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Cancer Behavior: An Optimal Control Approach

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Abstract

With special attention to cancer, this essay explains how Optimal Control Theory, mainly used in Economics, can be applied to the analysis of biological behaviors, and illustrates the ability of this mathematical branch to describe biological phenomena and biological interrelationships. Two examples are provided to show the capability and versatility of this powerful mathematical approach in the study of biological questions. The first describes a process of organogenesis, and the second the development of tumors.

Keywords

Cancer Behavior; Anaplasia; Apoptosis; Angiogenesis; Metastasis; Bio-Mathematics; Optimal Control Theory; Objective Function; Constraint Function; Reaction Function

1 Introduction

After being progressively applied to Physics in the XVI century (Galileo Galilei, J. Kepler,...), to Chemistry in the XVII and XVIII centuries (R. Boyle, A. Lavoisier, J. Dalton, ...) and to Economics in the XIX century (A. Cournot, L. Walras, I. Edgeworth,...), mathematics has begun to be used for the analysis of biological questions. Indeed, as a result of the ability of modern mathematics to describe complex and interrelated behaviors, the application of mathematical models to study biological and medical phenomena is on the increase.

Leaving aside pure exogenous factors, easy to formalize from the mathematical point of view¹, the main characteristic of biomedical phenomena is the existence of numerous and complex relationships between semi-autonomous entities. In a biological phenomenon where several bio-entities are involved, the behavior of the biological entities (cells, bacteria, human organs, genes, living beings,...) is in part autonomous and in part dependent on the behavior of the other entities. Therefore the specification of both the objective of the biological entity (autonomous dimension) and the nature of the interrelationships (dependent dimension) are necessary to explain the behavior of these bio-entities.

Mathematics were firstly applied to quantify these relationships and to obtain the correlation between observed behaviors. The mathematical description of the objective of a bio-entity is not a trivial question, but the quantification of the relationships between behaviors is easier.

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¹If biological behaviors were only the result of exogenous factors, the description and explanation of bio-medical phenomena would reduce to Physics and Chemistry laws.

Additionally, before any explanation of a bio-medical phenomenon, it is necessary to account for the interrelationships and correlations between bio-entities. The development of statistics in the XIX century made the mathematical description (but not the explanation) of these relationships and correlations possible. The statistical analysis of the biological behaviors soon proved its ability to specify the relationships between behaviors and the cause-effect directions, and as a result, biostatistics is today a basic tool in medicine and biology. Indeed, current Bio-Statistics is able not only to very accurately describe and characterize almost all the interrelationships between bio-entities, but also to analyze causality, to contrast hypotheses, to ascertain significance, etc.

When making use of statistical tools, medical and biological scientists verify the existence of a relationship between bio-entities, the subsequent step is to identify the origin of such relationships. Hand in hand with medical and biological experimentation, the use of systems of equations in the XX century helped to elucidate why the particular interrelationships between bio-entities appeared. The main virtue of the system of equations is their capability to explicitly state such interrelationships, therefore providing a first explanation of the interrelated behaviors. Indeed, today, equation systems are used to explain a wide variety of complex interrelated biological behaviors, and most of modern biomathematics relies on this kind of mathematical analysis initiated by Lotka (1925) and Volterra (1926). As a result, the use of systems of equations, and in particular of difference or differential equations, is today the most frequent mathematical technique to explain interrelated biological behaviors. However, the system of equations explains the interrelationships between bio-entities but not the origin of these interrelationships. A crucial question then remains open: why do these interrelationships appear?

The purpose of this paper is to answer this question. In particular, with special attention to cancer, we propose the use of the Optimal Control Theory to provide a complete explanation of the biological phenomena, not only of the relationships between bio-entities but also of the origin of these interrelationships. Optimal Control Theory is the contemporary setting for analyzing and solving optimization problems, born in the 1960's with the work of Pontryagin, Boltyanskii, Gamkrelidze and Mischenko (1962) on the basis of the previous contributions made by Lagrange (1788) and Hamilton (1827). In essence, Optimal Control Theory considers the problem of how to attain an objective subject to external constraints, and it has mainly been used in Economics. To our knowledge, concerning Biosciences, Optimal Control Theory has been applied to the design of optimal therapies, optimal harvest policies and optimal investments in renewable-resources, but not to elucidate the origin of the observed biological behaviors. When designing an optimal therapy, an optimal harvest or an optimal investment, the purpose is to achieve an objective external to the involved biological entities -namely, to minimize the negative effects of drugs and illness and to maximize the present value of revenues-, subject to the biological laws describing the existing cross effects. The suitable mathematical approach to this problem is therefore the Optimal Control Theory, and, indeed, in modern biomathematics there is a large body of work developed to study optimal drug therapies and optimal harvest policies².

However, in addition to such well known applications, Optimal Control Theory also constitutes the most appropriate approach to study biological phenomena understood as the result of the behavior of semi-autonomous bio-entities. If we assume that, in a biological phenomenon where several bio-entities are involved, each bio-entity has a specific objective,

²The interested reader can see optimal control techniques in the works of Nanda, Moore and Lenhart (2007) and Murray (2002, 2003). The books by Clark (1990) and Eisen (1988) provide the background for the optimal control theory we use and include some simple biological applications. The book of Martin and Teo (1994) applies optimal control to several detailed models of tumors, and provides a survey of many research results of optimal control applied to cancer.

and that to achieve this objective a particular bio-entity is affected by the behavior of other bio-entities, the problem of each bio-entity is an optimal control problem. The objective function is the goal of the bio-entity, and the biological laws describing the cross effects are the constraint functions. Therefore, the optimal control theory provides a complete explanation of the observed behaviors: the bio-entities pursue their own specific objectives, the actions of a bio-entity affects the possibilities of the other entities to achieve their objectives, and as a result, all the behaviors are interrelated. However, the interpretation of biological phenomena as the result of a set of optimal control problems has not yet been considered by current biomathematics. In this respect, taking economic oligopolistic models as our starting point, the purpose of this paper is to show how this application of Optimal Control Theory is a promising approach to the analysis of biomedical questions, specially to cancer.

After this introduction, section 2 briefly describes the proposed application of the Optimal Control Theory. Once the approach has been explained and making use of very simple examples, section 3 illustrates the possible applications, virtues and capabilities of the new method. Finally, section 4 concludes and discusses future extensions.

2 Optimal Control, Objectives and Constraints

Let us consider a biological phenomenon with a number N of involved bio-entity types. Let y_t^n , $n = 1, 2, \dots, N$, the population of type n bio-entity at instant t . As an autonomous being, at each instant t , each bio-entity type seeks an objective, which, in general terms, depends on its own population. This objective can be to increase the number of individuals as much as possible, to secrete or to eliminate a certain amount of substances, etc. In any case, those objectives are always dependent on the population number. This implies that, mathematically, each bio-entity type objective can be formulated as the attempt to maximize a function dependent on its population size y_t^n and a set or vector a^n of parameters which collect structural and exogenous factors, that is

$$\max F^n(y_t^n, a^n).$$

For instance, if the objective at each instant is to increase the number of individuals as much as possible, the function F^n provides the number of the new future individuals, which depends on the number of previously existing individuals y_t^n and on a set of relevant parameters (mortality and natality rates, available resources, etc.). If the objective is to secrete a certain amount of substance, the function F^n measures the proximity between this amount and the quantity of secreted substance, which, as is logical, depends on y_t^n and a set of parameters collecting the secretion capacity of each individual and the influence of external conditions.

