CEMRACS 2018: Mathematical modeling of cell aggregation and segregation

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Introduction

The starting point of this work was the model previously proposed in **Citation**. They provided a detailed multiscale analysis – from a microscopic model to a macroscopic description, and its qualitative analysis – of a system of particles interacting through a dynamical network. Indeed, their model describes point particles with local cross-links modeled by springs that are randomly created and destructed. The deduced in the mean field limit, assuming large number of particles and links that in the regime where the network evolution triggered by the linking/unlinking processes happens on a very short timescale, the link density distribution becomes a local function of the particle distribution density. The latter evolving on the slow time scale through an aggregation-diffusion equation, known also as the McKean-Vlasov equation. Their results have been extended and applied to the case of cell aggregation and segregation in [citation]. The aim of their work was to describe and explain the origin of cell aggregation and segregation during tissues morphogenesis. The ability of different cell types to segregate and aggregate is known to be a key process in many biological phenomenons as tissue differentiation especially in embryogenesis or tumor cells metastasis. However, In their model, it was assumed that the cell population remain constant over the time, which means that their no growth process. In this study, we want investigated the effect of cell division on the aggregation and segregation process. Therefore, we derive (as rigorously as possible) in a first time a macroscopic logistic equation from the microscopic models of two species of cell population introduced in [citation] by adding a local density-saturated growth process at the microscopic scale. The main difficulty of this first step is the varying number of the cells population due to the growth process. After the derivation of the macroscopic model, we perform stability analysis on the model and numerical simulations of the microscopic and the macroscopic model.

1 Mathematical model

In this section, we begin by describing the microscopic model introduced in [citation] for a cell population belonging to the same species. Then, after adding a mechanism of cell division to this microscopic model, we will study its convergence towards a macroscopic model. Finally, we will apply the same process to the case of two species of cells.

1.1 The one species logistic model: microscopic and macroscopic

1.1.1 from microscopic to macroscopic without growth

Introduction to the microscopic model   In this section we introduce the model presented in [citation]. The model describes the interactions between spherical particles of a system of N particles in which each particle is identified by their position X_i . The particles which are located at the positions X_i and X_j can be linked through a Poisson process with probability ν_f^N if their distance is less than a given radius of interaction R. And the created links can be destroyed with a probability ν_d^N. The probabilities ν_f^N and ν_d^N depends on the number particles in the whole system (N). the interactions between the particles are subject to a pairwise potential:

$$V(X_i, X_j) = U(|X_i - X_j|) \tag{1}$$

Therefore, between two linking or unlinking events, the equation of motion for each particle is:

$$dX_i = -\mu \nabla_{X_i} W dt + \sqrt{2D} dB_i, \quad i = 1, \ldots, N. \tag{2}$$

where, W denotes the energy related the potential of interaction V exerted by linked neighboring particles,

$$W = \sum_{k=1}^{K} V(X_{i(k)}, X_j(k)),$$

with $i(k), j(k)$ indexing particles connected by a link k. μ is a positive mobility coefficient and the positive coefficient D is the diffusion coefficient related to a 2-dimensional Brownian motion $B_i = (B_i^1, B_i^2)$.

Derivation of the macroscopic model The macroscopic model is derived in two steps, first, the limit of large number of individuals and links leading to the derivation of a kinetic model describing the evolution of the particles and the links density distributions (when the ratio between the number of links and the number of particles is finite at the limit), respectively:

$$f_N(x, t) = \frac{1}{N} \sum_{i=1}^{N} \delta_{X_i}(x);$$

and

$$g_K(x_1, x_2, t) = \frac{1}{2K} \sum_{k=1}^{K} \delta_{X_i(k), X_j(k)}(x_1, x_2) + \delta_{X_j(k), X_i(k)}(x_1, x_2);$$

where the symbol $\delta_{X_i}(x)$ is the Dirac delta centred at $X_i(t)$. And second, a large scale or fast network remodelling limit, denoted $\varepsilon \to 0$.

Theorem 1.1. *(J. Barré et al. [citation]) the kinetic system resulting from the large number of individuals and links limit as $N, K \to \infty$ provided that*

$$\lim_{K, N \to \infty} \frac{K}{N} = \xi > 0$$

is:

$$\begin{aligned}
&\partial_t f(x, t) = D \Delta_x f(x, t) + 2\mu \xi \nabla_x \cdot F(x, t), \\
&\partial_t g(x_1, x_2, t) = D(\Delta_{x_1} g(x_1, x_2, t) + \Delta_{x_2} g(x_1, x_2, t)) \\
&+ 2\mu \xi \left(\nabla_{x_1} \cdot \left(\frac{g(x_1, x_2, t)}{f(x_1)} F(x_1, t) \right) + \nabla_{x_2} \cdot \left(\frac{g(x_1, x_2, t)}{f(x_2)} F(x_2, t) \right) \right) \\
&+ \frac{\nu_f}{2\xi} h(x_1, x_2, t) \chi_{|x_1 - x_2| \leq R} - \nu_d g(x_1, x_2, t),
\end{aligned} \tag{3}$$

where

$$F(x, t) = \int g(x_1, x_2, t) \nabla_{x_1} V(x, y) dy,$$

$$h^N(x_1, x_2, t) = \frac{1}{N(N-1)} \sum_{i \neq j} \delta_{X_i(t), X_j(t)}(x_1, x_2), \text{ the number of pair of particles}$$

and

$$f(x, t) = \lim_{N \to \infty} f^N(x, t), \quad g(x_1, x_2, t) = \lim_{K \to \infty} g^K(x_1, x_2, t), \quad h(x_1, x_2, t) = \lim_{K \to \infty} h^N(x_1, x_2, t),$$

$$\nu_f = \lim_{N \to \infty} \nu_f^N(N-1), \quad \nu_d = \lim_{N \to \infty} \nu_d^N.$$

and in the large scale limit, we have the following proposition:

Proposition 1.1. *(J. Barré et al. [citation]) Assuming that time and space are defined such that $\mu = 1$ and $D = 1$ and assuming that the scaled particle pairs distribution $h_\varepsilon(x_1, x_2) = f_\varepsilon(x_1) f_\varepsilon(x_2)$, with $\varepsilon << 1$ the macroscopic scaling parameter, and that $V(X_i, X_j) = U(|X_i - X_j|)$, then provided the following limits exist*

$$f := \lim_{\varepsilon \to 0} f_\varepsilon, g := \lim_{\varepsilon \to 0} g_\varepsilon$$

they formally satisfy

$$\partial_t f(x,t) = \Delta_x f(x,t) + \frac{\nu_f}{\nu_d}\nabla_x \cdot (f(t,x)\nabla_x \cdot (V \star f)(t,x)),$$
$$g(x,y,t) = \frac{\nu_f}{2\xi\nu_d}f(x,t)f(y,t)\chi_{|x-y| \leq R}, \tag{4}$$

form some compactly supported potential $\tilde{V}$ such that :

$$\nabla_i \tilde{V}(x) = U'(|x|)\chi_{|x| \leq R}\vec{e_i}, \quad i = 1,2$$

We refer to [citation] for the details of the proofs.

