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CANCER TREATMENT AS A GAME: OPTIMAL CHEMOTHERAPY IN AN INDIVIDUAL-BASED, SPATIALLY-EXTENDED, EVOLUTIONARY MODEL

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A mio papá
alla mia famiglia
con amore e riconoscenza

Abstract

In the life, almost every challenge, from the easiest to the hardest one, can be mathematically modeled and analyzed as a game.
This thesis is an extension of the work previous done and exposed in the article "Cancer treatment as a game: integrating evolutionary game theory into the optimal control of chemotherapy" written by P. A. Orlando, R. A. Gatenby and J. S. Brown (2012). In few words in their work, the game is the cancer treatment where the antagonist players are the oncologist and the cancer. In this unsymmetrical game, the oncologists choose a therapy whereas tumors follow an adaptive strategy to the surrounding environment. It is supposed that the oncologist can gain an advantage in this game by choosing treatment strategies that anticipate the adaptations of the tumor. In particular, the article examines the potential benefit of exploiting evolutionary tradeoffs in tumor adaptations to therapy. Orlando et al. analyze a math model, without spatial structure and phenotypic diversity, where cancer cells face tradeoffs in allocation of resistance to two chemotherapy drugs. The tumor 'chooses' its strategy by natural selection and the oncologist, who can play rationally, chooses her strategy by solving a control problem. So the cancer treatment game has a distinctive leader-follower (or "Stackelberg") game dynamics, where the leader chooses her strategy and then the follower adapts. The oncologist should exploit this clear advantage. In this thesis, an individual-based evolutionary model is developed to model spatial heterogeneity and phenotypic diversity. In the first chapter the article "Cancer treatment as a game: integrating evolutionary game theory into the optimal control of chemotherapy" is summarized and explained. Then, after this introductory chapter, the new individual-based evolutionary stochastic discrete model is discussed and explained, in particular its state profile and its updating rules, which govern how the state profile changes from one step to the next one. We use probabilistic rules, obtaining so a stochastic model, in contrast with the deterministic one of the first chapter. The third chapter concerns the calibration of the two models, in order to then be able to make a reliable comparison. So the first experiments about cancer cells growth and their strategies evolution are performed and explained, investigating their adaptation to the surrounding environment.
Finally, the best oncologist strategy, i.e. the best chemotherapy protocol, is looked for using the gradient method. The research question is if a static protocol, i.e. a time invariant delivery of both drugs simultaneously, is a better oncologist strategy then a dynamic protocol, where the delivery of the two drugs negatively covaries.
The conclusion is that the knowledge of evolutionary tradeoff and the objective function to be optimized are crucial in planning optimal chemotherapy schedules for the patients.

Sommario

Nella vita, quasi ogni sfida, dalla più semplice alla più difficile, può essere modellizzata matematicamente e analizzata come un gioco. Questa tesi è un'estensione del lavoro svolto in precedenza ed esposto nell'articolo "La cura del cancro come gioco: integrare la teoria del gioco evolutivo nel controllo ottimale della chemioterapia" scritto da P. A. Orlando, R. A. Gatenby e J. S. Brown (2012). In sintesi nel loro lavoro, il gioco è il trattamento del cancro in cui i giocatori antagonisti sono l'oncologa e il cancro.
In questo gioco asimmetrico, le oncologhe scelgono una terapia mentre i tumori seguono una strategia adattiva all'ambiente circostante. Si presume che l'oncologa possa ottenere un vantaggio in questo gioco scegliendo strategie di trattamento che anticipano gli adattamenti del tumore. In particolare, l'articolo esamina il potenziale beneficio dello sfruttamento dei compromessi evolutivi negli adattamenti del tumore alla terapia. Orlando et al. analizzano un modello matematico, senza struttura spaziale e diversità fenotipica, in cui le cellule tumorali affrontano compromessi nell'assegnazione della resistenza a due farmaci chemioterapici. Il tumore "sceglie" la sua strategia per selezione naturale e l'oncologa, che può giocare razionalmente, sceglie la sua strategia risolvendo un problema di controllo. Quindi il gioco per la cura del cancro ha una dinamica tipica di gioco leader-follwer (o di "Stackelberg"), in cui il leader sceglie la sua strategia e poi il follower si adatta. L'oncologa dovrebbe sfruttare questo chiaro vantaggio. In questa tesi, viene sviluppato un modello evolutivo basato sull'individuo per modellizzare l'eterogeneità spaziale e la diversità fenotipica. Nel primo capitolo viene sintetizzato e spiegato l'articolo "Il trattamento del cancro come gioco: integrazione della teoria dei giochi evolutiva nel controllo ottimale della chemioterapia". Quindi, dopo questo capitolo introduttivo, viene esposto e discusso il nuovo modello evolutivo discreto stocastico basato sull'individuo, in particolare il suo profilo di stato e le sue regole di aggiornamento, che regolano il modo in cui il profilo di stato cambia da uno step al successivo. Usiamo regole probabilistiche, ottenendo così un modello stocastico, in contrasto con quello deterministico del primo capitolo. Il terzo capitolo riguarda la calibrazione dei due modelli, al fine di poter effettuare un confronto affidabile. Quindi vengono eseguiti e spiegati i primi esperimenti sull'evoluzione delle strategie e sulla crescita delle cellule tumorali, studiando il loro adattamento all'ambiente circostante.
Infine, si cerca la migliore strategia oncologica, ovvero il miglior protocollo di chemioterapia, usando il metodo del gradiente. La questione investigata è quale tra un protocollo statico, ovvero una somministrazione invariante nel tempo di entrambi i farmaci contemporaneamente, e un protocollo dinamico, in cui la somministrazione dei due farmaci covaria negativamentesia, sia la strategia migliore per l'oncologa.

La conclusione é che la conoscenza del compromesso evolutivo e la funzione obiettivo da ottimizzare sono cruciali nella pianificazione di programmi di chemioterapia ottimali per i pazienti.

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Introduction

Game theory is an applied mathematics branch that studies and analyzes the individual decisions of a subject, in situations of conflict or strategic interaction with other rivals, aimed at the maximum gain of each subject. From this point of view, cancer treatment is seen as a game [1], where the oncologist would like to eliminate or, at least, restrain the cancer, whereas the cancer goal is to grow and develop as much as possible, adapting itself to the surrounding environment. With few exceptions, cancers remain incurable. Treatments usually appear effective initially but almost invariably fail due to evolution of tumor resistance [2]. The mechanisms by which cancer cells achieve resistance are extremely diverse and can vary depending on the mechanism of action and molecular characteristics of the chemotherapeutic drug [3]. Even highly targeted therapy, such as Herceptin for breast cancer patients, typically produces only transient response with rapid evolution of adaptive strategies [4]. Thus, evolution of resistance to treatment is the ultimate cause of death in patients.

However, this is not a symmetric game, indeed the oncologist can play rationally and, solving a control problem, can understand evolution, while the cancer cannot, it can only evolve in response to what is happening and can never anticipate or predict future selection force. The cancer treatment game has a clear leader-follower game dynamics [5]. Indeed the oncologist chooses her strategy, then the cancer can only adapt to the oncologist strategy, following natural selection. The oncologist should exploit this advantage to fight the cancer.

We examine one potential component of the cancer treatment game by focusing on the potential exploitation of evolutionary tradeoffs to the advantage of the oncologist. For instance, if cancer cells face a tradeoff in resistance between two drugs, then it is possible to select for tumor resistance to one of the drugs, while simultaneously increasing tumor susceptibility to a second drug. This situation is referred to as an evolutionary double bind [6]. A scenario in which cancer can have three different tradeoffs is investigated. The different tradeoffs influence how cancer cells can allocate additively more, less or equal amount when generalizing resistance to two drugs versus specializing resistance to a single drug. In this thesis an individual-based evolutionary model [7] is developed in order to analyze spatial heterogeneity and phenotypic diversity. This is the novelty compared to the work done by Orlando et al.

Once developed the phenotypic individual-based model, some experiments are performed to calibrate the new model with the differential one proposed by Orlando et al. These experiments are also useful to understand the evolution of cancer but above all to test the individual-based evolutionary model overcoming both computational and theoretical problems.

The final intent is to understand the best strategy, i.e. the best oncological protocol, to fight the cancer and see if and how the results change from the ones obtained by Orlando et al. due to the use of the individual-based evolutionary model.

Chapter 1

The deterministic model

This chapter presents the work done in the article called "Cancer treatment as a game: integrating evolutionary game theory into the optimal control"[1] written by Orlando et al. and the inspirer of this thesis.

1.1 Introduction

The novelty of the article is to see cancer treatment as a game. The players of the game are the oncologist and cancer. They are not symmetric players. Indeed, only the oncologist can play rationally. Cancer cells, like all evolving organisms, can only adapt to current conditions: they can neither anticipate nor evolve adaptations for treatments that the oncologist has not yet applied. The oncologist can optimize cancer therapy using treatment strategies based on understanding evolutionary dynamics of cancer cell response and adaptation to treatment. While cancer cells can only evolve due to what is happening in the surrounding environment. This is a clear advantage in the game that should be exploited by the oncologists, planning strategies, i.e. long-term protocol, that anticipate evolutionary and ecological dynamics of the cancer cells. So the treatment has a distinctive leader-follower dynamics; the "leader" oncologist plays first and the "follower" cancer then responds and adapts to therapy. Orlando et al. examine one potential component of the cancer treatment game by focusing on the potential exploitation of evolutionary tradeoffs to the advantage of the oncologist. For instance, if cancer cells face a tradeoff in resistance between two drugs, then it is possible to select for tumor resistance to one of the two drugs, while simultaneously increasing tumor susceptibility to the other drug. They refer to this scenario as an evolutionary double bind [6]. They view the interactions between the oncologist and a cancer as a differential game and frame this hypothesis using evolutionary game theory to determine how

natural selection chooses the strategies that cancer cells deploy. Then, applying control theory, they want to determine the optimal treatment strategy available to the oncologist. Their work is based on the one done by Cunningham et al (2011) [8] to understand optimal treatment protocols that may result in a double-bind scenario. Previous studies have incorporated the evolution of resistance within an optimal control problem [9]. To understand the Darwinian evolutionary dynamics a G-function, or fitness, generating function is used [10]. The novelty of Orlando et a. consist on applying for the first time G-functions [11] in an optimal control framework, to understand how they can use the evolutionary competence of cancer to the oncologist advantage. Researchers have applied G-functions to cancer to understand how cancer adapts to the environment in a variety of publications over the last decade [12, 13]. The article [1] investigates different trade-offs resistance between two drugs, but also different relationship in their effects on cancer cells and the combination of these two phenomena on the optimal treatment protocols. The different tradeoffs affect whether cancer cells can allocate additively more, less, or equal amounts when generalizing resistance to two drugs as opposed to specializing to be resistant to a single drug. Tradeoffs are one way that affects how multiple drugs influence the fitness of cancer cells. Examining these scenarios oncologist would like to answer the therapy question: when is it an optimal protocol to give a static treatment of both drugs versus a dynamic treatment, which vary the concentration of drugs over time?

1.2 The model

Orlando et al. propose a predator-prey type model to describe tumor (the prey) growth subject to chemotherapy (the predator). In this model, in absence of the predator, the prey grows to his carring capacity described by the logistic growth equation. Once the tumor has grown, they then let two different therapies act as predators that induce tumor cell pharmacologic mortality:

$$\frac{dN}{dt} = N[r(1 - \frac{N}{K}) - d_1 y_1 - d_2 y_2 - \beta y_1 y_2] \tag{1.1}$$

In this model, N is the total tumor population size. The term in the brackets is the per capita growth rate of the tumor in the absence of therapy, where r is the intrinsic growth rate and K is the carrying capacity. Chemotherapy influences the per capita death rate of the cells in additive or non-additive ways. The terms d_1 and d_2 are per capita mortality rates per unit drug concentration for drug 1 and drug 2, respectively, and y_1 and y_2 are the concentrations of drugs 1 and 2, respectively.
Obviously, this model has not spatial structure. So, it is implicitly assumed that the

drug concentrations are equal throughout the tumor. This is a too reductive assumption for a disease as cancer and so in the next chapters the model is extended in this direction, providing a spatial model. The last term of the per capita growth rate determines the type and magnitude of drug interaction. The sign of β determines whether drugs are antagonistic ($\beta < 0$) or synergistic ($\beta > 0$). With antagonism, the presence of one treatment reduces the direct efficacy of the other and vice-versa. With synergism, each treatment type amplifies the effectiveness of the other at killing tumor cells.
The innovation of Orlando et al. is to transform this basic oncological model into an evolutionary model through the use of a fitness generating function or G-function [11] allowing them to model an evolutionary dynamics with a continuous spectrum of phenotypic resistance. G-functions [10] consider how the fitness of rare mutants in the population are influenced by the tumor resistance strategies, the resident population size as well as the environment. Their article is the first to apply G-functions in an optimal control framework, to understand how it is possible to use the evolutionary competence of cancer to give an advantage to the oncologist. In this function, tumor cell fitness is defined as per capita growth rate. The G-function models the potential fitness of rare mutant tumor cells. The fitness of a tumor cell is influenced by its heritable phenotype or strategy ($\mathbf{v}$), the resistance strategy of the resident population ($\mathbf{u}$), the cell population size (N), and the concentrations of the two drugs (y_1 and y_2) administered by the oncologist. Given a particular ecological circumstance, the G-function defines the fitness of all potential mutants contained within the phenotypically feasible strategy set (upper and lower bounds on $\mathbf{v}$). This allows Orlando et al. to determine how natural selection will act within a population, as they assert in their article [1]. For instance, if in a particular ecological circumstance, rare mutant cancer cells with higher resistance have higher fitness than the current resident strategy, and vice versa for mutants with lower resistance, then resistance will increase by natural selection.

To create the G-function, the ecological parameters of the model have to be a function of the evolutionary variables:

$$G(\mathbf{v}, N, y_1, y_2) = r\left(1 - \frac{N}{K(\mathbf{v})}\right) - d_1(\mathbf{v})y_1 - d_2(\mathbf{v})y_2 - \beta y_1 y_2 \tag{1.2}$$

This G-function does not directly depend on the current resident strategy ($\mathbf{u}$). Orlando et al. let the phenotypic strategy of a cell be vector valued with two evolutionary variables ($\mathbf{v} = [v_1, v_2]$). The first is a cell's overall investment in resistance (v_1) and the second is a cell's allocation of resistance to drug 1 (v_2). Finally, v_2' is a cell's allocation of resistance to drug 2, which is mathematically deduced from v_2, depending on the tumor evolutionary tradeoff.
To make clearer the notation and avoid confusion, from now onward the notation will

change: v is a cell's overall investment in resistance, while v_1 and v_2 are a cell's allocation of resistance to drug 1 and drug 2, respectively.

Orlando et al. assume that as much a cell spends in resistance, as much the cancer carrying capacity declines. They choose an exponential function as carrying capacity function

$$K = K_{max} e^{\frac{-v^2}{2\sigma_k^2}} \tag{1.3}$$

where v is the overall investment in resistance (which was v_1 in the article) and σ_k is the standard deviation parameter of a Gaussian function.

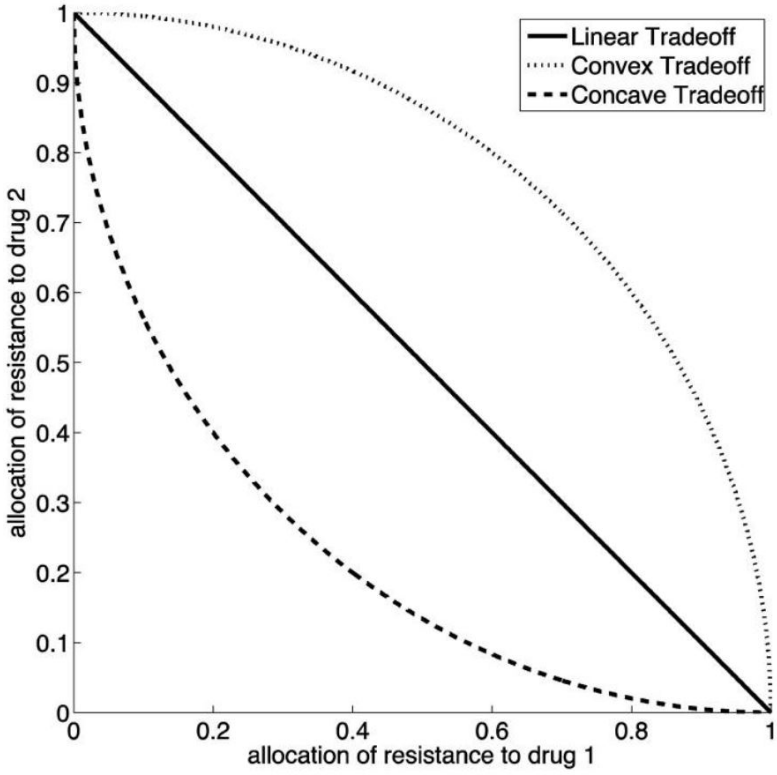

FIGURE 1.1: Three different tradeoffs in allocation of resistance between the two drugs.

