Fractional Tumour-Immune Model with Drug Resistance

Ana P. S. Koltun[1] · José Trobia[2] · Antonio M. Batista[1,2] · Ervin K. Lenzi[1,3] · Moises S. Santos[4] · Fernando S. Borges[1,5,6] · Kelly C. Iarosz[1,7] · Iberê L. Caldas[8] · Enrique C. Gabrick[1]

Abstract

Cancer is a group of diseases in which cells grow uncontrollably and can spread into other tissues. Various studies consider the interactions between cancer cells and the immune system as well as different types of treatment. Mathematical models have been used to study the growth of cancerous cells. We study a fractional order model that describes some aspects of the interactions among host, effector immune, and cancer cells. A drug treatment is considered to analyse the cancerous cells proliferation. Due to the chemotherapy, we split the fractional equation of the cancerous cells into drug sensitivity and resistance. We show that not only the chemotherapy but also the drug resistance plays an important role in the growth rate of cancer cells.

Keywords Tumour · Cancer model · Fractional calculus

1 Introduction

A tumour is an abnormal growth of cells in the body [1]. Depending on the type, the tumours can be benign or malignant [2]. A benign tumour does not invade nearby tissues and organs, and it does not spread to other regions of the body

✉ Ana P. S. Koltun
anapkoltun@gmail.com

1   Graduate Program in Science, State University of Ponta Grossa, 84030-900 Ponta Grossa, PR, Brazil

2   Department of Mathematics and Statistics, State University of Ponta Grossa, 84030-900 Ponta Grossa, PR, Brazil

3   Department of Physics, State University of Ponta Grossa, 84030-900 Ponta Grossa, PR, Brazil

4   Municipal Secretary of Education of Ponta Grossa, Ponta Grossa, PR, Brazil

5   Department of Physiology and Pharmacology, State University of New York Downstate Health Sciences University, Brooklyn, NY, USA

6   Center for Mathematics, Computation, and Cognition, Federal University of ABC, São Paulo, Brazil

7   University Center UNIFATEB, 84266-010, PR, Telêmaco Borba, Brazil

8   Physics Intitute, University of São Paulo, 05508-090 São Paulo, SP, Brazil

[3]. The malignant tumours are cancerous that not only grow uncontrollably, but also can spread to distant regions [4–9].

Procedures for cancer treatment depend on the type and stage of the tumours. Various methods of treatment for cancer have been available, such as surgery [10], radiation therapy [11], chemotherapy [12], immunotherapy [13, 14], and photodynamic therapy [15]. Combinations of treatments have been used in many patients, for instance combining immunotherapy and targeted therapies [16] and surgery with chemotherapy and radiation therapy [17].

It has been reported cancer resistance to chemotherapy [18]. The drug resistance is a serious challenge in the cancer treatment [19]. Shanker et al. [20] published a review article about the most common mechanisms related to drug resistance in lung cancer. The reduction in the effectiveness of chemotherapeutic agents was identified in various types of tumours, such as colon [21], pancreatic [22], and breast [23].

Mathematical models have been proposed to understand the dynamical behaviour of cancer cell proliferation [24]. Borges et al. [25] investigated a model for tumour growth under continuous and pulsed chemotherapy. Iarosz et al. [26] proposed a mathematical model of brain tumour with chemotherapy treatment. They found conditions for the inhibition of cancerous cell with a minimal effect on the neurons. A mathematical model of cancer treatment by immunotherapy was introduced by Nani and Freedman [27]. Mixed chemotherapy and immunotherapy were considered in a model developed by Pillis et al. [28]. It was shown that the

combination of therapies is able to eliminate cancer [29]. It has been developed and analysed cancer models that exhibit rich dynamic behaviour [30]. Recently, Sayari et al. [31] proposed a machine learning classification to identify fluctuations related to the growth rate of cancer cells.

