FROM PETRI NETS TO PARTIAL DIFFERENTIAL EQUATIONS

- A PETRI NET PERSPECTIVE ON SYSTEMS AND SYNTHETIC BIOLOGY -

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COMPUTER SCIENCE INSTITUTE

OUTLINE

FRAMEWORK

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

-> *our toolbox:*
Snoopy - Marcie - Charlie - Patty - S4

COLOURED PETRI NETS -> PDE

-> *Turing patterns (CPN)*

-> *phase variation (SPN)*

-> *planar cell polarity (hierarchical space)*

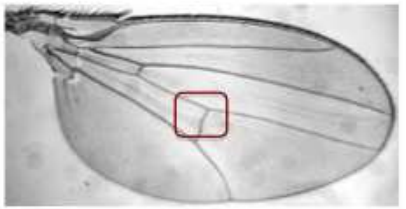
MODELLING BIO PETRI NETS

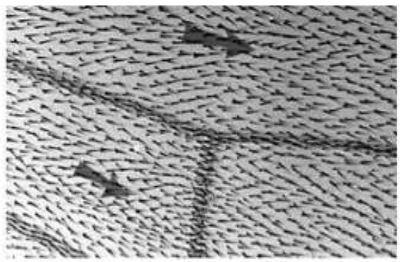
-> *composition from standard components*

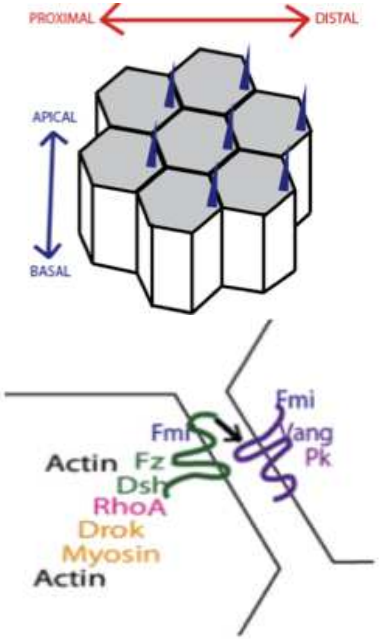
-> *bottom-up (reverse engineering)*

-> *modular modelling*

-> *genome-controlled model generation*







THE PETRI NET FRAMEWORK

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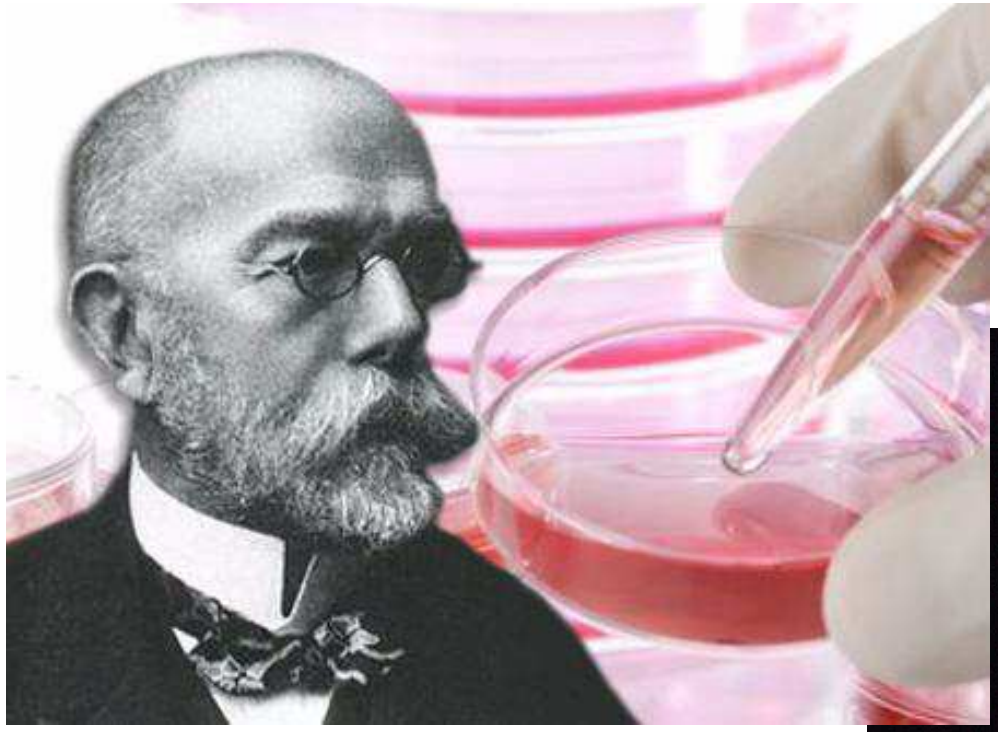
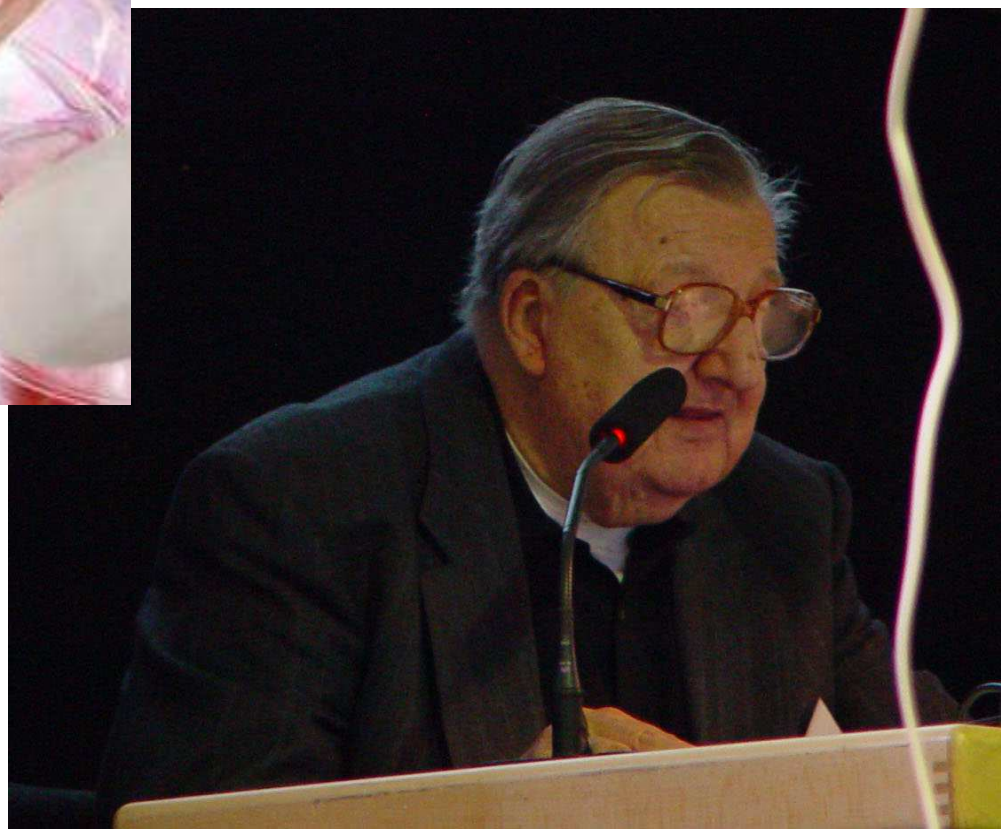
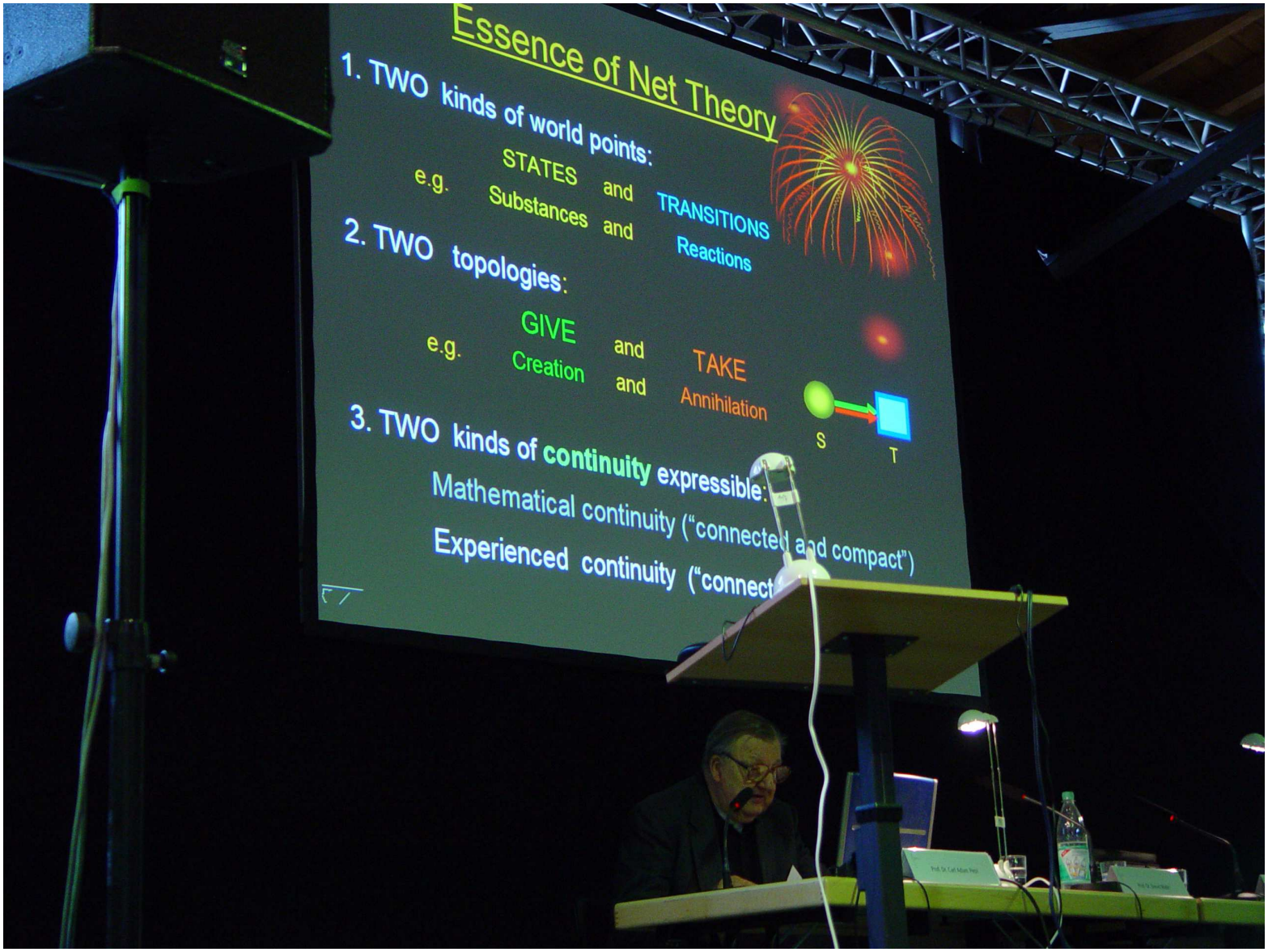


Julius Richard Petri, 1852 - 1921

Carl Adam Petri, 1926 - 2010



NOVEMBER 2006

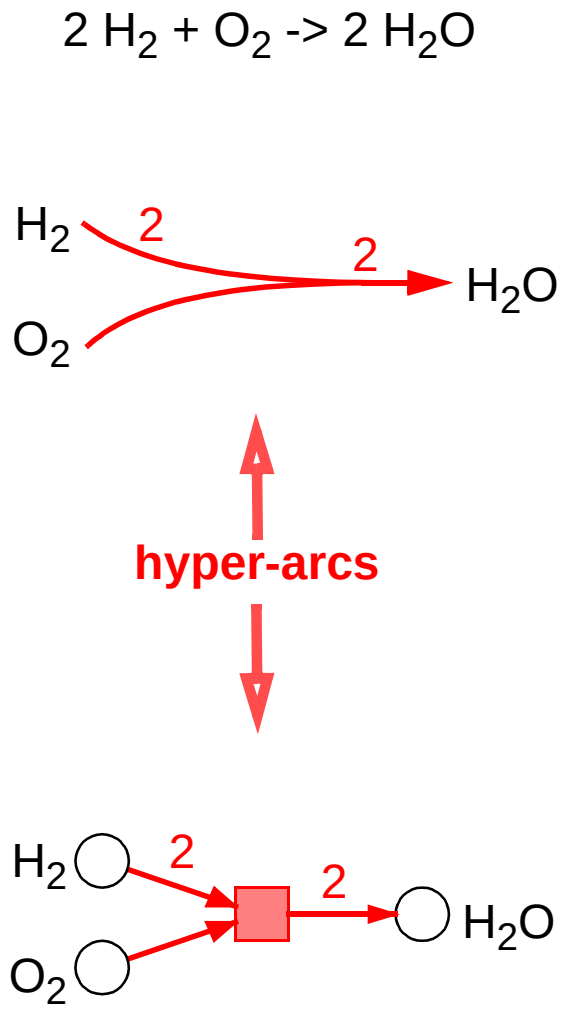

Essence of Net Theory
1. TWO kinds of world points:
STATES and TRANSITIONS
e.g. Substances and Reactions
2. TWO topologies:
GIVE and TAKE
e.g. Creation and Annihilation
S
T
3. TWO kinds of continuity expressible:
Mathematical continuity ("connected and compact")
Experienced continuity ("connect

. . .

ARE NETWORKS OF BIOCHEMICAL REACTIONS

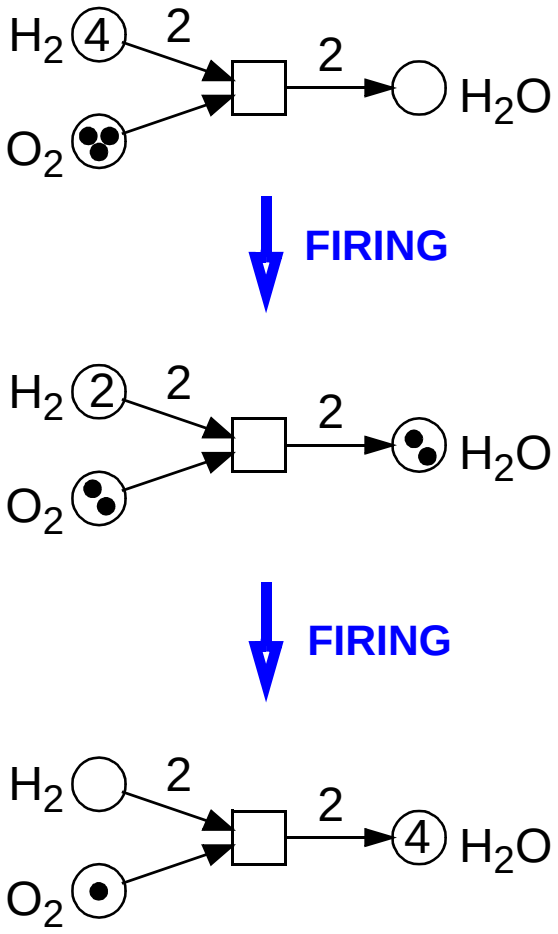
. . .

NATURALLY EXPRESSIBLE AS PETRI NETS



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

input compounds



output compounds

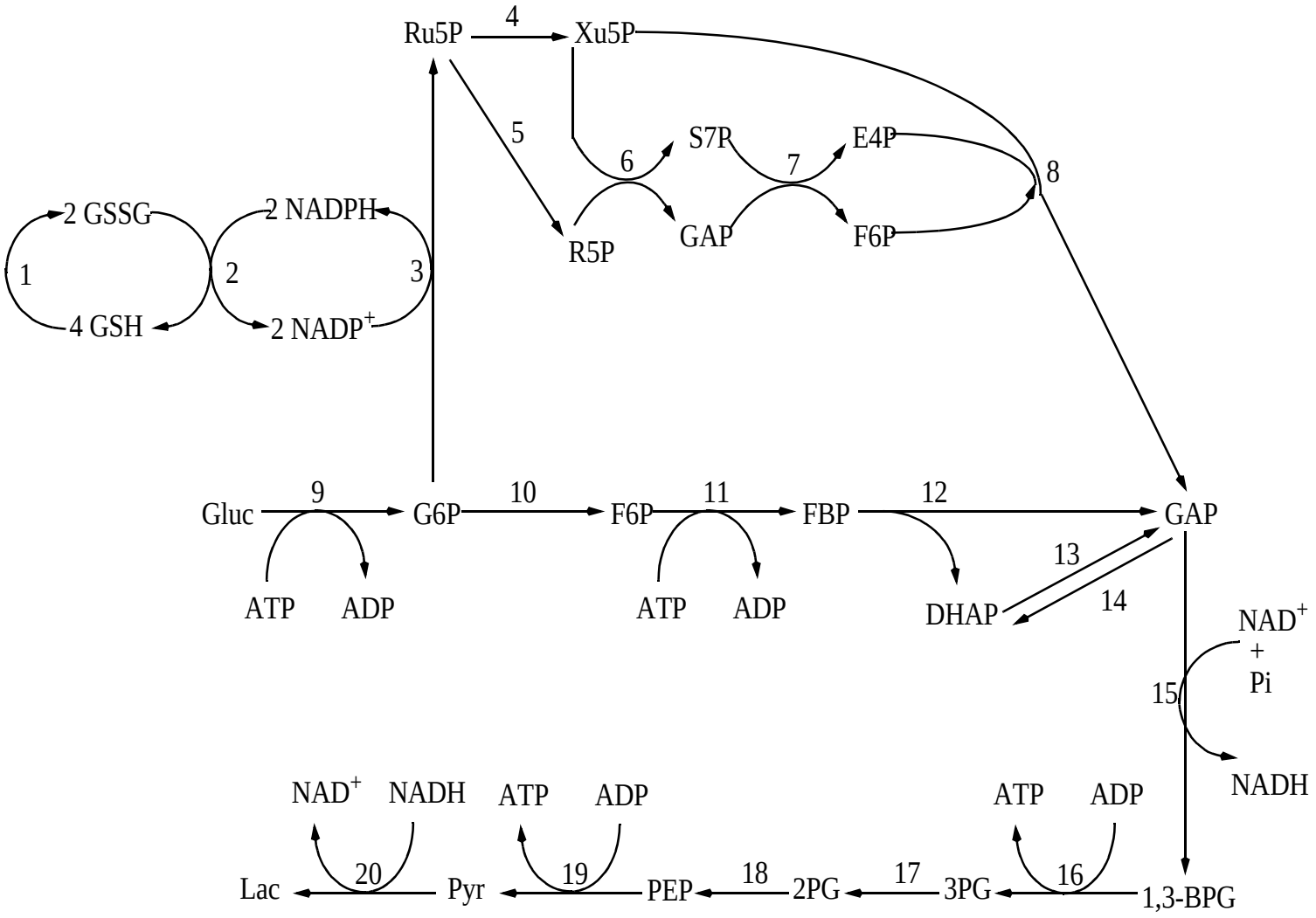
TOKEN GAME

DYNAMIC BEHAVIOUR

(substance/signal flow)

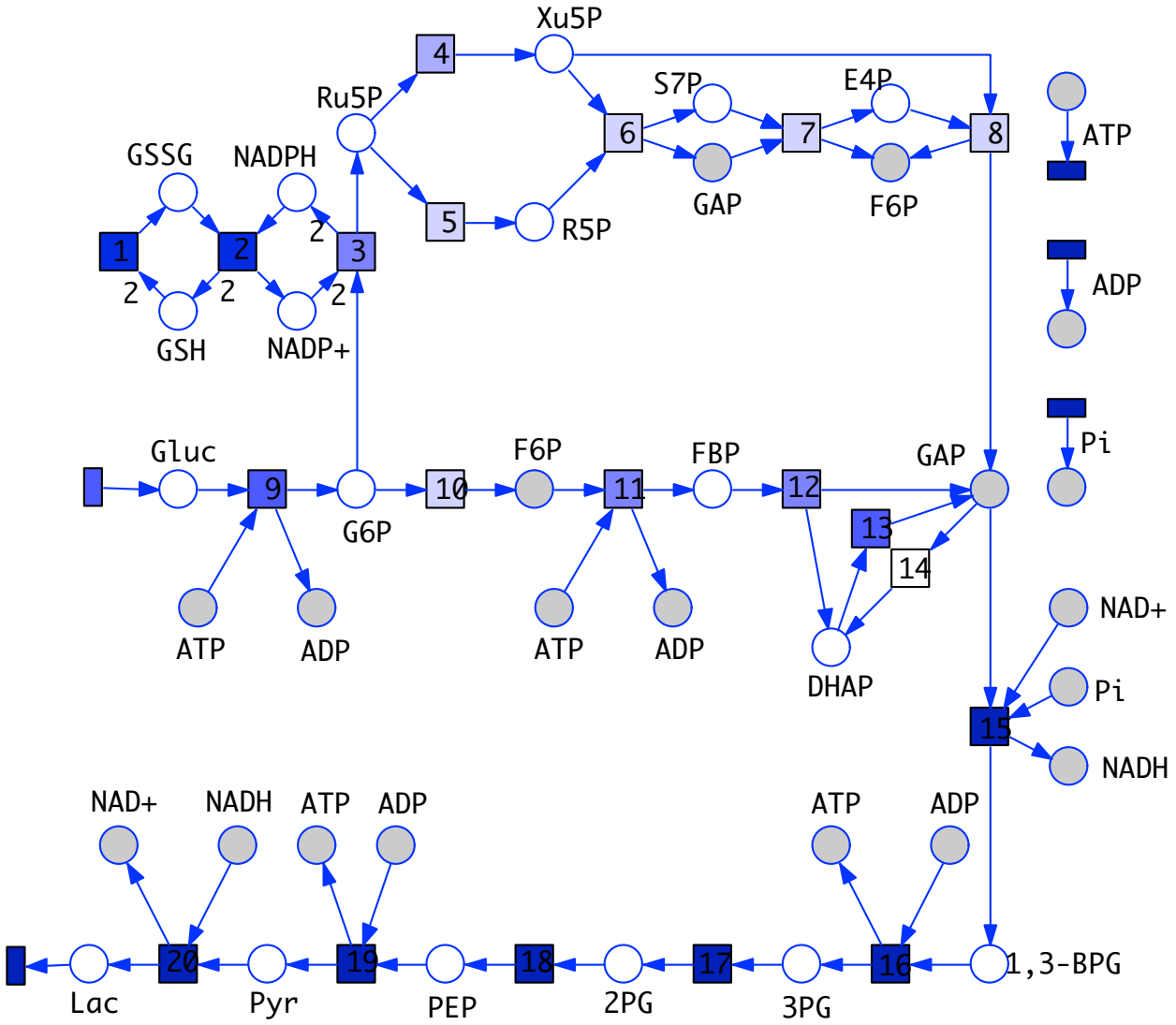
Ex: Glycolysis and Pentose Phosphate Pathway

[Reddy 1993]



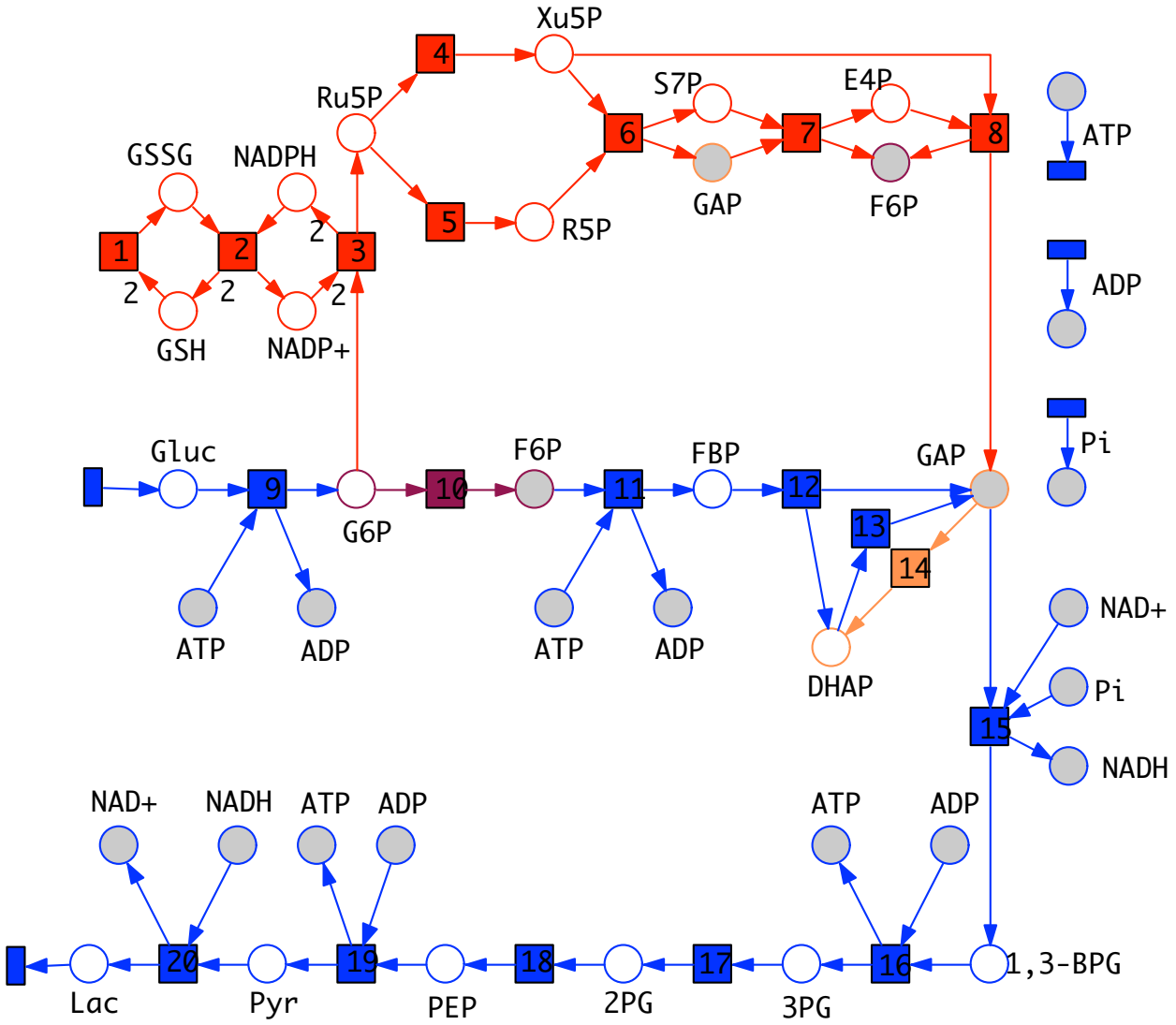
Ex: Glycolysis and Pentose Phosphate Pathway

[Reddy 1993]
[Heiner 1998]

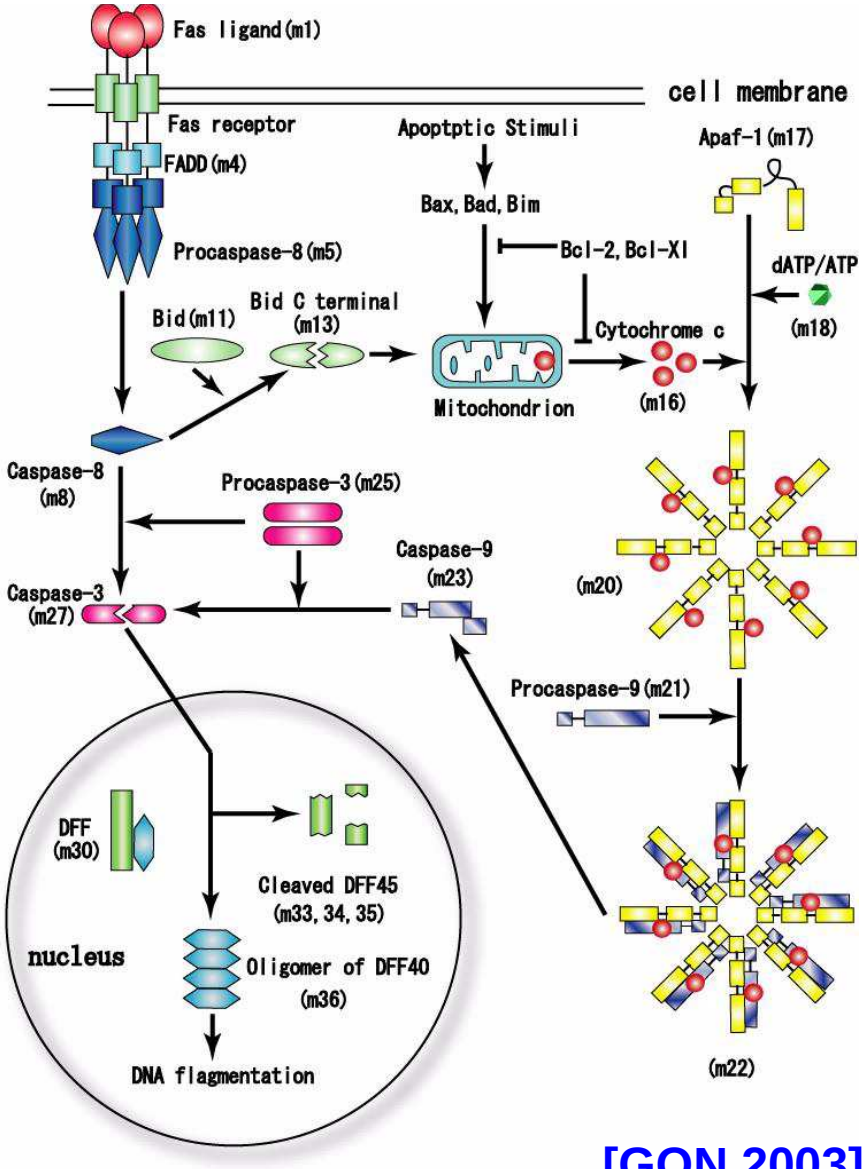


Ex: Glycolysis and Pentose Phosphate Pathway

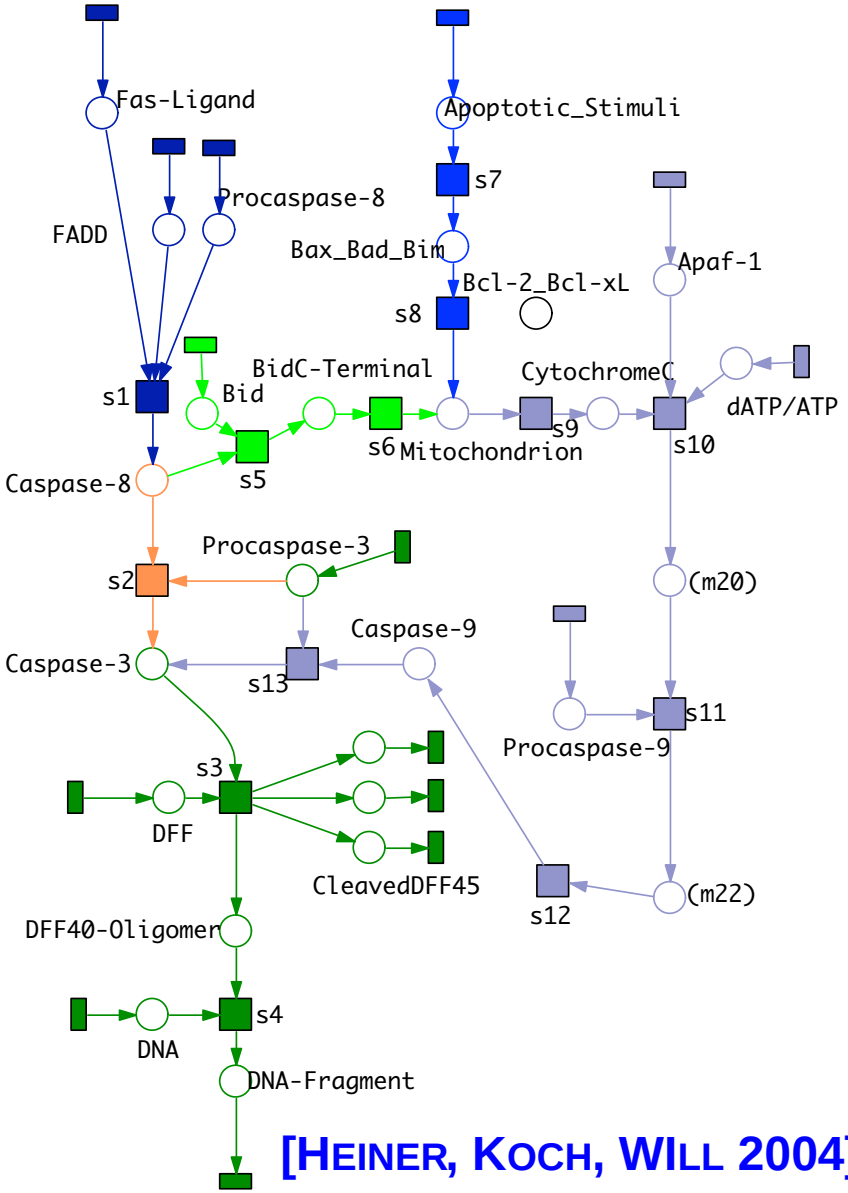
[Reddy 1993]
[Heiner 1998]
[Heiner 2009]



EX: APOPTOSIS IN MAMMALIAN CELLS



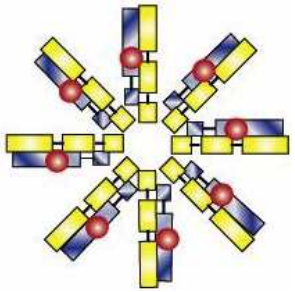
[GON 2003]

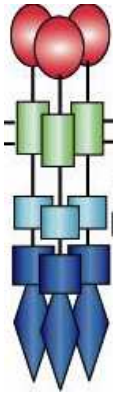


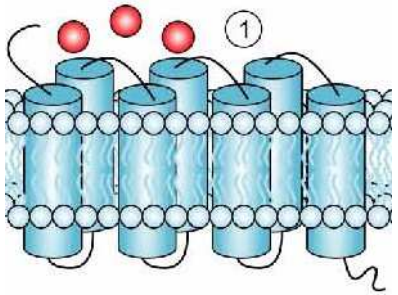
[HEINER, KOCH, WILL 2004]

PLACES, TRANSITIONS - SOME BIO INTERPRETATIONS

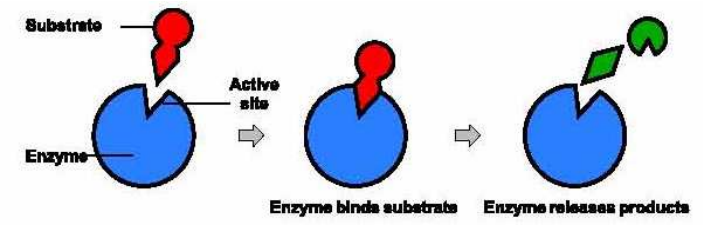
- **places -> model variables**
  - -> *(bio-) chemical compounds*
  - -> *proteins*
  - -> *protein conformations*
  - -> *complexes*
  - -> *genes, . . . , etc.*
  - *. . . in different locations*







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



- **place invariants / mojeties / mass conservation**
  -> *mass conserving net components*

- **transiton invariants /elementary modes / extreme pathways**
  -> *state-reproducing net components*
  -> *relative firing rates in the steady state*

- **structural criteria to decide**
  -> *boundedness: finite state space*
  -> *liveness: each reaction is forever able to contribute to the system behaviour*
  -> *reversibility: all system states are always reachable again*
  e.g., Siphon / Trap Property (STP)

- **property-preserving reduction of the net structure**

- Heiner, Gilbert: How Might Petri Nets Enhance Your Systems Biology Toolkit; Proc. PETRI NETS; LNCS 6709, 2011.

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

ELSEVIER

Journal of Biomedical Informatics

Available online 10 August 2016

In Press, Accepted Manuscript — Note to users

A Model-driven methodology for exploring complex disease comorbidities applied to autism spectrum disorder and inflammatory bowel disease

Judith Somekh[a, b], Mor Peleg[b], Alal Eran[a, g, i], Itay Koren[c], Ariel Feiglin[a], Alik Demishtein[d], Ruth Shiloh[e], Monika Heiner[f], Sek Won Kong[g], Zvulun Elazar[d], Isaac Kohane[a, g, h]

Show more

-> model-based prediction for comorbid tissues

. . . AND THEN THERE WAS TIME

Canary Wharf, 20/08/2011

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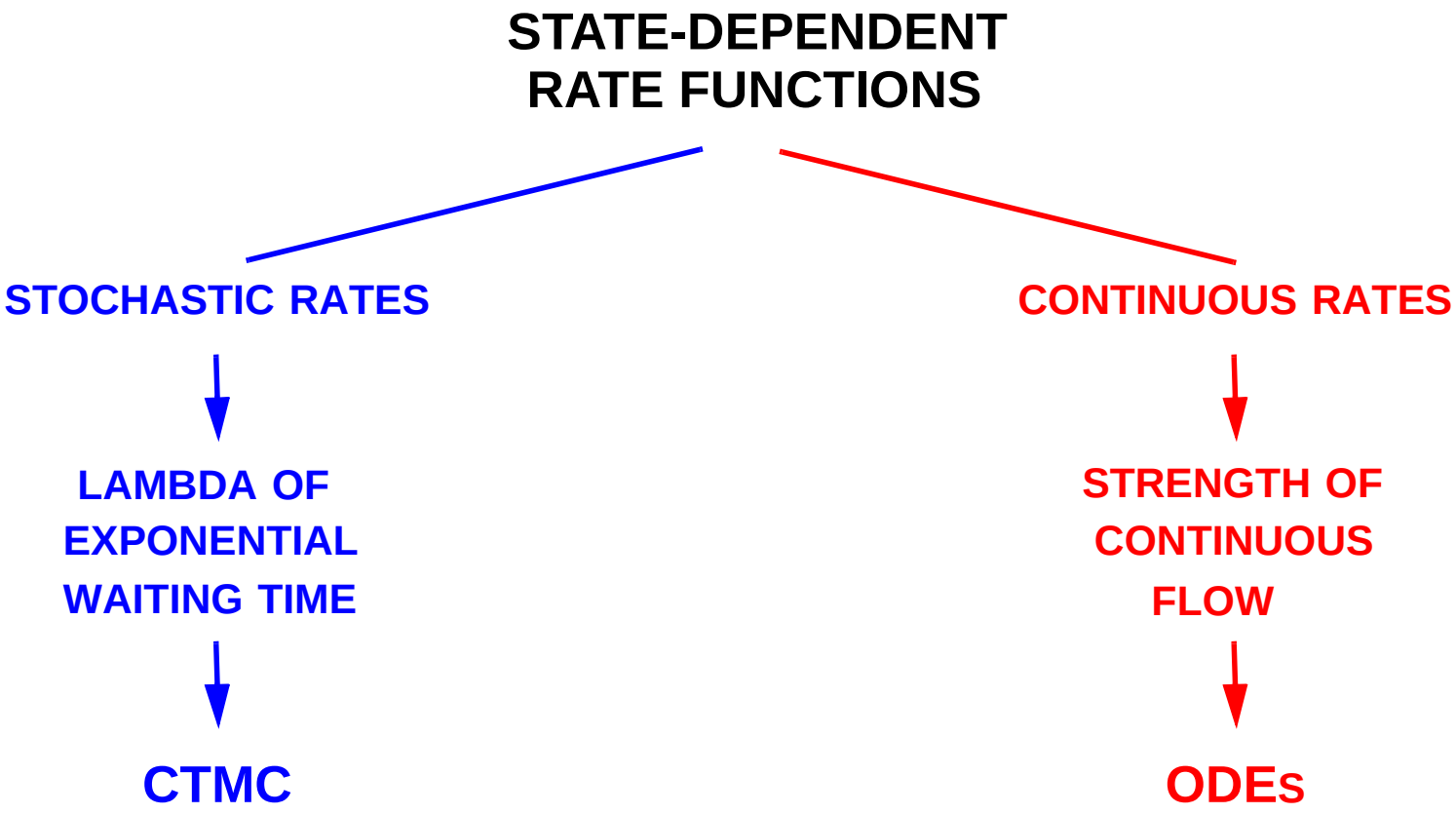
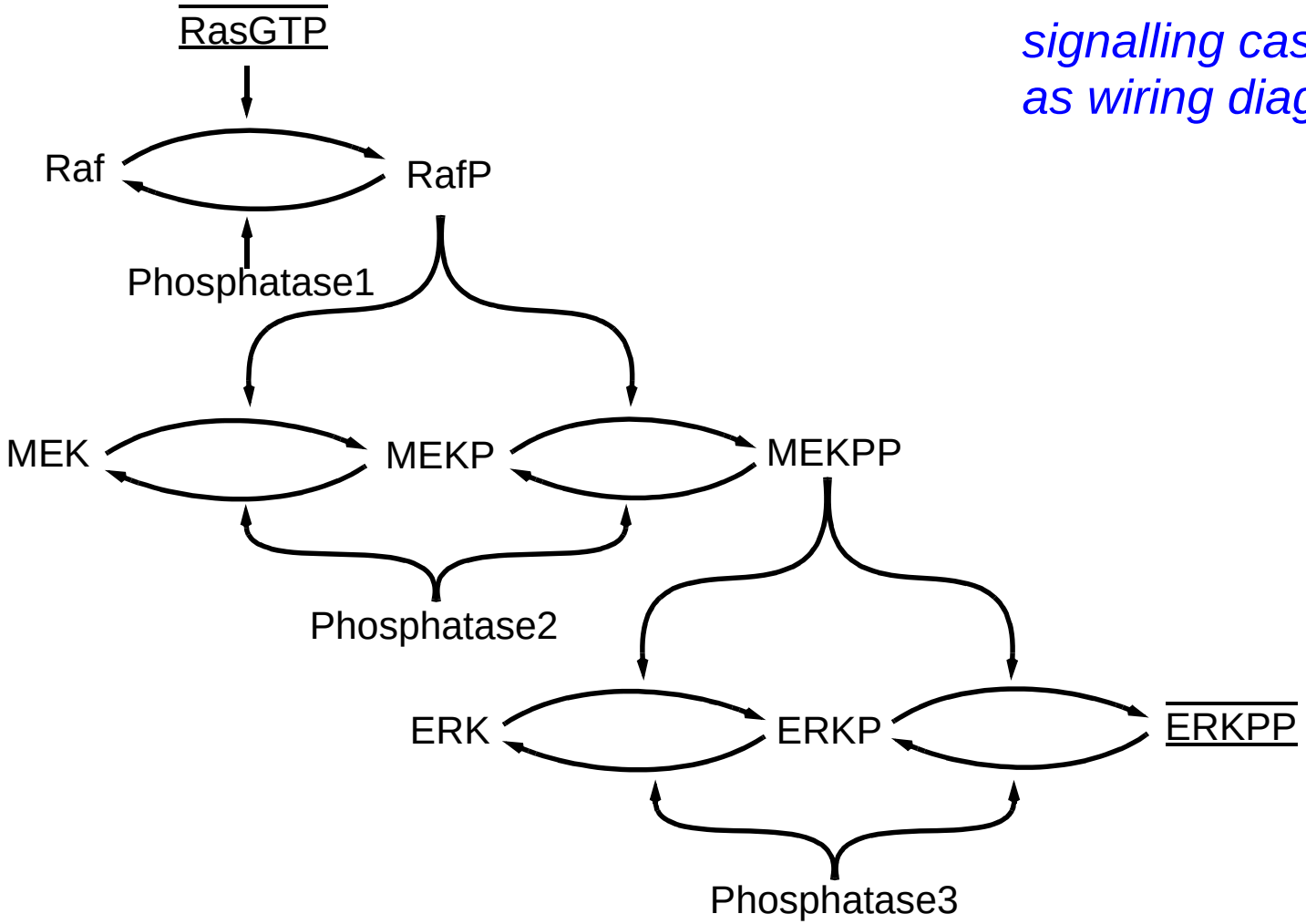
ADDING TIME TO TRANSITIONS / REACTIONS



