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Mathematical modelling of cancer: an ecological approach to the multiple myeloma bone disease

Relatore:
Prof. Marco Formentin

Laureanda:
Enia Ottavi
171072

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Introduction

During the past decades, the study of cancer has stimulated investigations in several scientific areas. Mathematicians, physicists and bioinformaticians tackled the problem with different approaches including modeling and simulations.
The purpose is to understand the dynamics inside the development of this disease and try to design good therapies to the patient affected.
Thus, large amounts of clinical data and quantitative models are required to reveal the key mechanism in cancer dynamics, therefore it is very difficult to give a proper approximation for each different situation.
In this landscape, the ecology of cancer has proved to have a crucial rule. In fact it has emerged that a mathematical model for cancer must take into account the evolutionary and ecological processes characterizing cancer dynamics.
Within the framework of cancer ecology, cancer can be considered as a result of interactions between cancerous cells and normal cells within a tissue, which becomes the microenviroment where this dynamics takes place.
In this thesis, we focus on the multiple myeloma bone disease, a malignant cell neoplasma within the bone tissue. Using tools of evolutionary game theory, we provide a model of the evolutionary dynamics in a healthy bone tissue and also in an insane tissue due to the development of the tumor.
The present thesis is organized as follows:
in the first chapter, we are going to provide a biological definition of cancer and how tools of cancer ecology are useful to describe cancer dynamics;
in the second chapter we describe a healthy bone tissue and how it is captured in terms of evolutionary game theory;
in the third chapter we describe the dynamics of a bone affected by multiple myeloma disease, paying more attention in how it dynamics evolves according to its fixed points;
in the last chapter we conclude by saying how this study can be applied to the therapies in order to get an improvement on patients.

Chapter 1

Cancer ecology

1.1 Mutation and cancer

Cancer is a genetic disease of multicellular organism, consequence of the accumulation of somatic mutations. It is characterized by an interruption of individual cells cooperation and a consequent growth of abnormal cells.
In fact, a single genetically altered cell going under uncontrolled replication and mutation, leads to the start of the progression of the cancer and to the following spread of invasive cells through a series of clonal expansions.[1].
It can be *benign* if it is localized in *situ* or *malignant* if it is invasive and causes metastasis.
Moreover, not all the possible somatic mutations that can occur are involved in the cancer expansion, in fact only the ones conferring a growth advantage enable these altered cells to more efficiently spread in the tissue.
In addition to that, also many different external factors, not strictly related to the above mentioned mutations, can cause a damage on the healthy cells genome.
All of these elements explain the diversity of mutation observed in tumor.
For this reason cancer can be considered as the result of a process of Darwinian evolution among cell populations embedded in their environment. As a Darwinian process, its development is marked by two features: firstly, the continuous acquisition of heritable genetic variations in individual cells by random mutations and secondly, the natural selection acting on the resultant phenotypic diversity. Therefore the tumorigenesis can be considered similar to the evolution of species.

1.2 Cancer ecology

The insurgence of cancer disrupts the cellular environment, introducing many uncontrolled interactions within healthy tissues. It is possible, as we said, to consider this process as an evolution of species where different types of cells are different species interacting with each other in an ecologic environment. Cancerous cells constitute an additional species, which entangles in the network and favors some species, damages others or does both at the same time.
The coexistence of several cell types suggests that the dynamics may be driven by mutualistic, exploitative, harmful or other type of ecological interactions. [1]
From this ecological perspective, cancer is a dynamical disease that continuously evolves and diversifies as an adaptive Darwinian system.
Moreover, the study of the interaction between malignant cells and their environment, based on the exchange of information in form of cytokines [2], gives more information about the dynamics of the tumor growth and its response to the therapy.
This interplay creates a complex signaling process that imposes costs and benefits to the participant cells. It can be conveniently recast in the form of a game pay-off matrix. Therefore the ensuing dynamics is well described in terms of evolutionary game theory [4].

1.3 Evolutionary game theory applied to cancer

In this section we are going to provide some tools of the evolutionary game theory (EGT) that can be used as an ecological approach of cancer.
The appearance of mutated cells may be described in terms of a new species that attempts to invade a resident species of normal cells. In this landscape, we can provide a description equivalent to that of the traditional equations of ecology.
The central equation of EGT is called *Replicator Equation (RE)*, which makes

[1] A *mutualistic* ecological interaction is one where different species work together and all have benefits from this cooperation.
An *exploitative* ecological interaction, that is also called as enemy-victim interaction, is one where one organism is the consumer of the other.

[2] Cytokines are substances secreted by cells of the immune system.

use of the concept of fitness [3] [5] .
It is usually used to describe the temporal evolution of many groups of cells, in particular the ecosystems with constant resources, since one of its properties is that the sum of the different populations, treated by this equation, stays constant over time.
We will show how it can be derived from an exponential model.

1.3.1 Replicator equation from exponential model

We now consider the classic exponential growth equation:

$$\dot{N}_i[t] = N_i f_i \qquad i = 1, .., n \tag{1.1}$$

Where N_i is a real function that represents the population of strategy i, strategies in our approximation stand for the different types of population interacting in the ecosystem, and $f_i(N_i, .., N_n)$ is the fitness of that strategy. Now we consider the relative frequencies defined as $x_i \equiv \frac{N_i}{P}$ where P is the total population and we get:

$$P[t] = \sum_i N_i[t] \tag{1.2}$$

We derive it and use the above mentioned model of exponential growth :

$$\dot{P} = \sum_i \dot{N}_i = \sum_i N_i f_i \tag{1.3}$$

Multiplying and dividing for P:

$$\dot{P} = P \sum_i \frac{N_i}{P} f_i = P \sum_i x_i F_i = P \langle F \rangle$$

where $\langle F \rangle = \sum_i x_i f_i$ is the average fitness of whole population.
We take the derivative of x_i and we have:

$$\dot{x}_i = \frac{\dot{N}_i}{P} - \frac{N_i \dot{P}}{P^2} = \frac{N_i f_i}{P} - \frac{N_i}{P}\frac{\dot{P}}{P} = x_i (f_i - \langle F \rangle)$$

where

$$\frac{\dot{P}}{P} = \langle F \rangle$$

[3] In biology, *fitness* is defined as the quantitative representation of individual reproductive success.

