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A simple chaotic model for development of HIV virus

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Abstract. Investigation into the spread of HIV virus as one of the fastest infectious viruses through human body is essential. Mathematical modeling facilitates the process and evaluation of the experimental tests. It can also help predict the disease progress and provide a better understanding of the virus development. In this study, a new nonlinear differential equation model was proposed to investigate the interaction between the HIV virus and body immune system. This physiological-based model was capable of representing complex behaviors. The bifurcation analysis of some variations of activated healthy T cells was carried out. It was shown that the chaotic development of the virus was detected in a number of activated healthy T cells. This may explain why the virus develops differently in different individuals or under different circumstances. The chaotic region contains some narrow periodic windows in which the chaotic mode suddenly ends at some critical points and the system exhibits a periodic behavior in a small range of active healthy T cells. This finding confirms the possibility of controllable development of the HIV virus, even when it is at a random-like phase. For further illustration, the state space of the system is represented.

1. Introduction

Given the increasing number of HIV-infected patients, the study on how this virus develops in the human body gains more significance than ever. As a result of delayed diagnosis and lack of proper treatment, most of these patients will be infected with Acquired Immuno-Deficiency Syndrome (AIDS) within 5–10 years [1]. Today, researchers have recognized the spread mechanism of AIDS and found suitable methods for treatment. A majority of researches have studied this infection from a theoretical perspective using mathematical modeling and computer simulations [2,3]. Some of these mathematical models are based on the decay characteristics of the virus in the infected body [4]. In fact, this procedure can help expand our knowledge on controlling virus development and suggest some new therapeutic approaches. More importantly, many therapeutic methods can be easily tested on a model and their effectiveness can be examined without any side effects for the patient. Furthermore, carrying out the trial-and-error process for therapeutic methods requires time, cost, and a plenty of samples, which usually makes them impractical. Since the therapeutic methods for managing the HIV virus usually interfere

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with one of the viral proliferation stages, the proposed model can reflect the efficiency of these methods if the viral proliferation stages are put together correctly. For this reason, developing models capable of representing the behaviors of the virus in the body can revolutionize the treatment of diseases.

One of the procedures for modeling biological systems is dynamical-based modeling [5,6]. Furthermore, chaotic behavior is regarded as a specific state of dynamical systems with particular and unique properties [7]. It is also a desirable phenomenon observed in living organisms [8]. Therefore, chaotic-based dynamical models have drawn considerable attention and gained significance in the modeling of biological systems [9]. Generally, chaotic behavior is the justification of many unknown behaviors formerly considered as random [10]. A number of studies have investigated chaos, its applications, and ways of controlling the chaotic systems, mainly focusing on chaotic oscillators, either individually or in a network. Discovering the chaotic behavior in the biological systems by scientists such as Yao and Freeman [11] led to fundamental changes to this context. Chaotic models offer qualitative demonstrations of the desired system rather than quantitative representations.

The HIV virus development is one of the biological mechanisms that seems to exhibit chaotic behavior. The disease caused by HIV has three main stages. In the first stage or acute infection, the patient may have a flu-like illness for a short time. This stage is called the incubation period. As the disease progresses, the more it interferes with the body immune system, the more infections or even tumors will spread [12]. However, this may not affect individuals with strong immune systems. Finally, the disease reaches the last stage called AIDS. In this stage, the number of T lymphocytes is less than 200 cells per microliter. The T lymphocytes are white blood cells mediating the immune system response, which is responsible for the elimination of the foreign invaders [13]. HIV-infected individuals are also reported to be at high risk of hepatitis B virus and hepatitis C viral infections [14].

A number of studies have been conducted on the modeling of HIV virus and its development in the human body using different theoretical approaches and mathematical models. While some of these studies have employed a cellular automata modeling approach [15], others have used nonlinear differential equations to survey the interactions of the HIV virus [16]. Moreover, some fractional models have been established owing to the strength of the fractal analysis in chaotic systems [17–22]. In cellular automata method, the virus attack process in human body is modeled using several healthy and infected immune cells arranged next to each other in a two- or three-dimensional space with some neighbor laws for transmission of the disease. Although this method makes it possible to reproduce some spatial localizations and interactions of the HIV infection, it also has some drawbacks. First, although the virus substance is different from the immune cells, the virus itself is not included in these models. Instead, only the aggregation of the healthy and nearby infected immune cells is considered. Second, the motion of virus and immune cells in blood vessels is not considered in these models. For instance, while an infected immune cell can transfer the disease only to its neighbor cells in these models, transference of the virus to the human body is not subjected to such limitations. In fact, an infected immune cell can infect many healthy immune cells by the produced viruses moving to different locations.

