- COLOURING SPACE -

A COLOURED FRAMEWORK FOR SPATIAL MODELLING IN SYSTEMS BIOLOGY

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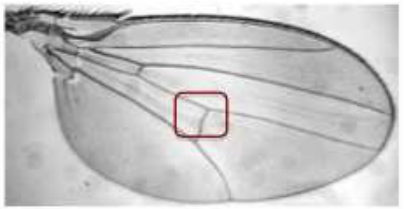
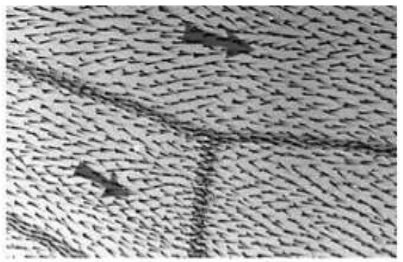
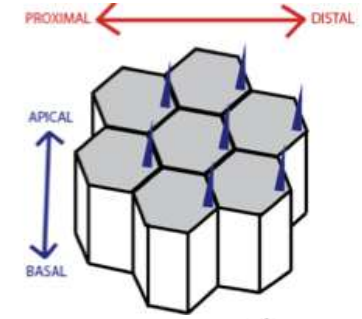
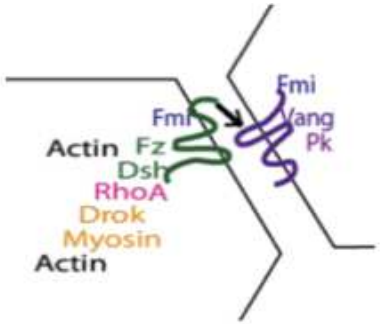
OUTLINE

- **FRAMEWORK**
  - -> *modelling, what for ?*
  - -> *unifying paradigms:*
    (coloured) QPN - SPN - CPN - HPN
- **EXAMPLE: DIFFUSION IN SPACE**
  - -> *encoding space - 1D / 2D*
  - -> *continuous paradigm*
- **EXAMPLE: MULTISTRAIN CELL COLONIES**
  - -> *stochastic paradigm*
- **SUMMARY & OUTLOOK**
  - -> *open problems*
  - -> *next steps*



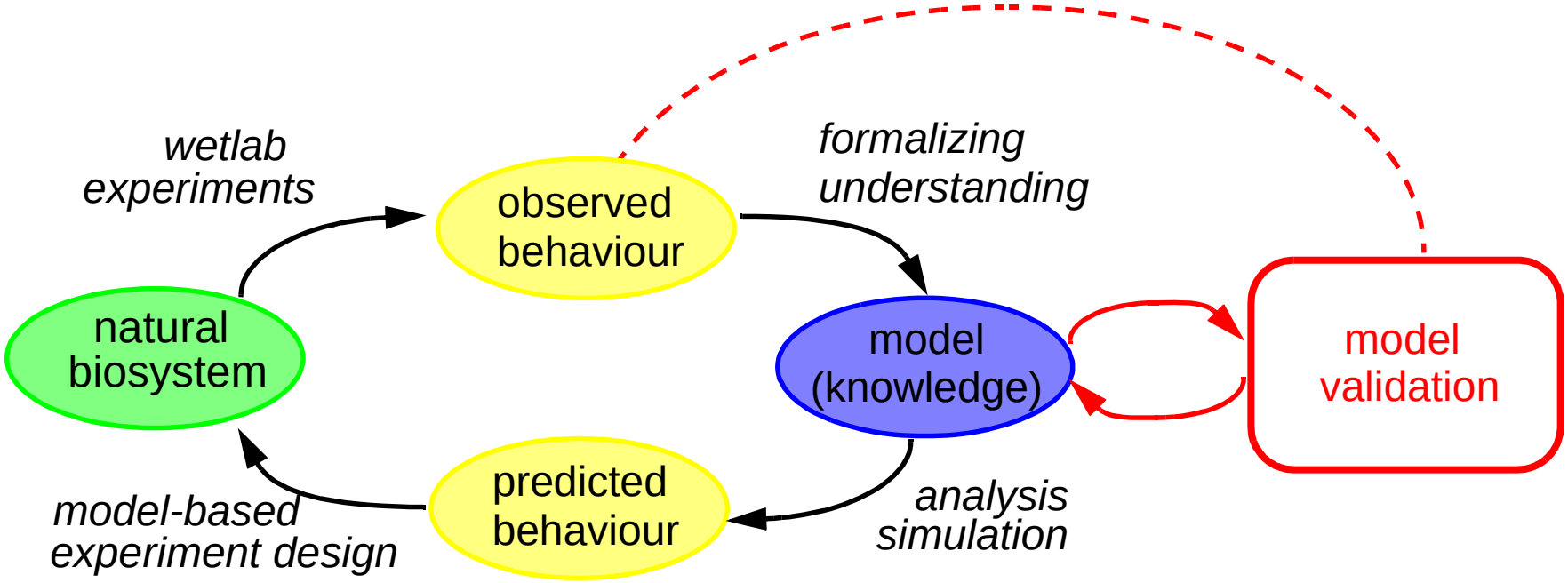






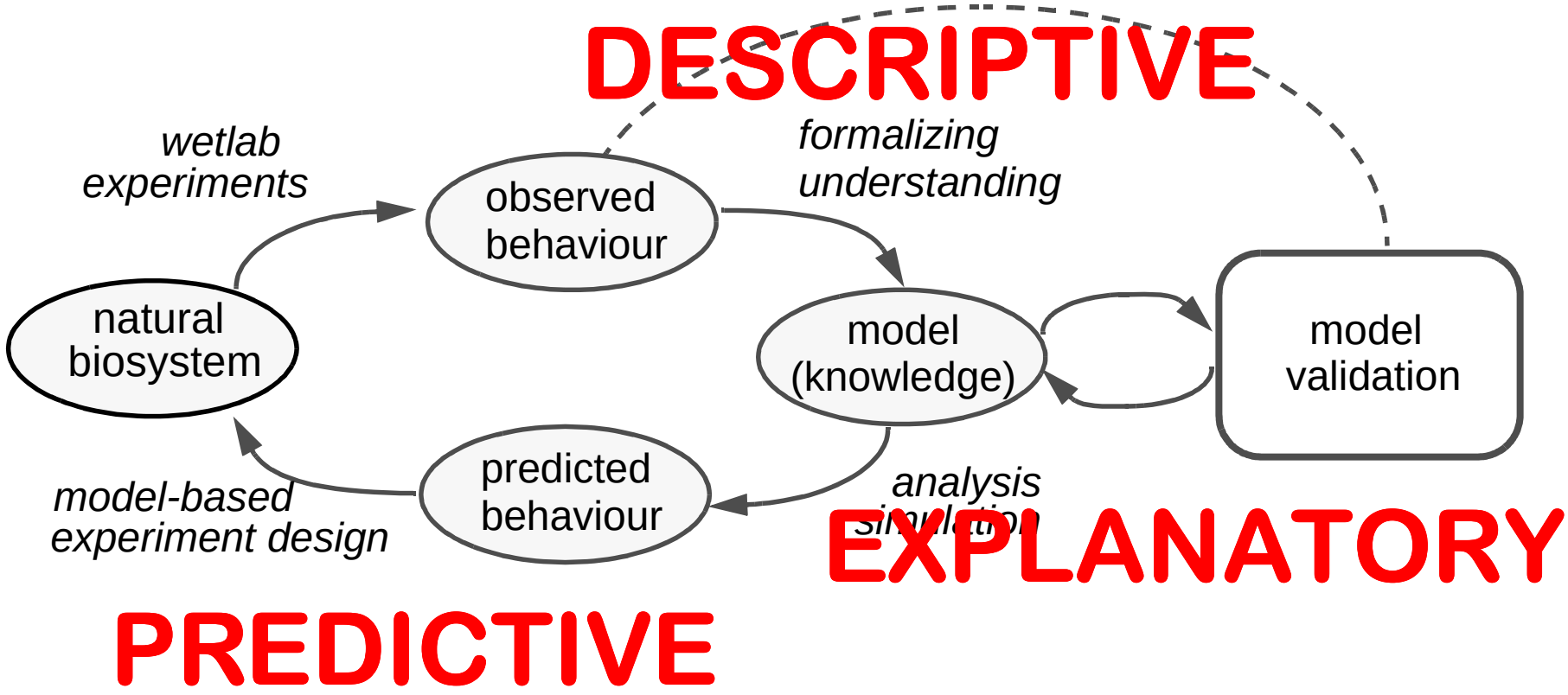
THE FRAMEWORK

MODELLING = FORMAL KNOWLEDGE REPRESENTATION



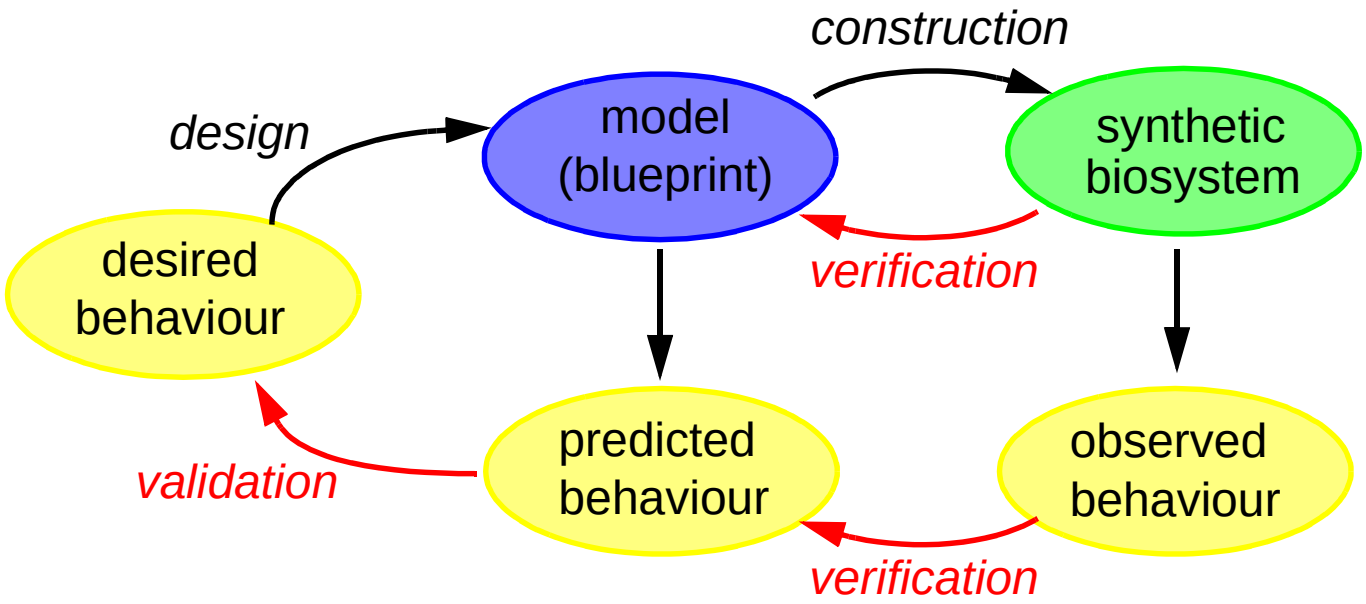
MODEL VALIDATION = CONFIDENCE INCREASE

MODELLING = FORMAL KNOWLEDGE REPRESENTATION



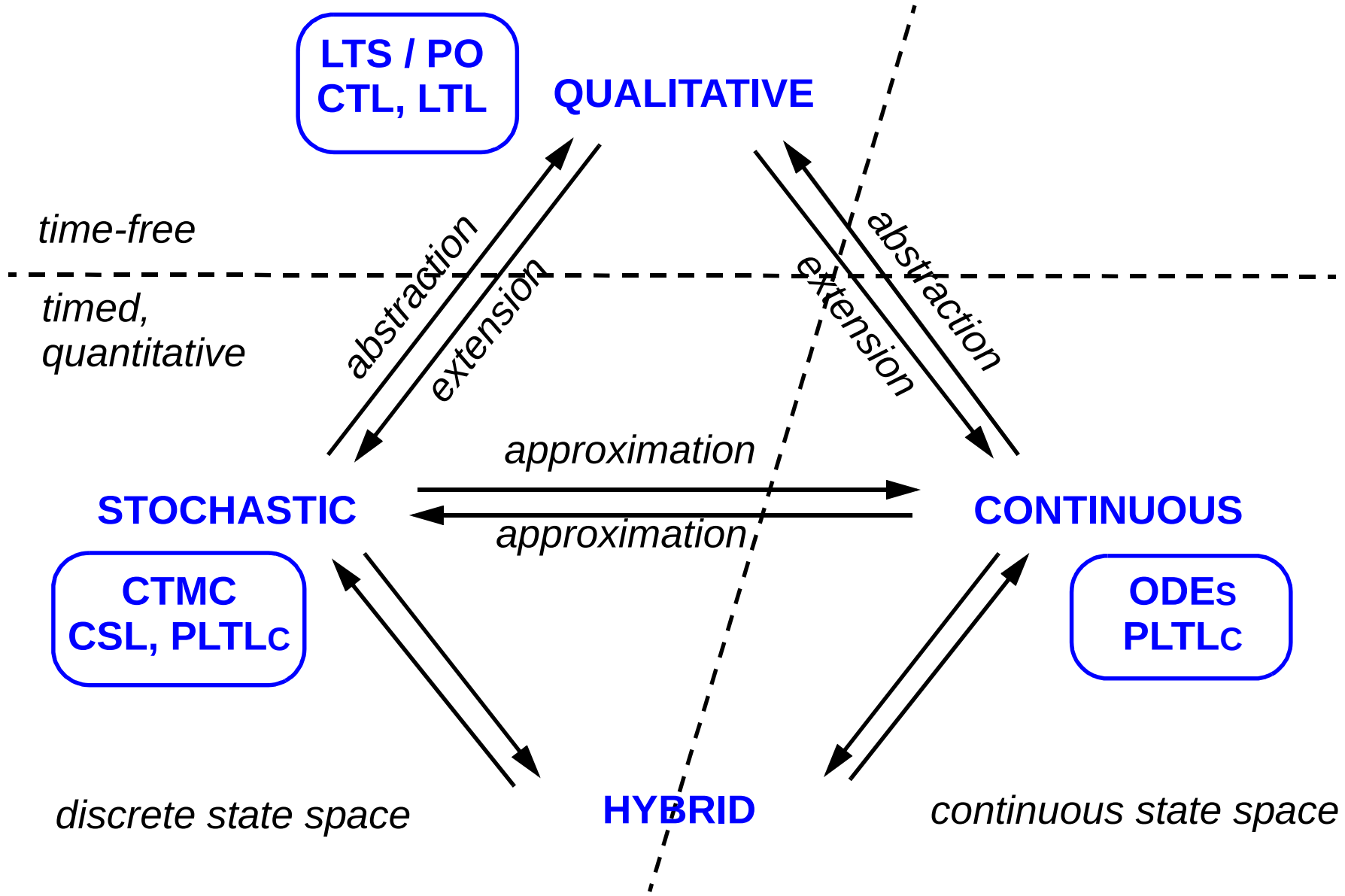
MODEL VALIDATION = CONFIDENCE INCREASE

MODELLING = BLUEPRINT FOR SYSTEM CONSTRUCTION

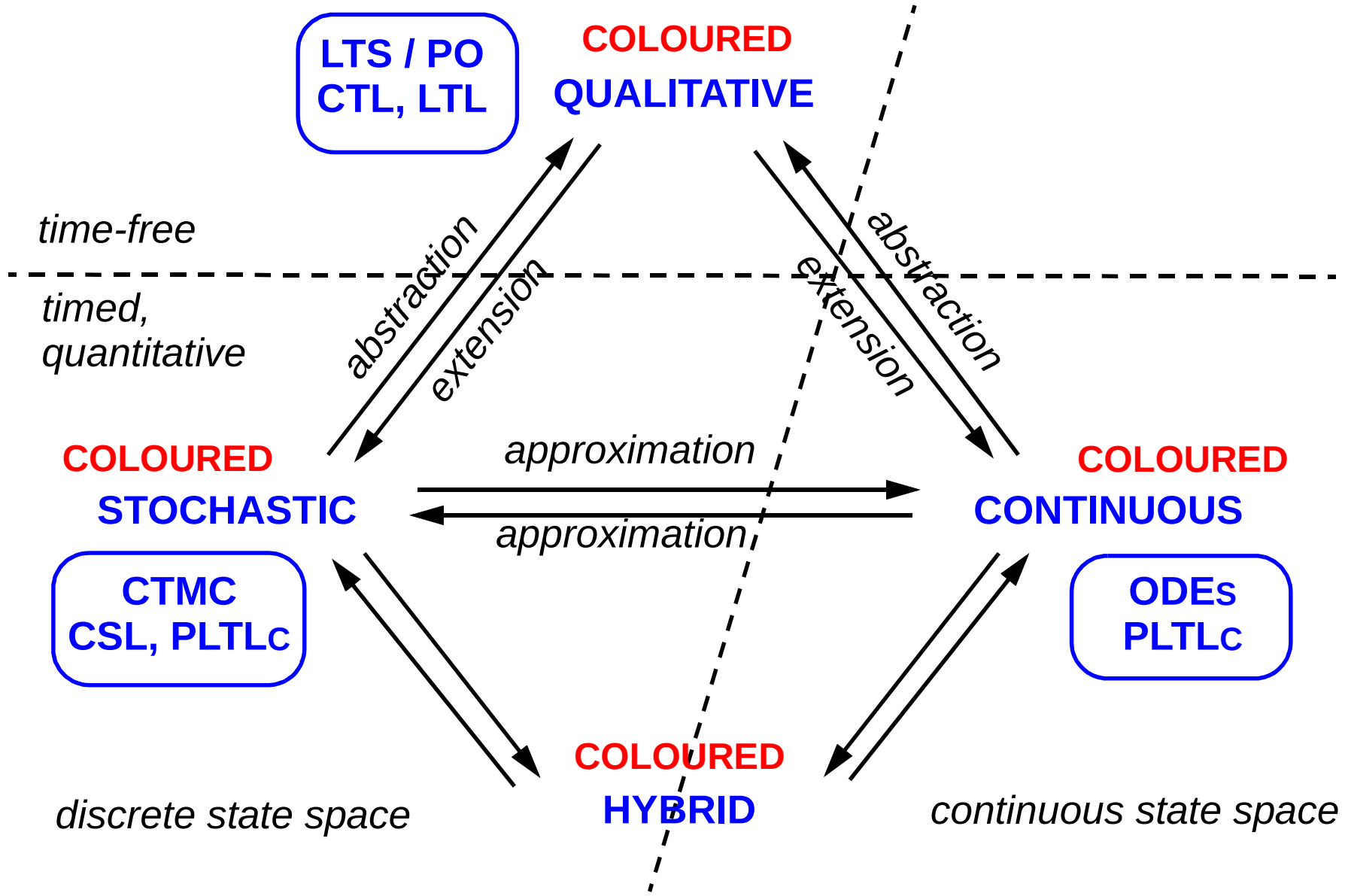


RELIABLE AND ROBUST ENGINEERING REQUIRES VERIFIED MODELS

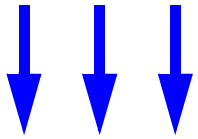
FRAMEWORK 2010



COLOURED FRAMEWORK 2011



4 MODELS SHARING STRUCTURE



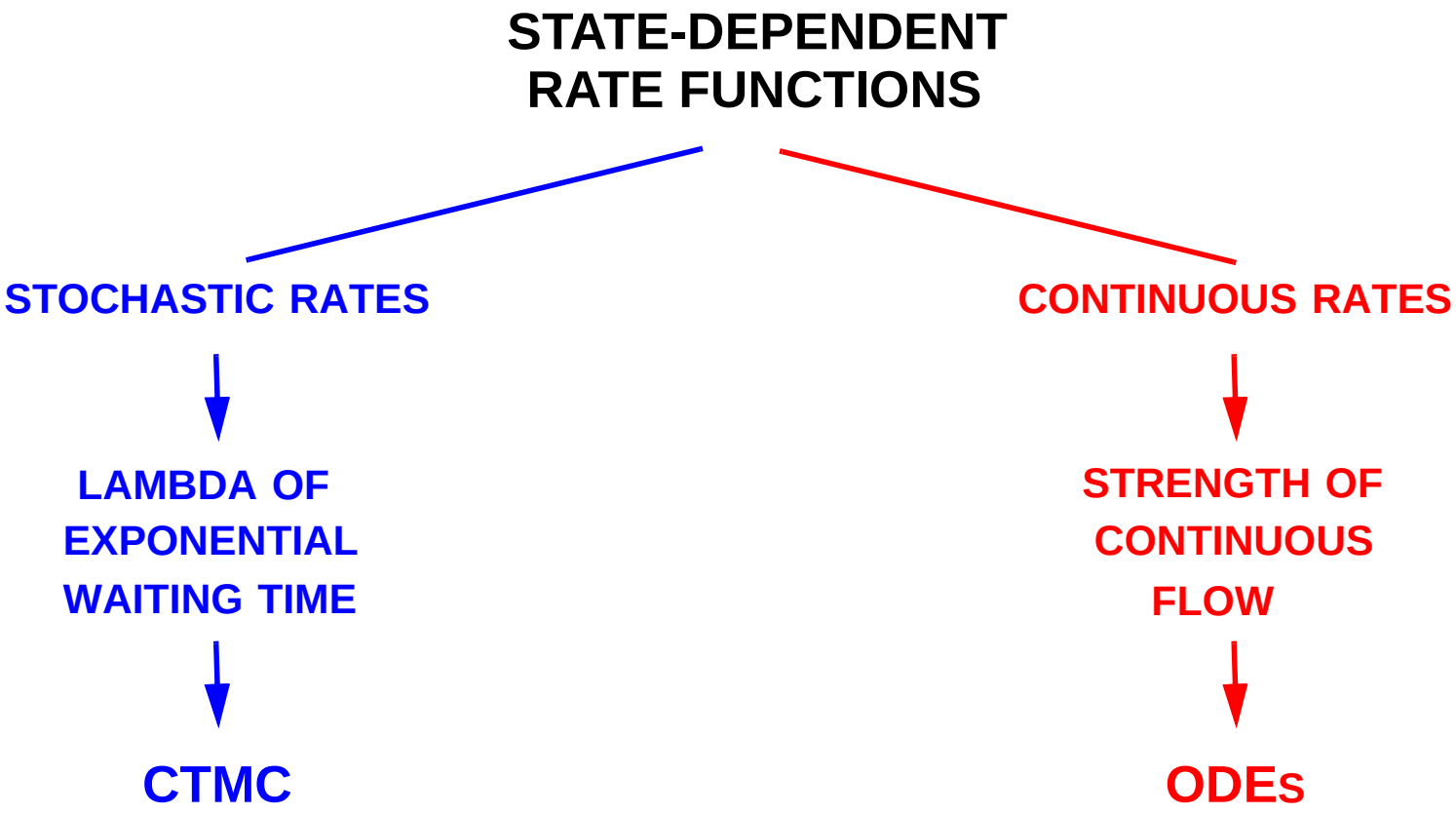
QUANTITATIVE MODEL = QUALITATIVE MODEL

+

RATE FUNCTIONS

(KINETICS)

CRUCIAL POINT



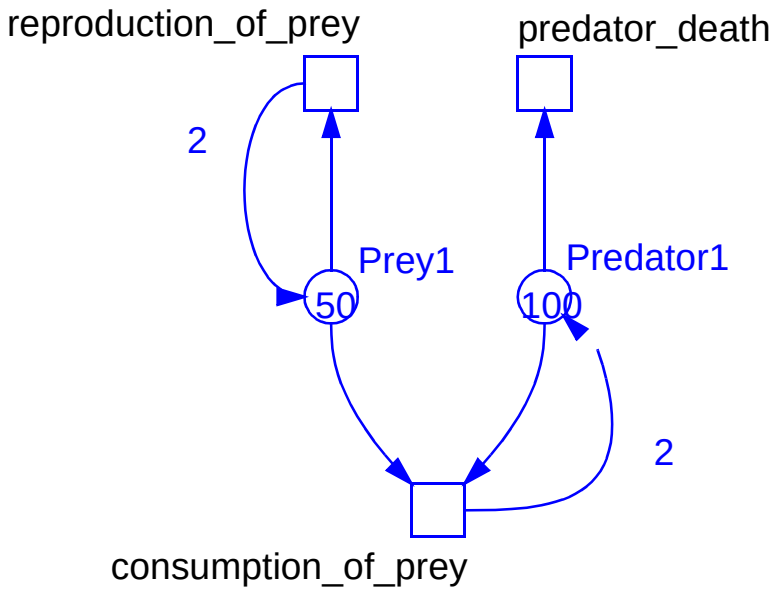
-> supported by, e.g., COPASI, Dizzy, ..., Snoopy

COLOUR -

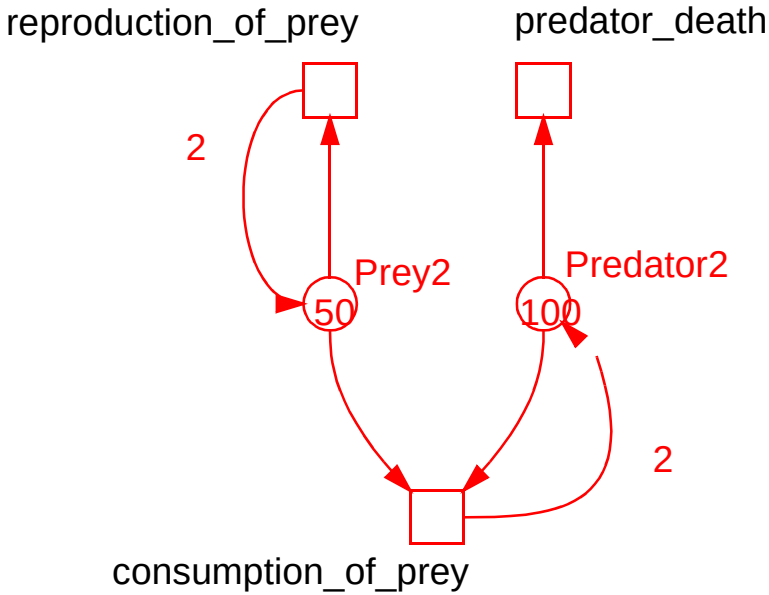
WHAT FOR ?

