

Mathematical modeling of apoptosis in cell collective dynamics

microscopic and macroscopic points of view

L. NAVORET¹ R. SUBLET¹ M. SZOPOS²

¹IRMA, Université de Strasbourg

²MAP5, Université Paris Cité

Doctoral seminar of Strasbourg



I. Introduction

II. Microscopic model

III. Macroscopic model

IV. Conclusion

Introduction

Objectif: Design a mathematical model to study the role of **apoptosis** (*i.e.* **programmed cell death**) on collective cell dynamics, from microscopic and macroscopic points of view.

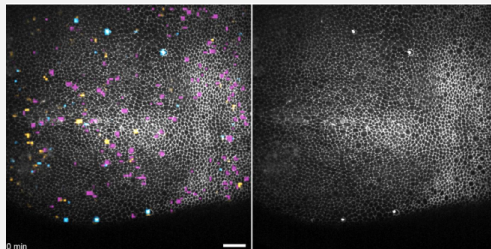


Figure: A. Villars et al., *Development* (2023)

Context: ANR MAPEFLU project in collaboration with biophysicists (IGBMC, Strasbourg) and biologists (Institut Pasteur, Paris).

I. Introduction

II. Microscopic model

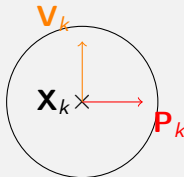
III. Macroscopic model

IV. Conclusion

Model

Consider N cells that evolve in a bounded domain $\Omega \subset \mathbb{R}^2$. Each cell has a position $\mathbf{X}_k(t) \in \mathbb{R}^2$, a velocity $\mathbf{V}_k(t) \in \mathbb{R}^2$, a polarity $\mathbf{P}_k(t) \in \mathbb{S}^1$, a radius $R_k(t) \in [0, R_{\max}]$ and an apoptotic state $\alpha_k \in \{0, 1\}$.

- ▶ positions: $\mathbf{X} = (\mathbf{X}_k)_k \in \mathbb{R}^{2N}$
- ▶ velocities: $\mathbf{V} = (\mathbf{V}_k)_k \in \mathbb{R}^{2N}$
- ▶ polarities: $\mathbf{P} = (\mathbf{P}_k)_k \in (\mathbb{S}^1)^N$
- ▶ radius of the cells: $R = (R_k)_k \in [0, R_{\max}]^N$
- ▶ apoptotic states: $\alpha = (\alpha_k)_k \in \{0, 1\}^N$
- ▶ birth and apoptotic times: $(T_p)_k, (T_a)_k \in \mathbb{R}$



Model ingredients

The proposed model includes the following ingredients:

- ▶ contact forces ¹
- ▶ soft attraction-repulsion forces ²
- ▶ polarity alignment interactions (Vicsek-type) ³
- ▶ apoptotic events

Adapted from a model validated against experimental data ⁴.

¹B. Maury and J. Venel, *ESAIM Math. Model. Numer. Anal.* (2011)

²C. Beatrice et al., *Soft Matter* (2023)

³T. Vicsek et al., *Phys. Rev. Lett.* (1995)

⁴S. L. Vecchio et al., *Nature Physics* (2024)

Equations on $\mathbf{X}$, $\mathbf{V}$, $\mathbf{P}$ and R

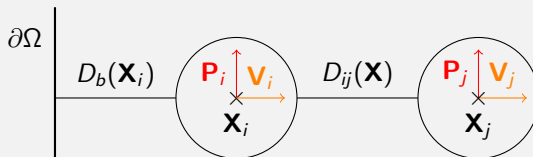
$$\begin{aligned}
 \frac{d\mathbf{X}_k(t)}{dt} &= \mathbf{V}_k(t) \\
 \mathbf{V} &= \text{Proj}_{\mathcal{C}_{\mathbf{X}}}(c\mathbf{P} + \gamma\mathbf{F}(\mathbf{X})) \\
 d\mathbf{P}_k &= \text{Proj}_{\mathbf{P}_k^\perp} \circ \left(\mu(\bar{\mathbf{P}}_k - \mathbf{P}_k)dt + \delta(\mathbf{V}_k / \|\mathbf{V}_k\| - \mathbf{P}_k)dt \right. \\
 &\quad \left. + \nu(\mathbf{L}_k - \mathbf{P}_k)dt + \sqrt{2D}(dB_t)_k \right) \\
 R_k(t) &= \begin{cases} \left(\min(R_0, \mathbb{1}_{[(T_p)_k, \infty[} \beta(t - (T_p)_k)) \right)_+ & \text{if } \alpha_k(t) = 0 \\ \left(R_0 + \mathbb{1}_{[(T_a)_k, +\infty[} \beta((T_a)_k - t) \right)_+ & \text{if } \alpha_k(t) = 1 \end{cases} \\
 \alpha_k(t) &= \mathbb{1}_{[(T_a)_k, +\infty[}(t)
 \end{aligned}$$

Proliferation and apoptosis: $(T_a)_k \sim \mathcal{E}(\lambda_a)$ and $(T_p)_k \sim \mathcal{E}(\lambda_p)$:
proliferation and apoptosis at rates λ_p and λ_a

$$\begin{aligned}\frac{d\mathbf{X}_k(t)}{dt} &= \mathbf{V}_k(t) \\ \mathbf{V} &= \text{Proj}_{\mathcal{C}_\mathbf{X}}(c\mathbf{P} + \gamma\mathbf{F}(\mathbf{X}))\end{aligned}$$

