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

proposed by L.Almeida, B.Perthame and D.Peurichard.

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August 22th 2018

Outline

Biological context

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

INTERFACE

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Research

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

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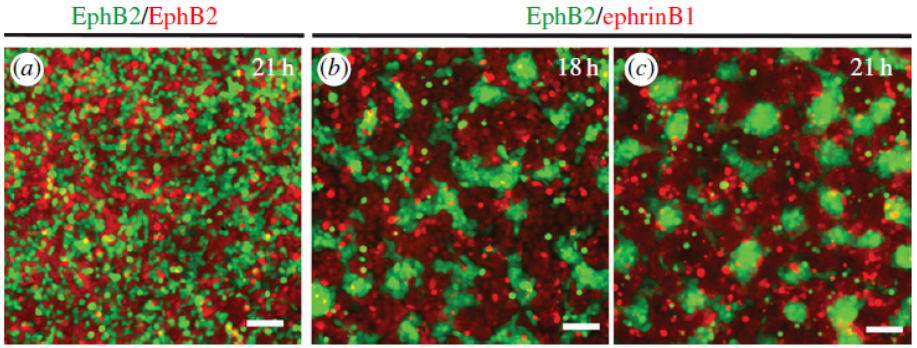
Working hypothesis: inter(heterotypic) and intra(homotypic) species repulsion control cell segregation and border sharpening. They have more influence than inter- or intra-species adhesion.
Goal: to understand the mechanisms of morphogenesis.



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 population size

Microscopic model

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

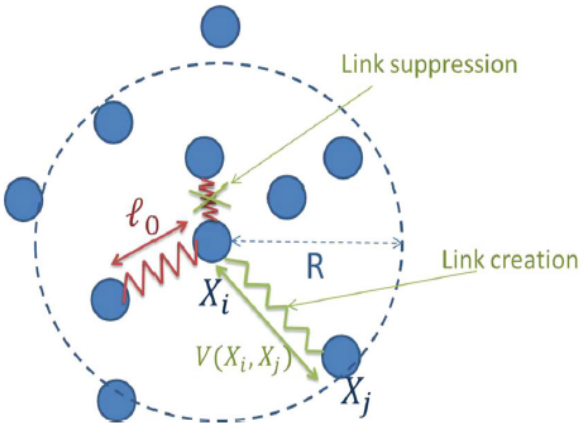
BUT

- Computationally expensive
- Theoretically harder

Microscopic framework

Individual Based Model for particles interacting through repulsion interactions:

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

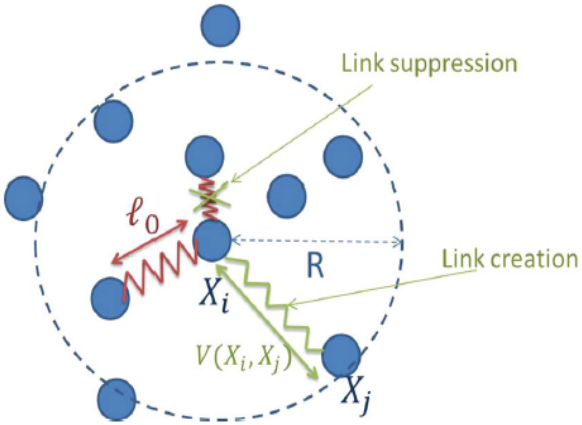


- $\mu > 0$ is the constant mobility coefficient,
- B_i is a 2-dimensional Brownian motion $B_i = (B_i^1, B_i^2)$ of intensity $D_A, D_B > 0$ respectively for species A and B,
- W^S total energy of the S-type particle, $S \in \{A, B\}$, defined as:

$$W^S(X^S, X^T) = \underbrace{\sum_{k_1=1}^{K_{SS}} \Phi^{SS}(X^S_{i(k_1)} - X^S_{j(k_1)}) + \sum_{k_3=1}^{K_{ST}} \Phi^{ST}(X^S_{i(k_3)} - X^T_{\ell(k_3)})}_{\text{sum over all pairwise link potentials acting on particles } S},$$

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^*.