A variety of dynamical models have been proposed using nonlinear differential equations to study the development of the HIV virus and potential therapeutic methods [22–26]. Bonhoeffer et al. suggested a three-dimensional differential equation model to describe the behavior of the HIV virus in the body at a rate that was dependent on the virus population and T cells [27]. Ho and Ling showed that the dynamics of the HIV virus model was sensitive to both parameters and initial conditions of the system [28]. In their study, the number of viruses was affected by the number of both CD4 lymphocytes and CD8 lymphocytes. The CD8 cells involve inhibition of viral transcription and they are associated with a long-term healthy state in the HIV infection [29]. While the CD8 lymphocytes play a resistant, fighting role, the CD4 lymphocytes have only a replicative role for the virus. Wang studied the interaction between HIV and T cells using differential equations in which the number of viruses as well as both healthy and infected T cells were taken into account [30]. Moreover, he suggested a prey-predator competitive relationship between the healthy and infected T cells. Lund et al. confirmed that chaotic dynamics could be developed in the interaction model between the HIV virus and immune system [13]. Hernandez-Vargas et al. presented a discrete-time neural observer tested, while it was applied to a model for HIV infection dynamics [31]. Revilla and Grcía-Ramos [32] and Yu and Zou [33] proposed a method using the recombinant virus, which is a manipulated HIV virus engineered by genetic engineers. This recombinant virus was sent to the HIV-infected body; then, it stuck to the infected T cells and forced them to reproduce, thus preventing the proliferation of the HIV virus. This recombinant virus does not attack the healthy T cells and its host cells are only the HIV-infected ones. In this regard, use of engineered therapeutic viruses called 'hunter' viruses to control the HIV and other viral infections was discussed in [34].

The results of these investigations revealed that

the HIV virus population in the human body behaved randomly, especially in the phase of AIDS [13]. However, some researchers confirmed that these behaviors were not random, but rather complex and chaotic [13]. In this study, a proper model capable of representing the complex, yet simple, behaviors was established. In this respect, three-dimensional differential equations with a special set of parameters were proposed where the system could be in the chaotic mode. Furthermore, the saturation phenomenon was included to avoid an endless increase in the population of activated healthy immune cells, infected immune cells, or the virus. It was shown that the proliferation rate of healthy T cells could highly affect the dynamics of virus development. It was also found that the healthy immune cells, in turn, determined whether the virus dynamics was periodic or chaotic. In addition, bifurcation behavior was shown to be available in a short range of activated healthy T cells. The proposed model in this study was able to make some specific ranges of activated healthy T cells exhibit chaotic behaviors while it followed a route to the periodic behavior of some other ranges. Moreover, the state space for some modes of the system was displayed for greater completeness.

This paper is organized as follows. The physiological background of the HIV infection process is discussed in Section 2. The mathematical model is illustrated in Section 3 that contains some further definitions to clarify the modeling approach. The numerical simulation and calculation results are represented in Section 4. Finally, the discussion and the conclusion are given in Sections 5 and 6, respectively.

2. The physiological background

Application of a physiologically-based model is essential for a better understanding of the mechanisms of HIV pathogenesis and developing treatments. Therefore, in this section, the physiology of the HIV virus infection process is briefly discussed. The virus replication cycle begins with the infection of a host cell and ends with the release of mature viral particles. The viruses must come into another cell nucleus since they are not able to be reproduced by themselves, given that reproduction requires energy and a proteinization mechanism, available only in the living cells. The host cell for the HIV virus is a vital subtype of immune cells called lymphocytes. This is the reason why the HIV virus is one of the best-known fatal viruses. The virus entry into the cell is made possible only for cells that carry the virus receptor, which is particularly the CD4 molecule for the HIV virus. The lymphocytes that take this type of receptor to absorb the virus are more likely to be infected by the virus, while the other cells resist infection so that any contact with the virus will be in vain. Once the virus enters the cell, its nucleic acid activity begins. The nucleic acids of the virus contain enough genes to inhibit the metabolism of the host cell and conduct the vital chemical reactions of the host cell to proliferate the virus. Then, the produced viruses exit the cell. This can take place in two different ways. In some cases, a large number of viruses are released as a result of decomposition of the host cell. However, in other cases such as the HIV virus, the virus exits the host cell without any decomposition of the host cell. In this case, the host cell is not destroyed and continues to proliferate the HIV virus until it dies.

