FROM PETRI NETS TO PARTIAL DIFFERENTIAL EQUATIONS

- SPATIAL MODELLING IN SYSTEMS BIOLOGY -

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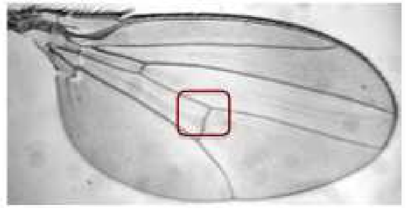
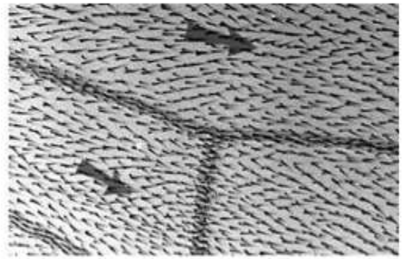
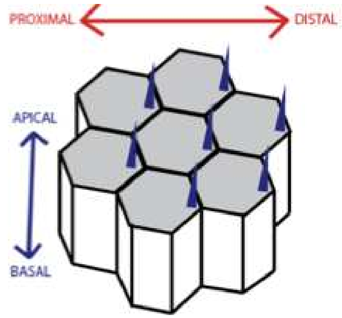
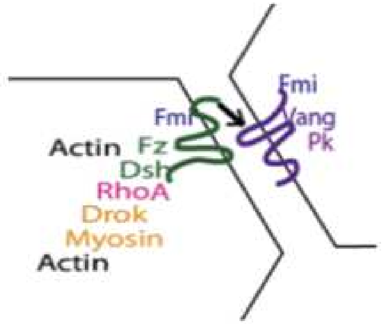
- **FRAMEWORK**
  - -> *unifying paradigms:*
    (coloured) QPN - SPN - CPN - HPN
  - -> *(bio) processes evolving in time and space*
  - -> *How to encode space ?*
- **COLOURING SPACE (VERSION 1)**
  - -> *diffusion in space*
  - -> *Turing patterns*
  - -> *phase variation in multistrain bacterial colonies*
  - -> *planar cell polarity in fly wing*
- **LIMITATION -> VERSION 2**
- **SUMMARY & OUTLOOK**
  - -> *next steps*



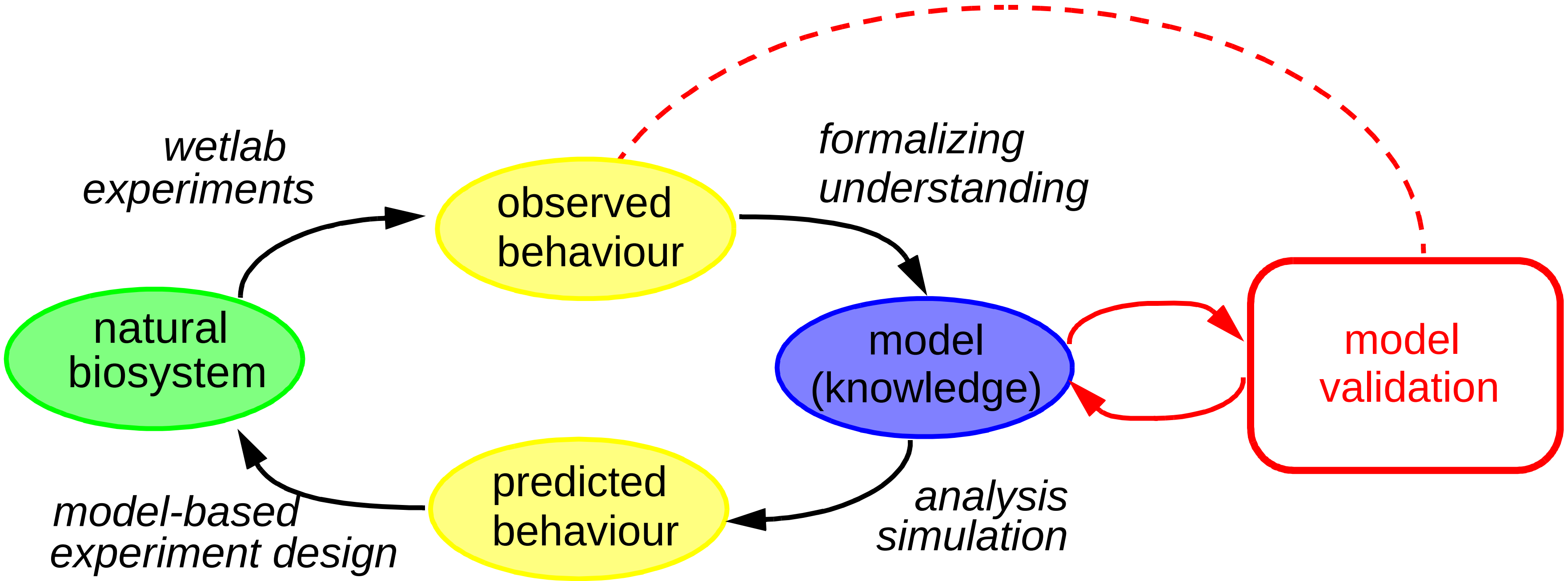






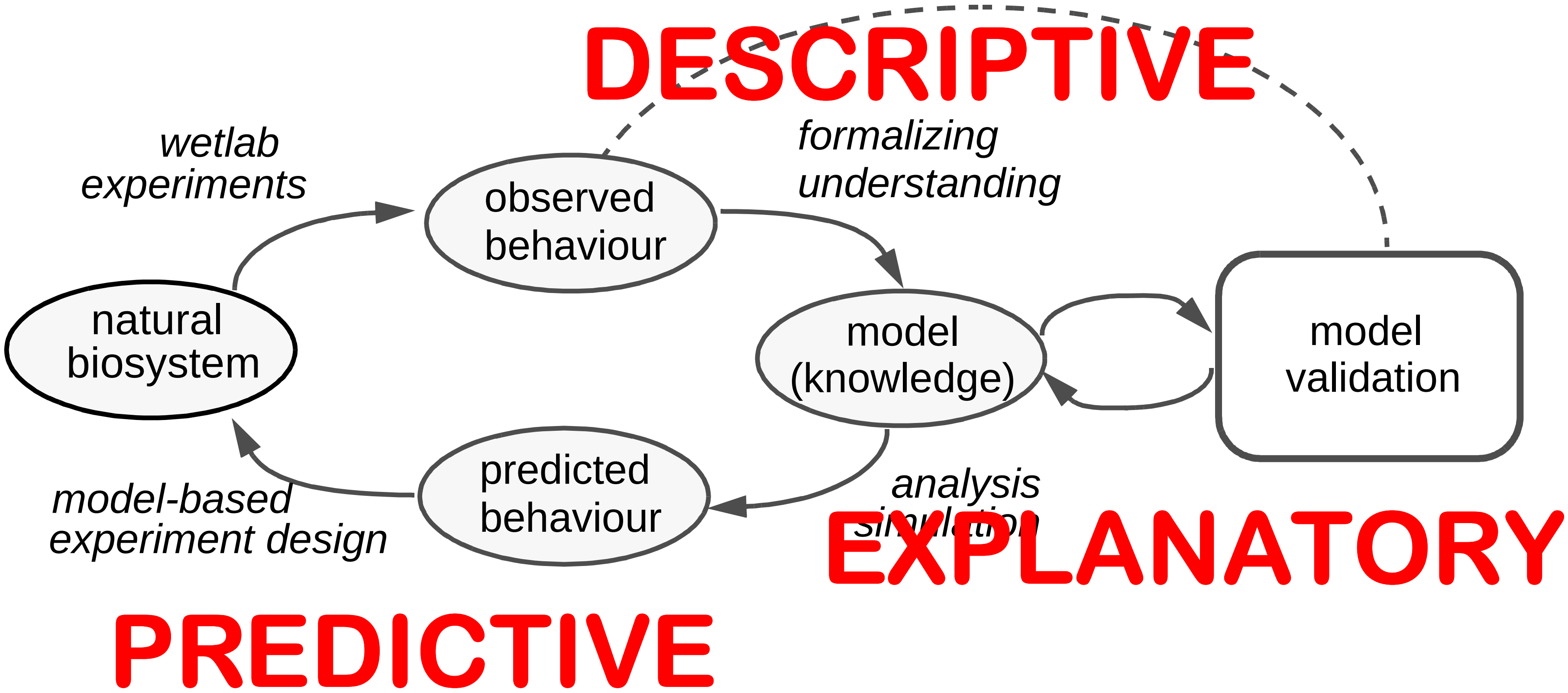
THE FRAMEWORK

MODELLING = FORMAL KNOWLEDGE REPRESENTATION

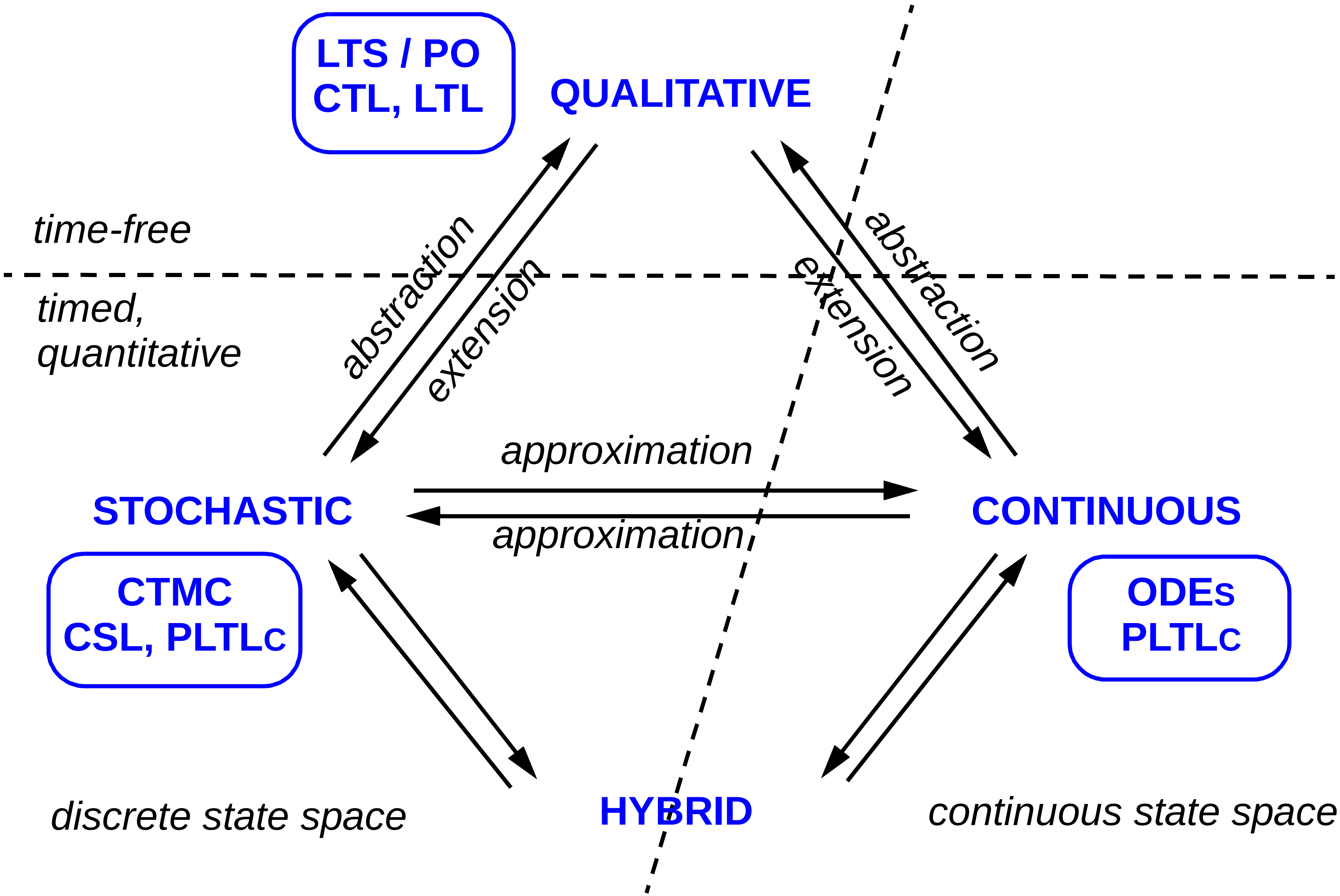


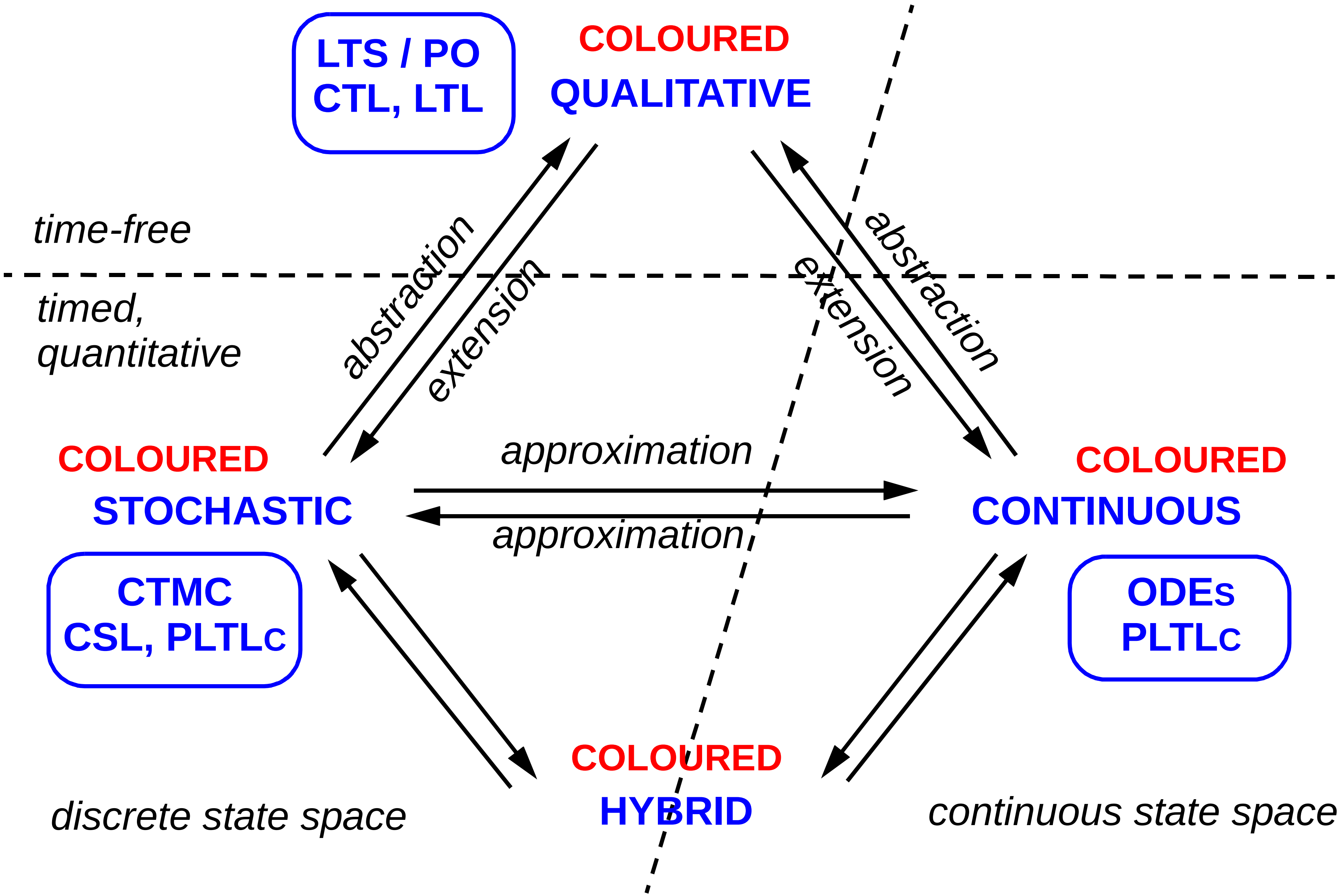
MODEL VALIDATION = CONFIDENCE INCREASE

MODELLING = FORMAL KNOWLEDGE REPRESENTATION



MODEL VALIDATION = CONFIDENCE INCREASE


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



LTS / PO
CTL, LTL
COLOURED
QUALITATIVE
time-free
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COLOURED
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COLOURED
CONTINUOUS
CTMC
CSL, PLTLc
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PLTLc
COLOURED
HYBRID
discrete state space
continuous state space

STATE-DEPENDENT RATE FUNCTIONS

STOCHASTIC RATES → **LAMBDA OF EXPONENTIAL WAITING TIME** → **CTMC**

CONTINUOUS RATES → **STRENGTH OF CONTINUOUS FLOW** → **ODEs**

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

4x2

MODELS SHARING STRUCTURE

QUANTITATIVE MODEL = QUALITATIVE MODEL

+

RATE FUNCTIONS

(KINETICS)

COLOUR -

WHAT FOR ?

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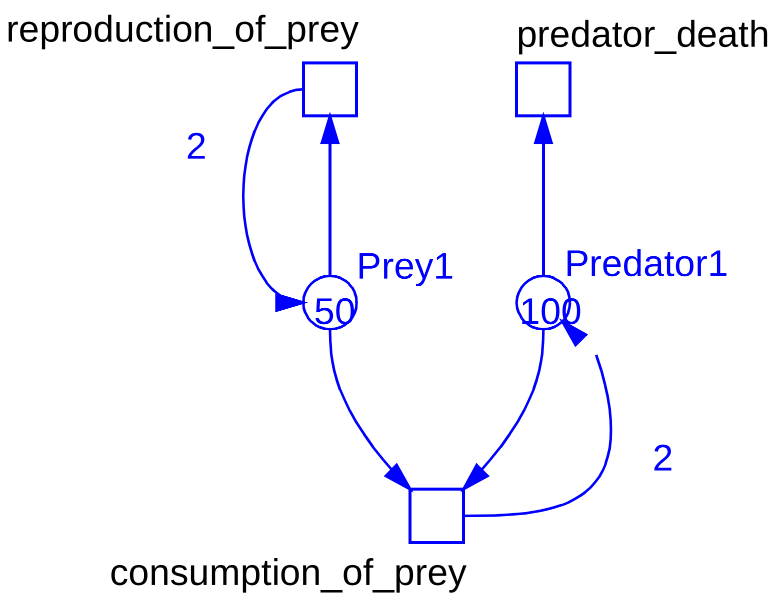
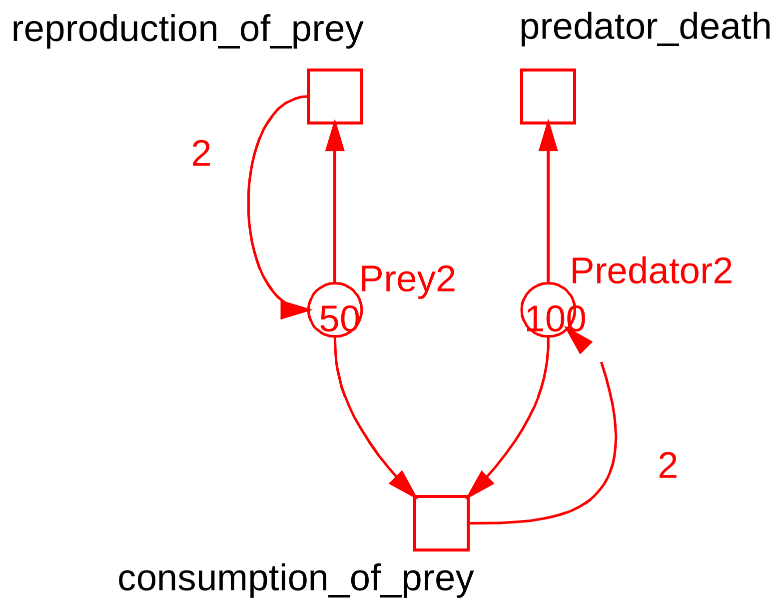
Ex: Prey - Predator

sub-system1



sub-system2



- **definitions**

  colourset *CS = 1-2;*

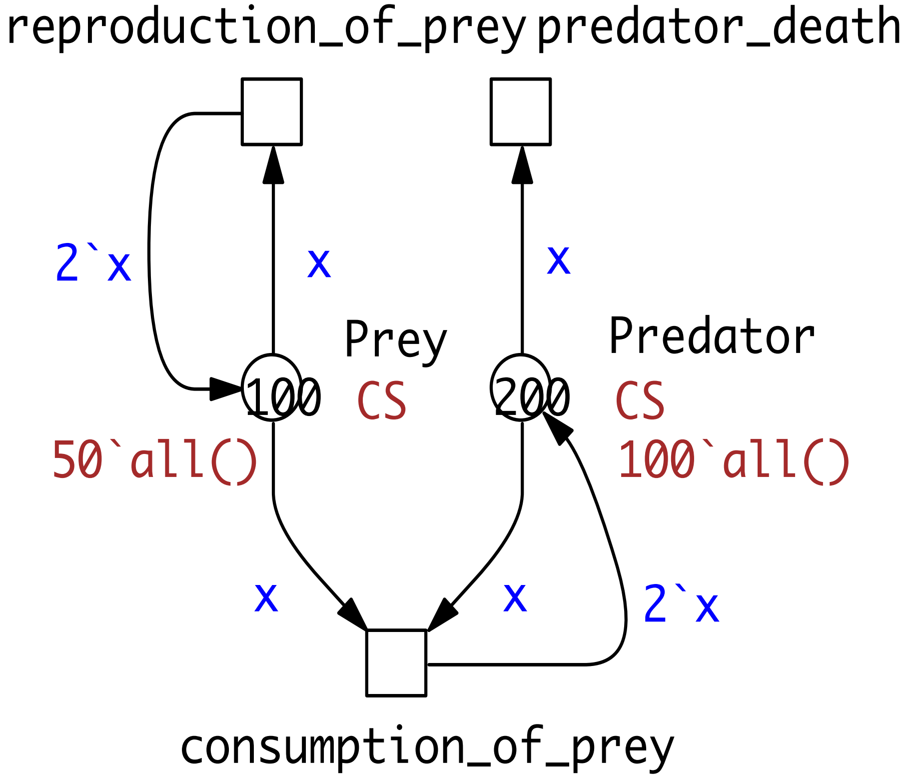
  var *x : CS;*

- **better:**

  const *SIZE = 2;*

  colourset *CS = 1-SIZE;*

  var *x : CS;*



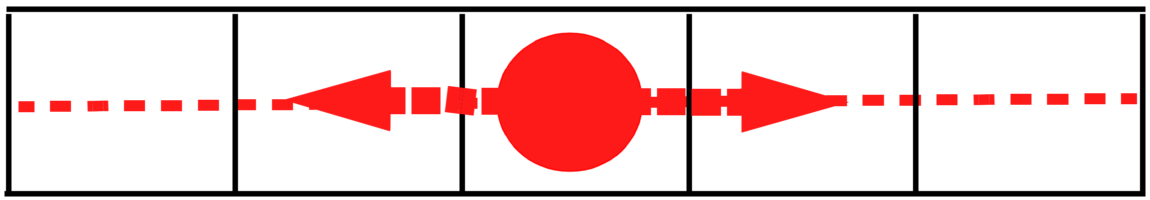
- **changing SIZE adapts the model to various scenarious**

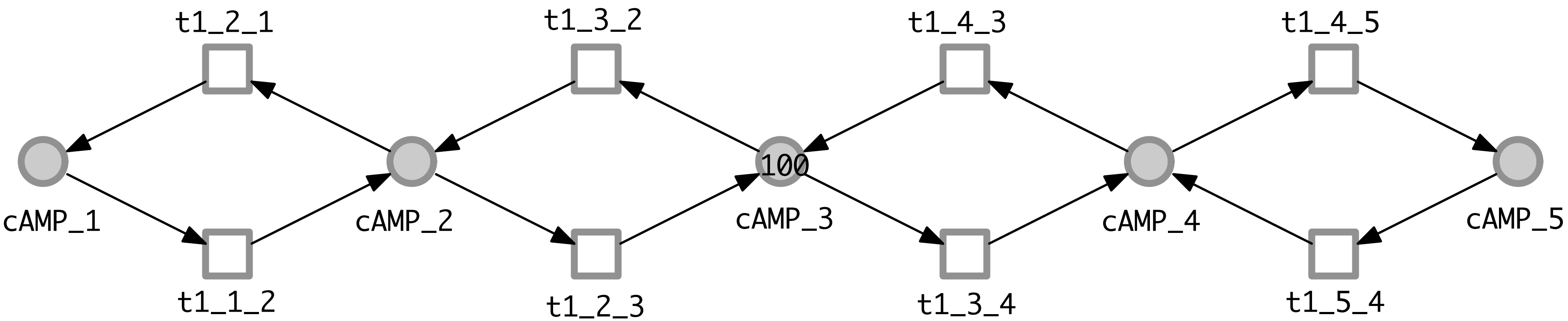
Richmond, 13/09/2011

Example 1:

Diffusion in Space

Ex1: Diffusion - 1D





- **definitions**

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

  ***const** MIDDLE = D1/2;*

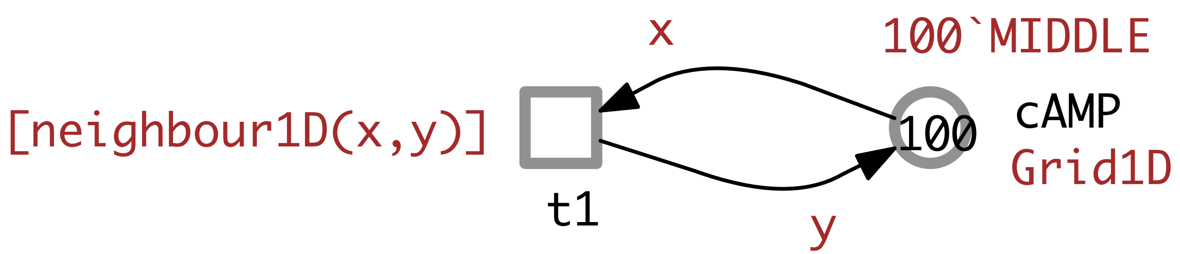
  ***colorset** CS = 1-D1;* *// grid positions*

  ***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**

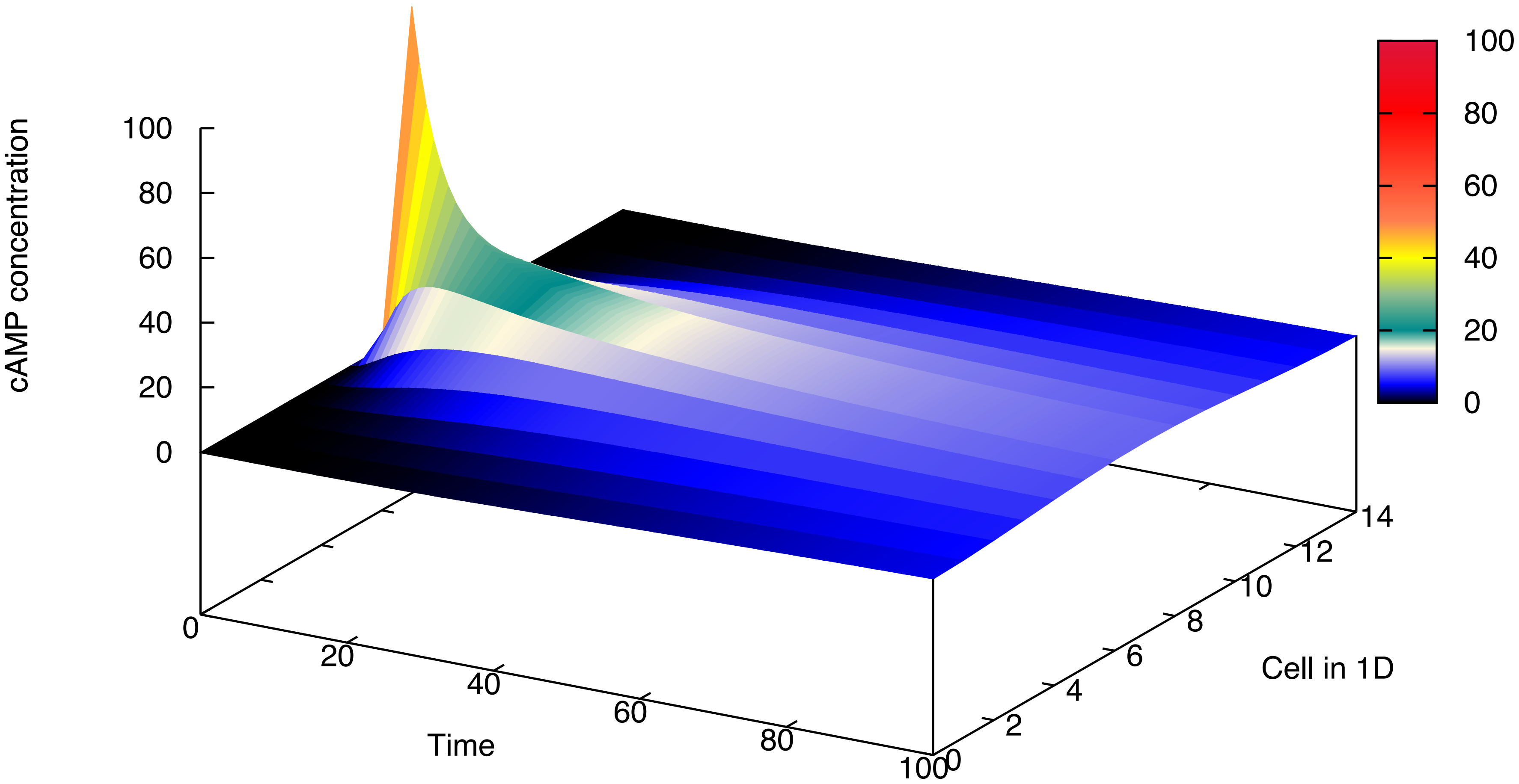
$$\frac{dc_1}{dt} = k \cdot c_2 - k \cdot c_1$$

$$\frac{dc_2}{dt} = k \cdot c_1 + k \cdot c_3 - 2 \cdot k \cdot c_2$$

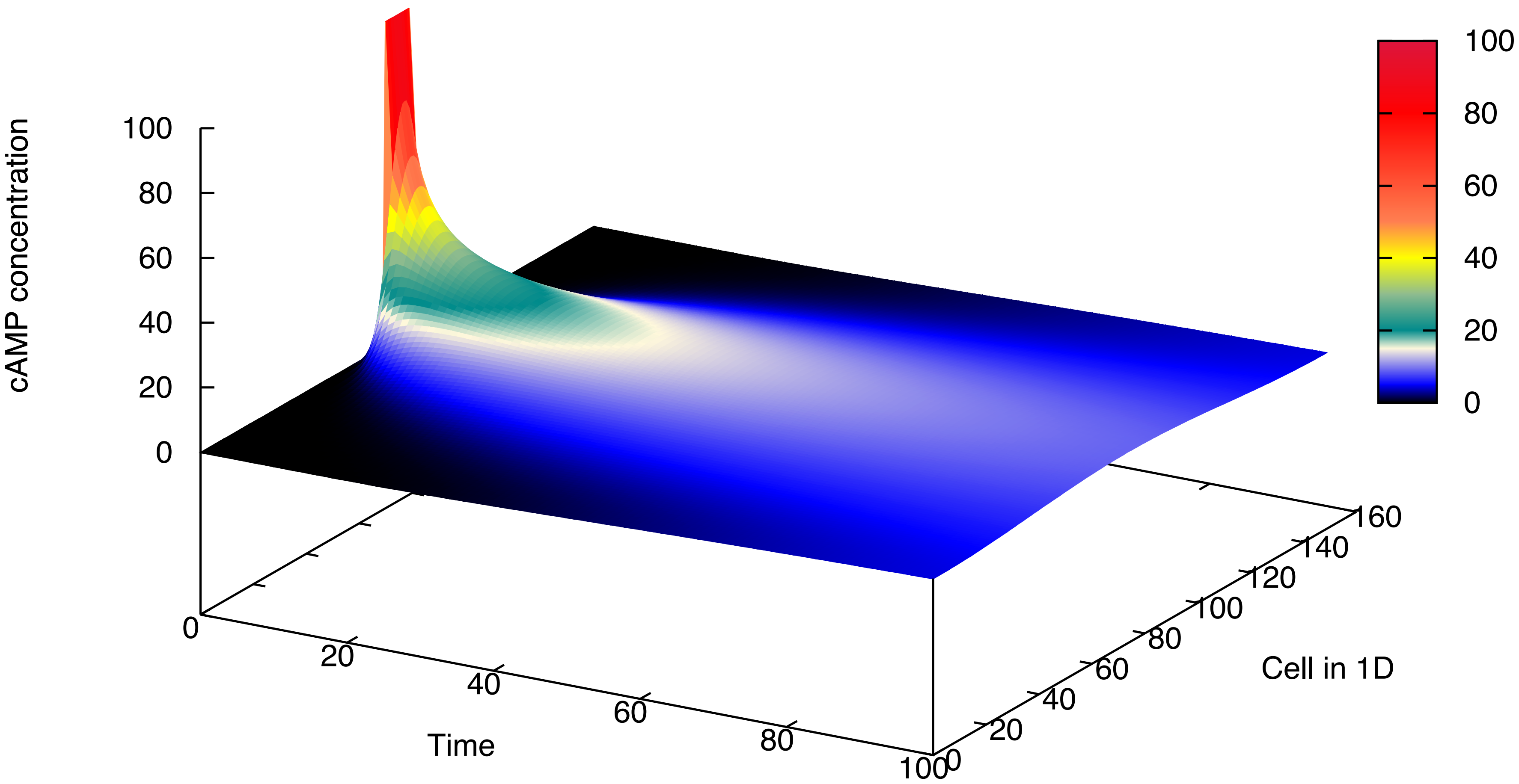
$$\frac{dc_3}{dt} = k \cdot c_2 + k \cdot c_4 - 2 \cdot k \cdot c_3$$