Three different functions, shown in figure 1.1, are used to caracterized a cell's allocation of resistance to both drugs:

1. a linear one given by

$$v_2 = 1 - v_1 \tag{1.4}$$

(which is $v_2' = 1 - v_2$ in the article).

In this case, specializing on a single drug or generalizing on both drugs, is equal in term of allocation.

2. a concave trade off given by

$$v_2 = 1 - \sqrt{1 - (v_1 - 1)^2} \tag{1.5}$$

($v_2' = 1 - \sqrt{1 - (v_2 - 1)^2}$ in the article)
Using this function, cells allocate additively more by specializing as opposed to generalizing.

3. a convex function given by

$$v_2 = \sqrt{1 - v_1^2} \tag{1.6}$$

($v_2' = \sqrt{1 - v_2^2}$ in the article)
In this last case, cells allocate additively more by generalizing as opposed to specializing.

The product of the overall cell's investment in resistance (v) and allocation to that drug (v_1 or v_2 for drug 1 and drug 2, respectively) is the cell's resistance to that drug. Indeed, for cell's per capita mortality rate, the following functions, which are influenced by drug resistance, are choosen:

$$d_1 = \frac{1}{k_1 + vv_1} \tag{1.7}$$

and

$$d_2 = \frac{1}{k_2 + vv_2} \tag{1.8}$$

for drug 1 and 2, respectively (k_1 and k_2 are the baseline levels of resistance to drugs). The article's authors derive the evolutionary dynamics, i.e. how the cancer cell 'choose' their strategy in the game against the oncologist, following Fisher's fundamental theorem of natural selection [14]: the direction of natural selection is given by the gradient of the fitness function with respect to the fitness of rare mutants. Thus, the evolutionary dynamics for each evolutionary variable of the resident is given by

$$\frac{du_i}{dt} = s\frac{dG}{dv_i}|_{v_i=u_i} \tag{1.9}$$

where s is a speed parameter, defined larger with increased genetic variance or mutation rate.

1.3 The optimal control problem

Using the just described model, Orlando et al. formulate a control problem where the goal is to minimize the tumor size at the end of the protocol period so that the oncologist can exploit the result to choose her strategy in the game against the tumor. The mathematical formulation of the problem, which is solved numerically with GPOPS software[15], is:

Minimize $N(t_f)$

Subject to

$$\begin{cases} \dfrac{dN}{dt} = NG|_{\mathbf{v}=\mathbf{u}} \\ \dfrac{du_1}{dt} = s\dfrac{dG}{dv}|_{v=u_1} \\ \dfrac{du_2}{dt} = s\dfrac{dG}{dv}|_{v_1=u_2} \\ \dfrac{dy_1}{dt} = w_1 - z_1 y_1 \\ \dfrac{dy_2}{dt} = w_2 - z_2 y_2 \\ w_1 \leq 10 \\ w_2 \leq 10 \\ N(0) = K_{max}, \\ y_1(0) = 0, \\ y_2(0) = 0, \\ u_1(0) = 0, \\ u_2(0) = 0.5, \\ t_f fixed \end{cases} \tag{1.10}$$

After the equations for the dynamics for the tumor population, the fourth and fifth equations of the problem are related to the concentration of the two chemotherapy drugs. In particular, w_1 and w_2 are the control variable, chosen by the oncologist, which represent the rates of drug delivery for drug 1 and 2, respectively. Drug clearance is modeled with basic first order pharmacokinetics, where z_1 and z_2 are per unit drug clearance rates. The upper bound on the total amount of drugs dosage is set to avoid toxicity to the patient.

1.4 Results

1.4.1 Cancer at its best and worst

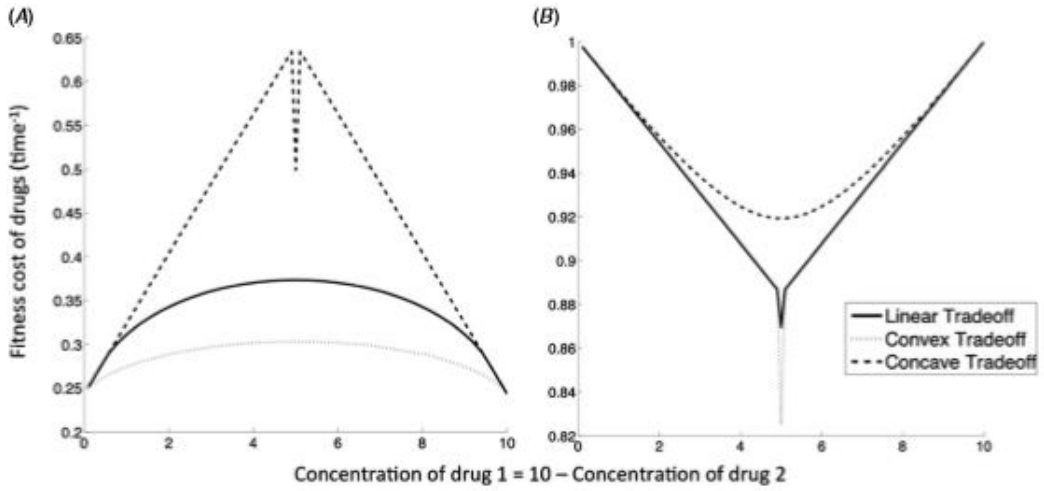

FIGURE 1.2: The effects of two drugs on cancer cell fitness in two different scenarios. In A the cancer cells are using their best evolutionary strategy against the combination of drugs. In B the cancer cells have a fixed level of resistance and are using their worst evolutionary strategy in terms of allocation to either drug. The linear, concave, and convex tradeoffs are represented by solid, dashed, and dotted lines, respectively. Note that the total concentration of drug 1 and drug 2 is fixed at 10, consistent with the optimization problem. Parameters in common for both panels: r = 1, K_{max} = 10, $\sigma_k = 30$, $k_1 = k_2 = 10$, $\beta = 0$. For panel B $u_1 = 3$.

To understand the effectiveness of the potential therapies from the cancer perspective, the G-function model is studied independently of any control by the oncologist. Orlando et al. optimize the fitness of the cancer using different ratios of the two drugs, both when cancer maximizes fitness and when minimizes fitness, to understand how cancer cell fitness change with different drug combination. These experiments suggest the nature of the protocol: whether it should be static (i.e. the oncologist do not vary drug concentrations over time) or dynamic (i.e. the oncologist should vary drug concentrations).
With fitness maximization and when a single drug is given, the cancer best strategy is a specialized resistance approach, while when both drugs are given, the best strategy is to generalize resistance (equally resistant to both drugs). Specialized resistance means becoming maximally resistant to the administered drug, but remain susceptible to the other one. Orlando et al. find out that cancer cells have higher fitness as specialists when given a single drug rather than generalists when given both drugs, as shown in figure 1.2(A). In other words, the cancer cells face a 'penalty of multitasking', since they are less fit when they try to generalize resistance to both drugs. Exploiting this 'penalty of multitasking', the best static treatment is to give both drugs simultaneously at maximum dose.

On the other hand, exploiting the case of fitness minimization, is possible to understand the effectiveness of a dynamical treatment strategy: if the oncologist varies drug concentrations rapidly, she can exploit the evolutionary tradeoff by treating cancer with the drug it is most susceptible to. So a dynamic treatment of switching drugs may work better. Figure 1.2(B) shows that all tradeoff types are susceptible to a dynamical treatment.

1.4.2 Solutions to the control problem without drug interactions

As guessed in the previous sub-chapter, the solutions to the control problem without drug interactions have a common beginning: an increase in both drugs simultaneously at the maximum rate to increase drug concentrations as quickly as possible until the upper limit of drugs concentration is hit. Then, the solution with the concave tradeoff becomes dynamical. On the other hand, with both linear and convex tradeoffs, in the optimal control solutions, after the initial phase of drugs increase, there is a constant chattering control, which appears to stochastically vary the drugs just slightly from equal concentrations for the rest of the planning period. Orlando et al. are curious as to how much of an improvement this chattering control is over a static control of equal drug concentrations after the initial drug increase phase. They find that there is virtually no difference. With both treatments at the end of planned treatment period, the tumor size is practically equal. This subtle difference is not clinically signicant, and they can regard the optimal control as static, in that the best strategy is to use as much drug as possible and in equal concentrations. This results are shown in figure 1.3.

1.4.3 Solutions to the control problem with drug interactions

Orlando et al. analyzed also the control problem with drug interactions finding that the interactions can increase or counteract the effect of tradeoffs. For instance, the linear tradeoff, with antagonist interaction, has a dynamical solution but also the solution to the concave tradeoff, with synergistic interaction, switches to a static solution. Finally, the convex tradeoff with an antagonist interaction surprisingly shifts from a static solution of two drugs to a static solution of a single drug, instead of switching to a dynamic solution, as shown in figure 1.4.

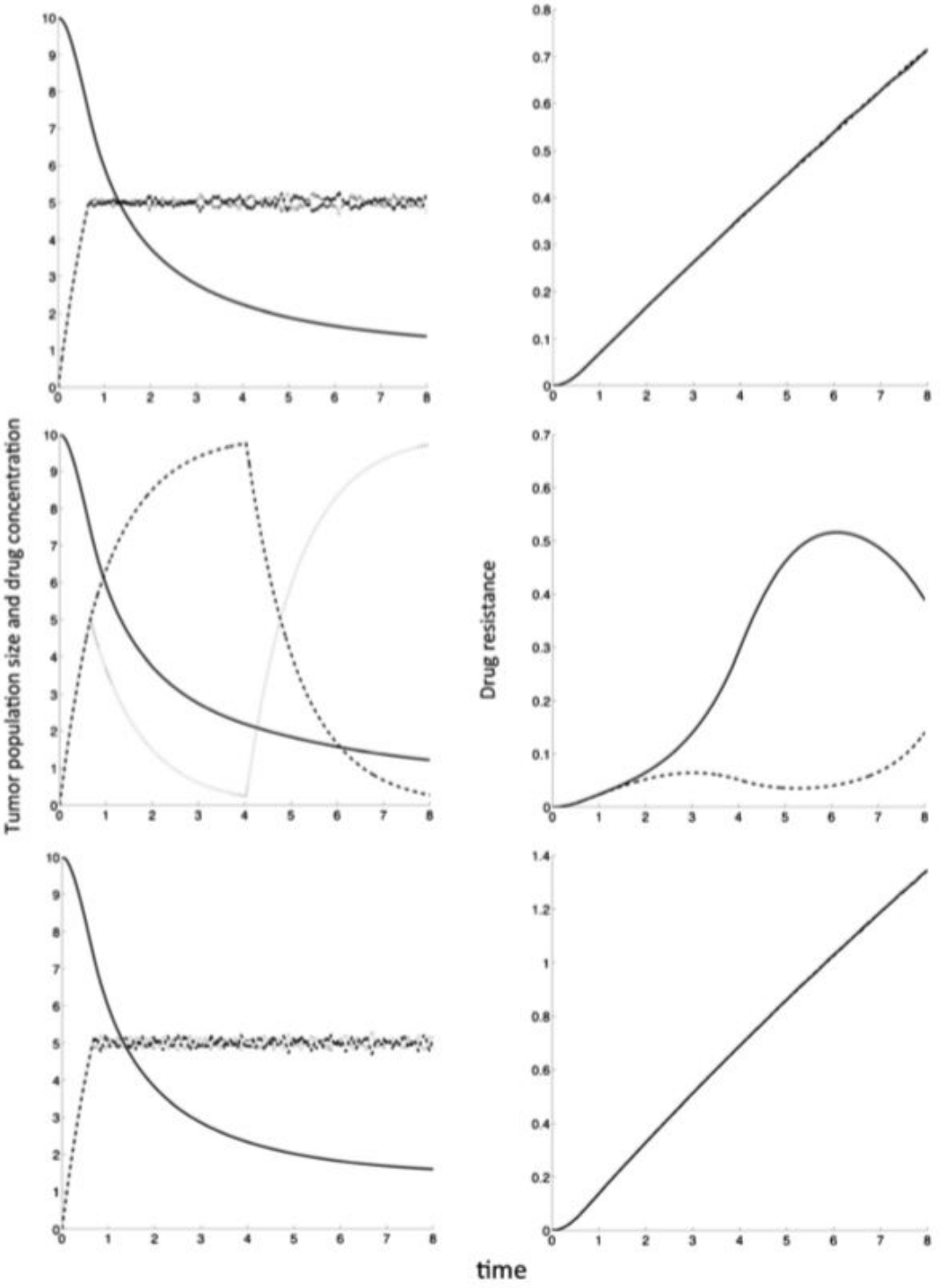

FIGURE 1.3: Optimal state profiles for the three different tradeoff types without drug interactions. The left panels show tumor cell densities (solid line) and the concentrations of drug 1 (dashed line) and drug 2 (dotted line). The right panel shows the tumor cells resistance to drug 1 (solid line) and drug 2 (dashed line). The top, middle, and bottom panels show the solutions for the linear, concave, and convex tradeoffs, respectively. Parameters in common to all panels: $r = 1, K_{max} = 10, \sigma_k = 30, k_1 = k_2 = 10,$ $\beta = 0, z_1 = z_2 = 0.9.$

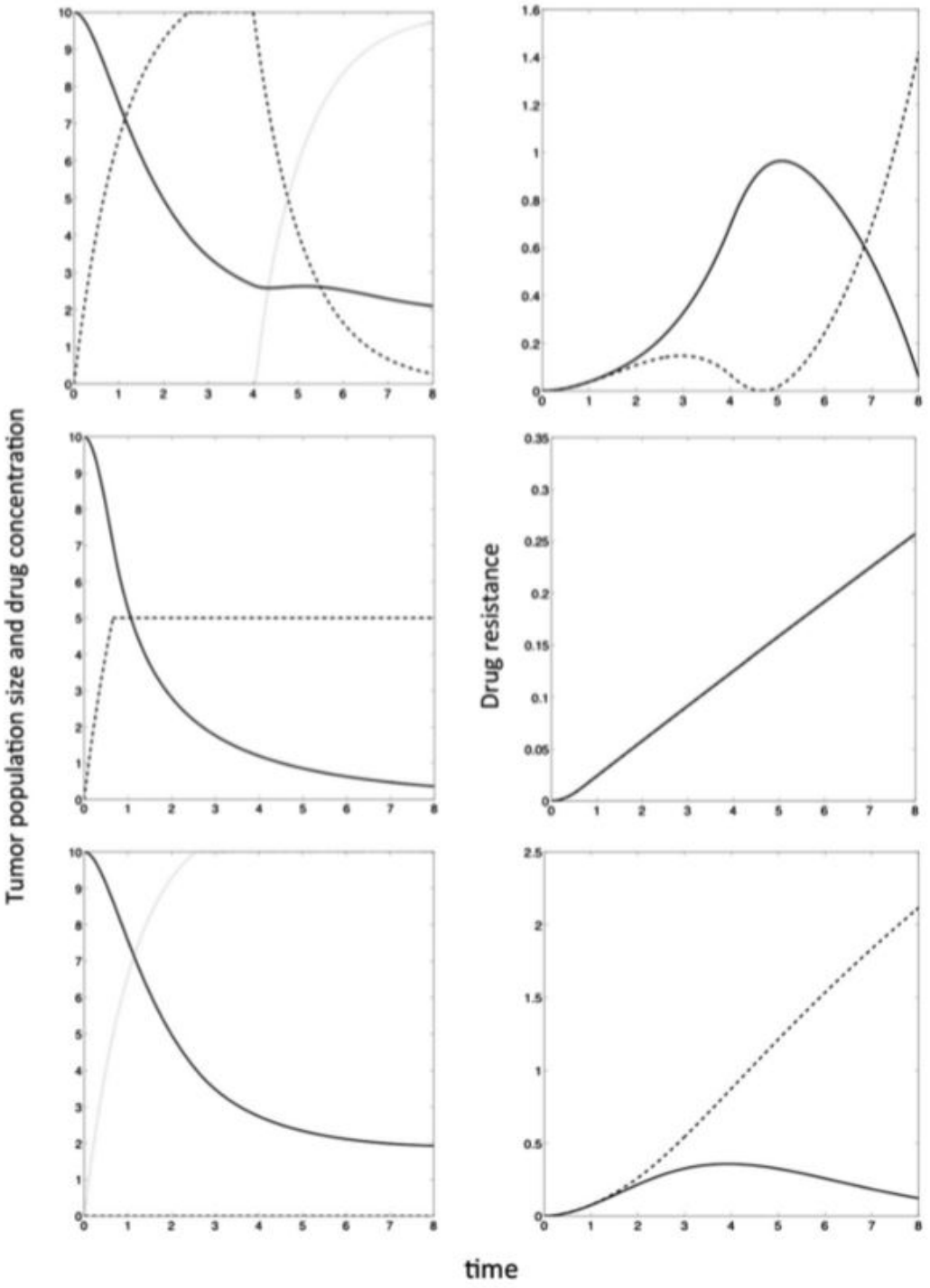

FIGURE 1.4: Optimal state profiles for the three different tradeoff types with drug interactions. The left panels show tumor cell densities (solid line) and the concentrations of drug 1 (dashed line) and drug 2 (dotted line). The right panel shows the tumor cells resistance to drug 1 (solid line) and drug 2 (dashed line). The top, middle, and bottom panels show the solutions for the linear tradeoff with antagonistic drugs ($\beta = 0.01$), concave tradeoff with synergistic drugs ($\beta = 0.01$), and convex tradeoff with antagonistic drugs ($\beta = 0.01$), respectively.Parameters in common to all panels: $r = 1, K_{max} = 10, \sigma_k = 30, k_1 = k_2 = 10, z_1 = z_2 = 0.9$.