Now we add on all the species and use the definition of $\langle F \rangle$ and we get:

$$\sum_i \dot{x}_i = \sum_i x_i f_i - \langle F \rangle \sum_i x_i = \sum_i x_i f_i - \sum_j x_j f_j \sum_i x_i \tag{1.4}$$

Considering that:

$$\sum_i x_i = \frac{\sum_i f_i}{P} = \frac{P}{P} \equiv 1$$

The Equation 1.4 becomes:

$$\sum_i \dot{x}_i \equiv 0$$

Now we cast away the environmental effects that can modify the fitness of the strategies and analyze the competition between the several strategies in the total population.
We can assume that:

$$f_i\left(N_1, ..., N_n\right) = F_i\left(\frac{N_1}{P}, .., \frac{N_n}{P}\right) = F_i\left(x_1, .., x_n\right)$$

With this assumption, the equation

$$\dot{x}_i = x_i\left(f_i - \langle F \rangle\right)$$

becomes the replicator equation:

$$\dot{x}_i = x_i\left(F_i - \langle F \rangle\right) \tag{1.5}$$

where now $\langle F \rangle = \sum_i x_i F_i$ is expressed in terms of the relative frequencies x_i. In this way we obtain the general form of the replicator equation.

1.3.2 The replicator equation in dynamics

As we have already explained, tumour progression and dynamics can be described in terms of evolutionary game theory, assuming that:

- the strategies are the types of populations interacting,
- the payoffs, defined as the reproductive rate of the species, can be considered equivalent to the fitness of each population,
- the replicator equation predicts the evolutionary outcome of population behavior.

We define an *evolutionary stable strategy* as the behavior that when it is adopted by all the members of a population, it is impossible for another population to invade it. It is proved to be stable from the dynamics point of view.
Formally we define it in the following way:

Definition 1.1. *If $W(I,Q)$ is the fitness of an individual of type I in a population of composition Q. A population consisting of I-types will be evolutionary stable if whenever a small amount of deviant J-types is introduced, the old type I fares better that the newcomers J. So for all $J \neq I$,*

$$W(J, \epsilon J + (1-\epsilon) I) < W(I, \epsilon J + (1-\epsilon) I)$$

for all sufficiently small $\epsilon > 0$.

Now we define the simplex

$$S_N = \left\{ p = (p_1, .., p_N) \in \mathbb{R}^N : \sum_{i=1}^{N} p_i = 1, p_i \geq 0, i = 1, .., N \right\}$$

where every point is a strategy and corresponds to the type of population.
We define the *state* of the population as the frequencies x_i of each type and the new matrix A where each entry $a_{ij} = p^i \cdot Up^j$ is the payoff obtained by a p^i strategist against p^j opponents.
We get that the fitness for each population is:

$$f_i(x) = \sum_j a_{ij} x_j = (Ax)_i$$

Now we'll consider the payoff matrix A as the fitness matrix of our types of population.

Definition 1.2. *We define a point $y \in S_N$ a Nash equilibrium if $x \cdot Ay \leq y \cdot Ay$ for all $x \in S$.*

So in our framework it means that a population, whose payoff-matrix is described by A, adopting a Nash equilibrium strategy reaches the higher possible pay-off, that is the higher advantage/disadvantage coming from the interaction with different type of populations.

We now provide the so- called Folk Theorem which allows us to predict the evolution of stable ecological system by studying Nash Equilibrium behavior of the populations.

Theorem 1.1. *Let y be a point of S_N then:*

- *if $y \in S_N$ is a Nash equilibrium of the game described by the payoff matrix A, then y is a rest point of the replicator equation.*
- *if y is the $\omega-$limit of an orbit $x(t) \in intS_N$, then y is a Nash equilibrium.*
- *if y is a Lyapunov stable, then it is a Nash equilibrium.*
- *if $y \in S_N$ is an evolutionarily stable state for the game with payoff matrix A, that means that $y \cdot Ax > x \cdot Ax$ for all $x \neq y$ in a neighborhood of y, then it is an asymptotically stable rest point of the RE.*

[4] In conclusion, we can study the stability properties of the replicator equation by applying the Lyapunov method, then thanks to the previous theorem we can deduce information about the adopted evolutionary strategy and the consequent dynamics.
In the following chapters we will be interested in understanding how the dynamics of the populations involved in our model evolves according to the behavior of its fixed point.

1.3.3 A particular case of the Replicator Equation

Let's now apply the RE found above to describe the evolution of two populations, one of normal cells named A and the other with mutant cells named B. In an unrealistic scenario, let us suppose that they have a constant rate of replication, respectively $\alpha > 0$ and $\beta > 0$ and an initial size $N_A(0)$ and $N_B(0)$.
Assuming infinite resources and that the overall population size increases exponentially, the equations of the time evolution of these populations are :

$$\frac{dN_A(t)}{dt} = \alpha N_A(t) \quad and \quad \frac{dN_B(t)}{dt} = \beta N_B(t) \tag{1.6}$$

Solving them we get:

$$N_A(t) = N_A(0)e^{\alpha t} \quad and \quad N_B(t) = N_B(0)e^{\beta t} \tag{1.7}$$

To understand the evolution of these two populations we have to focus on the ratio $\frac{\alpha}{\beta}$:
if $\frac{\alpha}{\beta} > 1$, the normal cells population will outnumber the mutant population, if $\frac{\alpha}{\beta} < 1$ the mutant cells population will increase over the normal cells population .

