DOI:10.25092/baunfbed.1498218 *J. BAUN Inst. Sci. Technol., 27(1), 126-144, (2025)*

The relationship between colon cancer and immune system: a fractional order modelling approach

Mehmet YAVUZ[1,2,*], Feyza Nur ÖZDEMİR[3], Kübra AKYÜZ[1], Naime Büşra BAYRAKTAR[1]

[1]*Necmettin Erbakan University, Department of Mathematics and Computer Sciences, Konya, Türkiye*
[2]*Department of Applied Mathematics and Informatics, Kyrgyz-Turkish Manas University, Bishkek 720038, Kyrgyzstan*
[3]*Necmettin Erbakan University, Department of Computer Engineering, Konya, Türkiye*

Geliş Tarihi (Received Date): 09.06.2024
Kabul Tarihi (Accepted Date): 22.10.2024

Abstract

In this paper, a new fractional-order differential equation system is developed for colon cancer to address the detailed analysis. In the model, the interaction between tumor cells, macrophage cells, dendritic cells and CD4+ T helper cells is established using Michaelis-Menten kinetics. In addition, mathematical analyses such as positivity and boundedness are also carried out. Numerical results are obtained to observe the intercellular course of colon cancer and biological interpretations are also included.

Keywords: *Fractional-order mathematical model, colon cancer, colorectal cancer, numerical simulation, Michaelis-Menten kinetics.*

Kolon kanseri ve bağışıklık sistemi ilişkisi: kesirli mertebeden bir modelleme yaklaşımı

Öz

Bu çalışmada, kolon kanseri için detaylı analize yönelik yeni bir kesirli mertebeden diferansiyel denklem sistemi geliştirilmiştir. Modelde tümör hücreleri, makrofaj hücreleri, dendritik hücreler ve CD4+ T yardımcı hücreleri arasındaki etkileşim, Michaelis-Menten kinetiği kullanılarak oluşturulmuştur. Ayrıca pozitiflik ve sınırlılık gibi matematiksel analizler de yapılmaktadır. Kolon kanserinin hücreler arası seyrini

[*]Mehmet YAVUZ, mehmetyavuz@erbakan.edu.tr, https://orcid.org/0000-0002-3966-6518
Feyza Nur ÖZDEMİR, ozdemirfeyzanur1@gmail.com, https://orcid.org/0000-0001-7803-7725
Kübra AKYÜZ, kubraaakyz@gmail.com, https://orcid.org/0009-0006-6642-1117
Naime Büşra BAYRAKTAR, naimebra97@gmail.com, https://orcid.org/0000-0001-7584-437X

gözlemlemeye yönelik sayısal sonuçlar elde edilmekte ve biyolojik yorumlara da yer verilmektedir.

Anahtar kelimeler: *Kesirli mertebeli matematiksel model, kolon kanseri, kolorektal kanser, sayısal simülasyon, Michaelis-Menten kinetiği.*

1. Introduction

The number of comprehensive studies in the literature on colon cancer, which is one of the cancer types that cause the most deaths in the world, is very limited. Cancer is a disease that occurs as a result of uncontrolled and continuous proliferation of cells in a certain part of the body under the influence of various genetic and environmental factors. Colon cancer is a type of cancer that develops in the colon or rectum (large intestine), which is part of the digestive system. Colon cancer is also called colorectal cancer. This term combines colon cancer with rectal cancer, which begins in the rectum. Abnormal cell growth in this area often begins with the development of small, benign tumors called polyps. These polyps are usually not cancerous, but some can turn into colon cancer over time. Since polyps do not cause symptoms in the body, it is of great importance to have regular screening tests. Finding and removing polyps before they turn into cancer helps prevent cancer.

The first 150 cm of the large intestine is called the colon and the last 15 cm is called the rectum [1]. The rectum is the last part connecting the large intestine to the anus. The colon and rectum are the longest part of the large intestine and are responsible for absorbing water from food in the final stages of the digestive process. The large intestine is a part of the digestive system and takes part in the final stage of digestion. Colon cancer symptoms include things like changes in bowel habits, abdominal pain, weight loss, constipation or diarrhea, bloody stools, and fatigue. Risk factors include age, family history, obesity, smoking, alcohol consumption, inadequate fiber intake, and inflammatory bowel disease.

Early diagnosis is important as it can be treated early. Colon cancer is diagnosed by methods such as colonoscopy, sigmoidoscopy, fecal occult blood test and imaging tests. Treatment options include surgery, chemotherapy [59], radiotherapy and targeted therapies. Regular screening tests can help detect colon cancer in its early stages and increase the chances of cure. Although colon cancer can occur at any age, it usually affects older adults.

In the formation of colon cancer; excessive fatty, red meat-based diet, obesity, smoking and alcohol consumption as well as polyps are effective. When polyps are detected in the large intestine during screening colonoscopies, it is possible to prevent the disease by removing them before they become cancerous. Having a history of breast and ovarian cancer in women also increases the risk of colon cancer in these people. It is recommended that people with breast and ovarian cancer be screened for colon cancer before they turn 50 [2].

