CHAPTER-1: INTRODUCTION

1.1. MATHEMATICAL MODEL

The real world object is represented by mathematical models in a formalized mathematical language. The advantage of mathematical models is that they can be analyzed in a precise way by means of mathematical theory and algorithms. In fact, the use of mathematical models to formulate many problems mathematically had been perceived since hundreds of years. However, the models are limited their use to qualitative analysis to very small and simple instances due to the want of the required computational work.

In the beginning of the twentieth century manual workers (most of the time low paid women) were used as “computers”, and the problem size was still very limited. As Electronic Numerical Integrator and Computer were started in 1945, models of previously unknown size became tractable. As a result of which, finding solution of practical problems of significant size became possible with the use of mathematical modeling for the first time. The computer technology gradually got its impetus which has been maintained since that time, resulted the huge gain in storage capacity and speed, which made mathematical modeling increasingly attractive for military and industry, and a special class of problems, optimization problems, became very important.

The reason behind the increasing demand for better and more complex models is the success in solving real world problems and the modeling process itself was probed. There are a number of books on modeling and branches of mathematics entirely devoted to solving practical problems and developing theory and algorithms for working on models. If we trace history, we’ll find that the structure of the models has changed from time to time, as the mathematical community gained increasing insight into the foundations of mathematics and formal logic. The introduction of variables, function spaces,
and of all the mathematical structural theory has made mathematical models increasingly formal for Bio Mathematical Models.

1.2. BIO MATHEMATICAL MODEL

The major concern of Mathematical biology is the mathematical representation, treatment and modeling of biological processes, using a variety of applied mathematical techniques and tools. Both theoretical and practical applications are apparent in biological, biomedical and biotechnology research. This requires accurate mathematical models. Describing systems in a quantitative manner means their behavior can be better simulated, and hence properties can be predicted that might not be evident to the experimenter.

Many of the emergent properties of inherently complex biological systems result from the interplay of numerous molecular components. Furthermore, the reactions of biochemical often obey nonlinear reaction kinetics that is, an increase in the amount of the starting material of the reaction does not necessarily lead to a proportional increase in the amount of the reaction product. Finally, other complexities, such as cell structure and compartmentalization or random effects, also often result in unexpected behavior of the entire system.

Researchers have found that mathematical models that take these factors into consideration have the features of complex biological systems and to understand how biological systems react to external or internal signals and perturbations, such as different growth or development conditions or stress triggered by agents such as alcohol.

One of the great advantages of mathematical models is of being amenable to computer simulations. Models describing biological systems are
usually complex in nature which makes it very difficult to solve analytically. Therefore, it is solved numerically that is, using computers to solve the mathematical equations that helps to predict the response of a biological system.

The response of a biological system to different conditions can be simulated relatively easily in silico once a mathematical model is available which is directly dependent on the availability of computer-based techniques for solving mathematical equations. These computer simulations (so-called “dry experiments”) in many cases require much lower investment and much less time compared with the typically more time-consuming and expensive biological experiments (sometimes referred to as “wet experiments”).

Mathematical models in biological sciences is the outcome of general approach for creating and using which is similar to the one followed in other scientific disciplines such as physics. It is provided the basis for communication between experimental and theoretical scientists. Theoretical biologists have already developed theories and mathematical formulas on the basis of existing experimental data which can be tested by experimentalists and used to predict the behavior of biological systems under as yet unexplored conditions.

The discrepancies if any between the predicted and measured results then need to be resolved, either by extending the theoretical framework (i.e., for instance by adding new equations to take into account other apparently important molecules that have not been considered in previous versions of the model) or by refining the experimental setup or data interpretation.

Several advantages of Mathematical models for biological systems and the associated computer simulations are evident. First, discrepancies
between systems behaviors predicted by a mathematical model and actual behaviors measured in experiments can point out components that still are missing from the mathematical model, thus helping in developing a complete picture of a biological process.

Even though if it is not clear which components are missing from the system under investigation, the results obtained with the mathematical model may help to guide the design of additional experiments to clarify the issue shown in Figure 1.1.

![Figure 1.1 Components of Mathematical Model](image_url)

In this research work considered a chaos theory [6, 19, and 53] mathematical models in to tumor mathematical models, for this consideration there is a lot of evidence in the literature [6, 7, 11, 15, 17, 21, 23, 24, 25, 28, 29, 31, 33, 34, 35, 36, 37, 41, 42, 45, 49, 54, 55, 58, 60, 61, 62, 63, 66, 67, 78, 79, 80 and 89]. The nonlinear system of ordinary differential equation models in the chaos theory, the system variables \(x, y, z\) as consider a host cell, effectors immune cell and Tumor cell respectively [50].
In this connection first introduce basic information about tumors and what are all the different types of tumor mathematical models describes as follows.

1.3. TUMOR MODEL

The generic term ‘Tumor’ designates a large class of diseases with a common pattern: the normal mechanism of cells proliferation and programmed death breaks down, giving place to a rapid creation of abnormal cells, which can grow beyond their usual boundaries and invade other organs.

Owing to the significant medical, scientific and technological developments over the last years, numerous types of tumors can be detected early for which there is effective treatments. Notwithstanding these remarkable advancements, our understanding of cancer is beyond reach and an established cure for this disease remains indefinable and extremely difficult to discover.

Undoubtedly, the analysis of tumor growth systems is critical to any attempt to study important phenomena involved in tumor growth and to predict its future behavior. Tumor growth systems represent a web of complex interactions among different body cells, based upon many important factors such as tumor severity, patient age, sex and immune system state, or treatment strategy, among other factors. The analysis and the understanding of this physiological complexity, historically studied through experimental and clinical observations, can be complemented with the study of mathematical models that incorporate critical interactions between tumor cells, host cells and effectors immune cells.

