Modelling interactions between tumour cells and supporting adipocytes in breast cancer

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Internship report

Contents

This internship report on the subject "Modelling interactions between tumour cells and supporting adipocytes in breast cancer", is a summary of the work accomplished during 6 months of internship at the Laboratoire Jacques-Louis-Lions (LJLL). Since this internship is intended to be followed by a PhD on the same subject, most of the work was bibliographical and aimed at understanding the biological background, the modelling and analysis of phenotypically structured populations, as well as the envisaged experiments, that are performed at the Laboratoire de Biologie et Thérapeutique des Cancers (LBTC) in Michèle Sabbah's team. Those experiments will allow for validation and parametrization of the models. An other part of the work was to start proving new mathematical results, and perform numerical simulations to investigate different scenarios.

Introduction

In breast cancer, invasion of the micro-environment implies potential bidirectional communication between cancer cells and the adipose tissue. Biological evidence suggests that adipocytes, in particular, are key-actors in tumorigenesis and invasion: they both enhance proliferation of the cancer cells and favor acquisition of a more invasive phenotype. To understand these effects, mathematical modelling (thanks to tools developed in theoretical ecology) is used to perform asymptotic analysis in number of cells and distribution of phenotypes. These models can be tuned through confrontation with experimental data coming from co-cultures of cancer cells with adipocytes.
The first part of this report is devoted to presenting the biological background on breast cancer and its environment. We then present the main aspects of the mathematical modelling, and how it is expected to be validated experimentally. In the third part, we summarize and prove many important results that have been obtained on a single integro-differential equation representing the evolution of a population of individuals structured with a phenotypic trait. The next part consists of a first glance at possible generalizations of those results to a system of integro-differential equations coupled mutualistically. In a fifth and last part, we introduce how we intend to parametrize the models through explicit computations and numerical simulations.

1 Breast cancer and its environment

1.1 Breast cancer : a brief overview

1.1.1 Some statistics in France

What follows is a summary from a survey issued by the IVS (Institut de Veille Sanitaire). The statistics are taken from the year 2012, exclusively in France. Note that the incidence and mortality figures have been roughly stable for the last decade.
In France, in 2012, around 50,000 new cases were reported, for around 10,000 deaths. One woman out of eight will have breast cancer at some time in life. After 5 years, the survival rate is about 86% (all types included). Age is a strong factor, as 45% of breast cancers are diagnosed between 50 and 69 years and around 33% after 69 years.

1.1.2 Location of breast cancers

Breast cancer is a malignant tumor, whose primary site is the mammary gland (i.e. the breast). A breast consists of 15 to 20 lobes, themselves composed of many lobules. The lobes are surrounded by the adipose tissue, which separates them from the skin. The lobules' function is to produce the milk, which is brought to the nipple by the milk ducts. Fig. 1 below provides a schematic representation of the mammary gland.

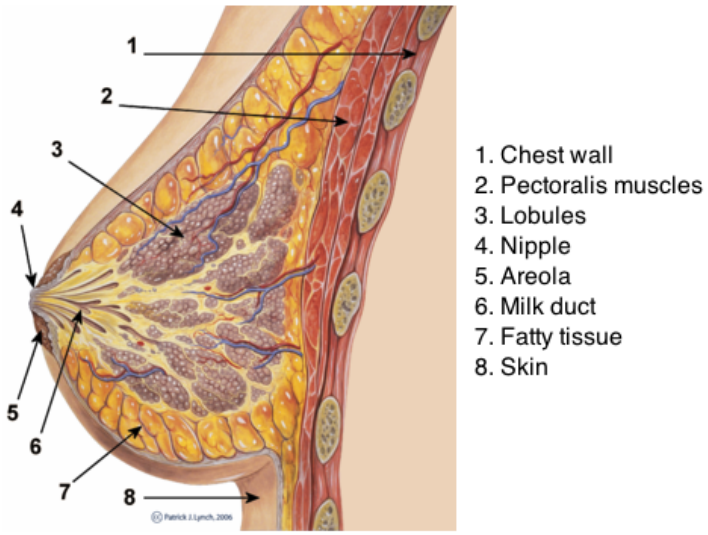

Figure 1: Cross-section scheme of the mammary gland (Wikipedia)

Breast cancers are first classified based on whether the tumour has invaded its local microenvironment or not:

- most cancers start either in the lobules or in the ducts, and as long as healthy cells are not invaded, the cancer is said to be *in situ*;
- if the cancer invades the adipose tissue, however, it is said to be an *invasive* cancer.

Around 90% of deaths due to breast cancer occur because of migration of cancers cells to other organs. The first metastases are often found in the lymph nodes of the armpit (the axillary lymph nodes). The breast cancer essentially metastasizes to the bone, lungs, regional lymph nodes, liver and brain (with bones representing the most common site).

1.1.3 Different types of breast cancers

Depending on the involved cancer cells' phenotype, two breast cancers can differ drastically, and this has very important implications in terms of therapeutical strategies and life expectancy. To cover the most prevalent types, it is enough to characterize a cancer cell based on the presence (+) of absence (−) of:

- hormone receptors for estrogens (ER) and progesterone (PR);
- the gene HER2, responsible for over-expression of the growth-promoting protein HER2.

From that, it is possible to distinguish 3 types of breast cancers:

- Luminal A (ER+, PR+, HER2-) and B (ER+, PR-, HER2+) → 70%;
- HER2 positive (ER-, PR- , HER2+) → 15%;
- "triple-negative" or "basal-like" (ER-, PR-, HER2-) → 15%,

where the percentages indicate the approximate contribution of each type to the total number of breast cancers in France (data taken from the Curie Institute website).

1.1.4 Therapeutics for breast cancer

As for other cancers, clinical treatment of breast cancers consists of several approaches than can be combined. The choice of one or several therapies, as well as their scheduling and duration, depends on a wide variety of factors, including which the type of cancer, its location (invasive or not, metastases), the size of the different tumors and, of course, the health status of the patient. One can identify 5 main approaches for a clinician facing a breast cancer:

- *chemotherapy*

Chemotherapy refers to chemical drugs that kill the cancer cells (*cytotoxic* effect) and/or block their proliferation (*cytostatic* effect). These are often very toxic drugs, which can also affect healthy cells.

- *surgery*

Cancer surgery is the removal of (part of) the tumor and its surrounding tissues.

- *radiotherapy*

Radiotherapy uses high-energy rays to target the cancer cells.

- *antiangiogenic drugs*

When a tumor grows, the cells at the center cannot access nutrients anymore and become quiescent (they stop dividing, waiting for better conditions). In those conditions, cancer cells are able to create their own vasculature, ensuring access to nutrients and potential migration. This is called angiogenesis, a process specifically targeted by antiangiogenic drugs.

- *blocking interactions between the tumor and its environment*

Although the immune system can fight cancer, cancer cells also use their environment to their advantage, so as to create better conditions for their survival and proliferation. In breast cancer, there are indeed mutualistic interactions between cancer cells and cells of the adipose tissue (see next section).

1.2 Interactions between the tumour and the adipose tissue

1.2.1 Short description of the adipose tissue

The main role of adipose tissue is to serve as an energy depot. There are few main types of cells in the adipose tissue, listed thereafter:

- *adipocytes*

Adipocytes are round cells, the most represented cells of the adipose tissue. They confer it its function, as adipocytes maintain an energy balance by storing excess fat and releasing it when needed in the form of fatty acids. They can also synthesize estrogens [12].

• *fibroblasts*

Fibroblasts are more elliptical cells. They synthesize many proteins than can be found in the extra-cellular matrix (ECM), thus contributing to structuring the stroma and having a wound-healing function.

• *endothelial cells*

Endothelial cells form a thin layer around the blood vessels.

• *macrophages*

Macrophages are cells that engulf and digest (this is called phagocytosis) anything that does not have the types of proteins specific to the surface of healthy body cells on its surface.

• *preadipocytes*

Preadipocytes are undifferentiated fibroblasts that can be stimulated to form adipocytes.

1.2.2 Mutualistic interactions

Epidemiological studies have shown a positive link between obesity and breast cancer, both in terms of risk of developing the disease and poor prognosis once it has been diagnosed [2, 9], at least for post-menopausal women. For pre-menopausal women, the latter also seems to hold true, while the former doesn't: many studies find an negative association between obesity and risk of developing the disease before menopause [9]. More precisely, obesity is linked to higher likelihood of larger tumours, recurrence of the disease, and death.
Those studies often use the BMI (body mass index) to define obesity, an index built as a measure of body fat. Thus, they provide strong evidence of existence of interactions between the tumour and the adipose tissue.

Furthermore, those conclusions also have biological support. First, obesity is associated with (subclinical) inflammation of the adipose tissue, a state of the micro-environment which has been proven to favor cancer progression [13]. Secondly, obesity leads to over-expression of aromatase, and subsequently, the hormon it synthesizes: estrogen [14]. Estrogens increase proliferation of ER positive cancer cells. It is also noteworthy that most post-menopausal breast cancers are ER positive.

Knowledge of such interactions already has applications in clinics: hormone therapy (drugs that compete with estrogens for binding to estrogen receptors) and aromatase inhibitors are used. Nonsteroidal anti-inflammatory drugs are also used.

1.3 The key role of adipocytes

Among cells of the adipose tissue, recent biological evidence suggests that adipocytes play a key role in cell proliferation, invasive phenotype and resistance to therapy as far as cancer cells are concerned. Adipocytes at the interface with the tumour exhibit a modified phenotype, and are now called Cancer-Associated Adipocytes (CAAs) [5, 15]. They are indeed characterized by a much smaller size (see Fig. 2) due to delipidation and a lower expression of adiponectin (a cytokine emitted by mature adipocytes).

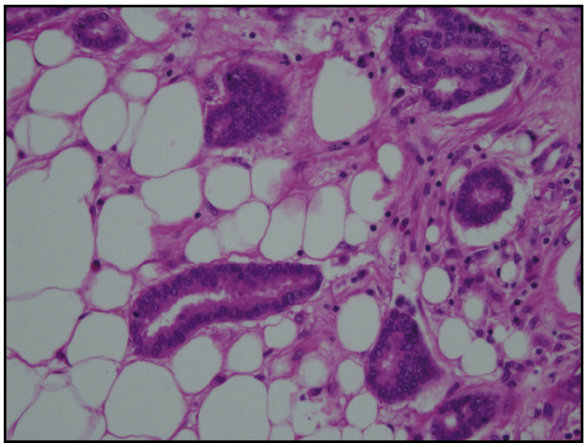

Figure 2: Histology of the invasive front of a human breast carcinoma. Data reproduced from [15]. In white: adipocytes, in purple: tumour.

1.3.1 In cell proliferation

When cultured in a medium containing soluble factors emitted by adipocytes, cancer cells are significantly more proliferative, a conclusion that does not hold if the factors are emitted by fibroblasts [7]. Similar conclusions are obtained in terms of cell proliferation in the case of cancer cells cultured with adipocytes in a three-dimensional collagen gel matrix [10].

1.3.2 In invasive phenotype

Epithelial to mesenchymal transition (EMT) is a reversible process by which epithelial cells partly lose their adherent properties (and their polarity), and thus become more motile. This transition is known to occur in cancer cells, and is strongly related to invasive properties of the cancer, and metastases. Put in contact with adipocytes through soluble factors only, cancer cells undergo the EMT [5], proving that adipocytes are linked to cancer invasion. Together with the change of adipocytes from mature adipocytes (A) to CAAs, this shows that crosstalk between both populations change their phenotype, a situation summarized in Fig. 3.

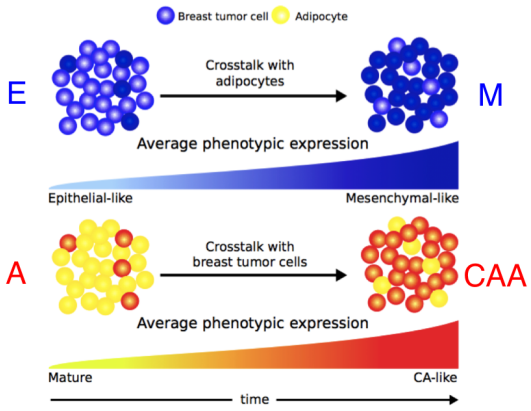

Figure 3: Bidirectional communication between adipocytes and cancer cells induce a change of phenotypes in both populations. E: epithelial, M: mesenchymal, A: (mature) adipocytes, CAA: cancer-associated adipocytes.