1.1.2 From microscopic to macroscopic with spatial logistic growth

In this section, we add a growth process to the microscopic model. thus, we assume that each individual can give birth to a new one with a probability β or die, with a probability α. To introduce the spatial logistic effect at the microscopic scale, we assume that the birth and death processes depend on the local density of individuals. Therefore,

$$\beta(X_i) = b_0 - (b_0 - \theta)\left(\frac{\mathcal{N}_{R_0}(X_i)}{N^*}\right) \tag{5}$$

$$\alpha(X_i) = d_0 + (\theta - d_0)\left(\frac{\mathcal{N}_{R_0}(X_i)}{N^*}\right) \tag{6}$$

where b_0 and d_0 are respectively the intrinsic birth rate and death rate of an individual, $\mathcal{N}_{R_0}(X_i)$ is the number of particles in a radius R_0 around the particle X_i, N^* is the carrying capacity of the ball of radius R_0 and the parameter θ is the turnover, which is equal to birth and death probabilities when the population reaches its local population carrying capacity (N^*), it must be taken in the range $d_0 < \theta < b_0$. we should bear in mind that, the probability of giving birth or dying within a small of time step τ is respectively:

$$\tau\beta(X_i) \text{ or } \tau\alpha(X_i) \tag{7}$$

Derivation of the macroscopic model The main difficulty in the derivation of the macroscopic model is the fact that the number of individuals varies due to the growth process. Therefore to deal with this problem, we will introduce a tool for studying stochastically evolving populations. In this paragraph, we will follow slightly the formulation used in [citation]

Fock space and population dynamics

- At a time t, we identify the population by the number of cells, k, and a vector, X_k, which contains the positions of all the k cells:

$$X_k := [x_1, x_2, \ldots, x_k] \tag{8}$$

- The Fock space is a probability space describing all the possible states of the particle system. It has a measure of probability which we will denote by $\mathbb{P}_k(X_k, t)$. This probability distribution is defined such that, $\mathbb{P}_k(X_k, t)dX_k$ is the probability of having k individuals at time t with each particle in a volume dx_i, $i = 1, \ldots, k$

- Normalization condition:

$$\sum_{k=0}^{\infty}\int \mathbb{P}_k(X_k, t)dX_k = 1. \tag{9}$$

- Permutation symmetry property: for all permutation $\sigma \in \{1, \ldots, k\}$

$$\mathbb{P}_k(x_1, \ldots, x_k, t) = \mathbb{P}_k(x_{\sigma(1)}, \ldots, x_{\sigma(k)}, t) \tag{10}$$

- Expectation in the Fock space: A function C_k defined on the Fock space is a collection :

$$\{C_k(X_k)\}_{k=0,\ldots,\infty}$$

and,

$$\langle C \rangle = \sum_{k=0}^{\infty}\int C_k(X_k)\mathbb{P}_k(X_k, t)dX_k \tag{11}$$

3

Reduced distribution functions The number cells in a volume $\mathcal{V}$ in system of k particles is by definition:

$$C_k = \sum_{p=1}^{k} \chi_{\mathcal{V}}(x_p)$$

let us denote by N this quantity. Using (11), we get:

$$\langle N \rangle = \sum_{k=0}^{\infty} \int \sum_{p=1}^{k} \chi_{\mathcal{V}}(x_p) \mathbb{P}_k(X_k, t) dX_k \tag{12}$$

Using the permutation symmetry property (10), we get:

$$\langle N \rangle = \sum_{k=1}^{\infty} k \int \chi_{\mathcal{V}}(x_1) \mathbb{P}_k(X_k, t) dX_k, \tag{13}$$

$$= \int \chi(x_1) f^{(1)}(x_1, t) dx_1. \tag{14}$$

where

$$f^{(1)}(x, t) = \sum_{k=1}^{\infty} k \int \mathbb{P}_k(x, X_{k-1}, t) dX_{k-1}, \tag{15}$$

is the concentration or **density of cells**,

$$f^{(1)}(x, t) = \langle \sum_{p=1} k \delta(x - x_p) \rangle. \tag{16}$$

We can also deduce the **density of pairs of (different) individuals**, $f^{(2)}(x, y, t)$ by computing $\langle N^2 - N \rangle$, where N^2 is defined by:

$$N^2 = \sum_{p=1}^{k} \sum_{q=1}^{k} \chi(x_p) \chi(x_q)$$

we get:

$$\langle N^2 - N \rangle = \int \int f^{(2)}(x, y, t) \chi(x) \chi(y) dx dy, \tag{17}$$

where:

$$f^{(2)}(x, y, t) = \sum_{k=2}^{\infty} k(k-1) \int \mathbb{P}_k(x, y, X_{k-2}, t) dX_{k-2} \tag{18}$$

we can also write on the form:

$$f^{(2)}(x, y, t) = \langle \sum_{\substack{p,q=1 \\ p \neq q}}^{k} \delta(x - x_p) \delta(y - x_q) \rangle. \tag{19}$$

Finally we can deduce a general expression of those distributions:

$$f^{(s)}(X_s, t) = \sum_{k=s}^{\infty} \frac{k!}{(k-s)!} \int \mathbb{P}_k(X_s, X_{k-s}, t) dX_{k-s}. \tag{20}$$