EX1: PREY - PREDATOR

sub-system1



sub-system2



EX1: PREY - PREDATOR

- **definitions**

  colourset *CS = 1-2;*

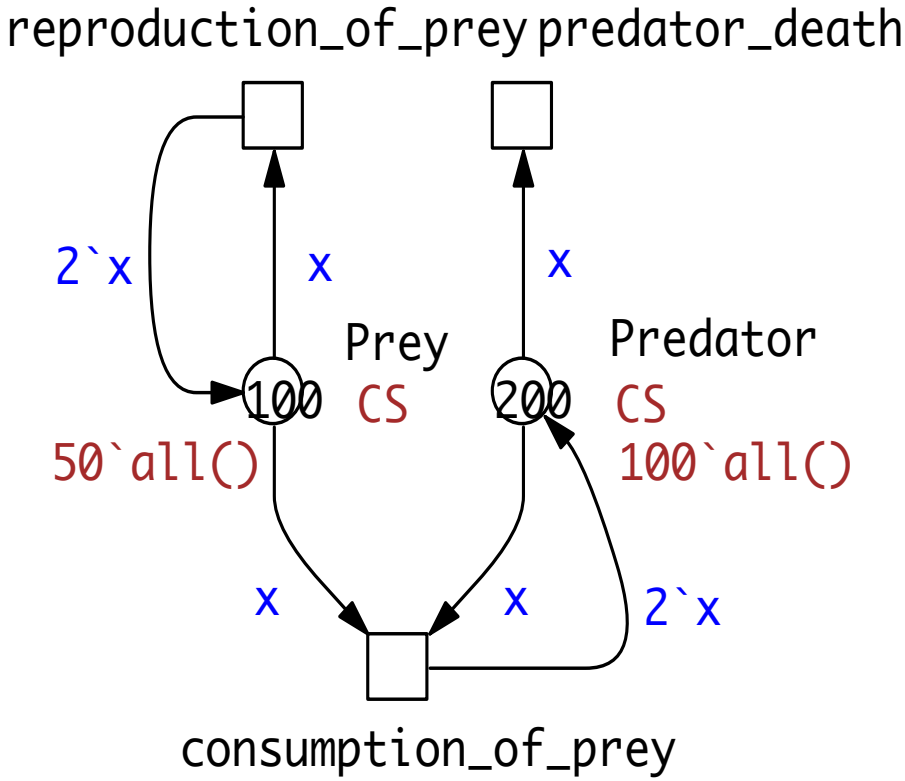
  var *x : CS;*

- **better:**

  const *SIZE = 2;*

  colourset *CS = 1-SIZE;*

  var *x : CS;*



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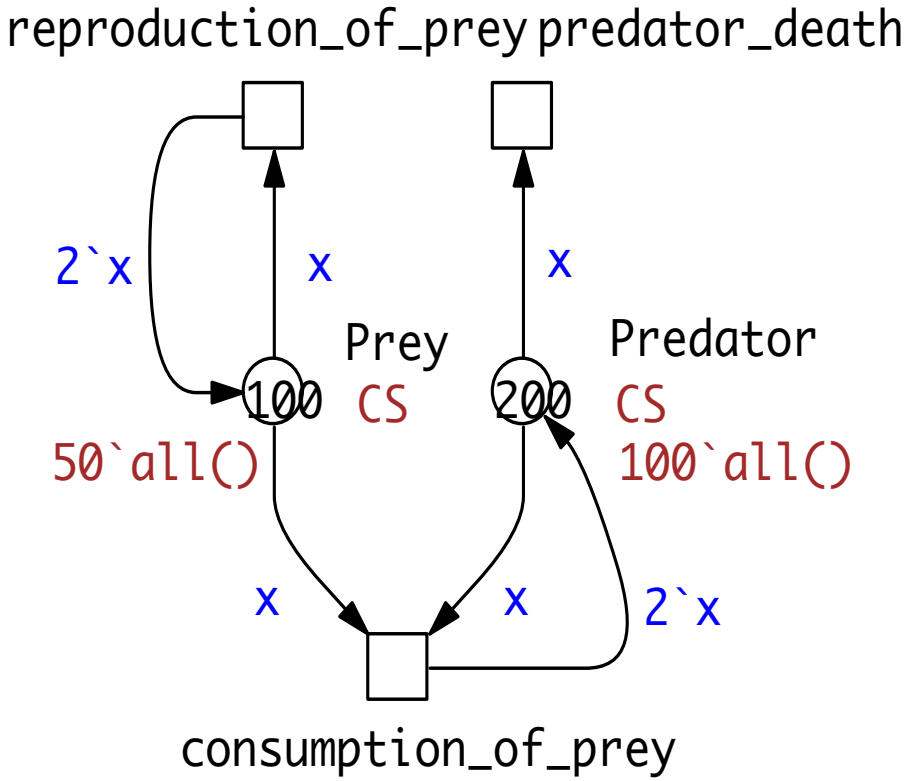
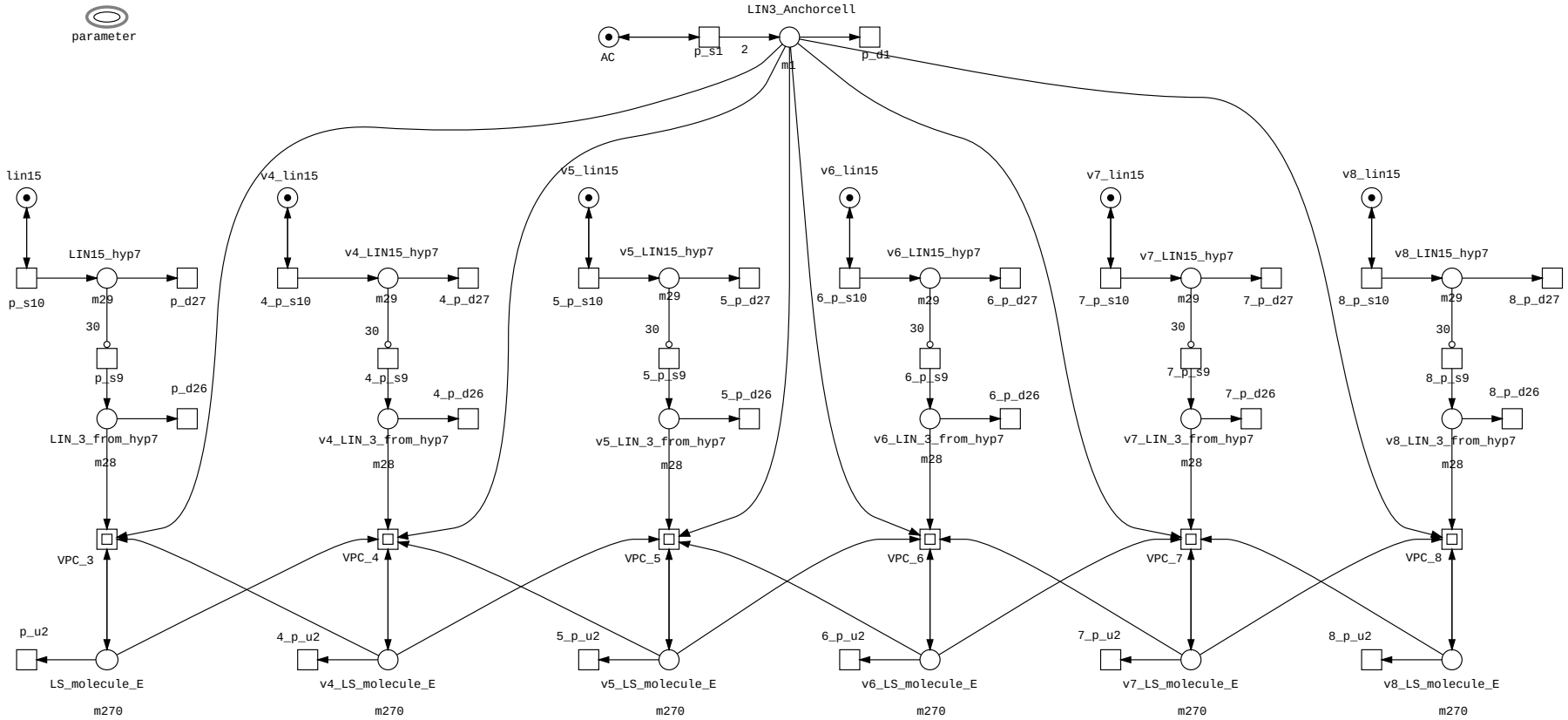


- **changing SIZE adapts the model to various scenarious**

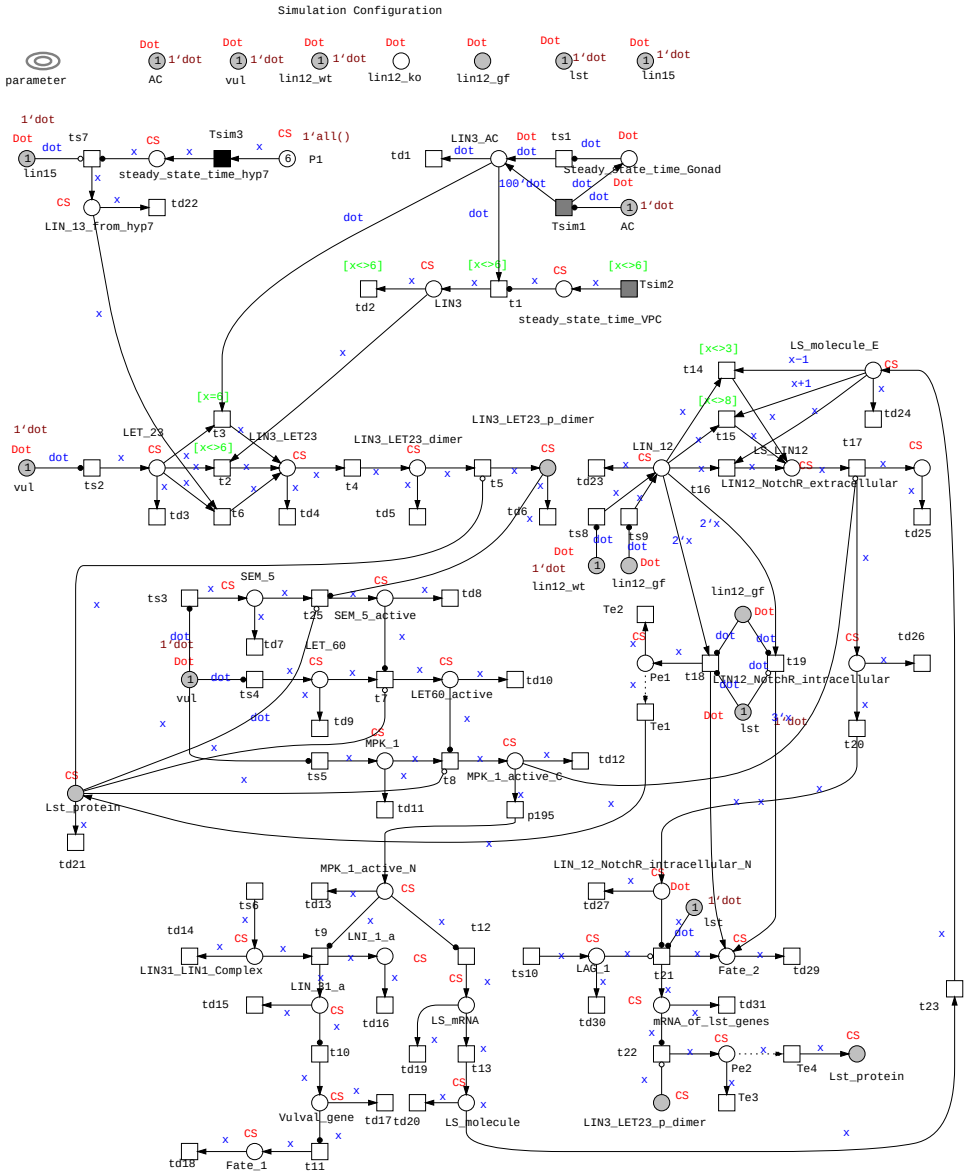
EX2: C. ELEGANS

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

PLACES: 206
TRANSITIONS: 366

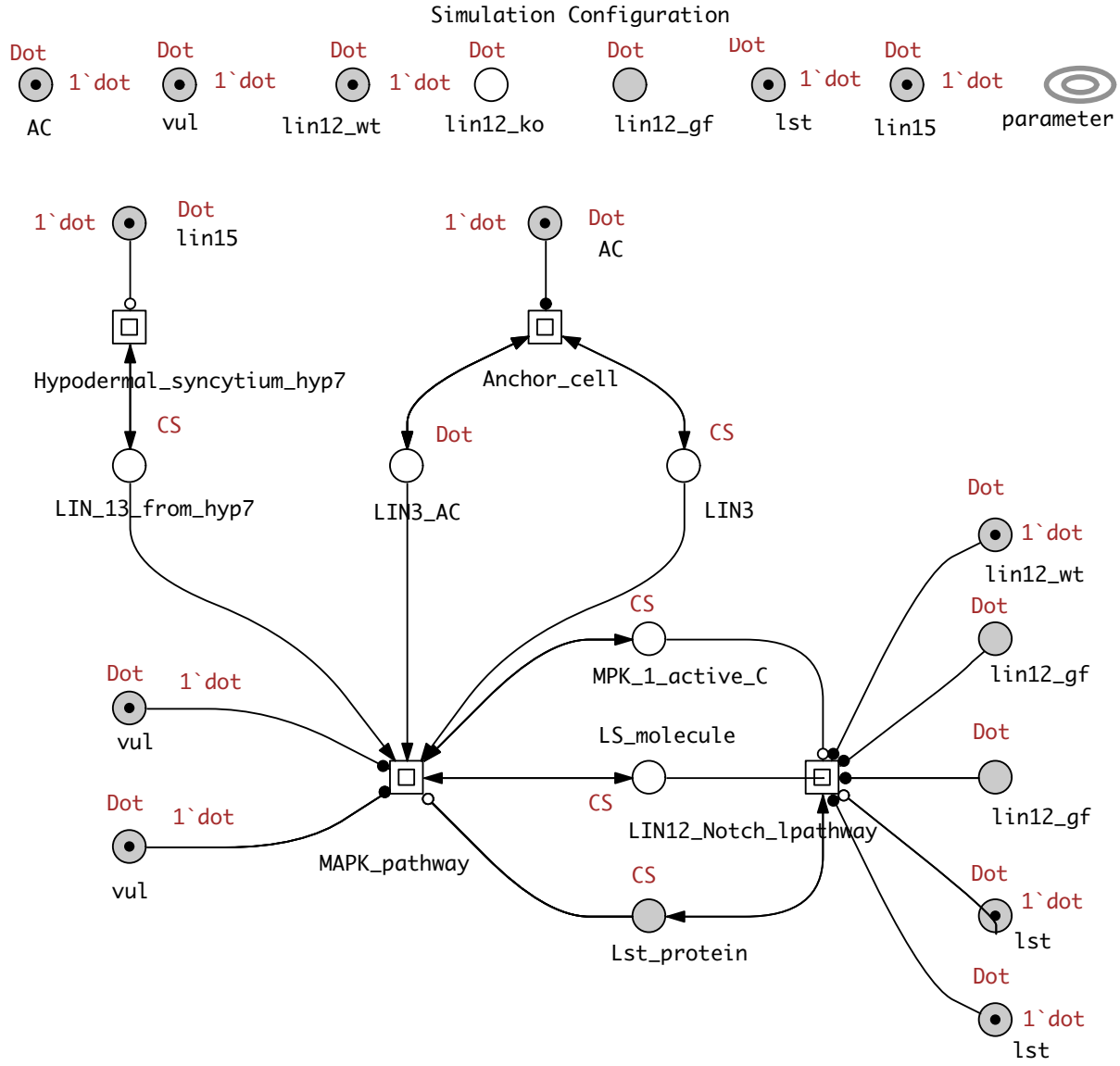


EX2: C. ELEGANS, COLOURED



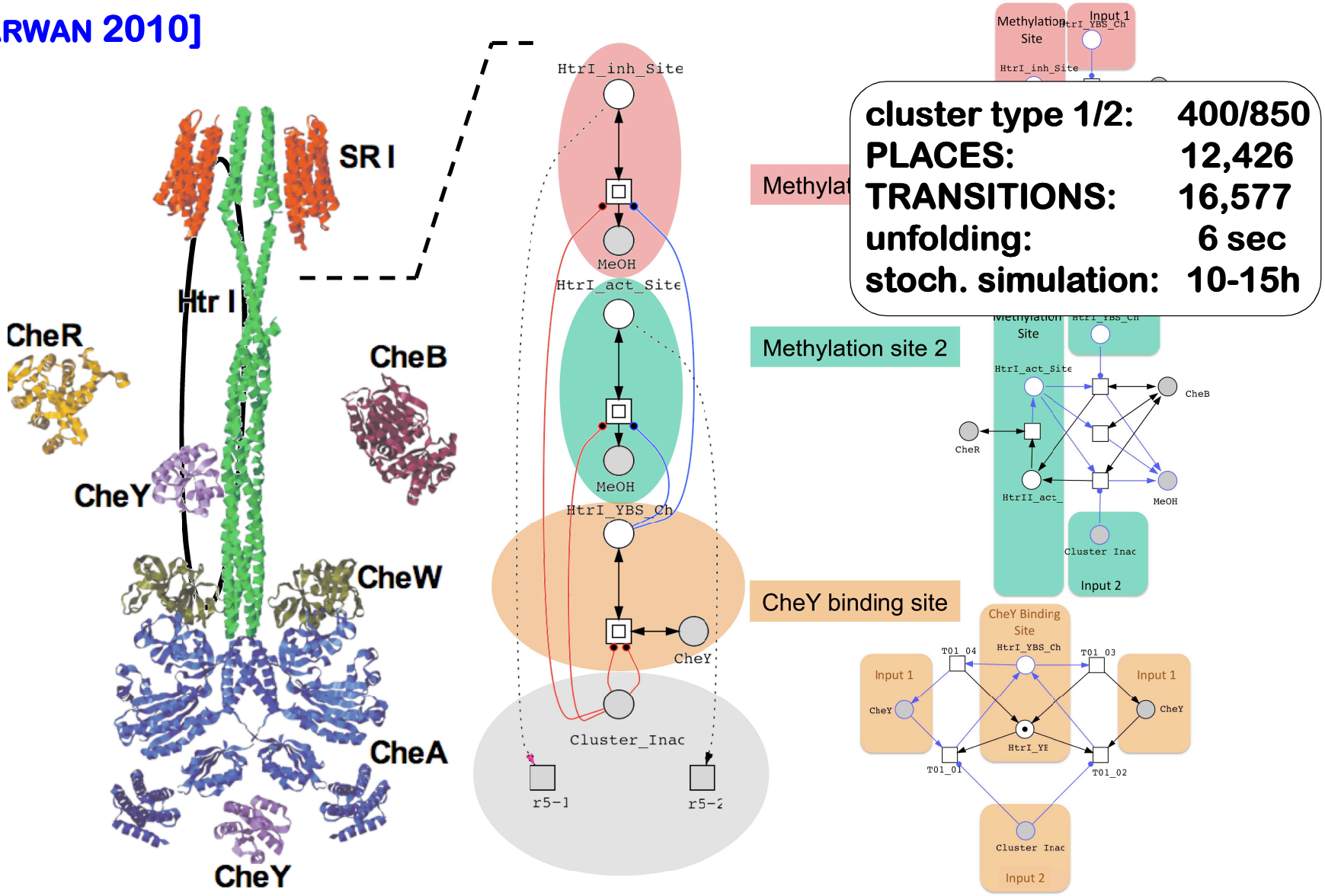
PLACES:	**44**
TRANSITIONS:	**72**

EX2: C. ELEGANS, COLOURED & HIERARCHIES



EX3 - HALOBACTERIUM SALINARUM

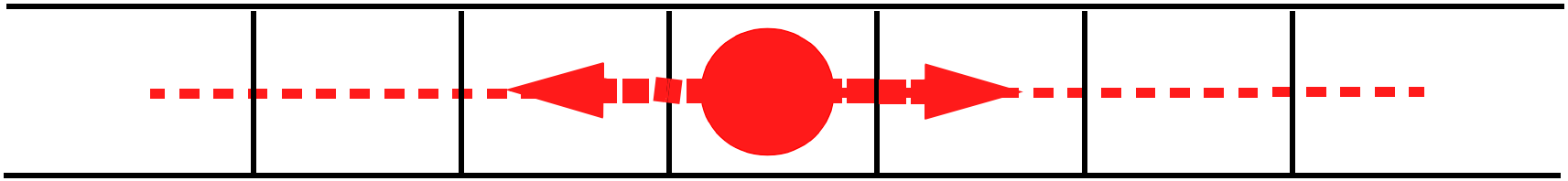
[MARWAN 2010]