3. The mathematical model

In this part, some definitions are presented to explain the basis of modeling the systems in which two species, materials, cells, etc. interact with one another. In such systems, an increase or decrease in the population of each group can influence the population of the other one. To describe the dynamics of two interacting species, a differential equation model known as the prey-predator model was proposed. Numerous researchers from different fields have employed this model to explain different interactive processes including chemical reactions. The prey-predator model is described as follows [35]:

$$\frac{dx}{dt} = a_1 x - a_2 xy,$$
$$\frac{dy}{dt} = a_3 xy - a_4 y, \tag{1}$$

where $x(t)$ and $y(t)$ represent the population of prey and predator, respectively, over the time t. Parameters a_1, a_2, a_3, a_4 are positive constants. Parameter a_1 is the natural growth rate of the prey species in the absence of the predator. Parameter a_2 reflects the effect of the predator on the prey population, and it is the only factor that reduces the prey population. Parameter a_3 shows the effect of the predator on the prey and it is the only factor that increases the predator population. Any increase in the population of a species depends on the number of available resources. Parameter a_4 denotes the rate of natural death of the predator species. Note that the components of Eq. (1) are not completely realistic. In fact, the endless increase in the population of the prey species in the absence of predator (for $a_2 = 0$) is not realistic. Furthermore, the endless decrease in the predator population in the absence of prey (for $a_3 = 0$) is not compatible with the laws of nature. Effort has been made in this study to compensate for this deficiency in the mathematical model by adding a saturation term to the model equations.

In our proposed model, the HIV virus is the predator species. It attacks the healthy immune cells

as the prey species and then, the healthy immune cells become infected. Hence, the healthy immune cell population declines. At the same time, the healthy immune cells attack the viruses and try to destroy them to preserve the body health. However, as described for the prey-predator equations, decreasing the prey population would consequently decrease the predator population. Further, due to the fundamental changes in the immune cells created by the virus, the infected immune cells begin producing virus. The main differences between the interactions of the HIV virus with the immune system and those in the prey-predator model are in two key points:

1. In the prey-predator model, the prey is destroyed upon being hunted by the predator. However, the immune cells are not eliminated; instead, they are infected by the HIV virus. Therefore, their internal structure is changed in a way that facilitates the proliferation of the virus;
2. In the prey-predator model, the predator consumes the prey and grows, thus reproducing itself more. However, the host cells are responsible for the proliferation of the virus since the virus is not capable of reproduction by itself.

This relationship between the virus and immune cell is such a circular causality because the production and survival of the virus rely on the immune cells, while the immune cells are also responsible for fighting the virus.

Given the above considerations, the revised model is described as follows:

$$\begin{aligned}
\frac{dx}{dt} &= rx - \beta xz - dx^2, \\
\frac{dy}{dt} &= \beta xz - ay - cx^2, \\
\frac{dz}{dt} &= \lambda y - bz - \sigma xz - ez^2,
\end{aligned} \tag{2}$$

where the variable x is the population of the activated healthy immune cells. Variable y represents the population of the infected immune cells. The activated healthy immune cells become infected after the virus attack. Variable z shows the population of the virus. Parameter r represents the proliferation of the active and healthy T cells. The population of the healthy T cells would decrease when the activated T cells become infected by HIV at the rate βxz. Parameter d is the saturation rate of the healthy T cells and it limits the population of healthy T cells even in the absence of the virus. Parameters α and c are the morality rate of the infected T cells and saturation coefficient of their population, respectively. Parameter λ is the proliferation of the virus by the infected T cells. Parameters b and e are the constant morality rate and saturation rate of the virus, respectively. The virus population would be destroyed in a struggle with the healthy T cells at the rate σxz. The parameter settings for Eq. (2) are given in Table 1 where r is the bifurcation parameter. The parameters of the model were identified by excessive computer search in a way that the model exhibited chaotic behavior.

Table 1. Parameters of Eq. (2).

Parameter	Value
β	0.90
d	0.28
α	1.29
c	0.65
λ	0.79
b	0.15
σ	1.24
e	0.39

4. Equilibrium points

To calculate the equilibrium points of the model, the right-hand side of Eq. (2) is assumed to be zero. The parameters are set according to Table 1 and r is the considered variable. Solving this equation gives rise to three fixed points as $E1 = (0, 0, 0)$, $E2 = (0, 0, -5/13)$, and $E3 = (25r/7, 0, 0)$. Consequently, the eigenvalues of the Jacobian matrix of the model will be $[0, -0.15, -1.29]$ for the first fixed point, $[0.35, 0.15, -1.29]$ for the second fixed point, and

$$\left[-r, -2.21r - \sqrt{4.9r^2 + 0.015r + 0.32} - 0.72, -2.21r + \sqrt{4.9r^2 + 0.015r + 0.32} - 0.72\right],$$

for the third fixed point. Therefore, the stability of the first fixed point is undefined, and the second fixed point is clearly unstable for any value of r. By considering the variation of r at the interval $[0.01, 0.04]$, all of the eigenvalues of the third fixed point will be negative and consequently, the third fixed point is stable.