What variables or aspects does each bio-entity control in order to achieve this objective? These variables can be numerous (as many as the capacities/abilities of the bio-entity), but they reduce to the population number y_t^n . The reason is simple: each bio-entity type cannot directly control the actions of the other bio-entities, it can only control its own capacities, and since the total capacity of the type n bio-entity is given by the number of individuals, this variable becomes the control variable. Returning to the above examples, when the objective is to increase as much as possible the number of individuals, each type n bio-entity can control the number of fertile individuals (for instance through hormonal secretion, structural changes, etc.), a number which, in its turn, is a fraction of the total number of individuals y_t^n . For the same reason, if the objective is to secrete or to absorb a certain

amount of substances, this capacity can only be controlled by varying its own population, since each individual has a certain capacity of secreting or absorbing the substances. In other words, everything that a bio-entity controls, everything that can be considered as autonomous, is controlled through its population, and then the control variable is, in the end, the population number y_t^n . In mathematical terms, the problem for each type n bio-entity is therefore

$$\max_{y_t^n} F^n(y_t^n, a^n).$$

This objective is the materialization of the autonomous goal of the bio-entity. However, as explained in the introduction, searching for this objective, each bio-entity type faces a set of constraints, consequence of the influences that the behaviors of other bio-entities have on the possibilities to attain its particular goal. For instance, if the objective of type n bio-entity is to maximize its population (to increase as much as possible the number of type n individuals), given that the population depends on the available resources, if there are other bio-entities consuming the same resources, the increase in the type n bio-entity population will depend on the existing populations of the competing bio-entities. If the objective of type n bio-entity is to secrete or to eliminate a certain amount of substances, the existence of other bio-entities secreting or absorbing compounds affecting the capacities of the type n bio-entity individuals, implies the dependence of the type n bio-entity objective consecution on the populations of the influencing bio-entities.

By the same arguments that allowed us to identify the population of a bio-entity as the control variable for this bio-entity, it is clear that the influence of a bio-entity on the conditions under which the other bio-entities look for their objectives is carried out through its existing population. This implies that, when pursuing its objective, type n bio-entity faces a number of constraints, which, mathematically, are functions of the other bio-entity populations and a set or vector of parameters.

These functions can be written

$$g_k^n(y_{t-1}^1, y_{t-1}^2, \dots, y_{t-1}^{n-1}, y_t^n, y_{t-1}^{n+1}, \dots, y_{t-1}^N, b_k^n) = 0, \\ k = 1, \dots, K_n,$$

where K_n is the total number of constraints faced by type n bio-entity, $k = 1, \dots, K_n$ denotes each particular constraint, b_k^n is the vector of parameters determining the influence on y_t^n of the existing populations of the other bio-entities, and g_k^n are the functions describing this influence. Therefore, the type n bio-entity problem is

$$\text{subject to } \left. \begin{array}{l} \max_{y_t^n} F^n(y_t^n, a^n) \\ g_1^n(y_{t-1}^1, \dots, y_{t-1}^{n-1}, y_t^n, y_{t-1}^{n+1}, \dots, y_{t-1}^N, b_1^n) = 0 \\ g_2^n(y_{t-1}^1, \dots, y_{t-1}^{n-1}, y_t^n, y_{t-1}^{n+1}, \dots, y_{t-1}^N, b_2^n) = 0 \\ \vdots \\ g_{K_n}^n(y_{t-1}^1, \dots, y_{t-1}^{n-1}, y_t^n, y_{t-1}^{n+1}, \dots, y_{t-1}^N, b_{K_n}^n) = 0, \\ y_t^n \geq 0 \end{array} \right\}$$

This problem, known as *constrained optimization problem* can be solved applying different techniques³, which provide as solution the function

$$y_t^n = \Psi^n(y_{t-1}^1, \dots, y_{t-1}^{n-1}, y_{t-1}^{n+1}, \dots, y_{t-1}^N, b_1^n, b_2^n, \dots, b_{K_n}^n, a^n).$$

This function is called *reaction function* of the type n bio-entity, and its meaning is the following: When the type n bio-entity is pursuing its objective and therefore deciding a population y_t^n for instant t , the possibilities of attaining this objective, consequence of the environmental conditions of the type n bio-entity, are dependent on the previously existing populations of the other bio-entities, that is on $y_{t-1}^1, \dots, y_{t-1}^{n-1}, y_{t-1}^{n+1}, \dots, y_{t-1}^N$, and on the relevant parameters. Given these parameters and populations, that is, given the external conditions under which the type n bio-entity decides, the type n bio-entity reacts according to the function Ψ^n in order to attain its objective.

This is the problem faced by all the involved bio-entities, and then the biological phenomenon can be mathematically described as

$$\left. \begin{array}{l} \max_{y_t^n} F^n(y_t^n, a^n) \\ \text{subject to } g_k^n(y_{t-1}^1, \dots, y_{t-1}^{n-1}, y_t^n, y_{t-1}^{n+1}, \dots, y_{t-1}^N, b_k^n) = 0 \\ y_t^n \geq 0 \\ k=1, \dots, K_n, \quad n=1, \dots, N. \end{array} \right\}$$

The solution of the former set of N constrained optimization problem is the system of reaction functions (one for each bio-entity)

$$\left. \begin{array}{l} y_t^1 = \Psi^1(y_{t-1}^2, \dots, y_{t-1}^N, b_1^1, \dots, b_{K_1}^1, a^1), \\ \dots \\ y_t^n = \Psi^n(y_{t-1}^1, \dots, y_{t-1}^{n-1}, y_{t-1}^{n+1}, \dots, y_{t-1}^N, b_1^n, \dots, b_{K_n}^n, a^n), \\ \dots \\ y_t^N = \Psi^N(y_{t-1}^1, \dots, y_{t-1}^{N-1}, b_1^N, \dots, b_{K_N}^N, a^N). \end{array} \right\} \quad (1)$$

The former system of reaction functions is indeed a dynamical system of equations, which completely describes the evolution of the populations of the N types of bio-entities and their relationships. This dynamical system of equations fully explains the biological phenomenon, providing information not only about the behaviors and the interrelationships but also their origins. Additionally, the dynamical system of equations (1) allows the properties of the biological phenomenon to be deduced and analyzed, in particular those concerning the convergence of the populations to steady state values, the existence of dominant bio-entities, and the responses to external changes. The interested reader can consult Eisen (1988), Clark (1990), Azariadis (1993), Murray (2002, 2003), Britton (2003) and Chiang and Wainwright (2005) for an analysis and discussion of the dynamical systems of equations.

In the next section we will apply this optimal control approach to explain two different biological phenomena. It is worth noting that the proposed formulation, although it does not

³The interested reader can consult Clark (1990), Azariadis (1993), Murray (2002, 2003) and Chiang and Wainwright (2005).

consider the possibility of behaviors with memory, which are dependent on the past values of the populations for several periods, can be easily modified to incorporate the existence of bio-entities with memory. Indeed, this simply requires the introduction of the relevant lagged values of the populations in the objective and/or in the constraint functions.

3 Biological Behaviors and Optimal Control: Two Models

As explained in the former section, optimal control theory appears as an appropriate and powerful mathematical tool to explain and describe biological phenomena. Indeed, this approach incorporates the main characteristics of the biological behaviors, namely, the presence of several entities with behaviors in part autonomous and in part dependent on the behavior of the other entities. In this section and inspired by the oligopolistic economic theory, we will illustrate the capacity of the suggested theoretical framework describing and explaining two biological phenomena: organogenesis and tumor formation.

3.1 Organogenesis

An organ is a group of differentiated tissues performing a similar function within an organism, working together and interconnected with other organs. From this definition, the suitability of the optimal control approach to describe the behavior of organs is clear. Indeed, an organ can be considered a bio-entity type, with an autonomous objective (the specific objective of the organ) that, when pursuing its goal, is conditioned by the behavior of the other organs in the living organism.

Can the optimal control theory describe the organogenic process? The main characteristics of the organogenic process are i) Organs grow until they reach a steady size; ii) Organs simultaneously grow; iii) Functions of organs are complementary. A model which aims to satisfactorily explain the organogenic process must incorporate at least these three features. In particular, since our purpose is to illustrate the capability of the optimal control approach, we propose a model describing an organogenic process with only two involved organs, organ *A* and organ *B*. This does not imply any loss of generality, since all the obtained results would hold for any number of organs.

