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How differential equations influence the tumor growth via mathematical models

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Abstract

This work demonstrates the importance of differential equations to develop mathematical model of tumor growth. Since the malignant tumor (cancer) grows voraciously, the scientists and mathematicians have tried to better understand how it grows. In view of mathematics, the modeling for tumour growth can be divided into two different categories: probabilistic and deterministic. Probabilistic model describes a set of measurement to evaluate the behaviour of individual cells, and deterministic model explains the behaviour of large populations of cells and their growth by changing the state in the transition from an active reproducing cell to a cell that is not reproducing. In this survey, we first answer the question: How ordinary and partial differential equations (ODE \ PDE) help to provide mathematical models in tumor growth? Secondly, how to use deterministic models and involve the ODE and PDE with some basic aspects of tumor growth to fit any mathematical model. Finally, we provide a relatively comprehensive list of existing models in this area and discuss other representative models in detail together with some possible future developments of mathematical modeling of cancerous cells.

Keywords: Cancerous cells, differential equations (ODE/PDE), immunotherapy, mathematical models, tumors.

1. Introduction

Cancer is a term used for diseases in which abnormal cells divide without control and are able to invade other tissues. These cells spread to other part of the body through the blood and lymph system. Historically, from 370 BC to 460 BC, Hippocrates explained several types of cancer, referring to them with the Greek word “Carcinos”. The surgical treatment of cancer was discovered in Egypt (approx.1600 BC). During 16^{th} and 17^{th} centuries, cancer became more acceptable for doctors to dissect bodies to discover the cause of death. Cancer affects the genetic material deoxyribonucleic acid (DNA) of a cell which becomes damaged or changed, producing mutations that affect normal cell growth and division. When this happens cells do not die when they should and new cells form when the body does not need them. The extra cells may form a mass of tissue called a tumor. Not all tumors are cancerous; tumor can be benign or malignant. A benign tumor is a mass of cells that do not spread to other parts of the body because it lacks the ability to invade neighbouring tissue or metastasize. These characteristics are required for a tumor to be defined as cancerous and so benign tumors are non-cancerous. In cancer, cells divide and grow uncontrollably, forming malignant tumors, and invade nearby parts of the body. The cancer may also spread to more distant parts of the body through the lymphatic system or bloodstream. This is how cancer cells spread from the primary tumor to form new tumor in other organs and this spread of cancer is called metastasis

Cancer is one of the five leading causes of death in all age groups among males and females. During 1999, the Australian Institute of Health and Welfare forecasted that one in three men and one in four women would be directly affected by cancer in first 75 years of life [3]. Based on the current trends, the Imperial Cancer Research Foundation predicts incidence of cancer in one individual out of two by the year 2010. Keeping in mind its devastating nature, a great deal of human and economic resources is devoted, with successful outputs but also with failures, to cancer research with special attention to experimental and theoretical immunology [5]. The immune system is composed by a variety of organs, cells and molecules acting in concert to achieve the basic functions of the immune system (viz. recognition, response and memory). When the immune system does not

work properly the result is a disease, as mammalian immune system is in charge of fighting against all kinds of potentially dangerous agents which destroy the anatomic barriers of the host organism. In the case of a tumor, the immune system should be able, to detect the anomalous cells and kill them. Failure in this task results in an uncontrolled growth of the cell mass [7]. Recently, the early steps in metastasis have suggested that solitary cancer cells that are neither proliferating nor undergoing apoptosis in sufficiently large numbers could contribute to metastatic recurrence after a period of 'clinical dormancy [34].A tumour which is 'nearly- steady-state' is represented by the term "cancer dormancy". Cancer dormancy is often observed in breast cancer, neuroblastoma, melanoma, osteogenic, sarcoma, and in many types of lymphomas and is often found accidently in tissue samples of healthy individuals who have died suddenly [47, 49, 53].

There are well documented clinical observations of latent dormant human tumours containing 10^9 cells or even more [47]. Factors such as age, stress factors, infections, act of treatment itself, or other alterations in the host can provoke the initiation of uncontrolled growth of initially dormant cancer cells and waves of metastases [13, 44]. Early stage of primary tumor formation occurs when there is absence of a vascular network and this may last up to several years [12, 9]. Patients with metastatic melanoma have a life expectancy of less than five years in 95% of the cases [41]. Several months or years may be required for the clinical manifestation [21, 23, 24, 45, 47, 55].

