Mathematical modeling of embryo axis elongation

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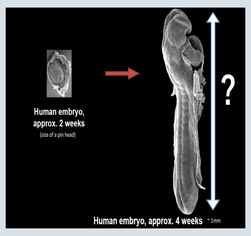
1 – Introduction to the biological model- Macroscopic

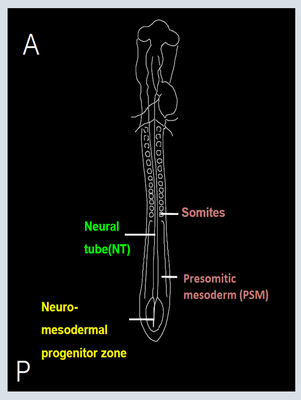
During embryonic development thousands of cells self-organize in a very precise and complex choreography to form the tissues and the future adult organs.



Human embryo developpment

Coordination between:

- Cellular proliferation
- Migration
- Adhesion
- Addition of new cells



Different tissues involved in bird development

How is this coordination contributing to the rise of mechanisms causing elongation?

2 – The viscous two species model

Consider the densities n_1 and n_2 of two cell populations in each tissue. Each tissue is endowed with a viscosity coefficient β_1 and β_2, a proliferation rate G_1 and G_2, a mechanical pressure $p_\epsilon = \epsilon \frac{n_1+n_2}{1-(n_1+n_2)}$, and a repulsion term $q_m = \frac{m}{m-1}((1+n_1n_2)^{m-1}-1)$, and v_1, v_2 the velocities of each tissue which follow the Brinkman law:

$$\partial_t n_1 + \nabla \cdot (n_1 v_1) + \alpha \nabla \cdot (n_1 \nabla(\Delta n_1)) = n_1 G_1(p_1), \quad (1)$$

$$\partial_t n_2 + \nabla \cdot (n_2 v_2) + \alpha \nabla \cdot (n_2 \nabla(\Delta n_2)) = n_2 G_2(p_2), \quad (2)$$

$$p_1 = p_\epsilon(n_1+n_2) + n_2 q_m(n_1 n_2), \quad (3)$$

$$p_2 = p_\epsilon(n_1+n_2) + n_1 q_m(n_1 n_2), \quad (4)$$

$$-\beta_1 \Delta v_1 + v_1 = -\nabla p_1 \quad (5)$$

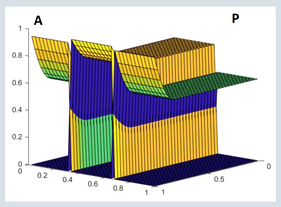
$$-\beta_2 \Delta v_2 + v_2 = -\nabla p_2 \quad (6)$$

with α a regularizing parameter (avoid bubble effect), ϵ and m parameters of the pressure laws.

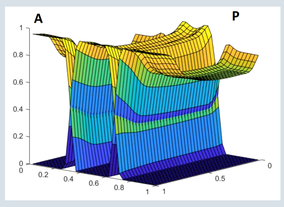
3 – Numerical Simulations for the Macroscopic model

We use a 2D finite volume scheme to simulate the evolution of the densities, and the flux in each tissue:

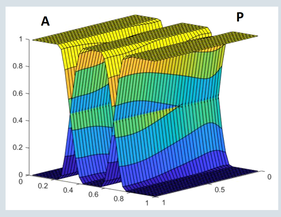
Density profile:



0h of development.

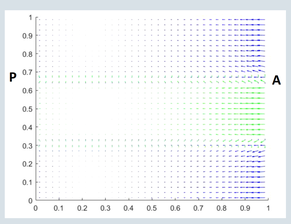


After 10min of development.

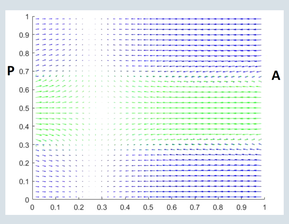


After 1h of development.

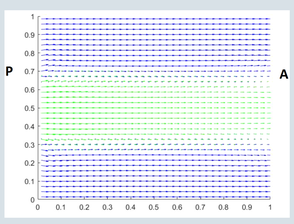
Flux profile:



0h of development.



After 10min of development.



