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Mathematical Modelling of Cancer Treatment with Immunotherapy and Magnetic Drug Targeting

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Abstract

Cancer remains one of the leading causes of death around the globe, whereas cancer therapy continues to be a major challenge for contemporary medicine due to tumor microenvironments which include growth factors (cytokines and hormones), immune cells, extracellular matrix, fibroblasts, signalling molecules (cytokines and chemokines), and other connective tissue cells. As a consequence, many interstitial barriers are lifted, interfering with both convective and diffusive mechanisms of therapeutic drug penetration. Recently, with the advancement of molecular and tumor biology, treatment options such as immunotherapy and magnetic drug targeting (MDT) have significantly changed the paradigm of cancer treatment. Innovative treatment strategies have both been developed to maximize efficacy while minimizing side effects. This research aims to use theoretical analysis and numerical tools to examine the mechanism of tumor-immune dynamics, as well as how to effectively disperse therapeutical drugs to tumor sites during magnetically targeted drug delivery. In this study, we focused on the role of immunotherapy in cancer treatment studied using a fractional-order model for tumor-immune interaction incorporating the treatment of cytokine interleukin-2 (IL-2) aimed at boosting the immune system's ability to fight cancer. Our results indicate that in some cases, adoptive cellular immunotherapy alone or a combination of the adaptive cellular immunotherapy and cytokine interleukin-2 can achieve satisfactory stable tumor control in such a way that; with little adoptive cellular immunotherapy alone to the system, the situation remains the same as without any treatment. In addition to that, a model magnetic drug targeting to determine the capture conditions on the efficient dispersion of drug-coated nanoparticles in a tumor environment was presented. Thus, drug-coated magnetic nanoparticles are taking longer times to reach the tumor as a result of higher volumes fractions of magnetic particles, the magnetization of the magnetic field, drug elimination, and source term. Furthermore, increases in tumor-magnet distance, permeability of the microvessels, Peclet number, and radius of the nanoparticles slow the ability of the drug-coated nanoparticles to reach the tumor. As a result of these observations, researchers are able to formulate essential considerations to be used in implementing potential therapeutic intervention aimed at reversing cancer therapy.

Keywords:

Tumor-immune interaction, Magnetic drug targeting, Sensitivity analysis, Drug-coated nanoparticles, Caputo derivative, Cardiovascular, Immunogenicity.

Dedications

This thesis is dedicated to my lovely Mother, Valentina Likalango, my brother, Mr. Protasi Protas Ndenda, my uncle Ditrick Nguvumali, my siblings, and the entire Ndenda family. Also in memory of my father, Mr. Protas Gerewasi Ndenda (May his soul rest in peace), as well as my grandfather and grandmother, Mr. and Mrs. Gerewasi Ndenda (May their souls rest in peace).

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List of Publications

Here is a list of the research articles that I have published during my Ph.D. program.

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4. **Ndenda, J. P.**, Njagarah, J. B. H., & Shaw, S. (2022). Influence of envi-ronmental viral load, interpersonal contact and infected rodents on Lassa fever transmission dynamics: Perspectives from fractional-order dynamic modeling. *AIMS Mathematics*, 7(5), 8975-9002. <https://doi.org/10.3934/math.2022500>
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6. **Ndenda, J. P.**, Njagarah, J. B. H., & Tabi, C. B. (2021). Fractional-order model for myxomatosis transmission dynamics: Significance of contact, vector control, and culling. *SIAM Journal on Applied Mathematics*, , 81(2), 641-665. <https://doi.org/10.1137/20M1359122>

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1. Introduction

1.1 Background

Cancer is a collection of over a hundred different diseases in which body cells grow uncontrollably and spread to other parts of the body [1, 2]. Cancer remains one of the leading causes of death worldwide, with an estimate of 19.3 million new cases and almost 10.0 million cancer-related deaths in 2020 [2, 3]. Globally, almost 1 in 6 deaths is due to a malignant tumor, with approximately 70% of these deaths occurring in low- and middle-income countries [1]. The World Health Organization (WHO) predicted that new cancer cases will increase by 70% over the next two decades [1]. Consequently, both cancer incidence and cancer mortality continue to rise worldwide, and by 2050 the global cancer mortality rate is predicted to double [1]. In general, the burden of cancer incidence and mortality is rapidly increasing around the world due to both aging and a growing population as well as changes in the prevalence and distribution of the main risk factors, some of which are associated with socio-economic development [3]. As the cancer burden grows globally, it exerts tremendous physical, emotional, and financial pressure on individuals, families, communities, and health systems.

Tumor usually arises anywhere in the human body when some of the body's cells grow out of control and spread to other parts of the body. A series of genetic and epigenetic mutations lead to the emergence of cancer cells. Gene mutations can cause cancer by speeding up cell division or blocking normal system mechanisms like cell cycle arrest or programmed cell death. Usually, when cells are damaged or die in any way, the body releases new cells to replace them by cell division. The body's normal control mechanisms stop working, resulting in abnormal cells growing, old or damaged cells surviving when they should die, and new cells forming when they are not needed. These extra, abnormal cells can accumulate to form a tumor, which is an abnormal mass of tissue in the body. Some tumors are benign and include cells that are not cancerous, such tumors won't invade nearby tissues or spread to other parts of the body (metastasize). A benign tumor is less harmful unless it presses on vital structures such as organs, tissues, nerves, or blood vessels. Benign tumors may be surgically removed and seldom recur, but if they do, they generally do so in the same location. On the contrary, a malignant tumor is capable of both invading adjacent parts of the body and spreading to other organs through the bloodstream or lymphatic system, forming new tumors (a process called metastasis). Metastasis refers to a growth that

forms from fragments of the primary tumor, detached and transported away from it [4, 5]. Most cancer-associated deaths are largely attributed to metastases, yet this complex process remains the least understood aspect of cancer biology [6]. Cancerous tumors may also be described as malignant tumors. Some benign tumors, such as intestinal polyps, are considered precancerous and should be removed immediately to avoid turning into malignant tumors [7]. Every second of each minute, a battle of

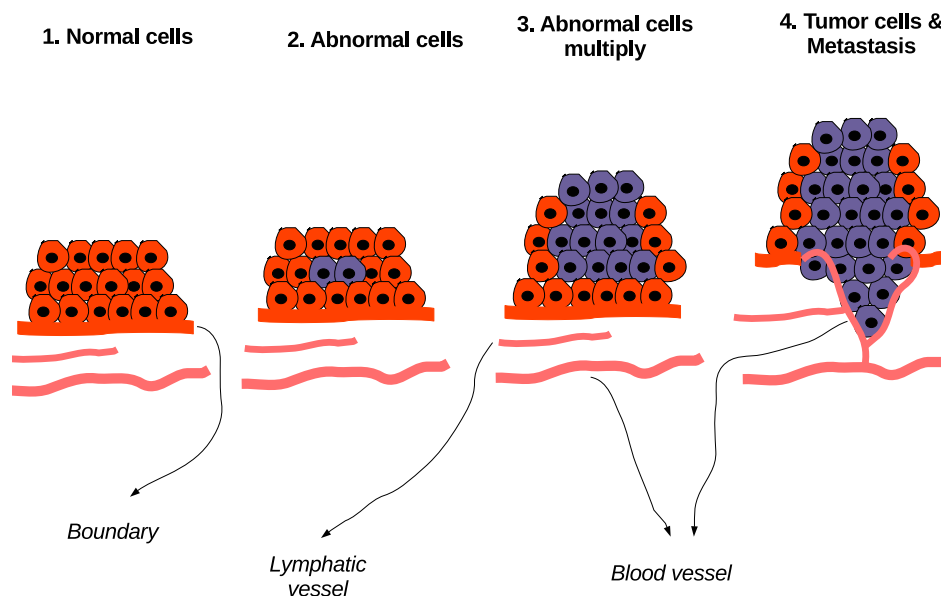


Figure 1.1: Illustration to show cancer cells development.

good and evil goes on inside our bodies. The good is the immune system, an army of cells designed to protect the body from disease and infection. The evil appears in the form of pathogens, viruses, bacteria, and mutant cells, which are programmed to cause harm. When it comes to cancer, the good guys don't always win, because cancer cells have ways to avoid being destroyed by the immune system. Cancer cells can also deactivate the immune response so that immune cells do not attack them, resulting in a weakened immune system, usually in cancer patients.

There are several cancer treatment options available to patients. In recent decades, chemotherapy, surgery, and radiotherapy have been used to treat different types of cancer. Tumor surgery is an operation or procedure to remove the tumor and possibly some surrounding tissue. Using high doses of radiation, radiotherapy kills cancerous cells and shrinks tumors. Chemotherapy involves the use of drugs or chemicals to destroy fast-growing cells, which are typical of cancerous cells [8, 9]. However, intravenous administration leads to a general systemic distribution of chemotherapy drugs which can have harmful side effects on healthy cells, resulting in severe unintended and undesirable side effects, such as nausea and loss of appetite due to their toxicity, and

extensive spread throughout the body [10]. In reality, the severe side effects caused by chemotherapy on healthy organs and tissues are at the root of the high mortality rate of cancer patients [10].

Due to the complexity in genetic and phenotypic expressions during cancer progression, tumors are highly heterogeneous, resulting in clinical diversity and resistance to therapy. In the majority of cases, a combination of standard therapies can efficiently treat the primary tumor, but it is currently ineffective in preventing the metastatic spread of the disease. Furthermore, in most cases, these therapeutics are reported to have low efficacy and high toxicity against non-cancerous healthy cells. To design precise and efficient therapies, a deep understanding of these complex phenomena is crucial. In recent years, several new treatment options, including but not limited to immunotherapy and magnetic drug targeting (MDT), have revolutionized cancer treatment. Considering the aims of our research, we focus on immunotherapy and nanotechnology in cancer drug delivery.

1.1.1 Immunotherapy

Biological therapy (also known as Immunotherapy) uses our immune system (natural defense) to fight cancer by improving the ability of the immune system to recognize, target, and kill cancerous cells in any part of the body. Generally, the main purpose of immunotherapy is to boost the immune system by regulating the immune microenvironment, so that immune cells are capable of attacking and eliminating tumor cells at several important nodes throughout the body. By stimulating immune cells and employing the body's own tumor-specific immune response to overcome tumor escape, immune cells can play a significant role in tumor monitoring and clearance. Anticancer immune effector cells such as lymphocytes, macrophages, dendritic cells, natural killer cells (NK cells), cytotoxic T lymphocytes (CTL), and others collaborate to protect the body from cancer by recognizing abnormal antigens displayed on tumor cells' surfaces. To combat cancer cells, it has become increasingly important to develop strategies that stimulate an efficient and effective immune response [11, 12, 13].

Immunotherapy refers to the combination of cytokines and adoptive cellular immunotherapy [14]. Adoptive Cellular Immunotherapy (ACI) is a promising immunotherapy method that uses cells that have grown extensively in vitro and have natural antitumor reactivity (such as lymphocytes) in a tumor-bearing host [15]. In this approach, tumor-specific T cells are infused into cancer patients to recognize, target, and destroy cancerous cells. Due to its strength of specificity, ease of preservation, and no drug resistance, ACI is becoming a key therapy option in tumor treatment. Moreover,

T cell responses are memory cells that retain their therapeutic effect for a long period of time after initial treatment [16]. Cytokines are small glycoproteins that bind to cell surface receptors and regulate the growth, survival, and function of immune cells. Therefore, cytokines are largely considered as potential therapeutic agents to manipulate the immune response of tumor cells. Interleukin 2 (IL-2) act as the main cytokine responsible for lymphocyte activation, growth and differentiation [14]. This kind of immunocytes can involve two approaches [17]. The first approach includes lymphokine-activated killer cells (LAK) therapy: These cells are extracted in vivo from the peripheral blood leukocytes of patients with high concentrations of IL-2, later on, LAKs are injected back into the cancer site. It is believed that these are mainly natural killer cells[14, 15]. Another approach includes the infiltrating tumor lymphocytes (ITL); ITLs are removed from a patient's tumor, then incubated in large quantities with high concentrations of IL-2 in vitro and comprised of activated NK cells and CTL cells, and then returned to the patient to help immune cells kill cancer cells [14]. Our understanding of IL-2 in lymphocyte regulation has progressed considerably, providing exciting new directions in cancer immunotherapy.

1.1.2 Magnetic Drug Targeting

In cancer therapy, one of the current challenges include delivering high concentrations of drug to the tumor tissue while minimizing systemic dosing, thereby limiting the off-target adverse effects [18]. One of the main goals of researchers these days is to deliver cancer medicine to the exact areas of disease tissues. As an example, chemotherapy is a contemporary treatment in which less than 0.1% of the medicine is absorbed by cancerous cells, while 99.9% is absorbed by healthy cells [19]. It is partially due to the delivery and transport limitations of anticancer drugs in the tumor interstitium. In early tumor growth and progression, cancer cells interact with normal cells and the surrounding tissue to create a microenvironment that promotes malignancy and induces changes that lead to a complex tissue microarchitecture [20].

Additionally, the extracellular matrix(ECM) density of tumor extravascular space is higher than normal tissue, creating a further barrier to interstitial drug transport [21, 22]. As a result of this, a process called desmoplasia, is closely associated with poor prognosis and resistance to systemic therapy [22, 23, 24]. The delivery of cancer therapies involves numerous steps and spans a wide variety of time scales and lengths from the place of injection to the desired cellular and intracellular targets [20, 25]. Thus, to improve treatment effectiveness as well as reduce side effects, new therapeutic and effective approaches need to be developed. Magnetic Drug Targeting (MDT) approach is one attempt toward targeting drugs to tumor position, and overcoming

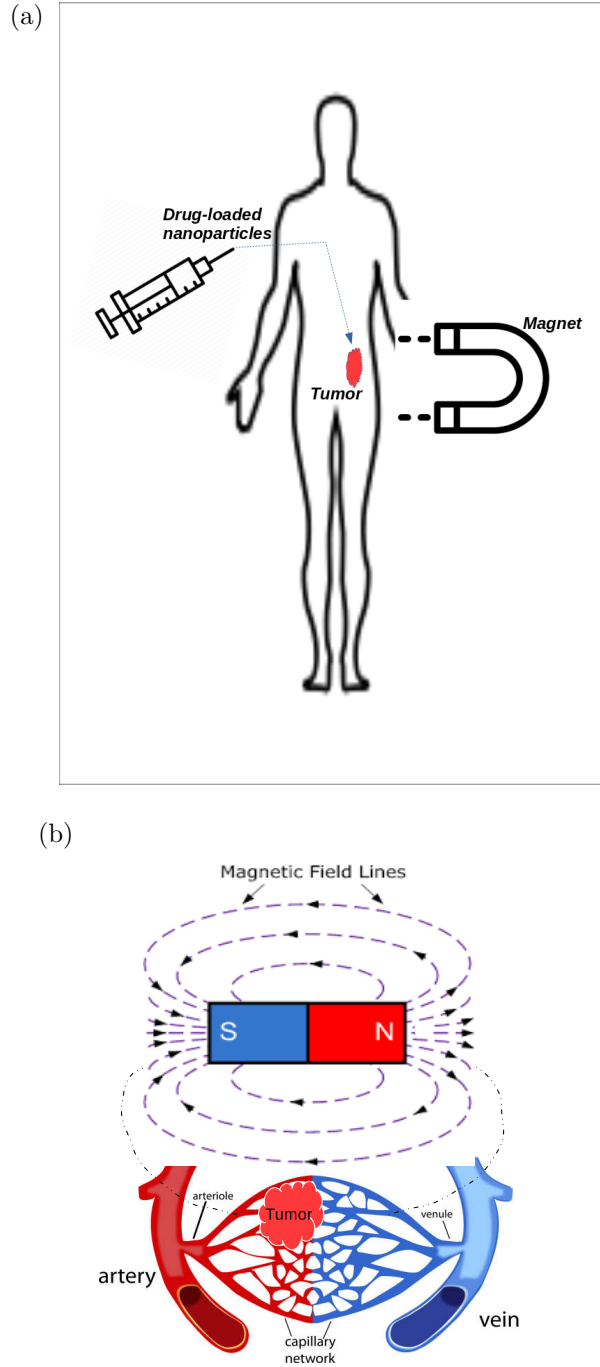


Figure 1.2: The schematic geometry shows (a) The drug-coated magnetic nanoparticles injected systemically and then absorbed into the solid tumor due to the external magnet.(b) The model of magnetically assisted drug-coated magnetic nanoparticles drug delivery.

these insufficiencies provides a controlled release of a high concentration of drug agents in a selected region of the body with minimal negative side effects [26].

In the MDT therapy, the carrier particles containing therapeutic drugs are coated with magnetic nanoparticles and injected systemically into the human body. To improve the accumulation of drugs in a tumor, an external magnetic field is placed outside the body surface near the tumor location to capture the loaded carrier particles towards the tumor site. These carriers are activated by pH, temperature, enzymes, or magnetic triggers that regulate magnetic particles in the body through magnetic actuators [19, 27, 28, 29]. Drugs incorporated with nanocarriers can alter both pharmacokinetics and pharmacodynamics. In addition, nanocarriers are designed for targeted drug delivery, improving the bioavailability of poorly water-soluble drugs, delivering macromolecules to the site of action inside the cells, and combining therapeutic agents with imaging techniques which may help visualize the location of drug delivery [30, 31]. Moreover, nanocarriers prevent early drug degradation, which depends on the route of administration, the most common being intravenous [30]. Nanoparticles (NPs) possess unique biological properties due to their small size (diameter within 1-100 nm) and large surface area to volume ratio, making them capable of binding, absorbing, and carrying anticancer agents, such as drugs, DNA, RNA, and proteins, as well as imaging agents [10, 32]. Currently, several nanoparticle-based therapeutics are approved for clinical use and many more are in different phases of preclinical testing. In cancer therapy, nanocarriers are divided into two categories, depending on their durability and molecular weight: those that employ organic molecules as a key building block material and those that use inorganic components (typically metals) as their core [33, 34]. Organic nanocarriers include liposomes, lipids, dendrimers, carbon nanotubes, emulsions, and synthetic polymers [33, 34]. On the other hand, inorganic NPs have also attracted researchers' attention in recent years due to their unique material- and size-dependent physicochemical properties, which are incomparable with materials such as lipids and polymers, leading to improved therapeutic efficacy, weakened side effects, and improved compliance by patients [32, 33, 34]. In particular, magnetite (Fe_3O_4) or its oxidized form maghemite (Fe_2O_3) are the most commonly employed for biomedical applications due to their extremely low cytotoxicity profile, magnetic responsiveness, tunability, and controlled size and surface modification [29, 35]. In delivering therapeutic drugs, nanomaterials have improved not only targeting specificity, but also circulation time, biodistribution, solubility, intracellular distribution, and ability to penetrate biological membranes. Thus, magnetic drug targeting can increase the drug dose in the cancerous site, as well as reduce side effects from other methodology to process anti-cancer drugs.

1.2 Statement of the problem

Microenvironments surrounding tumors include growth factors (such as cytokines and hormones), immune cells, extracellular matrix, fibroblasts, signalling molecules (cytokines and chemokines), as well as other connective tissue cells. All of these lift numerous interstitial barriers, which interfere with both convective and diffusive mechanisms of therapeutic drug penetration. As a result, cancer therapy continues to be one of contemporary medicine's most problematic challenges. With the advancement of knowledge in molecular and tumor biology, treatment options, including but not limited to immunotherapy and magnetic drug targeting, have significantly changed the paradigms of cancer treatment in recent years. Both of these novel treatment strategies have been developed to increase the efficacy of therapy while minimizing side effects. Therefore, it is critical to offer a complete picture of tumor-immune interactions and MDT using mathematical modelling tools to enhance the cancer treatment.

1.3 Aims and objectives

This research work aims to use theoretical analysis and numerical mathematical tools to determine the mechanism of tumor-immune dynamics, as well as to examine how to effectively disperse therapeutical drugs to the tumor site during magnetic drug targeting. To accomplish this aim, the following objectives are set;

1. To determine whether adaptive cellular immunotherapy (ACI) alone or in combination with cytokine interleukin-2 (IL-2) can be sufficient in tumor control.
2. To identify key biological parameters for effective dispersion of drug-coated nanoparticles in the tumor position during magnetic drug targeting.
3. To determine the impact of memory effect on shear augmented dispersion during magnetic drug targeting in a microvessel.

1.4 Structure of the thesis

Here is a summary of how the rest of this thesis is organized, following this introduction, Chapter 1.

In Chapter 2, we give a brief review of the modelling work done on tumor-immune interaction and Magnetic Drug Targeting, which has either directly influenced or indirectly influenced the development of the novel models presented in this thesis.

In Chapter 3, relevant mathematical concepts, definitions, and theories are presented. These are used throughout the thesis to aid the numerical and analytical implementation of the models developed.

Chapter 4, focuses on the role of immunotherapy in cancer treatment, studied using a fractional-order model for tumor-immune interaction incorporating the treatment of cytokine interleukin-2 (IL-2). The basic properties of the model such as positivity of the solutions and local stability analysis of the tumor-free equilibrium are studied and the conditions for tumor removal are highlighted. Furthermore, the existence and uniqueness of the solution of the model are proved using the fixed point theory. Given the uncertainty in the selection of model parameters, sensitivity analysis was performed using the Latin Hypercube Sampling scheme to determine model parameters that describe the processes that significantly influence the changes in the model state variables. The model was numerically solved for different orders of the fractional derivative using the Adams-Bashforth–Moulton Method.

In Chapter 5, a model on Magnetic Drug Targeting used to determine the capture conditions on the efficient dispersion of drug-coated nanoparticles in a tumor environment is presented. In this chapter, we investigate the capture conditions of carrier particles and the effective longitudinal dispersion of drug carriers in microvessels. The study focuses on particles injected into the microvascular system upstream of the cancerous tissue and captured in the tumor using an external applied magnetic field. The fluid velocity and the particle velocity due to the magnetic field are calculated analytically, while the solute transport equation is solved numerically by using the finite difference method. The influence of the model biological parameters in the dispersion of drug-coated nanoparticles in microvessels is also discussed

In Chapter 6, a Caputo fractional time derivative-based dispersion model is formulated, to predict the effective dispersion and saturated concentration of the drug carriers. The impact of the memory effect dependence of solutions on previous instances on the shear augmented dispersion is analyzed during the MDT in the microvessel. The nature of the blood flow into the vessel is considered as Casson fluid. The velocity of the drug carrier is solved analytically, while the fractional-order dispersion equation is solved numerically by using the finite difference method. The influence of fractional-order parameter and model biological parameters such as rheological, permeability parameter related to hydraulic conductivity, magnetization, volume fraction of nanoparticles, tumor-magnet distance, nanoparticle radius, drug elimination, and source term on the relative effective dispersion are discussed

Lastly, Chapter 7 summarizes the important contributions of our work, the overall overview of our study and suggested future work that can be considered.

2. Literature review

An overview of mathematical models describing the interactions between a malignant tumor and the immune system and nanotechnology in cancer drug delivery is presented in this chapter.

2.1 Mathematical modelling of tumor-immunology

Mathematical modelling has broadly been used in support of the preclinical and clinical investigation, as well as in decision-making in many fields, including oncology. Through mathematical models of tumor-immune interactions, we provide an analytical framework for discussing the immunological components that play a critical role in cancer therapy. Over the years, various researchers have developed several mathematical models of tumor-immune interactions. Many early mathematical models of tumor-immune interactions used the predator-prey approach, where immune cells serve as the predators and tumor cells as the prey. In 1979, Stepanova proposed a model for cancer growth with immune interaction that is symbolically representative [36]. Her formulation is based on two differential equations, which include the most important components of T-cell-mediated immune reactions towards cancerous cells:

$$\begin{cases} \frac{dx}{dt} = \mu x - \gamma xy \\ \frac{dy}{dt} = r(x - \beta x^2)y - \delta y + \kappa \end{cases} \quad (2.1)$$

where x represents tumor volume and y represents T-cell densities. In this model, μ is the proliferation rate of tumors, γ is the rate of elimination of cancer cells by activity of T cells, r models the production of T-cells product of the stimulation of cancer cells, β^{-1} is the saturation density up from which the immunological system is suppressed, δ is the natural death rate of T lymphocytes, and κ is the natural (constant) rate of influx of T cells from the primary organs. A very similar model was developed by Kuznetsov *et al.* [37], in 1994, to explain the cytotoxic T lymphocyte response to the growth of an immunogenetic tumor. Instead of an exponential growth rate, their model explained cancer cell growth using a logistic growth rate. According to their model, immune effector cells and cancer cells interact employing the kinetic scheme shown in Figure 2.1. Activated concentrations of effector cells are denoted by E, tumor cells are denoted by T, and E* and T* denote dead or inactivated effector and tumor cells, respectively. The immune effector cells, E and tumor cells, T form complexes at a kinetic rate of k_1 . These complexes can be split apart into effector and tumor cells

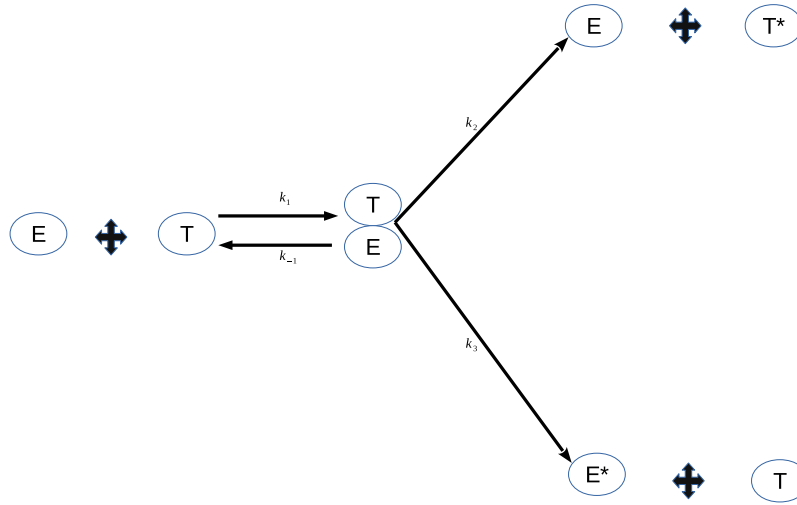


Figure 2.1: The kinetic scheme of tumor-immune interactions suggested by Kuznetsov *et al.* in [37].

at a negative kinetic rate of k_{-1} . Furthermore, they can cause tumor cell death while leaving the effector immune cells intact, which occurs at a rate of k_2 , or they can cause effector immune cell death while leaving cancer cells intact, which occurs at a rate of k_3 . The tumor-effector interaction Kuznetsov model is given as:

$$\begin{cases} \frac{dT}{dt} = rT(1 - bT) - c_1TE, \\ \frac{dE}{dt} = \sigma_1 + \frac{\rho T}{s+T}E - c_2ET - \mu_1E. \end{cases} \quad (2.2)$$

From their analysis, the model exhibits oscillatory growth patterns in tumors as well as several phenomena that can be observed in vivo, such as immunostimulation of tumor growth, "sneaking through" of the tumor, and the state of tumor dormancy [37].

Kirschner and Panetta (1998) were among the first theoretical studies to investigate the role of cytokines (IL-2) on tumor regression [14]. According to their model, immunotherapy using interleukin-2 might boost the immune system to fight tumors. To construct the model, Kirschner and Panetta describe the interaction between the populations of effector cells, tumor cells, and the cytokine IL-2 using the following model.

$$\begin{cases} \frac{dE}{dt} = cT - \mu_2E + \frac{p_1EI}{g_1+I} + s_1, \\ \frac{dT}{dt} = rT(1 - bT) - \frac{aTE}{g_2+T}, \\ \frac{dI}{dt} = \frac{p_2ET}{g_3+T} - \mu_3I + s_2, \end{cases} \quad (2.3)$$

where s_1 and s_2 represent external sources of effector cells such as LAK or TIL cells,

and external sources of IL-2 into the system, respectively. The model examines the effects of two types of continuous treatment: (a) the adoptive cell transfer (from one individual to another, or by in vitro amplification of harvested immune cells from one individual and reinjection) (if $s_1 > 0$) and (b) the injection of cytokines (if $s_2 > 0$). In recent decades, many mathematical models of tumor-immune interactions have been developed by researchers focusing on immunotherapy alone or immunotherapy in combination with other forms of therapy. To review these models comprehensively, the reader should refer to [38, 39, 40, 41].

2.2 Modelling drug delivery to solid tumors

Drug transport to solid tumors involves multiple physiological, pharmacological, and biophysical mechanisms. Through mathematical modelling and computational simulations, researchers are able to study the individual and combined effects of a wide range of parameters on drug delivery and therapeutic efficacy, which would not be possible or cost-effective if we used experimental methods. Moreover, computational modelling is increases significantly for understanding drug transport in solid tumors for a variety of reasons. Among them are: it allows for comprehensive parametric sensitivity analyses to pinpoint the most significant factors; it allows for individual and integrated examination of the complex steps in drug delivery; and, finally, clinically controllable factors such as drug dose and administration schedule can be incorporated into the model for in silico simulations, potentially reducing the number of laboratory and animal experiments [20]. A wide variety of mathematical models have been developed and extensively discussed in the literature. Historically, Senyei and Widder, (1978) [42, 43] are pioneers in employing a computational model to understand the drug delivery and control mechanism of carrier particles within the body using external magnetic fields. According to their first model [42], one particle flows in the presence of an externally applied magnetic field gradient and is subjected to Stokes drag. They considered flow rates that occur throughout the human cardiovascular system, ranging from $0.05 \frac{cm}{s}$ to $10 \frac{cm}{s}$. In vitro and later in vivo experiments were guided by the results from this study. Baxter and Jain used a mathematical model to conduct research studies series [44, 45, 46, 47] on drug delivery to study the impact of various properties of the tumor on drug delivery using the principles of fluid mechanics to investigate elevated interstitial fluid pressure, significant interstitial fluid flow, and concentration. As of the late 1990s, various computational studies have been published about drug delivery to solid tumors. Through an analytical solution and ex-vivo experiments, Netti *et al.* [48] (1995) proved the dependence of elevated interstitial fluid pressure (IFP) on variations of microvascular pressure and tumor blood flow. To suit magnetically targeted drug delivery on the near sites of the body's edge, Grief and Richardson [49] develop a two-

dimensional model on the magnetic drug targeting. Furlani and Furlani [50] studied a theoretical model of magnetic drug targeting in microvessels. Shaw *et al.* [51] and Shaw and Murthy [52] carried this work forward by taking the Herschel–Bulkley fluid model for blood in both impermeable and permeable microvessels, respectively. Shamsi *et al.* [53] considered simple homogeneous circle geometry to simulate the magnetic nano-drug distribution on the intraperitoneal solid tumor. They studied the effect of magnetic field intensity, tumor-magnet distance, and particle size on the penetration of MNP in the tumor site. To understand and optimize the control of magnetic particles, Cherry and Eaton [54] studied the magnetic drug targeting in a microvessel considering all forces expected to significantly affect the particles, including the interparticle magnetic force, dispersion due to collisions between particles and blood cells, and complex viscous force accounting for the shear-thinning nature of blood. Bose and Banerjee [55] have performed a numerical simulation to study the transport of magnetic carrier particles in a biomagnetic fluid flow in a stenosed bifurcated artery, taking into account both the magnetization and the electrical conductivity of the blood. Soltan *et al.* [56] studied the effect of tumor size and shape on interstitial fluid flow, where the capillary network is replaced by the uniform distribution of the mass source. Recently, Shojaei *et al.* [57] investigate the role of the capillary network in magnetic nanoparticle targeting, where the effect of nanoparticle size, magnetic intensity, and distance from the tumor in a heterogeneous tumor microenvironment were analyzed. To show that the high interstitial fluid pressure in the tumor is among the most important barriers to drug delivery, the effect of the magnetic field on the pressure and the preservation of the magnetized interstitial fluid is analyzed by Hosseinihah *et al.* [58], where the geometry includes the space porous of healthy tissue and tumor, as well as the parent vessel as a source and the lymphatic system as a sink modelled on the biology of the body. The performance of the nanoparticle will be affected by its physiological properties such as size, shape, stiffness, and surface functionality. The study by Ye *et al.* [59], details the impact of nanoparticles’ size and shape in their “passive” or “active (subjected to magnetic forces for instance)” transport in the bloodstream, in the area of drug delivery. Other forces induced by external magnetic fields (such as magnetic fields) are essential to guide the movement of the particles [60]. The study by Shah *et al.* [61] examined the flow of blood with magnetic particles through a cylindrical tube using the time fractional-order derivative of Caputo type. To demonstrate the difference between fractional-order time derivatives and integer-order derivatives, the authors in [62] used a Casson fluid model. As they used blood as a Casson fluid, their model result showed that fractional-order derivatives resulted in a remarkably different result than the ordinary derivative. To study the capture effectiveness of magnetic nanoparticles adhered to therapeutic compounds injected into the bloodstream, which are controlled by an external magnetic field, Maiti *et al.* [63] used a thermo-solutal

transport model with Caputo-Fabrizio fractional-order derivative. In summary, the above-mentioned studies, among others, aim to explain various key issues related to magnetic drug targeting, such as increased interstitial fluid pressure or uniform distribution of drug concentrations in tumors and healthy tissues, as well as determine the most effective parameters through sensitivity analysis.

3. Mathematical preliminaries and definitions

In this chapter, we briefly review some key definitions and concepts related to this thesis

3.1 Basic definitions

Definition 1. For $s > 0$, the Gamma function, $\Gamma(s)$ is defined as [64]

$$\Gamma(s) = \int_0^{\infty} e^{-t} t^{s-1} dt, \quad \operatorname{Re}(s) > 0. \quad (3.1)$$

Remark 1. The function $\Gamma(z)$ obeys the following properties:

1. $\Gamma(z+1) = z\Gamma(z)$

Proof. From the definition

$$\Gamma(z+1) = \int_0^{\infty} e^{-t} t^z dt$$

Using integration by parts, we obtain

$$\begin{aligned} \Gamma(z+1) &= (-t^z e^{-t})|_0^{\infty} + z \int_0^{\infty} e^{-t} t^z dt, \\ \Gamma(z+1) &= z\Gamma(z). \end{aligned} \quad (3.2)$$

□

2. $\Gamma(z+1) = n!$

3. $\Gamma\left(\frac{1}{2}\right) = \sqrt{\pi}$.