$$\frac{dc_4}{dt} = k \cdot c_3 + k \cdot c_5 - 2 \cdot k \cdot c_4$$

$$\frac{dc_5}{dt} = k \cdot c_4 - k \cdot c_5$$

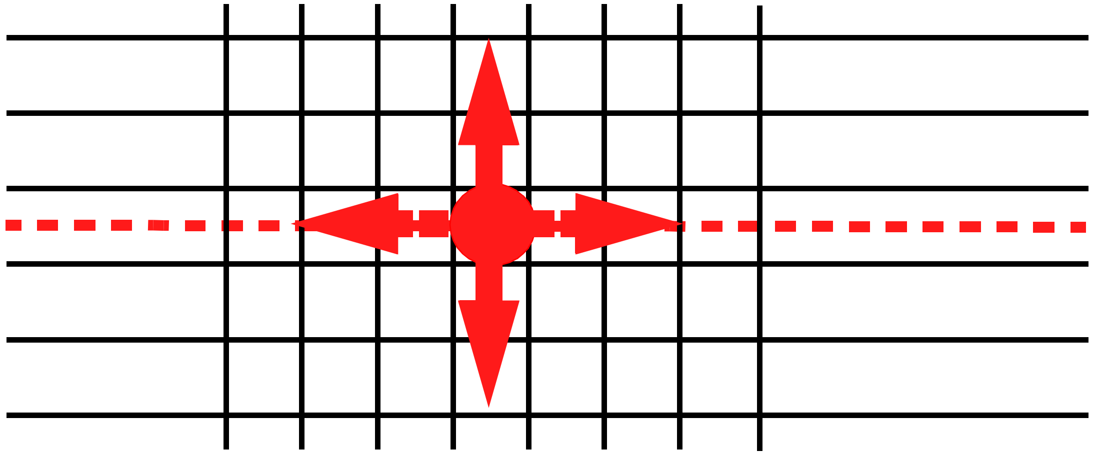


15 GRID POSITIONS



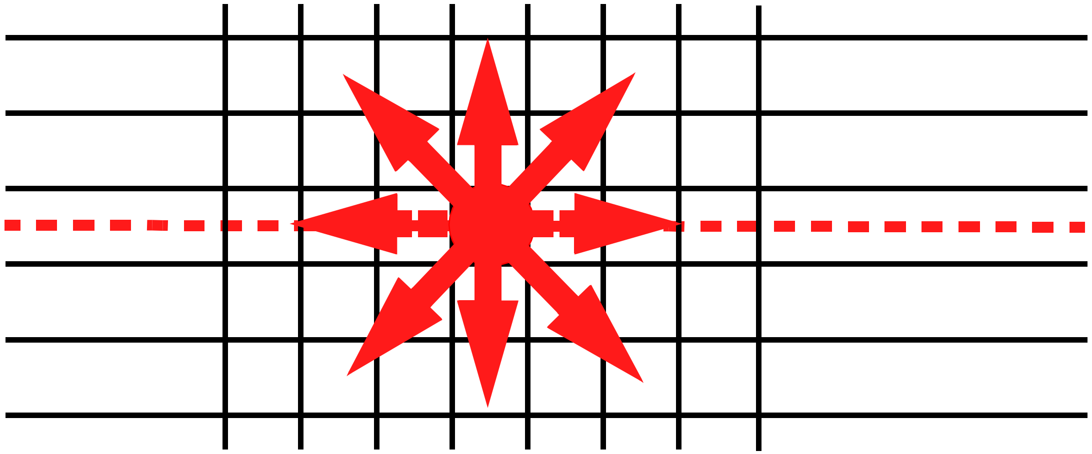
150 GRID POSITIONS, SCALING OF INITIAL MARKING AND RATES

- SCHEME

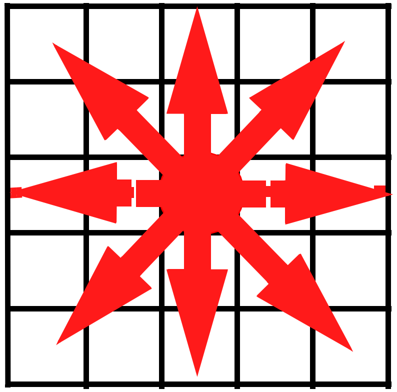


EX1: DIFFUSION - 2D

- 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;
```

EX1: DIFFUSION - 2D4 NEIGHBOURHOOD

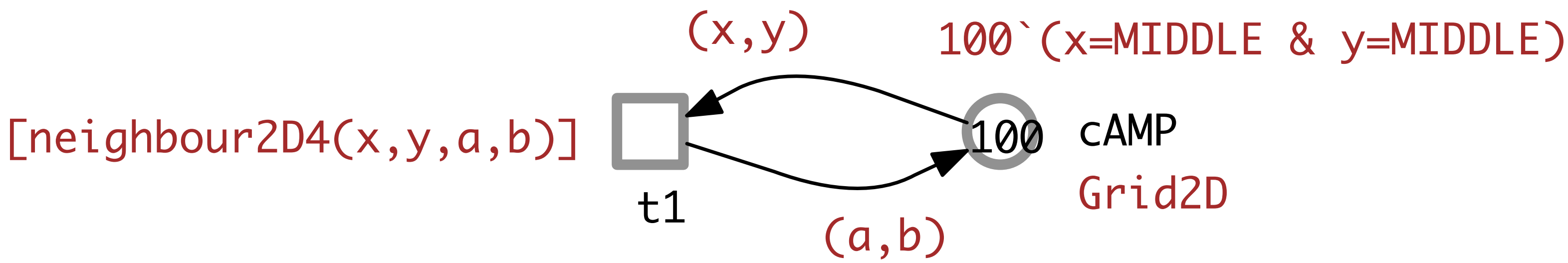
- **four neighbours**

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

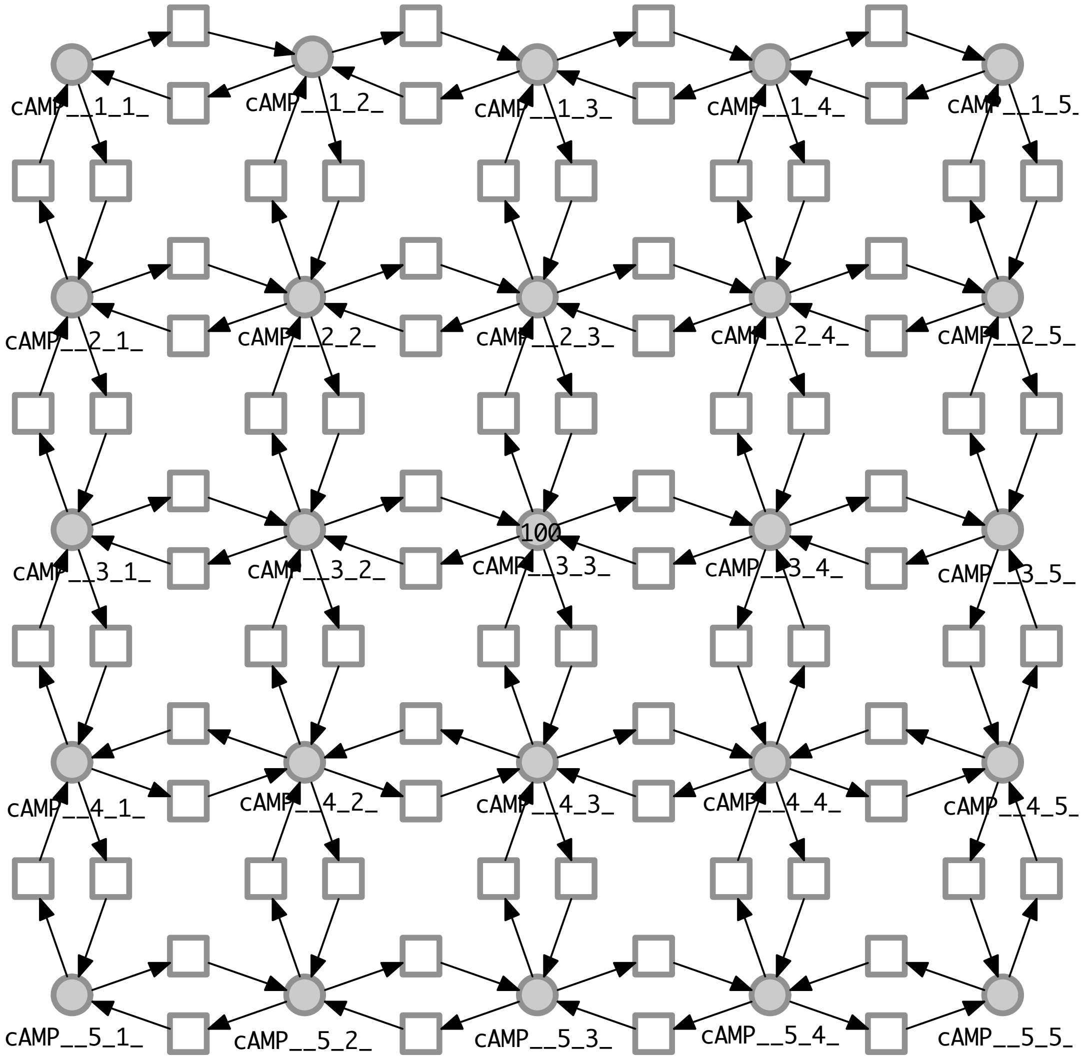
  // (a,b) is one of the up to four neighbours of (x,y)

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

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



EX1: DIFFUSION - 2D4 NEIGHBOURHOOD



EX1: DIFFUSION - 2D8 NEIGHBOURHOOD

- **eight neighbours**

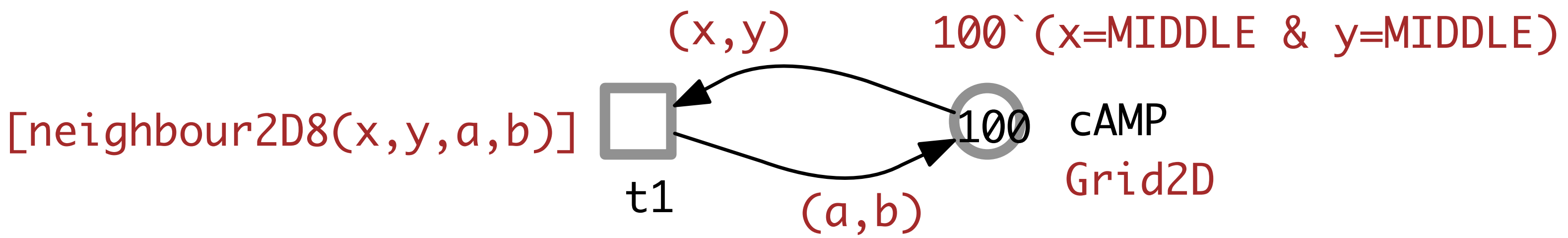
  function *neighbour2D8 (CD1 x, CD2 y, CD1 a, CD2 b)* ***bool****:*

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

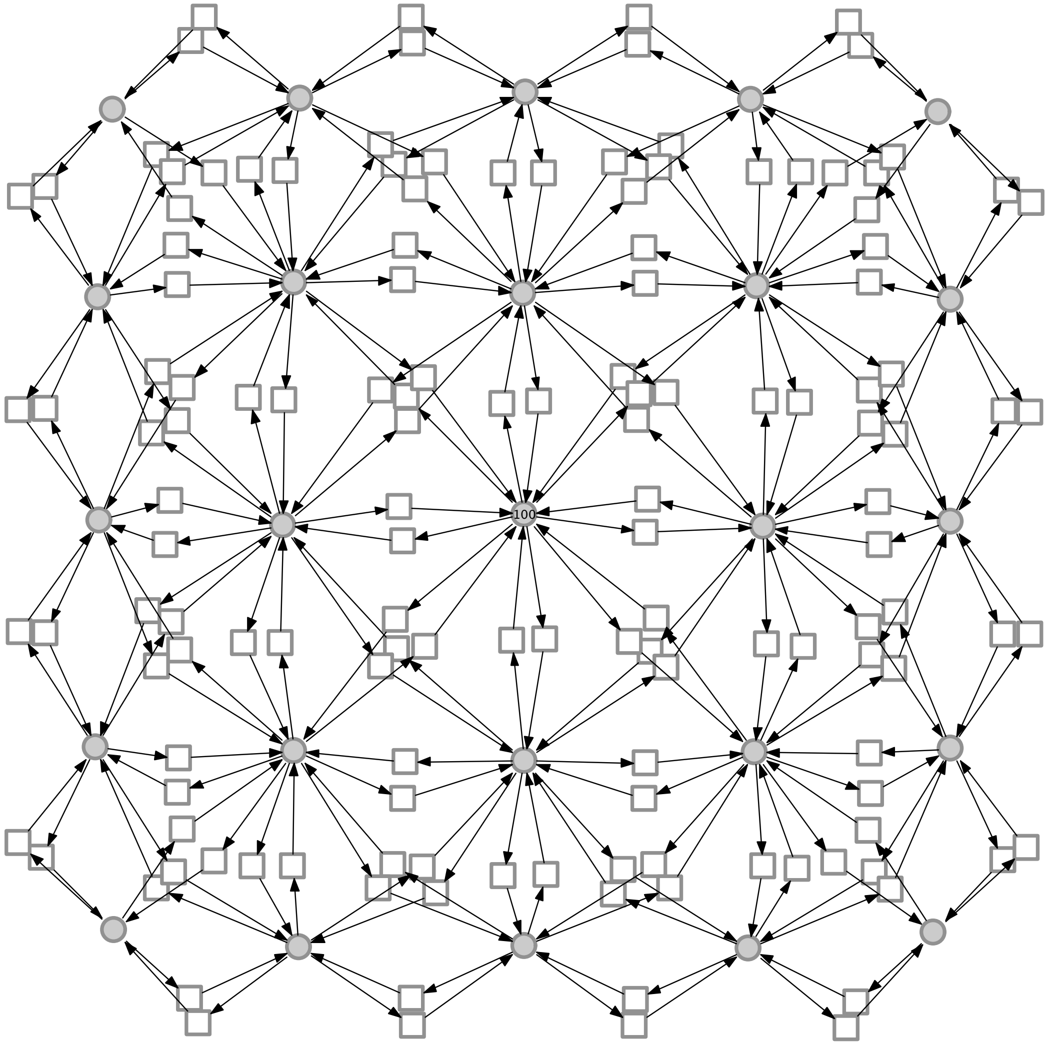
  (a=x-1 | a=x | a=x+1) & (b = y-1 | b=y | b=y+1)

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

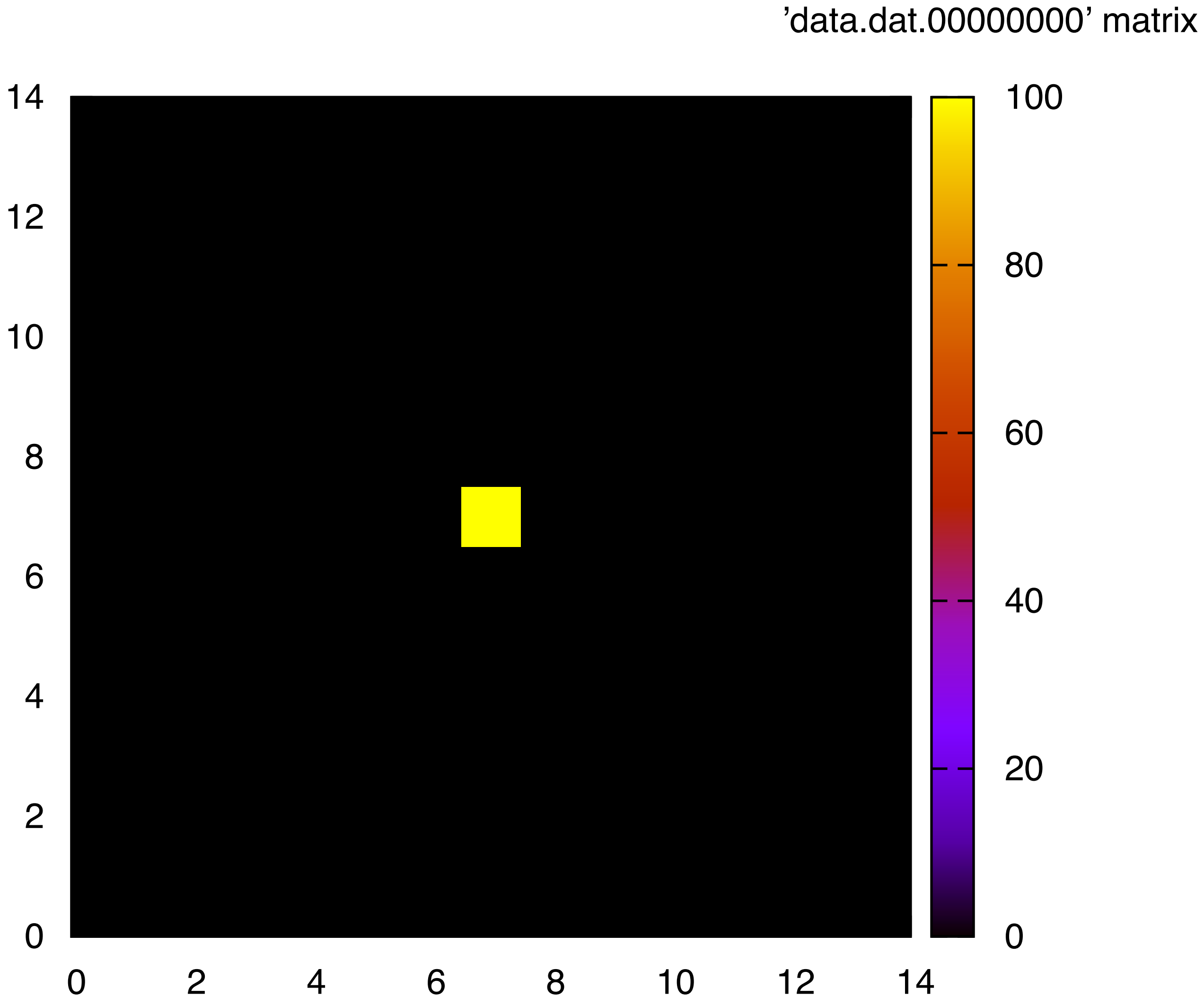
  & (1<=a & a<=D1) & (1<=b & b<=D2);



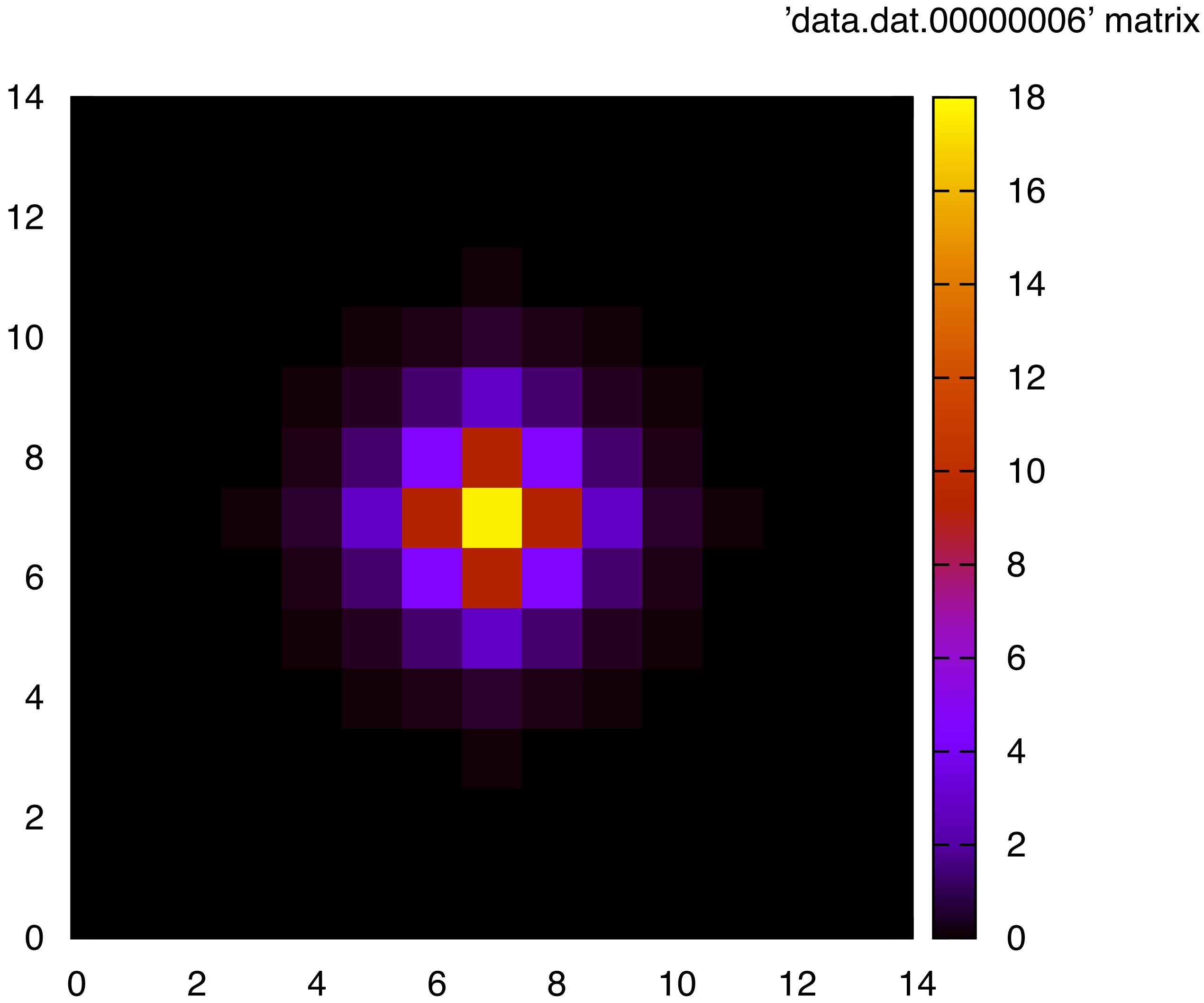
EX1: DIFFUSION - 2D8 NEIGHBOURHOOD



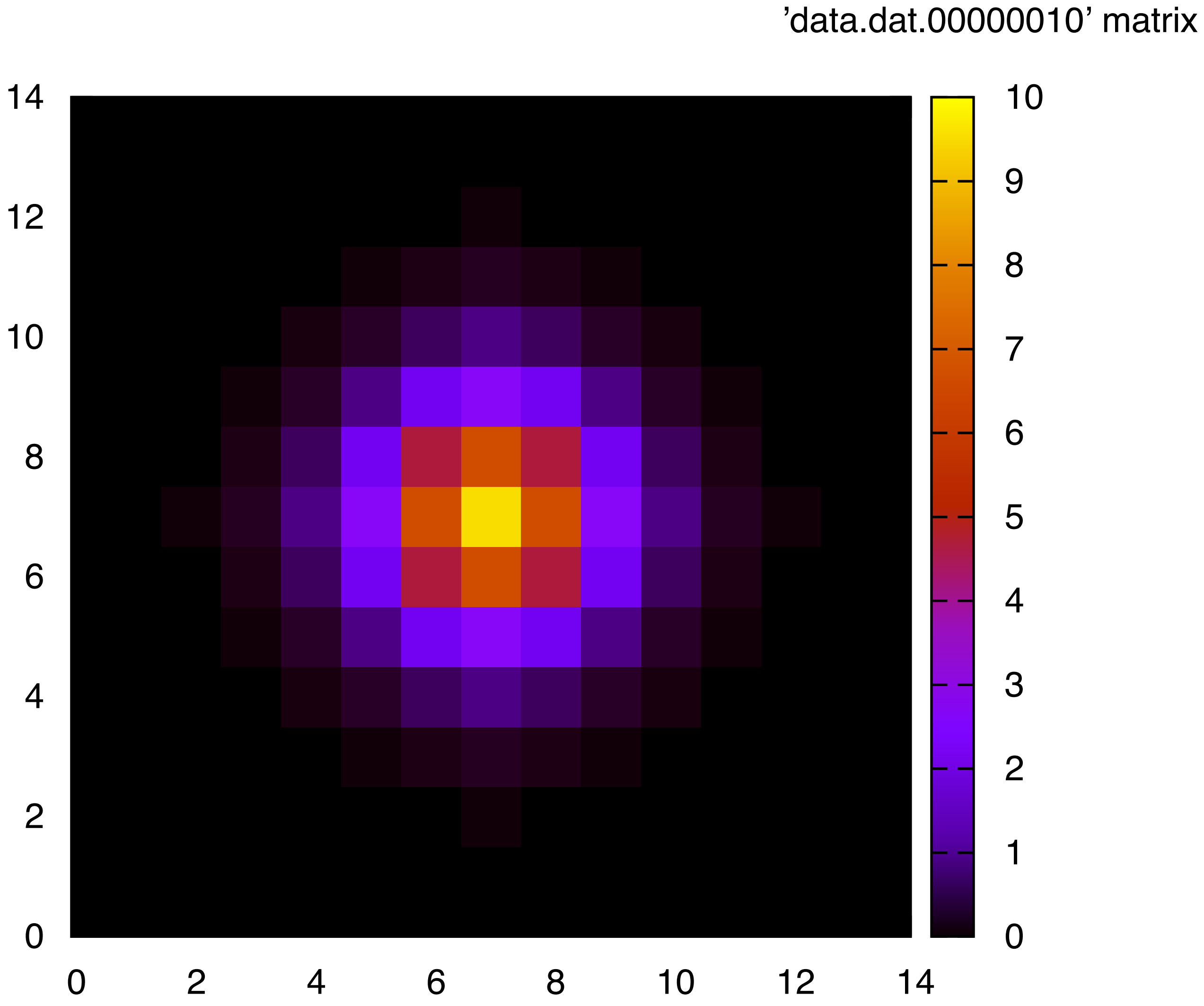
EX1: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15



Ex1: Diffusion - 2D4 Neighbourhood, 15x15



EX1: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15



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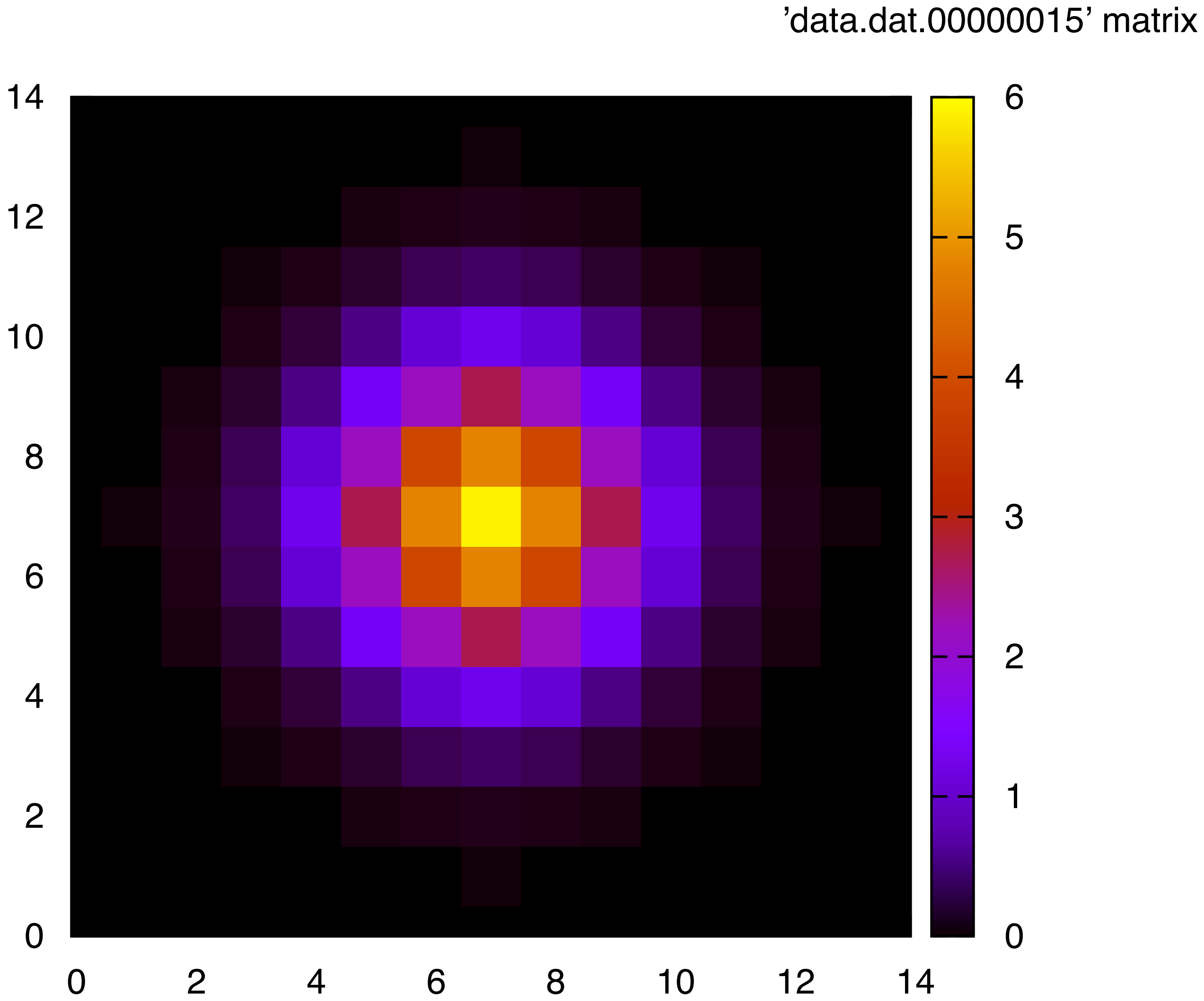
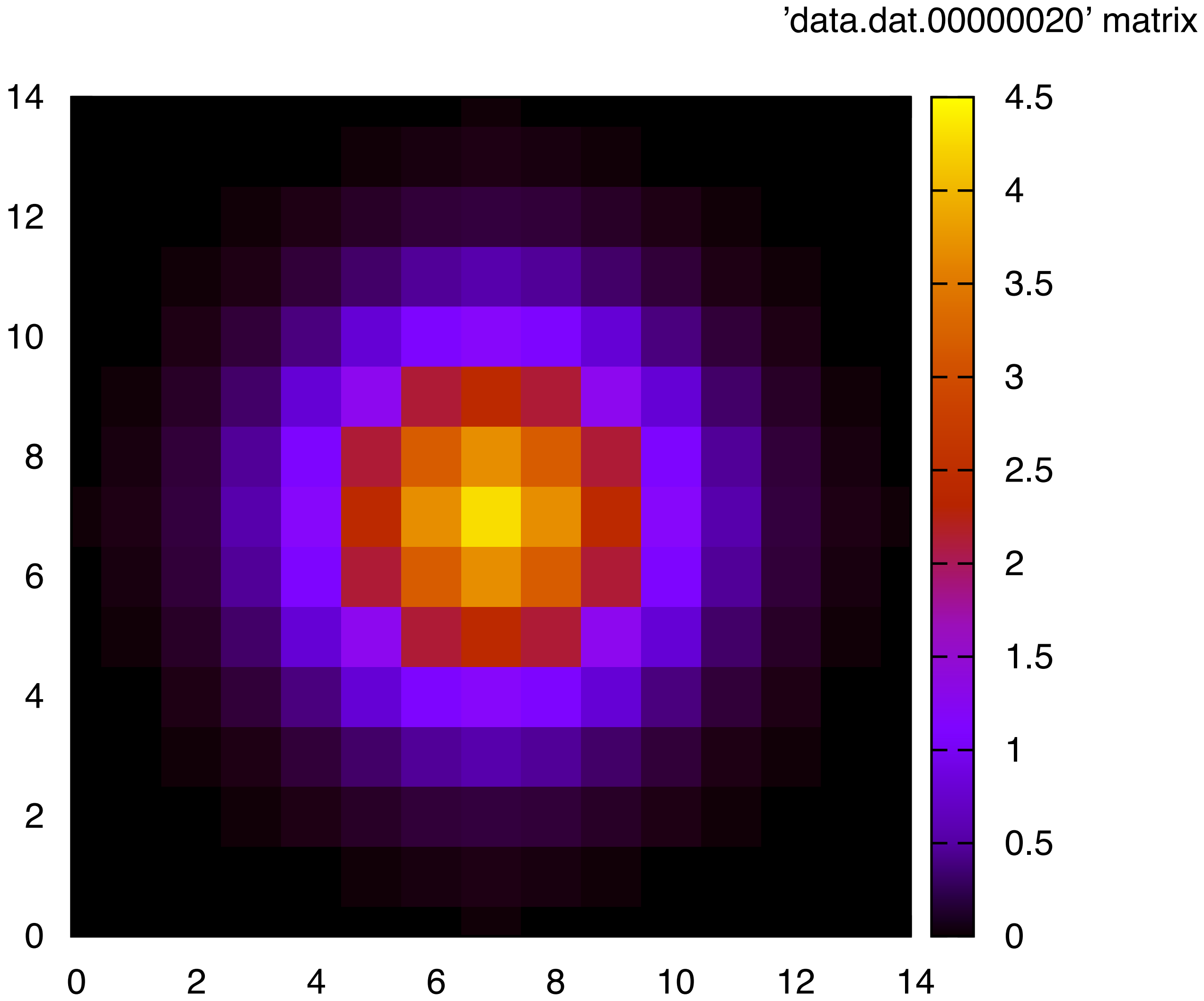
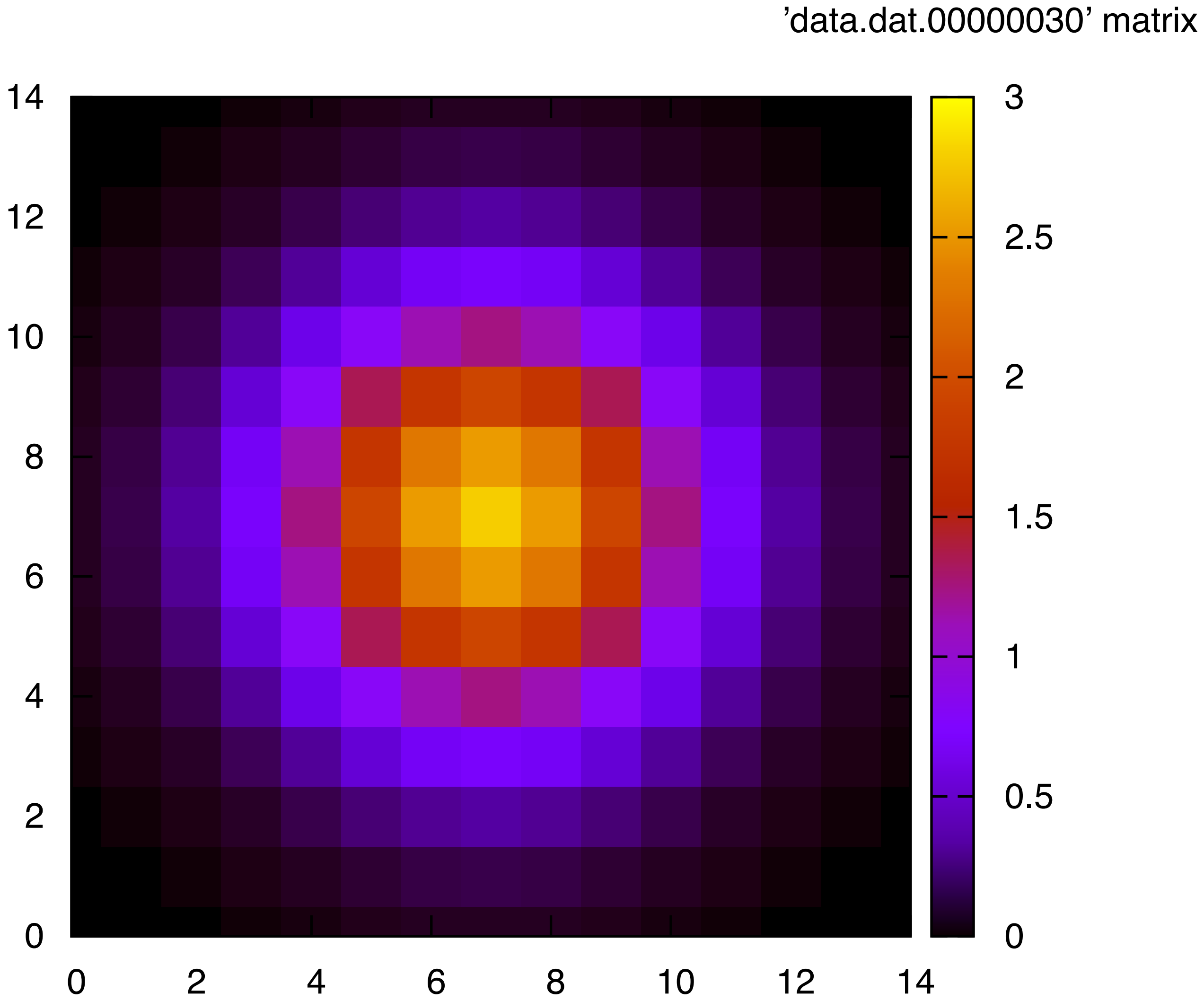
EX1: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15



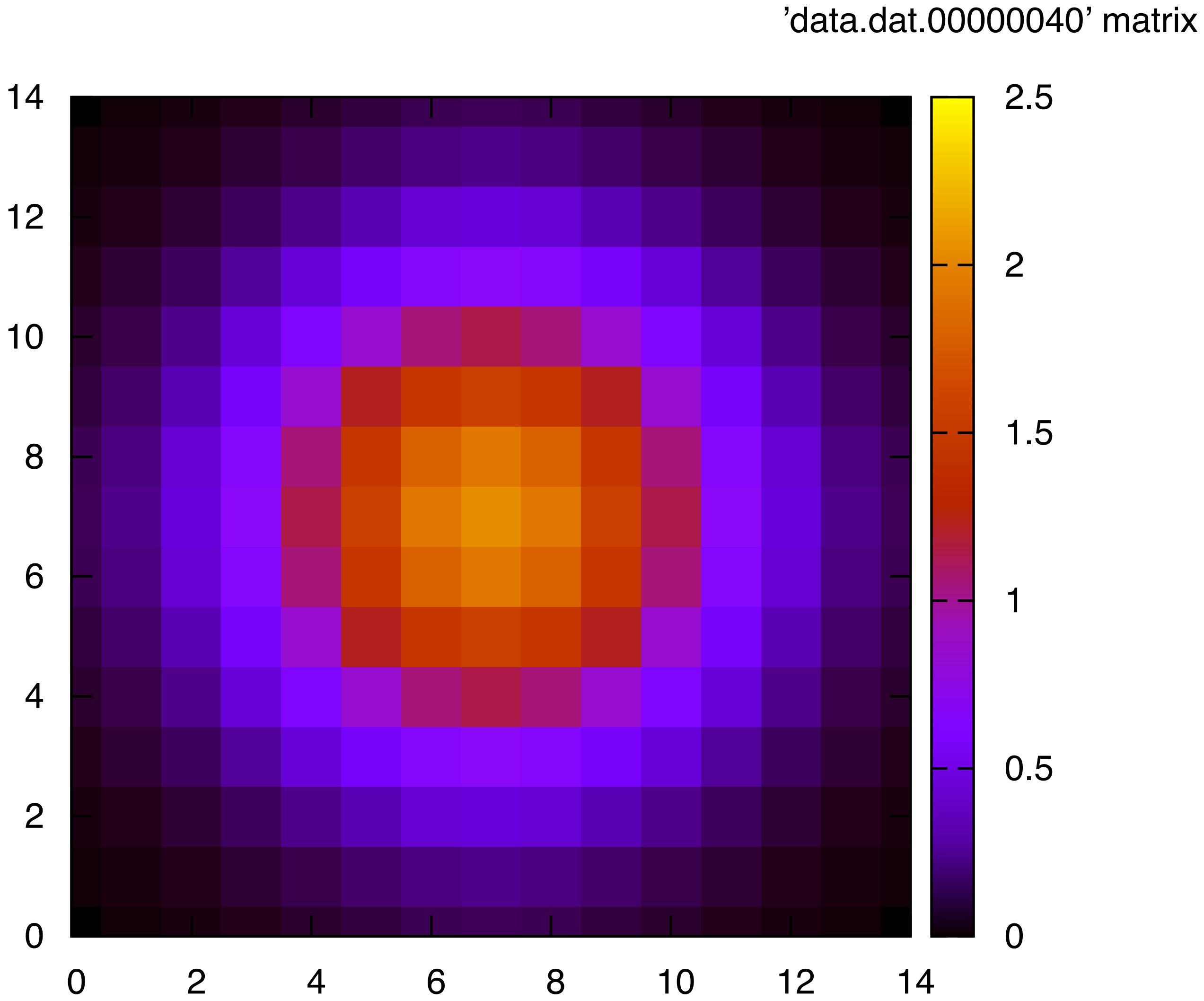
Ex1: Diffusion - 2D4 Neighbourhood, 15x15