5. Bifurcation analysis and Lyapunov spectrum

The ability of a biological model to exhibit complex behavior is a great virtue since biological systems exhibit unquestionable complexity. Conversely, lack of such complexity in a model indicates that it is insufficiently realistic. To be specific, a model can be appropriate for modeling the biological system

only if it is capable of demonstrating complex and rich behaviors. In dynamic systems theory, chaotic dynamics is recognized as the richest and the most elaborate dynamics. In this section, the qualitative behavior of the model through its bifurcation diagram and state space plot is investigated. The initial condition for the variables in the numerical calculations is $(x, y, z) = (-0.6, -0.66, 1.03)$. The model intends primarily to describe the qualitative characteristics of the real system and the changes in its dynamical behavior rather than to make detailed quantitative predictions. However, the model closely replicates the behavior reported in real systems including nonlinear behavior of the HIV virus.

There are numerous proposed differential equation models for HIV virus behavior in the human body. Given their inadequate richness and functionality, some of these models cannot exhibit the complex behavior. In this respect, adding more variables can enhance the richness of the mathematical model. For example, in Ref. [13], the interaction between the HIV and immune system was discussed using a five-dimensional differential equation model. The adequate number of variables helps the model exhibit the chaotic behavior. However, excessive variables make the model more complicated due to many irrelevant details. Although there are also some models with fewer variables, they are not able to represent the desired chaotic behavior. Therefore, the necessity of balancing the two factors of simplicity and richness should be taken into account in the model. In this regard, the model should be capable of demonstrating complex and chaotic behaviors with the least number of variables. To accomplish this objective, some more realistic hypotheses should be taken into consideration. As mentioned earlier, the proposed model in this study is based on the physiological properties of the HIV virus development that employs the concepts of prey-predator equations. Furthermore, a saturation phenomenon is assumed to be in the form of a logistic-like term to prevent an endless increase in the population of the +activated healthy immune cells, infected immune cells, or virus.

To illustrate the qualitative behavior of the model, the bifurcation diagram with a variation of the parameter r is shown in Figure 1(a). Bifurcation behavior is observed in a short range of activated healthy T cells for $0.01 < r < 0.04$, as shown in Figure 1(a). This confirms that the dynamics of the virus population is sensitive to the rate of activated healthy T cells. The chaotic behavior was observed for $r = 0.01$ to $r = 0.0141$, indicating different development of the virus in different individuals or under different circumstances. The dynamics of the system follows a route to the periodic behavior of r greater than 0.0141. The periodic development of the virus for $0.0141 < r < 0.0175$ is shown in Figure 1(a). For $r > 0.0175$, the virus dynamics is well controlled and exhibits a period-1 limit cycle. The corresponding Lyapunov Exponents (LEs) of the model and the Kaplan-Yorke dimension (D_{KY}) were calculated, as shown in Figure 1(b) and (c), respectively. Figure 1(b) shows that at the interval of $0.01 < r < 0.0141$, there are one positive, one zero, and one negative Lyapunov exponents and, hence, the behavior of the model is chaotic. Further, the Kaplan-Yorke dimension is greater than 2 (Figure 1(c)). At this interval, there is a periodic window. In the zoomed window of the Lyapunov spectrum, it can be observed that in this limited range, the largest Lyapunov exponent decays to zero and two other exponents are negative. For $r > 0.0141$, the chaotic