1.3.3 In resistance to therapy

Different biological studies have shown that, under the influence of adipocytes, cancer cells can develop a resistance to different therapies.
In [1] the authors show that cancer cells co-cultured with adipocytes have become resistant to radiotherapy. This effect is independent of whether cancer cells are left in co-culture with adipocytes, or not (at least on a window of 2 days).
In [6], cancer cells expressing HER2 (HER2+) are found to develop resistance to trastuzumab-mediated cytotoxicity (trastuzumab is a drug that blocks the extra-cellular part of the receptor for HER2) if co-cultured with adipocytes or preadipocytes.

2 Experimental setting and mathematical modelling

To further study the interactions between cancer cells and adipocytes, the goal is to perform experiments of co-culture of cancer cells with adipocytes. Mathematical modelling can then serve as an *in silico* laboratory to guide experiments and investigate scenarios that are not directly accessible, or too costly.

2.1 Experimental setting

2.1.1 Principle and cell lines

Given two populations of cells, of cancer cells and adipocytes, they can be grown in direct contact in a same Petri dish, or separately in two separate chambers. In the last case, interactions are allowed only by soluble factors (thus not considering possible the effect of direct physical contact). This is done experimentally thanks to a Transwell co-culture system, whose principle is presented in Fig. 4.

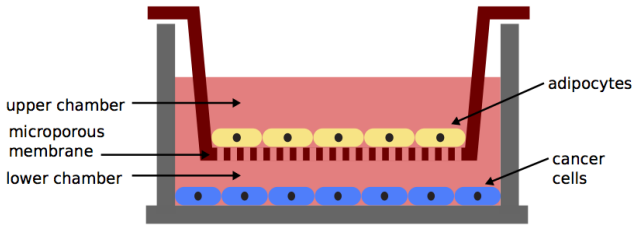

Figure 4: Principle of a co-culture with a Transwell system

The cell lines that will be used for the experiments are the following :

- Mature adipocytes (obtained by differentiating 3T3-F442A murine preadipocytes)
- Epithelial cancer cells MCF7 (human)
- Mesenchymal cancer cells MCF7-sh-WISP2 (human)

Cultures will be performed in a complete growth medium, and all possible combinations (including adipocytes and cancer cells alone) will be considered. Every culture will last for 72 hours.

2.1.2 Estimating cell proliferation and distribution in phenotypes

The number of viable cells will be estimated by cell count, using trypan blue exclusion (trypan blue colors dead cells) every 24 hours.
To quantify the phenotype distribution of the adipocytes, two methods are possible (and can be combined).

- Estimating the level of expression of adiponectin;
- Estimating the size of the adipocytes.

To quantify the distribution of cancer cells in phenotype, three methods are possible (and can be combined).

- Estimating the level of expression of E-cadherin;

- Estimating the adhesion properties of the cancer cells:
  these properties will be investigated through dispase disaggregation assay (DDA) following the protocol schematized in Fig. 5. Loosely speaking, independent monolayers of cancer cells will be grown until confluency. Cell monolayers will be detached from the culture dishes through incubation with a proper metalloproteinase dispase. Released monolayers will be disrupted by standardized pipetting, and a count of floating cell clusters will be performed. A higher number of floating clusters (i.e., a higher cell dissociation percentage) will indicate a lower cell-cell adhesion strength.

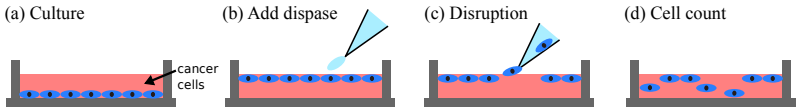

Figure 5: Assessing the adhesion properties of the cancer cells

- Estimating the invasion properties of the cancer cells:
  a gelatin-invadopodia-assay will be used to measure cell-associated degradation of the extracellular matrix. In brief, for each culture, cancer cells will be grown on a layer of green-fluorescein-labeled gelatin. Cell cultures will be stained with rhodamine phalloidin for actin rich invadopodia puncta (red). Visual inspection and image segmentation will be used to estimate the degree of degradation of the gelatin, and the concentration of invadopodia (see Fig. 6);

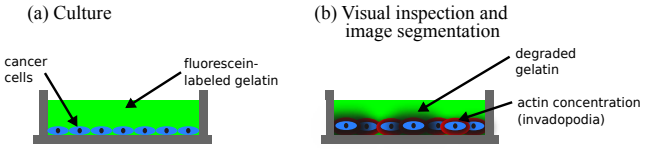

Figure 6: Assessing the invasion properties of the cancer cells

2.2 Mathematical modelling

2.2.1 Underlying principles

When one tries to model *in vivo* tumours, space is an important variable since the increasing number of cells leads to an increasing pressure and, consequently, to a less favourable environment for cells. In an experimental setting, however, similar pressure conditions are not observed. Also, we specifically wish to understand how the interaction between cancer cells and adipocytes leads to the selection of cancer cells that are more prone to migration, and to the selection of CAAs. To model the experiments, phenotype is thus a natural structuring variable, at least more relevant than space.
Consequently, for a given population of cells, we are interested in $n(t, x)$, which represents the density of cells at time t, of phenotype x. Here, x denotes a given trait or phenotype, which is considered to be particularly relevant to describe the biological variability within the celle population. Ideally, this variable must be experimentally identifiable. A typical example is the concentration of a protein, and x is thus considered to be a continuous variable (lying in some subset of $\mathbb{R}^d$).

Cells also compete for resources, so that the environment exerts a selective pressure, forcing the cells to adapt. A second feature is that a cell with a given phenotype might change its own phenotype and/or give birth to cells with a different phenotype (because of mutations and epimutations, see below for a definition). This situation suggests that modelling tools

provided by mathematical ecology (and more particularly, adaptive dynamics) can be used. This branch of mathematical biology focuses on understanding mathematically how selection occurs in a population of individuals interacting between themselves and with their environment (in a competitive and/or mutualistic way), and subject to mutations and epimutations [4, 8, 11].

2.2.2 Typical equation

Let us now introduce a prototype equation (coming from adaptive dynamics) describing the evolution of a population of cells defined by $n(t,x)$. Close models can for example be found in [3, 8, 11]. For simplicity, we will assume that the trait lies in some sub-interval of $\mathbb{R}$, say $X := [0\,,1]$. The equation for n is given by:

$$\frac{\partial n}{\partial t}(t,x) + \frac{\partial}{\partial x}\left(v(x)n(t,x)\right) = \beta\,\frac{\partial^2 n}{\partial x^2}(t,x) + R\left(x,\rho(t)\right)n(t,x). \tag{1}$$

with initial condition $n_0 \geq 0$ in $L^1(X)\cap L^\infty(X)$ and Neumann boundary conditions. We also assume that the adaptation velocity v vanishes at the boundary.

Each term models a different phenomenon:

- *The $R\left(x,\rho(t)\right)n(t,x)$ term.*
  R is a fitness function for the cells of phenotype x in the environment created by the total population (which is modelled by the dependence in the total population given by $\rho(t) := \int_X n(t,x)\,dx$). The most common example is

  $$R\left(x,\rho(t)\right) = r(x) - d(x)\rho(t) \tag{2}$$

  which amounts to saying that cells give birth at rate $r(x)$ and die at rate $d(x)\rho(t)$. The dependence in ρ is of logistic type, representing the idea that cells die faster when the total population is bigger, because of competition for nutrients and space.

- *The $\beta\,\dfrac{\partial^2 n}{\partial x^2}(t,x)$ term*
  The Laplacian models random epimutations, i.e. random heritable gene expressions that leaves the DNA unaffected. β quantifies the rate of epimutations. Note that we do not take mutations into account (usually modelled with a probability kernel) because they are supposed to occur much less frequently. They are thus here neglected.
  Such a term can be called of Darwin-type, since it implies that the emergence or selection of fitter individuals occurs because of random events.

- *The $\dfrac{\partial}{\partial x}\left(v(x)n(t,x)\right)$ term*
  This advection term means that the density is transported with velocity $v(x)$. It models non-random epimutations.
  Such a term can be called of Lamarck-type, since it implies that the emergence or selection of fitter individuals occurs because these individuals actively change their phenotype to adapt to their environment.

2.2.3 Equation for the interaction between adipocytes and cancer cells

To model the experiments of co-culture between cancer cells and adipocytes, we are interested in the behaviour of the two population densities $n_C(t,x)$ (cancer cells) and $n_A(t,y)$ (adipocytes). x and y stand for traits that characterize the phenotype of the individuals:

- for cancer cells, x ranges from 0 for an epithelial phenotype E to 1 for a mesenchymal phenotype M. x can be linked to the concentration of a protein through a proper normalization;

- for adipocytes, y ranges from 0 for mature adipocytes A to 1 for cancer-associated adipocytes CAA. y can be linked to the concentration of a protein through a proper normalization.

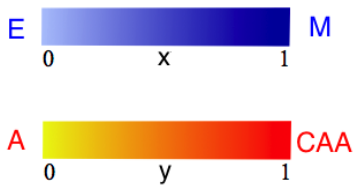

Figure 7: Meaning of the traits x and y.

We consider the following set of PDEs

$$\begin{cases} \dfrac{\partial n_C}{\partial t}(t,x) + \dfrac{\partial}{\partial x}\left(v_C\left(x,\varphi_A(t)\right) n_C(t,x)\right) \\ \qquad\qquad = \beta_C \dfrac{\partial^2 n_C}{\partial x^2} + \left[R_C\left(x,\rho_C(t)\right) + R_{CA}\left(x,\varphi_A(t)\right)\right] n_C(t,x) \\ \dfrac{\partial n_A}{\partial t}(t,y) + \dfrac{\partial}{\partial y}\left(v_A\left(y,\varphi_C(t)\right) n_A(t,y)\right) \\ \qquad\qquad = \beta_A \dfrac{\partial^2 n_A}{\partial y^2} + \left[R_A\left(y,\rho_A(t)\right) + R_{AC}\left(y,\varphi_C(t)\right)\right] n_A(t,y) \end{cases} \tag{3}$$

with initial conditions depending on the experiment and Neumann boundary conditions. The interaction is modelled through dependence of different terms on functions φ_A and φ_C, which aim at representing the chemical signal from adipocytes to cancer cells (resp. from cancer cells to adipocytes). A possible definition is

$$\begin{cases} \varphi_C(t) = \int_0^1 \psi_C(x)\, n_C(t,x)\, dx \\ \varphi_A(t) = \int_0^1 \psi_A(y)\, n_A(t,y)\, dy \end{cases} \tag{4}$$

with ψ_C, ψ_A increasing functions (modelling the fact that mesenchymal cells or CAAs are expected to emit more chemical messengers than, respectively, epithelial cells and mature adipocytes).

The interactions impact two terms:

- *The $R_{CA}\left(x,\varphi_A(t)\right) n_C(t,x)$ and $R_{AC}\left(y,\varphi_C(t)\right) n_A(t,y)$ terms.*
  Since the interaction is mutualistic in terms of cell proliferation (at least for cancer cells), we assume that $R_{CA}\left(x,\varphi_A\right) \geq 0$ with equality if and only if $\varphi_A = 0$ and, possibly, $R_{AC}\left(y,\varphi_C\right) \geq 0$ with equality if and only if $\varphi_C = 0$. Typically, we will take
  $$R_{CA}\left(x,\varphi_A\right) = s_C(x)\varphi_A \tag{5}$$
  with $s_C(x) \geq 0$ the sensitivity of cancer cells to the chemical messengers. Note that the population of adipocytes can be seen as inducing an added birth rate for the cancer cells.
- *The $\dfrac{\partial}{\partial x}\left(v_C\left(x,\varphi_A(t)\right) n_C(t,x)\right)$ and $\dfrac{\partial}{\partial y}\left(v_A\left(y,\varphi_C(t)\right) n_A(t,y)\right)$ terms*
  We still assume that v_C and v_A vanish at the boundary (independently of the value of φ_A and φ_C respectively) for well-posedness.
  Since cancer cells tend to naturally undergo the epithelial to mesenchymal transition, we assume $v_C \geq 0$. Since the interaction tends to lead to a change of phenotype from E to M and A to CAA, we also assume that v_C and v_A are increasing functions of φ_A and φ_C, respectively.

