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Non-Standard Finite Difference Schemes for Investigating Stability of a Mathematical Model of Virus Therapy for Cancer

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Abstract

In this paper, a special case of finite difference method called non-standard finite difference (NSFD) method was studied to compute the numerical solutions of the nonlinear mathematical model of the interaction between tumor cells and oncolytic viruses. The global stability of the equilibrium points of the discrete model is investigated by using the Lyapunov stability theorem. Some conditions were gained for the local asymptotical stability of the equilibrium points of the system. Finally, numerical simulations are carried out to illustrate the main theoretical results. The discrete system is dynamically consistent with its continuous model, it preserves essential properties, such as positivity, boundedness of the solution, stability properties of the equilibrium points.

Keywords: Asymptotic stability; Cancer; Equilibrium points; Non-standard finite difference; Oncolytic viruses; Positivity; Tumor cells

MSC Classification: 65L05, 65L07, 65L12, 65L20

1. Introduction

Many of the phenomena in the world around us are modeled with ordinary or partial differential equations. In general, finding the analytic solution of these equations is very complicated and it is difficult to find their exact solutions. Therefore, the use of numerical methods is very important for the approximation of these differential equations. The finite difference method is one of the most popular numerical methods. In many nonlinear problems, standard finite difference (SFD) schemes have numerical instability, Mickens (1994, 2000, 2005). In general, SFD schemes preserve the properties of differential equations if the length of step-size h is small enough. Therefore, in dynamical systems with large time intervals, the choice of small steps requires a lot of computational effort. Additionally, in some dynamical systems, SFD schemes cannot preserve the properties of the continuous system for each step-size. The proposed NSDF method by Mickens (2005), preserves the main properties of the corresponding differential equations, such as positivity, boundedness, stability, and so on. The discrete models with these properties are called dynamically consistent. A finite difference scheme is called non-standard if at least one of the following conditions is met, Mickens (2005):

- A nonlocal approximation is used. For example,

$$y = 2\,y - y\ \rightarrow 2y_k - y_{k+1},$$

$$y^2 = yy\ \rightarrow\ y_k y_{k+1}.$$

- The discretization of the first and second order derivatives is performed as follows:

$$\frac{dy}{dt} \rightarrow \frac{y_{k+1-\psi(h)y_k}}{\phi(h)},$$

$$\frac{d^2y}{dt^2} \rightarrow \frac{y_{k+1}-2y_k+y_{k-1}}{\varphi(h)},$$

where the function $\psi(h)$ is called the numerator function and the functions $\phi(h)$ and $\varphi(h)$ are called denominator functions and have the following properties:

$$\psi(h) = 1 + O(h),\ \phi(h) = h + O(h^2),\ \varphi(h) = h^2 + O(h^4), \tag{1}$$

where $\mathrm{h} = \Delta\mathrm{t}$, $t \rightarrow t_k = kh$ and $y(t) \rightarrow y_k$.

The initial foundation of NSFD schemes came from exact finite difference schemes. For constructing the NSFD schemes, we use the following rules, were given by Mickens (2005):

Rule 1.

The orders of the discrete derivative should be equal to the orders of the corresponding derivatives appearing in the differential equations.

Remark 1.

If the orders of the discrete derivatives are larger than those occurring in the differential equations then, in general numerical instabilities will occur.

Rule 2.

Denominator functions for the discrete derivatives must, in general, be expressed in terms of more complicated functions of the step-sizes than those conventionally used.

Rule 3.

Nonlinear terms should, in general, be replaced by nonlocal discrete representations.

Rule 4.

Special conditions that correspond to either the differential equation and/or its solutions should also correspond to the difference equation and/or its solutions.

Rule 5.

The discrete schemes should not produce extraneous or spurious answers.

Remark 2.

Many finite difference schemes generate certain answers that are not corresponding to any solution of the original differential equation.

In recent decades, the NSFD method has been considered by many researchers and significant results have been achieved, Mickens (1994, 2000, 2001, 2003, 2005, 2005, 2005, 2006, 2007), Namjoo (2018), Sweilam (2019). The stability of the equilibrium points of differential equations is one of these results because it plays a fundamental role in the study of the asymptotic behavior of differential equations. Constructing difference schemes that preserve the stability behavior of the equilibrium points is important in numerical simulation. In this paper, a mathematical model which described the interaction between two types of tumor cells has been studied. An NSFD scheme is designed to preserve the important features of the original model.

The rest of this paper is organized as follows: In Section 2, the model is outlined. In Section 3, the NSFD scheme is constructed. Section 4 deals with the stability analysis of the equilibrium points. In Section 5, numerical results are presented. The conclusion appears in Section 6.

2. Mathematical Model

Cancer is one of the greatest killers in the world and the control of tumor growth is very important. Various efforts have been done over many years to achieve mathematical modeling of cancer development, Novozhilov et al. (2006), Tari (2012), Wodarz (2001, 2004), Wodarz and Komarova (2005), Sedaghat and Ordokhani (2012). In this work, Wodarz’s model (2004), was analyzed.