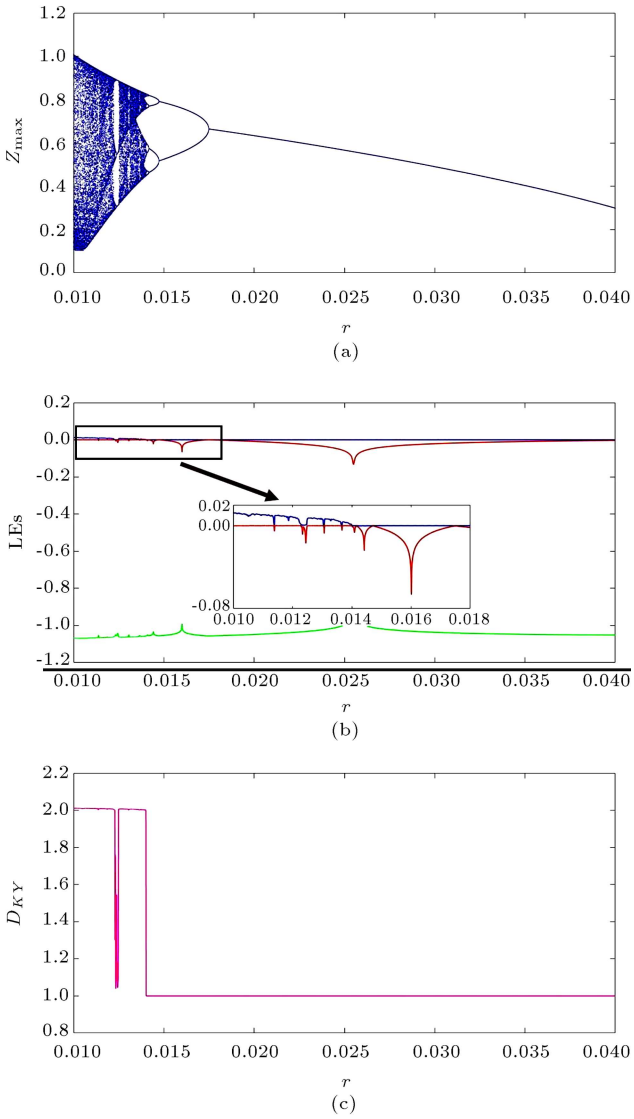

Figure 1. (a) The bifurcation diagram of HIV virus development based on Eq. (2) with a variation of active healthy immune cells (parameter r) for the parameters in Table 1 and initial conditions (x, y, z)=(–0.6, –0.66, 1.03). (b) The corresponding Lyapunov exponents. (c) The corresponding Kaplan-Yorke dimension.

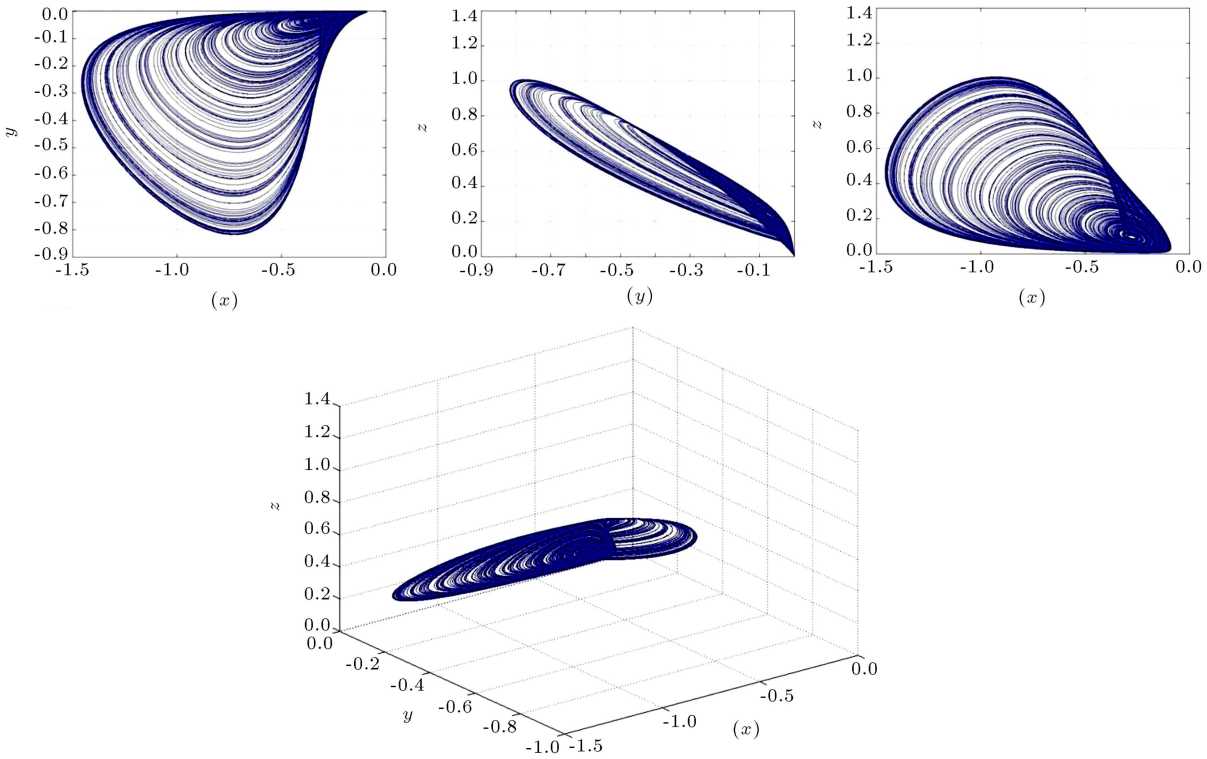

Figure 2. The state space plot of the system in Eq. (2) for $r = 0.01$ and the parameters in Table 1. The initial conditions are $(x, y, z) = (-0.6, -0.66, 1.03)$.

behavior changes to the periodic and there are two negative and one zero Lyapunov exponents. Hence, the Kaplan-Yorke dimension equals one.

