CEMRACS 2018 project: Mathematical modelling of cell aggregation and segregation.

Kevin Atsou, [1] Marta Marulli, [2] Remi Tesson. [3]

[1] Laboratoire J.A. Dieudonné, Université de Nice Sophia-Antipolis,

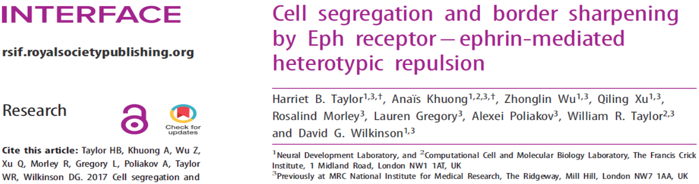
[2] LAGA, Université Paris 13, Università di Bologna,

[3] Institut Mathématiques de Marseille, Aix-Marseille Université.

August 22th 2018

Biological context

Cells of the same type can regroup into regions ⇒ spatial organisation.
Cell segregation and border sharpening in two-species systems:



INTERFACE

rsif.royalsocietypublishing.org

Research

Check for updates

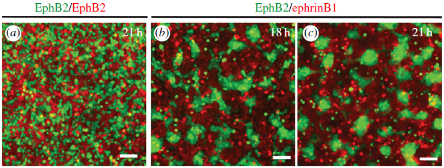
Cite this article: Taylor HB, Khuong A, Wu Z, Xu Q, Morley R, Gregory L, Poliakov A, Taylor WR, Wilkinson DG. 2017 Cell segregation and

Cell segregation and border sharpening by Eph receptor—ephrin-mediated heterotypic repulsion

Harriet B. Taylor[1,3,†], Anaïs Khuong[1,2,3,†], Zhonglin Wu[1,3], Qiling Xu[1,3], Rosalind Morley[3], Lauren Gregory[3], Alexei Poliakov[3], William R. Taylor[2,3] and David G. Wilkinson[1,3]

[1]Neural Development Laboratory, and [2]Computational Cell and Molecular Biology Laboratory, The Francis Crick Institute, 1 Midland Road, London NW1 1AT, UK
[3]Previously at MRC National Institute for Medical Research, The Ridgeway, Mill Hill, London NW7 1AA, UK

Working hypothesis: inter(heterotypic) and intra(homotypic) species repulsion control cell segregation and border sharpening. They have more influence than inter- or intra-species adhesion.
Goal: to understand the mechanisms of morphogenesis.



How to model?

Several mathematical models and differents approaches have been proposed for cell segregation.

Macroscopic model

- Continuous approach $\rightarrow$ analysis tools
- Theoretical framework to link the solutions to the model parameters

BUT

- Loss of info about cell-interactions
- No info about number of clusters size and popolation size

Microscopic model

- Agent-based models: simplicity and flexibility
- Precision of the modeling
- Link with experimental data

BUT

- Computational expensive
- Theoretically harder

Microscopic framework

Individual Based Model for particles interacting through repulsion interactions:

$$\begin{cases} dX_i^A = -\mu \nabla_{X_i^A} W^A(X^A, X^B)dt + \sqrt{2D_A}dB_i, & \forall i \in \{1,\dots,N_A\} \\ dX_i^B = -\mu \nabla_{X_\ell^A} W^B(X^A, X^B)dt + \sqrt{2D_B}dB_\ell, & \forall \ell \in \{1,\dots,N_B\} \end{cases} \tag{1}$$

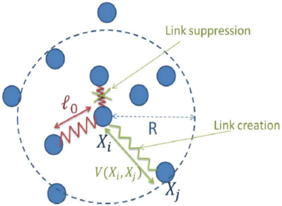
- $\mu > 0$ is the constant mobility coefficient,
- B_i is a 2-dimensional Brownian motion $B_i = (B_i^1, B_i^2)$ of intensity $D_A, D_B > 0$ respectively for species A and B,
- W^S total energy of the S-type particle, $S \in \{A, B\}$, defined as:

$$W^A(X^A, X^B) = \underbrace{\sum_{k_1=1}^{K_{AA}} \Phi^{AA}(X^A_{i(k_1)} - X^A_{j(k_1)}) + \sum_{k_3=1}^{K_{AB}} \Phi^{AB}(X^A_{i(k_3)} - X^B_{\ell(k_3)})}_{sum\ over\ all\ pairwise\ link\ potentials\ acting\ on\ particles\ A},$$

$$W^B(X^A, X^B) = \sum_{k_2=1}^{K_{BB}} \Phi^{BB}(X^B_{\ell(k_2)} - X^B_{m(k_2)}) + \sum_{k_3=1}^{K_{AB}} \Phi^{BA}(X^B_{\ell(k_3)} - X^A_{\ell(k_3)})$$

