MJFAS
Malaysian Journal of Fundamental and Applied Sciences

REVIEW ARTICLE

Mathematical modeling of cancer treatments with fractional derivatives: An Overview

Musiliu Folarin Farayola[a], Sharidan Shafie[a,*], Fuaada Mohd Siam[a], Rozi Mahmud[b], Suraju Olusegun Ajadi[c]

[a] Department of Mathematical Sciences, Faculty of Science, Universiti Teknologi Malaysia, Johor Bahru, Johor, Malaysia; [b] Imaging Department, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Malaysia; [c] Department of Mathematics, Faculty of Science, Obafemi Awolowo University, Ile-Ife, Nigeria

Abstract This review article presents fractional derivative cancer treatment models to show the importance of fractional derivatives in modeling cancer treatments. Cancer treatment has become a significant research area that has attracted many mathematical models developed by mathematicians to represent cancer treatment processes such as hyperthermia, immunotherapy, chemotherapy, and radiotherapy. However, many of these models were based on ordinary derivatives. The concept of fractional derivatives, which is still new to many mathematicians, is a generalized definition of a derivative whose order is a real number and has proved to be more effective and robust in modeling cancer treatments. Therefore, it is imperative to review fractional cancer treatment models to elucidate their significance and also predict future directions. The review was carried out by first presenting 22 various definitions of fractional derivatives. Thereafter, 11 articles were selected from different online databases which included Scopus, EBSCOHost, ScienceDirect Journal, SpringerLink Journal, Wiley Online Library, and Google Scholar. These articles were summarized, and the utilization of fractional derivative models was analyzed. Based on this analysis, the merit of modeling with fractional derivative, the most used fractional derivative definition, and the future direction for cancer treatment modeling were presented. From the results of the analysis, it was shown that fractional derivatives incorporated memory effects which gave it an advantage over ordinary derivatives for cancer treatment modeling. Moreover, the fractional derivative is a general definition for all derivatives. Furthermore, the review showed that the Caputo and its non-singular kernel versions are the most used in fractional derivative models. The current review concluded that the future direction of cancer treatment modeling lies in the adoption and effective use of fractional derivative models corroborated with accurate experimental or clinical data.

Keywords: Cancer treatments; fractional derivative; hyperthermia; Chemotherapy; Immunotherapy; Radiotherapy.

***For correspondence:** sharidan@utm.my

Received: 21 Nov 2020
Accepted: 7 Sept 2021

Introduction

The concept of fractional derivatives in applied science modeling might sound novel, but, the fractional derivative is not new in applied mathematics. Although the fractional derivative name has been accepted by mathematicians, the concept is a generalized definition of a derivative whose order is a real number. Historically, the concept could be traced back to September 30, 1695, when Leibnitz wrote a letter to L'Hospital where he raised the question of generalizing the definition of derivatives to include non-integers. Since this question was raised by Leibnitz, fractional derivatives had become a subject of study

over the years with major contributions from mathematicians like Liouville, Riemann, Weyl, Leibnitz, Abel, Fourier, Grunwald, Lacroix, and Letnikov. These various contributors produced different formulae for the fractional derivative. Despite the age of fractional derivatives, its use might still be new to scientists and engineers because many are not aware of its beauty and robustness.

Moreover, the fractional derivative is a generalized form of other integrals and derivatives due to its "backward compatibility". According to Ross [1], a fractional derivative should have five basic properties. The properties include: the fractional derivative of an analytic function is analytic, when the order of the fractional derivative is a positive integer then it becomes an ordinary derivative and when it is a negative integer then it becomes an integral (backward compatibility) when the order is zero it becomes the function, the fractional derivative must be linear, and the law of exponents holds. All the definitions of fractional derivative satisfied some of these properties, but the one that satisfied all these five properties is the Riemann-Liouville fractional derivative [1]. Despite these properties, all definitions of the fractional derivative must possess an important common feature. This important common feature is the non-locality, which gives the fractional derivative a history or memory effect.

The physical interpretation of this memory effect was explained by Du, et al. [2]. The authors used Scott-Blair's model to show that the fractional-order is an index of memory for the physical process. For instance, when the fractional order is zero, nothing is memorized, and when the fractional order is 1, then nothing is forgotten. However, many physical processes operate between these two extremes of memorizing nothing or forgetting nothing, therefore a fractional order will be most appropriate for modeling. As a result, the fractional derivative model should be used for describing physical processes over an interval. Furthermore, Du, et al. [2] used the fractional derivative model to fit the three-point bending test data of a viscoelastic creep of SiAYON ceramics at 1200^0C and 240 MPa. With a fractional order of 0.44, the model fitted SiAYON ceramics specimen perfectively for a time interval of 400 minutes. Apart from viscoelastic processes, the authors showed that the fractional derivative model is also suitable for modeling biological kinetics and processes with memory. This was shown by fitting the protein absorption kinetics of fibronectin over 1150 seconds using a model with fractional order of 0.435. The results showed a good fit of the model with test data. Also, the fractional derivative model was applied to cognitive dynamics in psychology. This was done by fitting the memorizing data implemented by Hermann Ebbinghaus which was reported in 1885. The model, with a fractional order of 0.71, fitted well with the test data. Based on these results, it can be concluded that fractional derivative models are suitable for describing memory-based processes in different fields. Since many real-life processes are memory-based, then fractional derivative models are more appropriate. One of the most important memory-based physical processes is the cancer treatment process. The fractional derivative model considers the cancer treatment as a process occurring over an interval and accounts for its memory effect. More importantly, each process requires a specific fractional-order to measure its memory. The three processes presented by Du, et al. [2] had distinct fractional orders. Hence, the value of the fractional-order is the memory-index for the physical process [2].

