Mathematical modeling of apoptosis in cell collective dynamics

microscopic and macroscopic points of view

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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.

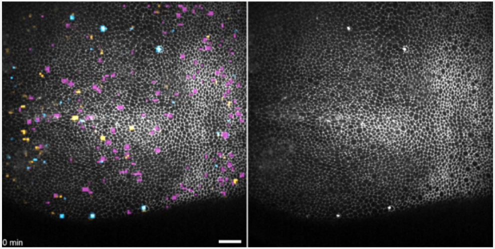

Figure: A. Villars, G. Letort, L. Valon, *et al.*, *Development* (2023)

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

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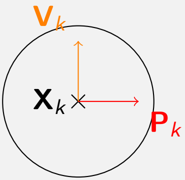
Model

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].

[1] B. Maury and J. Venel, *ESAIM Math. Model. Numer. Anal.* (2011)
[2] C. Beatrici, C. Kirch, S. Henkes, *et al.*, *Soft Matter* (2023)
[3] T. Vicsek, A. Czirók, E. Ben-Jacob, *et al.*, *Phys. Rev. Lett.* (1995)
[4] S. L. Vecchio, O. Pertz, M. Szopos, *et al.*, *Nature Physics* (2024)

Equations on **X**, **V**, **P** and R

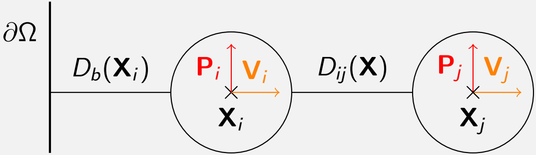
$$
\begin{aligned}
\frac{d\mathbf{X}_k(t)}{dt} &= \mathbf{V}_k(t) \\
\mathbf{V} &= \mathrm{Proj}_{\mathcal{C}_{\mathbf{X}}}(c\mathbf{P} + \gamma \mathbf{F}(\mathbf{X})) \\
d\mathbf{P}_k &= \mathrm{Proj}_{\mathbf{P}_k^{\perp}} \circ \Big(\mu(\overline{\mathbf{P}}_k - \mathbf{P}_k)dt + \delta\,(\mathbf{V}_k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

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.

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

Contact force: projection onto the set of admissible velocities:

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



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

Attraction-repulsion force

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

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

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

[a] C. Beatrici, C. Kirch, S. Henkes, *et al.*, *Soft Matter* (2023)

$$\frac{d\mathbf{X}_k(t)}{dt} = \mathbf{V}_k(t)$$
$$\mathbf{V} = \mathrm{Proj}_{\mathcal{C}_{\mathbf{X}}}(c\mathbf{P} + \gamma\mathbf{F}(\mathbf{X}))$$
$$d\mathbf{P}_k = \mathrm{Proj}_{\mathbf{P}_k^\perp} \circ \Big(\mu(\overline{\mathbf{P}}_k - \mathbf{P}_k)dt + \delta\left(\mathbf{V}_k / \left\|\mathbf{V}_k\right\| - \mathbf{P}_k\right)dt + \sqrt{2D}(dB_t)_k \Big)$$

Vicsek-type interactions: competition between

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

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

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

$$\frac{d\mathbf{X}_k(t)}{dt} = \mathbf{V}_k(t)$$
$$\mathbf{V} = \mathrm{Proj}_{\mathcal{C}_{\mathbf{X}}}(c\mathbf{P} + \gamma \mathbf{F}(\mathbf{X}))$$
$$d\mathbf{P}_k = \mathrm{Proj}_{\mathbf{P}_k^{\perp}} \circ \Big(\mu(\overline{\mathbf{P}}_k - \mathbf{P}_k)dt + \delta\left(\mathbf{V}_k / \|\mathbf{V}_k\| - \mathbf{P}_k\right)dt + \nu(\mathbf{L}_k - \mathbf{P}_k)\, dt + \sqrt{2D}(dB_t)_k\Big)$$

Apoptotic events: polarity

- closure towards the apoptotic cells

$$\mathbf{L}_k = \sum_{j, \|X_j - X_k\| \leqslant R_{\mathrm{int}}^{\mathrm{po}}} \alpha_j \frac{(X_j - X_k)}{\|(X_j - X_k)\|}$$