Wodarz presented a mathematical model which described the interaction between two types of tumor cells (the cells that are not infected but are susceptible to be infected so far as they have the cancer phenotype) with ratio dependent functional response between them.

$$\begin{cases} x' = rx\left(1 - \frac{x+y}{k}\right) - dx - \beta xy, \\ y' = \beta xy + sy\left(1 - \frac{x+y}{k}\right) - ay, \end{cases} \tag{2}$$

with the initial conditions $x(0) = x_0 > 0$ and $y(0) = y_0 > 0$, where x and y are two types of tumor cells, which respectively are the size of uninfected tumor cells and infected tumor cells by the virus, r is the growth rate of tumor, k is the maximum size that the tumor is allowed to occupy, d is death rate, β is the spread rate of virus in tumor cells, a is the death rate of infected tumor cells by virus and s shows growth rate in a logistic fashion.

The equilibrium points of the system (2) are as follows:

$$E_0 = (0, 0),$$

$$E_1 = (k(r-d)/r, 0),$$

$$E_2 = (0, k(s-a)/s),$$

$$E_3 = \left(\frac{\beta k(a-s)+ar-sd}{\beta(\beta k+r-s)}, \frac{\beta k(r-d)+sd-ar}{\beta(\beta k+r-s)}\right) \coloneqq (x^*,\ y^*). \tag{3}$$

The model (2) has the following properties, Ashyani et al. (2016):

(p_1) All the solutions of (2) starting in the positive orthant $(\mathbb{R}_0^+)^2$ either approach, enter or remain in the subset of $(\mathbb{R}_0^+)^2$ defined by

$$\Omega = \{(x, y) \in (\mathbb{R}_0^+)^2 : 0 < \mathrm{x} + \mathrm{y} \leq \mathrm{k}\}, \tag{4}$$

where $(\mathbb{R}_0^+)^2$ denotes the non-negative cone of $\mathbb{R}^2$ including its lower dimensional faces.

(p_2) The equilibrium point E_0 is locally asymptotically stable if and only if $r < d$ and $s < a$.

(p_3) The equilibrium point E_1 is locally asymptotically stable if and only if $d < r$ and $a > (\beta k(r-d) + ds)/r$.

(p_4) The equilibrium point E_2 is locally asymptotically stable if and only if $a < s$ and $a < s(\beta k + d)/(\beta k + r)$.

(p_5) The equilibrium point E_3 is locally asymptotically stable if and only if $\beta k + r - s > 0$ and $ds - ar < 0$.

(p_6) The equilibrium point E_0 is globally stable if E_1, E_2 and E_3 do not exist.

3. Non-Standard Schemes

In this section, we design the NSFD schemes that have all the properties (p_1)-(p_6). We construct the following NSFD schemes for approximating (2).

$$\begin{cases} \frac{x_{n+1}-x_n}{\varphi(h)} = rx_{n+1}\left(1-\frac{x_n+y_n}{k}\right) - dx_{n+1} - \beta x_{n+1}y_n, \\ \frac{y_{n+1}-y_n}{\varphi(h)} = \beta x_{n+1}y_n + sy_{n+1}\left(1-\frac{x_n+y_n}{k}\right) - ay_{n+1}, \end{cases} \tag{5}$$

where $\varphi(h) = h + O(h^2)$. For simplicity, we omit the argument h in the function $\varphi(h)$. By solving (5) in x_{n+1} and y_{n+1} we get,

$$\begin{cases} x_{n+1} = \frac{x_n}{1-\varphi r+\varphi d+{}^{\varphi r}/_k\,(x_n+y_n)+\beta\varphi y_n}, \\ y_{n+1} = \frac{(1+\varphi\beta x_{n+1})y_n}{1-\varphi s+\varphi a+{}^{\varphi s}/_k\,(x_n+y_n)}. \end{cases} \tag{6}$$

If we choose φ so that $\varphi < {}^{1}/_{\delta}$, where $\delta = \max\{r, s\}$, then, for all positive initial data, we have $x_{n+1}, y_{n+1} > 0$, therefore, the NSFD schemes (5)- (6) preserve the positivity property of the continuous system (2).

Theorem 1.

Assume that $\delta = \max\{r, s\}$, if $\varphi < {}^{1}/_{\delta}$, then, by starting from any initial condition in Ω, where Ω is defined by (4), the NSFD schemes (5)- (6) generate a unique sequence of positive vectors and the set Ω is invariant.

Proof:

From (6) the positivity and uniqueness of the solution is obvious. By mathematical induction we prove that the sequence (x_k, y_k), given by (6), is in Ω. Assume that $(x_0, y_0) \in \Omega$ and $(x_n, y_n) \in \Omega$, has been constructed (Induction assumption). It is suffice to show that $(x_{n+1}, y_{n+1}) \in \Omega$. Adding the equations in the system (5) gives,

$$\begin{aligned} \frac{(x_{n+1}+y_{n+1})-(x_n+y_n)}{\varphi} &= (rx_{n+1} + sy_{n+1})\left(1-\frac{(x_n+y_n)}{k}\right) - (dx_{n+1} + ay_{n+1}), \\ &\le \delta(x_{n+1} + y_{n+1})\left(1-\frac{(x_n+y_n)}{k}\right). \end{aligned}$$