The risk of developing the disease in people with a family history of colon cancer is 1.7 times higher than in healthy people. The risk is 2.7 times higher in people with more than

two family history of colon cancer. Colon cancer is associated with genetic factors as well as poor nutrition and a sedentary lifestyle [1].

The large intestine consists of 3 parts; the right, left and lower columns are sections with different structures. For this reason, symptoms differ depending on the area where the tumor is located. Since the right colon is wider than the left colon, an obstruction in this area will cause symptoms for a longer time and the disease will progress more latently. Since the left colon is narrower, existing obstruction in the intestine shows symptoms earlier. Polyps in the colon, which do not cause any symptoms at first, become cancerous over time, increase in number and begin to grow in size. Thus, symptoms of colon cancer appear in the person [1].

The first symptoms of colon cancer are usually changes in defecation patterns and unexplained abdominal pain. In colon cancer, bleeding that occurs in the digestive system appears in the stool. Increasing blood loss over time also leads to a decrease in the number of red blood cells, that is, anemia. Changes in defecation patterns manifest themselves as diarrhea or constipation. In colon cancer, the passageway for intestinal movements, called the lumen, is narrowed due to the tumor. The growing tumor can spread to deeper layers. This effect of colon cancer causes changes in bowel defecation habits. The person begins to experience irregular bowel movements, such as constipation, diarrhea, or a feeling that the intestines are not emptying. Tumor formed in the colon may block the colon. Since this blockage in the colon restricts the space for the stool to pass, the stool comes out in a thinner, pencil-like shape compared to its normal form.

Intestinal obstruction caused by a colon or rectal tumor blocking the passage of liquid or solid waste or gas causes abdominal pain, cramping and bloating. In addition, colon cancer affecting the right side of the intestine and colon cancer affecting the left side of the intestine may cause different symptoms. Since the left side of the intestine is a narrower region, complaints such as thinning of the stool, bleeding, and changes in stool pattern are more common in cancers of this region, while on the right side, since the intestine is wider, the cancer progresses insidiously there and takes longer to show symptoms [2].

T.R. for colon cancer, which is among the top 10 cancer types in Türkiye and can cause significant death or disability. The Ministry of Health has initiated the National Colon and Rectum (Colorectal) Cancer Screening Program for people in the target group. In this program, it is stated that the ideal screening method for occult blood in the feces should be performed every 2 years and a colonoscopy should be performed every 10 years. Taking into account Türkiye's conditions, the target audience to be screened is all men and women between the ages of 50-70. For high-risk individuals, screening starts at the age of 40. High-risk individuals are individuals with a first-degree relative with a history of colorectal cancer or adenomatous polyps, ulcerative colitis, Crohn's Disease, or hereditary polyposis or non-polyposis syndrome [1].

Colon cancer diagnosis is made within the framework of a screening program or when the patient consults a physician with colon cancer symptoms. The physician first takes the patient's history and then performs a physical examination.

After the diagnosis of colon cancer is clarified, staging is done. During the staging process, data obtained by radiological imaging methods such as tomography, magnetic

resonance imaging (MRI), chest radiography, positron emission tomography (PET), as well as pathological examination of tissue samples taken from the body are evaluated and the stage of the disease is determined [1].

Colon cancers are staged from 1 to 4. Treatment is applied according to the stage of the disease.

Colon cancer stages are as follows:

- Stage 1: Cancer has invaded (spread) the intestinal wall. However, it could not reach all intestinal layers.
- Stage 2: Cancer has invaded all layers of the intestine.
- Stage 3: Colon cancer has metastasized and spread to the regional lymph nodes.
- Stage 4: Cancer has spread to distant tissues and organs such as the liver, peritoneum and lungs.

For diagnosis, blood tests and fecal occult blood are examined. The collected stool is processed, and the presence of hemoglobin is investigated. If the first sample is positive, false positivity is investigated. For this purpose, examination is carried out in 3 consecutive tests, with 2 samples taken in each test. Blood tests: In addition to blood tests for anemia and general condition evaluation, carcinoembryonic antigen (CEA), which is a cancer marker, is requested. Although CEA is not specific for colon cancer, its elevation gives a clue for colon cancer. CEA level is used in disease monitoring after treatment.

Colonoscopy is an endoscopy instrument with light and helps to examine the inner surface of the large intestine in detail. Thanks to colonoscopy, which allows detecting existing lesions in the intestine and taking biopsies from the lesions, the tissue piece taken is examined in a laboratory environment. Depending on the pathological diagnosis, the person is diagnosed with colon cancer.

In recent years, it is possible to detect colon cancer at an early stage by looking at the genetic codes that come with the feces from polyps suitable for cancer in the large intestines, called fecal DNA.

Double contrast barium enema (enema): In this diagnostic method, the intestinal mucosa is coated with barium, air is injected into the colon through a catheter from the rectum, and many radiographs are taken under fluoroscopy. Patients should undergo bowel preparation before the examination. Sedation is usually not performed. Patients may feel cramp-like pain during the procedure, but they can return to work after the procedure. The examination can detect half of adenomas larger than 1 cm and 39 percent of all polyps [1].

