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Candidate

Sima Sarv Ahrabi
ID number 1686716

Thesis Advisor

Prof. Paola Loreti

Co-Advisor

Dr. Mirko D'Ovidio

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Author's email: sima.sarvahrabi@sbai.uniroma1.it

To my dear father

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Acronyms

ACI adoptive cellular immunotherapy.

ADM Adomian decomposition method.

DTM differential transform method.

FBSM forward-backward sweep method.

FDEs fractional differential equations.

FKP fractional model of Kirschner-Panetta.

FLE fractional logistic equation.

FLMM fractional linear multi-step method.

FLMMs fractional linear multi-step methods.

GA genetic algorithm.

IL-2 interleukin-2.

KP Kirschner-Panetta model.

LE logistic equation.

LMM linear multi-step method.

LMMs linear multi-step methods.

MFLE modified fractional logistic equation.

MSGDTM multi-step generalized differential transform method.

PC method of ABM predictor-corrector method of Adams-Bashforth-Moulton.

PSO particle swarm optimization.

TPBVPs two-point boundary value problems.

VIE Volterra integral equation.

WF West function.

Chapter 1

Introduction

Cancer is still a major cause of serious damage to the organs in the human body. Surgery, chemotherapies and radiotherapies have played key roles in medical care. However, these methods of treatment do not obviously represent a real cure, based on experiences. Surgery will scarcely suffice all by itself for a complete and long-term elimination of tumours. Radiotherapy and chemotherapy influence both malignant and healthy cells and make side effect issues. Preventive methods of cancer treatment and more successful strategies are obviously required observing. In recent decades, cancer immunotherapy has been the line, along which a lot of efforts are made to achieve the goal. Cancer immunotherapy aims at stimulating the human immune system in order to be able to fight cancer cells. Immunotherapy refers to the use of external sources of cytokines commonly with adoptive cellular immunotherapy (ACI therapy). The elimination of cancer cells and simultaneously the avoidance of side effects is a problem which must be dealt with, by formulation of an optimal control. Obviously, the optimality criteria are the minimization of cancer cells during and at the end of treatment, maximization of natural killer cells during clinical treatment and minimization of the administration. Over decades of research, knowledge of optimal control theory has advanced significantly. The highlights of these advancement are the introduction of calculus of variations elaborated by Leonhard Euler [53], dynamic programming pioneered by Richard Bellman [14] and maximum principle of Lev Pontryagin [120] for dealing with optimal control problem with constrained states and bounded controls. On the other hand, the numerical approaches to the optimization have developed significantly during recent years.

1.1 Research Topics and Motivations

The interaction between cancer cells and immune system can be modeled by dynamical systems. Various models describing the dynamics of cancer immunotherapy have been introduced. The model presented by Kirschner and Panetta [87] is one of the most famous mathematical models of cancer-immune interaction. An advanced version of the model may include a time dependent external sources of medical treatment. During the last three years, the focus of this research has been the presentation of an optimal therapeutic protocol for cancer-immunotherapy with using the state trajectories governed by the Kirschner and Panetta model. Solutions

to the optimal control problems, considered in this thesis, are usually piecewise continuous controls and more specifically, in most cases the optimal controls switch between the lower and upper bounds, the so-called bang-bang controls. The nature of these problems leads mainly to the reduction in the possibility of obtaining the optimal solution, generally related to numerical cause. Furthermore, these optimal problems belong to the class of two-point boundary value problems. In order to seek for the solution, an initial guess is required to initialize the process of finding the optimal control. But, the key issue is that any initial guess for control does not necessarily leads to finding the optimal control. In most cases, the initial guess is such that the process does not even converge to a solution and more important, the convergence to the optimal control is almost impossible. Therefore, in this thesis, a hybrid of the particle swarm optimization and the numerical methods of solving the optimal control problems is used to find the optimal therapeutic protocols.

Since most physical phenomena such as biological systems possess in their nature after-effect or persistent memory, they could be more appropriately described by fractional differential equations. This is the motivation behind consideration of a fractional model based on the Kirschner and Panetta model. In the thesis, the fractional optimal control problems have been dealt with, by using the particle swarm optimization, where the input functions are considered to be bang-bang controls.

The population of cancer cells can be described by a limit-growing function such as logistic equation. The sigmoidal behaviour of this function makes it useful to be utilized in a wide variety of applications and caused it to be one of the most versatile models in natural sciences and therefore the fractional logistic equation would be a relevant problem to be dealt with. The discussion of the fractional logistic equation is motivated by the relevance of this function to a wide range of applications and in addition, by the difficulties involved in the analysis of nonlinear fractional equations emerging from the biological systems. As it is known, the exact solution to fractional logistic equation is still an open problem to be solved. The only possible approach in solving the fractional logistic equation is numerical methods of solving fractional equations. In this regard, a fractional integro-differential equation is introduced, namely modified fractional logistic equation, for which an exact solution is represented. The behaviour of the solution to the modified fractional logistic equation (is illustrated that) is in good agreement with numerical solution of the fractional logistic equation. Indeed, finding the exact solution of fractional differential equations is even more difficult than those of classical differential equations. In the majority of cases, it is only possible to treat the fractional differential equations numerically. The interesting feature of the proposed integro-differential equation is that it possesses a term related to the classical logistic equation. The method which has been utilized for the fractional logistic equation may be suitable for the analysis of nonlinear fractional differential equations in any field of applied mathematics.

The fractional differential equations are much more difficult than classical differential equations to be numerically dealt with. As it is known, computational software such as MATLAB and MATHEMATICA have provided robust built-in codes to solve ordinary differential equations. On the other hand, solutions to the fractional differential equations have not been considered in almost all computing environments. Thus, researchers must try to solve these equations and to provide codes by themselves in order to numerically treat these equations. Non-local property

of fractional differentiation operators is a major difficulty in devising methods for numerical solutions to fractional differential equations. Another non-trivial issue is related to solutions of equations involved in implicit methods. It can be obviously seen that many researchers take the incorrect approach in solving fractional differential equations. Taking no notice of what the nature of fractional differential equations is, polynomial approximation based method are used to represent solutions to this kind of problems. This motivated us to describe in detail, for the first time, the incorrect basis on which these methods are devised.

As the fractional differential equations are proved extremely important for modeling natural phenomena such as biological systems, the inverse problem of determination of fractional order of these equations have been under specific consideration. Such problems have been investigated, for instance, in fractional diffusion equation and inverse boundary value problem for semi-linear fractional telegraph equation. Motivated by this, the inverse problem of order estimation of some classes of fractional linear differential equations is considered, based on asymptotic behaviour of solutions to these type of fractional equations. This topic includes also the linear fractional differential equations in the sense of sequential fractional derivatives. The fractional order estimation is, in addition, applied to the modified fractional logistic equations and asymptotic behaviour of its solution is analysed.

1.2 Publications Related to this Thesis

- Mirko D'Ovidio, Paola Loreti, and Sima Sarv Ahrabi. Modified fractional logistic equation. Physica A: Statistical Mechanics and its Applications, 505, 818–824, (2018)
- Sima Sarv Ahrabi and Alireza Momenzadeh. On Failed Methods of Fractional Differential Equations: the Case of Multi-step Generalized Differential Transform Method, (Accepted in Mediterranean Journal of Mathematics)
- Sima Sarv Ahrabi, Alireza Momenzadeh. Approximate solution of a cancer-immunotherapy model by the application of differential transform and Adomian decomposition methods, (submitted 2018)
- Sima Sarv Ahrabi. A hybrid method for optimal control applied to cancer-immunotherapy (submitted 2018).
- Sima Sarv Ahrabi. Optimal control in fractional model of cancer-immunotherapy (submitted 2018).
- Mirko D'Ovidio, Paola Loreti, Alireza Momenzadeh, and Sima Sarv Ahrabi. Determination of order in linear fractional differential equations (submitted 2017)

1.3 Contributions

The main contributions of the thesis are:

- Providing the optimal therapeutic protocols for cancer immunotherapy based on the KP model, by providing a MATLAB code devised on the basis of a hybrid of the PSO and numerical approaches to Pontryagin maximum principle
- Providing the optimal therapeutic protocols for cancer immunotherapy based on the fractional KP model, by providing a MATLAB code devised by using the PSO.
- Inverse problem of determination of fractional order for several types of fractional linear differential equations.
- Introduction of a novel fractional integro-differential equation, to which the exact solution is in good agreement to numerical solution to FLE in such a way that while the order tends to one, the proposed solution tends to the numerical solution to the FLE.
- A detailed explanation of some famous but failed methods of FDEs is provided such as MSGDTM. It is proved that the basis on which these type of approaches are devised, will be unfit to FDEs.

1.4 Thesis Outline

- Chapter 2 is allocated to introduce a model of cancer immunotherapy and finding the solutions by using methods based on polynomials approximations.
- In chapter 3 some preliminaries to fractional calculus are discussed and a fractional model of cancer immunotherapy is introduced. then the existence of the solutions and stability analysis are represented.
- Chapter 4 discusses numerical methods for fractional differential equations and. Then, a commonly used method, which has been constructed on incorrect basis, is described and illustrated to be unfit to fractional equations.
- In chapter 5, a fractional integro-differential equation, which is mentioned as modified fractional logistic equation, and its exact solution are introduced.
- Chapter 6 is allocated to the estimation of fractional-order in some linear fractional differential equations and in addition.
- Chapter 7 describes optimal control of the Kirschner and Panetta model in two cases: ordinary and fractional model of Kirschner and Panetta.
- Chapter 8 represents a brief review on the obtained results.

Chapter 2

Cancer Immunotherapy

Cancer is one of the most serious illnesses in all of the world. It is still a major cause of serious damage to the organs in the human body. Surgery, chemotherapies and radiotherapies have played key roles in medical care. However, these methods of treatment do not obviously represent a real cure, based on experiences. Surgery will scarcely suffice all by itself for a complete and long-term elimination of tumours. Radiotherapy and chemotherapy influence both malignant and healthy cells and make side effect issues. Preventive methods of cancer treatment and more successful strategies are obviously required observing. In recent years, wide research is conducted related to experimental and theoretical immunology. Pioneering research has been undertaken into the cancer immunotherapy as a method of enhancing the features of cancer treatment, leading to major medical advances [87, 127–129, 140]. Immunotherapy has been considered as one of the most effective methods of dealing reasonably with cancer by reinforcing humans' natural defenses in order to cope with cancer. Immunotherapy refers to the use of natural and synthetic substances to boost the immune response. The way that immunotherapy functions is as follows:

- restraining or decreasing the growth of tumours.
- preventing cancer cells from spreading to adjoining organs.
- increasing the immune system's capability to destroy cancer cells.

Stimulation of immune system could be achieved by using cytokines in addition to adoptive cellular immunotherapy (ACI). The main cytokine which regulates white blood cells and is mainly produced by $CD4^+$ T cells is named interleukin-2 (IL-2). If lymphocytes are cultured in the presence of IL-2, it leads to the development of effector cells (or simply effectors) such as lymphokine-activated killer cells (LAK cells) which are capable of killing cancer cells. Effector T cells are a particular case of effector cells. LAK cells are then injected into tumour bearing host. This is mentioned as IL-2 and is usually done in conjunction with large amounts of IL-2.

The dynamics of tumour-immune interaction have been studied over the past years and several theoretical models have been developed by researchers to indicate and analyse the influence of immune system and tumour on each other. In [89], the authors have presented a mathematical model involving ordinary differential equations describing the T lymphocyte response to the growth of an immunogenic

tumour. Adam [2] has developed and analysed a system consisting of two ordinary differential equations, which represents the effect of vascularization within a tumour. In [36] the authors have introduced some detailed models including 8-11 differential equations and 3-5 algebraic equations to illustrate the T lymphocyte interactions, which generates anti–tumour immune response. Kirschner and Panetta [87] have investigated the cancer dynamics and presented a model, which richly describes the interaction between the effector cells, the tumour cells and the concentration of IL-2 and addresses long-term and tumour recurrence and short-term tumour oscillations. Banerjee and Sarkar [13] have enhanced a system of delay ordinary differential equations to describe the reciprocal interaction between tumour, T-lymphocytes and T-helper cells. More mathematical models, incorporating delay and stochastic models could be observed in [51]. The Kirschner-Panetta model (KP), which has been first introduced in [87], has selected rich immune-tumour dynamics, nevertheless remains as straightforward as possible and incorporates crucial factors of cancer immunotherapy. The model will be described in more detail in Section 2.1.

2.1 Kirschner-Panetta Model

The KP model indicates the dynamics of immune-cancer by defining three populations, namely $E(t)$, the effector cells such as cytotoxic T-cells; $T(t)$, the tumour cells; and $I(t)$, the concentration of IL-2:

$$\frac{\mathrm{d}E}{\mathrm{d}t} = cT - \mu_2 E + \frac{p_1 EI}{g_1 + I} + s_1 \,, \tag{2.1}$$

$$\frac{\mathrm{d}T}{\mathrm{d}t} = r(T) - \frac{aET}{g_2 + T} \,, \tag{2.2}$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \frac{p_2 ET}{g_3 + T} - \mu_3 I + s_2 \,, \tag{2.3}$$

with the initial conditions:

$$E(0) = E_0 \,, \quad T(0) = T_0 \,, \quad I(0) = I_0 \,. \tag{2.4}$$

Equation (2.1) represents the rate of change in effector cells. The first and third term on the right-hand side of (2.1), show the stimulation of effector cells. The parameter c indicates the immunogenicity of the tumour, i.e. the ability of the tumour to provoke an immune response. The third term, which is the model of Michaelis-Menten kinetics shows the saturated effects of the immune response. The parameter s_1 represents an external source of effector cells as medical treatments. The parameter μ_2 indicates the decay rate of the effectors. The natural lifespan of the effector cells is in fact $\frac{1}{\mu_2}$ days. The rate of change of the tumour is described in (2.2). The tumour growth, $r(T)$, can be described in terms of a linear function or a limiting-growth function. The parameter a represents the ability of the immune system to resist the tumour, i.e. the rate of interaction between tumour and effector cells. Equation (2.3) indicates the rate of change of IL-2 concentration. The first term on the right-hand side of (2.3) has Michaelis-Menten kinetics and illustrates that effector cells are stimulated by the interaction with tumour cells and therefore this interaction will be a source of IL-2. The decay rate of IL-2 is expressed by the

parameter μ_3 and finally s_2 is an external source of IL-2 as medical treatment. The units of g_1, g_2, g_3 and b are volume and the units of the other parameters are day^{-1}.

2.1.1 Logistic Equation

The rate of change of the tumour cells, $r(T)$, can be described by a linear growth term such as $r(T) = r_2 T$, or by a type of limiting-growth term such as logistic growth or Gompertz model. The logistic equation (LE), which is mentioned on occasion as the *Verhulst* model, is a population growth model introduced and published by Pierre Verhulst [143], which is based on the competition between proliferation and death of the population. The model represents a well-known nonlinear differential equation in the field of biology and social sciences:

$$\frac{\mathrm{d}N(t)}{\mathrm{d}t} = kN(t)\left(1 - \frac{1}{N_{\max}}N(t)\right), \qquad t \geq 0, \tag{2.5}$$

where k is the rate of maximum population growth constrained to be a real positive number, $N(t)$ is the population and $N_{\max}$ is the carrying capacity, i.e. the maximum attainable value of population. Carrying capacity can be defined as maximum number of individuals in a population that can be supported by the environment. Both sides of (2.5) are divided by $N_{\max}$, and the normalization of population to its maximum sustainable value is named $u = \frac{N(t)}{N_{\max}}$:

$$\frac{\mathrm{d}u}{\mathrm{d}t} = ku(1-u), \qquad t \geq 0, \tag{2.6}$$

for which there is an exact solution

$$u(t) = \frac{u_0}{u_0 + (1-u_0)e^{-kt}}, \qquad t \geq 0, \tag{2.7}$$

where u_0 is the initial state at the time $t = 0$. The sigmoidal behavior of the solution to the LE has been used to model the tumor growth [55] and so forth. The logistic function is, therefore, utilized to show the rate of change of tumour cells in (2.2):

$$r(T) = r_2 T(1 - bT). \tag{2.8}$$

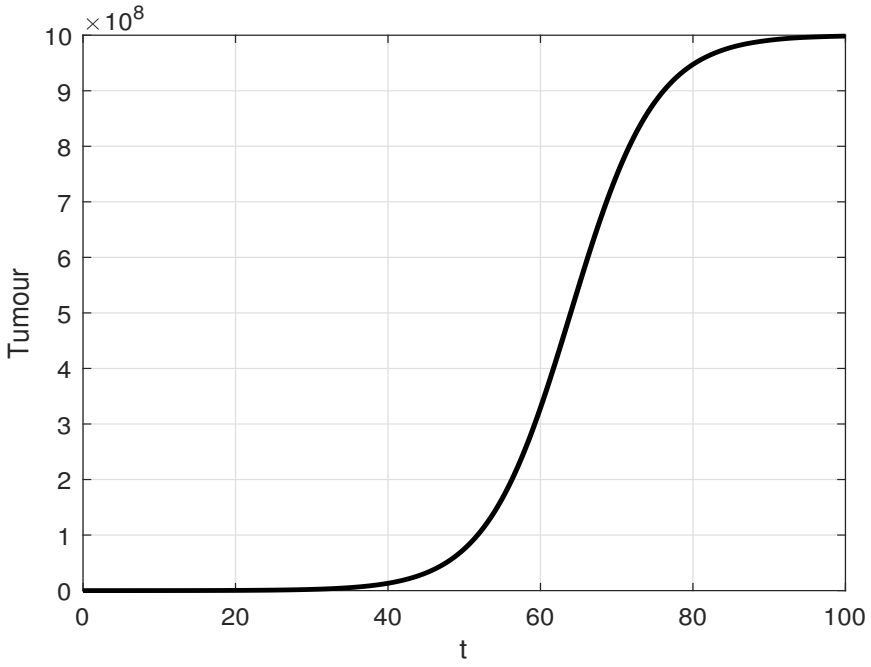

Figure 2.1. Graph of Tumour (T), for the initial condition $T_0 = 10^4$, the carrying capacity $\frac{1}{b} = 10^9$ and the immune response $a = 0$.

The value of the parameter c, which is defined as the immunogenicity, varies from patient to patient and depends greatly upon the cancer type. Larger values of c represent tumour cells showing a well-recognized antigen. The tumour immunogenicity plays the key role in the dynamics. As mentioned before, the parameter a, in (2.2), indicates the immune response. If the immune response is neglected, i.e. $a = 0$, the dynamics of the tumour cells will be governed by the LE:

$$\frac{\mathrm{d}T}{\mathrm{d}t} = r_2 T\left(1 - bT\right) , \tag{2.9}$$

where $r_2 = 0.18$ and $b = 10^{-9}$ are given in Table 2.1. The graph of tumour cells is illustrated in Fig. 2.1. By referring to (2.8) and Table 2.1, it is observed that the carrying capacity of the tumour cells, $\frac{1}{b}$, is equal to 10^9.

2.1.2 Scaling

The values of the parameters in (2.1)-(2.3) and (2.8) are given in Table 2.1.

Table 2.1. Values of parameters.

Parameters in (2.1)	Parameters in (2.2)	Parameters in (2.3)
$0 \leq c \leq 0.05$	$r_2 = 0.18$	$p_2 = 5$
$\mu_2 = 0.03$	$b = 1 \times 10^{-9}$	$g_3 = 1 \times 10^3$
$p_1 = 0.1245$	$a = 1$	$\mu_3 = 10$
$g_1 = 2 \times 10^7$	$g_2 = 1 \times 10^5$	

The KP model is a stiff system of ordinary differential equations, since a very small disturbance in time results in very large changes in some of the variables. Thus, without an appropriate scaling, the prevalent numerical methods of solving differential equations may fail. The following scaling could be utilized in order to normalize the model:

$$x = \frac{E}{E_0}\,, \quad y = \frac{T}{T_0}\,, \quad z = \frac{I}{I_0}\,,$$

with $E_0 = T_0 = I_0 = 10^4$. The non-dimensionalized coefficients are given in Table 2.2. The scaled model is obtained by eliminating the overbar notation:

Table 2.2. Scaled Coefficient.

Coefficients in (2.1)	Coefficients in (2.2)	Coefficients in (2.3)
$\bar{c} = \dfrac{cT_0}{E_0}$	$\bar{r}_2 = r_2$	$\bar{p}_2 = \dfrac{p_2 E_0}{I_0}$
$\bar{\mu}_2 = \mu_2$	$\bar{b} = bT_0$	$\bar{g}_3 = \dfrac{g_3}{T_0}$
$\bar{p}_1 = p_1$	$\bar{a} = \dfrac{aE_0}{T_0}$	$\bar{\mu}_3 = \mu_3$
$\bar{g}_1 = \dfrac{g_1}{I_0}$	$\bar{g}_2 = \dfrac{g_2}{T_0}$	$\bar{s}_2 = \dfrac{s_2}{I_0}$
$\bar{s}_1 = \dfrac{s_1}{E_0}$		

$$\begin{aligned}
\frac{\mathrm{d}x}{\mathrm{d}t} &= cy - \mu_2 x + \frac{p_1 xz}{g_1 + z} + s_1\,,\\
\frac{\mathrm{d}y}{\mathrm{d}t} &= r_2 y\,(1 - by) - \frac{axy}{g_2 + y}\,,\\
\frac{\mathrm{d}y}{\mathrm{d}t} &= \frac{p_2 xy}{g_3 + y} - \mu_3 z + s_2\,,
\end{aligned} \tag{2.10}$$

with the initial condition

$$x\,(0) = 1\,, \quad y\,(0) = 1\,, \quad z\,(0) = 1\,. \tag{2.11}$$

The values for scaled parameters is represented in Table 2.3.

Table 2.3. Values of scaled parameters.

Parameters in Eq. (2.1)	Parameters in Eq. (2.2)	Parameters in Eq. (2.3)
$0 \le c \le 0.05$	$r_2 = 0.18$	$p_2 = 5$
$\mu_2 = 0.03$	$b = 1 \times 10^{-5}$	$g_3 = 0.1$
$p_1 = 0.1245$	$a = 1$	$\mu_3 = 10$
$g_1 = 2 \times 10^3$	$g_2 = 10$	

2.2 Existence of Solutions

An improved version of KP model may include a time-dependent external sources of treatment. In this case, the KP model is expressed as follows:

$$\begin{aligned}\frac{\mathrm{d}x}{\mathrm{d}t} =& cy - \mu_2 x + \frac{p_1 xz}{g_1 + z} + s_1 u\left(t\right) ,\\ \frac{\mathrm{d}y}{\mathrm{d}t} =& r_2 y\left(1 - by\right) - \frac{axy}{g_2 + y} ,\\ \frac{\mathrm{d}z}{\mathrm{d}t} =& \frac{p_2 xy}{g_3 + y} - \mu_3 z + s_2 u\left(t\right) .\end{aligned} \tag{2.12}$$

In fact, the external sources of drugs are considered as the control functions. The control function $u\left(t\right)$ shows the percentage of the maximum amount of drugs. Thus, $u\left(t\right)$ belongs to the set of admissible controls, U, such that

$$U = \left\{ u\left(t\right) \text{ piecewise continuous } \mid 0 \leq u\left(t\right) \leq 1 \, , \forall\, t \in \left[0, t_f\right] , \; t_f \in \mathbb{R} \right\} . \tag{2.13}$$

In this section, the goal is to show the existence of solution to (2.12). At first, it is shown that the solutions to (2.12) are bounded. A detailed stability analysis and the positivity of solutions to (2.10) have been discussed in [87]. Solutions to (2.12) are positive for all $t \in [0, t_f]$ and therefor bounded below. The supersolution of (2.12) can be represented by the solution of

$$\begin{aligned}\frac{\mathrm{d}\bar{x}}{\mathrm{d}t} =& c\bar{y} + p_1\bar{x} + s_1 \, ,\\ \frac{\mathrm{d}\bar{y}}{\mathrm{d}t} =& r_2\bar{y} \, ,\\ \frac{\mathrm{d}\bar{z}}{\mathrm{d}t} =& p_2\bar{x} + s_2 \, ,\end{aligned} \tag{2.14}$$

which can be written as

$$\begin{bmatrix}\dot{\bar{x}}\\ \dot{\bar{y}}\\ \dot{\bar{z}}\end{bmatrix} = \begin{bmatrix}p1 & c & 0\\ 0 & r2 & 0\\ p2 & 0 & 0\end{bmatrix}\begin{bmatrix}\bar{x}\\ \bar{y}\\ \bar{z}\end{bmatrix} + \begin{bmatrix}s_1\\ 0\\ s_2\end{bmatrix} . \tag{2.15}$$

Equation (2.15) represents a linear system with constant coefficients in a finite time interval. Thus, the supersolutions $\bar{x}$, $\bar{y}$ and $\bar{z}$ are bounded and consequently the solution to system (2.12) is bounded.

Equation (2.12) can be represented as

$$\dot{X} = f(t, X, u) \, , \tag{2.16}$$

with the initial condition

$$X_0 = \begin{bmatrix}x\left(t_0\right)\\ y\left(t_0\right)\\ z\left(t_0\right)\end{bmatrix} , \tag{2.17}$$

where $(t_0, X_0) \in D$, and D is a nonempty open subset of $\mathbb{R} \times \mathbb{R}^3$, and the vectors X and $f : D \to \mathbb{R}^3$ denote respectively

$$X(t) = \begin{bmatrix} x(t) \\ y(t) \\ z(t) \end{bmatrix}, \tag{2.18}$$

and

$$f = \begin{bmatrix} f_1 \\ f_2 \\ f_3 \end{bmatrix} = \begin{bmatrix} cy - \mu_2 x + \dfrac{p_1 xz}{g_1 + z} + s_1 u(t) \\ r_2 y(1 - by) - \dfrac{axy}{g_2 + y} \\ \dfrac{p_2 xy}{g_3 + y} - \mu_3 z + s_2 u(t) \end{bmatrix}. \tag{2.19}$$

Vector f, represented in (2.19), is bounded above. The reason is as follows. Equation (2.19) is expressed as

$$f = \begin{bmatrix} f_1 \\ f_2 \\ f_3 \end{bmatrix} = \begin{bmatrix} cy - \mu_2 x + \dfrac{p_1 xz}{g_1 + z} \\ r_2 y(1 - by) - \dfrac{axy}{g_2 + y} \\ \dfrac{p_2 xy}{g_3 + y} - \mu_3 z \end{bmatrix} + \begin{bmatrix} s_1 u(t) \\ 0 \\ s_2 u(t) \end{bmatrix},$$

which is in the form of

$$f(t, X, u) = \bar{f}(X) + [s_1 \; 0 \; s_2]^T \; u(t),$$

where $\bar{f}$ is a vector valued function of X. The coefficients in f are bounded. Thus, it is obtained that

$$|f(t, X, u)| \leq \left| \begin{pmatrix} p_1 & c & 0 \\ 0 & r_2 & 0 \\ p_2 & 0 & 0 \end{pmatrix} \begin{pmatrix} x \\ y \\ z \end{pmatrix} \right| + \left| \begin{pmatrix} s_1 u(t) \\ 0 \\ s_2 u(t) \end{pmatrix} \right| \leq C|X| + s|u|$$

where C and s are bounded constants, which depend on the coefficients in (2.19). Thus f is bounded above. The existence of solution to (2.16) and (2.17) could be shown by referring to the well-known Carathéodory's existence theorem [102, theorem 9.2.1]. The hypothesis is stated in terms of the rectangular subset of $\mathbb{R} \times \mathbb{R}^n$ centred about (t_0, x_0):

$$R_{a,b} = \{(t, x) : \; |t - t_0| \leq a, \; |x - x_0| \leq b\}, \qquad a, b > 0. \tag{2.20}$$

In the following theorem the norm of $x \in \mathbb{R}^n$ with coordinates x_i $(i = 1, 2, \ldots, n)$ is

$$|x| = \max_{1 \leq i \leq n} |x_i|. \tag{2.21}$$

Theorem 2.2.1 (Carathéodory's existence theorem)**.** *The Cauchy problem* $\dot{x} = f(t, x(t))$ *and* $x(t_0) = x_0$ *has a solution if for some* $R_{a,b} \subset D$ *centred about* (t_0, x_0)*, the restriction of* f *to* $R_{a,b}$ *is continuous in* x *for fixed* t*, measurable with respect to* t *for fixed* x*, and satisfies*

$$|f(t, x)| \leq m(t) , \qquad (t, x) \in R_{a,b},$$

for some Lebesgue integrable function m *over the interval* $[t_0 - a, t_0 + a]$.

Each denominator in (2.12) is strictly positive. Thus, f is continuous with respect to x, y, and z. The function $u(t)$ belongs to a set of bounded and piecewise continuous functions. Thus, it can be easily shown that f is measurable in t. Each component of f in (2.19) has been demonstrated to be bounded above. Therefore, according to Theorem 2.2.1 there exists a solution to (2.12).

2.3 Solution to KP Model by Polynomial Approximations

It is obvious from (2.10) that the complicated nonlinearity of KP model causes the use of methods such as differential transform and Adomian decomposition to require more involved processes. In this section, for the sake of brevity, the basic concepts of differential transform method (DTM) and Adomian decomposition method (ADM) are discussed, then these two methods are utilized to present approximated solution to the KP model in the neighbourhood of initial condition.

2.3.1 Differential Transform Method

The DTM was first introduced in [122, 123, 152] and results in approximated polynomial solutions of differential equations based on the use of Taylor expansion. Although the concept of the technique is based on Taylor series expansion, it leads to solving recursive algebraic equations instead of the evaluation of derivatives. The main focus of attention is placed on the first order nonlinear ordinary differential equations:

$$\begin{cases} \dfrac{\mathrm{d}x(t)}{\mathrm{d}t} = f(x(t), t), \\ x(t_0) = \alpha . \end{cases} \tag{2.22}$$

The DTM leads to representing the solution to (2.22) in the form of a power series:

$$x(t) = \sum_{k \geq 0} X_k (t - t_0)^k , \tag{2.23}$$

where the unknown coefficients X_k are straightforwardly evaluated by the recurrence equation:

$$(k + 1) X_{k+1} = F(X_k, k) , \quad k = 0, 1, \cdots . \tag{2.24}$$

The first coefficient, X_0, is assessed to be equal to the initial state $x(t_0)$, i.e. $X_0 = \alpha$ (see [11]) and $F(X_k, k)$ is evaluated by using the rules and techniques briefly mentioned below:

1. If $f(t) = \dot{x}(t)$, then the differential transform of $f(t)$ is
$$F_k = (k+1) X_{k+1}.$$
2. If $f(t) = c\,x(t)$, then $F_k = c\,X_k$, where c is a real constant.
3. If $f(t) = x(t) \pm y(t)$, then $F_k = X_k \pm Y_k$.
4. If $f(t) = x(t)\,y(t)$, then $F_k = \sum_{i=0}^{k} X_i Y_{k-i}$.
5. If $f(t) = \dfrac{x(t)}{y(t)}$, then
$$F_k = \frac{1}{Y_0}\left(X_k - \sum_{i=0}^{k-1} F_i Y_{k-i}\right),\ k \geq 1,\ F_0 = \frac{X_0}{Y_0}.$$
6. $f(t) = [x(t)]^a$, then
$$F_k = \sum_{i=1}^{k} \left(\frac{a+1}{k} i - 1\right) \frac{X_i}{X_0} F_{k-i},\ k \geq 1,\ F_0 = X_0^a,\ a \in \mathbb{R}.$$
7. If $f(t) = t^n$, then $F_k = \delta_{k-n}$, where $\delta_{k-n} = \begin{cases} 1 & \text{if} \quad k = n \\ 0 & \text{if} \quad k \neq n\,. \end{cases}$
8. If $f(t) = \exp(\lambda t)$, then $F(k) = \frac{\lambda^k}{k!}$, $\lambda \in \mathbb{R}$.

Proofs and more detailed descriptions can be observed in [9, 18]. By evaluating the coefficients X_k up to the nth–order, the approximate solution to Eq. (2.22) is $x(t) = \sum_{k=0}^{n} X_k (t - t_0)^k$.

2.3.1.1 Application to KP model

The coefficients in system (2.10) are evaluated by referring to Table 2.3, where the initial conditions are:

$$x(0) = 1\,, \quad y(0) = 1\,, \quad z(0) = 1\,. \tag{2.25}$$

By applying the DTM, the differential transform of (2.10) could be obtained as follows:

$$\begin{cases} X_{k+1} &= \dfrac{1}{k+1}\left(cY_k - \mu_2 X_k + p_1 \bar{X}_k + s_1 \delta_k\right), \\ Y_{k+1} &= \dfrac{1}{k+1}\left(r_2 Y_k - r_2 b \sum_{i=0}^{k} Y_i Y_{k-i} - a\bar{Y}_k\right), \\ Z_{k+1} &= \dfrac{1}{k+1}\left(p_2 \bar{Z}_k - \mu_3 Z_k + s_2 \delta_k\right), \end{cases} \tag{2.26}$$

where $\bar{X}_k$, $\bar{Y}_k$ and $\bar{Z}_k$ are respectively equal to

$$\bar{X}_k = \begin{cases} \dfrac{X_0 Z_0}{g_1 + Z_0} & \text{if} \quad k = 0\,, \\ \dfrac{1}{g_1 + Z_0}\left(\sum_{i=0}^{k} X_i Z_{k-i} - \sum_{i=0}^{k-1} \bar{X}_i Z_{k-i}\right) & \text{if} \quad k \geq 1\,, \end{cases} \tag{2.27}$$

$$\bar{Y}_k = \begin{cases} \dfrac{X_0 Y_0}{g_2 + Y_0} & \text{if} \quad k = 0\,, \\ \dfrac{1}{g_2 + Y_0}\left(\sum_{i=0}^{k} X_i Y_{k-i} - \sum_{i=0}^{k-1} \bar{Y}_i Y_{k-i}\right) & \text{if} \quad k \geq 1\,, \end{cases} \tag{2.28}$$

$$\bar{Z}_k = \begin{cases} \dfrac{X_0 Y_0}{g_3 + Y_0} & \text{if} \quad k = 0\,, \\ \dfrac{1}{g_3 + Y_0}\left(\sum_{i=0}^{k} X_i Y_{k-i} - \sum_{i=0}^{k-1} \bar{Z}_i Y_{k-i}\right) & \text{if} \quad k \geq 1\,, \end{cases} \tag{2.29}$$

$$\delta_k = \begin{cases} 1 & \text{if} \quad k = 0\,, \\ 0 & \text{if} \quad k \geq 1 \end{cases} \tag{2.30}$$

and, as it was stated, the coefficients X_0, Y_0 and Z_0 are:

$$\begin{aligned} X_0 &= x\,(0) = 1\,, \\ Y_0 &= y\,(0) = 1\,, \\ Z_0 &= z\,(0) = 1\,. \end{aligned}$$

Case 1– No treatment ($s_1 = 0, s_2 = 0$): Without considering medical treatment, i.e. the external sources of effector cells and IL-2, s_1 and s_2, are both equal to zero, the approximated solution to (2.10) with initial conditions (2.25) is:

$$\begin{aligned} x\,(t) &= 1.0 + 0.0050622\,t + 0.0013137\,t^2 + 0.0005999\,t^3 - 0.0014141\,t^4\,, \\ y\,(t) &= 1.0 + 0.0890891\,t + 0.0041064\,t^2 + 0.0001009\,t^3 - 0.0000126\,t^4\,, \\ z\,(t) &= 1.0 - 5.4545450\,t + 27.302640\,t^2 - 91.007170\,t^3 + 227.51860\,t^4\,. \end{aligned} \tag{2.31}$$

where the immunogenicity of the tumour cells is $c = 0.035$ (see Table 2.3). The polynomials in (2.31) represent the solution to the KP model for a small neighbourhood of $t = 0$. In order to extend the solution to a large time T, the DTM can be utilized step-by-step, by a small step-size h.

Case 2– Immunotherapy ($s_1 > 0, s_2 = 0$): This involves the use of an external source of effectors for instance *lymphokine-activated killer cell* or *tumor infiltrating lymphocyte*, without using IL-2. For the sake of simplicity, the source of IL-2 is not considered ($s_2 = 0$). It must be mentioned that a detailed stability analysis of KP model has represented in [87]. In the absence of IL-2, there is one non-tumour equilibrium point, $E = (x, 0, z)$. This equilibrium point will be stable where s_1 is greater than its critical value $s_{1\,cr}$. According to Table 2.1, this critical value is $s_{1\,cr} = 540$. The approximated solutions to (2.10) with the initial conditions (2.25) is:

$$\begin{aligned} x\,(t) &= 1.0 + 0.0700622\,t + 0.0007861\,t^2 + 0.0005702\,t^3 - 0.0013962\,t^4\,, \\ y\,(t) &= 1.0 + 0.0890891\,t + 0.0011518\,t^2 - 0.0001385\,t^3 - 0.0000181\,t^4\,, \\ z\,(t) &= 1.0 - 5.4545450\,t + 27.450370\,t^2 - 91.500010\,t^3 + 228.75070\,t^4\,, \end{aligned} \tag{2.32}$$

where $c = 0.045$, $s_1 = 550$ and $s_2 = 0$.

2.3.2 Adomian Decomposition Method

One of the advantages of the ADM is presenting approximated polynomial solutions to rather broad range of nonlinearities without necessitating massive numerical procedures and restrictive assumptions. The method is widely used to solve problems involving algebraic, differential, integro differential, delay and partial differential equations and systems [3–5]. Equation (2.22) is first rewritten as follows

$$Lx = g(t) + Rx + Nx\,, \tag{2.33}$$

where L denotes the first order differential operator, R and N represent respectively the linear and nonlinear part of f, and $g(t)$ denotes the remainder part of f as an explicit function of t. Applying the inverse operator L^{-1} to (2.33), another expression of (2.22) is obtained:

$$L^{-1}[Lx] = L^{-1}[g(t)] + L^{-1}[Rx] + L^{-1}[Nx]\,, \tag{2.34}$$

where L^{-1} expresses the definite integral from t_0 to t, thus:

$$\begin{aligned} x(t) &= \underbrace{x(t_0) + \int_{t_0}^{t} g(t)\,\mathrm{d}t}_{x_0} + L^{-1}[Rx] + L^{-1}[Nx] \\ &= x_0 + L^{-1}[Rx] + L^{-1}[Nx]\,. \end{aligned} \tag{2.35}$$

The function x, which is the approximate solution to (2.22), and the nonlinear term Nx are respectively decomposed to

$$x = \sum_{k\geq 0} x_k\,, \tag{2.36}$$

and

$$Nx = \sum_{k\geq 0} A_k\,, \tag{2.37}$$

thus (2.35) is written as follows:

$$\sum_{k\geq 0} x_k = x_0 + L^{-1}\left[R\sum_{k\geq 0} x_k\right] + L^{-1}\left[\sum_{k\geq 0} A_k\right]\,, \tag{2.38}$$

and consequently

$$\begin{aligned} x_1 &= L^{-1}[Rx_0] + L^{-1}A_0 \\ x_2 &= L^{-1}[Rx_1] + L^{-1}A_1 \\ &\vdots \\ x_{k+1} &= L^{-1}[Rx_k] + L^{-1}A_k\,. \end{aligned} \tag{2.39}$$

The polynomials A_n are generated for each nonlinearity by using the formula

$$A_k = \frac{1}{k!}\frac{\mathrm{d}^k}{\mathrm{d}\lambda^k}\left[N\left(\textstyle\sum_{i\geq 0} x_i\lambda^i\right)\right]_{\lambda=0}\,. \tag{2.40}$$

For instance, a few terms of Adomian polynomials will be:

$$\begin{aligned} A_0 &= N(x_0) \\ A_1 &= x_1 N(x_0) \\ A_2 &= x_2 N(x_0) + \frac{1}{2!} x_1^2 N(x_0) \\ A_3 &= x_3 N(x_0) + x_1 x_2 N(x_0) + \frac{1}{3!} x_1^3 N(x_0) \,. \end{aligned}$$

If the series in (2.36) converges, the function $\phi_n = \sum_{i=0}^{n} x_i$ will be the approximate solution to (2.22).

2.3.2.1 Application to the KP model

The Adomian polynomials must be evaluated for each nonlinearity in the KP model. These nonlinearities are

$$\begin{aligned} M_{xz} &= \frac{xz}{g_1 + z} \,, \\ N_y &= y^2 \,, \\ P_{xy} &= \frac{xy}{g_2 + y} \,, \\ Q_{xy} &= \frac{xy}{g_3 + y} \,. \end{aligned}$$

By using (2.40), the Adomian polynomials for M_{xz} and N_y are calculated as below and the other two nonlinearities can be evaluated similar to M_{xz}. Since this nonlinearity includes a complex interaction between the variables x and z, the implementation of the ADM is very complicated. A MATLAB routine has been coded to calculate Adomian polynomials:

$$\begin{aligned} M_0 &= \frac{x_0 z_0}{g_1 + z_0} \,, \\ M_1 &= \frac{x_0 z_1 + x_1 z_0}{g_1 + z_0} - \frac{x_0 z_0 z_1}{(g_1 + z_0)^2} \,, \\ M_2 &= \frac{x_0 z_2 + x_1 z_1 + x_2 z_0}{g_1 + z_0} - \frac{x_0 z_1^2 + x_1 z_0 z_1 + x_1 z_0 z_2}{(g_1 + z_0)^2} + \frac{z_1^2}{(g_1 + z_0)^3} \,, \\ M_3 &= -\frac{x_0 z_3 + x_1 z_2 + x_2 z_1 + x_3 z_0}{g_1 + z_0} \\ &\quad - \frac{2 x_0 z_1 z_2 + x_1 z_0 z_2 + x_1 z_1^2 + x_2 z_0 z_1 - x_0 z_0 z_3}{(g_1 + z_0)^2} \\ &\quad + \frac{x_0 z_1^3 + x_1 z_0 z_1^2 - 2 x_0 z_0 z_1 z_2}{(g_1 + z_0)^3} + \frac{x_0 z_0 z_1^3}{(g_1 + z_0)^4} \,, \end{aligned} \tag{2.41}$$

and

$$\begin{aligned} N_0 &= y_0^2 \,, \\ N_1 &= 2 y_0 y_1 \,, \\ N_2 &= y_1^2 + 2 y_0 y_2 \,, \\ N_3 &= 2 (y_1 y_2 + y_0 y_3) \,. \end{aligned} \tag{2.42}$$

Case 1– No treatment ($s_1 = 0, s_2 = 0$): According to (2.35), x_0, y_0 and z_0 are equal to the initial state of (2.10), i.e.

$$\begin{aligned} x_0 &= 1\,, \\ y_0 &= 1\,, \\ z_0 &= 1\,, \end{aligned}$$

and therefore the approximate solution to the KP model is:

$$\begin{aligned} x\left(t\right) &= 1.0 + 0.0050622\ t + 0.0013136\ t^2 + 0.0005998\ t^3 - 0.0014141\ t^4\,, \\ y\left(t\right) &= 1.0 + 0.0890891\ t + 0.0041063\ t^2 + 0.0001008\ t^3 - 0.0000126\ t^4\,, \\ z\left(t\right) &= 1.0 - 5.4545450\ t + 27.302640\ t^2 - 91.007170\ t^3 + 227.51860\ t^4\,. \end{aligned} \tag{2.43}$$

The solutions to (2.10) for $y\left(t\right)$ are illustrated in Fig. 2.2. The approximate solutions are compared with the numerical solution to the system, which are evaluated by using the explicit fourth order Runge-Kutta method.