The clinical procedures used in treating or managing cancer include chemotherapy, immunotherapy, radiotherapy, hyperthermia, and surgery. Apart from surgery, the use of mathematical models has been significant in cancer treatment research. Many of these mathematical models were based on the ordinary derivative but fractional cancer treatment models are also gradually gaining prominence. Despite this prominence, the concept of a fractional derivative is still obscure to researchers and many are still not inclined towards the use of fractional treatment models in cancer treatment research. Therefore, in this review article, fractional derivative models in cancer treatment modeling are presented to show the flexibility and importance of fractional derivative models in cancer treatment modeling. As a result, 11 articles based on cancer treatment with fractional derivative models are reviewed, and the various contributions are summarized. The inclusion criteria are articles with fractional mathematical models for cancer treatments like chemotherapy, immunotherapy, hyperthermia, and radiotherapy. The articles were selected from various online databases which included Scopus, EBSCOHost, ScienceDirect Journal, SpringerLink Journal, Wiley Online Library, and Google Scholar. Also included are the various definitions of fractional derivative from different mathematicians. Subsequently, the future direction for cancer treatment research is suggested.

This review article is arranged in sections. In Section 2, the method used for the review is presented which includes the various definitions, and the summary of the selected articles from the databases. In Section 3, the reviewed articles are analyzed by presenting the cancer treatments and the fractional derivative in tabular form. Furthermore, based on the analysis, the future direction for cancer treatment research is suggested. Lastly, the article is concluded with a summary of the potential implications of this research and suggestions for further research.

Methods

This section presents the various definitions of fractional derivatives as well as the summary of the selected articles.

Definitions of fractional derivatives

The various definitions of fractional derivatives are given by Equations (1-22) with Equations (1-10) from Dalir and Bashour [3].

1. Riemann-Liouville

$$ {}_{a}^{RL}D_{t}^{\alpha} f(t) = \frac{1}{\Gamma(n-\alpha)}\left(\frac{d}{dt}\right)^{n} \int_{a}^{t} \frac{f(\tau)}{(t-\tau)^{\alpha+1-n}}\, d\tau \qquad n-1 \le \alpha < n \quad n \in R \tag{1} $$

2. M. Caputo (1967)

$$ {}_{a}^{C}D_{t}^{\alpha} f(t) = \frac{1}{\Gamma(n-\alpha)} \int_{a}^{t} \frac{f^{(n)}(\tau)}{(t-\tau)^{\alpha+1-n}}\, d\tau \qquad n-1 \le \alpha < n \tag{2} $$

3. L. Euler (1730)

$$ \frac{d^{\alpha}}{dt^{\alpha}} t^{n} = \frac{\Gamma(n+1)}{\Gamma(n-\alpha+1)} t^{n-\alpha} \tag{3} $$

4. J.B.J Fourier (1820-1822)

$$ \frac{d^{n}}{dx^{n}} f(x) = \frac{1}{2\pi} \int_{-\infty}^{\infty} f(z)dz \int_{-\infty}^{\infty} \cos\left(px - pz + n\frac{\pi}{2} \right) dp \tag{4} $$

5. N.H. Abel (1823-1826)

$$ s(x) = \frac{1}{\Gamma(1-\alpha)} \frac{d^{-\alpha}}{dx^{-\alpha}} \Psi(x) \tag{5} $$

6. J. Liouville (1832-1855)

$$ \frac{d^{\alpha}}{dx^{\alpha}} F(x) = \frac{(-1)^{\alpha}}{h^{\alpha}} \left(F(x)\frac{\alpha}{1} F(x+h) + \frac{\alpha(\alpha-1)}{1.2} F(x+2h) \ldots\ldots\ldots\ldots \right) \tag{6a} $$

$$ \frac{d^{\alpha}}{dx^{\alpha}} F(x) = \frac{1}{h^{\alpha}} \left(F(x)\frac{\alpha}{1} F(x-h) + \frac{\alpha(\alpha-1)}{1.2} F(x-2h) \ldots\ldots\ldots\ldots \right) \tag{6b} $$

7. N. Ya Sonin (1869), A.V. Letnikov (1872), H. Laurent (1884), N. Nekrasove (1888), K. Nishimoto (1987)

$$D^{\alpha} f(z) = \frac{\Gamma(\alpha+1)}{2\pi i} \int_{C}^{x+} \frac{f(t)}{(t-z)^{\alpha+1}} dt \tag{7}$$

8. Grunwald-Letnikov

$${}_{a}D_{t}^{\alpha} f(t) = \lim_{h\to 0} \frac{1}{h^{\alpha}} \sum_{j=0}^{\frac{t-a}{h}} (-1)^{j} \binom{\alpha}{j} f(t-jh) \tag{8}$$

9. Jumarie [4], *modified Riemann-Liouville*

$$D_{t}^{\alpha} f(t) = \frac{1}{\Gamma(n-\alpha)} \left(\frac{d}{dt}\right)^{n} \int_{0}^{t} \frac{f(\tau)}{(t-\tau)^{\alpha+1-n}} [f(\tau) - f(0)] d\tau \tag{9}$$

10. Reisz [5] 10a; [6] 10b

$${}^{R}D_{t}^{\alpha} f(t) = \frac{1}{\Gamma(n-\alpha)} \left(\frac{d}{dt}\right)^{n} \int_{a}^{b} \frac{f(\tau)}{|t-\tau|^{\alpha+1-n}} d\tau \qquad \alpha > 0 \tag{10a}$$

$$D_{x}^{\alpha}(f(x)) = -\frac{1}{2\cos\left(\alpha\frac{\pi}{2}\right)} \times \left\{ \frac{1}{\Gamma(\alpha)} \left(\frac{d}{dx}\right)^{n} \times \left(\int_{-\infty}^{\infty} (x-t)^{n-\alpha-1} f(t) dt + \int_{x}^{\infty} (t-x)^{n-\alpha-1} f(t) dt \right) \right\} \tag{10b}$$

