

Analysis of self-organization systems for cell polarisation

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A few words about cell polarisation

- Cell polarisation is an **essential step for many biological processes** such as cell migration, division, development and morphogenesis in widely varying cell types (yeast, dictyostelium, neutrophils and neurons ...), c.f. K. Weijer.
- Polarisation is characterised in its early stages by an **inhomogeneous distribution of specific molecular markers**.
- Often cell polarisation is driven by an external asymmetric signal (cells migrating along a chemical gradient performing chemotaxis).

Spontaneous cell polarisation

- Observations show that some systems can also **polarise spontaneously** in absence of any external cue (e.g. neutrophil cell migration, algae cell division, xenopus egg development and mating yeast).
- The two distinct polarisation processes, *driven or spontaneous*, are necessary for cells to fulfil different biological functions.
- However what determines whether a cell can polarise spontaneously or not is still not well understood, it is now widely recognised that the **cytoskeleton plays a crucial role** in this process.

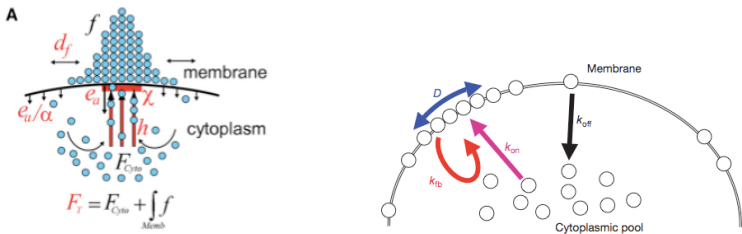
Role of the cytoskeleton in cell polarisation

- When, using LatA or myosin mutants, actin transport is disrupted:
 - the efficiency of formation of polar caps in yeast is reduced,
 - the polar caps formed are unstable.
- the cytoskeleton filaments mediate an **effective positive feedback in the dynamics of polarisation markers.**

Summary

Cell polarisation occurs when there is an **inhomogeneous** distribution of molecular markers on the membrane.

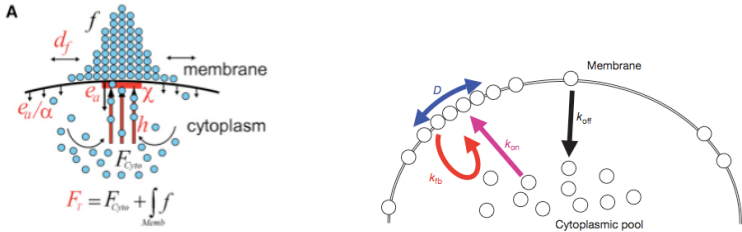
- What is the marker's dynamics?
- What are the links between the bulk and the membrane?



Existing models

- Many are **reaction-diffusion systems** in which polarisation emerges as a type of Turing instability.
- The full dynamics of markers is generally not considered and it is of two types:
 1. diffusion in the cell cytoplasm and on the membrane,
 2. active transport by molecular motors along cytoskeleton filaments, the dynamic organisation of which is regulated by the markers themselves.

Assumptions for the model



- Molecular markers are particles which can be either on the membrane or in the bulk cytoplasm of the cell. We denote by n the density of these particles.
- We assume that the cell is one- or bi-dimensional and we neglect curvature effects.

Plan

- Description of two models of molecular markers dynamics in dimension 2.
- Study of the mathematical properties of a one-dimensional model. Is such a model able to "produce concentration phenomenon"? Long time behaviour of the solution.
- Study of the mathematical properties of a coupled (pde/ode) one-dimensional model.
- Heuristics, numerical simulations and some mathematical results for the 2D models of molecular markers dynamics, are the two models able to "break" symmetries and "produce concentration phenomenon"?