3 Single integro-differential equation

We now turn our attention to studying mathematically the system of PDEs introduced in the mathematical modelling, in a simplified way: we assume there is no advection nor diffusion.

Canonical equation and goals

Before studying the system of equations, let us consider the case of a single equation, i.e. one population only. The case is now well understood [11]. The individuals are defined by a trait or phenotype x (lying in a given compact set, say $X \subset \mathbb{R}^d$), on which their birth and death rate depend. A simple model is thus:

$$\begin{cases} \frac{\partial n}{\partial t}(t,x) = [r(x) - d(x)\rho(t)]\ n(t,x),\ x \in X,\ t > 0 \\ \\ n(0,x) = n^0(x),\ x \in X \end{cases} \tag{6}$$

where $\rho(t)$ stands for the total population, that is $\rho(t) = \int_X n(t,x)\,dx$.

There are several main questions that have been addressed, including which:

- What are the dynamics of the total mass ?
- Are there traits selected, and if yes, which ones ?

A canonical and more general setting containing (6) is the following:

$$\begin{cases} \frac{\partial n}{\partial t}(t,x) = R\left(x, \rho(t)\right)\ n(t,x),\ x \in X,\ t > 0 \\ \\ n(0,x) = n^0(x),\ x \in X \end{cases} \tag{7}$$

R can be seen as the fitness of the individuals of trait x in the environment created by the total population $\rho(t)$. This is the equation that will thereafter be studied, bearing in mind the simpler case (6).

3.1 Existence and uniqueness

We first provide a priori bounds for ρ, before making sure there exists a unique non-negative solution with regularity $C\left(\mathbb{R}_+, L^1(X)\right)$. For that, we make some general and reasonable assumptions on the parameters and initial conditions, i.e.:

$$\begin{cases} R \in C^1\left(\mathbb{R}^d \times \mathbb{R}\right) \\ n^0 \geq 0 \in L^1(X) \end{cases} \tag{8}$$

and we assume that there exist positive constants ρ^m, ρ^M, d such that

$$\begin{cases} \forall x \in X,\ R(x,\rho^m) \geq 0 \text{ and } \exists x^m \in X,\ R(x^m,\rho^m) = 0 \\ \forall x \in X,\ R(x,\rho^M) \leq 0 \text{ and } \exists x^M \in X,\ R(x^M,\rho^M) = 0 \\ \frac{\partial R}{\partial \rho} \leq -d \end{cases} \tag{9}$$

The two first assumptions mean that ρ^m and ρ^M are (global) minimal and maximal capacities: if ρ is below ρ_m, the density of individuals of any trait increases. Similarly, if ρ is above ρ^M, the density decreases for any trait. Furthermore, the existence of x^m and x^M imply that they are the best constants to achieve this. The last statement models the idea that an increase in ρ results in greater competition. In view of (6), d can be seen as a minimal death rate.

3.1.1 A priori bounds

Lemma 3.1. *Suppose we have a solution of (7) in $C\left(\mathbb{R}_+, L^1(X)\right)$, with the initial data such that $\rho^m \leq \rho^0 := \int_X n_0(x)\,dx \leq \rho^M$.*
Then, for all $t > 0$:

$$\rho^m \leq \rho(t) \leq \rho^M.$$

Proof. Integrating the equation yields, for all $t \geq 0$:

$$\frac{d\rho}{dt}(t,x) \leq \left[\max_{x\in X} R\left(x, \rho(t)\right)\right] \rho(t)$$

Let $\epsilon > 0$. If $\rho(t)$ is close to $\rho^M + \epsilon$, its derivative becomes negative and this is enough to ensure $\rho(t) \leq \rho^M + \epsilon$ for all $t > 0$. We then let ϵ go to 0 to get the upper bound.
The same arguments provide the other inequality. □

3.1.2 Proof of existence and uniqueness

First, we notice that we have an implicit formula for $n(t,x)$:

$$n(t,x) = n^0(x) e^{\int_0^t R(x,\rho(s))\,ds} \tag{10}$$

which shows that n is necessarily non-negative.

Theorem 3.2. *Assume, as in Lemma (3.1), that n^0 is such that $\rho^m \leq \rho^0 := \int_X n_0(x)\,dx \leq \rho^M$.*
Then, there exists a unique non-negative global solution n to the equation (7).
It furthermore satisfies:

$$\rho^m \leq \rho(t) \leq \rho^M \text{ for all } t > 0.$$

Proof. The proof is based on the Banach fixed point theorem.

First step. We start by defining the appropriate Banach space. For $T > 0$ that will be chosen later, we consider the Banach space

$$E := C\left([0\,,T], L^1(X)\right) \text{ endowed with the norm } \|m\|_E := \sup_{0\leq t\leq T} \|m(t)\|_{L^1(X)}$$

We also consider the following closed subset of E:

$$F := \{m \in E \,/\, m \geq 0 \text{ and } \|m\|_E \leq K\}$$

where $K > \rho^M$ is some constant.

Second step. We now build the application. Let m be a fixed element in F, and let us define

$$\widetilde{\rho}(t) = \int_X m(t,x)\,dx$$

For fixed $x_0 \in X$, we consider the solution γ_{x_0} to the following differential equation:

$$\begin{cases} \frac{d\gamma_{x_0}}{dt} = R\left(x, \widetilde{\rho}(t)\right)\, \gamma_{x_0} \\ \gamma_{x_0}(0) = n^0(x_0) \end{cases}$$

which is global on $[0\,,T]$. [1]

[1] Note that this function is defined as an integral of m, and thus does not depend on the representative for the a.e. equivalence relation.

We now define for all (t,x) in $[0\,,T]\times X$ the function $n(t,x) := \gamma_x(t)$, thus building an application Φ through $\Phi(m) := n$.

Third step. We show that Φ maps F onto itself.
The equation (3.1.2) can be solved explicitly by

$$n(t,x) = n^0(x)e^{\int_0^t R(x,\widetilde{\rho}(s))\,ds}$$

It shows both $n \geq 0$ and $n \in E$. As in the a priori estimates, we bound $\frac{\partial n}{\partial t}(t,x)$ and integrate to get

$$\frac{d\rho}{dt}(t) \leq \left[\max_{x\in X} R\left(x,\widetilde{\rho}(t)\right)\right]\rho(t)$$

Using the bound on the initial data, together with $\max\limits_{x\in X} R\left(x,\widetilde{\rho}(t)\right) \leq \max\limits_{x\in X} R\left(x,0\right) =: \lambda$, we get

$$\rho(t) \leq \rho^M e^{\lambda T}$$

To obtain $n \in F$, it only remains to choose T small enough so that $\rho^M e^{\lambda T} \leq K$.

Fourth step. Let us now prove that Φ is a strong contraction from F onto F whenever T is small enough. Let $(m^1,m^2) \in F^2$ and (n^1,n^2) its image by Φ. We define $\widetilde{\rho}^i$ as before for $i = 1,2$.

$$(n^1-n^2)(t,x) = n^0(x)\left[e^{\int_0^t R\left(x,\widetilde{\rho}^1(s)\right)\,ds} - e^{\int_0^t R\left(x,\widetilde{\rho}^2(s)\right)\,ds}\right]$$

Now, since the argument of the exponentials can be bounded by λT, the mean value theorem yields

$$\begin{aligned}
|(n^1-n^2)|(t,x) &\leq n^0(x)e^{\lambda T}\left|\int_0^t \left[R\left(x,\widetilde{\rho}^1(s)\right) - R\left(x,\widetilde{\rho}^2(s)\right)\right]\,ds\right| \\
&\leq Cn^0(x)e^{\lambda T}\left[\int_0^T \left|\widetilde{\rho}^1(s) - \widetilde{\rho}^2(s)\right|\,ds\,ds\right] \\
&\leq Cn^0(x)Te^{\lambda T}\|m_1 - m_2\|_E \qquad (11)
\end{aligned}$$

by the mean value theorem again, with $C := \sup_{(x,\rho)\in X\times[0\,,K]}\left|\frac{\partial R}{\partial \rho}(x,\rho)\right|$. We now integrate with respect to x and take the supremum over $t \in [0\,,T]$ in (11) to uncover

$$\|n^1 - n^2\|_E \leq C\rho^M Te^{\lambda T}\|m^1 - m^2\|_E$$

This provides us with the contracting property for Φ whenever T is small enough.

Fifth step. We now conclude by noticing that T has been chosen small independently of the initial data, so that the argument can be iterated on $[0\,,T]$, $[T\,,2T]$, etc.
By the a priori estimates of the lemma, we also iteratively have the bounds stated in the theorem. □

3.2 Asymptotics

3.2.1 Convergence for ρ

The previous hypotheses are enough to show that ρ converges. It is also possible to identify the limit as the maximal capacity ρ^M, if we simply assume the following: among the x^Ms such that $R(x^M,\rho^M) = 0$, there exists x_0 such that n^0 does not vanish in a neighborhood of x_0.
Note that this is not really a restriction, since we can for example assume that n^0 is continuous, so that $n^0(x_0) > 0$ would be enough for our purpose (and if it were not true, we could define the set X and ρ^M differently, removing the traits for which n^0 is zero).

To show that ρ converges, we will prove that it has bounded total variation on $\mathbb{R}_+$ (see Appendix A for a reminder of the fact that a BV function on $\mathbb{R}_+$ converges).

Proposition 3.3. *ρ is a BV function and thus converges. Furthermore, its limit is ρ^M.*

Proof. We define $q := \dfrac{d\rho}{dt}$ and we need to prove that $q \in L^1(\mathbb{R}_+)$. We differentiate $\dfrac{d\rho}{dt} = \int nR$ to obtain:

$$\frac{dq}{dt} = \int nR^2 + \left(\int n\frac{\partial R}{\partial \rho}\right) q$$

It provides an upper bound for the negative part of q (see Appendix B):

$$\begin{aligned}\frac{dq_-}{dt} &\leq \left(\int n\frac{\partial R}{\partial \rho}\right) q_- \\ &\leq -d\rho^m q_-\end{aligned}$$

thanks to the hypothesis in (9) and the lower bound on ρ. We conclude that the negative part of q vanishes exponentially. Together with the upper bound on ρ, this proves the first result (see Appendix A for a proof that an upper bounded function whose derivative has integrable negative part, is BV).

We denote the limit with $\rho^\star$, and argue by contradiction by assuming $\rho^\star < \rho^M$.
Let $\epsilon > 0$ and $t_0 > 0$ such that $\rho(t) \leq \rho^M - \epsilon$ for all $t > t_0$. Then, for $x \in V$ a neighborhood of x_0 such that $R(x_0, \rho^M) = 0$ and $t > t_0$, we can write

$$\begin{aligned}\frac{\partial n}{\partial t}(t,x) &= R\left(x, \rho(t)\right) n(t,x) \\ &\geq R\left(x, \rho^M - \epsilon\right) n(t,x) \\ &\geq \eta\, n(t,x)\end{aligned}$$

for some $\eta > 0$ (choosing ϵ small enough). This now implies for $t > t_0$

$$\rho(t) \geq \int_V n(t,x)\, dx \geq \left[\int_V n^0(x)\right] e^{\eta(t-t_0)}$$

which contradicts the upper bound on ρ since the right hand side goes to $+\infty$.

