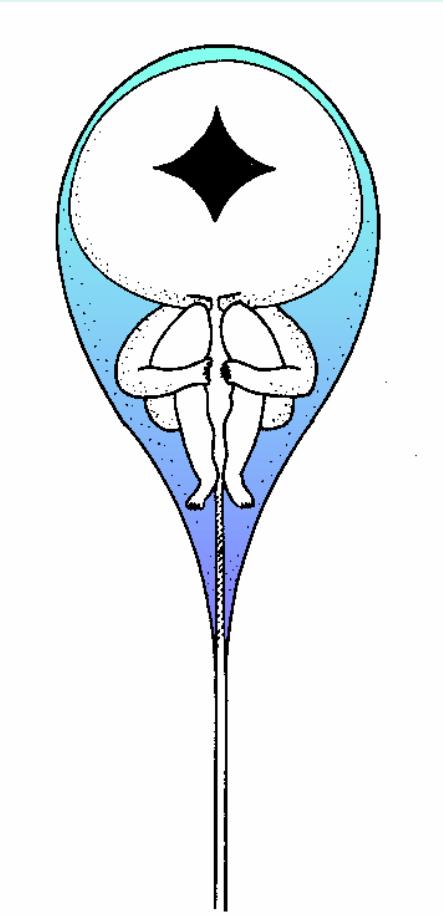


Preformation



De-velopment

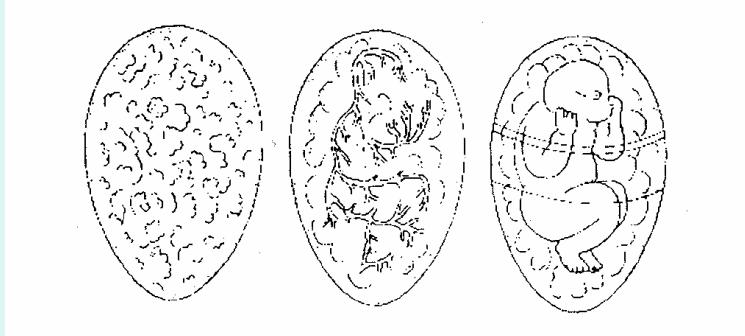


(K. Blossfeldt:
hairfern)

Homunculus

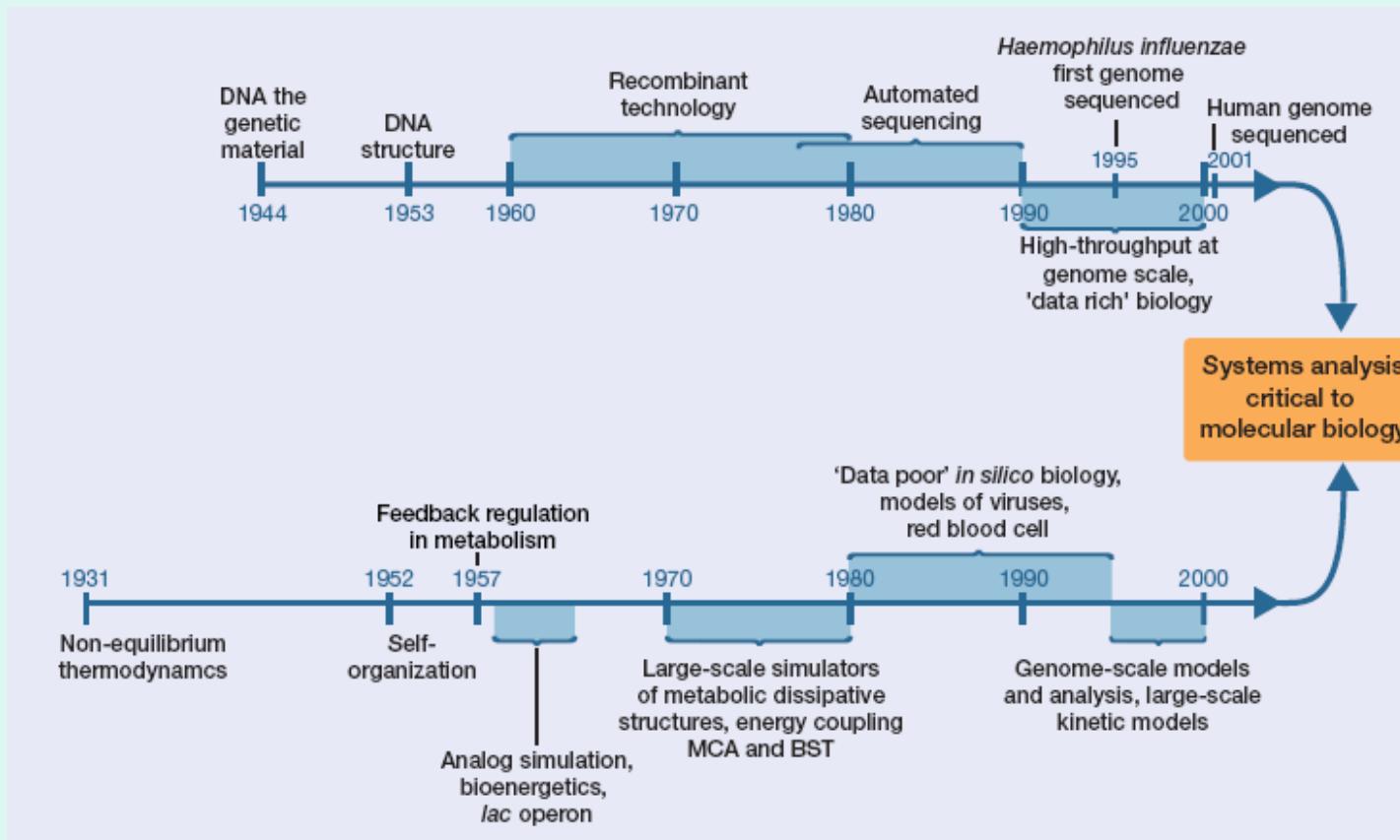
De-novo pattern formation

Epigenesis



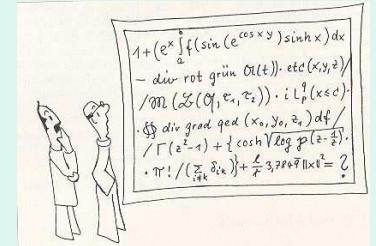
(after
Aristoteles)

Systems analysis

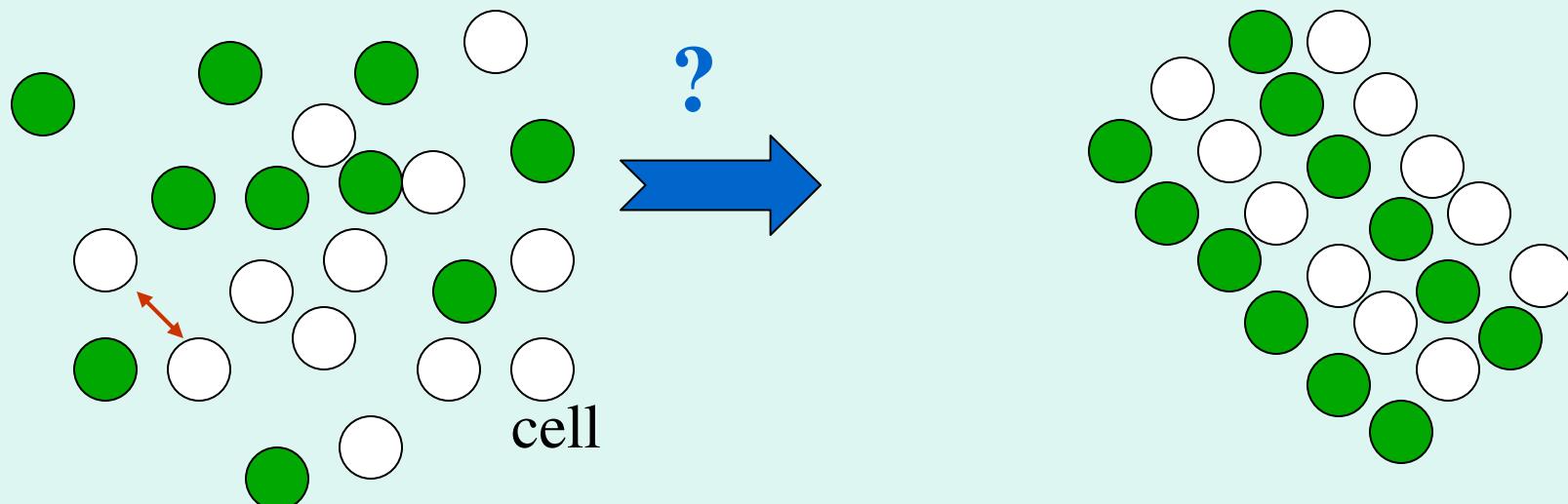


From: Westerhoff/Palsson, Nature Biotech. 22 (10), 2004

What are mathematical models good for?



- Mathematical models can help to explain *cooperative behavior*, in particular
spatio-temporal pattern formation

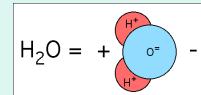


Interacting particles/cells



Many particles

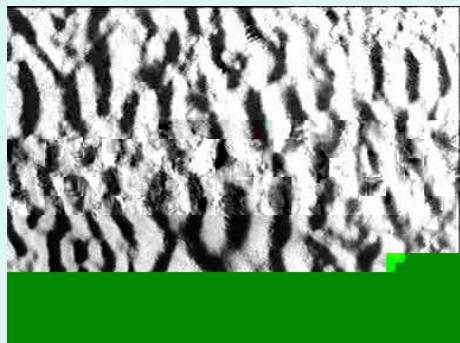
Components



Interactions

collisions,
conservation laws

identical



<-0.5mm-> **Many cells**
(Myxobacteria)



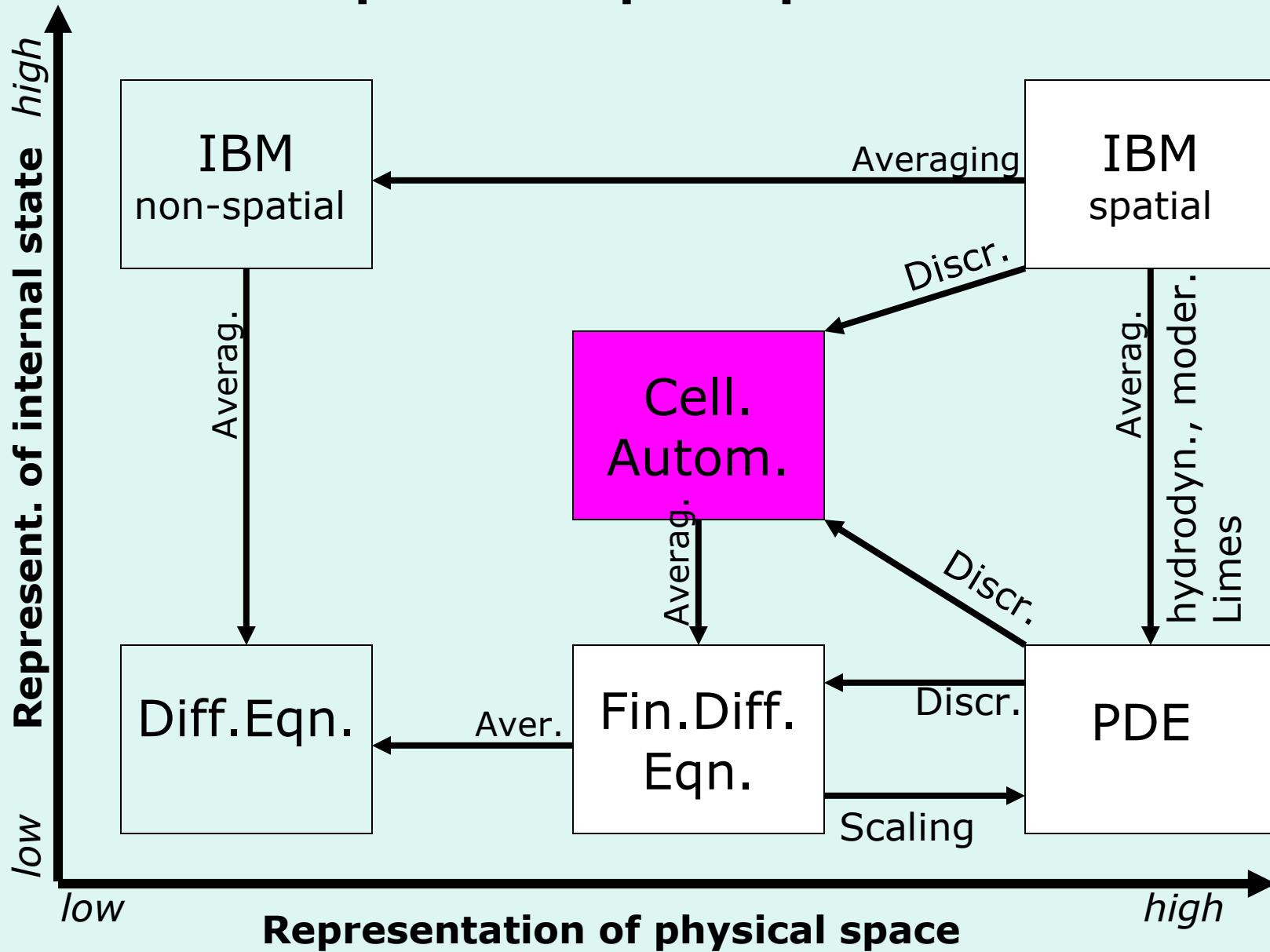
different(iated)

alignment,
adhesion,
repulsion...



