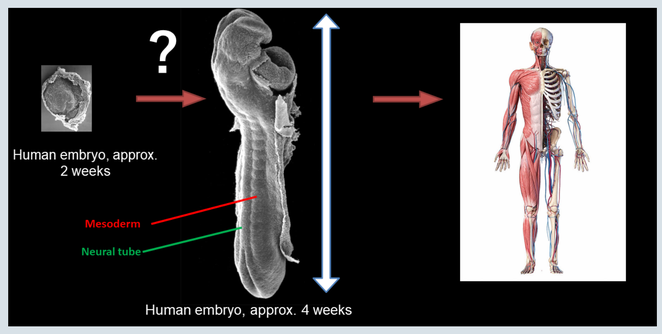
Heterogeneity in vertebrate embryo: a bio-mathematical point of view

Michèle Romanos – Institut de Mathématiques de Toulouse & Centre de Biologie Integrative

Supervisors: Bertrand Bénazéraf (CBI) and Ariane Trescases (IMT)

1 – Introduction to the biological model

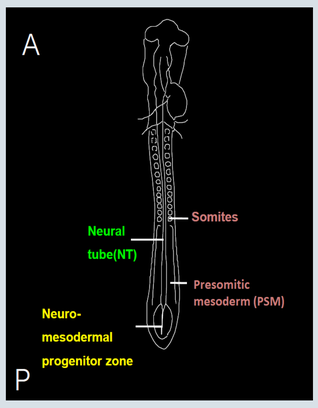
During embryonic development thousands of cells self-organize in a very precise and complex choreography to form the tissues and the future adult organs.



Mesoderm gives future muscles and neural tube gives future nervous system

What we know about NMPs:

- Provide new cells to the NT and PSM, some cells remain resident in the progenitor zone
- Resident cells can self renew
- Co-express markers of neural & mesodermal tissues (Brachyury (Bra) and Sox2)

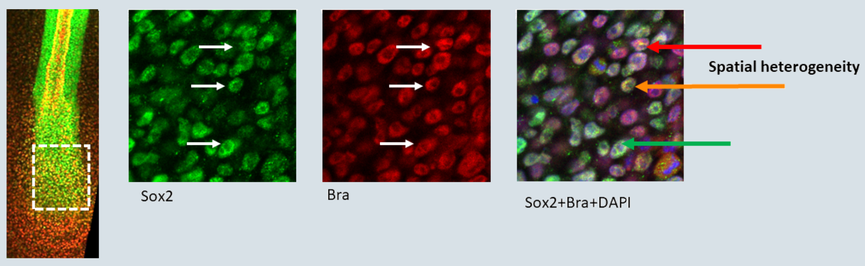


Different tissues involved in bird development

How do NMPs coordinate between maintenance and contribution to the NT and PSM ?

