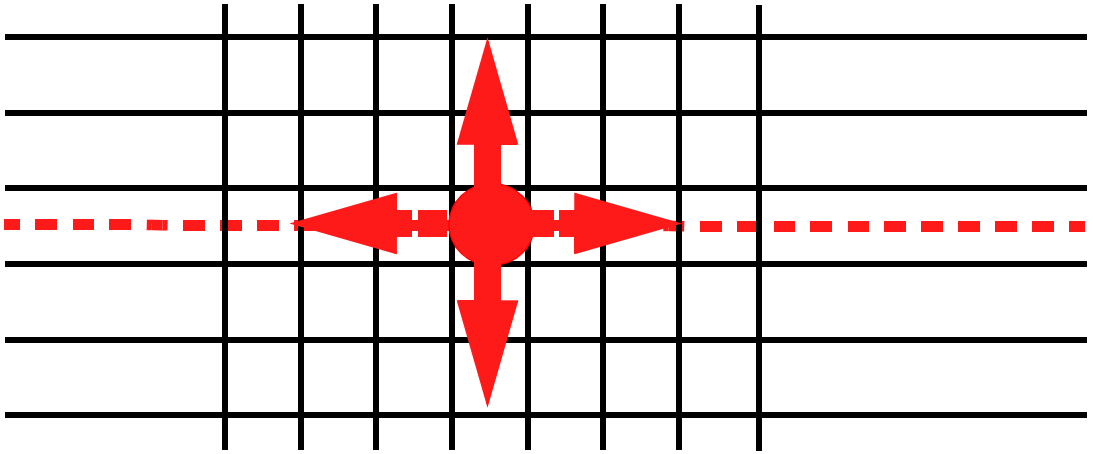
EX1: DIFFUSION - 1D



150 GRID POSITIONS, SCALING OF INITIAL MARKING AND RATES

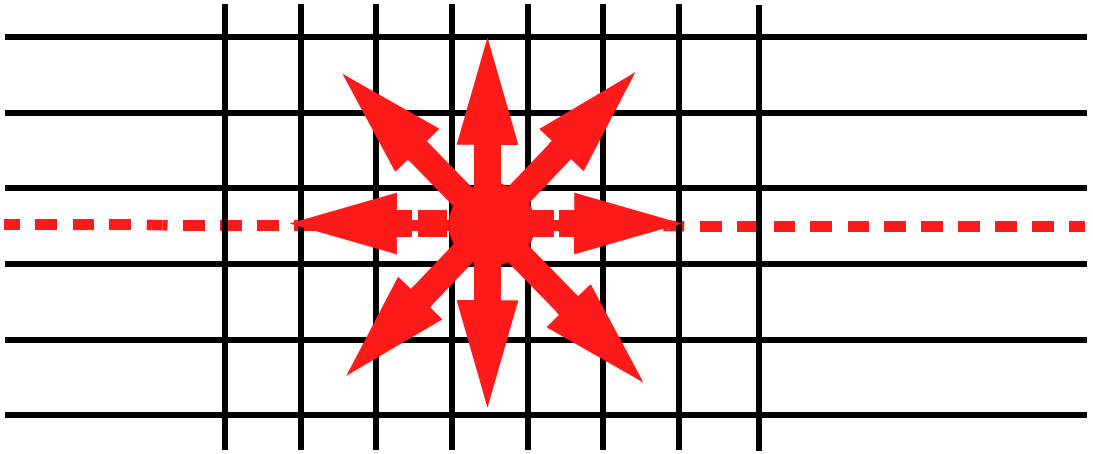
EX1: DIFFUSION - 2D

SCHEME



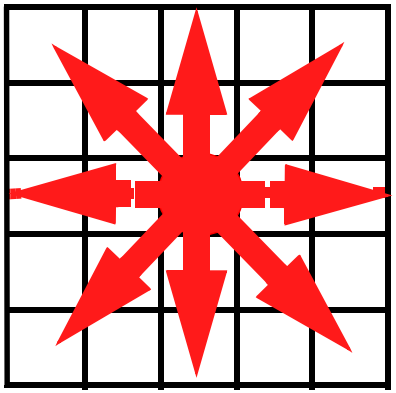
EX1: DIFFUSION - 2D

SCHEME



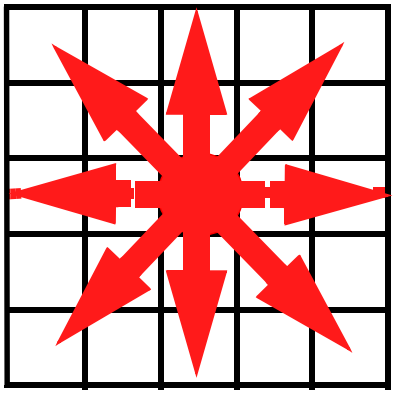
EX1: DIFFUSION - 2D

SCHEME



EX1: DIFFUSION - 2D

SCHEME



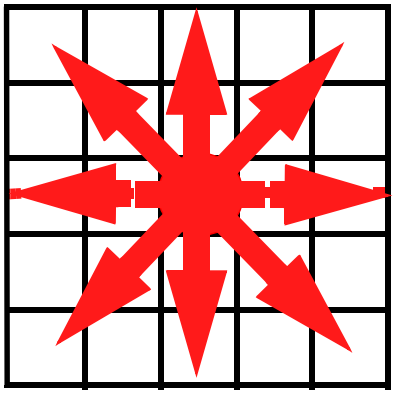
definitions

const *D1 = 5;* *// grid size first dimension*

const *D2 = D1;* *// grid size second dimension*

EX1: DIFFUSION - 2D

SCHEME

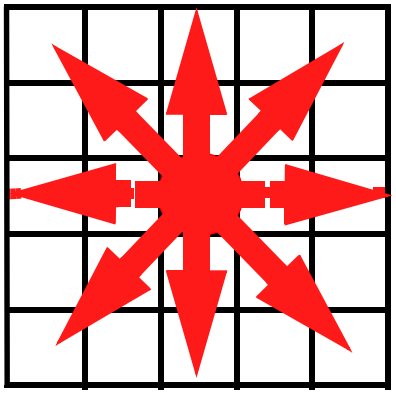


definitions

```
const D1 = 5;                    // grid size first dimension
const D2 = D1;                   // grid size second dimension
const MIDDLE = D1/2;

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

EX1: DIFFUSION - 2D

SCHEME



definitions

```
const D1 = 5;                    // grid size first dimension
const D2 = D1;                   // grid size second dimension
const MIDDLE = D1/2;