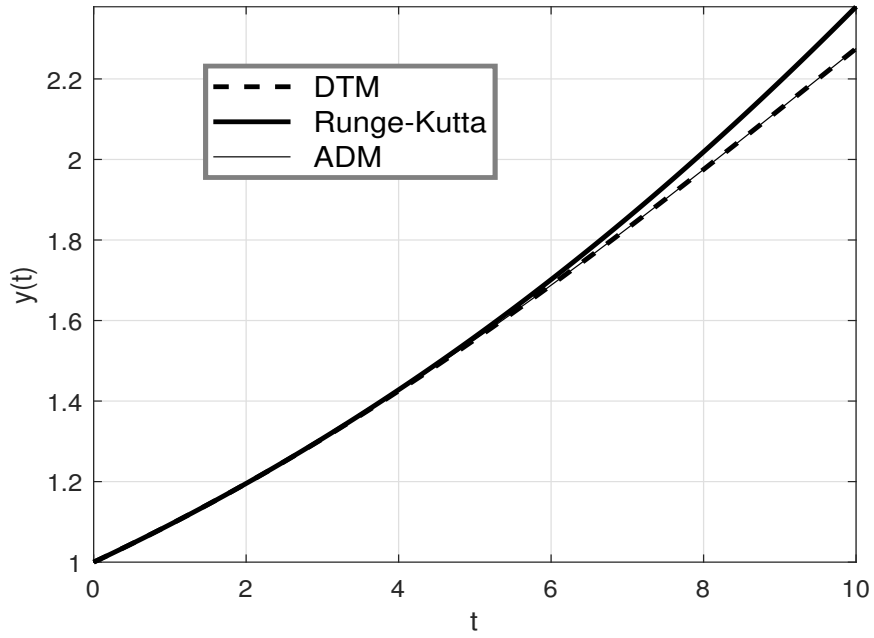

Figure 2.2. Approximate analytical solutions to KP model by using DTM and ADM, in comparison with Runge-Kutta method, for $c = 0.035$, $s_1 = 0$ and $s_2 = 0$.

Case 2– Immunotherapy ($s_1 > 0, s_2 = 0$): In this case, the first terms of the solution to the KP model are

$$\begin{aligned} x_0 &= 1 + \int_0^t s_1 \mathrm{d}t\,, \\ y_0 &= 1\,, \\ z_0 &= 1\,. \end{aligned}$$

The Approximate solution to the system is then as follows:

$$\begin{aligned} x(t) &= 1.0 + 0.0700622\,t + 0.0007861\,t^2 + 0.0005702\,t^3 - 0.0013962\,t^4 \\ &\quad -5\times 10^{-5}\,t^5 + 5\times 10^{-7}\,t^6 + 2.9\times 10^{-11}\,t^7 - 3.6\times 10^{-15}\,t^8\,, \\ y(t) &= 1.0 + 0.0890891\,t + 0.0011518\,t^2 - 0.0001385\,t^3 - 0.0000181\,t^4 \\ &\quad -1\times 10^{-7}\,t^5 + 4.3\times 10^{-9}\,t^6 + 4.2\times 10^{-11}\,t^7 - 3.2\times 10^{-13}\,t^8\,, \\ z(t) &= 1.0 - 5.4545455\,t + 27.450366\,t^2 - 91.500006\,t^3 + 228.75065\,t^4 \\ &\quad -2.0877809\,t^5 - 0.0000492\,t^6 + 1.6\times 10^{-8}\,t^7 - 4.8\times 10^{-12}\,t^8\,. \end{aligned} \tag{2.44}$$

Fig. 2.3 illustrates the approximate polynomial solutions to (2.10) for $y(t)$, which are compared with the numerical method obtained by using the explicit Runge-Kutta method.

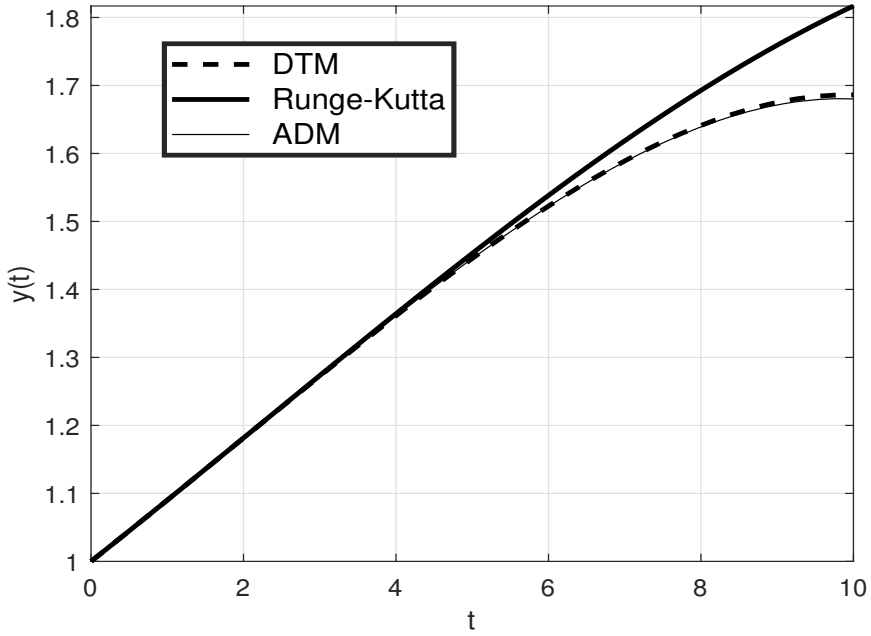

Figure 2.3. Approximate analytical solutions to KP model by using DTM and ADM, in comparison with Runge-Kutta method, for $c = 0.045$, $s_1 = 550$ and $s_2 = 0$.

The DTM and ADM are two reliable methods based on polynomial approximations. As it was stated, the complicated nonlinearity in KP causes the use of these methods to be very difficult. Specially, this difficulty is due to the presence of the variables in the numerator and denominator of the Michaelis-Menten term. All the processes to calculate Adomian polynomials and the solutions are coded in MATLAB environment.

Chapter 3

Fractional Model of Cancer Immunotherapy

Fractional calculus and its origin could be traced to the end of the seventeenth century, the time when G. W. Leibniz (1646-1716) introduced the symbol

$$\frac{\mathrm{d}^n}{\mathrm{d}x^n} f\left(x\right)$$

to indicate the nth derivative of a function f, on the assumption that $n \in \mathbb{N}$. Marquis de L'Hospital (1661-1704) debated what $\frac{\mathrm{d}^n}{\mathrm{d}x^n}$ means if $n = \frac{1}{2}$, and this is the first occurrence of what is today mentioned as *fractional derivative*. Marquis de L'Hospital specifically considered a fraction (rational number), which gave rise to the specific name of this branch of mathematics: "*fractional calculus*", even though there is no reason to restrict n to rational numbers only, and Indeed, any real number — rational or irrational — could be counted. Furthermore, any complex number may be allowed at least for analytical considerations. Many celebrated mathematicians developed the concept of fractional calculus, namely L. Euler (1707-1783), J.L. Lagrange (1736-1813), P.S. Laplace (1749-1828), J.B.J. Fourier (1768-1830), J. Liouville (1809-1882), B. Riemann (1826-1866), A.V. Letnikov (1837-1888), A.K. Grünwald (1838-1920) and so forth.

The simulation of systems and processes and mathematical modeling of which, based on the description of their attributes and properties in terms of fractional derivatives leads to differential equations of fractional order and the necessity of analysing and solving them. Over the last few decades the advancement of mathematical knowledge about fractional calculus has been motivated by the enormous applications of fractional differential equations in chemistry, physics, engineering, finance, and other branch of science. For instance, modeling of mechanical properties of materials has been observed in the research undertaken by Caputo [26, 27], and Caputo and Mainardi [29, 30]; research on the field of signal processing by Marks and Hall [106]; the behaviour of viscoelastic and viscoplastic materials [44, 45, 57]; bioengineering [56, 103]; the theory of random walks [69, 134]; control theory of fractional dynamical systems [25]. Several collections of such applications of fractional calculus could be observed in, for instance, [68, 105, 109, 119, 131] and the application of fractional calculus in various branch of mathematics has been also studied, such as special functions [88]. Many researchers and mathematicians have

pointed out that the behaviour of many physical phenomena could be appropriately described and modeled by fractional derivatives and integrals. Fractional-order differential equations have been demonstrated to be more adequate than classical ordinary differential equations in order to analyse physical processes, since fractional derivatives issue an sterling instrument for representation of memory and hereditary properties of many real materials and physical phenomena. This constructs the principal advantage of fractional derivatives over classical derivatives of integer-order.

3.1 Fractional Integral and Derivatives

As it is known, there is a very close relation between differential and integral operators:

Theorem 3.1.1. *Let $f : [a, b] \to \mathbb{R}$ be a continuous function and let $F : [a, b] \to \mathbb{R}$ be defined by*

$$F(x) = \int_a^b f(t)\,\mathrm{d}t$$

then F is differentiable and

$$F' = f\,.$$

The basic idea behind fractional calculus is to preserve this relation in an appropriately generalized sense.

Definition 3.1.1. *The operator D denotes a mapping of a differentiable function onto its derivative, i.e.*

$$Df(x) = f'(x)\,.$$

Definition 3.1.2. *The operator I_a denotes a mapping of an integrable function f on the compact interval $[a, b]$ onto its primitive centered at a for $x \in [a, b]$, i.e.*

$$I_a f(x) = \int_a^x f(t)\,\mathrm{d}t\,.$$

Definition 3.1.3. *For $n \in \mathbb{N}$ the symbols D^n and I_a^n are assumed to respectively denote the n-fold iterates of D and I_a, i.e. $D^1 := D$, $I_a^1 := I_a$, $D^n = DD^{n-1}$ and $I_a^n = I_a I_a^{n-1}$ for $n \geq 2$.*

The key issue in fractional calculus is to extend the concepts of Definition 3.1.3 also to $n \notin \mathbb{N}$. There exist various generalizations of Definition 3.1.3, from which the most significant ones for practical applications are discussed. It is well known that the integral operator I_a^n can be expressed by

$$I_a^n f(x) = \frac{1}{(n-1)!}\int_a^x (x-t)^{n-1} f(t)\,\mathrm{d}t\,, \tag{3.1}$$

and, moreover, the following relation is held true for the differential operator D and the integral operator I_a:

Lemma 3.1.1. *Let f be a function having a continuous nth derivative on the interval $[a, b]$ and let $m, n \in \mathbb{N}$ such that $m > n$. Then,*

$$D^n f = D^m I_a^{m-n} f\,.$$

Equation (3.1) and Lemma 3.1.1 are the base of generalization of integral and derivative operators. The extension of factorial into non-integer values is well known, provided by Euler gamma function. The Euler gamma function or briefly *gamma function* is the cornerstone of the study of special functions in fractional calculus, since many special functions could be represented in terms of gamma function. The gamma function could be defined by the so-called Euler integral of the second kind [85]

$$\Gamma(z) = \int_0^\infty t^{z-1} e^{-t} \mathrm{d}t\,, \qquad \Re(z) > 0\,. \tag{3.2}$$

This integral is convergent on the right side of the complex plain. The reduction formula

$$\Gamma(z+1) = z\Gamma(z)\,, \qquad \Re(z) > 0\,, \tag{3.3}$$

is held true for the gamma function, which could be obtained from (3.2) with using integration by parts. The gamma function may be extended to the left side of the complex plain, where $\Re(z) \leq 0$, by utilizing (3.3)

$$\Gamma(z) = \frac{\Gamma(z+n)}{(z)_n}\,, \quad \Re(z) > -n\,, \quad n \in \mathbb{N}\,, \quad z \notin \mathbb{Z}_0^-\,, \tag{3.4}$$

where $\mathbb{Z}_0^-$ denotes the non-positive integers and $(z)_n$ denotes the *Pochhammer symbol*

$$(z)_0 = 1\,, \quad (z)_n = z(z+1)\ldots(z+n-1) \quad z \in \mathbb{C}\,, \quad n \in \mathbb{N}\,. \tag{3.5}$$

By using (3.3) and (3.5), for a natural number $n \in \mathbb{N}$ the gamma function results in

$$\Gamma(n+1) = n!\,, \qquad n \in \mathbb{N}_0 \tag{3.6}$$

where 0! is defined to be equal to one. The most important property of this function has been expressed in (3.6).

3.1.1 Riemann-Liouville Fractional Integral

in this section, a generalization of the classical integral operator, I_a^n, is presented. The operator I_a^α denotes the Riemann-Liouville fractional Integral, which is defined on a finite interval of the real line as follows

Definition 3.1.4. *Let $\Omega = [a,b]$ $(-\infty < a < b < \infty)$ be a finite interval on the real axis $\mathbb{R}$ and let $\alpha \in \mathbb{R}_+$. The operator I_a^α, defined on $L_1[a,b]$ by*

$$\left(I_a^\alpha f\right)(x) = \frac{1}{\Gamma(\alpha)} \int_a^x (x-t)^{\alpha-1} f(t)\,\mathrm{d}t\,, \qquad (a \leq x \leq b)\,, \tag{3.7}$$

is called the Riemann-liouville fractional integral operator of order α.

The Riemann-Liouville fractional integral coincides with the classical integral operator for $\alpha \in \mathbb{N}$, except the domain is extended from Riemann integrable functions to Lebesgue integrable functions and the following theorem states firmly that the definition is justified.

Theorem 3.1.2. *Let $f \in L_1[a,b]$ and $n > 0$. The fractional integral of the function $f(x)$, $\left(I_a^\alpha f\right)(x)$, exists for almost every $x \in [a,b]$ and, moreover, $\left(I_a^\alpha f\right)(x) \in L_1[a,b]$.*

The following lemma [133] indicated the boundedness of the fractional integration operator for functions in $L_p(a,b)$:

Lemma 3.1.2. *The fractional integral operator I_a^α, with $\alpha > 0$ is bounded in $L_p(a,b)$, $p \geq 1$.*

Some properties of integer-order integrals are preserved by the fractional integral operator of Riemann-Liouville.

Theorem 3.1.3. *Let $f \in L_1[a,b]$ and $m, n \geq 0$. Then*

$$I_a^m I_a^n f = I_a^{m+n} f .$$

Corollary 3.1.1. *Under the assumption of Theorem 3.1.3,*

$$I_a^m I_a^n f = I_a^n I_a^m f .$$

It can be verified that the Riemann-Liouville fractional integral of the function $(x-a)^{\beta-1}$, leads to a power function of the same form.

Property 3.1.1. *For $\alpha, \beta > 0$ and $f(x) = (x-a)^{\beta-1}$, then*

$$\begin{aligned} I_a^\alpha f(x) &= \frac{1}{\Gamma(\alpha)} \int_a^x (x-t)^{\alpha-1} (t-a)^{\beta-1} \mathrm{d}t \\ &= \frac{\Gamma(\beta)}{\Gamma(\beta+\alpha)} (x-a)^{\beta+\alpha-1} . \end{aligned} \tag{3.8}$$

Specifically, for $\beta = 1$, the Riemann-Liouville integral of $f(x) = 1$ is

$$(I_a^\alpha 1)(x) = \frac{1}{\alpha\Gamma(\alpha)} (x-a)^\alpha . \tag{3.9}$$

3.1.2 Riemann-Liouville Fractional Derivative

Lemma 3.1.1 states $D^n f = D^m I_a^{m-n} f$, such that $m, n \in \mathbb{N}$ and $m > n$. By assumption that n is not an integer, the meaningfulness of $D^m I_a^{m-n} f$ is still preserved.

Definition 3.1.5. *Let $\alpha \in \mathbb{R}^+$ and $n = [\alpha] + 1$. The operator D_a^α, defined by*

$$\begin{aligned} D_a^\alpha f(x) &:= D^n I_a^{n-\alpha} f(x) \\ &= \frac{1}{\Gamma(n-\alpha)} \left(\frac{d}{dx}\right)^n \int_a^x (x-t)^{n-\alpha-1} f(t)\, \mathrm{d}t , \quad x > a . \end{aligned} \tag{3.10}$$

is called the Riemann-Liouville fractional differential operator of order α.

For $\alpha = 0$, the operator D_a^0 is defined as the identity operator, i.e. $D_a^0 \equiv I$. The operator D_a^α coincides with the ordinary differential operator D^n whenever $n \in \mathbb{N}$. The following two lemmas [41, 85] illustrate the conditions for existence of the Riemann-Liouville fractional derivative D_a^α:

Lemma 3.1.3. *Let $f \in A^1[a,b]$ and $0 < \alpha < 1$. Then $D_a^\alpha f$ exists almost everywhere in $[a,b]$. Moreover $D_a^\alpha f \in L_p[a,b]$ for $1 \leq p < \frac{1}{\alpha}$ and*

$$D_a^\alpha f(x) = \frac{1}{\Gamma(1-\alpha)} \left(\frac{f(a)}{(x-a)^\alpha} + \int_a^x f'(t) (x-t)^{-\alpha} \mathrm{d}t \right) . \tag{3.11}$$

Lemma 3.1.4. *Let $\alpha > 0$ and $n = [\alpha] + 1$. If $f \in A^n[a,b]$, then $D_a^\alpha f$ exists almost everywhere on $[a,b]$ and is represented by*

$$\begin{aligned} D_a^\alpha f(x) &= \sum_{k=0}^{n-1} \frac{f^{(k)}(a)}{\Gamma(1+k-\alpha)}(x-a)^{k-\alpha} \\ &\quad + \frac{1}{\Gamma(n-\alpha)}\left(\int_a^x f^{(k)}(t)(x-t)^{n-\alpha-1}\mathrm{d}t\right). \end{aligned} \tag{3.12}$$

The following statement shows that the fractional differentiation is an inverse operation to fractional integral [133]:

Lemma 3.1.5. *Let $\alpha > 0$ and $f \in L_p[a,b]$ $(p \geq 1)$, then the following relation is held true almost everywhere on $[a,b]$*

$$D_a^\alpha I_a^\alpha f(x) = f(x). \tag{3.13}$$

Property 3.1.2. *If $\alpha > \beta > 0$, then, for $f \in L_p[a,b]$ $(p \geq 1)$ the relation*

$$D_a^\beta I_a^\alpha f(x) = I_a^{\alpha-\beta} f(x), \tag{3.14}$$

is held true almost everywhere on $[a,b]$.

Theorem 3.1.4. *Let f_1 and f_2 be two functions defined on $[a,b]$ such that the Riemann-Liouville fractional derivative of them, i.e. $D_a^\alpha f_1(x)$ and $D_a^\alpha f_2(x)$ exist almost everywhere. Moreover, let $c_1, c_2 \in \mathbb{R}$. Then $D_a^\alpha(c_1 f_1 + c_2 f_2)$ exists almost everywhere and*

$$D_a^\alpha(c_1 f_1 + c_2 f_2) = c_1 D_a^\alpha f_1 + c_2 D_a^\alpha f_2, \quad \alpha > 0. \tag{3.15}$$

3.1.2.1 Riemann-Liouville Fractional Derivative of a Constant

It can be verified whenever Riemann-Liouville fractional differentiation operates on the power function, $f(x) = (x-a)^{\beta-1}$, results in a power function of the same form:

Property 3.1.3. *If $\alpha, \beta > 0$, and $f(x) = (x-a)^{\beta-1}$, then*

$$D_a^\alpha f(x) = \frac{\Gamma(\beta)}{\Gamma(\beta-\alpha)}(x-a)^{\beta-\alpha-1}. \tag{3.16}$$

Specifically, whenever $\beta = 1$, the Riemann-Liouville fractional derivative of a constant is not generally equal to zero, in contrast to the classical derivative operators:

$$(D_a^\alpha 1)(x) = \frac{1}{\Gamma(1-\alpha)}(x-a)^{-\alpha}, \quad 0 < \alpha < 1. \tag{3.17}$$

On the other hand, under particular circumstances, the fractional derivative of power functions is equal to zero:

Corollary 3.1.2. *Let $\alpha > 0$ and $n = [\alpha] + 1$. The equality $D_a^\alpha f(x) = 0$ is valid if, and only if,*

$$f(x) = \sum_{k=1}^{n} c_k (x-a)^{\alpha-k}, \tag{3.18}$$

where $c_k \in \mathbb{R}$ $(k = 1, \ldots, n)$ are arbitrary constants and in particular whenever $0 < \alpha \leq 1$, the relation $D_a^\alpha f(x) = 0$ is held true if, and only if, $f(x) = c(x-a)^{\alpha-1}$ with any $c \in \mathbb{R}$.

3.1.2.2 Riemann-Liouville Fractional Integral and Derivative on the Half-Axis

The Riemann-Liouville fractional integral and derivative on the half-axis, $\mathbb{R}^+$, are respectively defined as follows:

$$I_0^\alpha f(x) := \frac{1}{\Gamma(\alpha)} \int_0^x (x-t)^{\alpha-1} f(t)\,\mathrm{d}t\,, \quad x>0, \alpha>0\,, \tag{3.19}$$

and

$$\begin{aligned} D_0^\alpha f(x) &:= D^n I_0^{n-\alpha} f(x) \\ &= \frac{1}{\Gamma(n-\alpha)} \left(\frac{d}{dx}\right)^n \int_0^x (x-t)^{n-\alpha-1} f(t)\,\mathrm{d}t\,, \quad x>0, \alpha>0\,, \end{aligned} \tag{3.20}$$

where $n = [\alpha]+1$. Specifically whenever $0<\alpha<1$ and $x>0$, then

$$D_0^\alpha f(x) = \frac{1}{\Gamma(1-\alpha)} \frac{d}{dx} \int_0^x (x-t)^{-\alpha} f(t)\,\mathrm{d}t\,. \tag{3.21}$$

Theorem 3.1.5. *Let $\alpha, \beta > 0$, $p \geq 1$ and $\alpha + \beta < \frac{1}{P}$. If $f \in L_p(\mathbb{R}^+)$, then the semigroup property*

$$I_0^\alpha I_0^\beta f(x) = I_0^{\alpha+\beta} f(x)\,, \tag{3.22}$$

is held true.

Lemma 3.1.6. *Let $\alpha > 0$ and $f \in L_1(\mathbb{R}^+)$, then the relation*

$$D_0^\alpha I_0^\alpha f(x) = f(x)\,, \tag{3.23}$$

is held true.

Property 3.1.4. *If $\alpha > \beta > 0$, then, for $f \in L_1(\mathbb{R}^+)$, the relation*

$$D_0^\beta I_0^\alpha f(x) = I_0^{\alpha-\beta} f(x)\,, \tag{3.24}$$

is held true.

There is a fundamental distinction between differential operators of integer-order and the Riemann-Liouville fractional derivative. The classical differentiation operator is *local* in nature. Unlike integer-order derivatives, it is needed to know the function f throughout the interval $[a,x]$ in order to calculate $D_a^n f(x)$. This fact is shown even more appropriate in the following Lemma, where an alternative definition of Riemann-Liouville fractional derivative is represented. This expression is more practical for the development of certain numerical methods of solving fractional differential equations.

Lemma 3.1.7. *Let $\alpha > 0$, $\alpha \notin \mathbb{N}$ and $n = [\alpha]+1$. Moreover, let $f \in C^n[a,b]$. then*

$$D_a^\alpha f(x) = \frac{1}{\Gamma(-\alpha)} \int_a^x (x-t)^{-\alpha-1} f(t)\,\mathrm{d}t\,, \quad x \in [a,b]\,. \tag{3.25}$$

In Lemma 3.1.7, the integrand has a singularity of order $n+1$. Such an integral is defined according to Hadamard's finite-part integral concept [41].

3.1.3 Caputo Fractional Derivative

Fractional differentiation operator of Caputo type was first introduced in [26, 27] by Michele Caputo. In this section, the definition and some properties of Caputo fractional derivative, ${}^{C}D_{a}^{\alpha}$ are presented:

Definition 3.1.6. *Let $[a,b]$ be a finite interval of the real line, and let $\alpha > 0$, $n-1 < \alpha < n$ $(n \in \mathbb{N})$. Moreover, assume the function f is such that $D^n f \in L_1[a,b]$. The operator ${}^{C}D_{a}^{\alpha}$ defined by*

$$\begin{aligned} {}^{C}D_{a}^{\alpha} f(x) &:= I_{a}^{n-\alpha} D^n f(x) \\ &= \frac{1}{\Gamma(n-\alpha)} \int_a^x (x-t)^{n-\alpha-1} f^{(n)}(t)\,\mathrm{d}t\,, \quad x > a\,, \end{aligned} \tag{3.26}$$

is called the Caputo fractional differential operator of order α.

Whenever $\alpha \in \mathbb{N}$, n will be equal to α and ${}^{C}D_{a}^{\alpha} f(x)$ indicates

$$D_{a}^{\alpha} f(x) = I_{a}^{0} D^n f(x) = D^n f(x)\,, \tag{3.27}$$

that recovers the integer-order differential operator. The following Theorem states an important connection between fractional differential operators of Riemann-Liouville and Caputo types:

Theorem 3.1.6. *Let $\alpha \geq 0$ and $n = \lceil \alpha \rceil$. Moreover let $f \in A^n[a,b]$. Then,*

$${}^{C}D_{a}^{\alpha} f(x) = D_{a}^{\alpha} \left[f(x) - \sum_{k=0}^{n-1} \frac{f^{(k)}(a)}{k!} (x-a)^k \right]. \tag{3.28}$$

In particular, whenever $0 < \alpha < 1$, Eq. (3.28) will be in the following form:

$${}^{C}D_{a}^{\alpha} f(x) = D_{a}^{\alpha} \left[f(x) - f(a) \right], \tag{3.29}$$

and also if the Caputo and Riemann-Liouville fractional derivatives of the function f exist and if $\alpha \notin \mathbb{N}$, then ${}^{C}D_{a}^{\alpha} f(x)$ and $D_{a}^{\alpha} f(x)$ are connected with each other by the following relation:

$${}^{C}D_{a}^{\alpha} f(x) = D_{a}^{\alpha} f(x) - \sum_{k=0}^{n-1} \frac{f^{(k)}(a)}{\Gamma(k-\alpha+1)} (x-a)^{k-\alpha}\,, \tag{3.30}$$

and specifically, for $0 < \alpha < 1$, Eq. (3.30) is in the following form:

$${}^{C}D_{a}^{\alpha} f(x) = D_{a}^{\alpha} f(x) - \frac{f(a)}{\Gamma(1-\alpha)} (x-a)^{-\alpha}\,. \tag{3.31}$$

Equation (3.31) shows that the Caputo fractional derivative coincides with the Riemann-Liouville fractional derivative whenever $f(a) = 0$. Some properties of Caputo fractional differential operator are described below. Before that, let ${}^{C}D_{a}^{\alpha}[f(t)](x) \equiv {}^{C}D_{a}^{\alpha} f(x)$:

Property 3.1.5. *Let $\alpha, \beta > 0$ and $n = \lceil \alpha \rceil$. For $f(x) = (x-a)^{\beta-1}$ the following relation is held true:*

$$ {}^{C}D_a^{\alpha}\left[(t-a)^{\beta-1}\right](x) = \frac{\Gamma(\beta)}{\Gamma(\beta-\alpha)}(x-a)^{\beta-1}, \quad \beta > n. \tag{3.32}$$

and for $g(x) = (x-a)^m$, it is obtained that

$$ {}^{C}D_a^{\alpha}\left[(t-a)^m\right](x) = 0, \quad (m = 0, 1, \ldots, n-1). \tag{3.33}$$

Specifically, for $m = 0$, it is concluded that the Caputo derivative of a constant is equal to zero:

$$ {}^{C}D_a^{\alpha}[1](x) = 0. \tag{3.34}$$

The Caputo fractional derivative provides an operator inverse to the fractional integral operator of Riemann-Liouville, from the left:

Lemma 3.1.8. *Let $\alpha > 0$ and $f(x) \in C[a,b]$, then*

$$ {}^{C}D_a^{\alpha} I_a^{\alpha} f(x) = f(x). \tag{3.35}$$

Lemma 3.1.9. *Let $\alpha > 0$ and $n = \lceil \alpha \rceil$, and assume $f(x) \in C^n[a,b]$, then*

$$ I_a^{\alpha} {}^{C}D_a^{\alpha} f(x) = f(x) - \sum_{k=0}^{n-1} \frac{f^{(k)}(a)}{k!}(x-a)^k, \tag{3.36}$$

In particular, if $0 < \alpha \leq 1$ and $f(x) \in C[a,b]$, then

$$ I_a^{\alpha} {}^{C}D_a^{\alpha} f(x) = f(x) - f(a). \tag{3.37}$$

Lemma 3.1.10. *Let $\alpha > 0$, $\alpha \notin \mathbb{N}$ and $n = \lceil \alpha \rceil$, and assume $f(x) \in C^n[a,b]$. Then ${}^{C}D_a^{\alpha} f(x) \in C[a,b]$.*

The principal computational rules for the Caputo derivative are similar to those for the Riemann-Liouville derivative.

Theorem 3.1.7. *Let $f_1, f_2 : [a,b] \to \mathbb{R}$ such that the Caputo fractional derivative of them, i.e. ${}^{C}D_a^{\alpha} f_1(x)$ and ${}^{C}D_a^{\alpha} f_2(x)$ exist almost everywhere. Moreover, let $c_1, c_2 \in \mathbb{R}$. Then ${}^{C}D_a^{\alpha}(c_1 f_1 + c_2 f_2)(x)$ exists almost everywhere and*

$$ {}^{C}D_a^{\alpha}(c_1 f_1 + c_2 f_2)(x) = c_1 {}^{C}D_a^{\alpha} f_1(x) + c_2 {}^{C}D_a^{\alpha} f_2(x), \quad \alpha > 0. \tag{3.38}$$

The following Lemma represents the Caputo derivative of Mittag-Leffler function, $E_{\alpha}[\lambda(t-a)^{\alpha}](x)$, and indicates why Mittag-Leffler functions (more specifically those with one parameter) are very important in fractional calculus. The eigenfunctions of Caputo differential operator can be represented in terms of Mittag-Leffler functions. The so-called one parameter Mittag-Leffler function $E_{\alpha}(z)$ is defined as a power series, denoted by

$$ E_{\alpha}(z) = \sum_{k=0}^{\infty} \frac{z^k}{\Gamma(\alpha k + 1)}, \qquad \alpha > 0 \qquad z \in \mathbb{C}. \tag{3.39}$$

which was first introduced by G. M. Mittag-Leffler and could be considered as the generalization of the exponential function due to the replacement of $\Gamma(k+1)$ by $\Gamma(\alpha k + 1)$ in the exponential series formula (for instance, see [67, 119]). It could be obviously perceived that $E_{\alpha}(0) = 1$. The Mittag-Leffler function will be discussed in Section 5.1.1 in more detail.

Lemma 3.1.11. *If $\alpha > 0$ and $a, \lambda \in \mathbb{R}$, then*

$$ {}^{C}D_{a}^{\alpha} E_{\alpha}\left[\lambda(t-a)^{\alpha}\right](x) = \lambda E_{\alpha}\left[\lambda(x-a)^{\alpha}\right], \quad \alpha \notin \mathbb{N},\ x \geq a, \tag{3.40} $$

Particularly, whenever $\alpha = n \in \mathbb{N}$,

$$ D^{n} E_{\alpha}\left[\lambda(x-a)^{n}\right] = E_{\alpha}\left[\lambda(x-a)^{n}\right]. \tag{3.41} $$

3.1.3.1 Caputo Fractional Derivative on the Half-Axis

Equation (3.26) can be used to define the fractional derivative of Caputo type on the half axis $\mathbb{R}^{+}$. The Caputo fractional derivative of the function $f(x)$ with the order $\alpha > 0$ ($\alpha \notin \mathbb{N}$) is defined as follows:

$$ {}^{C}D_{0}^{\alpha} f(x) = \frac{1}{\Gamma(n-\alpha)} \int_{0}^{x} (x-t)^{n-\alpha-1} f^{(n)}(t)\, \mathrm{d}t, \quad x > 0. \tag{3.42} $$

Whenever $0 < \alpha < 1$, (3.42) takes the form below:

$$ {}^{C}D_{0}^{\alpha} f(x) = \frac{1}{\Gamma(1-\alpha)} \int_{0}^{x} (x-t)^{-\alpha} f'(t)\, \mathrm{d}t, \quad x > 0. \tag{3.43} $$

The Laplace transform of Caputo fractional derivative, ${}^{C}D_{a}^{\alpha} f(x)$, is asserted by the following:

Lemma 3.1.12. *Let $\alpha > 0$ and $n - 1 < \alpha \leq n$ ($n \in \mathbb{N}$) such that $f \in C^{n}(\mathbb{R}^{+})$ and $f^{(n)} \in L_{1}(0, b)$, for some $b > 0$ and the following estimate*

$$ \left| f^{(n)}(x) \right| \leq B e^{Ax}, \quad (x > b > 0), \tag{3.44} $$

is held true for constants $A, B > 0$. Moreover assume the Laplace transforms $\mathcal{L}f$ and $\mathcal{L}\left[f^{(n)}\right]$ exist and

$$ \lim_{x \to +\infty} f^{(n)}(x) = 0, \quad k = 0, 1, \ldots, n-1, \tag{3.45} $$

Then the relation

$$ \left(\mathcal{L}\, {}^{C}D_{0}^{\alpha} f\right)(s) = s^{\alpha} (\mathcal{L}f)(s) - \sum_{k=0}^{n-1} s^{\alpha-k-1} f^{(n)}(0). \tag{3.46} $$

In particular, whenever $0 < \alpha \geq 1$, then

$$ \left(\mathcal{L}\, {}^{C}D_{0}^{\alpha} f\right)(s) = s^{\alpha} (\mathcal{L}f)(s) - s^{\alpha-1} f(0). \tag{3.47} $$

Existence and uniqueness theorems of fractional differential equations (FDEs) are discussed in next section.

3.2 Existence and Uniqueness Theorems for FDEs

The investigations and examinations in the field of the existence and uniqueness of solutions to fractional differential equations have been carried out for mainly Riemann-Liouville and then Caputo fractional differentiation operators. Many researches have been conducted on the topic, the most popular of which are as follows:
An initial value problem (the so-called Cauchy problem) was studied in [7], by Al-Bassam for $0 < \alpha \leq 1$, in the space of continuous functions $C[a, b]$. Al-Bassam reduced the initial value problem

$$D_a^{\alpha} y(x) = f(x, y(x)), \quad 0 < \alpha < 1, \quad x > a, \tag{3.48}$$

equipped with the initial condition

$$I_a^{1-\alpha} y(a) = b, \quad b \in \mathbb{R}, \tag{3.49}$$

to the Volterra nonlinear integral equation

$$\begin{aligned} y(x) &= \frac{b(x-a)^{\alpha-1}}{\Gamma(\alpha)} \\ &\quad + \frac{1}{\Gamma(\alpha)} \int_a^x (x-t)^{\alpha-1} f(t, y(t))\, \mathrm{d}t, \quad x > a,\ 0 < \alpha < 1. \end{aligned} \tag{3.50}$$

and established existence of the continuous solution $y(x)$. He indicated, but not proved the equivalence of the Cauchy type problem and the Volterra integral equation (VIE). It is noted that the conditions suggested in [7] are not suitable for a general Cauchy type problem. Several other theorems of existence and uniqueness of solution to fractional differential equations could be observed in, for instance, [38, 46, 119]. In [20, 77] the fractional initial value problems with complex order, $\alpha \in \mathbb{C}$, were studied in the space $L_1(a, b)$ and the obtained results were extended to the system of such problems in [21]. The conditions for a unique solution to Cauchy type problems were established in [76, 79, 84]. The uniqueness and existence of a local continuous solution to fractional initial value problems was proved in [40].

These mentioned studies are devoted to ordinary fractional differential equations with Riemann-Liouville differentiation operator. But, such equations with Caputo derivative, ${}^{C}D_a^{\alpha} f(x)$, are not investigated extensively. The authors in [101] used the operational method to prove the uniqueness of solution to Cauchy type problems. Diethelm and Ford [42] investigated the nonlinear initial value problems in the sense of Caputo derivative for the fractional order $\alpha > 0$ and proved existence and uniqueness of a local continuous solution to the problem. Kilbas and Marzan [78, 83] studied the Cauchy problem with Caputo differentiation operator for $\alpha \in \mathbb{C}$ on a finite interval of $\mathbb{R}$ and established conditions for a unique solution to the problem

$$\begin{aligned} &{}^{C}D_0^{\alpha} y(x) = f(x, y(x)), \qquad (a \leq x \leq b), \\ &y^{(k)}(0) = b_k \in \mathbb{C}, \qquad (k = 0, 1, \ldots, n-1), \end{aligned}$$

where $n = [\Re(\alpha)] + 1$ for $\alpha \notin \mathbb{N}$ and $n = \alpha$ for $\alpha \in \mathbb{N}$. In [150], the author considered the Cauchy problem

$$\begin{aligned} &{}^{C}D_0^{\alpha} y(x) = f(x, y(x)) , \qquad (0 < x < 1) , \\ &y(0) = 0 , \end{aligned}$$

where the function f is continuous, and proved the uniqueness of a positive solution, $y(x) > 0$, to the problem. Additional aspects of the existence and uniqueness problems could be observed in [41, 81, 82, 133].

3.2.1 Equations with Riemann-Liouville Derivative

In this section, the conditions for a unique global solution to the Cauchy type problem

$$D_a^{\alpha} y(x) = f(x, y(x)) , \quad \alpha > 0 , \quad x > a , \tag{3.51}$$

equipped with the initial conditions

$$D_a^{\alpha-k} y(a) = b_k , \quad b_k \in \mathbb{R} , \quad (k = 1, \ldots, n) , \quad n = \lceil \alpha \rceil , \tag{3.52}$$

in the space of functions $\mathbb{L}^{\alpha}(a, b)$, defined for $\alpha > 0$ by

$$L^{\alpha}(a, b) := \{ y \in L_1(a, b) : D_a^{\alpha} \in L_1(a, b) \} \tag{3.53}$$

are given, where $L_1(a, b)$ is the space of integrable functions in a finite interval $[a, b]$ of the real axis $\mathbb{R}$. The notation $D_a^{\alpha-k} y(a)$ means

$$D_a^{\alpha-k} y(a) = \lim_{x \to a+} D_a^{\alpha-k} y(x) , \quad 1 \le k \le n-1 , \tag{3.54}$$

$$D_a^{\alpha-n} y(a) = \lim_{x \to a+} I_a^{n-\alpha} y(x) , \quad \alpha \ne n , \tag{3.55}$$

$$D_a^{0} y(a) = y(a) , \quad \alpha = n . \tag{3.56}$$

The approach is based on introducing the VIE equivalent to the Cauchy problem, in the sense that, if the function $y(x) \in L_1(a, b)$ satisfies the Eqs. (3.51)-(3.52) then it also satisfies the VIE

$$\begin{aligned} y(x) \quad = \quad & \sum_{j=1}^{n} \frac{b_j}{\Gamma(\alpha - j + 1)} (x - a)^{\alpha - j} \\ & + \frac{1}{\Gamma(\alpha)} \int_a^x (x - t)^{\alpha - 1} f(t, y(t)) \, dt , \qquad x > a , \end{aligned} \tag{3.57}$$

and vice versa.

By Lemma 3.1.2, the fractional integration operator, I_a^{α}, with $\alpha > 0$ is bounded in $L_1(a, b)$:

$$\| I_a^{\alpha} y \|_1 \le \frac{(b - a)^{\alpha}}{\Gamma(\alpha + 1)} \| y \|_1 . \tag{3.58}$$

Theorem 3.2.1. *Let $\alpha > 0$, $n = \lceil \alpha \rceil$, and let G be an open subset of $\mathbb{R}$. Moreover assume that the function $f : (a, b] \times G \to \mathbb{R}$ is such that $f \in L_1(a, b)$ for any $y \in G$. If $y(x) \in L_1(a, b)$, then the function $y(x)$ satisfies a.e. (3.51) and (3.52) if, and only if, $y(x)$ satisfies a.e. (3.57).*

Corollary 3.2.1. *Let $0 < \alpha < 1$ and G be an open subset of $\mathbb{R}$. Moreover let the function $f : (a, b] \times G \to \mathbb{R}$ be such that $f \in L_1(a, b)$ for any $y \in G$.*
If $y(x) \in L_1(a, b)$, then the function $y(x)$ satisfies a.e. (3.48) and (3.49) if, and only if, $y(x)$ satisfies a.e. (3.50).

The existence of a unique solution to the Cauchy problem (3.51) and (3.52) is established under the conditions of Theorem 3.2.1 and an additional Lipschitz condition on the function $f(x, y(x))$ with respect to the second variable, $y(x)$, i.e. for all $x \in (a, b]$ and for all $y_1, y_2 \in G \subset \mathbb{R}$

$$|f(x, y_1) - f(x, y_2)| \leq L |y_1 - y_2| , \quad 0 < L < \infty , \tag{3.59}$$

where the constant L does not depend on $x \in [a, b]$.

