Haptotaxis and Trail-Following: Qualitative Behavior of a Drift-Diffusion Model Coupled to an ODE

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In developmental systems cells interact in a variety of ways

(... birth, death, cell motion, ...)

in order to create functionally important structures/patterns.
Often diffusion and reaction of cellular signals play a role,
and also chemotaxis due to a diffusible signal.

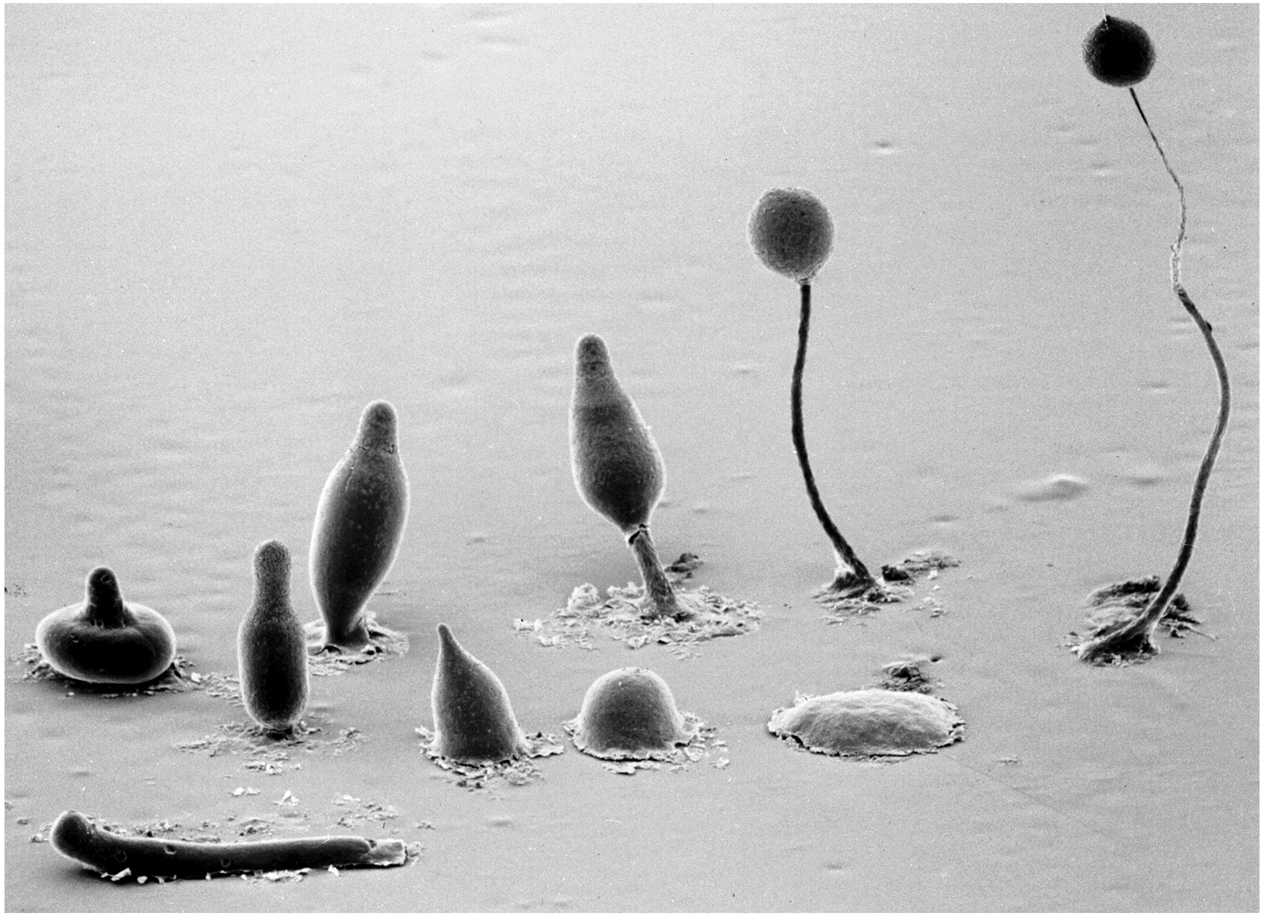
Additionally more localized interactions between cells
seem to play a role in developmental processes,
i.e. behavioral changes of cells arise due to direct cell-cell contact,
or due to molecules which are quite precisely positioned,
e.g. into the extra cellular matrix (ECM).