Contact force: projection onto the set of admissible velocities:

$$\mathcal{C}_\mathbf{X} = \{\mathbf{V} \in \mathbb{R}^{2N} \mid \forall i < j, D_{i,j}(\mathbf{X}) = 0 \implies \nabla D_{i,j}(\mathbf{X}) \cdot \mathbf{V} \geq 0, \\ \forall i, D_b(\mathbf{X}_i) = 0 \implies \nabla D_b(\mathbf{X}_i) \cdot \mathbf{V}_i \geq 0\}.$$



$$\begin{aligned}\frac{d\mathbf{X}_k(t)}{dt} &= \mathbf{V}_k(t) \\ \mathbf{V} &= \text{Proj}_{\mathcal{C}_X}(c\mathbf{P} + \gamma\mathbf{F}(\mathbf{X}))\end{aligned}$$

Attraction-repulsion force

$$\mathbf{F}_k(\mathbf{X}) = \sum_{j, \|\mathbf{X}_k - \mathbf{X}_j\| \leq R_{\text{int}}^{\text{ar}}} \nabla_{\mathbf{X}_k} W_j(\|\mathbf{X}_k - \mathbf{X}_j\|)$$

We consider the following interaction potential, inspired by ^a and adapted to account for apoptotic events:

$$W_j(r) = -((1 - \alpha_j)\kappa + \alpha_j\kappa_{\text{apop}}) (r^2/2 - r^3/(3D_c))$$

^aC. Beatrice et al., *Soft Matter* (2023)

$$\begin{aligned}
\frac{d\mathbf{X}_k(t)}{dt} &= \mathbf{V}_k(t) \\
\mathbf{V} &= \text{Proj}_{\mathcal{C}_X}(c\mathbf{P} + \gamma\mathbf{F}(\mathbf{X})) \\
d\mathbf{P}_k &= \text{Proj}_{\mathbf{P}_k^\perp} \circ \left(\mu(\bar{\mathbf{P}}_k - \mathbf{P}_k)dt + \delta(\mathbf{V}_k / \|\mathbf{V}_k\| - \mathbf{P}_k)dt \right. \\
&\quad \left. + \sqrt{2D}(dB_t)_k \right)
\end{aligned}$$

Vicsek-type interactions: competition between

- ▶ alignment to the local averaged polarity: $\bar{\mathbf{P}}_k = \frac{\sum_{j, \|x_j - x_k\| \leq R_{\text{int}}^{\text{po}}} \mathbf{P}_j}{\left\| \sum_{j, \|x_j - x_k\| \leq R_{\text{int}}^{\text{po}}} \mathbf{P}_j \right\|}$
- ▶ Gaussian white noise: dB_t

Relaxation to the velocity direction $\mathbf{V}_k / \|\mathbf{V}_k\|$

Projection on $\mathbf{P}_k^\perp$ so that the polarity remains of norm 1

$$\begin{aligned}
\frac{d\mathbf{X}_k(t)}{dt} &= \mathbf{V}_k(t) \\
\mathbf{V} &= \text{Proj}_{\mathcal{C}_X}(c\mathbf{P} + \gamma\mathbf{F}(\mathbf{X})) \\
d\mathbf{P}_k &= \text{Proj}_{\mathbf{P}_k^\perp} \circ \left(\mu(\bar{\mathbf{P}}_k - \mathbf{P}_k)dt + \delta(\mathbf{V}_k / \|\mathbf{V}_k\| - \mathbf{P}_k)dt \right. \\
&\quad \left. + \nu(\mathbf{L}_k - \mathbf{P}_k)dt + \sqrt{2D}(dB_t)_k \right)
\end{aligned}$$

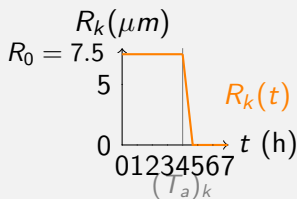
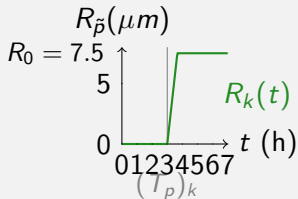
Apoptotic events: polarity

- closure towards the apoptotic cells

$$\mathbf{L}_k = \sum_{j, \|\mathbf{X}_j - \mathbf{X}_k\| \leq R_{\text{int}}^{\text{po}}} \alpha_j \frac{(\mathbf{X}_j - \mathbf{X}_k)}{\|(\mathbf{X}_j - \mathbf{X}_k)\|}$$

$$\begin{aligned}
\frac{d\mathbf{X}_k(t)}{dt} &= \mathbf{V}_k(t) \\
\mathbf{V} &= \text{Proj}_{\mathcal{C}_\mathbf{X}}(c\mathbf{P} + \gamma\mathbf{F}(\mathbf{X})) \\
d\mathbf{P}_k &= \text{Proj}_{\mathbf{P}_k^\perp} \circ \left(\mu(\bar{\mathbf{P}}_k - \mathbf{P}_k)dt + \delta(\mathbf{V}_k / \|\mathbf{V}_k\| - \mathbf{P}_k)dt \right. \\
&\quad \left. + \nu(\mathbf{L}_k - \mathbf{P}_k)dt + \sqrt{2D}(dB_t)_k \right) \\
R_k(t) &= \begin{cases} \left(\min(R_0, \mathbb{1}_{[(T_p)_k, \infty)}[\beta(t - (T_p)_k)]) \right)_+ & \text{if } \alpha_k(t) = 0 \\ \left(R_0 + \mathbb{1}_{[(T_a)_k, +\infty)}[\beta((T_a)_k - t)] \right)_+ & \text{if } \alpha_k(t) = 1 \end{cases}
\end{aligned}$$