Theorem 3.2.2. *Let $\alpha > 0$, $n = \lceil \alpha \rceil$, and let G be an open subset of $\mathbb{R}$. Moreover let the function $f : (a, b] \times G \to \mathbb{R}$ be such that $f \in L_1(a, b)$ for any $y \in G$ and (3.59) be satisfied. Then there is a unique solution $y(x)$ to the initial value problem (3.51) and (3.52) in the space $\mathbb{L}^{\alpha}(a, b)$.*

3.2.2 Equations with Caputo Derivative

In this section, the existence and uniqueness of solutions to the initial value problem

$${}^{C}D_0^{\alpha} y(x) = f(x, y(x)) , \quad \alpha > 0, \tag{3.60}$$

combined with the initial conditions

$$D^k y(0) = b_k , \quad b_k \in \mathbb{R} , \quad (k = 0, 1, \ldots, n-1) , \quad n = \lceil \alpha \rceil , \tag{3.61}$$

are discussed. All the results presented here can be extended to vector valued functions, i.e. systems of differential equations [41]. In many applications in Science and engineering, the fractional order α is constrained up to one, i.e. $0 < \alpha \leq 1$. In this case (3.60) and (3.61) will be reduced to the Cauchy problem

$${}^{C}D_0^{\alpha} y(x) = f(x, y(x)) , \quad 0 < \alpha \leq 1, \tag{3.62}$$

with the initial conditions

$$y(0) = b , \quad b \in \mathbb{R} . \tag{3.63}$$

Lemma 3.2.1. *Let $\alpha > 0$, $n = \lceil \alpha \rceil$ and $b_k \in \mathbb{R}$ $(k = 0, 1, \ldots, n-1)$. Let $K > 0$, and $h^* > 0$. Define the set R as*

$$R = \left\{ (x, y) : \ x \in [0, h^*] , \ \left| y - \sum_{k=0}^{n-1} \frac{x^k b_k}{k!} \right| \leq K \right\} .$$

Let the function $f : R \to \mathbb{R}$ be continuous. Define

$$M := \sup_{(x,z) \in R} |f(x, z)|$$

and

$$h := \begin{cases} h^* & \text{if } M = 0\,, \\ \min\left\{h^*, \left(\frac{K\Gamma(n+1)}{M}\right)^{\frac{1}{n}}\right\} & \text{otherwise.} \end{cases}$$

The function $y \in C[0,h]$ is a solution of (3.60) and (3.61) if and only if it is a solution to the nonlinear VIE of the second kind

$$y(x) = \sum_{k=0}^{n-1} \frac{x^k b_k}{k!} + \frac{1}{\Gamma(\alpha)} \int_0^x (x-t)^{\alpha-1} f(t, y(t))\, \mathrm{d}t$$

Theorem 3.2.3. *Assume the hypotheses of Lemma 3.2.1. There exists a function $y \in C[0,h]$ solving the initial value problem (3.60) and (3.61).*

Theorem 3.2.4. *Assume the hypotheses of Lemma (3.2.1), except that the set R, the domain of definition of the function f on the right-hand side of (3.60), is now considered to be $R = \mathbb{R}^2$. In addition, let f be continuous and there exist constants $c_1 \geq 0$, $c_2 \geq 0$ and $0 \leq \mu < 1$ such that*

$$|f(x,y)| \geq c_1 + c_2 |y|^{\mu} \qquad \text{for all } (x,y) \in R.$$

Then, there exists a function $y \in C[0,\infty)$ solving the initial value problem (3.60) and (3.61).

Theorem 3.2.5. *Let $\alpha > 0$, $n = \lceil \alpha \rceil$ and $b_k \in \mathbb{R}$ $(k = 0, 1, \ldots, n-1)$. Let $K > 0$, and $h^* > 0$. Define the set R as*

$$R = \left\{ (x,y) :\ x \in [0,h^*]\,,\ \left| y - \sum_{k=0}^{n-1} \frac{x^k b_k}{k!} \right| \leq K \right\}.$$

Let the function $f : R \to \mathbb{R}$ be continuous and fulfil a Lipschitz condition with respect to y:

$$|f(x,y_1) - f(x,y_2)| \geq L\,|y_1 - y_2|$$

where $L > 0$ is a constant independent of x, y_1 and y_2. Define h as

$$h := \begin{cases} h^* & \text{if } M = 0\,, \\ \min\left\{h^*, \left(\frac{K\Gamma(n+1)}{M}\right)^{\frac{1}{n}}\right\} & \text{otherwise}\,, \end{cases}$$

where M is defined as

$$M := \sup_{(x,z)\in R} |f(x,z)|\,.$$

Then, there exists a unique solution $y \in [0,h]$ to the initial value problem (3.60) and (3.61).

Theorem 3.2.6. *Assume the hypotheses of Theorem 3.2.5, except that the set R, the domain of the definition of the function f on the right-hand side of (3.60), is defined as $R = [0,\infty) \times \mathbb{R}$. Then, there exists a uniquely defined function $y \in [0,\infty)$ solving initial value problem (3.60) and (3.61).*

The following theorem [95], guarantees the existence of solution to the Cauchy problem

$$\begin{cases} {}^{C}D_{t_0}^{\alpha} x(t) = f(t, x(t)), & 0 < \alpha \leq 1 \\ x(t_0) = x_0 \end{cases} \tag{3.64}$$

where $(t_0, x_0) \in D$, with D a nonempty open subset of $\mathbb{R} \times \mathbb{R}^n$ and $f : D \to \mathbb{R}^n$. The hypothesis is stated in terms of the rectangular subset of $\mathbb{R} \times \mathbb{R}^n$ centred about (t_0, x_0), defined by (2.20). The norm of $x \in \mathbb{R}^n$ with coordinates x_i $(i = 1, 2, \ldots, n)$ is defined by (2.21).

Theorem 3.2.7. *The Cauchy problem (3.64) has a solution if for some $R_{a,b} \subset D$ centred about (t_0, x_0), the restriction of $f(t, x)$ to $R_{a,b}$ is continuous in x for fixed t, measurable with respect to t for fixed x, and satisfies*

$$|f(t, x)| \leq m(t), \qquad (t, x) \in R_{a,b},$$

for some Lebesgue integrable function $m \in L^2(I)$ for almost every t in $I = [t_0 - a, t_0 + a]$.

3.2.3 Existence of solution to the fractional KP model

The FKP can be expressed as follows

$$\begin{aligned} {}^{C}D_0^{\alpha} x(t) &= cy - \mu_2 x + \frac{p_1 xz}{g_1 + z} + s_1, \\ {}^{C}D_0^{\alpha} y(t) &= r_2 y(1 - by) - \frac{axy}{g_2 + y}, \\ {}^{C}D_0^{\alpha} z(t) &= \frac{p_2 xy}{g_3 + y} - \mu_3 z + s_2, \end{aligned} \tag{3.65}$$

with the initial condition

$$x(0) = x_0, \quad y(0) = y_0, \quad z(0) = z_0. \tag{3.66}$$

where ${}^{C}D_0^{\alpha}$ denotes the Caputo differentiation operator. Equation (3.65) can be expressed as

$$\begin{cases} {}^{C}D_0^{\alpha} X(t) = f(t, X(t)), & 0 < \alpha \leq 1 \\ X(0) = X_0 \end{cases} \tag{3.67}$$

where $f(t, X) = (f_1, f_2, f_3)^T$, $X(0) = (x_0, y_0, z_0)^T$, and

$$\begin{aligned} f_1 &= cy - \mu_2 x + \frac{p_1 xz}{g_1 + z} + s_1, \\ f_2 &= r_2 y(1 - by) - \frac{axy}{g_2 + y}, \\ f_3 &= \frac{p_2 xy}{g_3 + y} - \mu_3 z + s_2. \end{aligned} \tag{3.68}$$

The existence and uniqueness of solution to (3.67) is guaranteed by Theorem 3.2.6. While the external sources of drugs are expressed as control functions, then the

vector f will be as follows:

$$\begin{aligned} f_1 &= cy - \mu_2 x + \frac{p_1 xz}{g_1 + z} + s_1 u(t) , \\ f_2 &= r_2 y(1 - by) - \frac{axy}{g_2 + y} , \\ f_3 &= \frac{p_2 xy}{g_3 + y} - \mu_3 z + s_2 u(t) . \end{aligned} \tag{3.69}$$

The existence of solution to the Cauchy problem (3.67), in which f is defined by (3.69), is guaranteed by Theorem 3.2.7. This can be shown by following the procedure which has been mentioned in Section 2.2.

3.3 Stability of Fractional Differential Equations

The attention is restricted here to the class of nonlinear fractional differential equations

$$ {}^{C}D_0^{\alpha} y(x) = f(x, y(x)) , \qquad \alpha \in (0, 1) , \tag{3.70a}$$

$$ y(0) = y_0 . \tag{3.70b}$$

where ${}^{C}D_a^{\alpha} y(x)$ denotes the Caputo fractional derivative of the function $y(x)$. While the stability of a given differential equation is discussed, the behaviour of the solution to (3.70) is analysed for $x \to \infty$. Thus, only the problems, solutions of which exist on $[0, \infty)$ are considered. Furthermore, it is assumed that the initial value problem (3.70) has a unique solution on $[0, b)$ with some $b \leq \infty$. This implies that $f : [0, \infty) \times \Omega \to \mathbb{R}^n$, $\Omega \subset \mathbb{R}^n$ is continuous in x and Lipschitz in y on its domain.

Definition 3.3.1. *The constant y_{eq} is an equilibrium point of (3.70), if and only if*

$$ {}^{C}D_0^{\alpha} y(x)\Big|_{y(x)=y_{eq}} = f(x, y_{eq}) . \tag{3.71}$$

Without loss of generality, the equilibrium point could be supposed to be $y_{eq} = 0$. This condition means that $y(x) = 0$ is a solution of (3.70), which could be done by the change of variable $\bar{y}(x) = y(x) - y_{eq}$, by referring to Theorem 3.1.7 and (3.34)

$$\begin{aligned} {}^{C}D_0^{\alpha} y(x) &= f(x, y(x)) , \\ {}^{C}D_0^{\alpha} [\bar{y}(x) + y_{eq}] &= f(x, \bar{y}(x) + y_{eq}) , \\ {}^{C}D_0^{\alpha} \bar{y}(x) + {}^{C}D_0^{\alpha} [y_{eq}] &= g(x, \bar{y}(x)) , \\ {}^{C}D_0^{\alpha} \bar{y}(x) &= g(x, \bar{y}(x)) . \end{aligned}$$

Definition 3.3.2. *The solution $y(x) = 0$ of (3.70a) is called stable if, for every $\epsilon > 0$ there exists some $\delta > 0$ such that for any initial condition (3.70b), the solution of (3.70) satisfies*

$$\forall x \geq 0, \ \|y_0\| < \delta \to \|y(x)\| < \epsilon .$$

The solution $y(x) = 0$ of (3.70a) is asymptotically stable if, it is stable and there exists some $\gamma > 0$ such that

$$\|y_0\| < \gamma \to \lim_{x \to \infty} \|y(x)\| = 0 .$$

For $0 < \alpha < 1$, system (3.70) has the same equilibrium points as the integer-order system $\dot{y}(x) = f(x, y(x))$. The stability analysis of the homogeneous linear fractional differential equations with constant coefficients was studied by Matignon [107], where the necessary and sufficient condition of stability was proved. Consider the n-dimensional system of linear fractional differential equations ${}^{C}D_0^{\alpha} y(x) = Ay(x)$, where $A \in \mathbb{R}^{n\times n}$. The solution $y(x) = 0$ of the system ${}^{C}D_0^{\alpha} y(x) = Ay(x)$ is stable if and only if the eigenvalues λ_k $(k = 1, 2, \ldots, n)$ of the matrix A satisfy $|\arg \lambda_k| \geq n\pi/2$ and all eigenvalues with $|\arg \lambda_k| = n\pi/2$ have a geometric multiplicity that coincides with their algebraic multiplicity. In addition, the solution $y(x) = 0$ of the system ${}^{C}D_0^{\alpha} y(x) = Ay(x)$ is asymptotically stable if and only if all eigenvalues λ_k satisfy $|\arg \lambda_k| > n\pi/2$.

The stability of linear fractional systems has been studied in the last decades [115, 124,125]. By contrast, the stability of nonlinear fractional differential equations is very complex. Exponential stability cannot be applied in order to characterize asymptotic stability of fractional order systems [108]. Some researchers have weakened the criterion of stability, where the Mittag-Leffler stability [1,92] and the L^p-stability [90] were considered. Finally, in [39], the author proved the sufficient condition for the local asymptotical stability of nonlinear autonomous FDEs in the sense of Caputo derivative, where the order of fractional differentiation operator is restricted to one, i.e. $\alpha \in (0, 1)$:

Theorem 3.3.1. *The equilibrium $y_{eq} = 0$ of autonomous nonlinear fractional differential equation ${}^{C}D_a^{\alpha} y(x) = f(y(x))$ with $f'(y) \in C[a, +\infty)$ and $\alpha \in (0, 1)$ is locally asymptotically stable if $\lambda = f'(0) < 0$.*

Consider the system of FDEs:

$$ {}^{C}D_a^{\alpha_i} x_i(t) = f_i(x_1, x_2, \ldots, x_n), \qquad i = 1, 2, \ldots, n, \tag{3.72} $$

Equation (3.72) is called a system of incommensurate FDEs if all α_i's are rational numbers, i.e. $\alpha_i = \frac{v_i}{u_i}$, where $v_i, u_i \in \mathbb{Z}^+$ for $i = 1, 2, \ldots, n$. If in addition, $\alpha_i = \alpha_j$ for $i, j = 1, 2, \ldots, n$, then (3.72) is called a system of commensurate FDEs. The authors in [138] have proved the sufficient condition of asymptotical stability of commensurate fractional differential equations. Then, they presented a sufficient condition for incommensurate fractional differential equations [139]:

Theorem 3.3.2. *Let $\alpha_1 = \alpha_2 = \cdots = \alpha_n \equiv \alpha$. Then, the equilibrium point x_{eq} of (3.72) is asymptotically stable if all the eigenvalues λ_i's $(i = 1, 2, \ldots, n)$ of the Jacobian matrix $J = \partial f/\partial x|_{x_{eq}}$, where $f = [f_1, f_2, \ldots, f_n]^T$, satisfy the condition*

$$ |\arg(\mathrm{eig}(J))| = |\arg(\lambda_i)| > \alpha\frac{\pi}{2}, \quad i = 1, 2, \ldots, n. \tag{3.73} $$

Theorem 3.3.3. *Let m be the lowest common multiple of the denominators u_i's of α_i's, where $\alpha_i = v_i/u_i$, $v_i, u_i \in \mathbb{Z}^+$ and $(u_i, v_i) = 1$ for $i = 1, 2, \ldots, n$. Then, the equilibrium point x_{eq} of (3.72) is asymptotically stable if*

$$ |\arg(\lambda)| > \frac{\pi}{2m} \tag{3.74} $$

for all roots λ,s of

$$ \det(\mathrm{diag}([\lambda^{m\alpha_1} \lambda^{m\alpha_2} \ldots \lambda^{m\alpha_n}]) - J) = 0 \tag{3.75} $$

The notation $\text{diag}\left([\lambda^{m\alpha_1}\lambda^{m\alpha_2}\dots\lambda^{m\alpha_n}]\right)$ expresses the $n\times n$ diagonal matrix

$$\text{diag}\left([\lambda^{m\alpha_1}\lambda^{m\alpha_2}\dots\lambda^{m\alpha_n}]\right)=\begin{bmatrix}\lambda^{m\alpha_1} & 0 & \cdots & 0\\ 0 & \lambda^{m\alpha_2} & \cdots & 0\\ \vdots & \vdots & \ddots & \vdots\\ 0 & 0 & \cdots & \lambda^{m\alpha_n}\end{bmatrix}.$$

3.4 Stability of the FKP Model

In this section, asymptotical stability of the FKP model is discussed according to Theorems 3.3.2 and 3.3.3, where the fractional orders of all equations considered to be rational numbers. The main goal is the tumour-free states and therefore the equilibrium points, in which the tumour is zero, are only considered.

3.4.1 No treatment case

First, the commensurate FKP model is discussed, i.e. $\alpha_1=\alpha_2=\alpha_3$. In the case of no treatment ($s_1=0$ and also $s_2=0$) the only tumour-free equilibrium point is the trivial state, where all the populations are zero, namely $E_0=(0,0,0)$. In this case, the set of all eigenvalues of the Jacobian matrix is $A=\{-\mu_2,r_2,-\mu_3\}$ and

$$|\arg(-\mu_2)|=\pi,\quad |\arg(r_2)|=0,\quad |\arg(-\mu_3)|=\pi.$$

By referring to (3.73), E_0 is always unstable. Now, the incommensurate FKP model is discussed. Since the optimal therapeutic protocols for FKP model are only represented for four cases

$$\begin{aligned}&(1):\alpha_1=1, && \alpha_2=0.9, && \alpha_3=1,\\ &(2):\alpha_1=1, && \alpha_2=0.8, && \alpha_3=1,\\ &(3):\alpha_1=1, && \alpha_2=0.7, && \alpha_3=1,\\ &(4):\alpha_1=1, && \alpha_2=0.6, && \alpha_3=1,\end{aligned}$$

thus, the stability of the FKP model is also examined for these special cases. By referring to Theorem 3.3.3, the results are obtained as follows. The set of all the roots of the polynomial in (3.75) is $A=\left\{(-\mu_2)^{\frac{1}{m\alpha_1}},r_2^{\frac{1}{m\alpha_2}},(-\mu_3)^{\frac{1}{m\alpha_3}}\right\}$ where $m=10$ and $\alpha_1=1$, $\alpha_2=0.9$ and $\alpha_3=1$. Thus

$$\left|\arg\left((-\mu_2)^{\frac{1}{m\alpha_1}}\right)\right|=\frac{\pi}{10},\quad \left|\arg\left(r_2^{\frac{1}{m\alpha_2}}\right)\right|=0,\quad \left|\arg\left((-\mu_3)^{\frac{1}{m\alpha_3}}\right)\right|=\frac{\pi}{10},$$

therefore, according to Theorem 3.3.3, the equilibrium point is unstable. By the same calculations, the similar results are obtained for $\alpha_2=0.8$, $\alpha_2=0.7$, $\alpha_2=0.6$.

3.4.2 Adoptive cellular immunotherapy

In this case, the only external source of treatment is the effectors, i.e. $s_1 > 0, s_2 = 0$. In this case, there exists a more realistic non-tumor state, $E_1 = \left(\frac{s_1}{\mu_2}, 0, 0\right)$. This implies that the tumour cells are removed if this equilibrium is stable. The set of eigenvalues of Jacobian matrix is

$$A = \left\{-\mu_2, \frac{-as_1 + g_2 r_2 \mu_2}{g_2 \mu_2}, -\mu_3\right\}$$

and

$$|\arg(\lambda_1)| = \pi, \quad |\arg(\lambda_2)| = \left|\frac{-as_1 + g_2 r_2 \mu_2}{g_2 \mu_2}\right|, \quad |\arg(\lambda_3)| = \pi.$$

The arguments of λ_1 and λ_3 satisfy (3.73). Concerning λ_2, Fig. 3.1 shows the change of $|\arg\lambda_2|$ with respect to s_1. The critical value of s_1 is obtained as $s_{1,cr} = \frac{r_2 g_2 \mu_2}{a}$. For the case of incommensurate FKP model, by referring to Theorem 3.3.3, the

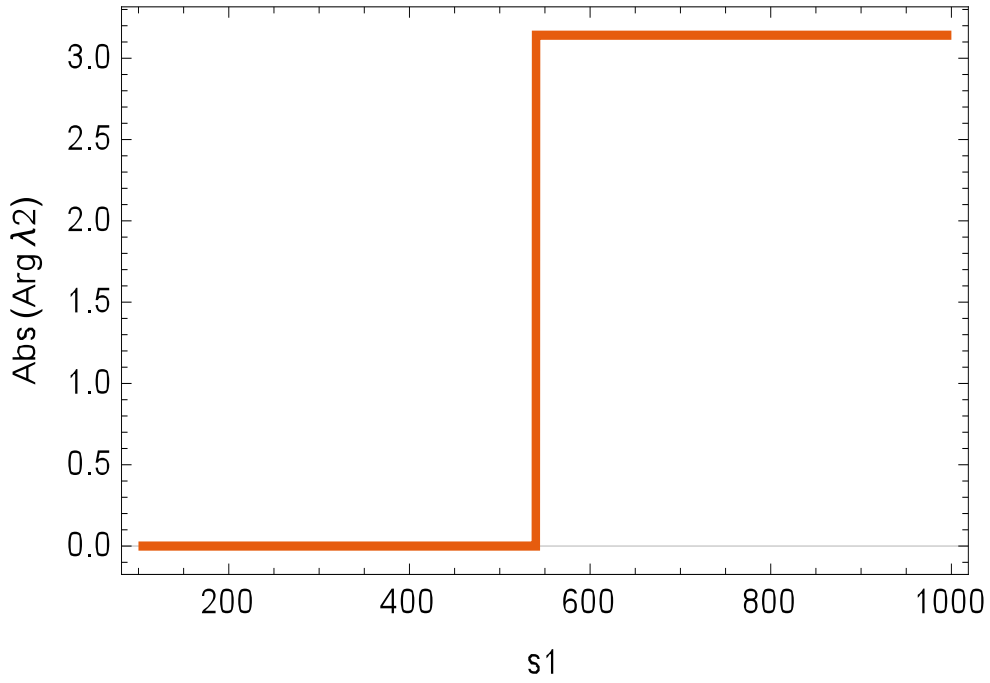

Figure 3.1. The change of $|\arg\lambda_2|$ with respect to s_1, $s_{1,cr} = 540$, $\text{Abs}(\text{Arg}\lambda 2) \equiv |\arg(\lambda_2)|$.

results are obtained as follows. The set of all the roots of the polynomial in (3.75) is

$$A = \left\{\left(\frac{1}{-\mu_2}\right)^{-\frac{1}{m\alpha_1}}, \left(\frac{-as_1 + g_2 r_2 \mu_2}{g_2 \mu_2}\right)^{\frac{1}{m\alpha_2}}, \left(\frac{1}{-\mu_3}\right)^{-\frac{1}{m\alpha_3}}\right\},$$

where $m = 10$ and $\alpha_1 = 1$, $\alpha_2 = 0.9$ and $\alpha_3 = 1$. The first and third roots, i.e. $\lambda_1 = \left(\frac{1}{-\mu_2}\right)^{-\frac{1}{m\alpha_1}}$ and $\lambda_3 = \left(\frac{1}{-\mu_3}\right)^{-\frac{1}{m\alpha_3}}$ satisfy (3.74). The results for the root $\lambda_2 = \left(\frac{-as_1 + g_2 r_2 \mu_2}{g_2 \mu_2}\right)^{\frac{1}{m\alpha_2}}$ are given in Figure 3.2. Obviously, for all values of α_2, the equilibrium point is stable if $s_1 > s_{1,cr}$, where $s_{1,cr} = 540$.

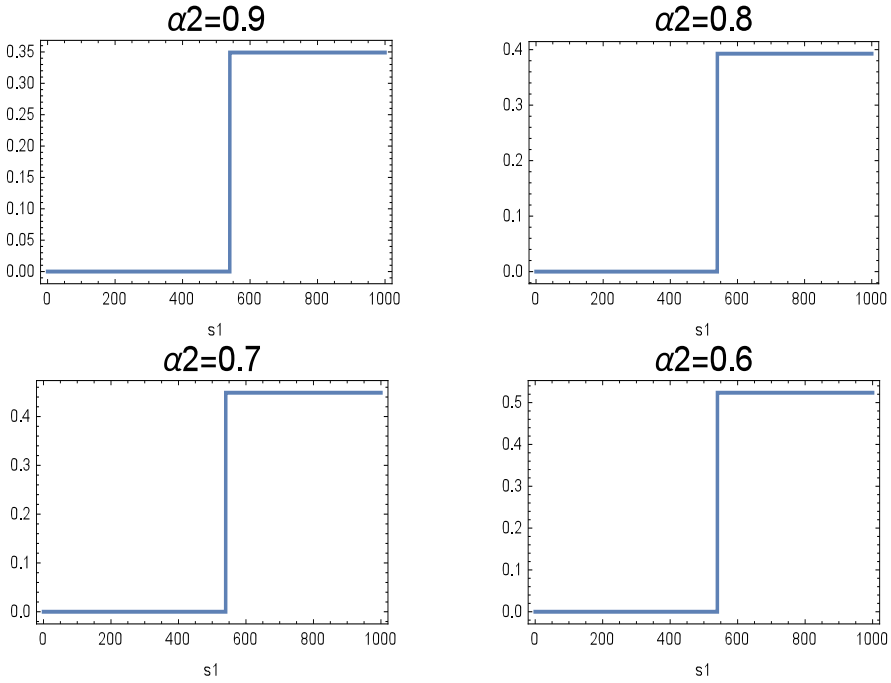

Figure 3.2. The change of $|\arg\lambda_2|$ with respect to s_1. The critical value of s_1 is 540.

3.4.3 Interleukin-2 therapy

The case, which will be discussed here, is $s_1 = 0, s_2 > 0$, where the only external therapy is the IL-2. The non-tumour equilibrium point is $E = \left(0, 0, \frac{s_2}{\mu_3}\right)$. The set of eigenvalues of the Jacobian at this equilibrium point is

$$A = \left\{ r_2, -\mu_3, \frac{p_1 s_2 - s_2\mu_2 - g_1\mu_2\mu_3}{s_2 + g_1\mu_3} \right\}$$

According to (3.73):

$$|\arg(\lambda_1)| = 0, \quad |\arg(\lambda_2)| = \pi, \quad |\arg(\lambda_3)| = \left| \frac{p_1 s_2 - s_2\mu_2 - g_1\mu_2\mu_3}{s_2 + g_1\mu_3} \right|$$

Since the argument of λ_1 does not satisfy (3.73), the equilibrium point is not stable. For the case of incommensurate FKP model, by referring to Theorem 3.3.3, the results are obtained as follows. The set of all the roots of the polynomial in (3.75) is

$$\left\{ \left(\frac{p_1 s_2 - s_2\mu_2 - g_1\mu_2\mu_3}{s_2 + g_1\mu_3} \right)^{\frac{1}{m\alpha_1}}, (r_2)^{\frac{1}{m\alpha 2}}, (-\mu_3)^{\frac{1}{m\alpha_3}} \right\}$$

where $m = 10$ and $\alpha_1 = 1$, $\alpha_2 = 0.9$ and $\alpha_3 = 1$. $\lambda_2 = (r_2)^{\frac{1}{m\alpha 2}}$ does not satisfy (3.74) and therefore the equilibrium point is not stable and this implies that the treatment with only IL-2 cannot remove the cancer cells.

3.4.4 Multi-immunotherapy with ACI and IL-2

First, the commensurate FKP model is considered for the case of multiple therapy ($s_1 > 0, s_2 > 0$). The tumor-free equilibrium is now

$$E = \left(-\frac{s_1 \left(s_2 + g_1 \mu_3 \right)}{p_1 s_2 - s_2 \mu_2 - g_1 \mu_2 \mu_3}, 0, \frac{s_2}{\mu_3} \right).$$

All the eigenvalues of the Jacobian matrix are:

$$\begin{aligned}
\lambda_1 &= \left(-\mu_3 \right), \\
\lambda_2 &= \left(\frac{p_1 s_2 - s_2 \mu_2 - g_1 \mu_2 \mu_3}{s_2 + g_1 \mu_3} \right), \\
\lambda_3 &= \left(\frac{g_2 p_1 r_2 s_2 + a s_1 s_2 - g_2 r_2 s_2 \mu_2 + a g_1 s_1 \mu_3 - g_1 g_2 r_2 \mu_2 \mu_3}{g_2 \left(-p_1 s_2 + s_2 \mu_2 + g_1 \mu_2 \mu_3 \right)} \right)
\end{aligned}$$

From λ_1 it is obtained that $|\arg\left(-\mu_3\right)| = \pi$, which satisfies (3.73). Fig. 3.3 shows the case for λ_2. The results for λ_3 are shown in Fig. 3.4. For the case of incommensurate

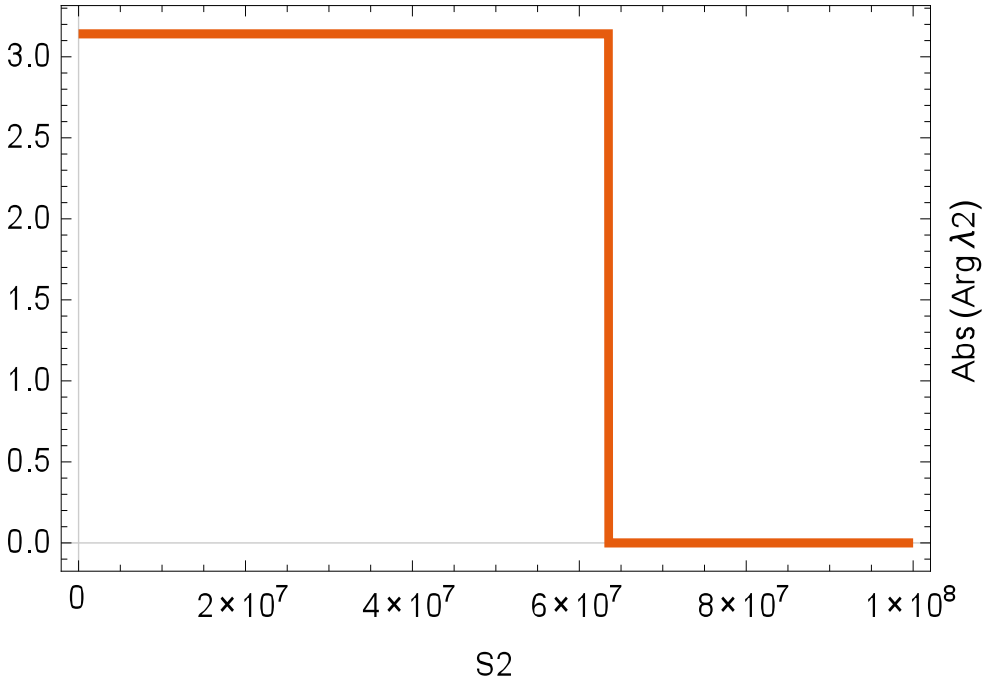

Figure 3.3. The change of $|\arg\lambda_2|$ with respect to s_2.

FKP model, by referring to Theorem 3.3.3, the results are obtained as follows. The set of all the roots of the polynomial in (3.75) is

$$\begin{aligned}
\lambda_1 &= \left(-\mu_3 \right)^{\frac{1}{m\alpha_3}}, \\
\lambda_2 &= \left(\frac{p_1 s_2 - s_2 \mu_2 - g_1 \mu_2 \mu_3}{s_2 + g_1 \mu_3} \right)^{\frac{1}{m\alpha_1}}, \\
\lambda_3 &= \left(\frac{g_2 p_1 r_2 s_2 + a s_1 s_2 - g_2 r_2 s_2 \mu_2 + a g_1 s_1 \mu_3 - g_1 g_2 r_2 \mu_2 \mu_3}{g_2 \left(-p_1 s_2 + s_2 \mu_2 + g_1 \mu_2 \mu_3 \right)} \right)^{\frac{1}{m\alpha_2}}
\end{aligned}$$

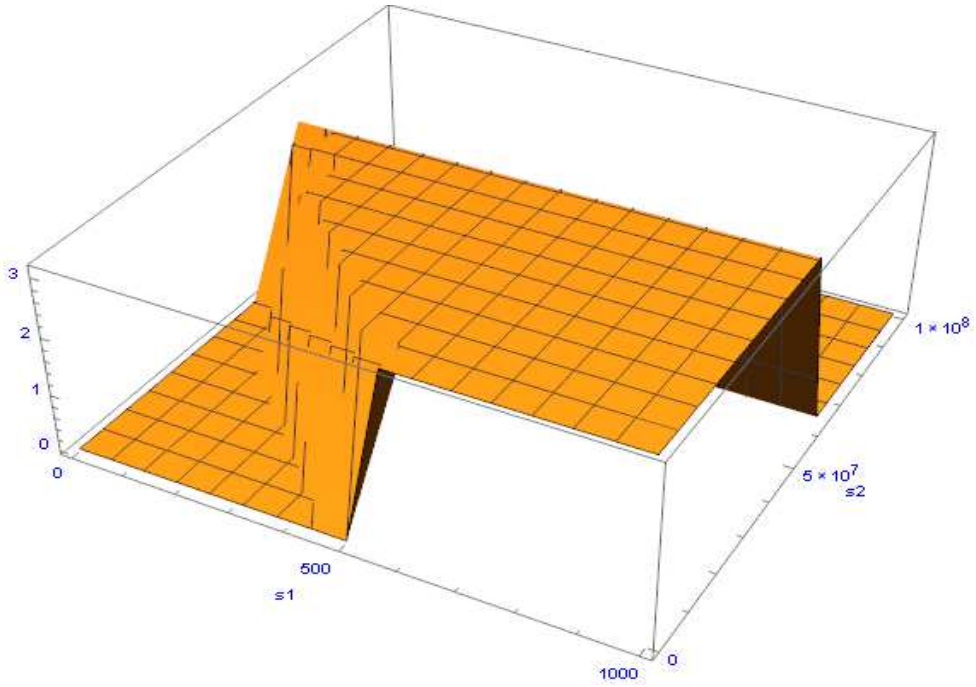

Figure 3.4. The change of $|\arg\lambda_3|$ with respect to s_1 and s_2.

where $m = 10$ and $\alpha_1 = 1$, $\alpha_2 = 0.9$ and $\alpha_3 = 1$. The root λ_1 satisfies (3.74). The conditions for λ_2 and λ_3 are respectively illustrated in Figs. 3.5 and 3.6.

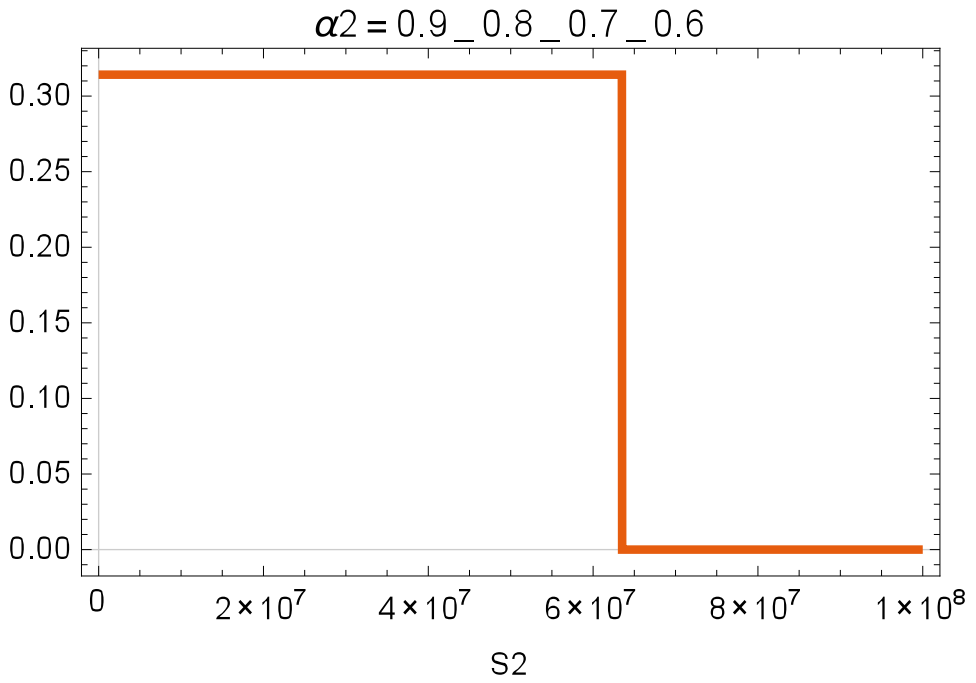

Figure 3.5. The change of $|\arg\lambda_2|$ with respect to s_2.

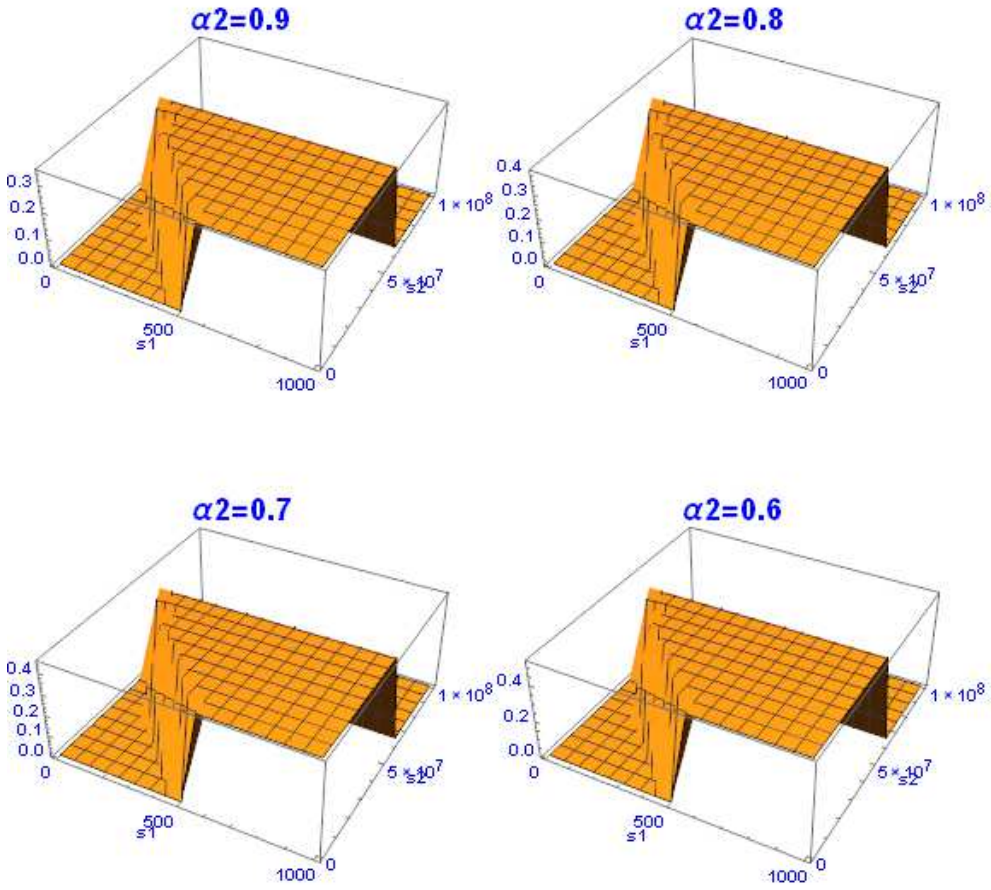

Figure 3.6. The change of $|\arg\lambda_3|$ with respect to s_1 and s_2.

Chapter 4

Numerical Methods for Fractional Differential Equations

Fractional differentiation operators (i.e. derivative operators of any real positive order) have non-local property, in the sense that they depend on the all previous time history and therefore are more appropriate to the systems, which possess persistent memory characteristics. Increasing applications of fractional calculus has been a major cause of the study and the development of numerical methods, which are specifically devised to deal with FDEs. Compared with classical (integer-order) differential equations, the construction of numerical methods of solving FDEs is much more difficult. These difficulties are primarily related to the non-local property of fractional differentiation operators, the low-order accuracy of the majority of the numerical methods, and so forth. Due to the fact that the fractional derivatives are not local in nature, multi-step methods are obvious choice for FDEs. In multi-step methods (in contrast to one-step methods), more previously approximated evaluations are required to compute the solution in each step. Fractional linear multi-step methods (FLMMs) [58, 64, 99, 100] and product-integration (PI) rules [64, 148] are two of the most effective and reliable classes of numerical methods for fractional-order problems. Other approaches can be also mentioned such as Predictor-Corrector approaches [43,45,59], generalized exponential integrators [65], spectral methods [149], methods based on matrix functions [121] and so on. The main goal in this chapter is to describe an inadequate approach, which has been proposed to be a method of solving FDEs, and to demonstrate that the basis on which the method has been devised is not appropriate to FDEs, the so-called multi-step generalized differential transform method (MSGDTM). In order to clarify the issue, the MSGDTM will be examined by referring to reliable and effective methods for FDEs such as FLMMs and predictor-corrector method of Adams-Bashforth-Moulton (PC method of ABM).

4.1 PC Method of ABM and FLMMs

The PC method of ABM can be considered as a fractional variant of the classical second-order Adams-Bashforth-Moulton method, which has been introduced in [45]

and a detailed stability properties of the method has been discussed in [59]. The main emphasis will be placed on the single-term Caputo fractional differential equations for $0 < \alpha \leq 1$, where α is the order of the fractional derivative. Consider the initial value problem

$$\begin{cases} D_{t_0}^{\alpha} y(t) = f(t, y(t)) , \\ y(t_0) = y_0 . \end{cases} \tag{4.1}$$

In order to assure the existence and uniqueness of the solution to (4.1), it is assumed that $f(t, y)$ is continuous and fulfils a Lipschitz condition with respect to the second variable (Theorem 3.2.6. Initial value problem (4.1) can be reformulated in terms of the weakly-singular VIE

$$y(t) = y_0 + \frac{1}{\Gamma(\alpha)} \int_{t_0}^{t} (t-s)^{\alpha-1} f(s, y(s)) \, \mathrm{d}s . \tag{4.2}$$

The method presents a numerical approach in solving (4.2) and is said to be PECE (Predict, Evaluate, Correct and Evaluate) type because an initial approximation y_k^P , the so-called predictor, is first evaluated:

$$y_k^P = y_0 + \frac{1}{\Gamma(\alpha)} \sum_{j=0}^{k-1} b_{j,k} f(t_j, y_j) , \tag{4.3}$$

where the nodes $t_k = t_0 + kh$ are used to calculate y_k^P with a constant step-size $h > 0$ for the sake of simplicity. The weights $b_{j,k}$ are computed by

$$b_{j,k} = \frac{h^{\alpha}}{\alpha} \left((k-j)^{\alpha} - (k-1-j)^{\alpha} \right) . \tag{4.4}$$

Then the method gives the corrector formula:

$$y_k = y_0 + \frac{1}{\Gamma(\alpha)} \left(a_{k,k} f\left(t_k, y_k^P\right) + \sum_{j=0}^{k-1} a_{j,k} f(t_j, y_j) \right) , \tag{4.5}$$

where the weights $a_{j,k}$ are given by

$$\begin{cases} a_{0,k} = \dfrac{h^{\alpha}}{\alpha(\alpha+1)} \left((k-1)^{\alpha+1} - k^{\alpha} (k-1-\alpha) \right) , \\ a_{j,k} = \dfrac{h^{\alpha}}{\alpha(\alpha+1)} \left((k+1-j)^{\alpha+1} + (k-1-j)^{\alpha+1} - 2(k-j)^{\alpha+1} \right) , \\ \qquad\qquad\qquad\qquad\qquad\qquad 1 \leq j \leq k-1, \\ a_{k,k} = \dfrac{h^{\alpha}}{\alpha(\alpha+1)} . \end{cases} \tag{4.6}$$

The basic algorithm, the PC method of ABM, can be completely described by (4.3) and (4.5) with the weights $b_{j,k}$ and $a_{j,k}$ defined by (4.4) and (4.6).