Fractional differential equations have been used to model the dynamical behaviour of processes related to cell population [32], as well as interactions between cancer and normal cells [33, 34]. Kumar et al. [35] investigated the dynamic behaviour of tumour and normal cells for different fractional order values. Farayola et al. [36] reported numerical simulation of a fractional order cancer model with radiotherapy. A model for cancer treatment based on chemotherapeutic and immunotherapeutic drug concentrations was proposed by Hassani et al. [37]. Gabrick et al. [34] studied the effects of fractional operators in the dynamics of a cancer model.

We consider a fractional cancer model based on the Lotka-Volterra equations [38, 39]. The Lotka-Volterra equations have been used in predator–prey relationship. It was initially proposed to explore the dynamic behaviour between herbivorous animals and plants, as well as to analyse predatory fish. Without predator, the quantity of prey grows exponentially. The predator population can increase due to the prey consumption. Depending on the parameters, the predator and prey populations can oscillate [40]. Competition between healthy and cancerous cells can be described by the Lotka-Volterra equations [41]. Logistic growth has been included in the competitive Lotka-Volterra model to mimic the interactions among healthy cells, cancerous cells, and chemotherapeutic agents. We focus on a fractional cancer model due to the fact that captures nonlocal relations in space and time by means of power-law memory kernels [42]. In this work, we modify the fractional cancer model by splitting the equation of the cancerous cells into drug sensitivity and resistance [43]. We show that the drug resistance plays a crucial role in the growth rate of cancer cells.

The paper is organised as follows. In Section 2, we introduce the cancer model with fractional order derivatives. Section 3 shows our results about chemotherapy treatment and resistant cancerous cells. Finally, in the last section, we draw the conclusions.

2 Fractional Tumour-Immune Model

We include cancer drug resistance in a model based on Lotka-Volterra equations [44] that describes the interactions among host, effector immune, and cancerous cells [45]. Figure 1 exhibits a schematic representation of the interactions among the cells. The host cells do not interact with the effector immune cells. The cancerous cells interact with the host and effector immune cells. The chemotherapy drugs attack all cells, except the resistant cancer cells. Due
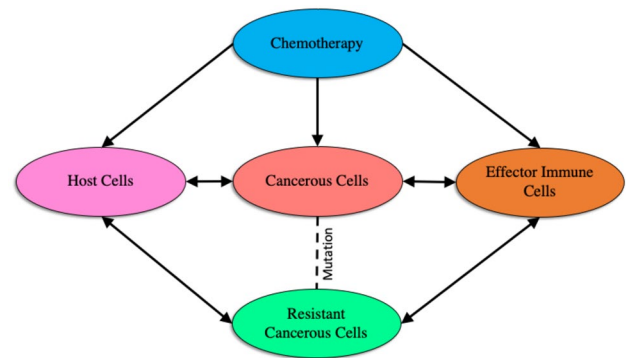

Fig. 1 Schematic representation of the model

to the chemotherapeutic agents, the sensitive cancerous cells convert to resistant cancerous cells by means of mutations.

As proposed in [39], these interactions can be described by the following set of normalised equations:

$$D^\gamma x = \rho_1 x(1-x) - \alpha_1 x(z_s + z_r) - \frac{a_1 xq}{b_1 + x}, \tag{1}$$

$$D^\gamma y = \frac{\rho_2 y(z_s + z_r)}{1 + (z_s + z_r)} - \alpha_2 y(z_s + z_r) - \delta_1 y - \frac{a_2 yq}{b_2 + y}, \tag{2}$$

$$D^\gamma z_s = z_s[1 - (z_s + z_r)] - xz_s - \alpha_3 yz_s - uF[q]z_s - \frac{a_3 z_s q}{b_3 + z_s}, \tag{3}$$

$$D^\gamma z_r = z_r[1 - (z_r + z_s)] - xz_r - \alpha_3 yz_r + uF[q]z_s, \tag{4}$$