Among imaging methods, ultrasonography has lower sensitivity. It may miss small-diameter polyps, but it may raise the physician's suspicion by showing non-specific findings such as increased intestinal wall thickening. There have been many studies in the literature on mathematical modelling of colon cancer. Some of them are given below:

Johnston et al. [3] modeled the dynamics of the cell population in colon crypt and colorectal cancer. The models they established as a result of their study revealed that increased cell renewal, which is equivalent to cell differentiation or cell death, can cause cancer to grow. Li et al. [4] pointed out that tumor heterogeneity is a major problem for

treatment and cancer research. Therefore, they built and analyzed a mathematical model, taking into account all possible mutation sequences in the APC and TP53 driver genes, which are important for colon cancer. Lo et al. [5] created a mathematical model of colitis-associated colon cancer for the first time. They emphasized that this study they created could be an informative resource for the early stage of colon cancer. Delilata and Lorenzi [6] developed a model that explains cancer dynamics in a cellular way. Their results showed that stem cells play an important role in cancer treatment.

Amilo et al. [7] wrote a fractional-order model to analyze metastatic colorectal cancer dynamics. In their studies, they covered basics such as immune response and tumor growth. As a result, the study helps in the treatment of colorectal cancer and the development of special drugs for colorectal cancer patients. Paterson et al. [8] analyzed a stochastic transformation model in the colon that quantifies the process of colorectal carcinogenesis through loss of tumor suppressors and gain of oncogenes in patients. In the study, they used experimentally measured mutation rates in the colon and the growth advantages provided by driver mutations. It has been shown that the sequence of causal events in colorectal cancer is determined primarily by the fitness effects they provide rather than by mutation rates. They concluded that significant immunosuppression may not occur in untreated lesions. Kirshtein et al. [9] developed a mathematical model of the interaction of colon cancer with the main components of the immune system. They grouped patients according to their immune patterns by estimating the relative abundance of each immune cell from the gene expression profiles of the tumors. They compared the tumor susceptibility and progression of patients in these groups, observing differences in tumor growth.

Anaya et al. [10] have established a mathematical model that models the relationship between chemotherapy concentration in the tumor area and treatment in colorectal cancer patients. The resulting findings are planned to be helpful in potentially treatable patients with colorectal cancer. Hesse et al. [11] created a mathematical model, emphasizing that planning the use of anticancer drugs on patients for 24 hours can increase the success rate of patients' treatments. In the model, they discussed the personalization of treatment timing for colon cancer. They created three different scenarios using mouse liver and two human colorectal cancer cells for in-vitro experiments. As a result, they said that in the future, the model could be used to create the most appropriate drug timing for patients and support personalized drug therapy. Sameen et al. [12] created a model addressing KRAS mutation in colorectal cancer. They analyzed the behavior of KRAS mutations occurring after moAb treatments. They developed equations for two types of tumor cells: mutated KRAS and wild-type KRAS. Their results revealed that the combined treatment they recommended could only be an effective method for patients with high immunity.

DePillis et al. [15] presented a new mathematical model for colorectal cancer progression and treatment of this cancer. The model includes patient-specific parameters to account for individual differences in immune system strength and anti-tumor drug efficacy. They also simulated experimental dosing schedules and found new schedules in their simulations to reduce tumor size more effectively than existing treatment schedules. De Mattei et al. [16] presented a mathematical model based on ordinary differential equations for the evolution of solid tumors and their response to treatment, using variables such as the number of cancer cells sensitive to chemotherapy, the number of cancer cells resistant to chemotherapy. Abernathy et al. [17] presented and analyzed a mathematical model of colorectal cancer treatment using a system of nonlinear ordinary differential equations.

Their model describes the effectiveness of immunotherapy and chemotherapy in the treatment of tumor cells and cancer stem cells (CSCs).

Recently Raeisi et al. [18] have constructed a mathematical model investigating the interactions between colon cancer and immune system with a deep learning algorithm. In the literature, studies on mathematical modelling of breast cancer [19-23], lung cancer [24–27], prostate cancer [28–31], ovarian cancer [32–35], liver cancer [36–39] and other types of infectious disease and cancers [40–45, 57-67] have also been performed.

2. Preliminaries

This section provides several definitions to be used in the next stages of the paper.

Definition 1: [46] The Caputo fractional derivative of order λ of $\xi(t)$, $t > 0$ is defined as

$$D^{\lambda}\xi(t) = \frac{1}{\Gamma(n-\lambda)}\int_0^t (t-\tau)^{n-\lambda-1}\xi^n(\tau)d\tau,$$

where $\Gamma(\cdot)$ is the Gamma function, $\lambda \in (n-1, n)$, $n \in Z^+$.