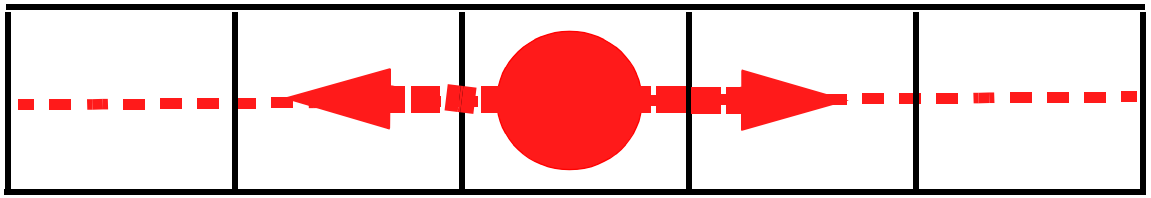
EXAMPLE:
DIFFUSION IN SPACE

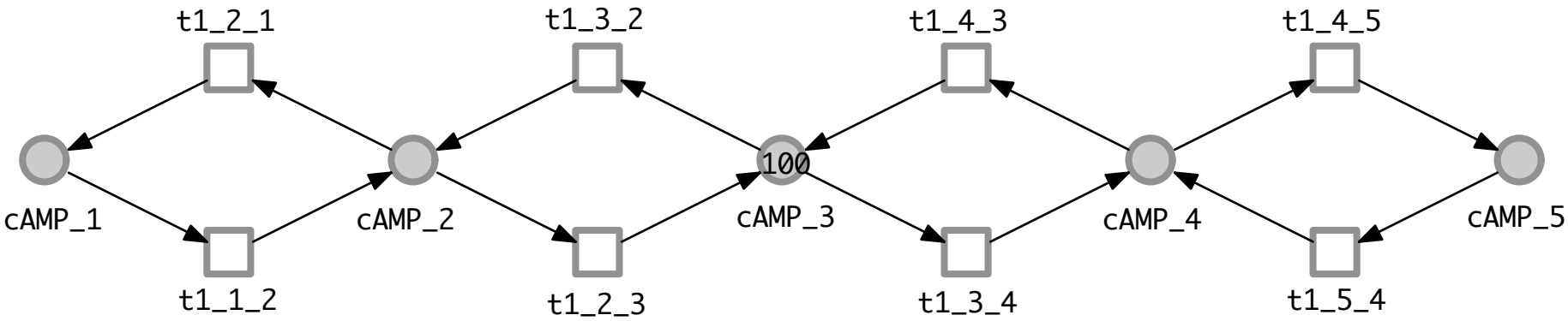
Richmond, 13/09/2011

EX4: DIFFUSION - 1D



EX4: DIFFUSION - 1D

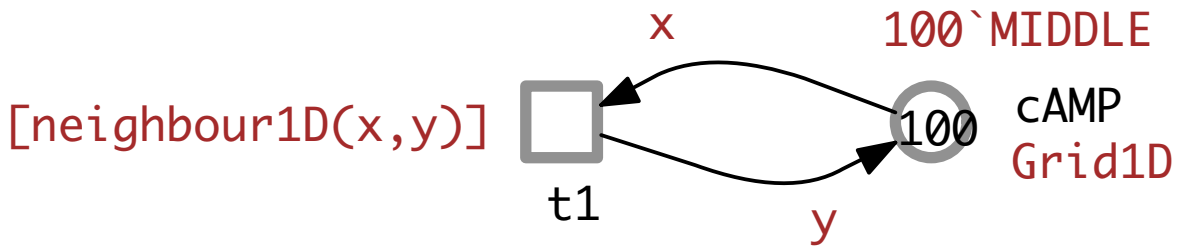




EX4: DIFFUSION - 1D

definitions

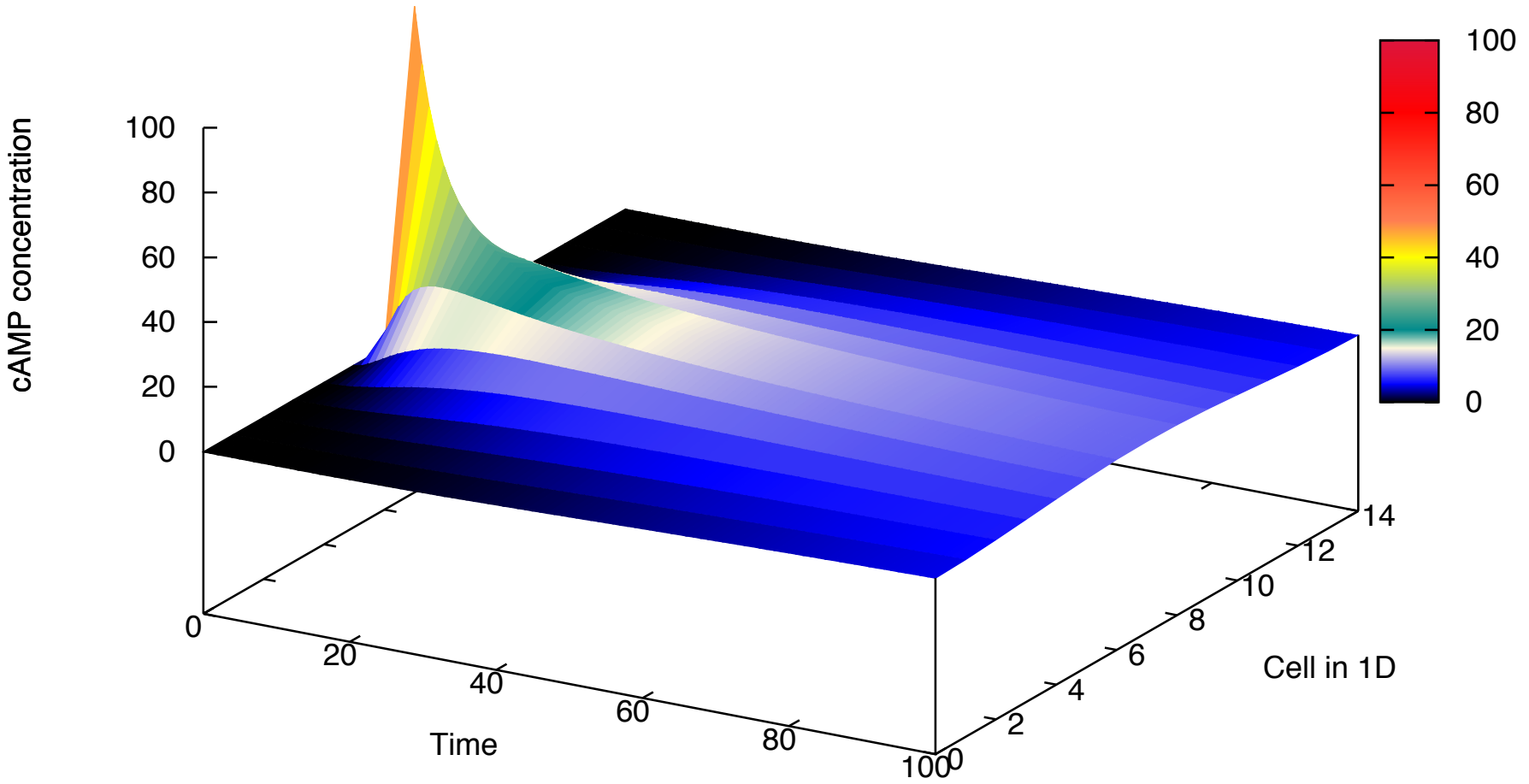
```
const D1 = 5;              // grid size
const MIDDLE = D1/2;
colorset CS = 1-D1;        // grid positions
var x,y : CS;

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



movement = changing colour

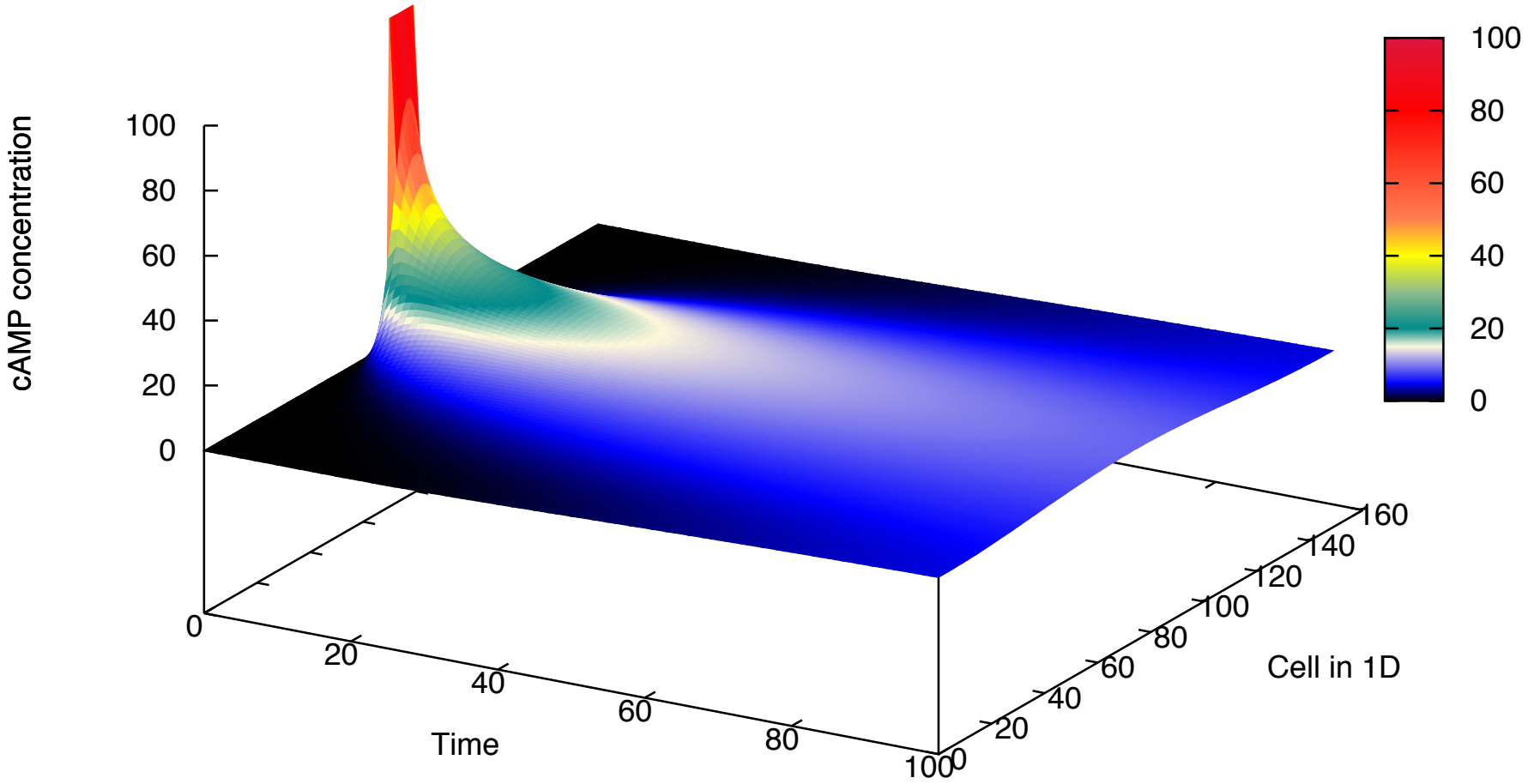
$$
\begin{aligned}
\frac{dc_1}{dt} &= k \cdot c_2 - k \cdot c_1 \\
\frac{dc_2}{dt} &= k \cdot c_1 + k \cdot c_3 - 2 \cdot k \cdot c_2 \\
\frac{dc_3}{dt} &= k \cdot c_2 + k \cdot c_4 - 2 \cdot k \cdot c_3 \\
\frac{dc_4}{dt} &= k \cdot c_3 + k \cdot c_5 - 2 \cdot k \cdot c_4 \\
\frac{dc_5}{dt} &= k \cdot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

EX4: DIFFUSION - 1D



15 GRID POSITIONS

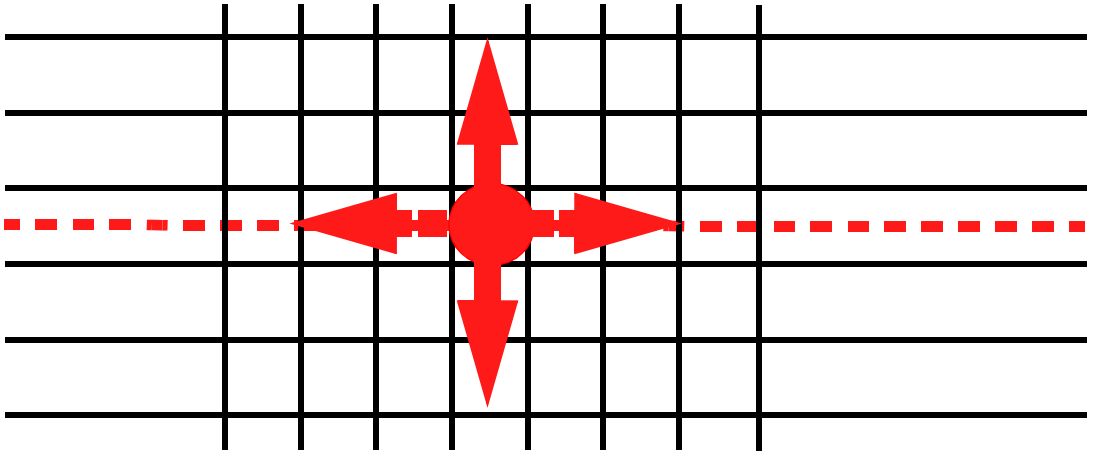
EX4: DIFFUSION - 1D



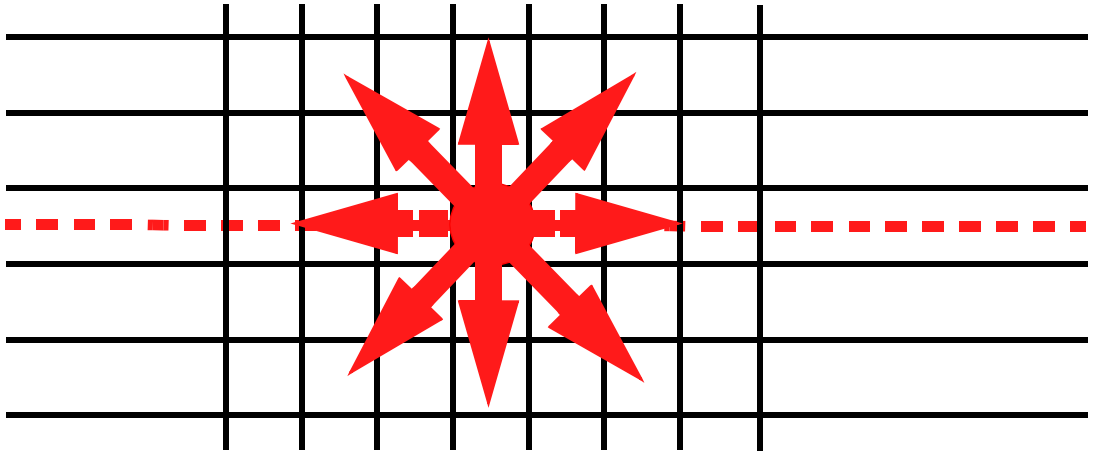
150 GRID POSITIONS, SCALING OF INITIAL MARKING AND RATES

EX4: DIFFUSION - 2D

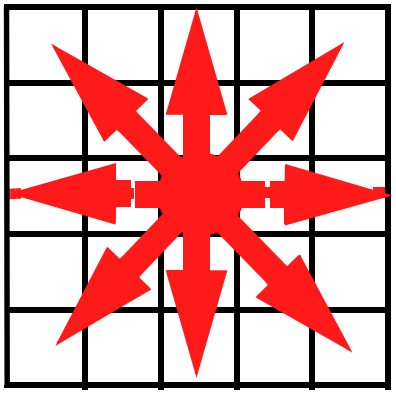
❑ SCHEME



SCHEME



SCHEME



definitions

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

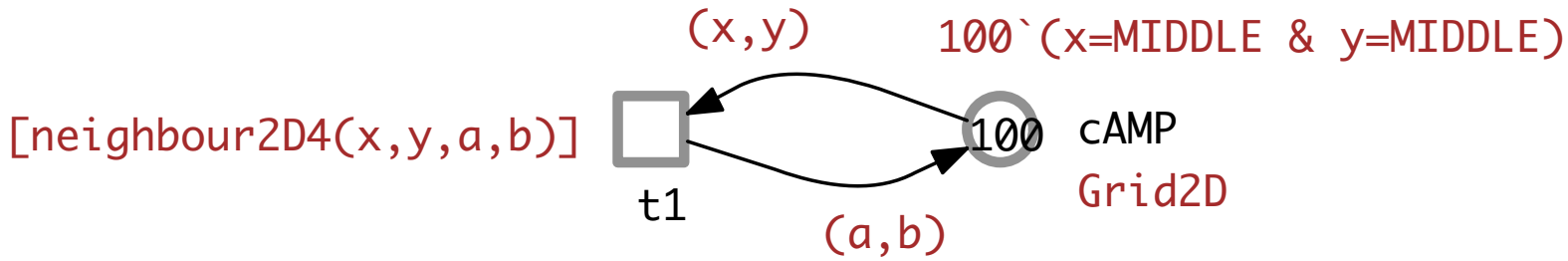
four neighbours

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

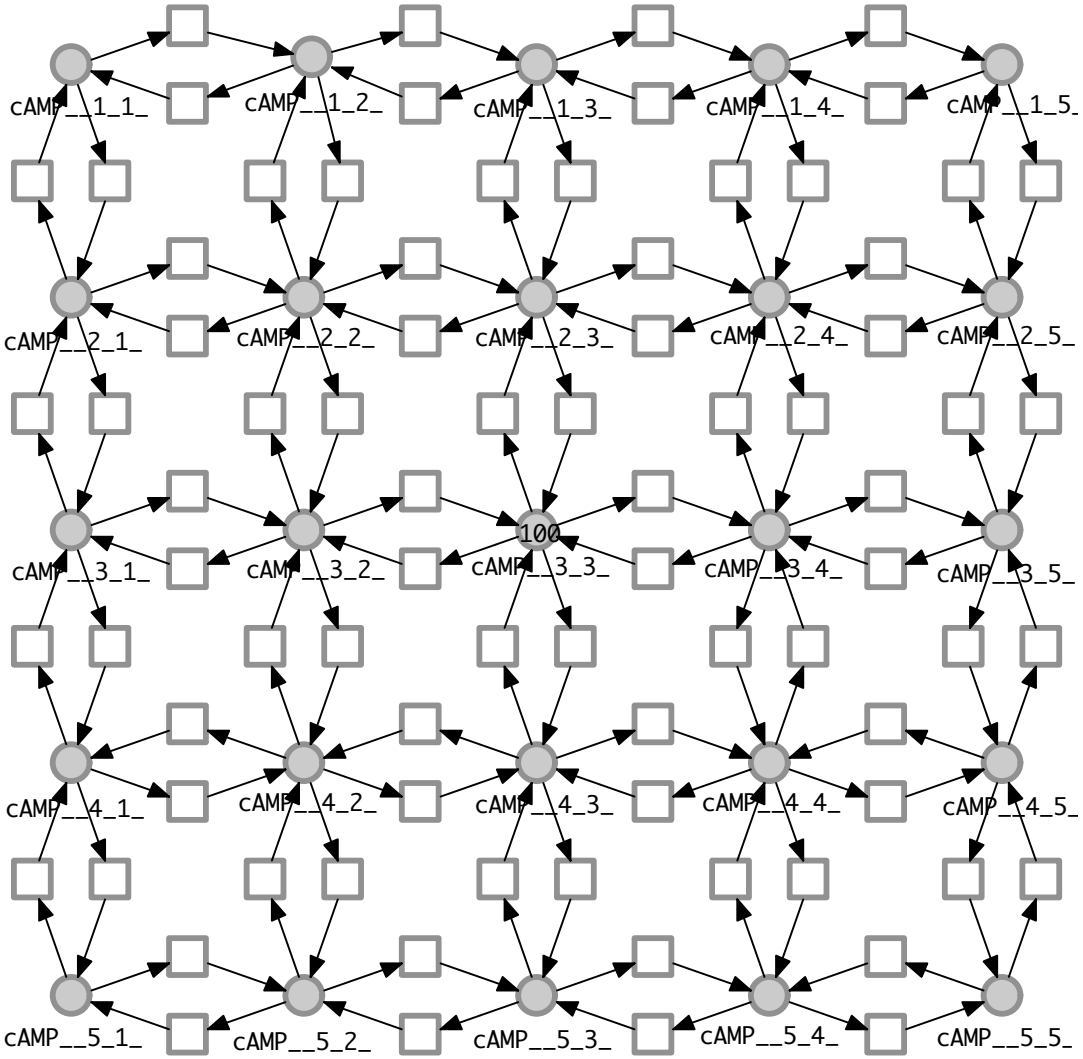
// (a,b) is one of the up to four neighbours of (x,y)

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

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



EX4: DIFFUSION - 2D4 NEIGHBOURHOOD



eight neighbours

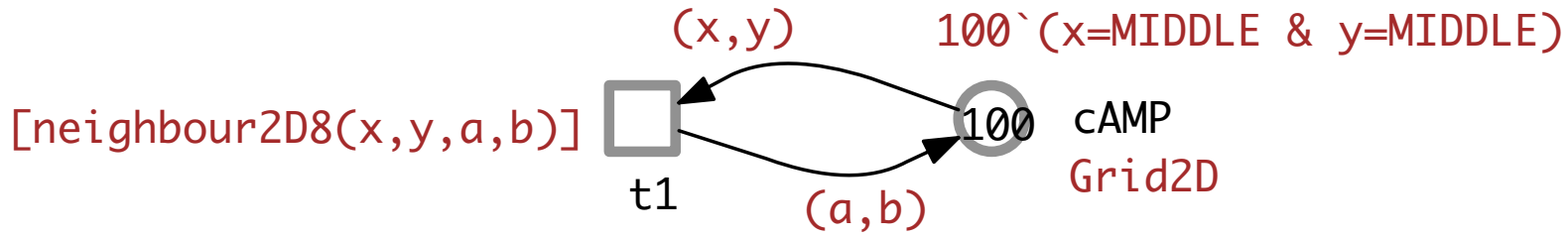
function *neighbour2D8 (CD1 x, CD2 y, CD1 a, CD2 b)* ***bool****:*

