Role of Ordinary and Partial Differential Equations as Mathematical Models in Tumor Growth

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Abstract. In this paper, we demonstrate the importance of Ordinary and Partial Differential Equations as mathematical models in tumor growth. Because the malignant tumor grows at a rapid rate, scientists and mathematicians have used ordinary and partial differential equations to better understand how the malignant tumor grows. To begin, we will introduce some tumor growth models that deal with Ordinary Differential Equations (ODEs) and discuss the relationship between such equations and cancer cell growth. Secondly, we will introduce some mathematical models using Partial Differential Equations (PDEs) and discuss their role in tumor growth.

Keywords: Cancerous cells, ODEs, PDEs, Mathematical Models, Tumor, Immune System

INTRODUCTION

The term "cancer" refers to a class of disorders in which cancerous tumors divide uncontrollably and have the ability to infiltrate additional tissues. Through the blood and lymph system, these cells grow in other parts of the body. The genetic material of a cell, deoxyribonucleic acid (DNA), is destroyed or altered in cancer, resulting in mutations that prevent normal cell growth and division. Among the world's leading causes of death, cancer ranks second. A 1999 report from the Australian Institute of Health and Welfare predicted that 1 in every 3 males and 1 in every 4 females will be diagnosed with cancer within their first 75 years of life [1]. In 2018, cancer claimed the lives of over 9.6 million people, accounting for almost 1 in every 6 fatalities (World Health Organization). Considering its staggering nature, cancer research gets a lot of human and monetary assets, with both fruitful and ineffective outcomes [2].

The immune system is the body's defense mechanism. whenever a foreign particle (antigen) enters the body, the immune system gets switched on and fights against even tiny invaders by activating B- cells and T-cells. The mammalian system is responsible for battling against a wide range of potentially harmful substances that wreak havoc on the host organism's anatomical barriers. Whenever the mammalian system neglects to work properly, the outcome is an illness. It is necessary for the immune system to recognize unusual cells and destroy them, in the case of a tumor. The cell mass will grow out of control if the process is not completed successfully [3].

A mathematical representation of a framework or phenomenon is known as a mathematical model. Statistical knowledge of organic phenomena is improved through mathematical modeling. Both clinical and experimental settings can benefit from this quantitative knowledge. The field of cancer biology [4,5] is quite possibly the main use of modeling exercises. Mathematical models help in the prediction of tumor size and the optimization of treatment procedures. To reflect some characteristics of cancer, many mathematical models have been constructed. These models range from simple models that try to stimulate tumor volume growth to complex models that include numerous biologically important molecular processes.

1. Role of Ordinary Differential Equations as a Mathematical Model in Tumor Growth

Mathematical modeling is a fundamental device that gives the approach to grasping tumor development and reaction to chemotherapy since the entire interaction includes a few distinct phases. Mathematical models should be able to accurately predict the origin of tumor development. Its movement and intrusion are responsible for the tumor tissue and the overall climate's heterogeneity. The dependency of tumor sites on schedule is communicated through mathematical modeling of tumor development.

Malthusian Model

Malthusian law is a set of rules devised by Malthusian. Rather than managing individual cells, this model regulates the tumor population. It is taken into account how the population grows over time. The population increases irregularly in case there is no treatment for the tumor. To put it another way, the population is a differentiable function of time and is approximately continuous. Given the tumor's population, suppose at time t, x is the number of individual cells. A differential equation can be derived by considering how population changes over time about the number of inhabitants.

$$\frac{dx}{dt} = Kx \quad (1)$$

A number of biological processes and mutations lead to an increase in the population x so that $\frac{dx}{dt} > 0$ we have K>0 from equation (1) with the following initial conditions.

$$x(t_0) = x_0 \quad (2)$$

By using the variable separable method and initial equations, the solution of the above equation is:

$$\dot{x} = x_0\, e^{(t- t_0)} \quad (3)$$

The Malthusian law refers to the law of population growth. Equation (3) denotes the exponential growth equation. The doubling time of the tumor growth is related to x in equation (3). For the first stages of tumor growth, this equation provides a promising model.

In many circumstances, a more realistic method of illustrating tumor cell population growth is to assume that the quantity x(t) of individuals cells at time t is determined by a differential equation of the form given below.

$$\frac{dx}{dt} = \alpha t - \beta x^2 \quad \text{(where } \alpha > 0 \text{ and } \beta > 0 \text{ are constants)} \quad (4)$$

$-\beta x^2$ is added as a result of a factor that tends to reduce the population growth in the long run. When the population grows as the tumor grows, these sources such as radiation therapy, biological therapy, and chemotherapy will have a quadratic effect on the patient.