Definition 2. For $s, z > 0$, the Beta function, $\mathcal{B}(s, z)$ is defined as [64]

$$\mathcal{B}(s, z) = \int_0^1 t^{s-1} (1-t)^{z-1} dt, \quad (\operatorname{Re}(s) > 0, \quad \operatorname{Re}(z) > 0). \quad (3.3)$$

Remark 2. By the Laplace transform in [65], the beta function can be written in terms of gamma function as

$$\mathcal{B}(s, z) = \frac{\Gamma(s)\Gamma(z)}{\Gamma(s+z)}. \quad (3.4)$$

Definition 3 (Two parameter Mittag-Leffler function). *For two parameters α and β , the two-parameter Mittag-Leffler function is defined as*

$$E_{\alpha,\beta}(x) = \sum_{n=0}^{\infty} \frac{x^n}{\Gamma(\alpha n + \beta)}, \quad \operatorname{Re}(\alpha) > 0, \quad \beta \in \mathbb{C}. \quad (3.5)$$

When $\beta = 1$, Equation (3.5) becomes the one-parameter Mittag-Leffler function given by

$$E_{\alpha,1}(x) = E_{\alpha}(x) = \sum_{n=0}^{\infty} \frac{x^n}{\Gamma(\alpha n + 1)}, \quad \alpha \in \mathbb{C}. \quad (3.6)$$

Remark 3. *For a particular value of $\alpha = 1$, Equation (3.6) becomes*

$$E_{1,1}(x) = \sum_{n=0}^{\infty} \frac{x^n}{n!} = e^x, \quad (3.7)$$

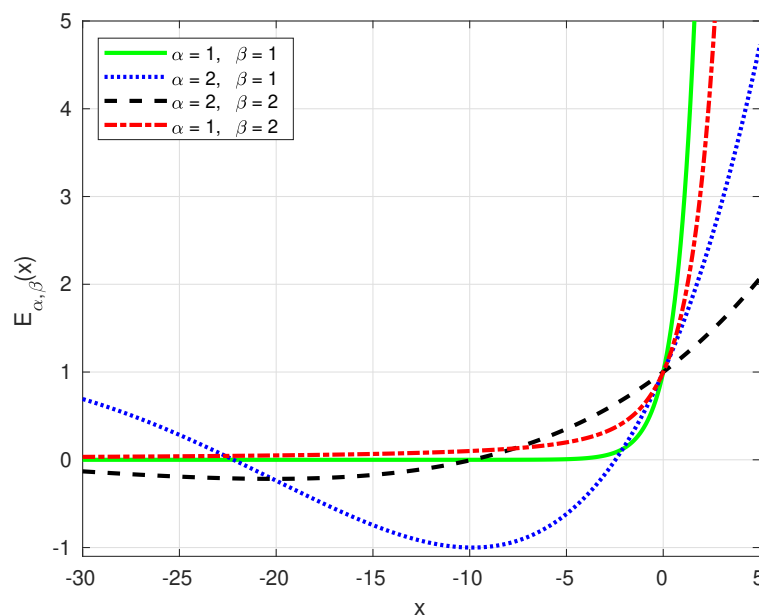


Figure 3.1: Graphical display of Mittag-Leffler functions for varying parameters α and β .

3.2 Laplace Transform

The Laplace transform is a very useful tool for deriving formulas and solving fractional differential equations.

Definition 4. *The Laplace transform of a function $f(t)$, denoted by $\mathcal{L}\{f(t)\}$, is defined*

as [64]

$$F(s) = \mathcal{L}\{f(t)\} = \int_0^\infty e^{-st} f(t) dt \quad (3.8)$$

Definition 5. If $\mathcal{L}\{f(t)\} = F(s)$, then we define the Inverse Laplace transform as

$$\mathcal{L}^{-1}\{F(s)\} = f(t) \quad (3.9)$$

$$\overline{f(t) = \mathcal{L}^{-1}\{F(s)\} \quad F(s) = \mathcal{L}\{f(t)\} \text{ [64]}}$$

1	$\frac{1}{s}$
e^{at}	$\frac{1}{s-a}$
$t^n, \ n = 1, 2, 3, \dots$	$\frac{n!}{s^{n+1}}$
$\sin at$	$\frac{a}{s^2+a^2}$
$\cos at$	$\frac{s}{s^2+a^2}$

Table 3.1: Laplace Transform, $\mathcal{L}\{f(t)\}$ of different functions $f(t)$

3.2.1 Some important properties of Laplace transform

1. Linearity [64]: For any constant a and b and any integrable function f and g then

$$\mathcal{L}\{af(t) + bg(t)\} = a\mathcal{L}\{f(t)\} + b\mathcal{L}\{g(t)\}. \quad (3.10)$$

2. Convolution property (Multiplication Theorem) [64]: If the function $f(t)$ and $g(t)$ have well-defined Laplace transform $\mathcal{L}\{f(t)\}$ and $\mathcal{L}\{g(t)\}$, then

$$\mathcal{L}\{f(t)g(t)\} = \int_0^t g(\tau)f(t-\tau)d\tau = \mathcal{L}\{f(t)\}\mathcal{L}\{g(t)\}. \quad (3.11)$$

3. Derivative property [64]:

$$\mathcal{L}\left\{\frac{d^n}{dt^n}f(t)\right\} = s^n F(s) - \sum_{k=1}^n s^{n-k} f^{k-1}(0) \quad (3.12)$$

4. Integral property [64]:

$$\mathcal{L}\left\{\int_0^t f(\tau)d\tau\right\} = \frac{F(s)}{s} \quad (3.13)$$

3.3 Fractional calculus

Differential equation models (of discrete and continuous type) have been predominantly used in various disciplines of science to describe the dynamic features of systems. Most dynamical systems are not regularly perfect and can be perturbed, and then the integer-order derivatives may not be enough to explain the dynamics of the state variables [66, 67]. As a consequence, fractional operators are used to model real-world phenomena in various areas of science and engineering such as biomathematics, biophysics, bio-rheology, travelling wave solutions, astrophysics, electromagnetic, thermodynamics, plasma physics, and optics, among others [68, 69]. Furthermore, fractional-order derivative describes slow relaxation processes characterized by stretched power-law response function [70]. The idea of Fractional Calculus was introduced after the French mathematician L'Hospital asked for the notation of differentiation of non integer order $\frac{1}{2}$ to Leibniz, in 1695 [71]. A lot of contributions to theory and its applications have come up from different mathematicians since then [72]. For example, Caputo and Fabrizio in [73], introduced a new derivative with the fractional order based on exponential kernel. Furthermore, Atangana and Beleanu in [74] suggested a new operator with fractional order based upon the Mittag-Leffler function. All these, among other Fractional derivative models, have been used successfully in modelling various real phenomena. The expression of fractional calculus is an extension of ordinary calculus. It can define the order of the derivative and integral for any real value. The use of Fractional Calculus in modelling real world phenomena gives a reliable mechanism to account for the memory exhibited by processes, which ensures the validity of predictions from the dynamical system [67]. In addition, by employing the fractional calculus models, we have a wide selection of orders of the fractional derivatives that we can consider that better describes the dynamics of the system [67].

3.3.1 Physical and Geometric meaning of Fractional Calculus

As is the case, classical integer derivatives and integrals have clear geometric and physical interpretations and are accepted to describe different concepts in real-world phenomena. For example, if $f(t)$ represents the position of the object that moves in time t , $f'(t)$ represents the velocity of the object and $f''(t)$ represents the acceleration in classical physics. Fractional derivatives and integrals are generalizations of integer derivatives and integrals, and include n^{th} derivatives and n -fold integrals as special cases. Therefore, we expect this physical and geometric interpretation of fractional order operators to provide links to the classical interpretation of known integer derivatives and integrals. Different authors presented the physical and geometric interpretations of fractional order derivatives and integrals based on different approaches.

For example, Moshrefi-Torbati, M and Hammond, J. K [75] considered the fractional operators as linear filters and gives the geometrical interpretation as fractal geometry; In [76], Podhebný provides a physical and geometric interpretation of fractional integral in terms of inhomogeneous equably flowing scale and homogenous timescale; Tavassoli *et al.* [77] presented the geometric interpretation based on the tangent line angle of a polynomial with coefficients of fractional derivative. However, there is still a lack of geometric and physical interpretation of fractional integral and derivative in literature until now, which is comparable with the simple interpretations of their integer-order counterparts.

3.3.2 Basic Fractional Calculus

In this section, we will introduce some fundamental definitions of fractional integrals and derivatives. The definitions of fractional integrals and derivatives are not unique, there exist many definitions including Grünwald-Letnikov [78], Weyl [79], Marchaud [80, 81], Hadamard [81, 82], Riesz [83], Riemann-Liouville [81, 84], and Caputo [81, 84], among others. In this article, we will focus on the definitions of Riemann-Liouville and Caputo, since they are the most commonly used definitions. We will also discuss some theorems, facts, and basic properties related to fractional calculus.

3.3.3 Fractional Integral and its properties

Starting with the Cauchy's formula [85, 86], for n^{th} -repeated (n^{th} -fold) integral I^n of the function $f(x)$,

$$I^n f(x) = \int_a^x \int_a^{x_1} \cdots \int_a^{x_{n-1}} f(x_n) dx_n \dots dx_2 dx_1 = \frac{1}{(n-1)!} \int_a^x (x-t)^{n-1} f(t) dt. \quad (3.14)$$

Bernhard Riemann and Joseph Liouville established the formulas for fractional integral by extending the integral formula (3.14) from positive integer value n to any arbitrary positive real number α and replacing $(\alpha-1)!$ with $\Gamma(\alpha)$

Definition 6. For every $\alpha > 0$ and a local integrable function $f(t)$ with finite interval $-\infty < a < b < t < \infty$ of $\mathcal{R}$, the Left and Right Riemann fractional integral of order α [64] is defined as:

$${}_a I_t^\alpha f(t) = \frac{1}{\Gamma(\alpha)} \int_a^t (t-u)^{\alpha-1} f(u) du, \quad t > a \quad (3.15)$$

and

$${}_t I_b^\alpha f(t) = \frac{1}{\Gamma(\alpha)} \int_t^b (t-u)^{\alpha-1} f(u) du, \quad t < b. \quad (3.16)$$

Remark 4. From Definition (6) above, for $\alpha = 0$, we set ${}_tI_a^0 = I$ is the identity operator [65].

$$\text{Thus, } {}_tI_a^0 f(t) = f(t).$$

Proof. Consider

$$\begin{aligned} \lim_{\alpha \rightarrow 0} {}_tI_a^\alpha f(t) &= \lim_{\alpha \rightarrow 0} \frac{1}{\Gamma(\alpha)} \int_a^t (t-u)^{\alpha-1} f(u) du \\ &= \lim_{\alpha \rightarrow 0} \frac{1}{\Gamma(\alpha)} \int_a^t f(u) d\left(\frac{(t-u)^\alpha}{\alpha}\right). \end{aligned}$$

Integration by parts and using of Equation (3.2) gives

$$\begin{aligned} \lim_{\alpha \rightarrow 0} {}_tI_a^\alpha f(t) &= \lim_{\alpha \rightarrow 0} \frac{1}{\Gamma(\alpha+1)} \left((t-a)^\alpha f(a) + \int_a^t (t-u)^\alpha f'(u) du \right), \\ &= \frac{1}{\Gamma(1)} \left(f(a) + \int_a^t f'(u) du \right), \\ &= f(t). \end{aligned}$$

□

Other important properties of Riemann-Liouville (RL) fractional integral are as follows:

Theorem 1. The exponential property [87]: Let $f(t)$ be continuous on $[0, \infty)$, and $\alpha, \beta > 0$. Then for all t

$${}_aI_t^\alpha {}_aI_t^\beta f(t) = {}_aI_t^{\alpha+\beta} f(t). \quad (3.17)$$

Proof. Let

$$F(t) = {}_aI_t^\beta f(t) = \frac{1}{\Gamma(\beta)} \int_a^t (t-y)^{\beta-1} f(y) dy,$$

then

$$\begin{aligned} {}_aI_t^\alpha {}_aI_t^\beta f(t) &= \frac{1}{\Gamma(\alpha)} \int_a^t (t-x)^{\alpha-1} F(x) dx, \\ &= \frac{1}{\Gamma(\alpha)} \int_a^t (t-x)^{\alpha-1} \left[\frac{1}{\Gamma(\beta)} \int_a^x (x-y)^{\beta-1} f(y) dy \right] dx. \end{aligned}$$

From the Dirichlet's formula [64]

$$\int_a^t \int_a^x f(y) dy dx = \int_a^t \int_y^t f(y) dx dy,$$

then

$${}_a I_t^\alpha {}_a I_t^\beta f(t) = \frac{1}{\Gamma(\alpha)} \frac{1}{\Gamma(\beta)} \int_a^t \int_y^t (t-x)^{\alpha-1} (x-y)^{\beta-1} f(y) dx dy$$

By letting $x = y + s(t-y) \Rightarrow dx = (t-y)ds$

$${}_a I_t^\alpha {}_a I_t^\beta f(t) = \frac{1}{\Gamma(\alpha)} \frac{1}{\Gamma(\beta)} \int_a^t (t-y)^{\alpha+\beta-1} f(y) \int_0^1 (1-s)^{\alpha-1} s^{\beta-1} ds dy$$

But

$$\int_0^1 (1-s)^{\alpha-1} s^{\beta-1} ds = \frac{\Gamma(\alpha)\Gamma(\beta)}{\Gamma(\alpha+\beta)},$$

by considering Equation (3.3), then

$$\begin{aligned} {}_a I_t^\alpha {}_a I_t^\beta f(t) &= \frac{1}{\Gamma(\alpha)} \frac{1}{\Gamma(\beta)} \frac{\Gamma(\alpha)\Gamma(\beta)}{\Gamma(\alpha+\beta)} \int_a^t (t-y)^{\alpha+\beta-1} f(y) dy \\ &= \frac{1}{\Gamma(\alpha+\beta)} \int_a^t (t-y)^{\alpha+\beta-1} f(y) dy. \end{aligned}$$

Therefore

$${}_a I_t^\alpha {}_a I_t^\beta f(t) = {}_a I_t^{\alpha+\beta} f(t).$$

□

Theorem 2. *The Commutative property: Let $f(t)$ be continuous on $[0, \infty)$, and $\alpha, \beta > 0$. Then for all t*

$${}_a I_t^\alpha {}_a I_t^\beta f(t) = {}_a I_t^\beta {}_a I_t^\alpha f(t). \quad (3.18)$$

Proof. The proof of the Commutativity property can be directly achieved by referring from the Theorem 1 above. □

Theorem 3. *The Linearity property [64]: Let $f(t)$ and $g(t)$ be continuous on $[0, \infty)$, and $\alpha > 0$. Then for the constants C_1 and C_2 ;*

$${}_a I_t^\alpha [C_1 f(t) + C_2 g(t)] = C_1 {}_a I_t^\alpha f(t) + C_2 {}_a I_t^\alpha g(t). \quad (3.19)$$

Proof.

$$\begin{aligned}
 {}_aI_t^\alpha [C_1 f(t) + C_2 g(t)] &= \frac{1}{\Gamma(\alpha)} \int_a^t (t-y)^{\alpha-1} [C_1 f(y) + C_2 g(y)] dy, \\
 &= C_1 \frac{1}{\Gamma(\alpha)} \int_a^t (t-y)^{\alpha-1} f(y) dy + C_2 \frac{1}{\Gamma(\alpha)} \int_a^t (t-y)^{\alpha-1} g(y) dy, \\
 &= C_{1a} I_t^\alpha f(t) + C_{2a} I_t^\alpha g(t).
 \end{aligned}$$

□

Example 1. Let $f(t) = t^n$, where $n \geq 0$. Then

$$\begin{aligned}
 {}_aI_t^\alpha t^n &= \frac{1}{\Gamma(\alpha)} \int_a^t (t-u)^{\alpha-1} u^n du \\
 &= \frac{1}{\Gamma(\alpha)} \int_a^t \left(t(1 - \frac{u}{t})\right)^{\alpha-1} u^n du \\
 &= \frac{t^{\alpha-1}}{\Gamma(\alpha)} \int_a^t \left(1 - \frac{u}{t}\right)^{\alpha-1} u^n du \\
 &= \frac{t^\alpha}{\Gamma(\alpha)} \int_a^t \left(1 - \frac{u}{t}\right)^{\alpha-1} u^n \frac{1}{t} du.
 \end{aligned}$$

By letting

$$y = \frac{u}{t}, \quad \Rightarrow u = yt \quad \text{and} \quad du = t dy,$$

then, we have

$${}_aI_t^\alpha t^n = \frac{t^{\alpha+n}}{\Gamma(\alpha)} \int_a^t (1-y)^{\alpha-1} y^n du.$$

Applying beta function in Equation (3.3), yields

$${}_aI_t^\alpha t^n = \frac{\Gamma(n+1)}{\Gamma(n+\alpha+1)} t^{\alpha+n}.$$

Remark 5. From Example 1 above, in particular when $n = 0$, the fractional integral of a constant K of order α [84] is given as

$${}_aI_t^\alpha K = \frac{K}{\Gamma(\alpha+1)} t^\alpha.$$

Example 2. Let $f(t) = (t - a)^n$, where $n \geq 0$ [64]. Then

$${}_a I_t^\alpha (t - a)^n = \frac{1}{\Gamma(\alpha)} \int_a^t (t - u)^{\alpha-1} (u - a)^n du.$$

By considering the change of variables such that

$$\frac{u - a}{t - a} = \varepsilon, \quad \Rightarrow du = (t - a)d\varepsilon,$$

yield

$${}_a I_t^\alpha (t - a)^n = \frac{(t - a)^{\alpha+n}}{\Gamma(\alpha)} \int_0^1 \varepsilon^n (1 - \varepsilon)^{\alpha-1} d\varepsilon.$$

Then, by employing the beta function in Equation (3.3), we have

$$\begin{aligned} {}_a I_t^\alpha (t - a)^n &= \frac{(t - a)^{\alpha+n}}{\Gamma(\alpha)} \frac{\Gamma(n + 1)\Gamma(\alpha)}{\Gamma(n + \alpha + 1)}, \\ &= \frac{\Gamma(n + 1)}{\Gamma(n + \alpha + 1)} (t - a)^{\alpha+n}. \end{aligned}$$

Theorem 4 (Laplace transform of Riemann-Liouville integral). The Laplace transform of Riemann-Liouville integral of order $\alpha > 0$ [65] is

$$\mathcal{L}\{{}_0 I^\alpha f(t)\} = \frac{F(s)}{s^\alpha}.$$

3.3.4 Fractional derivatives and its properties

After the introduction of the fractional integral operator, the fractional derivatives can be introduced as the inverse operators of the corresponding integral.

Definition 7. For $n - 1 < \alpha < n$, $\alpha > 0$ and $n = [\alpha]$, the Riemann-Liouville fractional derivative of order α can be given as :

$${}_a D_t^\alpha f(t) = \frac{d^n}{dt^n} ({}_a I_t^{n-\alpha} f(t)) = \frac{1}{\Gamma(n - \alpha)} \left(\frac{d}{dt} \right)^n \int_a^t (t - u)^{n-\alpha-1} f(u) du. \quad (3.20)$$

Due to the fact that the Riemann-Liouville derivative requires the initial conditions for the differential equations in terms of non-integer derivatives which is difficult to physically interpreted, then the Italian Mathematician Caputo in 1967 introduced the Caputo derivative, that uses the integer-order as initial conditions [88].

Definition 8. For $n - 1 < \alpha < n$, $\alpha > 0$ and $n = [\alpha]$, the Caputo fractional derivative

operator of order α can be given as:

$${}_a^C D_t^\alpha f(t) = {}_a I_t^{n-\alpha} \left(\frac{d^n}{dt^n} f(t) \right) = \frac{1}{\Gamma(n-\alpha)} \int_a^t (t-u)^{n-\alpha-1} \left(\frac{d}{du} \right)^n f(u) du. \quad (3.21)$$

Example 3. The $\frac{1}{2}$ derivative of a constant function $f(t) = C$. Using the Riemann-Liouville derivative and Caputo fractional derivative operator.

Case 1. By using the Riemann-Liouville derivative Operator;

$$\begin{aligned} {}_0 D_t^{\frac{1}{2}} f(t) &= \frac{1}{\Gamma(1-\frac{1}{2})} \left(\frac{d}{dt} \right)^1 \int_0^t (t-u)^{1-\frac{1}{2}-1} C du, \\ &= \frac{C}{\Gamma(\frac{1}{2})} \left(\frac{d}{dt} \right)^1 \int_0^t (t-u)^{-\frac{1}{2}} du, \\ &= \frac{C}{\Gamma(\frac{1}{2})} \frac{d}{dx} (2t^{\frac{1}{2}}), \\ &= \frac{C}{\sqrt{2t}}. \end{aligned}$$

Case 2. By using the Caputo fractional derivative operator.

$$\begin{aligned} {}_0^C D_t^{\frac{1}{2}} f(t) &= \frac{1}{\Gamma(1-\frac{1}{2})} \int_0^t (t-u)^{-\frac{1}{2}} \frac{d}{du} C du, \\ &= \frac{1}{\Gamma(1-\frac{1}{2})} \int_0^t (t-u)^{-\frac{1}{2}} \times 0 du, \\ &= 0. \end{aligned}$$

Properties of fractional derivatives

Property 1. If C is a constant, then [64]:

Case 1. the Riemann-Liouville derivative of C is ,

$${}_0 D_t^\alpha C = \frac{C t^\alpha}{\Gamma(1-\alpha)},$$

Case 2. while the Caputo derivative of C is

$${}_0^C D_t^\alpha C = 0.$$

Property 2 (Interpolation between integer derivatives). Let $0 \leq n-1 < \alpha < n$, and that the function $f(t)$ has $n-1$ continuous bounded derivative in $[a, T]$ for every $T > a$ [65]. Then

$$\lim_{\alpha \rightarrow n} {}_a^C D_t^\alpha f(t) = f^{(n)}(t), \quad \text{for } n = 1, 2, \dots$$

Similarly, for the Riemann-Liouville derivative interpolation property leads to

$$\lim_{\alpha \rightarrow n} {}_a D_t^\alpha f(t) = f^{(n)}(t), \quad \text{for } n = 1, 2, \dots$$

Property 3 (Composition property [65]). Suppose $m = 1, 2, \dots$; $n - 1 < \alpha < n$ then

$$\begin{aligned} {}^C D_t^\alpha ({}_a D_t^m) &= {}^C D_t^{\alpha+m} \neq {}^C D_t^m ({}_a D_t^\alpha), \quad \text{for Caputo derivative} \\ {}_a D_t^m ({}_a D_t^\alpha) &= {}_a D_t^{\alpha+m} \neq {}_a D_t^\alpha ({}_a D_t^m), \quad \text{for Riemann-Leouville derivative} \end{aligned}$$

Remark 6. The derivative operators in the Property 3 commute under different conditions, as

$$\begin{aligned} {}^C D_t^\alpha ({}_a D_t^m) &= {}^C D_t^m ({}_a D_t^\alpha) = {}^C D_t^{\alpha+m}, \quad \text{if } f^{(s)}(0) = 0, \text{ for } s = n, n-1, \dots, m \\ {}_a D_t^m ({}_a D_t^\alpha) &= {}_a D_t^\alpha ({}_a D_t^m) = {}_a D_t^{\alpha+m}, \quad \text{if } f^{(s)}(0) = 0, \text{ for } s = 1, 2, \dots, m. \end{aligned}$$

It is observed that contrary to the Riemann-Liouville derivative and there are no restrictions on the values of $f^{(s)}(0)$ ($s = 0, 1, \dots$) for the Caputo derivative. This difference has important applications [65].

Property 4 (Relation with fractional integral operator [65]). For $p > 0$ and $q > 0$, we have

$${}_a D_t^p ({}_a I_t^q f(t)) = {}_a D_t^{p-q} f(t) = {}_a I_t^{q-p} f(t). \quad (3.22)$$

Remark 7. From Property 4, if $p = q$ then, we have

$${}_a D_t^p ({}_a I_t^p f(t)) = f(t). \quad (3.23)$$

Similarly, for the Caputo derivative we have

$${}^C D_t^p ({}_a I_t^p f(t)) = f(t), \quad (3.24)$$

which mean that both Riemann-Liouville and Caputo derivatives are the Left inverse of the Riemann-Liouville integral operator of the same order p .

Remark 8. The fractional derivative of the integral (3.23) and (3.24) do not commute,

such that we have

$${}_a I_t^\alpha D_t^\alpha f(t) = f(t) - \sum_{j=1}^n \frac{f^{(\alpha-j)}(a)}{\Gamma(\alpha-j+1)} (t-a)^{\alpha-j}, \quad \text{for RL derivative and}$$

$${}_a I_t^{\alpha C} D_t^\alpha f(t) = f(t) - \sum_{k=0}^{n-1} \frac{f^{(k)}(a)}{k!} (t-a)^k, \quad \text{for Caputo derivative.}$$

Property 5 (Linearity property). *Both Riemann-Liouville and Caputo fractional derivatives of order α are linear operators [65], such that*

$$\begin{aligned} {}_a D_t^\alpha (Af(t) + Bg(t)) &= A {}_a D_t^\alpha f(t) + B {}_a D_t^\alpha g(t) \quad \text{for RL derivative and,} \\ {}_a^C D_t^\alpha (Af(t) + Bg(t)) &= A {}_a^C D_t^\alpha f(t) + B {}_a^C D_t^\alpha g(t) \quad \text{for Caputo derivative,} \end{aligned}$$

where A and B are constants.

Property 6 (Laplace of fractional derivatives' operator). *The Laplace transform of Riemann-Liouville and Caputo derivatives respectively given as [65];*

$$\begin{aligned} \mathcal{L}\{{}_a D_t^\alpha f(t)\} &= s^\alpha F(s) - \sum_{k=0}^{n-1} s^k {}_a D_t^{\alpha-k-1} f(t)|_{t=0} \quad \text{for } n-1 \leq \alpha < n, \\ \mathcal{L}\{{}_a^C D_t^\alpha f(t)\} &= s^\alpha F(s) - \sum_{k=0}^{n-1} s^{\alpha-k-1} f^{(k)}(0) \quad \text{for } n-1 < \alpha \leq n. \end{aligned}$$

Remark 9. *We note that the Laplace transform of the Riemann-Liouville derivative results that have initial conditions that include the limit values of the RL derivative at $t = 0$, can cause problems in physical interpretation. In contrast, the Laplace transform of the Caputo derivative results with any initial values of the classical integer derivative have a known physical interpretation (for example, $f(0)$ is the initial position, $f'(0)$ is the initial velocity and $f''(0)$ is the initial acceleration).*

Property 7 (Leibniz rule). *Let both $f(t)$ and $g(t)$ and its derivatives be continuous in $[a, t]$ and $\alpha \in \mathbb{R}$, such that $n-1 < \alpha < n \in \mathbb{N}$. Then, the Leibniz rule [65, 89] is*

given by

$${}_a D_t^\alpha (f(t)g(t)) = \sum_{k=0}^{\infty} \binom{\alpha}{k} ({}_a D_t^{\alpha-k} f(t)) g^{(k)}(t) \quad \text{for RL derivative and}$$

$${}_a^C D_t^\alpha (f(t)g(t)) = \sum_{k=0}^{\infty} \binom{\alpha}{k} ({}_a D_t^{\alpha-k} f(t)) g^{(k)}(t) - \sum_{k=0}^{n-1} \frac{t^{k-\alpha}}{\Gamma(k-\alpha+1)} ((f(t)g(t))^{(k)}(0)),$$

for Caputo derivative.

Property 8. Let $\alpha \in \mathbb{R}$, $n-1 < \alpha < n \in \mathbb{N}$. The relation between Riemann-Liouville and Caputo derivatives [89] is given by

$${}_0^C D^\alpha f(t) = {}_0 D^\alpha f(t) - \sum_{k=0}^{n-1} \frac{t^{k-\alpha}}{\Gamma(k-\alpha+1)} f^{(k)}(0).$$

Example 4. For $\alpha > 0$, $n-1 < \alpha < n$, $\beta > n-1$, let us calculate the fractional derivatives of the function $f(t) = t^\beta$.

Case 1. For Riemann-Leouville derivative, we have:

$${}_0 D^\alpha t^\beta = \frac{1}{\Gamma(n-\alpha)} \frac{d^n}{dt^n} \int_0^t u^\beta (t-u)^{n-\alpha-1} du.$$

Let $u = vt$, $\rightarrow du = t dv$, then

$${}_0 D^\alpha t^\beta = \frac{1}{\Gamma(n-\alpha)} \int_0^t (1-v)^{n-\alpha-1} v^\beta \frac{d^n}{dt^n} t^{n-\alpha+\beta} dv.$$

By applying

$$\frac{d^n}{dt^n} t^\lambda = \frac{\Gamma(\lambda+1)}{\Gamma(\lambda-n+1)} t^{\lambda-n}, \quad (3.25)$$

we have

$${}_0 D^\alpha t^\beta = \frac{1}{\Gamma(n-\alpha)} \frac{\Gamma(n-\alpha+\beta+1)}{\Gamma(\beta-\alpha+1)} t^{\beta-\alpha} \int_0^t (1-v)^{n-\alpha-1} v^\beta dv.$$

From the definition of beta function (3.3), gives

$${}_0 D^\alpha t^\beta = \frac{\Gamma(\beta+1)}{\Gamma(\beta-\alpha+1)} t^{\beta-\alpha}.$$

Case 2. For Caputo derivative, we have:

$${}_0^C D^\alpha t^\beta = \frac{1}{\Gamma(n-\alpha)} \int_0^t (t-u)^{n-\alpha-1} \left(\frac{d^n}{dt^n} u^\beta \right) du. \quad (3.26)$$

Using Equation (3.25), equation (3.26) yields

$${}_0^C D^\alpha t^\beta = \frac{1}{\Gamma(n-\alpha)} \int_0^t \frac{\Gamma(\beta+1)}{\Gamma(\beta-\alpha+1)} (t-u)^{n-\alpha-1} u^{\beta-\alpha} du.$$

Let $u = vt$, $\rightarrow du = t dv$, then

$${}_0^C D^\alpha t^\beta = \frac{1}{\Gamma(n-\alpha)} \frac{\Gamma(\beta+1)}{\Gamma(\beta-\alpha+1)} t^{\beta-\alpha} \int_0^1 (1-v)^{n-\alpha-1} v^{\beta-\alpha} dv.$$

Applying the definition of beta function in equation (3.3) gives

$${}_0^C D^\alpha t^\beta = \frac{\Gamma(\beta+1)}{\Gamma(\beta-\alpha+1)} t^{\beta-\alpha}.$$

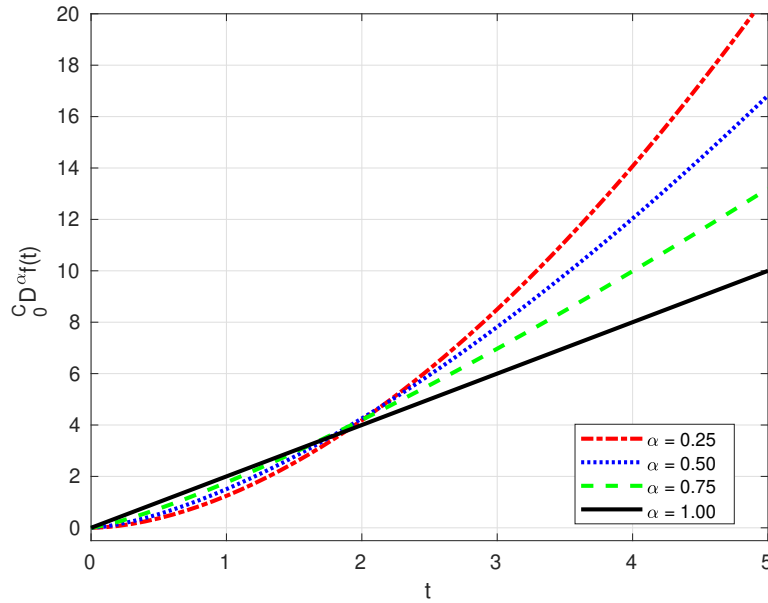


Figure 3.2: Caputo fractional derivatives of $f(t) = t^2$ for different values of order α .

Definition 9. For $f \in H^1(a,b)$, with $b > a, \alpha \in [0,1]$, then the Caputo-Fabrizio fractional order derivative is defined as

$$\mathcal{D}_t^\alpha(f(t)) = \frac{\mathcal{M}(\alpha)}{1-\alpha} \int_a^t f'(y) \exp \left[-\alpha \frac{t-y}{1-\alpha} \right] dy, \quad (3.27)$$

where $\mathcal{M}(\alpha)$ is a normalization function such that $\mathcal{M}(1) = \mathcal{M}(0) = 1$ [73]. Moreover, it can be reformulated as

$$\mathcal{D}_t^\alpha(f(t)) = \frac{\alpha\mathcal{M}(\alpha)}{1-\alpha} \int_a^t (f(t) - f(y)) \exp\left[-\alpha \frac{t-y}{1-\alpha}\right] dy \quad \text{for } f \notin H^1(a, b). \quad (3.28)$$

Remark 10. If $\sigma = \frac{1-\alpha}{\alpha} \in [0, \infty)$, $\alpha = \frac{1}{1+\sigma} \in [0, 1]$, subsequently, Equation (3.28) reduces to:

$$\mathcal{D}_t^\alpha(f(t)) = \frac{\mathcal{M}(\sigma)}{\sigma} \int_a^t f'(y) \exp\left[-\frac{t-y}{\sigma}\right] dy, \quad (3.29)$$

with $\mathcal{M}(1) = \mathcal{M}(\infty) = 1$.