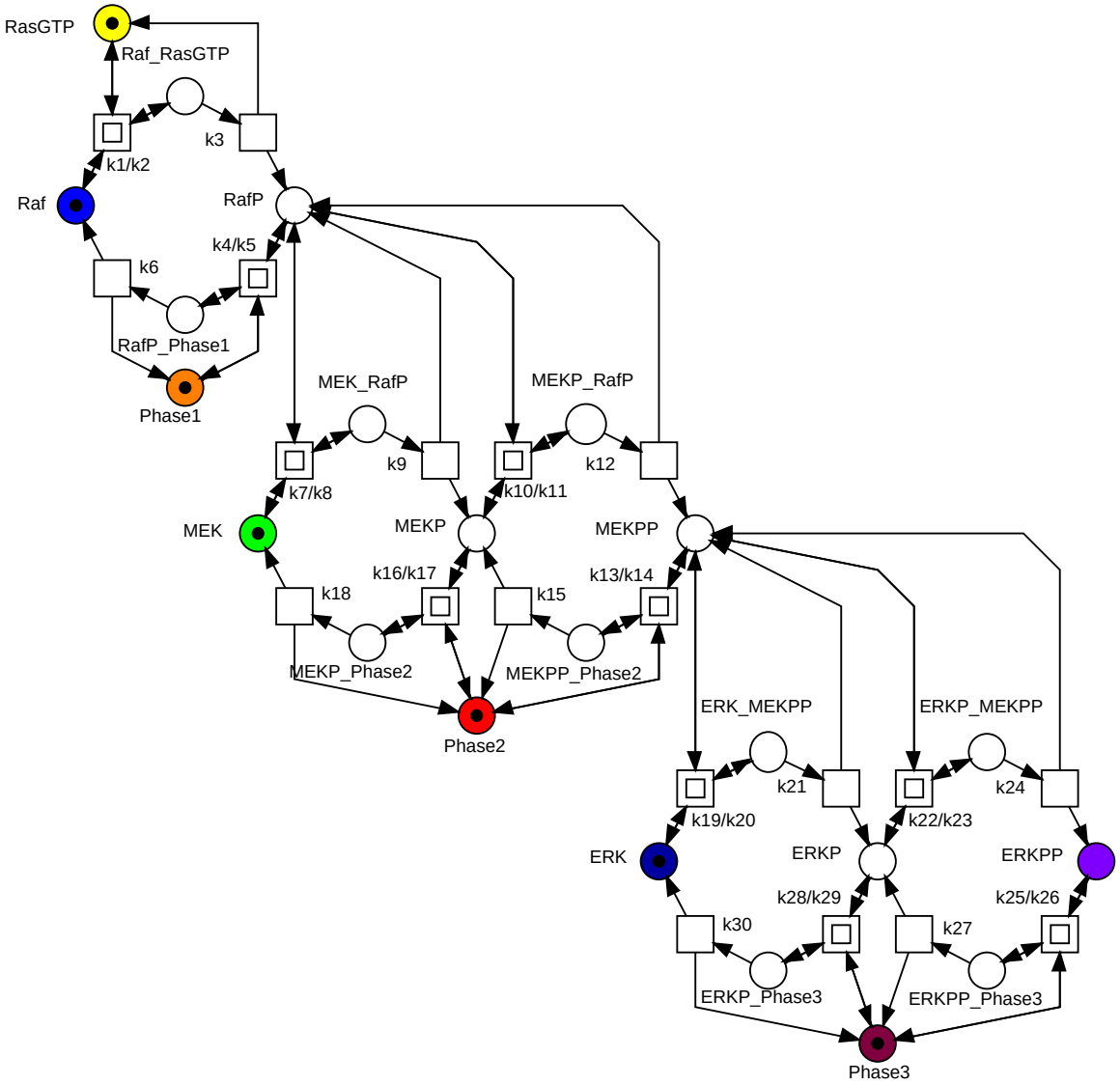
-> supported by, e.g., COPASI, Dizzy, ..., Snoopy

EX: SIGNALLING CASCADE



signalling cascade as wiring diagram

EX: SIGNALLING CASCADE

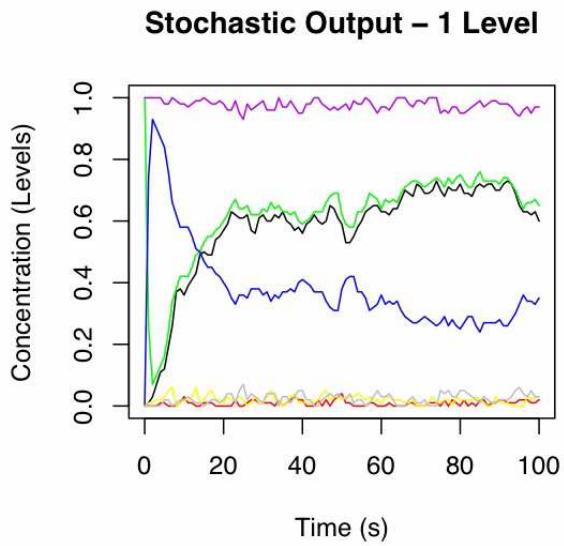


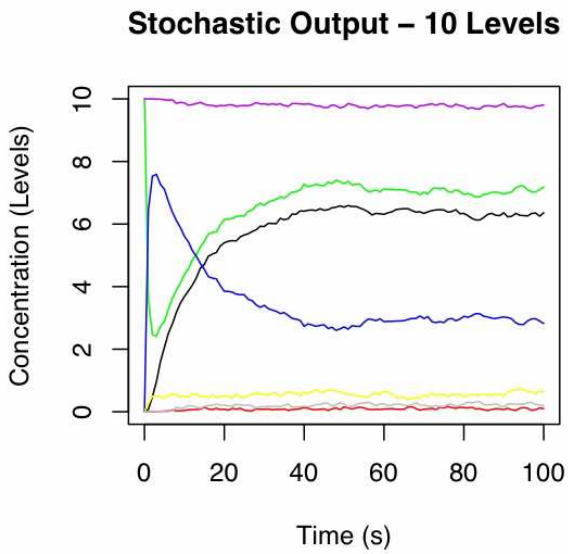
signalling cascade as Petri net

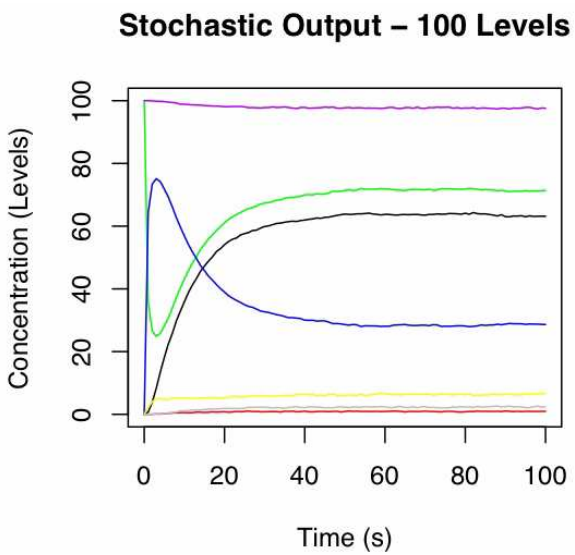
[GILBERT, HEINER, LEHRACK 2007]

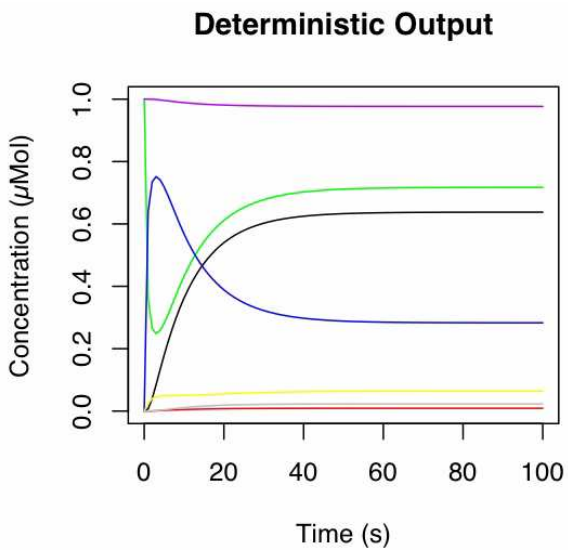
[HEINER, GILBERT, DONALDSON 2008]

EX: SIGNALLING CASCADE, SIMULATIONS









[GILBERT, HEINER, LEHRACK 2007]

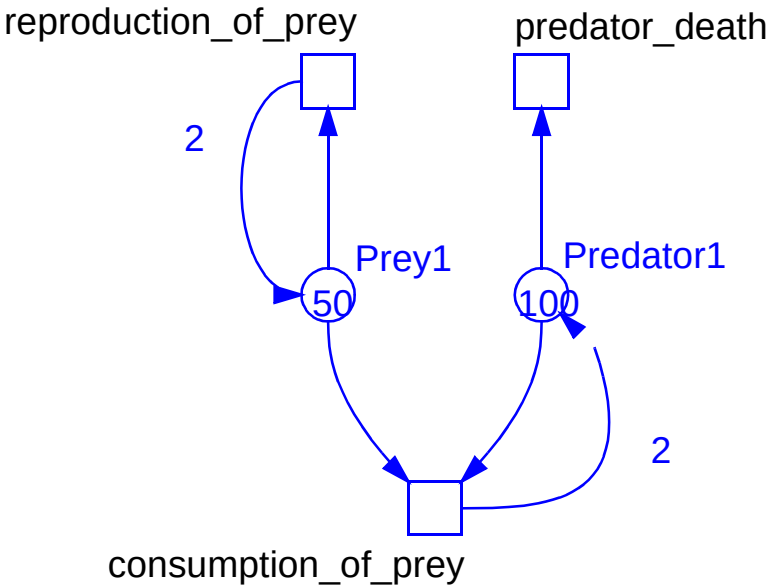
[HEINER, GILBERT, DONALDSON 2008]

. . . AND THEN THERE WAS COLOUR

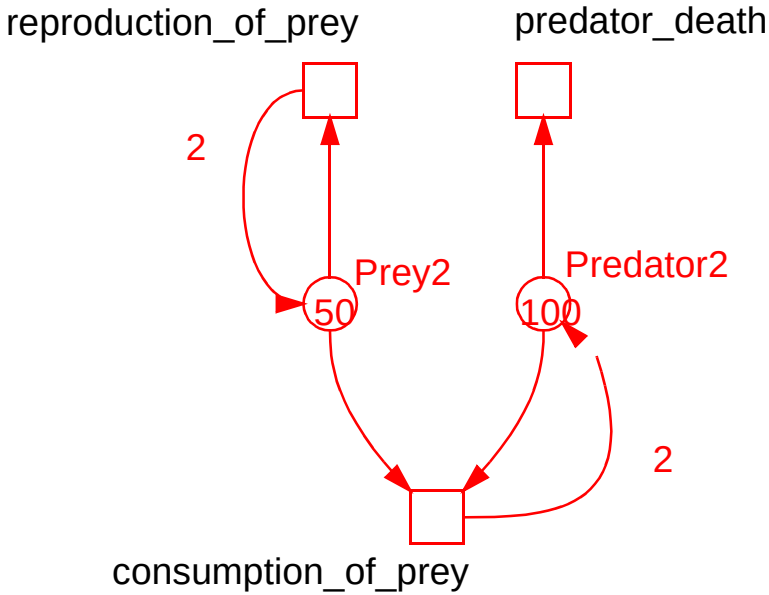
Kew Gardens, 24/04/2011

EX: PREY - PREDATOR

sub-system1



sub-system2



EX: PREY - PREDATOR

- **definitions**

  colourset *CS = 1-2;*

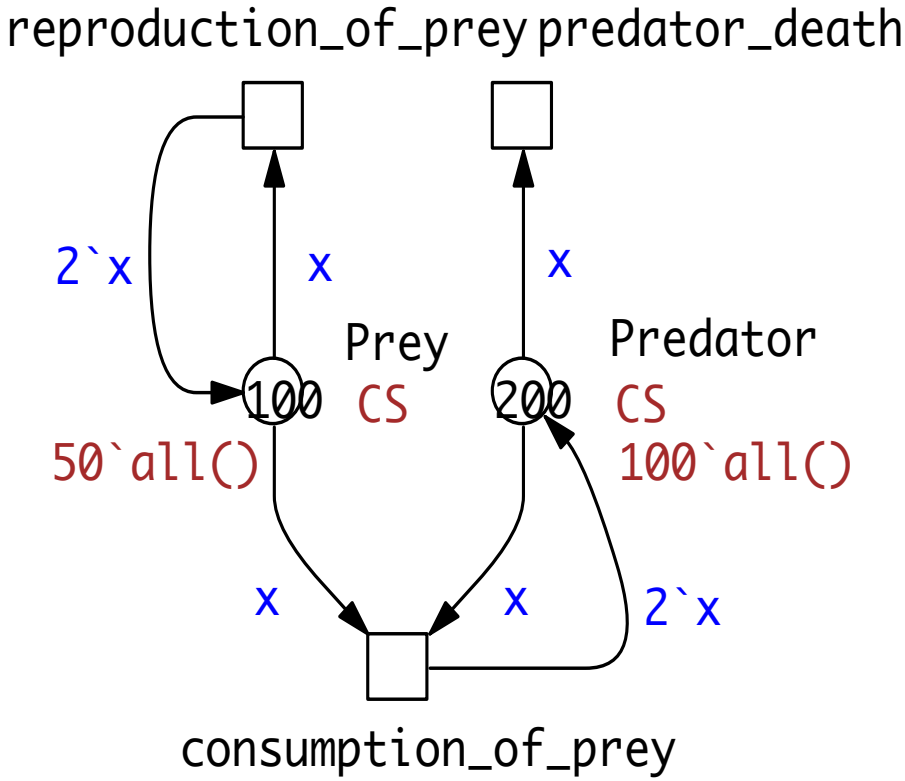
  var *x : CS;*

- **better:**

  const *SIZE = 2;*

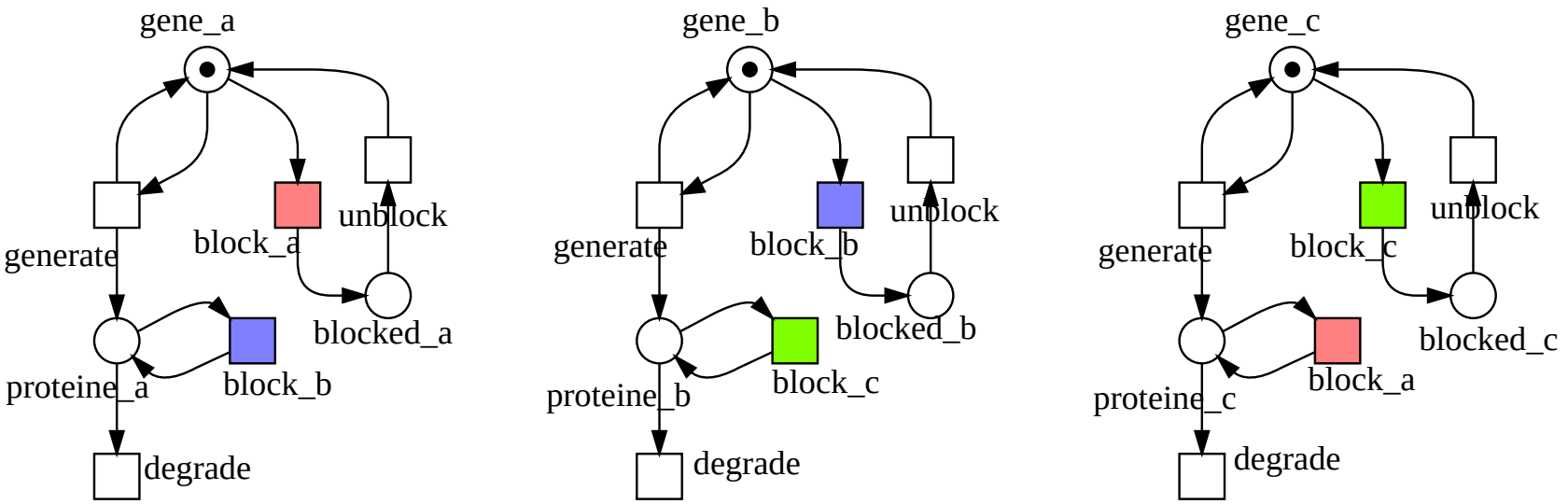
  colourset *CS = 1-SIZE;*

  var *x : CS;*



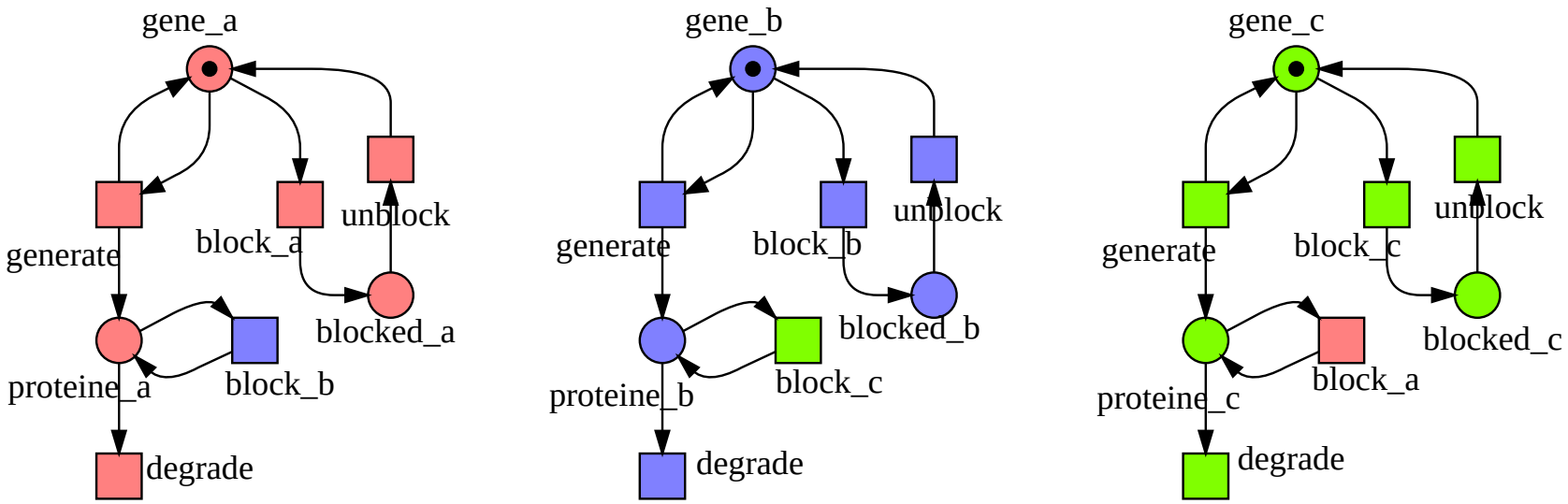
- **changing SIZE adapts the model to various scenarious**

EX: REPRESSILATOR



Blossey, Cardelli, Phillips:
Compositionality, stochasticity and cooperativity in dynamic models of gene regulation;
HFSP Journal 2008.

EX: REPRESSILATOR



Blossey, Cardelli, Phillips:
Compositionality, stochasticity and cooperativity in dynamic models of gene regulation;
HFSP Journal 2008.

EX: REPRESSILATOR

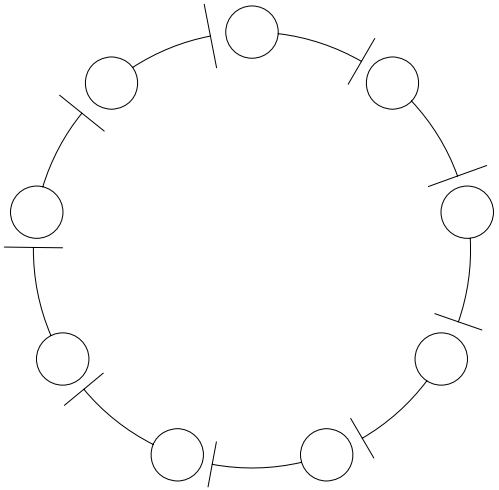
- **definitions**

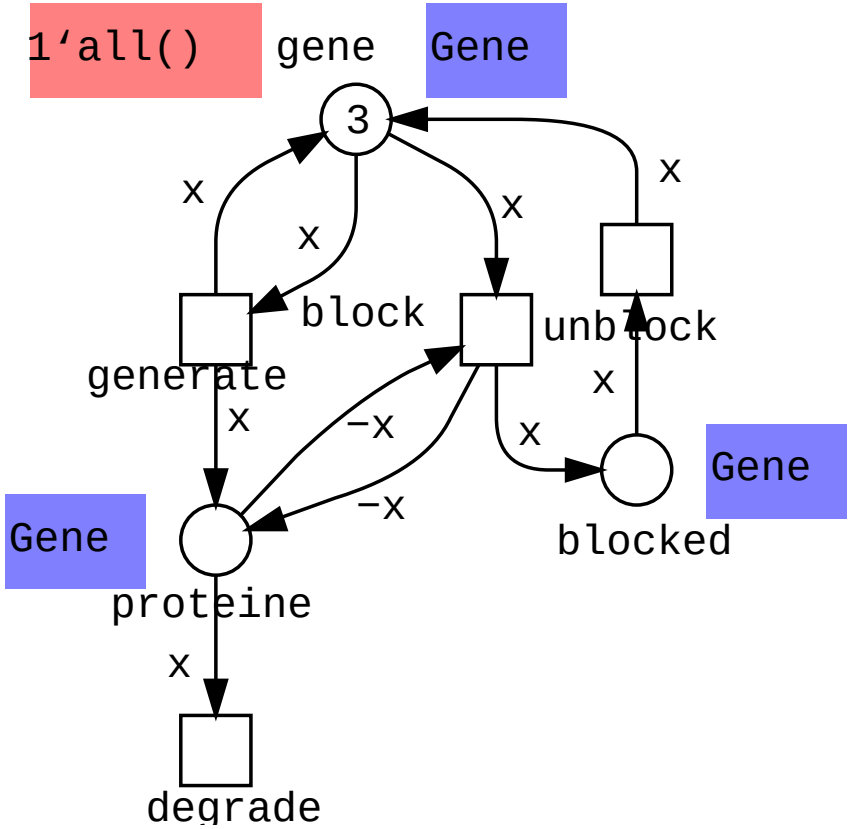
  colorset *Gene = enum a-c;*

  var *x : Gene;*

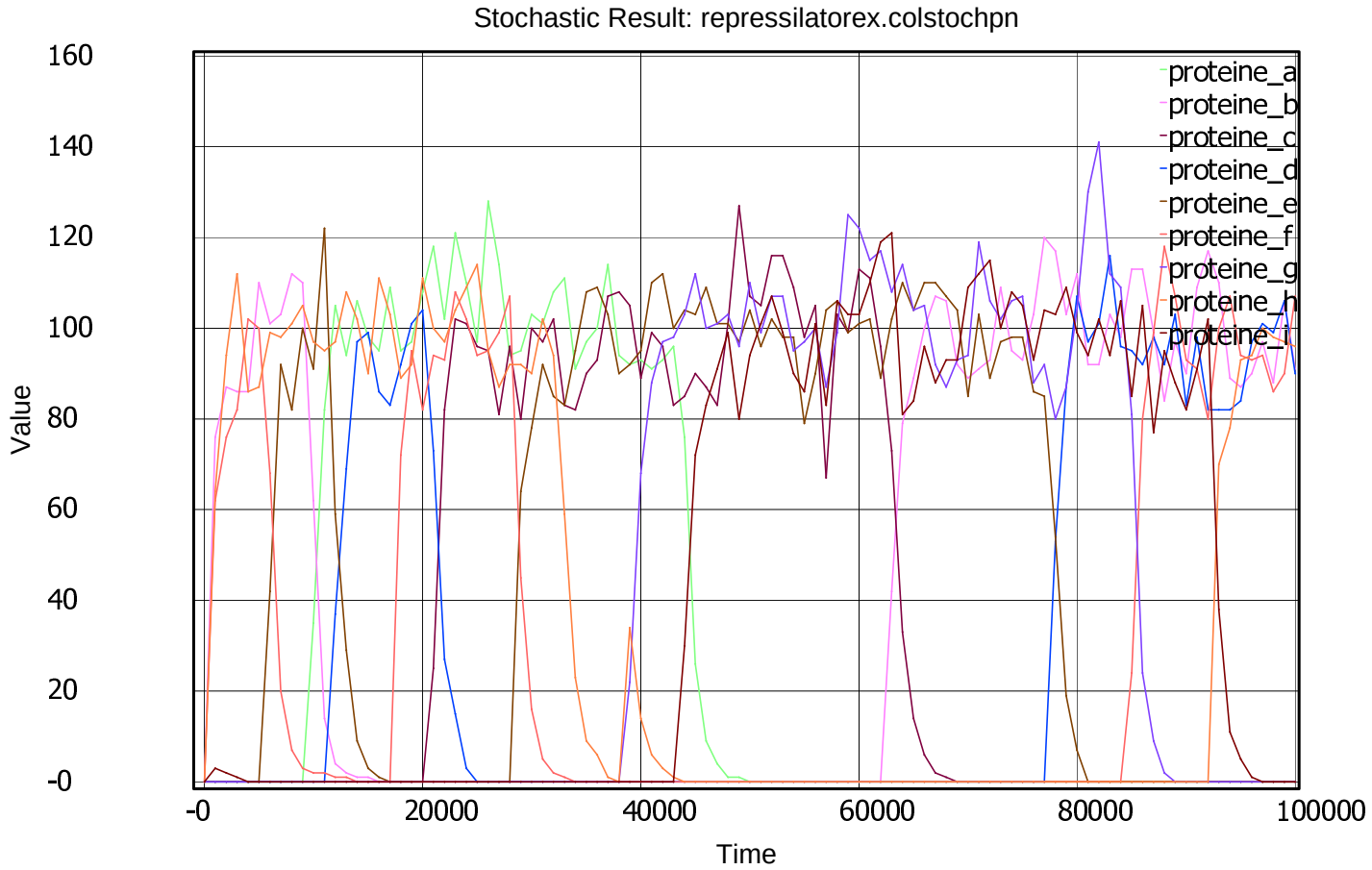
- **model scaling**

  colorset *Gene = enum a-i;*





EX: REPRESSILATOR, STOCHASTIC SIMULATION



COLOURING SPACE

.

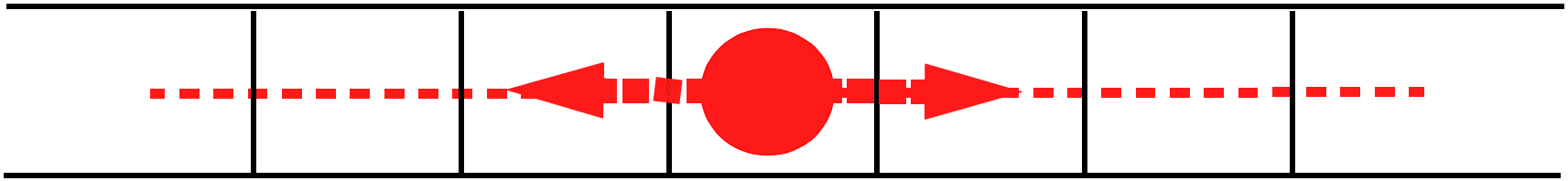
EXAMPLE 1:

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



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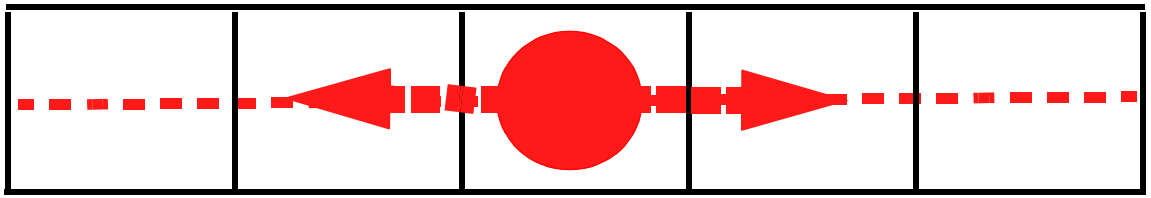

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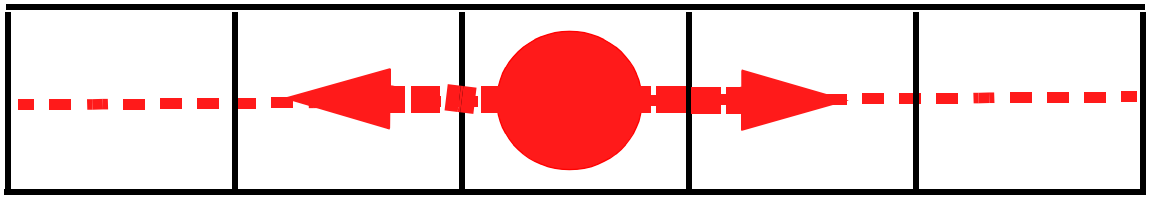
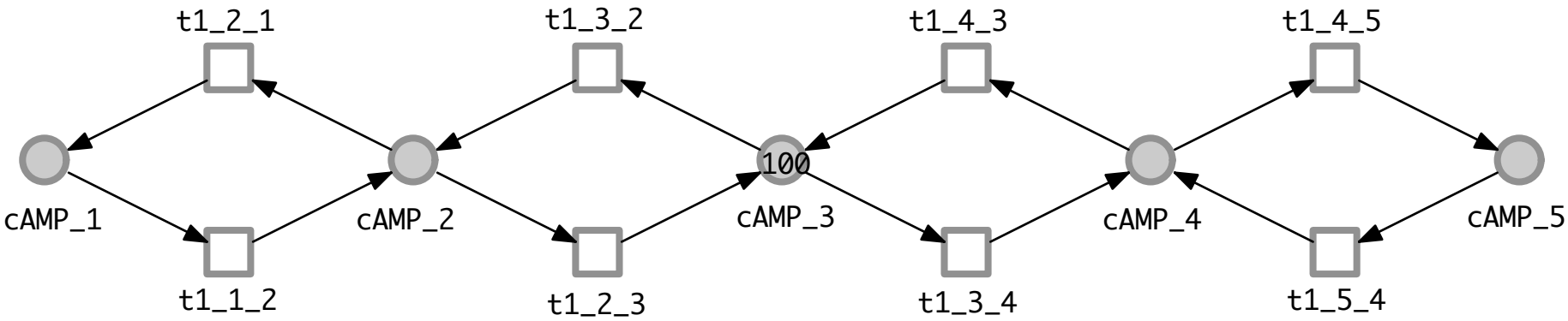


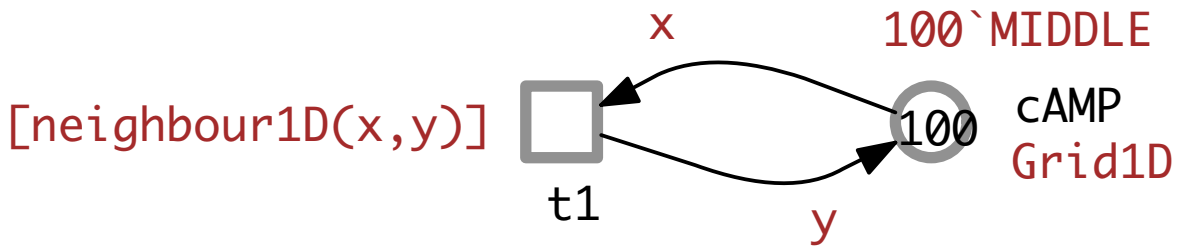


EX1: DIFFUSION - 1D

- **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);
```

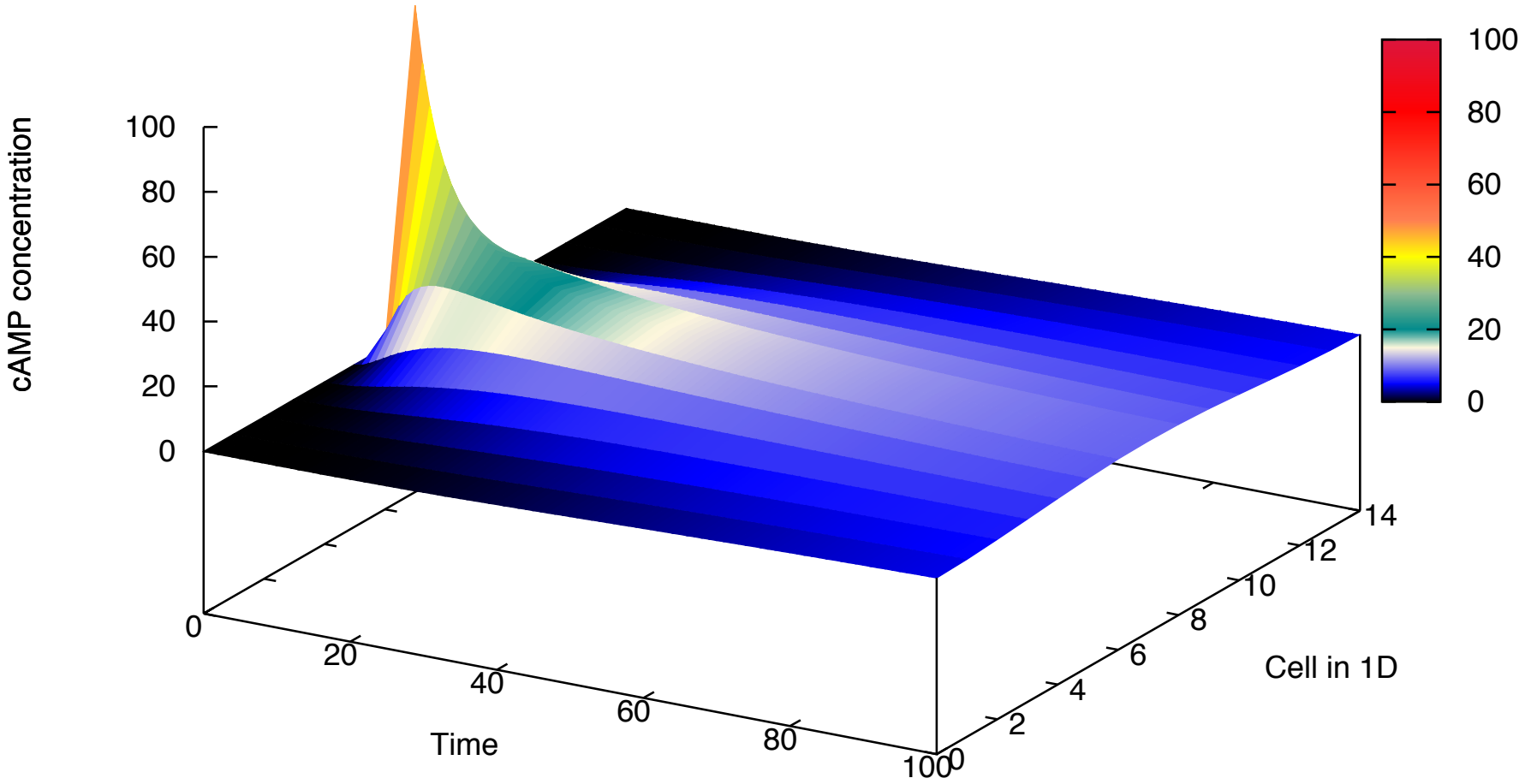


- **movement = changing colour**

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

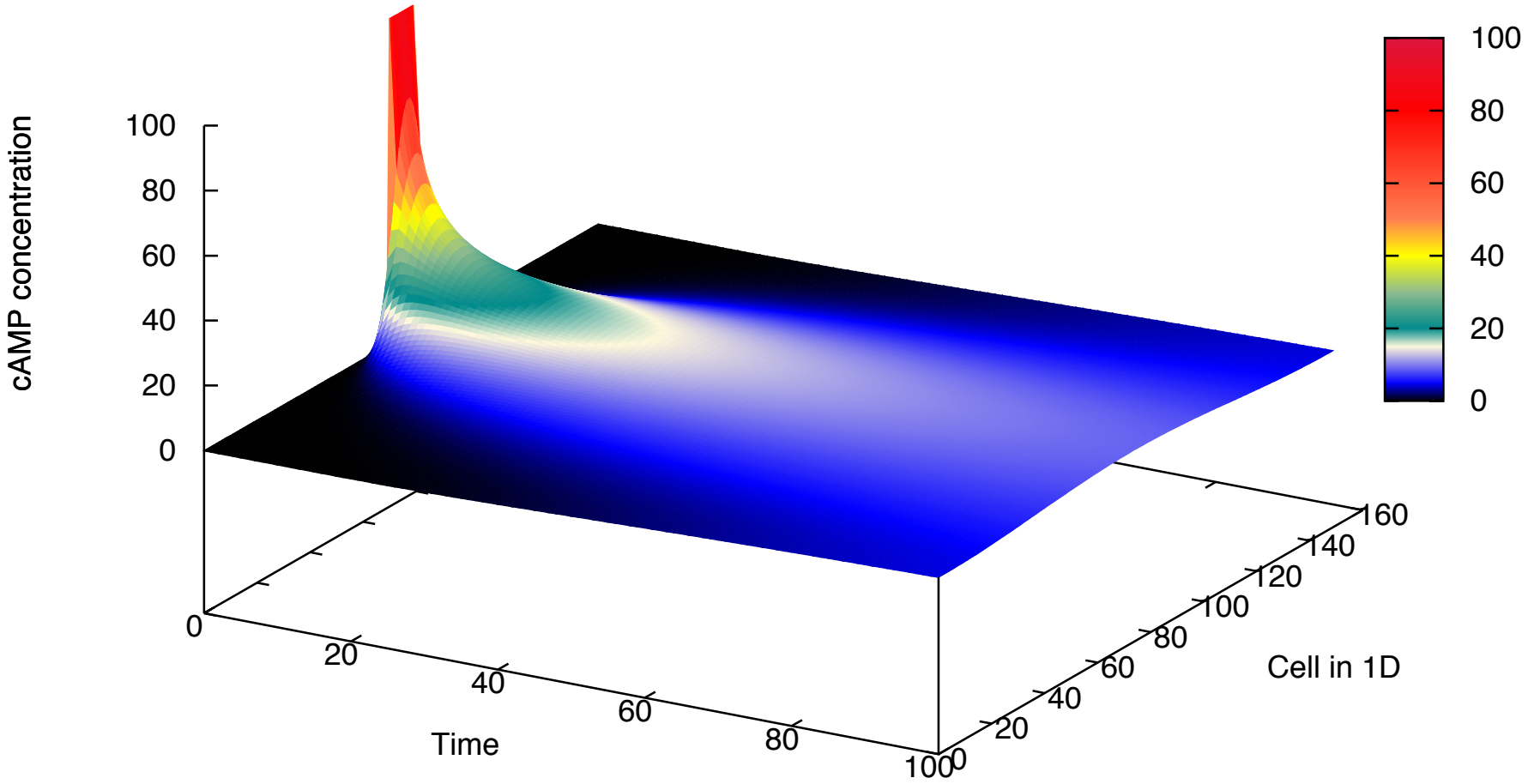
with c_i := cAMP_i

EX1: DIFFUSION - 1D



15 GRID POSITIONS

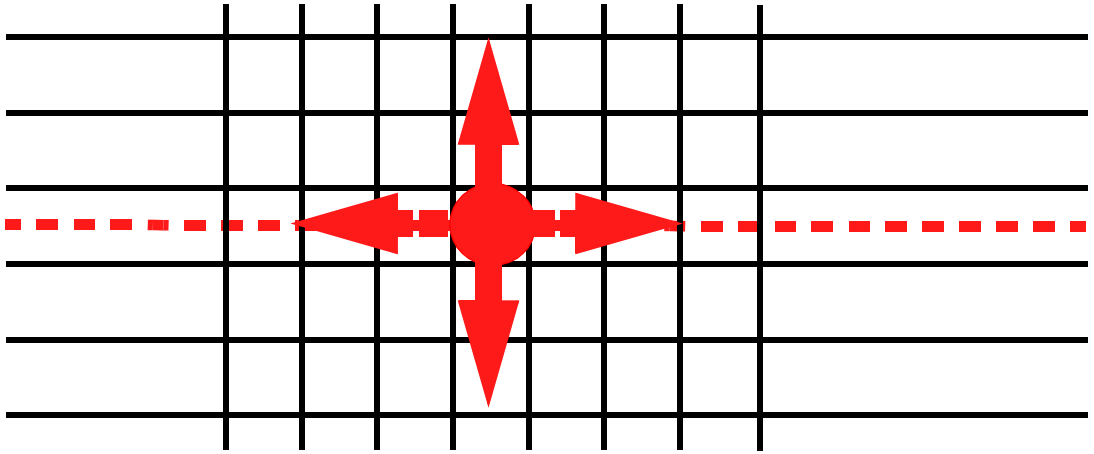
EX1: DIFFUSION - 1D



150 GRID POSITIONS, SCALING OF INITIAL MARKING AND RATES

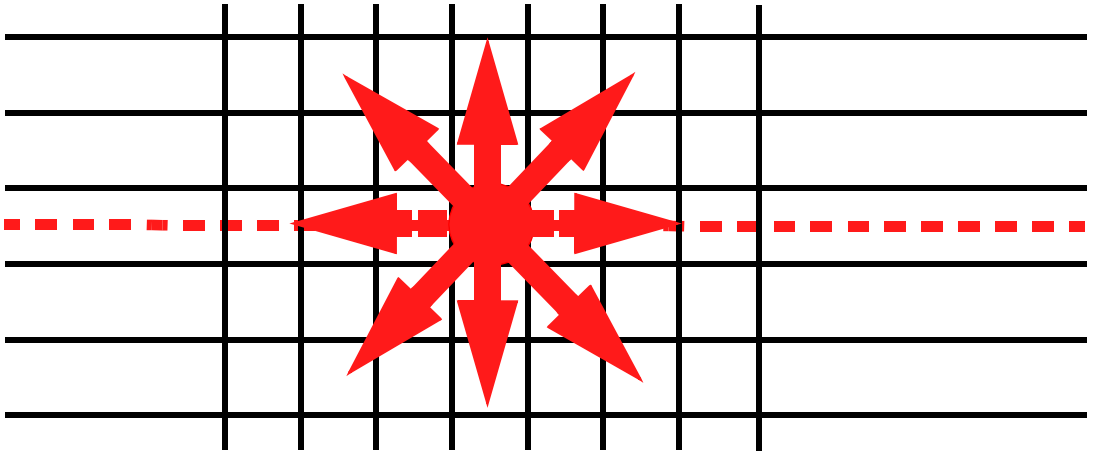
EX1: DIFFUSION - 2D

❑ SCHEME

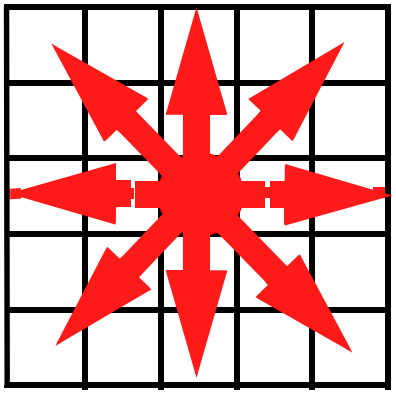


EX1: DIFFUSION - 2D

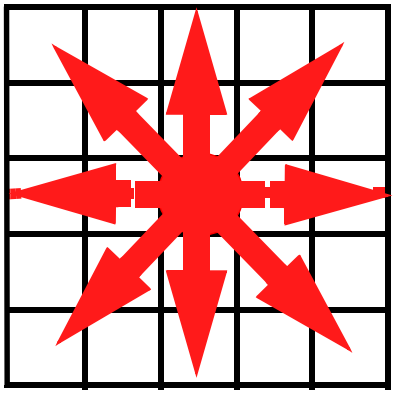
SCHEME



SCHEME



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;
```

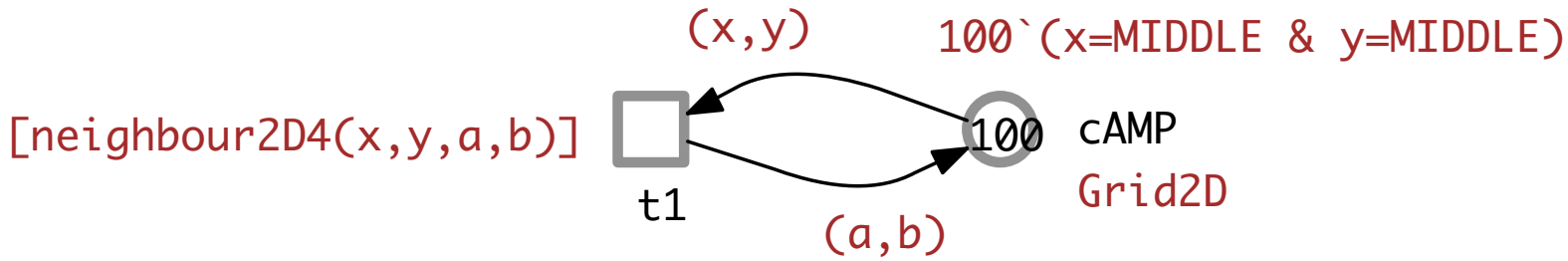
four neighbours

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

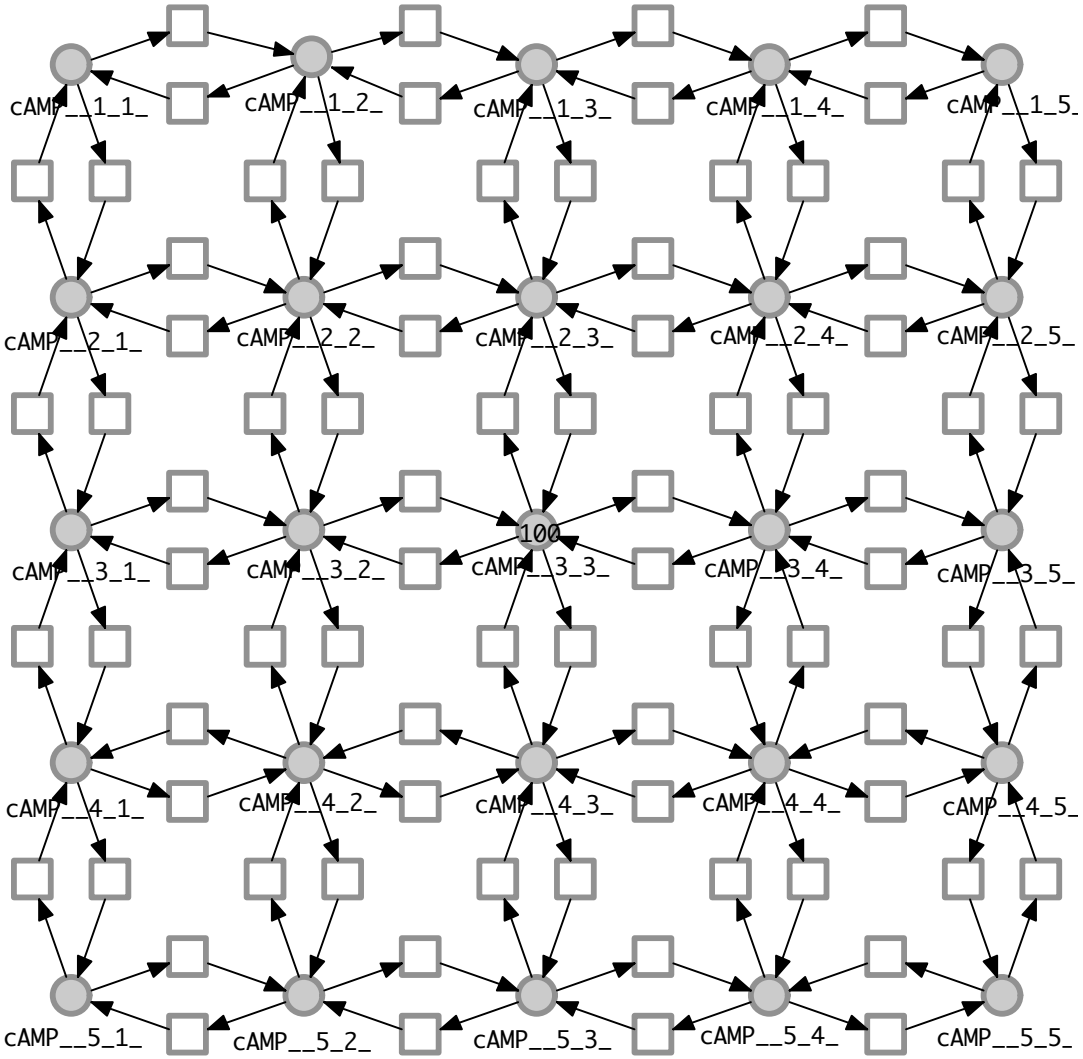
// (a,b) is one of the up to four neighbours of (x,y)

