Mathematical Models In the Interaction Between the Immune System and Cancer

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Abstract

Mathematical models of tumourimmune interactions provide an empirical basis in which to address specific questions regarding tumourimmune dynamics and tumour treatment options. Here we describe a mathematical model is a representation of a system of ordinary differential equations (ODE) governing the growth of cancer at the level of the cell population. In addition to a population of cancer cells, the model contains a population of immune cells and the population of cytokine (Interleukin-2) as well. Our purpose is to learn the dynamics of immune-mediated tumour rejection, as well as to explore the effects of applying the immune combination as a treatment. Throughout addition, a sensitivity analysis of parameters indicates that the model can predict which patients will respond positively to treatment. Simulations of *C* programming output reveal the interaction of cancer growth, effector cells, and cytokines which can control tumour growth, but in combination the therapies can eliminate the entire tumour.

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Chapter 1

Introduction

1.1 Background of study

Cancer is a major disease that is approaching as the leading cause of death in all around the world where we can find at the moment. In the knowledge of cancer, tumour growth is an important part which helps to cancer screening, planning and treatments basically. Effective mathematical model of tumour growth helps researchers understand the dynamics of cancer growth and evaluate screening strategies as well as to doctors and relative people to predict the efficacy of cancer therapies.

In this report, we can investigate several mathematical models for cancer growth and examine the behaviours of immune cells and cytokines (IL-2) and their solutions through ordinary differential equations.

1.2 Introduction to the Cancer

Cancer can be defined as an abnormal and unregulated proliferation (growth) of cells, arising from cells of a specific organ. This proliferation is allowed to continue and spread, which means cancer cells have the ability to create their own blood supply, break away from the organ of origin, travel and spread to other organs of the body. In fact, almost all cancer-relateddeaths are due to tumour spreading, a process called metastasis.

Considering cancer starts in the body, cancer genes work properly tends to grow and divide. When cells divide basically it does have a proper process. One cell divides into two identical cells then two cells divide into four and so on.

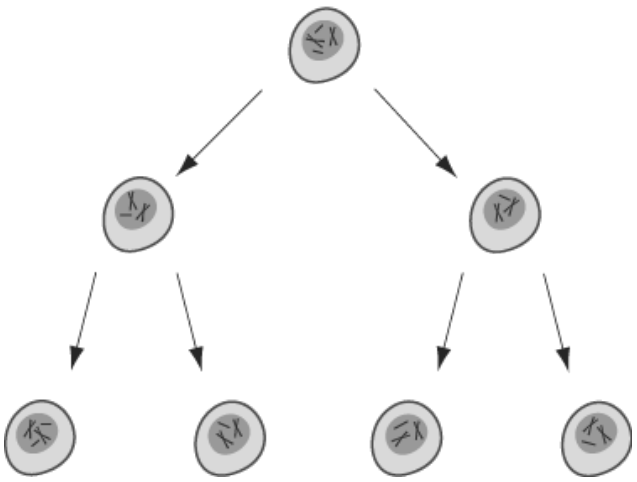

Figure 1.1: The Cell Division

And also there is a difference between cancer cells and normal cells. Normal cell knows and stays in its place of origin and knows when to replicate and when to die. Also cancer cell does not know when to stop growing and proliferate. It can travel from organ of origin to any place within the body. Cancer cells have gene mutations that turn the cell from a normal cell into a cancer cell. Basically there are different types of ways which cause to turn cancer such as,

- Genetic predisposition tobacco use
- lack of physical activity
- environment and diet
- virus
- sun exposure and etc.

1.3 The cancer immune system and cancer immunology

Although examining the immune system, the environment in which we reside includes a wide range of microbes-pathogens. This may cause infection, such as bacteria, viruses, and fungi. Defending the body against these toxins, avoiding diseases, is a fundamental work of our immune system. The immune system generally plays a major role in protecting us against cancer.

The immune system is divided into two parts called the innate and adaptive immune system. The innate immune system is made up of mechanical, chemical and cellular defenses that work to prevent pathogens from gaining a foothold in the body. The adaptive immune system is not, essentially, the same as the innate immune system. Researchers have already demonstrated that the adaptive immune system has been present since birth and that it is continuously involved and that it takes time to develop as well.

Macrophages, neutrophils, dendritic cells, and natural killer (NK) cells are the main effector cells of innate immunity. Natural killer cells (NK) originate from a common progenitor to TLs in the bone marrow, making up 5% to 20% of mononuclear blood cells. Considering how NK cells contribute to immunity, NK cells were originally described as cytolytic effector lymphocytes, which are an important line of unspecific defense, recognizing and lysing virus, bacteria and protozoa infected cells as well as tumour cells.

The relation between cancer and the immune system is complex and dynamic. Whereas there are cases where the immune processes lead to malignant tumor transformation and progression. Tumor immunology is known as immunoediting cancer, which consists of three phases elimination, equilibrium and escapes.

Elimination was thought to be carried by the innate and adaptive immune systems, and natural killer (NK), natural killer T (NKT), cluster of differentiation CD8+ cytotoxic and CD4+ lymphocytes, macrophages as well as dendritic cells (DC) that participating in the presentation, recognition and lysis of cells displaying tumour antigens.

CD8+ T cells and NK cells are both cytotoxic effector cells of the immune system, however, the mechanisms of identification, precision, responsiveness and memory differ wildly. Because of the heterogeneous nature of cancer, personalized cancer immunotherapy that combines the strength of both CD8+ T cells into adaptive immunity and NK cells into innate immunity may be the future path along with precise targeting and efficient delivery of tumor-specific, CD8+ T memory cells and NK cells.

1.4 Introduction to mathematical model in tumour growth

The main purpose of this chapter is to explain the basic concepts behind the dynamics of cells and how those dynamics contribute to cancer development. The basic mathematical model will be used to illustrate how mathematical models can offer insight into the biological process and many approximating hypotheses are needed.

1.4.1 Modeling tumour immune dynamics

There are many unanswered and important questions as to how the immune system interacts with a growing tumor and which components of the immune system play a significant role in immunotherapy responses. Mathematical models provide a theoretical context for answering these questions and these models can be used both in terms of explanation and prediction. Developing tumor growth models which include a representation of the immune response is important.

1.4.2 The importance of the immune system and immunotherapy

Within the multi-pronged strategies being developed to combat certain types of cancer, immunotherapies are increasingly becoming a significant component. The goal of immunotherapy is to improve the body's own natural ability to combat cancer by increasing the immune system's effectiveness.

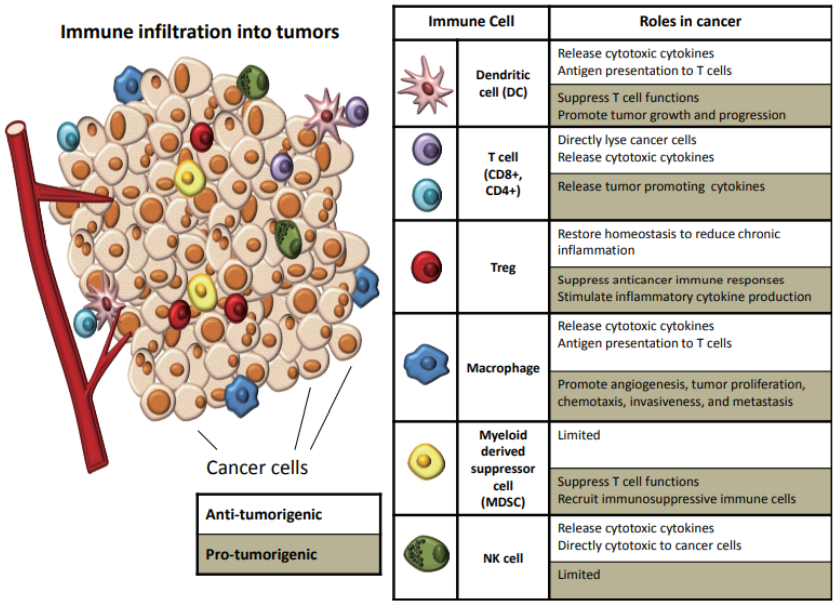

Figure 1.2: Diagram of key immune cells found in the tumor immune microenvironment

The massive role of the immune system in regulating the growth of cancer, both clinically and mathematically, suggests that models combining tumor growth and treatment would do well to include a part of the immune system. Once this component is in place, it is then possible to model how various immunotherapies, either individually or in combination with each other, can affect the system.

Immunotherapy and cancer vaccines

Scientific proof of the potential for the regulation of some malignancies by the immune the system has inspired new studies into the development of immunotherapies and cancer vaccine therapies.

There are important variations in the use of antiviral vaccines and anticancer vaccines and their effects. Although many infectious disease vaccines are preventative, cancer vaccines are intended for preventive use, treating the disease after it has begun, and avoiding the recurrence of the disease. Cancer vaccines are still considered highly controversial in comparison with other forms of cancer immunotherapy, but their ability to boost the immune response to certain forms of cancer is showing growing promise in early clinical trials.

1.4.3 Mathematical growth model

An important step in developing a tumor-immune model is to identify the dynamics of tumor cell population growth alone before considering, for example, growth-limiting interference from immune cells or competition from normal nutrient and space cells. Until now, there is no consensus on which basic growth models better represent tumor cell growth. But among the most commonly used ones are,

- Exponential growth
- Logistic growth
- Von Bertalanffy growth
- Gompertz growth

Considering the growth of cancer, it can be modelled through ordinary dierential equations by examining the change of cell population size x over time t. The most general equation describing the dynamics of tumour growth can be written,

$$x' = xf(x) \tag{1.1}$$

Exponential Growth

Cells grow in the early stages of tumor divide regularly, creating two cells for daughters each time. A normal definition of early cancer progression is the exponential model and which growth is proportional to population. The model was also used when evaluating tumor growth curves and appears to work predicting early growth very well.

