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Development of Fractional Mathematical Model Analysis for the Effects of Medicine Supplies to a solid Tumor Cells Density According to Recovery of Three Organs

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ABSTRACT
This study presents a generalized mathematical model to simulate the dynamic supply of medicine to a solid tumor based on the density of tumor cells and the recovery trajectories of three critical organs: the kidney, liver, and heart. The aim is to optimize drug dosage schedules that will balance tumor reduction with minimizing toxicity to healthy tissue. The generalized model that integrates pharmacokinetics and pharmacodynamics with tumor growth and organ recovery functions was solved analytically using the integral transformation method. By simulating varying levels of drug delivery and tracking the response of each organ, this solution allows for predicting optimal dosing regimens that can achieve effective tumor control without compromising organ function. The validation is carried out with a classical computational model, providing a basis for potential application in personalized cancer treatment strategies. The results show that the distribution of controlled medicine can significantly impact both tumor reduction and organ recovery. This model has a highly significant impact on clinical decision-making processes.

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INTRODUCTION

Tumor is a solid mass of tissue that forms that can affect or attach any organ or tissue of the body when abnormal cells grow uncontrollably, go beyond their usual boundaries to invade adjoining parts of the body and or spread to other organs. Most tumors undergo insufficient nutrition at an early vascular stage and have difficulty in wastes disposal, and thus the transfer of nutrients and wastes has been progressed through simple diffusion. Tumor cells stimulate endothelial cells located in the interior surface of blood vessels to obtain solutes, such as oxygen, for growth. If the tumor reaches dormant state, the cancer cells release a diffusible chemical substance called tumor angiogenesis factor (TAF). Successful treatment of tumor depends on the efficient deliveries of anticancer drugs. Tumor cell propagation creates an abnormal vascular structure causing an elevated interstitial fluid velocity, and chaotic vascular structure appeared commonly in advanced tumor disturbs the efficient drug delivery to solid tumors [1]. Vascular normalization using anti-angiogenic factors, thus, reduces the interstitial fluid velocity and strengthens the vessel perfusion and improves both drug and nutrients delivery to tumor cells [2, 3].

There are number of available studies for past decades on mathematical modeling and computational simulation techniques for predicting drug delivery and treatment for cancer tumor in the literature. They regard tumor as a porous environment and interstitial fluid pressure is an influential factor in drug delivery efficacy [4–7]. Soltani and Chen [8] have investigated the tumor

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shape and size effect on drug delivery to solid tumors using governing equations for fluid flow to physiological systems containing solid tumors. In the study, discretized form of the governing equations, with appropriate boundary conditions, was developed for predefined tumor geometries. The governing equations were solved using a numerical method, the element-based finite volume method. Results find out the influence of the surface area per unit volume of the tissue, vascular and interstitial hydraulic conductivity on drug delivery. While in [9] a non-continuous blood flow model through a capillary network induced by a tumor combined with interstitial flow in normal and tumor tissues in 2D. Result indicated that, higher interstitial pressure, almost two times, for realistic model compared to the one in [8].

One of the main challenges in cancer therapy is the presence of high interstitial pressure within the tumor's center which creates significant resistance opposite chemotherapy. Vazifehshenas and Bahadori [10] have addressed the issues raised in [8, 9] by introducing Soret effect to overcome the physicochemical and biological barriers involved in drug delivery into the targeted cells. They considered three transport phenomena such as macroscopic fluid transfer, macroscopic mass transfer and bio-heat transfer to investigate the behaviors of tumor cells.