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

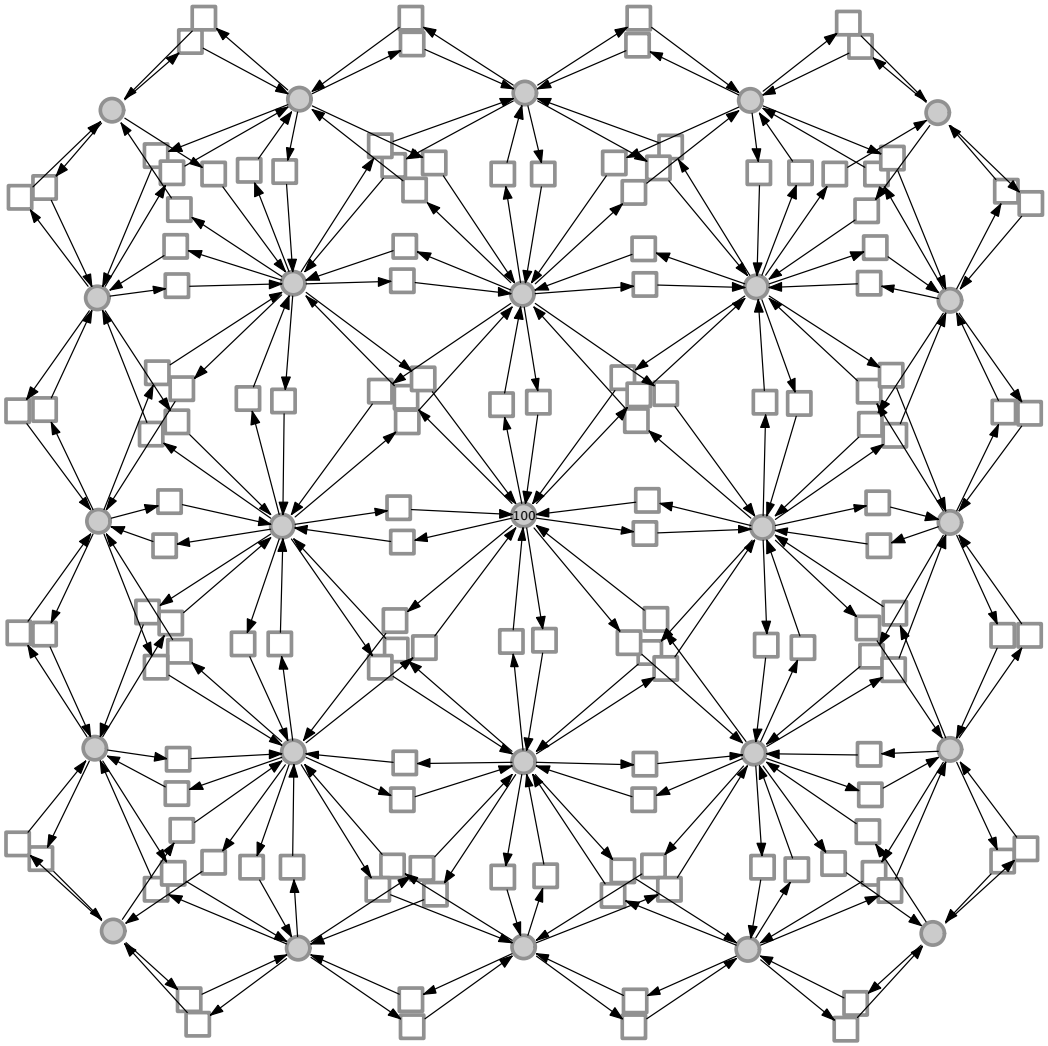
(a=x-1 | a=x | a=x+1) & (b = y-1 | b=y | b=y+1)

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

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



EX4: DIFFUSION - 2D8 NEIGHBOURHOOD



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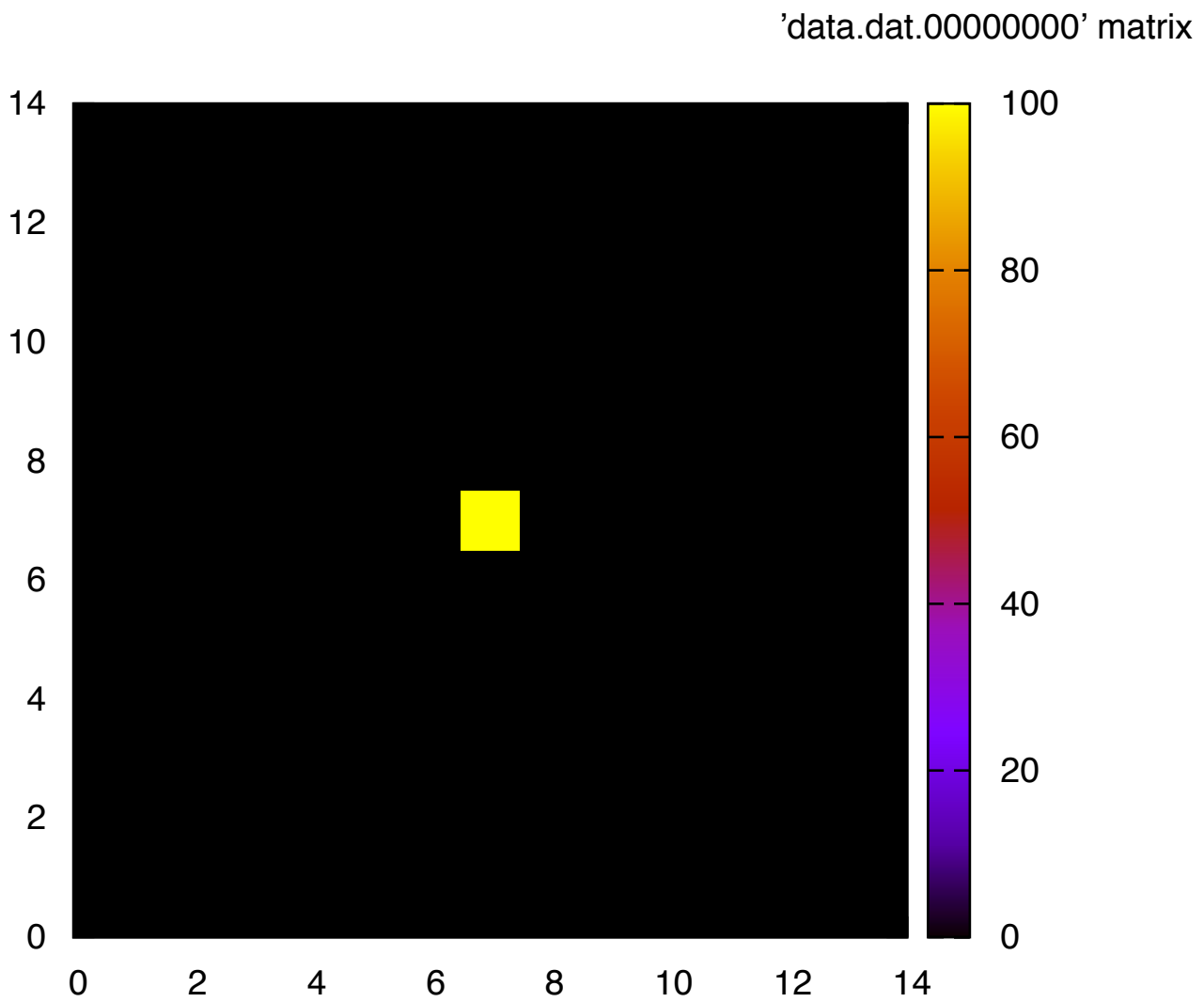
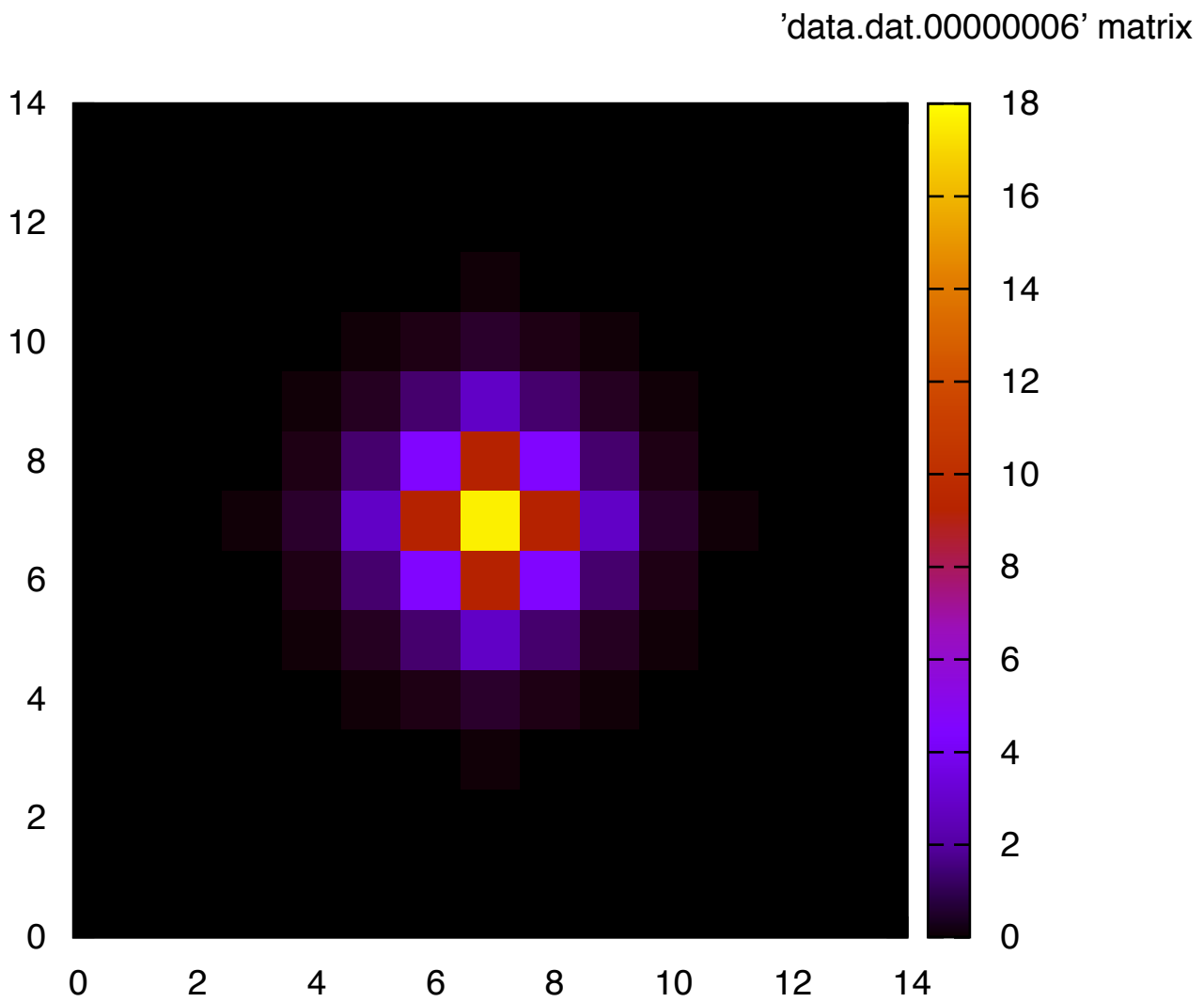
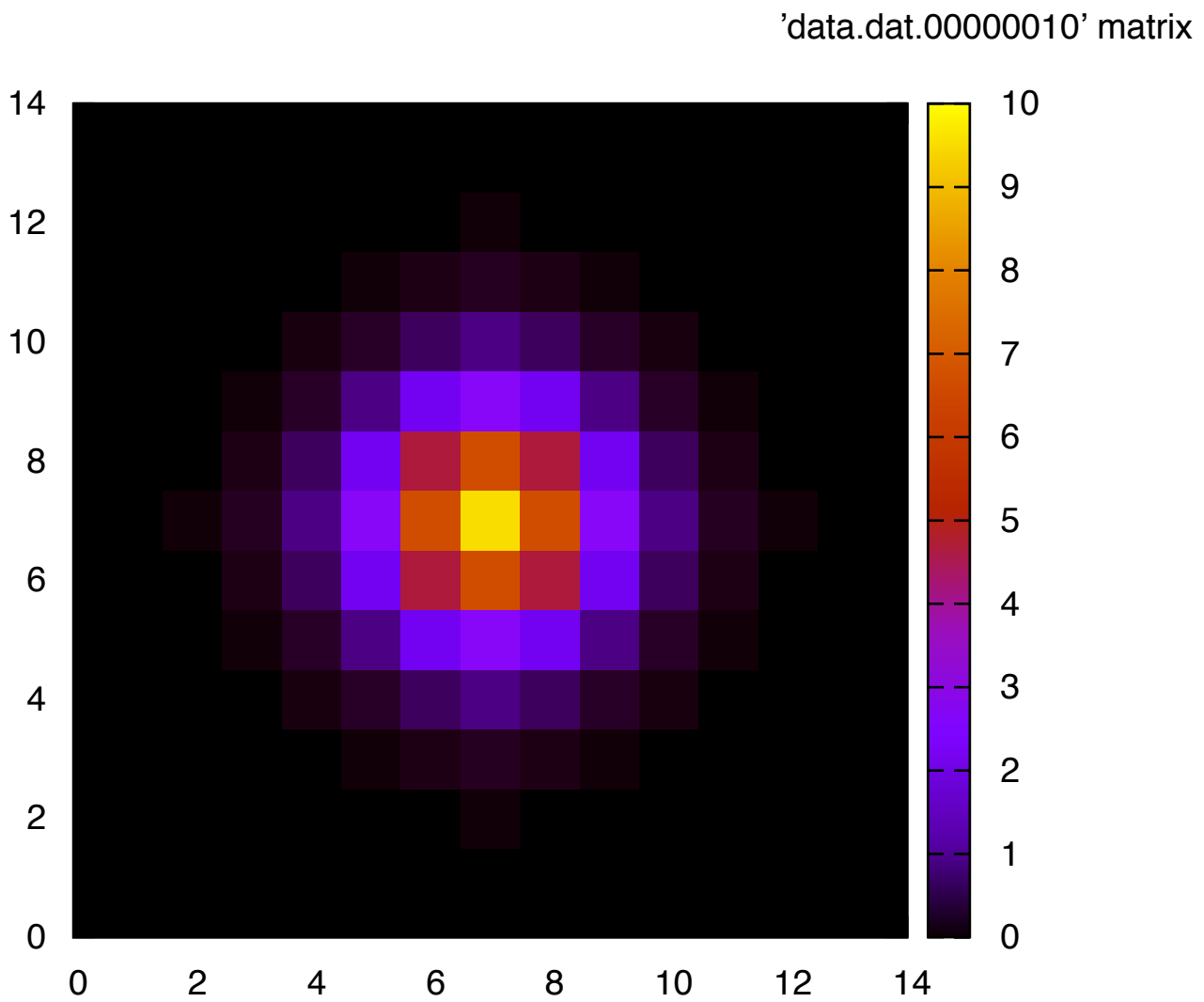
EX4: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15



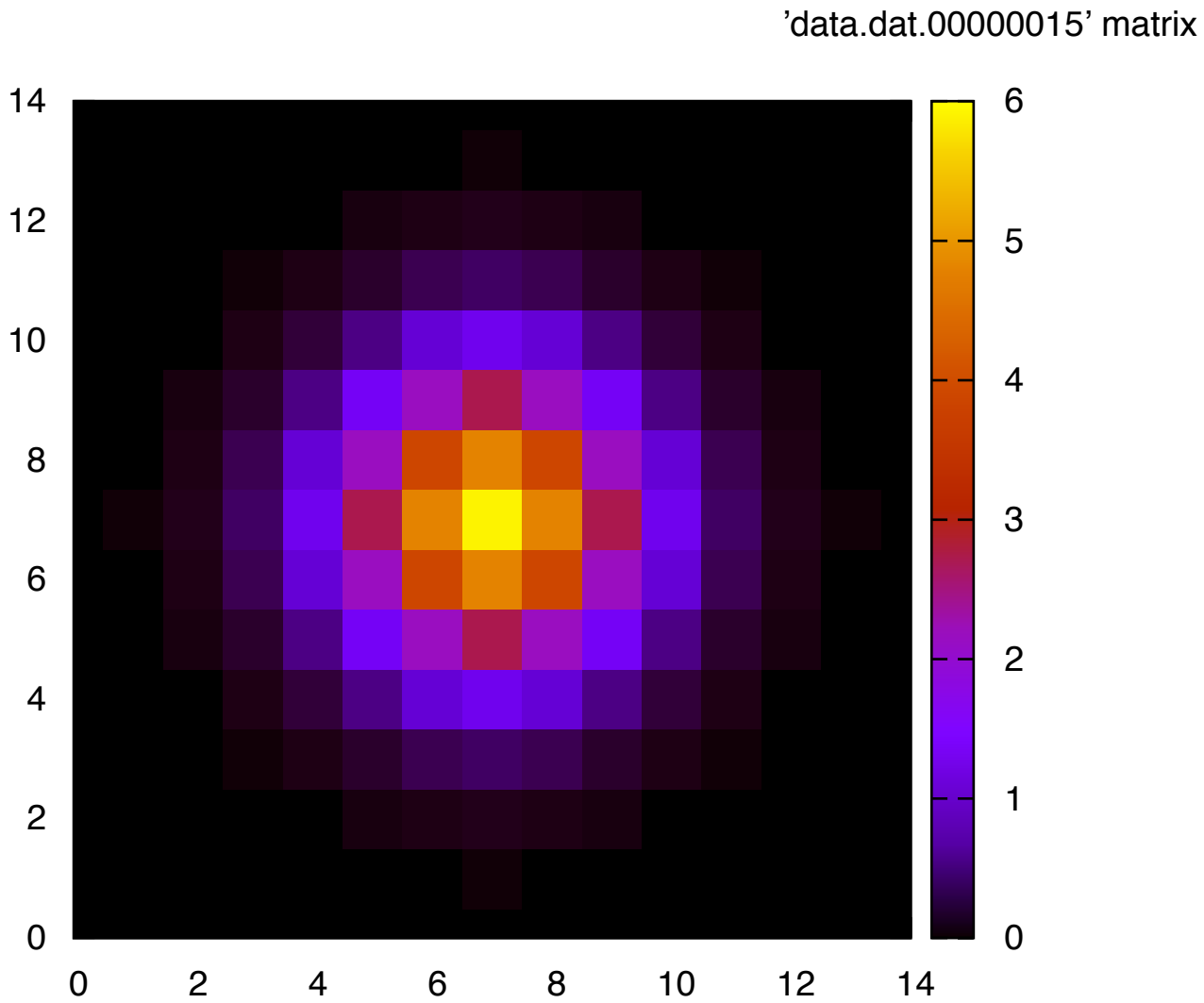
EX4: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15



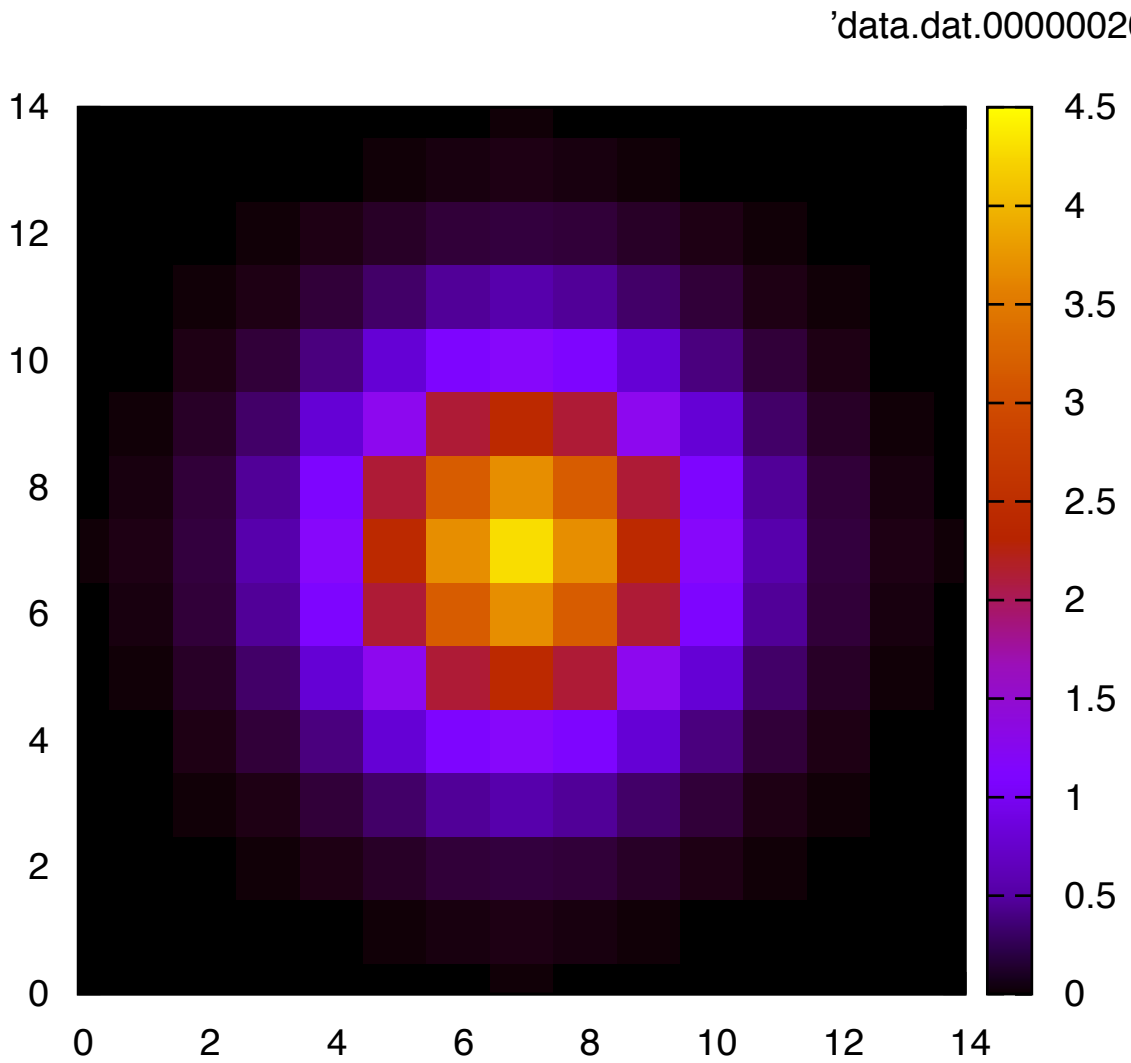
EX4: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15



EX4: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15



EX4: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15



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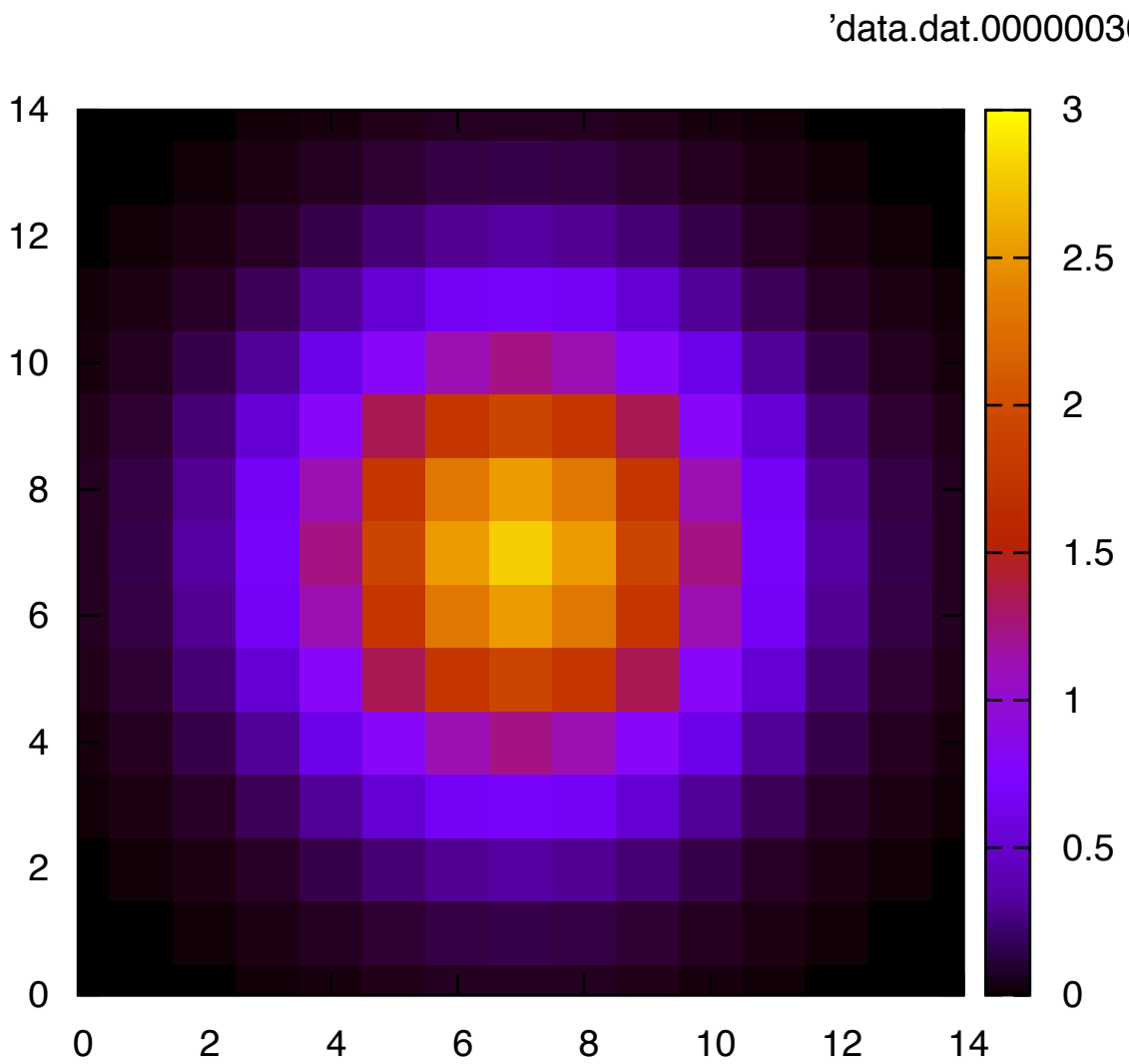

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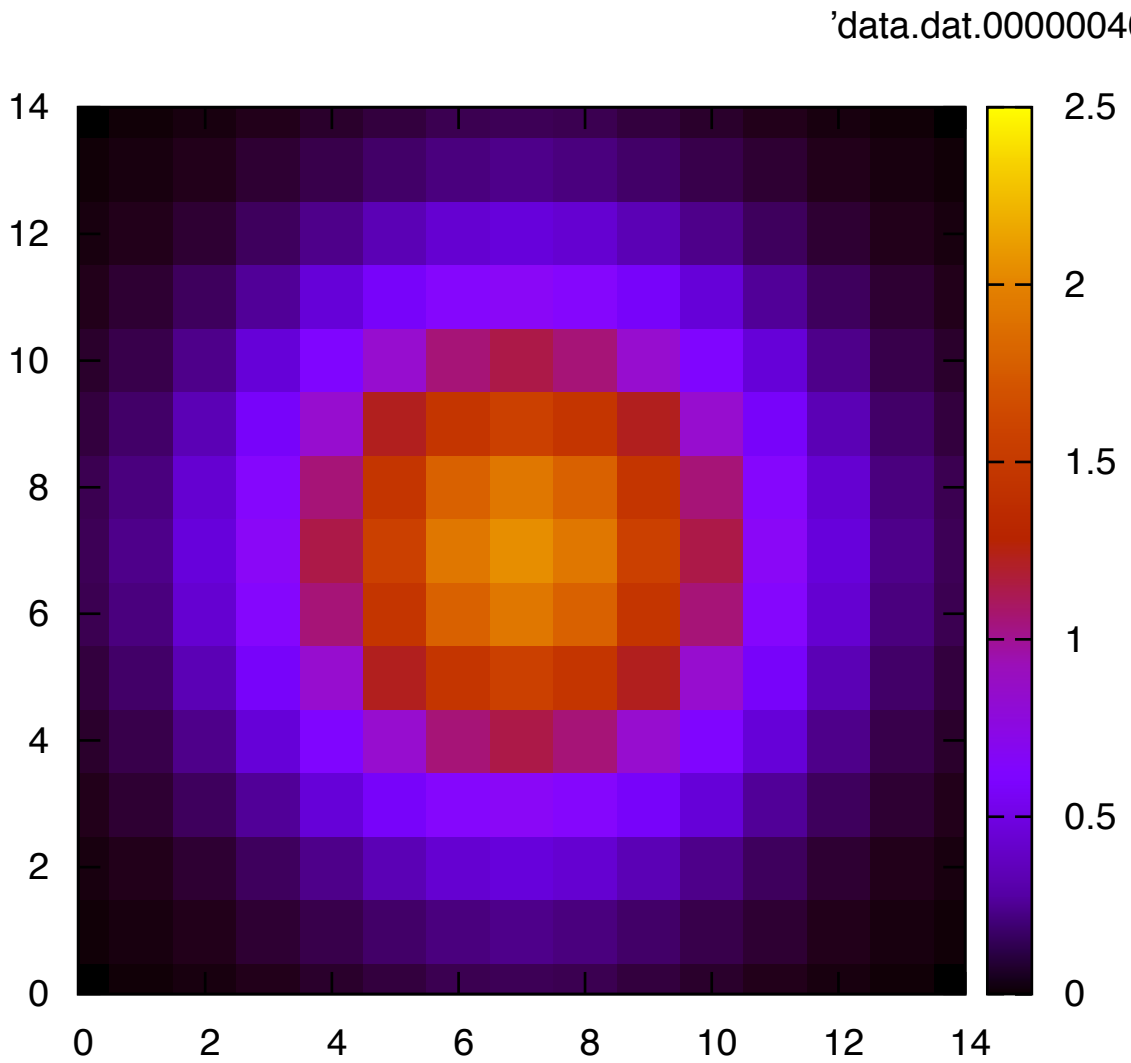

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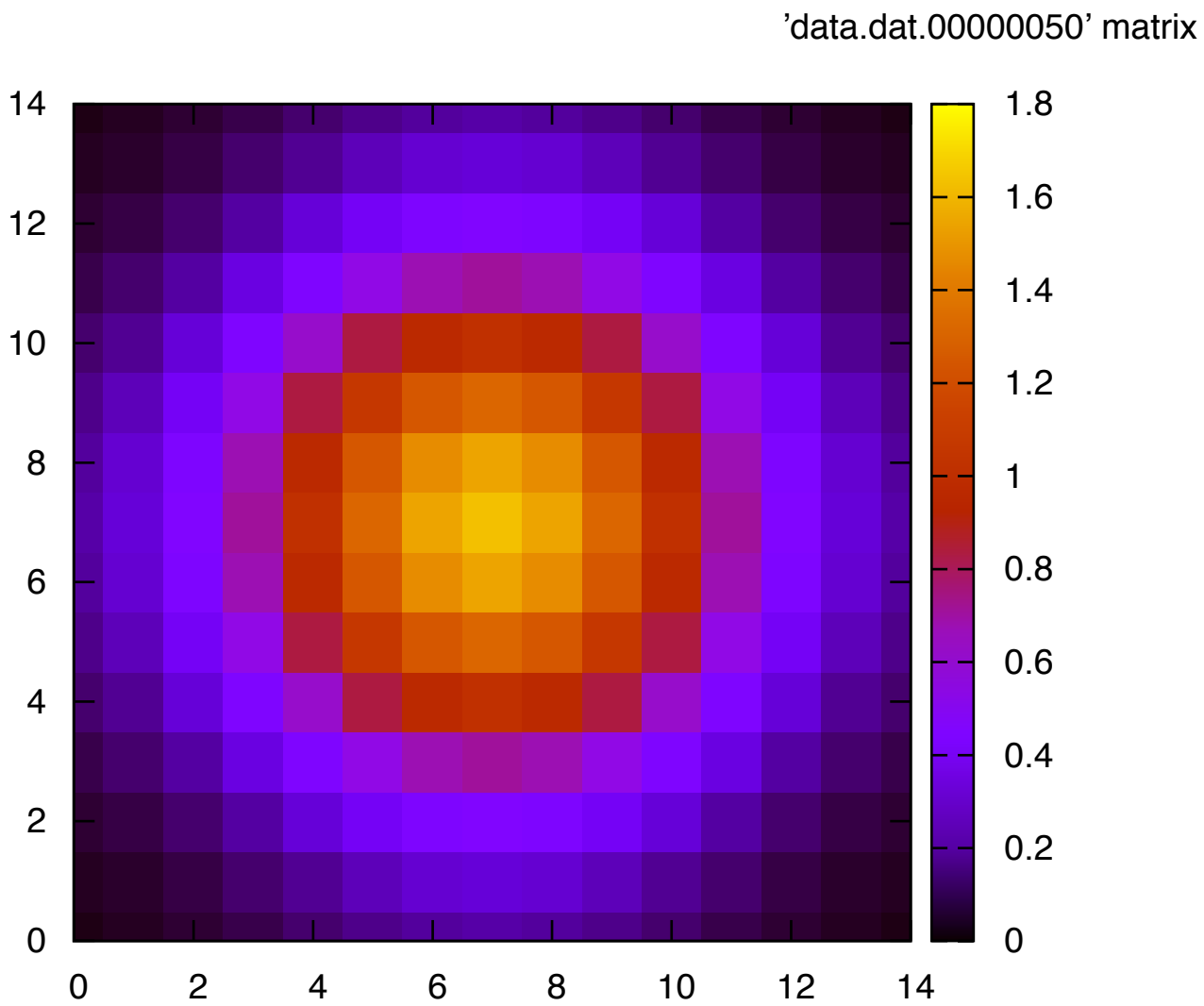
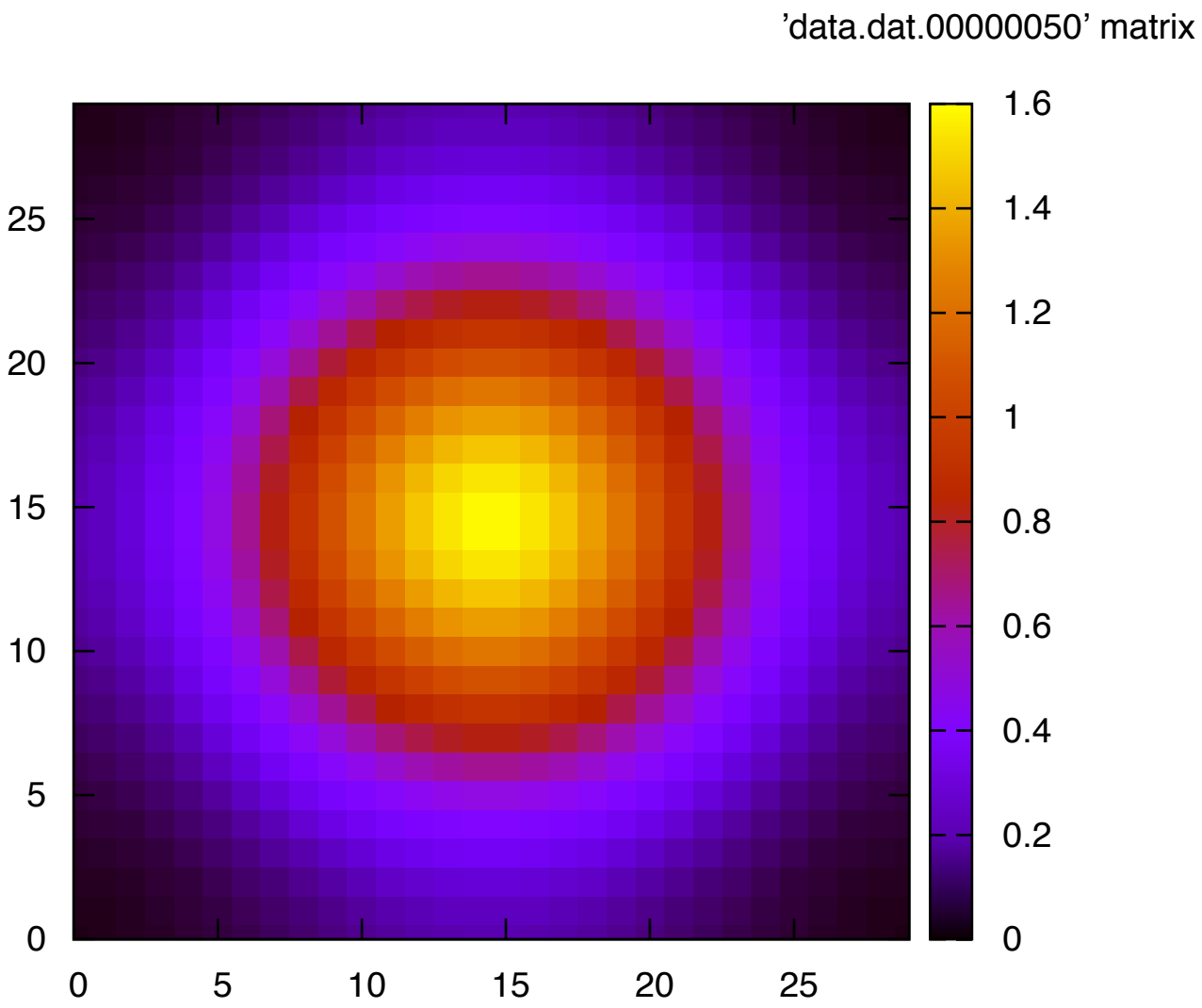
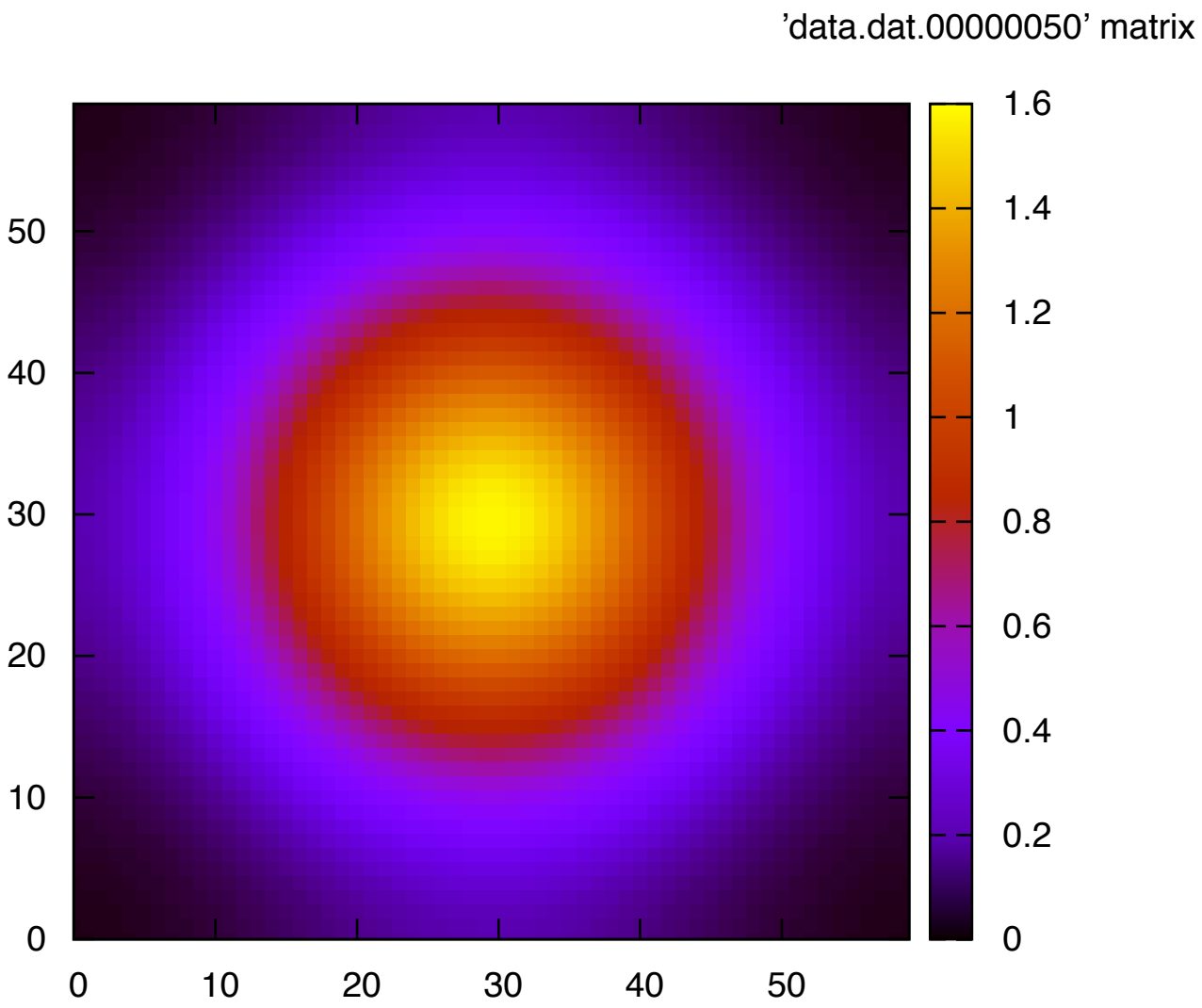


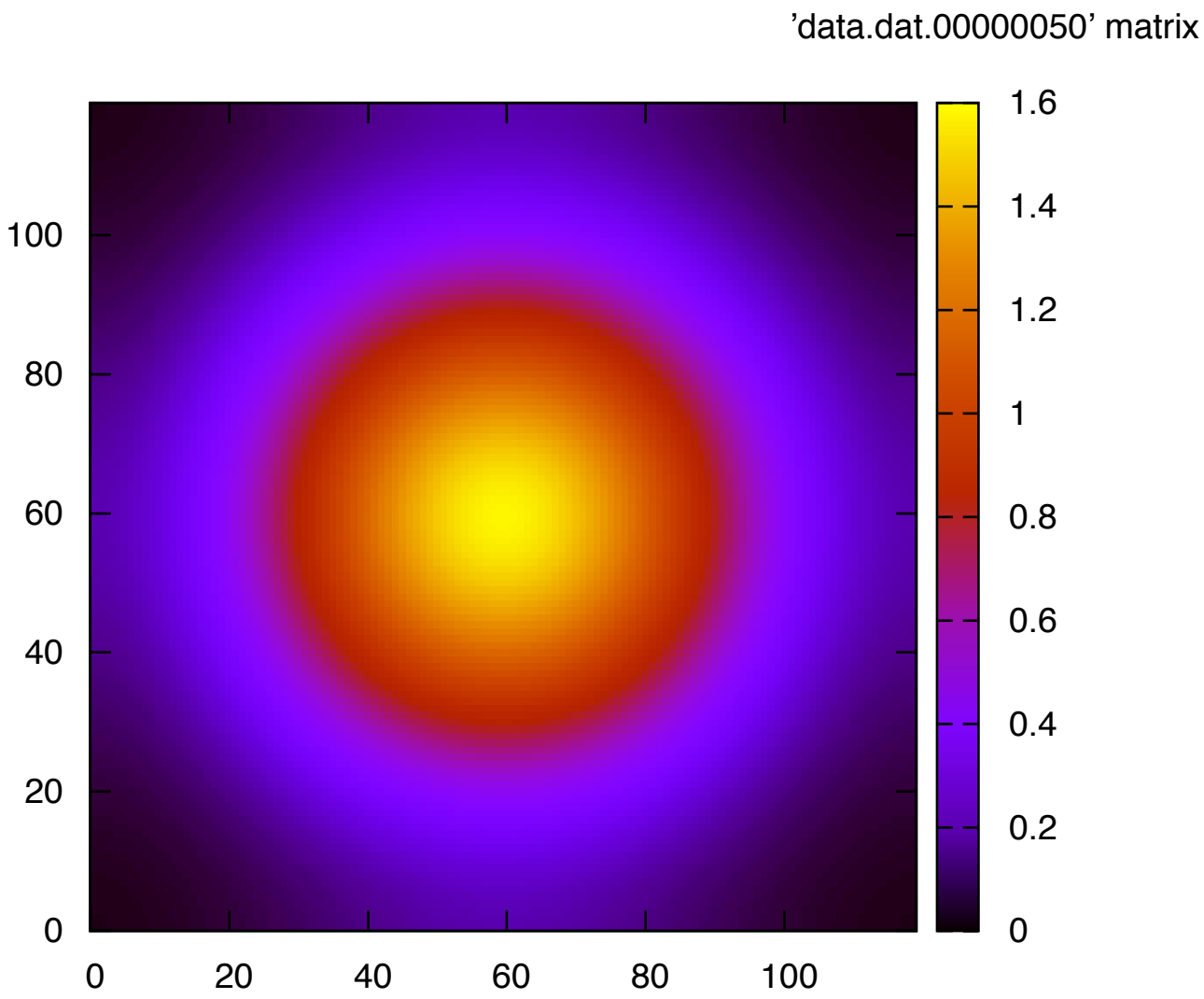
EX4: DIFFUSION - 2D4 NEIGHBOURHOOD, 30X30



EX4: DIFFUSION - 2D4 NEIGHBOURHOOD, 60X60



EX4: DIFFUSION - 2D4 NEIGHBOURHOOD, 120X120



EXAMPLE:

PHASE VARIATION IN

MULTISTRAIN CELL COLONIES

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BACKGROUND

- **method for dealing with rapidly varying environments without requiring random mutations**

- **contingency gene**