1.4.4 Comparing best and worst treatment protocols

Orlando et al., following the lead of Engelhart et al. [16], determine how effective the optimal control solution is by xing the total amount of drugs over the planning period and investigating the differences between maximizing the nal tumor population. So they compare best and worst treatment protocols for all the previous different scenarios. Without drug interaction, the result for the best and worst protocols are practically equal, but with drug interaction, the best protocol is clearly more effective, decreasing tumor size as much as 60% in the concave case with synergistic drugs interaction.

Chapter 2

The phenotypic individual-based spatial model

Orlando et al. claim, in their conclusions, that an individual-based approach would be interesting to describe spatial heterogeneity and or phenotypic diversity. This is how the model, presented in the previous chapter, is extended.

2.1 Individual-based models

Individual-based models (IB models in abbreviation) are a class of computational models aimed at computer simulation of actions and interactions of autonomous agents to evaluate their effects on the system as a whole [17].
IB models, also called agent-based models, indeed are a population and community modeling approach that allows for a high degree of complexity of individuals and of interactions among individuals or agents. So, populations or systems of populations are simulated as being composed of discrete individual organisms. These individuals might represent autonomous characters in games, plants and animals in ecosystems or people in communities.
Each individual has a set of state variables or attributes and behaviors. State variables can include spatial location, physiological traits and behavioral traits. These attributes vary among the individuals and can change through time.
Behaviors can include growth, reproduction, habitat selection, foraging, and death.
Unlike traditional differential equation population models, which are described in terms of imposed top-down population parameters, such as birth and death rates as the model described in the previous chapter, individual-based models are bottom-up models in

which population-level behaviors emerge from the interactions among autonomous individuals with each other and their environment. These models typically consist of an environment or framework in which the interactions occur and some number of individuals defined in terms of their behaviors (procedural rules) and characteristic parameters [18]. The individual state profile is updated at each time step, which is discrete, through specif rules, that typically depend on the interacting neighbors state profile. An advantage of individual-based models over traditional models is that they can incorporate any number of individual-level mechanisms. They are thus used whenever one or more of the following aspects, which are hard or impossible to represent in population-level differential equations, are considered essential for answering a research question or solving an applied problem: variation among individuals and of individuals during their life cycle; local interactions among individuals; and adaptive behavior, which includes physiology and energy budgets. This aspects are essentially to be described in cancer treatment research studies. When in a IB model some evolutionary dynamics are analyzed, the model is called individual-based evolutionary model [7]. Hence individual-based evolutionary models represent the frontier of modern population genetics and provide the richest and more realistic framework for describing demography and evolutionary change. Other than the genetic information, they can virtually incorporate any further detail, like age, stage, or space distribution of populations and environmental fluctuations. Thus individual-based methods can be predict better evolutionary outcomes [19]. Individual-based models are therefore particularly suited whenever the aim is to obtain long-term simulations of the stochastic process to be compared with field or laboratory data. However, the algorithms for the simulation of individual-based models typically require accurate tuning of several parameters and, in general, analytical analyses are complex to be carried out.

2.2 Model description

An individual-based evolutionary model [7] is built to analyze the cancer growth, especially its phenotypic diversity, and its response to a possible oncological treatment in order to understand the best protocol to fight the disease.
To represent the space and the agents, we use a two dimensional square network with freedom degree four, i.e. each node can communicate with its four neighbors, as shown in the figure 2.1 in the next page.
Each node represent a cell, an individual of our IB model. Each individual can be healthy or tumoral. The grid size is set to 100x100. The density in the grid represents the cancer dimension. As in the article [1], only the cancer individual characteristics will be analyzed.

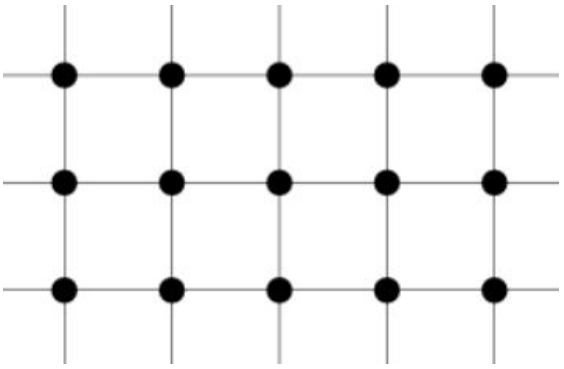

FIGURE 2.1: Image representing a grid with freedom degree four.
In graph theory it is called lattice graph or square grid graph.
The nodes represents cells.

2.2.1 State profile

The state of each agent, i.e. each cell or node in our IB model, is composed firstly by a boolean variable which is equal to 1 if the cell is a cancer cell, 0 if there is a healthy cell. If the node represents a cancer cell there are other attributes or state variables which represent its phenotypic strategy in the game. A real variable v, which is a cell's overall investment in resistance. Then, two variables v_1 and v_2 describe the cell's allocation of resistance to drug 1 and to drug 2, respectively.

Finally, y_1 and y_2 track the concentration in all nodes (cancer but also healthy) of drug 1 and drug 2, respectively.

Phenotypes are the basic characteristics of cancer cells individuals, thus the resulting evolutionary model is said phenotypic individual-based model [7].

2.2.2 Updating rules or behaviors

In this IB model, the discrete time describes the ecological one. From the time step (t) to (t+1), which corresponds to spending a minute in real life hypothetically, the status of all nodes is updated according to the following rules. Obviously, using probabilities to describe the updating rules, the IB spatial model is a stochastic model, in contrast with the previous chapter model which is a deterministic one. Moreover, evolutionary processes have three other important sources of stochasticity: first, genetic drift randomly alters phenotypes with no effect on fitness; second, mutations introduce new phenotypic

values at random into the populations; third, mutants arise initially as single individuals and consequently are liable to accidental extinction [20].

2.2.2.1 Duplication

Each cancer cell, with random order, reproduces itself with probability $b(v)$, i.e. with probability that depends on the cell's overall investment in resistance. $b(v)$ decreases with increasing v because more energy the cell spends in resistance, less energy has for reproduce itself.
Inspired by the declining carrying capacity function $K(v)$ used by Orlando et al., the birth probability is firstly set to

$$b(v) = b_{max} e^{-v^2/(2\sigma_b{}^2)} \tag{2.1}$$

where $b_{max} = 1$ and σ_b must be estimated.

Maintain adherence with parameter $r = 1$ of the logistics equation of the previous chapter is challenging and it could not have physical meaning. Indeed, r is a rate, precisely birth minus death rate at low cancer density, or rather cancer growth per unit of cancer and per unit of time at low cancer density. So it could be bigger than 1, while in the IB model at each discrete step, i.e. each unit of time, a cell can reproduces itself at most one time. A possible way to overcome the problem is to use Gillespie algorithm [21].
Another way is to set the time step fixed and equal to 1, in which at most one birth and one death event can occurred, and directly describe the death and birth probability.
So, following the second way, the birth probability is reviewed because it does not have to be a semi-exponential function. Orlando et al. use a semi-exponential function for the carrying capacity function. Hence, at most the regime capacity, with respect to the phenotype v, can result to be a semi-exponential function. Assuming that switching from $v = 0$ to $v = \epsilon > 0$ has a not negligible effect on the birth rate, the birth probability is set to

$$b(v) = e^{-b_1 v} \tag{2.2}$$

with first derivative in $v = 0$ negative, imposing parameter $b_1 > 0$.

In case of reproduction, the cell selects randomly a neighbour node and duplicates itself only if there is not another cancer cell, i.e. only if the selected node is an healthy cell, otherwise it does not reproduce itself.

The fact of reproducing in random order and only if the chosen cell is not already occupied by another cancer cell, implements a mechanism of competition for the space, analogous to the mortality quadratic term of the logistics cancer growth used in the article of Orlando et al. The mortality quadratic term describes, in a statistical framework, the number of encounters per unit of time that a well mixed gas molecule makes with other gas molecules. Imagining that every encounter can produce a death, the term of mortality is therefore proportional to this rate of meetings. Randomly selecting a neighbour cell therefore wants to describe the fact that randomly moving an individual can die, or in this case, not reproduce itself.

Mutation events During reproduction, two different evolutionary mutation events can occur: the copy overall investment in resistance and its allocation of resistance to the drugs can mutate from the ancestor ones. The probability of mutation is μ, with probability $1 - \mu$ the copy is not mutated. This two mutation events have the same probability and are independent of each other, in analogy with Orlando et al. deterministic model where the evolutionary dynamics for the evolutionary variable are governed by the same speed parameter s and are independent of each other (1.9).

Mutation of v

At first, the phenotype v is reported on a real scale defining

$$z = \ln v \tag{2.3}$$

The new variable z changes to the mutated one

$$z_\mu = z + \delta z \tag{2.4}$$

where δz is drawn from a normal distribution $N(0, \sigma_v^2)$, with $\sigma_v = 1$. The mutated phenotype is

$$v_\mu = e^{z_\mu} \tag{2.5}$$

This transition to the natural logarithm is very standard for drawing variations of non-negative variables and corresponds to take

$$v_\mu = v\rho_v \tag{2.6}$$

where ρ_v is drawn from a log-normal distribution $LN(0, \sigma_v^2)$.

In evolution strategies the normal or gaussian distribution is generally regarded as the best choice for mutation [22]. This is because the multivariate normal distribution has some advantages: maximum entropy; rotation symmetry; unimodal and centered in zero; can be rotated, scaled, adapted and sampled easily; infinite support.

The problem with this implementation occurs while the phenotype dynamics is analyzed. Indeed, before the oncologist gives the drugs to an ill patient, the cancer overall investment in resistance (v) is obviously null and so the transformed variable z is equal to minus infinity and therefore also $z' = -\inf$, effectively blocking the mutation. Also with v practically zero the same problem arises, in this case caused by the extremely flat tail of the exponential function. To avoid these problems the mutations are drawn directly on v, setting v null if the mutated phenotype is negative, thus obtaining

$$\begin{aligned} v_\mu &= v + \delta v \qquad && if\ v + \delta v \geq 0 \\ v_\mu &= 0 && if\ v + \delta v < 0 \end{aligned} \tag{2.7}$$

where δv is drawn from a normal distribution $N(0, \sigma_v^2)$, with $\sigma_v = 0.1$.

Mutation of v_1

The allocation of resistance v_1 (defined in the real interval [0,1]) is reported on a real scale with the transformation

$$z_1 = (2(v_1 - \frac{1}{2})) \tag{2.8}$$

The variable z_1 changes to the value

$$z_1 = z_1 + \delta_{z_1} \tag{2.9}$$

with δ_{z_1} drawn from a normal distribution $N(0, \sigma_{v_1}^2)$ [22]. The mutated v_1 is

$$v_{1\mu} = \frac{1}{2} + \frac{\tanh(z_1')}{2} \tag{2.10}$$

As explained just above in the v mutation event, to allow v_1 to mutate until the bounds 0 or 1 if needed, the mutations are drawn directly on v_1, truncating the mutations that exceed the limits, obtaining

$$\begin{aligned} v_{1\mu} &= v_1 + \delta v_1 \qquad && if \quad 0 \leq v_1 + \delta v_1 \leq 1 \\ v_{1\mu} &= 0 && if \quad v_1 + \delta v_1 < 0 \\ v_{1\mu} &= 1 && if \quad v_1 + \delta v_1 > 1 \end{aligned} \tag{2.11}$$

where δv_1 is drawn from a normal distribution $N(0, \sigma_v^2)$, with $\sigma_{v1} = 0.1$.

2.2.2.2 Mortality

Every time step, each cancer cell dies with probability

$$1 - e^{-d(v)} \tag{2.12}$$

where

$$d(v) = m(v) + d_1(v, v_1)y_1 + d_2(v, v_2)y_2 \tag{2.13}$$

In particular

$$m(v) = m_0 + m_1 v \tag{2.14}$$

represents the natural mortality, as it is neither induced nor influenced by drugs;

$$d_1(v, v_1) = \frac{1}{k_1 + vv_1} \tag{2.15}$$

and

$$d_2(v, v_2) = \frac{1}{k_2 + vv_2} \tag{2.16}$$

multiplied for the drug concentrations y_1 and y_2 respectively, represent the pharmacological mortality.

Note that the tumor cell's resistance to a single drug is represented by the product between the cell's overall investment in resistance v and the allocation of resistance to that drug (v_1 or v_2). The cell's mortality and fitness due to drug toxicity are influenced by drug resistance as shown in equations (2.15) and (2.16).

2.2.2.3 Drugs diffusion

One advantage of the IB model is that a mechanism of drugs diffusion can be described, which is clearly more realistic than supposing that the drugs concentrations are always equal in the space in the immediate vicinity of the tumor.
The concentrations of drug 1 y_1 and drug 2 y_2 of each grid node are updated synchronously from step i to step (i+1), adding the input term w_i, chosen by the oncologist and positive only in the drug arrival cells (i.e. the perimeter of the grid), to the diffusive one, obtaining

$$y_1(i+1) = w_1(i) + (1-z)y_1(i) + \frac{z}{4}\sum y_{1neighbors}(i) \tag{2.17}$$

and

$$y_2(i+1) = w_2(i) + (1-z)y_2(i) + \frac{z}{4}\sum y_{2neighbors}(i) \tag{2.18}$$

where z represents the node drug fraction dispersed in the four direction, which arrived to and from the four neighboring nodes (square grid graph in figure 2.1).

Chapter 3

Calibrating the two models

In this chapter we describe how the spatial model parameters are set in order to calibrate the spatial model on the deterministic one presented in the first chapter.
The stochastic spatial model is numerically analyzed and simulated using MATLAB software.
The first step is to understand how a cancer grows with a specific phenotype v. Subsequently, the mutations of the disease are studied firstly without drugs administration and then with drugs administration with the goal of comparing cancer evolution in the two models.