As pointed out above, let us consider that each organ is a different bio-entity, and that the objective of each organ/bio-entity is to perform its task at the maximum possible level. Following the reasonings in section 2, this objective is equivalent to maximizing the population increases, that is to grow as much as possible. By characteristic ii) the two organs grow simultaneously, and then this is the objective for both of them at each instant. This implies the following objective function

$$F^n(y_t^n, a^n) = I_{t+1}^n = N_{t+1}^n - D_{t+1}^n, \quad n=A, B,$$

where I_{t+1}^n is the increase in the population of organ *n* bio-entity at instant *t* + 1, given by the difference between the number of new individuals, N_{t+1}^n , and the number of dying individuals, D_{t+1}^n . The number of new individuals at instant *t* + 1 positively depends on the natality rate d^n , on the number of existing individuals at instant *t*, y_t^n , and on the available resources at period *t* + 1 for organ *n*, R_{t+1}^n . Let us assume for instance that

$$N_{t+1}^n = d^n R_{t+1}^n y_t^n, \quad n=A, B.$$

The number of dying individuals at instant $t + 1$ positively depends on the mortality rate, m^n , and on the number of existing individuals at instant t , that is

$$D_t^n = m^n y_t^n, \quad n = A, B.$$

Then the behavior of the two bio-entities/organs can be formulated as

$$\max_{y_t^n} I_t^n = N_t^n - D_t^n = d^n R_t^n y_t^n - m^n y_t^n, \quad n = A, B.$$

That is, by deciding at instant t the population y_t^n , the organ fixes the number of associated new future individuals, $N_{t+1}^n = d^n R_t^n y_t^n$, the number of dying individuals $D_t^n = m^n y_t^n$, and then also establishes the population increase I_{t+1}^n . The objective is to decide the optimal population at each instant t , which implies the maximum future population increase, the maximum growth, and the maximum performance of the organ's particular task.

Seeking this goal, each organ faces an obvious constraint: the available resources for the new individuals of type n organ, R_{t+1}^n , are those not consumed by the previously existing population of the other organ and the new fixed population of the type n organ. Denoting by T_{t+1}^n the maximum amount of resources available for the type n organ at instant $t + 1$,

$$R_{t+1}^A = T_{t+1}^A - c^A y_t^A - c^B y_{t-1}^B, \quad R_{t+1}^B = T_{t+1}^B - c^A y_{t-1}^A - c^B y_t^B,$$

where c^n , $n = A, B$, are the resource consumptions per individual. Additionally, since both organ functions are complementary (characteristic iii)), some effects beneficial to one organ derive from the growth of the other organ. In particular, we propose that the maximum amount of resources available for the type n organ is positively dependent on the number of individuals of the other organ per individual of the type n organ up to a bound $\bar{T}$:

$$T_{t+1}^A = \bar{T} - \frac{b^A}{\frac{y_{t-1}^B}{y_t^A}}, \quad T_{t+1}^B = \bar{T} - \frac{b^B}{\frac{y_{t-1}^A}{y_t^B}},$$

where b^n , $n = A, B$, are parameters measuring the response of each organ's available resources to the growth of the other organ. Through this assumption we identify the complementarity between organ functions with the increase in the capacity to grasp resources, but of course other kinds of complementarity are perfectly possible. For instance, it could be assumed that the natality rate-alternatively mortality rate- of type n organ individuals is positively dependent-alternatively negatively dependent- on the number of individuals of the other organ, reaching similar results.

With the former assumptions, the organogenic process can be formulated as the set of simultaneous problems

$$\text{subject to } \left. \begin{array}{l} \max_{y_t^A} d^A R_{t+1}^A y_t^A - m^A y_t^A \\ R_{t+1}^A = T_{t+1}^A - c^A y_t^A - c^B y_{t-1}^B, \\ T_{t+1}^A = \bar{T} - \frac{b^A}{\frac{y_{t-1}^B}{y_t^A}}, \\ y_t^A \geq 0, \end{array} \right\} \quad (2)$$

$$\text{subject to } \left. \begin{array}{l} \max_{y_t^B} d^B R_{t+1}^B y_t^B - m^B y_t^B \\ R_{t+1}^B = T_{t+1}^B - c^A y_{t-1}^A - c^B y_t^B, \\ T_{t+1}^B = \bar{T} - \frac{b^B}{\frac{y_{t-1}^A}{y_t^B}}, \\ y_t^B \geq 0, \end{array} \right\} \quad (3)$$

The solutions of problems (2) and (3) are, respectively, the functions

$$y_t^A(y_{t-1}^B) = \Psi^A(y_{t-1}^B) = \frac{d^A \bar{T} - d^A c^B y_{t-1}^B - m^A}{\frac{2d^A b^A}{y_{t-1}^B} + 2d^A c^A}, \quad (4)$$

$$y_t^B(y_{t-1}^A) = \Psi^B(y_{t-1}^A) = \frac{d^B \bar{T} - d^B c^A y_{t-1}^A - m^B}{\frac{2d^B b^B}{y_{t-1}^A} + 2d^B c^B}. \quad (5)$$

Function (4) is the reaction function of type A organ, which provides the number of type A organ individuals that maximizes the increase in the type A organ performance for each number of previously existing type B organ individuals (for each existing level of organ B performance). Analogously, function (5) is the reaction function of type B organ, that provides the number of type B organ individuals that maximizes the increase in the type B organ performance for each number of previously existing type A organ individuals (for each existing level of organ B performance).

These two reaction functions constitute a dynamical system of equations that completely describes the organogenic process. Applying the analysis techniques for dynamical systems⁴, the conditions under which steady states for the populations y_t^A and y_t^B exist can be deduced, as well as the trajectories for each population. In this particular case, since

⁴See the references provided in section 2.

$$\begin{aligned}
y_t^A = 0 &\Rightarrow \begin{cases} y_{t-1}^B = 0, \\ y_{t-1}^B = \frac{d^A \bar{T} - m^A}{c^B b^A}, \end{cases}, \\
\lim_{y_{t-1}^B \rightarrow 0} \frac{dy_t^A}{dy_{t-1}^B} &= \frac{d^A \bar{T} - m^A}{2d^A b^A}, \\
\frac{dy_t^A}{dy_{t-1}^B} = 0 &\Rightarrow \begin{cases} y_{t-1}^B = y_{M1}^B = \frac{-2b^A c^B d^A + \sqrt{(2b^A c^B d^A)^2 - 4c^A c^B d^A b^A (m^A - d^A \bar{T})}}{2d^A c^A c^B}, \\ y_{t-1}^B = y_{M2}^B = \frac{-2b^A c^B d^A - \sqrt{(2b^A c^B d^A)^2 - 4c^A c^B d^A b^A (m^A - d^A \bar{T})}}{2d^A c^A c^B}, \\ \frac{d^2 y_t^A}{d(y_{t-1}^B)^2} = -\frac{b^A (b^A c^B d^A + c^A (d^A \bar{T} - m^A))}{d^A (c^A y_{t-1}^B + b^A)^3}, \end{cases}
\end{aligned}$$

when $d^A \bar{T} - m^A > 0$ -that is when the maximum amount of resources implies a positive population-, the representation of the type A organ reaction function $y_t^A = \Psi^A(y_{t-1}^B)$ is that in figure 1 (the representation of the reaction function for type B organ would be analogous).

Then, if $d^A \bar{T} > m^A$, $d^B \bar{T} > m^B$ and

$$\arctan \frac{d^A \bar{T} - m^A}{2d^B b^A} + \arctan \frac{d^B \bar{T} - m^B}{2d^B b^B} > 90,$$

the organs will grow until they reach a steady state given by the solution of the system

$$y_{ss}^A = \frac{d^A \bar{T} - d^A c^B y_{ss}^B - m^A}{\frac{2d^A b^A}{y_{ss}^B} + 2d^A c^A}, \quad (6)$$

$$y_{ss}^B = \frac{d^B \bar{T} - d^B c^A y_{ss}^A - m^B}{\frac{2d^B b^B}{y_{ss}^A} + 2d^B c^B}. \quad (7)$$

Depending on the relative position of the reaction functions and the situation of the steady state values⁵, the system of dynamic equations formed by the two reaction functions is able to explain sigmoid growth curves, constant growth curves, decreasing growth rates, and even cyclical growth curves. Figure (3) depicts the case for sigmoid growth curves.