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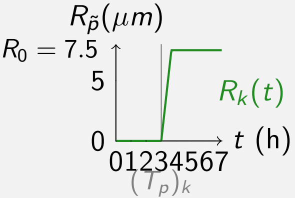
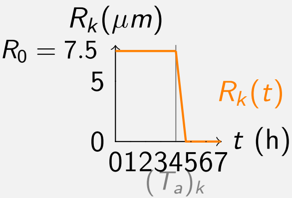
&\qquad + \nu(\mathbf{L}_k - \mathbf{P}_k)\,dt + \sqrt{2D}(dB_t)_k \Big)\\
R_k(t) &= \begin{cases} \left(\min(R_0, \mathbb{1}_{[(T_p)_k,\infty[}\beta(t-(T_p)_k))\right)_+ & \text{if } \alpha_k(t)=0\\ \left(R_0 + \mathbb{1}_{[(T_a)_k,+\infty[}\beta((T_a)_k - t)\right)_+ & \text{if } \alpha_k(t)=1 \end{cases}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

apoptotic events: radii dynamics





$$
\begin{aligned}
\frac{d\mathbf{X}_k(t)}{dt} &= \mathbf{V}_k(t) \\
\mathbf{V} &= \mathrm{Proj}_{\mathcal{C}_\mathbf{X}}(c\mathbf{P} + \gamma \mathbf{F}(\mathbf{X})) \\
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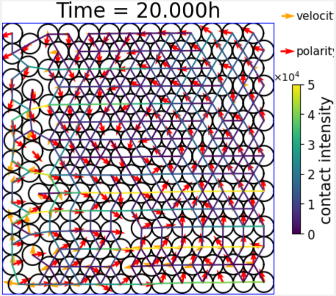
\alpha_k(t) &= \mathbb{1}_{[(T_a)_k, +\infty[}(t)
\end{aligned}
$$

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.

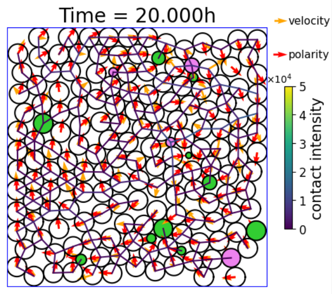
Simulations: on a maximum density

Simulation without apoptosis and cell division events:



- jammed configuration

Simulation with apoptosis and cell division events:



- motion created by apoptosis and proliferation

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Reminder: microscopic model

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

$(T_a)_k \sim \mathcal{E}(\lambda_a)$ 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 $N \to \infty$
- $f(\mathbf{x}, \mathbf{p}, R, t)$: 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, G. Dimarco, T. B. N. Mac, *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

$$\partial_t f_0 + \underbrace{\nabla_{\mathbf{x}} \cdot (v_f f_0)}_{\text{advected position}} + \underbrace{\partial_R (I(R) f_0)}_{\text{advected radius}} + \underbrace{\nabla_{\mathbf{p}} \cdot \left(\mathrm{Proj}_{\mathbf{p}^\perp}\left(\delta(v_f/\|v_f\|) + \nu L_{f_1} + \mu \overline{P}_f\right) f_0\right)}_{\text{advected polarity}}$$

$$= D\Delta_{\mathbf{p}} f_0 + \lambda_p \rho(t,x)\mathcal{M}(p) - \lambda_a f_0$$

$$\begin{aligned}
v_f(\mathbf{x},\mathbf{p}) &= c\mathbf{p} - \gamma \nabla_{\mathbf{x}} \mathcal{F}_f(\mathbf{x},t)\\
\mathcal{F}_f(\mathbf{x},t) &= \int_{\mathbb{S}^1\times\mathbb{R}^2\times\mathbb{R}^+} \mathcal{W}\left(\frac{\|\mathbf{x}-\mathbf{y}\|}{R_{\text{int}}^{\text{ar}}}, R\right) f(\mathbf{y},\mathbf{p},R,t)\, d\mathbf{p}d\mathbf{y}dR\\
L_{f_1}(\mathbf{x},t) &= \int_{\mathbb{S}^1\times\mathbb{R}^2\times\mathbb{R}^+} K\left(\frac{\|\mathbf{x}-\mathbf{y}\|}{R_{\text{int}}^{\text{po}}}\right) \frac{(\mathbf{y}-\mathbf{x})}{\|(\mathbf{y}-\mathbf{x})\|} f_1(\mathbf{y},\mathbf{p},R,t)\, d\mathbf{p}d\mathbf{y}dR\\
\overline{P}_f(\mathbf{x},t) &= \frac{\mathcal{J}_f(\mathbf{x},t)}{\|\mathcal{J}_f(\mathbf{x},t)\|}\\
\mathcal{J}_f(\mathbf{x},t) &= \int_{\mathbb{S}^1\times\mathbb{R}^2\times\mathbb{R}^+} K\left(\frac{\|\mathbf{x}-\mathbf{y}\|}{R_{\text{int}}^{\text{po}}}\right) f(\mathbf{y},\mathbf{p},R,t) p\, d\mathbf{p}d\mathbf{y}dR,
\end{aligned}$$

