Mathematical modeling of a growing tissue

Our basis: mechanical model for one tissue

Individual Based Models

↓

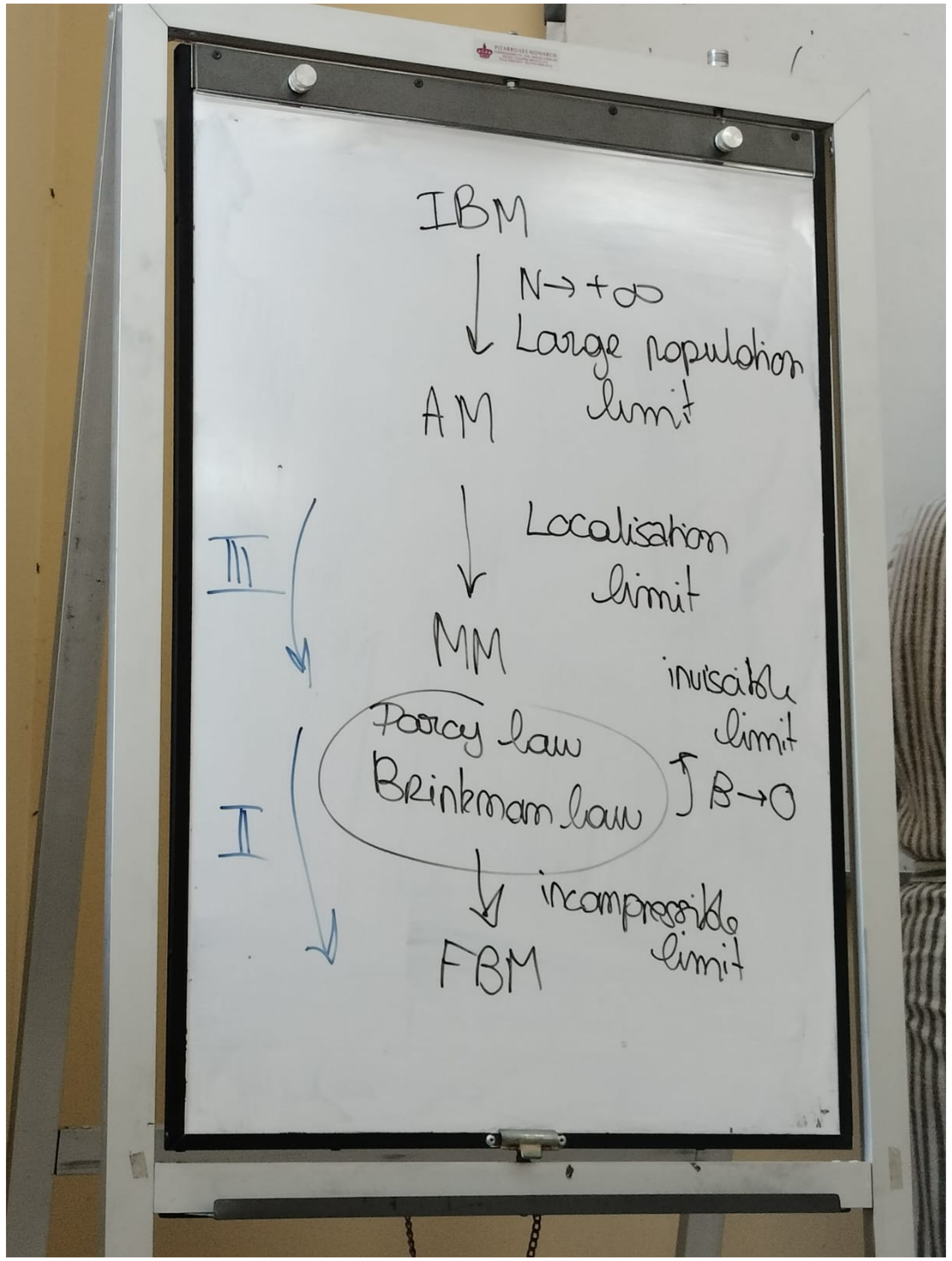
Aggregation Models

↓

Mechanical Models

↓

Free Boundary Models



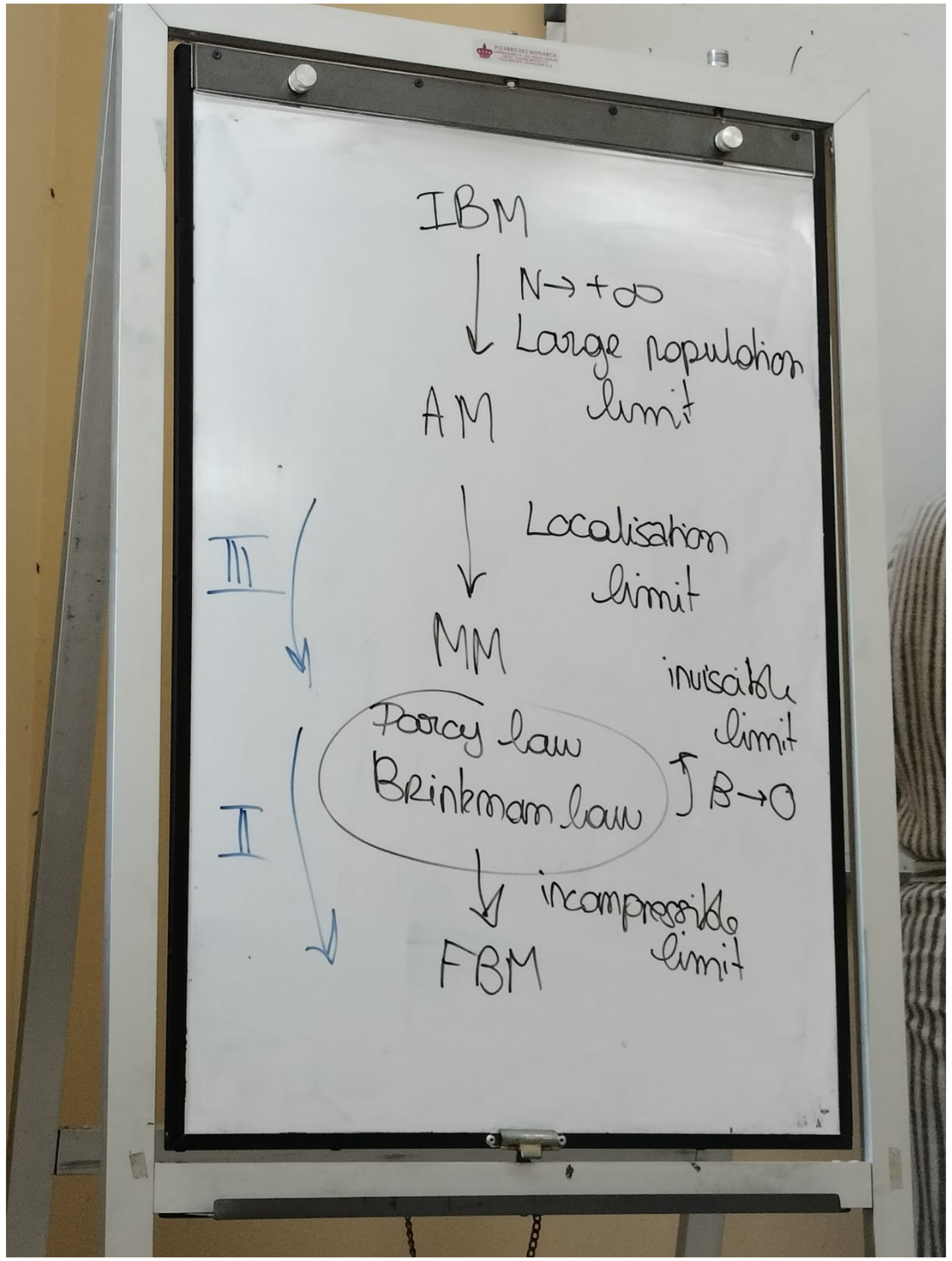
Refs : [Perthame Quiros Vazquez 2014] (power pressure law), Sophie Hecht's PhD works 2017-2020 (singular pressure law);
Sophie Hecht's course

Our basis: mechanical model for one tissue

$$\partial_t n + \nabla \cdot (nv) = nG(p),$$ Growth and migration

$$v = -\nabla p,$$ Darcy's law

$$p = p(n) = \epsilon \frac{n}{1-n},$$ Pressure law (singular)



$n(t,x)$	cell density of the tissue
$v(t,x)$	velocity of the tissue
$p(n)$	pressure due to congestion
G	pressure-dependent growth function

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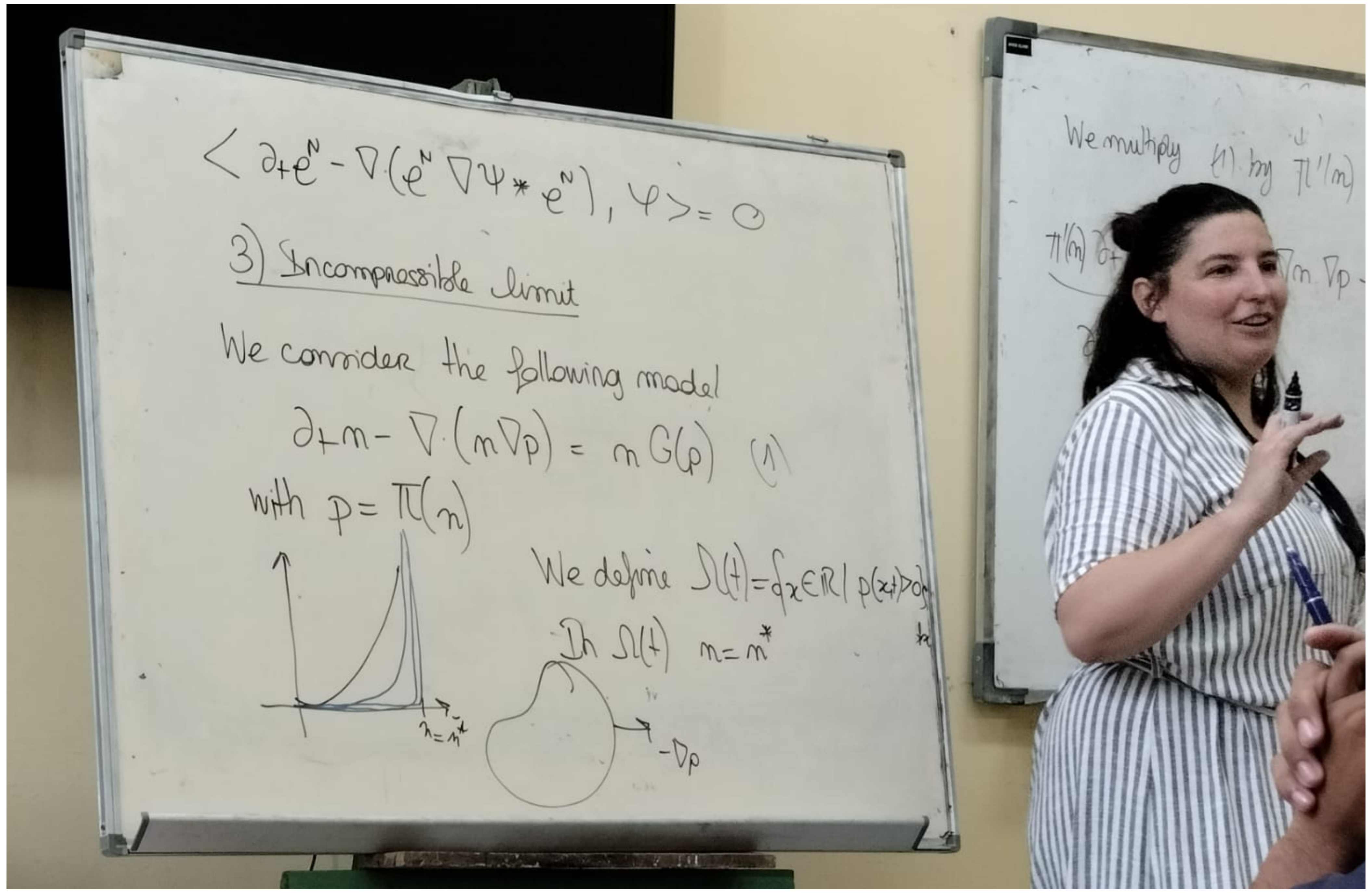

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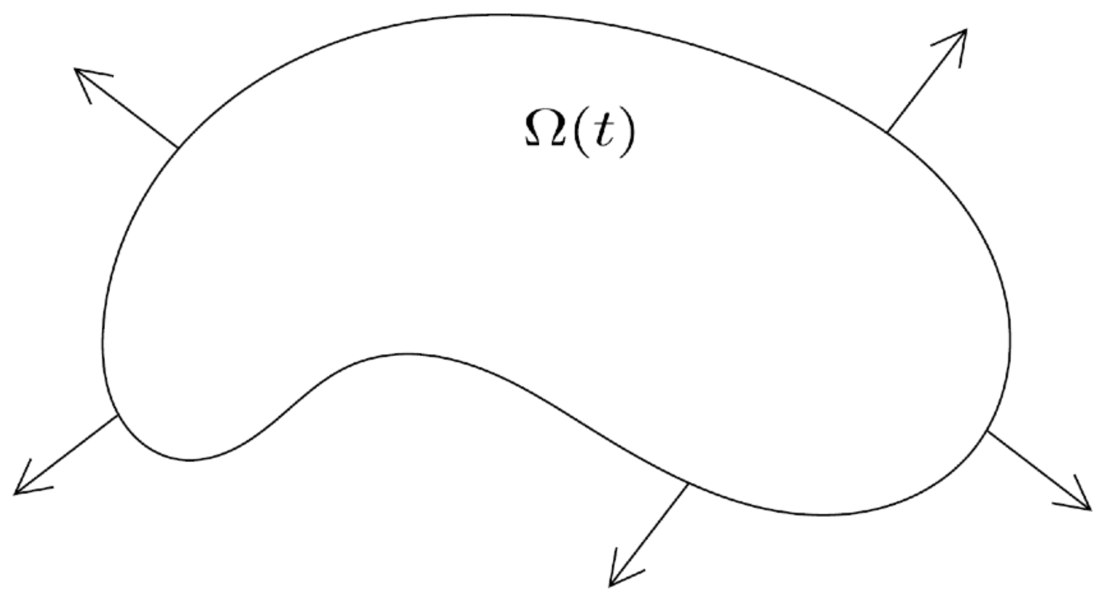
When the pressure parameter vanishes:



$$n = 1, \quad \text{in} \quad \Omega(t)$$
$$-\Delta p = G(p), \quad \text{in} \quad \Omega(t)$$
$$v_{\partial\Omega} = -(\nabla p \cdot \nu)\nu, \quad \text{on} \quad \partial\Omega(t)$$