**function
evolvability**

Mathematical models of spatio-temporal pattern formation



Cellular automaton modelling of spatio-temporal pattern formation in interacting cell systems

Andreas Deutsch

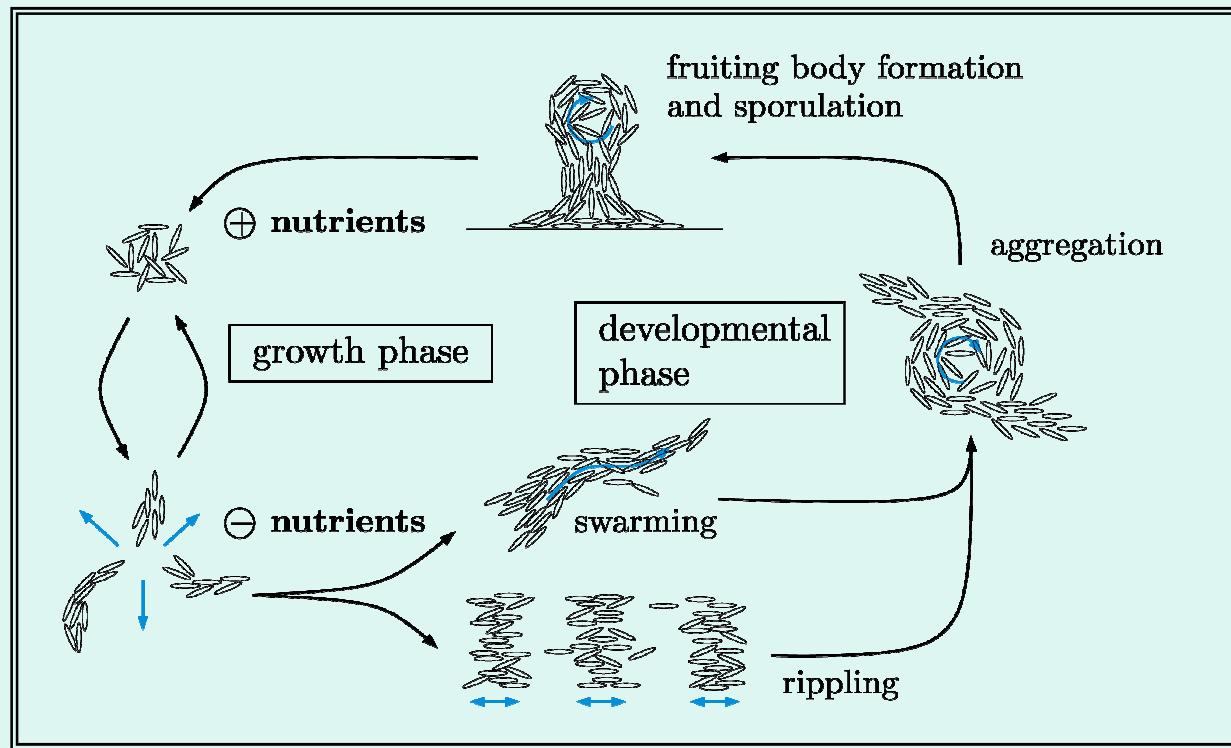
Technische Universität Dresden

„Automata 2007, Fields Institute, Toronto, August 27-29, 2007“

Overview

- **Ex. 1:** swarm formation
- **Ex. 2:** tumor growth/invasion
- Summary/outlook

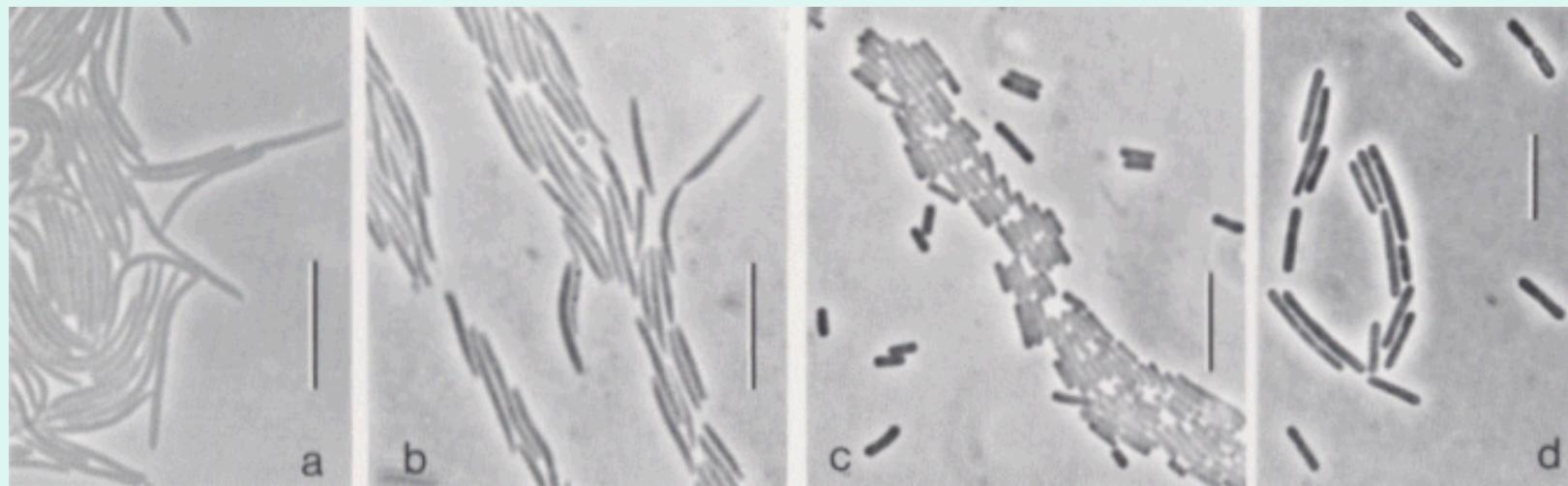
Life cycle of *Myxobacteria*



Collective motion in *Myxobacteria*

Swarm pattern:

cluster of oriented cells, moving collectively



Stigmatella erecta

Myxococcus xanthus

Polyangium sp.

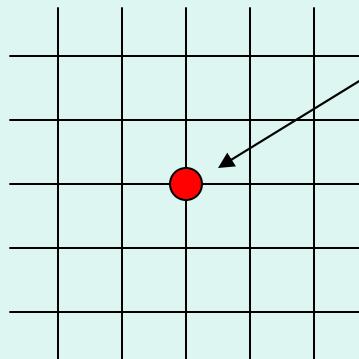
Cystobacter violaceus

- Hypothesis:**
1. Cells interact „locally“ (no leaders).
 2. Cells can perceive neighbour orientations (pili, „sensitivity“) and align locally.

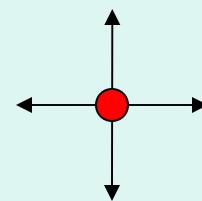
Model definition

1. Lattice:

$$L = \{\vec{r} = (r_1, r_2), r_i \in \mathbb{Z}\} \quad (\text{period. BC})$$



Velocity channels:



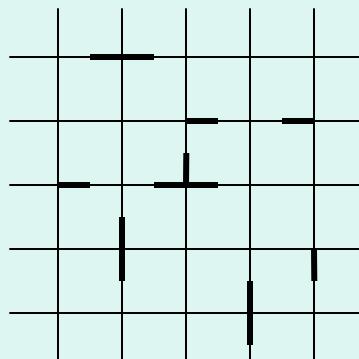
$$\begin{aligned}\vec{c}_1 &= (1, 0) \\ \vec{c}_2 &= (0, 1) \\ \vec{c}_3 &= (-1, 0) \\ \vec{c}_4 &= (0, -1)\end{aligned}$$

2. Time:

$$t = 0, 1, 2, \dots$$

3. State space:

$$S = \{\vec{s} = (s_i)_{i=1}^4, s_i \in \{0, 1\}\}$$



Node configuration:

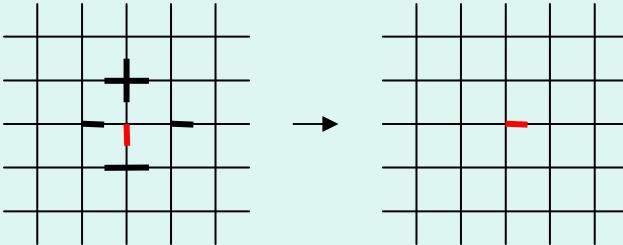
$$\vec{\eta}(\vec{r}, t) \in S$$

Lattice configuration:

$$\eta(t) = \{\vec{\eta}(r, t), \vec{r} \in L\}$$

4. Dynamics: $\eta(t) \rightarrow \eta(t+1), t = 0, 1, 2, \dots$

4a. Interaction



$P(\vec{\eta}(r, t) \rightarrow \vec{\eta}^I(r, t))$ indep. of $\vec{r} \in L, t = 0, 1, 2, \dots$

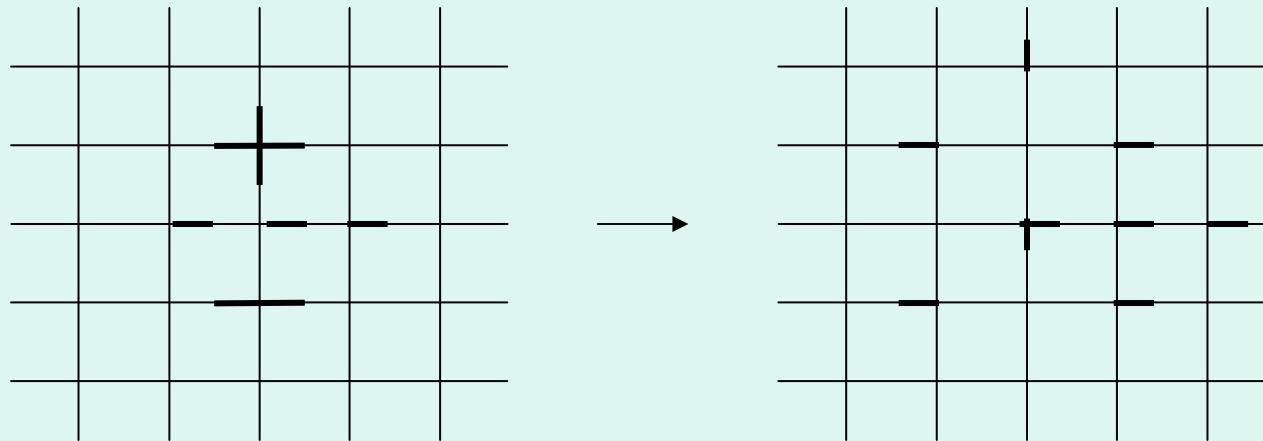
$$P(\vec{s} \rightarrow \vec{\sigma} \mid \vec{D}, \beta) = \frac{1}{Z(\vec{s})} \cdot e^{\beta \cdot \langle \vec{D}, \vec{J}(\sigma) \rangle} \cdot \delta(\rho(\vec{s}), \rho(\vec{\sigma}))$$

where $Z(\vec{s}) = \sum_{\sigma \in S} e^{\beta \cdot \langle \vec{D}, \vec{J}(s) \rangle} \cdot \delta(\rho(\vec{s}), \rho(\vec{\sigma}))$ **(normalization factor)**

$$\vec{D} = \sum_{p=1}^4 \sum_{i=1}^4 \vec{c}_i s_i (\vec{r} + \vec{c}_p) \quad \text{(„director field“)}$$