The steady–state of a fully malignant tumor deals with the potential for invasion and metastases, but one which is under the local control of the host (viz; the immune system, endocrine system, contact inhibition) and can persist for months or years [44]. One of the reasons for slow growth and regression of the tumor may be the reaction of the host immune system to the nascent tumor cells. The immune system has two main components, namely innate immunity and acquired immunity. Innate immunity is the non-specific components which is naturally present, even in absence of any invading cancer. The next component is adaptive or acquired immunity. It does not come into play until there is an antigenic challenge or development of cancer. The work of the immune system is to protect against the disease by identifying and killing pathogens and tumor cells, which is done together with innate immune response and adoptive immune response [7, 36]. Innate immune response is rapid but less specific than the adoptive response. Adoptive immunity is instead more specific and has the ability to recognize and remember specific pathogens and mount stronger attacks each time the pathogen is encountered.

Several studies have been undertaken to examine the different mechanism of migration and infiltration of immune cells and their interactions with the tumor cell population within such tumor models [28 10, 16]. The effect of the immune cells on the tumor cells has been crudely evaluated by the surviving tumors without a detailed spatio-temporal analysis of the tumor. Various problems are faced while interpreting and analysing data obtained from such experiments one of which is the lack of a quantitative methodology for the characterization of the spatio-temporal patterns of the distributions and the large variations at the cell level between different tumor cell types and different populations of immune cells. It is remarked that these differences affect the efficiency of the immune control of tumour growth and that it is not easy to control experimentally all the interacting elements in a tumor.

2. Mathematical models of tumor growth

The interaction between the immune system and the neoplasia (cancer) is attracting more interest in modeling. In modeling, differential equations are the most important branch of modern mathematics which occupies the core position of both pure as well as applied mathematics. Understanding any physical situation in terms of the mathematical formulation usually consists of the following: understanding the parameters of the situation; posing a corresponding precise mathematical problem to find an exact or approximate solution; and comparing the obtained result with the experimental data to check the validity of the model. Science studies the real world and human beings want to discover the laws and phenomena that govern the world. When we better understand the phenomena and then make valid prediction about future behaviour, the understanding then leads to intelligent efforts to control the phenomena or at least to influence them. It is often desirable to describe the behaviour of real life systems whether physical, sociological or even economical in mathematical terms. "The mathematical depiction of a system or phenomenon is called a mathematical model". A mathematical model of a complex phenomenon or situation has many advantages and limitations over other types of models. Scientists make some observations about the real world. They then wish to make some conclusions or predictions about the situation they have observed. One way to proceed is to conduct some experiments and record the results. The model

builder follows a different path; first he translates some necessary features of the real world into a mathematical system. Then by logical argument, he derives some mathematical conclusions. These conclusions are then interpreted as predictions about the real world. A mathematical model can be constructing as given below: Identify the variables that is responsible for changing the system; and make a set of reasonable assumptions or hypothesis about the system. Models are meant to describe real processes and any prediction based on the analysis of a model is compared with experimental observations. Since the assumption made about a system frequently involve a rate of change of one or more of the variables, the mathematical depiction of all these assumptions maybe one or more equations involving derivates. The theory of differential equations (ODE/PDE) has become an essential tool in biological and medical sciences. The application of mathematical reasoning to the discovery of engineering, finance, biology and other professions has recently rendered great services in the hands of mathematicians.

2.1 Role of ODE as Mathematical model in tumor growth

If a mathematical model is in the form of ODE, one is faced with the not so significant problem of trying to solve it. If the equation can be solved then it is deemed reasonable, as its solution is consistent with either experimental data or known facts about the behaviour of the system. But, if the predictions produced are poor, then it is either the resolution of the model has to be increased or an alternative assumption about the mechanism must be made (Pollak 2003). Challenge in mathematical modeling is "not to produce the most comprehensive descriptive model but to produce the simplest possible model that incorporates the major features of the phenomenon of interest".