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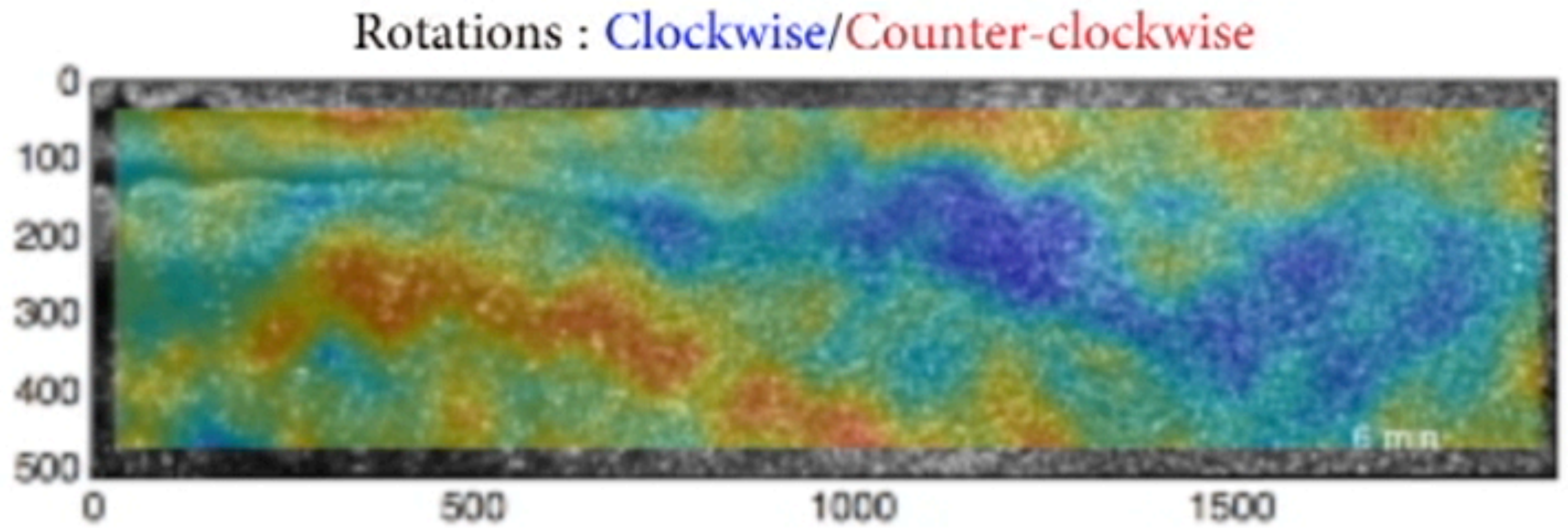
Viscosity and rotational

Using **Darcy's law**

$$v = -\nabla p,$$

we necessarily have a null rotational !



Rotational movements in the posterior zone of the embryo

Viscosity and rotational

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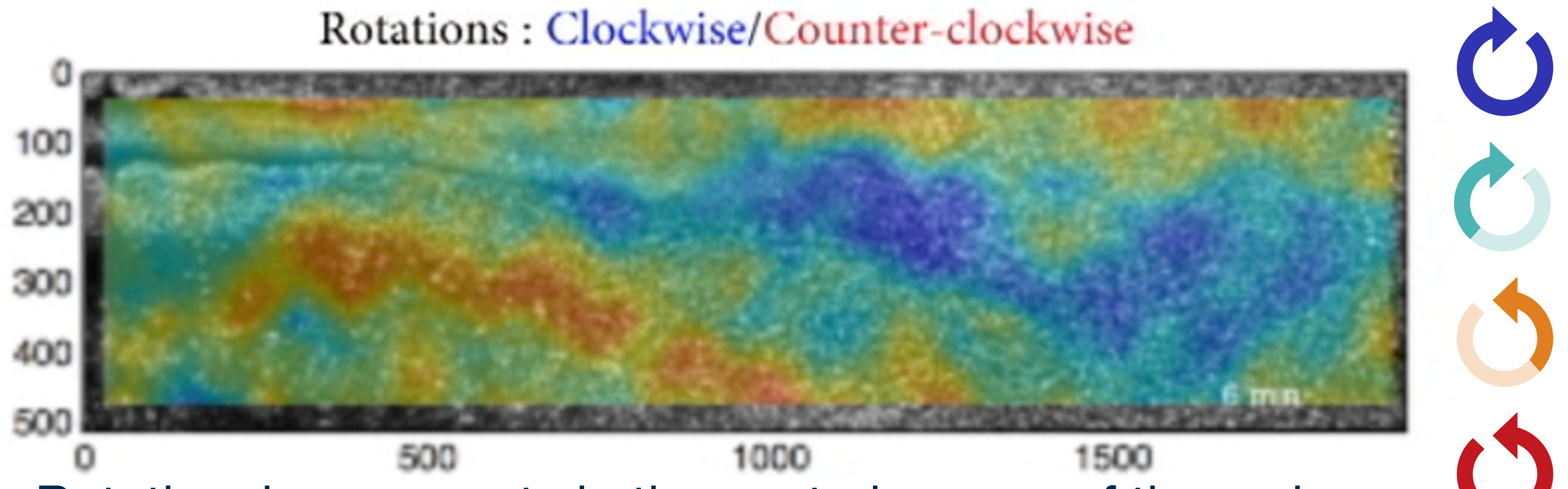

Rotational movements in the posterior zone of the embryo

To reproduce the rotational movements observed in the embryo, and take into account the (differential) viscosities of the tissues, we choose instead the **Brinkman form**:

$$-\beta \Delta v + v = -\nabla p$$

β viscosity of the tissue

Multi-tissue models

Mechanical model for two tissues (1)

$$\begin{cases} \partial_t n_1 + \nabla \cdot (n_1 v_1) = n_1 G_1(p_1), \\ \partial_t n_2 + \nabla \cdot (n_2 v_2) = n_2 G_2(p_2), \\ -\beta_1 \Delta v_1 + v_1 = -\nabla p_1, \\ -\beta_2 \Delta v_2 + v_2 = -\nabla p_2, \\ p_1 = p_\epsilon(n_1 + n_2), \\ p_2 = p_\epsilon(n_1 + n_2), \\ p_\epsilon(n) = \epsilon \frac{n}{1-n}. \end{cases}$$

n_i : density of each tissue

v_i : velocity of each tissue

p_i : pressure of each tissue

β_i : viscosity of each tissue

p_ϵ : congestion pressure, parametrized by $\epsilon > 0$

G_i : growth fonctions

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? mixing of the two tissues ?

Mechanical model for two tissues (1)

Propagated segregation: starting from initial segregated tissues

$$n_1^{ini} n_2^{ini} = 0$$

we get that the tissues remain segregated for all times

$$n_1(t,\cdot)n_2(t,\cdot) = 0, \ \ t > 0.$$

Mechanical model for two tissues (1)

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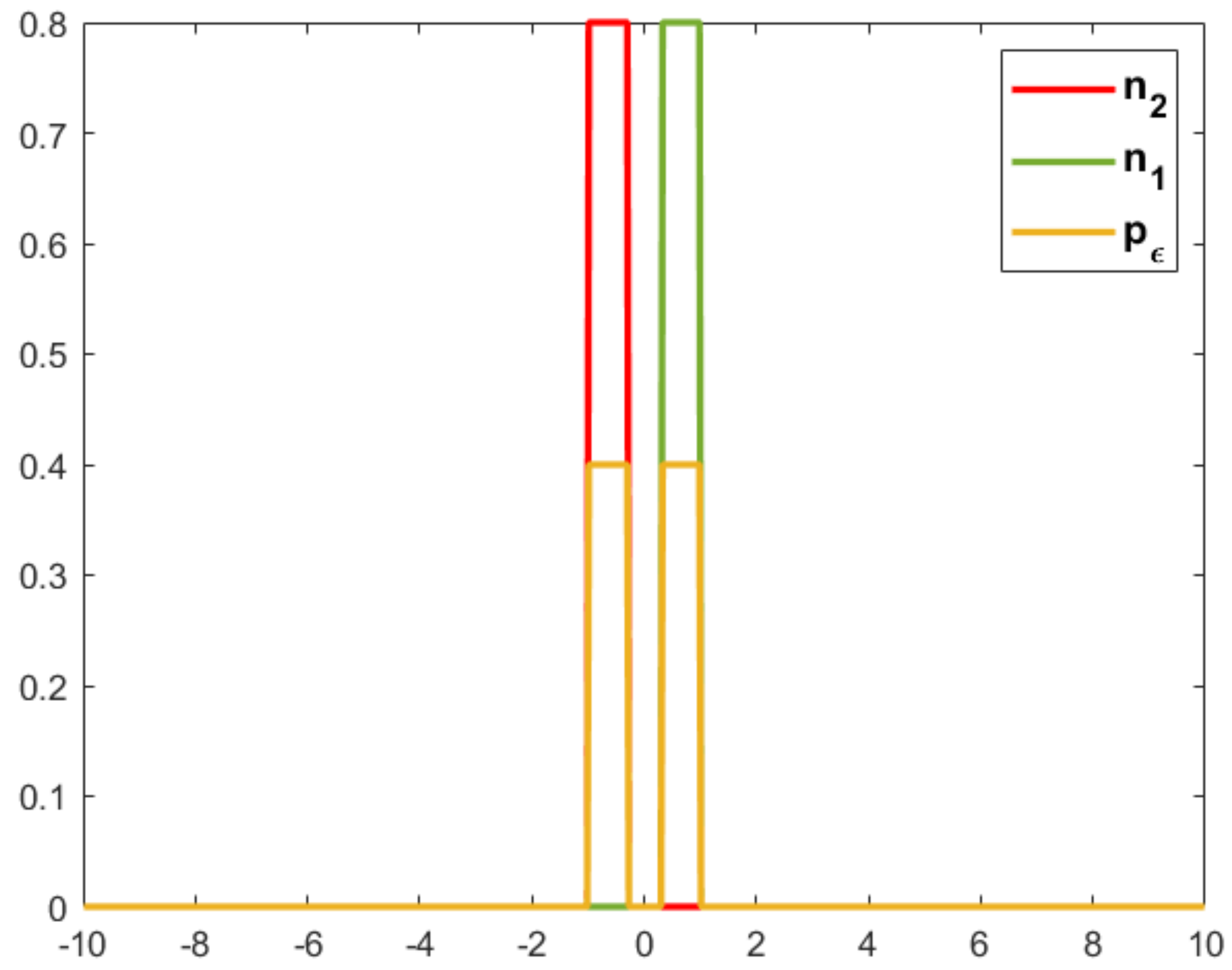
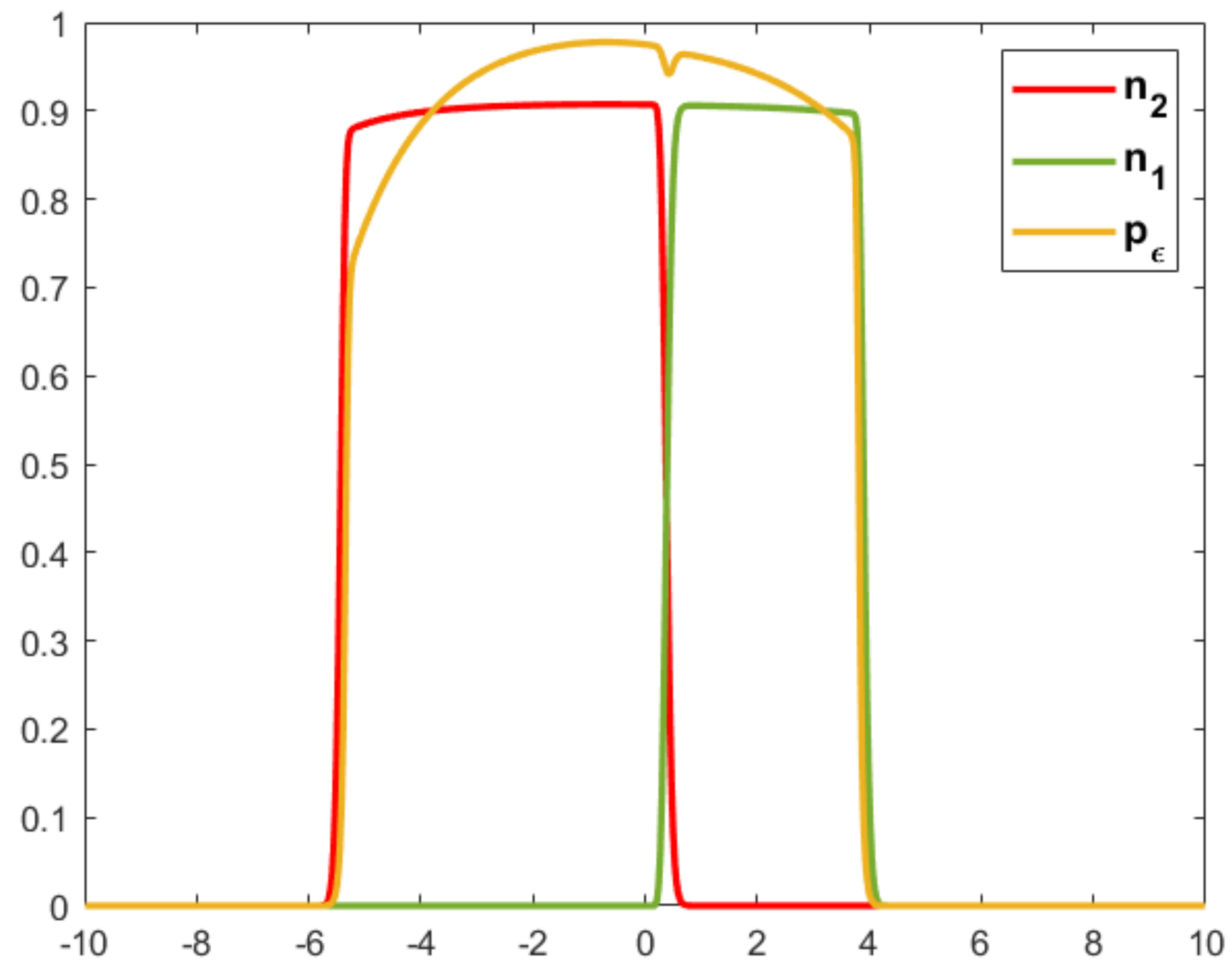
This property is *proved* for equal viscosities, and *numerically observed* for different viscosities.

densities
and
pressure
at t=0



$\beta_1 = 3, \; \beta_2 = 1.$



densities
and
pressure
at t=10

Mechanical model for two tissues (1)