□

3.2.2 Convergence for n

We now assume that there exists a single trait x_0 such that $R(\cdot, \rho^M)$ vanishes, which means that one trait has a selective advantage over all others. Our aim is to prove that the population asymptotically concentrates in x_0. The idea is that for all the other traits, $n(t,x)$ goes to 0 exponentially. The correct statement is given in the theorem hereafter:

Theorem 3.4. *Suppose there is a unique trait x_0 such that $R(x_0, \rho^M) = 0$. Then the population concentrates in x_0 with mass ρ^M, i.e.*

$$n(t,x) \rightharpoonup \rho^M \delta_{x_0}$$

Remark 3.5. *By the weak convergence here, we mean in the sense of the bounded measures $M^1(X)$, defined as the (topological) dual of $C(X)$ (the set of continuous functions on X).*

Proof. As explained in the remark, we have to show that

$$\forall \phi \in C(X),\ \int_X n(t,x)\phi(x)\, dx \to \rho^M \phi(x_0)$$

Note that we already know, by the Banach-Alaoglu theorem, that we have converging subsequences since $\forall t \geq 0$, $\|n(t,\cdot)\|_{L^1(X)} \leq \rho^M$: the family $(n(t,\cdot))_{t\geq 0}$ is thus uniformly bounded

in $M^1(X)$. Here, we won't use this result as we can directly determine the limit.

Let $\phi \in C(X)$. From

$$\left|\int_X n(t,x)\phi(x)\,dx - \rho^M\phi(x_0)\right| \leq \left|\int_X n(t,x)\phi(x)\,dx - \phi(x_0)\int_X n(t,x)\,dx\right| + \left|\phi(x_0)(\rho(t)-\rho^M)\right| \quad (12)$$

and since the last term goes to 0, it remains to show that the first one does as well.
Let $\epsilon > 0$. We choose $\eta > 0$ such that $B(x_0,\eta) \subset X$ and $\left|\phi(x)-\phi(x_0)\right| \leq \epsilon$ as soon as $\left|x-x_0\right| \leq \eta$, split the integral and estimate both terms:

$$\left|\int_X n(t,x)(\phi(x)-\phi(x_0))\,dx\right| \leq 2\|\phi\|_\infty \left(\int_{X\backslash B(x_0,\eta)} n(t,x)\,dx\right) + \rho^M\epsilon \quad (13)$$

As $R(\cdot,\rho)$ converges uniformly to $R(\cdot,\rho^M)$ on $X\backslash B(x_0,\eta)$ and $\max_{x\in X\backslash B(x_0,\eta)} R(\cdot,\rho^M) =: -\alpha < 0$, we can state that for t large enough, say $t \geq t_0$:

$$\forall x \in X\backslash B(x_0,\eta),\ R(x,\rho) \leq -\frac{\alpha}{2} \quad (14)$$

which allows us to write : $n(t,x) \leq n(t_0,x)e^{-\frac{\alpha}{2}(t-t_0)}$ on $X\backslash B(x_0,\eta)$ from the equation on n. Therefore, $\int_{X\backslash B(x_0,\eta)} n(t,x)\,dx$ goes to 0 and this completes the proof. □

Remark 3.6. *The proof also works if x_0 does not lie in the interior of X, for example if X is some interval of $\mathbb{R}$ and if x_0 is one of its extremities.*

4 System of two integro-differential equations

Canonical equation and goals

We now wish to investigate the dynamics of the coupled equations (without advection and diffusion), which we recall here with subscripts 1 and 2 rather than A and C. x can be taken as a variable for the traits structuring both populations, since they are independent.

$$\begin{cases} \dfrac{\partial n_1}{\partial t}(t,x) = \left[R_1\left(x,\rho_1(t)\right) + R_{12}\left(x,\varphi_2(t)\right)\right] n_1(t,x)\, x \in X,\ t>0, \\ \\ \dfrac{\partial n_2}{\partial t}(t,x) = \left[R_2\left(x,\rho_2(t)\right) + R_{21}\left(x,\varphi_1(t)\right)\right] n_2(t,x)\, x \in X,\ t>0, \end{cases} \tag{15}$$

with $x \in X$ as before and initial conditions

$$\begin{cases} n_1(0,x) = n_1^0(x) \geq 0,\ x \in X, \\ \\ n_2(0,x) = n_2^0(x) \geq 0,\ x \in X, \end{cases} \tag{16}$$

Also recall the definitions, for $i = 1, 2$:

$$\rho_i(t) = \int n_i(t,x)dx, \qquad \varphi_i(t) = \int \psi_i(x) n_i(t,x)dx, \quad \psi_i(\cdot) \geq 0. \tag{17}$$

The simpler model we have in mind is given by:

$$R_i\left(x,\rho_i(t)\right) = r_i(x) - d_i\rho_i(t) \tag{18}$$

and

$$R_{12}\left(x,\varphi_2\right) = s_1(x)\varphi_2,\ R_{21}\left(x,\varphi_1\right) = s_2(x)\varphi_1 \tag{19}$$

In agreement with the biological framework, we will study the mutualistic case, i.e. we assume:

$$R_{12}(\cdot),\ R_{21}(\cdot) \geq 0 \tag{20}$$

These functions must also vanish when the other population is absent, in other words

$$\forall x \in X,\ R_{12}(x,0) = R_{21}(x,0) = 0 \tag{21}$$

Also, for the mathematical analysis of these equations, we have so far focused on the case $\psi_{1,2} \equiv 1$, i.e. $I_{1,2} \equiv \rho_{1,2}$. Indeed, this case allows for fruitful comparisons with the usual mutualistic Lotka-Volterra 2×2 system (at the level of ρ). This is why we start by recalling some classical facts about these systems, in section 4.1.
In section 4.2, under new assumptions made natural by the Lotka-Volterra system, we prove a-priori bounds, existence and uniqueness for the general equation.
In section 4.3, under some stronger hypotheses, we prove BV bounds for $\rho_{1,2}$ to get convergence for the total populations of cells 1 and 2.

4.1 Mutualistic 2×2 Lotka-Volterra systems

Considering the simpler case (18, 19) and assuming that all coefficients are constant in x, the equations boil down to the dynamics of (ρ_1, ρ_2), which after integration is given by the following classical 2×2 Lotka-Volterra system:

$$\begin{cases} \dfrac{d\rho_1}{dt} = \left[r_1 - d_1\rho_1 + C_{12}\rho_2\right]\rho_1, \\ \\ \dfrac{d\rho_2}{dt} = \left[r_2 - d_2\rho_2 + C_{21}\rho_1\right]\rho_2, \end{cases} \tag{22}$$

This is why we wish to recall some classical results on such systems and their proof (which might in turn provide useful ideas for the general system).

With positive initial conditions $\rho_i^0 > 0$ for $i = 1, 2$, the exponential-like structure ensures that ρ_1 and ρ_2 remain positive for all times for which they are defined.

4.1.1 Possible blow-up

Suppose all coefficients are equal, and that the initial conditions for ρ_1 and ρ_2 are the same, so that we can write $\rho_1 = \rho_2 =: \rho$ for all times for which the solution is defined. ρ satisfies the equation $\frac{d\rho}{\partial t}(t,x) = r\rho - (d-C)\rho^2$ for which it is clear there is explosion if $d < C$. More explicitly, if $d < C$ and setting $\gamma := C - d > 0$, we have $\frac{d\rho}{dt} \geq \gamma\rho^2$. If we integrate, we find that ρ blows up before $T := \frac{1}{\gamma\rho(0)}$.

Directly finding an extension in the general case (22) in order to avoid blow-up can be achieved through studying the steady states. There are four steady states, three of which are always in the quadrant of interest : $(0,0)$, $(\rho_1^M, 0)$ and $(0, \rho_2^M)$ where ρ_i^M, $i = 1, 2$ stand for the carrying capacity for populations 1 and 2. They are given by $\rho_i^M = \frac{r_i}{d_i}$, $i = 1, 2$. The last steady state $(\hat{\rho}_1, \hat{\rho}_2)$ is:

$$\begin{cases} \hat{\rho}_1 = \dfrac{d_2 r_1 + C_{12} r_2}{d_1 d_2 - C_{12} C_{21}}, \\ \\ \hat{\rho}_2 = \dfrac{d_1 r_2 + C_{21} r_1}{d_1 d_2 - C_{12} C_{21}}, \end{cases} \tag{23}$$

and is of interest if and only if

$$d_1 d_2 > C_{12} C_{21} \tag{24}$$

which turns out to be the proper generalization of the non blow-up condition exhibited before. It is also worth mentioning that $\rho_i^M < \hat{\rho}_i$ for $i = 1, 2$, which means that, as the intuition would suggest, mutualism leads to a larger steady state than without interaction.

Standard phase plane arguments show that if the nullclines $r_1 - d_1\rho_1 + C_{12}\rho_2 = 0$ and $r_2 - d_2\rho_2 + C_{21}\rho_1 = 0$ do not intersect in the positive quadrant (i.e. if $d_1 d_2 \leq C_{12} C_{21}$), both populations grow unboundedly. We thus focus in the case where (24) is fullfilled in what follows, a case which will turn out to find a natural generalization for the general equation (15).

4.1.2 Convergence in the case (24)

Through a classical Lyapunov functional for Lotka-Volterra systems and under the condition (24), we prove simultaneously that the solution does not blow-up and that the steady state $(\hat{\rho}_1, \hat{\rho}_2)$ is globally asymptotically stable (in $(\mathbb{R}_+^\star)^2$).

Definition 4.1. *For a given $x^\star > 0$, we define the function*

$$\begin{array}{rccl} V_{x^\star} : & \mathbb{R}_+^\star & \longrightarrow & \mathbb{R}_+ \\ & x & \longmapsto & x - x^\star - x^\star \ln\left(\dfrac{x}{x^\star}\right) \end{array} \tag{25}$$

Remark 4.2. *The function $V_{x^\star}$ has the following properties*

- *$V_{x^\star}$ is a C^1 function;*

- $V_{x^\star}(x) > 0$ *for* $x \neq x^\star$ *and* $V_{x^\star}(x^\star) = 0$*;*
- $V_{x^\star}$ *is a proper function.*

This function being now defined, we can prove the:

Proposition 4.3. *Suppose that the condition (24) is satisfied. Then* (ρ_1, ρ_2) *is globally defined and the steady state* $(\hat{\rho}_1, \hat{\rho}_2)$ *is globally asymptotically stable.*

Proof. Let $\alpha_i > 0$, $i = 1, 2$ (to be chosen later), and $V(\rho_1, \rho_2) := V_{\hat{\rho}_1}(\rho_1) + V_{\hat{\rho}_2}(\rho_2)$, which is also a C_1 proper function (on $(R_+^\star)^2$) that satisfies $V(\rho_1, \rho_2) > 0$ for $(\rho_1, \rho_2) \neq (\hat{\rho}_1, \hat{\rho}_2)$ and $V(\hat{\rho}_1, \hat{\rho}_2) = 0$.
V is our candidate to be a Lyapunov function for the system (23) and we thus compute $\frac{d}{dt}V(\rho_1, \rho_2)$ for admissible $t > 0$ (bearing in mind that we don't know yet that the solutions are globally defined).

$$\begin{aligned}
\frac{d}{dt}V(\rho_1, \rho_2) &= \alpha_1 \left(1 - \frac{\hat{\rho}_1}{\rho_1}\right) \frac{d\rho_1}{dt} + \alpha_2 \left(1 - \frac{\hat{\rho}_2}{\rho_2}\right) \frac{d\rho_2}{dt} \\
&= \alpha_1 (\rho_1 - \hat{\rho}_1) [r_1 - d_1\rho_1 + C_{12}\rho_2] + \alpha_2 (\rho_2 - \hat{\rho}_2) [r_2 - d_2\rho_2 + C_{21}\rho_1] \\
&= \alpha_1 (\rho_1 - \hat{\rho}_1) [-d_1 (\rho_1 - \hat{\rho}_1) + C_{12} (\rho_2 - \hat{\rho}_2)] \\
&\qquad + \alpha_2 (\rho_2 - \hat{\rho}_2) [-d_2 (\rho_2 - \hat{\rho}_2) + C_{21} (\rho_1 - \hat{\rho}_1)]
\end{aligned}$$

The last equality is obtained by adding $0 = r_1 - d_1\hat{\rho}_1 + C_{12}\hat{\rho}_2 = r_2 - d_2\hat{\rho}_2 + C_{21}\hat{\rho}_1$, the very definition of the steady state $(\hat{\rho}_1, \hat{\rho}_2)$.
We now change variables by setting : $u = \rho_1 - \hat{\rho}_1$, $v = \rho_2 - \hat{\rho}_2$ so that the equation writes

$$\begin{aligned}
\frac{d}{dt}V(\rho_1, \rho_2) &= \alpha_1 u(-d_1 u + C_{12} v)\alpha_2 v(-d_2 v + C_{21} u) \\
&= -\left[\alpha_1 d_1 u^2 - (C_{12}\alpha_1 + C_{21}\alpha_2)\, uv + \alpha_2 d_2 v^2\right] \\
&= -\frac{1}{2} X^t A X
\end{aligned}$$

with $X = \begin{pmatrix} u \\ v \end{pmatrix}$ and $A = \begin{pmatrix} 2\alpha_1 d_1 & -(C_{12}\alpha_1 + C_{21}\alpha_2) \\ -(C_{12}\alpha_1 + C_{21}\alpha_2) & 2\alpha_2 d_2 \end{pmatrix}$.

