Rigorous analysis of stochastic particle based models in developmental biology

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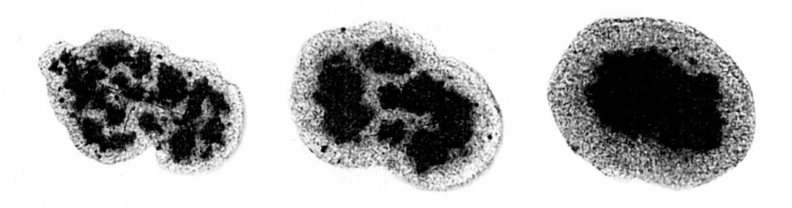
18.6.2009

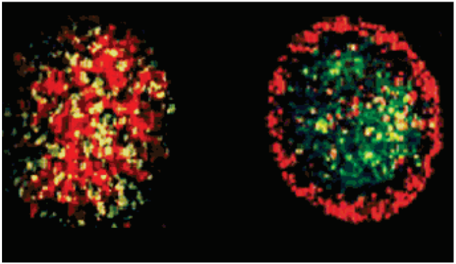
Contents

Sorting experiments: dissociated embryonic tissue



Beysens et al., 2000
→ chicken embryonic pigmented epithelial (dark) and neural retinal (light) cells, 17, 42 and 73 hours after mixing

Sorting experiments: any pair of tissues sort



Forgacs and Foty, 2004
→ sorting of two genetically transformed Chinese hamster ovary cell populations with ∼ 50% difference in N-cadherin expression, 4h and 24 h after mixing

Observations on different scales

- tissue scale: sorting
  - dissociated embryonic cells preferably associate with cells of same tissue
  - the kinetics of sorting proceeds via the coalescence of small islands of cells into larger ones
  - almost any pair of cells of distinct types segregates into distinct tissues
  - **Remarkable similarity to the de-mixing of immiscible liquids**

DAH (Steinberg, 1963): Quantitative differences in intercellular adhesion cause 'surface tension'. Mobile cells arrange themselves such that surface tension is minimized.

Observations on different scales

- cell scale: adhesion + migration
  - cells stick together
  - cell-type dependent strength of bonds
  - membrane interaction between neighboring cells
  - cells in a tissue are mobile
- protein scale:
  - very complex system of chemical reactions, various types of bonds
  - intercellular contacts are mediated by cell surface molecules which function in various intracellular processes

Hypothesis: Regulated spatiotemporal modulation of adhesion is driving force for major morphogenetic transitions during morphogenesis

Observations on different scales

- tissue scale: sorting
  - heterotypic cell populations in composite aggregates segregate into spatially confined homotypic cell clusters
  - DAH: measurable tissue surface tensions correspond to the mutual sorting behavior
- cell scale: 'adhesion' + migration
  - cell-type dependent cell affinity
  - membrane interaction between neighboring cells
  - cells in a tissue are mobile

Problem: What is the mechanism that couples intercellular adhesion and surface tension and what is the impact of cell migration?

Equilibrium models

e.g. Glazier and Graner, 1993; Mouchizuki et al., 1997:

- discrete space (lattice)
- (surface) energy functional (Hamiltonian) describes the assumed interdependence structure within cell aggregates
- assumption: typical sorted cell configurations are those with minimal surface energy
- exploration of equilibrium configurations by Markov chain Monte Carlo methods
- re-interpretation of the auxiliary Markov chain as a model for the system's temporal development

Equilibrium models characterize the systems state once the temporal development has stabilized.