Hadjicharalambous et al. [11] have studied the state-of-the-art in in silico cancer modeling of vascularised solid tumour growth, and identify the important advances and barriers to success of these models in clinical oncology. Sedaghatkish et al. [12] developed a computational model using acoustic, bioheat transfer, fluid flow and mass transfer equations for evaluating drug delivery system based on the use of Temperature-sensitive liposomes (TSL) and acoustic streaming for the treatment of tumors adjacent to large blood vessels. Results showed that acoustic streaming could facilitate drug delivery to adjacent tissue by increasing the mass flux toward the vessel wall. Kashkooli et al. [13] used a multi-scale computational model to presuppose drug delivery to a solid tumor and to evaluate the therapeutic excellence. Smaller nanoparticles or a low bind- ing affinity and drug release rate are required to increase treat- ment efficacy. Reza- eian et al. [14] developed mathematical model to analyzed drug targeting system as a solution to improve the drug penetration into the tumor. Considering the binding and internalization of the drug into the cancer cells, the mathematical model analyzed the drug distribution inside the tumor in three forms: free, bound, and internalized. The drug penetration area and the fraction of killed cells in the tumor were used to estimate the efficiency of the proposed drug delivery system.

We are mainly concern to a model of Medicine Supplies to a solid tumor in our research. This theoretical based model was proposed by Jaegwi Go [15], and it accurately described the changes of solute medicine in blood vessel and diffusible chemical substance concentration with respect to the flow rate of injected drugs into liver and heart. The outcomes show that the tumor cells react highly sensitive as soon as medicine supplies and tumor cell density is decreased drastically at the moment of medicine injection.
Following the research of Jaegwi Go [15], the given mathematical formulation was derived in the sense of integer order derivatives. At the present time, fractional order operators are very useful tools for modeling biological and physical processes due to its ability to capture hereditary and memory effects which are very significant in biological and physical phenomena [16]. There are different forms of fractional derives in the literature together with many recent developments [17-19].

In order to capture the hereditary and memory effects in Jaegwi Go [15], we proposed the generalization of the integer-order model given by Jaegwi Go [15] into the fractional-order sense using Caputo fractional derivative. The given research is formulated in number of sections. In section 2, we present the formulation of the problem in the sense of given time-fractional Caputo derivatives. In section 3, we derive the analytical solution of the problem in the Laplace domain. The inversion of the Laplace transform is obtained using the Stehfest algotithm [20]. In section 4, we perform number of graphs to justify

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the novelty of the research work. At the end, we conclude our findings.

Formulation of the problem

In the first part of this section, we present a brief summary of the fractional calculus used in this article.

Time-fractional Caputo derivatives. Basic elements

The function

$$\chi_c(t,\alpha) = \frac{t^{-\alpha}}{\Gamma(1-\alpha)},\ t>0,\ \alpha\epsilon[0,1) \quad (1)$$

is called Caputo kernel [22,23]

Denoting by $\hat{\chi}_c(s,\alpha) = \int_0^\infty \chi_c(t,\alpha)e^{-st}dt = L\{\chi_c(t,\alpha)\}$ the Laplace transform of the function $\chi_c(t,\alpha)$, we obtain the Laplace transform of the Caputo kernel in the form

$$\hat{\chi}_c(s,\alpha) = \frac{1}{s^{1-\alpha}} \quad (2)$$

The relationship (2) allows us to extend the definition (1) for $\alpha = 1$ as follows:

$$\hat{\chi}_c(s,1) = 1 = \lim_{\alpha\to 1} L\{\chi_c(t,\alpha)\} = L\left\{\lim_{\alpha\to 1}\chi_c(t,\alpha)\right\} = L\{\delta(t)\} \quad (3)$$

where $\delta(t)$ being the Dirac distribution.

Applying the inverse Laplace transform to Eq. (3) we have

$$\lim_{\alpha\to 1}\chi_c(t,\alpha) = \delta(t) \quad (4)$$

Now, the Caputo kernel can be defined as

$$\chi_c(t,\alpha) = \begin{cases} \frac{1}{\Gamma(1-\alpha)}t^{-\alpha}, & t>0,\ \alpha\epsilon[0,1), \\ \delta(t), & t>0,\ \alpha=1. \end{cases} \quad (5)$$