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;
```

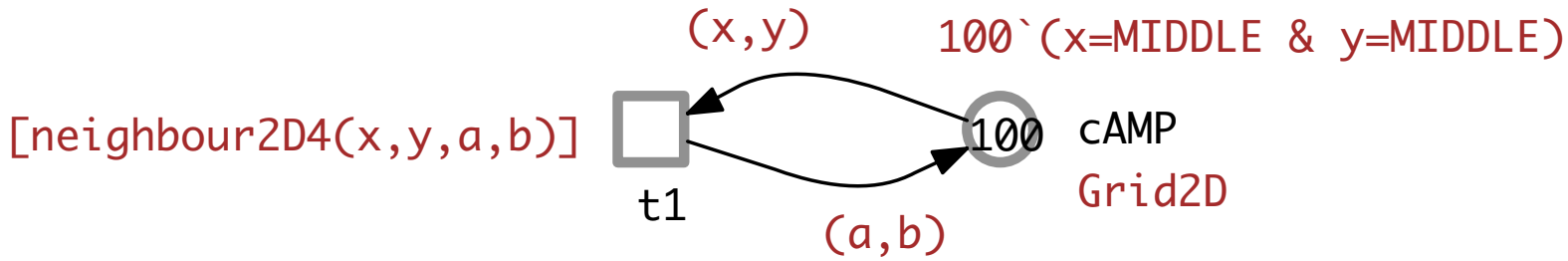
four neighbours

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

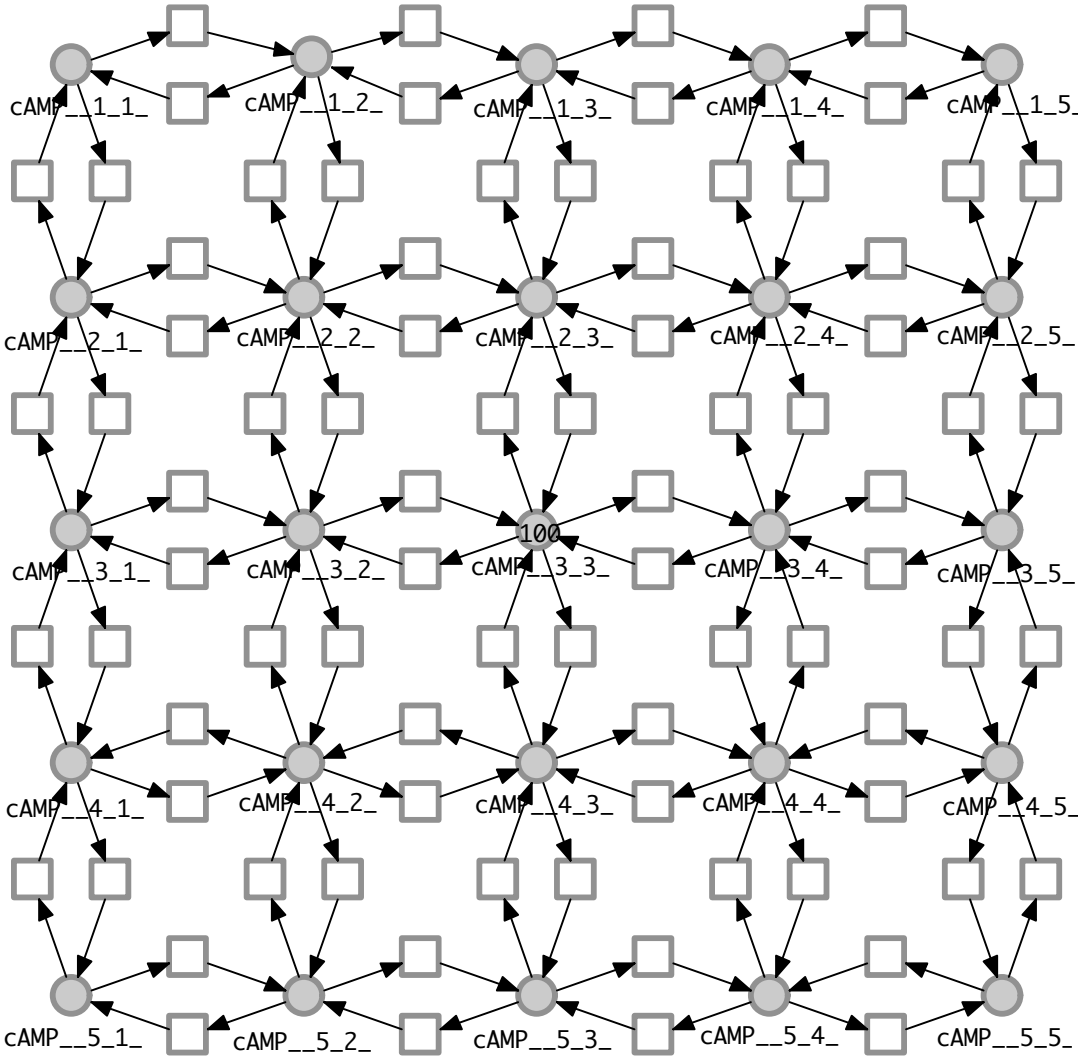
// (a,b) is one of the up to four neighbours of (x,y)

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

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



EX1: DIFFUSION - 2D4 NEIGHBOURHOOD



EX1: DIFFUSION - 2D8 NEIGHBOURHOOD

eight neighbours

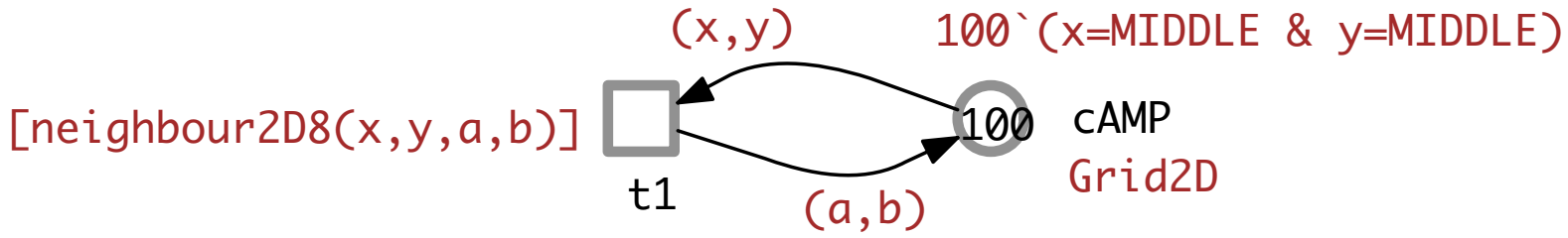
function *neighbour2D8 (CD1 x, CD2 y, CD1 a, CD2 b)* ***bool****:*

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

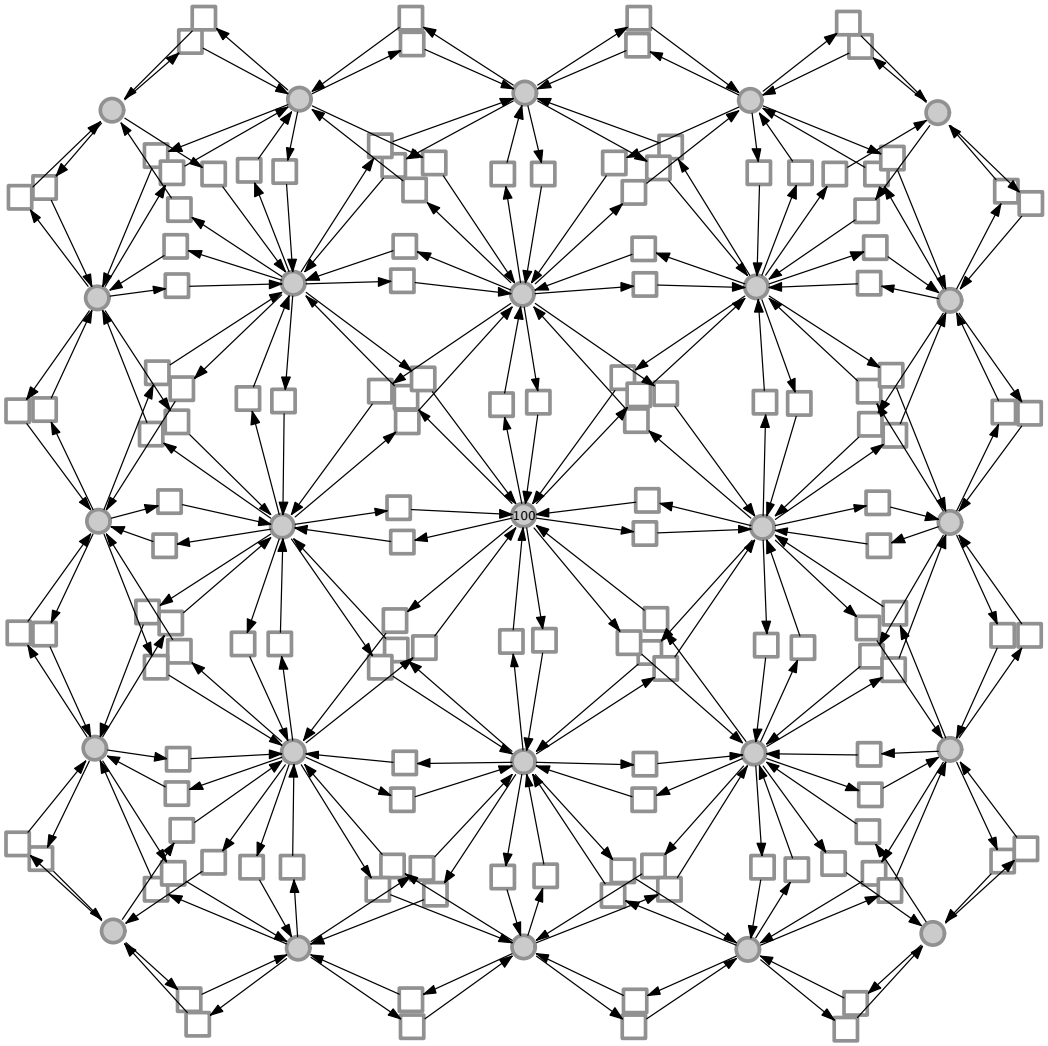
(a=x-1 | a=x | a=x+1) & (b = y-1 | b=y | b=y+1)

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

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



EX1: DIFFUSION - 2D8 NEIGHBOURHOOD



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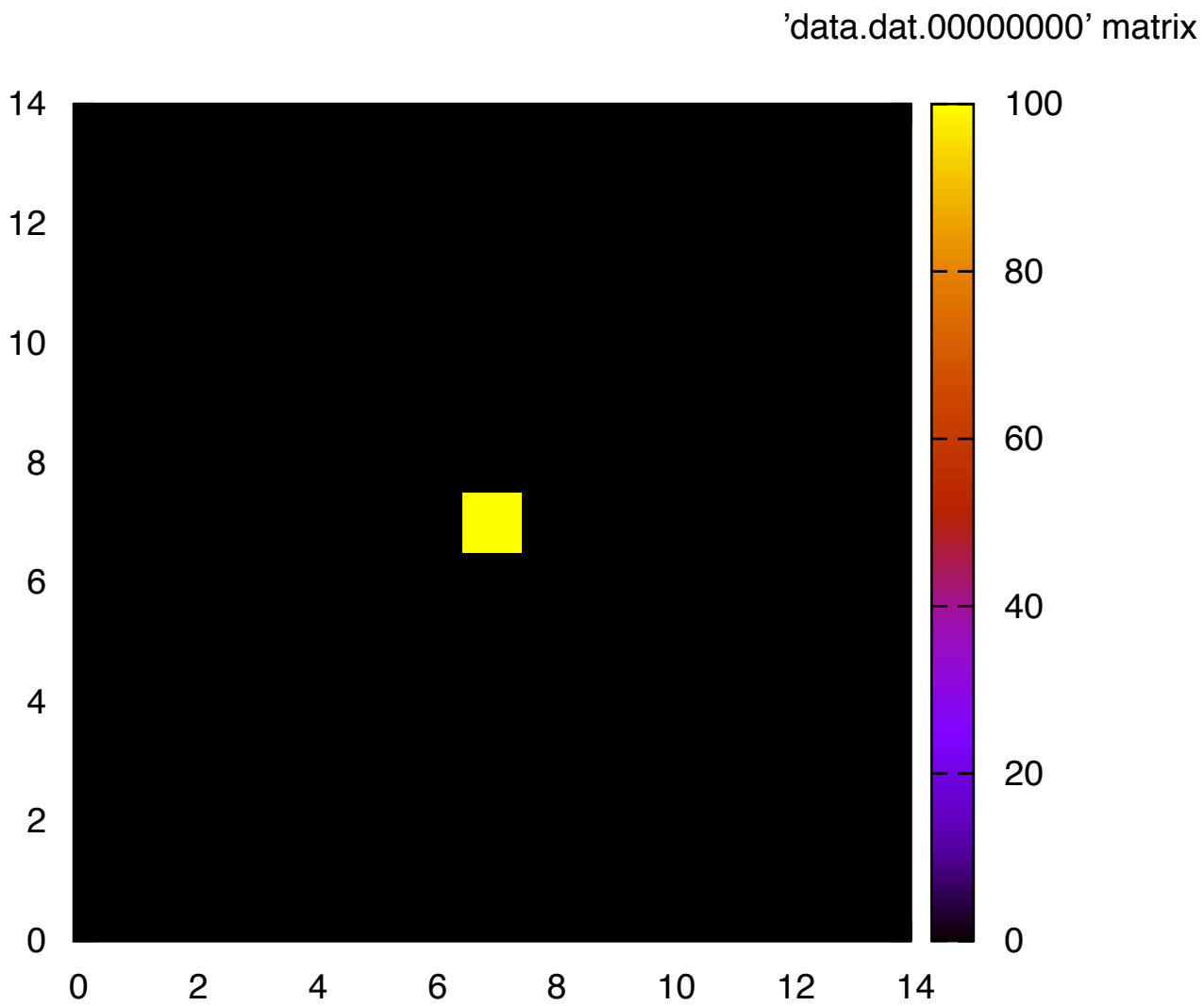
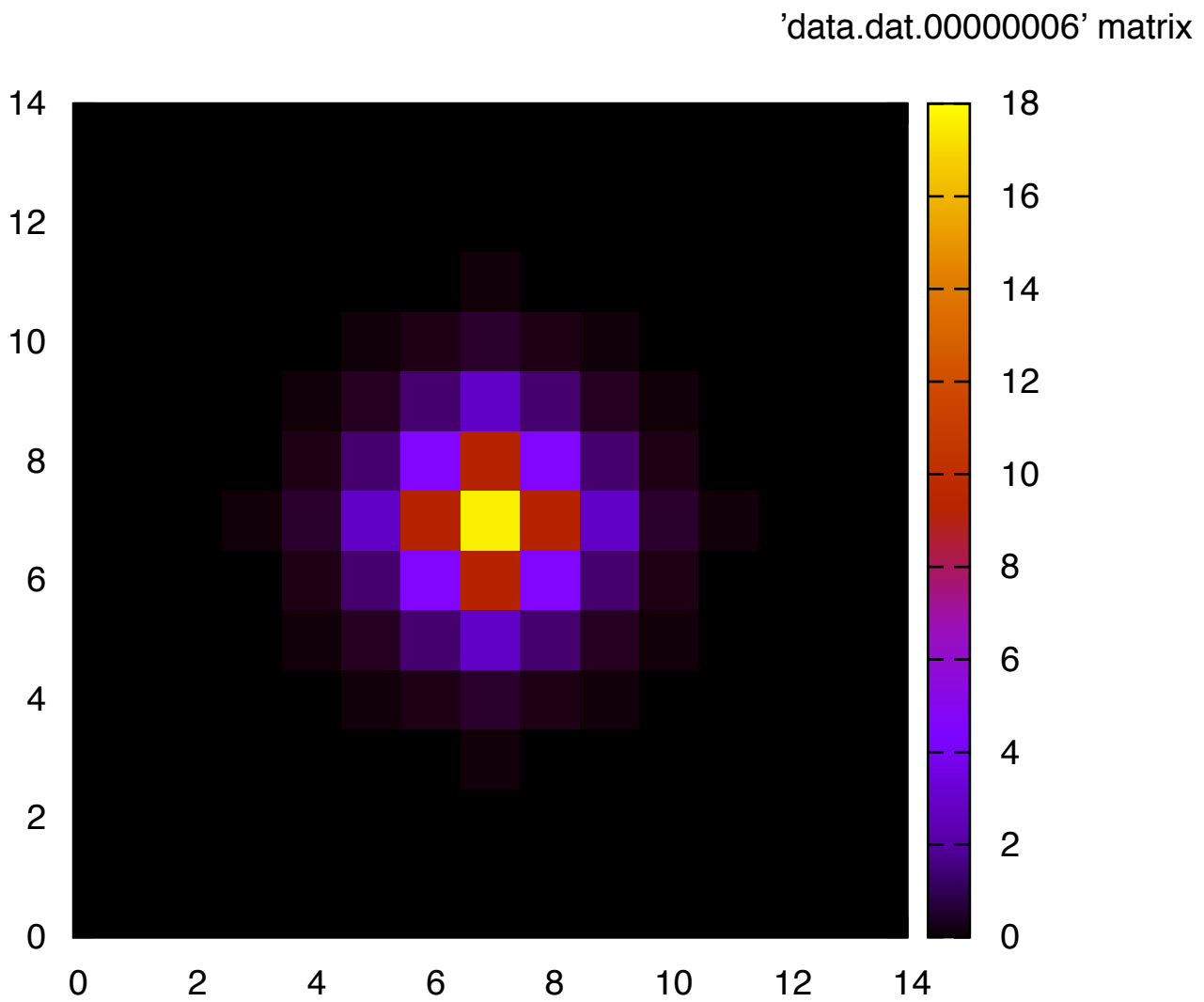
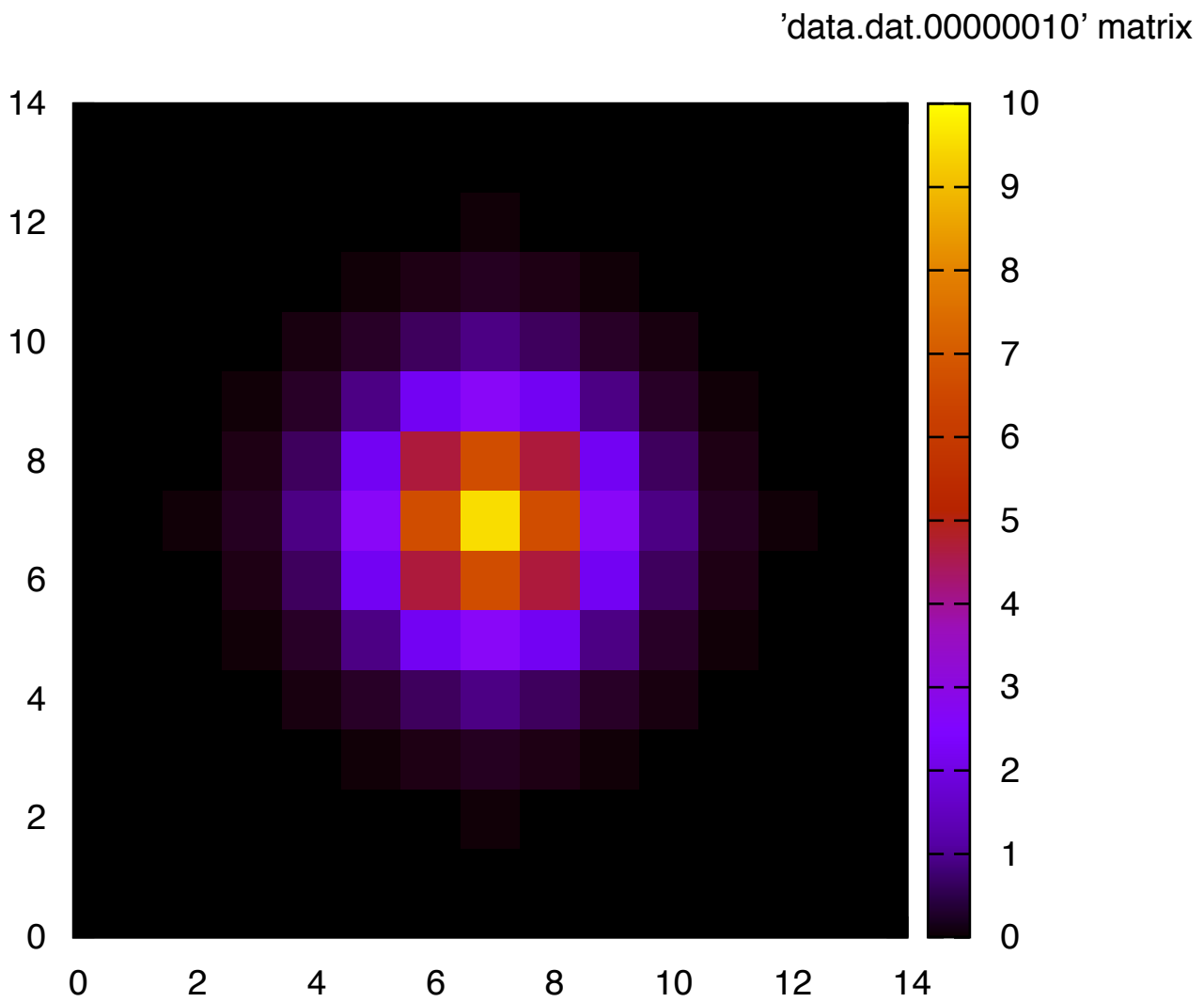
EX1: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15



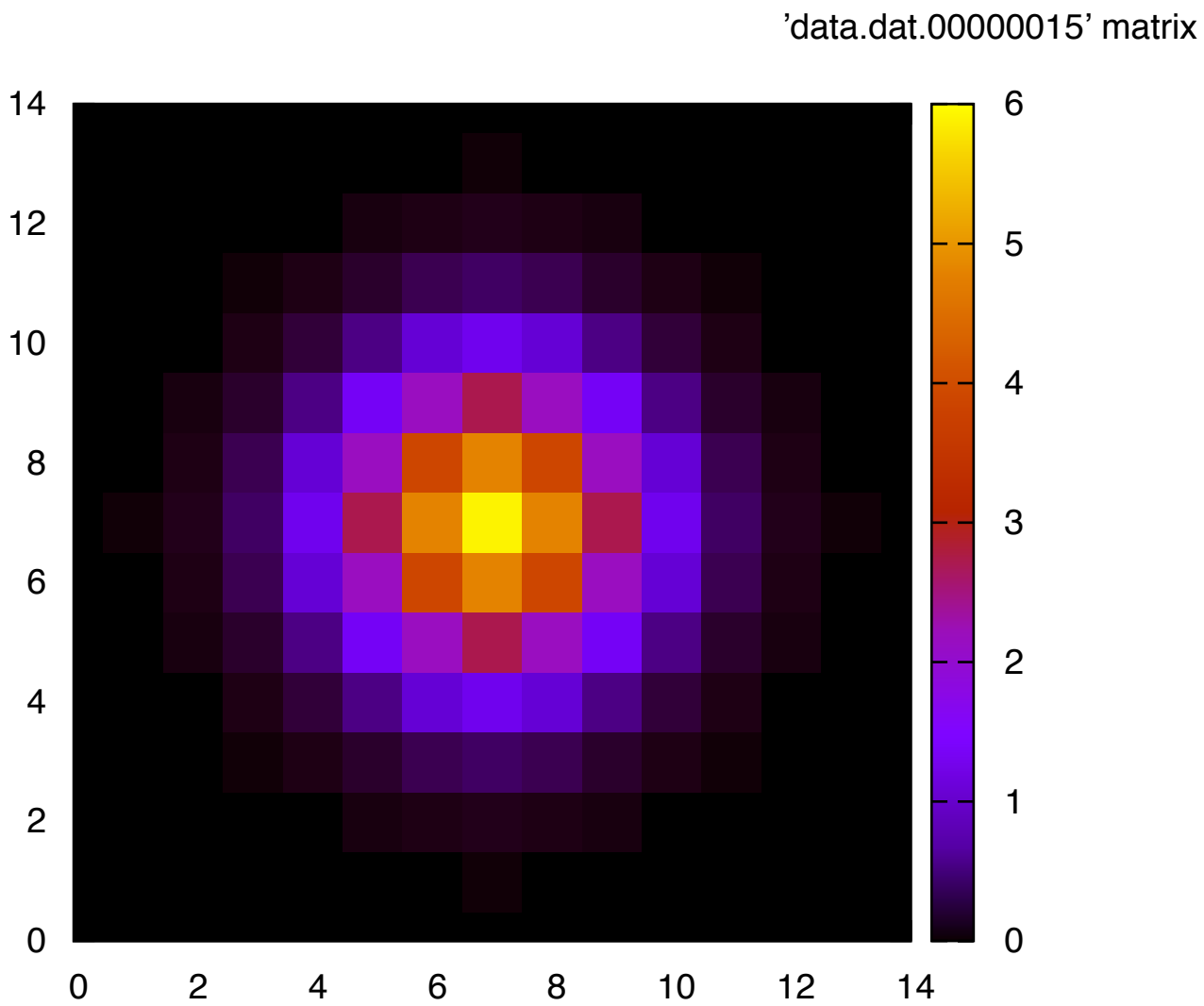
EX1: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15



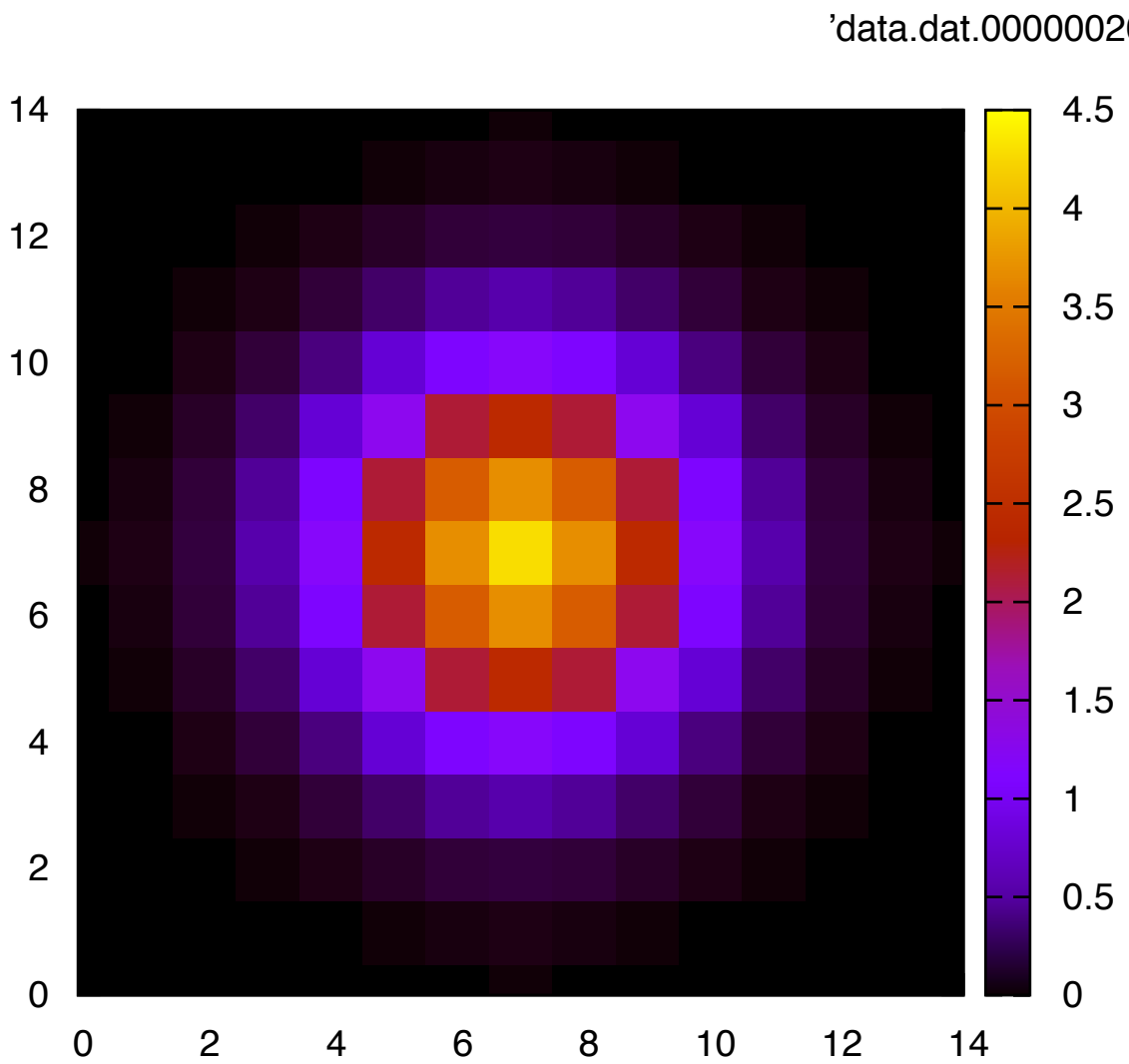
EX1: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15



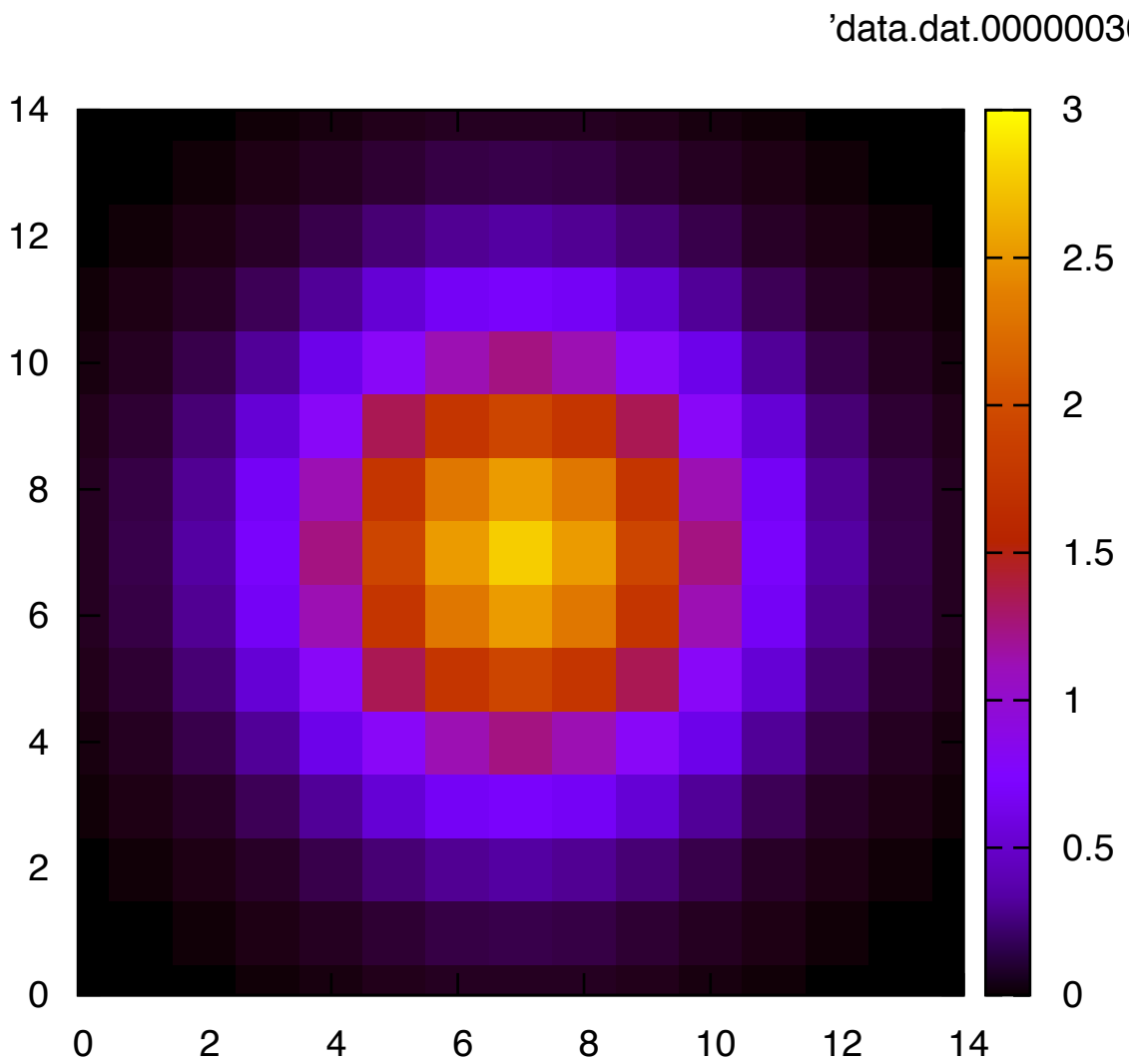
EX1: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15



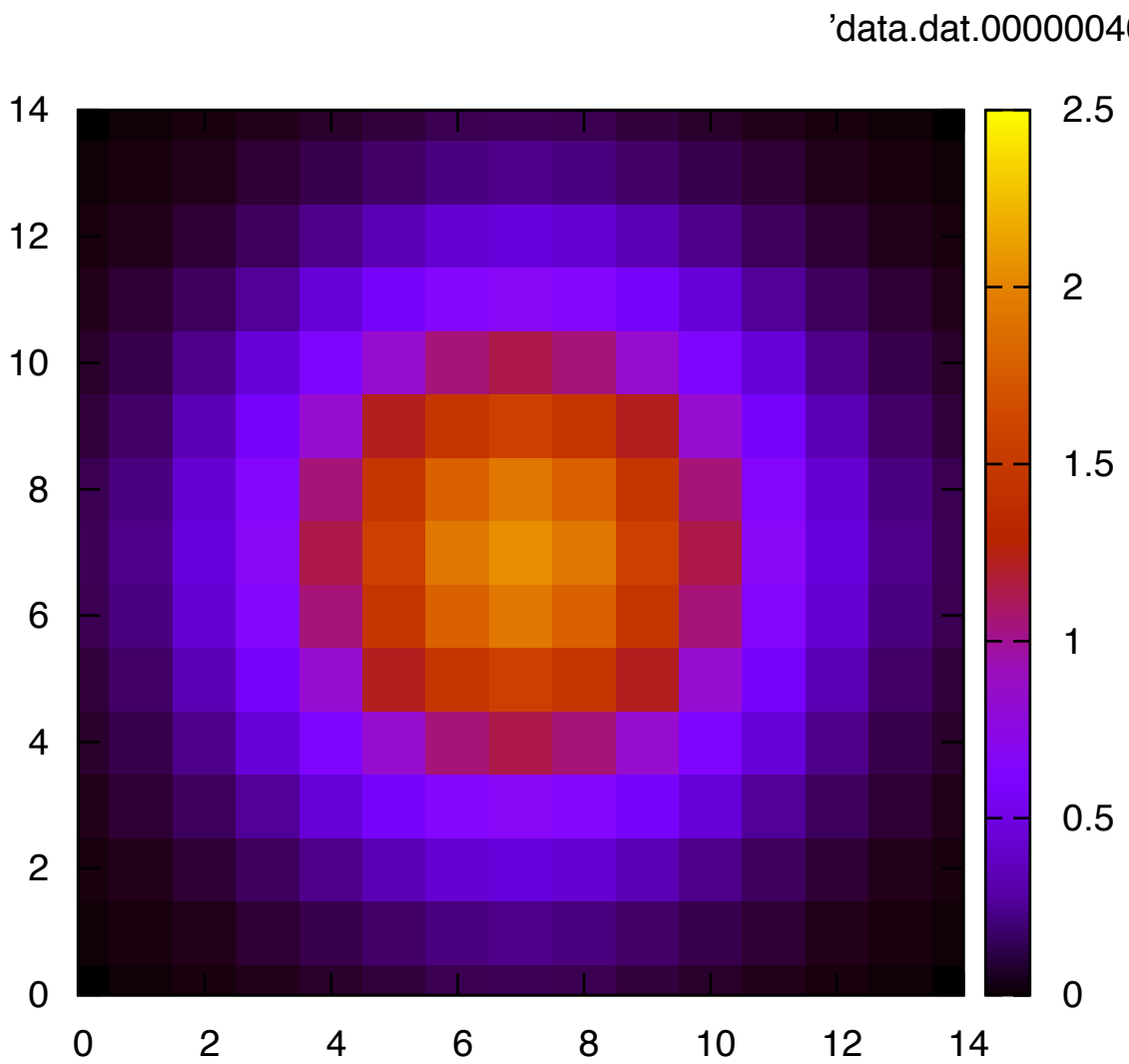
EX1: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15



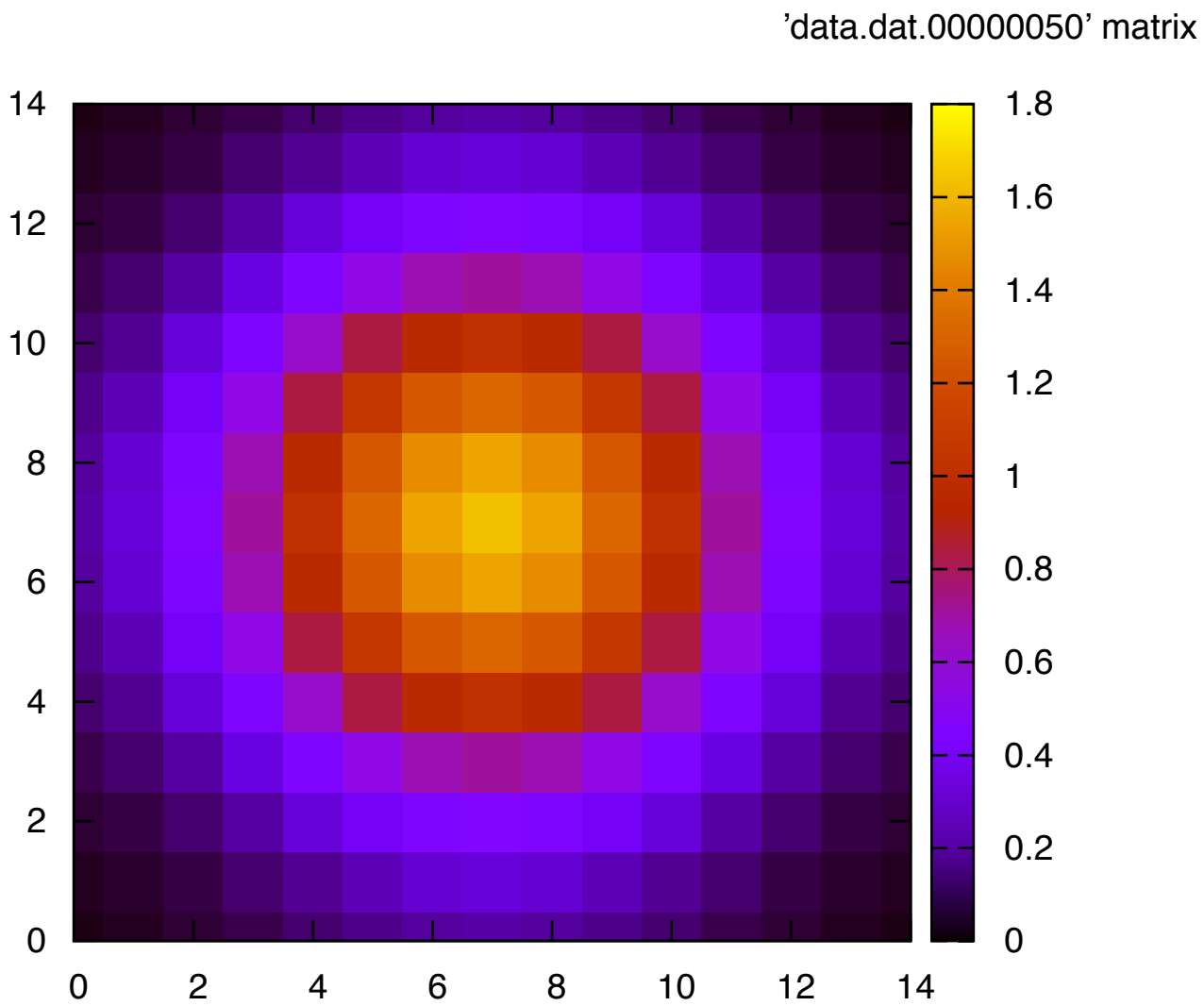
EX1: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15



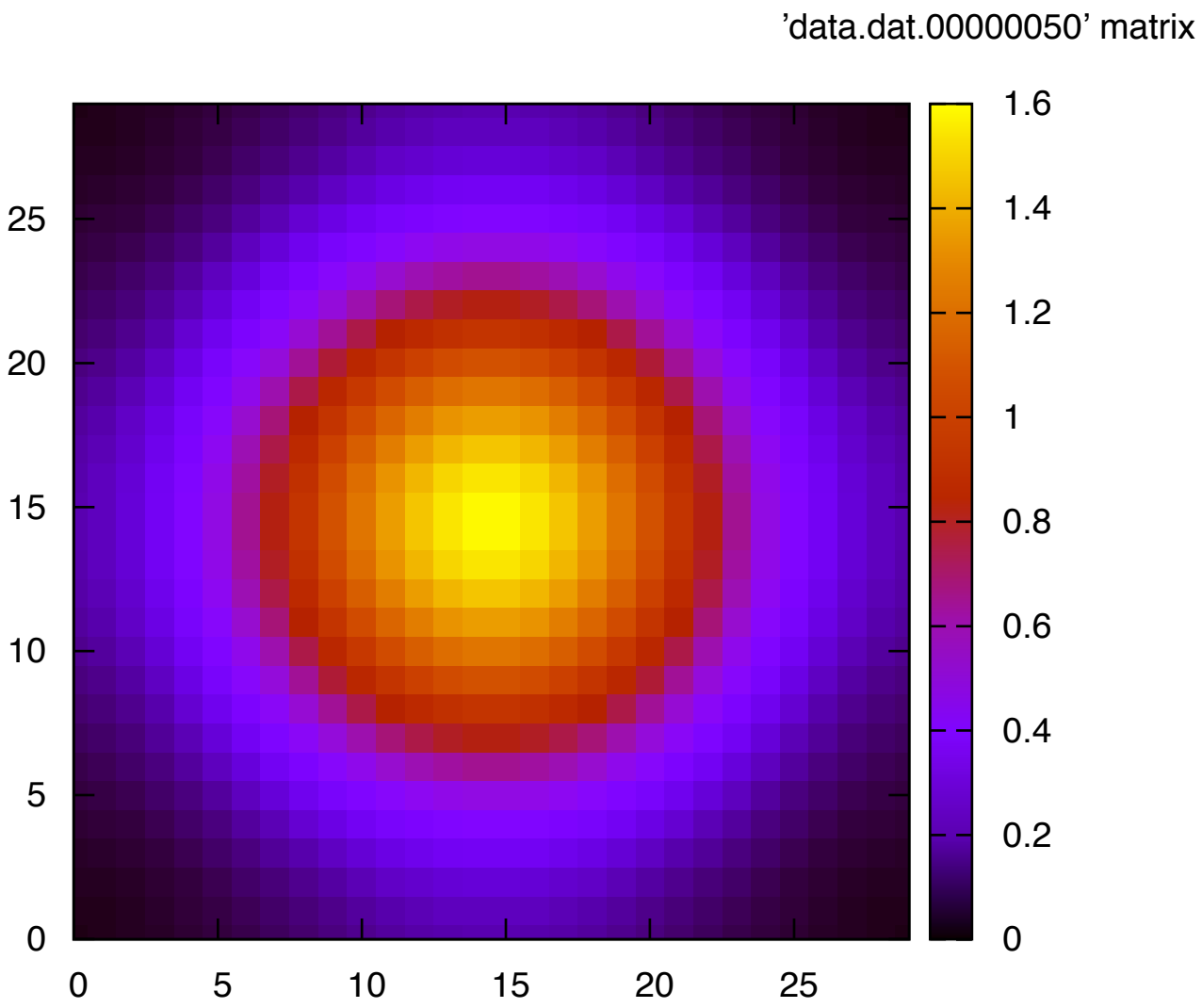
EX1: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15



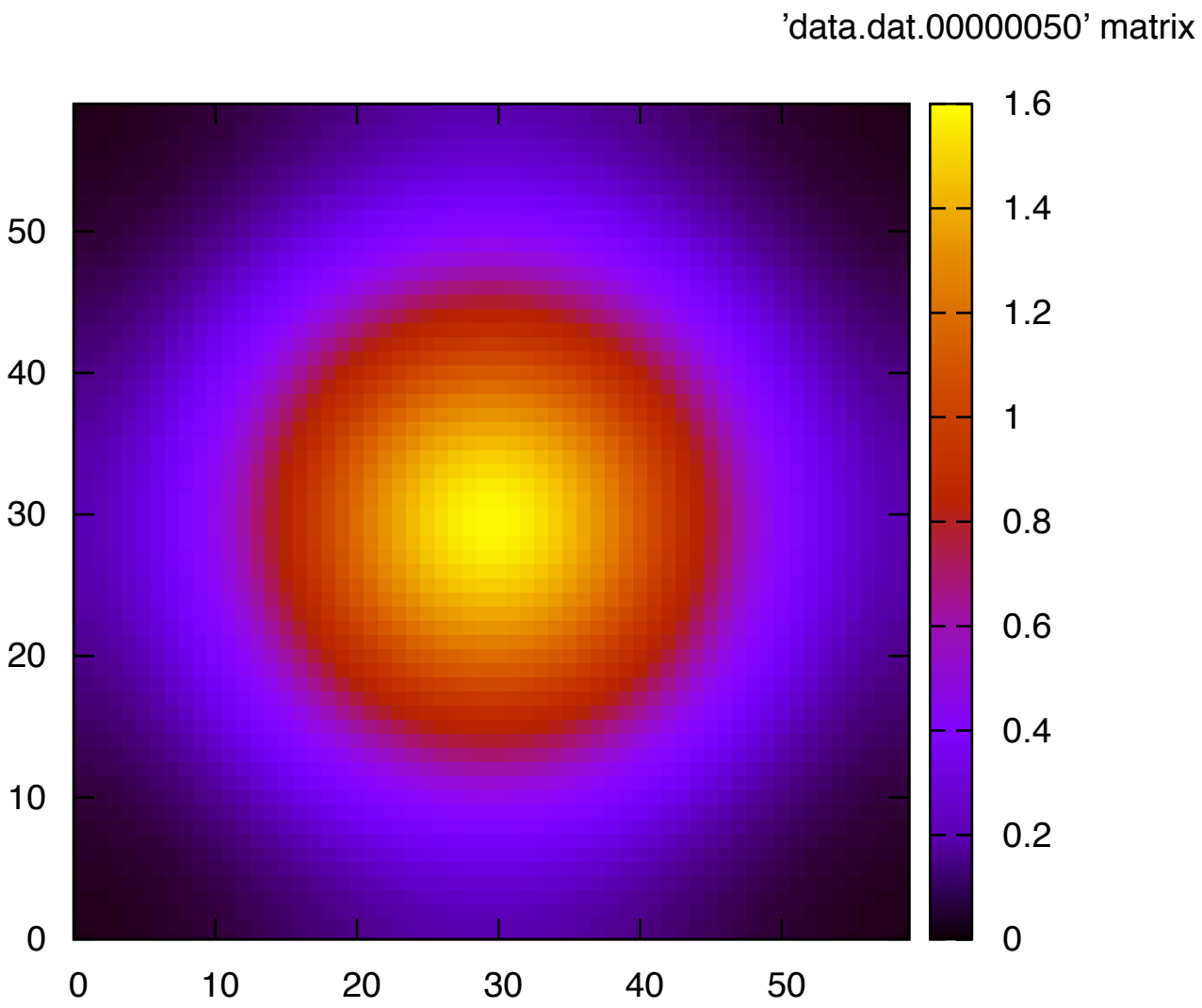
EX1: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15



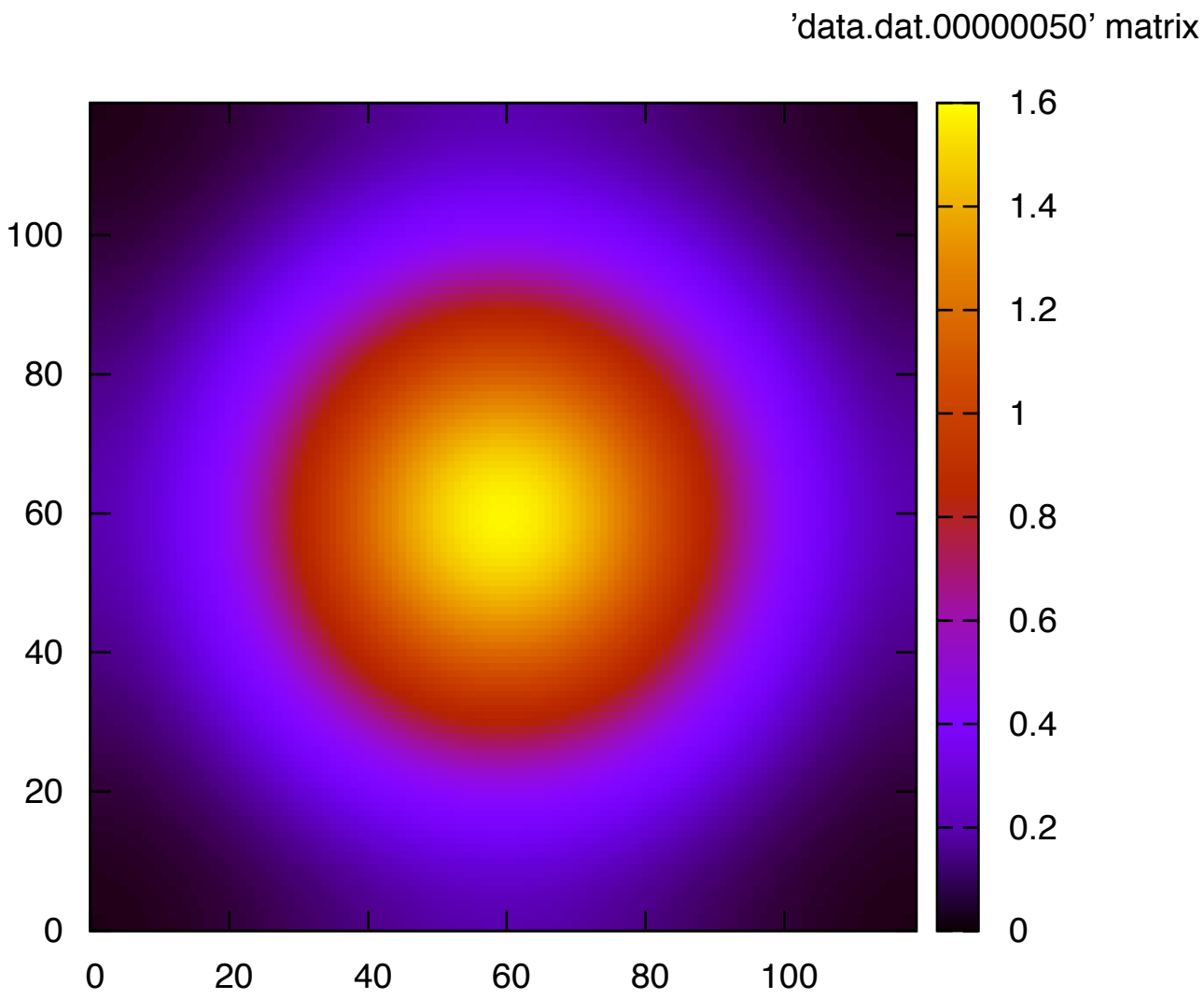
EX1: DIFFUSION - 2D4 NEIGHBOURHOOD, 30X30



EX1: DIFFUSION - 2D4 NEIGHBOURHOOD, 60X60



EX1: DIFFUSION - 2D4 NEIGHBOURHOOD, 120X120



EXAMPLE 2:

TURING PATTERNS

Liu, Blätke, Heiner, Yang:
Modelling and simulating reaction–diffusion systems using coloured Petri nets;
Computers in Biology and Medicine, 2014.

EX2: TURING PATTERNS