From Micro to Macro

- Proof of convergence in the case **without logistic growth** in J. Barré, J.A. Carrillo, P. Degond, D.Peurichard, E. Zatorska. *A two-species macroscopic model for cell segregation and border sharpening by Eph receptor ephrin-mediated repulsion; 2018, in preparation.*
- Proof of convergence to a logistic model in a simple case with birth and death of Brownian bugs in D.A.Birch, W.R. Young. *A master equation for a spatial population model with pair interactions; 2006, Theoretical Pop Bio.*

- Our goal is to merge these 2 methods in order to perform the convergence.

From Micro → Macro

The derivation of a macroscopic model from the microscopic model requires two limits:

1. limit of large number of individuals N_S and large number of links K_{ST}, $S \in \{A, B\}$,
2. limit of large scale or fast network remodelling limit.

Microscopic Model

$\{(X_i^A, X_i^B)\}$
Position of cells

$$\xrightarrow[\text{rescaling}]{N_S, K_{ST} \to \infty}$$

Macroscopic Model

$\{(f^A, f^B)\}$
Cell distribution

From Micro → Macro: sketch

What is challenging? The varying size of the cell population

- Fock Space:
  Probability space of all the possible states of the particle system $(X_k)_k$

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

  The density or concentration of cells can then be writen as:

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

From Micro → Macro: sketch

- Master equation

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

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

  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

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

From Micro $\rightarrow$ Macro: Master Equation

Using a Kramers-Moyal expansion and 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 kinetic model by summing and integrating the master equation.

- To obtain the macroscopic model we perform rescaling of the equations:

$$\tilde{x} = \sqrt{\varepsilon} x, \quad \tilde{t} = \varepsilon t$$

Taking $\varepsilon \rightarrow 0$ allow us to derive the macroscopic model.

Macroscopic framework

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

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

- 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:

$$\begin{cases} \partial_t f^A = \nabla \cdot (f^A \nabla_x (\Phi^{AA} * f^A) + f^A \nabla_x (\Phi^{AB} * f^B)) + D_A \Delta_x f^A + \nu_b^A f^A \left(1 - \frac{f^A + f^B}{f^*}\right) \\ \partial_t f^B = \nabla \cdot (f^B \nabla_x (\Phi^{BB} * f^B) + f^B \nabla_x (\Phi^{BA} * f^A)) + D_A \Delta_x f^A + \nu_b^B f^B \left(1 - \frac{f^A + f^B}{f^*}\right) \end{cases} \tag{3}$$

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 unstable if $s > s_L^*$.

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

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

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

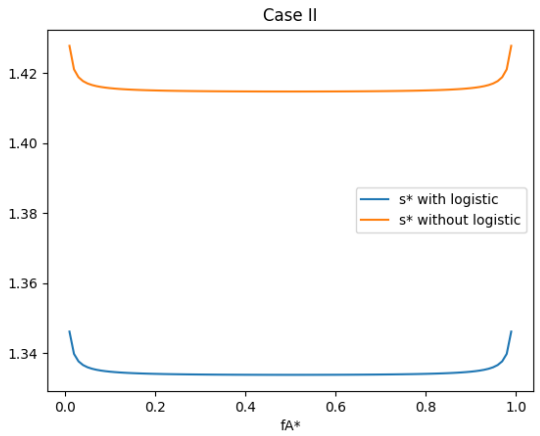
We compare critical values related to instability (aggregates):