3.1 Understanding cancer growth

The first MATLAB simulations are made with the aim of understanding how the cancer growth in the grid because, when the 'game' between the oncologist and the cancer starts, the disease is already at its regime status, in analogy with Orlando et al. study, where in the optimal control problem 1.10 the initial condition for N is $N(0) = K_{max}$, i.e. the cancer is at its maximum carrying capacity.
These simulations begin with four cancer cells in the middle of the grid, in absence of drugs and without mutations. Each step, the IB evolutionary model status is updated according with the updating rules describes in the previous chapter, subsection 2.2.2. A simulation is stopped when the cancer reaches its regime status. This denotes that the cancer cells mean number differs from the step after cancer cells mean number less than ϵ for a prefixed number of consecutive steps. ϵ is chosen equal to 0.01 and the number of consecutive steps equal to 300.
This study is done with the intent to calibrate the parameters of the IB model in order to have a cancer that grows up to occupy almost the whole grid for $v = 0$, which means no

energy spent on resistance to the drugs but all energy spent on growth, and which instead asymptotically occupies regions gradually smaller as v grows up to becomes extinct for v above a critical value. In System Theory this phenomenon, using the bifurcation jargon, is called transcritical bifurcation, i.e. in the system there is an exchange of equilibrium points stability. Indeed, for the IB model, below the critical value, for the cancer the extinction is an unstable equilibrium and its strictly positive regime status is a stable equilibrium, whereas, above the critical value, the two equilibria exchange their stability [23]. The now strictly negative regime becomes obviously unstable whereas the extinction becomes stable.
Recalling that the carrying capacity of the deterministic model is

$$K = K_{max} e^{\frac{-v^2}{2\sigma_k^2}} \tag{3.1}$$

with $K_{max} = 10$ and $\sigma_k = 30$, which is the standard deviation parameter of a Gaussian function, the parameters b_1, m_0 and m_1 of the birth and death probability, described in equations (2.2) and (2.14) respectively, are set in order to have cancer extinction, i.e. the transcritical bifurcation, for $v = 30$. Thirty is the value of the standard deviation of the carrying capacity function and it is chosen because in a Normal distribution, as it is well known, the interval $[mean \pm standard\ deviation]$ includes about 68% of all data. Including one standard deviation is a questionable choice, indeed it will modified due to a problem encountered in the next section 3.3.2. The parameter m_0 is set equal to $\frac{1}{k_1} = \frac{1}{k_2} = \frac{1}{10}$ of the deterministic model, which means to fix the measurement unit of the drugs. Indeed, the mortality induced at $v = 0$ by the dosage $y = 1$ of a drug is equal to the natural one. That is, $y = 1$ is that quantity of drug, for time unit, that doubles the mortality compared to the case, always with $v = 0$, without drug.
The parameter m_1 is to be estimated, together with b_1. With the idea to have the trade-off half on the birth rate and half on the mortality, the two parameters are chosen equal. The resulting estimate is $m_1 = b_1 = \frac{1}{70}$. Indeed, with these parameters the birth probability is more or less equal to the death probability but the mechanism of space competition, which is introduced to reflect the quadratic term of the logistic model and explained in the duplication section 2.2.2.1, cause the tumor extinction. The experimental results are shown in the next figure (3.1).

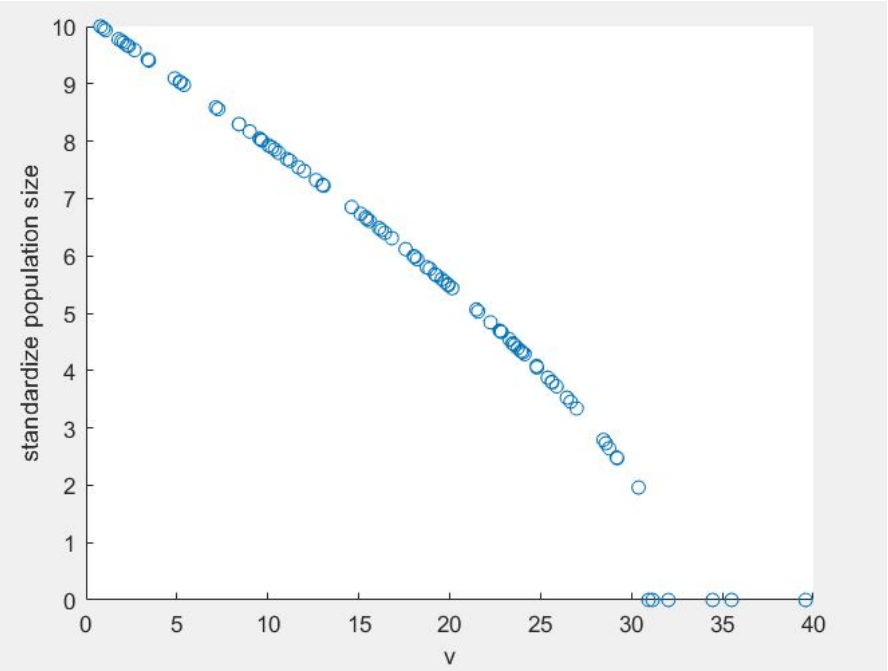

FIGURE 3.1: Standardize population size with respect to phenotype v, with model parameters $m_0 = \frac{1}{10}$, $m_1 = b_1 = \frac{1}{70}$. Linear tradeoff.

With this parameter, many simulations have been made, underlying that with a stochastic model only one result is practically insignificant, to see the relation between the phenotype v and the mean population regime size reaches by the cancer. Mean population size because the model is stochastic so little importance is given to the number, which is very variable, of the last step. To compare the results with the carrying capacity function $K(v)$ (1.3), which is equal to $K_{max} = 10$ for $v = 0$, the results have been divided by $0.1N_{max}$, where N_{max} is the biggest number of cancer cells reaches at regime, in order to have a new maximum equal to $10(= K_{max})$.

The relation between the population size and the phenotype seems more linear than exponential, as shows figure 3.1. However, these experiments are performed without drugs, so they are less significant since $K(v)$ depends on v which need drugs presence, in the real life, to be positive. A cancer develops resistance strategy v only in presence of chemotherapy.

The bifurcation event, which is a transcritical bifurcation, suddenly occurs at $v = 30$ approximately. This bifurcation represent the extinction threshold, since for $v > 30$ the cancer does not exist. This is caused by the fact that tumor spends too energy in resistance to drugs, which are not already present in these experiments, and remains with insufficient energy to proliferate.

3.2 Probability of mutation

In this section, it is explained how the mutation parameter μ, for mutation events 2.2.2.1, is chosen.
Here, the choice seems with less constraints, since in the deterministic model only one phenotype at time is present, forbidding a presence of phenotype diversity in the cancer. This is a clear limitation of Orlando et al. model, since it is well known that a cancer changes quickly and different types of cancer cells are present at the same time in the cancer mass [2, 24]. Moreover, in the optimal control problem exposed in section 1.3, the second and third equations, which determine the mutations, contain a speed parameter s, which is only specified that is larger with increased genetic variance or mutation rate.

To understand how a mutated cell evolves in a cancer mass in our IB models, a random phenotype v is selected and, after reached its regime in the grid as explained in the previous section 3.1, another advantaged phenotype v_μ is randomly selected and put in the center of the grid. Advantaged v_μ means obviously $v_\mu < v$ in absence of drugs, having no sense investing in resistance at the expense of the carrying capacity. Then, the simulation continues until only one phenotype is present in the cancer mass, which usually is the advantaged one, but not always for the space competition mechanism (the less advantage v has reached its regime before the appearance of v_μ) or simply because, as already stressed, the model is stochastic. So, the experiment is repeated numerous times and the average time T_r in which the mutated phenotype v_μ replaces v is calculated obtaining T_r almost 1000.
To remain adherent to the concentrated deterministic model of Orlando et al., the average time between two mutations, $\frac{1}{\mu}$, is smaller than the average time T_r required by v_μ for the replacement. However, to have a little more phenotypic heterogeneity, which, as said before, is true in the reality and possible only in the IB model and not in the deterministic one, the parameter μ is set to a value 10 times $\frac{1}{T_r}$, with the intent to focus the analysis on cancers that rapidly evolve to study their adaptation to drugs, obtaining $\mu = 0.01$.

3.3 Analyzing cancer evolution

Now that cancer cells parameters have been calibrated, the cancer evolution is studied through mutations, which are understood as the ultimate long-time driving force of evolution [25]. The experimental results are compared with the evolution in the deterministic model, using long simulations where several mutations occur with probability μ, just described. This analysis is performed without any control by the oncologist.
Two types of experiments are performed to see if the IB model allows cancer to evolve towards its best strategy in that situation of the game.

The first experiment only concerns the overall investment in resistance strategy v, since the environment is without drugs. A cancer, with strictly positive strategy v, is let reach its regime status, without mutation events. Once reached the regime, the cancer cells strategy has the possibility to mutate. It is expected that now, due to the absence of drugs, the cancer cells strategy mutates until the strategy v becomes equal to zero, which in this situation represents the best strategy. Indeed, for cancer cells, it makes no sense to spend energy on drugs resistance, since drugs are absent, and this saved energy can be spent reproduction.
The experiment is performed with several different starting phenotypes v.
The results are always in accordance with intuition and expectations, indeed in no case the evolution of the phenotype v does not tend towards 0, its best strategy. The figure 3.2 in the next page shows this evolution, in the plane (number of steps,v), in the worst case, i.e. with initial v almost equal to the extinction threshold, which is the worst strategy.

The second experiment concerns the dynamics of v together with the one of v_1, this time, however, in presence of drugs but again without any control by the oncologist, i.e. drugs delivery always constant and equal for drug 1 and 2.

So, before performing the experiment, it is necessary to calibrate the value of the control variables w_1, w_2, which are oncologist's strategies, and the z_1 and z_2 parameters, which is the per unit drug clearance rate, which govern the fourth and the fifth equations of the optimal control problem (1.10).

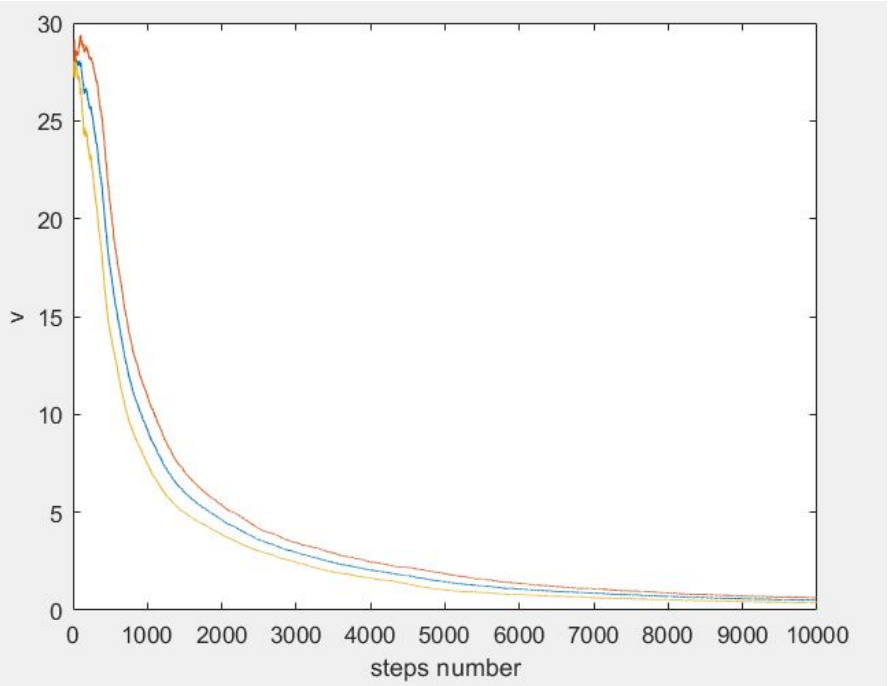

FIGURE 3.2: Evolution of the average phenotype $\bar{v}$ (blue line),$\bar{v}$-standard deviation (yellow line) and $\bar{v}$+standard deviation (red line) of the resident population tends to zero, the best strategy in that situation. Model parameters: $m_0 = \frac{1}{10}$, $b_1 = m_1 = \frac{1}{70}$. Linear tradeoff.

3.3.1 Calibrating drugs clearance and diffusion

For Orlando et al., drug clearance is modeled with basic first order pharmacokinetics, where z_1 and z_2 are per unit drug clearance rates (1.10). z_1 and z_2 are chosen equal, so from now on they will be indifferently called z_a. In the article [1], $\frac{1}{z_a}$ is the time constant with which the drug concentration $y(t)$ goes to zero if no drug is supplied to the patient. The idea is that the volume V of liquid that carries the drug is constant and that there is a constant flow rate F equal in entry and exit. The entry flow rate arrives with a drug concentration that is $w(t)$ divided by V. The output flow goes away with a concentration $y(t)$. Therefore the dynamics of concentration follows the equation

$$\frac{dy(t)}{dt} = \frac{w(t)}{V} - z_a y(t) \tag{3.2}$$

where, $z_a = \frac{F}{V}$. It should be noted that in Orlando et al. article the control variable w is the concentration of drug given to the patient for unit of time, or micro-grams per liter of volume of the treated mass, but it could be more natural to measure the dosage in the mass flow rate of the drug.

On the other hand, in the IB spatial model, we suppose that every cell in the grid, from step t to step (t+1), diffuses a fraction z of its liquid in four equal parts in the

four neighbors directions, as discussed in subsection 2.2.2.3 and we assume that each node receives the same incoming flow at null drug concentration. Thus, we obtain that the concentration goes to zero with dynamics $(1-z)^t$, so with time constant equal to $\frac{-1}{\ln(1-z)}$. The time constant is obtained passing through the exponential function, $f(t) = (1-z)^t = \exp(\ln(1-t)^t)$, and applying the definition of the time constant usually called τ: $\frac{df(t)}{dt} = -\frac{1}{\tau}(f(t)-c)$, where c is a constant.
Finally, equalizing the two time constants of the two models $\frac{1}{z_a} = \frac{-1}{\ln(1-z)}$, it is obtained $z = 1-\exp(-z_a)$. Since $z_a = 0.9$, it turns out $z = 0.5934$ approximately.

The control variable $w(t)$ in Orlando et al. article is measured in $\frac{mass}{volume \cdot time}$, where the volume V is that of the mass in which the drug is diluted, therefore difficult, if not impossible, to measure. As considered just above (3.2), the dynamics equation in continuous-time for the mass, incoming mass less outgoing mass, is

$$\frac{d(y(t)V)}{dt} = w(t) - y(t)F \tag{3.3}$$

where $w(t)$ is the control variable measured by $\frac{mass}{time}$ and $y(t)$ is the drug concentration, so $y \cdot V$ is the drug mass contained in the volume V, F is the flow rate of incoming and outgoing liquid, that are equal to maintain constant volume, and hence $y \cdot V$ is the outgoing mass of drug. Dividing by V, it is obtained

$$\frac{d(y(t))}{dt} = \frac{w(t)}{V} - z_a y(t) \tag{3.4}$$

where $z_a = \frac{F}{V}$ is the eigenvalue, which matches $\frac{1}{time}$. Discretizing, it is achieved

$$y(t+1) = y(t) + \frac{w}{V}\delta_t \tag{3.5}$$

where the value of $\frac{w}{V}$ is the same value of $w(t)$ of the article written by Orlando et al., in order to do analogous and comparable experiments.

3.3.2 Comparing cancer evolution at its regime status in the two models

In this section, as mentioned before, it is analyzed how the phenotype v and the cancer resistance allocation v_1 evolve in presence of drugs. Now that finally all the parameters of the IB spatial model have been calibrated on the deterministic model, we are able to compare the two cancer regime values in the same conditions.
To do this test, in analogy with Orlando et al., at the beginning cancer is allowed to develop, in absence of drugs, up to its regimen, as in the first experiments presented in this chapter 3.1. Obviously, when the cancer reaches its regime, in absence of drugs, all

its cells have strategies $v = 0$ and $v_1 = 0.5$, the best ones. Subsequently, the drugs are spread in order to understand how the two strategies evolve in the IB spatial model and compare the results with the deterministic model.

The experiment is performed in the case of linear trade-off (1.4) with constant control variable $w_1 = w_2 = 5$, in analogy to the optimal solution of Orlando et al. in their control problem with linear trade-off.

As explained in the mutation paragraph (2.2.2.1), it is forbidden to start the study of the dynamics of v with initially null phenotype, otherwise there would be no evolution. This problem is solved using a practically null phenotype. It is expected that, while administering the drugs, the phenotype v increases so that the cancer cells are more resistant to drugs by decreasing the cell's per capita mortality rate (2.15 and 2.16). Unexpectedly, this does not happen, as shown in figure 3.3 below.

