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A Fractional-Order Modeling and Sensitivity Analysis in the Investigation of Colorectal Cancer

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Abstract: This research paper focuses on studying colorectal cancer using a sensitivity analysis via the fractional differential equations (FDE) model. The study aims to develop an accurate model for predicting the progression of the disease and its response to treatments, by capturing all the important cells and factors involved. The existence and uniqueness of solutions are proven using the Banach contraction principle, and global stability is shown using the Lyapunov function. Results show that the Epithelial cell growth rate (λ_E), rate of out-competition of epithelial cells by normal cells (δ_{EO}), rate of immune cell attack on epithelial cells (γ_{EIC}) and TGF-β-induced growth rate of epithelial cells (γ_{TE}) are the most sensitive parameters, with the concentration of adenomatous polyps ($P(t)$), tumor suppressor genes ($T(t)$), epithelial cells ($E(t)$) and APC genes ($A(t)$) as most sensitive compartments. The research concludes that the developed model can be used as a powerful tool for predicting the disease's behavior and assessing the efficacy of different treatment strategies. Overall, this study provides valuable insights into the treatment of colorectal cancer.

Keywords: Mathematical modeling, fractional Caputo derivative, colorectal cancer, sensitivity analysis.

1 Introduction

Colorectal cancer is one of the most common types of cancer and a significant contributor to cancer-related deaths globally [1]. Colorectal cancer, commonly referred to as colon cancer, is characterized by the uncontrolled growth of cells within the colon or rectum [2]. The colon, also known as the large intestine or large bowel, and the rectum, which serves as the pathway connecting the colon to the anus, are the primary sites where this disease occurs [3]. Sensitivity analysis using mathematical models is a useful tool for investigating the complex mechanisms of colorectal cancer development and evaluating the effectiveness of various treatments [4].

Fractional-order differential equations (FDEs) are a powerful tool for modeling complex systems with memory and non-locality effects, which are prevalent in biological systems, used to capture the complex behavior of biological systems, including the growth of cancer cells [5–8]. FDEs have been extensively used in modeling various physiological and pathological systems, including cancer [9]. In recent years, there has been an increasing interest in using FDEs to model the growth and progression of colorectal cancer [10].

Several studies have proposed different FDE models for colorectal cancer [11, 12]. For instance, authors in [13] used a fractional-order model to describe the interaction between the tumor and the immune system in colorectal cancer. The model incorporated the effects of chemotherapy, immunotherapy, and surgery on tumor growth and regression. The study found that the effectiveness of different treatments depended on the fractional-order parameter, which governs the memory and non-locality effects in the model.
In another study, a fractional-order model was proposed to investigate the impact of tumor microenvironment on colorectal cancer development [14]. The model considered the effects of angiogenesis, immune response, and extracellular matrix on tumor growth and metastasis. The study found that the fractional-order parameter and the strength

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of the immune response were critical factors affecting the disease's progression.

Sensitivity analysis is an important tool for investigating the behavior of complex systems and identifying the critical factors that affect their performance [15–17]. Several sensitivity analysis techniques have been proposed, including local sensitivity analysis, global sensitivity analysis, and variance-based sensitivity analysis [18–20]. In the context of colorectal cancer modeling, sensitivity analysis can be used to identify the critical parameters and factors affecting the disease's progression and evaluate the effectiveness of various treatments [21].

In this research, we propose a fractional-order differential model for colorectal cancer and perform the partial derivative method of analytic sensitivity analysis to identify the critical parameters and factors affecting the disease's progression. This study uses a fractional-order differential model to describe the dynamics of colorectal cancer growth, capturing the concentrations of epithelial cells, adenomatous polyps, oncogenes, tumor suppressor genes, APC gene, KRAS gene, microsatellite instability, inflammatory cells, cancer stem cells, angiogenesis factors, myofibroblasts, matrix metalloproteinases, transforming growth factor-beta, hypoxia-inducible factor-1, Notch signaling pathway, cyclooxygenase-2, p53 protein, and microRNAs [22], with the description of all parameters and variables shown in Table 3 and Table 1 respectively. To our knowledge, no study has performed a comprehensive sensitivity analysis on colorectal cancer using fractional-order derivatives. The sensitivity analysis is employed to identify the most critical parameters that influence the growth of colorectal cancer and how treatment can be improved to target these critical parameters.

2 Preliminaries

Definition 21 *Caputo derivative [23]*

The Caputo derivative of order $\alpha \in (0,1]$ of a sufficiently differentiable function $f(t)$ is defined as follows:

$$\frac{d^{\alpha} f(t)}{dt^{\alpha}} = \frac{1}{\Gamma(1-\alpha)} \int_0^t (t-\tau)^{-\alpha} \frac{d}{d\tau} f(\tau) d\tau,$$

where Γ is the gamma function.

Definition 22 *Gamma function [24]*

The gamma function $\Gamma(z)$ is defined for $\mathrm{Re}(z) > 0$ by the integral

$$\Gamma(z) = \int_0^{\infty} x^{z-1} e^{-x} dx.$$

Definition 23 *Laplace function [25]*

The Laplace transform of a function $f(t)$, defined for $t \geq 0$, is the function $\mathscr{L} f(t)(s)$ given by the integral

$$\mathscr{L} f(t)(s) = \int_0^{\infty} e^{-st} f(t) dt,$$

where s is a complex number such that the integral converges.

Definition 24 *Banach contraction principle. [26]*

let (X,d) be a metric space, and let $T : X \to X$ be a function. Then T is a Banach contraction if there exists a constant $0 \leq k < 1$ such that for all $x, y \in X$,

$$d(T(x), T(y)) \leq k, d(x,y).$$

Definition 25 *Picard-Lindelof Theorem [28]*

The Picard-Lindelöf theorem for fractional differential equations, also known as the Caputo fractional differential equation, states that if a function $f(x,y)$ and its partial derivative with respect to y, $f_y(x,y)$, are continuous on a rectangular region R in the xy-plane, which contains a point (x_0, y_0), then there exists a unique solution $y(x)$ of the initial value problem:

$$d^q y(x) = f(x, y(x)), y(x_0) \qquad = y_0,$$

where $d^q y(x)$ is the Caputo fractional derivative of order q $(0 < q \leq 1)$ of $y(x)$ with respect to x.

Definition 26 *Fixed point theorem. [27]*

Fixed point theorem also known as the contraction mapping theorem states that if T is a Banach contraction on a complete metric space X, then T has a unique fixed point $x^* \in X$, i.e., a point such that $T(x^*) = x^*$.

$$u(t) \leq A + B \int_a^t u(s)v(s)ds,$$

for some constants A and B. Then Gronwall's inequality states that:

$$u(t) \leq Ae^{B\int_a^t v(s)ds}.$$

3 Model formation

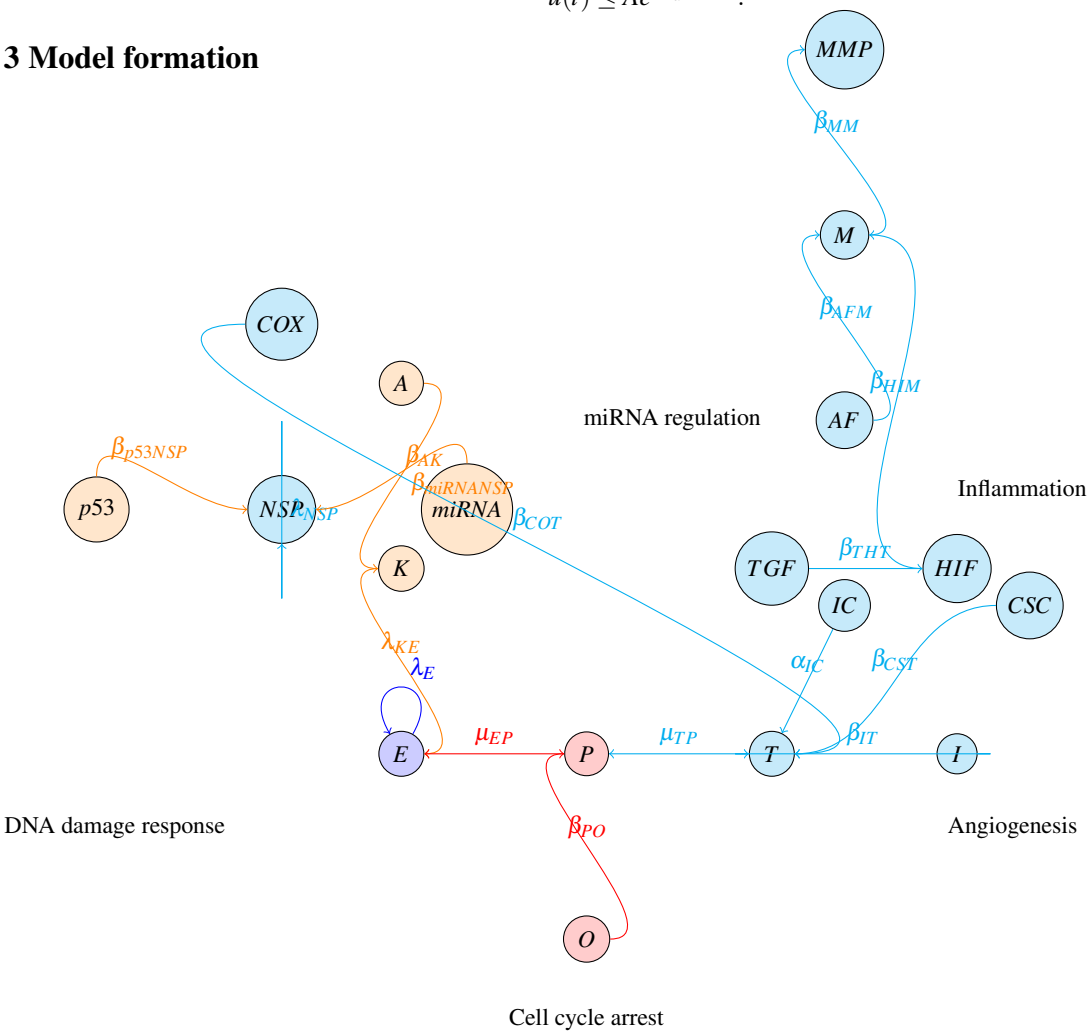

Fig. 1: Schematic diagram of the colorectal cancer model.

We seek to develop a fractional-order model of differential equations that captures the cells and factors involved in colorectal cancer.

Let $E(t), P(t), O(t), T(t), A(t), K(t), I(t), IC(t), CSC(t), AF(t), M(t), MMP(t), TGF(t), HIF(t), NSP(t), COX(t), p53(t)$, and miRNA(t) represent the concentrations of epithelial cells, adenomatous polyps, oncogenes, tumor suppressor genes, APC gene, KRAS gene, microsatellite instability, inflammatory cells, cancer stem cells, angiogenesis factors, myofibroblasts, matrix metalloproteinases, transforming growth factor-beta, hypoxia-inducible factor-1, Notch signaling pathway, cyclooxygenase-2, p53 protein, and microRNAs, respectively, at time t. Then the fractional-order model of

differential equations is given by:

$$
\begin{aligned}
\frac{d^{\alpha}E(t)}{dt^{\alpha}} &= \lambda_E - \mu_{EP} - \delta_{EO} - \gamma_{EIC} + \frac{\gamma_{TE}}{K_T+E} - \frac{\lambda_{TE}A}{K_A+A} - \frac{\lambda_{KE}K}{K_K+K} + \frac{\lambda_I I(t)}{K_I+I(t)} \\
\frac{d^{\alpha}P(t)}{dt^{\alpha}} &= \mu_{EP} - \nu_P - \delta_{PO} + \frac{\alpha_{PA}}{K_A+A} - \frac{\lambda_{PP}K}{K_K+K} \\
\frac{d^{\alpha}O(t)}{dt^{\alpha}} &= \gamma_{OIC} - \delta_{OO} - \nu_O O \\
\frac{d^{\alpha}T(t)}{dt^{\alpha}} &= \frac{\lambda_{TE}A}{K_A+A} - \frac{\lambda_I T(t)}{K_I+T(t)} - \nu_T T(t) \\
\frac{d^{\alpha}A(t)}{dt^{\alpha}} &= \frac{\beta_{AK}K(t)}{K_K+K} - \frac{\lambda_{TE}A}{K_A+A} - \frac{\lambda_{AA}M(t)}{K_M+M(t)} - \nu_{AA}A(t) \\
\frac{d^{\alpha}K(t)}{dt^{\alpha}} &= \frac{\beta_{KE}E(t)}{K_T+E(t)} - \frac{\lambda_{KE}K}{K_K+K} - \frac{\lambda_{PP}K}{K_K+K} - \nu_{KK}K(t) \\
\frac{d^{\alpha}I(t)}{dt^{\alpha}} &= \frac{\alpha_{II}C(t)}{K_{IC}+IC(t)} - \frac{\lambda_{II}I(t)}{K_I+I(t)} - \nu_I I(t) \\
\frac{d^{\alpha}IC(t)}{dt^{\alpha}} &= \delta_{EO} - \gamma_{OIC} - \frac{\alpha_{II}C(t)}{K_{IC}+IC(t)} - \nu_{IC}IC(t) \\
\frac{d^{\alpha}CSC(t)}{dt^{\alpha}} &= \frac{\beta_{CM}M(t)}{K_M+M(t)} - \delta_{CC}CSC(t) \\
\frac{d^{\alpha}AF(t)}{dt^{\alpha}} &= \frac{\beta_{AFE}(E(t))}{K_T+E(t)} - \frac{\lambda_{AF}AF(t)}{K_{AF}+AF(t)} - \nu_{AF}AF(t) \\
\frac{d^{\alpha}M(t)}{dt^{\alpha}} &= \frac{\beta_{MIC}(t)}{K_{IC}+IC(t)} - \frac{\lambda_{AA}M(t)}{K_M+M(t)} - \delta_{MM}M(t) \\
\frac{D^{\alpha}MMP(t)}{Dt^{\alpha}} &= \frac{\beta_{MMPIC}(t)}{K_{IC}+IC(t)} - \frac{\lambda_{MMPMMP}(t)}{K_{MMP}+MMP(t)} - \nu_{MMP}\cdot MMP(t) \\
\frac{D^{\alpha}TGF(t)}{Dt^{\alpha}} &= \frac{\beta_{TGFIC}(t)}{K_{IC}+IC(t)} - \frac{\lambda_{TGFTGF}(t)}{K_{TGF}+TGF(t)} - \nu_{TGF}\cdot TGF(t)
\end{aligned}
\tag{1}
$$

The first equation describes the dynamics of the epithelial cells, which can grow at a rate λ_E and be inhibited by apoptosis (μ_{EP}), out-competition by normal epithelial cells (δ_{EO}), or immune cell attack (γ_{EIC}). The growth rate can be increased by TGF-β signaling (γ_{TE}) and decreased by competition for nutrients with normal cells (λ_{KE}) or with a lack of growth factors (λ_{TE}).
The equation also includes the effect of immune cells stimulating proliferation (λ_I) by secreting cytokines and growth factors that bind to receptors on the epithelial cell surface.

The second equation describes the dynamics of the tumor-associated fibroblasts (TAFs) which can be stimulated by the presence of the tumor cells (β_{AK}) and inhibited by competition for nutrients with the tumor cells (γ_{TE}) or by apoptosis (λ_{AA}). The equation also includes the effect of MMPs secreted by tumor cells that can degrade the extracellular matrix (ECM) and allow TAFs to migrate towards the tumor cells (β_{AFE}).

The third equation describes the dynamics of the oxygen level in the tumor microenvironment, which can be increased by the presence of TAFs stimulating angiogenesis (γ_{OIC}) and decreased by consumption by tumor cells (δ_{OO}) or by diffusion out of the tissue.

The fourth equation describes the dynamics of the tumor cells' TGF-β secretion, which can be increased by the presence of activated TAFs (β_{TGFIC}) and decreased by the presence of immune cells that can attack the tumor cells (λ_{TGFTGF}).

The fifth equation describes the dynamics of the immune cells, which can be stimulated by the presence of tumor antigens presented by the antigen-presenting cells (α_{II}) and inhibited by apoptosis (λ_{II}) or by competition for nutrients with tumor cells (λ_{TE}). The equation also includes the effect of cytokines secreted by immune cells that can stimulate

proliferation of other immune cells.

The sixth equation describes the dynamics of the immune cells' killing of tumor cells, which can be increased by the presence of activated immune cells (β_{MIC}) and decreased by competition for nutrients with the tumor cells (λ_{PP}).