A master equation for the probability evolution To construct a master equation for the evolution of the (unreduced) probability density $\mathbb{P}_k(X_k, t)$, we shall model the evolution of the particles as a one step Markov process. we denote by $\mathbb{W}_k(X_k, t+\tau | X_k', t)$, the transition probability from a state X_k' with k particles to another state with X_k particles due to the particles motion. Therefore the master equation can be constructed as follow:

$$\mathbb{P}_k(X_k, t+\tau) = \int \mathbb{W}_k(X_k, t+\tau | X_k', t) \mathbb{P}_k(X_k', t) dX_k'$$

$$+ \tau \sum_{i=1}^{k-1} \beta(X_i) \mathbb{B} \mathbb{P}_{k-1} - \tau \left[\sum_{i=1}^{k} (\beta(X_i) + \alpha(X_i)) \right] \mathbb{P}_k(X_k, t) \tag{21}$$

$$+ \tau \int \sum_{k=1}^{k+1} \beta(X_i) \mathbb{P}_{k+1}(X_{k+1}, t) dx_i$$

Where the first term of the right hand side is,

$$A = \int \mathbb{W}_k(X_k, t + \tau | X_k', t) \mathbb{P}_k(X_k', t) dX_k'$$

is the probability of being in state X_k at time $t + \tau$, expressed in term of the transition probability $\mathbb{W}_k$ and the marginal probability $\mathbb{P}_k$, the second term:

$$B = \tau \sum_{i=1}^{k-1} \beta(X_i) \mathbb{BP}_{k-1},$$

is the production of individuals due to birth in a configuration with $k - 1$ cells. The term $\mathbb{BP}_{k-1}$ is an operator, describing the birth, it has been called "The Birth Operator" in [Citation]. It is expressed as follows:

$$Bo\mathbb{P}_{k-1} = \frac{2}{k(k-1)} \sum \sum_{1 \leq p < q \leq k} \delta_{pq} \mathbb{P}_{k-1}(X_{k|p}, t) \tag{22}$$

where $X_{k|p}$ is the collection X_k with x_p deleted. the normalization factor $\frac{2}{k(k-1)}$ ensures that

$$\int Bo\mathbb{P}_{k-1} dX_k = \int \mathbb{P}_{k-1} dX_{k-1} \tag{23}$$

so that the probability is conserved. The third term:

$$C = \tau \left[\sum_{i=1}^{k} (\beta(X_i) + \alpha(X_i)) \right] \mathbb{P}_k(X_k, t)$$

is the probability of losing an individual in a configuration of k individuals due to birth and death processes. And the final term:

$$D = \tau \int \sum_{k=1}^{k+1} \beta(X_i) \mathbb{P}_{k+1}(X_{k+1}, t) dx_i$$

is the probability of death in a configuration of $k + 1$ individuals passing the system to a configuration with k individuals.

The transition probability $\mathbb{W}_k(X_k, t + \tau | X_k', t)$ We can rewrite $\mathbb{W}_k$ on the form:

$$\mathbb{W}_k(X_k, t + \tau | X_k', t) = \int \delta(Y_k - X_k) \mathbb{W}_k(Y_k, t + \tau | X_k', t) dY_k \tag{24}$$

A Taylor series expansion at $Y_k = X_k$ of the δ function (we refer to R.Estrada et al. 1993) has the form:

$$\delta(Y_k - X_k) = \delta(X_k' - X_k + Y_k - X_k')$$
$$= \sum_{n_1=0}^{\infty} \cdots \sum_{n_k=0}^{\infty} \frac{\prod_{p=1}^{k}(y_p - x_p')^{n_p}}{\prod_{p=1}^{k} n_p!} \left(\frac{\partial^{\sum_{p=1}^{k} n_p}}{\partial x_1'^{n_1} \dots \partial x_k'^{n_k}} \delta(X_k' - X_k) \right)$$
$$= \sum_{n_1=0}^{\infty} \cdots \sum_{n_k=0}^{\infty} \left(\frac{(-\partial)^{\sum_{p=1}^{k} n_p}}{\partial x_1^{n_1} \dots \partial x_k^{n_k}} \frac{\prod_{p=1}^{k}(y_p - x_p')^{n_p}}{\prod_{p=1}^{k} n_p!} \delta(X_k' - X_k) \right)$$

on the last line, we use the fact that $\frac{\partial}{\partial x_p} \delta(X_k' - X_k) = -\frac{\partial}{\partial x_p} \delta(X_k' - X_k)$. Finally, we obtain:

$$\delta(Y_k - X_k) = \left[1 + \sum_{n_1=1}^{\infty} \cdots \sum_{n_k=1}^{\infty} \frac{(-\partial)^{\sum_{p=1}^{k} n_p}}{\partial x_1^{n_1} \dots \partial x_k^{n_k}} \frac{\prod_{p=1}^{k}(y_p - x_p')^{n_p}}{\prod_{p=1}^{k} n_p!} \right] \delta(X_k' - X_k) \tag{25}$$

In conclusion, by inserting (25) into (24) the transition probability is expressed as follows:

$$\mathbb{W}_k(X_k, t + \tau | X_k', t) = \left[1 + \sum_{|\alpha|>0} (-1)^{|\alpha|} \partial^\alpha \int \frac{1}{\alpha!} (Y_k - X_k')^\alpha \mathbb{W}_k(Y_k, t + \tau | X_k', t) dY_k \right] \delta(X_k' - X_k). \tag{26}$$

Where α is the multi-index; $(n_1, \ldots, n_k)$ with $|alpha| = \sum_{p=1}^{k} n_p$. Assuming that $|\alpha|$th order moment $\mathcal{M}^{|\alpha|}$ exist, we can rewrite (26) on the form:

$$\mathbb{W}_k(X_k, t + \tau | X_k', t) = \left[1 + \sum_{|\alpha|>0} (-1)^{|\alpha|} \frac{1}{\alpha!} \partial^\alpha \mathcal{M}^{|\alpha|}(X_k, t, \tau) \right] \delta(X_k' - X_k). \quad (27)$$

Where :

$$\mathcal{M}^{|\alpha|}(X_k, t, \tau) = \int (Y_k - X_k')^\alpha \mathbb{W}_k(Y_k, t + \tau | X_k', t) dY_k. \quad (28)$$

Indeed those moments can be expressed on the form:

$$\mathcal{M}^{|\alpha|}(X_k, t, \tau) = \langle [\xi(t + \tau) - \xi(t)]^\alpha \rangle |_{\xi(t) = X_k'}. \quad (29)$$