The exponential growth equation is the differential equation and if the size of the tumour after t hours is given by $x(t)$, then we can express this information in mathematical language in the form of an equation

$$x' = ax \tag{1.2}$$

Its solutions are exponential functions of the form

$$x = x_0 e^{at} \tag{1.3}$$

The proportionality constant a is the growth rate of the tumor and $a > 0$.

In words, this equation describes the rate at which the changes in x variable are proportional to the value of x. The result is that x grows, at first slowly and then very quickly. Finally, a phenomenon called exponential growth.

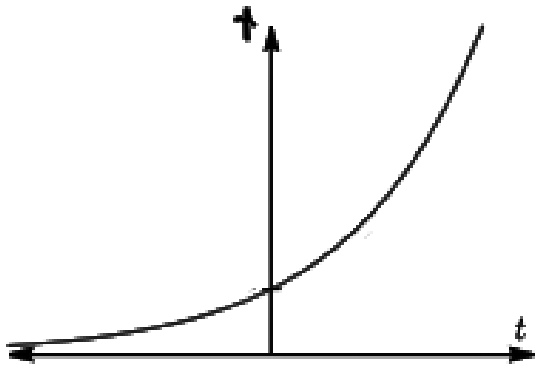

Figure 1.3: Exponential growth

Figure1.3 shows the graph of a typical exponential function, assuming $x_0 > 0$ and $a > 0$. Because of the factor of e^t, an exponential function increases quite quickly as t increases, as illustrated in Table1

The exponential model predicts the early stages of tumour growth. However exponential growth is not valid for the long-term growth of solid tumours.

Power Law

Under this topic a class of probability distributions known as power laws and a generalization of the exponential model is described by the power-law equation, introduced by Mendelsohn in 1963.

Given equation describes general form of Power Law.

$$x' = ax^b \tag{1.4}$$

Solutions to the Power Law used cell population growth laws,

$$x(t) = ((1-b)(at+C))^{\frac{1}{1-b}} \tag{1.5}$$

$$where \quad C = \frac{x_0^{1-b}}{(1-b)}$$

Von Bertalany

In 1938 von Bertalanffy derived this equation from basic statements in physiology. It would be the most commonly used growth curve, and is particularly important in studies of fisheries.

Consider that the rate of growth of an organism declines with size so that the rate of change in length, l, may be denoted by

$$\frac{dy}{dt} = K(l_\infty + l) \tag{1.6}$$

Where,

t is the time.

l is length (or some other measure of size).

K is the growth rate.

L_∞ termed 'L infinity' in fisheries science, is the asymptotic length at which growth is zero.

After that integrating we can get,

$$l_t = L_\infty(1 - e^{-K(t-t_0)}) \tag{1.7}$$

The parameter t_0 can be adjusted the equation for the initial size of the organism and also is known as the age at which the organisms are zero sized. Therefore, need to fit 3 parameters (L, K and t_0) by nonlinear regression to fit this equation.

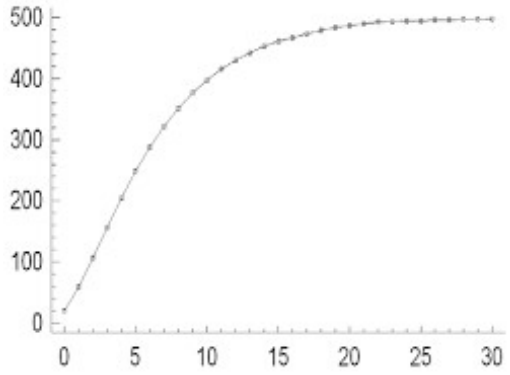

Figure 1.4: Example for Von Bertalany model

The graph 1.4 above shows an example plot of this equation. Typically, Bertalanffy curve explaining length growth showcases a sudden growth that begins to level off as KK approaches. Von Bertalanffy model has been successfully applied to describe human tumour growth as well.

Logistic Method

The logistic growth curve was first suggested by Pierre Verhulst in the period 1845, 1847 as a model of population development. An *S*-shaped (sigmoidal) curve is a logistic growth curve that can be used to model functions that slowly increase at first, then gradually faster in the middle growth period and slowly at the end. Its initial part is exponential, the growth rate accelerates as it reaches the midpoint of the curve. The rate of growth starts to reduce speed but keeps rising until it reaches an asymptote, K is known as the "Environmental Carrying Capability."

This type of curve is often used to predict biological growth rates where there is an initial exponential growth period followed by a levelling off as more and more of the population is infected, or as the supply of food or some other factor limits further growth.

Assume that the growth rate of the organism decreases with the size, so that the rate of change in the size can be described,

$$\frac{dl}{dt} = l(k - \delta) \tag{1.8}$$

Where,

t is time.

k is the growth rate.

δ which expresses the rate at which growth declines with size.

After integration as well as some rearrangement, we can get the 3-parameter logistic growth curve.

$$l_t = \frac{L_\infty}{1 + e^{-k(t-I)}} \tag{1.9}$$

Where,

I is the age at the inflection point.

$L\infty$ is the maximum size reach after infinite growing time.

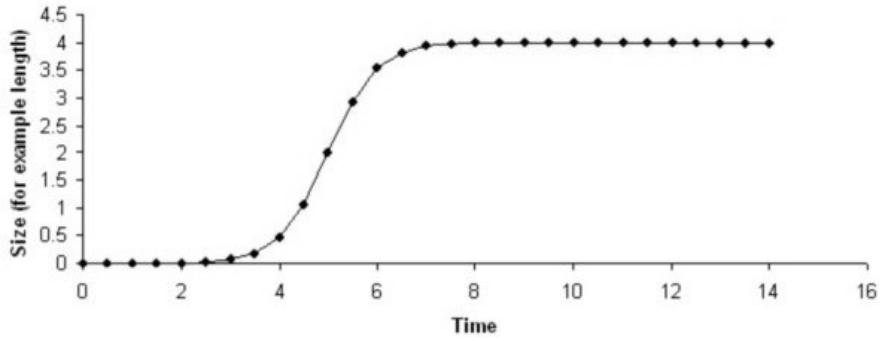

Figure 1.5: Three parameter logistic curve

Parameter	**Estimated value**	**Ref**
L	4	[17]
k	5	[17]
δ_1	0.5	[17]
δ_2	1	[17]
$\aleph$	1	[17]

Table 1.1: Estimated parameter values: based on [17]

The three parameter logistic method has a lower asymptote of 0. Where the induction occurs on the Y-axis,

$$I_y = \frac{L_\infty}{2} \tag{1.10}$$

This last formula (1.10) states that now the inflexion point has always been at 50% of the asymptotic size. Using the Logistic growth curve you can find modelling sigmoid growth processes in which the inflexion point is around $\frac{1}{2}$ of the maximum possible scale. If a non-zero asymptote, then the four parameter version of the equation is required.

$$l_t = \alpha + \frac{L_\infty = \alpha}{1 + e^{\frac{(k-t)}{\gamma}}} \tag{1.11}$$

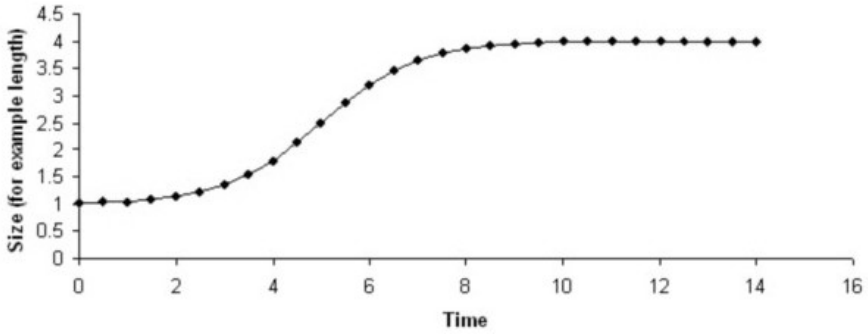

Figure 1.6: Four parameter logistic curve

Three parameter logistic curve 1.5 and four parameter logistic curve 1.6 are displayed by using parameter values of given in table 3.2.

Gompertz Method

The Gompertz curve was originally developed by Benjamin Gompertz to predict human mortality in 1825. He sought, in particular, a perfect analysis of the number of people alive as their ages act function of x, denoted in $L(x)$. Although Gompertz argued that human life tables show two distinct behaviors. In certain cases, $L(x)$ decays exponentially, or x decreases as a geometric series.

Assume an organism's growth rate decreases with size, so that the rate of change in length l may be described by,

$$\frac{dlogl}{dt} = K(logL_\infty - logl) \tag{1.12}$$

Where,

K is the growth rate.

L_∞, termed 'L infinity', is the asymptotic length at which growth is zero.

After integrating above equation becomes,

$$l_t = L_\infty(e^{e^{-k(t-I)}}) \tag{1.13}$$

Where t is age and I is the age at the inflection point.

The above equation is the Gompertz growth curve corresponding to the 3 parameter version.

