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Computational modeling of the growth of breast tumors with chemotherapy administered in cycles

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Abstract. Breast cancer is a disease caused by the disordered multiplication of breast cells. It is the most frequent cause of death from cancer among women in the world, affecting 2.1 million women each year. Considering the impact of breast cancer on global health, it is necessary to develop mathematical models that simulate the growth of breast tumors in response to treatment factors. Several methods have been used, such as those based on differential equations. Because of the complexity of tumor kinetics, some mathematical models seek to understand their behavior through application of laws that assist the study of chemotherapy treatment regimens and the action of drugs. This paper presents a model based on ordinary differential equations (ODE) to simulate breast tumor growth in two chemotherapy treatment regimens, executed in cycles, to analyze the effects of drugs on tumor and healthy tissue. To solve the ODE system, the fourth-order numerical Runge-Kutta method was used, implemented in MATLAB. The results show that chemotherapy treatment regimens comprised of two or more drugs (AC and FAC protocols) are more effective than only administering cyclophosphamide. The two protocols caused greater reduction of tumor cells and less destruction in healthy tissue.

Keywords: Computational Modeling, Breast Tumor Growth, Chemotherapy treatment in cycles

1 Introduction

Breast cancer is a disease caused by the disordered multiplication of breast cells. The causes are unknown, but its incidence is statistically related to environmental, behavioral, hormonal, genetic and hereditary factors. It is most prevalent in women over the age of 50 years (INCA [1]). According to the World Health Organization (WHO [2]), it is the leading cause of death by cancer among women in the world, affecting 2.1 million women a year. In Brazil, the forecast is for 66 280 new breast cancer cases a year between 2020 and 2022, corresponding to a rate of 61.61 new cases for each 100 thousand women (INCA [3]).

After diagnosis, treatment of breast cancer is planned considering: (i) the stage of the disease; (ii) the location and type of tumor (with carcinoma being most common); (iii) the general health state of the patient; and (iv) the possible side effects (Oncoguia [4]). Therapy has the objectives to cure in the initial stage and cases of locally advanced tumors, and to ameliorate symptoms, prolong life and improve quality of life in cases of metastasis (Wells et al. [5]). Treatment can also be localized (surgery and radiotherapy) or systemic (chemotherapy, hormonotherapy and biological therapy) (INCA [1]). The systemic treatment can be applied before surgery (neoadjuvant) or after surgery and radiotherapy (adjuvant). In the case of chemotherapy, the patient can receive a single drug (monochemotherapy) or a combination of various drugs (polychemotherapy). The use of combined chemotherapy offers several advantages and is widely used to diminish the toxicity to healthy cells and development of resistance of cancer cells to the drugs (Fisusi and Akala [6]).

Based on the impact of breast cancer in global health, interdisciplinary research is necessary to improve understanding of the disease. In this respect, several studies have sought to develop mathematical models with application in oncology. According to McKenna et al. [7], such studies need structured mathematical modeling based on mechanisms that consider all the clinical information, from the genetic aspects of the tumor to data from imaging tests, to enable making specific and measurable predictions of the therapeutic response of each

patient individually. Various methods have been used for this purpose, principally those based on differential equations. Because of the complexity of the tumor growth kinetics, some mathematical models have been designed to investigate the behavior of tumors and their response to drugs and explain laws to support chemotherapy. In this line of research, the objective of this article is to describe a model to simulate the growth dynamics of breast tumors considering two chemotherapy schemes involving cyclical administration of different drugs, to analyze their effects on the tumor and healthy tissue. For this purpose, we consider a model based on ordinary differential equations (ODEs) (Rodrigues [8]) and the recommendations of the Ministry of Health about the treatment protocols (Brazil [9]). To determine the numerical solution of the system of ODEs, we use the fourth-order Runge-Kutta method, implemented in the MATLAB code.

This study is limited to analyzing the growth dynamics of tumor cells in function of the treatment protocols. There is no discussion of the toxicity of the drugs considered.