Modeling

- Starting point: (qualitative) concept of the dynamical properties on the cellular scale
  - mobile cells (short-range random movement)
  - cell motility biased by (differential) adhesion: cell mobility is the lower the more the cell sticks to its neighbors
  - spatial competition
- Intention:
  - translate the above ideas into a precise *dynamical* model
  - predict the longtime emergent behavior on the tissue scale
  - (qualitatively) describe the geometry of cell segregation depending on the intercellular adhesion parameters
- Modeling assumptions:
  - continuous time
  - discrete space (square lattice)
  - smallest length scale $\sim$ cell diameter
  - constant cell numbers

Dynamics: random cell movement

- $S \subset \mathbb{Z}^d$, $d = 2, 3$, lattice
- $W = \{0, ..., n\}$, local state space,
  $n = 2$: 0 ... empty, 1 ... green, 2 ...red
  $n = 1$: 0 ... green, 1 ... red

A single type-w-cell performs SRW on S with rate 1.
$\longrightarrow$ transition rate matrix $p = (p(x, y)_{x,y \in S}$, where

$$p(x, y) = \begin{cases} 1, & |x - y| = 1, \\ 0, & \text{otherwise.} \end{cases}$$

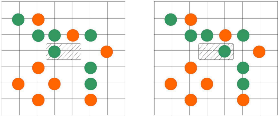
Dynamics: spatial competition

- $\mathbb{X} = W^S$ configuration space
- transitions: $\eta \to \eta^{xy}$, where $x, y \in \mathbb{Z}^2$, $|x - y| = 1$,

$$\eta^{xy}(z) := \begin{cases} \eta(z), & z \neq x, z \neq y \\ \eta(y), & z = x \\ \eta(x), & z = y \end{cases}$$

- transition rates dependent on neighborhood configuration:

$$c_0(x, y, \eta) = \begin{cases} p(x, y), & \text{if } \eta(x) \neq \eta(y) \\ 0, & \text{otherwise} \end{cases}$$



Dynamics: transitions biased by differential adhesion

- symmetric cell-type dependent adhesion parameter $\beta = (\beta_{uv})_{u,v \in W}$ (weighted bonds)
- biased transition rates:

$$c(x, y, \eta) =$$

$$= c_0(x, y, \eta) \exp \left\{ - \sum_{z:|z-x|=1} \beta_{\eta(x),\eta(z)} - \sum_{z:|z-y|=1} \beta_{\eta(y),\eta(z)} \right\}$$

- boundary conditions: fixed/periodic

$\Rightarrow$ well-defined Markov process with state space $\mathbb{X} = W^S$
... **Cell Sorting Model (CSM)**

Long-time behavior

Given:

- $|S| < \infty$
- η_0 ... initial configuration
- ν_t ... distribution at time $t \geq 0$
- $\theta = |S|^{-1} N(\eta_0)$ with $N : \mathbb{X} \to \mathbb{N}^W : N_w(\eta) = \sum_{x \in S} \mathbf{1}_{\eta(x)=w}$
  ... cell density (conserved quantity)

Theorem

(V.-B. and Deutsch, submitted) There exists a Hamiltonian H such that

$$\lim_{t \to \infty} \nu_t = \mu^\theta$$

where μ^θ is the canonical Gibbs measure w.r.t. H given the cell densities θ.

Canonical Gibbs measures

- $H : \mathbb{X} \to \mathbb{R}$ ... Hamiltonian,

$$H(\eta) = - \sum_{\substack{x,y \in S \\ |x-y|=1}} \beta_{\eta(x),\eta(y)}, \quad \eta \in \mathbb{X}.$$

- μ^θ ... canonical Gibbs measure w.r.t. H given the cell density $\theta \in [0,1]^W$,

$$\mu^\theta(\eta) = Z^{-1}(\theta) \exp\{-H(\eta)\} \mathbf{1}_{|S|^{-1}N(\eta)=\theta}, \quad \eta \in \mathbb{X},$$

where

$$Z(\theta) = \sum_{\substack{\zeta \in \mathbb{X} \\ |S|^{-1}N(\zeta)=\theta}} \mu^\theta(\zeta).$$

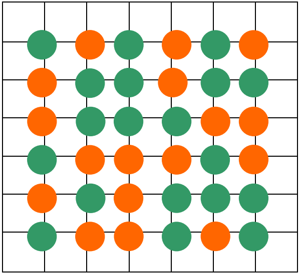
Detailed balance equation

(V.-B., submitted)

$$c(x,y,\eta)\exp\{-H(\eta)\} = c(x,y,\eta^{xy})\exp\{-H(\eta^{xy})\}, \quad x,y \in S, \eta \in \mathbb{X},$$

