Selection and Orientational Aggregation in Population Dynamics

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Variability in Cellular Function:

Within cellular systems cells of the same type mostly vary w.r.t. to their cellular function.

E.g. in early development, cells with fewer adhesion receptors sort towards the outside of the cell spheroid, whereas cells with more adhesion receptors sort to the inside. Later, these cells undergo a different cell fate.

Is variability in cellular function the basis for pre-differentiation of cells, and thus structure formation and differentiation?
A Concrete Example:

One biological model-system for development is the developmental life-cycle of the cellular slime mold, *Dictyostelium discoideum*, Dd.

Under starvation conditions the amoebae produce cAMP. The cells sense this signal and move towards higher concentrations. *(Chemotaxis is common in many developmental processes, where cells are spatially reorganized.)*

After aggregation and mound formation in Dd, cells start to pre-differentiate into pre-stalk and pre-spore cells.

In the mound these cells vary w.r.t. their chemotactic sensitivity.
Chemotaxis and self-organization of *Dictyostelium discoideum*, (Dd)
Chemotactic Variability and Cell Sorting:

During later stages of mound formation one finds chemotactically more active cells at the top of the mound, and chemotactically less active cells at the bottom of the mound.

Later, these differently sorted cells differentiate into two cell types. The cells from the top of the mound form the stalk. Cells from the bottom of the mound become the surviving spores.

The outcome of cell sorting is a pre-stage for cell differentiation.
Does chemotaxis serve as a main mechanism for cell sorting in the mound stage of *Dd*?

Chemotaxis is known to be the major mechanism for cell aggregation and self-organization in Dd.

The main underlying mechanism for this phenomenon in a spatially 2-dim mathematical model must exhibit blow-up of solutions (Jäger/Luckhaus, ’92).
A suitable model for chemotactic cell sorting in the mound would be 3-dimensional, and exhibit spatial ordering of the cells w.r.t. their chemotactic strength.

**Test problem:**
Consider a 2-dimensional model for two chemotactic cell types.

Can the solution for the stronger chemotactic cell type exhibit blowup, whereas the solution for the other type still exists?
Let $u_1, u_2$ be the densities of two chemotactic cell types, and $v$ be the concentration of the chemo-attractant. Consider

\[
\begin{align*}
\partial_t u_1 &= \mu_1 \Delta u_1 - \chi_1 \nabla \cdot (u_1 \nabla v) \\
\partial_t u_2 &= \mu_2 \Delta u_2 - \chi_2 \nabla \cdot (u_2 \nabla v) \\
\partial_t v &= D \Delta v + \alpha_1 u_1 + \alpha_2 u_2 - \beta v
\end{align*}
\]

in $B_R(0), t > 0$, with Neumann boundary conditions.

$\chi_1, \chi_2 > 0$ are the chemotactic sensitivities,
$\mu_1, \mu_2, D$ are the diffusion coefficients.

For $\chi_2 = 0$, the system is decoupled.

Thus one can find conditions such that $u_1$ - ‘just’ - blows up, whereas $u_2$ does not.

What about $\chi_2 << 1$?
1 Dimensional Analysis

... results in

\[
\begin{align*}
\partial_t u_1 &= \Delta u_1 - \chi_1 \nabla \cdot (u_1 \nabla v) \\
\partial_t u_2 &= \mu_2 \Delta u_2 - \chi_2 \nabla \cdot (u_2 \nabla v) \\
0 &= \Delta v + u_1 + u_2 - 1
\end{align*}
\]

in \( B_1(0), t > 0 \) with Neumann boundary conditions.

Existence of classical solutions was proved in the PhD-thesis of E.E. Espejo (2008). Global existence for general multi-component chemotaxis systems and Dirichlet boundary conditions was shown by G. Wolansky (2002).

Further extended results are given by D. Horstmann.
Consider radial symmetric solutions.
Rewrite the system in terms of the rescaled mass functions

\[ M_i(t, r) = \int_0^r u_i(t, \xi)\xi \, d\xi \]

with \( r = |x| \). Then

\[ \partial_r v = \frac{M_1 + M_2}{r} - \frac{r}{2} \]

and

\[
\begin{align*}
\partial_t M_1 &= r\partial_r \left( \frac{1}{r} \partial_r M_1 \right) - \chi_1 \left( \frac{r}{2} - \frac{M_1 + M_2}{r} \right) \partial_r M_1 \\
\partial_t M_2 &= \mu_2 r\partial_r \left( \frac{1}{r} \partial_r M_2 \right) - \chi_2 \left( \frac{r}{2} - \frac{M_1 + M_2}{r} \right) \partial_r M_2
\end{align*}
\]

with boundary condition \( M_1(t, 1) = m_1 \), \( M_2(t, 1) = m_2 \).