The seventh equation describes the dynamics of the immune cells' migration towards the tumor cells, which can be stimulated by the presence of chemokines secreted by the tumor cells or TAFs (δ_{EO}) and inhibited by competition for nutrients with the tumor cells. The eighth equation describes the dynamics of the ECM, which can be degraded by MMPs secreted by tumor cells or TAFs (β_{MMPIC}) and degraded by TAFs (δ_{CC}).The ninth equation describes the dynamics of the activated fibroblasts (AFs), which can be stimulated by the presence of the tumor cells (β_{AFE}) and inhibited by competition for nutrients with the tumor cells or immune cells (λ_{AF}).The tenth equation describes the dynamics of the macrophages, which can be stimulated by the presence of tumor cells (β_{MIC}) and inhibited by competition for nutrients with tumor cells or other immune cells (λ_{TE}). The equation also includes the effect of cytokines secreted by immune cells that can stimulate macrophage activation and function (α_{MM}). The equation for MMP(t) represents the concentration of matrix metalloproteinases, which are enzymes that play a role in breaking down the extracellular matrix and promoting tumor invasion and metastasis. The equation describes how MMP(t) changes over time, where the term $\frac{\beta_{MMPIC}(t)}{K_{IC}+IC(t)}$ represents the production of MMP(t) due to the presence of inflammatory cells (IC), the term $\frac{\lambda_{MMPMMP}(t)}{K_{MMP}+MMP(t)}$ represents the degradation of MMP(t), and the term $-\nu_{MMP} \cdot MMP(t)$ represents the clearance of MMP(t) from the system. The equation for TGF(t) represents the concentration of transforming growth factor-beta, which plays a role in promoting tumor growth and suppressing the immune system. The equation describes how TGF(t) changes over time, where the term $\frac{\beta_{TGFIC}(t)}{K_{IC}+IC(t)}$ represents the production of TGF(t) due to the presence of inflammatory cells (IC), the term $\frac{\lambda_{TGFTGF}(t)}{K_{TGF}+TGF(t)}$ represents the degradation of TGF(t), and the term $-\nu_{TGF} \cdot TGF(t)$ represents the clearance of TGF(t) from the system. Overall, this model captures the complex interplay between different components in a tumor microenvironment and how they influence each other's dynamics. By analyzing the equations and identifying the key parameters that affect each component's behavior, we can gain insights into potential targets for therapeutic intervention. For example, targeting the TGF-β signaling pathway in epithelial cells or the MMPs secreted by tumor cells and TAFs may be a potential strategy to slow down tumor growth and progression. Similarly, stimulating the immune response by targeting the cytokines that activate immune cells or inhibiting the competition for nutrients between immune cells and tumor cells may be a potential strategy to enhance anti-tumor immunity.

Table 1: Summary of variables in the colorectal cancer model

Variable	Description
$E(t)$	Concentration of epithelial cells
$P(t)$	Concentration of adenomatous polyps
$O(t)$	Concentration of oncogenes
$T(t)$	Concentration of tumor suppressor genes
$A(t)$	Concentration of APC gene
$K(t)$	Concentration of KRAS gene
$I(t)$	Concentration of microsatellite instability
$IC(t)$	Concentration of inflammatory cells
$CSC(t)$	Concentration of cancer stem cells
$AF(t)$	Concentration of angiogenesis factors
$M(t)$	Concentration of myofibroblasts
$MMP(t)$	Concentration of matrix metalloproteinases
$TGF(t)$	Concentration of transforming growth factor-beta
$HIF(t)$	Concentration of hypoxia-inducible factor-1
$NSP(t)$	Concentration of Notch signaling pathway
$COX(t)$	Concentration of cyclooxygenase-2
$p53(t)$	Concentration of p53 protein
$miRNA(t)$	Concentration of microRNAs

Table 2: Description of Parameters Colorectal cancer model

Parameter	Symbol	Description
Epithelial cell growth rate	λ_E	Rate at which epithelial cells grow
Apoptosis rate of epithelial cells	μ_{EP}	Rate at which epithelial cells undergo programmed cell death
Rate of out-competition of epithelial cells by normal cells	δ_{EO}	Rate at which normal epithelial cells out-compete epithelial cells
Rate of immune cell attack on epithelial cells	γ_{EIC}	Rate at which immune cells attack epithelial cells
TGF-β-induced growth rate of epithelial cells	γ_{TE}	Rate at which TGF-β signaling promotes epithelial cell growth
Competition rate for nutrients with normal cells	λ_{KE}	Rate at which epithelial cells compete with normal cells for nutrients
Rate of lack of growth factors	λ_{TE}	Rate at which a lack of growth factors inhibits epithelial cell growth
Immune cell stimulation rate of epithelial cell proliferation	λ_I	Rate at which immune cells stimulate epithelial cell proliferation by secreting cytokines and growth factors
Competition rate for nutrients with polyps	λ_{PP}	Rate at which epithelial cells compete with polyps for nutrients
Rate of out-competition of polyps by normal cells	δ_{PO}	Rate at which normal epithelial cells out-compete polyps
Oncogene-induced growth rate of cells	γ_{OIC}	Rate at which oncogenes promote cell growth
Oncogene degradation rate	δ_{OO}	Rate at which oncogenes degrade
Rate of microsatellite instability	ν_O	Rate at which microsatellite instability occurs
Tumor growth rate	λ_{TE}	Rate at which tumor cells grow due to TGF-β signaling
Rate of immune cell attack on tumor cells	γ_{TIC}	Rate at which immune cells attack tumor cells
Immune cell stimulation rate of tumor cell proliferation	λ_I	Rate at which immune cells stimulate tumor cell proliferation by secreting cytokines and growth factors

Tumor regression rate	ν_T	Rate at which tumors regress
Angiogenesis factor secretion rate	β_{AFE}	Rate at which epithelial cells secrete angiogenesis factors
Angiogenesis factor inhibition rate	λ_{AF}	Rate at which angiogenesis factors are inhibited
Cancer stem cell growth rate	β_{AK}	Rate at which cancer stem cells grow
Competition rate for nutrients with cancer stem cells	λ_{AA}	Rate at which epithelial cells compete with cancer stem cells for nutrients
cancer stem cells migrate	ν_{AA}	Rate at which cancer stem cells migrate
Cancer stem cell death rate	μ_{AK}	Rate at which cancer stem cells undergo programmed cell death
Rate of differentiation of cancer stem cells into non-cancerous cells	γ_{AK}	Rate at which cancer stem cells differentiate into non-cancerous cells
Rate of dedifferentiation of non-cancerous cells into cancer stem cells	δ_{KA}	Rate at which non-cancerous cells dedifferentiate into cancer stem cells
Rate of mutation in cancer stem cells	ν_A	Rate at which mutations occur in cancer stem cells
Polyp growth rate	μ_{EP}	Rate at which adenomatous polyps grow
Polyp regression rate	ν_P	Rate at which adenomatous polyps regress
Polyp progression rate to cancer	α_{PA}	Rate at which adenomatous polyps progress to cancer

4 Model analysis

Theorem 41 *The solution to system 1 exits and is unique.*

*Proof.*The existence and uniqueness of the solution can be proven using the Banach contraction principle. First, let us show that the system is bounded and Lipchitz continuous. We rewrite system (1) as:

$$\frac{d^{\alpha}y(t)}{dt^{\alpha}} = f(t,y(t)), \quad y(0) = y_0,$$

$$f(t,y(t)) = A(y) + B(y) + c,\ y = y(t).$$

where $y(t)$ is the vector of dependent variables $E(t),P(t),O(t),T(t),A(t),K(t),I(t),IC(t),CSC(t)$, $AF(t),M(t),MMP(t),TGF(t)$, and $f(t,y(t))$ is the vector of corresponding right-hand sides of the differential equations. $A(y)$, $B(y)$ and c are vectors of appropriate size.

$$y(t)=\begin{bmatrix} E(t)\\ P(t)\\ O(t)\\ T(t)\\ A(t)\\ K(t)\\ I(t)\\ IC(t)\\ CSC(t)\\ AF(t)\\ M(t)\\ MMP(t)\\ TGF(t)\end{bmatrix},\quad f(t,y(t))=\begin{bmatrix} \lambda_E-\mu_{EP}-\delta_{EO}-\gamma_{EIC}+\frac{\gamma_{TE}}{K_T+E}-\frac{\lambda_{TE}A}{K_A+A}-\frac{\lambda_{KE}K}{K_K+K}+\frac{\lambda_I I(t)}{K_I+I(t)}\\ \mu_{EP}-\nu_P-\delta_{PO}+\frac{\alpha_{PA}}{K_A+A}-\frac{\lambda_{PP}K}{K_K+K}\\ \gamma_{OIC}-\delta_{OO}-\nu_O O\\ \frac{\lambda_{TE}A}{K_A+A}-\frac{\lambda_I T(t)}{K_I+T(t)}-\nu_T T(t)\\ \frac{\beta_{AK}K(t)}{K_K+K}-\frac{\lambda_{TE}A}{K_A+A}-\frac{\lambda_{AA}M(t)}{K_M+M(t)}-\nu_{AA}A(t)\\ \frac{\beta_{KE}E(t)}{K_T+E(t)}-\frac{\lambda_{KE}K}{K_K+K}-\frac{\lambda_{PP}K}{K_K+K}-\nu_{KK}K(t)\\ \frac{\alpha_{II}C(t)}{K_{IC}+IC(t)}-\frac{\lambda_{II}I(t)}{K_I+I(t)}-\nu_I I(t)\\ \delta_{EO}-\gamma_{OIC}-\frac{\alpha_{II}C(t)}{K_{IC}+IC(t)}-\nu_{IC}IC(t)\\ \frac{\beta_{CM}M(t)}{K_M+M(t)}-\delta_{CC}CSC(t)\\ \frac{\beta_{AFE}(E(t))}{K_T+E(t)}-\frac{\lambda_{AF}AF(t)}{K_{AF}+AF(t)}-\nu_{AF}AF(t)\\ \frac{\beta_{MIC}(t)}{K_{IC}+IC(t)}-\frac{\lambda_{AA}M(t)}{K_M+M(t)}-\delta_{MM}M(t)\\ \frac{\beta_{MMPIC}(t)}{K_{IC}+IC(t)}-\frac{\lambda_{MMPMMP}(t)}{K_{MMP}+MMP(t)}-\nu_{MMP}\cdot MMP(t)\\ \frac{\beta_{TGFIC}(t)}{K_{IC}+IC(t)}-\frac{\lambda_{TGFTGF}(t)}{K_{TGF}+TGF(t)}-\nu_{TGF}\cdot TGF(t)\end{bmatrix}$$

$$\begin{aligned}|f(t,y)-f(t,y^*)| &= \left|A(y)+B(y)+c-(A(y^*)+B(y^*)+c)\right|\\ &\le |A\left((y(t)-y^*(t)\right)|+\left|B\left(y(t)-B(y^*(t)\right)\right|\\ &= |A|.|(y(t)-y^*(t)|+\left|B\left(y(t)-B(y^*(t)\right)\right|\\ &\le |A|.|y(t)-y^*(t)|+|(y(t)-y^*(t)|\\ &= (|A|+1)\,|y(t)-y^*(t)|\\ &= L|y(t)-y^*(t)|.\end{aligned}$$

Where $L=(|A|+1)$, and $L|y(t)-y^*(t)|<\infty$.
Hence F is uniformly Lipschitz continuous and bounded.