Basically there are three tumor mathematical models are there, Discrete Tumor mathematical model, the continuous Tumor mathematical Model and the hybrid Tumor Mathematical Models.
1.4. THE DISCRETE TUMOR MATHEMATICAL MODEL

Discrete models can easily incorporate on studying carcinogenesis, genetic instability, and natural selection, cell-cell and cell-matrix interaction mechanisms. However, discrete techniques also have drawbacks, which limit the model to a relatively small number of cells. As a result, a typical discrete model is usually designed with a lower domain size. These reason behinds, Tumor models are progressing to hybrid techniques that combine both continuum and discrete descriptions.

1.5. THE CONTINUOUS TUMOR MATHEMATICAL MODEL

Continuum models are good for larger scale system often a lesser choice in the exploration of tumor cell. Continuum model takes into account variables like cell volume, fractions, density, and cell substrate concentrations, (e.g., nutrient, oxygen, and growth factors). This model is considered when studying the effects of genetic, cellular, and microenvironment characteristics on overall tumor behavior. But continuum models cannot be used to study an individual cell dynamics and discrete events. Discrete models are suitable for addressing these shortcomings because they function at the individual cells in space and time.

1.6. THE HYBRID TUMOR MATHEMATICAL MODEL

In hybrid models cells are taken into account as discrete in some parts of the domain and as a continuum in others. Hybrid models have the potential to couple biological phenomena from the atomic scales to those at tumor scale. As in biological systems, the \textit{in silico} cell in the hybrid model can perform fundamental intrinsic core processes, specifically known to drive cancer invasion. The hybrid model has great predictive power, even though these core processes are not specified in molecular detail. Such molecular
details could be incorporated at a later date to refine the effects of particular core processes (such as the cell cycle, or cell–matrix interactions), owing to the open multi scale architecture of hybrid model. In fact, current hybrid model predictions have indicated molecular processes that are in need of better specification and/or parameterization.

1.7. PRELIMINARY INFORMATION ABOUT TUMORS

It has been shown in the literature that these interactions are the main components of these models which may yield a variety of dynamical results. The interest of applying chaos theory to biological systems, more specifically to chaotic tumor dynamics, relies in that chaos can give place to recognizable, repeatable structures at diverse scales, such as fractals, and both topological and dynamical properties can be studied to determine important and practical measures like predictability. Cancer is the uncontrolled growth of abnormal cells in the body.

The above mentioned three malignant properties of cancer differentiate malignant tumors from benign tumors, which do not grow uncontrollably, directly invade locally, or metastasis to regional lymph nodes or distant body sites like brain, bone, liver, or other organs. In order to understand the mechanism of the disease and to predict its future behavior, mathematical models for tumor growth have been extensively studied in the literature. Interactions of tumor cells with other cells of the body, i.e. healthy host cells and immune system cells are the main components of these models and these interactions may yield different outcomes.

A number of important phenomena of the tumor progression such as tumor dormancy, creeping through, and escape from immune surveillance have been investigated by using these models. Kuznetsov [49] proposed a model of second order, governed by ordinary differential equations, which includes the effectors immune cell and the tumor cell populations. They established that even with two cell populations, these models can provide
very rich dynamics depending on the system parameters and explained some very important aspects of the stages of cancer progression.

In fact, one can find numerous other models of the tumor-immune interactions with their dynamical study as well as investigations of optimal therapy effects. Although all these models include different cell populations, they share basic common characteristics such as existence of tumor free equilibrium which is the main attention of investigating the therapy effects; coexisting equilibrium where the tumor and other cells are present in the body and in competition, and finally the tumor escape and uncontrolled growth.

In the Literature have strong evidence mention in the Section 1.1, that chaos theory mathematical models are considered a tumor mathematical models. In this connection the following information are tumors as attractors, a scientific program to investigate tumors as strange attractors, from biological systems to strange attractors details as follows.

1.8. TUMORS AS ATTRACTORS

Cancer as a genetic disease that arises from mutations in susceptible genes and subsequent somatic evolution is the perspective that has driven oncologic research for decades. In the last few years this picture has been refined with the description of time dependent regulatory networks. These networks are rich in regulatory motifs that include positive or negative feedback as well as coherent and incoherent feed forward loops, whose regulation is difficult to understand because their effect on the dynamics of the systems is often non-linear [59].

Whether the origin of cancer is genetic and resides in the microscopic world of genes and mutations within single cells, or whether it is emerging from a failure of tissue organization, it actually manifests as a mesoscopic structure, the tumor. In fact, tumors are not simple aggregations of
genetically abnormal cells. They display an amazing genetic heterogeneity between the cells that compose them.

Those cells are not isolated from the outer world; rather establish complex interactions between them and with their microenvironment, which ultimately are expressed as selective pressures like hypoxia, lack of nutrients or apoptosis that govern the fate of the tumor as a whole. Hence, from a worldly point of view tumors are also complex dynamical systems and the natural language to analyze such systems is dynamical systems theory. This framework allows to handle concepts like complexity, non-linearity, robustness, sensitivity and (in) stability of a system, which actually emerge also in tumors [59], the cancer cells and the regulatory networks governing them. In this connection tumors considered as attractors for the further investigation the following section discuss about a scientific program to investigate tumors as strange attractors.

1.9. A SCIENTIFIC PROGRAM TO INVESTIGATE TUMORS AS STRANGE ATTRACTORS

Hypothesized that tumor dynamics behaves as strange attractors from the perspective of their organization and dynamics. In this regard, genetic instability plays the role of the local-scale driving force providing the source of local instability, while the selective pressures operating over the tumor cell populations act as a mesoscopic dissipative process.

Taking a scientific program into consideration, this vision of tumors as strange attractors is possible. It requires the development of experimental and computational tools to link the micro and mesoscopic perspective of tumor biology. From a computational perspective, the aim is to develop models able to generate a dynamical genotype-phenotype mapping of tumors. Hybrid, multi-level mathematical models, integrating information from different Spatio-temporal scales, seem the right tool to further develop in the
coming years. According to our point of view, this conceptual approach comprises an advanced setup of the Cancer Systems Biology paradigm.