The model

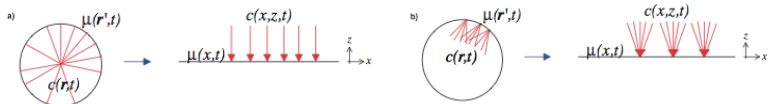
- describe the markers dynamics in the bulk:
 - directed transport through **microtubules or actine filaments**,
 - diffusion.
- describe markers dynamics on the membrane,
- take into account the positive feedback between the markers on the membrane and the density of either microtubules or actine filaments.

$$\partial_t n(t, x, z) = \Delta n(t, x, z) - \nabla \cdot (n(t, x, z)\mathbf{u}), \quad (x, z) \in \mathbb{R} \times \mathbb{R}_+.$$

Which choice **for \mathbf{u}** ? microtubules or actine filaments: two different expressions.

Two models in dimension 2

$$\partial_t n(t, x, z) = \Delta n(t, x, z) - \nabla \cdot (n(t, x, z) \mathbf{u}), \quad (x, z) \in \mathbb{R} \times \mathbb{R}_+.$$



- either the drift is normal to the boundary:

$$\mathbf{u}_1 = -n(t, x, 0) \mathbf{e}_z,$$

- or it is the gradient of a harmonic potential, for which the source term is located at the boundary:

$$\mathbf{u}_2 = \nabla c(t, x, z), \quad \begin{cases} -\Delta c(t, x, z) = 0 \\ -\partial_z c(t, x, 0) = n(t, x, 0) \end{cases}$$

Common features of the two models

$$\partial_t n(t, x, z) = \Delta n(t, x, z) - \nabla \cdot (n(t, x, z) \mathbf{u}) , \quad (x, z) \in \mathbb{R} \times \mathbb{R}_+ .$$

- \mathbf{u} depends on the concentration of molecular marker on the membrane making the term involving \mathbf{u} a **nonlinear coupling term**.
- The drifts \mathbf{u}_1 and \mathbf{u}_2 are both **divergence free**, and the **components that are normal to the boundary coincide**.

In addition, we impose a zero-flux boundary condition:

$$0 = \left(\nabla n - \mathbf{u} n \right) (t, x, 0) \cdot \mathbf{e}_z ,$$

which rewrites as:

$$\partial_z n(t, x, 0) + n^2(t, x, 0) = 0 .$$

Biological meaning of model 1: microtubules

$$\mathbf{u}_1 = -n(t, x, 0)\mathbf{e}_z,$$

- the active transport is mediated by an aster of filaments **nucleated at the cell centre**,
- these filaments, that grow towards the membrane, can be assumed to be **perpendicular to the membrane**,
- assuming a "search and capture model", their orientation is regulated by the polarity markers due to preferential stabilisation and growth in regions of high marker concentration,
- the velocity of directed transport is assumed to be **proportional to the concentration of the the markers on the membrane**,
- the previous model features the microtubules in neuron growth cones *e.g.*.

Biological meaning of model 2: actin

$$\mathbf{u}_2 = \nabla c(t, x, z), \quad \left\{ \begin{array}{l} -\Delta c(t, x, z) = 0 \\ -\partial_z c(t, x, 0) = n(t, x, 0) \end{array} \right. ,$$

- the active transport is mediated by filaments **nucleated at the membrane**,
- these filaments can be arranged in **asters centred on the membrane**,
- this mimics in a simplified way the organisation of cortical actin in budding yeast, where molecular markers (such as Cdc42, Spa2, septins) are transported along the filaments towards the membrane by myosin molecular motors,
- when active, these molecules in turn induce actin nucleation at the membrane thereby creating a positive feedback.

Spontaneous polarisation

- Inhomogeneous distribution of molecular markers on the membrane,
- When does spontaneous polarisation occur? If the number of markers is not too large, (*S. J. Altschuler et al.*, Nature (2008)),
- It depends on the geometry of nucleation of the filaments, (*R. Voituriez et al.*, PRL (2009)). This result is obtained by a linear perturbation analysis.
- Here we give the following answers
 - **in dimension one**: dichotomy result (global existence – blow-up) together with convergence results,
 - **in dimension two**: dichotomy for the drift \mathbf{u}_1 , global existence for \mathbf{u}_2 but we were not able to prove blow-up for \mathbf{u}_2 ,
 - **numerical simulations and heuristics** in dimension 2.