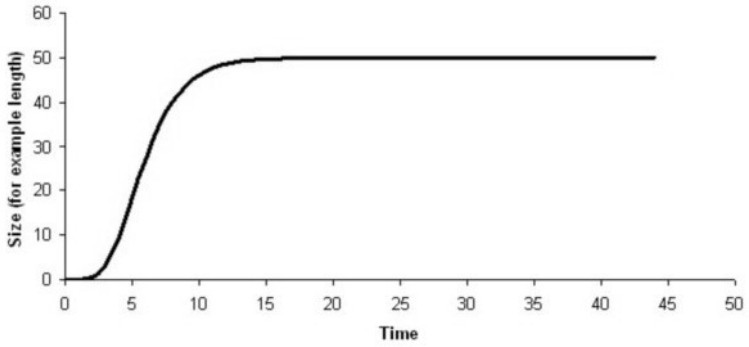

Figure 1.7: Example plot of 3 parameter version of the Gompertz growth curve

Fourth parameter version is,

$$l_t = A + Be^{e^{-k(t-I)}} \tag{1.14}$$

In here there are two different constants, which A is the lower asymptote and B is the upper asymptote minus A. The point of inflection on the y-axis occurs at,

$$I_y = \frac{B}{e} \tag{1.15}$$

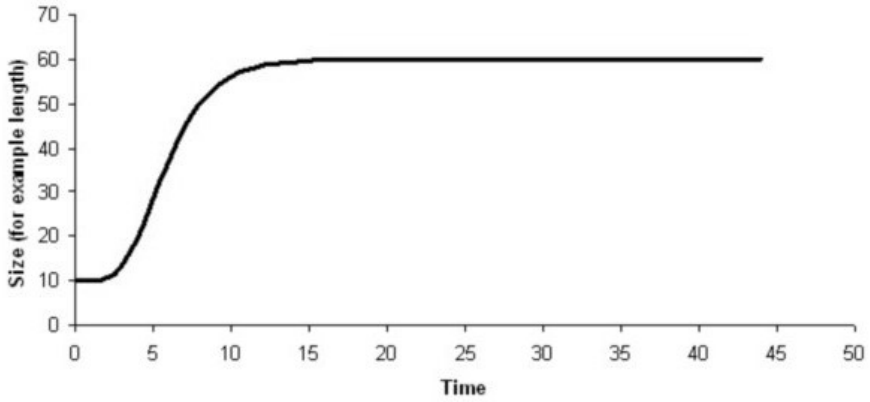

Figure 1.8: Four parameter with Gompertz model

Parameter	**Estimated value**	**Ref**
L_∞	50	[17]
k	0.5	[17]
I	5	[17]
A	10	[17]

Table 1.2: Estimated parameter values: based on [17]

The above graphs (1.7 and 1.8) show example plots of the 3 and 4 parameter in Gompertz model by using table 1.2 values.

This last equation says that the inflexion point is usually around 36.8 % of the asymptotic scale L_∞. And also consider the Gompertz growth curve to model sigmoid growth processes where the inflexion point is around 1/3 of the maximum possible size.

The Gompertz model shows an exponential decay of the growth rate. This model has been successfully used to model breast and lung cancer growth.

1.5 Objectives

As already mentioned in this project mathematical application of ordinary differential equations play a major role considering reviews of mathematical models of tumour growth and tumour-immune system interactions. In here review ODE(Ordinary Differential Equations) models starting from the very simplest (involving asingle equation) and build up too much more complex models that include successively more features of the tumour microenvironment and the immune system. These particular models help to identify the dynamical effects of including greater biological details.

And also the main aim is to present some of the mathematical approaches taken to investigate different aspects of tumour-immune system interactions, to elucidate the complexity of the problem. The concept of modelling implies observation and prediction of tumour growth of cancer as well.

Chapter 2

Problem Statement

2.1 Interactions Between the Immune System and Cancer

This report reviews the interactions between tumor cells and other components of the tumor micro-environment are complex and continuously changing. Therefore by using ODE with the simplest models derived to investigate the dynamics of populations of cancer cells.

While ODE provides a simpler framework within which to explore the interactions among tumour cells and the different types of immune and healthy tissue cells. Existing reviews of ODE models focus mostly on models described by one equation, and very briey treat two-equation, three-equation or four-equation models as well.

Considering the above mathematical equations their behaviours were described by using the numerical method of Runge Kutta method. In such a case, numerical methods are the only plausible way to compute solutions using C programming. Moreover, the differential equation can be solved analytically, involves integrations of general functions but more efficient to use numerical methods from the outset to solve the differential equation so far.

Chapter 3

Methodology

3.1 Modeling tumour-immune dynamics

3.1.1 One equation model relative to tumour growth

In this section we consider some mathematical equations and which have been derived to fit explain tumour growth data, to predict patient progress. The first step to understanding tumor growth is simply explaining the patterns of development. The tumor's initial growth is much faster than detectable tumor growth. Gompertz described this form of growth for the first time by mathematically modeling cell replication and death. His basic model generates a sigmoidal curve of population growth as shown Figure4.1(b)

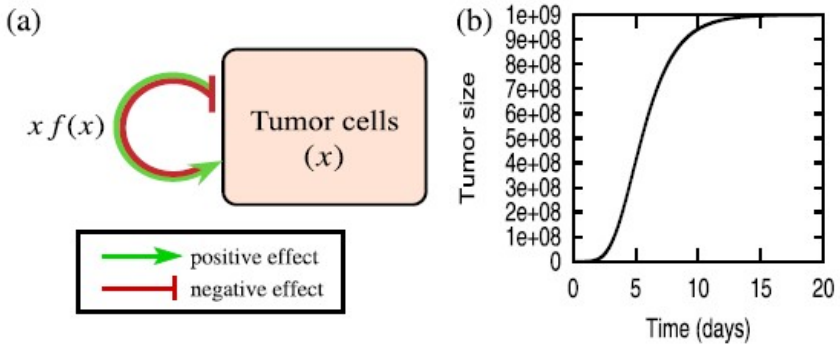

Figure 3.1: (a) Schematic representation of the dynamics of cancer cells as a result of autoregulatory cellcell interactions. Autoregulation can have either a positive or negative effect depending on the sign of the regulating factor $f(x)$, (b) Sigmoidal curve describing the growth of untreated tumors. [9]

Although The above shows speeding up growth for small populations and slowing development for large populations. The decelerating dynamics shown by the sigmoidal curve can be clarified in the case of a tumor cell population by the limited nutrient amount available to the tumor cells.

Several mathematical models were developed for fitting and describing tumor growth data, predicting patient survival and recommending treatment options. Some of these models suspect tumors are growing exponentially but most are suggesting decelerating growth.

The most general equation can be written,

$$x' = xf(x) \tag{3.1}$$

In above equation where x is the cell population size at time t, $x(0)$¿0, and the factor $f(x)$ defines the proliferation and death density dependence of the tumor cells.

And also the density dependence factor can be written more explicitly as,

$$f(x) = p(x) - d(x) \tag{3.2}$$

where,
$p(x)$ describes cell proliferation
$d(x)$ describes cell death.

The simplest examples can be expressed as power laws,

$$p(x) = ax^{\alpha} \tag{3.3}$$
$$d(x) = bx^{\beta} \tag{3.4}$$

with α = 0 and β = 1 for the logistic model and α = -1/3 and β = 0 for the von Bertalanffy model. If $p(x) = a$ and $d(x) = b\ln(x)$, then equation 3.1 reduces to the Gompertz model. Finally those models were analyzed from the Growth Definition perspective too.

There are well-known theoretical solutions of equation 3.1 for the logistic, Gompertz and many other basic forms of density dependence. Making the use of these models very easy to predict tumor dynamics, given tumor size measurements at a specific time. Overall, despite being based on a single equation describing cell-cell interaction, these models have been successful in explaining tumor growth patterns too.

3.1.2 Two equation model relative to tumour cells and generic effector cells

One immune response goal is to attack and kill harmfulc cells. Immune cells which are capable of killing are called effector cells.The immune system can prevent the growth of, and remove, very small tumors until they are clinically apparent. In this section, we introduce the effector cells into the tumor growth model. We use a competition model consisting of a system of two differential equations to the simplest realization and the easiest way to do that is to add one equation to the mentioned model in equation 3.1.

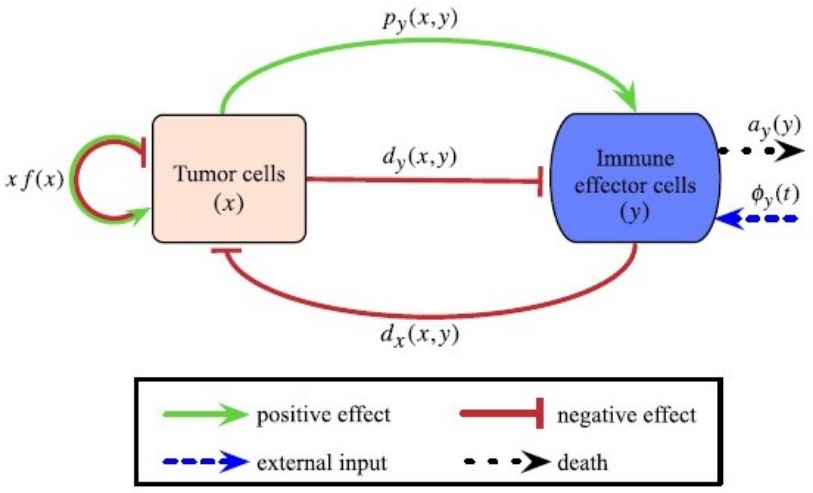

Figure 3.2: A schematic representation of the interactions involved in the two-equation models in Sect 3.1.2 , [9]

The precise nature of the immune cell population we include at this point need not be defined, but the aim is to mimic the behavior of cytotoxic immune cells such as called CD8+ T cells and NK cells. Already we know these are effectors cells and which can also monitor tumor growth by recognizing tumor antigens or surface ligands of tumor cells.

Now we are going to consider a generic effector cell population interacting with tumor cells which are usually of predator-prey type. In here let x denote the population of tumor cells, and y the population of effector cells. The classical predatorpreyrelationship assumes:

- The prey will grow in the absence of the predator;
- Interactions between predator and prey are harmful to the prey but benecial to the predator;
- The predators will die in the absence of prey;
- The number of interactions between predators and prey is proportional to the product of the two populations.

If we describe two population model of tumor and effector immune interactions, these assumptions yield the following system of differential equations.

$$x' = xf(x) - d_x(x, y) \tag{3.5}$$

$$y' = p_y(x, y) - d_y(x, y) - a_y(y) + \phi_y(t) \tag{3.6}$$

We can describe notaion and rate functions considering as shown below table 3.1.