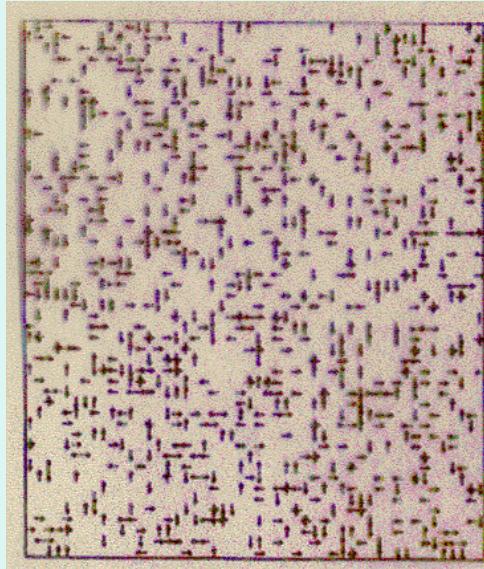
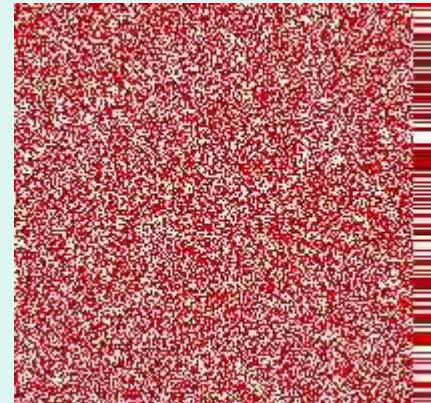
$$\rho(\vec{s}) = \sum_{i=1}^4 s_i, \quad \vec{J}(\vec{s}) = \sum_{i=1}^4 \vec{c}_i s_i, \quad \beta \geq 0 \quad \text{(sensitivity)}$$

4b. Migration

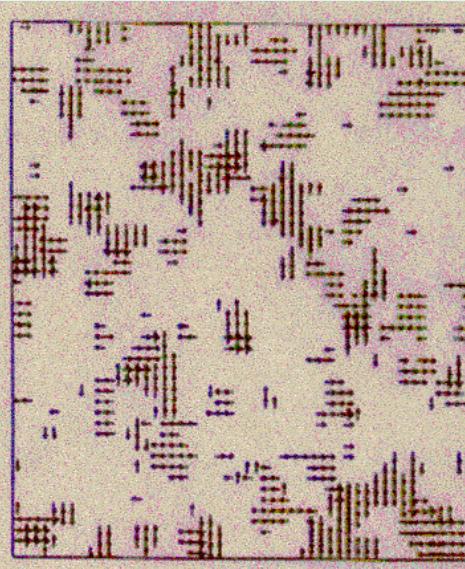


$$\eta_i(\vec{r} + c_i, t+1) = \eta^I(\vec{r}, t)$$

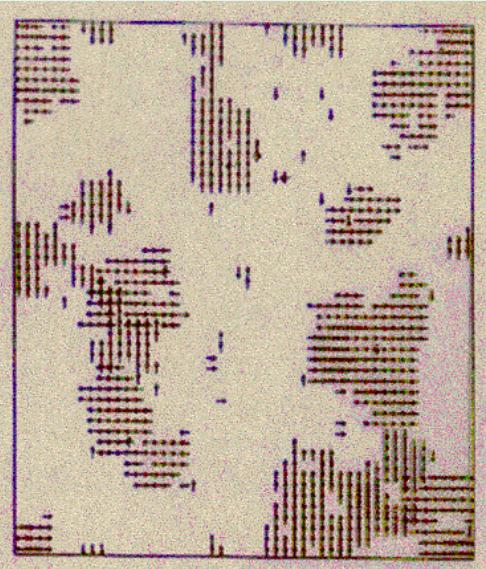
Simulation



$t=0$



$t=100$

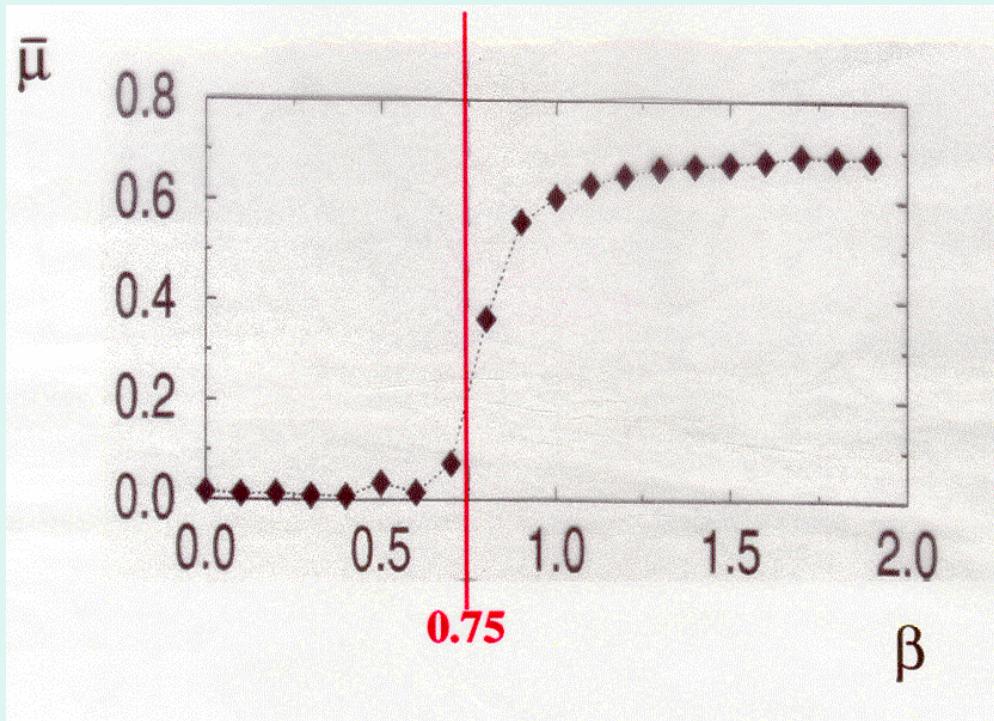


$t=2000$

(periodic b.c.)

$$\beta = 5, \bar{\rho} = 0.4, n = 50$$

Statistical analysis



$\bar{\rho} = 1.6$
 $N = 50$
 $t = 1000$

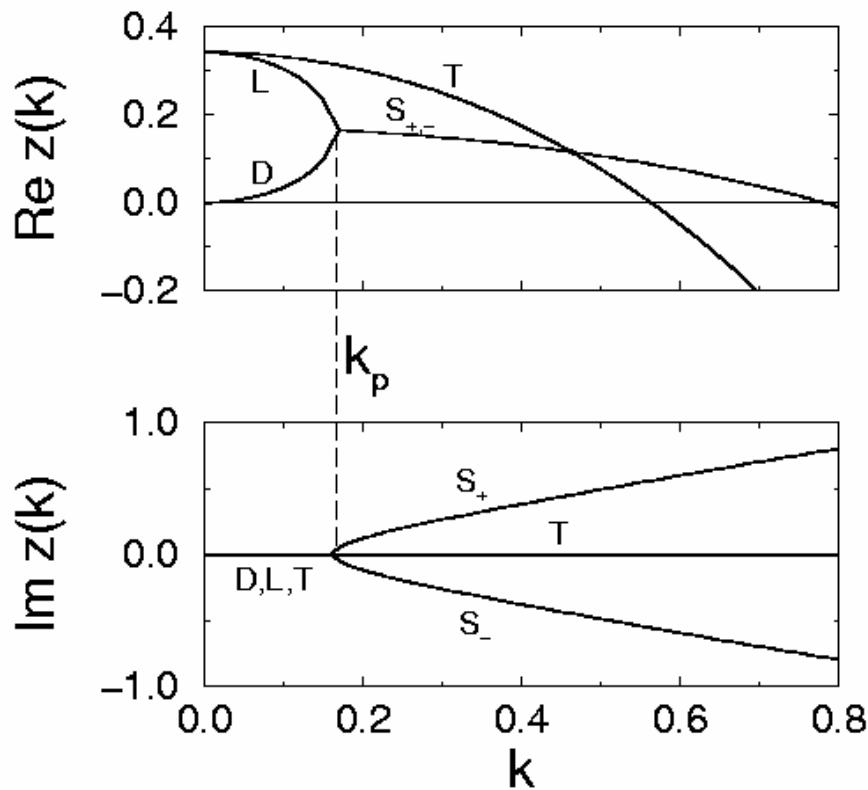
$$\bar{\mu}(t) = \frac{1}{N^2} \left| \sum_{\vec{r} \in L} \sum_{i=1}^4 \vec{c}_i s_i(\vec{r}, t) \right|, \quad 0 \leq \bar{\mu}(t) \leq 1$$

(mean average orientation)

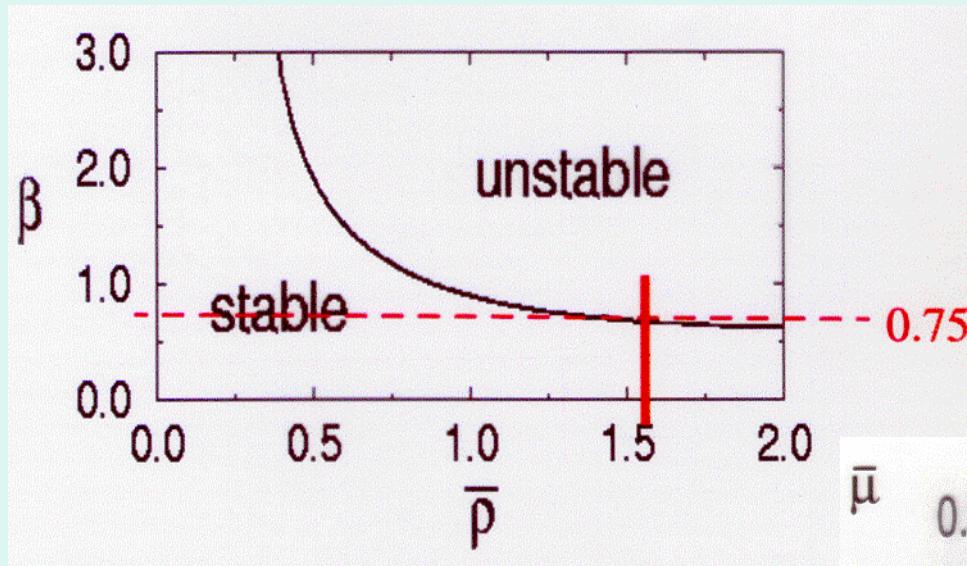
Analysis

- Automaton rules à equations (Boltzmann eqn.)
- Linear stability analysis around homogeneous states
- Eigenvalue spectrum
- Phase diagram

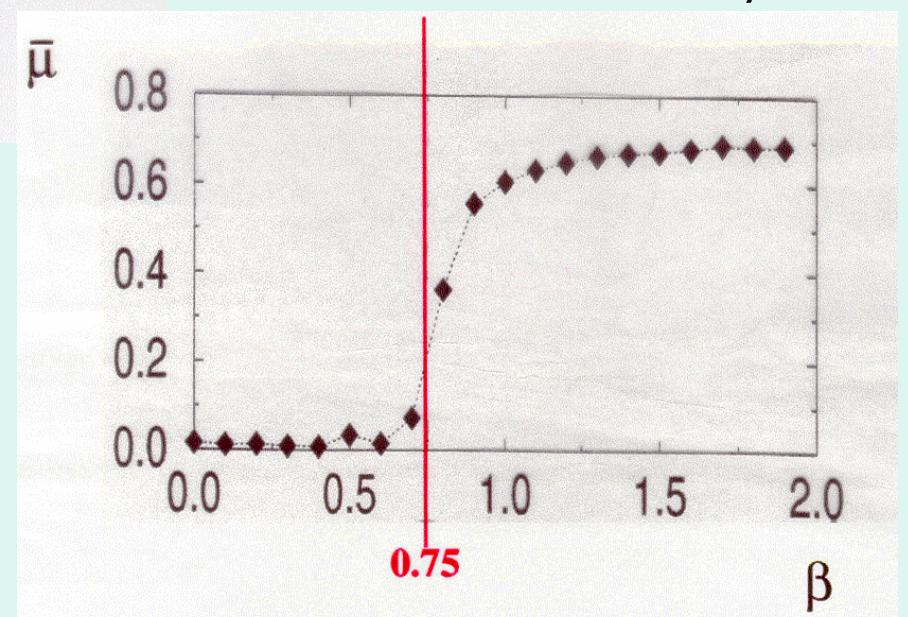
Eigenvalue spectrum



Phase diagram: two routes to swarming

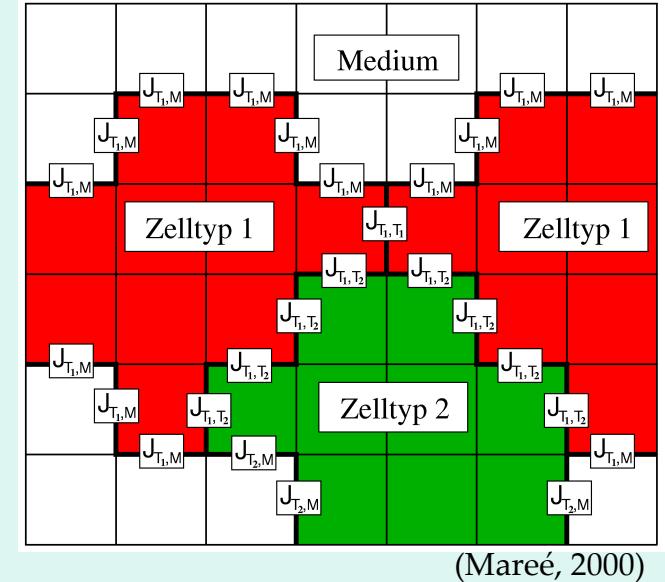


Statistical
analysis



Collective motion of rod-shaped Myxobacteria: Cellular Potts model

- * Discrete in time and space
- * Approximation of the rod-like cell shape
- * Hamiltonian: free energy of a lattice configuration
 - Interaction energy:
Local Interaction at cell boundaries
 - Energetic constraints
- * Simulation using Metropolis-Kinetics
 - Minimization of free energy
 - Stochastic perturbations
(depending on ‘temperature’ T)