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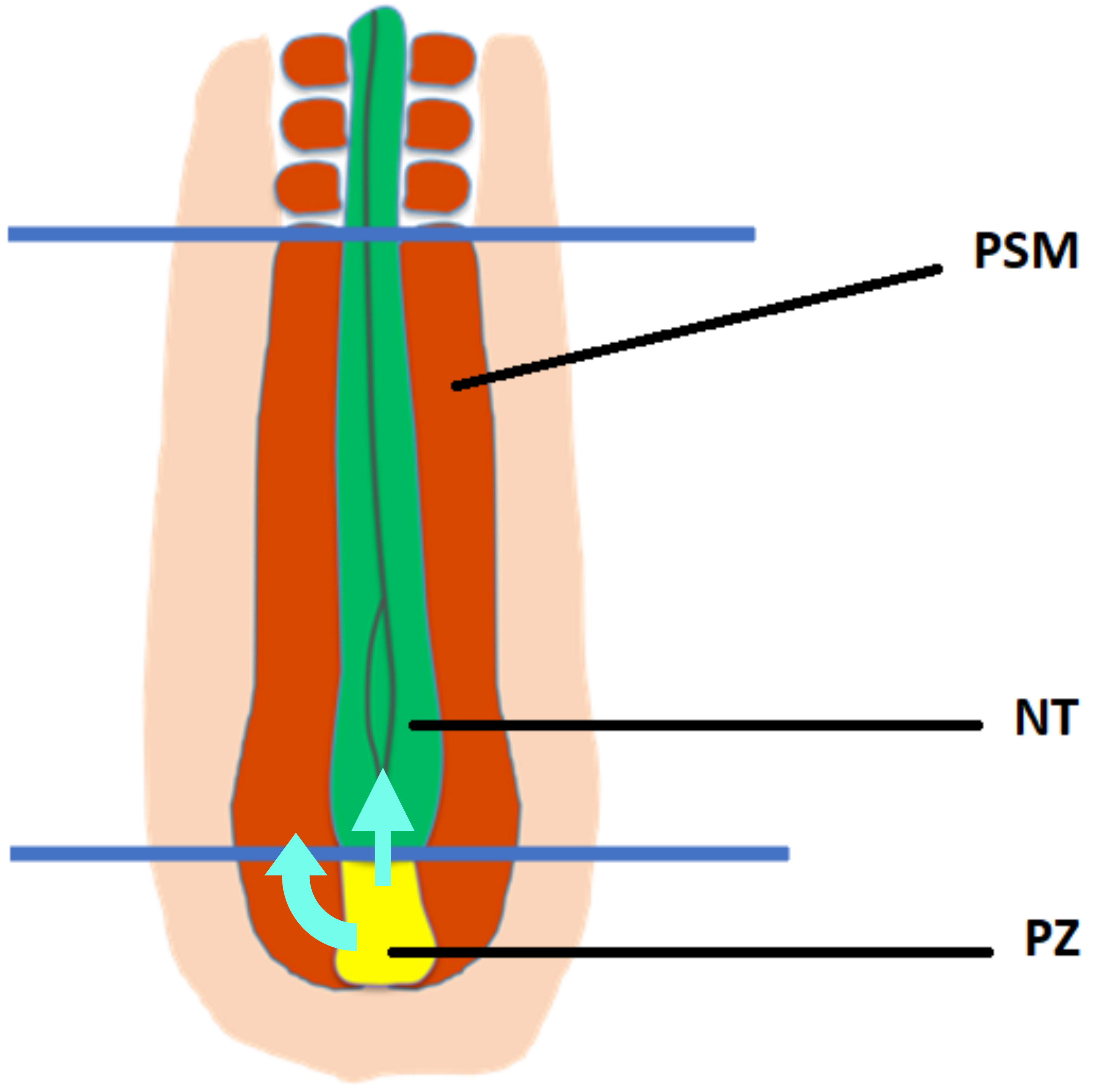
G_i : growth fonctions

Segregation is **propagated** from the initial data (**passive segregation**).

Mechanical model: origin of segregation ?



Cells of NT and PSM types migrate from the PZ towards the two other tissues

If the segregation is only propagated, then, what is its origin ?

What happens at the interface with the PZ, which is a mixed zone ?

Biological hypothesis: could it be that some active segregation is at play ?

We keep our first model with *passive segregation* but also build a model with *active segregation* in order to test this hypothesis.

Mechanical model for two tissues (2)

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\end{cases}
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v_i : velocity of each tissue

p_i : pressure of each tissue

β_i : viscosity of each tissue

p_ϵ : congestion pressure, parametrized by $\epsilon > 0$

G_i : growth fonctions

q_m : repulsion pressure, parametrized by $m > 0$

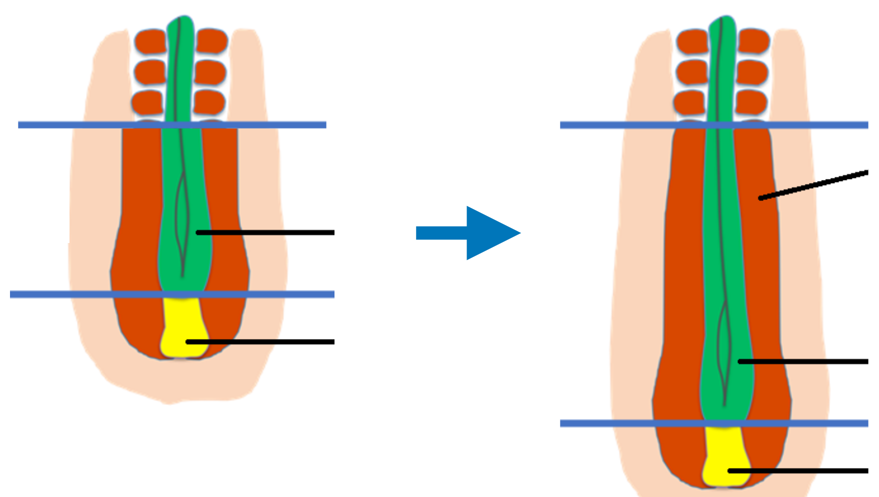
$\alpha > 0$: regularization parameter

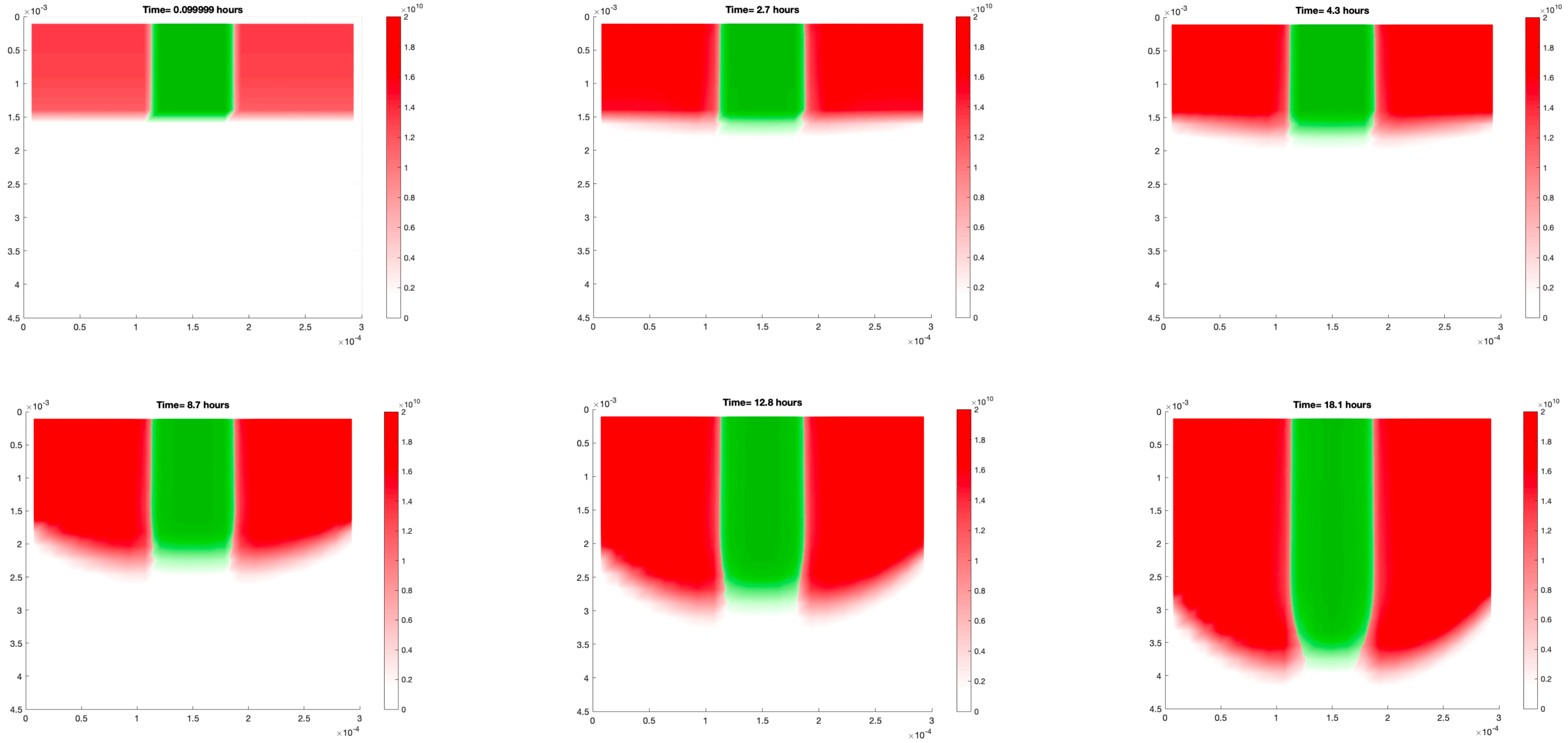
Active segregation

Ref : [Chertock Degond Hecht Vincent 2019] (bubble effect)

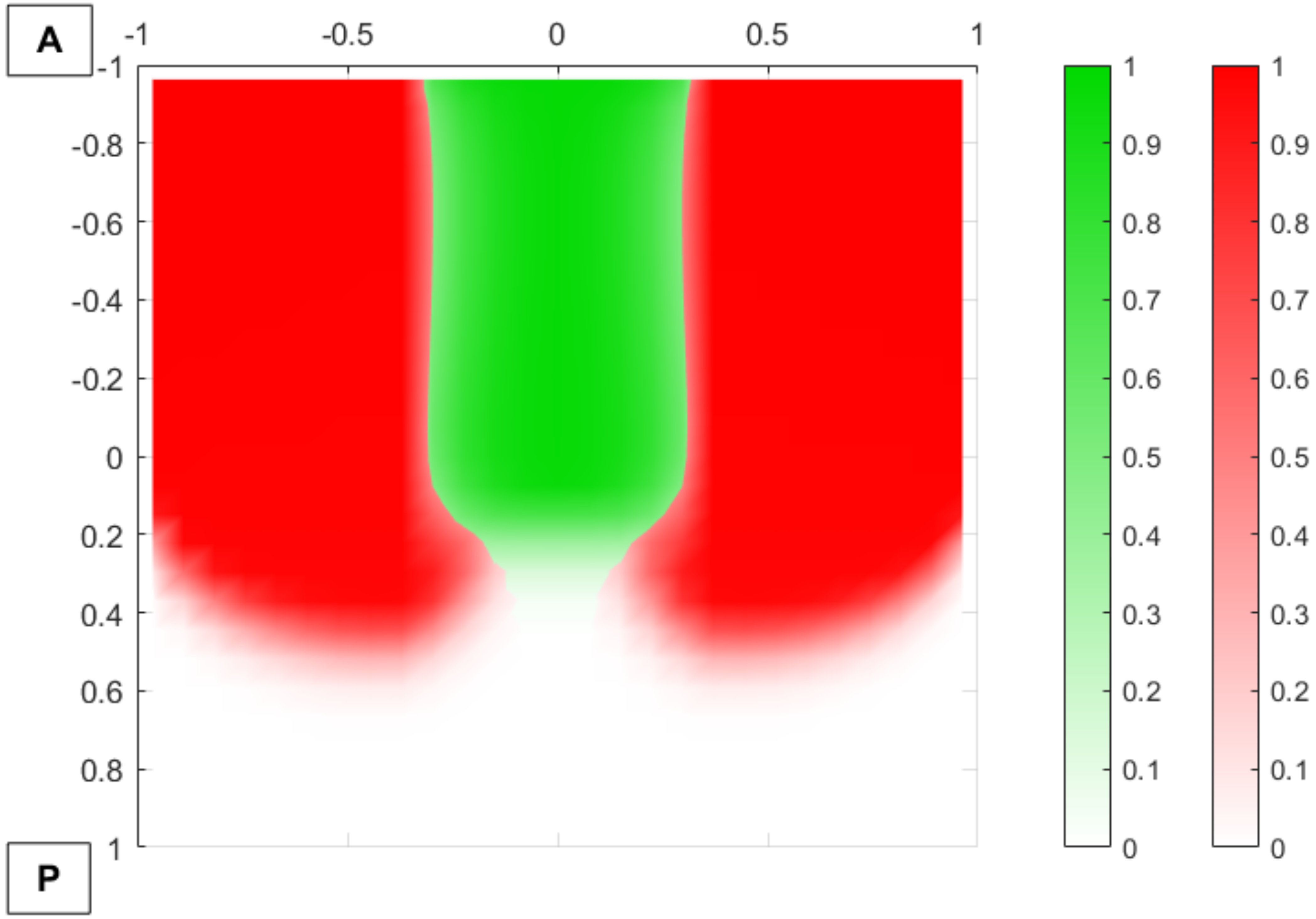
Numerical simulation and comparison with data

Model 1 (fluid, passive segregation)