Let $\varphi(t)$ be a differentiable function on the interval $[0,\infty)$. The Riemann-Liouville fractional integral operator is defined by

$$I_t^\alpha\varphi(t) = \chi_c(t,1-\alpha) * \varphi(t) = \frac{1}{\Gamma(\alpha)}\int_0^t (t-\tau)^{\alpha-1}\varphi(\tau)d\tau,\ \alpha>0, \quad (6)$$

The Laplace transform of the operation (6) is

$$L\{I_t^\alpha\varphi(t)\} = L\{\chi_c(t,1-\alpha)\}L\{\varphi(t)\} = s^{-\alpha}\hat{\varphi}(s) \quad (7)$$

The relationship (7) allows us to extend the definition (6) for $\alpha = 0$ as follows:

$$\lim_{\alpha\to 0} L\{I_t^\alpha\varphi(t)\} = L\left\{\lim_{\alpha\to 0} I_t^\alpha\varphi(t)\right\} = \hat{\varphi}(s) = L\{\delta(t)\}, \quad (8)$$

Therefore,

$$\lim_{\alpha\to 0} I_t^\alpha\varphi(t) = \varphi(t) \quad (9)$$

Now, the fractional integral operator is defined as

$$I_t^\alpha\varphi(t) = \begin{cases} \frac{1}{\Gamma(\alpha)}\int_0^t (t-\tau)^{\alpha-1}\varphi(\tau)d\tau, & \alpha>0, \\ \varphi(\tau), & \alpha=0. \end{cases} \quad (10)$$

The time-fractional Caputo derivative of function $\varphi(t)$ is defined by [22, 23]

$${}_cD_t^\alpha\varphi(t) = \chi_c(t,\alpha) * \dot{\varphi}(t) = \frac{1}{\Gamma(1-\alpha)}\int_0^t (t-\tau)^{-\alpha}\dot{\varphi}(\tau)d\tau,\ \alpha\epsilon[0,1), \quad (11)$$

where $\dot{\varphi}(t) = \frac{d\varphi(t)}{dt}$.

The Laplace transform of the Caputo derivative is

$$L\{{}_cD_t^\alpha\varphi(t)\} = L\{\chi_c(t,\alpha)\} * L\{\dot{\varphi}(t)\} = \frac{1}{s^{1-\alpha}}[s\hat{\varphi}(s) - \varphi(0)] = = s^\alpha\hat{\varphi}(s) - s^{\alpha-1}\varphi(0) \quad (12)$$

Using (7) and (12) one obtains

$$L\left\{I_t^\alpha\left({}_cD_t^\alpha\varphi(t)\right)\right\} = s^{-\alpha}L\{{}_cD_t^\alpha\varphi(t)\} = s^{-\alpha}[s^\alpha\hat{\varphi}(s) - s^{\alpha-1}\varphi(0)] = = \hat{\varphi}(s) - \frac{1}{s}\varphi(0) \quad (13)$$

By applying the inverse Laplace transform, we get

$$I_t^\alpha\left({}_cD_t^\alpha\varphi(t)\right) = \varphi(t) - \varphi(0) \quad (14)$$

On a similar path we have ${}_cD_t^\alpha\left(I_t^\alpha\varphi(t)\right) = s^\alpha L\{I_t^\alpha\varphi(t)\} - s^{\alpha-1}[s^\alpha\hat{\varphi}(s) - s^{\alpha-1}\varphi(0)]|_{t=0} = = s^\alpha.s^{-\alpha}\hat{\varphi}(s) = \hat{\varphi}(s), \quad (15)$

Therefore,

$${}_cD_t^\alpha\left(I_t^\alpha\varphi(t)\right) = \varphi(t) \quad (16)$$

Fractional mathematical model of the medicine in blood vessel

In this study we developed a generalized mathematical model of the problem investigated by Jaegwi Go [15], namely