The FLMMs have been introduced by Lubich in [100]. The main feature of the FLMMs is the generalization of quadrature rules, which are obtained from classical linear multi-step methods (LMMs). They have been specifically developed in order to yield a solid theoretical basis for the numerical treatment of FDEs. The FLMMs

are one of the most effective methods of solving FDEs. Detailed explanations of the methods have been given in [58, 63, 64]. The key element in FLMMs is the approximation of Riemann-Liouville integral (on the interval $[t_0, t]$ and of the order $\alpha > 0$)

$$I_{t_0}^{\alpha} f(t) = \frac{1}{\Gamma(\alpha)} \int_{t_0}^{t} (t-\tau)^{\alpha-1} f(\tau)\, \mathrm{d}\tau\,, \tag{4.7}$$

with the help of convolution quadrature. In the sense of Lubich, the generalization about an linear multi-step method (LMM) in order to deal with (4.7) results in the corresponding fractional linear multi-step method (FLMM) as

$${}_hI_{t_0}^{\alpha} f(t_k) = h^{\alpha} \sum_{j=0}^{k} \omega_{k-j} f(t_j) + h^{\alpha} \sum_{j=0}^{v} w_{k,j} f(t_j)\,, \tag{4.8}$$

on uniform nodes $t_k = t_0 + kh$. The convolution and starting quadrature wights ω_k and $w_{k,j}$ are independent of h. Starting quadrature weights $w_{k,j}$ play the major role in dealing successfully with the possible singularity of the integrand function at t_0. The features of the FLMM is specified by convolution quadrature weights ω_k.

In this thesis, all the numerical results for the FKP have been obtained by using MATLAB routines, which have been coded based on the PC method of ABM. The MATLAB codes can deal with multi-order systems of FDEs (i.e. each equation of the system has its own fractional order). When the MATLAB codes were written, there had not been provided any routines in computational environments such as MATLAB and Mathematica in order to deal with multi-order FDEs. For the sake of convenience, it is mentioned that the MATLAB code fde12.m has been devised to solve systems in which all equations have the same order. The MATLAB code flmm2.m, which implements three different FLMMs (i.e. the generalizations of the trapezoidal rule, the Newton-Gregory formula and the backward differentiation formula) has been introduced in [63]. Then, the author of [64] represented several more MATLAB routines to deal with multi-order FDEs, and multi-term FDEs.

4.2 MSGDTM

The DTM deals with the approximated solutions to integer-order differential equations and is based on polynomial approximations (a thorough literature on the DTM is available in [18]). The authors of [10] extended the DTM in order to solve non-integer differential equations, called as the fractional differential transform method (FDTM). Then, a rather different formulation of generalizing the DTM was introduced in [116], named as generalized differential transform method (GDTM). The GDTM provides the expansion

$$y(t) = \sum_{k=0}^{\infty} Y_k (t-t_0)^{k\alpha}\,, \tag{4.9}$$

as the solution to (4.1), where the coefficients Y_k are evaluated by the recurrence equation

$$Y_{k+1} = \frac{\Gamma(\alpha k + 1)}{\Gamma(\alpha(k+1)+1)} F(k, Y_k)\,. \tag{4.10}$$

The first coefficient Y_0 is assessed to be equal to the initial condition, $Y_0 = y(t_0)$. The term $F(k, Y_k)$, mentioned as the differential transform of $f(t, y(t))$, is determined by using the methods provided in [10, 52, 116].

Under general circumstances, these methods do not provide an accurate solution to FDEs. As demonstrated by Lubich [98], the solution to (4.2) is expanded in mixed (integer and fractional) powers, i.e. $\sum_{i,j\in\mathbb{N}} Y_{i,j}(t-t_0)^{i+j\alpha}$ and therefore shows a non-smooth behaviour at t_0. In the presence of non-smoothness at $t = t_0$, the solution cannot be properly approximated by methods based on polynomial approximations.

Moreover, these methods are originally based on Taylor expansion which allows to obtain the results only in a small neighborhood of t_0. In order to deal with this restriction, the authors of [52] applied the GDTM to FDEs by using step-by-step procedures, and mentioned it as MSGDTM. It is simply formed on the idea of dividing the time interval $[t_0, T]$ into n sub-intervals $[t_j, t_{j+1}]$ with a constant step-size $h = t_{j+1} - t_j$ $(j = 0, 1, \ldots, n-1)$:

$$y(t) = \begin{cases} y_1(t) = y_0 + \sum\limits_{k\in\mathbb{N}} Y_k^{(1)} (t-t_0)^{k\alpha}, & t \in [t_0, t_1], \\ y_2(t) = y_1(t_1) + \sum\limits_{k\in\mathbb{N}} Y_k^{(2)} (t-t_1)^{k\alpha}, & t \in [t_1, t_2], \\ . \\ . \\ y_n(t) = y_{n-1}(t_{n-1}) + \sum\limits_{k\in\mathbb{N}} Y_k^{(n)} (t-t_{n-1})^{k\alpha}, & t \in [t_{n-1}, T], \end{cases} \tag{4.11}$$

where the coefficients $Y_k^{(i)}$ $(i = 1, 2, \ldots, n)$ are computed by (4.10).

The MSGDTM takes the incorrect approach in numerical treatment of FDEs; in fact, the MSGDTM implements a step-by-step procedure which is not adequate to discretize nonlocal operators such as fractional derivatives (as it is normal for integer-order differential equations). For initial value problem

$$\begin{cases} \dot{y}(t) = f(t, y(t)), \\ y(t_0) = y_0, \end{cases} \tag{4.12}$$

it is possible to compute the solution at any point t_{k+1} as

$$y_{k+1} = y_k + \int_{t_k}^{t_{k+1}} f(s, y(s))\, \mathrm{d}s. \tag{4.13}$$

Differently, the solution to (4.2) at any point t_{k+1} cannot be evaluated as the solution at the previous point t_k plus the increment term related to the interval $[t_k, t_{k+1}]$ (usually done in integer-order differential equations). This is due to the presence of a real power in the kernel.

4.3 Illustrative Example

The statement about the MSGDTM is further verified by making a comparison with other effective and accurate methods such as the FLMMs and the PC method of

ABM. Thus, the MATLAB codes flmm2.m and fde12.m are employed to achieve the goal. Consider the fractional Riccati differential equation:

$$\begin{cases} D_0^{\alpha} y(t) = 2y - y^2 + 1, & t > 0, \quad 0 < \alpha \leq 1, \\ y(0) = 0. \end{cases} \tag{4.14}$$

The goal is to follow the MSGDTM for the interval $I = [0, 0.4]$ by dividing it into two sub-intervals $I_1 = [0, 0.2]$ and $I_2 = [0.2, 0.4]$. The differential transform of (4.14) is

$$\frac{\Gamma(\alpha(k+1)+1)}{\Gamma(\alpha k+1)} Y_{k+1} = 2Y_k - \sum_{k_1=0}^{k} (Y_{k_1} Y_{k-k_1}) + \delta_k, \tag{4.15}$$

where $Y(0) = y(0)$ and δ_k is computed as

$$\delta_k = \begin{cases} 1, & \text{if } k = 0, \\ 0, & \text{otherwise} \end{cases}$$

By using(4.9), (4.11), and (4.15) the results are obtained as:

$$\begin{aligned} y(t) &= 1.10\, t^{0.7} + 1.61\, t^{1.4} + 1.14\, t^{2.1} \\ &\quad -0.60\, t^{2.8} - 2.54\, t^{3.5}, \qquad 0 \leq t \leq 0.2, \end{aligned}$$

and

$$\begin{aligned} y(t) &= 0.55 + 1.98\,(t-0.2)^{0.7} + 1.30\,(t-0.2)^{1.4} - 1.54\,(t-0.2)^{2.1} \\ &\quad -3.07\,(t-0.2)^{2.8} + 0.66\,(t-0.2)^{3.5}, \qquad 0.2 \leq t \leq 0.4. \end{aligned}$$

where $\alpha = 0.7$. Fig. 4.1 illustrates the obtained results. The problem is solved one more time, for $t \in [0, 3]$ with a constant step-size $h = 0.01$ and the results are given in Fig.4.2. Fig. 4.3 shows the inaccuracy of the MSGDTM in the neighbourhood of the initial condition. As it was stated, methods based on polynomial approximations fail to give the accurate solutions at the initial condition.

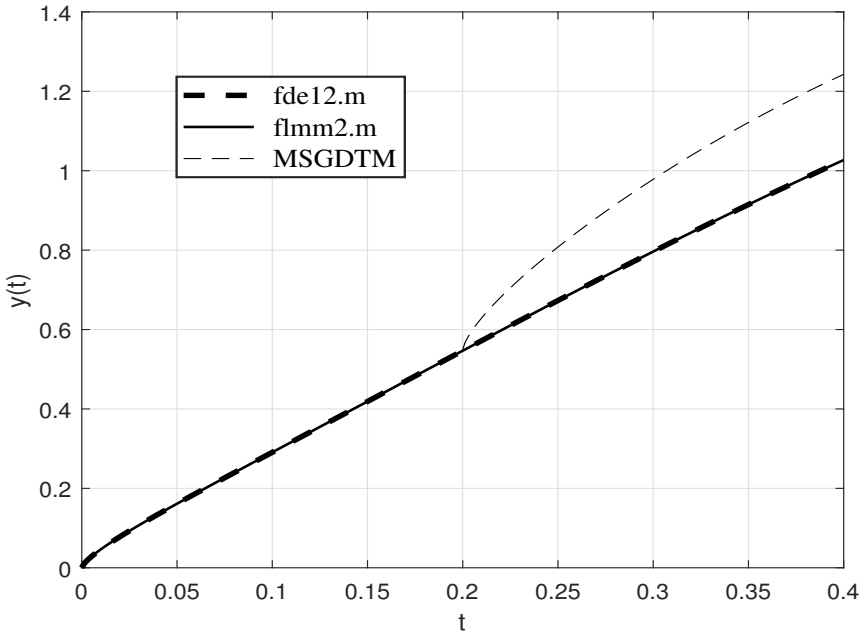

Figure 4.1. The result obtained by the MSGDTM compared with the solutions to Eq. (4.14) obtained by the FLMMs and the PC method of ABM, for $\alpha = 0.7$.

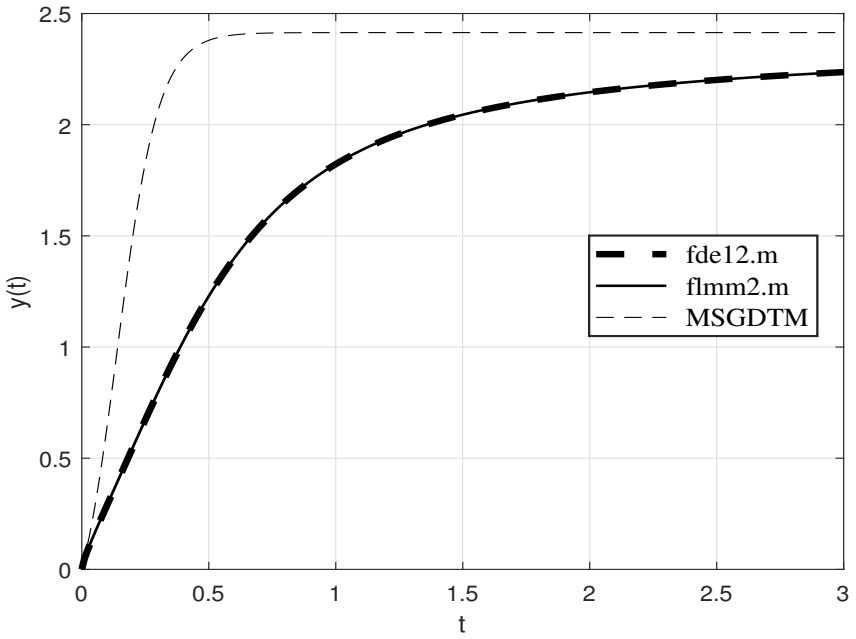

Figure 4.2. The result obtained by the MSGDTM compared with the solution to Eq. (4.14) obtained by the FLMMs and the PC method of ABM, for $\alpha = 0.7$.

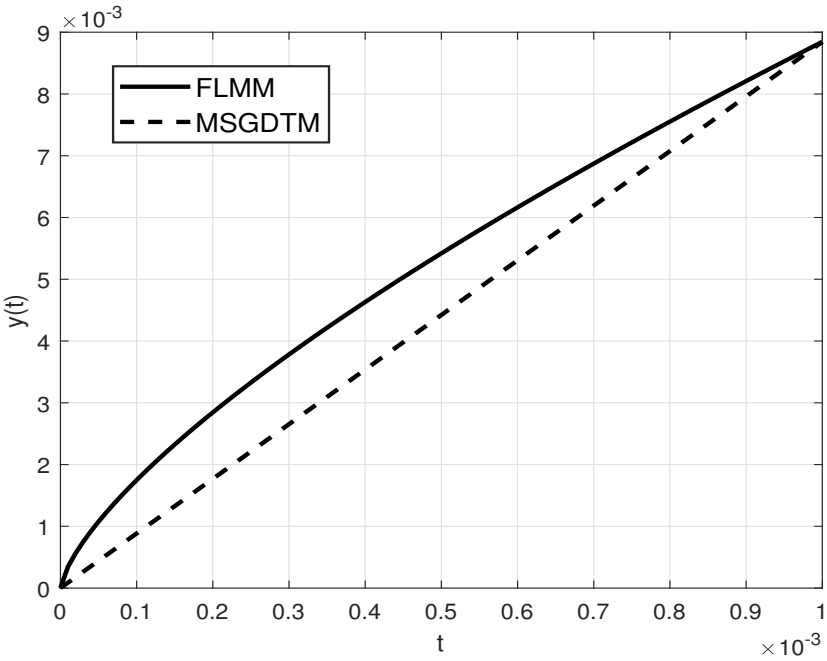

Figure 4.3. The result obtained by the MSGDTM compared with the solution to (4.14) obtained by the FLMMs over the neighbourhood of initial condition, $\alpha = 0.7$.

The MSGDTM fails obviously to give the solution of (4.14); in fact, in terms of the accuracy there is no comparison. As stated, the MSGDTM approaches the problem by dividing the solution at any time t_{n+1}, into the sum of the solution of previous time t_n and the increment related to the interval $[t_n, t_{n+1}]$.

This is a basic fact that, for $\alpha = 1$, the MSGDTM returns to its classical origin (i.e. the DTM for integer-order differential equations). In this case, solutions will be in agreement with those obtained by other classical methods such as Runge-Kutta approaches for integer-order differential equations. This fact cannot be referred to as a proof of the effectiveness of the MSGDTM for FDEs. It must be mentioned that there are several recently published papers on FDEs, in which MSGDTM and similar incorrect approaches could be seen (for instance, see [114]).

Thus, in this chapter, the main reasons due to which the MSGDTM (or any other similar approach) fails to solve FDEs, have been discussed. As proved by Lubich [98], the solution of (4.2) presents an expansion in mixed (i.e. integer and fractional) powers and shows a non-smooth behavior at $t = t_0$. Furthermore, the use of step-by-step procedures is not adequate to discretize nonlocal operators such as fractional derivatives. Thus, the MSGDTM and other similar methods are not suitable for FDEs.

4.4 Numerical Solution to KP Model

In this section, the numerical solutions to FKP model

$$\begin{aligned} {}^{C}D_0^{\alpha_1} x(t) &= cy - \mu_2 x + \frac{p_1 xz}{g_1 + z} + s_1 , \\ {}^{C}D_0^{\alpha_2} y(t) &= r_2 y(1 - by) - \frac{axy}{g_2 + y} , \\ {}^{C}D_0^{\alpha_3} z(t) &= \frac{p_2 xy}{g_3 + y} - \mu_3 z + s_2 , \end{aligned} \tag{4.16}$$

with the initial condition

$$x(0) = x_0 , \quad y(0) = y_0 , \quad z(0) = z_0 , \tag{4.17}$$

are represented. In order to numerically solve the FKP model, a MATLAB routine has been coded by using the PC method of ABM. The MATLAB code has been prepared in such a way to be able to deal with multi-order FKP (while each equation in (4.16) has its own order). Four different cases are taken to illustrate the solutions, where the fractional orders change. The numerical solutions are shown in Figs. 4.4-4.7. The solution to classical KP model (i.e. the order of each equation in the model is equal to one) is shown in Fig. 4.4. The maximum value of tumour cells for this case is larger than the maximum value of cancer cells in other three cases. In Fig. 4.5, all the fractional orders are equal to 0.9. The maximum value of tumour is larger than that shown in Fig. 4.6, where the fractional orders are equal to 0.8. These results show that the maximum value of cancer cells decreases by reducing the fractional order of the system. The best case is illustrated in Fig. 4.7, where the orders of first and third equations in (4.16) are equal to one, and the order of the second equation in (4.16) changes. All these samples are related to the case of no-treatment ($s_1 = 0$, $s_2 = 0$).

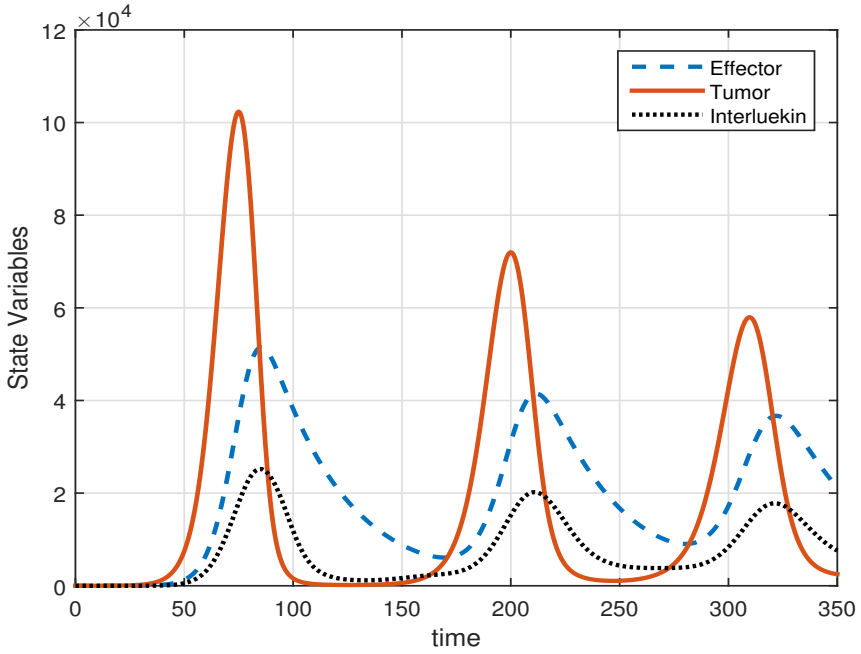

Figure 4.4. Numerical solution to (4.16), $\alpha_1 = 1$, $\alpha_2 = 1$, $\alpha_3 = 1$, $c = 0.035$, $s_1 = 0$, $s_2 = 0$.

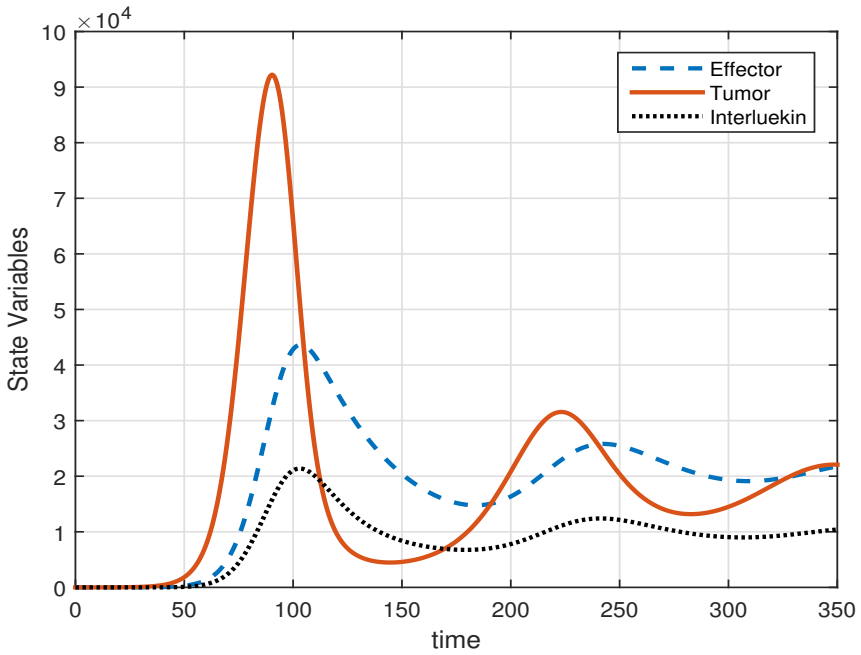

Figure 4.5. Numerical solution to (4.16), $\alpha_1 = 0.9$, $\alpha_2 = 0.9$, $\alpha_3 = 0.9$, $c = 0.035$, $s_1 = 0$, $s_2 = 0$.

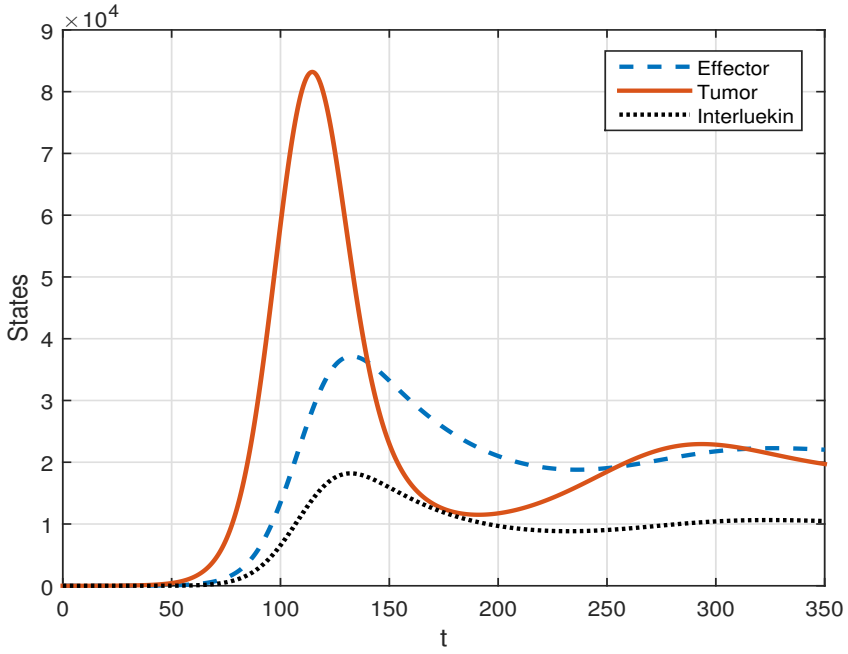

Figure 4.6. Numerical solution to (4.16), $\alpha_1 = 0.8$, $\alpha_2 = 0.8$, $\alpha_3 = 0.8$, $c = 0.035$, $s_1 = 0$, $s_2 = 0$.

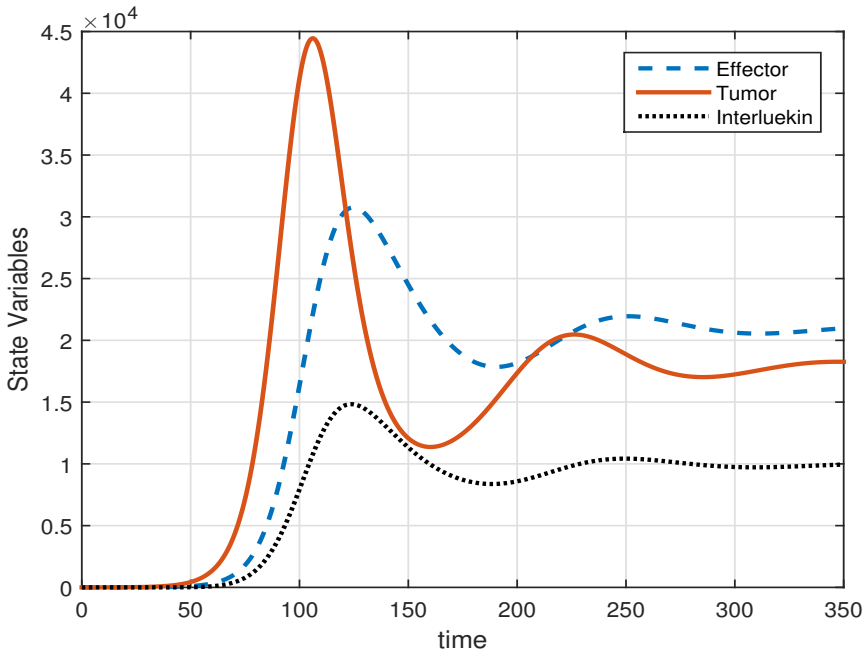

Figure 4.7. Numerical solution to (4.16), $\alpha_1 = 1$, $\alpha_2 = 0.8$, $\alpha_3 = 1$, $c = 0.035$, $s_1 = 0$, $s_2 = 0$.

It is obvious that the behaviour of tumor even without therapy has impressive changed with decreasing the α.

Chapter 5

Modified Fractional Logistic Equation

In [144], the author has obtained a function as the solution to FLE. As demonstrated later in [8], the function which is mentioned here as WF is not exactly the solution to FLE. nevertheless, it is in good agreement with the numerical solution to FLE. The WF indicates a compelling feature, in which the exponentials are substituted by Mittag-Leffler functions. In this chapter, a modified fractional logistic equation (MFLE) is introduced [47], to which the WF is a solution. The proposed fractional integro-differential equation possesses a nonlinear additive term related to the solution of the LE. The method which is utilized here, may be appropriately applied to the analysis of solutions to nonlinear fractional differential equations of mathematical physics.

5.1 Fractional Logistic Equation

The LE, which is mentioned on occasion as the Verhulst model, is a population growth model introduced and published by Pierre Verhulst. The model represents a well-known nonlinear differential equation in the field of biology and social sciences and was discussed in Section 2.1.1. The sigmoidal behavior of the solution to the LE has been also used to model the tumor growth. Since the logistic growth is one of the most versatile models in natural sciences, the FLE would be a relevant problem to be dealt with:

$$ {}^{C}D_{t}^{\alpha} w\left(t\right) = k^{\alpha} w\left(1-w\right) , \qquad \alpha \in (0,1] , \tag{5.1} $$

with the initial condition $w\left(0\right) = u_0$ (the initial condition is expressed by u_0 same as the initial condition for classical LE described in (2.6)), where ${}^{C}D_{t}^{\alpha}$ denotes the Caputo derivative with the fractional order, α, restricted to $0 < \alpha \leq 1$. The Laplace transform method cannot directly lead up to an exact solution of such a nonlinear fractional differential equation. In [35, 146], the authors represented some creative techniques to approximate the solution to FLE. In [117], the authors have studied the FLE with the Grünwald–Letnikov fractional derivative and assumed the solution to be in the form of a fractional Taylor series (as it was discussed in Section 4.2, these method fails to give an adequate solution to FDEs), where the coefficients in

the series are evaluated by a recursive relation. The Carleman embedding technique has been employed by West to construct a solution to (5.1). The proposed solution is mentioned as WF:

$$w(t) = \sum_{n=0}^{\infty} \left(\frac{u_0 - 1}{u_0}\right)^n E_\alpha\left(-nk^\alpha t^\alpha\right), \qquad \alpha \in (0,1], \tag{5.2}$$

where E_α denotes the so-called one parameter Mittag-Leffler function. In [8], the authors have illustrated that the WF is not exactly the solution to (5.1). However, as demonstrated in [144], the WF has been shown to be in good agreement with the numerical solution of the FLE.

The discussion on the FLE is motivated by the relevance of the model to a wide range of applications and by the mathematical difficulties involved in the analysis of nonlinear fractional equations emerging in mathematical biology. The aim is to investigate what equation may be satisfied by the WF (for the case $k = 1$), i.e. the goal is to seek for an equation which could be satisfied by

$$w(t) = \sum_{n=0}^{\infty} \left(\frac{u_0 - 1}{u_0}\right)^n E_\alpha\left(-nt^\alpha\right), \tag{5.3}$$

In this regard, the fractional integro-differential equation

$$\begin{aligned} {}^C D_t^\alpha w(t) &= w(t)(1 - w(t)) + u_0 \frac{t^{-\alpha}}{\Gamma(1-\alpha)} \\ &\quad + \int_0^\infty \int_0^\infty \left(u(s)\,u(z) - u^2(s)\right) l_\alpha(s,t) l_\alpha(z,t)\,\mathrm{d}s\,\mathrm{d}z, \end{aligned} \tag{5.4}$$

with the initial condition $w(0) = u_0$ is represented and proved to be satisfied by the function described in (5.3). In (5.4), which is called as MFLE, the function u is the solution to the LE (2.6) for the case $k = 1$. Thus, (5.4) has an additive term related to the solution of the classical logistic equation. The function $l_\alpha(s,t)$ is in such a way for which the Laplace transform is as follows:

$$\int_0^\infty e^{-\lambda s} l_\alpha(s,t)\,\mathrm{d}s = E_\alpha\left(-\lambda t^\alpha\right), \qquad \lambda > 0. \tag{5.5}$$

The function $l_\alpha(s,t)$ satisfies the following equation

$${}^C D_t^\alpha l_\alpha(s,t) = -\frac{\partial}{\partial s} l_\alpha(s,t), \tag{5.6}$$

with the initial condition

$$l_\alpha(s,0) = \delta(s), \tag{5.7}$$

where $\delta(s)$ stands for the Dirac's delta function, and the boundary condition

$$l_\alpha(0,t) = \frac{t^{-\alpha}}{\Gamma(1-\alpha)}. \tag{5.8}$$

Furthermore

$$\int_0^\infty l_\alpha(s,t)\,\mathrm{d}s = 1. \tag{5.9}$$

Further details about $l_\alpha(s,t)$ can be observed in, for instance, [17, 19].

Some necessary preliminaries about Mittag-Leffler function will be briefly discussed in the next section.

5.1.1 Mittag-Leffler Function

The exponential function, e^z, performs a significant role in the theory of differential equations with integer orders. The so-called *Mittag-Leffler function* is a generalization of the exponential function, which was first introduced by M. G. Mittag-Leffler (1846–1927) [113]

$$E_\alpha(z) = \sum_{k=0}^{\infty} \frac{z^k}{\Gamma(k\alpha+1)}, \quad \alpha, \beta, z \in \mathbb{C},\ \Re(\alpha) > 0. \tag{5.10}$$

Specifically when $\alpha = 1$, the Mittag-Leffler function is equal to the exponential function

$$E_1(z) = \sum_{k=0}^{\infty} \frac{z^k}{\Gamma(k+1)} = e^z. \tag{5.11}$$

The Mittag-Leffler type function, $E_{\alpha,\beta}(z)$, which is in addition mentioned as the *two-parameter Mittag-Leffler function*, first appeared in an article by Wiman [145] and then was introduced by Agarwal [6] and studied by Humbert and Agarwal [71]

$$E_{\alpha,\beta}(z) = \sum_{k=0}^{\infty} \frac{z^k}{\Gamma(k\alpha+\beta)}, \quad \alpha, \beta, z \in \mathbb{C},\ \Re(\alpha) > 0. \tag{5.12}$$

Henceforth, for the sake of simplicity, the two-parameter Mittag-Leffler function is mentioned as only Mittag-Leffler function. This function produces the (5.10), while β is equal to one, i.e. $E_{\alpha,1}(z) = E_\alpha(z)$.

The power series defined in Mittag-Leffler function, $E_{\alpha,\beta}(z)$, is convergent for all $z \in \mathbb{C}$, where $\Re(\alpha) > 0$ and $\Re(\beta) > 0$. The radius of convergence of the power series is infinity. In other words, the Mittag-Leffler function, $E_{\alpha,\beta}$, is an entire function of order $[\Re(\alpha)]^{-1}$ and type 1, and satisfies the following differentiation formulae, when α is equal to a natural number $n \in \mathbb{N}$

$$\left(\frac{\mathrm{d}}{\mathrm{d}z}\right)^n \left[z^{\beta-1} E_{n,\beta}(\lambda z^n)\right] = z^{\beta-n-1} E_{n,\beta-n}(\lambda z^n), \quad n \in \mathbb{N},\ \lambda \in \mathbb{C}, \tag{5.13}$$

and

$$\left(\frac{\mathrm{d}}{\mathrm{d}z}\right)^n \left[z^{n-\beta} E_{n,\beta}\left(\frac{\lambda}{z^n}\right)\right] = \frac{(-1)^n \lambda}{z^{n+\beta}} E_{n,\beta}\left(\frac{\lambda}{z^n}\right), \quad z \neq 0,\ n \in \mathbb{N},\ \lambda \in \mathbb{C}. \tag{5.14}$$

The usual derivative of Mittag-Leffler function could be calculated by

$$\left(\frac{\mathrm{d}}{\mathrm{d}z}\right)^n [E_{\alpha,\beta}(z)] = n! E^{n+1}_{\alpha,\beta+\alpha n}(z), \quad n \in \mathbb{N}, \tag{5.15}$$

and specifically

$$\left(\frac{\mathrm{d}}{\mathrm{d}z}\right)^n [E_\alpha(z)] = n! E^{n+1}_{\alpha,1+\alpha n}(z), \quad n \in \mathbb{N}, \tag{5.16}$$

where the function, $E^n_{\alpha,\beta}(z)$, is called the generalized Mittag-Leffler function, which is defined for all $z \in \mathbb{C}$, $\alpha, \beta, \rho \in \mathbb{C}$ and $\Re(\alpha)$ by

$$E^\rho_{\alpha,\beta}(z) = \sum_{k=0}^{\infty} \frac{(\rho)_k}{k!} \frac{z^k}{\Gamma(k\alpha+\beta)}, \tag{5.17}$$

where $(\rho)_k$ is the Pochhammer symbol. In particular, when $\rho = 1$, it coincides with the two-parameter Mittag-Leffler function

$$E^1_{\alpha,\beta}(z) = E_{\alpha,\beta}(z)\,, \quad z \in \mathbb{C}\,. \tag{5.18}$$

For the generalized Mittag-Leffler function, the following differentiation formula is held true

$$\left(\frac{\mathrm{d}}{\mathrm{d}z}\right)^n \left[E^\rho_{\alpha,\beta}(z)\right] = (\rho)_n E^{\rho+n}_{\alpha,\beta+\alpha n}(z)\,, \quad n \in \mathbb{N}\,, \tag{5.19}$$

and

$$\left(\frac{\mathrm{d}}{\mathrm{d}z}\right)^n \left[z^{\beta-1}E^\rho_{\alpha,\beta}(\lambda z^\alpha)\right] = z^{\beta-n-1}E^\rho_{\alpha,\beta-n}(\lambda z^\alpha)\,, \quad \lambda \in \mathbb{C},\ n \in \mathbb{N}\,. \tag{5.20}$$

5.1.2 Fractional Derivative of Mittag-Leffler function

The following formula indicates that the Riemann-Liouville fractional derivative of the Mittag-Leffler function results in the function of the same kind [119]:

$$D^\gamma_a\left[(x-a)^{\beta-1}E_{\alpha,\beta}(\lambda(x-a)^\alpha)\right] = (x-a)^{\beta-\gamma-1}E_{\alpha,\beta-\gamma}[\lambda(x-a)^\alpha]\,, \tag{5.21}$$

where $\lambda \in \mathbb{R}$, $\alpha, \beta > 0$ and $\gamma \geq 0$. If $\beta = 1$ and $a = 0$, by using the (5.21) the Riemann-Liouville fractional derivative of Mittag-Leffler function, $E_\alpha(\lambda x^\alpha)$ is:

$$D^\alpha_a E_\alpha(\lambda x^\alpha) = x^{-\alpha}E_{\alpha,1-\alpha}(\lambda x^\alpha)\,. \tag{5.22}$$

Consequently the ordinary derivative of the function $E_\alpha(\lambda x^\alpha)$ is obtained as follows:

$$\begin{aligned}\frac{d}{dx}E_\alpha(\lambda x^\alpha) &= x^{-1}E_{\alpha,0}(\lambda x^\alpha)\\ &= \lambda x^{\alpha-1}E_{\alpha,\alpha}(\lambda x^\alpha)\end{aligned} \tag{5.23}$$

The function $E_{\alpha,\beta}$ could be expressed by the integral representation

$$E_{\alpha,\beta}(z) = \frac{1}{2\pi}\int_{\mathcal{C}} \frac{t^{\alpha-\beta}e^t}{t^\alpha - z}\mathrm{d}t\,. \tag{5.24}$$

The loop, $\mathcal{C}$, which is the path of integration, starts and ends at $-\infty$ and encircles the disk $|t| \leq |z|^{1/\alpha}$ in the positive sense $|\arg(t)| \leq \pi$ on $\mathcal{C}$. Equation (5.24) is utilized to obtain the asymptotic behaviour of Mittag-Leffler function, $E_{\alpha,\beta}$, at infinity. This behaviour is strongly influenced by the value of α [119]. The asymptotic formulae are given in the following theorems, for $0 < \alpha < 2$ and $\alpha \geq 2$:

Theorem 5.1.1. *Let $0 < \alpha < 2$, $\beta, z \in \mathbb{C}$ and μ be an arbitrary real number such that*

$$\frac{\pi}{2}\alpha < \mu < \min(\pi, \pi\alpha)\,,$$

then for an arbitrary $n \in \mathbb{N}$, the following expansion holds

$$\begin{aligned}E_{\alpha,\beta}(z) &= \frac{1}{\alpha}z^{\frac{1-\beta}{\alpha}}\exp\left(z^{\frac{1}{\alpha}}\right) - \sum_{k=1}^{n}\frac{1}{\Gamma(\beta-k\alpha)\,z^k} + O\left(|z|^{-n-1}\right),\\ &\qquad |z| \to \infty\,, \qquad |\arg(z)| \leq \mu\,.\end{aligned} \tag{5.25}$$

Theorem 5.1.2. *Let $0 < \alpha < 2$, $\beta, z \in \mathbb{C}$ and μ be an arbitrary real number such that*

$$\frac{\pi}{2}\alpha < \mu < \min(\pi, \pi\alpha),$$

then for an arbitrary $n \in \mathbb{N}$, the following expansion holds

$$\begin{aligned} E_{\alpha,\beta}(z) &= -\sum_{k=1}^{n} \frac{1}{\Gamma(\beta - k\alpha) z^k} + O\left(|z|^{-n-1}\right), \\ &\quad |z| \to \infty, \qquad \mu \le |\arg(z)| \le \pi. \end{aligned} \tag{5.26}$$

Theorem 5.1.3. *Let $\alpha \ge 2$, $\beta, z \in \mathbb{C}$, then for an arbitrary $n \in \mathbb{N}$, the following expansion holds*

$$\begin{aligned} E_{\alpha,\beta}(z) &= \frac{1}{\alpha} \sum_{p} \left(z^{\frac{1}{\alpha}} \exp\left(\frac{2p\pi i}{\alpha}\right)\right)^{1-\beta} \exp\left(\exp\left(\frac{2p\pi i}{\alpha}\right) z^{\frac{1}{\alpha}}\right), \\ &\quad - \sum_{k=1}^{n} \frac{1}{\Gamma(\beta - k\alpha) z^k} + O\left(|z|^{-n-1}\right), \\ &\quad |z| \to \infty, \qquad |\arg(z)| \le \frac{\alpha\pi}{2}, \end{aligned} \tag{5.27}$$

where the first sum is taken over all integers p, satisfying the condition

$$|\arg(z) + 2p\pi| \le \left(\frac{\pi\alpha}{2}\right).$$

The main focus of attention will be the function

$$E_\alpha(-\lambda z^\alpha) = \sum_{k=0}^{\infty} (-1)^k \lambda^k \frac{z^{k\alpha}}{\Gamma(k\alpha + 1)}, \tag{5.28}$$

which provides the Laplace transform of l_α (see (5.5)). The asymptotic behaviour of the Mittag-Leffler function $E_\alpha(\lambda z^\alpha)$, for $0 < \alpha < 2$ and $z \in \mathbb{R}^+$, could be stated by using Theorems 5.1.1 and 5.1.2

$$\begin{aligned} E_\alpha(\lambda z^\alpha) &= \frac{1}{\alpha} \exp\left(\frac{z}{\lambda^\alpha}\right) - \sum_{k=1}^{n} \frac{z^{-k\alpha}}{\lambda^k \Gamma(1 - k\alpha)} \\ &\quad + O\left(|\lambda z^\alpha|^{-1-n}\right), \quad n \in \mathbb{N}, \lambda > 0, z \to +\infty, \end{aligned} \tag{5.29}$$

and

$$\begin{aligned} E_\alpha(\lambda z^\alpha) &= -\sum_{k=1}^{n} \frac{z^{-k\alpha}}{\lambda^k \Gamma(1 - k\alpha)} \\ &\quad + O\left(|\lambda z^\alpha|^{-1-n}\right), \quad n \in \mathbb{N}, \lambda < 0, z \to +\infty. \end{aligned} \tag{5.30}$$

Furthermore the following inequality is held true for all non-negative real numbers, i.e. $z \in [0, \infty)$ (e.g., see [119, theorem 1.6]):
For $0 < \alpha < 2$, there exists a constant $C(\alpha)$ such that

$$0 \le |E_\alpha(-z^\alpha)| \le \frac{C(\alpha)}{1 + z^\alpha}, \qquad 0 < \alpha < 2, \tag{5.31}$$

where $C(\alpha)$ is a real positive constant. The Riemann-Liouville derivative of the Mittag-Leffler function could be obtained by using (5.22)

$$D_a^{\alpha} E_{\alpha}(\lambda z^{\alpha}) = \frac{z^{-\alpha}}{\Gamma(1-\alpha)} + \lambda E_{\alpha}(\lambda z^{\alpha}), \quad \alpha \in \mathbb{R}^{+}, \quad \lambda \in \mathbb{C}. \tag{5.32}$$