QUESTION: Does this make a difference for structure/pattern formation or rather not?

A biological model-system for development:
life-cycle of the cellular slime mold,
Dictyostelium discoideum, Dd.

Under starvation conditions Dd produces cAMP, which diffuses.
The cells sense this signal and move towards higher concentrations.

(*Chemotaxis is very common in many developmental processes, where cells are spatially reorganized*.)



Chemotaxis and self-organization of *Dictyostelium discoideum*, (Dd)

Jäger/Luckhaus, '92, showed, that chemotaxis can serve as the main mechanism for self-organization of *Dd*.

The main mechanism for such a phenomenon in a 2-dim model must exhibit blow-up of solutions.

The classical Keller-Segel model:

u density of cells, v concentration of chemo-attractant cAMP

$$\begin{aligned} \partial_t u &= \Delta u - \chi \nabla \cdot (u \nabla v) \\ \partial_t v &= \eta \Delta v + \alpha u - \beta v \end{aligned}$$

with Neumann boundary conditions on $\partial\Omega$.
$\chi > 0$ is the chemotactic sensitivity.

Define $\bar{w} = \frac{1}{|\Omega|}\int_\Omega w\,dx$. Then

$$\bar{u}(t) = \bar{u}_0 \quad , \quad \frac{1}{\eta}(\partial_t + \beta)\bar{v} = \frac{\alpha}{\eta}\bar{u} = \frac{\alpha}{\eta}\bar{u}_0$$

Consider $\tilde{v} := v - \bar{v}$, then

$$\frac{1}{\eta}(\partial_t + \beta)\tilde{v} = \Delta\tilde{v} + \frac{\alpha}{\eta}(u - \bar{u}_0)$$

For large diffusion of cAMP we obtain the approximating system

$$\begin{aligned} \partial_t u &= \Delta u - \chi\nabla\cdot(u\nabla v) \\ 0 &= \Delta\tilde{v} + \tfrac{\alpha}{\eta}u - \tfrac{\alpha}{\eta}\bar{u}_0 \end{aligned}$$

The last equation can be further rescaled:

$$0 = \Delta v + u - 1$$

JL, '92, proved rigorously:

For $\Omega \subset \mathbb{R}^2$ open and bounded there exist a critical number $c(\Omega)$ such that for $\alpha \bar{u}_0 \chi < c(\Omega)$
there exists a unique, smooth, positive solution for all times.

For a disk Ω there exist $c^* > 0$ such that for $\alpha \bar{u}_0 \chi > c^*$
radially symmetric positive initial data can be constructed such that blow-up happens in the center of the disc in finite time.

E. Carlen / M. Loss pointed out, that the precise critical constant can be read off directly from the estimates in the proofs of JL, '92.

In JL, '92 it is mentioned, that a further important study
is the development of singularities after the finite blow-up time.

Remember the talk by Adrien Blanchet. Free energy:

$$E(u,v) = \int_{\mathbb{R}^2} \frac{u(x)\log u(x)}{\chi} - u(x)v(x) + \frac{1}{2}|\nabla v(x)|^2 + v(x)dx$$

Gradient flow structure:

$$\partial_t u = \nabla \cdot \left(u\chi\nabla \frac{\partial E}{\partial u} \right) \quad , \quad 0 = -\frac{\partial E}{\partial v}$$

Haptotaxis and Trail Following:

Consider a Keller-Segel model with non-diffusive memory, namely

$$\partial_t u = \Delta u - \nabla \cdot (u \nabla \log(v)) \quad , \quad \partial_t v = u v^{\lambda} \ .$$

Earlier results:

$\lambda = 0$ global solutions (Chen Hua et al),

$\lambda = 1$ blow-up for specific initial data (Levine and Sleeman).