Consider a differential equation of the type (4) represents the tumor population, with constants $\alpha > 0$ and $\beta > 0$ and initial conditions given by equation (2). In some circumstances, β is very tiny in comparison with α. Therefore, the term x prevails for a sufficiently small value of x and during that period, the tumor cell population grows quickly. In any case, as cancer spreads and x, becomes massive, x^2 becomes more influential, resulting in a slowdown in the tumor's quick development rate.

The logistic law of cancer growth refers to the population law as described above.

$$\frac{dx}{dt} = \alpha x - \beta x^2 \quad (5)$$

$$\frac{dx}{\alpha x - \beta x^2} = dt$$

By applying the initial conditions and using partial fraction, we get

$$x = \frac{\alpha y_0 e^{y(t-t_0)}}{1+\beta y_0\, e^{y(t-t_0)}} \quad (6)$$

where $y_0 = \frac{x_0}{\alpha - \beta x_0}$

Suppose that the differential equation (4) exists for time t and as $t \to \alpha$ then by using (4) and (5), $x \to \frac{\alpha}{\beta}$ to calculate the size of the cancer population.

The relationship between tumor growth and the immune system is depicted using a variety of mathematical models incorporating ordinary and partial differential equations. For effector cells and tumor cells Kuznetsov et al. [6] defined an ODE model. They predicted a limit beyond which tumor growth is out of control and beneath which the disorder is reduced with occasional intensification every 3 – 4 months, and they display that the model contains spiral, yet [7] proves that no steady orbits exist. To model, the population of immune and tumor cells [7] utilizes an ODE and observes that stimulating the immune system improves survival.

Bertalanffy Model

Von Bertalanffy introduced this concept as an organism growth model in 1838. According to this theory, the tumor's volume decreases as cells die and develop in proportion to its surface area. This model, according to Vaidya [8], predicts adequate human tumor growth. For this model, the equation is given as

$$\frac{dV}{dt} = \alpha V^{2/3} - bV \quad (7)$$

Where α is the intrinsic growth rate, t represents time, b is the antiangiogenic process's growth rate declaration and V represents the total tumor volume. Clinical data supports equation (7) which depicts the trend of breast cancer development. The experimental evidence regarding early tumor development is best fit by this hypothesis. The Bertalanffy model, on the other hand, would be ineffective in predicting cancer progression.

2. Role of Partial Differential Equations as the Mathematical Model in Tumor Growth

Even though ODE's models have ended up being a useful instrument for monitoring the tumor cells development over time, the absence of spatial consideration is the most evident flaw in this approach. The main cause of death of the patients is not the absolute quantity of malignant growth cells in their body, but since primary tumors penetrate the tissue locally and then they spread (metastasize) to different parts of the body to lay out secondary tumors. Metastatic spread and cancer invasion are two critical and intrinsically spatial processes, which can be stimulated using PDE's models. In many cancer models, PDEs contain spatial heterogeneity, oriental tissue structure, tissue firmness, and deformability. Wu et.al.[9] devised and investigated a PDE that explains how a mutational virus propagates inside a tumor and the impact it has on tumor growth. For virus meditated tumor elimination, they obtained approximate conditions under three different kinds of intra-tumoral viral inoculation. PDEs aid in constructing mathematical models for tumor growth, according to Khan [10,11]. The heat conduction equation, transmission lines, membranes, and atomic splitting. To clarify the job of oncolytic viruses on cancer advancement, a few numerical models were created [12,13]. By utilizing the arrangement of partial differential equations, express models of cancer virus elements that have special structures have been examined [14].

Gatenby and Gawlinski created the first spatial model of cancer intrusion [15]. This model thought about the impact of an overabundance of H^+ particles in debasing the neighborhood tissue, permitting the cancer cells to diffuse and multiply into the space created. We have discussed two mathematical models involving PDEs given below.