"How the Leopard Got Its Spots"

- **morphogenesis**
  - -> *developmental pattern formation in bio systems*
  - -> *the process that controls the organized spatial distribution of cells*
  - -> *tiger stripes, leopard spots, the precisely spaced rows of alligator teeth, etc.*

- **Turing's theory of biological pattern formation, 1952**
  - -> *patterns form as result of*

    the interactions between two chemicals
    that spread throughout a system at different rates

- **reactions**
  - -> *version of Brusselator model, http://en.wikipedia.org/wiki/Brusselator*

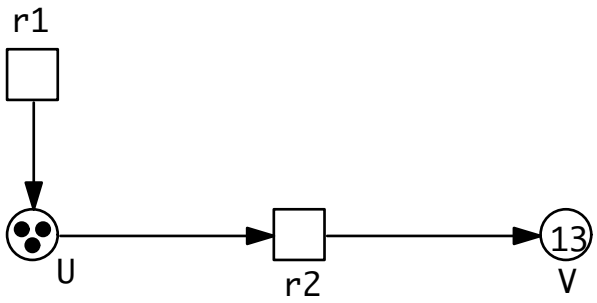
- **highly simplified and idealised take on biological patterning**

r1: -> U

EX2: TURING PATTERNS

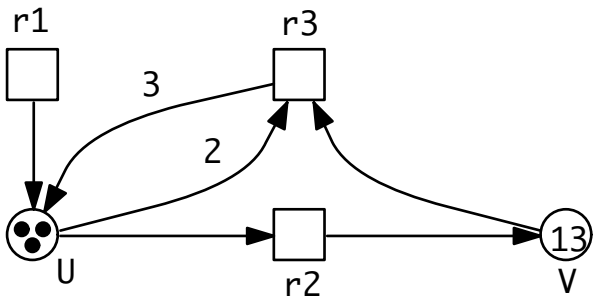
r1: -> U

r2: U -> V



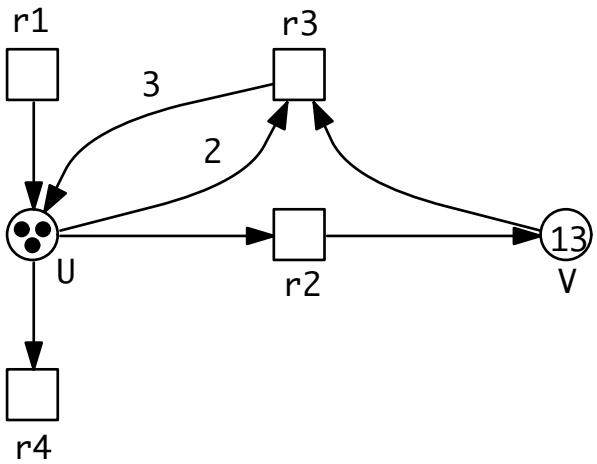
EX2: TURING PATTERNS

r1: -> U
r2: U -> V
r3: 2U + V -> 3U



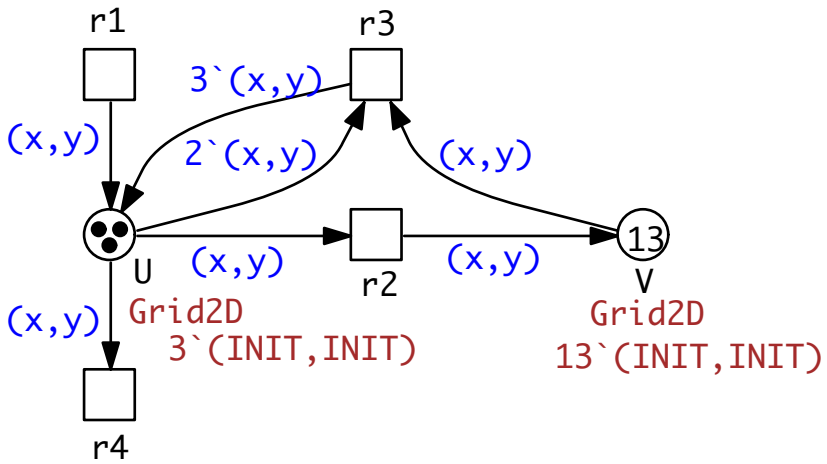
EX2: TURING PATTERNS

r1: -> U
r2: U -> V
r3: 2U + V -> 3U
r4: U ->



r1: -> U
r2: U -> V
r3: 2U + V -> 3U
r4: U ->

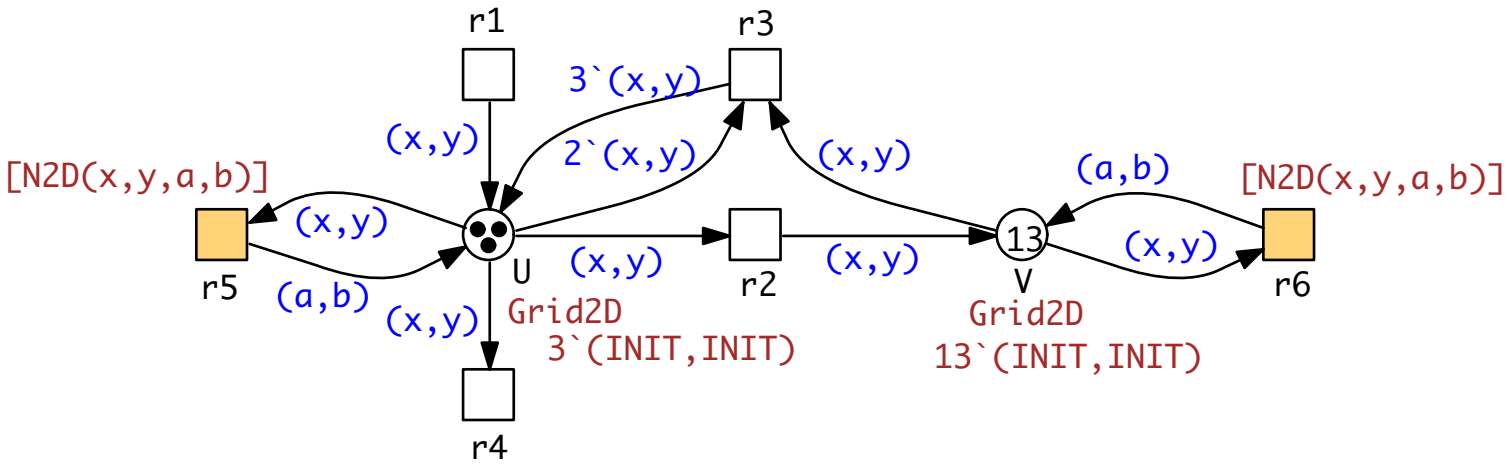
adding SPACE



EX2: TURING PATTERNS

r1: -> U
r2: U -> V
r3: 2U + V -> 3U
r4: U ->

diffusion:
r5: U_{xy} -- $1/h^2$ --> U_{ab}
r6: V_{xy} -- D/h^2 --> V_{ab}



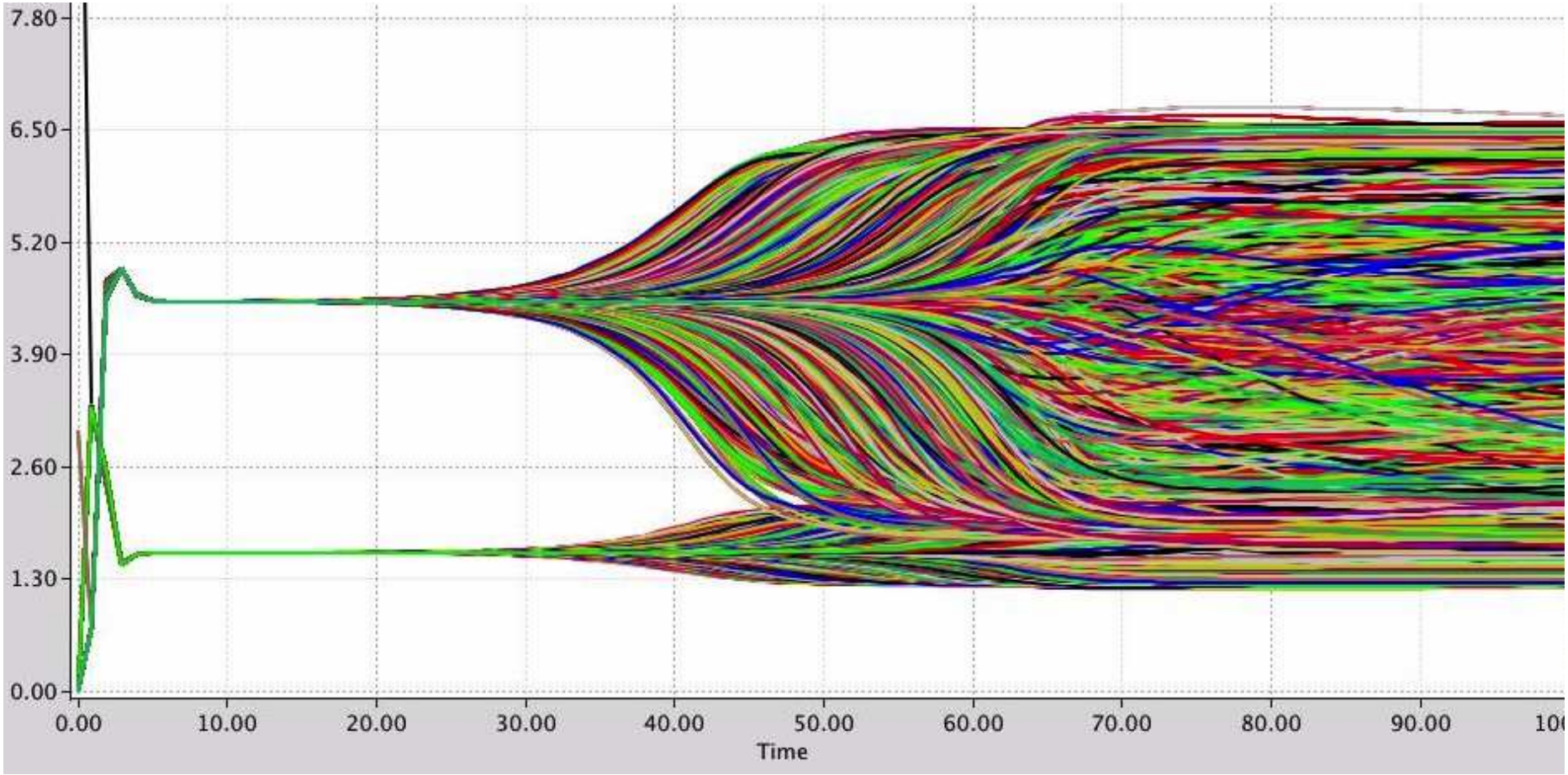
r1 - r4 follow mass action kinetics with rate constants:
r1: A, r2: B, r3: 1, r4: 1;

EX2: SOME EXPERIMENTS

- **parameters**
  - -> *Pena, Perez-Garcia: Stability of Turing patterns in the Brusselator model, Physical Review 2001*
  - -> *A = 4.5, B = 0.04 ..0.98, D = 128, h = 0.8*
- **unfolding**
  - -> *runtime (constraint solver, 4 threads): 128 sec*
  - -> *places: 32,768, transitions: 324,616*
- **continues simulation**
  - -> *BDF (Backward Differentiation Formulae, higher-order stiffly stable solver)*
  - -> *simulation time: 5,000 -> runtime: about 30h*

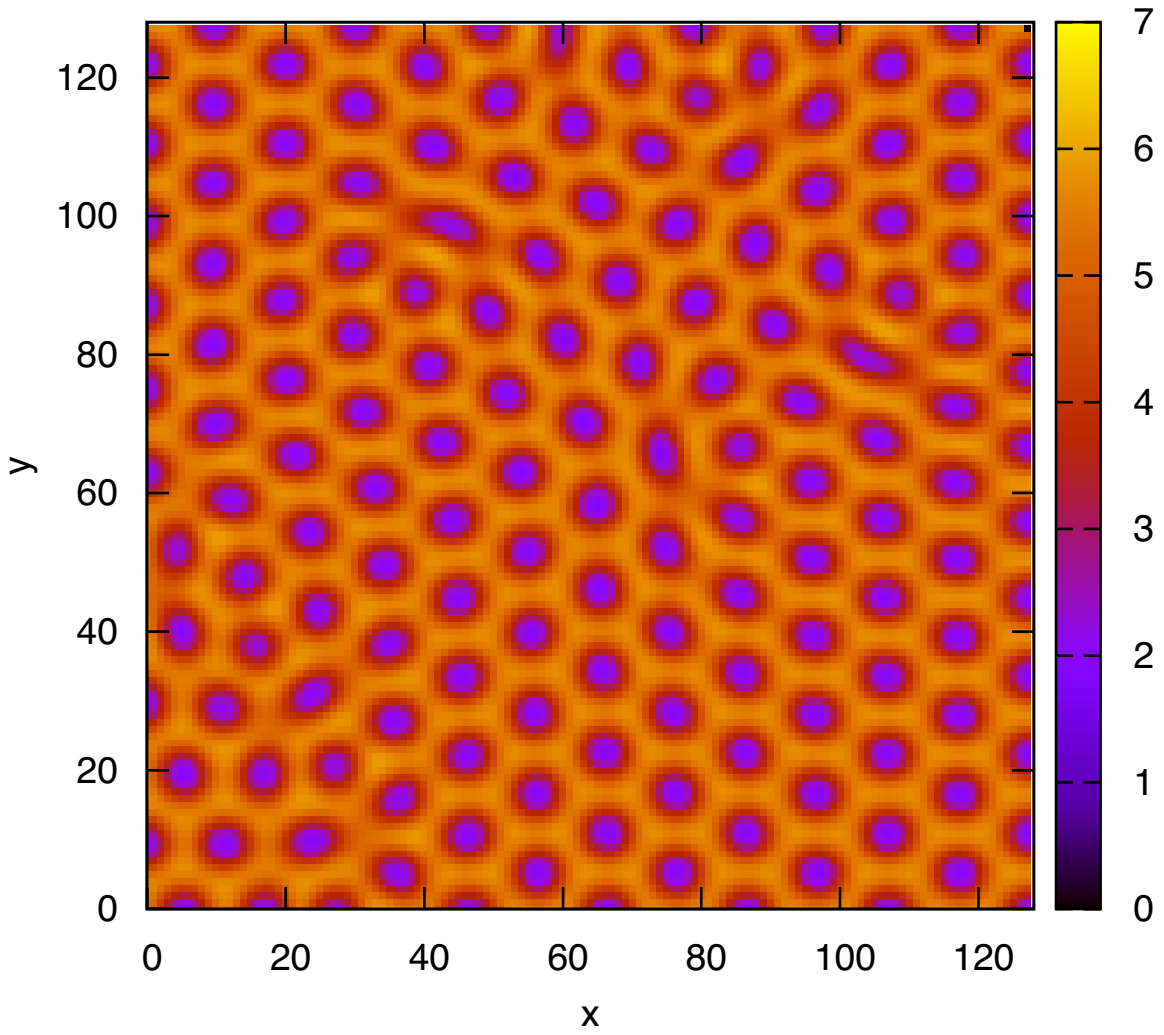
EX2: TRACES

-> EVOLUTION OF U,V IN ALL GRID POSITIONS OVER TIME



EX2: TURING PATTERNS

-> U IN ALL GRID POSITIONS AT TIME 5,000



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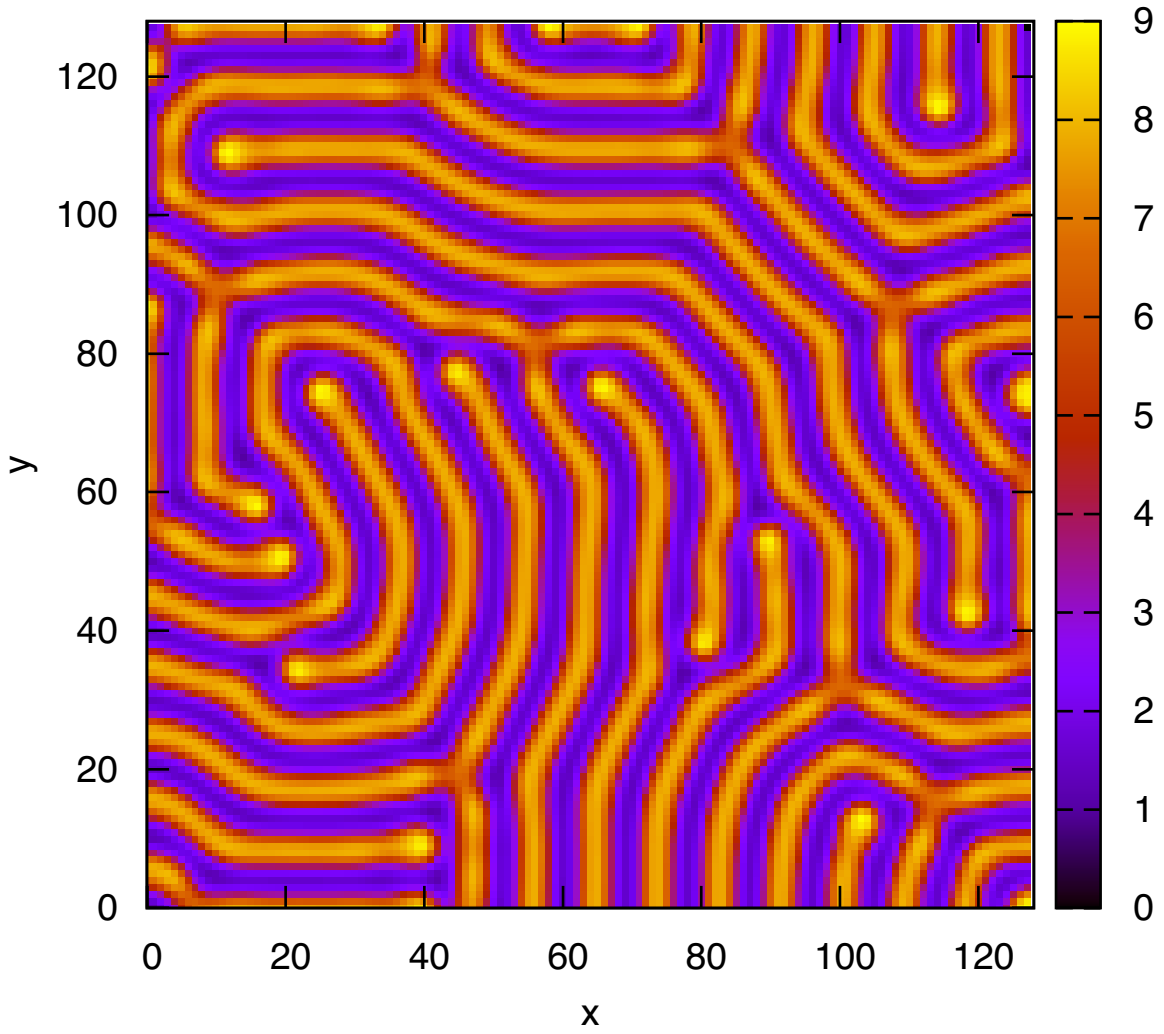
EX2: TURING PATTERNS



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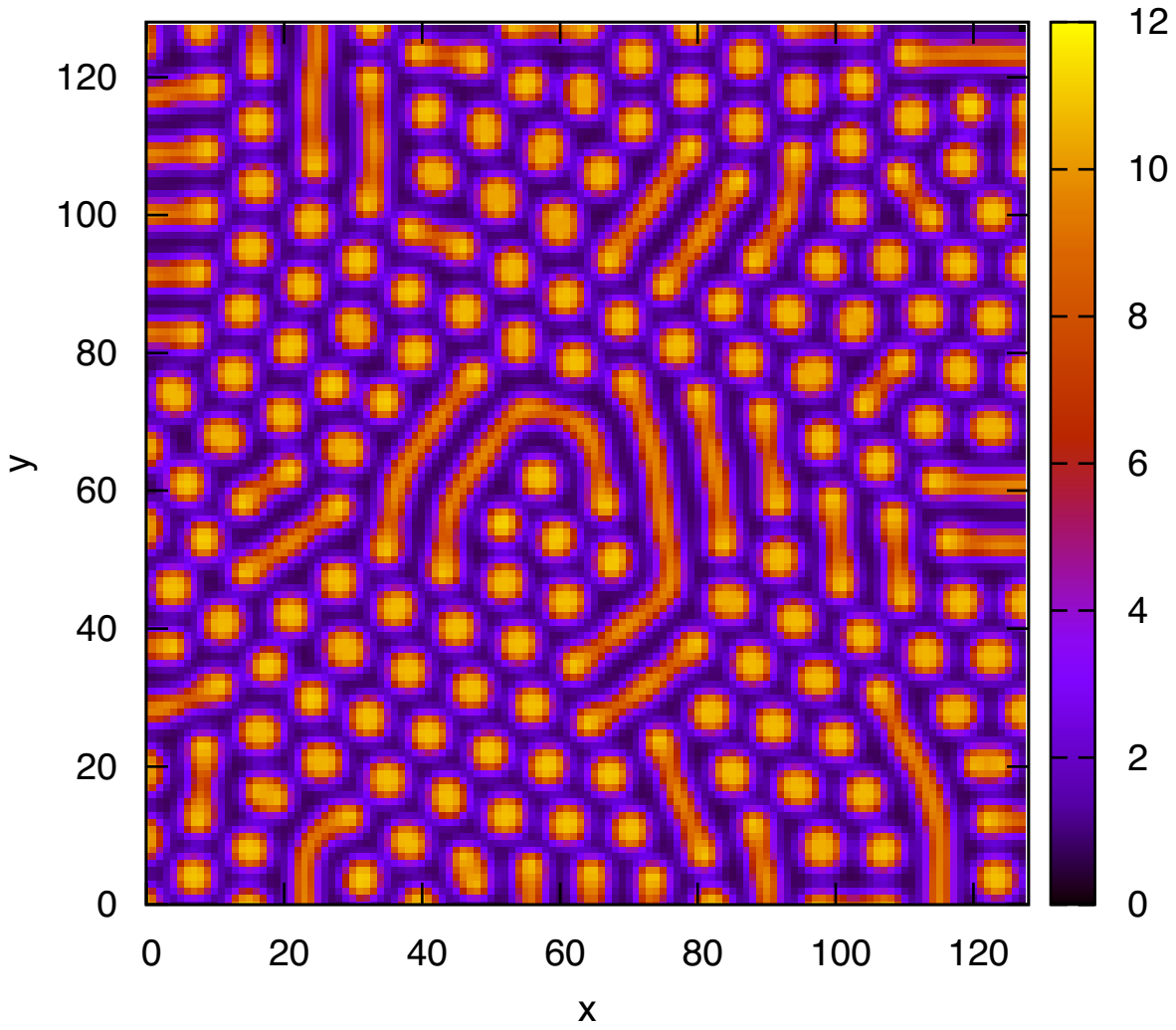