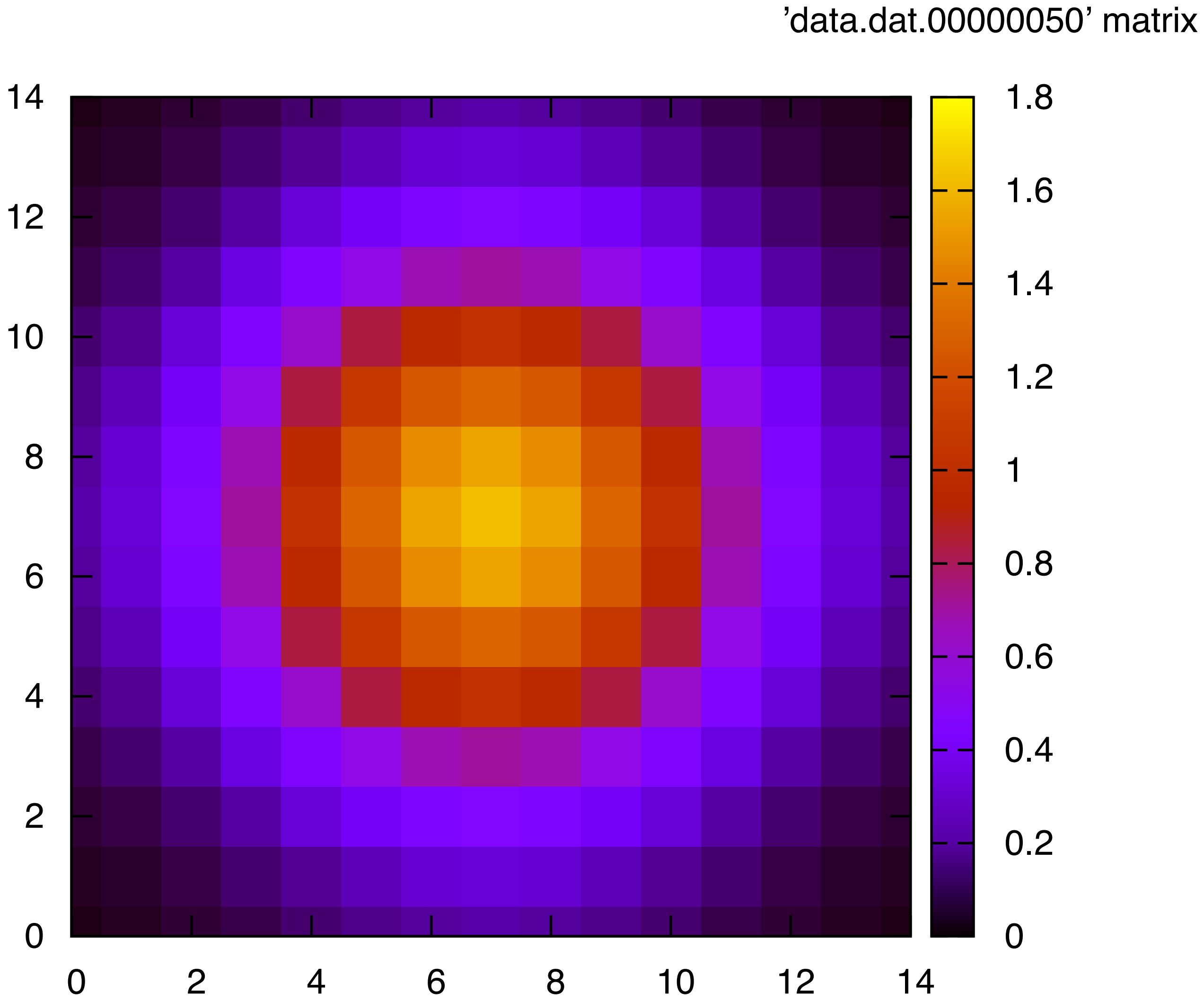
Ex1: Diffusion - 2D4 Neighbourhood, 15x15



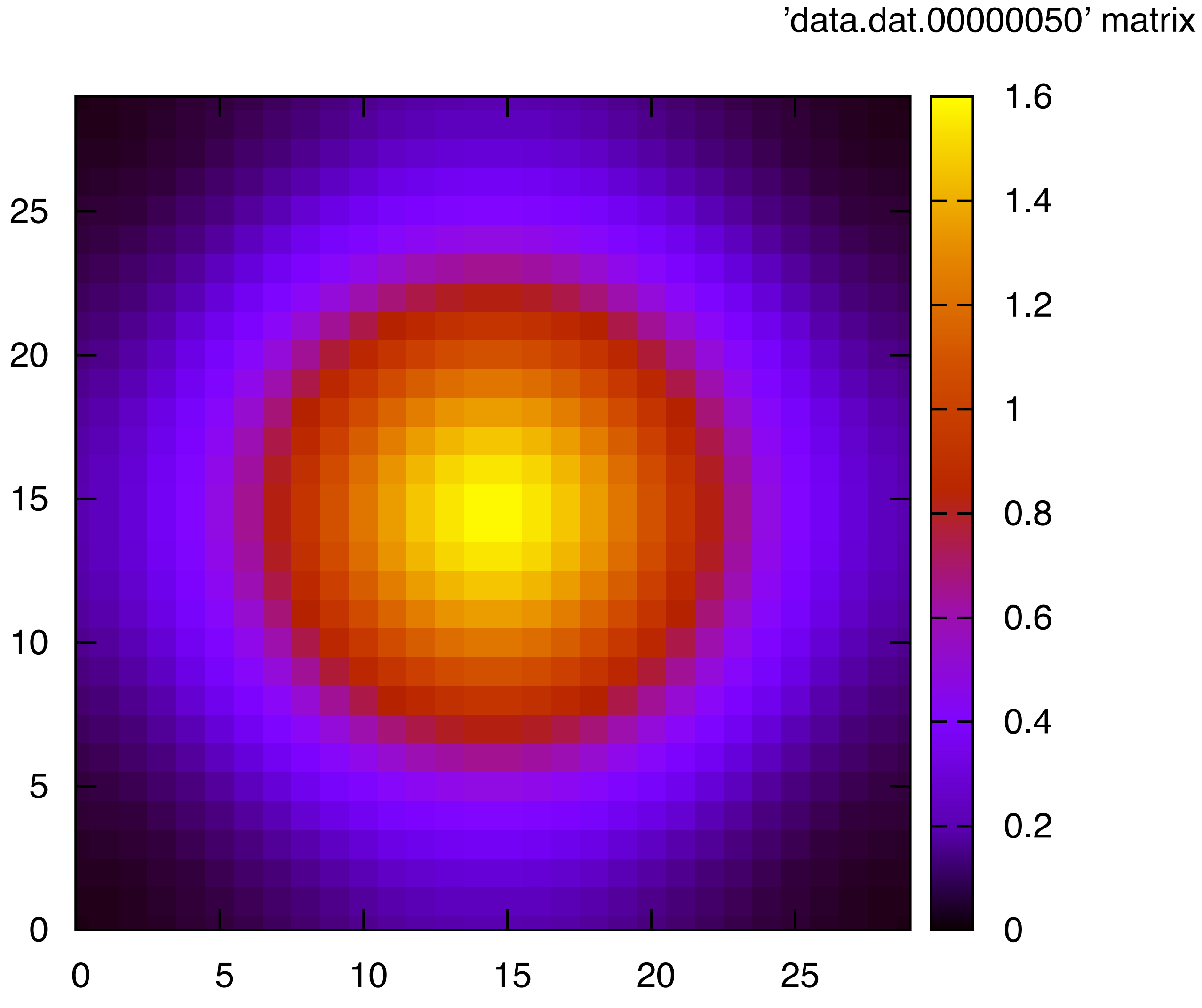
EX1: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15



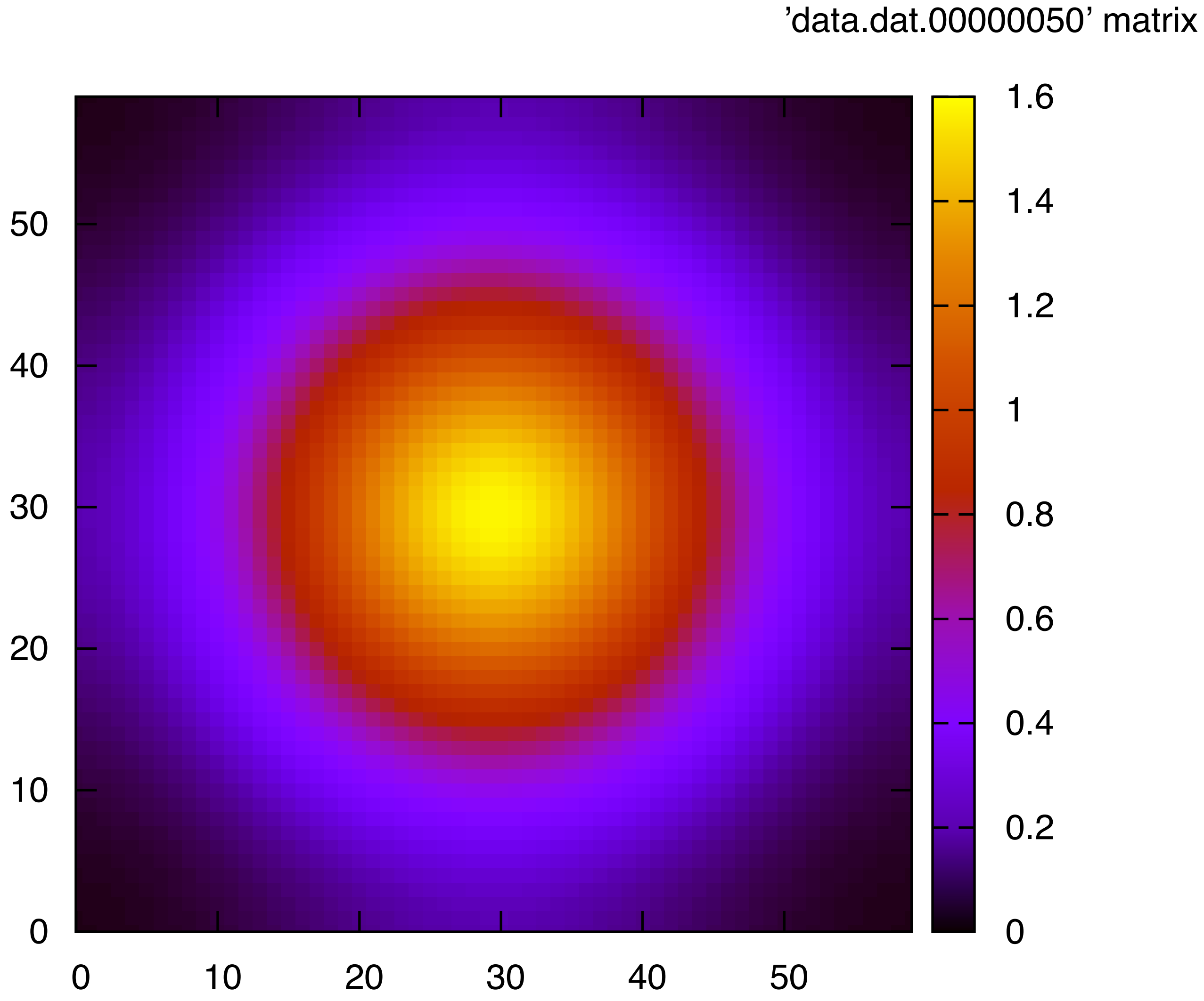
EX1: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15



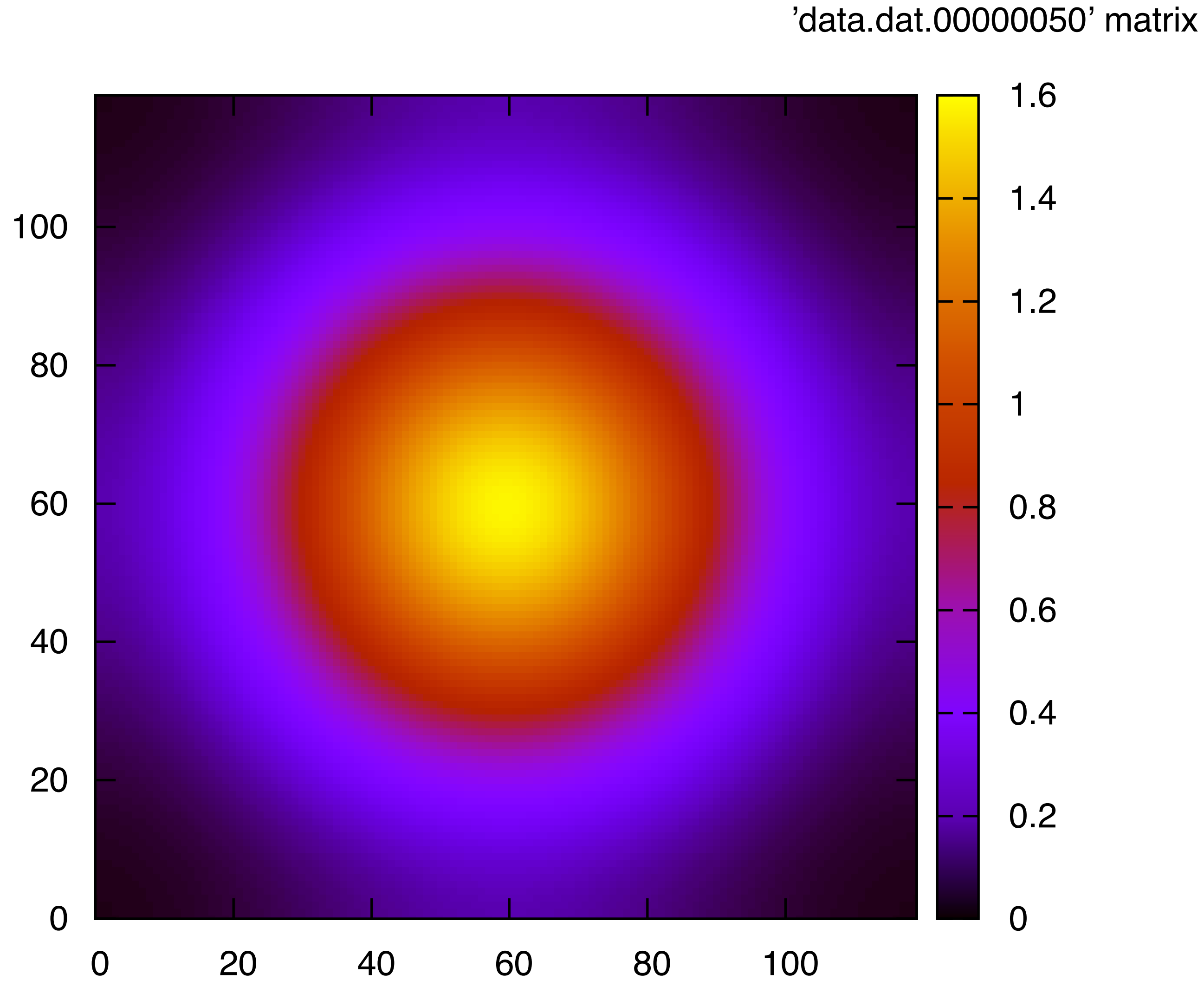
Ex1: Diffusion - 2D4 Neighbourhood, 30x30



Ex1: Diffusion - 2D4 Neighbourhood, 60x60



EX1: DIFFUSION - 2D4 NEIGHBOURHOOD, 120X120



EXAMPLE 2:

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

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

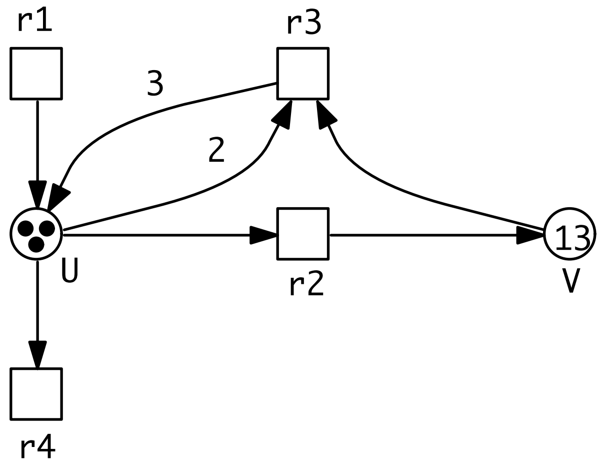
- **mathematical challenge**
  - -> *For which parameters do stable/oscillating Turing patterns exist ?*
  - -> *analysis of stability, multistability, bifurcation of non-linear PDE*

r1: -> U

r2: U -> V

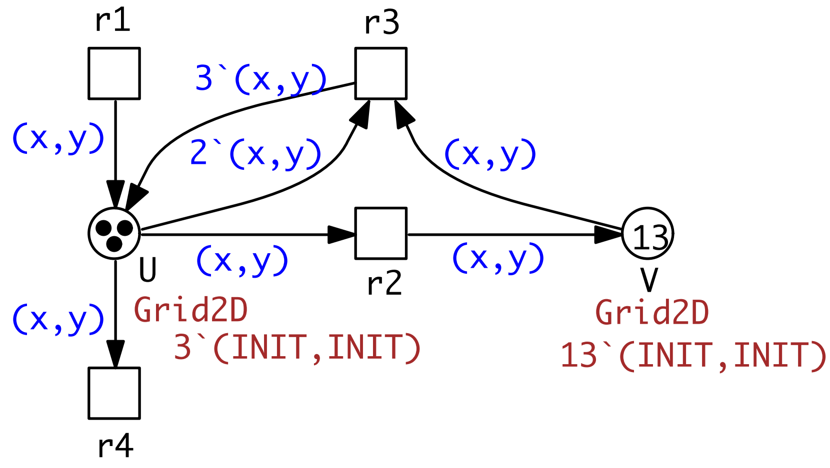
r3: 2U + V -> 3U

r4: U ->



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

adding SPACE



r1: -> U

r2: U -> V

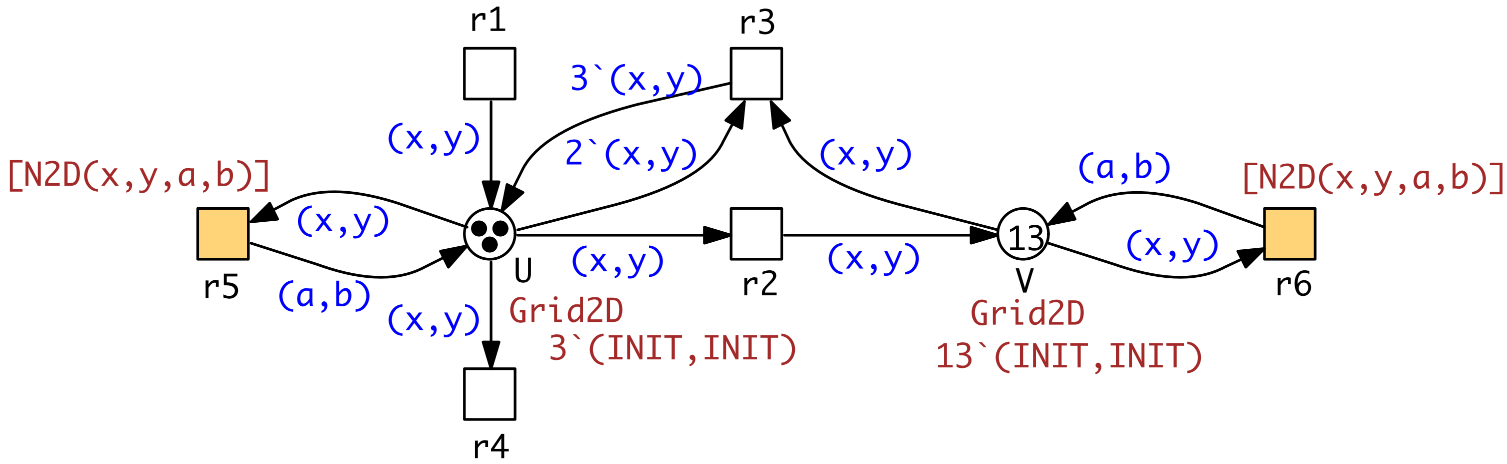
r3: 2U + V -> 3U

r4: U ->

diffusion:

r5: U_{xy} -- $1/h^2$ --> U_{ab}

r6: V_{xy} -- D/h^2 --> V_{ab}



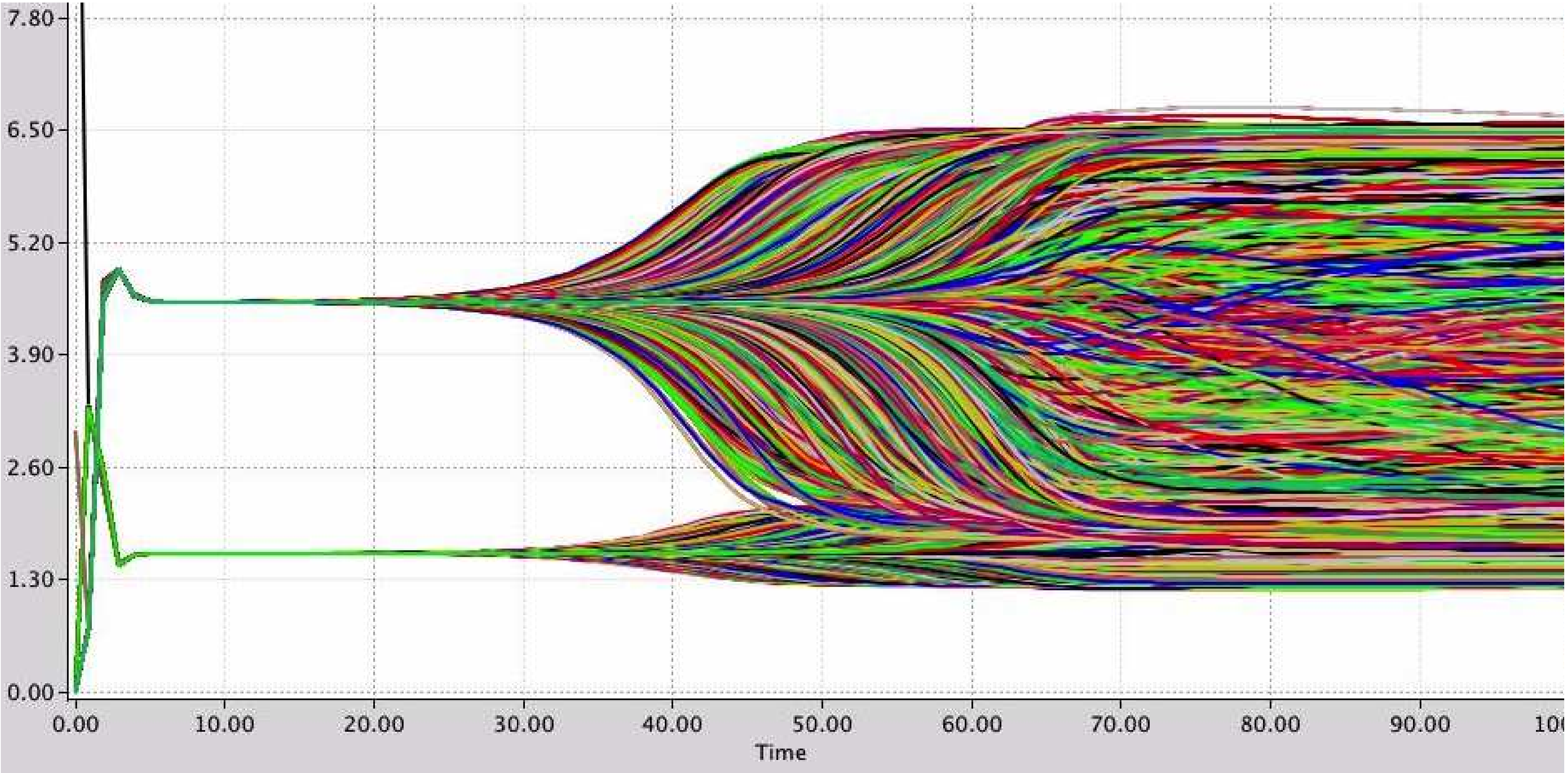
r1 - r4 follow mass action kinetics with rate constants:

r1: a, r2: b, r3: 1, r4: 1;

Ex2: Some Experiments

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


7.80
6.50
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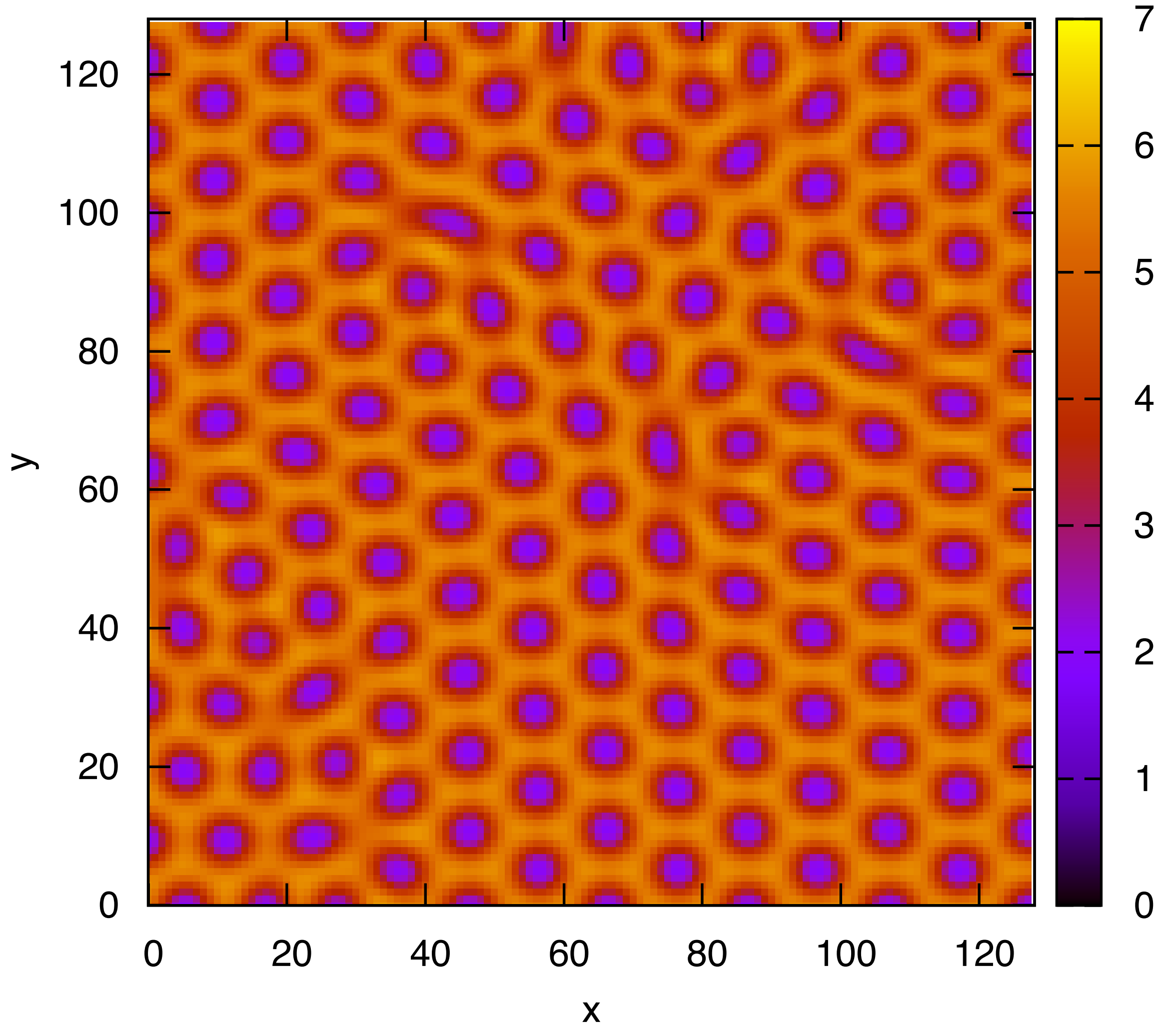
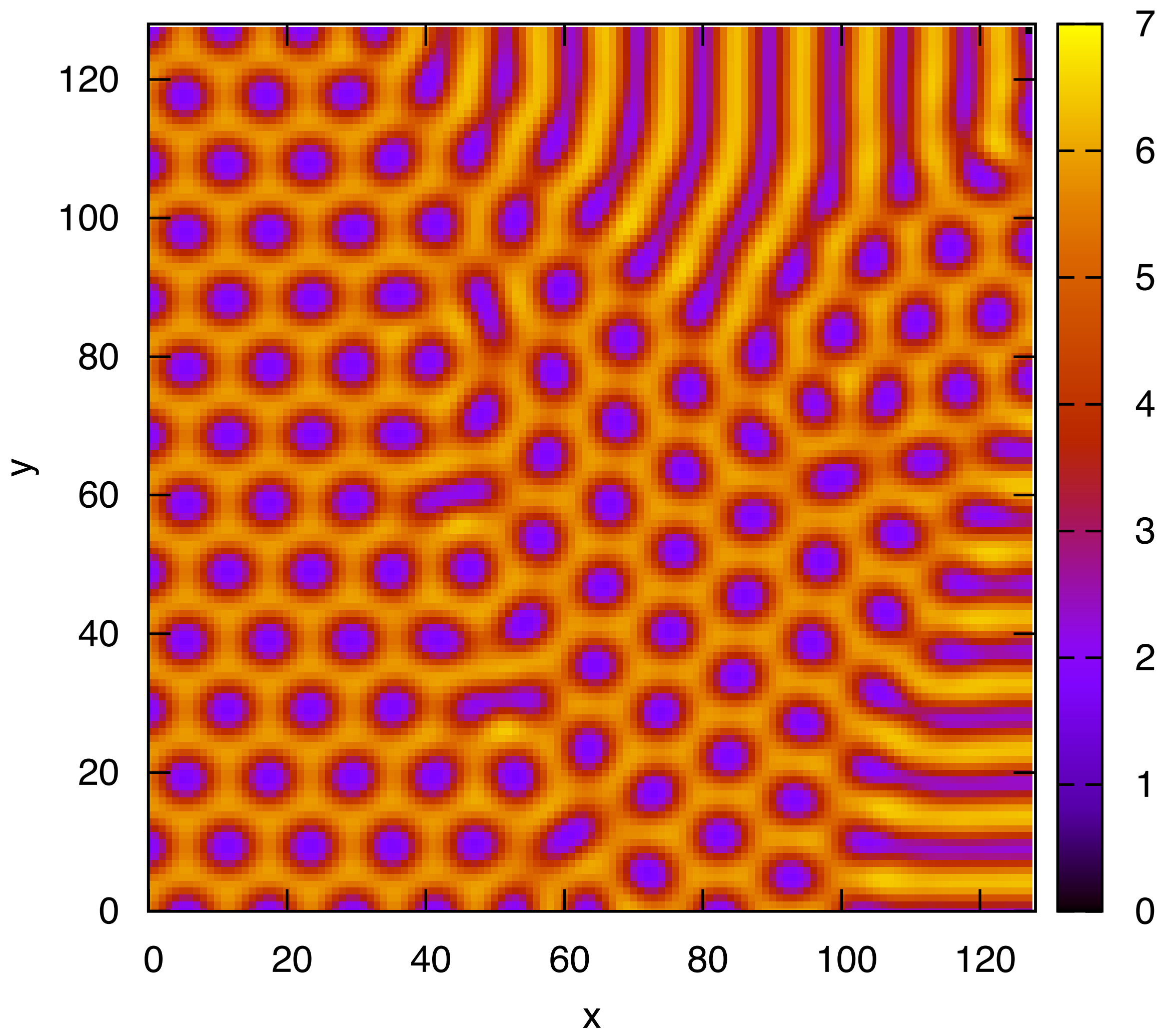
90.00
Time

Ex2: Turing Patterns





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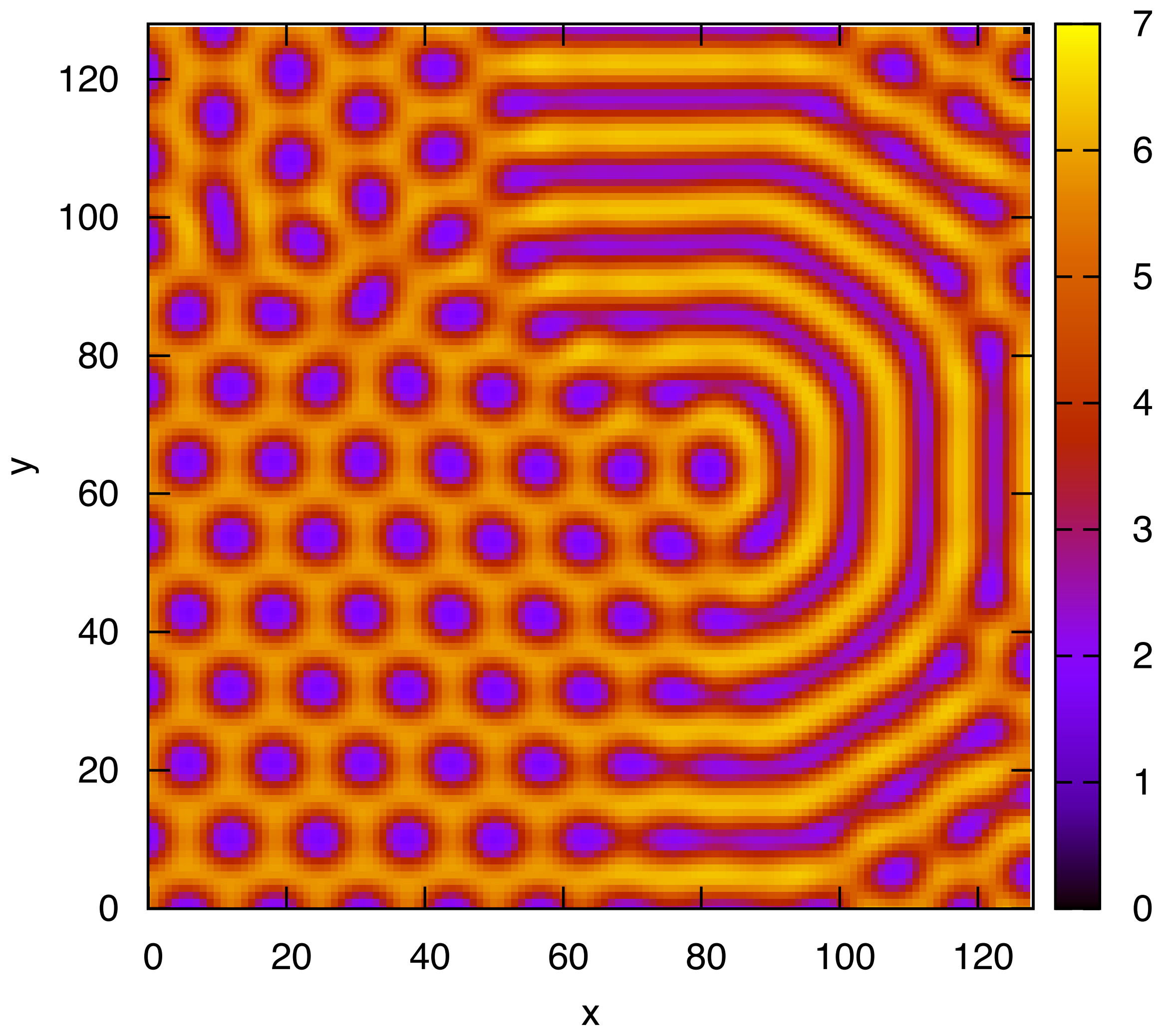
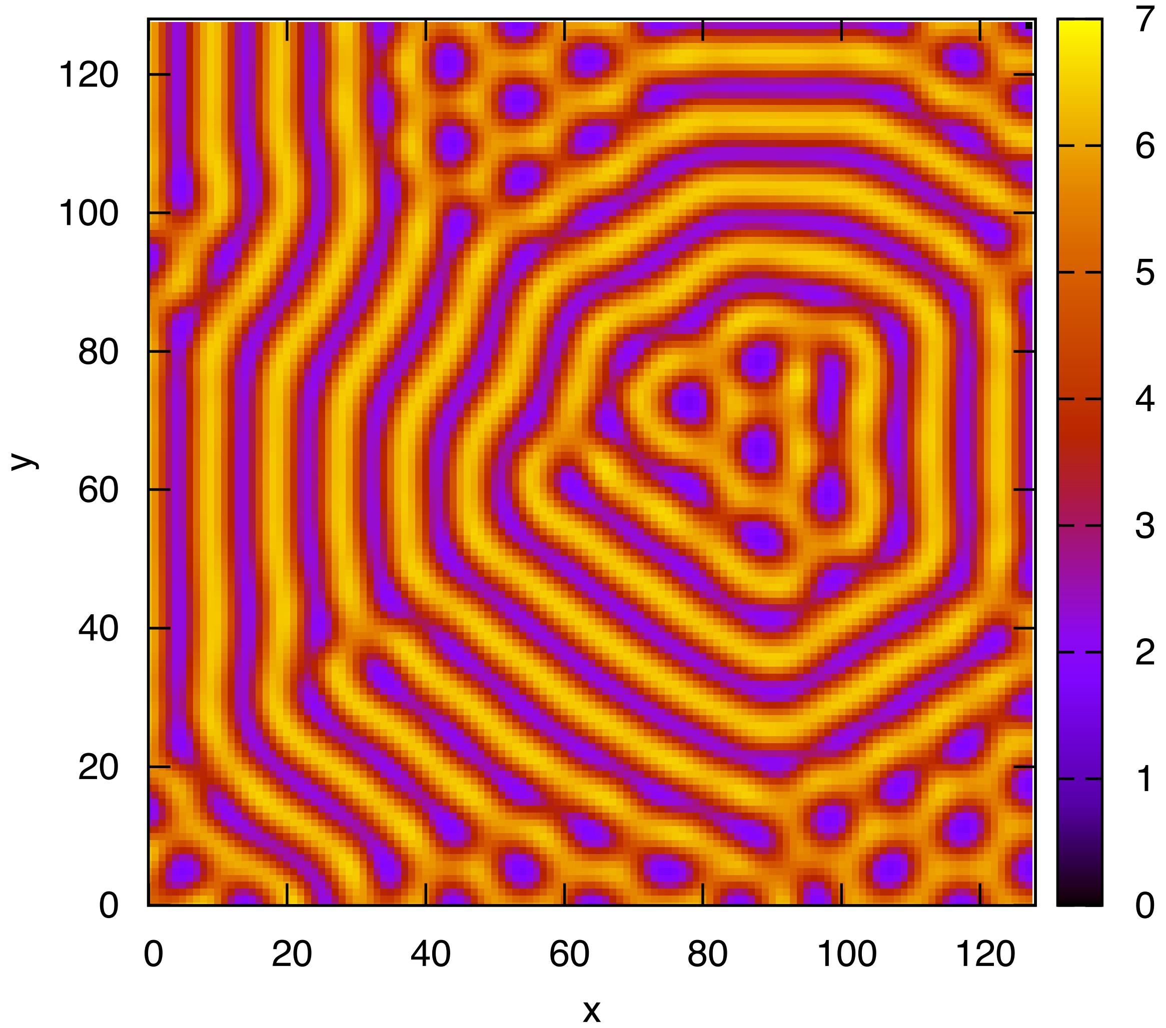
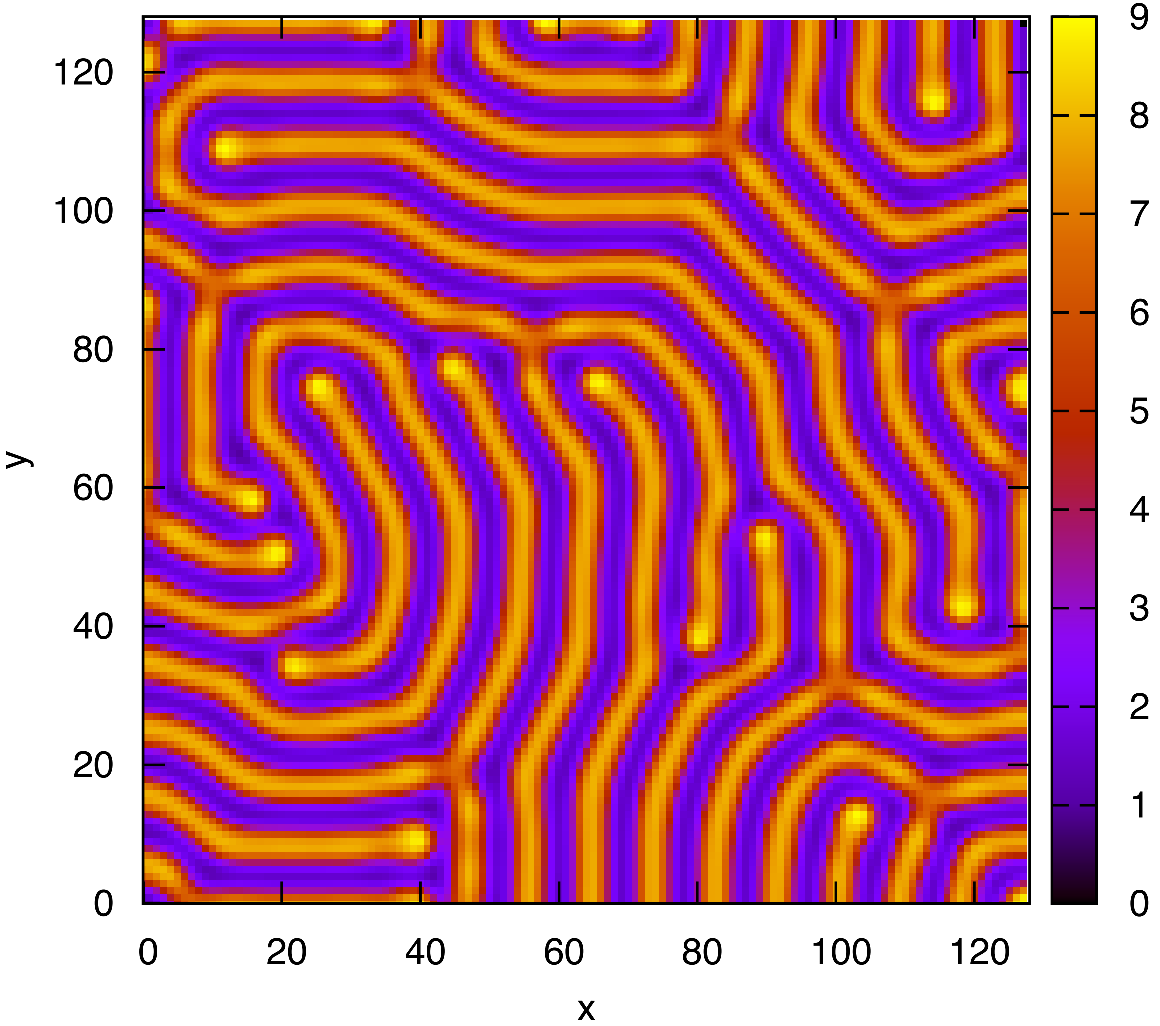
Ex2: Turing Patterns



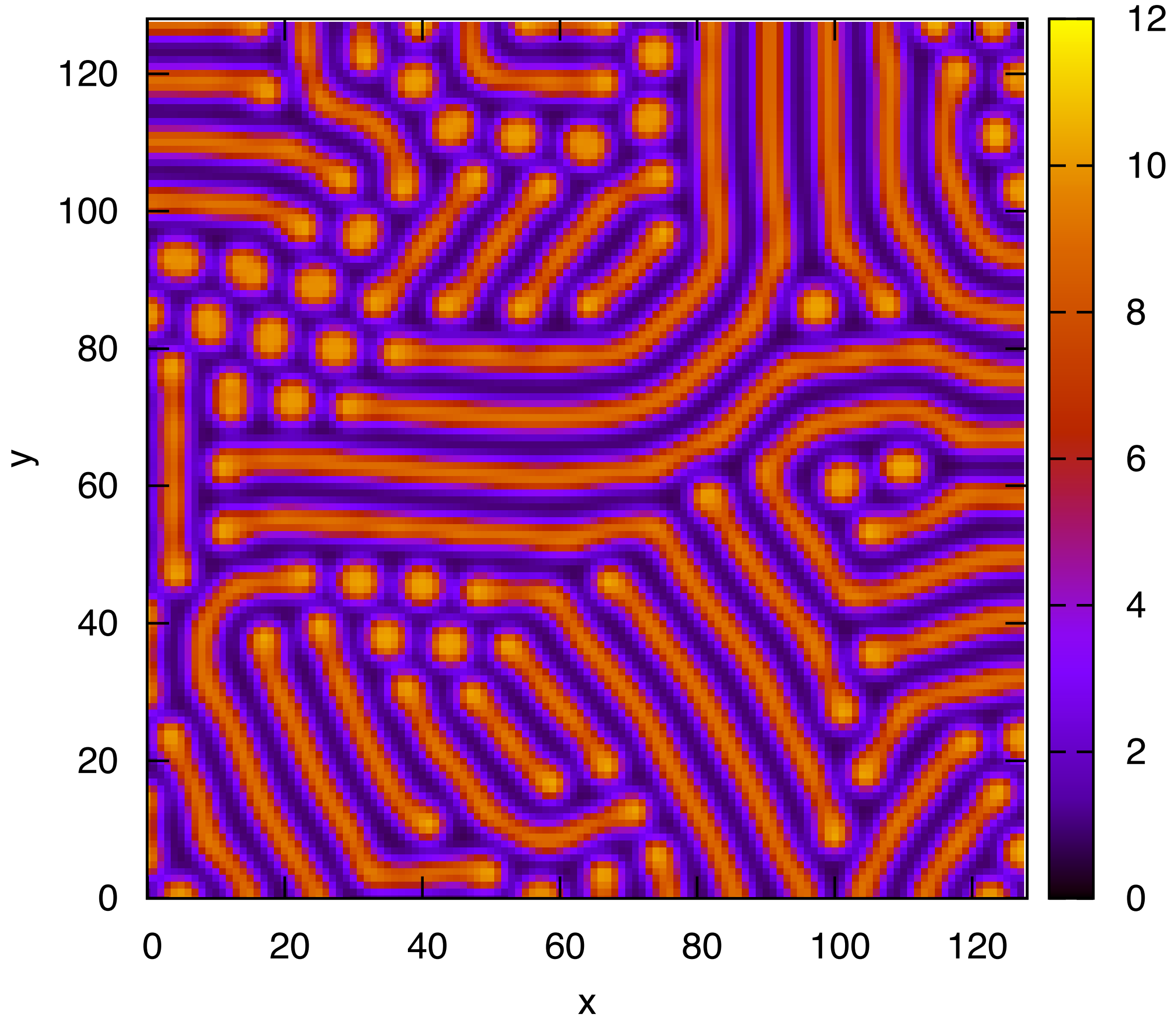
Ex2: Turing Patterns

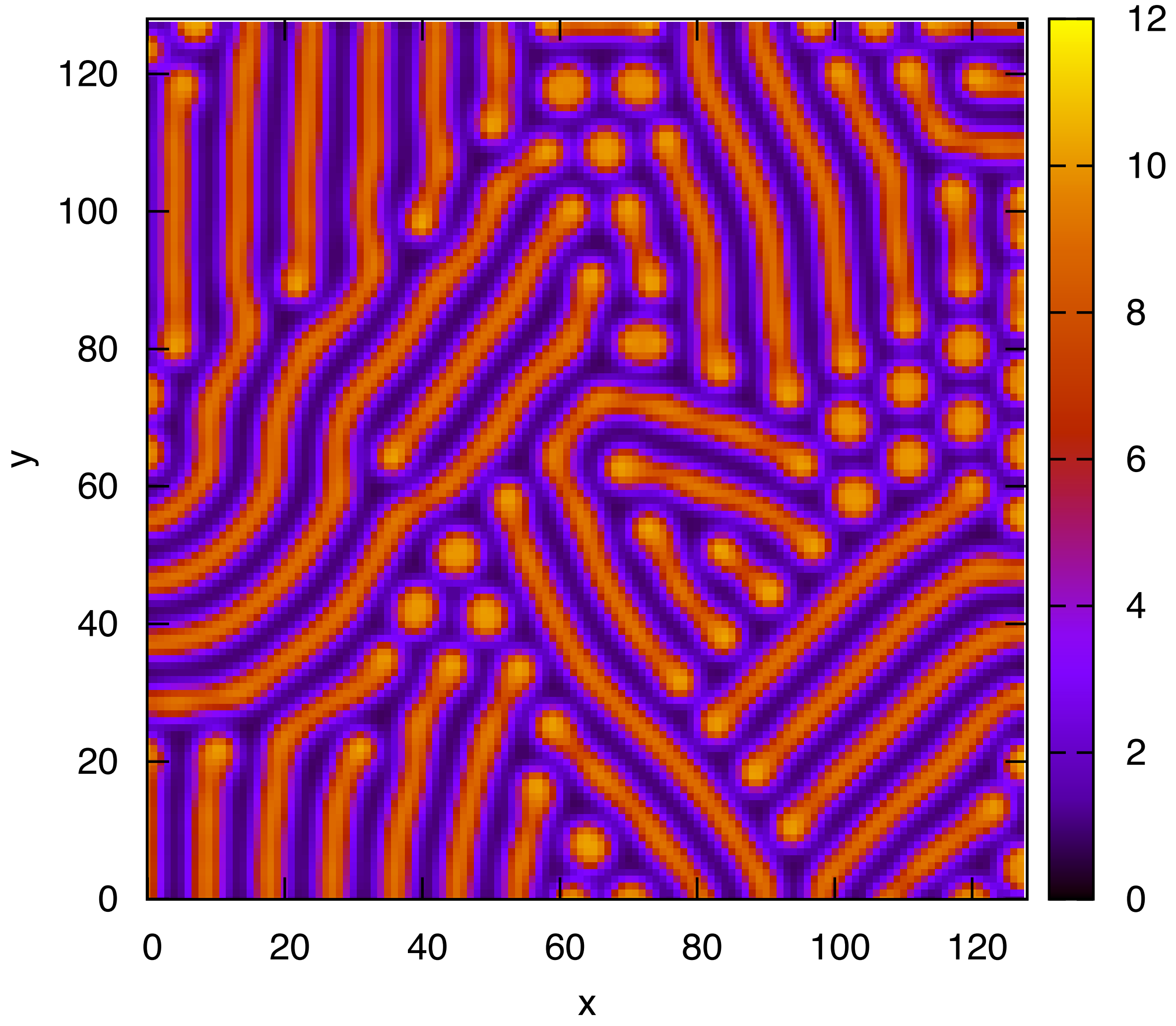


Ex2: Turing Patterns



EX2: TURING PATTERNS





y