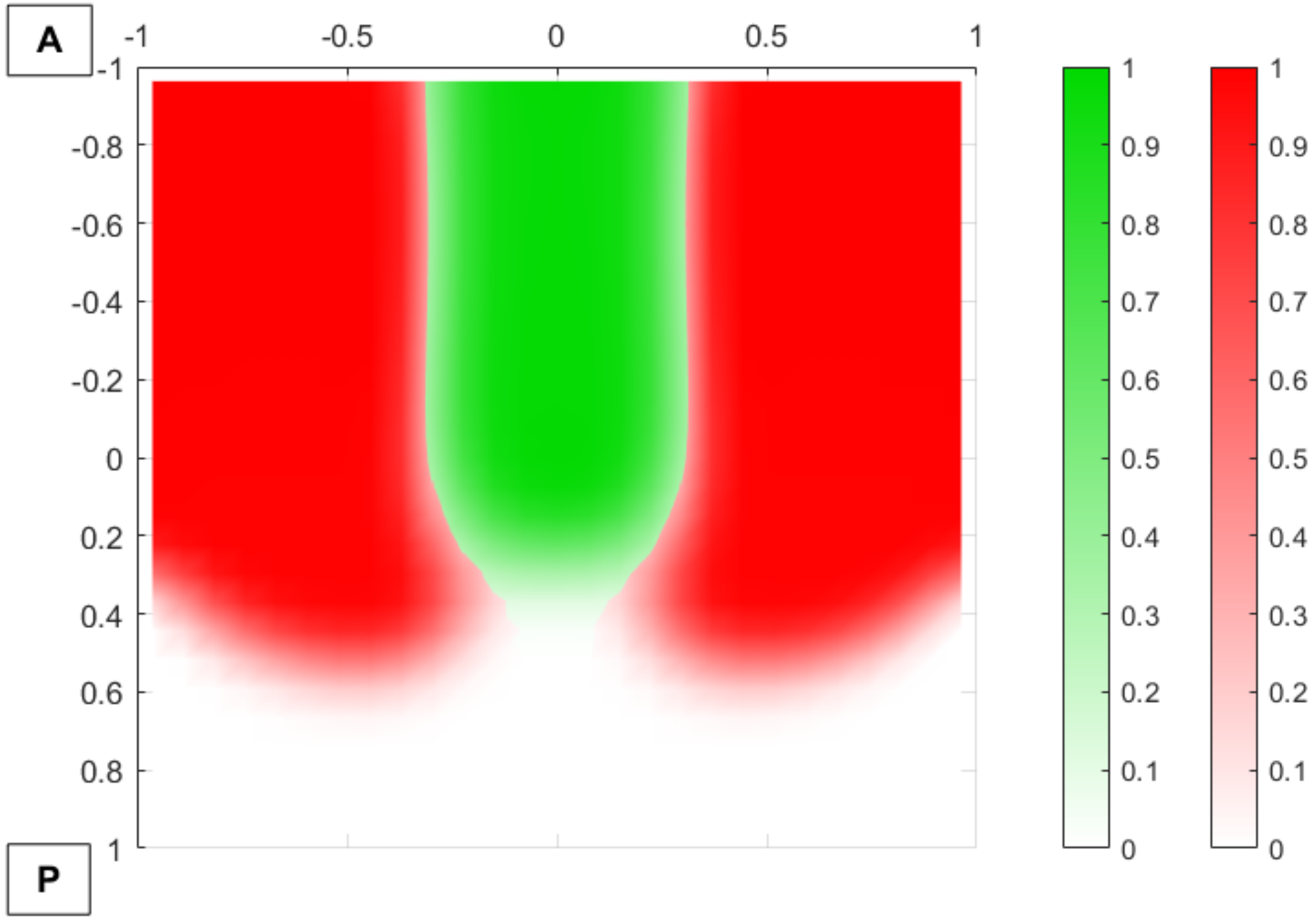




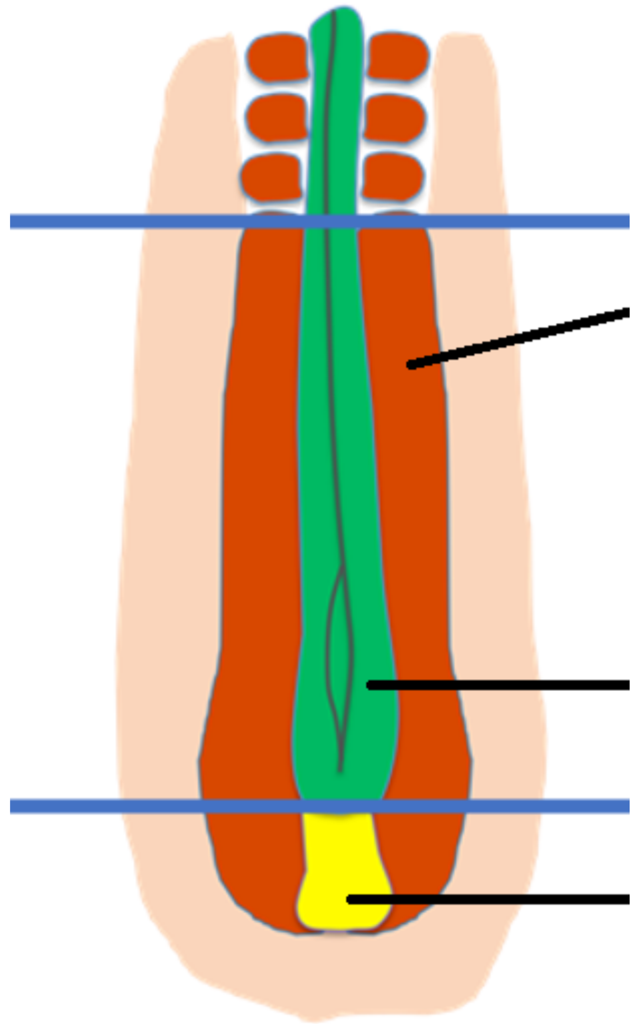
Comparison between models: densities



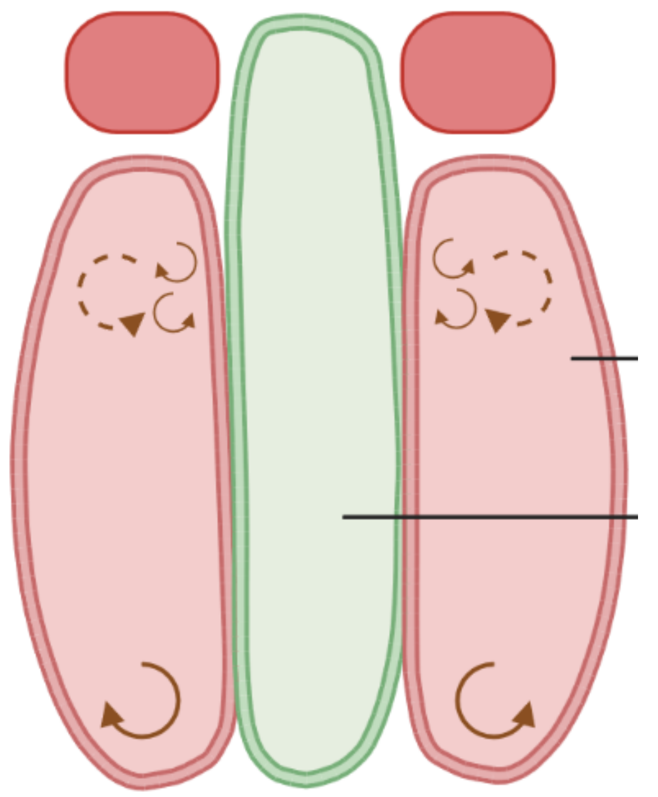
Fluid model,
Passive segregation

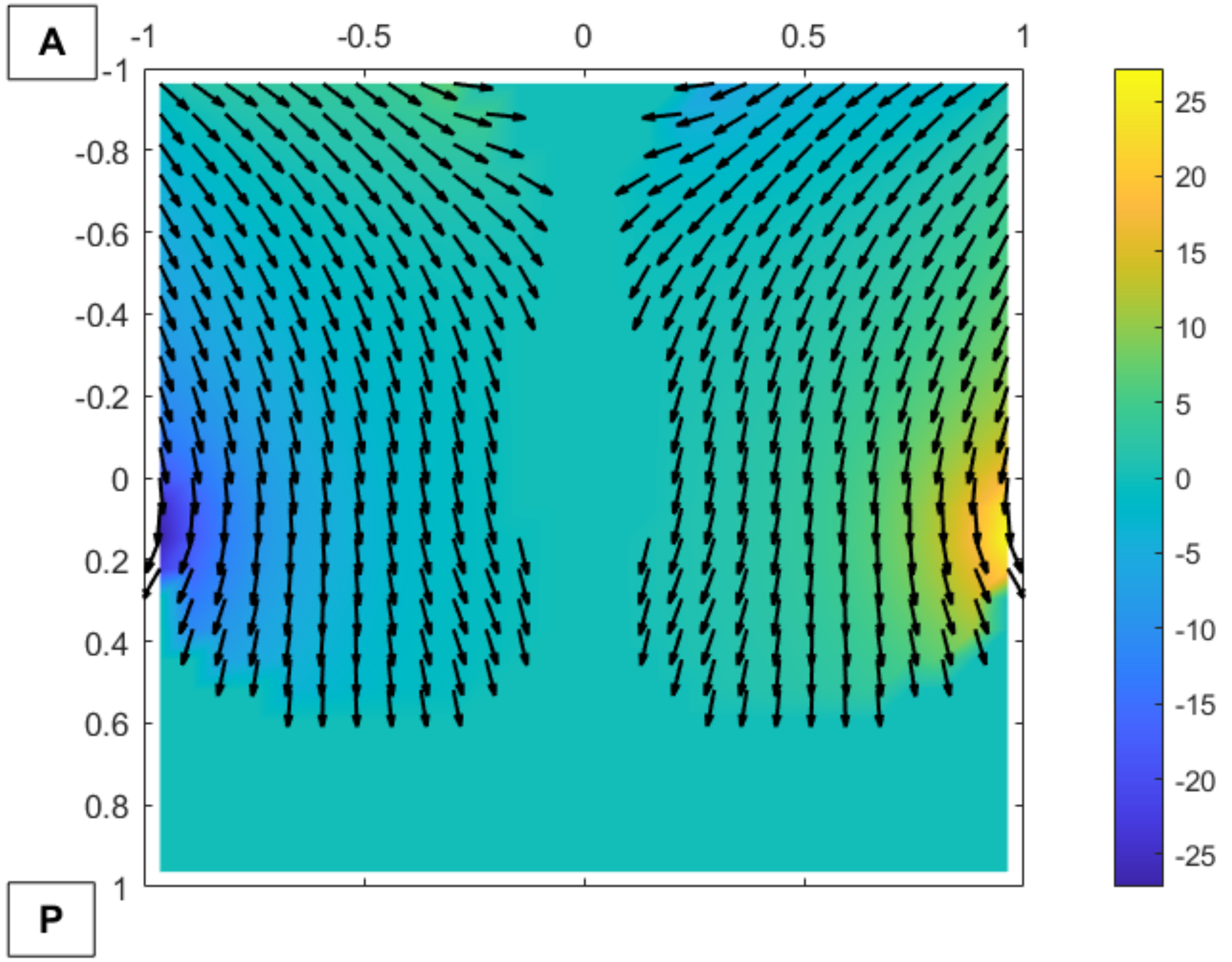


Fluid model,
Active segregation



Comparison between models: rotational





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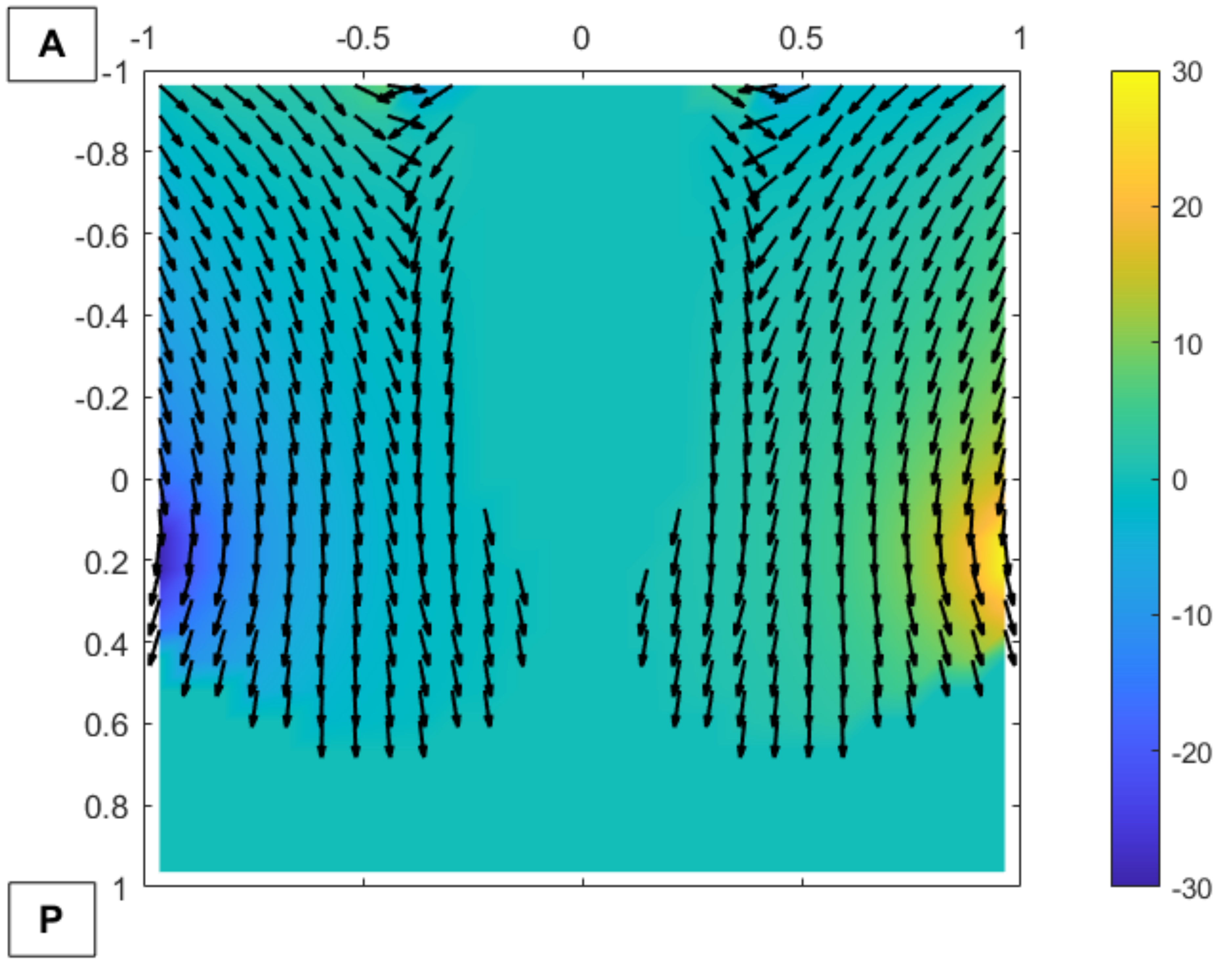