The fully occupied two-dimensional system

two interacting populations: $W = \{0, 1\}$



Phase segregation

- $\beta := \beta_{00} - 2\beta_{01} + \beta_{11}, \quad \beta_c = 1/2 \log(1 + \sqrt{2})$
- $p^*_\pm = \frac{1}{2}(1 \pm m(\beta))$ with $m(\beta) := \left[1 - (\sinh(2\beta))^{-4}\right]^{1/8}$ for $\beta > \beta_c$
- $S_N := [0, N-1]^2 \cap \mathbb{Z}^2$
- $p \in (0,1)$

- μ_N^θ ... canonical Gibbs measure on W^{S_N} w.r.t. H given the cell density $\theta = (1-p, p)$

Theorem

(Dobrushin et al., 1992) For any $\beta > \beta_c$, $p \in (p^*_-(\beta), p^*_+(\beta))$, there exists some curve $\gamma_{\beta,p}$ such that the ensemble $(\mu_N^\theta)_{N \in \mathbb{N}}$ exhibits asymptotic phase segregation along the curve $\gamma_{\beta,p}$.

Phase transition

Assumption : $\beta = \beta_{00} - 2\beta_{01} + \beta_{11} > 0$

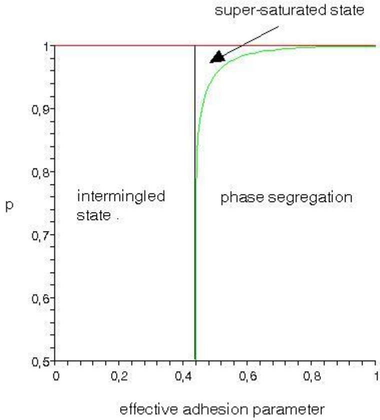
- $\beta \leq \beta_c$: no phase segregation, mixed configurations
- $\beta > \beta_c$: cell-density dependent geometry
  - $p > p^*_+$ or $p < p^*_-$: small islands of type-0 cells in large sea of type-1 cells
  - $p \in (p^*_-, p^*_+)$: two clear-cut separated regions consisting of virtually only one cell type

$\rightarrow$ *sorted* state

Result

Random cell migration + sufficiently differential adhesion which dampens cell motility ⇒ sorting.

Phase diagram



Geometry of typical sorted configurations

$$\beta = \beta_{00} - 2\beta_{01} + \beta_{11} > \beta_c, \quad p \in (p_-^*, p_+^*)$$

- The curve $\gamma_{\beta,p}$ separates two almost homo-typic regions.
- The volume proportion of these two regions is given by p.
- The (asymptotic) shape of the segregated regions, the so-called *Wulff shape*, is the solution of an iso-perimetric problem, that is $\gamma_{\beta,p}$ minimizes a functional called *total surface tension* among all closed self-avoiding rectifiable curves which enclose a given volume.
- There is a functional relationship between the adhesion parameters and the total surface tension functional.
- The shape of $\gamma_{\beta,p}$ sensitively depends on the shape of the considered bounded volume and the boundary conditions.

Sorting hierarchy

$$\beta = \beta_{00} - 2\beta_{01} + \beta_{11} > \beta_c, \quad p \in (p^*_-, p^*_+)$$

- Only the boundary conditions β_{ib} determine the sorting hierarchy.
- The cell type with less cell-boundary interaction sorts to the center of the aggregate.