Mathematical modeling is an essential tool that provides the way of comprehending tumor growth and response to chemotherapy, since the whole process involves several different stages. Mathematical models are required to systematically relate the initiation of tumor growth. Its progression and invasion account heterogeneity of both the tumor tissue and surrounding environment. Mathematical modeling of tumor growth expresses the dependence of tumor site on time. *Malthusian Law*: This model does not deal with individual cells, but the population of the tumor. The growth of a population as a function of time is considered. When there is no treatment of the tumor, the population tends to increase discontinuously. However, when the population is very large, individual increases are negligible, when compared to the entire population. In other words, the population increase is approximately continuous and is in fact a differentiable function of time. Given the population of the tumor, let *x* be the number of individual cells at time *t*. If we suppose that the rate of change of the population is proportional to the number of individuals in it at any time we have a differential equation.

$$\frac{dx}{dt} = Kx \qquad (2.1.1)$$

The population *x* is positive and increasing due to different biological factors and mutation and so $\frac{dx}{dt} > 0$

and from equation (2.1.1) we have K > 0 with the following initial condition

$$x(t_o) = x_o \qquad (2.1.2)$$

(2.1.1) can be solved by variable separable method and the solution is

$$x = x_o e^{y(t-to)} \qquad (2.1.3)$$

This law of population tumor growth is called Malthusian Law. Equation (2.1.3) is the equation for exponential growth. Here *y* in equation (2.1.3) is related to the tumor's doubling time. This equation is a good model of tumor for the earliest stage of growth.

The tumor cell population growth is represented more realistically in may cases by assuming that the number *x(t)* of individual cell in the population at time *t* is described by a differential equation (Bernoulli Equation) of the form

$$\frac{dx}{dt} = \alpha t - \beta x^2 \qquad \text{(where } \alpha > 0 \text{ and } \beta > 0 \text{ are constants)} \qquad (2.1.4)$$

$-\beta x^2$ is added due to the cause that tends to minimize the ultimate growth of the population. Such a cause could be the radiation therapy, chemotherapy or biological therapy when the population becomes sufficiently large as

the tumor grows which has a quadratic affect on the individual cell.

Let us assume that the tumor cell population is described by a differential equation of the form (2.1.4) with constants $\alpha > 0$ and $\beta > 0$ and initial condition of the form (2.1.2). In some cases, β is very small compared to α. Hence, for a sufficiently small number x, the term αx predominates and so the tumor cell population grows very rapidly for that time period. However, as the tumor grows by diffusion and x becomes sufficiently large, the term βx^2 is of greater influence and the result of this is a decrease in the rapid growth rate.

The law of population growth so described is called the logistic law of cancer tumor growth.

$$\frac{dx}{dt} = \alpha x - \beta x^2 \qquad \text{(where } \alpha \text{ and } \beta \text{ are positive constants)}$$

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

Using partial fraction and applying the initial conditions, we get

$$x = \frac{\alpha y_0 e^{y(t-t_0)}}{1 + \beta y_0 e^{y(t-t_0)}} \qquad (2.1.5)$$

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

Now to see how large the cancer cell population will ultimately be, let us assume that the differential equation (2.1.4) applies for time $t \to \alpha$ then as $t \to \alpha$ by using (2.1.4) and (2.1.5), $x \to \frac{\alpha}{\beta}$.

The tumor–immune interaction can be modelled using various mathematical methods such as ordinary or partial differential equations. In this context, Kuznetsov et al. [26] define an ordinary differential equation model for two main populations: effector cells and tumor cells. They predict a threshold above which there is uncontrollable tumor growth and below which the disease is attenuated with periodic exacerbations occurring every 3-4 months, and they also show that the model has spirals, but [6] shows that there are no stable closed orbits. [6] uses ordinary differential equation for the populations of immune and tumor cells and they show that survival increases if the immune system is stimulated.

The applications of first order differential equations (ODE) to absorption of drugs in cell, the problem of epidemiology and chemical reactions are just a few.