apoptotic events: radii dynamics



$$\begin{aligned}
\frac{d\mathbf{X}_k(t)}{dt} &= \mathbf{V}_k(t) \\
\mathbf{V} &= \text{Proj}_{\mathcal{C}_\mathbf{X}}(c\mathbf{P} + \gamma\mathbf{F}(\mathbf{X})) \\
d\mathbf{P}_k &= \text{Proj}_{\mathbf{P}_k^\perp} \circ \left(\mu(\bar{\mathbf{P}}_k - \mathbf{P}_k)dt + \delta(\mathbf{V}_k / \|\mathbf{V}_k\| - \mathbf{P}_k)dt \right. \\
&\quad \left. + \nu(\mathbf{L}_k - \mathbf{P}_k)dt + \sqrt{2D}(dB_t)_k \right) \\
R_k(t) &= \begin{cases} \left(\min(R_0, \mathbb{1}_{[(T_p)_k, \infty[} \beta(t - (T_p)_k)) \right)_+ & \text{if } \alpha_k(t) = 0 \\ \left(R_0 + \mathbb{1}_{[(T_a)_k, +\infty[} \beta((T_a)_k - t) \right)_+ & \text{if } \alpha_k(t) = 1 \end{cases} \\
\alpha_k(t) &= \mathbb{1}_{[(T_a)_k, +\infty[}(t)
\end{aligned}$$

Proliferation and apoptosis: $(T_a)_k \sim \mathcal{E}(\lambda_a)$ and $(T_p)_k \sim \mathcal{E}(\lambda_p)$:
proliferation and apoptosis at rates λ_p and λ_a

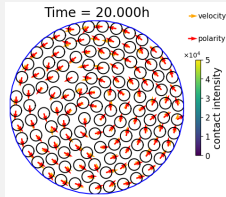
Parameters

Taken from S. L. Vecchio et al., *Nature Physics* (2024), IGBMC, calibrated numerically

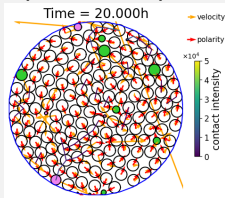
Cells radius	R_0	7.5	μm
Cells comfort radius	R_c	9.5	μm
Cells attraction-repulsion interaction radius	$R_{\text{int}}^{\text{ar}}$	19	μm
Cells polarity interaction radius	$R_{\text{int}}^{\text{po}}$	60	μm
Cell speed	c	21.6	$\mu\text{m h}^{-1}$
Angular diffusion	D	0.96	$\text{rad}^2 \text{h}^{-1}$
Relaxation parameter: polarity to mean polarity	μ	6.2	rad h^{-1}
Relaxation parameter: polarity to velocity	δ	6.2	rad h^{-1}
Rigidity constant	κ	16×10^4	$\text{pN } \mu\text{m}^{-1}$
Inverse friction coefficient	γ	10^{-4}	$\text{pN}^{-1} \text{h}^{-1} \mu\text{m}$
Apoptosis on P	ν	10	rad h^{-1}
Apoptosis spring force (on V)	κ_{apop}	$5 \cdot 10^4$	$\text{pN } \mu\text{m}^{-1}$
Speed of decreasing for radius	β	11.25	$\mu\text{m h}^{-1}$

Simulations: low density

On a disk domain:

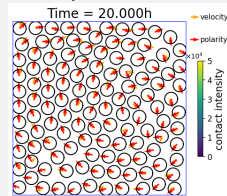


without
apoptosis and proliferation

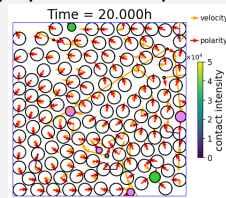


with
apoptosis and proliferation

On a square domain:



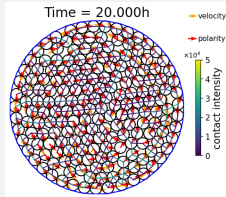
without
apoptosis and proliferation



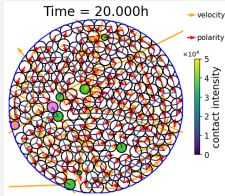
with
apoptosis and proliferation

Simulations: maximal density

On a disk domain:

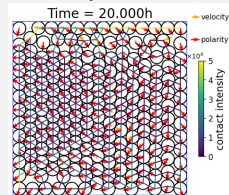


without
apoptosis and proliferation

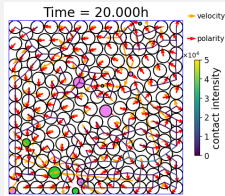


with
apoptosis and proliferation

On a square domain:



without
apoptosis and proliferation



with
apoptosis and proliferation

I. Introduction

II. Microscopic model

III. Macroscopic model

IV. Conclusion

Reminder: microscopic model

$$\left\{ \begin{array}{l} \frac{d\mathbf{X}_k}{dt} = \mathbf{V}_k \\ \mathbf{V}_k = c\mathbf{P}_k - \gamma \nabla_{\mathbf{X}_k} F(\mathbf{X}_k) \\ d\mathbf{P}_k = \text{Proj}_{\mathbf{P}_k^\perp} \circ \left(\mu(\bar{\mathbf{P}}_k(t) - \mathbf{P}_k)dt + \delta(\mathbf{V}_k / \|\mathbf{V}_k\| - \mathbf{P}_k)dt \right. \\ \quad \left. + \nu(\mathbf{L}_k - \mathbf{P}_k)dt + \sqrt{2D} dB_k^t \right) \\ \frac{dR_k}{dt} = \begin{cases} I(R_k) := \beta \left(1 - \frac{R_k(t)}{R_{\max}} \right) R_k(t), & \text{on } [(T_p)_k, (T_a)_k] \\ D(R_k(t)) := -\zeta \left(1 - \frac{R_k(t)}{R_{\max}} \right) R_k(t), & \text{on } [(T_a)_k, (T_f)_k] \end{cases} \end{array} \right.$$

$(T_a)_k \sim \mathcal{E}(\lambda_a)$ and $(T_p)_k \sim \mathcal{E}(\lambda_p)$: proliferation and apoptosis at rates λ_p and λ_a

Remark

Contact forces are replaced by repulsion forces, and radii dynamics are described by a differential equation.