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$$ {}_cD_t^{\alpha}K(t) = I_K(t) - R_K K(t), \quad (17)$$

$$ {}_cD_t^{\alpha}L_i(t) = I_{Li}(t) - R_{Li}L_i(t) + R_K K(t), \quad (18)$$

$$ {}_cD_t^{\alpha}H(t) = I_H(t) - (R_H + \beta)H(t) + R_{L_i}L_i(t), \quad (19)$$

$$ {}_cD_t^{\alpha}M(t) = \beta H(t), \quad (20)$$

where K, Li and H are the substances injected into kidney, liver and heart respectively, M is the medicine solute that flows into blood vessel to interfere the development of tumor angiogenesis factor (TAF), ${}_cD_t^{\alpha}\chi(t)$ is the time-fractional of function $\chi(t)$, of order $\alpha\epsilon[0,1], R_j, j\epsilon\{K, Li, H\}$ is the reaction rate coefficient of each organs and $\beta\epsilon[0,1]$ is the medicine flow rate.

Along with the fractional differential equations (17)-(20) we consider the initial conditions

$$K(0) = Li(0) = H(0) = 0, \quad M(0) = M_0 \quad (21)$$

The medicine functions $I_j(t)$ are given in [15]

$$I_j(t) = \gamma_j(1 - e^{t-t_j}), \ j\epsilon\{K, Li, H\} \quad (22)$$

Note that each medicine affects in the time interval $t\epsilon[0, t_j]$.

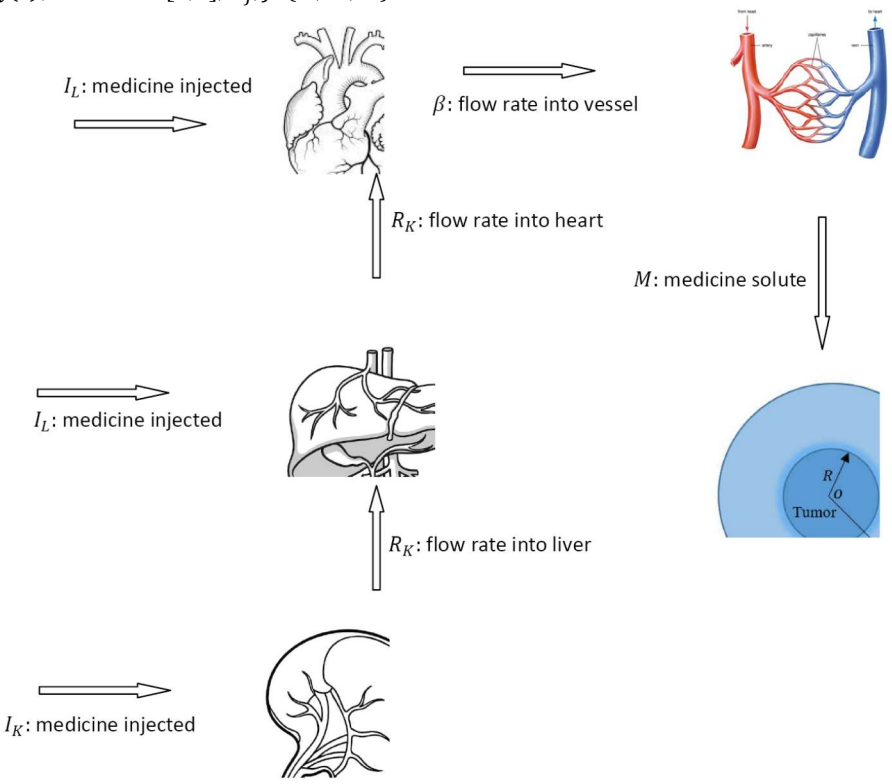

Figure 1: Physical Geometry

Analytical solution of the fractional model

The analytical solutions of the system of fractional differential equations (17)-(20) with the initial conditions (21) are determined using the Laplace transform. To avoid long calculations, we will first apply the fractional integral operator I_t^{α} to the equations (17)-(20), using equation (14) and the initial conditions (21) one obtains