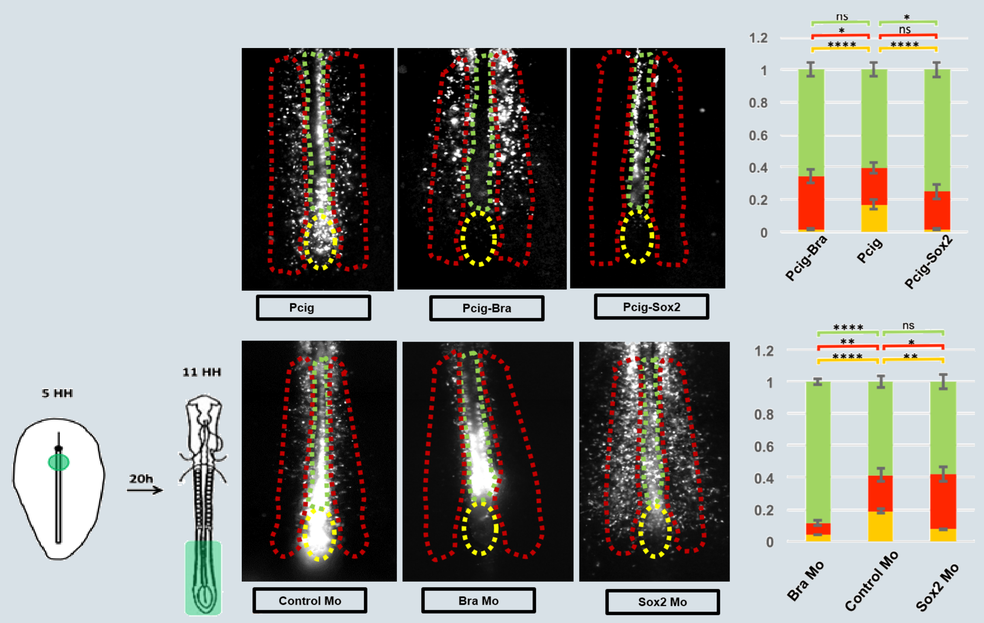
2 –Studying the NMPs

By immunodetection we see that Bra and Sox2 are heterogeneously expressed within the NMPs.



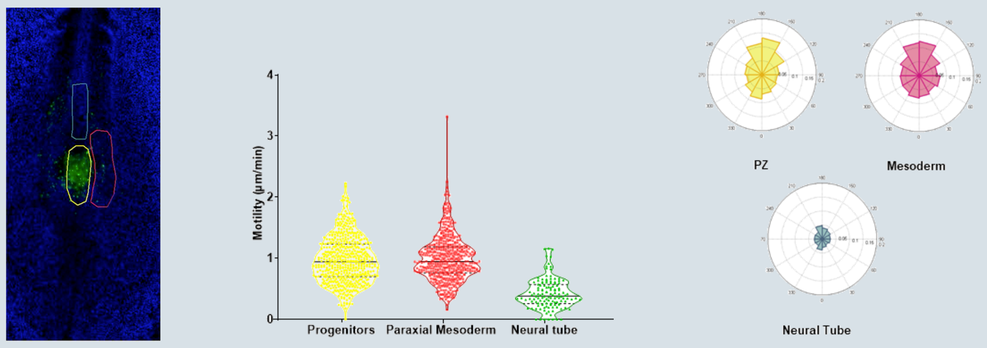
Is the ratio Sox2/Bra influencing NMPs destiny ?

By electroporation - LOF & GOF of Bra and Sox2 in the PZ - we found that Bra and Sox2 affect the distribution of NMPs in the tissues PZ, PSM & NT.



Sox2/Bra ratio in NMPs linked to cell velocity ?

By tracking cells in selected regions in the tissues, we see that PZ cells are highly motile without strong directionality in the WT embryo.



Can we explain the maintenance of progenitors & their contribution to the PSM & NT by the direct influence of Sox2/Bra heterogeneity on cell velocity ?

3 – Modeling heterogeneity- 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:

$$dr_i(t) = f(r_i(t))dt + k_r dB_1,$$

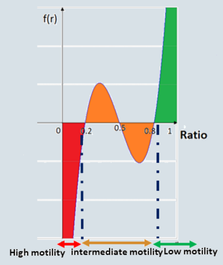
The ODE for cell position in 2D is governed by the ODE for brownian motion:

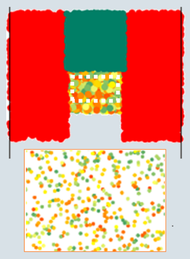
$$\begin{cases} dx_i(t) = k_x V(r_i) dB_2, \\ dy_i(t) = k_y V(r_i) dB_3, \end{cases}$$

with $dB_1, dB_2, dB3$ noises modeling signals cells receive, and k_r, k_x, k_y their respective intensities, and $V(r_i)$ the cell velocity. Depending on the densities of the neighboring cells, the jump might be redirected (maximum density) or cancelled (adhesion).

