Mathematical Modeling of Cancer Growth Process: A Review

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Abstract. Although cancer is a leading cause of death, a little is known about the mechanism of its growth and destruction. Mathematical models explaining these mechanisms are crucial to predict the behaviour of cancer cells proliferation. Perusal of the literature dealing with mathematical modelling of cancer initiation, proliferation and metastases is abundant. Mathematical models to simulate the growth rate of the cancer cells have been derived from both deterministic and stochastic considerations. Early model of tumor growth by diffusion was first introduced and then set the scene for many later mathematical models for solid tumors. In this article we review the deterministic and stochastic models that have been developing to discuss the tumor growth initiation and proliferation. The findings and interpretations are summarized, and the main research issues are highlighted.

Keywords: Mathematical Modeling*;* Cancer Growth, Deterministic Model; Stochastic Model

1. Introduction

Cancer is one of the world's deadliest diseases, second leading cause of death in the world. Approximately 9.6 million deaths, about 1 in 6 deaths is because of cancer in 2018 by World Health Organization report [1]. Putting lot of stress on the financial and health care system because of its chronic nature and expensive treatment, also side effects caused by the treatment [2][3]. Number of researchers putting their time and efforts to find an effective treatment and to improve the efficiency of current treatment with low cost[4][5]. Cancer is typically initiated by genetic mutations that lead to enhance the abnormal of proliferation rate and cell growth. After a certain size, cancer cell stops growing and start spreading to the other parts of body, this process is called metastases.

Number of mathematical models has been developed to understand the dynamical process of cancer cell proliferation. Mathematical models help to predict the stage of tumour and optimize the treatment procedure [6]. In deterministic form, there are seven models (Exponential, Mendelsohn, logistic, linear, surface, Gompertz, Bartalanffy) have been used to describe the behaviour of cancer cell proliferation [7][8][9]. Cancer cell proliferation is subjected to the uncontrolled factors or environmental noise which includes cellular metabolism, energy requirements, hormonal oscillations, respiration, and individual characteristics such as body mass index, genes, smoking and stress impact [10]. Deterministic models are inadequate to explain the dynamical process of the cancer cell proliferation. In such a case, research has been done to extend the deterministic model (logistic and Gompertz) to their stochastic counterpart [11].

This paper reviews the deterministic and stochastic models of cancer growth process. The review of the cancer growth process in the form of deterministic part is presented in Section 1. Section 2 considers the review of stochastic model counterpart. In section 4, the comparisons of both models are presented, and conclusion remarks are stated in Section 5.

2. Deterministic Model

Deterministic model in the form of exponential, logistic, Gomperzt and Bertalanffy have been widely used to model the cancer cell growth. This section reviews these four different models. They are designed to predict the rate of change in the volume of the tumour with respect to the changes in time, *t*. Logistic, Gompertz and Bertalanffy models share a common pattern of exponential model [9], thus this section starts by discussing the exponential model of tumour growth.

2.1. Exponential Model

Exponential model is the natural description of early stages of cancer growth [12]. In exponential model, each cancer cell split into two daughter cells in the affected area at the rate of constant, a. The exponential model is given by

$$dv(t) = av(t)$$

where a is the kinetic parameter and $v(t)$ is the volume of the cancer cells.

The cancer cell growth in exponential model is proportional to the population of the cancer [13][14]. Exponential model estimates the maximum tumour growth volume at doubling time. However, at the last stages, the exponential model fails to predict the angiogenesis process and reduction of the nutrient [13].

2.2. Logistic Model

The exponential model has limitations to predict the last stages of cancer growth and cannot describe the log-term growth rate. To overcome these problems, the logistic model was introduced for the improvement [11]. A general equation for the logistic model was first introduced by Pierre Francois Verhulst in 1883 to find out the elements of organic population, concentrating on the inherent development rate a, whose entire size is limited by carrying capacity of b. The logistic model equation describes that the growth proportional linearly with size unless the carrying capacity become zero, which produces S-shape curve for the volume of cancer cell [15], where a is the coefficient of proliferation kinetics. This model can interpret the mutual competition between the cells and it has been used to model cancer tumour in [16]. The generalized logistic model equation is

$$dv(t) = av(t)\left(1 - \frac{v(t)}{b}\right) \quad (1)$$

This model has been effectively utilized in different biological phenomena, which ranges from bacterial population and portrays tumour development [17][18].