$$K(t) = I_t^{\alpha}[I_K(t) - R_K K(t)],$$

$$L_i(t) = I_t^{\alpha}[I_{Li}(t) - R_{Li}L_i(t) + R_K K(t)], \quad (23)$$

$$H(t) = I_t^{\alpha}[I_H(t) - (R_H + \beta)H(t) + R_{Li}Li(t)],$$

$$M(t) - M(0) = \beta I_t^{\alpha}H(t).$$

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Applying the Laplace transform to Eq. (23) and using Eq. (7), we find the following algebraic expressions of the Laplace transforms of functions $K(t), L_i(t), H(t)$ and $M(t)$:

$$\hat{K}(s) = \frac{1}{s^{\alpha}+R_K}\hat{I}_K(s) + \frac{R_H}{(s^{\alpha}+R_k)(s^{\alpha}+R_S)}\hat{H}(s) \quad (24)$$

$$\hat{L}_i(s) = \hat{A}(s) + \hat{B}(s)\hat{H}(s) \quad (25)$$

$$\hat{H}(s) = \frac{\hat{I}_H(s)+\hat{L}_i(s)\hat{A}(s)}{s^{\alpha}+R_H+\beta-R_{Li}\hat{B}(s)} \quad (26)$$

$$\hat{M}(s) = \frac{1}{s}M_0 + \frac{\beta}{s^{\alpha}}\hat{H}(s) \quad (27)$$

where $\hat{A}(s) = \frac{1}{s^{\alpha}+R_{Li}}\hat{I}_{Li}(s) + \frac{R_K}{(s^{\alpha}+R_{Li})(s^{\alpha}+R_K)}\hat{I}_K(s)$, $\hat{B}(s) = \frac{R_K R_H}{(s^{\alpha}+R_{Li})(s^{\alpha}+R_K)}$

The analytical expressions of the Laplace transforms given by equations (24)-(27) are complicated. Even if these expressions can be written in equivalent forms for which the inverse Laplace transforms could be found, the obtained functions would be too complicated to be used for numerical simulations. For this reason, we will determine the inverse Laplace transforms of the above functions using Stehfest's algorithm for the numerical inversion of the Laplace transforms [21]. According to this algorithm, the inverse Laplace transform of the function $\hat{\psi}(s)$ is given by

$$\psi(t) = \frac{\ln 2}{t}\sum_{j=1}^{2p}(-1)^{j+p}\sum_{i=\left[\frac{j+1}{2}\right]}^{\min(j,p)}\frac{i^p(2i)!}{i!(p-i)!(i-1)!(j-1)!(2i-j)!}\hat{\psi}\left(\frac{j\ln 2}{t}\right) \quad (28)$$

where $p > 0, p \in \mathbb{N}$, $\left[\frac{j+1}{2}\right]$ denotes the integer part of the number $\frac{j+1}{2}$ and $\min(j,p) = \frac{j+p-|j-p|}{2}$. Kuznetov [25] rigorously demonstrated the convergence of the Stehfest algorithm for locally integrable functions on $t \in (0,\infty)$. In concrete cases, the value of the p parameter that characterizes the degree of approximation is chosen through tests with a precision imposed on the obtained results.

ANALYSIS OF RESULT AND DISCUSSIONS

Results presented in present work are compared with the results of Jaegwi Go [15] for validation as in Figure 2. This result in Figure 2, show the variation of medicine in liver as compare for classical and fractional models. Jaegwi Go [15] result indicated the medicine in liver is lower for time domain $0 \le t \le 0.7$ as compared to the fractional model. The result increases higher than fractional model as time $t > 0.7$. However, for case of heart (Figure 2 (b)) the medicine distribution in heart is same as compared to fractional model within time domain $0 \le t \le 0.7$ as time progress fractional accelerate medicine distribution as compared to one by Jaegwi Go [15].