Furthermore,

$$\lim_{\sigma \rightarrow 0} \frac{1}{\sigma} \exp\left[-\frac{t-y}{\sigma}\right] = \delta(y-t). \quad (3.30)$$

Definition 10. For $0 < \alpha < 1$, the integral of fractional order α of a function f is given as

$$I_t^\alpha(f(t)) = \frac{2(1-\alpha)}{(2-\alpha)\mathcal{M}(\alpha)} f(t) + \frac{2\alpha}{(2-\alpha)\mathcal{M}(\alpha)} \int_0^t f(s) ds, \quad \text{for } t \geq 0. \quad (3.31)$$

Remark 11. From Equation (3.31), we have

$$\frac{2(1-\alpha)}{(2-\alpha)\mathcal{M}(\alpha)} + \frac{2\alpha}{(2-\alpha)\mathcal{M}(\alpha)} = 1. \quad (3.32)$$

That yields $\mathcal{M}(\alpha) = \frac{2}{2-\alpha}$ for $0 < \alpha < 1$. In [90], the new Caputo derivative of order $\alpha \in [0, 1]$ is given by

$$\mathcal{D}_t^\alpha(f(t)) = \frac{1}{1-\alpha} \int_0^t f'(y) \exp\left[\alpha \frac{t-y}{1-\alpha}\right] dy. \quad (3.33)$$

3.3.5 Solution to the special Cauchy problem of Caputo type

In this subsection, we give the solutions of special Cauchy problem that will be useful in our analytical solutions. We give the details of the Cauchy problem based on work in [91] for convenience of the reader and easy reference when checking biological significance of the model in Chapter 4.

The solution to the Cauchy problem [91]

$${}^C\mathcal{D}_{a+}^\alpha y(x) - \lambda y(x) = g(x), \quad y(a) = b, \quad b \in \mathbb{R} \quad (3.34)$$

with $0 < \alpha < 1$ and $\lambda \in \mathbb{R}$ in terms of a Mittag-leffler function, takes the form,

$$y(x) = bE_\alpha[\lambda(x-a)^\alpha] + \int_a^x (x-t)^{\alpha-a} E_{\alpha,\alpha}[\lambda(x-t)^\alpha] g(t) dt,$$

while the solution to the homogeneous problem

$${}^C\mathcal{D}_{a+}^\alpha y(x) - \lambda y(x) = 0, \quad y(a) = b, \quad b \in \mathbb{R}$$

is given by

$$y(x) = bE_\alpha[\lambda(x-a)^\alpha], \tag{3.35}$$

where a is the lower limit and α is the order of fractional derivative. Thus, for a special case corresponding to the integer order derivative when $\alpha = 1$, Equation (3.35) becomes

$$y(x) = be^{\lambda(x-a)}.$$

In particular, the Cauchy problem

$${}^C\mathcal{D}_{a+}^{\frac{1}{2}} y(x) - \lambda y(x) = g(x), \quad y(a) = b, \quad b \in \mathbb{R}$$

has the solution given in terms of a Mittag-leffler function as

$$y(x) = bE_{\frac{1}{2}}[\lambda(x-a)^{\frac{1}{2}}] + \int_a^x (x-t)^{\frac{1}{2}-a} E_{\frac{1}{2},\frac{1}{2}}[\lambda(x-t)^{\frac{1}{2}}] g(t) dt.$$

Similarly, for the homogeneous case when $\alpha = \frac{1}{2}$, the solution to the Cauchy problem

$${}^C\mathcal{D}_{a+}^{\frac{1}{2}} y(x) - \lambda y(x) = 0, \quad y(a) = b \quad (b \in \mathbb{R})$$

is given by

$$y(x) = bE_{\frac{1}{2}}[\lambda(x-a)^{\frac{1}{2}}].$$

4. Role of immunotherapy in tumor-immune interaction: Perspectives from fractional-order modelling and sensitivity analysis

4.1 Introduction

Cancer is a collection of diseases that affect abnormal cell growth and can invade or spread to other parts of the body. Usually, when cells are damaged or die in any way, the body releases new cells to replace them by cell division. As this body's normal control mechanism stops operating, cells become more and more abnormal, old or damaged cells survive when they should die, and new cells form when they are not needed. These extra and abnormal cells may accumulate to form a mass of tissues called a tumor. Then the tumor grows and spreads to other parts of the body such as bones, liver, and lungs through the blood or lymph system and form new tumors. This process is referred to as metastasis. Metastasis of cancer is one of the primary causes of death from cancer [92]. Cancer is ranked as the second-deadliest disease globally, with an estimate of 9.6 million deaths in 2018, and most of these deaths occurred in the low and middle-income countries [1].

The body's immune system protects the body from diseases and infections caused by bacteria, viruses, fungi, or any other parasite. Therefore, it is sometimes called an immune response or effector cells, and some of these, such as Natural killer (NK) cells and Cytotoxic T lymphocytes (CTL) cells can recognize and kill abnormal cells. Unfortunately, this may not be enough to effectively fight upon the tumor. Thus, different researchers are trying to find the therapy that will improve cancer treatment. Available literature indicates that traditional therapies used to fight cancer are surgery, radiation, chemotherapy, and immunotherapy. Recently, the immunotherapy has been successfully used to treat malignant tumors.

Immunotherapy refers to the use of cytokines in combination with adoptive cellular

immunotherapy (ACI) [14]. ACI refers to the promising method of immunotherapy, harnesses the cells that largely expanded in vitro and have natural antitumor reactivity (such as lymphocytes) into tumor-bearing host [15]. Cytokines are small glycoproteins that bind to cell surface receptors and regulate immune cell development, survival, and function. Therefore, cytokines have been extensively considered as potential therapeutic agents to manipulate immune responses upon tumor cells.

Interleukin 2 (IL-2) act as the main cytokine responsible for lymphocyte activation, growth and differentiation [14]. This kind of immunocytes can involve two approaches [17]. The first approach includes lymphokine-activated killer cells (LAK) therapy: These cells are extracted in vivo from the peripheral blood leukocytes of patients with high concentrations of IL-2, later on, LAKs are injected back into the cancer site. It is believed that these are mainly natural killer cells [14, 15]. Another approach includes the infiltrating tumor lymphocytes (ITL); ITLs are removed from a patient's tumor, then incubated in large quantities with high concentrations of IL-2 in vitro and comprised of activated NK cells and CTL cells, and then returned to the patient to help immune cells kill cancer cells [14]. Our understanding of IL-2 in lymphocyte regulation has progressed considerably, providing exciting new directions in cancer immunotherapy.

Transmission dynamics of epidemics can be modelled mathematically to investigate disease behavior, severity and stopping mechanism. Differential equation models (of discrete and continuous type) have been predominantly used in various disciplines of science to describe the dynamic features of systems. Classical integer-order differential equation form is helpful for a local dynamic system in which the model cannot replicate the complexity of the dynamics of the epidemic, as the model seldom has crossover behavior that cannot be verified by a classical differential operator [66]. Tragically, most dynamic systems like tumor-immune interaction are not regular perfect and can be perturbed. So, integer derivatives may not be sufficient to explain the dynamics of state variables [67]. The representation of Fractional calculus model is an extension of the ordinary calculus models in such a way that the order of derivatives and integrals are defined for arbitrary real values. The theory of the Fractional calculus has been employed to investigate the dynamics of real-world problems in various areas such as physics, fluid mechanics, finance, and mathematical biology, see for instances [69, 93, 94, 95, 96]. Caputo and Fabrizio [73], introduced a new derivative with the fractional-order based on exponential kernel. Furthermore, Atangana and Beleanu in [74], suggested a new operator with fractional order based upon the Mittag-Leffler function. All these among other Fractional derivative models have been used successful in modelling various real phenomena.

The use of fractional calculus in mathematical biology gives a reliable mechanism to account for memory exhibited by biological and epidemic processes, which ensures biological meaningfulness in the dynamical system or epidemic modelled. The Caputo derivative has an advantage of flexibility in handling initial value problems. It is therefore reasonable to model the epidemic dynamics using the fractional-order differential equations of the Caputo-Fabrizio (CF) type [97]. By employing the CF fractional derivative to epidemic models such as Cancer models, we have wide selection of orders of the fractional derivatives that we can consider, while examining the best order to describe the dynamics of the system. Consequently, the numerical optimization method based on the least-squares approaches Adams-Bashforth and Adams-Moulton methods is applied to examine the order of the fractional operator of the dynamic system that better explains real data as well as associated parameters. The remaining sections of this paper are structured as follows: The mathematical model formulation and analysis including the positivity of the solutions, stability analysis, and existence and uniqueness of a system of the model solutions using the fractional-order calculus are presented in Section 2. Then, the numerical methods and simulations are given in Section 3. Finally, the conclusion is given in Section 4.

4.2 Mathematical Model Formulation and Analysis

Clear understanding of the tumor-immune interaction models is very helpful in investigating the tumor immunogenicity. The mathematical modelling of the interaction between tumor and immunity provides an analytical framework to address the components of the immune system to play an important role in cancer treatment. Literature shows that lot of work related to the development of various mathematical descriptions of the tumor and immune responses. Kuznetson in 1994 [37], introduced a mathematical model for tumor-immune interactions with the effect of CTL cells response. The interaction between effector cells E , tumor cells T population presented as follows:

$$\begin{cases} \frac{dT}{dt} = rT(1 - bT) - c_1TE, \\ \frac{dE}{dt} = \sigma_1 + \frac{\rho T}{s+T}E - c_2ET - \mu_1E. \end{cases} \quad (4.1)$$

In addition Kirschner and Panetta in [14], introduced immunotherapy with cytokine interleukin 2 (IL-2) in (4.1) model above to explain short-term tumor oscillations and long-term tumor recurrence in terms of tumor size. The authors, in [98], used a fractional-order model to study the cytotoxic T lymphocyte response with long-term tumor growth behavior and tumor elimination effect. Also, a simple fractional-order model to describe the dynamics of tumor-immune interactions has been investigated

in [99]. All these, among other tumor-immune interaction models, have been used successfully in cancer modelling.

Based on much existing scientific literature about the tumor-immune interaction and the development of immunotherapy (see: [100, 101, 102, 103, 104, 105, 106]), herein, we propose a fractional-order model that describes the tumor-immune dynamics together with the treatment of Interleukin-2 (IL-2) based on CF derivative type. The model includes the interactions of the tumor cells, $T(t)$; the effector cells, $E(t)$; and the concentration of the IL-2 in the single tumor site compartment, $I(t)$. Then, the following fractional-order model system governs the interactions of these three populations.

$$\begin{cases} D_t^\alpha T = rT(1 - bT) - c_1 TE, \\ D_t^\alpha E = \sigma_1 + \frac{\rho T}{s+T} E - c_2 ET - \mu_1 E + \frac{\beta I}{h+I} E, \\ D_t^\alpha I = \sigma_2 + \frac{\delta T}{g+T} E - \mu_2 I, \end{cases} \quad (4.2)$$

with initial conditions given as

$$T(0) = T_0 \geq 0, \quad E(0) = E_0 \geq 0 \quad \text{and} \quad I(0) = I_0 \geq 0, \quad (4.3)$$

where D_t^α represents the Caputo fractional derivative of order $0 < \alpha \leq 1$, defined as

$$D_t^\alpha f = \frac{1}{\Gamma(1-\alpha)} \int_0^t (t-s)^{-\alpha} f'(s) ds.$$

The new coefficients $r, b, c_1, \sigma_1, \rho, c_2, \mu_1, \beta, \sigma_2, \delta, \mu_2$ are the generalized parameters whose dimension units are chosen in such way to keep the dimensional homogeneity of the model's equation. For $\alpha = 1$ these parameters are the classical ones. The first equation of the model system (4.2) describes the rate of change of the tumor cells which follow the logistic growth in the absence of the immune response with the intrinsic growth rate, r and, the carrying capacity of the biological environment for tumor, b^{-1} . The final term of the first equation represents the elimination of the tumor cells due to interaction with tumor-specific effector cells, which obey the law of mass action.

The second equation describes the rate of change in the effector cells, where the first term represents the source of the immune effector cells, σ_1 , since the effector immune cells are present in the human body even in the absence of a particular threat[104]. The presence of tumor cells stimulates the production of new immune cells, and these immune cells are recruited to the tumor's location. However, the rate at which the human body produces these cells is limited. We then have a positive rate-limiting recruitment rate in the effector cells equation that is modelled by Michaelis–Menten

factor to specify the saturated effect of the immune response, as shown in the second term of the equation[98]. The effector cells can kill tumor cells in one of two ways: by using a protein called perforin to destroy the tumor cell membrane, or by triggering apoptosis (programmed cell death) through another protein called Fas and Fas Ligand (FasL). Due to the limited amount of protein produced by causal cells, each interaction reduces their ability to kill[104]. Therefore, we introduce a negative inactivation term into the effector cells, as represented in the third term of the final equation. In contrast, the fourth term, $\mu_1 E$, models the natural decay of the effector cells. The last term shows that the effector cells are also stimulated by IL-2 in an autocrine and paracrine manner.

The third equation gives the rate of change in IL-2 concentration. Its source is effector cells, stimulated by interaction with tumor, and has Michaelis–Menten dynamics to explain the self-limiting production of IL-2. $\mu_2 I$ models the natural decay of IL-2 concentration, and σ_2 is a treatment term representing the external input of IL-2 into the system. All the parameters of the system (4.2) are considered positive, and their details are summarized in Table 5.1.

Parameter	Description
r	tumor intrinsic growth rate
b	Reciprocal carrying capacity of the tumor cells
c_1	Fractional tumor cells killed by effector cells
σ_1	Constant external source of effector cells
ρ	Maximum rate of effector cell proliferation by tumor cells
s	Half saturation constant of the effector cells recruitment
c_2	Effector cells inactivation rate by tumor cells
μ_1	Death rate of effector cells
β	Maximum effector cells recruitment rate by IL-2
h	Steepness coefficient of the effector cells proliferation by IL-2
σ_2	Constant external source of IL-2
δ	Production rate of IL-2 due to tumor-immune interaction
g	Half saturation constant of the IL-2 due to tumor-immune cells competition
μ_2	Decay rate of the IL-2

Table 4.1: Description of the Cancer fractional-order model parameters.

4.2.1 Non-negative Solutions and Boundedness

In this section, we prove the non-negativity of the solutions in such a way that the system of fractional order differential equations (4.2) is mathematically well-defined and biologically meaningful.

Lemma 1 (Generalized Mean Value Theorem [107]). *Suppose that $f(t) \in C[a, b]$ and $D_t^\alpha f(t) \in C[a, b]$ for $a < \alpha \leq 1$, then*

$$f(t) = f(a) + \frac{1}{\Gamma(\alpha)} D_t^\alpha f(\xi)(t - a)^\alpha,$$

where $0 \leq \xi \leq t, \forall t \in (a, b]$.

Remark 12. [107] *Let the function $f(t)$ be α -differentiable on (a, b) , then it follows that:*

- *if $D_t^\alpha f(t) < 0, \forall t \in (a, b)$ then $f(t)$ is decreasing on (a, b) ,*
- *if $D_t^\alpha f(t) > 0, \forall t \in (a, b)$ then $f(t)$ is increasing on (a, b) ,*
- *and, if $D_t^\alpha f(t) = 0, \forall t \in (a, b)$ then $f(t)$ is constant on (a, b) .*

Theorem 5. *For all $t \in (0, \infty)$, the solutions of the state variables of model systems (4.2) whose initial conditions are non-negative are positive.*

Proof. To prove the Theorem 5, we ought to show that the domain $\Omega = \{(T, E, I) \in \mathbb{R}^3 : T(t) \geq 0, E(t) \geq 0, I(t) \geq 0\}$ is positive invariant region. Then, on the hyperplanes of region Ω we have

$$\begin{aligned} D_t^\alpha T(t)|_{T=0} &= 0, \\ D_t^\alpha E(t)|_{E=0} &= \sigma_1 \geq 0, \\ D_t^\alpha I(t)|_{I=0} &= \sigma_2 + \frac{\delta T}{g + T} E \geq 0, \end{aligned}$$

If $\{T(0), E(0), I(0)\} \in \Omega$, according to Lemma 1 and Remark 12, the solution $(T(t), E(t), I(t))$ can not escape from the hyperplanes Ω .

Thus, the solutions of the fractional-order model (4.2) are non-negative if the initial conditions are non-negative for all $t > 0$. $\square$

Theorem 6. *All the solutions of fractional order systems (4.2), which start in, $\mathbb{R}_+^3$ are uniformly bounded.*

Proof. From the first equation of the model (4.2), we have

$$D_t^\alpha T + c_1 T E = rT - r b T^2. \quad (4.4)$$

Let $m = \min_{t \geq 0} E(t)$, and $f(T) = rT - rbT^2$, from Equation (4.4) we form the Cauchy problem as

$$D_t^\alpha T + mc_1 T \leq f(T). \quad (4.5)$$

Since, the maximum value of $f(T) = \frac{r}{4b}$. Then, the inequality above can be written as

$$D_t^\alpha T + mc_1 T \leq \frac{r}{4b}. \quad (4.6)$$

Let us consider the initial condition $T(0) = T_0$, then the solution to (4.6), in terms of Mittag-Leffler function (see Lemma 3.2 [108]) is [91]

$$T(t) \leq T_0 E_\alpha[-mc_1 t^\alpha] + \frac{r}{4b} \int_0^t (t-s)^{\alpha-1} E_{\alpha,\alpha}[-mc_1(t-s)^\alpha] ds \quad (4.7)$$

Since, [109]

$$\int_0^t (t-s)^{\alpha-1} E_{\alpha,\alpha}[-mc_1(t-s)^\alpha] ds = t^\alpha E_{\alpha,\alpha+1}[-mc_1 t^\alpha] \quad (4.8)$$

Then, the solution (4.7) can be written as

$$T(t) \leq T_0 E_\alpha[-mc_1 t^\alpha] + \frac{r}{4b} t^\alpha E_{\alpha,\alpha+1}[-mc_1 t^\alpha] \quad (4.9)$$

As $t \rightarrow \infty$, $E_\alpha[-mc_1 t^\alpha] \rightarrow 0$ and $E_{\alpha,\alpha+1}[-mc_1 t^\alpha] \rightarrow \frac{1}{mc_1}$ [108]

$$\Rightarrow T(t) \leq \frac{r}{4bmc_2}.$$

Similarly, for the second equations of the model system (4.2),

$$\sup_{t \in [0, \infty]} \left(\frac{\rho T}{s + T} \right) = \rho, \quad \sup_{t \in [0, \infty]} \left(\frac{\beta I}{h + I} \right) = \beta,$$

then, we have a Cauchy problem given by

$$D_t^\alpha E \leq \sigma_1 - (c_2 n + \mu_1 - \rho - \beta) E, \quad (4.10)$$

where $n = \min_{t \geq 0} T(t)$. Let $\kappa = (c_2 n + \mu_1 - \rho - \beta)$, then, the solution of (4.10) can be given as

$$E(t) \leq E_0 E_\alpha[-\kappa t^\alpha] + \sigma_1 t^\alpha E_{\alpha,\alpha+1}[-t^\alpha] \quad (4.11)$$

$$\Rightarrow E(t) \leq \frac{\sigma_1}{\kappa}.$$

Employing similar techniques, the Cauchy problem for the last equation of the model system (4.2), is given as

$$D_t^\alpha I \leq \sigma_2 + \delta E - \mu_2 I \quad (4.12)$$

$$\Rightarrow I(t) \leq \frac{\sigma_2 \kappa + \sigma_1}{\mu_2 \kappa}.$$

Therefore, for the positive initial condition, the corresponding solutions of the model system (4.2) are bounded in their maximal interval for all $t \in (0, \infty)$. $\square$

4.2.2 Equilibria and Stability Analysis.

To understand the dynamics of the model system (4.2), firstly, we obtain the equilibrium points of the system. The steady states of the model system (4.2), are the intersections of the nullclines such that $D_t^\alpha T = 0$, $D_t^\alpha E = 0$ and $D_t^\alpha I = 0$. Then from

$$rT(1 - bT) - c_1 TE = 0, \quad \Rightarrow T = 0 \text{ and } r(1 - bT) - c_1 E = 0$$

Tumor free equilibrium point

By considering $T = 0$, and substitute to the rest of the zeros of the equations in the model system (4.2), yields the tumor free equilibrium point given as

$$\mathcal{E}_0 = \left\{ 0, \frac{h\mu_2\sigma_1 + \sigma_1\sigma_2}{\mu_1(\mu_2h + \sigma_2) - \beta\sigma_2}, \frac{\sigma_2}{\mu_2} \right\}$$

In which the tumor free equilibrium point $\mathcal{E}_0$ exist if $(\mu_2h + \sigma_2)\mu_1 > \beta\sigma_2$

Theorem 7. *The tumor free equilibrium point, $\mathcal{E}_0$ of the model system (4.2) exist and is locally asymptotically stable if the following conditions hold:*

$$\mu_1(\mu_2h + \sigma_2) > \beta\sigma_2, \text{ and } r < \frac{c_1(\mu_2\sigma_1h + \sigma_1\sigma_2)}{\mu_1(\mu_2h + \sigma_2) - \beta\sigma_2}$$

Proof. To study the stability of the equilibrium point $\mathcal{E}_0$, we consider the Jacobian matrix of the model system (4.2) at $\mathcal{E}_0$ as follows

$$J(\mathcal{E}_0) = \begin{bmatrix} r - \frac{c_1(\mu_2\sigma_1h + \sigma_1\sigma_2)}{\mu_1(\mu_2h + \sigma_2) - \beta\sigma_2} & 0 & 0 \\ \frac{(h\mu_2\sigma_1 + \sigma_1\sigma_2)(\rho - c_2s)}{s(h\mu_1\mu_2 - (\beta - \mu_1)\sigma_2)} & -\frac{\mu_1(h\mu_2 + \sigma_2) - \beta\sigma_2}{h\mu_2 + \sigma_2} & \frac{\beta h\mu_2^2\sigma_1}{(h\mu_2 + \sigma_2)(h\mu_1\mu_2 - \sigma_2(\beta - \mu_1))} \\ \frac{\delta(h\mu_2\sigma_1 + \sigma_1\sigma_2)}{g(h\mu_1\mu_2 - \sigma_2(\beta - \mu_1))} & 0 & -\mu_2 \end{bmatrix}$$

This yield to the eigenvectors

$$\lambda_1 = r - \frac{c_1(\mu_2\sigma_1h + \sigma_1\sigma_2)}{\mu_1(\mu_2h + \sigma_2) - \beta\sigma_2}, \quad \lambda_2 = -\frac{\mu_1(h\mu_2 + \sigma_2) - \beta\sigma_2}{h\mu_2 + \sigma_2}, \quad \text{and} \quad \lambda_3 = -\mu$$

Since, $\lambda_3 = -\mu < 0$, then directly we can show that, the equilibrium point $\mathcal{E}_0$ is asymptotically stable if

$$\mu_1(\mu_2h + \sigma_2) > \beta\sigma_2, \quad \text{and} \quad r < \frac{c_1(\mu_2\sigma_1h + \sigma_1\sigma_2)}{\mu_1(\mu_2h + \sigma_2) - \beta\sigma_2}$$

□

Theorem 8. *The coexisting equilibrium of model system (4.2), exists under the condition that:*

$$E^* < \frac{r}{c_1}, \quad (c_1\sigma_2 - \delta r)^2 + 4c_1\delta\sigma_2r(1 + bg) < 0,$$

and any one of the two conditions on a_1, a_2, a_3 and a_4 (ii-iii) for the polynomial Equation (4.15) above is satisfied.

Proof. On the other hand, if $T \neq 0$, the steady states are obtained by solving the value of T from

$$r(1 - bT) - c_1E = 0$$

and the rest of the equations in the model (4.2). Then, yield to the coexistence equilibrium point given as

$$\mathcal{E} = (T^*, E^*, I^*)$$

such that

$$T^* = k_1 - k_2E^* \quad \text{where} \quad k_1 = \frac{1}{b} \quad \text{and} \quad k_2 = \frac{c_1}{rb}, \quad (4.13)$$

$$I^* = \frac{\sigma_2k_3 + \delta rE^* - c_1\sigma_2E^* - c_1\delta E^{*2}}{\mu_2(k_3 - c_1E^*)} \quad \text{where} \quad k_3 = r(1 + bg) \quad (4.14)$$

By substituting equations (4.13) and (4.14) into the second equation of model (4.2) and simplify we obtain the following polynomial in E^* .

$$a_5E^{*5} + a_4E^{*4} + a_3E^{*3} + a_2E^{*2} + a_1E^* + a_0 = 0 \quad (4.15)$$

where

$$\begin{aligned}
 a_0 &= -hk_1k_3\mu_2\sigma_1 - hk_3\mu_2s\sigma_1 - k_1k_3\sigma_1\sigma_2 - k_3s\sigma_1\sigma_2 \\
 a_1 &= -\beta k_1k_3\sigma_2 - \beta k_3s\sigma_2 + c_1hk_1\mu_2\sigma_1 + c_1h\mu_2s\sigma_1 + c_1k_1\sigma_1\sigma_2 + c_1s\sigma_1\sigma_2 + c_2hk_1^2k_3\mu_2 \\
 &\quad + c_2hk_1k_3\mu_2s + c_2k_1^2k_3\sigma_2 + c_2k_1k_3s\sigma_2 - \delta k_1r\sigma_1 - \delta rs\sigma_1 + hk_1k_3\mu_1\mu_2 - hk_1k_3\mu_2\rho \\
 &\quad + hk_2k_3\mu_2\sigma_1 + hk_3\mu_1\mu_2s + k_1k_3\mu_1\sigma_2 - k_1k_3\rho\sigma_2 + k_2k_3\sigma_1\sigma_2 + k_3\mu_1s\sigma_2 \\
 a_2 &= \beta c_1k_1\sigma_2 + \beta c_1s\sigma_2 - \beta\delta k_1r - \beta\delta rs + \beta k_2k_3\sigma_2 - c_1c_2hk_1^2\mu_2 - c_1c_2hk_1\mu_2s - c_1c_2k_1^2\sigma_2 \\
 &\quad + c_1\delta k_1\sigma_1 - c_1c_2k_1s\sigma_2 + c_1\delta s\sigma_1 - c_1hk_1\mu_1\mu_2 + c_1hk_1\mu_2\rho - c_1hk_2\mu_2\sigma_1 - c_1h\mu_1\mu_2s \\
 &\quad + c_2\delta k_1^2r - c_1k_1\mu_1\sigma_2 + c_1k_1\rho\sigma_2 + c_2\delta k_1rs - 2c_2hk_1k_2k_3\mu_2 - c_2hk_2k_3\mu_2s - 2c_2k_1k_2k_3\sigma_2 \\
 &\quad + \delta k_1\mu_1r - c_2k_2k_3s\sigma_2 - c_1\mu_1s\sigma_2 - \delta k_1r\rho + \delta k_2r\sigma_1 + \delta\mu_1rs - hk_2k_3\mu_1\mu_2 + hk_2k_3\mu_2\rho \\
 &\quad - k_2k_3\mu_1\sigma_2 + k_2k_3\rho\sigma_2 - c_1k_2\sigma_1\sigma_2 \\
 a_3 &= \beta c_1\delta k_1 + \beta c_1\delta s - \beta c_1k_2\sigma_2 + \beta\delta k_2r - c_1c_2\delta k_1^2 - c_1c_2\delta k_1s + 2c_1c_2hk_1k_2\mu_2 + c_1c_2hk_2\mu_2s \\
 &\quad + 2c_1c_2k_1k_2\sigma_2 + c_1c_2k_2s\sigma_2 - c_1\delta k_1\mu_1 + c_1\delta k_1\rho - c_1\delta k_2\sigma_1 - c_1\delta\mu_1s + c_1hk_2\mu_1\mu_2 - c_1hk_2\mu_2\rho \\
 &\quad + c_1k_2\mu_1\sigma_2 - c_1k_2\rho\sigma_2 - 2c_2\delta k_1k_2r - c_2\delta k_2rs + c_2hk_2^2k_3\mu_2 + c_2k_2^2k_3\sigma_2 - \delta k_2\mu_1r + \delta k_2r\rho \\
 a_4 &= -\beta c_1\delta k_2 + 2c_1c_2\delta k_1k_2 + c_1c_2\delta k_2s - c_1c_2hk_2^2\mu_2 - c_1c_2k_2^2\sigma_2 + c_1\delta k_2\mu_1 - c_1\delta k_2\rho + c_2\delta k_2^2r \\
 a_5 &= -c_1c_2\delta k_2^2.
 \end{aligned}$$

We observe that a_5 and a_0 are always negative (i.e $a_5 < 0, a_0 < 0$). By applying the Descartes' rule of signs, we obtain the following conditions on a_1, a_2, a_3 and a_4 for the polynomial Equation (4.15) to have non-trivial positive roots.

1. If $a_1 < 0, a_2 < 0, a_3 < 0, a_4 < 0$ then there is no change of sign, so there exist no positive roots.
2. If $a_1 > 0, a_2 < 0, a_3 > 0, a_4 < 0$ or $a_1 > 0, a_2 < 0, a_3 < 0, a_4 > 0$ or $a_1 > 0, a_2 > 0, a_3 < 0, a_4 > 0$ or $a_1 > 0, a_2 < 0, a_3 > 0, a_4 > 0$ or $a_1 < 0, a_2 > 0, a_3 < 0, a_4 > 0$ then there is four changes of sign, so there exist four or two or no positive roots.
3. If $a_1 > 0, a_2 > 0, a_3 > 0, a_4 > 0$ or $a_1 < 0, a_2 > 0, a_3 > 0, a_4 > 0$ or $a_1 < 0, a_2 < 0, a_3 > 0, a_4 > 0$ or $a_1 < 0, a_2 < 0, a_3 < 0, a_4 > 0$ or $a_1 > 0, a_2 > 0, a_3 > 0, a_4 < 0$ or $a_1 < 0, a_2 > 0, a_3 > 0, a_4 < 0$ or $a_1 < 0, a_2 < 0, a_3 > 0, a_4 < 0$ or $a_1 > 0, a_2 > 0, a_3 < 0, a_4 < 0$ or $a_1 < 0, a_2 > 0, a_3 < 0, a_4 < 0$ or $a_1 > 0, a_2 < 0, a_3 < 0, a_4 < 0$ then there are two changes of sign, so there exist two no positive roots.