Variables/Function	**Meaning**
x	Cancer cells
y	Immune cells
z, w	Other cells or cytokines
$f(x)$	Growth of cancer cells
$d_j, j = x, y, z, w$	Inhibition of cells
$p_j, j = y, z, w$	Proliferation of cells/cytokines (type j)
$a_j(j), j = y, z, w$	Death (apoptosis) of cell (type j)
$\phi_j(t), j = y, z, w$	Time-dependent or time-independent treatment, or inux of cells/cytokines of type j

Table 3.1: Notation used in this project

Where x represents the size or density of the tumor cell population and y represents the size or density of the effector cell population. Recognize that for the tumor the structure of 3.13 is are very similar to 3.1, the only difference being that cancer cell death now results from both predation by effector cells $d_x(x, y)$ and autoregulation. In equation 3.14 immune cells includes a growth term $p_y(x, y)$ and a death term $d_y(x, y)$, Both depend on the interaction of the cancer cells and the effector cells. Although in here, there is another variable known as apoptosis term $a_y(y)$ and a time-dependent treatment term $\phi_y(t)$. We can see the term describes continuous immune cell growth, even in the absence of cancer cell.

Other functions $x(x, y), p_y(x, y), d_y(x, y), a_y(y)$, and (t) can be described as,

$$f(x) = a(1 - \beta(x)) \tag{3.7}$$

$$d_x(x, y) = nxy \tag{3.8}$$

$$p_y(x, y) = \frac{pxy}{g + x} \tag{3.9}$$

$$d_y(x, y) = mxy \tag{3.10}$$

$$a_y(y) = dy \tag{3.11}$$

$$\phi(t) = s \tag{3.12}$$

Models described by equation 3.13 and 3.14 can be adapted to most observed dynamics of the tumor immune system. Consequently, those who are very beneficial in clarifying basic mechanisms that may cause observed behaviors such as tumor regression and dormancy of tumors. The models exhibit a greater range of dynamics than experimentally observed, in particular we are unaware of any reports of oscillatory dynamics in solid tumors.

And also anti tumor activity can occur through a variety of immune cells, such as CD8+ T cells, NK cells, or macrophages, and each type of cell can interact with cancer cells in many ways. In addition, when considering the effects of specific immunotherapies, non-linear density-dependent interactions between different populations of immune cells may be very significant.

The innate immune response, including NK cells, represents an early defense against pathogens. NK cells recognise and kill tumor cells, amongst others, regardless of prior exposure. Natural killer cells are known to play a significant role in trying to prevent the clinical cancer from developing by killing abnormal cells before they multiply and grow. And also killer T cells are unlike NK cells as they have to be primed first to recognize a particular antigen and, in the case of cancer, to recognize a tumor-specific antigen.

3.1.3 Three equation models of interactions among cancer cells and two other components of the tumour micro-environment

Starting with one of the previous two-equation models and adding one more component is the most natural way to incorporate more biological detail. This part may be either a different type of immune cells in the tumor microenvironment, or healthy tissue cells or cytokines present in it.

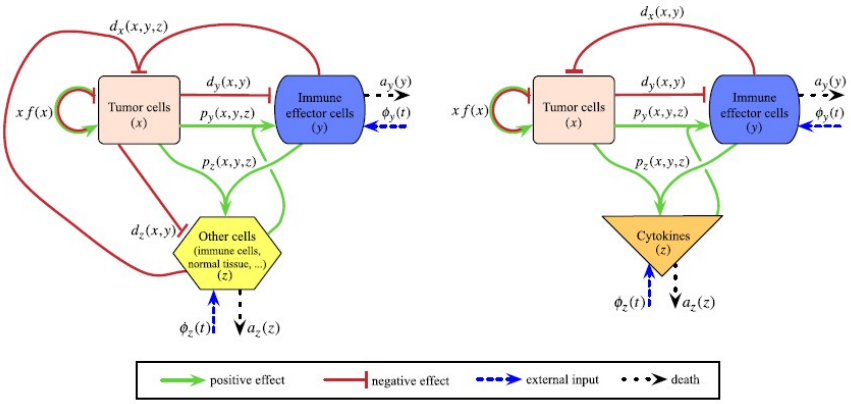

Figure 3.3: Schematic representation of the three-component models of cancer-immune system interactions. (a) Models involving three types of cell. (b) Models involving two types of cell and one type of signaling molecule. [9]

The three population tumor-immune mathematical model of tumorimmune interactions sheds light on the differing roles of the Natural Killer (NK) and CD8+ T cells in suppressing various tumor cell lines in humans. Every such immune cell uses a different mechanism and plays a role various function in lysis of the cells. In an attempt to shed light on these processes, there are numerous mathematical models for investigating the interactions between cancer cells and multiple immune cells, or between cancer cells, immune cells, and healthy tissue.

The cytokines constitute another essential part of the anti-tumor immune response. Most cancer immunotherapies concentrate on cytokines but the mechanisms by which they interact with cancer cells are not completely understood. To assist with these review mechanisms, other basic mathematical models were derived from the interactions between immune cells, cancer cells, and certain cytokines.

In this section we focus on three type of interaction review some of the most cited mathematical models that have followed above.

- Interactions between cancer cells and two types of effector cells, which are usually CD8+ T cells and NK cells.
- Interactions between cancer cells, effector cells, and normal tissue cells
- Interactions between cancer cells, effector cells, and cytokines (such as IL-2, TGF-, IFN-)

Other three-equation models focus on different types of interactions. Some models examine, the interactions between cancer cells, effector cells, and naive effector cells. Certain models study the interactions between antibodies and two forms of cancer cells. Either proliferating or quiescent or the interactions among cancer cells, normal effector cells and resting effector cells.

Some of the models mentioned below include treatment protocols. Such as continuous cytokine injection, continuous transmission of the effector cells, pulse like or constant administration of other medications, or dendritic cell immunization. In general, this based only on the possible dynamical behaviors of the models.

Although these three equation models would not appear to demonstrate any distinct behaviors beyond those revealed by the two equation models described in section 3.1.2. We consider how the three equation models help to reveal the potential mechanisms behind these interactions in the coming sections.

Tumour growth modulated by effector cells and cytokines

Cancer is still a leading cause of death in the world yet much is still not known about its mechanisms of establishment and destruction. While doing Chemotherapy and Radiotherapy have played a significant part in the diagnosis and which is also do not appear a cure. Attempts along these lines by Immunotherapy are now being investigated. Immunotherapy applies to cytokine usually along with adoptive cellular Immunotherapy (ACI).

Cytokines are protein hormones which are both normal and unique in natural immunity. Here mainly formed by the activated T cells (lymphocytes) during immunity that is mediated by the cell. The principal cytokine is Interleukin-2 (IL-2) and which is responsible for the activation, development and differentiation of lymphocytes.

To start a tumour-immune dynamics model, we first, look at some of the established models. In here already defined an ordinary differential equation (ODE) model for two main populations, effector cells and tumour cells. These expect a threshold over which tumour growth is uncontrollable, and under which the disease is attenuated by periodic exacerbation as well as.

We aim to get some of the best ideas in all of these systems but to maintain the model as simple as possible, while implementing key concepts Tumor-immune dynamics along with IL-2 dynamics feature. Therefore, It is possible to write the equations explaining the interactions between cancer cells (x), immune cells (y) and cytokines (z) in their most general form.

$$x' = xf(x) - d_x(x, y) \tag{3.13}$$

$$y' = \phi_t + p_y(x, y, z) - a_y(y) \tag{3.14}$$

$$z' = \phi_t + p_z(x, y, z) - a_z(z) \tag{3.15}$$

The Kirschner and Panetta (1998) [16] introduced unique functional forms,

$$f(x) = r_2(1 - bx) \tag{3.16}$$

$$d_x(x, y) = \frac{axy}{g_2 + x} \tag{3.17}$$

$$p_y(x, y, z) = cx + \frac{p_1 yz}{g_1 + z} \tag{3.18}$$

$$p_z(x, y, z) = \frac{p_2 xy}{g_3 + x} \tag{3.19}$$

$$d_y(x, y) = 0 \tag{3.20}$$

$$a_y(y) = \mu_2 y \tag{3.21}$$

$$a_z(z) = \mu_3 z \tag{3.22}$$

$$\phi_y(t) = s_1 \tag{3.23}$$

$$\phi_z(t) = s_2 \tag{3.24}$$

Equation (3.13) describes the changes that occur in the cancer cells population x over time. The term $r_2(1 - bx)$ represents the logistic growth of x (r_2 and b are parameters that define how the tumour cells will grow) and $(axy/g_2 + x)$ is the number of cancer cells killed by immune cells. r_2 and g_2 are parameters to adjust the model.

Although equation (3.14) describes the rate of change for the immune cell population y. Immune cells grow based on recruitment cx and proliferation $(p_1 yz/g_1 + z)$. In here c describes the antigenicity of the tumour cells x. The death rate of the immune cells is μ_2.

p_1 and g_1 are parameters used to calibrate the recruitment of immune cells and s_1 is the treatment that will boost the number of immune cells.

The Cytokines IL-2 population dynamics is explained by equation (3.15). $(p_2xy/g_3 + x)$ determines cytokines IL-2 production using parameters p_2 and g_3. μ_3 is the IL-2 loss. s_2 also represents the treatment.

The populations of agents, the cancer cells, immune cells and IL-2 and their behaviour is shown in figure 3.4

Agent	Transition	Mathematical equation	Transition rate
Effector Cell	Reproduce	$\frac{p_1.I_L E}{g1+IL\_2}$	$\frac{p_1.TotalIL\_2.TotalEffector}{g1+TotalIL\_2}$
	Die	$\mu_2 E$	mu2
	killTumour	$\frac{a_8 ET}{g2+T}$	$aa\frac{TotalTumour}{g2+TotalTumour}$
	ProduceIL2	$\frac{p2ET}{g3+T}$	$\frac{p2.TotalTumour}{g3+TotalTumour}$
Tumour Cell	Reproduce	$aT(1 - bT)$	$a - (TotalTumour.b)$
	Die	$aT(1 - bT)$	$a - (TotalTumour.b)$
	DieKilledByEffector	$\frac{a_8 TE}{g2+T}$	message from effector
IL-2	Loss	$\mu_3 I_L$	mu3

Figure 3.4: Parameters and behaviours cancer cells, immune cells, cytokines [20]

In the simulation model, apart from the agents, there are also two events.