Fluid model,
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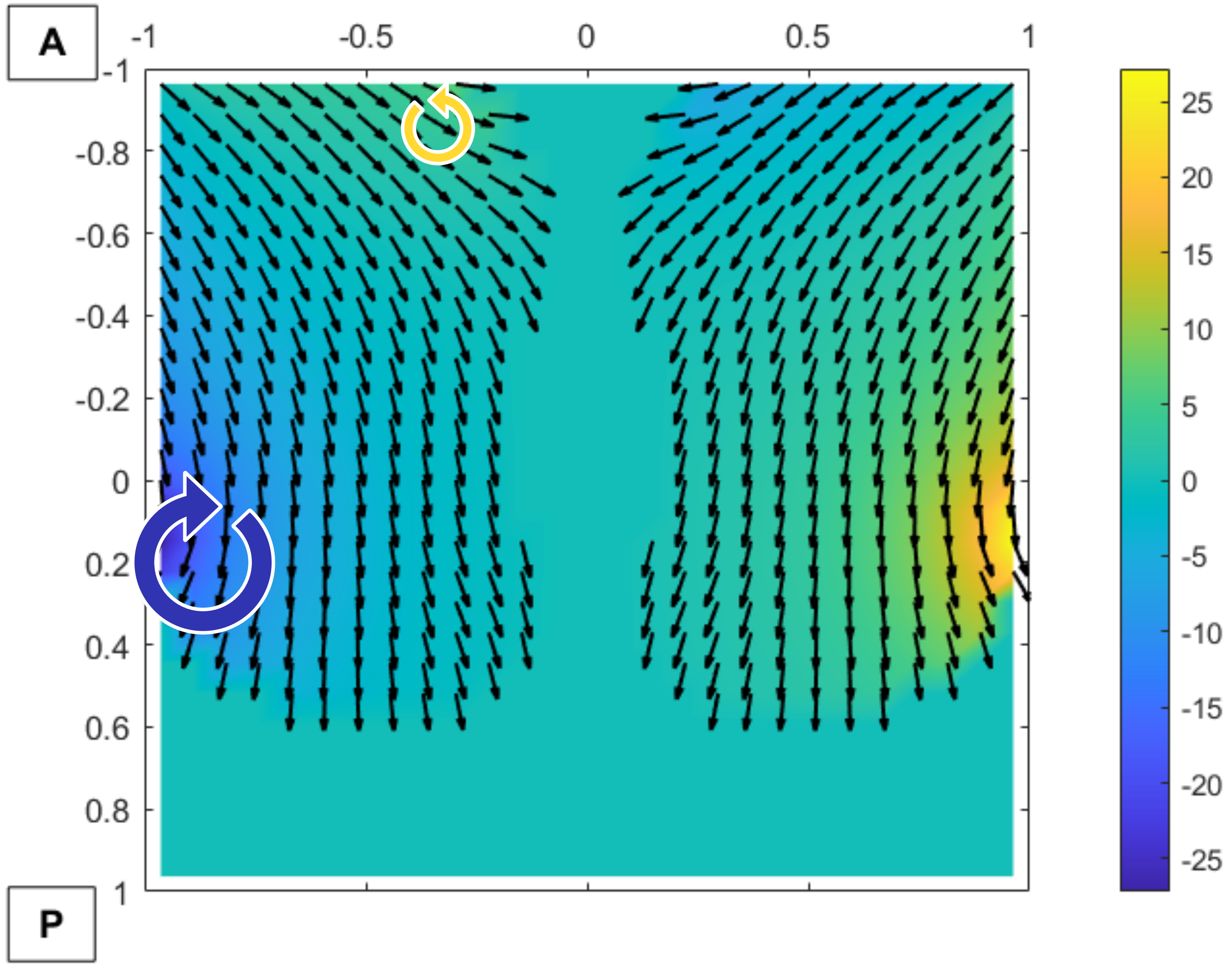
Comparison between models: rotational



Fluid model,
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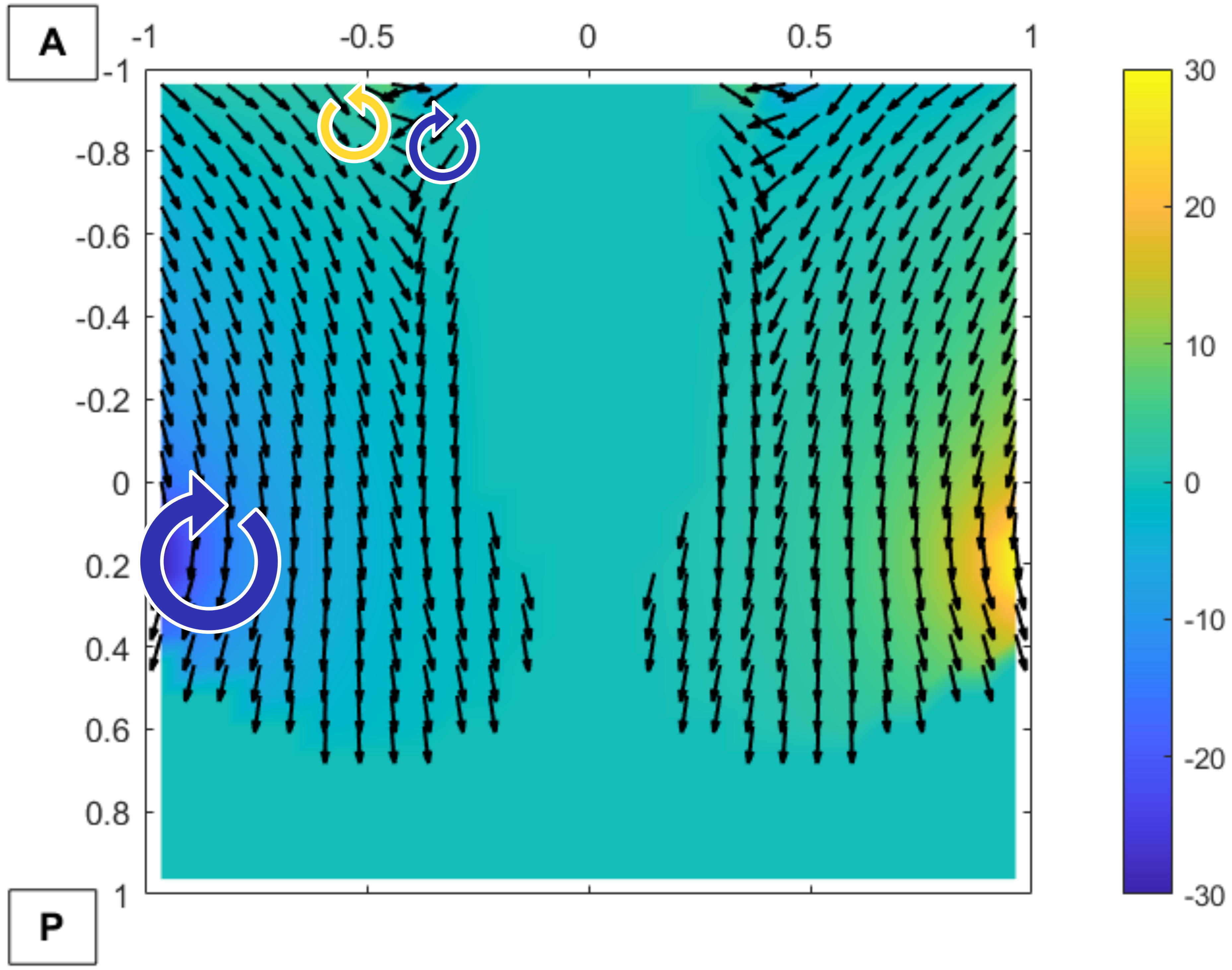

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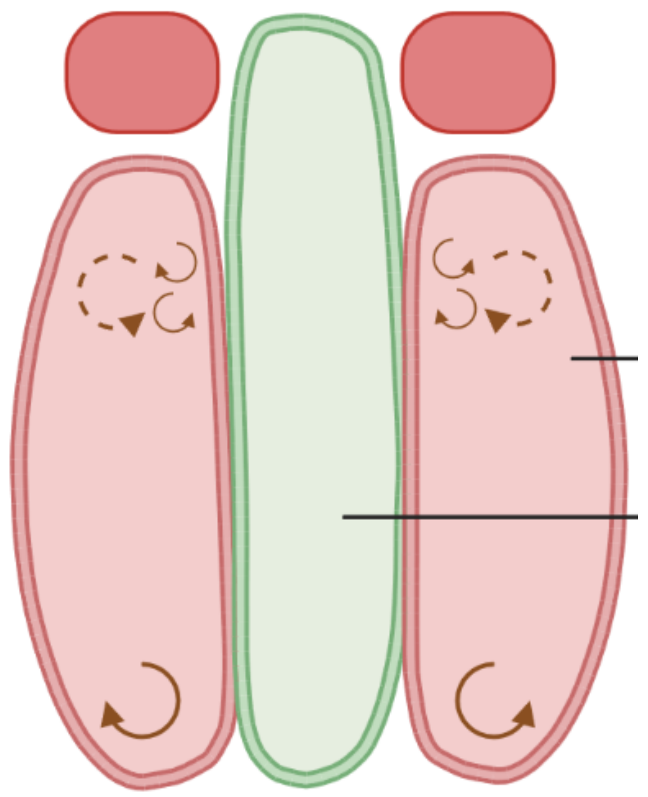

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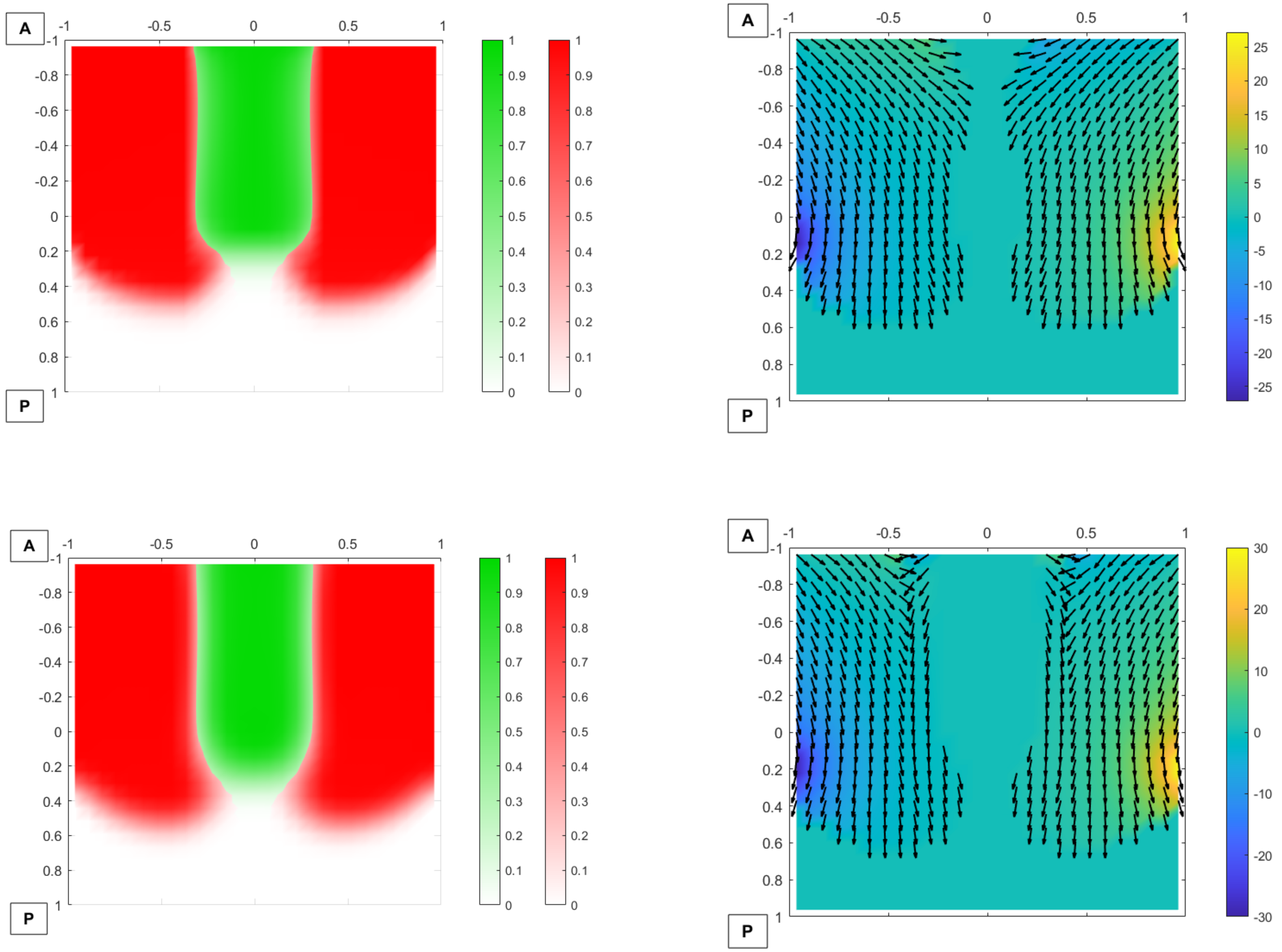


Fluid model,
Passive segregation

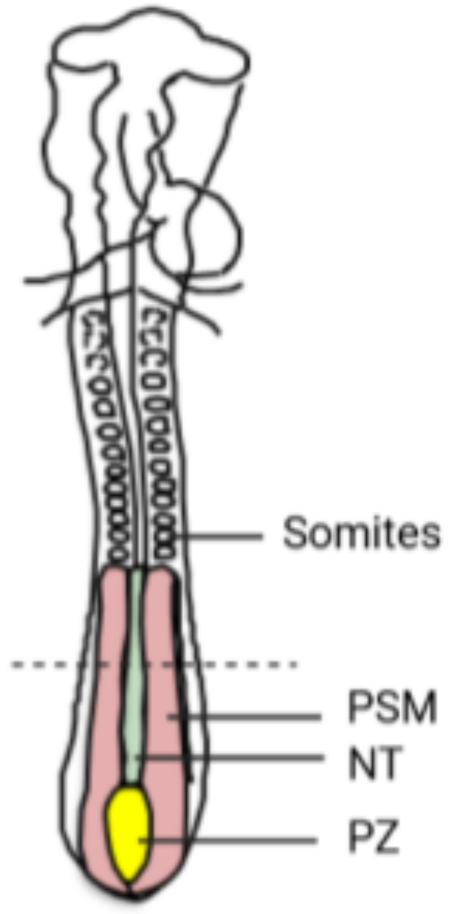
Fluid model,
Active segregation

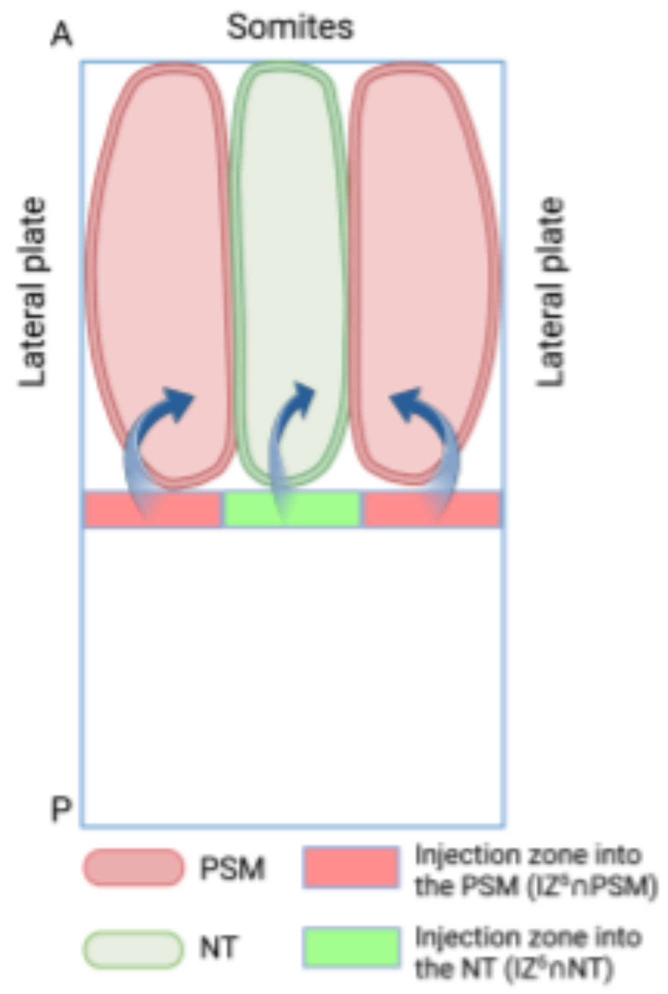
Our model suggests that some active segregation is at play.