Let's consider now that the total population stays constant at a fixed value, in order to survive in the environment. This new hypothesis modifies the previous equations 1.6 in the following way:

$$\frac{dN_A(t)}{dt} = N_A(t)(\alpha - \omega) \quad and \quad \frac{dN_B(t)}{dt} = N_B(t)(\beta - \omega) \tag{1.8}$$

where ω is the average reproductive rate of the population.
Imposing the conservation of the total size of the population we get:

$$N_T\omega = \alpha N_A(t) + \beta N_B(t) \tag{1.9}$$

Now the focus is on the comparison of α and β with ω: the population in which cells replicate at a higher than average rate will outcompete the other. [5]
From Equation (1.9) instead of two equations we can choose one of the population, for example the normal cells population, and obtain just one equation:

$$\frac{dN_A(t)}{dt} = N_A(t)(N_T - N_A(t))(\alpha - \beta) \tag{1.10}$$

We now suppose that population size is large enough to convert absolute cell numbers N_A into cell frequencies x, we may write:

$$\frac{dx(t)}{dt} = x(t)(1 - x(t))(\alpha - \beta) \tag{1.11}$$

This equation is a particular case of the RE.
It describes the evolutionary dynamics of a sub-population of cells which replicate at the same constant rate α in the presence of another sub-population of cells, all of which replicate at the constant rate β, with the condition that all the total population size is constant. [5]
In this model, we can state that cells which replicate faster will be more successful than the other cells, so they will also have a higher fitness than the other. Even though it is proved that fitness of different cell types does not depend only on their reproductive rate, if we consider the appropriate fitness of each species and the average fitness of the population, we can assume rate of cell replication as a convenient equivalent concept of the fitness and use this definition on the central equations of EGT.
In equation (1.11) we have supposed that the fitness of cells of each sub-population remains constant in time (since we have imposed a constant rate of replication for each population) and that it is not influenced by the total number of cells of given species.

If size matters, we have to consider fitness as a *frequency-dependent* function. So, defining $\varphi_A(x)$- the frequency of the normal cells- and $\varphi_B(x)$ -the frequency of the mutant cells-, and replacing respectively α and β with them in (1.11), we may write the following general form of the RE:

$$\dot{x} = x(1-x)(\varphi_A(x) - \varphi_B(x)) \tag{1.12}$$

Considering a *well-mixed approximation* where all the cells interact with each other with the same likelihood, we can show the result of these interactions on the so-called *pay-off matrix*, a matrix used in the evolutionary game theory where p_{ij} represents what a cell of type i can get from the interaction with a cell of type j, the rows are the specific group of cells and the columns are the type of cells they are interacting with.

$$\begin{array}{cc} & \begin{array}{cc} A & B \end{array} \\ \begin{array}{c} A \\ B \end{array} & \left[\begin{array}{cc} p_{AA} & p_{AB} \\ p_{BA} & p_{BB} \end{array}\right] \end{array}$$

Interaction, here, stands for exchange of information and competition for space and nutrients.
Using the previous pay-off matrix, we may write:

$$\varphi_A(x) = xp_{AA} + (1-x)p_{AB}$$

$$\varphi_B(x) = xp_{BA} + (1-x)p_{BB}$$

These two equations specify the form of frequency dependence deriving from the cells competition in a population of constant size by means of EGT.
We can get Equation (1.11), with no frequency-dependence behaviour, choosing $p_{AB} = p_{AA} = \alpha$ and $p_{BA} = p_{BB} = \beta$.
In this framework, it does not matter with which cell type a focal cell interacts, the result is always the same [5] .

In the following chapters we are going to see the application of the evolutionary game theory to the case of the multiple myeloma bone disease.

Chapter 2

Application of EGT to the normal bone remodeling

As we already said, cancer causes a change in the natural equilibrium existing between the healthy cells of a tissue.
In the following sections we are going to introduce the physiology of the healthy bone tissue and then a model of the normal bone remodeling .

2.1 Healthy Bone Tissue

Bone tissue is a mineralized connective tissue that exerts important functions in the body, such as locomotion, support and protection of tissues, calcium and phosphate storage.
The cells that can be found in this tissue are *osteoblasts, osteoclasts, osteocytes*. We will focus on osteoblasts and osteoclasts.
Osteoblasts are located along the bone surface. They produce the organic matrix and regulate the deposit of the inorganic one. They are mainly known for their bone formation function.
Osteoclasts are responsible for the bone matrix degradation, in fact they reabsorb the aged, damaged or immature matrix [3] .

Bone is a dynamic organ that is continuously reabsorbed by osteoclasts and rebuilt by osteoblasts.
The complex process of bone remodeling can be described in a cycle made up of three phases:

- initiation of bone resorption by osteoclasts
- transition from resorption to new bone formation

- the bone formation by osteoblasts

It is regulated by the *RANK/RANKL signaling pathway* [1] that leads to the start of bone resorption process, followed by the action of the *osteoprotegerin (OPG)* [2] which ends this process and differentiates the cells.
In conclusion, normal bone remodeling is the result of balance crosstalk among osteoclasts, osteoblasts and signaling molecules [6] .
An imbalance of bone resorption and formation results in several bone disease.

2.2 Model of the normal bone remodeling

The dynamic balance between osteoclast-mediated (OC) bone resorption and bone formation due to osteoblast (OB) activity can be captured trivially in the framework of EGT.
It requires an explicit frequency dependence to have a proper approximation of this dynamic.
In the healthy condition, we assume that we have two cell species (OB and OC cells) living in a stable balance between them. In terms of EGT, it can be obtained by a *coexistence game*, which can be realized by a pay-off matrix satisfying $p_{BA} > p_{AA}$ and $p_{AB} > p_{BB}$:

$$\begin{array}{c} \\ OC \\ OB \end{array} \begin{array}{c} \begin{array}{cc} OC & OB \end{array} \\ \begin{bmatrix} 0 & a \\ e & 0 \end{bmatrix} \end{array}$$

where a and e are both positive reals.
The coexistence condition means that the interaction between OB and OC cells (OC-OB is represented by a and OB-OC by e) are stronger than self-interactions.
Given the pay-off matrix above, we may write:

$$\varphi_{OC}(x) = (1-x)a$$

$$\varphi_{OB}(x) = xe$$

where x stands for the fraction of OC cells and *(1-x)* stands for the fraction of OB cells.

[1] *RANKL* is the acronym of receptor activator of nuclear factor kappa-β ligand, it is a protein involved in the tissue growth and it has immune functions.
RANK, acronym of receptor activator of nuclear factor kB is the receptor for *RANKL*

[2] *Osteoprotegerin* is one the most important regulator factor and it is a type of cytokines.