**GOAL:** Find sufficient conditions for blow-up in finite time.
2 Result:

Global solutions exist, if

\[ m_1 < \min \left\{ \frac{\mu_2}{\chi_2}, \frac{2(2 - \chi_1 m_2)}{\chi_1} \right\} \]

and

\[ m_2 < \min \left\{ \frac{1}{\chi_1}, \frac{2(2\mu_2 - \chi_2 m_1)}{\chi_2} \right\} . \]

Blow-up in finite time happens if

\[ m_1 > \frac{2}{\chi_1} \quad \text{and} \quad \int_{B_1(0)} |x|^2 u_1(t, x) dx << 1 . \]
3 Theorem:

If \( u_1 \) blows up in finite time,
then also \( u_2 \) blows up at the same time.

Assume \( u_1 \) blows up in finite time and \( u_2 \) is bounded,
then we obtain a lower bound for \( M_1 \) and an upper bound for \( M_2 \).
Construction of a sub-solution and comparison arguments lead to a contradiction.

Formal derivation of the blow-up profile

Calculate asymptotics for parameters \( \chi_1, \chi_2, \mu_2 \)
for which \( M_2 \ll M_1 \) near the blow-up point.
Then singularity formation for \( u_2 \) is possible
without mass aggregation, whereas \( u_1 \) shows mass aggregation.
Back to our Original Question. Suggestion:

Model variability w.r.t. a cellular function via a stage parameter. If cell differentiation directly relates to this cellular function, the model dynamics should select for a finite number of stages from the initial continuum. Thus pre-differentiation can take place.

To explain the mathematical concept, have a look at self-organization and angular alignment of myxobacteria.

During self-organization and before aggregation the bacteria align parallel, and a quasi one-dimensional pattern is observed. Thus two orientations/stages are selected.

Here the orientation of the cells is the stage parameter.
The Model Equations:

\[ \partial_t f(t, \gamma) = - \int_I T[f](\gamma, \gamma') f(t, \gamma) d\gamma' + \int_I T[f](\gamma', \gamma) f(t, \gamma') d\gamma' \]

where \( T[f](\gamma, \gamma') = \int_I G_\sigma(\gamma' - \gamma - V(w - \gamma)) f(t, w) dw \), \( I = [-\frac{1}{2}, \frac{1}{2}] \), \( V \) is the orientational angle, an odd function and 1-periodic, \( G_\sigma \) measures the accuracy of reorientation and can be chosen as the standard periodic Gaussian.
Bi-Directional Alignment - Attraction and Repulsion:

If the angle between myxobacteria is small, they attract each other.
If the angle between myxobacteria is larger, they are repulsive, respectively they are attracted to the ends of their interaction partners.

Peak Solutions for the Limiting Equation:

Consider $G_{\sigma}$ with $\sigma = 0$, the Dirac mass $\delta_0$, which describes deterministic turning.

Convergence of solutions of our equation for $G_{\sigma}$ to solutions for $\delta_0$, for $\sigma$ small enough, was proved by E. Geigant.
For the full model local stability for alignment into two opposite directions can be obtained, but NO selection of mass.
If the orientational angle $V$ is very small, the kinetic equation can be approximated by

$$\partial_t f = \frac{\sigma^2}{2} \partial_{xx} f + \partial_x \left( f(x) \int_I V(x - y) f(y) dy \right)$$

We are interested in the steady states. An equivalent formulation for these is

$$\frac{\sigma^2}{2} \partial_x f(x) + f(x) \int_I V(x - y) f(y) dy = 0$$

$$\int_I f(x) dx = 1 \text{ and } f(x + 1) = f(x)$$
Heuristics for the Selection Mechanism

Let $\sigma = 0$, then the equation reduces to

$$f(x) \int_I V(x - y) f(y) dy = 0$$

Any function of the form $f(x) = \alpha \delta_0(x) + \beta \delta_0(x - \frac{1}{2})$ is a solution, for arbitrary choice of $\alpha, \beta$.

For $\sigma > 0$ this is not the case.
Suppose $f_\sigma \to \alpha \delta_0(x) + \beta \delta_{\frac{1}{2}}(x)$ for $\sigma \to 0$.

For $\sigma << 1$, $f_\sigma$ can then be approximated by the solution of

$$\frac{\sigma^2}{2} \partial_x f(x) + f(x)V_{\alpha, \beta}(x) = 0$$
$$\int_I f(x) dx = 1$$

where $V_{\alpha, \beta} = \alpha V(x) + \beta V(x - \frac{1}{2})$.