Long-established opposing hypothesis have supported that the origin of cancer is either genetic and resides in the microscopic world of genes and mutations within single cells, or it is emerging from a failure of tissue organization. However, new experimental results concerning the tumor microenvironment interaction reveals that both hypotheses are not mutually exclusive.

Considering the tumor microenvironment interaction, given cancer genotypes may have the ability to induce tissue remodeling, whereas certain environmental changes may as well generate a microenvironment favorable to increase the usually low predisposition for mutations. Under such condition, tumors become definitively complex, multi scale, and highly nonlinear systems, prone to be described under the dynamical systems theory is proposed in this research work.

1.10. BIOLOGICAL SYSTEMS TO STRANGE ATTRACTORS

A quick guide to dynamical systems theory Natural systems are ensembles of physical entities that interact with each other. Biology, rather than being an exception, is a realization of this idea: biological entities are organized in systems, from interacting proteins to the entire biosphere. When biological systems become structurally complex (e.g., too many proteins), their analysis evades direct reasoning and intuition, making mathematical modeling as a necessary tool. There are many instances of mathematical models, but one very widespread class of models suitable to understand biochemical and cell population systems are ordinary differential equations.

These models describe Spatio-temporal changes of biological entities using equations with the following structure:

\[
\frac{d}{dt} C = \sum_i F_i(S, K, C) \quad (1.1)
\]
In the above equation (1.1), C are the time-dependent variables accounting for the biological entities whose evolution over time is analyzed (i.e., interacting proteins or tumor cell populations), F are the rate equations formalizing interactions between the biological entities, S are inputs (external stimulus affecting the system) and k are parameters (fixed numbers associated with given features like rate of proliferation or protein cleavage).

With this kind of model, one can trace the evolution of the system properties over time, the so-called trajectories. Under some conditions, the trajectories evolve towards steady-state configurations of the system in which the properties of the system C stay constant (stability), while others keep the system changing constantly and generate instability.

When biological systems are enriched with complex regulatory motifs like feedback and forward loops, changes in the value of critical biological parameters ‘k’ induce sudden transitions between stable and unstable configurations of the system, the so-called bifurcations (e.g., a mutation increasing the cell proliferation rate can transform a rather stable microscopic neoplastic lesion into a growing macroscopic tumor).

Furthermore, systems containing multiple interconnected instances of these motifs can display chaotic behavior, under some conditions. This behavior is characterized by a high sensitivity to initial conditions that makes the dynamics of the system appear irregular. This is the case of, for example, multi-looped negative feedback systems. Such systems must be described and analyzed through the use of chaos theory.

A dynamical structure that was discovered using this theory are strange or chaotic attractors. An attractor is a configuration (a set of values for the variables) towards which the system evolves over time. Finally, in a strange attractor the values of the system variables remain permanently confined in a delimited region of all the phase space. However, within that region the system will go through the same point more than once. This is a special kind of behavior detected in some nonlinear dynamical systems,
characterized by two contradictory properties: from a global perspective they are stable structures, but locally they are unstable.

In the strange attractor within the closed boundary there is an uncertainty and unpredictable as seen with the cancer progression. There are various events during different stages of cancer progression, serving as ‘strange attractors’ and regulates the effectiveness of antitumor treatment. Cancer progression is totally unpredictable and uncertain for example, if it the same cancer types it will behave differently in every patient in term of appearance, size and severity. However, the characteristics of dynamic system are totally dependent of initiation of cancer. In this connection, the sections 1.8, 1.9 and 1.10 are defines that, any nonlinear dynamical system can be considered as a Tumor Mathematical model.

1.11. SETTING THE CLOCK BACK TO ZERO PROPERTY

Still, what we have called the “setting the clock back to zero” [69,70,71,72,73 and 76] or an invariance property of a family of life distributions. This property ensures that the conditional distribution of the additional time of survival of a living organism or an industrial item, given that it has survived $x_0$ units, remains in the family.

This concept generalizes the lack of memory property of the exponential distribution, for which the conditional distribution of additional survival time is exactly the same as the original distribution. The advantage of having such a property appears in many epidemiological, biomedical and engineering investigations.

Let us assume that the data available for analysis are a sample from a population, for which the proportion of items placed in service and surviving at age $x$ is given by an unknown differentiable function of non-negative ages. This function will be called the survival function $s(x)$. This function is required to satisfy the conditions

$$s(0) = 1, s(\infty) = 1 and s'(x) \leq 0, x \geq 0$$
The function \( s(x) \) gives the probability that an item has not failed up to time \( x \). Clearly the survival function is related to the cumulative distribution function \( F(x) \) by the relationship \( s(x) = 1 - F(x) \). The mortality function, \( f(x) \), or the probability density function (p.d.f.) of the life length \( X \) of an item, is the instantaneous rate of decrease of \( s(x) \),

\[
f(x)dx = -ds(x)
\]

The force of mortality, \( \gamma(x) \), is the proportional rate of decrease of \( s(x) \), i.e.

\[
\gamma(x) = \frac{f(x)}{s(x)}
\]

This gives the differential equation

\[
\gamma(x)dx = -d\{\log s(x)\}
\]

Upon integration, it will be seen that the survival function can be expressed in terms of the force of mortality as

\[
s(x) = \exp\left\{-\int_0^x \gamma(u)du\right\} = \exp\{-\gamma(x)\}, \text{say},
\]

Where \( \gamma(x) \) is defined by the equation (Called the cumulative hazard function)

\[
\gamma(x) = \int_0^x \gamma(u)du
\]

Also, the mortality function \( f(x) \) may be expressed as

\[
f(x) = \gamma(x)\exp\{-\gamma(x)\}
\]

Several useful applications of the function \( \gamma(x) \) have been given in the literature under different names. Actuaries call it the force of mortality, with reference to a specific response or life time distribution, which describes the distribution of the lifetimes of individuals over a population of individuals, i.e.,
\( y(x)dx \) represents the probability that an individual of age \( x \) will die in the interval \((x, x + dx)\). In other words, \( y(x)dx \) is the conditional probability of death in the interval \((x, x + dx)\) given survival up to time \( x \). It is clear from equation that \( y(x) \) uniquely determines the probability density function \( f(x) \).