Therefore,

$$x_{n+1} + y_{n+1} \le \frac{x_n+y_n}{1-\delta\varphi+\left({}^{\delta\varphi}/_k\right)(x_n+y_n)}. \tag{7}$$

We set $z = x_n + y_n$. By induction assumption $0 < z \le k$, therefore, the right-hand side of (7) is equal to $f(z) = \frac{z}{1-\delta\varphi+\left(\delta\varphi/_k\right)z}$. Since $\varphi < \frac{1}{\delta}$, we have $f'(z) = \frac{1-\delta\varphi}{\left(1-\delta\varphi+\left(\delta\varphi/_k\right)z\right)^2} > 0$, so the maximum of $f(z)$ in the interval $(0, k]$ is obtained for $z = k$. Therefore, $f(z) = \frac{z}{1-\delta\varphi+\left(\delta\varphi/_k\right)z} \le \frac{k}{1-\delta\varphi+\left(\delta\varphi/_k\right)k} = k$. Hence, $0 < x_{n+1} + y_{n+1} \le k$. So, $(x_{n+1}, y_{n+1}) \in \Omega$. (i.e., the NSFD scheme (6) captures the invariance property of the continuous model (2), as guaranteed by the property (p_1)). ■

Now assume that $\lim_{k\to\infty} x_k = m$ and $\lim_{k\to\infty} y_k = n$, from (6) we have,

$$\begin{cases} m = \frac{m}{1-\varphi r+\varphi d+{}^{\varphi r}/_k\,(m+n)+\beta\varphi n}, \\ n = \frac{(1+\varphi\beta m)n}{1-\varphi s+\varphi a+{}^{\varphi s}/_k\,(n+m)}. \end{cases} \tag{8}$$

By solving (8) in m and n we obtain,

$$e_0(m,n) = E_0 = (0,0),$$

$$e_1(m,n) = E_1 = (k(r-d)/r, 0),$$

$$e_2(m,n) = E_2 = (0, k(s-a)/s),$$

$$e_3(m,n) = E_3 = \left(\frac{\beta k(a-s)+ar-sd}{\beta(\beta k+r-s)}, \frac{\beta k(r-d)+sd-ar}{\beta(\beta k+r-s)}\right).$$

It is observed that for any value of the step-size, the fixed points of the discrete models (5)- (6) are exactly the equilibrium points of the continuous model (2).

4. Stability Analysis of the Fixed Points of the discrete model

The stability property of the equilibrium points of differential equations is very important because it plays a fundamental role in the study of the asymptotic stability behavior of the solutions. In this section, we gain some conditions for the stability of the fixed points of the models (5)- (6). According to the right-hand side of the NSFD scheme (6), we define functions F and G as follows:

$$F(x,y) = \frac{x}{1-\varphi r+\varphi d+\left({}^{\varphi r}/_k\right)(x+y)+\beta\varphi y}, \quad G(x,y) = \frac{(1+\varphi\beta x)y}{1-\varphi s+\varphi a+\left({}^{\varphi s}/_k\right)(x+y)}.$$

The Jacobian matrix is as follows:

$$J = \begin{bmatrix} \partial F/\partial x & \partial F/\partial y \\ \partial G/\partial x & \partial G/\partial y \end{bmatrix}.$$

The fixed-point E_i is locally asymptotically stable if and only if the spectral radius of $J(E_i)$ is less than unity.

4.1. Local Stability Analysis of E_0

The matrix $J(E_0)$ is as follows:

$$J(E_0) = \begin{bmatrix} \frac{1}{1+\varphi(d-r)} & 0 \\ 0 & \frac{1}{1+\varphi(a-s)} \end{bmatrix}.$$

Therefore, E_0 is locally asymptotically stable if $r < d$ and $s < a$. Hence, E_0 is a stable equilibrium point if and only if E_1 and E_2 do not exist. Biologically, stability of E_0 means that both infected and uninfected cells are destroyed and therapy is successful.

4.2. Local Stability Analysis of E_1

To study the stability behavior of E_1, we compute the matrix $J(E_1)$ as follows:

$$J(E_1) = \begin{bmatrix} 1+\varphi(d-r) & \varphi(d-r)(1+{}^{\beta k}/_{r}) \\ 0 & \frac{1+\varphi\beta k(1-{}^{d}/_{r})}{1+\varphi(a-{}^{ds}/_{r})} \end{bmatrix}.$$

The eigenvalues of $J(E_1)$ are $\lambda_1 = 1+\varphi(d-r)$ and $\lambda_2 = \frac{1+\varphi\beta k(1-{}^{d}/_{r})}{1+\varphi(a-{}^{ds}/_{r})}$. $\lambda_1 < 1$ if and only if $d < r$. Also $\lambda_2 < 1$, if and only if $(\beta k(r-d)+ds)/r < a$.Therefore, E_1 is locally asymptotically stable if $d < r$ and $(\beta k(r-d)+ds)/r < a$. Furthermore, $E_1$is a saddle point if $(\beta k(r-d)+ds)/r > a$. Biologically, stability of E_1 means that the uninfected cells exist and are not destroyed which means after virus injection, all viruses are destroyed but tumor still exists. Hence, the stability of this point is not useful for cancer therapy.