Definition 2: [46] The fractional integral operator of Riemann-Liouville type for a function $\xi: (0,\infty) \to R$ of order $\lambda > 0$ is denoted as

$$ {}_0^{RL}D_t^{-\lambda}\xi(t) = \frac{1}{\Gamma(\lambda)}\int_0^t (t-\tau)^{\lambda-1}\xi(\tau)d\tau\,,\ t > 0, \tag{1}$$

or

$$ {}_0^{RL}I_t^{\lambda}\xi(t) = \frac{1}{\Gamma(\lambda)}\int_0^t (t-\tau)^{\lambda-1}\xi(\tau)d\tau\,,\ t > 0, \tag{2}$$

$$ {}_0^{RL}I_t^{0}\xi(\tau) = \xi(\tau).$$

Definition 3: [46] The fractional derivative of Riemann-Liouville type for a function $\xi: (0,\infty) \to R$ of order $\lambda > 0$ is denoted as

$$ {}_0^{RL}D_t^{\lambda}\xi(t) = \begin{cases} \frac{1}{\Gamma(n-\lambda)}\left(\frac{d}{dt}\right)^n \int_0^t \frac{\xi(\tau)}{(t-\tau)^{\lambda-n+1}}d\tau\,, & 0 \le n-1 < \lambda < n,\ n = [\lambda], \\ \left(\frac{d}{dt}\right)^n \xi(t), & \lambda = n \in N. \end{cases} \tag{3}$$

3. Mathematical model of colon cancer

In this section, we construct a new mathematical model for colon cancer. To construct a mathematical model of colon cancer that considers the interactions between tumor cells, macrophages, dendritic cells, and CD4+ T helper cells, we can use a system of differential equations. This type of model is commonly used in computational biology to describe the dynamic interactions between different cell populations over time. To incorporate

Michaelis-Menten kinetics [13] into the model, we adjust the interaction terms to include saturation effects. The Michaelis-Menten equation is often used to describe the rate of enzymatic reactions, but it can also be applied to describe the rate of cell-cell interactions where saturation occurs. We consider the following assumptions to extend the idea of modelling:

- Tumor Cells $T(t)$ grow at a rate g_T.
- Tumor cells are killed by macrophages and CD4+ T cells with Michaelis-Menten kinetics.

By incorporating the above conditions, we can obtain the following differential equation for tumor cells:

$$\frac{dT(t)}{dt} = g_T T(1 - \frac{T}{S_T}) - \beta_T \frac{TM}{S_M+T} - \omega_T \frac{TC}{S_C+T}, \tag{4}$$

where S_T is the carrying capacity of the environment for tumor cells.

- Macrophages $M(t)$ are recruited to the tumor site at a rate proportional to the tumor cell population.
- Macrophages can be activated to kill tumor cells with Michaelis-Menten kinetics.
- Macrophages die at a natural death rate.

Then we have the following differential equation for macrophage cells:

$$\frac{dM(t)}{dt} = g_M \frac{T}{S_M+T} - \beta_M M. \tag{5}$$

- Dendritic cells $G(t)$ are recruited at a rate that may depend on both tumor cells and macrophages.
- r_G is the production rate of dendritic cells.
- Dendritic cells present antigens to CD4+ T cells, activating them.
- Dendritic cells die at a natural death rate.

According to the assumptions above, we get the following equation for the dendritic cells:

$$\frac{dG(t)}{dt} = r_G + g_G \frac{T}{S_G+T} - \beta_G G. \tag{6}$$

- CD4+ T cells can be produced at a constant rate of r_C.
- CD4+ T cells $C(t)$ are activated by dendritic cells.
- Activated CD4+ T cells help macrophages and directly attack tumor cells with Michaelis-Menten kinetics.
- CD4+ T cells die at a natural death rate.

Following the mentioned assumptions yields:

$$\frac{dC(t)}{dt} = r_C + g_C G - \beta_C C. \tag{7}$$

The resulting dynamics of the interactions between colon cancer cells and the immune system in Eqs. (4)-(7) can be described by the following system of differential equations:

$$\begin{aligned}
\frac{dT(t)}{dt} &= g_T T\left(1-\frac{T}{S_T}\right) - \beta_T \frac{TM}{S_M+T} - \omega_T \frac{TC}{S_C+T}, \\
\frac{dM(t)}{dt} &= g_M \frac{T}{S_M+T} - \beta_M M, \\
\frac{dG(t)}{dt} &= r_G + g_G \frac{T}{S_G+T} - \beta_G G, \\
\frac{dC(t)}{dt} &= r_C + g_C G - \beta_C C,
\end{aligned} \tag{8}$$

where

- S_M is the half-saturation constant for macrophages,
- S_C is the half-saturation constant for tumor cells,
- S_G is the half-saturation constant for dendritic cells.

These constants represent the cell population at which the killing rate or recruitment rate is half its maximum value. In the system of Eq. (8), the killing terms for tumor cells by macrophages and CD4+T cells include saturation through the Michaelis-Menten functions.
Moreover, the recruitment terms for macrophages and dendritic cells also incorporate saturation effects, reflecting a more realistic biological scenario where recruitment rates are not linear at higher tumor cell populations. This extended model provides a more accurate representation of the dynamics in a colon cancer environment, capturing the nonlinear interactions between tumor cells and the immune response.