For further illustration, the respective state space plots for different values of r are also displayed. Figure 2 shows the state space for $r = 0.01$. As expected, a chaotic attractor is evident. The case with $r = 0.0124$ belongs to one of the periodic windows (the widest one) in the bifurcation diagram. The chaotic behavior ends abruptly and the system dynamics switches to the periodic behavior within this tiny window. The chaotic region contains many narrow periodic windows that is indicative of the controlled dynamical behavior of the virus growth, which is very sensitive to even small changes in the proliferation of active healthy T cells in different individuals or under different circumstances. The respective state space is shown in Figure 3 in which the period-3 behavior is observable. Figures 4 and 5 show the periodic behavior of the virus development for $r = 0.0155$ and $r = 0.025$, respectively.

6. Discussion

In this study, the interaction between the HIV virus and immune system of the human body was investigated using a new mathematical model. Unlike some previous studies, this model can exhibit the complex and chaotic behavior while preserving its simplicity by involving only three variables. The main difference between our proposed model and the previous ones lies in the two following key points:

1. A saturation phenomenon is assumed to be in the form of a logistic-like term to prevent an endless increase in the population of the activated healthy immune cells, infected immune cells, or virus;
2. Since the role of the infected immune cells has not been discussed in the literature, in this model, the infected immune cells do not play any role in absorption or elimination of the virus and it is just the healthy immune cells that struggle with the virus.

The bifurcation diagram with the variation of activated healthy T cells (parameter r) exhibits the qualitative behavior of the model. Chaotic dynamics is observed for a particular range of the parameter r, explaining why the virus develops differently in different individuals or under different circumstances. The chaotic region also contains some narrow periodic windows in which the chaotic mode suddenly ends at some critical points and the system starts a periodic behavior for a tiny range of the parameter r. This is a complex dynamical behavior where a periodic dynamic occurs amidst an otherwise chaotic process. It also suggests the possibility of controllable development of the HIV virus even when it is in a random-like phase of the disease. Furthermore, the system dynamics follows a route to