Case of dimension 1....

the membrane is $x = 0$ and the cytoskeleton is the half-line $x > 0$,

$$\partial_t n(t, x) = \underbrace{\partial_{xx} n(t, x)}_{\text{diffusion}} + \underbrace{n(t, 0) \partial_x n(t, x)}_{\text{non local convection}}, \quad t > 0, x \in (0, +\infty),$$

with boundary condition:

$$\partial_x n(t, 0) + n(t, 0)^2 = 0, \quad t \geq 0,$$

and initial condition:

$$n(t = 0, x) = n_0(x) \geq 0,$$

then

- $n(t, x) \geq 0$,
- mass conservation:

$$\int_{x>0} n(t, x) \, dx = \int_{x>0} n_0(x) \, dx = M.$$

Competition between antagonist phenomena

$$\partial_t n(t, x) = \partial_{xx} n(t, x) + n(t, 0) \partial_x n(t, x),$$

- **diffusion** : "smoothing" of the solution,
- non local convection term: concentration in $x = 0$,

which phenomenon is going to win?

"Dichotomy behaviour" of the solution

Theorem

Assume that $n_0(x)$ is continuous on $[0, +\infty)$ and that $n_0 \in L^1_+((1+x)dx)$.

- If $M \leq 1$ the solution is global in time.
- On the contrary if $M > 1$, assume in addition that n_0 is non increasing, then the solution blows-up in finite time.

Ideas of the proof: Blow-up if $M > 1$ (similar to blow-up for classical KS in dimension two)

- If n_0 is non increasing then $n(t, \cdot)$ is non increasing.
- $-\partial_x n(t, x)/n(t, 0)$ is a probability density and Jensen's inequality yields that

$$M^2 \leq 2n(t, 0) \int_{x>0} xn(t, x) dx.$$

- Introducing the first momentum $\mathbf{J}(t) = \int_{x>0} xn(t, x) dx$ we obtain that

$$\frac{d\mathbf{J}(t)}{dt} = n(t, 0) - Mn(t, 0) \leq \frac{M^2}{2\mathbf{J}(t)}(1 - M),$$
$$\frac{d\mathbf{J}(t)^2}{dt} \leq M^2(1 - M).$$

Remarks

- "Original" approach for the study of the paradigm **Convection/Diffusion**. Particularity of this model: dichotomy explosion vs global existence appears in the one-dimensional case.
- **Global Existence** is proved by using a mixt of Gagliardo-Nirenberg inequalities type together with interpolation inequalities, the novelty here is to use a trace like Sobolev inequality.
- **Link with Stefan problem**: A change of variables $\phi(t, x) = -u(t, s(t) - x)$ gives that:

$$\begin{cases} \partial_t \phi(t, x) = \partial_{xx} \phi(t, x) - s'(t) \partial_x \phi(t, x), & t > 0, x \in (0, +\infty), \\ \lim_{x \rightarrow +\infty} \partial_x \phi(t, x) = 0, & \phi(t, 0) = 0, \quad \partial_x \phi(t, 0) = -s'(t). \end{cases}$$

Differentiating this equation gives the "polarisation" model (with $n(t, x) = \partial_x \phi(t, x)$).

Remarks (2)

- Take less restrictive assumptions on $n_0(x)$ by using the smoothing effects of the Laplacian operator.
- Use the second momentum to prove the blow-up character of the solution, but this does not provide the critical mass.
- Use the Laplace transform to prove the blow-up character of the solution and this provides the critical mass.
- Long time behaviour of the solution?

