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Mathematical Modelling of Tumor Cell Growth and Treatment

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Abstract

Many scientific problems have been solved using mathematical models. Using mathematical models to simulate dynamic biological processes has a long history. A main goal of mathematical and computational oncology is to develop quantitative tools to determine the most effective therapies for each individual patient. Over the past couple of decades or so, quantitative approaches have also made their way into cancer research. An increasing number of mathematical, physical, computational and engineering techniques have been applied to various aspects of tumor growth. Here we propose the use of emerging, quantitative tumour imaging methods to initialize a new generation of predictive models. In this study, we investigated a mathematical model that integrated mechanisms of tumor angiogenesis and tumor-targeted cytotoxicity in immune cells. The model considered the interaction of cancer cells with the immune system and the treatment that combines unlicensed dendritic cells and anti-vascular endothelial growth factor antibodies. Here in we describe fundamental so mathematical modelling of tumor growth and tumor-host interactions, and summarize some of the seminal and most prominent approaches.

Keywords: Ordinary differential equation, partial differential equation, tumor modeling, angiogenesis

Introduction

Mathematical modeling of biological processes is widely used to enhance quantitative understanding of bio-medical phenomena. This quantitative knowledge can be applied in both clinical and experimental settings. One important application of modeling exercises is in the area of cancer biology. Many mathematical models have been developed to represent some aspects of cancer [1 - 3]. Mathematical models help to predict the tumor size and optimize the treatment procedure. In deterministic form, there are seven models including exponential, Mendelsohn, logistic, linear, surface, Gompertz and Bartalanffy that have been used to describe the behavior of cancer cell growth and proliferation .The mathematical model consists of a system of partial differential equations describing the production and/or activation of degradative enzymes by the tumor cells, the degradation of the matrix and the migratory response of the tumor cells. The mathematical model is a system of ODEs governing the tumor growth on a cell population level with a ratio-dependent like interaction between tumor cells and cytotoxic T cells. We will then discuss a number of different models and discuss their confirmative and predictive power for cancer biology.

Ordinary differential equation models of tumor growth

The number of cancer cells in a tumor is difficult to estimate due to constant changes in time Tumor cells may proliferate, rest in a quiescent state, or die. Describing the number of tumor cells as a function of time is therefore remarkably challenging. It is, however, straightforward to formalize what changes in cell number are expected as time changes. The number of living cells only changes when cells proliferate or die: difference in live cell number overtime interval number of cells created and died overtime interval How many and how often cells proliferate and how many cells die is dependent on the considered time difference, i.e., dt (where d stands for difference and t stands for time).Let us assume the cell cycle length of an arbitrary cancer cell is 24 hours. Then, over the course of one day, the probability that the cell divides is close to 100%. Without knowing at what position in the cell cycle a cell currently is, we can assume that the probability of this cell to divide within the time frame of one hour is 1/24. Not knowing the exact number of cells in a tumor population, the above example can be directly translated to the population level. For a population of unsynchronized cells with a cell cycle length of 24 hours we can assume that all cells divide once if dt = 24 hrs. Similarly, if dt = 1 hr, only a fraction of cells in the population (about 1/24) is expected to divide. One reasons similarly for cell death. We therefore must introduce the time difference as well as two parameters into the above equation : where α and β are respectively understood as the fraction of dividing and dying cells each dt, and hence denote the per capita growth and death rates of the total cell population. It is obvious that the cell number must increase after a proliferative event and decrease after a cell death event. Let us introduce variable c as number of cells. The difference in cell number then becomes dc, and the above equation can be written as: dc/dt = αc – βc is Called ODE.

Let us assume that at time t=0, i.e., the starting point of an experiment, we have one million cells, i.e. $c = 10^6$.Population growth dynamics can follow one of three fates: (i) if $\alpha = \beta$, then $dc/dt = 0$. In this case the number of cells in the population does not change and the population exhibits a state of tumor dormancy. It is of note that either $\alpha = \beta = 0$, that is all cells in the population are in state of cellular dormancy or quiescence, or $\alpha = \beta > 0$ in which case cell proliferation is balanced by cell death [4, 5]. If (ii) $\alpha > \beta$, then $dc/dt > 0$ and the cell population will continuously grow with greater α - β rates yielding faster growth. On the other hand, the population will monotonically decrease if (iii) $\alpha < \beta$ and thus $dc/dt < 0$ (figure1).