(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**

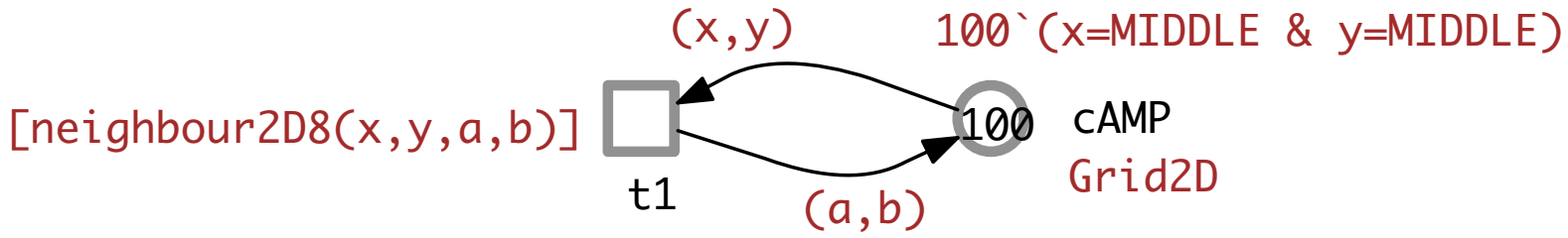
function *neighbour2D8 (CD1 x, CD2 y, CD1 a, CD2 b)* ***bool****:*

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

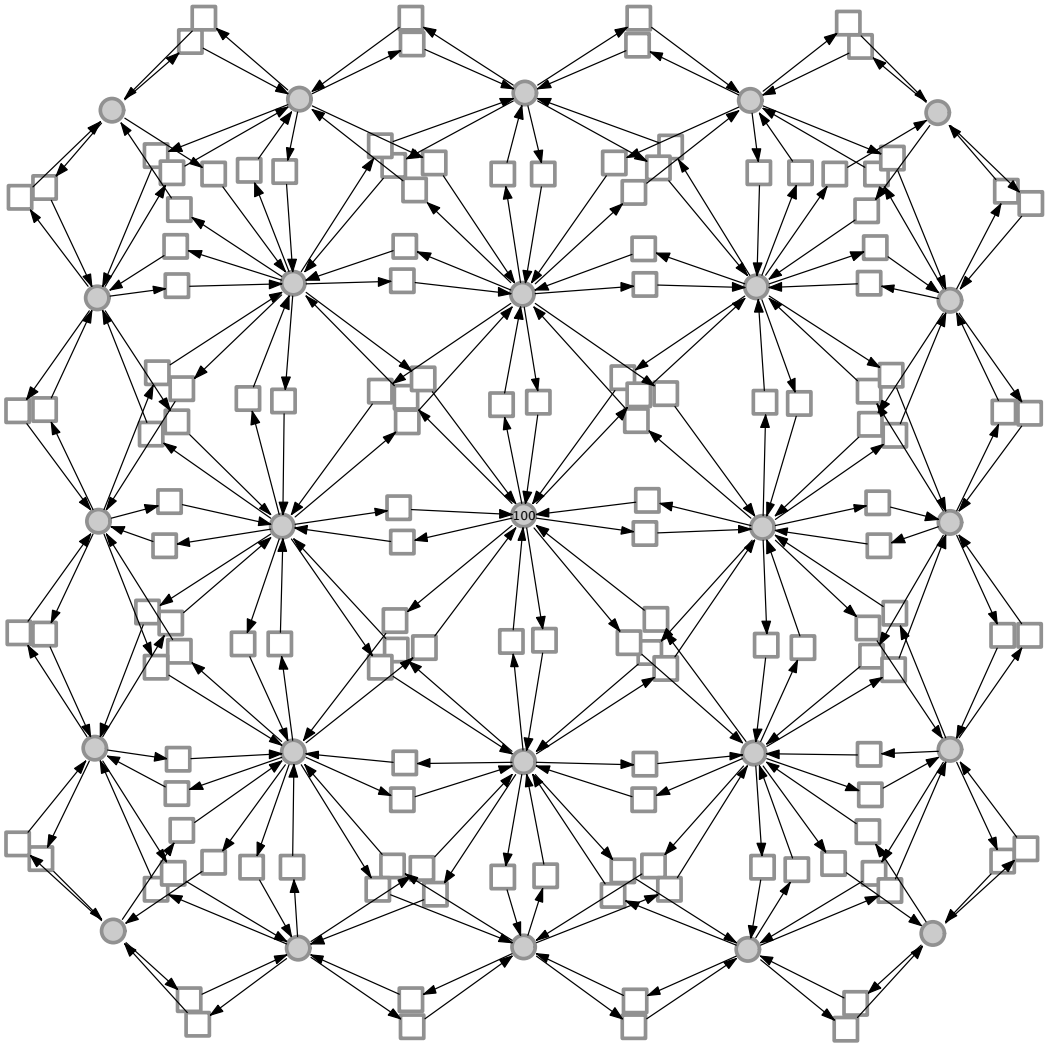
(a=x-1 | a=x | a=x+1) & (b = y-1 | b=y | b=y+1)

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

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



EX1: DIFFUSION - 2D8 NEIGHBOURHOOD



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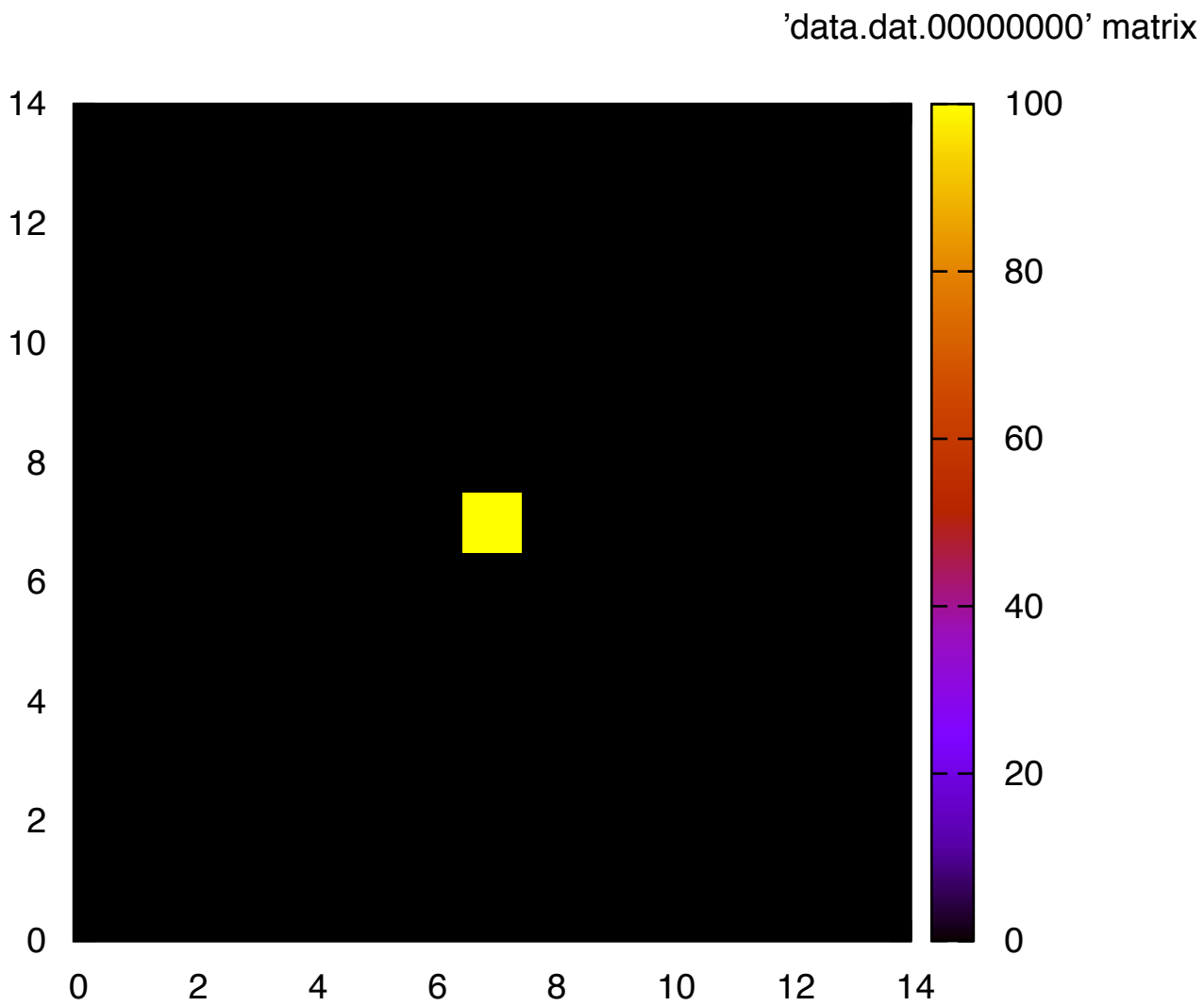
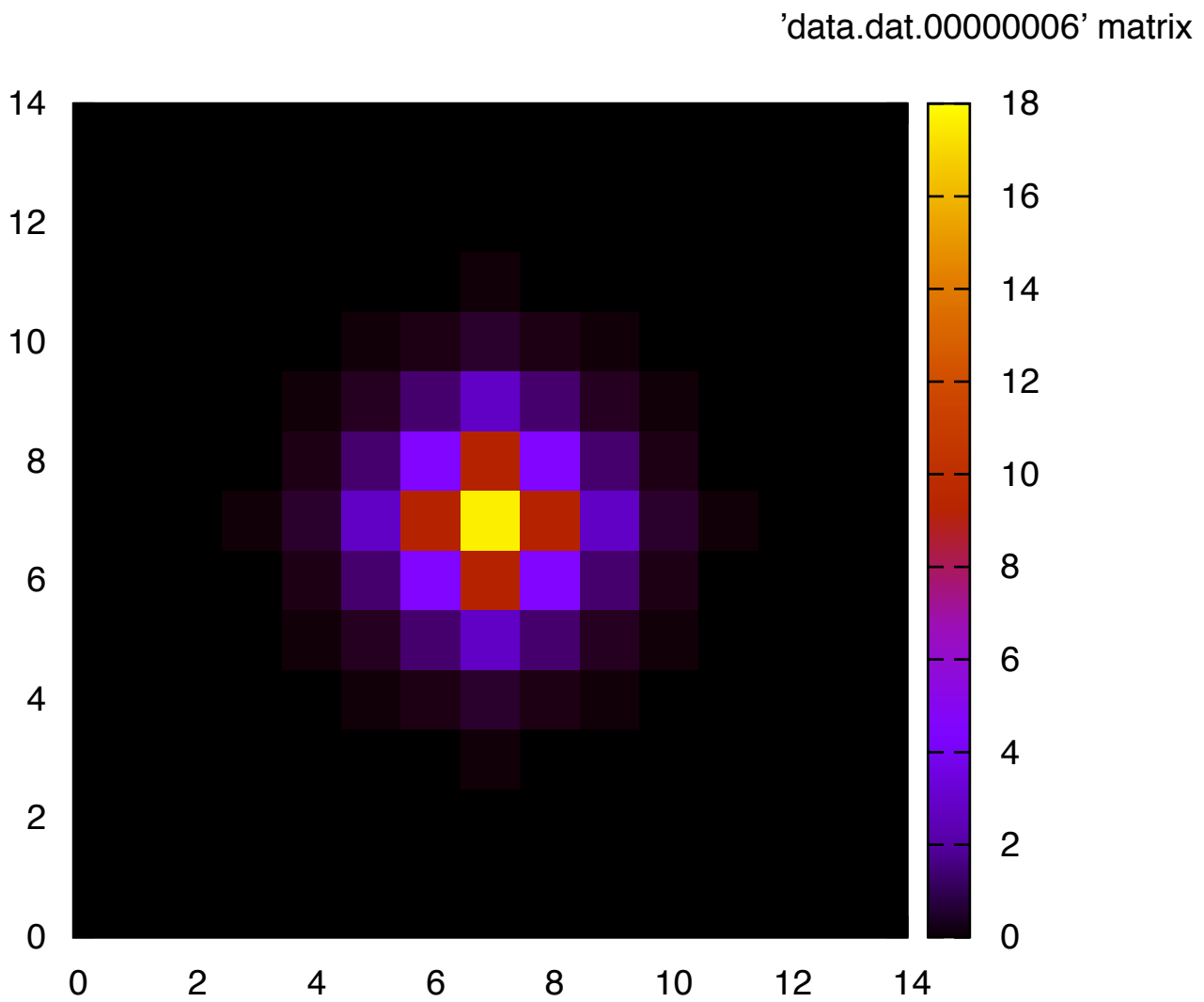
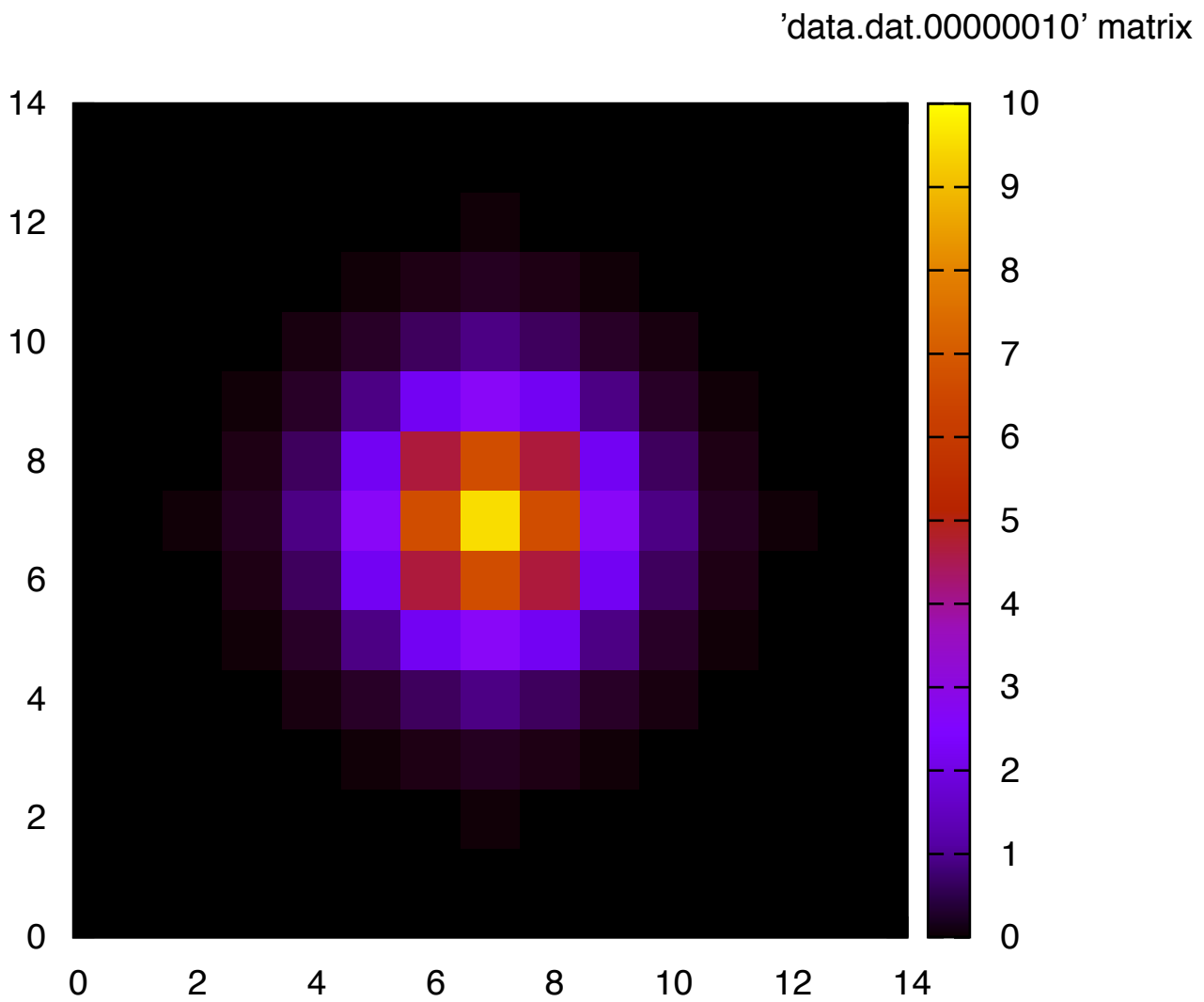
EX1: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15



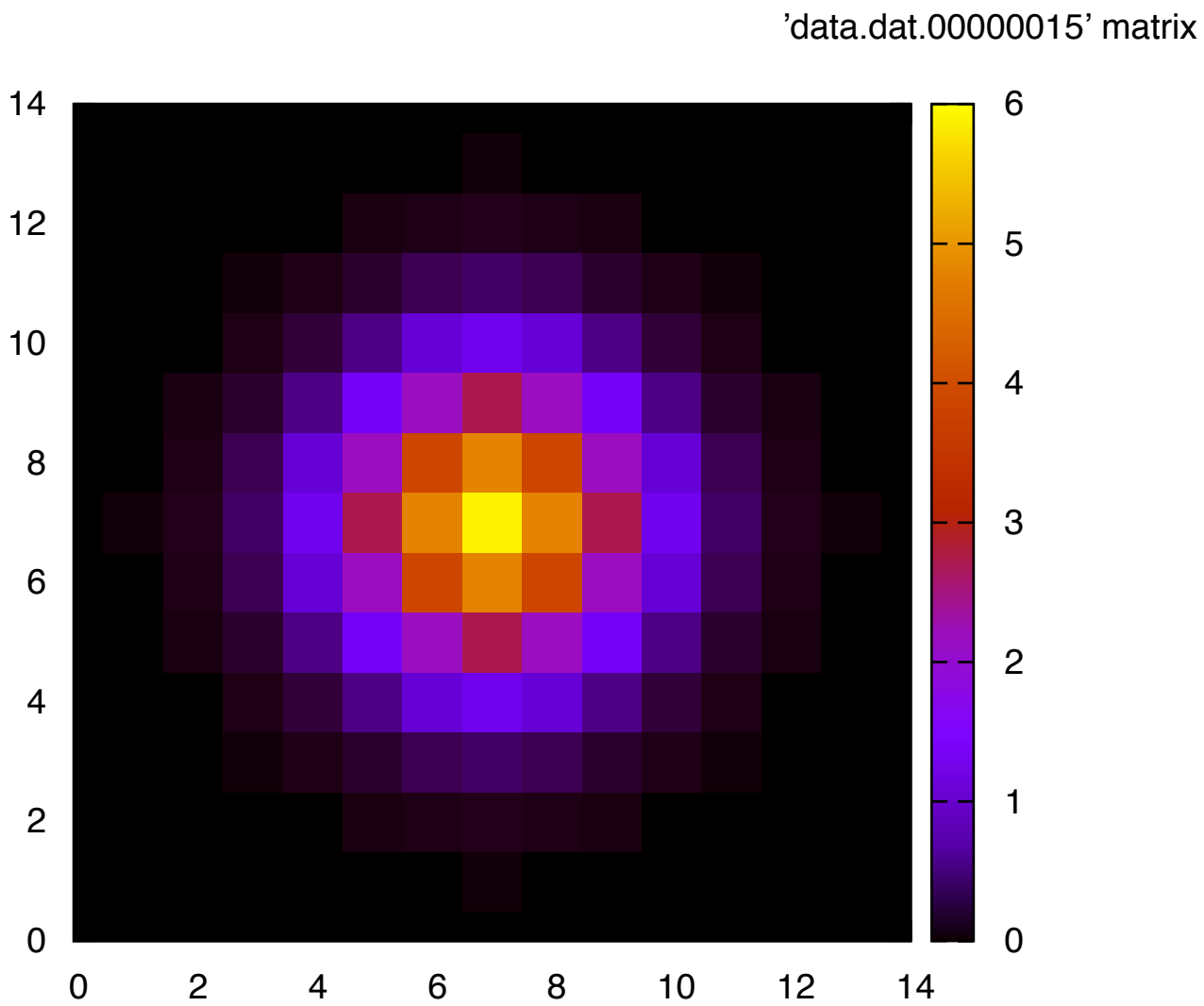
EX1: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15



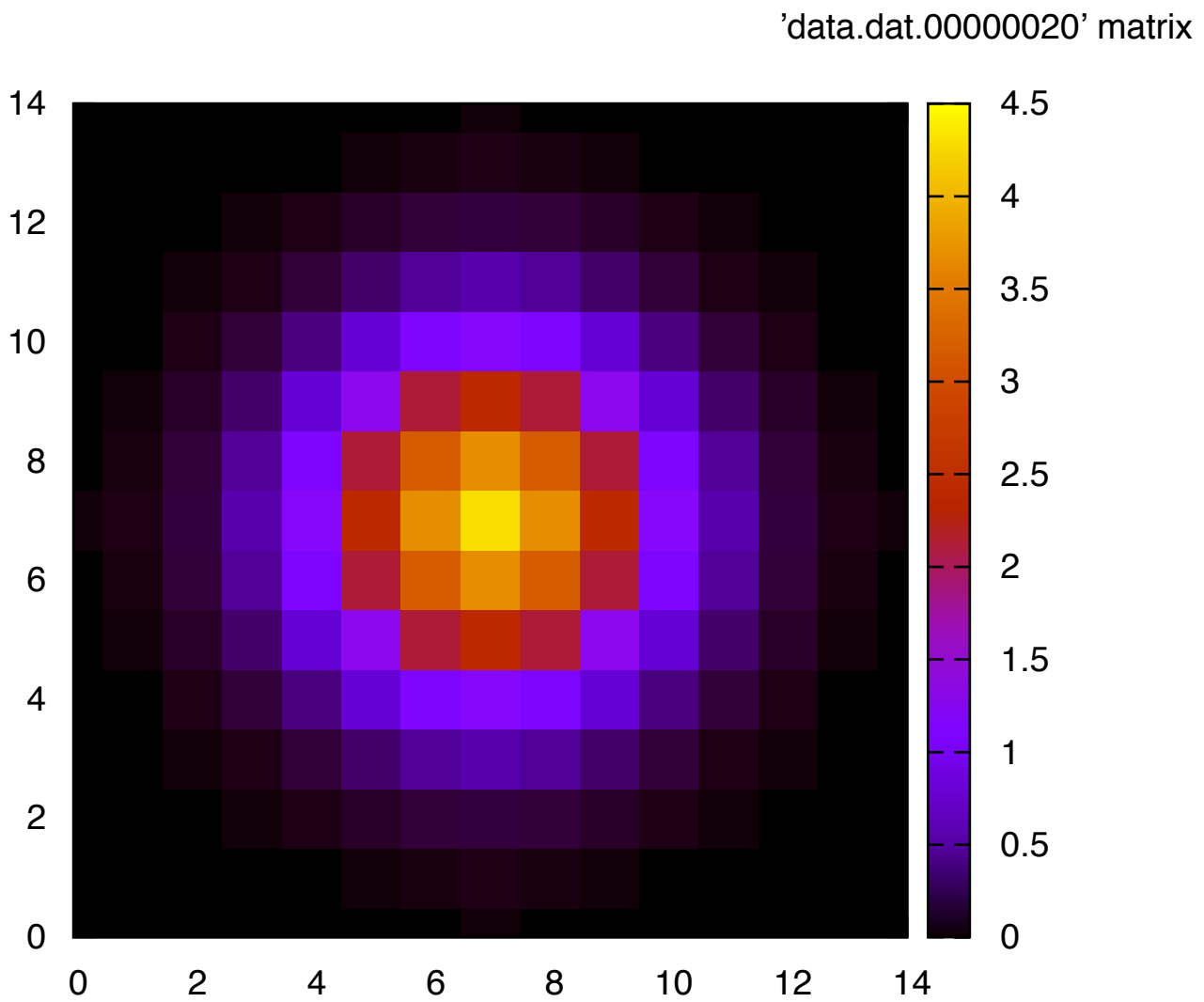
EX1: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15



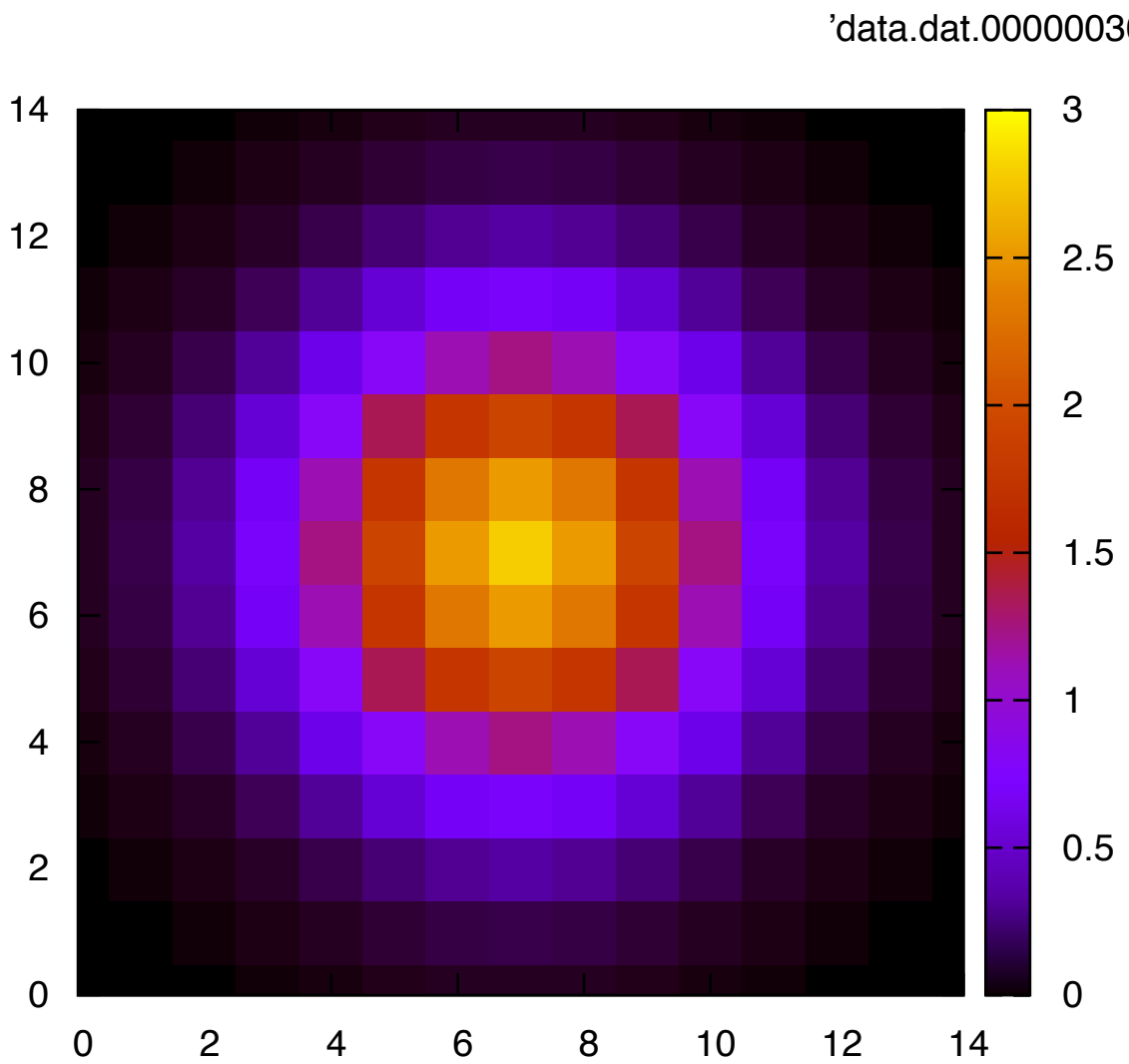
EX1: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15



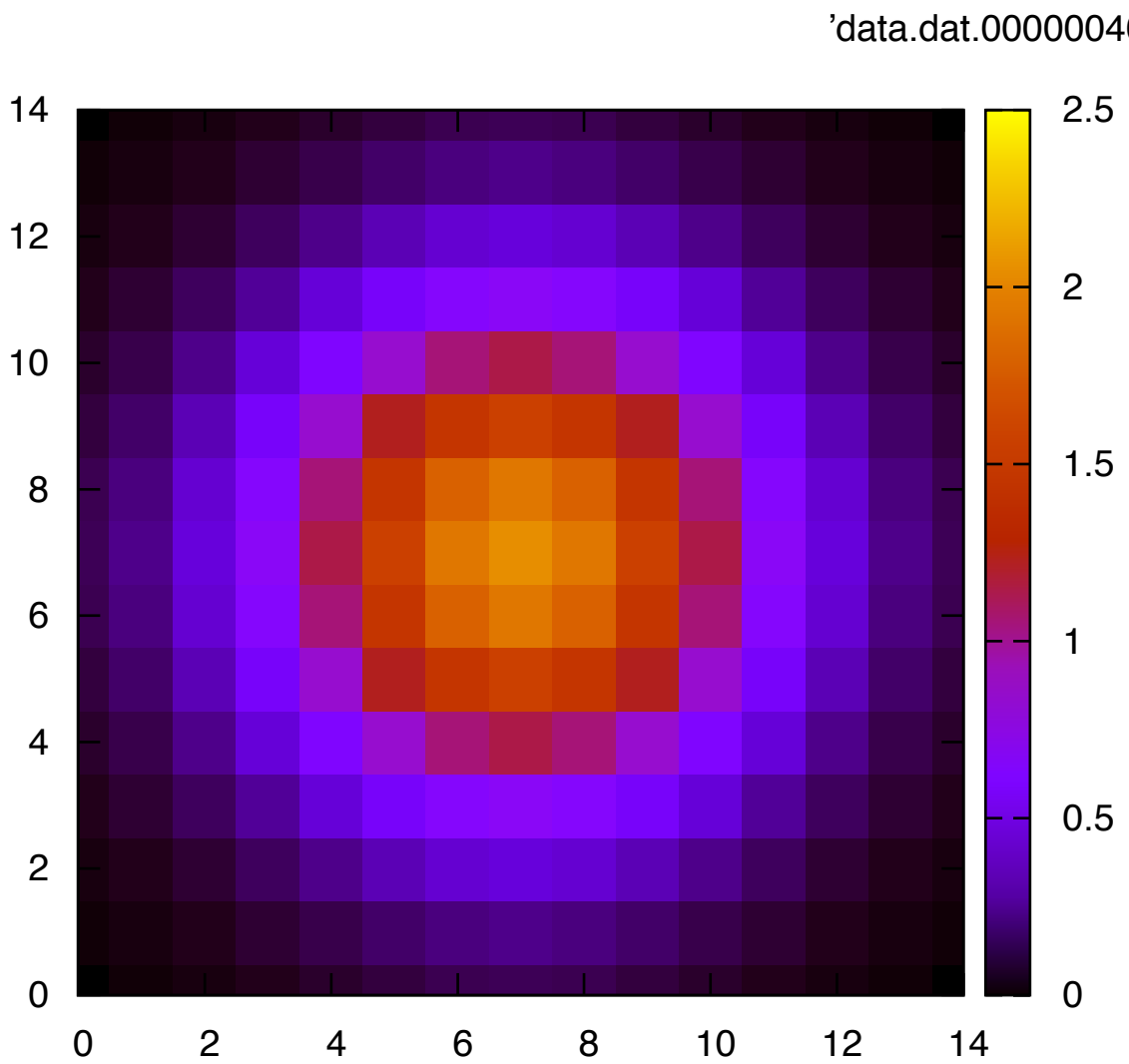
EX1: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15



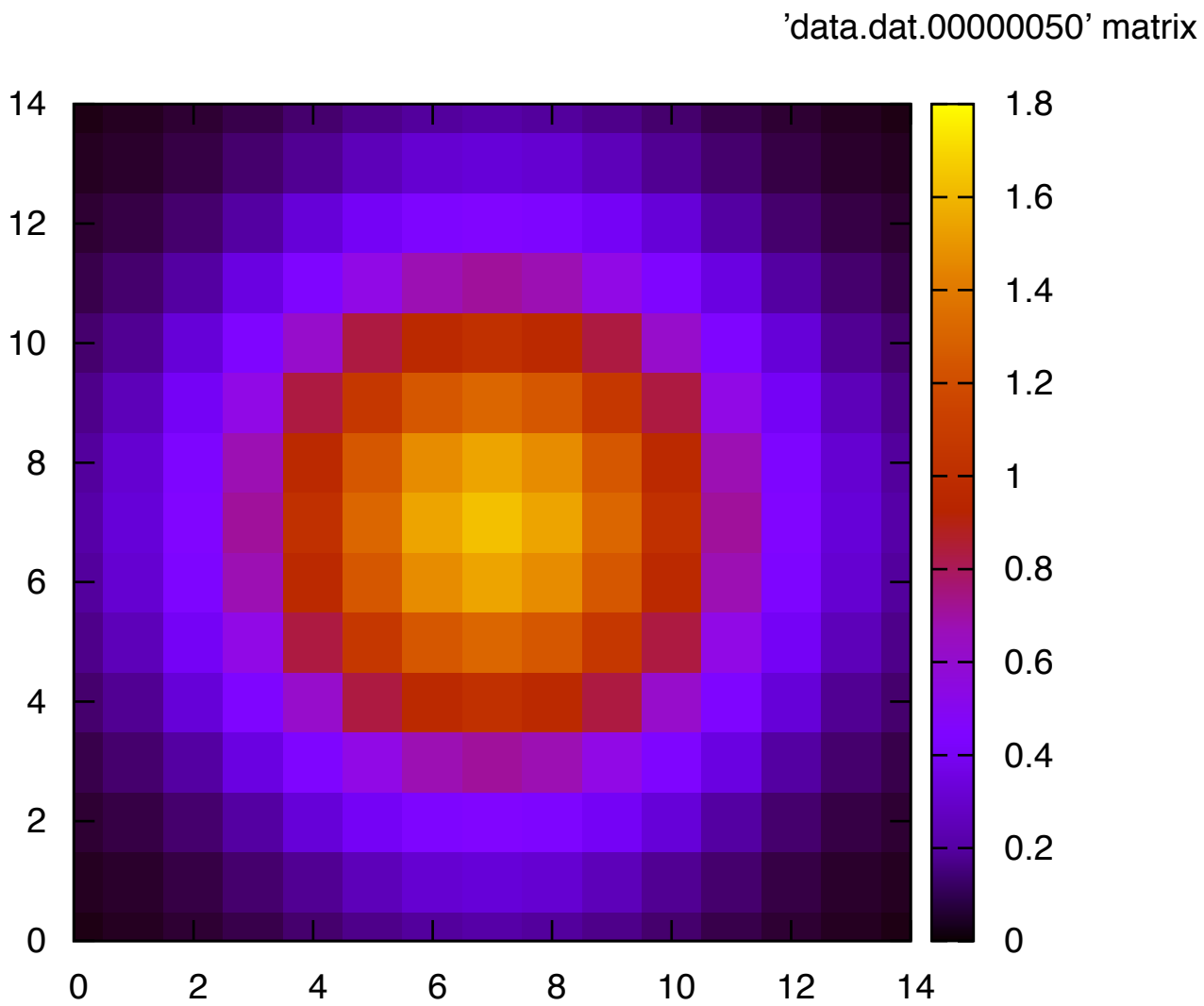
EX1: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15



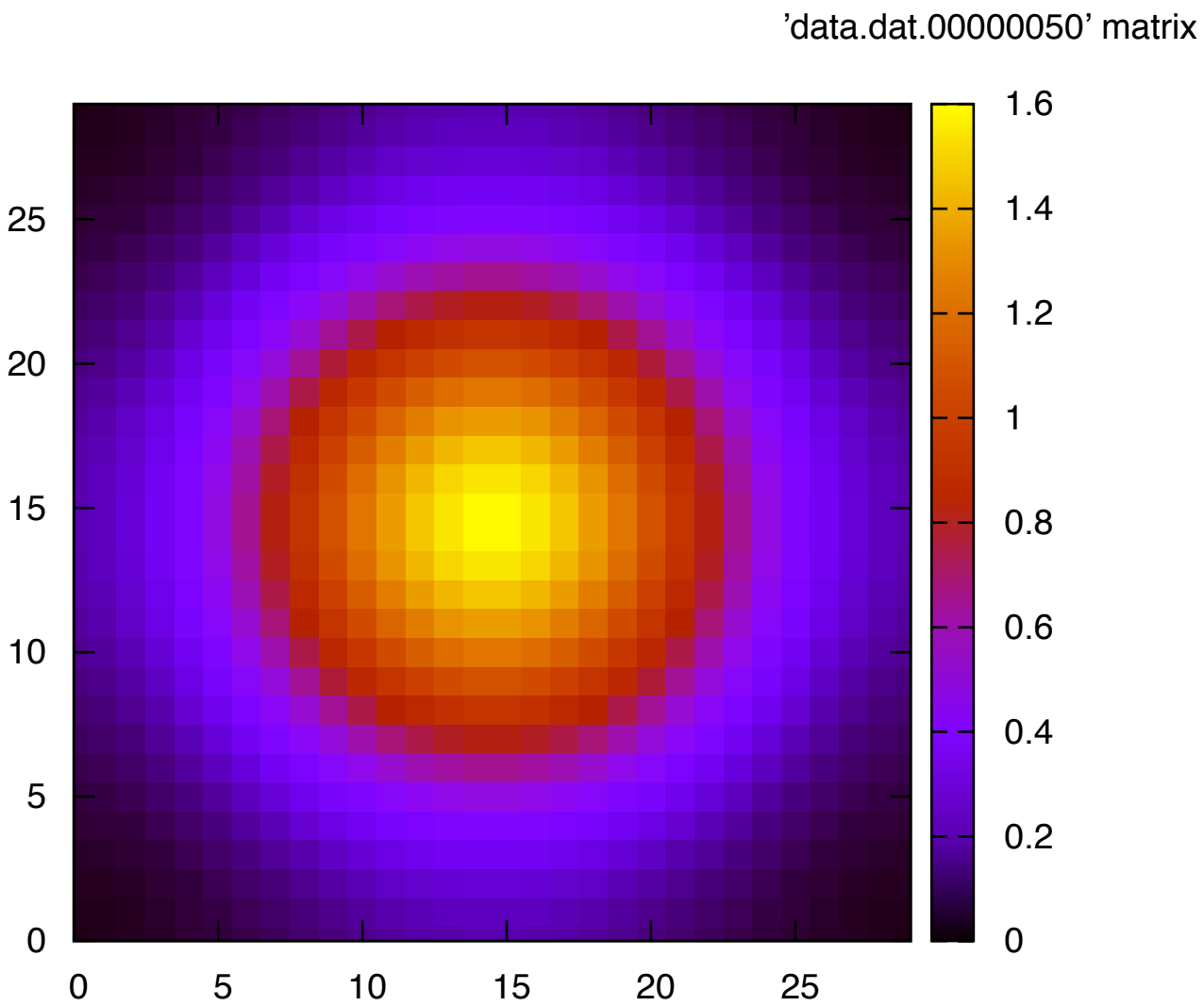
EX1: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15



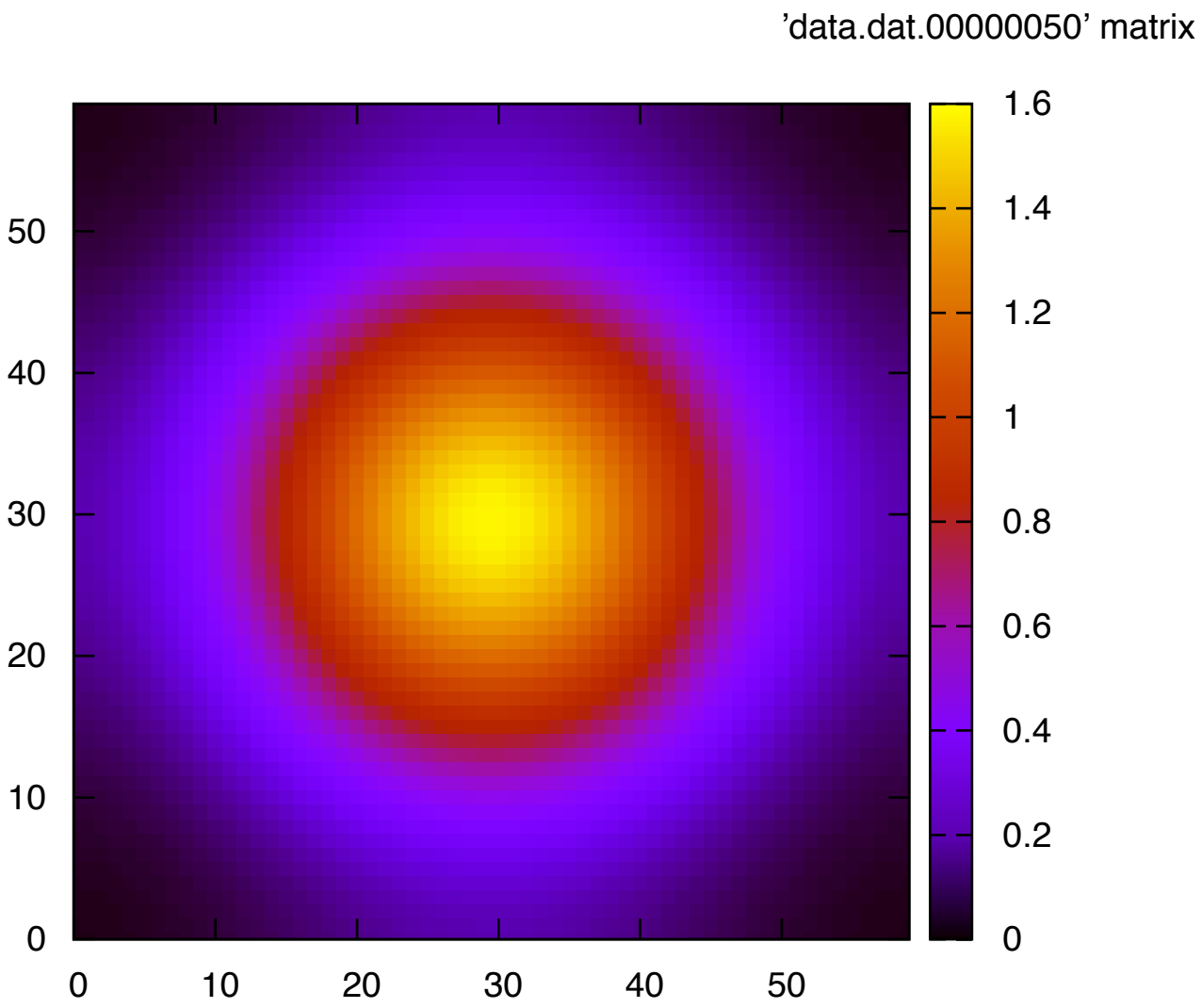
EX1: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15