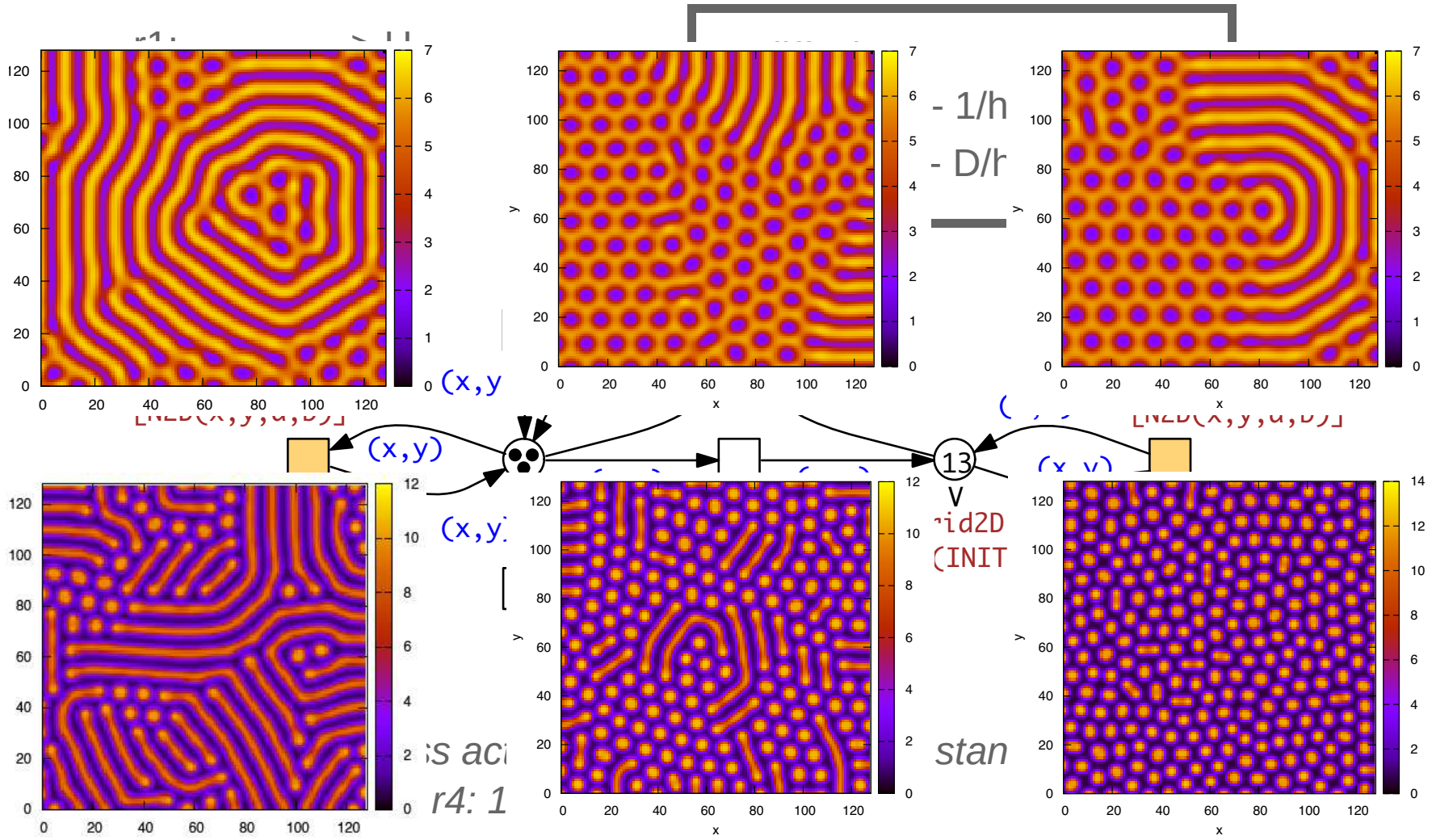
EX2: TURING PATTERNS



EX2: TURING PATTERNS



[LIU ET AL 2014]

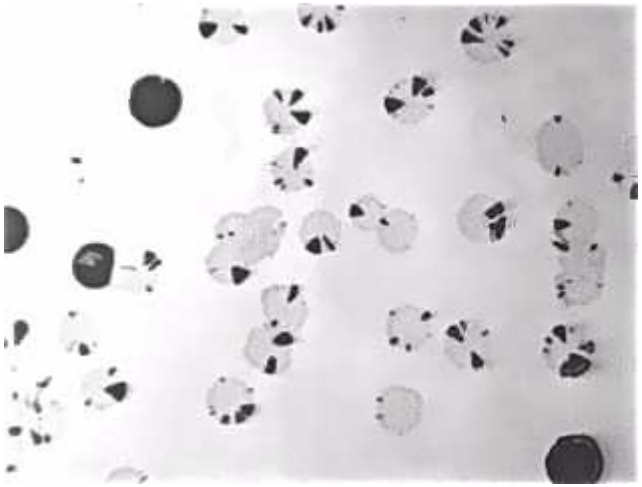
EXAMPLE 3:

PHASE VARIATION IN MULTISTRAIN CELL COLONIES

Pârvu, Gilbert, Heiner, Liu, Saunders, Shaw:
Spatial-temporal modelling and analysis of bacterial colonies with phase variable genes;
ACM TOMACS, 2015.

EX3: PHASE VARIATION IN CELL COLONIES

- **phase variation**
  - -> *method for dealing with rapidly varying environments without requiring random mutations*
- **contingency genes**
  - -> *populations include variants adapted to "foreseeable" frequently encountered environmental or selective conditions*
- **stochastic gene switching process**
  - -> *controlled by reversible gene mutations, inversions, or epigenetic modification*
  - -> *e.g. switch between two phenotypes A, B*
- **colonial sectoring**
  - -> *observable effect in cultures grown in vitro*



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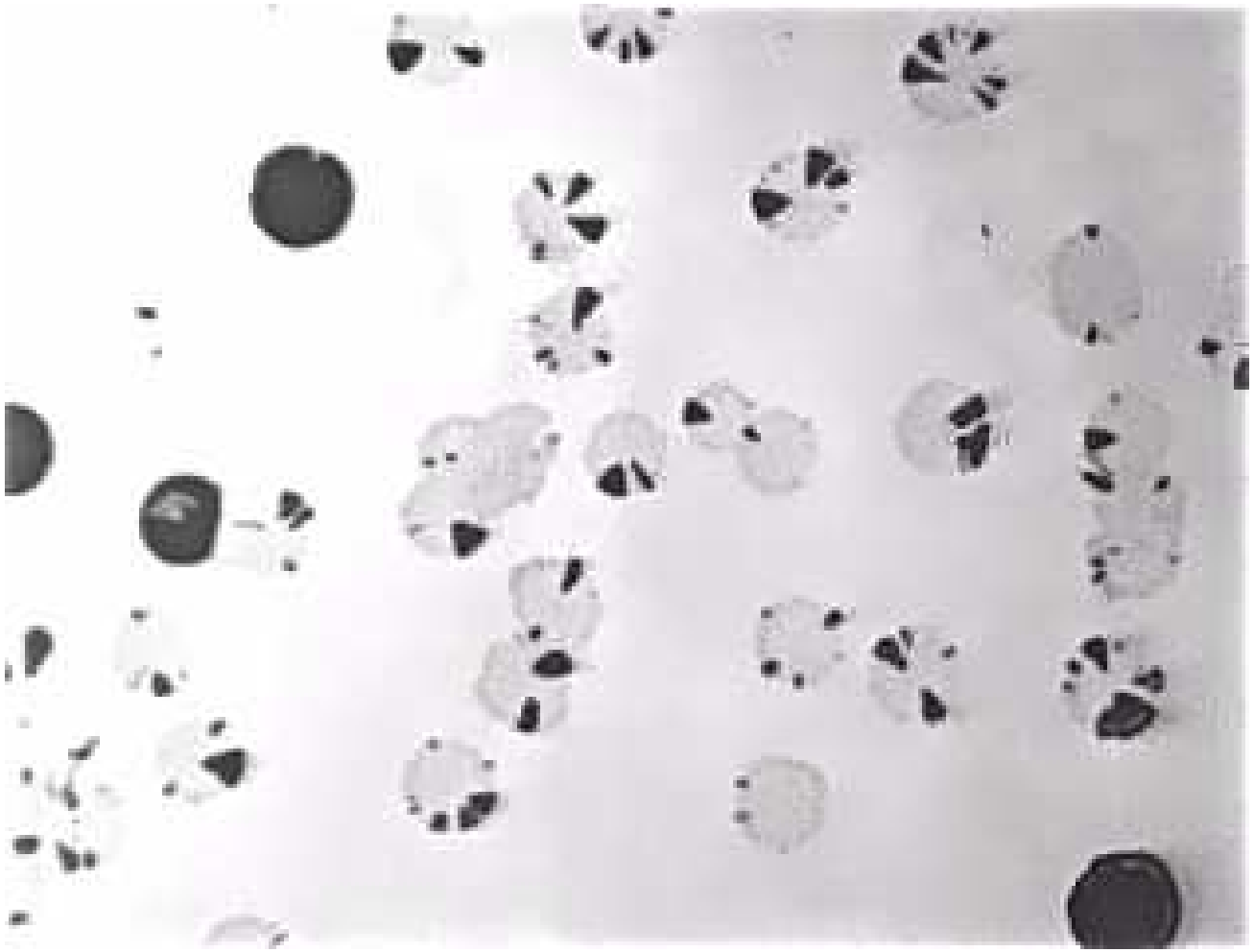
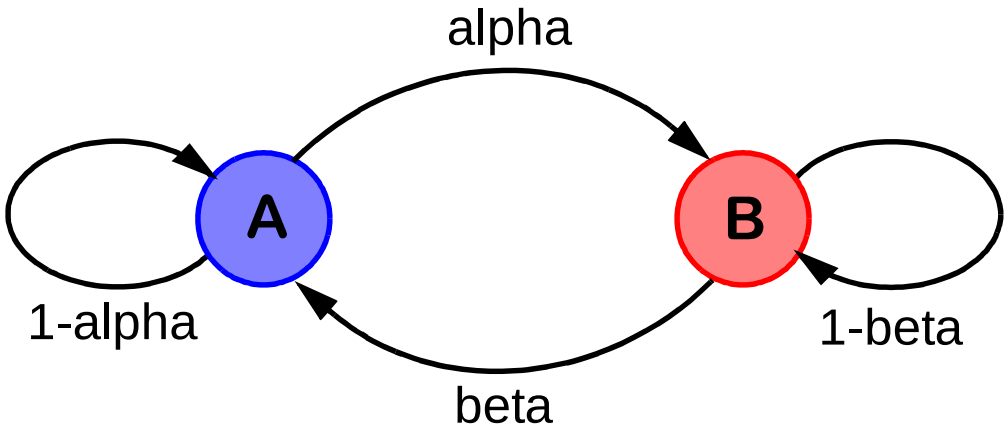
EX3: CELL COLONIES, WETLAB OBSERVATIONS

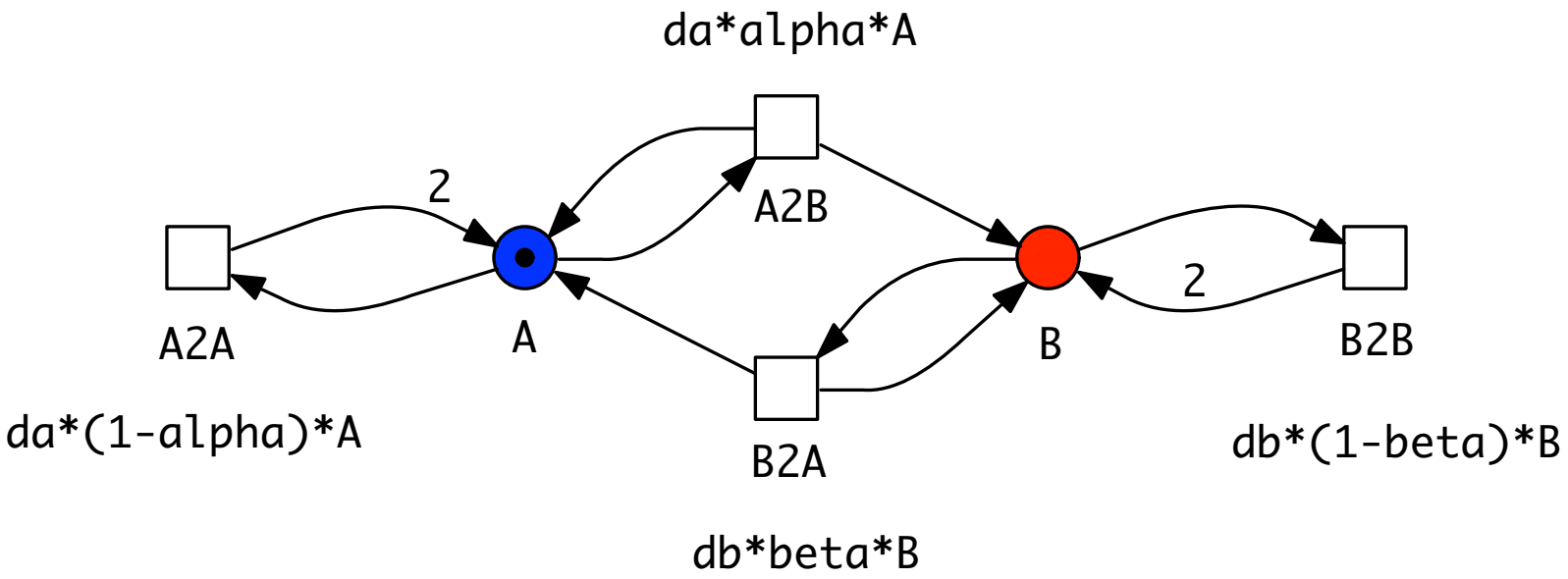


(courtesy of N Saunders)

- **two phenotypes: A and B**
- **cell divide**
  - -> *cell division may involve mutation of the offspring*
  - -> *parent cell keeps its phenotype*
- **model parameters**
  - -> *alpha = beta - mutation rates*
  - -> *da, db - fitness of A, B*
  - -> *da/db - relative fitness*
- **output**
  - -> *total number of cells*
  - -> *proportion of A = A / (A + B)*
  - -> *proportion of B = B / (A + B)*

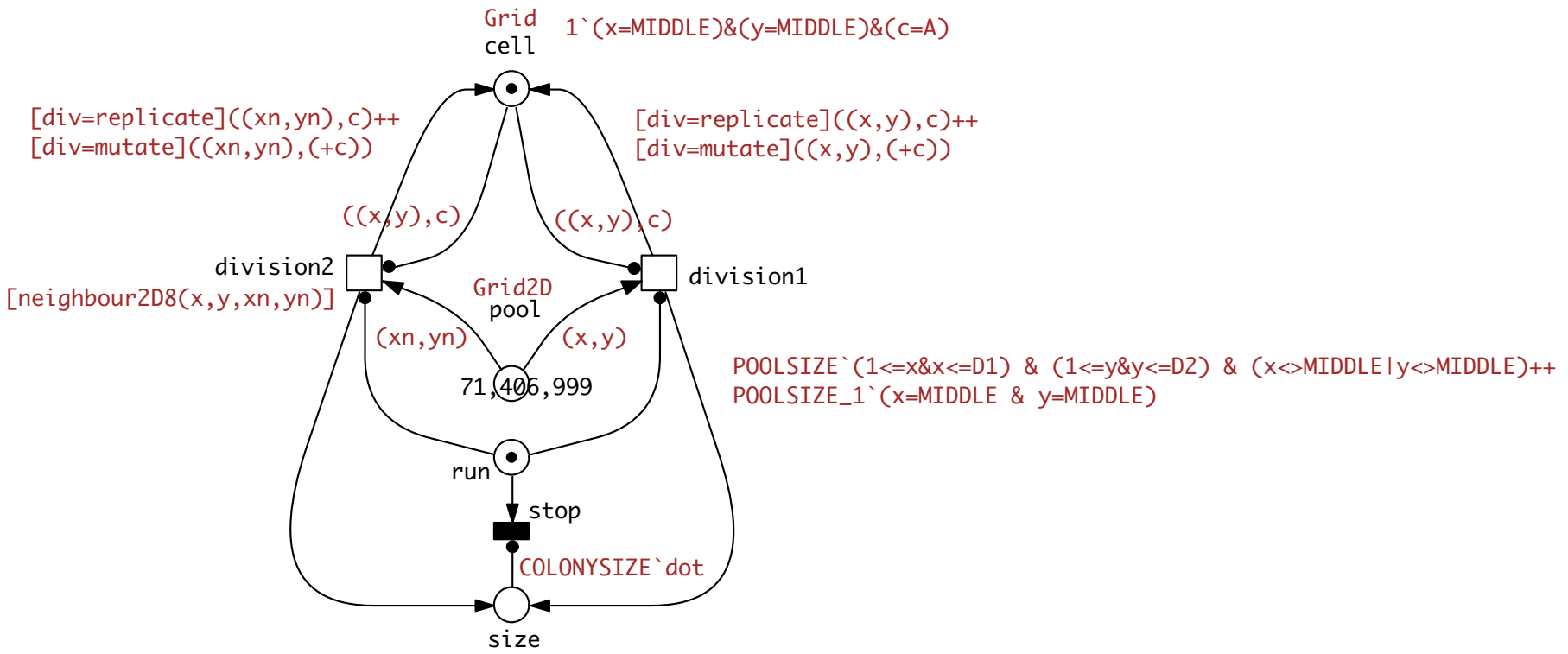


EX3: CELL COLONIES, PETRI NET



EX3: CELL COLONIES, CONTROLLING COLONY SIZE

colorset Grid = **product with** Grid2D x Phenotype;



EX3: CELL COLONIES, SOME DETAILS

model assumptions

-> *"If phase variation occurs, the progeny consists of one A and one B"*
(Saunders 2003)

-> *It is always the mutant who goes to a neighbouring position, if any.*

-> *constant biofilm thickness (so far)*

colony size - 24 h

-> *25 generations: 33.5 E+06*

-> *26 generations: 67 E+06*

-> *COLONYSIZE = 70,000,000*

grid size

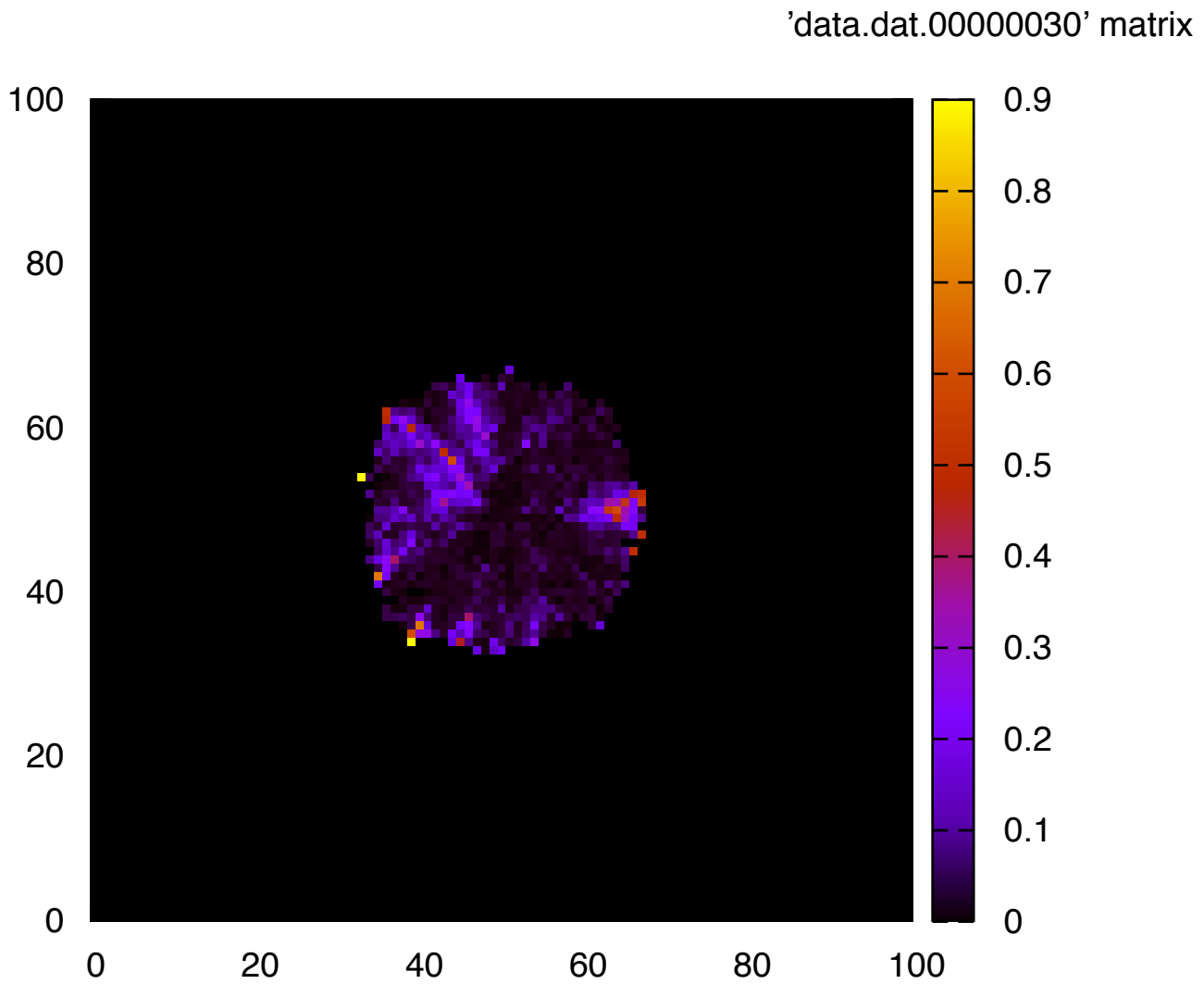
-> *61 x 61 grid: 11,163 P / 131,044 T; unfolding: 152 sec;*