Now we consider the RE of this system:

$$\dot{x} = x(1-x)(a(1-x) - ex) \tag{2.1}$$

From this equation we can study the dynamics of the system OC-OB.
Defining $f = x(1-x)(a(1-x) - ex)$ and imposing $f = 0$, we find the fixed points of the system:

$$x = 0$$
$$x = 1$$
$$x = \frac{a}{a+e}$$

We know apply the one dimensional version of the following theorem:

Theorem 2.1 (First Lyapunov theorem)**.** *Suppose that z^* is an equilibrium of the equation $\dot{z} = X(z)$ with $z \in \mathbb{R}^n$. Then*

1. *if $\frac{\partial X(z)}{\partial z}$ (z^*) has all the eigenvalues with negative real part, then z^* is asymptotically stable;*
2. *if $\frac{\partial X(z)}{\partial z}(z^*)$ has at least one eigenvalue with positive real part, then z^* is unstable*

So we derive f and obtain:

$$\frac{\partial f}{\partial x} = ex(-2+3x) + a(1-4x+3x^2) \tag{2.2}$$

Since it is a one dimensional function, to apply the previous theorem we can evaluating f in the fixed points and get:

$$f(0) = a > 0$$
$$f(1) = e > 0$$
$$f\left(\frac{a}{a+e}\right) = -\frac{ae}{a+e} < 0$$

According to the theorem, we can conclude that $x = 0$ and $x = 1$ are unstable points, while $x = \frac{a}{a+e}$ is stable.
In terms of population dynamics, this result means that populations made by one type of cells-i.e. $x = 0$ and $x = 1$- are unstable, while populations, where both OB and OC cells are present, are stable.
We can show it graphically, given the plot of $\dot{x}$. It is called *gradient of selection*, the horizontal axis shows the direction of selection associated with the sign of $\dot{x}$ in the domain of the cells fraction which is $0 < x < 1$.

We choose as parameters $\alpha = 0.5$ and $\beta = 0.5$, which will let us to prove that the stable point corresponds exactly to the perfect subdivision between the two groups of cells and therefore to their coexistence.

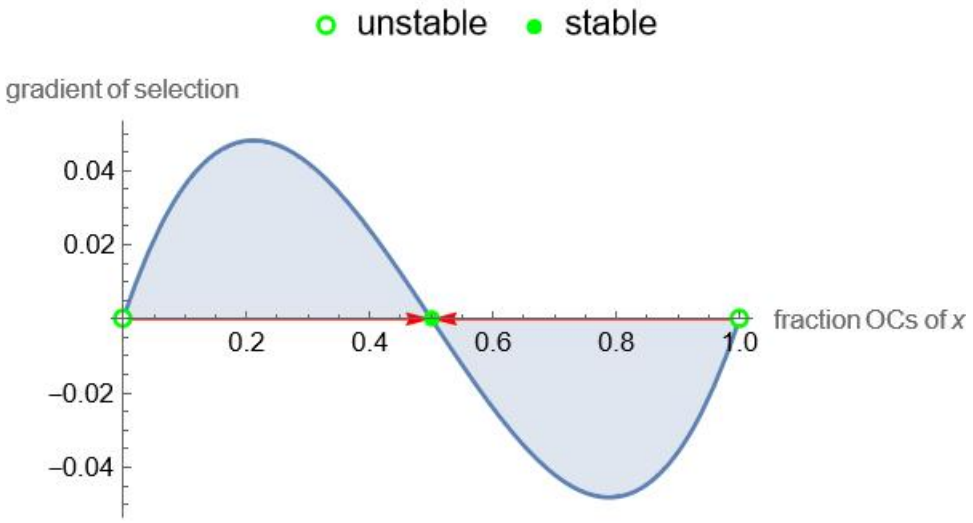

Figure 2.1: *Gradient of selection for the coexistence dynamics among OCs and OBs cells.*

The red arrows in the above figure underline the behavior of the dynamics: any perturbation deviating population from unstable points -i.e. $x = 0$ and $x = 1$- leads it to move away from those fixed points, otherwise a deviation from a stable point induces a dynamics which restores the equilibrium to that point.

Chapter 3

Multiple myeloma disease

We are going to describe how multiple myeloma disease affects a bone tissue and then provide a model of its dynamics.

3.1 MM cells

Multiple myeloma disease (MM) is a tumor characterized by the proliferation of MM cells in the bone marrow.
It is characterized by osteolytic bone lesions, hyper-calcaemia, anaemia, kidney failure, acquired immune anomalies.
MM cells, which are malignant mutant cells, induce alterations in the bone micro-environment and establish new interactions with the existing cells that favor their survival.
Histological studies of bone biopsies from MM patients have shown that a consequence of the presence of MM cells is an increased activity of osteoclasts. This has led to the hypothesis that local cytokines, produced or induced by MM cells, are responsible both for the osteoclasts formation and for the increased bone resorption activity. On the other side, osteoblasts activity is lowered, so MM cells decrease bone formation.
We provide a picture that shows the normal healthy bone equilibrium and how it changes in a pathological condition.