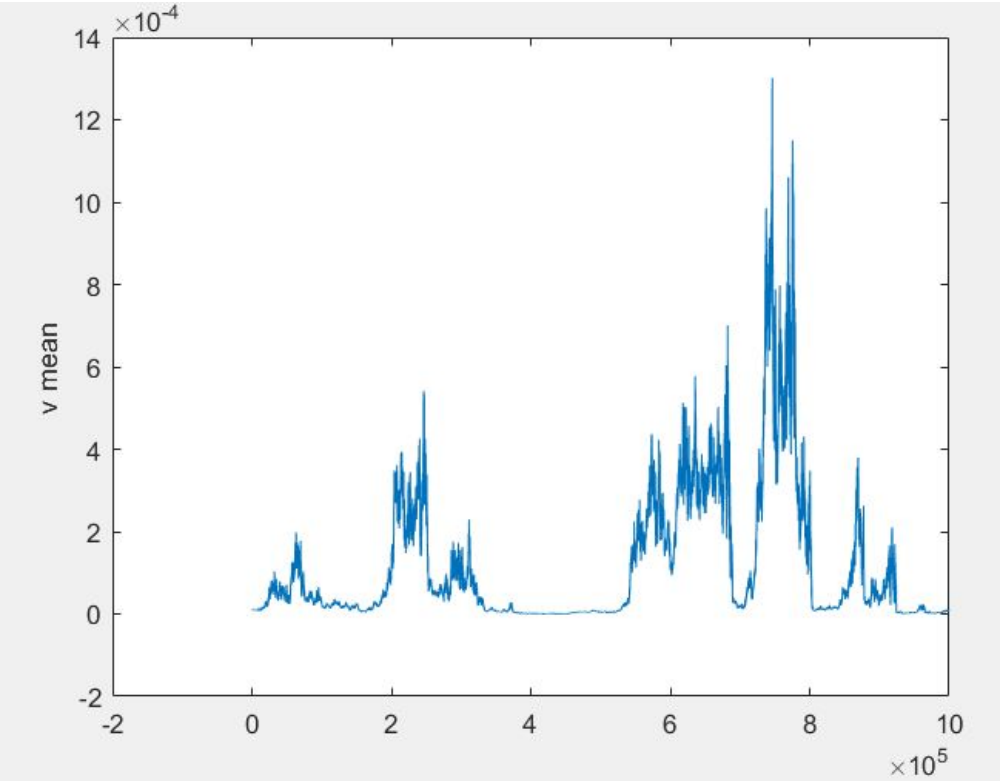

FIGURE 3.3: Graphic shows the mean strategy $\bar{v}$ of the resident population for one million of steps in the IB model. Model parameters: $\mu = 0.001$, $m_0 = \frac{1}{10}$, $b_1 = m_1 = \frac{1}{70}$. Linear tradeoff.

This phenomenon is caused by the parameters of the IB model. Indeed, the birth probability and natural mortality decrease and increase, respectively, too much with phenotype v, remembering that parameter b_1 is equal to m_1, compared to how the cell's per capita d_1 (2.15) and d_2 (2.16) pharmacological mortality effects decrease with v,

then, for the cancer cells, it is more convenient to evolve towards $v = 0$. So the parameterization is reviewed in order to have extinction at $v = 100$, because, remembering that the carrying capacity function (1.3) of the deterministic model is a semi-exponential function with standard deviation $\sigma_k = 30$, at this threshold almost all observable data fall in the interval. So parameters $b_1 = m_1$ are chosen equal to $\frac{1}{220}$.
The experiment is repeated with the new parameterization and, as expected, the strategy v evolves and it evolves up to the value 25, as shown in figure 3.4 below. Note that it seems that the evolution occurs sharply in few steps, caused by the passage through the exponential function (2.5) during mutations. But the evolution of the strategy v not always occurred. One example of a case where the strategy evolution does not take place is shown in figure 3.5.

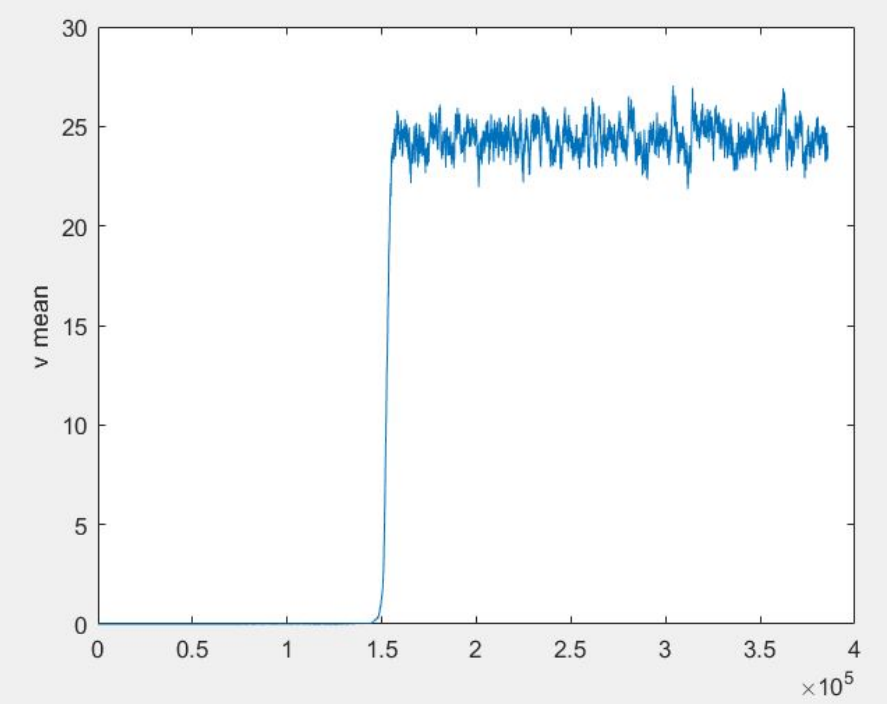

FIGURE 3.4: The evolution of the average phenotype $\bar{v}$ of the resident population for one million of steps in the IB model with parameters $m_0 = \frac{1}{10}$, $b_1 = m_1 = \frac{1}{220}$ and $\mu = 0.001$. Initial value of $v = 0.00001$. Linear tradeoff.

Repeating several times this experiment for different initial values of the phenotype v almost zero, however, it is observed that this growth of the phenotype always takes place only with starting v greater than 0.001.
The fact that starting from v very low the phenotype may not evolve, it may perhaps depend on the fact that some cells mutate with v_μ lower than v that numerically goes to minus infinity and so the evolution becomes impossible, as already explained. Or it may happens because the exponential function queue is so flat that even mutations with larger mutated phenotype are still very small and so they not give enough advantage to

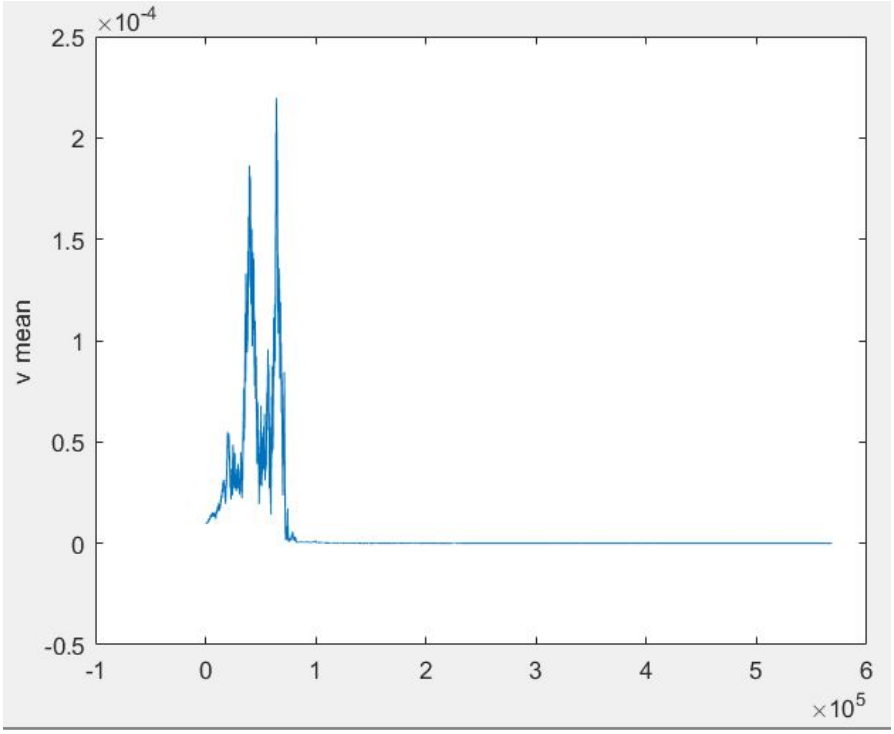

FIGURE 3.5: Example of a case, with initial $v = 0.00001$, in which the evolution of the average strategy $\bar{v}$ of the resident population tends to zero. IB model parameters:$m_0 = \frac{1}{10}$, $b_1 = m_1 = \frac{1}{220}$ and $\mu = 0.001$. Linear tradeoff.

allow the growth of the phenotype.

As discussed in the mutation paragraph (2.2.2.1), the solution lies in avoiding to go through the exponential function during mutation events and drawing mutations directly on v and v_1.

The experiment is performed with the new mutation rules and now the cancer phenotype v always evolves up to 25, also with initial value equal to 0, which is allowed with mutations directly on v. Note that, with this new implementation, evolution phenomenon does not occur briefly as before, but it is sweeter.
Since the concentration of the two drugs are equal and the experiments are done in the case of linear evolutionary tradeoff, with which generalizing to accommodate both drugs, or specializing on a single drug is equal in term of allocation, as expected, the strategy v_1 floats around the value 0.5, which means generalized resistance, because there is no advantage in a specialized resistance to a single drug in presence of both drugs with equal concentration.
This results of how the cancer strategies evolve are shown in figures 3.6 and 3.7.

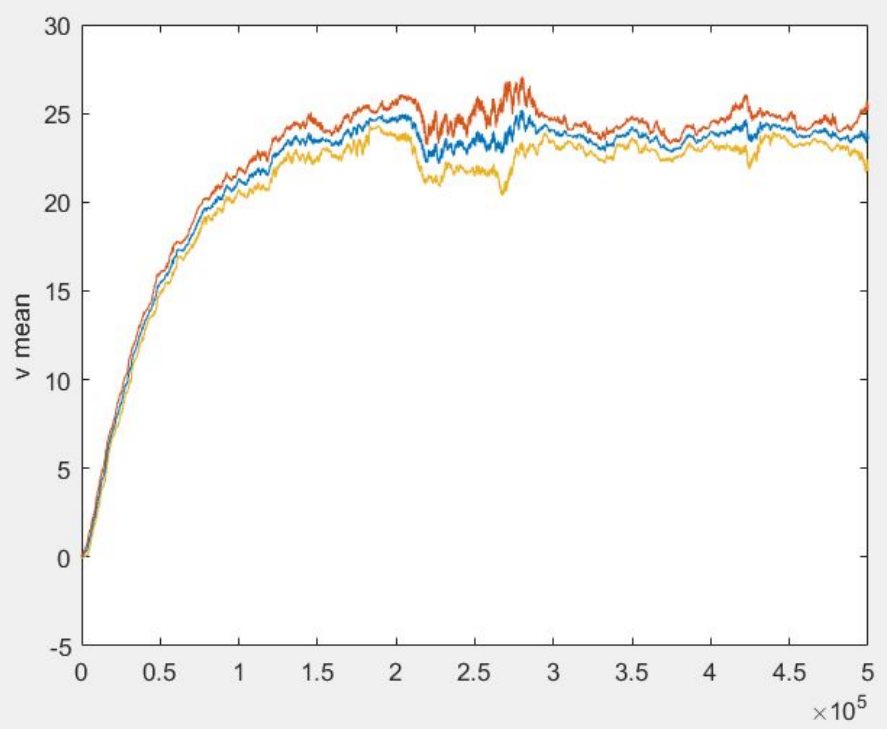

FIGURE 3.6: Evolution of the mean phenotype $\bar{v}$(blue line),$\bar{v}$-standard deviation (yellow line) and $\bar{v}$+standard deviation (red line) of the resident population that tends to 24 approximately with mutation directly drawn on v. IB model parameters: $m_0 = \frac{1}{10}$, $b_1 = m_1 = \frac{1}{220}$ and $\mu = 0.001$. Linear tradeoff.

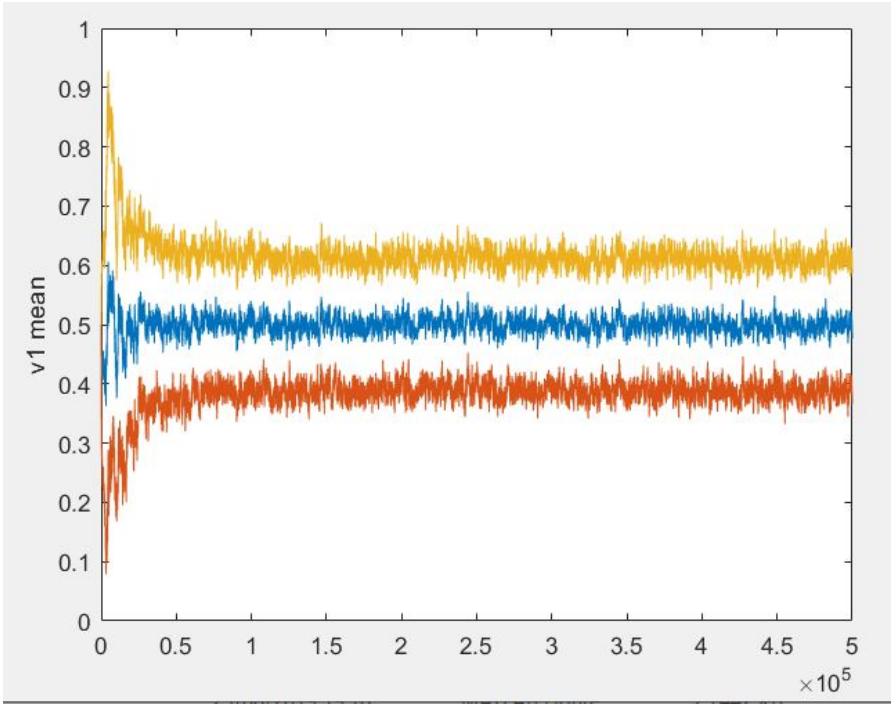

FIGURE 3.7: Evolution of the average phenotype $\bar{v_1}$(blu line),$\bar{v_1}$+standard deviation (yellow line) and $\bar{v_1}$-standard deviation (red line) of the resident population fluctuates around 0.5.IB model parameters: $m_0 = \frac{1}{10}$, $b_1 = m_1 = \frac{1}{220}$ and $\mu = 0.001$. Linear tradeoff.

3.3.2.1 The phenotypic regime of the deterministic model

Since the idea is to compare the phenotypic regime in the two models, we need to analyze the phenotypic regime in the deterministic model. Indeed, in the figure reported in the first section 1.3, which shows the optimal state profile, the time variable belongs only to the interval $[0, 8]$ and it clearly seems that the phenotypic variables, figure below, have not yet reached the regime. Since cells allocation of resistance is equal to both drugs, the graphic shows half of the evolution of strategy v.

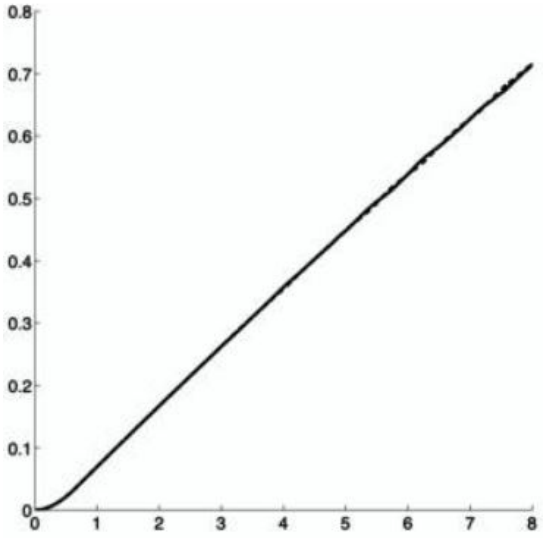

FIGURE 3.8: Evolution of the cells drug resistance to drug 1 of the resident population in the deterministic model with linear tradeoff(figure 1.3, top right panel). Since cells allocation of resistance is equal to both drugs, the graphic shows half of the evolution of strategy v.

To see the regime state of the system, the differential system is numerically solved using MATLAB, specifically with ode45. ODE solvers can solve systems of differential equations of the form $\frac{d(y(t))}{dt} y = f(t, y(t))$.
$[t, y] = ode45(odefun, tspan, y_0)$, where $tspan = [t_0, t_f]$, integrates the system of differential equations $\frac{d(y(t))}{dt} y = f(t, y(t))$ from t_0 to t_f with initial conditions specified in y_0. Each row in the solution array y corresponds to a value returned in column vector t.