Case: Hookean interaction potential

We suppose that the homotypic (AA,BB) species links and heterotypic (AB,BA) act as a springs of equilibrium length R between the particles that it is also detection radius for the interaction.



Case of Hookean springs

$$\Phi^{ST}(x) = \frac{\nu_c^{ST}}{\nu_d^{ST}} \frac{\kappa^{ST}}{2} \begin{cases} (|x| - R)^2, & \text{for } |x| \leq R \\ 0, & \text{for } |x| > R \end{cases}$$

with ν_c^{ST}, ν_d^{ST} Poisson processes frequencies and κ^{ST} interaction/repulsion intensity.

- Each particle can link/unlink with its neighbors located in a ball of radius R
- Links are not permanent: created and supressed via random processes
- Linking/unlinking processes are very fast

Logistic growth term

We add a growth process to the microscopic model as follows:

- Cell of type S divide into 2 cells with probability β_S and die with probability δ_S at each time step. $S \in \{A, B\}$
- Birth and death processes depend on the local density of individuals
- Birth occurs at distance r

$$\beta_S(X_i) = b_0^S - (b_0^S - \theta)\left(\frac{\mathcal{N}_0}{N^*}\right), \quad \delta_S(X_i) = d_0^S + (\theta - d_0^S)\left(\frac{\mathcal{N}_0}{N^*}\right) \tag{2}$$

Parameters:

- $\mathcal{N}_0 = \mathcal{N}_{R_0}(X_i^S)$: number of cells (of both population) at distance R_0 of the cell located in X_i^S
- N^* is the maximal number of cell in a radius R_0 allowing cell division.
- θ, constant coefficient that assures the randomness at the population N^*.

Micro macro

Form micro to macro

Fock space

- Main difficult the varying size of the cell population
- Introduction of the Fock Space:
- Probability space of all the possible states of the particle system

$$X_k := [x_1, x_2, \ldots, x_k]$$

$$\mathbb{P}_k(X_k, t)dX_k = \Pr\{\text{k cells, with one cell in } dx_1, \text{ another in } dx_2 \text{ etc. }\}$$

Form micro to macro

Reduced distribution function

- The density or concentration of cells is define by:

$$f(x,t) = \langle \sum_{p=1}^{k} \delta(x - x_p) \rangle.$$

which becomes

$$f(x,t) = \sum_{k=1}^{\infty} k \int \mathbb{P}_k(x, X_{k-1}, t) dX_{k-1},$$

- We define a master equation for the Probability $\mathbb{P}_k(X_k, t)$ time evolution:

Master Equation

$$\mathbb{P}_k(X_k, t+\tau) = \int \mathbb{W}_k(X_k, t+\tau | X_k^{'}, t)\mathbb{P}_k(X_k^{'}, t)dX_k^{'}$$
$$+ \tau \sum_{i=1}^{k-1} \beta(X_i)\mathbb{BP}_{k-1} - \tau \left[\sum_{i=1}^{k}(\beta(X_i) + \delta(X_i))\right] \mathbb{P}_k(X_k, t)$$
$$+ \tau \int \sum_{k=1}^{k+1} \beta(X_i)\mathbb{P}_k + 1(X_{k+1}, t)dx_i$$

with $\mathbb{W}_k(X_k, t+\tau | X_k^{'}, t)$ the transition probability from a state $X_k^{'}$ to a state X_k and

$$\mathbb{BP}_{k-1} = \frac{2}{k(k-1)} \sum \sum_{1 \le p < q \le k} \delta_{pq}\mathbb{P}_{k-1}(X_{k|p}, t) \tag{3}$$