A cellular Potts model for rod-shaped cells (J. Starruss)

Hamiltonian: Free energy of the system

Sums 1.) interaction energy, 2.) area constraint
and 3.),4.) deformation energies (length, curvature)

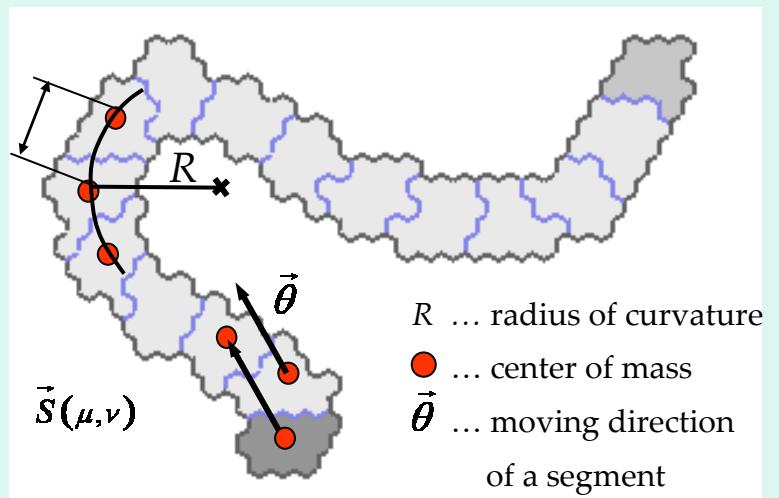
$$\begin{aligned} \mathcal{H} = & \sum_{\langle i,j \rangle \text{ Nachbarn}} \frac{1}{2} J_{\sigma(i), \sigma(j)} \\ & + \lambda \sum_{\mu=1}^c \sum_{\nu=1}^s \left(a(\mu) - A_s \right)^2 \\ & + \zeta \sum_{\mu=1}^c \sum_{\nu=1}^{s-1} \left(|\vec{s}(\nu+1) - \vec{s}(\nu)| - D_s \right)^2 \\ & + \xi \sum_{\mu=1}^c \sum_{\nu=1}^{s-2} 1 / R(\vec{s}(\nu), \vec{s}(\nu+1), \vec{s}(\nu+2))^2 \end{aligned}$$

Numerical Simulation:

with Metropolis kinetics
based on the change in Hamiltonian
and the propelling gradient ΔD .

$$\begin{aligned} \Delta H' &= \Delta H + \Delta D \\ \text{with } \Delta D &= \omega \left(\overrightarrow{\text{copy}} * \vec{\theta}(\sigma) + \overrightarrow{\text{copy}} * \vec{\theta}(\sigma') \right) \end{aligned}$$

Approximation of the **rod cell shape**
By a row of segments which consist of a set
automaton nodes.

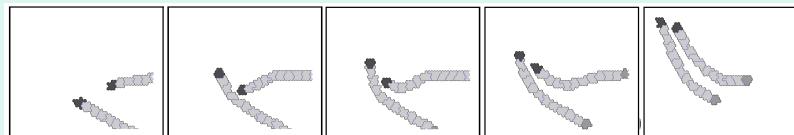


$\sigma = (\mu, \nu)$... state of an automaton cell (μ = cell, ν = segment)	
$\vec{s}(\mu, \nu)$... center of mass	s ... number of segments
$a(\mu, \nu)$... area	A_s ... optimal segment volume
$\theta(\mu, \nu)$... moving direction	D_s ... optimal segment distance
$J_{\sigma, \sigma'}$... interaction energy	$\overrightarrow{\text{copy}}$... direction of a single update

Roots: Glazier, Graner, Savill, Maree,...

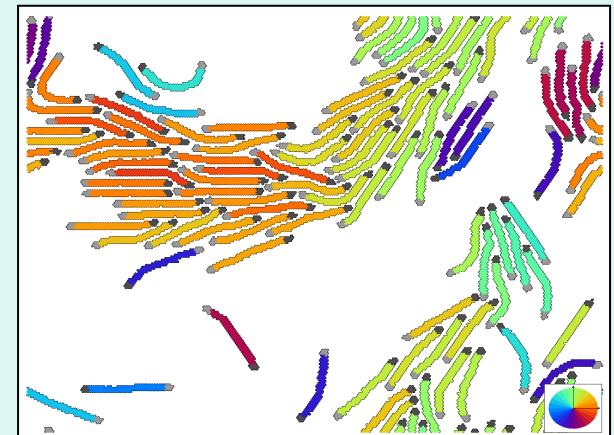
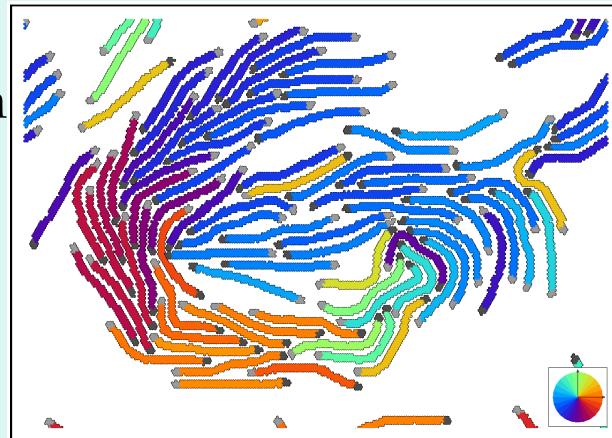
Results: Formation of cell patterns

Alignment of cells at the microscopic level leads to macroscopic patterns.

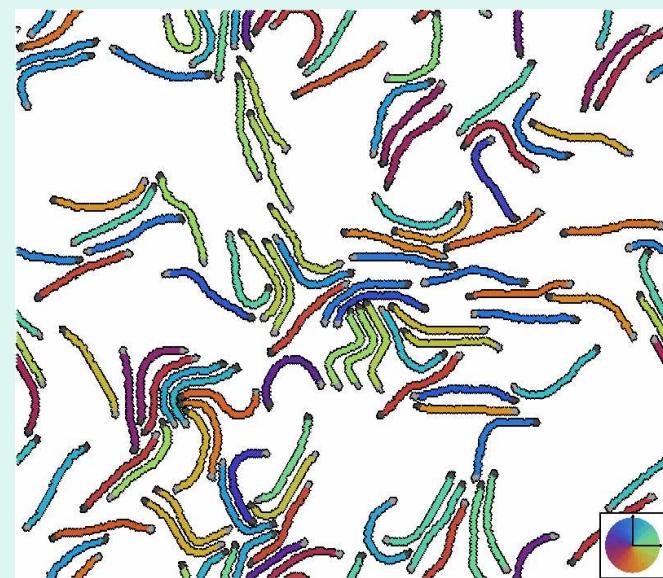
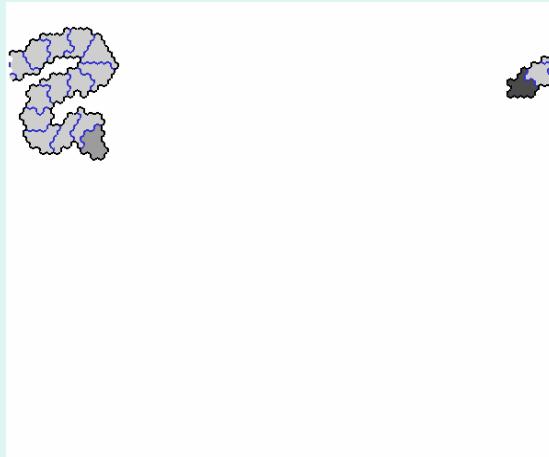


Temporal stable **swarming** patterns form due to multiple alignments and the cell arrangement in arrow formation.

Swarm collisions can afford unstable **vortex** patterns, the base pattern of the fruiting body



Simulations

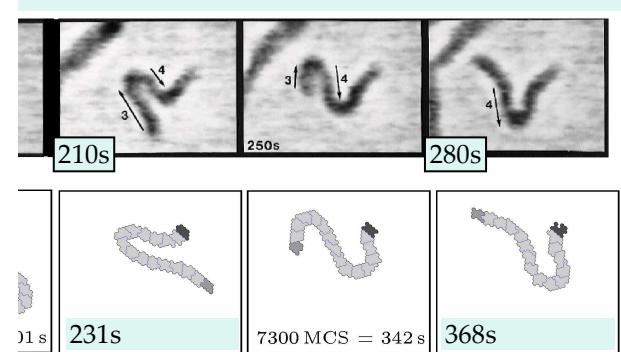
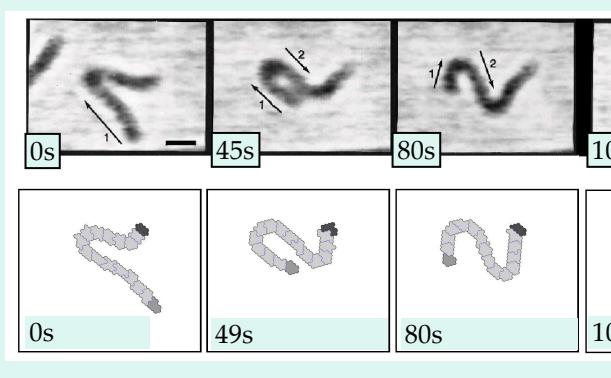


Parameter estimation

Biological parameters for *Myxococcus xanthus*

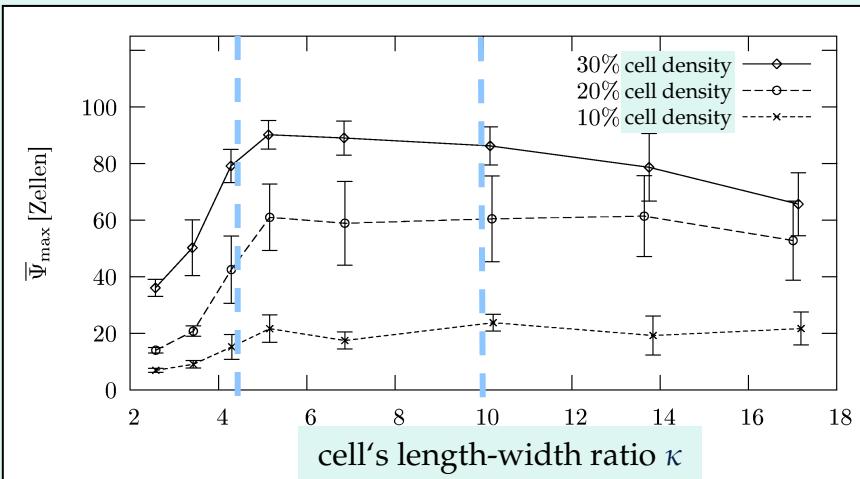
- Ratio of **stiffness** and **velocity** of a cell

