THESIS ABSTRACT

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Application of Mathematical Model of Cancer Treatment by Radiotherapy

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ABSTRACT

The aim of this study is achieve an analysis of the mathematical model governing radiotherapy as well as to achieve the concentration of healthy and cancerous cells to reduce the length of treatment and less damage to cancer treatment by this type of therapy. In order to obtain this, we used the latest mathematical radiotherapy model based on the Lotka-Volterra competitive equations and the Adomian decomposition method that is the one of the most advanced analytical solutions to solve differential equations to attain our goal. The calculation of the Adomian decomposition method was applied to the mathematical model governing radiotherapy, and then the concentration of healthy and cancerous cells was achieved with a very good approximation. Comparison of the behavior of healthy and cancerous cells concentrations based on experimental cases and the behavior of healthy and cancerous cells concentrations based on computations express the correctness of the work. ADM indicates the concentration of healthy and cancerous cells during the treatment stage and the no treatment stage can be effective in improving the modeling based on the competitive model of the Lotka-Volterra equations, which results in the reduction of the use of diagnostic devices, less radiation, the faster treatment process and decreasing the cost of treatment for patients and governments.

Keywords: Radiotherapy, Mathematical model, Lotka-Volterra, Adomian decomposition method

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INTRODUCTION:

Cancer is known as a disease that is increasing worldwide, and several methods have been proposed to treat it, such as: a) surgery, b) chemotherapy, c) radiotherapy, and immunotherapy. Each of these treatments has several advantages and disadvantages. To improve the outcome of any of these treatments, modeling can be effective. One of the treatments for cancer treatment is radiotherapy, which can play an important role in improving its outcome. In fact, radiotherapy is a treatment method that uses radiation to kill malignant cells[1, 2]. The intent of this paper is to introduce the dynamics model and interactions of healthy and cancer cells under radiation therapy. Recently, several mathematical models that apply to the treatment of cancer with radiotherapy have been proposed and investigated[3-6]. This is because of the importance of the study of periodic radiation under conditions in which both cancer and healthy cells are affected by radiation. One of the important mathematical models that covers this topic is the Lotka–Volterra model. The Lotka–Volterra model was first suggested by Lotka in 1925[7]. In this model, two coupled nonlinear differential equations are used to introduce the dynamics and equilibrium of a biological system in which the two cases interact as fish and fisherman. Indeed, Volterra applied the Lotka model and its data to analyze the reducing and increasing of fish populations in the Adriatic Sea[8]. Lotka and Volterra developed their model based on the logistic equation, which included the terms related to species' interaction.Since the classical Lotka-Volterra competitive system is an important population model, it has been studied by many authors[9-17]. The Lotka-Volterra model is often used to study the relationship between different biological states[18]. Lotka–Volterra model had been used by Geijzendorffer et al., to predict the long-term co-existence templats of grassland kinds[19]. Goodwin incorporated this model into the economy by applying it to business cycles outside the field of biology[20].The mathematical model of Lotka–Volterra mimics the dynamics of two species competing for common resources.In these equations, the relationship between the concentration of cancer and healthy cells is well known. In the 1980's, George Adomian suggested a new method for solving nonlinear equations such as Lotka–Volterra equations[21]. This method is given by the Adomian decomposition method (ADM) and has been the subject of much investigation[21-24]. The ADM involves separating the equation under investigation into linear and nonlinear components. The linear operator representing the linear component of the equation is inverted and the inverse operator is then applied to the equation. The nonlinear component is decomposed into a series of Adomian polynomials. This method creates a solution in the form of a series whose terms are calculated by a recursive relation using these Adomian polynomials. In this work, we used dynamical coupled ordinary differential equations between the normal and cancer cells forcancer treatment by radiotherapy. This article contains the following sections. In Section 2, we offer materials and methods that compare the numerical and ADM models for solving Lotka–Volterra equations. Discussion and results are obtained in Section 3. Finally, we present the conclusion.

METHODS:

So far, we have investigated the behavior of different concentrations of cancer and healthy cells versus time and versus each other. However, the concentrations of cancerous and healthy cells can be determined approximately. Determining the approximate concentration of cancer and healthy cells can cause: 1. Reduced use of diagnostic devices 2. Less radiation 3. Faster treatment processes 4. Decreased cost of treatment for patients and governments.

