CHAPTER-2: LITERATURE REVIEW

The plenty of research papers has been published on tumor growth of mathematical modeling so far. The Indian Institute of Health and Welfare highlighted basic information about tumor growth.

Why use mathematics to study something as intrinsically complicated and ill understood as development, angiogenesis, wound healing, interacting population dynamics, regulatory networks and marital interaction and so on?, rather theoretical modeling, must be used if ever hope to genuinely and realistically convert an understanding of the underlying mechanisms into a predictive science. Mathematics is required to bridge the gap between the level on which most of our knowledge is accumulating (in developmental biology it is cellular and below) and the macroscopic level of the patterns.

In wound healing and scar formation, for example, a mathematical approach lets us explore the logic of the repair process. Even if the mechanisms were well understood (and they certainly are far from it at this stage) mathematics would be required to explore the consequences of manipulating the various parameters associated with any particular scenario. In the case of such things as wound healing and cancer growth and now in angiogenesis with its relation to possible cancer therapy the number of options that are fast becoming available to wound and cancer managers will become overwhelming unless can find a way to simulate particular treatment protocols before applying them in practice. The latter has been already of use in understanding the efficacy of various treatment scenarios with brain tumors (glioblastomas) and new two step regimes for skin cancer.

The aim in all these applications is not to derive a mathematical model that takes into account every single process because, even if this were possible, the resulting model would yield little or no insight on the crucial interactions within the system. Rather the goal is to develop models which capture the essence of various interactions allowing their outcome to be more fully understood. As more data emerge from the biological system, the
models become more sophisticated and the mathematics increasingly challenging.

It has been stated recently that cancer is now poised to overtake heart disease as the major cause of premature death in the Western World (Byrne, 1999a)[15]. Indeed, a recent report on worldwide cancer rates by the World Health Organization’s International Agency for Research on Cancer (IARC) (Pisani et al., 2001)[67] illustrates that North America leads the world in the rate of cancers diagnosed in adults, followed closely by Western Europe and Australia and New Zealand. In 1994 in Britain, for example, one in three were expected to develop the disease over their lifetimes (Imperial Cancer Research Fund, 1994), with a likely increase to one in two by 2010 based on the trends at that time (Perumpanani, 1996)[62].

Similarly, a recent publication of the Australian Institute of Health and Welfare (1999) explains that at the incidence rates prevailing in 1999 (in Australia), it would be expected that one in three men and one in four women would be directly affected by cancer in the first 75 years of life. Further, an estimated 254000 potential years of life would be lost to the community each year as a result of people dying of cancer before the age of 75. Cancer currently accounts for 29% of male deaths and 25% of female deaths.

Reflecting on the seriousness of this disease, Perumpanani (1996)[62] remarks that the research community has taken on the challenge posed by cancer on a war footing and this has resulted in recent years in an explosion in our understanding of cancer’.

Interestingly, Alberts et al. (2002)[3] observe that the emphasis given to cancer research has profoundly benefited a much wider area of medical knowledge than that of cancer alone, explaining that the effort to combat cancer has driven many fundamental discoveries in cell biology. Nevertheless, the study of cancer is not new. Porter (1997)[66] claims that breast cancer operations date back to antiquity, giving the example of Aetius...
of Amida who had emphasized that the knife should cut healthy tissue around a tumor and that a cauterizing-iron should stanch the blood.

In a treatise on the history of breast cancer, Olson (2002)[60] further explains that medical practitioners the world over, today and eons ago, have struggled with the disease. Egyptians of the New Kingdom more than 3500 years ago were the first. Indeed, Ward (1997)[92] asserts that it is clear from various texts of ancient Greece, Egypt and Rome that the early physicians were well aware of the nature of cancer and were capable of making a correct diagnosis and performing successful therapy.

Clearly the study of tumor growth and the development of anti-cancer therapies are most worthwhile pursuits, having significant potential to enhance quality of life and increase life-expectancies, which may, in turn, yield considerable economic and social benefits. Notwithstanding recent advances, Gatenby (1998)[32] explains that recent research in tumor biology, particularly that using new techniques from molecular biology, has produced information at an explosive pace. Yet a conceptual framework within which all these new (and old) data can be fitted is lacking.

Gatenby and Maini (2003)[33] add that clinical oncologists and tumor biologists possess virtually no comprehensive theoretical model to serve as a framework for understanding, organizing and applying these data noting the necessity to (develop) mechanistic models that provide real insights into critical parameters that control system dynamics. Murray (2002)[58] concurs, asserting that the goal is to develop models which capture the essence of various interactions allowing their outcome to be more fully understood.

Indeed, Byrne (1999a)[15] asserts that in order to develop effective treatments, it is important to identify the mechanisms controlling cancer growth, how they interact, and how they can most easily be manipulated to eradicate (or manage) the disease. In order to gain such insight, it is usually necessary to perform large numbers of time consuming and intricate
experiments but not always. Through the development and solution of mathematical models that describe different aspects of solid tumor growth, applied mathematics has the potential to prevent excessive experimentation and also to provide biologists with complementary and valuable insight into the mechanisms that may control the development of solid tumors.