2 Mathematical modeling of breast cancer

Mathematical models that describe the growth of tumors have been formulated and studied for several decades and have attracted strong attention of researchers. Those based on ODEs qualitatively and quantitatively describe the temporal growth of the population of tumor cells (Rodrigues [8], Junior [10]). The more complete models involving partial differential equations (PDEs), such as those based on reaction-diffusion equations (Murray [11], Swanson [12], Swanson et al. [13], Swanson et al. [14]) which simulate the effects of radiotherapy and chemotherapy on gliomas, and those based on integro-differential equations, currently are attracting the greatest attention by mathematicians (Bellomo and Preziosi [15]). Besides these, there are methods that use cellular automata (Kansal et al. [16]) and those that consider the formation of fractals involving tumors that exhibit complex forms, as in the case of glioblastoma (cerebral), melanoma (skin) and breast tumors (Junior [10]).

da Silva et al. [17] presented the simulation of the tumor growth dynamics in response the chemotherapy with continuous administration of a single drug, cyclophosphamide. The authors considered a model with ODEs based on competition of cell populations (tumor and tissue), which interacted to obtain survival resources. Besides the qualitative analysis of the model, the study also included comparison of the growth dynamics of breast tumors in response to continuous administration of chemotherapy with the tumor growth dynamics without treatment (Gatenby [18]). The present article expands the scope of that study to consider cancer treatment protocols recommended by the Ministry of Health, aiming to carry out a more realistic simulation.

According to Rodrigues et al. [19], the ODE model representative of breast cancer, considering chemotherapy based on two cell populations (tumor and normal), respectively designated N_1 and N_2, that compete with each other for limited resources, such as oxygen and tissue space, is given by:

$$\begin{cases} \dfrac{dN_1}{dt} = r_1 N_1 \left(1 - \dfrac{N_1}{K_1} - \dfrac{\alpha_1 N_2}{K_1}\right) - \dfrac{\mu N_1 Q}{a+Q} \\ \dfrac{dN_2}{dt} = r_2 N_2 \left(1 - \dfrac{N_2}{K_2} - \dfrac{\alpha_2 N_1}{K_2}\right) - \dfrac{\nu N_2 Q}{b+Q} \\ \dfrac{dQ}{dt} = q(t) - \lambda Q. \end{cases} \tag{1}$$

In turn, the model with administration in cycles (Martin et al. [20]) is denoted by:

$$q(t) = \begin{cases} q > 0, \;\; n \leq t < n + \tau \\ 0, \;\; n + \tau \leq t < n + T. \end{cases} \tag{2}$$

Where: Q describes the chemotherapeutic agent; q denotes the drug infusion rate; T represents the drug administration cycle; n indicates the number of days of treatment (i.e., $0, T, 2T, 3T, ...$), and τ is the drug infusion time. The infusion of chemotherapy with administration in cycles for treatment of breast cancer is characterized by cycles that last 3 or 4 weeks, followed by a rest period, during which no drugs are administered to allow the patient to recover from the toxicity before undergoing a new cycle of treatment.

System (1) considers the tumor and normal cell population growth rates (r_1 and r_2, respectively); the capacity to support the tumor and normal cells (k_1 and k_2), the interspecific competition coefficients referring to population i ($\alpha_i, i = 1, 2$), the drug response rate (a and b), the decay rate of a given chemotherapy agent (λ), and the treatment rates of tumor and normal cells, respectively (μ and ν). For a treatment to make clinical sense, the effect of the drug on the tumor cells must be much greater than the effect on normal cells, i.e., $\mu \gg \nu$.

According to the Ministry of Health (Brazil [9]), among the polychemotherapy schemes involving cyclical administration, that of eq. (2) is suggested for treatment according to the risk of the patient and her hormonal status. Here we consider the protocols AC and FAC:

Table 1. Main characteristics of the polychemotherapy protocols to treat breast cancer

Protocol	Drug	Dose $\left(mg/m^2\right)$	Half-life $(days)$	Rate of decay $\left(day^{-1}\right)$
		d	$t_{1/2}$	$\lambda = \frac{\ln 2}{t_{1/2}}$
AC	Doxorubicin (A)	60†	$1/288$ (5 min)	$\approx$ 199.63§
	Cyclophosphamide (C)	600†	$1/6$ (4 hs)	$\approx$ 4.16§
FAC	5-Fluorouracil (5-FU)	500†	$1/90$ (16 min)	$\approx$ 62.38§
	Doxorubicin (A)	50†	-	-
	Cyclophosphamide (C)	500†	-	-

†The doses of each drug were obtained from the recommendation of the Ministry of Health (Brazil [9]).

§The values of λ were calculated based on the half-life of each drug: Adriblastina® [21], Genuxal® [22] and Fauldfluor® [23].