-> *101 x 101 grid: 30,603 P / 362,404 T; unfolding: 9 min;*

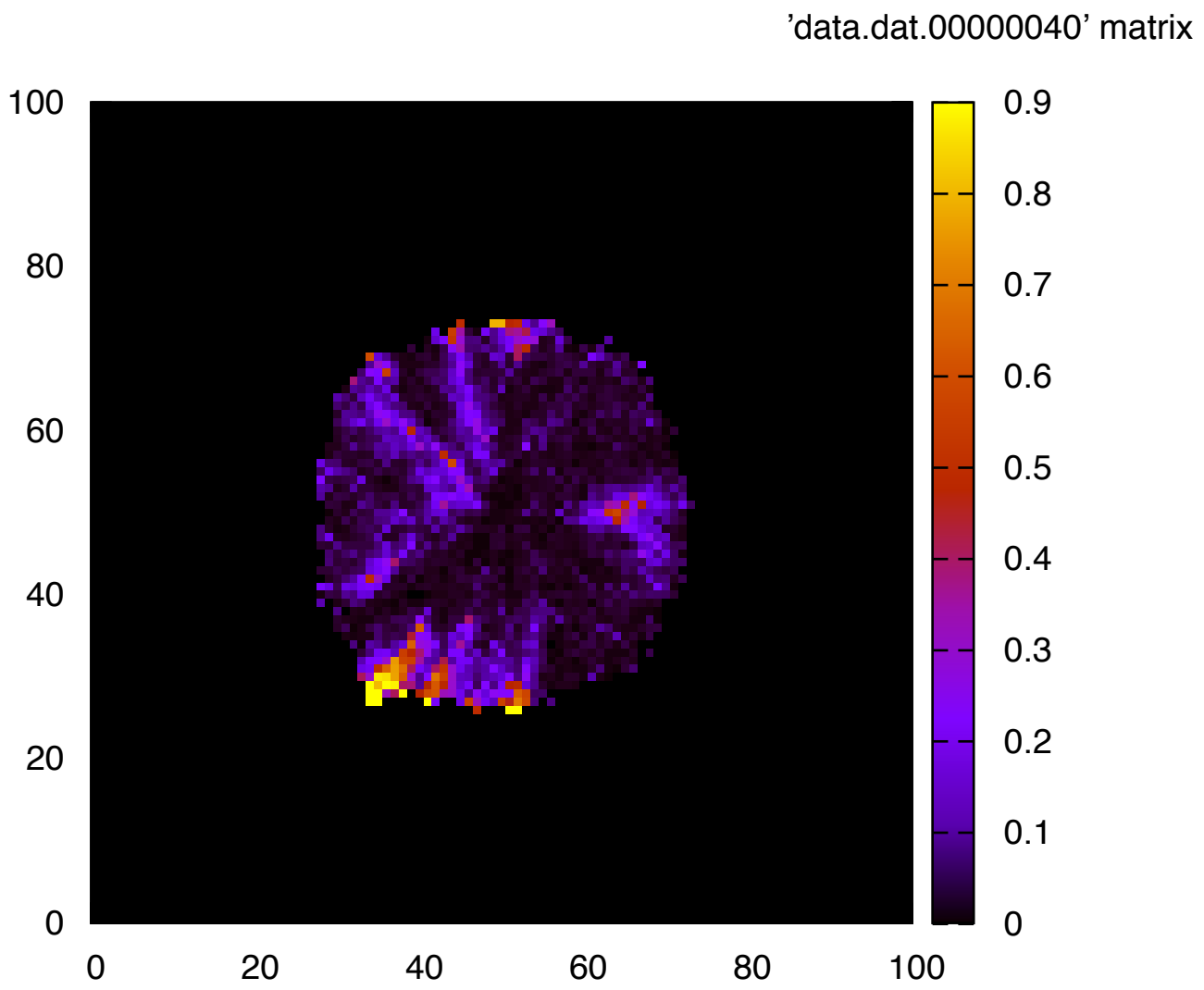
-> *runtime 1 stoch. simulation: 35-40 minutes*

. . . SOME EXPERIMENTS

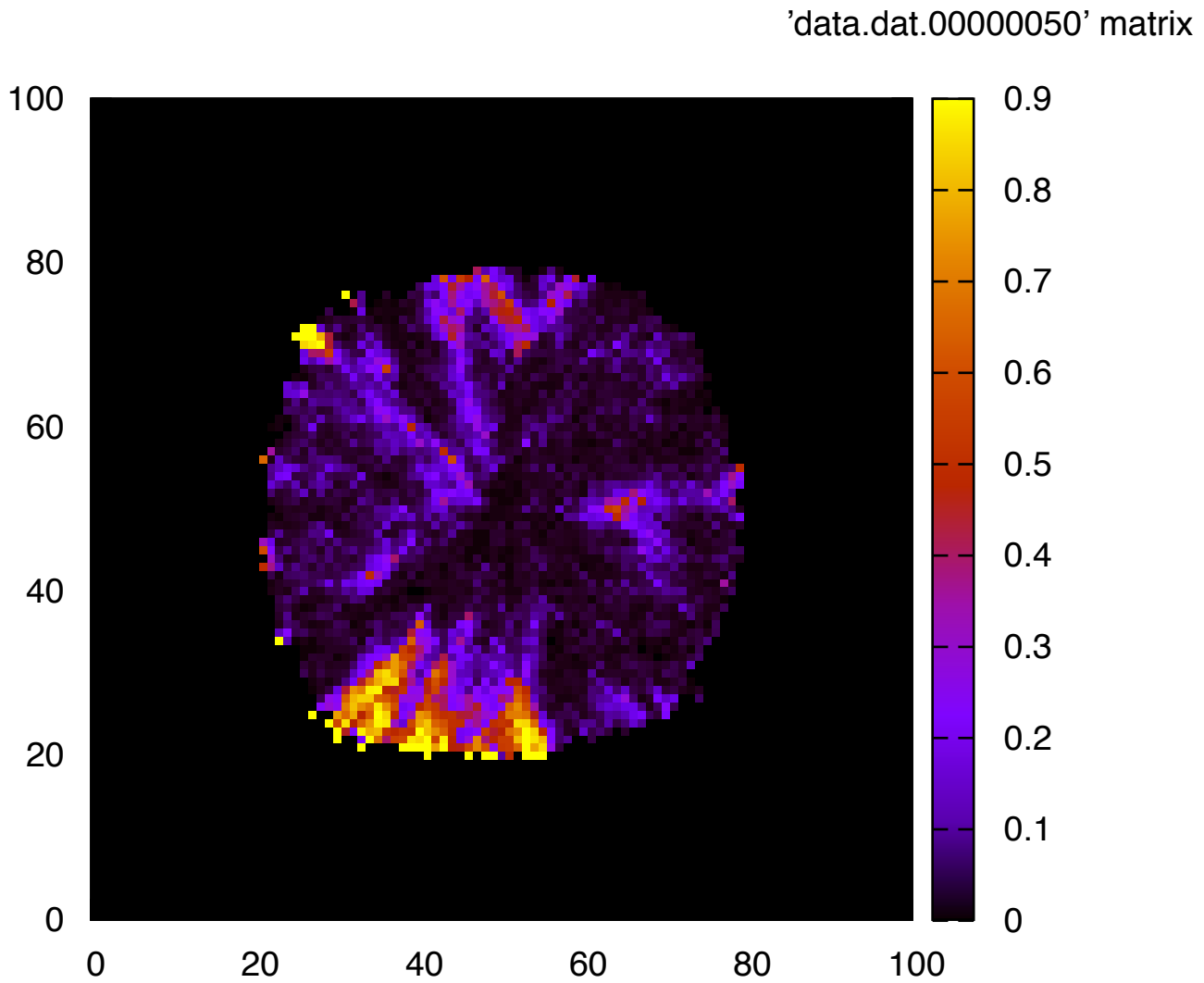
EX3: 2D - TRACE 1 (HIGH, F=1)



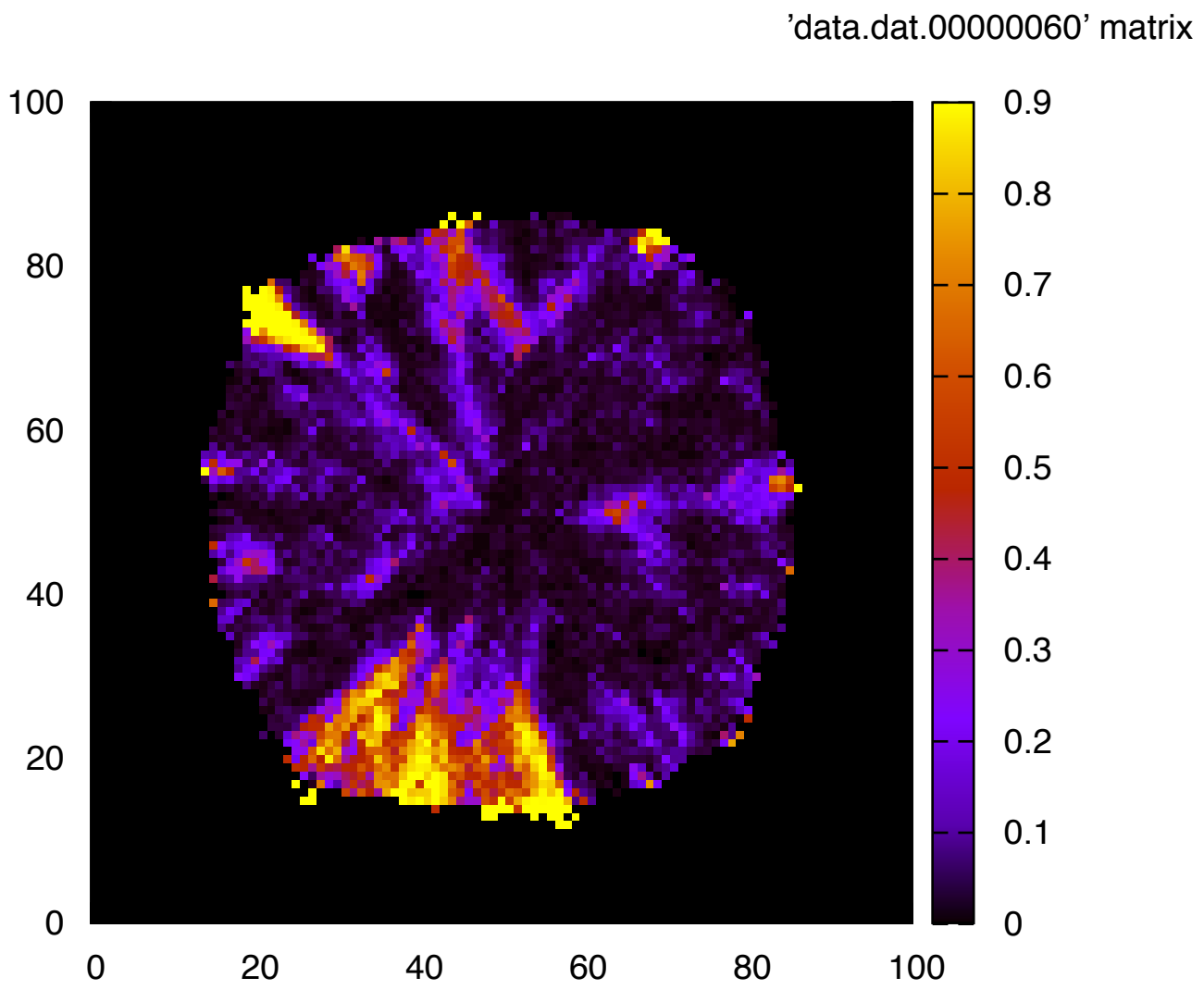
EX3: 2D - TRACE 1 (HIGH, F=1)



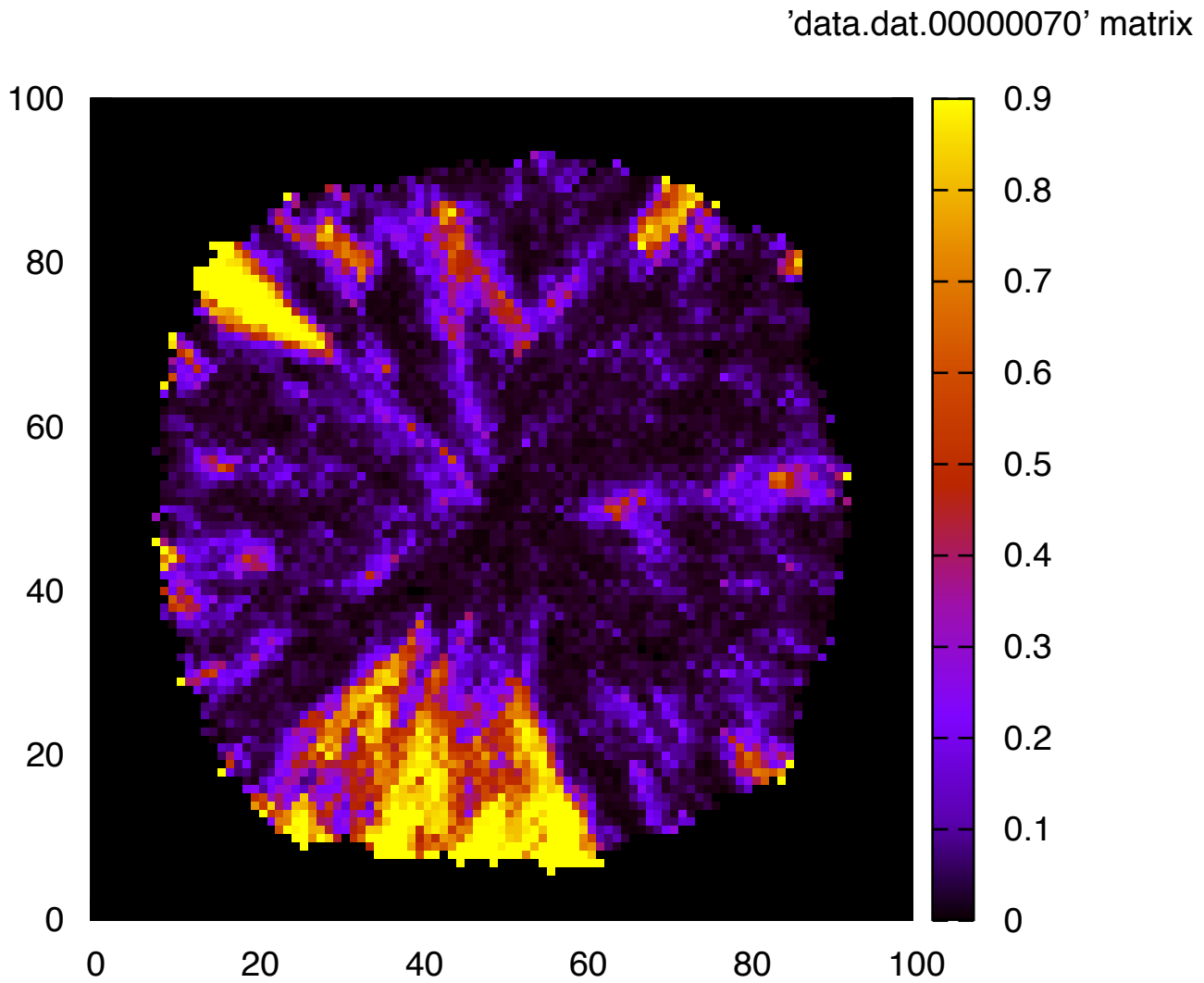
EX3: 2D - TRACE 1 (HIGH, F=1)



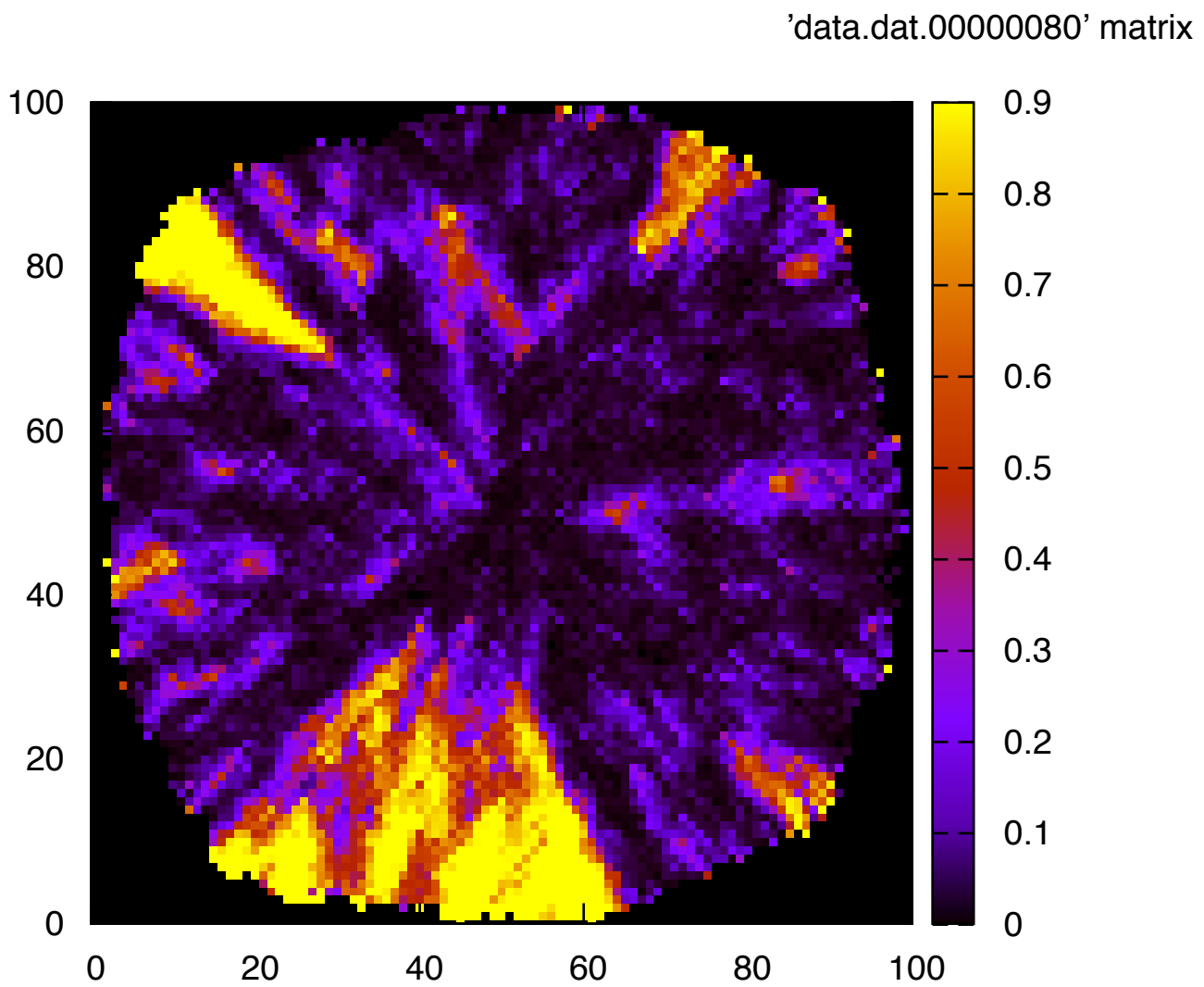
EX3: 2D - TRACE 1 (HIGH, F=1)



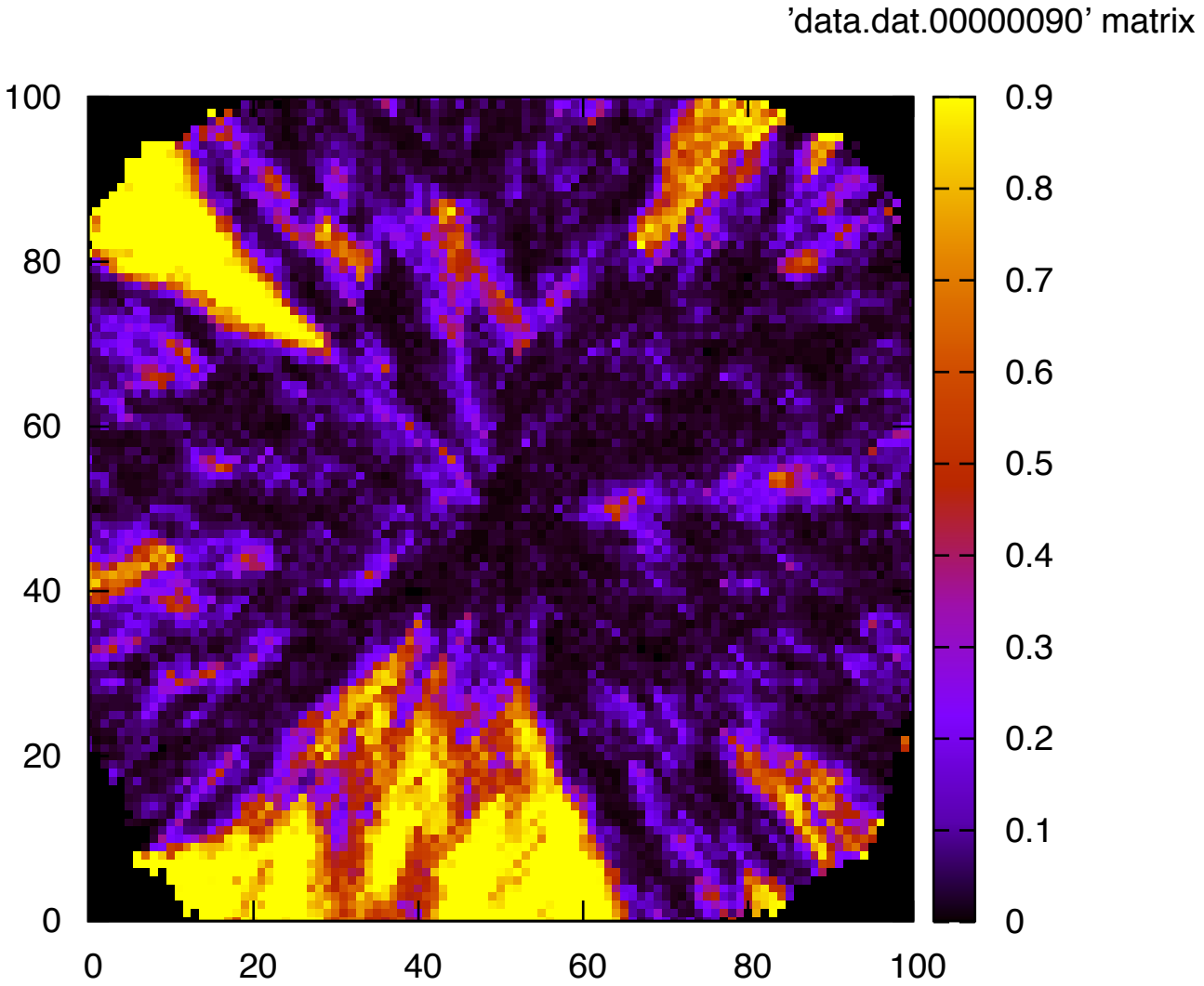
EX3: 2D - TRACE 1 (HIGH, F=1)



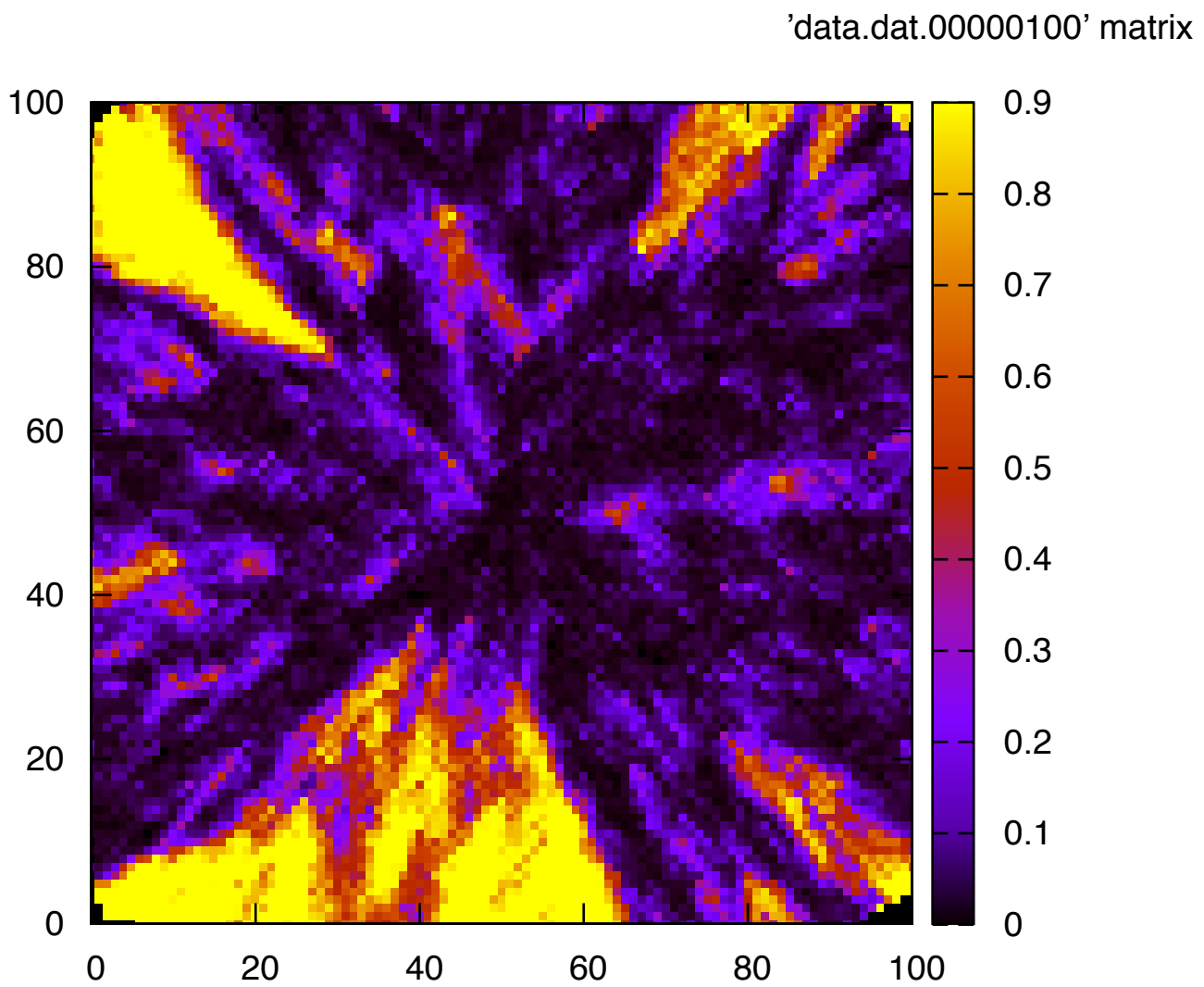
EX3: 2D - TRACE 1 (HIGH, F=1)



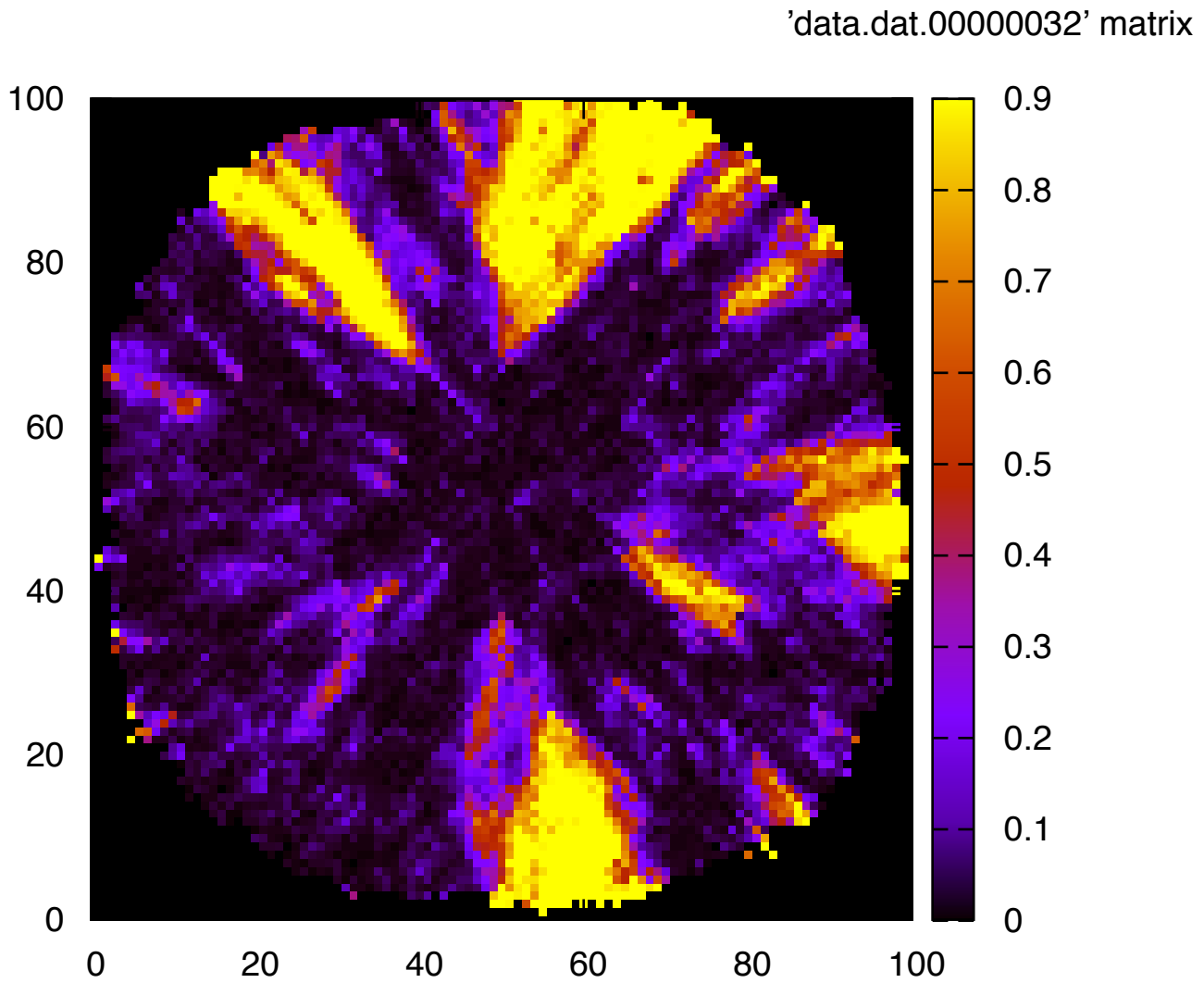
EX3: 2D - TRACE 1 (HIGH, F=1)



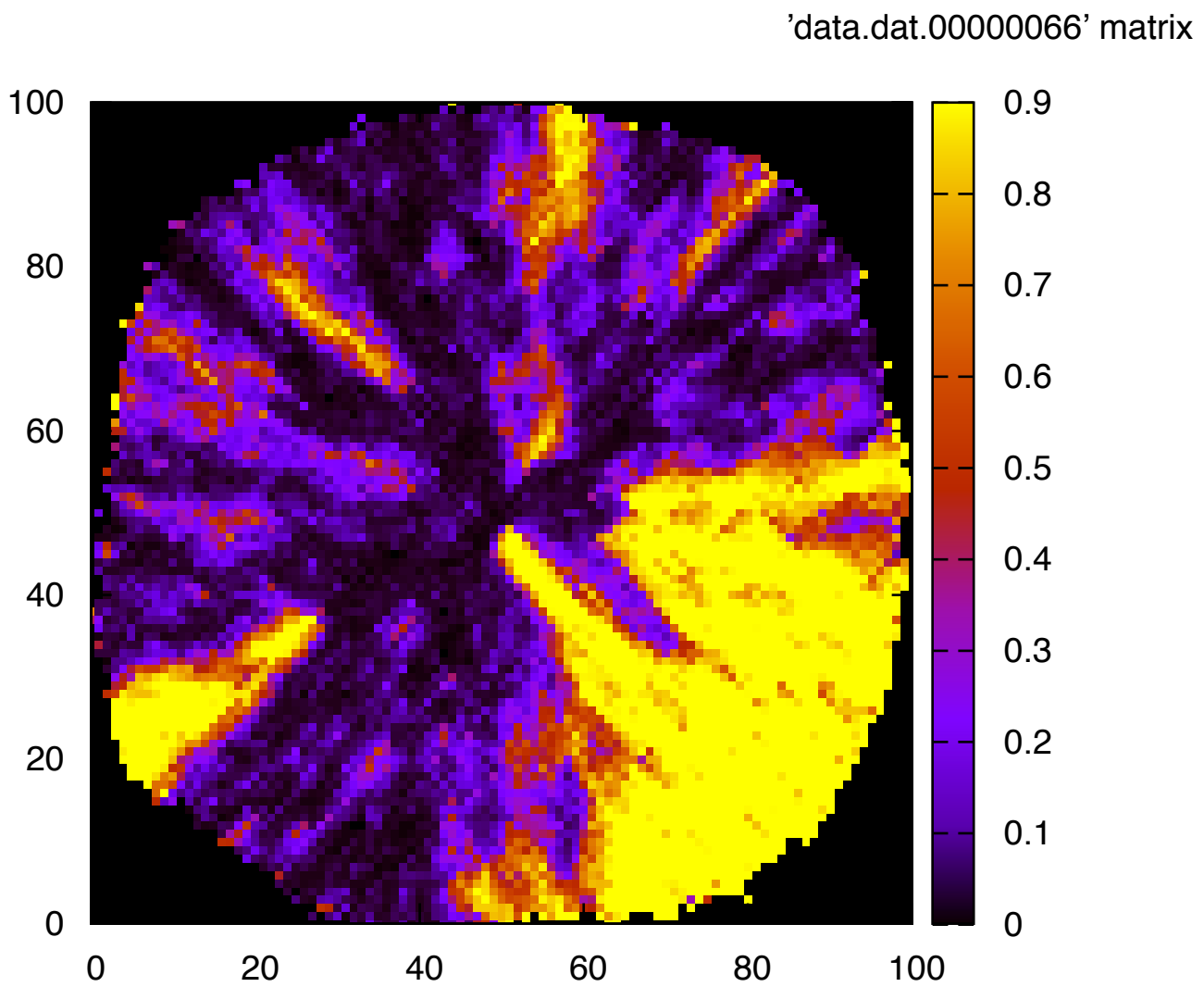
EX3: 2D - TRACE 1 (HIGH, F=1)



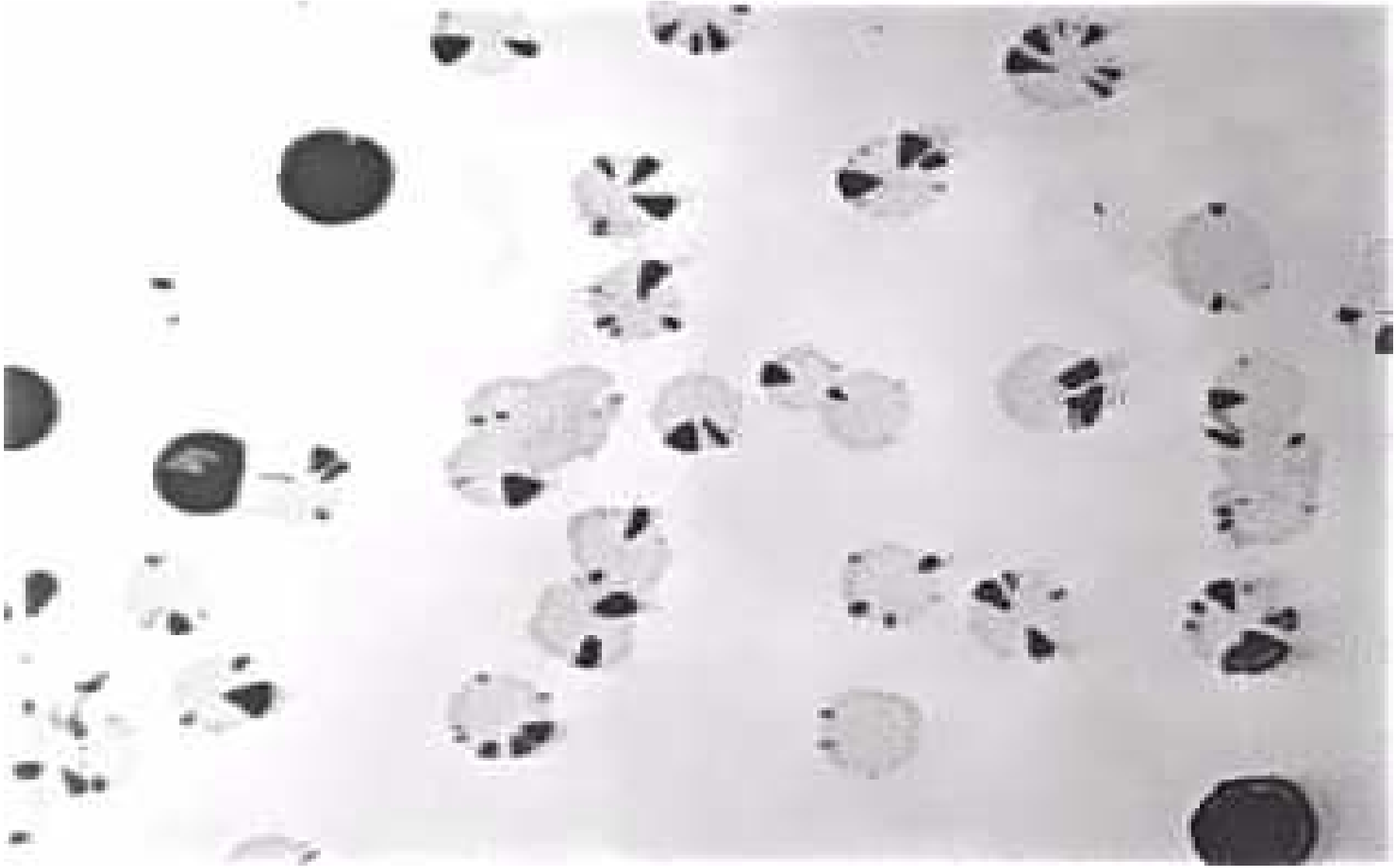
EX3: 2D - TRACE 2 (HIGH, F=1)



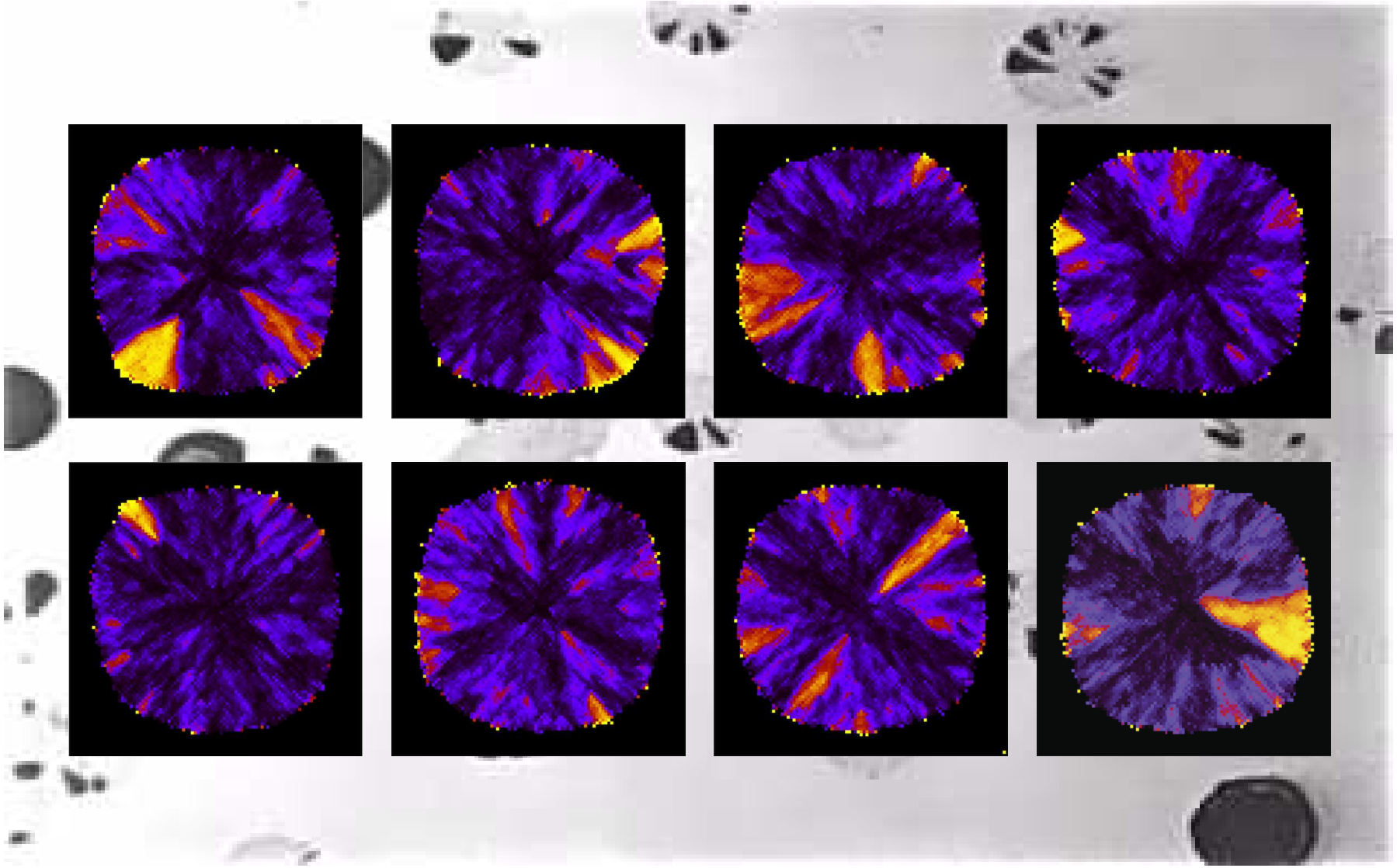
EX3: 2D - TRACE 3 (HIGH, F=1)



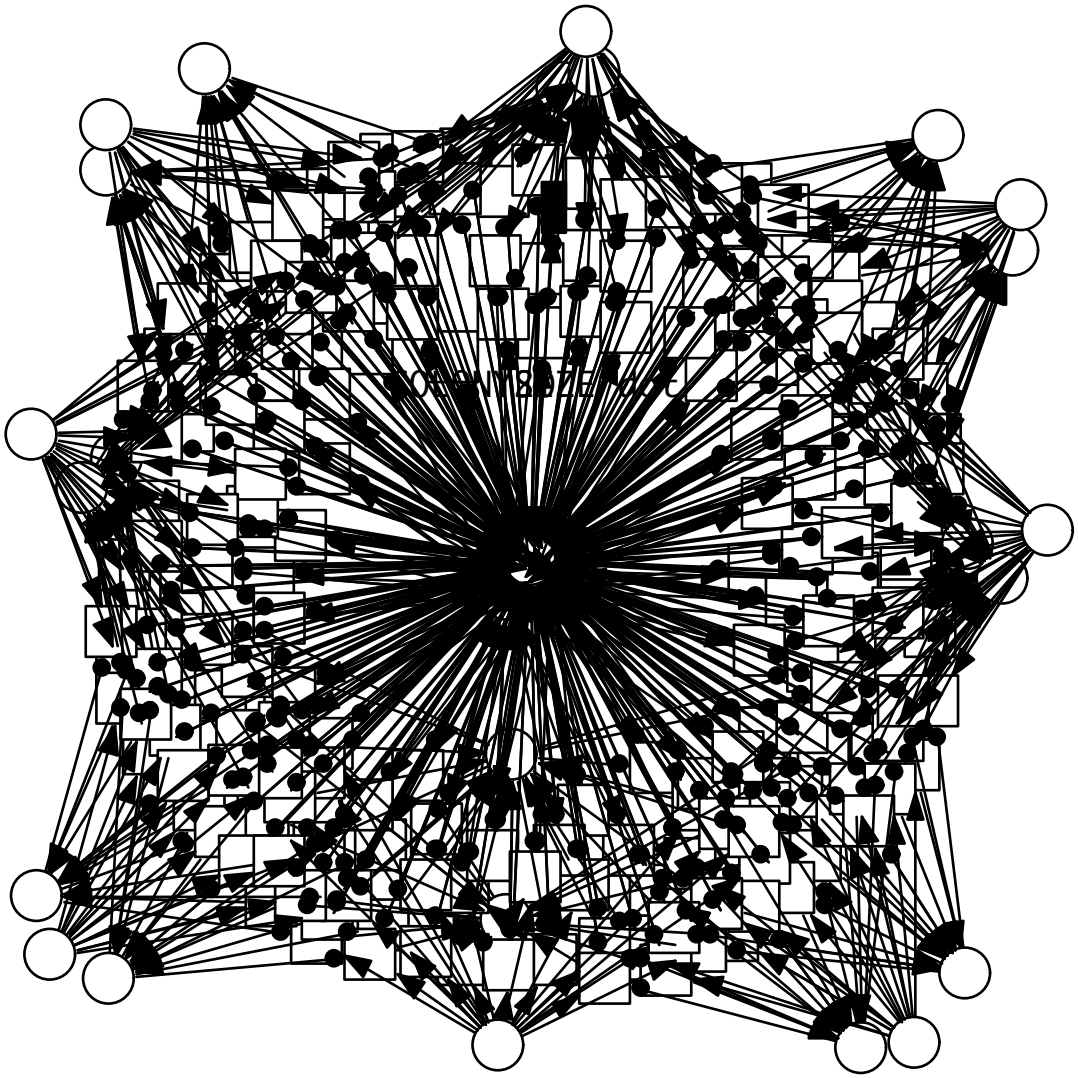
EX3: SOME FINAL STATES (HIGH, F=1)



EX3: SOME FINAL STATES (HIGH, F=1)



EX3: PLAIN MODEL (3X3)

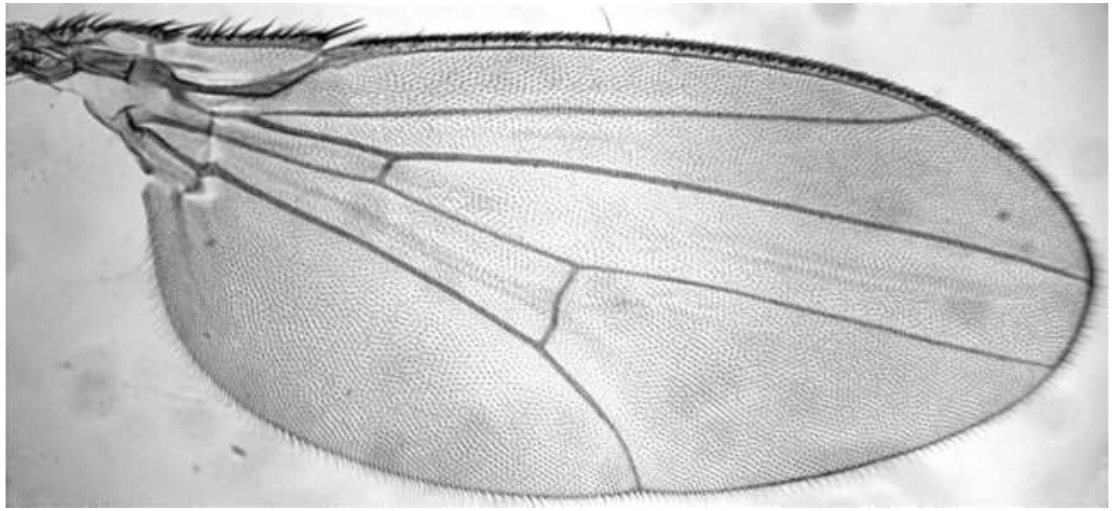


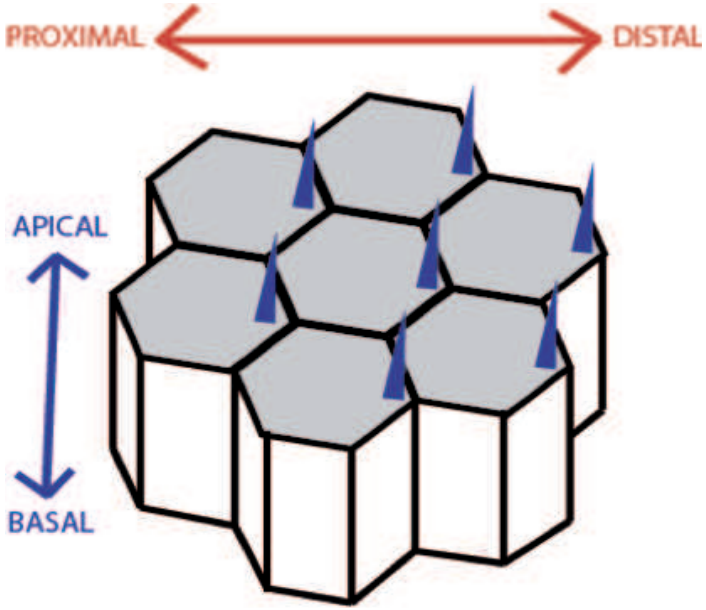
EXAMPLE 4:

PLANAR CELL POLARITY IN FLY WING

Gao, Gilbert, Heiner, Liu, Maccagnola, Tree:
Multiscale Modelling and Analysis of Planar Cell Polarity in the Drosophila Wing;
IEEE/ACM Transactions on Computational Biology and Bioinformatics, 2013.

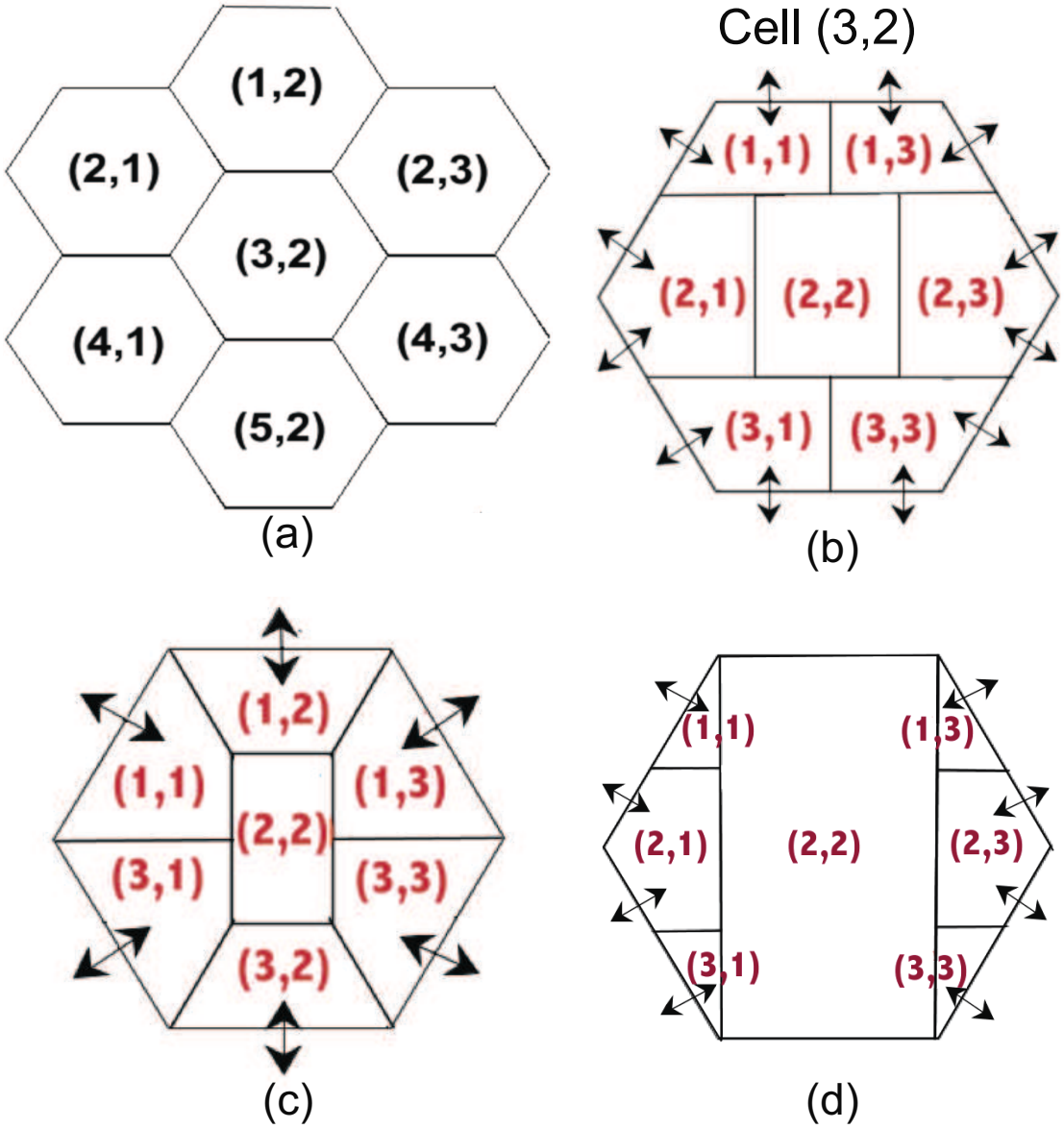
EX4: PLANAR CELL POLARITY



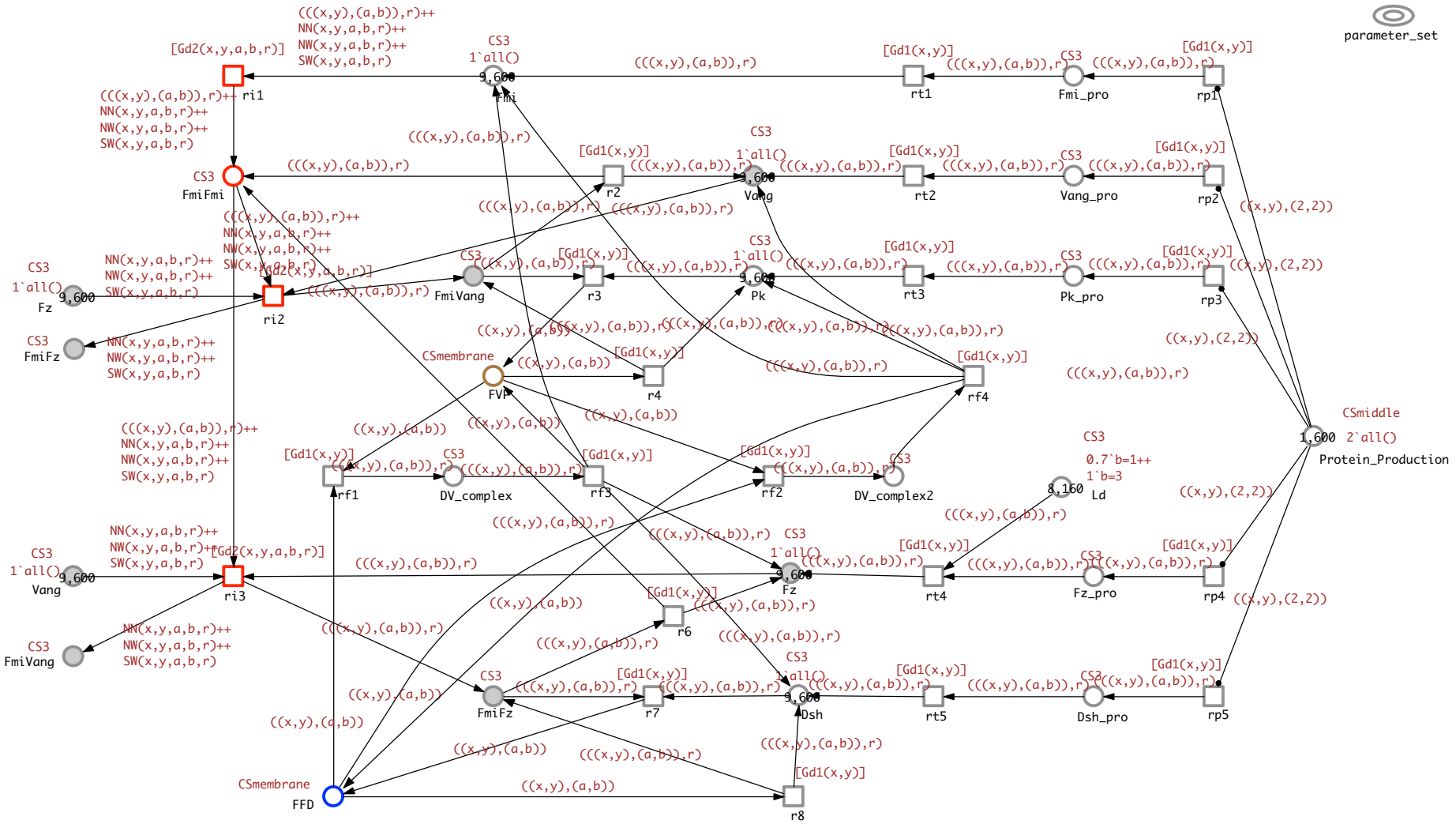


[BIOPPN 2011]
[CMSB 2011]

EX4: PLANAR CELL POLARITY

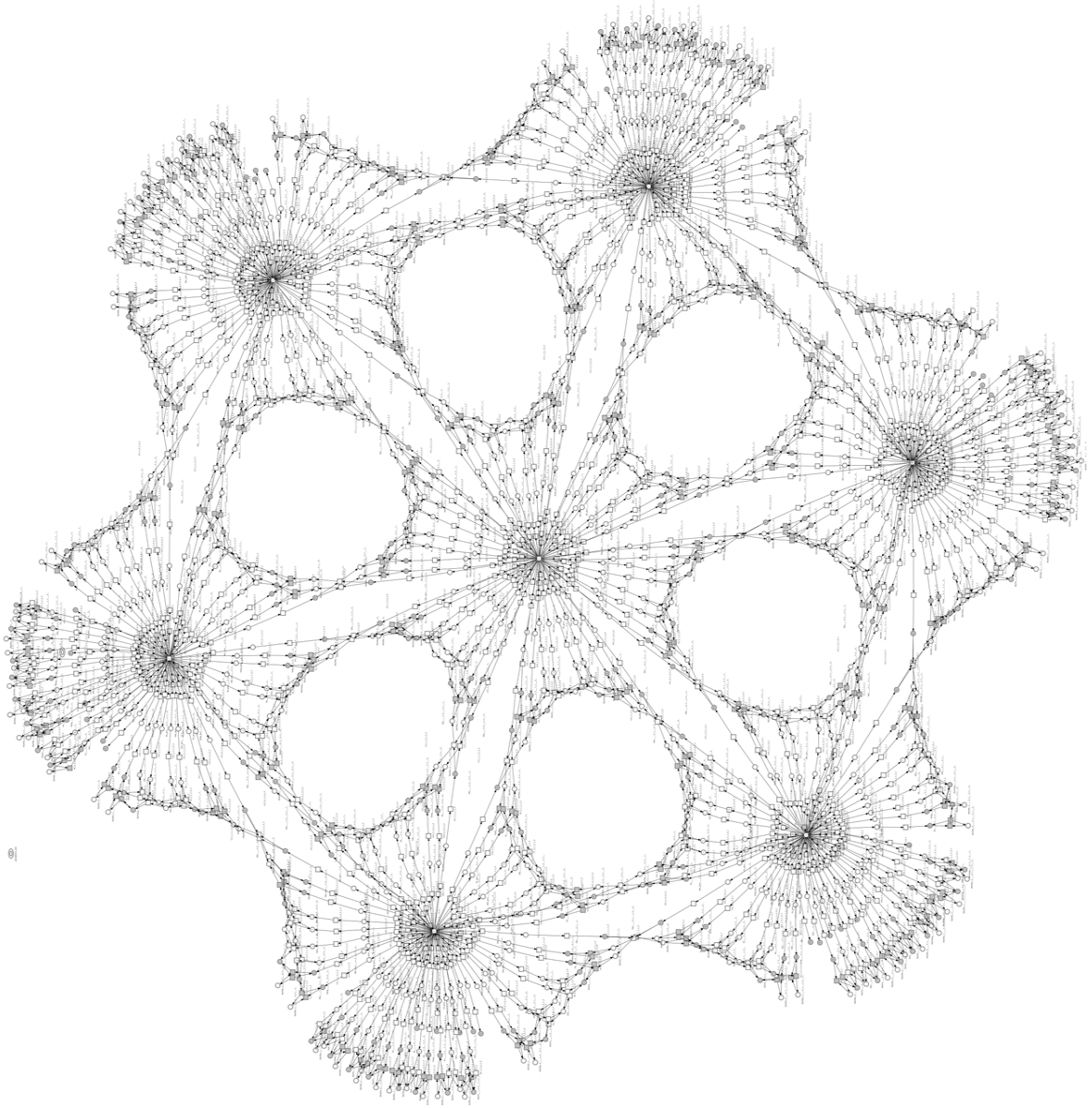


EX4: PLANAR CELL POLARITY



[QIAN GAO, PHD THESIS 2013]

EX4: PLANAR CELL POLARITY, PLAIN MODEL (7 CELLS)



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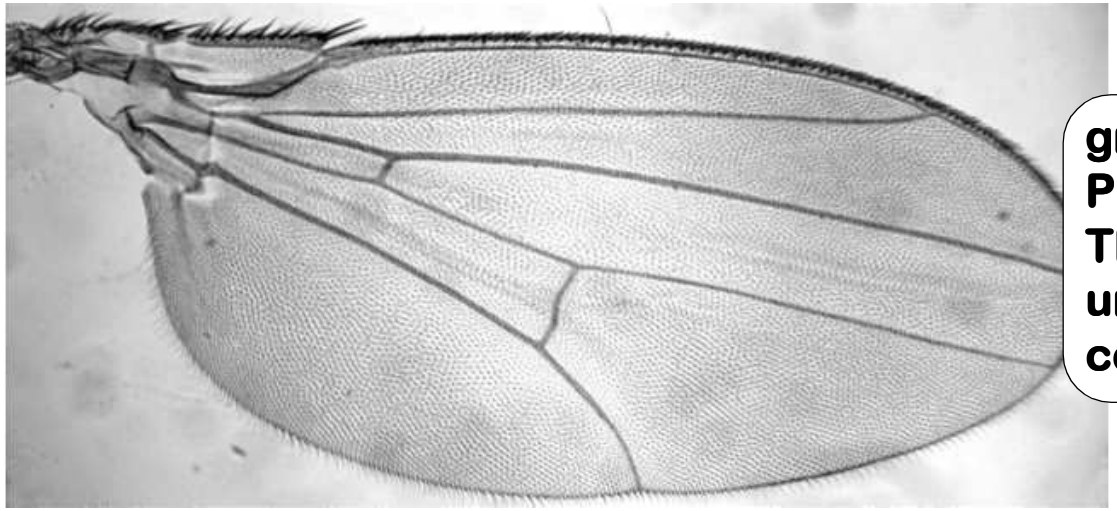
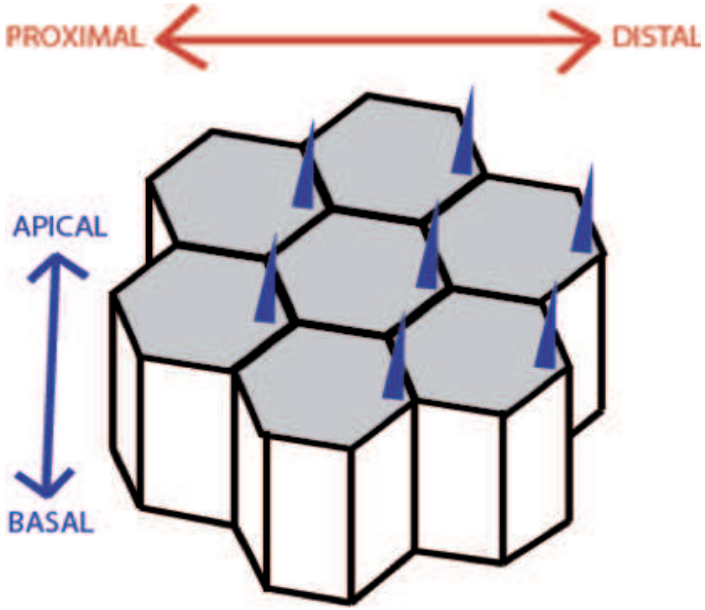
EX4 - PLANAR CELL POLARITY



grid size:	40 x 40
PLACES:	164,000
TRANSITIONS:	229,686
unfolding:	4 min
cont. simulation:	2 h



[BIOPPN 2011]
[CMSB 2011]

EX4 - PLANAR CELL POLARITY

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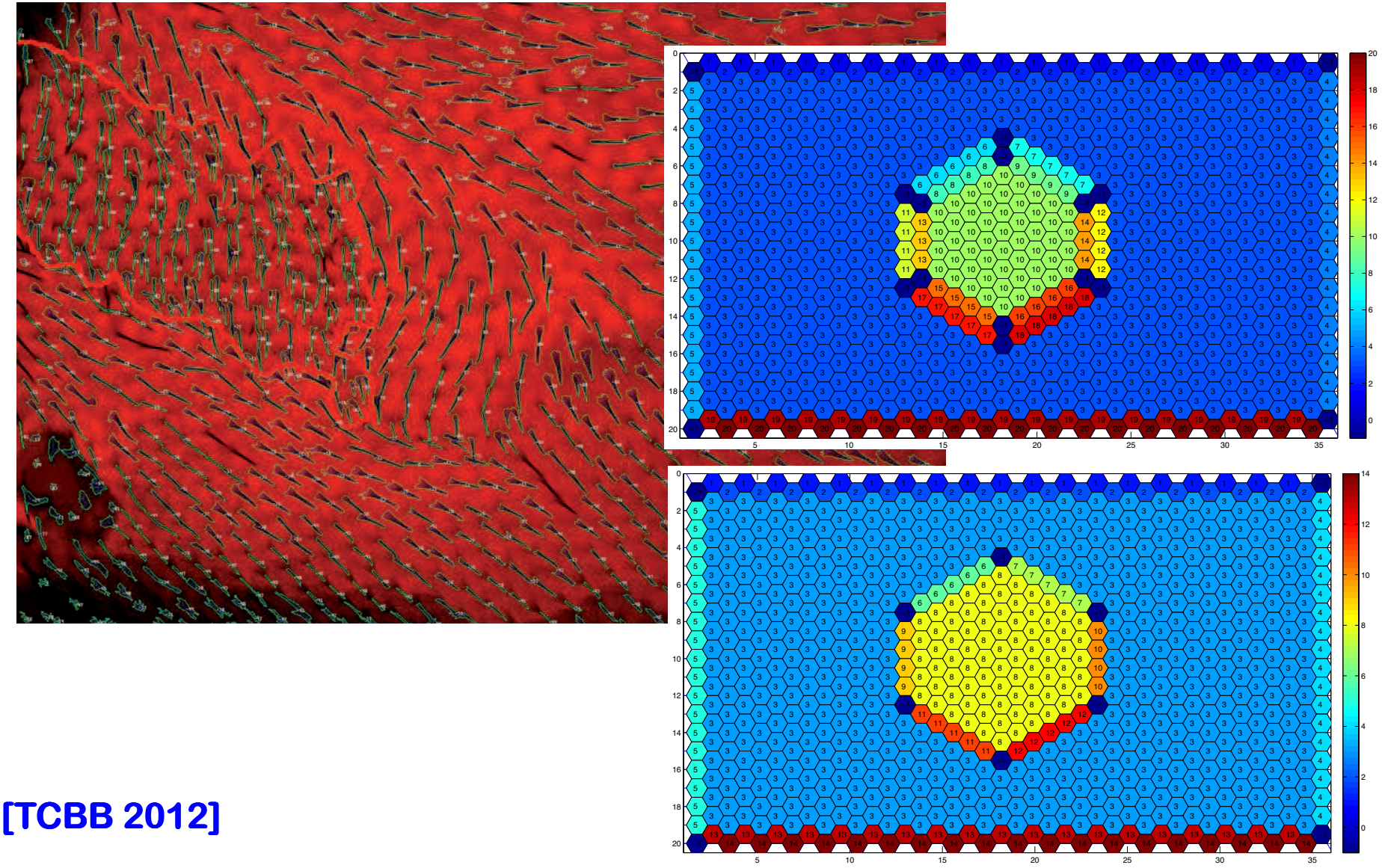
EX4 - PLANAR CELL POLARITY



[TCBB 2012]

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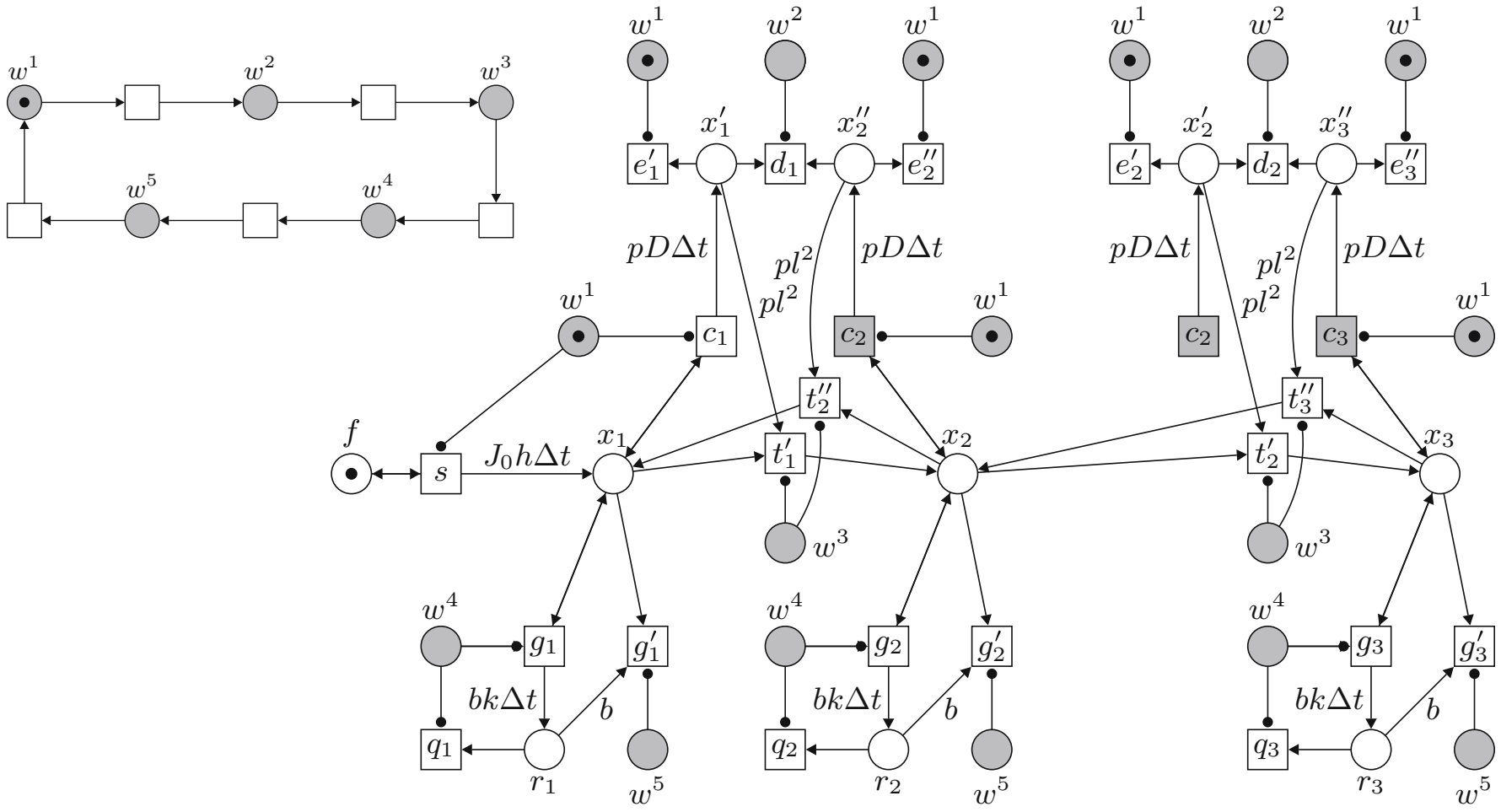