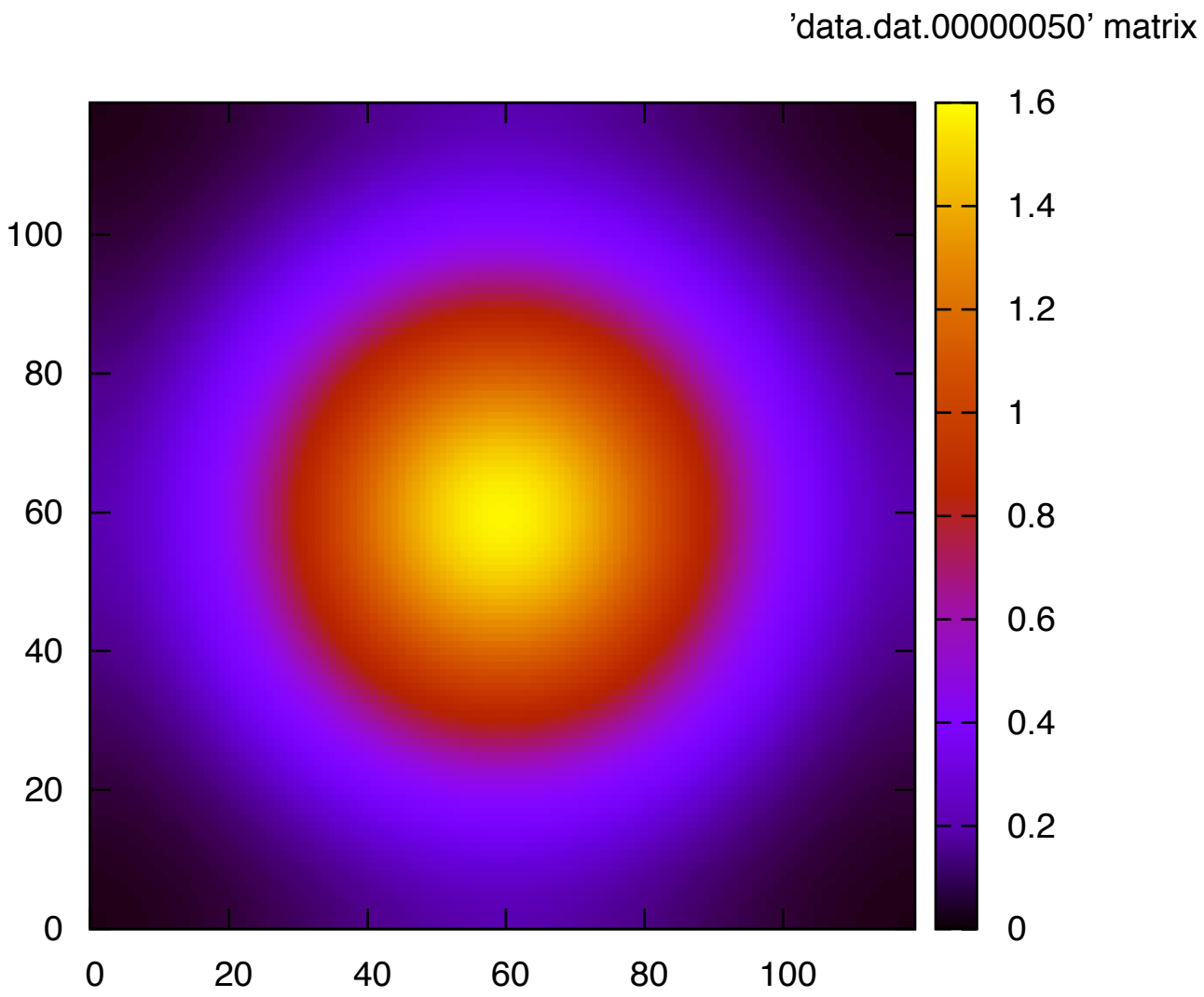
EX1: DIFFUSION - 2D4 NEIGHBOURHOOD, 30X30



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

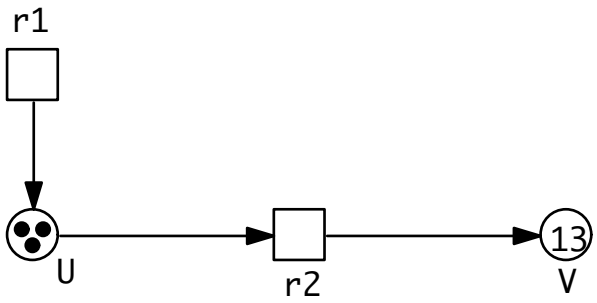
- **reactions**
  - -> *version of Brusselator model, http://en.wikipedia.org/wiki/Brusselator*

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

r1: -> U

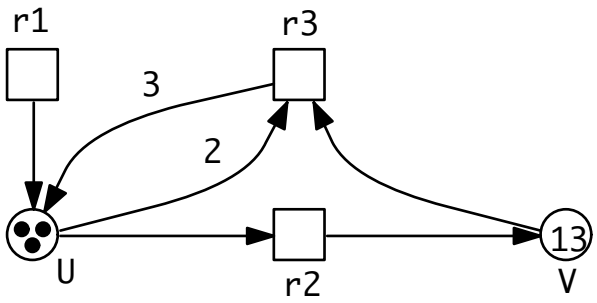
r1: -> U

r2: U -> V



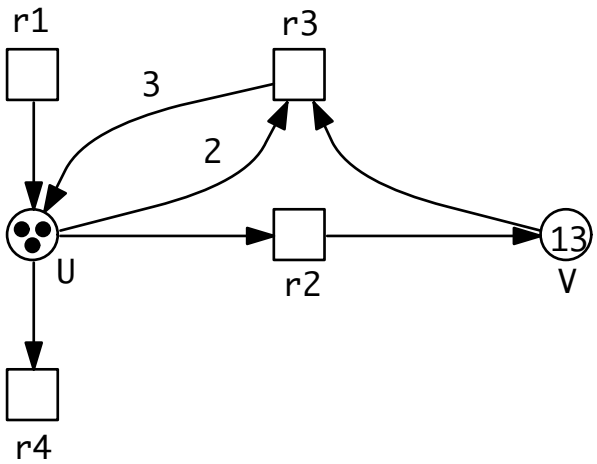
EX2: TURING PATTERNS

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



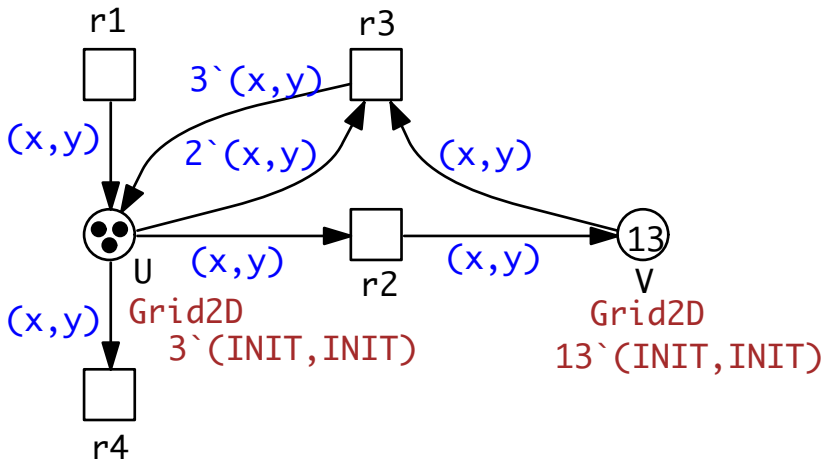
EX2: TURING PATTERNS

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



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

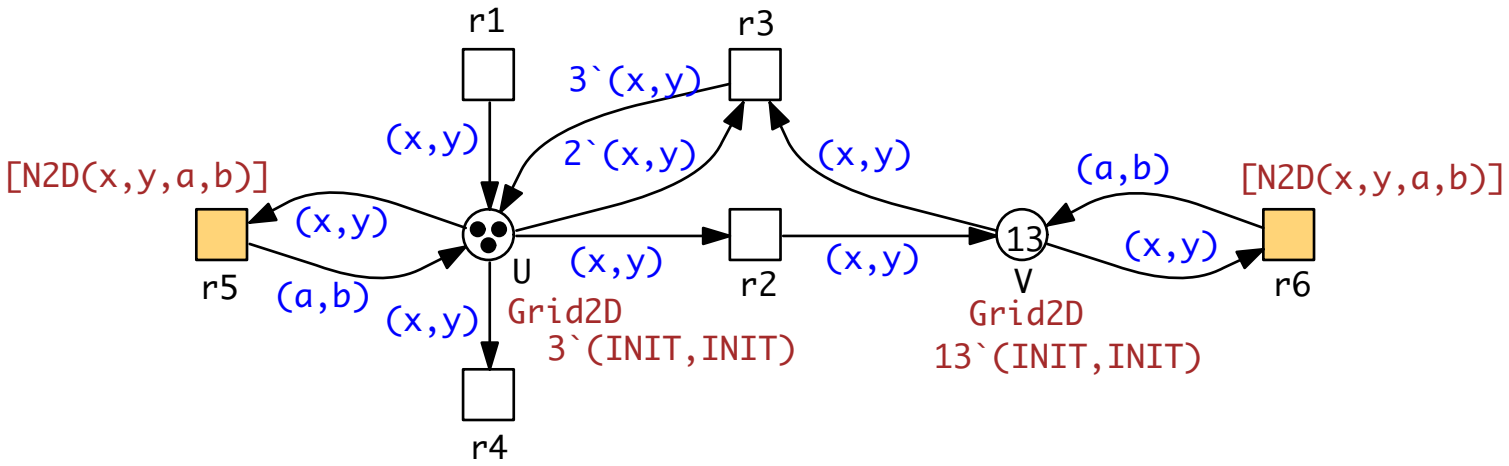
adding SPACE



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}



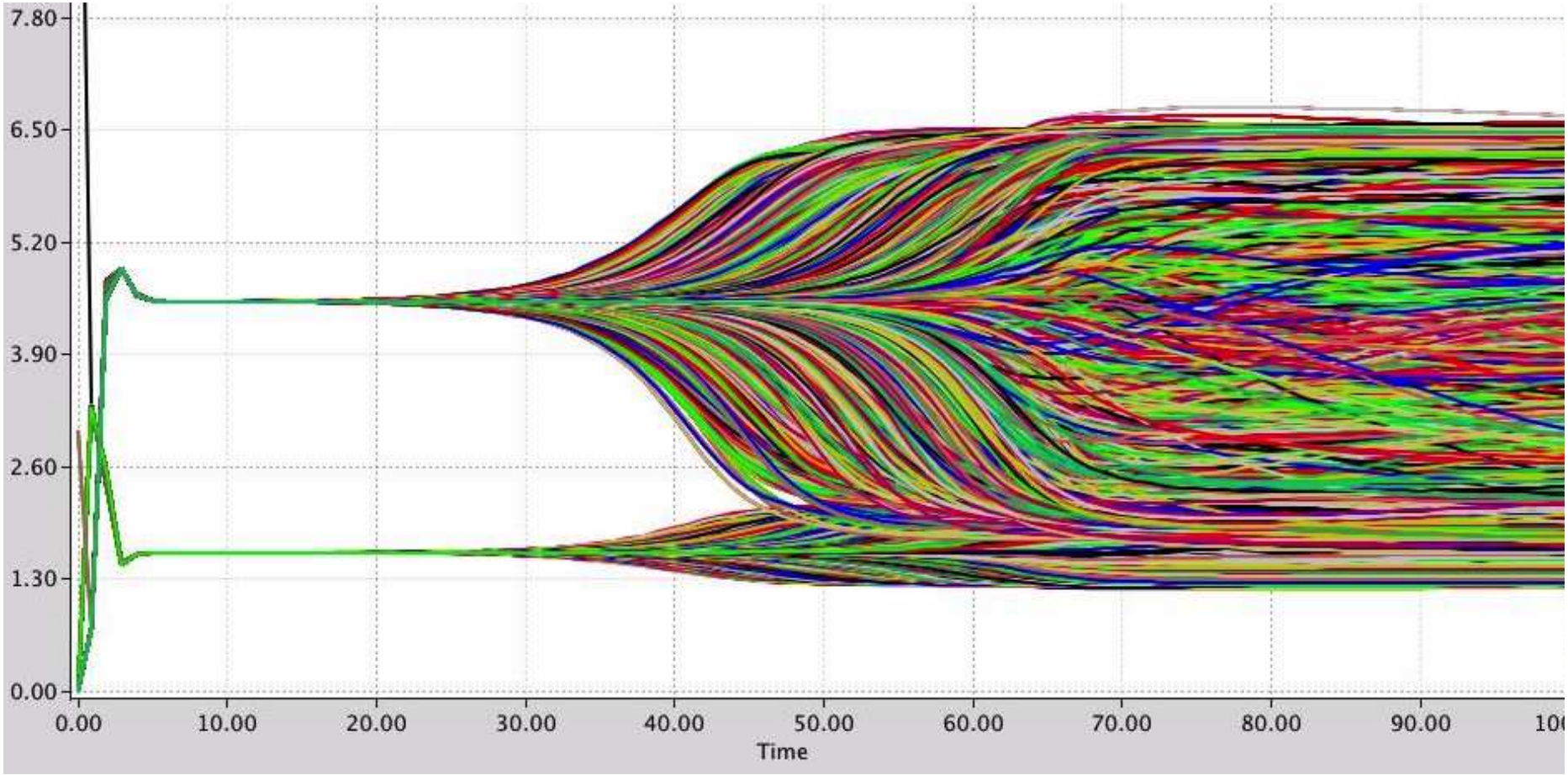
r1 - r4 follow mass action kinetics with rate constants:
r1: A, r2: B, r3: 1, r4: 1;

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*

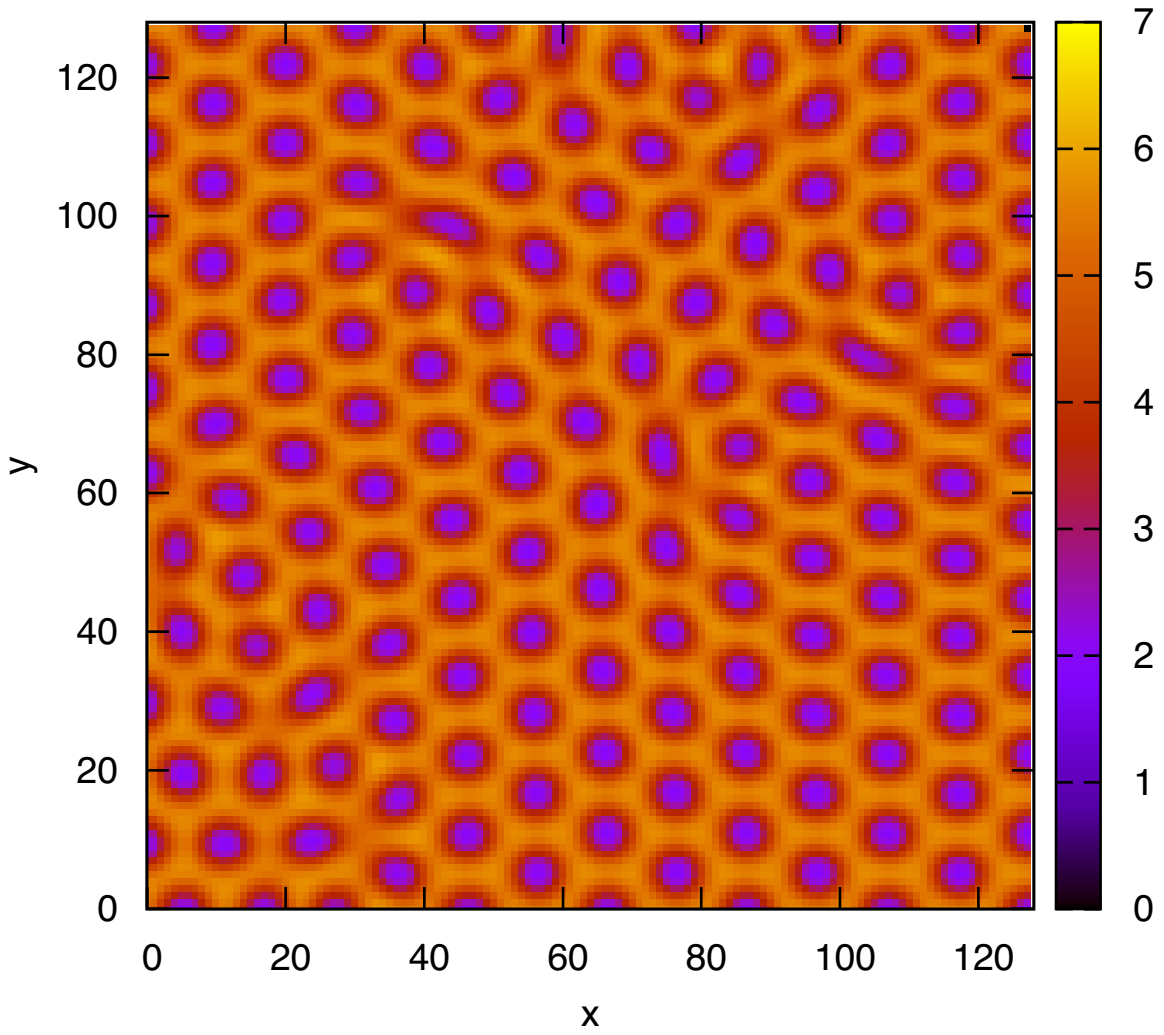
EX2: TRACES

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

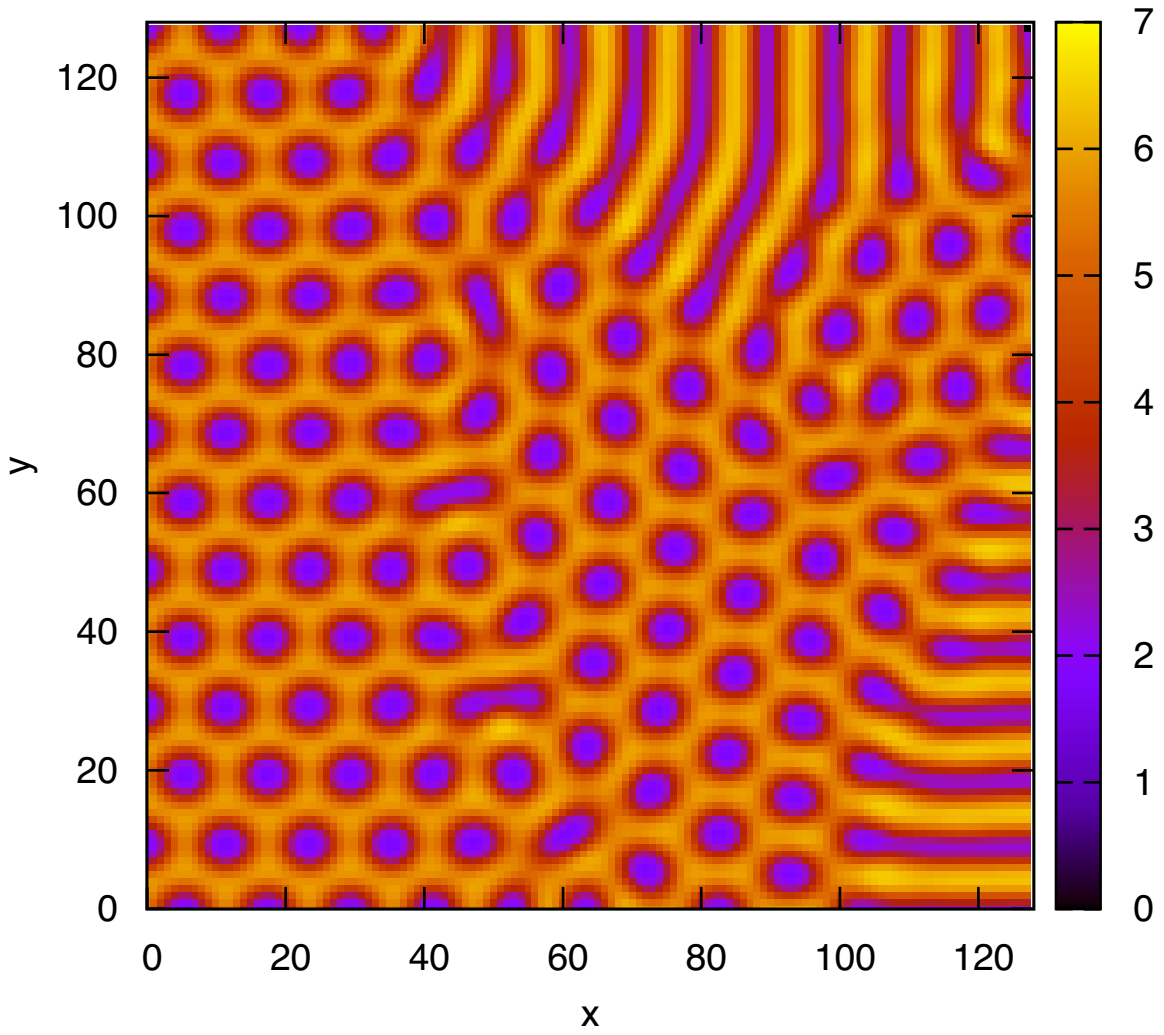


EX2: TURING PATTERNS

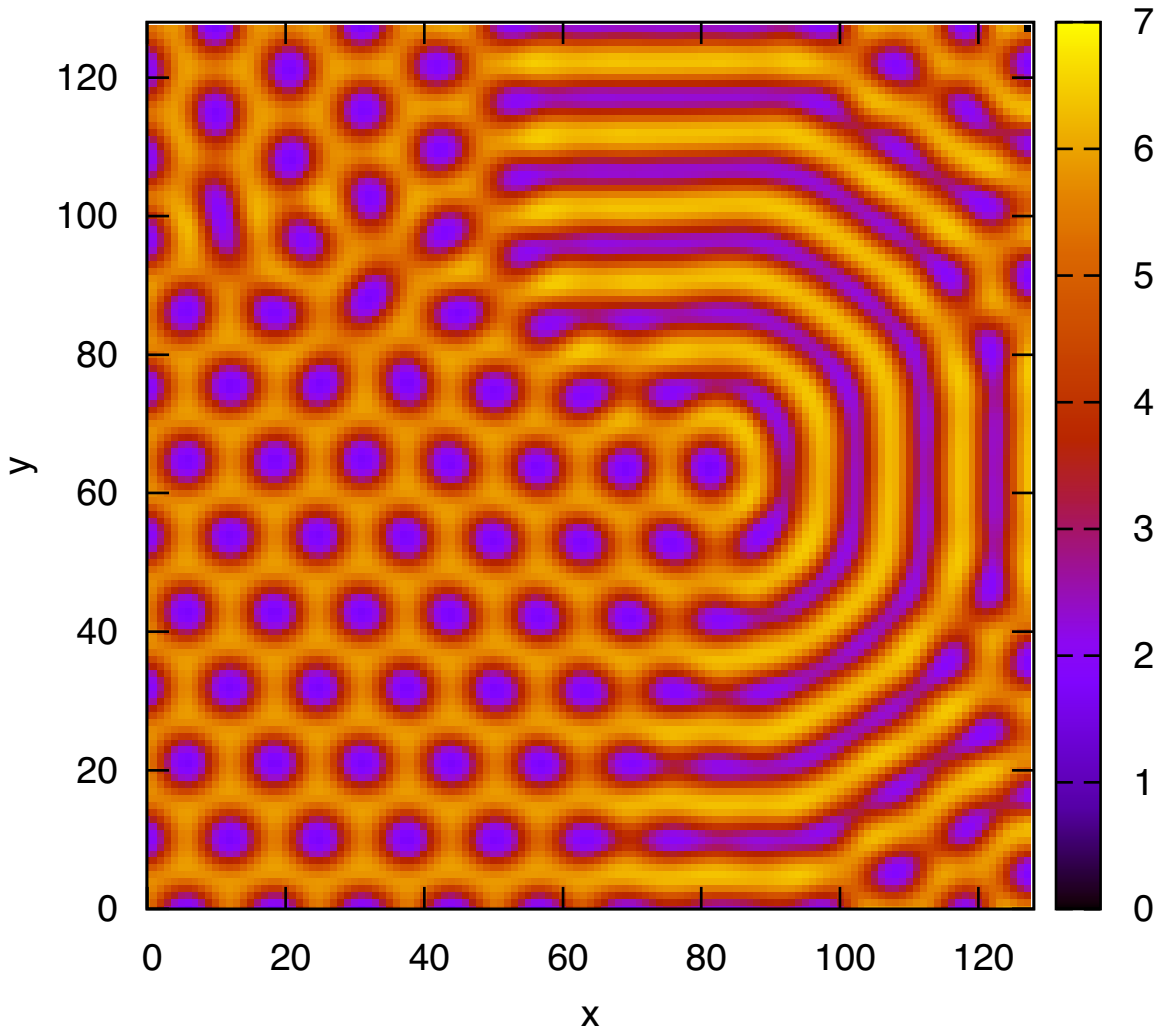
-> U IN ALL GRID POSITIONS AT TIME 5,000



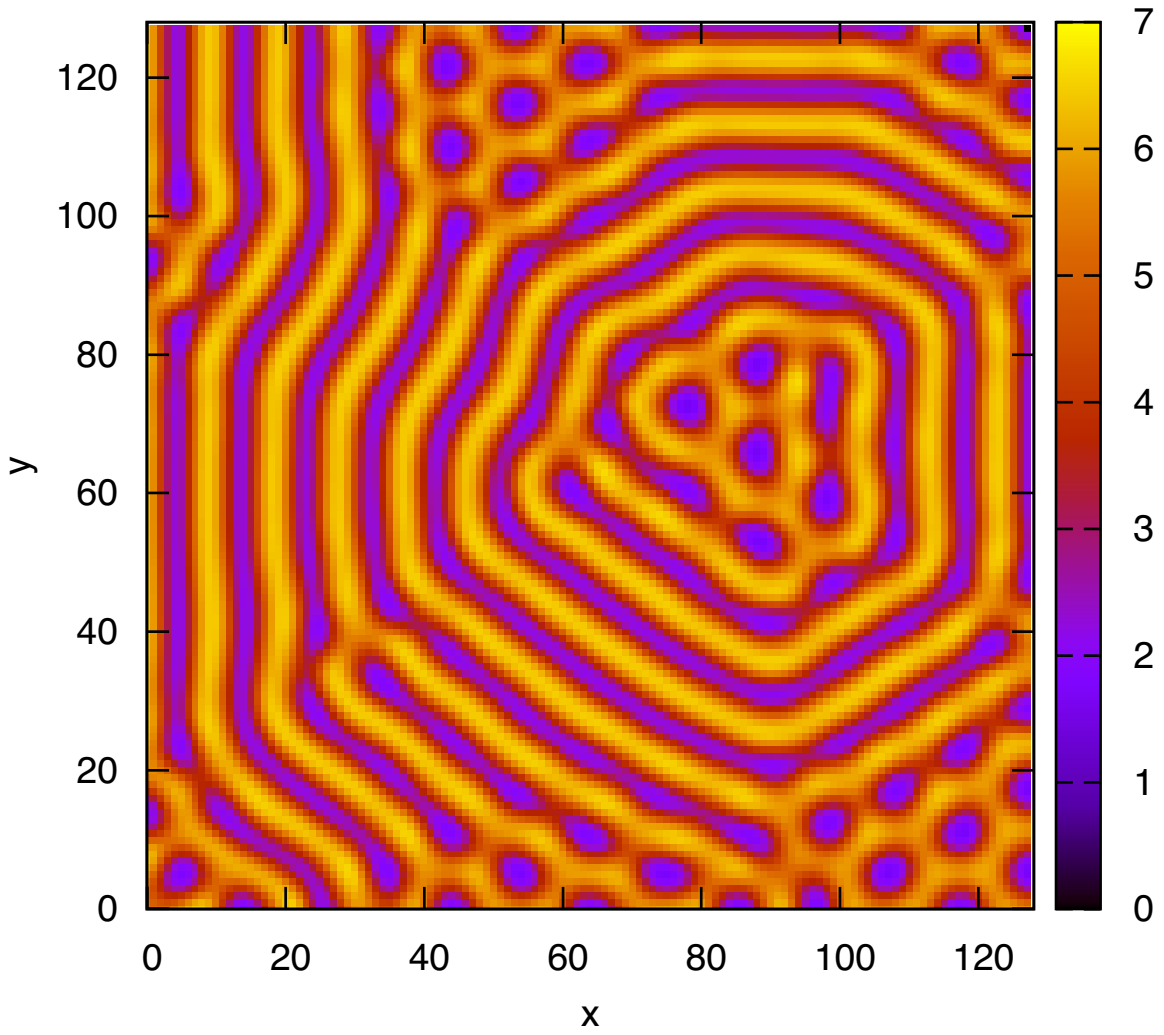
EX2: TURING PATTERNS



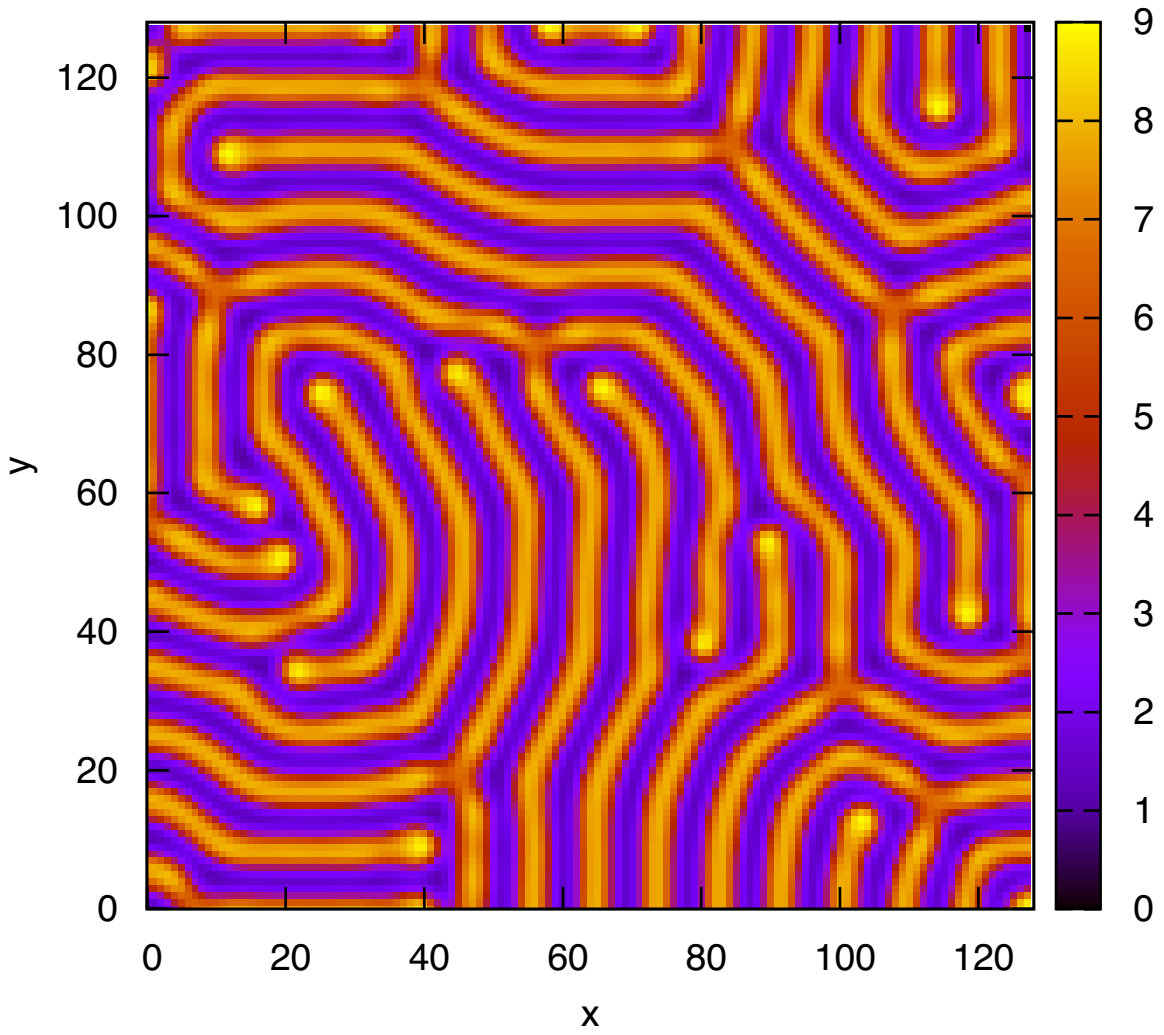
EX2: TURING PATTERNS



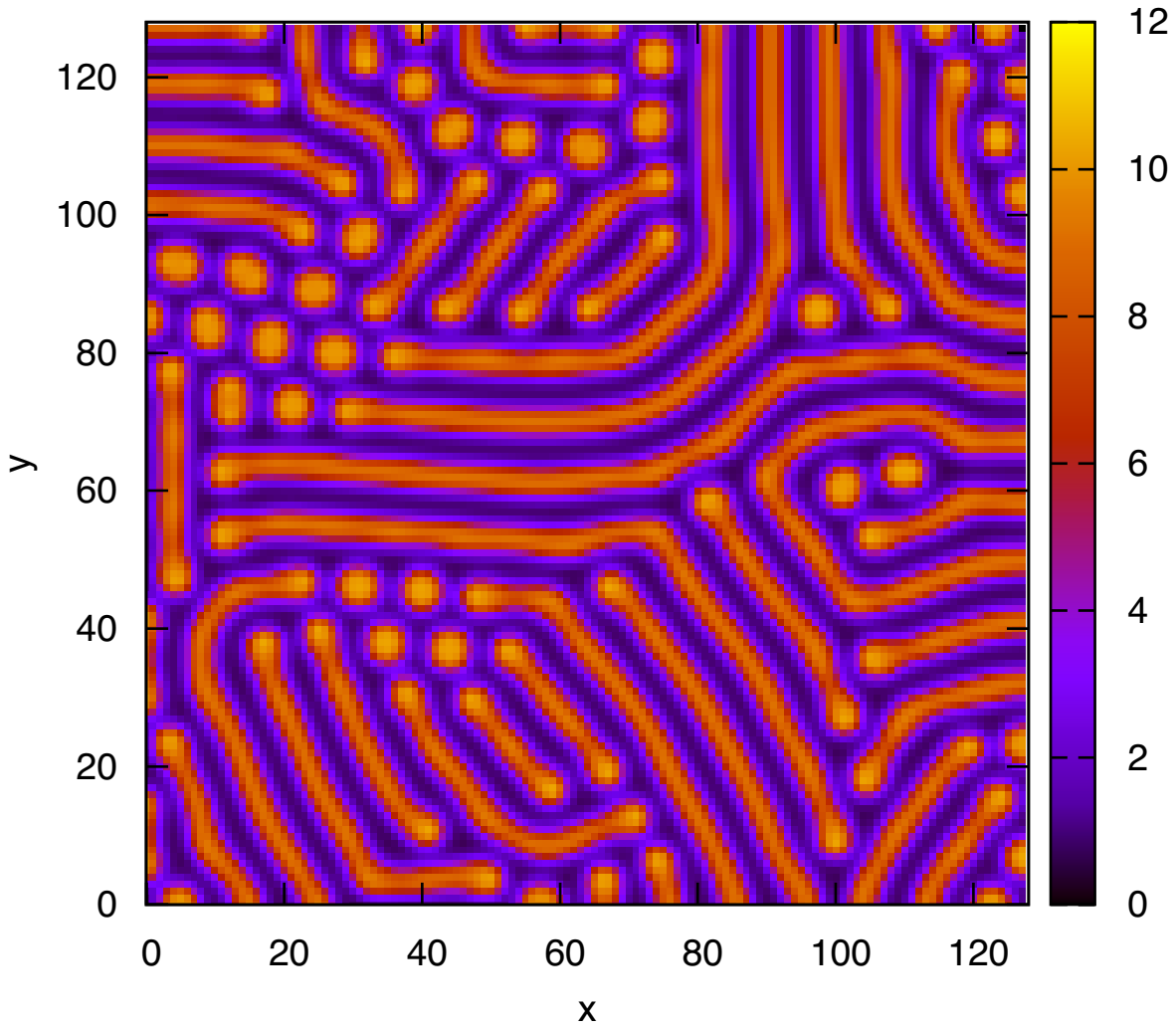
EX2: TURING PATTERNS



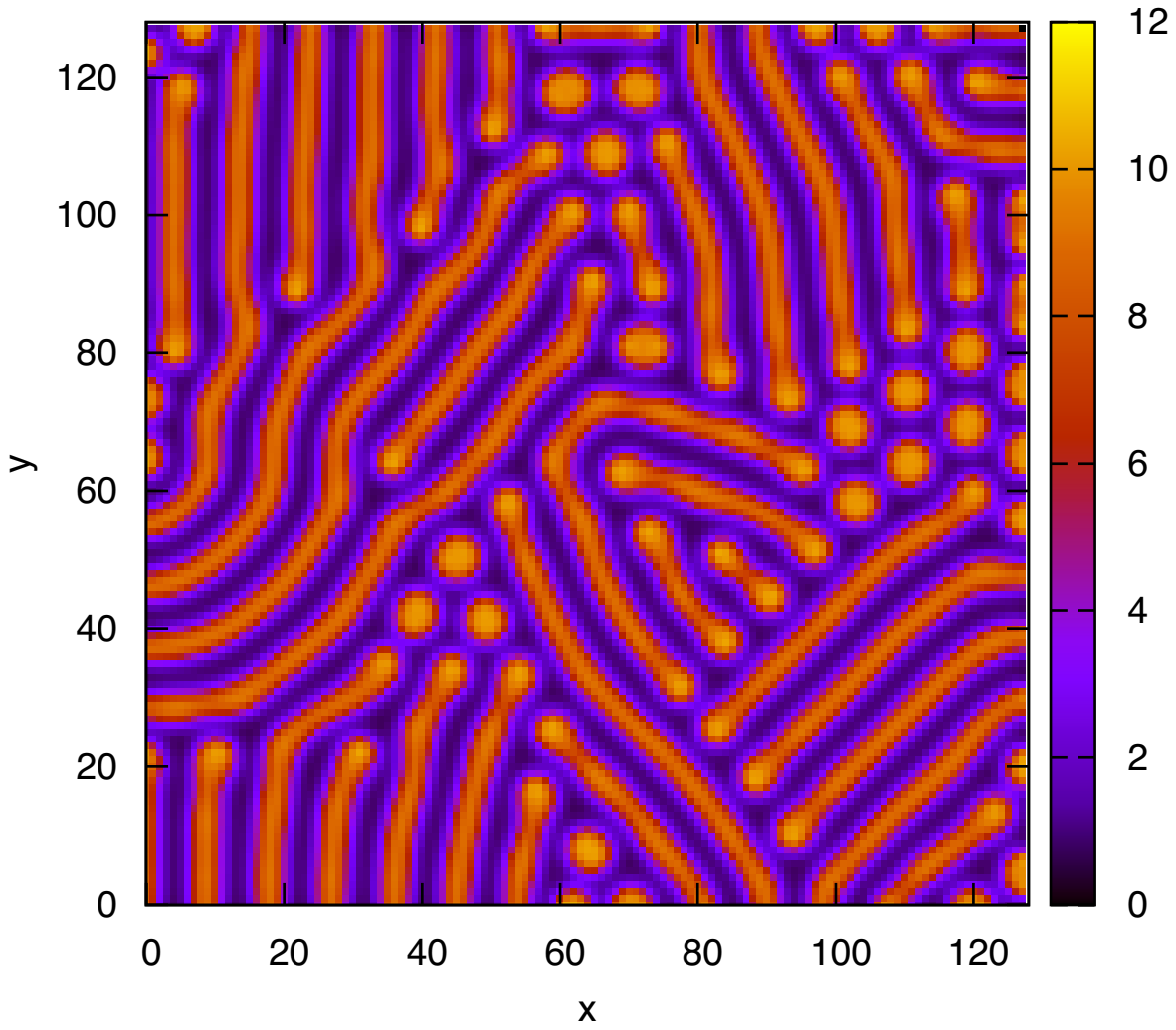
EX2: TURING PATTERNS



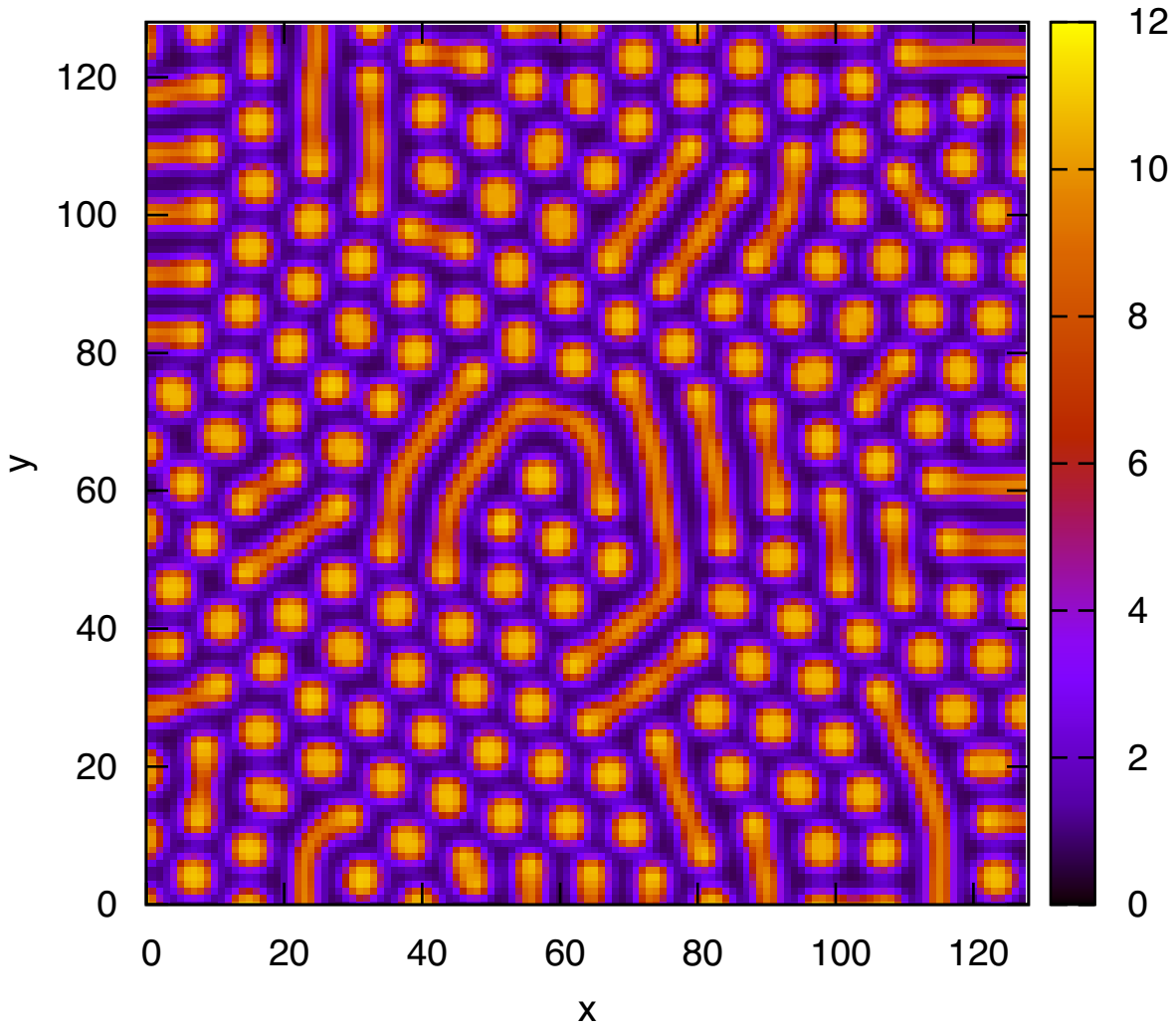
EX2: TURING PATTERNS



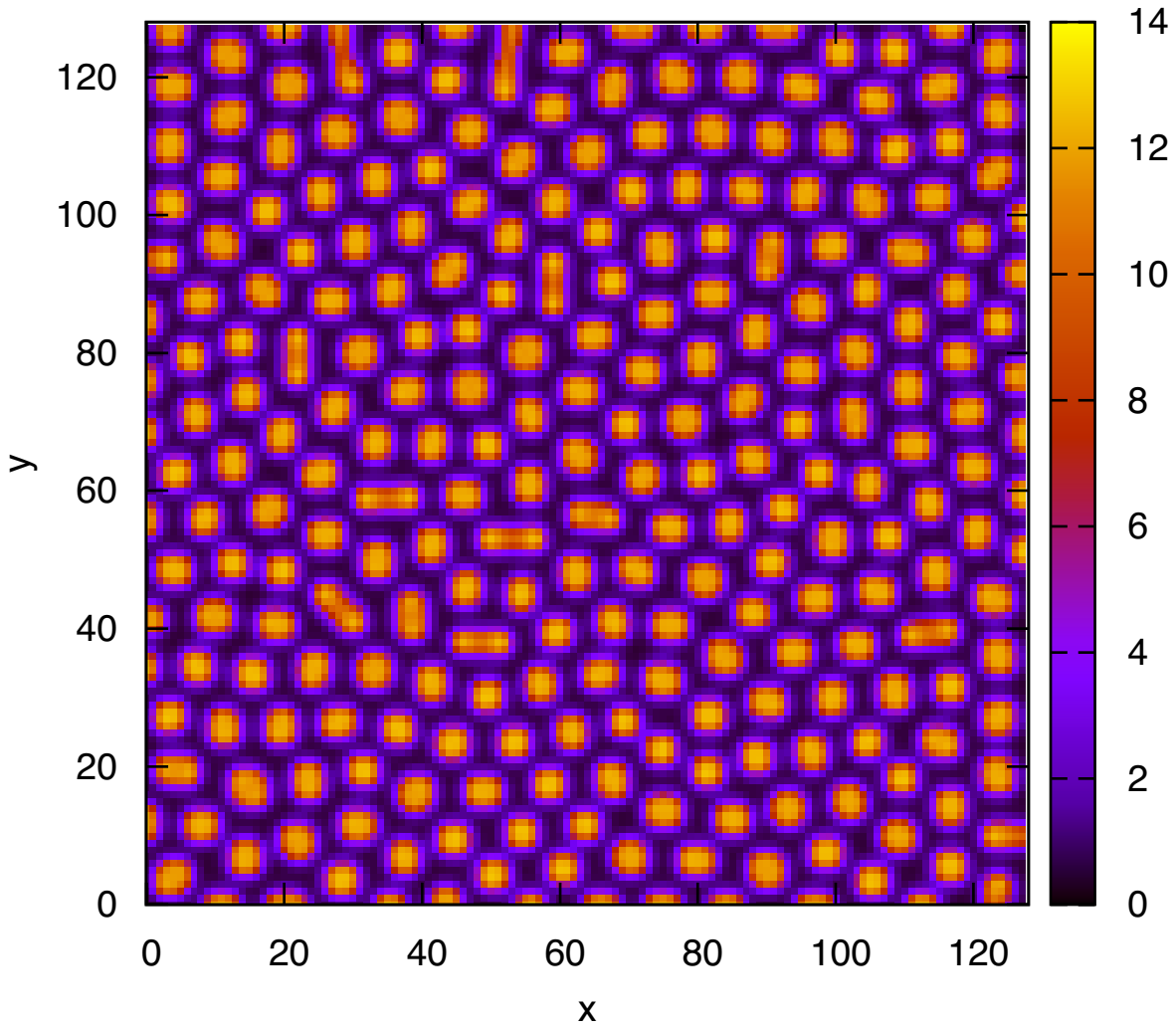
EX2: TURING PATTERNS



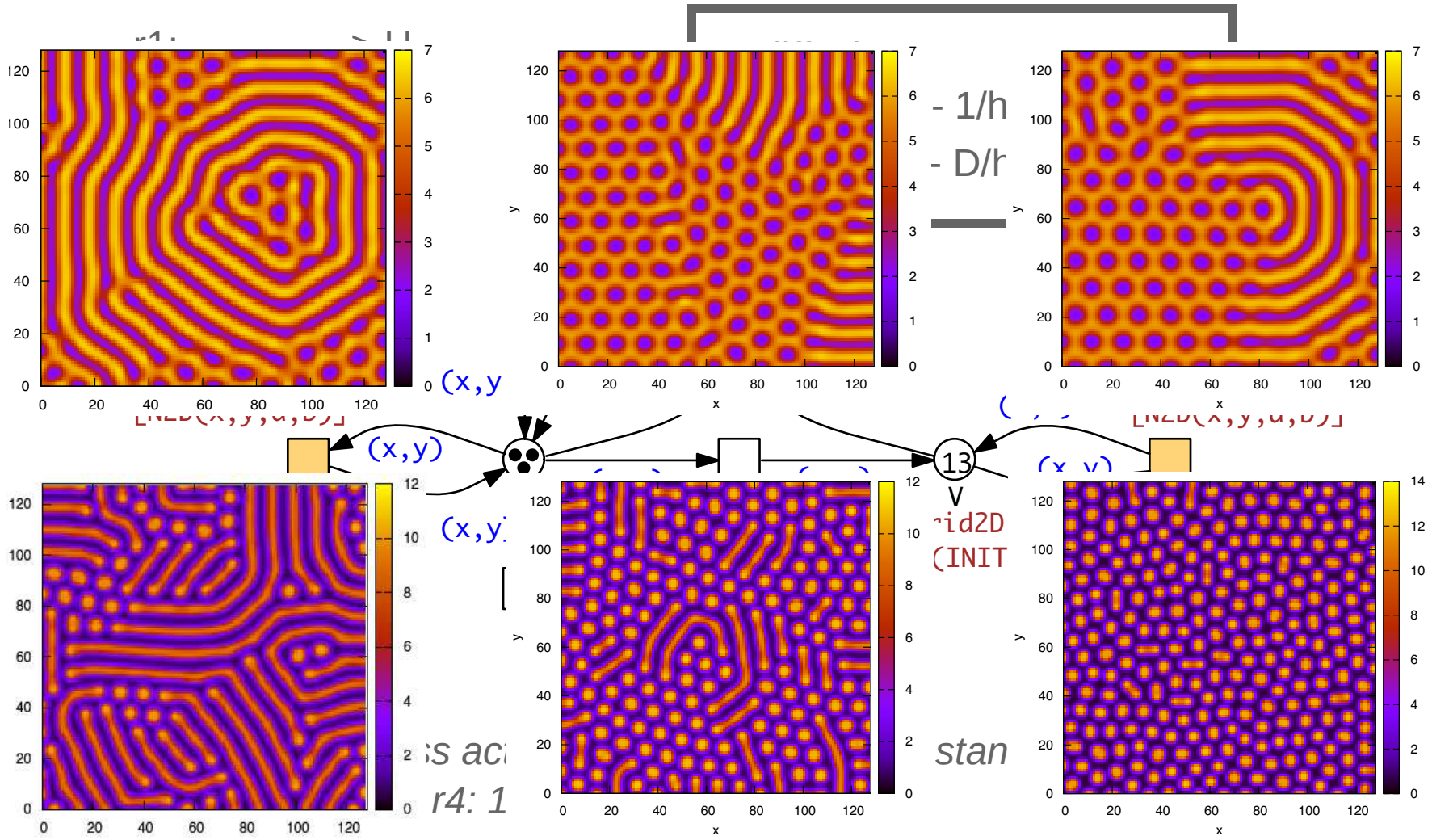
EX2: TURING PATTERNS



EX2: TURING PATTERNS



EX2: TURING PATTERNS



[LIU ET AL 2014]