4.3. Local Stability Analysis of E_2

By computing $J(E_2)$ we obtain,

$$J(E_2) = \begin{bmatrix} \frac{1}{1+\varphi[d-r+(\beta k+r)(1-{}^{a}/_{s})]} & 0 \\ \varphi[\beta k(1-{}^{a}/_{s})+a-s] & 1+\varphi(a-s) \end{bmatrix}.$$

All the eigenvalues of $J(E_2)$ are less than unity, if and only if $a < s(\beta k+d)/(\beta k+r)$ and $a < s$. Therefore, the equilibrium point E_2 is locally asymptotically stable if $a < s(\beta k+d)/(\beta k+r)$ and $a < s$. If $a > s(\beta k+d)/(\beta k+r)$ then, E_2 is a saddle point. Biologically, stability of E_2 means that the infected cells exist and are not destroyed which means after virus injection, all tumor cells are infected but did not disappear. Hence, the stability of this point is not useful for cancer therapy.

4.4. Local Stability Analysis of E_3

The matrix $J(E_3)$ is as follows:

$$J(E_3) = \begin{bmatrix} A^* & B^* \\ C^* & D^* \end{bmatrix},$$

where

$$A^* = \frac{1-\varphi r+\varphi d+{}^{\varphi r}/_{k}(x^*+y^*)+\varphi\beta y^*-{}^{\varphi r}/_{k}\, x^*}{\left(1-\varphi r+\varphi d+{}^{\varphi r}/_{k}(x^*+y^*)+\beta\varphi y^*\right)^2}, \quad B^* = -\frac{\varphi\left({}^{r}/_{k}+\beta\right) x^*}{\left(1-\varphi r+\varphi d+{}^{\varphi r}/_{k}(x^*+y^*)+\beta\varphi y^*\right)^2},$$
$$C^* = \frac{\varphi\beta y^*\left(1-\varphi s+\varphi a+{}^{\varphi s}/_{k}y^*\right)-{}^{\varphi s}/_{k}y^*}{\left(1-\varphi s+\varphi a+{}^{\varphi s}/_{k}(x^*+y^*)\right)^2}, \quad D^* = \frac{(1-\varphi s+\varphi a+{}^{\varphi s}/_{k}\, x^*)(1+\varphi\beta x^*)}{\left(1-\varphi s+\varphi a+{}^{\varphi s}/_{k}(x^*+y^*)\right)^2},$$

where x^* and y^* are defined by (3) and are the positive solutions of the following system,

$$\begin{cases} r\left(1-\frac{x+y}{k}\right)-d-\beta y = 0, \\ \beta x + s\left(1-\frac{x+y}{k}\right)-a = 0. \end{cases} \tag{9}$$

From (9) we get,

$$-\varphi r + \varphi d + {}^{\varphi r}/_{k}\,(x^* + y^*) + \varphi\beta y^* = 0, \tag{10}$$
$$-\varphi s + \varphi a + {}^{\varphi s}/_{k}\,(x^* + y^*) = \varphi\beta x^*. \tag{11}$$

Using (10) and (11), after some manipulation we obtain,

$$A^* = 1 - {}^{\varphi r}/_{k}\, x^*, \quad B^* = -\varphi\left({}^{r}/_{k}+\beta\right)x^*, \quad C^* = \frac{\varphi(\beta - s/k)y^*}{1+\varphi\beta x^*}, \quad D^* = 1 - \frac{{}^{\varphi s}/_{k}y^*}{1+\varphi\beta x^*}.$$

The characteristic polynomial of $J(E_3)$ is as follows:

$$\lambda^2 - (A^* + D^*)\lambda + (A^*D^* - B^*C^*) = 0.$$

The eigenvalues of $J(E_3)$ are

$$\begin{aligned} \lambda_{1,2} &= \tfrac{1}{2}(A^* + D^*) \pm \tfrac{1}{2}\sqrt{(A^* + D^*)^2 - 4(A^*D^* - B^*C^*)}, \\ &= \tfrac{1}{2}(A^* + D^*) \pm \tfrac{1}{2}\sqrt{(A^* - D^*)^2 + 4B^*C^*}, \\ &= 1 - \frac{\varphi}{2k}\left(rx^* + \frac{sy^*}{1+\varphi\beta x^*}\right) \pm \frac{\varphi}{2k}\sqrt{\left(\frac{sy^*}{1+\varphi\beta x^*} - rx^*\right)^2 - 4\frac{(\beta k+r)(\beta k-s)\, x^*y^*}{1+\varphi\beta x^*}}, \end{aligned}$$

$$= 1 - \frac{\varphi}{2k}\left[\left(rx^* + \frac{sy^*}{1+\varphi\beta x^*}\right) \pm \sqrt{\left(rx^* + \frac{sy^*}{1+\varphi\beta x^*}\right)^2 - 4\frac{\beta k(\beta k+r-s)\, x^* y^*}{1+\varphi\beta x^*}}\right].$$

Clearly, if $(\beta k + r - s) > 0$, then, $|\lambda_{1,2}| < 1$. Hence, the equilibrium point E_3 is locally asymptotically stable if $\beta k + r - s > 0$.