From Equation (4.13), we have

$$\begin{aligned}
 T^* &= k_1 - k_2E^* > 0, \\
 \Rightarrow E^* &< \frac{k_1}{k_2} = \frac{r}{c_1}
 \end{aligned} \tag{4.16}$$

Also, from Equation (4.14), we have

$$I^* = \frac{c_1 \delta E^{*2} - \delta r E^* + c_1 \sigma_2 E^* - \sigma_2 k_3}{\mu_2 (c_1 E^* - k_3)} > 0 \quad \text{where } k_3 = r(1 + bg) \quad (4.17)$$

By considering Equations (4.16) and (5.21a), we get

$$\begin{aligned} \mu_2 (c_1 E^* - k_3) &< 0, \\ \Rightarrow E &< \frac{r}{c_1} (1 + bg) \text{ and } c_1 \delta E^{*2} - \delta r E^* + c_1 \sigma_2 E^* - \sigma_2 r (1 + bg) > 0 \end{aligned} \quad (4.18)$$

Then for all values of E^* , we have

$$c_1 \delta E^{*2} + (c_1 \sigma_2 - \delta r) E^* - \sigma_2 r (1 + bg) > 0 \quad \text{if } (c_1 \sigma_2 - \delta r)^2 + 4c_1 \delta \sigma_2 r (1 + bg) < 0 \quad (4.19)$$

□

4.2.3 Existence and Uniqueness of a System of Solutions of Model

Here, we examine the existence and uniqueness of the model system solution. The Fixed Point Theory is applied to study the existence of the solutions of the model system (4.2). Using the fractional integral operator proposed by Losada and Nieto [90], we have

$$\begin{aligned} T(t) - T(0) &= {}_0^C I_t^\alpha \{rT(1 - bT) - c_1 TE\}, \\ E(t) - E(0) &= {}_0^C I_t^\alpha \left\{ \sigma_1 + \frac{\rho T}{s + T} E - c_2 ET - \mu_1 E + \frac{\beta I}{h + I} E \right\}, \\ I(t) - I(0) &= {}_0^C I_t^\alpha \left\{ \sigma_2 + \frac{\delta T}{g + T} E - \mu_2 I \right\}. \end{aligned} \quad (4.20)$$

Follow the notation used in [90], yields

$$\begin{aligned}
 T(t) - T(0) &= \frac{2(1-\alpha)}{(2-\alpha)M(\alpha)} \{rT(t)(1-bT(t)) - c_1T(t)E(t)\} \\
 &\quad + \frac{2\alpha}{(2-\alpha)M(\alpha)} \int_0^t \{rT(x)(1-bT(x)) - c_1T(x)E(x)\} dx \\
 E(t) - E(0) &= \frac{2(1-\alpha)}{(2-\alpha)M(\alpha)} \left\{ \sigma_1 + \frac{\rho T(t)}{s+T(t)} E(t) - c_2E(t)T(t) - \mu E(t) + \frac{\beta I(t)}{h+I(t)} E(t) \right\} \\
 &\quad + \frac{2\alpha}{(2-\alpha)M(\alpha)} \int_0^t \left\{ \sigma_1 + \frac{\rho T(x)}{s+T(x)} E(x) - c_2E(x)T(x) \right. \\
 &\quad \left. - \mu E(x) + \frac{\beta I(x)}{h+I(x)} E(x) \right\} dx \\
 I(t) - I(0) &= \frac{2(1-\alpha)}{(2-\alpha)M(\alpha)} \left\{ \sigma_2 + \frac{\delta T(t)}{g+T(t)} E(t) - \mu_2 I(t) \right\} \\
 &\quad + \frac{2\alpha}{(2-\alpha)M(\alpha)} \int_0^t \left\{ \sigma_2 + \frac{\delta T(x)}{g+T(x)} E(x) - \mu_2 I(x) \right\} dx.
 \end{aligned} \tag{4.21}$$

For simplicity, (4.21) can be written as

$$\begin{aligned}
 K_1(t, T) &= rT(t)(1-bT(t)) - c_1T(t)E(t), \\
 K_2(t, E) &= \sigma_1 + \frac{\rho T(t)}{s+T(t)} E(t) - c_2E(t)T(t) - \mu E(t) + \frac{\beta I(t)}{h+I(t)} E(t), \\
 K_3(t, I) &= \sigma_2 + \frac{\delta T(t)}{g+T(t)} E(t) - \mu_2 I(t).
 \end{aligned} \tag{4.22}$$

Lemma 2. *The kernels K_1, K_2 and K_3 satisfy the Lipschitz conditions and contraction, if the inequalities*

$$0 \leq \varphi_1, \varphi_2, \varphi_3 < 1,$$

holds, where

$$\varphi_1 = (r + rbm + c_1n), \quad \varphi_2 = \left(\frac{\rho\tau}{s+\tau} + c_1\tau + \mu + \frac{\rho\iota}{h+\iota} \right), \quad \text{and} \quad \varphi_3 = \mu_2.$$

Proof. First, we start with kernel K_1 . Let consider $T(t)$ and $T^*(t)$ are two functions, we have

$$\begin{aligned}
 K_1(t, T) - K_1(t, T^*) &= rT(t) - rbT^2(t) - c_1T(t)E(t) - \left(rT^*(t) - bT^{*2}(t) - c_1T^*(t)E(t) \right) \\
 \|K_1(t, T) - K_1(t, T^*)\| &= \|r(T(t) - T^*(t)) - rb(T(t) + T^*(t))(T(t) - T^*(t)) \\
 &\quad - c_1E(t)(T(t) - T^*(t))\|
 \end{aligned}$$

By using the triangular inequality, we get

$$\begin{aligned} \|K_1(t, T) - K_1(t, T^*)\| &\leq \|r(T(t) - T^*(t))\| + \|rb(T(t) + T^*(t))(T(t) - T^*(t))\| \\ &\quad + \|c_1 E(t)(T(t) - T^*(t))\| \end{aligned}$$

$$\Rightarrow \|K_1(t, T) - K_1(t, T^*)\| \leq (r + rbm + c_1n)\|(T(t) - T^*(t))\|$$

Considering that $\varphi_1 = (r + rbm + c_1n)$, where $n = \max_{t \geq 0} \|E(t)\|$ and $m = \max_{t \geq 0} \|T(t) + T^*(t)\|$ are bounded functions, then

$$\Rightarrow \|K_1(t, T) - K_1(t, T^*)\| \leq \varphi_1 \|(T(t) - T^*(t))\|$$

Hence, the kernel K_1 satisfies the Lipschitz condition and the contraction with $0 \leq (r + b + c_1n + q_1 + m) < 1$. Similarly, the remaining kernels meet the criteria for Lipschitz condition, and can be expressed as follows:

$$\begin{aligned} \|K_2(t, E) - K_2(t, E^*)\| &\leq \varphi_2 \|\{E(t) - E^*(t)\}\| \\ \|K_3(t, I) - K_3(t, I^*)\| &\leq \varphi_3 \|\{I(t) - I^*(t)\}\| \end{aligned}$$

where

$$\varphi_2 = \left(\frac{\rho\tau}{s + \tau} + c_1\tau + \mu + \frac{\rho\iota}{h + \iota} \right) \quad \text{and} \quad \varphi_3 = \mu_2$$

such that $\tau = \max_{t \geq 0} \|T(t)\|$ and $\iota = \max_{t \geq 0} \|I(t)\|$ □

Taking into account the kernels in (4.22), the system of equations (4.21) becomes

$$\begin{aligned} T(t) &= T(0) + \frac{2(1 - \alpha)}{(2 - \alpha)M(\alpha)} K_1(t, T) + \frac{2\alpha}{(2 - \alpha)M(\alpha)} \int_0^t K_1(x, T) dx \\ E(t) &= E(0) + \frac{2(1 - \alpha)}{(2 - \alpha)M(\alpha)} K_2(t, E) + \frac{2\alpha}{(2 - \alpha)M(\alpha)} \int_0^t K_2(x, E) dx \\ I(t) &= I(0) + \frac{2(1 - \alpha)}{(2 - \alpha)M(\alpha)} K_3(t, I) + \frac{2\alpha}{(2 - \alpha)M(\alpha)} \int_0^t K_3(x, I) dx. \end{aligned} \tag{4.23}$$

Then, we define the following recursive formulas

$$\begin{aligned} T_n(t) &= \frac{2(1 - \alpha)}{(2 - \alpha)M(\alpha)} K_1(t, T_{n-1}) + \frac{2\alpha}{(2 - \alpha)M(\alpha)} \int_0^t K_1(x, T_{n-1}) dx \\ E_n(t) &= \frac{2(1 - \alpha)}{(2 - \alpha)M(\alpha)} K_2(t, E_{n-1}) + \frac{2\alpha}{(2 - \alpha)M(\alpha)} \int_0^t K_2(x, E_{n-1}) dx \\ I_n(t) &= \frac{2(1 - \alpha)}{(2 - \alpha)M(\alpha)} K_3(t, I_{n-1}) + \frac{2\alpha}{(2 - \alpha)M(\alpha)} \int_0^t K_3(x, I_{n-1}) dx. \end{aligned} \tag{4.24}$$

with initial conditions as

$$T_0(t) = T(0), \quad E_0(t) = E(0), \quad \text{and} \quad I_0(0) = I(0).$$

In these cases, we present the differences between the successive terms as follows:

$$\begin{aligned}
 \psi_{1n} &= T_n(t) - T_{n-1}(t) \\
 &= \frac{2(1-\alpha)}{(2-\alpha)M(\alpha)} [K_1(t, T_{n-1}) - K_1(t, T_{n-2})] \\
 &\quad + \frac{2\alpha}{(2-\alpha)M(\alpha)} \int_0^t [K_1(x, T_{n-1}) - K_1(x, T_{n-2})] dx, \\
 \psi_{2n} &= E_n(t) - E_{n-1}(t) \\
 &= \frac{2(1-\alpha)}{(2-\alpha)M(\alpha)} [K_2(t, E_{n-1}) - K_2(t, E_{n-2})] \\
 &\quad + \frac{2\alpha}{(2-\alpha)M(\alpha)} \int_0^t [K_2(x, E_{n-1}) - K_2(x, E_{n-2})] dx, \\
 \psi_{3n} &= I_n(t) - I_{n-1}(t) \\
 &= \frac{2(1-\alpha)}{(2-\alpha)M(\alpha)} [K_3(t, I_{n-1}) - K_3(t, I_{n-2})] \\
 &\quad + \frac{2\alpha}{(2-\alpha)M(\alpha)} \int_0^t [K_3(x, I_{n-1}) - K_3(x, I_{n-2})] dx.
 \end{aligned} \tag{4.25}$$

It is essential to note that

$$T_n(t) = \sum_{i=0}^n \psi_{1i}, \quad E_n(t) = \sum_{i=0}^n \psi_{2i}, \quad \text{and} \quad I_n(t) = \sum_{i=0}^n \psi_{3i} \tag{4.26}$$

By applying a step-by-step approach, we get

$$\begin{aligned}
 \|\psi_{1n}\| &= \|T_n(t) - T_{n-1}(t)\| \\
 &= \left\| \frac{2(1-\alpha)}{(2-\alpha)M(\alpha)} [K_1(t, T_{n-1}) - K_1(t, T_{n-2})] \right. \\
 &\quad \left. + \frac{2\alpha}{(2-\alpha)M(\alpha)} \int_0^t [K_1(x, T_{n-1}) - K_1(x, T_{n-2})] dx \right\|
 \end{aligned} \tag{4.27}$$

Applying Triangular inequality, Equation (4.27) reduced to:

$$\begin{aligned}
 \|\psi_{1n}\| &\leq \frac{2(1-\alpha)}{(2-\alpha)M(\alpha)} \| [K_1(t, T_{n-1}) - K_1(t, T_{n-2})] \| \\
 &\quad + \frac{2\alpha}{(2-\alpha)M(\alpha)} \left\| \int_0^t [K_1(x, T_{n-1}) - K_1(x, T_{n-2})] dx \right\|
 \end{aligned} \tag{4.28}$$

Accepting the fact that the kernels satisfy the Lipschitz condition, we obtain:

$$\begin{aligned}\|\psi_{1n}\| &\leq \frac{2(1-\alpha)}{(2-\alpha)M(\alpha)}\phi_1 \|T_{n-1} - T_{n-2}\| + \frac{2\alpha}{(2-\alpha)M(\alpha)} \int_0^t \phi_1 \|T_{n-1} - T_{n-2}\| dx \\ &\Rightarrow \|\psi_{1n}\| \leq \frac{2(1-\alpha)}{(2-\alpha)M(\alpha)}\phi_1 \|\psi_{1n-1}(t)\| + \frac{2\alpha}{(2-\alpha)M(\alpha)} \int_0^t \phi_1 \|\psi_{1n-1}(x)\| dx\end{aligned}\quad (4.29)$$

Similarly, we obtain:

$$\Rightarrow \|\psi_{2n}\| \leq \frac{2(1-\alpha)}{(2-\alpha)M(\alpha)}\phi_2 \|\psi_{2n-1}(t)\| + \frac{2\alpha}{(2-\alpha)M(\alpha)} \int_0^t \phi_2 \|\psi_{2n-1}(x)\| dx \quad (4.30)$$

$$\Rightarrow \|\psi_{3n}\| \leq \frac{2(1-\alpha)}{(2-\alpha)M(\alpha)}\phi_3 \|\psi_{3n-1}(t)\| + \frac{2\alpha}{(2-\alpha)M(\alpha)} \int_0^t \phi_3 \|\psi_{3n-1}(x)\| dx \quad (4.31)$$

Theorem 9. *The fractional-order model has a solution if we can determine t_0 in the manner that*

$$\frac{2(1-\alpha)}{(2-\alpha)M(\alpha)}\phi_i + \frac{2\alpha}{(2-\alpha)M(\alpha)}\phi_i t_0 \leq 1, \quad i \in \{1, 2, 3\}.$$

Proof. In this regard, we consider that the state variables $T(t)$, $E(t)$, and $I(t)$ are bounded, and the kernel fulfills the Lipschitz condition. From the results of Equations (4.29), (4.30) and (4.31) we utilize the recursive techniques we have the following relation as follows:

$$\begin{aligned}\|\psi_{1n}\| &\leq \|T(0)\| \left[\frac{2(1-\alpha)}{(2-\alpha)M(\alpha)}\phi_1 + \frac{2\alpha}{(2-\alpha)M(\alpha)}\phi_1 t_0 \right]^n, \\ \|\psi_{2n}\| &\leq \|E(0)\| \left[\frac{2(1-\alpha)}{(2-\alpha)M(\alpha)}\phi_1 + \frac{2\alpha}{(2-\alpha)M(\alpha)}\phi_2 t_0 \right]^n, \\ \|\psi_{3n}\| &\leq \|I(0)\| \left[\frac{2(1-\alpha)}{(2-\alpha)M(\alpha)}\phi_1 + \frac{2\alpha}{(2-\alpha)M(\alpha)}\phi_3 t_0 \right]^n.\end{aligned}\quad (4.32)$$

Now, we ought to show that the functions in (4.32) are the system of solutions associated with the model system (4.2), we suppose that

$$\begin{aligned}T(t) - T(0) &= T_n(t) - U_n(t), \\ E(t) - E(0) &= E_n(t) - V_n(t), \\ I(t) - I(0) &= I_n(t) - W_n(t).\end{aligned}\quad (4.33)$$

Therefore, we have

$$\begin{aligned}
 \|U_n(t)\| &= \left\| \frac{2(1-\alpha)}{(2-\alpha)M(\alpha)} [K(t, T_n) - K(t, T_{n-1})] \right. \\
 &\quad \left. + \frac{2\alpha}{(2-\alpha)M(\alpha)} \int_0^t [K(x, T_n) - K(x, T_{n-1})] dx \right\| \\
 &\leq \frac{2(1-\alpha)}{(2-\alpha)M(\alpha)} \| [K(t, T_n) - K(t, T_{n-1})] \| \\
 &\quad + \frac{2\alpha}{(2-\alpha)M(\alpha)} \int_0^t \| [K(x, T_n) - K(x, T_{n-1})] \| dx \\
 &\leq \frac{2(1-\alpha)}{(2-\alpha)M(\alpha)} \phi_1 \|T_n - T_{n-1}\| + \frac{2\alpha}{(2-\alpha)M(\alpha)} \phi_1 \|T_n - T_{n-1}\| t
 \end{aligned}$$

By employing the recursive technique, it results in

$$\|U_n(t)\| \leq \left(\frac{2(1-\alpha)}{(2-\alpha)M(\alpha)} + \frac{2\alpha}{(2-\alpha)M(\alpha)} t \right)^{n+1} \phi_1^{n+1} \nu. \quad (4.34)$$

Taking the limit on Equation (4.34) as n tends to infinity, yields

$$\|U_n(t)\| \longrightarrow 0$$

Similarly, we get

$$\begin{aligned}
 \|V_n(t)\| &\longrightarrow 0 \\
 \|W_n(t)\| &\longrightarrow 0
 \end{aligned}$$

Hence, existence is satisfied. $\square$

Theorem 10. *The model system of equations (4.2) has a unique system of solutions if the condition*

$$\left(1 - \frac{2(1-\alpha)}{(2-\alpha)M(\alpha)} \phi_1 - \frac{2\alpha}{(2-\alpha)M(\alpha)} \phi_1 t \right) \geq 0, \quad (4.35)$$

satisfied.

Proof. We assume that there exists another system of solutions of the model system (4.2), such that $T_1(t)$, $E_1(t)$, and $I_1(t)$, then.

$$\begin{aligned}
 T(t) - T_1(t) &= \frac{2(1-\alpha)}{(2-\alpha)M(\alpha)} [K_1(t, T) - K_1(t, T_1)] \\
 &\quad + \frac{2\alpha}{(2-\alpha)M(\alpha)} \int_0^t [K_1(x, T) - K_1(x, T_1)] dx
 \end{aligned} \quad (4.36)$$

Applying the norm on Equation (4.36), yield

$$\begin{aligned} \|T(t) - T_1(t)\| &\leq \frac{2(1-\alpha)}{(2-\alpha)M(\alpha)} \| [K_1(t, T) - K_1(t, T_1)] \| \\ &\quad + \frac{2\alpha}{(2-\alpha)M(\alpha)} \int_0^t \| [K_1(x, T) - K_1(x, T_1)] \| dx \end{aligned} \quad (4.37)$$

By using the Lipschitz condition of the kernels, we have

$$\|T(t) - T_1(t)\| \leq \frac{2(1-\alpha)}{(2-\alpha)M(\alpha)} \phi_1 \|T(t) - T_1(t)\| + \frac{2\alpha}{(2-\alpha)M(\alpha)} \phi_1 t \|T(t) - T_1(t)\| \quad (4.38)$$

Thus, it becomes

$$\|T(t) - T_1(t)\| \left(1 - \frac{2(1-\alpha)}{(2-\alpha)M(\alpha)} \phi_1 + \frac{2\alpha}{(2-\alpha)M(\alpha)} \phi_1 t \right) \leq 0 \quad (4.39)$$

If the condition (4.35) holds, the equality of equation (4.39) only holds when

$$\|T(t) - T_1(t)\| = 0$$

In which case

$$T(t) = T_1(t).$$

Similarly, for the rest of the state variables, we obtain,

$$\begin{aligned} E(t) &= E_1(t), \quad \text{and} \\ A(t) &= I_1(t), \end{aligned}$$

which indicates that the solutions of model system (4.2) are unique. $\square$

4.3 Numerical Method and Simulations

There are several numerical techniques have been proposed to solve the fractional-order differential equations such as Adomian Decomposition Method, Homotopy Decomposition Method, Adams-Bashforth-Moulton Method, among others. Here we use the Adams-Bashforth-Moulton (ABM) Method to give the approximate solutions of the model system (1) based on the predictor-corrector algorithm. Firstly, we set $h = \frac{T}{N}$, $t_n = nh$ and $n = 0, 1, 2, \dots, N \in \mathbb{Z}^+$ [110, 111]. Then model system (4.2) can be discretized as follows.

The corrector values

$$\begin{aligned}
 T_{n+1} &= T_0 + \frac{h^\alpha}{\Gamma(\alpha+2)} \left(rT_{n+1}^p (1 - bT_{n+1}^p) - c_1 T_{n+1}^p E_{n+1}^p \right) \\
 &\quad + \frac{h^\alpha}{\Gamma(\alpha+2)} \sum_{j=0}^n x_{j,n+1} (rT_j (1 - bT_j) - c_1 T_j E_j), \\
 E_{n+1} &= E_0 + \frac{h^\alpha}{\Gamma(\alpha+2)} \left(\sigma + \frac{\rho T_{n+1}^p}{s + T_{n+1}^p} E_{n+1}^p - c_2 E_{n+1}^p T_{n+1}^p - \mu E_{n+1}^p + \frac{\beta I_{n+1}^p}{h + I_{n+1}^p} E_{n+1}^p \right) \\
 &\quad + \frac{h^\alpha}{\Gamma(\alpha+2)} \sum_{j=0}^n x_{j,n+1} \left(\sigma + \frac{\rho T_j}{s + T_j} E_j - c_2 E_j T_j - \mu E_j + \frac{\beta I_j}{h + I_j} E_j \right), \\
 I_{n+1} &= I_0 + \frac{h^\alpha}{\Gamma(\alpha+2)} \left(\sigma_2 - \mu_2 I_{n+1}^p + \frac{\delta T_{n+1}^p}{g + T_{n+1}^p} E_{n+1}^p \right) \\
 &\quad + \frac{h^\alpha}{\Gamma(\alpha+2)} \sum_{j=0}^n x_{j,n+1} \left(\sigma_2 - \mu_2 I_j + \frac{\delta T_j}{g + T_j} E_j \right).
 \end{aligned}$$

where

$$\begin{aligned}
 T_{n+1}^p &= T_0 + \frac{1}{\Gamma(\alpha)} \sum_{j=0}^n y_{j,n+1} (rT_j (1 - bT_j) - c_1 T_j E_j), \\
 E_{n+1}^p &= E_0 + \frac{1}{\Gamma(\alpha)} \sum_{j=0}^n y_{j,n+1} \left(\sigma + \frac{\rho T_j}{s + T_j} E_j - c_2 E_j T_j - \mu E_j + \frac{\beta I_j}{h + I_j} E_j \right), \\
 I_{n+1}^p &= I_0 + \frac{1}{\Gamma(\alpha)} \sum_{j=0}^n y_{j,n+1} \left(\sigma_2 - \mu_2 I_j + \frac{\delta T_j}{g + T_j} E_j \right)
 \end{aligned}$$

are the predictor values, such that

$$x_{j,n+1} = \begin{cases} n^{\alpha+1} - (n - \alpha)(n + 1), & \text{if } j = 0, \\ (n - j + 2)^{\alpha+1} + (n - j)^{\alpha+1} - 2(n - j + 1)^{\alpha+1}, & \text{if } 1 \leq j \leq n, \\ 1, & \text{if } j = n + 1 \end{cases}$$

and

$$y_{j,n+1} = \frac{h^\alpha}{\alpha} ((n - j + 1)^\alpha - (n - j)^\alpha), \quad 0 \leq j \leq n.$$

where p is the order of accuracy such that $p = \min(2, 1 + \alpha)$ [111].

4.3.1 Simulation Results and Discussion

In this section, we present the numerical simulations for model (4.2) to demonstrate the long term dynamics of our results. Our numerical simulations have been executed using the Adams-Bashforth-Moulton (ABM) method, based on the Predictor-corrector PECE scheme to the initial value problem [110]. The computational cost of our simu-

Parameter	Range	Value	Source
r	[0.05 - 0.5]	0.18	[37]
b	$[1 \times 10^6 - 5 \times 10^9]$	2×10^{-9}	[37]
c_1	$[1 \times 10^{-12} - 5 \times 10^{-7}]$	1.101×10^{-7}	[37]
ρ	[0 - 2.5]	0.1245	[37]
s		2.02×10^7	[37]
c_2	$[1 \times 10^{-12} - 5 \times 10^{-7}]$	3.42×10^{-10}	[37]
μ_1	[0.01 - 0.1]	0.06	
β	[0.0 - 0.5]	0.1245	[14]
h		2×10^7	[14]
δ	[0 - 10]	5	[14]
g		1×10^3	[14]
μ_2		10	[14]

Table 4.2: Parameter values used

lation (given the 700 points over which the solution is computed) is kept proportional to, $700 \log(700)^2$ instead of, what would have been 700^2 in the classical implementation. Interested readers may refer to [112] for more details about the stability properties of the computational procedure used, [111] concerning convergence and accuracy, and [93] for a guide to discretizing the FDE system. We fix the initial conditions as $T(0) = 250 \times 10^6$, $E(0) = 3.0 \times 10^6$ and $I(0) = 1500$ together with the values of the parameters used in Table 4.2.

Thus, compared to immune cell populations, we can study systems with large tumor cells. Before examining the therapeutic effect of both ACI and IL-2 on tumor-immune interaction, we obtain the numerical simulation of the tumor growth together with ACI or IL-2 response alone, to determine whether ACI or IL-2 responses are strong enough to fight cancer cells alone as shown in Figure 4.1.

In understanding the treatment effect of ACI alone, we consider the case when $\sigma_2 = 0$, when the model system (4.2) has a non-tumor realistic equilibrium point $(0, \frac{\sigma_1}{\mu_1}, 0)$, which indicates that the existence of effector cells alone can clear the tumor if this steady state is stable. By examining the eigenvalues, we have a locally stable steady state if $\sigma_1 > \frac{r\mu_1}{c_1}$ in which the case, for the parameter values given in Table 4.2, $\sigma_1 > 9.8093 \times 10^4$ and tumor remains and unstable otherwise as shown in Figure 4.1. Therefore, as ACI treatment increase, the tumor can be cleared. Furthermore, in the absence of ACI treatment ($\sigma_1 = 0$), we always have an unstable steady state $(0, 0, \frac{\sigma_2}{\mu_2})$. This implies that administering IL-2 treatment alone may not clear the tumor cells. However, large amounts of IL-2 treatment administered can lead to tumor clearance and uncontrolled growth of effector cells, as explained by [14]. This unlimited development of the immune system can lead to the harmful side effects seen in cancer patients

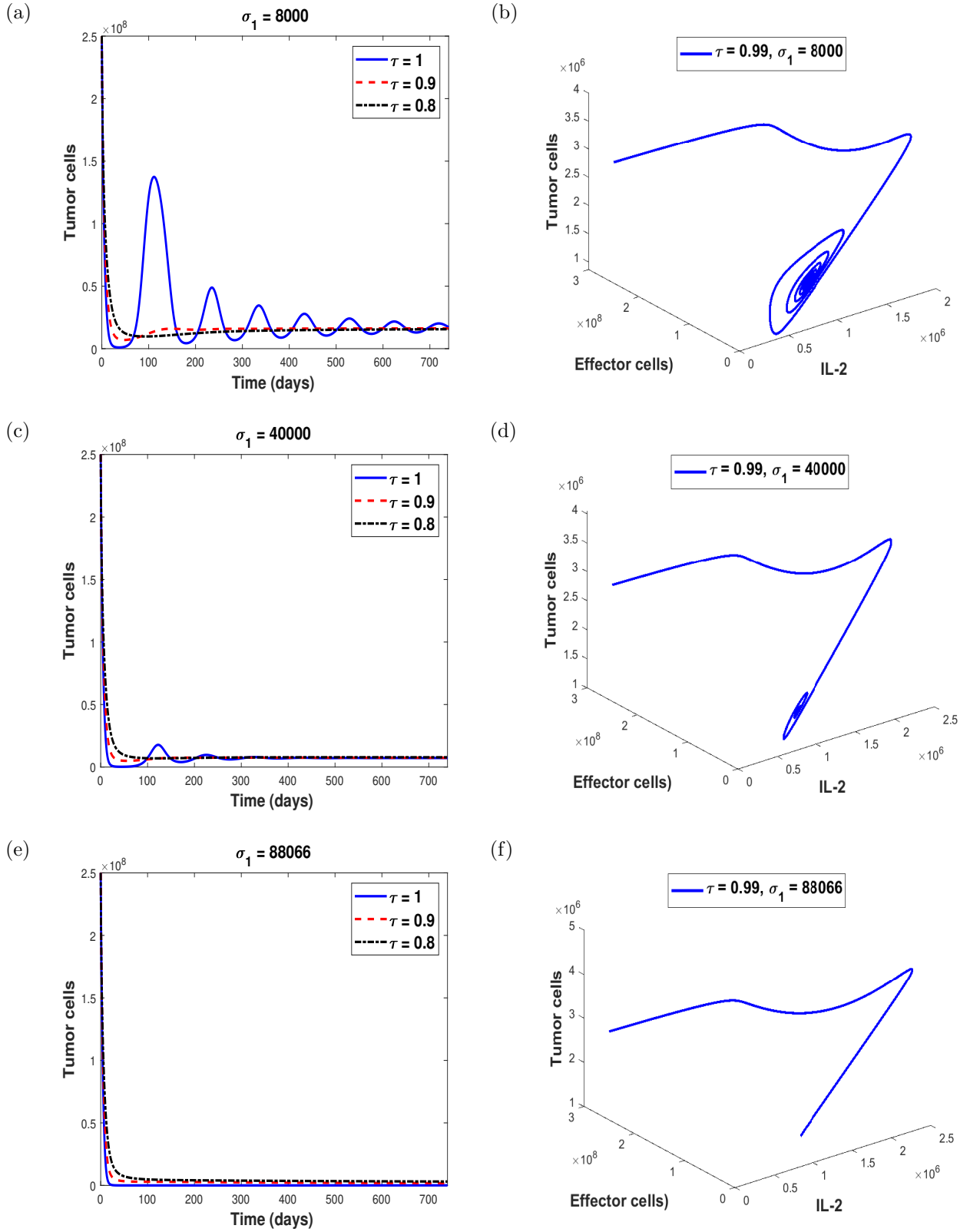


Figure 4.1: Numerical simulation and phase diagram of fractional-order model (4.2), without IL-2 treatment ($\sigma_2 = 0$) for different values of ACI treatment term (σ_1) with order $\alpha = 1, 0.9, 0.99, 0.8$, to show time series plot of the tumor cells

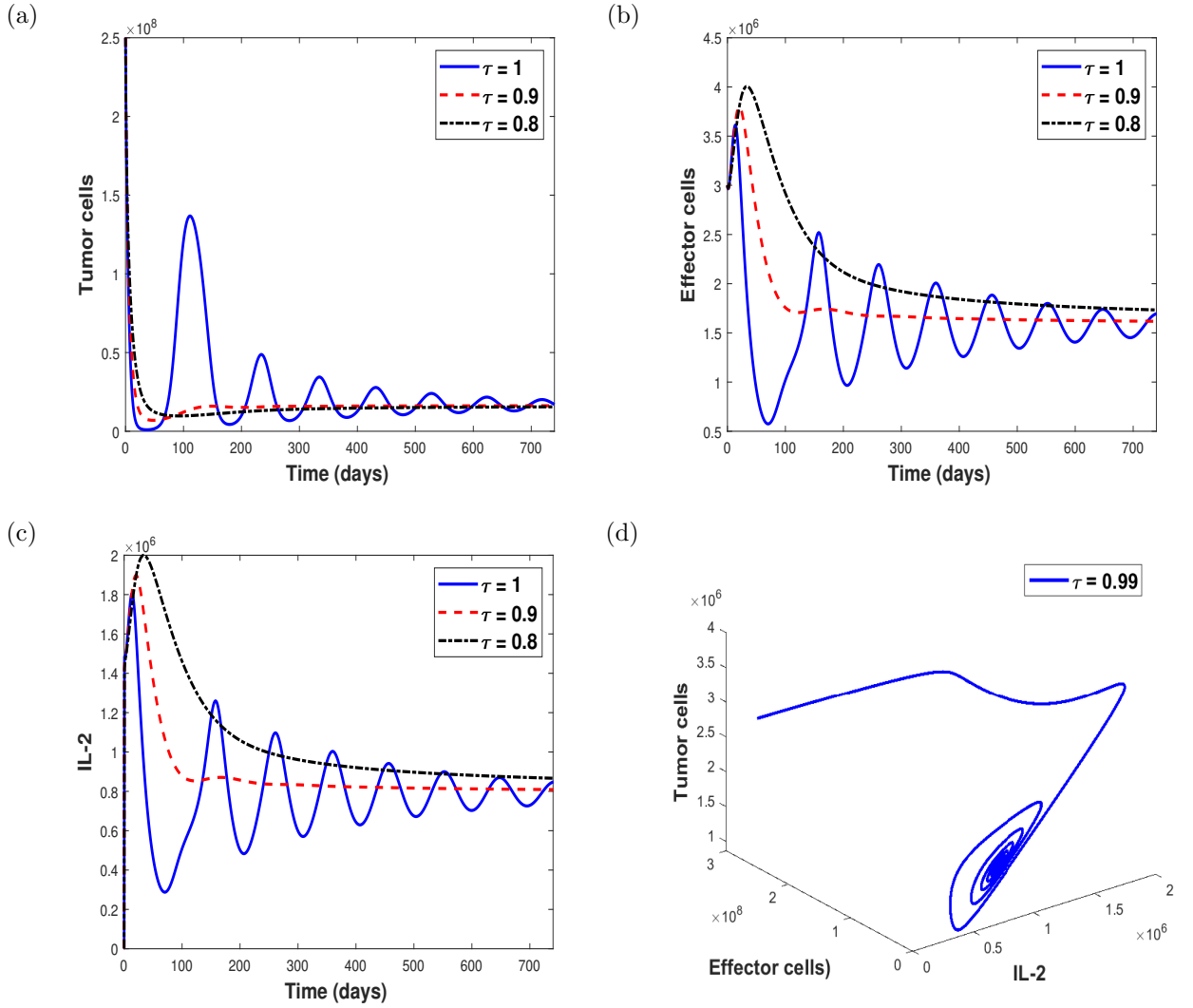


Figure 4.2: Numerical simulation and phase diagram of fractional-order model (4.2), where both ACI ($\sigma_1 = 8040$) and IL-2 ($\sigma_2 = 1000$) treatment involved for $\alpha = 1, 0.9, 0.99, 0.8$.

receiving immunotherapy [14].

Figure 4.2 shows that when both ACI and IL-2 treatments are involved, the tumor-free equilibrium is locally stable as stated in Theorem 7, such that $\sigma_2 < 1.8605 \times 10^8$ using the parameters values in Table 4.2. The combination of ACI and IL-2 treatment can provide the combined effect of monotherapy derived.

4.3.2 Sensitivity analysis

In order to check how changes in all parameters affect the model results, we perform sensitivity analysis by calculating partial rank correlation coefficients (PRCC), and each Latin Hypercube Sample (LHS) performs a total of 1000 simulations on the parameters [113].

Parameter	At $t = 10$ days			At $t = 400$ days			At $t = 700$ days		
	PRCC	p-value	Significance	PRCC	p-value	Significance	PRCC	p-value	Significance
r	-0.4636	0.000e+00	TRUE	0.3825	0.000e+00	TRUE	0.3994	0.0000000	TRUE
b	-0.9351	0.000e+00	TRUE	-0.9362	0.000e+00	TRUE	-0.9373	0.0000000	TRUE
c_1	-0.2698	0.000e+00	TRUE	-0.4013	0.000e+00	TRUE	-0.3946	0.0000000	TRUE
ρ	-0.0911	4.162e-03	TRUE	0.1007	1.528e-03	TRUE	0.1026	0.0012350	TRUE
s	-0.0396	2.141e-01	FALSE	-0.0067	8.332e-01	FALSE	-0.0043	0.8924000	FALSE
c_2	0.4386	0.000e+00	TRUE	0.3215	0.000e+00	TRUE	0.3210	0.0000000	TRUE
μ_1	0.0068	8.304e-01	FALSE	0.0969	2.302e-03	TRUE	0.1123	0.0004035	TRUE
β	-0.02589	4.166e-01	FALSE	0.01871	5.573e-01	FALSE	0.0213	0.5049000	FALSE
h	-0.2017	1.418e-10	TRUE	-0.1278	5.566e-05	TRUE	-0.1007	0.0015250	TRUE
δ	0.1694	8.057e-08	TRUE	0.1142	3.215e-04	TRUE	0.1174	0.0002153	TRUE
g	-0.1068	7.698e-04	TRUE	0.0599	5.985e-02	FALSE	0.0805	0.0114100	TRUE
μ_2	-0.1037	1.098e-03	TRUE	-0.0558	7.989e-02	FALSE	-0.0734	0.0210600	TRUE
σ_1	0.0539	9.071e-02	FALSE	-0.3425	0.000e+00	TRUE	-0.3490	0.0000000	TRUE
σ_2	0.06418	4.381e-02	TRUE	0.0847	7.703e-03	TRUE	0.0746	0.0190900	TRUE

Table 4.3: Tumor cells Parameter PRCC significance (FDR Adjusted p -values).