ANOTHER APPROACH TO COMBINE PDE AND PETRI NETS



Bertens, Kleijn, Hille, Heiner, Koutny,Verbeek:
Modeling biological gradient formation: combining partial differential equations and Petri nets;
Natural Computing 2015.

FRAMEWORK SUMMARY

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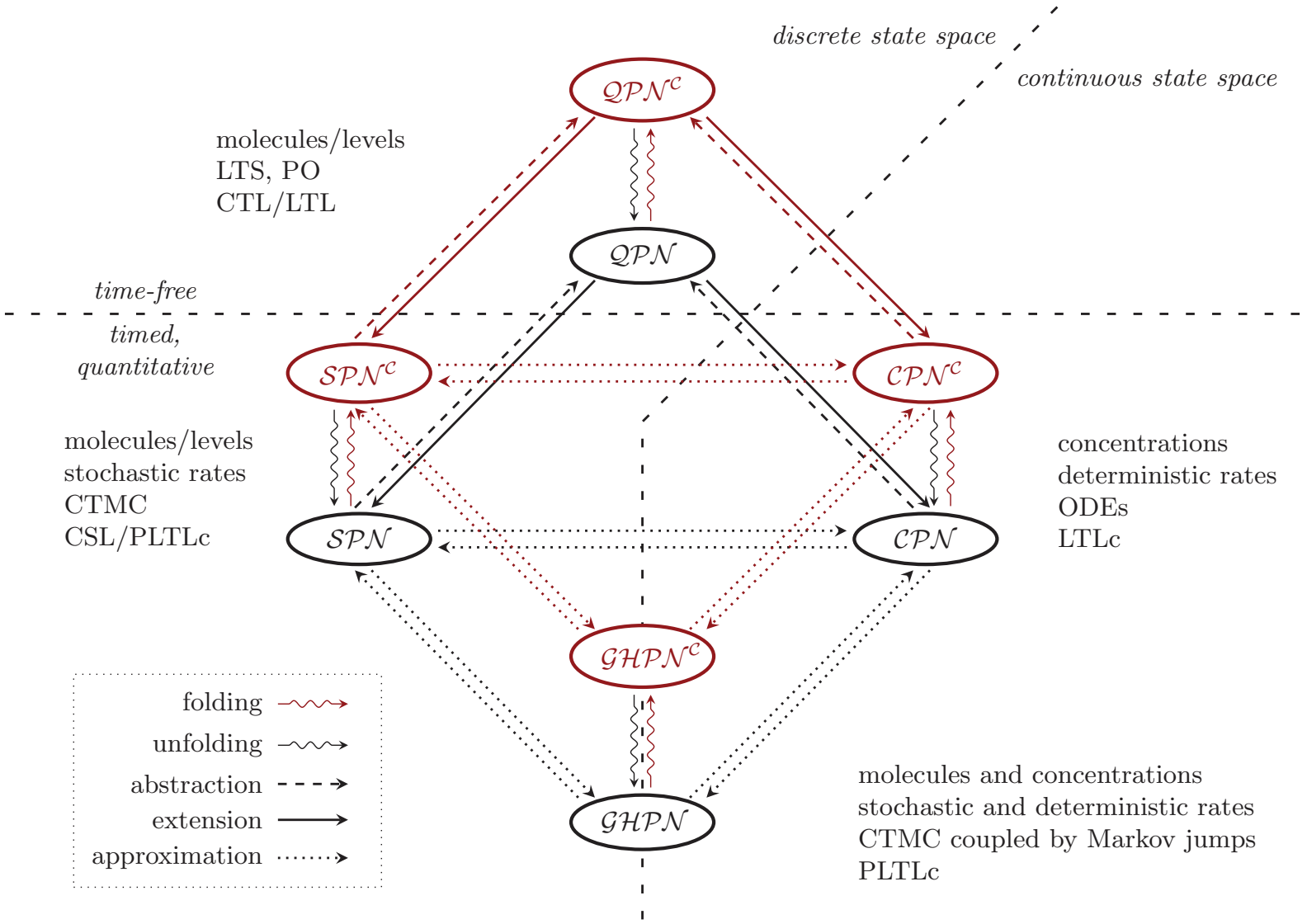
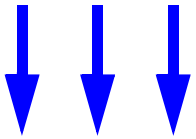
FRAMEWORK


discrete state space
continuous state space
molecules/levels
LTS, PO
CTL/LTL
time-free
timed,
quantitative
molecules/levels
stochastic rates
CTMC
CSL/PLTLc
concentrations
deterministic rates
ODEs
LTLc
molecules and concentrations
stochastic and deterministic rates
CTMC coupled by Markov jumps
PLTLc
folding
unfolding
abstraction
extension
approximation

4x2

MODELS SHARING STRUCTURE

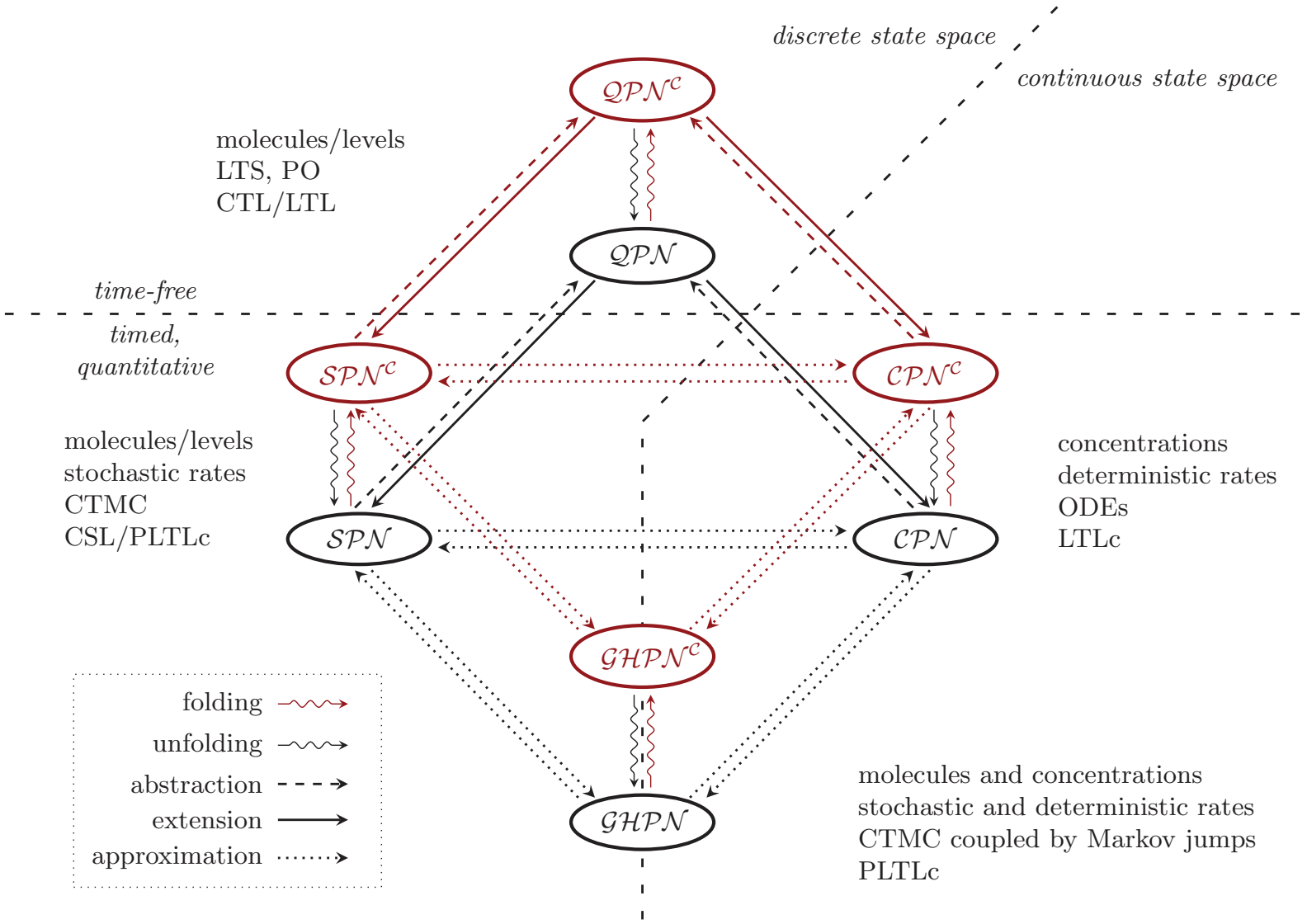


QUANTITATIVE MODEL = QUALITATIVE MODEL

+

RATE FUNCTIONS (KINETICS)

FRAMEWORK


discrete state space
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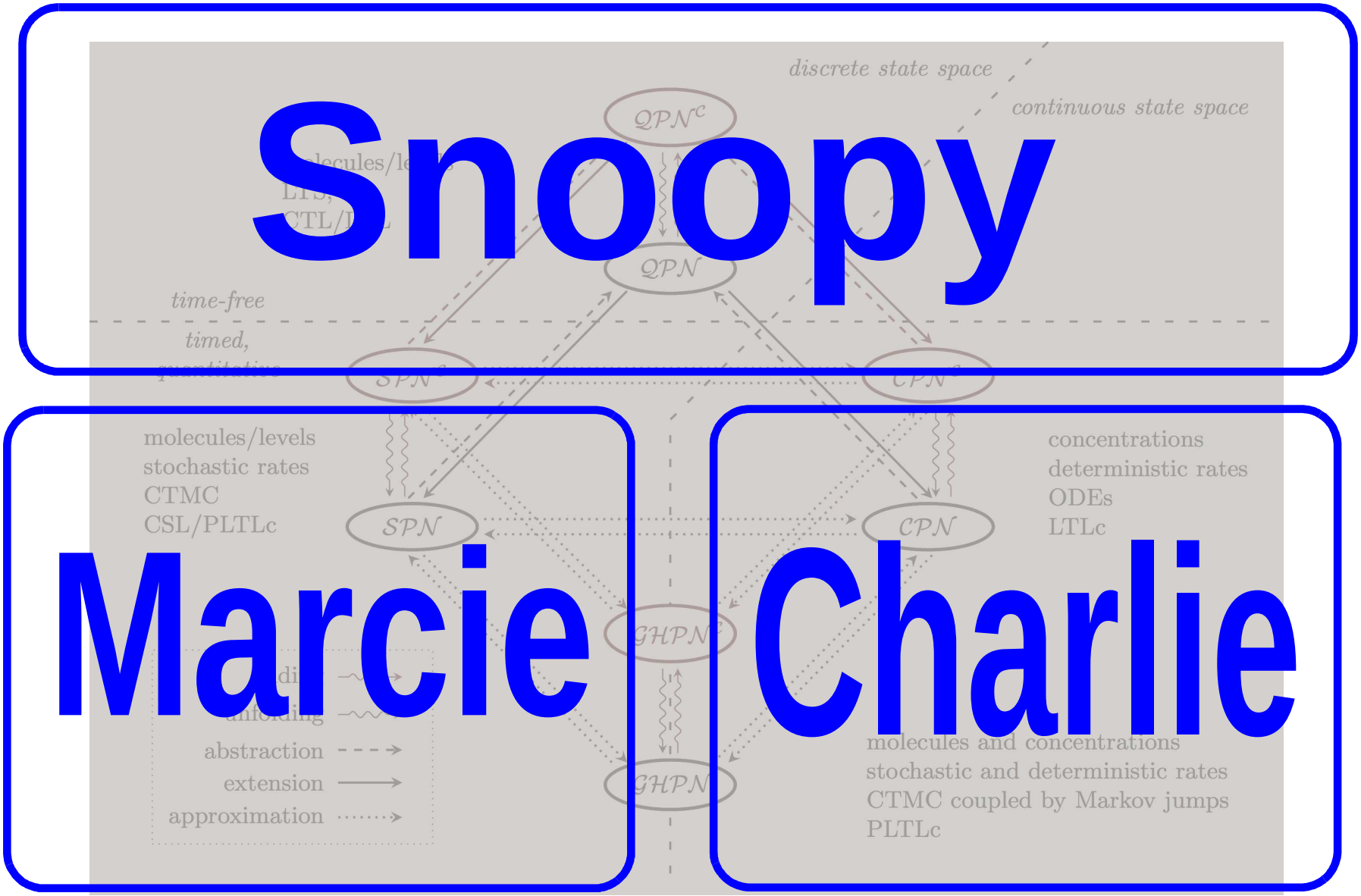
CSL/PLTLc
concentrations
deterministic rates
ODEs
LTLc
molecules and concentrations
stochastic and deterministic rates
CTMC coupled by Markov jumps
PLTLc
folding
unfolding
abstraction
extension
approximation


Petri net world
Markov world
hybrid world
ODE world
discrete state space
molecules/levels
LTS, PO
CTL/LTL
QPN
time-free
timed,
quantitative
SPN^C
CPN^C
molecules/levels
stochastic
concentrations
CPN
unfolding
unfolding
abstraction
extension
approximation
GHPN
molecules and concentrations
stochastic and deterministic rates
CTMC coupled by Markov jumps
PDETLc


Snoopy
discrete state space
continuous state space
QPN^C
QPN
time-free
timed,
SPN
CPN
molecules/levels
stochastic rates
CTMC
CSL/PLTLc
concentrations
deterministic rates
ODEs
LTLc
Marcie
Charlie
GHPN
abstraction
extension
approximation
molecules and concentrations
stochastic and deterministic rates
CTMC coupled by Markov jumps
PLTLc

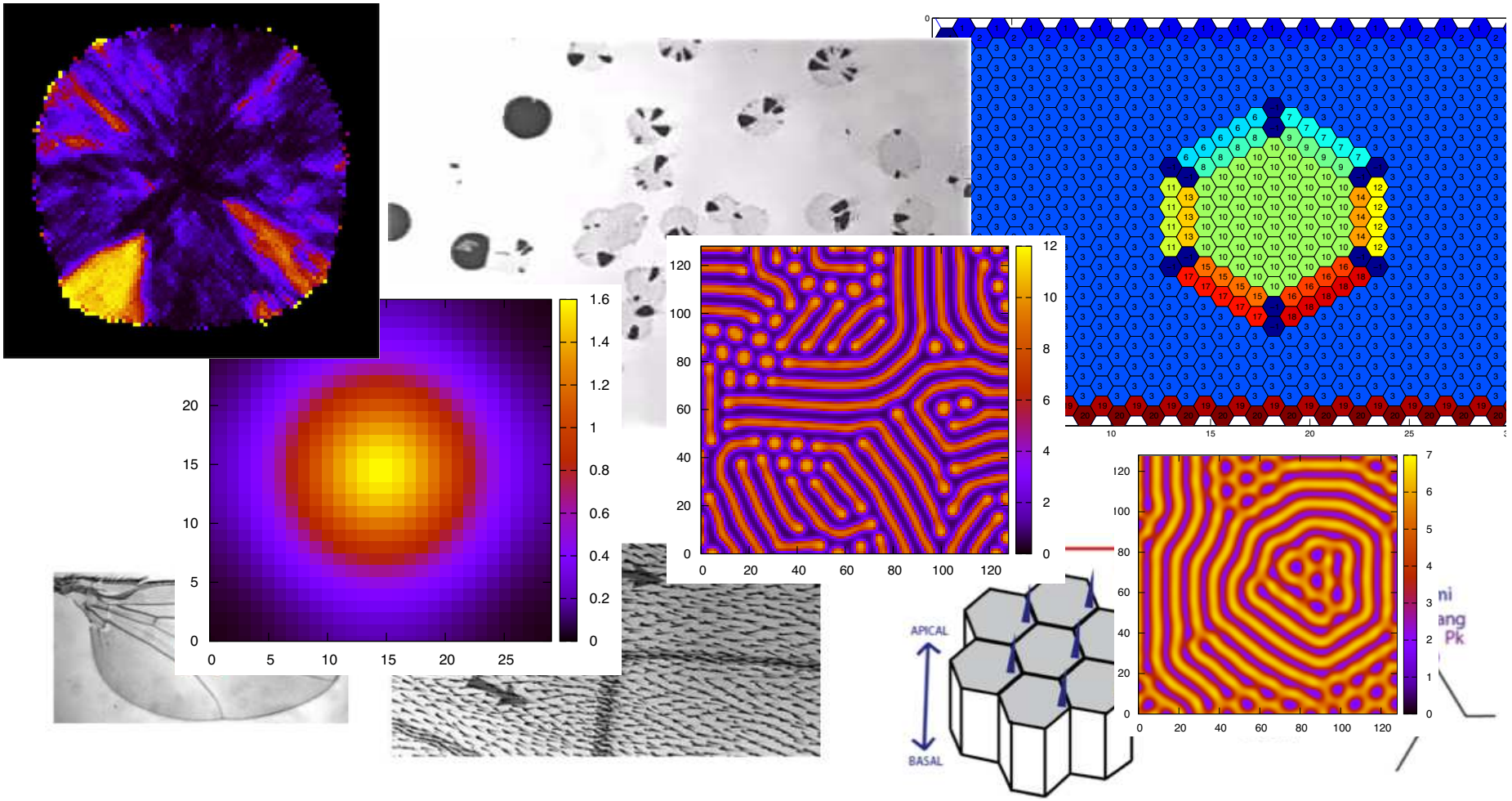
SBML import/export

EXPORT TO MATLAB AND MANY OTHER TOOLS

ACKNOWLEDGEMENT - CLOSE COLLABORATORS

- **David Gilbert**
  Brunel University London, UK
- **Wolfgang Marwan,**
  Otto-von-Guericke University Magdeburg, Germany
- **Fei Liu**