2.2 Role of PDE as Mathematical model in tumor growth

A partial differential equation model was formulated and studied by Wu et al. [53], which describes the special spread of a replication-component virus within a tumor and its impact on tumor growth. They also obtained approximate conditions for virus mediated tumour eradication under three types of intra-tumoral viral injection: uniform injection, core injection and rim injection. Further, they have improved their previous model by incorporating an immune response [55]. Khan [22, 23] includes in his review how partial differential equation (PDE) helps to provide mathematical models of tumor growth. A technique with the Green's function was applied to transform the coupled partial differential equations (PDEs) into implicit integral solutions facilitating the numerical calculations to handle arbitrarily specified model parameters of the PDEs. Further, the integral form solutions provided a better insight into the effects of the meaningful variables on the release behaviour than the direct numerical solutions to the PDEs. The applications of PDE include membrane, heat conduction equation, transmission lines and nuclear fission. Several mathematical models that explain the role of oncolytic viruses on tumor evolution were developed [51-53]. Explicit models of tumour–virus dynamics using system of partial differential equations have been discussed, these models are appropriate for tumours that have special structure [34].

2.3. List of existing models

*T*here are various kinds of diffusion but here we mean that the boundary of the tumor is moving and is unknown except in its initial stages. Through lab experiments scientist found out that a solid malignancy growing by diffusion alone leads the tumors to a dormant state.

In the early stages when the tumor is small, every cell receives adequate nourishment by diffusion. These circumstances will not persist for much time because as nutrients are consumed, fewer nutrients will reach the center of the tumor thereby stopping or preventing the nutrients from reaching the center of the cell eventually causing the cell to die. Then a central necrotic core will develop and the growth rate of the tumor makes it more difficult for the cell to receive nourishment. When the cells below the surface do not receive enough support and nutrients, they will eventually die and the tumor will dispose off the dead waste by diffusion. Because of the difficulty in determining the various rate of growth, we assume that the diffusion constants are non-dimensional. In this model, the growth of tumor by diffusion is discussed by the following assumptions:

a) the tumor has two layers (i) Outer shell; and (ii) Inner core of necrotic debris.

b) *u* denotes a function of nutrient supply *u(x, y, z, t)* depending on the critical level of nutrient below which the cell dies. Let y depend on u and its outer surface, where $y_1 = m(\sqrt{U} - U_1)$ for $U > U_1$ and $y = 0$ for $U < U_1$.

Suppose that *d*A = surface area of tumor and dv is the volume of live cells, so $dv = C_1 y_1 dA$, where C_1 = constant. The consumed nutrient by volume = $C_2 y_1 dA$, where C_2 = constant. Let the loss of necrotic cell volume per unit volume of debris be a constant and surface tension force = T. Also let q(x, y, z, t) = particle velocity and P(x, y, z, t) be proportional to internal pressure. The birth of new cells and the death of the old cells create an internal pressure. This pressure is differential and it causes the motion of cellular material.

2.4 Growth model by first order partial differential equation (Balance law)

Let us consider the tumor as a population of cancer cells during a time period when no individual cell leaves the population by termination through radiation therapy, chemotherapy or biological therapy. Let u(a,t) denote the number of cancer cells with age at a present time t. We offer a partial justification for assuming that u (a, t) satisfies the balance law.

$u_a + u_t = 0, \quad a > 0, \quad t > 0$ (2.4.1)

Suppose the number of cells grows discretely so that if there are n cells present at the *nth* time interval, then there will be x+n cells present at the end of the (n+1) interval.

Ex. Suppose there are M cells present at time t=0, having just become cancerous.

At time t=1, there are x M+ M cells present: x M of age zero, M of age one.

At time t = 2, $x[(x+1)M]+xM+M = (x+1)^2M$ cells present: M at age zero, xM at age one and M at age two.

At time t = 3, we have $x[(x+1)^2] + (x+1)^2M = (x+1)^3M$ cells present with: $x(x+1)^2$ *M* at age zero, *x* (x >1) *M* at age one, *x M* at age two and *M* at age three.

By induction we prove:

$u(a, t) = x(x+1)^{t-1-a} M$ for $0 \le a \le t-1$; $u(t, t) = 1.M$.

Therefore:

$u_a = x(x+1)^{t-1-a} M \ln(x+1)(-1) M$, where ($x > 0$, so $(x+1) > 1 \Rightarrow \ln(x+1) > 0$)

$u_t = x(x+1)^{t-1-a} M \ln(x+1)(+1) M$,

Then applying the argument that cancer cells increase with time, by induction, we find that u (a ,t) satisfies (2.4.1). Now if we assume that at time t=0 the cancer cells structure in the population is given by

$u(a, 0) = f(a), \quad a > 0$ (2.4.2)

and the individual number of cancer cell individuals at time t is given by:

$u(0, t) > g(t) \quad t > 0$ (2.4.3)

Then we can find that the population density in this cancer cell-structured population satisfies the initial-boundary-value problem by (2.4.1), (2.4.2) and (2.4.3).