Determination of the approximate concentration of cancer and healthy cells using Lotka-Volterra equations with numerical method

One of the predominant models of radiotherapy is the Lotka-Volterra Competitive model[21]:

$$\dot{x}_1 = \alpha_1 x_1\left(1-\frac{x_1}{k_1}\right) - \beta_1 x_1 x_2 - \varepsilon D(t) x_1 \quad (1-a)$$

$$\dot{x}_2 = \alpha_2 x_2\left(1-\frac{x_2}{k_2}\right) - \beta_2 x_1 x_2 - D(t) x_2 \quad (1-b)$$

Where $\dot{x}$ is: $\dot{x}=dx/dt$ and x1(t) and x2(t) show the concentration of healthy and cancer cells, respectively. The respective proliferation coefficients are :α_i >0 (i=1,2), the respective carrying capacities are : K_i (i=1,2), the respective competition coefficients are: β_i (i=1,2), ϵ and D(t) are the rate of the normal cells from the irradiation and the strategy of the radiotherapy, respectively. Selecting ω as periodic of treatment, we can assume that :D(t) $\equiv \gamma > 0$ when $t \in [n\omega, +L)$ (treatment stage) and D(t) $\equiv 0$ when $t \in [n\omega+L, (n+1))$ (no treatment stage) for all $n = 0, 1, 2, \ldots$, such that $0 < L < \omega$ is the radiation treatment time.

Determination of the approximate concentration of cancerous and healthy cells using Lotka-Volterra equations with the Adomian decomposition method

To obtain x_1 and x_2 values in system equations (1) in the form of analytical, we use Adomian decomposition method[6], as one of the methods to solve differential equations. When system equations (1) are simplified we have:

$$\dot{x}_1 = \alpha_1 x_1 - \frac{\alpha_1}{k_1} x_1^2 - \beta_1 x_1 x_2 - \varepsilon\gamma x_1 \quad (2-a)$$

$$\dot{x}_2 = \alpha_2 x_2 - \frac{\alpha_2}{k_2} x_2^2 - \beta_2 x_1 x_2 - \gamma x_2 \quad (2-b)$$

According to the Adomian decomposition method, the system equations (1) are given as the following canonical form:

$$x_1 = x_1(0) + \int_0^t (\alpha_1 - \varepsilon\gamma) x_1 dt - \int_0^t \frac{\alpha_1}{k_1} x_1^2 dt - \int_0^t \beta_1 x_1 x_2 dt \quad (3-a)$$

$$x_2 = x_2(0) + \int_0^t (\alpha_2 - \gamma) x_2 dt - \int_0^t \frac{\alpha_2}{k_2} x_2^2 dt - \int_0^t \beta_2 x_1 x_2 dt \quad (3-b)$$

Now instead of linear terms in equaton(3), we use[6]:

$$x_1 = \sum_{i=0}^{\infty} x_{1i} = (x_{10} + x_{11} + x_{12} + \cdots) \quad (4-a)$$

$$x_2 = \sum_{i=0}^{\infty} x_{2i} = (x_{20} + x_{21} + x_{22} + \cdots) \quad (4-b)$$

Where:

$$x_{1,i+1} = \int_0^t x_{1,i} dt \quad (5-a)$$

$$x_{2,i+1} = \int_0^t x_{2,i} dt \quad (5-b)$$

And instead of nonlinear terms in (3), we use[7]:

$$A_i = \frac{1}{i!}\left(\frac{d^i}{d\lambda^i} N\left(\sum_{m=0}^{\infty} x_m \lambda^m\right)\right)\Big|_{\lambda=0} \quad (6)$$