11. Reisz-Caputo [5]

$${}^{C}D_{t}^{\alpha} f(t) = \frac{1}{\Gamma(n-\alpha)} \int_{a}^{b} \frac{1}{|t-\tau|^{\alpha+1-n}} \left(\frac{d}{dt}\right)^{n} f(\tau) d\tau \qquad \alpha > 0 \tag{11}$$

12. Hadamard [7, 8]

$$D_{a}^{\alpha} f(x) = \frac{1}{\Gamma(n-\alpha)} \left(x\frac{d}{dx}\right)^{n} \int_{a}^{x} \left(\log\frac{x}{\tau}\right)^{n-\alpha-1} \frac{d\tau}{\tau} \qquad x > a \geq 0 \tag{12}$$

13. Erdelyi-Kober [3, 9]

Fractional integral operator

$$\left(I_{a+;\rho,\eta}^{\alpha} f\right)(x) = \frac{\rho x^{-\rho(\alpha+\eta)}}{\Gamma(\alpha)} \int_{a}^{x} \frac{\tau^{\rho\eta+\rho-1} f(\tau)}{\left(x^{\rho}-\tau^{\rho}\right)^{1-\alpha}} d\tau \qquad x > a \geq 0 \quad \mathrm{Re}(\alpha) > 0 \tag{13a}$$

and Fractional derivative

$$\left(D_{a+;\rho,\eta}^{\alpha} f\right)(x) = x^{-\rho\eta} \left(\frac{1}{\rho x^{\rho-1}} \frac{d}{dx}\right)^{n} x^{\rho(n+\eta)} \left(I_{a+;\rho,\eta+\alpha}^{n-\alpha} f\right)(x)$$

(13b)

$x > a$, $\mathrm{Re}(\alpha) > 0,\ \rho > 0$

14. Osler [10]

$$\left(D^{\alpha}_{a+;g} f\right)(x) = \frac{1}{\Gamma(n-\alpha)}\left(\frac{1}{g'(x)}\frac{d}{dx}\right)^{n}\int_{a}^{x}\frac{g'(\tau)f(\tau)}{\left[g(x)-g(\tau)\right]^{\alpha-n+1}}d\tau \tag{14}$$

Where $x > a$, $\mathrm{Re}(\alpha) \geq 0$, and $g(x)$ is an increasing and positive function on (α,∞) having a continuous derivative $g(x)$ on (a,∞)

15. Generalized fractional derivative [5, 11]

$$\left({}^{\rho}D^{\alpha}_{a+} f\right)(x) = \frac{\rho^{\alpha-n+1}}{\Gamma(n-\alpha)}\left(x^{1-\rho}\frac{d}{dx}\right)^{n}\int_{a}^{x}\frac{\tau^{\rho-1}f(\tau)}{\left(x^{\rho}-\tau^{\rho}\right)^{\alpha-n+1}}d\tau \tag{15a}$$

$$\left({}^{\rho}D^{\alpha}_{b-} f\right)(x) = \frac{\rho^{\alpha-n+1}}{\Gamma(n-\alpha)}\left(-x^{1-\rho}\frac{d}{dx}\right)^{n}\int_{x}^{b}\frac{\tau^{\rho-1}f(\tau)}{\left(\tau^{\rho}-x^{\rho}\right)^{\alpha-n+1}}d\tau \tag{15b}$$

$$D^{\alpha}(f)(t) = \lim_{h\to 0}\frac{f\left(te^{ht^{-\alpha}}\right)-f(t)}{h} \tag{15c}$$

Where $\alpha \in C$, $\mathrm{Re}(\alpha) \geq 0,\ \rho > 0,\ n = \left[\mathrm{Re}(\alpha)\right]+1,\ 0 \leq a < x < b \leq \infty$

16. Conformable fractional derivative [12]

$$T_{\alpha}(f)(t) = \lim_{h\to 0}\frac{f\left(t+ht^{1-\alpha}\right)-f(t)}{h} \qquad f:[0,\infty]\to R \text{ for all } t>0,\ \alpha\in(0,1) \tag{16}$$

17. Caputo-Fabrizio [13]

$$D^{\alpha}_{t} f(t) = \frac{M(\alpha)}{(1-\alpha)}\int_{a}^{t}\exp\left[-\frac{\alpha(t-\tau)}{1-\alpha}\right]\frac{d}{dt}f(\tau)d\tau \tag{17}$$

Where $M(\alpha)$ is a normalization function such that $M(0)=M(1)=1,\ \alpha\in[0,1],\ a\in[-\infty,t]$, and $f \in H^{1}(a,b)$, $b>0$, $H^{1}(a,b)$ is a Sobolev space.

18. New Caputo-Fabrizio [14]

$$D^{\alpha}_{t} f(t) = \frac{(2-\alpha)M(\alpha)}{2(1-\alpha)}\int_{0}^{t}\exp\left[-\frac{\alpha(t-\tau)}{1-\alpha}\right]\frac{d}{dt}f(\tau)d\tau \tag{18}$$

Where $M(\alpha)$ is a normalization function $t \geq 0$

19. Riesz partial fractional derivative [15] $1 < \alpha \leq 2$

$$\frac{\partial^{\alpha}u(x,t)}{\partial|x|^{\alpha}}=\frac{1}{2\cos\left(\alpha\frac{\pi}{2}\right)\Gamma(2-\alpha)}\frac{d^{2}}{dx^{2}}\int_{-\infty}^{\infty}|x-\xi|^{1-\alpha}u(\xi,t)d\xi \tag{19}$$

20. Weyl fractional derivative [6]

$$D_{x}^{\alpha}f(x)=\frac{1}{\Gamma(n-\alpha)}\left(\frac{d}{dx}\right)^{n}\int_{x}^{\infty}\frac{f(t)}{(x-t)^{\alpha+1-n}}dt \tag{20}$$

