



A review of models for cancer chemotherapy based on Optimal Control

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Abstract

Besides all the improvements regarding cancer research, cancer is still the major cause of death in developed countries.^[1] Indeed, the current therapies have several relevant limitations. Beyond chemotherapy inherent toxicity, cancer cells develop inevitably drug resistance.^[2] This stresses the necessity of better treatment options such as immunotherapy.^[2]

In this report some mathematical models for cancer chemotherapy are reviewed which consider the onset of drug resistance and the combination of a chemotherapeutic agent and an immune boost. Then optimal control problems are formulated. The objective is not to cure cancer^[3] but rather obtain the best therapy profile that will lead to the best clinical results.

1. INTRODUCTION

UNFORTUNATELY, even in the twenty-first century, cancer is still one of the most arduous conditions to treat clinically and the major cause of mortality in developed western societies.^[4] In fact, tumors are high-mortality diseases.^[1] Although they all differ from each other, all exhibit a derangement of cellular proliferation which usually results in an uncontrolled cell growth.^[1]

Currently, there are three therapies used for the cancer treatment. Surgery comprises the removal of the solid tumor; chemotherapy involves the administration of anti-cancer drugs and finally radiotherapy which uses X-rays.^[4] Although it has been witness a great investment in cancer

research and an advance in the knowledge of cancer biology, the overall efficiency of the current therapeutic approaches remains questionable.^[4] In fact, the last two approaches aforementioned have significative side-effects since some of the healthy proliferating cells are also undesirably affected.^[4] Therefore, the treatment itself causes significant morbidity and mortality.^[4] All this stresses the importance and interest of design new therapeutic approaches to treat cancer or overcome some of the current barriers associated with these therapeutics.^[4]

Biological systems are a highly complex dynamic nonlinear systems composed by many interacting variables.^[4] Therefore, modern applied mathematics plays an important role in clarifying several characteristics of their dynamical behaviour and at the same time enables the control and prediction of their evolution.^[4] Consequently, mathematical modulation is increasingly appreciated by experimentalists and even clinicians.^[4] By applying this mathematical modulation to cancer treatments, it is possible to modulate the immune response to cancer while designing an optimal immunotherapy treatment.^[4] However, in order to correctly design these mathematical models it is indispensable to understand how the immune system works and how it interact with tumors within the body.

The immune system is comprised by an interplay of a system of cells and molecules within the human body which are its basic defense against foreign organisms and pathogenic agents.^[5] The immune system can be divided into two distinct systems: the innate and the adaptive one.^[4]

The innate immune system of vertebrate animals uses three strategies of immune recognition: recognition of *microbial nonself* (recognition of conserved products of microbial metabolism unique to microorganisms); recognition of *missing self* (detection of markers unique to the host which culminates in the inhibition of immune responses against self) and recognition of *induced or altered self*.^[6] The last form of recognition comprises the detection of markers of abnormal self induced upon infection and cellular transformation.^[6] Then the affected cells are tagged for elimination by the immune system.^[6] Consequently the innate immune response is a rapid response which acts similarly as response to foreign substances, even in the case of repeated infections, since it does not “*distinguish fine differences among foreign substances*”.^[4] This system also integrates with the components of the adaptative one “*by stimulating and influencing the nature of adaptive immune responses*”.^[4] Cells such as natural killer cells, granulocytes, neutrophils, basophils, mast cells, monocytes and macrophages are components of the innate immune system.

The adaptive immunity come as a response to infection.^[4] However, contrary to the innate immune responses, the response of the adaptive immune system is highly specific for distinct macromolecules.^[4,7] In addition, the adaptive immune system has memory, so that if re-infected by the same organism, its response is faster and vigorous.^[4,7] Lymphocytes, which are a class of white blood cells, play an important role in this type of immunity.^[4] Each sub-population of lymphocytes express specific membrane proteins.^[4] B-lymphocytes comprise the humoral adaptive immune response and, when stimulated by pathogenic agents, produce antibody molecules which are released in the blood.^[4] These antibodies bind to to the antigens, marking them for elimination by other cells of the immune system, such as macrophages.^[4] In addition, these antibodies can coat antigens such as viruses, neutralizing them and preventing cell invasion.^[4] Moreover, they can also activate the complement system, system of blood enzymes, which binds to these antibody-coated structures and removes them.^[4,8] In turn, T-lymphocytes are responsible for cell-mediated immune responses.^[4] Their antigen receptors recognize and bind to specific structures on the membrane of target cells.^[4] These structures consist in heterotrimers of the major histocompatibility complex (MHC) and a bound antigenic peptide.^[4] Molecules of MHC class I are expressed practically on almost all cells of the human body and presented on their surface.^[4] In turn, MHC class II are only expressed by professional antigen presenting cells (APCs).^[4] When T-lymphocytes recognize the peptide presented on the surface of a target cell, they bind to the cell triggering several cell-signaling mechanisms.^[4]

Class II MHC-peptide complexes bind specifically to a sub-population of T-lymphocytes, called helper T-cells, which then release substances that stimulate various components and mechanisms of both immunity systems.^[4] Finally, class I MHC-peptide complexes bind to cytotoxic T-lymphocytes (CTLs), which then deliver apoptotic signals and kill the target cell.^[4]

Usually, tumor cells undergo several genetic and epigenetic events which lead to the appearance of specific antigens as result of certain biological events, such as synthesis of mutated proteins, under or overexpression of normal proteins and many others.^[1,9-11] All this triggers reactions by both the innate and adaptive immune system.^[1,9-11]

2. IMMUNE SYSTEM RESPONSE TO CANCER: CANCER DORMANCY

CANCER, or in other words a malignant tumor, is a “*tumor that invades surrounding tissues, traverses at least one basement membrane zone, grows in the mesenchyme at the primary site and has the ability to grow in a distant mesenchyme, forming secondary cancers or metastases*”.^[4]

The competitive interaction between the immune system and tumor cells is extremely complex, since it implies a considerable number of events and molecules, and the kinetics of the interplay is strongly nonlinear.^[1] The outcome of this interplay is not restricted to tumor suppression or tumor outbreak, since there exist many intermediate scenarios.^[1] Sometimes cancers can take months, days or even years until they present clinical manifestations.^[4,12-15] In fact, tumours can grow slowly or exist in a near-steady-state size for a long period which is described as cancer dormancy.^[4,15,16] This is a result of the establishment of a dynamic equilibrium between tumor and the immune system, allowing the tumor survival in a microscopic undetectable dormant state.^[17-19] The presence of these dormant cancer cells in the body actually dictates the outcome of the disease.^[4] However this equilibrium can be disrupted by sudden events influencing the immune system.^[1] Factors such as age, stress factors, disease related impairments of innate and adaptive immune systems, infections, cancer treatments, immuno-suppressive treatments or other alterations in the host can trigger the initiation of an uncontrolled growth of these cells and subsequent waves of metastases.^[1,4,20,21] Besides the causes related with immuno-suppression, there are also a major class of causes of disruption of this equilibrium.^[1] These causes are related with the adaptative process immuno-editing.^[22] As time goes by, the neoplasm may develop several strategies to overcome the action of the immune system.^[10,22] Therefore, it grows back^[18,22] reaching clinically apparent tumors.^[23]

The early stage of primary tumor formation, which can last up to several years^[24,25], is normally characterized by the absence of a vascular network^[4]. This limitation of growth could be due to the “*competition between tumor cells for metabolites, a direct cytostatic/cytotoxic effect produced by the tumor cells on each other, and the competition between tumor cells and cells of the immune system for metabolites*”.^[4] In addition, in solid tumours can occur an equilibrium between cell proliferation and cell death.^[4]

The slow growth of tumours and their regression can also be explained by the reaction of the host immune system to the emergent tumor cells.^[4] Therefore, a malignant tumor in this steady-state, if controlled locally by the host (e.g. via immune system) might persist for months or years.^[21]

In fact, tumours can express antigens at very early stages leading to their intensive lymphoid, granulocyte and monocyte infiltration.^[4] A particularly pronounced infiltration might be correlated with a favorable prognosis.^[26-28] In this early avascular stage and subsequent stages of tumor growth occurs a chronic inflammatory infiltration of neutrophils, eosinophils, basophils, monocytes/macrophages, T-lymphocytes, B-lymphocytes and natural killer (NK) cells.^[28-30] They penetrate and accumulate in the interior of the tumor “*due to attractants secreted from the tumor tissue and the high locomotive*

ability of activated immune cells [108]”.[4] In this stage, the tumor-infiltrating cytotoxic lymphocytes (TICLs), which can be cytotoxic lymphocytes, natural killer-like (NK-like) cells and/or lymphokine activated killer (LAK) cells, can eliminate effectively the tumor development.[12, 27, 30–32] Although less frequently, cytostatic/cytotoxic activity of monocytes/macrophages and granulocytes can be found in the tumor.[31–33]

Furthermore, the immuno-oncologic dynamics is influenced by a range of spatial phenomena.[1] The interplay between the tumor and the immune system is strongly dependent on the mobility of both tumor cells and the effector cells of the immune system.[19] Indeed, the spatial distribution of the TICLs seems to influence the outcome of the interactions between them and the tumor cells of a solid tumor.[4] Usually, there is a thick shell of lymphoid infiltration around the tumor[34, 35] and near the central hypoxic zone[36]. [4] Therefore, it is defined an internal structure formed by alternate regions of cell proliferation and cell death.[4, 37] The TICLs are located near the region of tumoural cell death.[37] However there is a limited understanding and knowledge of the “*spatiotemporal dynamics of TICLs in avascular tumours and in micrometastases in vivo*”.[4] Furthermore, cytoquines and other components of the immune system are also involved in the modulation of the local cellular immune response dynamics.[4]

Three-dimensional tissue cultures have been used in order to model the heterogeneity of microenvironmental and population changes in solid tumours.[4] Still, this approach has some issues.[4] For instance, it is difficult to control experimentally all of the interacting elements in a tumor.[4] Furthermore, the immune system is a complex biological system and the behavior of the cancer in vivo is not always the one predicted by experimental investigations in vitro.[38] In this sense, mathematical models of tumor–immune interactions and computer simulations have a fundamental hole in this area.[4, 39] They are helpful to understand some important features of these intricate systems[8, 38] and address specific questions related with tumor–immune dynamics and tumor treatment options[39].