This is known as Adomian polynomials. So we have:

$$\sum_{i=0}^{\infty} x_{1i} = x_1(0) + \int_0^t (\alpha_1 - \varepsilon\gamma) \sum_{i=0}^{\infty} x_{1i} dt - \int_0^t \left(\frac{\alpha_1}{k_1}\right) \sum_{i=0}^{\infty} A_i(x_{1i}^2) dt - \int_0^t \beta_1 \sum_{i=0}^{\infty} B_i(x_{1i} x_{2i}) dt \quad (7)$$

$$\sum_{i=0}^{\infty} x_{2i} = x_2(0) + \int_0^t (\alpha_2 - \gamma) \sum_{i=0}^{\infty} x_{2i} dt - \int_0^t \left(\frac{\alpha_2}{k_2}\right) \sum_{i=0}^{\infty} H_i(x_{2i}^2) dt - \int_0^t \beta_2 \sum_{i=0}^{\infty} B_i(x_{1i} x_{2i}) dt \quad (8)$$

We have Adomian polynomials as follows:

$$A_n = \sum_{k=0}^{n} x_{1k} x_{1(n-k)}$$

$$A_0 = x_{10}x_{10} = x_{10}^2 \quad ,$$

$$A_1 = x_{10}x_{11} + x_{11}x_{10} = 2x_{11}x_{10}$$

$$A_2 = x_{10}x_{12} + x_{11}x_{11} + x_{12}x_{10} = 2x_{12}x_{10} + x_{11}^2$$

$$A_3 = x_{10}x_{13} + x_{11}x_{12} + x_{12}x_{11} + x_{13}x_{10} = 2x_{10}x_{13} + 2x_{11}x_{12}$$,and so on.

Now for H_i :

$$H_n = \sum_{k=0}^{n} x_{2n} x_{2(n-k)},$$

$$H_0 = x_{20}x_{20} = x_{20}^2 \quad ,$$

$$H_1 = x_{20}x_{21} + x_{21}x_{20} = 2x_{21}x_{20}$$

$$H_2 = x_{20}x_{22} + x_{21}x_{21} + x_{22}x_{20} = 2x_{22}x_{20} + x_{21}^2$$,and so on.

Now for Bi :

$$B_n = \sum_{k=0}^{n} x_{1n} x_{2(n-k)}$$

$$B_0 = x_{10}x_{20} \quad , \quad B_1 = x_{10}x_{21} + x_{11}x_{20}$$

$$B_2 = x_{10}x_{22} + x_{11}x_{21} + x_{12}x_{20}$$, and so on.

By substituting A_i , B_i and H_i in Eq. (7) and Eq. (8) we find that:

x10=x1(0) , x20=x2(0)

$$x_{11} = \int_0^t [(\alpha_1 - \varepsilon\gamma)x_{10} - \left(\frac{\alpha_1}{k_1}\right)x_{10}^2 - \beta_1 x_{10}x_{2(}$$

$$x_{21} = \int_0^t [(\alpha_2 - \gamma)x_{20} - \left(\frac{\alpha_2}{k_2}\right)x_{20}^2 - \beta_2 x_{10}x_{20}]\, dt$$

$$x_{12} = \int_0^t [(\alpha_1 - \varepsilon\gamma)x_{11} - \left(\frac{\alpha_1}{k_1}\right)(2x_{11}x_{10}^2) - (x_{10}x_{21} + x_{11}x_{20})]\, dt$$

$$x_{22} = \int_0^t [(\alpha_2 - \gamma)x_{21} - \left(\frac{\alpha_2}{k_2}\right)(2x_{21}x_{20}^2) - \beta_2(x_{10}x_{21} + x_{11}x_{20})]\, dt \qquad (9)$$

And, so forth.

Therefore the approximate solution of the system equations(1) are:

$$x_1(t) = x_{10} + x_{11} + x_{12} + \cdots = x_1(0) + \int_0^t (\alpha_1 - \varepsilon\gamma)(x_{10} + x_{11} + x_{12} + x_{13} + x_{14} + \cdots)dt - \int_0^t \left(\frac{\alpha_1}{k_1}\right)\{x_{10}^2 + 2x_{11}x_{10} + (2x_{12}x_{10} + x_{11}^2) + (2x_{10}x_{13} + 2x_{11}x_{12}) + (2x_{10}x_{14} + 2x_{11}x_{13} + x_{12}^2) + \cdots\}dt - \int_0^t \beta_1\{x_{10}x_{20} + (x_{11}x_{20} + x_{10}x_{21}) + (x_{10}x_{22} + x_{11}x_{21} + x_{12}x_{20}) + (x_{10}x_{23} + x_{11}x_{22} + x_{12}x_{21} + x_{13}x_{20}) + (x_{10}x_{24} + x_{11}x_{23} + x_{12}x_{22} + x_{13}x_{21} + x_{14}x_{20}) + \cdots\}dt \qquad (10)$$

