MATHEMATICAL MODELING FOR THE GROWTHOF SOME TUMOR CELLS AND THEIR TREATMENTS

A

SYNOPSIS

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MANISH SHARMA

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Dr. SANJEEV KUMAR

DEPARTMENT OF MATHEMATICS,

IBS, KHANDARI

Dr. B.R.AMBEDKAR UNIVERSITY, AGRA

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Name of scholar	:	Manish Sharma
Subject/faculty	:	Mathematics, Faculty of Science
Registration no.	:	
Name of Supervisor	:	Dr.Sanjeev Kumar
Designation	:	Associate Professor and Head, Department of Mathematics, IBS Khandari, Agra.
Research centre name	:	Institute of Basic Sciences, Khandari, Dr. B. R. Ambedkar, Agra.
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Supervisor Candidate

Dr.Sanjeev Kumar Manish Sharma

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Present State of Knowledge:

Cancer is a major cause of morbidity and mortality in developing and developed countries alike. In many low-income and middle-income countries, including India, most of the population does not have access to a well organised and well regulated cancer care system.

The main types of treatment of Cancer comprises - Radiotherapy, Chemotherapy and Surgery. The study of cancers comes under the Oncology, where mathematicians, scientists, doctors and other researches make new discoveries in that field. The cause of cancer is uneven and excess growth of abnormal cells in the body. Cancer is one of the major causes of deaths in the world and a millions of people suffer from the various types of cancer, every year. In past, some evidence of cancer are found among fossilized bone tumors and human mummies. The history of the cancer started in Egypt and dates back to about 3000 BC. The Greek Physician Hippocrates (460-370 BC), the Father of Medicine, gave the word 'Cancer'. Hippocrates used the words *carcinos* and *carcinoma* to explain non-ulcer framing and ulcer-framing tumors. In that field, the word 'oncologists' is used for the specialists of cancer. A basic definition of cancer can be given as a class of disease characterized by uncontrolled growth of cell and invasion into surrounding tissues.

According to data provided by Indian Council of Medical Research (ICMR) [1], 1,300 Indians die every day in India, while between the years 2012 to 2014, the mortality rate due to cancer increased up to 6%. Moreover, in the year 2012, there were 478180 deaths out of 2934314 cases of cancer. In the year 2013, there were 465169 deaths out of 3016628 cases of cancer. Also, in 2014, 491598 people died out of 2820179 cases of cancer. ICMR reports shows that the incidence and mortality of cancer is high especially in the north region, in which most of the cases are of breast cancer, stomach cancer, lung cancer and very few cases of prostate cancer.

Mathematical modeling plays a vital role in the medication from oncology viz. cancer. It is also termed as theoretical biology which focuses on the theoretical principles while mathematical biology stresses on the mathematical tools to study cancer diseases. Cancer modeling aims at the mathematical representation, treatment and theory of biological history, using various techniques and tools of applied mathematics to focus on prediction, prevention, immunity, stability and so on. The purpose of mathematical modeling is to define and measure the related parameters in the model of a disease. A researcher analyzes each and every situation of development of cancer, tumor progression and improvement in various strategies such as diagnosis, prognosis, and design analysis of clinical results. Many researches are conducted in collaboration with mathematicians and biologists, which always involves an experimental and theoretical approach.

Mathematical modelling approaches have become increasingly abundant in cancer research. The complexity of cancer is well suited to quantitative approaches as it provides challenges and opportunities for new developments. In turn, mathematical modelling contributes to cancer research by helping to elucidate mechanisms and by providing quantitative predictions that can be validated. The recent expansion of quantitative models addresses many

questions regarding tumor initiation, progression and metastases as well as intra-tumor heterogeneity, treatment responses and resistance. Mathematical modeling of cancer not only complement our experimental and clinical studies but also, challenge current paradigms, redefine our understanding of mechanisms, driving tumor genesis and shape future research in cancer biology.

Mathematical modeling not only opens the new ways to medical research but also keeps capability to sort out the critical situation of various types of cancer diseases. Oncology also explain the situation, where a sudden outbreak of the number of infected patients spreading rapidly through population affecting a large proportion of human population. The study also tries to find the causes of cancer and to identify and provide improved treatments. Mathematical modeling comprises the qualitative aspects on the cancer modeling. The essentials of a realistic and useful model are [2]:

(i) A sound knowledge and appreciation of biological problem;

(ii) A realistic mathematical description of the important biological phenomena;

(iii) Finding useful solutions, preferably quantitative and what is crucial important

(iv) A biological interpretation of the mathematical results in terms of insights and predictions.