Parameter	At $t = 10$ days			At $t = 400$ days			At $t = 700$ days		
	PRCC	p-value	Significance	PRCC	p-value	Significance	PRCC	p-value	Significance
r	-0.1431	6.180e-06	TRUE	0.1061	8.345e-04	TRUE	-0.0241	4.487e-01	FALSE
b	0.0566	7.539e-02	FALSE	-0.2254	6.262e-13	TRUE	-0.0448	1.599e-01	FALSE
c_1	0.0925	3.621e-03	TRUE	-0.0451	1.567e-01	FALSE	-0.0081	8.001e-01	FALSE
ρ	-0.1710	1.248e-08	TRUE	0.2144	8.471e-12	TRUE	0.0822	9.800e-03	TRUE
s	0.1503	2.014e-06	TRUE	0.0511	1.084e-01	FALSE	0.0636	4.578e-02	TRUE
c_2	-0.0158	6.194e-01	FALSE	-0.2132	1.118e-11	TRUE	-0.1079	6.812e-04	TRUE
μ_1	-0.0235	4.610e-01	FALSE	-0.0319	3.161e-01	FALSE	-0.0003	9.930e-01	FALSE
β	0.0162	6.119e-01	FALSE	0.0055	8.620e-01	FALSE	0.0160	6.165e-01	FALSE
h	0.0934	3.315e-03	TRUE	-0.0824	9.570e-03	TRUE	-0.0814	1.046e-02	TRUE
δ	0.2920	0.000e+00	TRUE	0.2767	0.000e+00	TRUE	0.3423	0.000e+00	TRUE
g	0.1201	1.542e-04	TRUE	0.0214	5.026e-01	FALSE	-0.0664	3.696e-02	TRUE
μ_2	-0.1261	7.032e-05	TRUE	-0.0926	3.588e-03	TRUE	-0.0322	3.121e-01	FALSE
σ_1	0.0539	9.068e-02	FALSE	0.0231	4.682e-01	FALSE	0.0514	1.063e-01	FALSE
σ_2	0.0912	4.118e-03	TRUE	0.1580	5.798e-07	TRUE	0.2143	8.662e-12	TRUE

Table 4.4: Cytokines interleukin 2 (IL-2) Parameter PRCC significance (FDR Adjusted p -values).

Parameter	At $t = 10$ days			At $t = 400$ days			At $t = 700$ days		
	PRCC	p-value	Significance	PRCC	p-value	Significance	PRCC	p-value	Significance
r	0.4296	0.0000000	TRUE	-0.0957	2.608e-03	TRUE	-0.0957	2.608e-03	TRUE
b	0.7452	0.0000000	TRUE	0.7614	0.000e+00	TRUE	0.7614	0.000e+00	TRUE
c_1	-0.06296	0.0479900	TRUE	0.1869	3.008e-09	TRUE	0.1869	3.008e-09	TRUE
ρ	-0.1088	0.0006079	TRUE	-0.0326	3.065e-01	FALSE	-0.0326	3.065e-01	FALSE
s	0.06023	0.0585200	FALSE	-0.0635	4.614e-02	TRUE	-0.0635	4.614e-02	TRUE
c_2	-0.7902	0.0000000	TRUE	-0.7729	0.000e+00	TRUE	-0.7729	0.000e+00	TRUE
μ_1	-0.0241	0.4488000	FALSE	-0.0076	8.106e-01	FALSE	-0.0076	8.106e-01	FALSE
β	-0.1074	0.0007219	TRUE	-0.1016	1.378e-03	TRUE	-0.1016	1.378e-03	TRUE
h	0.0232	0.4663000	FALSE	0.1241	9.124e-05	TRUE	0.1241	9.124e-05	TRUE
δ	0.0127	0.6902000	FALSE	-0.0418	1.890e-01	FALSE	-0.0418	1.890e-01	FALSE
g	-0.1012	0.0014460	TRUE	-0.0653	4.015e-02	TRUE	-0.0653	4.015e-02	TRUE
μ_2	-0.1012	0.0014410	TRUE	-0.0012	9.709e-01	FALSE	-0.0012	9.709e-01	FALSE
σ_1	0.7414	0.0000000	TRUE	0.7406	0.000e+00	TRUE	0.7406	0.000e+00	TRUE
σ_2	0.0043	0.8926000	FALSE	-0.0545	8.675e-02	FALSE	-0.0545	8.675e-02	FALSE

Table 4.5: Effector cells Parameter PRCC significance (FDR Adjusted p -values).

A uniform distribution was chosen for each of the parameters when performing parameters sampling. If the absolute value of the PRCC is larger, the influence of the parameter in the model variable is greater. The sign of PRCC indicates how the model variable of interest is qualitatively related to each model parameter. It is assumed that if the p -value is greater than 0.01 ($p - value > 0.01$), then the parameter in a given model variable is not significant. Figure 4.3, shows the sensitivity analysis of parameters in tumor cells, effector cells, and IL-2 over the continuous-time period, where the Partial Rank Correlation Coefficients (PRCCs) calculated between each of the varied input parameters are presented in Tables 4.3, 4.5, and 4.4.

It can be seen from plot Figure 4.3a and Table 4.3, that the parameters $r, b, c_1, \rho, c_2, h, \delta$ and σ_2 are sensitive to the growth of tumor cells at continuously time. In such a way that, the parameters b, c_1 , and h have a negative PRCC, while c_2, δ , and σ_2 have a positive correlation and r and δ have both positive and negative associations with tumor cells. This means that increasing inactivation rates of effector cells (c_2), production rate of IL-2 due to tumor-immune interaction (δ), and constant external source of IL-2 (σ_2) leads to an increase in tumor cells (and vice versa). In addition, increasing b, c_1 , and h leads to a decrease in tumor cells (and vice versa). The effect of the tumor intrinsic growth rate, r and the maximum rate of effector cell proliferation by tumor cells, ρ varies with respect to the tumor cell population over time, in such a way that it is strongly negatively correlated in the early stages and then becomes positively correlated to its steady state as clear observed in Table 4.3. This shows that at the initial stage of tumor-immune interaction, the increase of r or ρ leads to a decrease in the tumor cells population due to the limited resources such as space and nutrients. On the other hand, the constant external source of effector cells (σ_1) seems to be not significant at the initial stage of the interaction then becomes positively significant to its steady-state. Finally, the parameters μ_1, g, μ_2 , and σ_1 appear to be both sensitive and insensitive to tumor cells continuously over time. Consequently, σ_1 is insensitive at the starting point and then becomes sensitive as time goes by, while μ_1 is sensitive then becomes insensitive, and parameters g and μ_2 are sensitive at time $t=10$ days and $t=700$ days, also insensitive at $t=400$ days as shown in Table 4.3. From Figure 4.3b and Table 4.5, we observe that the parameters r, b, c_1, c_2, β, g and σ_1 are more sensitive to the effector cells over continuous time, such that gradual increase of b and σ_1 leads to the increases of effector cells population while increasing c_2, β and g results in the decrease of the effector cells (and vice versa). Eventually, the parameters ρ, s, h , and μ_2 look to be both sensitive and insensitive to effector cells continuously over time, whereby parameters s and h are insensitive at the starting point and then becomes sensitive as time goes by, while ρ and μ_2 are sensitive at $t=10$ days, then becomes insensitive as time progress. Moreover, the parameters ρ, h, δ and σ_2 observed to be

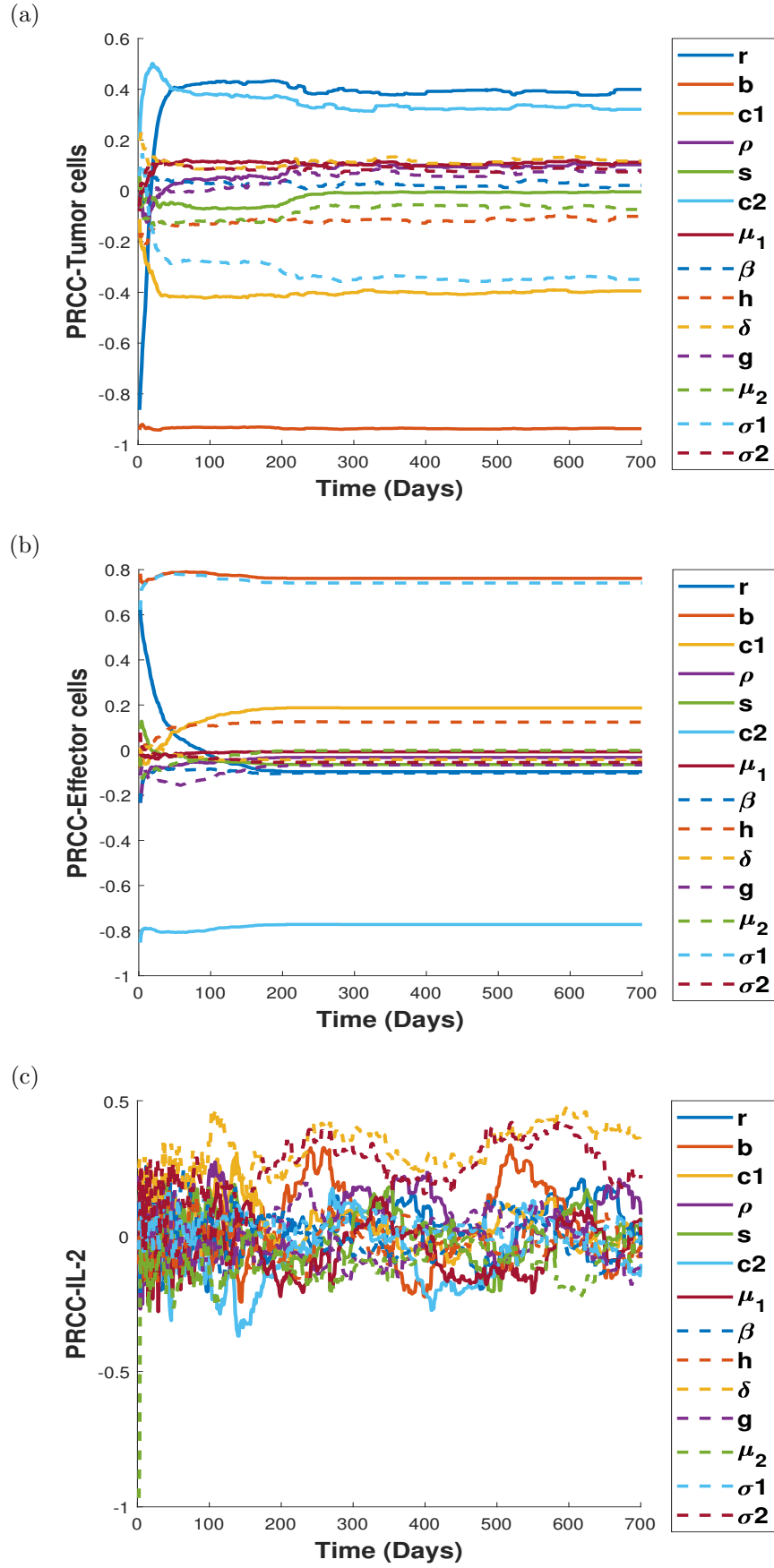


Figure 4.3: Sensitivity analysis of parameters to tumor cells (T), Effector cells (E) and cytokines interleukin 2 (IL-2).

more sensitive in such that δ and σ_2 have a positive correlation while ρ and h are both positively and negatively correlated with IL-2 as shown in Figure 6.11 and Table 4.4.

4.4 Conclusion

In this paper, we examined the fractional-order model for tumor-immune interaction, together with the treatment of cytokines interleukin 2 (IL-2). Essential properties of the model such as non-negativity and boundedness of the solutions are proved, to ensure that the model is well-posed. The existence and uniqueness of the solution for tumor-immune interaction fractional-order model were proved in detail using the fixed point theory. The equilibrium points of the model system were obtained, their existence and the stability of tumor-free steady-state point investigated. We also used an iterative method through the Adams-Bashforth-Moulton method based on the PECE scheme to the initial value problem, to obtain the numerical results of the fractional-order model system (4.2). Furthermore, we carried out a PRCC sensitivity analysis on tumor cells to determine which parameters become more significant as the number of tumor cells changes. Identifying these parameters can improve treatment design strategies for specific factors that can prevent immune surveillance of tumors. Results show that the parameters $r, b, c_1, \rho, c_2, h, \delta$ and σ_2 are sensitive to the growth of tumor cells at continuously time. Also, parameters r, b, c_1, c_2, β, g and σ_1 are more sensitive to the effector cells over continuous time. Additionally, some parameters are both sensitive and insensitive to the tumor-immune interactions.

The results indicate that in some cases, adoptive cellular immunotherapy alone or a combination of the adoptive cellular immunotherapy and cytokines interleukin-2 can achieve satisfactory stable tumor control in such a way that; with little adoptive cellular immunotherapy alone to the system, the situation remains the same as without any treatment. However, including moderate to high immunotherapy, the tumor can be cleared. Also, a large amount of IL-2 alone may boost the immune system, which is powerful enough to kill tumors, but this can lead to pathologic side effects such as capillary leak syndrome [114]. Therefore, it may be a better option to use adoptive cellular immunotherapy as mono therapy or in combination with cytokines interleukin-2 to treat tumors. The model also captures clinically observed but not yet fully understood phenomena of tumor dormancy and sneaking through effect.

Furthermore, the fractional derivatives of Caputo type have a sufficiently large order of magnitude stabilizing effect and can help in understanding control the effects of tumor elimination in tumor-immune interactions together with response to IL-2. The study can be further expanded in the future work to include the effect of normal cells

on tumor-immune interaction, as well as the effect of immunotherapy combined with chemotherapy for a better understanding of tumor dynamics and cancer treatment.

5. Solute dispersion of drug carrier during magnetic drug targeting for blood flow through a microvessel

5.1 Introduction

Cardiovascular disorder is ranked as the second-deadliest disease globally, with an estimate of 9.6 million deaths in 2018, and most of these fatalities occurred in the low and middle-income countries [1]. According to recent statistics, solid tumors account for 85% of human cancers [115]. The tumor microenvironment comprises physical parameters that reduce microvascular density, blood, and lymphatic microvessel compression, inadequately structured microvascular architecture, irregular blood flow, and creates an abnormal structure of the extracellular matrix at the region with elevated interstitial fluid pressure. All these provide lift to a number of interstitial barriers that prevent both the convective and diffusive mechanism of drug penetration [25].

Chemotherapy is one of the ways widely used to reduce the size and treating solid tumors. However, the therapeutic drugs administered intravenously lead to a general systemic distribution of chemotherapy drugs, resulting in harmful side effects on the healthy cells in the body owing to their toxicity and holistic spread throughout the body organs. In recent decades, various targeting methods have been introduced, such as polymers, liposomes, hydrogels, and other vehicles to overcome this problem. However, these vehicles lack an adequate mechanism to deliver high concentrations of drugs [26].

Magnetic drug delivery method is one of the major processes to target the drug towards the tumor position, and overcoming these insufficiencies provides a controlled release of a high concentration of drug agents in a selected region of the body with minimal negative side effects [26]. In this therapy, the carrier particles are loaded with therapeutic drugs and coated with magnetic nanoparticles, and injected systemically into the human body. A local magnetic field is placed, outside the body surface near the tumor position, to capture the loaded carrier particles towards the tumor site. It is believed that drug-coated magnetic nanoparticles (MNPs) may be more effective

and fruitful than other traditional drug targeting methods [116]. The growing interest in magnetic drug targeting is due to current progress in the advancement of carrier particles that are designed to target a specific region of malignant tissue and affect local therapy at the tumor site [117, 118]. One of the challenges of effective magnetic drug targeting is to use an external magnetic field from an electromagnet to guide the accumulation of magnetic nanoparticles in the human body and target deeper tissues. No such experiments have been performed in human patients, but in vitro tests and simulations have demonstrated the potential of dynamic control to achieve this goal [119]. Computational fluid dynamics can model and clarify the entire process of drug administration and drug delivery from the injection site to absorption by solid tumors. Mathematical models and numerical simulations are now used in conjunction with clinical research to clarify our understanding of drug delivery mechanisms, improve treatment efficacy, and examine how physiological parameters affect tumor behavior. Through mathematical modelling, Baxter and Jain [44, 45, 46, 47] conducted fundamental pioneering researches on drug delivery to study the impact of various properties of the tumor on drug delivery using the principles of fluid mechanics to investigate elevated interstitial fluid pressure, significant interstitial fluid flow, and concentration. Following the late 1990s, various computational researches on drug delivery to solid tumors have been presented (see [120, 121, 122, 123, 124]). All of these, among others, try to explain different key issues related to drug delivery, such as elevated interstitial fluid pressure in the tumor area, uniform distribution of drug concentration in tumors and healthy tissues, and drug penetration, as well as determine the most effective parameters through sensitivity analysis.

Continuing this path, by considering an experimental setup, Ritter *et al.* [125] developed a 2D mathematical model for magnetic carrier particles in which they applied a high gradient magnetic separation (HGMS) principle using FEMLAB simulation on the magnetic drug targeting. To suit magnetically targeted drug delivery on the near sites of the body's edge, Grief and Richardson [49] develop a two-dimensional model on the magnetic drug targeting. Furlani and Furlani [50] studied a theoretical model of magnetic drug targeting in microvessels. Shaw *et al.* [51] and Shaw and Murthy [52] carried this work forward by taking the Herschel–Bulkley fluid model for blood in both impermeable and permeable microvessels, respectively. Shamsi *et al.* [53] considered simple homogeneous circle geometry to simulate the magnetic nano-drug distribution on the intraperitoneal solid tumor. They studied the effect of magnetic field intensity, tumor-magnet distance, and particle size on the penetration of MNP in the tumor site.

To understand and optimize the control of magnetic particles, Cherry and Eaton [54] studied the magnetic drug targeting in a microvessel considering all forces expected

to significantly affect the particles, including the interparticle magnetic force, dispersion due to collisions between particles and blood cells, and complex viscous force accounting for the shear-thinning nature of blood. Bose and Banerjee [55] have performed a numerical simulation to study the transport of magnetic carrier particles in a biomagnetic fluid flow in a stenosed bifurcated artery, taking into account both the magnetization and the electrical conductivity of the blood. Soltan *et al.* [56]. studied the effect of tumor size and shape on interstitial fluid flow, where the capillary network is replaced by the uniform distribution of the mass source. Recently, Shojaee *et al.* [57] investigate the role of the capillary network in magnetic nanoparticle targeting, where the effect of nanoparticle size, magnetic intensity, and distance from the tumor in a heterogeneous tumor microenvironment were analyzed. To show that the high interstitial fluid pressure in the tumor is among the most important barriers to drug delivery, the effect of the magnetic field on the pressure and the preservation of the magnetized interstitial fluid is analyzed by Hosseinikhah *et al.* [58], where the geometry includes the space porous of healthy tissue and tumor, as well as the parent vessel as a source and the lymphatic system as a sink modelled on the biology of the body. The performance of the nanoparticle will be affected by its physiological properties such as size, shape, stiffness, and surface functionality. The study by Ye, *et al.* [59], details the impact of nanoparticles' size and shape in their "passive" or "active (subjected to magnetic forces for instance)" transport in the bloodstream, in the area of drug delivery. Other forces induced by external magnetic fields (such as magnetic fields) are essential to guide the movement of the particles [60]. In this study, we investigate the capture conditions of carrier particles and the effective longitudinal dispersion of drug carrier in microvessel. We have considered a magnetic drug carrier in line with blood, incorporating the effects of magnetic particles on fluid properties. We also assume that the blood vessel is porous, and therefore the velocity at the wall is the slip velocity. Solving fluid flow and solute transport equations simultaneously, the influence of the model biological parameters such as volume fraction of nanoparticles, magnetization, tumor-magnetic distance, the permeability of capillary, Peclet number, drug elimination, source term and radius of nanoparticle on the dispersion of drug-coated nanoparticles in microvessel are also discussed. The simulations from this study are interesting and meaningful to provide a way to deepen our understanding of the physics behind the characteristics of blood flow from a microscopic perspective.

5.2 Governing equations

In this study, we investigate the distribution of spherical carrier particle transport in the process of magnetic drug targeting in the microvascular system to the tumor site. The carrier particle consists of several spherical magnetic nanoparticles with non-

magnetic cores made up of therapeutic agents. The equations governing intravascular blood flow, interstitial flow, the magnetic force created velocity, and solute transport are proposed. Figs. 1.2 and Fig. 5.1 shows the general overview of the problem.

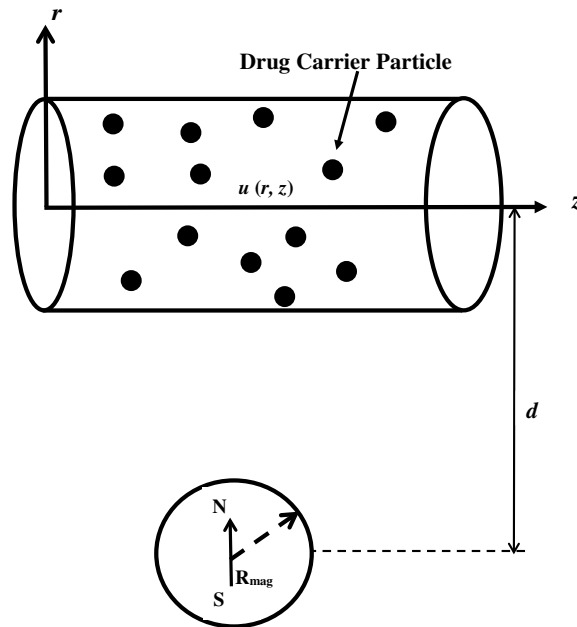


Figure 5.1: The schematic geometry shows Physical model of magnetic targeting and reference frame.

5.2.1 Fluid velocity

We assume that the blood along with the drug carrier flow is axially symmetric, laminar, steady, incompressible through a porous medium within a cylindrical vessel of radius R under the influence of a transverse magnetic field perpendicular to flow direction. Furthermore, the induced magnetic field is assumed to be negligible compared to the applied magnetic field, and hence the blood flow is affected by its electric conductivity only [126, 127]. The flow in the artery is governed by a cylindrical coordinate system (r, θ, z) whose origin is located on the vessel axis, such that the z -axis is taken along the axis of the artery while r is taken along the radial direction. Since the flow is considered to be axisymmetric, the effect of angle, θ is ignored. Holding these assumptions, the momentum equations governing the flow is given by [127]:

$$\frac{\partial \bar{p}}{\partial z} = \frac{\mu}{r} \frac{\partial}{\partial r} \left(r \frac{\partial \bar{u}_i}{\partial r} \right) - \sigma \beta_0^2 \bar{u}_i, \quad (5.1)$$

where u_i is the axial velocity of the flow, μ is the viscosity of the fluid, σ is the electric conductivity, β_0 is the strength of applied magnetic field and p is the pressure of the fluid. Due to the mathematical properties of blood, a plasma layer or a low hematocrit

region forms near the wall of the cylindrical vessel, and a high concentration layer of red blood cells develops near the central axis of the cylindrical vessel. The presence of the cell-depleted wall significantly reduces the apparent viscosity. The apparent viscosity of the blood depends on the diameter of the vessel and the hematocrit, experimentally validated by the following theoretical formula [128, 129, 116, 130].

$$\mu = \mu_{plasma} \left[1 + (\mu_{0.45} - 1) \frac{(1 - H_D)^C - 1}{(1 - 0.45)^C - 1} \left(\frac{D}{D - 1.1} \right)^2 \right] \times \left(\frac{D}{D - 1.1} \right)^2,$$

where

$$\mu_{0.45} = 6e^{-0.085D} + 3.2 - 2.44e^{-0.06D^{0.645}}, \text{ and}$$

$$C = (0.8 + e^{-0.075D}) \left(-1 + \frac{1}{1 + 10^{-11} \cdot D^{12}} \right) + \frac{1}{1 + 10^{-11} D^{12}},$$

such that μ is the apparent blood viscosity, μ_{plasma} is the blood plasma viscosity, $\mu_{0.45}$ is the relative apparent viscosity of the blood for fixed discharge hematocrit of 45%, D is the vessel diameter in micrometers and H_D is the discharge hematocrit of 39%.

Using dimensionless variables

$$r = \frac{\bar{r}}{R}, \quad p = \frac{\bar{p}}{\pi_i}, \quad u_i = \frac{\bar{u}_i}{u_0}, \quad z = \frac{\mu u_0}{\pi_i R^2} \bar{z}, \quad \text{and} \quad m^2 = \frac{\sigma \beta_0^2 R^2}{\mu},$$

The governing flow equation (5.1), becomes:

$$\frac{\partial p}{\partial z} = \frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial u_i}{\partial r} \right) - m^2 u_i. \quad (5.2)$$

The above-formulated model equation corresponds to the following boundary conditions:

$$\begin{cases} u_i = u_s \text{ (slip velocity constant) at } r = 1, \text{ and} \\ u_i = \text{finite at } r = 0. \end{cases} \quad (5.3)$$

Solving Equation (5.2) using the boundary condition (5.3), we obtain the axial velocity of the fluid flow as

$$u_i = C_1 I_0(mr) - \frac{1}{m^2} \frac{\partial p}{\partial z}, \quad (5.4)$$

with

$$C_1 = \frac{u_s + \frac{1}{m^2} \frac{\partial p}{\partial z}}{I_0(m)},$$

where I_0 is the modified Bessel function of the first kind.

The corresponding instant flow rate, Q is calculated as

$$Q = 2\pi \int_0^1 u_i(r, z) r dr,$$

implies

$$Q = \frac{2\pi C_1 I_1(m)}{m} - \frac{\pi}{m^2} \frac{\partial p}{\partial z}, \quad (5.5)$$

where I_1 is the modified Bessel function of the first kind.

In the present analysis, the microvessel wall is permeable but non-absorbent for solutes so that nanoparticles easily pass through the permeable wall [131]. On account of the permeability of the wall, the flows laterally across the vessel fenestration [132]. The lateral flux across the permeable wall affects the mean velocity of the flow, which decreases along the channel [116, 131]. By considering the aforementioned assumptions, the mass continuity equation can be written as

$$\frac{\partial Q}{\partial z} + V_p \lambda_p = 0, \quad (5.6)$$

where Q is the flow rate, and $V_p \lambda_p$ denotes the volume flow rate along the permeable wall per unit length, such that $\lambda_p = 2\pi R$ is the perimeter of the permeable microvessel. Using the Darcy's law the perfusing velocity, V_p can be given as

$$V_p = -L_p(\pi_i - \bar{p}); \quad L_p = \frac{k}{\mu\delta}, \quad (5.7)$$

with L_p is the vascular hydraulic conductivity that is given in terms of thickness δ , permeability of the microvessel wall k , and the effective viscosity of the fluid μ , the interstitial fluid pressure π_i , and the local mean value of the vascular pressure p . Substituting Equation (5.7) in (5.6) and expressing the flow rate Q as the function of pressure p , yields

$$-\frac{\pi R^2}{\mu m^2} \frac{\partial^2 p}{\partial z^2} - L_p(\pi_i - \bar{p}) \lambda_p = 0. \quad (5.8)$$

We apply the following non-dimensional parameters

$$p = \frac{\bar{p}}{\pi_i} \quad \text{and let } \Gamma = m \sqrt{\frac{L_p \pi_i \lambda_p}{\pi}},$$

to the Equation (5.8) and written the equation to a non-dimensional form

$$\frac{\partial^2 p}{\partial z^2} + \Gamma^2(1 - p) = 0. \quad (5.9)$$

where Γ is the permeability parameter of the capillary wall. The pressure distribution equation along the channel obtained by solving Equation (5.9), under the boundary conditions of $p(0) = p_0$ (inlet pressure) and $p(1) = p_1$ (outlet pressure) as

$$p(z) = \frac{\frac{(1-e^{2\Gamma}) + ((p_0-1) - (p_1-1)e^\Gamma)e^{\Gamma z}}{1-e^{2\Gamma}} + \frac{((p_1-1)e^\Gamma - (p_0-1)e^{2\Gamma})e^{-\Gamma z}}{1-e^{2\Gamma}}}{1-e^{2\Gamma}}.$$

The mean velocity of the fluid, u_{a_i} is given by

$$u_{a_i} = \frac{Q}{\pi R^2} = 2 \int_0^1 u_i(r, z) r dr = \frac{2C_1 I_1(m)}{m} - \frac{1}{m^2} \frac{\partial p}{\partial z}. \quad (5.10)$$

5.2.2 Magnetic force created velocity

Therapeutic drugs are associated with magnetic nanoparticles, which provide an option for their control by an external magnetic force. The present physical configuration is similar to that described in [53, 57], where magnetic nanoparticles and carrier particles are assumed to be spherical. We assumed that, the N_{mnp} identical magnetic nanoparticles embedded in the carrier particle will experience a total of the magnetic force on the carrier particle that depends on the magnetic field and the field gradient around it given by [133]

$$F_m = \mu_0 N_{mnp} V_{mnp} \frac{\mathcal{X}}{1 + \frac{\mathcal{X}}{3}} (\mathbf{H}_a \cdot \nabla) \mathbf{H}_a,$$

where $V_{mnp} = \frac{4}{3}\pi a^3$ is the magnetic nanoparticle volume with radius of the magnetic nanoparticle a , $\mathbf{H}_a$ is the applied magnetic field intensity at the center of a carrier particle, $\mathcal{X}$ is the magnetic susceptibility of magnetic nanoparticles, and μ_0 is the permeability of the magnetic particles. We also assume that the susceptibility of the magnetic particles is much higher than that of the blood, which ensures that the particles start far enough upstream where the influence of the magnetic field and the force are negligible, and the distance of the magnet is very large relative to the radius of the microvessel [133]. Applying the above assumptions, the magnetic force components in $r - z$ plane are given by

$$F_{mr} = 3\mu_0 N_{mnp} V_{mnp} M_s^2 R_{mag}^4 \frac{d}{2[d^2 + z^2]^3}, \quad (5.11)$$

$$F_{mz} = 3\mu_0 N_{mnp} V_{mnp} M_s^2 R_{mag}^4 \frac{z}{2[d^2 + z^2]^3}, \quad (5.12)$$

where M_s , R_{mag} , d , and z are the magnetization of the magnet, the radius of the magnet, the tumor-magnetic distance, and the distance of the particle at the z -axis, re-

spectively. From Equations (5.11) and (5.12), we get the resulting magnetic force as

$$F_m = 3\mu_0 N_{mnp} V_{mnp} M_s^2 R_{mag}^4 \frac{1}{2[d^2 + z^2]^{\frac{5}{2}}}, \quad (5.13)$$

Now, using the magnetic force to the stokes drag force $F_m = (6\pi a\eta)u_e$, we derive the magnetic force created velocity u_e as:

$$u_e = \frac{3\mu_0 N_{mnp} V_{mnp} M_s^2 R_{mag}^4}{12\pi a\eta} \frac{1}{[d^2 + z^2]^{\frac{5}{2}}}, \quad (5.14)$$

where η is the dynamic viscosity of the interstitial fluid and a is the radius of the magnetic nanoparticles. Now, as the carrier particle contains the β_{vf} volume fraction of magnetic nanoparticles, the total amount of nanoparticles present in the carrier particle is $N_{mnp} V_{mnp}$ is represented in terms of a volume fraction, $\beta_{vf} V_{cp}$ of the carrier particle [133, 116], then the magnetic force created velocity is given as

$$u_e = \frac{3\mu_0 \beta_{vf} V_{cp} M_s^2 R_{mag}^4}{12\pi a\eta} \frac{1}{[d^2 + z^2]^{\frac{5}{2}}}. \quad (5.15)$$

5.2.3 Solute Transport

The transport of solutes within the concentric suspension of particles may be augmented by the effects of shear-induced diffuse particle migration [134]. Since the shear-induced diffusivity of the fluid elements within the suspension should be similar to that of the particles, the motion of blood enhance the transport of solutes within the blood [134]. The solute (drug) transport in porous media governed by convection and diffusion mechanisms, where the convection term is downing to the product of velocity and concentration, and the diffusion term derived from the first Fick's law [57]. Further, assume that both solid particles and fluid phases flow with the same velocity. The governing advection-diffusion equation is given by

$$\frac{\partial \bar{C}}{\partial \bar{t}} + \bar{u} \frac{\partial \bar{C}}{\partial \bar{z}} = \frac{D}{\bar{r}} \frac{\partial}{\partial \bar{r}} \left(\bar{r} \frac{\partial \bar{C}}{\partial \bar{r}} \right) + D \frac{\partial^2 \bar{C}}{\partial \bar{z}^2} - \bar{\lambda}_1 \bar{C} + \bar{\lambda}_2 \quad (5.16)$$

where $\bar{C}(\bar{t}, \bar{r}, \bar{z})$ is the solute concentration, $\bar{u} = u_{a_i} + u_e$ is the velocity of the magnetic nanoparticles which is the sum of interstitial fluid mean velocity u_{a_i} and the magnetic force created velocity u_e , and D is the effective diffusion coefficient of magnetic nanoparticles in the tissues. The term $\bar{\lambda}_1$ in Equation (5.16) describe the drug elimination from the tissue, and $\bar{\lambda}_2$ is the source term that summing the vascular, lymphatic, and cellular contributions [53].

The initial and boundary conditions for solving equation (5.16) are :

$$\bar{C}(0, \bar{r}, \bar{z}) = 0 \quad \text{at} \quad t = 0 \quad (5.17a)$$

$$\bar{C} = \frac{\partial \bar{C}}{\partial \bar{z}} = 0 \quad \text{for} \quad z = \pm\infty \quad (5.17b)$$

$$\frac{\partial C}{\partial r} = 0 \quad \text{at} \quad r = R \quad (5.17c)$$

$$\frac{\partial C}{\partial r} = 0 \quad \text{at} \quad r = 0 \quad (5.17d)$$

where the Equation (5.17a) describes the initial condition where it considered that at time $t = 0$, there is an absence of the drug-coated magnetic nanoparticles in the domain. Open boundary condition is applied to establish mass transport across boundaries where both convection flow and outflow can occur and is defined by equation (5.17b). Furthermore, the impermeability of the salute at the capillary wall together with the axial symmetry condition is shown by Equations (5.17c) and (5.17d) respectively [135, 134].

5.3 Solution Procedure

By introducing the following dimensionless variables :

$$C = \frac{\bar{C}}{C_0}, \quad u = \frac{\bar{u}}{u_0}, \quad t = \frac{\bar{t}D}{R^2}, \quad Pe = \frac{u_0 R}{D}, \quad D = \frac{\mu u_0}{\pi_i},$$

$$\lambda_1 = \frac{\bar{\lambda}_1 R^2}{D}, \quad \text{and}, \quad \lambda_2 = \frac{\bar{\lambda}_2 R^2}{C_0 D}.$$

The governing solute concentration transport Equation (5.16) with conditions (5.17a)-(5.17d) can be expressed as

$$\frac{\partial C}{\partial t} + u \frac{\partial C}{\partial z} = \frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial C}{\partial r} \right) + \frac{1}{Pe^2} \frac{\partial^2 C}{\partial z^2} - \lambda_1 C + \lambda_2, \quad (5.18)$$

together with boundary conditions

$$C(0, r, z) = 0 \quad \text{at} \quad t = 0, \quad (5.19a)$$

$$C = \frac{\partial C}{\partial z} = 0 \quad \text{for} \quad z = \pm\infty, \quad (5.19b)$$

$$\frac{\partial C}{\partial r} = 0 \quad \text{at} \quad r = 1, \quad (5.19c)$$

$$\frac{\partial C}{\partial r} = 0 \quad \text{at} \quad r = 0, \quad (5.19d)$$

where Pe is the Peclet number, λ_1 is the drug elimination parameter, and λ_2 is source term parameter. In this study, we assume that the concentration distribution of solute transport is uniform along the radial direction (r -axis) and is the function of z and t only, the concentration gradient along the r direction is removed. Therefore, the final modified mass transport equation is

$$\frac{\partial C}{\partial t} + u \frac{\partial C}{\partial z} = \frac{1}{Pe^2} \frac{\partial^2 C}{\partial z^2} - \lambda_1 C + \lambda_2, \quad (5.20)$$

together with initial and boundary conditions

$$C = 0 \quad \text{for} \quad t = 0, \quad (5.21a)$$

$$C = \frac{\partial C}{\partial z} = 0 \quad \text{for} \quad z = \pm\infty, \quad (5.21b)$$

Finite difference scheme is the most suitable technique for solving nonlinear problems related to regular geometry [136]. Therefore, the governing solute transport equation model (5.20) is solved using a finite difference method, adopting a standard implicit backward time centered space (BTCS) scheme. We implemented a MATLAB code to obtain the numerical results for the fluid pressure (p), mean fluid velocity (u_{a_i}), and the magnetic force created velocity (u_e) from the analytical solutions (5.10), (5.10), and (5.15) respectively. The results, for the fluid pressure p and total fluid velocity u , were used for the transient convection-diffusion equation of drug transport. The numerical solution is shown in Fig 5.2. As a result, the transient equation of drug transport (5.16) is discretized with time-space Δt and grid spacing of Δz , where the discretization concentration, $C(z, t)$ is written as $C(z_i, t_n) = C_i^n$.

$$z_i = i\Delta z, \quad t_n = n\Delta t, \quad i = 1, 2, 3, \dots, n_z; \quad n = 1, 2, 3, \dots, n_t \quad (5.22)$$

where

$$\Delta z = \frac{L_z}{n_z}, \quad \text{and} \quad \Delta t = \frac{T}{n_t}, \quad 0 \leq z \leq L_z \quad \text{and} \quad 0 \leq t \leq T. \quad (5.23)$$

The time derivative is approximated by a Backward difference as

$$\frac{\partial C}{\partial t} = \frac{C_i^{n+1} - C_i^n}{\Delta t}, \quad (5.24)$$

and the first spatial partial derivative is approximated by a centered difference

$$\frac{\partial C}{\partial z} = \frac{C_{i+1}^{n+1} - C_{i-1}^{n+1}}{2\Delta z}. \quad (5.25)$$

The second derivative is approximated by

$$\frac{\partial^2 C}{\partial z^2} = \frac{C_{i+1}^{m+1} - 2C_i^{m+1} + C_{i-1}^{m+1}}{(\Delta z)^2}. \quad (5.26)$$

Parameter	Description	Value	Unit	Ref
p_0	Inlet pressure	2	-	[131]
p_1	Outlet pressure	0.5	-	[131]
R_{mag}	Radius of the magnet	0.03	m	[133]
μ_0	Magnetic permeability	$4\pi \times 10^{-7}$	NA^{-2}	[57, 53]
η	Dynamic viscosity of the interstitial fluid	1.12×10^{-3}	Pa s	[53]

Table 5.1: Description of parameters used for the dispersion of drug-coated magnetic nanoparticles' simulation.

5.4 Results and Discussion

In this section, we want to examine the rate of penetration of drug-coated nanoparticles concentration into tumor tissue. In that respect, the numerical simulation results are presented in Fig.5.3-5.13, where the drug-coated magnetic drug carrier concentrations are displayed through graphs, and saturated concentration and time to reach the saturation concentration displayed through tables. The effect governing parameters such as volume fraction of nanoparticle (β_{vf}), magnetization (M_s), tumor-magnet distance (d), permeability of capillary (Γ), Peclet number (Pe), drug elimination (λ_1), and source term (λ_2), on the relative effective delivery of drug-coated magnetic nanoparticle concentrations are addressed. For the whole computations, the relevant physical parameters considered for the present study are summarized in Table 5.1. To achieve targeted delivery, nanoparticles are generally coated with ligands that specifically bind to specific types of receptors on the cell surface [137]. Nanoparticles targeted delivery to the vascular system includes transport, hydrodynamic force, and multilevel interactions with specific biosurfaces [134]. As nanoparticles are injected into the bloodstream, they are dispersed into the vessel under the combined effects of diffusion and fluid flow. From both Fig.5.3 and Fig.5.4, we observe that the concentration of drug-coated magnetic nanoparticles increases over time and then slowly converges to steady values after a time, as clearly presented in Fig. 5.4. The concentration of drug-coated nanoparticles is maximum when the particle is near the center point along the microvessel axis and then slowly decreases to steady values after reach its peak value as shown in Fig. 5.3. This implies that initially, the drug goes all over the body via blood circulation and accumulates to a certain extent in the target location to accomplish its therapeutic effect [59].

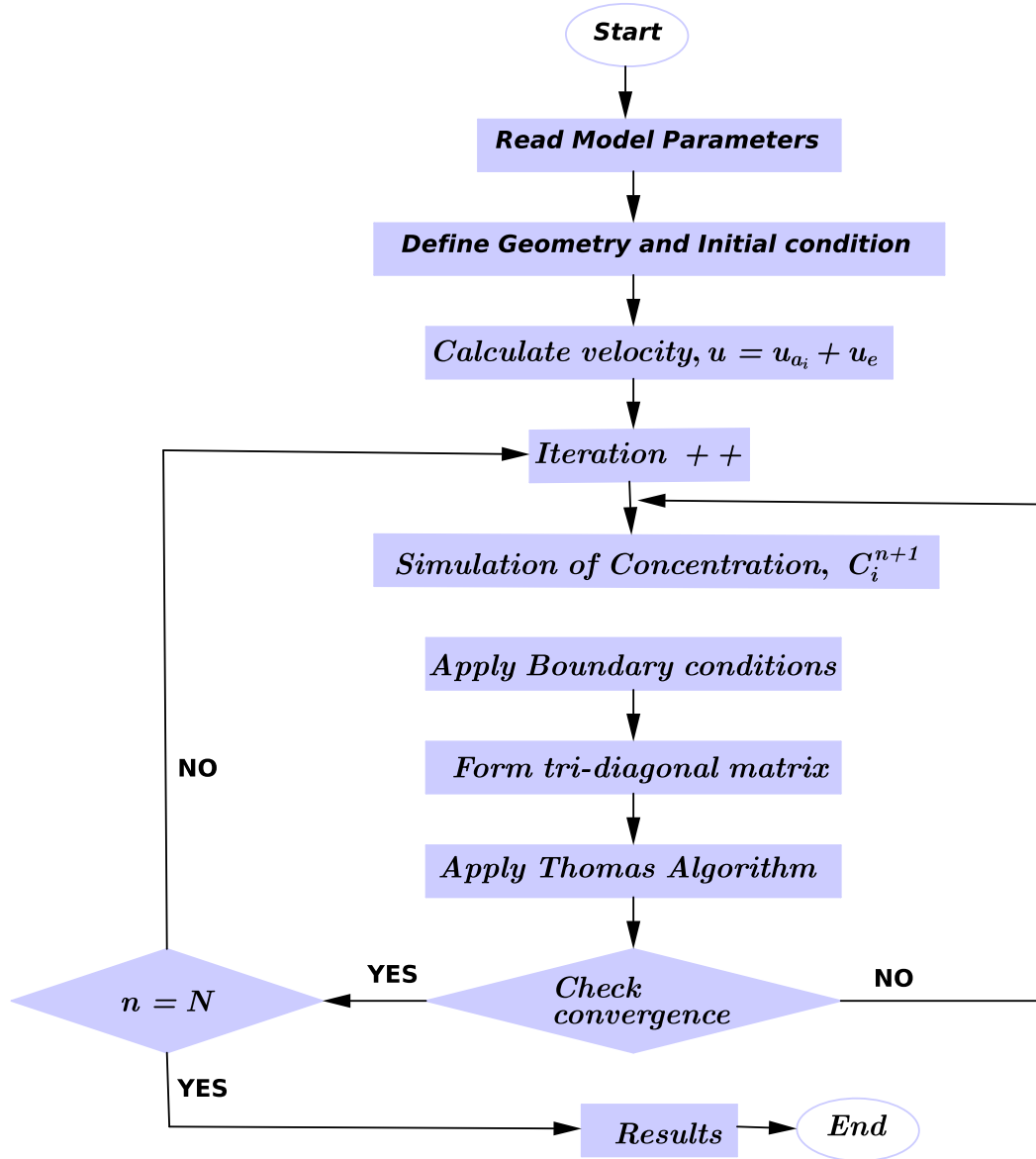


Figure 5.2: Schematic diagram of the numerical solution for the model governing equations

5.4.1 The effect of volume fraction of nanoparticles

The volume fraction of magnetic nanoparticles represents the percentage of the volume of magnetic nanoparticles relative to the volume of the carrier particles. Fig. 5.5, and Table 5.2 show the effect of volume fraction parameter on the dispersion of drug-coated magnetic nanoparticles in tumor tissues after intravenous bolus injection. In this case, $d = 0.055$ m, $\Gamma = 5$, $M_s = 1 \times 10^6$, $Pe = 3.0$, $\lambda_1 = 0.10$, $\lambda_2 = 0.8$, and $a = 200$ nm. From both Fig. 5.5, and Table 5.2, we observe that the concentration of drug-coated magnetic nanoparticles increases linearly with the increase in volume fraction of the magnetic particle, and then saturated to steady values after a certain time. This phenomenon is due to the gradual increase in magnetic forces on drug carrier between

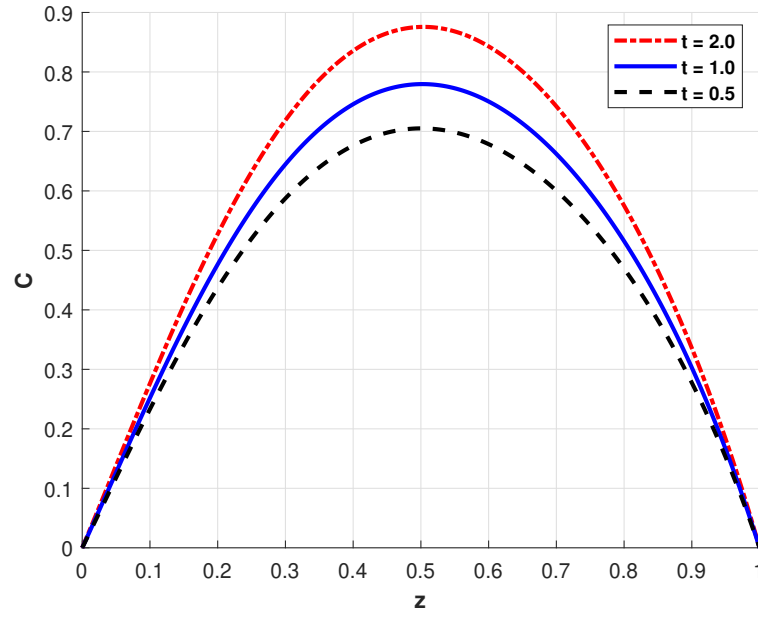


Figure 5.3: Dispersion of drug-coated magnetic nanoparticles' concentration at time, $t = 0.5$, $t = 1.0$, and $t = 2.0$.

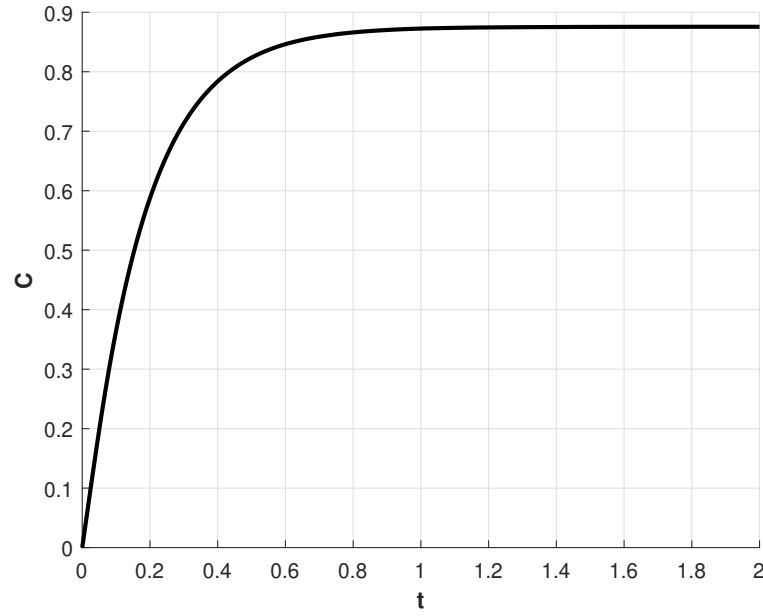


Figure 5.4: Concentration profile of drug-coated magnetic nanoparticles at $z = 0.5$.

β_{vf}	Saturation Concentration value, C_s	Time to reach C_s
0.4	0.8880	1.82
0.6	0.8886	1.79
0.8	0.8892	1.75

Table 5.2: Saturated concentration and time to reach the saturated concentration with different values of β_{vf}

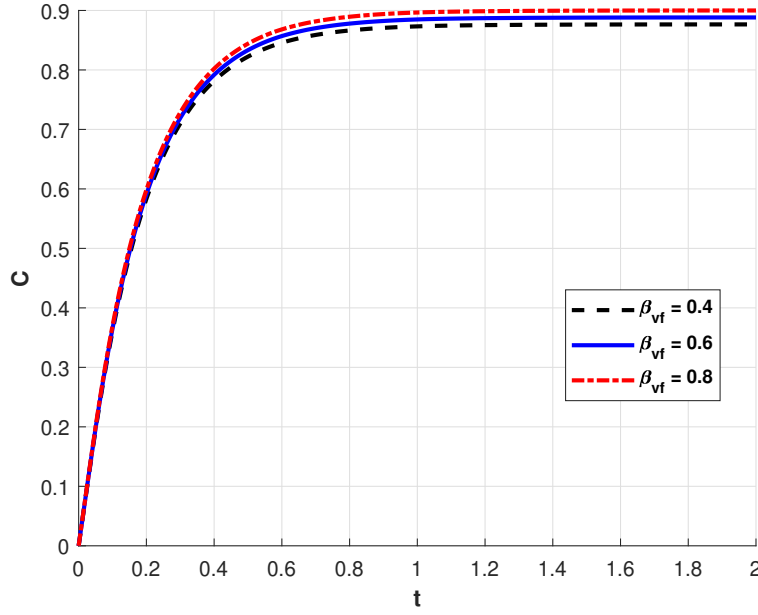


Figure 5.5: Concentration profile of drug-coated magnetic nanoparticles at $z = 0.5$ for different volume fraction parameter, β_{vf} .

the magnet and the drug carrier, and hence having a higher velocity, which then induces drug-coated magnetic nanoparticles concentrations. Also, the time to reach the saturation concentration of drug-coated magnetic nanoparticles in the microvessel along the channel decreases with an increase in the volume fraction, as clear shown in Table 5.2. With an increase in the volume fraction parameter, the magnetic force created velocity (refer, Equation (5.15)) boost up, and therefore the drug-coated carrier particles quickly reach the tumor position. It then suggests that much larger forces are required to cause fluid flow as with increase in the nanoparticles' volume fraction. Table 5.2 shows the value of the saturation concentration and the time to reach the saturation point. It is observed that the saturated concentration value increases with increase in the volume fraction. This is because, the higher volume fraction supported the velocity due to magnetic field and the resultant velocity of the drug carrier as a results more drug carrier. A similar phenomenon was observed in [138], where the greater nanoparticle volume fraction shows a greater attraction by the wire.

5.4.2 The effect of magnetization

The effect of magnetization is shown in Fig. 5.6, and Table 5.2, where $\beta_{vf} = 0.6$, $d = 0.055$ m, $\Gamma = 3.0$, $Pe = 3.0$, $\lambda_1 = 0.10$, $\lambda_2 = 0.8$, and $a = 200$ nm. It is well-known that increasing magnetization increases magnetic force. Hence, the peak of drug-coated magnetic nanoparticle concentrations increases as the magnetization parameter increases from 1×10^6 to 3×10^6 , as shown in Fig 5.6. Also, the time to reach

the saturation concentration of drug-coated magnetic nanoparticles in the microvessel along the channel decreases with an increase in the magnetization, as shown in Table 5.3. Additionally, we observe that the drug-coated magnetic nanoparticles benefit

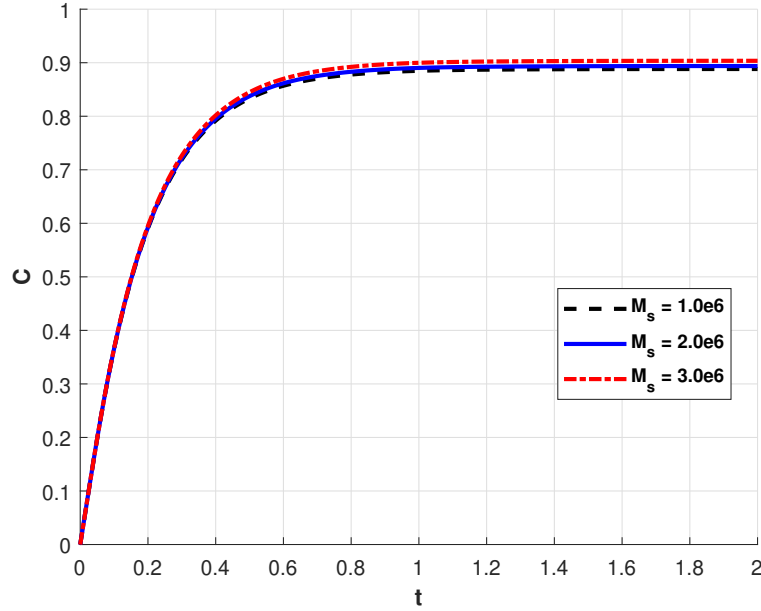


Figure 5.6: Concentration profile of drug-coated magnetic nanoparticles at $z = 0.5$ for different magnetization parameters, M_s .

from the imposition of magnetic forces that help them overcome interstitial transport barriers by increasing their velocity. The increased magnetic force, by magnetization effect, causes the particles to move faster towards the walls of the capillaries and experiences an attraction towards the tumor as shown in Table 5.3. Therefore, as magnetization increases, particles are easily trapped near the location of the tumor. Through the experimental study by Avile *et al.* [138], it was observed that magnetic field strength increases the CE (capture efficiency) and hence the concentration of drug carriers. Similar results obtained from clinical studies have shown that increasing magnetization improve the accumulation and penetration of nanoparticles near the location of the tumor [139, 140].

M_s	Saturation Concentration value, C_s	Time to reach C_s
1×10^6	0.8886	1.79
2×10^6	0.8942	1.70
3×10^6	0.9042	1.69

Table 5.3: Saturated concentration and time to reach the saturated concentration for different values of magnetization parameters, M_s

5.4.3 The effect of tumor-magnet distance

The tumor-magnet distances can vary depending on the location of the tumor. Herein, we consider the tumor-magnet distance parameter in the range of 0.045 m to 0.065 m, while $\beta_{vf} = 0.6$, $\Gamma = 3.0$, $Pe = 3.0$, $\lambda_1 = 0.10$, $\lambda_2 = 0.8$, and $a = 200$ nm. The magnetic force is inversely proportional to the tumor-magnetic distance. Fig. 5.7

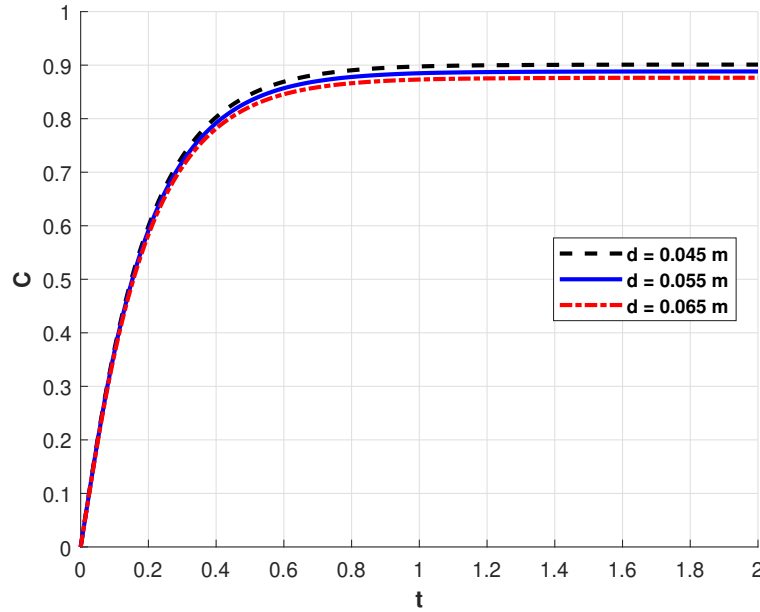


Figure 5.7: Concentration profile of drug-coated magnetic nanoparticles at $z = 0.5$ for different tumor-magnet distance parameters, d

d	Saturation Concentration value, C_s	Time to reach C_s
0.045	0.8902	1.70
0.055	0.8886	1.79
0.065	0.8878	1.81

Table 5.4: Saturated concentration and time to reach the saturated concentration for different values of tumor-magnet distance parameters, d .

shows the effect of tumor-magnet distance on drug-coated magnetic carrier particle concentrations. With increase in the tumor-magnet distance reduces the drug carrier concentrations. Therefore, when the magnet is placed away from the body, the carrier particles are not easily captured at the tumor location. Table 5.4 shows saturation concentration values and the time to reach the saturation concentration of carrier particles. It shows that the time to react the saturated concentration in the microvessel along the channel decreases with an increase in the tumor-magnet distance, as it weaker the strength of the magnetic field between the drug carrier and magnet. For the same reason, it takes more time to reach the saturation point. Therefore, this suggests that it is better to keep the magnet near to the tumor position for better results.

5.4.4 The effect of permeability of capillary

The permeability of the capillaries varies significantly with the location of the capillaries from organ to organ and is written in ascending order as Brain, Skin, Skeletal muscle, Lung, Heart, and Glomerulus in kidney [131, 132]. In this study, we consider a range of permeability of the microvessel, where the effect of permeability of the capillary on the dispersion of drug-coated magnetic nanoparticle concentrations along the microvessels axis is graphically shown in Fig 5.8 and 5.9. The value of the parameters considered as $\beta_{vf} = 0.6$, $d = 0.055$, $M_s = 1 \times 10^6$, $Pe = 3.0$, $\lambda_1 = 0.10$, $\lambda_2 = 0.8$, and $a = 200$ nm. Fig.5.8 shows the distribution of fluid pressure along the microvessel axis. It's evident that at a flexural point when $p = 1$, a zero pressure gradient is predicted. The pressure gradient has a direct effect on the magnitude of the interstitial fluid flow. Nearby the pressure flexural point, the longitudinal average fluid velocity is minimum. The minimum decreases significantly with the permeability of the capillary wall and may lead to zero, to prevent flow, as also observed in [131, 141]. Further, observed that as the permeability of capillary increases, the nanoparticle concentrations increase (see Fig 5.9). The drug carrier concentration increases with increase in the permeability parameters and this phenomena more supportive in the tumor region as the permeability of the tumor region is higher than the normal healthy region. Moreover, the time to reach the saturation concentration of drug-coated magnetic nanoparticles in the microvessel along the channel increases with an increase in the permeability of the capillary, as clearly shown in Table 5.5. This because with an increase in the permeability, the perfusing fluid velocity through the inner wall of the microvessel increases. It is noted that the blood flows towards the capillary wall, supported the movement of carrier particles towards the blood wall, mainly where the tumor is located. The higher permeability has been correlated with higher tumor grade and shown to decrease in response to antiangiogenic therapy with decreased tumor growth predicting tumor response. This is an indication that the probability of the carrier particle being captured at the tumor location increases with the increase in permeability of the capillary.

Γ	Saturation Concentration value, C_s	Time to reach C_s
3	0.8581	1.77
5	0.8886	1.79
7	0.9022	1.84

Table 5.5: Saturated concentration and time to reach the saturated concentration for different permeability parameters, Γ .

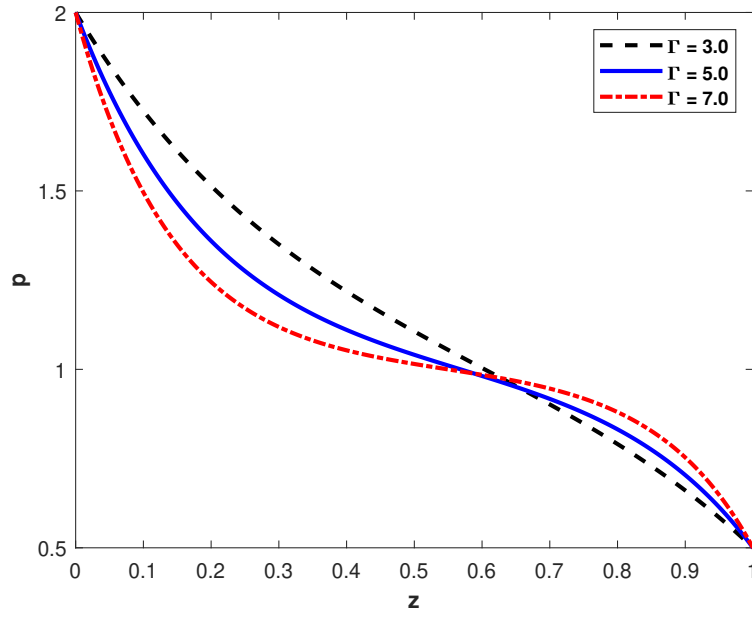


Figure 5.8: Pressure distribution along the microvessel for different permeability parameters Γ .

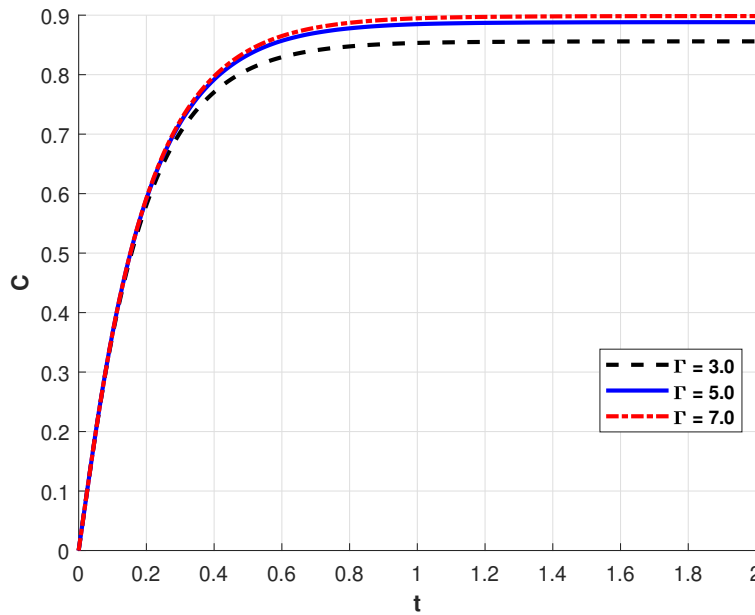


Figure 5.9: Concentration profile of drug-coated magnetic nanoparticles at $z = 0.5$ for different permeability parameters, Γ .

5.4.5 The effect of Peclet number

The effect of the Peclet number is shown in Fig 5.10, and Table 5.6. The Peclet number measures the relative importance of convective flow to diffusive flow, where a small Peclet number ($Pe < 1$) indicates diffusion effects dominate convective transport, while the reverse is generally true for a large number Peclet number ($Pe > 1$). Herein,

we set $\beta_{vf} = 0.6$, $d = 0.055$, $M_s = 1 \times 10^6$, $Pe = 3.0$, $\lambda_1 = 0.10$, $\lambda_2 = 0.8$, and $a = 200$ nm. Peclet number defines a ratio between the advective transport rate with the diffusion transport rate. From Fig 5.10, we observe that with an increase in the Peclet number, the solute transport rate boosts up. Furthermore, the saturated concentration and time to reach the saturated concentration in the microvessel along the channel increases with an increase in the Peclet number, as shown in Table 5.6.

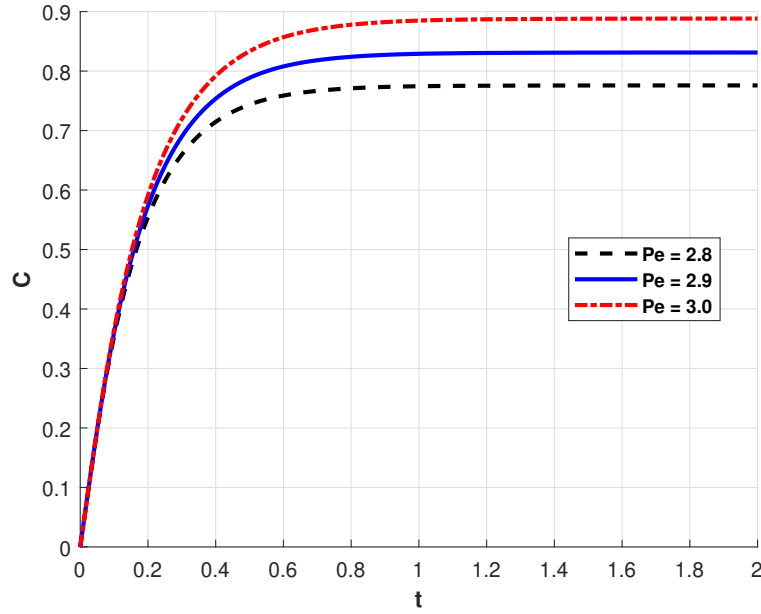


Figure 5.10: Concentration profile of drug-coated magnetic nanoparticles at $z = 0.5$ for different Peclet number, Pe .

Pe	Saturation Concentration value, C_s	Time to reach C_s
2.8	0.7761	1.58
2.9	0.8315	1.71
3.0	0.8886	1.79

Table 5.6: Saturated concentration and time to reach the saturated concentration for different Peclet number, Pe .

5.4.6 The effect of drug elimination parameter

Drug elimination refers to the irreversible removal of a drug or its metabolites from the body. The chief organ involved is the liver, although the gastrointestinal tract, kidney, lung, and skin may also contain drug-metabolizing enzymes and may contribute to regional concentrations of the drug and the metabolites. Drug intake into and distribution within the body must be balanced with elimination so that adequate concentrations can be achieved at receptor sites. Fig 5.11 shows the effect of the drug

elimination parameter for $\beta_{vf} = 0.6, d = 0.055, M_s = 1 \times 10^6, Pe = 3.0, \lambda_2 = 0.8$, and $a = 200$ nm. It observes that decreasing the drug elimination parameter increases drug carrier concentrations. Drug metabolites enzyme boost up the drug release from the drug carrier at the tumor region. Hence, naturally, it took less time to reach the saturation concentration. Hence, the concentration of the solute enhanced with increase in the drug elimination parameters. Further, it takes less time to reach the concentration point with increase the drug elimination parameters as observed in Table 5.7.

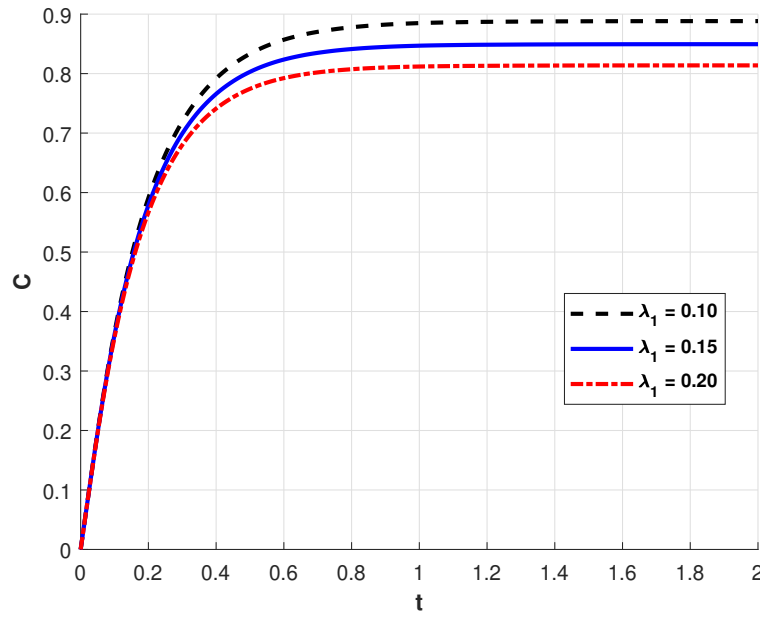


Figure 5.11: Concentration profile of drug-coated magnetic nanoparticles at $z = 0.5$ for different drug elimination parameter, λ_1 .