$$x_2(t) = x_{20} + x_{21} + x_{22} + \cdots = x_2(0) + \int_0^t (\alpha_2 - \gamma)(x_{20} + x_{21} + x_{22} + \cdots)dt - \int_0^t \left(\frac{\alpha_2}{k_2}\right)\{x_{20}^2 + 2x_{21}x_{20} + (2x_{22}x_{20} + x_{21}^2) + (2x_{20}x_{23} + 2x_{21}x_{22}) + (2x_{20}x_{24} + 2x_{21}x_{23} + x_{22}^2) + \cdots\} dt - \int_0^t \beta_2\{x_{10}x_{20} + (x_{11}x_{20} + x_{10}x_{21}) + (x_{10}x_{22} + x_{11}x_{21} + x_{12}x_{20}) + (x_{10}x_{23} + x_{11}x_{22} + x_{12}x_{21} + x_{13}x_{20}) + (x_{10}x_{24} + x_{11}x_{23} + x_{12}x_{22} + x_{13}x_{21} + x_{14}x_{20}) + \cdots\}dt + \cdots \qquad (11)$$

Using programming, we obtain relations (10) and (11) that are the approximate solutions of equations (1). According to **Table 1**, the numerical values of $x_1(t)$ and $x_2(t)$ are written in terms of relations (12) and (13) using the code of MATLAB, version.17:

Table 1. The required coefficients of the system equations.[1, 25]

L	γ	ε	w	t	x2(0)	x1(0)	k2	k1	β1	β1	α2	α1
15	0.34	0.05	50	1000	0.8	0.5	1	0.65	0.15	0.11	0.45	0.1

$$x_1(t) = 0.5 - 0.3605769230t + .01622567492t^2 - 0.006518907908t^3 + 0.002600991768t^4 - 0.001036039511t^5 + 0.0004120450067t^6 - 0.0001636342637t^7 + 0.00006489393210t^8 - 0.00002570246930t^9 + 0.00001016778396t^{10} - 0.00004017873327t^{11} + 0.000001586061672t^{12} - 6.255048103 \times 10^{-7}t^{13} + 2.464667712 \times 10^{-7}t^{14} - 9.703563645 \times 10^{-8}t^{15} \quad (12)$$

$$x_2(t) = 0.8 - 0.2680000000t + 0.09529346154t^2 - 0.03398211866t^3 + 0.01213807645t^4 - 0.004341747321t^5 + 0.001555014810t^6 - 0.0005575937360t^7 + 0.0002001634327t^8 - 0.00007193054615t^9 + 0.00002587543949t^{10} - 0.000009317428132t^{11} + 0.000003358378422t^{12} - 0.000001211664028t^{13} + 4.375719131 \times 10^{-7}t^{14} - 1.581715740 \times 10^{-7}t^{15} \quad (13)$$

Relations (10) and (11), as the solution of the equations of the system equations (1) indicate the concentrations of healthy and cancerous cells, respectively. Based on relations (10) and (11), the amounts of healthy and cancerous cells can be obtained at any time during treatment. In order to have a better comparison of the results of the Adomian decomposition calculations with the numerical solution method of the Lotka-Volterra, according to the Table of experimental values (**Table 1**)25, we present the solution diagrams of the Adomian decomposition method in the next section.