Figure 3 shows the variation of medicine concentration in blood vessel for various medicine flow rate β when $t_S = t_{Lu} = t_K = t_{Li} = t_H = 5$, $R_S = R_{Lu} = R_K = R_{Li} = R_H = 1$. The quantity of medicine concentration in blood vessel increases with the decline of medicine flow rate β and the increasing aspect is an exponential form according to the steady decreasing of medicine flow rate. The distribution of drug concentration exhibits little change over the interval $0 < \tau < 4$ and sudden decrease occurs after $\tau = 4$, reflecting the time level $t_i = 5$.

The performance of heart reaction rate R_H on medicine concentration in blood vessel is shown in Figure 4 when $t_S = t_{Lu} = t_K = t_{Li} = t_H = 1$, $R_S = R_{Lu} = R_K = R_{Li} = 1$, $\alpha = 0.5$. The amount of drug concentration in blood vessel

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grows as heart reaction rate R_H increases and the distribution profile is proportional to the change of heart reaction rate. The decreasing patterns of drug concentration along the time *t*are analogous, while the decline rate of distribution grows with the increment of heart reaction rate R_H after insignificant time period. The reason is the augmented medicine concentration according to the increase of heart reaction rate R_H.

The variations of medicine concentration distribution in blood vessel against time t for various kidney reaction rate R_K are shown in Figure 5 when *t S* = *t Lu* = *t K* = *t Li* = *t H* = 1, *α*= 0.5. The magnitude of drug concentration in blood vessel decreases with the increase of reaction rate R_K. The decrease pattern of drug concentration for the chosen reaction rate R_K is similar along the time t. Smaller change appears over the interval $0 < t < 0.7$ and a higher reduction develops after $t = 0.7$. This behavior is more significant for the case of classical model in Figure 5(b) as compared to fractional model in Figure 5 (b). The fractional model has advantage of reducing drug concentration in blood vessel as the reaction rate increases. Figure 6 displays medicine concentration in blood vessel along the time *t* for various liver reaction rate R_{Li} in the case of Figure 6 (a) for fractional model $\alpha = 0.5$ and 6 (b) for classical model $\alpha = 1$. The largest medicine concentration distribution is appeared in liver as compared to Kidney and Heart over the interval $0 \leq t \leq 2$. The magnitude of drug concentration scales is higher in classical model as compared to fractional model.

Figures 7-9 analyze medicine concentration distribution in Kidney, Liver and Heart over the time. The largest medicine concentration distribution is appeared in Kidney and Liver over the interval $0 \leq t \leq 2$ 0, while Liver shows the largest medicine distribution for $t \to 2$ as compare to Kidney (Figure) and Heart (Figure). Medicine concentration in Heart (Figure) shows the smallest distribution over entire domain among Kidney and Liver. This result is because Heart is connected with blood vessel and medicine amount is controlled by medicine flow rate from heart into blood vessel.

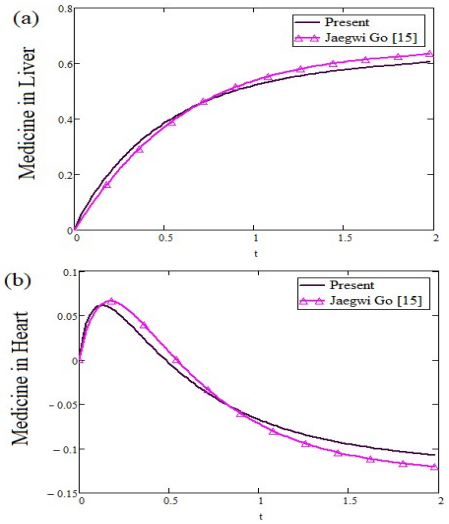

Figure 2: Validation of the results with the previously published articles [15] based on the classical and fractional model formulation.