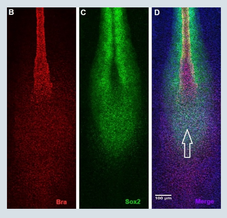
After 1h of development.

Main challenges: Blow up of the pressure for maximum density, strict CFL conditions, calibration of the model parameters to fit the biological data ...

4 – Introduction to the biological model- Agent-Based

Brachyury (Bra) and Sox2 are transcription factors involved in the generation and patterning of the posterior body, through cross-regulation.

- Bra : mesodermal marker, promotes cell motility
- Sox2: neural marker, promotes cell adhesion
- Co-expression in the Progenitor zone



Heterogeneity of the transcription factors

Cellular behavior:

- Diffusion: Erratic movement
- Repulsion: Non-mixing
- Adhesion: Cells of the same type adhere to each other
- Proliferation

Cells involved:

- PSM cells: move erratically, with intense noise
- NT cells: move very little, and adhere
- Progenitor cells: move erratically

Do these cellular mechanisms explain the organization (elongation) of the posterior body ?

5 – The agent-based model

We consider N cells, each cell i is described by its type $r_i = \frac{[Sox2]}{[Bra]+[Sox2]}$ and its position (in $2D$, diffusion process depending on r_i).

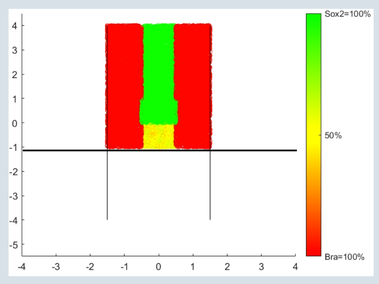
The concentration r_i in transcription factors is goverened by the ODE:

$$d_t r_i(t) = f(r_i(t)) + k_r U = 100(r_i(t)-0.5)(r_i(t)-0.2)(r_i(t)-0.8) + k_r U,$$

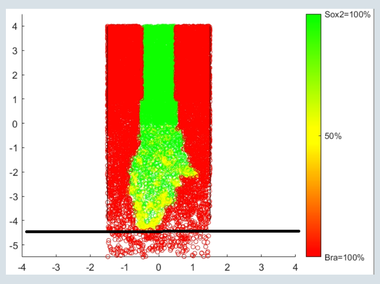
with U a noise modeling cellular specification rate and k_r its intensity.
The evolution of the cell position: a jump in x and in y (random walk). Depending on the densities of the neighboring cells, the jump might be redirected (repulsion) or cancelled (adhesion).

6 – Numerical Simulations for the agent-based model

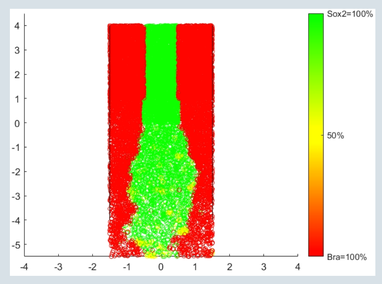
The formation of the posterior body:



0h of development.



After 1h08min of development.



After 3h of development.

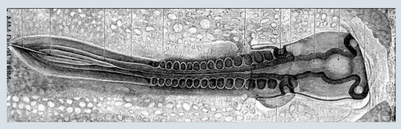
Remarks: Initial configuration matching biological data, calibration of model parameters to fit biological data...

7 – Experimentally - Ongoing work

Objective: Validate both models and generate new biological hypotheses

To validate the new hypotheses of the models i will harvest quail eggs and:

- Inhibit proliferation (Electroporation of P27)
- Control the incoming flux from the progenitor zone (gain and loss of function of Sox2 and Bra)
- Track cells using live imaging to compare with in silico experiments



8 – Conclusion and Perspectives on the models

MACROSCOPIC. We observe:

- Sliding between the tissues
- Differential growth

Varying proliferation rates and the incoming flux of new cells in healthy and pathological cases we can determine the effect of these parameters on elongation. A mathematical analysis of the models is in the works.

AGENT-BASED. We observe:

- Effect of diffusion and cell specification on elongation and on tissue shape
- Effect of gain and loss of function of Sox2 and Bra

Perspective: Quantify these observations and compare simulations with experimental data.