RESULTS AND DISCUSSION

The aim of this section is numerical solving of the coupled differential equations (1-a) and (1-b) in different conditions in order to determine the time variations of the concentration of healthy(x_1) and cancer cells, (x_2). According to the data presented in parts I, II and III, we have obtained the results of the numerical solution of equations 1-a and 1-b in Figures 1, 2 and 3:

I. According to Fig. 1(a) green and purple we see that, (note that in this Fig. we use the conditions: α_1=0.1, α_2=0.45, β_1=0.11, β_2=0.15, K_1=0.65 and K_2=1, γ = 0.35, L = 15 hours and the rate of the healthy cells due to the radiation is chosen as ε=0.05), by considering 50 hours as a treatment period, then the system of equations(1) have a unique globally asymptotically stable positive 50-periodic solutions.

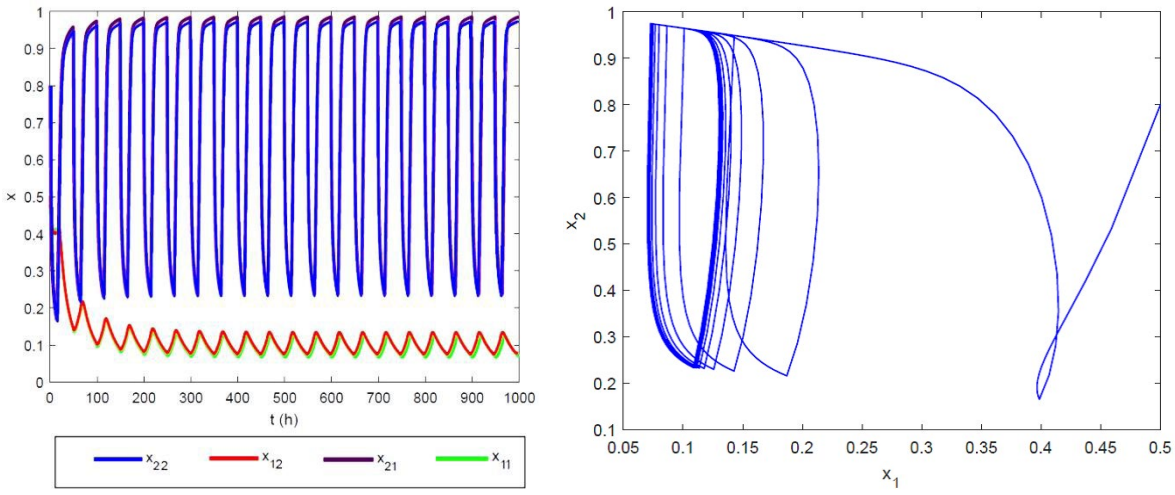
II. To present universal existence and the cancer radiation periodic solution, the coefficients can be considered as: α_1=0.2, α_2=0.5, β_1=0.5, β_2=0.55, K_1=0.65, K_2=1, γ=0.65, ε=0.3. The treatment period is chosen as ω = 10 hours. (See Fig. 2 (a- green) (L = 8 hours) and **Fig. 2** (b- green) (L = 9 hours)

III. The following coefficients were considered to review the uniqueness and global stabilities of the cancer with periodic solutions: α1 = 0.2, α2 = 0.5, β_1 = 0.48, β_2 = 0.05, K_1 = 0.65 and K_2 = 1. In this case, the cancer treatment period and the rate of the healthy cells from the radiation are chosen as ω =

10 hours and ε=0.3, respectively. In Fig. 3(a- purple) the treatment time is L = 2 hours. See Fig. 3 (b- purple) in which treatment time is L = 1 hour.

