Improving cancer treatments via dynamical biophysical models

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Abstract

Despite significant advances in oncological research, cancer nowadays remains one of the main causes of mortality and morbidity worldwide. New treatment techniques, as a rule, have limited efficacy, target only a narrow range of oncological diseases, and have limited availability to the general public due their high cost. An important goal in oncology is thus the modification of the types of antitumor therapy and their combinations, that are already introduced into clinical practice, with the goal of increasing the overall treatment efficacy. One option to achieve this goal is optimization of the schedules of drugs administration or performing other medical actions. Several factors complicate such tasks: the adverse effects of treatments on healthy cell populations, which must be kept tolerable; the emergence of drug resistance due to the intrinsic plasticity of heterogeneous cancer cell populations; the interplay between different types of therapies administered simultaneously. Mathematical modeling, in which a tumor and its microenvironment are considered as a single complex system, can address this complexity and can indicate potentially effective protocols, that would require experimental verification. In this review, we consider classical methods, current trends and future prospects in the field of mathematical modeling of tumor growth and treatment. In particular, methods of treatment optimization are discussed with several examples of specific problems related to different types of treatment.

Keywords: mathematical oncology, mathematical medicine, optimization

Contents

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1. Introduction

1.1. Basic facts about cancer

Cancer may be defined as a disease able to affect any tissue in multicellular organisms, especially animals [1]. It is characterized by a loss of control of cell division, and the ability to invade adjacent and remote tissues and organs, which significantly contributes to the malignancy, i.e., to the gravity, of the disease. Another characteristic of cancer – however less obvious through a conventional static viewpoint with respect to the timescale of animal tissue growth – involves loss of control on cell differentiation (i.e., maturation in a cell lineage from a totally immature stem state to a totally differentiated, mature, state), which is a very dynamic process [2]. The more plastic (i.e., endowed with poor control on differentiations, see Section 1.2) a cancer cell population is, the more malignant is the disease.

Evidence of bone cancer, although disputable, has been found in fossil records, including that of a human ancestor as old as 1.7 million years [3], and that of a dinosaur, dated more than 75 million years ago [4]. Being quite a rare phenomenon in ancient human societies, nowadays cancer has become one of the leading causes of global mortality. The probable reasons for that are the harmful environmental and lifestyle factors, that trigger its emergence, and the increase in life expectancy, since the risk of of developing a cancer increases with age. Cancer results in approximately ten million annual deaths only by official data [5], and its incidence continues to grow, greatly stimulating theoretical and therapeutic research.

It seems that the best treatment choice, that humanity has had for centuries, has been surgical removal of cancerous tumors, and even nowadays it frequently remains a best option. However, it was already known to ancient Romans and Greeks that surgery could be successful only for superficial tumors, and that in many cases it could even worsen the patient's condition [6]. The first major breakthrough happened at the turn of the 19th and 20th centuries with the discovery of X-rays and the introduction of anticancer radiotherapy. Up to that time, little was known about the origins of cancer as well. Different researchers assigned the role of the main causes of cancer to various factors [7]. Among them were physical traumas, nowadays generally not considered as direct causes of cancer, and parasitic infections, today indeed associated with the development of certain cancer types [8], but by no means the majority. The genetic nature and progression of cancer was likely firstly recognized – at the level of chromosomes – by T. Boveri as early as 1914 [9, 10, 11], however, it took decades for this hypothesis to become widely accepted [12]. Introduction of chemotherapy into clinical use starting from 1940s was another major breakthrough in oncology. Today a much wider spectrum of treatment modalities and a constant improvement of treatment protocols result in steady increase in survival for most cancer types. However, the pace of change is rather moderate. Each of the new treatment techniques has quite limited efficacy, is aimed only at a narrow range of oncological diseases and has restricted availability to the general public due to its high cost. A prominent example is the new method from the field of immunotherapy, the authors of which were awarded the Nobel Prize in Medicine in 2018, i.e., the use of the so-called immune checkpoint inhibitors. This method leads to a long-term decrease in tumor volume – not meaning complete recovery – in only about one fifth of patients, who were previously selected as potential responders [13]. The cost of a course of such treatment can reach hundreds of thousands of dollars [14]. Surgery, radiotherapy and chemotherapy are still the most widespread modalities in cancer treatment. Nevertheless, cancer death rates remain very significant, and even in developed countries, like the United States, as many as about 30% of cancer patients ultimately die of it [15]

Cancer emerges and progresses due to irreversible mutations of the *genome* and reversible changes in the *epigenome*. The genome is the complex of genes borne by the deoxyribonucleic acid (DNA) sequence. The epigenome is the complex of the reversible specific chemical changes on these genes, like methylation or acetylation, that regulate their expression, and thus define the actual morphological and functional traits for different cells, that constitute a multicellular organism, i.e., their phenotypes (cells of different types within the same organism, like muscle, nerve, gut and skin cells, have identical genome but different epigenomes). The determination of all cell phenotypes from the genome of a given individual, ensemble of dynamic changes in the epigenomes of the cells of a same organism, is called *epigenesis* in normal animal development. In every mature animal, it is continued and dynamically achieved in each cell lineage at the level of cells, starting from stem cells, by the process of cell differentiation, which may or may not occur at cell division along a given cell lineage. For instance, in the case of hematopoiesis, it starts from multipotent hematopoietic stem cells until mature lymphocytes, mature neutrophils, mature megacaryocytes or reticulocytes, according to the hematopoietic lineages.

It is generally estimated that from this process of differentiations until complete cell maturity (i.e., terminal differentiation), a human organism is normally constituted of about 200 to 400 different cell types [16]. However, in cancer, the poor control on differentiations that is constantly observed (and, as previously stated, the more malignant the cancer, the poorer the control on differentiations) results in many more different, immature, i.e., not completely differentiated, and thus functionally unstable, in other words *plastic*, cell types. This results in highly genetically and epigenetically heterogeneous cell populations, meaning by this that tumors contain a large number of phenotypically different cell subpopulations that constitute them. The progression of a cancer disease has nothing to do with the very well determined genetic program of epigenesis that normally leads to a well-constituted multicellular organism. Instead, it is the result of the *stochastic* evolution of malignant cells under the influence of natural selection, imposed by a variety of factors, including their own genetic instability and epigenetic plasticity, nutrient availability and immune response [17]. This, in particular, means that the microenvironment of cancerous tumors plays an active role in their progression and, vice versa, is largely influenced by the activity of tumor cells. Furthermore, due to elementary intratumoral cooperation between cell subclones [18, 19, 20], cancerous tumors may be seen as coarse organs rather than mere accumulations of cells. Generally, cancer progression results in the acquisition of the following common advantageous features, or hallmarks, that virtually all malignant tumors possess, despite their diversity [21, 22].

1. *Self-sufficiency in growth signals.* Normal cells require stimulatory signals for their proliferation, that they receive when signaling molecules in extracellular space bind to specific receptors, usually located on cell membranes. Cancer cells can generate their own growth signals, thus promoting their growth by themselves. Moreover, they can enhance such signaling by overexpressing receptors of the corresponding type, thus becoming hyperresponsive to growth factors. Cancer cells can even become independent of them, e.g., by producing alternate versions of receptors, that continuously transmit the proliferation-inducing signal.
2. *Insensitivity to anti-growth signals.* Analogically, the growth of normal cells can be inhibited by other signaling molecules, located, e.g., on the surface of nearby cells (paracrine signaling), which prevents normal tissue from excessive proliferation. Cancer cells can overcome this signaling in different ways.
3. *Evading apoptosis*, i.e., programmed cell death. Normal cells can undergo a complex and highly regulated process of self-destruction in response to specific external stimuli or stress factors, like high temperature or mechanical damage. In healthy organism such process allows, in particular, to eliminate cells, infected by viruses. Apoptosis is also a master sculptor of organism shapes, since it allows creating intricate structures, like fingers, from a rough block of tissue [23]. The presence of such mechanism acts as a barrier for emergence of cancer, therefore, its cells have to develop resistance to apoptosis.
4. *Limitless replicative potential.* Normal cells, except for eggs and sperm, cannot undergo more than a certain number of divisions – for human cells this limit is around 60 (the so-called Hayflick limit). It may seem to be more than enough for a single initial cell to create a macroscopic tumor. However, in reality it is not sufficient: during the process of carcinogenesis premalignant cells do undergo apoptosis; moreover, only a fraction of cancer cells in sufficiently large tumors are exposed to sufficient nutrient levels for their proliferation and for their survival as well. Therefore, obtaining cellular immortality is a crucial process in cancer development.

5. *Sustained angiogenesis*, i.e., formation of new blood vessels, supplying tumor with nutrients. This process is triggered by nutrient deficiency and has been shown to be crucial for a tumor to grow beyond a few millimeters in diameter [24]. Interestingly, angiogenesis seems to be important for hematological malignancies as well, e.g., blood cancers, as evidenced by increase of microvessel density in the bone marrow and in the lymph nodes that accompany them [25].

6. *Invasion of nearby tissues and metastases to distant organs.* This feature allows cancer cells to move away from the main tumor mass, escaping strong competitive fight for nutritional resources. The degree of invasiveness and metastatic potential inversely correlates with the chances of survival. In the case of invasive tumors, there is no clear boundary between them and the normal surrounding tissue, which greatly complicates the treatment, in particular by surgical intervention. It is worth noting that this hallmark is a direct indicator of malignant cancer, while all the previous ones can be, to one degree or another, specific to benign tumors as well [26]. The pattern of metastatic spread of every cancer is not random – in order to create secondary tumors, the "seed", i.e., tumor cells with metastatic potential, needs a proper "soil", i.e., tissue with a favorable environment for its growth [27]. Notably, blood cancer cells can as well have inherent motility and can as well acquire the ability to metastasize during cancer progression [28].

7. *Deregulated energetic metabolism.* The main way for a normal cell to obtain energy is the respiratory oxidative phosphorylation of various nutrients, with oxygen being essential for this process. Under lack of oxygen, normal cells have to rely on less effective metabolic pathways. The main option is anaerobic glycolysis, which yields about 8 times less energy per consumed mole of glucose, than oxidative phosphorylation. However, it can happen 400 times faster, as it takes place in all the cytoplasm, whereas oxidative phosphorylation is confined to the mitochondria. The relative role of glycolysis as energy-generating metabolic pathway is significantly increased in cancer cells, this phenomenon being known as the Warburg effect. The cell-energetic theory, firstly advocated by Warburg, states that cancer is always due to a malfunction of the mitochondrion, as main provider of energy to the cell processes, or due to its impaired relations with the nucleus and with the other cytoplasmic organelles. The adverb "always" lent here to Warburg's ideas is certainly excessive, as it has been shown that in different cases cancer cells are able to make use of the mitochondrial respiratory oxidative phosphorylation mechanism [29]. However, cancer cell populations with not completely altered mitochondria seem to optimize their fitness, i.e., their proliferation rate, by relying on the glycolytic switch from oxidative to glycolytic metabolism, even under abundance of oxygen. Note that this same glycolytic switch has been observed in normal proliferating tissues [30].

8. *Evading the immune system.* The adaptive immune system can recognize and eliminate cancer cells that produce foreign proteins that are absent in a healthy body. In order for cancer to grow continuously,

its cells have to develop mechanisms of overcoming this immune capacity, namely immunosurveillance.

9. *Genome instability and mutations.* This feature is referred to as an enabling characteristic, since all cancer hallmarks are acquired through heritable genetic and epigenetic mutations. Importantly, cancer cells demonstrate very high rates of mutations in comparison with normal cells. The hypothesis of a mutator phenotype in cancer cells suggests that early steps in carcinogenesis should therefore include alterations of the enzymes that are responsible for the accuracy of DNA replication as well as for the repair of DNA damage. Such alterations can be chemically or physically favored, in particular, by carcinogens, like tobacco smoke or ultraviolet radiation [31].

10. *Tumor-promoting inflammation.* Inflammation is a complex protective response of the innate immune system to harmful stimuli, aimed at their elimination and tissue repair. Somewhat paradoxically, it has stimulating effects on cancer progression. In particular, inflammation can support tumors with growth factors, survival factors, proangiogenic factors and extracellular matrix-modifying enzymes that facilitate angiogenesis, invasion, and metastasis. Moreover, chronic inflammation by itself increases the risk of developing certain types of cancer [32]. One prominent example is stomach cancer, the most common cause of which is infection by the bacterium *Helicobacter pylori*.

The specific alterations in cell genome and epigenome, that result in the manifestation of these hallmarks, are diverse, however certain patterns of mutation are prevalent for all types of cancer indifferently, and some are manifested for different types of cancer. For example, more than half of human cancers have in the genome of their cells a mutation in the gene TP53, called the “guardian of the genome”. This gene codes for DNA repair enzyme and it can also initiate apoptosis in case of irreparable damage [33]. One major approach in cancer treatment is targeted therapy, various types of which are aimed at interfering with specific molecules, aiming at thwarting their ability to promote cancer growth. Design of targeted drugs requires expensive research i.e., with a high attrition rate due to insufficiently known mechanisms of cancer progression, often explored blindfold with lots of candidate drugs and “druggable targets”, which most of the time does not end with a successful result. Nevertheless, drugs of this type have in particular revolutionized treatment of two forms of leukemia: chronic myelogenous leukemia and acute promyelocytic leukemia, drastically improving their survival rates. This was possible due to precisely known molecular events, leading to these diseases, that in both cases are aberrant chromosome translocations [34]. However, in the majority of cases, the treatment efficacy is much more modest, giving rise to treatment escape due to drug resistance by adaptation of cancer cell populations to drug insults. Classical types of anticancer treatment – radiotherapy and cytotoxic chemotherapy – act in a much rougher way, interfering with the process of cell division and leading to cell death. Their major disadvantage is that their action is not selective, therefore, they can have significant side effects associated with serious damage to normal cells. Moreover, they induce resistance in cancer cells, and these are the points to have in mind when attempting to optimize treatments of cancer.

1.2. Debates about the origin of cancer

The widely recognized list of cancer hallmarks does not, however, shed light on the question of how carcinogenesis is initiated in the first place. This problem has given rise to less consensus nowadays, and different theories exist. The somatic mutation theory (SMT) is the presently dominating theory among oncologists [11, 35]. It states that the only source of neoplasm is a sufficiently mutated ancestor cell, with its accumulated mutations allowing it to divide uncontrollably. This theory considers quiescence, i.e., absence of proliferation, as the default state of cells in multicellular organisms. The tissue organization field theory (TOFT) is a newer, less widely accepted, theory, that states that cancer is a tissue disorder. In TOFT proliferation is considered as the default condition for all cells, while their quiescence in multicellular organisms is achieved by interactions between tissue elements [36]. Cancer, therefore, cannot arise simply from a multitude of mutations in one cell, it requires a coordinated interaction of all tissue elements, including its stroma, i.e., the supportive framework, that does not perform specific functions of the organ. Nevertheless, this theory tells little about how such tissue disorganization occurs.

The atavistic theory of cancer is an even deeper and less widely accepted theory, yet quite intelligible from an evolutionary viewpoint [37, 38]. It has been supported by indirect arguments so far [39, 40, 41, 42, 43]. It states that cancer is a condition in which a local coherent part of the body switches back to a more primitive regime, which prevailed at some initial stage of evolution of multicellular organisms. Such regime, that is normally – but only transiently – present today in early animal development, is characterized by transient relaxation of control on differentiations, that themselves are always achieved through epigenetic modifications. According to the atavistic theory, the mechanisms enabling such transient behavior were elaborated during the course of billions of years of evolution to face fast adaptation hostile and frequently changing conditions of life on Earth. They are still stored in the genome of cells of multicellular organisms, nevertheless being normally silenced in the terminally differentiated cells of healthy individuals. Cancer cells have followed according to this theory a reverse evolution towards a less differentiated, less stable but more adaptable status in the course of a de-coherence process of the host organism. They are thus able to shift dynamically between differentiated and undifferentiated states, this feature being usually referred to as plasticity, which, as previously mentioned, promotes adaptability of cancer cells and intra-tumor heterogeneity. To consistently explain such de-coherence, one may advance that cancer cells, have forsaken the stability controls on differentiation that make a functionally and anatomically cohesive multicellular organism. Newly endowed with functional plasticity, they are able to hijack ancient adaptation mechanisms reactivated in this process of de-coherence. The atavistic theory of cancer is supported by a growing body of biological observations [44]. Relying on theoretical considerations, suggested by philosophers of science [2, 45, 46], it has recently been proposed that plasticity in cancer arises due to an anatomically localized loss of control of cell differentiation. This should result from impairments of mechanisms of maintenance of tissue cohesion and functional coherence, that themselves rely on intercellular signaling pathways and can be regarded as part of the immune system [47, 48]. Moreover, maintenance of a differentiated cell status – at the level of a growing cell population, when differentiation occurs at asymmetrical mitoses – requires much energy for the activity of epigenetic enzymes. Therefore, at lowered energy levels in the cells, differentiation cannot be successfully maintained [49], so that de-differentiation can emerge due to mitochondria malfunction (following Warburg's hypothesis) or to mere oxygen and nutrient deficiency, which are always manifested in the cores of sufficiently large tumors [49]. In this sense, cancer is essentially "a deunification of the individual" [45], that induces local reverse evolution towards an ancient regime of functioning as a simple cell colony. It may happen due to gene mutations or to alterations of the mitochondria, resulting in deregulation of epigenetic enzymes [50], to malfunction of intercellular gap junctions. Or else, again in the perspective of a lowered cell energy status, it might be due to mitochondrion impairment [51]. It might also be due to tissue environmental perturbations of chemical or physical nature, resulting in annihilation of the hypothesized "unifying" intercellular signaling pathways. One may see that the atavistic theory can thus be compatible with both SMT and TOFT.

Plasticity in cancer (reviewed in [52]) does not necessarily require the participation of so-called cancer stem cells, i.e., cancer cells, for which the loss of control on differentiation is altered from the very beginning of the maturation lineage [53], and which possess an infinite capacity of self-renewal, i.e., cell division with (at least one of the) daughter cells identical to the mother cell. Plasticity only implies deregulated mechanisms of the control of cell differentiation processes, possibly resulting in particular cases in cell fates characterized by partial de-differentiation or transdifferentiation (the latter term being defined as direct reprogramming from a somatic cell lineage to another one [54]). Plasticity may also manifest itself by stochastic adaptation from an undetermined or partly determined cell status, which is different from determined reprogramming. In the metaphoric Waddington epigenetic landscape, this can be illustrated by local reversal of the flow direction in a differentiation valley (de-differentiation), or hopping over an epigenetic barrier from a differentiation valley onto another one nearby (transdifferentiation).

1.3. The role of mathematical modeling

Mathematical modeling in oncology can be considered as a rather old area of research. The first article, in which the equation for the growth of solid tumors was formulated on the basis of general reasoning and applied to experimental data, appeared as early as 1932 [55]. In recent decades, this area actively developed due to the increased availability of computing power and to the essential progress in the understanding of cancer biology. As shown in Fig. 1, in recent years the annual number of relevant articles, published only in journals indexed in the Web of Science Core Collection, has exceeded five hundred. Moreover, while in the last century such articles were published only in specialized journals as well as journals focused on exact sciences, in the present century, studies using mathematical models began to appear in leading biological and oncological journals. The relative number of such studies among oncological studies remains modest, but their importance is increasingly emphasized by researchers of various profiles [56, 57, 58, 59].