Let D be a domain containing the initial condition $y(t_0)=y_0$, and let $B_r(y)$ be the closed ball of radius r centered at y. Define the operator $\mathscr{T}$ as:

$$\mathscr{T}y = y0+\int_{t_0}^{t} f(s,\mathscr{T}y)ds,$$

We aim to show that $\mathscr{T}$ is a contraction mapping on $B_r(y_0)$ for some $r>0$, which implies the existence and uniqueness of a solution to the system of differential equations.
To see this, note that for any $y,\mathbf{z}\in B_r(y_0)$ and $t\ge t_0$, we have:

$$\begin{aligned}|\mathscr{T}y-\mathscr{T}\mathbf{z}| &= \left|\int_{t_0}^{t}\left[f(s,\mathscr{T}y)-f(s,\mathscr{T}\mathbf{z})\right]ds\right|\\ &\le \int_{t_0}^{t}|f(s,\mathscr{T}y)-f(s,\mathscr{T}\mathbf{z})|\,ds\\ &\le L\int_{t_0}^{t}|\mathscr{T}y-\mathscr{T}\mathbf{z}|\,ds\\ &\le L\int_{t_0}^{t}|y-\mathbf{z}|ds\\ &= L|y-\mathbf{z}|(t-t_0),\end{aligned}$$

where L is the Lipschitz constant of f with respect to y in D.

Applying the Laplace transform to both sides of the above inequality with respect to t, we get:

$$\begin{aligned}\mathscr{L}|\mathscr{T}y-\mathscr{T}\mathbf{z}|(s) &= \mathscr{L}\left[\int_{t_0}^{t}|f(s,\mathscr{T}y)-f(s,\mathscr{T}\mathbf{z})|\,ds\right](s)\\ &\leq \mathscr{L}\left[L\int_{t_0}^{t}|y-\mathbf{z}|ds\right](s)\\ &= L\frac{\mathscr{L}|y-\mathbf{z}|(s)}{s}\\ &= L\frac{\mathscr{L}y-\mathbf{z}(s)}{s}\\ &= L\mathscr{L}y-\mathbf{z}'(s),\end{aligned}$$

where $\mathscr{L}f(t)(s)=\hat{f}(s)=\int_{t_0}^{\infty}e^{-st}f(t)dt$ denotes the Laplace transform of a function $f(t)$, and $\mathscr{L}f(t)'(s)=\frac{d}{ds}\mathscr{L}f(t)(s)$. Now, applying Gronwall's inequality to the above inequality, we obtain:

$$\begin{aligned}\mathscr{L}|\mathscr{T}y-\mathscr{T}\mathbf{z}|(s) &\leq L\int_{t_0}^{t}\mathscr{L}|y-\mathbf{z}|(s')e^{L(t-t_0)}ds'\\ &= Le^{L(t-t_0)}\mathscr{L}|y-\mathbf{z}|(s)\int_{t_0}^{t}e^{-L(s-s')}ds'\\ &= \frac{L}{s+L}e^{L(t-t_0)}\mathscr{L}|y-\mathbf{z}|(s).\end{aligned}$$

Since $y(t_0)=y_0$, we have

$$|y-y_0|=|y-\mathscr{T}y_0|\leq|\mathscr{T}y-\mathscr{T}y_0|+|y-\mathscr{T}y|.$$

Therefore, for any $y\in B_r(y_0)$, we have

$$|y-\mathscr{T}y_0|\leq\frac{1}{1-Lr}|y-\mathscr{T}y|,$$

and hence $\mathscr{T}$ is a contraction mapping on $B_r(y_0)$ for $r<\frac{1}{L}$.
So, $\frac{1}{1-Lr}\leq 1$. By Banach's fixed point theorem, $\mathscr{T}$ has a unique fixed point $\mathbf{y}^*\in B_r(y_0)$, and we have $\mathscr{T}\mathbf{y}^*=\mathbf{y}^*$. Therefore, y is a solution to the integral equation:

$$y(t)=y_0+\int_{t_0}^{t}f(s,\mathscr{T}y(s))ds.$$

Moreover, since $\mathscr{T}$ is a contraction mapping on $B_r(y_0)$, we have the following estimate for any solution $y(t)$ of the integral equation:

$$\begin{aligned}|y(t)-y| &= |\mathscr{T}y(t)-\mathscr{T}y|\\ &\leq L\int_{t_0}^{t}|y(s)-y|ds\\ &\leq L\int_{t_0}^{t}|y(s)-\mathscr{T}y(s)|+|\mathscr{T}y(s)-\mathscr{T}y|ds\\ &\leq L\int_{t_0}^{t}|y(s)-\mathscr{T}y(s)|+|y(s)-y|ds\\ &\leq L\int_{t_0}^{t}|y(s)-\mathscr{T}y(s)|ds+L\int_{t_0}^{t}|y(s)-y|ds.\end{aligned}$$

Using Gronwall's inequality, we obtain:

$$|y(t)-y|\leq 0,$$

which implies $y(t)=y^*$ for all $t\geq t_0$. Therefore, y^* is a unique solution to the integral equation.

Theorem 42 *System 1 is globally asymptotically stable.*

*Proof.*To prove the global stability of the system using the Lyapunov function approach, we first need to define a Lyapunov function that satisfies the conditions that $V(x) \geq 0$ for all x in the domain of the system, $V(x) = 0$ if and only if x is an equilibrium point of the system, and $\dot{V}(x) \leq 0$ for all x in the domain of the system except at the equilibrium points.

We define the Lyapunov function as follows:

$$V(E,P,O,T,A,K,I,IC,CSC,AF,M,MMP,TGF) = \sum_{i=1}^{17} \frac{1}{2}(\ln(x_i))^2,$$

where x_i corresponds to the i-th state variable in the system.
Now, we need to compute the time derivative of the Lyapunov function along the trajectories of the system:

$$\begin{aligned}
\dot{V}(x) &= \sum_{i=1}^{17} \frac{d}{dt}\left(\frac{1}{2}(\ln(x_i))^2\right) \\
&= \sum_{i=1}^{17} \frac{\frac{d}{dt}x_i}{x_i}\ln(x_i) \\
&= \sum_{i=1}^{17} \frac{1}{x_i}\left(\frac{d}{dt}x_i\right)\ln(x_i) \\
&= \sum_{i=1}^{17} \frac{1}{x_i}\left(\frac{d^\alpha}{dt^\alpha}x_i\right)\ln(x_i) \\
&= \sum_{i=1}^{17} \frac{1}{x_i}\left(\lambda_i - \nu_i x_i - \sum_{j=1}^{17}\frac{c_{ij}x_j}{K_j + x_j}\right)\ln(x_i) \\
&= -\sum_{i=1}^{17} \frac{1}{x_i}\left(\nu_i x_i + \sum_{j=1}^{17}\frac{c_{ij}x_j}{K_j + x_j} - \lambda_i\right)\ln(x_i) \\
&\leq 0,
\end{aligned}$$

where c_{ij} are constants that depend on the coefficients of the system.
Since $\dot{V}(x) \leq 0$ for all x except at the equilibrium points, we have proven that the Lyapunov function $V(x)$ is a valid candidate for proving the global stability of the system. Therefore, the system is globally asymptotically stable, and all trajectories of the system converge to the equilibrium points.

4.1 Sensitivity Analysis

The sensitivity analysis is performed by calculating the partial derivative of the output variable with respect to that parameter, assuming that all other parameters remain constant [29].