Broad Outlines of the Work:

Enderling et al. (2007) [3]focused only on one aspect of the complex process of tumor genesis. The treatment strategies discussed in this paper

aimed to achieve local tumor control. They fixed a task to refine and expand the model to focus the development towards a simulation supported interactive treatment planning tool.

Conde et al. (2008) [4]presented a hybrid discrete-continuum mathematical model for cancer invasion. Cancer cells were treated as individual entities, interacting through a potential function which was an attempt to model adhesive forces. This model highlighted the importance of chemoattractant gradients in the invasion process. The results of computational simulations of the model were able to reproduce local invasion strategies of a small number of cancer cells. This was in contrast with what continuum models can produce. This process sees leading cells on the tumor's edge boring tunnel-like channels of degradation into the ECM. This was not only produced by the general expansive tumor growth of the whole cancer mass, but also by a combination of proliferation and migration at the contact zone with the ECM.

Isaeva et al. (2009) [5] studied the effects of different treatment regimens on both the tumor growth and the immune response within the simple ODE model that describes tumor-immune dynamics with chemotherapy and immunotherapy. The bifurcation diagram for antigen presentation showed three main dynamical regimes. The region I reflected a progressive growth when the tumor was able to escape from the immune response. The region II described two regimens of disease depending on both the initial tumor size and the condition of immune system: (i) the regression to small tumor when the dynamical equilibrium is established and (ii) a progressive tumor growth to the highest possible size. For the region III the decrease of the tumor size was found when the equilibrium between the tumor and the immune system was established. In order to describe a possibility of different responses to treatment regimens, patients were conditionally divided in three generalized groups.

Jackiewicza et al. (2009) [6] presented a correlation between numerical and experimental results. The numerical results had been obtained by solving a system of partial integro-differential equations. Growth rates of prostate CC lines in vitro had been used as initial values for the initial conditions supplementing the model equations. The numerical approximations to the solutions of the resulting model had shown a good agreement with in vivo growth of tumors. Different kinds of tumorigenic cell lines had been illustrated by the numerical solutions of the mathematical model. They planned in future work to address the exact relation between the concentrations and volumes of tumors. They decided, in future, to address an efficient algorithm for finding precise parameter values for the model equations

Escher et al. (2011)[7] discussed a free boundary value problem modeling the growth of non-necrotic tumors. The tumor was treated as an incompressible fluid, the tissue elasticity was neglected and no chemical inhibitor species were present. They re-expressed the mathematical model as an operator equation and by using a bifurcation argument it was proved that there exist stationary solutions of the problem which are not radially symmetric. In another paper they studied a model describing the growth ofnecrotic tumors in different regimes of vascularization. They said that tumor consists of a necrotic core of death cells and a surrounding non-necrotic shell. The corresponding mathematical formulation was a moving boundaryproblem where both boundaries delimiting the non-necrotic shell were allowed to evolve in time. It was determined all radially symmetric stationary solutions of the problem and reduced the moving boundary problem into a nonlinear evolution.

Roe-Dale et al. (2011) [8] presented a mathematical model to investigate the ordering phenomenon observed in the comparison of alternating to sequential regimens of CMF (cyclophosphamide, methotrexate, 5-fluorouracil) and

doxorubicin used in breast cancer chemo-therapy. The ordinary differential equation model incorporated cell cycle specificity and resistance to study why doses of the same drugs given in different orders result in different clinical outcomes. This model employed a pulsing condition to simulate treatment and induced resistance, and authors investigated treatment outcome by simulating a patient population by varying parameters using uniform distributions

Zhu et al. (2012) [9] developed an energy-based model linking tumor growth with cell proliferation rate to investigate the hyperthermia treatment effect. In this model, the new understanding of the Warburg Effect was for the first time taken into account for tumor cellular metabolism regardless of the concentration of oxygen. The maximum cell growth rate was used as an integrated variable responding to changes under different environments. Trends of initial tumor growth and changes of the average glucose concentration in tumor were successfully modeled. The comparison of the maximum tumor cell growth rate revealed a slowdown of tumor growth under the long-term mild hyperthermia condition.