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

$$\partial_t f_0 + \underbrace{\nabla_{\mathbf{x}} \cdot (v_f f_0)}_{\text{advected position}} + \underbrace{\partial_R(I(R) f_0)}_{\text{advected radius}} + \underbrace{\nabla_{\mathbf{p}} \cdot \left(\mathrm{Proj}_{\mathbf{p}^\perp}\left(\delta(v_f/\|v_f\|) + \nu L_{f_1} + \mu \overline{P}_f\right) f_0\right)}_{\text{advected polarity}}$$

$$= D\Delta_{\mathbf{p}} f_0 + \lambda_p \rho(t,x)\mathcal{M}(p) - \lambda_a f_0$$

$$\partial_t f_1 + \underbrace{\nabla_{\mathbf{x}} \cdot (v_f f_1)}_{\text{advected position}} + \underbrace{\partial_R(D(R) f_1)}_{\text{advected radius}} + \underbrace{\nabla_{\mathbf{p}} \cdot \left(\mathrm{Proj}_{\mathbf{p}^\perp}\left(\delta(v_f/\|v_f\|) + \nu L_{f_1} + \mu \overline{P}_f\right) f_1\right)}_{\text{advected polarity}}$$

$$= D\Delta_{\mathbf{p}} f_1 + \lambda_a (f_0 - f_1)$$

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

  $\hookrightarrow \varepsilon \ll 1$

$$\varepsilon\Big[\partial_t f_0^\varepsilon + \nabla_{\mathbf{x}} \cdot (v_{f^\varepsilon} f_0^\varepsilon) + \delta \nabla_{\mathbf{p}} \cdot (\mathrm{Proj}_{\mathbf{p}^\perp} \frac{v_{f^\varepsilon}^\varepsilon}{\|v_{f^\varepsilon}^\varepsilon\|} f_0^\varepsilon) + \nabla_{\mathbf{p}} \cdot (\mathrm{Proj}_{\mathbf{p}^\perp} G_{f^\varepsilon} f_0^\varepsilon)$$

$$+ \nu \tilde{Z}_0 \nabla_{\mathbf{p}} \cdot (\mathrm{Proj}_{\mathbf{p}^\perp} \nabla_{\mathbf{x}} \rho_1^\varepsilon f_0^\varepsilon) + \partial_R (I(R) f_0^\varepsilon) - \lambda_p \rho^\varepsilon \mathcal{M}(\mathbf{p}) + \lambda_a f_0^\varepsilon\Big]$$

$$= Q_{\mathbf{p}}(f_0^\varepsilon)$$

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

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

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

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

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

  $\hookrightarrow\ \varepsilon \ll 1$

$$\varepsilon\Big[\partial_t f_0^\varepsilon + \nabla_{\mathbf{x}}\cdot(v_{f^\varepsilon} f_0^\varepsilon) + \delta\nabla_{\mathbf{p}}\cdot\Big(\mathrm{Proj}_{\mathbf{p}^\perp}\frac{v_{f^\varepsilon}^\varepsilon}{\|v_{f^\varepsilon}^\varepsilon\|} f_0^\varepsilon\Big) + \nabla_{\mathbf{p}}\cdot(\mathrm{Proj}_{\mathbf{p}^\perp} G_{f^\varepsilon} f_0^\varepsilon)$$

$$+\nu\tilde{Z}_0\nabla_{\mathbf{p}}\cdot(\mathrm{Proj}_{\mathbf{p}^\perp}\nabla_{\mathbf{x}}\rho_1^\varepsilon f_0^\varepsilon) + \partial_R(I(R)f_0^\varepsilon) - \lambda_p\rho^\varepsilon\mathcal{M}(\mathbf{p}) + \lambda_a f_0^\varepsilon\Big]$$

$$= Q_{\mathbf{p}}(f_0^\varepsilon)$$

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

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

$\hookrightarrow$ 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 $Q_{\mathbf{p}}$: equilibria