The following three choices give closed forms for the survival and force of mortality functions.

(i) \( y(x) = a \text{ constant } \theta \), which gives an exponential distribution for the life length with the p.d.f. \( f(x) = \theta e^{-\theta x}, x \geq 0, \theta > 0 \)

(ii) \( y(x) = px^{p-1}, p > 0 \) which gives the Weibull distribution for the life length, with the p.d.f \( f(x) = px^{p-1}e^{-xp}, x \geq 0, p > 0 \)

(iii) \( y(x) = ke^{ax}, k > 0 \) which gives the Gompertz distribution for the life length, with the p.d.f. \( f(x) = ke^{ax} \exp\left\{-\frac{k}{a}(e^{ax} - 1)\right\}, x \geq 0, k > 0 \) The parameter \( a \) may be positive or negative.

A variety of other families of distributions, such as the gamma, the truncated normal and the log-normal distributions, have been used for the fatigue failure of materials and the life length of electronic and mechanical components in industrial applications.

The exponential distribution has been used by Epstein and Sobel (1953)[11] in industrial life testing. Zelen(1966)[93] applied this model to analyze survival data in animal tumor systems and acute leukaemia. The Weibull model has been used in several applications in engineering, industry and cancer research; see Bain (1978)[10]. The Gompertz model for \( y(x) \) been used by Garg, Raja Rao and Redmond (1972)[69], who have studied its properties and obtained maximum likelihood estimates of its parameters.

These distributions can, of course, be generalized by replacing \( x \) by \( x - b \), where \( b \) represents, what is called the ‘guarantee’ time in industry, where no item can fail before \( b \) units of time have elapsed. In epidemiological or biomedical applications, the parameter \( b \) might represent the ‘latent’
period of some disease. This period may be simply defined as the time elapsed between first exposure to an agent and the appearance of a symptom.

In cancer research problems, we may regard the parameter $b$ as the time elapsed between first exposure to a carcinogen and the appearance of a tumor. In many epidemiological and biomedical studies, individuals or patients do not enter a study as soon as they are born, but rather when they have reached an age $x_0$ say. Their survival time or period of observation is measured from the time $x_0$ onwards, satisfying $X \geq x_0$. In other words, the population of their survival times, given that they are of age $x_0$, becomes a truncated distribution, often with a form different from the original lifetime distribution of individuals, defined for ages $X \geq 0$. If a transformation of the form $X_1 = X - x_0$, is introduced, so that the new lifetimes satisfy $X_1 \geq 0$, the situation does not improve. This shows that certain families of life distributions have the “setting the clock back to zero” property, also called the invariance property.

A family of life distributions with survival functions $\{s(x, \beta); \beta \in \Omega\}$ is said to have the “setting the clock back to zero” property (or to be ‘invariant’) if for each $\beta \in \Omega$ and $x_0 > 0$, the survival function satisfies the condition

$$\frac{s(x + x_0, \beta)}{s(x_0, \beta)} = s(x, \beta^*) \text{ with } \beta^*(x_0, \beta) \in \Omega$$

This means that the conditional distribution of the additional time of survival, given that it has survived $x_0$ units remains in the family. This property generalizes the lack of memory property of the exponential distribution for which the conditional distribution of additional survival time is exactly the same as the original distribution.

In other words, the form of the original distribution remains unchanged under the following operations except for the values of its parameters:

1. truncating the original distribution at some point $x_0 \geq 0$
(2) considering the observable distribution for life times $X \geq x_0$

(3) changing the origin by means of the transformation given by $X_1 = X - x_0$ so that $X_1 \geq 0$

From the equation, it may be seen that

$$\frac{s(x + x_0, \beta)}{s(x_0, \beta)} = \exp\{-y(x + x_0, \beta) - y(x_0, \beta)\}$$

Thus invariance implies, and is implied by

$$y(x + x_0, \beta) - y(x_0, \beta) = y(x, \beta^*)$$

$$y(x + x_0, \beta) = y'(x + x_0, \beta) = y'(x, \beta) = y(x, \beta^*)$$

Apply this setting the clock back to zero property in our research work in the hybrid dynamical system that is the system of nonlinear ordinary differential equation models to identify the growth of exponential variation. The Setting Clock Back to Zero property is used to identify the exponential growth for Tumor models to validate the real time data.

1.12. TECHNIQUES FOR SOLVE OUR MODELS

The differential equations have played a vital role in every aspect of applied mathematics for every long time and with the advent of the computer, their importance has increased further. Thus investigation and analysis of differential equations cruising in applications lead to many deep mathematical problems; therefore there are so many different techniques in order to solve differential equations.

In order to solve the differential equations, the integral transforms were extensively used thus there are several words on the theory and applications of integral transforms such as the Laplace, Fourier, Mellin, Hankel and Smmudu, Etc. In our research work the Differential transform, Elzaki transform and Fractional Order Multi stage Homotopy Perturbation methods has been taken for analysis of adopted models.
1.12.1 DIFFERENTIAL TRANSFORM METHOD

A variety of methods, exact, approximate, and purely numerical are available for the solution of systems of differential equations. Most of these methods are computationally intensive because they are trial-and-error in nature, or need complicated symbolic computations. Integral transforms such as Laplace and Fourier transforms are commonly used to solve differential equations and usefulness of these integral transforms lies in their ability to transform differential equations into algebraic equations which allows simple and systematic solution procedures.

However, using integral transform in nonlinear problems may increase its complexity. In the present work, some partial differential equations with non homogeneous initial conditions aimed to solve by the differential transformation method [1, 2, 8, 13, 14, 44, 90 and 95]. The differential transformation is a numerical method for solving differential equations. The concept of differential transform was introduced by Zhou (1986) [95], who solved linear and nonlinear initial value problems in electric circuit analysis.

