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Effects of the obesity on optimal control schedules of chemotherapy on a cancerous tumor

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ABSTRACT

Obesity as a risk factor has been found in different types of cancers such as breast cancer and colorectal cancer among others. This challenges us to study the cancer–obesity relationship and the tumor response to chemotherapy. In this work, we study and analyze optimal control protocols for chemotherapy treatments for a mathematical model of cancerous growing tumor that is interacting with the healthy cells, the immune system cells and the stored fat in the organism. This model considers different cell populations using a population dynamics approach. Our main interest is to provide insights about the qualitative and quantitative possible affects of a low/high caloric diet on the chemotherapy protocols when different immune system responses are considered. According to our model the immune system response and the diet are important factors and their inclusion could lead to improved chemotherapy protocols.

1. Introduction

In this work, we propose and analyze a cancer–obesity model for the growth of a tumor where chemotherapy schedules are obtained using optimal control techniques. Our aim is to study how the diet can affect different tumor growth scenarios when chemotherapy is applied. This is motivated by the reported relationship between obesity and cancer in several experimental studies such as [1–4]. Among the cancers that present this relationship are colorectal cancer, breast cancer in postmenopausal women, endometrium cancer, renal cancer, and esophagus cancer [5]. Our model includes an equation for the stored fat in the organism based on logistic growth which includes a parameter to model the carrying capacity of the system. We claim that this parameter, the carrying capacity, is related to anthropometric measurements of in-body fat such as the Body Mass Index (BMI) and Waist-to-Hip ratio. Moreover, a high direct correlation between each of these anthropometric measurements and the increment in the mortality rate due to cancer has been found, for instance, in breast cancer [6], and [7].

The mechanisms that contribute to an increment in the mortality rate in obese people are complex, and usually, they are not well understood as it is described in [8]. However, in order to get some insights about this problem, we assume that an increment of fat in the organism increases the growth rate of the tumor. This idea is suggested by the fact that tumor progression uses the glycolysis process to obtain energy. This process consists in generating energy from glucose without

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the presence of oxygen which demanding high quantities of insulin and calories, see [3]. In fact, therapeutic strategies have also been proposed to explore treatments based on the interruption of the glycolytic metabolism as it is described in [9].

Another aspect included in the model is the dynamics of the immune system cells, particularly the T8+ cells. This type of cells are related to the regress of small tumors caused by the response of the immune system. We assume that the immune response is a natural control that kills tumor cells in order to keep a healthy organism. Besides that, the interaction between adipose cells and the immune system has been established in the literature. There is experimental evidence that obesity causes chronic inflammation which is also related to bad prognosis of cancer, see [10]. On the other side, it has been found that the presence of immune cells in tumors can promote the angiogenesis which is necessary for the tumor growth and spread, a detailed discussion on this topic can be found in [11]. Let us say, that this phenomenon is not considered in our model.

A literature review of the models of obesity and cancer shows different approaches. One of them corresponds to the use of simulation models to assess background mortality of obesity on cancer patients [10]. In the same fashion, there are regression models which attempt to establish a direct relationship between the BMI and the risk of developing cancer, see for example [12]. A different approach is to model the obesity–inflammation–cancer relationship by an agent-based model such as in [13]. There, the authors use evolutionary principles to link the involved mechanisms with epidemiological data that relate inflammation and oncogenesis. They also proposed a process by which inflammation drives tumor mutability and adaptive potential. This is a crucial mechanism to understand tumor progression. There are also models that study the growth dynamic of adipocytes or fat cells which focus on the description of their size distribution or signaling chain to activate different cell processes such as [14,15]. However, in order to keep a simple model, we have not included an equation for such a population, but instead for the stored fat in the fat cells.

The use of optimal control to model a chemotherapy treatment is not a new idea, but it is a well known tool to study chemotherapy protocols with constraints. For example, in [16] it is used optimal control chemotherapy treatments to study the resistance to a drug in a heterogeneous cancerous tumor. There, it is concluded that the drug must be given at the maximum rate in order to reduce the resistance. This type of conclusion is also reported in [17]. An overview of chemotherapy models using optimal control is presented in [18] and a discussion of the potential of application of this technique is given in [19]. Our model proposal is based on the De Pillis and Radunskaya model, reported in [20,21] which also models the chemotherapy treatment using control theory. Their goal is to minimize the tumor cells while keeping the healthy cells above a predetermined level. However in their model, the obesity effect on the cancer development is not considered.

This paper is organized as follows. In Section 2, we describe the model and the equilibria analysis considering the obesity factor. In Section 3, we pose the optimal control problem for our model by describing the objective function, the restrictions and the co-state variables. The next Section 4, we explain the results of the application of optimal control and we compare scenarios where the organism gains or loses weight for different immune system parameters. Finally, conclusions on the optimal control protocols are presented in Section 5.

2. A cancer–obesity model with chemotherapy

In this section, we present and describe a cancer model for the growth of a tumor under the immune system surveillance and the effect of obesity on the tumor growth rate. As we have mentioned, this model is based on the model by De Pillis et al. [20], but we have introduced an additional equation to model the dynamics of the stored fat in the cells in order to model the effect of obesity on the tumor growth rate. Moreover, we will include a continuous chemotherapy treatment by means of the optimal control approach in Section 3. In the following paragraphs, we describe the general assumptions made for this model.

2.1. Model assumptions

The development of a cancer tumor is a complex biological process that involves the interaction of different cell populations. Our model assumes the following:

Immune response. We consider that the presence of immune cells and that their growth can be stimulated by the presence of tumor cells, and also, that tumor cells can be destroyed by immune cells. This kind of interaction corresponds to an immunogenetic tumor and has been reported in [11]. This means that the response of the immune system is to kill the tumor cells and a possible outcome could be a tumor regression. There are other possible effects, for example, the presence of immune cells in a tumor could lead to the release of pro-angiogenic and metastatic factors [11], but in this model such effects are not considered and will be a matter of future work.

Immune surveillance. It refers to the capacity of the immune system to stop the growth of small tumors preventing the formation of large tumors. We assume that immune surveillance can fail to control a small tumor, and eventually it could grow rapidly leading to a large cancerous tumor.

Competition. Other assumption in this model is that normal cells and tumor cells compete for the available resources. For the immune and tumor cells, we assume a Lotka–Volterra type competition.

Fat cells. We have assumed that the amount of fat increases following the logistic growth law in which its solution tends quickly to the equilibrium point $1/K$, where K is the carrying capacity of the system. The logistic equation solution is similar to the behavior reported in [15], where it is shown that the growth rate of mice fat cells under a high or low caloric diet