3. TUMOR GROWTH MODELS

The tumor growth model is a positive-valued, continuous, monotonically increasing function which describes the tumor cell population per unit time.[40] Ideally, any growth model should have a physiological basis, a minimum number of arbitrary constants and also measurable variables to enable the collection of experimental data.[41] In addition, it should give a good fit to the experimental data, predict the tumor growth with reasonable accuracy and it should be applicable to different patients or animals with the same type of tumor.[41]

The models used for the modulation of tumor growth can be phenomenological or mechanistic. The phenomenological models are descriptive models, which are not based on mechanistic or biological processes and parameters.[42] In turn, the mechanistic ones are explicative models, which incorporate the influence of complex biological factors and processes such as angiogenesis, effects of the immune system on cancer, influence of cancer stem cells on cell-growth pattern and therapy resistance, or tumor heterogeneity.[42]

While phenomenological models, which are simpler than the mechanistic ones, proved to be able to forecast and describe experimental or clinical data; mechanistic models have limited preclinical and no clinical application until to date.[42] This sophisticated models are based only on *in silico* testing, with no correlation with experimental clinical observations.[42] Therefore, there are several questions regarding their reliability and applicability in the development of drug regimens in patients.[42]

Whereas the majority of the current computational oncology models study cancer at a single biological scale (e.g. angiogenesis or metastatic spreading), there are also multiscale models, which

encompasses at least two spatial scales and/or includes physical or biological processes that occur at two or more temporal scales.^[42] These models articulate a variety of molecular, subcellular, cellular, tissue, and whole-body processes whose combination results in a global more-realistic model of tumour growth, enabling the translation of the complexity of cancer systems biology into clinical applications.^[42] In other words, lower-level (molecular and subcellular levels) processes are coupled with small spatial scales and fast dynamics.^[42] In turn, higher-level (cellular and tissues levels) processes, which generally occur at large spatial scales, are coupled with slow dynamics.^[42] However, it is far more difficult to develop multiscale cancer models than single scale models since it requires the quantification of many parameters based on the available literature and preclinical and/or clinical data, and definition of the relationships between various biological processes.^[43] The simulation of several treatment approaches (with variable drugs, dosing, and scheduling) *in silico* remains an authentic challenge.^[42]

3.1. Phenomenological Models

In this section the most important phenomenological models will be analyzed, dividing them accordingly to the shape of their solution. Figure 1 depicts the tumor growth curves of all the phenomenological models discussed in this subsection.

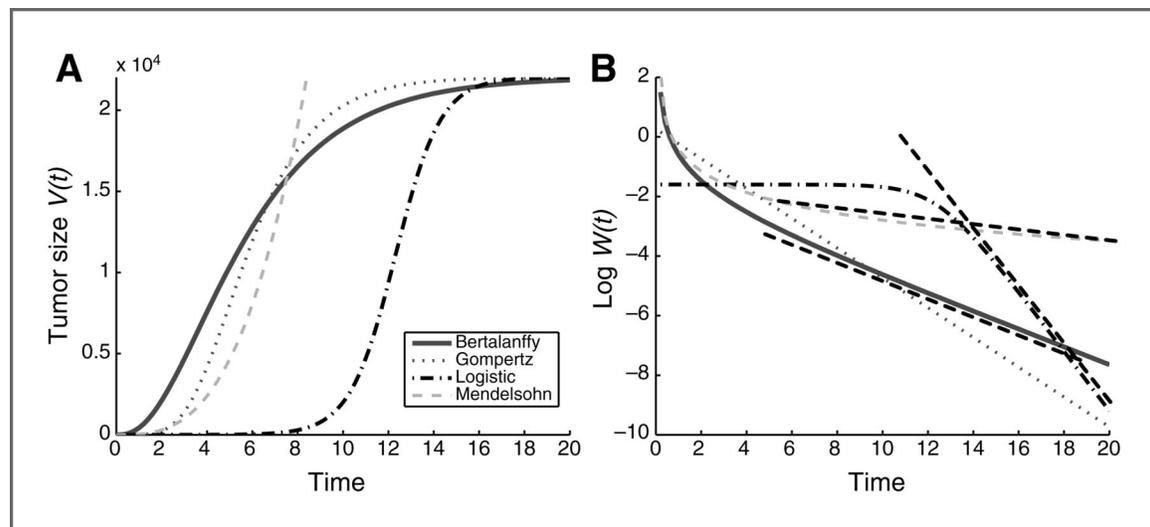


Figure 1: "Tumor growth curves. **A**, the growth curves for 4 different models of tumor growth. The Gompertz (dotted), Bertalanffy (solid), and Logistic (dash-dotted) tend to a asymptotic value, whereas the Mendelsohn model (dashed) gives rise to unconstrained growth. **B**, the quantity $\log \log x(t)/x(t-1)$ plotted for the different tumor growth models. This quantity decreases linearly for the Gompertz model and is used as a means to determine the parameters of the model. However, the other models also exhibit an approximately linear decrease, suggesting that these may explain data that is fitted to the Gompertz model".^[44]

3.1.1 Exponential Shaped Models

Exponential Growth Law The exponential growth law is the simplest tumor growth model. It is based on the assumption that all cells proliferate with a constant cell cycle duration T_C .^[45] The expo-

ponential growth law (equation (1)) is a special case ($b = 1$) of the Mendelsohn model (equation (2)):^[44]

$$\dot{x}(t) = rx(t)^b \quad (1) \qquad \dot{x}(t) = rx(t) \quad (2)$$

where x is the tumor volume and $r = \frac{\ln(2)}{T_c}$.^[40] Equations (2) and (1) have the following analytical solutions, respectively:^[44]

$$x(t) = [(1 - b)(rt + C)]^{\frac{1}{1-b}} \quad (3) \qquad x(t) = x_0 e^{rt} \quad (4) \text{ where}$$

C , in equation (1) is a constant related to the initial condition x_0 .

The exponential law is also valid in the cases whether occurs the proliferation of a constant fraction of the volume or the cell cycle length is a random variable with exponential distribution, assuming the independence and identical distribution of the individual cell cycle length distributions.^[45] Although the exponential growth match the early stages of tumor growth, it is unable to explain growth dynamics of tumors in the longer term.^[44] Furthermore, the exponential curve is unbounded as time increases^[46] which results in a unrealistic unrestricted growth^[47]. In the majority of cancers, the doubling time is not constant over time, it increases and continues to do so for the remainder of the disease.^[44] Furthermore, the fraction of cells that become quiescent is not constant, but also increasing as the tumor growth progresses, reason why the tumor growth slows as the mass of the tumor increases.^[40, 44] Before tumor angiogenesis, tumors contain a proliferating region of roughly constant width, and consequently, an ever diminishing fraction of active cells.^[44] This cannot be reproduced using an exponential model.

Nevertheless, it is possible to modify the equation (1) to have an initial exponential phase followed by a linear growth phase, obtaining the Exponential-linear model:^[45]

$$\dot{x} = \begin{cases} r_0 x(t), & t \leq \tau \\ r_1, & t > \tau \end{cases} \quad (5)$$

where $r_0 = p \frac{\ln(2)}{T_c}$, p is the fraction of proliferative cells and T_c is either the constant cell cycle length or the mean cell cycle length (under the assumption of exponentially distributed cell cycle lengths).^[45] The coefficient r_1 drives the linear phase. By assuming a continuously differentiable solution for (5) the value of τ is uniquely determined by:^[45]

$$\tau = \frac{1}{r_0} \log \left(\frac{r_1}{r_0 x_0} \right) \quad (6)$$

where x_0 denotes the initial volume.

3.1.2 Sigmoid Shaped Models

There is an other class of tumor growth models that have a sigmoid shape.^[45] They are characterized by an increasing curve which has one inflection point that asymptotically converges to a maximal volume, the carrying capacity or plateau population K , beyond which the population size cannot grow.^[45] This plateau population is above the level that is lethal to the host.^[40] Thereby, in all these sigmoidal growth functions, the growth rate of the tumour decreases with increasing tumour volume.^[40] Therefore, these models are consistent with general patterns of organ and organismal growth since they reproduce the experimentally observed growth slowdown.^[45]

Gompertz Model Equation (7) represents the most familiar form of the Gompertz growth model, while equation (8) is its latter variation:

$$\begin{cases} \dot{x}(t) = r(t)x(t) \\ \dot{r}(t) = -\rho r(t) \end{cases} \quad (7) \quad \dot{x}(t) = \rho x(t) \ln \left(\frac{K(t)}{x(t)} \right) \quad (8)$$

The growth pattern of the Gompertz law is also similar to that of exponential growth in the early stages, but plateaus as tumor size increases.^[46] Despite the similarities between equation (7) and the exponential law, equation (2), the growth rate is now time dependent, $r = r(t)$. It is also assumed that $r(t)$ decreases proportionally to its current value at a constant rate ρ .^[44] It reaches a constant asymptote with value $x_\infty = x_0 e^{\frac{x_0}{\rho}}$ that is a time independent carrying capacity.^[44] This equation assumes that a constant fraction of the tumor cells cycles and therefore the growth is exponential but with a smaller growth rate.^[44] However, what happens is that only parts of solid tumors are quiescent, and the cells dividing do this at a rate comparative to the one at early stages of tumor progression.^[44] Therefore, the decaying growth rate of $\dot{r}(t)$ does not have any natural biologic meaning, because it represents the joint effect of many confounding factors.^[44] Furthermore, to match the early phases of tumor growth, the doubling times have to take on unrealistically small values, suggesting fundamental problems with the modeling approach.^[44]