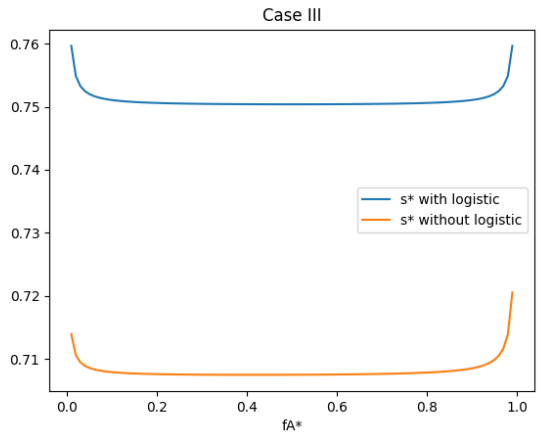
Logistic growth model

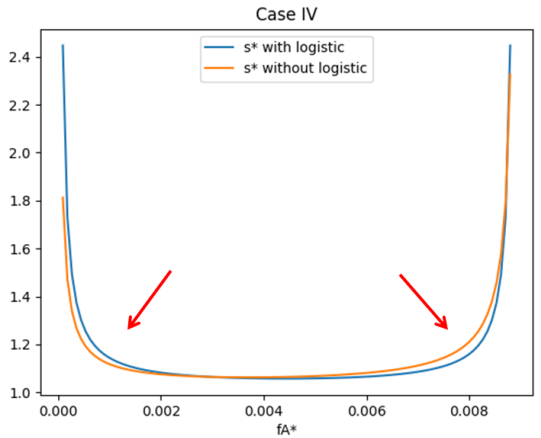
$$s_L^* = \frac{(24D_A + c'^{AA})\nu_b^B \bar{f}^B + (24D_B + c'^{BB})\nu_b^A \bar{f}^A}{\nu_b^B \bar{f}^B \tilde{c}'^{AB} + \nu_b^A \bar{f}^A \tilde{c}'^{BA}},$$

No logistic model (by literature)

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







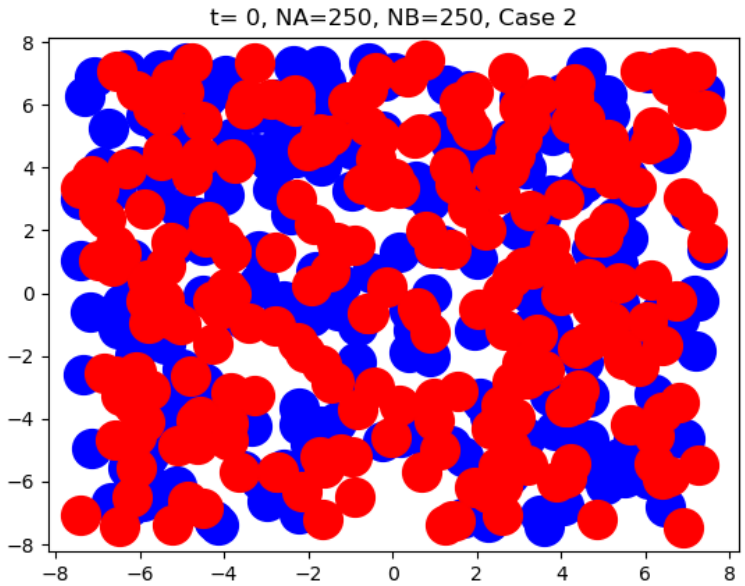
→ Depending on the parameters, logistic growth can either support or repress aggregation

Numerical simulations

CELL A: blue, CELL B: red
Case III: κ^{AA}, $\kappa^{BB} = 2$, $\kappa^{AB} = s$, $\kappa^{BA} = 2s$.

Repulsion A $\rightarrow$ B $>$ Repulsion B $\rightarrow$ A

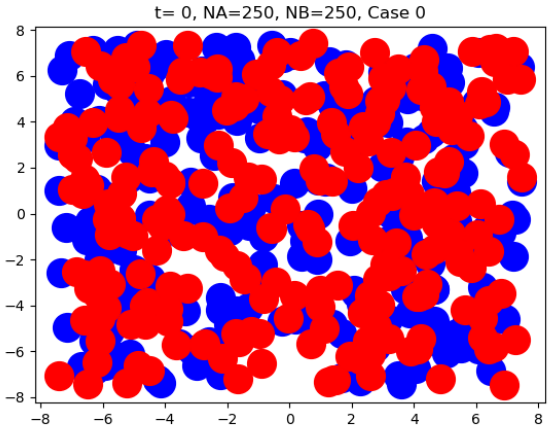
Test	ν_b^A	ν_b^B	s_L^*	s
I	10^{-5}	10^{-4}	1.9	1.7
IIIa	10^{-4}	10^{-4}	1.39	1.43
IIIb	10^{-4}	10^{-4}	1.39	1
IIIc	10^{-4}	10^{-4}	1.39	2
V	10^{-4}	10^{-5}	1.09	1.3