Diving deeper into the biological data

One step forward towards biology:

- we add injection (duly *quantified*)
- other parameters taken from the biological literature





Parameter	Source	Value	Unit
NT viscosity (β_1)	Michaut 2018	10^4 - 10^5	Pa • s
PSM viscosity (β_2)	Mahadevan 2017, Michaut 2018	10^4 - 10^5	Pa • s
Proliferation rate of the NT (g_1)	Bénazéraf 2017	1/10.83	1/ hour
Proliferation rate of the PSM (g_2)	Bénazéraf 2017	1/8.75	1/ hour
Injection rate from the PZ into the NT (κ_{NT})	Measured experimentally	5	Cells/ hour/ 10µm
Injection rate from the PZ into the PSM (κ_{PSM})	Measured experimentally	10	Cells/ hour/ 10µm
Total maximal density (n_{max})	Bénazéraf 2017	2800	Cells/ 100 µm³
Pressure sensing (ϵ)	Estimated free parameter	1	Pa
Tissue friction with surroundings (μ)	Mahadevan 2017, Michaut 2018	10^{12} - 10^{13}	Pa • s/m²
Growth sensitivity near the maximal density (α)	Estimated free parameter	8	Dimensionless
Width of injection zone (δ)	Measured experimentally	214	µm

Tissue growth

Cell proliferation **Cell Injection**

$$\partial_t n_1 + \nabla \cdot (n_1 v_1) = n_1 g_1 \left(1 - \left(\frac{n_1}{n_{max}}\right)^{\alpha}\right)_+ + \frac{\kappa_{NT}}{\delta} \chi_{IZ^{\delta} \cap NT},$$

$$\partial_t n_2 + \nabla \cdot (n_2 v_2) = n_2 g_2 \left(1 - \left(\frac{n_2}{n_{max}}\right)^{\alpha}\right)_+ + \frac{\kappa_{PSM}}{\delta} \chi_{IZ^{\delta} \cap PSM},$$

Time-space evolution of the NT density and of the PSM density

$$-\beta_1 \Delta v_1 + \mu v_1 = -\nabla p,$$

$$-\beta_2 \Delta v_2 + \mu v_2 = -\nabla p,$$

Brinkman's law for the NT and PSM velocities

$$p = \epsilon \frac{n}{n_{max} - n}, \qquad n = n_1 + n_2.$$

Congestion pressure

Diving deeper into the biological data

One step forward towards biology:

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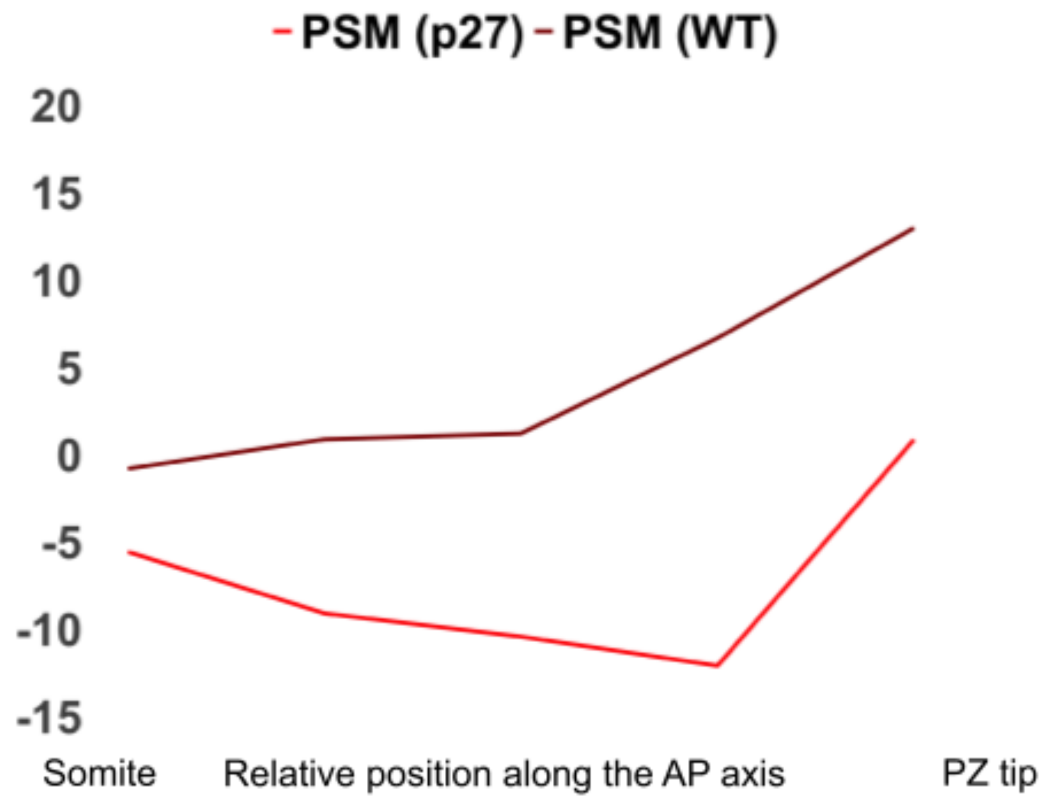
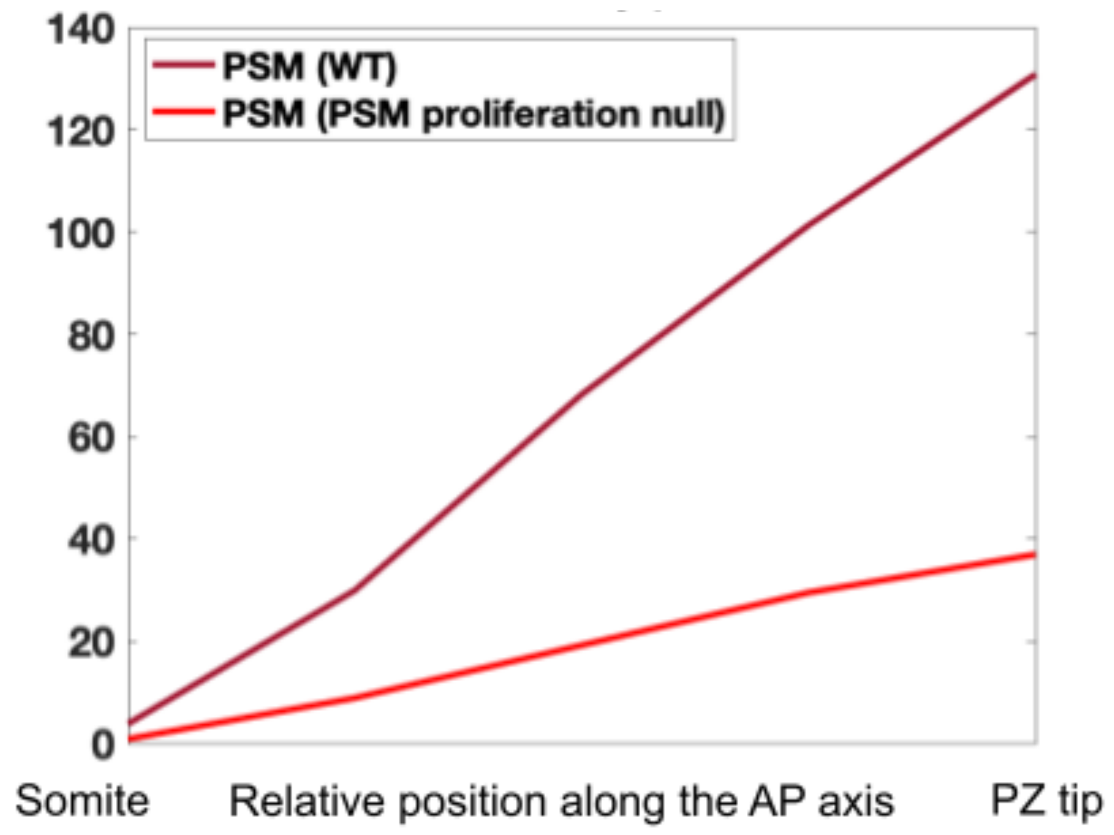
- other parameters taken from the biological literature

Validation of the model:

- with « natural » parameters, compared with *wild type* data (« healthy » embryo)
- with pathological parameters, compared with experiments *in vivo* (proliferation suppressed, …)

In particular, the model reproduces well the differential elongation and the sliding between tissues.





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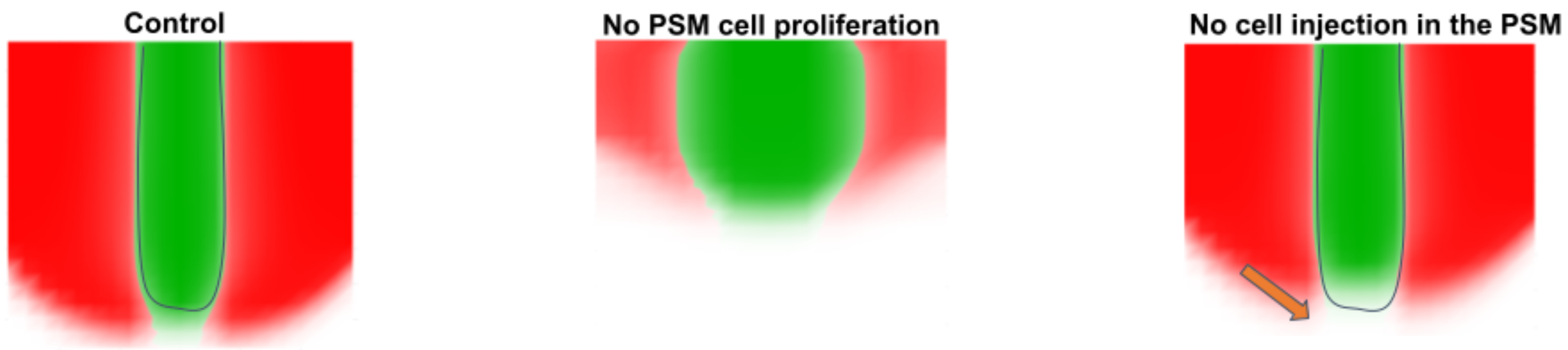
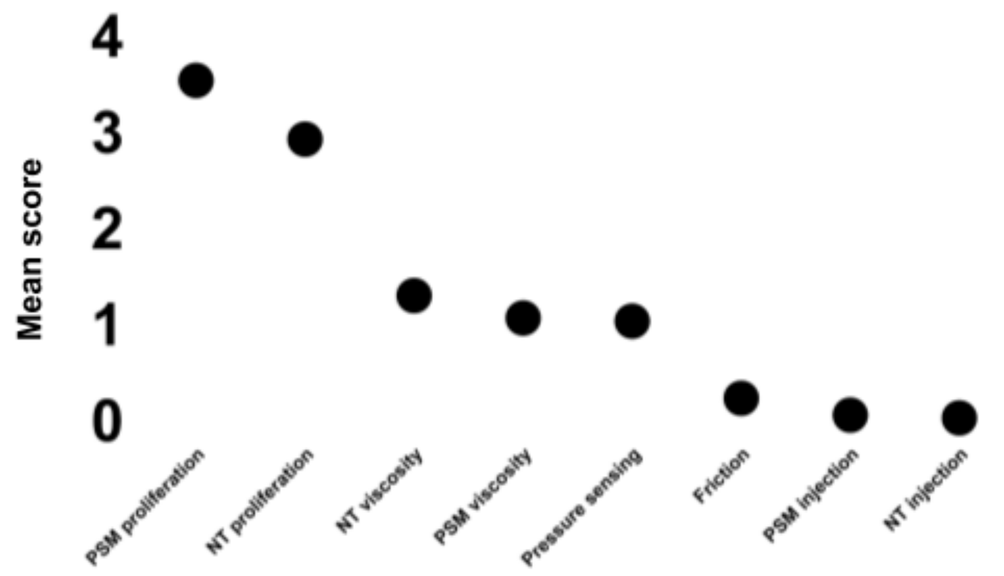
Output of the model: we perform a sensitivity analysis based on relevant outputs characterizing shapes and velocities of the tissues. This analysis reveals the underestimated importance of (differential) tissue proliferation in the embryogenesis.





Score:= density, pressure, tissue width (mid AP axis), velocities, elongation rate

Mathematical analysis: a few words

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Ref : [Degond Hecht Romanos Trescases 2022]

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Can we compute the incompressible limit ?

$\epsilon \to 0$, $m \to \infty$ **and** $\alpha \to 0$

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p_\epsilon(n) = \epsilon \frac{n}{1-n}, \\
q_m(r) = \frac{m}{m-1}((1+r)^{m-1} - 1).
\end{cases}
$$

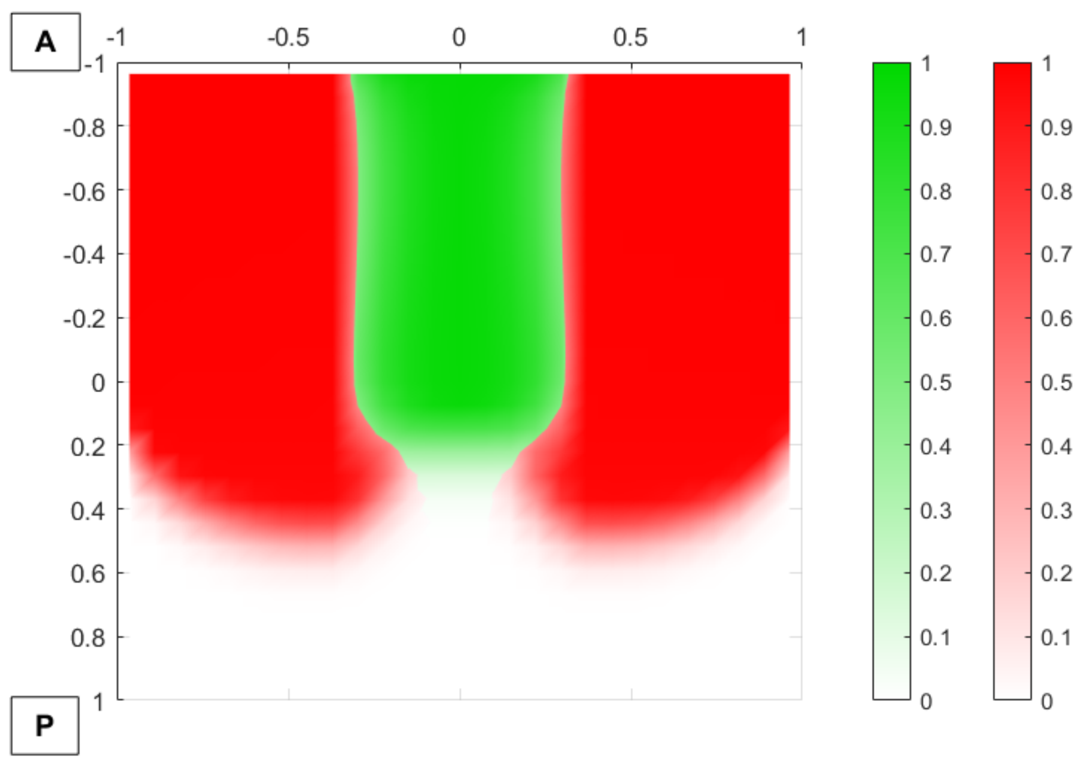
Can we compute the incompressible limit ?

