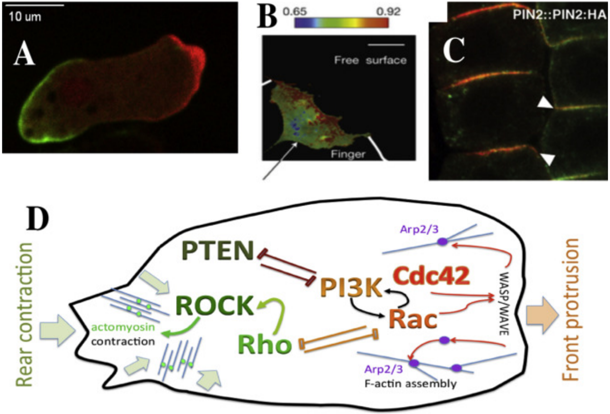
An obstacle problem for cell polarization

Barbara Niethammer

Institut für Angewandte Mathematik
Universität Bonn

joint work with
Anna Logioti (Bonn), Matthias Röger (Dortmund)
and Juan Velázquez (Bonn)

Cell polarization



Mechanisms of cell polarization

(Rappel & Edelstein-Keshet '17)

Setting

Active/inactive protein on membrane

$$u, v \colon \Gamma \to [0, \infty)$$

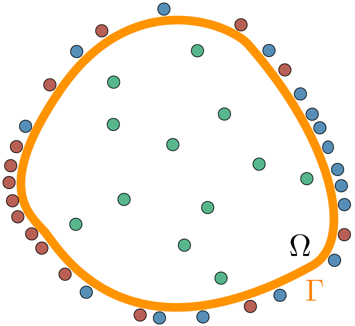
Inactive protein in cell

$$w \colon \Omega \to [0, \infty)$$

External signal:

$$f \colon \Gamma \to \mathbb{R}$$

$$0 < f_{\min} \leq f \leq f_{\max}$$



Overview

- Mechanisms that we take into account
- A bulk-surface reaction-diffusion system: steady states
- **Scaling limit I:**

$$D := \frac{\text{Diffusion coefficient cytosol}}{\text{Diffusion coefficient membrane}} \to \infty$$

- **Scaling limit II:**
  Large rate constants $\rightsquigarrow$ obstacle problem
- **Analysis of obstacle problem:**
  characterization of polarized states
- **Time-dependent problem:** Convergence to steady states
- The case $D < \infty$

Mechanisms

- Activation by external signal

  Linear kinetic law, rate constant: r

- Exchange inactive protein on membrane/interior of cell

  Linear kinetic law, attach-/detachment rates: a, b

- Deactivation needs catalization by enzymes

  Michaelis-Menten law: $s\frac{u}{1+u}$

- Time scale such that diffusion constant on membrane set to one

Reaction-diffusion model (Rätz & Röger, '12)

Bulk-surface-reaction-diffusion

$$
\begin{aligned}
\partial_t u &= \Delta u + r\, fv - s\frac{u}{1+u} && \text{on } \Gamma \times (0, T) \\
\partial_t v &= \Delta v - r\, fv + s\frac{u}{1+u} - av + bw && \text{on } \Gamma \times (0, T) \\
\partial_t w &= D\Delta w && \text{in } \Omega \times (0, T) \\
-D\partial_n w &= -av + bw && \text{on } \Gamma \times (0, T)
\end{aligned}
$$

Here

- $a, b > 0$: attachment/detachment rates
- $r, s > 0$: reaction rates
- $u \mapsto \frac{u}{1+u}$ Michaelis-Menten law

Well-posedness, properties and steady states

Theorem I: (Hausberg & Röger, ’18)
For nonnegative L^2-data there exists a unique non-negative weak solution for all times. This solution conserves the mass, that is

$$\int_\Omega w\,dx + \int_\Gamma (u+v)\,ds = m \qquad \text{for all } t \geq 0$$