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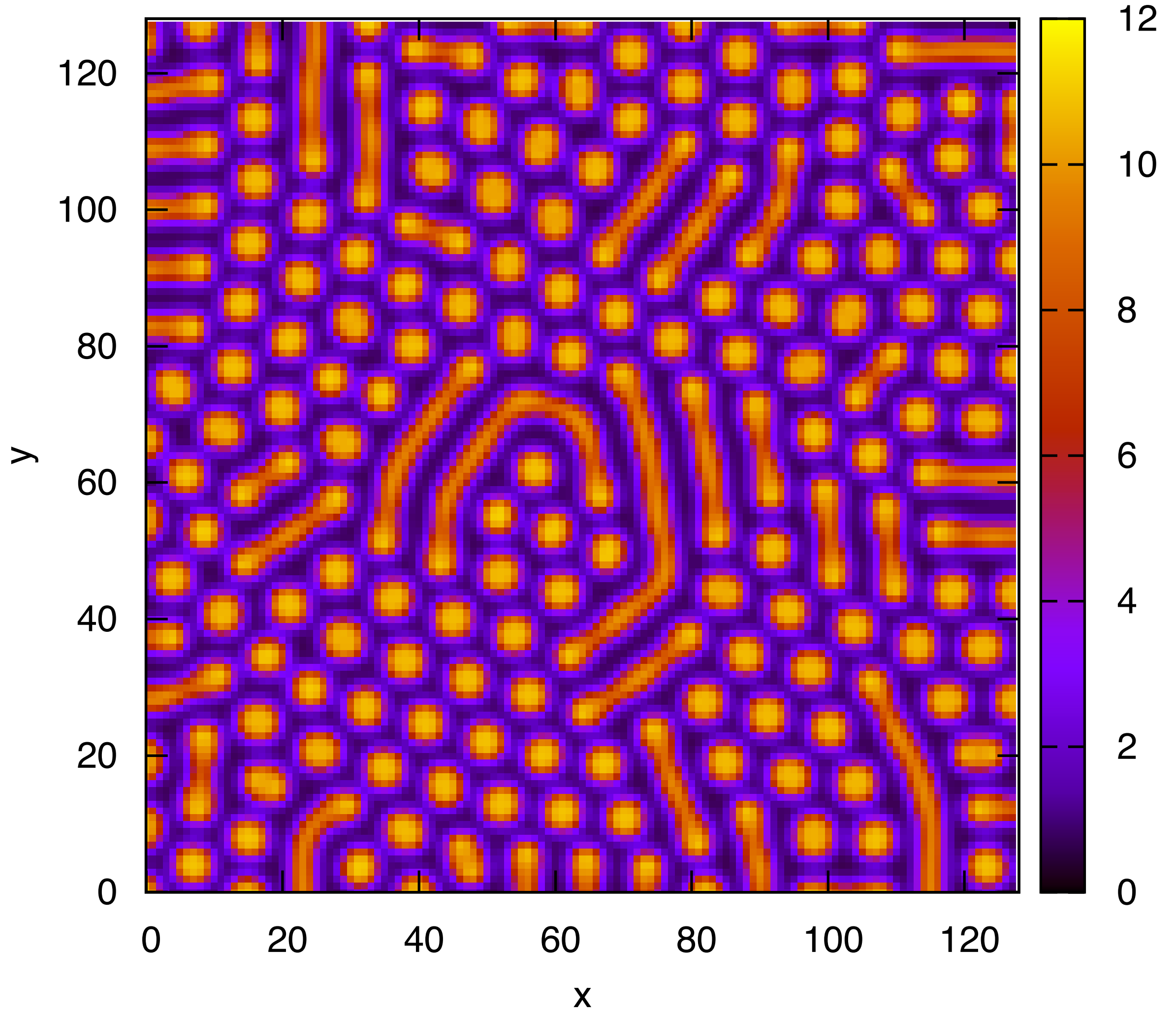
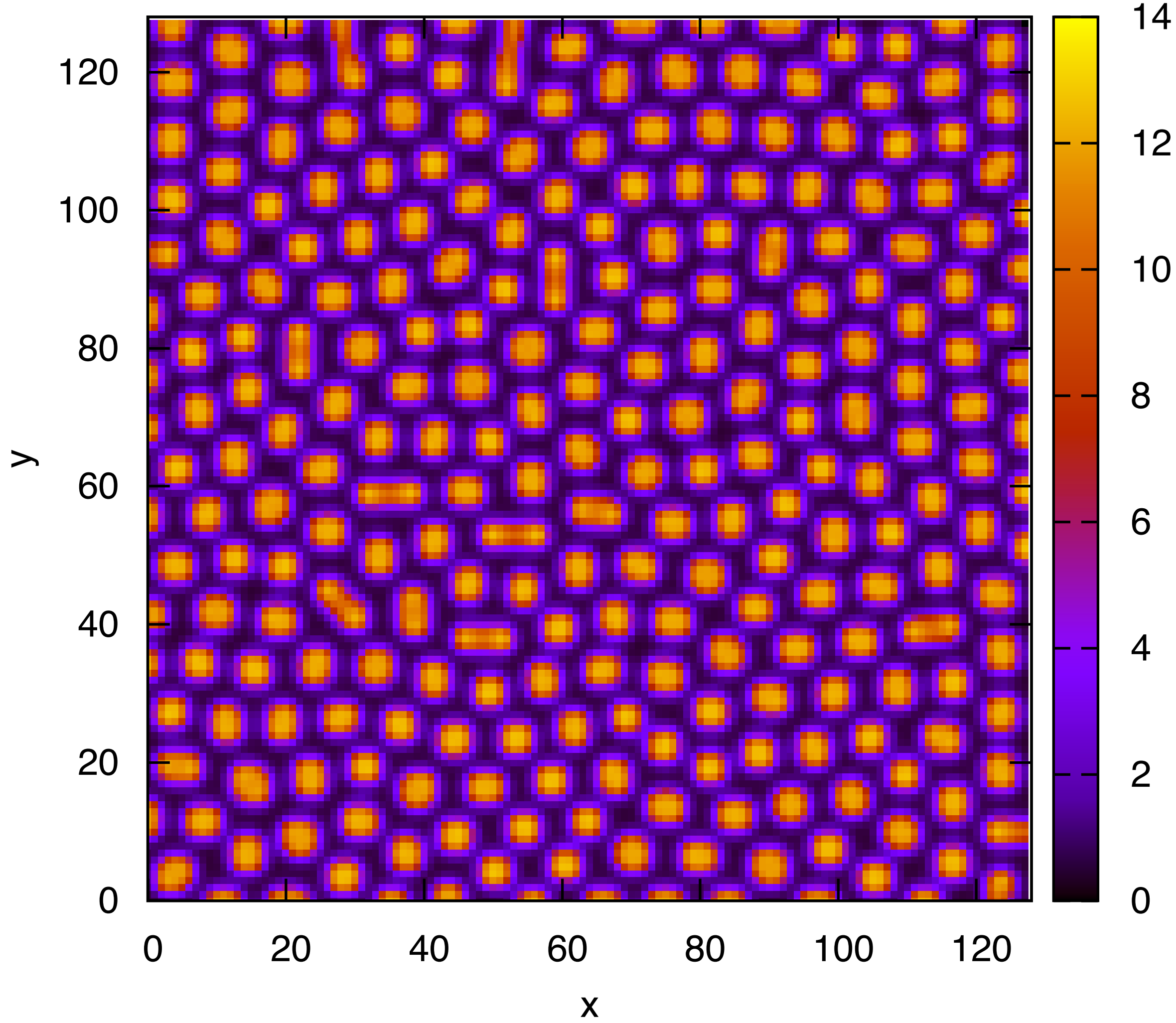
Ex2: Turing Patterns



Ex2: Turing Patterns



EXAMPLE 3:

PHASE VARIATION IN MULTISTRAIN CELL COLONIES

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*

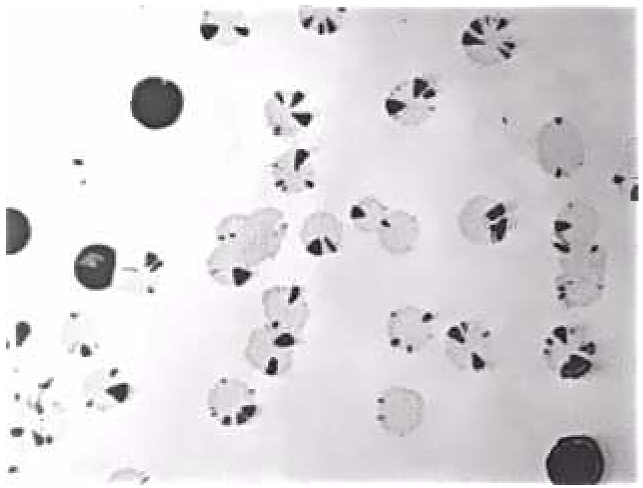
- **stochastic gene switching process**

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

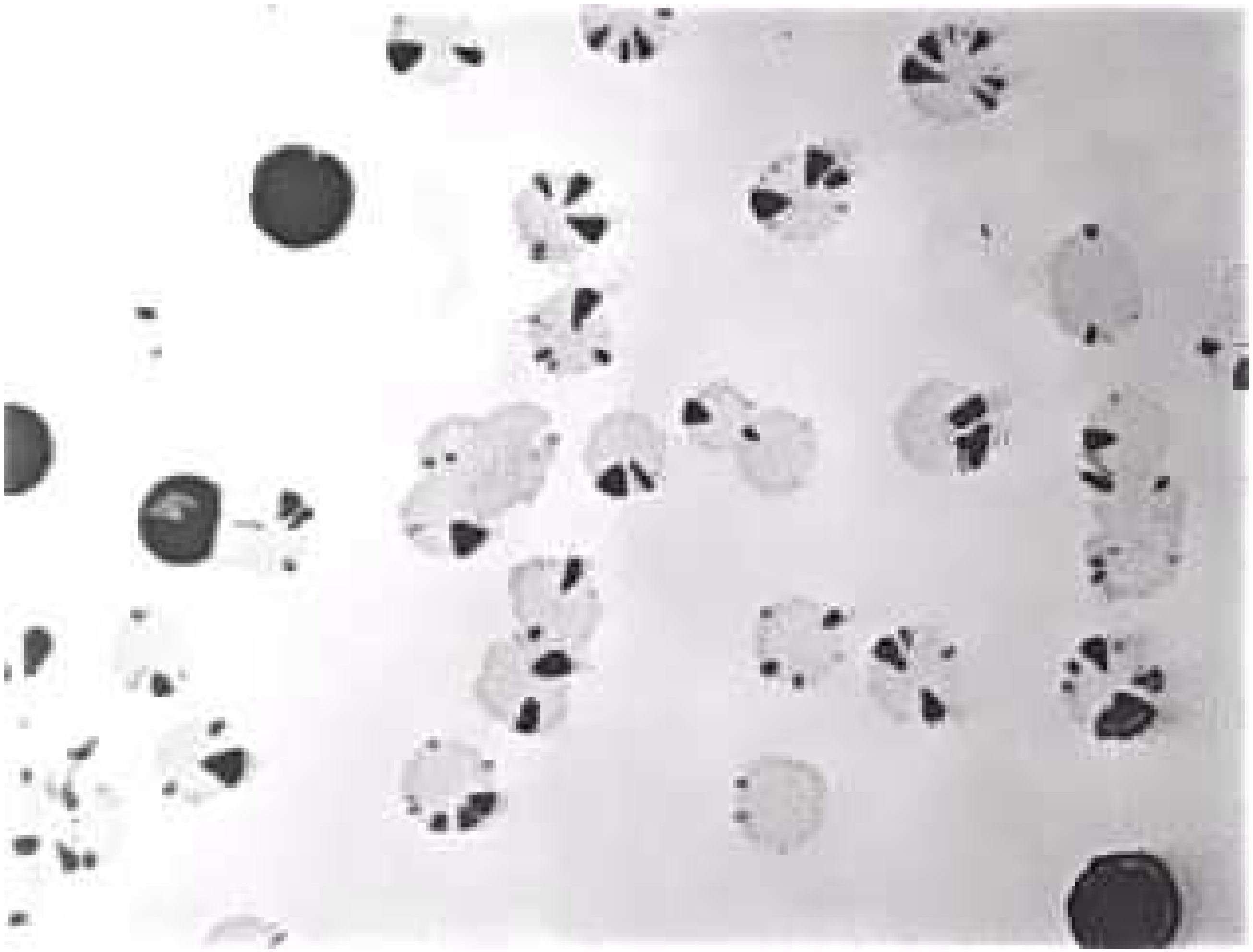
  -> *e.g. switch between two phenotypes A, B*

- **colonial sectoring**

  -> *observable effect in cultures grown in vitro*



EX3: CELL COLONIES, WETLAB OBSERVATIONS



(courtesy of N Saunders)

Microbiology (2003), **149**, 485–495

DOI 10.1099/mic.0.25807-0

Mutation rates: estimating phase variation rates when fitness differences are present and their impact on population structure

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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.

Microbiology (2003), **149**, 485–495

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Mutation rates: estimating phase variation rates when fitness differences are present and their impact on population structure

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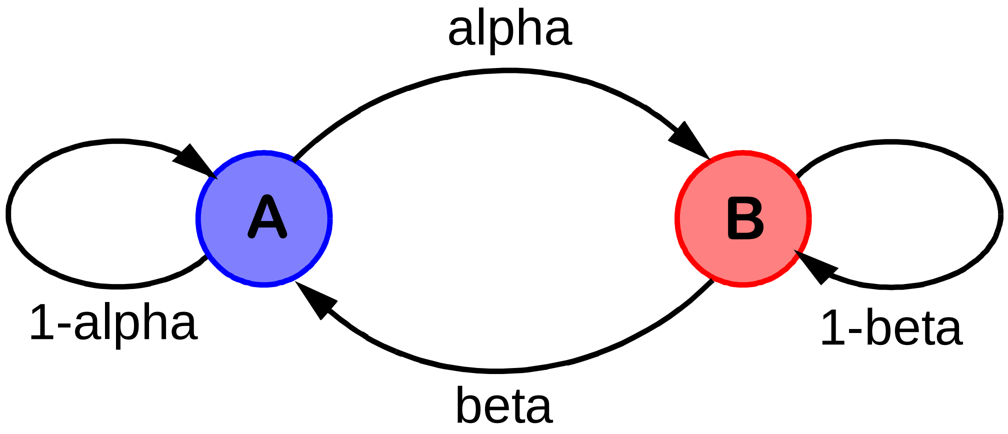
Phase variation is a mechanism of ON–OFF switching that is widely utilized by bacterial pathogens. There is currently no standardization to how the rate of phase variation is determined experimentally.

NO SPACE

EX3: CELL COLONIES, BASICS

- **two cell types: phenotype A and B**

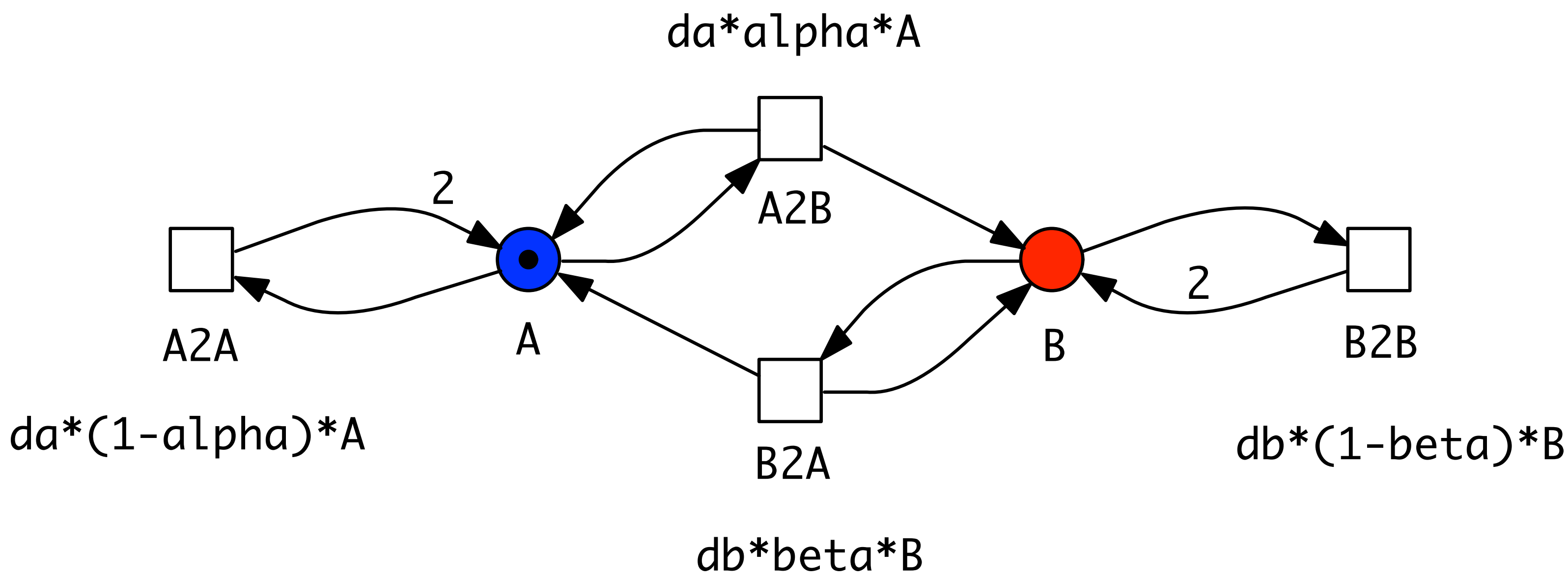
- **cell divide**
  - -> *cell division may involve mutation of the offspring*
  - -> *parent cell keeps its phenotype*



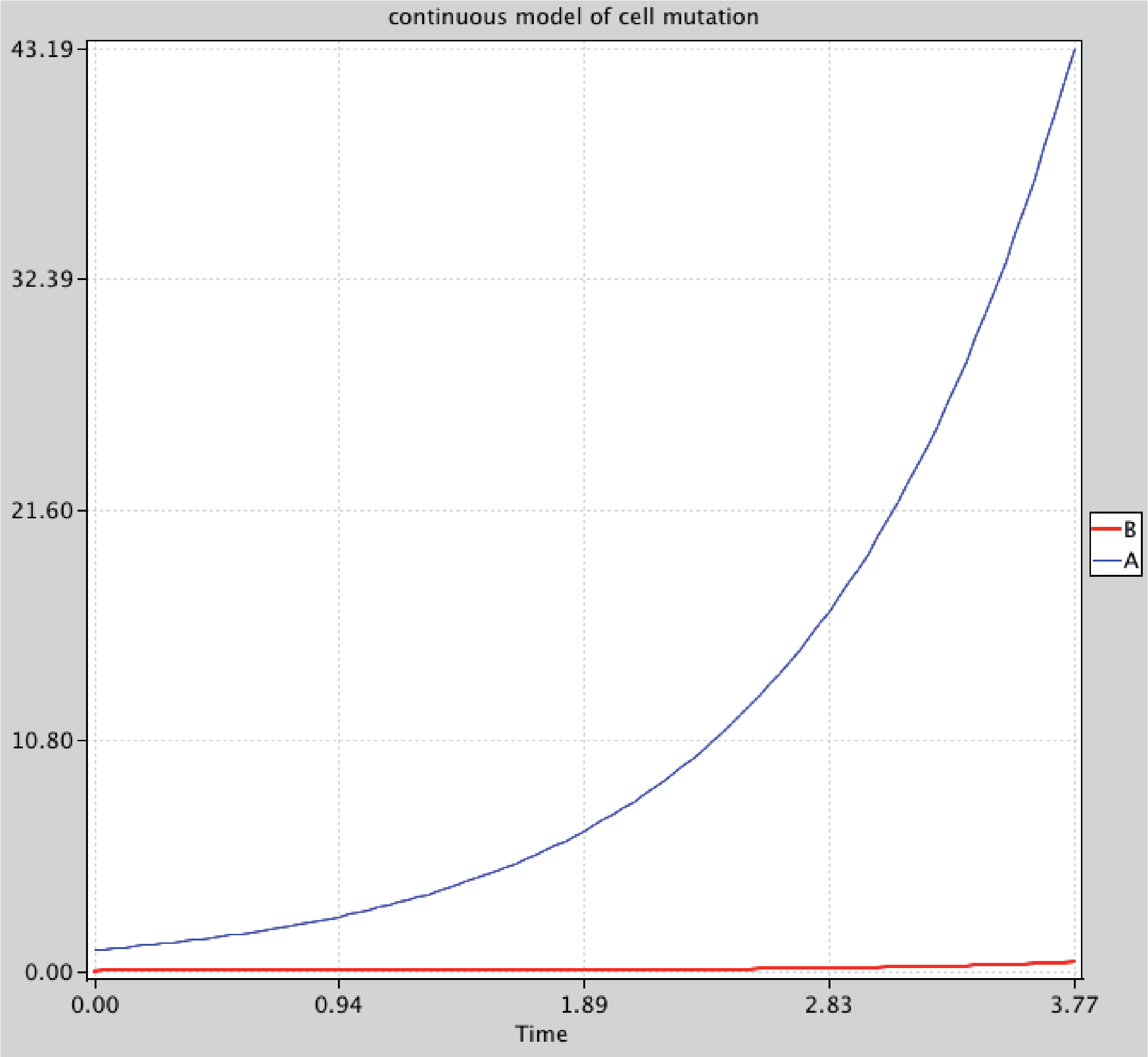
- **model parameters**
  - -> *alpha = beta - mutation rates*
  - -> *da, db - fitness of A, B*
  - -> *da/db - relative fitness*

- **output**