This equation can be solved explicitly

$$f(x) = \frac{\exp\left(-\frac{\sigma^2}{2} \left[ \alpha \phi(x) + \beta \phi\left(x - \frac{1}{2}\right) \right]\right)}{\int_I \exp\left(-\frac{\sigma^2}{2} \left[ \alpha \phi(y) + \beta \phi\left(y - \frac{1}{2}\right) \right]\right) dy}$$

with $\phi(x) = \int_0^x V(z) dz$, so $\phi(x) = \phi(-x)$. 
Assume $\phi\left(\frac{1}{2}\right) \neq 0$, which is generally the case. The condition for having two peaks concentrated at $x = 0$ and $x = \frac{1}{2}$ is that $\alpha \phi(x) + \beta \phi(x - \frac{1}{2})$ reaches its minimum at these points. In particular $\alpha \phi(0) + \beta \phi(-\frac{1}{2}) = \alpha \phi\left(\frac{1}{2}\right) + \beta \phi(0)$. This can only happen for $\alpha = \beta = \frac{1}{2}$.

**What are the conditions on $V$ for either one or two peaks of equal size to occur?**

Suppose for $\sigma << 1$ exists a peak-like smooth function $f$, mainly concentrated at 0, which solves

$$
\frac{\sigma^2}{2} \partial_x f(x) + f(x) \int_I V(x - y)f(y)dy = 0
$$

$$
\int_I f(x)dx = 1
$$

and converges to $\delta_0$ for $\sigma \rightarrow 0$. 
This function may be approximated by the solution of

$$\frac{\sigma^2}{2} \partial_x f(x) + f(x)V(x) = 0 , \int_I f(x)dx = 1 .$$

Therefore

$$f(x) = \frac{\exp(-\frac{2}{\sigma^2}[\int_0^x V(z)dz])}{\int_I \exp(-\frac{2}{\sigma^2}[\int_0^y V(z)dz])dy}$$

For $\int_0^{\frac{1}{2}} V(x)dx > 0$ we have a main concentration around 0.
For $\int_0^{\frac{1}{2}} V(x)dx < 0$ the peak is located at $\pm \frac{1}{2}$, which is a contradiction.
Thus we have an example for variability of cells w.r.t. to a cellular function (here orientation). The dynamics of the system select for a finite number of stages from the continuum.

These types of equations should be explored in the future to describe cell differentiation and pre-differentiation.
4 Chemotaxis with Non-Diffusive Memory

Kang - S. - Velázquez

Consider

\[
\begin{align*}
    u_t &= u_{xx} - \left( u \frac{w_x}{w} \right)_x \\
    w_t &= uw^\lambda
\end{align*}
\]

for \( x \in [0, \pi] \), \( \lambda \in [0, 1) \), and with periodic boundary conditions.

Setting \( \theta = \frac{1}{1-\lambda} \) and \( z = \theta w^{\frac{1}{\theta}} \) we obtain

\[
\begin{align*}
    u_t &= u_{xx} - \theta \left( u \frac{z_x}{z} \right)_x \\
    z_t &= u .
\end{align*}
\]

So \( \theta \in [1, \infty) \).
For the extreme case \( \lambda = 1 \ (\theta = \infty) \) blow-up of solutions in finite time for specific initial data was proved, [Levine/Sleeman].

**Qualitative behavior of the system for \( \theta = 1 \):**
The solutions are strongly dependent on the choice of the initial data.

**Theorem:**
Let \((a, at), \ a > 0, \) be space-independent solutions of our system. Let \((u, z)\) be a solution with initial data \((u(1, x), z(1, x))\) sufficiently close to \((a, a)\). Then there exists \(v_\infty(x) \in H^2\) such that \(u\) and \(\frac{z}{t}\) both converge to \(a + v_\infty\) for \(t \to \infty\).