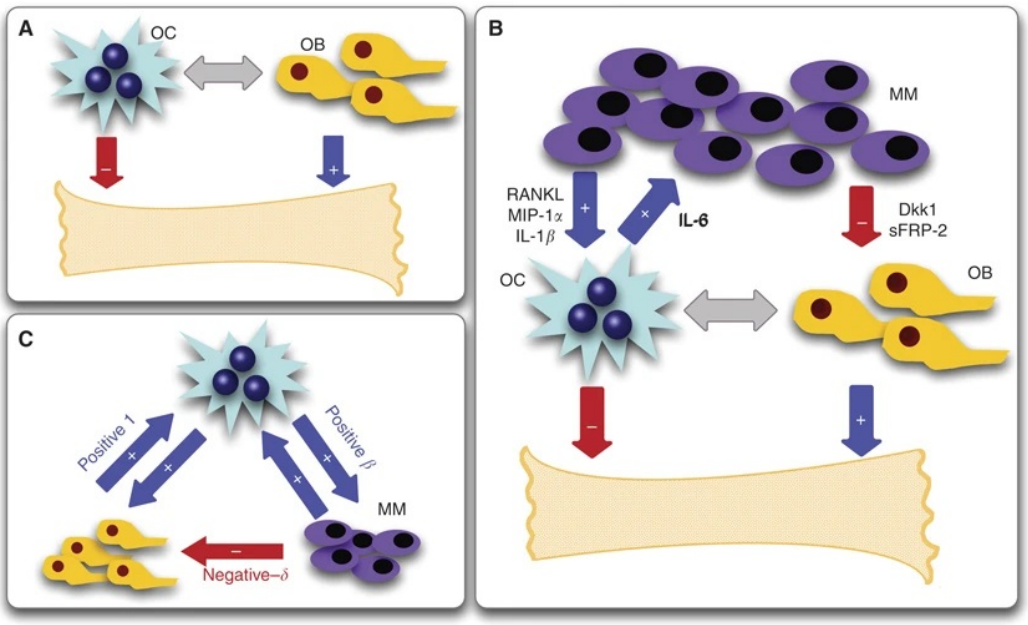

Figure 3.1: *Picture taken from [2] .*
In `A` it is shown an outline of the normal process of bone remodelling. In fact the interaction between OC and OB cells and also how their activity affects the bone itself are illustrated.
In `B` it is shown the process that occurs in the presence of MM cells and are also represented all the varieties of cytokynes and the regulatory factors involved, such as RANK,RANKL.
In `C` we have a framework of the interactions between all cells in the presence of the multiple myeloma bone disease. In here, these interactions are represented by two parameters β and δ, which will be used in the model in the following section.

3.2 MM cells model

The healthy bone model changes in the presence of MM cells. These cells disrupt the dynamic equilibrium between OB and OC in favour of OC.
Now we assume that no mutations occur during tumor dynamics, except the initial one, and that cell population dynamics is deterministic.
The replicator equations force the tumor dynamics, characterized by three types of cells, within the *simplex*

$$S = \left\{(x_1, x_2, x_3) \in \mathbb{R}^3 : \sum_{i=1}^{3} x_i = 1, x_i \geq 0, i = 1, 2, 3\right\}$$

We can see that it is invariant for the RE, in fact:

$$\frac{d}{dt}\left(\sum_{i=1}^{3} x_i\right) = \sum_{i=1}^{3} \frac{dx_i}{dt} = \sum_{i=1}^{3} x_i \left(Ax\right)_i - \underbrace{\sum_{i=1}^{3} x_i}_{1} \sum_{j=1}^{3} x_j \left(Ax\right)_j = 0$$

It means that, considering A as a payoff matrix, the property of the constancy of the total population in the replicator equation is satisfied.
The simplex is a two-dimensional space, its edges represent population composed by one type of cells, the interior corresponds to population where all cell types coexist.
At every point of this, we have that the sum of the relative frequencies of OB,OC and MM populations is equal to 1.
Let's denote each relative frequency in the following way: $x_1(t)$ the OC cells one, $x_2(t)$ the OB cells , $x_3(t)$ the MM cells and, according to what we said above, we have that $\sum_{i=1}^{3} x_i = 1$.
The replicator equations, which rule the dynamics for three types of cells,become:

$$\dot{x}_i(t) = x_i(t)(F(x_1, x_2, x_3) - \langle F \rangle) \qquad (i = 1, 2, 3) \tag{3.1}$$

where the average fitness of the population is

$$\langle F \rangle = \sum_{i=1}^{3} \sum_{k=1}^{3} x_i A_{ij} x_k \tag{3.2}$$

The following pay-off matrix, A_{ij}, shows the interactions between these three cells:

$$\begin{array}{c} \\ OC \\ OB \\ MM \end{array} \begin{array}{c} \begin{array}{ccc} OC & OB & MM \end{array} \\ \begin{pmatrix} 0 & a & b \\ e & 0 & -d \\ c & 0 & 0 \end{pmatrix} \end{array}$$

where all the parameters *a,b,c,d* are non-negative.
If they have a plus sign they stand for an advantage that a cell receives when it is put in contact with one of a different type, otherwise a minus sign represents a disadvantage.
This matrix will generate a system whose fixed points will be used to study the evolutionary dynamics that we are interested in.
Now we prove that we can simplify the form of this matrix and, thanks to the properties of the RE and the EGT, we don't change the nature of the fixed points and the ensuing dynamics of the system.

Proposition 3.1. *: The new replicator equation:*

$$\dot{y}_i = \left(y_i \sum_{k=1}^{n} B_{ik} y_k - y_i \sum_{j=1}^{n} \sum_{k=1}^{n} y_j B_{jk} y_k \right)$$

obtained from

$$\dot{x}_i(t) = x_i(t)(F(x_1, x_2, x_3) - \langle F \rangle)$$

with the following projective transformation of the relative frequencies:

$$y_i = \frac{\varphi_i x_i}{\sum_{k=1}^{3} \varphi_k x_k} \tag{3.3}$$

is equivalent to the prevoius one (that means that stability/instability character should be guaranteed from fixed point not from position).
Moreover the matrix A will be replaced by B matrix with

$$B_{ij} = \frac{A_{ij}}{\varphi_j}$$

Proof. : Suppose that x_i with $i = 1, .., n$ satisfy the replicator equation with matrix A and we could calculate the equation for y_i:

$$\frac{d}{dt} y_i = \frac{\dot{x}_i \varphi_i}{\underbrace{\sum_{j=1}^{n} x_j \varphi_j}_{c}} - \frac{x_i \varphi_i}{\underbrace{\left(\sum_{j=1}^{n} x_j \varphi_j \right)^2}_{c^2}} \left(\sum_{j=1}^{n} \dot{x}_j \varphi_j \right)$$

Using the RE:

$$\dot{x}_i [t] = x_i [t] \left(\sum_{k=1}^{n} A_{ik} x_k - \sum_{h=1}^{n} \sum_{k=1}^{n} x_h A_{hk} x_k \right)$$

the previous equation becomes:

$$\frac{d}{dt} y_i = y_i \sum_{k=1}^{n} A_{ik} x_k - y_i \sum_{h=1}^{n} \sum_{k=1}^{n} x_h A_{hk} x_k - \frac{y_i}{c} \left(\sum_{j=1}^{n} x_j \varphi_j \sum_{k=1}^{n} A_{ik} x_k - \sum_{j=1}^{n} x_j \varphi_j \sum_{h=1}^{n} \sum_{k=1}^{n} x_h A_{hk} x_k \right)$$

$$\frac{d}{dt} y_i = y_i \sum_{k=1}^{n} A_{ik} x_k - y_i \sum_{h=1}^{n} \sum_{k=1}^{n} x_h A_{hk} x_k - y_i \left(\sum_{j=1}^{n} y_j \sum_{k=1}^{n} A_{jk} x_k - \underbrace{\sum_{j=1}^{n} y_j}_{1} \sum_{h=1}^{n} \sum_{k=1}^{n} x_h A_{hk} x_k \right)$$