In compliance with the medication package inserts (Adriblastina® [21], Genuxal® [22] and Fauldfluor® [23]), the doses of the protocols presented in Table 1 were administered as being a mixture of the drugs involved together with a solution of 0.9% sodium chloride, considering an infusion time (τ) of $1/8$ day (3 $hours$) for a period of 21 days (T) and 4 infusions ($n = 0, 21, 42, 63$).

The half-life of each drug mixture was calculated by the weighted mean of the times presented in Table 1. Therefore, we obtained $t_{1/2}^{AC} \approx$ 1/6.12 day and $t_{1/2}^{FAC} \approx$ 1/6.49 day for protocols AC and FAC, respectively. The corresponding decay rates were $\lambda^{AC} \approx 4.24\ day^{-1}$ and $\lambda^{FAC} \approx 4.49\ day^{-1}$.

According to Mosteller [24], the body surface area (BSA, in m^2) of a patient with weight W (em Kg) and height h (in cm) is given by:

$$BSA = \sqrt{\frac{h\ (cm) \cdot W\ (Kg)}{3600\ (cm \cdot Kg/m^4)}}. \tag{3}$$

In particular, the BSA of a model patient weighing 70 Kg and with height of 170 cm is approximately 1.82 m^2. Thus, based on the doses specified in Table 1 and eq. (3), it was possible to determine the infusion rate (in mg/day) of each drug independently, as well as the polychemotherapy treatments by protocols AC and FAC for this patient, as described in the following Table:

Table 2. Infusion rate of the drugs and polychemotherapy protocols for treatment of breast cancer

Protocol	Drug	Infusion rate (mg/day) $q = \frac{d \cdot BSA}{\tau}$	
AC	Doxorubicin (A)	873.60	$q_{AC} =$ 9 609.60
	Cyclophosphamide (C)	8 736	
FAC	5-Fluorouracil (5-FU)	7 280	
	Doxorubicin (A)	728	$q_{FAC} =$ 15 288
	Cyclophosphamide (C)	7 280	

The values presented in Table 1 and Table 2 enable the simulation of dynamics of the tumour growth due to the chemotherapy protocols through of eq. (1) and eq. (2).

3 Results

The method to solve the ODE system was implemented in the MATLAB interactive software, by applying the function ode45, which applies the fourth-order Runge-Kutta method. In all the simulations, we considered tolerance of 10^{-8} as stopping criterion. Besides this, we adopted the parameter values in Table 3, corresponding to a model patient with weight of 70 Kg and height of 170 cm, suffering from breast carcinoma with intermediate risk and normal post-menopause hormonal status (Brazil [9]). The graphs below depict the evolution of the cells of the patient when submitted to the polychemotherapy protocols AC and FAC and each drug composing the treatments independently.

Table 3. Parameters considered for the numerical simulations of breast cancer

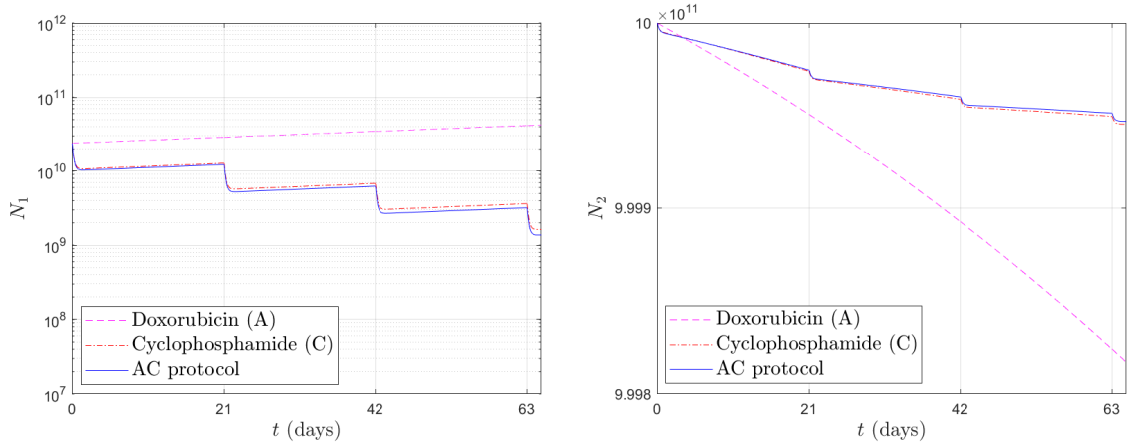
Parameter	Value used	Reference
$N_1(0)$	2.4×10^{10} tumor cells	da Silva and Silva [25]
$N_2(0)$	10^{12} tumor cells	-
$Q(0)$	$0\ mg$	-
k_1	10^{12} cells	Spratt et al. [26], Weinberg [27]
k_2	10^{12} cells	$k_2 \sim k_1$
α_1, α_2	9×10^{-2}	$\alpha_1 < \frac{k_1}{k_2}$ (general hypothesis for cancer)
a, b	$2 \times 10^3\ mg,\ 5 \times 10^6\ mg$	Rodrigues [8]
λ	Table 1	-
μ, ν	$8\ day^{-1},\ 8 \times 10^{-2}\ day^{-1}$	$\nu \ll \mu$ Rodrigues [8]
r_1, r_2	$10^{-2}\ day^{-1},\ 10^{-3}\ day^{-1}$	Spratt et al. [26]
q	Table 2	-