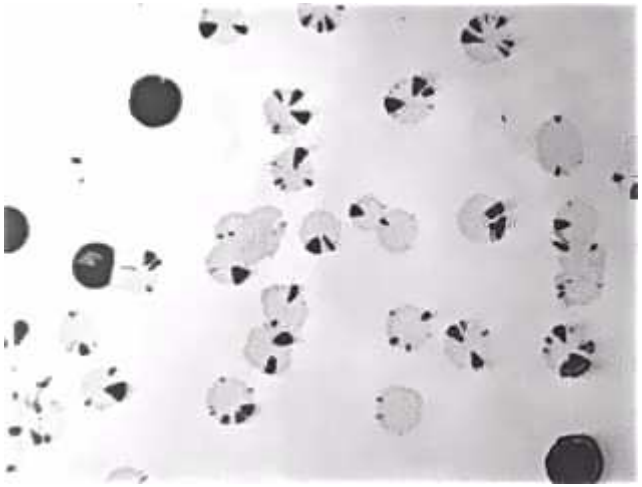
EXAMPLE 3:

PHASE VARIATION IN MULTISTRAIN CELL COLONIES

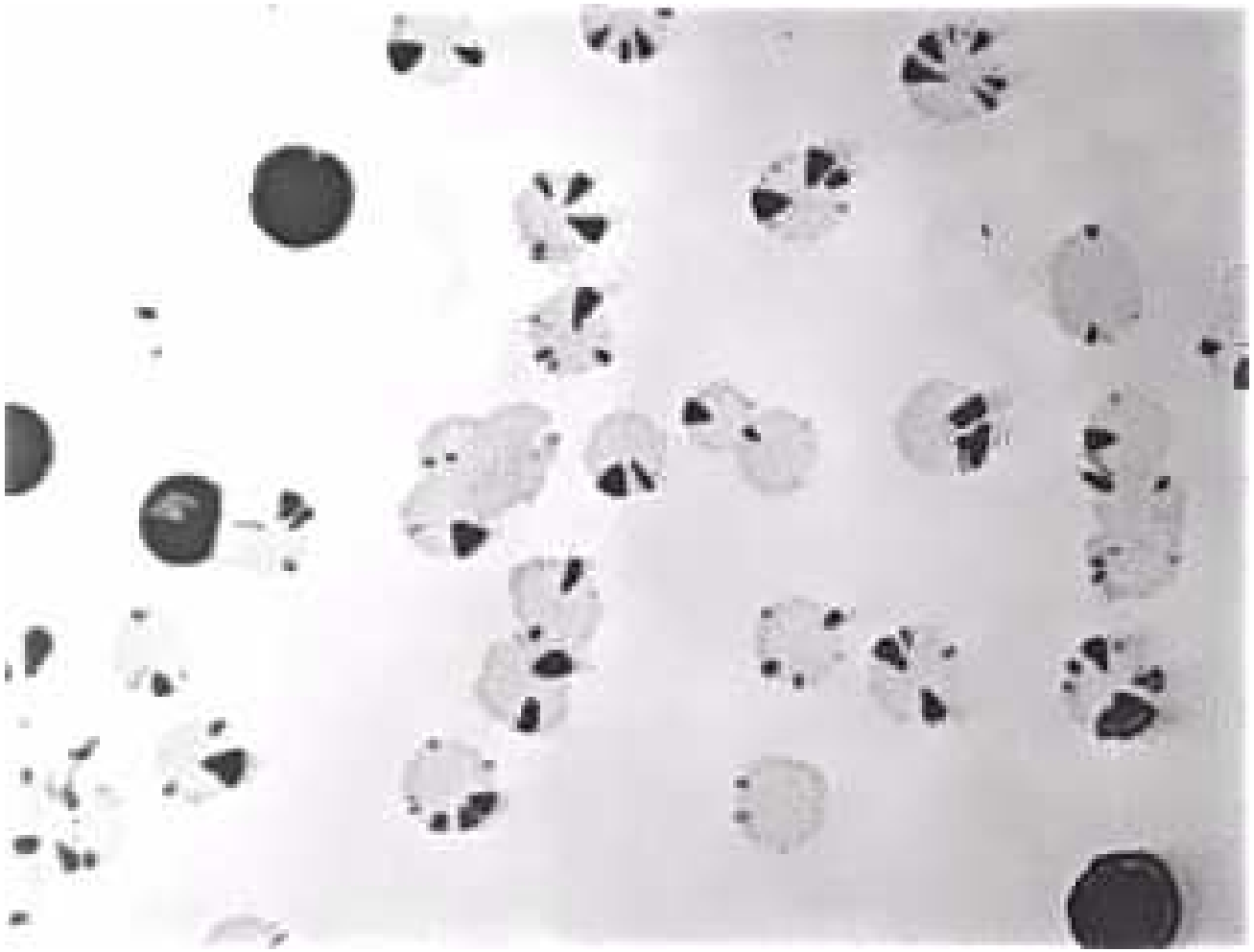
Pârvu, Gilbert, Heiner, Liu, Saunders, Shaw:
Spatial-temporal modelling and analysis of bacterial colonies with phase variable genes;
ACM TOMACS, 2015.

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*



EX3: CELL COLONIES, WETLAB OBSERVATIONS



(courtesy of N Saunders)

Microbiology (2003), **149**, 485–495

DOI 10.[illegible]/mic.0.25807-0

Mutation rates: estimati[illegible] phas[illegible] variation [illegible]t[illegible] when fitness diff[illegible]nce[illegible] a[illegible] pre[illegible]nt a[illegible]d their impact on po[illegible]latio[illegible] st[illegible]

Nigel J.[illegible]1† E[illegible]ichard M[illegible]xon[1] and Mike B. Gravenor[2]

[1]Molecular Inf[illegible]ious D[illegible]ases Group, Institute of Molecular Medicine, University of Oxford, [illegible]eadington, O[illegible]X3 9DS, UK

[2]Institute for Animal Health, Compton, Berkshire RG20 7NN, UK

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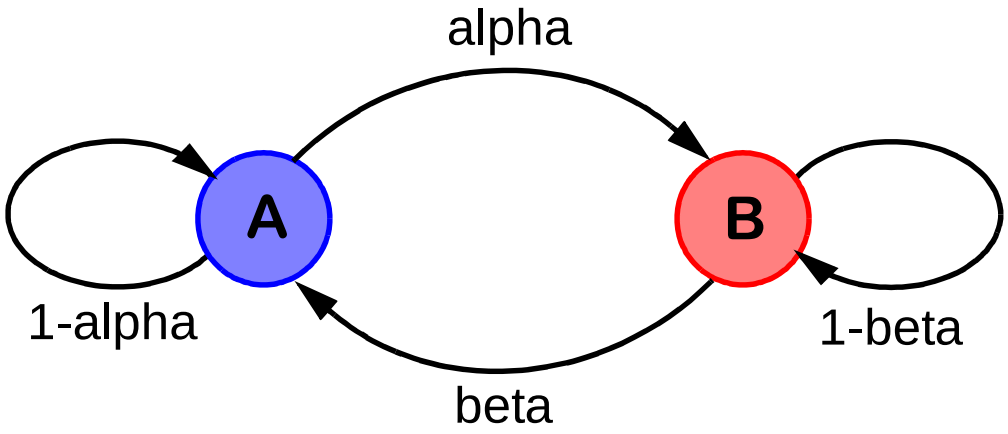
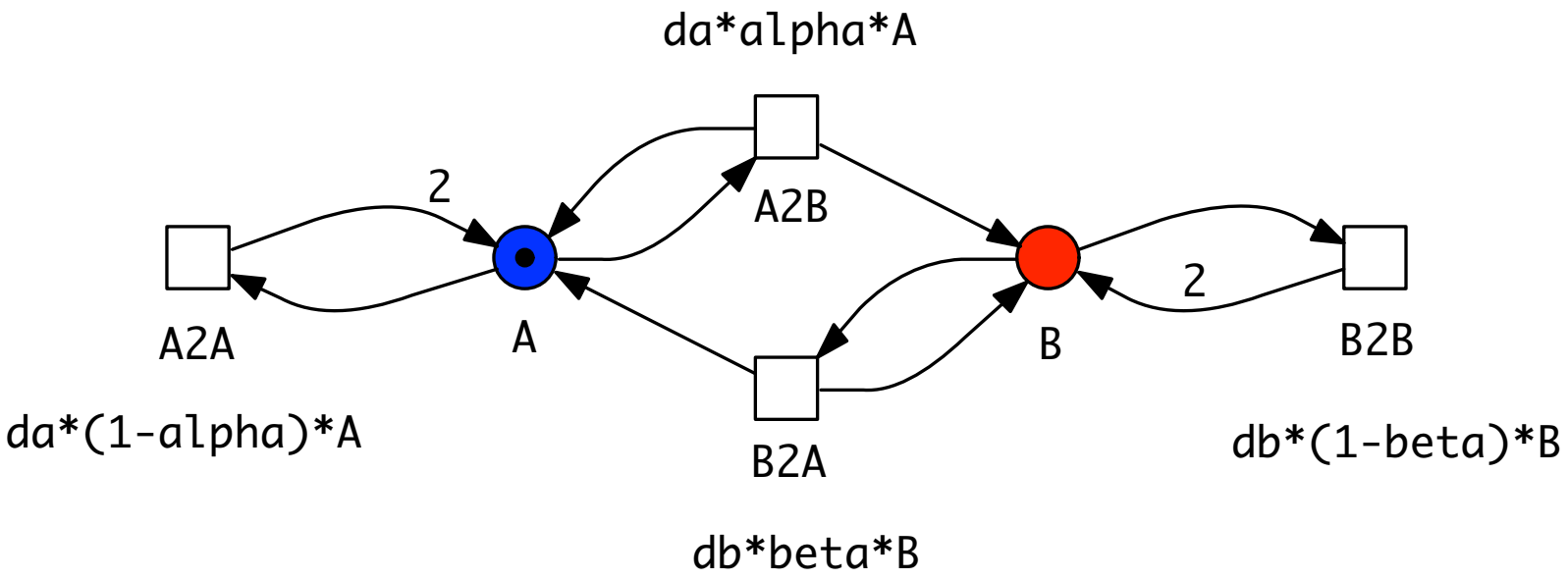
Phase variation is a mechanism of ON–OFF switching that is widely utilized by bacterial pathogens. There is currently no standardization to how the rate of phase variation is determined experimentally.

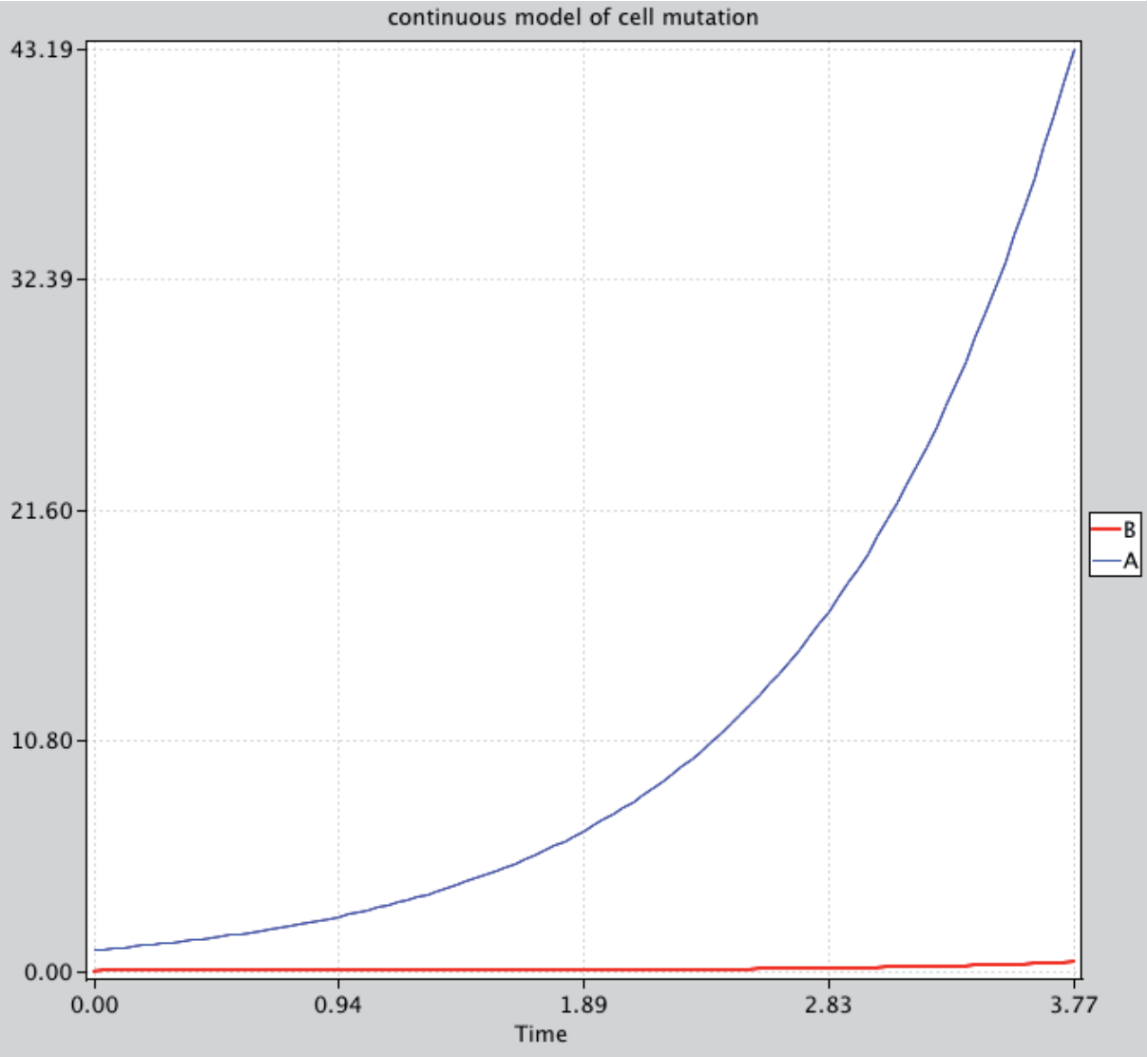
- **two phenotypes: A and B**
- **cell divide**
  - -> *cell division may involve mutation of the offspring*
  - -> *parent cell keeps its phenotype*
- **model parameters**
  - -> *alpha = beta - mutation rates*
  - -> *da, db - fitness of A, B*
  - -> *da/db - relative fitness*
- **output**
  - -> *total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



EX3: CELL COLONIES, PETRI NET



EX3: CELL COLONIES, CONTINUOUS PLOT



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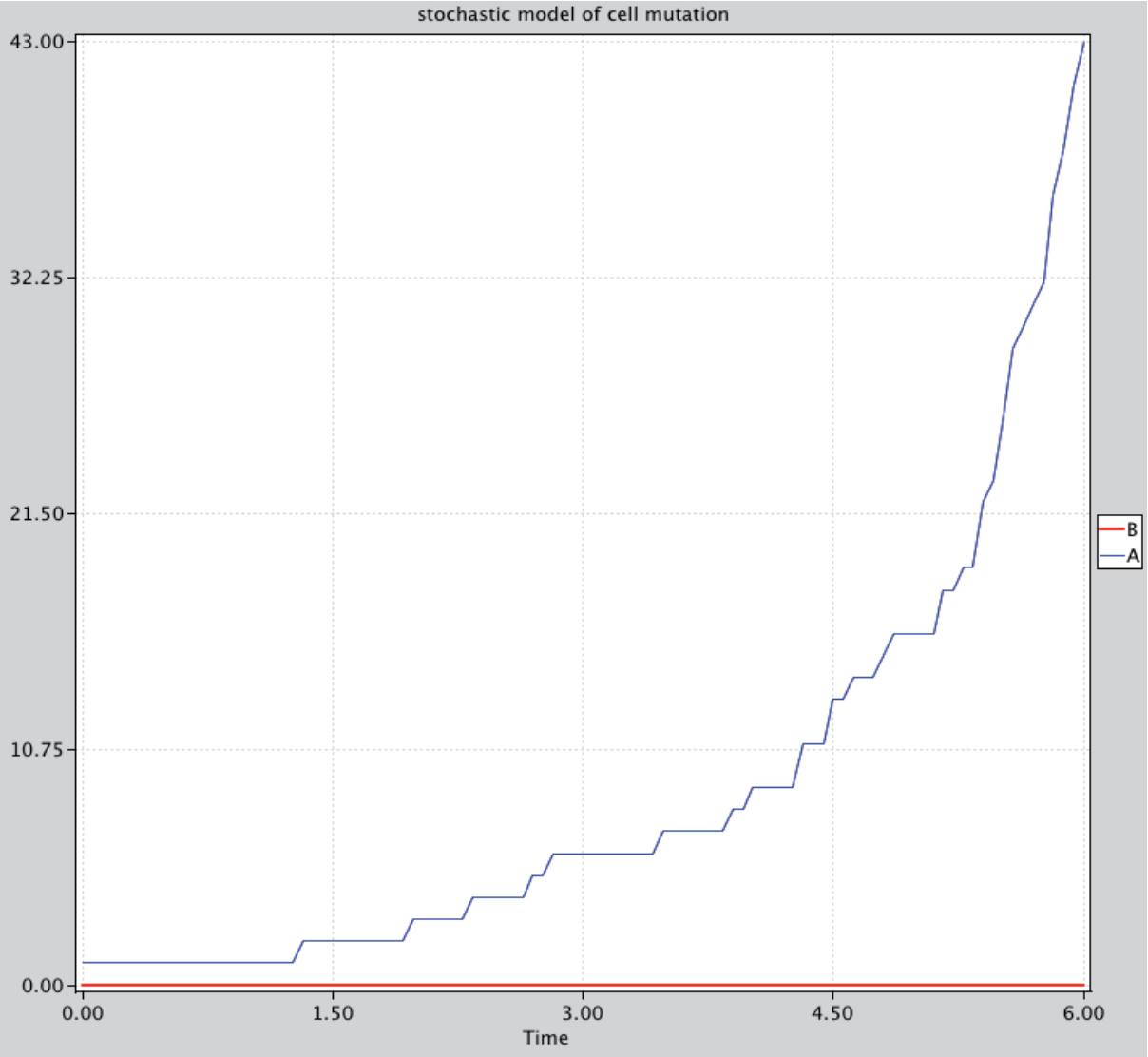
EX3: CELL COLONIES, STOCHASTIC PLOT



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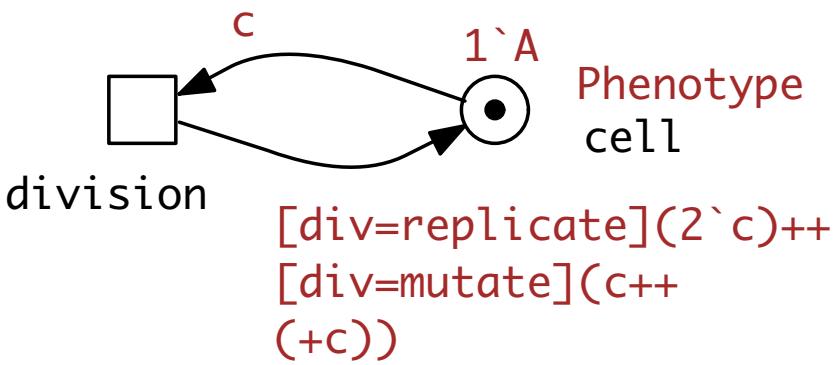
EX3: CELL COLONIES, BASIC MODEL

colorset Phenotype = **enum with** A, B;
colorset DivisionType = **enum with** replicate , mutate ;




```
(c=A) & (div=replicate) : cell*da*(1-alpha)
(c=A) & (div=mutate) : cell*(da*alpha)
(c=B) & (div=replicate) : cell*(db*(1-beta))
(c=B) & (div=mutate) : cell*(db*beta)
```

colorset Phenotype = **enum with** A, B;
colorset DivisionType = **enum with** replicate , mutate ;

ADDING SPACE

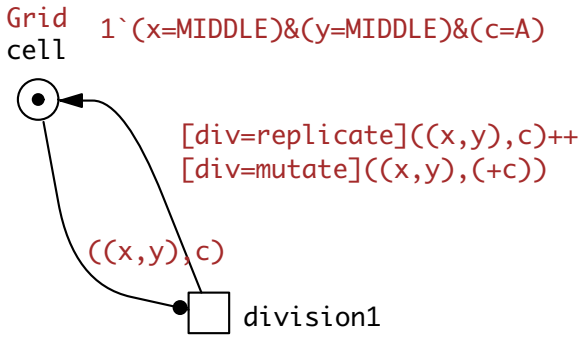
CONTROLLING COLONY SPREADING

CONTROLLING THICKNESS

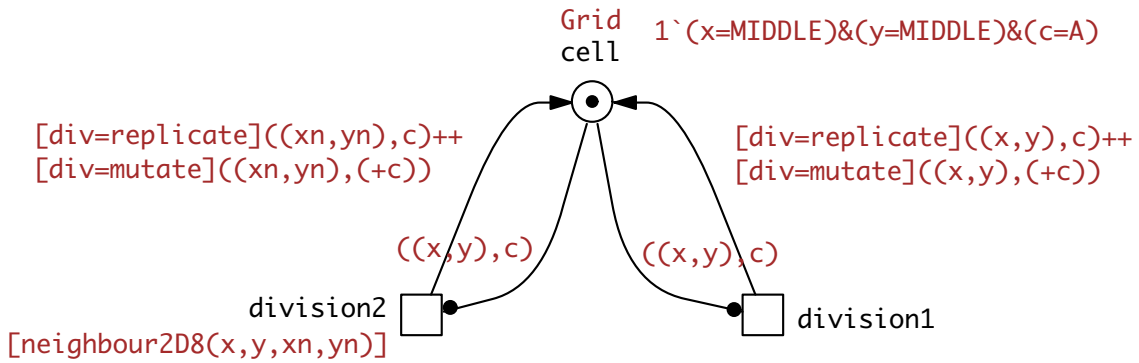
```
(c=B) & (div=mutate) : cell*(db*beta)
```

CONTROLLING COLONY SIZE

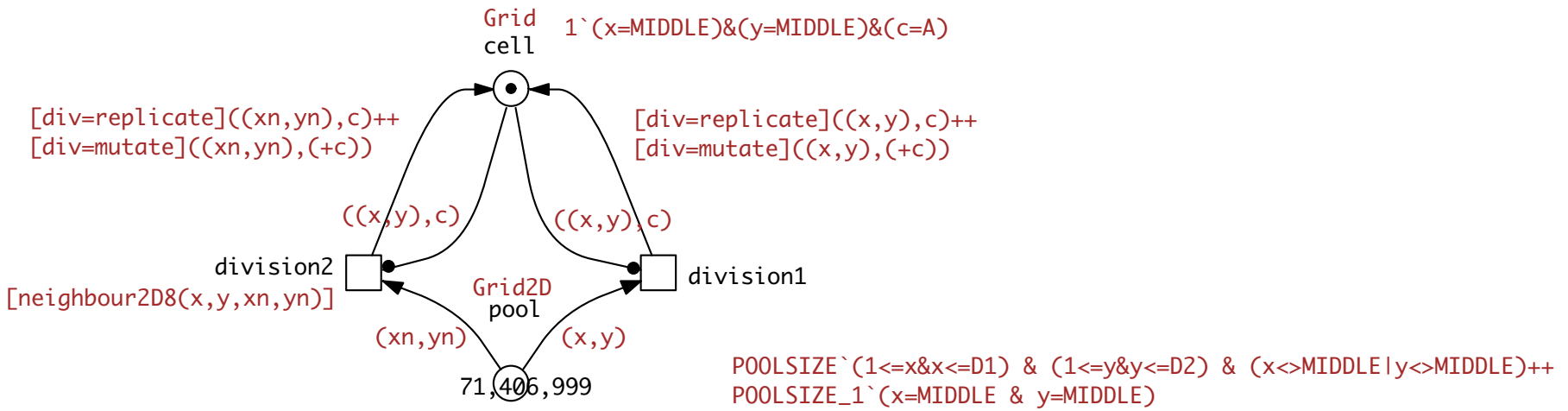
colorset Grid = **product with** Grid2D x Phenotype;



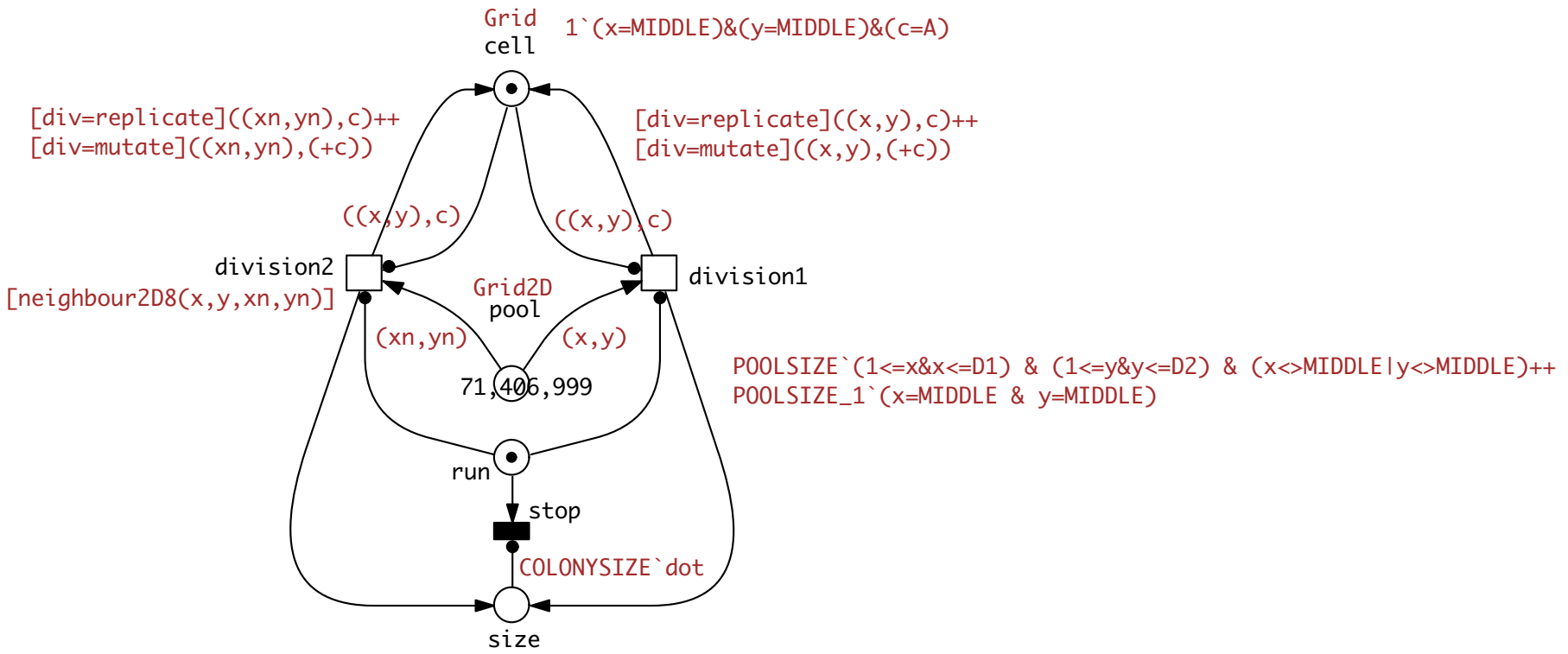
colorset Grid = **product with** Grid2D x Phenotype;



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



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

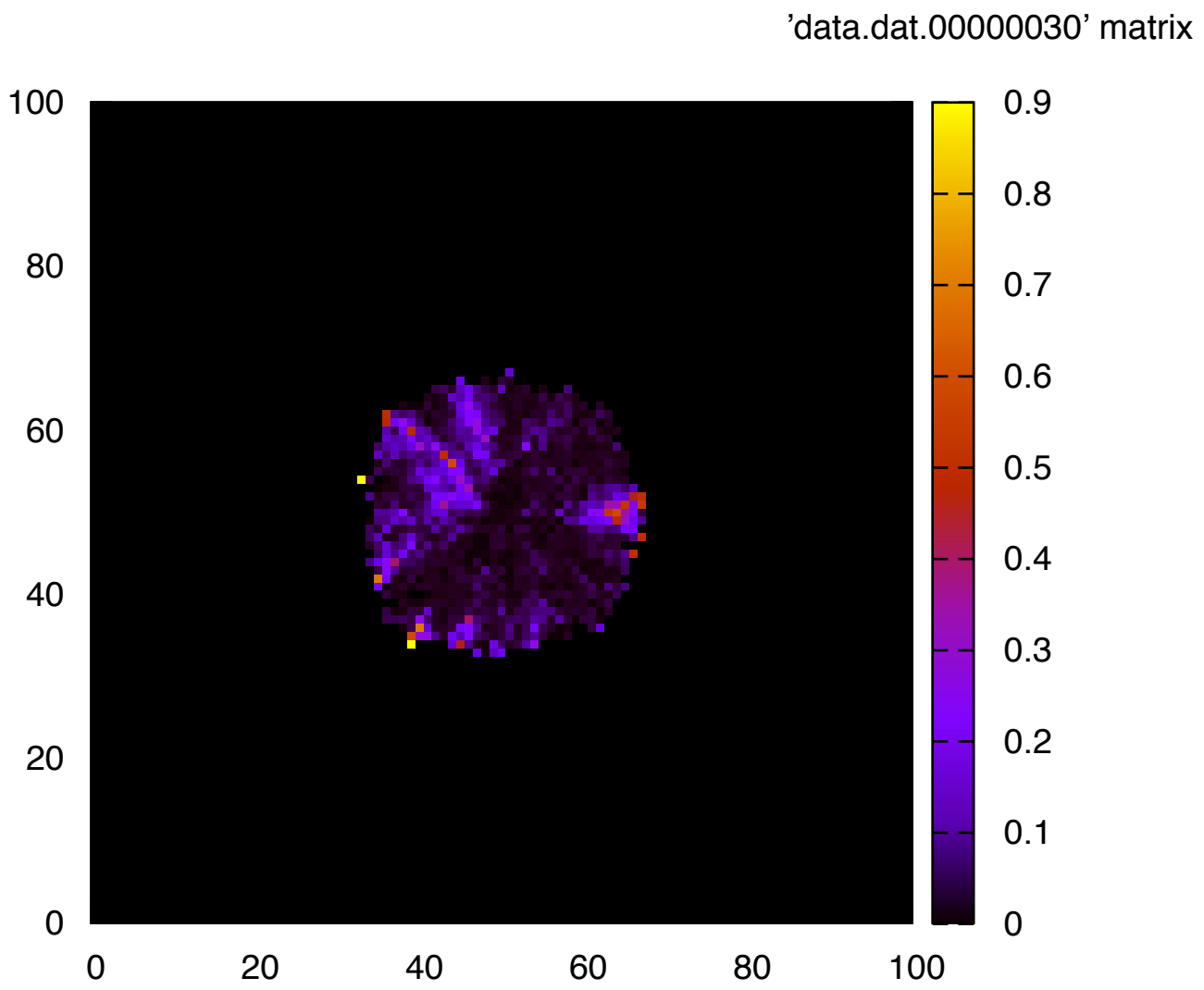
-> *61 x 61 grid: 11,163 P / 131,044 T; unfolding: 152 sec;*

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

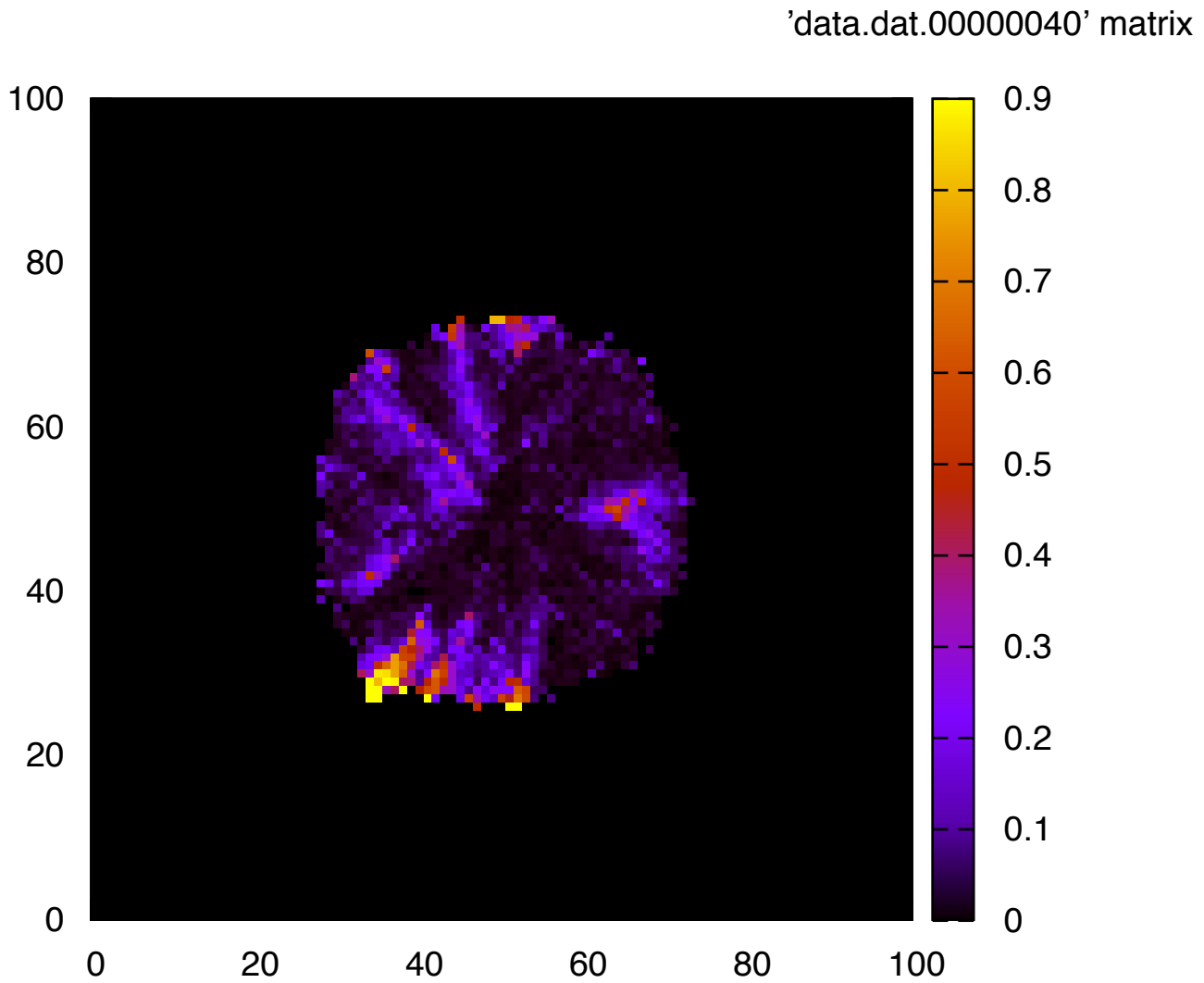
-> *runtime 1 stoch. simulation: 35-40 minutes*

. . . SOME EXPERIMENTS

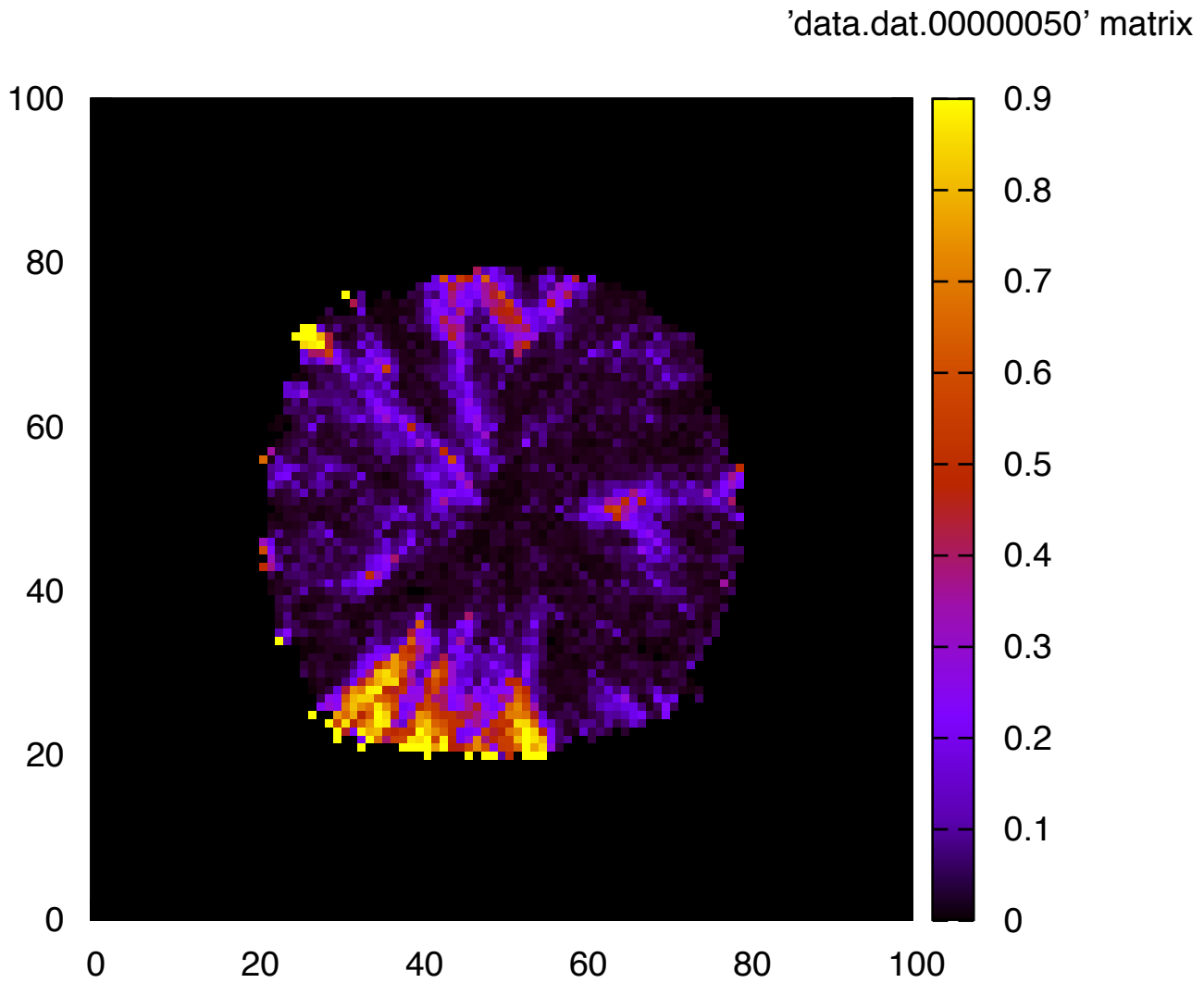
EX3: 2D - TRACE 1 (HIGH, F=1)