The differential equations and their initial conditions are the one of the optimal control problem (1.10):

$$\begin{cases} \dfrac{dN}{dt} = NG|_{\mathbf{v=u}} \\ \dfrac{du_1}{dt} = s\dfrac{dG}{dv}|_{v=u_1} \\ \dfrac{du_2}{dt} = s\dfrac{dG}{dv}|_{v_1=u_2} \\ \dfrac{dy_1}{dt} = w_1 - z_1 y_1 \\ \dfrac{dy_2}{dt} = w_2 - z_2 y_2 \\ N(0) = K_{max},\ y_1(0) = 0,\ y_2(0) = 0, \\ u_1(0) = 0,\ u_2(0) = 0.5,\ t_f fixed \end{cases} \tag{3.6}$$

The control variables are set $w_1 = w_2 = 5$, inspired by the optimal solution found in the linear tradeoff (figure 1.3, top right panel). In the article the value of the speed parameter s is not specified, but it has been empirically found that with $s = 2$ and $t_f = 8$ the solution obtained with ode45 coincides with the solution presented by Orlando et al.. The final time t_f is set equal to 5000, in order to see if and how the system reached its regime in a long time interval. The results are shown in figures 3.9, 3.10 and 3.11. The overall investment in energy u_1, of the resident population, which corresponds to our variable v, converges almost to the value 22.5, while u_2 is always equal to 0.5, which means generalized resistance, i.e. equal resistance to both drugs, which is an intuitive strategy in this case of linear tradeoff and control variable equal and constant. These are the best cancer strategies in the specified environment.

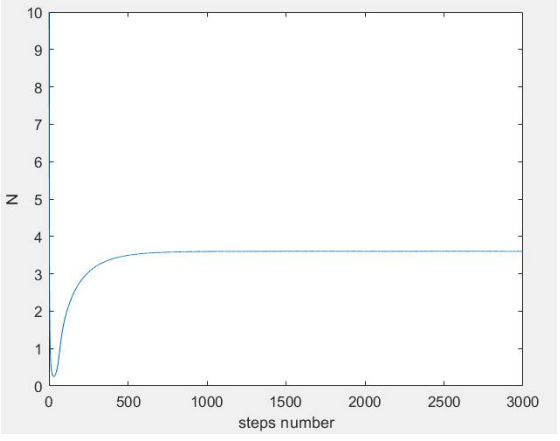

FIGURE 3.9: Evolution of the cancer population size N in the deterministic model with linear tradeoff.

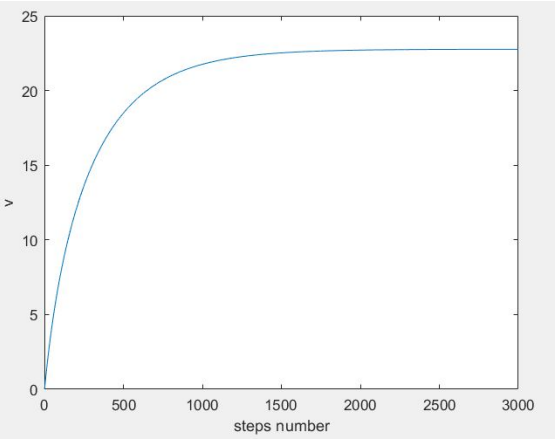

FIGURE 3.10: Evolution of the strategy v in the deterministic model with linear tradeoff.

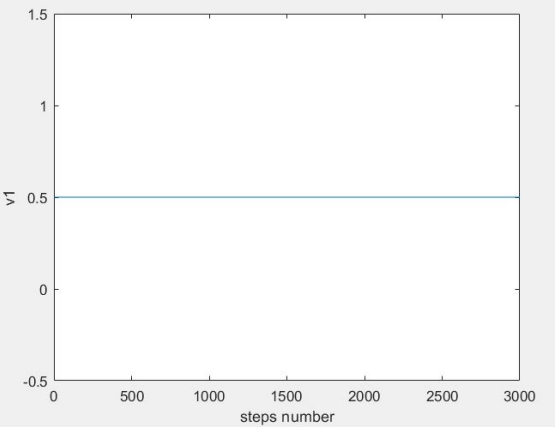

FIGURE 3.11: Evolution of the strategy v_1 in the deterministic model with linear tradeoff.

The best cancer strategies are almost equal in the two models, having both generalized resistance, or $v_1 = 0.5$, but the overall investment in energy in the IB model is slightly greater. This is probably due to the choice to have cancer extinction in v=100. So parameters $b_1 = m_1$ are reset equal to $\frac{1}{210}$ in order to have also in the IB spatial model the overall mean investment in energy that converges almost to 22.5. This is done empirically, repeating the experiment changing the parameters until the convergence hit the desired value.

Note that, since in the IB model a phenotopyc diversity is present, convergence refers to the mean resident population value.

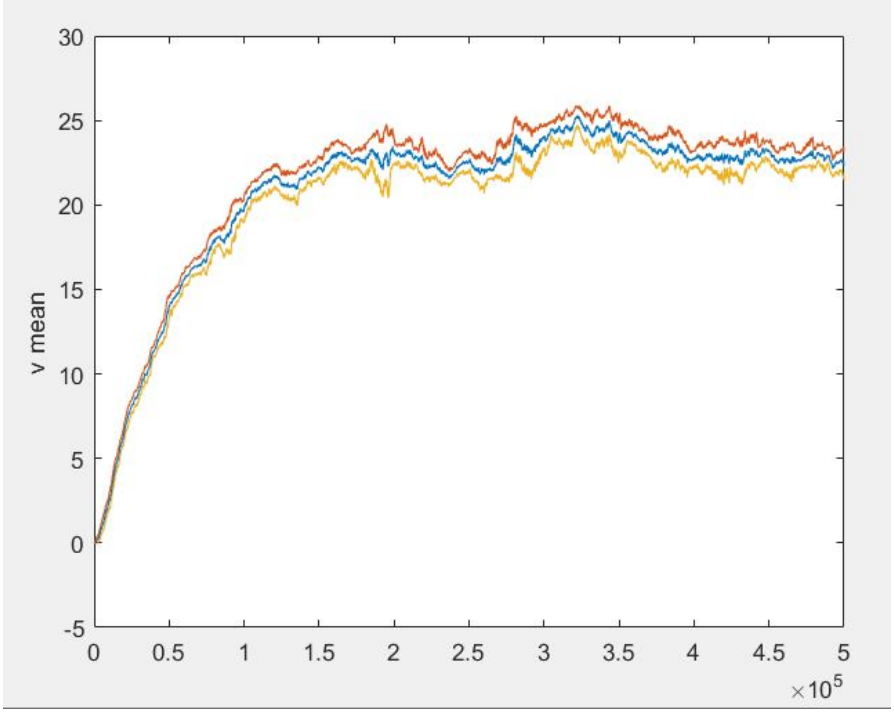

FIGURE 3.12: Evolution of the mean phenotype $\bar{v}$(blue line),$\bar{v}$-standard deviation (yellow line) and $\bar{v}$+standard deviation (red line) of the resident population that tends to 22.5 approximately with mutation directly drawn on v. IB model parameters: $m_0 = \frac{1}{10}$, $b_1 = m_1 = \frac{1}{210}$ and $\mu = 0.001$. Linear tradeoff.

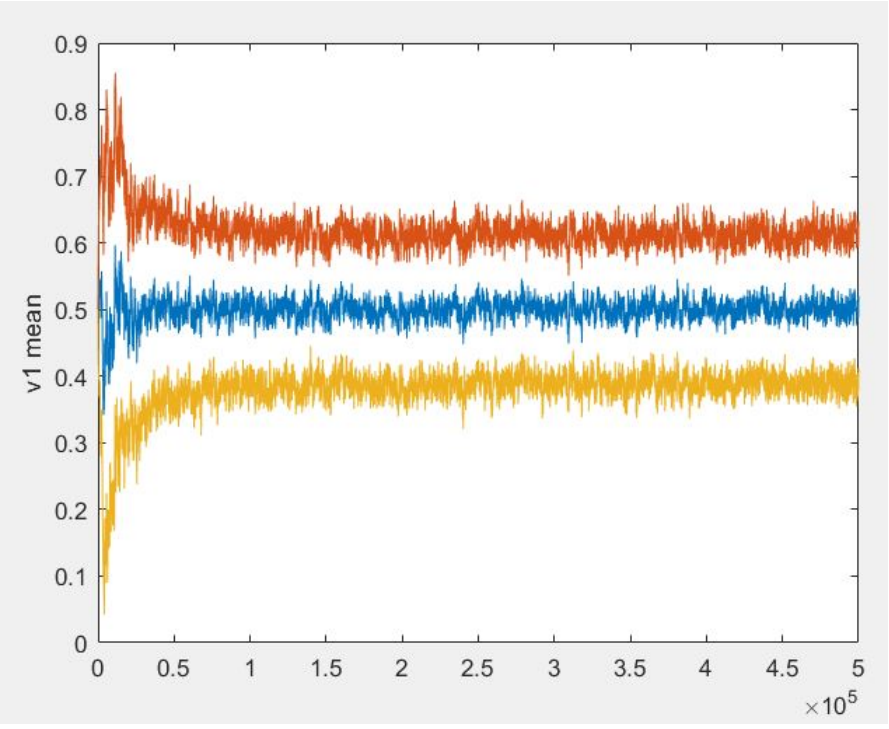

FIGURE 3.13: Evolution of the average phenotype $\bar{v_1}$(blu line),$\bar{v_1}$-standard deviation (yellow line) and $\bar{v_1}$+standard deviation (red line) of the resident population fluctuates around 0.5. IB model parameters: $m_0 = \frac{1}{10}$, $b_1 = m_1 = \frac{1}{210}$ and $\mu = 0.001$. Linear tradeoff.

Chapter 4

Oncologist best strategy

Once calibrated the IB stochastic model, we need to understand which is the best strategy for the oncologist, who can think ahead and can design strategy to fight cancer, which instead follows only its evolutionary boost to adapt itself as much as possible to the environment and to grow up, as in a leader-follower game[5]. So, we want to understand in which direction the cancer growth gradient pushes with respect to the control variables, so that the oncologist can try to push its growth in the opposite direction. With this goal, the gradient descent method is presented and applied to look for the best oncologist protocol.

4.1 Gradient descent method

Generally speaking, gradient descent method is a first-order iterative optimization algorithm for finding a minimum, or a maximum in the case of gradient ascent method, of a function. To find a local minimum of a function, the idea of the gradient descend is to take steps proportional to the negative of the function gradient, which indicates the direction of local maximum function growth, at the current point. It is also possible to use an approximation of gradient if the function is not well known, such as in cancer growth case, it only needs that the function is defined and differentiable in a neighborhood of the current point. These are our assumptions. So, the method generates a sequence of points with decreasing objective function. The draw back of this method is the fact that every local minimum has null gradient and therefore the gradient descent method solution usually is the local minimum closest to the starting point.

4.2 Searching optimal control variables

In this research, the function to be minimized is the number of cancer cells and its parameters are the control variables w_1 and w_2 of the oncologist. To simplify the study, it is considered a short period of time, which ideally corresponds to a real month, where each discrete step of the IB model correspond to a real minute, and it is supposed that in this period the oncologist can vary its control variable every two days, however obtaining fifteen parameters to be optimized, not so few.
As the model is stochastic, not only the number N of cancer cells of the last step is looked at, but the mean cells number N, in the last 1% of steps, is the objective function to be optimized. To reduce stochastic error, the results are the mean of five MATLAB simulations obtained with different random number generator.
Orlando et al. impose a constraint on the total amount of drugs concentration to avoid toxicity to the patient, $y_1 + y_2 \leq 10$. We think that even clinically it is more practical to put a limit for the oncologist on the dosage of a drug, rather than a limit on the concentration that the drug has in a certain tissue, which should therefore be measured every times or, in any case, with regularity, in this study the constraint is directly put on the control variables w_1 and w_2. These are the rates of drug delivery for drug 1 and drug 2, respectively. Moreover in the IB model presented in this thesis, by imposing the constraint on the control variables $w_1 + w_2 \leq 10$, it is automatically satisfied also the constraint on the drugs concentration $y_1 + y_2 \leq 10$.
Since the problem is analyzed in an optimal control framework, it is clear that the solution lies on the constraint upper bound. Indeed, any solution having $w_1 + w_2 < 10$ can be improved, or at least equaled, being the goal minimizing the number of cancer cells, increasing up to the limit the supply of drugs that can only decrease the final cancer population size. The more drug is present in a cancer cell, the more likely it is to die the next step in the model. So, at the end, only one control variable w_1 must be optimized, from which the other control variable will be automatically obtained by imposing $w_2 = 10 - w_1$.
The idea is relative simple but the application is numerically quite complex.
In Orlando et al. optimal control problem the initial conditions are cancer population size $N(0) = K_{max}$, overall resistance $v = 0$, generalized resistance $v_1 = 0.5$ and null drug concentrations $y_1(0) = y_2(0) = 0$. In analogy with their study, we let cancer reach its regime status with null overall investment in resistance, i.e. with $v = 0$, without drug presence and with generalized resistance ($v_1 = 0.5$). This situation represents the case of a cancer developing in an individual still unaware of the disease. Once a cancer reaches its regime, the one-month treatment period begins, where the control variable can change value every two days. The starting control variable is constant along the whole month and its value is 5, so the situation is $w_1 = 5$ and therefore $w_2 = 10 - w_1 = 5$ for all

protocol period. With this signal, the objective function is calculated, called F_0. Now we need to estimate the gradient of the objective function, using the incremental ratio, with respect to the fifteen parameters of the oncologist control variable. Therefore the first parameter is took and increased by a δ. If it violates the constraint on maximum drug delivery or on the positiveness, it is set equal to the limit value. All other parameters are left unchanged. With this new control signal, the objective function, called F_1 because the first parameter has been changed, is calculated. Now the gradient with respect to the first parameter p_1 is estimated as

$$\frac{\partial F}{\partial p_1} = \frac{F_1 - F_0}{(p_1 + \delta) - p_1} = \frac{F_1 - F_0}{\delta} \tag{4.1}$$

where $\delta = 0.5$. Calculated the incremental ratio with respect to the first parameter, p_1 is put back to the value it had before adding the delta, i.e. in the base signal with which F_0 has been calculated. Then the process is repeated for the second parameter p_2. So p_2 is increased by δ, and, leaving all the other parameters unchanged with respect to the base signal as before, the objective function F_2 is calculated and therefore the incremental ratio with respect to the second parameter $\frac{\partial F}{\partial p_2} = \frac{F_2 - F_0}{\delta}$.
This procedure is repeated for all fifteen parameters, thus obtaining an estimate of the gradient of the objective function with respect to the base signal. Then, once the gradient is normalized, the signal moves, in a space with dimension fifteen, in the opposite gradient direction of a step of length $r = 1$. With this obtained new control signal, the objective function is calculated. If it is less than the one calculated with the previous base signal (so a better solution has been found), the new signal becomes the new base signal and the procedure is repeated, i.e. it is estimated the gradient of the new base signal and then the signal is moved in the opposite direction. On the other hand, if the objective function is increased instead of decreased, the step is halved until a lower objective function is found. The halving is repeated until a better objective function is found or the length step r becomes smaller than a certain threshold ϵ, which is chosen equal to $\frac{1}{2^6} = \frac{1}{64}$. If we do not find a better objective function before crossing the threshold ϵ, the last base signal used to calculate the objective function F_0 is the researched optimal solution.

4.3 Results

This procedure is applied for all three different tradeoffs with a common set of parameters.
The method is found to be particularly heavy numerically. One real month correspond to fifty thousand steps almost. To take a possible step with the gradient method, we need to calculate the objective function for all fifteen parameters incremented by δ plus the case with the base signal. To reduce the stochastic error, we mediate these results on five different cases, getting simulations that last several hours and perform almost four millions of steps.

4.3.1 Linear tradeoff

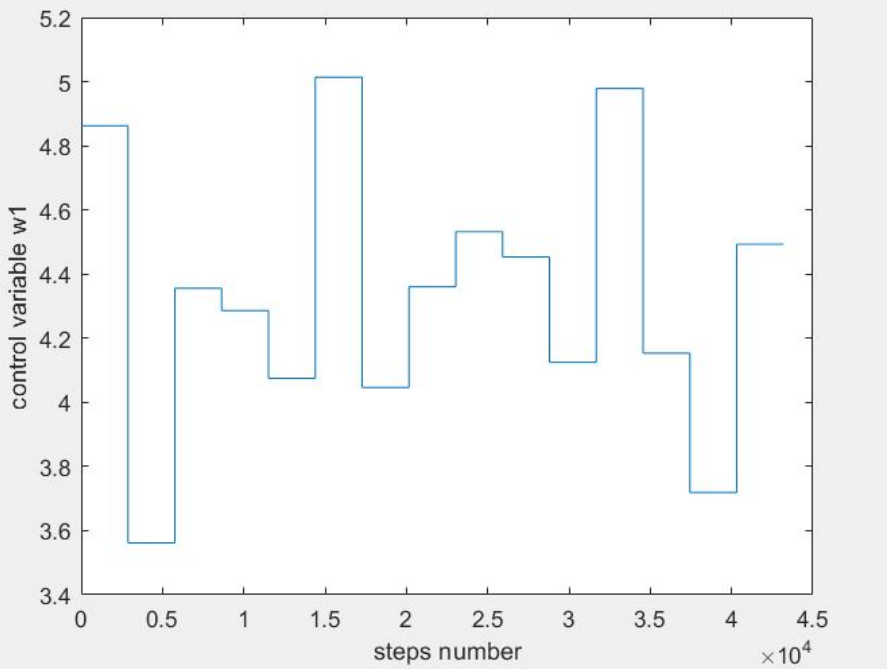

FIGURE 4.1: The figure shows the optimal control variable w_1 ($w_2 = 10 - w_1$) obtained with linear tradeoff. Model parameters: $m_0 = \frac{1}{10}$, $b_1 = m_1 = \frac{1}{210}$ and $\mu = 0.001$.