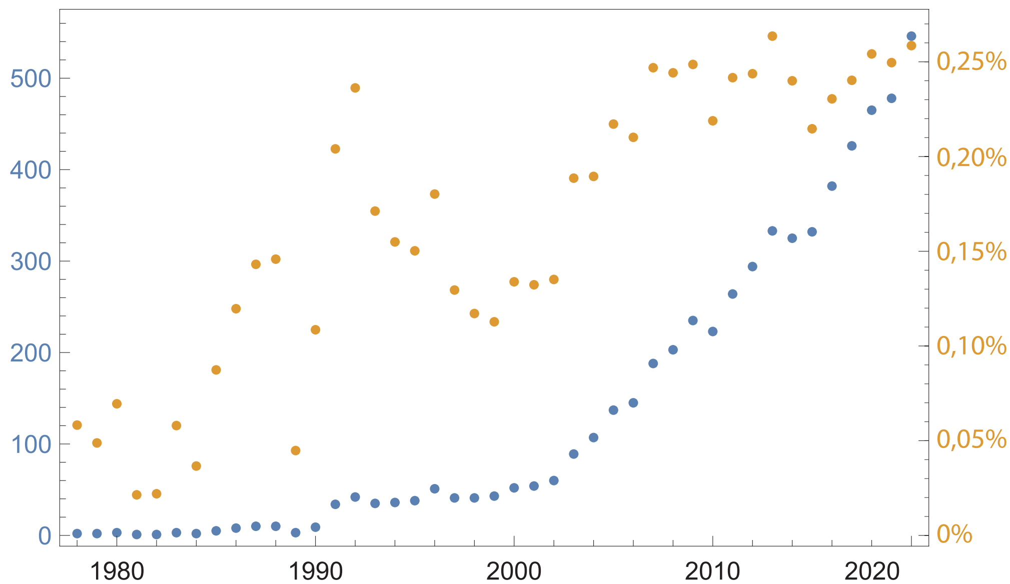

Figure 1: The number of articles on the topic of mathematical modeling in oncology (blue dots) and their fraction in the total number of articles on the topic of oncological diseases (orange dots) by years, according to the bibliographic database Web of Science Core Collection. The search was carried out using the terms ("cancer" or "tumor") and ("mathematical model" or "mathematical modeling"). The total number of articles is estimated by searching for the term "cancer".

It should be emphasized that all mathematical models are reductionist, and the more variables are considered, the more parameters their calibration demands, and the more difficult it is to perform mathematical analyses on them. On one extreme end are systems biology models, aiming at an exhaustive description of the biological phenomena under study, with often monstrous systems of coupled cell populations and connecting signals between them. Moreover, their calibration is necessarily incomplete and relies on Bayesian techniques or artificial intelligence methods. On the other end are simple deterministic models, theoretically identifiable provided that they are well designed, amenable to a mathematical analysis of their behavior (sometimes even leading to theorems), and to a deterministic analysis of their control (optimization and optimal control).

There is a large variety of mathematical models used in cancer modelling listed here only briefly and considered in more detail in the following sections:

1. Simple growth models describing the behavior of one cell population.
2. Compartmental models, that assume coupling between cell populations, each of which is biologically homogeneous and described by a simple law, that can consist of a probabilistic process or an ordinary differential equation (ODE). Communications between populations are ensured by binary, probabilistic

or deterministic ODE representations.

3. Partial differential equations (PDEs) that represent, firstly within one cell population, its between-cell biological variability, i.e., heterogeneity, by continuous, so-called structuring, variables present in each cell: space, age, size, functional phenotype.
4. Mixed PDE models, such as structured in space and phenotype, the structuring variables being chosen as relevant to a given problem under study.
5. Agent-based models, that are based on probabilistic or deterministic rules for their evolution, the agents being here cells that can include any type of spatial, phenotypic, age-related and other variables. If they are well designed, then by averaging their trajectories, or by passages to the limit (for the number of cells $N \to \infty$ and for the size of cells $\varepsilon \to 0$), they lead to continuous models. However, without such probabilistic or continuous limit analyses, they can provide only computer simulations.
6. Any kind of mixed models between these types, e.g., agent-based models for cell populations connected by signaling molecules, the behavior of which is described by spatially structured PDEs in a given intercellular medium.

Let us note that optimization and optimal control methods can be applied to deterministic, both ODE and PDE models, having in mind that therapeutic optimization may resort to these methods. In the same way, game theoretical methods can be used to study best strategies for cell populations. "Best" meaning here either for therapists who try to eradicate or contain them, or for plastic cancer cell populations that aim at thriving or at least surviving.

The relevance of the model mainly depends on the biological question at stake, and secondarily only (as qualitative results are at least as important as quantitative ones to guide therapeutic choices) on the amount of data available to calibrate the parameters of the model. It is impossible to describe all types of biological questions here. Nevertheless, a short list of such questions related to cancer cell populations and anticancer therapeutic optimization, possibly determining the choice of methods to be used, could be:

- taking into account toxic side effects as limiting constraints in chemotherapies;
- modeling chronotherapy of cancer and the cell division cycle;
- taking into account drug-induced drug resistance (e.g., by adaptive dynamics models);
- modeling dormancy of cancer cell populations;
- taking into account immunoediting in immune checkpoint inhibitor therapies;
- modeling drug and nutrient diffusion in tumor spheroids;
- combating epithelial to mesenchymal transition (EMT), that is at the origin of metastases;

- modeling bet hedging in cancer cell populations as a fail-safe strategy to escape drug insults.

Mathematical modeling in oncology has great potential. Firstly, at present, in many areas of experimental research on oncological diseases, an enormous amount of experimental data has been accumulated that require systematic analysis [60, 61, 62, 63]. Secondly, the study of mathematical models of growth and therapy of malignant tumors helps to reveal non-obvious or non-intuitive aspects and allows putting forward new hypotheses [64, 65, 66, 67, 68]. Thirdly, the study of such models can help to suggest optimization of anticancer therapies, already introduced into clinical practice [69, 70, 71, 72, 73]. Importantly, the overall efficacy of a treatment can be largely influenced by the specific schedule of drugs administration. There are several reasons for that, including the complexity of the effect of drugs on the tumor and its microenvironment, the treatment-induced alterations in drug delivery and the ambiguous interplay between the actions of different drugs. Formally, the search for optimal clinical protocols requires a large number of trials, that use different protocols for each set of investigated therapies and for each type of cancer. This task cannot be performed physically, moreover, it is associated with ethical difficulties, since the result of alterations of clinical protocols may well reduce the overall treatment efficacy.

One must admit that thus far, compared with traditional, widely empirical methods of cancer research, methods based on mathematical modeling of tumor growth and therapy have not led to significant success in clinical oncology. There are many reasons for this, including difficulties in finding a common language between mathematicians and medical workers and reconciling the rigor of mathematical models with the level of uncertainty prevailing in clinical sciences [74]. However, mathematical modeling has already led to several predictions, validated using retrospective data [67, 75, 76], preclinical successes [73, 77, 78] as well as initiated clinical trials [70, 71, 79, 80].

2. Approaches to modeling tumor growth and dynamics

2.1. Biological background

All cancers, except blood cancers, form solid tumors, which begin their growth as avascular masses. Modeling the avascular stage of tumor growth has been covered widely in literature – see, e.g., [81, 82, 83] for review. Here we recall the main facts about it, and on its example we discuss the main approaches, existing in oncological modeling.

The first four hallmarks of cancer, described in Section 1.1, can be combined into one concept, namely that malignant cells can divide indefinitely under favorable conditions, in particular, under sufficient provision of nutrients. This concept is clearly confirmed in *in vitro* experiments with multicellular tumor spheroids (MTS), i.e., three-dimensional aggregates of malignant cells, in a nutrient-rich medium. In such studies it has been repeatedly shown that after a short initial phase of exponential growth the MTS radius increases approximately linearly with time. At this stage the spheroid acquires a characteristic layered structure, consisting of a central necrotic core and an outer layer of living cells, the thickness of which remains constant over time [84, 85]. The living layer of the spheroid consists not only of proliferating cells – a significant part of it consists of quiescent cells, i.e., cells that do not move along the cell cycle. The thickness of this layer is determined by the diffusion of nutrients from the solution surrounding the MTS. With an increase in the concentration of metabolites in the surrounding medium, the rate of MTS growth increases proportionally. The maximum volume of MTS is limited due to several effects including the outflow of necrotic material through the surface of the spheroid, the shedding of cells from its surface into the surrounding solution [86], and the stress-induced growth inhibition [87].

The structure of a solid tumor, growing in a tissue, can either correspond to the structure of the MTS, or differ significantly from it. In general, the compact type of growth, with tumor structure similar to that of MTS, is intrinsic to benign and low-stage malignant tumors, and the invasive type of growth, marked by infiltration in the surrounding tissue, plays an increasingly important role with tumor progression (see Fig. 2). It is worth noting that benign tumors, growing compactly, can reach enormous sizes – namely, tens of centimeters in diameter with a mass of several kilograms [88]. However, such pattern of tumor development is an exception.

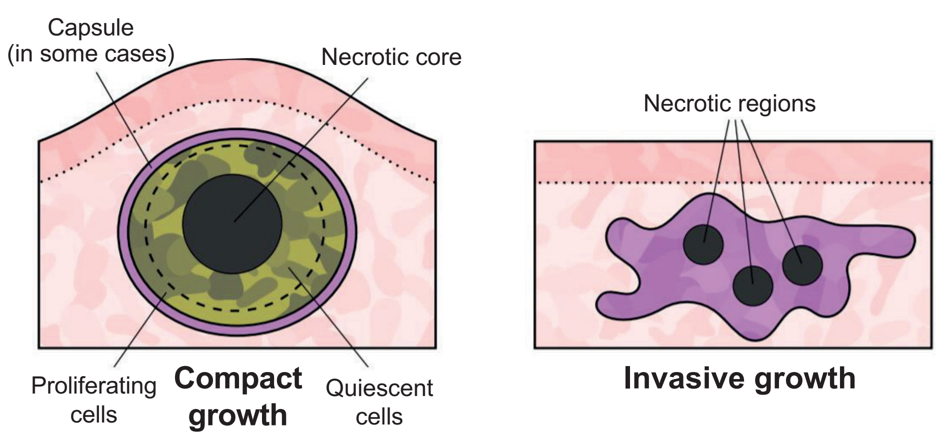

Figure 2: Types of growth of solid tumors.

Tumor growth can be mathematically reproduced with models of different types and complexity. Developing more and more detailed models can be a tempting activity, however, it is usually associated with certain difficulties. First of all, as it has been already stated above, models of increasing complexity are associated with the problem of incomplete calibration. Another problem is that the quantitative agreement of predictions of biological models with experiments cannot be as accurate as in exact sciences, for example, physics. The reasons for this include the heterogeneity of biological objects, their variability and significant sensitivity to external factors.

The work [86] by Casciari, Sotirchos and Sutherland provides a wonderful example of a carefully parametrized model of MTS growth. It takes into account tumor cells, oxygen, glucose, carbon dioxide and five ions, interacting via the glycolysis process and the Krebs cycle. The parameters of this model were obtained by fitting experimental data on the consumption of substances by tumor cells in a monolayer at varying concentrations of these substances and at varying pH. Despite so many factors taken into account, the quantitative predictions of the model had rather moderate precision due to the above-discussed objective limitations. For example, the predicted levels of oxygen and glucose consumption in a spheroid with a diameter of 1 mm exceed the corresponding experimental averages by $\approx 25-35\%$. In this work one qualitative result was also obtained, which was subsequently confirmed experimentally – that the acidity in the center of the tumor should be significantly higher than at its border. A similar result was obtained later by Gatenby and Gawlinski with the use of a simpler model [89], which consists of three equations for cancer cells, normal cells and hydrogen ions. The latter model also allows for the prediction of the existence of a hypocellular (i.e., containing very few cells) gap at the tumor-normal tissue interface. The proposed qualitative mechanism was later confirmed [67], while previously it was believed that this phenomenon was caused by a combination of a large number of factors.

2.2. Simple ODE models of tumor growth

In the simplest case, modeling tumor growth via ODEs includes one equation for the dependence of tumor volume on time, the trajectory of it being a growth curve. The typical growth curve of MTS and compact tumor is an sigmiod curve with three phases: an initial exponential phase, a phase of approximately linear growth, and a phase of growth saturation, at which the tumor growth curve tends to reach a plateau [90]. It should be noted that in practice the plateau may turn out to be unattainable, since the carrier of the tumor (in general a laboratory rodent) may die long before the tumor volume approaches it.

A famous example of a function, which exhibits such qualitative behavior, is the logistic curve. It is governed by the following equation, used in a huge number of various biological studies:

$$V'(t) = B \cdot V(t)[1 - \frac{V(t)}{K}], \tag{2.1}$$

where $V(t)$ is the time-dependent tumor volume, B is the maximum rate of cell proliferation, K is maximum tumor volume often referred to as its carrying capacity. Its solution is:

$$V(t) = \frac{K \cdot V_0 e^{Bt}}{V_0[e^{Bt} - 1] + K}, \tag{2.2}$$

where $V(0) = V_0$ is the tumor volume at the beginning of measurements. Another famous example of an sigmoid function, also used for various biological tasks, is the function produced by the Gompertz model. It assumes that the growth rate, initially equal to B_0, by itself drops exponentially with time:

$$\begin{cases} V'(t) = B(t) \cdot V(t), \\ B'(t) = -\gamma \cdot B(t). \end{cases} \tag{2.3}$$

Its solution is:

$$V(t) = V_0 e^{\frac{B_0}{\gamma}[1-e^{-\gamma t}]}, \tag{2.4}$$

it tends to $V_\infty = V_0 e^{B_0/\gamma}$ as $t \to \infty$. From this explicit solution, a straightforward calculation shows that a convenient one-dimensional form of the Gompertz model is also

$$V'(t) = -rV(t) \ln\left(\frac{V(t)}{K}\right), \tag{2.5}$$

where $K = V_\infty$ is the carrying capacity of the tumor.

Another, less popular example, is given by the Bertalanffy equation:

$$V'(t) = B \cdot V(t)^{2/3} - M \cdot V(t), \tag{2.6}$$

the analytical solution of which, expressed through $V(0) = V_0$, is rather cumbersome. Bertalanffy's equation can be derived under two assumptions. Firstly, since the proliferation rate of tumor cells is restricted by diffusion of nutrients across its surface, then it should be approximately proportional to the tumor surface area. Secondly, the rate of tumor volume loss due to cell death should be proportional to the tumor volume. Of note, an initial exponential stage of growth is neglected in this equation.

Examples of the given growth curves are shown in Fig. 3. In order to fit experimental data to each of the three sigmoid functions, one needs to identify the initial tumor volume and two more parameters, which are therefore varied in practice in order to achieve the best fit. In the case of the Gompertz model in its 1-dimensional form, for instance, these are V_0, r and the carrying capacity K. The Gompertz model is very popular among radiologists and in general is probably the most commonly used model among experimentalists. However, in different works, where these models are compared with each other on certain experimental samples, different opinions are expressed about which of the models is the most acceptable in different cases [91, 92].

On testing pharmacotherapies, these models are most of the time completed on the right-hand side of the equation with an added death term of the form $-c_1(t)V(t)$, where the function c_1 represents the effects of a drug at the tumor site, at least when it is *cytotoxic*, i.e., directly killing tumor cells. However, it can also be possible to influence a natural proliferation rate $B(V,t)$, e.g., linked to the velocity of the cell division cycle, that can be slowed down by *cytostatic* drugs such as antagonists of growth factor receptors (e.g., tyrosine

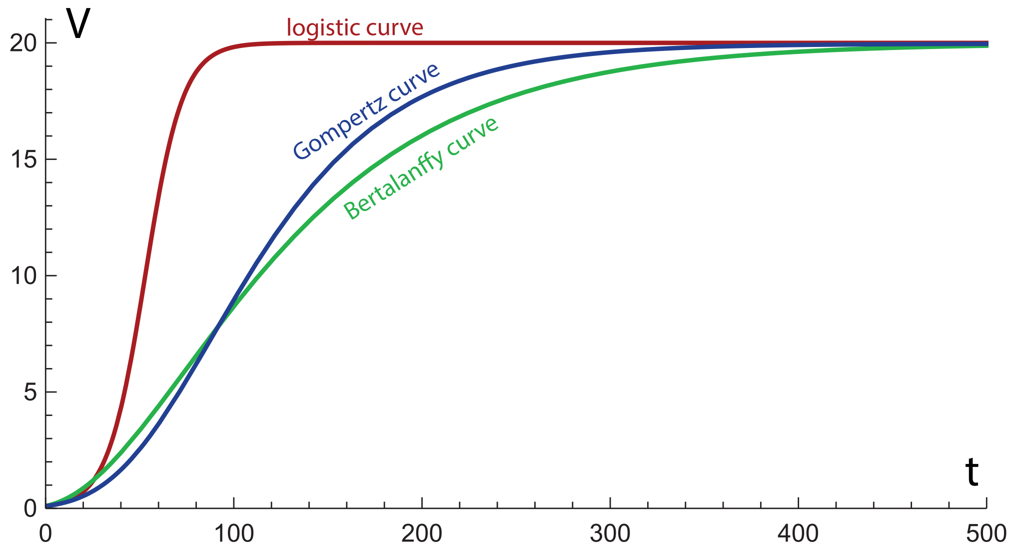

Figure 3: Time dependencies of tumor volume at cell proliferation rate $B = 0.1$ and initial volume $V_0 = 0.1$, governed by the following models: red line – logistic equation (2.1) at $K = 20$; blue line – Gompertz model (2.3) at $\gamma = 0.01887$; green line – Bertalanffy equation (2.6) at $M = 0.03685$.

kinase inhibitors) without killing the cells. In case of an association of a cytotoxic drug c_1 with a cytostatic one c_2, one can propose a basic equation of the form

$$V'(t) = \left(\frac{B(V,t)}{1 + c_2(t)} - c_1(t) \right) V(t), \tag{2.7}$$

thus allowing a two-handle control of tumor growth, which is indeed a most frequent case in the clinical treatment of cancers. This point will be more developed later in Sections 2.3.3 and 4.4.

Of note, especially when dealing with optimization of therapeutics under constraints linked to unwanted side effects on healthy cell populations, it may be natural to simultaneously study the growth of a tumor and, in parallel, the (homeostatic) growth of healthy cells. This is certainly a situation that arises very naturally in oncology, when tumor and healthy tissue are simultaneously exposed to the influence of the same treatment in a whole-body perspective. This has been in particular studied to control hematotoxicity of a temozolomide treatment in children [93] and of an etoposide treatment in adults [94]. As such models are supposed to be used for quantitative prediction and control in the effective treatment of cancers, they very often combine the representation of the action of drugs at the tumor and at the healthy cell population sites. This includes what the drug does to the body, namely its pharmacodynamics (PD), and the representation of the drug fate from its infusion or ingestion until the – wanted or unwanted – target cell population site. It also includes what the body does to the drug, namely its pharmacokinetics (PK), resulting in so-called

PK-PD models [95].

The ODE models that have been briefly mentioned above are adjustable on growth curves, and are aimed at a macroscopic, phenomenological description of the growth picture itself [96, 97]. They do not explicitly take into account the structure of the tumor nor the main processes that determine the rate of its growth. These issues can be overcome in structured models taking into account the heterogeneity of the cells that constitute it. When something is known about the geometry of the tumor (e.g., if it is a spheroid), spatially-distributed models are certainly relevant to describe its heterogeneity. However, the relevant heterogeneity to be represented depends on the therapeutic question at stake, and space is not always relevant to describe it. The distribution of the cells by ages, i.e., phases of the cell-division cycle, or by individual internal traits (evolutionary phenotypes) describing drug-induced resistance, or more generally cancer cell plasticity, i.e., adaptability to changing tumor microenvironments (due to drugs or other modifications), may be much more relevant than space. Such structured models will be presented in the next section.

2.3. PDE models of tumor growth structured by space, age, or phenotypical internal variables

2.3.1. Spatial models

There are three main types of cell motion, which are described in different ways in mathematical models: random active movement due to the intrinsic cell motility; chemotactic/haptotactic movement, i.e., active movement along the gradient of concentration of a substance; and passive convective motion caused by dynamics of different phases of tissue. The latter type of movement, in particular, leads to an effect of repulsion of the surrounding tissue elements by dividing tumor cells and subsequently to increase in volume of a compactly growing tumor.