  -> *populations include variants adapted to "foreseeable" frequently encountered environmental or selective conditons*

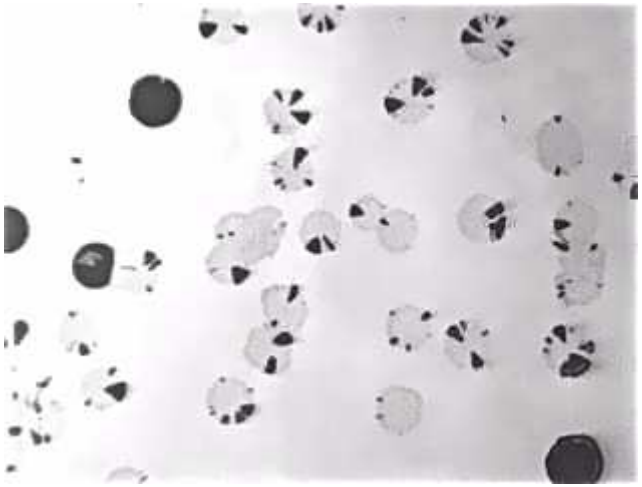
- **stochastic gene switching process**

  -> *controlled by reversible gene mutations, inversions, or epigenetic modification*

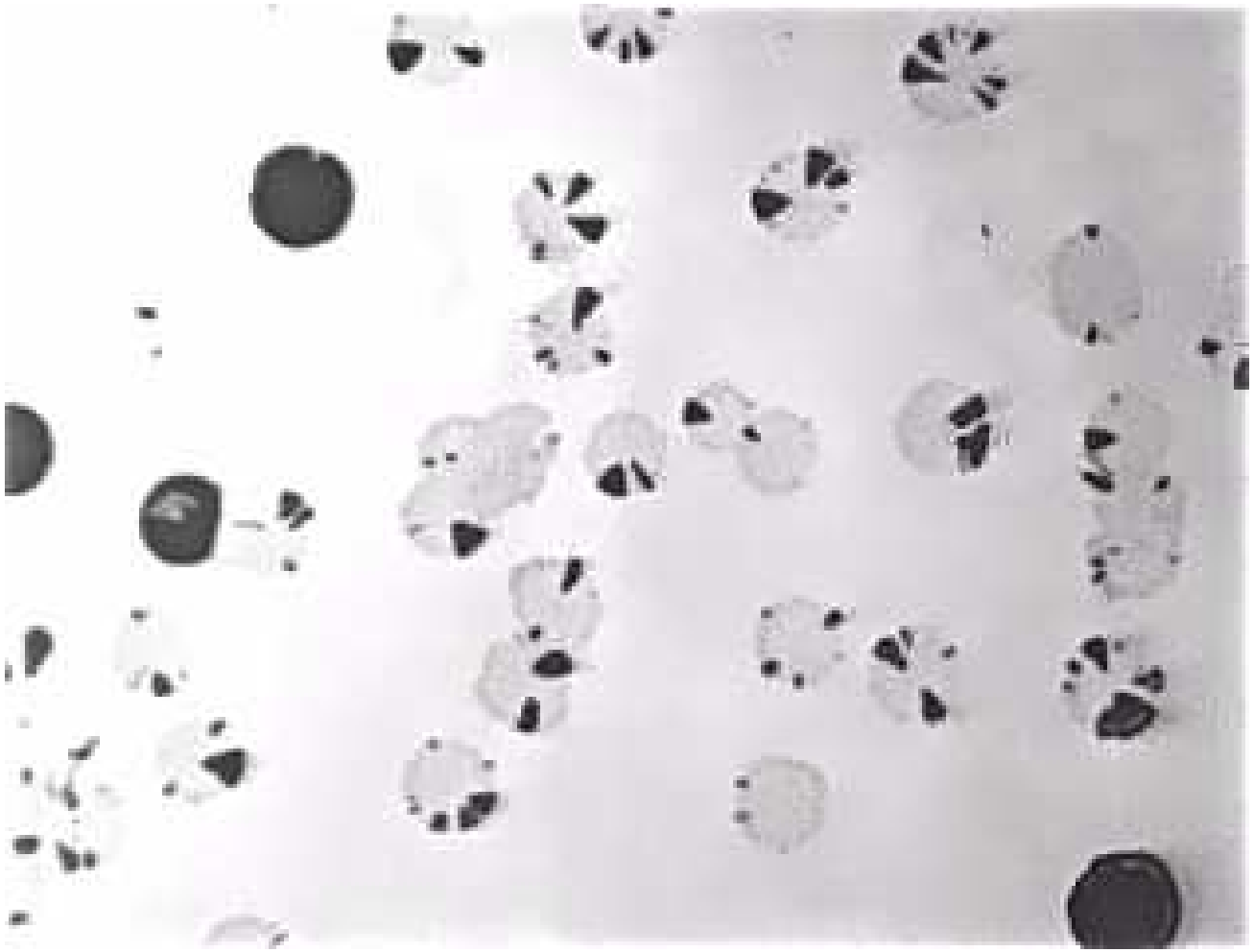
  -> *e.g. switch between two phenotypes A, B*

- **colonial sectoring**

  -> *observable effect in cultures grown in vitro*



EX5: 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] when fitness diff[illegible]nce[illegible] a[illegible] pre[illegible]nt a[illegible]d their impact on po[illegible]latio[illegible] st[illegible]

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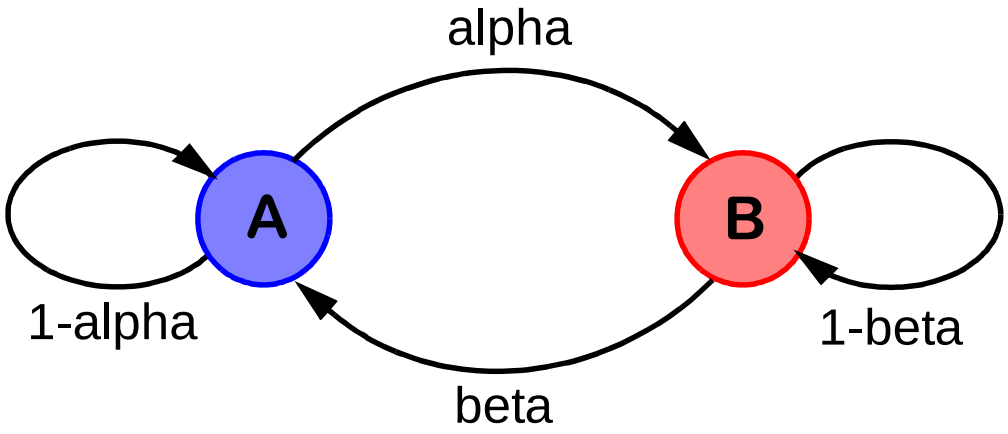
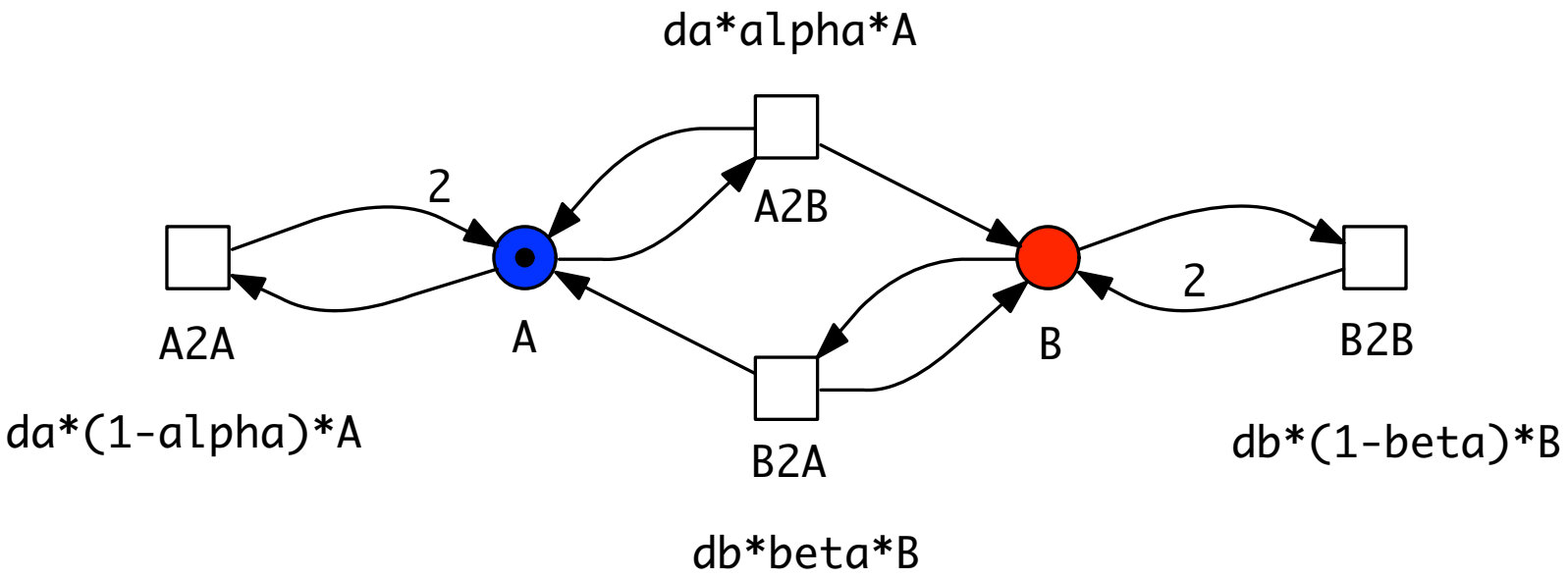
Phase variation is a mechanism of ON–OFF switching that is widely utilized by bacterial pathogens. There is currently no standardization to how the rate of phase variation is determined experimentally.

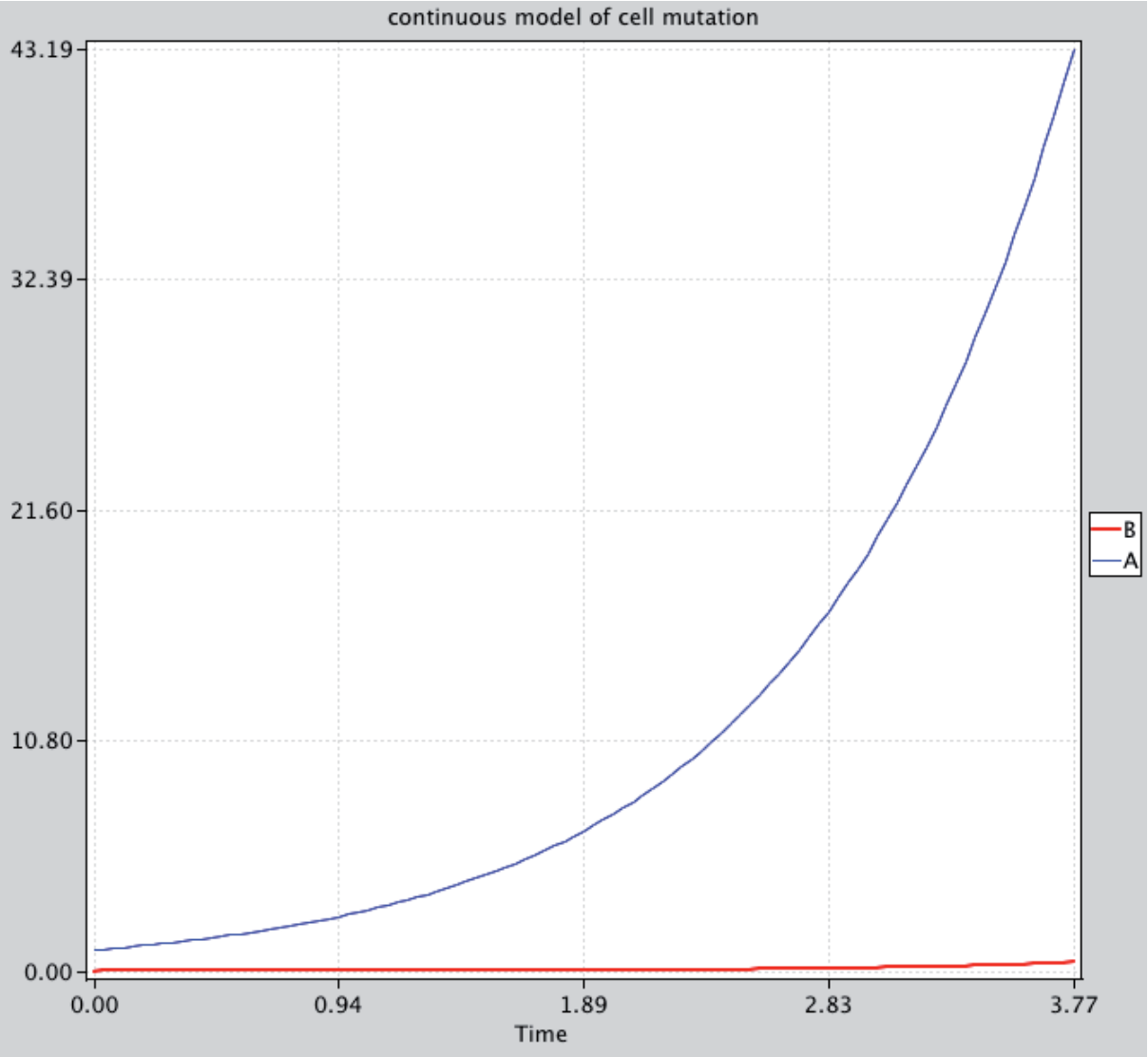
- **two cell types: phenotype A and B**
- **cell divide**
  - -> *cell division may involve mutation of the offspring*
  - -> *parent cell keeps its phenotype*
- **model parameters**
  - -> *alpha = beta - mutation rates*
  - -> *da, db - fitness of A, B*
  - -> *da/db - relative fitness*
- **output**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



EX5: CELL COLONIES, PETRI NET



EX5: CELL COLONIES, CONTINUOUS PLOT



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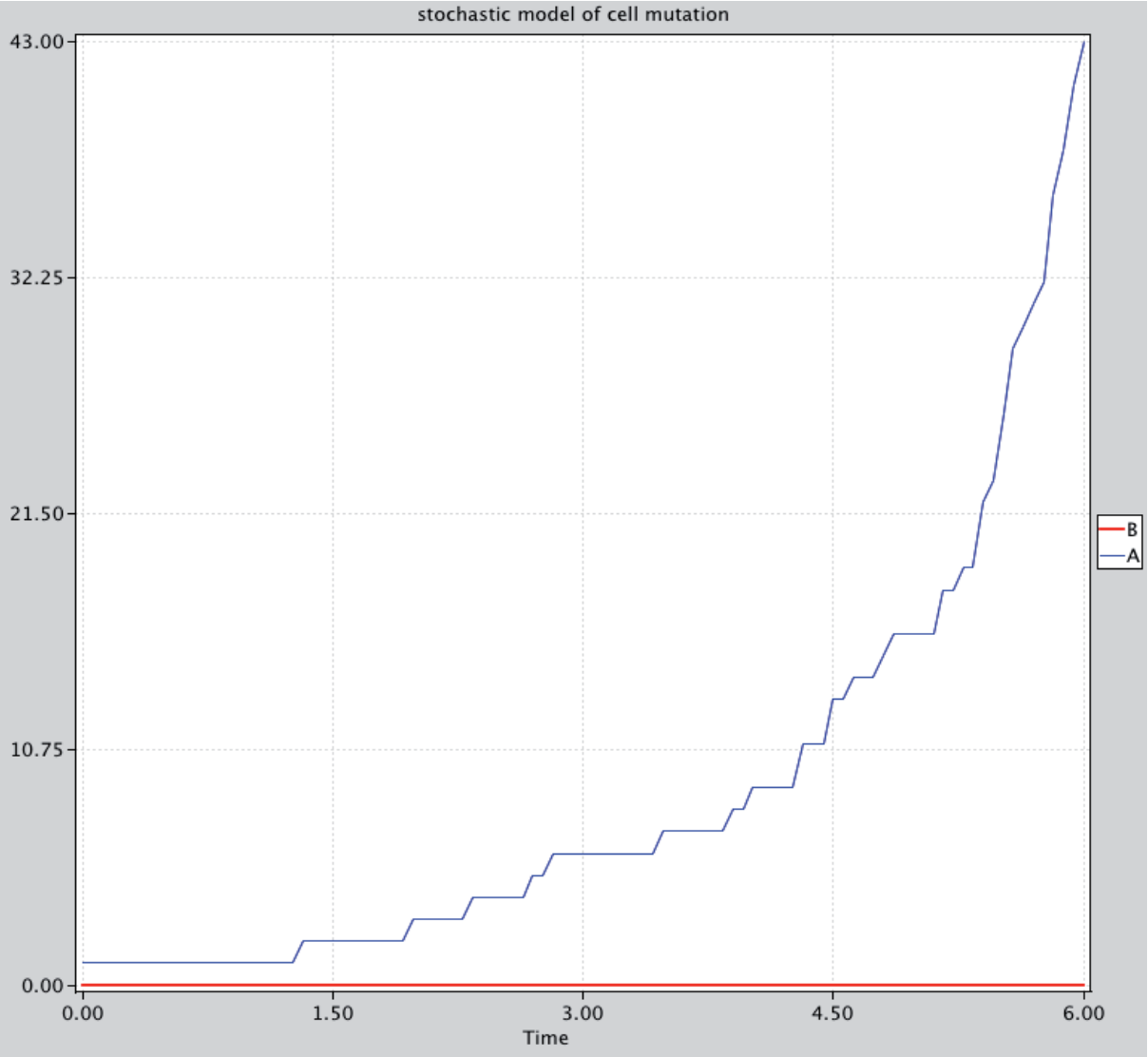
EX5: CELL COLONIES, STOCHASTIC PLOT



. . . AND THEN THERE WAS COLOUR

Kew Gardens, 24/04/2011

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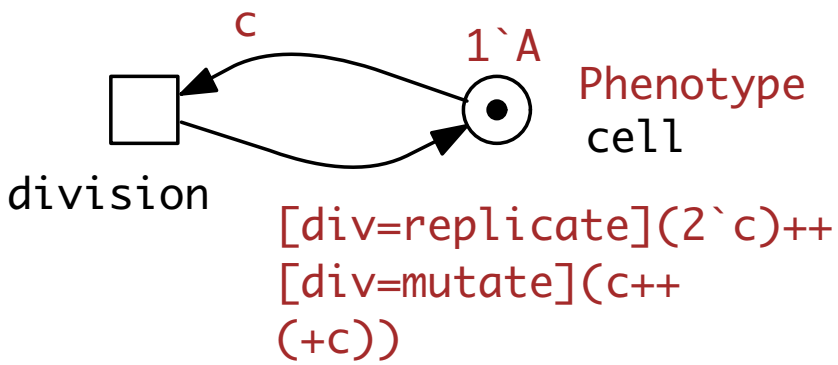
EX5: CELL COLONIES, BASIC MODEL