Fixing a cell at the top leads to a snake-like cell motion

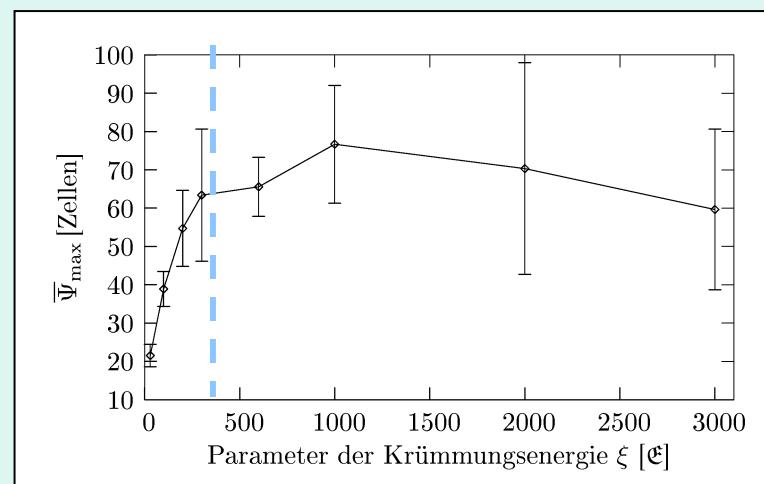


Results: competence to form swarms

- $\bar{\Psi}_{\max}$ - temporal mean of maximum swarm size in “the final state”



cell stiffness



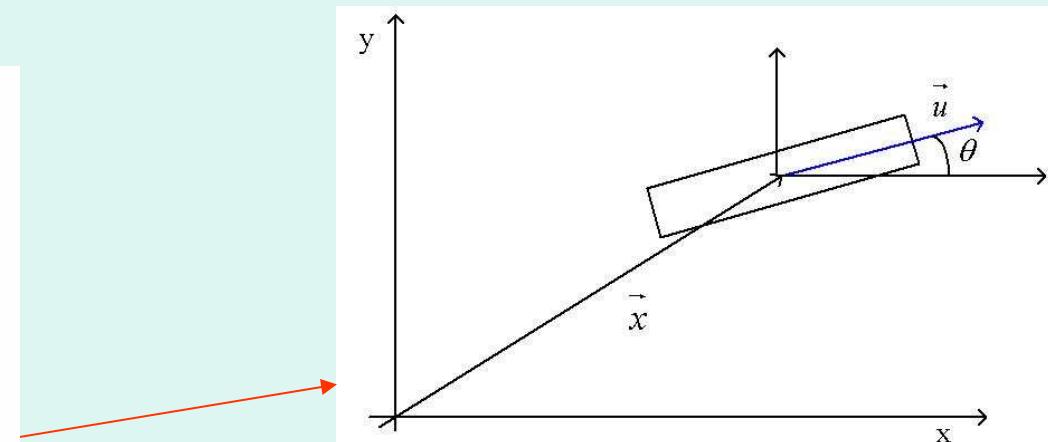
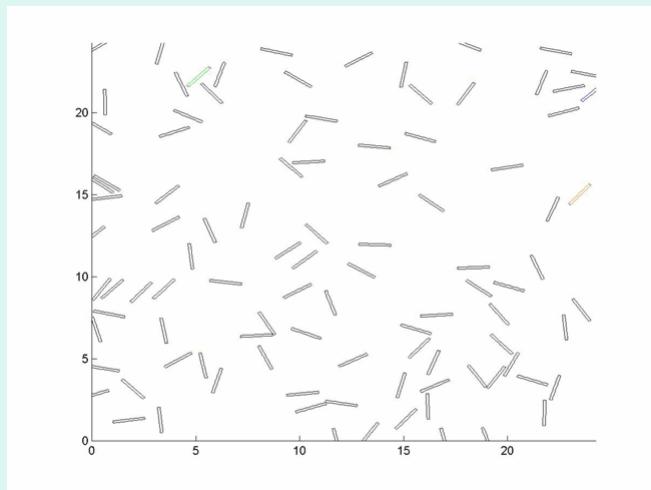
- Intense swarm formation at $\varepsilon > 4$
- Length/width ratio of *Myxobacteria* cells is optimal

- Intense swarm formation at $\xi > 300$ ϵ
- Cell stiffness obtained for *Myxococcus xanthus* is almost optimal

Off-lattice model (F. Peruani, M. Bär)

Bacterium representation

The bacteria inside the box:



Position: x, y
Orientation: Θ

Equations of motion

We consider the over-damped situation in which we have:

Self-Propelling force

With interactions
and with noise

$$\left\{ \begin{array}{l} (v_{\parallel}, v_{\perp}) = \left(\frac{1}{\zeta_{\parallel}} (R_{\parallel}(t) + F + F_{Inter_{\parallel}}), \frac{1}{\zeta_{\perp}} (R_{\perp}(t) + F_{Inter_{\perp}}) \right) \\ \frac{d\theta}{dt} = \frac{1}{\zeta_R} (\tilde{R}(t) + M_{Inter}) \end{array} \right.$$

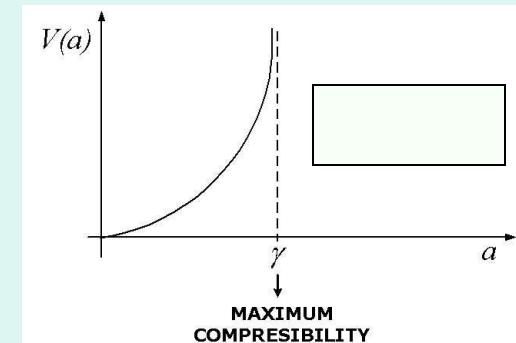
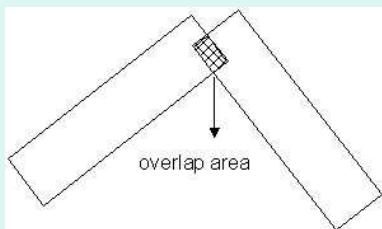
Interactions

$R_{\parallel}, R_{\perp}, \tilde{R}$ are white noises!

Off-lattice model

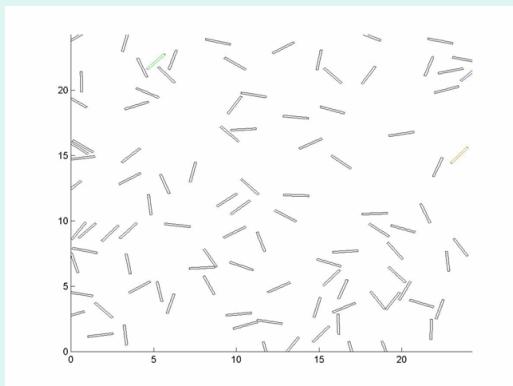
The Interactions

- Particles interact by soft vol. exclusion.
- The potential avoids interpenetration of bacteria causing *torque* and *force*.
- The potential depends on the overlapping area.
- β controls the stiffness of the particle.
- \tilde{C} is the interaction strength.

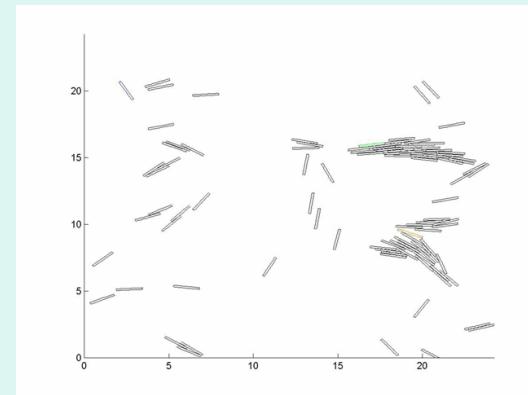


$$V(\vec{x}, \theta, \vec{x}', \theta') = \tilde{C} \left\{ \frac{1}{(\gamma - a(\vec{x}, \theta, \vec{x}', \theta'))^\beta} - \frac{1}{\gamma^\beta} \right\}$$

Simulations



Initial condition



"steady state"

We propose a *mean field approximation* which describes the system in terms of a time-dependent cluster size distribution $\{n_j(t)\}_{j=1}^{\infty}$

This description neglects two important facts:

- The existence of geometrically different cluster structures of the same size
- The existence of spatial fluctuations

We make three more assumptions:

- The total number of bacteria in the system is conserved
- We consider only binary cluster collisions: $C_i + C_j \longrightarrow C_{i+j}$
- A probability of spontaneously suffering a fission: $C_j \longrightarrow C_{j-1} + C_1$

The evolution equation for the cluster size distribution

$$\dot{n}_1 = 2 \frac{\tilde{V}}{R} \sqrt{2} n_2 + \sum_{k=3}^N \frac{\tilde{V}}{R} \sqrt{k} n_k - \sum_{k=2}^{N-1} \tilde{V} \sigma_0 \left(\sqrt{k} + 1 \right) \frac{n_k n_1}{V}$$

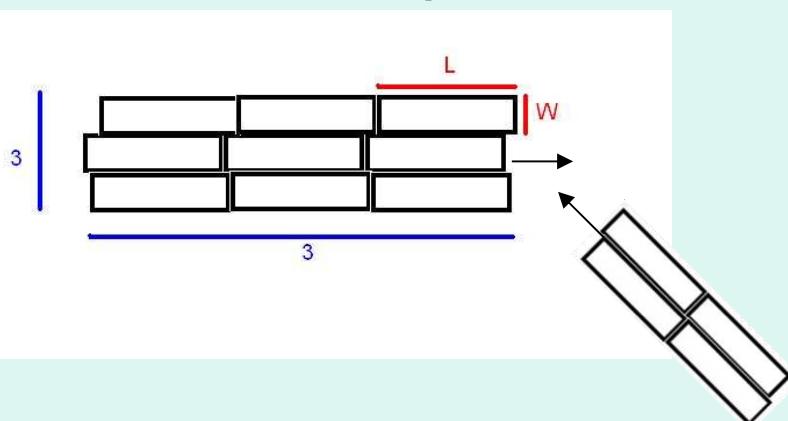
$$\dot{n}_j = \frac{\tilde{V}}{R} \sqrt{j+1} n_{j+1} - \frac{\tilde{V}}{R} \sqrt{j} n_j - \sum_{k=1}^{N-j} \tilde{V} \sigma_0 \left(\sqrt{k} + \sqrt{j} \right) \frac{n_k n_j}{V} + \sum_{k+l=j} \left(1 - \frac{1}{2} \delta_{k,l} \right) \tilde{V} \sigma_0 \left(\sqrt{k} + \sqrt{l} \right) \frac{n_k n_l}{V}$$

$$\dot{n}_N = - \frac{\tilde{V}}{R} \sqrt{N} n_N + \sum_{k+l=N} \left(1 - \frac{1}{2} \delta_{k,l} \right) \tilde{V} \sigma_0 \left(\sqrt{k} + \sqrt{l} \right) \frac{n_k n_l}{V}$$

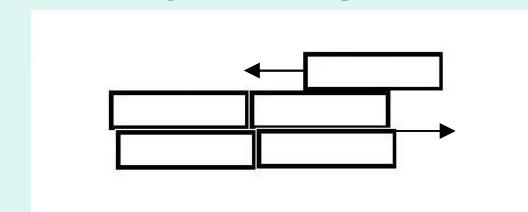
$$\tilde{V} \sigma_0 \left(\sqrt{k} + \sqrt{l} \right) \frac{n_k n_l}{V} = coll$$

$$\frac{\tilde{V}}{R} \sqrt{j} n_j = desint$$

collisions per unit time



disintegrations per unit time

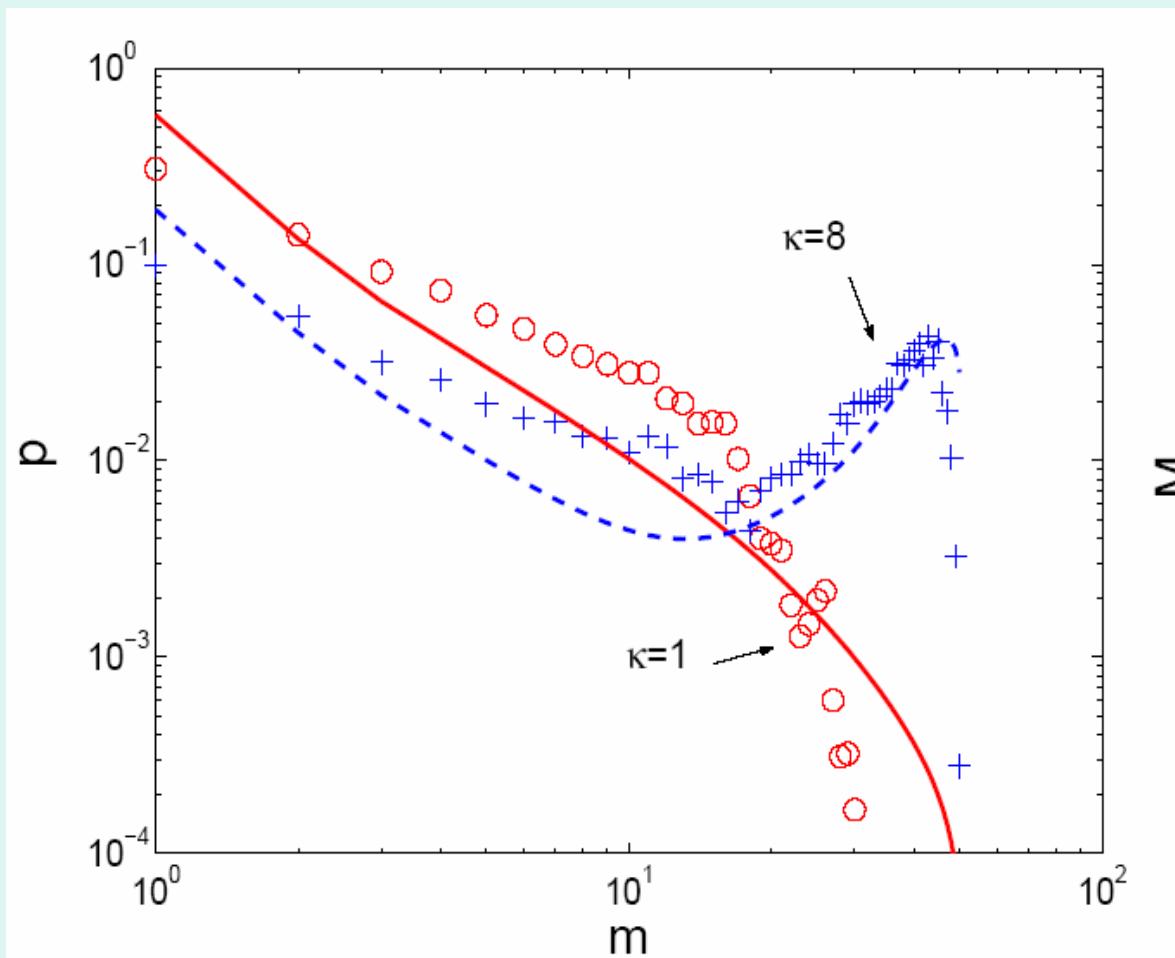


Key parameter of the set of equations:

κ

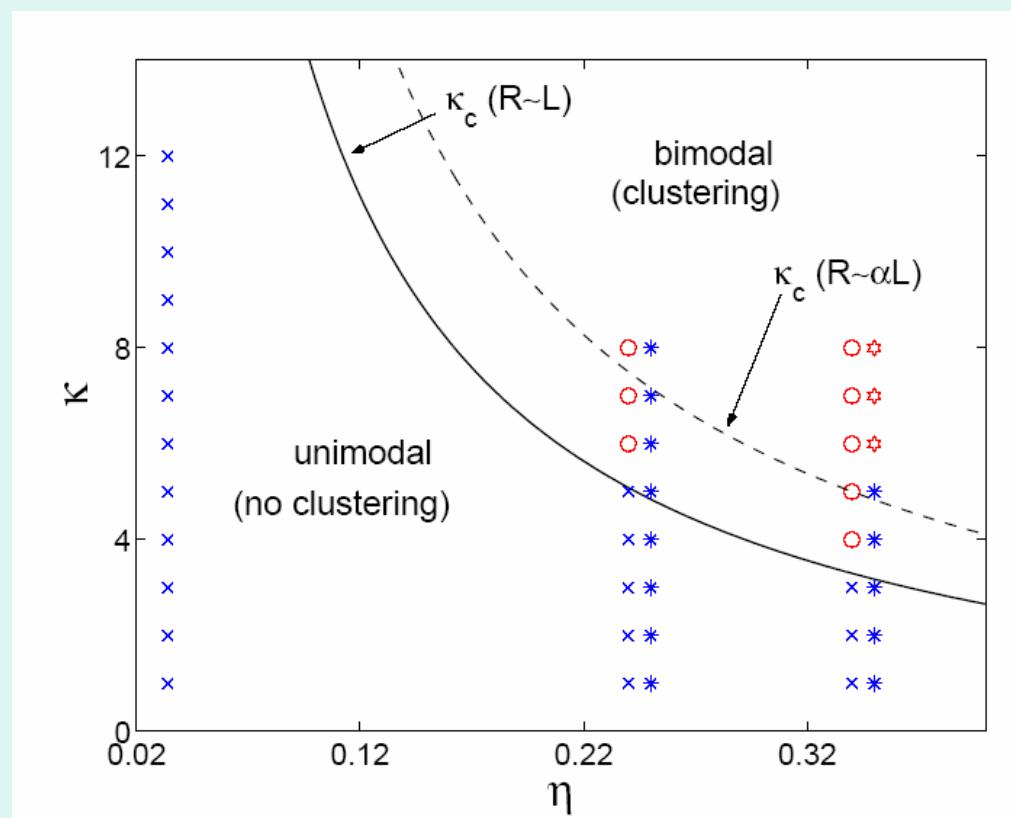
$$\sigma_0 \sim L + W = \sqrt{a} \left(\sqrt{\kappa} + \frac{1}{\sqrt{\kappa}} \right) \quad R \sim L = \sqrt{a\kappa}$$

Integrating the N previous equations we obtain a good agreement with the simulations:

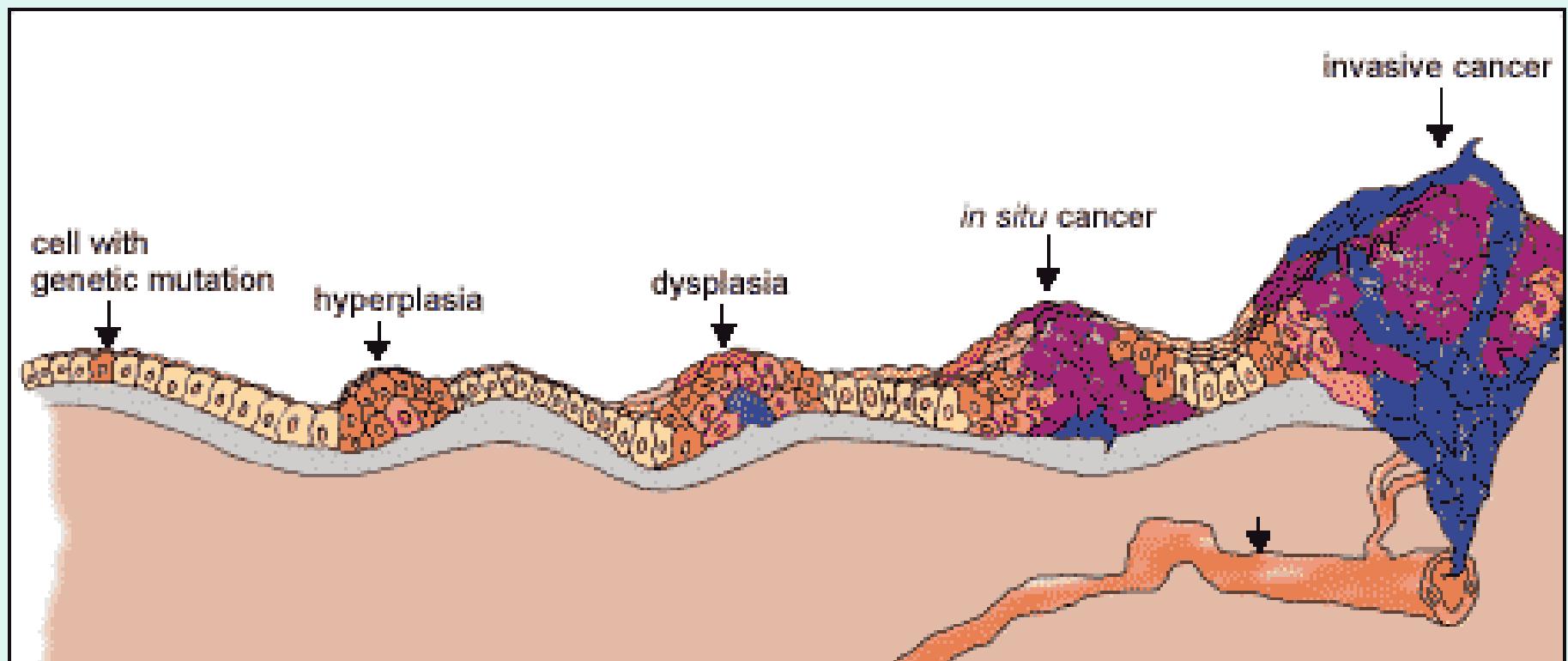


Phase diagram of the problem:

$$\kappa_c = \frac{C}{\eta} - 1$$

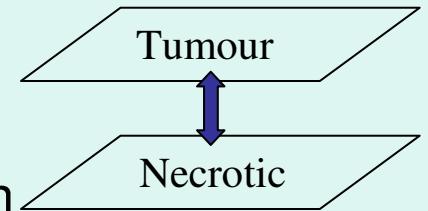


Cancer development



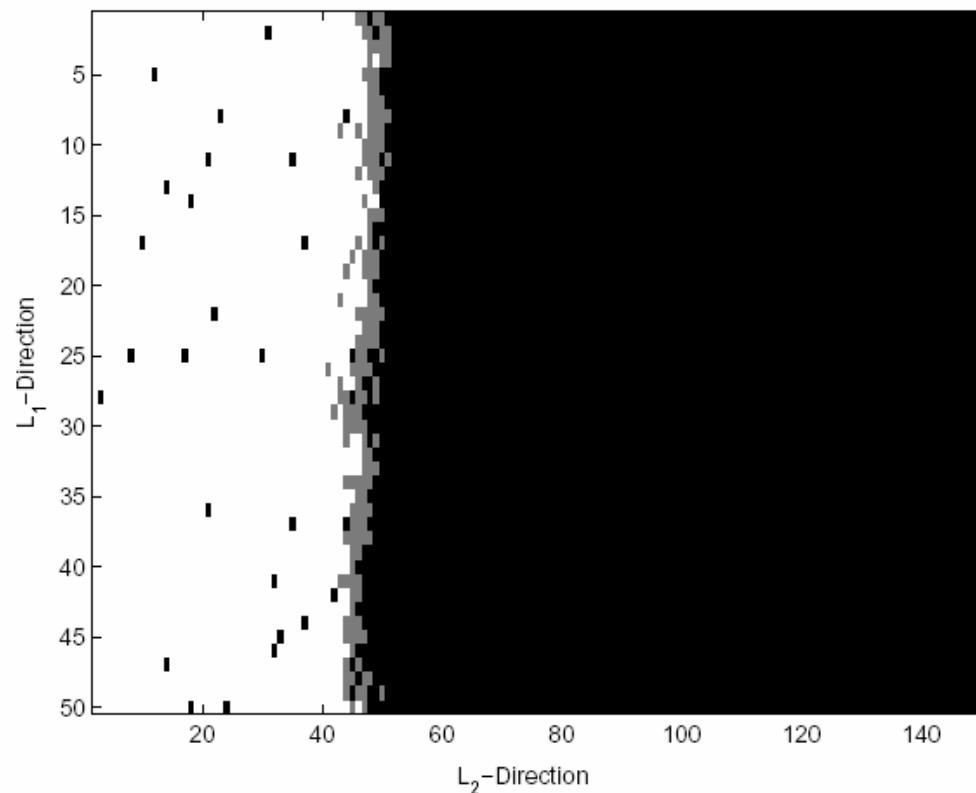
Invasion model

- We model explicitly two cell populations: **cancer** and **necrotic** particles (cells). They interact on 2 parallel lattices
- Cell reactions are probabilistic rules that control cancer and necrotic cell populations.
- Two processes are considered: *mitosis*, *necrosis* with given rates r_M , r_N . Each process is depending on the local node density thresholds θ_M, θ_N