Since it is $\sum_{j=1}^{n} y_j = 1$, we can delate the second and last term and get:

$$\dot{y_i} = y_i \sum_{k=1}^{n} A_{ik} x_k - y_i \sum_{j=1}^{n} \sum_{k=1}^{n} y_j A_{jk} x_k$$

Multiplying and dividing within the summaries for φ_k and c:

$$\dot{y_i} = y_i \sum_{k=1}^{n} \frac{A_{ik}}{\varphi_k} \frac{x_k \varphi_k}{c} c - y_i \sum_{j=1}^{n} \sum_{k=1}^{n} y_j \frac{A_{jk}}{\varphi_k} \frac{x_k \varphi_k}{c} c$$

and now defining $B_{jk} = \frac{A_{jk}}{\varphi_k}$ and $y_k = \frac{x_k \varphi_k}{c}$, we finally obtain:

$$\dot{y_i} = \left(y_i \sum_{k=1}^{n} B_{ik} y_k - y_i \sum_{j=1}^{n} \sum_{k=1}^{n} y_j B_{jk} y_k \right) c$$

This is the replicator equation with less than a c-factor that can be erased by rescaling the time $\widetilde{t} = \frac{t}{c}$ and this concludes our proof.

Coming back to our model, we consider φ_i positive constants given by $(\varphi_1, \varphi_2, \varphi_3) = (e, a, \frac{be}{c})$ and we have that:

$$B_{ij} = \begin{array}{c} \\ OC \\ OB \\ MM \end{array} \begin{array}{c} \begin{array}{ccc} OC & OB & MM \end{array} \\ \begin{pmatrix} 0 & 1 & \beta \\ 1 & 0 & -\delta \\ \beta & 0 & 0 \end{pmatrix} \end{array}$$

That leads to define two new parameters in this way:

$$\beta = \frac{c}{e}$$

and

$$\delta = \frac{dc}{be}$$

Using the B matrix in the replicator equation, we obtain:

$$\begin{cases} \dot{x}(t) = x\left(y + \beta z - 2xy - 2\beta xz + \delta zy\right) \\ \dot{y}(t) = y\left(x - \delta z - 2xy - 2\beta xz + \delta zy\right) \\ \dot{z}(t) = z\left(\beta x - 2xy - 2\beta xz + \delta zy\right) \end{cases} \tag{3.4}$$

where x represents the concentration of type OC cells, y the one of the OB cells and z the one of MM cells.

3.2.1 The fixed points

Studying the fixed points of the dynamic system is crucial to understand how the solution evolves.
We impose the stationary condition to the system 3.4 , that means putting all the equations equal to zero, and obtain:

$$(x, y, z) = (0, 0, 1)$$

$$(x, y, z) = (1, 0, 0)$$

$$(x, y, z) = (0, 1, 0)$$

$$(x, y, z) = (1/2, 1/2, 0)$$

$$(x, y, z) = (1/2, 0, 1/2)$$

$$(x, y, z) = \left(\frac{\delta}{1 - 2\beta + \delta\beta + \beta^2 + \delta}, \frac{\beta(-1 + \beta + \delta)}{1 - 2\beta + \delta\beta + \beta^2 + \delta}, \frac{-\beta + 1}{1 - 2\beta + \delta\beta + \beta^2 + \delta} \right) \tag{3.5}$$

The existence conditions of these fixed points are $x + y + z = 1$ and that they are all positive. We have to check that the last point satisfies these properties.
It can be easily proved that the sum of each component of 3.5 is equal to 1, then we have that:

$$\frac{\delta}{1 - 2\beta + \delta\beta + \beta^2 + \delta} \geq 0 \Rightarrow \left(1 - 2\beta + \delta\beta + \beta^2 + \delta\right) \geq 0$$

and we know that both the parameters δ and β are defined positive, assuming the denominators positive for y and z we get:

$$\frac{-\beta + 1}{1 - 2\beta + \delta\beta + \beta^2 + \delta} \geq 0 \Rightarrow 1 - \beta \geq 0 \Rightarrow \beta \leq 1$$

and

$$\frac{\beta(-1 + \beta + \delta)}{1 - 2\beta + \delta\beta + \beta^2 + \delta} \geq 0 \Rightarrow \beta(-1 + \beta + \delta) \geq 0 \Rightarrow \beta + \delta \geq 1$$

So the components of 3.5 are actually relative frequencies, according to our model hypothesis.

The analysis of the stability allows us to find out the evolutionary winning strategies. In fact, applying the previous mentioned Lyapunov method

to this case, we can study the nature of these fixed points and how it changes according to the parameters β and δ.
These parameters and their relative balance in the pay-off matrix give us information about the expanding MM population and consequently about how the tumor grows.

We now show some results where different values for β and δ are used.
In the first graph there will be a 2D-graphic, which is the projection of the equilateral triangle when $z = 0$. The horizontal axis represents OC cells frequency, while the vertical one is the OB type frequency. MM cells are represented by the origin of the axis, thanks to the relation $z = 1 - x - y$.
There will be shown how the dynamics of the system develops according to the nature of its fixed points.
The second graph represents the time evolution of the three cellular frequencies once set an initial point.