21. $\Psi-Hilfer$ (left-sided and right-sided) fractional derivative of the function $f\in C^{n}(a.b)$, $n-1<\alpha<n$, $0\le\beta\le1$, and I are the fractional integrals [16]

$$D_{a+}^{\alpha,\beta}f(x)=I_{a+}^{\gamma-\alpha}\left(\frac{d}{dx}\right)^{n}I_{a+}^{(1-\beta)(n-\alpha)}f(x) \tag{21a}$$

$$D_{b-}^{\alpha,\beta}f(x)=I_{b-}^{\gamma-\alpha}\left(-\frac{d}{dx}\right)^{n}I_{b-}^{(1-\beta)(n-\alpha)}f(x) \tag{21b}$$

22. Atangana-Baleanu-Caputo (ABC) new fractional derivative and the Atangana-Baleanu-Riemann (ABR) new fractional derivative are given by equations

$${}_{b}^{ABC}D_{t}^{\alpha}f(t)=\frac{B(\alpha)}{(1-\alpha)}\int_{b}^{t}f'(x)E_{\alpha}\left[-\frac{\alpha(t-x)^{\alpha}}{1-\alpha}\right]dx \tag{22a}$$

and

$${}_{b}^{ABR}D_{t}^{\alpha}f(t)=\frac{B(\alpha)}{(1-\alpha)}\frac{d}{dt}\int_{b}^{t}f(x)E_{\alpha}\left[-\frac{\alpha(t-x)^{\alpha}}{1-\alpha}\right]dx \tag{22b}$$

respectively. Where $\alpha\in[0,1]$, $f\in H^{1}(a,b)$, $b>a$, $B(\alpha)$ is the same as in Caputo-Fabrizio fractional derivative and E_{α} is the Mittag-Leffler function given by

$$E_{\alpha}(-t^{\alpha})=\sum_{K=0}^{\infty}\frac{(-t)^{\alpha K}}{\Gamma(\alpha K+1)} \tag{22c}$$

These two equations (22a) and (22b) have non-local and non-singular kernels [17]. It can be observed in (22a) that if the function is a constant, the fractional derivative becomes zero.

Despite these various definitions for fractional derivatives, the most popular ones are the *Riemann-Liouville* and the *Caputo* fractional derivatives. However, the *Riemann-Liouville* fractional derivative of a constant is not zero, but that of the *Caputo* fractional derivative is zero. Hence, the *Caputo* fractional derivative is more commonly used for mathematical modeling than the *Riemann-Liouville* fractional derivative. Also, the *Caputo-Fabrizio* fractional derivative of Caputo and Fabrizio [13] and [14], and the new fractional derivative of Atangana and Baleanu [17] are non-singular kernel versions of the *Caputo* fractional derivative.

Fractional cancer treatment models

This section presents a summary of the selected articles with fractional cancer treatment models. The articles spanned from 2014 to 2020, and the selections from the online databases are in the following order Scopus (1 article), EBSCOHost (4 articles), ScienceDirect Journal (1 article), SpringerLink Journal (1 article), Wiley Online Library (1 article), and Google Scholar (3 articles). The summaries are presented below.

Firstly, an interesting application of fractional derivative in cancer treatment modeling was done by Damor, et al. [18]. The authors used the Caputo fractional derivative for the Pennes bioheat equation to represent the hyperthermia cancer treatment process where the pathological tissue's temperature is raised above cytotoxic temperature (41^0C-45^0C) and the healthy tissues are not overexposed. The success of hyperthermia depends on the knowledge of the heat transfer mechanism in the blood perfused tissue. Hence, the authors used the fractional Pennes bioheat model to determine the temperature profile and thermal damage to the treatment process over the treated region. The variables and parameters of the model include density, specific heat, thermal conductivity, temperature, time, and distance. Also included are the artile temperature rate, blood perfusion rate, metabolic heat generation, and the external heat source in the skin tissue. Subsequently, the fractional bioheat model was solved numerically with an implicit finite difference scheme while the stability of the scheme was discussed using the Fourier analysis. The model, with different fractional orders, was then used to simulate temperatures profiles in the tissue domain. It was shown that the time required to reach the temperature 46 ^{o}C was less with the use of the fractional Pennes bioheat model than with the use of the classic Pennes bioheat model. From the results of the simulations, this time decreased as the fractional orders decreased. Also, when the fractional order decreases, the penetration distance and the maximum temperature increase in the affected region. Finally, the required value of the thermal damage was obtained from the fractional model by using the fractional-order of 0.7.

Similarly, Kumar and Rai [19] used the fractional dual-phase-lag bioheat transfer (DPLBHT) model to investigate the thermal behavior of living biological tissues during the treatment of tumors with thermal therapy (hyperthermia). The authors also used the Caputo fractional derivative and subjected the model to the Dirichlet boundary condition in the presence of metabolic and electromagnetic heat sources during the thermal treatment. The authors solved the model numerically with the appropriate physiological parameters by using the finite element Legendre wavelet Galerkin method (FELWGM). The finite element different scheme was used to spatially discretize the model, this discretization converted the model into a system of time-fractional ordinary differential equations which was then solved by converting to the Sylvester matrix equation using the Legendre wavelet Galerkin approach with the block pulse function in sense of Caputo fractional derivative. Also, different fractional orders were used for numerical analysis, the numerical solutions were compared with the exact solution in a specific case and the results coincided. The numerical results showed the temperature distribution in the tissue. From the analysis, it was observed that the temperature distribution in the tissue increased as the values of the fractional-order derivative increased with respect to space. Furthermore, the model parameters such as the time-fractional derivative, lagging times, blood perfusion coefficient, metabolic heat source, and the transmitted power on temperature distribution were varied and the effects on the temperature distribution in the skin tissue were analyzed. It was concluded that the success of thermal therapy for treating metastatic cancer depended on the time-fractional order derivative to precise prediction and control of temperature.