4.5. Global Stability Analysis of E_0

Theorem 2.

The equilibrium point E_0 of the model (5) is globally stable if E_1, E_2, and E_3 do not exist.

Proof:

Notice that the global stability of (5) and (6) are equivalent. Therefore, we prove that E_0 is a globally stable equilibrium point of the model (6). Consider the Lyapunov function

$$V(x, y) = x + y.$$

Clearly, in the invariant set Ω, where Ω is defined by (4), the function V is positive definite. Moreover, for a discrete dynamical system $X(k+1) = f\big(X(k)\big)$, we have $\Delta V(X) = V\big(f(X)\big) - V(X)$. Therefore, according to (6) we obtain,

$$\begin{aligned}\Delta V(x_k, y_k) &= (x_{k+1} + y_{k+1}) - (x_k + y_k),\\ &= \left(\frac{x_k}{1+\varphi(d-r)+\left({}^{\varphi r}/_{k}\right)(x_k+y_k)+\beta\varphi y_k} + \frac{(1+\varphi\beta x_{k+1})y_k}{1+\varphi(a-s)+\left({}^{\varphi s}/_{k}\right)(x_k+y_k)}\right) - (x_k + y_k).\end{aligned}$$

Since E_1 and E_2 do not exist, $d - r > 0$ and $a - s > 0$. Since E_3 does not exist, $\Delta V(x_k, y_k) \neq 0$. Hence, for $(x_k, y_k) \in \Omega$, we have $\Delta V(x_k, y_k) < 0$. Therefore, by the Lyapunov stability theorem, Khalil (2002), the global stability of E_0 is ensured. ■

Consequently, we proved that the NSFD schemes (5)- (6) captures all the properties $(p_1) - (p_6)$ of the continuous model (2).

5. Numerical Simulation

In this section, in order to confirm the validity of obtained results and to demonstrate the efficiency of the designed NSFD scheme, we present some numerical results of the NSFD scheme obtained in the previous sections. Assume that $\varphi(h) = \frac{1-e^{-\delta h}}{\delta}$, Mickens (2005). Note that $\varphi(h) < {}^{1}/_{\delta}$ and $\varphi(h) = h + O(h^2)$. We set the parameter as follows, Ashyani et al. (2016):

$$a = 3,\ \ d = 1,\ \ k = 5,\ \ r = 0.1,\ \ s = 2,\ \ \beta = 5. \tag{12}$$

In this case, the equilibrium points E_1, E_2, and E_3 do not exist. Hence, according to the theorem 2, E_0 is globally stable. Moreover, the eigenvalues of $J(E_0)$ are $\lambda_1 \approx 0.8597$ and $\lambda_2 \approx 0.8465$. In Figures 1 and 2, with $x_0 = y_0 = 0.5$ and parameters given in (12), $x(t)$ and $y(t)$ are attracted to the components of $E_0 = (0, 0)$. In Table 1, the numerical solutions are given at a few points. It is seen that the numerical solutions tend to $E_0 = (0, 0)$.

Now we set the parameters as follows:

$$a = 2, \;\; d = 0.01, \;\; k = 70, \;\; r = 0.2, \;\; s = 1, \;\; \beta = 0.1. \tag{13}$$

In this case, $(\beta k + r - s) = 6.2 > 0$ and $ds - ar = -0.39$. Hence, the equilibrium point $E_3 = (11.9194, 1.5161)$, is locally asymptotically stable. The eigenvalues of $J(E_3)$ are $\lambda_{1,2} \approx 0.9975 \pm 0.0360\, i$. Therefore, $|\lambda_{1,2}| = 0.9981$. In Figures 3 and 4, with $x_0 = y_0 = 0.5$ and the parameters given in (13), $x(t)$ and $y(t)$ are attracted to the components of E_3.

In Table 2, the numerical solutions of the NSFD scheme (6) with parameters (13) are given at a few points. It is seen that the numerical solutions tend to the equilibrium point $E_3 = (11.9194, 1.5161)$.

We set the parameters as follows:

$$a = 1, \;\; d = 0.1, \;\; k = 29, \;\; r = 0.2, \;\; s = 1.001, \;\; \beta = 0.1. \tag{14}$$

In this case, $(\beta k + r - s) = 2.099 > 0$ and $ds - ar = -0.0999$. Hence, the equilibrium point $E_3 = (0.4621, 0.9057)$, is locally asymptotically stable. The eigenvalues of $J(E_3)$ are $\lambda_{1,2} \approx 0.9984 \pm 0.0050\, i$. Therefore, $|\lambda_{1,2}| = 0.9984$. In Figures 5 and 6, with $x_0 = y_0 = 0.5$ and the parameters given in (14), $x(t)$ and $y(t)$ are attracted to the components of E_3.

In Table 3, the numerical solutions of the NSFD scheme (6) with parameters (14) are given at a few points. It is seen that the numerical solutions tend to the equilibrium point $E_3 = (0.4621, 0.9057)$.