3.2.2 Case $\beta = 1/2$ and $\delta = 1/3$

We consider the previous system 3.4 choosing as parameters $\beta = 1/2$ and $\delta = 1/3$. It stands for the situation in which $\beta < 1$ and $\beta + \delta < 1$, the population of MM cells can go extinct and OB and OC may again re-establish the stable dynamic equilibrium. Therefore the tumuor will be extinguished. (See (b))

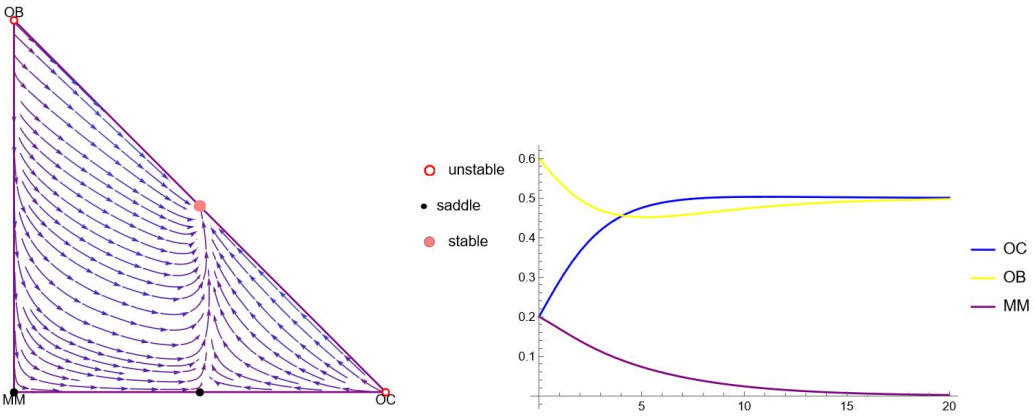

Figure 3.2: *(a):Evolutionary dynamics of OB-OC-MM cells system in the case of* $\beta = 1/2$ *and* $\delta = 1/3$.
(b) Time evolution with starting point $(x, y, z) = (0.2, 0.6, 0.2)$.

In this case, as shown in (a), edges of the simplex are unstable points,

while the origin of the axis (standing for the population made by only MM cells) and the fixed point $\left(\frac{1}{2}, 0, \frac{1}{2}\right)$ are saddle points. The only stable point is $\left(\frac{1}{2}, \frac{1}{2}, 0\right)$ which represents the coexistence of OB and OC cells.

3.2.3 Case $\beta = 1/2$ and $\delta = 1$

Choosing $\beta = 1/2$ and $\delta = 1$, we represent the situation in which $\beta < 1$ and $\delta + \beta > 1$. The co-evolutionary process can still lead to the normal homeostasis but it isn't the only possible 'end-game'. In this case the prediction of the growth of cancer is more complex. Therapies that change β can be useful to overall disease eradication.
For this reason we are going to show two graphs of the time evolution of the cells changing the starting points of the system.

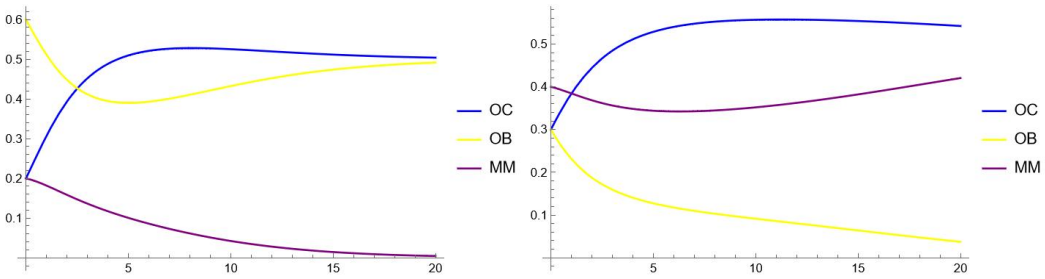

Figure 3.3: *Time evolution of the three population cells with initial condition:*
(a) $(x, y, z) = (0.2, 0.6, 0.2)$
(b) $(x, y, z) = (0.3, 0.3, 0.4)$

In fact, in the graph on the left it is shown an example where the OC-OB equilibrium is re-established and the MM cells lead to zero. While in the case on the right,where we have changed the starting point with a higher presence of MM cells, we have a different deadline: there is a typical scenario of the tumour development, where OC cells and MM cells are increased while OB cells are decreased.
The study of the evolutionary dynamics that we obtain with these parameters arises the presence of two stable points $\left(\frac{1}{2}, \frac{1}{2}, 0\right)$ and $\left(\frac{1}{2}, 0, \frac{1}{2}\right)$. They represent respectively the normal bone balance between OB and OC cells and the interaction only between OC and MM cell, underling the two possible 'end-games' of the system. Edges are still unstable points, but a saddle point, $\left(\frac{4}{7}, \frac{1}{7}, \frac{2}{7}\right)$, appears inside the simplex, which according to the evolutionary dynamics properties cannot be stable.

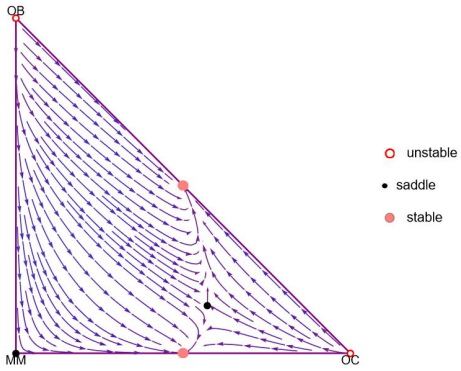

Figure 3.4: *Evolutionary dynamics of OB-OC-MM cells system in the case of* $\beta = 1/2$ *and* $\delta = 1$.

3.2.4 Case $\beta = 2$ and $\delta = 0$

Choosing $\beta = 2$ and $\delta = 0$, we have an example of the most common existing scenarios where $\beta > 1$. In this case, the only stable equilibrium is the coexistence of MM and OC cells. In particular, a part of bone is completely devoid of OB, thus there is an increasing risk of fracture. The case with $\delta = 0$ stands for the neutral interaction between MM and OB cells. So the evolutionary selection is in favour of the mutant cells. The evolution of the three cells in Figure 3.5(b) highlights the balance between OC and MM cells and the absence of OB cells.