$$D^\gamma q = \Phi - \theta q, \tag{5}$$

where x and y are the normalised population of host and effector immune cells, respectively. The normalised variable z_s corresponds to the sensitive tumour cell, z_r is the resistant, and $F(x)$ is defined as

$$F(x) = \begin{cases} 0, & x \leq 0, \\ 1, & x > 0. \end{cases} \tag{6}$$

The chemotherapeutic agent concentration is denoted by q. We have a fractional operator, and D^γ is the Caputo fractional differential operator and defined by

$$D^\gamma f(t) = \frac{1}{\Gamma(1-\gamma)} \int_0^t \frac{1}{(t-t')^\gamma} \frac{df}{dt'} dt', \tag{7}$$

where $\Gamma()$ is the gamma function and $\gamma \in [0, 1]$ [46].

The first term in Eq. (1) is a logistic function, the second term is the inhibition of the host cells by the tumour cells, and the third term describes the chemotherapy on the host cells. In Eq. (2), the first term (Michaelis-Menten term) is associated with the immunatory system stimulated by the

Table 1 Parameter values and description [39, 43]

Parameter	Values	Description
ρ_1	0.3–1.0	Proliferation rate
ρ_2	4.5	Proliferation rate
α_1	1.5	Loss influence
α_2	0.2	Loss influence
α_3	2.5	Loss influence
Φ	0–500	Infusion rate of chemotherapy
θ	0.3	Washout rate of chemotherapy
δ_1	0.5	Death rate
u	0.01–0.0001	Mutation rate
$a_1 = a_2 = a_3$	0.0001	Interaction coefficients
$b_1 = b_2 = b_3$	1	Holling type 2

tumour cells, the second term is the inactivation of the effector immune cells by the tumour cells, the third term corresponds to the natural die, and the fourth term describes the chemotherapy. In Eqs. (3) and (4), the first term is a logistic function, the second term represents the competition between host and tumour cells, and the third term corresponds to the death of the tumour by the effector immune cells. The term associated with the chemotherapy agent does not appear in Eq. (4). Equation (5) corresponds to the chemotherapy. The model parameters [39, 43] are described in Table 1.

Figure 2 displays the time evolution of $x(t)$, $y(t)$, and $z_s(t)$ for $q = 0$, $\gamma = 1$, (a) $\rho_1 = 04$, and (b) $\rho_1 = 0.5$. Without chemotherapeutic agents, z_r is equal to zero over time. In Fig. 2a, the normalised population of cells exhibit periodic behaviour after a transient time. Depending on the parameter values, it is possible to observe aperiodic behaviour, as shown in Fig. 2b.

3 Chemotherapy Treatment

Anticancer drugs can be put into the body by means of different protocols. One type of protocol is the continuous injection or infusion [47]. Dixon et al. [48] analysed
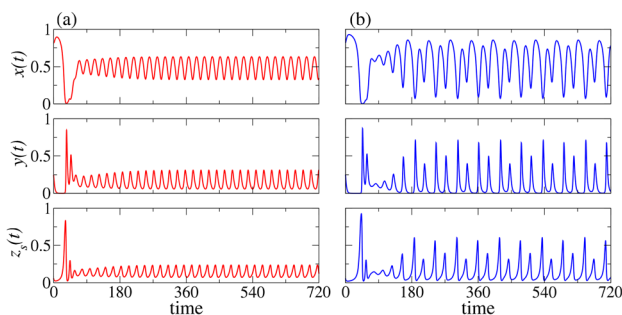
Fig. 3 Time evolution of $z_s(t)$ and $z_r(t)$ for $\Phi = 150$, $\rho_1 = 0.5$, $u = 0$ (blue line), $u = 10^{-3}$ (red line), and $\gamma = 1$ in **a** and **b**, and $\gamma = 0.9$ in **c** and **d**

continuous chemotherapy in responsive metastatic breast cancer. Tuettenberg et al. [49] demonstrated that continuous low-dose chemotherapy with temozolomide is a promising treatment option for patients with glioblastoma.