Function of distribution

- ▶ Statistical description of the dynamics in the limit $N \rightarrow \infty$
- ▶ $f(\mathbf{x}, \mathbf{p}, R, t)$: distribution function of cells in the phase space
 $\mathbf{x} \in \mathbb{R}^2$, $\mathbf{p} \in \mathbb{S}^1$, $R \in \mathbb{R}^+$
- ▶ $f(\mathbf{x}, \mathbf{p}, R, t) \delta \mathbf{x} \delta \mathbf{p} \delta R \approx$ number of cells in
 $[\mathbf{x}, \mathbf{x} + \delta \mathbf{x}] \times [\mathbf{p}, \mathbf{p} + \delta \mathbf{p}] \times [R, R + \delta R]$.
- ▶ $f(\mathbf{x}, \mathbf{p}, R, t) = \underbrace{f_0(\mathbf{x}, \mathbf{p}, R, t)}_{\text{non apoptotic cells}} + \underbrace{f_1(\mathbf{x}, \mathbf{p}, R, t)}_{\text{apoptotic cells}}$

We develop a similar methodology to the one proposed in:

- ▶ P. Degond et al., *Communications in Mathematical Sciences* (2015)
- ▶ P. Degond and S. Motsch, *Mathematical Models and Methods in Applied Sciences* (2008)

Mean field equation

► $f(\mathbf{x}, \mathbf{p}, R, t) = \underbrace{f_0(\mathbf{x}, \mathbf{p}, R, t)}_{\text{no apoptotic cells}} + \underbrace{f_1(\mathbf{x}, \mathbf{p}, R, t)}_{\text{apoptotic cells}}$

- transport equation whose characteristic equations are given by the microscopic model

$$\begin{aligned} \partial_t f_0 + \underbrace{\nabla_{\mathbf{x}} \cdot (v_f f_0)}_{\text{advected position}} + \underbrace{\partial_R (I(R) f_0)}_{\text{advected radius}} + \underbrace{\nabla_{\mathbf{p}} \cdot (\text{Proj}_{\mathbf{p}^\perp} \left(\delta(v_f / \|v_f\|) + \nu L_{f_1} + \mu \bar{P}_f \right) f_0)}_{\text{advected polarity}} \\ = D \Delta_{\mathbf{p}} f_0 + \lambda_p \rho(t, x) \mathcal{M}(p) - \lambda_a f_0 \end{aligned}$$

$$v_f(\mathbf{x}, \mathbf{p}) = c\mathbf{p} - \gamma \nabla_{\mathbf{x}} \mathcal{F}_f(\mathbf{x}, t)$$

$$\mathcal{F}_f(\mathbf{x}, t) = \int_{\mathbb{S}^1 \times \mathbb{R}^2 \times \mathbb{R}^+} \mathcal{W} \left(\frac{\|\mathbf{x} - \mathbf{y}\|}{R_{\text{int}}^{\text{ar}}}, R \right) f(\mathbf{y}, \mathbf{p}, R, t) d\mathbf{p} dy dR$$

$$L_{f_1}(\mathbf{x}, t) = \int_{\mathbb{S}^1 \times \mathbb{R}^2 \times \mathbb{R}^+} K \left(\frac{\|\mathbf{x} - \mathbf{y}\|}{R_{\text{int}}^{\text{po}}} \right) \frac{(\mathbf{y} - \mathbf{x})}{\|(\mathbf{y} - \mathbf{x})\|} f_1(\mathbf{y}, \mathbf{p}, R, t) d\mathbf{p} dy dR$$

$$\bar{P}_f(\mathbf{x}, t) = \frac{\mathcal{J}_f(\mathbf{x}, t)}{\|\mathcal{J}_f(\mathbf{x}, t)\|}$$

$$\mathcal{J}_f(\mathbf{x}, t) = \int_{\mathbb{S}^1 \times \mathbb{R}^2 \times \mathbb{R}^+} K \left(\frac{\|\mathbf{x} - \mathbf{y}\|}{R_{\text{int}}^{\text{po}}} \right) f(\mathbf{y}, \mathbf{p}, R, t) p d\mathbf{p} dy dR,$$

Mean field equation

$$\blacktriangleright f(\mathbf{x}, \mathbf{p}, R, t) = \underbrace{f_0(\mathbf{x}, \mathbf{p}, R, t)}_{\text{no apoptotic cells}} + \underbrace{f_1(\mathbf{x}, \mathbf{p}, R, t)}_{\text{apoptotic cells}}$$

- transport equation whose characteristic equations are given by the microscopic model

$$\begin{aligned} \partial_t f_0 + \underbrace{\nabla_{\mathbf{x}} \cdot (v_f f_0)}_{\text{advected position}} + \underbrace{\partial_R(I(R)f_0)}_{\text{advected radius}} + \underbrace{\nabla_{\mathbf{p}} \cdot (\text{Proj}_{\mathbf{p}^\perp} \left(\delta(v_f / \|v_f\|) + \nu L_{f_1} + \mu \bar{P}_f \right) f_0)}_{\text{advected polarity}} \\ = D\Delta_{\mathbf{p}} f_0 + \lambda_p \rho(t, x) \mathcal{M}(p) - \lambda_a f_0 \end{aligned}$$

$$\begin{aligned} \partial_t f_1 + \underbrace{\nabla_{\mathbf{x}} \cdot (v_f f_1)}_{\text{advected position}} + \underbrace{\partial_R(D(R)f_1)}_{\text{advected radius}} + \underbrace{\nabla_{\mathbf{p}} \cdot (\text{Proj}_{\mathbf{p}^\perp} \left(\delta(v_f / \|v_f\|) + \nu L_{f_1} + \mu \bar{P}_f \right) f_1)}_{\text{advected polarity}} \\ = D\Delta_{\mathbf{p}} f_1 + \lambda_a (f_0 - f_1) \end{aligned}$$