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 ;

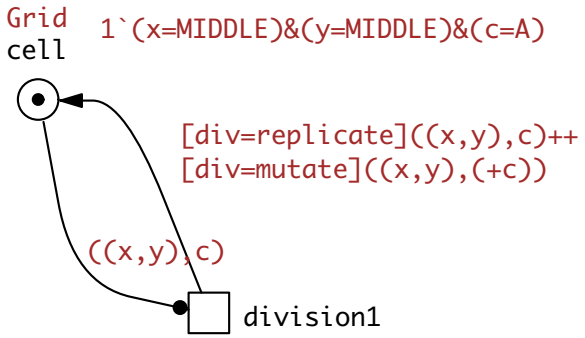
ADDING SPACE

CONTROLLING COLONY SPREADING

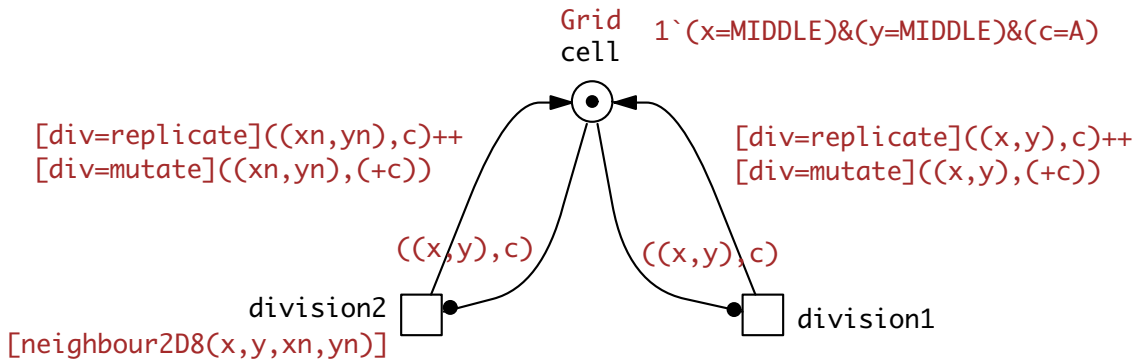
CONTROLLING THICKNESS

CONTROLLING COLONY SIZE

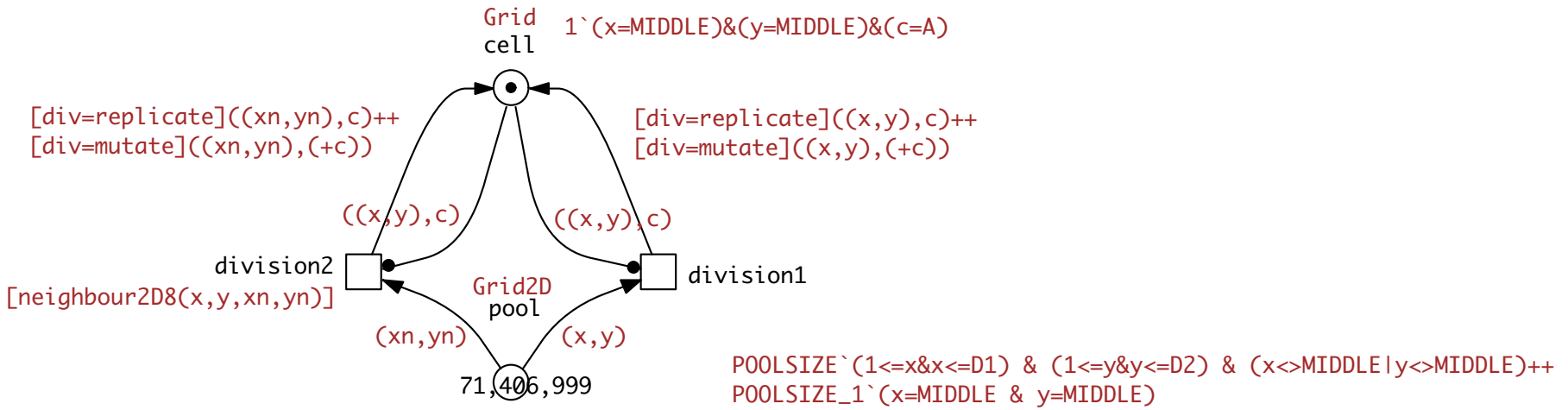
colorset Grid = **product with** Grid2D x Phenotype;



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

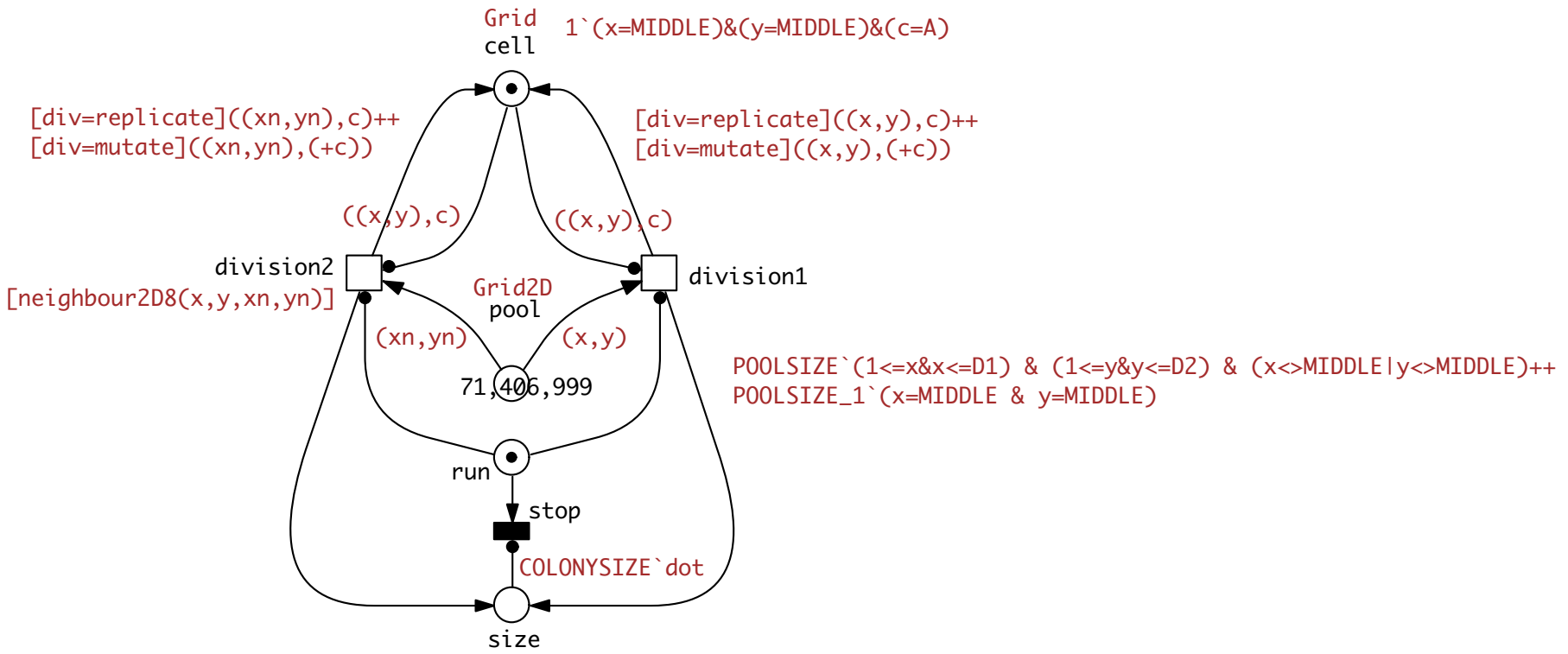


colorset Grid = **product with** Grid2D x Phenotype;



EX5: CELL COLONIES, CONTROLLING COLONY SIZE

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



EX5: 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

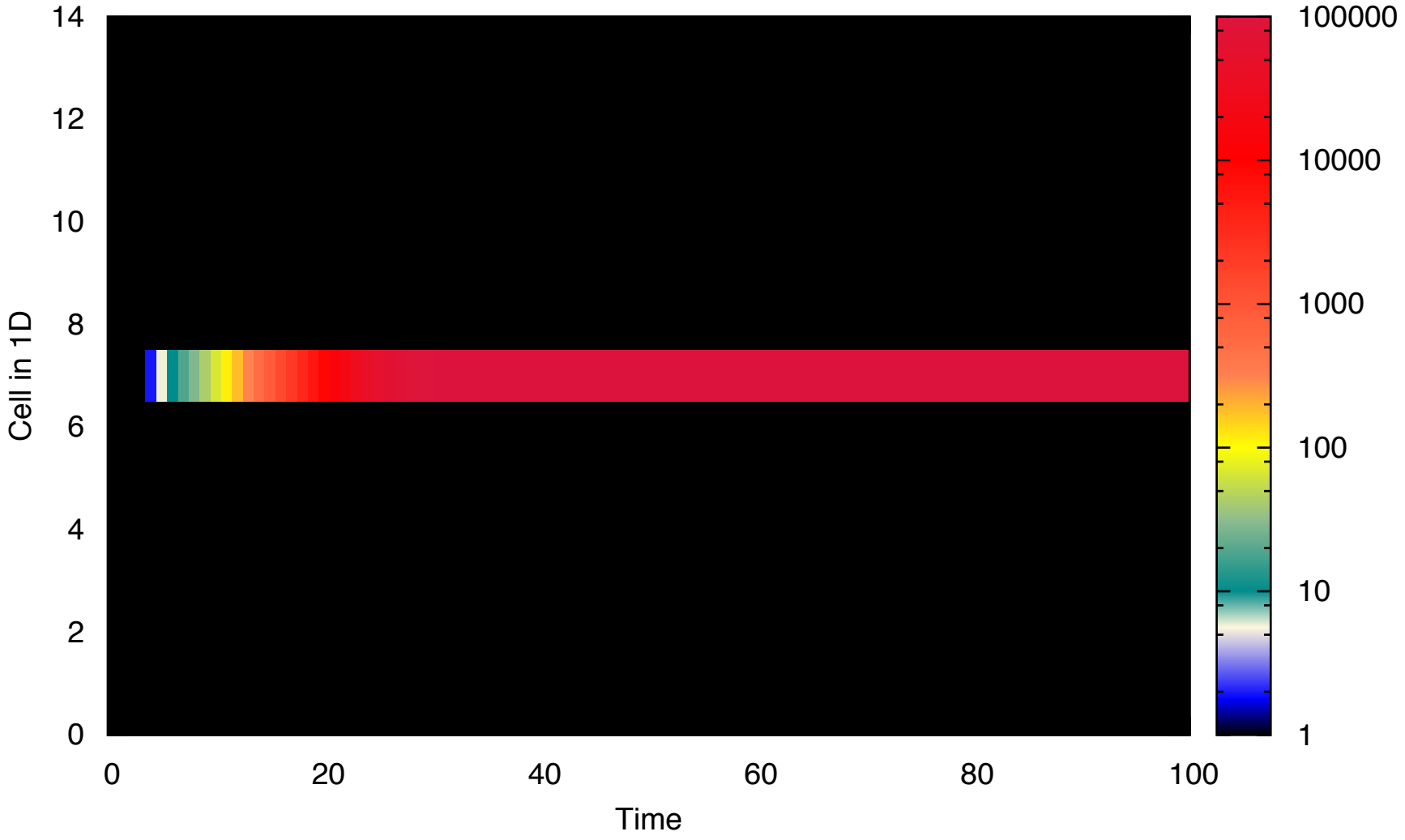
-> *61 x 61 grid: 11,163 P / 131,044 T; unfolding: 152 sec;*

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

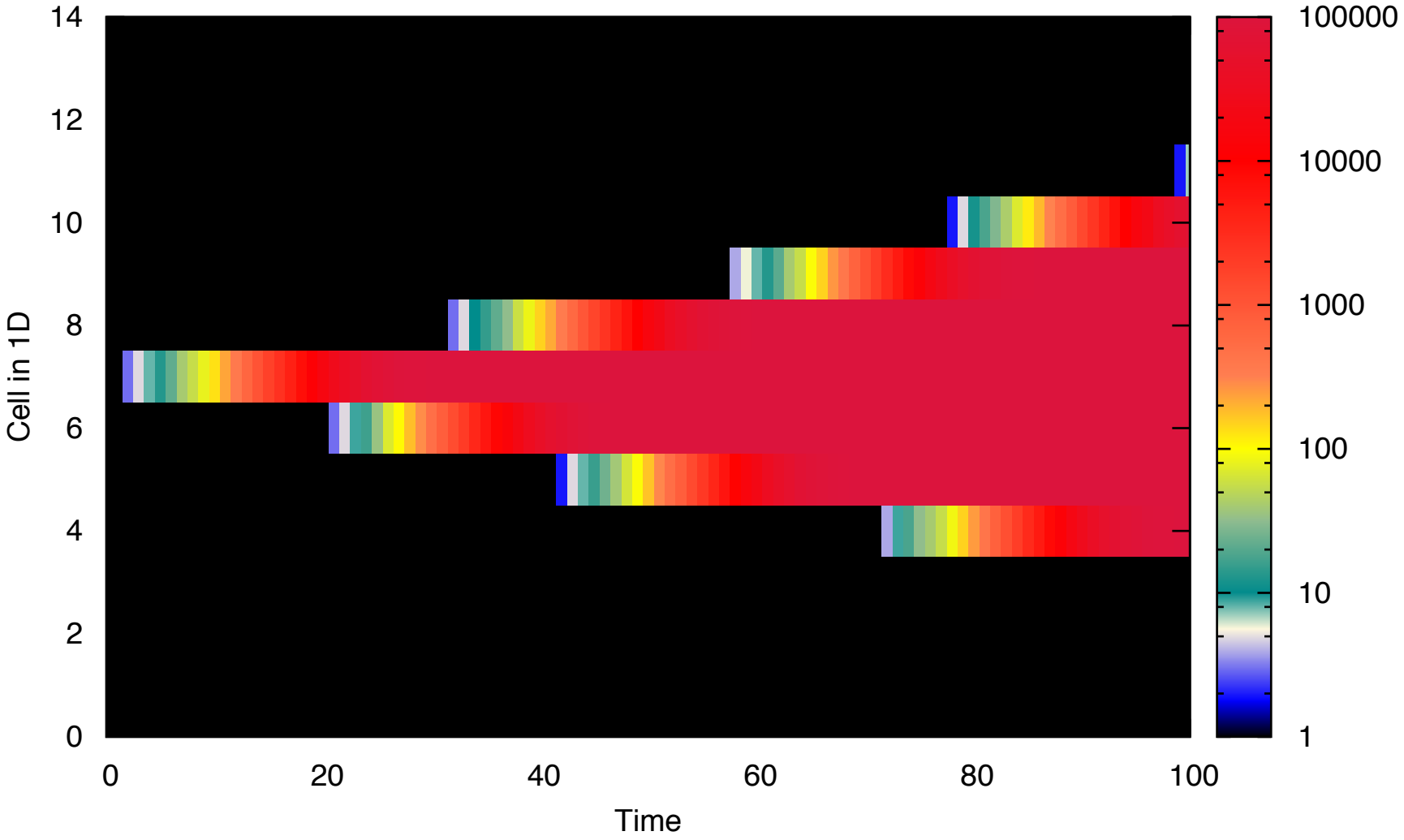
-> *runtime 1 stoch. simulation: 35-40 minutes*

. . . SOME EXPERIMENTS

EX5: 1D15 - VARYING MOBILITY, GAMMA = 100



EX5: 1D15 - VARYING MOBILITY, GAMMA = 99.999



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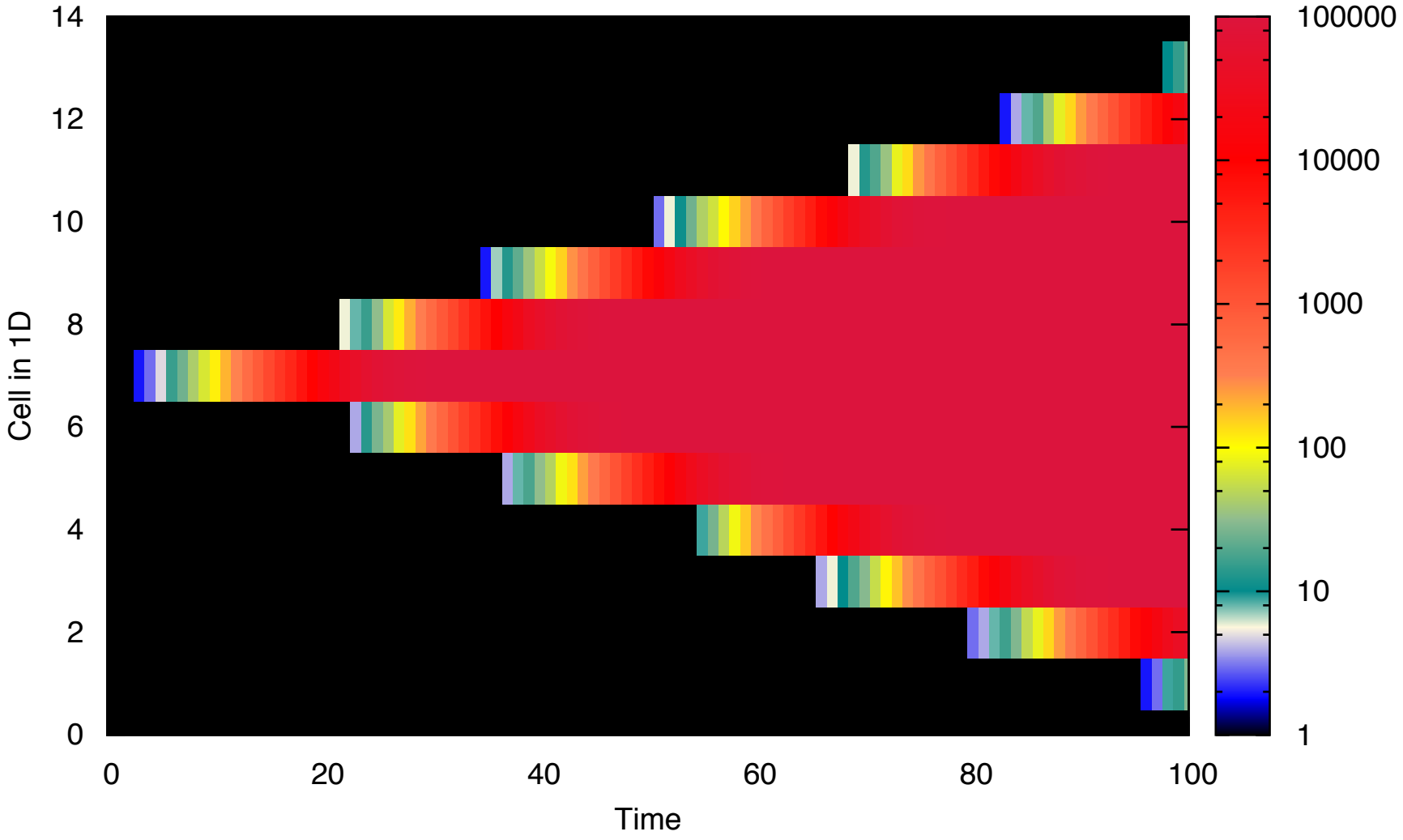
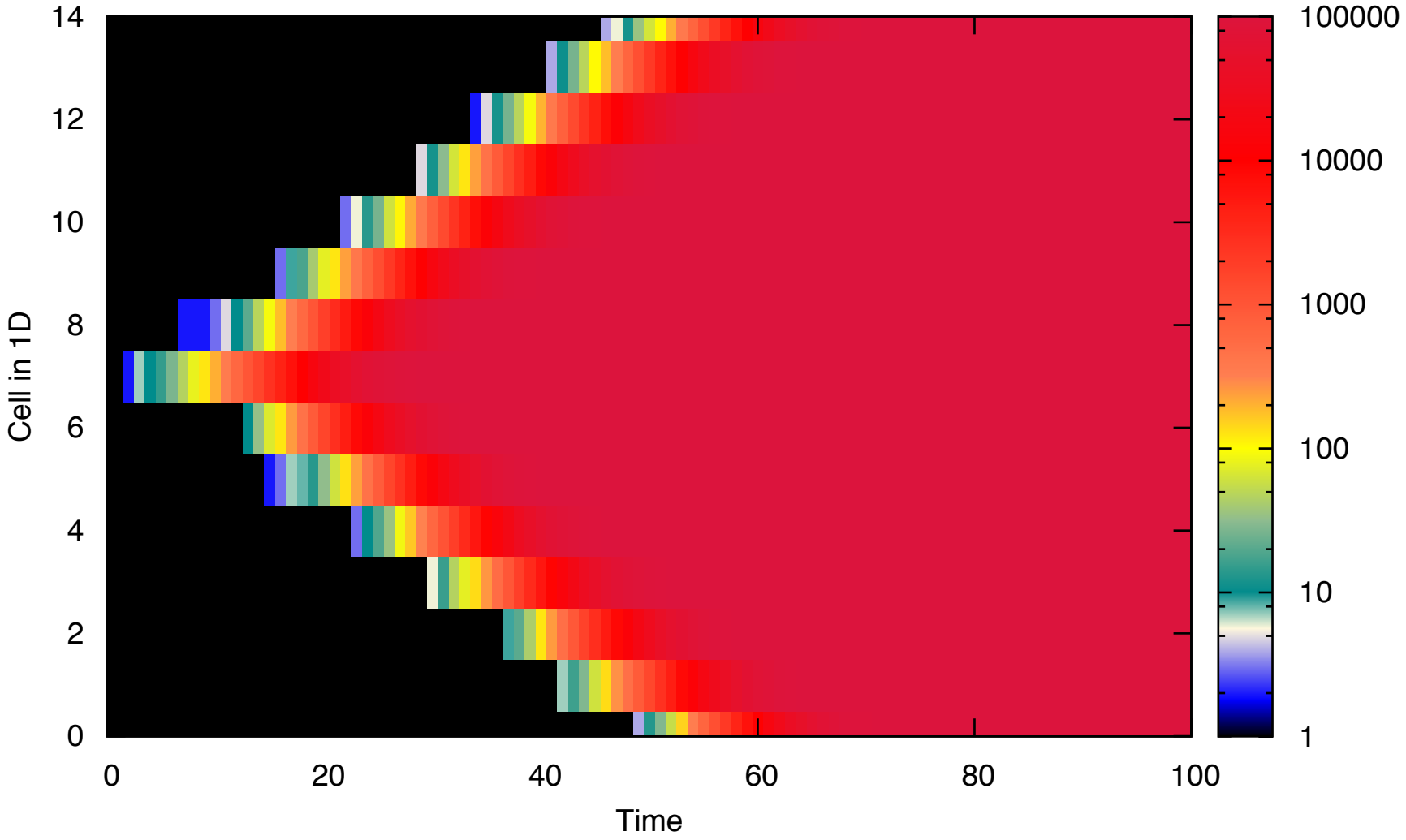
Ex5: 1D15 - Varying Mobility, Gamma = 99.99



EX5: 1D15 - VARYING MOBILITY, GAMMA = 90



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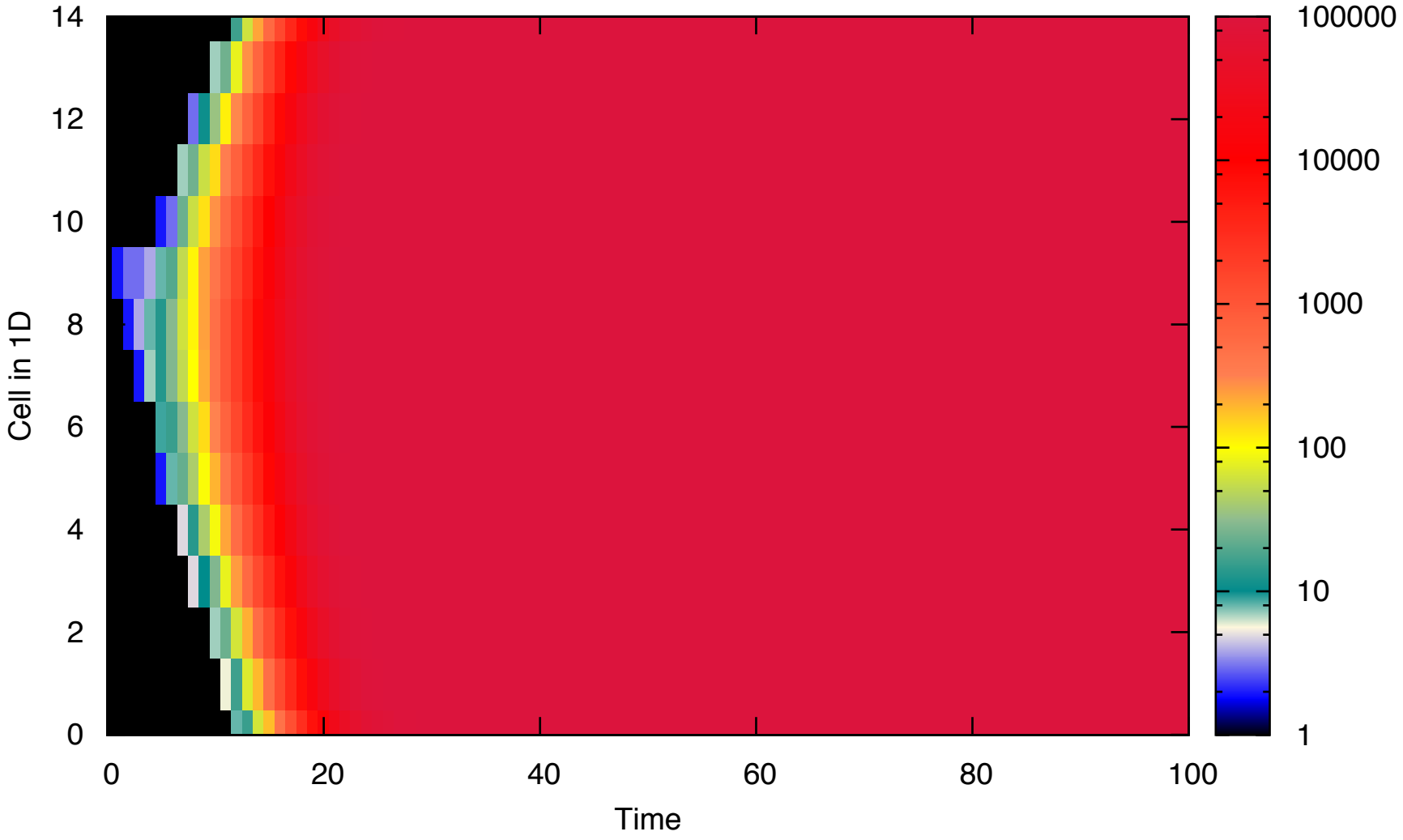
Ex5: 1D15 - Varying Mobility, Gamma = 50



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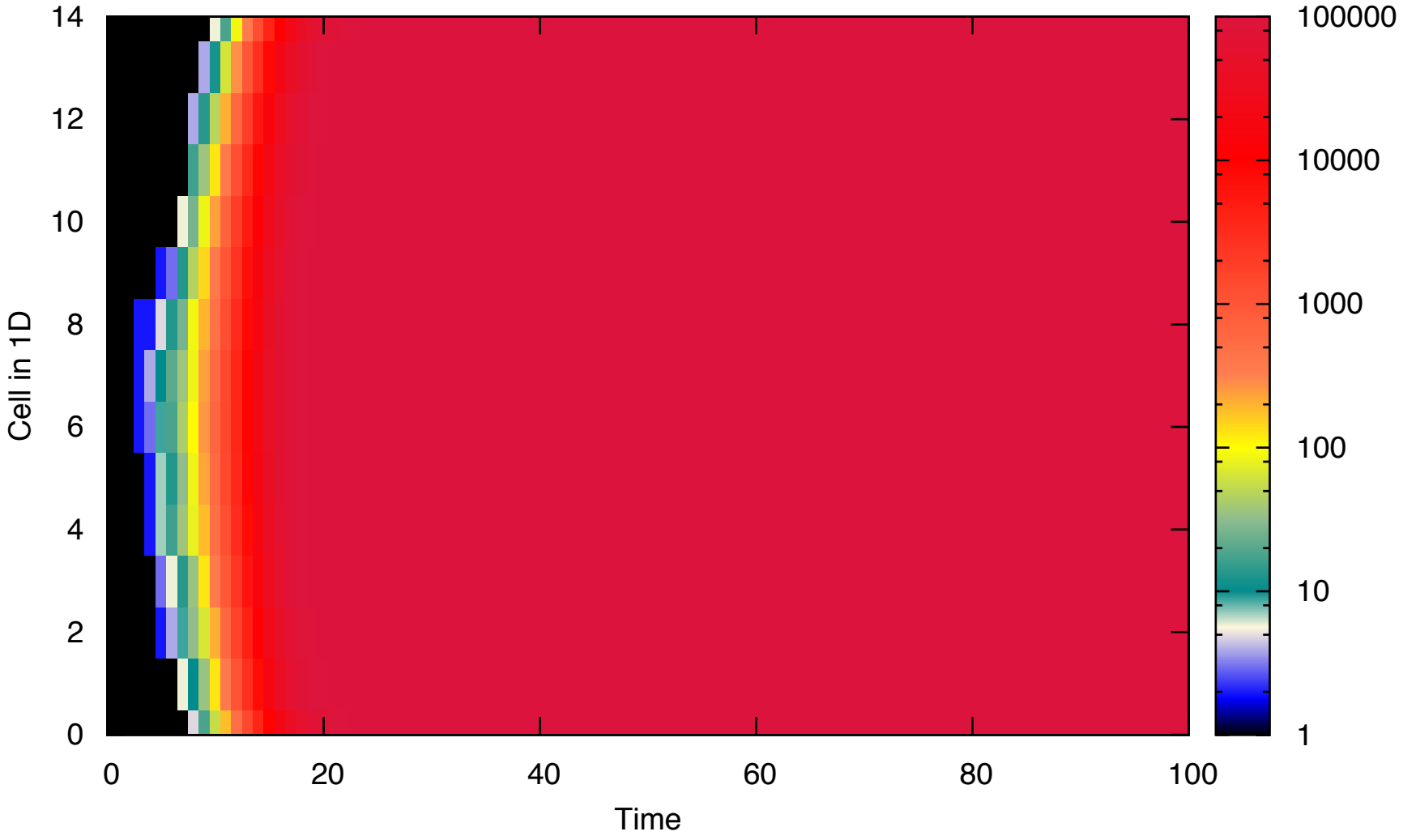
Ex5: 1D15 - Varying Mobility, Gamma = 1



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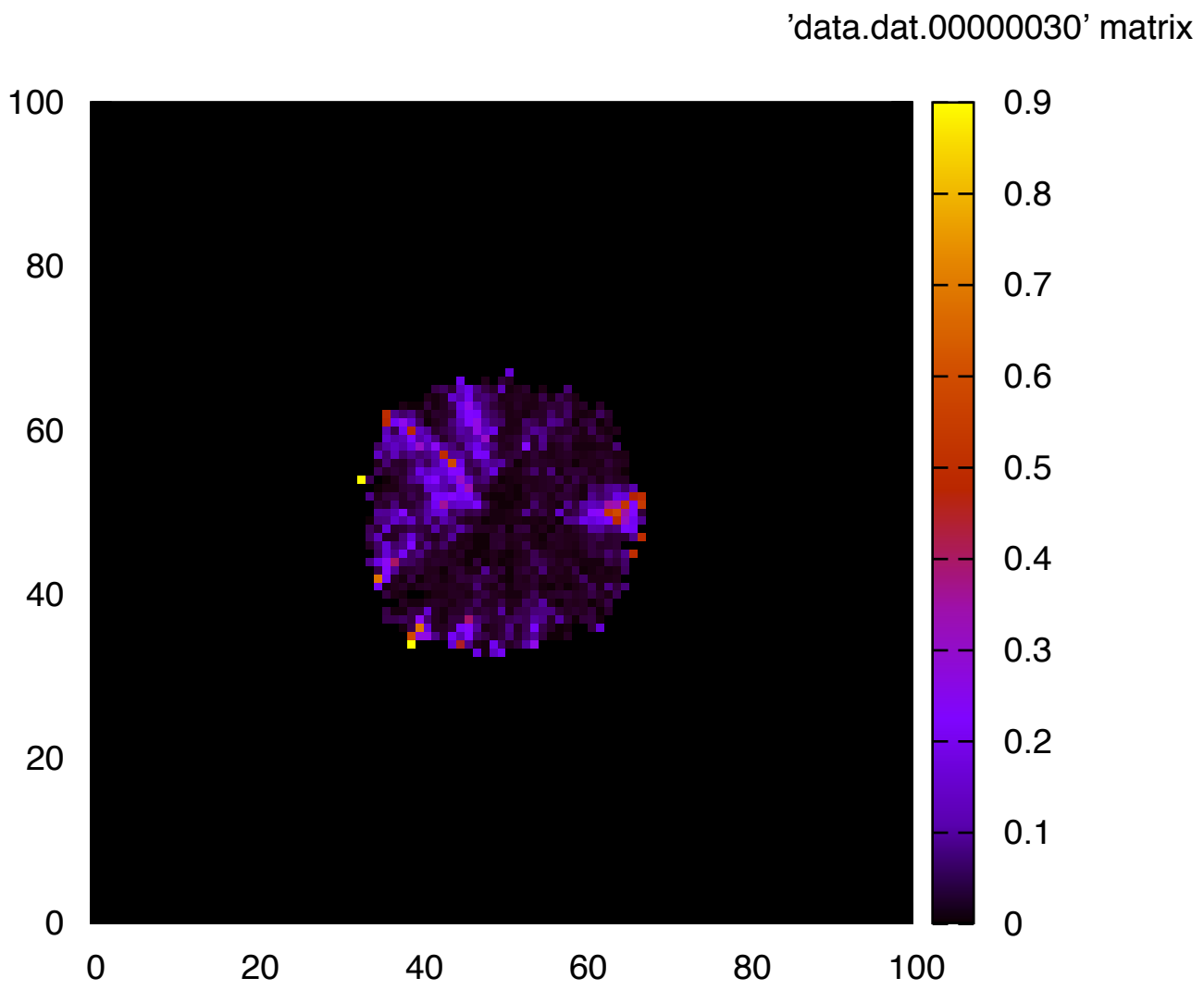
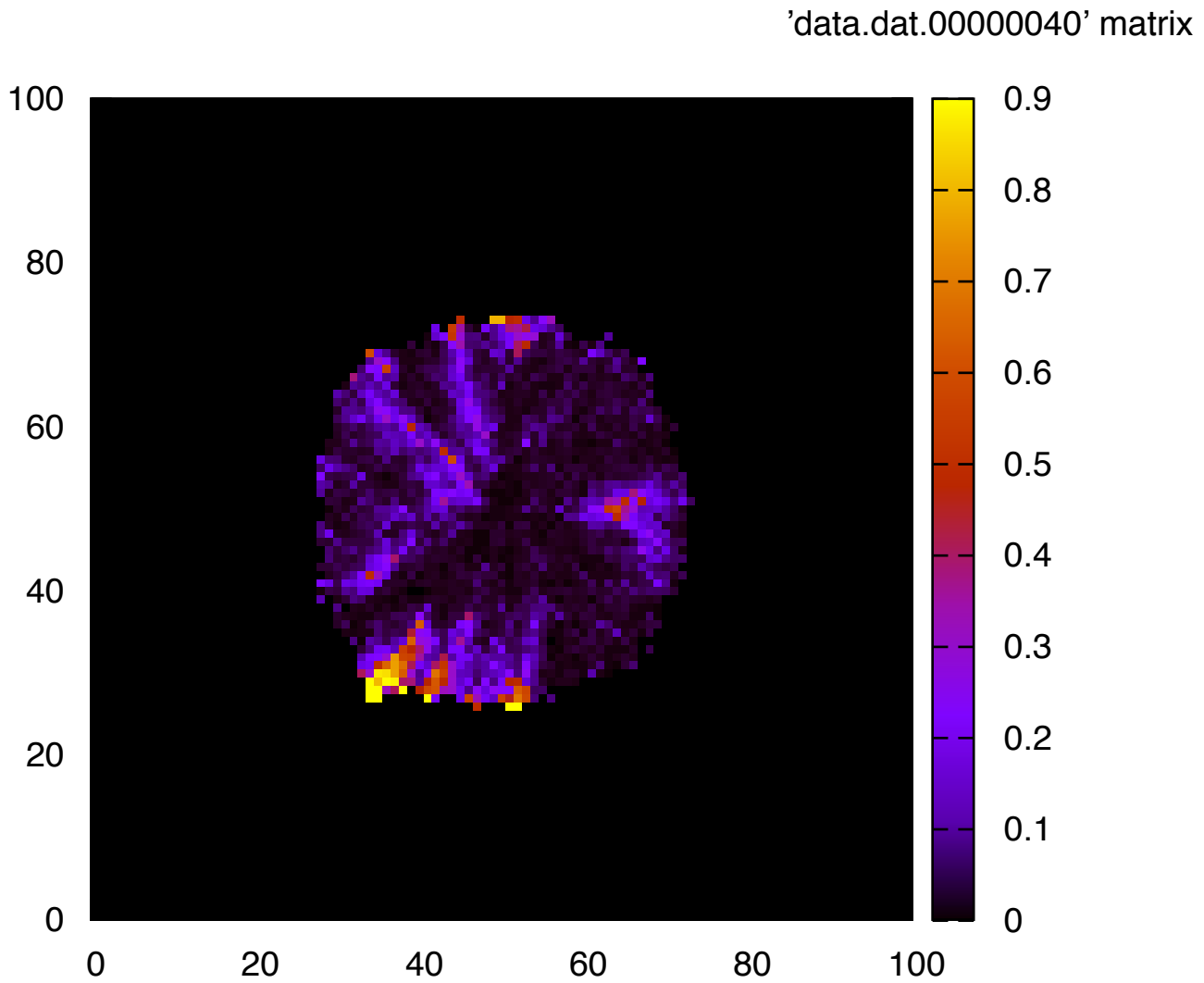
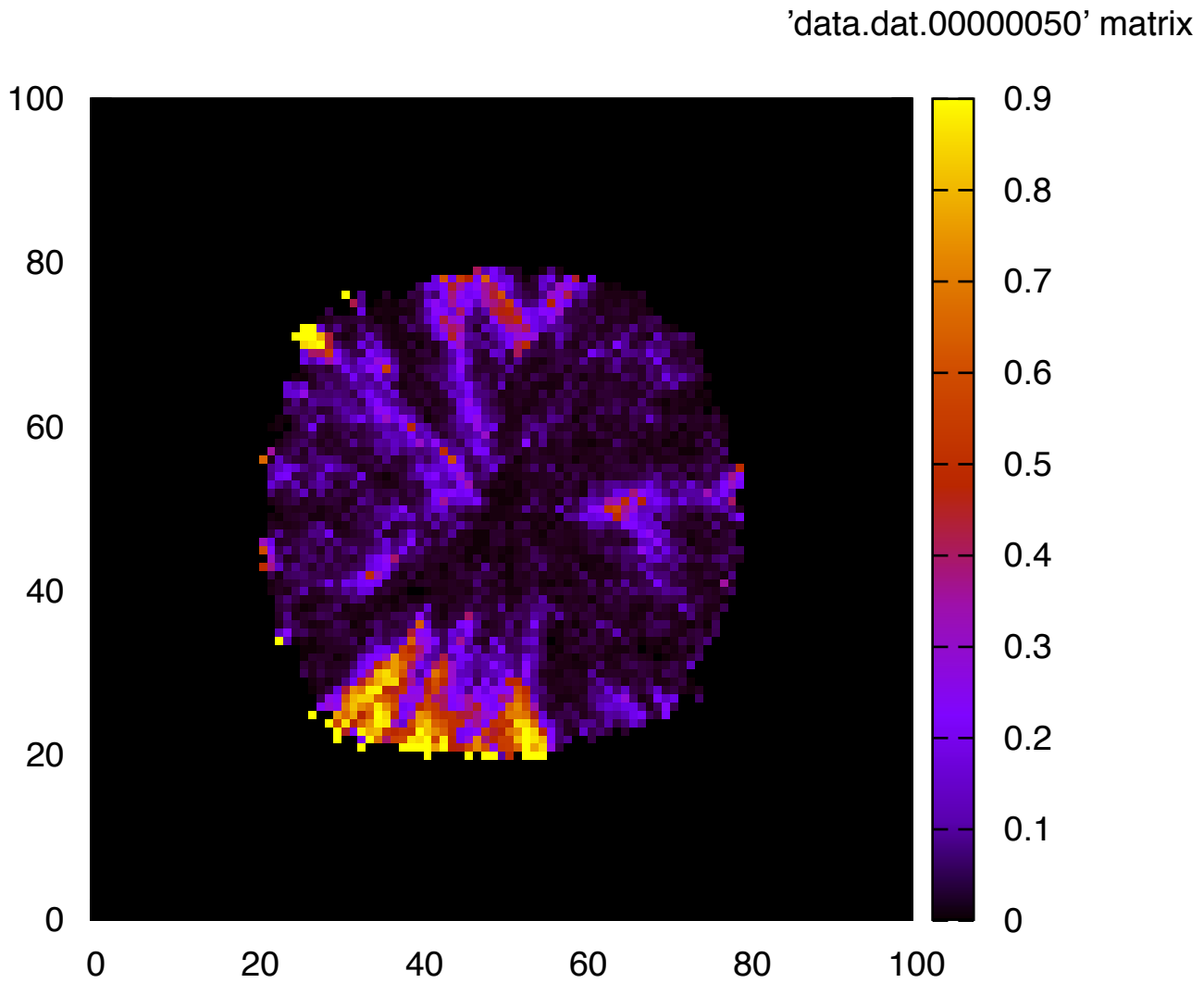
EX5: 2D - TRACE 1 (HIGH, F=1)