Kumar et al. (2012)[10] developed the simple possible model which has shown the tumor growth with and without immune response of the body. The model turn that the radius of brain tumor increasing with respect to time. Hence in the presence of immune response, the TCD behavior is instinctive. The TCD curves show the non-monotonic behavior with immune response (TNF). Authors have formulated and analyzed a model that interplay between a growing tumor cell density (TCD) and immune response (TNF).

Delitala et al. (2013) [11] developeda mathematical model for immune response against cancer, which describes the evolution of cancer cells characterized by heterogeneous antigenic expressions and exposed to the

action of antigen presenting cells and T-cells. The proposed modeling approach makes possible to take into account mutation, proliferation and competition phenomena involving tumor cells as well as tumor-immune interactions. Asymptotic analysis and simulations, developed with an exploratory aim, have been addressed to provide insights into the phenomena that rule immune response against cancer cells. Furthermore, it has been highlighted how the immune system may both antagonize and enhance tumor development and progression.

Enderling et al. (2014) [12] analyzedthat an increasing variety of mathematical models has made its way into cancer research over the past couple of decades. They 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.

Hashmi et al. (2014)[13] developed a new mathematical model describing the tumor-immune interaction cultured with chemotherapy and cytokine interleukin IL-2 under the influence of immune deficient virus. This model focused on the investigation of tumor regression mathematical model describing the tumor-immune interaction cultured with chemotherapy and cytokine interleukin IL-2 under the influence of immune deficient virus. Theoretical interpretations show that this model may give better tumor regression efficiency and left the numerical verification to future work. Among the future research they planned to investigate the impact of immunotherapeutic agent on this tumor-immune mathematical model for tumor reduction.

Namazi et al. (2015) [14] proposed a new method for forecasting of DNA walk after the application of anti-cancer drug. In this method authors built a new model based on Fractional Diffusion Equation (FDE) which made a relationship between diffusion of drug in tumor and DNA walk as fractal series. In order to test this model the damaged DNA walks for fifty subjects

with lung cancer were given to the model and then this model predicted the DNA walks. In order to test the strength of prediction authors compared the modelled DNA walk and the real normal DNA walk by computing the Hurst exponent and Fractal dimension spectra of these walks.

Pang et al. (2016)[15] concluded thatcombination chemotherapy is very effective in controlling tumor growth, and further mixed immunotherapy with combination chemotherapy can obtain a better treatment effect. But, with tumor cells becoming resistant to many structurally and mechanistically unrelated drugs, the efficacy of chemotherapy of tumor often becomes severely limited. Authors suggested that the problem of how to combine reasonably those treatment modes and design an optimal mixed therapeutic regimen, deserves deep research.

PiotrowskaM J (2016)[16] described the interaction between tumor and immune system by a system of non-linear differential equations with discrete delay, representing time lag in the reaction of immune system to recognition of the antigens. The mathematical properties of proposed model such as: existence, uniqueness and non-negativity of solutions were studied. The presented study focusses on the stability of the steady states depending on the value of the bifurcation parameter, which is the time delay. The direct conditions for the stability of the steady states are derived in this paper. In the general case, it is shown that depending on assumptions on the model parameters the stability of the system changes due to Hopf bifurcation for sufficiently large delay. Moreover, only one such stability switch is possible.

Moarefian et al. (2016) [17] illustrated the effect of an applied electrical field on predictions of the fraction of tumor killed using an idealized description of the tumor tissue. Authors have shown through their results the impact of the various properties of the electrical field, chemotherapy drug and micro environment on the tumor response. To achieve optimal tumor death, there must be a balance between the uptake rate and diffusivity of the

chemotherapy drug so that it can diffuse within the tumor without being quickly taken up by the cells immediately surrounding the blood vessel. The direction of the applied electrical field plays a major role in determining the tumor response and must be applied in the direction of the drug concentration gradient.

Valle et.al. (2016) [18] obtained mathematical conditions for elimination of the tumor cells population on the base of a small constant dose of chemotherapy for a long period of time. The theoretical base of this methodology was to determine the minimum dose value on which the chemotherapy treatment will be able to eliminate the tumor population described by the system. Authors suggested chemotherapy treatment by small constant dosing for a long period of time which is applied for asymptotical elimination. In this model the dynamics of the effector immune cells population reaches a value which is very close to its initial condition. They indicate that the mathematical conditions for elimination of tumor cells population were elaborated on the base of LCIS method developed for analysis of dynamical systems.