Figure 3 shows the normalised population of sensitive (z_s) and resistant (z_r) cancer cells as a function of the time for $\Phi = 150$ and $\rho_1 = 0.5$. In the panels a and b, we consider $\gamma = 1$. For $u = 0$ (blue line), there is no mutation to resistant cells ($z_r = 0$), and z_s exhibits an oscillatory behaviour. Considering $u = 10^{-3}$ (red line), z_r increases as a consequence of the drug resistance and z_s transforms into z_r, going to a value equal to zero. For $\gamma = 0.9$, as shown in the panels c and d, z_s goes to a constant value, and z_r remains equal to zero for $u = 0$ (blue line). When u is equal to 10^{-3}, the sensitive cancerous cells are killed by the chemotherapeutic agents while the normalised population of resistant cancerous cells increases. Our model exhibits a similar behaviour which was recently reported by Rabé et al. [50]. Due to the chemotherapy and mutation, the sensitive cancerous cells are suppressed, while the resistant cells can survive. According to Fig. 3b and d, z_r can display oscillatory behaviour by varying some parameters. By varying the parameters, it is possible to identify periodic and aperiodic behaviours.

Fig. 2 Time evolution of $x(t)$, $y(t)$, and $z_s(t)$ for $\phi = 0$ and $\gamma = 1$. We consider $\rho_1 = 0.4$ and $\rho_1 = 0.5$ in the panels **a** and **b**, respectively
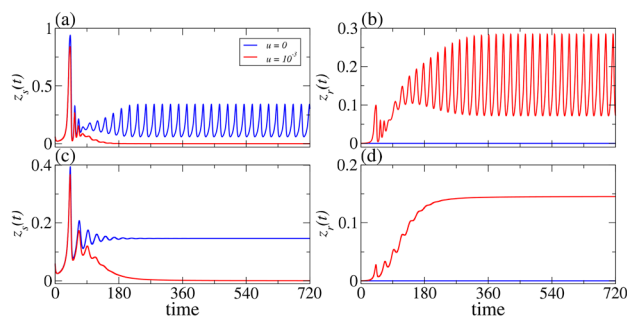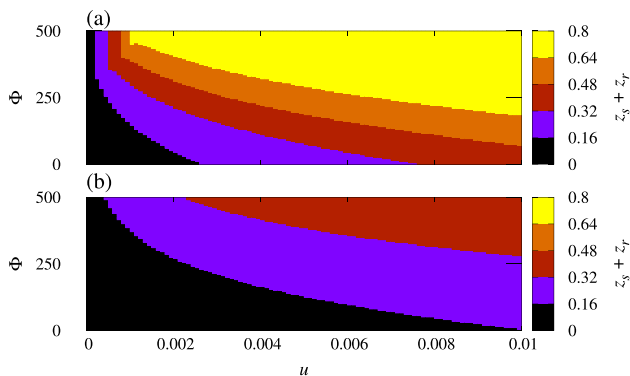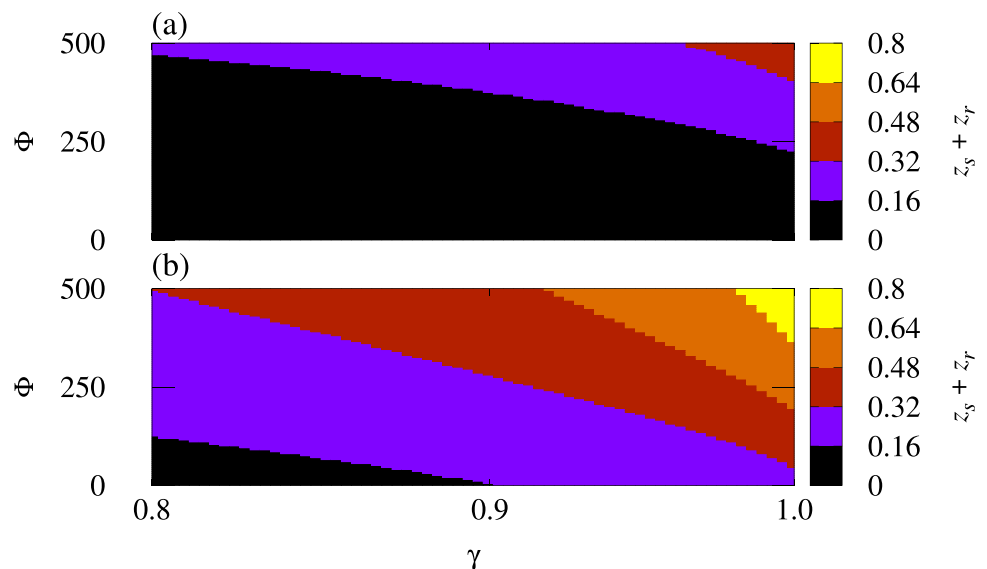
Fig. 4 Parameter space $\Phi \times u$ with $\rho_1 = 0.5$ for **a** $\gamma = 1$ and **b** $\gamma = 0.9$. The colour bar indicates the maximum value of $z_s + z_r$ in a time interval