We count then on a model of organogenesis able to explain the complementarity between organ functions, the simultaneous growth of organs until they reach a steady size, and a multiplicity of growth dynamics, including the most observed growth curve, the sigmoid growth curve. This organogenesis model is only an illustrative example of the capability of the optimal control approach to describe biological behaviors. Alternative and/or additional assumptions and constraints are perfectly possible, leading to different reaction functions and then to different interrelationships between organ populations. For instance, we can assume that the resources available for organ n not only have a maximum but also a positive minimum, and that therefore a positive number of organ n cells can live even if the number of other organ cells is zero.

⁵As is logical, it is the parameter values that are ultimately responsible.

In particular, if for organ B the amount of available resources is given by

$$T_{t+1}^B = \bar{T} - \frac{b^B}{\frac{y_{t-1}^A + G}{y_t^B}},$$

the maximum available resources are $\bar{T}$, and the minimum resources, those when $y_{t-1}^A = 0$, are no longer zero as in the previous case but

$$T_{t+1}^B = \bar{T} - \frac{b^B}{\frac{G}{y_t^B}}.$$

In this case, the organ B reaction function is

$$y_t^B(y_{t-1}^A) = \Psi^B(y_{t-1}^A) = \frac{d^B \bar{T} - d^B c^A y_{t-1}^A - m^B}{\frac{2d^B b^B}{y_{t-1}^A + G} + 2d^B c^B}. \quad (8)$$

whose representation, for a sufficiently large $\bar{T}$, is that in figure (4). It is worth noting that the dynamic analysis of the system does not change, but that, as explained above, a positive number of type B organ cells can exist even when the number of organ A cells is $y_{t-1}^A = 0$.

3.2 Tumor Formation

As a result of successive random genetic mutations and other rare events, normal cells become tumor cells. Tumor cells present some distinctive features, the most important of which are the following: i) Tumor cells are immortal, a capacity defined as *apoptosis absence*; ii) Tumor cells present *anaplasia*, that is, lack of differentiation; iii) Tumor cells self-multiply much faster than normal cells; iv) Tumor cells stimulate blood-vessel formation to self ensure blood supply, a feature defined as *angiogenesis*; v) Tumor cells destroy normal cells through invasion and expulsion; vi) Tumor cells escape from migration control processes, spreading from the original organ to numerous distant organs, a process known as *metastasis*.

These distinctive features are deeply interrelated. Firstly, together with some phenotypic characteristics of the tumor cells, angiogenesis constitutes a necessary condition for metastasis. Secondly, anaplasia seems to be responsible for the apoptosis absence and for the high self-multiplying capacity of tumor cells, and also one of the causes of metastasis. The interested reader can consult the basic aspects of cancer in King and Robins (2006) and Weinberg (2007). More advanced analyses of these relationships between the tumor main features can be found in Russo and Russo (2004a, 2004b), Han, Russo, Kohwi and Kohwi-Shigematsu (2008), Careliet and Jain (2000) and the references given by these authors.

When tumor cells are detected by the immune system, the organs produce effector cells, which combine with the tumor cells and destroy them by splitting, a phenomenon named *lysis*. As is logical, the number of effector cells produced is positively related to the number of tumor cells.

Depending on their destructive capacity, tumors are classified in benign tumors and malignant tumors or cancer. A benign tumor does not grow without limit, does not destroy the host organ, and does not metastasize. In other words, a benign tumor grows locally up to a limited size without destroying the host organ, and does not invade other organs or metastasize. On the contrary, a malignant tumor or cancer grows in an unlimited manner, destroys the host organ, and invades and metastasizes other organs. Then, the properties of malignancy are unlimited growth, destruction of the host organ and metastasis. It is worth noting that any of the aforementioned characteristics implies malignancy: a tumor that does not grow in an unlimited manner and does not destroy the organ but that metastasizes is a cancer, as well as a tumor that destroys the host organ but does not metastasize. Indeed, although in most cancers both unlimited growth and metastasis come together, 10% of cancer patients present metastasis without unlimited growth of cancer cells or destruction in the host primary organ.

Our purpose in this sub-section is to design a model, based on the optimal control theory, able to explain the tumor formation process and the distinct types of tumors. To do so, we take the organogenesis model as our starting point, and we introduce the aforementioned tumor cell characteristics and the existence of an immune system response.

Let y_t^A and y_t^B be, respectively, the number of normal cells of organ A and B . Let us assume that due to random genetic mutations and other causes, there appear tumor cells in organ A , whose number will be denoted by y_t^C . The original problem of the type A cells

$$\left. \begin{array}{l} \max_{y_t^A} d^A R_{t+1}^A y_t^A - m^A y_t^A \\ \text{subject to } R_{t+1}^A = T_{t+1}^A - c^A y_t^A - c^B y_{t-1}^B, \\ T_{t+1}^A = \bar{T} - \frac{\mu^A}{\frac{y_{t-1}^B}{y_t^A}}, \\ y_t^A \geq 0, \end{array} \right\}$$

becomes

$$\left. \begin{array}{l} \max_{y_t^A} d^A R_{t+1}^A y_t^A - M^A y_t^A \\ \text{subject to } R_{t+1}^A = T_{t+1}^A - c^A y_t^A - c^B y_{t-1}^B - c^C y_{t-1}^C, \\ T_{t+1}^A = \bar{T} - \frac{\mu^A}{\frac{y_{t-1}^B}{y_t^A}}, \\ M^A = \alpha y_{t-1}^C + m^A, \\ y_t^A \geq 0, \end{array} \right\} \quad (9)$$

Firstly, in the constraint

$$R_{t+1}^A = T_{t+1}^A - c^A y_t^A - c^B y_{t-1}^B - c^C y_{t-1}^C,$$

we introduce the fact that the existence of y_{t-1}^C tumor cells reduce the available resources for type A cells in $c^C y_{t-1}^C$, where c^C is the amount of resources detracted by one tumor cell.

Secondly, after the tumor apparition, the mortality rate of type A cells increases as does the number of tumor cells. Then, the new mortality rate of type A cells, M^A , is the normal mortality rate, m^A , plus a term positively dependent on y_{t-1}^B . In our example, the parameter α measures this dependence, $\alpha > 0$.

Solving the problem (9) for the type A normal cells, we get the reaction function for those cells,

$$y_t^A(y_{t-1}^B, y_{t-1}^C) = \Psi^A(y_{t-1}^B, y_{t-1}^C) = \frac{d^A \bar{T} - d^A c^B y_{t-1}^B - d^A c^C y_{t-1}^C - \alpha y_{t-1}^C - m^A}{\frac{2d^A c^B}{y_{t-1}^B} + 2d^A c^A}, \quad (10)$$

which provides the response of the number of type A normal cells for each previous numbers of type B cells and of type C tumor cells.

Assuming that the tumor only affects organ A , the problem for organ B is the original problem, that is

$$\text{subject to } \left. \begin{array}{l} \max_{y_t^B} d^B R_{t+1}^B y_t^B - m^B y_t^B \\ R_{t+1}^B = T_{t+1}^B - c^A y_{t-1}^A - c^B y_t^B, \\ T_{t+1}^B = \bar{T} - \frac{b^B}{\frac{y_{t-1}^A}{y_t^B}}, \\ y_t^B \geq 0. \end{array} \right\} \quad (11)$$

whose solution is the reaction function

$$y_t^B(y_{t-1}^A) = \Psi^B(y_{t-1}^A) = \frac{d^B \bar{T} - d^B c^A y_{t-1}^A - m^B}{\frac{2d^B b^B}{y_{t-1}^A} + 2d^B c^B}. \quad (12)$$

Concerning the type C tumor cells, since the tumor's objective is to grow as much as possible, the problem is

$$\text{subject to } \left. \begin{array}{l} \max_{y_t^C} D^C R_{t+1}^C y_t^C - M^C y_t^C \\ D^C = d^A(1+D), \\ M^C = \gamma y_t^C + m^C, \\ m^C = 0, \\ R_{t+1}^C = T_{t+1}^C - c^A y_{t-1}^A - c^C y_t^C, \\ T_{t+1}^C = \bar{T}(1 + \rho y_t^C), \\ y_t^C \geq 0. \end{array} \right\} \quad (13)$$

The first constraint $D^C = d^A(1 + D)$ captures the increase in the natality rate of tumor cells with respect to the normal natality rate d^A , an increase quantified in percentage by the constant $D > 0$. Since the increment in the natality rate of tumor cells is directly related to their lack of differentiation, the constant D measures the anaplasia degree.