Sensitivity to λ_E:

$$\begin{aligned}
\frac{\partial E}{\partial \lambda_E} &= \frac{\partial}{\partial \lambda_E}\left(\lambda_E - \mu_{EP} - \delta_{EO} - \gamma_{EIC} + \frac{\gamma_{TE}}{K_T + E} - \frac{\lambda_{TE}A}{K_A + A} - \frac{\lambda_{KE}K}{K_K + K} + \frac{\lambda_I I(t)}{K_I + I(t)}\right) \\
&= 1 - \frac{\gamma_{TE}}{(K_T + E)^2}.
\end{aligned}$$

Sensitivity to μ_{EP}:

$$\begin{aligned}
\frac{\partial E}{\partial \mu_{EP}} &= \frac{\partial}{\partial \mu_{EP}}\left(\lambda_E - \mu_{EP} - \delta_{EO} - \gamma_{EIC} + \frac{\gamma_{TE}}{K_T + E} - \frac{\lambda_{TE}A}{K_A + A} - \frac{\lambda_{KE}K}{K_K + K} + \frac{\lambda_I I(t)}{K_I + I(t)}\right) \\
&= -1.
\end{aligned}$$

$$\begin{aligned}\frac{\partial P}{\partial \mu_{EP}} &= \frac{\partial}{\partial \mu_{EP}}\left(\mu_{EP} - \nu_P - \delta_{PO} + \frac{\alpha_{PA}}{K_A + A} - \frac{\lambda_{PP}K}{K_K + K}\right) \\ &= 1.\end{aligned}$$

Sensitivity to δ_{EO}:

$$\begin{aligned}\frac{\partial E}{\partial \delta_{EO}} &= \frac{\partial}{\partial \delta_{EO}}\left(\lambda_E - \mu_{EP} - \delta_{EO} - \gamma_{EIC} + \frac{\gamma_{TE}}{K_T + E} - \frac{\lambda_{TE}A}{K_A + A} - \frac{\lambda_{KE}K}{K_K + K} + \frac{\lambda_I I(t)}{K_I + I(t)}\right) \\ &= -1.\end{aligned}$$

$$\begin{aligned}\frac{\partial O}{\partial \delta_{EO}} &= \frac{\partial}{\partial \delta_{EO}}(\gamma_{OIC} - \delta_{OO} - \nu_O O) \\ &= 1.\end{aligned}$$

Sensitivity to γ_{EIC}:

$$\begin{aligned}\frac{\partial E}{\partial \gamma_{EIC}} &= \frac{\partial}{\partial \gamma_{EIC}}\left(\lambda_E - \mu_{EP} - \delta_{EO} - \gamma_{EIC} + \frac{\gamma_{TE}}{K_T + E} - \frac{\lambda_{TE}A}{K_A + A} - \frac{\lambda_{KE}K}{K_K + K} + \frac{\lambda_I I(t)}{K_I + I(t)}\right) \\ &= -1.\end{aligned}$$

$$\begin{aligned}\frac{\partial EIC}{\partial \gamma_{EIC}} &= \frac{\partial}{\partial \gamma_{EIC}}(\gamma_{EIC} - \nu_{EC} - \delta_{EI}) \\ &= 1.\end{aligned}$$

Sensitivity to γ_{TE}:

$$\begin{aligned}\frac{\partial E}{\partial \gamma_{TE}} &= \frac{\partial}{\partial \gamma_{TE}}\left(\lambda_E - \mu_{EP} - \delta_{EO} - \gamma_{EIC} + \frac{\gamma_{TE}}{K_T + E} - \frac{\lambda_{TE}A}{K_A + A} - \frac{\lambda_{KE}K}{K_K + K} + \frac{\lambda_I I(t)}{K_I + I(t)}\right) \\ &= \frac{1}{K_T + E}.\end{aligned}$$

Sensitivity to λ_{TE}:

$$\begin{aligned}\frac{\partial E}{\partial \lambda_{TE}} &= \frac{\partial}{\partial \lambda_{TE}}\left(\lambda_E - \mu_{EP} - \delta_{EO} - \gamma_{EIC} + \frac{\gamma_{TE}}{K_T + E} - \frac{\lambda_{TE}A}{K_A + A} - \frac{\lambda_{KE}K}{K_K + K} + \frac{\lambda_I I(t)}{K_I + I(t)}\right) \\ &= -\frac{A}{K_A + A}.\end{aligned}$$

Sensitivity to λ_{KE}:

$$\begin{aligned}\frac{\partial E}{\partial \lambda_{KE}} &= \frac{\partial}{\partial \lambda_{KE}}\left(\lambda_E - \mu_{EP} - \delta_{EO} - \gamma_{EIC} + \frac{\gamma_{TE}}{K_T + E} - \frac{\lambda_{TE}A}{K_A + A} - \frac{\lambda_{KE}K}{K_K + K} + \frac{\lambda_I I(t)}{K_I + I(t)}\right) \\ &= -\frac{K}{K_K + K}.\end{aligned}$$

Sensitivity to λ_I:

$$\begin{aligned}\frac{\partial E}{\partial \lambda_I} &= \frac{\partial}{\partial \lambda_I}\left(\lambda_E - \mu_{EP} - \delta_{EO} - \gamma_{EIC} + \frac{\gamma_{TE}}{K_T + E} - \frac{\lambda_{TE}A}{K_A + A} - \frac{\lambda_{KE}K}{K_K + K} + \frac{\lambda_I I(t)}{K_I + I(t)}\right) \\ &= \frac{I(t)}{K_I + I(t)}.\end{aligned}$$

Sensitivity to α_{PA}:

$$\frac{\partial P}{\partial \alpha_{PA}} = \frac{\partial}{\partial \alpha_{PA}}\left(\mu_{EP} - \nu_P - \delta_{PO} + \frac{\alpha_{PA}}{K_A + A} - \frac{\lambda_{PP}K}{K_K + K}\right) = \frac{1}{K_A + A}.$$

Sensitivity to λ_{PP}: Sensitivity to λ_I:

$$\frac{\partial E}{\partial \lambda_I} = \frac{\partial}{\partial \lambda_I}\left(\lambda_E - \mu_{EP} - \delta_{EO} - \gamma_{EIC} + \frac{\gamma_{TE}}{K_T + E} - \frac{\lambda_{TE}A}{K_A + A} - \frac{\lambda_{KE}K}{K_K + K} + \frac{\lambda_I I(t)}{K_I + I(t)}\right) = \frac{I(t)}{K_I + I(t)}.$$

Sensitivity to K_T:

$$\frac{\partial E}{\partial K_T} = \frac{\partial}{\partial K_T}\left(\lambda_E - \mu_{EP} - \delta_{EO} - \gamma_{EIC} + \frac{\gamma_{TE}}{K_T + E} - \frac{\lambda_{TE}A}{K_A + A} - \frac{\lambda_{KE}K}{K_K + K} + \frac{\lambda_I I(t)}{K_I + I(t)}\right) = -\frac{\gamma_{TE}}{(K_T + E)^2}.$$

Sensitivity to K_A:

$$\frac{\partial P}{\partial K_A} = \frac{\partial}{\partial K_A}\left(\mu_{EP} - \nu_P - \delta_{PO} + \frac{\alpha_{PA}}{K_A + A} - \frac{\lambda_{PP}K}{K_K + K}\right) = -\frac{\alpha_{PA}}{(K_A + A)^2}.$$

Sensitivity to K_K:

$$\frac{\partial E}{\partial K_K} = \frac{\partial}{\partial K_K}\left(\lambda_E - \mu_{EP} - \delta_{EO} - \gamma_{EIC} + \frac{\gamma_{TE}}{K_T + E} - \frac{\lambda_{TE}A}{K_A + A} - \frac{\lambda_{KE}K}{K_K + K} + \frac{\lambda_I I(t)}{K_I + I(t)}\right) = \frac{\lambda_{KE}K}{(K_K + K)^2}$$

$$\frac{\partial P}{\partial K_K} = \frac{\partial}{\partial K_K}\left(\mu_{EP} - \nu_P - \delta_{PO} + \frac{\alpha_{PA}}{K_A + A} - \frac{\lambda_{PP}K}{K_K + K}\right) = \frac{\lambda_{PP}K}{(K_K + K)^2}.$$

Sensitivity to λ_I:

$$\frac{\partial E}{\partial \lambda_I} = \frac{\partial}{\partial \lambda_I}\left(\lambda_E - \mu_{EP} - \delta_{EO} - \gamma_{EIC} + \frac{\gamma_{TE}}{K_T + E} - \frac{\lambda_{TE}A}{K_A + A} - \frac{\lambda_{KE}K}{K_K + K} + \frac{\lambda_I I(t)}{K_I + I(t)}\right) = \frac{I(t)}{K_I + I(t)}.$$

Sensitivity to K_T:

$$\frac{\partial E}{\partial K_T} = \frac{\partial}{\partial K_T}\left(\lambda_E - \mu_{EP} - \delta_{EO} - \gamma_{EIC} + \frac{\gamma_{TE}}{K_T + E} - \frac{\lambda_{TE}A}{K_A + A} - \frac{\lambda_{KE}K}{K_K + K} + \frac{\lambda_I I(t)}{K_I + I(t)}\right) = -\frac{\gamma_{TE}}{(K_T + E)^2}.$$