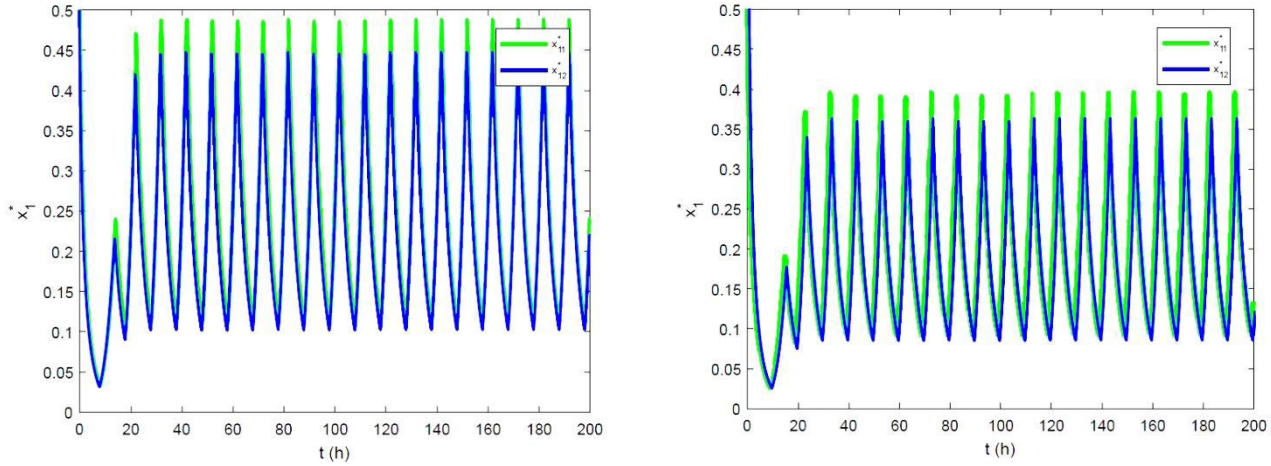
According to **Figures 1** to **3**, using the selected values of ω, ε, D (t) ≡γ, L in the Lotka-Volterra equations, we found that healthy and cancerous cells coexist, the cancer cells are win, or the cancer cells are radiated. Therefore, measurement and determination of each should be done accurately. It should be noted that the initial values are: x_1 (0) = 0.5 and x_2 (0) = 0.8. According to the these diagrams, we can see the only behavior of the concentrations of cancerous and healthy cells in terms of time and versus each other, which shows improvement of effect of radiotherapy. If we want to see the degree of agreement between the numerical and analytical solutions, we need to compare the diagrams more accurately. Hence we plot and match the diagrams of numerical solution and analytical solution using ADM, which is visible in **Fig. 1** (a).

Where x_{11}, x_{21}, x_{12}, and x_{22} represent the concentrations of healthy and cancerous cells based on the numerical solutions and ADM analytical method, respectively. As can be seen in **Fig. 1** (a), the concentrations of healthy and cancerous cells based on the numerical solution are very similar to the concentrations of healthy and cancerous cells based on the analytical method. **Fig. 1** (b) shows the phase diagram of the concentration of healthy (x_1) and cancer cells (x_2) which shows the behaviors of the concentrations of healthy (x_1) and cancer cells (x_2) in terms of each other. Since these cases have similar behaviors, therefore the numerical solutions and the ADM analytical method are equal for both phase diagrams and are perfectly matched. However, if we want to compare the behaviors of the concentrations of healthy cells vs. time for the cancer radiation periodic solution $x^*_1(t)$ in the numerical and analytical solutions, we need to match the graphs drawn based on the numerical solutions and the ADM analytical method. In **Fig. 2**, x^*_{11} and x^*_{12} represent behaviors of concen-



(a) **(b)**

Figure 1. The comparison of system equations (1) with L = 15 for (a) time variations of healthy x1 and cancer cells x2 based on numerical solutions (green (x1) and purple (x2)) and ADM analytical method (blue (x1) and red (x2)). (b) Phase diagrams of cancerous cells in terms of healthy cells based on the numerical solutions and ADM analytical method (hint :the two diagrams with black and blue colors are equal).



(a) (b)