- Treatment s_1, which adds effector cell agents according to the parameter s_1 .
- Treatment s_2, which adds IL-2 agents according to the parameter s_2.

An also the state charts for each agent type are shown in figure 3.5

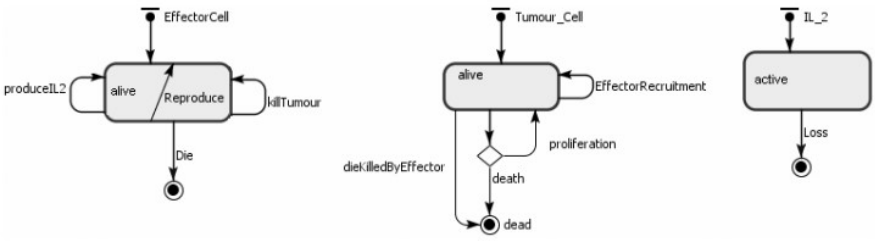

Figure 3.5: The state charts for the x, y, z cells [20]

In the absence of any treatment, analytical and numerical results show model 3.13, 3.14 and 3.15 may exhibit three behaviors when ($s_1 = s_2 = 0$).

- Persistence of large tumours (for low antigenic tumours).
- Oscillation between macroscopic and microscopic tumours (for moderately antigenic tumours).
- Persistence of dormant tumours, which is persistence of residual tumour cells (for highly antigenic tumours).

The model does not provide for in the non-treatment ($s_1 = s_2 = 0$) case tumour clearance complete.

Here list all of the parameters used in the model, their meaning and their estimated values by using reference [16] and [18].

Parameter	**Units**	**Description**	**Estimated value**	**Ref**
a	day^{-1}	Cancer clearance term	1	[16], [18]
b	cells^{-1}	Logistic growth of cancer capacity	1×10^{-9}	[16], [18]
r_2	day^{-1}	Cancer growth rate	day	[16], [18]
g_1	cells	Half-saturation for proliferation term	2×10^{9}	[16], [18]
g_2	cells	Half-saturation for cancer clearance	1×10^{5}	[16], [18]
g_3	cells	Half-saturation of production	1×10^{3}	[16], [18]
p_1	day^{-1}	Proliferation rate of immune cells	0.1245	[16], [18]
p_2	day^{-1}	Production rate of effector molecule	5	[16], [18]
μ_2	day^{-1}	Death rate of immune cells	0.03	[16], [18]
μ_3	day^{-1}	Half-life of effector molecule	10	[16], [18]

Table 3.2: Estimated parameter values: based on [16] and [18]

3.2 Numerical methods for solving an ordinary differential equations

Numerical methods are techniques to approximate mathematical procedures such example as integrals. When considering the above case approximations are needed because we either cannot solve the procedure analytically. Because the solving a set of a thousand simultaneous linear equations for a thousand unknowns by using analytical method is intractable. Therefore in this section, we will be able to apply the numerical methods for the following mathematical procedures in topics differentiation, nonlinear equations and ordinary differential equations.

3.2.1 Runge Kutta Method (Fourth order)

The Eulers method to solve the differential equation numerically is less efficient and also it is not very useful in practical problems since it requires a very small step length h for obtaining a reasonable accuracy. Therefore Runge-Kutta methods are among the most popular ODE solver and which scores over earlier methods in obtaining greater accuracy of the solution and at the same time avoiding the need for higher-order derivatives.

Runge-Kutta fourth-order method is most common and it is quite accurate, stable, and easy to program. The commonly used form of the Runge-Kutta method differential equation is,

$$y_{i+1} = y_i + (c_1K_1 + c_2K_2 + c_3K_3 + c_4K_4)h \tag{3.25}$$

Where K_1, K_2, K_3 and K_4 have the form,

$$K_1 = f(x_i, y_i)$$

$$K_2 = f(x_i + a_2h, y_i + b_{21}K_1h$$

$$K_3 = f(x_i + a_3h, y_i + b_{31}K_1h + b_{32}K_2h)$$

$$K_4 = f(x_i + a_4h, y_i + b_{41}K_1h + b_{42}K_2h + b_{43}K_3h)$$

In here, there are 13 constants.

$c_1, c_2, c_3, c_4, a_2, a_3, a_4, b_{21}, b_{31}, b_{32}, b_{41}, b_{42}, b_{43}$

By matching coefficients with those of the Taylor series method of order $N = 4$, Runge and Kutta were able to obtain the following system of equations.

Then the solution for the remaining variables is,

$c_1 = c_2 = \frac{1}{6}$ $\quad$ $c_2 = c_3 = \frac{1}{3}$ $\quad$ $a_2 = a_3 = b_{21} = b_{32} = \frac{1}{2}$

$a_4 = b_{43} = 1$ $\quad$ $b_{31} = b_{41} = b_{42} = 0$

By using above remaining values substituted into equation 3.25 and K_1, K_2, K_3 and K_4 forms, We can obtain the formula for the standard Runge-Kutta method of order $N = 4$, which is stated as follows

$$y_{i+1} = y_i + \frac{1}{6}(K_1 + 2K_2 + 2K_3 + K_4)h \tag{3.26}$$

$K_l = f(x_i, y_i)$

$K_2 = f(x_i + \frac{1}{2}h, y_i + \frac{1}{2}K_1 h)$

$K_3 = f(x_i + \frac{1}{2}h, y_i + \frac{1}{2}K_2 h)$

$K_4 = f(x_i + h, y_i + K_3 h)$

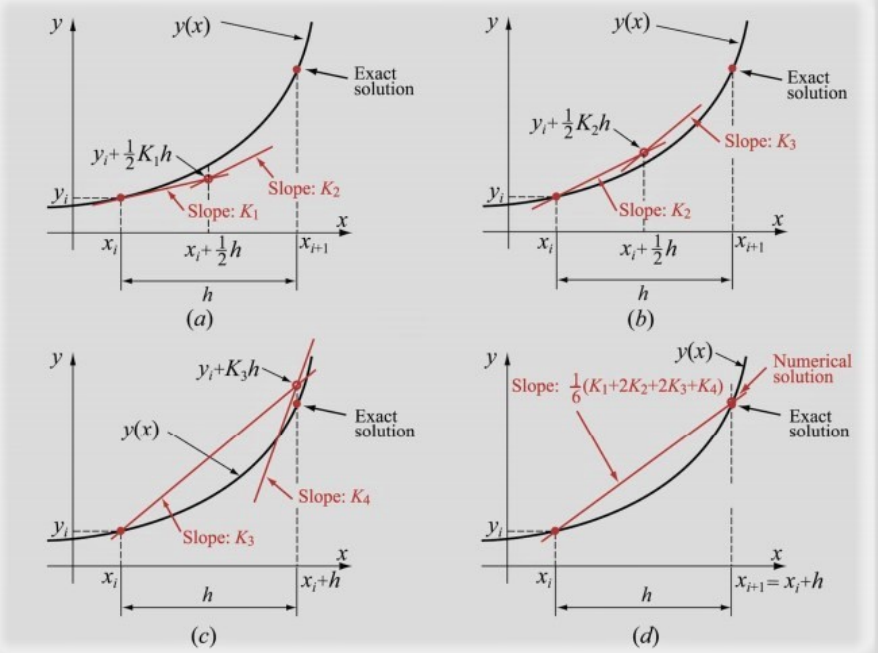

Figure 3.6: Graphical Representation: (Runge-Kutta Method Of Order Four)

As shown in the figure above, each of the K's represents a slope. And also the last equation then represents a weighted average of these to arrive at the improved slope.

The formula basically computes next value y_{i+1} using current y_i plus weighted average of four increments.

- K_1 is the increment based on the slope at the beginning of the interval, using y.
- K_2 is the increment based on the slope at the midpoint of the interval, using $y + \frac{1}{2}hK_1$.
- K_3 is again the increment based on the slope at the midpoint, using using $y + \frac{1}{2}hK_2$.
- K_4 is the increment based on the slope at the end of the interval, using $y + hK_3$.

These mentioned formulas yield an approximation of the fourth degree in h, that is, the expansion in powers of h of y_i+$_l$ defined by these formulas agrees through terms of the fourth degree with the expansion of y_i+$_l$ obtained directly from the differential equation.

3.2.2 The solution by using Runge Kutta method (Fourth order)

In here, we have denoted three functions with their relative parameters to solve the given problem. (func$_1$,func$_2$,func$_3$)

func$_1$, func$_2$ and func$_3$ describe x', y' and z' corresponding to reference respectively in 3.13, 3.14 and 3.15

$$var_4 = x * r_2 * (1 - b * x) - ((a * x * y)/(g_2 + x))$$

$$var_5 = s_1 + c * x + ((p_1 * y * z)/(g_1 + z)) - m_2 * y$$

$$var_6 = s_2 + ((p_2 * x * y)/(g_3 + x)) - m_3 * z$$

Count number of iterations using step size or step height h,

$$h = (t_n - t_0)/l$$

Where,

t_0 initial value for t.

t_n time.

l number of steps.