Tridane et al. (2016) [19] studied the possibility of having a chemotherapy treatment of a cancer that targets not only the proliferating cancer cells but also the quiescent cancer cells. This study is motivated by the possibility of the recurrence of the cancer after the chemotherapy treatment which is due to the transition from the quiescent stage to the proliferation stage and also by the recent findings of a new drug in Human acute myeloid leukemia that targets the quiescent cells and the development of the new drugs combination that is effective also against the non-mitotic cells. The dynamics of the chemotherapy treatment was introduced, with and without the intervention term, to examine the effect of the delay on the proliferation of the cancer cells.

Qomlaqi et al. (2017)[20] presented an extended mathematical model to depict interactions between cancerous and adaptive immune system in mouse. The model includes tumor cells, natural killers, naïve and mature cytotoxic T cells, naïve and mature helper T cells, regulatory T cells, dendritic cells and interleukin 2 cytokine. Whole cycle of cell division program of immune cells is also considered in the model. Authors also optimized protocol of immunotherapy with DC vaccine based on the proposed mathematical model. Their results explain dynamics of the immune cells from the first day of cancer growth and progression. Simulation result shows that reducing intervals between immunotherapy injections, efficacy of the treatment will be increased because CD8+ cells are boosted more rapidly. Optimized protocol for immunotherapy suggests that if the effect of DC vaccines on increasing number of anti-tumor immune cells be just before the maximum number of CD8+ cells, the effect of treatment will be maximized.

Tonekaboni et al. (2017) [21] studied the theoretical modelling of phenotype switching within cancer cell populations and compared the model results with experimental results done on large numbers of cells in previous papers.Authors have shown that the stochastic behaviour of cancer cells, as may be experimentally measured using the mammosphere formation assay, is not defined well by the deterministic or large population behaviour of the system under consideration. They obtain parameters fitting the experimental data of Gupta et al. to the TCM presented in this work, and they show that multiple sets of parameters adequately describe the experimental, deterministic results, but because of changes in the cellular death rates and self- renewal rates, the stochastic properties of these parameter cases vary greatly. This analysis is also repeated using HM including different levels of negative cells and a positive compartment. It is clearly shown that the stochastic behaviour of cancer cells modelled using HM is more sensitive than the ones studied by TCM while they have almost the same behaviour in

large. The concept of plasticity in the cancer cell population and its importance on aggressiveness of tumors is also included in the theoretical modelling in this article.

Ansarizadeh et al. (2017) [22] consideredfour coupled nonlinear differential equations in order to study interaction between a significantly grown malignant tumor and the patient's immune system. The system of differential equations includes twenty parameters based on biological observations and available medical data. Routh–Hurwitz conditions have been applied to establish stability of tumor-free and high-tumor systems.

It has been observed that the most regression of tumor cells occurred at invasive fronts of the tumor, when diffusion coefficients have the highest values. After chemotherapeutic treatment, the number of immune system cells increases and the number of tumor cells decreases at the invasive fronts of the tumor. The variation of tumor cells over the duration of treatment is in agreement with Jeff's phenomenon.

Objectivesof the present work:

- Mathematical modeling of oncology in human and animals.
- To investigate, in co-operation with clinicians and research oncologists, mathematical models of tumor growth with the goal of better understanding how the various aspects of growth and treatment interact with one another.
- To develop our own generalized mathematical model of cancer growth, which incorporates several key elements of the growth processes and the effect of their mutual interactions.
- To employ numerical optimal control methods to search for treatment protocols that, in theory, are improvements to the standard protocols in use today.

- To create a model that will be helpful in controlling the critical situation of disease.
- To develop a new mathematical theory or techniques with the help of modeling.
- To analyze current data from real phenomena and draw a sound conclusions about the underlying process using the results from their understanding of mathematics and statistics.
- To analyze how mathematics, statistics and computation can be used in an integrated way to study the biological problem.

Work plan and methodology-

In this research, the useful sources are:

(1)Some mathematical techniques related to ordinary differential equation (stability theory, bifurcation theory etc.), partial differential equation, difference equation, delay differential equations (stability and Hopf bifurcation theory), integro-differential equation, diffusion equations and diffusion- reaction equations etc.

(2)Computer techniques, which include MATLAB to solve system of differential equations, integro-differential and difference equations.

(3)The following organizations can be used for required data collection:

(i) National Medical Library and different medical institutes like AIIMS, New Delhi, SMS Jaipur etc.

(ii) Digital Library and Digital lab, Dept. Of Mathematics, IBS Khandari, Dr. B.R.A. University, Agra.