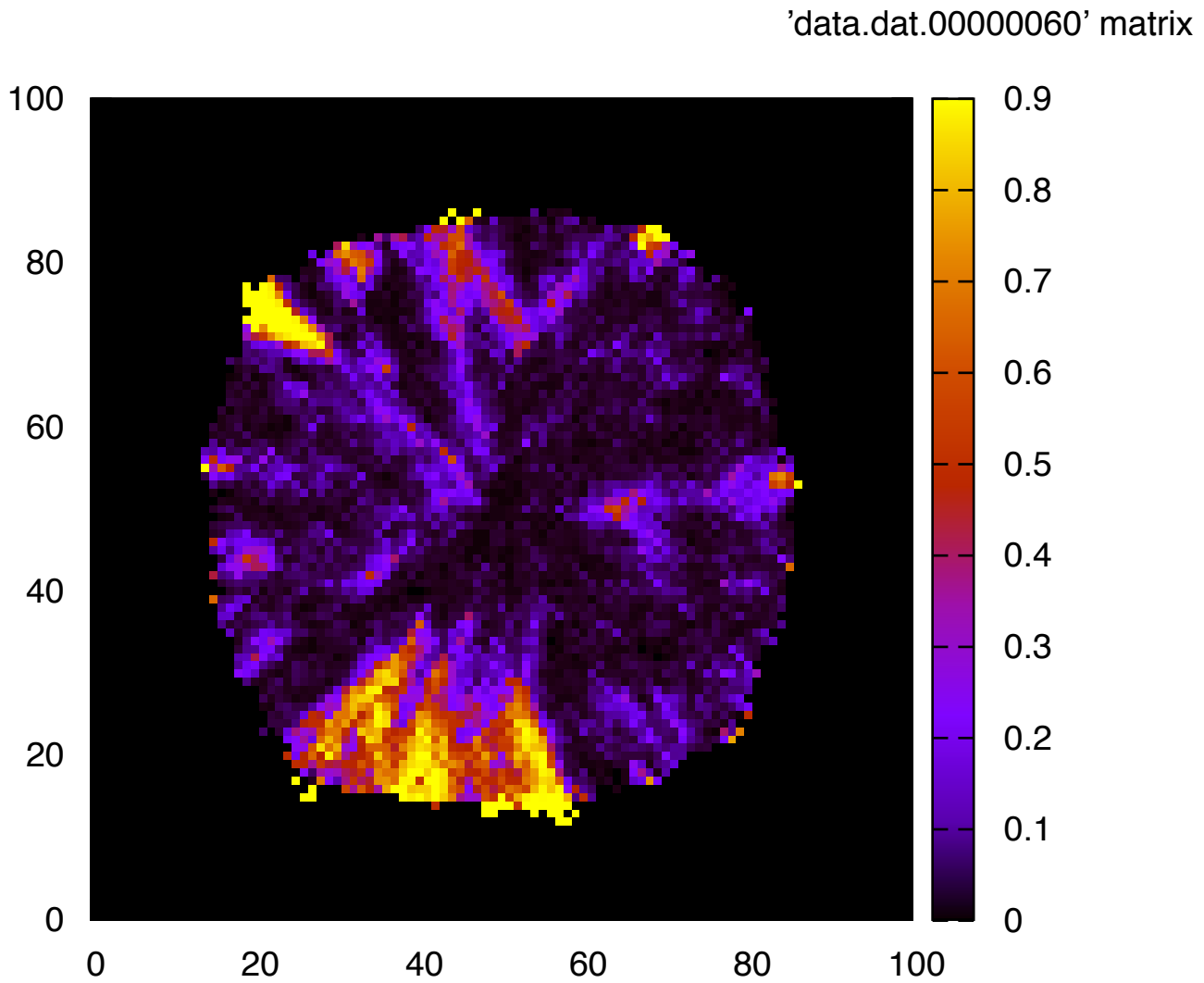
EX3: 2D - TRACE 1 (HIGH, F=1)



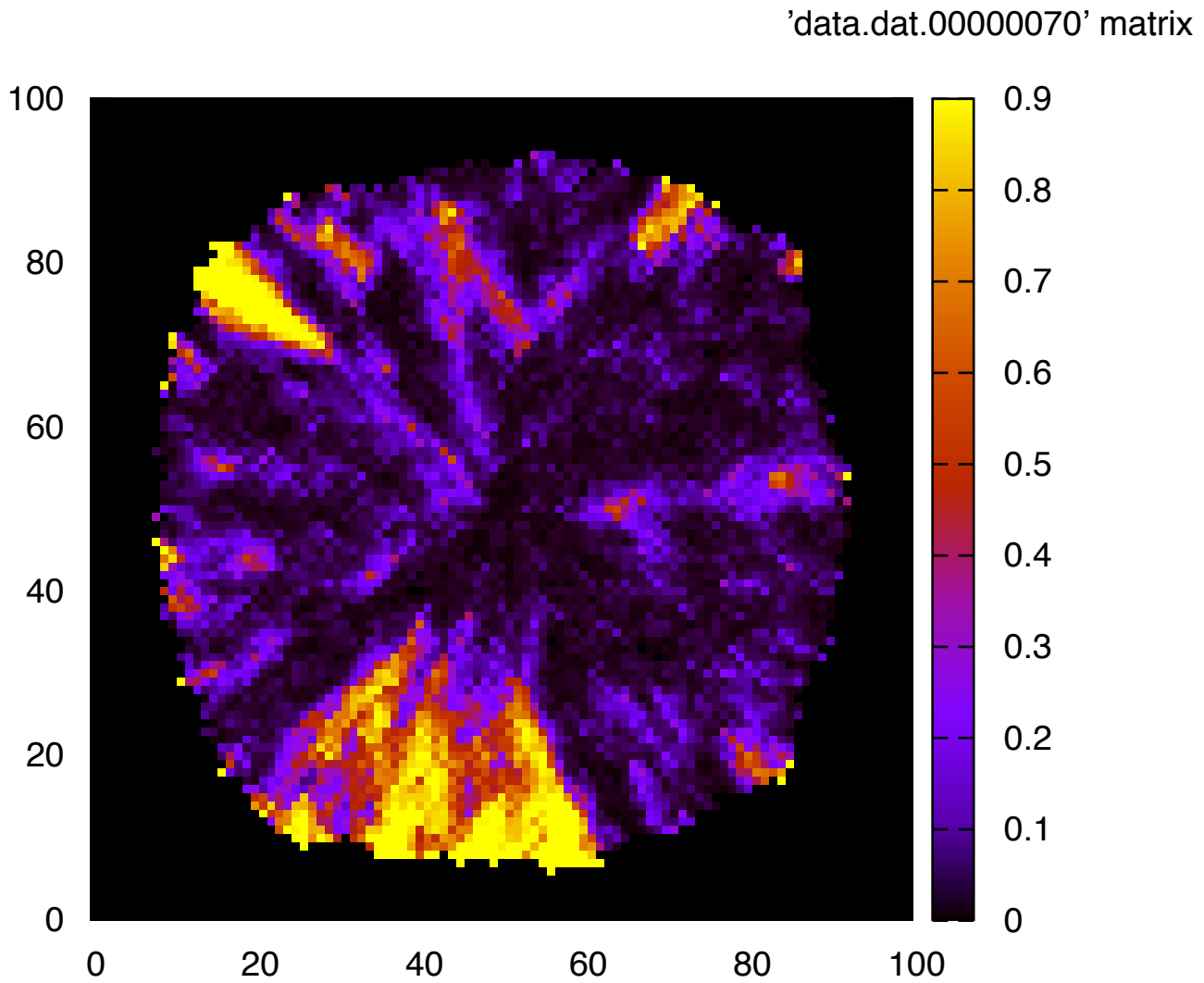
EX3: 2D - TRACE 1 (HIGH, F=1)



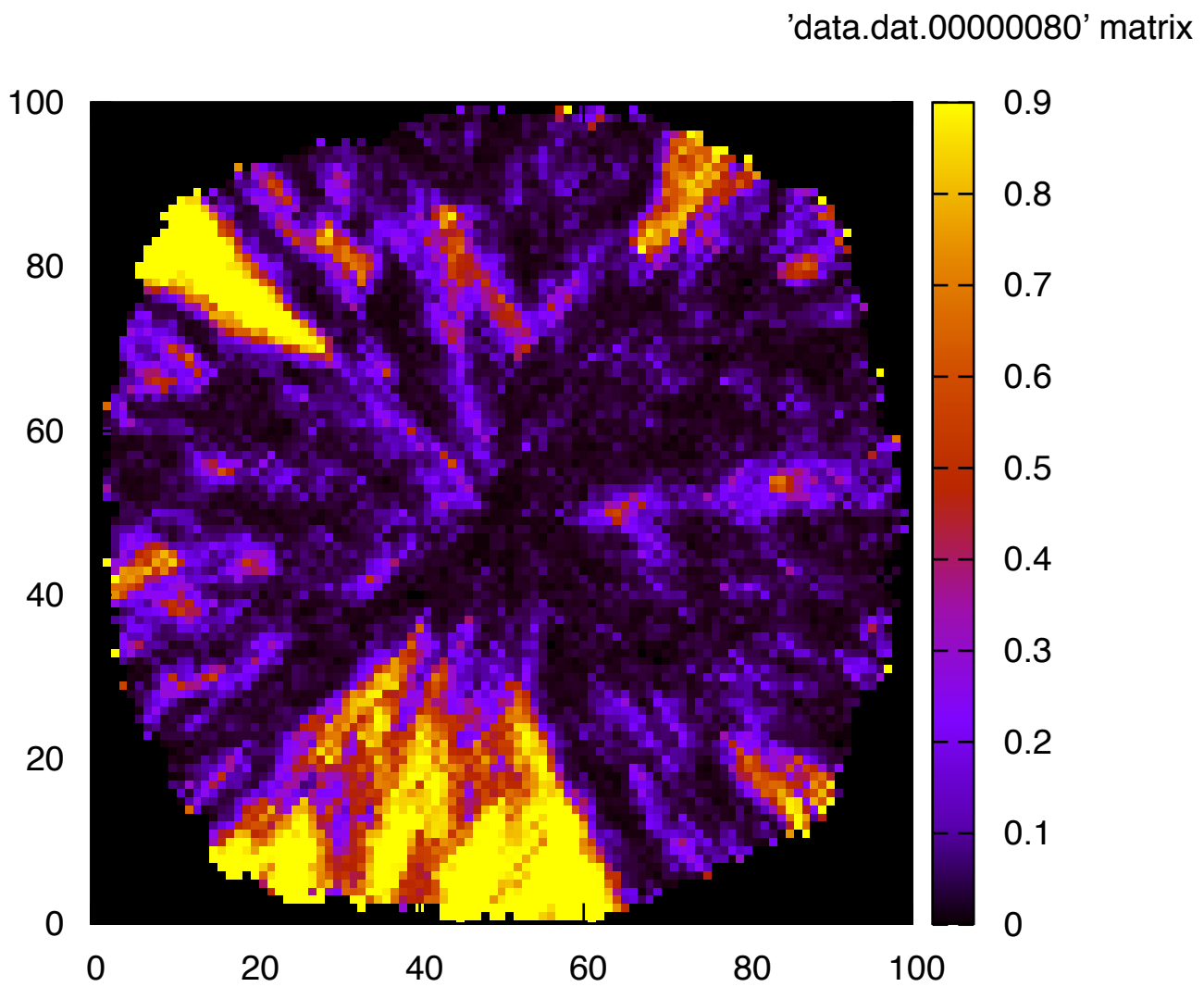
EX3: 2D - TRACE 1 (HIGH, F=1)



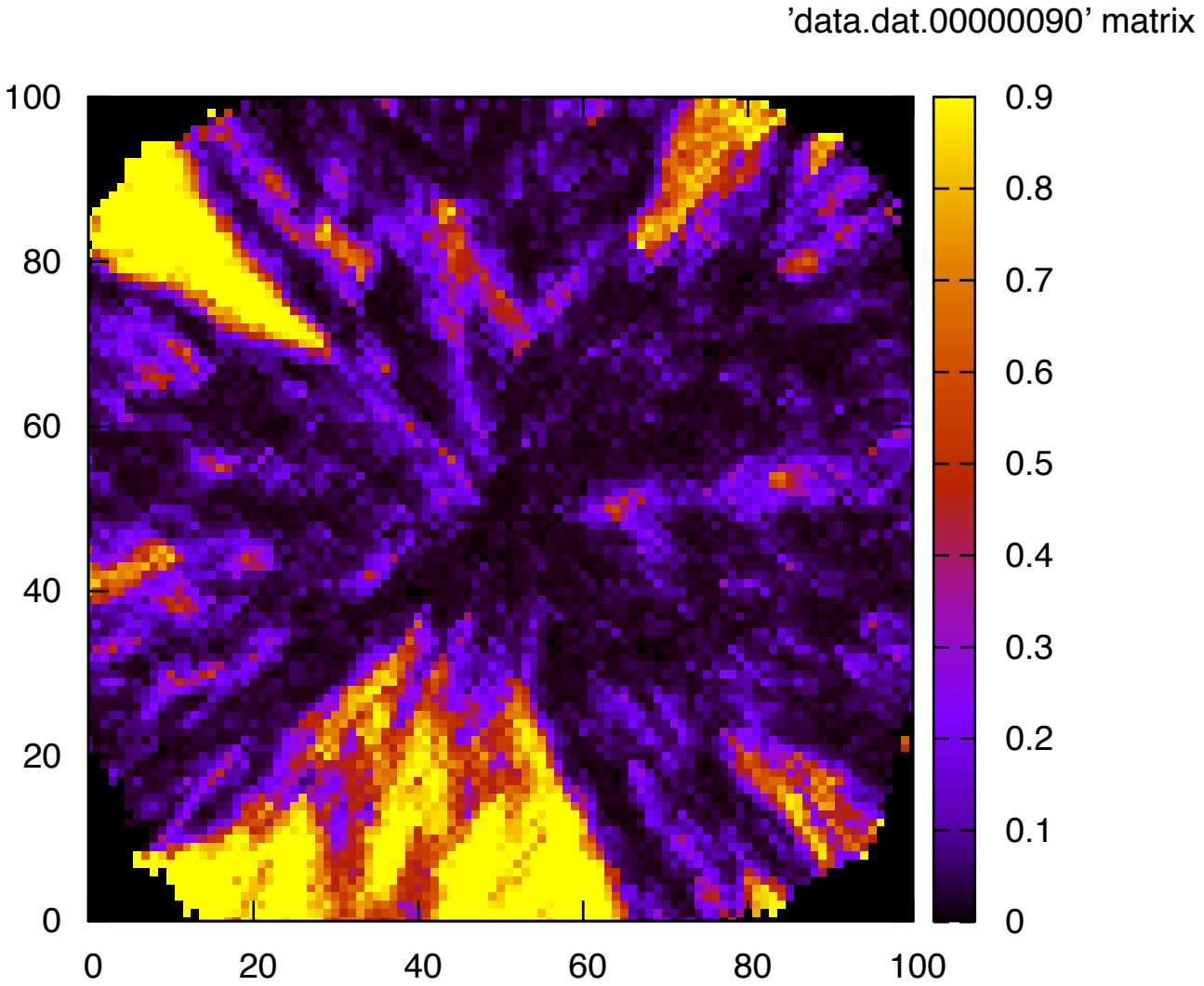
Ex3: 2D - Trace 1 (High, F=1)



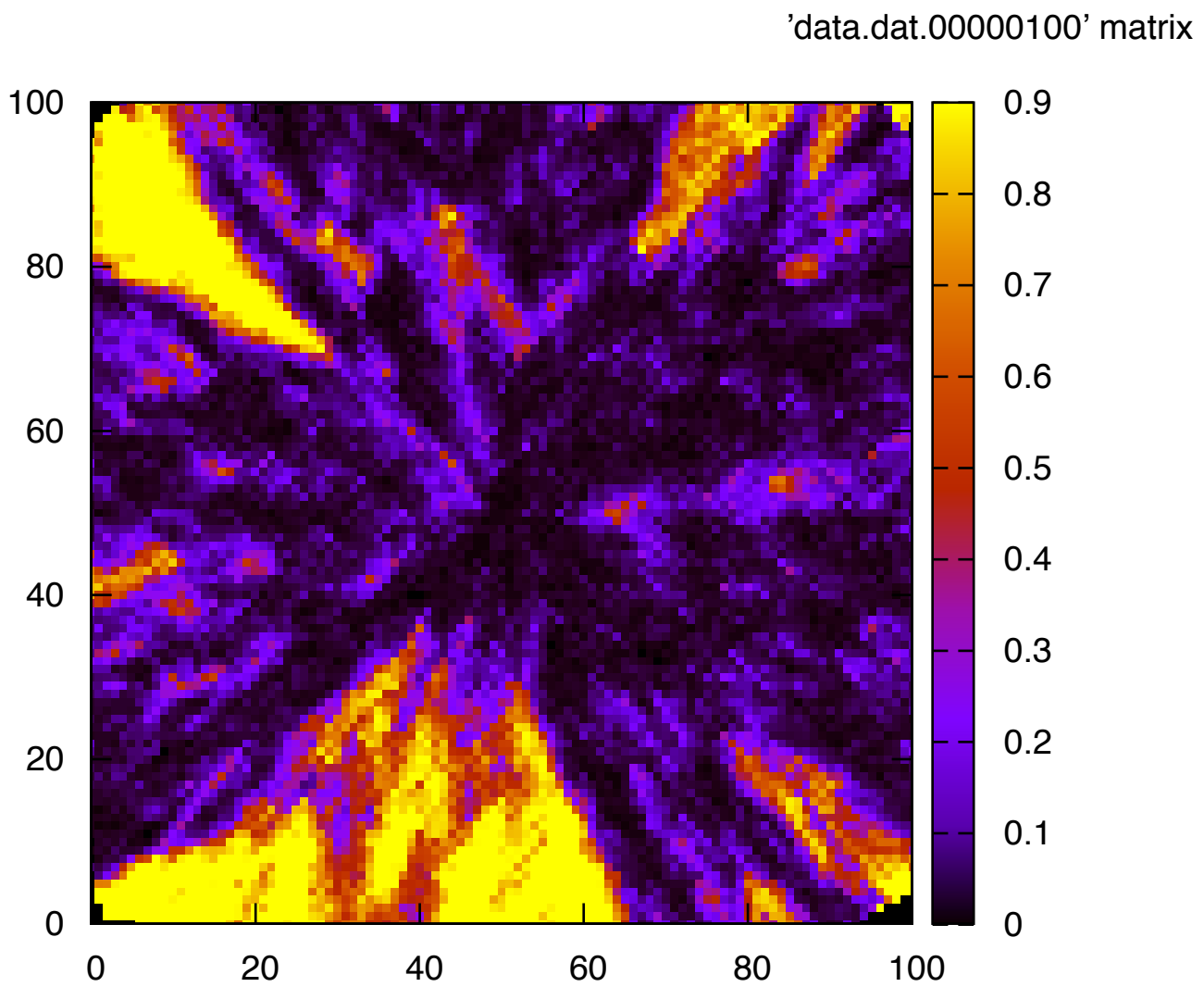
EX3: 2D - TRACE 1 (HIGH, F=1)



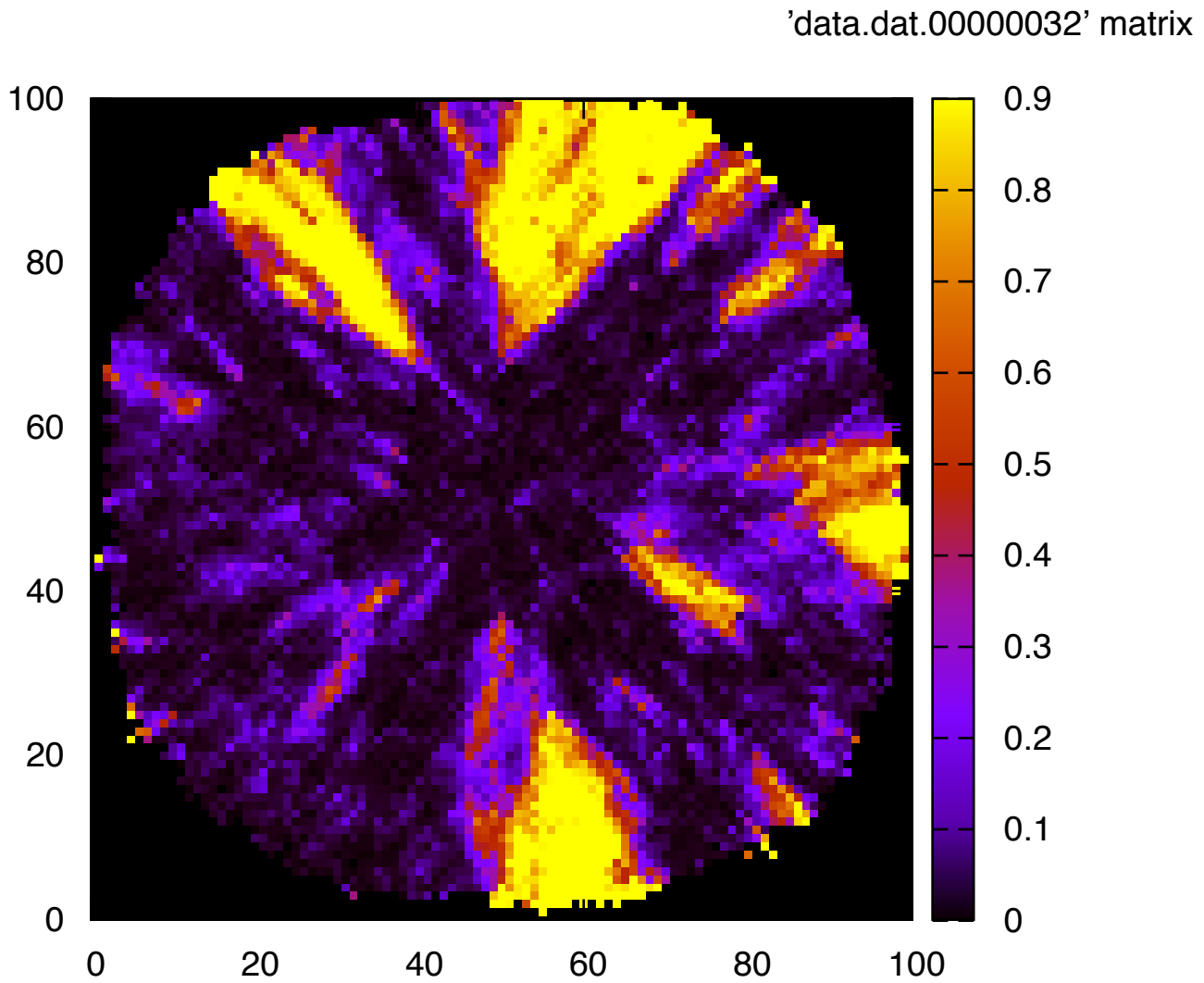
EX3: 2D - TRACE 1 (HIGH, F=1)



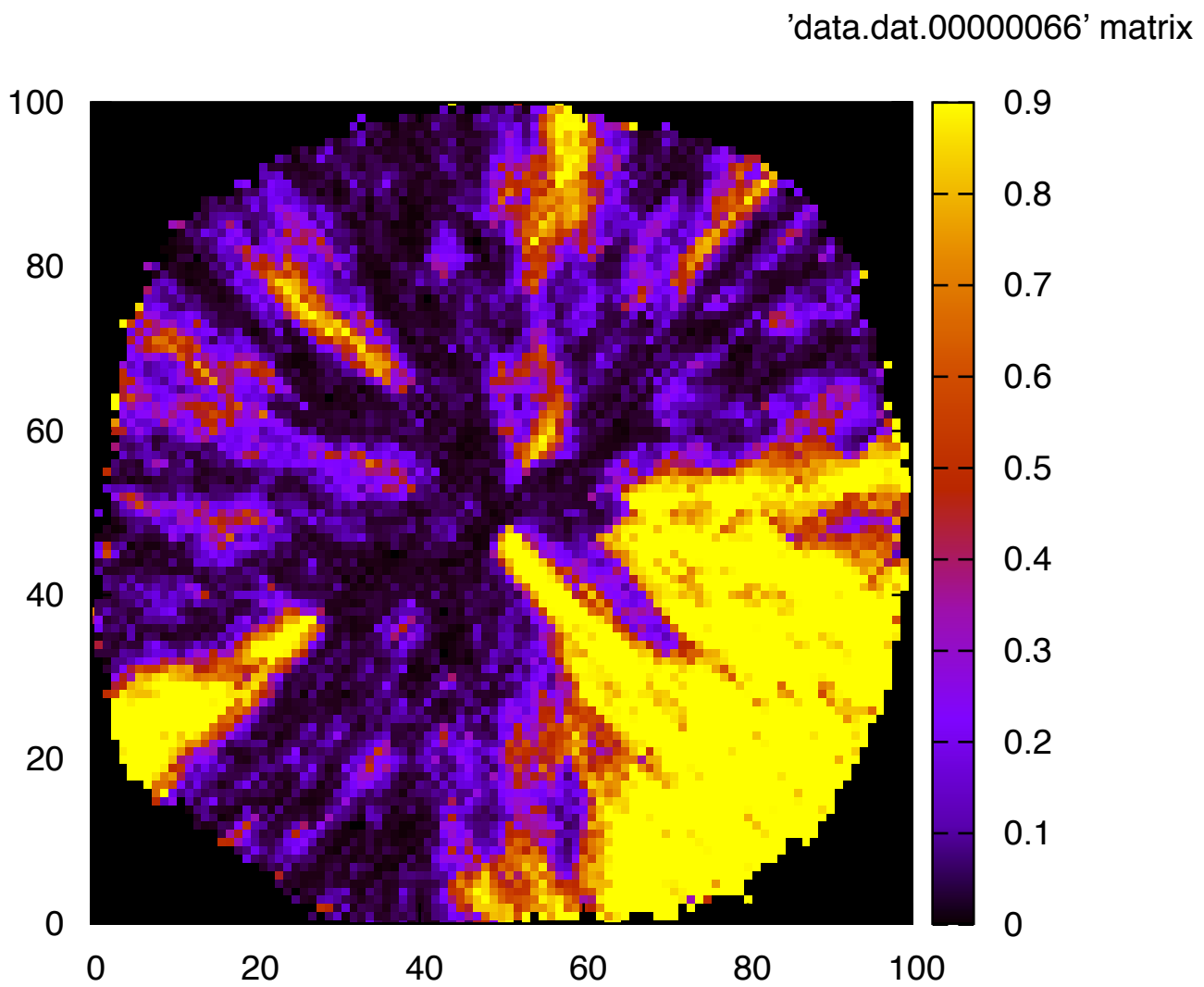
EX3: 2D - TRACE 1 (HIGH, F=1)



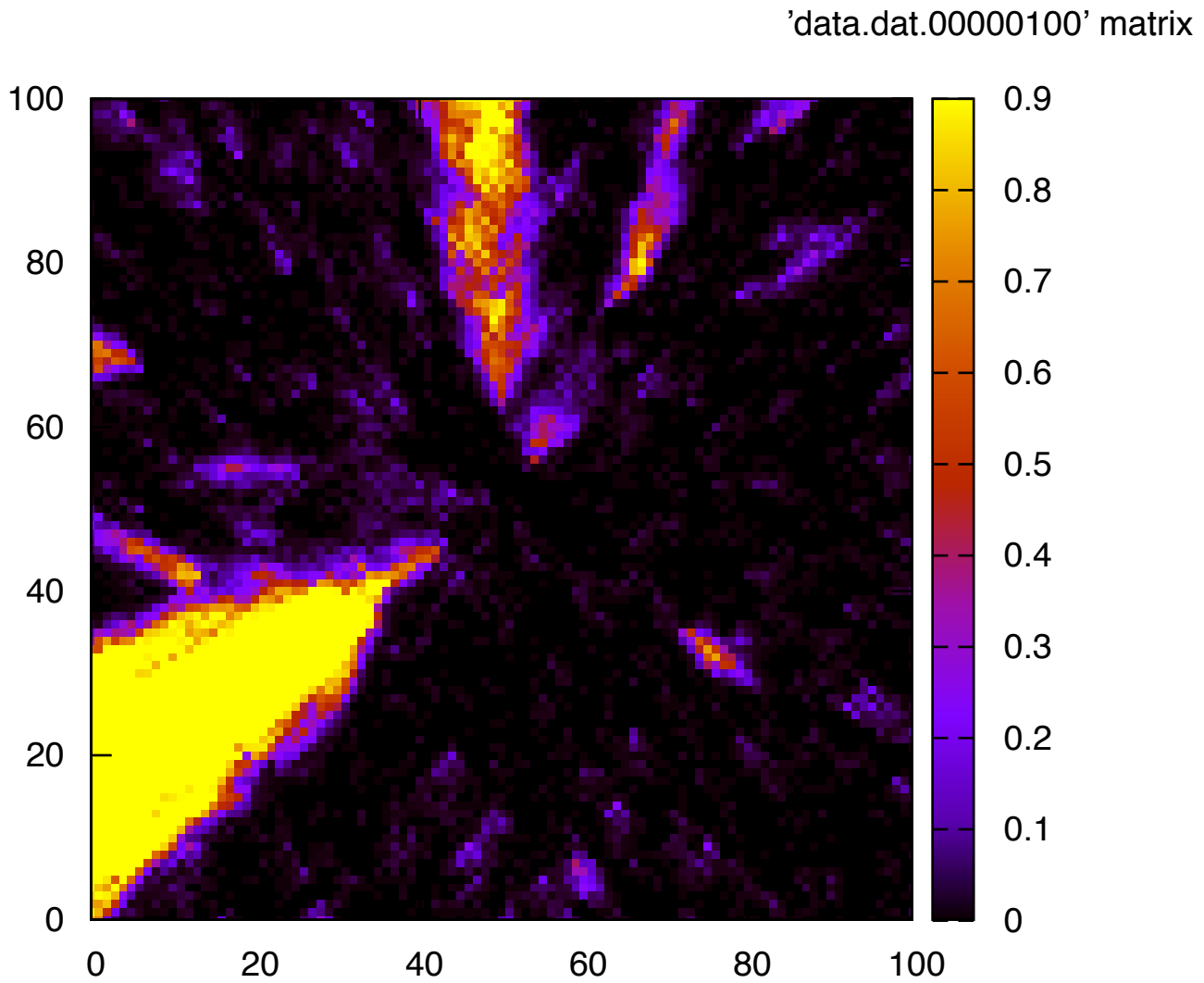
EX3: 2D - TRACE 2 (HIGH, F=1)



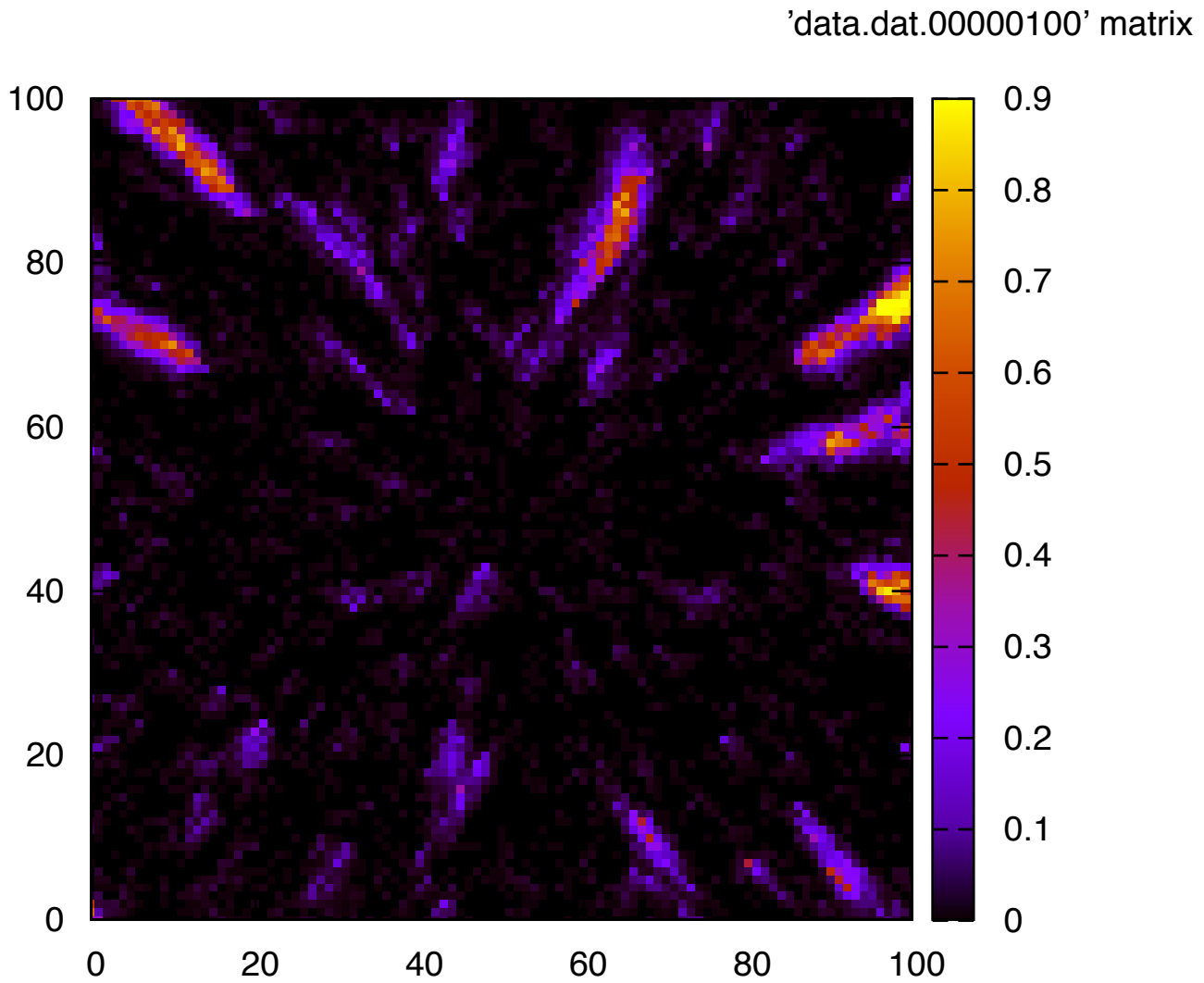
EX3: 2D - TRACE 3 (HIGH, F=1)



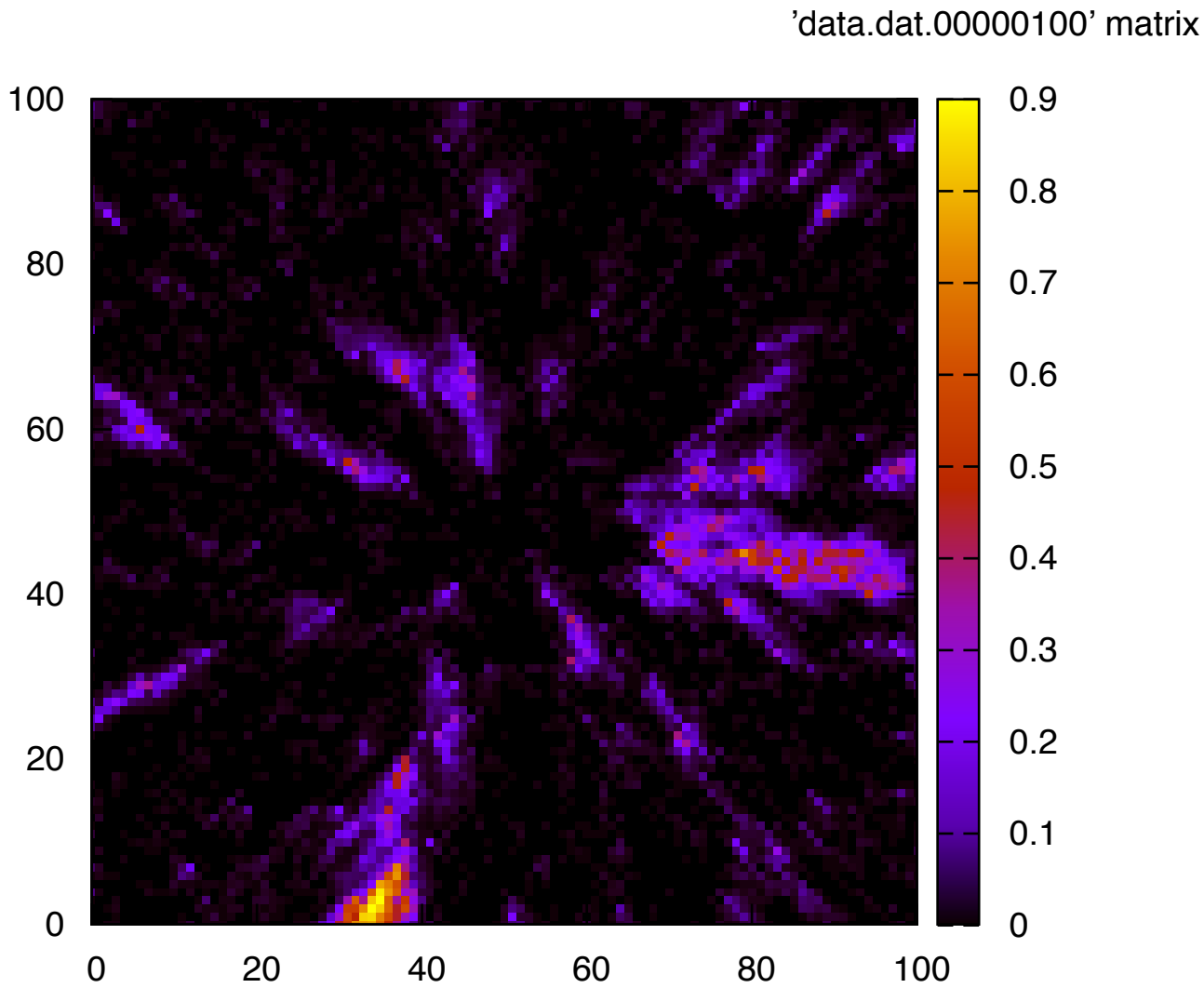
EX3: 2D - VARYING FITNESS, TRACE 1 (MEDIUM, F=1)



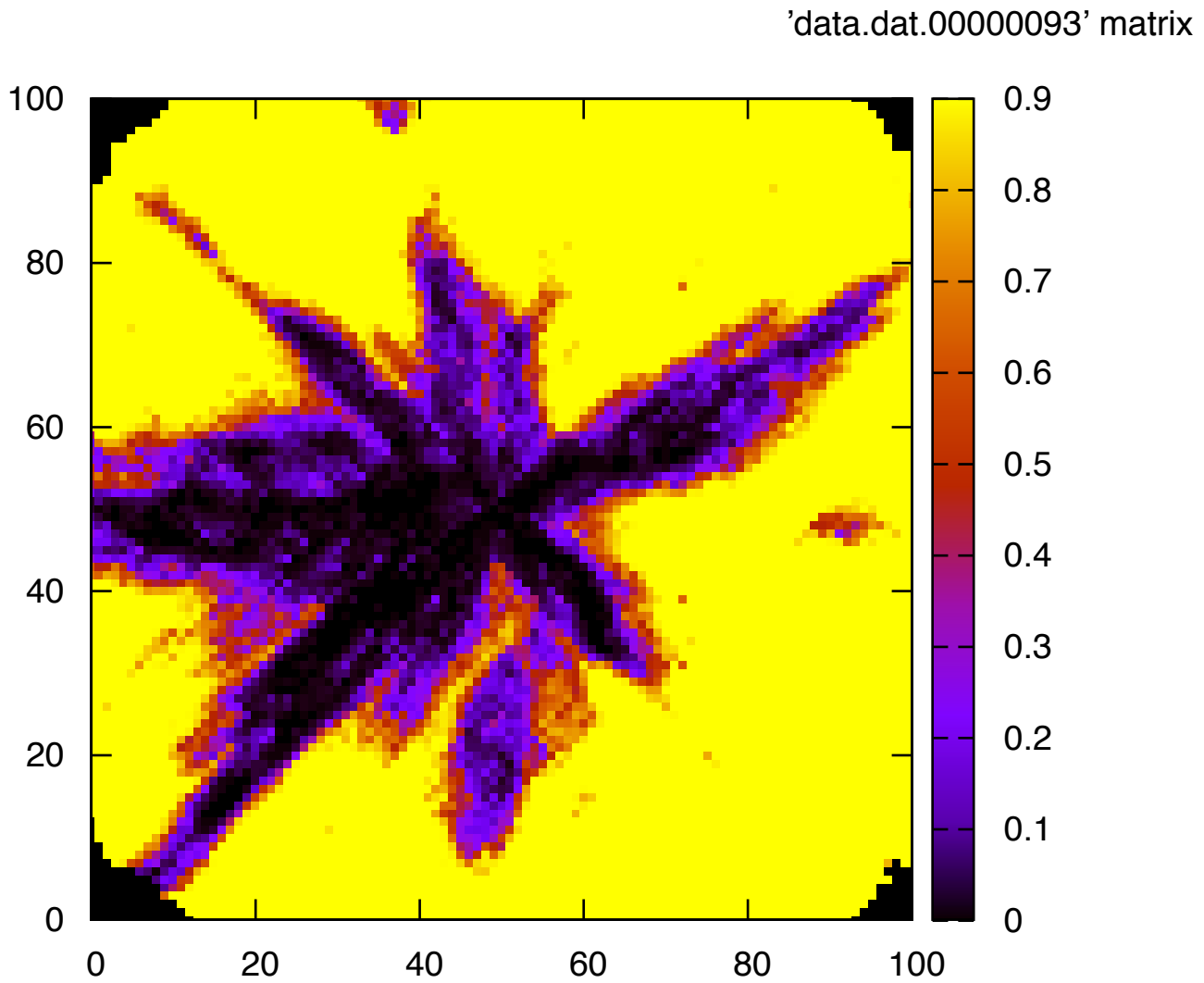
EX3: 2D - VARYING FITNESS, TRACE 2 (MEDIUM, F=1)



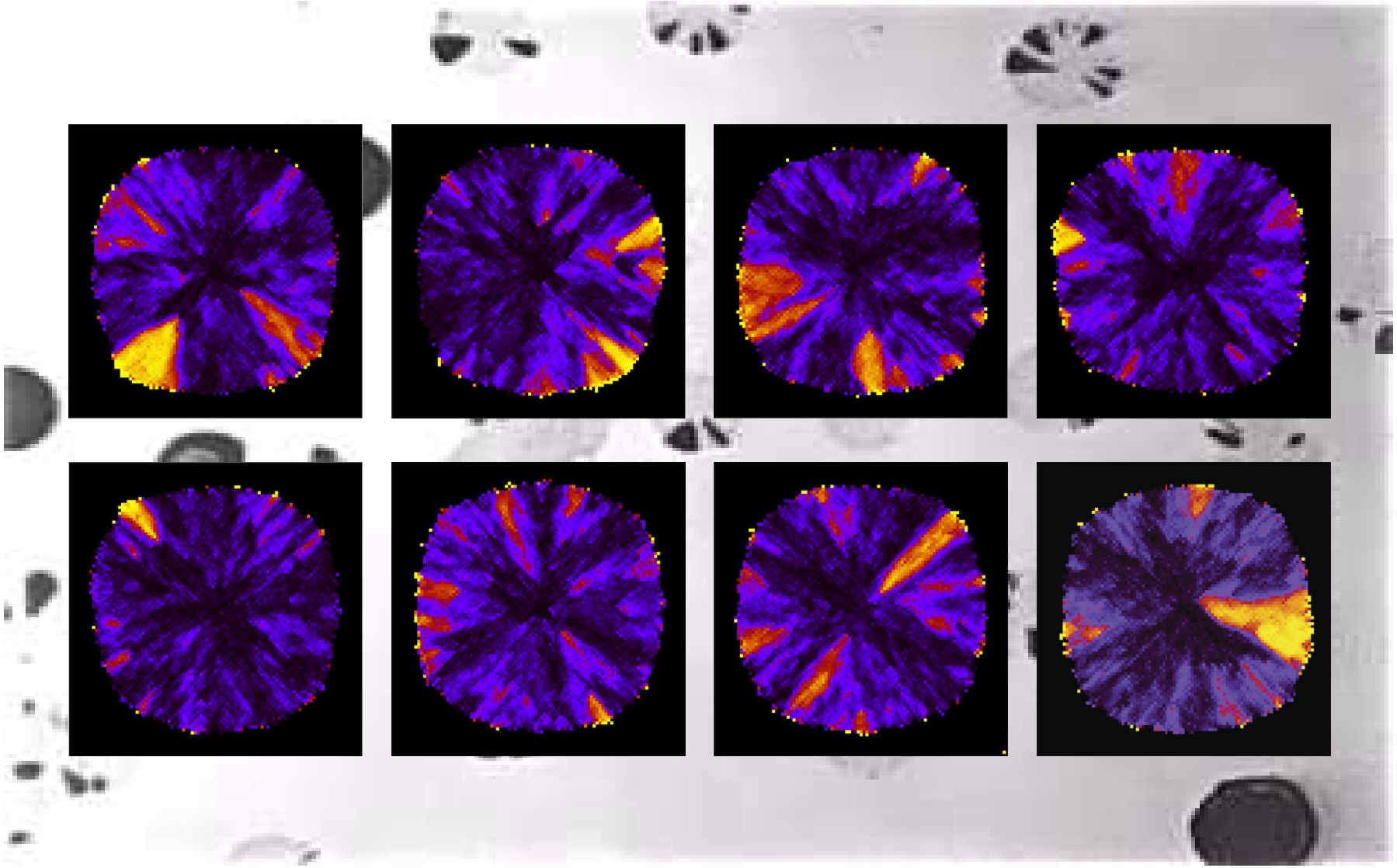
EX3: 2D - VARYING FITNESS, TRACE 1 (MEDIUM, F=0.99)



EX3: 2D - VARYING FITNESS, TRACE 1 (MEDIUM, F=0.90)

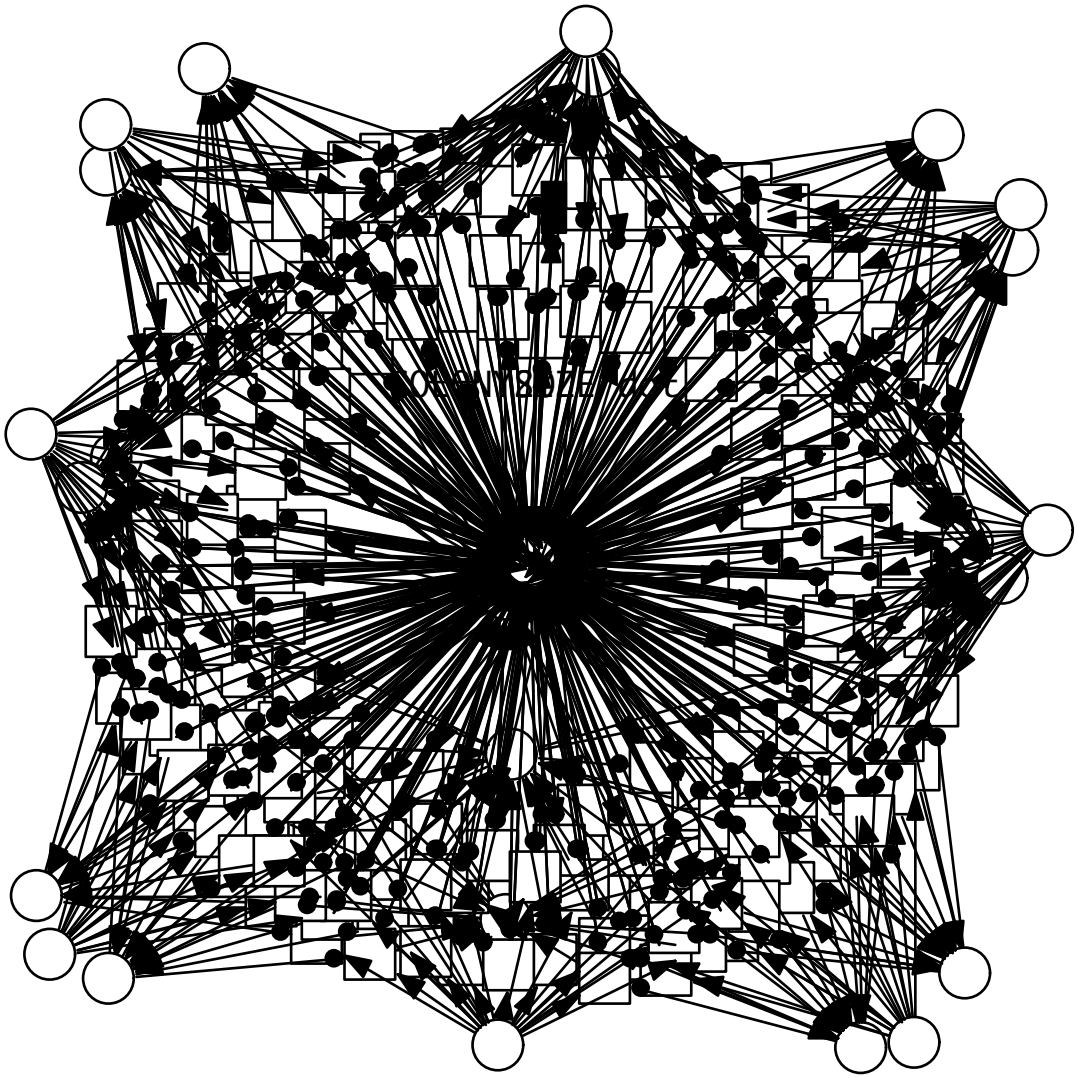


Ex3: Some Final States (High, F=1)



monika.heiner@b-tu.de

EX3: PLAIN MODEL (3X3)

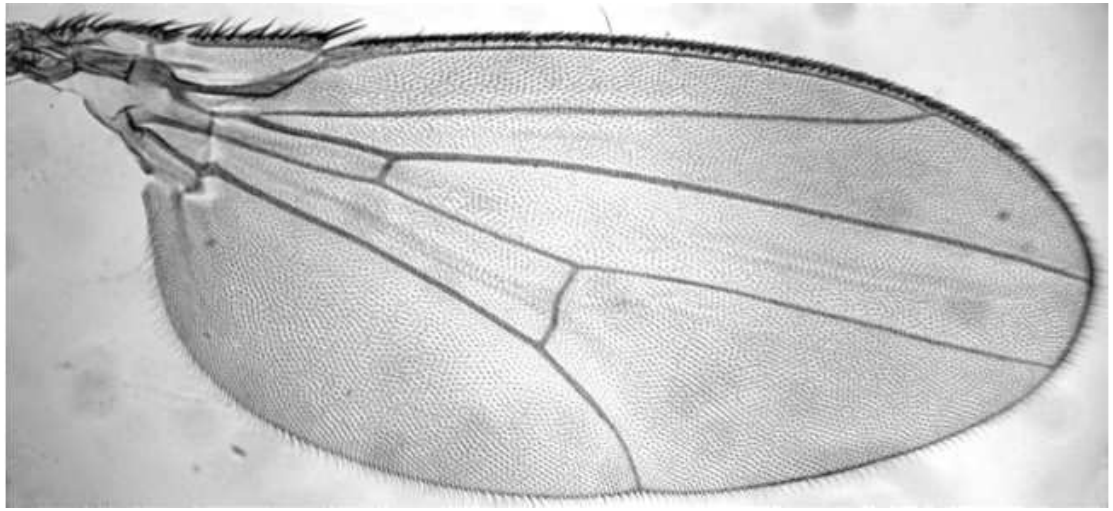


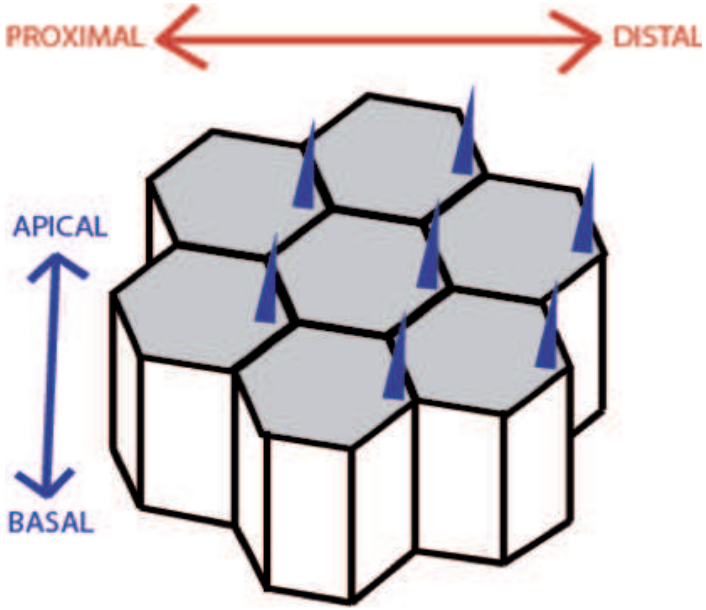
EXAMPLE 4:

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.