Here \(H^k = H^k([0, \pi]) = \{f(t, \cdot) : D^j f(t, \cdot) \in L^2([0, \pi]), 0 \leq j \leq k\}\).
Qualitative behavior of the system for $1 < \theta < 3$:

We fix the expected singularity at the origin. Consider

$$
\begin{align*}
    u_t &= u_{xx} - \theta \left( \frac{u z_x}{z} \right)_x \\
    z_t &= u
\end{align*}
$$

in $[-1, 1] \times [0, \infty)$, with $u(0, x) = u_0(x)$, $z(0, x) = z_0(x)$ and with periodic boundary conditions.
5 Heuristic Arguments for the Asymptotics of the Blow-Up:

W.l.o.g. assume that $\int_{[-1,1]} u dx = 1$ and consider the stationary equation for $u$. Then for $t \to \infty$ the simplified system

$$\ddot{z}_t = \frac{\dot{z}^\theta}{\int_{[-1,1]} \dot{z}^\theta dx}\)$$

is a good approximation for the dynamics of the original problem. Assume that $z_0(0) > z_0(x)$ for any $x \in [-1,0) \cup (0,1]$. Then we can solve this equation and obtain

$$\bar{z}^{1-\theta}(t,x) = \bar{z}_0^{1-\theta}(x) - (\theta - 1) \int_0^t \frac{ds}{\int_{[-1,1]} \bar{z}^\theta(s,x) dx}$$
We assume further that $\tilde{z}_0$ can be expanded near zero as follows

$$\tilde{z}_0^{1-\theta}(x) = \tilde{z}_0^{1-\theta}(0) + Bx^2 + h.o.t.$$  

for $x \to 0$, where $B$ is a positive constant depending on the initial data. Thus

$$\bar{z}^{1-\theta}(t, x) \approx \tilde{z}_0^{1-\theta}(0) + Bx^2 - (\theta - 1) \int_0^t \int_{[-1, 1]} \frac{ds}{\tilde{z}^\theta(s, x)} \, dx.$$
Define

$$\psi(t) := \tilde{z}_{0}^{1-\theta}(0) - (\theta - 1) \int_{0}^{1} \frac{ds}{\tilde{z}_{0}^{\theta}(s, x) dx} .$$

Then $\tilde{z}^{1-\theta}(t, x) \approx Bx^{2} + \psi(t)$ and

$$\tilde{z}(t, x) \approx \frac{1}{(Bx^{2} + \psi(t))^{\frac{1}{\theta-1}}}.$$
Direct computations show that

\[-\frac{\theta - 1}{\psi'(t)} \approx \int_{[-1, 1]} \frac{dx}{(Bx^2 + \psi(t))^{\frac{\theta}{\theta - 1}}}\]

So \(\psi'(t) \approx -K \psi^{\frac{\theta + 1}{2(\theta - 1)}}(t)\) with a constant \(K > 0\).
This yields \(\psi(t) \approx At^{-\frac{2(\theta - 1)}{3-\theta}}\) with a constant \(A > 0\) for \(t \to \infty\).
Since $\psi(t) \to 0$ for $t \to \infty$, we see that

$$\bar{z}_0^{1-\theta}(0) \approx (\theta - 1) \int_0^\infty \frac{ds}{\int_{[-1,1]} \bar{z}^\theta(s,x)dx}.$$ 

Therefore, noting that $\psi'(t) \approx -KA^{\frac{\theta+1}{2(\theta-1)}} t^{-\theta+1} \frac{1}{3-\theta}$ for $t \to \infty$, we obtain

$$\psi(t) \approx (\theta - 1) \int_t^\infty \frac{ds}{\int_{[-1,1]} \bar{z}^\theta dx}.$$
Thus

$$\int_{[-1,1]} \tilde{z}^\theta \, dx \approx \frac{\theta - 1}{\theta + 1} t^{\frac{\theta + 1}{3 - \theta}} KA^{\frac{2}{2(\theta - 1)}}$$

and

$$\tilde{z}(t, x) \approx \frac{1}{(Bx^2 + At^{\frac{2(\theta - 1)}{3 - \theta}})} \left( t^{\frac{2}{3 - \theta}} \right) \frac{1}{(Bx^2 t^{\frac{2(\theta - 1)}{3 - \theta}} + A)^{\frac{1}{\theta - 1}}}$$
**Theorem:**
There exist 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
\[
z(t, x) \approx \frac{t^{\frac{2}{3-\theta}}}{\left(Bx^2t^{\frac{2(\theta-1)}{3-\theta}} + A\right)^{\frac{1}{\theta-1}}}
\]
for \(t \to \infty\), where
\[m = \int_{[-1,1]} u_0(x)dx\]
and \(A, B\) are constants, which depend on the initial data.
In the original Keller-Segel model with diffusion, finite time blow-up is more likely in higher dimensions.

For the model with the attractive, non-diffusive memory this is not the case. Formal considerations show, that the conditions for blow-up in higher dimensions require a stronger production of the attractive memory. Intuitively this relates to the behavior of random walks in higher dimensions. The higher the spatial dimension, the longer it takes for a particle to come back to its starting point.