Kangalgil and Ayaz (2008) [44] developed this method for PDEs and obtained closed form series solutions for linear and nonlinear initial value problems. The differential transforms method gives an analytical solution in the form of a polynomial.

It is different from the traditional high order Taylor series method, which requires symbolic computation of the necessary derivatives of the data functions. The Taylor series method is computationally taken long time for large orders. The present method reduces the size of computational domain and applicable to many problems easily. Adomian decomposition method which is given by Jin and Liu (2005) [41], for approximate solution of linear and nonlinear differential equations and to the solutions of various scientific models such that in El-Wakil and Abdou (2007)[27], Khalifa et al. (2007) [47].
A distinctive practical feature of the differential transformation method DTM is applied to solve linear or nonlinear differential equations. In fact, DTM are very efficient methods to find the numerical and analytic solutions of differential-difference equations, delay differential equations as well as integral Equations as in Karakoc and Bereketoglu (2009) [45], Arikoglu and Ozkol (2006)[8]. Higher-order dimensional differential transformations are applied to a some initial value problems to show that the solutions obtained by the proposed method DTM coincides with the approximate solution and the analytic solutions.

1.12.1.1. Definition 1. :
Consider the analytical function of one variable $u(x)$ which is defined on $D = [0,X] \subset \mathbb{R}$ and $x_0 \in D$ one dimensional differential transform of $u(x)$ denoted by $U(K)$ and is defined on $\mathbb{N} \cup \{0\}$ as the following:

1.12.1.2. Definition 2:
The one-dimensional differential transform of function $u(x)$ is defined as follows:
$$U(K) = \frac{1}{k!} \left[ \frac{d^k u(x)}{dx^k} \right]_{x=x_0}$$
Where $u(x)$ is the original function and is $U(K)$ called the transformed function.

1.12.1.3. Definition 3:
Inverse differential transform of $U(K)$ in the equation defined as follows :
$$u_0(x) = \sum_{k=0}^{\infty} U(K)(x-x_0)^k$$
Since $u(x)$ is an analytical function, it is clear that $u(x) = u_0(x)$

1.12.1.4. Definition 4: $u_0(x) = \frac{1}{k!} \left[ \frac{d^k u(x)}{dx^k} \right]_{x=0}$

1.12.1.5. Definition 5:
The differential inverse transform of $U(K)$ is defined as follows:
$$u_0(x) = \sum_{k=0}^{\infty} U(K)(x)^k$$
Substituting then
$$u_0(x) = \frac{1}{k!} \left[ \frac{d^k u(x)}{dx^k} \right]_{x=0} x^k$$
In real applications, the function $u(x)$ by a finite series can be written as
\[ u(x) = \sum_{k=0}^{\infty} U(K)(x)^k \]

And implies that
\[ u(x) = \sum_{k=n+1}^{\infty} U(K)(x)^k \]

Usually, the values of \( n \) are decided by a convergence of the series coefficients. From the definition of (3) and (4), it is readily proved that the transformed functions comply with the basic mathematical operations. The fundamental mathematical properties of one-dimensional differential transform can readily be obtained and are summarized in the standard theorems.

1.12.2. ELZAKI TRANSFORM

The concept of the Elzaki Transform Method (ETM) [5, 82, 83, 84, 85, 86, 87 and 88] was first proposed by Tarig M. Elzaki is an efficient method for solving the linear and non-linear system of ordinary differential equations. The final solution is obtained by iteration procedure.

The Elzaki transform easier than the Laplace transform for the beginners to understand and apply. The former transform can still serve as an auxiliary method to the latter. Very little on the power series transformation or Elzaki transform, probably because it is little known, and not widely used.

The Elzaki transform rivals the Laplace transform in problem Solving, its main advantage is the rivals that it may be used to solve problems without resorting to a new frequency domain because it preserve scales and units of properties.

1.12.2.1. Definition 1:
Consider functions in the set \( A \) defined by
\[ A = \left\{ f(t) : \exists M, k_1, k_2 > 0, |f(t)| < Me^{\frac{|t|}{k}}, \text{ if } t \in (-1)^j \times [0, \infty) \right\} \]

Where \( M \) a constant is must be finite number and \( k_1, k_2 \) can be finite or infinite.
1.12.2.2. Definition 2: 
Elzaki transform denoted by the operator $E(\circ)$, is defined by the integral equation:

$$E[f(t)] = T(u) = u \int_{0}^{\infty} f(t)e^{-ut} dt, -k_1 \leq u \leq k_2, t \geq 0$$

1.12.2.3. Definition 3: 
Elzaki transform denoted by

$$T(v) = E[f(t), v] = v \int_{v}^{\infty} f(t)e^{-vt} dt, v \in [-k_1, k_2]$$

$$T(v) = E[f(t), v] = v^2 \int_{v}^{\infty} f(t)e^{-vt} dt, k_1, k_2 > 0$$

1.12.2.4. Definition 4: 
For any function, or by the convention rule

$$T(v) = \sum_{n=0}^{\infty} n! a_n v^{n+2}$$

1.12.2.5. Definition 5: 
Let $T(u)$ be the Elzaki transform of $f(t)$ denoted as

$$[E(f(t)) = T(v)]$$

(i) $E[f'(t)] = \frac{T(v)}{u} - v f(0)$

(ii) $E[f''(t)] = \frac{T(v)}{u^2} - f(0) - v f'(0)$

(iii) $E[t f'(t)] = v^2 \frac{d}{dv} \left[ \frac{T(v)}{v} - f(0) - v f'(0) \right] - v \left[ \frac{T(v)}{v^2} - f(0) - v f'(0) \right]$ 

(iv) $E[t^2 f''(t)] = v^2 \frac{d}{dv} \left[ \frac{T(v)}{v^2} - f(0) - v f'(0) \right]$ 

(v) $E[t^2 f'''(t)] = v^4 \frac{d^2}{dv^2} \left[ \frac{T(v)}{v^2} - f(0) - v f'(0) \right]$ 

1.12.3. MULTI STAGE HOMOTOPY PERTURBATION METHOD

Perturbation theory comprises mathematical methods for finding an approximate solution to a problem, by starting from the exact solution of a related problem. A critical feature of the technique is a middle step that breaks the problem into "solvable" and "perturbation" parts.
Perturbation theory is applicable if the problem at hand cannot be solved exactly, but can be formulated by adding a "small" term to the mathematical description of the exactly solvable problem.

