Mathematical Modeling of Cancer Growth Process: A Review

Mathematical Modeling of Cancer Growth Process: A Review

Shabana Tabassum[1, a], Norhayati Binti Rosli[1, b], Mazma Sayahidatul Ayuni Binti Mazalan[1, c]

[1]Centre for Mathematical Sciences,
Universiti Malaysia Pahang, 26300 UMP Kuantan, Pahang, MALAYSIA

Email: [1]shabanadec25@gmail.com, [2]norhayati@ump.edu.my

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.

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 (World Health Organization). Nearly 70% of the world's annual death due to cancer is accounted from the developing countries. Cancer prevention and control have been considered as priorities by policy makers to ensure the valuing cancer-related will not affected the productivity of the nation [1][2]. Number of researchers also have put time and efforts in finding an effective treatment, improving efficiency of current low cost treatment and finding the ways to help the patient develop their immune system that enable them to fight cancer [3][4]. 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 starts spreading to the other parts of body and this process is called metastases. The major cause of cancer mortality and morbidity is cancer metastasis. Approximately 90% of cancer deaths are due to cancer metastasis.

Mathematical models have been developed to understand the dynamical process of cancer cell proliferation. Mathematical models help to predict the tumour 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 behaviour of cancer cell growth and proliferation [5][6][7]. Cancer cell growth and 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 [8]. Deterministic models in fact are inadequate to explain the dynamical process of the cancer cell proliferation. In such a case, research has been done to extend the deterministic models of logistic and Gompertz to their stochastic counterpart [9].

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 2. Section

3 considers the review of stochastic model counterpart. In section 4, the comparisons of both models are presented and concluding 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 that have been employed to explain the cancer cell proliferation process. The models 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 [10], 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 [11]. 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

$$dv(t) = av(t) \tag{1}$$

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 [12][13]. 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 [12]. Extension of the exponential model to predict the early stage of cancer cell proliferation and its angiogenesis process thus is required.

2.2. Logistic Model

The exponential model has limitations to predict the long-term growth rate of cancer cell proliferation. To overcome these problems, a logistic model was introduced to explain the behaviour of cancer cell growth and proliferation [9]. General equation for the logistic model was first introduced by Pierre Francois Verhulst in 1883. The model was proposed 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 until the growth of the cells reach the carrying capacity, b. Logistic equation produces S-shape curve for the volume of cancer cell [14]. This model can interpret the mutual competition between the cells and it has been used to model the cancer cell by [15]. The generalized logistic equation is

$$\frac{dV}{dt} = aV\left(1 - \frac{V}{b}\right) \tag{2}$$

This model has been effectively utilized in different biological phenomena, which ranges from bacterial population and portrays tumour development [16][17].

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. It has a sigmoidal curve and was applied to ultimately model the size of the cell growth for the entire organisms. It was shown to provide the best prediction quality for the growth of breast and lung cancer [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 [18]. The mathematical equation for the model is

$$\frac{dV}{dt} = aVln\left(\frac{b}{V+c}\right) \tag{3}$$

where *a, b* and *c* are parameters that can be adjusted to describe a particular data set. V is the volume of tumour and *t* is function of time. $\frac{dV}{dt}$ is directly proportional to the number of cells in tumour. This model is popular for modelling the tumour growth [12][13] as it slows down the process of tumour growth as the size of tumour increases. Tjørve et al. in [18] has used Gompertz model in thriving experimental

trials [19][19][20]. This model was shown the best fits for both clinical and experimental data for breast and lung cancer [18]. The Gompertz model and logistic model estimate the maximum tumour volume.

2.4. Bertalanffy 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 Vaidya [15] this model predicts adequate human tumour growth. The equation of this model is

$$\frac{dV}{dt} = aV^{2/3} - bV \tag{4}$$

where, a is the intrinsic growth rate, b is the growth rate declaration factor of antiangiogenic process, V is the descriptive variable for total tumour volume and t is time. Equation (4) describe the pattern of breast cancer growth and consistent with the clinical data. For the early tumour growth, this model indicates best fits to the experimental data. However, Bertalanffy model would not be good in prediction the progression of cancer growth [20].