The models expressed in PDE settings, usually consider variables of tumor cells and other tissue elements, which may be normal cells, interstitial fluid, less often also the extracellular matrix. The key equations for their dynamics most often represent a special case of the system of equations of the following form:

$$\frac{\partial n_i}{\partial t} = \nabla \cdot (D_i \nabla n_i) + \nabla \cdot (\gamma_i \nabla \chi) - \nabla \cdot (\mathbf{I_i} n_i) + F_i(\mathbf{n}, \mathbf{C}), \tag{2.8}$$

where $\mathbf{n}$ is a vector of tissue elements n_i and $\mathbf{C}$ is a vector of the concentrations of substances, including nutrients. The convective speeds of tissue elements are $\mathbf{I_i}$, D_i are their intrinsic motilities, F_i are sums of their birth, transition (e.g., into dead tissue) and destruction rates, that depend on the densities of other tissue elements and on the concentrations of substances. Finally, χ is the concentration of a specific substance, i.e., chemoattractant, along the gradient of which tumor cells move with characteristic motility γ_i. The motilities of cells can be either constant or dependent on other variables, in this case $D_i = D_i(\mathbf{n}, \mathbf{C})$, $\gamma_i = \gamma_i(\mathbf{n}, \mathbf{C})$.

The distribution of substances is most often modeled by reaction-diffusion equations of the general form

$$\frac{\partial C_j}{\partial t} = D_j \Delta C_j + F_j(\mathbf{n}, \mathbf{C}), \tag{2.9}$$

where F_j is the sum of local production and consumption of a substance, rarely also of the rates of its chemical transitions, and D_j is its diffusivity. More complex situations, e.g., accounting for charged particles, can also include the terms for directed movement, caused in this example by an electric field [86]. Most models consider one generic nutrient, which concentration determines the rates of proliferation and death of tumor cells.

It should be noted that most frequently only one type of motion of tumor cells is considered in the corresponding models. Simultaneous consideration of different types of motion can be used for specific tasks. The examples are the simulation of solid tumor progression towards an increasingly invasive phenotype [98] and the investigation of the effect of internalization of less motile cells into the tumor spheroid [99].

The growth of an invasive tumor is sometimes approximated by a single reaction-diffusion equation. The representation of the local proliferation rate of tumor cells in it is usually restricted to a simple logistic term, which naturally leads to its decrease within the tumor core even without consideration of nutrient deficiency. In the case of constant intrinsic motility of tumor cells, D, the corresponding model takes the form of the celebrated KPP-Fisher equation:

$$\frac{\partial n}{\partial t} = D \Delta n + Bn(1 - n), \tag{2.10}$$

where n is the local density of tumor cells, B is their maximum proliferation rate. There is an important result for this equation in case where its initial condition $n(x, 0)$ has a compact support, i.e., the region where it is not equal to zero is finite, which is suitable for description of initially localized group of malignant cells. In this case initial condition evolves to a traveling wavefront solution with the speed $2\sqrt{BD}$ [100]. Models based on this equation are often used for the description of the dynamics of glioblastoma, the most common and most aggressive type of brain tumor. Such models can be based on patient-specific parameters, assessed using medical imaging procedures [69]. They can simulate the response of brain tumors to different treatments, which was performed in the works of Kristin Swanson and her colleagues [101, 102].

Reaction-diffusion models are also convenient for the consideration of problems in which the decisive role is played not by the rate of tumor growth and the effect of external influences on it, but by various aspects of the interaction of tumor with its microenvironment [89, 103]. Such models are usually more easily tractable analytically and numerically than reaction-advection models described further.

The growth of a compact tumor can be modeled via consideration of passive convective (advective) motion only:

$$\frac{\partial n_i}{\partial t} = -\nabla \cdot (\mathbf{I_i} n_i) + F_i(\mathbf{n}, \mathbf{C}), \tag{2.11}$$

Frequently, the convective velocity of all tissue phases is considered the same, which, in particular, is justified when only tumor and normal cells are taken into account. In this case velocity $\mathbf{I}$ can be determined from the equations of motion, such as Darcy equations for a porous medium,

$$\mathbf{I} = -\frac{K}{\mu}\nabla p, \tag{2.12}$$

where p is pressure, K is permeability and μ viscosity. Other options are Navier-Stokes equations and more complex equations of motion taking into account non-Newtonian properties of the medium. Equations (2.11), (2.12) should be completed by an equation on the state. In the case of a compressible medium, the pressure can be considered as a given function of the total cell concentration n, $p = p(n)$. The function $p(n)$ equals zero for sufficiently small n, i.e., $n \leq n_0$, such that cells must be distant enough from each other. For sufficiently large total cell density, $p(n)$ is an increasing positive function approaching the incompressibility limit for large n. For intermediate values of total cell density, $p(n)$ may be set negative, reflecting attractive forces between cells due to intercellular adhesion. For the incompressible medium, for which $\sum n_i$ is constant, taking a sum of equations (2.11), we obtain the equation

$$\nabla \cdot \mathbf{I} = \sum F_i(\mathbf{n}, \mathbf{C}), \tag{2.13}$$

closing the problem. Let us note that velocity $\mathbf{I}$ can be excluded from equations (2.12), (2.13) giving the Poisson equation for the pressure. One of the earliest models of this kind is Harvey Greenspan's 1976 model [104], whose approach was developed in the 90s by Helen Byrne and Mark Chaplain [105], followed by other publications. In such models, the supply of nutrients from an outer region of the tumor and their consumption within it result in a fast switch from the initial exponential growth to a linear increase in tumor radius accompanied by layered tumor structure [106]. Modeling growth saturation demands consideration of additional processes governing the removal of dead cells, which would make up for the ongoing proliferation of cells in the outer layer, subject to high nutrient availability. An example of the model accounting for growth saturation is the following, which is a simplified form of a system presented in [107]:

$$\frac{\partial n}{\partial t} = Bn \cdot \Theta(g - g_t) \cdot \Theta(s - s_{cr}) - Mn \cdot \Theta(g_d - g) - \frac{1}{r^2} \frac{\partial(\mathbf{I} n r^2)}{\partial r};$$

$$\frac{\partial h}{\partial t} = -\frac{1}{r^2} \frac{\partial(\mathbf{I} h r^2)}{\partial r};$$

$$\begin{aligned} \frac{\partial g}{\partial t} &= Ph[1 - g] + \frac{D_g}{r^2} \frac{\partial^2 (g r^2)}{\partial r^2} - Q_p n \cdot \Theta(g - g_t) \cdot \Theta(s - s_{cr}) \\ &\quad - Q_q n[\Theta(g_t - g) \cdot \Theta(s_{cr} - s) + \Theta(s - s_{cr})] \cdot \Theta(g - g_d); \end{aligned} \tag{2.14}$$

$$\mathbf{I} = A\frac{\partial s}{\partial r}, \quad \textit{where } s = 1 - (h + n), \; A = \frac{P_{cr}}{\mu[s_0 - s_{cr}]}.$$

Here $n,\ h,\ s$ are volumetric fractions of tumor cells, normal tissue and extracellular space; g is the concentration of glucose, chosen as the key nutrient, the symbol Θ represents Heaviside functions. Tumor cells proliferate under sufficiently high levels of glucose $g > g_t$, and sufficiently high fraction of extracellular space $s > s_{cr}$. The latter, according to what was discussed above, corresponds to sufficiently low solid pressure. When sufficiently high pressure levels are reached, as well as below insufficient levels of glucose, tumor cells stop proliferating, and below even lower glucose levels, $g < g_d$, they die and merely disappear for simplicity. Glucose inflows from normal tissue, diffuses and is consumed by tumor cells, as proliferating cells consume it faster. The convective velocity $\mathbf{I}$ is assumed to be proportional to the negative value of the pressure gradient, which in its turn is linearly proportional to the local concentration of cells. That leads to the displayed relation between convective velocity and gradient of extracellular space fraction. Spherically-symmetrical geometry is considered, all parameters are positive.

Figure 4 provides an example of the distribution of variables in this model where tumor growth is halted. In this state, the total rate of death of tumor cells, which occurs in a sphere of radius about 2.1 mm, where $g < g_d$, is equal to the total rate of tumor cell proliferation, which happens in a small spherical layer situated $\approx 2.65 - 2.8$ mm from the tumor center, where $g > g_t,\ n > 0$. The convective velocity, which is proportional to the negative gradient of cell density, is negative throughout the tumor and equals zero at the tumor center and at its surface, where the fraction of extracellular space is equal to its value for normal tissue s_0. Such velocity distribution means that new tumor cells, which appear at the outer tumor rim, move towards the necrotic core, where they disappear.

Radial symmetry is a frequent assumption in spatially-distributed continuous models of tumor growth, which allows ignoring spatially heterogeneous effects other than radially oriented proliferative heterogeneity. However, the absence of radial symmetry may significantly influence tumor growth in reaction-advection models, i.e., result in corrugation of the surface of a spheroid and its disintegration [104]. Importantly, the approach to account for the solid pressure, described above, treats tumor as a fluid-like substance, which is,

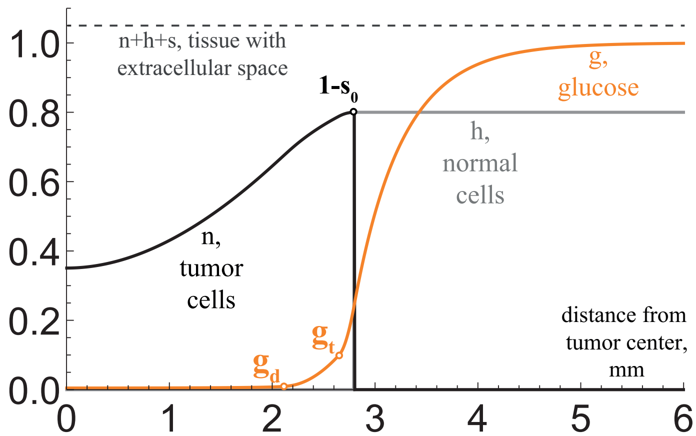

Figure 4: Distribution of variables in the system governed by Eqs. (2.14) when the tumor has achieved stationary state. Solid black line denotes the density of tumor cells n, solid gray line – the density of normal cells h, dashed gray line – the total tissue density, normalized to unity, orange line – glucose level in tissue. Next, s_0 is the fraction of extracellular space for normal tissue, g_t is the level of glucose below which cells tumor cells don't divide, g_d is the level of glucose below which they die.

certainly, a strong simplification. In particular, is does not allow reproducing the fact that the normal tissue surrounding tumor stretches during its growth exerting additional pressure on the tumor. More complex approaches exist adapted from the area of solid mechanics, which are able to reproduce this effect [108, 109]. It should be noted, however, that living tissues, especially the ones susceptible to significant deformations, as in the case of tumor growth, are very different from non-living solids. Therefore, the constitutive assumptions about tissue mechanics always have a non-obvious degree of correspondence with the growth of real tumors. At that, their choice may play a crucial role in the outcome of the study [110] and may even yield non-physical behavior under fairly adequate assumptions [111].

2.3.2. Age-structured models

A lot of models of cancer and of its therapies take into account the age structure of the cell division cycle, that is the basis of all cell proliferation: when one mother cell divides into two daughter cells. This is all the more true as physiological inputs, such as (hormonal and nervous) messages from the circadian central clock, and anticancer drugs, some of which are specific of one cycle phase or of transitions between phases, influence the course of this cell division cycle. A detailed example of such a model, up to drug delivery optimization, will be given in Section 4.3. Age-structured models are concerned with describing the cell cycle as divided into phases, in each of which the structure variable, physiological age x (one age for each phase), is reset to zero when a cell enters it. There may be just one phase, from entering the cycle until cell division at the end of mitosis, and there may also be considered the four classic biological phases G_1, S, G_2 and M, with transitions between them at so-called checkpoints. There may also exist intra-phase checkpoints, as in the case of the S-phase. Age x may be represented as bounded or (in the absence of any known physiological limit to it) unbounded but with a probability of duration showing exponential decay. Such models date back to McKendrick (1926) [112] in a general context and have been popularized by many followers for the cell cycle (Ważewska-Czyżewska & Lasota [113], Mackey [114], Arino & Kimmel [115], and others) in the form of a simple transport equation describing evolution in each phase, together with transition probabilities between phases. The common structure of these models runs as

$$\begin{cases} \dfrac{\partial}{\partial t} n_i(t,x) + \dfrac{\partial}{\partial x} n_i(t,x) &= -[d_i(t,x) + K_{i\to i+1}(t,x)] n_i(t,x), \\ \\ n_i(t, x=0) &= \displaystyle\int_{y\geq 0} K_{i-1\to i}(t,y)\, n_{i-1}(t,y)\, dy, \quad 2 \leq i \leq I, \\ \\ n_1(t, x=0) &= 2\displaystyle\int_{y\geq 0} K_{I\to 1}(t,y)\, n_I(t,y)\, dy. \end{cases} \tag{2.15}$$

where transition functions $K_{i\to i+1}(t,x) \geq 0$, and death rates $d_i(t,x) \geq 0$ are bounded and such that: if $\min\limits_{0\leq t\leq T} K_{i\to i+1}(t,x) := k_{i\to i+1}(x)$, and $\max\limits_{0\leq t\leq T} [d_i + K_{i\to i+1}] := \mu_i(x)$, then

$$\prod_{i=1}^{I} \int_0^{\infty} k_{i\to i+1}(y) e^{-\int_0^x \mu_i(u)du} dy > 1/2,$$

so as to ensure strict growth of the total population, births then prevailing over deaths. The integer I, number of phases, may be just 1, in which case only the second boundary condition remains. It is also possible to add a G_0 (resting) phase representing those cells in the population that are not engaged in the cell division cycle, with exchanges between G_0 and G_1. The targets for physiological (circadian) or therapeutic control may be the death rates, with drugs possibly specific of one particular phase of the cell cycle, or the transition functions, as some drugs (e.g., cyclin dependent kinase inhibitors) are known to block phase transitions. Some of these models, with only one age phase for the cell division cycle, the resting phase G_0 having or not age structure, resort more to proliferation-quiescence (PQ) models, as [116, 117, 118, 119]. Note that such PQ models may be transformed, with some additional hypotheses, into delay-differential models [114, 120], the delay, representing the duration of the cell division cycle, being either fixed or distributed according to a probability density function.

An interesting property of these age-structured models is, provided that there is no feedback from the environment (or provided that such feedback is fixed at stationary states, as in [117, 118]), their linear structure, which endows their solutions with exponential behavior. Indeed, their asymptotic behavior is governed by an eigenvector (found as a solution) attached to its highest eigenvalue, namely a positive real number λ. In other words, the dominating solution of the system is of the form $e^{\lambda t}$, multiplied by some bounded function of x and t. Then, in a control perspective, as will be mentioned later, it is possible to use such dominating eigenvalue as an objective function, the targets for control being as presented above death rates and phase transition functions [121, 122] (see also [123] for a close approach).

It may also be shown [124] that, if one assumes for simplicity that death rates and transition rates depend only on age, i.e., $d_i(t,x) = d_i(x)$ and $K_{i\to i+1}(t,x) = K_i(x)$, then the exponent λ is the unique solution of the so-called Euler-Lotka integral equation

$$\frac{1}{2} = \prod_{i=1}^{I} \int_0^{+\infty} K_i(x) e^{-\int_0^x \{K_i(\xi)+d_i(\xi)\}d\xi} e^{-\lambda x}\, dx, \tag{2.16}$$

which precisely means that the first eigenvalue λ may be interpreted as an artificial death rate, that should be added to the $d_i(x)$ in all phases to stabilise the cell population by exactly annihilating its growth due to doubling at the end of the I-th phase. The transition functions and the death rates being given, solving numerically the Euler-Lotka equation in λ yields the growth exponent that governs the asymptotic behavior of the population.

One may enrich the model by introducing age velocities $v_i(x)$ in the phases by setting $\frac{\partial}{\partial x}\{v_i(x)n_i(t,x)\}$ instead of $\frac{\partial}{\partial x}n_i(t,x)$ in the transport equation, which slightly changes the Euler-Lotka equation, as presented in the general form of the model [124]. For instance, such velocities in a 2-phase $G_1/S - G_2 - M$ model of the cell division cycle have been assessed on data in different growth factor conditions for the same populations [125], obtaining that the richer were the growth factor conditions, the faster were the cell cycle phase velocities. No wonder, as this is consistent with physiological knowledge.

2.3.3. Internal trait (or phenotype)-structured models

In the same way as space or age in the cell division cycle yield structure variables to take into account heterogeneity in a population of cells when cell motion or progression in the cell cycle are at stake, other structure variables may be considered. Such structure variables represent internal traits (aka phenotypes), characteristic of a relevant diversity in a cell population (the relevance of which depends on the therapeutic question under consideration). For bacteria, size may be such a structure variable, added to age in the division cycle. However, it does not seem to be that relevant to represent heterogeneity in cancer cell populations, as progression and division in the cell cycle in multicellular organisms depends on growth factors, not on size. Size is an obvious phenotype, but other traits can be invisible under the microscope, and only revealed by indirect observation.

Indeed, traits that are much more relevant in cancer are linked to the fate of cells in a proliferative state, namely proliferation potential (fecundity), potential to resist deadly insults (viability) and potential to quickly adapt to changing local metabolic environments (plasticity). Models of *adaptive dynamics*, initially developed to represent the fate of populations of individuals (most often animals and plants) in theoretical ecology, have been transferred to cell populations, healthy and cancer, to study the evolution of such traits with time when the populations are exposed to an environmental pressure, e.g., due to the introduction of anticancer drugs. The trait under consideration may be multidimensional, e.g., (fecundity, viability) as in [126], also described in the survey [127].

A first question that naturally arises about cancer cell populations exposed to such drugs is how to represent evolution towards drug resistance, i.e., resistance that is not of genetic origin, but induced by adaptation of the cells to the drug. A way to do this is, contrary to first attempts towards this direction, that assumed the existence of a totally resistant subpopulation and of a totally sensitive one (which would lead to compartmental ODE models), to represent evolving resistance by a continuous structure variable. This amounts to define for the density of tumor cells $n(t,.)$ a phenotype x taking all possible values between 0 and 1, from 0 corresponding to no expression of resistance genes at all (total sensitivity to the drug under study) to 1 corresponding to maximal expression of resistance genes (total resistance, i.e., no effect of the drug at all, neither on proliferation rate nor on death rate).

This has been done in different settings with reaction-diffusion equations in [128, 129, 130, 131], and in a general form with theoretical results in [132, 133, 134], reviewed in the survey [135]. To reduce the question to a simple integro-differential equation (no mutation, no advection, no diffusion) that nevertheless allows following the evolution with time t of the resistance phenotype x under drug infusion, a general non-local Lotka-Volterra setting for the cell population $n(t,x)$ is:

$$\frac{\partial n}{\partial t}(t,x) = \big(r(x) - d(x)\rho(t)\big)n(t,x), \tag{2.17}$$

with

$$\rho(t) := \int_0^1 n(t,x)\,dx \quad \text{and} \quad n(0,x) = n^0(x).$$

The nonlocal logistic term $-d(x)\rho(t)$ stands here to represent the competition, in particular for space and nutrients, between each cell and all its kin in the population. This allows for the simultaneous study of

1. evolution with time in density of cells constituting the population

$$t \mapsto \rho(t) = \int_0^1 n(t,x)\ dx \qquad (\text{if, e.g., } x \in [0,1]),$$

2. evolution with time of the trait distribution in the cell population

$$x \mapsto \lim_{t\to+\infty} \frac{n(t,x)}{\rho(t)},$$

which for cancer cell populations means tumor growth and asymptotic distribution of trait x correspondingly.

It can be shown that $\rho(x)$ is of bounded variation (BV) and converges, from which it results that $n(t,x)$ asymptotically concentrates on a discrete set of traits x on $[0,1]$.

It is noteworthy that such trait-structured models represent *reversible* evolution towards drug resistance. For this reason they should be called more appropriately (adopting a biological terminology) models of drug tolerance than models of drug resistance. If one wants to set fixation (irreversibility) in the drug *resistance* process, then one may make use of PDMPs (piecewise deterministic Markov processes), introducing switches of irreversible genetic branching between episodes of deterministic, but reversible, evolution. This will not be presented here, as we are not aware of works on this mixed deterministic-probabilistic topic related to cancer evolution.