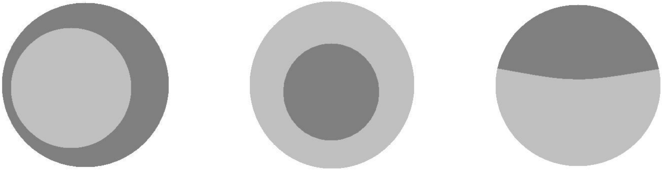


Figure: Sorting of type-0 cells (dark grey) and type-1 cells (light grey), $\beta_{0b} > \beta_{1b}$ (left), $\beta_{0b} < \beta_{1b}$ (middle), $\beta_{0b} \approx \beta_{1b}$ (right)

Discussion

- non-physical dynamical model
- minimal model
- new concept of intercellular adhesion; (Harris, 1976)
- functional relation between tissue surface tension and intercellular adhesion
- phase transition; (Shi et al., 2008; Steinberg, 1963)
- typical patterns: sorted, unsorted, (checkerboard)
- sorting hierarchy; (Ninomiya and Winklbauer, 2007)
- significance of the behavior at the boundary; (Krieg et al., 2008)

- dynamical behavior on characteristic scales
- growing domains
- more than two cell types

Collective Migration

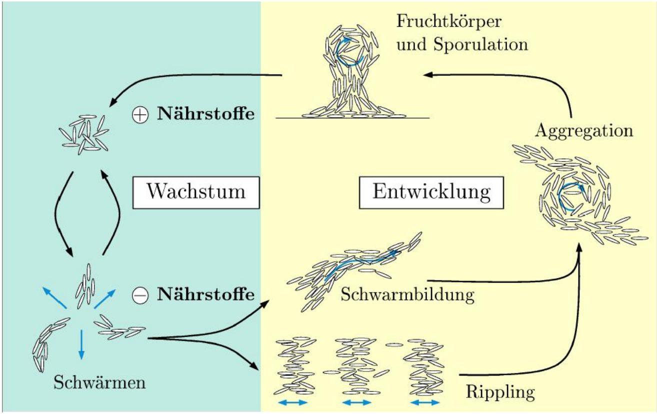
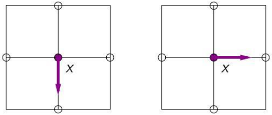


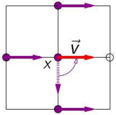
Figure: Life cycle of Myxococcus xanthus.

IPS model

- $S \subset \mathbb{Z}^d$, $d = 2, 3$, lattice
- $W = \{0, \pm e_1, \ldots, \pm e_d\}$, local state space
  - $w = 0$: no cell
  - $w \neq 0$: cell with orientation w
- Dynamics: alignment and oriented migration

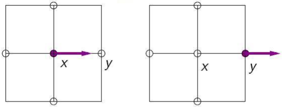
Alignment





$$\sum_{y:\,||y-x||=1} v \circ \eta(y)$$

Migration



konstante Geschwindigkeit m

Dynamics: alignment and oriented migration

- alignment parameter $\gamma \geq 0$ (sensitivity)
- migration parameter $m \geq 0$ (mobility)

$$c_T(\eta, v) := \begin{cases} m, & \tau_T(\eta, v) \text{ is a migration;} \\ \exp\left\{\gamma \sum_{y:\|y-x\|=1} v \circ \eta(y)\right\} & \\ & \tau_T(\eta, v) \text{ is an alignment;} \\ 0, & \text{otherwise.} \end{cases}$$

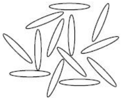
- boundary conditions: periodic

$\Rightarrow$ well-defined Markov process with state space $\mathbb{X} = W^S$
... **Collective Migration Model (CCM)**

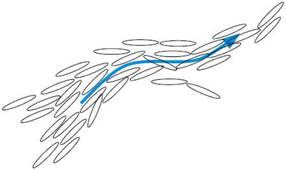
Simulation

(Klauß and V.-B., 2009)

- $d = 2$;
- time-discrete simulation algorithm: embedded Markov chain (Klauß and V.-B., 2008);
- order parameters to distinguish *global disorder* and *global alignment*



global disorder



global alignment

Order parameters

- mean orientation

$$MO : \mathbb{X} \to [0,1] : MO(\eta) = \frac{1}{N(\eta)} \left\| \sum_{x \in S} \eta(x) \right\| ;$$