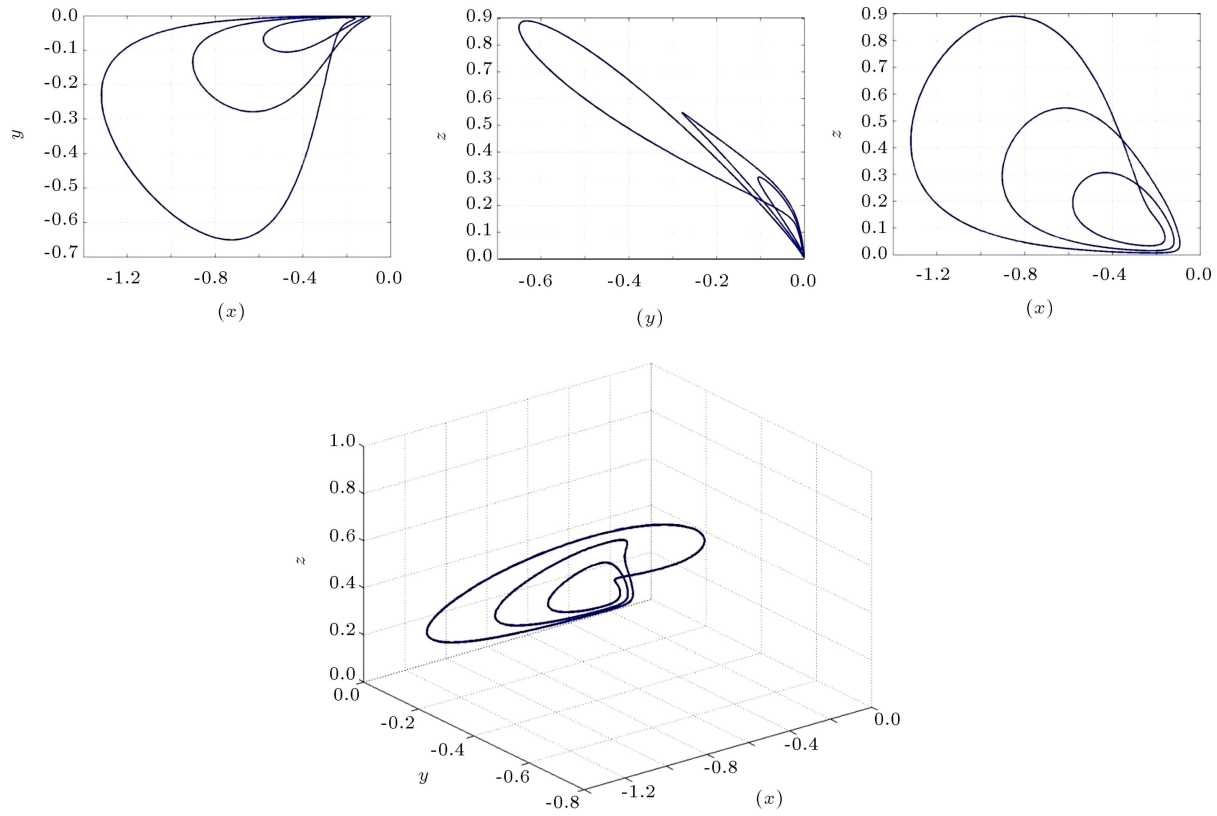

Figure 3. The state space of the system in Eq. (2) for $r = 0.0124$ and the parameters in Table 1. The initial conditions are $(x, y, z) = (-0.6, -0.66, 1.03)$.

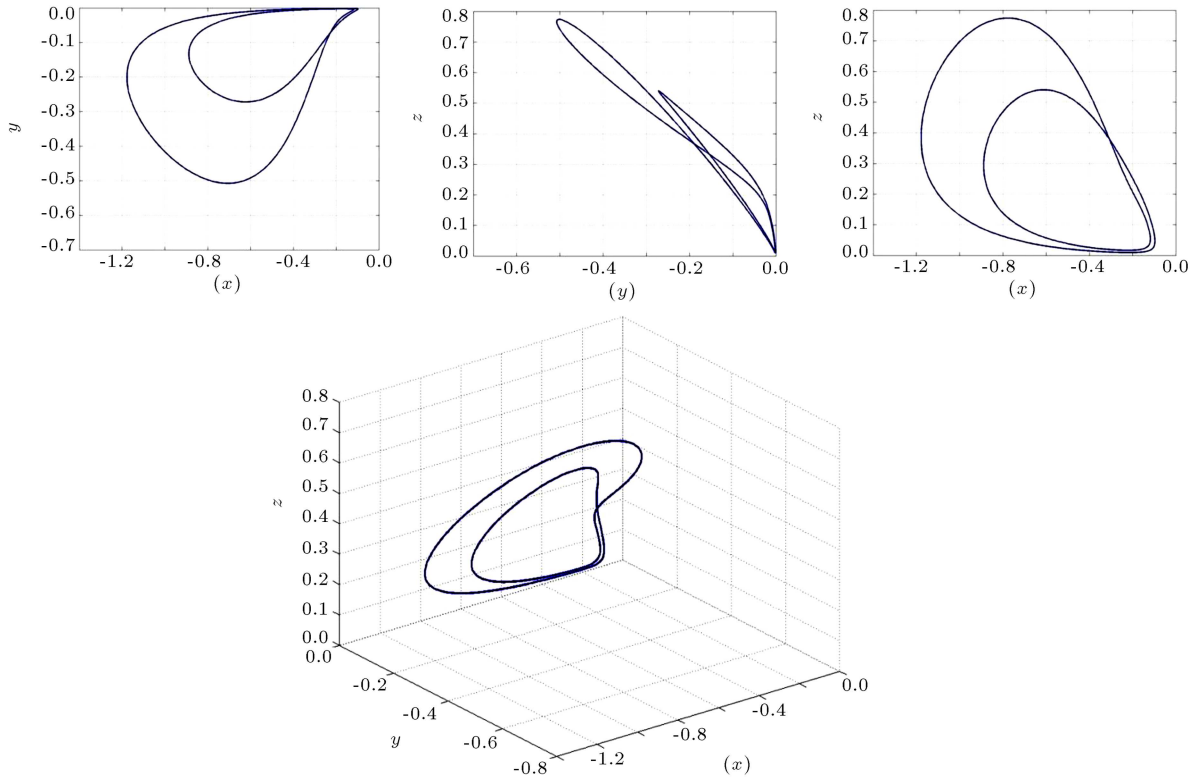

Figure 4. The state space plot of the system in Eq. (2) for $r = 0.0155$ and the parameters in Table 1. The initial conditions are $(x, y, z) = (-0.6, -0.66, 1.03)$.

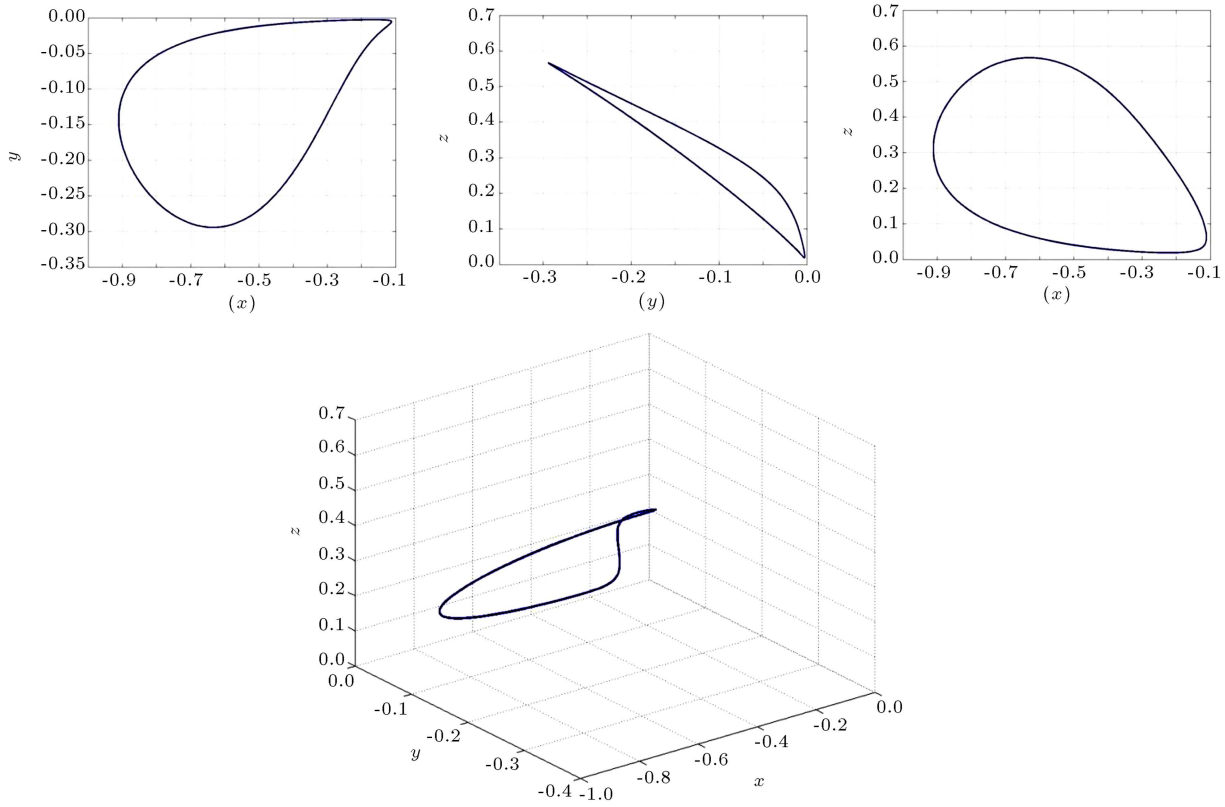

Figure 5. The state space of the system in Eq. (2) for $r = 0.025$ and the parameters in Table 1. The initial conditions are $(x, y, z) = (-0.6, -0.66, 1.03)$.

the periodic development of the virus for some ranges of the parameter r. Then, different dynamics of the population of the virus for some specific values of the activated healthy T cells is illustrated in the state space diagram. For $r = 0.01$, the system exhibits chaotic behavior which might represent the high sensitivity of the virus population to the conditions. However, as the activated healthy T cells increased, for $r = 0.0155$ and $r = 0.025$, for example, the virus population can be efficiently controlled, which is demonstrated in the form of periodic behavior of the activated healthy T cells.

7. Conclusion

This paper proposed a new simple mathematical model capable of representing complex behaviors. According to the findings, the healthy immune cells, in turn, determined whether the virus dynamics was periodic or chaotic. Moreover, bifurcation behavior was observed in a short range of activated healthy T cells. The proposed model could encourage chaotic behavior for some ranges of activated healthy T cells while following a route to the periodic behavior for some other ranges. Moreover, the state space for some modes of the system was displayed for the sake of comprehensive analysis.

The actual dynamics of the immune cell regulation or virus proliferation is quite complicated. Therefore, understanding these dynamical behaviors could develop better treatments and even theoretical predictions to optimize the experimental examinations. The model of HIV virus infection represented in this study was not perfectly accurate due to many applied reductions and simplifications. However, the strength of this model lies in its richness and ability to demonstrate complex chaotic behavior while involving only three main variables. The main objective of the present study was to develop theoretical studies and more particularly, improve the differential equation models used for elaborating some aspects of this disease. To highlight some of the key works done in this research, the following points can be mentioned:

- The model was mathematically simple, involving only three main variables;
- The model was elegant [7];
- The model was rich, capable of representing the complex chaotic behavior.

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