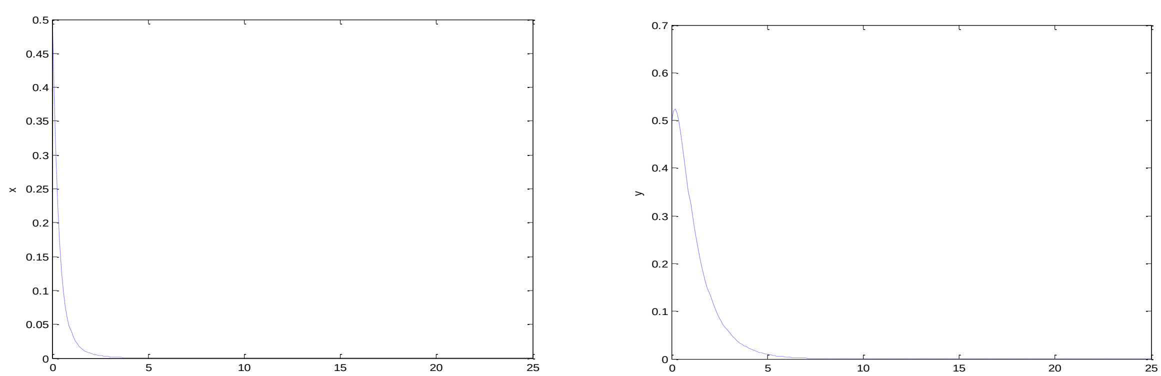

Figure 1. Convergence of the NSFD scheme (6) to the components of $E_0 = (0, 0)$, for parameters given in (12) with $x_0 = y_0 = 0.5, h = 0.1$

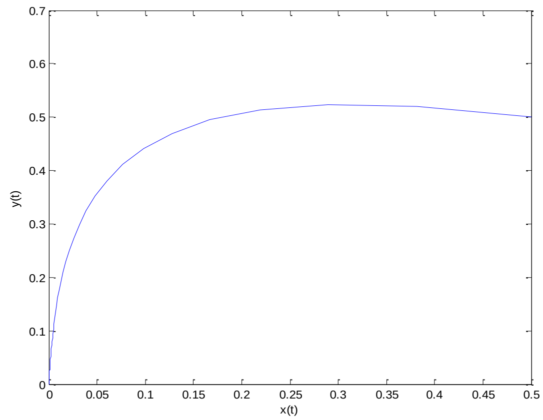

Figure 2. Stable limit cycles for parameters given in (12) and initial conditions $x_0 = y_0 = 0.5, h = 0.1$

Table 1. The numerical solutions of the NSFD scheme (6) with parameters given in (12)

t_n	x_n	y_n
0	0.5000	0.5000
2	0.0017	0.1349
4	8.6110e-04	0.0233
6	1.6294e-04	0.0041
8	3.3383e-05	7.2021e-04
10	6.9362e-06	1.2701e-04
12	1.4447e-06	2.2399e-05
14	3.0106e-07	3.9505e-06
16	6.2739e-08	6.9673e-07
18	1.3075e-08	1.2288e-07
20	2.7248e-09	2.1672e-08

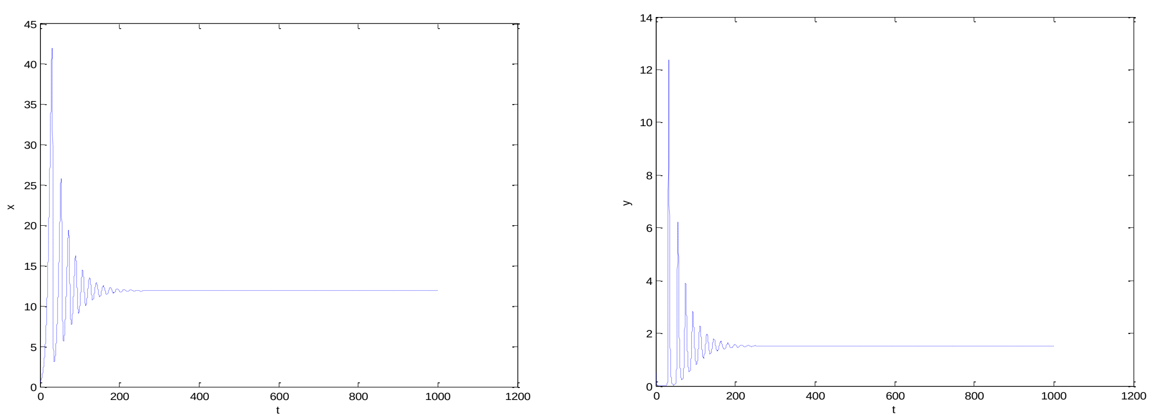

Figure 3. Convergence of the NSFD scheme (6) to the components of $E_3 = (11.9194, 1.51613)$, for parameters given in (13) with $x_0 = y_0 = 0.5, h = 0.1$

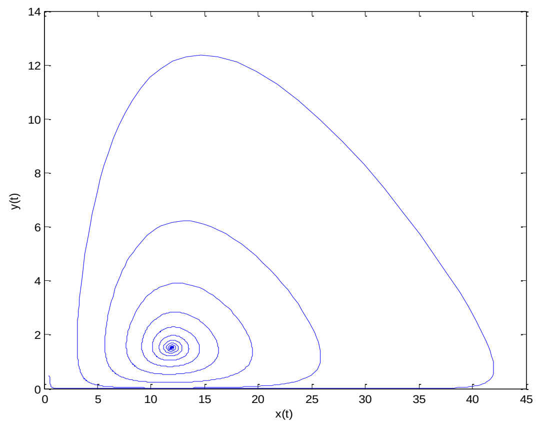

Figure 4. Stable limit cycles for parameters given in (13) and initial conditions $x_0 = y_0 = 0.5, h = 0.1$