In turn, equation (8) makes use of the carrying capacity $K(t)$ that varies with time, which is imposed by some environmental limitation such as nutrients. When $K(t) = x(t) \Rightarrow \ln \left(\frac{K(t)}{x(t)} \right) = 0$, in other words the growth rate is equal to zero. There are also separated equations for $K(t)$ related with the tumor angiogenic response, which take in account the influence of the tumor mass on the dynamics of the vasculature.^[44]

Logistic Model As the Gompertz model, the logistic model has a sigmoid shape and therefore can also capture a decrease in tumor growth rate over time and an asymptotic mass.^[44] Equation (9) represents the generalized logistic function and equation (10) the well known logistic model, which is a particular case ($\nu = 1$) of the last one. In both equations, the coefficient a is related to proliferation kinetics.^[45]

$$\dot{x}(t) = rx \left[1 - \left(\frac{x(t)}{K} \right)^\nu \right] \quad (9) \quad \dot{x}(t) = rx(t) \left[1 - \left(\frac{x(t)}{K} \right) \right] \quad (10)$$

Whereas the Gompertz equation assumes an exponentially decreasing growth rate, the logistic model is characterized by a linear decrease of the relative growth rate proportional to the tumor volume x , until it becomes equal to zero when it reaches the carrying capacity $x(t) = K$.^[44] This results, for instance, from a mutual competition between the cells for both nutrients and/or space.^[45] Therefore, the instantaneous probability for a cell to proliferate is proportional to $1 - \left(\frac{x}{K} \right)$.^[45] Since initially the tumor volume is much smaller than K , the exponential and logistic growth functions are close in value until the tumour burden comes within an order of magnitude of the plateau population.^[45] However, this derivation ignores many other important factors, such as limited nutrients, that are also important to the process.^[44] ” *This leaves the model hanging in a phenomenological void, also inhabited by the Gompertz model, with the possible advantage that it has a mechanistic derivation.*”^[44]

Equations (9) and (10) have the explicit solution (11) and (12), respectively:^[45]

$$x(t) = \frac{x_0 K}{[x_0^\nu + (K^\nu - x_0^\nu) e^{-r\nu t}]^{\frac{1}{\nu}}} \quad (11) \quad x(t) = \frac{x_0 K}{x_0 + (K - x_0) e^{-rt}} \quad (12)$$

Von Bertalanffy Model This model, first proposed by Von Bertalanffy, derives general laws of organic growth from basic energetics principles.^[45] However, this model has received considerably less attention.^[44] In this model, it is assumed that the growth occurs proportional to surface area and the loss of tumor mass due to cell death occurs in proportion to the volume of the tumor with a constant b , related to the commonly used cell loss factor:^[44]

$$\dot{x} = ax^\gamma - bx \quad (13)$$

Usually, $\gamma = \frac{2}{3}$. The explicit solution of equation (13) is:

$$x = \left[\frac{a}{b} + \left(x_0^{1-\gamma} - \frac{a}{b} \right) e^{-b(1-\gamma)t} \right]^{\frac{1}{1-\gamma}} \quad (14)$$

Equation (14) is also sigmoidal, converging to a fixed volume in which the growth and loss term balance each other out.^[44] Besides matching well experimental tumor growth curves, this model has a derivation with biologically meaningful parameters.^[44]

3.1.3 Description and Prediction of Experimental Tumor Growth

There are not conclusive studies regarding which is the best model to describe and predict different tumor growths. Although several mathematical models have been proposed to represent tumor growth, little is available regarding comparative studies. Table 1 resumes some of the existent studies related with this topic.

In terms of matching actual growth curves, the logistic and Gompertz equation are quite similar. However there are some little differences. Whereas the Gompertz curve is asymmetric and the point of inflection (the time point where the growth rate is maximal) occurs after 37% of the tumor final size has been reached, in the logistic model this occurs after half of the growth has occurred.^[44]

As seen in table 1, there is no single model that commands universal superiority over the others. However, it is believed that the Gompertz equation does better when the complete history of the tumor growth is analyzed, comparing to the logistic or the Bertalanffy equation.^[41] There is a physical explanation for the results obtained by Dethlefsen *et al.* (1968).^[50] Assuming that the tumor is spherical in shape with volume V , its surface area scales as $V^{\frac{2}{3}}$.^[44] Considering the growth of the tumor limited by nutrients and/or oxygen, which enter through the surface, then the growth rate of the tumor is proportional to its surface area, $V^{\frac{2}{3}}$.^[44] In this case, the solution is given by $V(t) \sim t^3$, or in terms of the of the tumor radius $R(t) = \sqrt[3]{V(t)} \sim t$.^[44] In other words, the radius of the tumor grows linearly with time, which can be by assuming that only a thin layer of cells at the surface of the tumor are in fact dividing.^[44]

There is a theoretical and practical reason why the Gompertz model has remained the most applied model to describe tumor growth curves.^[44] The theoretical one is related with the purpose of modeling, which can be the understanding of a system and/or the prevision of its future behavior.^[44] If the prediction is the main objective, using a model disconnected from reality in terms of mechanisms and dynamics is acceptable, as long as it does the job of predicting.^[44] However, if the objective is to understand the system, then the model must be derived from, and based on, real mechanisms and entities within the system.^[44] Since usually growth curves are used to predict the future size of the tumor, it is not surprising that the phenomenological Gompertz model has dominated.^[44] The second reason is related to the method with which the experimental data to the Gompertz model.^[44] It is only necessary to take the logarithm of the tumor volume $V(t)$ twice (figure 1 B)), reason why it is quite easy to fit the model to data that follows a completely different growth law.^[44]

However, this last reason must not determine the use of Gompertz model over other more accurate models that are grounded in biology (which the Gompertz model is not), enabling only

Table 1: Conclusion of articles that describe and/or predict the tumor growth of a given tumor, using some phenomenological tumor growth models.

Authors	Tumor	Models	Results
(Hartung et al., 2014) ^[48]	Orthotopic human breast tumor xenograft in mice.	Exponential, Mendelsohn, Gompertz, Logistic, Von Bertalanffy	Bertalanffy and Gompertz models described better primary tumor growth. Doubling times estimated below the experimentally determined <i>in vitro</i> . Bertalanffy models missed the doubling time and the initial size x_0 by several orders of magnitude. Creation of hybrid models (Bert-Ex and Gomp-Ex).
(Benzekry et al., 2014) ^[45]	Lewis lung carcinoma, orthotopic xenografted human breast carcinoma.	Exponential, Exponential-linear, Gompertz, Logistic, Generalized logistic, von Bertalanffy	Breast: Gompertz and exponential-linear models captured better the dynamics with prediction scores of 80%; Lung: Gompertz and Mendelsohn provided the most parsimonious and parametrically identifiable description. None achieved a substantial prediction rate (70%) beyond the next day data point. Adjunction of a priori information on the parameter distribution led to considerable improvement..
(Vaidya and Alexandro, 1982) ^[41]	Primary human lung carcinoma, induced sarcoma in mice.	Exponential, Gompertz, Logistic, Von Bertalanffy	Lung: Logistic equation gave the best fit (7 in 7 patients), followed by Gompertz (4 in 7 patients) and Bertalanffy and Exponential (1 in 7 patients); Mice: Bertalanffy give the best fit (7 in 10 mice) followed by Gompertz and Logistic (2 in 10 mice) and Exponential (0 in 10 mice).
(Simpson-Herren et al., 1970) ^[49]	Nine experimental tumors	Gompertz	Gompertz used to fit nine experimental tumors. ^[41] Article not available.
(Dethlefsen et al., 1968) ^[50]	Mouse mammary tumors.	Mendelsohn	Data fitted by Mendelsohn with $b = \frac{2}{3}$.
(Laird, 1964 and 1965) ^[51, 52]	19 examples of 12 different tumors in mice, rats and rabbits	Exponential, Gompertz	The growth of a transplanted or primary tumor is well described by the Gompertz equation.

predictions, but also insight into the underlying dynamical process of tumor growth.^[44] In some sense the Bertalanffy model achieves this. It produces growth curves that are nearly indistinguishable from the well-known Gompertz model, but has the advantage of being biologically motivated, has few arbitrary constants, can be verified experimentally and gives good results in predicting the volume.^[41,44]

4. MATHEMATICAL MODELS AND OPTIMAL CONTROL PROBLEM FORMULATION

IN this section, some mathematical models for cancer chemotherapy will be reviewed. As an introduction, the Stepanova’s mathematical model for cancer immune response is first analyzed. Then, more complex models of cancer chemotherapy are introduced. These models consider the onset of drug resistance and the combination of a chemotherapeutic agent and an immune boost.

4.1. Stepanova’s Mathematical Model for Cancer Immune Response

By 1980 Stepanova created a simple mathematical model regarding the interactions between cancer cell growth and the activity of the immune system during its development.^[53] It consists of two ordinary differential equations and using the appropriate parameters it is possible to obtain medically observed features.^[53] In the course of time this basic model have become the basis for numerous extensions and generalizations giving rise to several other models Vldar and Gonzalez, d’Onofrio (for instance Vldar and Gonzalez model, d’Onofrio models).^[53]

As aforementioned, under certain conditions the immune system can effectively control small cancer volumes.^[53] In turn, large cancer volumes can suppress the immune dynamics and therefore the two systems become separated.^[53] In addition exists a intermediate case in which “*both a benign (microscopic or macroscopic) stable equilibrium exists and uncontrolled growth is possible as well*”.^[53] In fact, there is an unstable equilibrium point and its stable manifold separates the benign region from the malignant one of uncontrolled cancer growth.^[53] The objective is then to shift an initial condition of the system through therapy from the region of uncontrolled growth into the region of attraction of the benign equilibrium, controlling the cancer.^[53]

Considering the application of a therapeutic agent and assuming the log-kill hypothesis, which states that the elimination terms are proportional to tumor volume (x) and immunocompetent cell densities (y), the following dynamics are obtained:^[53]

$$\dot{x} = \mu_C x F(x) - \gamma xy - \kappa_X xu \tag{15}$$

$$\dot{y} = \mu_I (x - \beta x^2) y - \delta y + \alpha - \kappa_Y yu \tag{16}$$

The terms $\kappa_X xu$ e $\kappa_Y yu$ were subtracted from x and y , respectively to normalize the control set ($0 \leq u \leq 1$). Table 2 presents the list of the model parameters and variables, their significance as well as their typical values. Figure 2 presents the meaning of each variable and parameter in a more and descriptive way.