Figure 1 describes the cell growth dynamics considering the polychemotherapy protocol AC and the two drugs independently (Doxorubicin (A) and Cyclophosphamide (C)). Figure 1(a) shows that the effects, both of (C) alone and the combination in the AC protocol on the cells, were very near each other, with elimination of cells in a constant proportion, according to the log-kill hypothesis (Skipper et al. [28]). This result was expected, since the AC protocol is mainly composed of (C). Figure 1(b), in turn, shows the impact these drugs on normal cells, since for the same reason the variations in the cells caused by the AC protocol and by (C) alone were very similar. In general, the AC protocol was slightly more effective than the use of (C) by itself. Another important observation of this graph is that (A), when applied alone, caused a significant reduction of the number of normal cells starting on the fourth day of treatment during the first cycle, indicating that combination with (C) causes less harmful effects.

Figure 2 depicts the information about cell growth dynamics considering the polychemotherapy protocol FAC and the drugs that compose it separately (5-Fluorouracil (5-FU), Doxorubicin (A) and Cyclophosphamide (C)). Figure 2(a) presents the variation of the tumor cells over time. The FAC protocol had greater efficacy in reducing the tumor than the drugs composing it alone. Figure 2(b) shows that the FAC protocol was also effective, since its impact on normal cells was lower in comparison with the drugs administered separately, mainly when (A) or (5-FU) was given.

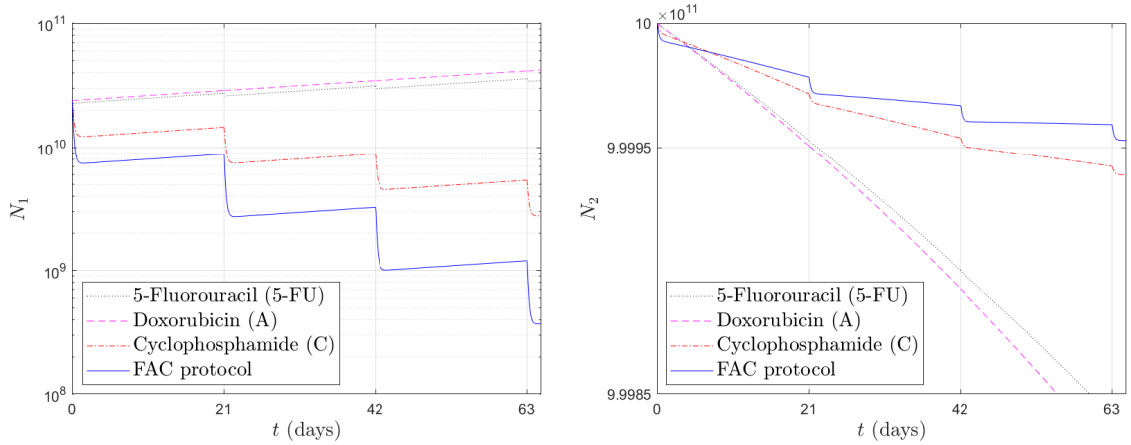
The loss percentages of tumor and normal cells after 63 treatment days, with AC, FAC and (C) isolated protocols, are shows in Fig. 3. The C^{AC} and C^{FAC} symbols are considered in Fig. 3 to represent the therapies results with Cyclophosphamide (C) alone, which is considered for comparison purposes in the simulations of the (AC), shown in Fig. 1, and (FAC) shown in Fig. 2.