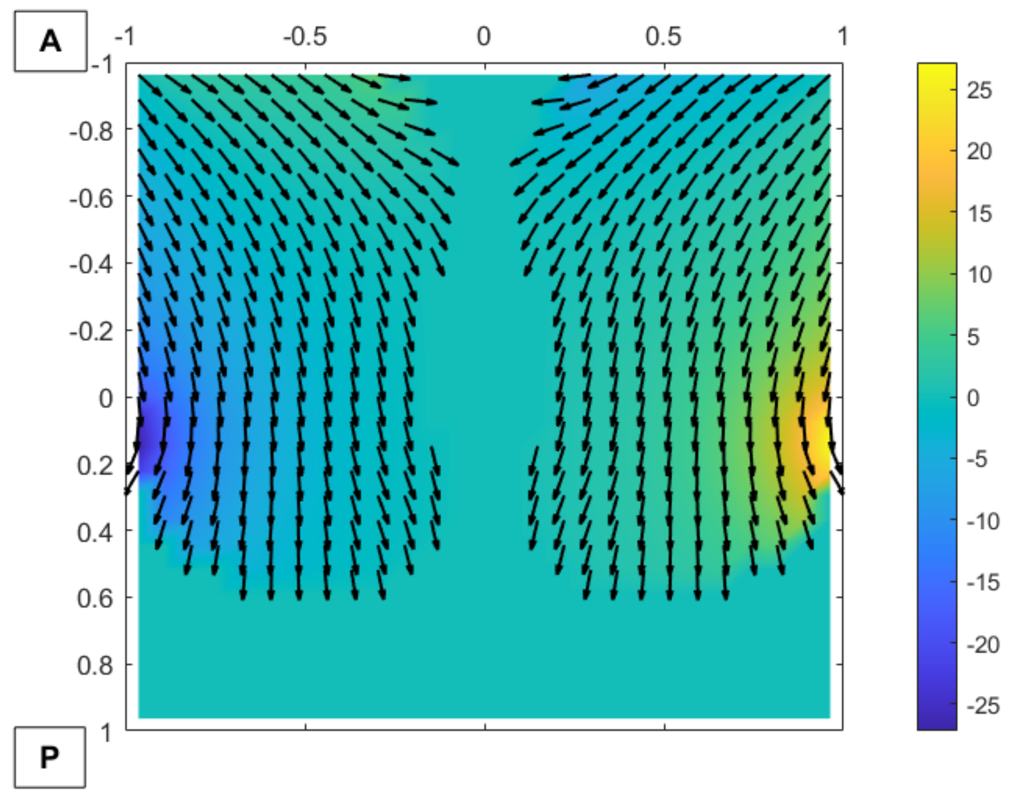
$\epsilon \to 0,\ m \to \infty$ **and** $\alpha \to 0$

Formally, YES.

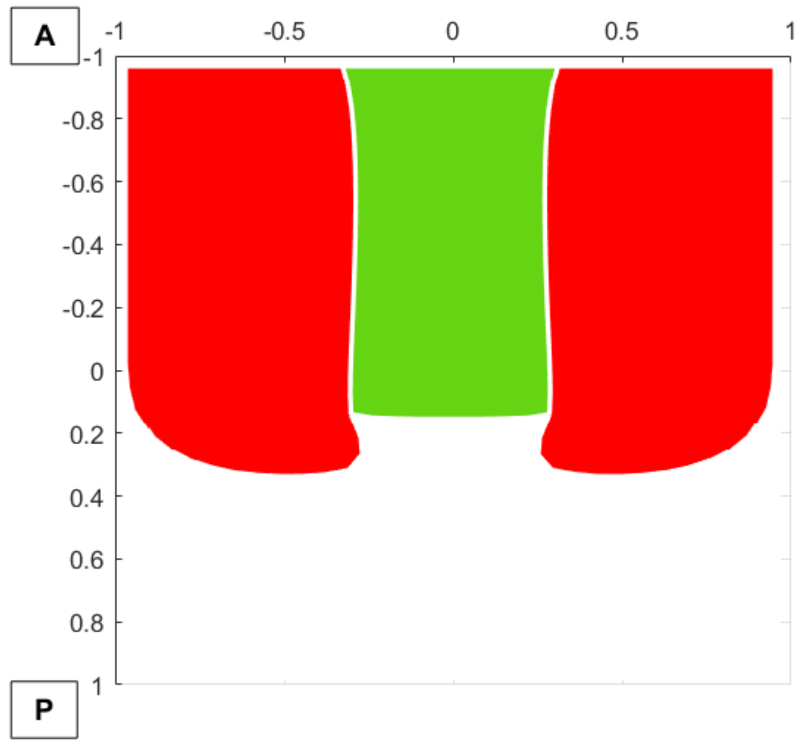
Ref : [Degond Hecht Romanos Trescases 2022]

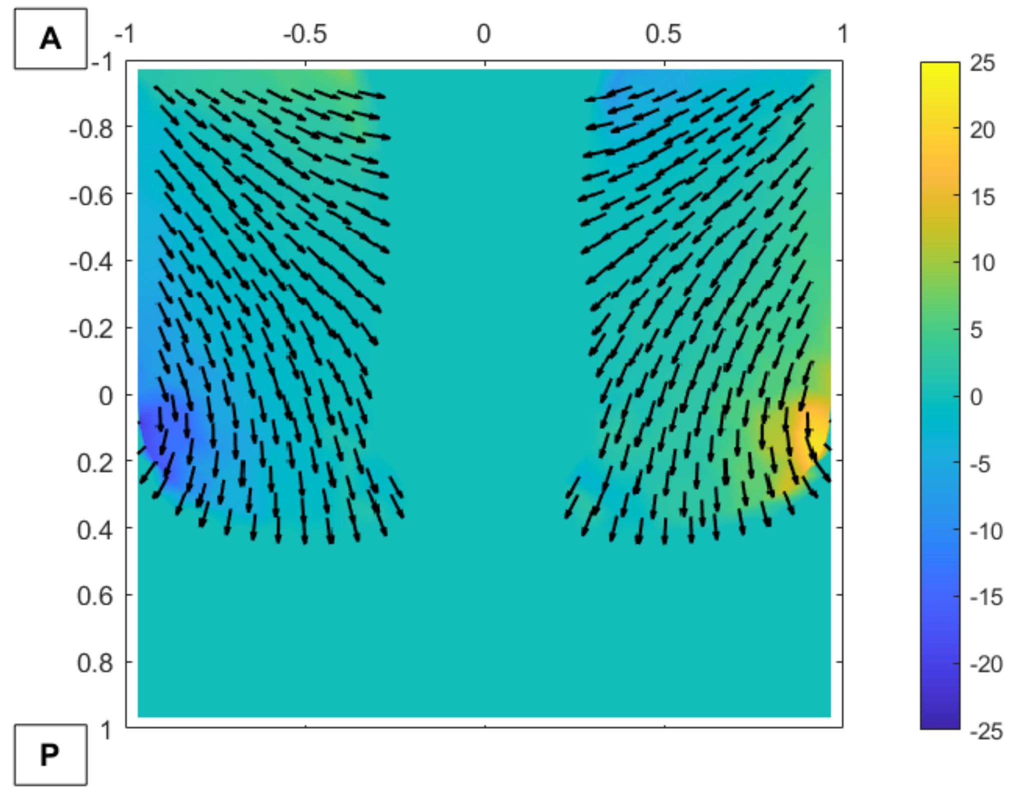
Simulation before and at the limit





Fluid model,
Passive segregation





Geometrical model,
Passive segregation

Ref : [Degond Hecht Romanos Trescases 2022]

Analysis at the incompressible limit

Under simplifying assumptions (in a bounded domain in 2D, stationary case, linearly decreasing growth function, smooth subdomains, given segregation pressure in L^2), and under an *ellipticity condition*, we prove:

- well-posedness (weak solution in H^1)

- smoothness inside each subdomain

- equivalence with a transmission problem

- pressure jump at the interface (when the segregation pressure is null)

Ref : [Degond Hecht Romanos Trescases 2022]

Transmission problem

$$\text{on } \Omega_1 : (T_1) \begin{cases} -\beta_1 \Delta v_1 + v_1 - \dfrac{1}{g_1} \nabla \nabla \cdot v_1 = 0, \\ -\beta_2 \Delta v_2 + v_2 - \dfrac{1}{g_1} \nabla \nabla \cdot v_1 = 0, \end{cases}$$

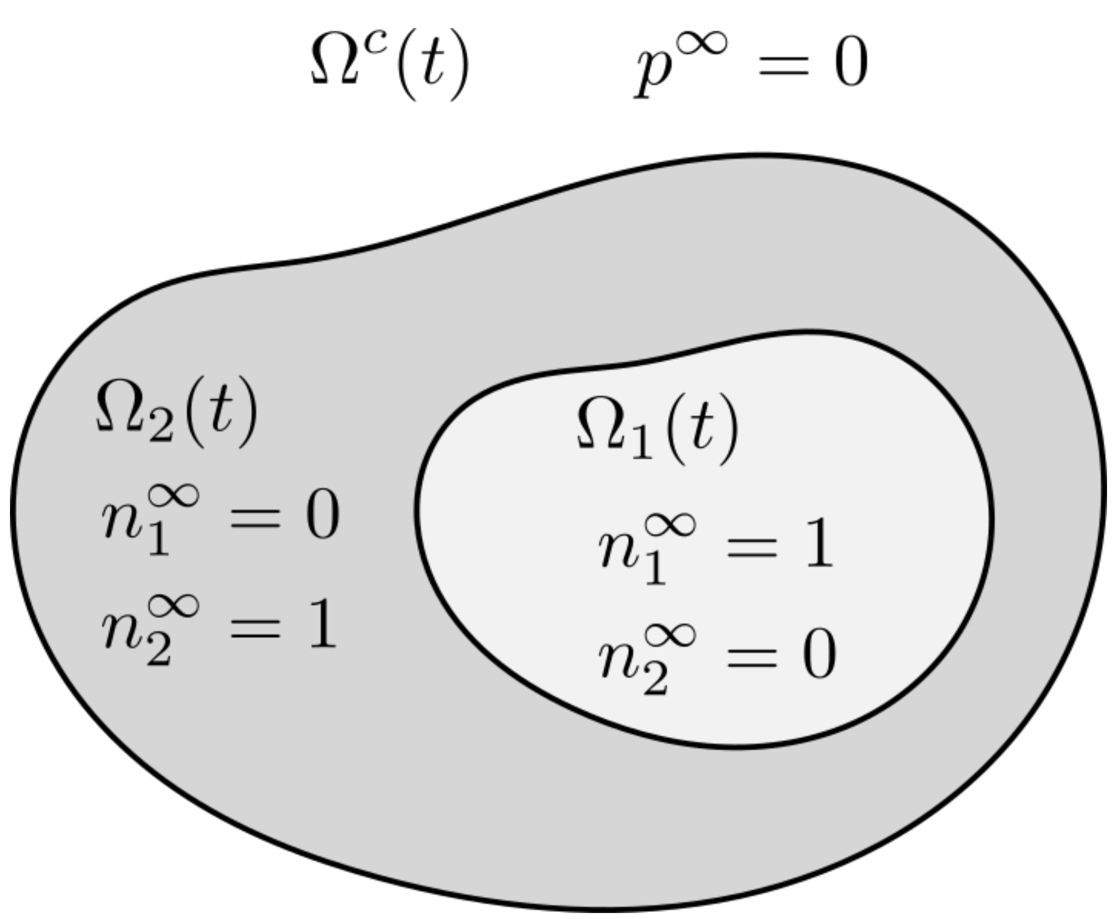
$$\text{on } \Omega_2 : (T_2) \begin{cases} -\beta_1 \Delta v_1 + v_1 - \dfrac{1}{g_2} \nabla \nabla \cdot v_2 = 0, \\ -\beta_2 \Delta v_2 + v_2 - \dfrac{1}{g_2} \nabla \nabla \cdot v_2 = 0, \end{cases}$$

$$\text{on } \Omega^c : (T_3) \begin{cases} -\beta_1 \Delta v_1 + v_1 = 0, \\ -\beta_2 \Delta v_2 + v_2 = 0. \end{cases}$$

$$\text{on } \Gamma_1 : (C_1) \begin{cases} \beta_1 [(\nabla v_1)_{\Omega_1} - (\nabla v_1)_{\Omega^c}] \cdot \vec{\nu} = [p_1^\star - \dfrac{1}{g_1} (\nabla \cdot v_1)_{\Omega_1}] \vec{\nu}, \\ \beta_2 [(\nabla v_2)_{\Omega_1} - (\nabla v_2)_{\Omega^c}] \cdot \vec{\nu} = [p_1^\star - \dfrac{1}{g_1} (\nabla \cdot v_1)_{\Omega_1}] \vec{\nu}, \\ (v_1)_{\Omega_1} = (v_1)_{\Omega^c}, \quad (v_2)_{\Omega_1} = (v_2)_{\Omega^c}, \end{cases}$$

$$\text{on } \Gamma_2 : (C_2) \begin{cases} \beta_1 [(\nabla v_1)_{\Omega_2} - (\nabla v_1)_{\Omega^c}] \cdot \vec{\nu} = [p_2^\star - \dfrac{1}{g_2} (\nabla \cdot v_2)_{\Omega_2}] \vec{\nu}, \\ \beta_2 [(\nabla v_2)_{\Omega_2} - (\nabla v_2)_{\Omega^c}] \cdot \vec{\nu} = [p_2^\star - \dfrac{1}{g_2} (\nabla \cdot v_2)_{\Omega_2}] \vec{\nu}, \\ (v_1)_{\Omega_2} = (v_1)_{\Omega^c}, \quad (v_2)_{\Omega_2} = (v_2)_{\Omega^c}, \end{cases}$$

$$\text{on } \Gamma : (C_3) \begin{cases} \beta_1 [(\nabla v_1)_{\Omega_1} - (\nabla v_1)_{\Omega_2}] \cdot \vec{\nu} = [(p_1^\star - p_2^\star) + \dfrac{1}{g_2} (\nabla \cdot v_2)_{\Omega_2}) - \dfrac{1}{g_1} (\nabla \cdot v_1)_{\Omega_1}] \vec{\nu}, \\ \beta_2 [(\nabla v_2)_{\Omega_1} - (\nabla v_2)_{\Omega_2}] \cdot \vec{\nu} = [(p_1^\star - p_2^\star) + \dfrac{1}{g_2} (\nabla \cdot v_2)_{\Omega_2}) - \dfrac{1}{g_1} (\nabla \cdot v_1)_{\Omega_1}] \vec{\nu}, \\ (v_1)_{\Omega_1} = (v_1)_{\Omega_2}, \quad (v_2)_{\Omega_1} = (v_2)_{\Omega_2}, \quad v_1 \cdot \vec{\nu} = v_2 \cdot \vec{\nu}. \end{cases}$$



Ref : [Degond Hecht Romanos Trescases 2022]

The rigorous incompressible limit

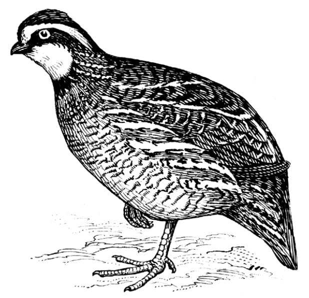
For the passive segregation model:
- recently proven for viscous tissues *in the whole domain*

refs: [Perthame Vauchelet 2015] (one tissue); [Dębiec Schmidtchen 2020] and [Dębiec Perthame Schmidtchen Vauchelet 2021] (multi-species, *same viscosities*)
- still open in a bounded domain
- still open for different viscosities

The active segregation model is another challenge..!