3. Applications in Special functions

The mathematical solution of physical problems depends on the properties of certain special functions. These functions are determined jointly by the differential equation describing the physical phenomena at interior points and the conditions defining its behavior on the boundary.

One such special function is the hypergeometric function denoted by ${}_pF_q$ and is defined in [37] as follows for $a_1, \dots, a_p, b_1, \dots, b_q, \quad z \in C$:

$$ {}_pF_q(a_1,\dots,a_p;b_1,\dots,b_q;z) = \sum_{j=0}^{\infty} \frac{(a_1)_j,\dots,(a_p)_j}{(b_1)_j,\dots,(b_q)_j} \qquad (3.1)$$

where, for some parameter μ the Pochhammer symbol $(\mu)_j$ is defined as

$(\mu)_0 = 1; (\mu)_j = \mu(\mu+1)...(\mu+j-1); j = 1,2,...q$.

The values of a_j, b_j, z will be complex unless otherwise specified. However, the hypergeometric function is not defined if any b_j; j = 1, . . . , q are real and equal to a non-positive integer, and there are numerical issues in its computation if one or more values of b_j are close to a non-positive integer.

The generalized hypergeometric function ${}_pF_q$ satisfies the following differential equation [64].

$$z[z\frac{d}{dz}[z\frac{d}{dz}+b_1-1)...(z\frac{d}{dz}+b_q-1)-(z\frac{d}{dz}+a_1)...(z\frac{d}{dz}+b_p)]w=0 \qquad (3.2).$$

A great number of common mathematical functions are expressible in terms of hypergeometric functions (viz: see detailed in [3, 37]).

4. Future outlooks

A natural extension of Spinelli et al.'s [42] model would include distinct cell cycle phases within the proliferating cell compartment, each with its own cell cycle phase age. For such related age and phase structured modeling approaches see [4, 12, 34, 53,54].The findings of mathematical modeling [33], when coupled with these clinical research, could result in successful treatment methods to combat the killer disease such as cancer. This model admits of a number of extensions. In this context, virotherapy revealed that innate immune response to oncolytic viruses play an important role in the clearance of such viruses [12]. This effect can be incorporated to improve models in [33]. Mukhopadhyay and Bhattacharyya [33] have considered only virus specific CTL (an immune system component)-response. But oncolytic viruses can stimulate tumor-specific CTLs that enhance the antitumor potency of the oncolytic adenovirus. Finally, the future challenge for modeling will be to build the significant platform and synthesize it in appropriate systems framework; and also systemically incorporate appropriate systems biological descriptions of cellular behaviour to take predictive platform to the next stage. Such as: formulation of a system based model that incorporates cellular signalling network details at an appropriate level.

5. Conclusion

The treatment of cancer focuses on chemo-and radiotherapies directed at the tumor. One can explore treatment that serves to boost the immune system's capacity to fight the cancer. Immunotherapy attempts to use cytokines, the communication proteins produced, released, and used by cells, to enhance cellular activity. The cytokine most effective in this regard is interleukin-2, as it is the key interleukin responsible for T cell growth and differentiation; the cells that orchestrate the immune response. Krischner and Panetta [24] suggested that immunotherapy with IL-2 may boost the immune system to fight tumours and adoptive cellular immunotherapy can potentially restore or enhance these effects. We then overview the effects of adoptive cellar immunotherapy on the model and describe under what circumstances the tumour can be eliminated. The relationship between melanoma and immune system has been recognised for decades [5]. Case reports of spontaneous tumor regression in patients with metastatic melanoma have suggested that immunotherapy can influence the regression of tumor growth [7].Cancer is now recognized as a system biological malfunction, which involves dysregulation of multiple pathways governing cell processes such as apoptosis, proliferation, differentiation and migration [25]. Mathematical models of cancer evolution are essential for quantifying the effects of mutation, selection and tissue architecture. Tissue architecture determines the rates at which different type of mutations accumulate.

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