In the case of linear tradeoff, the optimal signal seems to fluctuate randomly around the value $w_1 = 4.3$, approximately. The fact that the signal fluctuates is in agreement with Orlando et al. solution (figure 1.3, top left panel), which however fluctuates less and around the value 5, that is about drugs equal dosage. In this situation, the tumor keeps generalized resistance, i.e. equal to both drugs. In their concentrated differential model, tumor has its strategy, unique for all cancer cells, which are not studied individually. Instead, with our IB model, each cancer cell is allowed to have its own strategy to play the game against the oncologist. This situation reflects better the reality, where

in a tumor coexist different type of mutated cells with different strategy [24]. Here, we appreciate the richness of the IB model [19]. This is an improvement of the IB model on the differential one, which allows tumor to have only one general strategy. The oscillations of the optimal signal are more marked with our model so that tumor has enough drug and time to develop cancer cell's resistance to the drug with higher concentration (figure 4.2), in this case drug 2. The oncologist can now exploit this situation providing the patient with a greater dosage of the other drug, here drug 1, to which the tumor is more susceptible. The tumor responds by gaining resistance to drug 1. Now, the oncologist can again hit the tumor with the drug 2 which the cancer cells are less resistant to. This scenario is called evolutionary double bind [6]. The experimental results with this oncologist strategy are shown in figure 4.2.
In their study, Orlando et al. wonder how much their optimal solution, in which the drugs vary randomly just slightly from equal concentration (chattering control), differs from the case of constant control, with equal drugs concentration. They find that in practice there is no difference. So they assert that the optimal control is static. Also in the IB model the optimal solution does not significantly vary from the solution with equal drugs concentration. Numerically, the solution obtained with the optimal signal, figure 4.1, decreases to 3012.5 from 3036.72 mean cancer cells number, achieved with $w_1 = 5$ along all protocol. There is practically no clinical difference in the tumor final population size.

In conclusion, in the linear tradeoff case, we find that the optimal protocol is dynamic, where drugs concentration varies along time according with the control variable w_1 shown in figure 4.1. However, we note that a static protocol, where the best strategy is to use the maximum drugs amount, avoiding patient toxicity, and in equal concentrations, gains practically the same effect.

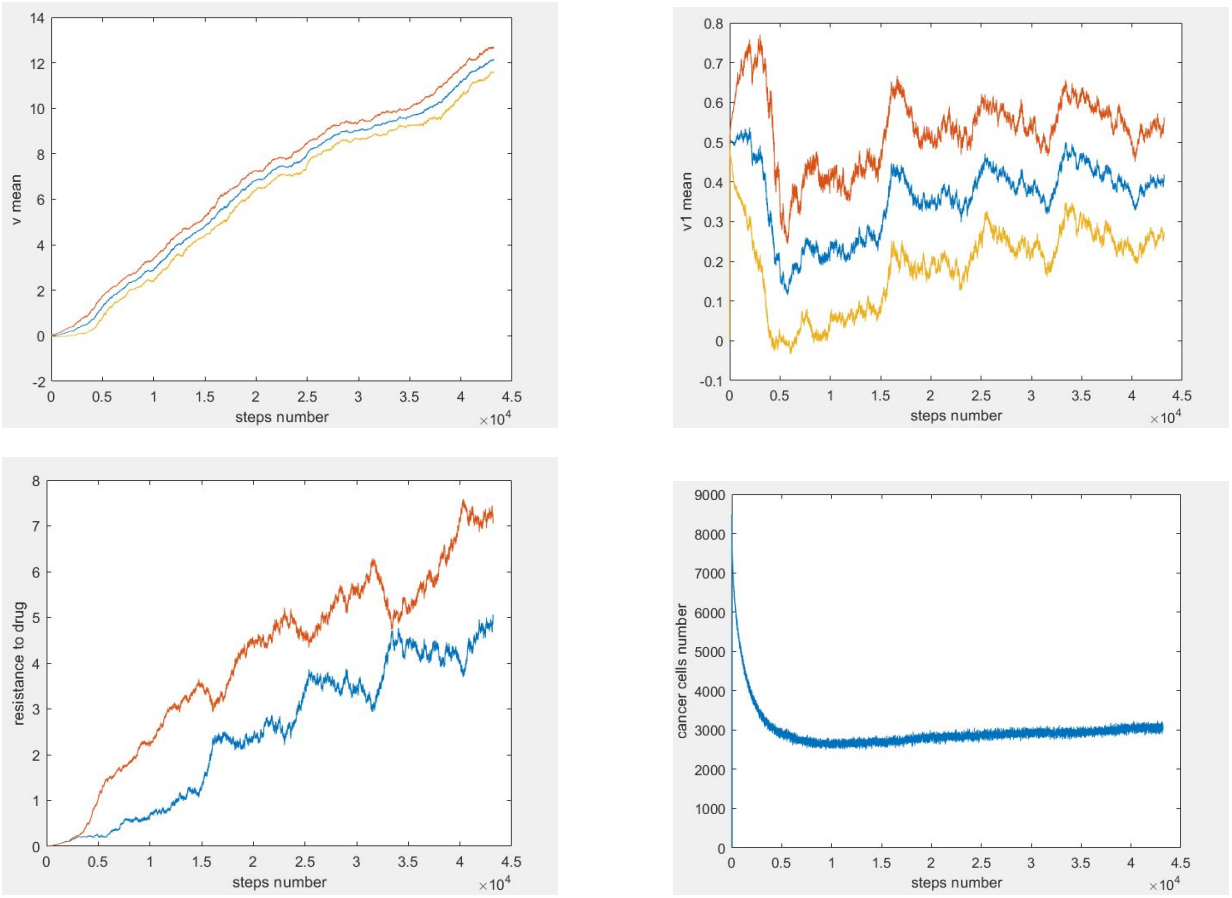

FIGURE 4.2: Cancer state profile evolution for the case of linear tradeoff. The top panels show the evolution of the mean cell's overall investment in resistance $\bar{v}$ (blue line), $\bar{v}$+standard deviation (red line) and $\bar{v}$-standard deviation (yellow line) on the right, and the cell's mean allocation of resistance to drug 1 $\bar{v_1}$ (blue line), $\bar{v_1}$+standard deviation (red line) and $\bar{v_1}$-standard deviation (yellow line) on the left. The left bottom panel shows the tumor cell's resistance to drug 1 (blue line) and drug 2 (red line). The right bottom panel show the number of cancer cell step by step. Model parameters: $m_0 = \frac{1}{10}$, $b_1 = m_1 = \frac{1}{210}$ and $\mu = 0.001$.

4.3.2 Convex tradeoff

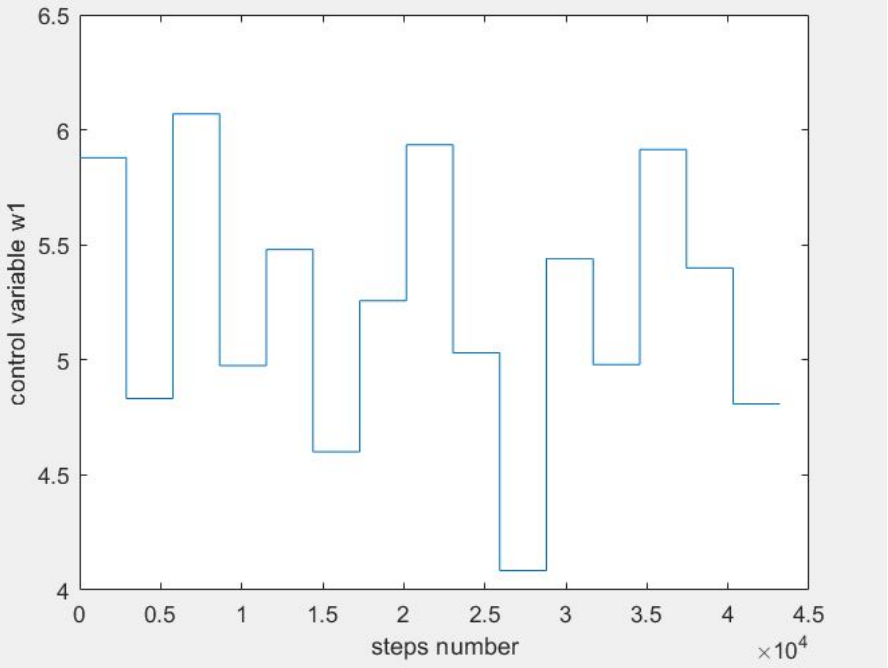

FIGURE 4.3: The figure shows the optimal control variable w_1 ($w_2 = 10 - w_1$) obtained with convex tradeoff. Model parameters: $m_0 = \frac{1}{10}$, $b_1 = m_1 = \frac{1}{210}$ and $\mu = 0.001$.

Even with the convex tradeoff, the optimal signal (figure 4.3) fluctuates but, in this case, the oscillations seem less random. In fact, after an increase in a drug concentration there is usually a decrease and vice versa. Therefore the signal seems to rise and fall (not fluctuate randomly), but with relatively large amplitudes, on average amplitude one, around the situation of equal concentration. Also in this case, the difference with the solution obtained with the differential model (figure 1.3, down right and left panels) is due to the high degree of phenotypic diversity of the IB model. Indeed, since each cell plays with its own strategy, which is allowed to mutate also in the situation with equal drugs concentration, there is no reason that all cancer cells have equal generalized resistance [24]. So the oncologist can induce and try to control the cancer cells allocation of resistance, exploiting the evolutionary double bind [6] as just explained in the case of linear tradeoff. This is done with unequal values of control variables, as in the solution found (figure 4.3). Therefore, clearly there are resistance allocations, or v_1 strategies, different within the tumor. Thus an optimal solution is an oscillating solution, that tries to control and induce the development of resistance, with the aim of providing some days more drug amount of the type which the cancer is more susceptible to.

The improvement obtained with this oscillating solution, that exploits the phenotypic diversity and the evolutionary double bind, is better than in the linear case, but not so significant. The resident population mean number decreases from 3583.9, achieved with static solution ($w_1 = w_2 = 5$), to 3567.9. The obtained reduction is approximately

1%, which is not particularly numerically significant. But we are focusing on qualitative results, since to have quantitative reliable result the IB evolutionary model should be more detailed and related to a specific tumor type. Cancers are a large family of diseases that involve abnormal cell growth, in so many different possible forms.

So, as in the linear case, the optimal control is a dynamic protocol, in which drugs concentration varies along time according with the control variable w_1 shown in figure 4.3. However, as in the linear tradeoff, a static protocol, with $w_1 = w_2 = 5$, obtains practically the same effect.

Moreover, we are investigating tumor with rapid evolution to analyze their adaptation to the surrounding environment. Fighting tumor with slow evolution, the effectiveness of a dynamic protocol should be more evident.

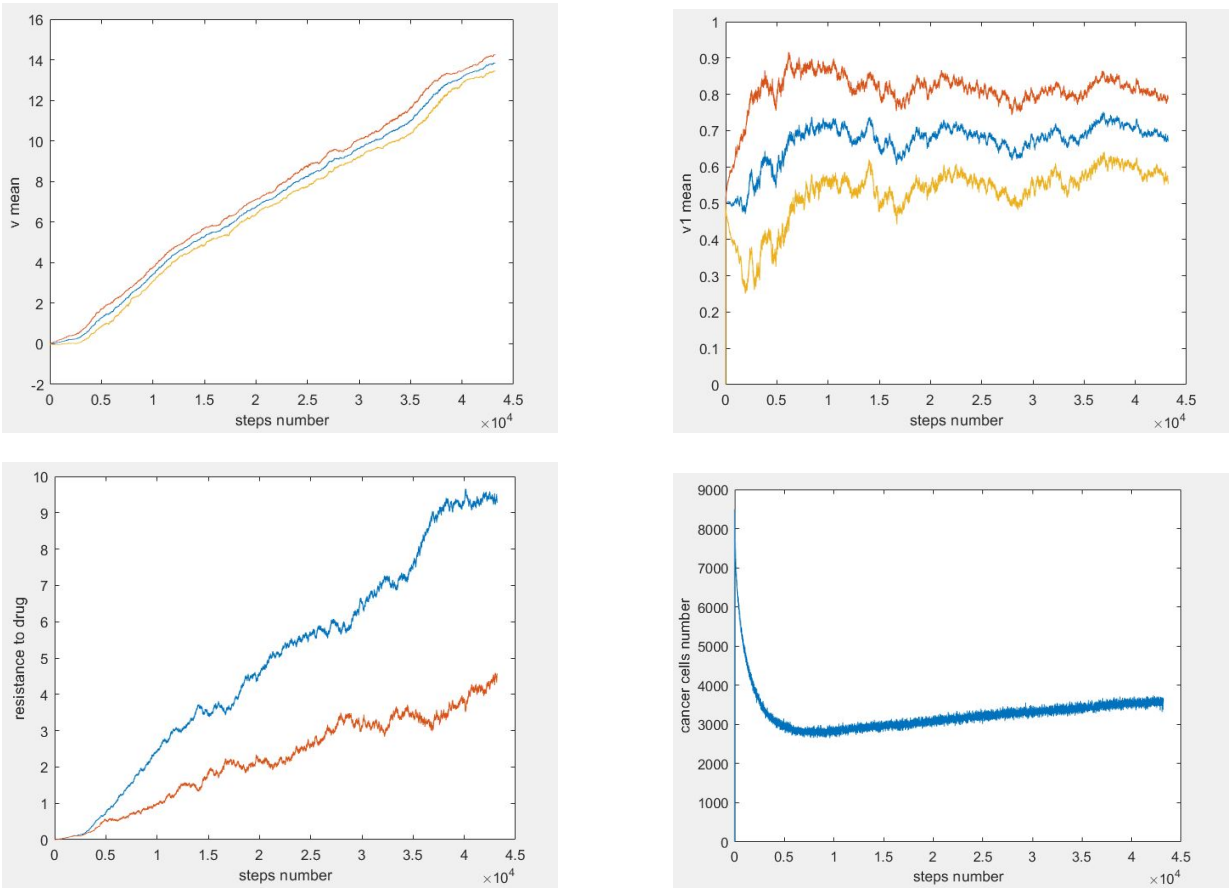

FIGURE 4.4: Cancer state profile evolution for the case of convex tradeoff. The top panels show the evolution of the mean cell's overall investment in resistance $\bar{v}$ (blue line), $\bar{v}$+standard deviation (red line) and $\bar{v}$-standard deviation (yellow line) on the right, and the cell's mean allocation of resistance to drug 1 $\bar{v_1}$ (blue line), $\bar{v_1}$+standard deviation (red line) and $\bar{v_1}$-standard deviation (yellow line) on the left. The left bottom panel shows the tumor cell's resistance to drug 1 (blue line) and drug 2 (red line). The right bottom panel show the number of cancer cell step by step. Model parameters: $m_0 = \frac{1}{10}$, $b_1 = m_1 = \frac{1}{210}$ and $\mu = 0.001$.