Long time behaviour of the solution

$$\partial_t n(t, x) = \partial_{xx} n(t, x) + n(t, 0) \partial_x n(t, x),$$

- Does there exist stationary solutions? (yes iff $M = 1$)
- If $M = 1$ does the solution **tend** to the stationary solution?
- What if $M < 1$?

Long time behaviour of the solution in the critical case

$M = 1$

Equilibrium configuration is given by:

$$h_\alpha(x) = \alpha e^{-\alpha x}, \text{ with } \alpha^{-1} = \mathbf{J}(0) > 0.$$

Lemma

As time goes to infinity, the molecular markers density converges (in relative entropy) towards $h_\alpha(x)$.

The relative entropy is:

$$\mathbf{H}(t) = \int_{x>0} \frac{n(t, x)}{h_\alpha(x)} \log \left(\frac{n(t, x)}{h_\alpha(x)} \right) h_\alpha(x) \, dx.$$

Ideas of the proof

Compute the time evolution of the relative entropy:

$$\begin{aligned} \mathbf{H}(t) &= \int_{x>0} \frac{n(t,x)}{h_\alpha(x)} \log\left(\frac{n(t,x)}{h_\alpha(x)}\right) h_\alpha(x) dx \\ \frac{d\mathbf{H}(t)}{dt} &= \int_{x>0} \partial_t n(t,x) (\log(n(t,x)) + 1 - \log \alpha + \alpha x) dx \\ &= -4 \int_{x>0} (\partial_x \sqrt{n}(t,x))^2 dx + n(t,0)^2 + \alpha n(t,0)(1-M) \\ &\leq 0. \end{aligned}$$

The last inequality is a consequence of the trace inequality

$$n(t,0)^2 \leq 4M \int_{x>0} (\partial_x \sqrt{n}(t,x))^2 dx.$$

and $M = 1$.

Long time behaviour of the solution in the sub-critical case

$$M < 1$$

One expects the density $n(t, x)$ to decay self-similarly. For this purpose the density is appropriately rescaled:

$$n(t, x) = \frac{1}{\sqrt{1+2t}} u \left(\log \sqrt{1+2t}, \frac{x}{\sqrt{1+2t}} \right).$$

The new density $u(\tau, y)$ satisfies:

$$\partial_\tau u(\tau, y) = \partial_{yy} u(\tau, y) + u(\tau, 0) \partial_y u(\tau, y) + \partial_y (yu(\tau, y)),$$

and no-flux boundary conditions: $\partial_y u(\tau, 0) + u(\tau, 0)^2 = 0$.

Long time behaviour of the solution in the sub-critical case $M < 1$ (ctd)

The expected self-similar profile writes: $g_\alpha(y) = \alpha \exp(-\alpha y - y^2/2)$, where α is given by the relation $P(\alpha) = M$ and P is the increasing function given by:

$$P(\alpha) = \int_{y>0} \exp\left(-y - \frac{y^2}{2\alpha^2}\right) dy, \quad \left\{ \begin{array}{l} \lim_{\alpha \rightarrow 0} P(\alpha) = 0 \\ \lim_{\alpha \rightarrow +\infty} P(\alpha) = 1 \end{array} \right. .$$

Lemma

As time goes to infinity, the first momentum $\mathbf{J}(\tau)$ of the density converges to $\alpha(1 - M)$ and the molecular markers density converges (in relative entropy) towards $g_\alpha(y)$.