Conesidering a Gompertzian growth function, the phase portrait of this system has three equilibria: an *asymptotically stable focus*, a *saddle point* and an *asymptotically stable node*.^[53] Ideally the system should move towards the asymptotically stable focus and avoid the asymptotically stable node.^[53]

Table 2: List of parameters and variables, their significance and typical values of the dynamics (15) and (16).

Variables	Significance	Typical values
x	Tumor volume;	-
y	Immunocompetent cell densities;	-
$F(x)$	Tumor growth model;	-
μ_C	Tumor growth coefficient;	0.5618
μ_I	Calibration constant;	0.00484
γ	Constant rate of cancer cells elimination by T-cells;	1
β	Calibration constant;	0.00264
δ	Constant rate of natural death of the T-cells;	0.37451
α	Constant rate of influx of T-cells.	0.1181
κ_x	Normalization coefficient.	-
κ_y	Normalization coefficient.	-

When $u = 1$, the system has only one equilibrium which is a globally asymptotically stable focus.^[53] Therefore, in principle, “*it would always be possible (ignoring side effects) to reduce the cancer volume to a small enough chronic state*”.^[53] However the the drugs side effects invalidate this approach. Therefore, the initial condition (x_0, y_0) in the region of malignant cancer growth for the uncontrolled system must be transfer in an optimal way into the region of attraction of the stable, benign equilibrium point, which in this case is the saddle point.^[53] To do this, it is generally necessary to minimize the cancer cells x without depleting the T-cell density y too strongly.^[53]

Considering an exponential growth model, there is one saddle point in the phase portrait of the system and this separatrix is given by the stable manifold of this saddle.^[53] However, it is impossible to obtain an analytic description of this manifold, so it is used the stable eigenvector of the saddle point as a first approximation.^[53] Since the separatrix considered is almost linear, it will be reasonable to minimize an objective of the form $ax - by$ where a and b are positive coefficients determined by the stable eigenvector.^[53]

The side effects of the treatment can be modeled using 17, which have to be minimized:^[53]

$$J(u) = ax(T) - by(T) + \varepsilon \int_0^T u(t)dt, \quad \varepsilon > 0 \quad (17)$$

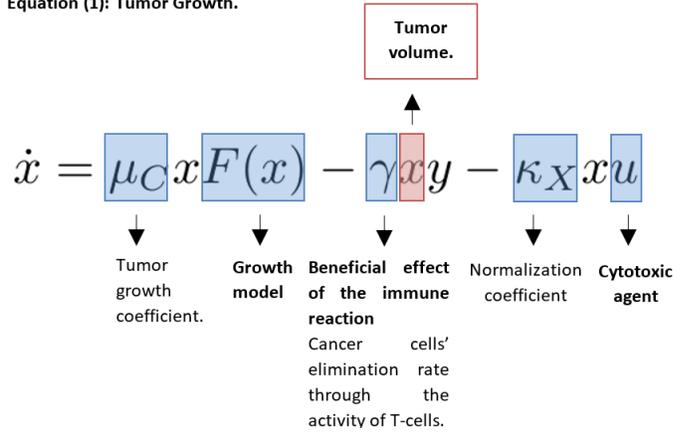
Figure 3 clarify the meaning of each part of the objective that has to be minimized.

However, even after the minimization, the amount obtained can exceed any tolerable limits in order to obtain the “optimal” benefit.^[53] Alternatively, the overall amount A of cytotoxic agents to be given can be limited a priori:^[53]

$$\int_0^T u(t)dt \leq A \quad (18)$$

Hereupon it is necessary to understand how this amount can best be applied.^[53] Time T does not correspond to a therapy horizon.^[53] In fact it only represents the time when the minimum for the objective is achieved. Therefore, the solution of this optimal control problem enables the determination of an appropriate therapy interval.^[53]

Equation (1): Tumor Growth.



Equation (2): Main features of the immune system's reaction to cancer in a one-compartment model with the T-cells as the most important indicator.

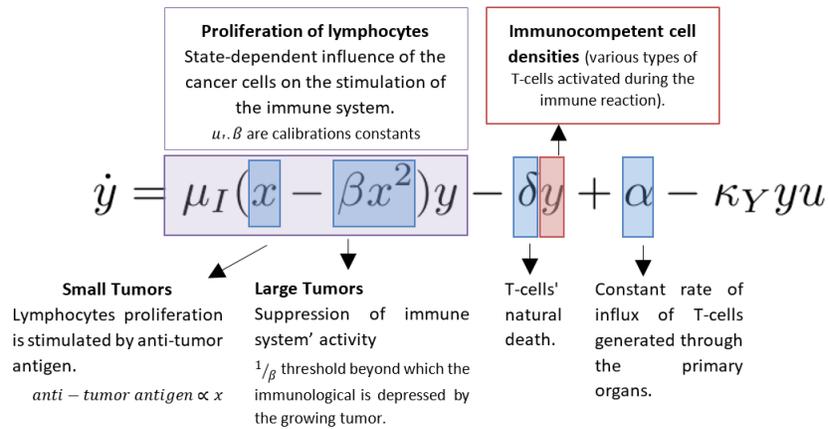


Figure 2: Explanation of the variables meaning of the dynamics (15) and (16), respectively.

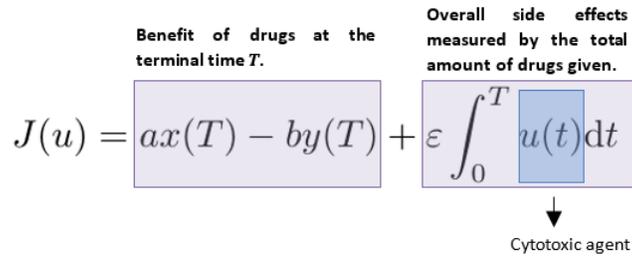


Figure 3: Explanation of the variables meaning of equation (17).

Joining all this information and using the last approach we obtain the following problem of optimal control:^[53]

[OC] for a free terminal time T , minimize the objective

$$J(u) = ax(T) - by(T), \quad a > 0, b > 0, \quad (19)$$

subjected to the dynamics

$$\dot{x} = \mu_C x F(x) - \gamma xy - \kappa_X xu, \quad x(0) = x_0, \quad (20)$$

$$\dot{y} = \mu_I (x - \beta x^2) y - \delta y + \alpha - \kappa_Y y u, \quad y(0) = y_0, \quad (21)$$

$$\dot{z} = u, \quad z(0) = 0, \quad (22)$$

over all Lebesgue measurable functions $u : [0, T] \rightarrow [0, 1]$ for which the corresponding trajectory satisfies $Z(T) \leq A$.

The trajectories considered are only the ones that lie in the region G (region in which immune activity can have some influence, but on the other hand, by itself it is not able to suppress the cancer):^[53]

$$G = (x, y, z) : x > \frac{1}{2\beta}, y > 0 \quad (23)$$

where the cancer volume is fairly large.^[53] It is also considered that the elimination effects on the immunocompetent cells are much smaller than on the tumor cells, $\kappa_Y \ll \kappa_X$, and for simplicity $\kappa_Y = 0$.^[53]

4.2. Combination of Chemo- and Immunotherapy

Immunotherapies are now becoming an important component in the multi-pronged approaches to treat certain forms of cancer.^[39] They strength the body's natural defenses against cancer by enhancing the effectiveness of the immune system.^[39] In other words, immunotherapies stimulate the immune system so it can fight better a cancer and hopefully eradicate it.^[1] The immune response has an critical role in the fight against cancer.^[39] Also, the immune system controls cancer growth, as aforementioned.^[39] Therefore, models which incorporate tumor growth and treatment should incorporate as well an immune system component.^[39] Thus, it would possible to understand how the diverse immunotherapies might affect the system, either singly or in combination with one another.^[39] There is some recent clinical data which indicates that there is potential benefit in harnessing the power of the immune system in combination with traditional chemotherapy.^[39] It can even extend patient survival times than either one of these therapies alone.^[54]

Besides being very similar to the previous model, the model introduced here will only consider generic immunostimulations, for example via cytokines.^[1] Consequently, most of the information of this subsection is a repetition of the last one.

Analysing classical finite dimensional models regarding interactions between tumor and the immune system^[55-58], it is possible to observe several dynamical features that result from the tumor-immune system competition^[1]. As aforementioned, there is a tumor free equilibrium.^[1]

Furthermore, a tumor can grow to a macroscopic size or beyond limits to ∞ .^[1] Moreover, both small or tumor-free and large tumor-size equilibria can exist.^[1] There is a constant influx of effector cells and their proliferative profile varies since it depends on the tumor burden.^[1] In addition, their death rates depend on the size of the tumor.^[1] In fact, “a cancer-free or microscopic equilibrium may coexists with other stable equilibria or with unbounded growth, so that the success of treatment or cure very much depends on the initial conditions”.^[1]

Taking into account all these features, d’Onofrio created the following family of models:^[1]

$$\dot{x} = x(f(x) - \phi(x)y) \quad (24)$$

$$\dot{y} = \beta(x)y - \mu(x)y + \sigma q(x) + \theta(t) \quad (25)$$

Table 3 presents the list of the model parameters and their significance. Figure 4 is the graphic representation of table 3:

Table 3: List of parameters of the dynamics (24) and (25) and their significance.