The constraints $M^C = \gamma y_t^C + m^C$ and $m^C = 0$ describe the mortality rate of the tumor cells, which is the addition of a zero natural mortality rate (apoptosis absence), $m^C = 0$, plus the mortality rate caused by the effector cells. Since the number of effector cells depends on the number of tumor cells y_t^C , the tumor cells mortality rate is also a consequence of this concentration according to a constant $\gamma > 0$, which measures the immune system response.

The constraint $R_{t+1}^C = T_{t+1}^C - c^A y_{t-1}^A - c^C y_t^C$ captures the competition for resources between the organ A normal cells, y_{t-1}^A , and the organ A tumor cells⁶, y_t^C .

Finally, the constraint $T_{t+1}^C = \bar{T}(1 + \rho y_t^C)$, which provides the available resources for the tumor cells, incorporates the angiogenesis characteristic of tumors. Since tumor cells stimulate blood-vessel formation to self ensure blood supply, they are able to increase the maximum level of available resources as does the number of tumor cells by a percentage ρy_t^C , where $\rho > 0$ is a constant that measures the angiogenesis characteristic.

Solving the tumor cells' problem (13), we get the reaction function

$$y_t^C(y_{t-1}^A) = \Psi^C(y_{t-1}^A) = \frac{d^A(1+D)(\bar{T} - c^A y_{t-1}^A) - m^C}{2[d^A(1+D)(c^C - \rho \bar{T}) + \gamma]}. \quad (14)$$

If we assume that

$$\frac{dT^C}{dy_t^C} = \rho \bar{T} < c^C,$$

that is, that the angiogenesis process does not fully satisfy the resource requirements of the tumor cells, then the reaction function (14) describes the behavior of the tumor cells population for each number of previously existing normal cells⁷.

Finally, since the metastasis occurrence is directly related to the anaplasia and angiogenesis characteristics of the tumor, we can consider that metastasis to organ B happens if a real-valued function $O(D, \rho)$ verifying

$$\frac{\partial O(D, \rho)}{\partial D} > 0, \quad \frac{\partial O(D, \rho)}{\partial \rho} > 0,$$

takes values above a threshold $\bar{O}$ that depends on the phenotypic characteristics of the tumor cells.

The inequality

⁶Since organ B is not affected by the tumor, the competition for resources constraint does not include the term $-c^B y_{t-1}^B$.

⁷Mathematically, the inequality $\frac{dT^C}{dy_t^C} = \rho \bar{T} < c^C$ is a sufficient condition for the second order condition in the maximization problem (13).

$$O(D, \rho) > \bar{O}$$

is then a *metastasis condition*, which we will call *malignancy condition (1)*. If $O(D, \rho) > \bar{O}$, metastasis occurs and the tumor in organ A extends to organ B . Therefore the problem (11) for organ B becomes

$$\left. \begin{array}{l} \max_{y_t^B} d^B R_{t+1}^B y_t^B - M^B y_t^B \\ \text{subject to } R_{t+1}^B = T_{t+1}^B - c^B y_t^B - c^A y_{t-1}^A - c^C y_{t-1}^C, \\ T_{t+1}^B = \bar{T} - \frac{d^B}{y_{t-1}^B}, \\ M^B = \beta y_{t-1}^C + m^B, \\ y_t^A \geq 0, \end{array} \right\} \quad (15)$$

a problem analogous to problem (9) of organ A and with the same interpretation. Solving problem (15) we reach the reaction function

$$y_t^B(y_{t-1}^A, y_{t-1}^C) = \Psi^B(y_{t-1}^A, y_{t-1}^C) = \frac{d^B \bar{T} - d^B c^C y_{t-1}^A - d^B c^C y_{t-1}^C - \beta y_{t-1}^C - m^B}{\frac{2d^B c^B}{y_{t-1}^A} + 2d^B c^B}, \quad (16)$$

which provides, when metastasis occurs, the response of the type B cells number for each previous numbers of type A cells and type C tumor cells.

Metastasis also implies the apparition of an additional problem for the type C tumor cells,

$$\left. \begin{array}{l} \max_{y_t^C} D^C R_{t+1}^C y_t^C - M^C y_t^C \\ \text{subject to } D^C = d^A(1+D), \\ M^C = \gamma y_t^C + m^C, \\ m^C = 0, \\ R_{t+1}^C = T_{t+1}^C - c^B y_{t-1}^B - c^C y_t^C, \\ T_{t+1}^C = \bar{T}(1 + \rho y_t^C), \\ y_t^C \geq 0. \end{array} \right\} \quad (17)$$

as a consequence of the development of the tumor in the organ B , and with the same interpretation as problem (13). The solution of the cancer problem (17) is the reaction function

$$y_t^C(y_{t-1}^B) = \Psi^C(y_{t-1}^B) = \frac{d^A(1+D)(\bar{T} - c^B y_{t-1}^B) - m^C}{2[d^A(1+D)(c^C - \rho \bar{T}) + \gamma]}. \quad (18)$$

Let us now consider the different possibilities. When metastasis does not occur, that is when the metastasis condition does not verify and $O(D, \rho) \leq \bar{O}$, the dynamical system of equations formed by the three reaction functions

$$y_t^A(y_{t-1}^B, y_{t-1}^C) = \Psi^A(y_{t-1}^B, y_{t-1}^C) = \frac{d^A \bar{T} - d^A c^B y_{t-1}^B - d^A c^C y_{t-1}^C - \alpha y_{t-1}^C - m^A}{\frac{2d^A b^A}{y_{t-1}^B} + 2d^A c^A}, \quad (19)$$

$$y_t^B(y_{t-1}^A) = \Psi^B(y_{t-1}^A) = \frac{d^B \bar{T} - d^B c^A y_{t-1}^A - m^B}{\frac{2d^B b^B}{y_{t-1}^A} + 2d^B c^B}. \quad (20)$$

$$y_t^C(y_{t-1}^A) = \Psi^C(y_{t-1}^A) = \frac{d^A(1+D)(\bar{T} - c^A y_{t-1}^A)}{2[d^A(1+D)(c^C - \rho \bar{T}) + \gamma]}. \quad (21)$$

describes the interrelated behavior between organ *A* normal cells, organ *B* normal cells, and organ *A* tumor cells. These are the reaction functions corresponding to problems (9), (11) and (13), when the tumor only affects organ *A*.

These reaction functions are, graphically, those in figures (5), (6) and (7). In figure (5), where the reaction function of the organ *A* normal cells is depicted, it is possible to explore the effects on organ *A* of an increase in the number of tumor cells y_t^C . Given the expressions of the slope at $y_t^B=0$

$$\lim_{y_{t-1}^B \rightarrow 0} \frac{dy_t^A}{dy_{t-1}^B} = \frac{d^A \bar{T} - m^A - (d^A c^C + \alpha) y_{t-1}^C}{2d^A b^A},$$

and of the abscissa at $y_t^A=0$,

$$\frac{d^A \bar{T} - m^A - (d^A c^C + \alpha) y_{t-1}^C}{c^B d^A},$$

and since

$$y_{M1}^B = \frac{-2b^A c^B d^A + \sqrt{(2b^A c^B d^A)^2 - 4c^A c^B d^A b^A (m^A + (d^A c^C + \alpha) y_{t-1}^C - d^A \bar{T})}}{2d^A c^A c^B},$$

it can be concluded that an increment in the number of tumor cells implies a downward displacement of the reaction function and a decrease in y_{M1}^B .

The reaction function of the organ *B* cells, $y_t^B = \Psi^B(y_{t-1}^A)$, remains unchanged, as depicted in figure (6).