Fig. 5 Parameter space $\Phi \times \gamma$ with $\rho_1 = 0.5$ for **a** $u = 10^{-3}$ and **b** $u = 10^{-2}$. The colour bar indicates the maximum value of $z_s + z_r$ in a time interval

In Fig. 4, we plot the parameter space $\Phi \times u$ with $\rho_1 = 0.5$ for $\gamma = 1$ and $\gamma = 0.9$ in the panels a and b, respectively. The colour bar represents the maximum value of $z_s + z_r$ in the time interval between 0 and 720. The best situation is denoted by the black region, in which $z_s + z_r < 0.16$. In the yellow region, it is possible to observe values of $z_s + z_r$ greater than 0.64. Figure 4a displays a large yellow region and a small black region, whereas there are no yellow and orange regions in Fig. 4b. Increasing u, even increasing Φ, the regions with high values of $z_s + z_r$ appear due to the drug resistance.

We compute the parameter space, $\Phi \times \gamma$, for $\rho_1 = 0.5$, as shown in Fig. 5. The colour bar indicates the values of $z_s + z_r$. In the panels a and b, we consider $u = 10^{-3}$ and $u = 10^{-2}$, respectively. Increasing u, the black region disappears and the yellow region increases for larger Φ values. We verify that $z_s + z_r$ depends not not only u and Φ, but also γ. Therefore, γ plays an important role in our model for continuous chemotherapy treatment.

4 Conclusions

Drug resistance has been a challenge to the effectiveness of cancer therapy. Many mechanisms can promote the drug resistance in cancerous cells, such as DNA damage repair, drug inactivation, and drug target alteration [51]. Advances in the understanding of resistant cells can provide novel strategies for cancer treatments.

We analyse the effects of drug resistance in a tumour-immune model. We propose a mathematical model governed by differential equations of fractional order, namely noninteger order differential equations. The model describes the interactions between host, effector immune, and cancer cells, as well as chemotherapeutic agents. We extend the tumour-immune model splitting the equation of the cancerous cells into two equations: an equation for the sensitive cells and another for the resistant ones.

Due to the chemotherapy, sensitive cancer cells (z_s) can suffer mutation and transform into resistant ones (z_r). We compute the maximum number of cancerous cells ($z_s + z_r$) in a time interval. In a continuous drug delivery, the maximum $z_s + z_r$ values depend on the chemotherapy dose (Φ) and the mutation rate (u). The efficiency of the treatment changes according to Φ and u.

In this work, we show that the order of the equation differential plays a crucial role in modelling a tumour-immune system with drug resistance. The dynamical behaviour is changed according to the order. We verify that the size of the parameter space region in which the cancer is suppressed depends on the order value.