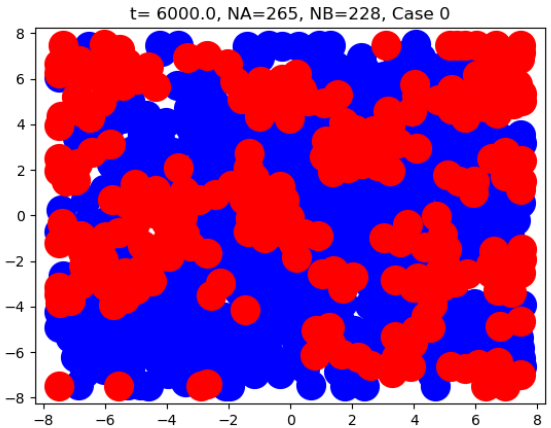


Test I: $s_L^* < s < s_C^*$

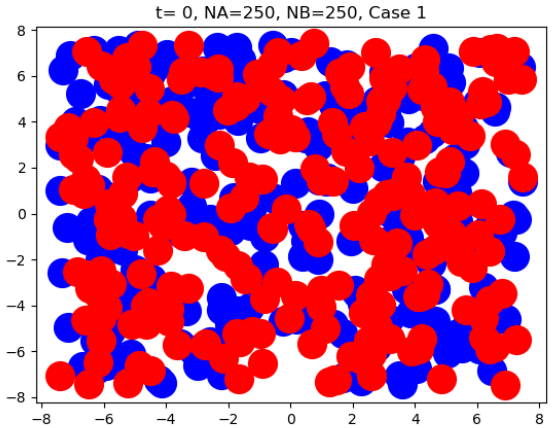
Repulsion A $\rightarrow$ B $>$ Repulsion B $\rightarrow$ A