Parameters	Significance
x	Tumor volume;
y	Effector cells (ECs);
$f(x)$	Tumor growth model;
$\phi(x)$	
$\beta(x)$	
$\mu(x)$	Tumor induced loss of ECs;
$q(x)$	
$\theta(x)$	Influx of ECs from the primary organs.

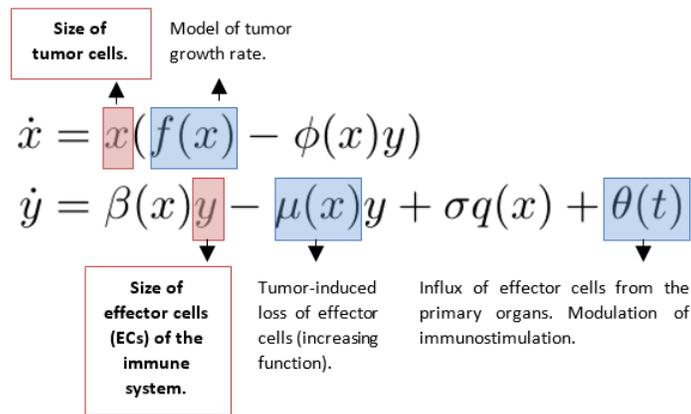


Figure 4: Explanation of the variables meaning of the dynamics (24) and (25).

In figure 4, size refers to total number, cell volumes, densities or adimensional quantities of tumor cells (x) or ECs (y).^[1] The function $f(x)$ is assumed to respect $0 < f(0) \leq +\infty$ and be nonincreasing,

i.e., $f'(x) \leq 0$.^[1] In some relevant cases it is admissible to suppose that $\lim_{x \rightarrow 0^+} xf(x) = 0$ and that “there exists a positive carrying capacity K , i.e., $f(K) = 0$ ”.^[1] As seen before these models can have an exponential, a logistic, a generalized logistic or a Gompertzian growth model and many more.^[1]

Furthermore, ϕ is positive and decreasing, $\phi(0) = 1$, and $x\phi(x) \rightarrow \ell \leq +\infty$; β is nonnegative, monotonically nondecreasing with $\beta(0) = 0$.^[1] The function $q = q(x)$ satisfies $q(0) = 1$.^[1] This function can be nonincreasing or also initially increasing and then decreasing, so it is possible to assume that “the growth of the tumor either decreases the influx of immune cells or that, on the contrary, it actually initially stimulates this influx before leading to an inhibitory pattern”.^[1] In fact, it has been observed experimentally that for some cases of cancer its progression may cause generalized immunosuppression.^[1] This evidence is reflected in an assumption of the type $q'(x) \leq 0$ for $x \gg 1$.^[1] Finally, the term $\theta(t)$ is a positive function.^[1]

The metamodel introduced in this section has as particular cases the Stepanova^[55], Kuznetsov, Makalkin, Taylor and Perelson^[56] and de Vladar and Gonzazalez^[58] models.^[1] For instance, regarding the Stepanova model^[55], the tumor growth is exponential, so $f(x) \equiv \alpha = \text{const}$ and:

$$\phi(x) \equiv 1, \quad \beta(x) = \beta_1 x, \quad \mu(x) = \mu_0 + \mu_2 x^2, \quad q(x) \equiv 1. \quad (26)$$

The terms of Vladar and Gonzalez model^[58] are similiares to the previous one, but it uses a Gompertzian tumor growth, i.e. $f(x) = \alpha \log(\text{frac}Kx)$ ^[58]. In turn, the model by Kuznetsov et al.^[56] uses a logistic tumor growth model, $f(x) = \alpha \left(1 - \frac{x}{K}\right)$, and the functions are given by:

$$\phi(x) \equiv 1, \quad \beta(x) = \frac{\beta_\infty x}{m + x}, \quad \mu(x) = \mu(0) + \mu_1 x, \quad q(x) \equiv 1. \quad (27)$$

However, these models need to be expanded so they can be biologically more accurate.^[1] The uptake rate of T-cells (a nonmonotone function of the tumor burden) should be considered as well as the possible cooperative and/or competitive effects between effector cells.^[1] Therefore, the uptake rate of T-cells should also be a nonlinear function of the number of effector cells.^[1] All these lead to the following dynamics of tumor cells:^[1]

$$\dot{x} = x(f(x) - \gamma\xi(t) - \phi(x)\pi(y)) \quad (28)$$

$$\dot{y} = (P(x, y) - \mu(x) - \eta\xi(t))y + \sigma q(x) + \theta(t) \quad (29)$$

Table 4 presents the list of the model parameters and their significance. Figure 5 explains the meaning of some of the variables of the dynamics (28) and (29):

Table 4: List of parameters of the dynamics (24) and (25) and their significance.

Parameters	Significance
x	Tumor volume;
y	Effector cells (ECs);
$f(x)$	Tumor growth model;
$\xi(t)$	Blood profile of the cytotoxic chemotherapy;
$\phi(x)$	
$\Pi(x)$	Predatory function;
$P(x, y)$	Proliferation stimulation dependent on the relative abundance of competing populations;
$\mu(x)$	Tumor induced loss of ECs;
$q(x)$	
$\theta(x)$	Influx of ECs from the primary organs.

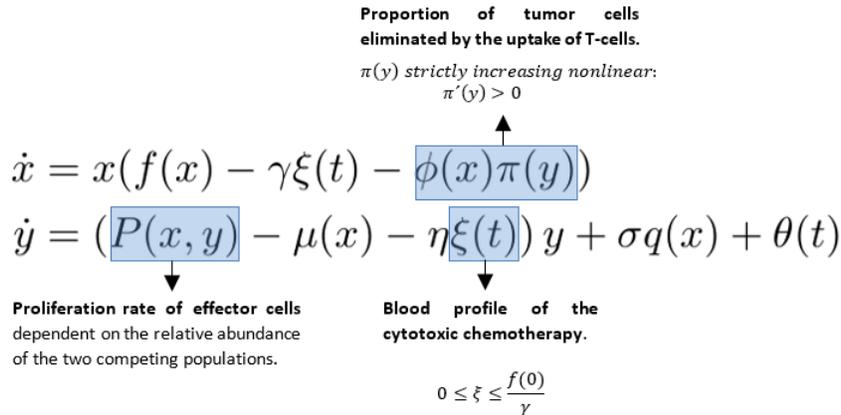


Figure 5: Explanation of the variables meaning of the dynamics (28) and (29).

Here, the overall functional response of tumor cells, $U(x) = x\phi(x)$, can be nonmonotone.^[1] It is also considered that the proliferation of the effector cells of the immune system depends on y .^[1] Indeed, besides the crowding effects, the proliferation stimulation can, in fact, be dependent on the relative abundance of the two competing populations.^[59] Furthermore, it was also considered that the cytotoxic chemotherapy with blood profile $\xi(t)$ might also affect the effector cells of the immune system.^[1] The $\xi(t)$ was chosen to be constant.^[1] Furthermore, the proliferation rate $P = P(x, y)$ is strictly increasing in x , nonincreasing in y and satisfies $P(0, y) = 0$.^[1] Forsys et al.^[59] proposed the following relationship:

$$P(x, y) = \beta_\infty \frac{\left(\frac{x}{y}\right)^\alpha}{1 + \left(\frac{x}{y}\right)^\alpha} = \beta_\infty \frac{x^\alpha}{x^\alpha + y^\alpha} \quad (30)$$

Due to the undesirable and harmful side effects of cytotoxic drugs as well as drugs that boost the immune system, an indefinite administration of agents cannot be considered.^[1] As before, the

objective is to understand how the therapeutic agents should be best administered.^[1] It should be noted that the dynamics (28) and (29) are very similar to the dynamics of the Stepanova's model (15) and (16), respectively, since this model is in fact an extension of it.^[1] Therefore, the formulation of the optimal control problem will be also similar to the one made for the Stepanova's model. Once again, the initial condition (x_0, y_0) , which rests in the region of malignant cancer growth for the uncontrolled system, has to be transferred in the most efficient and effective way into the region of attraction of the stable, benign (microscopic) equilibrium point, thereby controlling the volume of the cancer.^[1]

The stable manifolds of unstable equilibria dictates the boundary between the benign and malignant regions.^[1] For most models, for instance the classical version of Stepanova's model^[55] or its extension by de Vladar and Gonzalez^[55], there is a single saddle point whose stable manifold defines this boundary, the so-called separatrix.^[1] However, usually is quite difficult to obtain an analytic descriptions of these manifolds.^[1] Therefore, their tangent spaces are used as a first approximation for the separatrix.^[1] Accordingly, there will be a term in the mathematical objective whose minimization induces the system to move across this boundary.^[1] The saddle point has a unique stable eigenvector $v_s = (B, A)^T$ once this is a two-dimensional system, with positive coefficients.^[1] *“Thus, by including a penalty term $Ax(T) - By(T)$ at the final time, this not only conforms with the heuristic notion of minimizing cancer cells and maximizing effector cells, but in a very precise mathematical way justifies the chosen weights by providing an incentive for the system to move across the separatrix into the benign region”*.^[1]