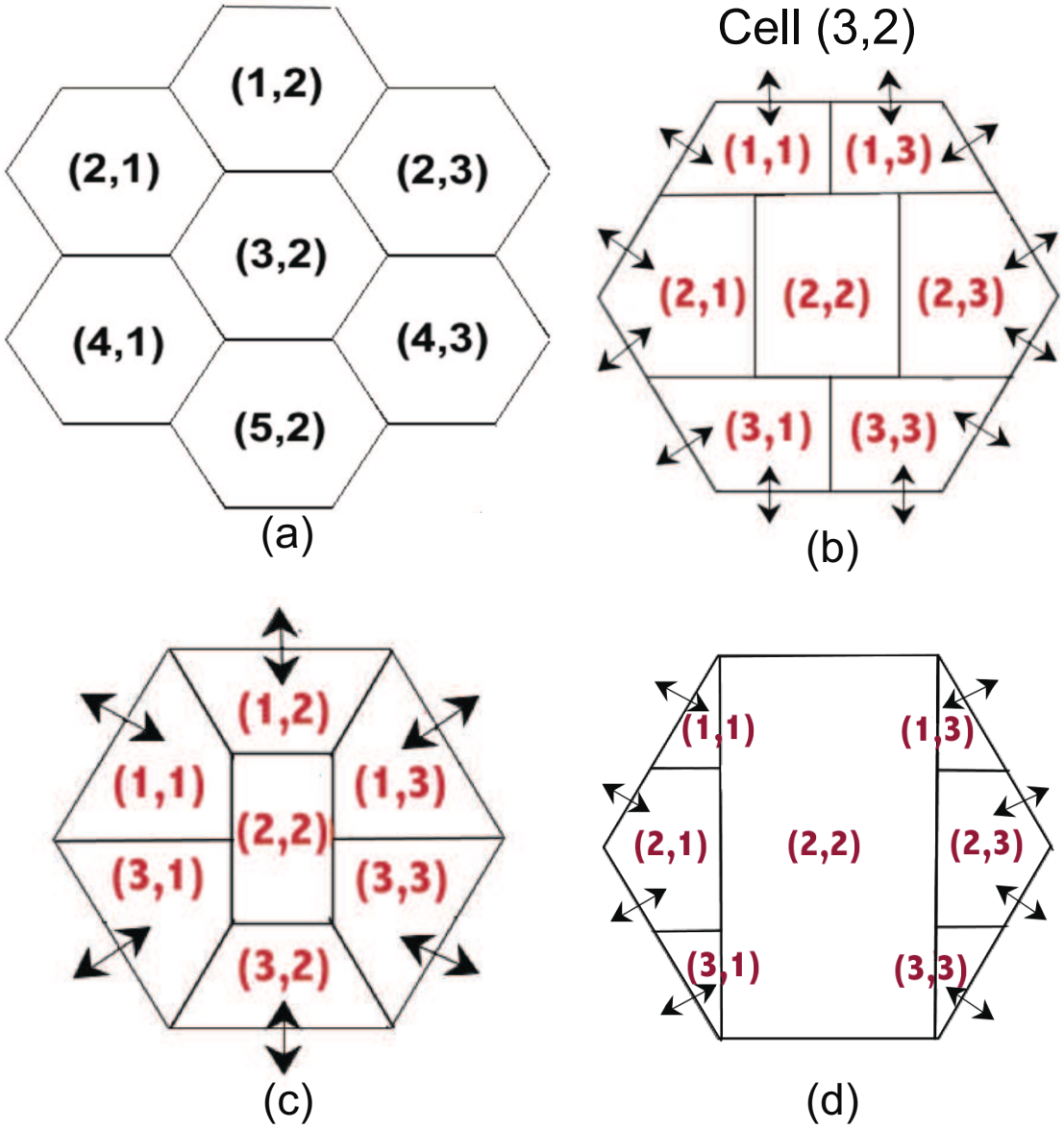
EX4: PLANAR CELL POLARITY



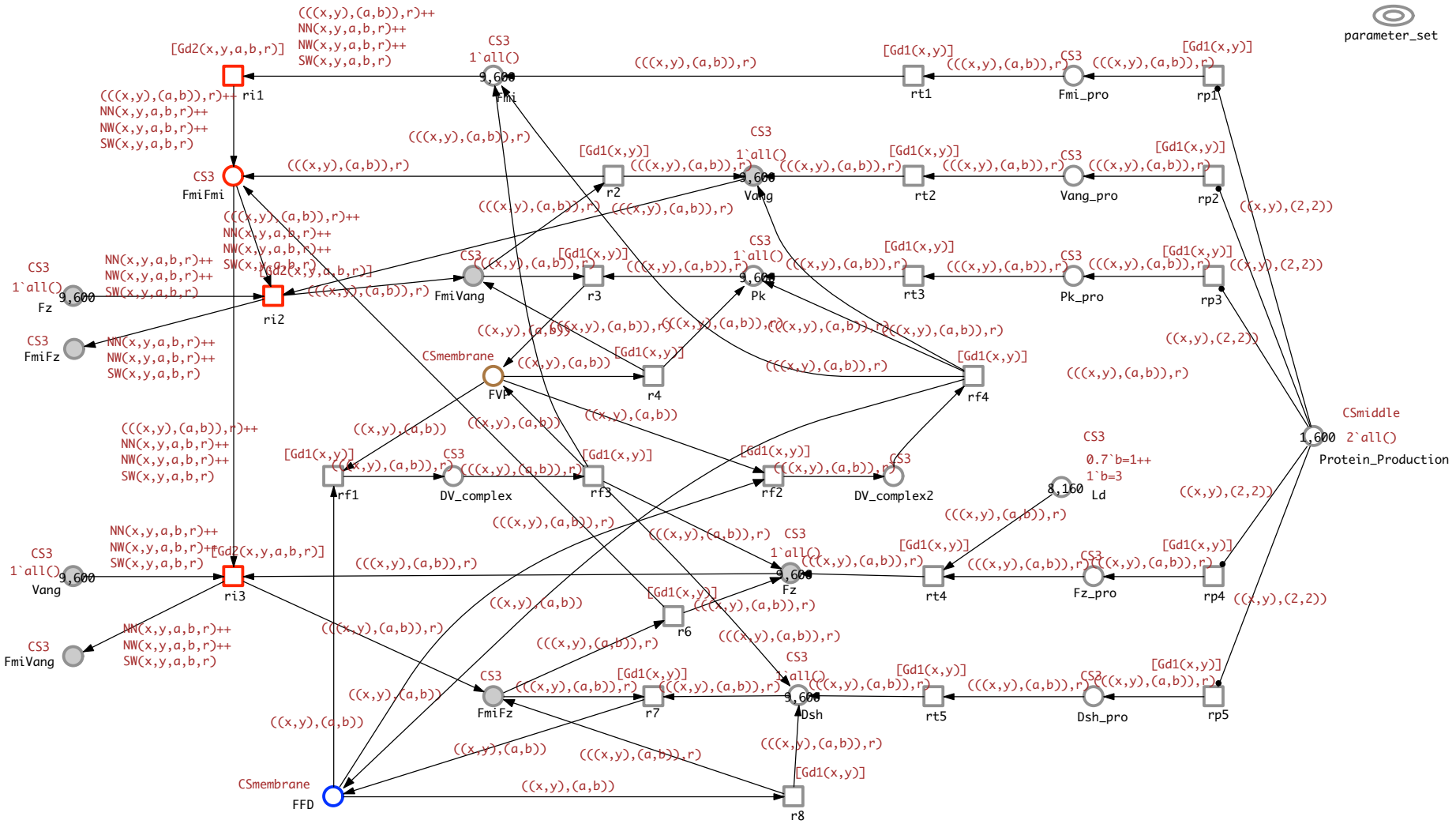


[BIOPPN 2011]
[CMSB 2011]

EX4: PLANAR CELL POLARITY

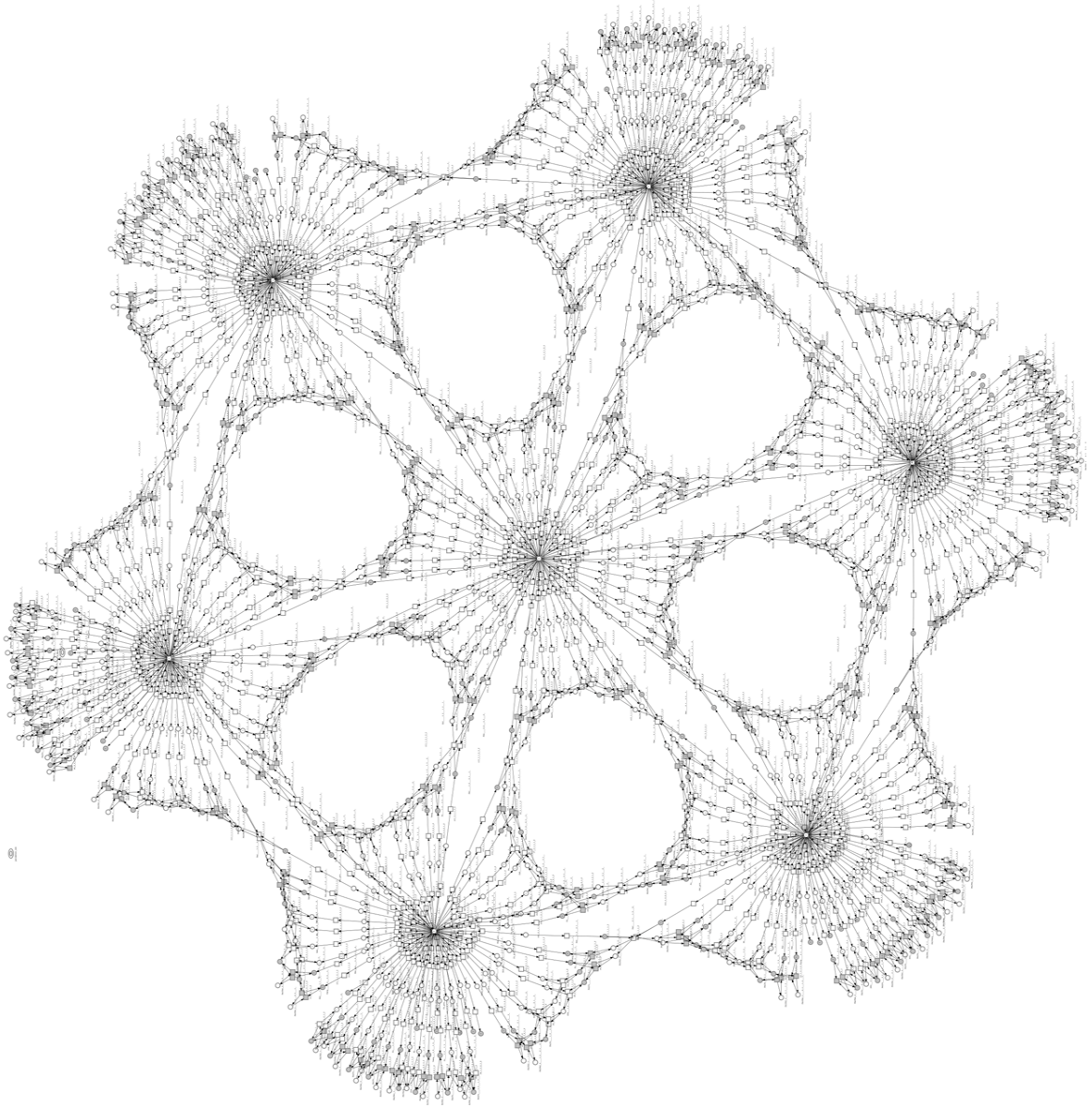


EX4: PLANAR CELL POLARITY

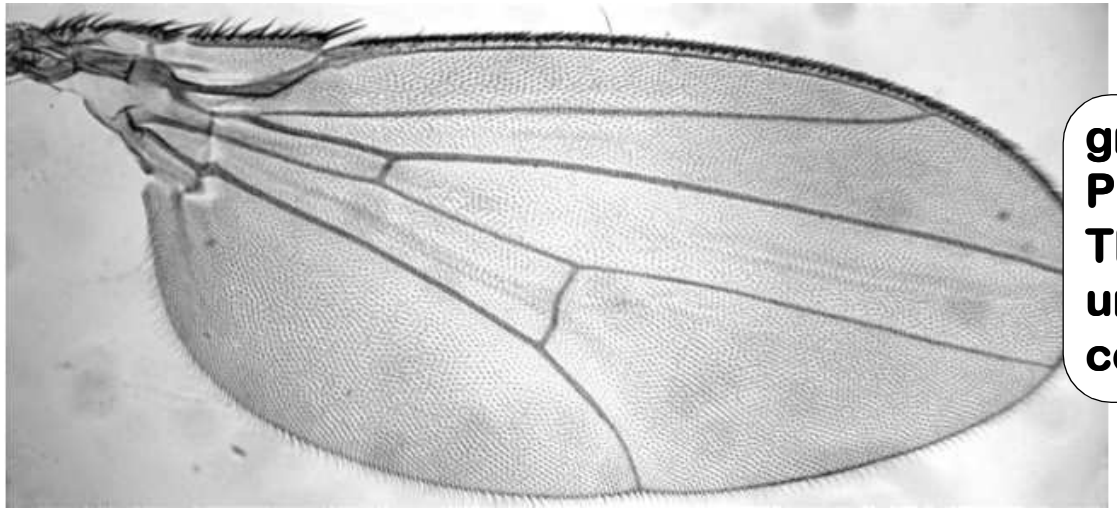


[QIAN GAO, PHD THESIS 2013]

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



EX4 - PLANAR CELL POLARITY



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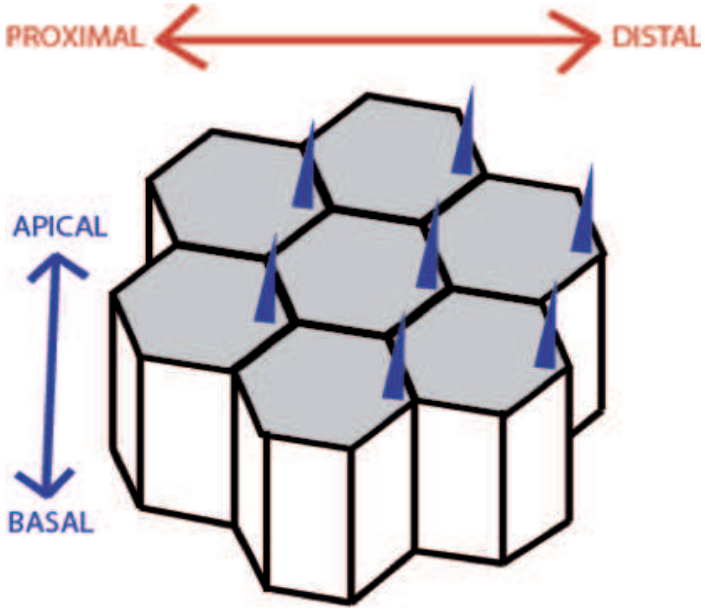
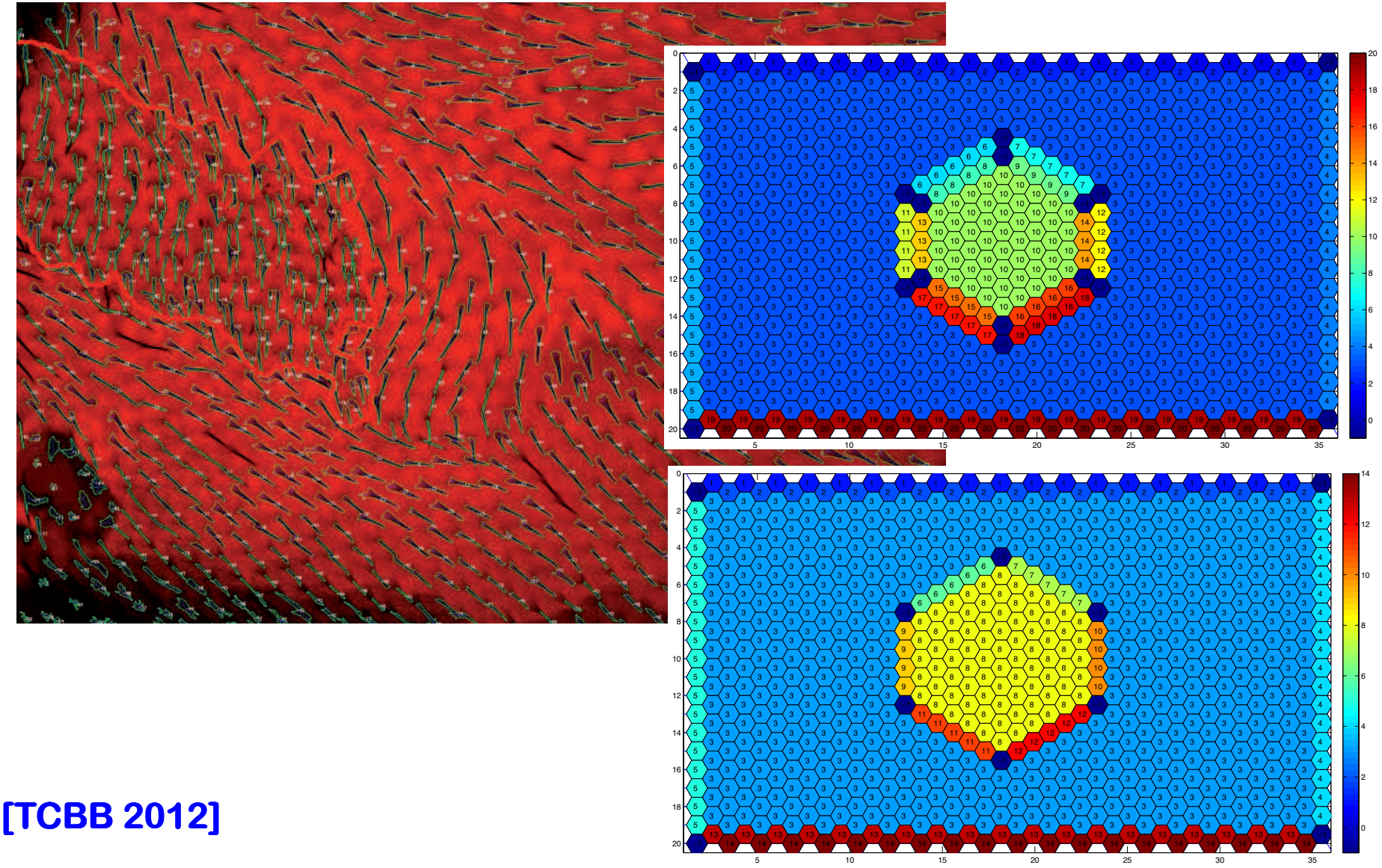
PLACES:	164,000
TRANSITIONS:	229,686
unfolding:	4 min
cont. simulation:	2 h



[BIOPPN 2011]
[CMSB 2011]

EX4 - PLANAR CELL POLARITY



[TCBB 2012]

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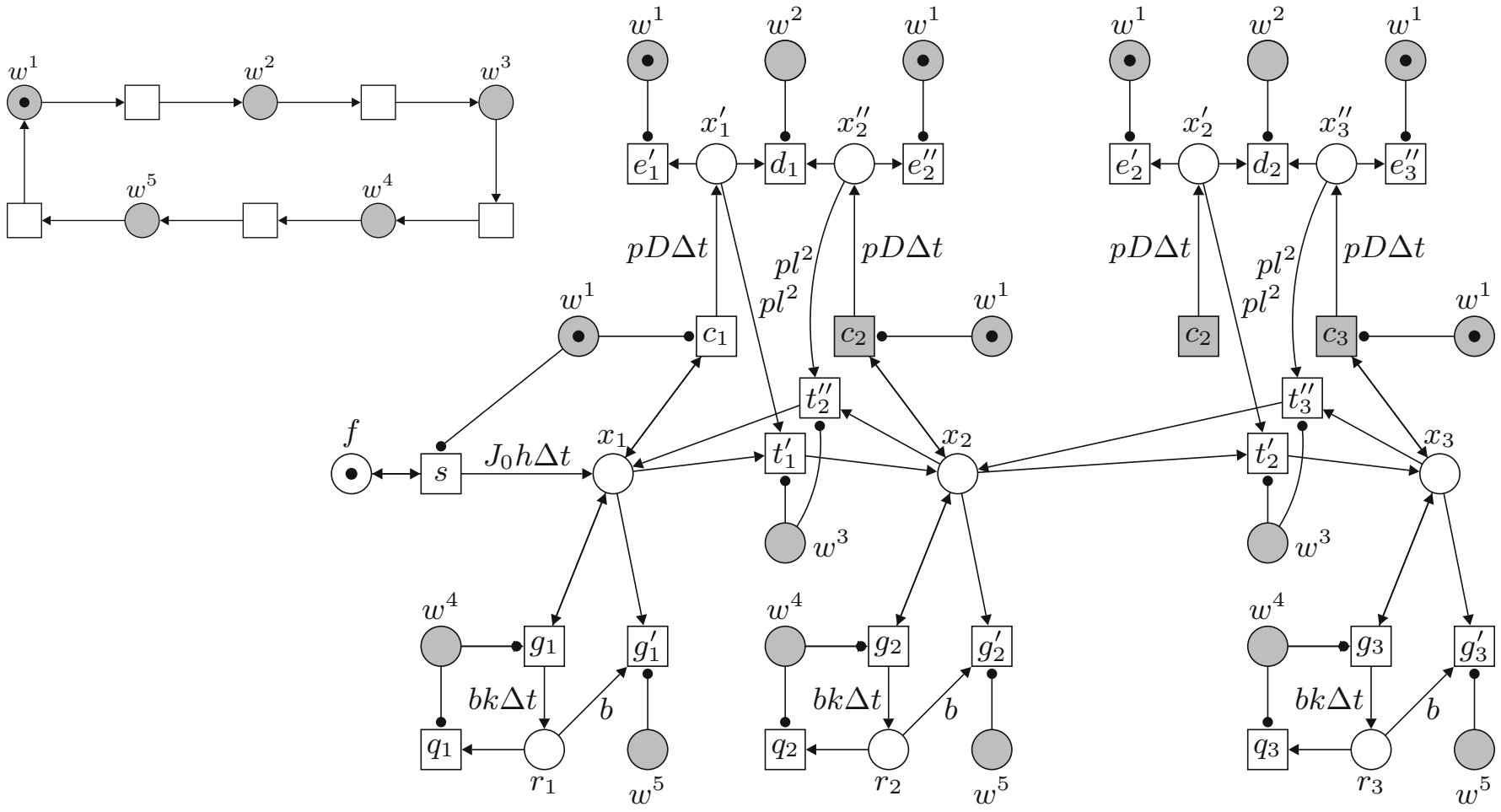
ANOTHER APPROACH TO COMBINE PDE AND PETRI NETS



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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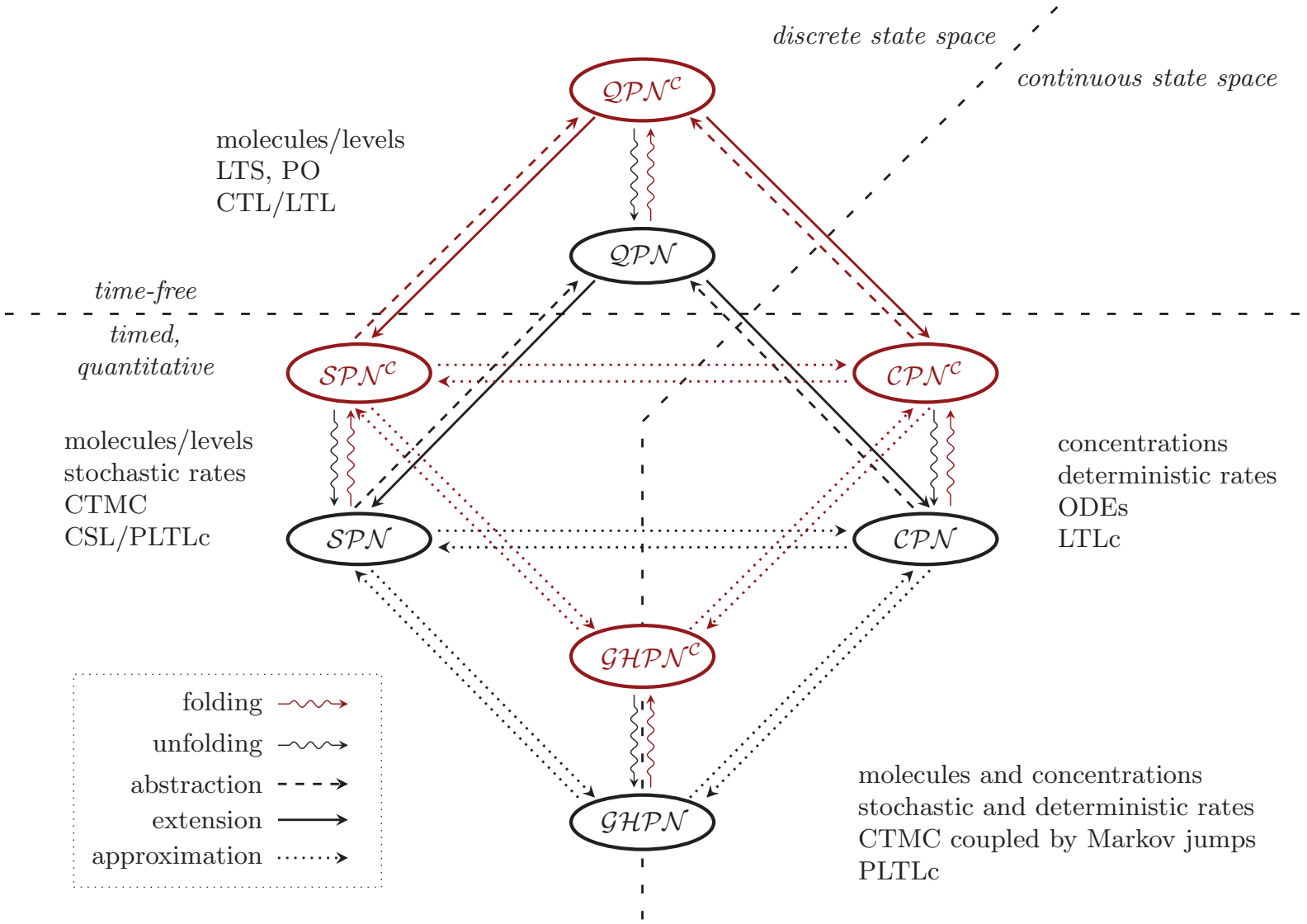
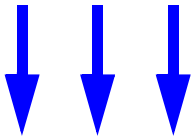
FRAMEWORK


discrete state space
continuous state space
molecules/levels
LTS, PO
CTL/LTL
$\mathcal{QPN}^c$
$\mathcal{QPN}$
time-free
timed,
quantitative
$\mathcal{SPN}^c$
$\mathcal{CPN}^c$
molecules/levels
stochastic rates
CTMC
CSL/PLTLc
concentrations
deterministic rates
ODEs
LTLc
$\mathcal{SPN}$
$\mathcal{CPN}$
$\mathcal{GHPN}^c$
$\mathcal{GHPN}$
folding
unfolding
abstraction
extension
approximation
molecules and concentrations
stochastic and deterministic rates
CTMC coupled by Markov jumps
PLTLc

4x2

MODELS SHARING STRUCTURE

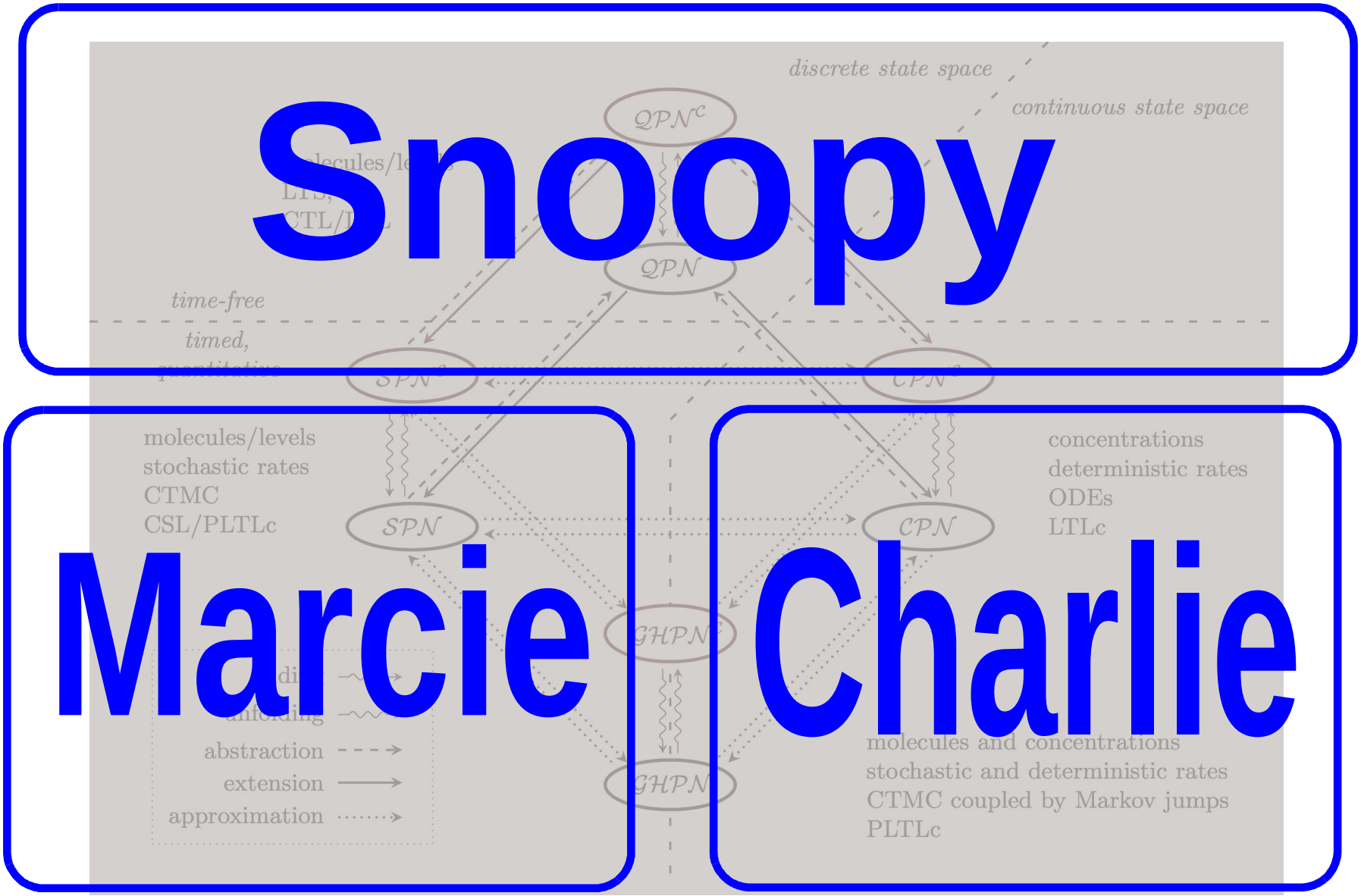


QUANTITATIVE MODEL = QUALITATIVE MODEL

+

RATE FUNCTIONS (KINETICS)


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
GHPN
abstraction
extension
approximation
molecules and concentrations
stochastic and deterministic rates
CTMC coupled by Markov jumps
HTLc


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 MATAB AND MANY OTHER TOOLS

MODELLING
BIO (PETRI) NETS

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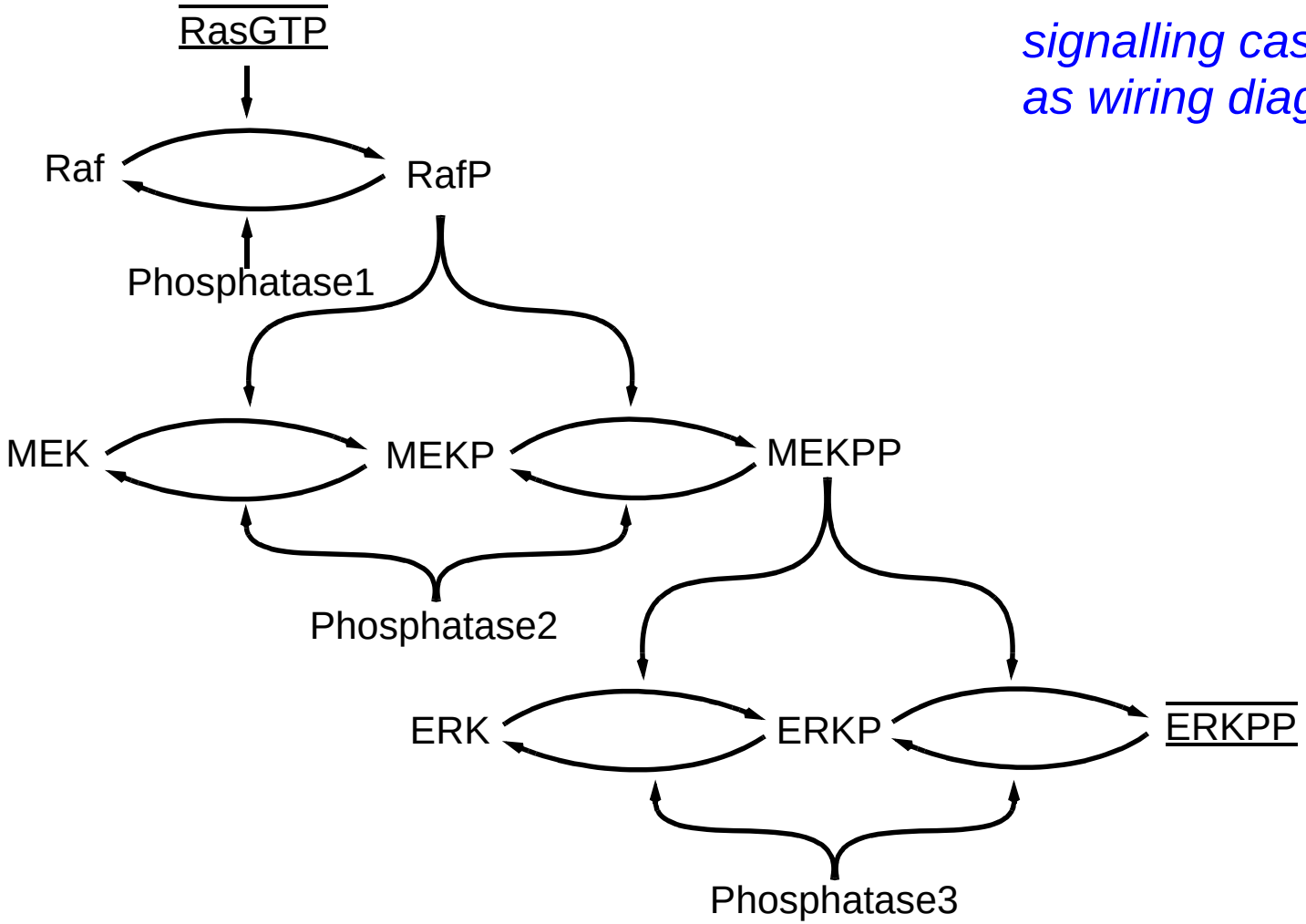
APPROACH 1

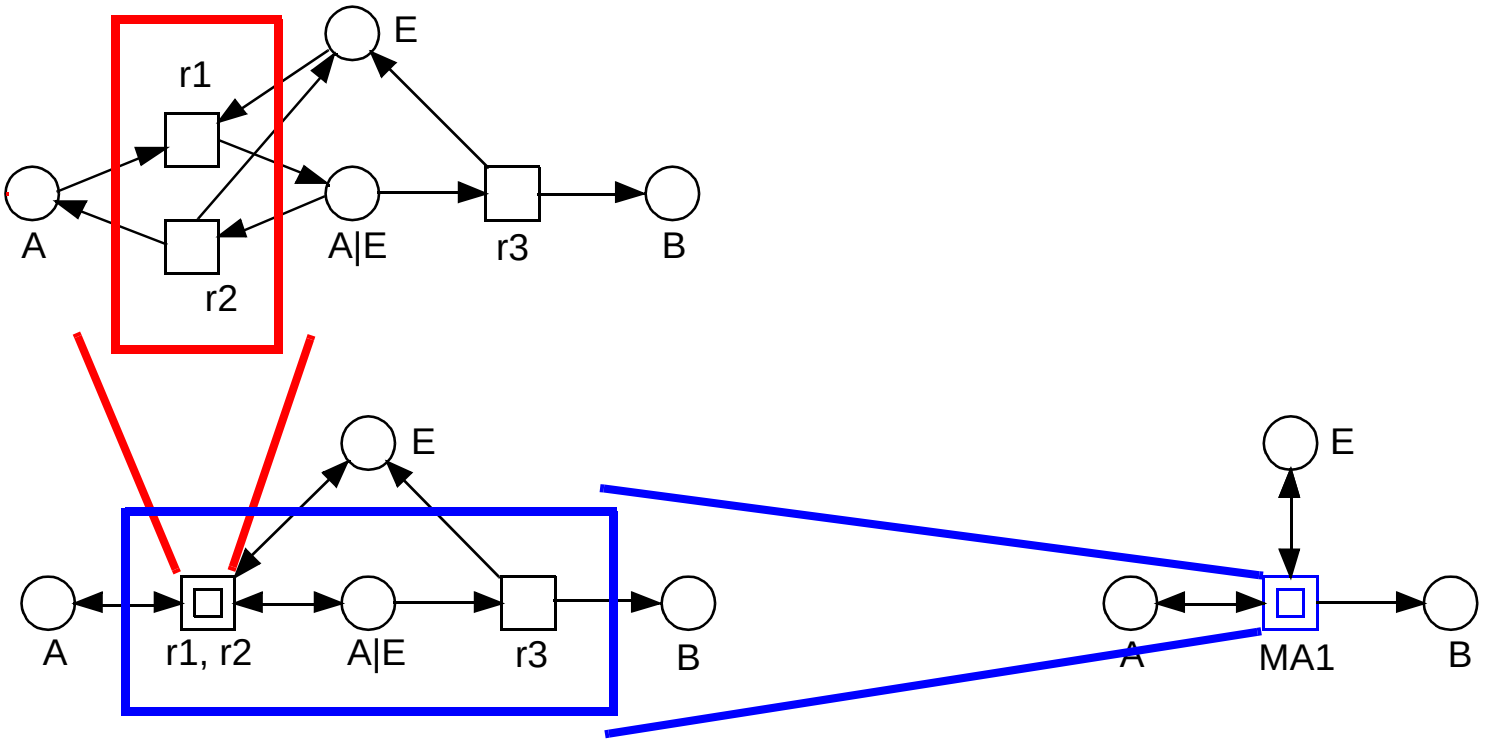
signalling cascade as wiring diagram



BASIC STRUCTURE

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

enzymatic reaction,
mass-action kinetics



BASIC STRUCTURE

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enzymatic reaction,
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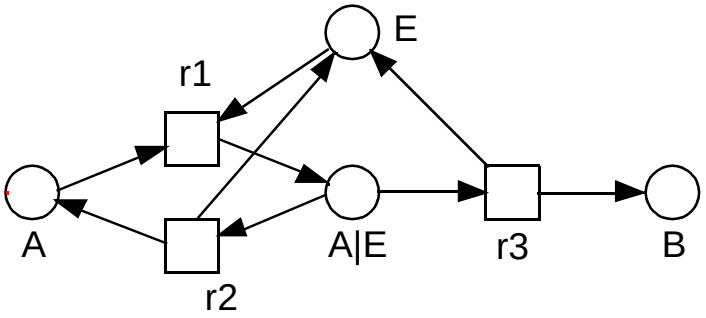
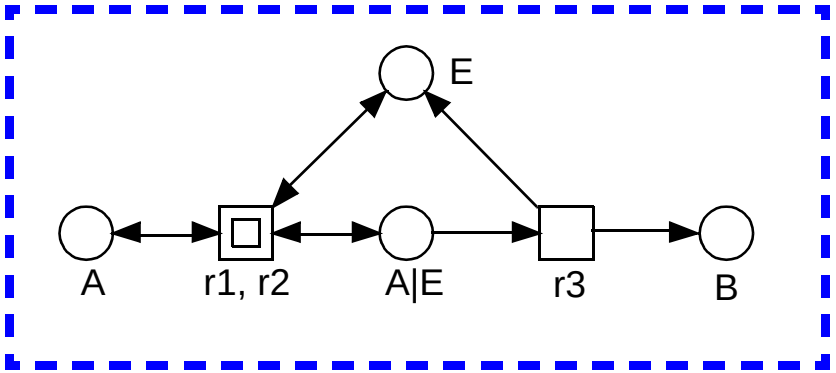
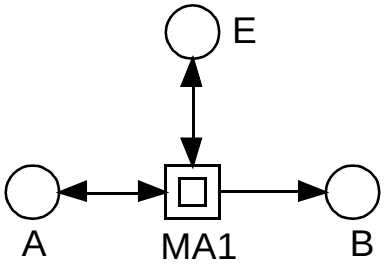
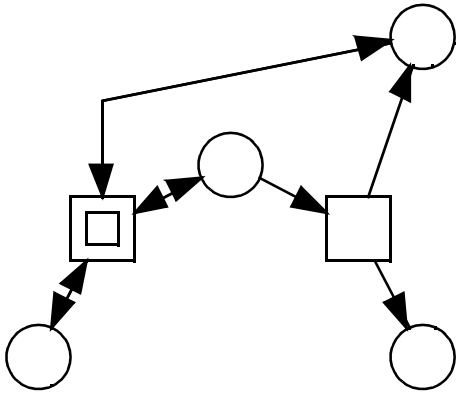