5.1.3 Laplace Transform of Mittag-Leffler Function

Equation (5.11) shows obviously that the Mittag-Leffler function, $E_{\alpha,\beta}$, is a generalization of the exponential function. The Laplace transform of this function can be obtained with the help of the analogy between this function and exponential function:

$$\mathcal{L}\left[E_{\alpha,\beta}(t)\right](s) = \int_0^{\infty} e^{-st} E_{\alpha,\beta}(t)\,\mathrm{d}t = \sum_{k=0}^{\infty} \frac{k!}{\Gamma(\alpha k+\beta)\, s^{k+1}}. \tag{5.33}$$

The well-known Laplace transform of the functions $t^k e^{at}$ and $t^k e^{-at}$ are respectively

$$\mathcal{L}\left[t^k e^{\lambda t}\right](s) = \int_0^{\infty} e^{-st} t^k e^{\lambda t}\mathrm{d}t = \frac{k!}{(s-\lambda)^{k+1}}, \qquad \Re(s) > |\lambda|, \tag{5.34}$$

and

$$\mathcal{L}\left[t^k e^{-\lambda t}\right](s) = \int_0^{\infty} e^{-st} t^k e^{-\lambda t}\mathrm{d}t = \frac{k!}{(s+\lambda)^{k+1}}, \qquad \Re(s) > |\lambda|. \tag{5.35}$$

A pair of Laplace transform of the functions

$$t^{\alpha m+\beta-1} E_{\alpha,\beta}^{(m)}(\lambda t^{\alpha})$$

and

$$t^{\alpha m+\beta-1} E_{\alpha,\beta}^{(m)}(-\lambda t^{\alpha})$$

could be respectively calculated by using (5.34) and (5.35), where $E_{\alpha,\beta}^{(m)}(t)$ denotes the mth derivative of the Mittag-Leffler function, i.e. $E_{\alpha,\beta}^{(m)}(t) \equiv \frac{\mathrm{d}^m}{\mathrm{d}t^m} E_{\alpha,\beta}(t)$:

$$\begin{aligned}\mathcal{L}\left[t^{\alpha m+\beta-1} E_{\alpha,\beta}^{(m)}(\lambda t^{\alpha})\right](s) &= \int_0^{\infty} e^{-st} t^{\alpha m+\beta-1} E_{\alpha,\beta}^{(m)}(\lambda t^{\alpha})\,\mathrm{d}t \\ &= \frac{m! s^{\alpha-\beta}}{(s^{\alpha}-\lambda)^{m+1}}, \quad \Re(s) > |\lambda|^{\frac{1}{\alpha}}\end{aligned} \tag{5.36}$$

and

$$\begin{aligned}\mathcal{L}\left[t^{\alpha m+\beta-1} E_{\alpha,\beta}^{(m)}(-\lambda t^{\alpha})\right](s) &= \int_0^{\infty} e^{-st} t^{\alpha m+\beta-1} E_{\alpha,\beta}^{(m)}(-\lambda t^{\alpha})\,\mathrm{d}t \\ &= \frac{m! s^{\alpha-\beta}}{(s^{\alpha}+\lambda)^{m+1}}, \quad \Re(s) > |\lambda|^{\frac{1}{\alpha}}\end{aligned} \tag{5.37}$$

Specifically, with the help of (5.36) and (5.37), the Laplace transform of the Mittag-Leffler functions $E_{\alpha}(\lambda t^{\alpha})$ and $E_{\alpha}(-\lambda t^{\alpha})$ are obtained:

$$\mathcal{L}\left[E_{\alpha}(\lambda t^{\alpha})\right](s) = \int_0^{\infty} e^{-st} E_{\alpha}(\lambda t^{\alpha})\,\mathrm{d}t = \frac{s^{\alpha-1}}{s^{\alpha}-\lambda}, \quad \Re(s) > |\lambda|^{\frac{1}{\alpha}}, \tag{5.38}$$

and

$$\mathcal{L}\left[E_{\alpha}(-\lambda t^{\alpha})\right](s) = \int_0^{\infty} e^{-st} E_{\alpha}(-\lambda t^{\alpha})\,\mathrm{d}t = \frac{s^{\alpha-1}}{s^{\alpha}+\lambda}, \quad \Re(s) > |\lambda|^{\frac{1}{\alpha}}. \tag{5.39}$$

5.2 Modified fractional logistic equation

In [144], the author has utilized the Carleman embedding technique to construct an infinite–order system of linear fractional differential equations equivalent to the nonlinear fractional differential equation (5.1) and has obtained a solution in terms of a weighted sum over the Mittag-Leffler functions. The authors in [8] indicated later that the Carleman embedding technique solves integer-order differential equations, not the fractional ones. Nonetheless, for $\alpha = 1$, the WF results in the solution to classical LE. As illustrated in Fig. 5.1, it is observed that the WF for the case $k = 1$, which is expressed in (5.3), is in good agreement with the numerical integration of FLE. Fig. 5.1 shows the graph of the numerical solution to (5.40)

$$ {}^{C}D_{t}^{\alpha} w\left(t\right) = w\left(1 - w\right) , \qquad \alpha \in (0, 1] . \tag{5.40} $$

and the WF represented in (5.3) for the fractional order $\alpha = 0.7$. The MATLAB code fde12.m [60] is used in order to represent the numerical solution of (5.40). The WF is numerically evaluated by means of the MATLAB code ml.m [61], which is based on the numerical inversion of the Laplace transform of Mittag-Leffler function [62]. The goal is to demonstrate that the WF, which has been expressed in (5.3), is the

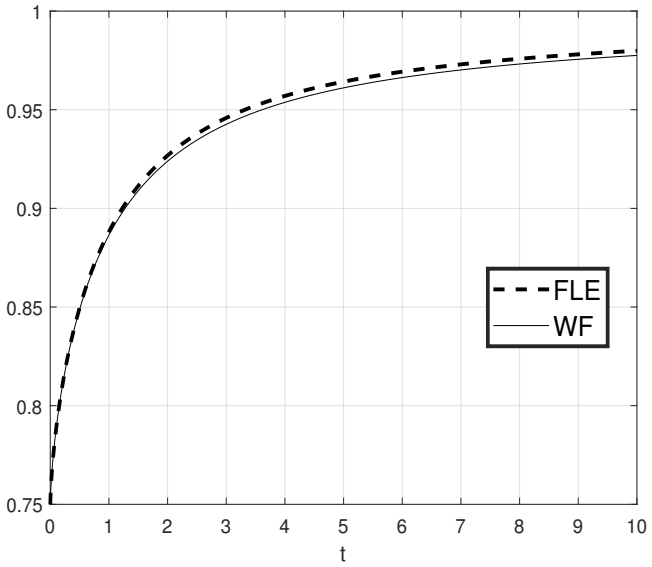

Figure 5.1. Comparison of the WF expressed in (5.3) and the numerical integration of the FLE, for $\alpha = 0.7$ and $u_0 = 0.75$.

solution to fractional integro-differential equation (5.4). In Section 2.1.1, the solution to LE (2.6) was expressed. Equation (2.7), which represents the solution to LE, can be reformulated as below

$$ u\left(t\right) = \sum_{k=0}^{\infty} \left(\frac{u_0 - 1}{u_0}\right)^{k} e^{-kt} . \tag{5.41} $$

By using (5.5) and (5.41), the function $w(t)$, represented in (5.3), can be expressed in terms of $l_\alpha(s,t)$

$$\begin{aligned} w(t) &= \sum_{k=0}^{\infty}\left(\frac{u_0-1}{u_0}\right)^k E_\alpha(-kt^\alpha) \\ &= \sum_{k=0}^{\infty}\left(\frac{u_0-1}{u_0}\right)^k \int_0^\infty e^{-ks} l_\alpha(s,t)\,\mathrm{d}s \\ &= \int_0^\infty \sum_{k=0}^{\infty}\left(\frac{u_0-1}{u_0}\right)^k e^{-ks} l_\alpha(s,t)\,\mathrm{d}s \\ &= \int_0^\infty u(s)\, l_\alpha(s,t)\,\mathrm{d}s\,. \end{aligned} \tag{5.42}$$

It could be obtained, by using (5.3), that

$$\begin{aligned} w^2(t) &= \sum_{k=0}^{\infty}\sum_{i=0}^{\infty}\left(\frac{u_0-1}{u_0}\right)^{k+i} E_\alpha(-it^\alpha)\,E_\alpha(-kt^\alpha) \\ &= \sum_{k=0}^{\infty}\sum_{i=0}^{\infty}\left(\frac{u_0-1}{u_0}\right)^{k+i} \int_0^\infty e^{-ks} l_\alpha(s,t)\,\mathrm{d}s \int_0^\infty e^{-iz} l_\alpha(z,t)\,\mathrm{d}z \\ &= \int_0^\infty\int_0^\infty \sum_{k=0}^{\infty}\sum_{i=0}^{\infty}\left(\frac{u_0-1}{u_0}\right)^{k+i} e^{-ks}e^{-iz} l_\alpha(s,t)\, l_\alpha(z,t)\,\mathrm{d}s\mathrm{d}z \\ &= \int_0^\infty\int_0^\infty u(s)\,u(z)\, l_\alpha(s,t)\, l_\alpha(z,t)\,\mathrm{d}s\mathrm{d}z\,. \end{aligned} \tag{5.43}$$

The substitution of (5.43) for the term $w^2(t)$ in (5.4) leads to

$$\begin{aligned} {}^C D_t^\alpha w(t) &= \frac{u_0 t^{-\alpha}}{\Gamma(1-\alpha)} + w - \int_0^\infty\int_0^\infty u^2(s)\, l_\alpha(s,t)\, l_\alpha(z,t)\,\mathrm{d}s\mathrm{d}z \\ &= \frac{u_0 t^{-\alpha}}{\Gamma(1-\alpha)} + w - \int_0^\infty \left(u^2(s)\, l_\alpha(s,t)\int_0^\infty l_\alpha(z,t)\,\mathrm{d}z\right)\mathrm{d}s\,, \end{aligned} \tag{5.44}$$

it is eventually obtained by using (5.6), (5.9), and (5.44) that

$$\begin{aligned} {}^C D_t^\alpha w(t) &= \frac{u_0 t^{-\alpha}}{\Gamma(1-\alpha)} + w - \int_0^\infty u^2(s)\, l_\alpha(s,t)\,\mathrm{d}s \\ &= \frac{u_0 t^{-\alpha}}{\Gamma(1-\alpha)} + \int_0^\infty \Big(u(s) - u^2(s)\Big)\, l_\alpha(s,t)\,\mathrm{d}s \\ &= \frac{u_0 t^{-\alpha}}{\Gamma(1-\alpha)} + \int_0^\infty u'(s)\, l_\alpha(s,t)\,\mathrm{d}s \\ &= \frac{u_0 t^{-\alpha}}{\Gamma(1-\alpha)} + u(s)\, l_\alpha(s,t)|_{s=0}^\infty - \int_0^\infty u(s)\,\partial_s l_\alpha(s,t)\,\mathrm{d}s \\ &= \frac{u_0 t^{-\alpha}}{\Gamma(1-\alpha)} + \left(0 - u_0\frac{t^{-\alpha}}{\Gamma(1-\alpha)}\right) + \int_0^\infty u(s)\,{}^C D_t^\alpha l_\alpha(s,t)\,\mathrm{d}s \\ &= {}^C D_t^\alpha \int_0^\infty u(s)\, l_\alpha(s,t)\,\mathrm{d}s \\ &= {}^C D_t^\alpha w(t)\,. \end{aligned} \tag{5.45}$$

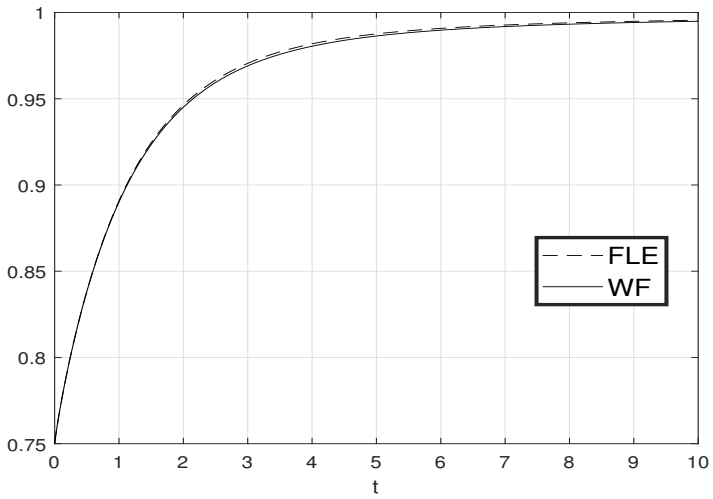

Figure 5.2. Comparison of the WF expressed in (5.3) and the numerical integration of the FLE, for $\alpha = 0.9$ and $u_0 = 0.75$.

Therefore the function $w(t)$, expressed in (5.3), satisfies (5.4). Fig. 5.2 illustrates the graphs of the WF and numerical solution to (5.40) and shows that the WF is in good agreement with the numerical solution of FLE. Specifically, as mentioned in [144], the WF and numerical solution to FLE coincide for $\alpha = 1$. As it is obvious from (5.3), the solution to MFLE is obtained by means of a series of Mittag-Leffler functions. Thus, series of Mittag-Leffler functions seem to play an interesting role in the context of FLE. The properties of series of Mittag-Leffler functions have been studied in [118].

5.3 Determination of Order for MFLE

The determination of the order of fractional differential equations is an issue, which has been analysed and discussed in recent years [48, 70] and it has a wide range of applications in physical phenomena such as fractional diffusion equations. In [48], fractional order estimation has been conducted for some classes of linear fractional differential equations. The details is left until Chapter 6. In this section, the relationship between the fractional order and the asymptotic behaviour of the solution to MFLE is proved. The solution to (5.4) could be asymptotically expressed by referring to (5.30):

$$\begin{aligned} w(t) &= \sum_{k=0}^{\infty} \left(\frac{u_0 - 1}{u_0} \right)^k E_\alpha \left(-kt^\alpha \right) \\ &= 1 + \sum_{k=1}^{\infty} \left(\frac{u_0 - 1}{u_0} \right)^k E_\alpha \left(-kt^\alpha \right), \end{aligned} \tag{5.46}$$

and for large t, by using (5.30), $w(t)$ will be approximately equal to

$$\begin{aligned} w(t) &\approx 1+\sum_{k\geq 1}\left(\frac{u_0-1}{u_0}\right)^k \sum_{s\geq 1}(-1)^{s+1}\left(\frac{1}{kt^{\alpha}}\right)^s \frac{1}{\Gamma(1-\alpha s)} \\ &\approx 1+\sum_{k\geq 1}\sum_{s\geq 1}(-1)^{s+1}\left(\frac{u_0-1}{u_0}\right)^k \frac{t^{-s\alpha}}{k^s}\frac{1}{\Gamma(1-\alpha s)} \\ &\approx 1+\frac{t^{-\alpha}}{\Gamma(1-\alpha)}\sum_{k\geq 1}\left(\frac{u_0-1}{u_0}\right)^k \frac{1}{k} \\ &\quad +\sum_{s\geq 2}(-1)^{s+1}\frac{t^{-s\alpha}}{\Gamma(1-\alpha s)}\sum_{k\geq 1}\left(\frac{u_0-1}{u_0}\right)^k \frac{1}{k^s}, \end{aligned} \tag{5.47}$$

Remark 5.3.1. *By observing (5.47), it is obviously found that the function $w(t)$ has the limit $w_\infty = 1$, which is independent of the fractional order, α, as time tends to infinity.*

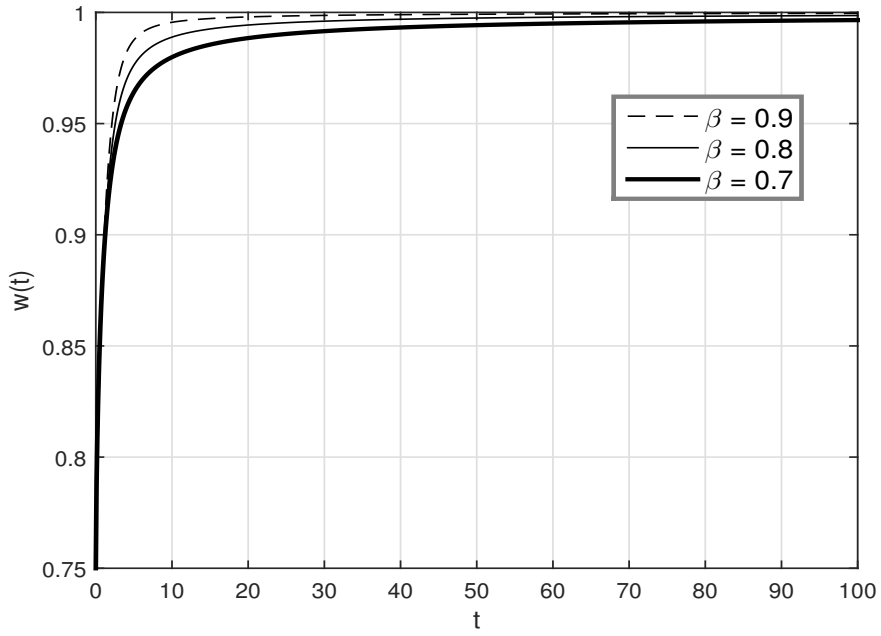

Figure 5.3. The graph of the WF for $\alpha = 0.7$, $\alpha = 0.8$, $\alpha = 0.9$.

Fig. 5.3 shows that the solution to MFLE is asymptotically independent of the fractional order, α, and its limit is equal to one as t goes to infinity. For $u_0 \geq \frac{1}{2}$, (5.47) is as follows

$$\begin{aligned} w(t) &\approx 1+\frac{t^{-\alpha}}{\Gamma(1-\alpha)}\ln u_0 + \\ &\quad \sum_{s\geq 2}(-1)^{s+1}\frac{t^{-s\alpha}}{\Gamma(1-\alpha s)}\sum_{k\geq 1}\left(\frac{u_0-1}{u_0}\right)^k \frac{1}{k^s}, \quad u_0 \geq \frac{1}{2} \end{aligned} \tag{5.48}$$

As t tends to infinity, by neglecting the third term of the right-hand side of (5.48), the function $w(t)$ is asymptotically equal to

$$w(t) \approx 1 + \frac{t^{-\alpha}}{\Gamma(1-\alpha)} \ln u_0 \,, \quad u_0 \geq \frac{1}{2} \,. \tag{5.49}$$

Therefore, by using the asymptotic behaviour of the function $w(t)$, the order of (5.4) is determined

$$\lim_{t \to +\infty} \frac{t w'(t)}{1 - w(t)} = \alpha \,. \tag{5.50}$$

Chapter 6

Determination of Order in Linear FDEs

In this chapter, the order of some classes of fractional linear differential equations is determined, based on asymptotic behaviour of the solution as time tends to infinity. The order of fractional derivative has been proved to be of great importance in an accurately appropriate simulation of the system under study. Specifically, by representing the asymptotic expansion of the solution, it could be obviously demonstrated that the decay rate of the solution is influenced by the order of fractional differentiation. The numerical investigation is conducted into the proven formulae. The practical significance of fractional calculus has been recently discerned as a vastly superior method of describing the long-memory processes and had a remarkable development over the last few years, both in mathematical and non-mathematical fields [12, 28, 41, 80, 105, 131].

More specifically, FDEs have been proven extremely important for more accurately modelling of many physical phenomena [31, 72, 104, 130]. Inverse problems to FDEs occur in many branches of science. Such problems have been investigated, for instance, in fractional diffusion equation [33, 70, 97, 132, 151] and inverse boundary value problem for semi-linear fractional telegraph equation [96]. Specifically in [70], it has been demonstrated that determination of β, the order of fractional differential operator, is definitely crucial to the appropriate simulation of the anomalous diffusion in order to specify that the transport phenomenon exhibits sub-diffusion or super-diffusion for respectively $\beta < 1$ and $\beta > 1$. The authors in [70] have presented and proven a theorem, the idea behind which is seeking solutions to an inverse problem, i.e. determination of the order of a fractional diffusion equation; therefore, this persuaded us to prove formulae indicating the relationship between the fractional order and the asymptotic behaviour of the exact solutions to several different class of fractional differential equations. The following sections are allocated to some necessary preliminaries, the main results and numerical simulation.

6.1 Preliminaries

It is appropriate to briefly recall some critical bases of fractional calculus. The Mittag-Leffler function $E_{\alpha,\beta}(z)$ satisfies the recurrence property

$$E_{\alpha,\beta}(z) = -\frac{1}{z\Gamma(\beta-\alpha)} + \frac{1}{z}E_{\alpha,\beta-\alpha}(z). \tag{6.1}$$

By the fractional differentiation operator of the Riemann-Liouville type $D_0^\gamma f$ ($\gamma \in \mathbb{R}$), the Mittag-Leffler function satisfies the following differentiation formula [119]

$$D_0^\gamma\left(z^{\alpha k+\beta-1}E_{\alpha,\beta}^{(k)}(\lambda z^\alpha)\right) = z^{\alpha k+\beta-\gamma-1}E_{\alpha,\beta-\gamma}^{(k)}(\lambda z^\alpha). \tag{6.2}$$

The particular case of the relationship (6.2) for $n \in \mathbb{N}$ has the form below

$$\left(\frac{d}{dz}\right)^n\left(z^{\beta-1}E_{\alpha,\beta}(\lambda z^\alpha)\right) = z^{\beta-n-1}E_{\alpha,\beta-n}(\lambda z^\alpha), \tag{6.3}$$

and the following practical formulae could be directly derived from (6.3):

$$\frac{d}{dz}E_\alpha(\lambda z^\alpha) = \frac{1}{z}E_{\alpha,0}(\lambda z^\alpha) = \lambda z^{\alpha-1}E_{\alpha,\alpha}(\lambda z^\alpha), \tag{6.4}$$

$$\frac{d}{dz}\left(E_{\alpha,\alpha}(\lambda z^\alpha)\right) = \frac{1}{z}E_{\alpha,\alpha-1}(\lambda z^\alpha) + \frac{(1-\alpha)}{z}E_{\alpha,\alpha}(\lambda z^\alpha), \tag{6.5}$$

$$\frac{d}{dz}\left(z^{\beta-1}E_{\alpha,\beta}(\lambda z^\alpha)\right) = z^{\beta-2}E_{\alpha,\beta-1}(\lambda z^\alpha), \tag{6.6}$$

$$\frac{d}{dz}\left(zE_{\alpha,2}(\lambda z^\alpha)\right) = E_\alpha(\lambda z^\alpha). \tag{6.7}$$

6.1.1 Asymptotic behaviour of Mittag-Leffler function

In this section, the asymptotic behaviour of Mittag-Leffler function is briefly stated for the case $0 < \alpha < 2$. Suppose that $0 < \alpha < 2$, $\beta, z \in \mathbb{C}$ and μ be an arbitrary real number such that $\frac{\pi}{2}\alpha < \mu < \min(\pi, \pi\alpha)$. Then the following expansions hold

$$E_{\alpha,\beta}(z) = \frac{1}{\alpha}z^{\frac{1-\beta}{\alpha}}\exp\left(z^{\frac{1}{\alpha}}\right) - \sum_{k=1}^{n}\frac{1}{\Gamma(\beta-k\alpha)z^k} + O\left(|z|^{-n-1}\right), \quad |z|\to\infty, \quad |\arg(z)| \le \mu. \tag{6.8}$$

and

$$E_{\alpha,\beta}(z) = -\sum_{k=1}^{n}\frac{1}{\Gamma(\beta-k\alpha)z^k} + O\left(|z|^{-n-1}\right), \quad |z|\to\infty, \quad \mu \le |\arg(z)| \le \pi. \tag{6.9}$$

By applying the expansion (6.9) to the reals ($z \in \mathbb{R}$), the following advantageous formulae could be acquired

$$E_\alpha(\lambda z^\alpha) = -\frac{z^{-\alpha}}{\lambda\Gamma(1-\alpha)} + O\left(\frac{1}{|\lambda|^2 z^{2\alpha}}\right), \quad z\to\infty, \quad z>0, \quad \lambda<0, \tag{6.10}$$

$$E_{\alpha,\alpha}(\lambda z^\alpha) = \frac{\alpha z^{-2\alpha}}{\lambda^2\Gamma(1-\alpha)} + O\left(\frac{1}{|\lambda|^3 z^{3\alpha}}\right), \quad z\to\infty, \quad z>0, \quad \lambda<0. \tag{6.11}$$

6.1.2 Sequential Fractional Derivative

The main idea of fractional calculus, which was mentioned before, is to replace the integer-valued parameter n in the symbol

$$\frac{\mathrm{d}^n}{\mathrm{d}x^n} f(x) ,$$

with a non-integer parameter α. However, there is another approach which is a matter of great importance to many applications. This approach states that in fact, an nth order derivative is a series of first order derivative:

$$\frac{\mathrm{d}^n f}{\mathrm{d}x^n} = \underbrace{\frac{\mathrm{d}}{\mathrm{d}x}\frac{\mathrm{d}}{\mathrm{d}x}\cdots\frac{\mathrm{d}}{\mathrm{d}x}}_{n} f .$$

Replacing the first order derivative, $\frac{\mathrm{d}}{\mathrm{d}x}$, with the derivative of non-integer order, D^α, where $0 < \alpha \leq 1$, results in another fractional differentiation operator, which is called as sequential fractional derivative [85] denoted by

$$\mathcal{D}^{n\alpha} f(x) = \underbrace{D^\alpha D^\alpha \dots D^\alpha}_{n} f(x) ,$$

where D^β could be Riemann-Liouville, Caputo or any other type of fractional differential operator. For instance, for the Riemann-Liouville fractional derivative, the operator $\mathcal{D}_a^{n\alpha} f(x)$ denotes the Riemann-Liouville sequential fractional derivative:

$$\begin{aligned} \mathcal{D}_a^\alpha f &= D_a^\alpha f \\ \mathcal{D}_a^{n\alpha} f &= \mathcal{D}_a^\alpha \mathcal{D}_a^{(n-1)\alpha} f , \quad (n = 2, 3, \dots) . \end{aligned} \tag{6.12}$$

The general theory of sequential linear fractional differential equations is essentially discussed in [85, 112]. In this section, the fractional order, α, is considered to be a real number restricted to one, i.e. $0 < \alpha \leq 1$ and $D_a^\alpha y(x)$ denotes the Riemann-Liouville fractional derivative of the function $y(x)$.

Definition 6.1.1. *Let $n \in \mathbb{N}$. The equation*

$$\sum_{k=0}^{n} a_k(x) \mathcal{D}_a^{k\alpha} y(x) = f(x) \qquad a < x < b , \ (k = 1, \dots, n) , \tag{6.13}$$

is called as linear sequential fractional differential equation of order $n\alpha$, where $a_k(x)$ are known real functions and $\mathcal{D}_a^{k\alpha}$ denotes the fractional sequential derivative, i.e.

$$\begin{aligned} \mathcal{D}_a^0 y &:= y , \\ \mathcal{D}_a^\alpha y &:= D_a^\alpha y , \\ \mathcal{D}_a^{k\alpha} y &:= \mathcal{D}_a^\alpha \mathcal{D}_a^{(k-1)\alpha} \qquad (k = 2, 3, \dots) . \end{aligned}$$

If $a_n(x) \neq 0$ for all $x \in [a, b]$, (6.13) may be presented by

$$\mathbf{L}_{n\alpha} y(x) = f(x) ,$$

where $\mathbf{L}_{n\alpha}y(x)$ denotes

$$\begin{aligned}\mathbf{L}_{n\alpha}y(x) &= \mathcal{D}_a^{n\alpha}y(x)+\sum_{k=0}^{n-1}a_k(x)\,\mathcal{D}_a^{k\alpha}y(x)\\ &= \mathcal{D}_a^{n\alpha}y(x)+a_{n-1}(x)\,\mathcal{D}_a^{(n-1)\alpha}y(x)+\cdots+a_1(x)\,\mathcal{D}_a^{\alpha}y(x)+y(x)\end{aligned}$$

Definition 6.1.2. *Any solution to the equation $\mathbf{L}_{n\alpha}y(x)=f(x)$ is referred to as the general solution of this equation, which depends on n independent constants.*

The next theorem represents the existence and uniqueness of global solutions to the equation $\mathbf{L}_{n\alpha}y(x)=f(x)$ with specified initial conditions:

Theorem 6.1.1. *Let $x_0\in(a,b)$ and $y_0^k\in\mathbb{R}$ $(k=0,1,\ldots,n-1)$ be given real numbers, and let $a_i(x)\in C([a,b])$ $(i=0,1,\ldots,n-1)$ and $f(x)\in C([a,b])$. Then, there exists a unique solution $y(x)\in C([a,b])$ of the initial value problem*

$$\mathbf{L}_{n\alpha}y(x)=f(x) \tag{6.14a}$$

$$\mathcal{D}_a^{k\alpha}y(x_0)=y_0^k\qquad(k=0,1,\ldots,n-1)\,. \tag{6.14b}$$

Proposition 6.1.1. *Any linear combination of solutions to the homogeneous equation*

$$\mathbf{L}_{n\alpha}y(x)=0\,, \tag{6.15}$$

is also a solution to this equation.

Proposition 6.1.2. *If the function $y_p(x)$ is a particular solution to the equation*

$$\mathbf{L}_{n\alpha}y(x)=f(x)\ ,$$

then the general solution to this equation will be given by

$$y(x)=y_p(x)+y_h(x)\ ,$$

where $y_h(x)$ is the general solution to the corresponding homogeneous equation

$$\mathbf{L}_{n\alpha}y(x)=0\,.$$

Consider the homogeneous equation

$$\mathbf{L}_{n\alpha}y(x)=\mathcal{D}_a^{n\alpha}y(x)+\sum_{k=0}^{n-1}a_k\mathcal{D}_a^{k\alpha}y(x)=0\,, \tag{6.16}$$

in which a_k $(k=1,\ldots,n-1)$ are real constants. The solution to (6.16) can be sought in the form of

$$y(x)=e_\alpha^{\lambda(x-a)}=(x-a)^{\alpha-1}E_{\alpha,\alpha}\left(\lambda(x-a)^\alpha\right)\ .$$

By referring to Eq. (6.16), it follows that

$$\mathbf{L}_{n\alpha}e_\alpha^{\lambda(x-a)}=P_n(\lambda)\,e_\alpha^{\lambda(x-a)}\,,$$

where

$$P_n(\lambda)=\lambda^n+\sum_{k=1}^{n-1}a_k\lambda^k\,, \tag{6.17}$$

is the characteristic polynomial associated with the equation $\mathbf{L}_{n\alpha}y(x)=0$, where $\lambda\in\mathbb{C}$.

Lemma 6.1.1. *If λ is a root of the characteristic polynomial (6.17), then*

$$\frac{\partial}{\partial\lambda}\left(\mathbf{L}_{n\alpha}e_{\alpha}^{\lambda(x-a)}\right)=\mathbf{L}_{n\alpha}\left(\frac{\partial}{\partial\lambda}e_{\alpha}^{\lambda(x-a)}\right),$$

and

$$\frac{\partial^{l}}{\partial\lambda^{l}}e_{\alpha}^{\lambda(x-a)}=(x-a)^{l\alpha}\,e_{\alpha,l}^{\lambda(x-a)},$$

where $l\in\mathbb{N}$ and

$$e_{\alpha,l}^{\lambda(x-a)}=l!\,(x-a)^{(\alpha-1)}\,E_{\alpha,(l+1)\alpha}^{l+1}\left(\lambda\,(x-a)^{\alpha}\right)$$

Proposition 6.1.3. *If λ_1 is a root of multiplicity μ_1 of the characteristic polynomial (6.17), then the functions*

$$y_{1,l}(x)=(x-a)^{l\alpha}\,e_{\alpha,l}^{\lambda_1(x-a)},\qquad(l=0,\ldots,\mu_1-1)$$

are solutions to the equation $\mathbf{L}_{n\alpha}y(x)=0$.

Corollary 6.1.1. *Let λ_j $j=1,\ldots,k$ be k distinct roots of the characteristic polynomial (6.17) with multiplicity μ_j $j=1,\ldots,k$. Then the functions*

$$\bigcup_{m=1}^{k}\left\{(x-a)^{l\alpha}\,e_{\alpha,l}^{\lambda_m(x-a)}\right\}_{l=0}^{\mu_m-1}$$

are linearly independent solutions of (6.15).

Proposition 6.1.4. *If λ_1 and $\bar{\lambda_1}$ $(\lambda_1=b+ic,c\neq0)$ are two complex solutions of multiplicity σ_1 of the characteristic polynomial (6.17), then the functions*

$$\left\{\sum_{j=0}^{\infty}(-1)^{j}\,\frac{c^{2j}}{(2j)!}\,(x-a)^{(2j+l)\alpha}\,e_{\alpha,l+2j}^{b(x-a)}\right\}_{l=0}^{\sigma_1-1}$$

and

$$\left\{\sum_{j=0}^{\infty}(-1)^{j}\,\frac{c^{2j+1}}{(2j+1)!}\,(x-a)^{(2j+l+1)\alpha}\,e_{\alpha,l+2j+1}^{b(x-a)}\right\}_{l=0}^{\sigma_1-1}$$

form $2\sigma_1$ linearly independent real solutions of Eq. (6.15).

Corollary 6.1.2. *Assume that $\left\{\lambda_m,\bar{\lambda_m}\right\}_{m=1}^{p}$, $(\lambda_m=b_m+ic_m,c_m\neq0)$ are all distinct pairs of complex conjugate solutions of multiplicity $\{\sigma_m\}_{m=1}^{p}$ of the characteristic polynomial (6.17) for Eq. (6.15). Then the functions*

$$\bigcup_{m=1}^{p}\left\{\sum_{j=0}^{\infty}(-1)^{j}\,\frac{c_m^{2j}}{(2j)!}\,(x-a)^{(2j+l)\alpha}\,e_{\alpha,l+2j}^{b_m(x-a)}\right\}_{l=0}^{\sigma_m-1}$$

and

$$\bigcup_{m=1}^{p}\left\{\sum_{j=0}^{\infty}(-1)^{j}\,\frac{c_m^{2j+1}}{(2j+1)!}\,(x-a)^{(2j+l+1)\alpha}\,e_{\alpha,l+2j+1}^{b_m(x-a)}\right\}_{l=0}^{\sigma_m-1}$$

determine a linearly independent set of solutions to (6.15)

Theorem 6.1.2. *Assume the characteristic polynomial, represented by (6.17), for Eq. (6.15). Let $\{\lambda_j\}_{j=1}^{k}$ be the all distinct real roots of (6.17) of the multiplicity $\{\mu_j\}_{j=1}^{k}$, and let $\{r_j, \bar{r_j}\}_{j=1}^{p}$, $(r_j = b_j + ic_j)$ be the set of the all distinct pairs of complex conjugate roots of (6.17) of the multiplicity $\{\sigma_j\}_{j=1}^{p}$ such that*

$$\sum_{j=1}^{k} \mu_j + 2\sum_{j=1}^{p} \sigma_j = n\,.$$

Then the functions

$$\bigcup_{m=1}^{k} \left\{ (x-a)^{l\alpha}\, e_{\alpha,l}^{\lambda_m (x-a)} \right\}_{l=0}^{\mu_m - 1}, \tag{6.18}$$

$$\bigcup_{m=1}^{p} \left\{ \sum_{j=0}^{\infty} (-1)^j \frac{c_m^{2j}}{(2j)!} (x-a)^{(2j+l)\alpha}\, e_{\alpha,l+2j}^{b_m (x-a)} \right\}_{l=0}^{\sigma_m - 1}, \tag{6.19}$$

and

$$\bigcup_{m=1}^{p} \left\{ \sum_{j=0}^{\infty} (-1)^j \frac{c_m^{2j+1}}{(2j+1)!} (x-a)^{(2j+l+1)\alpha}\, e_{\alpha,l+2j+1}^{b_m (x-a)} \right\}_{l=0}^{\sigma_m - 1} \tag{6.20}$$

form the fundamental system of solutions of (6.15).

6.2 Order Estimation of Linear FDEs

This section is intended to determine the order of several classes of fractional differential equations by using the asymptotic behaviour of the exact solutions, as time tends to infinity.