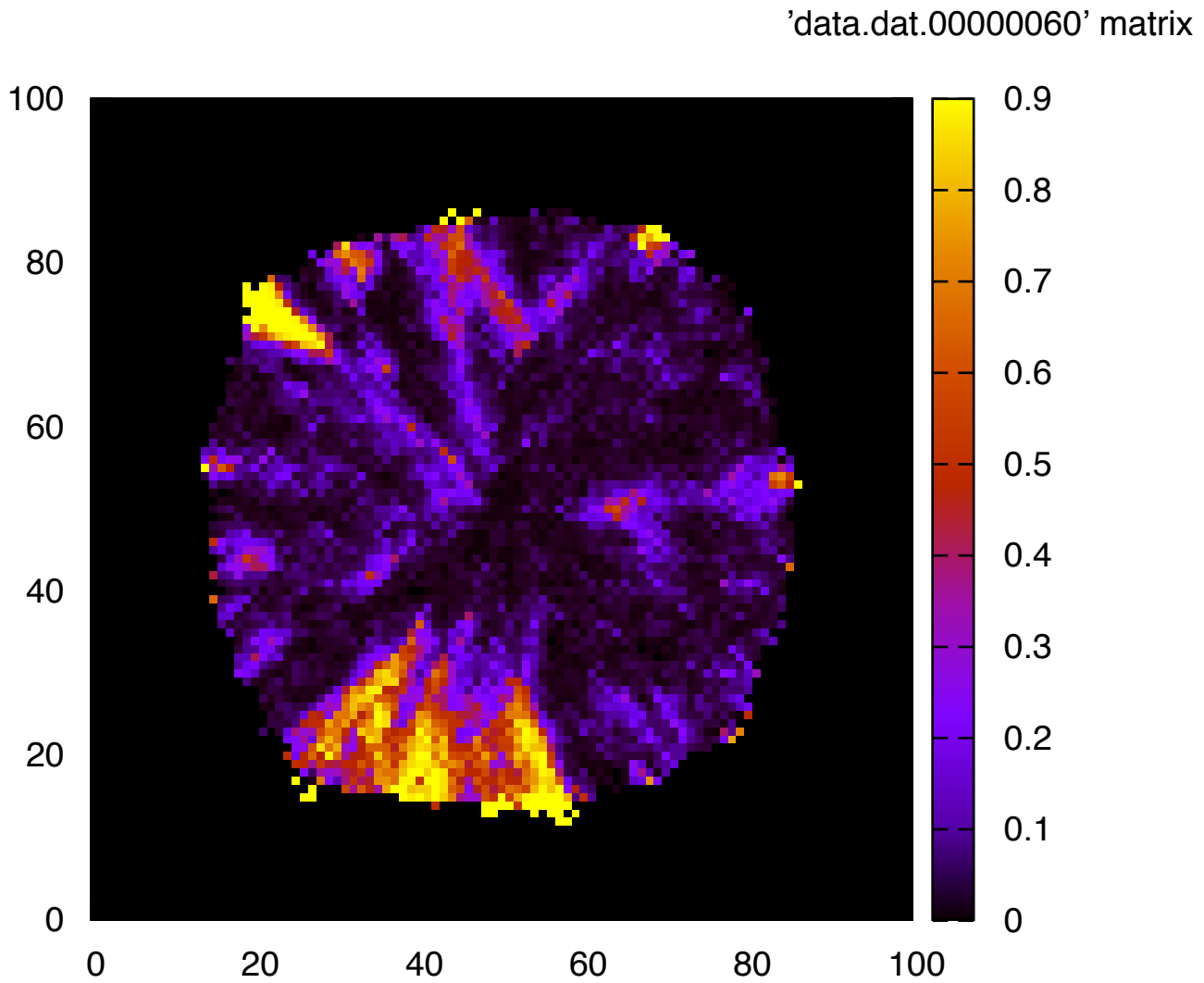
EX5: 2D - TRACE 1 (HIGH, F=1)



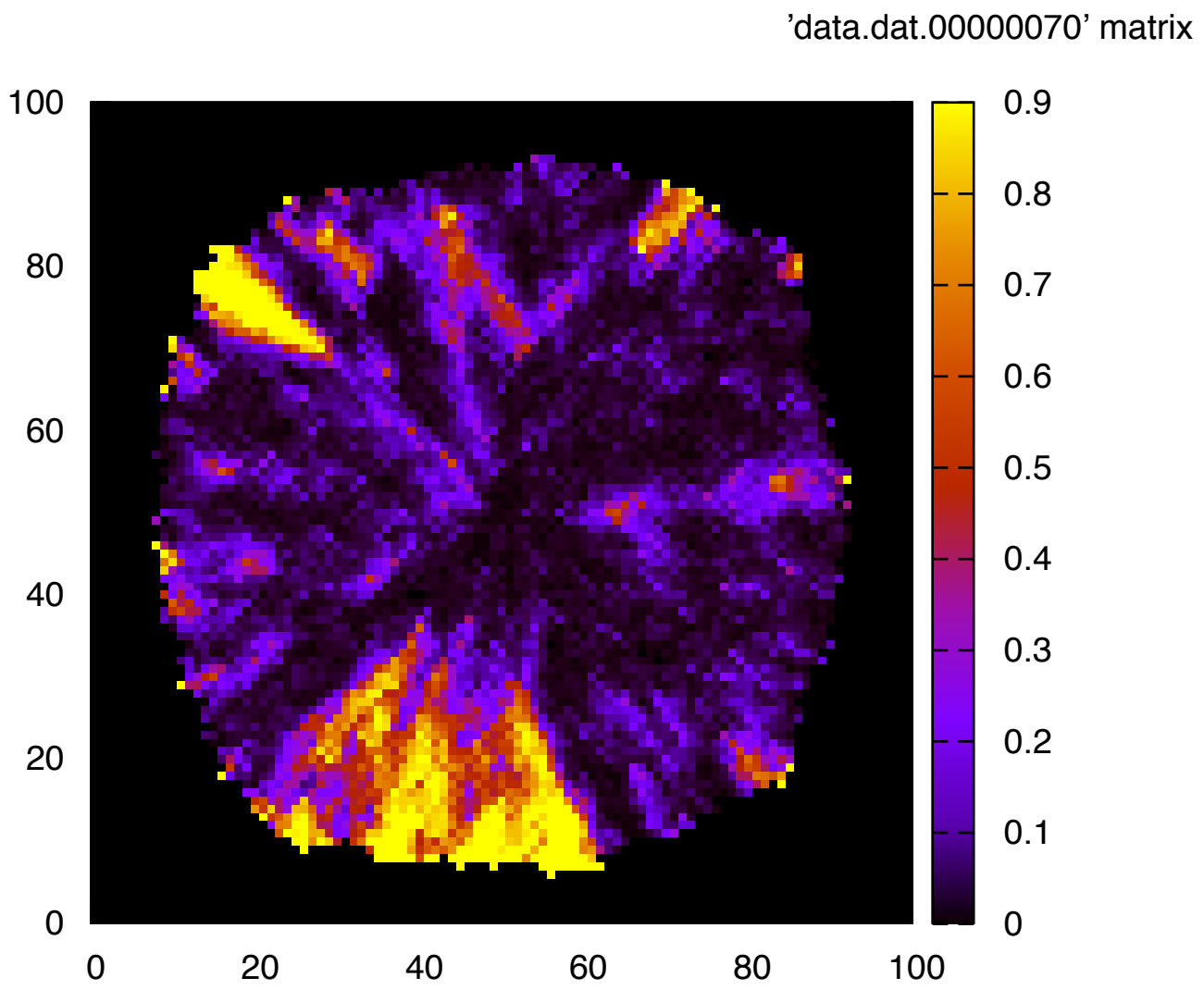
EX5: 2D - TRACE 1 (HIGH, F=1)



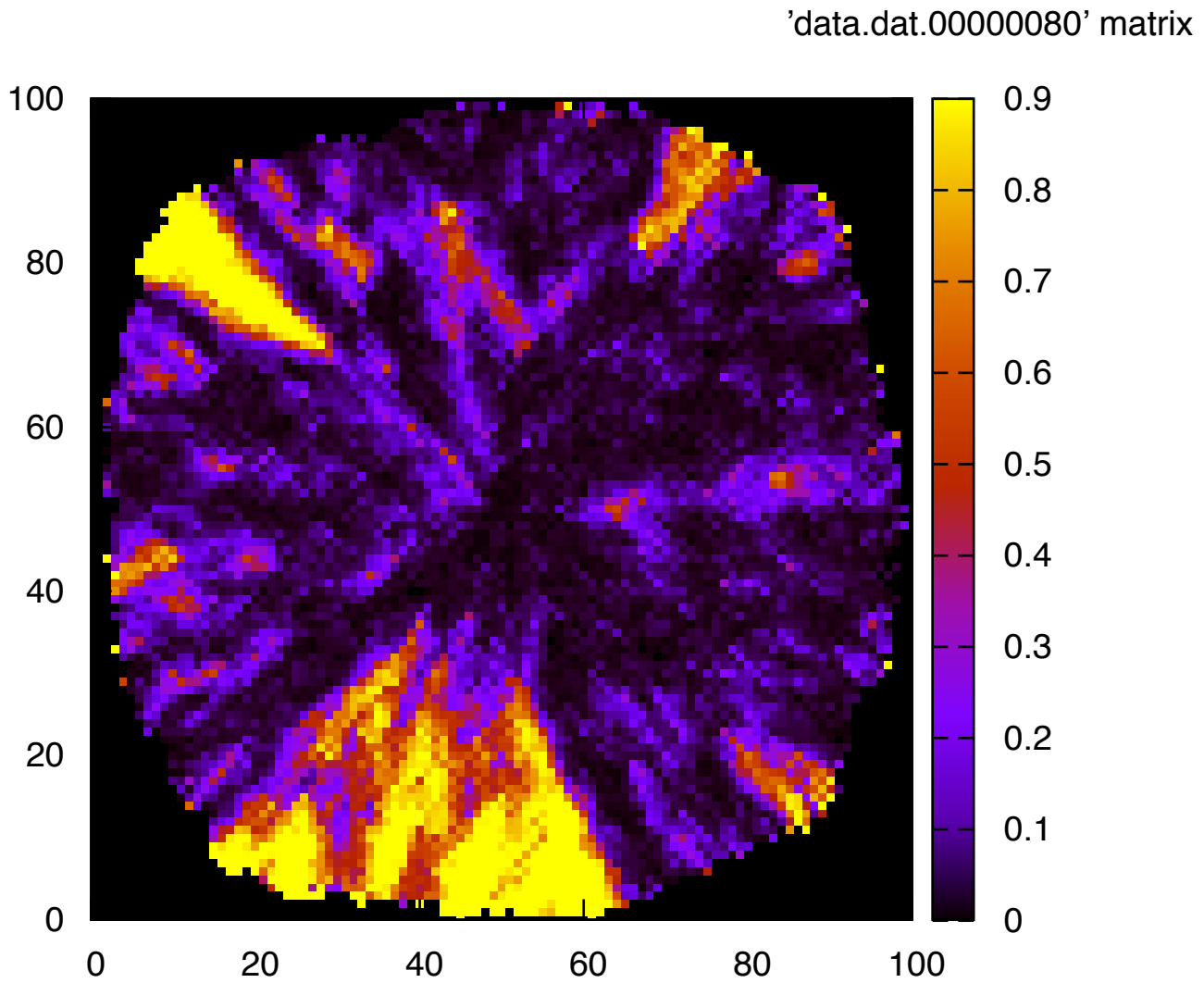
Ex5: 2D - Trace 1 (High, F=1)



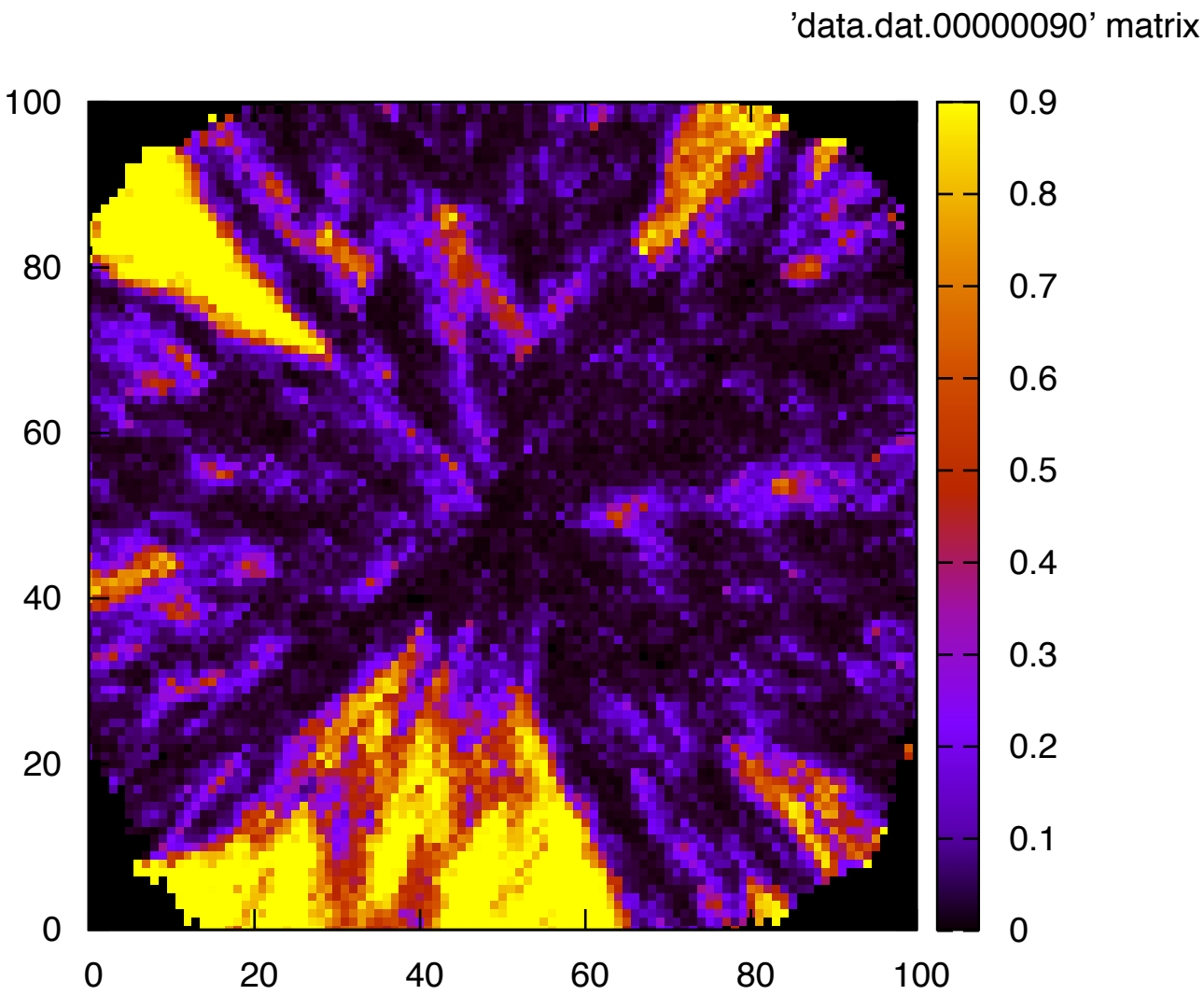
EX5: 2D - TRACE 1 (HIGH, F=1)



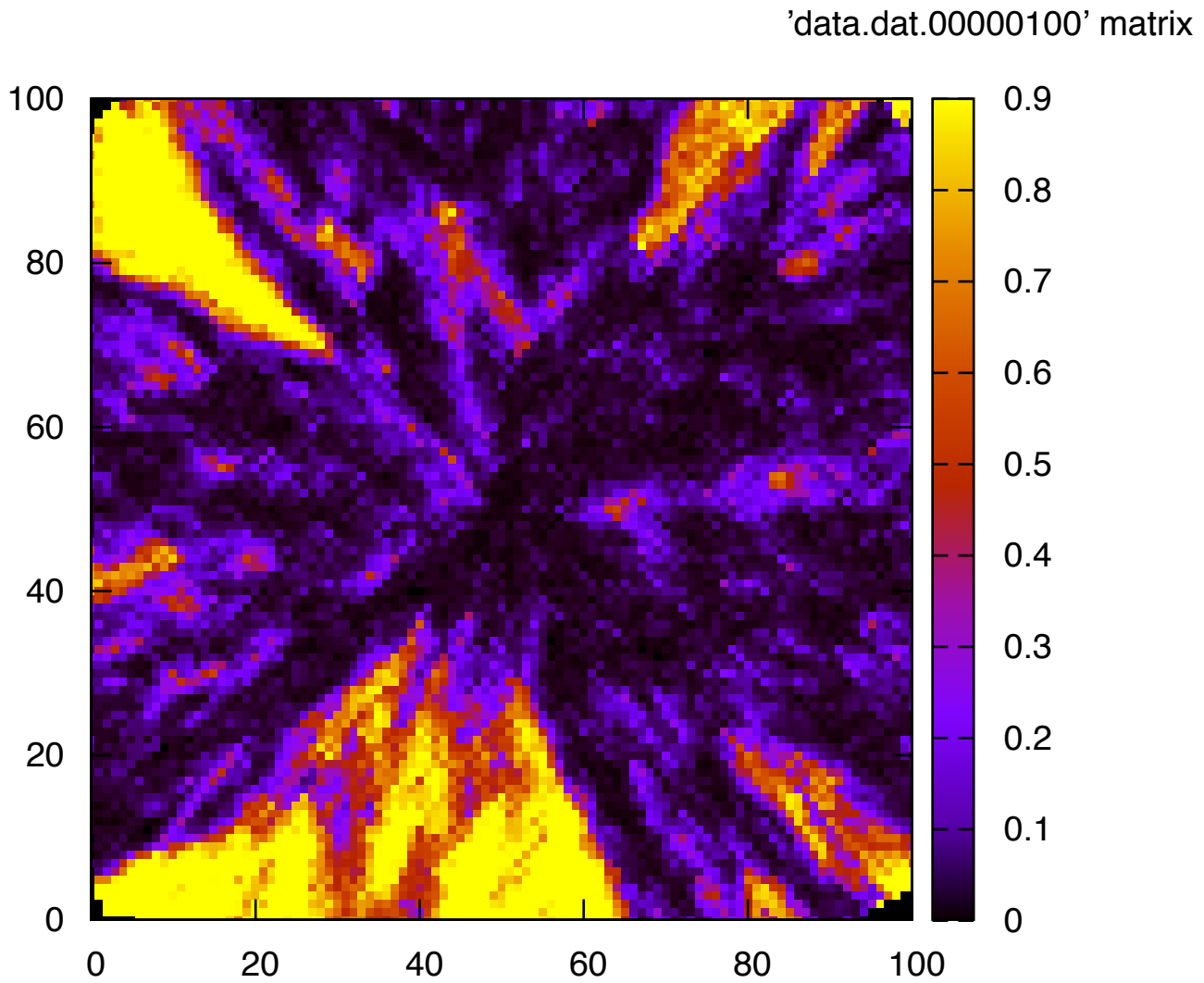
EX5: 2D - TRACE 1 (HIGH, F=1)



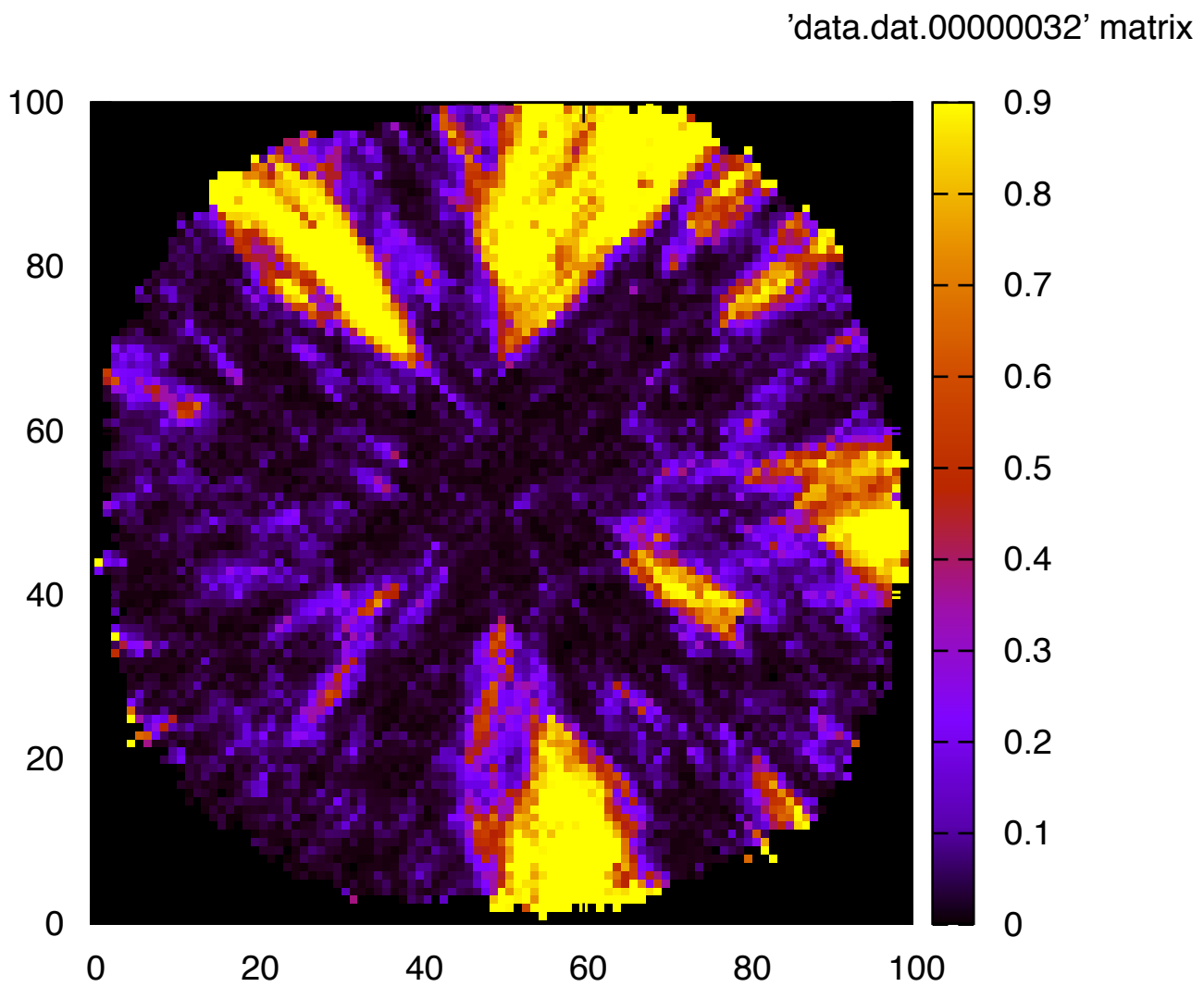
EX5: 2D - TRACE 1 (HIGH, F=1)



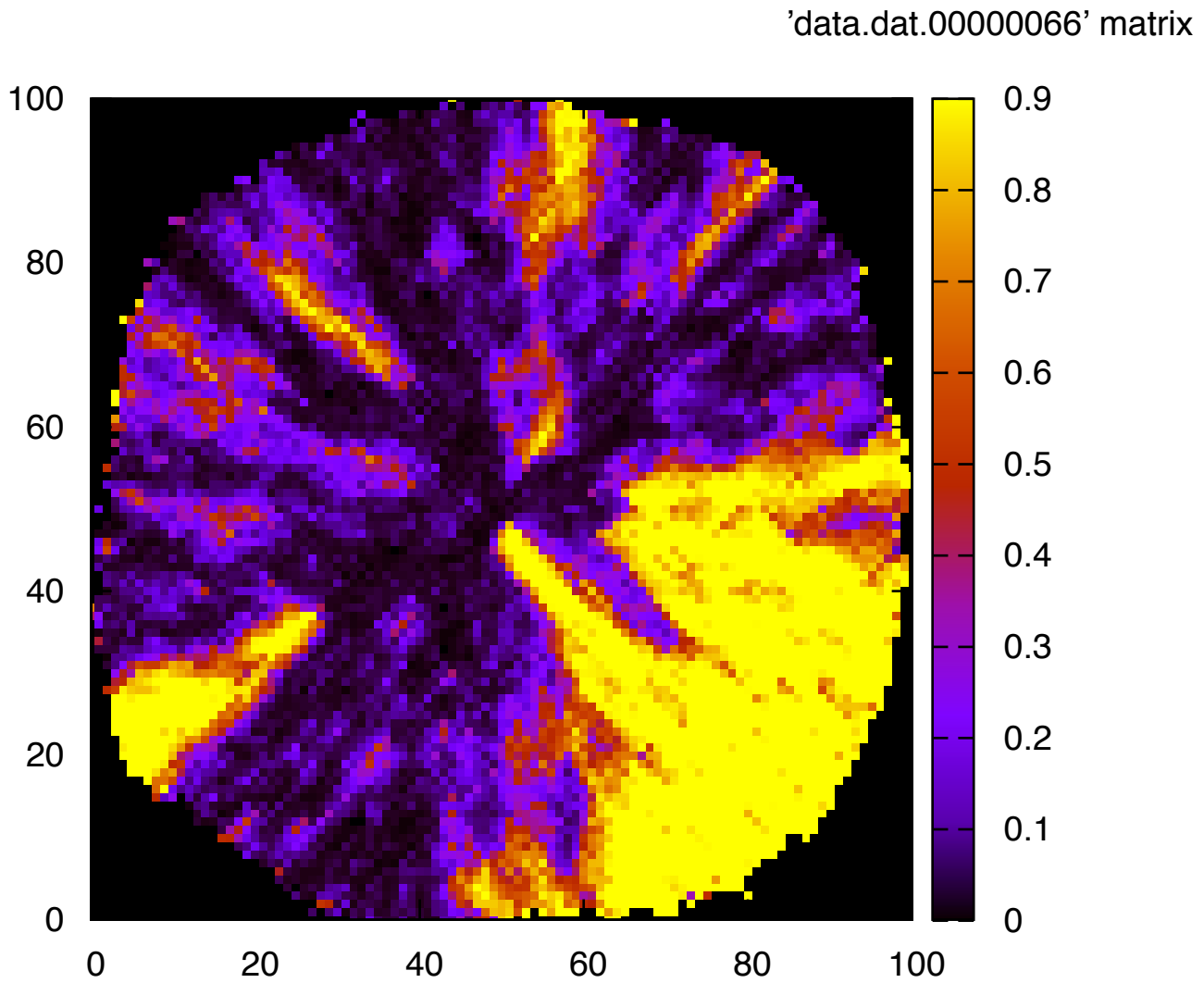
EX5: 2D - TRACE 1 (HIGH, F=1)



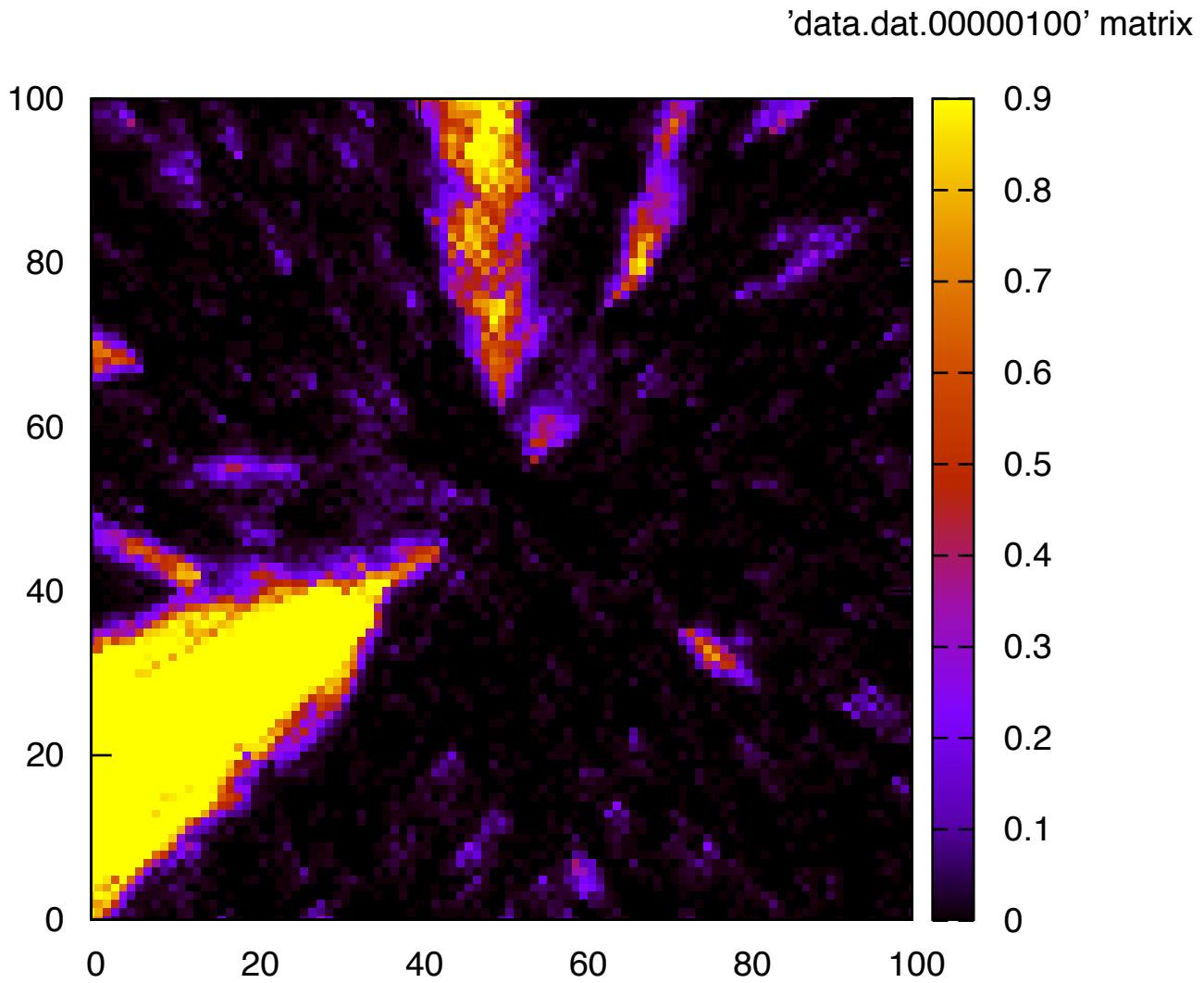
EX5: 2D - TRACE 2 (HIGH, F=1)



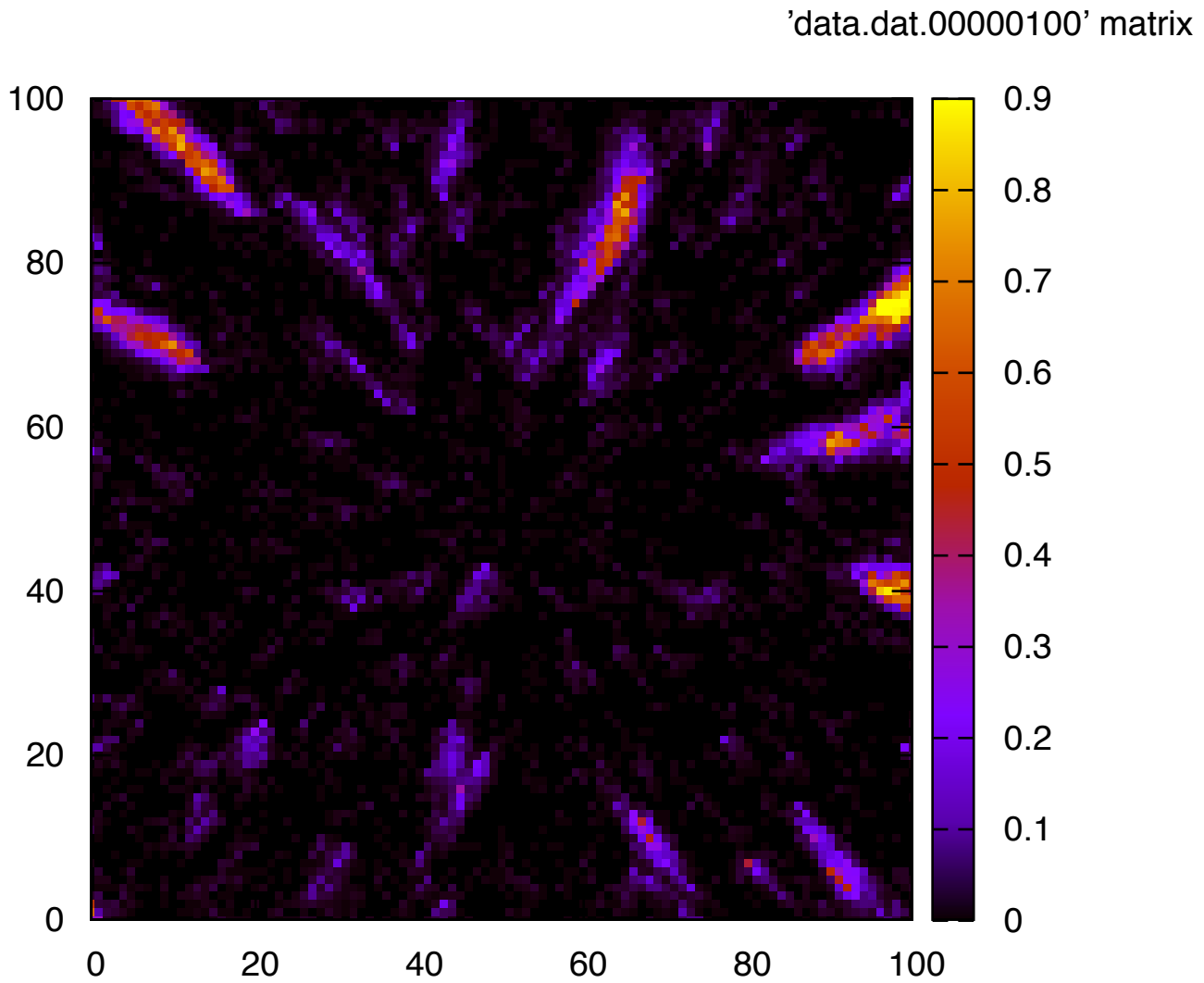
EX5: 2D - TRACE 3 (HIGH, F=1)



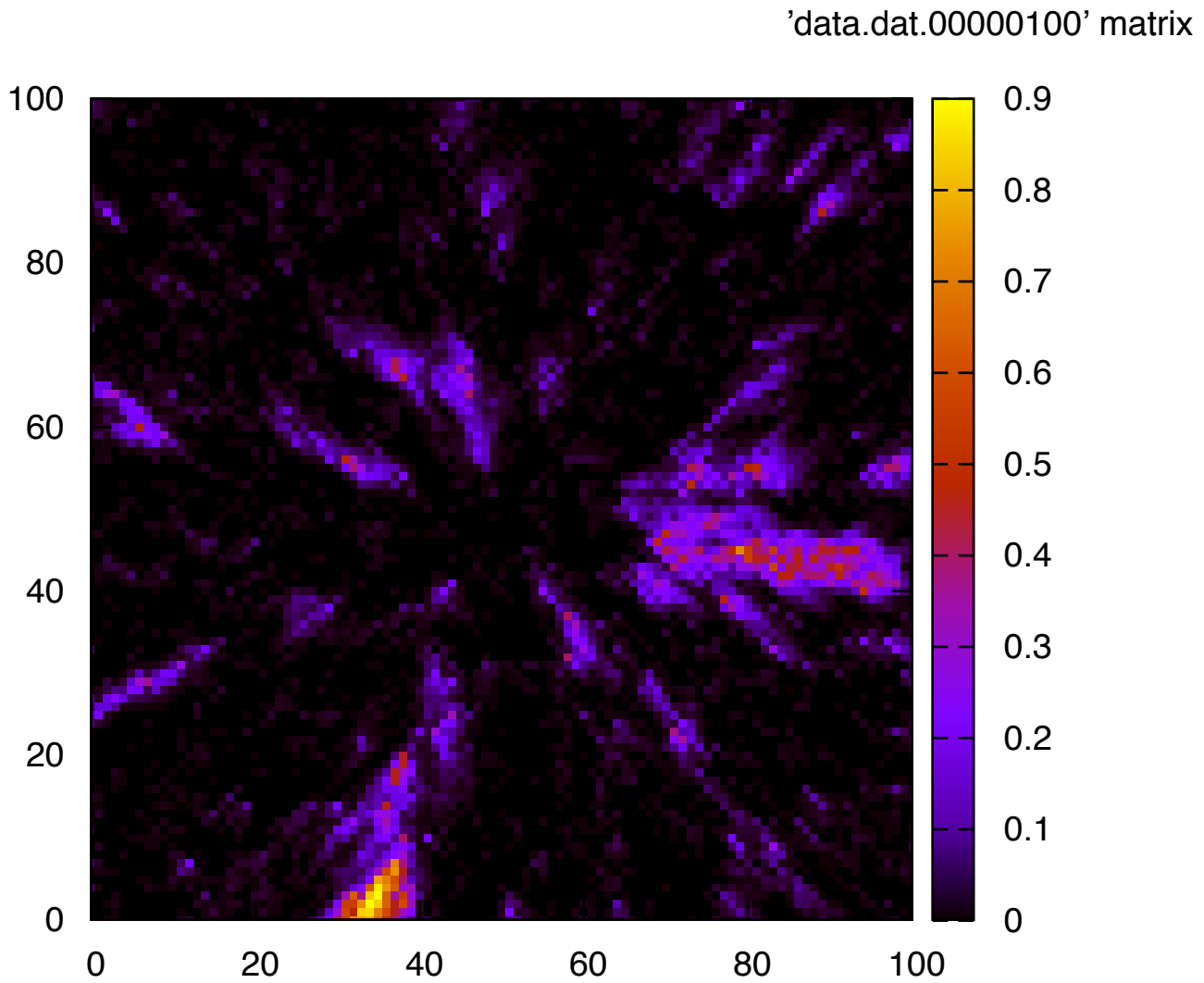
EX5: 2D - VARYING FITNESS, TRACE 1 (MEDIUM, F=1)



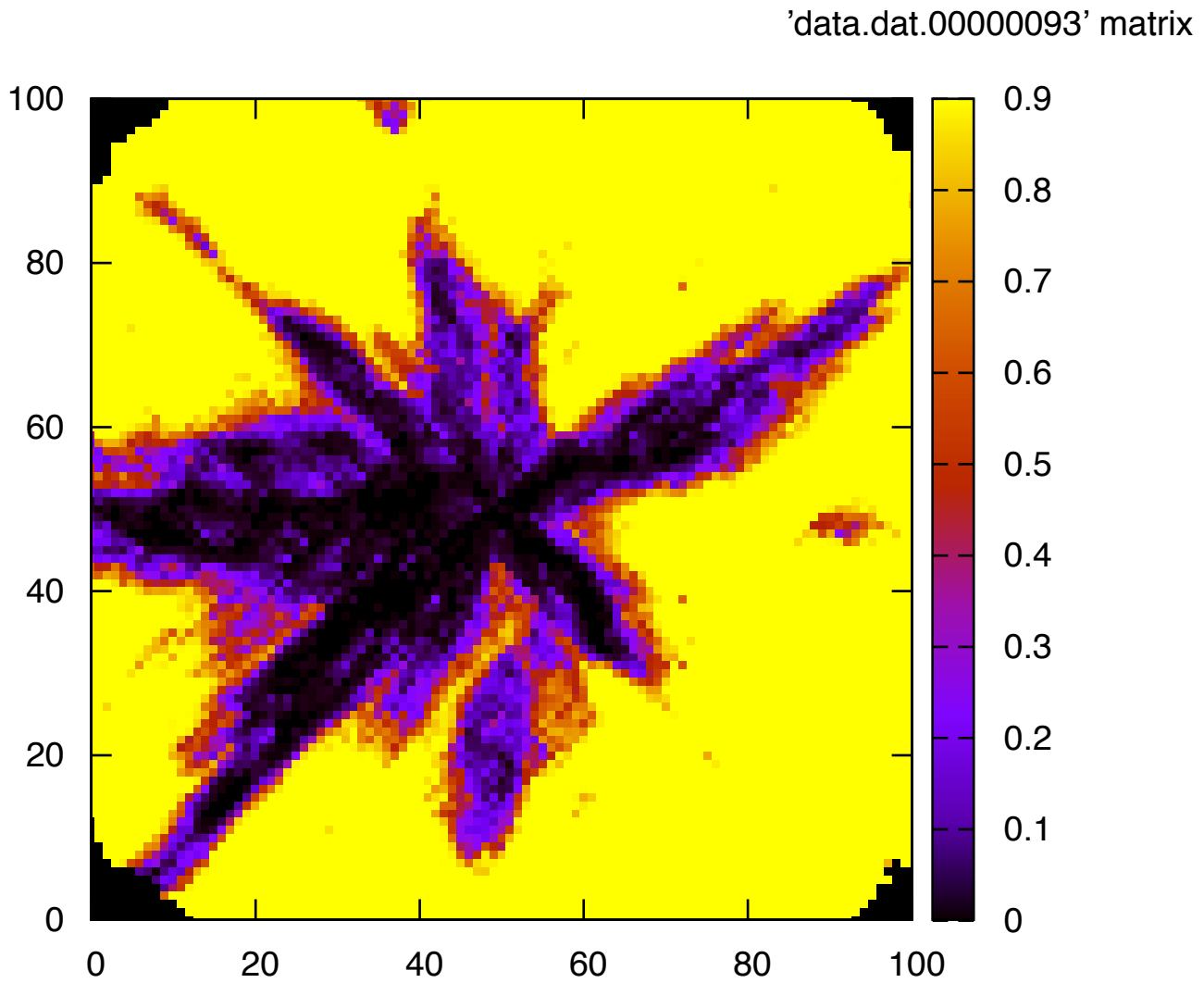
EX5: 2D - VARYING FITNESS, TRACE 2 (MEDIUM, F=1)



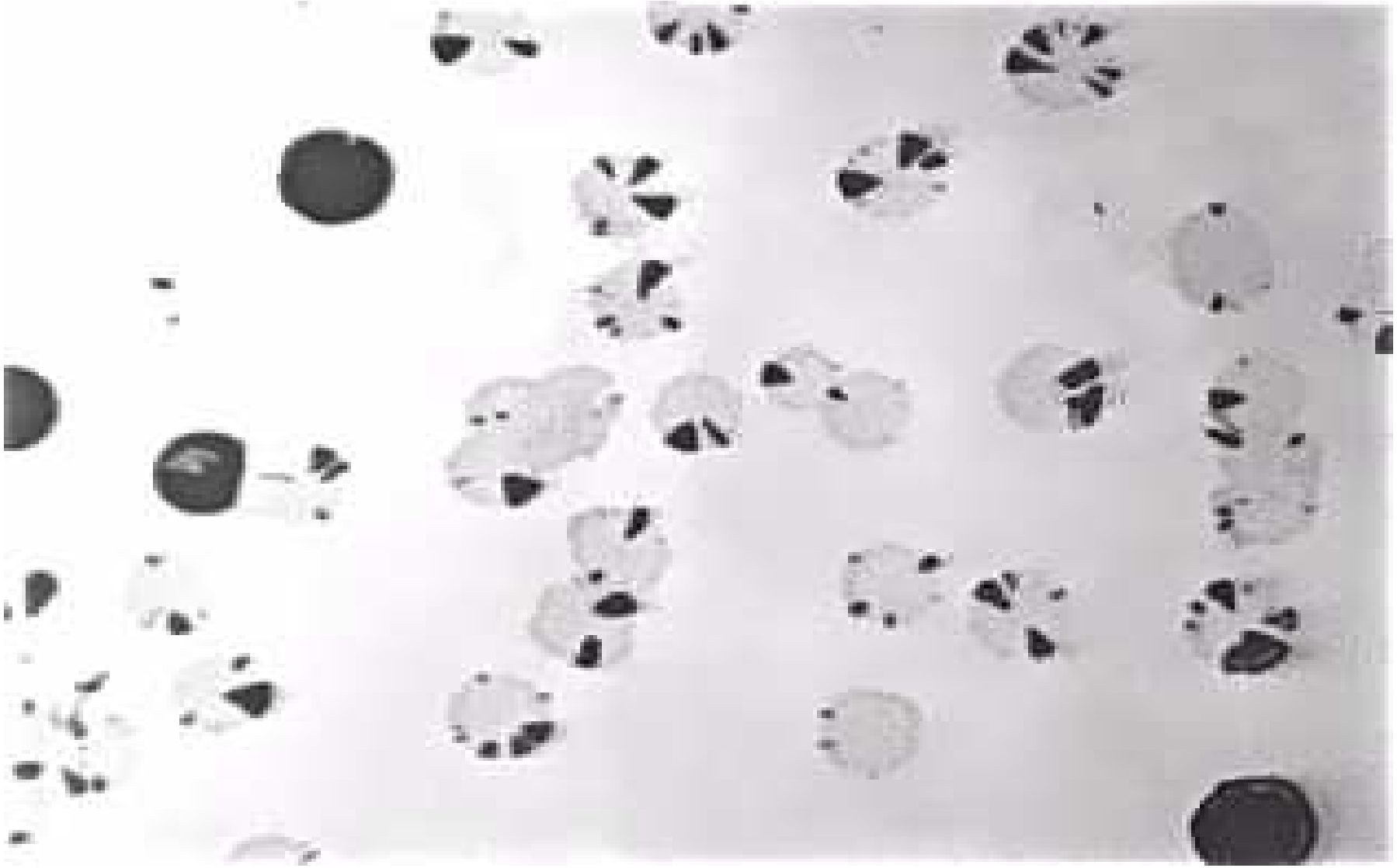
EX5: 2D - VARYING FITNESS, TRACE 1 (MEDIUM, F=0.99)



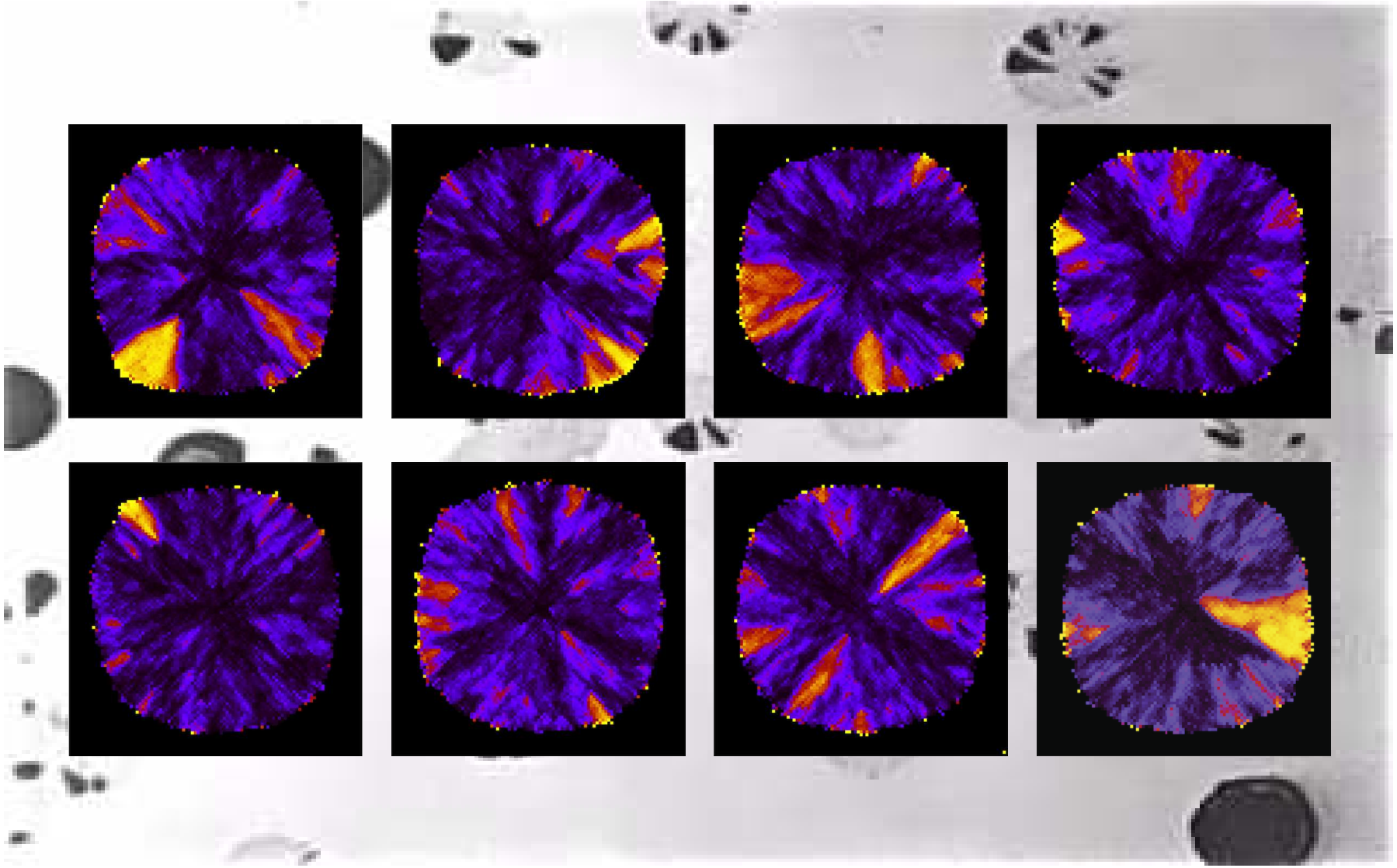
EX5: 2D - VARYING FITNESS, TRACE 1 (MEDIUM, F=0.90)



EX5: SOME FINAL STATES (HIGH, F=1)



EX5: SOME FINAL STATES (HIGH, F=1)



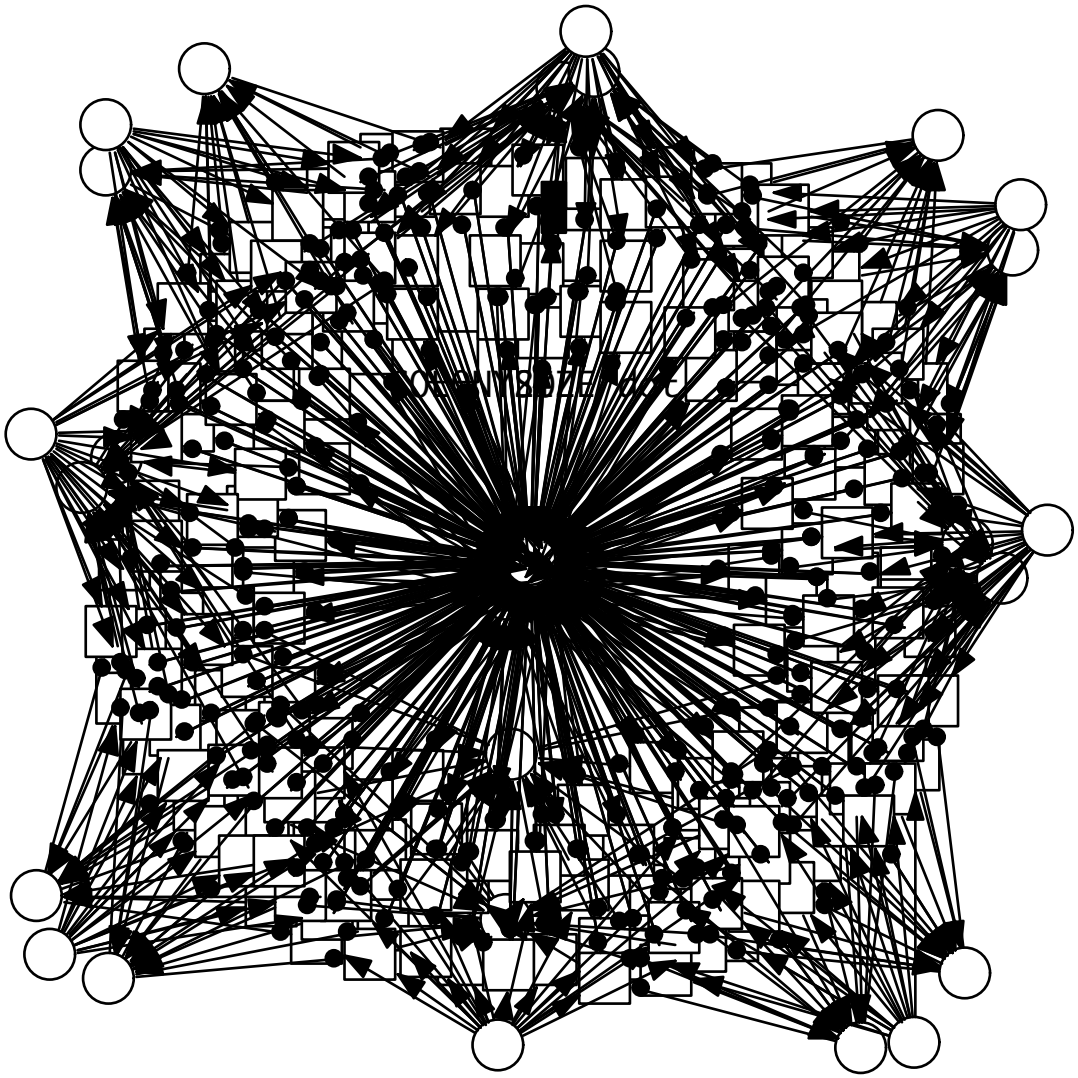
SUMMARY

ADVANTAGES OF OUR APPROACH

- **the spatial modelling principle can be equally applied to all paradigms**
  - -> *qualitative, stochastic, continuous, and hybrid*
  - -> *model transformations preserve all spatial attributes*
- **all space-related information is encoded in colour**
  - -> *reuse in other models*
- **changing the notion of space**
  - -> *adapt colour-related definitions*
  - -> *net structure itself needs not to be touched.*
- **use of a priori finitely discretised space preserves model analysibility**

- **automatic unfolding**