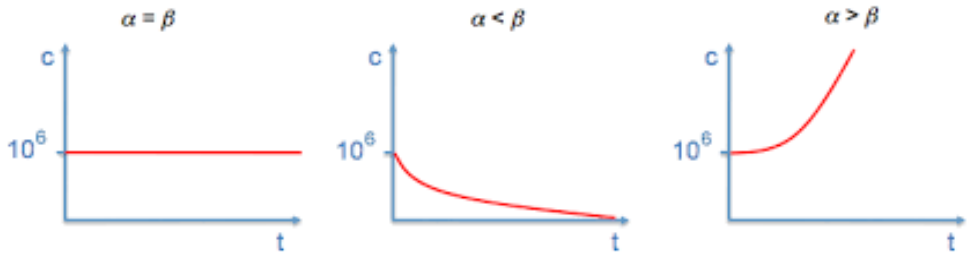


Figure1. Growth dynamic so f cell population *c*over time *t* ordiffeentrelativeratesof cell proliferation α and cell death β; $c = 10^6$ cells at time t=0.Eqn. (1) can be reduced to a one-parameter problem. The terms αc - βc can be combined into the single term $(\alpha - \beta)c$, and we introduce the single parameter, λ, $\lambda = \alpha - \beta$, which is called then at population growth rate. The differential equation describing cell population change over time is then $\frac{dc}{dt} = \lambda c$ As before, if $\lambda<0$, $\lambda=0$, or $\lambda>0$ the population decreases, remains at a constant size, or increases respectively. Experimental

data from *in vitro* or *in vivo* population studies can then be used to parameterize such model (figure 2).

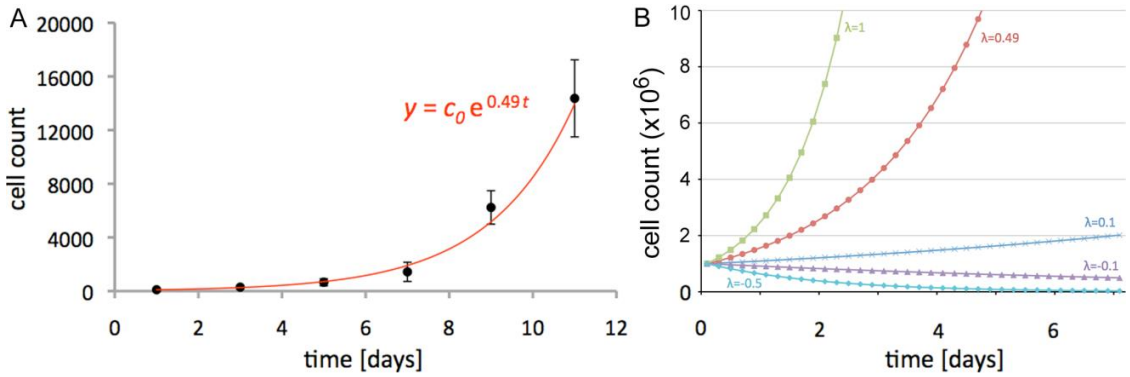


Figure 2. A) Mock population growth comparable to *in vitro* experimental data with 5% standard error bars (black dots) and calculated trend line (red).**B)** Mathematical model results of population growth for different parameters of λ.