- **Rescaling in time:** polarity interaction much faster than the other interactions

$$\hookrightarrow \varepsilon \ll 1$$

$$\begin{aligned} \varepsilon & \left[\partial_t f_0^\varepsilon + \nabla_{\mathbf{x}} \cdot (v_{f^\varepsilon} f_0^\varepsilon) + \delta \nabla_{\mathbf{p}} \cdot (\text{Proj}_{\mathbf{p}^\perp} \frac{v_{f^\varepsilon}^\varepsilon}{\|v_{f^\varepsilon}^\varepsilon\|} f_0^\varepsilon) + \nabla_{\mathbf{p}} \cdot (\text{Proj}_{\mathbf{p}^\perp} G_{f^\varepsilon} f_0^\varepsilon) \right. \\ & \left. + \nu \tilde{Z}_0 \nabla_{\mathbf{p}} \cdot (\text{Proj}_{\mathbf{p}^\perp} \nabla_{\mathbf{x}} \rho_1^\varepsilon f_0^\varepsilon) + \partial_R (I(R) f_0^\varepsilon) - \lambda_\rho \rho^\varepsilon \mathcal{M}(\mathbf{p}) + \lambda_a f_0^\varepsilon \right] \\ & = Q_{\mathbf{p}}(f_0^\varepsilon) \end{aligned}$$

$$v_{f^\varepsilon}^\varepsilon(\mathbf{x}, \mathbf{p}, t) = \mathbf{p} - \nabla_{\mathbf{x}} \int_{\mathbb{R}^+} \left[W(R) \int_{\mathbb{S}^1} f^\varepsilon(\mathbf{x}, \mathbf{p}, R, t) d\mathbf{p} \right] dR$$

$$Q_{\mathbf{p}}(f_0) = -\mu \nabla_{\mathbf{p}} \cdot (\text{Proj}_{\mathbf{p}^\perp} \mathbf{P}_f f_0) + \Delta_{\mathbf{p}} f_0$$

$$\mathbf{P}_f(\mathbf{x}, t) = \frac{J_f}{\|J_f\|}, \quad J_f(\mathbf{x}, t) = \int_{\mathbb{S}^1 \times \mathbb{R}^+} f(\mathbf{x}, \mathbf{p}, R, t) \mathbf{p} d\mathbf{p} dR$$

$$G_f(\mathbf{x}, t) = \frac{k_0}{\|J_f\|} \text{Proj}_{\mathbf{p}_f^\perp} \Delta_{\mathbf{x}} J_f.$$

- **Rescaling in time:** polarity interaction much faster than the other interactions

$$\hookrightarrow \varepsilon \ll 1$$

$$\begin{aligned} & \varepsilon \left[\partial_t f_0^\varepsilon + \nabla_{\mathbf{x}} \cdot (v_{f^\varepsilon} f_0^\varepsilon) + \delta \nabla_{\mathbf{p}} \cdot (\text{Proj}_{\mathbf{p}^\perp} \frac{v_{f^\varepsilon}^\varepsilon}{\|v_{f^\varepsilon}^\varepsilon\|} f_0^\varepsilon) + \nabla_{\mathbf{p}} \cdot (\text{Proj}_{\mathbf{p}^\perp} G_{f^\varepsilon} f_0^\varepsilon) \right. \\ & \quad \left. + \nu \tilde{Z}_0 \nabla_{\mathbf{p}} \cdot (\text{Proj}_{\mathbf{p}^\perp} \nabla_{\mathbf{x}} \rho_1^\varepsilon f_0^\varepsilon) + \partial_R (I(R) f_0^\varepsilon) - \lambda_p \rho^\varepsilon \mathcal{M}(\mathbf{p}) + \lambda_a f_0^\varepsilon \right] \\ & = Q_{\mathbf{p}}(f_0^\varepsilon) \end{aligned}$$

$$Q_{\mathbf{p}}(f_0) = -\mu \nabla_{\mathbf{p}} \cdot (\text{Proj}_{\mathbf{p}^\perp} \mathbf{P}_f f_k) + D \Delta_{\mathbf{p}} f_k$$

$$\mathbf{P}_f(\mathbf{x}, t) = \frac{J_f}{\|J_f\|}, \quad J_f(\mathbf{x}, t) = \int_{\mathbb{S}^1 \times \mathbb{R}^+} f(\mathbf{x}, \mathbf{p}, R, t) \mathbf{p} \, d\mathbf{p} dR$$

$\hookrightarrow$ collision operator $Q_{\mathbf{p}}(f_0)$: non-linear Fokker-Planck operator

$\hookrightarrow$ identical in both equations (on f_0 and f_1)

Study of the operator $Q_{\mathbf{P}}$: equilibrium

Von Mises probability distribution:

$$M_{\mathbf{P}}(\mathbf{p}) = C \exp \left(\frac{\mathbf{p} \cdot \mathbf{P}}{D/\mu} \right), \quad \int_{\mathbb{S}^1} M_{\mathbf{P}}(\mathbf{p}) d\mathbf{p} = 1$$

$$\begin{aligned} Q_{\mathbf{P}}(f_0) &= -\mu \nabla_{\mathbf{p}} \cdot (\text{Proj}_{\mathbf{p}^\perp} \mathbf{P}_f f_k) + D \Delta_{\mathbf{p}} f_k \\ &= \frac{D}{\mu} \nabla_{\mathbf{p}} \cdot \left(M_{\mathbf{P}_f} \nabla_{\mathbf{p}} \left(\frac{f_k}{M_{\mathbf{P}_f}} \right) \right) \end{aligned}$$

Equilibria:

$$\mathcal{E} = \{f \in H^1(\mathbb{S}^1) \mid Q_{\mathbf{P}}(f) = 0\} = \{g M_{\mathbf{P}}(\mathbf{p}) \mid g \in \mathbb{R}_+, \mathbf{P} \in \mathbb{S}^1\}$$

$\hookrightarrow \mathcal{E}$ is of dimension 2.