Expanding the moments for small τ

$$\frac{\mathcal{M}^{|\alpha|}(X_k, t, \tau)}{\alpha!} = D^{|\alpha|}(X_k, t)\tau + O(\tau^2), \quad (30)$$

where the coefficients $D^{(\alpha)}$ are the so-called Kramers-Moyal expansion coefficients with:

$$D^{|\alpha|}(X_k, t) = \frac{1}{\alpha!} \lim_{\tau \to 0} \frac{1}{\tau} \langle (\xi(t + \tau) - X_k)^\alpha \rangle |_{\xi(t) = X_k}. \quad (31)$$

the resulting Master Equation By inserting (30) and (27) into the term A, we obtain:

$$A = \left[1 + \sum_{|\alpha|>0} (-1)^{|\alpha|} \partial^\alpha \left(D^{|\alpha|}(X_k, t)\tau + O(\tau^2) \right) \right] \mathbb{P}_k(X_k, t). \quad (32)$$

The Master Equation now takes the form:

$$
\begin{aligned}
\mathbb{P}_k(X_k, t + \tau) &= \left[1 + \sum_{|\alpha|>0} (-1)^{|\alpha|} \partial^\alpha \left(D^{|\alpha|}(X_k, t)\tau + O(\tau^2) \right) \right] \mathbb{P}_k(X_k, t) \\
&+ \tau \sum_{i=1}^{k-1} \beta(X_i) \mathbb{B} \mathbb{P}_{k-1} - \tau \left[\sum_{i=1}^{k} (\beta(X_i) + \alpha(X_i)) \right] \mathbb{P}_k(X_k, t) \\
&+ \tau \int \sum_{k=1}^{k+1} \beta(X_i) \mathbb{P}_{k+1}(X_{k+1}, t) dx_i
\end{aligned}
\quad (33)
$$

The reduced equation on $f^{(1)}(x, t)$ Using the definition (15), We can deduce the reduced equation on $f^{(1)}(x, t)$ by summing and integrating the master equation

1.2 The two species microscopic model

For the microscopic model, we start from the model presented in **citation**, using the same dynamics for each individuals.

$$
\begin{cases}
dX_i^A = -\mu \nabla_{X_i^A} W^A(X^A, X^B) dt + \sqrt{2D_A} dB_i, & \forall i \in \{1, \ldots, N_A\} \\
dX_i^B = -\mu \nabla_{X_\ell^A} W^B(X^A, X^B) dt + \sqrt{2D_B} dB_\ell, & \forall \ell \in \{1, \ldots, N_B\}
\end{cases}
\quad (34)
$$

The main change on the model is to introduce a cell birth and death process. We base the modelisation of the birth and death process on the one proposed in **citation**. The idea is that at each time step, a cell of population S has a probability β_S to divide into two cells and a probability δ_S to die. The probability depend on the size of the population. Here we add also a spatial dependencie for the probability rate:

$$\beta_S(X_i^S) = b_0^S - (b_0^S - \theta_S) \left(\frac{\mathcal{N}_{R_0}(X_i^S)}{N^*} \right), \qquad \delta_S(X_i^S) = d_0^S + (\theta_S - d_0^S) \left(\frac{\mathcal{N}_{R_0}(X_i^S)}{N^*} \right) \quad (35)$$

where the coefficient $\mathcal{N}_{R_0}(X_i^S)$ is the number of cell (of both population) at distance R_0 of the cell located in X_i^S and N^* is the maximal number of cell in a radius R_0 allowing cell division. The coefficient θ must be taken in the range $d_0^S < \theta < b_0^S$.

6

1.3 Macroscopic model

The Macroscopic model presented in **citation** can be derived from the microscopic model in a large population assumption. Here, we modify this model, simply by adding a logistic term to the equations. We assume for the moment that the obtained model can also be derived from the microscopic one.

$$
\begin{cases}
\partial_t f^A = \nabla \cdot (f^A \nabla_x (\Phi^{AA} * f^A) + f^A \nabla_x (\Phi^{AB} * f^B)) + D_A \Delta_x f^A + \nu^A f^A \left(1 - \frac{f^A + f^B}{f^*}\right) \\
\partial_t f^B = \nabla \cdot (f^B \nabla_x (\Phi^{BB} * f^B) + f^B \nabla_x (\Phi^{BA} * f^A)) + D_A \Delta_x f^A + \nu^A f^A \left(1 - \frac{f^A + f^B}{f^*}\right)
\end{cases}
\tag{36}
$$

where the function Φ correspond to an Hookean interaction potential:

$$
\Phi^{ST}(x) = \frac{\nu_c^{ST}}{\nu_d^{ST}} \frac{\kappa^{ST}}{2}
\begin{cases}
(|x| - R)^2, & \text{for } |x| \le R \\
0, & \text{for } |x| > R
\end{cases}
\tag{37}
$$

The logistic growth involve both cells of population A and B in the same way. The coefficient f^* is the carrying capacity of the environment.

2 From Micro to Macro model

3 Stability analysis

In this section we perform a linear stability analysis of macroscopic model with logistic term. We will linearize around the homogeneous states, i.e. we consider the constant steady states $\bar{f}^A$ and $\bar{f}^B$ which satisfy:

$$
\begin{cases}
\partial_t f^A - \nabla \cdot (f^A \nabla_x (\Phi^{AA} * f^A)) - \nabla \cdot (f^A \nabla_x \Phi^{AB} * f^B) - D_A \Delta_x f^A - \nu^A f^A \left(1 - \frac{f^A + f^B}{f^*}\right) = 0 \\
\partial_t f^B - \nabla \cdot (f^B \nabla_x (\Phi^{BB} * f^B)) - \nabla \cdot (f^B \nabla_x \Phi^{BA} * f^A) - D_A \Delta_x f^A - \nu^B f^B \left(1 - \frac{f^A + f^B}{f^*}\right) = 0
\end{cases}
\tag{38}
$$

Since $\bar{f}^A, \bar{f}^B$ do not depend on time and space, all derivative terms are zero and it leads us to following equations:

$$
\begin{cases}
\nu^A f^A \left(1 - \frac{f^A + f^B}{f^*}\right) = 0 \\
\nu^A f^A \left(1 - \frac{f^A + f^B}{f^*}\right) = 0
\end{cases}
$$