Theorem 6.2.1. *Let $0 < \beta \leq 1$, $t_0 > 0$ and also let $D_{t_0}^{\beta} u$ represents the Riemann-Liouville differentiation operator. Consider the sequential linear differential equation of fractional order*

$$\mathcal{D}_{t_0}^{2\beta} u + a_1 \mathcal{D}_{t_0}^{\beta} u + a_0 u = 0, \tag{6.21}$$

with the initial condition $u(t_0) = u_0$ and $\mathcal{D}_{t_0}^{\beta} u(t_0) = u_1$, and let a_0 and a_1 are reals such that r_1 and r_2, the roots of the characteristic equation $r^2 + a_1 r + a_0 = 0$, are distinct and real negative numbers. The following formula holds

$$\beta = -1 - \lim_{t \to \infty} \frac{tu'}{u} \tag{6.22}$$

Proof. The exact solution to (6.21) has the form [80]

$$u(t) = c_1 t^{\beta-1} E_{\beta,\beta}\left(r_1 t^{\beta}\right) + c_2 t^{\beta-1} E_{\beta,\beta}\left(r_2 t^{\beta}\right). \tag{6.23}$$

where c_1 and c_2 depend on the initial conditions. The first derivative of $u(t)$ could be calculated by using (6.6) as below

$$u'(t) = c_1 t^{\beta-2} E_{\beta,\beta-1}\left(r_1 t^{\beta}\right) + c_2 t^{\beta-2} E_{\beta,\beta-1}\left(r_2 t^{\beta}\right). \tag{6.24}$$

By referring to (6.9), the asymptotic expansion of $u(t)$ and $u'(t)$ are respectively

$$u(t) = \frac{-t^{-\beta-1}}{\Gamma(-\beta)}\left(\frac{c_1}{r_1^2}+\frac{c_2}{r_2^2}\right) + c_1 t^{\beta-1} O\left(|r_1|^{-3} t^{-3\beta}\right) + c_2 t^{\beta-1} O\left(|r_2|^{-3} t^{-3\beta}\right) \quad (6.25)$$

and

$$\begin{aligned} u'(t) = \frac{(\beta+1)\, t^{-\beta-2}}{\Gamma(-\beta)}\left(\frac{c_1}{r_1^2}+\frac{c_2}{r_2^2}\right) &+ c_1 t^{\beta-2} O\left(|r_1|^{-3} t^{-3\beta}\right) \\ &+ c_2 t^{\beta-2} O\left(|r_2|^{-3} t^{-3\beta}\right). \end{aligned} \quad (6.26)$$

Therefore

$$\frac{tu'}{u} = \frac{\frac{(\beta+1)t^{-\beta-1}}{\Gamma(-\beta)}\left(\frac{c_1}{r_1^2}+\frac{c_2}{r_2^2}\right) + c_1 t^{\beta-1} O\left(|r_1|^{-3} t^{-3\beta}\right) + c_2 t^{\beta-1} O\left(|r_2|^{-3} t^{-3\beta}\right)}{\frac{-t^{-\beta-1}}{\Gamma(-\beta)}\left(\frac{c_1}{r_1^2}+\frac{c_2}{r_2^2}\right) + c_1 t^{\beta-1} O\left(|r_1|^{-3} t^{-3\beta}\right) + c_2 t^{\beta-1} O\left(|r_2|^{-3} t^{-3\beta}\right)} \quad (6.27)$$

As $t \to \infty$, (6.27) leads to

$$-\lim_{t\to\infty} \frac{tu'}{u} = -\lim_{t\to\infty} \frac{\frac{(\beta+1)t^{-\beta-1}}{\Gamma(-\beta)}\left(\frac{c_1}{r_1^2}+\frac{c_2}{r_2^2}\right)}{\frac{-t^{-\beta-1}}{\Gamma(-\beta)}\left(\frac{c_1}{r_1^2}+\frac{c_2}{r_2^2}\right)} = \beta+1 \quad (6.28)$$

and proof is completed. □

Theorem 6.2.2. *Let $0 < \beta < \frac{1}{2}$, $\gamma, \mu \in \mathbb{R}$ such that $0 < \gamma < \mu^2$, and let $D_t^\beta u$ indicates the Caputo differentiation operator. For the initial value problem*

$$D_t^{2\beta} u(t) + 2\mu D_t^\beta u(t) + \gamma u(t) = 0 \quad (6.29)$$

with the initial condition $u(0) = 1$, and also for sequential linear differential equation of fractional order

$$\mathcal{D}_t^{2\beta} u + 2\mu \mathcal{D}_t^\beta u + \gamma u = 0 \quad (6.30)$$

with the initial condition $\mathcal{D}_t^\beta u(0) = 0$ and $u(0) = 1$, the following formula holds

$$\beta = -\lim_{t\to\infty} \frac{tu'}{u} \quad (6.31)$$

Remark 6.2.1. *If $\mathcal{D}_t^\beta u(0) = 0$, then $c_1 r_1 + c_2 r_2 = 0$ and $\mathcal{D}_t^{2\beta} u = D_t^{2\beta} u$. The case of $\mathcal{D}_t^\beta u(0) \neq 0$ leads to $c_1 r_1 + c_2 r_2 \neq 0$ and therefore, the coefficients c_1 and c_2 are not the same as those represented in the proof of Theorem 6.2.2 and must be calculated.*

Proof. The equations (6.29) and (6.30) have the exact solution [49], represented by

$$u(t) = c_1 E_\beta\left(r_1 t^\beta\right) + c_2 E_\beta\left(r_2 t^\beta\right), \quad (6.32)$$

where the coefficients c_1 and c_2 are respectively equal to $\frac{1}{2}\left(1+\frac{\mu}{\sqrt{\mu^2-\gamma}}\right)$ and $\frac{1}{2}\left(1-\frac{\mu}{\sqrt{\mu^2-\gamma}}\right)$, and the parameters r_1 and r_2 equal to $-\mu+\sqrt{\mu^2-\gamma} < 0$ and

$-\mu-\sqrt{\mu^2-\gamma}<0$ respectively. The asymptotic behaviour of Mittag-Leffler function at infinity is applied to (6.32). By using (6.10)

$$u(t)=-\frac{t^{-\beta}}{\Gamma(1-\beta)}\left(\frac{c_1}{r_1}+\frac{c_2}{r_2}\right)+c_1O\left(r_1^{-2}t^{-2\beta}\right)+c_2O\left(r_2^{-2}t^{-2\beta}\right). \tag{6.33}$$

The first derivative of (6.32) could be obtained by referring to (6.4)

$$u'(t)=c_1r_1t^{\beta-1}E_{\beta,\beta}\left(r_1t^{\beta}\right)+c_2r_2t^{\beta-1}E_{\beta,\beta}\left(r_2t^{\beta}\right), \tag{6.34}$$

and using (6.11) and applying the asymptotic behaviour of Mittag-Leffler function to (6.34), leads to

$$u'(t)=\frac{\beta t^{-\beta-1}}{\Gamma(1-\beta)}\left(\frac{c_1}{r_1}+\frac{c_2}{r_2}\right)+t^{\beta-1}\left(c_1r_1O\left(r_1^{-3}t^{-3\beta}\right)+c_2r_2O\left(r_2^{-3}t^{-3\beta}\right)\right). \tag{6.35}$$

Therefore

$$\frac{tu'}{u}=t\frac{\frac{\beta t^{-\beta-1}}{\Gamma(1-\beta)}\left(\frac{c_1}{r_1}+\frac{c_2}{r_2}\right)+t^{\beta-1}\left(c_1r_1O\left(r_1^{-3}t^{-3\beta}\right)+c_2r_2O\left(r_2^{-3}t^{-3\beta}\right)\right)}{-\frac{t^{-\beta}}{\Gamma(1-\beta)}\left(\frac{c_1}{r_1}+\frac{c_2}{r_2}\right)+c_1O\left(r_1^{-2}t^{-2\beta}\right)+c_2O\left(r_2^{-2}t^{-2\beta}\right)}. \tag{6.36}$$

As $t\to\infty$, from (6.36) the result could be obtained

$$-\lim_{t\to\infty}\frac{tu'}{u}=-\lim_{t\to\infty}t\frac{\frac{\beta t^{-\beta-1}}{\Gamma(1-\beta)}\left(\frac{c_1}{r_1}+\frac{c_2}{r_2}\right)}{-\frac{t^{-\beta}}{\Gamma(1-\beta)}\left(\frac{c_1}{r_1}+\frac{c_2}{r_2}\right)}=\beta. \tag{6.37}$$

□

Theorem 6.2.3. *Let $1<\beta<2$, and r be a real negative number. For the fractional differential equation with Caputo derivative*

$$D_t^{\beta}u-ru=0, \tag{6.38}$$

with the initial condition $u(0)=1$ and $u'(0)=1$, the following relationship holds

$$\beta=1-\lim_{t\to\infty}\frac{tu'}{u} \tag{6.39}$$

Proof. The exact solution to (6.38) is

$$u(t)=E_{\beta}\left(rt^{\beta}\right)+tE_{\beta,2}\left(rt^{\beta}\right). \tag{6.40}$$

The first derivative of $u(t)$ could be calculated by referring to (6.4) and (6.7)

$$u'(t)=rt^{\beta-1}E_{\beta,\beta}\left(rt^{\beta}\right)+E_{\beta}\left(rt^{\beta}\right). \tag{6.41}$$

The asymptotic expansions of $u(t)$ and $u'(t)$ at infinity are respectively

$$u(t)=-\frac{t^{-\beta}}{r\Gamma(1-\beta)}\left(1+\frac{t}{1-\beta}\right)+O\left(|r|^{-2}t^{-2\beta}\right)+tO\left(|r|^{-2}t^{-2\beta}\right) \tag{6.42}$$

and

$$u'(t) = \frac{t^{-\beta}}{r\Gamma(1-\beta)}\left(\frac{\beta}{t} - 1\right) + rt^{\beta-1}O\left(|r|^{-3}t^{-3\beta}\right) + O\left(|r|^{-2}t^{-2\beta}\right) \tag{6.43}$$

therefore

$$\frac{tu'}{u} = \frac{\frac{t^{-\beta}}{r\Gamma(1-\beta)}(\beta - t) + rt^{\beta}O\left(|r|^{-3}t^{-3\beta}\right) + O\left(|r|^{-2}t^{-2\beta}\right)}{-\frac{t^{-\beta}}{r\Gamma(1-\beta)}\left(1 + \frac{t}{1-\beta}\right) + O\left(|r|^{-2}t^{-2\beta}\right) + tO\left(|r|^{-2}t^{-2\beta}\right)}. \tag{6.44}$$

As $t \to \infty$, (6.44) leads to

$$\lim_{t\to\infty}\frac{tu'}{u} = \lim_{t\to\infty}\frac{tu'}{u}\frac{\frac{t^{-\beta}}{r\Gamma(1-\beta)}(\beta - t)}{-\frac{t^{-\beta}}{r\Gamma(1-\beta)}\left(1 + \frac{t}{1-\beta}\right)} = 1 - \beta \tag{6.45}$$

and proof is completed. □

Theorem 6.2.4. *Let $0 < \beta < 1$, and r be a real negative number. For the fractional differential equation (6.38) with the initial condition $u(0) = 1$, the following relationship holds*

$$\beta = -\lim_{t\to\infty}\frac{tu'}{u} \tag{6.46}$$

Proof. The exact solution to (6.38), with $0 < \beta < 1$ is in the form [94]

$$u(t) = E_{\beta}\left(rt^{\beta}\right). \tag{6.47}$$

The first derivative of $u(t)$ could be calculated by referring to (6.4)

$$u'(t) = rt^{\beta-1}E_{\beta,\beta}\left(rt^{\beta}\right). \tag{6.48}$$

The asymptotic expansions of $u(t)$ and $u'(t)$ are respectively

$$u(t) = -\frac{t^{-\beta}}{r\Gamma(1-\beta)} + O\left(|r|^{-2}t^{-2\beta}\right), \tag{6.49}$$

and

$$u'(t) = \frac{\beta t^{-\beta-1}}{r\Gamma(1-\beta)} + rt^{\beta-1}O\left(|r|^{-3}t^{-3\beta}\right). \tag{6.50}$$

Therefore

$$\frac{tu'}{u} = \frac{\frac{\beta t^{-\beta}}{r\Gamma(1-\beta)} + rt^{\beta-1}O\left(|r|^{-3}t^{-3\beta}\right)}{-\frac{t^{-\beta}}{r\Gamma(1-\beta)} + O\left(|r|^{-2}t^{-2\beta}\right)}. \tag{6.51}$$

As $t \to \infty$, (6.51) results in

$$\lim_{t\to\infty}\frac{tu'}{u} = \lim_{t\to\infty}\frac{\frac{\beta t^{-\beta}}{r\Gamma(1-\beta)}}{-\frac{t^{-\beta}}{r\Gamma(1-\beta)}} = -\beta. \tag{6.52}$$

□

6.3 Numerical Investigation

Example: Consider the initial value problem

$$D_t^{2\beta}u + 2D_t^{\beta}u + 0.7u = 0, \qquad t \geq 0, \qquad 0 < \beta < \frac{1}{2} \tag{6.53}$$

with the initial condition $u(0) = 1$. The exact solution to (6.53) has the form

$$u(t) = c_1 E_\beta\left(r_1 t^\beta\right) + c_2 E_\beta\left(r_2 t^\beta\right), \tag{6.54}$$

where $r_1 = -0.4523$, $r_2 = -1.5477$, $c_1 = 1.4129$, $c_2 = -0.4129$. Fig. 6.1 represents the graph of $-\frac{tu'}{u}$, which has been evaluated for several different values of β, by using the exact representation of u' and u. It could be obviously seen that $-\frac{tu'}{u}$ tends asymptotically to β, as t goes to infinity. Numerical results coincide exactly with the result of the Theorem 6.2.2 and the rate of the convergence of $-\frac{tu'}{u}$ is greatly influenced by the value of β.

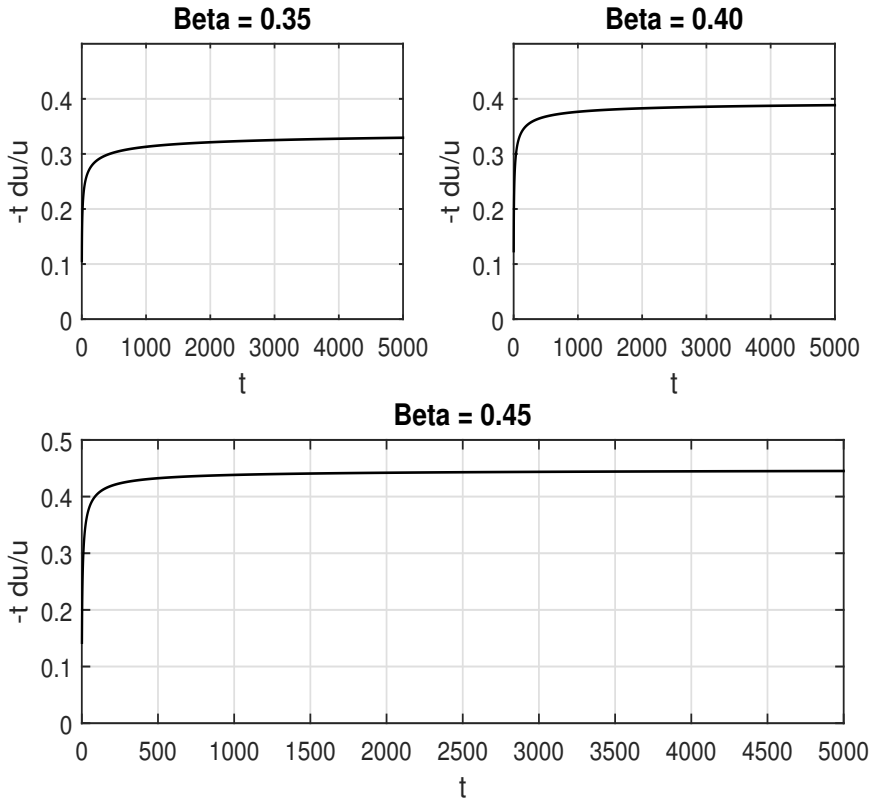

Figure 6.1. Graph of $-\frac{tu'}{u}$ for $\beta = 0.35$, $\beta = 0.40$ and $\beta = 0.45$.

Example: Consider the fractional differential equation

$$\begin{cases} D_t^{\beta}u + 2u = 0 \\ u(0) = 1 \\ u'(0) = 1 \end{cases} \tag{6.55}$$

where $1 < \beta < 2$ and $D_t^{\beta} u$ is in the sense of Caputo derivative. The exact solution is in the form of

$$u(t) = E_{\beta}\left(-2t^{\beta}\right) + tE_{\beta,2}\left(-2t^{\beta}\right). \tag{6.56}$$

According to Theorem 6.2.3, the term $1 - \frac{tu'}{u}$ tends to the order β as t goes to the infinity. The numerical evaluation of $1 - \frac{tu'}{u}$ has been conducted for different values of β, by using the exact expressions of u' and u, shown in Fig. 6.2. As it could be seen, $1 - \frac{tu'}{u}$ converges to β with a rate, which is obviously affected by the value of β, i.e. the convergence will be faster if the fractional order β tends to 2.

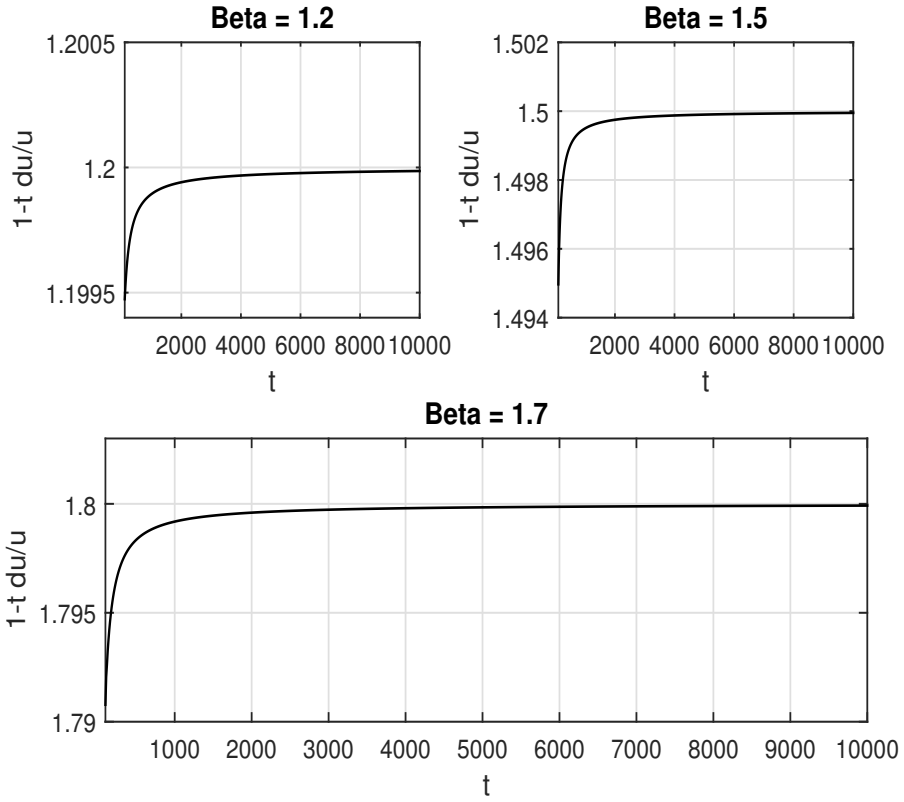

Figure 6.2. Graph of $1 - \frac{tu'}{u}$ for $\beta = 1.2$, $\beta = 1.5$ and $\beta = 1.7$.

Inverse problem occurs in many branches of science and have been also examined in fractional differential systems. For instance, determination of the order of fractional systems has been indicated to be of such crucial importance that it could influence how anomalous diffusion equations must be appropriately simulated. Thus, the exact solution to several classes of linear fractional differential equations represented, for which the fractional order determination was demonstrated by using asymptotic expansion of Mittag-Leffler functions.

Chapter 7

Optimal Control to Cancer Immunotherapy

This chapter is allocated to representation of therapeutic controls for cancer immunotherapy model of KP and FKP.

7.1 Variational approach to optimal control

7.1.1 Introduction

Optimal control theory deals with the control of an operating dynamical system, while its objective is to determine the inputs of the system in such a way that physical constraints and simultaneously, the minimization (or maximization) of some performance criterion are satisfied during the process of the system. An optimal control problem requires in general:

- The mathematical model of dynamical process to be controlled.
- Statements of physical constraints.
- Specification of a performance criterion to be optimized.

A crucial part of a control problem is the mathematical model describing the dynamical process. The discussion is restricted to the models specified by the ordinary differential equations. If

$$x_1(t), x_2(t), \dots, x_n(t)$$

are the state variables (or simply the states) of the dynamical process at time t, and

$$u_1(t), u_2(t), \dots, u_m(t)$$

are the inputs (or control inputs) to the process at time t, then the process is described by the system of ordinary differential equations

$$\begin{cases} \dot{x}_1(t) = f_1(x_1(t), \dots, x_n(t), u_1(t), \dots, u_n(t), t), \\ \dot{x}_2(t) = f_2(x_1(t), \dots, x_n(t), u_1(t), \dots, u_n(t), t), \\ \vdots \\ \dot{x}_n(t) = f_n(x_1(t), \dots, x_n(t), u_1(t), \dots, u_n(t), t). \end{cases} \tag{7.1}$$

The state vector of the system could be defined as

$$\mathbf{x}(t) = \begin{bmatrix} x_1(t) \\ x_2(t) \\ \vdots \\ x_n(t) \end{bmatrix} \tag{7.2}$$

and the control vector as

$$\mathbf{u}(t) = \begin{bmatrix} u_1(t) \\ u_2(t) \\ \vdots \\ u_m(t) \end{bmatrix} \tag{7.3}$$

therefore (7.1), can be represented in the vector state form:

$$\dot{\mathbf{x}}(t) = \mathbf{f}(\mathbf{x}(t), \mathbf{u}(t), t), \tag{7.4}$$

where the initial state of the system is

$$\mathbf{x_0} = \mathbf{x}(t_0) = \begin{bmatrix} x_1(t_0) \\ x_2(t_0) \\ \vdots \\ x_n(t_0) \end{bmatrix}, \tag{7.5}$$

and the vector $\mathbf{f}$ is apparently equal to

$$\mathbf{f}(t) = \begin{bmatrix} f_1(t) \\ f_2(t) \\ \vdots \\ f_n(t) \end{bmatrix}. \tag{7.6}$$

Definition 7.1.1. *Let the system (7.4) be defined for the time interval $[t_0, t_f]$, where t_0 and t_f denote respectively the initial and the final time. an input, $u(t)$, to the system satisfying all the control constraints during the entire time interval $[t_0, t_f]$ is called an admissible control.*

Definition 7.1.2. *A trajectory which satisfies the state variable constraints during the entire time interval $[t_0, t_f]$, is called an admissible trajectory.*

The set of all admissible controls is denoted by U and therefore the notation $u \in U$ means that the control, u, is admissible. In order to quantitatively evaluate the performance quality of a system, an index must be considered to be minimized or maximized during the process of control. This index is called as *performance measure* or *performance index*. It is assumed that the performance of a system is evaluated by a performance index in the form

$$J = h(\mathbf{x}(t_f), t_f) + \int_{t_0}^{t_f} g(\mathbf{x}(t), \mathbf{u}(t), t)\, \mathrm{d}t, \tag{7.7}$$

where t_0 and t_f are the initial and final time respectively. The final time (or terminal time), t_f, is either fixed or free. The scalar functions g and h are respectively called

running cost and *terminal cost*. The system starts from an initial state, $\mathbf{x_0} = \mathbf{x}(t_0)$, then by applying a control input for the time interval $[t_0, t_f]$, the system follows a state trajectory to the final or terminal state $\mathbf{x_f} = \mathbf{x}(t_f)$ which is either fixed or free. The performance index defined by (7.7) assigns a unique real value to the state trajectory. The structure of an optimal control problem consists in finding an admissible control which causes the system to follow an admissible trajectory in order to minimize the performance measure (7.7). The control and the state which minimize the performance index are respectively called the *optimal control* and the *optimal trajectory*, and are expressed by $\mathbf{u}^*$ and $\mathbf{x}^*$.

While the performance index is determined for a system, the next step is to find an optimal control. The methods of dynamic programming, which was developed by R. Bellman [15], and Pontryagin maximum principal [120] have been developed to accomplish the minimization. The variational approach of Pontryagin leads to solving nonlinear two-point boundary value problems, which must be solved to obtain an optimal control.

7.1.2 Fundamental Concepts

Suppose Ω is an open subset of $\mathbb{R}^n$, i.e. $\Omega \subseteq \mathbb{R}^n$ and suppose $\mathbf{x}^* \in \Omega$ to be the local minimum of the function $f \in C^1(\Omega)$. For a fixed $\mathbf{d} \in \Omega$, where $\mathbf{d} \neq 0$, and for all $\varepsilon \in \mathbb{R}$, where ε is small enough in such a way that $\mathbf{x}^* + \varepsilon\mathbf{d} \in \Omega$, the function $g(\varepsilon)$ is defined as follows:

$$g(\varepsilon) = f(\mathbf{x}^* + \varepsilon\mathbf{d}). \tag{7.8}$$

Obviously $\varepsilon^* = 0$ is the minimum of the function $g(\varepsilon)$. By using the first-order Taylor expansion for g around $\varepsilon^* = 0$:

$$g(\alpha) \approx g(0) + g'(0)\,\varepsilon. \tag{7.9}$$

It can be proved that $g'(0) = 0$ and

$$g'(\varepsilon) = \left[\frac{\partial f(\mathbf{x}^* + \varepsilon\mathbf{d})}{\partial \mathbf{x}}\right]^T \mathbf{d}. \tag{7.10}$$

Setting $\varepsilon = 0$ in (7.10) it is obtained that

$$g'(0) = \left[\frac{\partial f(\mathbf{x}^*)}{\partial \mathbf{x}}\right]^T \mathbf{d} = \nabla f(\mathbf{x}^*)\,\mathbf{d}, \tag{7.11}$$

and therefore

$$\nabla f(\mathbf{x}^*) = 0, \tag{7.12}$$

which is derived from the first-order Taylor expansion and therefore is called the *first-order necessary condition* for optimality. The point $\mathbf{x}^*$, which satisfies the (7.12), is called a *stationary point*. The second-order necessary condition can be obtained by using the second-order Taylor expansion of the function $f(\mathbf{x})$, under the stronger hypothesis that $f \in C^2(\Omega)$:

$$g(\alpha) \approx g(0) + g'(0)\,\varepsilon + \frac{1}{2}g''(0)\,\varepsilon^2. \tag{7.13}$$

It can be indeed proved that $g''(0) \geq 0$. By differentiating the (7.10), g'' is obtained

$$g''(\varepsilon) = \mathbf{d}^T \nabla^2 f(\mathbf{x}^* + \varepsilon \mathbf{d})\, \mathbf{d}\,, \tag{7.14}$$

and therefore

$$g''(0) = \mathbf{d}^T \nabla^2 f(\mathbf{x}^*)\, \mathbf{d}\,, \tag{7.15}$$

where $\nabla^2 f$ is defined as

$$\nabla^2 f := \begin{bmatrix} \frac{\partial^2 f}{\partial x_1 \partial x_1} & \cdots & \frac{\partial^2 f}{\partial x_1 \partial x_n} \\ \vdots & \ddots & \vdots \\ \frac{\partial^2 f}{\partial x_n \partial x_1} & \cdots & \frac{\partial^2 f}{\partial x_n \partial x_n} \end{bmatrix}, \tag{7.16}$$

and is called the *Hessian* matrix of f. Since $g''(0) \geq 0$, it is concluded that $\nabla^2 f(\mathbf{x}^*)$ must be positive semidefinite:

$$\nabla^2 f(\mathbf{x}^*) \geq 0\,. \tag{7.17}$$

At a local maximum, the Hessian must be negative semidefinite, i.e.

$$\nabla^2 f(\mathbf{x}^*) \leq 0\,. \tag{7.18}$$

The combination of the strengthened second-order necessary condition with the first-order necessary condition results in the second-order sufficient condition. If the function $f \in C^2(\Omega)$ satisfies

$$\nabla f(\mathbf{x}^*) = 0 \qquad \text{and} \qquad \nabla^2 f(\mathbf{x}^*) > 0\,, \tag{7.19}$$

then $\mathbf{x}^*$ is a strict local minimum of the function f. The objective of an optimal control problem is to determine a function, by which a specified functional–the so-called performance index–is minimized.

Definition 7.1.3. *A rule of correspondence, which assigns a unique real number to each function* $\mathbf{x}$ *of a certain class of functions* Ω *is called a functional.*

Definition 7.1.4. *The increment of the functional* J*, denoted by* ΔJ*, is defined as*

$$\Delta J(\mathbf{x}, \delta\mathbf{x}) = J(\mathbf{x} + \delta\mathbf{x}) - J(\mathbf{x})\,, \tag{7.20}$$

where $\mathbf{x}$ *and* $\mathbf{x} + \delta\mathbf{x}$ *are functions for which the functional* J *is defined. The function* $\delta\mathbf{x}$ *by an infinitesimal but arbitrary amount, is called the variation of the function* $\mathbf{x}$*.*

Suppose $J : D \to \mathbb{R}$ to be a real-valued functional defined on a function space D, and consider some function $x \in D$. The derivative of the functional J at x, which is a linear functional on D, is called the first variation of J and is denoted by δJ. the function $x + \varepsilon y$ is considered in D, where $y \in D$ and ε is a very small real parameter, then definition of first variation is as follows

Definition 7.1.5. *The functional* $\delta J|_x : D \to \mathbb{R}$ *is called the first variation of* J *at* x*, if for all* $y \in D$ *and for all* ε *the relation*

$$J(x + \varepsilon y) = J(x) + \varepsilon \delta J|_x(y) + o(\varepsilon)\,, \tag{7.21}$$

is held true, where $o(\varepsilon)$ *satisfies*

$$\lim_{\varepsilon \to 0} \frac{o(\varepsilon)}{\varepsilon} = 0.$$

For all admissible perturbation y, the first-order necessary condition for optimality is as follows [93]:

$$\delta J|_{x^*}(y) = 0\,. \tag{7.22}$$

Definition 7.1.6. *A quadratic form $\delta^2 J\big|_x : D \to \mathbb{R}$ is called the second variation of J at x, if for all $y \in D$ and for all ε the relation*

$$J(x+\varepsilon y) = J(x) + \varepsilon\,\delta J|_x(y) + \varepsilon^2\,\delta^2 J\Big|_x(y) + o^2(\varepsilon)\,, \tag{7.23}$$

is held true.

The second-order necessary condition for optimality can be established. If x^* is a local minimum of J over D, then for all admissible perturbations y:

$$\delta^2 J\Big|_{x^*}(y) \geq 0\,. \tag{7.24}$$

7.1.3 Pontryagin's Maximum Principle

The control system, which is studied, takes the form

$$\dot{\mathbf{x}} = f(t, \mathbf{x}, \mathbf{u})\,, \qquad \mathbf{x}(t_0) = \mathbf{x_0}\,, \tag{7.25}$$

where $\mathbf{x} \in \mathbb{R}^n$ is the state vector, $\mathbf{u} \in U \subset \mathbb{R}^m$ is the control vector, $t \in \mathbb{R}$ is the time, t_0 is the initial time, and x_0 is the initial state. Both the state and control vector are functions of time, i.e. $\mathbf{x} = \mathbf{x}(t)$ and $\mathbf{u} = \mathbf{u}(t)$. The set of admissible controls U is normally a closed subset of or the entire $\mathbb{R}^m$. The methods of variational calculus [86] is utilized to determine necessary conditions for optimal control problem. The problem is to find an admissible control $\mathbf{u}^*$ that causes (7.25) to follow an admissible trajectory $\mathbf{x}^*$ maximizing the performance measure

$$J(\mathbf{u}) = h(t_f, \mathbf{x_f}) + \int_{t_0}^{t_f} g(t, \mathbf{x}, \mathbf{u})\,\mathrm{d}t, \tag{7.26}$$

where t_f and $\mathbf{x_f} = \mathbf{x}(t_f)$ are respectively the final (terminal) time and state, $g : \mathbb{R} \times \mathbb{R}^n \times U \to \mathbb{R}$ is the running cost and $h : \mathbb{R} \times \mathbb{R}^n \to \mathbb{R}$ is the terminal cost. Such optimal problem, in which the performance measure is introduced by (7.26) are mentioned as problems in the *Bolza form*. An important special case of Bolza problem is the Lagrange problem, for which there is no terminal cost function, i.e. $h \equiv 0$. The terminal cost can be rewritten as follows:

$$\begin{aligned} h(t_f, \mathbf{x_f}) &= h(t_0, \mathbf{x_0}) + \int_{t_0}^{t_f} \frac{\mathrm{d}}{\mathrm{d}t} h(t, \mathbf{x})\,\mathrm{d}t \\ &= h(t_0, \mathbf{x_0}) + \int_{t_0}^{t_f} \left(\frac{\partial h(t, \mathbf{x})}{\partial \mathbf{x}} \dot{\mathbf{x}} + \frac{\partial h(t, \mathbf{x})}{\partial t} \right) \mathrm{d}t\,, \end{aligned} \tag{7.27}$$

therefore the (7.26) can be expressed in the Lagrange form:

$$J(\mathbf{u}) = h(t_0, \mathbf{x_0}) + \int_{t_0}^{t_f} \left(g(t, \mathbf{x}, \mathbf{u}) + \frac{\mathrm{d}}{\mathrm{d}t} h(t, \mathbf{x}) \right) \mathrm{d}t\,. \tag{7.28}$$

Since the term $h(t_0, \mathbf{x_0})$ is a constant, thus the functional

$$J(\mathbf{u}) = \int_{t_0}^{t_f} \left(g(t, \mathbf{x}, \mathbf{u}) + \frac{\mathrm{d}}{\mathrm{d}t} h(t, \mathbf{x}) \right) \mathrm{d}t \,, \tag{7.29}$$

is only considered to be minimized. As a prior assumption, the set of admissible controls, U, and the region of admissible states are considered to be unbounded. By using the (7.27), the performance measure (7.29) can be written as follows:

$$J(\mathbf{u}) = \int_{t_0}^{t_f} \left(g(t, \mathbf{x}, \mathbf{u}) + \left[\frac{\partial h(t, \mathbf{x})}{\partial \mathbf{x}} \right]^T \dot{\mathbf{x}} + \frac{\partial h(t, \mathbf{x})}{\partial t} \right) \mathrm{d}t \,, \tag{7.30}$$

It is known that the optimal control problem is a constraint problem subjected to $\dot{\mathbf{x}} = f(t, \mathbf{u}, \mathbf{x})$. In order to convert the problem to an unconstraint problem, the Lagrange multiplier

$$\lambda(t) = \begin{bmatrix} \lambda_1(t) \\ \lambda_2(t) \\ \vdots \\ \lambda_n(t) \end{bmatrix} , \tag{7.31}$$

is defined. Multiplication of Lagrange multiplier and the state system leads to:

$$\lambda^T \left(f(t, \mathbf{x}, \mathbf{u}) - \dot{\mathbf{x}} \right) = 0 \,. \tag{7.32}$$

By adding the (7.32) to the integrand of (7.30), the augmented performance measure, which is denoted by $J_a(\mathbf{u})$, will be as below:

$$J_a(\mathbf{u}) = \int_{t_0}^{t_f} \left(g(t, \mathbf{x}, \mathbf{u}) + \left[\frac{\partial h(t, \mathbf{x})}{\partial \mathbf{x}} \right]^T \dot{\mathbf{x}} + \frac{\partial h(t, \mathbf{x})}{\partial t} + \lambda^T \left(f(t, \mathbf{x}, \mathbf{u}) - \dot{\mathbf{x}} \right) \right) \mathrm{d}t \,, \tag{7.33}$$

The integrand in (7.33) is denoted by g_a:

$$\begin{aligned} g_a(t, \mathbf{x}, \dot{\mathbf{x}}, \mathbf{u}, \lambda) \;\; = \;\; & g(t, \mathbf{x}, \mathbf{u}) + \left[\frac{\partial h(t, \mathbf{x})}{\partial \mathbf{x}} \right]^T \dot{\mathbf{x}} + \frac{\partial h(t, \mathbf{x})}{\partial t} \\ & + \lambda^T \left(f(t, \mathbf{x}, \mathbf{u}) - \dot{\mathbf{x}} \right) \,, \end{aligned} \tag{7.34}$$

therefore, the augmented performance index, $J_a(\mathbf{u})$, can be expressed by the integral:

$$J_a(\mathbf{u}) = \int_{t_0}^{t_f} g_a(t, \mathbf{x}, \dot{\mathbf{x}}, \mathbf{u}, \lambda) \, \mathrm{d}t \,, \tag{7.35}$$

where the integrand in (7.35) is mentioned as the *Lagrangian* and by introducing *Hamiltonian*

$$H(t, \mathbf{x}, \mathbf{u}, \lambda) = g(t, \mathbf{x}, \mathbf{u}) + \lambda^T f(t, \mathbf{x}, \mathbf{u}) \,, \tag{7.36}$$

then, g_a can be expressed by Hamiltonian as follows:

$$g_a(t, \mathbf{x}, \dot{\mathbf{x}}, \mathbf{u}, \lambda) = H(t, \mathbf{x}, \mathbf{u}, \lambda) + \left[\frac{\partial h(t, \mathbf{x})}{\partial \mathbf{x}} \right]^T \dot{\mathbf{x}} + \frac{\partial h(t, \mathbf{x})}{\partial t} - \lambda^T \dot{\mathbf{x}} \,. \tag{7.37}$$

It is mentioned that the terminal time, t_f, and the terminal state, $\mathbf{x_f}$, are both considered to be free. The state $\mathbf{x}^*$ and the control $\mathbf{u}^*$ are considered as the optimal state and control respectively. For perturbed condition, it is needed to introduce the variations of $\delta\mathbf{x}$, $\delta\mathbf{u}$, $\delta\dot{\mathbf{x}}$, δt_f and $\delta\mathbf{x_f}$. Under the condition of perturbation, the performance measure will be as follows:

$$\begin{aligned} J_p(\mathbf{u}) &= \int_{t_0}^{t_f+\delta t_f} \Bigg(g\left(t, \mathbf{x}^* + \delta\mathbf{x}, \mathbf{u}^* + \delta\mathbf{u}\right) + \left[\frac{\partial h\left(t, \mathbf{x}^*\right)}{\partial \mathbf{x}}\right]^T (\dot{\mathbf{x}} + \delta\dot{\mathbf{x}}) \\ &\quad + \frac{\partial h\left(t, \mathbf{x}^*\right)}{\partial t} + \lambda^T \left(f\left(t, \mathbf{x}^* + \delta\mathbf{x}, \mathbf{u}^* + \delta\mathbf{u}\right) - (\dot{\mathbf{x}} + \delta\dot{\mathbf{x}})\right) \Bigg) \mathrm{d}t\,, \end{aligned} \tag{7.38}$$

The integrand in (7.38) is denoted by $g_p\left(t, \mathbf{x}^* + \delta\mathbf{x}, \mathbf{u}^* + \delta\mathbf{u}, \dot{\mathbf{x}} + \delta\dot{\mathbf{x}}\right)$, therefore

$$\begin{aligned} g_p\left(.\right) &= g\left(t, \mathbf{x}^* + \delta\mathbf{x}, \mathbf{u}^* + \delta\mathbf{u}\right) + \left[\frac{\partial h\left(t, \mathbf{x}^*\right)}{\partial \mathbf{x}}\right]^T (\dot{\mathbf{x}} + \delta\dot{\mathbf{x}}) \\ &\quad + \frac{\partial h\left(t, \mathbf{x}^*\right)}{\partial t} + \lambda^T \left(f\left(t, \mathbf{x}^* + \delta\mathbf{x}, \mathbf{u}^* + \delta\mathbf{u}\right) - (\dot{\mathbf{x}} + \delta\dot{\mathbf{x}})\right)\,, \end{aligned} \tag{7.39}$$

Equation (7.38) can be written as follows:

$$J_p(\mathbf{u}) = \int_{t_0}^{t_f} g_p\left(.\right) \mathrm{d}t + \int_{t_f}^{t_f+\delta t_f} g_p\left(.\right) \mathrm{d}t\,. \tag{7.40}$$

The increment of the performance function is

$$\Delta J(\mathbf{u}) = J_p(\mathbf{u}) - J_a(\mathbf{u}^*)\,. \tag{7.41}$$

By using the (7.34) and (7.40), it is obtained that

$$\Delta J(\mathbf{u}) = \int_{t_0}^{t_f} g_p\left(.\right) \mathrm{d}t + \int_{t_f}^{t_f+\delta t_f} g_p\left(.\right) \mathrm{d}t - \int_{t_0}^{t_f} g_a\left(.\right) \mathrm{d}t\,, \tag{7.42}$$

The second term on the right-hand-side of the (7.42) can be approximated by the area under the curve of g_a from t_f to $t_f + \delta t_f$. Thus

$$\begin{aligned} \Delta J(\mathbf{u}) &\approx \int_{t_0}^{t_f} g_p\left(.\right) dt + \left(g_a\left(t, \mathbf{x}^*, \dot{\mathbf{x}}^*, \mathbf{u}^*, \lambda^*\right)|_{t=t_f} \delta t_f\right) - \int_{t_0}^{t_f} g_a\left(.\right) dt \\ &\approx \int_{t_0}^{t_f} \left(g_p\left(.\right) - g_a\left(.\right)\right) dt + \left(g_a\left(t, \mathbf{x}^*, \dot{\mathbf{x}}^*, \mathbf{u}^*, \lambda^*\right)|_{t=t_f} \delta t_f\right)\,. \end{aligned} \tag{7.43}$$

By using the Taylor series for $\Delta g = g_p - g_a$ in (7.43), the first variation of the performance measure, $J\left(\mathbf{u}\right)$, is obtained:

$$\begin{aligned} \delta J &= \int_{t_0}^{t_f} \left[\frac{\partial g_a\left(t, \mathbf{x}^*, \dot{\mathbf{x}}^*, \mathbf{u}^*, \lambda^*\right)}{\partial \mathbf{x}} - \frac{\mathrm{d}}{\mathrm{d}t} \frac{\partial g_a\left(t, \mathbf{x}^*, \dot{\mathbf{x}}^*, \mathbf{u}^*, \lambda^*\right)}{\partial \dot{\mathbf{x}}}\right]^T \delta\mathbf{x}\, \mathrm{d}t \\ &\quad + \int_{t_0}^{t_f} \left[\frac{\partial g_a\left(t, \mathbf{x}^*, \dot{\mathbf{x}}^*, \mathbf{u}^*, \lambda^*\right)}{\partial \mathbf{u}}\right]^T \delta\mathbf{u}\, \mathrm{d}t \\ &\quad + \left[\frac{\partial g_a\left(t, \mathbf{x}^*, \dot{\mathbf{x}}^*, \mathbf{u}^*, \lambda^*\right)}{\partial \dot{\mathbf{x}}}\right]^T \Bigg|_{t=t_f} \delta\mathbf{x}\left(t_f\right) \\ &\quad + g_a\left(t, \mathbf{x}^*, \dot{\mathbf{x}}^*, \mathbf{u}^*, \lambda^*\right)|_{t=t_f}\, \delta t_f \end{aligned} \tag{7.44}$$

The variation of x can be expressed by the variation of the state at the terminal time, i.e.

$$\delta x_f = \delta \mathbf{x}(t_f) + \dot{\mathbf{x}}(t_f)\,\delta t_f\,, \tag{7.45}$$

or

$$\delta \mathbf{x}(t_f) = \delta x_f - \dot{\mathbf{x}}(t_f)\,\delta t_f\,. \tag{7.46}$$

By putting (7.46) into (7.44) it is attained that

$$\begin{aligned}\delta J = &\int_{t_0}^{t_f}\left[\frac{\partial g_a(t,\mathbf{x}^*,\dot{\mathbf{x}}^*,\mathbf{u}^*,\lambda^*)}{\partial \mathbf{x}} - \frac{\mathrm{d}}{\mathrm{d}t}\frac{\partial g_a(t,\mathbf{x}^*,\dot{\mathbf{x}}^*,\mathbf{u}^*,\lambda^*)}{\partial \dot{\mathbf{x}}}\right]^T \delta\mathbf{x}\,\mathrm{d}t\\ &+\int_{t_0}^{t_f}\left[\frac{\partial g_a(t,\mathbf{x}^*,\dot{\mathbf{x}}^*,\mathbf{u}^*,\lambda^*)}{\partial \mathbf{u}}\right]^T \delta\mathbf{u}\,\mathrm{d}t\\ &+\left[\frac{\partial g_a(t,\mathbf{x}^*,\dot{\mathbf{x}}^*,\mathbf{u}^*,\lambda^*)}{\partial \dot{\mathbf{x}}}\right]^T\Bigg|_{t=t_f}(\delta x_f - \dot{\mathbf{x}}(t_f))\,\delta t_f\\ &+g_a(t,\mathbf{x}^*,\dot{\mathbf{x}}^*,\mathbf{u}^*,\lambda^*)|_{t=t_f}\,\delta t_f\end{aligned} \tag{7.47}$$

The following lemma is utilized to derive the first order necessary conditions for the optimal control problem:

Lemma 7.1.1. *If a continuous function $\xi : [a,b] \to \mathbb{R}$ is such that*

$$\int_a^b \xi(t)\,\eta(t)\,\mathrm{d}t = 0$$

for all function $\eta \in C^1[a,b]$ with $\eta(a) = \eta(b) = 0$, then $\xi \equiv 0$.

Using Lemma 7.1.1 and (7.44) it is concluded that

$$\frac{\partial g_a(t,\mathbf{x}^*,\dot{\mathbf{x}}^*,\mathbf{u}^*,\lambda^*)}{\partial \mathbf{x}} - \frac{\mathrm{d}}{\mathrm{d}t}\frac{\partial g_a(t,\mathbf{x}^*,\dot{\mathbf{x}}^*,\mathbf{u}^*,\lambda^*)}{\partial \dot{\mathbf{x}}} = 0\,, \tag{7.48}$$

and also

$$\frac{\partial g_a(t,\mathbf{x}^*,\dot{\mathbf{x}}^*,\mathbf{u}^*,\lambda^*)}{\partial \mathbf{u}} = 0\,, \tag{7.49}$$

therefore (7.47) will be in the form below

$$\begin{aligned}\delta J = &\left[\frac{\partial g_a(t,\mathbf{x}^*,\dot{\mathbf{x}}^*,\mathbf{u}^*,\lambda^*)}{\partial \dot{\mathbf{x}}}\right]^T\Bigg|_{t=t_f}(\delta x_f - \dot{\mathbf{x}}(t_f))\,\delta t_f\\ &+g_a(t,\mathbf{x}^*,\dot{\mathbf{x}}^*,\mathbf{u}^*,\lambda^*)|_{t=t_f}\,\delta t_f\end{aligned} \tag{7.50}$$

or

$$\begin{aligned}\delta J = &\left(g_a(t,\mathbf{x}^*,\dot{\mathbf{x}}^*,\mathbf{u}^*,\lambda^*) - \left[\frac{\partial g_a(t,\mathbf{x}^*,\dot{\mathbf{x}}^*,\mathbf{u}^*,\lambda^*)}{\partial \dot{\mathbf{x}}}\right]^T \dot{\mathbf{x}}\right)\Bigg|_{t=t_f}\delta t_f\\ &+\left[\frac{\partial g_a(t,\mathbf{x}^*,\dot{\mathbf{x}}^*,\mathbf{u}^*,\lambda^*)}{\partial \dot{\mathbf{x}}}\right]^T\Bigg|_{t=t_f}\delta x_f\end{aligned} \tag{7.51}$$

Equation (7.51) is called the *transversality conditions* or boundary condition. As a conclusion, the necessary conditions for the optimal control problem are expressed by (7.48), (7.49) and (7.51).