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 provide best fits to the experimental and clinical data. It explains the growth of the breast and lung cancer data adequately. The cancer cell growth and proliferation is in fact not in deterministic pattern. Cancer cell growth subject to the uncontrolled factors of factors of cellular metabolism, energy requirements, hormonal oscillations, respiration, and individual characteristics such as body mass index, genes, smoking and stress impact [8]. Thus, modelling the cancer growth process using deterministic models of exponential, logistic, Gomperzt and Bertalanffy is not adequate to describe the actual behaviour of the cancer growth. The extension of these models to their stochastic counterpart is required. Section 3 reviews the extension of deterministic logistic and Gompertz models into the form of stochastic differential equations (SDEs). To this date, only logistic and Gompertz models have been extended to their stochastic counterpart.

3. Stochastic Model

Cancer is a complex disease. Stochastic model is suitable to provide 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 [8]. The perturbation of randomness into deterministic model has been done by few authors.

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 and cervical cancers compare than deterministic model. The mathematical equation of Gompertz Stochastic model is formulated by perturbing the growth rate parameter a with a Wiener process, $W(t)$ such that

$$dV(t) = \big(aV(t) - bV(t)lnV(t)\big)dt + \sigma V(t)dW(t) \tag{5}$$

where $\sigma > 0$ is the diffusion coefficient and $W(t)$ is a Wiener process having Gaussian distribution with mean zero and variance dt is given by the increment in time, t. This mathematical model provides the good prediction with the low value of root mean square error (RMSE). It describes the uncontrolled factors that influence the growth of cancer cell.

3.2. Stochastic Logistic Model

Logistic model with random perturbation has been proposed by [23]. The deterministic logistic model given by (2) is perturbed by random process of $W(t)$ through the intrinsic growth rate parameter *a* to yield

$$dV(t) = (aV(t) - bV(t))dt + \sigma V(t)dW(t) \quad (6)$$

where, $\sigma > 0$ is the diffusion coefficient. The model is employed to predict the cell growth proliferation of cervical cancer. Clinical data of cervical cancer are used to measure the efficiency of the stochastic logistic model. The comparison between Gompertz and logistic stochastic models have been performed and numerical solution of Gompertz model shows low values of RMSE hence indicate best fits in explaining the cancer growth process.

4. Model Comparison

Deterministic and stochastic models are significance models to describe the behaviour of cancer cell process. Deterministic models can be extended to their stochastic counterpart by perturbing the most significance parameters that reflect the presence of noisy behaviour with the Wiener process. Amongst of the deterministic models of exponential, logistic, Gompertz and Bertalanffy, the logistic and Gompertz models are best fits the experimental and clinical data of cancer growth process. Exponential and Bertalanffy models are good in explaining early cancer growth progression. However, as competition within species and angiogenesis take place, exponential and Bertalanffy models fail to predict the behaviour of cancer cell growth and proliferation. Due to the ability of deterministic logistic and Gompertz in describing the behaviour of cancer cells, these two models are amongst the interest of the researchers. Extension of these models to their stochastic counterpart have been done by [9] and [23]. The intrinsic growth rate parameter, *a* is perturbed with a Wiener process so that the mathematical models in the form of stochastic logistic and Gompertz arise. The examination on the prediction quality of the stochastic logistic and Gompertz models show that, Gompertz model has low values of RMSE. This indicates that stochastic Gompertz best fits the experimental data compare than stochastic logistic model.

5. Conclusion

The present manuscript have provided 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 and logistic model show better accuracy than other determinsitic models. Gompertz and logistic deterministic models have been extended to stochastic setting by perturbing the growth rate parameter, *a.* Stochastic Gompertz model is the best fits model compare than stochastic logistic model and other deterministic models.