Wodarz et al. Model

Wodarz et al. [16],[17] provided a model of multifocal cancer development based on competing for angiogenesis promoter and inhibitor effects. With populations, I and P, cancer cells from population C generate inhibitors and promoters respectively. As a result, regional blood flow promotes the expansion of cancer cells, which is a decreasing function of I and increasing function of P. Cancer cells are assumed to move and the inhibitor to disseminate, but the promoter spread is thought to be minimal. The model is expressed by the (PDEs) shown below.

$$\frac{\partial c}{\partial t} = \left(\frac{rC}{\epsilon C+1}\right)\left(\frac{P}{I+1}\right) - \delta C + \frac{D_c \delta^2}{\delta x^2} \quad (8)$$

$$\frac{\partial P}{\partial t} = a_p C - b_p P \quad (9)$$

$$\frac{\partial I}{\partial t} = a_I C + b_I I + D_I \frac{\partial^2 I}{\partial x^2} \quad (10)$$

Here a_I and a_p are the rates at which tumor cells produce inhibitor and promoter, respectively, and b_I and b_P are the rates at which they decay. R is a measure that describes growth saturation as the tumor grows larger and R also denotes the intrinsic growth rate of cancer cells. The number of dying and migrating cells is indicated by ∂. The inhibitor's diffusion rate is given by D_I. The promoter's production and decay dynamics should also be quick enough for it to be in quasi-equilibrium with the tumor cell population. (i.e $P = a_P C/b_P$). When C and I are substituted into the system of PDEs, we get a system of two connected PDEs. It is assumed that these PDEs obey zero flux boundary conditions.

Finding a numerical solution for these two coupled equations is not difficult. The equations, on the other hand, have a zero stable steady-state C = 0, I = 0. The steady-state is positive for C > 0, I > 0, and also stable when there is an inhomogeneous perturbation, but may be unstable when there is inhomogeneous turmoil of a variety of spatial

frequencies. To put it in another way, the equations may have a Turing bifurcation, which indicates that the long-term steady states are spatially periodic and contain cancer cells peak for some values of the parameters. As a bifurcation parameter, parameter a_I is employed. If the system is exceedingly massive, it will collapse to a zero steady-state. Because secretion of the powerful inhibitor blocks growth elsewhere, if the production rate of inhibitor(a_I) is reduced, it restricts the growth of cancer cells only to a single peak of the domain centre. As it reduces further, it is possible to stop the growth of cancer cells with respect to the peak range of malignant growth cells, and many tumor lesions can emerge in the domain. As the strength of the inhibition reduces, the distance between lesions decreases. Eventually, tumor cells infiltrate the whole space when a_I is small, resulting in a stable homogenous positive steady state.

Ferreira et al Model

Tumor development and immune system dynamics have received a lot of research during the last three decades. Various, mathematical models that link tumor progression to immune system dynamics have also been developed. Burton's [18] and Greenspan's [19] early chemical diffusion and differential equations models have recently been applied to describe the progression of malignant tumors using PDEs. Here we discuss the, as well as the nutrient-restricted development of a starting phase tumor. A blend of reaction-diffusion equations for the nutrient species with some groundbreaking rules for cyto-autonomous characterization of different cell types involved in tissue and tumor environment. Burton [18] and Greenspan [19] were among the first researchers to apply reaction-diffusion equations to the mathematical analysis of nutrients, as well as many other chemical species, to model tumor growth. Based on reaction-diffusion equations, a model is developed to model the distribution of two substances essential for mitosis and cell viability. Ferreira et al [20,21] took into account two nutrient species in their research. Cell division requires the first nutrient, while cellular survival requires the second. The nutrients disperse all through the tissue space, where they are consumed by various tissue cells. The equations below regulate the nutrient species.

$$\frac{\partial N}{\partial t} = D_N \nabla_N^2 - k_1 HN - k_2 TN - k_3 IN \quad (11)$$

$$\frac{\partial M}{\partial t} = D_M \nabla_M^2 M - k_4 HM - k_5 TM - k_6 IM \quad (12)$$

The nutrients N and M provide for proliferation and survival, respectively. H, T, and I represent cells belonging to the host, the tumor, and the immune system respectively. Furthermore, the coefficients for the two nutrients are represented by D_N and D_M respectively. Also, k_1,k_2 and k_3 indicate how much nutrition's consumed by the of host, tumor, and immune cell, respectively. The equivalent rates for survival nutrient consumption are represented by k_4, k_5,and k_6.The comparison with Ferreira et al, on which the previous equations are based, has been brilliantly maintained by Mallet and Pillis [22].

CONCLUSION

In this review paper, we first discussed the role of ODEs in tumor growth and then we applied the Malthusian model and explained how it helps in monitoring tumor growth. We also discussed the Bertalanffy model which predicts adequate tumor growth. Secondly, we discussed that due to the lack of spatial consideration in ODE models we prefer PDE models for monitoring the tumor growth and then we introduced Wodarz et al which depicts multifocal tumor growth based on the competing effects of angiogenesis promoter and inhibitor. The Ferreira et al model, in which reaction-diffusion processes are utilized to represent the distribution of two substances involved in mitosis and cell survival, was also discussed.

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