Ideas of the proof

Again it relies on the evolution of relative entropy:

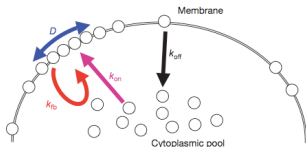
$$\mathbf{H}(\tau) = \int_{y>0} \frac{u(\tau, y)}{g_\alpha(y)} \log \left(\frac{u(\tau, y)}{g_\alpha(y)} \right) g_\alpha(y) \, dy,$$

$$\begin{aligned} \frac{d\mathbf{H}(\tau)}{d\tau} &= \int_{y>0} \partial_t u(\tau, y) \left(\log(u(\tau, y)) + \alpha y + \frac{y^2}{2} \right) \, dy \\ &= - \int_{y>0} u(\tau, y) \left(\frac{\partial_y u(\tau, y)}{u(\tau, y)} + y \right)^2 \, dy + u(\tau, 0)^2 - u(\tau, 0)\mathbf{J}(\tau) \\ &\quad + \alpha u(\tau, 0) - \alpha \mathbf{J}(\tau) - \alpha u(\tau, 0)M. \end{aligned}$$

The "crucial" inequality is:

$$(u(\tau, 0) - \mathbf{J}(\tau))^2 \leq M \int_{y>0} u(\tau, y) \left(\frac{\partial_y u(\tau, y)}{u(\tau, y)} + y \right)^2 \, dy.$$

Analysis of a coupled ODE/PDE model



In this new setting, the chemical is supplied by a quantity $\mu(t)$ which evolves by exchanging particles at the boundary $x = 0$:

$$\begin{cases} \partial_t n(t, x) = \partial_{xx} n(t, x) + \mu(t) \partial_x n(t, x), & t > 0, x \in (0, +\infty) \\ \mu'(t) = n(t, 0) - \mu(t), \end{cases}$$

together with the initial conditions: $n(t = 0, x) = n_0(x) \geq 0$ et $\mu(t = 0) = \mu_0$.

The conservation of the total mass of particles:

$$\int_{x>0} n(t, x) \, dx + \mu(t) = M,$$

and boundary condition:

$$\partial_x n(t, 0) + \mu(t) n(t, 0) = \mu'(t).$$

Long time convergence if $M > 1$

$$m(t) = \int_{x>0} n(t, x) \, dx.$$

(note that $m'(t) + \mu'(t) = 0$).

We introduce again the relative entropy:

$$\mathbf{H}(t) = \int_{x>0} \frac{n(t, x)}{m(t)h(x)} \log \left(\frac{n(t, x)}{m(t)h(x)} \right) h(x) \, dx,$$

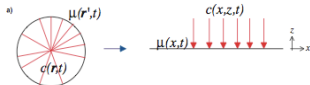
where the expected profile h is given by:

$$h(x) = \bar{\mu} \exp(-\bar{\mu}x), \quad \bar{\mu} = M - 1.$$

Lemma

As time goes to infinity, the mass $m(t)$ of the density converges to 1 and the molecular markers density converges (in relative entropy) towards $h(x)$.

Two dimensional case: Model 1

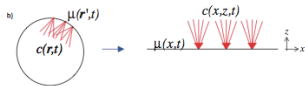


Theorem (Blow-up in dimension two)

Assume that $n_0 \in L^2 \cap L^1((1 + |\mathbf{x}|^2) dx)$. Assume in addition that $\mathbf{I}(0) < CM^3$. Then the solution to model 1 blows up in finite time.

This does not mean polarisation!

Two dimensional case: Model 2



???? about blow-up character

Only heuristics.

Heuristics

1. Goal is to give formal arguments motivating the differences arising in the dynamics of the two models.
2. Notice that the two possible drifts \mathbf{u}_1 and \mathbf{u}_2 **share common features**: they are both divergence free and their normal components at the boundary coincide:

$$u_1 \cdot \mathbf{e}_z = u_2 \cdot \mathbf{e}_z = -n(x, 0), \quad \text{on } \mathbb{R} \times \{0\}.$$

3. On the other hand, **a key difference** holds when looking at the tangential component:

$$u_1 \cdot \mathbf{e}_x = 0, \tag{1}$$

$$u_2 \cdot \mathbf{e}_x = -\pi \mathcal{H}n(\cdot, 0), \tag{2}$$

where \mathcal{H} denotes the one-dimensional Hilbert transform (with respect to the x variable):

$$\mathcal{H}\rho(x) = \frac{1}{\pi} \text{p.v.} \int_{\mathbb{R}} \frac{1}{x-y} \rho(y) dy. \tag{3}$$