Theorem II: For any $m > 0$ there exists a smooth nonnegative stationary solution with mass m

$$\begin{aligned} 0 &= \Delta u + r\,fv - s\tfrac{u}{1+u} && \text{on } \Gamma \\ 0 &= \Delta v - r\,fv + s\tfrac{u}{1+u} - av + bw && \text{on } \Gamma \\ 0 &= D\Delta w && \text{in } \Omega \\ -D\partial_n w &= -av + bw && \text{on } \Gamma \end{aligned}$$

Infinite cytosolic diffusion

Motivation:

typically cytosolic diffusion $\gg$ diffusion on membrane

Infinite diffusion: For $D \to \infty$ we obtain

$$
\begin{aligned}
0 &= \Delta u + r\, fv - s\tfrac{u}{1+u} && \text{on } \Gamma \\
0 &= \Delta v - r\, fv + s\tfrac{u}{1+u} - av + bw && \text{on } \Gamma \\
w &= m - \int_\Gamma (u+v)\, ds
\end{aligned}
$$

Scaling regime

Rescaling

$$a, b, r, s \rightsquigarrow \frac{a}{\varepsilon}, \frac{b}{\varepsilon}, \frac{r}{\varepsilon}, \frac{s}{\varepsilon}, \qquad m \rightsquigarrow \frac{m}{\varepsilon}, \qquad u_\varepsilon := \varepsilon u$$

Rescaled equations: $(a, b, r, s = 1)$

$$\begin{aligned} 0 &= \Delta u_\varepsilon + f v_\varepsilon - \tfrac{u_\varepsilon}{\varepsilon + u_\varepsilon} && \text{on } \Gamma \\ 0 &= \varepsilon \Delta v_\varepsilon - f v_\varepsilon + \tfrac{u_\varepsilon}{\varepsilon + u_\varepsilon} - v_\varepsilon + w_\varepsilon && \text{on } \Gamma \\ \varepsilon w_\varepsilon &= m - \int_\Gamma \big(u_\varepsilon + \varepsilon v_\varepsilon\big)\, ds \end{aligned}$$

Scaling limit: $\varepsilon \to 0$

$$0 = \Delta u_\varepsilon + f v_\varepsilon - \frac{u_\varepsilon}{\varepsilon + u_\varepsilon} \qquad \text{on } \Gamma \tag{1}$$

$$0 = \varepsilon \Delta v_\varepsilon - f v_\varepsilon + \frac{u_\varepsilon}{\varepsilon + u_\varepsilon} - v_\varepsilon + w_\varepsilon \qquad \text{on } \Gamma \tag{2}$$

$$\varepsilon w_\varepsilon = m - \int_\Gamma (u_\varepsilon + \varepsilon v_\varepsilon)\, ds \tag{3}$$

Procedure:

- From (3): $\int_\Gamma u_\varepsilon \leq m$
- Integrating (1): $\int_\Gamma v_\varepsilon \leq C$
- Hence there exist weak limits

$$u_\varepsilon \rightharpoonup u\,, \qquad v_\varepsilon \rightharpoonup v \quad \text{in } \mathcal{M}_+$$

- Integrating (2): $w_\varepsilon = \frac{1}{|\Gamma|} \int_\Gamma v_\varepsilon \to := \alpha$
- Equation (3): $\int_\Gamma u\, ds = m$

Scaling limit (ctd.)

$$0 = \Delta u_\varepsilon + f v_\varepsilon - \frac{u_\varepsilon}{\varepsilon + u_\varepsilon} \qquad \text{on } \Gamma$$

$$0 = \varepsilon \Delta v_\varepsilon - f v_\varepsilon + \frac{u_\varepsilon}{\varepsilon + u_\varepsilon} - v_\varepsilon + w_\varepsilon \qquad \text{on } \Gamma$$

Procedure (ctd.):

- $$\frac{u_\varepsilon}{\varepsilon + u_\varepsilon} \overset{*}{\rightharpoonup} \xi \in [0,1] \text{ weakly* in } L^\infty(\Gamma)$$
- From (2):
  $$(f+1)v_\varepsilon \rightharpoonup \xi + \alpha \quad \Rightarrow \quad f v_\varepsilon \to \frac{f}{f+1}(\xi + \alpha)$$
- From (1):
  $$-\Delta u = g\alpha - (1-g)\xi \quad \text{with } g := \frac{f}{f+1}$$
- $u_\varepsilon \to u$ in $L^1(\Gamma) \Rightarrow \xi u = u$ a.e.