On the other hand, fractional-order differential equations can be used to model systems with memory effects, which can be more accurate for biological systems like cancer dynamics. The Caputo derivative [14] is often used for such models. Solving fractional-order differential equations using the Caputo derivative requires a different approach than integer-order differential equations. One common method to handle Caputo derivatives is to use numerical techniques such as the Adams-Bashforth-Moulton method for fractional differential equations. In order to achieve this idea, we extend the model to the fractional-order differential equation system as:

$$\begin{aligned}
\frac{d^\lambda T(t)}{dt^\lambda} &= g_T^\lambda T\left(1-\frac{T}{S_T}\right) - \beta_T^\lambda \frac{TM}{S_M+T} - \omega_T^\lambda \frac{TC}{S_C+T}, \\
\frac{d^\lambda M(t)}{dt^\lambda} &= g_M^\lambda \frac{T}{S_M+T} - \beta_M^\lambda M, \\
\frac{d^\lambda G(t)}{dt^\lambda} &= r_G^\lambda + g_G^\lambda \frac{T}{S_G+T} - \beta_G^\lambda G, \\
\frac{d^\lambda C(t)}{dt^\lambda} &= r_C^\lambda + g_C^\lambda G - \beta_C^\lambda C,
\end{aligned} \tag{9}$$

where λ is the order of fractional differential equations. The term $g_T^\lambda T\left(1-\frac{T}{S_T}\right)$ represents the logistic growth of tumor cells with the memory effect, considering a carrying S_T. The terms $\beta_T^\lambda TM$ and $\omega_T^\lambda TC$ represent the killing of tumor cells by macrophages and CD4+ T cells with the memory effect, respectively. The term $g_M^\lambda T$ represents the recruitment of macrophages in response to the presence of tumor cells with the memory effect. The term $g_G^\lambda T$ represents the recruitment of dendritic cells in response to the presence of tumor cells with the memory effect. The term $g_C^\lambda G$ represents the activation of CD4+ T cells by dendritic cells with the memory effect.

The parameter explanations and their values are represented in Table 1.

Table 1. Parameters used for the HBV model and their values

Par.	Biological description	Value	Sources
g_T	Intrinsic growth rate of tumor cells	0.1	Estimated
S_T	Carrying capacity of the environment for tumor cells	1000	Estimated
S_M	Half-saturation constant for macrophages	50	Estimated
S_G	Half-saturation constant for dendritic cells	50	Estimated
S_C	Half-saturation constant for CD4+ T cells	50	Estimated
r_G	The production rate of Dendritic cells	0.3	[18]
r_C	The production rate of CD4+ T cells	0.7	[18]
β_T	Rate at which tumor cells are killed by macrophages	0.1	Estimated
ω_T	Rate at which tumor cells are killed by CD4+ T cells	0.3	[48]
g_M	Recruitment rate of macrophages by tumor cells	0.2	Estimated
β_M	Natural death rate of macrophages	0.5	Estimated
g_G	Recruitment rate of dendritic cells by tumor cells	0.3	[48]
β_D	Natural death rate of dendritic cells	0.4	[48]
g_C	Activation rate of CD4+ T cells by dendritic cells	0.1	Estimated
β_C	Natural death rate of CD4+ T cells	0.7	Estimated
$T(0)$	Initial Tumor Cells	10	Estimated
$M(0)$	Initial Macrophage Cells	0	Estimated
$G(0)$	Initial Dendritic Cells	0	Estimated
$C(0)$	Initial CD4+ T Helper Cells	0	Estimated

4. Mathematical investigations of the model

4.1 Positivity and boundedness

Since each class in system (9) denotes the cell population, we get to show all variables $T(t), M(t), G(t), C(t)$ are all positive for time $t \geq 0$. We prove this in the form of the following theorem.

Before proceeding with the proof of the main theorem regarding the non-negativity of the obtained solutions, here we first need the following Lemma [47]:

Lemma 1: Let function $\xi(t) \in C[a,b]$ and Caputo fractional derivative ${}_0^C D_t^\lambda \xi(t) \in C(a,b]$ for $0 < \lambda \leq 1$, then we have

$$\xi(t) = \xi(x) + \frac{1}{\Gamma(\lambda)} {}_0^C D_t^\lambda \xi(\psi)(t-x)^\lambda,$$

with $0 \leq \psi \leq t, \forall t \in (a,b]$.

Remark 1: Let function $\xi(t) \in C[0,b]$ and Caputo fractional derivative ${}_0^C D_t^\lambda \xi(t) \in C(0,b]$ for $0 < \lambda \leq 1$. It is clear from the *Lemma 1* that if ${}_0^C D_t^\lambda \xi(t) \geq 0, \forall t \in (0,b]$, then the function $\xi(t)$ is non-decreasing and if ${}_0^C D_t^\lambda \xi(t) \leq 0, \forall t \in (0,b]$, then the function $\xi(t)$ is non-increasing $\forall t \in (0,b]$.

Theorem 1: All the solutions of model (9) with nonnegative initial conditions remain positive for all $t \geq 0$.