Conclusion

Conclusion



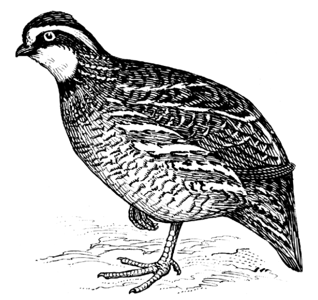
Summary

- We developed multi-tissue mechanical models with *passive* or *enforced* segregation
- We derived from it (formally) a geometrical model
- We analyzed the geometrical model: stationary state, pressure jump
- We simulated the model and compared it with biological data

Biological conclusions

- Suggests the existence of a segregation force
- Highlights the underestimated role of differential tissue proliferation rates

Conclusion



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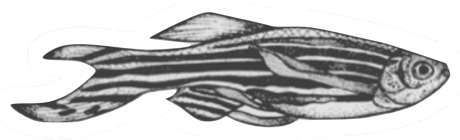
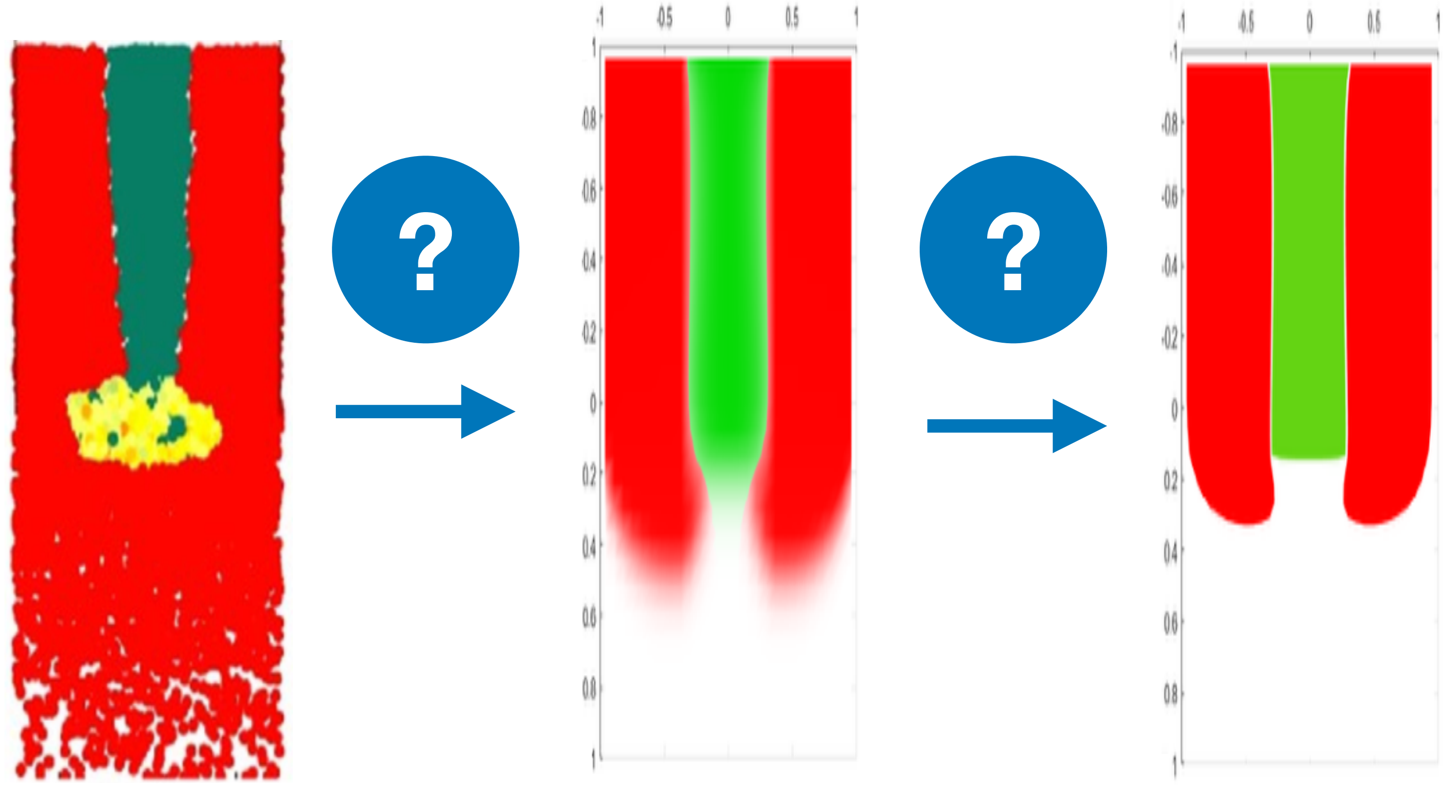


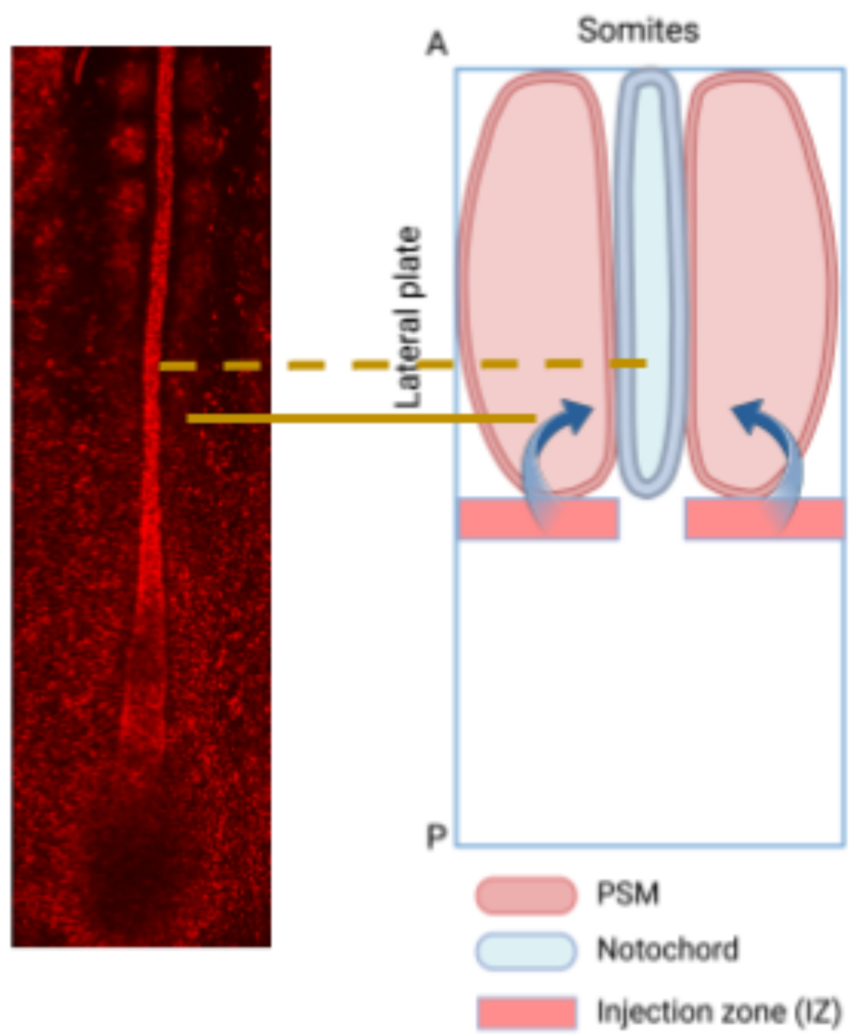
Biological conclusions

- Suggests the existence of a segregation force
- Highlights the underestimated role of differential tissue proliferation rates

Perspectives

- More tissues, 3D, …
- Diverse species
- Link with microscopic models
- Rigorous incompressible limit

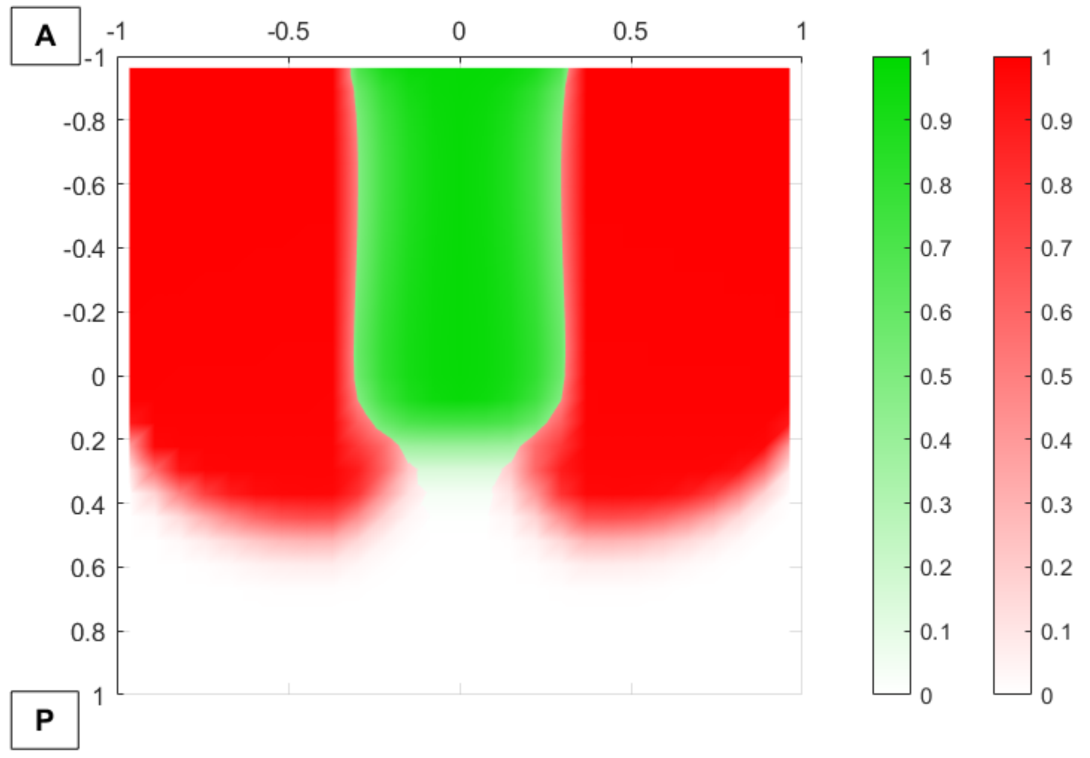




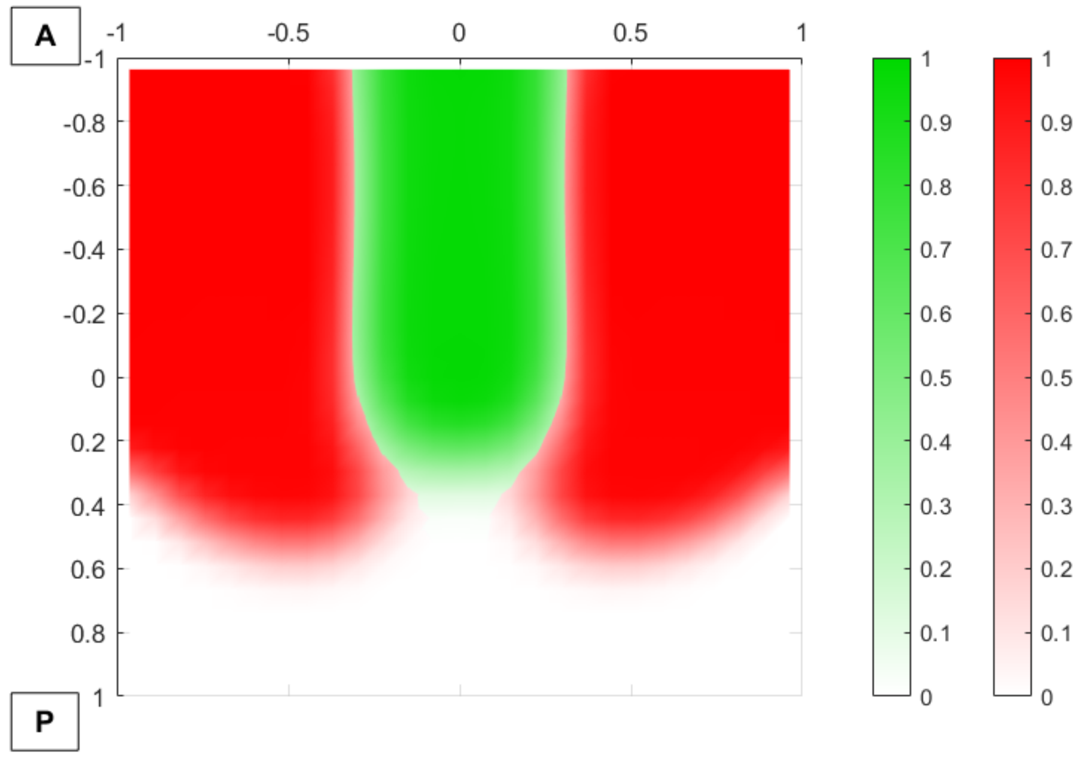
Thank you for your attention

Numerical schemes

Mechanical model (1):
Finite volume semi-implicit scheme - Matlab



Mechanical model (2):
Finite volume semi-implicit scheme, with a relaxation method (order reduction) - Matlab



Geometrical model:
Finite elements - Freefem++