Scaling limit

Proposition: For $\varepsilon \to 0$

$$u_\varepsilon \to u \geq 0 \qquad \text{in } L^1(\Gamma)$$

$$\tfrac{u_\varepsilon}{\varepsilon + u_\varepsilon} \overset{*}{\rightharpoonup} \xi \in [0,1] \qquad \text{weakly* in } L^\infty(\Gamma) \quad \text{with } \xi u = u \quad \text{a.e. on } \Gamma$$

and there exists $\alpha \geq 0$ such that

$$-\Delta u = \alpha g - (1-g)\xi \qquad \text{on } \Gamma$$

$$\int_\Gamma u \, ds = m$$

Furthermore $u \in W^{2,p}(\Gamma)$ for all $p \in [0, \infty)$

Analysis of steady states

$$-\Delta u = \alpha g - (1-g)\xi \qquad \text{on } \Gamma$$

$$\int_\Gamma u \, ds = m$$

Formulas for α:

$$\alpha = \frac{\int_{\{u>0\}}(1-g)\,ds}{\int_{\{u>0\}} g\,ds} = \frac{\int_\Gamma (1-g)\xi\,ds}{\int_\Gamma g\,ds}$$

Polarized states:

$$\text{if} \quad |\{u>0\}| > 0 \;\text{ and }\; |\{u=0\}| > 0$$

First observations for $-\Delta u = \alpha g - (1-g)\xi$

Observation I:

u is constant iff g is constant $\Rightarrow$ assume g is not constant

Observation II:

$$\alpha = \frac{\int_\Gamma (1-g)\xi \, ds}{\int_\Gamma g \, ds} \leq \alpha_* := \frac{\int_\Gamma (1-g) \, ds}{\int_\Gamma g \, ds}$$

and

$$\alpha_0 := \frac{1-g_{\max}}{g_{\max}} < \alpha_* = \frac{\int_\Gamma (1-g) \, ds}{\int_\Gamma g \, ds}$$

Another viewpoint for $-\Delta u = \alpha g - (1-g)\xi$

Fix $0 \le \alpha \le \alpha_*$ and consider

$$u = \arg\min \left\{ \tfrac{1}{2} \int_\Gamma |\nabla v|^2 + \int_\Gamma (1-g)v - \alpha g v \mid v \in H^1(\Gamma)\,,\ v \ge 0 \right\}$$

Minimizers $\leftrightarrow$ solutions to the obstacle problem

Lemma:

- $\forall\, 0 \le \alpha \le \alpha_*$ a minimizer exists.
- Minimizer $u \equiv 0$ if $\alpha \in [0, \alpha_0)$
- Minimizers unique for $\alpha < \alpha_*$
  unique up to additive constant for $\alpha = \alpha_*$.
- The map $\alpha \mapsto (u, \xi)$ is strictly increasing on (α_0, α_*)

Construction of critical mass

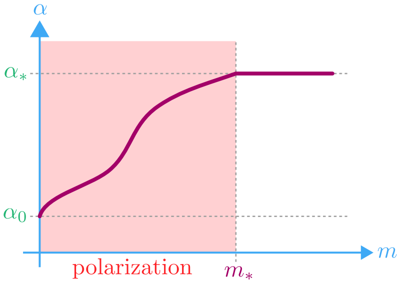
Critical mass:

Let u_* be the unique solution to

$$-\Delta u_* = -(1-g) + \alpha_* g$$
$$\min u_* = 0$$

and set

$$m_* := \int_\Gamma u_* \, ds$$



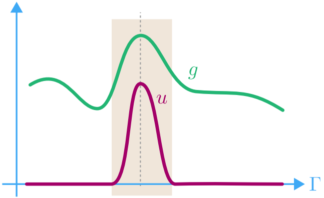
Theorem: For any $m > 0$ there exists a unique solution (u, α)