  - -> *total number of cells*
  - -> *proportion of A = A / (A + B)*
  - -> *proportion of B = B / (A + B)*

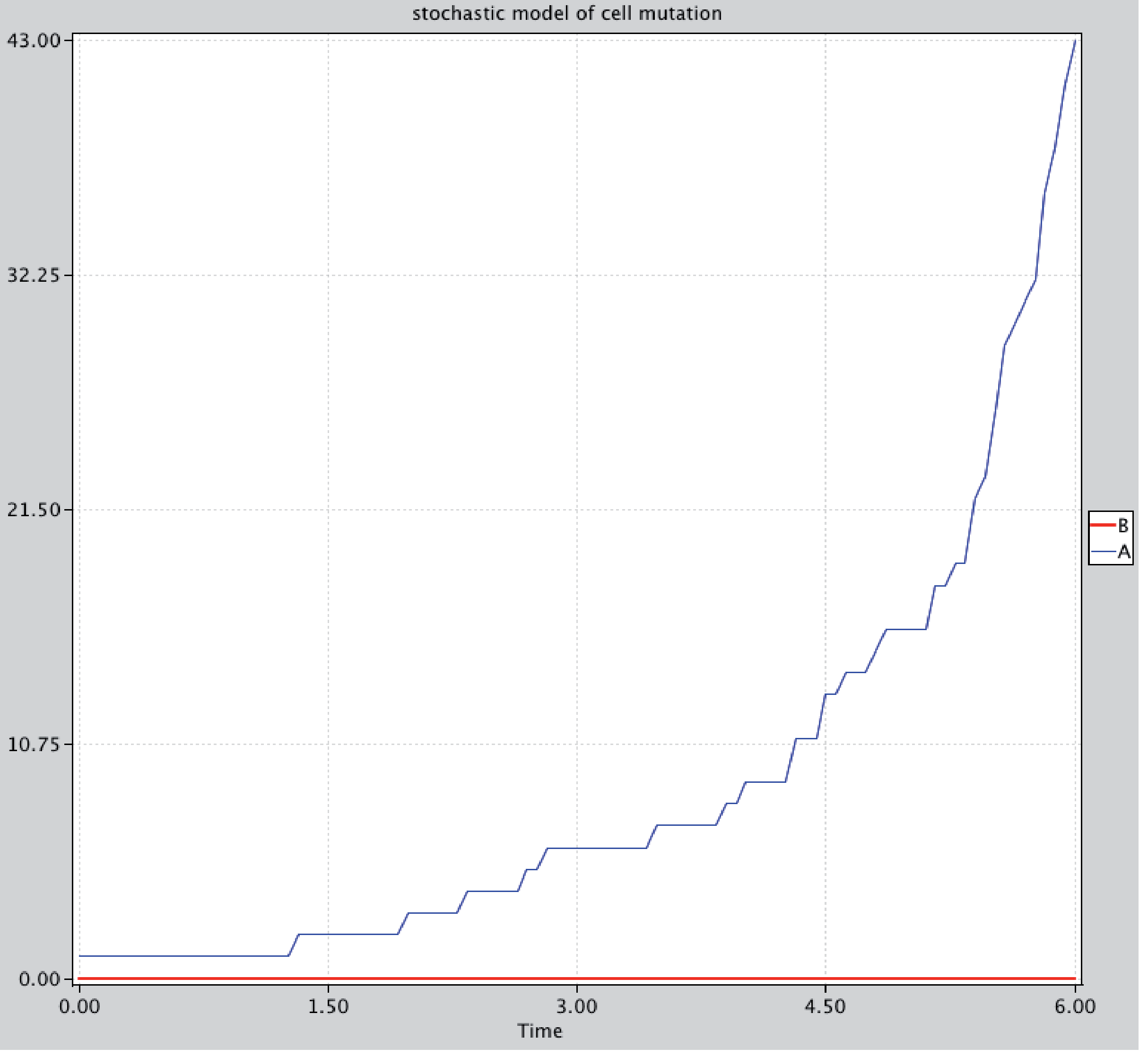
Ex3: Cell Colonies, Petri Net



Ex3: Cell Colonies, Continuous Plot



EX3: CELL COLONIES, STOCHASTIC PLOT



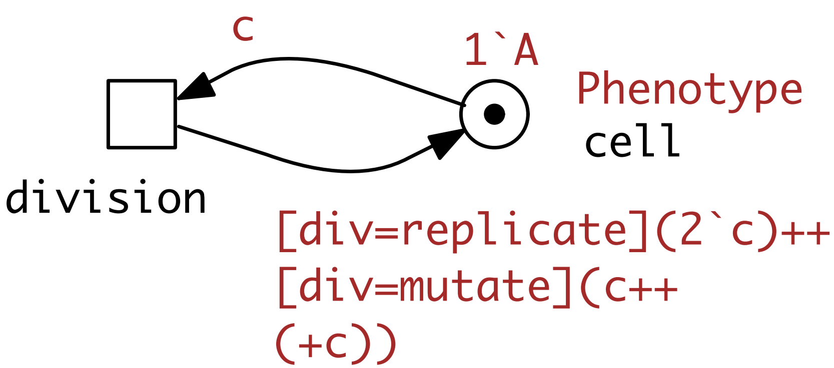
. . . AND THEN THERE WAS COLOUR

Kew Gardens, 24/04/2011

monika.heiner@tu-cottbus.de

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

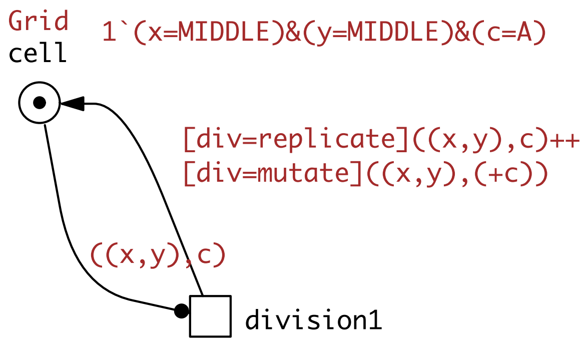
CONTROLLING COLONY SPREADING

CONTROLLING THICKNESS

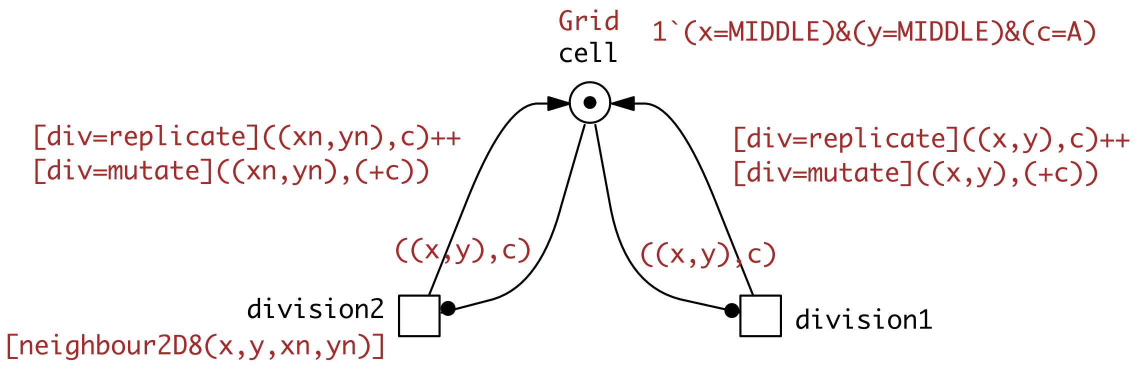
(c=A) & (div=replicate) : cell*(da*(1-alpha))
(c=A) & (div=mutate) : cell*(da*alpha)
(c=B) & (div=replicate) : cell*(db*(1-beta))
(c=B) & (div=mutate) : cell*(db*beta)

CONTROLLING COLONY SIZE

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

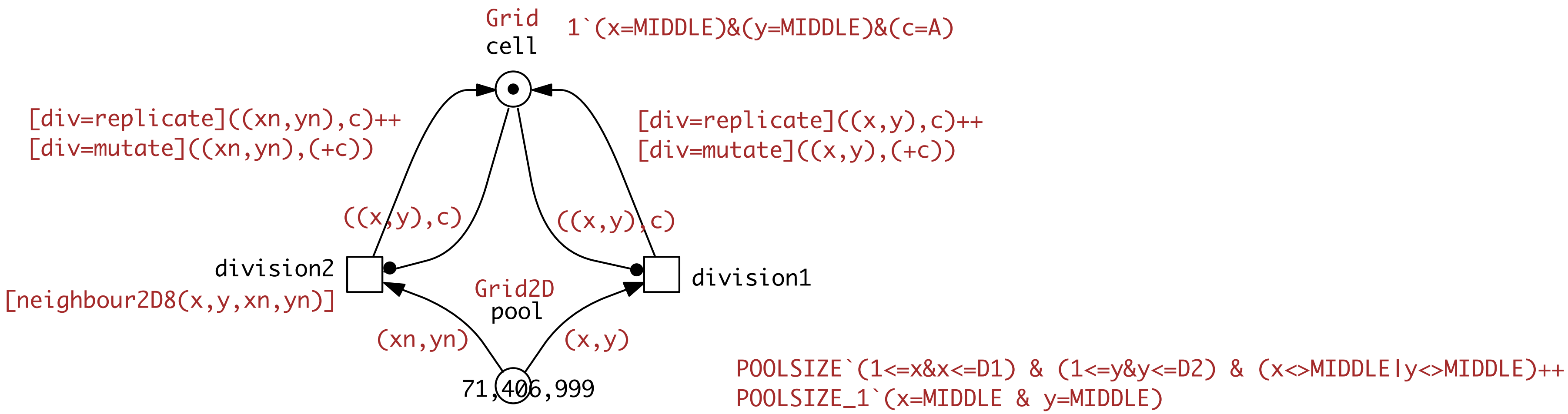


colorset Grid = **product with** Grid2D x Phenotype;



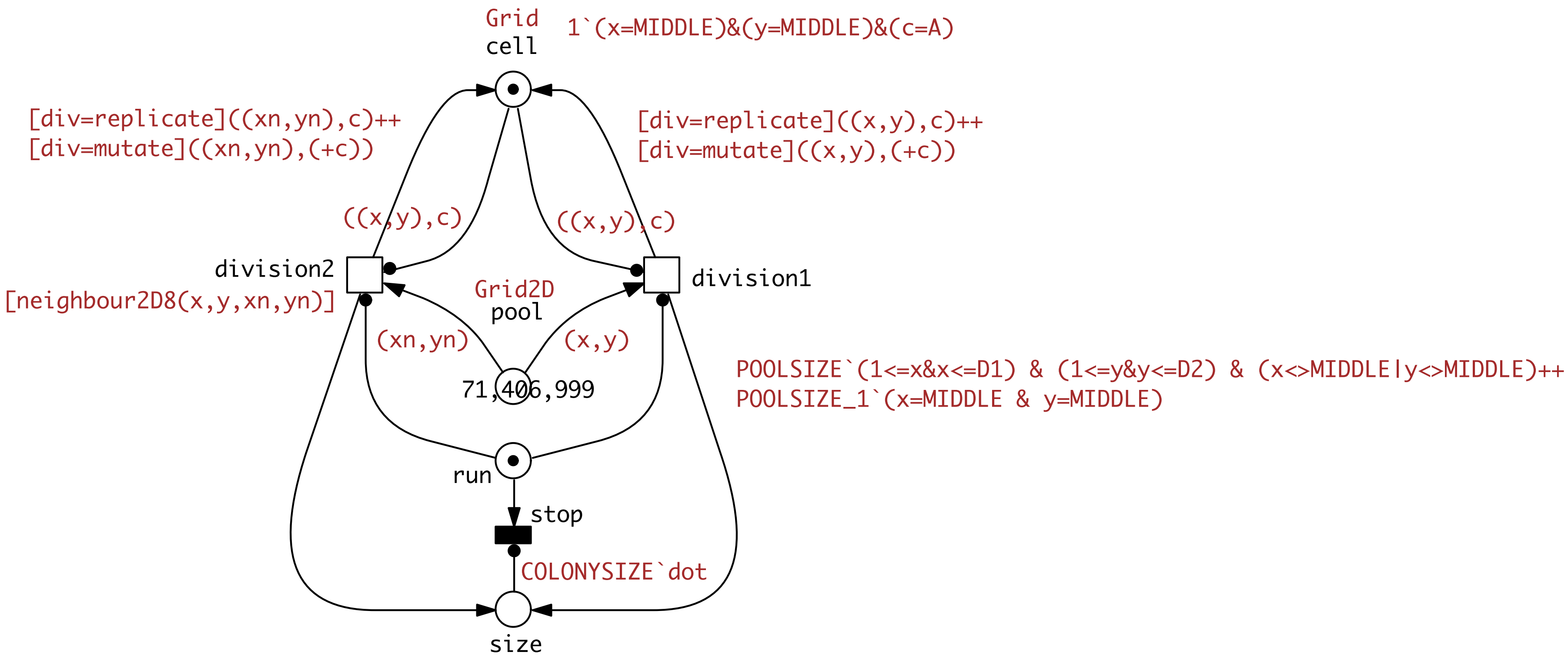
EX3: CELL COLONIES, CONTROLLING THICKNESS

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



Ex3: Cell Colonies, Controlling Colony Size

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

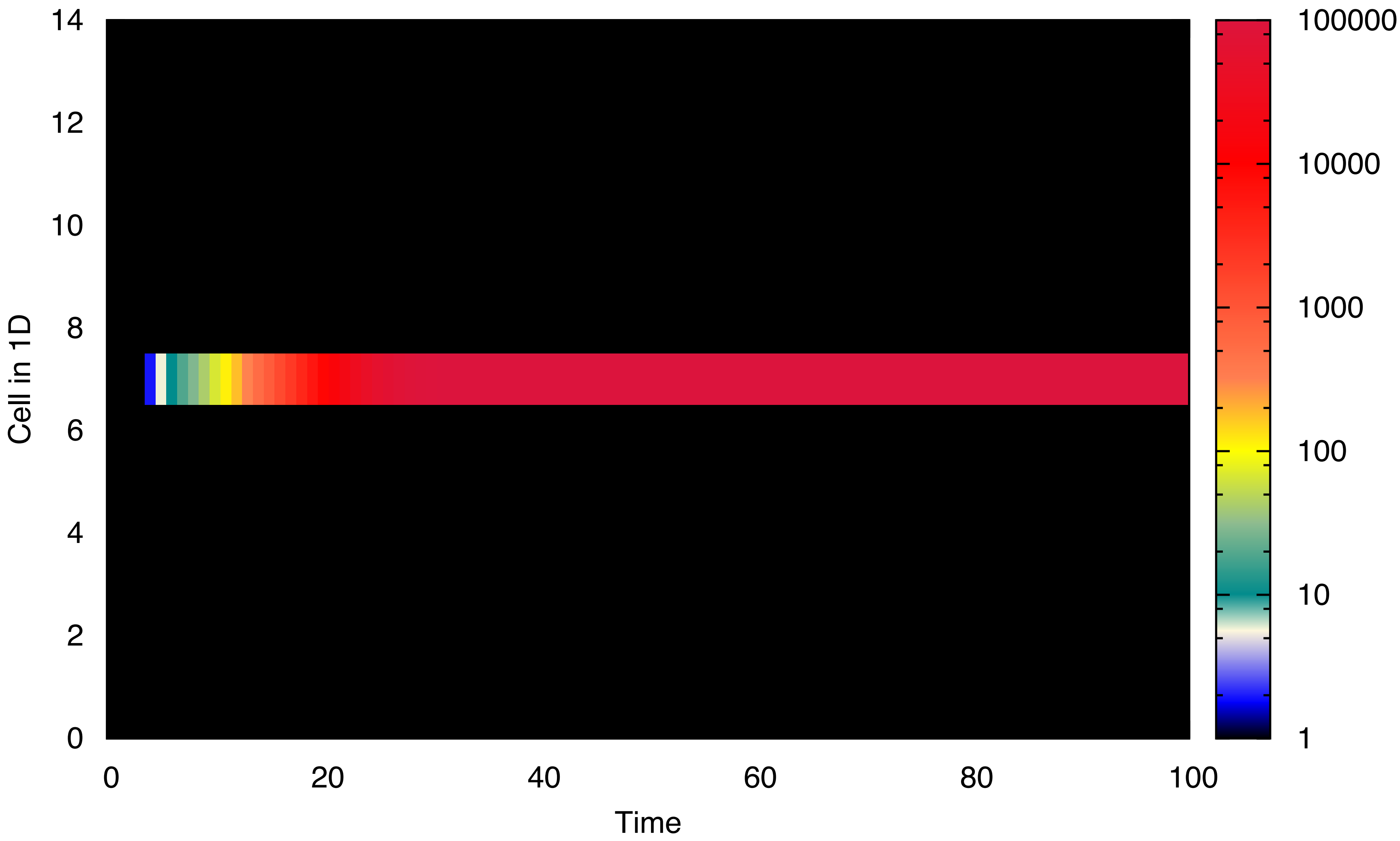


EX3: CELL COLONIES, SOME DETAILS

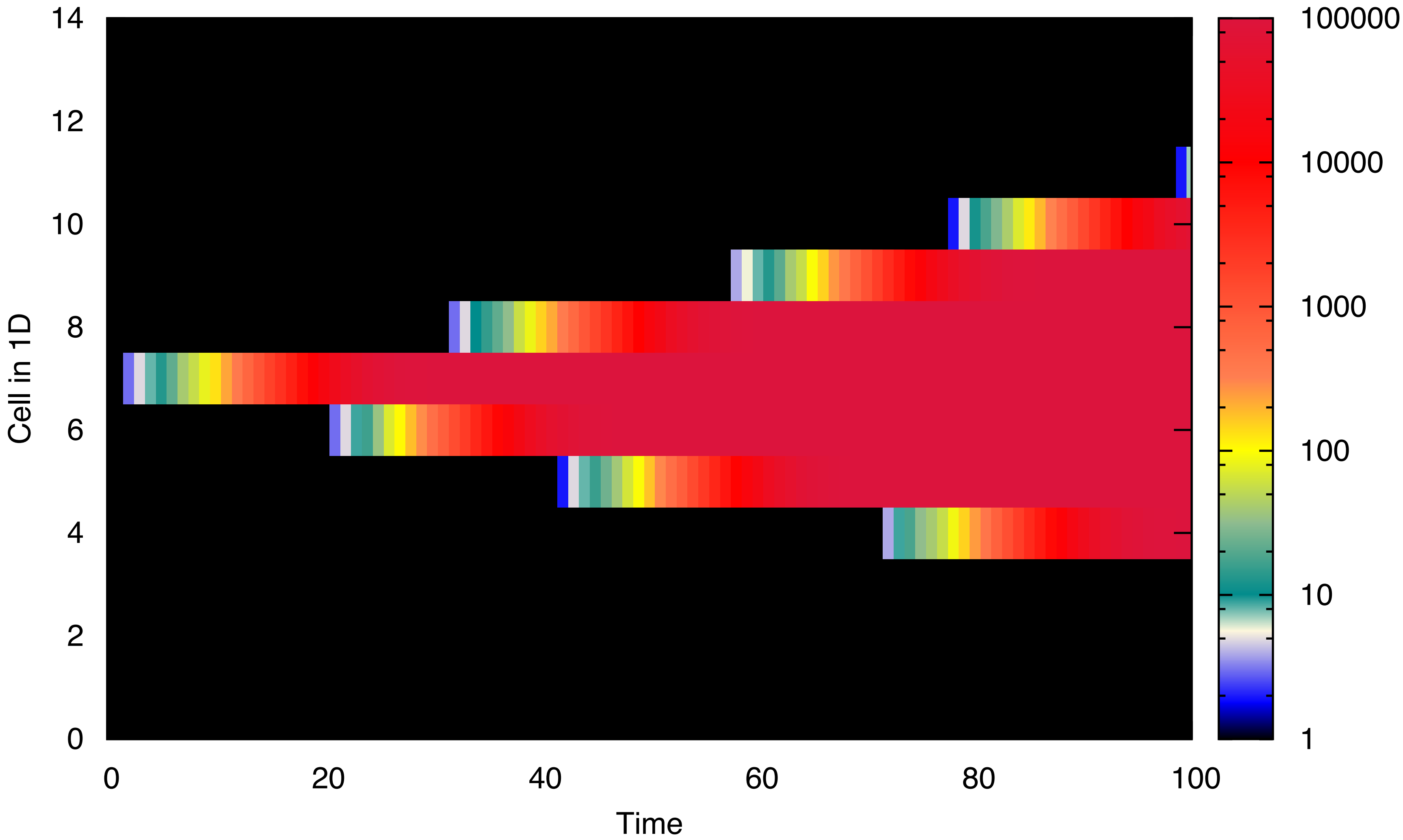
- **model assumptions**
  - -> *"If phase variation occurs, the progeny consists of one A and one B"* *(Saunders 2003)*
  - -> *It is always the mutant who goes to a neighbouring position, if any.*
  - -> *constant biofilm thickness (so far)*
- **colony size - 24 h**
  - -> *25 generations: 33.5 E+06*
  - -> *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

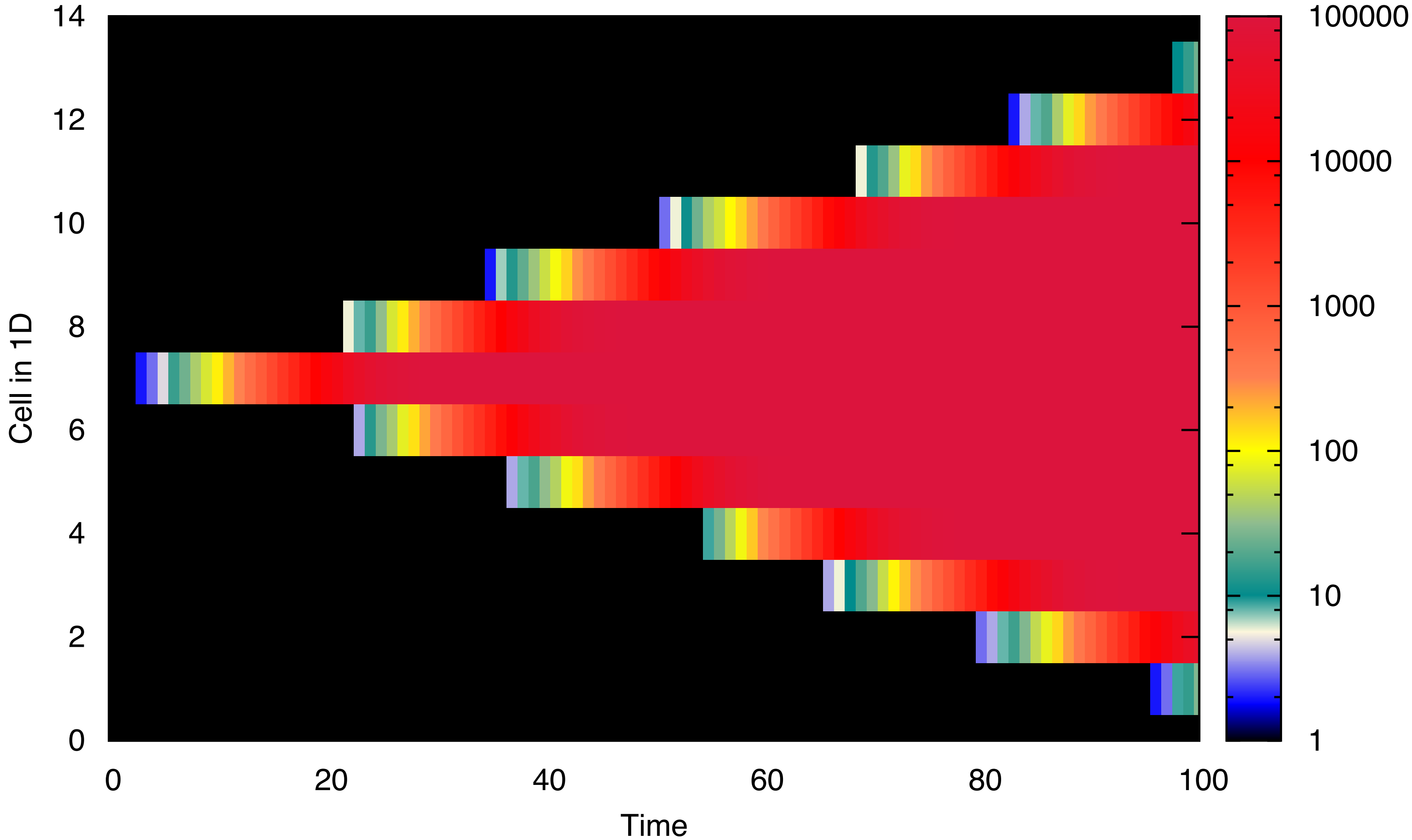
EX3: 1D15 - VARYING MOBILITY, GAMMA = 100



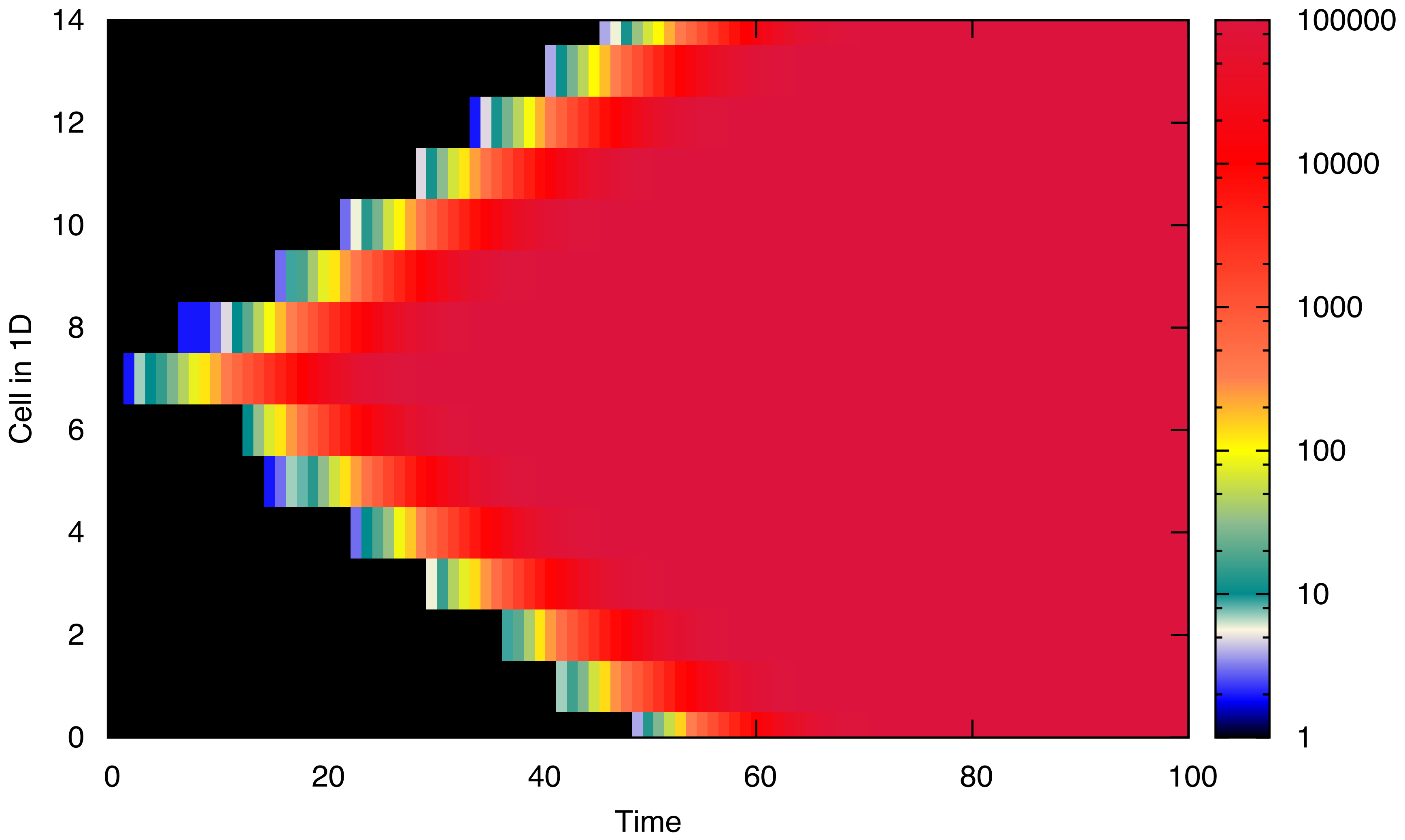
Ex3: 1D15 - Varying Mobility, Gamma = 99.999



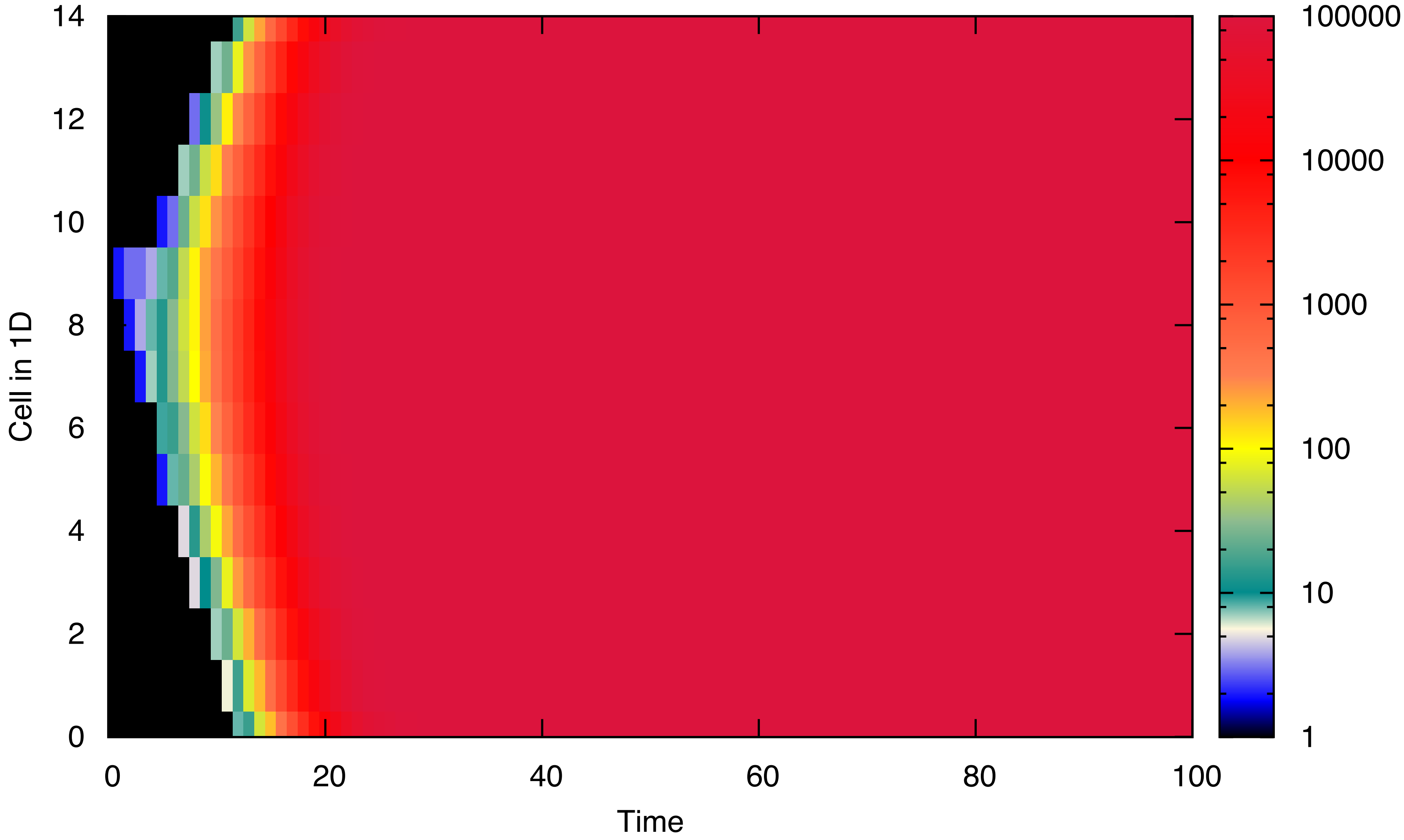
Ex3: 1D15 - Varying Mobility, Gamma = 99.99