The first equation is satisfied either when $\bar{f}^A = 0$ or $f^A \left(1 - \frac{f^A + f^B}{f^*}\right) = 0$ and the second one is satisfied by $\bar{f}^B = 0$ or $f^B \left(1 - \frac{f^A + f^B}{f^*}\right) = 0$. In this case we obtain the following relation:

$$
\bar{f}^A + \bar{f}^B = f^*
$$

which means that, at the homogeneous states, we have reached the maximum carrying capacity. We perform a stability analysis, using perturbation term and Fourier transform, in order to understand if a possible perturbation can have effects on our model and it corresponds to the appearance of some clusters.
We obtain the following system:

$$
\partial_t \begin{pmatrix} \hat{f}^A \\ \hat{f}^B \end{pmatrix} (y, t) =
\tag{39}
$$

$$
\begin{pmatrix}
-|y|^2 (2\pi \bar{f}^A \hat{\Phi}^{AA}(y) + D_A) - \nu_b^A \frac{\bar{f}^A}{f^*} & -|y|^2 2\pi \bar{f}^A \hat{\Phi}^{AB}(y) - \nu_b^A \frac{\bar{f}^A}{f^*} \\
-|y|^2 \bar{f}^B \hat{\Phi}^{BA}(y) - \nu_b^B \frac{\bar{f}^B}{f^*} & -|y|^2 (2\pi \bar{f}^B \hat{\Phi}^{BB}(y) + D_B) - \nu_b^B \frac{\bar{f}^B}{f^*}
\end{pmatrix}
\begin{pmatrix} \hat{f}^A \\ \hat{f}^B \end{pmatrix} (y, t)
\tag{40}
$$

$$
= M(y) \begin{pmatrix} \hat{f}^A \\ \hat{f}^B \end{pmatrix} (y, t)
\tag{41}
$$

This is a linear ODE system, hence its solution is:

$$\begin{pmatrix} \hat{f}^A \\ \hat{f}^B \end{pmatrix}(y,t) = c_1(y)exp^{\lambda_1(y)t}u_1(y) + c_2(y)exp^{\lambda_2(y)t}u_2(y).$$

where $\lambda_1(y), \lambda_2(y)$ are the eigenvalues of the matrix and $u_1(y), u_2(y)$ the corrisponding eigenvectors. In general case, the constant steady state will be stable only if the eigenvalues of the matrix $M(y)$ are both negative, otherwise it will be unstable if the eigenvalues have different signs. Since we know that $det(M(y)) = \lambda_1 \cdot \lambda_2$ and $tr(M(y)) = \lambda_1 + \lambda_2$, then we can consider different possibilities. The determinant of $M(y)$ is:

$$det(M(y)) = |y|^4 \left[(\bar{f}^A 2\pi\hat{\Phi}^{AA} + D_A)(\bar{f}^B 2\pi\hat{\Phi}^{BB} + D_B) - \bar{f}^A\bar{f}^B 4\pi^2\hat{\Phi}^{AB}\hat{\Phi}^{BA} \right] + \quad (42)$$

$$+|y|^4 \left[\nu_b^B \frac{\bar{f}^B}{f^*}(\bar{f}^A 2\pi\hat{\Phi}^{AA} + D_A - \bar{f}^A 2\pi\hat{\Phi}^{AB}) - \nu_b^A \frac{\bar{f}^A}{f^*}(\bar{f}^B 2\pi\hat{\Phi}^{BB} + D_B - \bar{f}^B 2\pi\hat{\Phi}^{BA}) \right]. \quad (43)$$

We find the critical value of model with logistic term and without it and we compare them. We are interested in instability that implies the appearance of cell aggregates. In the case of model with logistic term we have:

$$s^*_{\nu_b,\nu_d \neq 0} = \frac{(24D_A + c'^{AA})\nu_b^B\bar{f}^B + (24D_B + c'^{BB})\nu_b^A\bar{f}^A}{\nu_b^B\bar{f}^B\tilde{c}'^{AB} + \nu_b^A\bar{f}^A\tilde{c}'^{BA}} \quad (44)$$

with $\bar{f}^A$ and $\bar{f}^B$ constant steady states, not necessarily equal and $c'^{ST} = \frac{2\pi k^{ST}\bar{f}^A\nu_c^{ST}R^4}{\nu_d^{ST}}$, $S,T \in \{A,B\}$. As did in [cit], we introduce a parameter $s \in \mathbb{R}$ to scale the interspecies potential intensities such that $\kappa^{ST} = s\tilde{\kappa}^{ST}$. We define $c'^{AA} = k_1\bar{f}^A, c'^{BB} = k_2\bar{f}^B, c'^{AB} = k_3\bar{f}^A, c'^{BA} = k_4\bar{f}^B$. By $\bar{f}^B = f^* - \bar{f}^A$ we rewrite the following s_L^*:

$$s_L^* = \frac{(24D_A + k_1\bar{f}^A)\nu_b^B(f^* - \bar{f}^A) + (24D_B + k_2(f^* - \bar{f}^A))\nu_b^A\bar{f}^A}{\nu_b^B(f^* - \bar{f}^A)k_3\bar{f}^A + \nu_b^A\bar{f}^A k_4(f^* - \bar{f}^A)} \quad (45)$$

To simplify notation, we take into account the following function depending on $\bar{f}^A$ and its derivative :

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

with parameters

$$\alpha = 24D_B\nu_b^A - 24D_A\nu_b^B + k_1\nu_b^B f^* + k_2\nu_b^A f^*, \quad \beta = -k_1\nu_b^B - k_2\nu_b^A, \quad (46)$$

$$\gamma = 24D_A\nu_b^B f^*, \quad \delta = k_3\nu_b^B f^* + k_4\nu_b^A f^*, \quad \varepsilon = -\nu_b^B k_3 - \nu_b^A k_4. \quad (47)$$

Remark 3.1. The condition $\delta\bar{f}^A + \varepsilon(\bar{f}^A)^2 \neq 0$ ensures the existence of function, in other words we get $\bar{f}^A \neq 0$ or $\bar{f}^A \neq -\frac{\delta}{\varepsilon} = f^*$.