The model considered above does not incorporate healthy cells and tissue.^[1] Consequently, side effects are only modeled indirectly.^[1] Chemotherapy and immunotherapies are assumed to have a proportional effect on healthy tissue.^[1] Hence, the weighted integral terms $\int_0^T u(t)dt$ and $\int_0^T v(t)dt$ that measure, respectively, the total amounts given of a cytotoxic agent u and an immunostimulator v , respectively are added to the objective to be minimized with proper weights.^[1] Although the side effects of the immune boosts are less serious, they cannot be ignored.^[1] These amounts could alternatively be limited a priori so the minimization problem would be subject to the following isoperimetric constraints:^[1]

$$\int_0^T u(t)dt \leq U_{max}; \quad \int_0^T v(t)dt \leq V_{max}. \quad (31)$$

Although the terminal time T is kept problem formulation free, due to the existence of a tumor-free or a microscopic benign equilibrium, trajectories can use the zero controls over very long time horizons.^[1] These trajectories lead to a mathematically ill posed problem formulation as no minimum may exist in this case.^[1] When the control switches to follow $u = 0$ and $v = 0$ and the controlled trajectory intersects the separatrix, then *“follows the separatrix for an infinite time to the saddle and then again leaves this saddle point along the unstable manifold, once more taking an infinite time”*.^[1] Even though this is the optimal solution, it is not an admissible trajectory.^[1] To avoid this scenario, a penalty term was included on the final time as well.^[1] Biologically, this addition induces optimal solutions to give more drugs and therefore reach the benign equilibrium point faster, forcing the system into the benign region more quickly.^[1] Hence, this term provides both desired robustness and stability properties to the underlying real system.^[1] The mathematical objective takes the following form:^[1]

$$J(u) = Ax(T) - By(T) + C \int_0^T u(t)dt + D \int_0^T v(t)dt + ST \quad (32)$$

Figure 6 summarizes all the information regarding the objective to be minimized:

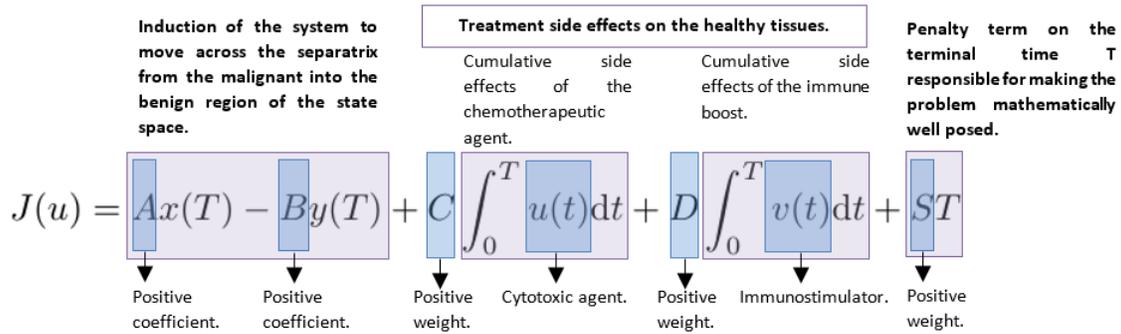


Figure 6: Explanation of the variables meaning of the dynamics (24) and (25).

The coefficients A and B may be chosen to calibrate the response of the system.^[1] In turn, the choice of the “weights aims at striking a balance between the benefit at the terminal time T , $Ax(T) - By(T)$, and the overall side effects (...) while it guarantees the existence of an optimal solution by also penalizing the free terminal time T ”.^[1] The values of C and D reflect the severity of each drug used.^[1] Obviously, the specific type of tumor and its stage will be reflected into the calibration of these coefficients.^[1] For instance, if the cancer is in a more advanced stage, higher side effects need to be tolerated and therefore C and D will have smaller values.^[1]

Summing up all, the following optimal control problem arises:

[OC] for a free terminal time T , minimize the objective

$$J(u) = Ax(T) - By(T) + C \int_0^T u(t)dt + D \int_0^T v(t)dt + ST \quad (33)$$

over all Lebesgue measurable functions

$$(u, v) = [0, T] \rightarrow [0, 1] \times [0, 1], \quad t \mapsto (u(t), v(t)) \quad (34)$$

subject to the dynamics (24) and (25) respectively (28) and (29).

The states x and y must remain positive for positive initial conditions x_0 and y_0 and arbitrary admissible controls u and v .^[1] The region $P = (x, y) : x > 0, y > 0$ is positively invariant and therefore it is not necessary to impose positivity constraints on the variables.^[1]

4.3. Drug Resistance In Cancer Chemotherapy

Besides affecting undesirably healthy proliferating cells^[53], there is another major limitation regarding chemotherapy^[60]. In fact, the development of drug resistance by cancer cells is the main reason for the failing of chemotherapy.^[3, 60]

Each drug acts by its own complicated biochemical processes triggering many cellular defense mechanisms.^[3] For instance, some drugs are susceptible to ABC transport proteins.^[3] These transporter proteins remove molecules out of the cell.^[3] Therefore, their overexpression, for example by gene amplification, constitutes an mechanism for resistance to several drugs.^[3] Alternatively, the

cytotoxic agents can lead to the activation of repair systems within the cells.^[3] Consequently, cells are able to overcome the damage done by the drug.^[3] Furthermore, cancer cells can experience a quickly development of acquired resistance to anti-cancer drugs due to a single mutational event or random mutations over time.^[3] These cells can also be intrinsically resistant to the drug being used.^[3] In other words, the specific activation mechanism of the drug just does not work.^[3]

In this case, the objective is not to cure cancer but rather delay the onset of resistance, keeping the resistant population small as long as feasible.^[3] Nevertheless, cancer cells can in fact lose acquired drug resistance through gene deamplification.^[61, 62] Nevertheless, during the breaks between the administration of the drug occurs an unrestricted growth of the tumor.^[63] Therefore, it is of utmost importance and it is important to inhibit the repopulation process.^[63] Alternate treatments with a combination of drugs with distinct operation mechanisms may prolong the onset of resistance.^[3] However, these approaches often lead to multidrug resistance and unacceptable levels of toxicity to the patient.^[3]

In the literature there are already several probabilistic models considering the development of drug resistance.^[3] The models of Coldman and Goldie analyze the tumor size as a stochastic process and maximize the probability to have no resistant cells.^[64] It uses a simple non cell-cycle specific two-compartment models in which only resistant and sensitive cells are distinguish.^[3] Westman et al.^[65, 66] created a probabilistic model considering the evolution of the cancer population sensitive to the drug from a single mutational cell in a cell-cycle specific context, distinguishing between the clonogenic (or quiescent) fraction and the growth (or proliferating) fraction.^[3] In this model, drug resistance is seen as a sudden event, only distinguishing resistant and sensitive cells.^[3] In contrast, Harnevo and Agur^[67, 68] and Kimmel and Axelrod^[69, 70] describe drug resistance as a branching process. Swierniak et al.^[71–73] formulated infinite-dimensional deterministic models, which only allow a limited analysis due to their high dimensionality.

Before analyze a mathematical model for cancer chemotherapy with multiple killing agents under evolving drug resistance, lets first consider one with a single killing agent. The mechanism considered for the acquisition of drug resistance is gene amplification.^[3] In fact, the acquisition of additional copies of genes can make the cells more resistant to certain drugs.^[3] This resistance is proportional to the number of copies present of such a gene within the cell, even when subjected to higher concentrations of the drug.^[3] As in the models of Harnevo and Agur^[67, 68], the development of drug resistance by gene amplification follows the one-copy forward gene amplification hypothesis. In other words, it is assumed that in each “*cell division at least one of the two daughter cells will be an exact copy of the mother cell while the second one with some positive probability undergoes gene amplifications*”.^[3] In order to simplify the model, drug resistance is treated as a “*complete event*”^[66]. Therefore, there is only a distinction between resistant and sensitive compartments of cancer cells.^[3]

4.3.1 Mathematical Models for Cancer Chemotherapy with a Single Killing Agent under Drug Resistance

If it is only considered a single killing agent, the model is given by:^[3]

$$\dot{S} = -aS + (2 - q)aS + rcR, \quad (35)$$

$$\dot{R} = -cR + (2 - r)cR + qaS \quad (36)$$

As explained above, since this model follows the one-copy forward gene amplification hypothesis, if a sensitive or resistant mother cell undergoes cell division, the mother cell dies and one of the

daughters will remain sensitive and resistant, respectively.^[3] However the daughter cell's can change their phenotype with a certain probability.^[3]

Table 5 presents the list of the model parameters and their significance. Figure 7 explains the meaning of some parts of these equations.

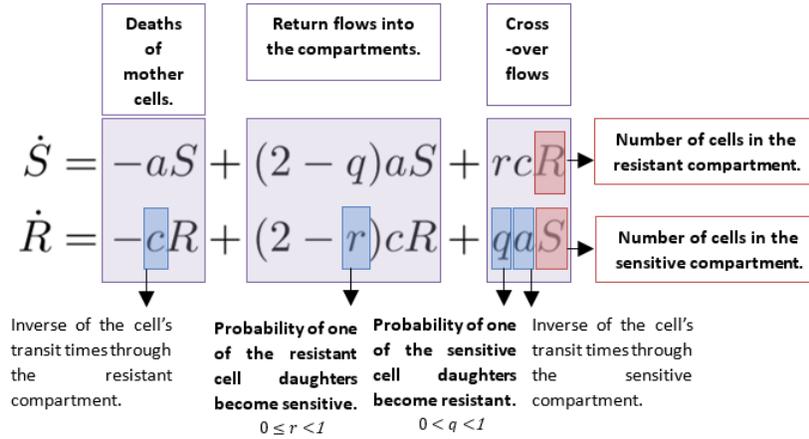


Figure 7: Explanation of the variables meaning of the dynamics (35) and (36).

When $r = 0$ the gene amplification is stable.^[3] On the contrary, when $r > 0$ the gene amplification is unstable.^[3]

It is assumed that the cytotoxic agent only kills sensitive cells and has no effect on the resistant population.^[3] u denote the drug dose, $0 \leq u \leq u_{max} \leq 1$.^[3] $u = 0$ means that no drug is being used and $u = u_{max}$ corresponds to a full dose.^[3] For simplicity it is assumed that the dosage, the concentration and even the effect of the drug are equal, on other words, pharmacokinetics or pharmacodynamics are not modelled.^[3] Also, the drug is assumed to kill a fixed proportion u of the outflow of the sensitive cells at time t :^[3]

$$\dot{S} = -aS + (2 - q)(1 - u)aS + rcR, \quad S(0) = S_0, \quad (37)$$

$$\dot{R} = -cR + (2 - r)cR + (1 - u)qaS, \quad R(0) = R_0, \quad (38)$$

Table 5: List of variables and parameters of the dynamics (37) and (38) and their significance.