Apply Runge Kutta Formulas to find next values.

$$k_1 = h * (func_1((x_0), (y_0), (z_0), (t_0)))$$
$$m_1 = h * (func_2((x_0), (y_0), (z_0), (t_0)))$$
$$w_1 = h * (func_3((x_0), (y_0), (z_0), (t_0)))$$

$$k_2 = h * (func_1((x_0 + k_1/2), (y_0 + m_1/2), (z_0 + w_1/2), (t_0 + h/2)))$$
$$m_2 = h * (func_2((x_0 + k_1/2), (y_0 + m_1/2), (z_0 + w_1/2), (t_0 + h/2)))$$
$$w_2 = h * (func_3((x_0 + k_1/2), (y_0 + m_1/2), (z_0 + w_1/2), (t_0 + h/2)))$$

$$k_3 = h * (func_1((x_0 + k_2/2), (y_0 + m_2/2), (z_0 + w_2/2), (t_0 + h/2)))$$
$$m_3 = h * (func_2((x_0 + k_2/2), (y_0 + m_2/2), (z_0 + w_2/2), (t_0 + h/2)))$$
$$w_3 = h * (func_3((x_0 + k_2/2), (y_0 + m_2/2), (z_0 + w_2/2), (t_0 + h/2)))$$

$$k_4 = h * (func_1((x_0 + k_3), (y_0 + m_3), (z_0 + w_3), (t_0 + h)))$$
$$m_4 = h * (func_2((x_0 + k_3), (y_0 + m_3), (z_0 + w_3), (t_0 + h)))$$
$$w_4 = h * (func_3((x_0 + k_3), (y_0 + m_3), (z_0 + w_3), (t_0 + h)))$$

Update next values,

$$k = (k_1 + (2 * k_2) + (2 * k_3) + k_4)/6$$
$$m = (m_1 + (2 * m_2) + (2 * m_3) + m_4)/6$$
$$w = (w_1 + (2 * w_2) + (2 * w_3) + w_4)/6$$

Final answer to $\frac{dx}{dt}$,

$$x_1 = x_0 + k$$

Final answer to $\frac{dy}{dt}$,

$$y_1 = y_0 + m$$

Final answer to $\frac{dz}{dt}$.

$$z_1 = z_0 + w$$

Chapter 4

Discussion

4.1 Modeling tumour-immune dynamics

The first model introduced in this the chapter includes tumour-immune interactions and highlights the qualitative disparity between innate immune response and kill frequencies (The effect of the NK cells). Although which described the adaptive response (the effect of the CD8+ cells). With its two different functional forms for kill rates, the model provides a good fit with experimental data resulting from priming and rechallenge, with various tumour cell types combinations. The fact that two distinct functional types have to explain regarding the interactions between tumour cells and the two branches of the immune system. Looking at given forms in section 3.1.2 which predator-prey kill rates can obey either a rational law or a power law. And also here basic models which introduce a caricature of the immune surveillance mechanism, where each immune system identifies and destroys foreign cells considering cancer cells and generic immune cells. In section 3.1.3 evaluate models (including three equations) which examine interactions between cancer cells, immune cells, and other types of cells or signalling proteins (cytokines).

Together with the parameter sensitivity analysis, the experimental and simulated results provided in this chapter emphasize the significance of CD8+ T cell activation on the disease's time course. Model results appear to confirm that a focus on increasing CD8+ T cell activity may be necessary to promote tumour regression. In addition, may suggest that there may be a strong positive association between the patient-specific efficacy of the CD8+ T cell reaction as calculated by cytotoxicity assays and a patient's probability of responding favourably to certain immunotherapy treatments.

4.2 The output of the after compiled C code

Considering section 3.1.3 below given algorithm was made by using computer language of *C* programming. Which displays behavoirs of (x) cancer cells, (y) immune cells, and (z) cytokines and finally could get results of figures input corresponding to mentioned initial values.

4.2.1 The persistence of large tumours (for low antigenic tumours)

After complied *C* programming we can get a display as shown in figure 4.1. Then we have to give initial conditions as below given, considering reference [9].

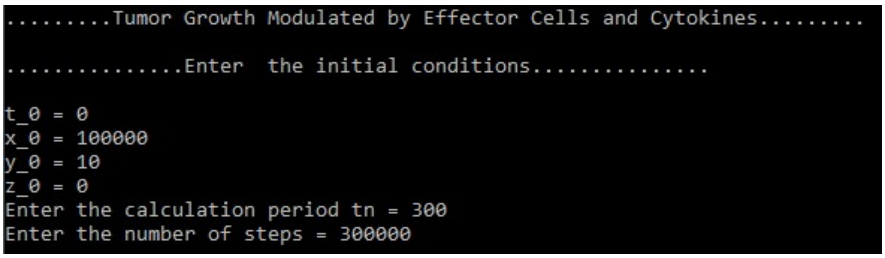

Figure 4.1: Input initial conditions in c code : persistence of large tumours

Parameter	**Estimated value**	**Ref**
t_0	0	[9]
x_0	100000	[9]
y_0	10	[9]
z_0	0	[9]
tn	600	[9]
c	0.002	[9]
Enter the number of steps (l)	600000	[9]

Table 4.1: Estimated parameter values: based on [9]

And also here concerned c value in equation (3.14), considering the reference [9] and which helps to get a graph of the persistence of large tumours (for low antigenic tumours) 4.3.

Thus there will be no console performance. Alternatively, by opening the newly generated file in preferred text editor, then you can access file contents. Finally, after completing all the operations the data text file here can be viewed by going through the GitHub link below.

https : *//github.com/sachinkavindaa/My_file*1

When click the GIthub link you may can see following figure that describes what are the files which have. There are three files you can see on given figure 4.2.

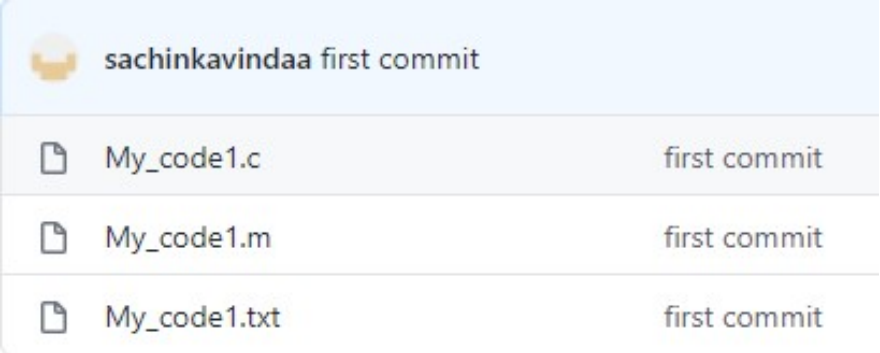

Figure 4.2:

My_code1.c = *C* code.

My_code1.m = MATLAB file for the grpahs.

My_code1.txt = the output data in Txt file.

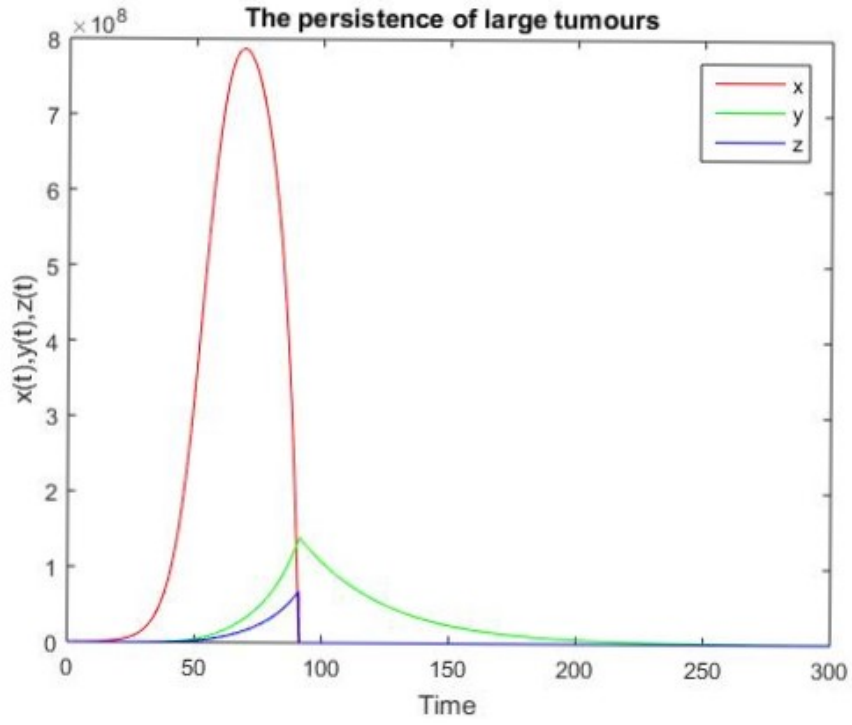

Figure 4.3: The persistence of large tumours

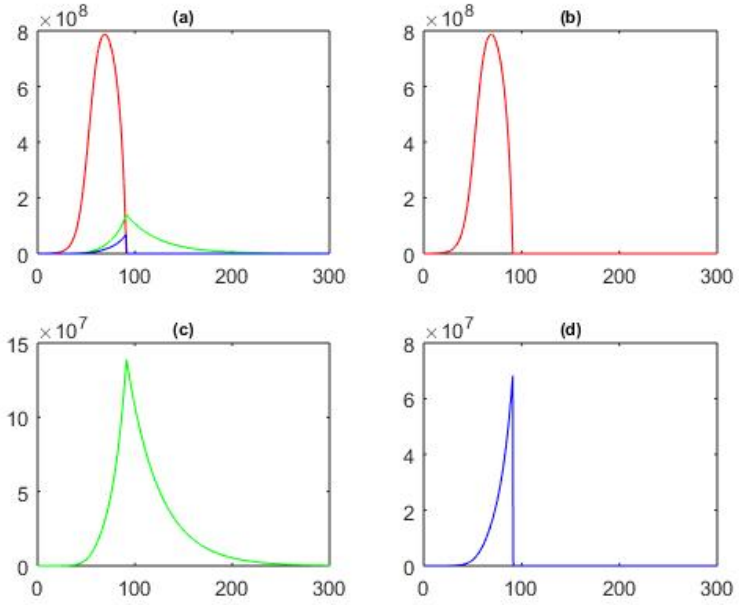

Figure 4.4: The persistence of large tumour ; (*a*) x, y, z all behaviours, (*b*) Cancer cell behaviour x, (*c*) Immune cells behaviour y, (*d*) Cytokines behaviour z

4.2.2 Oscillation between macroscopic and microscopic tumours (for moderately antigenic tumours)

You can also see an image 4.5 with the initial conditions corresponding to the reference [9] given here.