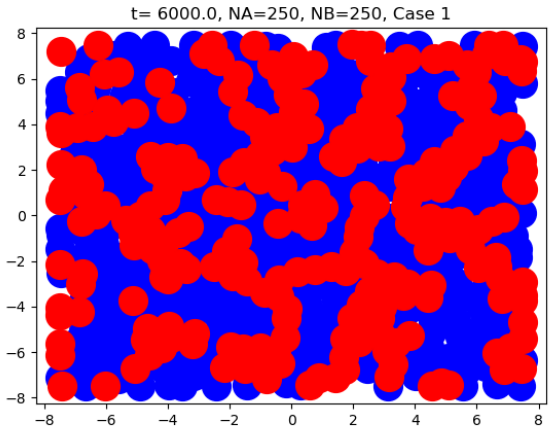
Logistic





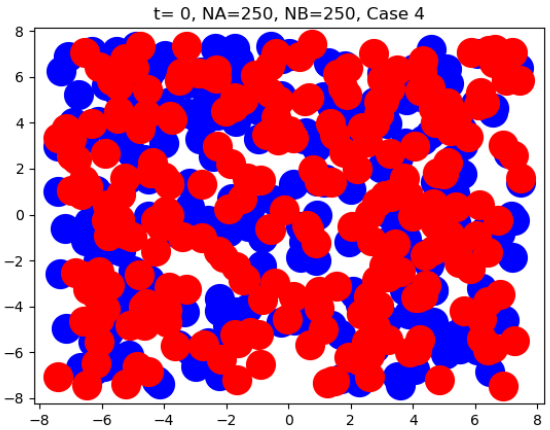
NO logistic

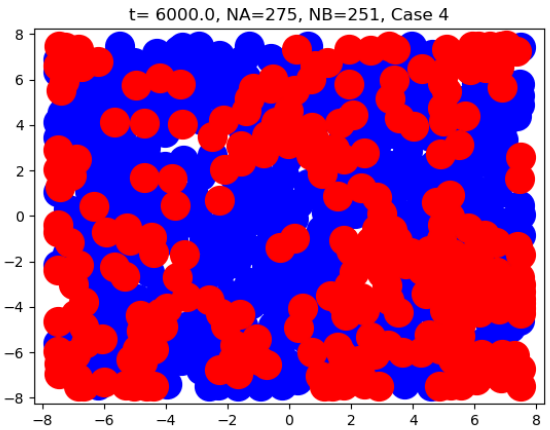




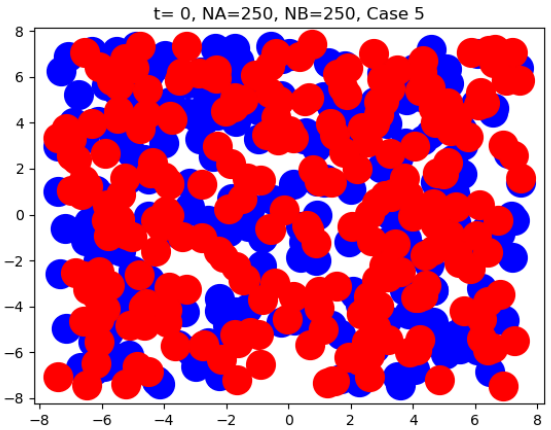
Test IIIa: $s_L^* < s < s_C^*$

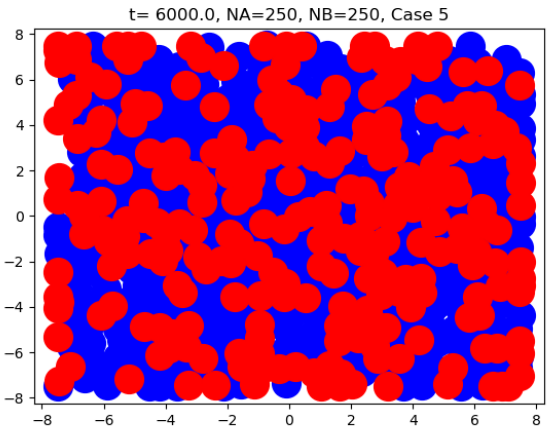
Logistic





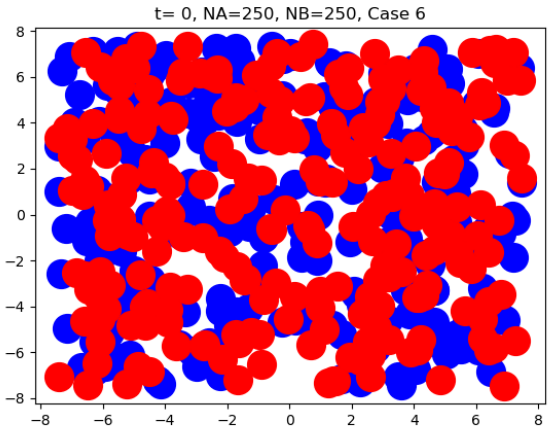
NO logistic

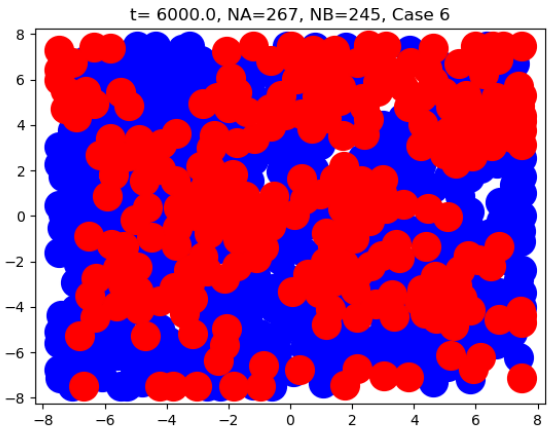




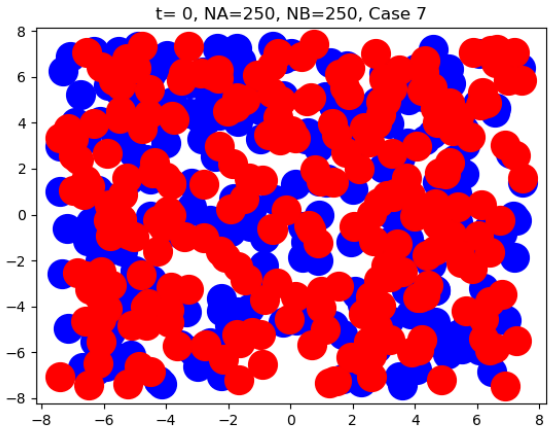
Test IIIb: $s < s_L^* < s_C^*$

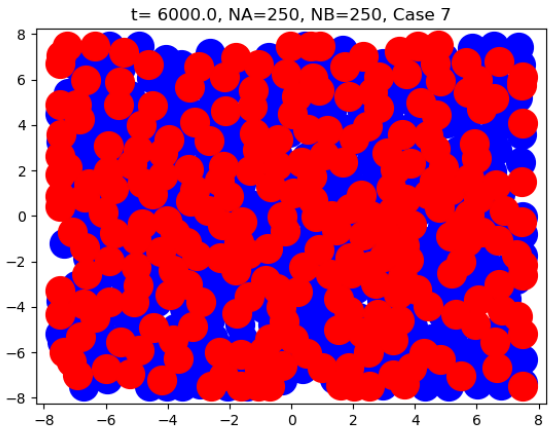
Logistic





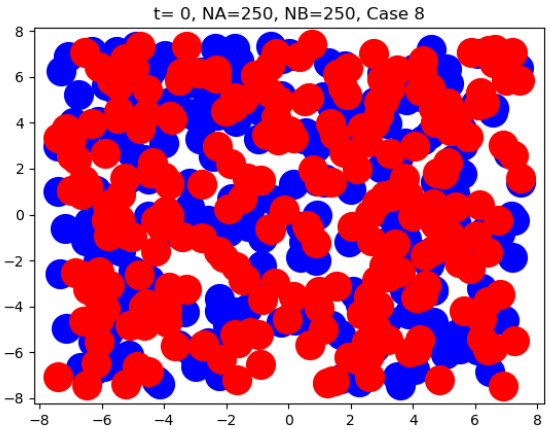
NO logistic

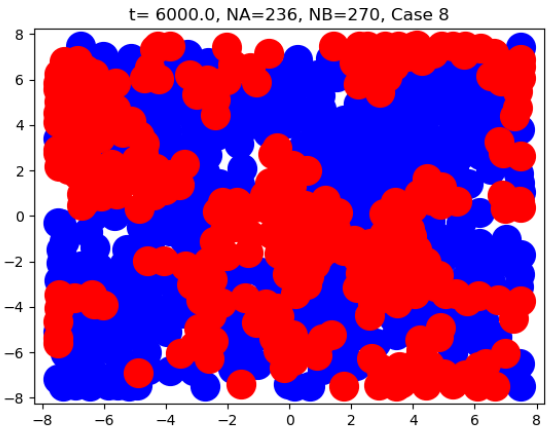