Concerning the reaction function of the organ A tumor cells $y_t^C = \Psi^C(y_{t-1}^A)$, a straight line with slope

$$\frac{dy_t^C}{dy_{t-1}^A} = - \frac{d^A(1+D)c^A}{2[d^A(1+D)(c^C - \rho\bar{T}) + \gamma]}$$

and ordinate at $y_t^B=0$

$$\frac{\bar{T}}{C^A},$$

the representation is that in figure (7).

It is also useful to represent the reaction function of the organ A normal cells $y_t^A = \Psi^A(y_{t-1}^B, y_{t-1}^C)$ in the space (y_t^A, y_t^C) .

In this case, since the slope is

$$\frac{dy_t^A}{dy_{t-1}^C} = - \frac{d^A c^C \bar{T} + \alpha}{2 \frac{d^A c^B}{y_{t-1}^B} + 2d^A c^A},$$

the ordinate at $y_{t-1}^C=0$ is

$$y_t^A = \frac{d^A \bar{T} - d^A c^B y_{t-1}^B - m^A}{\frac{2d^A c^B}{y_{t-1}^B} + 2d^A c^A},$$

and the abscissa at $y_t^A=0$ is

$$y_{t-1}^C = \frac{d^A \bar{T} - d^A c^B y_{t-1}^B - m^A}{d^A c^C + \alpha},$$

the representation is that in figure (8).

From the expressions of the slope, ordinate at $y_{t-1}^C=0$ and abscissa at $y_t^A=0$, it is clear that a decrease in y_{t-1}^B originates a decrease in the absolute value of the slope, an increase in the abscissa at $y_t^A=0$, and a decrease in ordinate at $y_{t-1}^C=0$. As is logical, the contrary occurs if y_{t-1}^B increases.

It is worth noting that although this model of tumor processes is very simple, it allows some interesting conclusions to be deduced. In particular, the proposed model can provide a

dynamic explanation of how tumors affect the distinct organs, and allows several varieties of tumor processes to be distinguished.

To see this, let me consider the system of equations (19)–(21) describing the interrelated behavior of organ *A*, organ *B* and tumor when metastasis to organ *B* does not occur. Let me also assume that the genesis of organs *A* and *B* is characterized by sigmoid growth curves⁹ such as those originated by the reaction functions depicted in figure (3).

Before the apparition of tumor cells, the steady numbers of organ *A* and *B* normal cells are y_{ss0}^A and y_{ss0}^B . The initial situation, that corresponding to $y_{t-1}^C=0$, is represented by points *E* and *E'* in figure (9), since the curve $\Psi^A(y_{t-1}^B, y_{t-1}^C)$ in the space (y_t^A, y_t^C) must be that associated with $y_{t-1}^C=0$ and $y_{t-1}^B=y_{ss0}^B$.

However, once the tumor cells appear, since this implies $dy_{t-1}^C > 0$, the number of organ *A* normal cells reacts according to the reaction function $\Psi^A(y_{t-1}^B, y_{t-1}^C)$ in the space (y_t^A, y_{t-1}^C) , and, simultaneously, the reaction function $\Psi^A(y_{t-1}^B, y_{t-1}^C)$ turns downward on the origin in the space (y_t^A, y_{t-1}^C) . Consequently, the number of organ *B* normal cells changes according to $\Psi^B(y_{t-1}^A)$, and then the number of organ *A* normal cells also varies, given by the new $\Psi^A(y_{t-1}^B, y_{t-1}^C)$.

Now, the number of organ *A* tumor cells reacts to the new number of organ *A* normal cells according to $\Psi^C(y_{t-1}^A)$, and the described process is repeated taking into account that, in the space (y_t^A, y_{t-1}^C) , the new number of organ *A* normal cells is given by a different reaction function since y_t^B has changed.

This dynamic process, represented in figure (9), is the following:

$$y_0^C > 0 \Rightarrow y_1^A \Rightarrow y_2^B \Rightarrow y_3^A \Rightarrow y_4^C \Rightarrow y_5^A \Rightarrow \dots$$

Although the dynamic analysis looks complicated and the casuistry seems to be very large, the analysis of the tumor processes reduces to a simple exercise in the space (y_t^A, y_{t-1}^C) . This is due to two reasons.

The first is that, in the space (y_t^A, y_{t-1}^C) , the ordinate at $y_{t-1}^C=0$ of $\Psi^A(y_{t-1}^B, y_{t-1}^C)$ must always be lower than the ordinate at $y_{t-1}^C=0$ of $\Psi^C(y_{t-1}^A)$. Since the ordinate at $y_{t-1}^C=0$ of $\Psi^A(y_{t-1}^B, y_{t-1}^C)$,

$$\frac{d^A \bar{T} - d^A c^B y_{t-1}^B - m^A}{\frac{2d^A b^A}{y_{t-1}^B} + 2d^A c^A},$$

⁸Like the organogenesis model, this tumor formation model is only an illustrative example of the capability of the optimal control approach to describe biological behaviors. As with the organogenesis model, alternative and/or additional assumptions and constraints are perfectly possible, leading to different reaction functions and then to different interrelationships between normal and tumor cells.

⁹This is the more usual growth curve. Other assumptions about the growth curves would not modify the reasonings.

is the maximum number of organ *A* normal cells when the number of organ *B* cells is y_{t-1}^B , this number must be always be lower than the maximum number of organ *A* normal cells when $y_{t-1}^B=0$ and $y_{t-1}^C=0$, given by $\bar{y}_{t-1}^A$, just the ordinate at $y_{t-1}^C=0$ of $\Psi^C(y_{t-1}^A)$. The second reason is that the changes in the number of organ *B* cells merely cause shifts of $\Psi^A(y_{t-1}^B, y_{t-1}^C)$, shifts that can never violate the above mentioned fact.

In particular, the dynamic analysis of the system of equations (19)–(21) in the space (y_t^A, y_{t-1}^C) allows two kinds of tumor processes to be distinguished.

In the first case, the evolution of the normal and tumor cell numbers is such that the sequence of reaction functions $\Psi^A(y_{t-1}^B, y_{t-1}^C)$ always lies below the reaction function $\Psi^C(y_{t-1}^A)$. In this type of tumor, it is easy to show by

carrying out the standard dynamic analysis that the tumor grows without limit until the complete destruction of the organ *A*, and then the tumor is a cancer.

To see how this malignant tumor proceeds, let us assume that the initial reaction functions $\Psi^A(y_{ss0}^B, y_{t-1}^C)$ and $\Psi^C(y_{t-1}^A)$ are those represented in figures (10) or (11). Once the tumor appears, from the initial situation $(y_{ss0}^A, y_{ss0}^B, y_{t-1}^C=0)$, represented by points *E* and *E'*, the system evolves as we previously explained, an evolution depicted in figures (10) and (11). Firstly, since the number of tumor cells is $y_0^C > 0$, the number of organ *A* cells reacts according to $y_1^A = \Psi^A(y_{ss0}^B, y_0^C)$, and, for this number, in the space (y_t^A, y_{t-1}^B) , the number of organ *B* cells changes to y_2^B due to the modification of y^A . Then, in the space (y_t^A, y_{t-1}^C) , the reaction function for the organ *A* normal cells changes to $\Psi^A(y_2^B, y_{t-1}^C)$, which, as assumed, lies below $\Psi^C(y_{t-1}^A)$. Since in the space (y_t^A, y_{t-1}^B) the reaction function $\Psi^A(y_{ss0}^B, y_0^C)$ is below the initial one, the number of organ *A* normal cells corresponding to y_2^B , given by $y_3^A = \Psi^A(y_2^B, y_0^C)$, is lower than y_2^A , and therefore, according to $\Psi^C(y_{t-1}^A)$, the number of tumor cells increases to y_4^C . This process continues until the total disappearance of the organ *A* normal cells. If we represent the initial and final reaction functions for the type *A* cells, the initial situation is depicted by *E* and *E'* whilst the final situation is represented by *F* and *F'*.