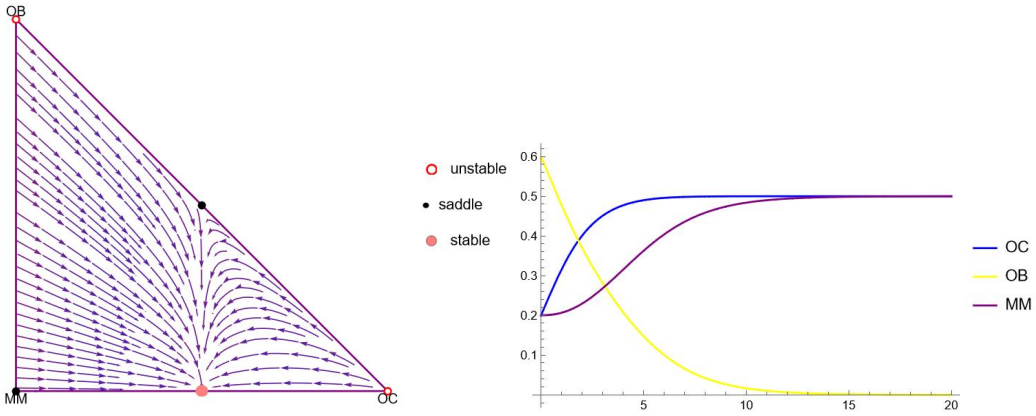

Figure 3.5: *(a): Evolutionary dynamics of OB-OC-MM cells system in the case of* $\beta = 2$ *and* $\delta = 0$.
(b): Time evolution of the cells with starting point $(x, y, z) = (0.2, 0.6, 0.2)$

In Figure 3.5(a) edges are unstable and $\left(\frac{1}{2}, \frac{1}{2}, 0\right)$ is a saddle point, in fact the normal homeostasis isn't possible in this scenario. The only stable point is $\left(\frac{1}{2}, 0, \frac{1}{2}\right)$ which represents the coexistence of MM and OC cells.

We have proved that under the model assumptions, β and δ are sufficient to characterize multiple myeloma bone disease and its progression in time. It is important to say that the development of the disease and its physiology is also affected by some particular features of myeloma cells that can vary from patient to patient. Moreover, also the entries of the pay-off matrix A_{ij}, i.e. $\{a,b,c,d,e\}$, and consequently β and δ, are specific for each patient.

Chapter 4

Conclusions

4.1 Therapies and parameters

From the previous examples, it is possible to understand how therapies should change parameters to have an improvement on the patients affected by multiple myeloma bone disease.
We remind that the parameter β represents the interactions between OC and MM cells, while δ stands for MM and OB interactions.
A higher β means more bone destruction and a faster development of the tumour burden. So suppressing or reducing this parameter, the number of bone lesions and the speed of the disease progression should decrease.
A therapy that decreases δ should reduce the myeloma burden, slow the progression of the disease and improve bone mass [7] .
On the contrary, increasing δ for a fixed β - that is, increasing the disadvantage of OB cells in the presence of MM cells- leads to a bone loss without an increase in the MM population [5] .
Similarly, the model would suggest that any therapy designed to suppress OC growth should indirectly improve outcomes in patient with myeloma.
The most used therapies are drug treatment and/or transplantation.
In cases in which the presence of a large number of MM cells leads to the growth of the tumour, an autologous bone marrow transplantation (BMT) is chosen as a way to ameliorate the patient's condition.
Moreover, if the condition of the patient can be represented by a system where $\beta > 1$ and there is no drug treatment, BMT is not curative.
Let us prove it considering a system, like 3.4, where $\beta = 3.0$ and $\delta = 1$. The evolutionary dynamics of OC-OB-MM cells presents an unstable point on $\left(\frac{1}{2}, \frac{1}{2}, 0\right)$, the representation of the coexistence of OB and OC cells. According to our previous study, the MM cells will out-compete the other cells,

while the ratio OB/OC will lead to zero since the decrease of the presence of OB cells. We will see it graphically in the 4.1 (a)
In this case, BTM should not change the relative proportion of OB and OC cells and should decrease the MM cells. However it is proved that this improved condition is just temporary, since relapse is inevitable.
On the other hand, drug treatment changing β to values lower than 1, leads to the appearance of saddle points. This situation can have different 'endgames' and all depends on the time when the drug is provided to the patient. In those cases where the disease is diagnosed too late, drug treatment and BMT are still not curative.
A more hopeful scenario is the cases in which the patient is treated at the beginning of the MM disease.
Let us consider the same previous system with $\beta = 3.0$ and $\delta = 1$. We now show two different graphs of the time evolution of MM cells and the ratio between OB/OC cells.
In the first graph, we have a frame of what happens if no drug treatment and no BMT is given to the patient, according to what we previously stated .
Now we suppose that at time $t = 5$ seconds, treatment and BMT are administered to the patient and our parameter β becomes lower than 1.
The disease progression is different now: BMT changes the initial condition of the system, the drug treatment transforms our parameters to $\beta = 1/2$ and $\delta = 1$, so the evolutionary dynamics shows a possible decrease of MM cells and an advantage in the relation between OB and OC cells.

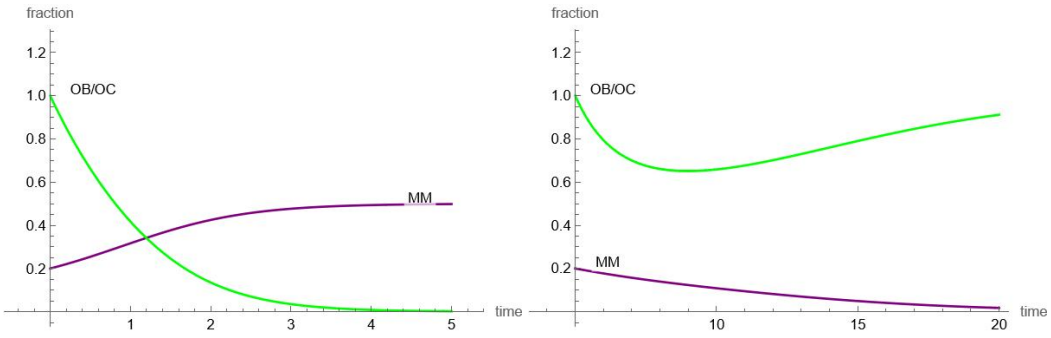

Figure 4.1: *(a)Time evolution of MM cells and the relation between OB/OC with no drug treatment provided to a patient.*
(b) Time evolution of MM cells after their reduction caused by BMT and drug treatment

To sum up, it is possible to state that therapies, given properly and at the right time, are able to change the dynamics of the system, enabling normal

cells to outcompete the malignant one, managing to have a total remission as a result.

In conclusion, cancer ecology combined with the evolutionary game theory manages to give a proper model where it is possible to understand and to study the dynamics of cancer. It provides a new way to deal with cancer eradication based on the evolutionary forces of the different cell dynamics to eradicate cancerous cells. Then, we have also proved that therapies should aim at changing the inner interactions between all the cells involved to gain the possibility to have actual benefits for the patient.

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