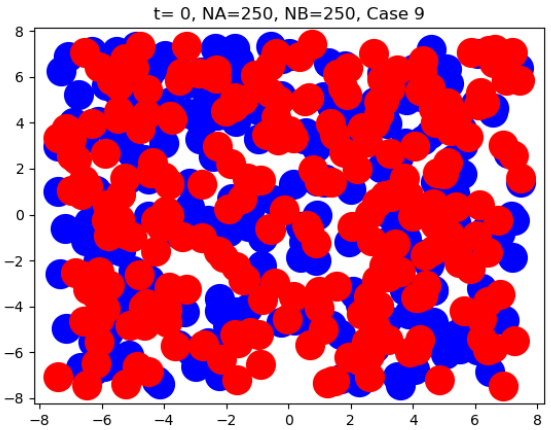
Test IIIc: $s_L^* < s_C^* < s$

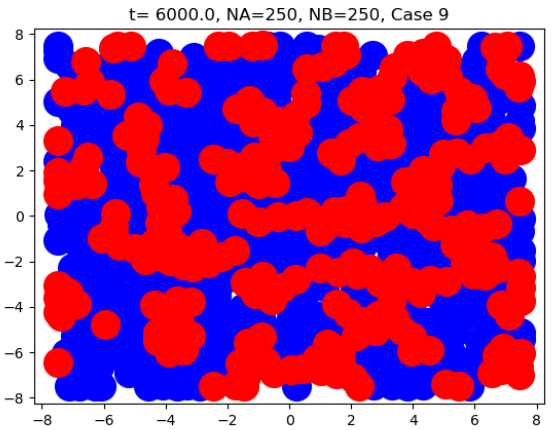
Logistic





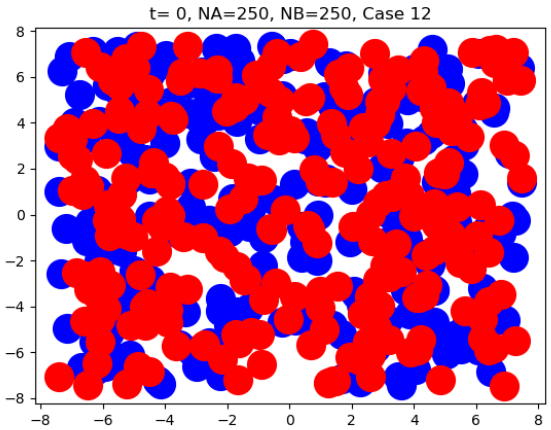
NO logistic

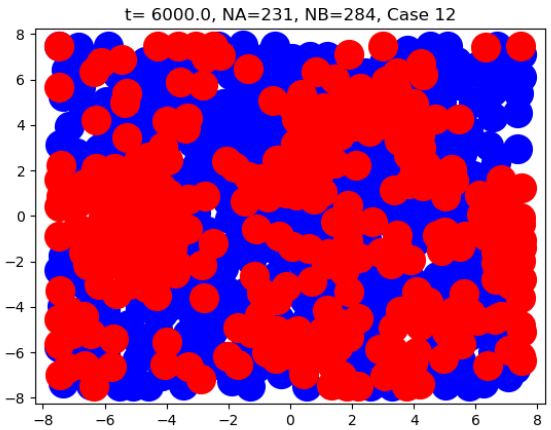




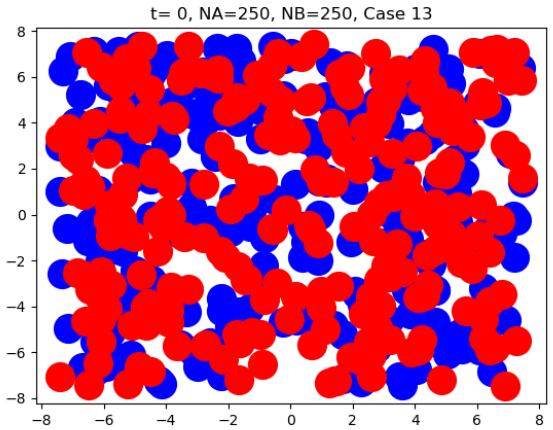
Test V: $s_L^* < s < s_C^*$

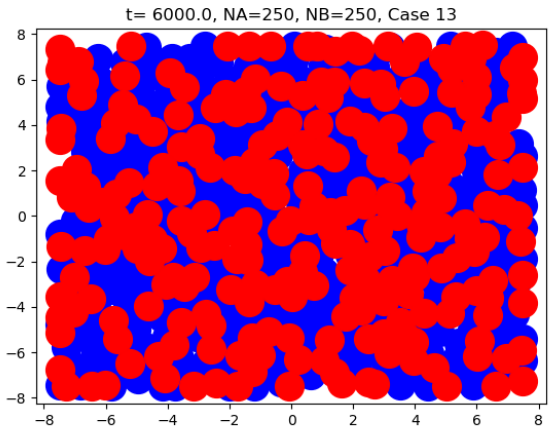
Logistic





NO logistic





Conclusions and Perspectives:

- We present a **two-species models** of cell segregation,
- we take into account microscopic and macroscopic approach,
- we focus on the influence that homotypic/heterotypic **repulsion** has on this process,
- we add **logistic growth** term in a model proposed in the literature,
- we study the logistic growth effects on the **stability** of steady states,
- we perform **numerical simulations** on the individual agent-based model to confirm the results provided by stability analysis

Work in progress...

- Numerical simulations of the macroscopic model
- **Rigorous derivation** of macroscopic model
- To understand differences between macro- micro- simulation results and stability analysis.

Thank you for your attention! Merci! Grazie! Akpé!