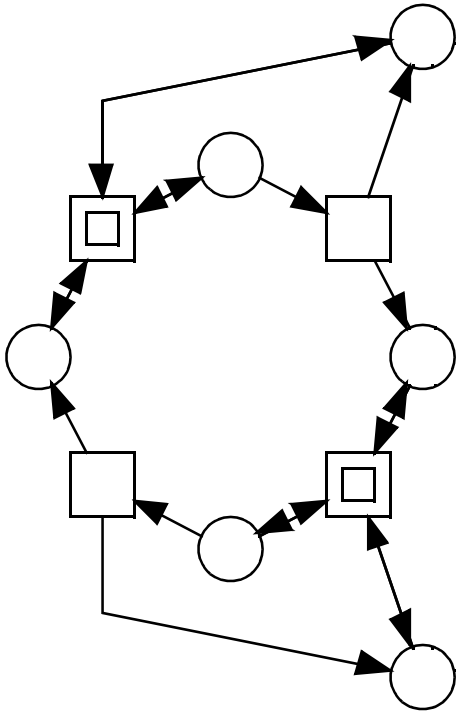


NET COMPOSITION FROM BUILDING BLOCKS

SINGLE
MASS-ACTION STEP

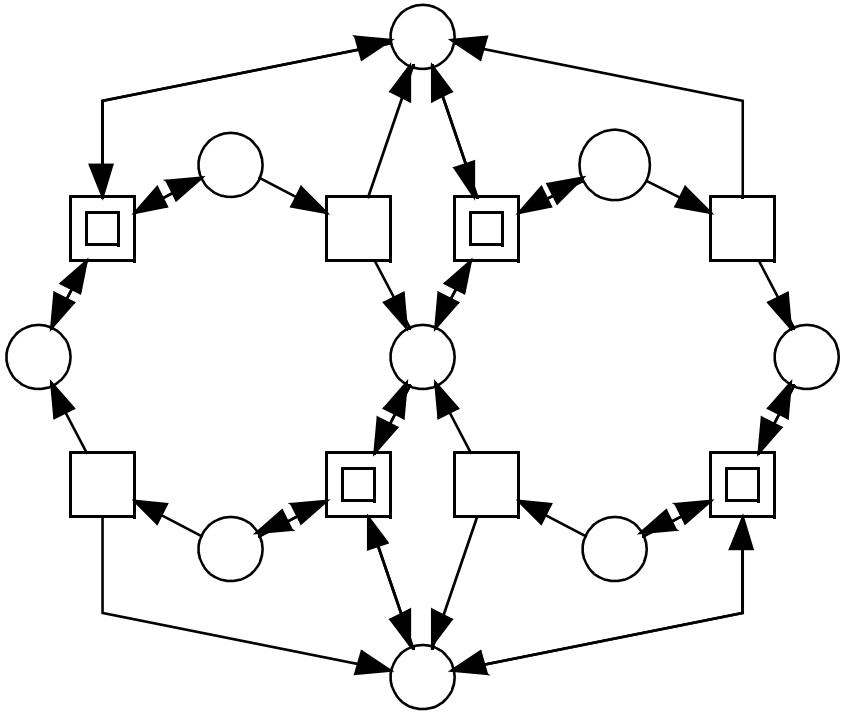


NET COMPOSITION FROM BUILDING BLOCKS

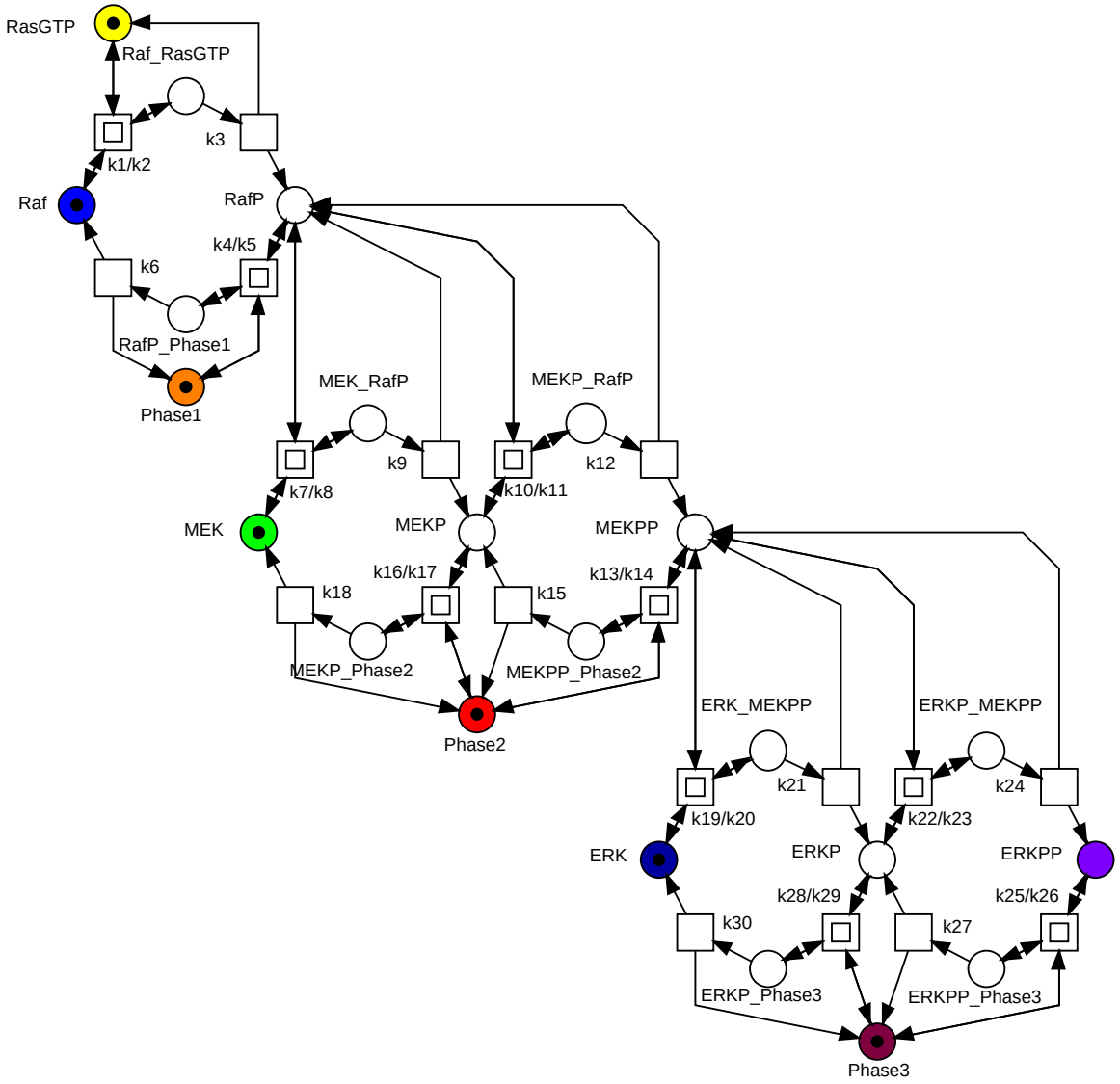


SINGLE
PHOSPHORYLATION / DEPHOSPHORYLATION

DOUBLE PHOSPHORYLATION / DEPHOSPHORYLATION



SIGNALLING CASCADE AS PETRI NET

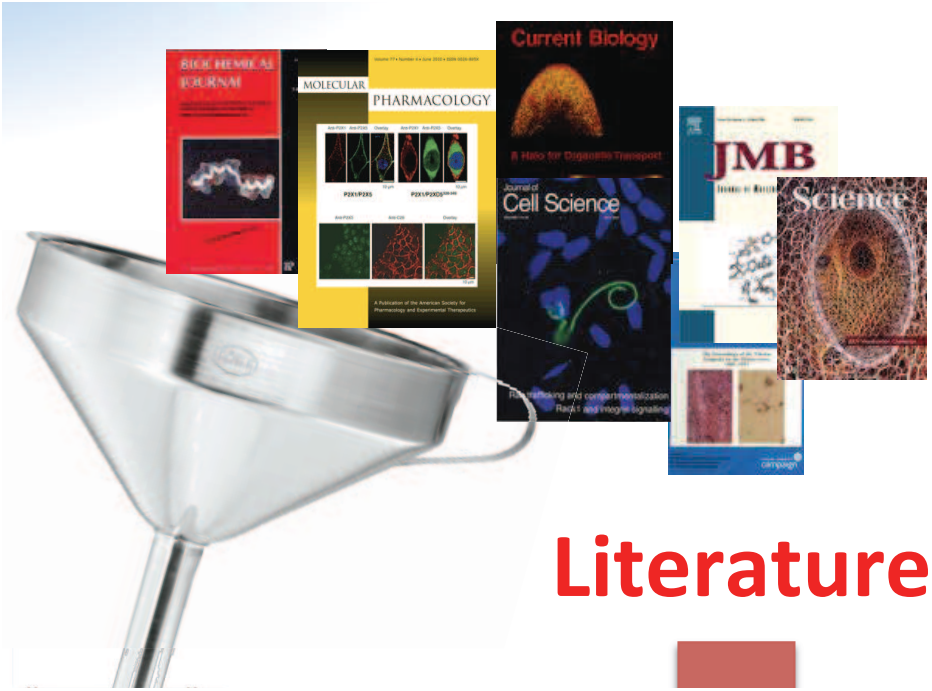


[GILBERT, HEINER, LEHRACK 2007]

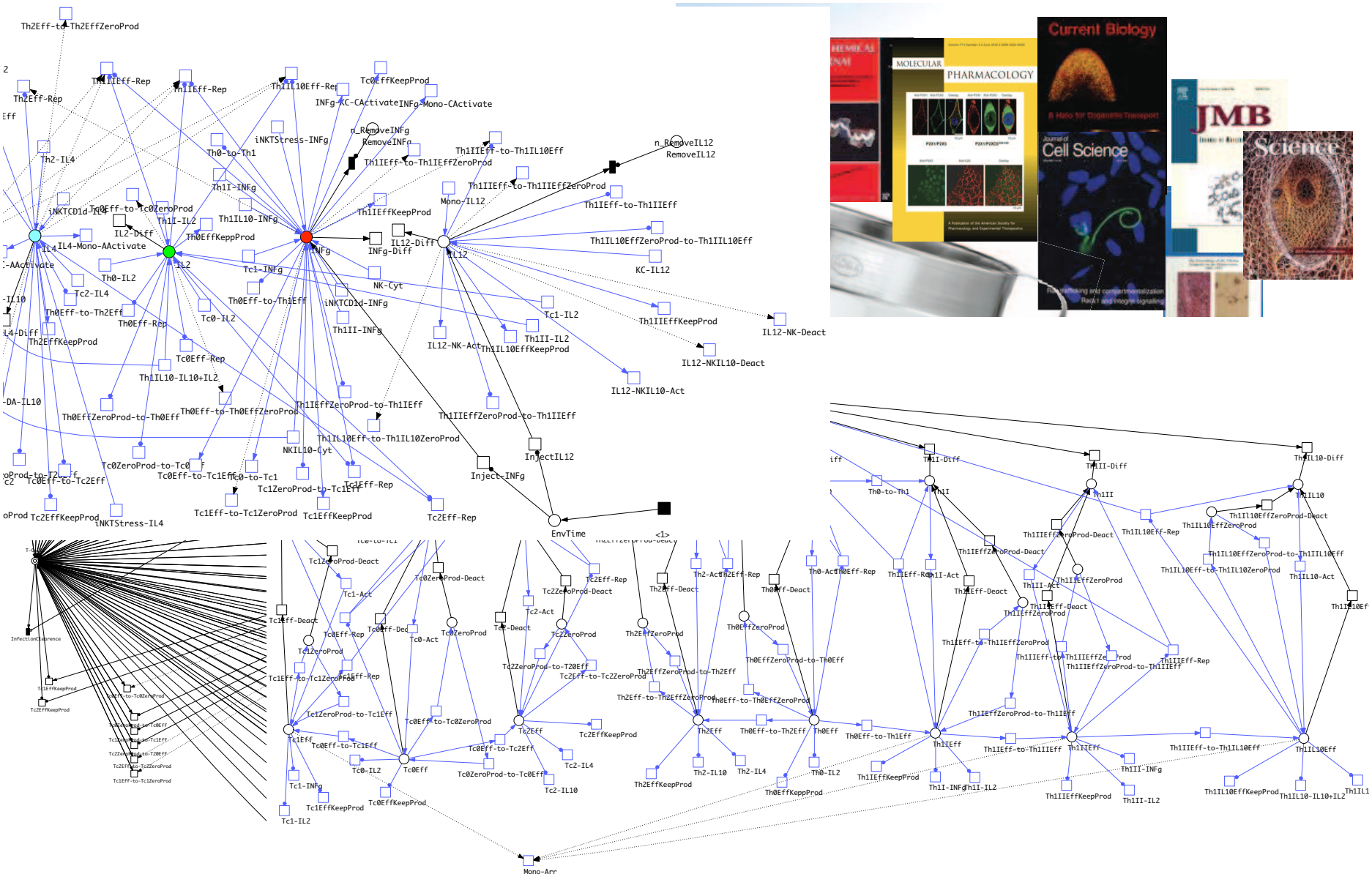
[HEINER, GILBERT, DONALDSON 2008]

APPROACH 2

FROM LITERATURE TO MODELS

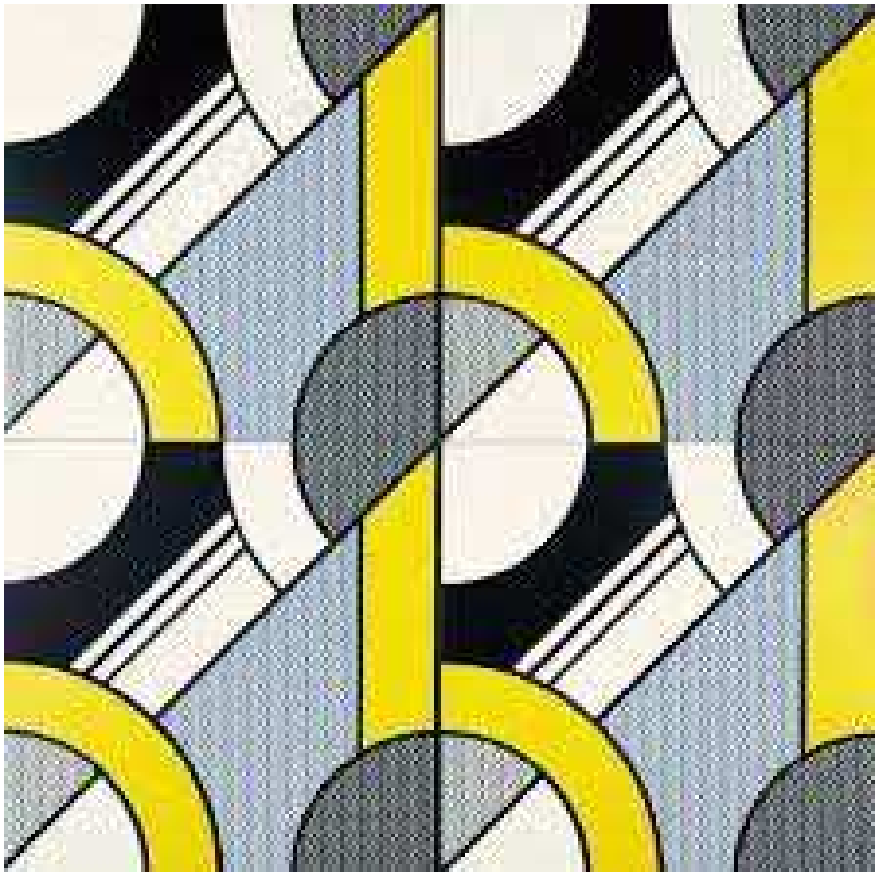


FROM LITERATURE TO MODELS



APPROACH 3

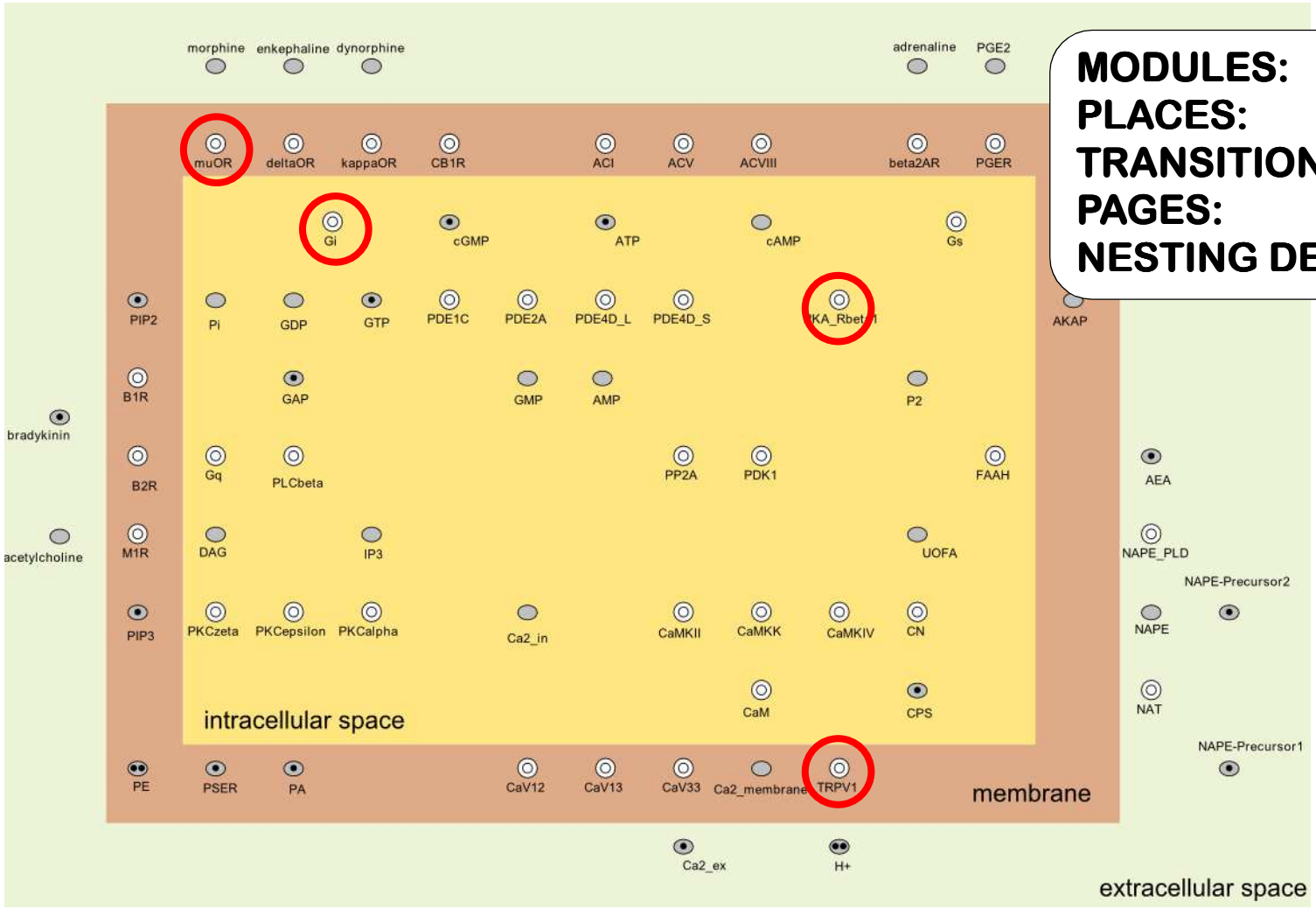
MODULAR MODELLING



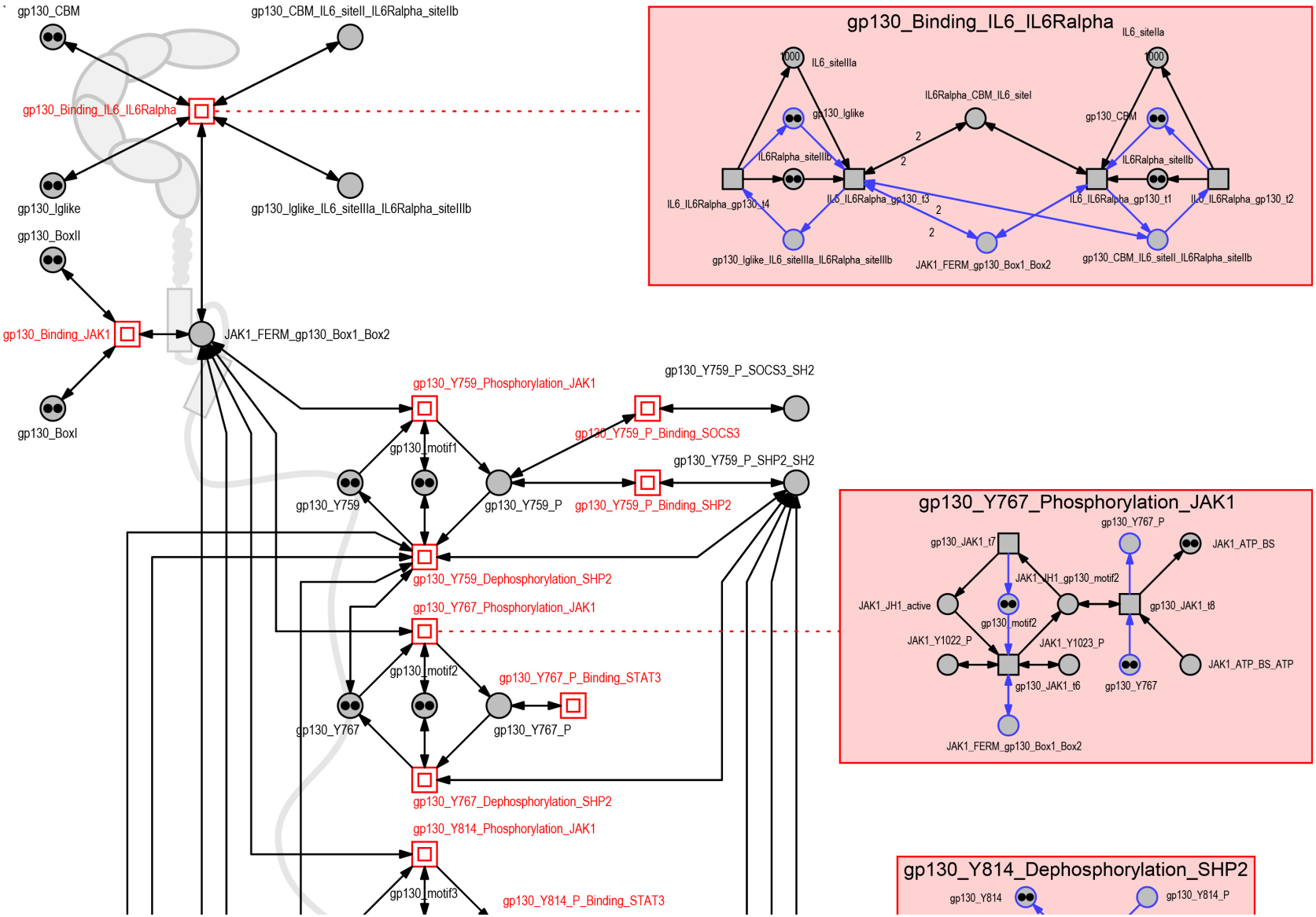
JOINT WORK WITH
MARY ANN BLÄTKE, WOLFGANG MARWAN

[BLÄTKE, MEYER, MARWAN 2011]

-> A PROTEIN-ORIENTED MODULAR MODELLING CONCEPT



MODULE GP130 TRANSMEMBRANE RECEPTOR



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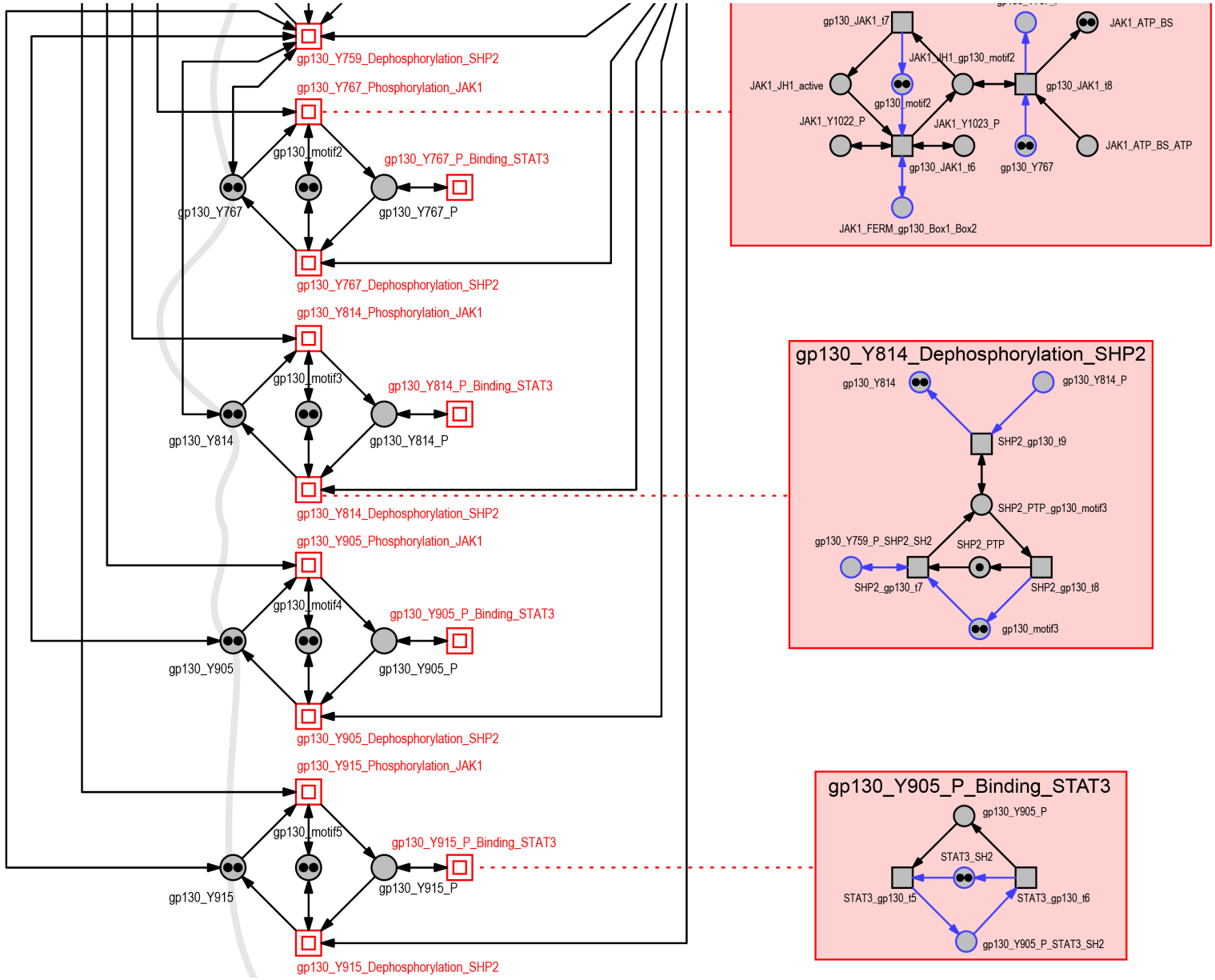
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gp130_Y767_Phosphorylation_JAK1
gp130_motif2
gp130_Y767_P_Binding_STAT3
gp130_Y767
gp130_Y767_P
gp130_Y767_Dephosphorylation_SHP2
gp130_Y814_Phosphorylation_JAK1
gp130_motif3
gp130_Y814_P_Binding_STAT3
gp130_Y814
gp130_Y814_P
gp130_Y814_Dephosphorylation_SHP2
gp130_Y905_Phosphorylation_JAK1
gp130_motif4
gp130_Y905_P_Binding_STAT3
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gp130_motif5
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gp130_Y915_P
gp130_Y915_Dephosphorylation_SHP2
gp130_JAK1_t7
JAK1_ATP_BS
JAK1_JH1_gp130_motif2
JAK1_JH1_active
gp130_JAK1_t8
gp130_motif2
JAK1_Y1022_P
JAK1_Y1023_P
JAK1_ATP_BS_ATP
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gp130_Y767
JAK1_FERM_gp130_Box1_Box2
gp130_Y814_Dephosphorylation_SHP2
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gp130_Y814_P
SHP2_gp130_t9
SHP2_PTP_gp130_motif3
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gp130_motif3
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gp130_Y905_P
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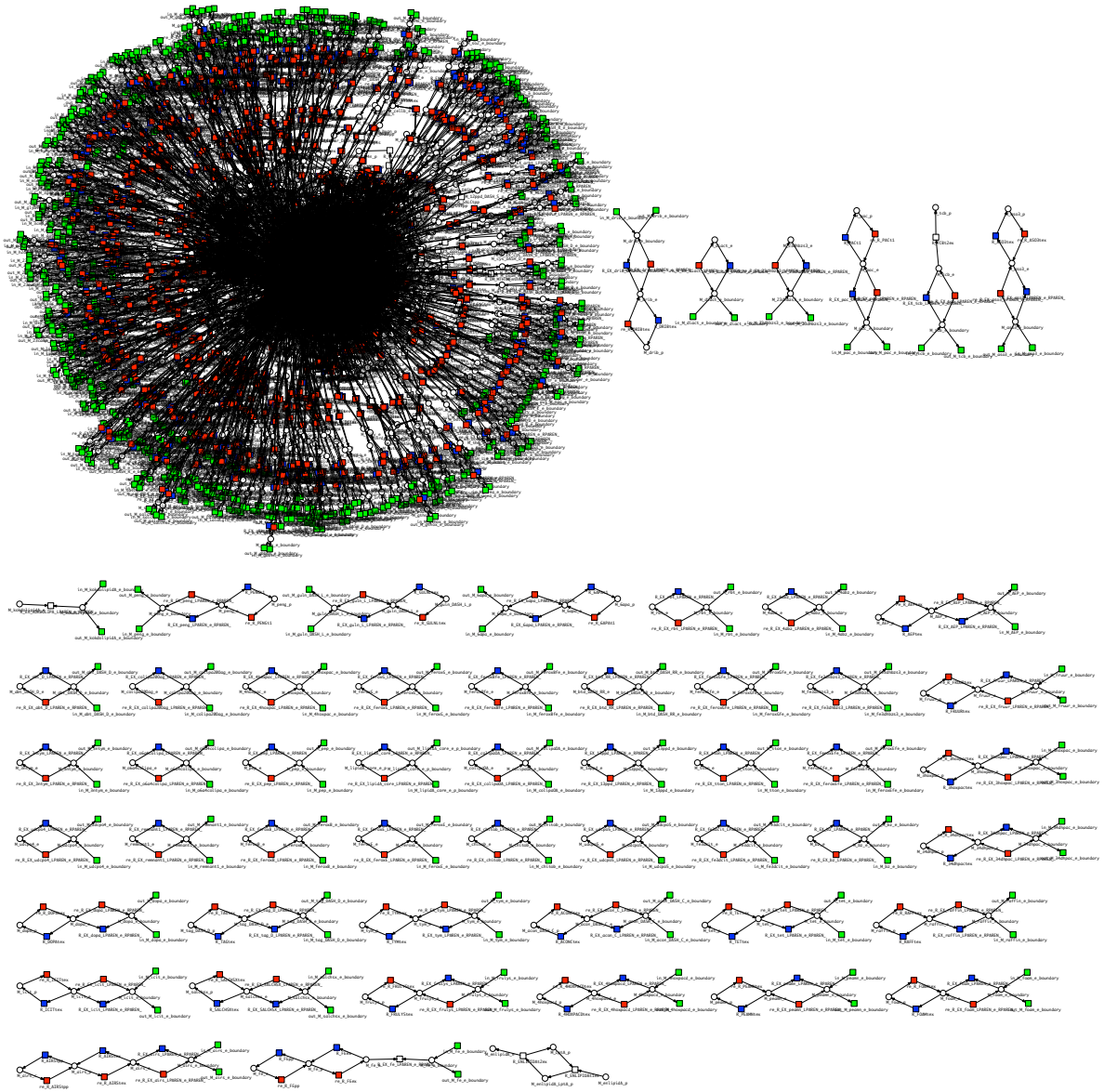
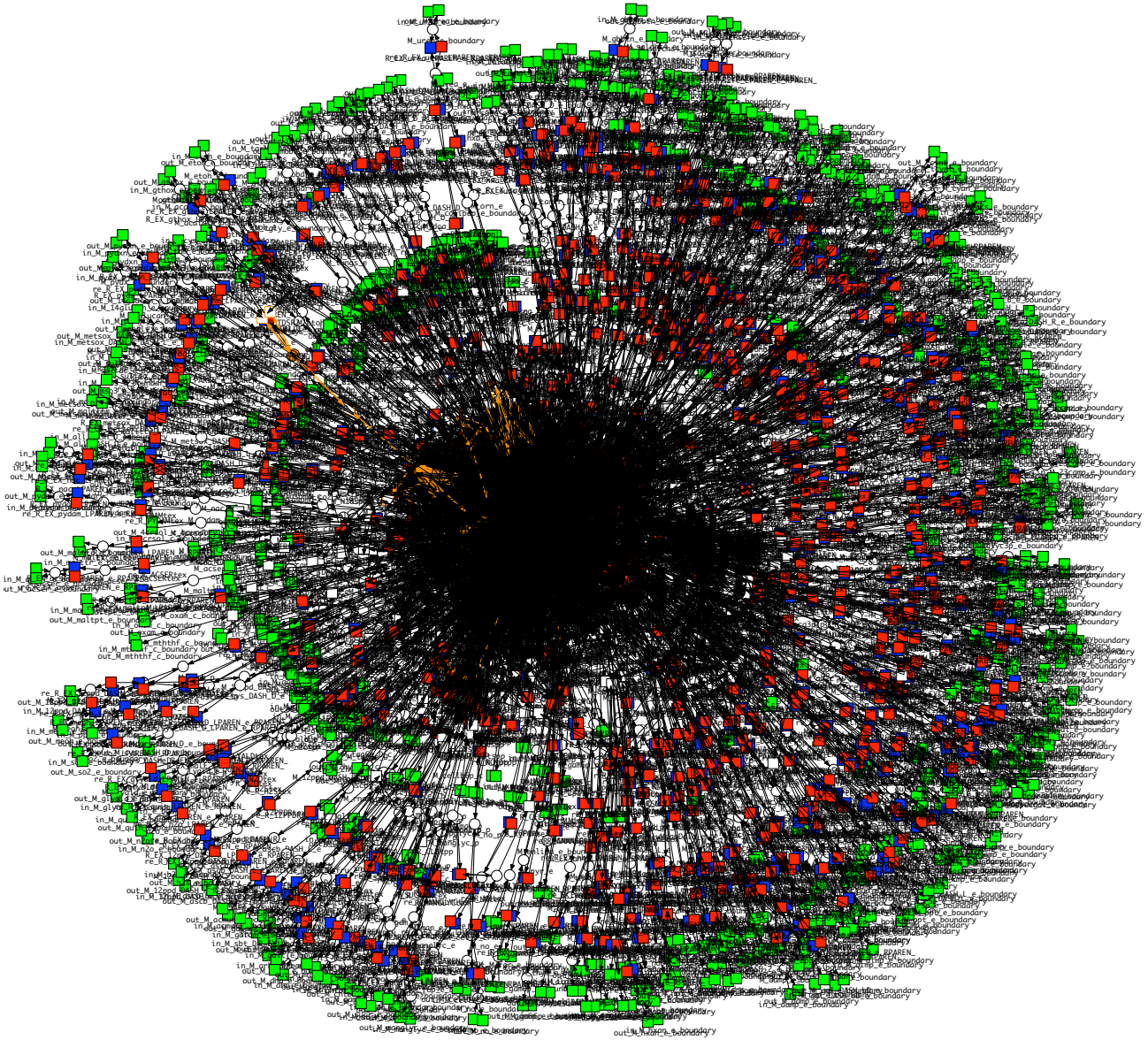
APPROACH 4

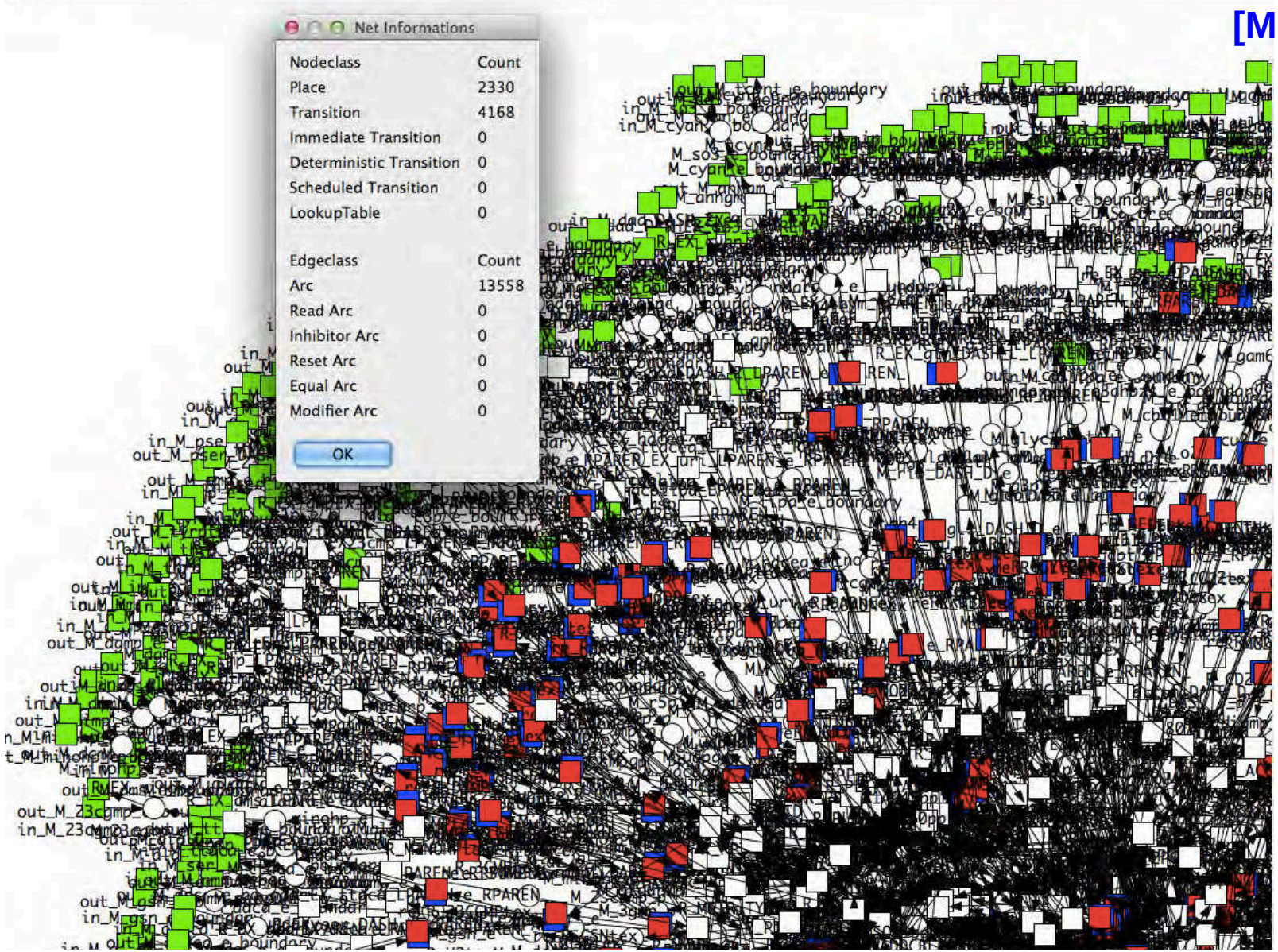
[Monk 2013]



[Monk 2013]



[Monk 2013]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Nodeclass Count
Place 2330
Transition 4168
Immediate Transition 0
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Scheduled Transition 0
LookupTable 0
Edgeclass Count
Arc 13558
Read Arc 0
Inhibitor Arc 0
Reset Arc 0
Equal Arc 0
Modifier Arc 0
OK

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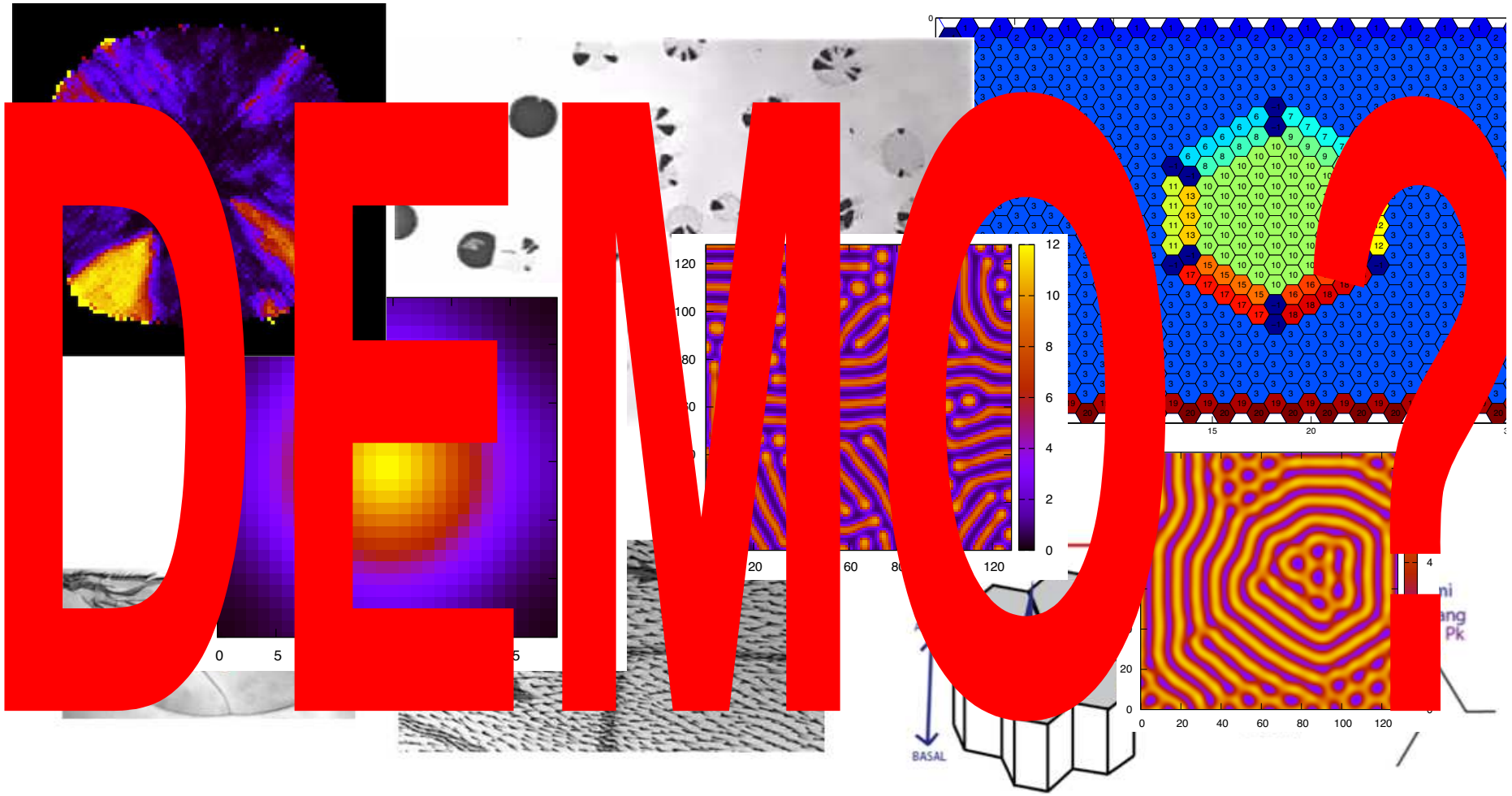
SUMMARY



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