Table 2. The numerical solutions of the NSFD scheme (6) with parameters given in (13)

t_n	x_n	y_n
0	0.5000	0.5000
100	9.8451	1.0089
200	11.8447	1.5761
300	11.9333	1.5173
400	11.9195	1.5158
500	11.9193	1.5161
600	11.9194	1.5161
700	11.9194	1.5161
800	11.9194	1.5161
900	11.9194	1.5161
1000	11.9194	1.5161

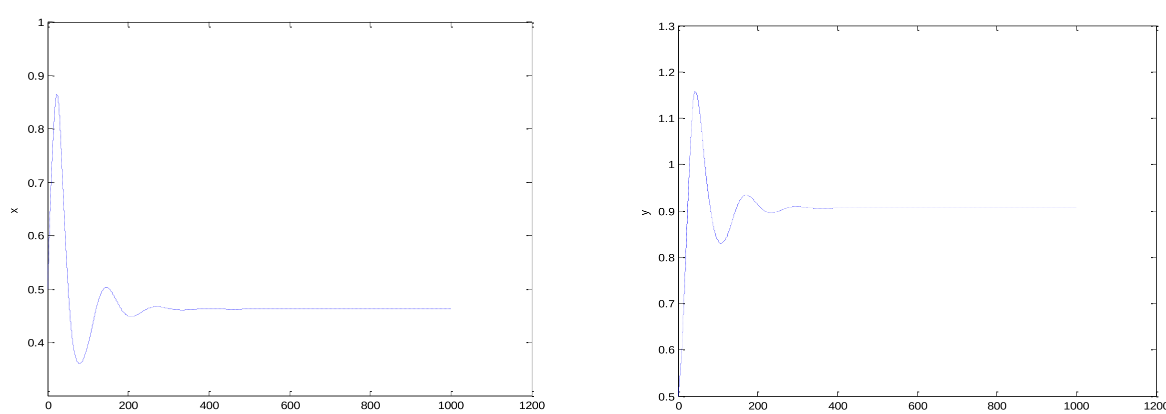

Figure 5. Convergence of the NSFD scheme (6) to the components of $E_3 = (0.4621, 0.9057)$, for parameters given in (14) with $x_0 = y_0 = 0.5,\ h = 0.1$

Table 3. The numerical solutions of the NSFD scheme (6) with parameters given in (14)

t_n	x_n	y_n
0	0.5000	0.5000
100	0.3939	0.8363
200	0.4497	0.9140
300	0.4608	0.9092
400	0.4620	0.9057
500	0.4622	0.9055
600	0.4621	0.9057
700	0.4621	0.9057
800	0.4621	0.9057
900	0.4621	0.9057
1000	0.4621	0.9057

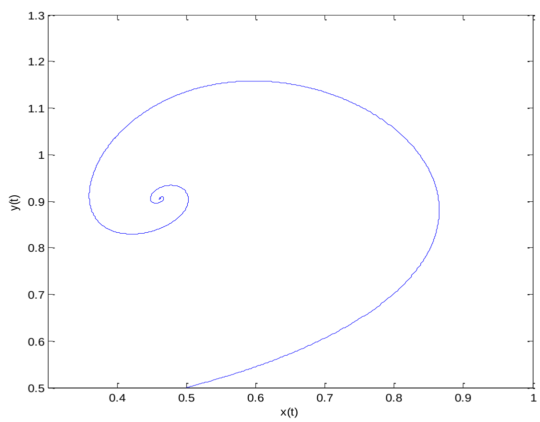

Figure 6. Stable limit cycles for parameters given in (14) and initial conditions $x_0 = y_0 = 0.5$ with $h = 0.1$

6. Conclusion

In this paper, we have constructed the non-standard finite difference scheme for investigating the stability of the equilibrium points of the mathematical model of virus therapy for cancer which is a nonlinear system of ordinary differential equations. The constructed scheme captures many of the essential dynamical features of the continuous-time model (2) such as positivity, boundedness, invariance of a solution, and convergence to the equilibrium point. Therefore, in the numerical simulations, the non-standard finite difference method always gave numerical results that are dynamically consistent with those of the continuous-time model. The use of non-standard finite difference method and its approximations play an important role for the formation of stable numerical methods. The main advantage of the schemes is that the algorithm is very simple and very easy to implement. Thus, this method may be applied as a simple and accurate solver for ODEs and PDEs and it can also be utilized as an accurate algorithm to solve linear and nonlinear equations arising in physics and other fields of applied mathematics. The graphical results in figures show that the presented scheme has good accuracy.