2.3. Gompertz Model

This model is generalization of logistic model with an asymmetric curve with the point of inflection. This model has ability to draw the latent stages of cancer tumour. The curve was applied ultimately to model growth in the size for whole organisms and the best curve for the growth of breast and lung cancer was noticed [27]. This model was first developed by Gompertz in 1825 to explain the human mortality curve, which further was employed by many researchers to fit and describe the tumour growth data [19]. The mathematical equation for the model is

$$\frac{dv}{dt} = avln\left(\frac{b}{v+c}\right) \quad (2)$$

This model is popular for modelling the tumour growth [13][14] as it slows down the process of tumour growth as the size of tumour increases. Tjørve et al. [18] has used mathematical model in thriving experimental trials[20]. This model worked good for both clinical and experimental data for breast and lung cancer[19]. Ultimately the curve was used to model the growth of whole organisms [21]. The Gompertz model and logistic model estimate the maximum tumour volume.

2.4. Bertalantfy Model

This model was introduced as organism growth model by Von Bertalantfy in 1838. This model shows that the volume of tumour decreases with cell death and increases related to the surface area. According to [16] this model predicts adequate human tumour growth. The equation of this model is as

$$\frac{dv}{dt} = av(t)^{2/3} - bv(t)$$

For the early tumour growth experimental data this model give the best results, but this model would not be good to predict the progression of cancer growth was stated by [22].

All the aforementioned models have limitation to predict the last phases of cancer growth and cannot predict long-term tumour growth rate. However, amongst of them, Gompertz model has been shown to fit and explain the growth of the breast and lung cancer data adequately. The deterministic models are not exposed to the uncontrolled factors, thus inadequate to describe the actual behaviour of the cancer growth. Section 3 reviews the extension of logistic and Gompertz models to their stochastic counterpart.

3. Stochastic Model

Cancer is a complex stochastic system. Stochastic model is suitable in providing the analysis of tumour growth process and development. It considers the uncontrolled factors of cellular metabolism, energy requirements, hormonal oscillations, respiration, and individual characteristics such as body mass index, genes, smoking and stress impact [10]. The perturbation of randomness into deterministic model has been done few authors on Gompertz model and it is presented in Section 3.1.

3.1. Stochastic Gompertz Model

Gompertz deterministic model has been extended to the stochastic Gompertz model by [9] and [23]. The numerical results of Gompertz stochastic model are shown to be consistent with the clinical data of breast cancer compare than deterministic model. The mathematical equation is formulated by perturbing the growth rate parameter a such that equation (2) become

$$dA(t) = \big(av(t)lnv(t)\big)dt + \sigma v(t)dW(t) \tag{3}$$

where a is the intrinsic growth rate, b is the growth rate declaration factor of antiangiogenic process and $W(t)$ is a Wiener process with mean zero and variance given by the increment in time, t. Equation (3) describe the pattern of breast cancer growth and consistent with the clinical dataThis mathematical model provides the good prediction with the low value of MSE (Mean Square Error).

5. Conclusion

We have provided here a brief review of the deterministic and stochastic models for cancer cell growth. The simplest form of mathematical model in determinsitic setting is exponential model. The equation has been extended to the form of logistic, Gompertz and Bertalanffy to describe the volume of the cancer cells. It is found that, Gompertz model shows better accuracy than other determinsitic models. Gompertz deterministic model has been extended to stochastic setting by perturbing the growth rate parameter, *a.* Stochastic Gompertz model explain the cervical and breast cancer data adequately as shown by [9][26].

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7. References

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