For $w = \log v$ we obtain:

$$\partial_t u = \Delta u - \nabla \cdot (u \nabla w) \quad , \quad \partial_t w = u w^{\lambda - 1}$$

For $\lambda = 1$ remember talk by Adrien Blanchet. Free energy:

$$E(u, v) = \int_{\mathbb{R}^2} u(x) \log u(x) - u(x) v(x) dx$$

Gradient flow structure

$$\partial_t u = \nabla \cdot \left(u \nabla \frac{\partial E}{\partial u} \right) \quad , \quad \partial_t v = -\frac{\partial E}{\partial v}$$

Let $\theta = \frac{1}{1-\lambda}$ and $z = \frac{1}{1-\lambda} v^{(1-\lambda)} = \theta v^{\frac{1}{\theta}}$, then

$$\partial_t u = \Delta u - \theta \nabla \cdot (u \nabla \log(z)) \quad , \quad \partial_t z = u \quad , \quad \theta \in (0, \infty)$$

[Kang - S.- Velázquez]:

Space Dimension 1: periodic boundary conditions.

For $\theta = 1$, i.e. $\lambda = 0$ formally every space dependent function is asymptotically a steady state for $t \to \infty$.
It was shown, that the long time dynamics are strongly dependent on the initial data.

For $1 < \theta < 3$, i.e. $0 < \lambda < \frac{2}{3}$ it was rigorously proved that solutions converge to a Dirac mass for $t \to \infty$.

First we give a heuristic argument:

Let $I = [-1, 1]$, $\int_I u dx = m$. Consider

$$\bar{z}_t = \frac{\bar{z}^\theta}{\int_I \bar{z}^\theta dx},$$

which results from the quasisteady approximation

$$\begin{aligned} 0 &= \nabla \cdot (\nabla u - \theta u \nabla \log(z)) \\ \partial_t z &= u \end{aligned}$$

Assume that this is a good approximation
for the original problem for $t \to \infty$.

For $\bar{z}(0,0) > \bar{z}(0,x)$ we obtain
$\bar{z}^{1-\theta}(t,x) = \bar{z}^{1-\theta}(0,x) - (\theta - 1)\int_0^t \frac{ds}{\int_I \bar{z}^\theta(s,x)dx}$

Assume the following expansion:
$\bar{z}^{1-\theta}(0,x) = \bar{z}^{1-\theta}(0,0) + Bx^2 + h.o.t.$ for $x \to 0$.

Thus $\bar{z}^{1-\theta}(t,x) \approx \bar{z}^{1-\theta}(0,0) + Bx^2 - (\theta - 1)\int_0^t \frac{ds}{\int_I \bar{z}^\theta(s,x)dx}$.

So $\bar{z}^{1-\theta}(t,x) :\approx Bx^2 + \psi(t)$, therefore $\bar{z}(t,x) \approx (Bx^2 + \psi(t))^{\frac{1}{1-\theta}}$.

Explicit calculations show that

$\frac{1-\theta}{\psi'(t)} \approx \int_I \frac{dx}{(Bx^2+\psi(t))^{\frac{\theta}{\theta-1}}}$, and

$\psi'(t) \approx -K\psi^{\frac{\theta+1}{2(\theta-1)}}(t)$, so $\psi(t) \approx At^{\frac{2(1-\theta)}{3-\theta}}$.

With this we can calculate, that

$$\bar{z}(t,x) \approx \frac{t^{\frac{2}{3-\theta}}}{\left(Bx^2 t^{\frac{2(\theta-1)}{3-\theta}} + A\right)^{\frac{1}{\theta-1}}}$$

Theorem:

There exist a family of initial data $(u_0, z_0) \in C^{2,\alpha}$ such that the corresponding solutions (u, z) of our system satisfy

$u(t,x) \to m\delta(x)$ and

$$\bar{z}(t,x) \quad \approx \quad \frac{t^{\frac{2}{3-\theta}}}{\left(Bx^2 t^{\frac{2(\theta-1)}{3-\theta}} + A\right)^{\frac{1}{\theta-1}}}$$

for $t \to \infty$, and where A, B are constants, which depend on the initial data.