  - -> *resue of all analysis and simulation techniques of uncoloured Petri nets*

PHASE VARIATION, PLAIN MODEL (3X3)



WHAT NEXT?

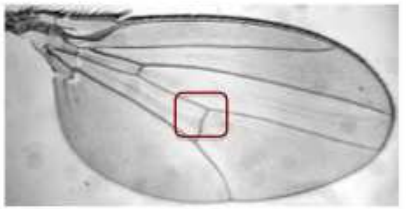
- **how to analyse visual data?** **-> CMSB 2013**
  - -> *auxiliary variables derived from model variables*
  - -> *clustering techniques*
  - -> *shape recognition*
  - -> *visual analytics*

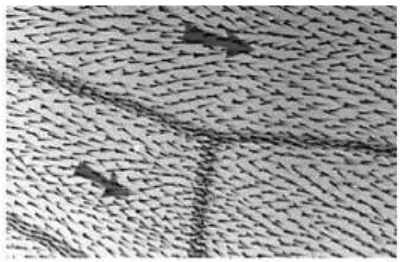
- **use model to predict**
  - -> *mutation rates by measuring the mutation sectors,*
    or just the number of sectors?
  - -> *fitness by measuring angel of sectors*

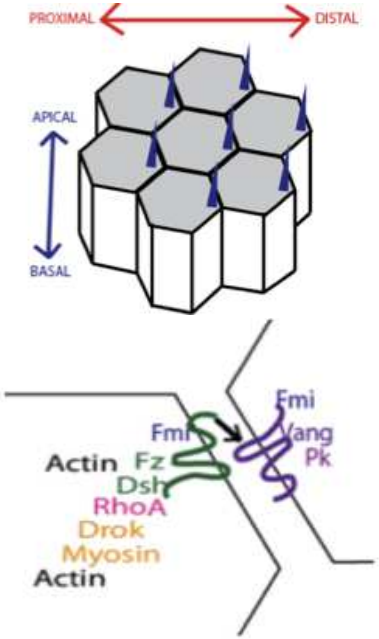
- **possible model extensions / variations**
  - -> *fine tuning of biofilm thickness*
  - -> *multiple gene on/off and their dependencies*
  - -> *log pedigree and/or mobility*

MULTISCALE CHALLENGES

- repetition of components
- variation of components
- organisation of components
- communication between components
- mobility / motility
- replication / deletion of components
- hierarchical organisation of components
- dynamic grid size
- irregular / semi-regular organisation of components







CREDITS

- **EPSRC Research Grant EP/I036168/1**
- **Snoopy + Charlie + Marcie development**

  Christian Rohr, Fei Liu, Mostafa Herayj

  Martin Schwarick, Jan Wegener
- **Plots**

  Mary Ann Blätke, Daniele Maccagnola, Ovidiu Parvu, Christian Rohr, Jan Wegener
- **further case studies**

  Halo bacterium - Wolfgang Marwan

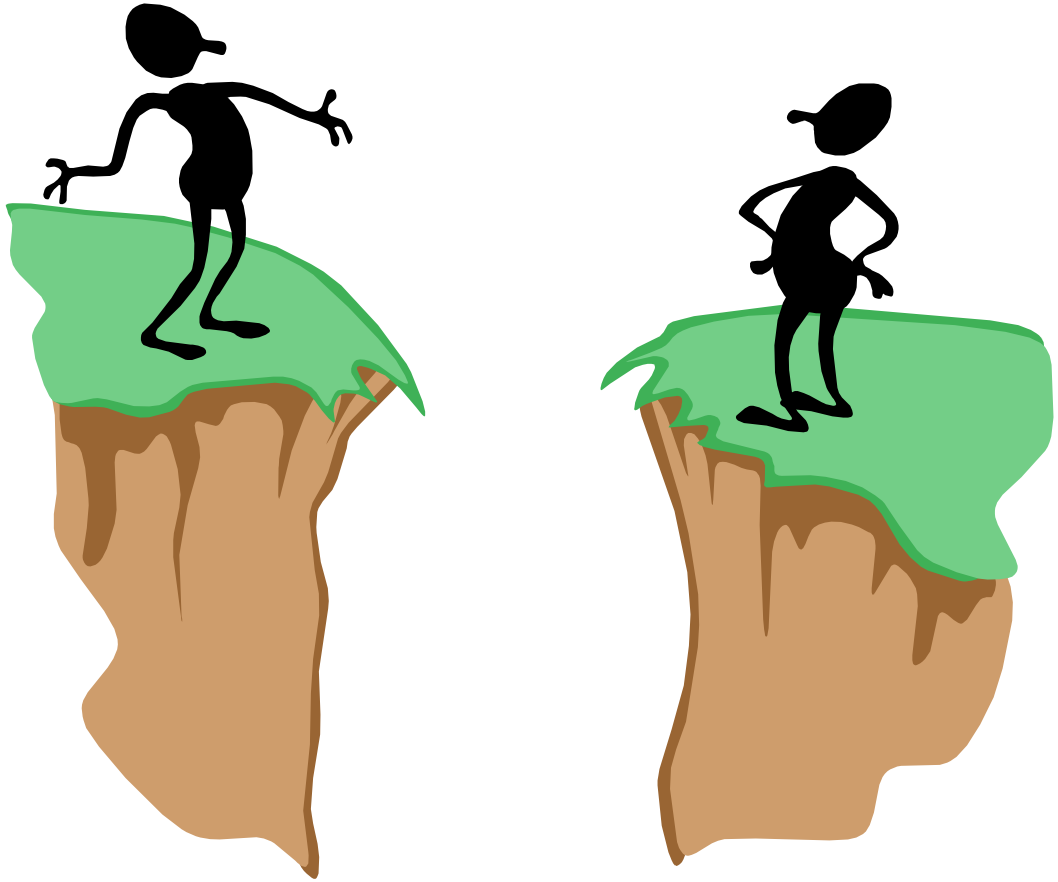
  PCP in fly wing - Pam Gao, David Tree

  Ca channel - Fei Liu

  Brusselator - Mary Ann Blätke, Fei Liu

  Dictopat - Andrzej Kierzek, Simon Hardy, ..., Mary Ann Blätke, Ovidiu Parvu

OUTLOOK



THANKS !

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