Proof. To prove the non-negativity of each component in system (9), we use the assumption of contradiction process, that is, let's suppose that there exists a first time t_1, such that

$$min\ \{\Lambda(t_1)\} = 0 \quad and \quad min\ \{\Lambda(t)\} > 0, \quad for\ all \quad t \in [0, t_1).$$

Here, $\Lambda(t) = T(t),\ M(t),\ G(t),\ C(t)$, separately. As per our assumption, we first let,

$$min\ \{\Lambda(t_1)\} = T(t_1).$$

This gives $T(t_1) = 0\ and\ T(t) > 0 \quad for\ all \quad t \in [0, t_1)$. But from the first equation of system (9), we get

$$\begin{aligned} {}_0^C D_t^\lambda T(t_1) &= g_T^\lambda T(1 - \tfrac{T}{S_T}) - \beta_T^\lambda \tfrac{TM}{S_M + T} - \omega_T^\lambda \tfrac{TC}{S_C + T} \\ &\leq g_T^\lambda T(1 - \frac{T}{S_T}), \end{aligned}$$

which contradicts our assumption $T(t_1) = 0$. Hence $T(t) > 0\ for\ all \quad t \geq 0$. In a similar way, we can prove that all solution components are nonnegative in all other cases $for\ all \quad t \geq 0$. Therefore according to Lin [47] from *Lemma 1* and *Remark 1*, we get the proof of *Theorem 1*.

Theorem 2: The closed region

$$K = \left\{(T, M, G, C) \in R_+^4 : \Phi(t) \leq \tfrac{s_G^\lambda + s_C^\lambda}{\beta^\lambda}\right\}$$

is a biologically feasible region which means it is a positively invariant set for the model (9) that attracts all positive solutions.

Proof. To prove the theorem, we have from the total population $\Phi(t)$ for model (9) after taking its derivation as

$$\begin{aligned} \frac{d^\lambda \Phi(t)}{dt^\lambda} &= g_T^\lambda T(1 - \frac{T}{S_T}) - \beta_T^\lambda \frac{TM}{S_M + T} - \omega_T^\lambda \frac{TC}{S_C + T} + g_M^\lambda \frac{T}{S_M + T} - \beta_M^\lambda M + g_G^\lambda \frac{T}{S_G + T} \\ &\quad -\beta_G^\lambda G + g_C^\lambda G - \beta_C^\lambda C \\ &\leq s_G^\lambda + s_C^\lambda - \beta^\lambda \Phi(t). \end{aligned}$$

Therefore, applying the Laplace transform of Caputo derivative follows that

$$\Phi(t) \leq \tfrac{s_G^\lambda + s_C^\lambda}{\beta^\lambda}.$$

That is, $\Phi(t)$ is bounded and all solutions beginning in K approach, enter and remain in K. Therefore, as per *Lemma 1* [47], on each hyperplane bounding the non-negative orthant, the vector field points into R_+^4. As a result, the model represented by (9) can be regarded as a positively invariant set being well-posed. This proves *Theorem 2*.

5. Numerical solutions to the colon cancer model

The system of integer-order ODEs given in Eq. (8) can be solved numerically using methods such as the Runge-Kutta, Euler, etc. methods. Moreover, there have been several semi-analytical methods to solve the integer order models such as homotopy methods,

decomposition methods, iteration methods, etc. Then the solutions of the system give us the population dynamics of tumor cells, macrophages, dendritic cells, and CD4+T helper cells over time.

5.1. Methodology for the solution

There are many strong arguments in favor of employing numerical methods for solving systems of fractional ODEs. Because of the presence of derivatives of non-local and non-integer order in fractional calculus, analytical solutions to problems involving fractional ODEs are notoriously difficult and rarely useful as can be seen in [49- 52]. In many cases, it is impossible to find or extremely challenging to create a closed-form solution. Numerical approaches provide another option for approximating the solutions of systems of fractional ODEs. Numerical methods simplify the modelling of complex fractional ODE systems. By allowing for a wide range of boundary conditions, initial conditions, and nonlinearities, they facilitate the detailed investigation of a large range of physical processes and systems.

This versatility comes in handy when traditional methods of analysis fail to produce fruitful outcomes. Numerical approaches can provide fast and precise results to problems involving fractional ODEs. Accurate and reliable solutions can now be obtained with the use of increasingly complex computational tools and algorithms. By modelling and analyzing systems containing fractional ODEs, researchers can get insight into their behavior and dynamics. Numerical instability is typical of fractional ODE systems because of the presence of non-local and non-integer-order derivatives. Numerical algorithms can be engineered for stability and protection against error amplification. Using various numerical techniques, such as implicit schemes and stabilizing algorithms, it is possible to maintain stability and accuracy when modelling fractional ODE systems. The use of numerical approaches enables experimental confirmation of results from fractional ODE systems. Direct experimental measurements are often unavailable or impracticable due to the complexity of the system.

By simulating the system with numerical tools, researchers can make sure their predictions hold up under real-world conditions. This allows for the accuracy of the numerical models to be verified and re-verified. Numerical approaches are useful for optimizing systems of fractional ODEs. The system can be made to behave as desired by scientists by first identifying an optimization issue and then employing numerical optimization techniques to locate an ideal answer. As a result, parameter spaces can be optimized and explored, even for systems that are hard to analyze analytically. In conclusion, numerical techniques provide a useful and efficient means of solving fractional ODE systems when analytical solutions are unavailable or insufficient. Their adaptability, efficiency, precision, stability, and verifiability against experimental data make them useful instruments for studying and analyzing complex fractional ODE systems.