Moreover, experimentalists and clinicians are becoming increasingly aware of the role of mathematical modeling as a new way forward, recognizing that current medical techniques and experimental approaches are often unable to distinguish between various possible mechanisms underlying important aspects of tumor growth (Kunz Schughart et al., 1998)[48].

In the literature survey, it is observed that the basic information about the mathematical model of tumor growth discussed by the following researchers

Roland et al., 1997 [75] discussed several aspects of nonlinear dynamics have been explored in medical science indicating the ubiquitous and pivotal role of dynamical processes. In general, cancer reflects a dynamical and multistage process. Complex and dynamical systems can be described mathematically by the chaos theory, which becomes visualized in fractal geometry. Therefore, one may ask whether a connection between chaos and cancer exists and if so, does this knowledge lead to applications in diagnosis and/or therapy?

Here, attempt to interpret carcinogenesis in a chaos dynamic manner at the cellular and the tissue level. The author discussed as Present fractal properties of tumor features well known in pathology. A fractal tumor appearance may indicate a basic power law that governs tumor growth. Considering the possible relationship between fractals, chaos, and cancer, he discusses potential applications of this new scientific approach in diagnosis and therapy of cancer.

Dalgleish 1999[21] discussed as Non-linear mathematics or 'chaos' theory was first applied in the prediction of complex systems such as the
weather. Chaotic systems exhibit not only apparently random unpredictability, but also a degree of determinism, in that randomness remains confined within specific parameters. Biological systems manifest many of the features of chaotic systems, including the inherent repetition of self, fractal structure, and the existence of strange attractors. The interaction between a tumor and the immune system is examined with regard to the capacity for immunotherapy to influence these two complex systems beneficially. It is postulated that judicious immunization may lead to profound changes in the stability of this interaction, in the favor of the immune system’s ability to recognize tumor cells.

Janecka 2007 [39] discussed as cancer is a significant medical and societal problem. This reality arises from the fact that an exponential and an unrestricted cellular growth destabilizes human body as a system. From this perspective, cancer is a manifestation of a system-in-failing.

Kazuyuki et al., 2010[45] discussed as deals with a fertile region of hybrid dynamical systems that are characterized by the coexistence of continuous and discrete dynamics. It is now well known that there exist many hybrid dynamical systems with discontinuities such as impact, switching, friction and sliding. The first aim of this Issue is to discuss recent developments in understanding nonlinear dynamics of hybrid dynamical systems in the two main theoretical fields of dynamical systems theory and control systems theory.

A combined study of the hybrid systems dynamics in the two theoretical fields might contribute to a more comprehensive understanding of hybrid dynamical systems. In addition, mathematical modeling by hybrid dynamical systems is particularly important for understanding the nonlinear dynamics of biological and medical systems as they have many discontinuities such as threshold-triggered firing in neurons, on off switching of gene expression by a transcription factor, division in cells and certain types of chrono therapy for prostate cancer.
Hence, second aim is to discuss recent applications of hybrid dynamical systems in biology and medicine. Thus, this Issue is not only general to serve as a survey of recent progress in hybrid systems theory but also specific to introduce interesting and stimulating applications of hybrid systems in biology and medicine.

As the introduction to the topics in this Theme Issue, we provide a brief history of nonlinear dynamics and mathematical modeling, different mathematical models of hybrid dynamical systems, the relationship between dynamical systems theory and control systems theory, examples of complex behavior in a simple neuron model and its variants, applications of hybrid dynamical systems in biology and medicine as a road map of articles in this Theme Issue and future directions of hybrid systems modeling.

Tanaka et al. 2010 [81] discussed as Hormone therapy in the form of androgen deprivation is a major treatment for advanced prostate cancer. However, if such therapy is overly prolonged, tumor cells may become resistant to this treatment and result in recurrent fatal disease. Long-term hormone deprivation also is associated with side effects poorly tolerated by patients. In contrast, intermittent hormone therapy with alternating on- and off-treatment periods is a possible clinical strategy to delay progression to hormone-refractory disease with the advantage of reduced side effects during the off-treatment periods. First overview previous studies on mathematical modeling of prostate tumor growth under intermittent hormone therapy.

The model is categorized into a hybrid dynamical system because switching between on-treatment and off-treatment intervals is treated in addition to continuous dynamics of tumor growth. Next, he presents an extended model of stochastic differential equations and examine how well the model is able to capture the characteristics of authentic serum prostate-specific antigen (PSA) data.
He also highlights recent advances in time-series analysis and prediction of changes in serum PSA concentrations. Finally, he discusses practical issues to be considered towards establishment of mathematical model-based tailor-made medicine, which defines how to realize personalized hormone therapy for individual patients based on monitored serum PSA levels.

Osborne 2010 [61] discussed as, review multi-scale models of solid tumor growth and discuss a middle-out framework that tracks individual cells. By focusing on the cellular dynamics of a healthy colorectal crypt and its invasion by mutant, cancerous cells, he compare a cell-centre, a cell-vertex and a continuum model of cell proliferation and movement. All models reproduce the basic features of a healthy crypt: cells proliferate near the crypt base, they migrate upwards and are sloughed off near the top.