Author Contribution All authors discussed the results and contributed to the final manuscript.

Declarations

Conflict of Interest The authors declare no competing interests.

References

1. D. Ambrosi, F. Mollica, On the mechanics of a growing tumor. Int. J. Eng. Sci. **40**, 1297–1316 (2002)

2. T. Sinha, Tumors: benign and malignant. Canc. Therapy Oncol. Int. J. **10**, 1 (2018)

3. S. Ohshika, T. Saruga, T. Ogawa, H. Ono, Y. Ishibashi, Distinction between benign and malignant soft tissue tumors based on an ultrasonographic evaluation of vascularity and elasticity. Oncol. Lett. **21**, 281 (2021)

4. R.A. Weinberg, How cancer arises. Sci. Am. **275**, 62–70 (1996)

5. J. Balogh, D. Victor III., E.H. Asham, S.G. Burroughs, M. Boktour, A. Saharia, X. Li, R.M. Ghobrial, H.P. Monsour Jr., Hepatocellular carcinoma: a review. J. Hepatocell Carcinoma **3**, 41–53 (2016)

6. M. Belson, B. Kingsley, A. Holmes, Risk factors for acute leukemia in children: a review. Environ. Health Perspect. **115**, 138–145 (2007)

7. R. Küppers, The biology of Hodgkin's lymphoma. Nat. Rev. Cancer **9**, 15–27 (2009)

8. D. Schadendorf, A.C.J. van Akkooi, C. Berking, K.G. Griewank, R. Gutzmer, A. Hauschild, A. Stang, A. Roesch, S. Ugurel, Melanoma. The Lancet **392**(10151), 971–984 (2018)

9. M. Weller, W. Wick, K. Aldape, M. Brada, M. Berger, S.M. Pfister, R. Nishikawa, M. Rosenthal, P.Y. Wen, R. Stupp, G. Reifenberger, Glioma. Nat. Rev. Dis. Primers. **1**, 1–18 (2015)

10. L. Wyld, R.A. Audisio, G.J. Poston, The evolution of cancer surgery and future perspectives. Nat. Rev. Clin. Oncol. **12**, 115–124 (2015)

11. R. Baskar, K.A. Lee, R. Yeo, K.-W. Yeoh, Cancer and radiation therapy: current advances and future directions. Int. J. Med. Sci. **9**, 193–199 (2012)

12. B.A. Chabner, T.G. Roberts Jr., Timeline: chemotherapy and the war on cancer. Nat. Rev. Cancer **5**, 65–72 (2005)

13. J.N. Blattman, P.D. Greenberg, Cancer immunotherapy: a treatment for the masses. Science **305**, 200 (2005)

14. A.D. Waldman, J.M. Fritz, M.J. Lenardo, A guide to cancer immunotherapy: from T cell basic science to clinical practice. Nat. Rev. Immunol. **20**, 651–668 (2020)

15. D.E. Dolmans, D. Fukumura, R.K. Jain, Photodynamic therapy for cancer. Nat. Rev. Cancer **3**(5), 380–387 (2003)

16. M. Vanneman, G. Dranoff, Combining immunotherapy and targeted therapies in cancer treatment. Nat. Rev. Cancer **12**, 237–251 (2012)

17. H.B. Caglar, E.H. Baldini, M. Othus, M.S. Rabin, R. Bueno, D.J. Sugarbaker, S.J. Mentzer, P.A. Jänne, B.E. Johnson, A.M. Allen, Outcomes of patients with stage III nonsmall cell lung cancer treated with chemotherapy and radiation with and without surgery. Cancer **115**, 4156–4166 (2009)

18. C. Holohan, S. Van Schaeybroeck, D.B. Longley, P.G. Johnston, Cancer drug resistance: an evolving paradigm. Nat. Rev. Cancer **13**, 714–726 (2013)