Given all of this, we tried to solve the Caputo system in (9) by using a popular numerical method called the fractional Adams method (FAM). The FAM uses a predictor-corrector structure, which is explained in [46, 53]. In order to quickly and accurately resolve fractional ordinary differential equations, the Adams-Bashforth-Moulton (ABM) fractional numerical approach combines explicit and implicit procedures. The use of fractional derivatives in numerical simulations can improve precision, robustness, and robustness against stiff equations. We use the system of nonlinear fractional-order differential equations given by [53] to get an approximation of the solution of the Caputo

model (9) via ABM:

$$ {}_0^C D_t^{\lambda} G(t) = F\big(t, G(t)\big),\ 0 \le t \le t_f,\ \ G^{(j)}(0) = G_0^j,\ \ j = 0,1,2,\ldots,m-1, \tag{10} $$

where $\lambda > 0$ and $m = \lceil \lambda \rceil$ is the integer greater than or equal to λ. The λ order fractional derivative of $G(t)$ in the Caputo sense given in Definition 1 and denoted by ${}_0^C D_t^{\lambda} G(t)$ is defined by

$$ {}_0^C D_t^{\lambda} G(t) = \frac{1}{\Gamma(n-\lambda)} \int_0^t (t-r)^{n-\lambda-1} G^{(n)}(r)\, dr\,,\ \ n-1 < \lambda < n,\ \ n \in Z^+. $$

Note that the notation $G^{(n)}(r)$ denotes the nth integer order derivative of $G(r)$. It is worth mentioning that the theorems of existence and uniqueness for the fractional IVP in (10) can be found in [53]. The fractional differential Eq. (10) is also equivalent to the Volterra integral equation given by

$$ G(t) = \sum_{j=0}^{m-1} G_0^{(j)} \frac{t^j}{j!} + \frac{1}{\Gamma(\lambda)} \int_0^t (t-r)^{\lambda-1} F(r, G(r))\, dr \sum_{j=0}^{m-1} G_0^{(j)} \frac{t^j}{j!} + {}_0^C D_t^{-\lambda} F(r, G(r)). \tag{11} $$

The predictor-corrector type method (FAM) is used in several existing research works such as [54, 55] for integrating equations of the type (11). Each equation in the Caputo fractional-order model (9) can be discretized by using *Definition 1* in the following way:

$$ G_{n+1}^P = G_0 + \sum_{j=0}^{n} b_{j,n+1} F\big(t_j, G_j\big)\,,\ \ G_{n+1} = G_0 + \sum_{j=0}^{n} a_{j,n+1} F\big(t_j, G_j\big) + a_{n+1,n+1} F(t_{n+1}, G_{n+1}^P), \tag{12} $$

where

$$ a_{j,n+1} = \frac{\Delta t^{\lambda}}{\Gamma(\lambda+2)} \{ n^{\lambda+1} - (n-\lambda)(n+1)^{\lambda},\ \ if\ j = 0, (n-j+2)^{\lambda+1} - 2(n-j+1)^{\lambda+1} + (n-j)^{\lambda+1},\ \ \ if, 1 \le j \le n, 1,\ \ if\ j = n+1. \tag{13} $$

The above-discussed fractional Adams method is employed to simulate the Caputo model given in (9). We have used MATLAB R2023b software installed on a Windows laptop with 24GB RAM to run the required numerical simulations.

5.2 Numerical outcomes and discussion

In this section, we obtain the numerical solutions to the constructed model (9) of fractional order by considering the solution procedures given in the previous Section 5.1. In the following, we provide several figures regarding the model to understand the behavior of colon cancer by simulating the parameter values. Especially, we consider the growth rates and recruitment rates for each cell population to point out the future size of the populations. Indeed, due to the difficulty of collecting real data for patients, we use the random values for each parameter stated in the model. According to Figure 1, tumor cells grow logistically as time passes through different values of growth rates. As the growth rate increases. The peak point of tumor cells rises rapidly.

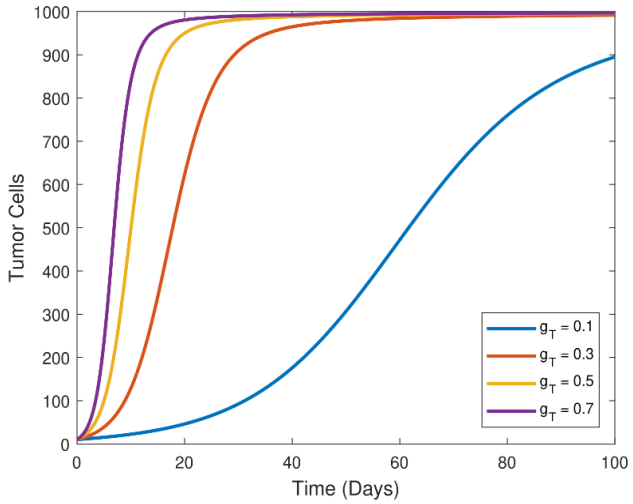

Figure 1. Tumor cell behaviors for the various values of the growth rate.