In the case of drug resistance, considering a population $n_H(t,x)$ of healthy cells and a population $n_C(t,x)$ of cancer cells exposed to the same drugs u_1 cytotoxic (death-inducing) and u_2 cytostatic (slowing down the intrinsic proliferation rate, i.e., the cell division cycle course velocity), this can be exemplified by the following model [136]:

$$\begin{aligned}
\frac{\partial}{\partial t} n_H(t,x) &= \left(\frac{r_H(x)}{1+\alpha_H u_2(t)} - d_H(x) I_H(t) - u_1(t)\mu_H(x) \right) n_H(t,x), \\
\frac{\partial}{\partial t} n_C(t,x) &= \left(\frac{r_C(x)}{1+\alpha_C u_2(t)} - d_C(x) I_C(t) - u_1(t)\mu_C(x) \right) n_C(t,x),
\end{aligned} \tag{2.18}$$

where $\rho_H(t) = \int_0^1 n_H(t,x)\,dx$, $\rho_C(t) = \int_0^1 n_C(t,x)\,dx$ are the total cell populations, healthy and cancer, $I_H(t) = a_{HH} \cdot \rho_H(t) + a_{HC} \cdot \rho_C(t)$, $I_C(t) = a_{CH} \cdot \rho_H(t) + a_{CC} \cdot \rho_C(t)$ stand for the common cellular environmental pressure in each species, and the nonlocal logistic terms $d_H(x)I_H(t)$ and $d_C(x)I_C(t)$ represent intrinsic death due to cell competition for space and nutrients, independently of the effect of the drugs u_1 and u_2.

In the case of constant controls (u_1, u_2) and under simple hypotheses (C^1 for functions r, d, μ of trait x), one can show [136] for $n_H(t,.)$ and $n_C(t,.)$ at the same time both convergence towards stationary values (a plateau for ρ_H and ρ_C) and concentration of phenotypes x in each cell population (i.e. a discrete support for the structure variables x). The proof relies on the definition of a Lyapunov functional [133].

The model may then be used to define and solve an optimal control problem, as will be presented in Section 4.4.

2.4. Agent-based models

Apart from continuous approaches in modeling, there exist discrete approaches, in which the dynamics of each tumor cell (less often – of small groups of cells) is considered separately. Each cell is characterized by its position in space, sometimes also by its velocity, and by a state that depends, e.g., on the phase in its cell division cycle, on various chemical processes occurring in the cell, on the local extracellular density of nutrients and other substances, etc. In the case of an explicit consideration of chemical substances, their dynamics, as a rule, is modeled by continuous reaction-diffusion equations, which formally makes such models hybrid [137]. The internal dynamics of cells may also be modeled by ODEs.

In cellular automata, the most popular type of discrete models, space is discrete, and each of its grid elements can contain one or another specific number of cells [138, 139]. A typical cellular automaton rule regulates the probability of cell division, death, movement, or of entering a new state, depending on the occupancy of neighboring cells, on the concentration of considered substances, and on its internal chemical processes. In Potts' models [140], each cell occupies several points of the space lattice. In other agent-based models, space can be continuous, while the cells are given positions and sizes, and there exists a set of restrictions on their location in space [141]. Mechanical interactions between cells are sometimes described not via explicit consideration of physical laws, which is a computationally expensive approach, but with the help of simplified assumptions about the rules for cell movement. In off-lattice models, cells can be considered as hard or soft spheres with their interaction described by pairwise attractive or repulsive forces and their motion governed by Newton's second law or some other equations. In a more detailed description, biological cells can be considered as polyhedra with vertices connected by elastic springs and forces depending on the distances and angles between them (see, e.g., [142] and the references therein).

The strength of the discrete approach is its comparative simplicity for consideration of random processes [143] and heterogeneous tumor populations, which, in particular, arise due to the mutations of tumor cells [141]. Discrete models can provide excellent visualization of the initial stages of tumor growth, and of events, linked to single cells, which is obviously impossible in continuous models [144]. However, they require colossal computational resources when considering the growth of large tumors. Therefore, in such models often only a relatively small number of cells is considered – of the order of thousands – while even smallest detectable tumors contain at least about tens of millions of cells [145]. Moreover, discrete models can only be analyzed computationally, unlike continuous models, which, at least in not too much complicated cases, can be amenable to analytical investigation (i.e, in the most favorable cases, leading to theorems, which is precluded in discrete models). Another problem of discrete approaches is the fact that the specific structure of the computational lattice can influence the global behavior of the system, in a similar way to how errors arise in the numerical solution of partial differential equations. However, while the latter effect can usually be quantified using mathematical analysis, it is quite difficult to quantify this for discrete models. This drawback can be overcome in off-lattice models but the passage to the continuous limit (cell size $\varepsilon \to 0$, cell number $N \to \infty$) is more difficult to justify for them than for lattice models. Moreover, discrete models usually contain a large number of parameters, the values of at least some of which are difficult or impossible to estimate from experimental data. Therefore, the influence of their variation on the modeling result should be studied, which requires additional layers of numerical complexity.

3. Therapeutic means that are available in oncology

Asclepios, the legendary founder of Greek medicine, and later Hippocrates and Avicenna are all said to have defined their practice as consisting of “the word, the plant and the knife”. The word is not only restricted to words of solace to the patient, it may also be related to the description of signs and diagnosis of diseases, so as to orient the treatment – and for us this can be extended to the investigation of diseases through mathematical models; the plant is what our modern pharmacopoea, i.e., drugs of natural or synthetic origin, comprises; the knife is clearly surgery, but also radiotherapy or any direct physical intervention on the body. In the sequel, we will firstly deal with chemotherapies and targeted therapies, leaving immunotherapy (that addresses the immune response against cancer, not cancer cells directly) and radiotherapy for the end of this section.

A classic distinction exists between cytotoxic and cytostatic drugs, the former (cell-killing drugs by destination) are more often plainly called chemotherapies now, whereas the latter term (that refer to drugs that slow down cancer cell proliferation, e.g., by antagonizing growth factor receptors or by blocking some non immediately vital intracellular pathways) tends however to be of lesser use, as cytostatic drugs may become cytotoxic when given at very high doses. In the sequel, we will refer to (cytotoxic) chemotherapies, targeted therapies (i.e., drugs that antagonize or block receptors or intracellular pathways, mainly those linked with proliferation), antiangiogenic therapies (here artificially isolated from the previous ones in the category of cytostatic drugs), immunotherapies and radiotherapy.

3.1. Drugs: chemotherapy and targeted therapies

The principles on which these proposed strategies rely consist in identifying targets in the proliferation process of cancer cell populations for which pharmacological means of action have also been identified, either per chance, sometimes by knowledge from plants, or by systematic chemical investigation. Pharmacologists of the single cell have identified many intracellular pathways involved in the fates of cells: proliferation, apoptosis, differentiation and senescence, and search for so-called “druggable targets” in these pathways. When identified, the pharmacological industry scans thousands of molecules susceptible to block or stimulate them, first step before investigating their toxicity to healthy tissues, the next step before developing them as new anticancer drugs.

This has left oncologists with many molecules for which indications (i.e., what type of cancer?) have been determined, and therapeutic regimes little by little elaborated by trials and errors. Anticancer drugs are most of the time delivered to the whole organism, so that constraints on their toxicity to healthy cells, and acquired resistance, by adaptation, of cancer cell populations to their use should as much as possible be considered. These are the elements of any optimization scenario in oncology: given targets to be hit and means of control available, what is the objective function to be optimized (usually eradication or containment of cancer cells), by what tunable pharmacological means, and under what constraints?

For such drugs, some must be known of their mechanisms of action and, in as much as their use should go to clinical oncology, of their fate in the organism before they reach their targets, i.e., as detailed in Section 2.2, the object of PK-PD [95]. Optimization of pharmacotherapy concerns mainly pharmacodynamics, as pharmacokinetics have only to be known, not modified, to represent the journey from actual delivery to the patient by infusion or ingestion to the wanted as well as unwanted drug targets.

In fact, when such a target has been identified, one may introduce it as a tunable parameter or function in a model of tumor growth assumed to be relevant for the description of tumor growth under tits exposure to the drug that affects it. The simplest way to do it for a chemotherapy is by adding a death term due to the drug in an equation describing the growth of the tumor. It can also be done by only slowing down the cell cycle, by targeting functions $K_{i\to i+1}(t,x)$ in (2.15), a case that will be exemplified in Section 4.3. When different drugs are combined, then different targets should be built-in features of the model. This will be exemplified by death functions $f(t)$ and $g(t)$ added in a modified form of the RHS of (4.35) for the combination of a chemotherapy and an antiangiogenic therapy, in Section 4.2. This will also be presented in the case of a combination of a cytotoxic drug (a chemotherapy) and a cytostatic drug (a targeted therapy slowing down proliferation without killing cells), by functions u_1 and u_2 in Eqs. (2.18), a classical case in clinical oncology, in Section 2.3.3.

3.2. Antiangiogenic therapy

Nutrients flow into avascular tumors from capillaries, located in the peritumoral region, which are pushed away by the proliferating tumor mass. This results in nutrient limitation, which, as has been discussed in Section 2.1, ultimately restricts the rate of tumor growth. One way for the tumor cells to overcome this is enabling invasion of nearby tissues. Invasive tumors can co-opt the capillaries, i.e., embed them within the tumor mass [146]. However, capillaries usually gradually degrade over time inside the tumor due to the pressure caused by proliferation and migration of tumor cells [147], as well as due to various chemical factors [148]. Moreover, proliferating tumor cells consume a much more important quantity of nutrients than the corresponding normal cells [30], which contributes to a sharp decrease in the level of nutrients inside the tumor. Under metabolic stress, tumor cells produce signaling molecules, that stimulate the formation of new vessels – tumor (neo)angiogenesis. The most crucial of such molecules is vascular endothelial growth factor, or VEGF, which stimulates the formation of capillaries – the thinnest vessels, through the surface of which the exchange of substances between blood and tissue takes place [149].

In a healthy tissue the process of angiogenesis happens, e.g., during wound healing, and leads to an ordered vascular system, finely tuned for each organ. However, excessive production of VEGF by the tumor leads to the formation of a chaotically organized network, the capillaries of which are much more permeable to substances dissolved in the blood. Currently, more than a dozen anti-angiogenic drugs are used, the action of which is aimed at neutralizing the effect of VEGF on endothelial cells. This leads to the cessation of formation of new capillaries, to the normalization of structure of already formed tumor capillaries, which occurs within several hours [150], and to the normalization of the density of the capillary network, which is a longer process [151]. Moreover, such treatment normalizes tumor-associated edema, which initially forms due to high-permeable tumor capillaries [152].

There are several approaches to modeling tumor growth taking into account angiogenesis, which have their pros and cons. The simplest approach is by using systems of ODEs, wherein, due to evolving tumor vascularization and administration of antiangiogenic therapy, the tumor carrying capacity itself may be presented as varying. The first model of this kind was published in 1999 by Philip Hahnfeldt and his colleagues [153] and can be reproduced in general form as:

$$
\begin{aligned}
V'(t) &= -rV(t)\ln\frac{V(t)}{K}, \\
K'(t) &= A(V(t), K) - g(t)K,
\end{aligned}
\tag{3.19}
$$

in which one can recognize the Gompertz model in the first equation, in its one-dimensional form that explicitly takes into account the carrying capacity K of the tumor. The second equation describes the evolution of the carrying capacity of the tumor, where $A(V, K)$ is the total efficacy of intrinsic pro- and anti-angiogenic factors in the body of the tumor carrier and $g(t)$ is the concentration of the antiangiogenic drug. Such models can be very convenient for preclinical and clinical studies [154, 155]. However, like all phenomenological models, they are close to statistical data processing, and do not take into explicit account the multitude of processes, that accompany angiogenesis and antiangiogenic therapy, some of which were listed above.

The most popular approach for modeling angiogenesis and antiangiogenic therapy is hybrid modeling, in which the dynamics of capillaries is described by discrete methods, and the dynamics of pro- and antiangiogenic factors by continuous equations. Often, such models take into account blood flow [156, 157]. The main purpose of these works is to study the influence of changes in various physical and biological parameters of the model on the architecture of the developing capillary network and on the blood flow in it. Such works can provide interesting insights. In the work [158], it was suggested that there should be a correlation between the degree of vascular compression as a result of active proliferation of tumor cells and of the proportion of oxyhemoglobin in the tumor blood flow. This may be an indicator of the efficacy of drug delivery to the tumor. The possibility of modeling tumor capillary networks at the microlevel and the consequent possibility of considering their spatial heterogeneities are undoubtedly advantages of hybrid models. However, these features require significant computational costs, which only increase with the growth of tumors. To reduce them, it is possible to use various simplifications. Such models are actively developed by the research group of Michael Welter, Heiko Rieger and their colleagues, and their works give a good example of what simplifications can be made. In their first works, made in the 2000s, the tumor is modeled using a discrete approach [159]. In the 2013 paper [160] the tissue containing the tumor is considered as a continuous medium. And in the work of 2016 [158] the tumor is considered simply as a growing spherically symmetric object surrounded by a concentric shell of a fixed thickness, in which the process of angiogenesis takes place. It is probably because of the computational complexity that hybrid models of this kind, to the best of our knowledge, have not so far been used to simulate an entire course of antiangiogenic therapy, not to mention the study of its optimization.

A third major option is the use of continuous spatially-distributed models that include a separate variable c to account for the capillary network. A simple form of equation for it may look the following way:

$$\frac{\partial c(x,t)}{\partial t} = \mu \frac{v(x,t)}{v(x,t)+v^*} c(x,t) - d_c n(x,t) c(x,t), \tag{3.20}$$

where the two terms in the right-hand side of this equation are responsible for vasculature proliferation, described by classical Michaelis-Menten kinetics, in the presence of VEGF, v, and vasculature degradation in the presence of tumor cells n [161, 162]. One of the drawbacks of such approach is the impossibility to reproduce microscopic features of the capillary network, such as branching of capillaries, formation of loops and cessation of blood flow in capillaries when the vessel located upstream is destroyed. Also, this method is associated with questions about the validity of the choice of mathematical expressions describing the dynamics of the microcirculatory network, and the choice of the values of the corresponding parameters. However, with the help of such method, it is possible to describe the processes that make possible a dynamic representation of the capillary network at a qualitative level under moderate computational costs.

3.3. Immunotherapy

In the modern understanding of the interactions of cancer with the immune system, the key concept is the cancer-immunity cycle [163]. This cycle can be represented in a simplified form as a sequence of the following step-by-step processes, the implementation of which is necessary for the effective destruction of cancer cells by the immune system:

1. Dendritic cells uptake and process neoantigens (i.e., foreign proteins, absent in the healthy body), produced by tumor cells.
2. Dendritic cells migrate to regional lymph nodes and present neoantigens, bound to their surface, to T-lymphocytes.
3. In response to neoantigen presentation T-lymphocytes activate and proliferate, resulting in a population of so-called effector T-cells, in particular, cytotoxic T-killers, which are specific to particular neoantigen.
4. T-killers move to the tumor through the bloodstream.

5. T-killers infiltrate the tumor.
6. T-killers bind to the tumor cells through the interaction between T-cell receptors and their corresponding antigens, bound to the surface of tumor cells.
7. Tumor cells are killed by cytotoxins, released by T-killers.

The killing of tumor cells leads to the release of additional tumor-associated antigens. Their uptake by dendritic cells closes the described cycle, leading to the expansion of the range of recognized antigens and to the intensification of the immune response during further movement along the cycle.

Violation of any of the stages of the described cycle can lead to the suppression of the immune response. The reasons for this may be: impaired detection of tumor antigens, impaired activation of T-lymphocytes, impossibility of their penetration into the tumor, suppression of effector T-lymphocytes by the tumor cells or by various factors in tumor microenvironment (in particular, by regulatory T-lymphocytes) [164]. The term "antitumor immunotherapy" (IT) encompasses a wide range of concepts and methods, the efficacy and practicability of using each of which directly depends on the specific type of violation of the cancer-immunity cycle. These methods can be active, i.e., specifically target tumor cells, like cancer vaccines that contain specific antigens, or passive, i.e., enhance the immune system's ability to attack cancer cells instead of directly targeting them, like checkpoint inhibitors.

Clinical data, obtained over the past two decades, suggest that for many types of cancer the cancer-immunity cycle is disrupted only at its last stage, i.e., killing of tumor cells by T-killers. One crucial mechanism of suppression of T-killers is the binding of the PD-L1 protein, which, according to various estimates, is produced by from a fifth to a half of cancerous tumors [165], to the programmed cell death receptor PD-1 on the surface of T-lymphocytes [166]. The so-called blockade of immune checkpoints, which inhibits the interaction between PD-1 and PD-L1, formed the basis for the development of anti-PD-L1 and anti-PD-1 drugs, the response rate to which reaches 38% for some types of cancer (see [167, 168] for reviews of clinical trials). The first drug of this type, approved for clinical use in 2016, is the anti-PD-L1 drug atezolizumab (trademark Tecentriq).

Most of the works on modeling antitumor immunotherapy (IT) are based on systems of ordinary differential equations (ODEs) and are focused mainly on the last steps of cancer-immunity cycle, i.e., binding of tumor cells with T-killers and death of tumor cells as well as inactivation of T-killers [169, 170, 171, 172]. At that stage, the expression and recognition of antigens is usually implied by variation of the rates of activation and proliferation of T-lymphocytes and of killing of tumor cells. The works in this direction are often based on the classical model, suggested by Stepanova in 1979 [173], which consists of two phenomenological equations for tumor and immune system, and on the model by Kuznetsov of 1994 [174]. The equations of Stepanova's model can be represented as

$$\begin{aligned} \dot{V} &= F(V) - \gamma VT, \\ \dot{T} &= \mu(V - \beta V^2)T - \delta T + \alpha, \end{aligned} \tag{3.21}$$

where V is the tumor volume and T represents the amount of various types of T-cells. The function $F(V)$ corresponds to any of the growth curves, discussed in Section 2.2, γ is the rate of tumor cells elimination by T-cells, μ is the maximum value of proliferation rate of T-cells, which tends to its value under low tumor cell density. It is implicitly assumed here that T-cells proliferation is stimulated by the antigen, generated by tumor cells. The parameter β is a coefficient of immune system suppression by large tumors, δ denotes the rate of natural death of T-cells, α is the rate of their generation by the immune system.

The main feature that unites almost all studies of this type is the conclusion that the immune system can effectively inhibit the growth of small tumors, whereas large enough tumors are able to overcome the immune response. From a mathematical point of view, this is expressed in the corresponding models by the presence of an unstable manifold, that separates the basins of attraction of stable points, which correspond to a benign tumor and a malignant neoplasm, as Fig. 5 exemplifies for Eqs. (3.21). Under such mathematical formulation, an important problem is the question of how it is possible, with the help of a therapeutic intervention, to move the initial state of the system, located in a malignant area, to a benign area. Such problems are as a rule formulated as optimal control problems and are solved analytically [175, 176].

Most of the existing spatially-distributed models, that consider antitumor IT, are also focused on the interactions of tumor and immune cells, notably T-killers, which infiltrate the tumor [177, 178, 179, 180]. The works of this type demonstrate different modes of spatiotemporal dynamics of immune and tumor cells, in particular, their non-uniform stationary distributions in dormant tumors [181]. The account of the dynamic expression and recognition of antigens was implemented in the work of 2019 [182]. It allowed the authors to illustrate the ambiguous effect of the frequency of mutations of tumor antigens on the efficacy of the immune response.

The account for the heterogeneity of antigens and the evolution of their expression profile can be realized via the use of integro-differential equations. Such approach was implemented in the work [183], which has an illustrative nature, as well as in the works that do not consider oncological diseases, but are of significant interest in their context. These works are devoted to modeling the development of autoimmune diseases, which can manifest themselves in cancer patients as well [184], and to the search for methods to counteract the dynamics of "chase and escape", which can develop under heterogeneous time-varying expression of antigens [185].