Parameters	Significance
S	Number of tumor cells in the sensitive compartment;
R	Number of tumor cells in the resistant compartment;
q	Probability of a sensitive cell change to a resistant cell;
r	Probability of a resistant cell change to a sensitive cell;
a	Inverse of the cell's transit times through the sensitive compartment;
c	Inverse of the cell's transit times through the resistant compartment;
μ	Cytotoxic agent dose.

Figure 8 explains the meaning of each term:

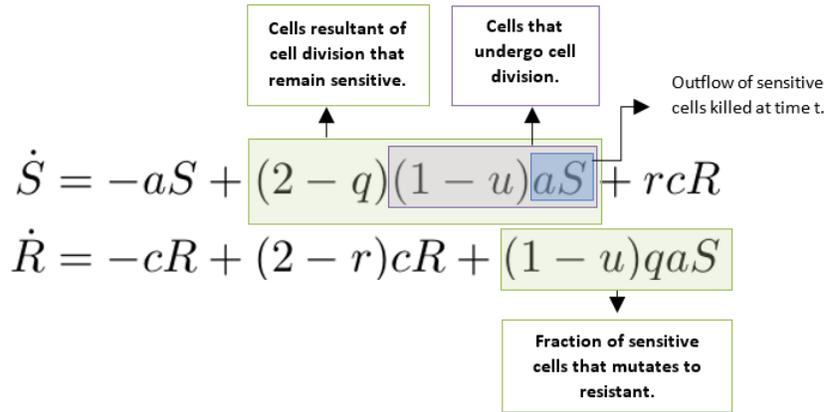


Figure 8: Explanation of the variables meaning of the dynamics (37) and (38).

Considering $N = (S, R)^T$, this dynamic can be described by a bilinear system

$$\dot{N} = (A + uB)N, \quad (39)$$

where

$$A = \begin{pmatrix} (1-q)a & rc \\ qa & (1-r)c \end{pmatrix}; \quad B = a \begin{pmatrix} q-2 & 0 \\ -q & 0 \end{pmatrix}. \quad (40)$$

Hereupon, let's analyze the asymptotic properties of this model.^[3] In the case of $u \equiv 0$, i.e. no control applied, the dynamics takes the form of a simple model of exponential growth:^[3]

$$\dot{R} + \dot{S} = aS + cR \quad (41)$$

where a is in fact the sensitive cells growth rate and c the resistant cells growth rate.^[3] The quotient $x = \frac{S}{R}$ satisfies a Riccati equation:^[3]

$$\dot{x} = rc + ((1-q)a - (1-r)c)x - qax^2, \quad x(0) > 0 \quad (42)$$

which has unique stable equilibrium in this interval at:^[3]

$$\bar{x} = \frac{(1-q)a - (1-r)c + \sqrt{((1-q)a - (1-r)c)^2 + 4rqac}}{2rc} > 0. \quad (43)$$

Therefore, if left alone, cancer cells would grow exponentially reaching $S = \bar{x}R$.^[3]

On the other hand, if the full control is applied, i.e. $u \equiv 1$ on $[0, \infty)$ the sensitive cells would be reduced at rate a .^[3] In turn, the resistant compartment still would grow at rate c .^[3]

$$\dot{R} + \dot{S} = -aS + cR \quad (44)$$

Since $aS > cR$ cancer cells can be reduced through chemotherapy. however, the drug will diminish only the sensitive population.^[3] Eventually the resistant population takes over the total number of cancer cells, so $q = 0$, which grow exponentially:^[3]

$$\dot{x} = rc + (a + (1 - r)c)x \quad (45)$$

which has a stable equilibrium at:^[3]

$$\dot{x} = -\frac{rc}{a + (1 - r)c} \quad (46)$$

Since r is small or even 0, it is obvious that almost all cells will become resistant to the drug, what is consistent with medical experience.^[3] However, in a specific case (favorable value of the parameters) it may take a very long time.^[3] These are precisely the situations when chemotherapy is successful.^[3] Accordingly, the main objective of chemotherapy is to “*kill as many of the sensitive cancer cells possible while limiting both the size of the resistant subpopulation and the overall toxicity to the patient*”.^[3] This can be translated into the following problem of optimal control:^[3]

[OC] minimize the objective

$$J = \int_0^T L(N, u)dt + \varphi(T, N(T)), \quad (47)$$

subjected to the dynamics

$$\dot{N} = (A + uB)N, \quad N(0) = N_0, \quad (48)$$

over all Lebesgue measurable functions $u : [0, T] \rightarrow [0, u_{max}]$ and with positive components, for which the corresponding trajectory satisfies $N^* : [0, T] \rightarrow P = (S, R) : S > 0, R > 0$.

The form of L , the Langrangian, and φ , the penalty function, determine the structure of optimal controls.^[3] Since, there is not a clear biological indication for the choice of a given mathematical objective, usually objectives quadratic in control are usually selected:^[3]

$$L(N, u) = N^T Q N + u^2, \quad \varphi(N) = N^T Q_T N, \quad (49)$$

in which Q and Q_T are positive semi-definite matrices.^[3] Since the objectives are quadratic in the control, the Hamiltonian will be strictly convex with a unique minimum.^[3] However, this minimum will be a function of N and λ , $u = u(\lambda, N)$, i.e. is dependent on the multiplier what leads to an numerical analysis.^[3] In fact, the bilinear dynamics results in nonstandard nonlinear equations.^[3] The possible existence of multiple solutions to the two-point boundary value problem complicate the structure of solutions.^[3] “*At least they raise the issue of optimality of any numerically found solution*”.^[3] However, sufficient conditions for optimality can be formulated which allow to verify at least strong local minimality of such solutions.^[3]

Furthermore, these types of objectives lead to solutions that are not yet realistically medically.^[3] Indeed, quadratic objectives in the control undermine the side effects and favors giving partial doses.^[3] Thus, typically solutions present segments in which the control is given by the stationary point of the Hamiltonian “*implying the use of time-varying partial doses dependent on the number of cancer cells at the moment*”.^[3]

Alternatively, the objective can be linear in control.^[3] In this case, there is some biological justification for this provided that the numbers of cells killed is considered equal to the numbers of ineffective cell divisions, which, in turn, is supposedly proportional to the overall amount of drugs given.^[3] Mathematically, the objective to be minimized takes the form:^[3]

$$J = kN(T) + \int_0^T (\ell N(t) + u(t))dt \rightarrow \min \quad (50)$$

Figure 9 explains the meaning of each variable:

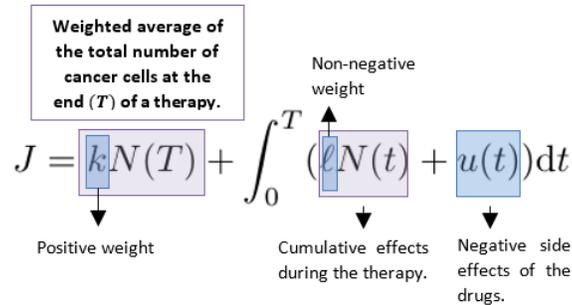


Figure 9: Explanation of the variables meaning of the equation (50).

Although the Hamiltonian has to be linear in the control u , its structure in N can be rather arbitrary.^[3]

$$J = \varphi(N(T)) + \int_0^T (L(N(t)) + u(t))dt \rightarrow \min \quad (51)$$

Smooth penalty functions φ and Lagrangian L can depend on the state N if such an effect is considered important.^[3] Consequently, to solve this mathematical problem it is necessary find a Lebesgue-measurable function $u : [0, T] \rightarrow [0, u_{max}]$ which minimizes (51) subject to the dynamical equations (35) and (36).^[3]

4.3.2 Mathematical Models for Cancer Chemotherapy with Multiple Killing Agents under Evolving Drug Resistance

The alternative therapy strategy aforementioned which is based in a combination of drugs with distinct operation mechanisms may effectively prolong the onset of resistance.^[3] However, this results mathematically in a structurally quite different model.^[3] For instance, considering two killing agents the dynamics will be quadratic in the controls as result of the interactions between the drugs.^[3] They will also have an indefinite structure and the Hamiltonian needs to be minimized over a compact control set.^[3] This model is “*probabilistic, branching random walk model with a finite number of states^[69], but averaged over the populations in individual compartments*”.^[3]

Consider u_1 and u_2 the dosage of two cytostatic killing agents, both with values in intervals $[0, u_{max}^i], i = 1, 2$.^[3] The 0 represents no dose and u_{max} the full dose.^[3] The state space is comprised of four compartments.^[3] The capital Roman letters in each one denotes the average number of cells in that specific compartment.^[3] All this is represented in figures 10 which also explain the meaning of each variable.