The Homotopy Perturbation Method (HPM) is a universal one which can be applied to various kinds of linear and nonlinear equations. It usually needs only a few iterations to lead to the active approximate analytical solutions for a given system. The approximate solutions generally, as shall be shown in the numerical experiments, not valid for large t. The HPM treated as an algorithm in a sequence of intervals for finding accurate approximate solution to the system. The modified HPM, i.e. the Multi Stage Homotopy Perturbation Method [4, 12, 18, 20, 22 and 38] can give the valid solutions for a long time. This method applied for fractional order Chua, Chen and Lorenz systems.

1.12.3.1. BASIC DEFINITION AND PRELIMINARY FOR FMHP

Over the last decades, fractional order differential equations (FODEs) have been used to describe a variety of systems in interdisciplinary fields, such as viscoelasticity, biology, physiology, medicine, hydraulics geology and engineering. Based on the extension of applications of FODEs, the Chaos theory fractional order systems become a new topic due to its potential applications especially in secure communication, encryption and control processing.

For better understanding the dynamic behavior of a chaos field fractional order system, the solution of the Chua’s fractional order system is much involved. In general, it is difficult to obtain the exact solution for nonlinear FODEs. Finding accurate and efficient methods for solving FODEs has been an active research undertaking. Some analytical and numerical methods have been proposed for the solutions of FODEs. The classical approaches include Laplace transform method, Mellin transform method, fractional Green’s function method and power series method.
In the literatures of fractional chaos field, two approximation methods have been advised for the numerical solutions of the fractional order systems. One method is based on the approximation of the fractional order system behavior in the frequency domain and time domain. The other method is the well-known predictor correctors scheme. According to the theory of fractional calculus, our concern in this work is to extend the MHPM to consider the approximate numeric analytic solutions of the chaos field fractional order systems. The MHPM is a very effective and simple method for the accurate approximate solutions of the chaos field fractional order systems for a long time. Here give some basic definitions and properties of fractional calculus which are used further in this research work.

1.12.3.2. Definition: 1

A real function $h(t), t > 0$ is said to be in the space $C_{\mu}, \mu \in R$, if there exist a real number $p(> \mu)$, such that $h(t) = t^p h_1(t) \in [0, \infty)$, and it is said to be in the space $C_{\mu}^n$ if and only if $h^{(n)} \in C_{\mu}, n \in N$.

1.12.3.3. Definition: 2

The Riemann-Lowville fractional integral operator $(aJ_t^\alpha)$ of order $\alpha \geq 0$ of a function $h \in C_{\mu}, \mu \geq -1$ is defined as

$$aJ_t^\alpha h(t) = \frac{1}{\Gamma(\alpha)} \int_a^t (t - \tau)^{\alpha-1} h(\tau) d\tau, (\alpha > 0)$$

$$aJ_t^\alpha h(t) = h(t)$$

where $t \geq a \geq 0$, $\Gamma(.)$ is the well-known Gamma function. Some of the properties are given as follows: For $h \in C_{\mu}, \mu \geq -1, a, \alpha, \beta \geq 0, \gamma \geq -1$

(i) $aJ_t^\alpha aJ_t^\beta h(t) = aJ_t^{\alpha + \beta} h(t)$

(ii) $aJ_t^\alpha aJ_t^\beta h(t) = aJ_t^\beta aJ_t^\alpha h(t)$
\[(iii) \ aJ^\alpha_t (t-a)^\gamma = \frac{\Gamma(\gamma+1)}{\Gamma(\alpha+\gamma+1)} (t-a)^{\alpha+\gamma}\]

1.12.3.4. Definition: 3

The Caputo fractional derivative \(aD^\alpha_t\) of \(h(t)\) is defined as

\[aD^\alpha_t h(t) = \frac{1}{\Gamma(n-\alpha)} \int_a^t (t-\tau)^{n-\alpha-1} h^{(n)}(\tau)d\tau\]

for \(n-1 < \alpha \leq n, n \in N, t \geq a \geq 0\) and \(h \in C^n\_1\).

Hence, following properties have

(i) If \(n-1 < \alpha \leq n, n \in N, and h \in C^n_\mu, \mu \geq -1\), then \(aD^\alpha_t aJ^\alpha_t h(t) = h(t)\) and

\[aJ^\alpha_t aD^\alpha_t h(t) = h(t) - \sum_{k=0}^{n-1} h^{(k)}(a) \frac{(t-a)^k}{k!}\]

(ii) let \(h(t) \in C^n_{n-1}, n \in N\). Then \(aD^\alpha_t h, 0 \leq \alpha \leq n\) is well defined and \(aD^\alpha_t h \in C^n_{n-1}\).

1.12.3.5. ANALYSIS OF THE METHOD

In this section, extension of the application of the MHPM to the fractional order differential equations in the following form:

\[
\begin{align*}
aD^{\alpha_1}_t y_1(t) &= f_1(t,y_1,y_2,y_3,\ldots,y_n), \\
aD^{\alpha_2}_t y_2(t) &= f_2(t,y_1,y_2,y_3,\ldots,y_n) \\
aD^{\alpha_3}_t y_3(t) &= f_3(t,y_1,y_2,y_3,\ldots,y_n) \\
\vdots & \quad \vdots \\
aD^{\alpha_n}_t y_n(t) &= f_n(t,y_1,y_2,y_3,\ldots,y_n)
\end{align*}
\]

Subject to the following initial condition: \(y_i(a) = c_i, i = 1,2,3,\ldots,n\)

where \(0 < \alpha_i \leq 1, t \geq a \geq 0\), \(f_i\) is an arbitrary linear or nonlinear function.