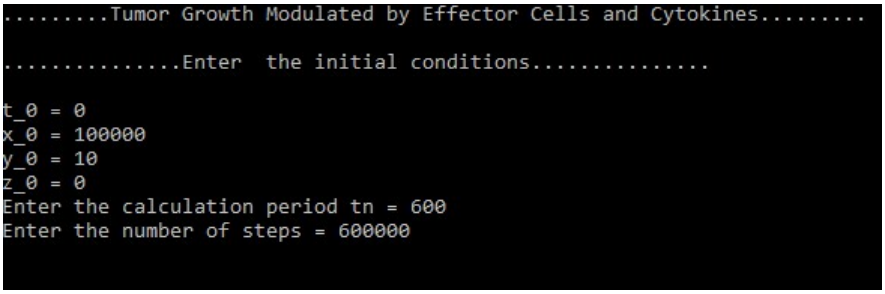

Figure 4.5: Input initial conditions in c code: Oscillation between macroscopic and microscopic tumour

Parameter	**Estimated value**	**Ref**
t_0	0	[9]
x_0	100000	[9]
y_0	10	[9]
z_0	0	[9]
tn	600	[9]
c	0.05	[9]
Enter the number of steps (l)	600000	[9]

Table 4.2: Estimated parameter values: based on [9]

According to the reference [9] determined c value and the following figures (4.3 and 4.7) are recorded using a data text file that can be accessed through this given Github link.

$https://github.com/sachinkavindaa/My\_file2$

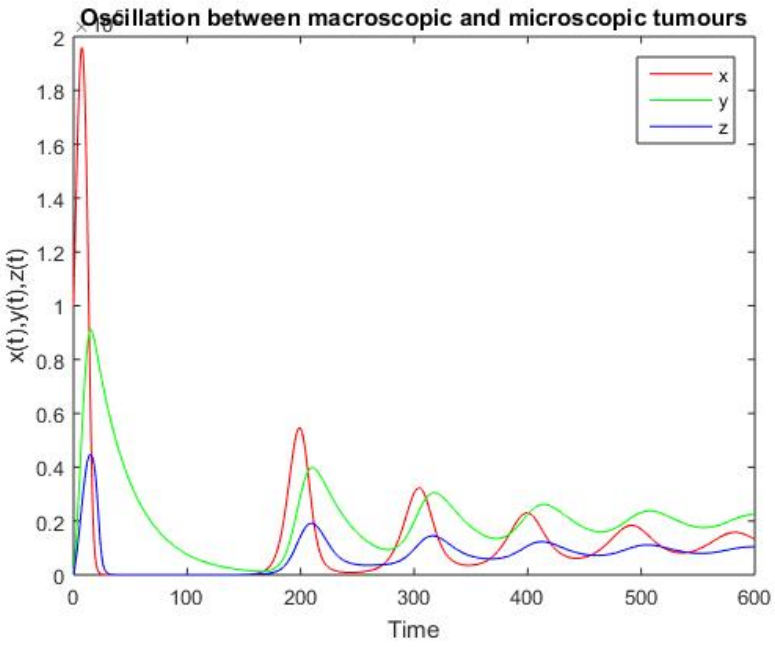

Figure 4.6: oscillation between macroscopic and microscopic tumours (for moderately antigenic tumours)

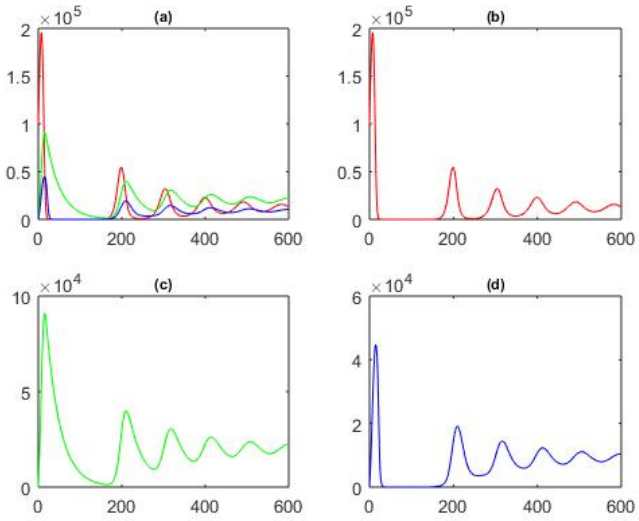

Figure 4.7: oscillation between macroscopic and microscopic tumours: (a) x, y, z all behaviours, (b) Cancer cell behaviour x, (c) Immune cells behaviour y, (d) Cytokines behaviour z

4.2.3 Persistence of residual tumour cells (for highly antigenic tumours)

Considering the reference [9], the persistence of residual tumour cells is described by these initial values and which helps to display numbers corresponding to the value of the variable c.

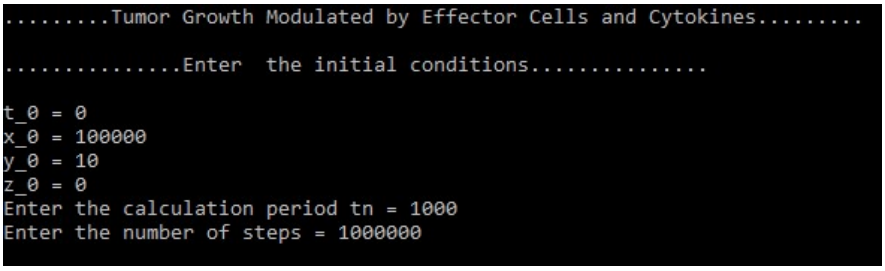

Figure 4.8: Input initial conditions in c code: Persistence of residual tumour cells

Parameter	**Estimated value**	**Ref**
t_0	0	[9]
x_0	100000	[9]
y_0	10	[9]
z_0	0	[9]
tn	600	[9]
c	0.02	[9]
Enter the number of steps (l)	600000	[9]

Table 4.3: Estimated parameter values: based on [9]

To construct this file, using a similar algorithm as above we approach the problem and after eventually the output will be written as a text file. This is the Github link of the above mentioned text file.

https : *//github.com/sachinkavindaa/My_file*3

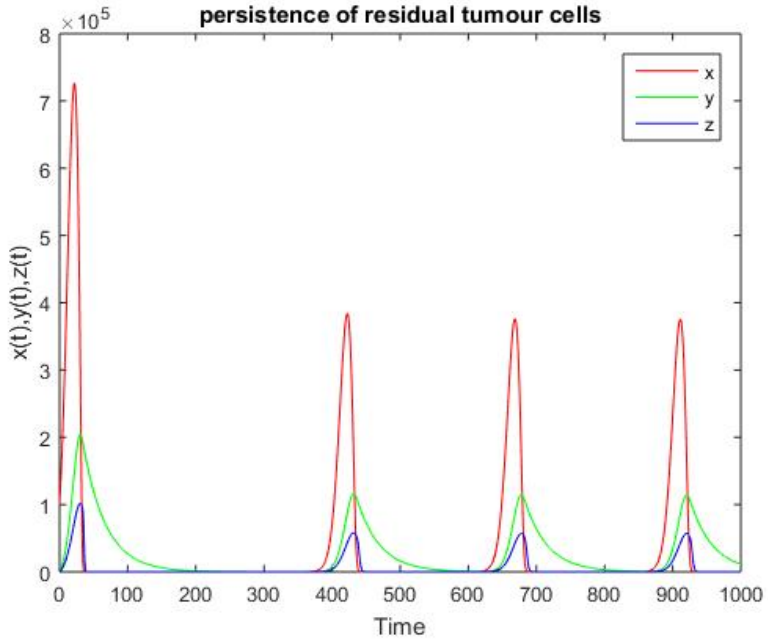

Figure 4.9: Persistence of residual tumour cells (for highly antigenic tumours)

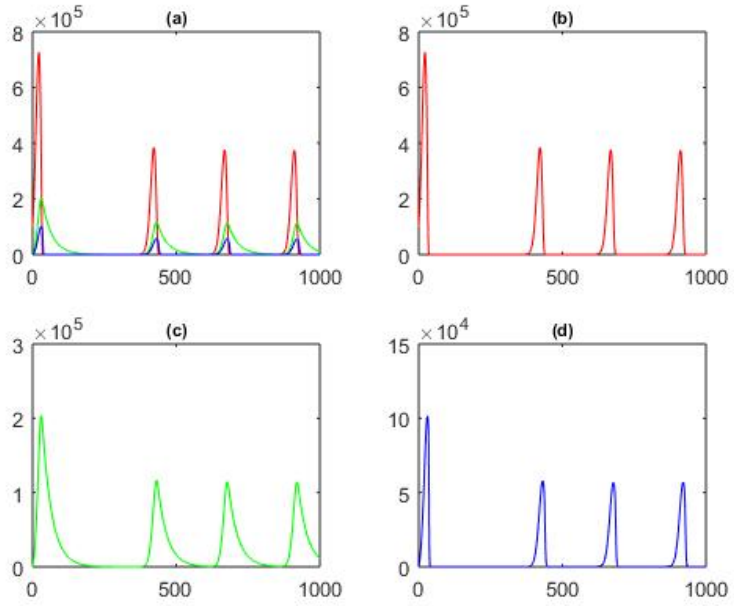

Figure 4.10: Persistence of residual tumour cells (for highly antigenic tumours: (*a*) x, y, z all behaviours, (*b*) Cancer cell behaviour x, (*c*) Immune cells behaviour y, (*d*) Cytokines behaviour z

The above equations show that tumour cell growth rate stability varies greatly as the antigenicity parameter c (an ability of the immune system to detect a tumour) increases beyond certain thresholds. There are three categories for the dynamics as c is varied and these can each be seen in figures 4.4, 4.7 and 4.10. Here also there are three lines in different colours red, green and blue in each graph that appear to represent the actions of cancer cells, immune cells and cytokines in respectively.