Acknowledgments

We would like to thank Universiti Malaysia Pahang for financial support under UMP Internal Grant with Vote Number RDU1703190.

References

[1] Zeeshan A, Majeed A and Ellahi R 2016 Effect of magnetic dipole on viscous ferrofluid past a stretching surface with thermal radiation *Journal of Molecular Liquids* **215** pp 549-554

[2] Ramli N, Ahmad S and Pop I 2017 Slip effects on MHD flow and heat transfer of ferrofluids over a moving flat plate *AIP Conference Proceedings* **1870** 1 pp 040015

[3] Rashad A 2017 Impact of anisotropic slip on transient three dimensional MHD flow of ferrofluid over an inclined radiate stretching surface *Journal of the Egyptian Mathematical Society* **25** 2 pp 230-237

[4] Hussanan A, Salleh M Z and Khan I 2018 Microstructure and inertial characteristics of a magnetite ferrofluid over a stretching/shrinking sheet using effective thermal conductivity model *Journal of Molecular Liquids* **255** pp 64-75
[5] Jusoh R, Nazar R and Pop I 2018 Magnetohydrodynamic rotating flow and heat transfer of ferrofluid due to an exponentially permeable stretching/shrinking sheet *Journal of Magnetism and Magnetic Materials* **465** pp 365-374
[6] Yasin S H M, Mohamed M K A, Ismail Z, Widodo B and Salleh M Z 2019 Numerical Solution on MHD Stagnation Point Flow in Ferrofluid with Newtonian Heating and Thermal Radiation Effect *CFD Letters* **11** 2 pp 21-31
[7] Mohamed M K A, Ismail N A, Hashim N, Shah N M and Salleh M Z 2019 MHD Slip Flow and Heat Transfer on Stagnation Point of a Magnetite (Fe3O4) Ferrofluid towards a Stretching Sheet with Newtonian Heating *CFD Letters* **11** 1 pp 17-27
[8] Mohamed M K A, Anwar M I, Shafie S, Salleh M Z and Ishak A 2014 Effects of Magnetohydrodynamic on the Stagnation Point Flow past a Stretching Sheet in the Presence of Thermal Radiation with Newtonian Heating *International Conference on Mathematical Sciences and Statistics 2013 Selected Papers* (Springer) pp 155-163
[9] Chamkha A J, EL-Kabeir S M M and Rashad A M 2015 Unsteady coupled heat and mass transfer by mixed convection flow of a micropolar fluid near the stagnation point on a vertical surface in the presence of radiation and chemical reaction *Progress in Computational Fluid Dynamics, an International Journal* **15** 3 pp 186-196
[10] Anwar M I, Shafie S, Kasim A R M and Salleh M Z 2016 Radiation effect on mhd stagnation-point flow of a nanofluid over a nonlinear stretching sheet with convective boundary condition **47** 9 pp 797-816
[11] Zokri S M, Arifin N S, Mohamed M K A, Salleh M Z, Kasim A R M and Mohammad N F 2017 Influence of radiation and viscous dissipation on magnetohydrodynamic Jeffrey fluid over a stretching sheet with convective boundary conditions *Malaysian Journal of Fundamental and Applied Sciences* **13** 3 pp
[12] Blasius H 1908 Grenzschichten in flssigkeiten mit kleiner reibung *Zeitschrift für Angewandte Mathematik und Physik* **56** pp 1-37
[13] Ishak A 2010 Similarity solutions for flow and heat transfer over a permeable surface with convective boundary condition *Applied Mathematics and Computation* **217** 2 pp 837-842
[14] Bataller R C 2008 Radiation effects in the Blasius flow *Applied Mathematics and Computation* **198** pp 333-338
[15] Roşca N C and Pop I 2014 Unsteady boundary layer flow of a nanofluid past a moving surface in an external uniform free stream using Buongiorno's model *Computers & Fluids* **95** pp 49-55