1.12.3.6. SOLUTION BY HPM

The HPM is a universal one which can be applied to various kinds of linear and nonlinear equations. It usually needs only a few iterations to lead to the active approximate analytical solutions for a given system. In view of the HPM, we construct a homotopy for the Equations which satisfies the following relations:
\[ aD_t^{\alpha_n} y_i(t) = pf_i(t, y_1, y_2, y_3, \ldots, y_n) \] ---(A)

Where \( i = 1, 2, 3 \ldots n, p \in [0,1] \) is an embedding parameter. When \( p = 0 \), equation (A) becomes linear \( aD_t^{\alpha_n} y_i = 0 \), and when \( p = 1 \), equation (A) turns out to be the original equation. The basic assumption is that the solution of above equation can be expanded as power series in \( p \).

\[ y_i(t) = y_{i0} + py_{i1} + p^2y_{i2} + p^3y_{i3} + \ldots \] ---(B)

And the initial conditions are taken as

\[ y_{i0}(a) = y_i(a) = c_i, y_{ik}(a) = 0, k = 1, 2, 3 \ldots \]

where \( y_{ij}(t), j = 0, 1, 2, 3 \ldots \) are the functions to be determined later.

Substituting equation (B) into equation (A), collecting the terms of the same powers of \( p \), we obtain

\[ P^0: \quad _0D_t^{\alpha} y_{i0} = 0 \]
\[ P^1: \quad _0D_t^{\alpha} y_{i1} = f_{i1}(t, y_{10}, y_{20}, y_{30}, \ldots, y_{n0}) \]
\[ P^2: \quad _0D_t^{\alpha} y_{i2} = f_{i2}(t, y_{10}, y_{20}, y_{30}, \ldots, y_{n0}, y_{11}, y_{21}, y_{31}, \ldots, y_{n1}) \]
\[ P^3: \quad _0D_t^{\alpha} y_{i3} = f_{i3}(t, t, y_{10}, y_{20}, y_{30}, \ldots, y_{n0}, y_{11}, y_{21}, y_{31}, \ldots, y_{n1}, y_{12}, y_{22}, y_{32}, \ldots, y_{n2}) \]

Where \( f_{i1}, f_{i2} \ldots \) satisfy the following equation

\[ f_i(t, y_{10} + py_{11} + p^2y_{12} + \ldots, y_{n0} + py_{n1}, p^2y_{n2} + \ldots) = f_{i1}(t, y_{10}, y_{20}, y_{30}, \ldots, y_{n0}) + p f_{i2}(t, y_{10}, y_{20}, y_{30}, \ldots, y_{n0}, y_{11}, y_{21}, y_{31}, \ldots, y_{n1}) \]
\[ + p f_{i3}(t, t, y_{10}, y_{20}, y_{30}, \ldots, y_{n0}, y_{11}, y_{21}, y_{31}, \ldots, y_{n1}, y_{12}, y_{22}, y_{32}, \ldots, y_{n2}) + \ldots \]

Applying the integral operator \( _aD_t^{\alpha_i}(\cdot) \) on both sides of the above fractional order equation, which considering the initial condition, by using the properties of the Caputo fractional derivative, we can determine the unknown function \( y_{ij}(t) \).

By setting \( p = 1 \) in the HPM series solutions to equations are given as

\[ y_i(t) = \sum_{j=0}^{\infty} y_{ij}(t) \]
Where \( i = 1, 2, 3 \ldots n \). The N-term approximation of the HPM series can be expressed as

\[
y_i(t) \approx \emptyset_{iN}(t) = \sum_{j=0}^{N-1} y_{ij}(t), \quad i = 1, 2, 3 \ldots n.
\]

1.12.3.7 SOLUTIONS BY MHPM

The approximate solutions generally, as shall be shown in the numerical experiments of this research work, not valid for large \( t \). The HPM treated as an algorithm in a sequence of intervals for finding accurate approximate solution to the equations. The modified HPM, The MHPM, can give the valid solutions for a long time.

The time interval \([a, t]\) can be divided into a sequence of subintervals \([t_0, t_1), [t_1, t_2), [t_2, t_3) \ldots [t_{j-1}, t_j]\), in which \( t_0 = a, t_j = t \). Without loss of generality, the subintervals can be chosen as the same length \( \Delta t. \Delta t = t_i - t_{i-1}(l = 2, 3, \ldots j) \). Furthermore, the equations can be solved by HPM in every sequential interval \([t_{i-1}, t_i)(l = 2, 3, \ldots j)\) Chosing the initial approximations as

\[
y_{i0}(t^*) = y_i(t^*) = c_i, \quad y_{ik}(t^*) = 0, \quad i = 1, 2, 3 \ldots, n, \quad k = 1, 2, 3 \ldots
\]

Where \( t^* \) is the left-end point of each sub interval, but in general, we only having the initial values at the point \( t^* = t_0 = a \). A simple way to obtain the other necessary values could be by means of the previous N-terms approximate solutions

\[
\emptyset_{iN(t^*)}, \quad i = 1, 2, 3 \ldots n \text{ of the preceding subinterval } [t_{l-2}, t_{l-1}), (l = 2, 3, \ldots j), \text{ i.e}
\]

\[
y_{i0}^{l}(t^*) = \emptyset_{iN(t^*)}.
\]

Finally, the unknown functions \( y_{ij}(t), \quad i = 1, 2, 3 \ldots n, \quad j = 0, 1, 2, 3 \ldots \) can be obtained by the fractional integral operator

\[
t t y_{ij}(t) = \frac{1}{\Gamma(a_i)} \int_{t^*}^{t} (t - \tau)^{a_i - 1} y_{ij}(\tau) d\tau
\]