19. H. Zahreddine, K.L.B. Borden, Mechanisms and insights into drug resistance in cancer. Front. Pharmacol. **4**, 28 (2013)

20. M. Shanker, D. Willcutts, J.A. Roth, R. Ramesh, Drug resistance in lung cancer. Lung Cancer Targets Ther. **1**, 23–36 (2010)

21. T. Hu, Z. Li, C.-Y. Gao, C.H. Cho, Mechanisms of drug resistance in colon cancer and its therapeutic strategies. World J. Gastroenterol. **22**, 6876–6889 (2016)

22. J. Long, Y. Zhang, X. Yu, J. Yang, D.G. LeBrun, C. Chen, Q. Yao, M. Li, Overcome drug resistance in pancreatic cancer. Expert Opin. Ther. Targets **15**, 817–828 (2011)

23. Y. Tang, Y. Wang, M.F. Kiani, B. Wang, Classification, treatment strategy, and associated drug resistance in breast cancer. Clin. Breast Cancer **16**, 335–343 (2016)

24. C. Altrock, L.L. Liu, F. Michor, The mathematics of cancer: integrating quantitative models. Nat. Rev. Cancer **15**, 730–745 (2015)

25. F.S. Borges, K.C. Iarosz, H.P. Ren, A.M. Batista, M.S. Baptista, R.L. Viana, S.R. Lopes, C. Grebogi, Model for tumour growth with treat by continuous and pulsed chemotherapy. Biosyst. **116**, 43–48 (2014)

26. K.C. Iarosz, F. Borges, A.M. Batista, M.S. Baptista, R.A.N. Siqueira, R.L. Viana, S.R. Lopes, Mathematical model of brain tumour with glia-neuron interactions and chemotherapy treatment. J. Theor. Biol. **368**, 113–121 (2015)

27. F. Nani, H.I. Freedman, A mathematical model of cancer treatment by immunotherapy. Math. Biosci. **163**, 159–199 (2000)

28. L.G. de Pillis, W. Gu, A.E. Radunskaya, Mixed immunotherapy and chemotherapy of tumors: modeling, applications and biological interpretations. J. Theor. Biol. **238**, 841–862 (2006)

29. L. de Pillis, K.R. Fister, W. Gu, C. Collins, M. Daub, D. Gross, J. Moore, B. Preskill, Mathematical model creation for cancer chemo-immunotherapy. Comput. Math. Methods Med. **10**, 2009 (2008)

30. M.R. Gallas, M.R. Gallas, J.A.C. Gallas, Distribution of chaos and periodic spikies in a three-cell population model of cancer. Eur. Phys. J. Special Topics **223**, 2131–2144 (2014)

31. E. Sayari, S.T. da Silva, K.C. Iarosz, R.L. Viana, J.D. Szezech Jr., A.M. Batista, Prediction of fluctuations in a chaotic cancer model using machine learning. Chaos Soliton Fract. **164**, 112616 (2022)

32. S. Mashayekhi, S. Sedaghat, Fractional model of stem cell population dynamics. Chaos Soliton Fract. **146**, 110919 (2021)

33. J.E. Solís-Pérez, J.F. Gómez-Aguilar, A. Atangana, A fractional mathematical model of breast cancer competition model. Chaos Soliton Fract. **127**, 38–54 (2019)

34. E.C. Gabrick, M.R. Sales, E. Sayari, J. Trobia, E.K. Lenzi, F.S. Borges, J.D. Szezech Jr., K.C. Iarosz, R.L. Viana, I.L. Caldas, A.M. Batista, Fractional dynamics and recurrence analysis in cancer model. Braz. J. Phys. **53**, 145 (2023)

35. S. Kumar, A. Kumar, B. Samet, J.F. Gómez-Aguilar, M.S. Osman, A chaos study of tumor and effector cells in fractional tumor-immune model for cancer treatment. Chaos Soliton Fract. **141**, 110321 (2020)