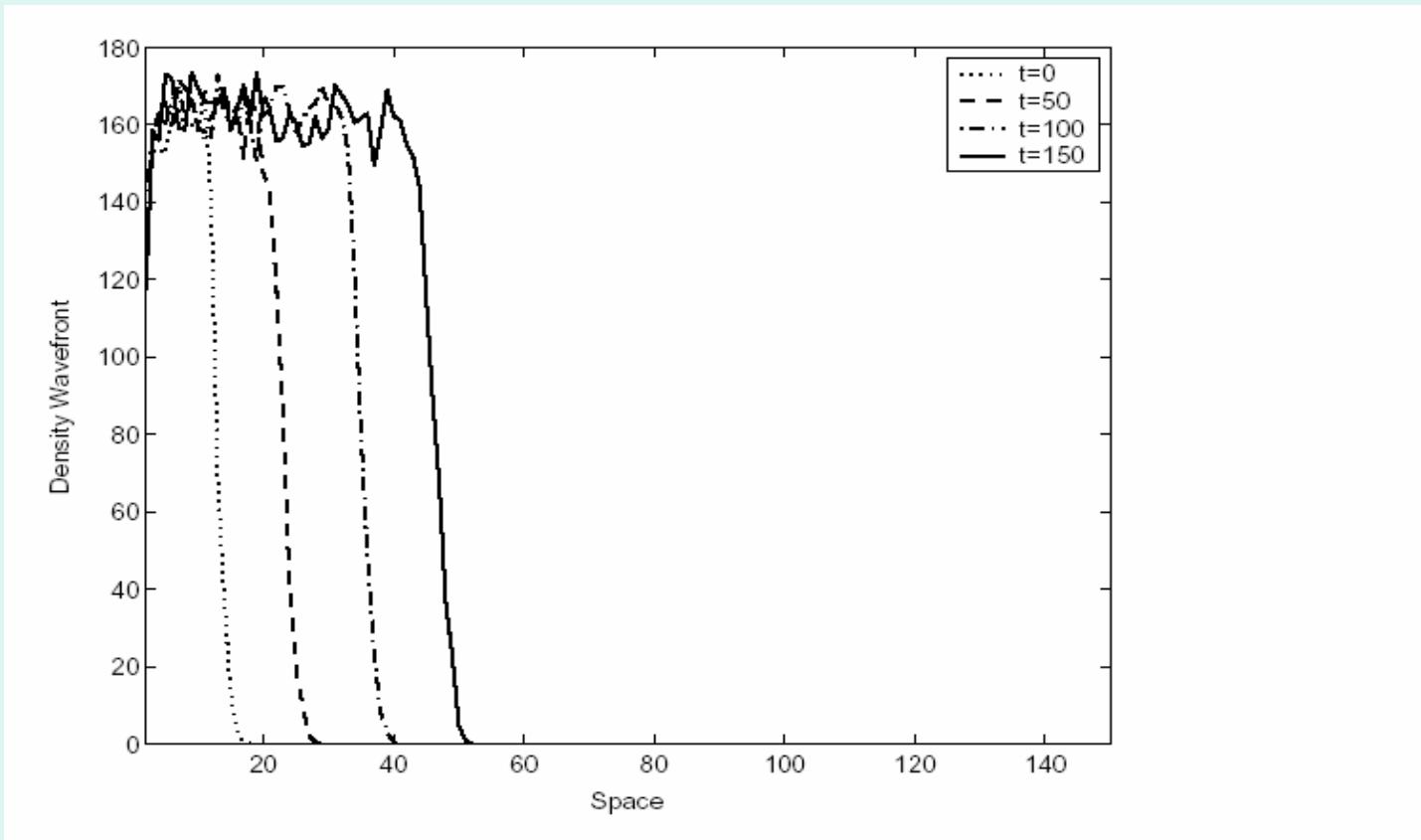
$$P(n_C(r, k) \rightarrow n_C^R(r, k)) := \begin{cases} \tilde{b}, & \text{w. p. } r_M \text{ if } n_C(r, k) \leq \theta_M \\ 0, & \text{w. p. } r_N \text{ if } n_C(r, k) \geq \theta_N \\ n_C(r, k), & \text{else} \end{cases}$$

Simulation



(Babis Hatzikirou)

Invasion



From Mean Field Analysis to Macroscopic Equations

- Mean field assumption à Lattice Boltzmann Equation
- Linearization: around the fixed point (0,0), i.e. the empty lattice (corresponds to healthy tissue in which the tumour invades)
- Fourier transformation
- Dispersion equation: For small wave numbers and small mitotic rates
- The derived dispersion equation corresponds to the following reaction-diffusion PDE

$$\frac{\partial u_C}{\partial t}(\mathbf{x}, t) = D \nabla^2 u_C(\mathbf{x}, t) + r_M u_C(\mathbf{x}, t)$$

Speed of travelling fronts

- We reduce the R-D equation to 1D
- By standard methodology, we calculate the minimal travelling wave speed

$$c_{min} = 2\sqrt{Dr_M} = \sqrt{r_M}$$

Travelling front: Simulation and MF analysis

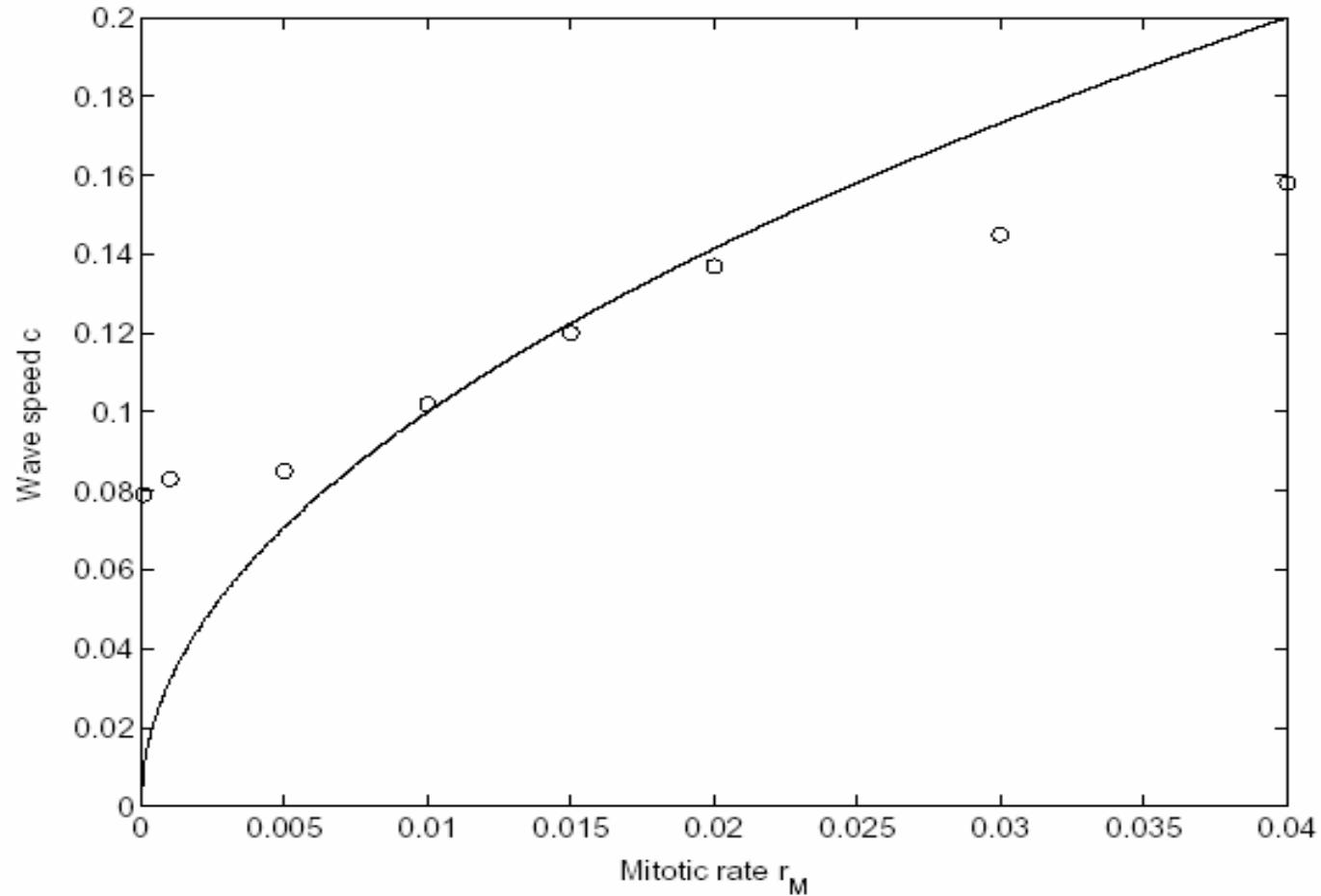
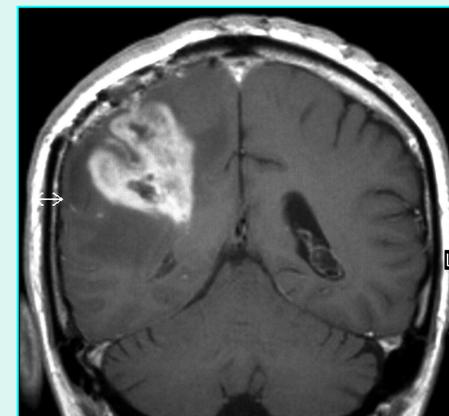
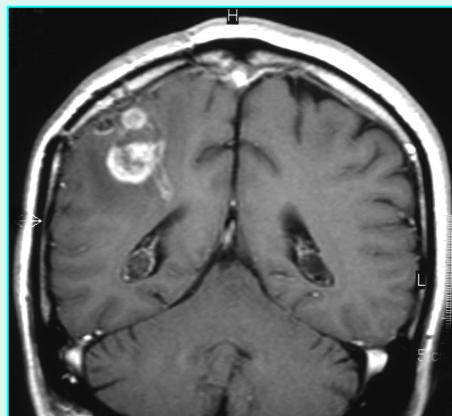
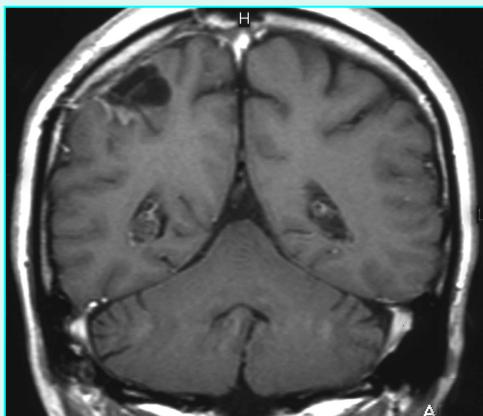


Fig. 5. The graph shows the comparison between the simulated (circles) and the analytically calculated (line) values of the tumour front speed. We observe that the mean field approximation correctly predicts the front speed for a small range of the mitotic rate r_M (the necrotic rate for the simulation was and $r_N = 0.7$).

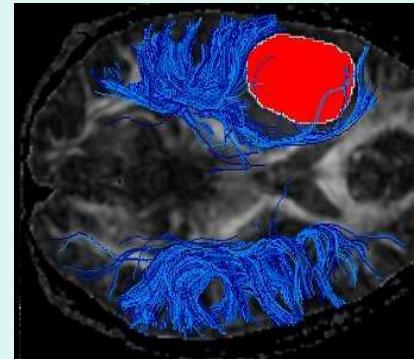
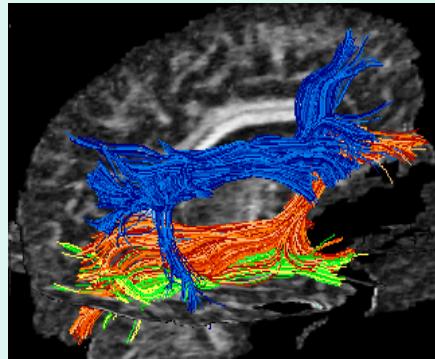
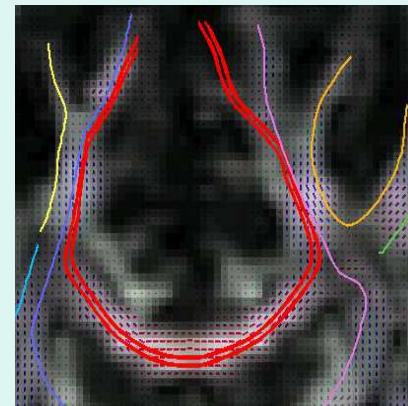
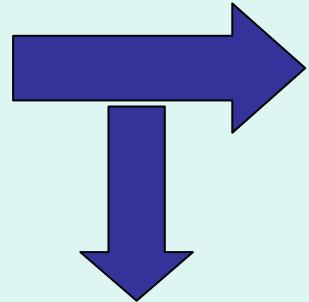
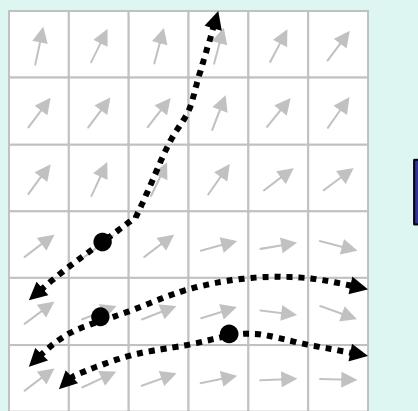
Glioma invasion: biomedical problem

- Glioblastoma multiforme (GBM) is the most frequent and malignant primary brain tumour

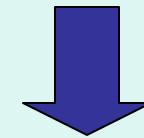


- Current imaging techniques identify max 90% of the tumour
- Usual therapy is resection followed by chemotherapy. Tumour recurrence is almost sure (see picture) due to the „invisible“ part