If we find (α_1, α_2) such that A, which is symmetric, is also definite positive, then $\frac{d}{dt}V(\rho_1, \rho_2) \leq 0$ with equality if and only if $(u, v) \neq (0, 0)$, i.e. if and only if $(\rho_1, \rho_2) = (\hat{\rho}_1, \hat{\rho}_2)$. Consequently, it remains to find (α_1, α_2) such that A has positive determinant (since it already has positive trace) and we will have found a Lyapunov function for the system, proving both claims of the theorem.
Now, $det(A) = 4\alpha_1\alpha_2 d_1 d_2 - (C_{12}\alpha_1 + C_{21}\alpha_2)^2$. Choosing $\alpha_1 = \frac{1}{C_{12}}$ and $\alpha_2 = \frac{1}{C_{21}}$, we have to check that $4\frac{d_1 d_2}{C_{12}C_{21}} > 4$, which is indeed true thanks to assumption (24).

□

Remark 4.4. *From classical Cauchy-Lipschitz arguments, it is easy to check that if* $\rho_1(0) \leq \hat{\rho}_1$ *and* $\rho_2(0) \leq \hat{\rho}_2$*, then we have for all times* $\rho_1 \leq \hat{\rho}_1$ *and* $\rho_2 \leq \hat{\rho}_2$*.*

4.2 Existence and uniqueness

4.2.1 Regularity and non blow-up assumptions

We start by making regularity assumptions. Since we wish to study how the coupling affects the behaviour of a single equation, it is natural to keep the assumptions for R_1, R_2, n_1^0 and n_2^0, i.e. we assume for $i = 1, 2$ that

$$\begin{cases} R_i \in C^1\left(\mathbb{R}^d \times \mathbb{R}\right) \\ n_i^0 \geq 0 \in L^1(X) \end{cases} \tag{26}$$

and that there exist ρ_i^m, ρ_i^M, d_i such that

$$\begin{cases} \forall x \in X,\, R_i(x, \rho_i^m) \geq 0 \\ \forall x \in X,\, R_i(x, \rho_i^M) \leq 0 \\ \frac{\partial R_i}{\partial \rho_i} \leq -d_i \end{cases} \tag{27}$$

As for the coupling functions R_{12} and R_{21}, we will assume they are $C^1\left(\mathbb{R}^d \times \mathbb{R}\right)$ functions, and there exist some non-negative constants C_{12}, C_{21} such that

$$\begin{cases} \frac{\partial R_{12}}{\partial \rho_2} \leq C_{12} \\ \\ \frac{\partial R_{21}}{\partial \rho_1} \leq C_{21} \end{cases} \tag{28}$$

If we are in the model case (18), with constant coefficients in x, it is clear that ρ_1, ρ_2 satisfy a classical Lotka-Volterra system as in section (2). This is the reason why we will assume

$$d_1 d_2 > C_{12} C_{21} \tag{29}$$

which (as will be proved thereafter) will be the condition under which blow-up is avoided. The Lotka-Volterra case then shows that these are optimal conditions.
Still from the simpler case with constant coefficients, it is possible to infer possible bounds for ρ_1, ρ_2. Indeed, if $R_1(x, \rho_1) = r_1 - d_1 \rho_1$ and $R_{12}(x, \rho_2) = C_{12}\, \rho_2$ (and similarly for the second equation), then $\rho_{1,2}^M = \frac{r_{1,2}}{d_{1,2}}$. From the values $\hat{\rho}_1$ and $\hat{\rho}_2$, we thus define $\bar{\rho_1}$ and $\bar{\rho_2}$ (by substituting $d_{1,2}\, \rho_{1,2}^M$ for $r_{1,2}$):

$$\begin{cases} \bar{\rho}_1 = \dfrac{d_2\left(d_1 \rho_1^M + C_{12} \rho_2^M\right)}{d_1 d_2 - C_{12} C_{21}}, \\ \\ \bar{\rho}_2 = \dfrac{d_1\left(d_2 \rho_2^M + C_{21} \rho_1^M\right)}{d_1 d_2 - C_{12} C_{21}} \end{cases} \tag{30}$$

Consequently, we have:

$$-d_1\left(\bar{\rho}_1 - \rho_1^M\right) + C_{12}\bar{\rho}_2 = -d_2\left(\bar{\rho}_2 - \rho_2^M\right) + C_{21}\bar{\rho}_1 = 0 \tag{31}$$

4.2.2 A priori bounds for ρ_1 and ρ_2

In order to prove that ρ_1 and ρ_2 are indeed bounded above by $\bar{\rho}_1$ and $\bar{\rho}_2$ respectively, we use the sub-solution and supersolution technique.
The classical theorem of sub-solution and supersolution for ODEs is usually stated in the case of a one-dimensional ODE. Its extension to a system requires some monotonicity assumptions, this is why we state (or recall) the result thereafter (in a fairly general fashion that is sufficient for our purpose here):

Lemma 4.5. *Let I be an interval of $\mathbb{R}$. Let f_1, $f_2 : I \times \mathbb{R}^2 \to \mathbb{R}$ be two functions that satisfy the hypotheses of Cauchy Lipschitz (i.e. they are continuous and locally Lipschitz with respect to the second variable). Also suppose that for all $(t, x_1, x_2) \in I \times \mathbb{R}^2$, the functions $f_1(t, x_1, \cdot)$ and $f_2(t, \cdot, x_2)$ are non-decreasing. Let (x_1, x_2) a couple of functions solving the following Cauchy*

problem

$$\begin{cases} \dfrac{dx_1}{dt} = f_1(t, x_1, x_2) \\ \dfrac{dx_2}{dt} = f_2(t, x_1, x_2) \\ x_1(t_0) = x_1^0,\ x_2(t_0) = x_1^0 \end{cases}$$

on some sub-interval J of I with $t_0 \in J$.
Suppose we have a sub-solution of the equation on J, i.e. a couple of functions (u_1, u_2) such that, on J:

$$\begin{cases} \dfrac{du_1}{dt} \leq f_1(t, u_1, u_2) \\ \dfrac{du_2}{dt} \leq f_2(t, u_1, u_2) \\ u_1(t_0) \leq x_1^0,\ u_2(t_0) \leq x_1^0 \end{cases}$$

Then, for all $t \geq t_0$, $t \in J$:

$$u_1(t) \leq x_1(t),\ u_2(t) \leq x_2(t)$$

We now state the theorem:

Theorem 4.6. *Suppose we have a solution of (15) in $\left(C\left(\mathbb{R}_+, L^1(X)\right)\right)^2$, and that the initial data is such that for $i = 1, 2$: $\rho_i^m \leq \rho_i^0 := \int_X n_i^0(x)\, dx \leq \bar{\rho}_i$.*
Then, for all $t > 0$ and $i = 1, 2$:

$$\rho_i^m \leq \rho_i(t) \leq \bar{\rho}_i$$

Proof. The lower bounds are straightforward, as the sign assumption (20) ensures that the technique used for the single equation is still valid.

For the upper bound, we estimate the different terms (focusing on the first equation).

- Using assumption (21), $R_{12}(x, \rho_2) \leq C_{12}\, \rho_2$ for all x.
- For $x \in X$, $R_1(x, \rho_1) = R_1\left(x, \rho_1^M\right) + \frac{\partial R_1}{\partial \rho_1}(x, \tilde{\rho})\left(\rho_1 - \rho_1^M\right)$ for a certain $\tilde{\rho}$ depending on x. This allows us to bound by (27) $R_1(x, \rho_1) \leq \frac{\partial R_1}{\partial \rho_1}(x, \tilde{\rho})\left(\rho_1 - \rho_1^M\right)$. At this stage, we have not managed to compare the equation with the expected "Lotka-Volterra" one, i.e. we cannot write $R_1(x, \rho_1) \leq -d_1\left(\rho_1 - \rho_1^M\right)$ in general. Indeed, we have to distinguish at whether ρ_1 is above ρ_1^M to be able to do so.

First note that if $C_{12} = 0$, then $R_{12} \equiv 0$ and the bound follows from the single equation case (since $\bar{\rho}_1 = \rho_1^M$ if $C_{12} = 0$). That allows us to consider only the case of $C_{12}, C_{21} > 0$, which is equivalent to $\bar{\rho}_1 > \rho_1^M$, $\bar{\rho}_2 > \rho_2^M$.

For a generic interval $I := [t_1, t_2]$ $(t_2 > t_1)$ suppose that ρ_1 and ρ_2 are above ρ_1^M and ρ_2^M respectively, globally on I.
Then, we can write on I from the previous estimations above:

$$\frac{d\rho_1}{dt} \leq \left[-d_1\left(\rho_1 - \rho_1^M\right) + C_{12}\rho_2 \right] \rho_1$$

The same reasoning for the second equation implies that (ρ_1, ρ_2) satisfies the following differential system of inequalities on I:

$$\begin{cases} \dfrac{d\rho_1}{dt} & \leq \left[-d_1 \left(\rho_1 - \rho_1^M\right) + C_{12}\rho_2 \right] \rho_1 \\ \dfrac{d\rho_2}{dt} & \leq \left[-d_2 \left(\rho_2 - \rho_2^M\right) + C_{21}\rho_1 \right] \rho_2 \end{cases}$$

(ρ_1, ρ_2) is thus a sub-solution of the system

$$\begin{cases} \dfrac{d\widetilde{\rho_1}}{dt} = \left[-d_1 \left(\widetilde{\rho_1} - \rho_2^M\right) + C_{12}\widetilde{\rho_2} \right] \widetilde{\rho_1}, \\ \dfrac{d\widetilde{\rho_2}}{dt} = \left[-d_2 \left(\widetilde{\rho_2} - \rho_2^M\right) + C_{21}\widetilde{\rho_1} \right] \widetilde{\rho_2}, \end{cases}$$

with initial conditions chosen to be $\widetilde{\rho_1}(t_1) = \rho_1(t_1)$, $\widetilde{\rho_2}(t_1) = \rho_2(t_1)$.
This system is a Lotka-Volterra one, as introduced in the previous section, whose solutions are thus globally defined and they remain below $\bar{\rho}_1$ and $\bar{\rho}_2$ respectively. The functions involved clearly satisfy the assumptions of the lemma, allowing us to state:

$$\forall t \in I,\ \rho_1(t) \leq \widetilde{\rho_1}(t) \leq \bar{\rho}_1,\ \rho_2(t) \leq \widetilde{\rho_2}(t) \leq \bar{\rho}_2$$