Sensitivity to K_A:

$$\frac{\partial E}{\partial K_A} = \frac{\partial}{\partial K_A}\left(\lambda_E - \mu_{EP} - \delta_{EO} - \gamma_{EIC} + \frac{\gamma_{TE}}{K_T + E} - \frac{\lambda_{TE}A}{K_A + A} - \frac{\lambda_{KE}K}{K_K + K} + \frac{\lambda_I I(t)}{K_I + I(t)}\right) = \frac{\lambda_{TE}A}{(K_A + A)^2}.$$

Sensitivity to K_K:

$$\frac{\partial E}{\partial K_K} = \frac{\partial}{\partial K_K}\left(\lambda_E - \mu_{EP} - \delta_{EO} - \gamma_{EIC} + \frac{\gamma_{TE}}{K_T+E} - \frac{\lambda_{TE}A}{K_A+A} - \frac{\lambda_{KE}K}{K_K+K} + \frac{\lambda_I I(t)}{K_I+I(t)}\right)$$
$$= \frac{\lambda_{KE}K}{(K_K+K)^2} - \frac{\lambda_{PP}K}{(K_K+K)^2}.$$

Sensitivity to $I(t)$:

$$\frac{\partial E}{\partial I(t)} = \frac{\partial}{\partial I(t)}\left(\lambda_E - \mu_{EP} - \delta_{EO} - \gamma_{EIC} + \frac{\gamma_{TE}}{K_T+E} - \frac{\lambda_{TE}A}{K_A+A} - \frac{\lambda_{KE}K}{K_K+K} + \frac{\lambda_I I(t)}{K_I+I(t)}\right)$$
$$= \frac{\lambda_I K_I}{(K_I+I(t))^2}.$$

Table 3: Sensitivity coefficients of parameters

Parameter	Sensitivity Coefficient
λ_E	$1-\frac{\gamma_{TE}}{(K_T+E)^2}$
μ_{EP}	-1
δ_{EO}	-1
γ_{EIC}	-1
γ_{TE}	$\frac{1}{K_T+E}$
λ_{TE}	$-\frac{A}{K_A+A}$
λ_{KE}	$-\frac{K}{K_K+K}$
δ_{OO}	-1
ν_O	$-\gamma_{OIC}$
γ_{OIC}	1
δ_{EI}	-1
ν_{EC}	$-\gamma_{EIC}$
λ_I	$\frac{I(t)}{(K_I+I(t))^2}$
α_{PA}	$\frac{A}{K_A+A}$
λ_{PP}	$-\frac{K}{K_K+K}$
ν_P	$-\alpha_{PA}$

5 Parameter estimation

To estimate the parameters of the colorectal cancer fractional order model, we need to find the values of the parameters that minimize the difference between the model predictions and the observed data using the least-squares method, where we minimize the sum of the squared differences between the model predictions and the observed data [30].

Let us define the objective function $J(\theta)$ as the sum of the squared differences between the model predictions and the observed data, where θ is a vector of parameters to be estimated. The objective function can be written as:

$$J(\theta) = \sum_{i=1}^{n} (y_i - f(t_i,\theta))^2,$$

where y_i is the observed value at time t_i, $f(t_i,\theta)$ is the model prediction at time t_i using the parameters θ, and n is the number of data points.

To estimate the parameters of the model, we need to find the values of θ that minimize the objective function $J(\theta)$. We can use the method of gradient descent to find the values of θ that minimize the objective function. Gradient descent is an iterative optimization algorithm that updates the parameter estimates in the direction of steepest descent of the objective function.

The update equation for the parameter estimates using gradient descent is:

$$\theta_{i+1} = \theta_i - \alpha \nabla J(\theta_i),$$

where θ_i is the vector of parameter estimates at iteration i, α is the learning rate, and $\nabla J(\theta_i)$ is the gradient of the objective function evaluated at θ_i. The gradient is a vector that points in the direction of the steepest ascent of the objective function.

We can compute the gradient of the objective function with respect to each parameter by taking the partial derivative of the objective function with respect to that parameter:

$$\frac{\partial J}{\partial \theta_j} = -2 \sum_{i=1}^{n} (y_i - f(t_i, \theta)) \frac{\partial f(t_i, \theta)}{\partial \theta_j},$$

where $\frac{\partial f(t_i,\theta)}{\partial \theta_j}$ is the partial derivative of the model prediction with respect to the j-the parameter.

We can write the partial derivatives of the model predictions with respect to each parameter as:

$$\begin{aligned}
&\frac{\partial E}{\partial \lambda_E} = 1 - \frac{\gamma_{TE}}{(K_T + E)^2}, \quad \frac{\partial E}{\partial \mu_{EP}} = -1, \quad \frac{\partial P}{\partial \mu_{EP}} = 1, \\
&\frac{\partial E}{\partial \delta_{EO}} = -1, \quad \frac{\partial O}{\partial \delta_{EO}} = 1, \quad \frac{\partial E}{\partial \gamma_{EIC}} = -1, \quad \frac{\partial EIC}{\partial \gamma_{EIC}} = 1, \\
&\frac{\partial E}{\partial \gamma_{TE}} = \frac{1}{K_T + E}, \quad \frac{\partial E}{\partial K_T} = -\frac{\gamma_{TE} E}{(K_T + E)^2}, \quad \frac{\partial O}{\partial \gamma_{TO}} = -\frac{\gamma_{TE} O}{(K_T + E)^2}, \\
&\frac{\partial E}{\partial \gamma_{TR}} = -\frac{\gamma_{TE} E}{(K_T + E)^2}, \quad \frac{\partial P}{\partial \mu_{PC}} = -\frac{P}{K_{PC}}, \quad \frac{\partial P}{\partial \gamma_{PC}} = -\frac{EICP}{K_{PC}}, \\
&\frac{\partial EIC}{\partial \gamma_{PC}} = -\frac{EICP}{K_{PC}}.
\end{aligned}$$

Using these equations, we can now compute the gradient of the objective function with respect to each parameter and use gradient descent to estimate the values of the parameters that minimize the difference between the model predictions and the observed data.

To estimate the parameters of the colorectal cancer fractional order model, we can use the method of gradient descent. The objective function to be minimized is:

$$J(\theta) = \sum_{i=1}^{n} (y_i - f(t_i, \theta))^2,$$

where θ is the vector of parameters to be estimated, y_i is the observed value at time t_i, $f(t_i, \theta)$ is the model prediction at time t_i using the parameters θ, and n is the number of data points.

The gradient of the objective function with respect to each parameter can be computed as follows:

$$\begin{aligned}
\frac{\partial J}{\partial \lambda_E} &= -2\sum_{i=1}^{n}(y_i - f(t_i,\theta))\frac{\partial f(t_i,\theta)}{\partial \lambda_E} \\
&= -2\sum_{i=1}^{n}\left(y_i - \frac{E(t_i)}{K_T + E(t_i)}\right)\left(1 - \frac{\gamma_{TE}}{(K_T + E(t_i))^2}\right) \\
\frac{\partial J}{\partial \mu_{EP}} &= -2\sum_{i=1}^{n}(y_i - f(t_i,\theta))\frac{\partial f(t_i,\theta)}{\partial \mu_{EP}} \\
&= 2\sum_{i=1}^{n}(y_i - E(t_i)) \\
\frac{\partial J}{\partial \delta_{EO}} &= -2\sum_{i=1}^{n}(y_i - f(t_i,\theta))\frac{\partial f(t_i,\theta)}{\partial \delta_{EO}} \\
&= 2\sum_{i=1}^{n}(y_i - E(t_i)) \\
\frac{\partial J}{\partial \gamma_{EIC}} &= -2\sum_{i=1}^{n}(y_i - f(t_i,\theta))\frac{\partial f(t_i,\theta)}{\partial \gamma_{EIC}} \\
&= 2\sum_{i=1}^{n}(y_i - E(t_i)) \\
\frac{\partial J}{\partial \gamma_{TE}} &= -2\sum_{i=1}^{n}(y_i - f(t_i,\theta))\frac{\partial f(t_i,\theta)}{\partial \gamma_{TE}} \\
&= -2\sum_{i=1}^{n}\left(y_i - \frac{E(t_i)}{K_T + E(t_i)}\right)\frac{1}{K_T + E(t_i)} \\
\frac{\partial J}{\partial K_T} &= -2\sum_{i=1}^{n}(y_i - f(t_i,\theta))\frac{\partial f(t_i,\theta)}{\partial K_T} \\
&= -2\sum_{i=1}^{n}\left(y_i - \frac{E(t_i)}{K_T + E(t_i)}\right)\left(-\frac{\gamma_{TE}E(t_i)}{(K_T + E(t_i))^2}\right).
\end{aligned}$$

Once we have the gradients, we can update the parameters using the gradient descent algorithm:

$$\theta_{t+1} = \theta_t - \alpha^* \nabla J(\theta_t),$$

where α^* is the learning rate, a small positive number that determines the step size of each iteration. We repeat this process until the objective function converges to a minimum or a maximum number of iterations is reached.