Brain Tumors I



Diffusion Tensor Imaging allows for identification of brain fiber tracks

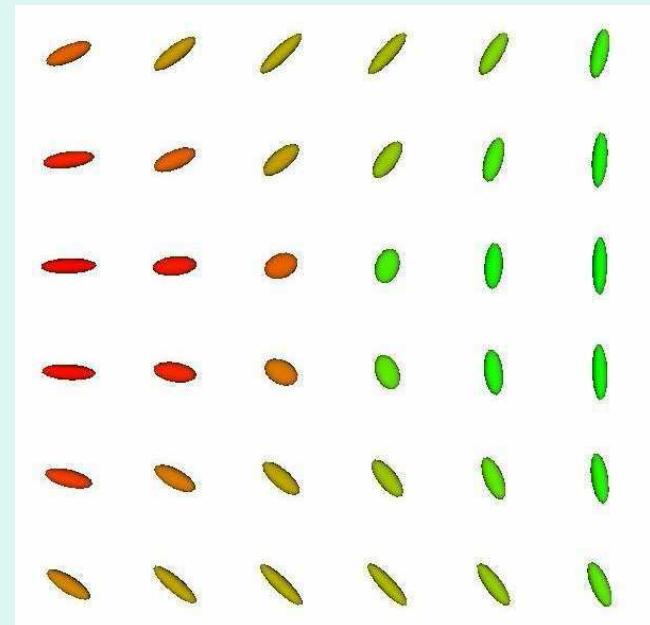


Tensor field data

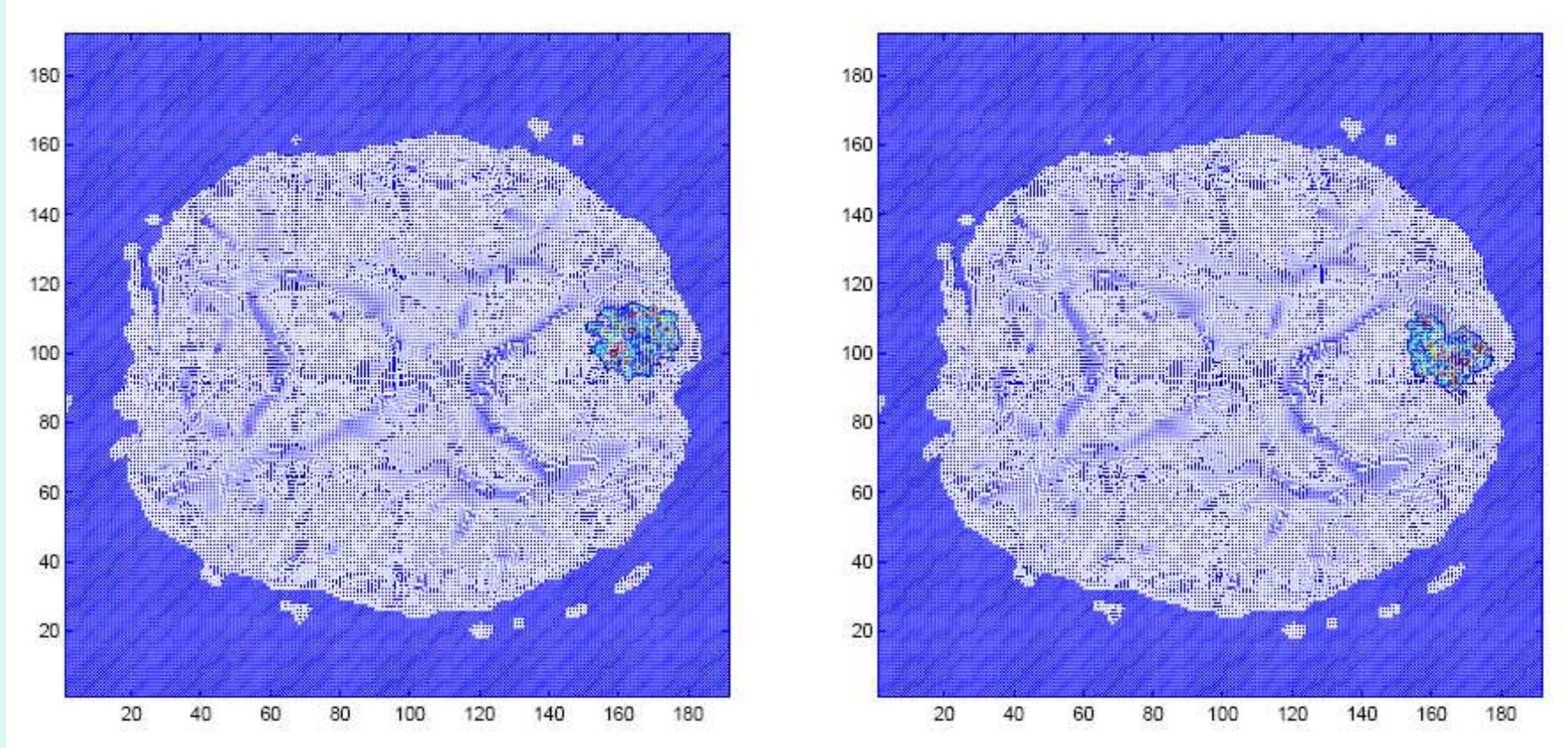
Model for cell migration in heterogeneous environments

(see poster B. Hatzikirou)

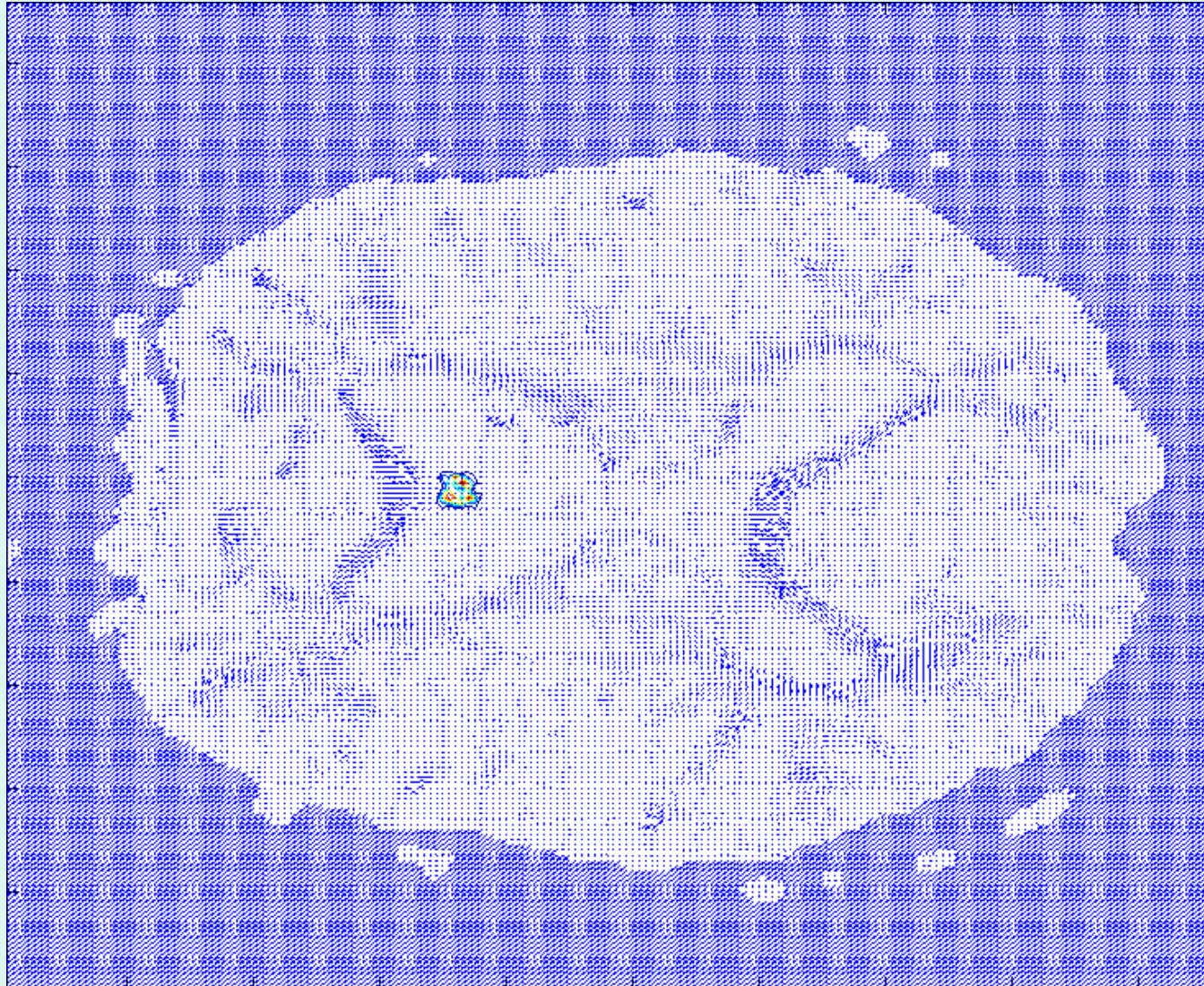
- Alignment process in a fibrillar environment of a non-proliferative cell population
- Representation of environment by a 2nd rank tensor field
- Preprocessing: we extract the principal eigenvector of the tensors at each point.



Brain Tumors II



Simulations



*LGCA,
ext. Field
(DTI Data)*

Can computers/simulations help?

- **Organization principles** of cancer growth
- Simulation of **treatments**
- **Carcinogenesis:** evolutionary models
(mutations, microenvironment)
à *Game-theoretic perspectives on somatic cancer evolution, D. Basanta, AD, 2007, to appear*
- **Pattern recognition:** cancer surface, scaling analysis
- **Genetic analysis:** bioinformatics à cancer genes

Modeling pattern formation of interacting cell systems with cellular automata

- ***Self-organization:*** Single cell behavior à cooperative behavior
- ***Simulations & analysis:*** mean-field analysis, linear stability analysis...
- ***Interactions:*** Local (e.g. adhesion, contact inhibition) and nonlocal (e.g. chemotaxis)
- ***Resolution:*** cell size and the fastest biological process to be modeled determine the spatio-temporal resolution
- ***Algorithm:*** easy parallel. (large cell no.)

Cellular Automaton Modeling of Biological Pattern Formation

Characterization, Applications, and Analysis

Andreas Deutsch and Sabine Dörmann

This book focuses on a challenging application field of cellular automata—pattern formation in biological systems, such as the growth of microorganisms, dynamics of cellular tissue and tumors, and formation of pigment cell patterns. These phenomena, resulting from complex cellular interactions, cannot be deduced solely from experimental analysis, but can be more easily examined using mathematical models, in particular, cellular automaton models.

While there are various books treating cellular automaton modeling, this interdisciplinary work is the first one covering biological applications. The book is divided into three parts: Part I deals with general principles, theories, and models of pattern formation; Part II examines cellular automaton modeling; and Part III explains various applications. The models and analytic techniques described may be extended to other exciting applications in biology, medicine, and immunology.

Key topics and features:

- Provides an introduction and historical account of the principles of biological pattern formation (morphogenesis)
- Gives an overview of mathematical modeling approaches to morphogenesis, and an introduction to cellular automata and analytic techniques
- A supplementary web-based Java applet—*Cellular Automaton Simulator*—enables interactive simulation of various cellular automaton applications described in the book; available on the internet at: www.biomodeling.info
- Self-contained presentation is accessible to a broad audience; only basic calculus and linear algebra are required
- Careful balance of theory, models, and applications useful to both experimentalists and theoreticians
- Includes suggestions for further research topics

The book is aimed at researchers, practitioners, and students in applied mathematics, mathematical biology, computational physics, bioengineering, and computer science interested in a cellular automaton approach to biological modeling. The book's accessible presentation and interdisciplinary approach make it suitable for graduate and advanced undergraduate courses and seminars in mathematical biology, biomodeling, and biocomputing.

Birkhäuser

ISBN 0-8176-4281-1
www.birkhauser.com



Deutsch
Dörmann

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of Biological Pattern Formation

*Modeling and Simulation in
Science, Engineering and Technology*

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*Characterization,
Applications, and Analysis*

Andreas Deutsch
Sabine Dörmann

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2005

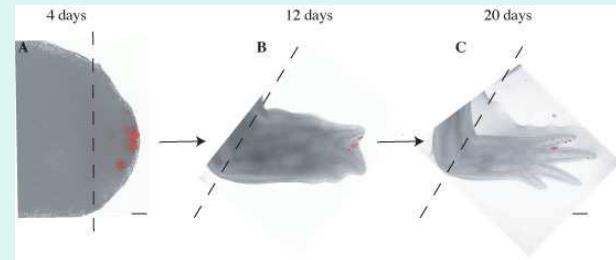
Outlook

- ***Microorganisms***



Myxococcus x.

- **Regeneration**



- **Mathematical analysis:**
Comparison of cell-based models

Thanks

- D. Basanta, **B. Hatzikirou**, F. Peruani,
J. Peter, J. Starruss (Dresden)
- M. Bär (Berlin)
- S. Dormann (Frankfurt)
- L. Soegaard-Andersen (Marburg)

Thank you very much!