Note that this final situation can imply a zero population of organ *B* cells ($y_F^B=0$) if the reaction functions are as in figure (2), but also a positive number of organ *B* cells ($y_F^B>0$) if the reaction functions are as in figures (4) and (11).

In addition to this malignant tumor case, our simple model also predicts the existence of benign tumors that grow locally and do not destroy the host organ. In this second case, the evolution of the numbers of normal and tumor cells is such that the sequence of reaction functions $\Psi^A(y_{t-1}^B, y_{t-1}^C)$ implies the cut between the final reaction function of organ *A* normal cells $\Psi^A(y_F^B, y_{t-1}^C)$ and the reaction function of the tumor cells $\Psi^C(y_{t-1}^A)$. Following the standard dynamic analysis, it is easy to show that, in this case and as depicted in figures (12) and (13), the steady number of cells (y_F^A, y_F^B, y_F^C) are all positive, that the organ *A* is not destroyed by the tumor, and that the tumor cells and the organ *A* normal cells coexist. To see how this benign tumor proceeds, let us assume that the initial reaction functions $\Psi^A(y_{ss0}^B, y_{t-1}^C)$ and $\Psi^C(y_{t-1}^A)$ are the represented in figures (12) or (13). Once the tumor

appears, from the initial situation $(y_{ss0}^A, y_{ss0}^B, y_{t-1}^C=0)$, represented by points E and E' , the system evolves as we previously explained, an evolution depicted in figures (12) and (13). Firstly, since the number of tumor cells is $y_0^C > 0$, the number of organ A cells reacts according to $y_1^A = \Psi^A(y_{ss0}^B, y_0^C)$, and, for this number, in the space (y_t^A, y_{t-1}^B) , the number of organ B cells changes to y_2^B due to the modification of y^A . Then, in the space (y_t^A, y_{t-1}^C) , the reaction function for the organ A normal cells changes to $\Psi^A(y_2^B, y_{t-1}^C)$, which, as assumed, lies below $\Psi^C(y_{t-1}^A)$. Since in the space (y_t^A, y_{t-1}^B) the reaction function $\Psi^A(y_{ss0}^B, y_0^C)$ is below the initial, the number of organ A normal cells corresponding to y_2^B , given by $y_3^A = \Psi^A(y_2^B, y_0^C)$, is lower than y_2^A , and therefore, according to $\Psi^C(y_{t-1}^A)$, the number of tumor cells increases to y_4^C . This process continues until the system reaches the steady state (y_F^A, y_F^B, y_F^C) . If we represent the initial and final reaction functions for the type A cells, the initial situation is depicted by E and E' whilst the final situation is represented by F and F' .

From the mathematical point of view, the crucial characteristic determining whether a tumor is malignant or benign is the relationship between the abscissas at $y_t^A=0$ of the reaction functions $\Psi^A(y_F^B, y_{t-1}^C)$ and $\Psi^C(y_{t-1}^A)$. According to the standard stability analysis, if

$$\frac{d^A \bar{T} - d^A c^B y_F^B - m^A}{d^A c^C + \alpha} < \frac{d^A (1+D) \bar{T}}{2[d^A (1+D)(c^B - \rho \bar{T}) + \gamma]},$$

the steady value for the organ A normal cells is zero, the organ A is destroyed, and the tumor is malignant, while if

$$\frac{d^A \bar{T} - d^A c^B y_F^B - m^A}{d^A c^C + \alpha} > \frac{d^A (1+D) \bar{T}}{2[d^A (1+D)(c^B - \rho \bar{T}) + \gamma]},$$

the steady value for the organ A normal cells is positive, the organ A is not destroyed, and the tumor is benign. Then, from the mathematical point of view, the condition

$$\frac{d^A \bar{T} - d^A c^B y_F^B - m^A}{d^A c^C + \alpha} < \frac{d^A (1+D) \bar{T}}{2[d^A (1+D)(c^B - \rho \bar{T}) + \gamma]} \quad (22)$$

is a malignancy condition when there is no metastasis, which we will call *malignancy condition* (2).

The mathematical analysis of this *malignancy condition* (2) is interesting from the bio-medical perspective. Since in a malignant tumor this condition must be verified, the malignant case is more probable when i) D is higher; ii) α is higher; iii) ρ is higher. In other words, the more intense the tumor characteristics are (in mathematical terms, the higher the parameters capturing these characteristics are), the higher the probability of organ destruction. Indeed, since

$$\frac{d}{dD} \left(\frac{d^A(1+D)\bar{T}}{2[d^A(1+D)(c^B - \rho\bar{T}) + \gamma]} \right) > 0, \quad (23)$$

$$\frac{d}{d\rho} \left(\frac{d^A(1+D)\bar{T}}{2[d^A(1+D)(c^B - \rho\bar{T}) + \gamma]} \right) > 0, \quad (24)$$

$$\frac{d}{d\alpha} \left(\frac{d^A\bar{T} - d^A c^B y_F^B - m^A}{d^B c^B + \alpha} \right) < 0, \quad (25)$$

the higher the anaplasia characteristic of the tumor cells, the higher their angiogenesis capacity, and the higher the tumor induced mortality, the higher the term

$$\frac{d^B(1+D)\bar{T}}{2[d^B(1+D)(c^B - \rho\bar{T}) + \gamma]}$$

and the higher the probability of an unlimited growth of the tumor and of the destruction of the host organ.

Additionally, since

$$\frac{d}{d\gamma} \left(\frac{d^B(1+D)\bar{T}}{2[d^B(1+D)(c^B - \rho\bar{T}) + \gamma]} \right) < 0, \quad (26)$$

the higher γ is, the higher the probability of organ survival is. In other words, the stronger the immune system response is, the higher the probability of a steady size of the tumor without destruction of the organ.

It is worth noting that, according to our model, when there is no metastasis, the crucial cancer characteristic determining malignancy is angiogenesis, in the sense we are explaining¹⁰. Since

$$\lim_{D \rightarrow \infty} \frac{d^A(1+D)\bar{T}}{2[d^A(1+D)(c^B - \rho\bar{T}) + \gamma]} = \frac{\bar{T}}{2(c^B - \rho\bar{T})},$$

the capacity of a tumor to grow indefinitely and to completely destroy an organ through raising its self-multiplying capacity, measured by D , is limited. In other words, given the values for α , ρ and γ , the mere increase of D is not sufficient to lead to organ destruction.

¹⁰As explained before, angiogenesis is also determinant of metastasis, and then constitutes the main malignancy condition.

In the same sense, since the tumor destroys the organ A normal cells by expulsion and invasion, the parameter α has a natural limit given by the size of a tumor cell or, alternatively, the unity. If we call this limit $\bar{\alpha}$, since

$$\lim_{\alpha \rightarrow \bar{\alpha}} \frac{d^A \bar{T} - d^A c^B y_F^B - m^A}{d^A c^C + \alpha} = \frac{d^A \bar{T} - d^A c^B y_F^B - m^A}{d^A c^C + \bar{\alpha}},$$

we can conclude that the capacity of a tumor to grow indefinitely and to completely destroy an organ through raising its normal cell destruction capacity, measured by α is limited. In other words, given the values for D , ρ and γ , the increase of α up to its limit value is not sufficient to lead to organ destruction.

However, given that

$$\lim_{\rho \rightarrow \frac{c^C}{\bar{T}}} \frac{d^A (1+D) \bar{T}}{2[d^A (1+D)(c^B - \rho \bar{T}) + \gamma]} = \infty,$$

simply by bringing its angiogenesis capacity ρ closer to the very low value of $\frac{c^C}{\bar{T}}$, the tumor can always grow indefinitely and completely destroy the host organ.

Concerning the capacity of the immune system to avoid tumor growth and organ destruction, since

$$\lim_{\gamma \rightarrow \infty} \frac{d^A (1+D) \bar{T}}{2[d^A (1+D)(c^B - \rho \bar{T}) + \gamma]} = 0,$$

a strong enough response of the immune system would always be able to stop the tumor growth and to ensure the survival of the organ.