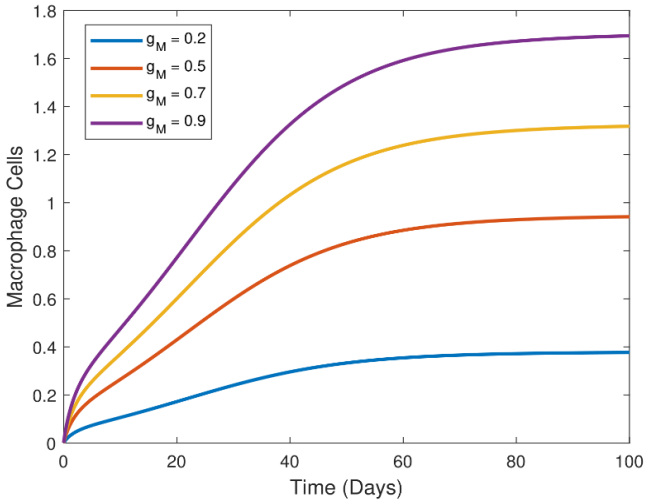

Figure 2. Macrophage cell behaviors for the various values of the growth rate.

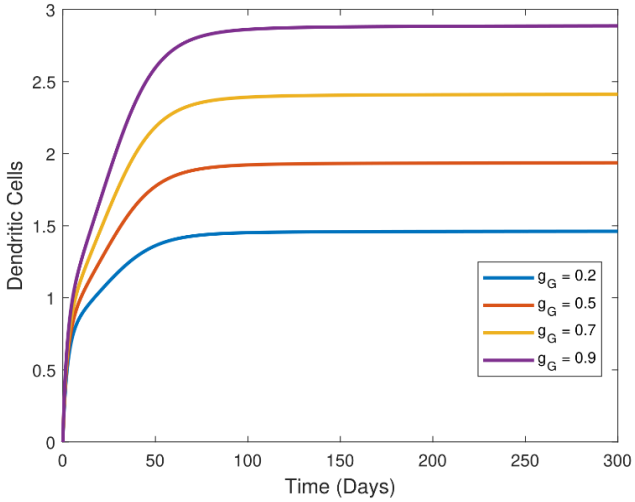

Figure 3. Dendritic cell behaviors for the various values of the growth rate.

In Figure 2, we represent the macrophage cell behaviors for the various values of the growth rate. As the value of growth rate increases, the number of macrophage cells increases as well. Figure 3 shows the dendritic cell behaviors for the various values of the growth rate. After 50^{th} days, the number of dendritic cells become stable. As the growth rate increases, the number of dendritic cells increases, too. In Figure 4, we figure out the behaviour of Hepler T cells for the various values of the growth rate.

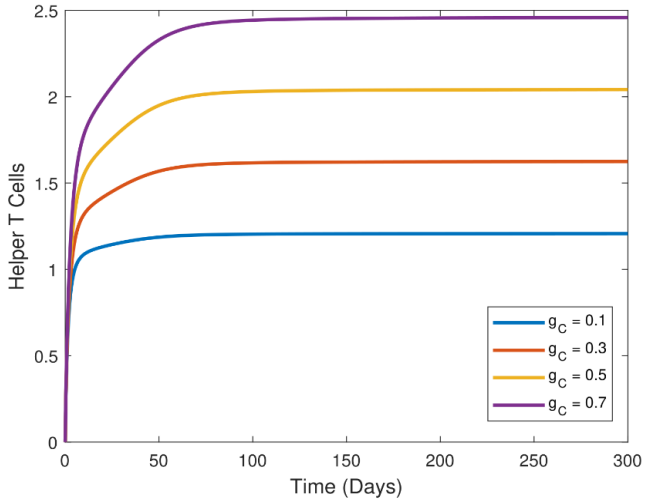

Figure 4. Helper T cell behaviors for the various values of the growth rate.

5. Conclusions

Colon cancer is a disease with a genetically complex structure. To better understand the complexity and structure of colon cancer cells, we have developed a mathematical model in this study. Our model includes a new fractional order differential equation system for colon cancer. In our model, the interaction between tumor cells, macrophage cells, dendritic cells, and CD4+ T helper cells was determined using Michaelis-Menten kinetics. The purpose of this article is to observe the cancer cell behavior along with the parameters that play an important role in the entire process or elimination of the cancer cells in the model from the moment they settle in the body. However, many parameters in the model are difficult to estimate because they are patient-specific. Moreover, biological interpretations have been performed. In addition, mathematical analysis such as positivity and boundedness have also been carried out. Numerical results have been obtained to observe the intercellular course of colon cancer and estimate its future direction. Using a numerical solution algorithm, detailed simulations of the most reliable model behavior might be possible in the coming periods. Our sensitivity analysis of the relationship between parameters and cancer cell population can guide future research and treatment strategies. To summarize, in our work we highlight the potential of using fractional differential equations to optimize the resulting application for colon cancer treatment. The information we obtained and the results we provided give important information about the complex structure of colon cancer and its interaction with the immune system and may guide future research and treatment approaches for this disease.

Acknowledgments

This research was supported by Scientific and Technological Research Council of Türkiye (TÜBİTAK) under the undergraduate research project.

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