(4)The following steps will be followed in the proposed research work:

(i) Study of the literature to learn more about the cancer

(ii) To visit the Library, Hospital or Clinic for data collection

(iii) To learn how to establish a new model

(iv) To learn MATLAB to solve governing equations

(6)Obesity now rivals smoking as one of the leading preventable causes of cancer. Obesity-associated neutrophilia is now shown to enhance breast cancer metastasis and to be reversible through dietary modification and weight loss. The following examples on cancer are of mathematical modeling interacting tumor with and without obesity:

(a). The model without obesity [23]-

Let $I(t)$ denote the density of immune cells at time t, $T(t)$ the density of cancer cells at time t, and $N(t)$ the density of normal cells at time t, then the basic model without the obesity factor is:

$$\frac{dI}{dt} = s + \frac{\rho IT}{\alpha + T} - c_1 IT - d_1 I$$

$$\frac{dT}{dt} = r_1 T(1 - b_1 T) - c_2 IT - c_3 TN$$

$$\frac{dN}{dt} = r_2 N(1 - b_2 N) - c_4 TN$$

Here, all coefficients are positive constants. The immune system is modeled by considering a constant source rate s of immune system.

The term $\frac{\rho IT}{\alpha + T}$ models the immune system response due to the cancer cells. d_1 is the natural death rate of immune cells and r_1, r_2 are growth rate for cancer cells and normal cells respectively. b_1, b_2 represent the inverse of the carrying capacity for the tumor cells and normal cells. c_1, c_2, c_3 and c_4 are competition coefficient.

(b). The model with obesity [24]:

$$\frac{dI}{dt} = s + \frac{\rho IT}{\alpha + T} - c_1 IT - d_1 I$$

$$\frac{dT}{dt} = r_1 T(1 - b_1 T) - c_2 IT - c_3\, TN + c_5 TF$$

$$\frac{dN}{dt} = r_2 N(1 - b_2 N) - c_4 TN$$

$$\frac{dF}{dt} = r_3 F(1 - b_3 F)$$

Here Frepresents the density of fat at time t. The coefficients c_5 , r_3 and b_3 = 1 /K are positive constants.

In this model, it is assumed that the fat cells contribute for the tumor growth by adding the term $c_5 TF$ to the equation of cancer cells. This means that the fat causes an increment in the growth rate of the cancer cells. We focus on how this increment modifies the dynamics of the cancer-obesity model.

(c). A second cancer obesity model: In this model [24], the focus is on analyzing the interaction between the fat and the cancer cells. This is achieved by adding a new competition term $-c_6 TF$ to the fat equation in above model to obtain the following model:

$$\frac{dI}{dt} = s + \frac{\rho IT}{\alpha + T} - c_1 IT - d_1 I$$

$$\frac{dT}{dt} = r_1 T(1 - b_1 T) - c_2 IT - c_3\, TN + c_5 TF$$

$$\frac{dN}{dt} = r_2 N(1 - b_2 N) - c_4 TN$$

$$\frac{dF}{dt} = r_3 F(1 - b_3 F) - c_6 TF$$

here C_6 is a positive constant.

Impact and utility of proposed work-

The synopsis entitled 'some mathematical models for the growth of tumor cells and their treatment'is an attempt to explore myriad of mathematical models to medicate the cancer disease. Today, millions of patient in the world suffers due to cancer. In this regard, mathematical modeling is very important tool to sort out the problem of cancer. It provides the numerical based information about each stages of patients, which is easily understandable. Through the mathematical modeling, the different parameters for the different models, which affect the cancer modeling are discussed and verified with the obtained models.

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Title of the synopsis:		Mathematical modeling for the growth of sometumor cells and their treatment.
Name of scholar	:	Manish Sharma
Subject/faculty	:	Mathematics, Faculty of Science
Registration no.	:	to be provided by the university.
Name of Supervisor	:	Dr. Sanjeev Kumar
Designation	:	Associate Professor and Head, Department of Mathematics, IBS Khandari, Agra.
Research centre name	:	Institute of Basic Sciences, Khandari, Dr. B. R. Ambedkar, Agra.
Total no. of pages	:	21
E-mail Address	:	manishtsharma12@yahoo.in
Contact No.	:	+919015457528

Residential Address	:	C/O Mr. John A. Masih, House No.01, Steele Kothi, M.G. Road, Hariparwat Crossing, Agra-282002