  South China University of Technology
- **Mostafa Herajy**
  Port Said Universit, Egypt
- **Mary Ann Blätke**
  IPK Gatersleben, Germany

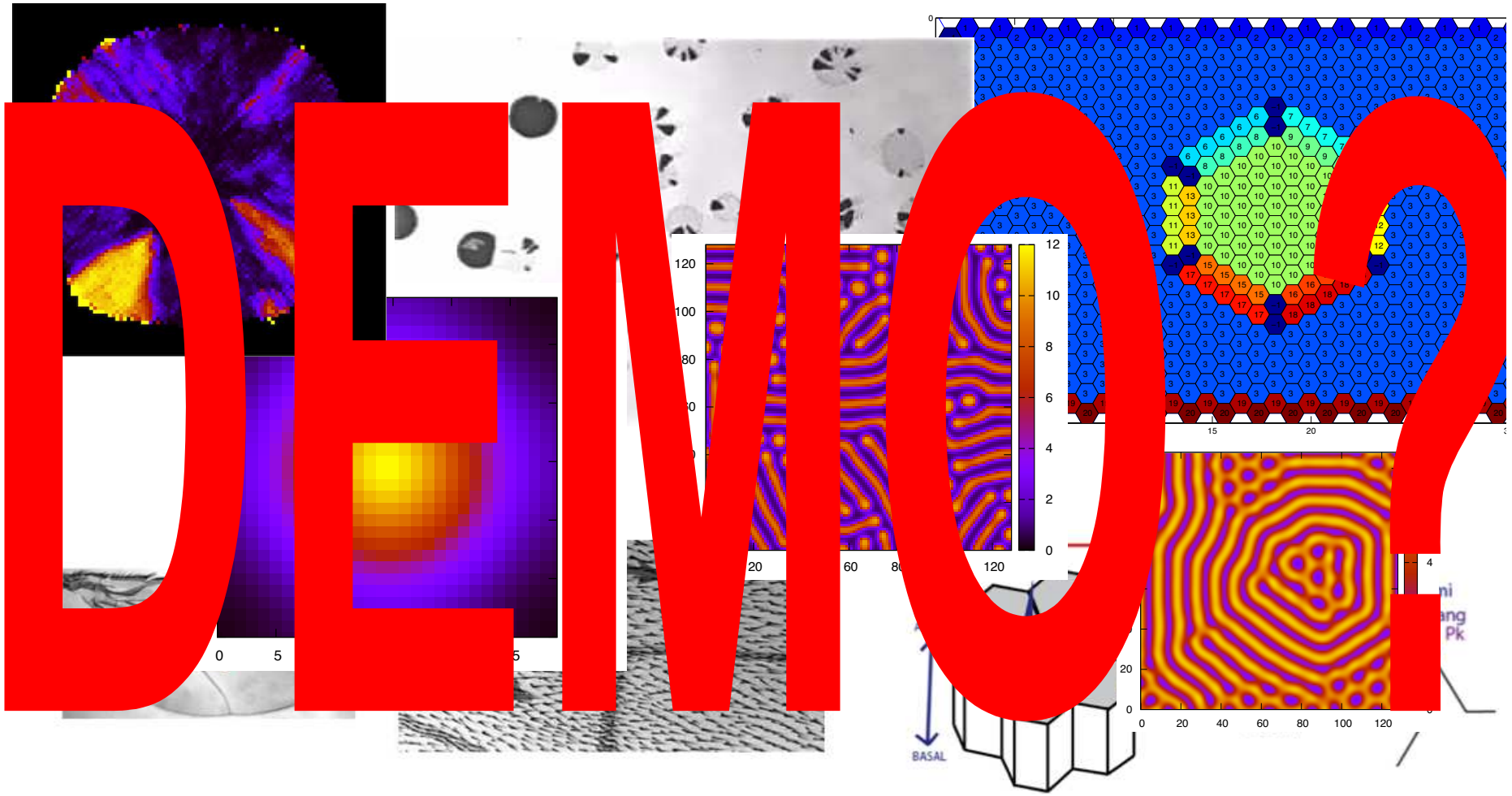
SUMMARY



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

HTTP://MULTISCALEPN.BRUNEL.AC.UK

SUMMARY



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HTTP://MULTISCALEPN.BRUNEL.AC.UK

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MODELLING
BIO (PETRI) NETS

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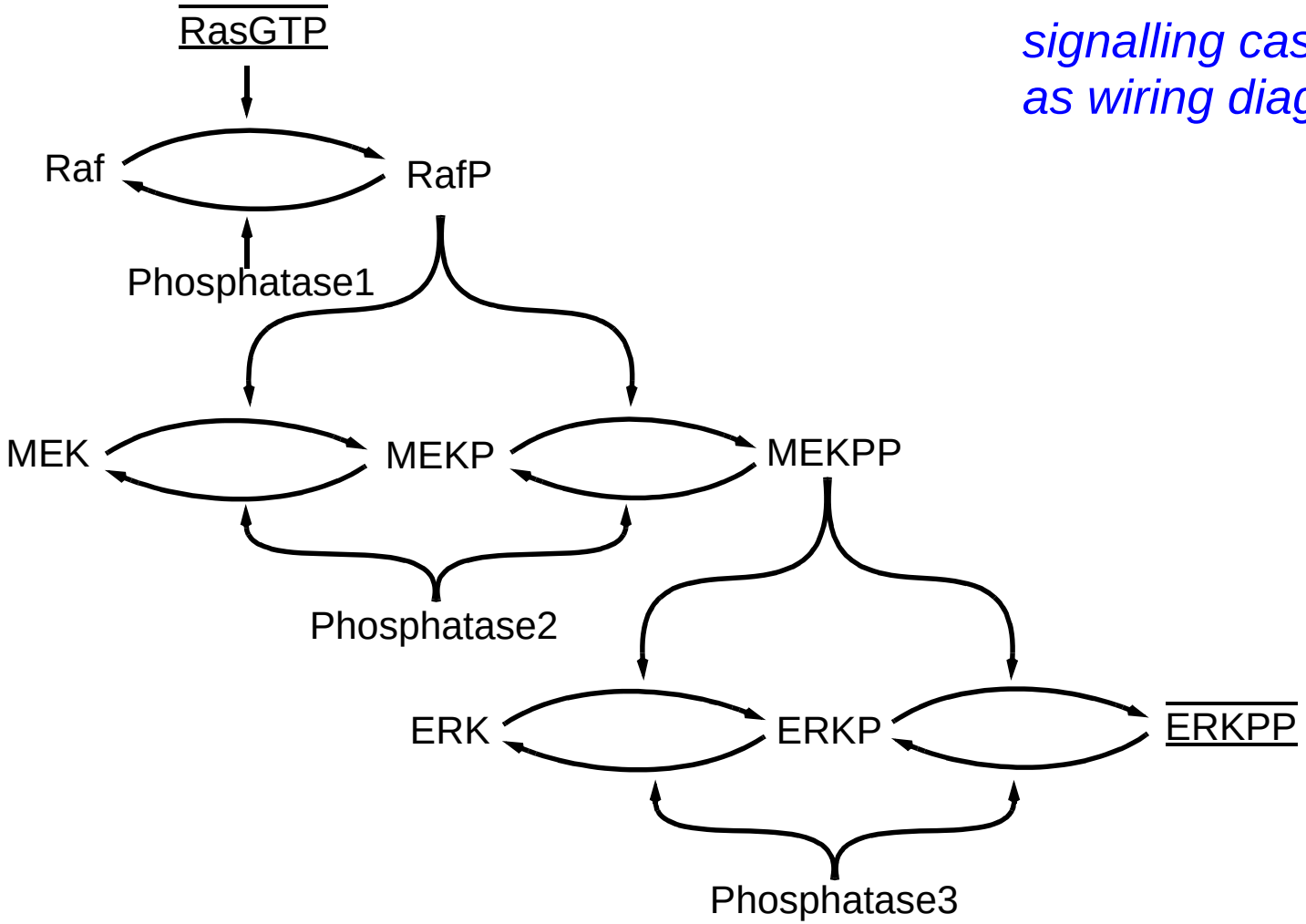
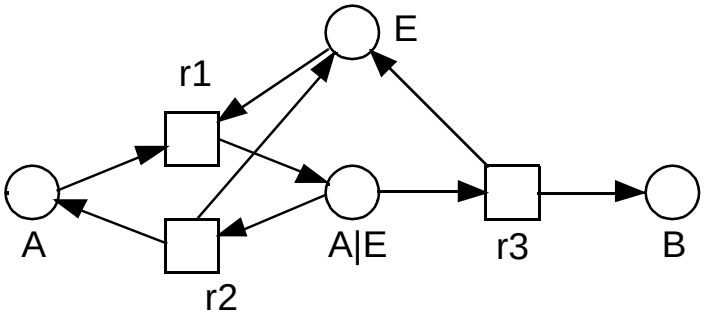
APPROACH 1



signalling cascade as wiring diagram

BASIC STRUCTURE

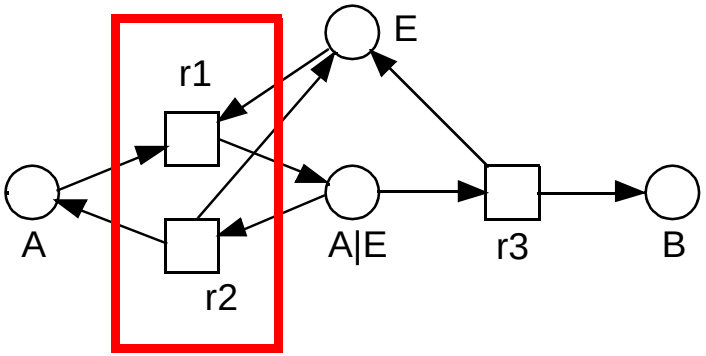
A <E--> A|E --> B



enzymatic reaction,
mass-action kinetics

BASIC STRUCTURE

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

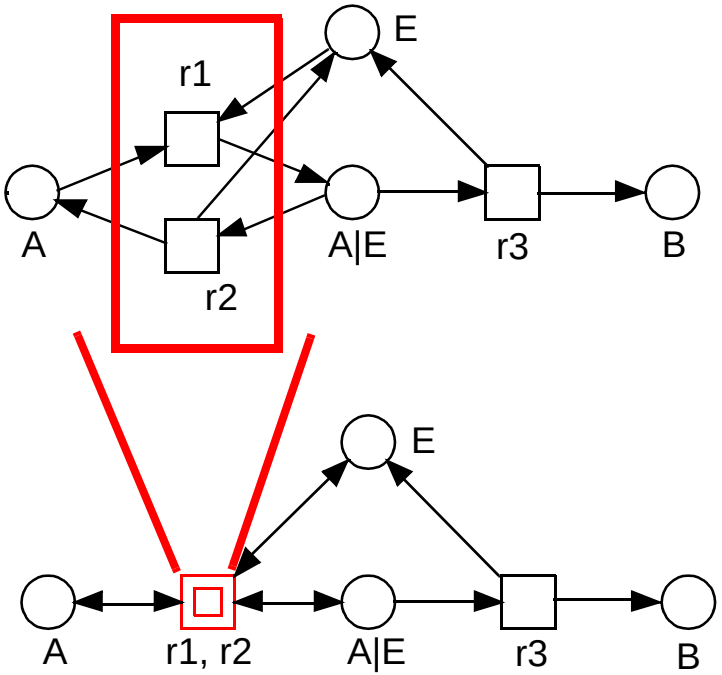


enzymatic reaction,
mass-action kinetics

BASIC STRUCTURE

$$A \xleftrightarrow{E} A|E \rightarrow B$$

enzymatic reaction,
mass-action kinetics



BASIC STRUCTURE

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enzymatic reaction,
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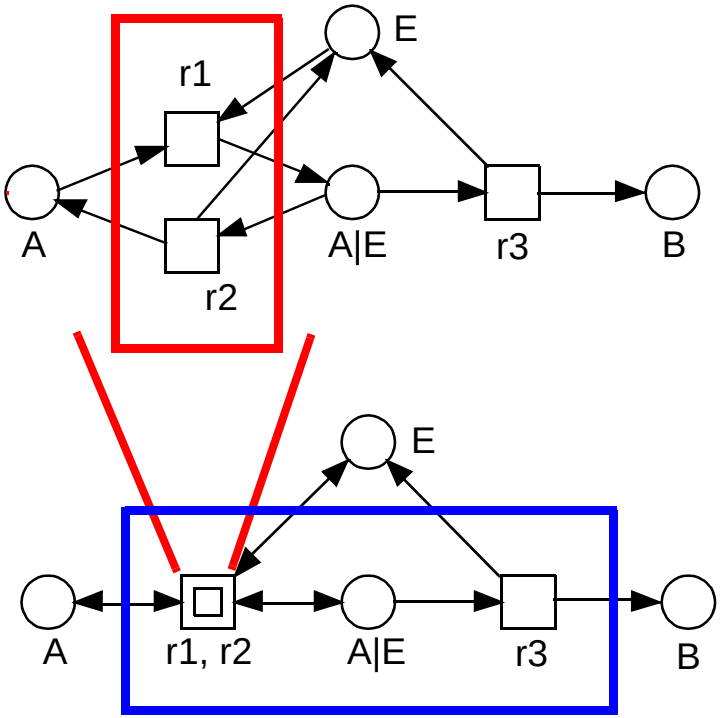
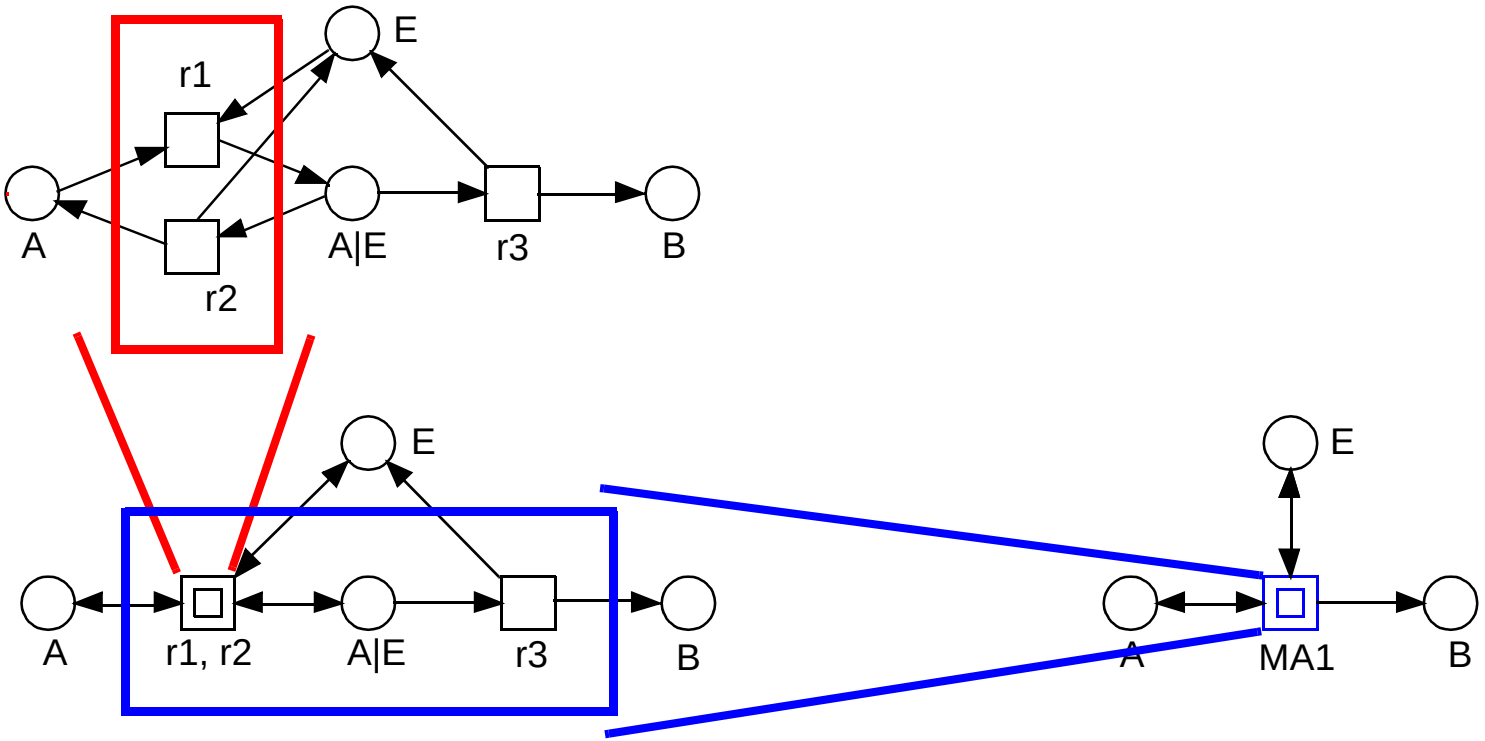


BASIC STRUCTURE

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

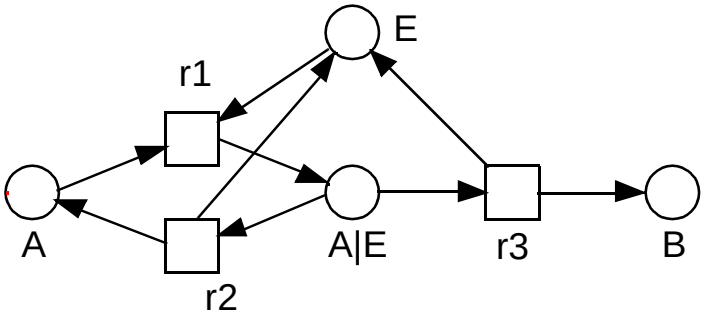
enzymatic reaction,
mass-action kinetics

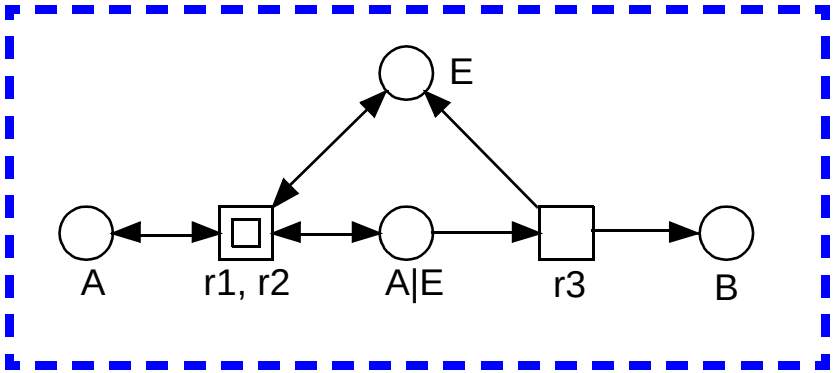


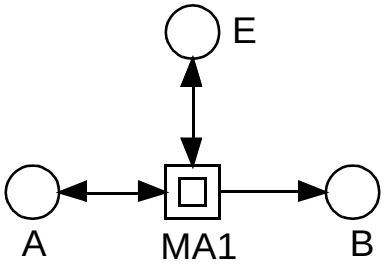
BASIC STRUCTURE

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

enzymatic reaction,
mass-action kinetics

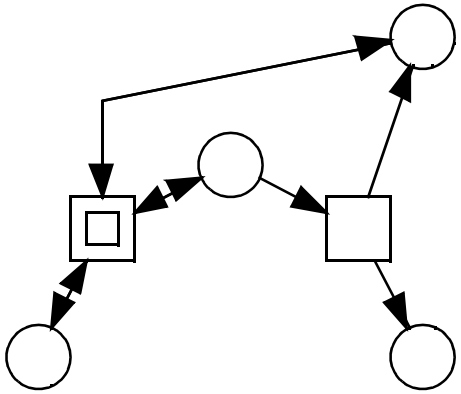




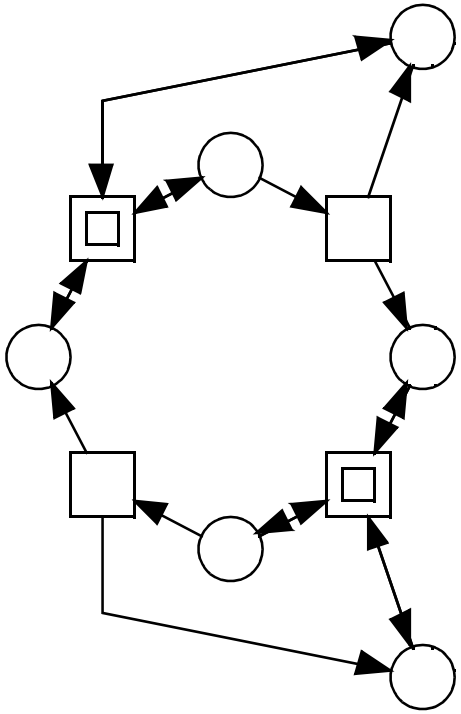


NET COMPOSITION FROM BUILDING BLOCKS

SINGLE
MASS-ACTION STEP

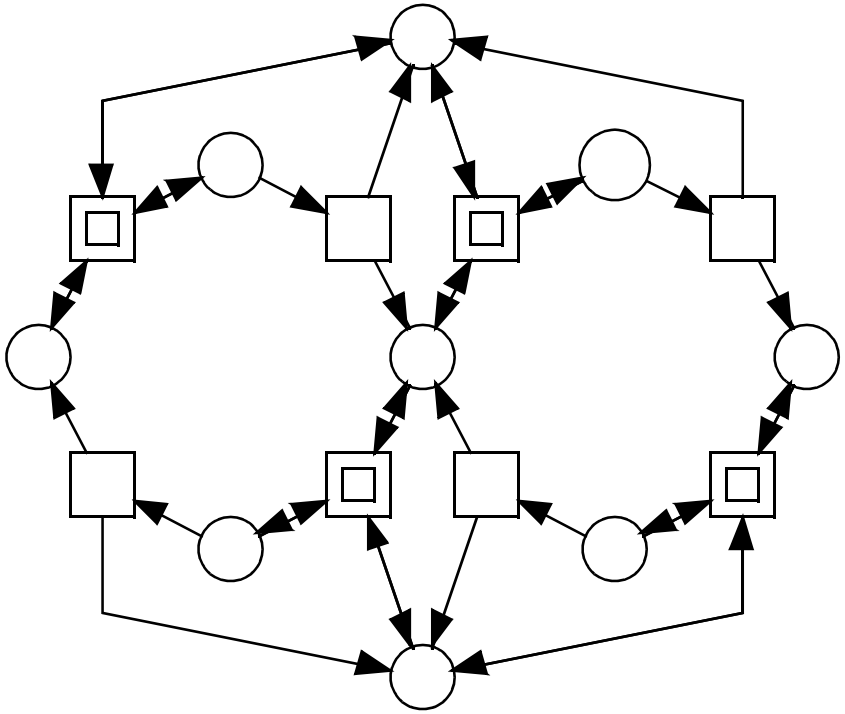


NET COMPOSITION FROM BUILDING BLOCKS

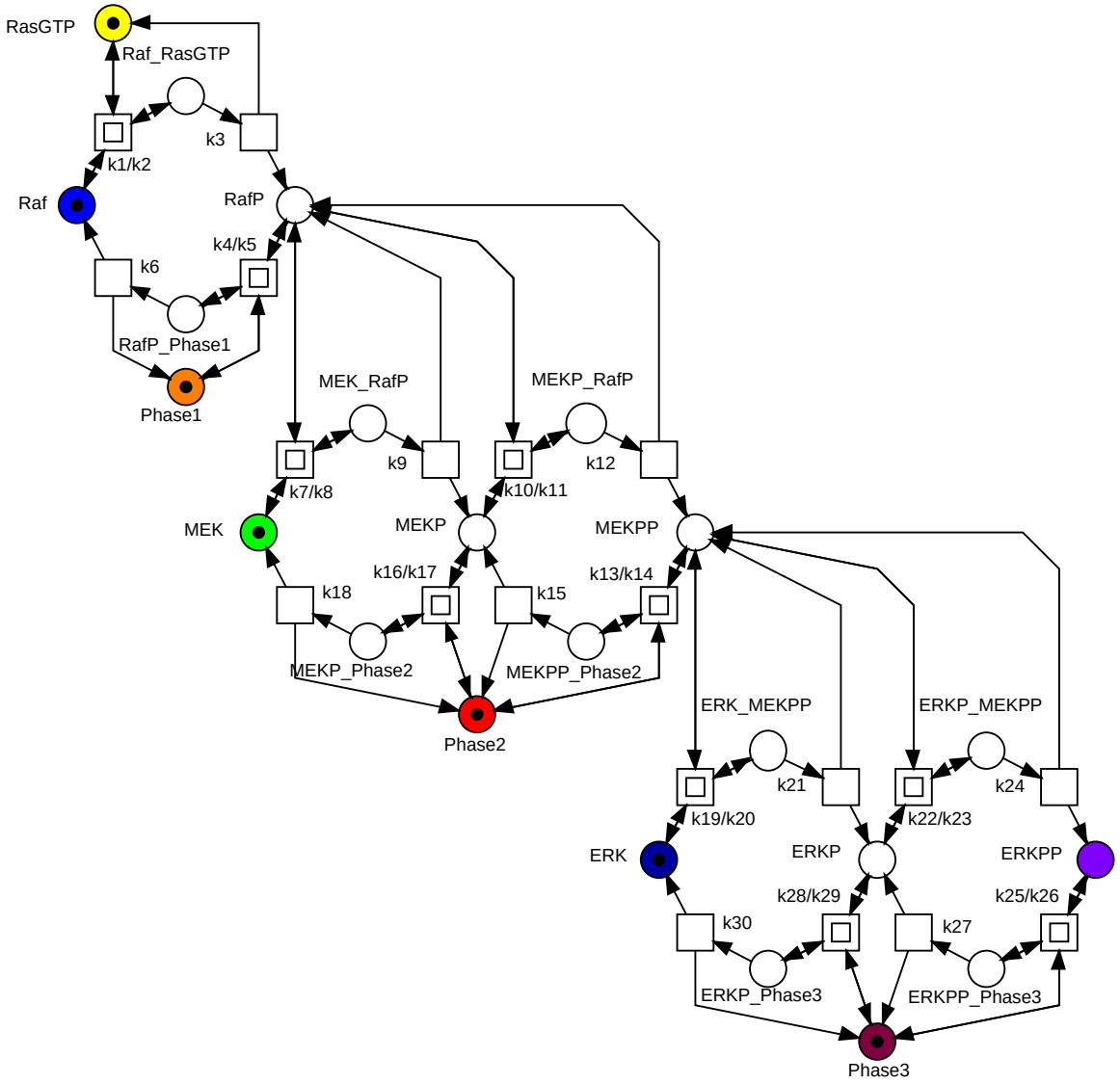


SINGLE
PHOSPHORYLATION / DEPHOSPHORYLATION

DOUBLE PHOSPHORYLATION / DEPHOSPHORYLATION



SIGNALLING CASCADE AS PETRI NET

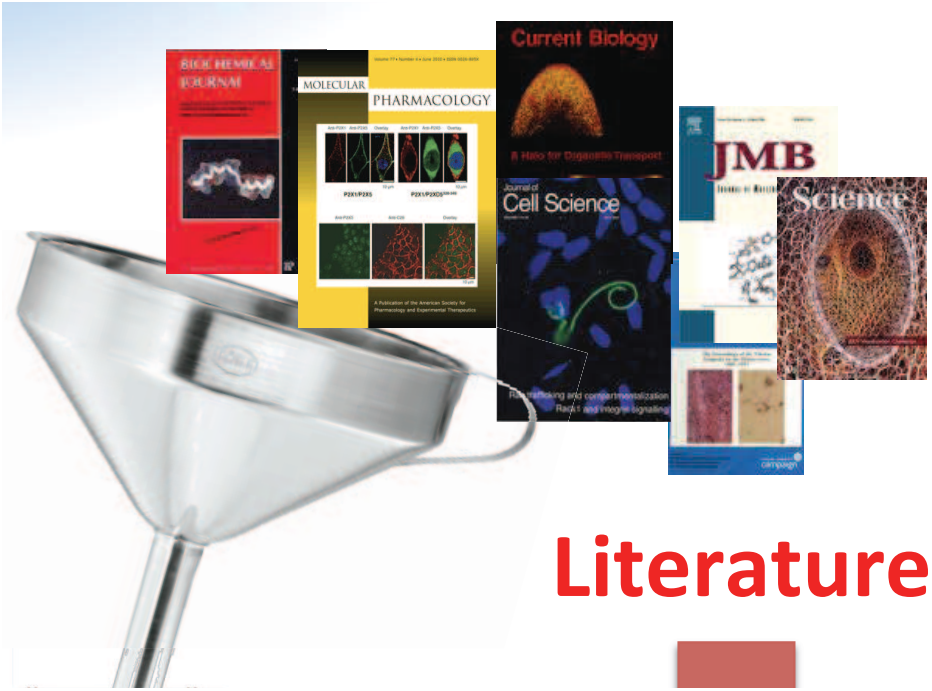


[GILBERT, HEINER, LEHRACK 2007]

[HEINER, GILBERT, DONALDSON 2008]

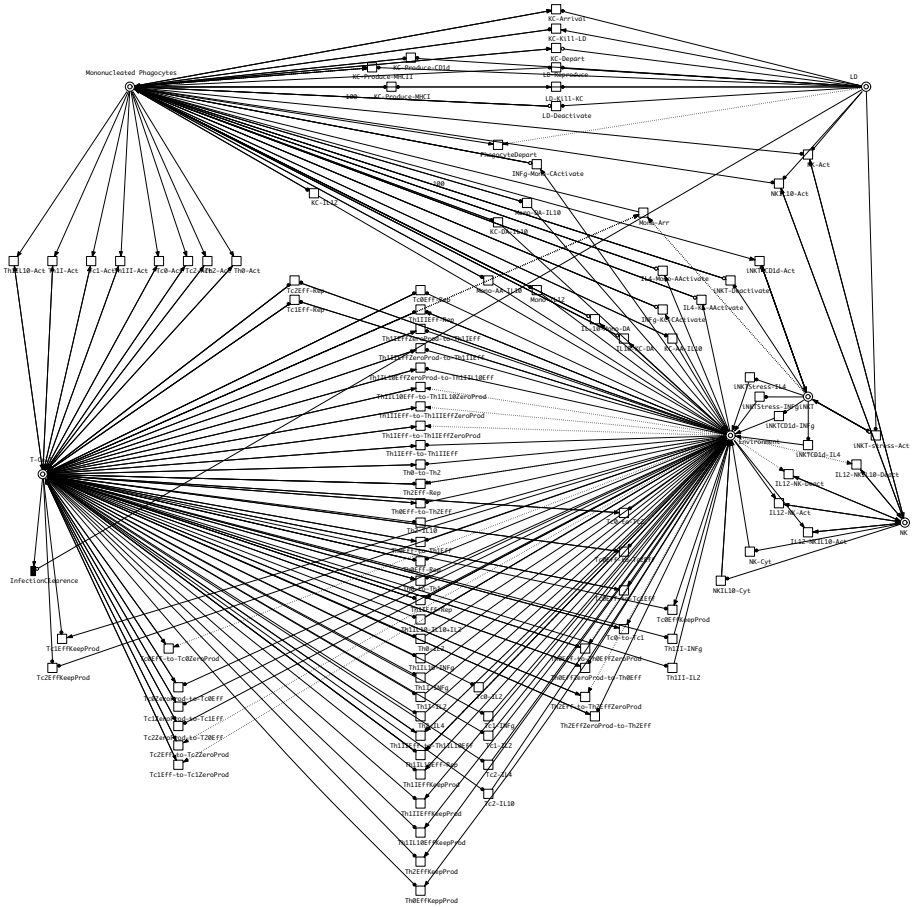
APPROACH 2

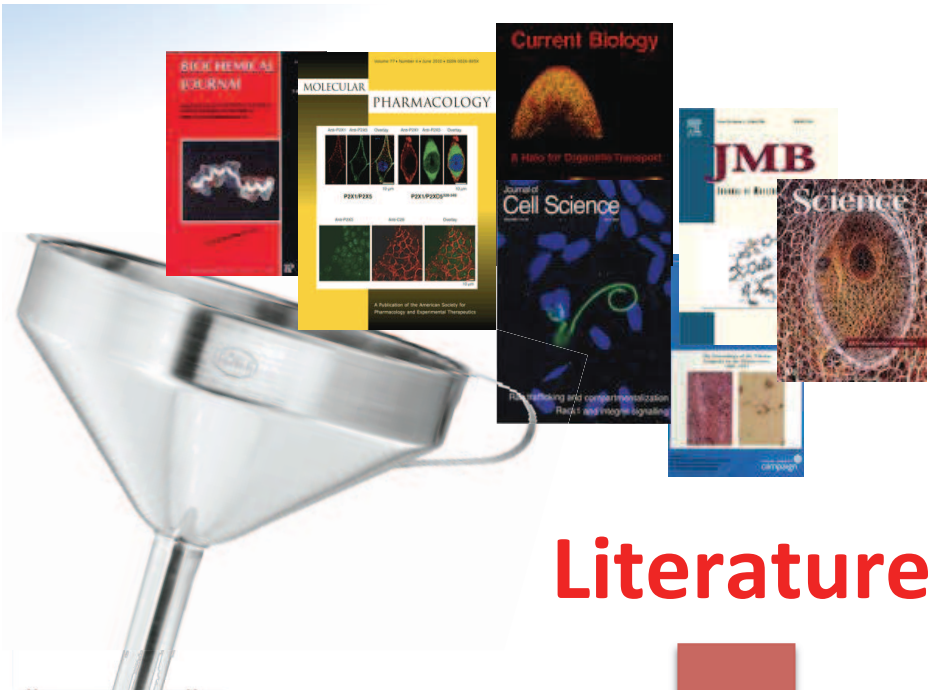
FROM LITERATURE TO MODELS