Limit $\varepsilon \rightarrow 0$

$$\begin{aligned}
 & \varepsilon \left[\partial_t f_0^\varepsilon + \nabla_{\mathbf{x}} \cdot (v_{f^\varepsilon} f_0^\varepsilon) + \delta \nabla_{\mathbf{p}} \cdot (\text{Proj}_{\mathbf{p}^\perp} \frac{v_{f^\varepsilon}^\varepsilon}{\|v_{f^\varepsilon}^\varepsilon\|} f_0^\varepsilon) + \nabla_{\mathbf{p}} \cdot (\text{Proj}_{\mathbf{p}^\perp} G_{f^\varepsilon} f_0^\varepsilon) \right. \\
 & \quad \left. + \nu \tilde{Z}_0 \nabla_{\mathbf{p}} \cdot (\text{Proj}_{\mathbf{p}^\perp} \nabla_{\mathbf{x}} \rho_1^\varepsilon f_0^\varepsilon) + \partial_R (I(R) f_0^\varepsilon) - \lambda_p \rho^\varepsilon \mathcal{M}(\mathbf{p}) + \lambda_a f_0^\varepsilon \right] \\
 & = Q_{\mathbf{p}}(f_0^\varepsilon)
 \end{aligned}$$

► in the limit $\varepsilon \rightarrow 0$, $f_0^\varepsilon \rightarrow f_0$ with

► $Q_{\mathbf{p}}(f_0) = 0$

► $f_0 \in \mathcal{E}$

Therefore:

$$f_0^\varepsilon(\mathbf{x}, \mathbf{p}, R, t) \rightarrow g_0(\mathbf{x}, R, t) M_{\mathbf{P}(\mathbf{x}, t)}(\mathbf{p}), \quad \text{when } \varepsilon \rightarrow 0$$

$$f_1^\varepsilon(\mathbf{x}, \mathbf{p}, R, t) \rightarrow g_1(\mathbf{x}, R, t) M_{\mathbf{P}(\mathbf{x}, t)}(\mathbf{p}), \quad \text{when } \varepsilon \rightarrow 0$$

Need to determine equations on g_0 , g_1 and $\mathbf{P}$.

$$f_k^\varepsilon(\mathbf{x}, \mathbf{p}, R, t) \rightarrow g_k(\mathbf{x}, R, t) M_{\mathbf{p}(\mathbf{x}, t)}(\mathbf{p}), \quad \text{when } \varepsilon \rightarrow 0$$

What do $g_0(\mathbf{x}, R, t)$ and $g_1(\mathbf{x}, R, t)$ represent?

$$\begin{aligned} \int_{\mathbb{R}^+ \times \mathbb{S}^1} f_k^\varepsilon(\mathbf{x}, \mathbf{p}, R, t) d\mathbf{p} dR &\rightarrow \int_{\mathbb{R}^+ \times \mathbb{S}^1} g_k(\mathbf{x}, R, t) M_{\mathbf{p}(\mathbf{x}, t)}(\mathbf{p}) d\mathbf{p} dR \\ &\rightarrow \int_{\mathbb{R}^+} g_k(\mathbf{x}, R, t) dR = \rho_k(\mathbf{x}, t) \end{aligned}$$

as $\varepsilon \rightarrow 0$.

Here, $\rho_k(\mathbf{x}, t)$ denotes the density of type- k cells at position $\mathbf{x}$ and time t .

► Equations on g_0 and g_1

↪ Thanks to the conservation of mass: $\int_{\mathbb{S}^1} Q_{\mathbf{p}}(f_k) d\mathbf{p} = 0$

$$f_k^\varepsilon(\mathbf{x}, \mathbf{p}, R, t) \rightarrow g_k(\mathbf{x}, R, t) M_{\mathbf{p}(\mathbf{x}, t)}(\mathbf{p}), \quad \text{when } \varepsilon \rightarrow 0$$

► Equations on g_0 and g_1

↪ Thanks to the conservation of mass: $\int_{\mathbb{S}^1} Q_{\mathbf{p}}(f_k) d\mathbf{p} = 0$

Idea of the calculus:

$$\begin{aligned} & \varepsilon \left[\partial_t f_0^\varepsilon + \nabla_{\mathbf{x}} \cdot (v_{f^\varepsilon} f_0^\varepsilon) + \delta \nabla_{\mathbf{p}} \cdot (\text{Proj}_{\mathbf{p}^\perp} \frac{v_{f^\varepsilon}^\varepsilon}{\|v_{f^\varepsilon}^\varepsilon\|} f_0^\varepsilon) + \nabla_{\mathbf{p}} \cdot (\text{Proj}_{\mathbf{p}^\perp} G_{f^\varepsilon} f_0^\varepsilon) \right. \\ & \quad \left. + \nu \tilde{Z}_0 \nabla_{\mathbf{p}} \cdot (\text{Proj}_{\mathbf{p}^\perp} \nabla_{\mathbf{x}} \rho_1^\varepsilon f_0^\varepsilon) + \partial_R(I(R) f_0^\varepsilon) - \lambda_\rho \rho^\varepsilon \mathcal{M}(\mathbf{p}) + \lambda_a f_0^\varepsilon \right] \\ & = Q_{\mathbf{p}}(f_0^\varepsilon) \end{aligned}$$