It should however be noted that despite a present great interest in modeling for immunotherapy, this area is relatively recent, making immunotherapeutic models toddlers in the field of oncology thus far. What greatly complicates their development is the fact that immunotherapy by itself often leads to unpredictable

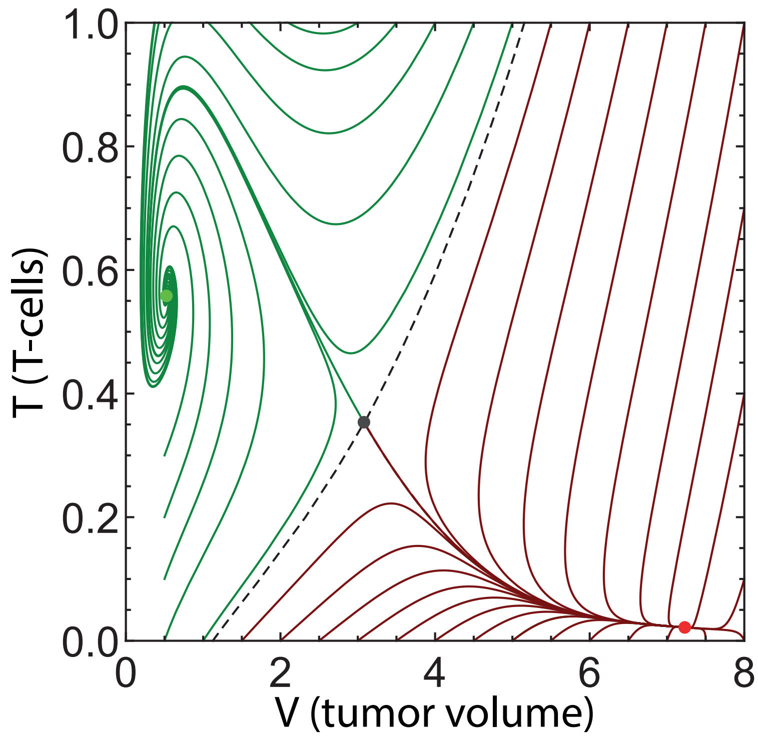

Figure 5: Phase portrait of the system (3.21) under $F(V) = BV(1 - V/K)$, $B = 0.6$, $K = 7.5$, $\gamma = 1$, $\mu = 0.5$, $\beta = 0.3$, $\delta = 0.4$, $\alpha = 0.1$. Green dot denotes stable solution ($\approx 0.524, \approx 0.558$), that corresponds to benign tumor, black dot denotes unstable solution ($\approx 3.080, \approx 0.354$), red dot denotes stable solution ($\approx 7.230, \approx 0.022$), that corresponds to malignant tumor.

outcomes and can induce severe adverse effects, which will be further highlighted in Section 3.6.4. Most of the relevant modeling works are of purely theoretical interest. In the work [186] the authors themselves admit that the model used in their study describes the action of the immune system too simplistically and therefore has no practical significance, although it provides interesting theoretical conclusions. At the same time, there is a small number of works based on fitting specific experimental data [187, 188, 176], but probably, at the moment, no experimental confirmation has been acquired for the recommendations, theoretically derived in these works.

3.4. Radiotherapy

Approximately half of the patients diagnosed with cancer undergo radiotherapy [189]. This type of treatment uses high-energy electromagnetic waves or particles, that cause damage to cell DNA, leading to cellular death. The source of radiation may be situated inside the body, however the most frequent option is the use of a radiation source external to the patient. Till today, most frequently photon radiation is used, while the use of high-energy charged particles, primarily protons, is becoming more and more accessible for the treatment of tumors.

The effect of irradiation on cells can be expressed via the so-called "linear-quadratic model", which is known to fit experimental data well in a wide range of clinical parameters [190]. According to it, the fraction of cells that survive after a single radiation dose D, which correlates with radiation energy per tissue mass, can be estimated as

$$S(D) = e^{-\alpha D - \beta D^2}, \tag{3.22}$$

where α and β are radiosensitivity parameters. In clinical practice, the course of external beam radiotherapy is most frequently fractionated, i.e., split into several doses, delivered over prolonged time intervals, usually several weeks. Such procedure may seem illogical immediately from Eq. (3.22), since splitting one total dose leads to a decrease in the effect of the quadratic term. However, this equation by itself does not account for the space- and time-dependent effects, that are widely referred to as the four "R"s of radiotherapy [191].

The first such effect is the redistribution inside the cell division cycle. The radiosensitivity of a single cell depends on the current stage of its cell cycle. In particular, non-proliferating cells are more radioresistant – therefore, during every single irradiation some of the non-synchronized cells are relatively more radioresistant than others. The second effect is reoxygenation. The damage to the cell DNA caused by radiation can be direct or indirect, i.e., mediated by free radicals, formed by radiolysis of water. Indirect damage can be chemically restored, oxygen being an important inhibitor of this process, and thus, an important radiosensitizer. *In vitro* experiments demonstrate that radiosensitivity of cells in air and under hypoxia may vary three-fold in the case of photon therapy [192]. Of note, the strength of this effect declines with increasing size of the particles used for irradiation. Therefore, the hypoxic fraction of cells within the cancerous tissue is also relatively radioresistant (it should be noted, however, that other theoretical explanations of this oxygen effect also exist). The third effect, that should be accounted for while fractionation of radiotherapy, is the repopulation of tumor cells that takes place between the irradiations. The fourth effect is the repair of subletal damage, which allows cells to survive despite being damaged. However, it is performed in several hours after the irradiation and can be neglected if the time interval between irradiations is longer [193].

It should be noted that radiosensitivity parameters vary dramatically between various tumor cell lines and, moreover, may significantly differ from patient to patient even for tumors of the same type. The radiosensitivity variability is sometimes referred to as the fifth "R" of radiotherapy [194]. In addition, more and more attention is nowadays paid to both immunostimulating and immunosuppressive effects of radiotherapy, which influence the therapeutic outcome [195]. Some of such aspects will be considered further in Section 3.5. Finally, another very important reason for fractionation follows from the fact that radiotherapy affects normal tissue as well, which will be discussed further in Section 3.6.1.

3.5. Combination of different treatments and emerging difficulties

In clinical practice, different treatment modalities are often combined for various reasons. Chemotherapy, immunotherapy, radiotherapy, as well as hormonotherapy for certain types of cancer, can be used prior to surgical resection of the tumor, which is called “neoadjuvant therapy” in oncology. The aim of such their use to shrink tumor and make it more distinguishable and less adherent to surrounding vessels and vital organs, therefore reducing the difficulty of surgery and increasing the chances of favorable outcome. Different types of therapy can as well be administered after surgical resection in order to eliminate undetected tumor cells, that otherwise may lead to a relapse. Furthermore, various treatment modalities can be administered one after another in a sequence of so-called lines of treatment. They are used in case it turns out that tumor has intrinsic or acquired resistance for the treatment in a previous line, or else if it causes inadmissible adverse effects.

Moreover, different modalities can be administered simultaneously, especially if it is expected that their combined action should lead to a synergistic effect – e.g., cytotoxic and cytostatic drugs are frequently administered together in clinical practice, as it has already been mentioned in Section 2.2. Nowadays, various combinations of different types of treatment, described in Sections 3.1-3.4, are either used in a combined antitumor therapy, or are of considerable interest as potential clinical options. In particular, the idea of combining radiotherapy as a technique of local treatment with chemotherapy in order to reach undetectable metastatic cells, appeared right after the introduction of chemotherapy into clinical use, and chemoradiotherapy is widely used nowadays [196]. However, due to the complexity of interactions of two or more types of therapy acting simultaneously, they may as well provide antagonistic effect on each other's action. Preclinical experiments and mathematical modeling can provide valuable insights into the possible outcomes of combined treatments. A prominent example here are the combinations of antiangiogenic therapy with other types of treatment, the investigation of which represents an open challenge for mathematical modeling.

Due to its mediated type of action on the tumor, antiangiogenic therapy by itself is unable to eradicate all tumor cells. Most clinically approved regimens that include antiangiogenic drugs combine them with various chemotherapy agents [197]. However, antiangiogenic therapy affects the inflow not only of nutrients, but also of chemotherapeutic drugs into the tumor. Depending on many factors, antiangiogenic therapy can either transiently increase the flow of the drug [198] or weaken its effects right from the beginning of its administration [199]. This in particular means that the schedule of drug administration should significantly influence the final efficacy of such combined therapies [200]. This question will be discussed in more detail in Section 4.2.

An interesting feature of antiangiogenic therapy is that it can lead to an increase in the oxygen level inside the tumor [201], that lasts for several days. Since oxygen is a potent radiosensitizer, this effect creates the basis for the optimization of combined radiotherapy and antiangiogenic therapy. This phenomenon is as a rule explained by the fact that the normalization of microvessels structure, caused by the cessation of their exposure to VEGF, leads to an improvement in blood flow and subsequently oxygen inflow in tumors [202]. It was suggested via mathematical modeling that there can be another reason for this effect, due to the fact that microvessels normalization affects the inflow of different substances differently. Therefore, it should affect the metabolism of tumor, leading to decrease in its oxygen consumption [203]. Importantly, whatever the contribution of these reasons in the effect of the alleviation of intratumoral hypoxia may be, its manifestation does not guarantee that the addition of antiangiogenic therapy to radiotherapy will increase the overall effectiveness of treatment. Indeed, one of the end results of antiangiogenic therapy is the escalation of hypoxia in the long term. Naturally arising questions, which mathematical modeling can address, are what should influence the efficacy of such treatment and how to optimize it [204, 205]. However, the existing works devoted to mathematical optimization of combined radiotherapy and antiangiogenic therapy do not account for oxygen dynamics [206, 207]. One of these works will be discussed in Section 4.1.1.

Combined use with antiangiogenic therapy is also one of the approaches aimed at increasing the efficacy of immunotherapy. A lot of attention has recently been paid to the experimentally observed fact that VEGF by itself has immunosuppressive effects, that are, in particular, due to the interactions of VEGF with various immune cells, that express its complementary receptors (see [208] for review). Such effects can be relieved by antiangiogenic therapy. In May 2020, the immune checkpoint inhibitor atezolizumab in combination with bevacizumab was approved by FDA for patients with inoperable or metastatic hepatocellular carcinoma. Earlier, in 2018, a combination of atezolizumab, bevacizumab and the chemotherapeutic drugs paclitaxel and carboplatin was approved for patients with metastatic non-squamous non-small cell lung carcinoma. However, antiangiogenic therapy may as well compromise the inflow of immunotherapeutic drugs, which leads to analogical questions of schedule optimization of such combined treatments. The first steps towards this goal have been performed in a recent paper [209], wherein a complex mathematical model is provided, fitted on the data of a number of experimental works. Its investigation suggested that the result of the combination of antiangiogenic therapy with immunotherapy should depend on the dose of the antiangiogenic drug in a non-monotonic manner, relatively low doses of the antiangiogenic drug possibly being more effective than higher doses.

Combinations of immunotherapy with chemotherapy and radiotherapy as well present significant interest, including from the point of view of mathematical modeling [210, 211, 212, 213]. It is known that the death of tumor cells due to irradiation or chemotherapeutic drugs leads to the release of tumor-associated antigens [214, 215], which increases their uptake by dendritic cells and stimulates the cancer-immunity cycle, as described in Section 3.3. However, these treatments also induce a multitude of other complex effects, some of which are of immunosuppressive nature [216, 214]. The pursuit to account for all these effects results in classical problems in modeling of complex systems, which were highlighted in Sections 1.3-2.1. More parameters demand more calibration in experiments, which always demonstrate high variability and cannot be complete, while increasing of a nonlinear system's complexity complicates its analysis and can even render it chaotic in some parameter region and therefore inherently unpredictable.

3.6. Constraints and limitations linked to unwanted effects of these various modes of therapies

3.6.1. Chemotherapy, radiotherapy: unwanted toxic side effects on healthy cells

Chemotherapy, apart from almost inevitably inducing resistance effects in the cancer cell population in case of a prolonged treatment, has major effects on healthy cells, as it exerts its action on cells that are engaged in the cell cycle. This category involves not only cancer cells, but also cells in fast renewing tissues: hematopoietic bone marrow, gut, skin and other epithelial tissues. Side effects on healthy cells are thus inevitable, and therapeutic optimization procedures must take them as constraints limiting the delivery of drugs in the general circulation. A "lazy" way to do it is by respecting maximal instantaneous flows and total delivered dose as prescribed by oncologists. A more adapted way consists of representing the healthy cell population in parallel with the cancer one, and define dynamic constraints on the state of the healthy cell population. This will be illustrated below in particular in Sections 4.3 and 4.4.

Radiotherapy as well affects all proliferating healthy tissues, the cells of which obey the same linear-quadratic law, expressed by Eq. (3.22), as cancer cells, but correspond to other values of radiosensitivity parameters. Usually cancer cells have higher values of linear radiosensitivity parameter α than corresponding normal cells, which justifies radiotherapy at low radiation doses. However, normal tissues as a rule have lower α/β ratio, which restricts the use of high doses [217]. One option to reduce normal tissue damage is to focus the radiation dose within the tumor mass. This idea has led to complex techniques that are actively used in clinical oncology, like intensity-modulated radiotherapy, which uses computer imaging and simulations for targeting tumor localization and defining the intensities of many differently-oriented beams of various energy for conforming the tumor shape [218]. That is especially relevant for proton therapy due to the small transverse scattering of protons and to the release of a significant part of energy shortly before their stop (the so-called Bragg peak), that allow for better localization possibility. However, such option carries risks even for tumors with clear boundaries, due to leakage radiation [219]. Another option to reduce normal tissue damage, that does not exclude the first one, but on the contrary is frequently used together with it, is to fractionate the total radiation dose over time. This leads to the need to account for specific effects, that were discussed in Section 3.4.

Typical radiotherapy fractionation schemes consist of fractions of 1.8 to 2.0 Gy, usually delivered once a day on weekdays within a period of several weeks [217]. However, different fractionation protocols were shown to lead to improvement in tumor cure and patient survival for some tumor types [220]. Of note, the vast majority of the tested schemes are uniform, i.e., the irradiation doses in them are distributed equally between the fractions. The varied parameters of the schemes are the number of the fractions, the interval between them and the single fractional dose, which are related through the constraint of total admissible damage to the healthy tissue.

3.6.2. High plasticity of cancer cells yields various forms of treatment-resistant subpopulations

Plasticity in cancer cell populations [52], as presented in Section 1.2, may be defined at the cell population level as a loss of control on differentiations. It is a concept that makes sense only in multicellular organisms, the only organisms that are subject to cancer. In multicellular organisms, development from the initial fecundated egg, the zygote, leads by maturing of cells along trees of cell differentiations to a finite number of terminally differentiated cell types that constitute stable tissues and organs. The succession of these differentiations along such trees is physiologically strictly controlled and, with the exception of rare cases such as wound healing, irreversible in adult organisms. This is a necessary condition to obtain stable compatibility and cooperativeness between tissues, which is the basis of multicellularity.

However, in cancer, control on differentiations is locally lost, which yields in such anatomic locations in the organism cells with uncertainly determined maturation fate. In particular, de-differentiation and transdifferentiation of cells have been observed [52]. In multicellular organisms, all functional fates are contained in a potential state in the genome of every cell (some genes being expressed, others repressed, this being controlled by epigenetic enzymes). Loss of control on differentiations, i.e., plasticity, may locally lead to aberrant expression or de-repression of genes, allowing concerned cells to become less differentiated (de-differentiated), or transdifferentiated. While de-differentiation may be seen as reversing the course of differentiation, transdifferentiation may be thought of as hopping over an epigenetic barrier between differentiation valleys, in the metaphor of the Waddington epigenetic landscape.

Such plasticity may be used by cancer cells to recruit ancient genes that have normally been epigenetically silenced in the course of evolution, to face hostile environmental conditions that were present in a remote past of our planet. Cancer cells may thus express them to face deadly insults such as cytotoxic drugs, low oxygen supply, or isotopic radiations. Thus, plasticity becomes a form of adaptability to various forms of cellular stress, which may endow cancer cell populations with capacities of drug resistance (or tolerance) and radioresistance.

Taking into account such plasticity of cancer cells as structuring heterogeneity in cancer cell populations may thus help develop therapeutic strategies that tend to avoid the establishment of drug-induced drug resistance, as will be developed in Section 4.4.

3.6.3. Antiangiogenic therapy: promoting invasive phenotypes

Antiangiogenic therapy by itself is not devoid of side effects, associated with the action of angiogenesis inhibitors on non-tumor vessels, including gastrointestinal perforations, impaired wound healing, bleeding, hypertension and thrombosis [221, 222]. Of course, this type of treatment is prohibited for pregnant women. One of the major medical disasters occurred in the late 1950s and early 1960s, when more than ten thousand babies were born with severe body deformities due to their mothers taking thalidomide, the antiangiogenic properties of which were not yet known at that time [223]. However, the rate of adverse effect for antiangiogenic treatment is significantly lower than that for chemotherapy and radiotherapy. There nevertheless exists another major obstacle associated with administration of antiangiogenic therapy.

Early experiments on murine tumor models have shown promising results with regard to the use of antiangiogenic drugs in monotherapy, since their use has allowed significant delays in tumor growth. The first antiangiogenic drug, bevacizumab, gained accelerated approval by the US agency FDA, however, in most clinical trials, its administration in monotherapy did not lead to any noticeable increase in patient survival [224]. It is assumed that this discrepancy is associated with one obvious qualitative difference between preclinical and clinical tests. While the former were mainly carried out on localized primary tumors, the latter were focused on the late stages of the disease, which is a standard situation for clinical trials [225].

To explain this phenomenon, several mechanisms of tumor resistance to antiangiogenic therapy have been proposed [226]. Two of them are aimed at minimizing an effect of therapy: protecting the capillary system of the tumor from destruction, e.g., by thickening the layer of supportive cells, pericytes; as well as the production of other pro-angiogenic factors that can affect the VEGF receptors either by tumor cells or by recruited proinflammatory cells [227]. Another mechanism should act even when the maximum possible antiangiogenic effect is achieved. This is the acceleration of invasion and metastasis of tumor cells, which allows them to move away from areas with a lack of nutrients. Based on these observations, it has been suggested that tumors that initially have an invasive phenotype should be less susceptible to AAT than compactly growing tumors [226]. This effect has recently been demonstrated by analysis of a rather simple continuous spatially-distributed mathematical model that accounts for both convective movement and migration of tumor cells [228].

To date, there is a significant body of experimental evidence that antiangiogenic therapy often accelerates tumor progression towards increasingly invasive and metastatically active phenotypes [225]. Ironically, Judah Folkman, who was first to express the idea of antiangiogenic therapy in the early 70s [229], wrote that this therapy should be able to stop the metastasis of tumor cells due to the restriction of their access to the blood vessels. It should be noted that promoting aggressive phenotypes by antiangiogenic therapy represents a particular case of analogical general tumor response to harsh microenvironment conditions. Such effects were demonstrated in published works [230, 231].

3.6.4. Immunotherapy: partial successes and some unpredictable failures

An issue of immunotherapy, from the 19th century until more recent developments about adverse events related to immune checkpoint inhibitor therapies [232], is the lack of rationale to understand when it works, when it does not, and when it worsens the clinical scene. William Coley, a New York surgeon, sometimes called "the father of immunotherapy" [233], had noticed in the years 1890 that one of his patients had been completely cured of his cancer after spontaneously overcoming a serious infectious disease. This was an erysipelas, due to the coccus *Streptococcus pyogenes*. He tried to cure other patients with cancer by inoculating cultures of this coccus on them, expecting a "reaction of their organisms" to the pathogen (in 1890, almost nothing was known of the immune system) that would eradicate both the pathogen and the tumor. He obtained partial regressions in some of these patients, however many others died of septicemia, which led to forsaking this daring innovation in cancer treatment [233].

In modern immunotherapies, the occurrence of adverse events is not necessarily a bad omen for the patients, provided that these adverse events may be kept under check (by interruption of the treatment or by delivery of corticoids), as it shows an efficacious immune response. Nevertheless, some of these immune-related adverse events may endanger the patient's life, in particular so-called cytokine (mainly IL-6) storms, that may go beyond control and alter essential organs. Such cytokine storms have been evidenced in CAR T-cell therapy, leading to as much as 20% of letal effects, but fortunately are rare – although not exceptional – and not known with such severity in immune checkpoint inhibitor therapies [234].