Cell behavior :

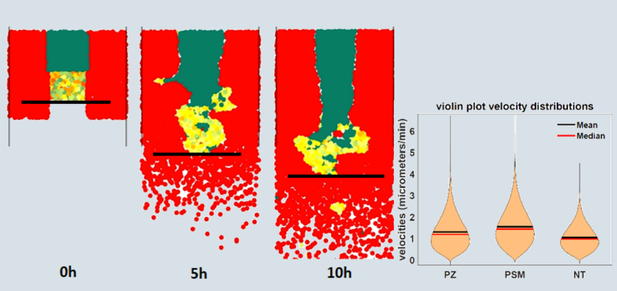
- Diffusion
- Non-mixing
- Differential adhesion
- Proliferation



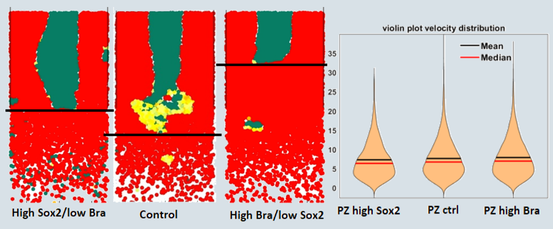


4 – Numerical Simulations of the agent-based model

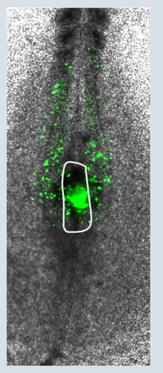
Model reproduces biological reality:

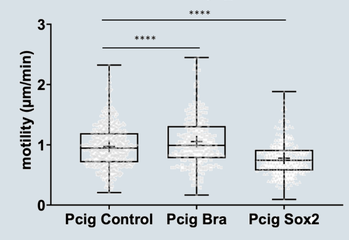


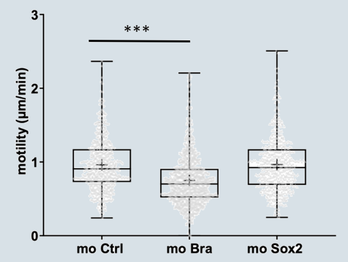
Simulations of deregulated Sox2/ Bra ratios suggest that they have antagonistic activities on cell velocity in the PZ :



Validation of model hypothesis.



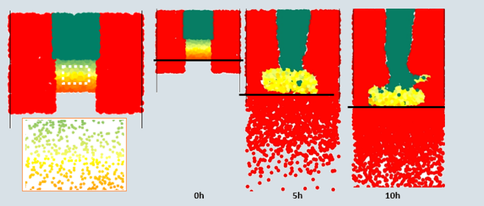




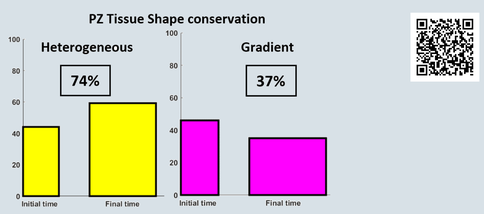
5 – Modeling the importance of heterogeneity

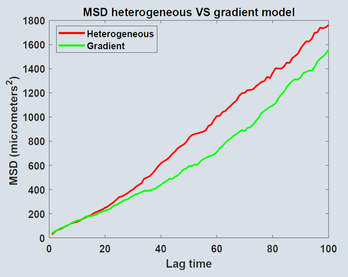
To understand the importance of spatial heterogeneity, we developped a model in which cells of the PZ are organized in an opposite gradient of Sox2/Bra.

The models suggest that a heterogeneous distribution is more beneficial than a gradient one.



Elongation rate(gradient)=0.9au
Elongation rate(heterogeneous)=1.9au.





6 – Take home messages

- Sox2/Bra spatial heterogeneity allows progenitor organization in the tissues .
- Spatial heterogeneity has several advantages on morphogenesis & auto-organization compared to a gradient-like distribution.
- Sox2/Bra control progenitor motility in the tissues.