Literature

FROM LITERATURE TO MODELS





Literature

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FROM LITERATURE TO MODELS

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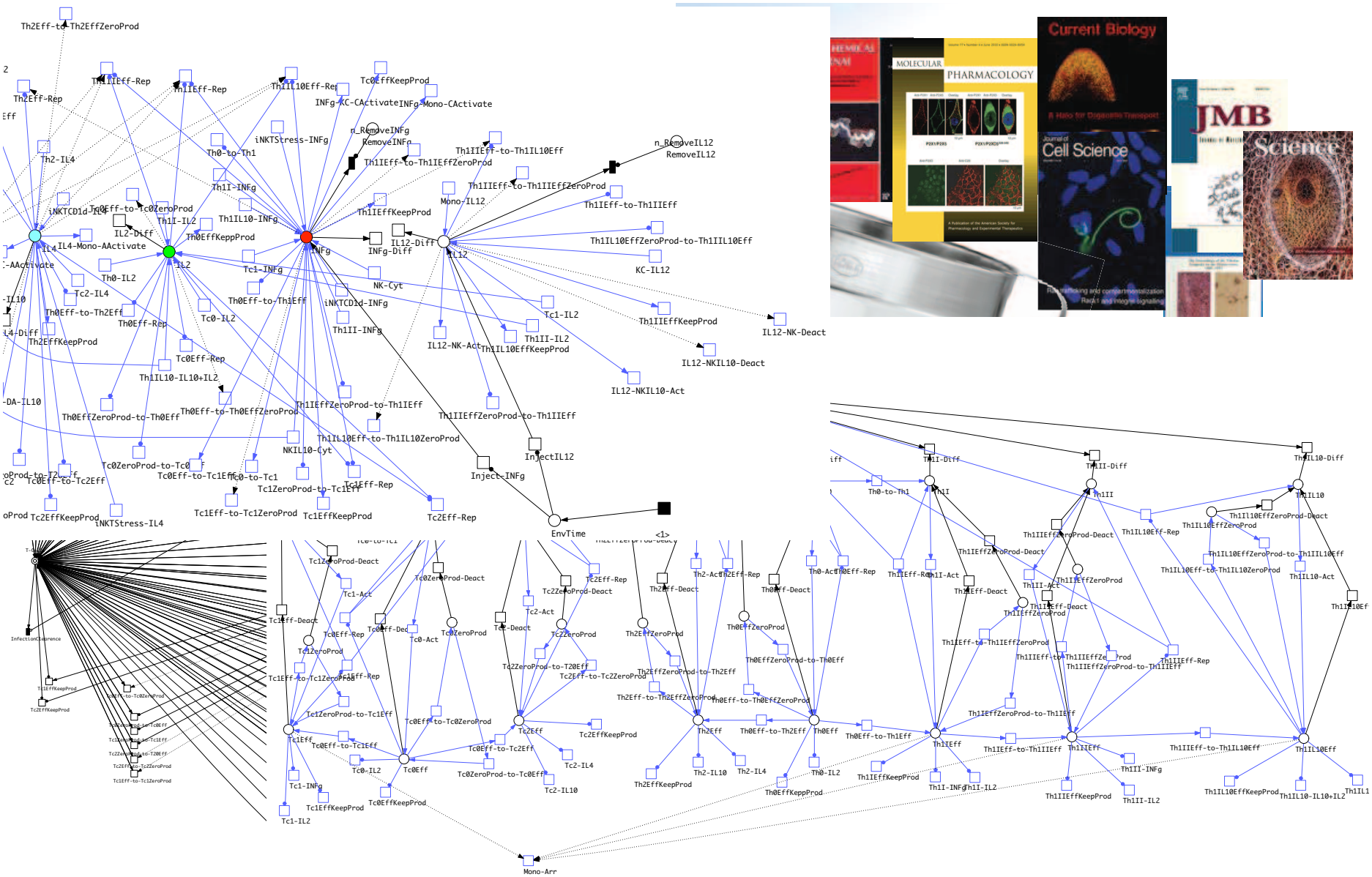
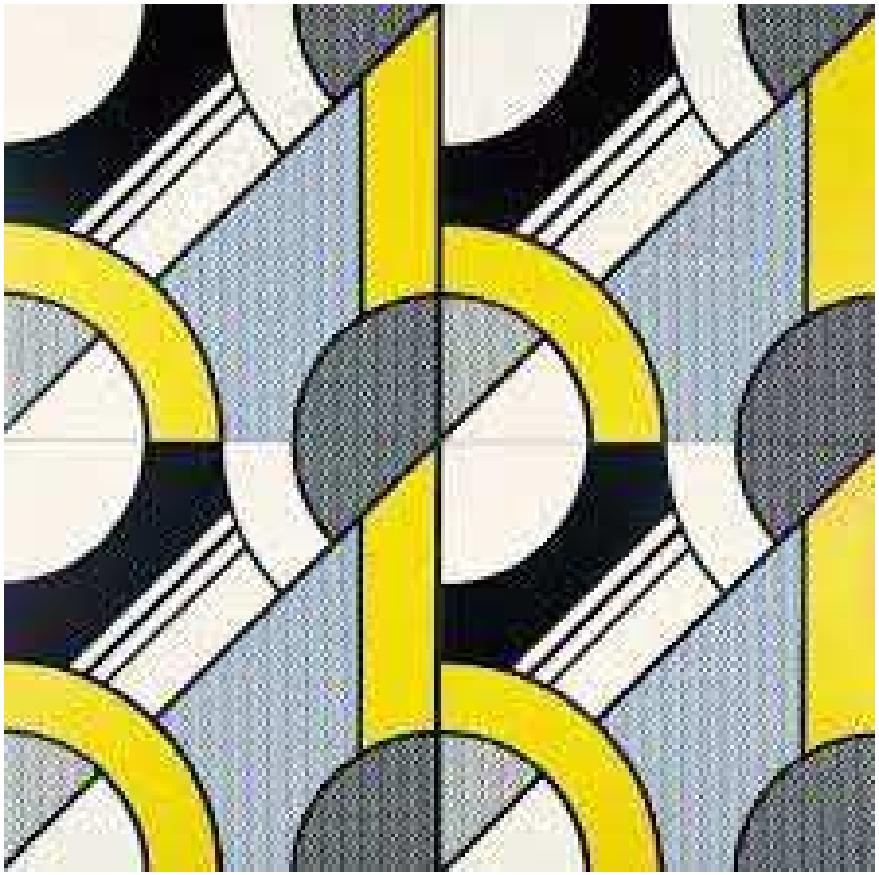
FROM LITERATURE TO MODELS



APPROACH 3

MODULAR MODELLING

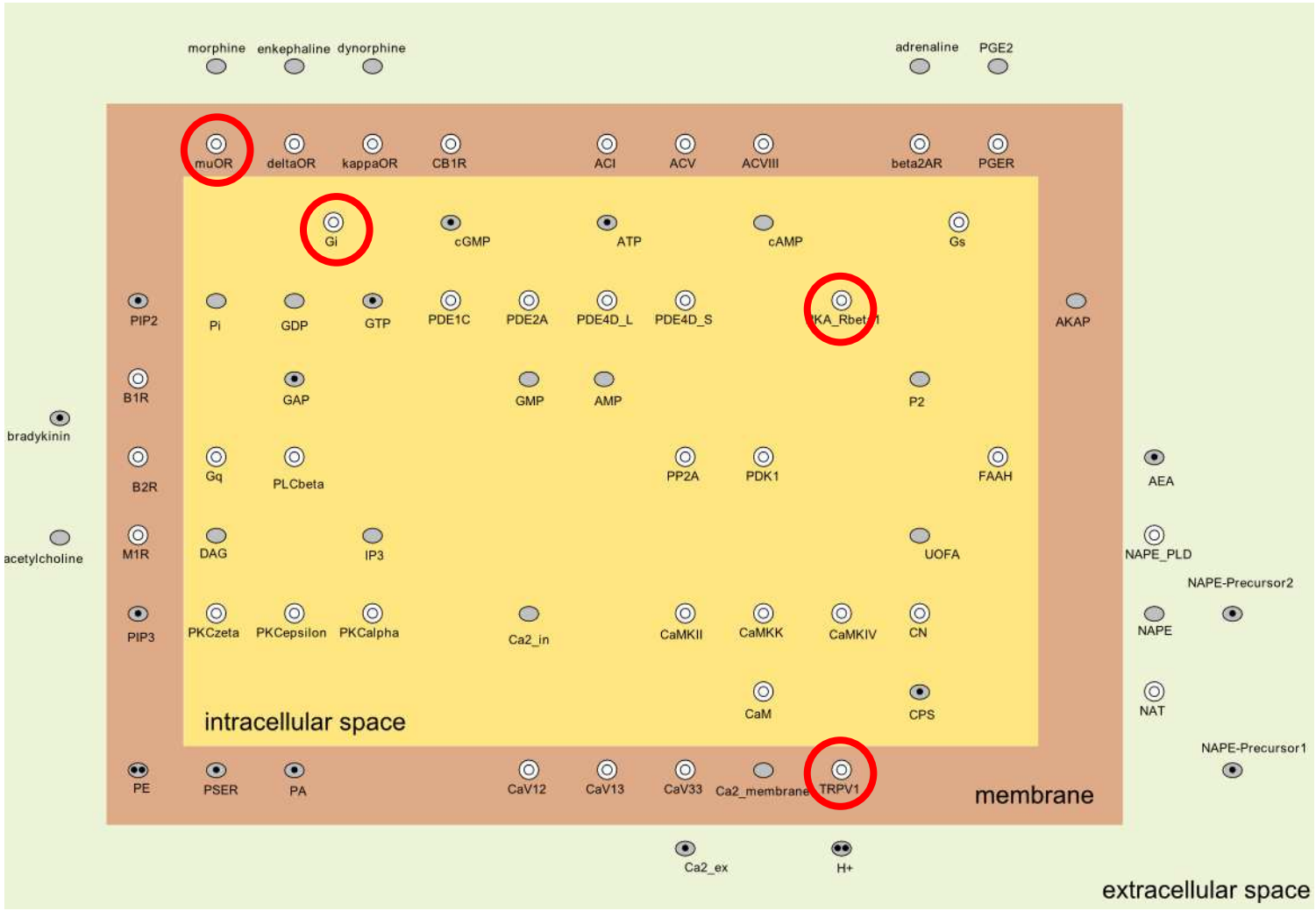


JOINT WORK WITH
MARY ANN BLÄTKE, WOLFGANG MARWAN

monika.heiner@b-tu.de

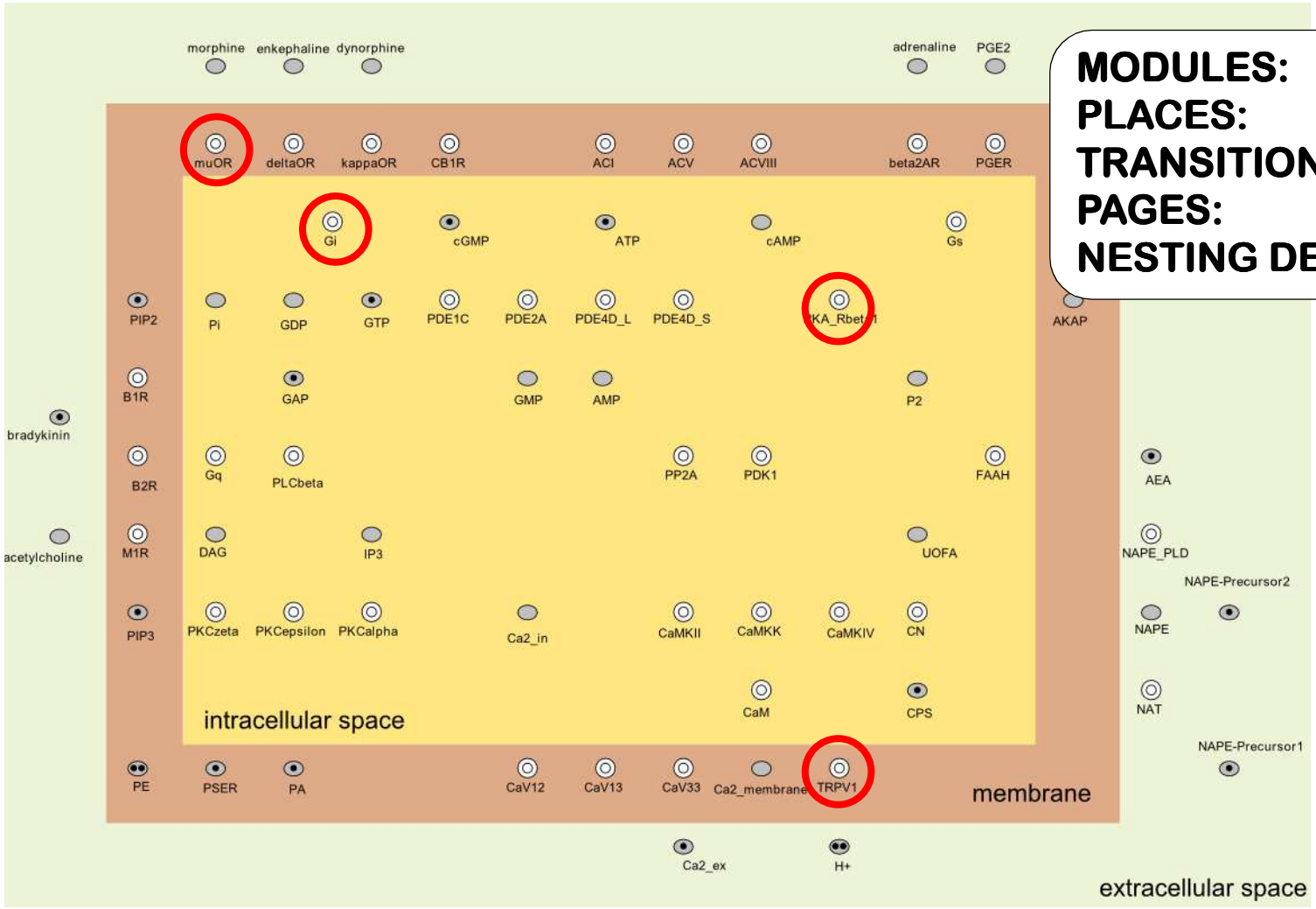
[BLÄTKE, MEYER, MARWAN 2011]

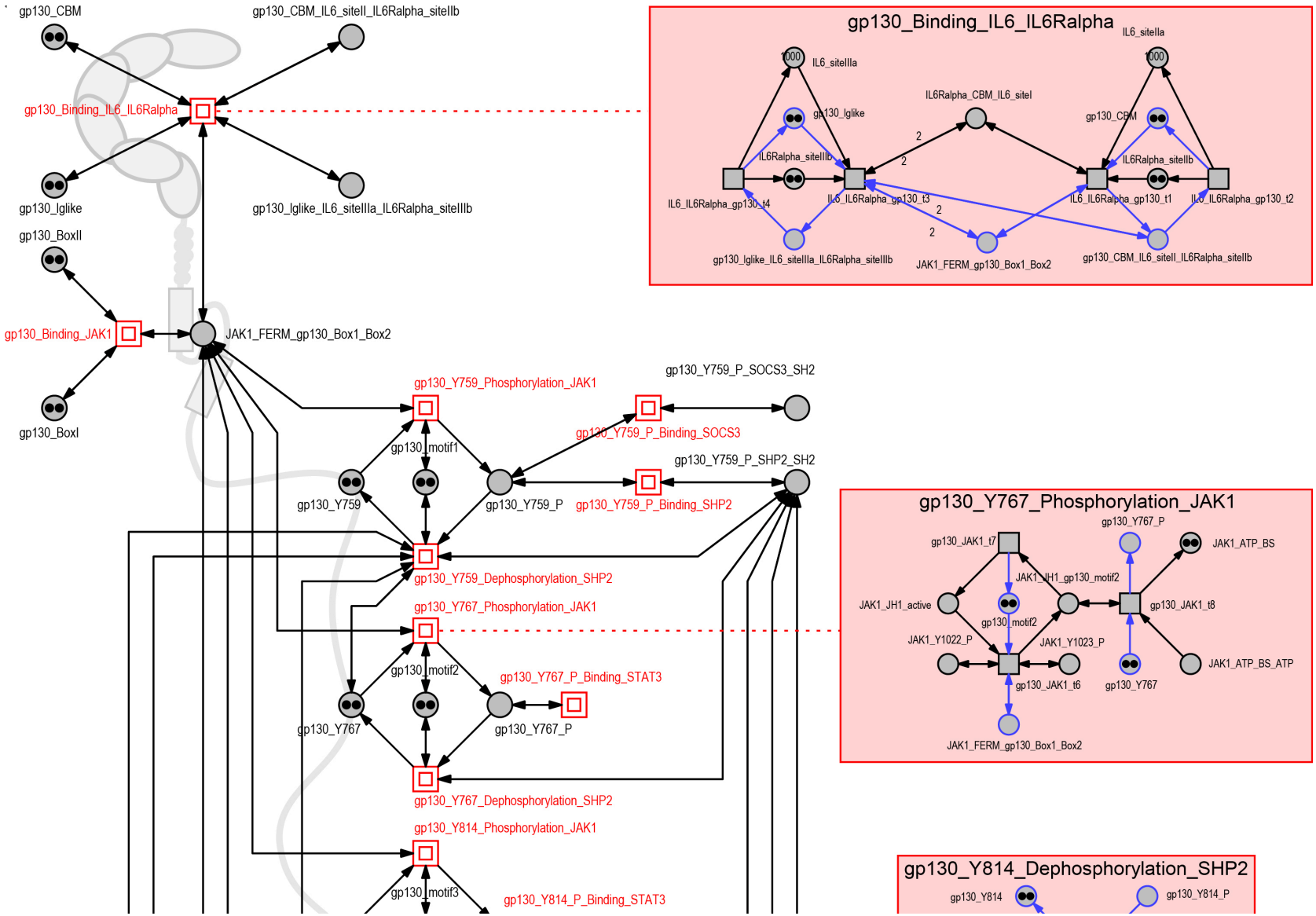
-> A PROTEIN-ORIENTED MODULAR MODELLING CONCEPT



[BLÄTKE, MEYER, MARWAN 2011]

-> A PROTEIN-ORIENTED MODULAR MODELLING CONCEPT

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gp130_BoxII
gp130_Binding_JAK1
JAK1_FERM_gp130_Box1_Box2
gp130_BoxI
gp130_Y759_Phosphorylation_JAK1
gp130_Y759_P_SOCS3_SH2
gp130_Y759_P_Binding_SOCS3
gp130_motif1
gp130_Y759_P_SHP2_SH2
gp130_Y759
gp130_Y759_P
gp130_Y759_P_Binding_SHP2
gp130_Y759_Dephosphorylation_SHP2
gp130_Y767_Phosphorylation_JAK1
gp130_motif2
gp130_Y767_P_Binding_STAT3
gp130_Y767
gp130_Y767_P
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gp130_Y814_Phosphorylation_JAK1
gp130_motif3
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IL6_siteIIIa
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gp130_lglike
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JAK1_FERM_gp130_Box1_Box2
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JAK1_JH1_active
gp130_motif2
gp130_JAK1_t8
JAK1_Y1022_P
JAK1_Y1023_P
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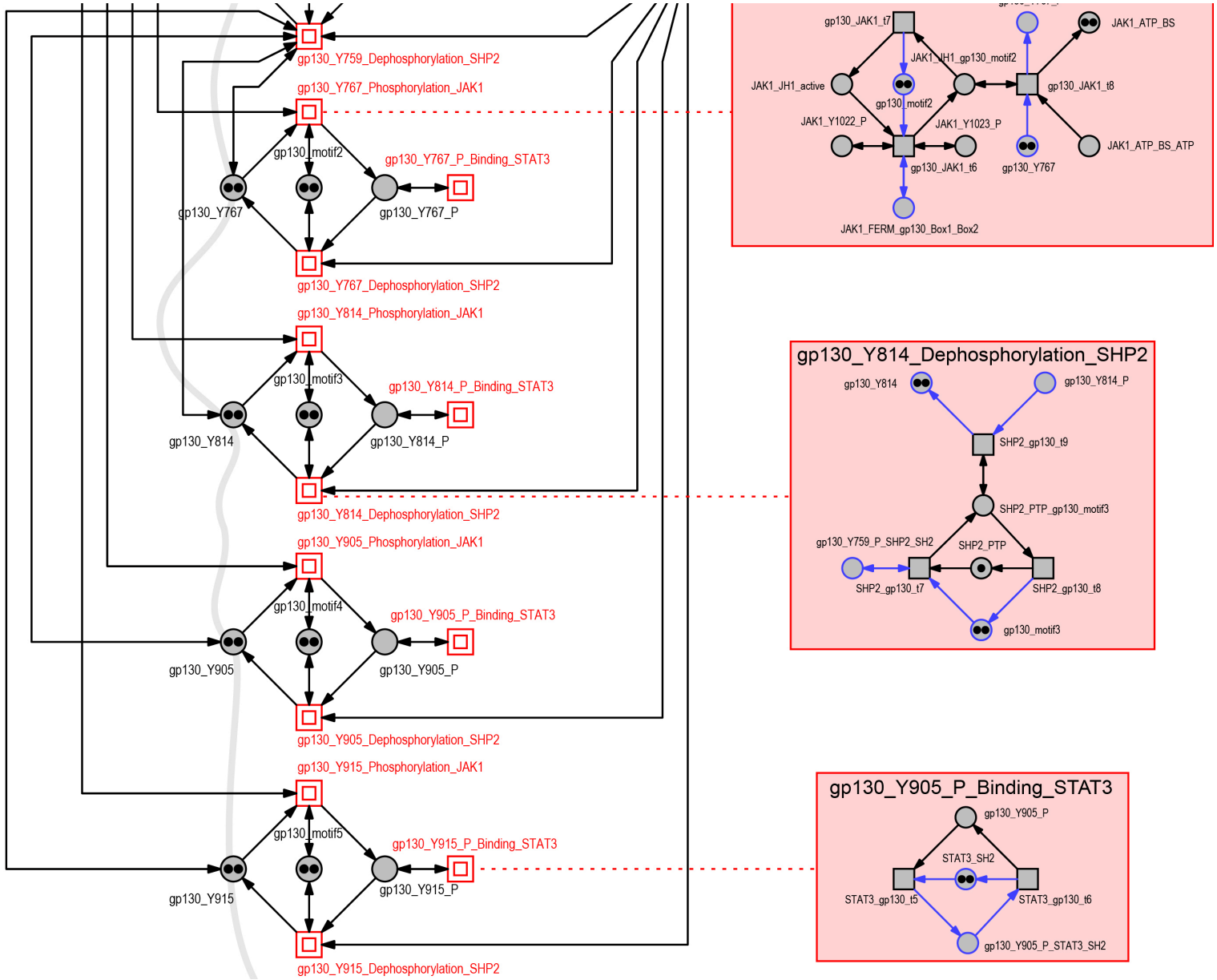
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gp130_Y814_Phosphorylation_JAK1
gp130_motif3
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gp130_motif4
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gp130_Y814_P
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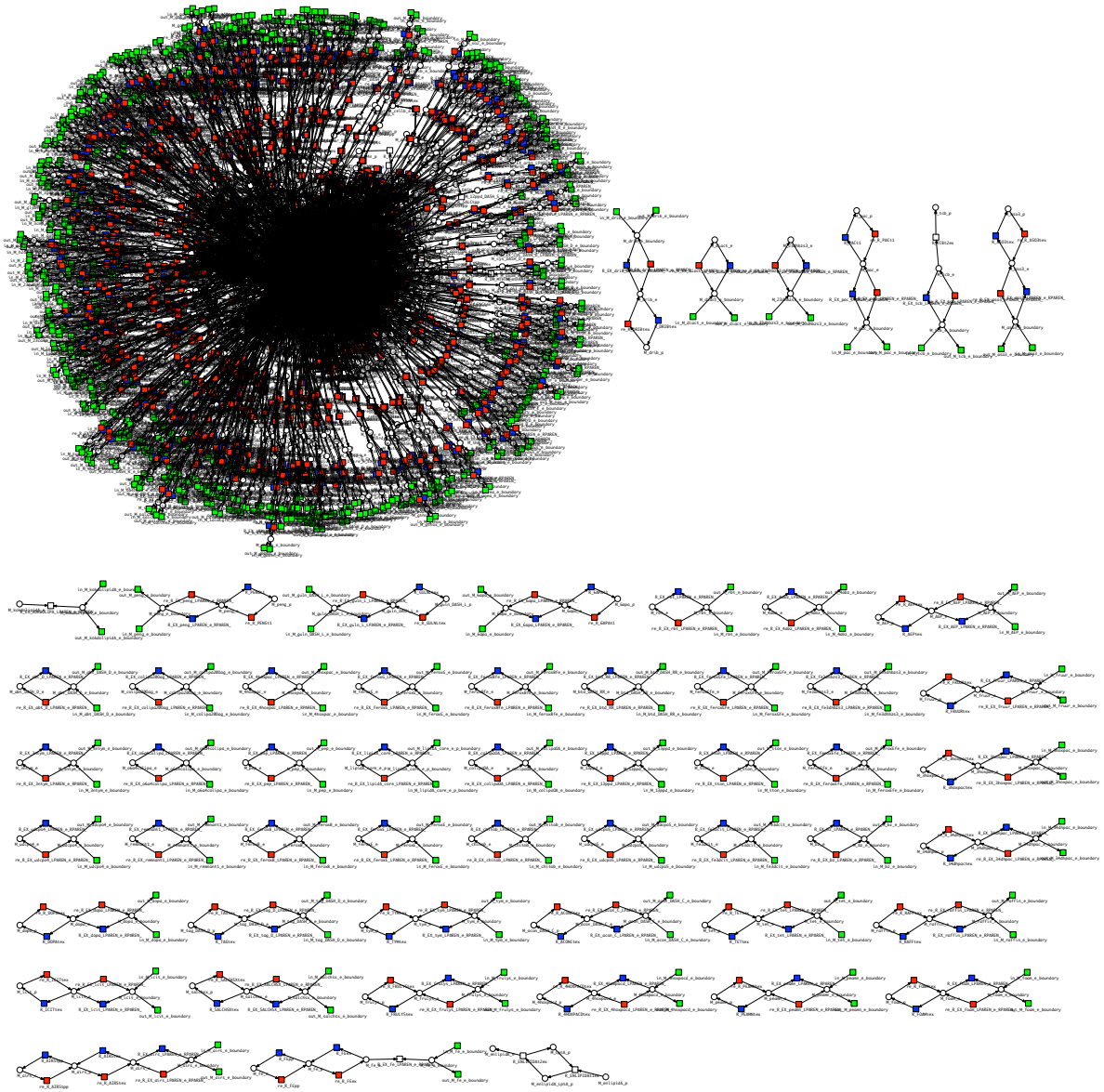
APPROACH 4

[Monk 2013]



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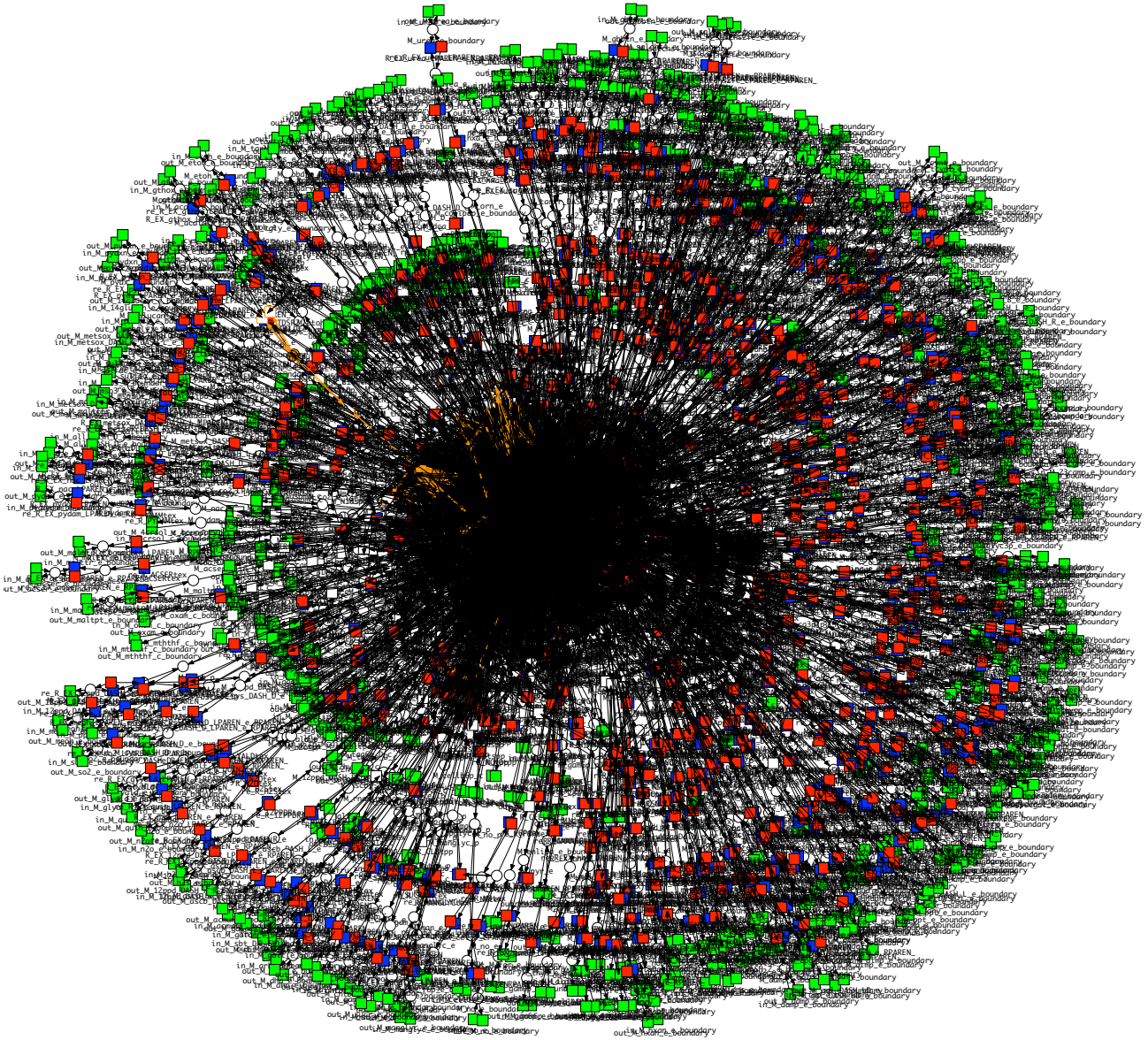

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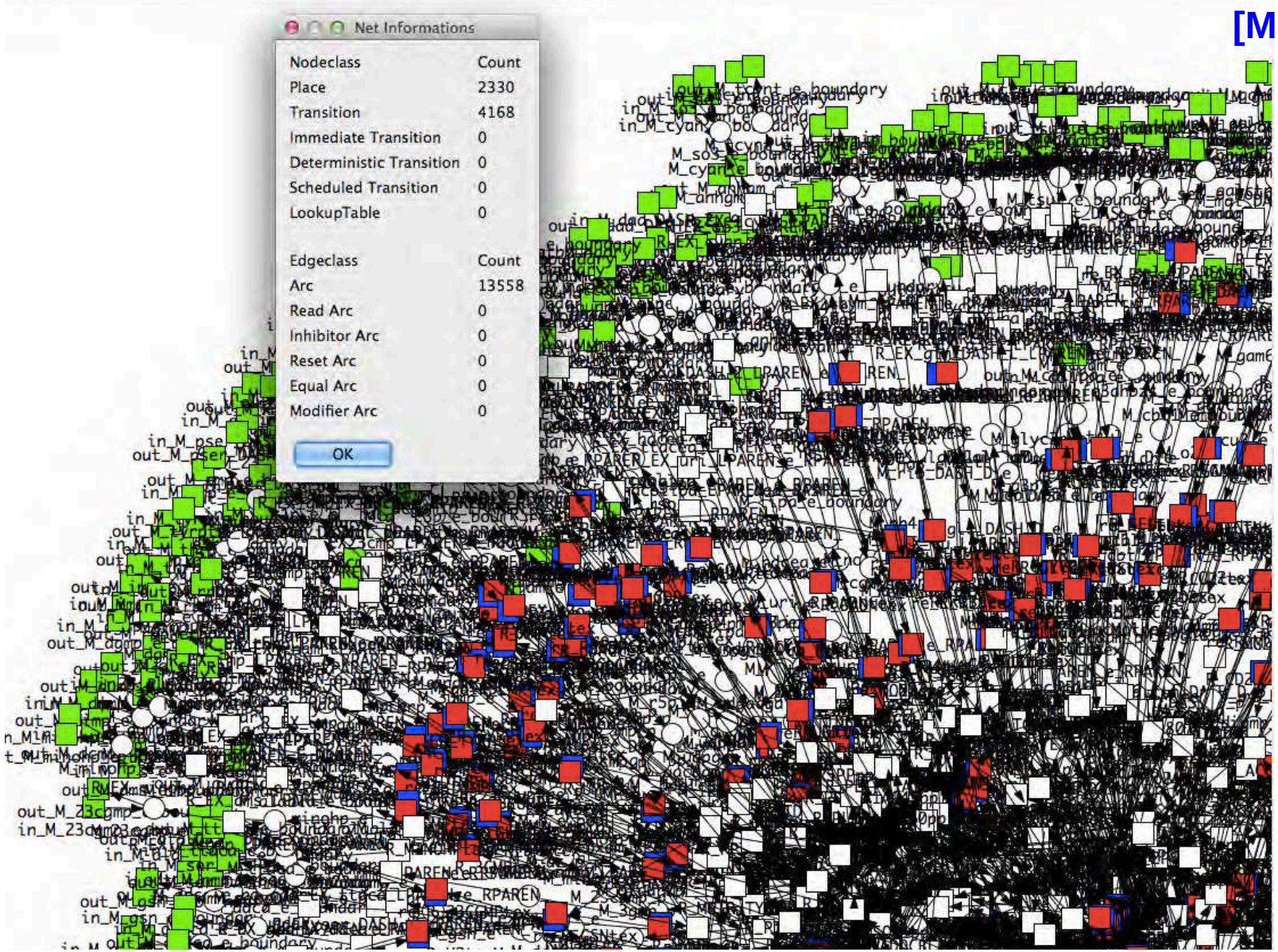
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