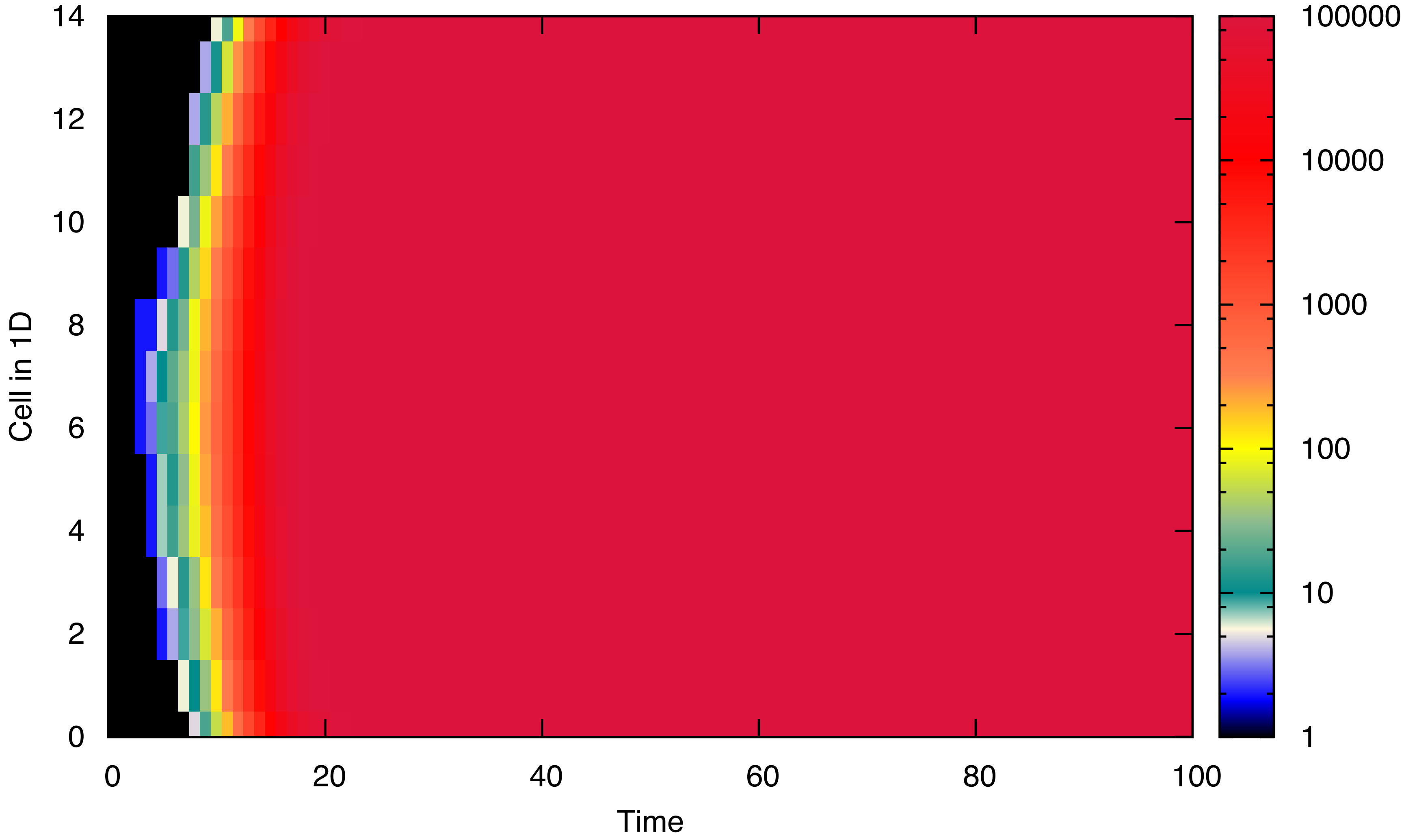
Ex3: 1D15 - Varying Mobility, Gamma = 90



Ex3: 1D15 - Varying Mobility, Gamma = 50



Ex3: 1D15 - Varying Mobility, Gamma = 1



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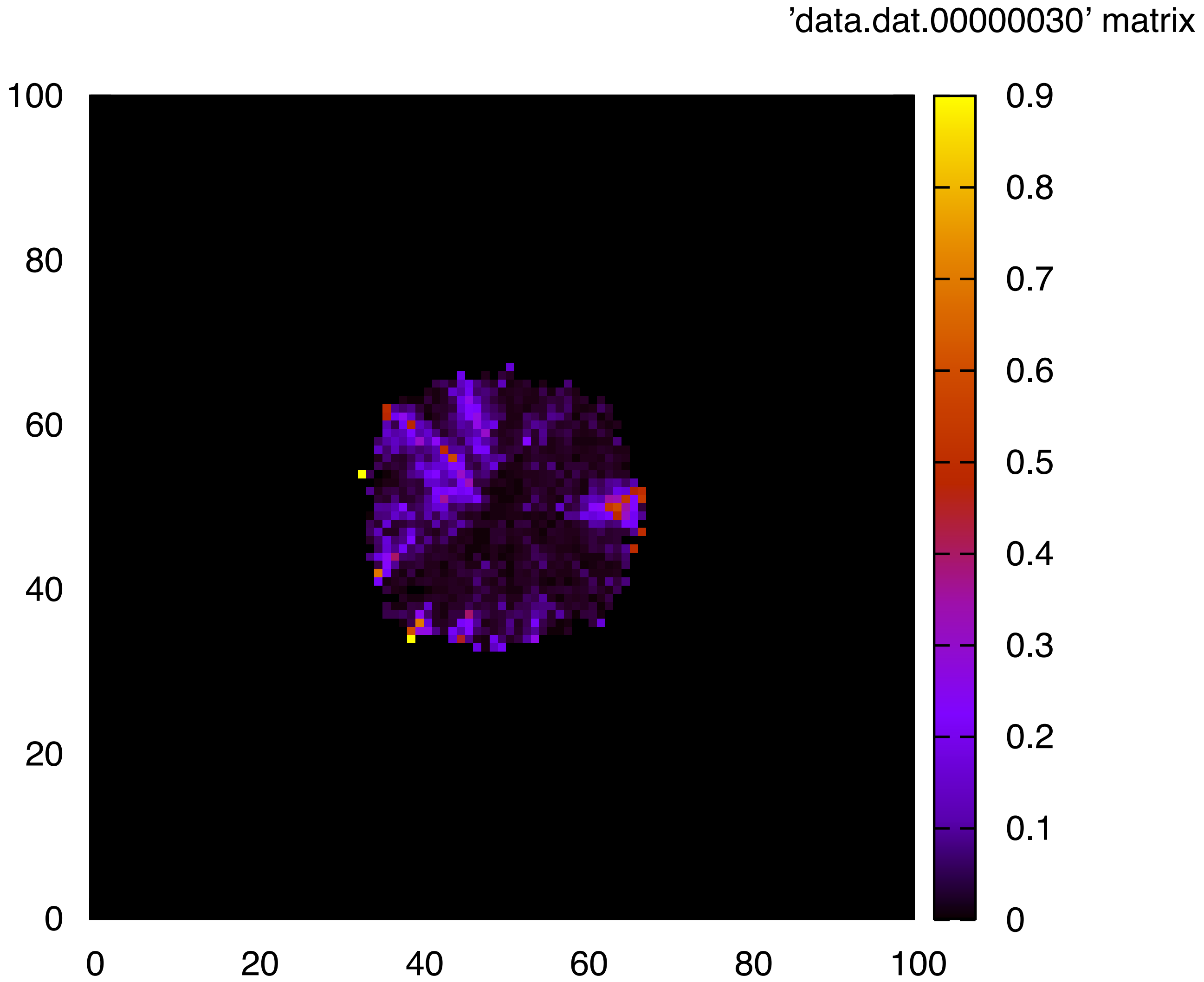
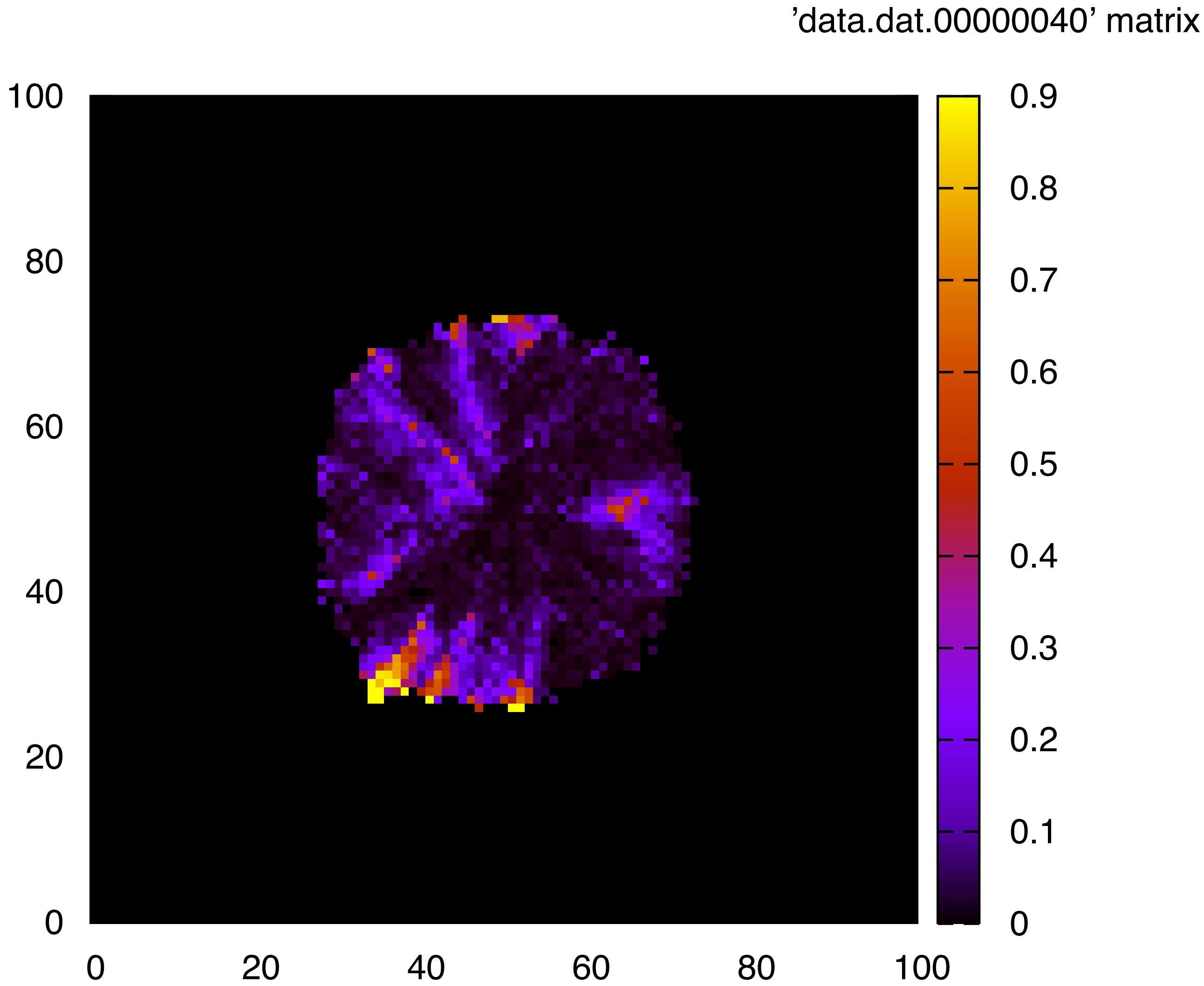
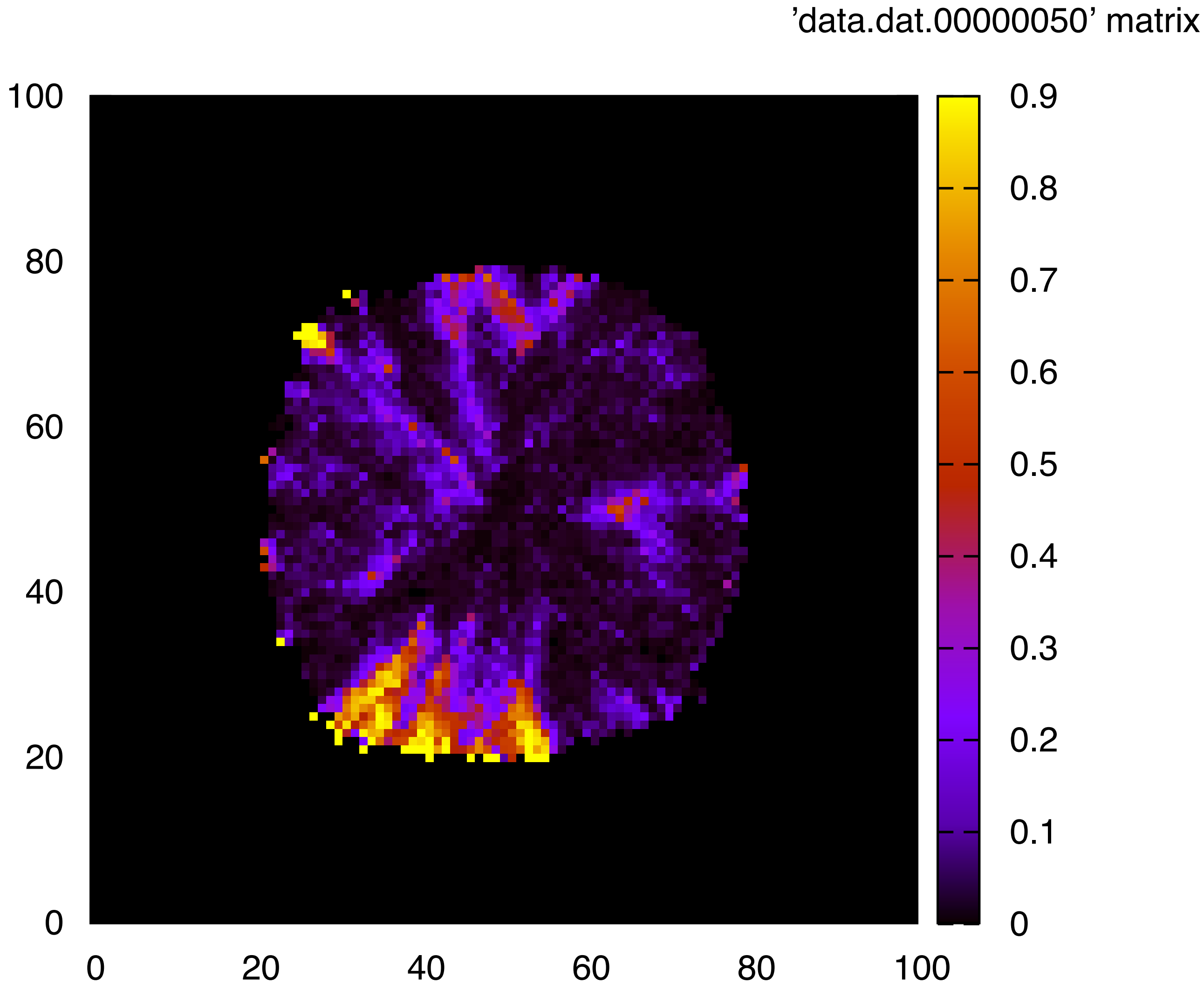
EX3: 2D - TRACE 1 (HIGH, F=1)



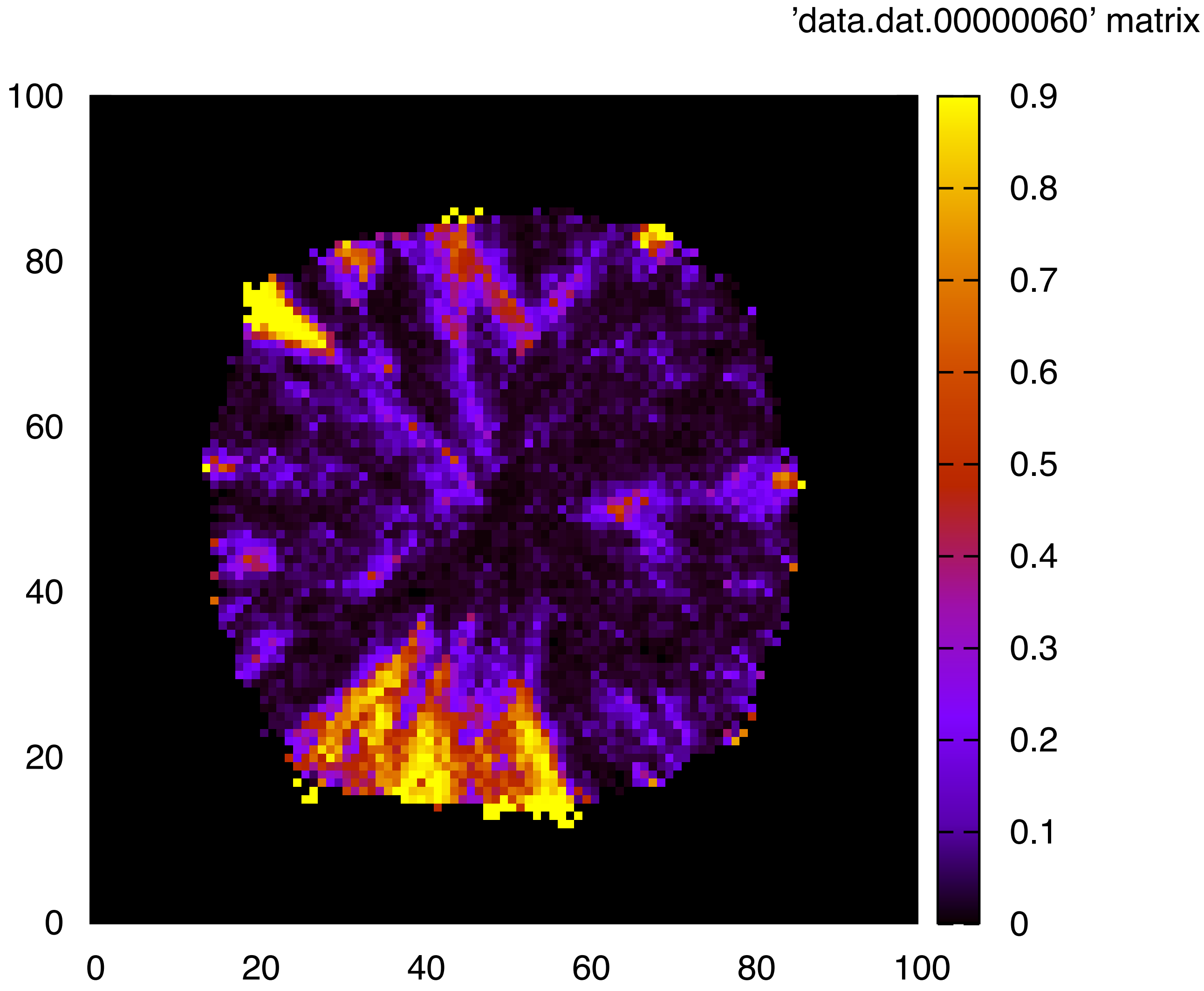
EX3: 2D - TRACE 1 (HIGH, F=1)



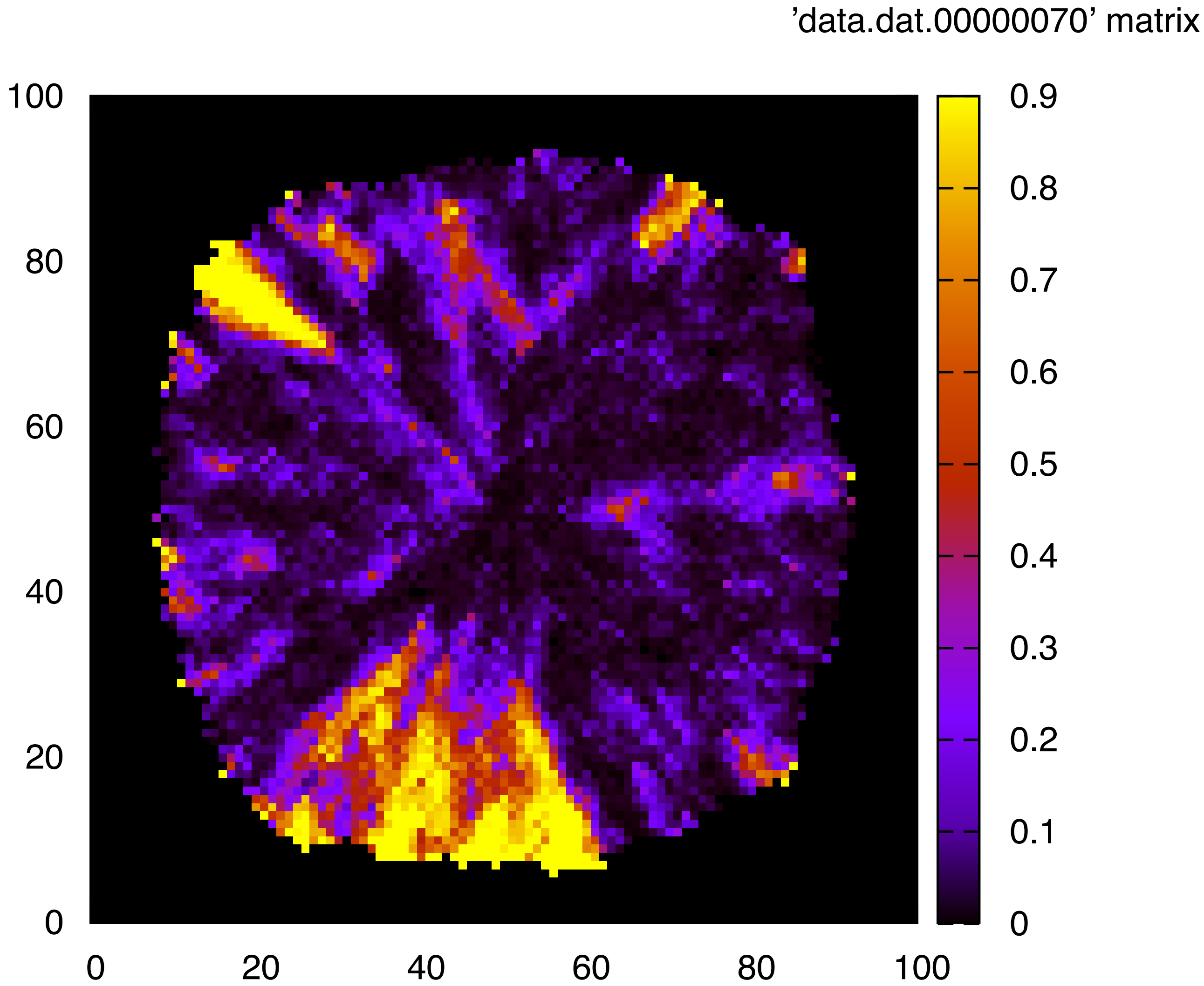
Ex3: 2D - Trace 1 (High, F=1)



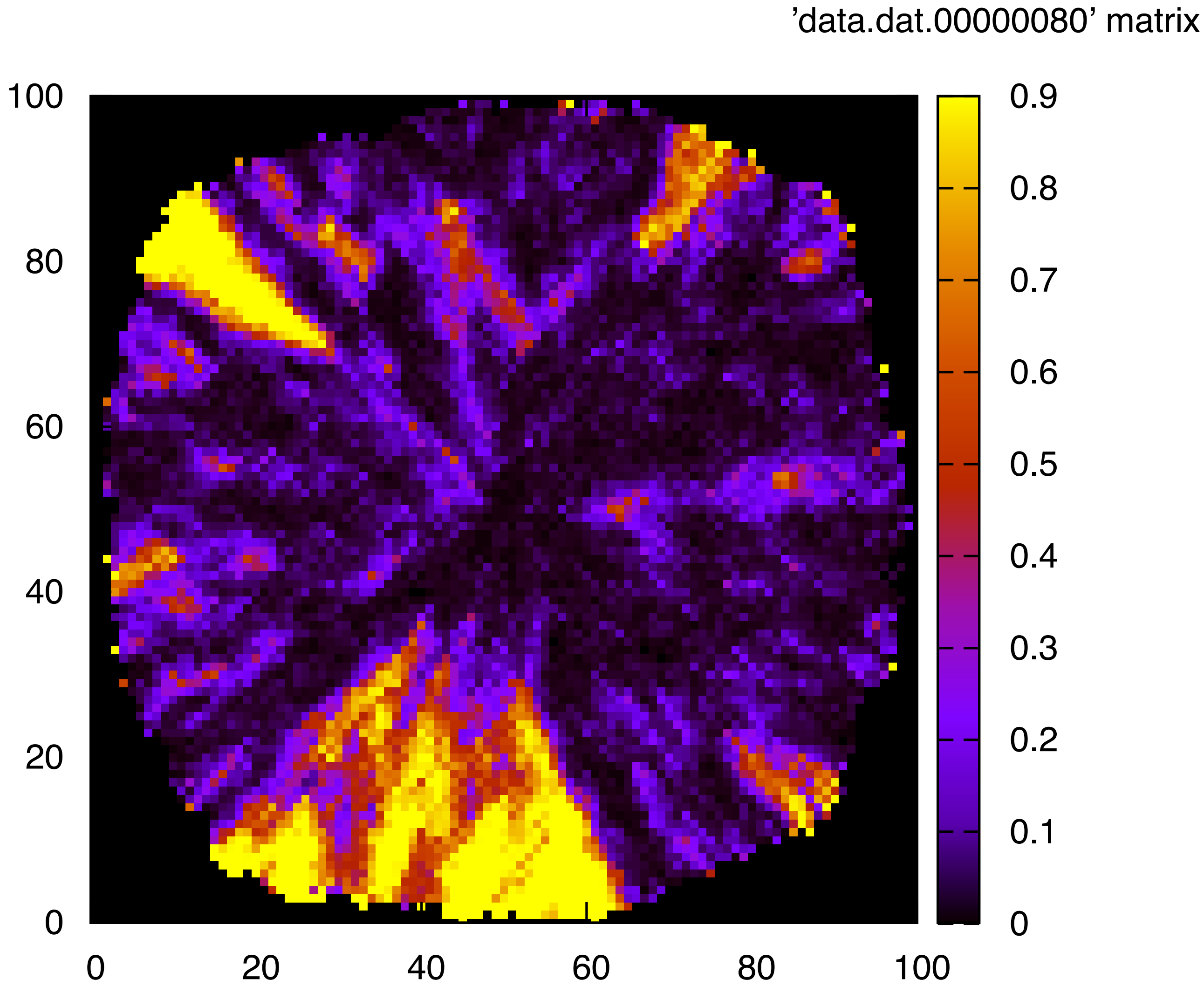
EX3: 2D - TRACE 1 (HIGH, F=1)



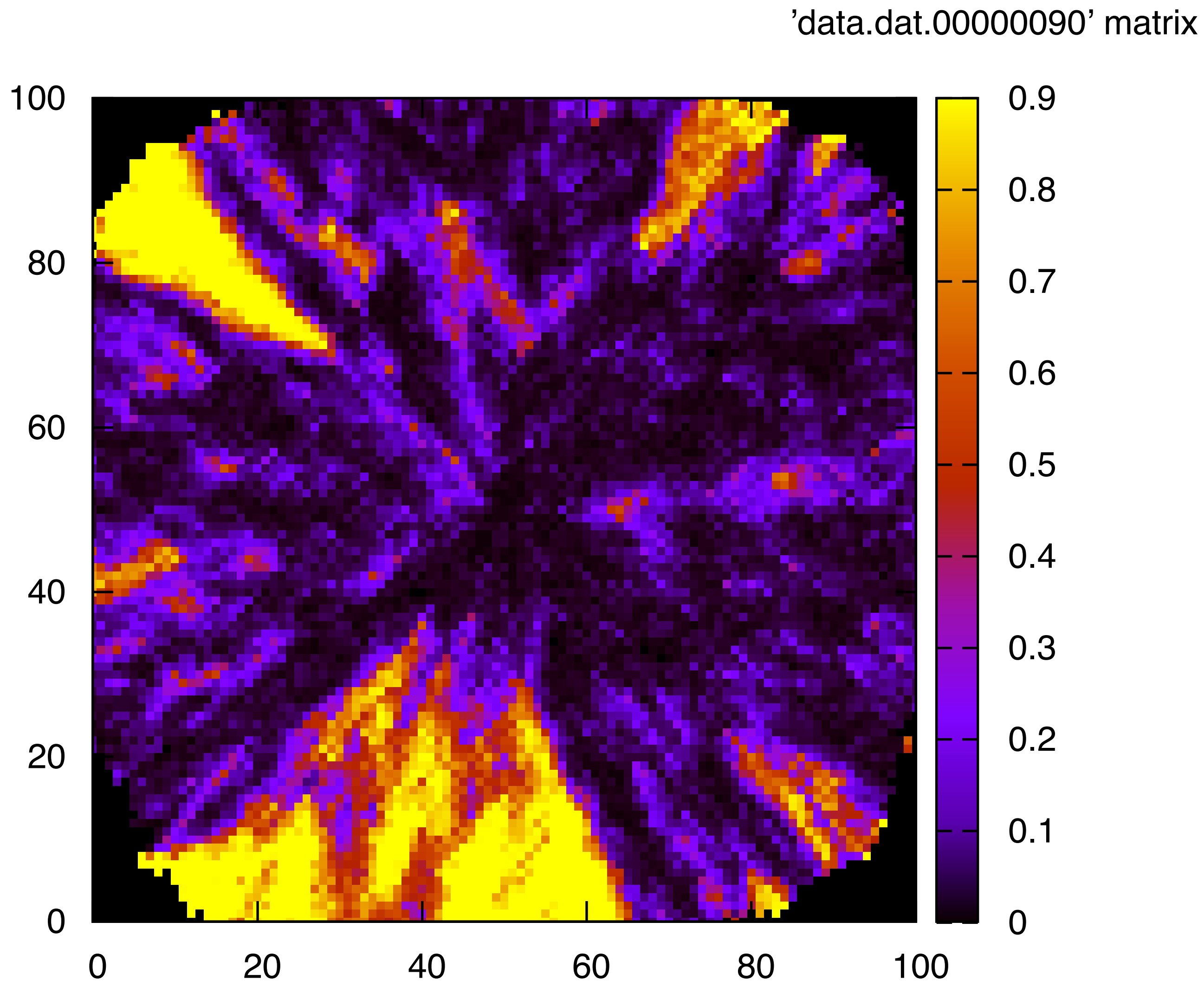
EX3: 2D - TRACE 1 (HIGH, F=1)



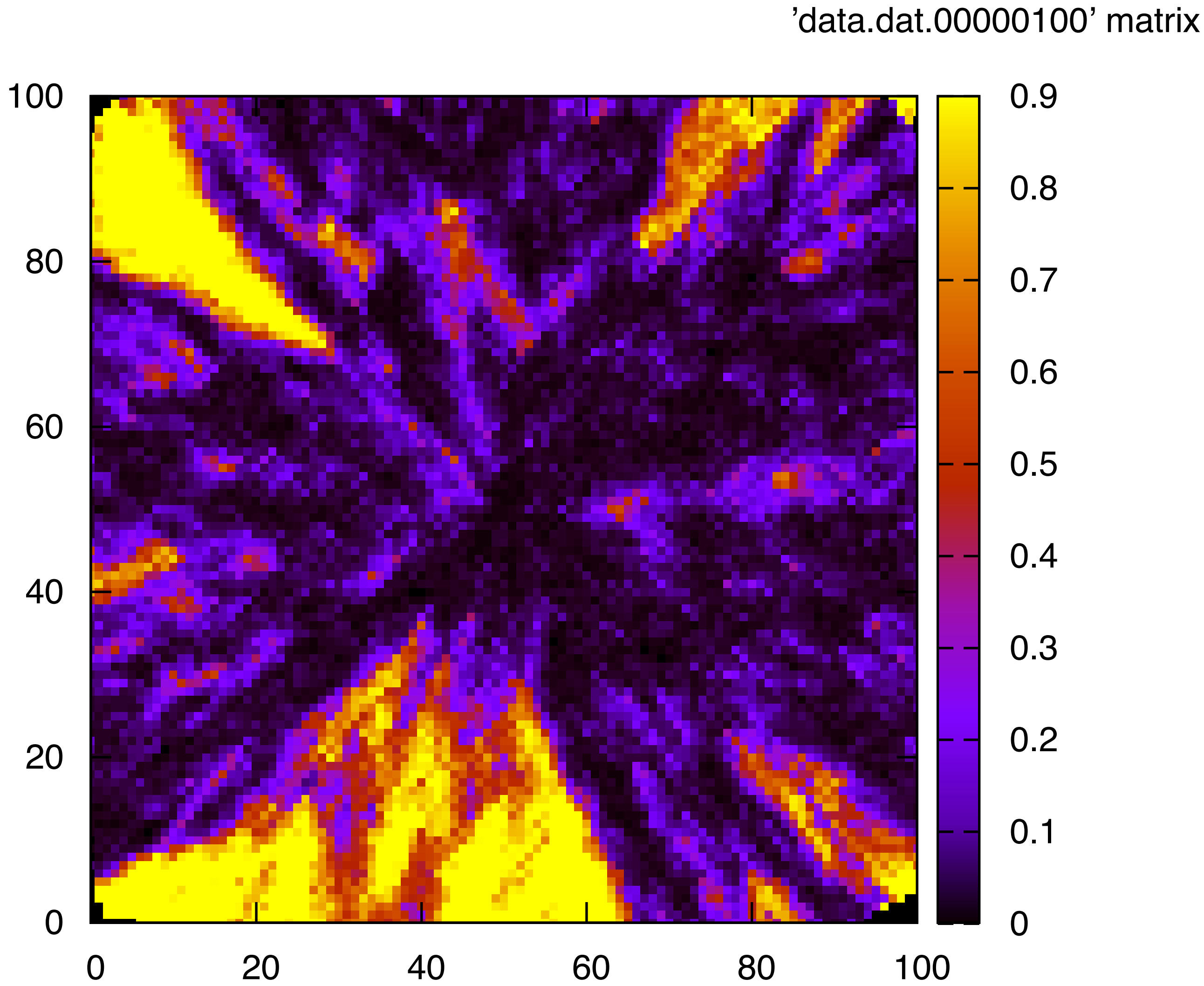
EX3: 2D - TRACE 1 (HIGH, F=1)



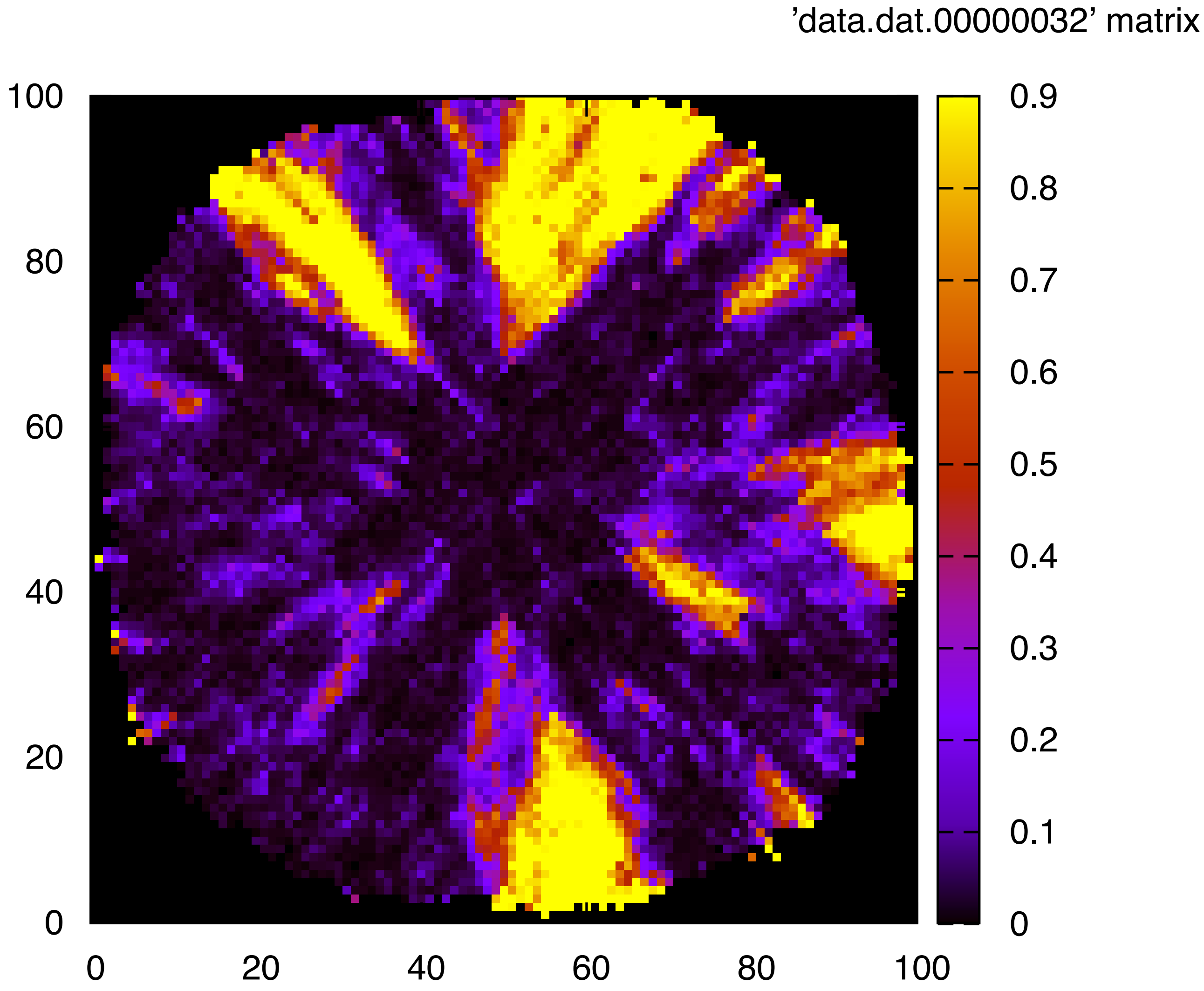
EX3: 2D - TRACE 1 (HIGH, F=1)



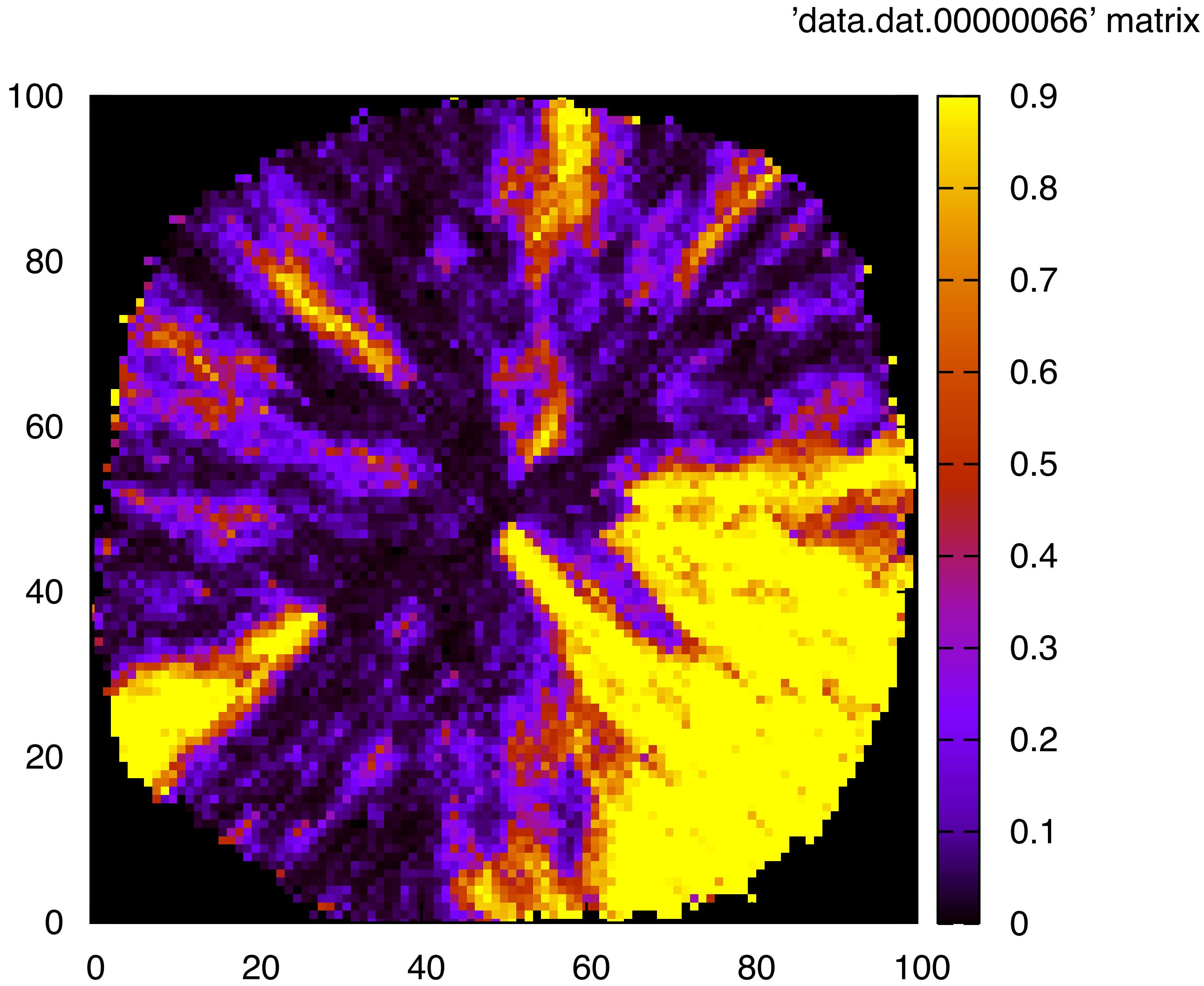
Ex3: 2D - Trace 1 (High, F=1)



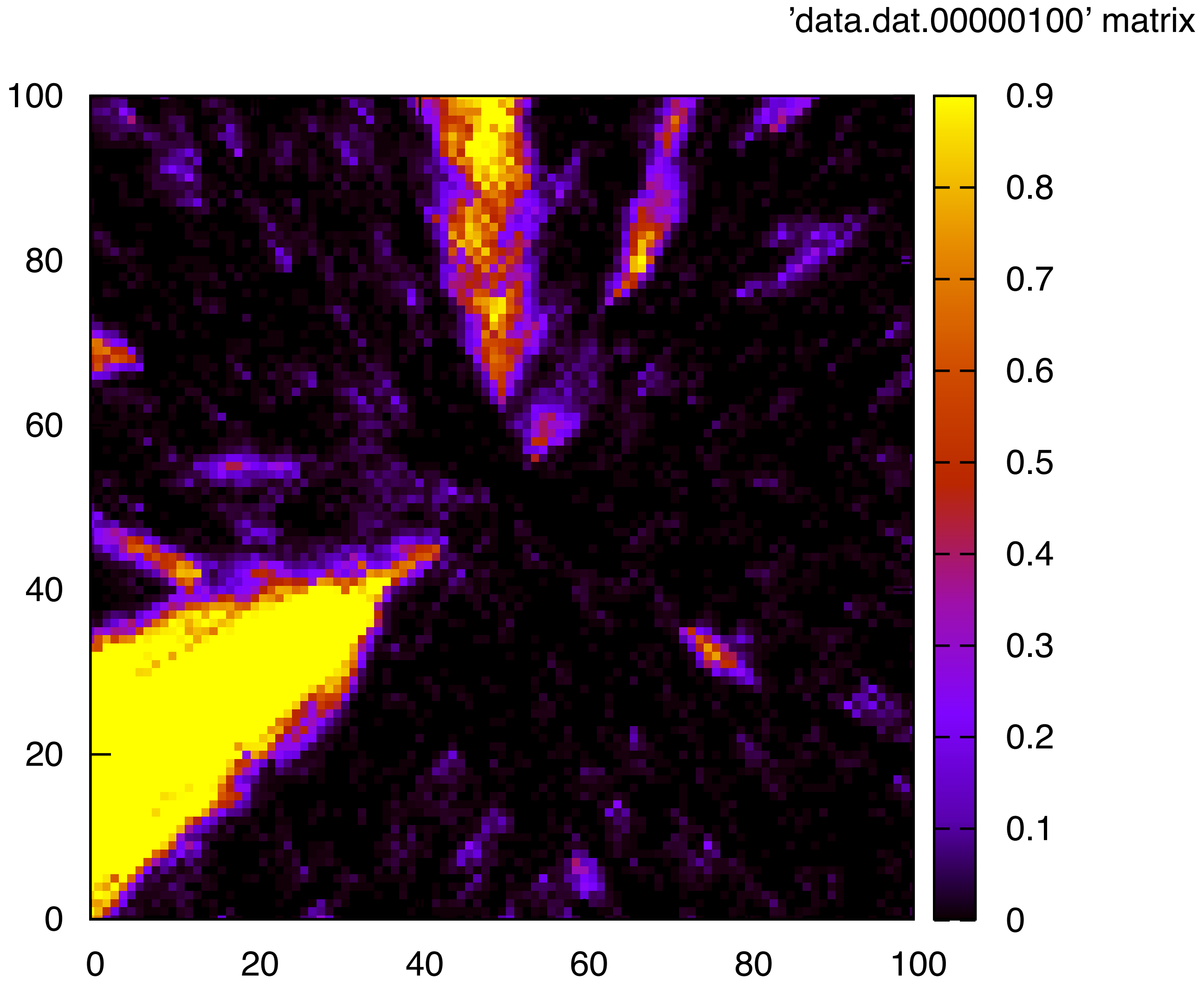
Ex3: 2D - Trace 2 (High, F=1)



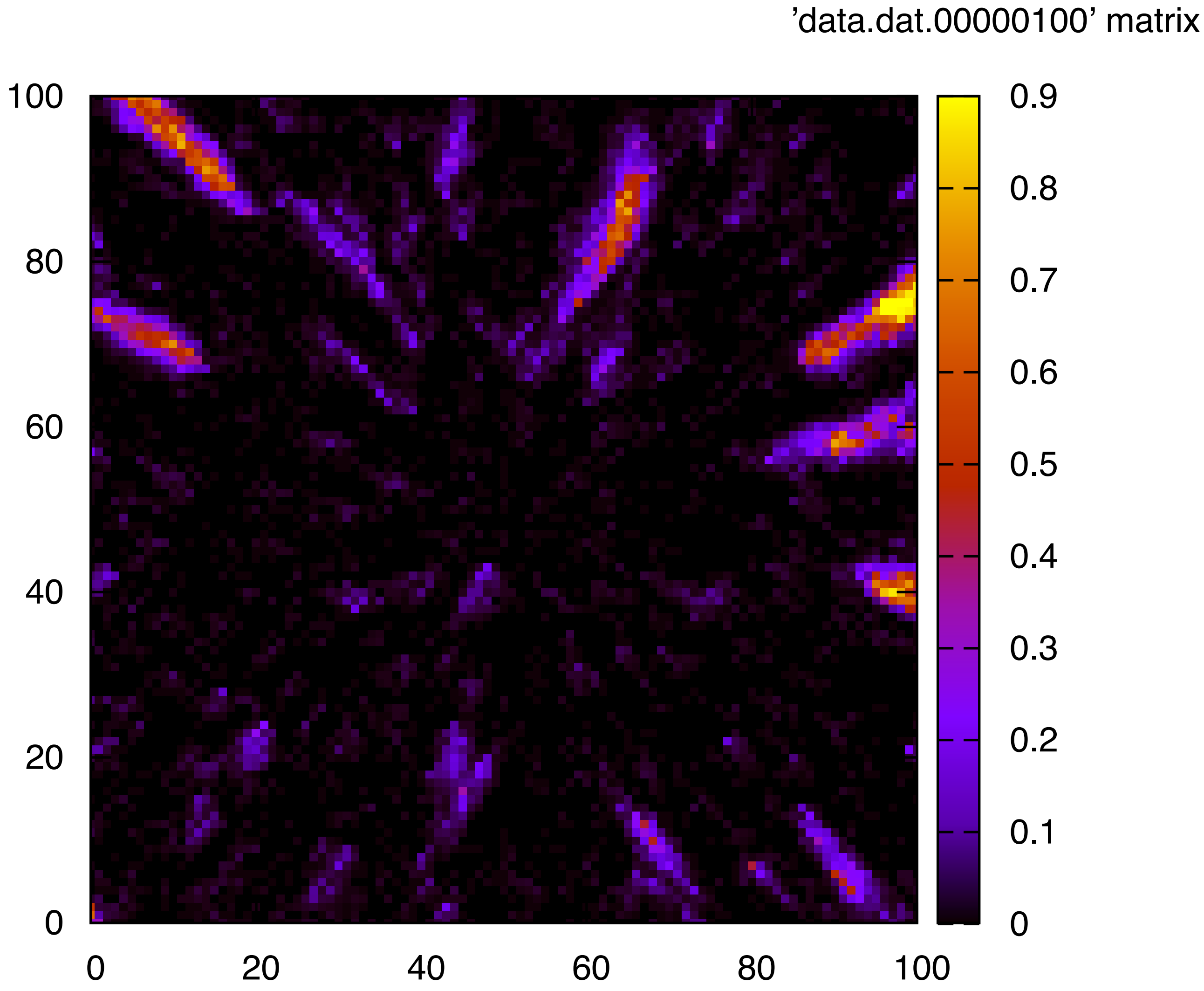
Ex3: 2D - Trace 3 (High, F=1)



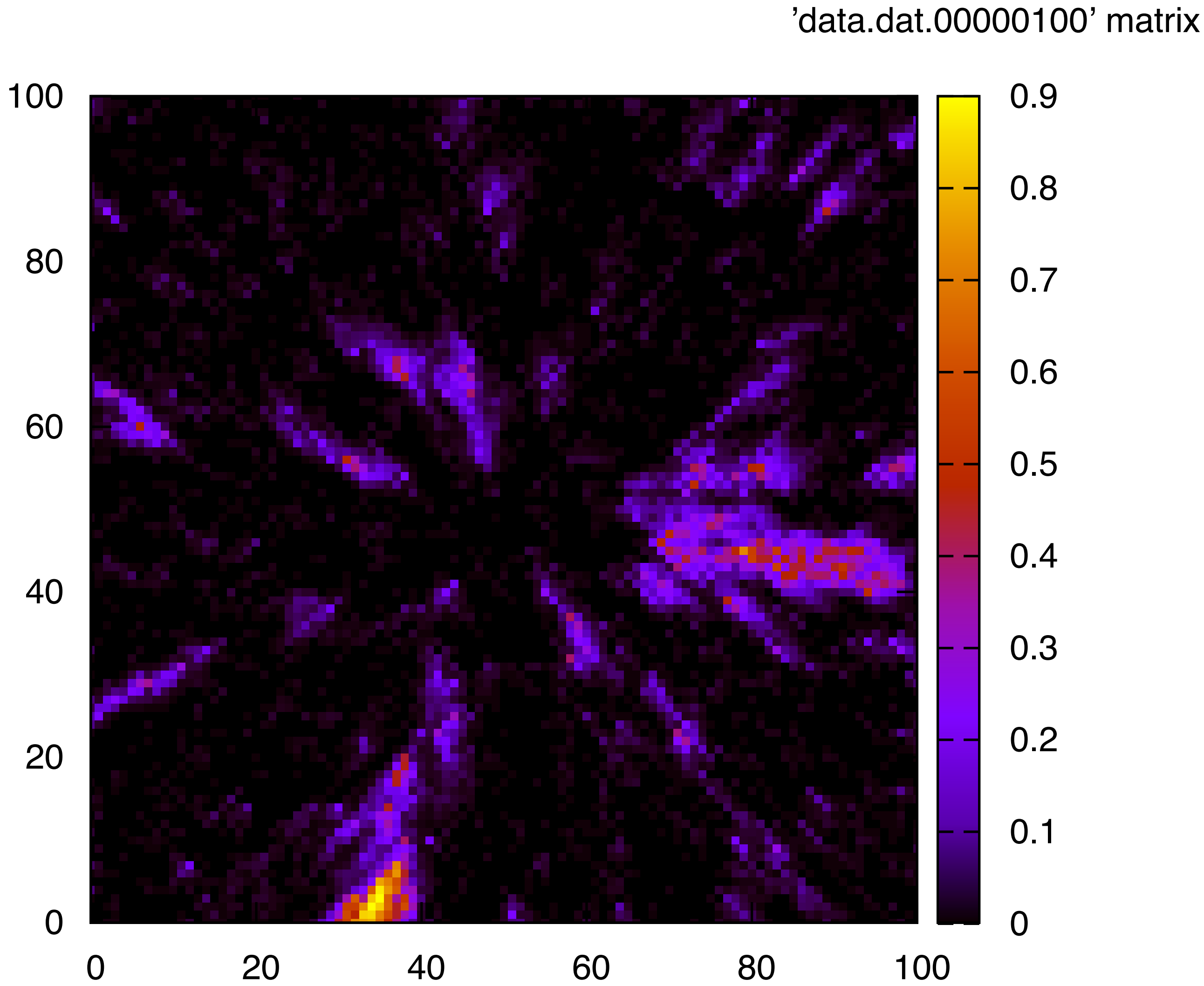
Ex3: 2D - Varying Fitness, Trace 1 (Medium, F=1)



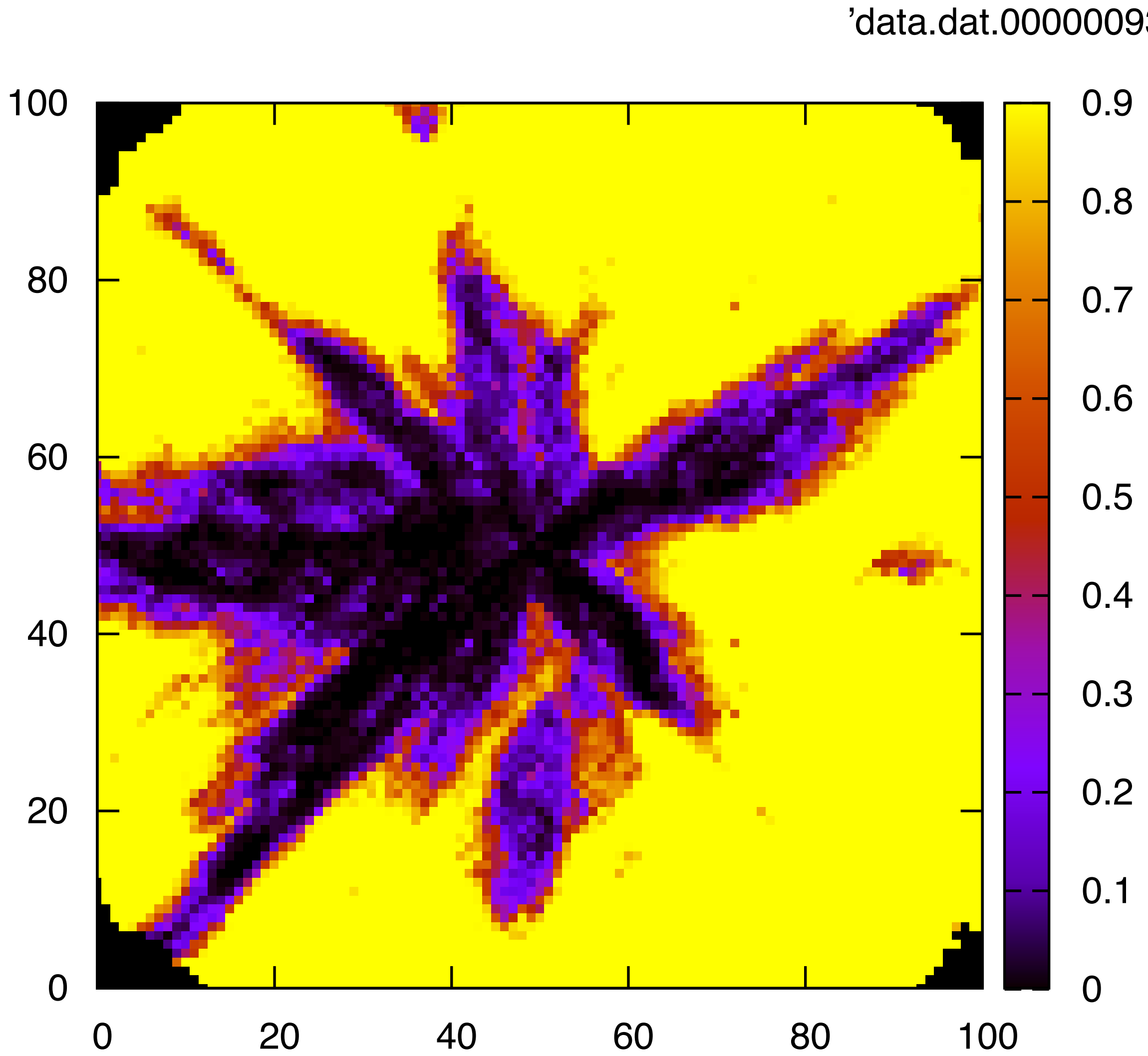
EX3: 2D - VARYING FITNESS, TRACE 2 (MEDIUM, F=1)



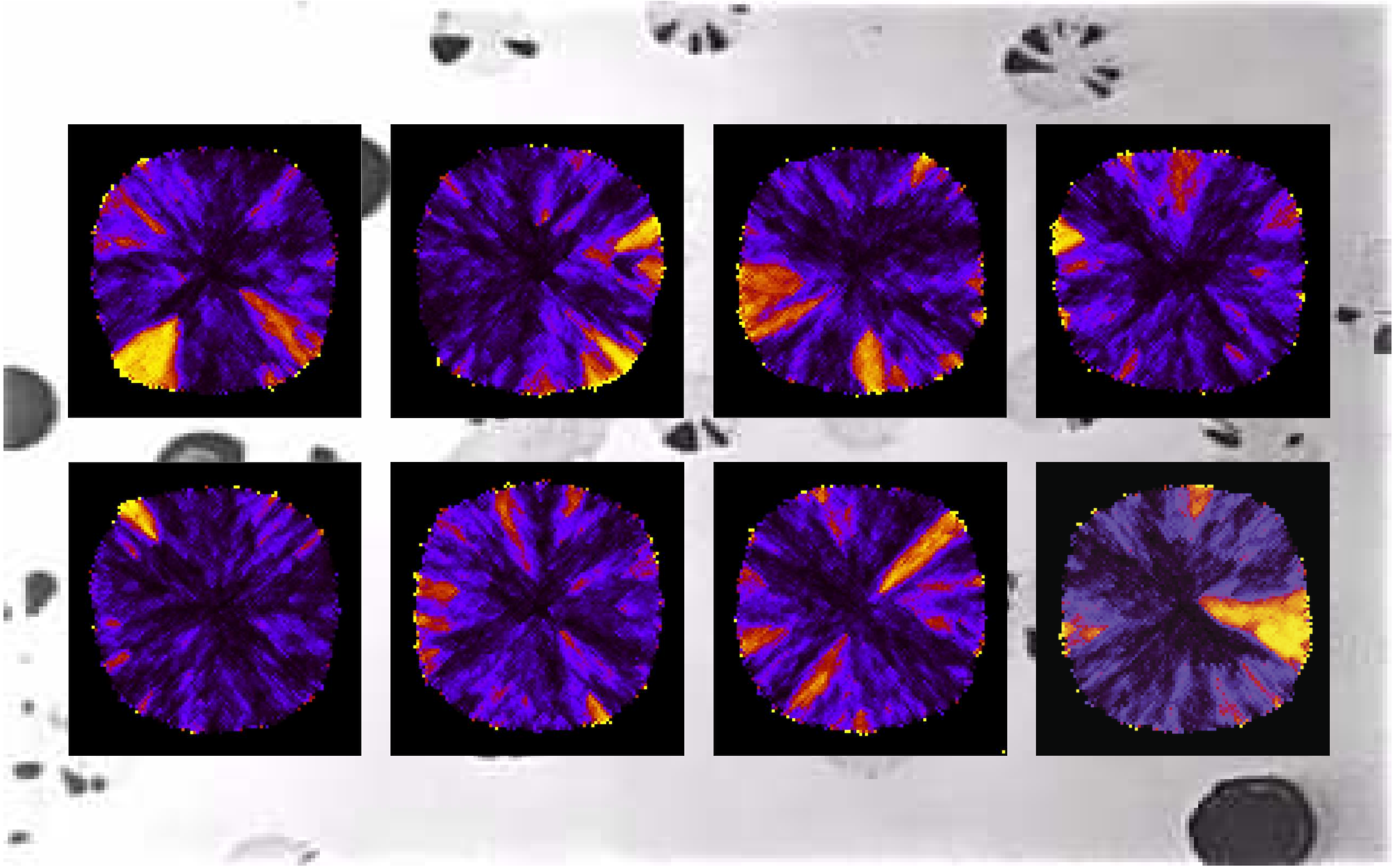
Ex3: 2D - Varying Fitness, Trace 1 (Medium, F=0.99)



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



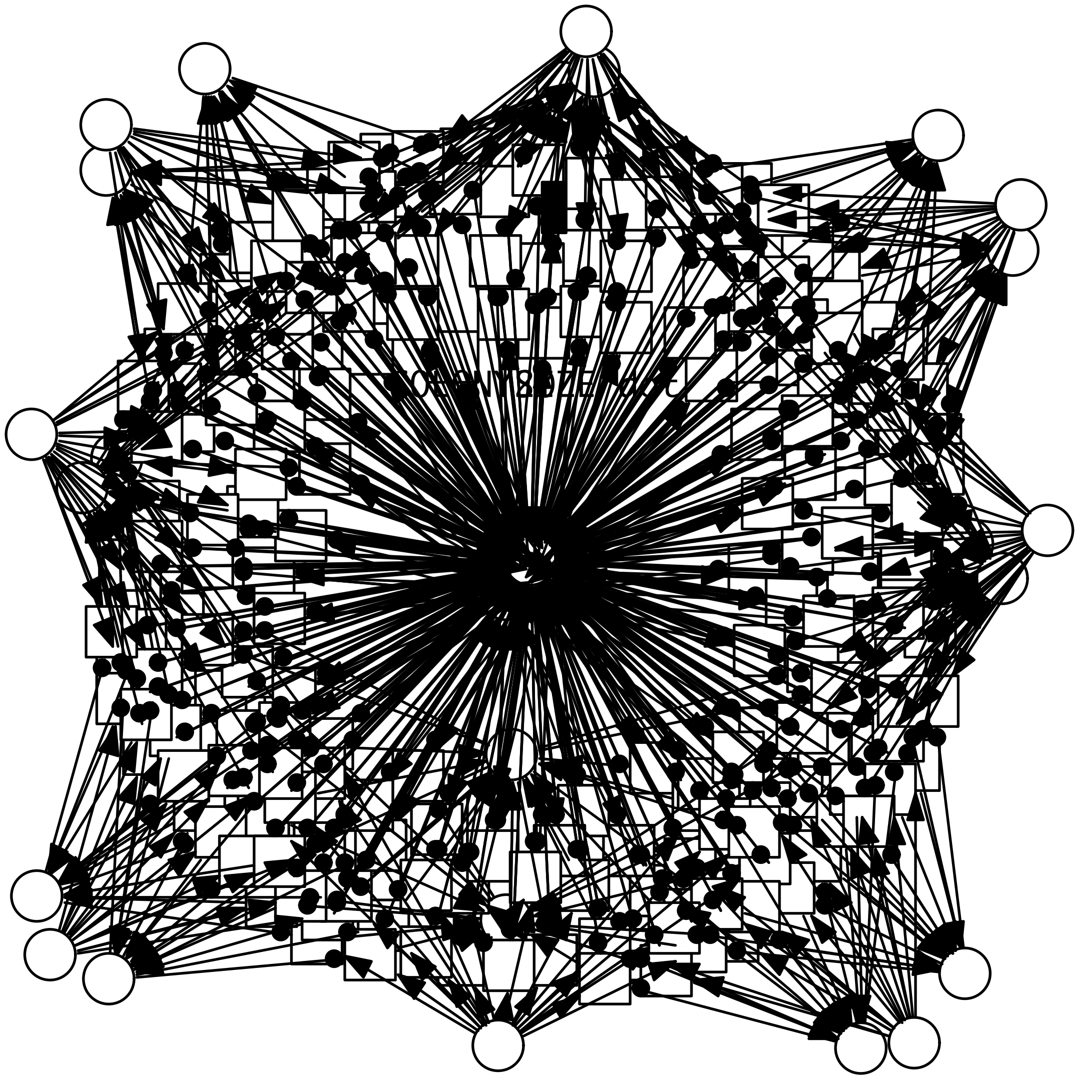
EX3: SOME FINAL STATES (HIGH, F=1)



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*

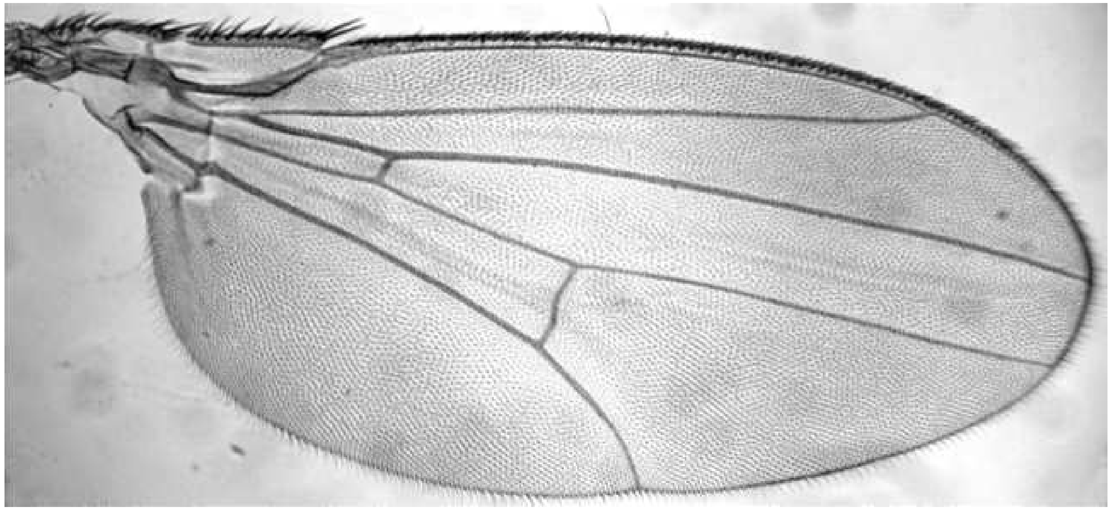
Phase Variation, Plain Model (3x3)

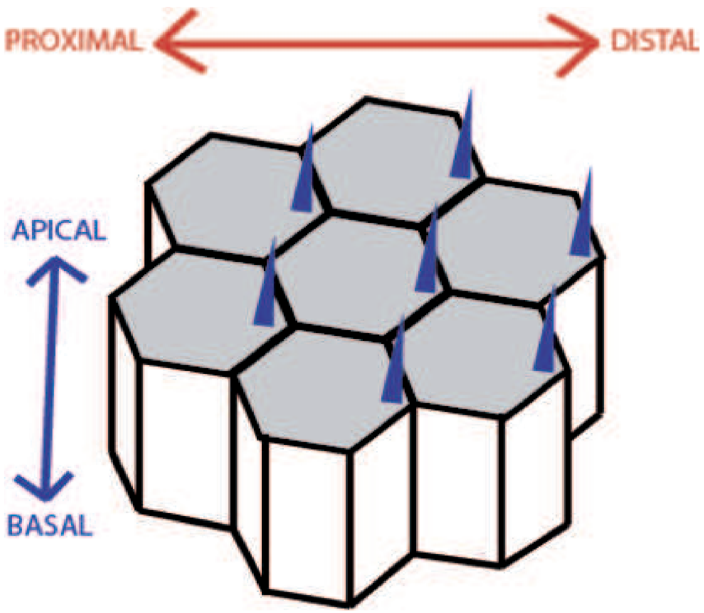


EXAMPLE 4:

PLANAR CELL POLARITY
IN FLY WING

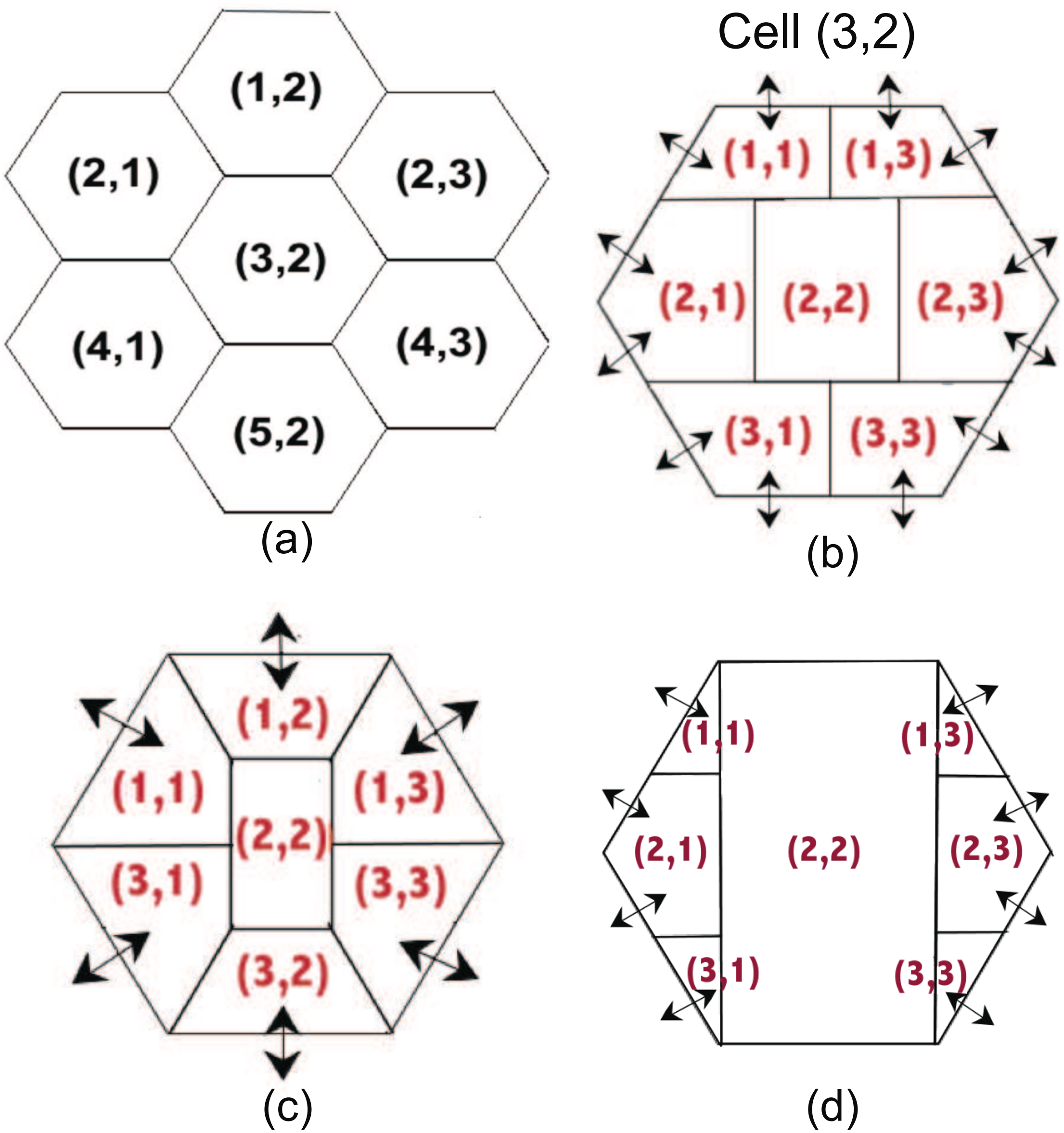
EX4 - PLANAR CELL POLARITY



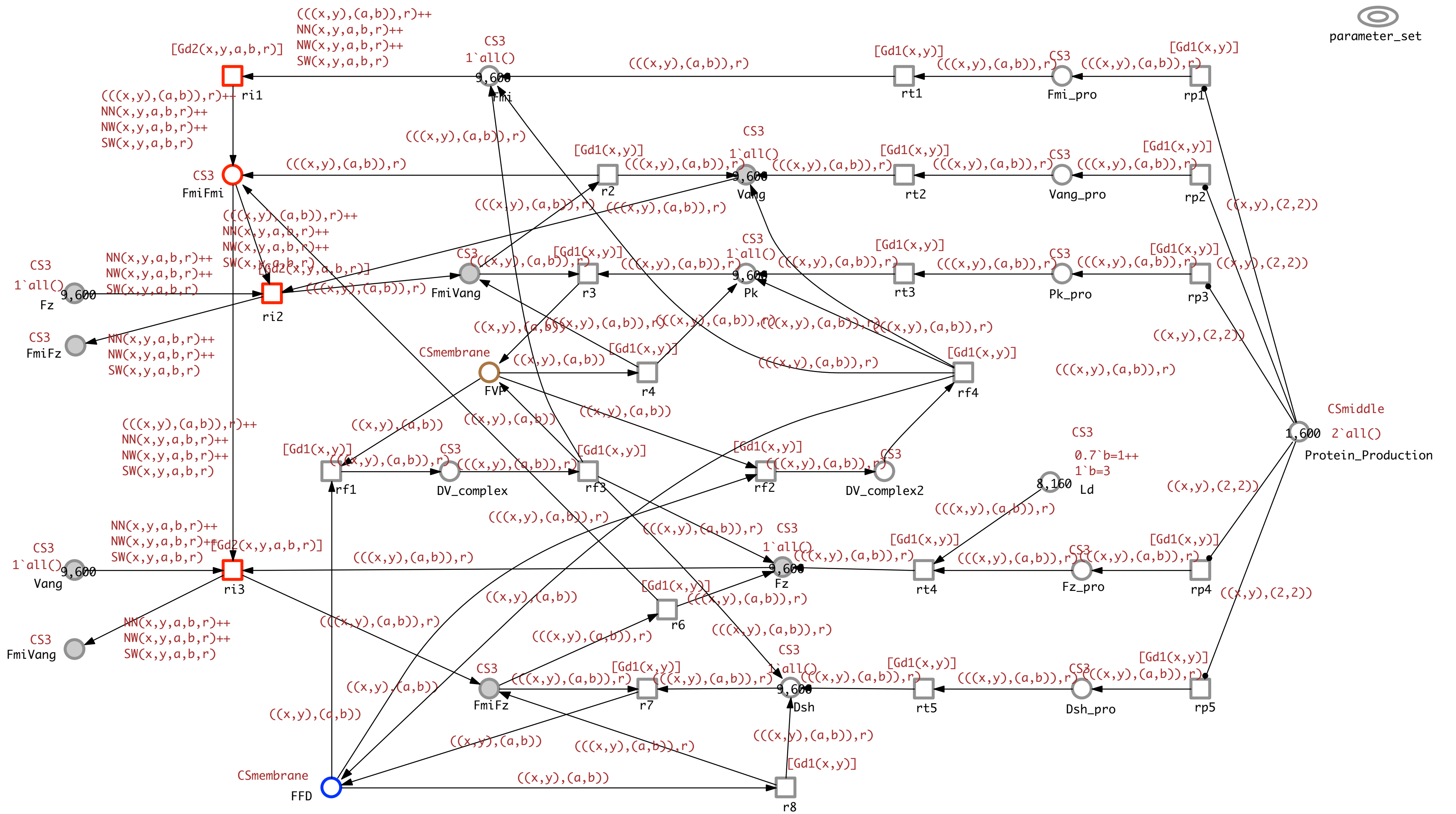


[BIOPPN 2011]
[CMSB 2011]

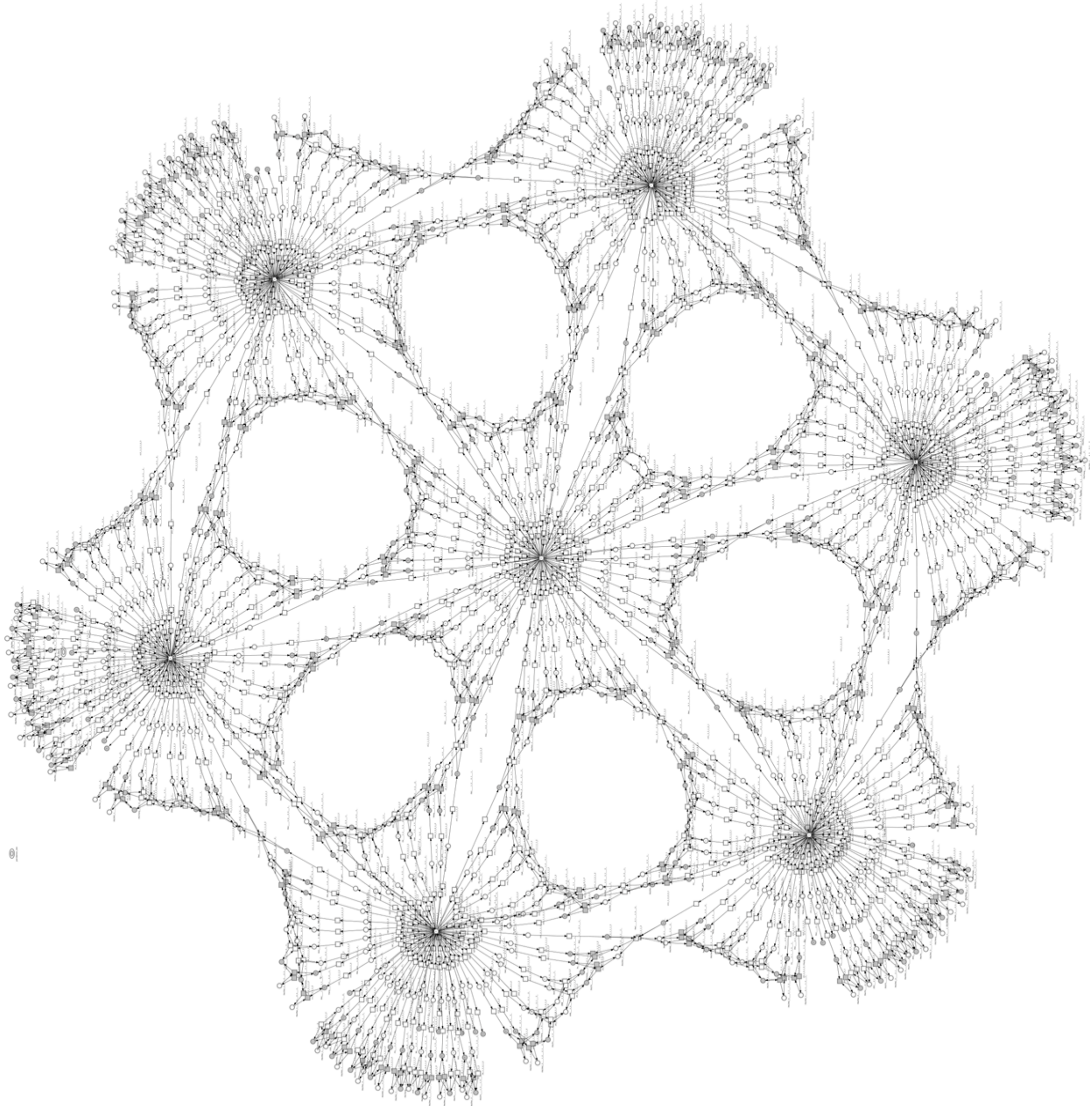
EX4 - PLANAR CELL POLARITY