Furthermore, the Caputo time-fractional derivative was used by Akman Yıldız, et al. [20] to model the effect of obesity on cancerous tumor growth when chemotherapy and immunotherapy treatments were administered. The authors justified the use of fractional derivatives based on its memory feature, and they considered an optimal control problem which gave the minimum treatment doses for the tumor population destruction. The model was a coupled system of fractional differential equations (FDEs) whose state variables include the tumor cells, the immune cells, the fat cells, and the chemotherapeutic and immunotherapeutic drug concentrations. Also, the model's control variables include the doses of the chemotherapeutic and immunotherapeutic drugs. The objective of the optimal control problem was to find the value of cost function for the control variables which minimized the tumor population and the drug doses over a finite time interval. The authors established the conditions for the existence of unique positive solutions and optimal solutions for the model and thereafter investigated the existence and stability of the tumor-free and coexistence equilibrium points. The model was solved numerically by discretizing the system of FDEs using the L1 method, and then the nonlinear state equation was linearized with the Newton method, after which the resulting matrix system was solved iteratively. The numerical analysis was used to investigate three cancer treatment strategies which were chemotherapy, immunotherapy, and the combination

of the two. This was done by examining the value of the decay rate of the chemotherapeutic drug to the value of the cost function. Also, the fractional orders of the Caputo fractional derivatives used for the numerical analysis were 0.65, 0.75, 0.85, and 0.95. The numerical values used for the analysis were obtained from previous literature and estimated values. From the results of the analysis, the authors concluded that the combination of immunotherapy and chemotherapy gave the optimal control for the cancerous tumor in the presence of obesity.

Additionally, Yıldız, et al. [21] used the fractional derivatives to formulate a fractional optimal control problem (FOCP) model governed by the cancer-obesity with and without a singular kernel. The author used the Caputo fractional derivative with a singular kernel and Caputo-Fabrizio fractional derivative without a singular kernel. The FOCP model aimed to determine the optimal doses of chemotherapeutic and immunotherapeutic drugs that give the minimum difference between the populations of the tumor cells and the normal cells. Also, the FOCP model was used to investigate the effects of obesity on the choice and treatment schedules for the patients based on low and high caloric diets. The fractional model was a coupled system of FDEs whose variables represented the tumor cells, the immune cells, the normal cells, the fat cells, and the injected chemotherapeutic and immunotherapeutic drugs. Furthermore, the two control variables were included to obtain the optimal doses for the chemotherapeutic and immunotherapeutic drugs. The model parameters represented the treatment process which involved the growth rates, the competitions, the response rates, the decay rates, and the interaction between the cells and the control drugs. Subsequently, the existence and stability of the tumor-free and the coexistence equilibrium points. The authors then solved the fractional model numerically using the L1 formula. From the numerical solutions, the authors simulated different treatment schedules over 100 days with fractional orders 0.85, 0.9, and 0.95. The different simulated treatment schedules included no control, immunotherapy, chemotherapy, and combined immunotherapy and chemotherapy. The presented simulated solutions were the populations of the tumor and fat cells for low and high caloric diets under no control conditions; populations of the tumor cells, immune cells, fat cells, and normal cells for low caloric diet under immunotherapy; populations of the tumor cells, immune cells, fat cells, normal cells, as well as the drug doses for low caloric and high caloric diet during chemotherapy. Also simulated were the populations of the cells and the doses of the drugs for low and high caloric diets during a combined immunotherapy and chemotherapy treatments. Finally, the authors compared the results obtained from the simulations and by the two derivatives and concluded that a combined therapy provided the best results while the Caputo-Fabrizio fractional derivative was more efficient for the fractional model.

In continuation, Sweilam and AL-Mekhlafi [22] presented a Caputo fractional tumor model under immune suppression. The proposed model aimed to give the optimal control mechanism for the minimization of the tumor cells. The model was a system of 11 FDEs whose variables represented the interacting cells and the concentration of chemotherapeutic drugs in the bloodstream. The interacting cells included the tumor cells, the Natural killer (NK) cells, the $CD8^+$ T cells, the unlicensed and licensed dendritic cells, the $CD4^+$ T cells, the *(IL-2)* cells, the regulatory T cells, the $(TGF-\beta)$ cells, and the *(IL -10)* cells. Also, the model parameters represented the tumor immune suppression processes. These processes were partitioned into the innate immune response, the adaptive immune response, and the immune suppression. Subsequently, the authors introduced two control functionals into the model to measure the optimal control for chemotherapy and immunotherapy. The authors used numerical values obtained from previous publication for the model parameters, after which they gave necessary conditions for the existence and uniqueness of solution for the control problem. The model was then solved numerically with the transversality conditions by using the Nonstandard Generalized Euler Method (NGEM) and the Generalized Euler Method (GEM). The authors used fractional orders of 0.8, 0.90, 0.95, and 1 to simulate the evolution of the model state variables over time by considering the no treatment case and the immunosuppressive effects with the control case. Finally, the stability analysis of the NGEM was done and it was concluded that the NGEM was conditionally stable. Also, the results of the control functionals from the methods were compared and it was shown that the NGEM produced better results.

Another important contribution was presented by Asjad [23], the author used the fractional energy balance model to represent hyperthermia breast cancer therapy in a porous medium. The fractional model was studied with the Caputo and the ABC fractional derivatives. The author solved the model and obtained semi exact solutions with the use of Laplace transforms. From the solutions, the steady-state time needed to reach the therapeutic temperature that causes the death of the tumor cell was computed. The author also showed that the ABC fractional derivative was better suited for representing the memory effect of the temperature function. Also, Morales-Delgado, et al. [24] presented a fractional-order cancer chemotherapy effect model. The authors introduced the Caputo-Fabrizio and the Atangana-Baleanu fractional derivates in the Liouville-Caputo sense,

into the classical cancer chemotherapy effect model. The model consists of four differential equations whose variables represented the normal cells, the tumor cells, the immune cells, and the chemotherapeutic drugs. Also, the chemotherapeutic treatment processes were represented with the model parameters. The authors obtained approximate-analytical solutions for the model with the use of the Laplace homotopy perturbation method and the modified homotopy analysis transform method. The Laplace homotopy perturbation method was a combination of the homotopy analysis method and the Laplace transform while the modified homotopy analysis transform method was a combination of the homotopy analysis method and Laplace transform with homotopy polynomial. Subsequently, the model was solved analytically and numerically. The authors developed general schemes to produce approximate solutions of the fractional equations, these solutions were given in a series form which converged rapidly. The approximate solutions from the fractional equations agreed with previous results from classical equations as well as the numerical solutions, which suggested that the model was well-posed and effective. Although the authors did not use real-life clinical data, the model can be used for analyzing the effects of chemotherapeutic drugs during cancer treatment.

Also, Baleanu, et al. [25] presented a fractional-order model for analyzing the tumor-immune surveillance and optimal control mechanism. The model was a system of six FDEs whose variables included the various interacting cells' populations. The interacting cells comprised the NK cells, the activated $CD8^+$ cytotoxic T lymphocyte (CTL) cells, and the naive tumor cells with no mechanism to escape the immune cells. The remaining three model variables represented the tumors cells that flee the activated $CD8^+$ CTL cells, NK cells, and both the CTL and NK cells, respectively. The tumor-immune mechanism was represented by the model parameters. These parameters represented the NK cells' external influx, the CTL cells' death rate, the tumor cells' growth rate, the tumor cells' carrying reciprocal capacity, the NK and CTL cells' binding rates to the naïve tumor cells, the CTL cells' rate survived from CTL tumor complex, and the recruitment rates of CTL cells due to the tumor complex in naive-type and wild-type respectively. The other parameters represented the CTL and NK cells' detached from the tumor complex wild-type, the tumor cells' proportion in wild-type fled from CTL and NK cells, the NK cells and CTL cells' ratio survived from the naive-type tumor cells, the naïve-type tumor cells ratio that flees the interplay with CTL and NK cells, and the maximum extraction of CTL cells by the tumor immunogenetic cells. The chemotherapy effects on the tumor cells were then investigated by introducing a control variable, which represented the chemotherapy drug concentration, into the model. The introduced control variable turned the model to a fractional optimal control tumor-immune model. This chemotherapy control variable induced tumor cells' death which was represented by cell death parameters. These parameters were the chemotherapy-induced tumor cells' death rate which flees from activated $CD8^+$ CTL cells, NK cells, and both $CD8^+$ CTL and NK cells. Also represented were the chemotherapy-induced $CD8^+$ CTL and NK cells' death rates. Subsequently, the authors assigned numerical values to the model parameters and solved the tumor-immune numerically with the predictor-corrector method. The numerical solutions and the stability analysis were done with three types of fractional derivatives which included the Caputo, Caputo-Fabrizio, and the Atangana-Baleanu-Caputo (ABC) fractional derivatives. The numerical solutions were used to simulate the growth of the tumor and immune cells' populations over 60 days. These numerical solutions were done by using the fractional orders of 0.9, 0.93, 0.96, and 0.99 with each of the defined fractional derivatives. The numerical simulations were done with and without chemotherapy control variables. The authors corroborated the model by comparing the simulated results of the growth of the naive tumor cells' populations with reported clinical data given by Mahasa, et al. [26]. The orders of the fractional derivatives which coincided with the reported clinical data were 0.952 for the Caputo, 0.92 for Caputo-Fabrizio, and 0.9 for the ABC fractional derivatives. From the results, it was concluded that the fractional model was well suited for modeling the biological process, but the performance of the fractional model depended on the fractional-order and the type of fractional derivative.

In addition, we present the fractional radiotherapy cancer treatment models. Dokuyucu, et al. [27] presented a fractional radiotherapy cancer treatment model which was a fractional version of the previous ordinary derivative cancer treatment model formulated by Belostotski and Freedman [28]. Dokuyucu, et al. [27] integrated the Caputo-Fabrizio fractional derivative into the previous cancer treatment model. Thereafter, the authors used the fixed-point theory to establish the conditions for the existence and uniqueness of solutions for the model. Therefore, based on the established conditions, the authors showed that the presented fractional cancer treatment model has a unique positive solution. Similarly, Awadalla, et al. [29] presented the same model but with a different type of fractional derivative in the model. Awadalla, et al. [29] integrated the Hadamard fractional derivative into the cancer treatment model. The authors also established the conditions for the existence and uniqueness of a positive solution for the fractional model. The fractional cancer treatment models presented by Dokuyucu, et al. [27] and Awadalla, et al. [29] were limited to theoretical formulations and were not corroborated with clinical or empirical data.

Finally, Farayola, et al. [30] presented a radiotherapy cancer treatment model based on the Caputo fractional derivative. The model was formulated by improving the previous ordinary derivative cancer treatment model by Belostotski and Freedman [28]. The authors integrated the Caputo fractional derivative into the previous ordinary derivative cancer treatment model and incorporated the linear-quadratic with the repopulation model into it to account for the cells' population decay due to radiotherapy. The model variables represented the populations of the normal and cancer cells coexisting in the same region. Also, the model parameters represented the radiotherapy process which included the proliferation rates of the cells, the competition coefficients between the cells that reduce the cells' populations, and the radiation-induced cell deaths. Thereafter, the model was used to simulate the treatment process of six uterine cervical cancer patients treated with radiotherapy. From the results of the simulations, the final populations of the normal and cancer cells were obtained. From these final populations of cells, the final tumor volumes as well as the final volumes occupied by the normal cells were simulated and the simulated volumes agreed with the published clinical data. Also, the sensitivity analysis of the model was done to establish the relative importance of each model factor and it was concluded that the most sensitive controllable model factor was the fractional order of the Caputo fractional derivative. Thereafter, the authors also used the biologically effective dose (BED) formula to simulate 96 different treatment protocols from the data of the six patients. These simulated protocols were then used to formulate a regression equation for estimating an approximate fractional-order for the Caputo fractional derivative from the value of the radiation dose.

Results and discussion

This section presents a table of the summarized articles. Table 1 gives the authors, the year, the title of the article, the type of cancer treatment, and the type of fractional derivative used in the summarized articles. From the table, the future direction for cancer treatment is suggested.

Table 1. Fractional cancer treatment models

Author(s)	Year	Title	Cancer treatment	Fractional Derivative
Damor, R., Kumar, S., & Shukla, A.	2014	Numerical simulation of fractional bioheat equation in hyperthermia treatment	Hyperthermia	Caputo
Kumar, D., & Rai, K.	2017	Numerical simulation of time fractional dual-phase-lag model of heat transfer within skin tissue during thermal therapy	Thermal therapy (Hyperthermia)	Caputo
Akman Yıldız, T., Arshad, S., & Baleanu, D.	2018	Optimal chemotherapy and immunotherapy schedules for a cancer-obesity model with Caputo time fractional derivative	Chemotherapy & Immunotherapy	Caputo
Yıldız, T. A., Arshad, S., & Baleanu, D.	2018	New observations on optimal cancer treatments for a fractional tumor growth model with and without singular kernel	Chemotherapy, Immunotherapy, & Combined	Caputo & Caputo-Fabrizio

Author(s)	Year	Title	Cancer treatment	Fractional Derivative
Sweilam, N., & AL-Mekhlafi, S.	2018	Optimal control for a nonlinear mathematical model of tumor under immune suppression: A numerical approach	Immune suppression & Chemotherapy	Caputo
Asjad, M. I.	2019	Fractional mechanism with power law (singular) and exponential (non-singular) kernels and its applications in bio heat transfer model.	Hyperthermia	Caputo & ABC
Morales-Delgado, V. F., Gómez-Aguilar, J. F., Saad, K., & Escobar Jiménez, R. F.	2019	Application of the Caputo-Fabrizio and Atangana-Baleanu fractional derivatives to mathematical model of cancer chemotherapy effect.	Chemotherapy	Caputo-Fabrizio & ABC
Baleanu, D., Jajarmi, A., Sajjadi, S., & Mozyrska, D.	2019	A new fractional model and optimal control of a tumor-immune surveillance with non-singular derivative operator	Tumor-immune surveillance chemotherapy	Caputo, Caputo-Fabrizio, & ABC
Dokuyucu, M. A., Celik, E., Bulut, H., & Baskonus, H. M.	2018	Cancer treatment model with the Caputo-Fabrizio fractional derivative	Radiotherapy	Caputo-Fabrizio
Awadalla, M., Yameni, Y., & Abuassba, K.	2019	A new Fractional Model for the Cancer Treatment by Radiotherapy Using the Hadamard Fractional Derivative	Radiotherapy	Hadamard
Farayola, M. F., Shafie, S., Siam, F. M., & Khan, I.	2020	Mathematical modeling of radiotherapy cancer treatment using Caputo fractional derivative	Radiotherapy	Caputo

Future direction for cancer treatment modelling

The cancer treatment is a process that spans over a period and the use of the fractional derivative model represents this entire process in a more accurate way due to its memory effect as well as its non-locality. From Table 1, it was shown that all the different types of cancer treatment can be modeled with fractional derivative models. It can also be seen that despite the various definitions of fractional derivatives, the Caputo fractional derivative and its non-singular kernel versions, Caputo-Fabrizio and ABC fractional derivatives, were used more in the models. However, the major bottleneck in using the fractional derivative is the choice of the fractional-order because it is the most sensitive controllable model factor [30] and it is also a memory-index for the specific process [2]. However, this bottleneck can be solved by corroborating the model with experimental or clinical data. Therefore, the future direction for cancer treatment modeling is the use of fractional derivative models, especially the Caputo fractional derivative and its non-singular kernel versions. Furthermore, to choose the appropriate fractional-order and guarantee more accurate results, the models should be corroborated with experimental or clinical data. By formulating and using corroborated fractional derivative models, \the simulated results will be more clinically relevant and such simulated results can be used for analyzing and predicting different cancer treatment protocols. Hence, mathematicians in collaboration with clinical scientists can make impactful contributions to cancer treatment research.

Conclusions

In this review article, the various definitions of fractional derivatives were presented as well as previous works on fractional derivative cancer treatment models. The fractional models were used for different cancer treatments like hyperthermia, immunotherapy, chemotherapy, combined chemotherapy and immunotherapy, and radiotherapy. The most used fractional derivatives in the cancer treatment models were the Caputo fractional derivative and its non-singular kernel versions. It was concluded that prospects for cancer treatment modeling lie in fractional derivative models corroborated with experimental or clinical data.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Acknowledgments

The authors would like to acknowledge the Ministry of Higher Education Malaysia and Research Management Centre-UTM, Universiti Teknologi Malaysia (UTM) for financial support through vote numbers FRGS/1/2019/STG06/UTM/02/22 ,4B583, 02M40 and 07G75.

References

[1] B. Ross, "A brief history and exposition of the fundamental theory of fractional calculus," in *Fractional calculus and its applications*, ed: Springer, 1975, pp. 1-36.
[2] M. Du, Z. Wang, and H. Hu, "Measuring memory with the order of fractional derivative,"*Scientific reports,* vol. 3, pp. 1-3, 2013.
[3] M. Dalir and M. Bashour, "Applications of fractional calculus," *Applied Mathematical Sciences,* vol. 4, pp. 1021-1032, 2010.
[4] G. Jumarie, "Modified Riemann-Liouville derivative and fractional Taylor series of nondifferentiable functions further results," *Computers & Mathematics with Applications,* vol. 51, pp. 1367-1376, 2006.
[5] U. N. Katugampola, "A new approach to generalized fractional derivatives," *Bull. Math. Anal. Appl,* vol. 6, pp. 1-15, 2014.
[6] A. Atangana and A. Secer, "A note on fractional order derivatives and table of fractional derivatives of some special functions," in *Abstract and applied analysis*, 2013.
[7] J. Hadamard, *Essai sur l'étude des fonctions, données par leur développement de Taylor*: Gauthier-Villars, 1892.
[8] A. A. Kilbas, H. M. Srivastava, and J. J. Trujillo, *Theory and applications of fractional differential equations* vol. 204: Elsevier, 2006.
[9] A. Erdélyi and H. Kober, "Some remarks on Hankel transforms," *The QuarterlyJournal of Mathematics,* pp. 212-221, 1940.
[10] T. J. Osler, "Leibniz rule for fractional derivatives generalized and an application to infinite series," *SIAM Journal on Applied Mathematics,* vol. 18, pp. 658-674, 1970.
[11] U. N. Katugampola, "A new fractional derivative with classical properties," *arXiv preprint arXiv:1410.6535,* 2014.
[12] R. Khalil, M. Al Horani, A. Yousef, and M. Sababheh, "A new definition of fractional derivative," *Journal of Computational and Applied Mathematics,* vol. 264, pp. 65-70, 2014.
[13] M. Caputo and M. Fabrizio, "A new definition of fractional derivative without singular kernel," *Progr. Fract. Differ. Appl,* vol. 1, pp. 1-13, 2015.
[14] J. Losada and J. J. Nieto, "Properties of a new fractional derivative without singular kernel," *Progr. Fract. Differ. Appl,* vol. 1, pp. 87-92, 2015.
[15] C. Çelik and M. Duman, "Crank–Nicolson method for the fractional diffusion equation with the Riesz fractional derivative," *Journal of computational physics,* vol. 231, pp. 1743-1750, 2012.
[16] J. V. d. C. Sousa and E. C. de Oliveira, "On the ψ-Hilfer fractional derivative," *Communications in Nonlinear Science and Numerical Simulation,* vol. 60, pp. 72-91, 2018.
[17] A. Atangana and D. Baleanu, "New fractional derivatives with nonlocal and non-singular kernel: theory and application to heat transfer model," *arXiv preprint arXiv:1602.03408,* 2016.
[18] R. Damor, S. Kumar, and A. Shukla, "Numerical simulation of fractional bioheat equation in hyperthermia treatment," *Journal of Mechanics in Medicine and Biology,* vol. 14, p. 1450018, 2014.
[19] D. Kumar and K. Rai, "Numerical simulation of time fractional dual-phase-lag model of heat transfer within skin tissue during thermal therapy," *Journal of Thermal Biology,* vol. 67, pp. 49-58, 2017.
[20] T. Akman Yıldız, S. Arshad, and D. Baleanu, "Optimal chemotherapy and immunotherapy schedules for a cancer-obesity model with Caputo time fractional derivative," *Mathematical Methods in the Applied Sciences,* vol. 41, pp. 9390-9407, 2018.

[21] T. A. Yıldız, S. Arshad, and D. Baleanu, "New observations on optimal cancer treatments for a fractional tumor growth model with and without singular kernel," *Chaos, Solitons & Fractals,* vol. 117, pp. 226-239, 2018.
[22] N. Sweilam and S. AL-Mekhlafi, "Optimal control for a nonlinear mathematical model of tumor under immune suppression: A numerical approach," *Optimal Control Applications and Methods,* vol. 39, pp. 1581-1596, 2018.
[23] M. I. Asjad, "Fractional mechanism with power law (singular) and exponential (non-singular) kernels and its applications in bio heat transfer model," *International Journal of Heat and Technology,* vol. 37, pp. 846-852, 2019.
[24] V. F. Morales-Delgado, J. F. Gómez-Aguilar, K. Saad, and R. F. Escobar Jiménez, "Application of the Caputo-Fabrizio and Atangana-Baleanu fractional derivatives to mathematical model of cancer chemotherapy effect," *Mathematical Methods in the Applied Sciences,* vol. 42, pp. 1167-1193, 2019.
[25] D. Baleanu, A. Jajarmi, S. Sajjadi, and D. Mozyrska, "A new fractional model and optimal control of a tumor-immune surveillance with non-singular derivative operator," *Chaos: An Interdisciplinary Journal of Nonlinear Science,* vol. 29, p. 083127, 2019.
[26] K. J. Mahasa, R. Ouifki, A. Eladdadi, and L. de Pillis, "Mathematical model of tumor–immune surveillance," *Journal of theoretical biology,* vol. 404, pp. 312-330, 2016.
[27] M. A. Dokuyucu, E. Celik, H. Bulut, and H. M. Baskonus, "Cancer treatment model with the Caputo-Fabrizio fractional derivative," *The European Physical Journal Plus,* vol. 133, p. 92, 2018.
[28] G. Belostotski and H. Freedman, "A control theory model for cancer treatment by radiotherapy," *Int. J. Pure Appl. Math,* vol. 25, pp. 447-480, 2005.
[29] M. Awadalla, Y. Yameni, and K. Abuassba, "A new Fractional Model for the Cancer Treatment by Radiotherapy Using the Hadamard Fractional Derivative," *Online Math.,* vol. 1, pp. 14-18, 2019.
[30] M. F. Farayola, S. Shafie, F. M. Siam, and I. Khan, "Mathematical modeling of radiotherapy cancer treatment using Caputo fractional derivative," *Computer Methods and Programs in Biomedicine,* vol. 188, p. 105306, 2020.