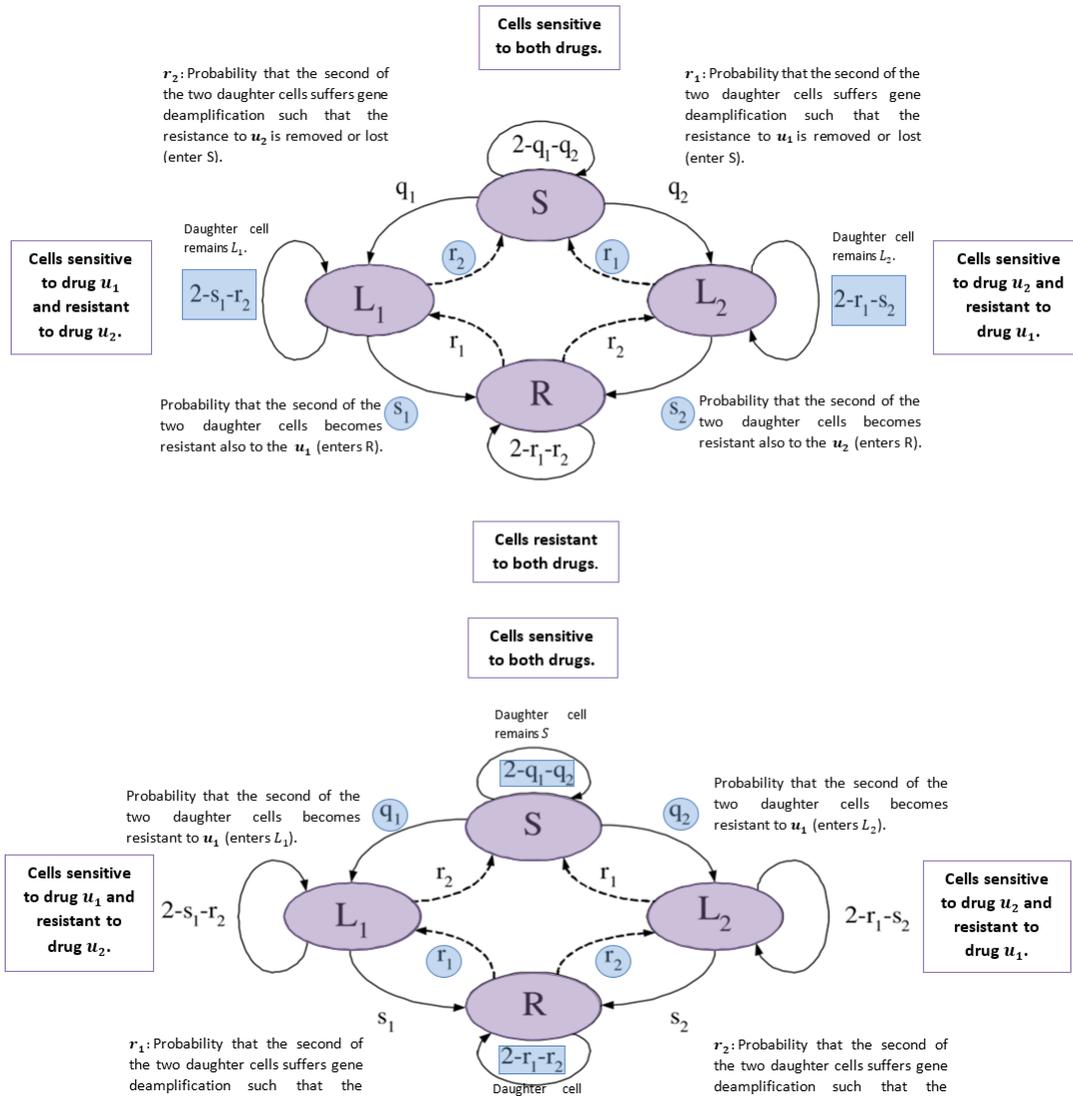


Figure 10: Chemotherapy model with several killing agents under evolving drug resistance.

As before, drugs are assumed to kill a fixed proportion u_1 respectively u_2 of the outflow of the sensitive cells at time t .^[3] Only the remaining fraction of cells suffers cell division.^[3]

Denoting the mean inverse transit times through the compartments by a (compartment S), b_1 (compartment L_1), b_2 (compartment L_2) and c (compartment R), for example, only a fraction $(1 - u_1)(2 - s_1 - r_2)b_1L_1$ of cells from L_1 reenters L_1 .^[3]

It is noteworthy that, in the sensitive compartment, the terms related with cross-over flows change substantially.^[3] This is due to the fact that the two drugs cannot kill the same cell twice.^[3] It is plausible to assume that the drugs act independently once they interact with a large numbers of cancer cells.^[3] Nevertheless, it is possible to postulate other dependency relations.^[3] However, they will change the sensitive compartment return flows.^[3] The return flow is then quadratic in the

controls:^[3]

$$(1 - u_1)(1 - u_2)(2 - q_1 - q_2)aS \quad (52)$$

Overall, the dynamics are given by:^[3]

$$\dot{S} = -aS + (1 - u_1)(1 - u_2)(2 - q_1 - q_2)aS + (1 - u_1)r_2b_1L_1 + (1 - u_2)r_1b_2L_2, \quad (53)$$

$$\dot{L}_1 = -b_1L_1 + (1 - u_1)(2 - s_1 - r_2)b_1L_1 + (1 - u_1)(1 - u_2)q_1aS + r_1cR, \quad (54)$$

$$\dot{L}_2 = -b_2L_2 + (1 - u_2)(2 - s_2 - r_1)b_2L_2 + (1 - u_1)(1 - u_2)q_2aS + r_2cR, \quad (55)$$

$$\dot{R} = -cR + (2 - r_1 - r_2)cR + (1 - u_1)s_1b_1L_1 + (1 - u_2)s_2b_2L_2. \quad (56)$$

Table 6 presents the list of the model parameters and variables and their significance:

Table 6: List of variables and parameters of the dynamics (53),(54),(55)and (56) and their significance.

Parameters	Significance
S	Tumor cells sensitive to μ_1 and μ_2 ;
R	Tumor cells resistant to μ_1 and μ_2 ;
μ_i	Dosage of cytostatic killing agent i ;
L_i	Tumor cells sensitive to μ_1 and resistant to the other cytostatic killing agent;
q_i	Probability that one cell in S cells remains sensitive to μ_i and become resistant to the other cytostatic agent, entering in L_i ;
s_i	Probability that one cell in L_i become resistant to μ_i too, entering in R ;
r_i	Probability that one cell become sensitive to μ_i ;
a_i	
b_i	
c	

The equations above become more transparent and simpler if the control variable is changed to $v_i = 1 - u_i$:^[3]

$$\dot{N} = (A + v_1B_1 + v_2B_2 + v_1v_2C)N \quad (57)$$

where:

$$A = \begin{pmatrix} -a & 0 & 0 & 0 \\ 0 & -b_1 & 0 & r_1c \\ 0 & 0 & -b_2 & r_2c \\ 0 & 0 & 0 & (1 - r_1 - r_2)c \end{pmatrix}; \quad C = a \begin{pmatrix} 2 - q_1 - q_2 & 0 & 0 & 0 \\ q_1 & 0 & 0 & 0 \\ q_2 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}; \quad (58)$$

$$B_1 = b_1 \begin{pmatrix} 0 & r_2 & 0 & 0 \\ 0 & 2 - s_1 - r_2 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & s_1 & 0 & 0 \end{pmatrix}; \quad B_2 = b_2 \begin{pmatrix} 0 & r_1 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 2 - s_2 - r_1 & 0 & 0 \\ 0 & s_2 & 0 & 0 \end{pmatrix}. \quad (59)$$

This can be translated into the following problem of optimal control:^[3]

[OC] choose Lebesgue measurable functions $v_i : [0, T] \rightarrow [v_{min}^i, 1]$, in which $v_{min}^i = 1 - u_{max}^i$, $i = 1, 2$, to minimize the objective

$$J = kN(T) + \int_0^T (\ell N(t) - mv(t))dt \rightarrow min, \quad (60)$$

where $m = (m_1, m_2)$ is a row-vector of positive weights, subjected to the dynamics:

$$\dot{N} = (A + v_1 B_1 + v_2 B_2 + v_1 v_2 C)N. \quad (61)$$

5. CONCLUSION

NOWADAYS, the main contributions of mathematical modeling for cancer chemotherapy are related with qualitative ideas for chemotherapy scheduling rather than practical quantitative applications.^[3] This is due to the current limitations in both biomedicine and mathematics.^[3]

In fact, biologically, there are some relevant cell processes that are not yet well understood.^[3] Furthermore, some crucial model parameters are not known.^[3] In other cases, they vary far too much from case to case.^[3] This variation or uncertainty in the relevant parameter values from patient to patient results in studies of limited quantitative practical value.^[3] Therefore, personalize medicine is needed.^[3] “*The best average treatment may be the poorest option for a particular patient*”.^[74]

In turn, mathematically, numerical simulation studies which rely on computational power^[75] are necessary to deal with realistic models that are high-dimensional, complicated and intricate models^[3]. On the other hand, theoretical analysis do not lead to results either feasible or applicable quantitatively since it is limited to small and overly simplified models.^[3]

The main limiting factor in chemotherapy, although not the only one, is the emergence of resistant clones, or on other words the onset of drug resistance by cancer cells.^[3,60] Therefore, by applying optimal control methods to cancer chemotherapy models that consider the development of drug resistance is possible to schedule chemotherapy sessions which delay the onset of drug resistance, keeping the resistant population small as long as feasible, and thus giving a higher life expectancy to the patient.^[3] Alternatively, a treatment with further drugs can be made. Indeed, alternate treatments with a combination of drugs whose operation mechanisms are distinct may prolong the onset of resistance even further.^[3] However, these treatments can lead to multidrug resistance and unacceptable levels of toxicity to the patient.^[3]

Despite these efforts, the treatment of advanced stage cancer is still a serious clinical problem since conventional cancer therapy often cannot control the progression of the tumor.^[2] The development of the aforementioned tumor cell resistance to chemotherapy as well as the inherent toxicity of these modalities stresses the necessity of better treatment options.^[2] Cancer immunotherapy has advantages over other cancer therapy strategies^[2], however it lacks efficacy^[76]. Recent evidence clearly suggests that the combination of immunotherapy and chemotherapy for the treatment of cancer provides substantial clinical benefits for patients with advanced disease.^[2]

In this report, a small approach to the immune system as well as its response to cancer is made. Firstly is described an simple mathematical model of the cancer. Then, other more complex models of cancer chemotherapy are discussed regarding the combination of a chemotherapeutic agent and an immune boost and drug resistance with respect to single and multiple killing agents. Methods of optimal control are used to solve the problem, i.e. “*transfer the system from an initial condition in*

the malignant region of the state space through therapy into a benign region”^[1].

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