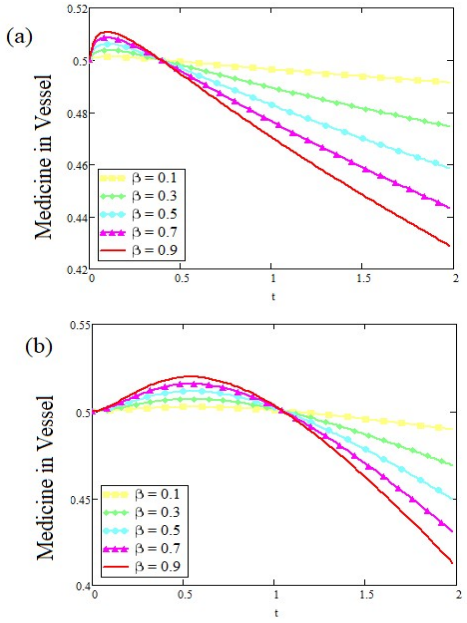

Figure 3: Medicine concentration in blood vessel along the time *t* for various medicine flow rate β: (a) for fractional model $\alpha = 0.5$ and (b) for classical model $\alpha = 1$

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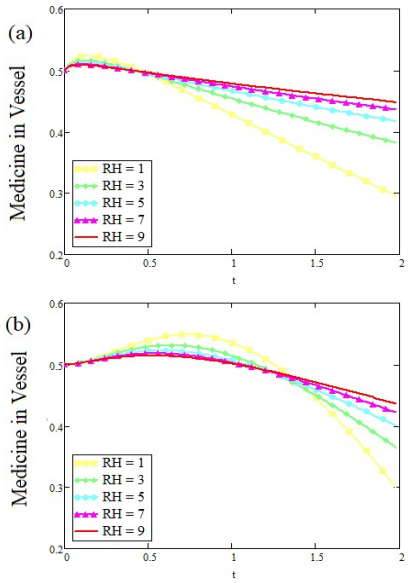

Figure 4: Medicine concentration in blood vessel along the time t for various heart reaction rate R_H: (a) for fractional model $\alpha = 0.5$ and (b) for classical model $\alpha = 1$

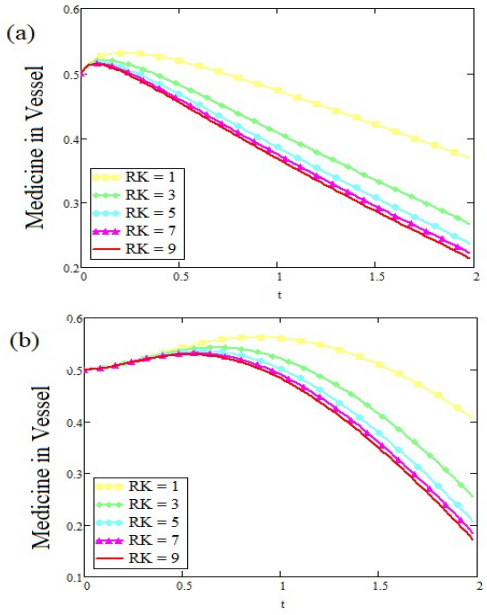

Figure 5: Medicine concentration in blood vessel along the time t for various kidney reaction rate R_K: (a) for fractional model $\alpha = 0.5$ and (b) for classical model $\alpha = 1$

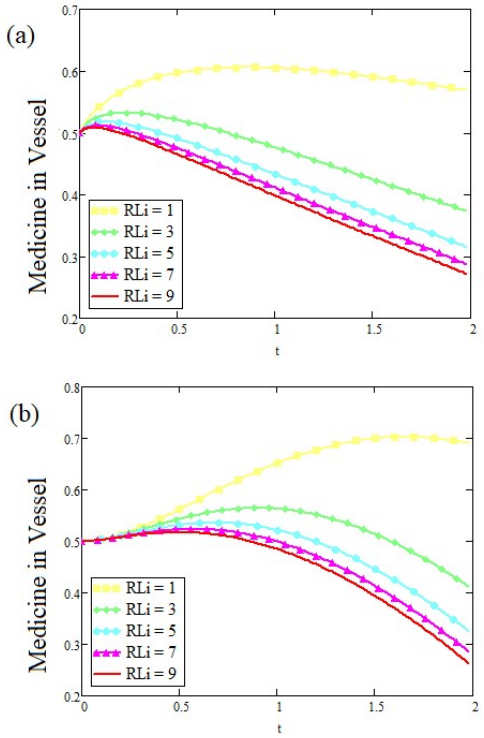

Figure 6: Medicine concentration in blood vessel along the time t for various liver reaction rate R_{Li}: (a) for fractional model $\alpha = 0.5$ and (b) for classical model $\alpha = 1$

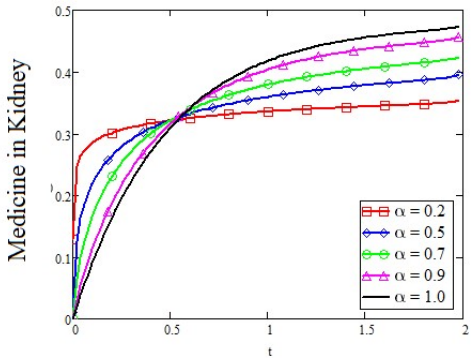

Figure 7: Medicine concentration in Kidney along the time t

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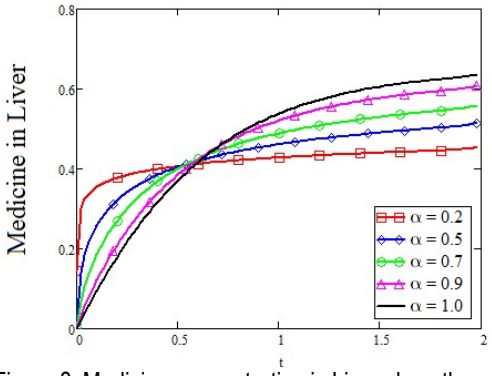

Figure 8: Medicine concentration in Liver along the time t

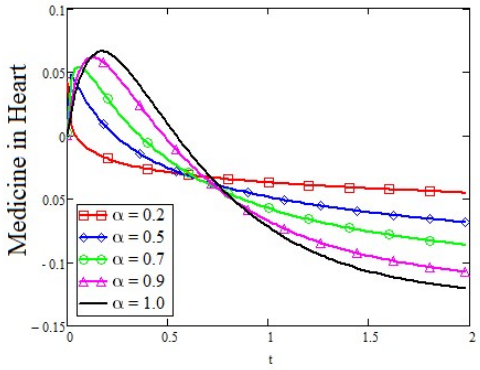

Figure 9: Medicine concentration in Heart along the time t

CONCLUSION

In this work a generalized mathematical model is proposed to investigate the behaviors of tumor cells taking into account drug supplies generated by the functional recovery of three organs namely kidney, liver and heart. The fractional mathematical model analysis is developed for the solute circulation among three organs and influx into blood vessel neglecting any side effect in any organs. The fractional mathematical model has been developed to interpret the variations of solute medicine amount in blood vessel and concentration with respect to reaction rate, time level, and medicine flow rate.

The main findings are summarized as follows:

1. The generalized mathematical model based on fractional derives provide more accurate representation behaviors of tumor cells density and drug supplies generated by the functional recovery of three organs.
2. The fractional order parameter in the generalized mathematical model allows adjusting medicine concentration in blood vessel and three organs.
3. The magnitude of drug concentration in blood vessel decreases with the increase of reaction rate
4. The amount of drug concentration in blood vessel grows as heart reaction rate increases.
5. The quantity of medicine concentration in blood vessel increases with the decline of medicine flow rate.
6. The medicine made through functional enhancement of five representative organs is highly influential to restrain the activity of TAF.
7. The fractional parameter, reaction rate, time level, and medicine flow rate are crucial factors in the determination of medicine amount in blood vessel and to control TAF concentration.
8. The presented generalized mathematical model has the potential for the profound analysis of solute medicine amount in blood vessel, TAF concentration, and the alteration of tumor cells density according to the functional recovery of five organs.
9. The generalized mathematical approach may be applicable in the analyses of tumor cells mobility on the basis of complex interaction among human organs.

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