Master Equation

Using Kramers-Moyal expansion on the term $\int \mathbb{W}_k(X_k, t+\tau | X_k^{'}, t)\mathbb{P}_k(X_k^{'}, t)dX_k^{'}$:

$$\begin{aligned}
\mathbb{P}_k(X_k, t+\tau) = & \left[1 + \sum_{|\alpha|>0} (-1)^{|\alpha|} \partial^\alpha \left(D^{|\alpha|}(X_k, t)\tau + O(\tau^2)\right)\right] \mathbb{P}_k(X_k, t) \\
& + \tau \sum_{i=1}^{k-1} \beta(X_i) \mathbb{B}\mathbb{P}_{k-1} - \tau \left[\sum_{i=1}^{k} (\beta(X_i) + \delta(X_i))\right] \mathbb{P}_k(X_k, t) \\
& + \tau \int \sum_{k=1}^{k+1} \beta(X_i) \mathbb{P}_{k+1}(X_{k+1}, t) dx_i .
\end{aligned}$$

Master Equation

the coefficients $D^{|\alpha|}$ are the so-called **Kramers-Moyal** expansion coefficients with:

$$D^{|\alpha|}(X_k, t) = \frac{1}{\alpha!} \lim_{\tau \to 0} \frac{1}{\tau} \langle (\xi(t+\tau) - X_k)^{\alpha} \rangle |_{\xi(t)=X_k}.$$

Using the definition :

$$f(x,t) = \sum_{k=1}^{\infty} k \int \mathbb{P}_k(x, X_{k-1}, t) dX_{k-1},$$

we can deduce the reduced equation on $f(x,t)$ by summing and integrating the master equation.

Macroscopic framework

Macroscopic model should provide an approximation of the agent-based model:

$$\begin{cases} \partial_t f^A = \nabla \cdot \underbrace{(f^A \nabla_x (\Phi^{AA} * f^A) + f^A \nabla_x (\Phi^{AB} * f^B))}_{interaction\ \ potential} + \underbrace{D_A \Delta_x f^A}_{diffusion} + \underbrace{\nu_b^A f^A \left(1 - \frac{f^A + f^B}{f^*}\right)}_{logistic\ \ term} \\ \partial_t f^B = \nabla \cdot (f^B \nabla_x (\Phi^{BB} * f^B) + f^B \nabla_x (\Phi^{BA} * f^A)) + D_B \Delta_x f^B + \nu_b^B f^B \left(1 - \frac{f^A + f^B}{f^*}\right) \end{cases}$$

- f^*: carrying capacity of the environment
- ν_b^A, ν_b^B growth rates

Remark: f^A, f^B play the same role in logistic term

Analysis of the macroscopic model

We recall macroscopic equations for f^A and f^B:

$$\begin{cases} \partial_t f^A = \nabla \cdot (f^A \nabla_x (\Phi^{AA} * f^A) + f^A \nabla_x (\Phi^{AB} * f^B)) + D_A \Delta_x f^A + \nu_b^A f^A \left(1 - \frac{f^A + f^B}{f^*}\right) \\ \partial_t f^B = \nabla \cdot (f^B \nabla_x (\Phi^{BB} * f^B) + f^B \nabla_x (\Phi^{BA} * f^A)) + D_A \Delta_x f^A + \nu_b^B f^B \left(1 - \frac{f^A + f^B}{f^*}\right) \end{cases} \quad (4)$$

Linearization around constant steady states $\bar{f}^A$, $\bar{f}^B$ and Fourier transform:

$$\partial_t \begin{pmatrix} \hat{f}^A \\ \hat{f}^B \end{pmatrix} = \underbrace{\begin{pmatrix} -|y|^2(2\pi \bar{f}^A \hat{\Phi}^{AA}(y) + D_A) - \nu_b^A \frac{\bar{f}^A}{f^*} & -|y|^2 2\pi \bar{f}^A \hat{\Phi}^{AB}(y) - \nu_b^A \frac{\bar{f}^A}{f^*} \\ -|y|^2 \bar{f}^B \hat{\Phi}^{BA}(y) - \nu_b^B \frac{\bar{f}^B}{f^*} & -|y|^2(2\pi \bar{f}^B \hat{\Phi}^{BB}(y) + D_B) - \nu_b^B \frac{\bar{f}^B}{f^*} \end{pmatrix}}_{M(y)} \begin{pmatrix} \hat{f}^A \\ \hat{f}^B \end{pmatrix}$$