► divide by ε

► integrate over $\mathbb{S}^1$

► take the limits $\varepsilon \rightarrow 0$

$$f_k^\varepsilon(\mathbf{x}, \mathbf{p}, R, t) \rightarrow g_k(\mathbf{x}, R, t) M_{\mathbf{p}(\mathbf{x}, t)}(\mathbf{p}), \quad \text{when } \varepsilon \rightarrow 0$$

► Equations on g_0 and g_1

↪ Thanks to the conservation of mass: $\int_{\mathbb{S}^1} Q_{\mathbf{p}}(f_k) d\mathbf{p} = 0$

$$\begin{aligned} \partial_t g_0 + \nabla_{\mathbf{x}} \cdot (g_0 U) + \partial_R (I(R) g_0) &= \lambda_p \rho - \lambda_a g_0 \\ \partial_t g_1 + \nabla_{\mathbf{x}} \cdot (g_1 U) + \partial_R (D(R) g_1) &= \lambda_a (g_0 - g_1) \end{aligned}$$

where the velocity $U = c_1 \mathbf{P} - \nabla_{\mathbf{x}} \int_{\mathbb{R}^+} [W(R) g(\mathbf{x}, R, t)] dR$.

$$f_k^\varepsilon(\mathbf{x}, \mathbf{p}, R, t) \rightarrow g_k(\mathbf{x}, R, t) M_{\mathbf{P}(\mathbf{x}, t)}(\mathbf{p}), \quad \text{when } \varepsilon \rightarrow 0$$

► Equations on g_0 and g_1

↪ Thanks to the conservation of mass: $\int_{\mathbb{S}^1} Q_{\mathbf{p}}(f_k) d\mathbf{p} = 0$

$$\begin{aligned} \partial_t g_0 + \nabla_{\mathbf{x}} \cdot (g_0 U) + \partial_R (I(R) g_0) &= \lambda_p \rho - \lambda_a g_0 \\ \partial_t g_1 + \nabla_{\mathbf{x}} \cdot (g_1 U) + \partial_R (D(R) g_1) &= \lambda_a (g_0 - g_1) \end{aligned}$$

where the velocity $U = c_1 \mathbf{P} - \nabla_{\mathbf{x}} \int_{\mathbb{R}^+} [W(R) g(\mathbf{x}, R, t)] dR$.

► Equation on $\mathbf{P}$

► $\mathbf{P}(\mathbf{x}, t)$ is the averaged orientation at position $\mathbf{x}$ and time t

↪ no conservation of momentum: $\int_{\mathbb{S}^1} Q_{\mathbf{p}}(f) \mathbf{p} d\mathbf{p} \neq 0$

Generalized Collisional Invariants (GCI)

Definition: Generalized Collisional Invariants ^a

^aP. Degond and S. Motsch, *Mathematical Models and Methods in Applied Sciences* (2008)

For any $\mathbf{P} \in \mathbb{S}^1$, a generalized collision invariant of $Q_{\mathbf{p}}$ is a function $\psi_{\mathbf{p}}$ such as:

$$\int_{\mathbb{S}^1} Q_{\mathbf{p}}(f) \psi_{\mathbf{p}}(\mathbf{p}) d\mathbf{p} = 0, \quad \forall f \text{ such as } \mathbf{P} = \mathbf{P}_f$$

- There exists a GCI $\psi_{\mathbf{p}}(\mathbf{p})$ different from 1

- Equation on $\mathbf{P}$ obtain thanks to the GCI $\psi_{\mathbf{P}}$.

$$\rho(\partial_t \mathbf{P} + (\mathbf{V} \cdot \nabla_{\mathbf{x}}) \mathbf{P}) + \text{Proj}_{\mathbf{P}^\perp} T(\rho, \rho_1) = \eta \text{Proj}_{\mathbf{P}^\perp} \Delta_{\mathbf{x}}(\rho \mathbf{P})$$

$$\hookrightarrow \text{Density: } \rho = \int_{\mathbb{R}^+} (g_0 + g_1) dR$$

$$\hookrightarrow \text{Velocity: } \mathbf{V} = c_2 \mathbf{P} - \nabla_{\mathbf{x}} \int_{\mathbb{R}^+} [W(R)g(\mathbf{x}, R, t)] dR$$

$$\hookrightarrow \text{Viscosity: } \eta = k_0 [d + c_2]$$

$$T(\rho, \rho_1) = d \nabla_{\mathbf{x}} \rho + \frac{\delta}{\|v_g M_{\mathbf{P}}\|} [d + c_2] \rho \nabla_{\mathbf{x}} \int_{\mathbb{R}^+} [W(R)g(\mathbf{x}, R, t)] dR \\ - \nu \tilde{Z}_0 (d + c_2) \rho \nabla_{\mathbf{x}} \rho_1$$

- Equation on $\mathbf{P}$ obtain thanks to the GCI $\psi_{\mathbf{P}}$.

$$\rho(\partial_t \mathbf{P} + (\mathbf{V} \cdot \nabla_{\mathbf{x}}) \mathbf{P}) + \text{Proj}_{\mathbf{P}^\perp} T(\rho, \rho_1) = \eta \text{Proj}_{\mathbf{P}^\perp} \Delta_{\mathbf{x}}(\rho \mathbf{P})$$

$$\hookrightarrow \text{Density: } \rho = \int_{\mathbb{R}^+} (g_0 + g_1) dR$$

$$\hookrightarrow \text{Velocity: } \mathbf{V} = c_2 \mathbf{P} - \nabla_{\mathbf{x}} \int_{\mathbb{R}^+} [W(R)g(\mathbf{x}, R, t)] dR$$

$$\hookrightarrow \text{Viscosity: } \eta = k_0 [d + c_2]$$

$$T(\rho, \rho_1) = d \nabla_{\mathbf{x}} \rho + \frac{\delta}{\|v_g M_{\mathbf{P}}\|} [d + c_2] \rho \nabla_{\mathbf{x}} \int_{\mathbb{R}^+} [W(R)g(\mathbf{x}, R, t)] dR \\ - \nu \tilde{Z}_0 (d + c_2) \rho \nabla_{\mathbf{x}} \rho_1$$