From a modeling point of view, directed towards applications in clinical oncology, it would be good to be able to understand the mechanisms of occurrence of such adverse events, so as to predict them and take them into account as treatment-limiting constraints. The same is true of the non-occurrence of a positive immune reaction: when should the treatment considered as ineffective and should be stopped? However, to the best of our knowledge, in both cases, clinical empiricism is the rule to face such unpredictable therapeutic failures, which so far leaves little room for the design of optimal control strategies with immunotherapies.

4. Examples of therapeutic problems in oncology and how to cope with them theoretically

4.1. Principles: targets and means of control with examples of radiotherapy optimization

Optimization of an antitumor treatment usually implies determining what should be the best schedule, i.e., dose distribution and timing for a treatment that affects the tumor cell population as well as healthy (usually fast renewing) cell populations. In a clinical use perspective, unwanted toxicity is often overlooked, when one accepts to strictly follow the clinicians' habits, that usually consist in empirical determination of a therapeutic admissible range of concentrations or dose per day. In the same way, resistance is often neglected, clinicians plainly deciding when the drug delivery is no longer efficacious that the treatment has to be stopped. However, from a more demanding point of view, as already stated, modeling how toxicity and drug resistance may be represented as *dynamic* constraints is not out of reach and has to be attempted. It is the object of some of the following examples of theoretical treatment optimization.

4.1.1. Optimal control methods

Optimal control theory is applied in a huge number of investigations of different natures and has become popular in mathematical oncology as well. In this subsection we provide only a very brief introduction to the theory in the context of cancer diseases, while a lot of reviews exist, that provide much more detailed information on this topic (see, e.g., [235, 236, 237]).

An optimal control problem should incorporate several elements. The first one is a dynamical system, e.g., a system of equations that governs tumor growth, which can be influenced by external actions described by a control variable $c(t)$. The simplest case of one equation with a single state variable of tumor volume $V(t)$ is as follows:

$$\frac{\partial V}{\partial t} = F(V(t), c(t), t), \tag{4.23}$$

subject to initial conditions $V(t_0) = V_0$. In the absence of external influences, i.e., $c(t) \equiv 0$, the trajectories of the dynamical system F may correspond to any of the growth curves discussed in Section 2.2. The control variable $c(t)$ describes the action of a therapy and may be a vector in the case of a combined treatment, like in Eq. 2.7, where increase of one of its components inhibits proliferation rate of tumor cells, and increase of another speeds up their death rate.

A second element is an objective function of state and control variables, which is to be minimized, and the general form of which can be as follows:

$$J = E(V(t_f), t_f) + \int_{t_0}^{t_f} R(V(t), c(t), t)dt, \tag{4.24}$$

where t_f is the time of the end of treatment. Functions E and R are referred to as endpoint cost and running cost, and one of them may be equal to zero depending on the chosen goal. The simplest example of a goal is to provide minimal tumor volume at the fixed end time of the treatment, $J = V(t_f)$. A less trivial situation consists in also including a penalty term, proportional to the total amount of drug, that may reflect, for example, the toxicity of a treatment or its monetary value: $J = V(t_f)+K \int_{t_0}^{t_f} c(t)dt$. Another way to consider limitations of this kind is to incorporate them within a problem as direct constraints. Imposed constraints are the third element of an optimal control problem, and usually two of their types are considered:

$$\begin{aligned} r(V(t), c(t), t) &\leq 0, \\ e(V(t_f), t_f) &= 0, \end{aligned} \tag{4.25}$$

referred to, correspondingly, as path constraints and endpoint (or boundary) conditions. With this approach, more stringent condition on the maximum total amount of drug can be set: $\int_{t_0}^{t_f} c(t)dt \leq C_{max}$. Another mandatory constraint is an upper limit in the rate of drug inflow: $c(t) \leq c_{max}$. Of note, the state equation, Eq. (4.23), can be by itself referred to as a (first-order) dynamic constraint.

The solution of the imposed problem, i.e., an optimal control problem, is the path of the control variable $c(t)$ that minimizes the objective function, given by Eq. (4.24) for a dynamical system (4.23) under constraints (4.25). One major approach for optimal control problems is the use of *indirect* methods. They are most often based on Pontryagin's maximum principle, or the dynamic programming principle, that reduce the initial problem to an alternative problem, which contains analytic expressions for the conditions of optimality. Their solution results in a set of differential equations, that govern optimal control. Usually, an optimal control represents a concatenation of so-called bang controls, $c(t) = 0$ and $c(t) = c_{max}$, and singular arcs, which are time-varying dosing regimes, typically governed by feedback formulas, that depend on the current state of the system. The transition between different types of controls is governed by the behavior of auxiliary switching functions. The optimal control that consists of two bang-controls with instantaneous switch between them, is referred to as bang-bang control.

Indirect methods can be relatively simple and therefore very useful for consideration of dynamical models governed by linear or weakly nonlinear systems of ODEs with continuous control functions and fixed time period of treatments. Their use can often guarantee the global optimality of the solutions, and therefore it may be tempting from a mathematical point of view to simplify a problem into a form more easily tractable by indirect methods. A prominent example is the use of objective functions with squared control variables, e.g., $J = \int_{t_0}^{t_f} c(t)^2 dt$, which considerably simplifies the analysis. However, while such terms arise naturally in physical problems (in relation to the energy of a system), it is difficult to assign reasonable biological meaning to them. Nevertheless, such objective functions are commonly used in biological optimal control problems (see [235] for review). The use of continuous control functions also represents a simplification for the majority of treatments. For instance, external beam radiotherapy is administered in irradiations that last several minutes, and a lot of drugs are administered via rapid (compared to intervals between them) intravenous injections, after which their blood concentration decreases, in particular, due to their clearance from the body. However, in the case of drug administration the use of continuous control functions can be justified, e.g., when considering continuous infusion functions in a model that accounts for drug pharmacokinetics, or merely as approximations of blood level of a drug, that is kept close to the desired value by repeated injections. It is much more difficult to interpret from a biological point of view the delivery of irradiation as a continuous function.

Such approach is not popular, however, it exists and is based on modeling the radiation damage in the form that accounts for the repair of sublethal damage. As was discussed in Section 3.4, it becomes crucial when the interval between irradiations is less than several hours, and it must therefore be considered for continuous irradiation. The dynamics of tumor volume in such approach can be represented as follows:

$$\frac{\partial V}{\partial t} = F(V(t)) - \{\alpha + \beta \int_0^t w(s) exp(-\rho[t-s]) ds\} \cdot w(t)V(t), \tag{4.26}$$

where $F(V(t))$ is any of the standard growth curves, ρ is the tumor repair rate, and $w(t)$ is the control variable. This dynamics can be conveniently represented with a system of equations:

$$\begin{aligned} \frac{\partial V}{\partial t} &= F(V(t)) - [\alpha + \beta \rho r(t)] \cdot w(t)V(t), \\ \frac{\partial r}{\partial t} &= -\rho r(t) + w(t). \end{aligned} \tag{4.27}$$

In the case of constant control variable, $w(t) \equiv \hat{w}$, the rate of tumor damage tends to a steady state value corresponding to the linear-quadratic law:

$$\frac{\partial V}{\partial t} = F(V(t)) - [\alpha \hat{w} + \beta \hat{w}^2] \cdot V(t). \tag{4.28}$$

Unfortunately, we are unaware of works aimed at optimizing monoradiotherapy via this approach, but in the work [207] this approach is used to search for the solution of an optimal control problem for combined radiotherapy and antiangiogenic therapy with dynamics of microvasculature introduced in a way similar to the Hahnfeldt model, given by Eqs. 3.19, with the main modification that microvasculature is as well susceptible to radiation damage. The results suggest that the treatment that would minimize the tumor volume (treatment end time is not specified) should begin with a short maximum-dose administration of a single antiangiogenic agent. It should be followed by its sharp drop and a long period of its administration along a singular arc. This singular arc is governed by an optimal relation between the tumor volume and its carrying capacity, for which tumor cell elimination due to decreasing carrying capacity is maximized. During this period, the control on the antiangiogenic agent increases monotonically until the drug runs out. Of note, this solution is identical for the monoantiangiogenic therapy case. The accompanying optimal radiotherapy control is almost bang-bang, with a finite but very short switch from no irradiation to its maximum allowable intensity along a singular arc happening during the administration of antiangiogenic drug.

The difficulty of using indirect methods intensifies with the increasing complexity of a problem. In particular, derivation of analytic expressions for the optimality conditions may be extremely complex for highly nonlinear problems resulting, for example, from the consideration of temporal variations in tumor radiosensitivity [238]. *Direct* methods overcome such necessity. These methods transform infinite-dimensional optimal control problems into finite-dimensional nonlinear constrained optimization problems via discretization of the control and state functions on a time grid. The resulting problem can be solved numerically via nonlinear programming algorithms. It should be noted, however, that the use of indirect methods by itself rarely goes without numerical calculations, since the optimal control solutions often cannot be presented in a closed form and still have to be estimated numerically.

4.1.2. Optimization algorithms for pulse-like treatment administration

The use of numerical methods significantly increases the range of tasks that can be considered. In particular, optimizations of pulse-like treatment administrations can be naturally handled by numerical optimization algorithms. For example, consider the following general task of radiotherapy optimization. Let some dynamical system govern the growth of a tumor exposed to radiotherapy. One has to find an optimal fractionation scheme $\mathbf{D}$ expressed as a vector of non-negative numbers representing the values of doses measured in Grays. The irradiations are administered successively at 24-hour intervals for 6 weeks, so $\mathbf{D} = (D_i),\ i \in [1, 42]$. As the standard reference scheme the following vector can be used, which corresponds to a typical course consisting of 30 doses of 2 Gy delivered every weekday:

$$\mathbf{D^{st}} = (D_i^{st}),\ D_i^{st} = \begin{cases} 0 \quad if\ i = 6 + 7[k-1]\ \vee\ i = 7k, \quad k \in \mathbb{N}; \\ 2 \quad otherwise; \end{cases} \qquad i \in [1, i_{max}], i_{max} = 42. \tag{4.29}$$

The resulting scheme has to satisfy the constraint that the biologically effective dose delivered to the healthy tissue cannot exceed its value for the standard scheme:

$$BED(\mathbf{D}) \equiv \sum_{i=1}^{i_{max}} [(\alpha_h/\beta_h) \cdot D_i + D_i^2] \leq BED_{max} \equiv BED(\mathbf{D^{st}}), \tag{4.30}$$

where (α_h/β_h) is the ratio of normal tissue radiosensitivity parameters. The optimality of the scheme implies decreasing the value of the following objective function as much as possible:

$$F(\mathbf{D}) = \min_t(N(\mathbf{D}, t)), \tag{4.31}$$

where $N(\mathbf{D}, t)$ is the total number of tumor cells. That condition should correspond to the increase in the tumor cure probability [239].

Probably, the simplest algorithm that one may suggest for this task will involve random selection of a dose D_i and increasing it by a small parameter δ at the expense of decreasing another dose $D_j, j \neq i$ by a value leading to conservation of $BED(\mathbf{D})$. Then it should be checked whether the resulting scheme actually leads to the decrease of $F(-D-)$. If this is the case, the procedure can be repeated iteratively with the newly constructed scheme until there is no opportunity to further decrease $F(\mathbf{D})$. One can immediately see that the aspects of the dynamical system under consideration does not interfere with such algorithm, which makes it in principle applicable to models of any complexity, including discrete models. However, application of optimization algorithms to them is still a rare situation due to the resulting overall numerical cost of the problem [240].

Importantly, numerical methods of this kind cannot guarantee the global optimality of the solution, that is, in case of several locally-optimal solutions $\mathbf{D}$ is likely to converge to a solution, which is closer to the initial scheme. However, it is important to point out two aspects. Firstly, finding the globally optimal solution for a specific set of parameters is by itself a task of little practical use. All significant characteristics are likely to vary dramatically in a sample of patients, and therefore, for each person there should exist her/his own globally optimal schedule. A more practical task is therefore to find a schedule that will outperform the standard one in a wide region of the parameter space. Secondly, there exist different approaches leading to significant progress towards approaching globally optimal solutions compared to this most simple example [241]. For example, one of the straightforward options is merely repeating the simulations with various initial schemes. Notably, heuristic guesswork based on the knowledge of the problem can help to make significant progress in solving it.

A prominent example of a work that utilizes numerical optimization is [73], where the use of a non-uniform fractionation protocol is proposed by the optimization algorithm. It was shown by a preclinical study to significantly increase the survival rate of mice with glioblastoma compared to the standard scheme that has the same total amount of administered radiation (such constraint is suitable if $\beta_h \to 0$). In this work, the so-called simulated annealing algorithm was used in order to improve the performance in terms of optimality of the solution. In short and in relation to our simple example, this algorithm always accepts a scheme obtained at N-th iteration, $\mathbf{D_N}$, that provides decreased value of $F(\mathbf{D_N}) < F(\mathbf{D_{N-1}})$. But also, this algorithm sometimes accepts a scheme with poorer performance, that occurs with probability $exp(\phi N[F(\mathbf{D_{N-1}}) - F(\mathbf{D_N})])$, where ϕ is a positive constant. Note that this value always lies between 0 and 1 and tends to 0 with increasing number of iterations. The model in the work [73] considers dynamical radiosensitivity of tumor cells, being based on the assumption that radiosensitivity of the cells decreases after their exposure to radiation. Interestingly, the works taking into account uniform and constant radiosensitivity of tumor cells come, via similar numerical optimization techniques, to a conclusion that locally optimal solutions lie extremely close to the initial uniform standard protocols [242, 243].

Another approach, which demands, in general, significantly less iterations to find a locally optimal solution, was suggested in the work [244]. It represents an adaptation of the classical gradient descent method and can be, with some simplifications, illustrated via a block scheme depicted in Fig. 6. In this algorithm, during the first step of every iteration, it is determined to what extent a small increase of every dose influences the performance function $F(\mathbf{D})$. During the second step, every dose is increased or decreased by a value proportional to the measured change in $F(\mathbf{D})$ introduced by variation of this dose during the first step. As initial scheme, the most optimal among the uniform fractionation schemes is used. Note that this algorithm is deterministic in the sense that it does not involve a random selection of doses and will always provide the same result for the same task under the same set of parameters.

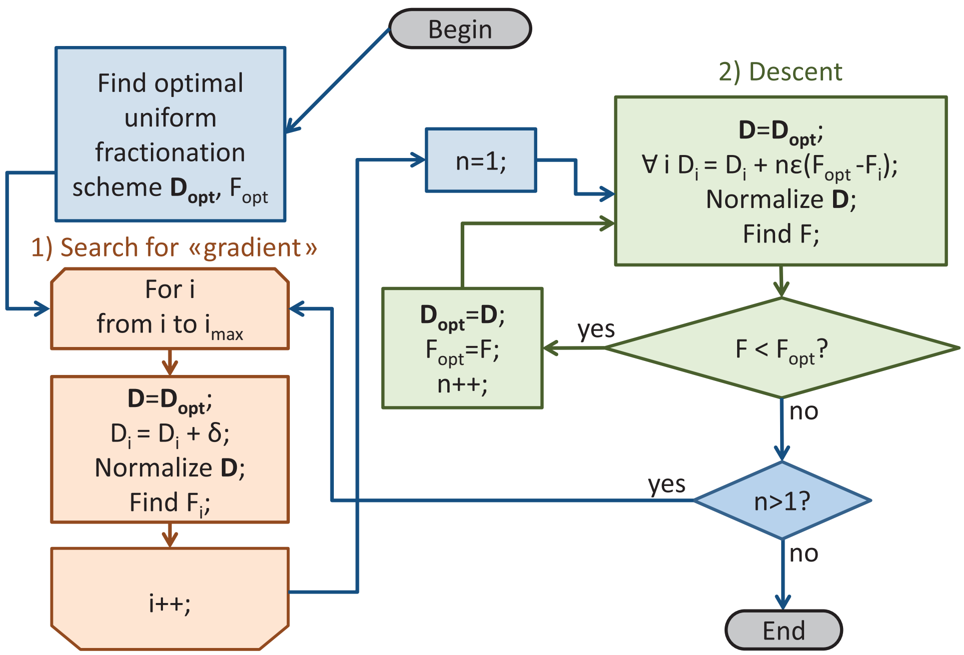

Figure 6: Block scheme of the algorithm for optimization of radiotherapy fractionation, δ and ϵ are its parameters. Normalization of a scheme $\mathbf{D}$ implies its adjustment by multiplication of all doses by the same coefficient in order to comply the restrictions $BED(\mathbf{D}) \leq BED_{max}$ (see Eq. 4.30) and $D_i < D_{max}$ $\forall i$. F is the objective function (see Eq. 4.31).

In the work [244] this algorithm was applied to a continuous spatially-distributed mathematical model of tumor growth in tissue. This model takes into account spatiotemporal changes in the radiosensitivity of tumor cells due to the variations of the levels of oxygen and glucose, assuming that the latter affects the proliferating activity of cells. The optimization procedure showed that in a large range of parameters the optimized schemes consist of two stages, the fractional doses during the second stages being significantly higher. This is justified, in particular, by the fact that close to the end of a sufficiently effective course of radiotherapy, the levels of nutrients inside the tumor rise, since fewer tumor cells remain there, that consume nutrients (see Fig. 7). Thus, radiosensitivity of the remaining cells increases, which makes the final doses more effective. A somewhat similar clinical method is known as concomitant boost technique, which was shown to be favorable in trials for some tumor types [245]. In this method, two fractions per day are administered near the end of a course. Such method also allows the control of the repopulation of small tumors, which regenerate more quickly than large ones. Other interesting results consistent with this notion were obtained by numerical optimization in the work [238] that considers varying composition and radiosensibility of a tumor. It aims at finding optimal fractionation of radiotherapy administered only on weekdays. Its results suggest, in particular, using larger fractions on Friday afternoons, when tumors are more sensitive than on the previous weekdays, and, in case of two fractions per day, using greater fractional doses in the evenings, that is, before longer 16-hour break till next irradiation.

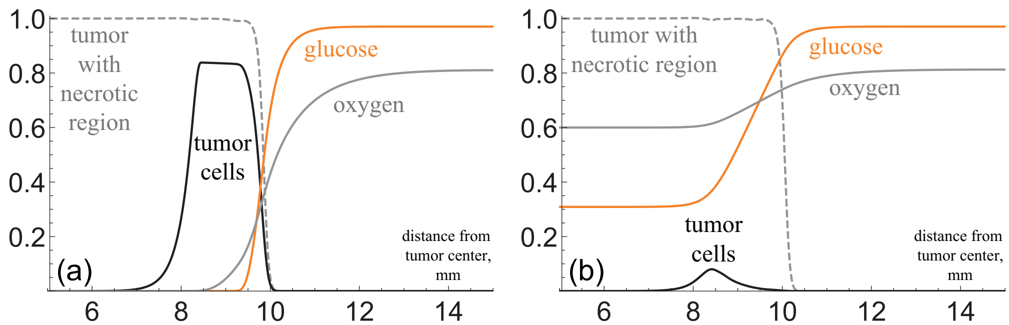

Figure 7: Example of the distributions of model variables in work [244] 1) on the first day of standard radiotherapy, 2) on its nineth day. Black line denotes tumor cells density, gray dashed line – total fraction of alive and dead tumor cells, orange and gray solid lines – levels of glucose and oxygen in tissue.