λ_1	Saturation Concentration value, C_s	Time to reach C_s
0.10	0.8886	1.79
0.15	0.8498	1.73
0.20	0.8141	1.56

Table 5.7: Saturated concentration and time to reach the saturated concentration for different drug elimination parameter λ_1 .

5.4.7 The effect of source term parameter

The source term required an addition of vascular, lymphatic, and cellular contributions. The effect of the source term parameter is shown by Fig 5.12, with $\beta_{vf} = 0.6, d = 0.055$ m, $\Gamma = 3.0, Pe = 3.0$, and $\lambda_1 = 0.10$. It observed that the drug carrier concentration is higher for larger value of the source term.

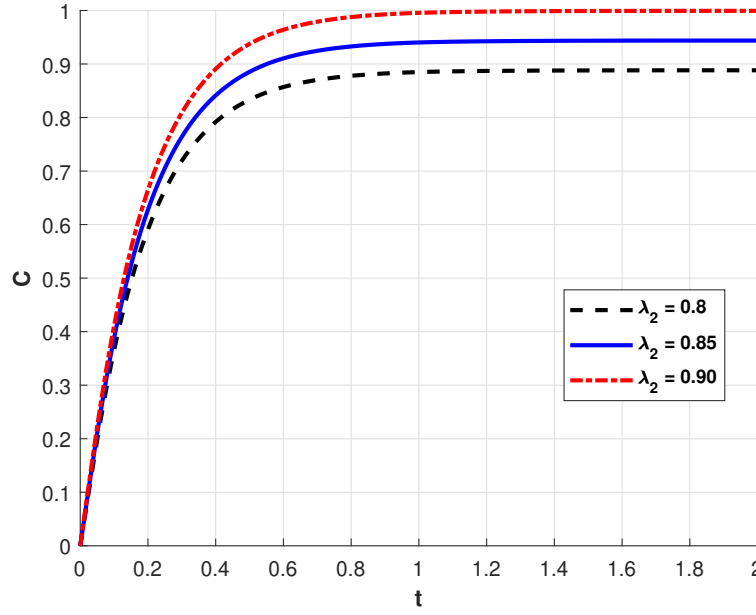


Figure 5.12: Concentration profile of drug-coated magnetic nanoparticles at $z = 0.5$ for different source term parameter, λ_2

λ_2	Saturation Concentration value, C_s	Time to reach C_s
0.80	0.8886	1.79
0.85	0.9441	1.69
0.90	0.9996	1.62

Table 5.8: Saturated concentration and time to reach the saturated concentration for different source term parameter, λ_2 .

The drug carrier concentration boost up with increase in the source term parameter and manage to reach the higher saturation concentration. It helps to reach drug carrier quickly at the saturation position and took less time to reach the saturation point as depicted in Table 5.8.

5.4.8 The effect of radius of nanoparticle

The effect of the nanoparticle radius on the dispersion of drug-coated magnetic nanoparticle concentrations along the microvessels is shown in Figure 5.13 and Table 5.9, where $\beta_{vf} = 0.6$, $M_s = 1 \times 10^6$, $d = 0.055$ m, $\Gamma = 3.0$, $Pe = 3.0$, $\lambda_1 = 0.10$, and $\lambda_2 = 0.8$. Figure 5.13 shows that a smaller radius of the nanoparticle may increase the drug carrier concentrations. In addition, Table 5.9 clearly shows that the drug carriers quickly reach the saturation point as we decrease the radius of the nanoparticle. Several experimental studies [142, 143, 144] validate that the smaller the nanoparticle size, the higher the likelihood of penetrating the tumor. This indicates that the smaller particles improve the distribution and tumor accumulation of cancer drugs.

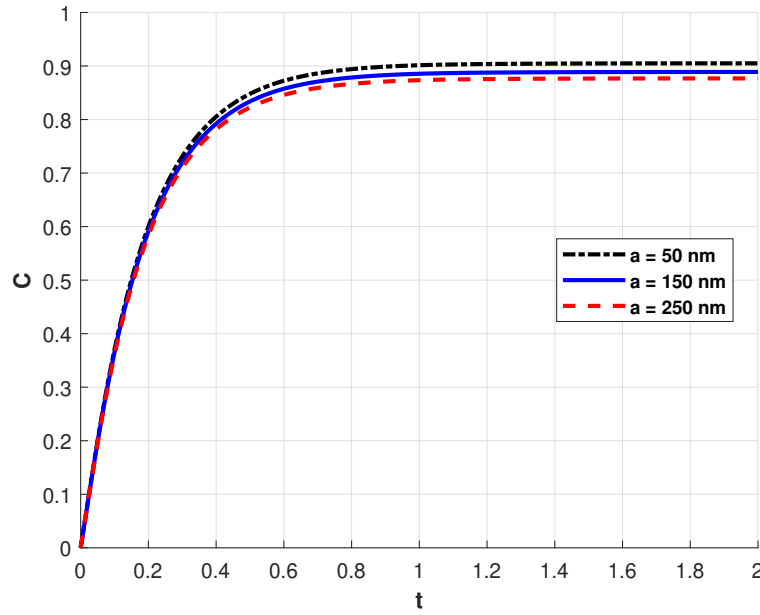


Figure 5.13: Concentration profile of drug-coated magnetic nanoparticles at $z = 0.5$ for different radius of nanoparticle, a

a	Saturation Concentration value, C_s	Time to reach C_s
250	0.8882	1.82
150	0.8892	1.79
50	0.8942	1.67

Table 5.9: Saturated concentration and time to reach the saturated concentration for different radius of nanoparticle, a .

5.5 Conclusion

In the present study, a mathematical model on magnetic drug targeting is developed, to predict the capture conditions on the effective dispersion of drug-coated nanoparticles concentration in the tumor position. Notable, the effects of different governing parameters such as volume fraction of nanoparticle, magnetization, tumor-magnet distance, permeability of capillary, Peclet number, drug elimination, source term, and radius of nanoparticle on the dispersion of drug carrier concentration are discussed. To verify the accuracy of the numerical model, several related experimental observations that have been done are in accordance with our current model results. The following general concluding remarks can be drawn from the present study:

- With increase in the volume fraction of the magnetic particles, the magnetization of the external magnet, the permeability of the microvessel, Peclet number, and the source term increases the concentration of drug-nanoparticles in the solid tumor position.

- Decrease in the tumor-magnetic distance, the drug elimination, and the radius of nanoparticle leads to an increase in drug-coated nanoparticle concentration.
- The higher volume fraction of the magnetic particles, the magnetization of the magnet, the drug elimination, and the source term leading to fast drug-coated magnetic nanoparticles reach the tumor position
- Increasing the tumor-magnetic distance, the permeability of the microvessel, the Peclet number, and the radius of nanoparticle slower the drug-coated magnetic nanoparticles to the tumor position.

Thus, the present study can be of particular consequence on understanding the qualitative aspects of magnetic drug targeting in a microvessel, especially on the effective dispersion of drug-coated nanoparticles towards the tumor position. Different design maps can be drawn by considering the effects of governing parameters offering a tool for tailoring the capture conditions of carrier particles and the effective longitudinal dispersion of drug carriers, which can be considered as a potential approach for clinical application during magnetic drug targets.

6. Shear induced fractionalized dispersion during Magnetic Drug Targeting in a permeable microvessel

6.1 Introduction

Cancer is one of the world's top public health concerns, accounting for 10 million fatalities each year as of 2020 [1]. The majority of these deaths and cases observed in non-developed countries [1, 145]. Recent statistics show that solid tumors account for 85% of human cancer. The environment around a tumor includes environmental parameters leading to reduced microvascular density, compression of blood and lymphatic microvessels, an irregular flow phenomena and an unstructured microvascular network results in an unusual extracellular matrix structure in the region with up-raised interstitial fluid pressure. These give a significant impact to several interstitial barriers and preventing the mechanisms of drug delivery. Currently, chemotherapy, targeted therapy, radiation therapy, surgery, or immunotherapy are the common traditional tumor treatments. Although chemotherapy is effective for some tumors, it is limited by poor specificity and often cannot cross the blood-spinal barrier. Due to their toxicity and widespread distribution throughout the body, therapeutic drugs administered intravenously can also have harmful side effects on healthy cells due to the general systemic distribution of chemo drugs.

The magnetic drug delivery method is one of the promising methods for targeting drugs to the tumor site. It is essential in overcoming deficiencies and providing control to release the high concentrations of drugs to selected areas of the body while minimizing side effects [26]. So far, the US Food and Drug Administration has approved five nano-carriers, international agencies have approved four, and several are in clinical investigation and development [146]. The therapy involves the carrier particles that are coated with magnetic nanoparticles (MNPs) along with the therapeutic drugs and then systemically administered into the human body. To capture charge-carrying particles at the tumor location, a magnetic field is positioned near the tumor site outside the body surface. Due to recent advancements in carrier particles designed to target particular regions of malignant tissue and local tumor healing, magnetic drug targeting

is gaining prominence [117, 118]. The theoretical results [147, 148, 149] on this new magnetic drug targeting method have been very positive so far. Targeting cytotoxic agents at tumor cells allows the delivery of higher localized drug doses while reducing the dose in non-target areas [149]. The goal of magnetic drug targeting is to maximize the effectiveness of the magnetic nanoparticles by guiding them to reach the larger vessels of the human body at deeper tissues with an external magnetic field [147]. The process of administering macromolecules and the transportation of nanoparticles in biomedical applications systematically varies depending on vessels' properties, sizes, and shapes.

Unlike other tissues, blood is a multi-phase solution consisting of corpuscles components (such as red blood cells, white blood cells, and platelets) suspended in a fluid plasma consisting of organic molecules, proteins, and minerals [150]. Due to the high volume fraction of rheological properties of blood such as RBCs aggregation, haematocrit, and deformability lead to cell-free layer formation at the wall, which depends on the diameter of the vessel and flow rate [151, 152, 153, 154]. The authors in [155] conducted a study on the rheology of blood under varying concentrations of haematocrit, plasma proteins, and low shear rates. The authors observed decay in the viscosity with the shear rate as a result of cell-protein interactions. Apostolidis *et al.* [156], undertook a systematic investigation on the blood rheology in steady-state shear flow and found that yield stress occurs only when the haematocrit exceeds a critical value, which is determined by fibrinogen concentration. Using seven different animal species, the authors in [157] present detailed measurements of the rheology of blood under uniform conditions to those used previously to investigate human blood, including steady-state and various shear transients.

Through computational fluid dynamics, the whole process of drug delivery and absorption can be modelled and illustrated. In conjunction with clinical research, mathematical models and numerical simulations help develop a deeper understanding of drug delivery processes, enhance treatment efficacy, and identify how physiological factors influence solid tumor behaviour. Baxter and Jain [44, 45, 46, 47, 158] pioneered the investigation of the effect of various tumor characteristics on medication delivery using mathematical models, employing fluid mechanics concepts to explore elevated interstitial fluid pressure, substantial interstitial fluid flow, and concentration. Sheikholeslami and Ellahi [159] used Lattice Boltzmann Method (LBM) to investigate the influence of a spatially varying magnetic field on Fe_3O_4 - plasma nanofluid flow in a vessel as a targeted drug delivery system. According to their study, the skin friction coefficient is a decreasing function of the Reynolds number and magnetic number. In another study, Sohail *et al.* [160] used a computational approach to anal-

use the flow of ferroliquid during magnetic drug targeting. Over the past couple of decades, several computational studies have been conducted on drug targeting (see [161, 162, 163, 120, 121, 123, 122, 124, 164, 165]). The authors of all these studies, among others, attempted to explain numerous vital aspects of effective drug administration, including elevated interstitial fluid pressure in the tumor region, distribution of drug concentration in healthy and tumor tissues, drug penetration, and identification of the useful parameters.

Due to the high heterogeneity and the very long spatial autocorrelation, solute transport in microvessels have a high level of transitions between flow-limited and diffusion-limited transport [166]. In cases where transition probabilities follow a power law, it is better to model solute transport in microvessels by using fractional advection-dispersion equation [167]. Time nonlocal modelling, which includes time-fractional advection-dispersion equations, can effectively model the transport process and distinct particle status [168]. Furthermore, fractional-order derivative describes slow relaxation processes characterized by stretched power-law response function [70]. In recent years, the theory of fractional calculus has proved to be a useful tool in describing many real-world phenomena in various areas of science and engineering, where nonlocality is essential (see for instance [169, 170, 93, 171, 61, 62, 63]). Traditionally, the fractional-order operator has been defined as an extension of an ordinary order operator, in which the order is defined for an arbitrary real number. In addition, the fractional-order approach provides a reliable mechanism that accounts for the memory exhibited by the processes. As a consequence, fractional operators are used to model biophysics, bio-rheology, travelling wave solutions, astrophysics, electromagnetism, thermodynamics, plasma physics, and optics [68]. The study by Shah *et al.* [61] examined the flow of blood with magnetic particles through a cylindrical tube using the time fractional-order derivative of Caputo type. To demonstrate the difference between fractional-order time derivatives and integer-order derivatives, the authors in [62] used a Casson fluid model. As they used blood as a Casson fluid, their model results showed that fractional-order derivatives resulted in a remarkably different result than the ordinary derivative. To study the capture effectiveness of magnetic nanoparticles adhered to therapeutic compounds injected into the bloodstream which are controlled by an external magnetic field, Maiti *et al.* [63] used a thermo-solutal transport model with Caputo-Fabrizio fractional-order derivative.

In this work, we look at the capture conditions and efficient dispersion of spherical carrier particles during magnetic drugs delivery to tumor locations in the microvascular system using Caputo fractional derivative. We suppose that a magnetic drug carrier that incorporates magnetic particle impacts on fluid characteristics is comparable to

blood. Furthermore, we assumed that in nanoparticle transport, the effective diffusion coefficient depends on the permeability of the capillaries and the rheology of the blood. Casson flow velocity, magnetic force-created velocity, and solute transport equations are simultaneously solved to examine the impact of model biological factors on drug-coated nanoparticle dispersion in microvessels.

6.2 The Governing Equation

Our study examines how spherical carrier particles disperse in the microvascular system during magnetic targeting of drugs to tumor sites. In this section, we propose the equations that govern Casson flow velocity, magnetic force-created velocity, and solute transportation. The schematic diagram of the problem is shown in Fig. 6.1. The blood vessel is assumed to be cylindrical. The z -axis is considered as the axis of the blood vessel and r -axis in radial direction.

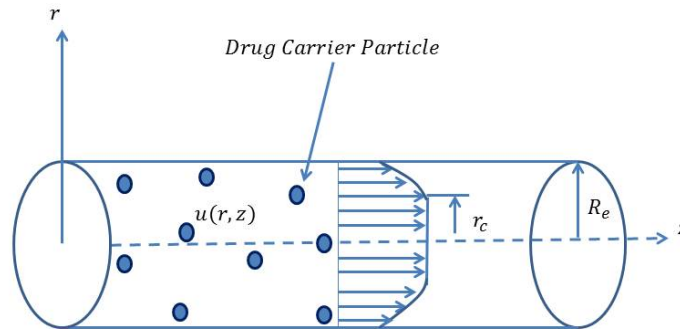


Figure 6.1: Nanoparticle trajectories in a capillary with Carson velocity profile.

6.2.1 Velocity profile for Casson fluid

Assuming that the lateral flow of the fluid across the permeable wall only affects the flow rate, due to the conservation of mass, it is expected that the average velocity U decreasing along the vessel wall. In Casson fluid, the mean velocity profile is described by the piecewise relation [135]

$$U(r) = -\frac{R_e^2}{4\eta} \frac{d\bar{p}}{d\bar{z}} \times \begin{cases} 1 - \frac{8}{3}\xi^{\frac{1}{2}} + 2\xi - \frac{1}{3}\xi^2 & \text{for } r < r_c, \\ 1 - \left(\frac{r}{R_e}\right)^2 - \frac{3}{8}\left(1 - \left(\frac{r}{R_e}\right)^{\frac{3}{2}}\right)\xi^{\frac{1}{2}} + 2\left(1 - \left(\frac{r}{R_e}\right)\right)\xi & \text{for } r > r_c, \end{cases} \quad (6.1)$$

where $\xi = \frac{r_c}{R_e}$, is the rheological parameters which represent a ratio between the plug radius r_c and the radius of the vessel R_e . The corresponding flow rate Q is calculated as [172]

$$Q = -\frac{\pi R_e^4}{8\eta} \frac{d\bar{p}}{d\bar{z}} A(\xi), \quad (6.2)$$

where,

$$A(\xi) = 1 - \frac{16}{7}\sqrt{\xi} + \frac{4}{3}\xi - \frac{1}{21}\xi^4.$$

From Eq. (6.2), the mean fluid velocity is given by

$$U_i = \frac{Q}{\pi R_e^2} = -\frac{1}{8\eta} \frac{d\bar{p}}{d\bar{z}} R_e^2 A(\xi). \quad (6.3)$$

We further note that the term $A(\xi)$ tends to 1 as ξ approaches zero, which physically represents the classic Poiseuille relations for $u(r)$ and Q . Similarly, for $\xi = 1$, the average velocity of the fluid U decreases to zero. In this case, no deformation of the flow occurs, as the yield stress of the fluid is not overcome by the pressure drop along the capillary. As a result of the mathematical properties of blood, near the wall of the cylindrical vessel a layer of plasma or low haematocrit region develops, and a high concentration layer of red blood cells generates near the central axis. Viscosity appears to be significantly reduced when the cells are depleted. The apparent viscosity of blood depends on the diameter of the vessel and the haematocrit, as validated experimentally by the following theoretical formula [116, 128, 129, 130, 164].

$$\eta = \eta_{plasma} \left[1 + (\eta_{0.45} - 1) \frac{(1 - H_D)^C - 1}{(1 - 0.45)^C - 1} \left(\frac{D}{D - 1.1} \right)^2 \right] \times \left(\frac{D}{D - 1.1} \right)^2,$$

where

$$\eta_{0.45} = 6e^{-0.085D} + 3.2 - 2.44e^{-0.06D^{0.645}}, \text{ and}$$

$$C = (0.8 + e^{-0.075D}) \left(-1 + \frac{1}{1 + 10^{-11} \cdot D^{12}} \right) + \frac{1}{1 + 10^{-11} D^{12}},$$

such that η is the apparent blood viscosity, η_{plasma} is the blood plasma viscosity, $\eta_{0.45}$ is the relative apparent viscosity of the blood for fixed discharge haematocrit of 45%, D is the vessel diameter in micrometers and H_D is the discharge haematocrit of 39%.

The mass continuity equation can be written as

$$\frac{\partial Q}{\partial \bar{z}} + V_p \lambda_p = 0, \quad (6.4)$$

where Q is the flow rate, and $V_p \lambda_p$ denotes the volume flow rate along the permeable wall per unit length, such that $\lambda_p = 2\pi R$ is the perimeter of the permeable microvessel. Employing Darcy's law [131, 135], the perfusing velocity, V_p is given as

$$V_p = -L_p(\pi_i - p); \quad L_p = \frac{k}{\eta \delta},$$

L_p is the vascular hydraulic conductivity that is given in terms of thickness δ , permeability of the microvessel wall k , and the effective viscosity of the fluid η , the interstitial fluid pressure π_i , and the local mean value of the vascular pressure p , can be written in the non-dimensional form as

$$-\frac{\pi R_e^4}{8\eta} \frac{d^2 \bar{p}}{d\bar{z}^2} - L_p(\pi_i - \bar{p})\lambda_p = 0, \quad (6.5)$$

where $\bar{p}$ the vascular pressure, and with non-dimensional parameters are defined as

$$z = \frac{\bar{z}}{l}, \quad \text{and} \quad \Omega = \frac{\bar{p}_0 - \pi_i}{\bar{p}_1 - \pi_i} = \frac{p_0 - 1}{p_1 - 1},$$

such that

$$p = \frac{\bar{p}}{\pi_i},$$

p_0 and p_1 are inlet and outlet pressure respectively. The vascular dimensionless pressure distribution along the channel is derived as

$$p(\xi, \Gamma, z, \Omega) = (p_1 - 1)\Omega \cosh(\Gamma(\xi)z) + \frac{(p_1 - 1)(1 - \Omega \cosh(\Gamma(\xi)))}{\sinh(\Gamma(\xi))} \times \sinh(\Gamma(\xi)z) + 1, \quad (6.6)$$

together with the permeability parameter $\Gamma(\xi)$ given by

$$\Gamma(\xi) = \frac{4l}{R_e} \sqrt{\frac{\eta}{R_e} L_p} \frac{1}{A(\xi)} = \frac{\Pi}{\sqrt{A(\xi)}}.$$

Combining Equations (6.3) and (6.6), the mean Casson flow velocity in a permeable capillary can be obtained as

$$U_i(\xi, \Gamma, \Omega, z) = \cosh(z\Gamma(\xi)) - \frac{\Omega \cosh(\Gamma(\xi) - z\Gamma(\xi))}{1 - \Omega \cosh(\Gamma(\xi))} U_{i_0}, \quad (6.7)$$

where

$$U_{i_0} = \frac{[(p_1 - 1) - (\Omega(p_1 - 1)) \cosh(\Gamma(\xi))] \cosh(\Gamma(\xi)) \pi R_e^2}{8\eta l} \times \Gamma(\xi) A(\xi), \quad (6.8)$$

is the mean velocity at the capillary inlet $z = 0$.

6.2.2 Magnetic force influenced velocity

Therapeutic drugs adhere to magnetic nanoparticles, offering an alternative to controlling them externally with magnetic forces. Additionally, a magnetic nanoparticle and a carrier particle are considered spherical [53, 57, 164]. According to our model, the N_{mnp} magnetic nanoparticles ingrained in the carrier particles are subjected to total magnetic forces, which depend directly on the magnetic field and the gradient of the surrounding field [133, 164]. The magnetic force is thus given by

$$f_m = \mu_0 N_{mnp} V_{mnp} \frac{\mathcal{X}}{1 + \frac{\mathcal{X}}{3}} (\mathbf{H}_a \cdot \nabla) \mathbf{H}_a,$$

where $V_{mnp} = \frac{4}{3}\pi a^3$ is the volume of magnetic nanoparticle with a radius of the magnetic nanoparticle a , $\mathbf{H}_a$ is the applied magnetic field intensity at the centre of a carrier particle, $\mathcal{X}$ is the magnetic susceptibility of magnetic nanoparticles, and μ_0 is the permeability of the magnetic particles. Moreover, the susceptibility of the blood much lower than magnetic susceptibility of the magnetized particles and these phenomena allows the magnetic nanoparticle embedded drug carriers to travel with upstream where the impact of the magnetic field and force are not significant, and the distance between the magnet and the microvessel is very large [164, 133]. Employing all the above assumptions, the resulting magnetic force f_m is given by

$$f_m = 3\mu_0 N_{mnp} V_{mnp} M_s^2 R_{mag}^4 \frac{1}{2[d^2 + z^2]^{\frac{5}{2}}}, \quad (6.9)$$

such that M_s is the magnetization of the magnet, R_{mag} is the radius of the magnet, d is the magnetic-tumor distance, and z is the position of the particle at the z -axis. We note that the carrier particle contains the β_{vf} volume fraction of magnetic nanoparticles, the total amount of nanoparticles present in the carrier particle is $N_{mnp} V_{mnp}$ is represented in terms of a volume fraction, $\beta_{vf} V_{cp}$ of the carrier particle [116, 133, 164]. Now, applying the magnetic force to the stokes drag force $f_m = (6\pi a \eta) U_e$, we derive the magnetic force created velocity U_e given as [164]

$$U_e = \frac{3\mu_0 \beta_{vf} V_{cp} M_s^2 R_{mag}^4}{12\pi a \eta} \frac{1}{[d^2 + z^2]^{\frac{5}{2}}}, \quad (6.10)$$

where η is the dynamic viscosity of the interstitial fluid and a is the radius of the magnetic nanoparticles.

6.2.3 Solute transport

Following [164], solute dispersion in a cylindrical capillary is described by the generalized advection-diffusion equation

$$\frac{\partial \bar{C}}{\partial \bar{t}} + \bar{u} \frac{\partial \bar{C}}{\partial \bar{z}} = \frac{D}{\bar{r}} \frac{\partial}{\partial \bar{r}} \left(\bar{r} \frac{\partial \bar{C}}{\partial \bar{r}} \right) + D \frac{\partial^2 \bar{C}}{\partial \bar{z}^2} - \bar{\lambda}_1 \bar{C} + \bar{\lambda}_2 \quad (6.11)$$

where $\bar{C}(\bar{t}, \bar{r}, \bar{z})$ is the solute concentration, $\bar{u}$ is the velocity of the magnetic nanoparticles which is the sum of interstitial fluid mean velocity and the magnetic force created velocity, and D is the effective diffusion coefficient of magnetic nanoparticles in the tissues. The term $\bar{\lambda}_1$ in Eq. (6.11) describe the drug elimination from the tissue, and $\bar{\lambda}_2$ is the source term that summing the vascular, lymphatic, and cellular contributions [53]. Using the dimensionless variables

$$C = \frac{\bar{C}}{C_0}, \quad u = \frac{\bar{u}}{u_0}, \quad t = \frac{\bar{t}D}{R^2}, \quad Pe = \frac{u_0 R}{D}, \quad D = \frac{\eta u_0}{\pi_i}, \quad \lambda_1 = \frac{\bar{\lambda}_1 R^2}{D}, \quad \text{and}, \quad \lambda_2 = \frac{\bar{\lambda}_2 R^2}{C_0 D},$$

then Eq. (6.11) can be written in dimensionless form as

$$\frac{\partial C}{\partial t} + u \frac{\partial C}{\partial z} = \frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial C}{\partial r} \right) + \frac{1}{Pe^2} \frac{\partial^2 C}{\partial z^2} - \lambda_1 C + \lambda_2. \quad (6.12)$$

where $u = U_i + U_e$ is the velocity of the magnetic nanoparticles which is the sum of mean Casson flow velocity U_i , and the magnetic force created velocity U_e . The non-dimensional parameter Pe is the Peclet number, λ_1 is the drug elimination, and λ_2 is the source term. The corresponding transformed model from the ordinary time derivative to Caputo fractional time derivative of the equation (6.12), gives

$$\frac{\partial^\alpha C}{\partial t^\alpha} + u \frac{\partial C}{\partial z} = \frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial C}{\partial r} \right) + \frac{1}{Pe^2} \frac{\partial^2 C}{\partial z^2} - \lambda_1 C + \lambda_2, \quad (6.13)$$

where the time derivative operator of Caputo fractional derivative given by [65, 84, 173]

$$\frac{\partial^\alpha C(t, r, z)}{\partial t^\alpha} = \begin{cases} \frac{1}{\Gamma(1-\alpha)} \int_0^t \frac{\partial C(\iota, r, z)}{\partial \iota} \frac{d\iota}{(t-\iota)^\alpha}, & 0 < \alpha < 1, \\ \frac{\partial C(t, r, z)}{\partial t}, & \alpha = 1, \end{cases} \quad (6.14)$$

with α being the fractional-order parameter. In our study, we assume that the radius of blood vessel is very smaller than the length of blood vessel. Hence, we have considered

an average velocity at the radial direction and the dispersion of drug particle is uniform along radial axis (r) and is a function of z and t . As a result, the modified mass transport equation is

$$\frac{\partial^\alpha C}{\partial t} + u \frac{\partial C}{\partial z} = \frac{1}{Pe^2} \frac{\partial^2 C}{\partial z^2} - \lambda_1 C + \lambda_2, \quad (6.15)$$

together with initial and boundary conditions

$$C = 0 \quad \text{for} \quad t = 0, \quad (6.16a)$$

$$C = \frac{\partial C}{\partial z} = 0 \quad \text{for} \quad z = \pm\infty. \quad (6.16b)$$

where equation (6.16a) describes the initial condition at time $t = 0$, such that there is an absence of the drug-coated magnetic nanoparticles in the domain, and Eq. (6.16b) describes the open boundary condition that applied to establish mass transport across boundaries where both convection flow and outflow occur.

6.3 Numerical scheme

The governing solute transport equation (6.15) is solved using the finite difference method adapting a standard explicit forward-time centred-space (FTCS) scheme [174, 175, 173], we applied MATLAB to solve the computational problem. The analytical results, for total fluid velocity u , were used for the transient advection-diffusion equation of drug transport. As a result, the transient equation of drug transport (6.15) is discretized with time-space τ and grid spacing of h , where the discretization concentration, $C(t, z)$ is written as $C(t_n, z_i) = C_i^n$.

$$z_i = ih, \quad t_n = n\tau, \quad i = 1, 2, 3, \dots, n_z; \quad n = 1, 2, 3, \dots, n_t \quad (6.17)$$

where

$$h = \frac{L_z}{n_z}, \quad \text{and} \quad \tau = \frac{T}{n_t}, \quad 0 \leq z \leq L_z \quad \text{and} \quad 0 \leq t \leq T. \quad (6.18)$$

An explicit finite difference representation of the transient advection-diffusion equation of drug transport can be obtained by a FTCS difference scheme as

$$\frac{\tau^{-\alpha}}{\Gamma(2-\alpha)} \sum_{j=0}^n b_j^\alpha (C_i^{n-j+1} - C_i^{n-j}) + u_i^n \frac{C_{i+1}^n - C_{i-1}^n}{h} = \frac{1}{Pe^2} \frac{C_{i+1}^n - 2C_i^n + C_{i-1}^n}{h^2} - \lambda_1 C_i^n + \lambda_2, \quad (6.19)$$

where

$$b_j^\alpha = (j+1)^{1-\alpha} - j^{1-\alpha}.$$

Then Eq. (6.19) gives

$$C_i^{n+1} = b_n C_i^0 + \sum_{j=0}^{n-1} (b_j - b_{j+1}) C_i^{n-j} - a_1 u_i^n (C_{i+1}^n - C_{i-1}^n) + a_2 (C_{i+1}^n - 2C_i^n + C_{i-1}^n) - a_3 C_i^n + a_4, \quad (6.20)$$

where

$$\begin{aligned} a_1 &= \frac{\tau^\alpha \Gamma(2 - \alpha)}{2h}, \quad a_2 = \frac{\tau^\alpha \Gamma(2 - \alpha)}{Pe^2 h^2}, \\ a_3 &= \tau^\alpha \Gamma(2 - \alpha) \lambda_1 \quad \text{and} \quad a_4 = \tau^\alpha \Gamma(2 - \alpha) \lambda_2. \end{aligned}$$

In terms of the approximate values C_{i+1}^n , C_i^n , and C_{i-1}^n at time level n , the Eq. (6.20) expresses the approximate value C_i^{n+1} at time level $(n + 1)$ explicitly. To compute the concentration of drug-coated nanoparticles, the mesh grid size for the axial direction was $h = 0.01$ as the step size, and the time step chosen to be $\tau = 0.001$. The results were observed to converge with the accuracy of order 10^{-6} , with the stability criteria being $\max\left(\frac{\tau}{h^2}\right) \leq 0.5$.

6.4 Numerical Results and Discussion

In this section, the rate of penetration of drug-coated nanoparticles concentration at the tumor tissue site is evaluated numerically. For all the computations of this study, we assumed that the inlet pressure, $p_0 = 2$ [131]; outlet pressure, $p_1 = 0.5$ [131]; radius of the magnet, $R_{mag} = 0.03m$ [131, 133]; magnetic permeability, $\mu_0 = 4\pi \times 10^{-7} NA^{-2}$ [53, 57]; dynamic viscosity, $\eta = 1.12 \times 10^{-3} \text{ Pa s}$ [53]; Peclet number, $Pe = 3$ [131]. In this regard, Figs. 6.2 - 6.10 show numerical results, where the effect of fractional-order parameter and different governing parameters on concentration of the drug-coated magnetic carrier are graphically shown, and the saturation concentration and time to reach saturation concentration are shown in Table 6.1.