- if $m > m_*$ then $\alpha = \alpha_*$, $|\{u = 0\}| = 0$ and $u = u_* + m - m_*$
- if $m < m_*$ then $|\{u = 0\}| > 0$ and $\alpha < \alpha_*$
- if $m = m_*$ then polarization may or may not occur

Localization for $m \to 0$

Set where g is maximal:

$$S := \{x \in \Gamma \mid g(x) = g_{\max}\}$$



Theorem: Let $m_n \to 0$. Then

- $u_n \to 0$ in $H^2(\Gamma)$
- $\forall \delta > 0\ \exists n_0$ such that if $\mathrm{dist}(x, S) > \delta$ then $u_n(x) = 0\ \forall n \geq n_0$

The parabolic obstacle problem ($D = \infty$)

Equation:

$$\begin{aligned} \partial_t u - \Delta u &= -(1-g)\xi + \alpha g && \text{on } \Gamma \times (0, T) \\ u \geq 0\,, \qquad u\xi &= u && \text{on } \Gamma \times (0, T) \\ u(\cdot, 0) &= u_0 && \text{on } \Gamma \end{aligned}$$

Here

$$\alpha(t) = \frac{\int_\Gamma (1-g)\xi\, ds}{\int_\Gamma g\, ds} = \frac{\int_{\{u(\cdot,t)>0\}} (1-g)\, ds}{\int_{\{u(\cdot,t)>0\}} g\, ds}$$

Mass conservation

$$\int_\Gamma u(\cdot, t)\, ds = \int_\Gamma u_0\, ds =: m$$

L^1-contraction

Theorem: Let (u_1, ξ_1, α_1) and (u_2, ξ_2, α_2) be two solutions, then

$$t \mapsto \int_\Gamma \left(u_1 - u_2\right)_+ (\cdot, t)\, ds \qquad \text{is decreasing on } [0, \infty)$$

Corollary: Uniqueness of solutions

Theorem: If $g = g(x)$, then steady states are globally stable.

The limit model for $D < \infty$

Nonlocal obstacle problem:

$$
\begin{aligned}
\partial_t u - \Delta u &= -(1-g)\xi + gw && \text{on } \Gamma_T \\
\xi u &= u && \text{on } \Gamma_T \\
0 &= \Delta w && \text{in } \Omega_T \\
-D\partial_n w &= (1-g)\xi - gw && \text{on } \Gamma_T
\end{aligned}
$$

Results: (analogous to the case $D = \infty$)

- Existence and uniqueness of steady states
- Existence of critical mass for polarization
- L^1-contraction and global stability of steady states

Further aspects: regularity

Recall:

$$
\begin{aligned}
\partial_t u - \Delta u &= -(1-g)\xi + \alpha g && \text{on } \Gamma \times (0,T) \\
u \geq 0\,, \qquad u\xi &= u && \text{on } \Gamma \times (0,T) \\
u(\cdot,0) &= u_0 && \text{on } \Gamma
\end{aligned}
$$

Here

$$
\alpha(t) = \frac{\int_\Gamma (1-g)\xi \, ds}{\int_\Gamma g \, ds} = \frac{\int_{\{u(\cdot,t)>0\}} (1-g) \, ds}{\int_{\{u(\cdot,t)>0\}} g \, ds}
$$

So far: $\alpha \in L^\infty(0,T)$

Question: Can we expect that α and $\{u(\cdot,t) > 0\}$ change continuously in time?

On the continuity of α

Continuity as $t \to 0$:

- Needs

$$-(1-g) + \alpha(0)g \leq -\theta < 0 \quad \text{in } \{u_0 = 0\} \qquad (*)$$

  and $\mathcal{H}^2(\partial\{u_0 > 0\}) = 0$
- If $(*)$ is not satisfied, then in general $\lim_{t\to 0} \alpha(t) \neq \alpha(0)$ and the positivity set of u jumps
- Characterization of jump possible

Remark:

- For specific data: global continuity in time

Summary and Outlook

Starting point:

- Bulk-surface reaction-diffusion model for cell-polarization

Fast reaction limit

- Obtain obstacle type problem

Main results:

- Critical mass for polarization of steady states
- Localization
- Global stability of steady states
- Regularity theory delicate

Outlook:

- Fast changing external signal

Literature

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