- ρ_1 is the density of apoptotic cells
- $\mathbf{P}$ is orienting towards high-density regions of apoptotic cells

Macroscopic equation

$$\begin{aligned}\partial_t g_0 + \nabla_{\mathbf{x}} \cdot (g_0 U) + \partial_R(I(R)g_0) &= \lambda_p \rho - \lambda_a g_0 \\ \partial_t g_1 + \nabla_{\mathbf{x}} \cdot (g_1 U) + \partial_R(D(R)g_1) &= \lambda_a(g_0 - g_1)\end{aligned}$$

$$\rho(\partial_t \mathbf{P} + (V \cdot \nabla_{\mathbf{x}}) \mathbf{P}) + \text{Proj}_{\mathbf{P}^\perp} T(\rho, \rho_1) = \eta \text{Proj}_{\mathbf{P}^\perp} \Delta_{\mathbf{x}}(\rho \mathbf{P}),$$

where

$$\begin{aligned}U &= c_1 \mathbf{P} - \nabla_{\mathbf{x}} \int_{\mathbb{R}^+} \left[W(R) g(\mathbf{x}, R, t) \right] dR, \\ V &= c_2 \mathbf{P} - \nabla_{\mathbf{x}} \int_{\mathbb{R}^+} \left[W(R) g(\mathbf{x}, R, t) \right] dR, \\ T(\rho, \rho_1) &= d \nabla_{\mathbf{x}} \rho + \frac{\delta}{\|v_{gM\mathbf{P}}\|} [d + c_2] \rho \nabla_{\mathbf{x}} \int_{\mathbb{R}^+} \left[W(R) g(\mathbf{x}, R, t) \right] dR \\ &\quad - \nu \tilde{Z}_0 [d + c_2] \rho \nabla_{\mathbf{x}} \rho_1, \\ \eta &= k_0 [d + c_2].\end{aligned}$$

I. Introduction

II. Microscopic model

III. Macroscopic model

IV. Conclusion

Conclusion & perspectives

- ▶ Construction of a mathematical and computational model describing cell collective dynamics
- ▶ Include the phenomena of apoptosis
- ▶ Observation of different behavior with or without apoptosis and proliferation
- ▶ Macroscopic model derived from the microscopic one

- ▶ Comparison with experience:
 - ▶ *in vitro*: MDCK cells in square or disk (Experience made by Rodrigo MORENA CUSTODIO at IGBMC, Strasbourg)
 - ▶ *in vivo*
- ▶ Different regimes for the macroscopic domain
- ▶ Simulation in the macroscopic case

Conclusion & perspectives

- ▶ Construction of a mathematical and computational model describing cell collective dynamics
- ▶ Include the phenomena of apoptosis
- ▶ Observation of different behavior with or without apoptosis and proliferation
- ▶ Macroscopic model derived from the microscopic one
- ▶ Comparison with experience:
 - ▶ *in vitro*: MDCK cells in square or disk (Experience made by Rodrigo MORENA CUSTODIO at IGBMC, Strasbourg)
 - ▶ *in vivo*
- ▶ Different regimes for the macroscopic domain
- ▶ Simulation in the macroscopic case

Thank you for your attention!

Biblio I

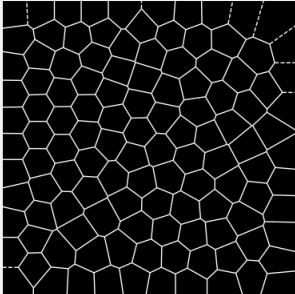
- [1] A. Villars, G. Letort, L. Valon, and R. Levayer, “Dextrusion: Automatic recognition of epithelial cell extrusion through machine learning in vivo,” *Development*, vol. 150, no. 13, 2023.
- [2] B. Maury and J. Venel, “A discrete contact model for crowd motion,” *ESAIM Math. Model. Numer. Anal.*, vol. 45, no. 1, pp. 145–168, 2011.
- [3] C. Beatrice, C. Kirch, S. Henkes, F. Graner, and L. Brunnet, “Comparing individual-based models of collective cell motion in a benchmark flow geometry,” *Soft Matter*, vol. 19, no. 29, pp. 5583–5601, 2023.
- [4] T. Vicsek, A. Czirók, E. Ben-Jacob, I. Cohen, and O. Shochet, “Novel type of phase transition in a system of self-driven particles,” *Phys. Rev. Lett.*, vol. 75, no. 6, p. 1226, 1995.
- [5] S. L. Vecchio, O. Pertz, M. Szopos, L. Navoret, and D. Riveline, “Spontaneous rotations in epithelia as an interplay between cell polarity and boundaries,” *Nature Physics*, 2024.

Biblio II

- [6] P. Degond, G. Dimarco, T. B. N. Mac, and N. Wang, “Macroscopic models of collective motion with repulsion,” en, *Communications in Mathematical Sciences*, vol. 13, no. 6, pp. 1615–1638, 2015, ISSN: 15396746, 19450796. DOI: 10.4310/CMS.2015.v13.n6.a12.
- [7] P. Degond and S. Motsch, “Continuum limit of self-driven particles with orientation interaction,” *Mathematical Models and Methods in Applied Sciences*, vol. 18, no. supp01, pp. 1193–1215, 2008.

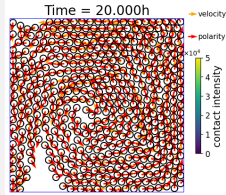
Extra simulation

Voronoi representation:



square domain with low
density

More cells:



Even more:

