ESAIM: PROCEEDINGS AND SURVEYS, Vol. ?, 2019, 1-10
Editors: Will be set by the publisher

CEMRACS 2018: MATHEMATICAL MODELING OF CELL AGGREGATION AND SEGREGATION

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Abstract. ...

Résumé. ...

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 there is no growth process. In this study, we investigate 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 populations 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.

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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 study its convergence towards a macroscopic model. Finally, we 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:

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

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. BarrÃĺ 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

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

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

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. BarrÃl' 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

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

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:
$$X_k := [x_1, x_2, \dots, x_k] \tag{8}$$
- 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, $i = 1, \dots, k$
- Normalization condition:
$$\sum_{k=0}^{\infty} \int \mathbb{P}_k(X_k, t)dX_k = 1. \tag{9}$$
- Permutation symmetry property: for all permutation $\sigma \in \{1, \dots, k\}$
$$\mathbb{P}_k(x_1, \dots, x_k, t) = \mathbb{P}_k(x_{\sigma(1)}, \dots, x_{\sigma(k)}, t) \tag{10}$$
- Expectation in the Fock space: A function C_k defined on the Fock space is a collection :
$$\{C_k(X_k)\}_{k=0,\dots,\infty}$$
and,
$$\langle C \rangle = \sum_{k=0}^{\infty} \int C_k(X_k)\mathbb{P}_k(X_k, t)dX_k \tag{11}$$

Reduced distribution functions. The number of 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:

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

proceeding the same as for $\langle N \rangle$ we get:

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

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:

$$\begin{aligned} \mathbb{P}_k(X_k, t+\tau) = & \int \mathbb{W}_k(X_k, t+\tau|X_k^{'},t)\mathbb{P}_k(X_k^{'},t)dX_k^{'} \\ & + \tau \sum_{i=1}^{k-1} \beta(X_i)\mathbb{B}\mathbb{P}_{k-1} - \tau \left[\sum_{i=1}^{k} (\beta(X_i) + \alpha(X_i)) \right] \mathbb{P}_k(X_k,t) \\ & + \tau \int \sum_{k=1}^{k+1} \beta(X_i)\mathbb{P}_{k+1}(X_{k+1},t)dx_i \end{aligned} \tag{21}$$

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:

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

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:

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

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:

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

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:

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

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:

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

Where :

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

Indeed those moments can be expressed on the form:

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

Expanding the moments for small τ

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

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

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

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

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

The Master Equation now takes the form:

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

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.

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

The main change in the model is to introduce a cell birth and death process. Our modeling is based on the birth and death process proposed in **citation**. The idea is that a cell of population of type S has a probability β_S to divide into two cells and a probability δ_S to die at each time step. This probability depends on the population size. Here we add also a spatial dependence to the probability rate:

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

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 $d_0^S < \theta < b_0^S$.

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:

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

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

The macroscopic model consists in an aggregation-diffusion equation with nonlocal terms which are related to interaction between neighbors of the same family and ones of the other family. In this section we perform a linear stability analysis of macroscopic model with logistic term in order to explore the formation of aggregates. Subsequently, the stability of the homogeneous steady states will characterize the appearance or not of clusters in the model.

3.1. **Stability of homogeneous steady states**

The purpose of this section is to obtain a criterion to decide if a given steady state is stable or not, through a critical value called s_L^* after which the homogeneous state will be unstable. We linearize around the homogeneous states, i.e. we consider the constant steady states $\bar{f}^A$ and $\bar{f}^B$ which satisfy system (36). Since $\bar{f}^A, \bar{f}^B$ do not depend on time and space, we can reduce the system to:

$$\begin{cases} \nu^A \bar{f}^A \left(1 - \frac{\bar{f}^A + \bar{f}^B}{f^*}\right) = 0 \\ \nu^B \bar{f}^B \left(1 - \frac{\bar{f}^A + \bar{f}^B}{f^*}\right) = 0 \end{cases} \tag{38}$$

We deduce that the non-trivial constant steady states are defined through the relation:

$$\bar{f}^A + \bar{f}^B = f^*, \tag{39}$$

which means that, at the homogeneous states, we have reached the maximum carrying capacity. The system (38) is satisfied also either when $\bar{f}^A = 0$ or $\bar{f}^B = 0$ or f^B, but we are not considering this case.
In order to perform our linear stability analysis, we use perturbation terms and Fourier transform as done in [3]. In fact we are looking on a neighbourhood of the homogeneous state and for this reason the perturbations are supposed to be small. After computation for system (36), we obtain:

$$\partial_t \begin{pmatrix} \hat{f}^A \\ \hat{f}^B \end{pmatrix}(y,t) = M(y) \begin{pmatrix} \hat{f}^A \\ \hat{f}^B \end{pmatrix}(y,t) \tag{40}$$

with matrix M defined as:

$$M(y) = \begin{pmatrix} -|y|^2(2\pi\bar{f}^A\hat{\Phi}^{AA}(y) + D_A) - \nu^A\frac{\bar{f}^A}{f^*} & -|y|^2 2\pi\bar{f}^A\hat{\Phi}^{AB}(y) - \nu^A\frac{\bar{f}^A}{f^*} \\ -|y|^2\bar{f}^B\hat{\Phi}^{BA}(y) - \nu^B\frac{\bar{f}^B}{f^*} & -|y|^2(2\pi\bar{f}^B\hat{\Phi}^{BB}(y) + D_B) - \nu^B\frac{\bar{f}^B}{f^*} \end{pmatrix}. \tag{41}$$

We want to point out that in (40) the non linear terms appearing because of perturbations have been neglected. In general case, the constant steady state will be stable only if the real part of the eigenvalues of the matrix $M(y)$ are both negative, otherwise it will be unstable. Since we know that $det(M(y)) = \lambda_1 \cdot \lambda_2$ and $tr(M(y)) = \lambda_1 + \lambda_2$, with $\lambda_1(y), \lambda_2(y)$ eigenvalues, the stability occurs only if:

$$det(M(y)) > 0 \quad \text{and} \quad tr(M(y)) < 0.$$

At first we compute the trace of matrix $M(y)$:

$$tr(M(y)) = -|y|^2(2\pi\bar{f}^A\hat{\Phi}^{AA}(y) + D_A) - \nu^A\frac{\bar{f}^A}{f^*} - |y|^2(2\pi\bar{f}^B\hat{\Phi}^{BB}(y) + D_B) - \nu^B\frac{\bar{f}^B}{f^*}. \tag{42}$$

We recall the fact that we consider the following assumption, as in [3]:

Hypothesis 1. *The intraspecies (or homotypic) links generate repulsive interactions, i.e* $\kappa^{AA} > 0$ *and* $\kappa^{BB} > 0$.

We can easily note that under the H1, the trace is always negative. Then we compute the determinant of matrix $M(y)$:

$$\begin{aligned} det(M(y)) = |y|^4 &\left[(\bar{f}^A 2\pi\hat{\Phi}^{AA} + D_A)(\bar{f}^B 2\pi\hat{\Phi}^{BB} + D_B) - \bar{f}^A\bar{f}^B 4\pi^2\hat{\Phi}^{AB}\hat{\Phi}^{BA}\right] + \\ &+ |y|^2\left[\nu^B\frac{\bar{f}^B}{f^*}(\bar{f}^A 2\pi\hat{\Phi}^{AA} + D_A - \bar{f}^A 2\pi\hat{\Phi}^{AB}) - \nu^A\frac{\bar{f}^A}{f^*}(\bar{f}^B 2\pi\hat{\Phi}^{BB} + D_B - \bar{f}^B 2\pi\hat{\Phi}^{BA})\right]. \end{aligned} \tag{43}$$

The first part with term in $|y|^4$ is exactly the determinant computed in [3] without logistic term. The second one is due to the introduction of logistic growth.
In order to understand if a possible perturbation can have effects on our model and it corresponds to the appearance of some clusters, we introduce a parameter $s \in \mathbb{R}$ to scale the interspecies (heterotypic) link potential intensities such that $\kappa^{AB} = s\widetilde{\kappa}^{AB}$ and $\kappa^{BA} = s\widetilde{\kappa}^{BA}$ and we consider the following hypothesis on heterotypic interactions:

Hypothesis 2. *The interspecies (or heterotypic) links interactions are both repulsive or both attractive, i.e* $\kappa^{AB}\kappa^{BA} > 0$.

Following the same workflow and approach of [3], we find the critical value s_L^*, such that, if $s > s_L^*$ and H2 holds, we should observe the formation of clusters:

$$s_L^* = \frac{(24D_A + c^{AA}\bar{f}^A)\nu^B\bar{f}^B + (24D_B + c^{BB}\bar{f}^B)\nu^A\bar{f}^A}{\nu^B\bar{f}^B c^{AB}\bar{f}^A + \nu^A\bar{f}^A c^{BA}\bar{f}^B}, \tag{44}$$

with $c^{SS} = \frac{2\pi\kappa^{SS}\nu_c^{SS}R^4}{\nu_d^{SS}}$ and $c^{ST} = \frac{2\pi\widetilde{\kappa}^{ST}\nu_c^{ST}R^4}{\nu_d^{ST}}$, $S \neq T \in \{A, B\}$ and recalling that now $\kappa^{AB} = s\widetilde{\kappa}^{AB}$ and $\kappa^{BA} = s\widetilde{\kappa}^{BA}$.

We want to draw attention to the fact that in our analysis we do not consider the case of population extinction, such as the case of $\bar{f}^A = 0$ or $\bar{f}^B = 0$. In practice, the addition of logistic term allows to state that a vanishing population is not attained. Si $\bar{f}^A = 0$ ou $\bar{f}^B = 0$, on a $det > 0$, donc stability?

3.2. Study of aggregation formation

We carry out the linear stability analysis of the system that leads to the aggregation condition which can be biologically interpreted. The system with logistic term and its linear analysis are interesting, not only because of aggregation process but also because in this case there is an infinite number of steady states. It is necessary that all of them are unstable, in order to ensure the formation and appearance of clusters and then that the states do not converge towards the state of equilibrium.

The critical value s_L^* provides information about stability of a given steady state.

By $\bar{f}^B = f^* - \bar{f}^A$ we rewrite the following s_L^*:

$$s_L^* = \frac{(\nu^B c^{AA} + \nu^A c^{BB})\bar{f}^A(f^* - \bar{f}^A) + (24D_B\nu^A - 24D_A\nu^B)\bar{f}^A + 24D_A\nu^B f^*}{\bar{f}^A(f^* - \bar{f}^A)(\nu^B c^{AB} + \nu^A c^{BA})}, \tag{45}$$

Moreover it is easy to check that under H1, H2, $\lim_{\bar{f}^A \to f^*} s_L^*(\bar{f}^A) = +\infty$ and $\lim_{\bar{f}^A \to 0} s_L^*(\bar{f}^A) = +\infty$, meaning that the states corresponding to one domintaing population are always stable.

We are looking then for the minimum of function s_L^*, i.e the zero points of $\frac{\partial s_L^*(\bar{f}^A)}{\partial \bar{f}^A}$. After computation we find only one minimum $\bar{f}_m^A$ in $[0, f^*]$:

- If $D_A\nu^B - \nu^A D_B = 0$, the minimum is $\bar{f}_m^A = \frac{f^*}{2}$
- If $D_A\nu^B - \nu^A D_B \neq 0$, the minimum is given by:

$$\bar{f}_m^A = \frac{f^*(D_A\nu^B - \sqrt{D_A D_B \nu^B \nu^A})}{D_A\nu^B - \nu^A D_B}. \tag{46}$$

The minimum of function s_L^* correspond to the less stable steady state. When the two population have the same ratio between diffusion and growth, the less stable configuration is the symmetric one. It is very logical because increasing parameter s correspond to introduce asymmetry between the population, promoting an asymmetric steady state.

We report on Fig 1 the plot of our function with its parameters, provided by numerical simulation. As mentioned before, we can see that for a given value of the parameters, there is still stable steady states corresponding to the case of a dominating population. But with relevant parameters we can observe a plateau meaning that a large part of the steady states are unstable in practice. Hence, we can hope, if one population does not dominate the other at the initial condition to observe apparition of aggregates.

3.3. Impact of the logistic growth on aggregation

In this subsection we explore a comparison between two models, the one with the addition of growth term and the other one studied and analyzed in [3]. Their comparison is not so simple since it is not expected to have the same initial condition. In the model without logistic term the evolution of the particle distributions

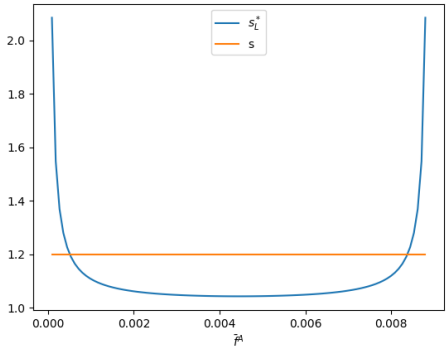

FIGURE 1. Coefficient s and s_L^* with biologically relevant parameters.

f^A and f^B do not change, whereas in the case we studied the starting condition is clearly influenced by births and deaths. It is also not expected to provide and foresee the total mass of type A and B population because it is not always the same. Therefore, it is actually difficult to assert if we are comparing the same state of equilibrium in both models.
With regard to model without logistic term, we report the following critical value as in [3], in order to do this comparison between the two values:

$$s_C^* = \left[\frac{576}{c^{AB}c^{BA}f^A f^B}\left(D_A + \frac{c^{AA}f^A}{24}\right)\left(D_B + \frac{c^{BB}f^B}{24}\right)\right]^{\frac{1}{2}}. \tag{47}$$

Looking for critical points, we get as previously only one minimum:

- If $D_A\nu^B - \nu^A D_B = 0$, the minimum is $\bar{f}_m^A = \frac{f^*}{2}$
- If $D_A\nu^B - \nu^A D_B \neq 0$, the minimum is given by:

$$\bar{f}^A = \frac{-(24D_AD_B + D_Ac^{BB}f^*) \pm \sqrt{\widetilde{\Delta}}}{D_Bc^{AA} - D_Ac^{BB}}, \tag{48}$$

with $\widetilde{\Delta} = (24D_AD_B + D_Ac^{BB}f^*)^2 + 24D_AD_B^2c^{AA}f^* - 24D_A^2D_Bc^{BB}f^* + D_AD_Bc^{AA}c^{BB}(f^*)^2 - D_A^2c^{BB^2}(f^*)^2$. As it has been already said, both critical values s_C^*, s_L^* are markers of instability and we will discuss some simulations to compare them. As remarked in **citation**, the diffusion and intraspecie repulsion tend to homogenize the system, then the interspecies forces must be large enough to compensate this aspect. Thanks to stability analysis, we can observe and conclude that logistic growth can either support or repress aggregation, depending also on the parameters choice. The aggregation is viewed as a breakdown of stability caused by changes in the parameters which characterize the system. We want to explore and discuss some different cases:

- 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 previous one and instability for logistic model and no aggregates for the other one when $s \in (s_L^*, s_C^*)$.

In the next section we will discuss some numerical simulations on the individual agent-based model to confirm the results provided by stability analysis.

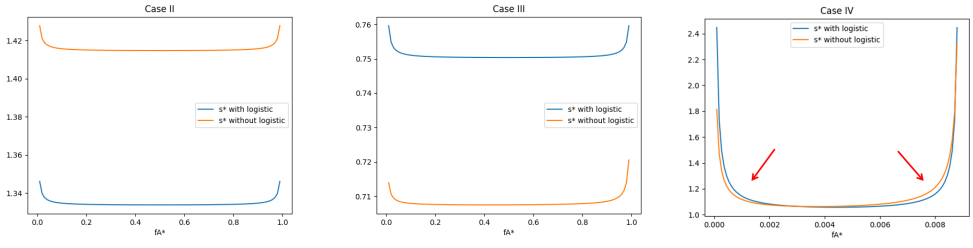

FIGURE 2. Placeholder critical values

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

TABLE 1. Placeholder values table

4. NUMERICAL SCHEME

4.1. **Macroscopic model**

The equations for the macroscopic model can be written as:

$$\partial_t f^S = \mathcal{L}(f^S, f^T) + \mathcal{D}(f^S) + \mathcal{R}(f^S, f^T), \quad S \neq T \in \{A, B\} \tag{49}$$

with

$$\mathcal{L}(f^S, f^T) = \nabla \cdot (f^S \nabla_x (\Phi^{SS} * f^S)) + \nabla \cdot (f^S \nabla_x \Phi^{ST} * f^T) \tag{50}$$

$$\mathcal{D}(f^S) = D_S \Delta_x f^S \tag{51}$$

$$\mathcal{R}(f^S, f^T) = \nu^S f^S \left(1 - \frac{f^S + f^T}{f^*}\right) \tag{52}$$

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:

$$\frac{df^S_{j,k}}{dt} = \mathcal{L}_{j,k} + \mathcal{D}_{j,k} + \mathcal{R}_{j,k} \tag{53}$$

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 :

$$\mathcal{L}_{j,k} = -\frac{F^x_{j+\frac{1}{2},k} - F^x_{j-\frac{1}{2},k}}{\Delta x} - \frac{F^y_{j,k+\frac{1}{2}} - F^y_{j,k-\frac{1}{2}}}{\Delta y}, \tag{54}$$

with

$$F^x_{j+\frac{1}{2},k} = u^+_{j+\frac{1}{2},k} f^E_{j,k} - u^-_{j+\frac{1}{2},k} f^W_{j+1,k}, \quad F^y_{j,k+\frac{1}{2}} = u^+_{j,k+\frac{1}{2}} f^N_{j,k} - u^-_{j,k+\frac{1}{2}} f^S_{j,k+1}$$

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:

$$\frac{f^{S,n+1}_{j,k} - f^{S,n}_{j,k}}{\Delta t} = \mathcal{L}^n_{j,k} + \mathcal{D}^{n+1}_{j,k} + \mathcal{R}^n_{j,k} \tag{55}$$

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 (34) we have the following time discretization:

$$X^{n+1}_i = X^n_i - \mu \nabla_{X_i} W(X^n) \Delta t^n + \sqrt{2D\Delta t^n} \mathcal{N}(0, 1) \tag{56}$$

$\mathcal{N}(0, 1)$ 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 $r = 0.5$.

$$\beta_A = b^A_0 - (b^A_0 - \theta_A) \left(\frac{N_A + N_B}{N^*} \right), \qquad \delta_A = d^A_0 + (\theta_A - d^A_0) \left(\frac{N_A + N_B}{N^*} \right) \tag{57}$$

5. Results

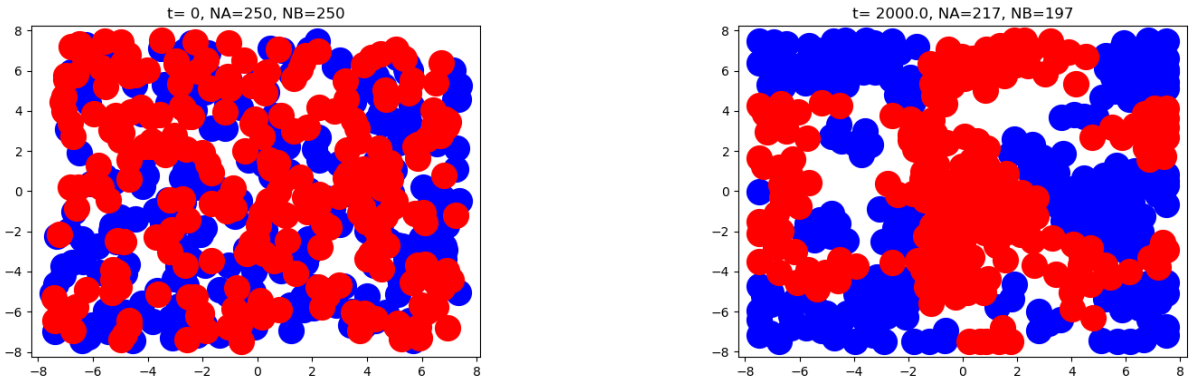

FIGURE 3. case I: A-cells blue, B-cells red with $k^{AA} = k^{BB} = 2$, $k^{AB} = k^{BA} = 8$; $b0_A = b0_B = 10^{-3}$, $d0_A = d0_B = 7 \cdot 10^{-4}$, $\theta_A = \theta_B = 8 \cdot 10^{-4}$

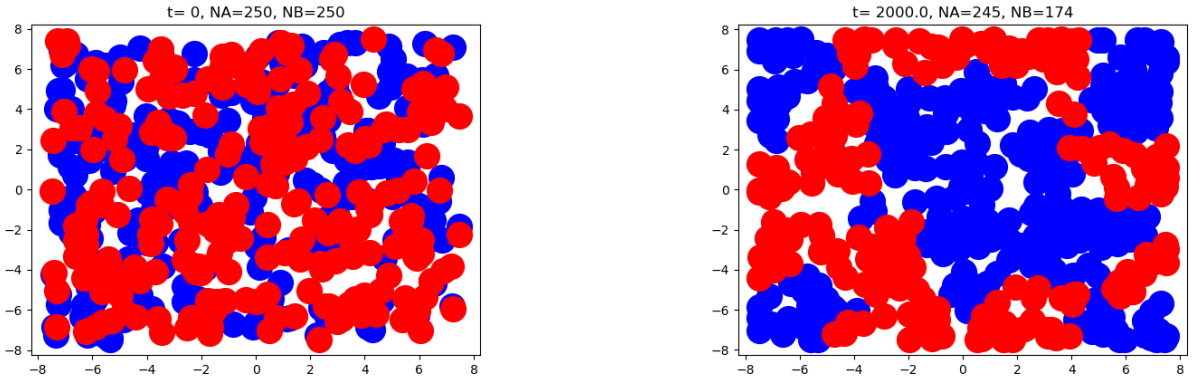

FIGURE 4. case I: A-cells blue, B-cells red with $k^{AA} = k^{BB} = 2$, $k^{AB} = k^{BA} = 8$; $b0_A = b0_B = 2 \cdot 10^{-3}$, $d0_A = d0_B = 7 \cdot 10^{-4}$, $\theta_A = \theta_B = 8 \cdot 10^{-4}$

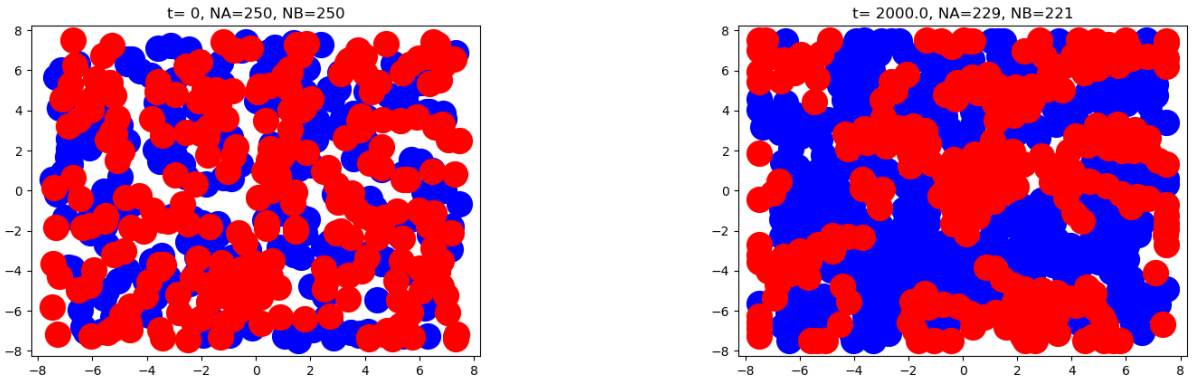

FIGURE 5. case I: A-cells blue, B-cells red with $k^{AA} = k^{BB} = 2$, $k^{AB} = k^{BA} = 8$; $b0_A = b0_B = 10^{-4}$, $d0_A = d0_B = 7 \cdot 10^{-5}$, $\theta_A = \theta_B = 8 \cdot 10^{-5}$

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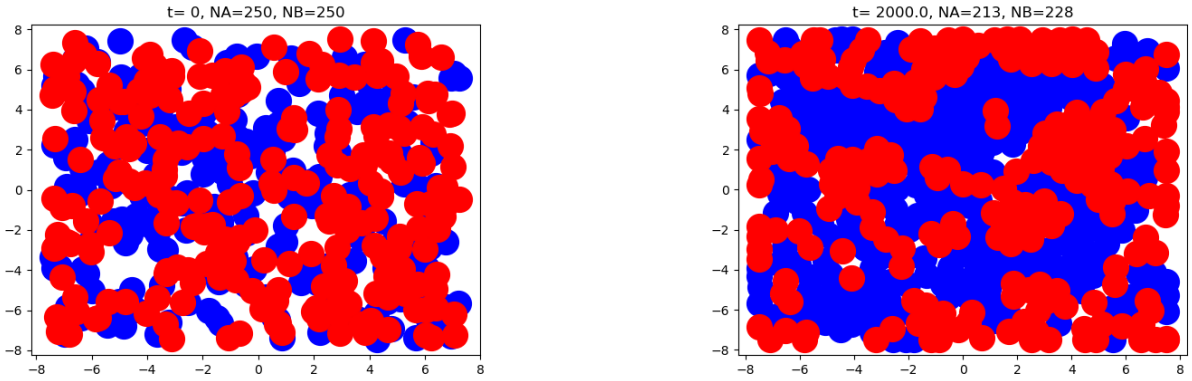

FIGURE 6. case I: A-cells blue, B-cells red with $k^{AA} = k^{BB} = 2$, $k^{AB} = k^{BA} = 4$; $b0_A = b0_B = 10^{-4}$, $d0_A = d0_B = 7 \cdot 10^{-5}, \theta_A = \theta_B = 8 \cdot 10^{-5}$

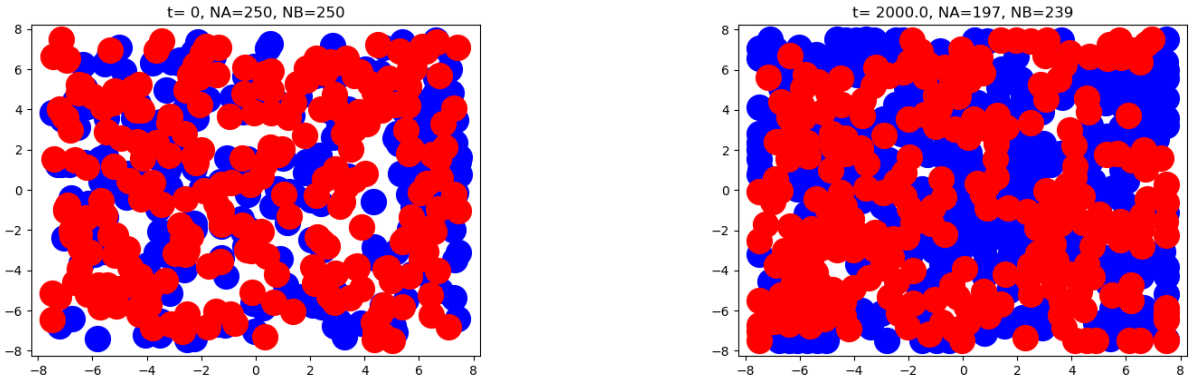

FIGURE 7. case I: A-cells blue, B-cells red with $k^{AA} = k^{BB} = 2$, $k^{AB} = k^{BA} = 2$; $b0_A = b0_B = 10^{-4}$, $d0_A = d0_B = 10^{-5}, \theta_A = \theta_B = 8 \cdot 10^{-5}$