We can now conclude the theorem : suppose by contradiction that there exists $t_0 > 0$ such that $\rho_1(t_0) > \bar{\rho}_1$ or $\rho_2(t_0) > \bar{\rho}_2$.
We can thus define $t^\star := inf\left\{t < t_0 \text{ such that } \rho_1(t) > \bar{\rho}_1 \text{ or } \rho_2(t) > \bar{\rho}_2\right\}$, and the assumption above ensures that $t^\star < t_0$. Also, $\rho_1(t^\star) = \bar{\rho}_1$ or $\rho_2(t^\star) = \bar{\rho}_2$ and without loss of generality we can consider only the case when $\rho_1(t^\star) = \bar{\rho}_1$.
We compute

$$\begin{aligned} \frac{d\rho_1}{dt}(t^\star) &= \left[-d_1 \left(\bar{\rho}_1 - \rho_1^M\right) + C_{12}\rho_2(t^\star) \right] \bar{\rho}_1 \\ &= C_{12} \left(\rho_2(t^\star) - \bar{\rho}_2\right) \bar{\rho}_1 \end{aligned}$$

If $\rho_2(t^\star) < \bar{\rho}_2$, then the right hand side is negative, which means that in the immediate past of t_1, ρ_1 was strictly above $\bar{\rho}_1$, a contradiction.
If $\rho_2(t^\star) = \bar{\rho}_2$, this is not enough to conclude.
However, thanks to $\bar{\rho}_1 > \rho_1^M$, $\bar{\rho}_2 > \rho_2^M$, this implies that, locally around $t^\star$ (say on $I = [t^\star, t_2]$ with $t_2 > t^\star$), $\rho_1 > \rho_1^M$ and $\rho_2 > \rho_2^M$, so that the differential system of inequalities holds true on I. From that we deduce that both functions remain below $\bar{\rho}_1$, $\bar{\rho}_2$ on I, which would imply $t^\star \geq t_2$, a contradiction. □

Remark 4.7. *The proof above also works if we had kept the functions ψ in the definition of functions φ. If they are bounded on X by ψ_i^M, then $\bar{\rho}_i$ $(i = 1, 2)$ has to be changed by substituting $C_{12}\psi_1^M$ to C_{12} and $C_{21}\psi_2^M$ to C_{21}, respectively.*

4.2.3 Existence and uniqueness

As the proof of existence and uniqueness for the system (15) resembles the one used in the single equation case, we do not give it here.

4.3 Asymptotics

4.3.1 Convergence for ρ_1 and ρ_2

In order to prove that both ρ_1 and ρ_2 converge, we use the same approach as for equation, i.e. we prove that they are BV functions on $\mathbb{R}_+$. However, there is no reason here that this limit should be $\bar{\rho}$ as the bounds $\frac{\partial R_i}{\partial \rho_i} \leq -d_i$ and $\frac{\partial R_{ij}}{\partial \rho_2} \leq C_{ij}$ are not necessarily attained for the same trait.
More importantly, the convergence is obtained under a restrictive condition.

Proposition 4.8. *If*

$$d_1 d_2 \rho_1^m \rho_2^m > C_{12} C_{21} \bar{\rho}_1 \bar{\rho}_2, \tag{32}$$

then ρ_1 and ρ_2 are BV functions and thus converge.

Proof. We define $q_1 := \dfrac{d\rho_1}{dt}$ and differentiate $\dfrac{d\rho_1}{dt} = \int n_1 \left[R_1 + R_{12}\right]$ to obtain:

$$\frac{dq_1}{dt} = \int n_1 \left[R_1 + R_{12}\right]^2 + \left(\int n_1 \frac{\partial R_1}{\partial \rho_1}\right) q_1 + \left(\int n_1 \frac{\partial R_{12}}{\partial \rho_2}\right) q_2$$

It provides an upper bound for the negative part of q_1:

$$\begin{aligned}
\frac{d(q_1)_-}{dt} &\leq \left(\int n_1 \frac{\partial R_1}{\partial \rho_1}\right) (q_1)_- + \left(\int n_1 \frac{\partial R_{12}}{\partial \rho_2}\right) (q_2)_- \\
&\leq -d_1 \rho_1 (q_1)_- + C_{12} \rho_1 (q_2)_- \\
&\leq -d_1 \rho_1^m (q_1)_- + C_{12} \bar{\rho}_1 (q_2)_-
\end{aligned}$$

Together with the same inequalities for the second equation, this yields the following system:

$$\begin{cases}
\dfrac{d(q_1)_-}{dt} & \leq -d_1 \rho_1^m (q_1)_- + C_{12} \bar{\rho}_1 (q_2)_- \\
\dfrac{d(q_2)_-}{dt} & \leq -d_2 \rho_2^m (q_2)_- + C_{21} \bar{\rho}_2 (q_1)_-
\end{cases}$$

Using the lemma (4.5) (or more precisely a generalization of it), this implies that we have globally on $\mathbb{R}_+$: $(q_1)_- \leq y_1$ and $(q_2)_- \leq y_2$ where (y_1, y_2) solves the corresponding system with same initial conditions:

$$\begin{cases}
\dfrac{dy_1}{dt} & = -d_1 \rho_1^m y_1 + C_{12} \bar{\rho}_1 y_2 \\
\dfrac{dy_2}{dt} & = -d_2 \rho_2^m y_2 + C_{21} \bar{\rho}_2 y_1
\end{cases}$$

From assumption (32), the matrix associated to this linear differential system has negative trace and positive determinant. The functions y_1 and y_2 consequently both converge exponentially to 0, and so do $(q_1)_-$ and $(q_2)_-$.
The upper bound on ρ_1 and ρ_2 finally ensures that both functions are BV.

□

Remark 4.9. *Note that the condition (32) is stronger than (24). Also note that the first (and thus, the latter) is automatically verified if the interspecific competition is very small compared to the intraspecific competition.*
At this stage, it is not clear if oscillations can exist if (24) is met, but not (32). No oscillations have been observed numerically in this case.

Remark 4.10. *By differentiating $u = max\left((q_1)_-, (q_2)_-\right)$, one can check that the conclusion also holds in the case where*

$$d_1 \rho_1^m + d_2 \rho_2^m > C_{12} \bar{\rho}_1 + C_{21} \bar{\rho}_2, \tag{33}$$

5 Parametrization of the model

We now wish to investigate techniques to parametrize the canonical model we have introduced in the second section. By parametrizing, we mean first identify key terms in the equations (and, doing so, neglect some of them if necessary), then estimate the functions involved in the remaining terms.
Two strategies will be presented: the first one consists of trying to obtain explicit formulas for the solutions in a simplified setting, the second to produce numerical simulations.

5.1 With explicit formulas

5.1.1 Main ideas and model simplification

Although the following calculations might be generalized to a system (which would require further questionable simplifications), we here focus on trying to get explicit solutions for a single equation. This can allow for estimating parameters or terms which are not involved in the interaction. We will consider the following equation structured by $x \in \mathbb{R}$, which can be seen as a simplification of the equation (1):

$$\frac{\partial n}{\partial t}(t,x) + v\,\frac{\partial n}{\partial x}(t,x) = \beta\,\frac{\partial^2 n}{\partial x^2}(t,x) + R\left(x,\rho(t)\right)n(t,x). \tag{34}$$

$$R\left(x,\rho\right) := \left(\gamma - \epsilon x^2\right) - d\rho \tag{35}$$

and Gaussian initial condition of total mass ρ_0, mean μ_0 and standard deviation σ_0. In other words, the initial condition is:

$$n(0,x) = n_0(x) := \frac{\rho_0}{\sqrt{2\pi}\sigma_0} e^{-\frac{(x-\mu_0)^2}{2\sigma_0^2}} \tag{36}$$

The idea is then to search for a solution $n(t,x)$ which has a Gaussian shape for every $t > 0$. This probability distribution is natural since it solves the Fokker-Planck equation, i.e. the previous one without the R term. It also has biologically grounds, because a classical argument is to say that complex systems can be seen as the result of adding many independent random events. In such a case, assuming that these events are independent and identically distributed, the central limit theorem ensures that the limiting distribution should be Gaussian.

Here is a list of the simplifications, the reason behind each of them and potential drawbacks.

- $x \in \mathbb{R}$
  This assumption is needed in order to have an Gaussian solution. Although it might seem very restrictive, or in contradiction with the fact that a compact set of traits can be expected, this feature of the new model does not necessarily lead to a great loss of mass ρ: the selection term R can ensure that the population remains centered on traits that make sense biologically. The tails at infinity, as it is usually done in such cases, do not make sense biologically but can be neglected. A real drawback in terms of modelling is the fact that if x is seen as the concentration level of a protein, concentration of the population around a very low level of expression cannot really be expected to look Gaussian. Also, it is not necessarily the case that the initial condition is Gaussian.

- Constant functions v and d
  From comparing the model (34) to (1), one can see that we here take constant velocity $v(x) := v$ and constant death rate $d(x) := d$. Both make computations possible. The first doesn't allow for modelling the fact that near boundaries (i.e. traits that cannot be overpassed biologically), we can expect that the velocity vanishes. The second is usual for the modelling of cells.

- Shape of R
  The shape of R, especially the birth rate given by $\gamma - \epsilon x^2$, means that the trait $x = 0$ has a selective advantage over all others. A polynomial of order at most 2 is necessary to perform calculations.

5.1.2 Explicit formulas

From the previous considerations, we thus look for a Gaussian solution to equation (34), given by:

$$n(t,x) = \frac{\rho(t)}{\sqrt{2\pi}\sigma(t)} e^{-\frac{(x-\mu(t))^2}{2\sigma(t)^2}} \tag{37}$$

Plugging this formula into the equation and solving several differential equations for functions σ, μ and ρ leads to an explicit solution. Also, we prove that all three functions converge. The full computations and proofs can be found in appendix C.

Formula for σ
We define $a := 2(\epsilon\beta)^{\frac{1}{2}}$ and

$$\sigma_\infty := \left(\frac{\beta}{\epsilon}\right)^{\frac{1}{2}}. \tag{38}$$

The variance σ^2 is given by

$$\sigma^2(t) = \begin{cases} \sigma_\infty^2 \tanh(\alpha + at) & \text{if } \sigma_0 < \sigma_\infty \text{ with } \alpha := \operatorname{arctanh}\left(\frac{\sigma_0^2}{\sigma_\infty^2}\right) \\ \sigma_\infty^2 & \text{if } \sigma_0 = \sigma_\infty \\ \sigma_\infty^2 (\tanh(\widetilde{\alpha} + at))^{-1} & \text{if } \sigma_0 > \sigma_\infty \text{ with } \widetilde{\alpha} := \operatorname{arctanh}\left(\frac{\sigma_\infty^2}{\sigma_0^2}\right) \end{cases} \tag{39}$$

Whatever the case, $\lim_{t\to+\infty} \sigma(t) = \sigma_\infty$, and the convergence is exponential and controlled by $2a = 4(\epsilon\beta)^{\frac{1}{2}}$ when the variance is not identically equal to σ_∞.
The asymptotic value is increasing with the rate of random epimutations, decreasing with the strength of the selection. However, the speed of convergence to this asymptotic value is increasing with both.

Formula for μ
The mean μ is given by

$$\mu(t) = e^{-2\epsilon\int_0^t \sigma^2(s)\,ds}\left[\mu_0 + v\int_0^t e^{2\epsilon\int_0^s \sigma^2(z)\,dz}\,ds\right]. \tag{40}$$

This expression can be made more explicit through cumbersome integrations (see the appendix for an example).
More interesting is the fact that μ has a limit, given by

$$\mu_\infty := \frac{v}{a} = \frac{v}{2(\epsilon\beta)^{\frac{1}{2}}} \tag{41}$$

Thus, although $x = 0$ has a selective advantage, it is not selected: there is a compromise between the drift v and the selection strength ϵ which leads to the selection of another trait.