We are looking for the zero points of $\frac{\partial F(\bar{f}^A)}{\partial\bar{f}^A}$, i.e. $\bar{f}^A = \frac{2\varepsilon\gamma \pm \sqrt{\Delta}}{2(\beta\delta - \alpha\varepsilon)}$ with the discriminant $\Delta = 4\varepsilon^2\gamma^2 + 4\gamma\beta\delta^2 - 4\gamma\delta\alpha\varepsilon = 4\varepsilon^2(24D_A\nu_b^B f^*)(24D_B\nu_b^A f^*)$. After computations we can conclude:

$$\bar{f}^A = \frac{f^*(D_A\nu_b^B \pm \sqrt{D_A D_B\nu_b^B\nu_b^A})}{D_A\nu_b^B - \nu_b^A D_B}. \quad (48)$$

If we look at those two values, we can find that:

$$0 < \frac{f^*(D_A\nu_b^B - \sqrt{D_A D_B\nu_b^B\nu_b^A})}{D_A\nu_b^B - \nu_b^A D_B} < f^*. \quad (49)$$

and

$$\left| \frac{f^*(D_A\nu_b^B + \sqrt{D_A D_B\nu_b^B\nu_b^A})}{D_A\nu_b^B - \nu_b^A D_B} \right| > f^*. \quad (50)$$

With regard to model without logistic term, we obtain the following critical value:

$$s_C^* = \left[\frac{576}{\tilde{c}'^{AB}\tilde{c}'^{BA}} \left(D_A + \frac{c'^{AA}}{24} \right) \left(D_B + \frac{c'^{BB}}{24} \right) \right]^{\frac{1}{2}}$$

8

We simplify notation as already done taking:

$$\alpha = 24D_B k_3 - 24D_A k_4 + k_3 k_4 f^*, \quad \beta = k_3 k_4, \quad \gamma = 576 D_A D_B + 24 D_A k_4 f^*, \tag{51}$$

$$\delta = k_1 k_2 f^*, \quad \varepsilon = k_1 k_2. \tag{52}$$

Then, we obtain:

$$s_c^* = F(\bar{f}^A) = \left[\frac{\gamma + \alpha \bar{f}^A - \beta(\bar{f}^A)^2}{\delta \bar{f}^A - \varepsilon(\bar{f}^A)^2}\right]^{\frac{1}{2}}, \quad \frac{\partial F(\bar{f}^A)}{\partial \bar{f}^A} = \frac{1}{2}\frac{(\bar{f}^A)^2(\varepsilon\alpha - \delta\beta) + 2\varepsilon\gamma\bar{f}^A - \delta\gamma}{(\gamma + \alpha\bar{f}^A - \beta(\bar{f}^A)^2)^{1/2}(\delta\bar{f}^A - \varepsilon(\bar{f}^A)^2)^{3/2}}.$$

We want to find the point that minimizes this function, i.e $\frac{\partial F(\bar{f}^A)}{\partial \bar{f}^A} = 0$.

Remark 3.2. Also in this case we find the following relation: $\frac{\delta}{\varepsilon} = f^*$ and we consider $\bar{f}^B = f^* - \bar{f}^A$.

We get: $\bar{f}^A = \frac{-2\varepsilon\gamma \pm \sqrt{\Delta}}{2(\varepsilon\alpha - \delta\beta)} = \frac{-2\varepsilon\gamma \pm \sqrt{\Delta}}{2\varepsilon(\alpha - f^*\beta)}$.
After additional simplifications we can write:

$$\bar{f}^A = \frac{-(24D_A D_B + D_A k_4 f^*) \pm \sqrt{\Delta'}}{D_B k_3 - D_A k_4} \tag{53}$$

with $\Delta' = (24D_A D_B + D_A k_4 f^*)^2 + 24D_A D_B^2 k_3 f^* - 24D_A^2 D_B k_4 f^* + D_A D_B k_3 k_4 (f^*)^2 - D_A^2 k_4^2 (f^*)^2$.
Both critical values s_C^*, s_L^* are markers of instability and we perform some simulations to compare them.

- case $s_C^* < s_L^*$. If $s < s_c^*$ we should observe stability for both model, if $s \in (s_C^*, s_L^*)$ we should observe instability for model and no aggregates for with logistic one. In the case of $s > s_L^*$ we expect instability and cell aggregates for both models.

- case $s_C^* > s_L^*$. We should observe the opposite behavior compared to the prevoius one and instability for logistic model and no aggregates for the other one when $s \in (s_L^*, s_C^*)$.

4 Numerical scheme

4.1 Macroscopic model

The equations for the macroscopic model can be written as:

$$\partial_t f^S = \mathcal{L}(f^S, f^T) + \mathcal{D}(f^S) + \mathcal{R}(f^S, f^T), \quad S \neq T \in \{A, B\} \tag{54}$$

with

$$\mathcal{L}(f^S, f^T) = \nabla \cdot (f^S \nabla_x (\Phi^{SS} * f^S)) + \nabla \cdot (f^S \nabla_x \Phi^{ST} * f^T) \tag{55}$$

$$\mathcal{D}(f^S) = D_S \Delta_x f^S \tag{56}$$

$$\mathcal{R}(f^S, f^T) = \nu^S f^S \left(1 - \frac{f^S + f^T}{f^*}\right) \tag{57}$$

4.1.1 Spatial Discretization

First we focus on the spatial discretization of the equations. A general semi-discrete finite-volume scheme can be written as follows:

$$\frac{df_{j,k}^S}{dt} = \mathcal{L}_{j,k} + \mathcal{D}_{j,k} + \mathcal{R}_{j,k} \tag{58}$$

The discrtization of the terms $\mathcal{D}_{j,k}$ and $\mathcal{R}_{j,k}$ is straightforward and we will present only the details for the link operator $\mathcal{L}_{j,k}$. As in **citation**, we set :

$$\mathcal{L}_{j,k} = -\frac{F_{j+\frac{1}{2},k}^x - F_{j-\frac{1}{2},k}^x}{\Delta x} - \frac{F_{j,k+\frac{1}{2}}^y - F_{j,k-\frac{1}{2}}^y}{\Delta y}, \tag{59}$$

with

$$F_{j+\frac{1}{2},k}^x = u_{j+\frac{1}{2},k}^+ f_{j,k}^E - u_{j+\frac{1}{2},k}^- f_{j+1,k}^W, \quad F_{j,k+\frac{1}{2}}^y = u_{j,k+\frac{1}{2}}^+ f_{j,k}^N - u_{j,k+\frac{1}{2}}^- f_{j,k+1}^S$$

where $u^+ = \max(u, 0)$, $u^- = -\min(u, 0)$ and with

$$u_{j+\frac{1}{2},k} = -\frac{\xi_{j+1,k} - \xi_{j,k}}{\Delta x}, \quad u_{j,k+\frac{1}{2}} = -\frac{\xi_{j,k+1} - \xi_{j,k}}{\Delta y}$$

.

$$\xi_{j,k} = \Delta x \Delta y \sum_{i,\ell} \tilde{\Phi}^{SS}_{j-i,k-\ell} f^S_{i,\ell} + \tilde{\Phi}^{ST}_{j-i,k-\ell} f^T_{i,\ell}$$

with $\Phi^{SS}(x_j - x_i, x_k - x_\ell)$. We compute te convolution term with a FFT method.

4.1.2 Time Discretization

The time discretization of the equations is done with an Euler scheme. The diffusion term is treated implicitly whereas the link term and the logistic term are treated explicitly. This leads to the following scheme:

$$\frac{f^{S,n+1}_{j,k} - f^{S,n}_{j,k}}{\Delta t} = \mathcal{L}^n_{j,k} + \mathcal{D}^{n+1}_{j,k} + \mathcal{R}^n_{j,k} \tag{60}$$

4.2 Microscopic model

We perform numerical simulations on a $2D$ domain as in [cit] $[-L, L] \times [-L, L] = [-7.5, 7.5]^2$ with periodic boundary conditions. We set diffusion constants $D_A = D_B = 10^{-4}$ and investigate different values of inter- and intra- species intensities such as $\kappa^{AA}, \kappa^{BB}, \kappa^{AB} = s\tilde{\kappa}^{AB}, \kappa^{BA} = s\tilde{\kappa}^{BA}$. For each equation of system (**??**) we have the following time discretization:

$$X^{n+1}_i = X^n_i - \mu \nabla_{X_i} W(X^n) \Delta t^n + \sqrt{2D\Delta t^n} \mathcal{N}(0,1) \tag{61}$$

$\mathcal{N}(0,1)$ is the normal distribution with mean 0 and standard deviation 1.
By the addition of logistic growth term in the model, the number of particles N_A, N_B changes at each time step. Daughter cells are supposed to born at distance r from 'parent' cells that divide themselves. In our model we set $r = 0.5$.

$$\beta_A = b^A_0 - (b^A_0 - \theta_A)\left(\frac{N_A + N_B}{N^*}\right), \qquad \delta_A = d^A_0 + (\theta_A - d^A_0)\left(\frac{N_A + N_B}{N^*}\right) \tag{62}$$

5 Results

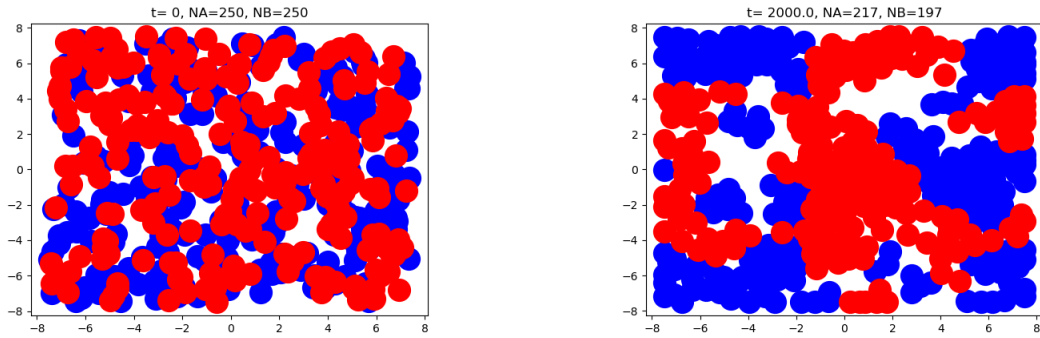Figure 1: case I: A-cells blue, B-cells red with $k^{AA} = k^{BB} = 2$, $k^{AB} = k^{BA} = 8$; $b0_A = b0_B = 10^{-3}$, $d0_A = d0_B = 7 \cdot 10^{-4}$, $\theta_A = \theta_B = 8 \cdot 10^{-4}$
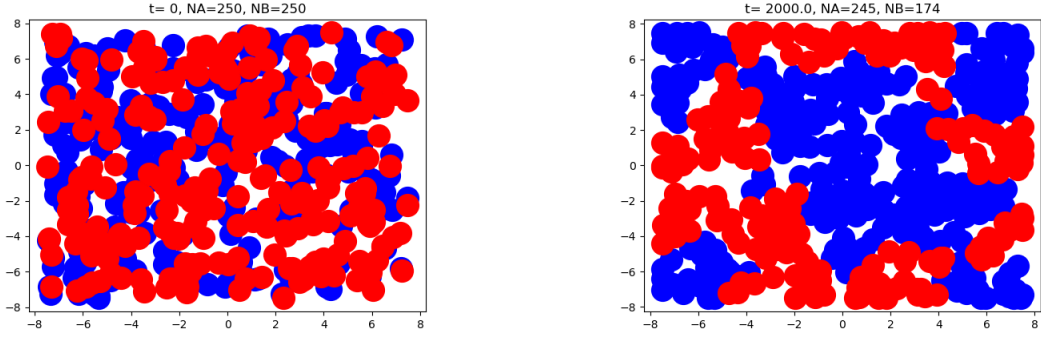
Figure 2: case I: A-cells blue, B-cells red with $k^{AA} = k^{BB} = 2$, $k^{AB} = k^{BA} = 8$; $b0_A = b0_B = 2 \cdot 10^{-3}$, $d0_A = d0_B = 7 \cdot 10^{-4}$, $\theta_A = \theta_B = 8 \cdot 10^{-4}$
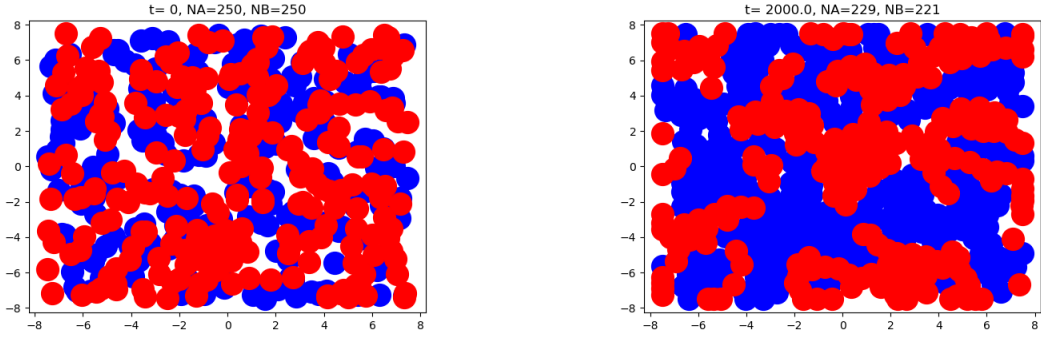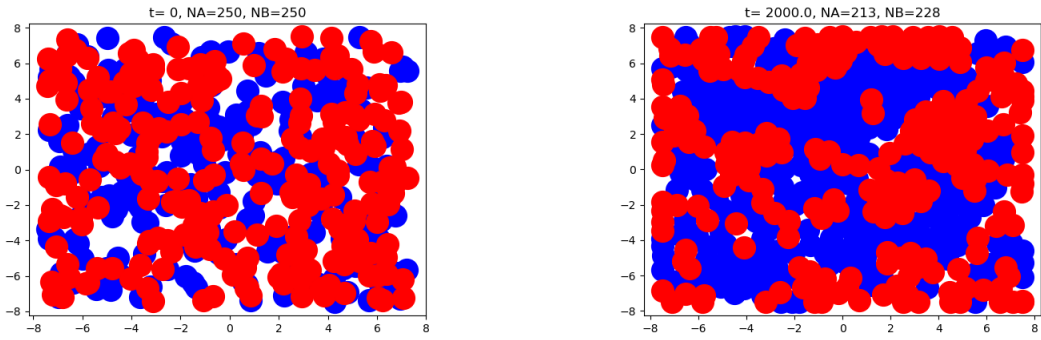

Figure 3: case I: A-cells blue, B-cells red with $k^{AA} = k^{BB} = 2$, $k^{AB} = k^{BA} = 8$; $b0_A = b0_B = 10^{-4}$, $d0_A = d0_B = 7 \cdot 10^{-5}$, $\theta_A = \theta_B = 8 \cdot 10^{-5}$

Figure 4: case I: A-cells blue, B-cells red with $k^{AA} = k^{BB} = 2$, $k^{AB} = k^{BA} = 4$; $b0_A = b0_B = 10^{-4}$, $d0_A = d0_B = 7 \cdot 10^{-5}$, $\theta_A = \theta_B = 8 \cdot 10^{-5}$
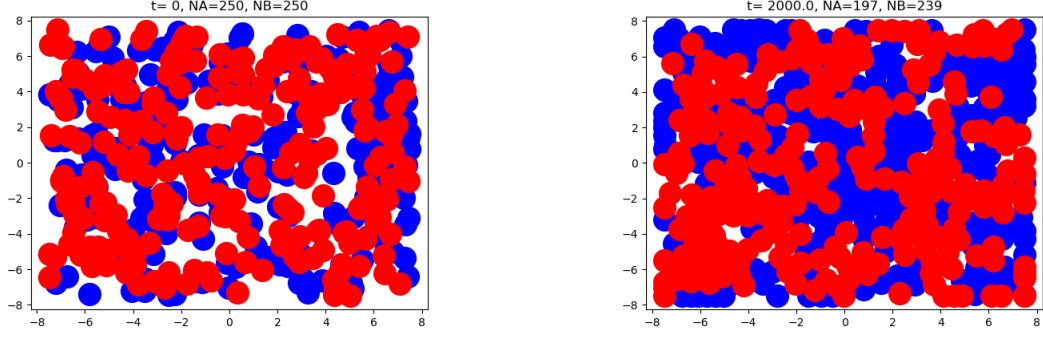
Figure 5: case I: A-cells blue, B-cells red with $k^{AA} = k^{BB} = 2$, $k^{AB} = k^{BA} = 2$; $b0_A = b0_B = 10^{-4}$, $d0_A = d0_B = 10^{-5}$, $\theta_A = \theta_B = 8 \cdot 10^{-5}$
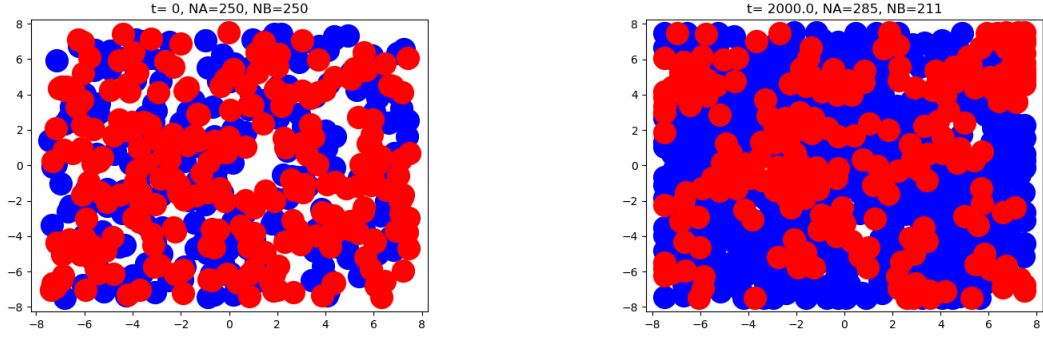

Figure 6: case II logistic: A-cells blue, B-cells red with $k^{AA} = k^{BB} = 2$, $k^{AB} = 1.38$, $k^{BA} = 2 \cdot k^{AB}$; $b0_A = b0_B = 10^{-4}$, $d0_A = d0_B = 10^{-5}$, $\theta_A = \theta_B = 8 \cdot 10^{-5}$

Figure 7: case II NO logistic: A-cells blue, B-cells red with $k^{AA} = k^{BB} = 2$, $k^{AB} = 1.38$, $k^{BA} = 2 \cdot k^{AB}$.
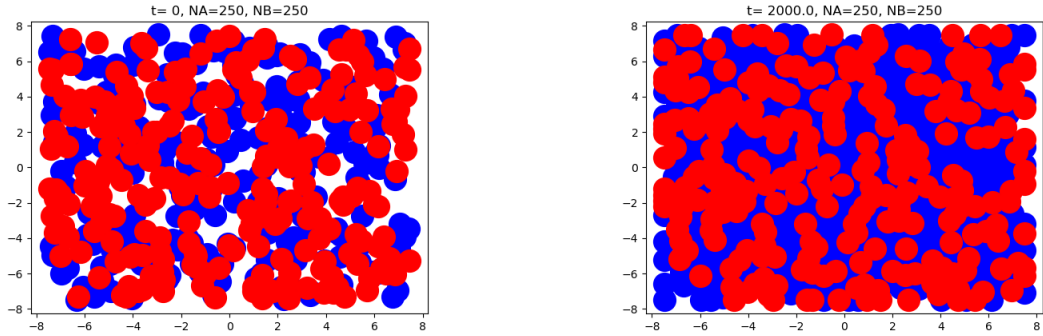

Figure 8: case III NO logistic $(s_c^* < s_L^*)$: A-cells blue, B-cells red with $k^{AA} = 2$, $k^{BB} = 1$, $k^{AB} = k^{BA} = 2 \cdot 0.73$.

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