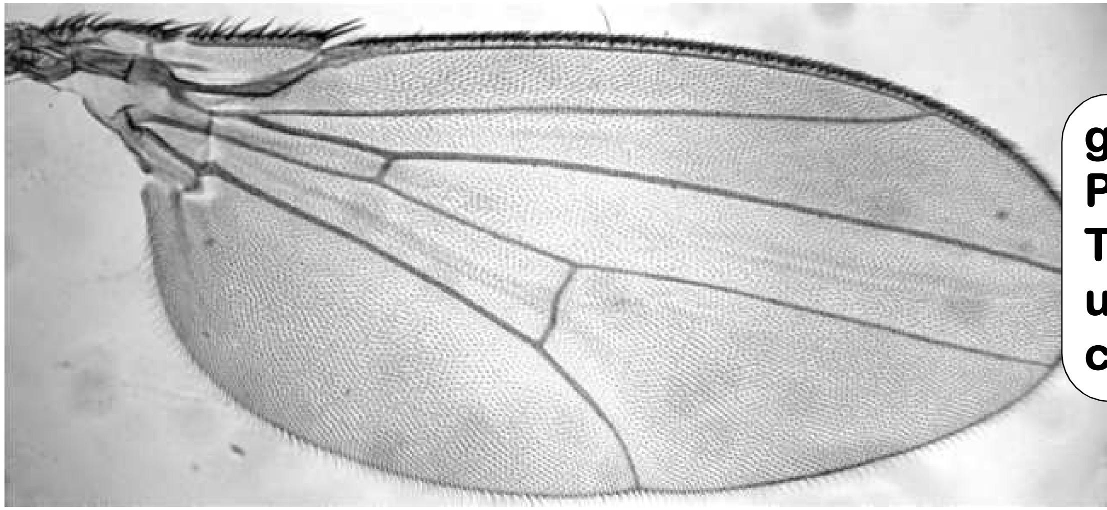
Ex4: Planar Cell Polarity



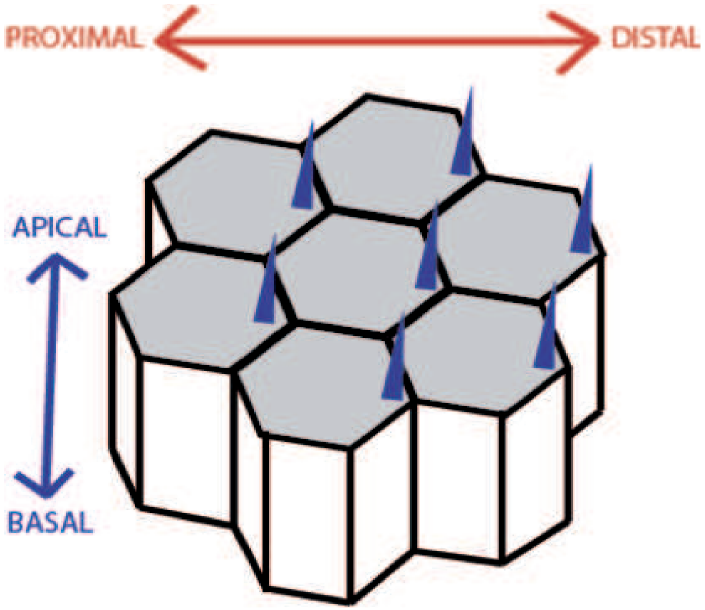
[Qian Gao, PhD Thesis 2013]



Ex4 - Planar Cell Polarity

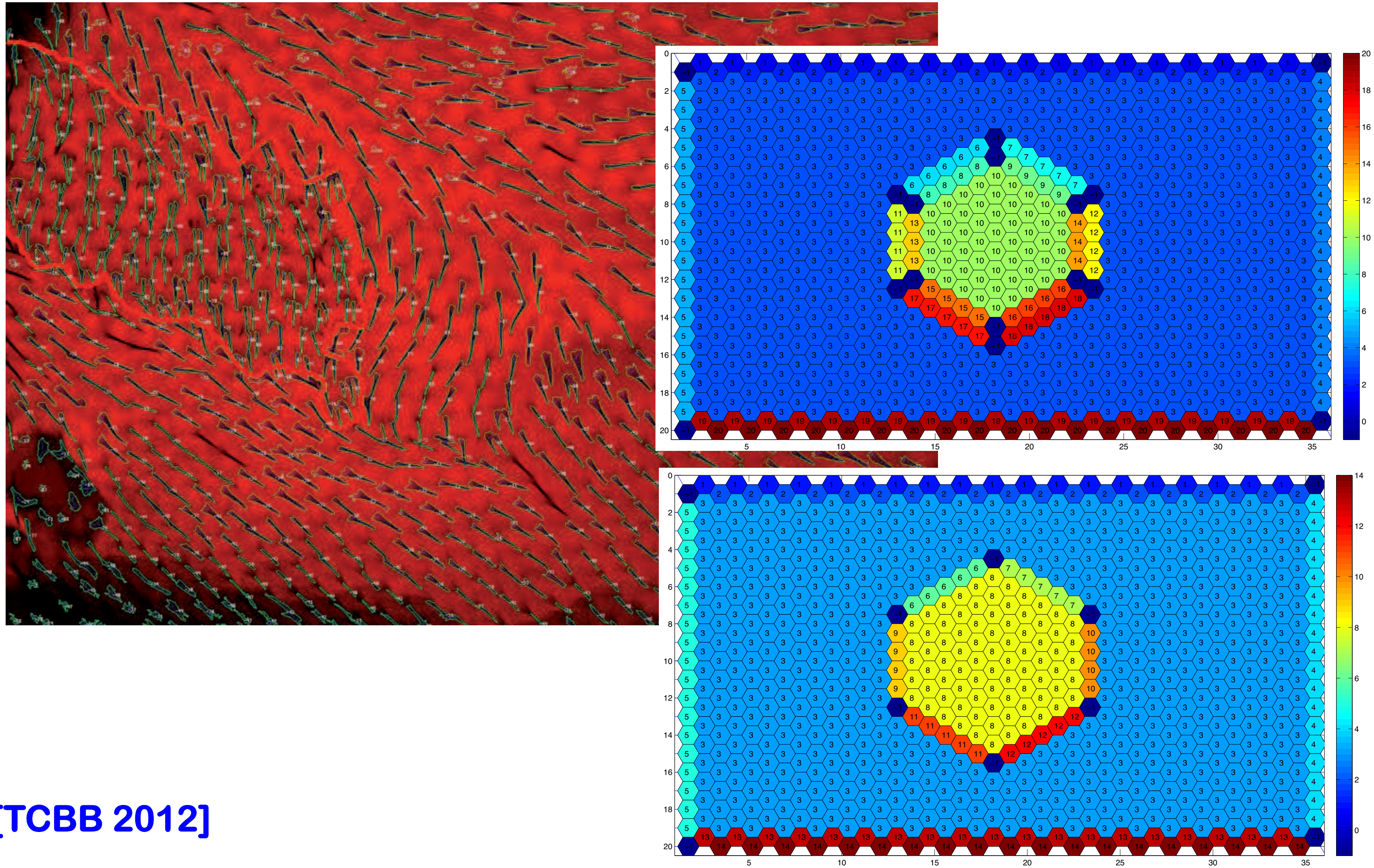


grid size:	40 x 40
PLACES:	164,000
TRANSITIONS:	229,686
unfolding:	4 min
cont. simulation:	2 h



[BioPPN 2011]
[CMSB 2011]

EX4 - PLANAR CELL POLARITY



[TCBB 2012]

ADVANTAGES OF THIS 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*

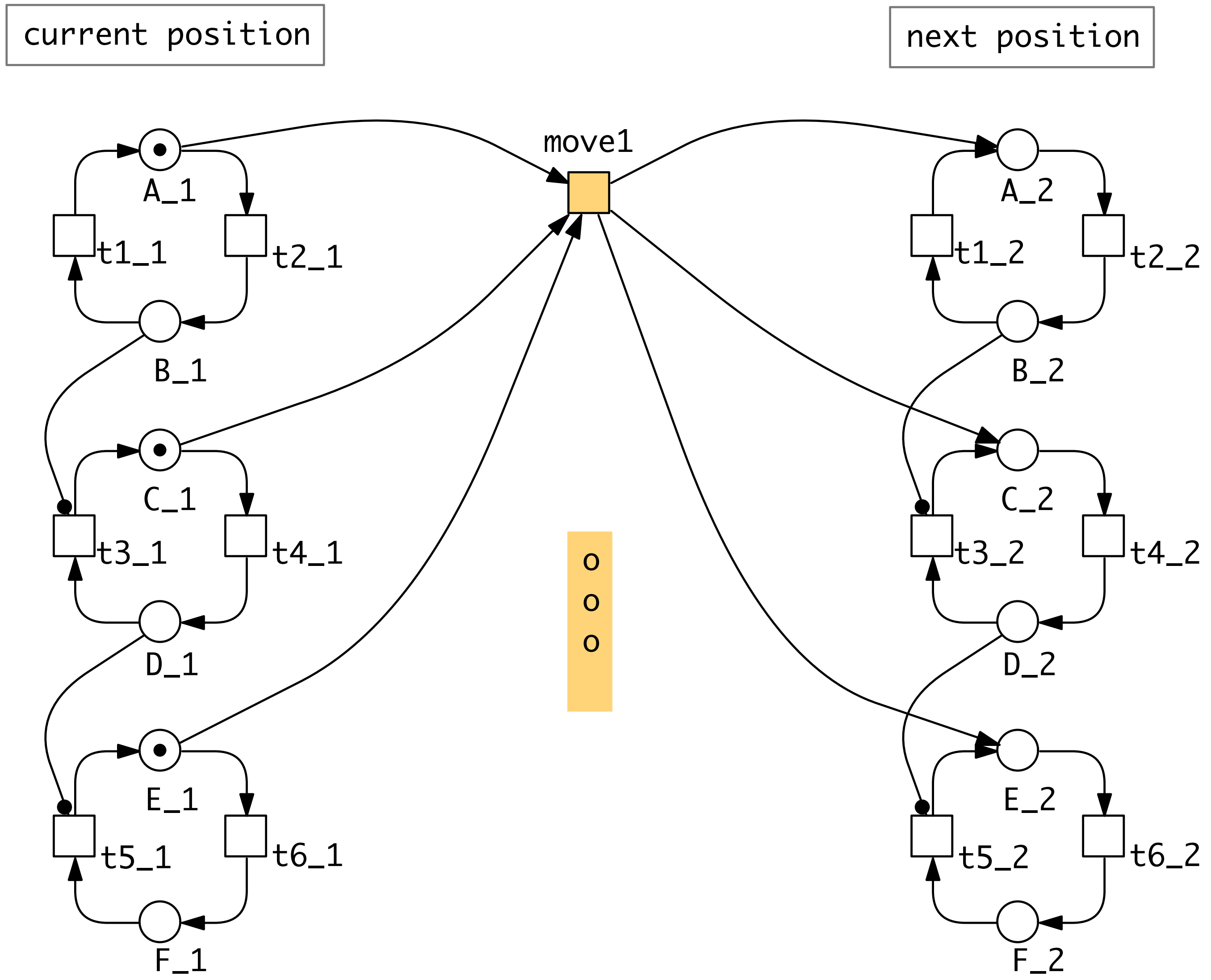
  -> *net structure itself needs not to be touched.*

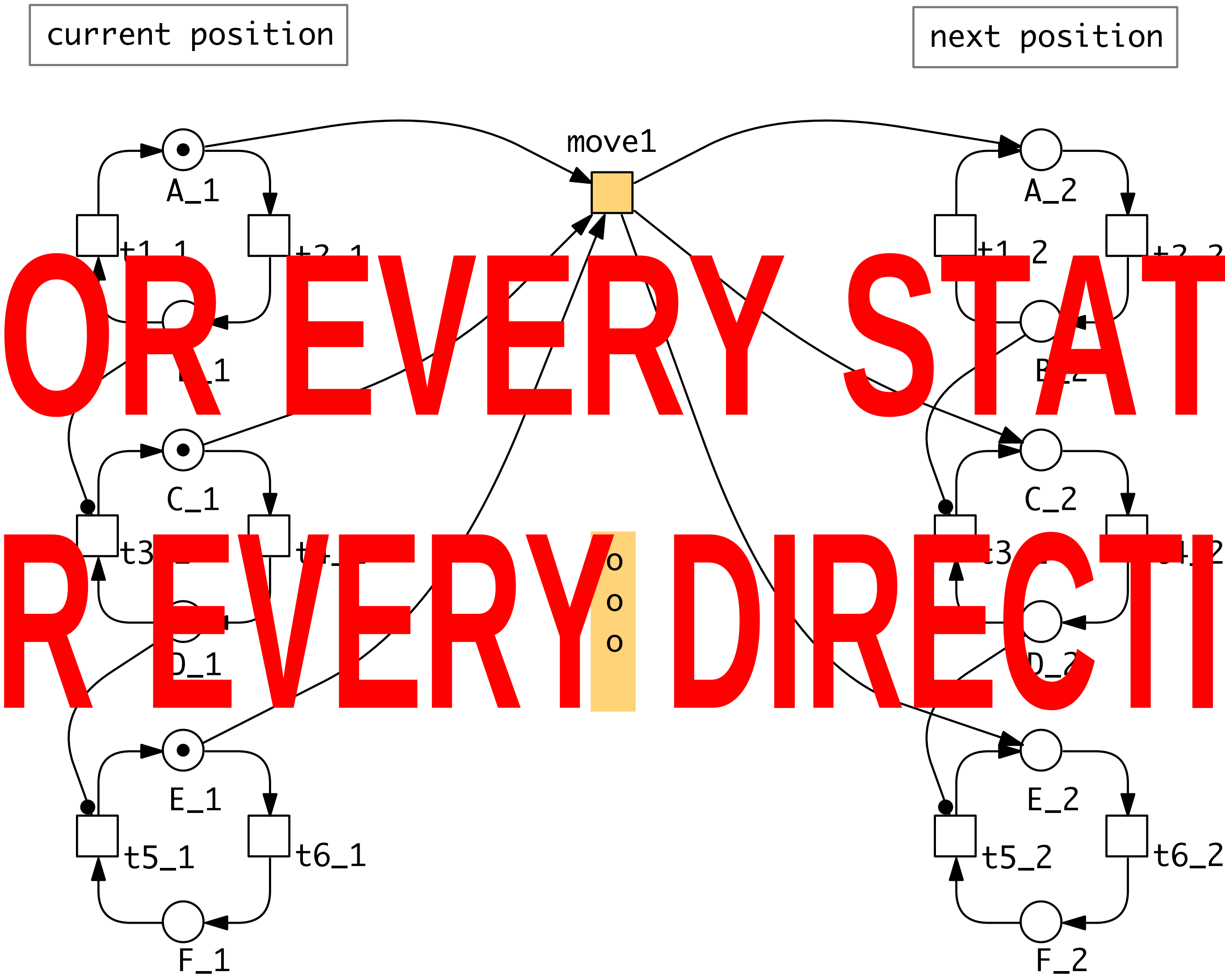
- **use of a priori finitely discretised space preserves model analysibility**

- **automatic unfolding**

  -> *reuse of all analysis and simulation techniques of uncoloured Petri nets*

How to Encode Space, Version 1 - the Big Cons


current position
next position
move1
A_1
t1_1
t2_1
B_1
C_1
t3_1
t4_1
D_1
E_1
t5_1
t6_1
F_1
A_2
t1_2
t2_2
B_2
C_2
t3_2
t4_2
D_2
E_2
t5_2
t6_2
F_2
o
o
o

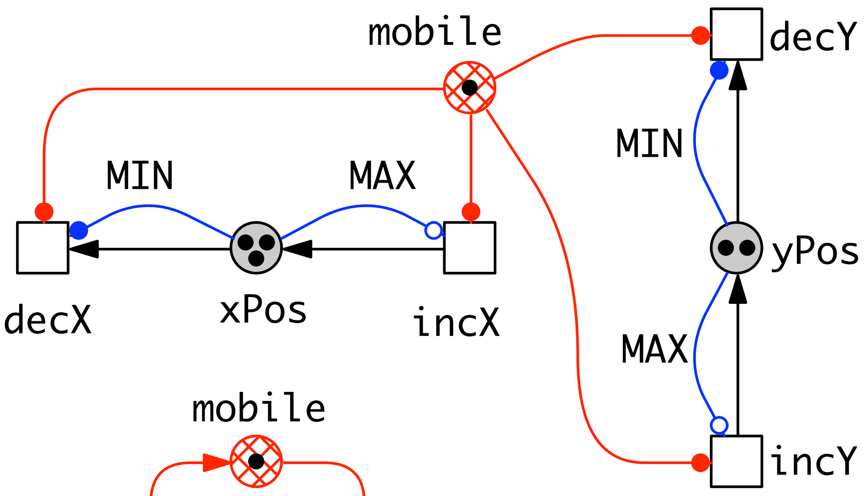


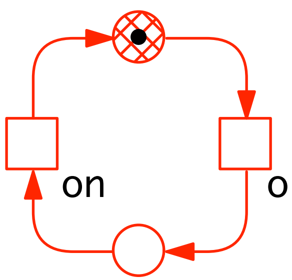
FOR EVERY STATE

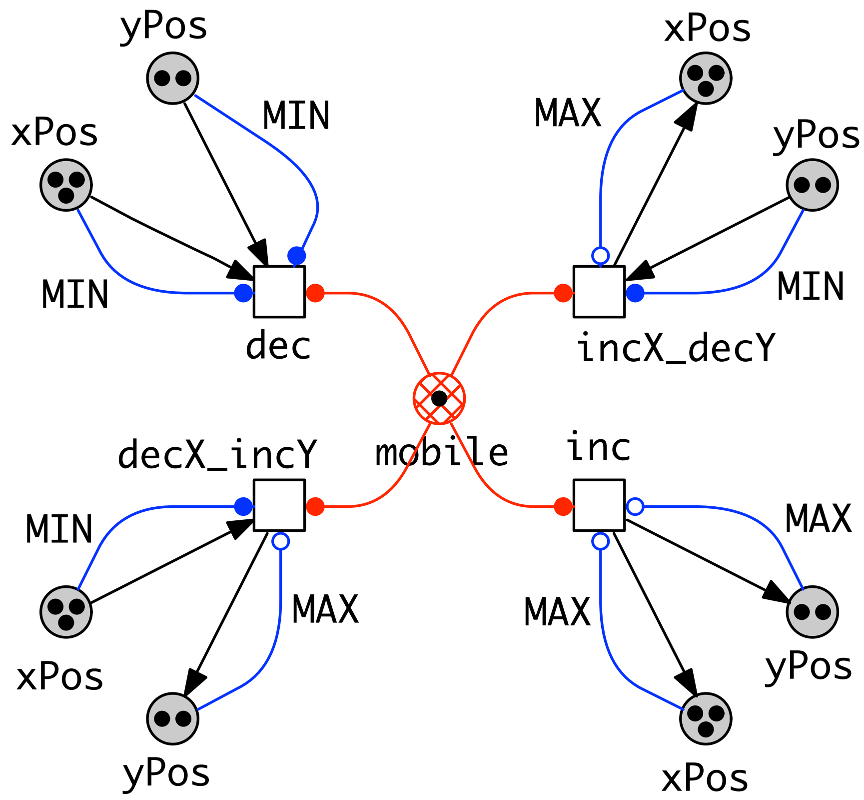
FOR EVERY DIRECTION

HOW TO ENCODE SPACE ?
VERSION 2

fence in







permit movement on/off

Encoding Space, Comparison

Version1

- **a priori finite space**
- **unfolding generates PN for the whole finite universe**
  -> many places might be empty
- **requires atomic moving objects**

Version2

- **potentially infinite space**
- **size of the unfolded PN does not dependent on size of the universe**
- **local states in moving objects possible**

Pro

- **state-dependent rates as usual**

Con

- **state-dependent rates require special tool support**
  -> observer variables

SUMMARY

& OUTLOOK

OUR TOOL BOX

- **SNOOPY**

  -> *modelling and animation/simulation of hierarchical graphs,*
  e.g. (extended) fault trees,
  various Petri net classes, e.g. QPN, XQPN, SPN, XSPN, CPN, TPN,