Formula for ρ
Defining the function $Q := \gamma - \epsilon(\sigma^2 + \mu^2)$, we have a formula for the total mass ρ:

$$\rho(t) = \left(e^{-\int_0^t Q(s)\,ds}\left[\frac{1}{\rho_0} + d\int_0^t e^{\int_0^s Q(z)\,dz}\,ds\right]\right)^{-1} \tag{42}$$

The asymptotic behaviour of ρ depends on $Q_\infty := \gamma - \epsilon\left(\sigma_\infty^2 + \mu_\infty^2\right)$.
If $Q_\infty < 0$, then ρ goes to 0: the whole population dies. If $Q_\infty > 0$, ρ converges to $\rho_\infty := \frac{d}{Q_\infty}$, i.e. to

$$\rho_\infty = \frac{1}{d}\left[\gamma - \left((\epsilon\beta)^{\frac{1}{2}} + \frac{v^2}{4\beta}\right)\right]. \tag{43}$$

Note that the extinction is possible, since the birth rate $\gamma - \epsilon x^2$ becomes negative for x great enough (which can be seen as a way of saying that such individuals are not viable). The formula for Q_∞ is coherent with this idea: γ has to be great enough, notably with respect to the asymptotical mean μ_∞ (the selected trait).

5.2 By means of numerical simulations

5.2.1 Numerical scheme

To present how the equation (3) can be simulated, we focus on the principles behind the simulation of a single equation, i.e. (1) since it generalizes immediately to two equations and it makes notations simpler. We recall the equation thereafter, together with the Neumann boundary conditions and initial conditions:

$$\begin{cases} \dfrac{\partial n}{\partial t}(t,x) + \dfrac{\partial}{\partial x}\left(v(x)n(t,x)\right) = \beta\,\dfrac{\partial^2 n}{\partial x^2}(t,x) + R\left(x,\rho(t)\right)n(t,x),\ t>0,\ x\in[0\,,1] \\ n(0,x) = n^0(x),\ x\in[0\,,1] \\ \dfrac{\partial n}{\partial t}(t,0) = \dfrac{\partial n}{\partial t}(t,1) = 0,\ t>0. \end{cases} \tag{44}$$

We discretize the time t on some interval $[0\,,T]$ and x in $[0\,,1]$ as follows: for given steps Δt and Δx such that $P := \frac{T}{\Delta t}$ and $K := \frac{1}{\Delta x}$ are integers, we denote $t_p := p\Delta t$ and $x_k = k\Delta x$ for generic times and traits where $p = 0,\dots,P$ and $k = 0,\dots,K$.
The goal is to approach $n(t_p,x_k)$ for such k and p's by values that we will denote n_k^p, thanks to a time-splitting scheme.
We also define $n_k^0 = n^0(x_k)$, and the scheme consists of recursively computing n_k^p for all $0\le k\le K$, incrementing p from the value 0 to $P-1$.

First step: diffusion and advection
We start by taking into account the diffusion and advection terms only, thus defining intermediate values $n_k^{p+\frac{1}{2}}$, thanks to an explicit finite-difference scheme:

$$\frac{n_k^{p+\frac{1}{2}} - n_k^p}{\Delta t} = -\frac{v(x_k)n_k^p - v\left(x_{k-1}\right)n_{k-1}^p}{\Delta x} + \beta\frac{n_{k+1}^p - 2n_k^p + n_{k-1}^p}{\Delta x^2}$$

for all $1\le k\le K-1$. This scheme is stable if both following CFL conditions hold:

$$\|v\|_{L^\infty}\frac{\Delta t}{\Delta x} < 1 \text{ and } \beta\frac{\Delta t}{\Delta x^2} < 1.$$

Neumann boundary conditions are ensured thanks to $n_0^{p+\frac{1}{2}} = n_1^{p+\frac{1}{2}}$ and $n_K^{p+\frac{1}{2}} = n_{K-1}^{p+\frac{1}{2}}$.

Second step: selection
To get a more stable scheme (but obtaining an explicit CFL condition is difficult there) for discretizing the selection term, we define $R_+ := \max(0,R)$ and $R_- := \max(0,-R)$ and use an implicit-explicit finite-difference scheme:

$$\frac{n_k^{p+1} - n_k^{p+\frac{1}{2}}}{\Delta t} = R_+\left(x_k,\rho^{p+\frac{1}{2}}\right)n_k^{p+\frac{1}{2}} - R_-\left(x_k,\rho^{p+\frac{1}{2}}\right)n_k^{p+1}$$

for all $0 \leq k \leq K$. Here $\rho^{p+\frac{1}{2}}$ is the approximation through the rectangle method of the value of ρ at the intermediate time $p + \frac{1}{2}$. In other words, $\rho^{p+\frac{1}{2}} = \Delta x \sum_{k=0}^{K} n_k^{p+\frac{1}{2}}$.

5.2.2 Examples of results

Our aim is to fix the parameters and to enlighten the role of each term the dynamics of n and ρ through presentation of simulations of the model (1). This is done in the case of a single equation to understand the main features, as data is still expected for the co-cultures in order to compare them to the model (3). Here, n is seen as the cancer cell population with phenotype x ranging from 0 (epithelial) to 1 (mesenchymal).

The parameters and functions involved in the model are $v(x) = 5.10^{-3}(1 - x^2)$, $\beta = 1.10^{-3}$ and $R(x, \rho) = r(x) - d\rho$ with $r(x) = 2.5.10^{-2}(2 - x)$, $d = 2.5.10^{-2}$.
Thus, 0 here has a selective advantage, but the drift pushes x to the right: it can be seen as a modelling of the fact that epithelial cells have a selective advantage if not under stress, but that the environment (adipocytes, for example) make them actively change their phenotype to a mesenchymal one.

Initial condition is given by $n_0(x) = \frac{C}{\sqrt{2\pi}\sigma_0} e^{-\frac{x^2}{2\sigma_0^2}}$ with initial standard deviation $\sigma_0 = 0.02$ and C a normalizing constant chosen so that $\rho(0) = 1$.
Thus, we start with a total mass equal to 1, and the phenotype is concentrated in 0.

We take $T = 1000$ and discretization parameters $\Delta t = 5.10^{-4}$ and $\Delta x = 1.10^{-2}$. For all simulations, we plot $\rho(\cdot)$ and $n(t, \cdot)$ for $t = 0$, $t = \frac{T}{2}$ and $t = T$.

1. Selection only
By selection only, we mean taking temporarily $\beta = 0$ and $v \equiv 0$.

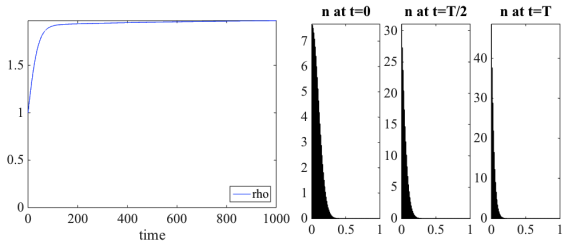

Figure 8: Numerical simulation of the solution to (1) without diffusion and advection.

From the third section, we are supposed to have convergence of ρ and of n to a Dirac mass in 0, as it is indeed the case. Also, the limit for ρ is ρ^M with the notations of the third section. Here $\rho^M = 2$ and this is what we observe numerically.

2. Selection and advection
By selection and advection, we mean taking temporarily $\beta = 0$.

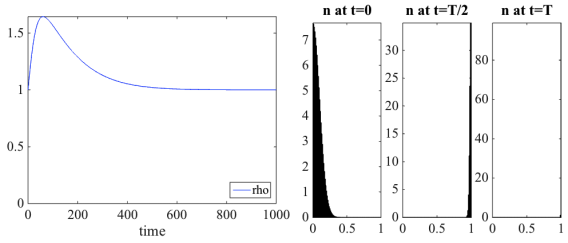

Figure 9: Numerical simulation of the solution to (1) without diffusion.

Here, we see that the advection term is strong enough to lead to a selection of $x = 1$, in the sense of convergence of n to a Dirac mass in 1. The asymptotic mass is different from the previous case.

3. Selection, advection, and diffusion
Now, all terms are considered.

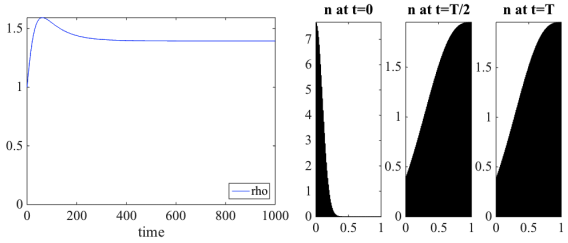

Figure 10: Numerical simulation of the solution to (1).

With diffusion, the trait 1 is still more selected than the others. However, we do not observe convergence to a Dirac mass: there is still a limiting profile but it lies in $L^1([0\,,1])$. Thus, we also still have convergence of ρ.

Let us now show numerically that with a weaker advection (i.e. $v(x) = 5.10^{-5}(1-x^2)$), there can be selection of a trait which is neither 0 nor 1. There is a thus a compromise between advection and selection, as in the explicit computations on the whole $\mathbb{R}$. The following simulations are performed with no diffusion ($\beta = 0$) and we take $T = 20000$. The selected trait is approximately 0.2.

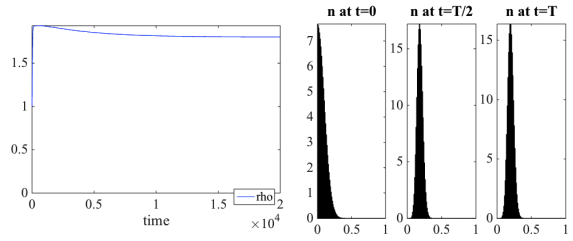

Figure 11: Numerical simulation of the solution to (1) without diffusion, and with lower advection.

A BV functions on $\mathbb{R}_+$

We here recall some results about BV functions on $\mathbb{R}_+$, i.e. functions whose derivative is integrable on $\mathbb{R}_+$.
The most important one is of course:

Proposition A.1. *Let ρ be a BV function on $\mathbb{R}_+$. Then it has a limit as t goes to $+\infty$.*

Proof. Let $(t_n)_{n\in\mathbb{N}}$ be any sequence going to $+\infty$. Then $\rho(t_n) - \rho(t_k) = \int_{t_n}^{t_k} \rho'(u)\,du$, which yields:

$$\begin{aligned}\big|\rho(t_n) - \rho(t_k)\big| &\leq \left|\int_{t_n}^{t_k} \big|\rho'(u)\big|\,du\right| \\ &\leq \int_{t_n}^{+\infty} \big|\rho'(u)\big|\,du + \int_{t_k}^{+\infty} \big|\rho'(u)\big|\,du\end{aligned}$$

Both quantity go to 0 as n and k go to $+\infty$ respectively, thanks to the integrability of f'. It proves that $(\rho(t_n))_{n\in\mathbb{N}}$ is a Cauchy sequence, which thus has a limit. We denote it by l.
Now, if $(s_n)_{n\in\mathbb{N}}$ is another sequence going to $+\infty$, we write:

$$\big|\rho(s_n) - l\big| \leq \big|\rho(s_n) - \rho(t_n)\big| + \big|\rho(t_n) - l\big|$$

The second term goes to 0 by definition of l, the first as well by the same inequalities as above. Thus all subsequences extracted from ρ converge and have the same limit, which proves the result.

□

We now state a useful lemma to prove that a function is BV.

Lemma A.2. *Let ρ be a function defined on $\mathbb{R}_+$ that is bounded from above and such that $(\rho')_-$ is integrable. Then ρ is BV on $\mathbb{R}_+$. (Of course, we have the same result if ρ is bounded from below and $(\rho')_+$ is integrable)*

Proof. Let $q := \rho'$.
For $t > 0$, we want to bound $\int_0^t \big|q(s)\big|\,ds$ independently of t, which would prove that q is an integrable function. Since $\big|q\big| = q_+ + q_- = q + 2q_-$, we can write :

$$\begin{aligned}\int_0^t \big|q(s)\big|\,ds &= \int_0^t \rho'(s)\,ds + 2\int_0^t q_-(s)\,ds \\ &= \rho(t) - \rho(0) + 2\int_0^t q_-(s)\,ds\end{aligned}$$

with all terms being bounded thanks to the hypotheses. □

B Handling positive and negative parts for ODEs

It is often useful to be able to "differentiate" the positive and negative parts of a function that satisfies an ODE.