Von Mises probability distribution:

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

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

Equilibria:

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

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

Limit $\varepsilon \to 0$

$$\varepsilon\Big[\partial_t f_0^\varepsilon + \nabla_{\mathbf{x}} \cdot (v_{f^\varepsilon} f_0^\varepsilon) + \delta \nabla_{\mathbf{p}} \cdot \Big(\mathrm{Proj}_{\mathbf{p}^\perp} \frac{v_{f^\varepsilon}^\varepsilon}{\|v_{f^\varepsilon}^\varepsilon\|} f_0^\varepsilon\Big) + \nabla_{\mathbf{p}} \cdot (\mathrm{Proj}_{\mathbf{p}^\perp} G_{f^\varepsilon} f_0^\varepsilon)$$

$$+ \nu \tilde{Z}_0 \nabla_{\mathbf{p}} \cdot (\mathrm{Proj}_{\mathbf{p}^\perp} \nabla_{\mathbf{x}} \rho_1^\varepsilon f_0^\varepsilon) + \partial_R (I(R) f_0^\varepsilon) - \lambda_p \rho^\varepsilon \mathcal{M}(\mathbf{p}) + \lambda_a f_0^\varepsilon\Big]$$

$$= Q_{\mathbf{p}}(f_0^\varepsilon)$$

- in the limit $\varepsilon \to 0$, $f_0^\varepsilon \to f_0$ with
  - $Q_{\mathbf{p}}(f_0) = 0$
  - $f_0 \in \mathcal{E}$

Therefore:

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

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

Need to determine equations on g_0, g_1 and P.

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

- Equations on g_0 and g_1
  - $\hookrightarrow$ Thanks to the conservation of mass: $\int_{\mathbb{S}^1} Q_{\mathbf{P}}(f_k) d\mathbf{p} = 0$

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

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

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

- Equations on g_0 and g_1

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

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

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

- Equation on $\mathbf{P}$

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

Generalized Collisional Invariants (GCI)

Definition: Generalized Collisional Invariants [a]

[a] P. 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:

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

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

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

$$\boxed{\rho\left(\partial_t \mathbf{P} + (V \cdot \nabla_x)\mathbf{P}\right) + \mathrm{Proj}_{\mathbf{P}^\perp} T(\rho, \rho_1) = \eta \mathrm{Proj}_{\mathbf{P}^\perp} \Delta_{\mathbf{x}}(\rho \mathbf{P})}$$

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

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

$\hookrightarrow$ Viscosity: $\eta = k_0 \left[d + c_2 \right]$

$$T(\rho, \rho_1) = \quad d \nabla_{\mathbf{x}} \rho + \frac{\delta}{\left\| v_{gM_{\mathbf{P}}} \right\|} \left[d + c_2 \right] \rho \nabla_{\mathbf{x}} \int_{\mathbb{R}+} \Big[W(R) g(\mathbf{x}, R, t) \Big]\, dR$$
$$- \nu \tilde{Z}_0 \left(d + c_2 \right) \rho \nabla_{\mathbf{x}} \rho_1$$

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

$$\boxed{\rho\left(\partial_t \mathbf{P} + (V \cdot \nabla_x)\mathbf{P}\right) + \mathrm{Proj}_{\mathbf{P}^\perp} T(\rho,\rho_1) = \eta \mathrm{Proj}_{\mathbf{P}^\perp} \Delta_{\mathbf{x}}(\rho \mathbf{P})}$$

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

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

Macroscopic equation

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

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

where

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

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
- Different regimes for the macroscopic domain
- Simulation in the macroscopic case

Conclusion & perspectives

- Construction of a mathematical and computational model describing cell collective dynamics
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Thank you for your attention!

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