4.1.3. Other methods

The mathematical problem of protocol optimization can be reduced in such a way that it will be possible to obtain its solution in a rather straightforward manner, without using optimal control theory or optimization algorithms. An interesting example is given in the work [246], where a problem of optimization of radiotherapy of a slowly growing brain tumor, a low-stage glioma, is formulated in the following way. The volume of a tumor in the course of its free growth follows a classic logistic curve expressed by Eq. (2.1) with tumor capacity normalized to unity, and the fraction of surviving cells after a single instantaneous irradiation obeys the linear-quadratic law governed by Eq. (3.22). The task is to find a protocol that would keep the tumor volume below a certain critical level V^* for the longest possible time, not exceeding the total admissible damage to the healthy tissue expressed by Eq. (4.30). According to the authors' suggestion, such optimization should correspond to a decrease in the risk of malignant transformation of the tumor. Importantly, only uniform schemes are considered, with doses per fraction d considered as a parameter linked with the number of fractions $N(d)$ through the normal tissue damage constraint:

$$N(d) = \frac{BED_{max}}{d[\alpha_h/\beta_h] + \{d[\alpha_h/\beta_h]\}^2} \, . \tag{4.32}$$

This allows the derivation of the explicit formula for the time to malignant transformation:

$$TMT(N, \Delta, d) = N(d)\Delta + \frac{1}{B} log[\frac{V^*\{1 - V_N(d)\})}{V_N(d)\{(1 - V^*)\}}], \tag{4.33}$$

where V_N is the tumor volume at the time of the end of treatment $N(d)\Delta$:

$$V_N(d) = \frac{V_0[exp(BN(d) - \alpha d - \beta d^2)]^N(d)}{1 + V_0[\alpha - 1][\frac{\{exp(BN(d)-\alpha d-\beta d^2)\}^N(d)-1}{exp(BN(d)-\alpha d-\beta d^2)-1}]}. \tag{4.34}$$

Upon such a formulation, it is possible to select for every parameter set the optimal values of d and Δ, which fully characterize the optimal protocol via a numerically cheap direct search. The results of the work [246] suggest that metronomic schemes, characterized by substantially lower doses and by a greater time interval between them, should be much more effective for benign slowly-growing brain tumors than the schedules used in clinical practice. The latter are the same as those used for high-grade fast-growing brain tumors (i.e., glioblastomas). Metronomic schemes have been shown in simulations to be able to increase the time period at which the tumor volume is kept below the critical level by periods of an order of years. It should be noticed, however, that such schemes completely exclude the possibility of complete tumor elimination, since from their beginning, contrary to the standard approach, the tumor volume increases. Moreover, it stays near the critical value for a long time making its precise determination crucial to the success of metronomic schemes.

In general, suggesting an optimization for a specific therapy via mathematical modeling does not necessarily require a solution to an optimization task. Direct comparison of different therapeutic protocols can also be a valuable option able to yield promising results. Such approach is developed in the work [247] for the retrospective data of non-small cell lung cancer patients treated with a standard fractionation scheme. The results of the work suggest that the patient's proliferation saturation index, defined as the ratio of current tumor volume to its capacity, is an indicator of potential benefit of the use of hyperfractionated protocols, in which smaller doses are administered more frequently. Direct comparison of schemes is especially relevant for the models that use a discrete approach, since they will require high computational costs when solving optimization tasks with representative numbers of tumor cells [248].

4.2. Combining chemotherapy and antiangiogenic therapy

Modeling of combined chemotherapy and antiangiogenic therapy provides a representative example illustrating the difference of the results obtained via modeling approaches focusing on different aspects of the same oncological problem. The work [249] considers such combined treatment in correspondence with the classical methods described in Sections 2.2 and 3.2. The model used in this work is governed by systems of ordinary differential equations which may be represented as follows:

$$\begin{aligned} \dot{V}(t) &= -\gamma V(t) \ln \frac{V(t)}{K} - \phi f(t) V(t), \\ \dot{K}(t) &= bV(t) - [\mu + bV(t)^{2/3}]K(t) - \alpha g(t) K(t) - \beta f(t) K(t). \end{aligned} \tag{4.35}$$

The first equation describes the change of tumor volume with time, $V(t)$, under the influence of a chemotherapeutic drug with concentration $f(t)$. The second equation corresponds to the dynamics of carrying capacity of the tumor $K(t)$. The first term in it stands for the action of proangiogenic factors secreted by nutrient-deficient tumor cells. The second term represents the degradation of the capillary network, partly intrinsic and partly induced by proliferating tumor cells and therefore proportional to the tumor surface. The third and fourth terms correspond to an inhibiting action of both types of drugs on the tumor microvasculature. Thus, the cytotoxic drug interferes with angiogenesis as well, since this process involves active proliferation of endothelial cells. The goal of the problem is to find piecewise continuous drug delivery functions $f(t)$ and $g(t)$ that provide minimal tumor volume at a predefined time, $V(T)$. The total amounts of both drugs are determined a priori and their delivery rates cannot exceed given limits:

$$\int_0^T f(t)dt \leq F_{max}, \ \int_0^T g(t)dt \leq G_{max}, \ 0 < f(t) \leq f_{max}, \ 0 < g(t) \leq g_{max}. \tag{4.36}$$

The solution of this task suggests that for a large range of realistic parameters and initial conditions, the optimal treatment includes the control of the antiangiogenic drug identical to that discussed in Section 4.1.1. The delivery of the chemotherapeutic drug $f(t)$ follows a bang-bang control beginning in the middle of antiangiogenic treatment and continuing until the drug is used up.

Another approach for the consideration of combined chemotherapy and antiangiogenic therapy is suggested in the work [250] using a spatially-distributed model of tumor growth in tissue expressed in a PDE setting. The model describes tumor microvasculature via two variables that correspond to its normal and abnormal parts. The permeability of abnormal capillaries to drugs and nutrients is higher than that for normal ones. Capillaries grow due to the action of VEGF and degrade inside the tumor, which is similar to the previously described approach. However, a new considered aspect is that their structure becomes abnormal in the presence of VEGF, and it normalizes under its removal as a result of the antiangiogenic therapy. This result corresponds to the experimentally observed action of VEGF [150]. The model also considers simple pharmacokinetics for both drugs, and the drug injections are simulated as instantaneous increases in their blood levels.

The simulations of this model suggest a quite opposite type of optimization, which should allow eradication of more tumor cells. That is beginning the treatment with monochemotherapy and starting antiangiogenic therapy only at its end. This is justified by the fact that in this case more chemotherapeutic drug should flow through the walls of more numerous abnormal capillaries and get inside the tumor tissue. However, this result was obtained via direct comparison of different protocols in a fairly small parametric region. Moreover, the model accounts for diffusive limitation of drugs inflow from capillaries in tissue, which is valid only for small-molecular-weight drugs. For large molecules, the convective part of inflow from blood to tissue along with the fluid plays a considerable role. This process is influenced not only by the sizes and number of the pores, but also by the hydrostatic and oncotic pressures in the interstitial fluid, which are affected by antiangiogenic therapy [202]. All of the abovementioned results stress an implicitly supposed but extremely important principle of mathematical modeling: the results of model studies are correct only within the framework of the conditions and constraints of the model. Therefore, obtaining physiologically grounded results for combined chemotherapy and antiangiogenic therapy, and in particular, indicating under which conditions which protocol adjustments should be beneficial, represents a big challenge for mathematical oncology.

4.3. Cancer chronotherapeutics: taking simultaneously into account anticancer efficacy and unwanted toxicity, with circadian optimization

Circadian clocks and their genes have been evidenced in all nucleated cells in humans and animals, beginning with the fruitfly Drosophila melanogaster fifty years ago [251] and twenty years later with mammalians [252]. They have been found to control and synchronize not only hormonal secretion (this was known, e.g., for cortisol a long time ago), but also cell proliferation in organs of multicellular organisms. Among possible mechanisms for this control on cell divisions, the impact of circadian genes Per, Cry, Clock and Bmal1 on cyclins and Cdks (cyclin-dependent kinases) and on the "guardian of the genome", protein p53. They regulate passages from one cell cycle phase to the next one at checkpoints G_1/S and G_2/M, and they have been shown to be of major importance in cell cycle control. Different mathematical models have been proposed to represent this control. Some of them, very complete, concern the single cell level and rely on ODEs [253, 254]. However, to take into account heterogeneity in physiological age in cell cycle phases, G_1, S, G_2 and M, in dividing cell populations, that are not intrinsically synchronized (except in the very first divisions of a developing embryo), age-structured models are relevant. Circadian clocks have been shown to exert such control by *gating* on phase transitions [255], i.e., to allow or not cells of various ages in a given phase of the cell division cycle to transit to the next phase.

This control by circadian clocks has been mathematically represented in age-structured models, as mentioned earlier (2.3.2). In [121, 122], two different cell populations are considered, one tumoral and one healthy, without communication between them, but simultaneous targets of a chemotherapy, corresponding to a common clinical situation in which therapeutic effects and unwanted side effects concern distant cell populations, e.g., a colorectal cancer and the hematopoietic bone marrow. The goal pursued in chronotherapeutic optimization is to maximize killing in the tumor cell population while preserving up to a predefined level the healthy cell population, by taking advantage of different characteristics of circadian clock control on the two cell populations. Indeed, tumor cells are known to escape to a large extent control mechanisms coming from the surrounding host organism [21], and this is particularly true for synchronizing messages coming from the central circadian clock, whereas healthy cells respond normally to them. It is also shown in [122] that desynchronization of cells at phase transitions in a diving cell population accelerates proliferation (i.e, in the proposed linear model, increases the growth exponent).

This is represented in [122] by, respectively, loose ("lazy") and sharp circadian gating at checkpoint transitions between cell cycle phases, where the circadian clock influence is exerted by a cosine-like function of usual time t in factor of the gating transition function of age x. More precisely, in system (2.15), the transition function $K_{i \to i+1}(t,x) = \psi(t)\kappa(x)$, where ψ is a circadian cosine-like function and κ is some step-like function of age x (that can be identified on experimental data [121, 122]) authorizing cells in phase i to transit to phase $i+1$. The delivery of a chemotherapy that acts like a gate closer is represented by an added factor $(1 - g_i(t))$ (so that $K_{i \to i+1}(t,x) = \psi(t)\kappa(x)(1 - g_i(t))$, with $0 \leq g_i(t) \leq 1$), where the drug delivery flow g_i at the target site has to be optimized.

In fact, the objective and constraint target functions subject to control have been chosen to be not the cell population densities, but the growth exponents (first eigenvalues) of the two populations, λ_C and λ_H, respectively for the cancer and healthy populations. The optimization problem then consists in minimizing λ_C while maintaining λ_H over a given threshold Λ. And this works nicely, with the help of an optimization procedure described in [122]... at least it works theoretically, as no experimental preclinical nor clinical confirmation has been possible thus far. Of note, the shape of the g_i optimal function, that is obviously common for the two cell populations, as the drug is delivered through the general circulation, mimics the sharp circadian gating function of healthy cells, so as to sharpen the loose shape of the circadian gating function of tumor cells, multiplying it by zero when the closing is too "lazy", as illustrated in Figs. 8 and 9. The interested reader is referred to [122] for details and more figures.

Note however, as mentioned earlier about PK-PD, that to be of practical clinical use, the pharmacokinetic characteristics of the drug should be added to this study. Starting from an actual drug infusion flow in the general circulation, the resulting PK-filtered (likely by a sequence of ODEs) flow at the target sites might be difficult to adjust to the theoretically computed solutions $g_i(t)$.

4.4. Adaptive dynamics: taking simultaneously into account anticancer efficacy, unwanted toxicity and drug-induced drug resistance, with optimal control

The structure of the built-in targets for external control of the model presented in Section 2.3.3 has been chosen so that the target for the cytostatic drug does not increase the death rate, which is represented by a denominator under the intrinsic growth rate r. Indeed, cytostatic drugs slow down the cell division cycle, e.g., by blocking the sites of growth factor receptors, as in the case of so-called targeted therapies, that are often EGFR antagonists. On the contrary, the target for the cytotoxic drug, that is supposed to directly kill cells, additively increases the death rate, thus directly threatening the life of the cell population. In this sense, the model represents the evolution of two cell populations exposed to two drugs. The first one, the cytotoxic drug, is a brake that immediately endangers the survival of the population and strongly forces it to adapt by developing resistance (or rather, tolerance) to it. The other one, the cytostatic drug, represents a milder action as lifting the foot on an accelerator. The combination of the two drugs is a classic strategy

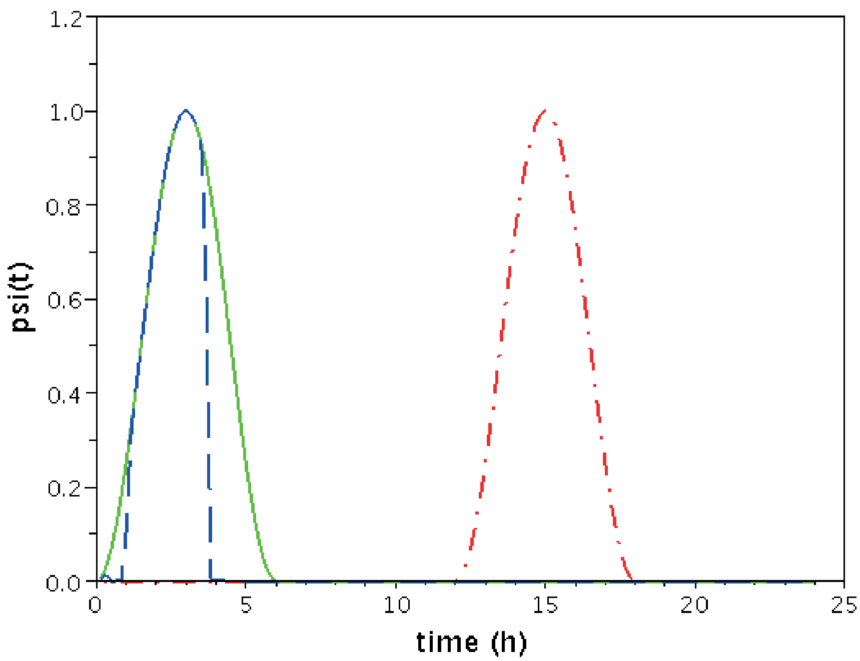

Figure 8: Drug and circadian controls, healthy cell ("sharp") population case. Cosine-like functions modelling the drug (g_i) and circadian ($\psi(t)$) controls for transition from G_1 to $S/G_2/M$ (dash-dotted line) and for transition from $S/G_2/M$ to G_1 in healthy cells. The "natural" drug-free control ($\psi(t)\kappa(x)$) for $S/G_2/M$ to G_1 transition corresponds to the solid line, the optimized drug-induced one ($K_{i\to i+1}(t,x) = \psi(t)\kappa(x)(1-g_i(t))$) to the dashed line. The drug (e.g., 5-FU) is assumed to be active during S phase, thus visible on $S/G_2/M$ to G_1 transition only. Reproduced with permission from [122].

in oncology. No wonder, the first resistance that has to be developed by an adaptive cell population is to the cytotoxic drug, and this will appear in the optimal control strategy.

Following the integro-differential model presented in Section 2.3.3, taking advantage of its built-in targets for external control, it is possible to apply optimal control methods with functions representing varying drug infusion flows on contact with the targets. These targets, wanted and unwanted, respectively, are tumor cell population and a general healthy cell population for unwanted toxic side effects. In fact, the model has been designed for this purpose. The differences between the two populations, as exemplified in simulations and shown in figures in [136], consist of differences in the functions d, r, μ that define the sensitivity (μ) of the populations to the drug and the proliferation and death rates (r, d). All are dependent on the resistance trait x, and they represent their capacity of adaptation to the deadly environment pressure induced by the cytotoxic drug.

These functions are the same for the two populations, but, roughly speaking, their parameters have been chosen so as to show twice as much reactivity in cancer cells as in healthy cells. As regards the cytostatic

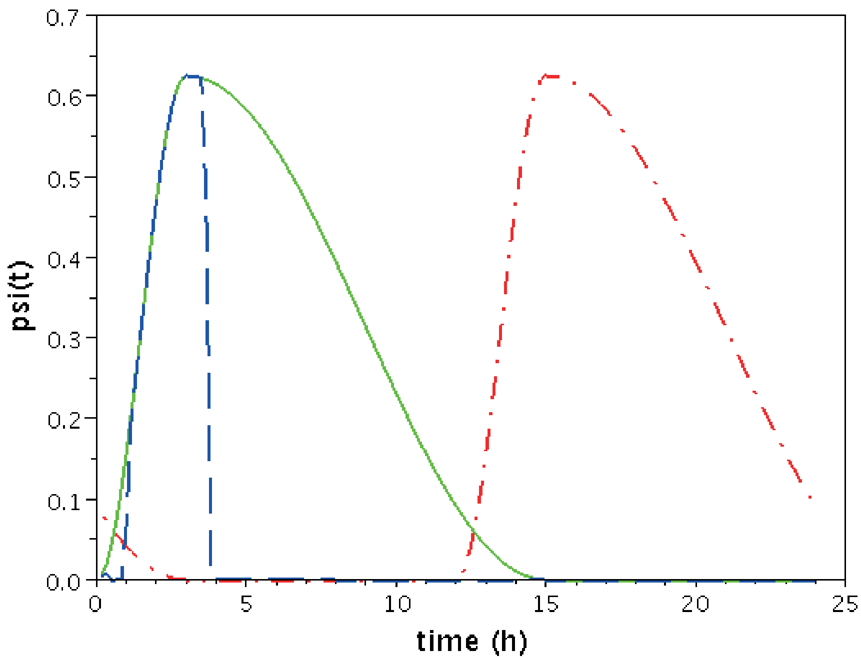

Figure 9: Drug and circadian controls, cancer cell ("lazy") population case. Cosine-like functions modelling the drug and circadian controls for transition from G_1 to $S/G_2/M$ (dash-dotted line) and for transition from $S/G_2/M$ to G_1 in cancer cells. The "natural" drug-free control ($\psi(t)\kappa(x)$) for $S/G_2/M$ to G_1 transition corresponds to the solid line, the optimized drug-induced one ($K_{i\to i+1}(t,x) = \psi(t)\kappa(x)(1-g_i(t))$)-induced one to the dashed line. The drug (e.g., 5-FU) is assumed to be active during S phase, thus visible on $S/G_2/M$ to G_1 transition only. Reproduced with permission from [122].

drug, the sensitivity of the cancer cell population to it has been chosen in simulations to be 100 times stronger than its equivalent in the healthy cell population. These choices are supposed to represent the relative plasticities (abilities to adapt to a changing environment) in the two populations.

As shown in [136], the optimal combined strategy consists in firstly applying a mild and constant dose of cytostatic, and no cytotoxic at all, so as to let the resistance phenotype decrease close to zero. Then it should be followed by applying the maximum tolerated dose of the cytotoxic drug for a brief duration, during which cancer cells are at the top of their sensitivity to the cytotoxic drug. Finally, the cytotoxic flow must be lowered to an intermediate dose while the cytostatic is maintained at its maximum tolerated dose. All these controls are bang-bang, except for a singular arc during the time of the increase to the maximum tolerated dose of the cytotoxic drug. The fact that the best strategy consists in particular in delivering nothing of the cytotoxic drug during a possibly long period of time may seem counter-intuitive. However, it is actually performed in clinical oncology, provided that the tumor burden has been firstly reduced to a reasonable extent. Then the question comes: what to do next? What is often practiced in oncology is then the so-called "drug holiday" strategy: do nothing with the aggressive drug for a sufficient duration of time. It may be considered as a a way to let the patient recover from toxicity, but also, as shown by this theoretical study, to prepare a patient's tumor to be maximally receptive (sensitive) to the cytotoxic drug.

The results of this optimal control strategy are summed up in Fig. 10 at an arbitrary fixed horizon time $T = 30$.

As mentioned in Section 2.3.3, this integro-differential model describes completely reversible dynamics. It is suggested in [127] that a non-genetic phenotypic change may become fixed by a subsequent mutation (in which case a PDMP, with a probabilistic mutation rate depending on the evolution of the phenotypic trait during the deterministic process time, would be a complementary modeling option). The above mentioned strategy should be used before such mutation, so as to render it improbable.

To the best of our knowledge, this optimal control strategy is still theoretical, and the clinical drug holiday strategy, for which this study offers a rationale, is still empirical in clinical oncology. Note that other studies with different settings, that also apply optimal control methods, begin to emerge in the medical oncology literature, as exemplified by [256].

4.5. Testing different treatment protocols with hybrid models

Hybrid discrete-continuous models provide an appropriate method to study cell population dynamics with some limitations, as previously discussed in Section 2.4, related to the number of cells and to the determination of parameters, especially for intracellular regulation mechanisms. In this section we will consider some examples of the application of hybrid models to test treatment protocols in blood cancers, such as leukemia or multiple myeloma [257, 258, 259]. We will consider off-lattice hybrid models where biological cells are treated as soft spheres with pairwise mechanical interaction between them, their motion being described by Newton's second law. Cell fate, that is the choice between proliferation, differentiation and death, is determined by the intracellular regulation described by ordinary differential systems of equations for the intracellular concentrations. It can also be influenced by various extracellular molecules (nutrients, hormones, growth factors), the concentrations of which are described by partial differential equations.