Proof:

- Eigenvalue problem for steady state eqn. in u.
- Operator ist self-adjoined w.r.t. weighted integral with weight dx/z^θ.
- Negative upper bound for the second eigenvalue
- Sobolev inequality with weighted norm by adaptation of a result by Maz'ja given in a more accessible formulation by Horiuchi.
- Since z does not behave like a power law, the estimate by Horiuchi can not be used directly.
  A boundary layer estimate has to be introduced.

Asymptotic Results in $\mathbb{R}$ (S.-Velázquez)

The asymptotics in $\mathbb{R}$ for $\theta = 1, \lambda = 0$ interestingly compare
to the asymptotics calculated by Merkl and Rolles
for the formally corresponding reinforced random walk
on the one-dimensional lattice,
i.e. in both models the size of the region
where the particle is mainly located
is asymptotically of the same size.

Consider again

$$\begin{aligned} \partial_t u &= \Delta u - \nabla \left(u \frac{\nabla v}{v} \right) \\ \partial_t v &= u v^{\lambda} \end{aligned}$$

for $x \in \mathbb{R}^n$, $t > 0$, and suitable initial conditions for u and v.

Depending on the space dimension n, the growth exponent λ and the regularity properties of the initial conditions, blow-up in finite time, mass aggregation in infinite time, or mass spreading can be observed.

1 Intuitive Understanding of the Model in $\mathbb{R}^d$

The exponent λ measures the strength of the localized reinforcement, thus the tendency for aggregation increases with larger values of λ, respectively larger values of θ.

The dynamics of the cells are described by random motility and by chemotactic drift towards higher concentrations of v. The number of times that a brownian particle approaches a given point in space depends very strongly on the space dimension. Thus the environment, where the cells move, is modified stronger in lower dimensions than it is in higher dimensions. So in this model the tendency to aggregate increases for smaller spatial dimension.

In contrast to this, in the original Keller-Segel model with diffusion finite time blow-up is more likely in higher dimensions.

Regular initial data, $n = 1$:

The reinforced random walk in one dimension suggests $\lambda = 0$ as critical parameter.

- For $\lambda > \frac{2}{3}$ we observe blow-up in finite time.
- For $0 < \lambda < \frac{2}{3}$ we observe blow-up in infinite time.
  The rate of growth is a power law.
- For $\lambda = \frac{2}{3}$ also blow-up in infinite time can be observed.
  The rate of growth is exponential.
- For $\lambda = 0$ the solution is highly sensitive on the initial data.
  These play an important role for the diffusive tails of the solution.
- For $\lambda < 0$ self-similar behavior can be observed.
  The reinforcement plays a non-trivial role.
  The solution behaves non-diffusive.

Regular initial data, $n = 2$:

- For $\lambda > 1 - \frac{1}{1+\frac{2}{n}} = \frac{1}{2}$ we observe blow-up in finite time.
- For $0 < \lambda \leq 1 - \frac{1}{1+\frac{2}{n}} = \frac{1}{2}$ we observe blow-up in infinite time.
- For $\lambda \leq 0$ non-diffusive self-similar behavior without mass aggregation can be observed.

Regular initial data, $n \geq 3$

- For $\lambda \geq \frac{2}{n}$ both, finite time blow-up without mass aggregation and diffusive self-similar behavior without mass aggregation can be observed.
- For $1 - \frac{1}{1+\frac{2}{n}} < \lambda < \frac{2}{n}$ blow-up in infinite time and diffusive self-similar behavior without mass aggregation can be observed.
- For $\lambda \leq 1 - \frac{1}{1+\frac{2}{n}}$ diffusive self-similar behavior without mass aggregation can be observed.

Further, the size of the region w.r.t. time was calculated, where an amount of mass of order one is distributed during the aggregation process.

The classical Keller-Segel model.