Equations (3.13), (3.14) and (3.15) together with initials conditions table 3.2 represent the tumour immune model in the absence of treatment. We start by exploring the steady-states when there are no treatment terms, such that both s_1 and s_2 are zero. Variations in antigenicity (c) give rise to three qualitatively different types of tumors. There is a stable, steady state with a large tumor for low antigenicity and large amplitude, time stable limit interval for moderate antigenicities which both are often approached by the system. There is a slight amplitude here, a limited time limit, and the body can finally eliminate the tumour for exceptionally high antigenicity.

Mathematically, Panetta and Kirschner modelled the relationship between tumour cells and the immune system and immune therapists. And even that model also demonstrated the tumour immune balance both system and tumour size oscillatory activity around the equilibrium. The loss of tumour cells can be characterized by a Michaelis Menten interaction term ($axy/(g_2 + x)$) due to the immune effector cells. The activation also occurs due to the presence of IL-2 hormones and is given under the term ($p_1yz/(g1 + z)$). The change in IL-2 concentration is expressed as ($p_2xy/(g3 + x)$), which would be the activation induced by the tumour presence.

To see the qualitative behavior of the system, we can plot the three populations as functions of time. A typical plot (4.6 and 4.7) is displayed below. One tumour converges to a dormant state with reducing oscillations, and another tumour converges to a cycle of limitations where the tumour's size and composition change periodically. When the size of the tumour becomes very small, it is more likely cleared by the immune system rather than regrowing as expected by the model. Also assume logistic growth for the proliferating cancer cells to reduce the proliferating tumour size even in the absence of immune response.

The mass of tumours oscillates between very high and very low values. As c increases, these oscillations a decrease in amplitude and duration. This means damped oscillations may occur in the tumour mass until it becomes tiny and dormant.

In figures 4.9 and 4.10, we present simulation results for the persistence of residual tumour cells (for highly antigenic tumours) varies with th c value of 0.02. Stability is observed between a stable limit period that oscillates with a small amplitude over an unstable stable state corresponding to a small tumour load and a stable steady state with a large tumour burden corresponding to tumour escape. Thus the system will enter either the stable limit period or the stable steady-state with a wide tumour burden at long times depending on the option of initial conditions. The tumour, immune cells and cytokines populations oscillate out of phase for the periodic solution, tumour growth induces the proliferation of cytokines, which in turn facilitates the proliferation of immune cells and drives the tumour population downwards.

Chapter 5

Conclusion

5.1 Summary

This study shows nonlinear ordinary differential equations to consider a mathematical model for the impact of immunotherapy on immunogenic cancer cells. The model is analyzed using the Runge-Kutta method (Fourth order) of numerical simulations to get rich consequences running through *C* programming. We researched the effects of regularly pulsed immunotherapy on tumour-immune interactions, taking into consideration cancer cells and immune cells linked to tumour suppression cytokine (IL-2). In relapse, the immune system fights cancer cells, and interactions between cancer cells, immune cells, and cytokines (IL-2) can cause long-term cancer recurrence. Here we have found tumour cells grow logistically to fixed carrying capacity and the cells of the effector lead to an expansion that is directly proportional to both the tumour size and its antigenicity. While the effector cells form cytokine (IL-2), at a rate that exceeds the limit as the tumour grows indefinitely and cytokine (IL-2) decays at a constant rate. The model is analyzed numerically for a given case using the Runge -Kutta method to substantiate the simulation findings. Besides, numerical simulation is conducted for various initial values to demonstrate and the results are shown graphically in figures 4.3, 4.6 and 4.9. Numerically, the cancer cell population has been found to be very sensitive to the rate of proliferation of killing cells due to external immune cell infusion during immunotherapy. In the no-treatment case, variations in antigenicity give rise to three qualitatively different types of tumors called as for low antigenicity, for moderate antigenicities and for high antigenicity. In the non-treatment case, antigenicity variations result in three entirely different tumor types such as low antigenicity, moderate antigenicity, and high antigenicity. Antigenicity of the tumour parameter (c) the higher this value is the easier it is to detect tumour presence.

Appendix

```
#include<stdio.h>
#include<math.h>

//The dynamics between the cancer cells

double  func_1( double x, double y, double z, double t)
{
double   b   = 1 *pow( 10 , -9);
double   g_2 = pow(10 , 5);
double   r_2 = 0.18;
double   a   = 1;

double   var_4;
var_4 = x * r_2 * ( 1 - b * x ) - ((a * x * y)/(g_2 + x ));
return var_4;
}

//The dynamics between the immune cells

double  func_2( double x, double y, double z, double t)
{
double   s_1 = 0;
double   p_1 = 0.1245;
double   g_1 = 2 * pow(10,7);
double   m_2 = 0.03;
double   c   = 0.002; // The value of the parameter c varies according to the change cond

double   var_5;
var_5 = s_1 + c * x + ((p_1 * y * z)/(g_1 + z)) - m_2 * y ;
return var_5;
}
//The dynamics between the cytokines

double  func_3(double x, double y, double z, double t)
{
double   s_2 = 0;
double   p_2 = 5;
double   g_3 = 1000;
double   m_3 = 10;

double   var_6;
var_6 = s_2 + ((p_2 * x * y)/(g_3 + x)) - m_3 * z;
```

```
return var_6;
}

int main(){
FILE *fp;
fp =fopen("My_code1.txt","w+");
if(fp==NULL)
{
printf("\n unable to open");
return 0;
}

double   a , l, c;
double   t_0 , x_0 , y_0 , z_0 , t_n , h , x_1 , y_1 , z_1;
double   k_1 , k_2 , k_3 , k_4 , k , m_1 , m_2 , m_3 , m_4 , m , w_1 , w_2 , w_3 , w_4 ,
printf("\n");
printf(".........Tumor Growth Modulated by Effector Cells and Cytokines.........\n");
printf("\n");
printf("...............Enter  the initial conditions...............\n");
printf("\n");

printf("t_0 = "); //Initial value for t
scanf("%lf",&t_0);
printf("x_0 = "); //Initial value for x
scanf("%lf",&x_0);
printf("y_0 = "); //Initial value for y
scanf("%lf",&y_0);
printf("z_0 = "); //Initial value for y
scanf("%lf",&z_0);
printf("Enter the calculation period tn = ");
scanf("%lf",&t_n);
printf("Enter the number of steps l = ");
scanf("%lf",&l);

//Solving mathematical models using the Runge Kutte (Fourth order) method.


//Calculating step size
h = (t_n - t_0) / l;

printf("\n  tn\t\t     x1\t\t   y1\t\t   z1\t\t");
printf("\n");
printf("...........................................................\n");
printf("\n");
for ( a=0 ; a<l ;  a++ )
{
k_1 = h * ( func_1 ( (x_0) , (y_0) , (z_0) , (t_0) ) );
m_1 = h * ( func_2 ( (x_0) , (y_0) , (z_0) , (t_0) ) );
w_1 = h * ( func_3 ( (x_0) , (y_0) , (z_0) , (t_0) ) );
k_2 = h * ( func_1 ( (x_0 + k_1/2) , (y_0 + m_1/2) , (z_0 + w_1/2) , (t_0 + h/2) ) );
m_2 = h * ( func_2 ( (x_0 + k_1/2) , (y_0 + m_1/2) , (z_0 + w_1/2) , (t_0 + h/2) ) );
```

```
w_2 = h * ( func_3 ( (x_0 + k_1/2) , (y_0 + m_1/2) , (z_0 + w_1/2) , (t_0 + h/2) ) );

k_3 = h * ( func_1 ( (x_0 + k_2/2) , (y_0 + m_2/2) , (z_0 + w_2/2) , (t_0 + h/2) ) );
m_3 = h * ( func_2 ( (x_0 + k_2/2) , (y_0 + m_2/2) , (z_0 + w_2/2) , (t_0 + h/2) ) );
w_3 = h * ( func_3 ( (x_0 + k_2/2) , (y_0 + m_2/2) , (z_0 + w_2/2) , (t_0 + h/2) ) );

k_4 = h * ( func_1 ( (x_0 + k_3) , (y_0 + m_3) , (z_0 + w_3) , (t_0 + h) ) );
m_4 = h * ( func_2 ( (x_0 + k_3) , (y_0 + m_3) , (z_0 + w_3) , (t_0 + h) ) );
w_4 = h * ( func_3 ( (x_0 + k_3) , (y_0 + m_3) , (z_0 + w_3) , (t_0 + h) ) );

k  = ( k_1 + ( 2 * k_2 ) + ( 2 * k_3 ) + k_4 ) / 6;
m  = ( m_1 + ( 2 * m_2 ) + ( 2 * m_3 ) + m_4 ) / 6;
w  = ( w_1 + ( 2 * w_2 ) + ( 2 * w_3 ) + w_4 ) / 6;

x_1 = x_0 + k;  //final answer for the var_4 equation model

y_1 = y_0 + m;  //final answer for the var_5 equation model

z_1 = z_0 + w;  //final answer for the var_6 equation model

//Print the final answer of the t_0, x_1 , y_1 , z_1

printf(" %.8lf\t\t   %0.8lf\t\t  %0.8lf\t\t   %0.8lf\n", t_0, x_1 , y_1 , z_1 );

fprintf(fp, "%0.8lf\t\t   %0.8lf\t\t  %0.8lf\t\t   %0.8lf\n ", t_0 , x_1 , y_1 , z_1 );

t_0 = t_0 + h;

x_0 = x_1;
y_0 = y_1;
z_0 = z_1;

}

}
```

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