1.12.4. FRACTIONAL DERIVATIVES
Two commonly used definitions for the general fractional differ integral are the Grunwald definition and the Riemann Liouville definition (Oldham and Spanier, 1974). The Riemann Liouville definition of the fractional integral is given here as

\[
a D_q^t f(t) = \frac{d^q f}{dt^q} = \frac{1}{\Gamma(n-q)} \left( \frac{d}{dt} \right)^n \int_a^t \frac{f(\tau)}{(t-\tau)^{q-n+1}} d\tau, n - 1 \leq q \leq n
\]

\[
a D_q^t f(t) = \frac{d^q f}{dt^q} = \frac{1}{\Gamma(-q)} \int_0^t \frac{f(\tau)}{(t-\tau)^{q+1}} d\tau, q < 0
\]

Where \( q \) can have non integer values, and thus the name fractional differ-integral. Notice that the definition is based on integration and more importantly is a convolution integral for \( q < 0 \). When \( q > 0 \), then the usual integer \( n \)th derivative must be taken of the fractional \((q - n)\)th integral, and yields the fractional derivative of order \( q \) as

\[
\frac{d^q f}{dt^q} = \frac{d^n}{dt^n} \left[ \frac{d^{q-n} f}{dt^{q-n}} \right], q > 0 \text{ and } n \text{ an integer } > q
\]

1.12.5 RUNGE KUTTA FOURTH ORDER METHOD

Runge Kutta method is a powerful tool for the solution of ordinary differential equations. Most of the research has been oriented towards improving the accuracy or the flexibility (to accommodate problems of diverse nature) of the classical Runge Kutta method. The solution of a class of non-linear partial differential equations (PDE) is obtained by using this method.

The solution of non-linear PDE is feasible by the Runge Kutta method; it yields more accurate results than that obtained by finite difference methods. The use of Runge Kutta methods to solve problems of this type is a novel approach. The method described as follows

\[
\frac{dy}{dt} = f(t, y(t)) \text{ with initial condition } y(t_0) = y_0
\]

\[
a = dtf(u_n, t_n)
\]

\[
b = dtf \left( y_n + \frac{a}{2}, t_n + \frac{1}{2} \right)
\]
The prime objective of this research is to study three different typical nonlinear chaos theory ODE models Chua, Chen, Lorenz representing Tumor Model-1, Tumor Model-2 and Tumor Model-3 respectively and to analyze the solution of these models to obtain concrete inferences. The above mentioned system of ODEs is solved employing the various techniques, namely, Differential Transform Method, Elzaki Transform Method and Multistage Homotopy perturbation method.

Further the study is extended to two different PDE models of tumor growth detailed as follows: The Anderson Enderling, Spatio-temporal system of coupled PDEs (Four dimensional Tumor PDE model).

1.13. MOTIVATION BEHIND THIS RESEARCH WORK

Various medical procedures such as chemotherapy, radiation therapy, surgery, hormone therapy, biological therapy and targeted therapy are available for the patients. There has been intensive research on cancer and its related factors viz. medicine, curing techniques, drug delivery and instrumentation. These methods, being pretty much costlier, no doubt provide significant benefits in curing cancer. But being a Mathematician, we can also play an excellent role in supporting this fight against cancer. Mathematical models provide most promising approaches to be tested in labs, which are otherwise very expensive and time consuming.

To help this reason, mathematical modeling is a valuable technique that has been developing since last decades Mathematical modeling provides an interdisciplinary tool to bring together clinicians, biologists and mathematical and computational modelers. People worldwide are working with mathematical models in various fields to bring out the best possible results so as to get a better approximation to the validity of their experimental results. The pace of the research can be accelerated by the use of
mathematical models as these models may predict the action of the drug on the cancer cells as well as on the healthy cells.

With the help of these models a better understanding of the interaction of the drug and cells can be achieved which may provide better future strategies for the treatment and the quality and duration of patient’s life can be improved. Mathematical modeling of cancer may help to understand the dynamics of cancer progression, its cure and is economic way to deal with such a disease. Not only for cancer but for various biological processes, mathematical modeling plays an important role.

Different types of models focusing on different types of prevailing cancers have been put forward by numerous people working in this noble cause Mamat et al [56], Rachel roe-dale et al [67] in their papers have studied cancer treatment with a mathematical approach. People at international level have contributed much more in this field. However, researcher being really efficient at theoretical mathematics, the status of mathematical handling of cancer in India is at a preliminary level. The level of theoretical research is not at par with the severity of disease in India. Henceforth, there lies a wide scope of research in this area.

1.14. ARRANGEMENT OF CHAPTERS


In Chapter 2, a brief summary on research papers published by various authors is given as the review of literature.
In Chapter.3, The detailed discussion as introduction to Chua’s model as Tumor model-1 and the solution of the model by Differential Transform Method, Elzaki transform method and Fractional order Multistage Homotopy Perturbation method. The numerical solutions Tumor model-1 is obtained and represent graphically. It is shown that the result is perfectly in agreement with the established basic principles of tumor microenvironment.

In Chapter.4, The detailed discussion as introduction to Chen’s model as our Tumor model-2 and the solution of the model by Differential Transform Method and Fractional order Multistage Homotopy Perturbation method. The numerical solutions Tumor model-2 is obtained and represent graphically. It is shown that the results are perfectly in agreement with the established basic principles of tumor microenvironment.

In Chapter.5, The detailed discussion about as introduction to Lorenz’s model as our Tumor model-3 and the solution of the model by Differential Transform Method and Fractional order Multistage Homotopy Perturbation method. The numerical solutions Tumor model-3 is obtained and represent graphically. It is shown that the results are perfectly in agreement with the established basic principles of tumor microenvironment.

In Chapter.6, The detailed discussion about as introduction to Anderson Enderling Tumor Model and Spatio-temporal Tumor Model, these Models solutions are obtained by Classical Runge kutta fourth order method. The numerical solutions these two are obtained and represent graphically. It is shown that the results are perfectly in agreement with the established basic principles of tumor microenvironment.

In Chapter.7, a brief discussion about the summary of entire research work and conclusions.