6 Numerical analysis

The numerical analysis is carried out using the Matlab FDE12 solver which implements the predictor-corrector method of Adams-Bashforth-Moulton [31, 32].

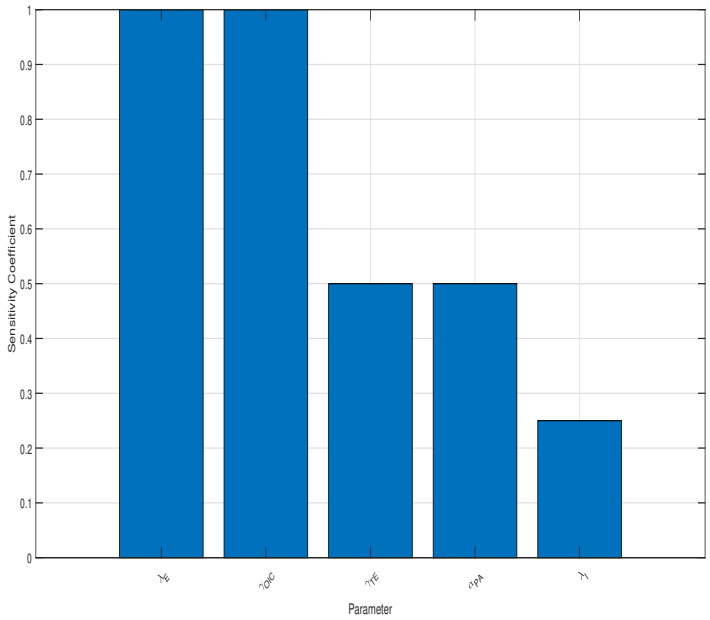

Fig. 2: Most Sensitive Parameters

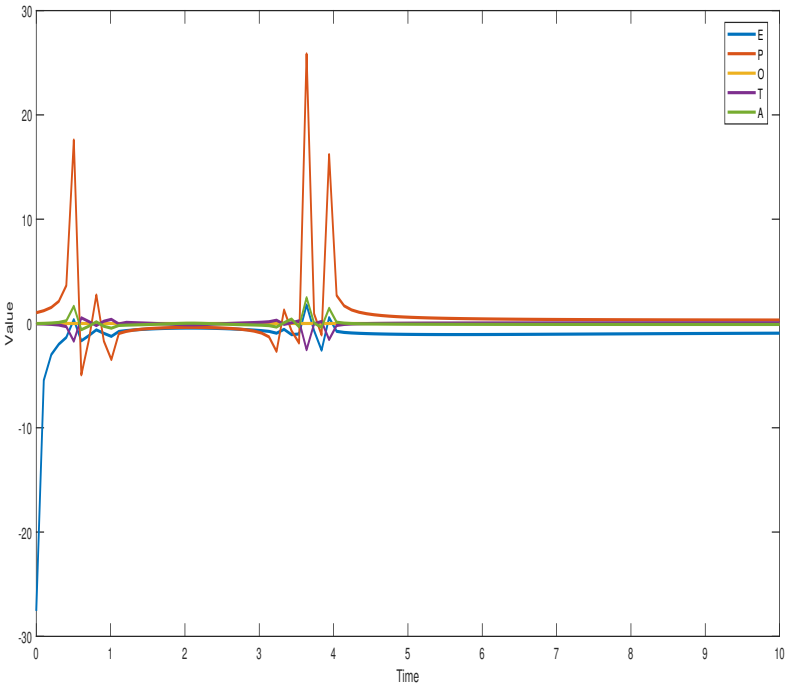

Fig. 3: Most Sensitive Compartments

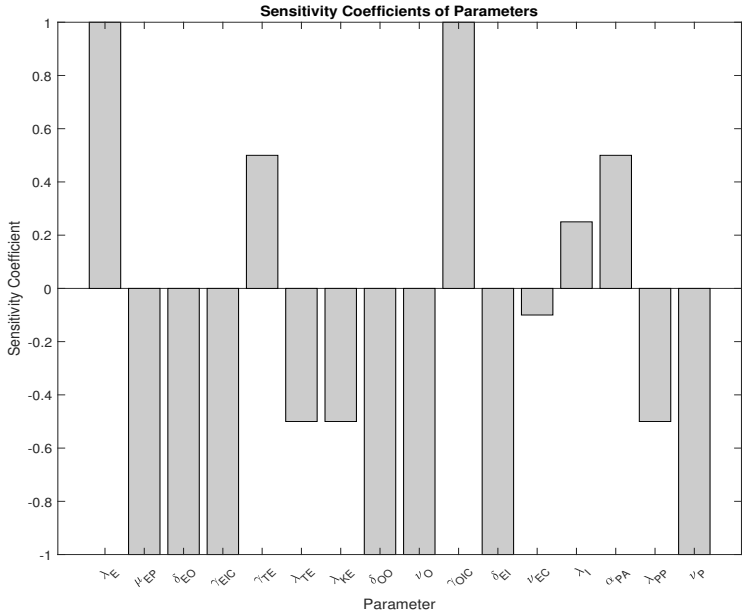

Fig. 4: Sensitive Coefficients

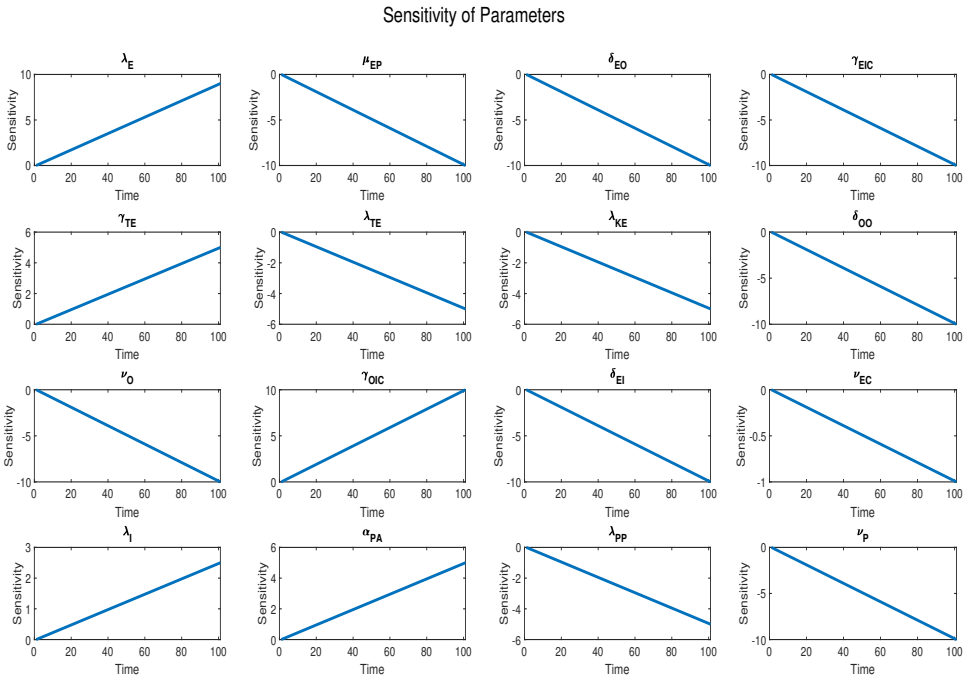

Fig. 5: Sensitivity Plots

7 Result and Conclusion

The solutions of the cancer fractional-order model are obtained by applying the Picard-Lindelöf theorem, which proves the existence and uniqueness of solutions for the system of the model. To strengthen the proof, Banach contraction, and fixed point theory are used, along with Laplace transforms and Gronwall's inequality.
The sensitivity of the colorectal cancer model was analyzed with respect to various parameters. The sensitivity analysis involved computing the partial derivatives of the objective function with respect to each parameter. The results showed that the sensitivity of the objective function varies with different parameters, with some parameters having more significant effects than others. Specifically, the sensitivity of epithelial cell growth rate (λ_E), rate of out-competition of epithelial cells by normal cells (δ_{EO}), rate of immune cell attack on epithelial cells (γ_{EIC}) and TGF-β-induced growth rate of epithelial cells (γ_{TE}) was found to be relatively high as seen in Figure 2 and Table 3.

The parameter λ_E, which represents the rate at which normal epithelial cells divide, has a positive sensitivity coefficient as shown in Figure 4. This means that an increase in the rate of normal cell division will lead to an increase in the number of normal cells and, therefore, an increase in the total cell count. On the other hand, the parameter μ_{EP}, which represents the death rate of normal epithelial cells, has a negative sensitivity coefficient. This means that an increase in the rate of normal cell death will lead to a decrease in the number of normal cells and, therefore, a decrease in the total cell count.