Lemma B.1. *Let q be a function defined on $\mathbb{R}_+$ that satisfies the ODE $\frac{dq}{dt} = f(t,q)$ with f a continuous function on $\mathbb{R}_+ \times \mathbb{R}$.*
Then

$$\frac{d(q_+)}{dt} = f(t,q)\,\mathbb{1}_{\{q>0\}}.$$

Remark B.2. *the latter is to be understood in the integral sense, i.e.*

$$\forall t > 0,\ q(t)_+ - q(0)_+ = \int_0^t f(u, q(u))\, \mathbb{1}_{\{q(u)>0\}}\, du$$

Since these are Lipschitz functions, we can also say (thanks to the Rademacher's theorem) that the equality $\frac{d(q_+)}{dt} = f(t,q)\, \mathbb{1}_{\{q>0\}}$ *holds a.e. on* $\mathbb{R}_+$.

Proof. The idea is that if we denote the positive part function by s, then formally: $\frac{d}{dt}s(q) = \frac{dq}{dt}s'(q)$ with $s'(q) = \mathbb{1}_{\{q>0\}}$.
To be more rigorous, we use $(s_\delta)_{\delta>0}$, a family of smooth functions approximating the positive part function s. More precisely, we choose the family such that

$$\begin{cases} 0 \leq s_\delta \leq 1 \\ s_\delta = 0 \qquad \text{on } (-\infty\,, \delta] \\ s_\delta = x - \delta \text{ on } [2\delta\,, +\infty) \end{cases}$$

We also impose that s_δ converges uniformly towards s on $\mathbb{R}$, s'_δ converges pointwise towards $\mathbb{1}_{\{\cdot>0\}}$ on $\mathbb{R}$.
We compute

$$\begin{aligned} \frac{d}{dt}s_\delta(q) &= \frac{dq}{dt}\, s'_\delta(q) \\ &= f(t,q)\, s'_\delta(q) \end{aligned}$$

Fixing some $t_0 > 0$ and integrating on $[0\,, t_0]$, we obtain:

$$s_\delta(t_0) - s_\delta(0) = \int_0^{t_0} f(u, q(u))\, s'_\delta(q(u))\, du \tag{45}$$

The left-hand side converges to $s(t_0) - s(0)$. Also, $s'_\delta(q(u))$ converges to $\mathbb{1}_{\{q(u)>0\}}$ for all $u > 0$, and the integrated function is bounded uniformly in δ by the supremum of f on an appropriate compact set.
Since s is nothing but the positive-part function, we get the expected result.

□

Remark B.3. *With the same arguments, one can prove that:*

$$\frac{d(q_-)}{dt} = -f(t,q)\, \mathbb{1}_{\{q<0\}}.$$

C Computations for the explicit solution to the equation on $\mathbb{R}$

Recall that we wish to solve explicitly

$$\frac{\partial n}{\partial t}(t,x) + v\, \frac{\partial n}{\partial x}(t,x) = \beta\, \frac{\partial^2 n}{\partial x^2}(t,x) + R\,(x, \rho(t))\, n(t,x).$$

by assuming that we have a Gaussian initial condition

$$n(0,x) = n_0(x) := \frac{\rho_0}{\sqrt{2\pi}\sigma_0} e^{-\frac{(x-\mu_0)^2}{2\sigma_0^2}}$$

and looking for a Gaussian solution for all time $t > 0$:

$$n(t,x) = \frac{\rho(t)}{\sqrt{2\pi}\sigma(t)} e^{-\frac{(x-\mu(t))^2}{2\sigma(t)^2}}$$

Rather than computing the standard deviation σ directly, we define $\eta(t) = \dfrac{1}{2\sigma(t)^2}$ leading to:

$$n(t,x) = \rho(t)\sqrt{\frac{\eta(t)}{\pi}}e^{-\eta(t)(x-\mu(t))^2}, \tag{46}$$

so that

$$\ln(n) = \frac{1}{2}\ln\left(\frac{\eta}{\pi}\right) + \ln(\rho) - \eta\,(x-\mu)^2$$

We now compute

$$\begin{aligned}
\frac{1}{n}\frac{\partial n}{\partial t} &= \frac{1}{2}\frac{\eta'}{\eta} + \frac{\rho'}{\rho} - \eta'\,(x-\mu)^2 + 2\eta\mu'\,(x-\mu)\,,\\
\frac{1}{n}\frac{\partial n}{\partial x} &= -2\eta\,(x-\mu)\\
\frac{1}{n}\frac{\partial^2 n}{\partial x^2} &= -2\eta + 4\eta^2\,(x-\mu)^2\,.
\end{aligned}$$

Plugging it into the equation, we are led to:

$$\begin{aligned}
&\frac{1}{2}\frac{\eta'}{\eta} + \frac{\rho'}{\rho} - \eta'\,(x-\mu)^2 + 2\eta\mu'\,(x-\mu) - 2v\eta\,(x-\mu)\\
&\qquad\qquad = -2\beta\eta + 4\beta\eta^2\,(x-\mu)^2 + \left(\gamma - \epsilon x^2\right) - d\rho
\end{aligned}$$

1. Formula for σ

We start by equating the coefficients in front of x^2:

$$\eta' + 4\beta\eta^2 = \epsilon \tag{47}$$

$w := \eta - \sqrt{\frac{\epsilon}{4\beta}}$ then satisfies the ODE $w' + 4\beta w\,(w+d) = 0$ with $d := \sqrt{\frac{\epsilon}{\beta}}$.

The equation can be written $\frac{w'}{w(w+d)} = -4\beta$, and since $\frac{1}{X(X+d)} = \frac{1}{d}\left[\frac{1}{X} - \frac{1}{X+d}\right]$, integration is possible and yields:

$$w(t) = \frac{Cde^{-2at}}{1 - Ce^{-2at}}$$

where C is some constant fixed by the initial conditions and $a := 2\,(\epsilon\beta)^{\frac{1}{2}}$. Now, solving for σ, we obtain

$$\sigma^2(t) = \sigma_\infty^2\,\frac{1 - Ce^{-2at}}{1 + Ce^{-2at}}$$

with

$$\sigma_\infty^2 := \left(\frac{\beta}{\epsilon}\right)^{\frac{1}{2}}.$$

We distinguish now two cases: if the constant C is fixed from the initial condition σ_0, and we do not know its sign a priori.

Suppose first that C is positive so that we can write $C := e^{2\alpha}$ and $\sigma^2(t) = \sigma_\infty^2 \tanh(\alpha + at)$ with $\alpha := \operatorname{arctanh}\left(\frac{\sigma_0^2}{\sigma_\infty^2}\right)$. This requires $\sigma_0 < \sigma_\infty$.

If C is negative, then we end up with $\sigma^2(t) = \sigma_\infty^2\,(\tanh(\widetilde{\alpha} + at))^{-1}$ with $\widetilde{\alpha} := \operatorname{arctanh}\left(\frac{\sigma_\infty^2}{\sigma_0^2}\right)$, which requires $\sigma_0 > \sigma_\infty$.

Reciprocally, we have covered all cases (except $\sigma_0 = \sigma_\infty$ which leads to $\sigma(t) = \sigma_\infty$ for all t).

Since we clearly have $\lim_{t\to+\infty} w(t) = 0$, $\sigma(t)$ converges to σ_∞.

2. Formula for μ

We now equate the coefficients in front of x^1 to uncover:

$$2\eta'\mu + 2\eta\mu' - 2v\eta = -8\beta\eta^2\mu$$

which can be written $\left(\eta' + 4\beta\eta^2\right)\mu + \eta'\mu - v\eta = 0$. Thanks to (47), this leads to the following ODE:

$$\mu' + 2\epsilon\sigma^2\mu = v, \tag{48}$$

an equation providing a formula for $\mu(t)$:

$$\mu(t) = e^{-2\epsilon\int_0^t \sigma^2(s)\,ds}\left[\mu_0 + v\int_0^t e^{2\epsilon\int_0^s \sigma^2(z)\,dz}\,ds\right].$$

This can be made more explicit since the function σ^2 has an explicit primitive.[2]

Let us study the asymptotics for μ. Given the convergence of σ towards σ_∞, it is natural to compare μ to the solution $\tilde{\mu}$ of the equation:

$$\tilde{\mu}' + 2\epsilon\sigma_\infty^2\tilde{\mu} = v$$

which converges asymptotically to

$$\mu_\infty := \frac{v}{a}.$$

Our aim is to prove that this also holds true for μ.

We first notice that σ is bounded from below by a positive constant. This allows us to write $\mu' + a\mu \le v$ for some positive constant a. Integrating this differential inequality shows that μ is bounded.

We now define $g := \mu - \tilde{\mu}$ and we are left with proving that g converges to 0 in order to identify the limit for μ. We compute a differential equation for g:

$$\begin{aligned} g' &= 2\epsilon\sigma_\infty\tilde{\mu} - 2\epsilon\sigma\mu \\ &= -2\epsilon\sigma_\infty g + 2\epsilon\left(\sigma_\infty - \sigma\right)\mu \end{aligned}$$

Given that μ is bounded, $2\epsilon\left(\sigma_\infty - \sigma\right)\mu$ goes to 0 as t goes to $+\infty$, which is enough to prove, after integration, that g converges to 0 as well.

3. Formula for ρ

We finally equate the constant coefficients:

$$\frac{1}{2}\frac{\eta'}{\eta} + \frac{\rho'}{\rho} - \eta'\mu^2 - 2\eta\mu'\mu + 2v\eta\mu = -2\beta\eta + 4\beta\eta^2\mu^2 + \gamma - d\rho$$

We rewrite this as:

$$\frac{\rho'}{\rho} = \left[-\frac{1}{2}\frac{\eta'}{\eta} - 2\beta\eta + \gamma\right] + \mu\left[\eta'\mu + 4\beta\eta^2\mu + 2\eta\mu - 2v\eta\right] - d\rho$$

[2]For example, in the case where $\sigma_0 < \sigma_\infty$,

$$\mu(t) = \frac{\cosh\alpha}{\cosh\left(\alpha + at\right)}\left[\mu_0 - \frac{v}{a}\frac{\sigma_0^2}{\sigma_\infty^2}\right] + \frac{v}{a}\tanh\left(\alpha + at\right)$$

From (47) and (48), the first bracket is equal to $-\frac{\epsilon}{2\eta}+\gamma$, the second to $-\epsilon\mu^2$. We end up with an ODE for ρ:

$$\frac{\rho'}{\rho} = Q - d\rho \tag{49}$$

where the function Q is given by $Q := -\frac{\epsilon}{2\eta}+\gamma-\epsilon\mu^2 = \gamma - \epsilon\left(\sigma^2+\mu^2\right)$.
To solve it, we define $h := \frac{1}{\rho}$ for which we have the ODE:

$$h' + Qh = d$$

Because it satisfies this ODE, h cannot change sign. Consequently, this is also true for ρ which is positive for all time. ρ is given by:

$$\rho(t) = \left(e^{-\int_0^t Q(s)\,ds}\left[\frac{1}{\rho_0} + d\int_0^t e^{\int_0^s Q(z)\,dz}\,ds\right]\right)^{-1}$$

where all integrals could be actually be computed more explicitly.
As for μ, we focus on studying the asymptotical behaviour of ρ. Since Q has a limit given by $Q_\infty := \gamma - \epsilon\left(\sigma_\infty^2+\mu_\infty^2\right)$, which we assume to be a positive quantity, the same arguments applied to (48) can be used to prove that h converges to $\frac{d}{Q_\infty}$.
Eventually, it ensures that ρ converges to $\rho_\infty := \frac{Q_\infty}{d}$. As a function of the original parameters only, it is given by:

$$\rho_\infty = \frac{1}{d}\left[\gamma - \left((\epsilon\beta)^{\frac{1}{2}} + \frac{v^2}{4\beta}\right)\right].$$

If Q_∞ is negative, the arguments above do not apply and the formula for ρ actually shows that it converges to 0.

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