36. M.F. Farayola, S. Shafie, F.M. Siam, I. Khan, Numerical simulation of normal and cancer cell's populations with fractional derivative under radiotherapy. Comput. Methods Programs Biomed. **187**, 105202 (2020)

37. H. Hassani, J.A.T. Machado, S. Meharabi, An optimization technique for solvin a class of nonlinear fractional optimal control problems: application in cancer treatment. Appl. Math. Model. **93**, 868–884 (2021)

38. L. Xuan, S. Ahmad, A. Ullah, S. Saifullah, A. Akgül, H. Qu, Bifurcations, stability analysis and complex dynamics of Caputo fractal-fractional cancer model. Chaos Solitons Fract. **159**, 112113 (2022)

39. C. Letellier, F. Denis, L.A. Aguirre, What can be learned from a chaotic cancer model? J. Theor. Biol. **322**, 7–16 (2013)

40. E. Diz-Pita, M.V. Otero-Espinar, Predator-prey models: a review of some recent advances. Mathematics **9**, 1783 (2021)

41. M. Itik, S.P. Banks, Chaos in a three-dimensional cancer model. Int. J. Bifurcat. Chaos **20**, 71–79 (2010)

42. F. Liu, M.M. Meerschaert, S. Momani, N.N. Leonenko, W. Chen, O.P. Agrawal, Fractional differential equations. Int. J. Differ. Equ. **2010**, 215856 (2010)

43. J. Trobia, K. Tian, A.M. Batista, C. Grebogi, H.-P. Ren, M.S. Santos, P.R. Protachevicz, F.S. Borges, J.D. Szezech Jr., R.L. Viana, I.L. Caldas, K.C. Iarosz, Mathematical model of brain tumour growth with drug resistance. Commun. Nonlinear Sci. Numer. Simul. **103**, 106013 (2021)

44. V.A. Kuznetsov, I.A. Makalkin, Nonlinear dynamics of immunogenic tumors: parameter estimation and global bifurcation analysis. Bull. Math. Biol. **56**, 295–321 (1994)

45. L.G. de Pillis, A. Radunskaya, The dynamics of an optimally controlled tumor model: a case study. Math. Comput. Modelling **37**, 1221–1244 (2003)

46. L.R. Evangelista, E.K. Lenzi, Fractional diffusion equations and anomalous diffusion. Cambridge University Press (2018)

47. N.J. Vogelzang, Continuous infusion chemotherapy: a critical review. J. Clin. Oncol. **2**, 1289–1304 (1984)

48. A.R. Dixon, L. Jackson, S.Y. Chan, R.A. Badley, R.W. Blamey, Continuous chemotherapy in responsive metastatic breast cancer: a role for tumour markers? Br. J. Cancer **68**, 181–185 (1993)

49. J. Tuettenbert, R. Grobholz, T. Korn, F. Wenz, R. Erber, P. Vajkoczy, Continuous low-dose chemotherapy plus inhibition of cyclooxygenase-2 as an antiangiogenic therapy of blioblastoma multiforme. J. Cancer Res. Clin. Oncol. **131**, 31–40 (2005)

50. M. Rabé, S. Dumont, A. Álvarez-Arenas, H. Janati, J. Belmonte-Beitia, G.F. Calvo, C. Thibault-Carpentier, Q. Séry, C. Chauvin, N. Joalland, F. Briand, S. Blandi, E. Scotet, C. Pecqueur, J. Clairambault, L. Oliver, V. Perez-Garcia, A. Nadaradjane, P.-F. Cartron, C. Gratas, F.M. Vallette, Identification of a transient state during the acquisition of temozolomide resistance in glioblastoma. Cell Death Dis. **11**, 19 (2020)

51. G. Housman, S. Byler, S. Heerboth, K. Lapinska, M. Longacre, N. Snyder, S. Sarkar, Drug resistance in cancer: an overview. Cancers **6**, 1769–1792 (2014)