4.3.3 Concave tradeoff

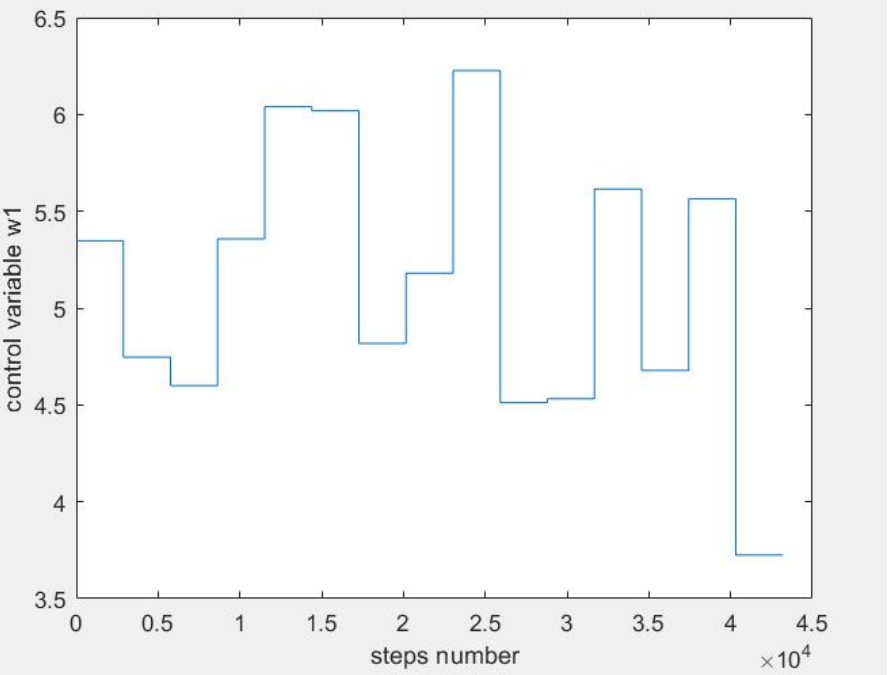

FIGURE 4.5: The figure shows the optimal control variable w_1 ($w_2 = 10 - w_1$) obtained with concave tradeoff. Model parameters: $m_0 = \frac{1}{10}$, $b_1 = m_1 = \frac{1}{210}$ and $\mu = 0.001$.

Finally, analyzing the case of concave tradeoff, the mechanism of alternating drugs is more evident compared to the other two tradeoffs. In this case, we find large variations but in some consecutive days there are small, or almost null, variations. With this type of solution, it is clear that the oncologist should exploit the evolutionary tradeoff, by inducing cancer cells specialized resistance and then exploiting tumor susceptibility to the other drug, i.e. exploiting the evolutionary double bind [6]. As figure 4.6 shows, cancer cells are driven by the oncologist to adapt their resistance to a single drug (here drug 2), before varying the drug concentration in favor of the other drug (drug 1). So she treats the tumor with the more effective drug. The tumor responds by gaining resistance to the last drug (in this case drug 1), until its resistance becomes specialized to that drug. So the oncologist exploits again this situation hitting the tumor with the more effective drug (drug 2), and so on.

The optimal protocol is dynamic, similarly to the one analyzed by Orlando et al. one (figure 1.3, middle panels). However the difference, in the solutions obtained with the two models, consists on drugs concentration optimal profile. In the IB model one drug does not completely alternate with the other one, as it happens with the differential model. The idea behind the protocol is the same: to induce the specialization of cancer cells resistance and then to hit the tumor with the other drug to which it is not resistant. In the IB model the tumor resistance becomes specialized to a single drug even if drugs oscillations do not go from zero up to ten (the maximum value). These experimental

results are illustrated in figure 4.2, which shows the tumor evolution along the monthly cure protocol. The improvement obtained with this optimal oscillating solution is definitely better than in the other two evolutionary tradeoffs but not extremely significant. The resident population mean number reduces from 2567.9 to 2460.6, i.e. obtaining more or less a 5% reduction, which is clinically significant in only one month protocol therapy and it could be probably improved over a longer care period.
So, in the concave evolutionary tradeoff case, the best treatment protocol is a dynamic one, where drug concentrations are negatively covaried over time.

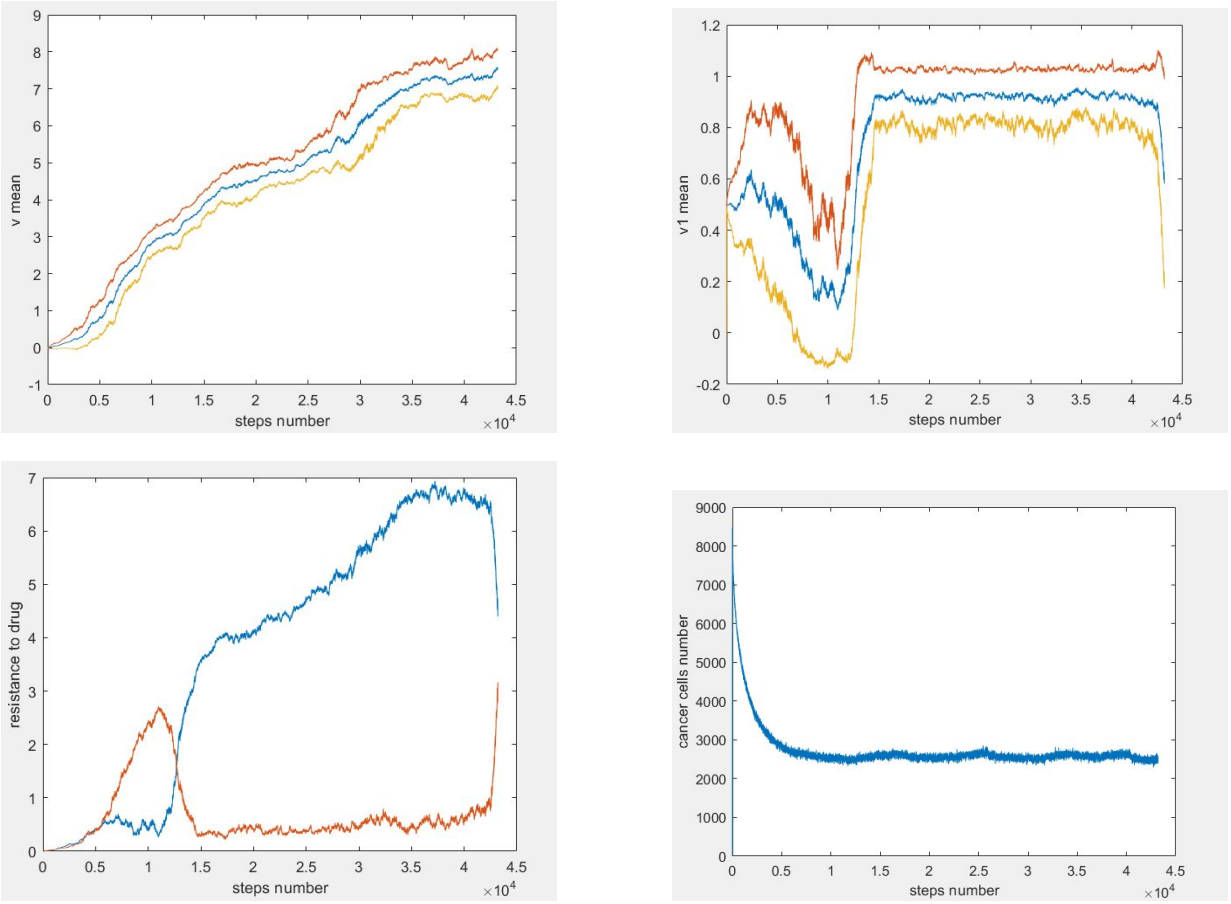

FIGURE 4.6: Cancer state profile evolution for the case of concave tradeoff. The top panels show the evolution of the mean cell's overall investment in resistance $\bar{v}$ (blue line), $\bar{v}$+standard deviation (red line) and $\bar{v}$-standard deviation (yellow line) on the right, and the cell's mean allocation of resistance to drug 1 $\bar{v_1}$ (blue line), $\bar{v_1}$+standard deviation (red line) and $\bar{v_1}$-standard deviation (yellow line) on the left. The left bottom panel shows the tumor cell's resistance to drug 1 (blue line) and drug 2 (red line). The right bottom panel show the number of cancer cell step by step. Model parameters: $m_0 = \frac{1}{10}$, $b_1 = m_1 = \frac{1}{210}$ and $\mu = 0.001$.

Moreover this advantage, exploited by the oncologist and given by the evolutionary tradeoff, can become more effective with drug interaction in comparison to the one obtained by Orlando et al. Indeed, the effect of drugs interaction is mathematically expressed as $\beta y_1 y_2$, where β determines the type and amplitude, and y_1, y_2 are the drug 1 and 2 concentration, respectively. The effect is maximum with equal concentration and minimum, i.e. null, in presence of only one drug. So the dynamic optimal protocol, where concentration varies a little around equal concentration, becomes more efficacious with drug interaction, which is almost to its maximum effectiveness. Drugs interactions appear to be prevalent in cancer chemotherapy. The problem consists on that patients usually suffer for drug interaction. Indeed, a review article reports 1/3 of chemotherapy patients suffer from drug interactions [26]. Hence, understanding the type of drug interaction [27] and discovering it before the drugs are already in use is crucial in planning optimal protocol for a patient.

4.4 Optimal protocol

In conclusion, as in the solutions obtained by Orlando et al., the phenotypic IB spatial model drives differences in the optimal treatment protocols, based on the different evolutionary tradeoffs in cancer cells allocation of resistance.
We investigate different type of control variables solutions, such as the case in which only one drug is administered during whole protocol, or in which the drugs completely alternate their presence. The local optimal solutions found with the gradient method are probably also the best solutions, but it is difficult to say with certainty in a space of fifteen dimensions. One way to overcome the problem is using a Monte Carlo method. It consists on generating a set of random initial solutions to use as starting points in the gradient method. Since with our IB models this method results too computational heavy, we investigate only some different solutions arbitrarily chosen. We have never found better solutions than the ones previously discussed. We have observed that for all three tradeoffs analyzed, the tumor has higher fitness with specialized resistance, when a single drug is administered, rather than with generalized resistance, when both drugs are administered. This phenomenon in Evolutionary Theory is called 'penalty of multitasking', since cancer cells are less fit when they try to generalize resistance to both drugs. In the concave case, however, the cancer faces an evident local 'benefit of multitasking', meaning that even though the cancer cells have higher fitness as specialist rather than generalist, when the cancer cells do generalize, they have higher fitness as balanced generalist (equal resistance to both drugs) as opposed to slightly imbalanced generalists. In Evolutionary Theory, 'benefit of multitasking' means that cancer cells have higher fitness when they generalize resistance in response to a multidrug therapy as opposed to specializing in response to a single drug therapy. So the optimal solution with concave tradeoff found with the IB model is an oscillating solution, as figure 4.5 shows, where never the delivery of one drug reaches the value ten nor drops to zero, but both drugs are always present and negatively covary during all protocol. Thus the best treatment strategy is a dynamic one, which can exploit tumor susceptibility hitting it with the drug it is more vulnerable to. When the cells develop resistance to that drug, they are hit with the other drug, which they are not evolutionarily prepared for. So the cancer adapts to the last drug and consequently is hit with the other one by the oncologist, who exploits the drug to which the cancer vulnerability is greater.

Contrary to this, both the linear and convex tradeoffs not lead to a clear local 'benefit of multitasking'. In both those tradeoffs, with the oscillating solutions found, the cancer develops more resistance with respect to the drug present in greater amount. Therefore the oncologist varies the concentration exploiting the drug to which cancer is more susceptible, but the difference with a static protocol appears not particularly

clinically significant from the point of view of the final cancer population size. So the best oncologist strategy protocol can be dynamic, where the control variables negatively covary according to figures 4.1 and 4.3, or static, where both drugs are maintained at equal concentration level.

It should be noted, however, that cancer arrives at the end of treatments with different evolutionary strategies using different protocols. Therefore from this point of view a dynamic treatment appears more effective with the aim of controlling the phenotypes. This is clearly true also for the concave tradeoff. Moreover, in the last year, optimal control framework in cancer literature is apparently changing the objective function: enforcing a static tumor volume and controlling cancer cells phenotype is likely a better objective function than reducing tumor size [2, 28]. From controlling tumor phenotype point of view, the optimal protocol is dynamic for all evolutionary tradeoffs. Indeed, as already discussed, with oscillating control variables the oncologist can induces and control cancer cells phenotype evolution [6, 29].
Analyzing instead the cancer cells number, bottom right panels in figures 4.2, 4.4 and 4.6, in case of convex tradeoff the tumor gives the impression of being adapted to the protocol and having developed a strategy that allows it to resume its growth. While, with both linear and concave tradeoffs, using a dynamic protocol, exploiting the evolutionary double bind [6], the oncologist is able to enforce a static tumor volume, especially in the concave tradeoff case [2].
In this thesis, however, we are focusing more on qualitative than quantitative result, i.e. if the optimal protocol should be static or dynamic. Each real tumor, indeed, has its own specific characteristics, while our IB model is quite generic to obtain reliable quantitative experimental results. We consider generally tumors with rapid evolution to investigate how their strategies change to adapt them to chemotherapy. The dynamic protocols appear more effective, especially in a controlling framework.

Chapter 5

Conclusion

In this thesis we develop a phenotypic individual-based model [7] to analyze cancer evolution, starting from the differential model presented in the first chapter, focusing on if and how the results change considering spatial heterogeneity and phenotypic diversity. We investigate experimental results to understand if the best oncologist protocol should be static or dynamic. It is well known that in real life tumors develop itself in heterogeneous environments and with phenotypic diversity, also in a scenario with equal drugs concentration [24]. The richness of individual cancer cells diversity and the spatial structure, given by the IB model, can not be investigated in the differential model. Those improvements brings to different, but partially in agreement, results and strategies, related to different evolutionary tradeoffs. The IB model, however, is more challenging to accommodate in an optimal control framework. If the objective function is reducing the final population size, we find that the best protocols for the oncologist are almost in agreement with the ones obtained with the differential model 1.4.2. For the concave tradeoff the optimal protocol is evidently dynamic.
In the linear and convex case, we discover optimal dynamic protocols (4.1 and 4.3), which slightly vary the drugs concentrations from equal concentration level. We note, however, that their effectiveness is practically equal to the one obtained with a static protocol. These optimal dynamic protocols may work better if the objective function switch on enforcing a static tumor volume and or controlling tumor phenotype. In the last years, cancer modeling literature is going in this direction[2, 28].
In the concave tradeoff, the optimal oncologist strategy is evidently a dynamic protocol, as founded by Orlando et. The difference lies in how the drugs amounts vary. With the IB model, to exploit optimally the evolutionary trade-off, the oncologist does not need to bring the supply of a drug up to the maximum. From the analysis, it is clear that it is sufficient to supply drugs in slightly different quantities (such as $w_1 = 6$ and so $w_2 = 10 - w_1 = 4$ for example) to induce cancer cells to specialize their resistance.

Then, the oncologist can exploit this specialization, hitting the tumor with the other drug to which tumor resistance is almost null. Moreover, a dynamic protocol, where drugs concentration varies few around equal concentration, probably becomes more efficacious with drug interaction, which is almost to its maximum effectiveness with this type of dynamic protocol.

We discover optimal dynamic protocols for the linear and convex tradeoffs, but with practically the same effectiveness of the optimal static protocols, in a framework of optimizing the final population size. These dynamic protocols become more successful if the objective function changes to enforce a static volume or to control tumor phenotype. The conclusion is that the knowledge of the cancer evolutionary tradeoff and the objective function to be optimized are crucial in planning optimal chemotherapy schedules for the patients.

5.1 Future research direction

A major challenge for the individual-based approach is the development of theoretical and empirical methods to investigate optimal control strategies in cancer chemotherapy. In this thesis we focus on qualitative results, obtained with the gradient descent method, that allow to confirm and validate our IB model with respect to the differential model. We suggest to investigate those experiments in a more realistic setting, i.e. with a longer time horizon, since a one month oncological protocol is quite short, and also with a more realistic clinical constrain, as break period without drugs during chemotherapy.
In this IB evolutionary model, the tumor spreads itself growing up in the grid, but there is no geometry in the shape of the tumor. The hypothesis is that the density with which the tumor occupies the grid reflects the actual dimensions of the tumor in a real life. To have a model that investigates tumor geometry (e.g.[30] and[31]), we propose to change the natural mortality function and use a function that increases with the number of neighbors occupied by a cancer cell.
We suggest investigation in the optimal framework using an adaptive dynamics [7]. This is an optimization scheme of genetic inspiration, not to be confused with the genetics of cancer cells, also called particle filter. The idea briefly consists on starting with a set of control signals, which are the particles, each with its own expected value of the objective function. The particles are then reproduced with probability linked to the associated value of the objective function, with mutations that randomly modify the signal. Leaving the particles evolve, the final population will be composed of signals with the best objective functions. We computationally develop this method, but it find out to be extremely heavy. The simulation could last several days, also analyzing very small signal populations.
Finally, investigating with enforcing a static tumor volume and or controlling tumor phenotype could be a better objective function following cancer modeling literature.

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