Having analyzed the non-metastasis case, let us consider the evolution of the tumor when metastasis occurs. If the metastasis condition verifies, that is when $O(D, \rho) > \bar{O}$, the tumor extends to organ B , and the problems defining the behavior of the involved cells are problem (9) (problem of organ A when the tumor affects organ A), problem (13) (problem of tumor cells affecting organ A), problem (15) (problem of organ B when the tumor affects organ B), and problem (17) (problem of tumor cells affecting organ B). Then, the set of reaction functions defining the interrelated behavior is

$$y_t^A(y_{t-1}^B, y_{t-1}^{C(A)}) = \Psi^A(y_{t-1}^B, y_{t-1}^{C(A)}) = \frac{d^A \bar{T} - d^A c^B y_{t-1}^B - d^A c^C y_{t-1}^{C(A)} - \alpha y_{t-1}^{C(A)} - m^A}{\frac{2d^A c^A}{y_{t-1}^B} + 2d^A c^A}, \quad (27)$$

$$y_t^{C(A)}(y_{t-1}^A) = \Psi^{C(A)}(y_{t-1}^A) = \frac{d^A (1+D)(\bar{T} - c^A y_{t-1}^A)}{2[d^A (1+D)(c^C - \rho \bar{T}) + \gamma]}, \quad (28)$$

$$y_t^B(y_{t-1}^A, y_{t-1}^{C(B)}) = \Psi^B(y_{t-1}^A, y_{t-1}^{C(B)}) = \frac{d^B \bar{T} - d^B c^C y_{t-1}^A - d^B c^C y_{t-1}^{C(B)} - \beta y_{t-1}^{C(B)} - m^B}{\frac{2d^B y_{t-1}^B}{y_{t-1}^A} + 2d^B c^B}, \quad (29)$$

$$y_t^{C(B)}(y_{t-1}^B) = \Psi^{C(B)}(y_{t-1}^B) = \frac{d^A(1+D)(\bar{T} - c^B y_{t-1}^B) - m^C}{2[d^A(1+D)(c^C - \rho \bar{T}) + \gamma]}, \quad (30)$$

where $C(A)$ and $C(B)$ denote, respectively, the number of cancer cells in organs A and B .

The analysis of this dynamic system of equations is very similar to those obtained for the non-metastasis case, so we will not discuss the different cases¹¹ when metastasis occurs.

However, it is worth relating the metastasis and non-metastasis cases and verifying that the two obtained malignancy conditions are consistent with the observed behavior of tumors. In particular, when none of the malignancy conditions verify, the tumor is a benign tumor that grows locally until reaching a steady size and without destroying the host organ. Since both malignancy conditions positively depend on the anaplasia and angiogenesis degrees, the lower these tumor characteristics are, the higher the probability of benignity of the tumor. On the contrary, for the same reason, when anaplasia and angiogenesis degrees are high, the verification of the two malignancy conditions is more probable, and the tumor will grow in an unlimited manner, will destroy the host organ, and will also metastasize to other organs. Indeed, as predicted by our model, most cancers present these characteristics jointly, but there also exist cancers that metastasize and do not destroy the host organ, and cancers that grow without limit and completely undermine the host organ but do not metastasize. In our proposed model, these cases would be those corresponding to values of D and ρ such that only one of the two malignancy conditions verifies. In particular, if the anaplasia and angiogenesis degrees imply values for D and ρ for which

$$O(D, \rho) \leq \bar{O}$$

and

$$\frac{d^A \bar{T} - d^A c^B y_F^B - m^A}{d^A c^C + \alpha} < \frac{d^A(1+D)\bar{T}}{2[d^A(1+D)(c^B - \rho \bar{T}) + \gamma]},$$

then the tumor does not metastasize, but grows without limit destroying the host organ. In the other case, when

$$O(D, \rho) > \bar{O}$$

¹¹It is easy to show that, in this case, the cancer can grow in organs A and B with or without limit, depending on the verification of the corresponding malignancy condition (2) for each organ.

and

$$\frac{d^A \bar{T} - d^A c^B y_F^B - m^A}{d^A c^C + \alpha} > \frac{d^A (1+D) \bar{T}}{2[d^A (1+D)(c^B - \rho \bar{T}) + \gamma]},$$

the tumor grows without destroying the host organ but metastasizes.

Finally, with respect to the tumor growth dynamics, the proposed model is able to explain a wide variety of growth curves, including the usually observed sigmoid growth curve. For instance, the dynamic processes in figures (11) and (13) -for a malignant and benign tumor, respectively-, imply the sigmoid growth curve for the tumors depicted in figure (14), first accelerating and the decelerating up to a limit. Applying the above explained dynamic analysis for alternative reaction functions, different tumor growth curves could be obtained, including constant, decreasing and cyclical growth curves.

4 Conclusions

In a biological phenomenon where several bio-entities are involved, the behavior of each bio-entity is in part autonomous and in part dependent on the behavior of the other bio-entities. Given these characteristics, optimal control theory appears as the most appropriate approach to study biological phenomena. In essence, optimal control theory considers the problem of achieving an objective subject to some external constraints. We can then consider that the objective is the goal of the bio-entity (the autonomous component of the behavior), and that the constraints describe the influence of the other bio-entities. Therefore, the optimal control theory provides a complete explanation of the observed behaviors: the bio-entities pursue their own specific objectives, the actions of a bio-entity affects the possibilities of the other entities to achieve their objectives, and as a result, all the behaviors are interrelated. However and to our knowledge, the interpretation of biological phenomena as the result of a set of optimal control problems has not yet been considered by current biomathematics. In this respect, taking economic oligopolistic models as our starting point, the purpose of this paper is to show how this application of optimal control theory is a promising approach to the analysis of biomedical questions.

To illustrate the ability of the optimal control approach to explain and describe biological behaviors, we have built two simple models. The first model, an organogenesis model, allows the main characteristics of this process to be replicated, in particular the simultaneous growth of organs, the existence of limit steady sizes, and the role of the complementarity between organ functions. Additionally, the model explains a wide variety of growth curves, including sigmoid growth curves.

The second model, a tumor formation model, is also able to mathematically reproduce the observed behavior of tumors. More specifically, the proposed optimal control model agrees with medical and biological findings, and allows the role of the tumor main characteristics to be quantified and clarified. In particular, we explain the existence of malignant and benign tumors, we identify two malignancy conditions that rest on the angiogenic and anaplastic characteristics of the tumor, we explain the observed different types of malignant tumors on the basis of these malignancy conditions, we conclude that angiogenesis is specially significant in determining malignancy, and we obtain a wide variety of tumor growth curves including the sigmoid growth curve.

As explained in the introductory section, the purpose of this paper is to show how optimal control theory can help the analysis of biomedical questions and phenomena. From this perspective, the proposed models must be understood as simple and illustrative examples of the capabilities of the optimal control approach in the study of biological behaviors. Therefore, future research will require both theoretical and empirical efforts. Firstly, from the empirical point of view, it would be necessary to build operative models with descriptive and therapeutic applications. This would require, through medical and biological experimentation, the finding of accurate quantitative measures of the involved objective functions, constraint functions and parameters, mainly in order to estimate the two malignancy conditions. Secondly, from the theoretical point of view, it would be advisable to continue studying the application of optimal control theory to the analysis of biological behaviors, and to develop specific optimal control models for each bio-medical phenomenon.

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Figure 1.
Reaction Function of Organ A.

Figure 2.
Organogenesis Dynamics.

Figure 3.
Organ A Sigmoid Growth Curve.

Figure 4.
Organogenesis Dynamics.

Figure 5.
Organ A Normal Cells Reaction Function.

Figure 6.
Organ B Cells Reaction Function.

Figure 7.
Tumor Cells Reaction Function.

Figure 8.
Organ A Normal Cells Reaction Function

Figure 9.
Tumor Dynamics.

Figure 10.
Malignant Tumor Case: Unlimited Growth and Destruction of the Host Organ.

Figure 11.
Malignant Tumor Case: Unlimited Growth and Destruction of the Host Organ without Metastasis.

Figure 13.
Benign Tumor Case.

Figure 14.
Tumor Sigmoid Growth Curve.