4.5.1. Chronotherapy in Ara-C leukemia treatment

Leukemia is a malignant disease characterized by abnormal proliferation of immature blood cells or hematopoietic stem cells within the bone marrow. There are four types of leukemia: myelogenous and lymphocytic, according to the hematopoietic lineage involved in the disease. Each of them can be acute (rapid increase of immature blood cells, with their fast invasion of the bone marrow, endangering the patient's life) or chronic (slowly established excessive production of immature blood cells, clinically well tolerated to a large extent, possibly during years).

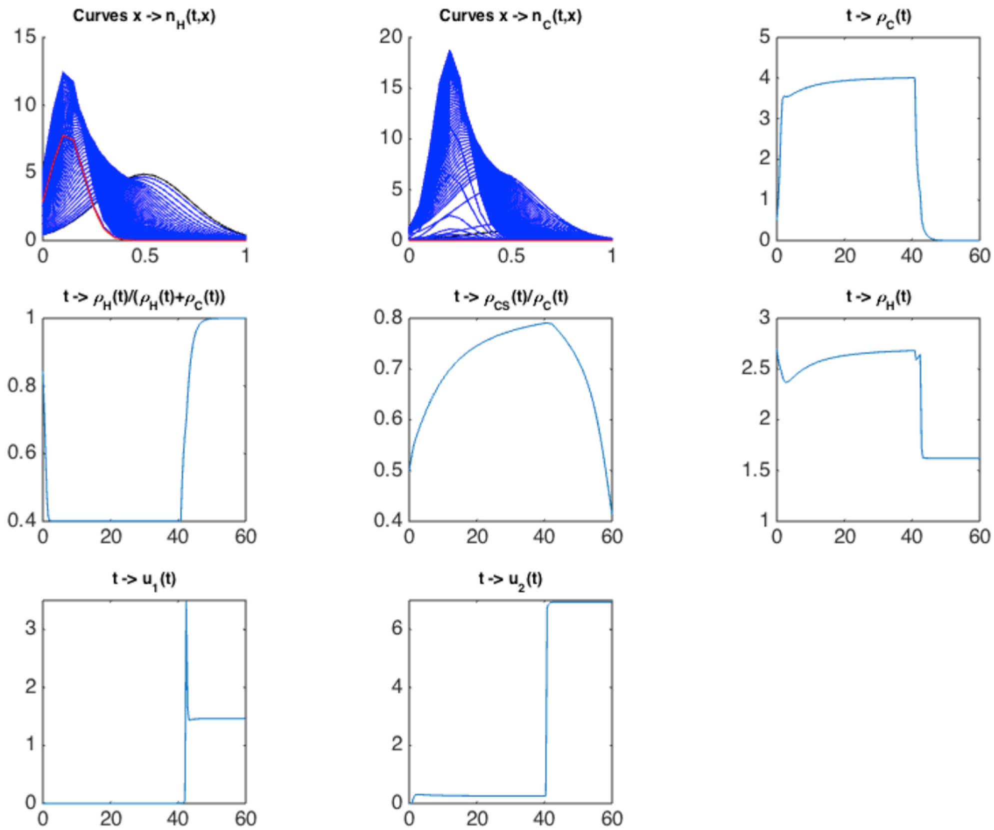

Figure 10: Optimal control strategy to circumvent drug resistance. Sequentially, from left to right and from top to bottom: **1.** and **2.** Evolution of resistance trait x in the two populations, healthy (n_H) and cancer (n_C). Starting from a medium-centered gaussian distributed trait, both populations evolve toward a sensitive trait around $x = 0.1$. However, when the drugs are delivered at their maximal tolerated doses (MTD), the healthy population trait sticks to this value, whereas the cancer cell population evolves towards resistance but quickly crumbles down. **3.** Evolution of total cancer population, firstly converging towards a stationary value, then crumbling down when the drugs are delivered. Compare with **6.** for the healthy population, that is also affected, however constrained to remain over a predefined threshold. **4.** Evolution of the ratio of the healthy over total population: a minimum threshold of 40% of the initial value is strictly preserved. **5.** Evolution of the ratio of drug-sensitive $\rho_{CS}(t) = \int_0^1 (1-x) n_C(t,x)dx$ over total cancer cell population $\rho_C(t) = \int_0^1 n_C(t,x)dx$. **7.** and **8.** Solution to the optimal control problem: delivery flows for cytotoxic drug u_1 and cytostatic drug u_2, illustrating the "drug holiday" strategy, provided that the situation is under control ("what to do next?"). Firstly do nothing with the life-threatening cytotoxic u_1 and almost nothing with the milder cytostatic u_2 until the cancer cell population has become sensitive enough. Then hit hard (at MTD) for a short period of time with u_1 (and u_2), thus avoiding the effects of fast adaptation to drug resistance in the cancer cell population. Finally hit at MTD with u_2 and at a moderate dose with u_1. Reproduced with permission from [136].

During the past decade, the first line of therapy for acute myelogenous leukemia (AML) patients has been anthracyclins (daunorubicin or idarubicin) in combination with cytosine arabinoside (Ara-C). The latter is characterized by a short half-life and targeting cells during DNA synthesis (S-phase of the cell cycle). After intravenous administration, the drug is rapidly metabolized, by deamination in the liver and kidney, to its inactive form uracil arabinoside (Ara-U). When in the bone marrow, it penetrates the membrane of proliferating cells and it can be transformed into its active form arabinoside triphosphate (Ara-CTP), which participates in DNA duplication, replacing natural nucleotides. When the proportion of Ara-CTP in the DNA becomes sufficiently high, the cell dies by apoptosis.

Ara-C acts on all proliferating cells whether they are leukemic or normal. Therefore, the aim in optimizing the drug administration schedule is to increase cytotoxicity for leukemic cells and tolerance for normal cells. One possible approach to this problem is based on chronotherapy (Section 4.3), in which drug administration is varied in time (chronomodulated) to exploit the small differences in the temporal organization of the cell cycle between normal and leukemic cells.

In the case of erythroleukemia, one of the sub-types of AML, erythroid progenitors show specific daily variation in their DNA synthesis activity. Twenty-four-hour studies of healthy bone marrow cells showed circadian (about 24 hour) rhythms in proliferative activity [260]. On average, the percentage of total bone marrow cells in the DNA synthesis phase is greater at midday than at midnight. Myeloid and erythroid precursor cells display a daily peak in the S-phase at 1:00 p.m. [261]. In contrast, leukemic cells display reduced rhythmicity or can even be arrhythmic [262]. This difference between healthy and leukemic cells can be exploited to reach maximal efficacy and minimal toxicity by treating patients at specific times of the day. This strategy, termed chronotherapy, aims at decreasing toxicity and improving efficacy of the treatment by synchronizing drug delivery with biological rhythms [263, 264].

A hybrid discrete-continuous model is used to describe leukemia treatment based on periodic administration of Ara-C where normal cells are assumed to have a circadian rhythm that influences their cell cycle progression, whereas leukemic cells are assumed to escape circadian rhythms [257]. A detailed pharmacodynamic/pharmacokinetic model of Ara-C is proposed and used to simulate the treatment. It has been shown that the period of treatment and delivery time can have a strong influence on the outcome of treatment with the best treatment protocol (among tested) based on periodic 48 hours drug administration at 1:00 a.m. One should also note that treatment should be adapted to the individual patients taking into account the duration of the cell cycle of leukemic cells.

4.5.2. Erythropoiesis and multiple myeloma

Multiple myeloma (MM) infiltrates the bone marrow and causes anemia by disrupting erythropoiesis, which occurs in structural and functional units in the bone marrow termed erythroblastic islands (EBIs) [265, 266]. An EBI consists of a central macrophage surrounded by erythroid cells in various stages of differentiation with more centrally located colony-forming units-erythroid (CFU-Es), their immediate progeny the proerythroblasts (Pro- EBs) and more peripherally located maturing erythroblasts [267] (Fig. 11, upper image). Central macrophages and marrow stromal cells produce growth factors required by CFU-Es and ProEBs: stem cell factor (SCF), under normal conditions, and bone morphogenetic protein-4 (BMP4), under erythropoietic stress conditions [268, 269].

Myeloma cells infiltrating the bone marrow may impair function and structure of EBIs by secreting cytokines. Transforming growth factor-β (TGF-/*beta*) secreted by myeloma cells may decrease adhesion and growth of earlier progenitors, thereby decreasing CFU-E numbers [270]. Expression of FAS ligand and TNF-related apoptosis-inducing ligand (TRAIL) by myeloma cells may induce apoptosis of erythropoietin (EPO)-dependent progenitors [271, 272]. MM patients may have decreased EPO production due to renal disease from nephrotoxic monoclonal immunoglobulins or light chain components [273]. A second mechanism by which infiltrating MM can decrease erythropoiesis is physical disruption of EBIs (Fig. 11, lower image). Total macrophages in bone marrows of patients with myeloma are inversely correlated with the area of marrow infiltrated by myeloma [274]. Although central macrophages of EBIs are a minor percentage of total marrow macrophages, a proportional decrease in the central macrophage population of the marrow would decrease EBI numbers and erythropoietic activity.

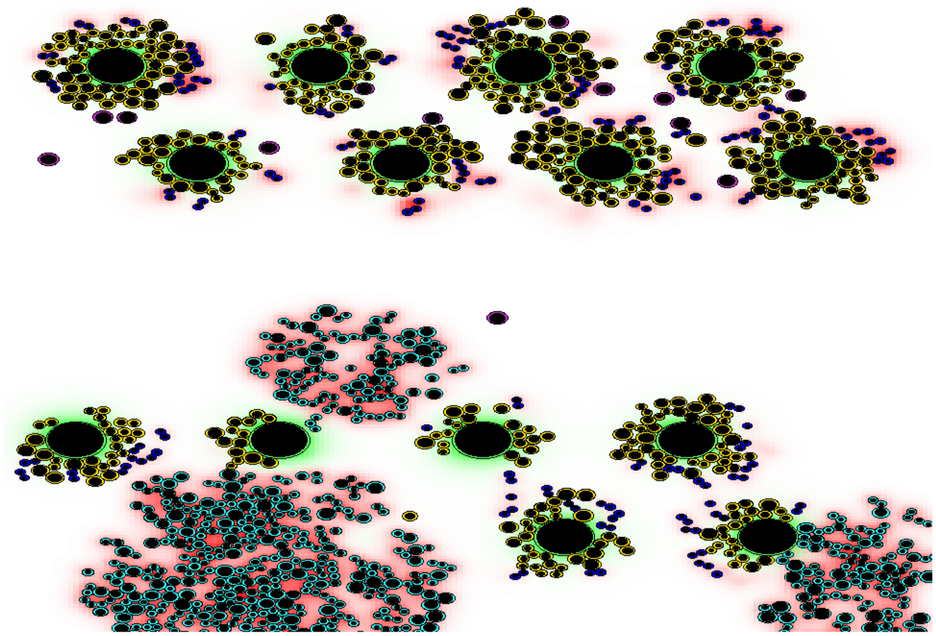

Figure 11: Erythroblastic islands in the normal bone marrow (upper figure) and during the invasion by multiple myeloma (lower figure). Central macrophages are the large central cells in the EBIs. CFU-E and erythroblasts are the yellow cells surrounding the central macrophages. Marrow reticulocytes prior to their entry into the blood are dark blue on the periphery of the EBIs. Myeloma cells are light blue. Black solid circles inside cells show their incompressible parts. Secreted proteins shown extracellularly are green for BMP4 and/or SCF produced by central macrophages and red for FAS ligand produced by mature erythroblasts and reticulocytes within EBIs, and FAS ligand and/or TRAIL produced by infiltrating myeloma cells. Reproduced from [258] with permission.

A hybrid discrete-continuous model of erythropoiesis based on the EBI structure and function [275] has been used to study the relationship between marrow infiltration and the degree of anemia in MM [258]. Models are developed and simulations performed using data from newly diagnosed MM patients who were treated uniformly with lenalidomide, bortezomib, and dexamethasone (LBD) chemotherapy [276] to induce remission prior to autologous stem cell transplantation. Mathematical models provide information about the degree of marrow infiltration by MM, its effects on EBI structure/function and the development of anemia, and the potential of nonerythrotoxic therapies to reverse marrow infiltration and improve anemia.

For mathematical modeling of the patients' responses to LBD chemotherapy, parameters were chosen to fit the clinical data, and different variations of the LBD protocol were considered in [258]. With the same total amount of chemotherapeutical drugs, the second protocol (LBD2) intensifies therapy by administering in week one of each cycle the total LBD doses normally given over two weeks. The third protocol (BD) reduces intensity by using two drugs (bortezomib, dexamethasone) while increasing the number of cycles from four to five within the similar 112-day period. Based on these simulations, LBD2 would be most effective at clearing myeloma from the marrow. However, in practice it would be more neurotoxic since the concentration of drugs during the first week of every cycle is higher. Less intensified therapy with BD would be less effective than LBD at clearing myeloma from the marrow.

Drug resistance to tyrosine kinase inhibitors (TKI) in multiple myeloma is studied in [277] with a similar hybrid model. It is shown that the combination of high-dose pulsatile TKI treatment with high-dose daily PPP inhibitor therapy can potentially eradicate the tumor with controlled toxicity effects of the chemotherapy.

5. Conclusions and perspectives

Mathematical methods have already become necessary tools in oncology with numerous examples such as the linear-quadratic model for radiotherapy planning [190], pharmacokinetic models of drugs via statistical processing of experimental data [278], the use of artificial intelligence in analyzing medical images and genomic data [279], optimization of intensities of external radiation beams in order to conform the tumor shape [218]. These are just a few instances of problems in which computer simulations already bring significant benefits in clinical oncology. However, until today, little success has been achieved in clinical oncology by mathematical modelling of cancer, understood as the use of dynamical mathematical models, which consider tumor – and often its microenvironment – as a single dynamic complex system. Mathematical modelling generally pursues two main objectives: qualitative explanation and description of biological phenomena, that accompany tumor growth and therapy, and optimization of treatment protocols. Its incorporation into clinical research is a long and laborious road, which should overcome traditional difficulties of interdisciplinary research in a very complex and dynamic field at the border of fundamental science and public health. Some of the corresponding aspects are discussed below.

5.1. Why have mathematical models met thus far so little success in clinical oncology?

Coming from different schools of applied mathematics, many different methods have been proposed to represent the dynamics of cancer cell populations and strategies to optimize the delivery of anticancer drugs or other means of therapeutic control on cancer. However, to the best of our knowledge, nothing has emerged as a prominent clinical methodology to optimize clinical anticancer treatments at patient's bedside. In the early 2000 years, some collaborations of mathematical modelers with innovating clinical oncologists [93, 94] have led to apparently fruitful results with theoretical strategies that were experimented in clinical oncology. Nonetheless, no spectacular benefits for the patients seem to have emerged from such collaborations. Optimization and optimal control, strongly though they may have been recently advocated in journals aiming at clinical applications [237], are mathematical methods that have thus far failed to convince of their interest most clinical oncologists.

This situation may due to at least two reasons. One is the intrinsic difficulty to take into account all dimensions of the cancer disease in its complexity, associated with the increasing specialization of research teams involved in therapeutics, which leads associations of mathematicians and clinicians to approach a very limited part of the scenery (e.g., representing and optimizing the delivery of a given targeted therapy in a given cancer), leading to limited and usually short-lived clinical improvements, in particular because resistance to the treatment inevitably develops. Another one is the limited training of oncologists in mathematics and physics of living matter, which in particular makes most of them look away when equations are presented to them, to say nothing of the limited time clinicians can dedicate to theoretical considerations.

The world of oncology is not totally devoid of researchers trained in both mathematics and medicine at a theoretical and practical level; however, very often, even when they are animated with the best will, clinicians are tempted to propose a limited problem to mathematicians, taking them more for "math providers" (i.e., technicians called to mathematically treat biological problems they have defined on their own, and not interactively) than for scientific collaborators on equal terms (i.e., from whom they may learn even in their own field of knowledge, provided that these collaborators should avoid the catastrophic attitude of some mathematicians saying: we shall now explain you how cancer works). Conversely, a symmetric utilitarian attitude exists among mathematicians and engineers, tending to make them use open questions in cancer as just "food for thought". Nevertheless, the complexity of the cancer disease affects not only clinical oncology, this is also true of cancer modeling, and a dialogue on equal terms and without prejudice between the two sides can be enriching and full of new opportunities.

5.2. What could be done to enhance the penetration of mathematical models in clinical oncology

In oncology, as in many fields of clinical medicine, staff meetings involve psychologists who shed complementary light on patients' cases. Why not applied mathematicians? Some research teams in oncology already hire philosophers of science, who are seldom trained as clinical physicians. We contend that professional mathematicians with clinical sensitivity, possibly having partially or completely followed a course of medical studies, might be useful in proposing at least a dynamic view of the disease of a given patient.

Of course, the higher in both fields a training will be, the most useful to a clinical team will be the immersed mathematician. This is particularly true of mathematicians trained in optimization and optimal control, who are thus far not so many worldwide, so that this situation should be improved in university training courses, with possible specialization in oncology and promised immersion in clinical oncology teams.

There is clearly a long way to go to reach such a situation. Likely, to obtain a favorable advice towards it from medical schools, case studies with spectacular improvements for the benefit of the patient due to mathematical models, and their wide broadcast worldwide, would be a big push forward for mathematics in interdisciplinary clinical studies [237].

5.3. Need to rethink cancer? The so-called "philosophy of cancer"

Confronted with the undoubtable successes met in the last 50 years in clinical oncology, nevertheless encountering more and more limitations as new treatments emerge, oncologists together with evolutionary biologists, immunologists, physicists and mathematicians, have begun to lower barriers between their disciplines. This trend of interdisciplinary research has recently reached even up to philosophers [2, 46, 280, 281, 282] who have thus emerged as a community of "philosophers of cancer".

The will to think cancer in a transdisciplinary way seems however to have widely avoided so far the atavistic theory of cancer, that nevertheless appears at least in a recent chapter by C.H. Lineweaver and P.C.W. Davies [44] of the book [283] dedicated to the physics of cancer. We here again advocate its importance, as it has already been comforted by some convincing observations (already mentioned earlier and in the seminal article [37]) and as it unifies in a consistent way old and modern views on cancer. Moreover, it allows to think cancer therapeutics differently [284, 285]. It certainly suffers from direct evidence, as factual arguments in its favor have come mainly from paleogenetics [41, 42, 43] and phylostratigraphic analyses between species of multicellular organisms [39, 40], including humans. This may explain why it is so often overlooked by cancer biologists, who are more accustomed to tracking hypotheses in direct experimental observations. Note, however, that it is strongly advocated, not only by physicists [37, 44] *a priori* external to cancer biology, but also by oncologists [286, 38]. Does this situation of legitimate doubt in science not remind us of the misfortunes of Alfred Wegener's theory of continental drift when he proposed it to the community of geologists a hundred years ago? It is now well established as, starting from a unifying scientific hypothesis, it has given rise to the theory of plate tectonics, which has been abundantly proved from geological evidence a few decades after Wegener first stated his hypothesis on the drift of continents. Closer to the topic of this review, the somewhat limited acceptation that Darwin's book "The evolution of species" met when it was published is another example of a theory that took some time to be generally accepted by the scientific community. Can we expect that a comparable fate awaits the atavistic theory of cancer, or will it be finally rejected? We might have to wait for some time until more scientific methods emerge to support it or reject it by more arguments. Thus far, it is only a good candidate to the role of a physically plausible, unifying theory of cancer.

We contend that the role of mathematics in this more and more transdisciplinary field of research that is modern oncology, must be taken not only as a tool to analyze biophysical phenomena. It is also a powerful method of analysis in eco-evolutionary biology of species (this is already the case), which naturally extends to cancer thanks to the atavistic theory of cancer (this is beginning to also be the case). This should open new golden gangways between oncology, biology, philosophy and mathematics.

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