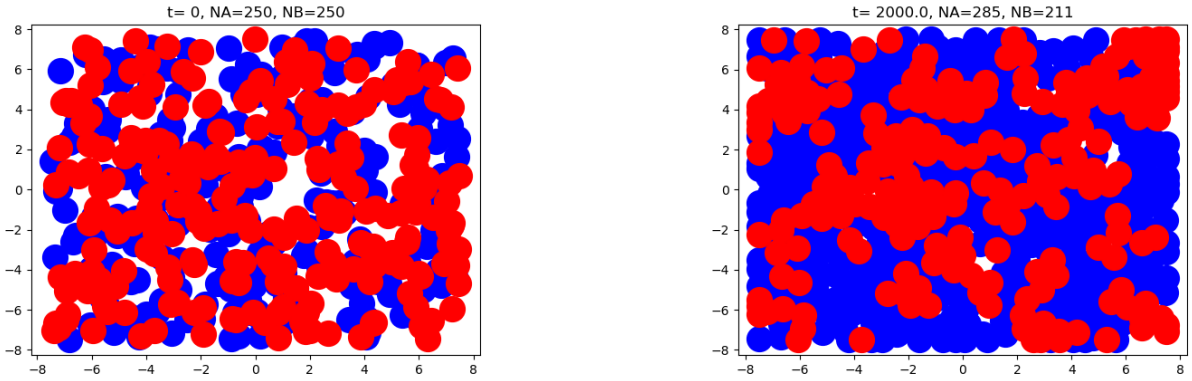

FIGURE 8. case II logistic: A-cells blue, B-cells red with $k^{AA} = k^{BB} = 2$, $k^{AB} = 1.38, k^{BA} = 2 \cdot k^{AB}$; $b0_A = b0_B = 10^{-4}$, $d0_A = d0_B = 10^{-5}, \theta_A = \theta_B = 8 \cdot 10^{-5}$

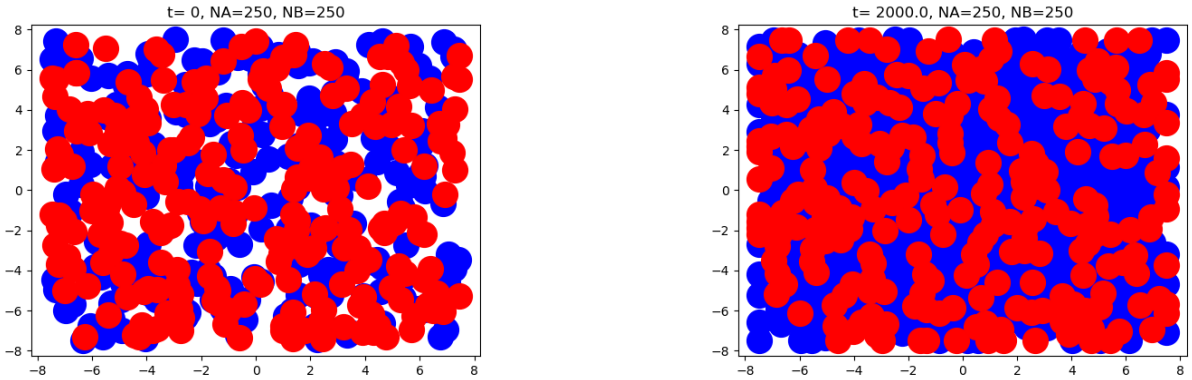

FIGURE 9. case III NO logistic ($s_c^* < s_L^*$): A-cells blue, B-cells red with $k^{AA} = 2, k^{BB} = 1$, $k^{AB} = k^{BA} = 2 \cdot 0.73$.