The constant steady states will be unstable if:

- $\nu^B \frac{\bar{f}^A}{f^*}(\bar{f}^A 2\pi \hat{\Phi}^{AA} + D_A - \bar{f}^A 2\pi \hat{\Phi}^{AB}) < \nu^A \frac{\bar{f}^A}{f^*}(\bar{f}^B 2\pi \hat{\Phi}^{BB} + D_B - \bar{f}^B 2\pi \hat{\Phi}^{BA})$.

We want to focus on the ratio of homo- and hetero-typic species repulsion.
We introduce a parameter $s \in \mathbb{R}$ s.t.: $\kappa^{ST} = s\tilde{\kappa}^{ST}$

Analysis of the macroscopic model

We find critical value s_L^* related to instability:

$$s_L^* = \frac{(24D_A + c'^{AA}\bar{f}^A)\nu_b^B \bar{f}^B + (24D_B + c'^{BB}\bar{f}^B)\nu_b^A \bar{f}^A}{\nu_b^B \bar{f}^B c'^{AB}\bar{f}^A + \nu_b^A \bar{f}^A c'^{BA}\bar{f}^B}$$

with $\bar{f}^A$ and $\bar{f}^B$ constant steady states and $c'^{ST} = \frac{2\pi\kappa^{ST}\nu_c^{ST}R^4}{\nu_d^{ST}}$, $S, T \in \{A, B\}$.

The constant steady states are unstables if $\boxed{s > s_L^*}$.

To simplify notation and since $\bar{f}^B = f^* - \bar{f}^A$, we obtain:

$$F(\bar{f}^A) = \frac{\beta(\bar{f}^A)^2 + \alpha\bar{f}^A + \gamma}{\varepsilon(\bar{f}^A)^2 + \delta\bar{f}^A},$$

with parameters:

$$\alpha = 24D_B\nu_b^A - 24D_A\nu_b^B + c'^{AA}\nu_b^B f^* + c'^{BB}\nu_b^A f^*, \quad \beta = -c'^{AA}\nu_b^B - c'^{BB}\nu_b^A,$$

$$\gamma = 24D_A\nu_b^B f^*, \quad \delta = c'^{AB}\nu_b^B f^* + c'^{BA}\nu_b^A f^*, \quad \varepsilon = -\nu_b^B c'^{AB} - \nu_b^A c'^{BA}.$$

Logistic vs. no logistic

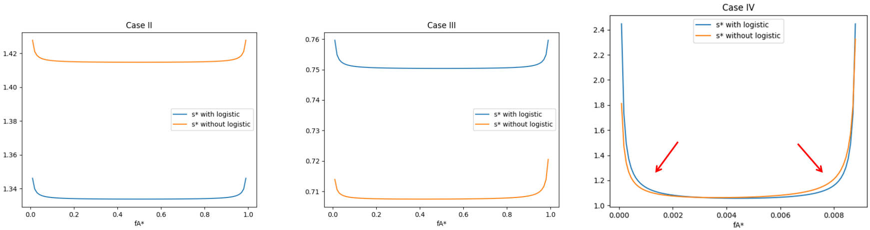
We compare critical values related to instability:

Logistic growth model

$$s_L^* = \frac{(24D_A + c'^{AA})\nu_b^B \bar{f}^B + (24D_B + c'^{BB})\nu_b^A \bar{f}^A}{\nu_b^B \bar{f}^B \tilde{c}'^{AB} + \nu_b^A \bar{f}^A \tilde{c}'^{BA}},$$

No logistic model

$$s_C^* = \sqrt{\frac{576}{\tilde{c}'^{AB}\tilde{c}'^{BA}}\left(D_A + \frac{c'^{AA}}{24}\right)\left(D_B + \frac{c'^{BB}}{24}\right)}$$



Numerical simulations

Numerical simulations

Micro

Macro

blabla

Thank you!