The mentioned necessary conditions could be more appropriate to be represented by referring to the notation of Hamiltonian. By referring to (7.36), the necessary conditions in Hamiltonian system are as follows:

$$\frac{\partial H\left(t, \mathbf{x}^*, \mathbf{u}^*, \lambda^*\right)}{\partial \mathbf{x}} = -\dot{\lambda}^*\left(t\right) , \tag{7.52}$$

which is called *adjoint (costate) equation*,

$$\frac{\partial H\left(t, \mathbf{x}^*, \mathbf{u}^*, \lambda^*\right)}{\partial \mathbf{u}} = 0 , \tag{7.53}$$

mentioned as *optimality condition (Hamiltonian maximization property)* and

$$\frac{\partial H\left(t, \mathbf{x}^*, \mathbf{u}^*, \lambda^*\right)}{\partial \lambda} = \dot{\mathbf{x}}\left(t\right) , \tag{7.54}$$

which is known as *state equation*, and the transversality condition

$$\left(H\left(t, \mathbf{x}^*, \mathbf{u}^*, \lambda^*\right) + \frac{\partial h\left(\mathbf{x}, t\right)}{\partial t}\right)\Big|_{t=t_f} \delta t_f + \left[\frac{\partial h\left(\mathbf{x}^*, t\right)}{\partial \mathbf{x}} - \lambda^*\left(t\right)\right]^T\Big|_{t=t_f} \delta \mathbf{x_f} = 0 . \tag{7.55}$$

Whenever the terminal time is fixed and the terminal state is free, meaning that $\delta t_f = 0$ and $\delta \mathbf{x_f} \neq 0$, the transversality condition (7.55) will be as follows:

$$\left[\frac{\partial h\left(\mathbf{x}^*, t\right)}{\partial \mathbf{x}} - \lambda^*\left(t\right)\right]\Big|_{t=t_f} = 0 . \tag{7.56}$$

Equation (7.53) provides the necessary condition (but not sufficient) for $\mathbf{u}^*$ to be an optimal control. If (7.53) is satisfied, then the sufficient condition, which guarantees the Hamiltonian to be a local minimum, is expressed by

$$\frac{\partial^2 H\left(t, \mathbf{x}^*, \mathbf{u}^*, \lambda^*\right)}{\partial \mathbf{u}^2} > 0 . \tag{7.57}$$

where the notation $\frac{\partial^2 H}{\partial \mathbf{u}^2} > 0$ means that the matrix $\left[\frac{\partial^2 H}{\partial \mathbf{u}^2}\right]_{m\times m}$ is positive definite.

The variational approach, which was presented in Section 7.1.2, leads to necessary conditions for the optimal problem. The necessary conditions were expressed by state and adjoint equations, Hamiltonian maximization property, and the transversality condition. However the variational approach are based on several restrictions.
Bounded controls: in (7.38), the starting point is to consider a perturbed $\mathbf{u}$ in the form $\delta\mathbf{u}$. Such a perturbation is allowed where the control $\mathbf{u}$ is an interior element of the set of admissible controls U. This may not be the case while the set U has a boundary. Bounded controls are prevalent in control applications and achievable controls are restricted to physical constraints. The effect of bounded controls definitely influences the necessary conditions of the optimal control problem. Even in such a situation the Hamiltonian function must be maximized at $\mathbf{u}^*$, nonetheless,

this cannot be achieved by using the variational approach. In fact, the optimality condition expressed in (7.53) i.e. $\frac{\partial H}{\partial \mathbf{u}} = 0$, need not be equal to zero while the maximum is achieved at a boundary point of the set U.
Differentiability: while the first and second variation of performance index is established, it is assumed that the Hamiltonian function is differentiable with respect to $\mathbf{u}$ in addition to the state variables $\mathbf{x}$. In other words, the variational approach requires restrictive regularity assumptions to be imposed on the system, and in addition, to the performance index. Instead, the Hamiltonian maximization property is desired to be established not via derivatives.

In brief, some restrictive assumptions of variational approach must be dealt with such as differentiability and more specifically it is required to apply constraints on the controls and final state of the system. The Pontryagin maximum principle [120], which extends the variational approach, was established and introduced by Lev Pontryagin and his students in 1956.

Assume that the system and the performance index, which must be maximized, are respectively as below:

$$\dot{\mathbf{x}}(t) = \mathbf{f}(\mathbf{x}(t), \mathbf{u}(t), t) , \tag{7.58}$$

with the initial state $\mathbf{x_0}$ and

$$J = h(\mathbf{x}(t_f)) + \int_{t_0}^{t_f} g(\mathbf{x}(t), \mathbf{u}(t), t)\, \mathrm{d}t , \tag{7.59}$$

in which the final time, t_f, is considered to be fixed. The Hamiltonian function is:

$$H(t, \mathbf{x}, \mathbf{u}, \lambda) = g(t, \mathbf{x}, \mathbf{u}) + \lambda^T f(t, \mathbf{x}, \mathbf{u}) . \tag{7.60}$$

For this special optimal problem, the statement of Pontryagin maximum principle is as follows:

Pontryagin Maximum Principle. *Let $\mathbf{u}^* : [t_0, t_f] \to U$ be an optimal control and let $\mathbf{x}^* : [t_0, t_f] \to \mathbb{R}^n$ be the corresponding optimal state trajectory. Then there exists a vector $\lambda^* : [t_0, t_f] \to \mathbb{R}^n$, such that the following conditions are satisfied:*
1) The vectors $\mathbf{x}^*$ and λ^* satisfy respectively the equations

$$\dot{\mathbf{x}}^*(t) = \frac{\partial H(t, \mathbf{x}^*, \mathbf{u}^*, \lambda^*)}{\partial \lambda} , \tag{7.61}$$

with the initial state $\mathbf{x_0}$, and

$$\dot{\lambda}^*(t) = -\frac{\partial H(t, \mathbf{x}^*, \mathbf{u}^*, \lambda^*)}{\partial \mathbf{x}} . \tag{7.62}$$

2) For all $t \in [t_0, t_f]$ and all $\mathbf{u} \in U$

$$H(t, \mathbf{x}^*, \mathbf{u}^*, \lambda^*) \geq H(t, \mathbf{x}^*, \mathbf{u}, \lambda^*) . \tag{7.63}$$

3) Transversality condition:

$$\lambda^*(t_f) = \left.\frac{\mathrm{d}h(\mathbf{x})}{\mathrm{d}\mathbf{x}}\right|_{t=t_f} . \tag{7.64}$$

A special case of the Maximization of Hamiltonian occurs while the Hamiltonian function is time-independent, i.e. $\frac{\partial H}{\partial t} = 0$ [135]. In this case:

$$H\left(t, \mathbf{x}^*, \mathbf{u}^*, \lambda^*\right) = \text{constant}\,. \tag{7.65}$$

The characterization of the optimal control can be constructed as follows [91]: Consider the performance index (7.59), subject to system (7.58) and $a \leq u\left(t\right) \leq b$, where a and b are real constants ($a < b$). Assume that u^* and $\mathbf{x}^*$ are respectively the optimal control and optimal state trajectory. Suppose that $v\left(t\right)$ is a piecewise continuous function and there exists a positive constant ϵ_0, such that $a \leq u_\epsilon\left(t\right) = u^* + \epsilon v\left(t\right) \leq b$ for all $\epsilon \in (0, \epsilon_0]$. The performance index corresponding to u_ϵ is

$$\begin{aligned} J \;\; = \;\; & h\left(\mathbf{x}\left(t_f\right)\right) + \int_{t_0}^{t_f} g\left(\mathbf{x}_\epsilon, u_\epsilon, t\right) + \lambda^T \mathbf{f}\left(\mathbf{x}_\epsilon, u_\epsilon, t\right) + \mathbf{x}_\epsilon^T \dot{\lambda} \mathrm{d}t \\ & -\lambda\left(t_0\right)\mathbf{x_0} + \lambda\left(t_f\right) + h\left(\mathbf{x}\left(t_f\right)\right)\,, \end{aligned} \tag{7.66}$$

where $\mathbf{x}_\epsilon$ corresponds with u_ϵ and λ is the adjoint variable. Since the maximization of J occurs at u^*, therefore,

$$\left.\frac{\mathrm{d}J}{\mathrm{d}\epsilon}\right|_{\epsilon=0} = \lim_{\epsilon \to 0^+} \frac{J\left(u_\epsilon\right) - J\left(u^*\right)}{\epsilon} \leq 0\,. \tag{7.67}$$

By using (7.62), (7.66) and (7.67) are reduced to

$$\int_{t_0}^{t_f} \left(g_u + \lambda^T \mathbf{f}_u\right) v\left(t\right) \mathrm{d}t \leq 0\,. \tag{7.68}$$

Assume that u^* is continuous at time t_1 and $g_u + \lambda^T \mathbf{f}_u > 0$ at t_1. There is a small interval I including the point t_1, such that $g_u + \lambda^T \mathbf{f}_u$ is strictly positive on the interval I and $u^* < b$. Suppose that u_{max} is the maximum value of u^* on the interval I

$$u_{max} = \max\left\{u^*\left(t\right) :\; t \in I\right\}\,.$$

By defining

$$\bar{v}\left(t\right) = \begin{cases} b - u_{max} & \text{if} \;\; t \in I \\ 0 & \text{otherwise.} \end{cases}$$

Therefore

$$\int_{t_0}^{t_f} \left(g_u + \lambda^T \mathbf{f}_u\right) \bar{v}\left(t\right) \mathrm{d}t = \int_I \left(g_u + \lambda^T \mathbf{f}_u\right) \bar{v}\left(t\right) \mathrm{d}t > 0\,,$$

which is in contradiction to (7.68). This implies that $g_u + \lambda^T \mathbf{f}_u \leq 0$ at t_1. Now, it is assumed that $g_u + \lambda^T \mathbf{f}_u < 0$ at t_1. In a similar way, it can be shown that this assumption is not true, therefore, $g_u + \lambda^T \mathbf{f}_u = 0$ where $a < u^* < b$. In summary:

$$\begin{aligned} u^*\left(t\right) = a \quad & \text{implies} \quad \frac{\partial H}{\partial u} \leq 0 \quad \text{at } t\,, \\ a < u^*\left(t\right) < b \quad & \text{implies} \quad \frac{\partial H}{\partial u} = 0 \quad \text{at } t\,, \\ u^*\left(t\right) = b \quad & \text{implies} \quad \frac{\partial H}{\partial u} \geq 0 \quad \text{at } t\,. \end{aligned} \tag{7.69}$$

7.2 Optimal Control Applied to the KP Model

In this section the goal is to determinate an optimal therapeutic protocol in cancer immunotherapy, by applying the Pontryagin maximum principle to the KP model. Thus the optimal control problem is described as below:
Maximize the given objective functional (performance index)

$$\max_{u\in U} J(u)\,, \tag{7.70}$$

where $J(u)$ is described by

$$J(u) = -Ay(t_f) + \int_0^{t_f}\left(x(t) - y(t) + z(t) - \frac{1}{2}B(u(t))^2\right)\mathrm{d}t\,, \tag{7.71}$$

subject to

$$\begin{aligned}\frac{\mathrm{d}x}{\mathrm{d}t} &= cy - \mu_2 x + \frac{p_1 xz}{g_1 + z} + s_1 u(t)\,,\\ \frac{\mathrm{d}y}{\mathrm{d}t} &= r_2 y(1 - by) - \frac{axy}{g_2 + y}\,,\\ \frac{\mathrm{d}z}{\mathrm{d}t} &= \frac{p_2 xy}{g_3 + y} - \mu_3 z\,,\end{aligned} \tag{7.72}$$

with the initial state

$$x(0) = 1,\ y(0) = 1,\ z(0) = 1\,, \tag{7.73}$$

where the final state is free.

The parameters appeared in (7.72) are represented in Table 2.3. It has been assumed that there is no external source of IL-2 and the function $u(t)$ is the control which represents the percentage of the external effector cells for medical treatment. Thus the set of admissible control functions, U, is defined as (2.13). The term $-Ay(t_f)$ denotes the goal of minimization of tumour cells at the final time t_f, where A is a real positive constant. The aim of maximization of the performance index in (7.71) is to keep the effector cells and IL-2 concentration at the maximized level, and to minimize the level of cancer cells during the medical treatment, while the cost of the control is minimized. The weight parameter B represents the importance of minimization of $u(t)$ in the performance index. The function J, represented in (7.71), is concave with respect to u.

7.2.1 Existence of Optimal Control

The existence of an optimal control with finite performance index represented by (7.71) can be guaranteed by the existence theorem developed by Fleming and Rishel [54]:

Theorem 7.2.1. *Let (7.72) be represented in the form of*

$$\dot{X} = f(t, X, u)\,,$$

with the initial state $x(0) = 1$, $y(0) = 1$, $z(0) = 1$ *and free final state. Assume the performance index* $J(u)$ *is represented by*

$$J(u) = -Ay(t_f) + \int_0^{t_f} g(t, X, u)\,\mathrm{d}t\,, \tag{7.74}$$

where $g(t, X, u)$ *is*

$$g(t, X, u) = x(t) - y(t) + z(t) - \frac{1}{2}B(u(t))^2\,, \tag{7.75}$$

and the control u *belongs to the convex and closed set of admissible controls* U*, on the interval* $[0, t_f]$*. Then, there exists an optimal control* u^* *such that* $J(u^*) = \max_{u \in U} J(u)$ *if the following conditions are satisfied:*

1. *there exists* $\alpha(t, X)$ *and* $\beta(t, X)$ *such that*

$$f(t, X, u) = \alpha(t, X) + \beta(t, X)\,u(t)\ .$$

2. *There exists constants* $C_1 > 0$ *and* $C_2 > 0$ *such that*

$$|f(t, X, u)| \leq C_1\,|X| + C_2\,|u|$$

3. $g(t, X, u)$ *is concave in* u *and bounded above by* $C_3 - C_4\,|u|^2$*, where* $C_3 > 0$ *and* C_4 *are constants.*

Proof. The first and second conditions were proved in Section 2.2. The function $g(t, X, u)$ is obviously concave in u. Furthermore, $x(t)$, $y(t)$, and $z(t)$ are bounded above. Thus there exists a constant $C_3 > 0$ such that

$$x(t) - y(t) + z(t) \leq x(t) + z(t) \leq C_3\,,$$

therefore

$$g(t, X, u) \leq C_3 - C_4\left|u(t)^2\right|\,,$$

where $C_4 = B/2$. □

7.2.2 Characterization of Optimal Control

Since the main goal in immunotherapy is to remove the tumour cells with the least probable medication side effects, an advanced version of the model may include a time dependent external sources of medical treatment, meaning that the parameters s_1 and s_2 could be considered as control functions of time and therefore the optimum use of medical sources can be evaluated in order to achieve the optimal measure of an objective function (the so-called *performance index*). Thus the main goal, the elimination of cancer cells by using the minimum amount of medical sources, can be expressed in terms of an optimal control problem.

Burden et al. [24] have investigated the Kirschner-Panetta model by using optimal control theory in order to examine under what circumstances the tumor could be removed. They have considered a single ACI therapy in which there is not an external source of IL-2. In [66], the authors have presented an optimal ACI therapy for the

same model by making a slight modification to the performance index considered in [24]. Then, the results were compared with those of the article [24]. In this section the optimal control problem, which has been represented in [66], has been improved by using Pontryagin maximum principle and also the problem is solved in Section 7.4 by utilizing a hybrid method of the particle swarm optimization (PSO) and a method for two-point boundary value problems (TPBVPs), it is demonstrated that the obtained results are more appropriate for cancer treatment than those represented in [66].

The necessary conditions, represented in Section 7.1.3, is now utilized to find an optimal control u^* for the problem stated in Section 7.2. The goal is to organise a therapeutic protocol in order to eliminate the tumour at the end of treatment. A payoff term, i.e. $-Ay\left(t_f\right)$ is considered due to this reason. In addition, the integrand of the performance index includes the term $x\left(t\right)-y\left(t\right)+z\left(t\right)$ with the intention of keeping the cancer cells at the lower (and the effectors and IL-2 at the higher) level, during the therapy. A quadratic term $-\frac{1}{2}Bu^2$ is considered to minimize the amount of external source of the effectors. Referring to Pontryagin's maximum principle and characterization of optimality condition, expressed in (7.69), the optimality system is constructed. By using (7.71) and (2.12), the Hamiltonian function is obtained as follows:

$$\begin{aligned} H &= x-y+z-\frac{1}{2}Bu^2+\lambda^T\mathbf{f} \\ &= x-y+z-\frac{1}{2}Bu^2+\lambda_1\left(cy-\mu_2x+\frac{p_1xz}{g_1+z}+s_1u\right) \\ &\quad +\lambda_2\left(r_2y\left(1-by\right)-\frac{axy}{g_2+y}\right)+\lambda_3\left(\frac{p_2xy}{g_3+y}-\mu_3z\right). \end{aligned} \tag{7.76}$$

The state equation is

$$\begin{aligned} \frac{\mathrm{d}x}{\mathrm{d}t} &= cy-\mu_2x+\frac{p_1xz}{g_1+z}+s_1u\left(t\right), \\ \frac{\mathrm{d}y}{\mathrm{d}t} &= r_2y\left(1-by\right)-\frac{axy}{g_2+y}, \\ \frac{\mathrm{d}z}{\mathrm{d}t} &= \frac{p_2xy}{g_3+y}-\mu_3z, \end{aligned}$$

with the initial state

$$x\left(0\right)=1,\ y\left(0\right)=1,\ z\left(0\right)=1.$$

Equation (7.62) gives the adjoint equations as below:

$$\begin{aligned} \frac{\mathrm{d}\lambda_1}{\mathrm{d}t} &= -\left[1+\lambda_1\left(-\mu_2+\frac{p_1z}{g_1+z}\right)-\frac{ay}{g_2+y}\lambda_2+\frac{p_2y}{g_3+y}\lambda_3\right], \\ \frac{\mathrm{d}\lambda_2}{\mathrm{d}t} &= -\left[-1+c\lambda_1+\left(r_2-2r_2by\right)\lambda_2-\frac{ag_2x}{\left(g_2+y\right)^2}\lambda_2+\frac{p_2g_3x}{\left(g_3+y\right)^2}\lambda_3\right], \\ \frac{\mathrm{d}\lambda_3}{\mathrm{d}t} &= -\left[1+\frac{p_1g_1x}{\left(g_1+z\right)^2}\lambda_1-\mu_3\lambda_3\right], \end{aligned}$$

where the values of adjoint variables at time t_f can be evaluated by using the transversality condition (7.64):

$$\lambda_1(t_f) = 0\,, \qquad \lambda_2(t_f) = -A\,, \qquad \lambda_3(t_f) = 0\,.$$

The characterization of optimality is obtained by (7.69). The derivative of Hamiltonian (7.76) with respect to u is

$$\frac{\partial H}{\partial u} = -Bu + \lambda_1 s_1\,,$$

and u is in the set U defined by (2.13). There are three cases:

1. If $u(t) = 0$, then $\frac{\partial H}{\partial u} \leq 0$, therefore $\lambda_1 \leq 0$.
2. If $0 < u(t) < 1$, then $\frac{\partial H}{\partial u} = 0$, therefore $u = \frac{s_1}{B}\lambda 1$, where $0 < \lambda_1 < \frac{B}{s_1}$.
3. If $u(t) = 1$, then $\frac{\partial H}{\partial u} \geq 0$, therefore $\lambda_1 \geq \frac{B}{s_1}$.

Thus the characterization of optimality is:

$$u(t) = \begin{cases} 0 & \text{if } \lambda_1 \leq 0 \\ \frac{s_1}{B}\lambda 1 & \text{if } 0 < \lambda_1 < \frac{B}{s_1} \\ 1 & \text{if } \lambda_1 \geq \frac{B}{s_1} \end{cases}$$

7.2.3 Solution to optimality system

In summary, the optimality system is as follows:

State equations:

$$\begin{aligned} \frac{\mathrm{d}x}{\mathrm{d}t} =& cy - \mu_2 x + \frac{p_1 xz}{g_1 + z} + s_1 u(t)\,, \\ \frac{\mathrm{d}y}{\mathrm{d}t} =& r_2 y(1 - by) - \frac{axy}{g_2 + y}\,, \\ \frac{\mathrm{d}z}{\mathrm{d}t} =& \frac{p_2 xy}{g_3 + y} - \mu_3 z\,, \end{aligned} \tag{7.77}$$

with the initial states $x(0) = 1$, $y(0) = 1$, $z(0) = 1$.

Adjoint equations:

$$\begin{aligned} \frac{\mathrm{d}\lambda_1}{\mathrm{d}t} =& -1 - \left(-\mu_2 + \frac{p_1 z}{g_1 + z}\right)\lambda_1 + \frac{ay}{g_2 + y}\lambda_2 - \frac{p_2 y}{g_3 + y}\lambda_3\,, \\ \frac{\mathrm{d}\lambda_2}{\mathrm{d}t} =& 1 - c\lambda_1 - \left(r_2 - 2r_2 by - \frac{ag_2 x}{(g_2 + y)^2}\right)\lambda_2 - \frac{p_2 g_3 x}{(g_3 + y)^2}\lambda_3\,, \\ \frac{\mathrm{d}\lambda_3}{\mathrm{d}t} =& -1 - \frac{p_1 g_1 x}{(g_1 + z)^2}\lambda_1 + \mu_3\lambda_3\,, \end{aligned} \tag{7.78}$$

with the transversality condition $\lambda_1(t_f) = 0\,, \lambda_2(t_f) = -A\,, \lambda_3(t_f) = 0$.

Optimality conditions

$$u(t) = \begin{cases} 0 & \text{if } \lambda_1 \leq 0\,, \\ \frac{s_1}{B}\lambda 1 & \text{if } 0 < \lambda_1 < \frac{B}{s_1}\,, \\ 1 & \text{if } \lambda_1 \geq \frac{B}{s_1}\,. \end{cases} \tag{7.79}$$

It is obvious that there is an initial condition for state system (7.77). On the other hand, there is a final time condition for adjoint system (7.78). Thus the optimal problem is in fact of TPBVPs. The shooting method [32] can be used to solve this type of problems. Nonetheless, since the state system is independent of the adjoint variables, it can be solved as an initial value problem by using, for instance, fourth order Runge-Kutta method or any other numerical method of solving initial value problems. Thus, instead of application of standard methods of solving TPBVPs, an intuitive method, referred to as forward-backward sweep method (FBSM), is used to solve the optimality system. an outline of the algorithm is mentioned as follows:

Step 1. An initial guess is made for u over the interval.

Step 2. Using the control u and the initial state, the state system is solved forward in time.

Step 3. Using the transversality condition and the values of state, the adjoint system is solved backward in time.

Step 4. The control u is updated by using the adjoint variables and the optimality conditions.

Step 5. If the differences of the current and previous values of the states variables, adjoint variables and control are within an acceptable error range, output the current values as the solutions. If not, return to Step 2.

In order to numerically solve state system (7.77), the forth order Runge-Kutta method is used. A simple description of the method is given. Assume the state system has the form

$$\mathbf{x} = \mathbf{f}(t, \mathbf{x}, u)\ .$$

Given a step size h, in order to evaluate $\mathbf{x}_{i+1} = \mathbf{x}(t_i + h)$ by using $\mathbf{x}_i = \mathbf{x}(t_i)$, the fourth-order formula of Runge-Kutta method is as follows:

$$\begin{aligned} k_1 &= \mathbf{f}(t_i, \mathbf{x}_i, u_i)\ , \\ k_2 &= \mathbf{f}\left(t_i + \frac{h}{2}, \mathbf{x}_i + \frac{h}{2}k_1, \frac{1}{2}(u_i + u_{i+1})\right)\ , \\ k_3 &= \mathbf{f}\left(t_i + \frac{h}{2}, \mathbf{x}_i + \frac{h}{2}k_2, \frac{1}{2}(u_i + u_{i+1})\right)\ , \\ k_4 &= \mathbf{f}(t_i + h, \mathbf{x}_i + hk_3, u_{i+1})\ , \end{aligned}$$

where i denotes the evaluation of the variable at ith step, $u_i = u(t_i)$, and $u_{i+1} = u(t_i + h)$ and

$$\mathbf{x}_{i+1} = \mathbf{x}_i + \frac{h}{6}(k_1 + 2k_2 + 2k_3 + k_4)\ .$$

In order to solve the adjoint system (7.78) backward in time, suppose that the system is in the form of

$$\lambda = \mathbf{f}\left(t, \mathbf{x}, \lambda\right) .$$

The fourth-order formula of Runge-Kutta method, backward in time is as follows:

$$\begin{aligned}
k_1 &= \mathbf{f}\left(t_i, \lambda_i, \mathbf{x}_i\right) , \\
k_2 &= \mathbf{f}\left(t_i - \frac{h}{2}, \lambda_i - \frac{h}{2}k_1, \frac{1}{2}\left(\mathbf{x}_i + \mathbf{x}_{i-1}\right)\right) , \\
k_3 &= \mathbf{f}\left(t_i - \frac{h}{2}, \lambda_i - \frac{h}{2}k_2, \frac{1}{2}\left(\mathbf{x}_i + \mathbf{x}_{i-1}\right)\right) , \\
k_4 &= \mathbf{f}\left(t_i - h, \lambda_i - hk_3, \mathbf{x}_{i-1}\right) ,
\end{aligned}$$

and

$$\lambda_{i-1} = \lambda_i - \frac{h}{6}\left(k_1 + 2k_2 + 2k_3 + k_4\right) .$$

Assume that u is the current evaluated control in numerical simulation, and u_{old} is the previous control. In order to test the convergence of the solution, the relative error must be negligibly small, i.e.

$$\frac{\|u - u_{\text{old}}\|}{\|u\|} \leq \delta \,, \tag{7.80}$$

where δ is the accepted tolerance. In order to include the zero controls, the previous relation is rewritten as below:

$$\delta \|u\| - \|u - u_{\text{old}}\| \geq 0 \,, \tag{7.81}$$

and this requirement must be considered for all variables, not just the control. For multiple-therapy, the critical values for s_1 and s_2 in order to be able to remove the tumor is [87]

$$s_2 < \frac{g_1\mu_2\mu_3}{p_1 - \mu_2} = s_2^{Crit} \tag{7.82}$$

and

$$s_1 > \frac{g_2 r_2}{a}\left[\frac{s_2\left(\mu_2 - p_1\right) + g_1\mu_2\mu_3}{g_1\mu_3 + s_2}\right] \tag{7.83}$$

For the parameters given in Table 2.1, the critical value for IL-2 is $s_{2,cr} = 63492063$.

7.3 Particle Swarm Optimization

The PSO is one of the most noticeable features of the field of nature-inspired metaheuristics. In optimization problems, a metaheuristic is a procedure which select or generate a search algorithm in order to provide solutions to optimization problems. The PSO deals with an optimization problem by iteratively trying to improve the solutions. In a basic PSO algorithm, an imaginary population (swarm) of particles is defined. The particles move in the search space. Each particle represents a suggestion (solution) for the optimization problem. any particle is able to save its best solution and its best position, while moving around and compares them with

the best solutions and the best positions of the neighbour particles. All particles are controlled to move towards the best local positions and then update their suggested solutions. This process is reiterated until the best solution will be obtained. The PSO was originally introduced in [73, 136] and was first planned to simulate social behaviour as a representation of the movement of organisms in a bird flock or fish school. The PSO is mentioned by some authors to belong to the concept of *swarm Intelligence* [16]. In [50], Kennedy and Eberhart describe many philosophical aspects of PSO and swarm intelligence. Swarm intelligence is based on a population (referred to as a swarm) of particles. There is a local interaction and information flow between the particles. The swarm possesses the ability to arrange its particles in a purposeful manner (self-organization). Particle swarm optimization [73] is an optimization algorithm dealing with problems, for which an optimal solution can be represented in an n-dimensional space. Nonetheless, the algorithm is categorised as a metaheuristic, since it makes few or no assumptions about the problem, which is intended to be optimized and searches a large space of candidate solutions. The differentiability of the problem is not required by PSO as it is required by classical optimization methods such as gradient descent method and so forth.

Presume that the optimal control problem is to minimize (or maximize) a performance index, $J(u)$, where u denotes the input of a system, which governs the performance index. The proposed swarm consists of n particle, where $n \in \mathbb{N}$ and $n > 1$. The ith particle possesses five characteristics, namely the current position of the particle, $x_i(k)$, at the kth iteration, the performance index evaluated at the position $x_i(k)$, the current direction of the particle's movement, $v_i(k)$, the best position experienced by the particle up to the kth iteration, $x_{i,best}(k)$, and finally the best performance index evaluated by the particle up to the kth iteration. The next direction (or velocity) of the ith particle is evaluated based on a combination of its current direction, the direction towards its best position and the direction towards the best position among all particles, which is represented by $x_{gbest}(k)$. This can be mathematically formulated as follows:

$$\begin{aligned} v_i(k+1) &= wv_i(k) + c_1 r_1 \left(x_{i,best}(k) - x_i(k)\right) \\ &\quad + c_2 r_2 \left(x_{gbest}(k) - x_i(k)\right), \end{aligned} \tag{7.84}$$

where w is called as the inertia weight ($w_1 < w < w_2$). The lower and upper bound of the inertial weight are respectively w_1 and w_2. The coefficients r_1 and r_2 are both random constants uniformly distributed in $[0, 1]$, which provide the element of randomness into the movement of the swarm. The coefficients c_1 and c_2 are mentioned as acceleration coefficients. The next position of each particle is obtained by the formula

$$x_i(k+1) = x_i(k) + v_i(k+1). \tag{7.85}$$

Equations (7.84) and (7.85) represent the self-organization for the PSO, meaning that each particle of the whole swarm will update its position by the rule expressed in (7.84) and (7.85).

The PSO algorithm has experienced many changes since its introduction in [73]. Many research has been conducted on the theoretical effects of the various parameters and aspects of the algorithm. For instance, a neighbour set of particle i can be

defined, which is denoted by $T_i(k)$:

$$T_i(k) \subseteq \{1, 2, \cdots, n\} . \tag{7.86}$$

where n denotes the total amount of particles. The set $T_i(k)$ is a subset of all particles which contribute to the velocity update rule of particle i at iteration k. The strategy which is employed to construct $T_i(k)$, is called the topology of the swarm. The topology might be different for various types of PSO algorithm [74, 75, 110]. Many topologies have been defined for the PSO, namely the traditional particle swarm topology known as global best topology, ring lattice, wheel topology, pyramid topology ; each of them has advantages and disadvantages over the others [23]. Global best topology (gbest) provides the most immediate connection between particles and the best solution over the search space. On the opposite side, the ring lattice, which is mentioned as "lbest", provide the most indirect and slowest pattern [74, 111].

In order to implement the PSO algorithm, the following procedure can be used:

1. Assign a random position to each particle for initialization of the swarm.
2. Evaluate the objective function (or functional) for each particle and save the particle's evaluation.
3. For every particle, compare the particle's evaluation with its best previous evaluation. If the current evaluation is better that its best previous evaluation, then assign this value as the best evaluation.
4. Find the particle with the best global value of the objective function.
5. Update the velocity and position of each particle.
6. Repeat steps 2 to 5 until a stopping criterion is satisfied.

7.3.1 Inertia Weight

The strategy to incorporate the inertia weight, w, in (7.84), has been first suggested in [136]. The inertia weight represents the influence of the previous velocity on the current velocity of the particle. assigning the upper bound of the inertia weight to w gives this opportunity to the particle i to move more freely in the search space and globally search for the optimization, without considering the communication with other particles. In this case, the PSO relies on the global exploration in the search space and therefore the connection between the particle i and its neighbour particles decreases. On the other hand lower values of w help in searching the local search area, as the communication between particle i and other neighbour particles increases. In fact, the particle is influenced by the information received from the neighbor particles and is able to exploit this information. Thus the smaller values of w causes the PSO algorithm to locally converge faster.

The PSO relies on the global exploration (upper values of w) and the local exploitation (lower values of w) in order to achieve a good performance. More exploration must be conducted in the early stages, where the algorithm deals with a low level of information about the search space. In contrast, during the later stages,

the algorithm must be able to exploit the previous information and therefore the connection between neighbour particles must be increased. The concept of adaptive w is discussed in [137, 147]. One strategy for adapting the inertia weight is to allow it to linearly decrease from the upper bound, w_2, to the lower bound ,w_1. Thus the value of w at kth iteration is obtained by:

$$w(k) = (w_2 - w_1)\frac{k_{\max} - k}{k_{\max}} + w_1 . \tag{7.87}$$

where $k_{\max}$ denotes the maximum iteration.

7.3.2 Acceleration Coefficients

In (7.84), the parameters c_1 and c_2 are called as the acceleration coefficients. The parameter c_1 is mentioned as the cognitive acceleration coefficient, while the other parameter, c_2 is called as the social acceleration coefficient. Higher values of c_1 allow particle i to deviate from its neighbourhood and therefore improve the global exploration of the PSO algorithm. On the other hand the higher values of c_2 make the particle move in the direction of the current best global solution and therefore this causes the algorithm to globally converge faster to the current best solution. In [126] the time variant acceleration coefficients have been formulated in order to maintain an appropriate balance between global exploration and local exploitation:

$$\begin{aligned} c_1(k) &= (c_{1,lb} - c_{1,ub})\frac{k}{k_{\max}} + c_{1,ub} , \qquad c_{1,lb} \le c_1 \le c_{1,ub} , \\ c_2(k) &= (c_{2,ub} - c_{2,lb})\frac{k}{k_{\max}} + c_{1,lb} , \qquad c_{2,lb} \le c_2 \le c_{2,ub} , \end{aligned} \tag{7.88}$$

where c_1 is reduced from its upper bound, $c_{1,ub}$, to the lower bound, $c_{1,lb}$; and c_2 is increased from its lower bound, $c_{2,lb}$, to the upper bound, $c_{2,ub}$.

7.3.3 Coefficients of Constriction

In traditional particle swarm optimization, a divergence of swarm may occur. The convergence, in relation to PSO, refers to two different definitions. The first definition states that the best position of the particles tends to an optimum. The other definition refers to the convergence of the sequence of solutions, in which all particles tend to a point in the search-space, whether or not the point is the optimum. Convergence of the sequence of solutions has been investigated in [141]. These analyses have leaded to formulae which give the parameters of PSO in such a way that prevent divergence of the swarm's particles. In [22, 34, 142], the authors have proven that PSO need some modification to guarantee a local optimum. A possible strategy to prevent the divergence of the swarm population is to define a maximum velocity in order to restrict the step size or velocity. In [34], it is demonstrated that the implementation of appropriately defined constriction coefficients prevents explosion of the swarm and furthermore, these coefficients cause particles to converge on local optima. The general idea is to define an intermediate parameter $\phi = \phi_1 + \phi_2$, by which the acceleration coefficients c_1 and c_2 are expressed to observe the criterion of convergence. The parameters ϕ_1 and ϕ_2 are assumed to be real positive variables.

The stability analysis was conducted to find the best situation in order to achieve a fast convergence. the research in [34] resulted in finding what are called as constriction coefficients:

$$\begin{aligned} \phi &= \phi_1 + \phi_2 > 4\,, \\ \phi_1 &> 0\,, \\ \phi_2 &> 0\,, \\ w &= \frac{2}{\phi - 2 + \sqrt{\phi^2 - 4\phi}}\,, \\ c_1 &= \frac{2\phi_1}{\phi - 2 + \sqrt{\phi^2 - 4\phi}}\,, \\ c_2 &= \frac{2\phi_2}{\phi - 2 + \sqrt{\phi^2 - 4\phi}}\,, \end{aligned} \tag{7.89}$$

which result in a good performance of convergence to optima. It was obtained that the best performance is achieved, while $\phi_1 = \phi_2 = 2.05$.

7.3.4 Advantage of the PSO

Particle swarm optimization is an evolutionary computation technique inspired by the social behaviour of bird flocking and fish schooling. The algorithm has some advantages over the other similar algorithm like genetic algorithm (GA). The GA algorithm is another technique, which is used in engineering to evaluate approximately optimization problems, inspired by evolutionary biology like inheritance, mutation, natural selection and recombination [37]. The PSO is not mainly influenced by the nonlinearity of the problem, and could converge to the solution in many cases. Furthermore, PSO has several advantages over the other similar techniques:

- easy to implement, since there are less parameters to adjust
- each particle saves its best values, in addition to the best value of neighbours and therefore having more effective memory capability than GA.
- in PSO, all the particles receive information from the best particle at each iteration, whereas in GA, worse solutions are removed and therefore the particles evolve around a subset of the best individuals.

The concept behind PSO is based on both social and computer science. It uses the swarm intelligence concept, where the particles interact locally with neighbours to create coherent global patterns. In swarm intelligence, the population must evaluate space and time computations, respond to quality factors in the environment and not change its mode while the environment changes [50].

7.3.5 Topology of the Particle Swarm

Particles may be in an interaction with each other in two general types of neighbourhood, namely global best (mentioned as gbest) or local best (called as lbest) [50, 75]. While the particles are attracted to the position of the particle with best evaluation

among the whole swarm, the topology of the neighbourhood is gbest. This type of topology represents a fully connected network, in which every single particle interacts with all other particles. On the other hand, in an lbest topology, each particle will interacts with only its neighbour particles, according to a certain topology, which define the concept of the neighbourhood. The two most common local best topologies are mentioned as ring topology, in which each particle is in an interaction with two neighbours, an the wheel topology, in which all the particles are isolated from one another and the information is communicated to a central particle.

7.4 Immunotherapy Protocols

In this section, the optimal control problems formulated based on the Pontryagin maximum principle, are solved by using an approach which is a hybrid of the PSO and FBSM. The results are compared with those of [66]. It is explained how the FBSM could be enlisted to improve the process of obtaining the optimal controls, then the obtained optimal controls are demonstrated to be more appropriate to the elimination of cancer cells by using fewer amounts of external sources of medicines.

7.4.1 Results and Discussion

The results are obtained for three different cases, based on the choice of different values for c, s_1, and B. The duration of therapy is consider to be 350 days, i.e. $t_f = 350$:

Case 1: $c = 0.04$, $s_1 = 500$, and $B = 1$. Fig. 7.1 shows the state variables, i.e. tumor cells (x), the effector cells (y), and the concentration of IL-2 (z). The non-tumor equilibrium point in this case is unstable because the value of s_1 is smaller than critical value $s_{1,cr} = 540$ [87]. Nonetheless, the control pushes the system to the area with smaller cancerous cells. In this work, in comparison with the work done in [66], the amount of total used drug has been decreased (Fig. 7.2), and the maximum value of IL-2 is larger. The most important thing, in this work, is that the objective function is maximized ($J = 6449194$) which is larger than the objective function obtained in [66].

Case 2: $c = 0.025$, $s_1 = 550$, and $B = 1$. The results are shown in Figs. 7.3 and 7.4. Since $s_1 > s_{1,cr}$, the non-tumour state is stable. Thus, it is expected that the tumor completely inhibited. Fig. 7.3 shows that the maximum value of the tumour has been minimized over the treatment. In addition, as it is illustrated in Fig. 7.4, The performance index has been maximized in comparison with [66].

Case 3: $c = 0.04$, $s_1 = 550$, and $B = 10000$. The results are shown in Figs. 7.5 and 7.6. Since $s_1 > s_{1,cr}$, the non-tumour state is stable. The stress is here on minimizing the total amount of administration, since the parameter B has been chosen to be very large. The performance index has been maximized in comparison with the work done in [66]. The maximum value of tumour cells are at a lower level compared with [66].

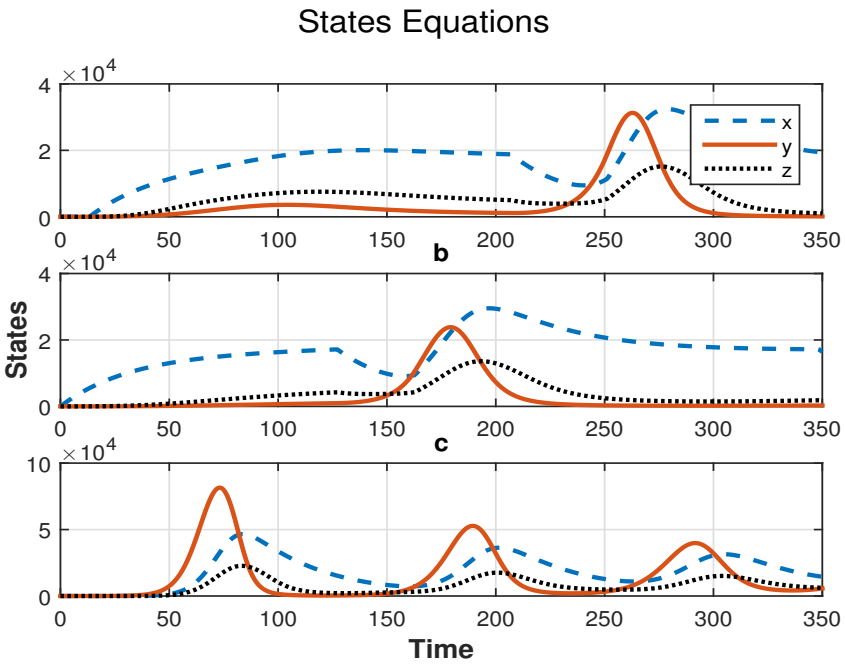

Figure 7.1. State variables, (a): in this work, (b): in [66], (c): in [87] for $c = 0.04$, $s1 = 500$, $B = 1$.

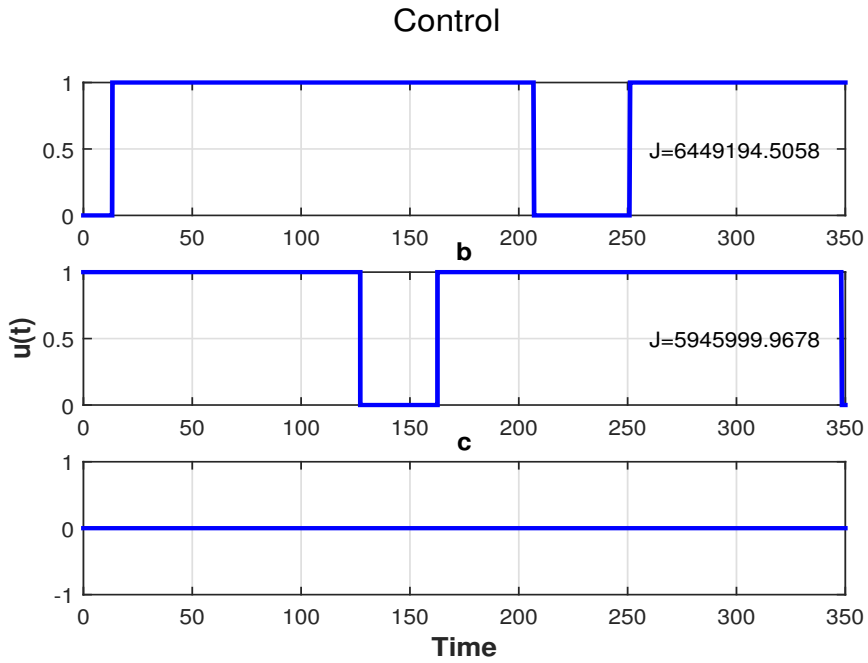

Figure 7.2. Optimal Control, (a): in this work, (b): in [66], (c): in [87] for $c = 0.04$, $s1 = 500$, $B = 1$.