  . . . ,
  free style graphs

- **CHARLIE**

  -> *QPN, XQPN, Time/Timed Petri nets (TPN)*
  -> *mostly standard analysis techniques of Petri net theory*

- **MARCIE**

  -> *XQPN, SPN, XSPN, SRN*
  -> *symbolic and simulative model checking*

- **Patty**

  -> *animation via web browser*

- **SNOOPY**
  - -> *modelling and animation/simulation of hierarchical graphs,*
    e.g. (extended) fault trees,
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- **CHARLIE**
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- **MARCIE**
  - -> *XQPN, SPN, XSPN, SRN*
  - -> *symbolic and simulative model checking*
- **Patty**
  - -> *animation via web browser*

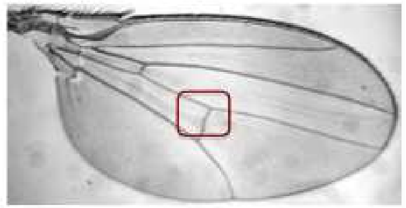
+

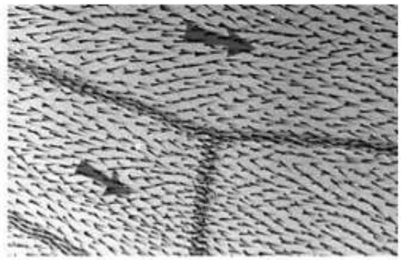
SBML import/export

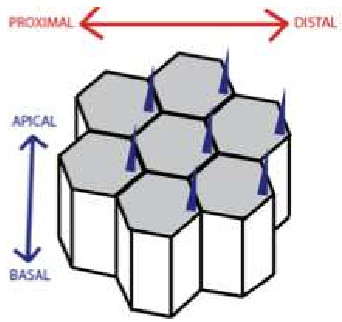
EXPORT TO MATAB AND MANY OTHER TOOLS

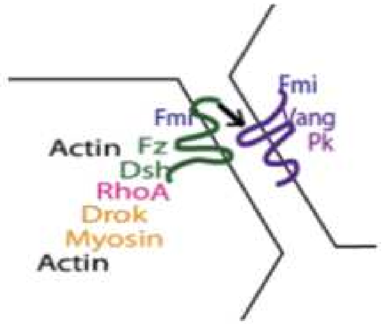
- **efficient simulation of very large Petri nets**
  - -> *stochastic*
  - -> *continuous*
  - -> *hybrid*
- **(hierarchical) space**
- **hierarchical organisation of components**
- **observables**
- **dynamic grid size**
- **shape and volume of components**
- **biosystem development**

Multiscale Challenges









CREDITS

- **EPSRC Research Grant EP/I036168/1**
- **collaborators**

  David Gilbert, Brunel University, London, UK

  Wolfgang Marwan, Otto-von-Guericke University, Magdeburg, Germany
- **case studies**

  Turing Patterns - Mary Ann Blätke, Fei Liu

  bacterial colony - Ovidiu Parvu, David Gilbert, Nigel Saunders

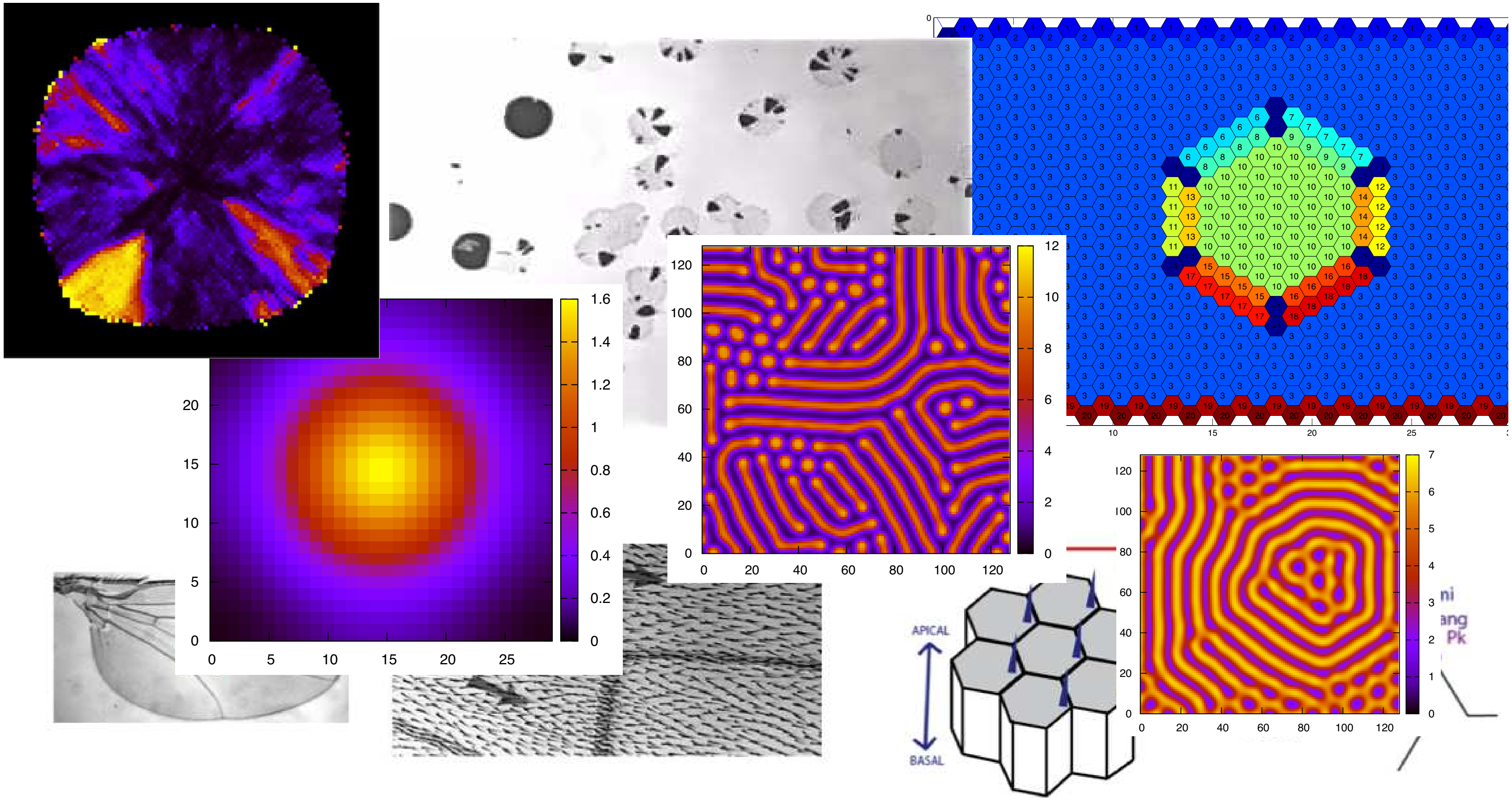
  PCP in fly wing - Pam Gao, David Gilbert, David Tree
- **Snoopy + Charlie + Marcie development**

  Christian Rohr, Fei Liu, Mostafa Herayj

  Martin Schwarick, Jan Wegener
- **plots**

  Mary Ann Blätke, Daniele Maccagnola, Ovidiu Parvu, Christian Rohr, Jan Wegener

Thanks !



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