In Fig. 6.2, the impact of the memory effect on the concentration of the drug-coated carrier is explored. The time-memory is incorporated in the mathematical model to using the fractional-order derivatives. It describes the history of the movement of the drug carriers (dispersion) in the system towards the diseased region. Lower dependency of the flow of particles in previous states is associated with faster movement of the drug particles in the blood stream, hence reaching the diseased region in a shorter time. Furthermore, it observed that the drug concentration is an increasing function of time. Initially the concentration smoothly increasing with time and then gradually converges to a saturation value after some time. After reaching the satu-

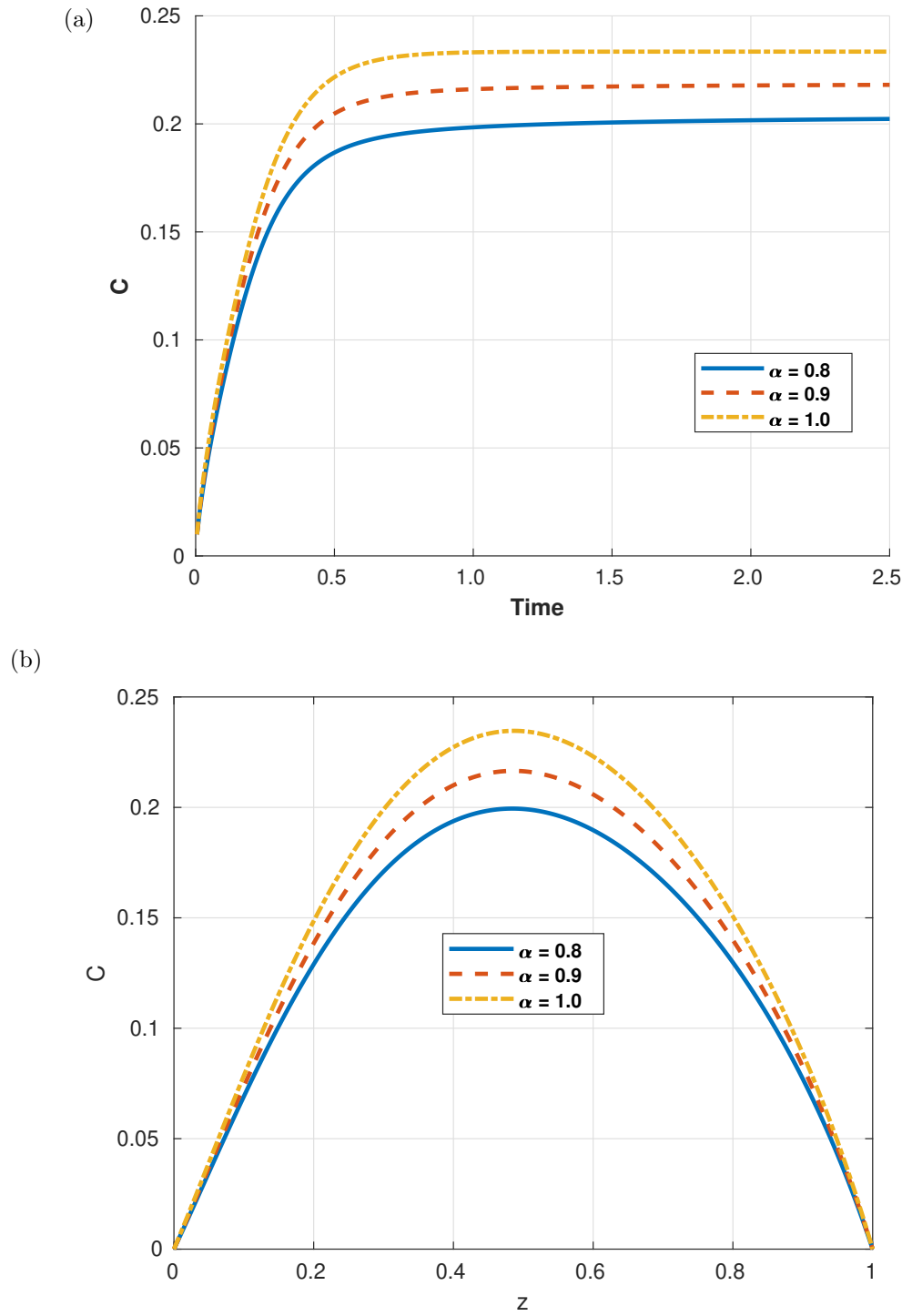


Figure 6.2: The variation of drug carriers concentration with different values of the fractional-order parameter, α , when $\xi = 0.45$, $\Pi = 2.0$, $M_s = 1 \times 10^6$, $\beta_{vf} = 0.6$, $d = 0.05m$, $a = 100nm$, $\lambda_1 = 0.008$, and $\lambda_2 = 0.10$.

ration point, a higher decay of the drug is observed, resulting in a reduction in the concentration. Furthermore, it is clearly shown in Table 6.1, that the variation of fractional-order parameter, α affects the solute concentration significantly, such as the memory effect that accelerates drug-coated magnetic nanoparticles in the capillaries

Parameter	Value	Saturation concentration, C_s	Time to reach C_s
α	0.8	0.2023	2.370
	0.9	0.2181	2.255
	1.0	0.2334	1.075
ξ	0.450	0.2334	1.075
	0.475	0.2412	1.015
	0.500	0.2510	0.910
β_{vf}	0.4	0.2151	1.360
	0.6	0.2334	1.075
	0.8	0.2433	0.920
d	0.045	0.2474	0.680
	0.050	0.2334	1.075
	0.055	0.2118	1.420
M_s	0.8×10^6	0.2236	1.220
	1×10^6	0.2334	1.075
	1.2×10^6	0.2402	1.000
a	100	0.2334	1.075
	125	0.2236	1.220
	150	0.2151	1.360
Π	2.00	0.2334	1.075
	2.15	0.2392	1.030
	2.20	0.2402	0.975
λ_1	0.008	0.2334	1.075
	0.009	0.2251	1.060
	0.010	0.2173	1.480
λ_2	0.08	0.1868	1.130
	0.09	0.2101	1.095
	0.10	0.2334	1.075

Table 6.1: Saturated concentration and time to reach drug carrier saturated concentration for different parameter values.

along the channel. The case for the value of α equal to 1 is related to the aspect dynamics with no memory effect and is based on the usual integer-order differential equation. A balance of the memory effect is observed for $\alpha \in (0, 1)$. In Fig. 6.3, the effect of rheological parameter, ξ on the dispersion of drug-coated nanoparticles concentration in the tumor tissues is shown. The value of the rheological parameter depends on the accumulation of the red blood cells at the centre of the blood vessel. Robertson *et al.* [176] demonstrated the microscopic behaviour and properties of the blood in vitro and in vivo through their rheometric experiment. It is revealed that with the increase in the value of ξ , the drug carriers are concentrated in a large amount at the tumor region and concentration rate gear up faster before being saturated to a constant for a continuous-time, as also observed in [177]. Moreover, we note that the concentration saturation rate of drug-coated nanoparticles is significantly affected by rheological parameter, ξ [178] as clearly detailed in Table 6.1. This explains the

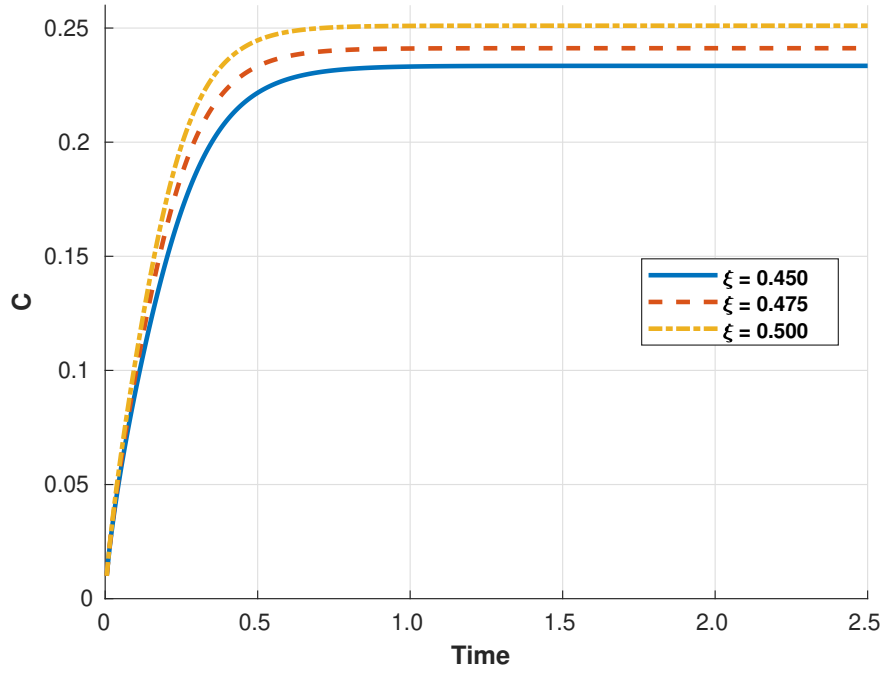


Figure 6.3: Concentration profile of drug-coated magnetic nanoparticles for different values of ξ , when $\Pi = 2.0$, $M_s = 1 \times 10^6$, $\beta_{vf} = 0.6$, $d = 0.05$ m, $a = 100$ nm, $\lambda_1 = 0.008$, $\lambda_2 = 0.10$ and $\alpha = 1.0$.

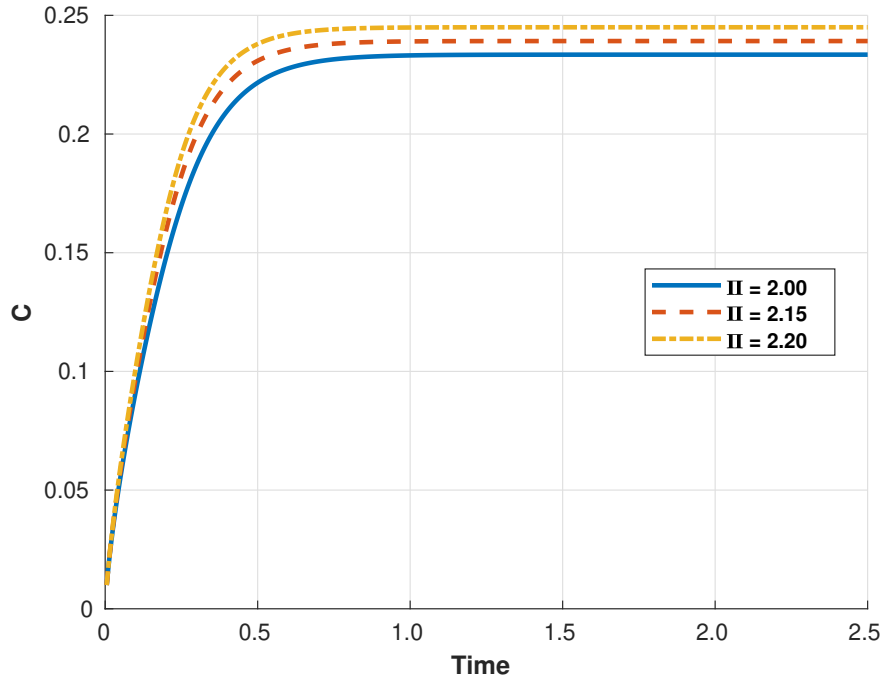


Figure 6.4: Concentration profile of drug-coated magnetic nanoparticles for different values of Π , when $\xi = 0.45$, $M_s = 1 \times 10^6$, $\beta_{vf} = 0.6$, $d = 0.05$ m, $a = 100$ nm, $\lambda_1 = 0.008$, $\lambda_2 = 0.10$, and $\alpha = 1.0$.

observation that as ξ increases, the central region of the capillary with a flat velocity distribution increases as the thickness of the lateral cells free layer decreases, which push the particles close to the wall and enhanced the concentration. It is important to

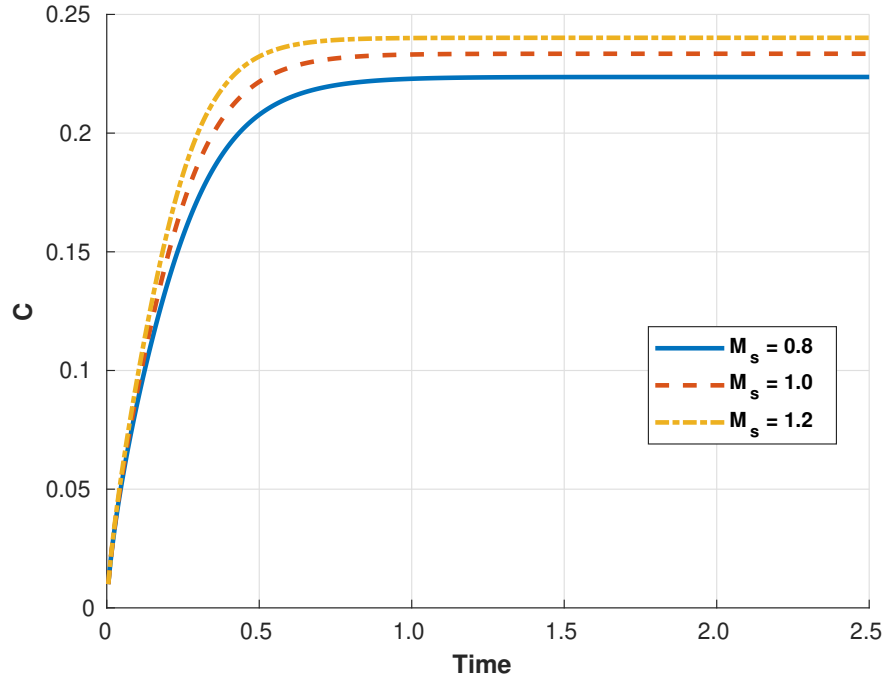


Figure 6.5: Concentration profile of drug-coated magnetic nanoparticles for different values of M_s , when $\xi = 0.45$, $\Pi = 2.0$, $\beta_{vf} = 0.6$, $d = 0.05$ m, $a = 100$ nm, $\lambda_1 = 0.008$, $\lambda_2 = 0.10$, and $\alpha = 1.0$.

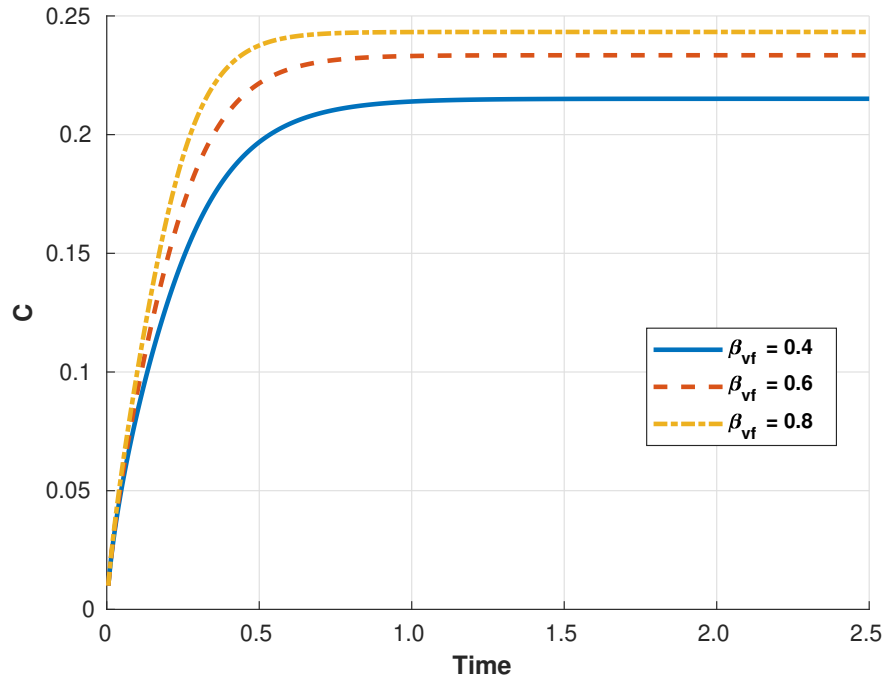


Figure 6.6: Concentration profile of drug-coated magnetic nanoparticles for different values of β_{vf} , when $\xi = 0.45$, $\Pi = 2.0$, $M_s = 1 \times 10^6$, $d = 0.05$ m, $a = 100$ nm, $\lambda_1 = 0.008$, $\lambda_2 = 0.10$, and $\alpha = 1.0$.

note that the enhancement in the rheological parameter increases the non-Newtonian rheology of the blood [179]. This due to the fact that red blood cells in microvessels encountered lateral movement in the channel and blunted velocity profile that is affected

by haematocrit and membrane deformability. Further, the particles are designed to

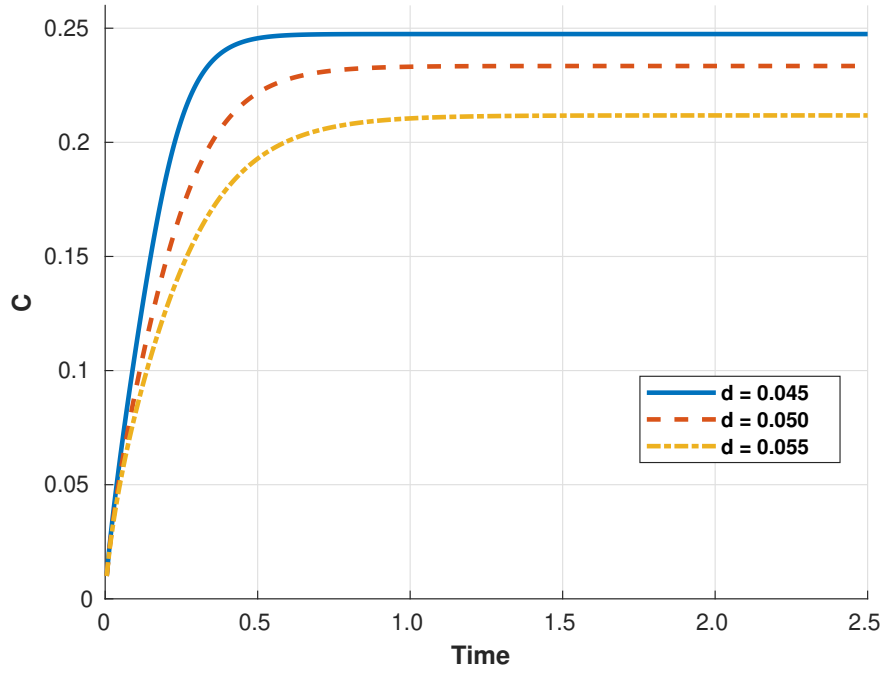


Figure 6.7: Concentration profile of drug-coated magnetic nanoparticles for different values of d (m), when $\xi = 0.45$, $\Pi = 2.0$, $M_s = 1 \times 10^6$, $\beta_{vf} = 0.6$, $a = 100$ nm, $\lambda_1 = 0.008$, $\lambda_2 = 0.10$, and $\alpha = 1.0$.

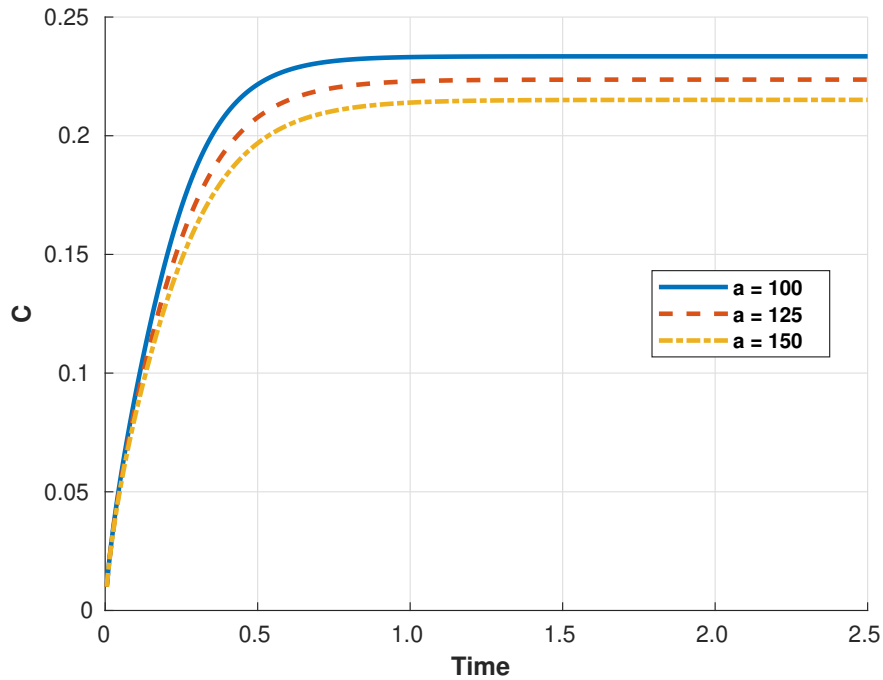


Figure 6.8: Concentration profile of drug-coated magnetic nanoparticles for different values of a (nm), when $\xi = 0.45$, $\Pi = 2.0$, $M_s = 1 \times 10^6$, $\beta_{vf} = 0.6$, $d = 0.05$ m, $\lambda_1 = 0.008$, $\lambda_2 = 0.10$, and $\alpha = 1.0$.

accumulate within the cell-free layer and therefore slow down its motion. It is also

linked to the thickness of the plug region with the relation $\xi = \frac{r_c}{R_e}$. The mean haematocrit of $46.8 \pm 3.2\%$ was observed for the healthy controls, while $49.1 \pm 2.4\%$ for the chronic coronary disease controls [180]. The influence of the permeability parameter, related to hydraulic conductivity, Π on the dispersion of drug-coated nanoparticles is shown in Fig. 6.4. It has been found that the delivery outcomes of drug carriers are more sensitive to changes in hydraulic conductivity-related permeability parameters. Usually, the hydraulic conductivity value of the capillaries, L_p changes in a good manner with the position of the capillaries from one organ to another [131, 135]. The drug-embedded carrier concentration increases with an increase in permeability parameter related to hydraulic conductivity, Π . This is due to the fact that in the tumor region a higher permeability is expected compared to the normal healthy tissues [120]. It makes it easy for the drugs to be delivered to a proper target. In addition, with increasing Π , the time to reach the saturation concentration of the drug-embedded nanoparticles in the capillaries along the channel increases (see Table 6.1). As noted that when magnetization increases, the magnetic force also increases. In Fig. 6.5, we observe that magnetic drug carriers concentration increases with the increase of the strength of the magnetization. Moreover, Table 6.1 displays that the time to reach saturation concentration point in the microvessel along the channel reduces as the magnetization increases. Due to the application of magnetic force, drug-embedded nanoparticles are able to overcome the limitations of interstitial transport by increasing their resultant velocity. Hence, particle trapping near the tumor site is easier with increasing magnetization. Aviles *et al.*, (2008) [138] showed a similar phenomenon in which the magnetic field strength increases the efficiency of drug capture and, consequently, the concentration of drug carriers in the microvasculature. Similarly, clinical studies [139, 140] results indicate that increased magnetization can improve nanoparticle accumulation and penetration near the tumor site. After intravenous bolus injection of magnets coated with drug, Fig. 6.6 illustrates the effects of volume fraction of magnetic nanoparticles on the dispersion of these particles in tumor tissues. Volume fraction of the magnetic nanoparticle represents the volume of the nanoparticle with respect to the total volume of the drug carrier particle. As the volume fraction of magnetic particles increases, the amount of the magnetic particles is enhanced, which controls and boost the magnetic force created velocity of the drug carriers. Due to this phenomenon, the magnetic force between the magnet and the drug carrier increases regularly. Consequently, it amplifies the velocity of the drug particles and the concentration of the drug-coated magnetic nanoparticles. Due to the enhanced velocity, the drug particles reach the diseased region much faster and reach the saturated concentration within a short time span. This phenomenon is highlighted in Table 6.1, with indication that; with an increase in the volume fraction, the time it takes for the drug carriers to reach saturation concentration in the capillaries along

the channel decreases.

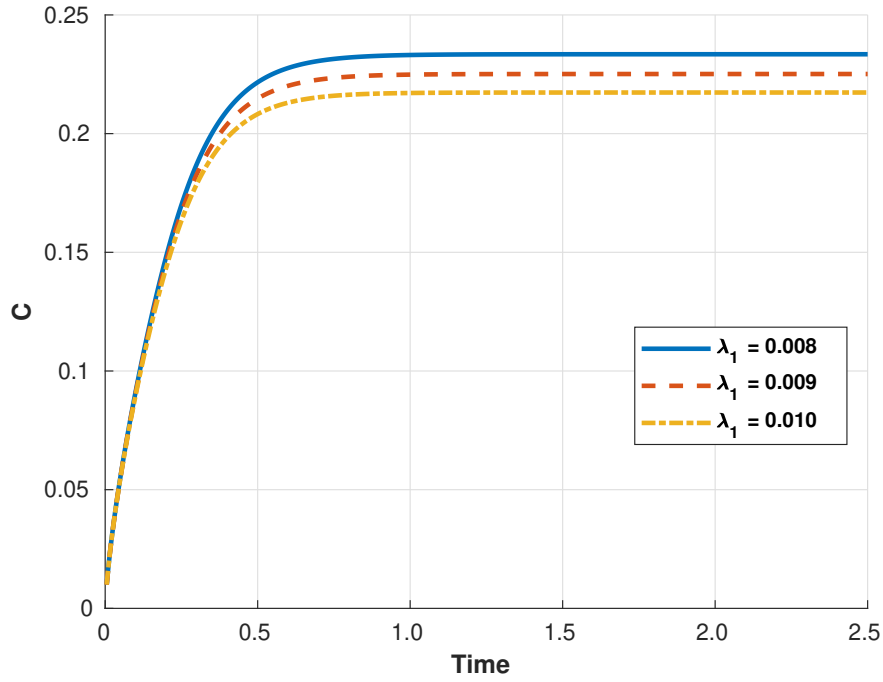


Figure 6.9: Concentration profile of drug-coated magnetic nanoparticles for different values of λ_1 , when $\xi = 0.45, \Pi = 2.0, M_s = 1 \times 10^6, \beta_{vf} = 0.6, d = 0.05$ m, $a = 100$ nm, $\lambda_2 = 0.10$, and $\alpha = 1.0$.

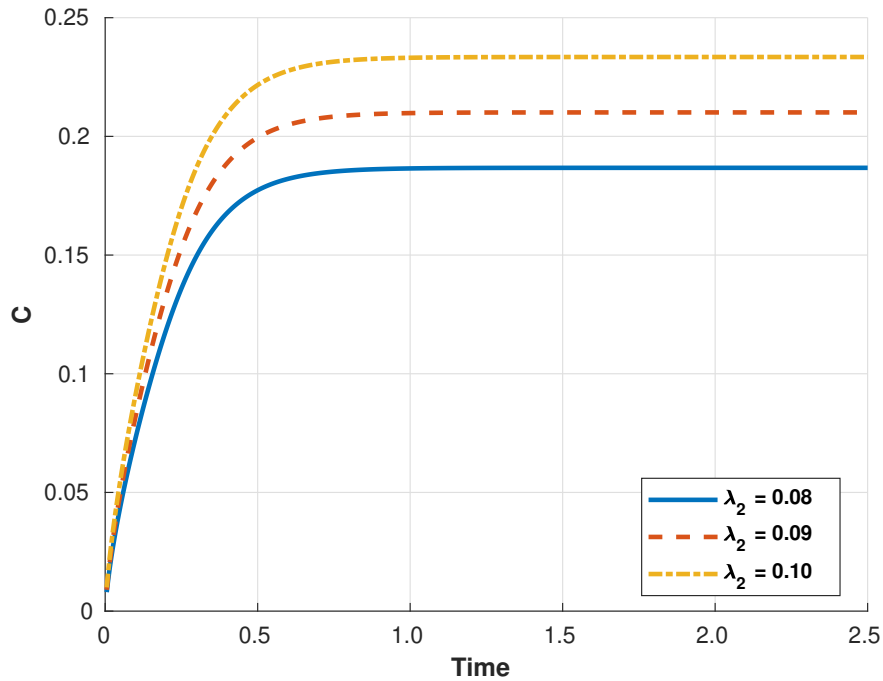


Figure 6.10: Concentration profile of drug-coated magnetic nanoparticles for different values of λ_2 , when $\xi = 0.45, \Pi = 2.0, M_s = 1 \times 10^6, \beta_{vf} = 0.6, d = 0.05$ m, $a = 100$ nm, $\lambda_1 = 0.008$, and $\alpha = 1.0$.

Therefore, the higher volume fraction of nanoparticles shows a higher attraction of

nanoparticles near the tumor position. The distance between the tumor and the magnet, depending on the tumor position. Increasing the distance between the tumor and the magnet will decrease the concentration of the drug carrier, as shown in Fig. 6.7. Hence, the velocity due to magnetic field decreases. As a result, a reduction is observed in the saturation concentration in the microvessels along the channel with increase in the distance between the tumor-magnet distance. This indicates that it is best to place the magnet close to the tumor site for the most reliable outcomes. Fig. 6.8 demonstrates how the radius of the nanoparticle affects the concentration of drug-coated magnetic nanoparticles along the microvessels, in which a smaller nanoparticle radius can result in higher concentrations of drug carriers. This is because the velocity is higher for the smaller particles [181]. We observe the results in Table 6.1, the radius of the nanoparticle decreases, the drug carrier rapidly reaches saturation. This indicates that small particles enhance drug delivery and the accumulation of anticancer drugs, as supported in [141, 143, 144]. Further, the small radius drug particles can easily reach to cellular and subcellular regions.

Drug elimination is one of the important parameters which relate with the contribution of the local drug and metabolic concentration. This phenomenon is mainly linked with the organs like liver, gastrointestinal tract, kidney, lungs, and skin and highly influenced by the self-contained drug-metabolizing enzymes. From Fig. 6.9, we observe that a reduction in the drug elimination increases drug carrier concentrations. In addition, less time is needed to reach the saturation point of concentration with an increase in the drug elimination parameters, as seen in Table 6.1. Further, in this study, we have considered the source term in form of vascular, cellular or lymphatic contribution. The importance of this involvement is observed in Fig. 6.10, and it shows a higher concentration of drug-embedded nanoparticles accumulating at the tumor region due to the enhancement of the source term. The involvement of the drug carrier boosted by increasing the source term parameters and achieves the highest drug carrier saturation concentrations. Moreover, with increased source term, it took less time to reach the drug carrier saturation point, as shown in Table 6.1.

6.5 Conclusion

In this study, a fractionalized magnetic drug targeting model was developed and analysed to examine the effective dispersion and capture efficiency of drug-carriers concentration close to a tumor site. The significant impact of different controlling biological parameters, such as non-Newtonian rheology, permeability related to hydraulic conductivity, volume fraction of nanoparticles, magnetization, tumor-magnet distance, nanoparticle radius, drug elimination, and source term, on the relative effective dis-

persion of drug carrier concentration is presented concentration was presented. Both rheological parameters and volume fraction increase the concentration of drug carrier particles as they increase, and it takes longer to reach the saturation point. A reduction in tumor-magnet distance and drug elimination leads to an increase in the concentration of drug-coated nanoparticles in the tumor position, but slows its motion to peak saturation concentration. It is beneficial to increase the magnetization parameter, the permeability parameter related to the hydraulic conductivity, and the source term to improve the concentration of drug-coated carriers at the tumor site. A low memory effect is observed with the change in the fractional-order parameter values, that is associated with high concentration of drug carriers, which accelerates the drug carrier particles to the tumor position. Therefore, the outcomes of this study will give a better understanding on the dispersion phenomena of drug carriers during the magnetic drug targeting used for the treatment of cardiovascular disorders. Further, these results will inspire the development of medical procedures that can be used to control the drug carriers under certain circumstances, which can be considered as a potential approach for clinical application during magnetic drug targeting

7. Conclusions and Implications

In this thesis, we used theoretical analysis and numerical mathematical tools to determine the mechanism of tumor-immune interaction dynamics, as well as to examine the capture conditions on the effective dispersion of drug-coated nanoparticles in a tumor position during magnetic drug targeting in microvessels.

In the first part, we focused on the role of immunotherapy in cancer treatment. Immunotherapy plays a vital role in strengthening the immune system and enhancing its ability to fight cancer during the tumor-immune interaction. This interaction is a complex process, and biological studies are still ongoing to explore the tumor microenvironment with the action of the immune system. The limitations associated with ethical consideration and the costs associated with the biological experiments on human samples, motivate researchers to use other available means, including mathematical modelling, to find possible solutions to the problems. We used a fractional-order model for tumor-immune interaction incorporating the treatment of cytokine interleukin-2 (IL-2) aimed at boosting the immune system's ability to fight cancer. The basic properties of the model such as positivity of the solutions and local stability analysis of the tumor-free equilibrium are studied and the conditions for tumor removal are highlighted. Furthermore, the existence and uniqueness of the solution of the model is proved using the fixed point theory. Given the uncertainty in the selection of model parameters, sensitivity analysis was performed using the Latin Hypercube Sampling scheme to determine model parameters that describe the processes that significantly influence the changes in the model state variables. The model was numerically solved for different orders of the fractional derivative using the Adams–Bashforth–Moulton Method. Our results suggest that satisfactory stable tumor control can be achieved by adoptive cellular immunotherapy (ACI) alone, or through a combination of ACI and IL-2. We further observed that the processes affecting the tumor-immune system interaction influence the dynamics variably at different stages of the disease.

In the second part, a model on magnetic drug targeting is developed to determine the capture conditions for the efficient dispersion of drug-coated nanoparticles in a tumor environment. These particles consist of a non-magnetic core material containing embedded magnetic nanoparticles and a therapeutic agent (such as a photodynamic sensitizer). In the present problem, we have studied the solute dispersion during magnetic drug targeting through a microvessel. The particles are injected into the microvascular system upstream of the cancerous tissue and captured in the tumor using an applied

magnetic field. The fluid velocity and the particle velocity due to the magnetic field are calculated analytically, while the solute transport equation is solved numerically by using the finite difference method. The fluid force is assumed on the capillary and the carrier undergoing magnetic force due to an external magnetic field. Solving the equations of fluid flow and solute transport simultaneously, the influence of the model biological parameters, such as volume fraction of the nanoparticles, magnetization, magnet–tumor distance, the permeability of the capillaries, Peclet number, drug elimination, source term, and radius of the nanoparticle in the dispersion of drug-coated nanoparticles in microvessels, is also discussed. The results show that higher values of volume fraction of the magnetic particles, the magnetization of the magnet, drug elimination, and source term associated with longer times are taken by drug-coated magnetic nanoparticles to reach the tumor position. Moreover, an increase in the tumor–magnet distance, permeability of the microvessel, Peclet number, and radius of the nanoparticle slows the rate at which the drug-coated magnetic nanoparticles reach the tumor position.

Then this work was extended to predict the effective dispersion of the drug carriers and the impact of the memory effect dependence of solutions on previous instances of the shear augmented dispersion during the magnetic drug targeting in the microvessel by using the Caputo fractional time derivative-based dispersion model. The nature of the blood flow into the vessel is considered Casson fluid. The velocity of the drug carrier is solved analytically, while the fractional-order dispersion equation is solved numerically by using the finite difference method. The influence of fractional-order parameters and model biological parameters such as rheological parameter, permeability parameter related to hydraulic conductivity, magnetization, the volume fraction of nanoparticles, tumor-magnet distance, nanoparticle radius, drug elimination, and source term on the relative effective dispersion are discussed. The outcomes showed that both rheological parameters and volume fractions increase drug carrier particle concentration, and that saturating occurs at a later time as they increase. In addition, the memory effect on drug delivery is observed with the change in the value of fractional parameters, and it leads to the increase in drug-embedded magnetic nanoparticles' concentration that results in fastening these drug-carriers particles to the tumor position.

Therefore, these observations are vital in informing researchers about the essential processes of emphasis when implementing therapeutic intervention measures aimed at curtailing the progression of cancer.

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