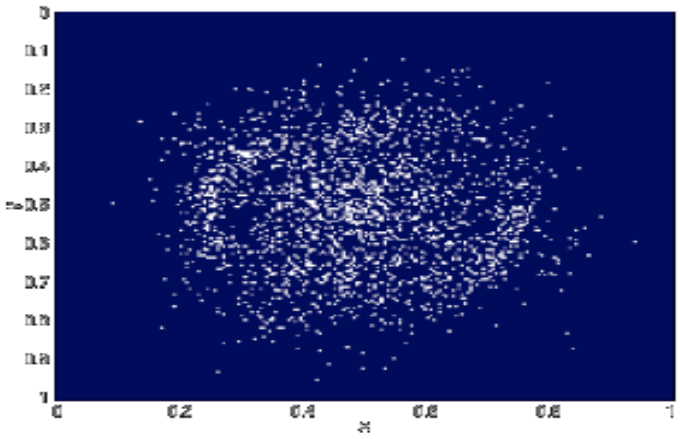
Partial differential equation models of tumor growth

Although ordinary differential equation models have proven to be a useful tool to simulate the evolution of the total tumor cell number over time, the most apparent short coming of this approach is the lack of spatial consideration. Patients do not die because of the total number of cancer cells in their bodies but because the primary tumors locally invade the tissue and spread (metastasize) to distant sites of the body to establish secondary tumors. It is these metastatic masses that are the main cause of death in cancer patients. Cancer invasion and metastatic spread are two crucial and inherently spatial processes, which can be simulated using partial differential equation (PDE) models. In such models, a population *n* at spatial positions *(x)*, *(x , y)*, or *(x, y, z)* in one, two, or three-dimensional space, respectively, is often described as a density, or fraction of maximum available volume at this position, and thus scaled between 0%-100%, or 0-1. The variable *n* is no longer only dependent on changes in time *t*, but also on variations in considered spatial dimensions. The equation for *n* therefore involves the partial derivatives of its independent variables. Omitting the considered spatial domain, the partial derivative of *n* with respect to time *t* is written as $\frac{\partial n}{\partial t}$.Invasion of tissue is a key aspect of the growth and spread of cancer and is vital for successful metastasization. The process of invasion consists largely of three components: (i)

the cancer cells secrete various matrix degrading enzymes (MDEs); (ii) the MDEs destroy the surrounding tissue or extracellular matrix (ECM); (iii) the cancer cell s actively spread into the surrounding tissue through proliferation and migration.

Discrete models of tumor growth

In addition to being the first 2-dimensional continuum model of cancer invasion focusing on the role of haptotaxis, the paper of Anderson et al. [6] was also the first to consider discrete model of cancer cell invasion (now also including proliferation at a discrete level), derived from the continuum PDE model. The computational simulation results of this model explored the observation that individual cancer cells can migrate beyond a "visible margin" of cancerous tissue, which was "detectable" by surgeons. This was perhaps the first paper to explore the issue of stochastic events and probability in invasion models. Figure 8 shows a sample result of a computation simulation of the discrete modeling a 2-dimensional domain. The individual cancer cells are secreting degrading enzymes and proliferating and migrating into the space created (through diffusion and haptotaxis). As can be seen from the figure, because of the stochastic nature of the discrete model, individual cancer cells mathematically possess the ability to penetrate the normal tissue at a greater depth then would be predicted by a deterministic PDE model.



Specimen simulation result from the discrete invasion model of Anderson et al.

The figure shows that individual cancer cells can penetrate the normal tissue at great depth. Other discrete models of invasion have subsequently been developed using a variety of techniques such as the Potts Model [7, 8], cellular automata and agent-based models, hybrid continuum-discrete approaches [9, 10] and individual, force-based model. One advantage discrete models have over continuum models is that events at the level of single cells can be considered. Using discrete models, important events such as mutations can be taken into account as well as different phenotypic properties. The introduction of discrete models have also led to the development of so-called " multiscale models ", where intracellular events can be modeled using systems of ordinary differential equations and these can then be linked to cellular level parameters [11,12].

Discussion

An increasing variety of mathematical models has made its way into cancer research over the past couple of decades. Herein we have illustrated how simple quantitative models are developed and compared with experimental data, and showed how they can be used to simulate complex biological

processes and interactions. We have chosen seminal papers as examples, and for simplicity have had to leave out a large body of excellent mathematical modeling literature. The interested reader is referred to recent review articles and books that give a more inclusive overview of the state-of-the-art in cancer modeling [13-16]

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