Heuristics (2)

- **Numerical simulations** suggest that in the super-critical case, the density $n(t, x, z)$ concentrate on the boundary $\{z = 0\}$.
- Postulating the ansatz $n(t, x, z) = \nu(t, x)\delta(z = 0)$, we can formally write the dynamics of $\nu(t, x)$ for the two cases. Integrating the equation with respect to z , we obtain:

$$\partial_t \int_{z>0} n(t, x, z) dz = \partial_{xx} \left(\int_{z>0} n(t, x, z) dz \right) - \partial_x \left(\int_{z>0} n(t, x, z) \mathbf{u} \cdot \mathbf{e}_x \right)$$

- $\mathbf{u}_1 \cdot \mathbf{e}_x = 0$: **diffusion equation** for ν :

$$\partial_t \nu(t, x) = \partial_{xx} \nu(t, x).$$

- $\mathbf{u}_2 \cdot \mathbf{e}_x = -\pi \mathcal{H}n(\cdot, 0)$:

$$\partial_t \nu(t, x) = \partial_{xx} \nu(t, x) + \pi \partial_x (\nu(t, x) \mathcal{H} \nu(t, x)).$$

This latter equation exhibits **blow-up** if $\int_{\mathbb{R}} \nu(t, x) dx$ is above 2
c.f. V. Calvez, B. Perthame and M. Sharifi Tabar.

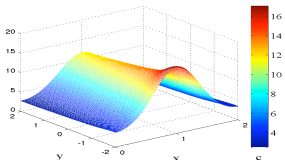
Heuristics (3)

To conclude:

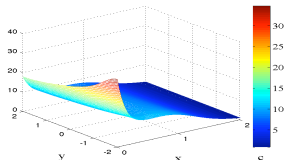
- we expect the solution to concentrate on the boundary in the super-critical case for both choices of \mathbf{u} ,
- however transversal dynamics are very different:
 - boundary diffusion dominates in the first case,
 - in the second case, the attraction kernel within this peculiar variant of Keller-Segel equation possesses a logarithmic singularity, therefore it admits a critical mass phenomenon and may lead to blow-up if the mass is large enough.

Verification on **numerical simulations**.

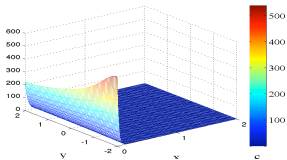
Numerical simulations u_1



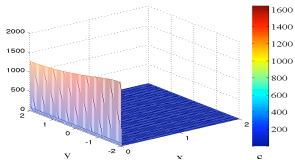
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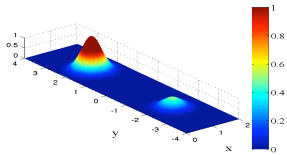


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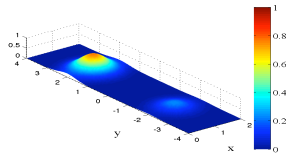


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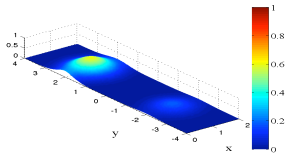
Numerical simulations u_2



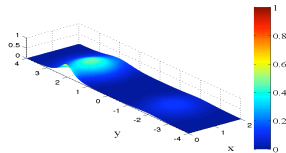
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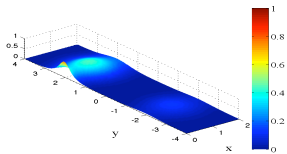
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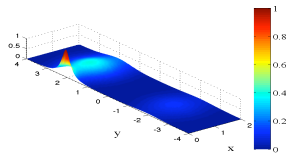
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Thank you for your attention....