$d = 1$	$d = 2$	$d \geq 3$
No singularities	Mass aggregation in finite time for $M > M_{crit}$	Mass aggregation in finite time with arbitrary mass
	Non-diffusive self-similar behavior for $M < M_{crit}$	Singularity formation without mass aggregation in finite time
		Diffusive self-similar behavior without mass aggregation

In [*S. '95*], [*Othmer - S., '97*] the following limiting systems were formally derived from self-reinforced, attractive random walk models:

a) edge reinforcement:

$$
\begin{aligned}
\partial_t u &= \nabla \cdot (\nabla u - u \nabla \log v) \\
\partial_t v &= f(u,v) = uv^\lambda
\end{aligned}
$$

b) vertex reinforcement:

$$
\begin{aligned}
\partial_t u &= \nabla \cdot (\nabla u - 2u \nabla \log v) \\
\partial_t v &= f(u,v) = uv^\lambda
\end{aligned}
$$

For $\theta = \frac{1}{1-\lambda}$ and $z = \frac{1}{1-\lambda} v^{(1-\lambda)} = \theta v^{\frac{1}{\theta}}$ we have

$$\begin{aligned} \partial_t u &= \nabla \cdot (\nabla u - \theta(u \nabla \log(z)) \\ \partial_t z &= u \quad , \quad \theta \in (0, \infty) \end{aligned}$$

If $\theta = \theta_e$ then the formal limit of vertex reinforcement gives $\theta_v = \frac{2}{(1-\lambda)} = 2\theta$.

So $\frac{1}{2}\theta_v = \theta_e$ shows the same equation/effect.

In general the asymptotics of our PDE-ODE model do
not coincide with those of the discrete random walk.
BUT the PDE-ODE model correctly recovers the critical θ for which the particle switches from visiting all integers infinitely often to being trapped in a finite number of integers.

For a better approximation consider a quasistationary approximation, discrete in time, e.g. in 1-dim [*S. - Velázquez*]

$$\frac{z(e_r(n_l), t_0 + \tau(t_0)) - z(e_r(n_l), t_0)}{\tau(t_0)} = \frac{(z(e_r(n_l), t_0))^\theta}{\sum_{k \in \Omega(t_0)} (w(e_r(n_k), t_0))^\theta}$$

for suitable lattice points.

This equation formally reflects many qualitative features which are known for reinforced random walks,
e.g. 'trapping' versus 'non-trapping' of the particle
and the number of points on which the particle is 'trapped',

The approximation recovers and predicts the following:

1-dim edge reinforcement:

$\theta_e > 1$: trapping in two points (Davis)
$\theta_e = 1$: trapping in a bounded region (Merkl - Rolles)
$\theta_e < 1$: spreading dominated by boundary layers (Toth)

1-dim vertex reinforcement:

$\theta_v = 1$: trapping in 5 points (Tarres)
$\theta_v = \frac{1}{2}$: critical case
$\frac{1}{2} < \theta_v < 1$: trapping in many points

Interestingly (*compare the PDE relation between* θ_v *and* θ_e)
for the discrete $\theta_e \in (0,1)$ and the discrete $\theta_v \in (0, \frac{1}{2})$,
both below their respective critical value,
the asymptotic behavior of the discrete $z_v(\theta)$
'coincides' with that of $z_e(\frac{\theta}{2})$.
Stochastic simulations confirm this prediction.

Similar asymptotics are done for the higher dimensional cases,
in order to make educated guesses about the behavior
of the respective self-attracting random walk.

- The classical Keller-Segel system for chemotaxis behaves in a different way than the PDE-ODE-system presented.
  The later one behaves ‘more hyperbolic’.
  The reaction to an attractive but localized signal creates a different long time behavior if compared to attractive diffusible signals.
- Edge and vertex reinforcement make a difference in the one particle setting, but in certain parameter regimes they behave surprisingly similar.
  The PDE-ODE-model astonishingly gave hints for the critical parameter in reinforced random walks but does not provide the right asymptotics.
  The critical parameter seems to be very robust w.r.t. approximations.