Figure 3(a) shows the loss percentage of tumor cell in the FAC protocol. It is observed that in the most effective protocol the reduction of the number of tumor cells is 98.45% and the least effective, the C^{FAC} alone, compared to FAC, reduces in 88.47% of the number of these cells. About the normal cells reductions in Fig. 3(b) shows, 0.00470% in FAC protocol and 0.00529% in the AC protocol. These treatment regimens are the ones that reduce the most the normal cells numbers. This fact agrees with Fisusi and Akala [6] about drugs composing (polychemotherapy) are better to decrease the toxicity in normal cells and to reduce the tumor cells medicines resistances.



(a) Tumor cells (b) Normal cells

Figure 1. Comparison of the cell evolution when the model patient was submitted to the polychemotherapy protocol AC and when the drugs composing the treatment were administered separately



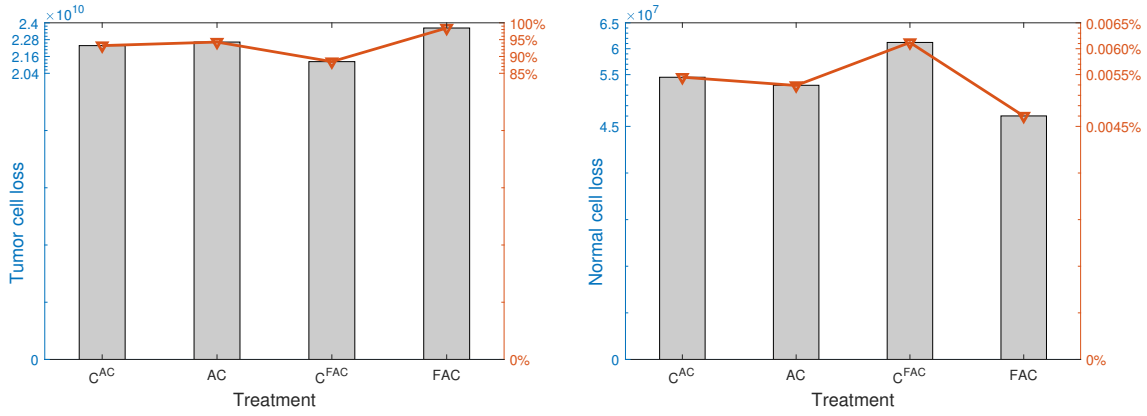
(a) Tumor cells (b) Normal cells

Figure 2. Comparison of the cell evolution when the model patient was submitted to the polychemotherapy protocol FAC and when the drugs composing the treatment were administered separately

4 Conclusions

The objective of this study was to simulate the breast tumor growth dynamics in response to treatment with two polychemotherapy protocols, with the drugs administered in cycles, by analyzing the effects of the drugs on tumor and healthy tissue. These treatment schemes are part of a set of protocols recommended by the Brazilian Ministry of Health for treatment of some types of breast carcinomas, based on combinations of drugs to increase the efficacy of treatment.

The mathematical model of the chemotherapy proposed, based on ordinary differential equations, permitted comparison of different treatment protocols. The numerical simulations carried out showed that for a model patient with weight of 70 Kg and height of 170 cm, suffering from breast carcinoma with intermediate risk and post-menopause hormonal status, the treatment with combined chemotherapy (polychemotherapy) was more effective than when applying any of the drugs alone. Both protocols (AC and FAC) produced a greater reduction of the number of tumor cells with less damage to healthy cells. However, this fact was more evident in the FAC regimen.It had the loss percentage of tumor cells number close to 98.45% and,of normal cells number around 0.00470%. While the AC protocol had 94.28% and 0.00529%, respectively.This pattern was more evident in the FAC protocol, likely due to the presence of (5-FU), which was not used in AC protocol.



(a) Tumor cells (b) Normal cells

Figure 3. Loss percentages of tumor and normal cells after four cycle of chemotherapy

It is also verified that, because the dose of (C) is higher than the dose of (A) in the AC protocol, the cell reduction dynamics is similar to that of the treatment regimen with (C) alone. In this case, the loss percentage of tumor cells number is around 93.23% in C^{AC} and 94.28% in AC. For normal cells it is 0.00545% and 0.00529%, respectively. This shows the dose of drugs influence on the cancer cells decrease.

It is concluded that the combined chemotherapy regimens, AC and FAC, showed more effective results, with greater loss of tumor cells and less of normal cells, when compared to chemotherapy with a single drug. This corroborates research that shows breast cancer treatments with polychemotherapy as an evolution in the treatment of the disease.

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