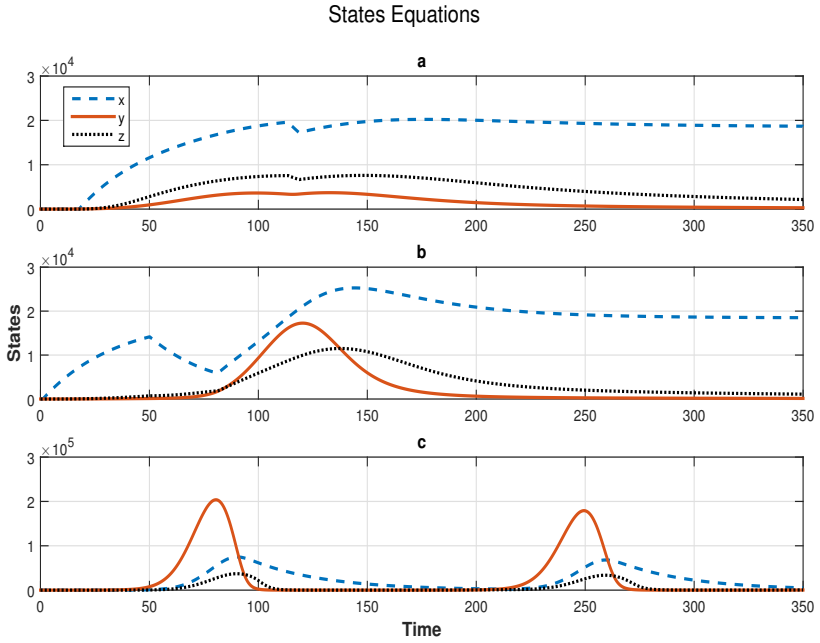

Figure 7.3. State variables, (a): in this work, (b): in [66], (c): in [87] for $c = 0.025$, $s1 = 550$, $B = 1$.

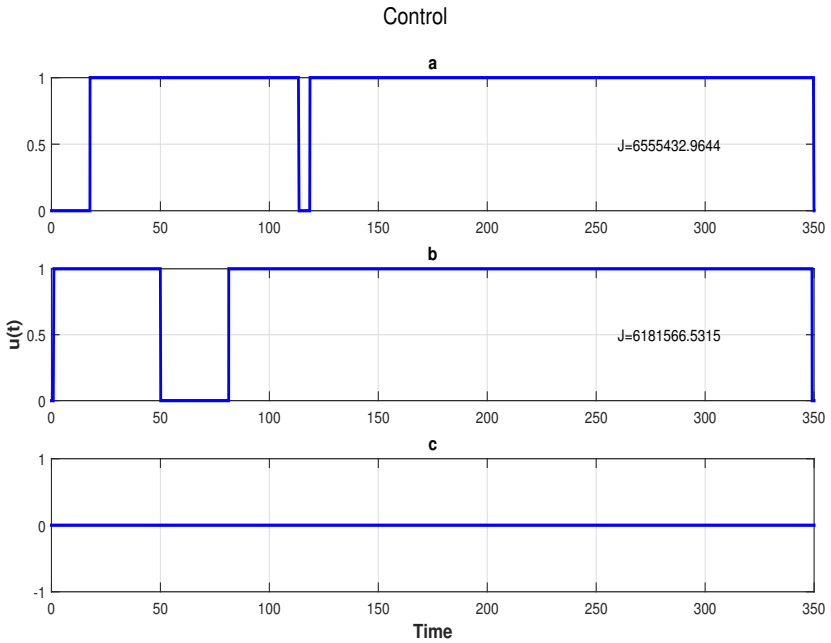

Figure 7.4. Optimal Control, (a): in this work, (b): in [66], (c): in [87] for $c = 0.025$, $s1 = 550$, $B = 1$.

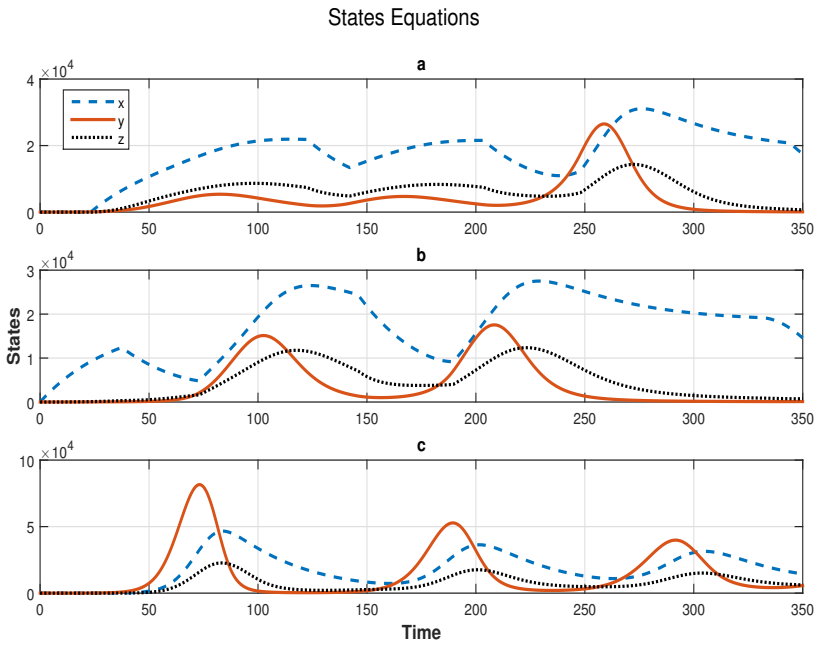

Figure 7.5. State variables, (a): in this work, (b): in [66], (c): in [87] for $c = 0.04$, $s1 = 550$, $B = 10000$.

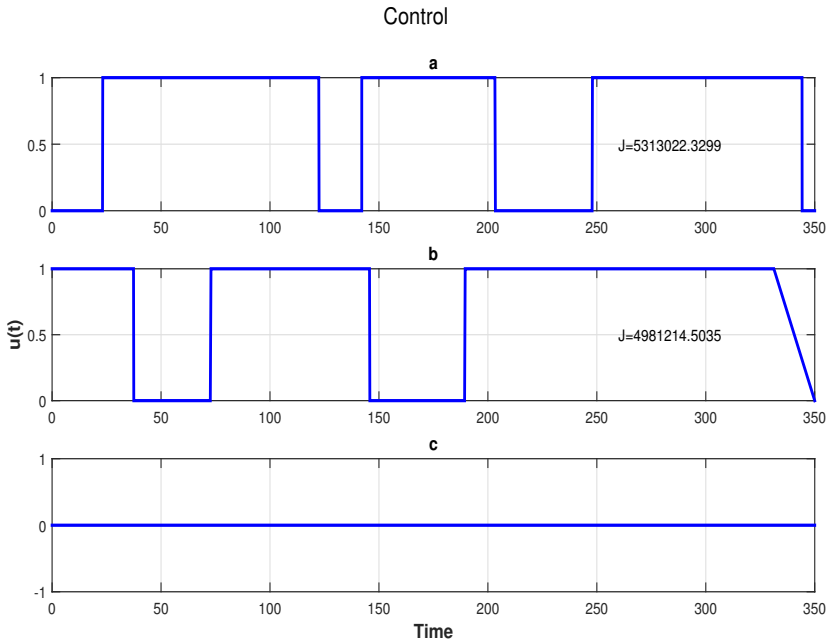

Figure 7.6. Optimal Control, (a): in this work, (b): in [66], (c): in [87] for $c = 0.04$, $s1 = 550$, $B = 10000$.

As it was shown, by using the hybrid method of PSO-FBSM the obtained results are much better and more acceptable than those represented in other research. Using the PSO algorithm along with classical methods for numerical solution of optimal controls definitely improves the performance of finding the optimal control. It is a fact that classical approaches are very time-consuming, since any initial guess cannot guarantee the convergence.

7.5 Immunotherapy Protocols for FKP Model

Since the FDEs better indicate physical phenomena, the optimal control applied to fractional models is definitely more real and reliable. First, the solutions to the FKP model are represented in Figs.7.7 and 7.8 for different fractional order. The numerical observation shows that when α_2 changes, and α_1 and α_1 are fixed to one, the maximum value of the tumour is reduced. In fact, by reducing the value of $alpha_2$, the persistent effect of drugs administration is considered in the model, which is more real than the model described by classical integer-order differential equations. When the order of equation, which describes the change of tumour with respect to drugs, is considered to be a fractional order, the memory effect of administration is appropriately considered. Thus, for the optimal control problem, the fractional order in (2.2) changes while the other two orders set to be equal to one. In Fig. 7.7,

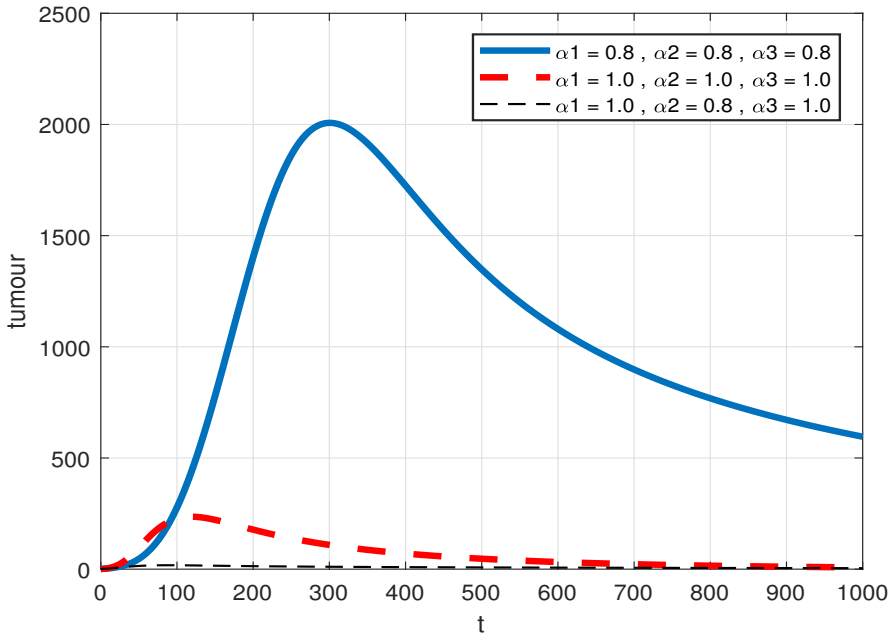

Figure 7.7. Graph of tumour in FKP model for different values of α_2, $s1 = 550$ and $s2 = 0$.

three cased are compared with each other:

- Case 1: all the orders are fractional and equal to each other.
- Case 2: all the orders are integer (classical KP model).

- Case 3: only α_2 is fractional.

The results in Fig. 7.7 show that the best case is case 3, in which the fractional order is only considered for tumour. The value of α_2 is equal to 0.9. Fig. 7.8 shows the same results as Fig. 7.7, except that the value of α_2 is equal to 0.8. The results illustrate that the maximum value of cancer cells decreases when the fractional order of (2.2) is reduces. Figs.7.7 and 7.8 illustrate that the maximum value of cancer

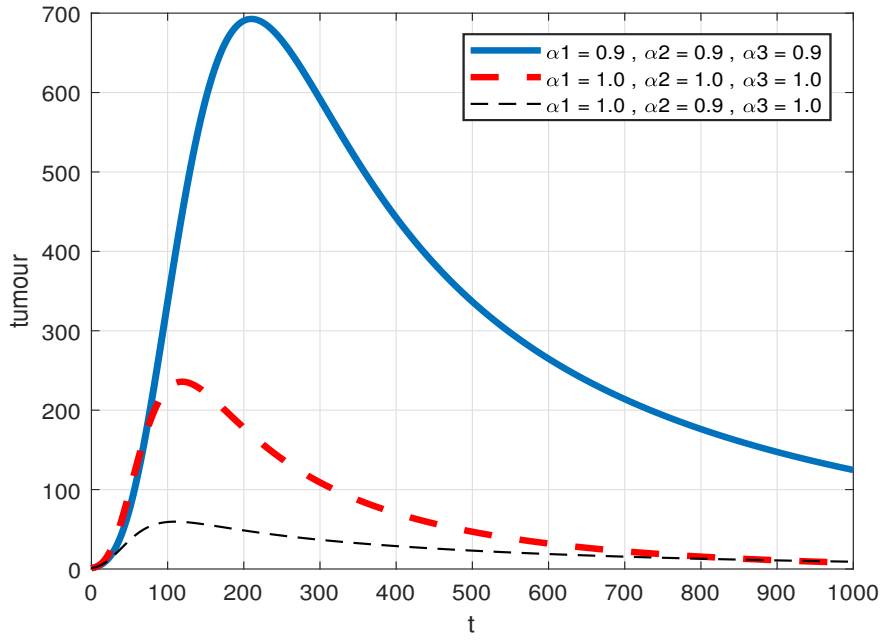

Figure 7.8. Graph of tumour in FKP model for different values of α_2, $s_1 = 550$ and $s_2 = 0$.

cells reduces by considering a fractional order for (2.2).

The approach in solving the optimal control problem for FKP is the use of PSO, where the solutions are considered to be *bang-bang* controls. All the three cases in Section 7.4.1 are examined for FKP.

Case 1:

- Fig. 7.9: $c = 0.04$, $s_1 = 500$, $B = 1$, $\alpha_2 = 0.9$, and $\alpha_1 = \alpha_3 = 1$.
- Fig. 7.10: $c = 0.04$, $s_1 = 500$, $B = 1$, $\alpha_2 = 0.8$, and $\alpha_1 = \alpha_3 = 1$.
- Fig. 7.11: $c = 0.04$, $s_1 = 500$, $B = 1$, $\alpha_2 = 0.7$, and $\alpha_1 = \alpha_3 = 1$.

In Figs. 7.9, 7.10, and 7.11 it is shown that the tumour has significantly decreased during and at the end of treatment by decreasing the fractional order $alpha_2$. As it is illustrated in Fig. 7.11, the amount of tumor has been minimized, and simultaneously the level of IL-2 increases by making a reduction in α_2. Compared to the ordinary optimal control (Fig. 7.1 and 7.2), the total use of drugs are a bit larger, but the tumour has dropped to a lower level during treatment. **Case 2:**

- Fig. 7.12: $c = 0.04$, $s_1 = 550$, $B = 10000$, $\alpha_2 = 0.9$, and $\alpha_1 = \alpha_3 = 1$.

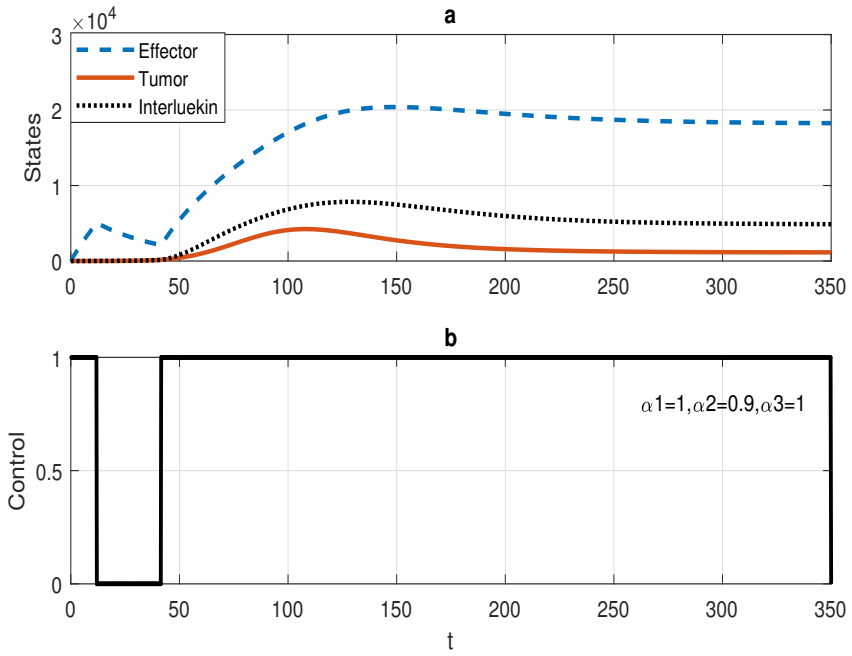

Figure 7.9. a: optimal states, b: optimal control, $\alpha_2 = 0.9$, $c = 0.04$, $s_1 = 500$, $B = 1$.

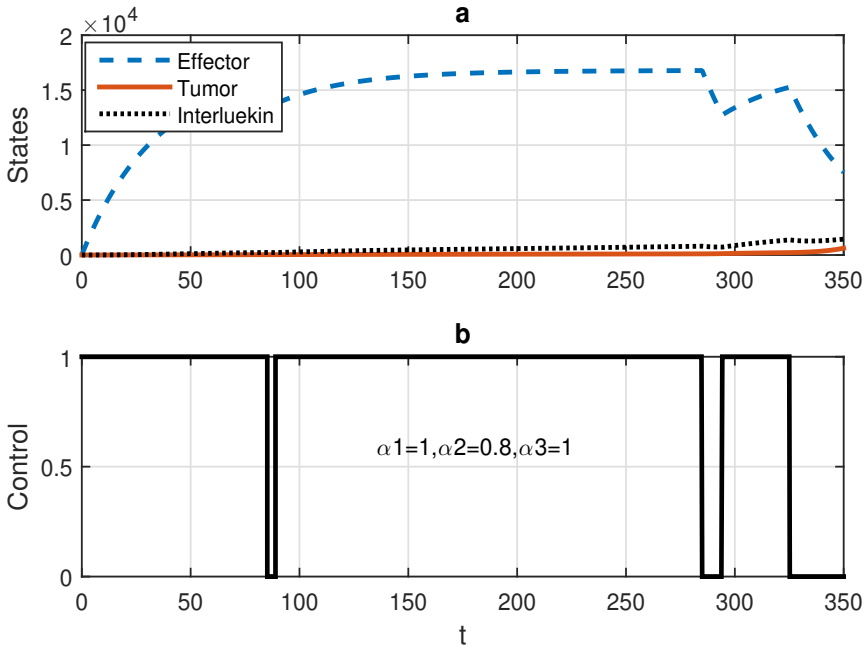

Figure 7.10. a: optimal states, b: optimal control, $\alpha_2 = 0.8$, $c = 0.04$, $s_1 = 500$, $B = 1$.

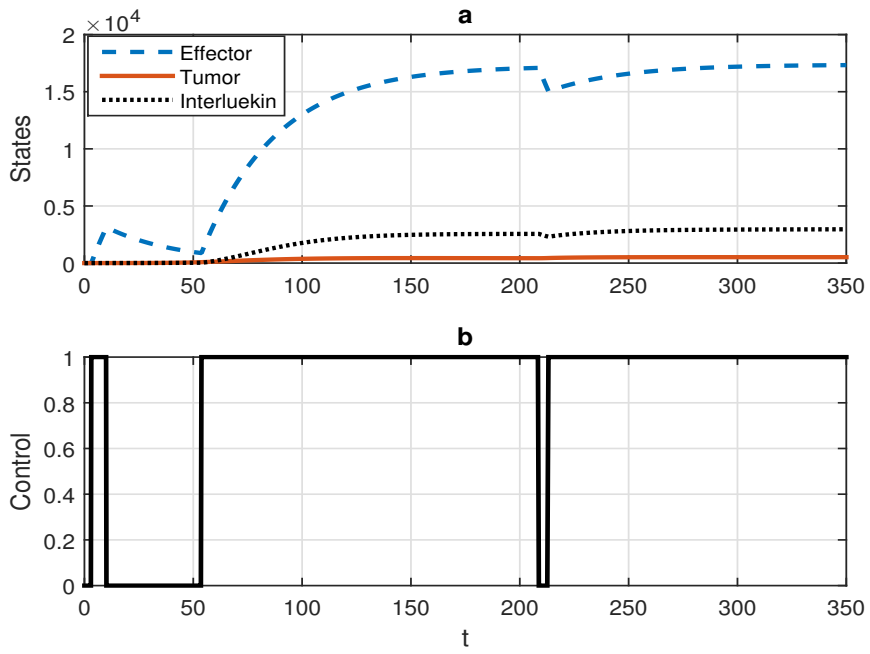

Figure 7.11. a: optimal states, b: optimal control, $\alpha_2 = 0.7$, $c = 0.04$, $s_1 = 500$, $B = 1$.

- Fig. 7.13: $c = 0.04$, $s_1 = 550$, $B = 10000$, $\alpha_2 = 0.8$, and $\alpha_1 = \alpha_3 = 1$.
- Fig. 7.14: $c = 0.04$, $s_1 = 550$, $B = 10000$, $\alpha_2 = 0.7$, and $\alpha_1 = \alpha_3 = 1$.

The value of the parameter B is set to 10000. The results are depicted in Figs. 7.12, 7.13, and 7.14. Reduction in α_2 causes a significant reduction in the tumour, i.e. under the same condition, lower values of α_2 cause the amount of tumor during and at the end of treatment decreases a lot. A higher value of B shows that the stress is on the minimizing the total use of drugs. Consumption of drug seems to be increased in comparison with classical KP model. **Case 3:**

- Fig. 7.12: $c = 0.025$, $s_1 = 550$, $B = 1$, $\alpha_2 = 0.9$, and $\alpha_1 = \alpha_3 = 1$.
- Fig. 7.13: $c = 0.025$, $s_1 = 550$, $B = 1$, $\alpha_2 = 0.8$, and $\alpha_1 = \alpha_3 = 1$.

Figures 7.15 and 7.16 show that in case 3, the tumour level during the treatment is low as possible, even for $\alpha_2 = 0.9$. In Fig. 7.16, it is shown that for $\alpha_2 = 0.9$, the value of IL-2 increases without any external source of IL-2.

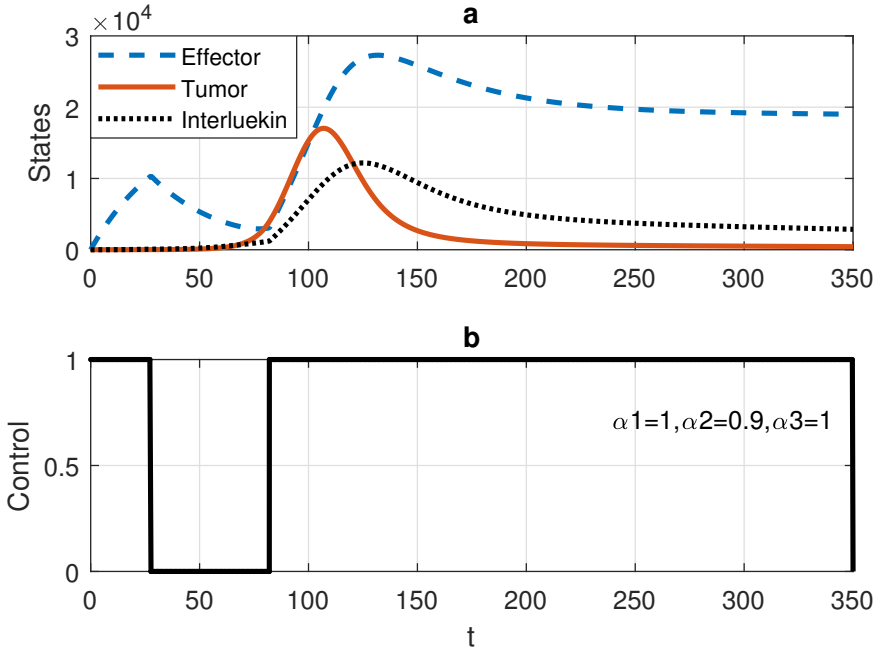

Figure 7.12. a: optimal states, b: optimal control, $\alpha_2 = 0.9$, $c = 0.04$, $s_1 = 550$, $B = 10000$.

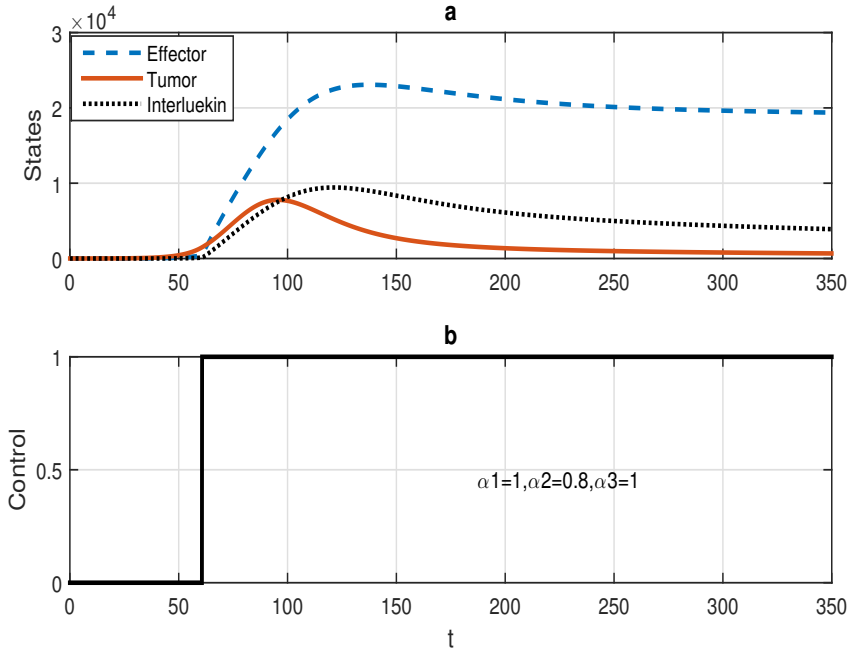

Figure 7.13. a: optimal states, b: optimal control, $\alpha_2 = 0.8$, $c = 0.04$, $s_1 = 550$, $B = 10000$.

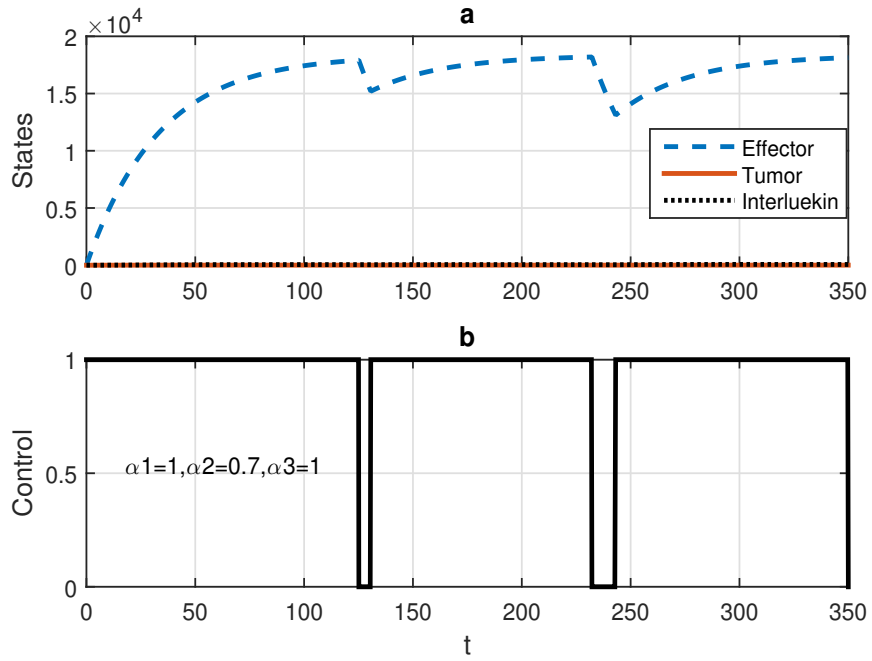

Figure 7.14. a: optimal states, b: optimal control, $\alpha_2 = 0.7$, $c = 0.04$, $s_1 = 550$, $B = 10000$.

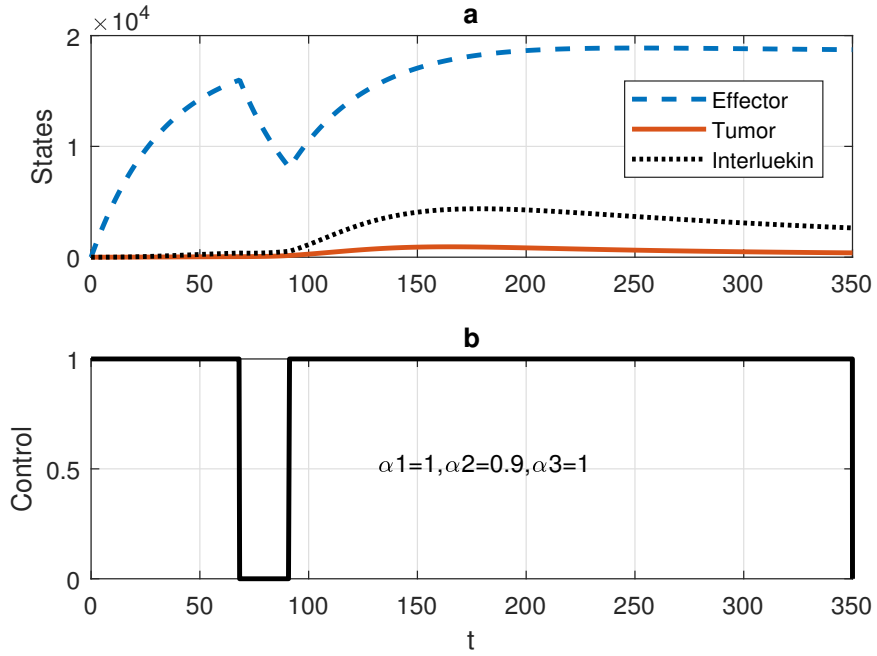

Figure 7.15. a: optimal states, b: optimal control, $\alpha_2 = 0.9$, $c = 0.025$, $s_1 = 550$, $B = 1$

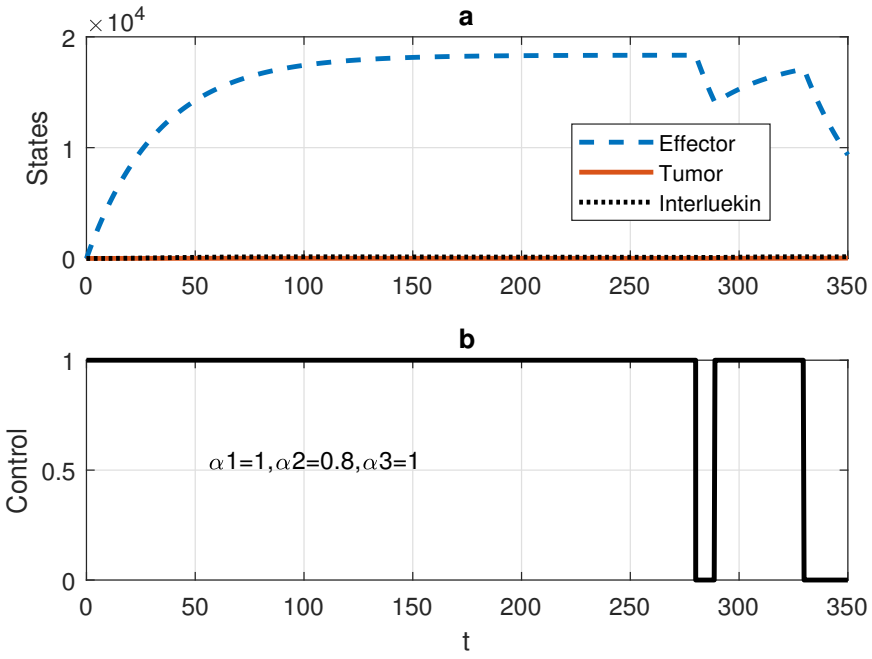

Figure 7.16. a: optimal states, b: optimal control, $\alpha_2 = 0.8$, $c = 0.025$, $s_1 = 550$, $B = 1$

7.5.1 Immunotherapy with both ACI and IL-2

The stability analysis of the FKP illustrated that the chance of destruction of the tumor will be higher in the case of multiple-therapy, i.e. administration of both the ACI and IL-2 shows a more effective treatment in suppressing the tumour cells and simultaneously increasing the effector cells and IL-2.

Fig. 7.17 shows that even a very small administration of IL-2 ($s_2 = 25000$) makes a situation in which the tumour is completely eliminated. This result is expected because the values of s_1 and s_2 are in the range, for which the non-tumor state is stable (see Fig. 3.6). Fig. 7.18 shows the case, where a large amount of IL-2 is used, i.e. $s_2 = 5$. In this case, it is observed that the total number of days, for which there is no drug administration is reduced. Fig. 7.19 illustrates a case for which the tumour-free steady state is not stable, i.e. the case $s_1 = 450$. A rather large amount of IL-2 ($s_2 = 1e5$) is used. Although the level of tumour is very low during the treatment, but this case is not capable of completely destroying the tumour. At the end of the therapy, the growth of tumor is obvious. This result was anticipated, since the value of s_1 is in the range of unstable non-tumor state (See Fig. 3.6).

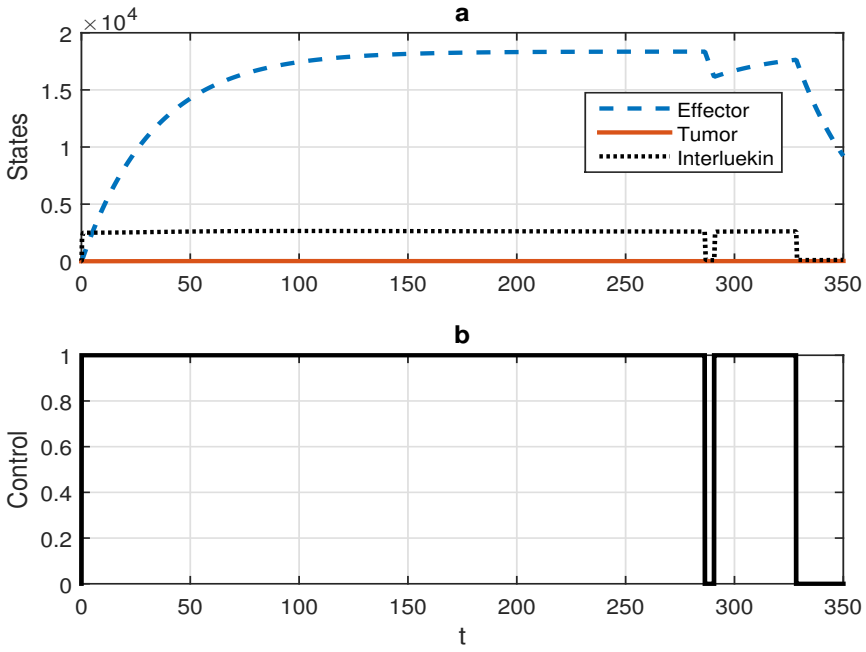

Figure 7.17. a: optimal states, b: optimal control, case of multi-therapy, $\alpha 2 = 0.9$, $c = 0.04$, $s1 = 550$, $s2 = 25000$, $B = 1$

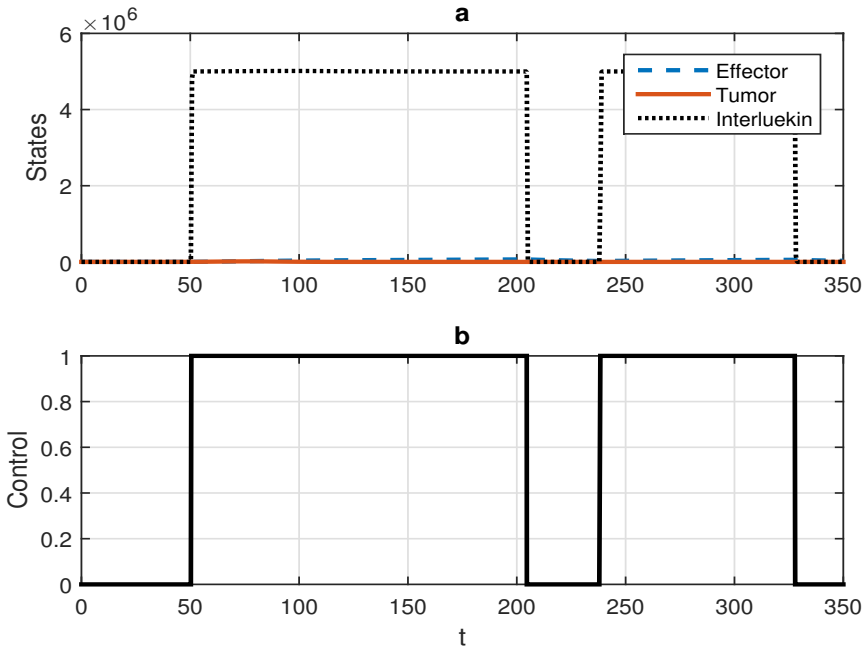

Figure 7.18. a: optimal states, b: optimal control, case of multi-therapy, $\alpha_2 = 0.9$, $c = 0.04$, $s_1 = 550$, $s2 = 5e7$, $B = 1$

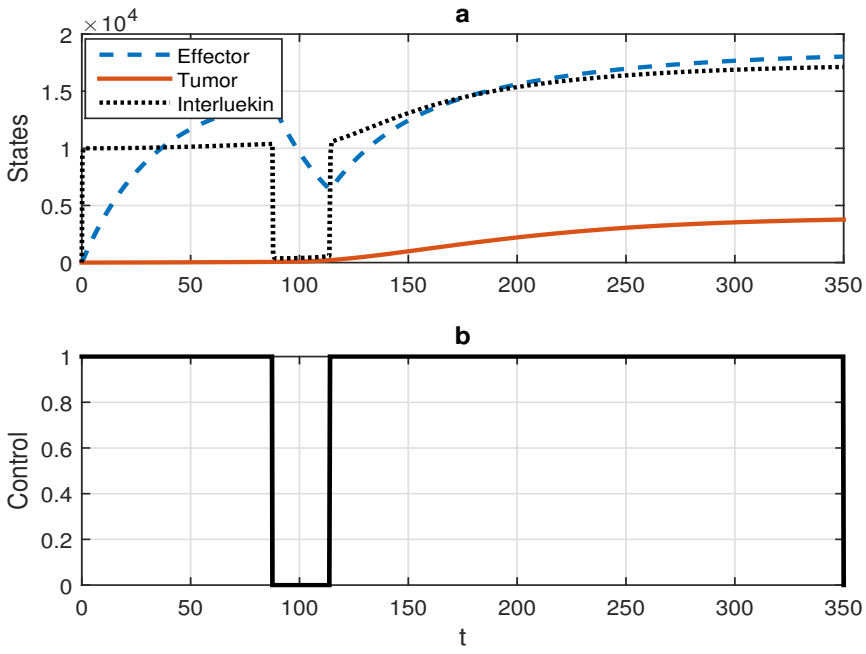

Figure 7.19. a: optimal states, b: optimal control, case of multi-therapy, $\alpha_2 = 0.8$, $c = 0.025$, $s_1 = 450$, $s_2 = 1e5$

Chapter 8

Conclusion

This thesis is focused on the representation of therapeutic protocols for cancer immunotherapy based on the well-known model of Kirschner and Panetta. The approach in optimal control has been based on Pontryagin maximum principle. Two general cases have been analysed, namely the KP and FKP models. The results obtained for the classical KP model show that the common controls for these type of problems are bang-bang. As mentioned, common methods of solving optimal control problem, formulated based on Pontryagin maximum principle, do not lead to convergence in most cases. The key issue here is the initial guess for the control function in order to initialize the precess of solution. Any initial guess does not guarantee the convergence to the optimal control and even in most cases it is almost impossible to find the solution by using this approach. Finding the most appropriate initial guess is time-consuming. Thus the approach in solving the problem has been devised on a hybrid of PSO and the usual numerical methods for TPBVPs. First, the problem is solved by using the PSO. When the solution converges, the algorithm switches to the FBSM, where the control found at the previous stage is used as an initial guess for the next stage. The optimal control problem for FKP model has been dealt with, by using the PSO algorithm while the control functions are considered to be of the bang-bang form. The results are much better than those obtained for KP model in terms of the use smaller amount of medicine and the perfect elimination of the tumour, during and at the end of treatment.

Since the tumour population is described by logistic function and in addition, this type of limiting-growth function is frequently used in many biological and other physical applications, it is appropriate to consider fractional logistic equation. In this regard, the function mentioned as WF was demonstrated to behave in good agreement with numerical solution to FLE. Therefore, a fractional integro-differential equation has been presented which is satisfied by the proposed equation, namely MFLE. It is known that solutions of FDEs are much more difficult to be find in comparison with classical integer-order differential equations. The approach taken here, may be appropriate to nonlinear fractional differential equations which arisen in mathematical physics.

The inverse problem for order estimation of several classes of linear fractional differential equations has constructed another part of this thesis. The determination of order in FDEs is very important in such a way that, for instance, in fractional

diffusion equations whether or not the fractional order is smaller or greater that unit, it is very important to the appropriate simulation of the anomalous diffusion in order to specify that the transport phenomenon exhibits sub-diffusion or super-diffusion. For those linear fractional differential equations discussed in this thesis, the order estimation have been conducted based on the asymptotic behaviour of Mittag-leffler functions involved in their solutions.

Solutions to nonlinear FDEs are much more difficult than ordinary differential equations to be calculated, and also numerical treatment to FDEs is also more challenging. These non-trivial difficulties are mainly related to the persistent memory of FDEs and the non-smoothness of solutions to them at the initial time. a wide variety of numerical approaches have been devised based on incorrect assumptions and it is seen that many researcher use these methods to find the numerical solutions of FDEs. Thus a general description of such methods are presented. A specific case, the so-called MSGDTM, is explained in details, then it is stated that the basis on which the method has been devised is incorrect and unfit to FDEs.

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