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A mathematical model for the effect of obesity on cancer growth and on the immune system response

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ABSTRACT

Several experimental studies have found that obesity is a risk factor for different types of cancer. In this work we present a mathematical model of cancer tumor growth that takes into account the immune system response and the effects of obesity on the organism with cancer. This model consists of four ordinary differential equations with a logistic equation for the growth of the amount of fat stored. We analyze the stability of the equilibria obtained using parameter values reported in the literature. Our simplified model succeeds to reproduce different scenarios reported in clinical studies, such as, the negative effect of obesity on the cancer patient and the anticancer effect of a low caloric diet.

1. Introduction

Obesity and excess weight are two major problems mostly caused by a sedentary life style and overnutrition. This situation is a public health issue in several countries all around the world. The main problem is that obesity might cause other serious diseases which could be fatal, for example type II diabetes, hypertension, heart problems, cancer, etc.

Cancer is also a health problem that causes many deaths every year. The relationship between cancer and obesity has been observed in several experimental studies such as [1–4]. Moreover, in 2002, the International Agency for Research on Cancer (IARC) reported sufficiently linking cancer-obesity evidence for colorectal cancer, breast cancer in postmenopausal women, endometrium cancer, renal cancer, and esophagus cancer [5].

In this work, we are interested in the relationship between cancer and obesity. We propose and analyze a cancer-obesity model in ordinary differential equations. We focus on the role of obesity as a risk factor which might cause the cancer to be more aggressive. Also, we would like to take into account the interaction between adipose cells and the immune system. This interaction has been reported in [6], which describes that an immune response such as inflammation is caused by adipocytes or fat cells. Let us remark that the effect of obesity on tumor growth is well known, but we know of no papers where the interrelations are explicitly given or that the effects of obesity are quantified. Our aim is that this study, together with potential clinical experiments, help better understand what is the effect of obesity on tumors. Our model could be

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helpful to answer questions such as the effect of obesity on the tumor growth rate, the possible reduction in tumor size when obesity is decreased, etc.

A review of the existing models of obesity and cancer shows different approaches. Some models address the obesity from a mathematical point of view by using the ideas of epidemiological models to describe the spread of the obesity as a contagious disease [7,8]. Another approach focuses on the study of the growth dynamics of adipocytes or fat cells [9]. These dynamics are complex and there are major open questions related to the turnover of fat cells, their size distribution and the signaling chain to active different cell processes [10,11]. Another important research trend relates the link between adipocytes and chronic inflammation [12] which might lead to cancer in some cases [13]. Another implicit and important aspect in the relationship between cancer and obesity is the glycolysis. This process consists of generating energy from glucose without the presence of oxygen which demands high quantities of insulin and calories which are stored in the fat cells. This process is highly inefficient but it is preferred by cancer cells, for example, in breast cancer [3]. Therapeutic strategies have also been proposed to exploit or interrupt tumor glycolytic metabolism. Several antiglycolisys methods to reduce cancer tumors are described in [14].

Some important models that relate the immune system and the tumor cells are described by De Pillis [15,16], Kutnetsov [17], Kirschner and Panetta [18], D'Onofrio [18] and Bellomo [19]. Even though this list is not exhaustive, it illustrates the wide variety of immune cancer models. Our model proposal is based on the De Pillis and Radunskaya model, reported in [15,16], in order to add the obesity factor. This model is a generalization of the model proposed by Kutnetsov [17] which also models the chemotherapy treatment using control theory. In our case, there is no attempt to study the chemotherapy effects.

This paper is organized as follows. In Section 2 we describe the characteristics of our model. In particular, we describe the model without considering the obesity factor, but we also explain the choice of the equation to model the obesity. The next Sections 3 and 4 deal with more elaborated models of cancer-obesity by adding interaction terms between the different types of cells and the fat. In each section, a numerical analysis of the model using bifurcation theory is presented using the software by Doedel [20]. Finally, conclusions are presented in Section 5.

2. A first cancer-obesity model

2.1. The model without obesity

Our models are based in the model analyzed by De Pillis and Radunskaya [15]. It is important to mention that the selection of this model is based on its simplicity and the fact that it analyzes a chemotherapy protocol. In this work we study the interactions between tumor cells, healthy cells, immune cells and adipose cells, and these interactions can then be added to other models such as the one described in [21].

In model [15], the immune system cell growth is stimulated by the presence of tumor cells. It is considered that a tumor is present because the immune response was not enough to eradicate it. Another hypothesis is that normal cells and tumor cells compete for the available resources using Lotka-Volterra interactions. A similar interaction occurs between the immune cells and the cancer cells. The tumor is assumed to be homogeneous and the growth rates for the cancer and normal cells are logistic. We present the nondimensional form of this model as in [16].

Let $I(t)$ denote the density of immune cells at time t, $T(t)$ the density of cancer cells at time t, and $N(t)$ the density of normal cells at time t, then the basic model without the obesity factor is:

$$\begin{aligned}\dot{I} &= s + \frac{\rho IT}{\alpha + T} - c_1 IT - d_1 I\\ \dot{T} &= r_1 T(1 - b_1 T) - c_2 IT - c_3 TN\\ \dot{N} &= r_2 N(1 - b_2 N) - c_4 TN.\end{aligned} \tag{1}$$

All coefficients are positive constants. As can be observed from the first equation, the immune system is modeled by considering a constant source rate s of immune cells. The term $\frac{\rho IT}{\alpha+T}$ models the immune system response due to the cancer cells. This term has been analyzed in detail by Kutnetsov [17]. d_1 is the natural death rate of the immune cells. The growth rate for the cancer cells and normal cells are r_1 and r_2, respectively. b_1, b_2 represent the inverse of the carrying capacity for the tumor cells and the normal cells, respectively. c_1, c_2, c_3 and c_4 are competition coefficients. This model fits better the behavior of immune cell such as T CD8 cells or polarized macrophages. There are many others immune cells [22], but we are interested in those that fights the tumor.

This model has the following type of equilibria: one point called *tumor-free* where the population of the tumor cells is zero and the normal cells survive. There are two death points: (a) type 1, in which both normal and tumor cell populations are zero and (b) type 2, that we will call *total invasion point* because the normal cells die, but the cancer cells survive. Finally, there are *coexistence* points where the normal cells, immune system cells and cancer cells all survived. There can be one, two or three points of this type, depending on the set of parameters used in the model. All the solutions of this model are bounded and they converge to one of the several equilibria.