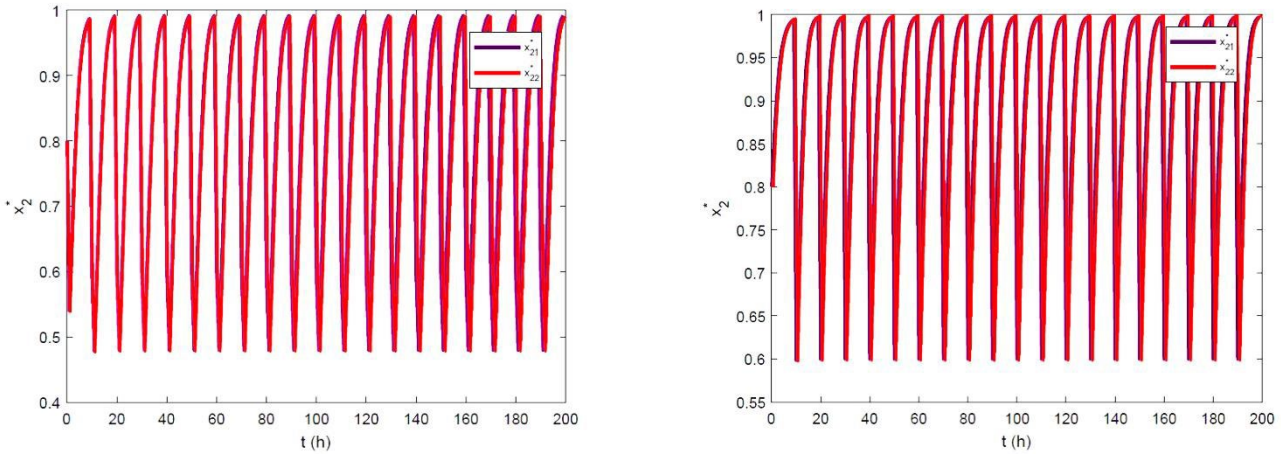
Figure 2. (a) Comparisons of concentrations of healthy cells vs. time for the cancer eradication periodic solution x*1(t) with L= 8 and γ = 0.65 (The green diagram is drawn numerically and the blue diagram is drawn based on the ADM analytical method). (b) Behaviors of concentrations of healthy cells vs. time for the cancer eradication periodic solution x*1(t) with L = 9 and γ= 0.65 (The green diagram is drawn numerically and the blue diagram is drawn based on the ADM analytical method).

trations of healthy cells vs. time for the cancer radiation periodic solutions based on numerical solutions and behaviors of concentrations of healthy cells vs. time for the cancer radiation periodic solutions based on the ADM analytical method, respectively. This is summarized for ease of drawing. By observing **Fig. 2** ((a) and (b)), it can be seen that the behaviors of healthy cells vs. time for the cancer radiation periodic solutions are closely matched. Behaviors of concentrations of cancerous cells vs. time for the cancer win periodic solution $x_2^*(t)$ based on the analytical and numerical solutions can also be compared by matching (see **Fig. 3** (a and b)).

In the **figure 3**, x_{21}^* and x_{22}^* represent the behaviors of concentrations of cancer cells vs. time for the cancer win periodic solution based on the numerical solution and behaviors of concentrations of cancer cells vs. time for the cancer win periodic solution based on the ADM analytical method, respectively. This is summarized for ease of drawing. **Fig. 3**((a) and (b)) depict a combination of behaviors of concentrations of cancer cells vs. time for the cancer win periodic solution $x_2^*(t)$with respect to numerical solution and ADM analytical method to better compare the concentration behavior of cancer cells vs. time. These comparisons show close agreement between the numerical and analytical solutions.

CONCLUSION

In this paper, the analytical solutions of the Lotka-Volterra competitive equations system were proposed as a model for radiotherapy using the Adomian decomposition method. Lotka-Volterra competitive equations can be used to determine the concentration of healthy and cancerous cells during and after treatment. **Figs. 1-3** were drawn up in an analytical method on the basis of the three experimental cases cited in **Table 1**. Considering the calculated answers and the obtained graphs, we observe good agreement between the analytical and numerical solutions. Analytical responses that indicate



(a) (b)

Figure 3. (a) Comparisons of concentrations of cancer cells vs. time for the cancer win periodic solutions $x_2^*(t)$ with γ = 0.4 and L = 2 (The purple diagram is drawn numerically and the red diagram is drawn based on the ADM analytical method). (b) Behaviors of concentrations of cancer cells vs. time for the cancer win periodic solution $x_2^*(t)$ with γ = 0.6 and L = 1(The purple diagram is drawn numerically and the red diagram is drawn based on the ADM analytical method) .

the concentration of healthy and cancerous cells during the treatment stage and the no treatment stage can be effective in improving modeling based on the competitive model of the Lotka-Volterra equations, which results in reduced use of diagnostic devices, less radiation, a faster treatment process and decreased cost of treatment for patients and governments.

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