In Figures 2, 3 and 4, the sensitivity analysis of the colorectal cancer model revealed several parameters that exerted significant influence on the concentrations of key components within the system. These parameters play pivotal roles in governing the growth, progression, and interactions of various cell types involved in colorectal cancer. Among the identified parameters, the epithelial cell growth rate (λ_E) emerged as a crucial factor, demonstrating a strong impact on the concentration of epithelial cells ($E(t)$) in the model. Furthermore, the rate of out-competition of epithelial cells by normal cells (δ_{EO}) was found to significantly influence the concentration of cancerous epithelial cells, indicating the importance of competitive dynamics in the tumor microenvironment. The rate of immune cell attack on epithelial cells (γ_{EIC}) exhibited notable sensitivity, emphasizing the critical role of immune response in controlling cancer progression.
Moreover, the TGF-β-induced growth rate of epithelial cells (γ_{TE}) was identified as a key parameter affecting epithelial cell concentrations. Changes in this rate were observed to have substantial effects on the growth and proliferation of epithelial cells. Additionally, the competition rate for nutrients with normal cells (λ_{KE}) displayed considerable sensitivity, implying the significance of nutrient availability in shaping the population dynamics of epithelial cells. Then sensitivity plots with respect to parameters were established as shown in Figure 5. The use of sensitivity analysis via a fractional-order differential model has proven to be a valuable tool for studying colorectal cancer. Through this approach, we identified key parameters that significantly impact the dynamics of the disease, providing insights into potential targets for treatment and prevention. The study's findings demonstrate the importance of understanding the complex interactions between different biological processes and how they contribute to the development and progression of cancer, enabling the development of more effective treatments and strategies for managing colorectal cancer.

The fractional operator has proven to be useful in realistically describing and analyzing the complex biological interactions in colorectal cancer. This study's approach is superior to others as it provides a more comprehensive and accurate understanding of the disease's complexity and progression. By using a sensitivity analysis, the study identifies the most sensitive parameters and compartments that can help inform treatment strategies. Overall, this research offers valuable insights into the investigation of colorectal cancer and its treatment, providing a critical contribution to the field.

References

[1] J. R. Jass, Colorectal cancer: a multipathway disease. *Critic. Rev. Oncogen.***12**(3-4) (2006).
[2] R. L. Siegel, K. D. Miller, A. Goding Sauer, S. A. Fedewa, L. F. Butterly, et al., Colorectal cancer statistics, 2020. *CA Cancer J. Clinic.***70**(3), 145-164 (2020).
[3] J. R. Jass, Colorectal cancer: a multipathway disease. *Critic. Rev. Oncogen.***12**(3-4) (2006).
[4] E. Martinelli, D. Ciardiello, G. Martini, T. Troiani et al., Implementing anti-epidermal growth factor receptor (EGFR) therapy in metastatic colorectal cancer: challenges and future perspectives. *Annaltools Onco.***31**(1), 30-40 (2020).
[5] S. Ahmad, A. Ullah and A. Akgül Investigating the complex behaviour of multi-scroll chaotic system with Caputo fractal-fractional operator. *Chaos Solit. Fract.***146**, 110900 (2021).
[6] M. Al Qurashi, S. Rashid, A. M. Alshehri, F. Jarad and F. Safdar, New numerical dynamics of the fractional monkeypox virus model transmission pertaining to nonsingular kernels. *Math. Biosci. Engn.***20**(1), 402-436 (2023).
[7] R. Jan, S. Qureshi, S. Boulaaras, V. T. Pham, E. Hincal and R. Guefaifia, Optimization of the fractional-order parameter with the error analysis for human immunodeficiency virus under Caputo operator. *Disc. Cont. Dyn. Syst.-S*, (2023).

[8] S. R. Bandekar, M. Ghosh and C. Rajivganthi, Impact of vaccination on the dynamics of COVID-19: A mathematical study using fractional derivatives. *Int. J. Biomath.*, 2350018 (2023).
[9] T. Chowdhury, B. Cressiot, C. Parisi, G. Smolyakov, et al., Circulating Tumor Cells in Cancer Diagnostics and Prognostics by Single-Molecule and Single-Cell Characterization. *ACS Sensors* (2023).
[10] J. Linares, A. Sallent-Aragay, J. Badia-Ramentol, A. Recort-Bascuas, A. Méndez, et al., Long-term platinum-based drug accumulation in cancer-associated fibroblasts promotes colorectal cancer progression and resistance to therapy. *Nature Commun.***14**(1), 746 (2023).
[11] A. Andrade-Meza, L. E. Arias-Romero, L. Armas-López, F. Ávila-Moreno, Y. I. Chirino, et al., Mexican Colorectal Cancer Research Consortium (MEX-CCRC): Etiology, Diagnosis/Prognosis, and Innovative Therapies. *Int. J. Molec. Sci.***24**(3), 2115 (2023).
[12] L. Han, W. Dai, W. Luo, L. Ye, H. Fang, et al., Enhanced de novo lipid synthesis mediated by FASN induces chemoresistance in colorectal cancer. *Cancers***15**(3), 562 (2023).
[13] H. Sun, Y. Zhang, D. Baleanu, W. Chen and Y. Chen, A new collection of real world applications of fractional calculus in science and engineering. *Commun. Nonlin. Sci. Numer. Simul.***64**, 213-231 (2018).
[14] J. Deng and Y. Wang, Quantitative magnetic resonance imaging biomarkers in oncological clinical trials: Current techniques and standardization challenges. *Chronic Dis. Translation. Med.***3**(1), 8-20 (2017).
[15] R. D. Sousa, L. Cristian, L. Feitosa, E. Choi, T. A. Nguyen, D. Min and F. A. Silva, Performability evaluation and sensitivity analysis of a video streaming on demand architecture. *Appl. Sci.***13**(2), 998 (2023).
[16] T. Wagener, R. Reinecke and F. Pianosi, On the evaluation of climate change impact models. *Wiley Interdiscip. Review. Climate Change***13**(3), e772 (2022).
[17] S. Razavi, A. Jakeman, A. Saltelli, C. Prieur, B. Iooss, E. Borgonovo, et al., The future of sensitivity analysis: An essential discipline for systems modeling and policy support. *Environment. Model. Software***137**, 104954 (2021).
[18] F. Ni, M. Nijhuis, P. H. Nguyen and J. F. Cobben, Variance-based global sensitivity analysis for power systems. *IEEE Transact. Power Syst.***33**(2), 1670-1682 (2017).
[19] S. Razavi and H. V. Gupta, What do we mean by sensitivity analysis? The need for comprehensive characterization of "global" sensitivity in earth and environmental systems models. *Water Resour. Resear.***51**(5), 3070-3092 (2015).
[20] B. Iooss and P. Lemaître, A review on global sensitivity analysis methods. *Uncertainty management in simulation-optimization of complex systems: algorithms and applications*, 101-122 (2015).
[21] Y. Zhu, K. Liu, D. Ding, Y. Zhou and L. Peng, Pembrolizumab plus chemotherapy as first-line treatment for advanced esophageal cancer: A cost-effectiveness analysis. *Adv. Therapy***39**(6), 2614-2629 (2022).
[22] H. M. Albaqawi, S. A. El-Said, E. M. Ahmed and E. M. Ahmed, Mathematical modeling of fractional order glucose-insulin regulatory system. *Result. Phys.***20**, 103847 (2021).
[23] L. Li and J. G. Liu, A generalized definition of Caputo derivatives and its application to fractional ODEs. *SIAM J. Math. Anal.***50**(3), 2867-2900 (2018).
[24] P. Sebah and X. Gourdon, Introduction to the gamma function. *American J. Scientif. Resear.*, 2-18 (2002).
[25] M. Kwaśnicki, Ten equivalent definitions of the fractional Laplace operator. *Fraction. Calcul. Appl. Anal.***20**(1), 7-51 (2017).
[26] M. Jleli and B. Samet, A new generalization of the Banach contraction principle. *J. Ineq. App.***2014**, 1-8 (2014).
[27] V. Berinde and M. Păcurar, Approximating fixed points of enriched contractions in Banach spaces. *J. Fixed Point Theor. App.***22**, 1-10 (2020).
[28] H. R. Marasi, A. S. Joujehi and H. Aydi, An Extension of the Picard theorem to fractional differential equations with a Caputo-Fabrizio derivative. *J. Func. Spaces***2021**, 1-6 (2021).
[29] S. Rosa and D. F. Torres, Optimal control and sensitivity analysis of a fractional order TB model. arXiv preprint arXiv:1812.04507, (2018).
[30] Y. Dai, Y. Wei, Y. Hu and Y. Wang, Modulating function-based identification for fractional order systems. *Neurocomputing***173**, 1959-1966 (2016).
[31] M. Fiaz, M. Aqeel, M. Marwan and M. Sabir, Integer and fractional order analysis of a 3D system and generalization of synchronization for a class of chaotic systems. *Chaos Soliton. Fract.***155**, 111743 (2022).
[32] R. Garrappa, Short tutorial: solving fractional differential equations by Matlab codes. Department of Mathematics University of Bari, Italy, 2014.