The main contribution of this paper is that we have established analysis of the stability of the equilibrium points of a mathematical model which described the interaction between two types of tumor cells which presented by Wodarz. The stability of the equilibrium points of differential equations plays a fundamental role in the study of the asymptotic behavior of differential equations. Constructing difference schemes that preserve the stability behavior of the equilibrium points is important in numerical simulation. The global stability of the disease-free equilibria E_0 is done by applying the techniques of Lyapunov function. Stability of the equilibrium point E_0 means that both infected and uninfected cells are destroyed and therapy is successful. Stability of E_1 means that the uninfected cells exist and are not destroyed which means after virus injection, all viruses are destroyed but tumor still exists. Therefore, the stability of this point is not useful for cancer therapy. Stability of E_2 means that the infected cells exist and are not destroyed which means after virus injection, all tumor cells are infected but did not disappear. Hence, the stability of this point is not useful for cancer therapy. The equilibrium point E_3 is important in biology. Existence of this point means that both of the uninfected and infected tumor cells exist and its stability means that the tumor growth is controlled in a way that it cannot reach to the carrying capacity k. Hence, the tumor exists and does not completely destroy but we could control the size of tumor. therefore, if we provide conditions for parameters in subsection 4.4 it means that with this therapy we could control the size of tumor and therapy is effective.

We didn't prove the global stability of endemic equilibrium point E_3, because the calculations are tedious, we plan to pursue it on a separate paper.

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REFERENCES

Ashyani, A., Mohammadinejad, H., Rabiei Motlagh, O. (2016). Stability Analysis of Mathematical Model of Virus Therapy for Cancer, *Iranian Journal of Mathematical Sciences and Informatics, Vol.* **11**, No. 2, **pp**. 97-110.

Khalil, H. K. (2002). *Nonlinear Systems (3***rd** *Edition),* Prentice Hall, Upper Saddle River.

Mickens, R. E. (1994). *Nonstandard Finite Difference Models of Differential Equations,* World Scientific, Singapore.

Mickens, R. E. (2000). *Applications of Nonstandard Finite Difference Schemes*, World Scientific, Singapore.

Mickens, R. E. (2001). A non-standard Finite Difference Scheme for a Nonlinear PDE Having Diffusive Shock Wave Solutions, *Mathematics and Computers in Simulation, Vol.* **55, pp.** 549-555.

Mickens, R. E. (2003). A non-standard Finite Difference Scheme for a Fisher PDE Having Nonlinear Diffusion, *Comput. Math. App, Vol.* **145**, **pp.** 429-436.

Mickens, R. E. (2005). Nonstandard Finite Difference Schemes for Differential Equations, *Journal of Difference Equations and Applications, Vol.* **8**, No. 9, **pp**. 823-847

Mickens, R. E. (2005). A non-standard Finite Difference Scheme for a PDE Modeling Combustion with Nonlinear Advection and Diffusion, *Mathematics and Computers in Simulation, Vol.* **69**, **pp.** 439-446.

Mickens, R. E. (2005). *Advances in the Applications of non-standard Finite Difference Schemes*, World Scientific, Singapore.

Mickens, R. E. (2006). Calculation of Denominator Functions for non-standard Finite Difference Schemes for Differential Equations Satisfying a Positivity Condition, *Wiley Inter Science, Vol.* **23**, **pp.** 672-682.

Mickens, R. E. (2007). Determination of Denominator Functions for a NSFD Scheme for the Fisher PDE with Linear Advection, *Mathematics and Computers in Simulation, Vol.* **74**, **pp.** 127-195.

Namjoo, M., Zeinadini, M., Zibaei, S. (2018). Nonstandard finite-difference scheme to approximate the generalized Burgers-Fisher equation, *Mathematical Methods in the Applied Sciences, Vol.* **41,** No. 17,**pp.** 8212-8228.

Novozhilov, A. S., Berezovskaya, F. S., Koonin, E. V., Karev, G. P. (2006). Mathematical modeling of tumor therapy with oncolytic viruses: regimes with complete tumor elimination within the framework of deterministic models, *Biology Direct, Vol.* **1**, **pp**. 6-24.

Sedaghat, S., Ordokhani, Y. (2012). Stability and numerical solution of time variant linear systems with delay in both the state and control, *Iranian Journal of Mathematical Sciences and Informatics, Vol.***7**. No. 1, **pp**. 43-57.

Sweilam, N. H., Nagy, A. M., Elfahri, L. E., (2019). Nonstandard Finite-Difference Scheme for the Fractional Order Salmonella Transmission Model, *Journal of Fractional Calculus and Applications, Vol.* **10,** No. 1,**pp.** 197-212.

Tari, A. (2012). the differential transform method for solving the model describing biological species living together, *Iranian Journal of Mathematical Sciences and Informatics, Vol.* **7**, No**.** 2, **pp**. 63-74.

Wodarz, D. (2001). Viruses as antitumor weapons: defining conditions for tumor remission, *Cancer Research, Vol.* **61**, **pp**. 3501-3507.

Wodarz, D. (2004). Computational approaches to study oncolytic virus therapy: insights and challenges, *Gene Ther Mol Biol, Vol.* **8**, **pp**. 137-146.

Wodarz, D., Komarova, N. (2005). *Computational biology of cancer: Lecture notes and mathematical modeling*, World Scientific Publishing Company, Singapore.