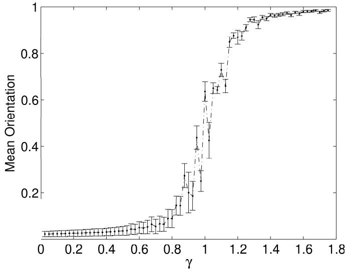
- orientation entropy

$$E : \mathbb{X} \to [0,1] : E(\eta) = - \sum_{i=1}^{4} \frac{h_i(\eta) \ln h_i(\eta)}{\ln(4)} ;$$

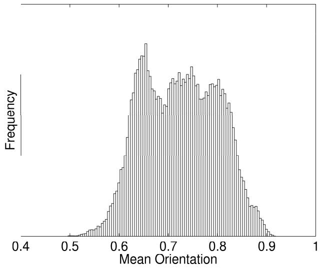
global disorder	global alignment
$E \approx 1, \; MO \approx 0$	$E \approx 0, \; MO \approx 1$

Longtime behavior – high cell density

$N = 24,\ \varrho = 0.7,\ m = 100$



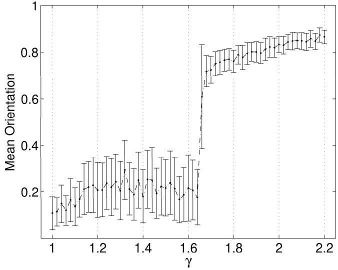
Phase transition in MO as γ is varied;

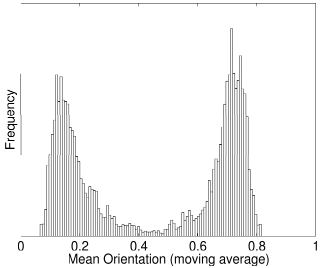


Unimodal distribution of MO for critical $\gamma = 1.1$.

Longtime behavior – low cell density

$N = 24,\ \varrho = 0.09,\ m = 100$





Phase transition in MO as γ is varied;

Bimodal distribution of MO for critical $\gamma = 0.7$.

Results and Discussion

- collective migration is observed for sufficiently large γ, ϱ, *m* $\longrightarrow$ minimal model;
- disorder persists for small γ, ϱ, *m*;
- complex interplay of parameters;
- different types of phase transition in low and high density regimes.

- asses boundary effects;
- develop order parameters that describe emergent dynamics;
- approve existence of phase transition theoretically.

Mathematical Challenges

- description of the emergent dynamics $\longrightarrow$ formal and rigorous spatio-temporal limit procedures
- meaningful macroscopic variables $\longrightarrow$ order parameters
- theory of marked (colored) IPS
- finite size and boundary effects, geometry of the state space, growing domains

Thank you for your attention.

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Cellular Potts model

(Glazier and Graner, 1993)

- one cell covers several lattice sites (~ 40)
- Hamiltonian:
    - cell-type dependent surface-energy parameter $J = (J_{ij})$
    - elastic term λ that weighs deviations from cell type dependent target size
    - temperature T controls impact of Hamiltonian
- mixture of Voter and Metropolis dynamics to sample typical configurations
- interpretation of dynamics: membrane fluctuations

Ising-like model of Mouchizuki

(Mouchizuki et al., 1997)

- one cell covers one lattice site
- Hamiltonian:
  - cell-type dependent cell-affinity $\lambda = (\lambda_{ij})$
  - migration parameter m
- Kawasaki dynamics to sample typical configurations
- interpretation of dynamics: exchange of cell positions

Alternate rates

- $c(x,y,\eta) = \exp\{H_{xy}(\eta)\} f(\eta(x),\eta(y))$
  cell sorting model (exclusion process with speed change)
- $c_1(x,y,\eta) = \dfrac{1}{1+\exp\{H_{xy}(\eta^{xy}) - H_{xy}(\eta)\}}$
  Kawasaki dynamics
- $c_2(x,y,\eta) = \begin{cases} 1, & \text{if } H_{xy}(\eta^{xy}) - H_{xy}(\eta) \leq 0 \\ \exp\{-H_{xy}(\eta^{xy}) + H_{xy}(\eta)\}, & \text{if } H_{xy}(\eta^{xy}) - H_{xy}(\eta) > 0 \end{cases}$
  Metropolis dynamics with conservation law