The models are used to establish conditions under which mutant cells are able to colonize the crypt either by top-down or by bottom-up invasion. While the continuum model is quicker and easier to implement, it can be difficult to relate system parameters to measurable biophysical quantities. Conversely, the greater detail inherent in the multi-scale models means that experimentally derived parameters can be incorporated and, therefore, these models offer greater scope for understanding normal and diseased crypts, for testing and identifying new therapeutic targets and for predicting their impacts.

Itik M. et al., 2010[36] discussed as develop a new dynamical model of cancer growth, which includes the interactions between tumor cells, healthy tissue cells, and activated immune system cells, clearly leading to chaotic behavior. We explain the biological relevance of our model and the ways in which it differs from the existing ones. We perform equilibrium analysis, indicate the conditions where chaotic dynamics can be observed, and show rigorously the existence of chaos by calculating the Lyapunov exponents and the Lyapunov dimension of the system. Moreover, we demonstrate that Shilnikov’s theorem is valid in the parameter range of interest.
Wang Wei et al., 2010 [91] discussed as The Shilnikov sense Smale horseshoe chaos in a simple 3D nonlinear system is studied. The proportional integral derivative (PID) controller is improved by introducing the quadratic and cubic nonlinearities into the governing equations. For the discussion of chaos, the bifurcate parameter value is selected in a reasonable regime at the requirement of the Shilnikov theorem.

The analytic expression of the Shilnikov type homoclinic orbit is accomplished. It depends on the series form of the manifolds surrounding the saddle-focus equilibrium. Then the methodology is extended to research the dynamical behaviors of the simplified solar-wind-driven-magnetosphere-ionosphere system. As is illustrated, the Lyapunov characteristic exponent spectra of the two systems indicate the existence of chaotic attractor under some specific parameter conditions.

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Fathalla A. Rihan 2013 [31] discussed as a class of fractional-order differential models of biological systems with memory, such as dynamics of tumor-immune system and dynamics of HIV infection cells. Stability and non-stability conditions for disease-free equilibrium and positive equilibrium are obtained in terms of a threshold parameter (minimum infection parameter) for each model. We provide unconditionally stable method, using the Caputo fractional derivative of order and implicit Euler’s approximation, to find a numerical solution of the resulting systems. The numerical simulations confirm the advantages of the numerical technique and using fractional-order differential models in biological systems over the differential equations with integer order. The results may give insight to infectious disease specialists.

Jorge Duarte 2013 [41] discussed as Dynamical systems modeling tumor growth have been investigated to determine the dynamics between tumor and healthy cells. Recent theoretical investigations indicate that these interactions may lead to different dynamical outcomes, in particular to homoclinic chaos. In the percent study, he analyses both topological and dynamical properties of recently characteristic chaotic attractor governing the dynamics of tumor cells interacting with healthy tissue cells and effectors cells of immune system.

Letellier C et al., 2013 [50] discussed as a simple model of three competing cell populations (host, immune and tumor cells) is revisited by using a topological analysis and computing observability coefficients. Our aim is to show that a non-conventional analysis might suggest new trends in understanding the interactions of some tumor cells and their environment. The action of some parameter values on the resulting dynamics is investigated. Our results are related to some clinical features, suggesting that this model thus captures relevant phenomena to cell interactions.

Mammat M. et al., 2013 [55] discussed as mathematical model of cancer treatments have been presented and analyzed using coupled ordinary differential equations. This model describes cancer growth on a cell population level with combination immunotherapy and chemotherapy.
treatments are often called biochemotherapy. This model also describes the effect of tumor infiltrating lymphocytes, interleukin-2 and interferon alpha on dynamics of tumor cells under the influence of immunotherapy, chemotherapy and biochemotherapy. Through this mathematical model, numerical simulations of immunotherapy, chemotherapy and biochemotherapy for some cases such as variation of tumor size and variation of parameter are analysed.

**Enderling 2014 [28]** Using mathematical models to simulate dynamic biological processes has a long history. 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, with the ultimate goal of understanding the response of the cancer population to clinical intervention.

So called in silico trials that predict patient-specific response to various dose schedules or treatment combinations and sequencing are on the way to becoming an invaluable tool to optimize patient care. It describes fundamentals of mathematical modeling of tumor growth and tumor-host interactions, and summarize some of the seminal and most prominent approaches.

From the literature survey, there is a correlation of chaotic models and the tumor mathematical models, therefore chaos mathematical models are considered a tumor mathematical model. The typical nonlinear Model discussed by **Chua 1986 [19]**, **Chen 2001[16]** and **Lorenz 1963 [53]** in chaos theory. The system variables as Host Cell, Effectors Immune Cell and Tumor Cell is considered in the nonlinear ordinary Tumor Model-1, Tumor Model-2 and Tumor Model-3. The Nonlinear Partial Differential Equation Tumor Mathematical Models of **Anderson et al., 2008 [6]** and **Ivancevic et al., 2008 [37]** are also considered.