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Dynamical Analysis Within-Host and Between-Host for HIV\AIDS with the Application of Optimal Control Strategy

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Abstract

The aims of this paper is investigating the spread of AIDS both within-host, through the contact between healthy cells with free virus inside the body, and between-host, through sexual contact among individuals and external sources of infectious. The outbreak of AIDS is described by a mathematical model consisting of two stages. The first stage describes the within-host spread of AIDS and is represented by the first three equations. While the second stage describes the between-host spread of AIDS and represented by the last four equations. The existence, uniqueness and boundedness of the solution of the model are discussed and all possible equilibrium points are determined. The local asymptotic stability (LAS) of the model is studied, while suitable Lyapunov functions are used to investigate the global asymptotic stability (GAS) of the model. Optimal control strategy is used to control the outbreak of AIDS. Finally, a numerical simulation is carried out to confirm the analytical results and understand the effects of varying the parameters on the spread of disease.

Keywords: HIV\AIDS, AIDS within-host body; AIDS between-host individuals, Stability, Optimal control.

تحليل ديناميكية داخل المضيف وبين المضيف لفيروس نقص المناعة البشرية / الإيدز مع تطبيق استراتيجية التحكم المثلى

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الخلاصه

يهدف البحث الى دراسة انتشار مرض نقص المناعة (الايدز) داخل جسم الضحية الواحده من خلال الاتصال بين الخلايا السليمة و الفيروسات الحرة وكذلك بين افراد الضحية من خلال الاتصال الجنسي والمصادر الخارجية المسببة للعدوى. قمنا بوصف تفشي مرض نقص المناعة بنموذج رياضي يتكون من مرحلتين. تصف المرحلة الاولى انتشار مرض نقص المناعة داخل جسم الضحية حيث مثلت هذه المرحلة بالمعادلات الثلاثة الاولى من النموذج. بينما تصف المرحلة الثانية انتشار المرض بين افراد الضحية وتمثل المعادلات الاربعة الاخيرة هذه المرحلة. ناقشنا وجود ، وحدانية وحدود الحل للنموذج المقترح. درسنا الاستقرارية المحلية بعد حساب جميع نقاط التوازن. استخدمنا دوال لينابوف المناسبة لدراسة الاستقرارية الشاملة. كذلك استخدمنا ستراتيجية السيطرة المثلى للسيطرة على تفشي المرض. واخيرا تم اجراء محاكاة عددية لتاكيد نتائجنا التحليلية وفهم تاثير تغير المعلمات على انتشار المرض.

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1. Introduction

The Human Immunodeficiency Virus (HIV) causes a disease that attacks the human immune system and destroys white blood cells. This disease is still a major threat to human life for the last three and half decades. Since its discovery in the early 1980, tremendous research works on how to contain or eradicate the disease were carried out [1]. It is an acute intestinal infectious disease caused by an Acquired Immunodeficiency Syndrome (AIDS) as a result of HIV infection. Statistics for the last few years show an outbreak that affected 38.8 million and caused a mortality rate of 1.2 million in 2015, with the infection rate being relatively constant at 2.6 million per year from 2006 to 2015 [2]. Mathematical modeling of viral infections has led to enhance the understanding of virus dynamics and helped in predicting and controlling the spread of viral diseases such as HIV and hepatitis A, B, and C. The first epidemiological model on HIV was studied in 1985, followed by many studies [3-9]. Knox [3] studied the transmission of AIDS, while Anderson et al. [4] described some preliminary attempts to formulate mathematical models of the transmission dynamics of HIV infection in homosexual communities. Anderson [5] reviewed the role of mathematical models in the study of HIV transmission, the epidemiology and demographic impact of AIDS, and the course of infection within an individual. Mohsen [6] proposed and studied the dynamics of a mathematical model of HIV\AIDS involving the effects of external sources. In another study [7], Pourbashash et al. described a new within-host model of HIV infection that incorporates two mechanisms, namely the infection by free virions and the direct cell-to-cell transmission, and then investigated their global stability. Agosto et al. [8] discussed recent data which suggest that contact-mediated transmission largely manifests itself in vivo as CD4+ T-cell depletion. A deterministic model that incorporates prophylaxis was developed by Tireito et al [9] to assess the impact of the use prophylaxis on the transmission of HIV/AIDS.

Anderson [10] summarized the major themes that had emerged from mathematical and statistical research on the epidemiology of HIV over the past years. Kirschner and Webb [11] investigated the strategies of monotherapy treatment of HIV infection in the presence of drug-resistant (mutant) strains. DeBoer and Perelson [12] developed various mathematical models of the clinical latency stage of HIV-1 infection, assuming that this infection is limited either by the availability of cells that HIV can infect or by a specific anti-HIV cellular immune response. Culshaw and Ruan [13] simplified an *ODE* model of cell-free viral spread of HIV into one consisting of only three components, namely the healthy $CD4^+$ T-cells, infected $CD4^+$ T-cells, and free virus. They discussed the existence and stability of the infected steady state and then introduced a discrete time delay to the model to describe the time between the infection of a $CD4^+$ T-cell and the emission of viral particles on a cellular level. Culshaw et al [14] presented an optimal control model of drug treatment of HIV. Naji and Ahmed [15] considered a model of epidemic disease, assuming that infection is spread directly from infected to susceptible individuals, and described the effects of immigrants. Roxana [16] studied the effects of age and social structures on *SI* epidemic models with specific applications to HIV epidemics in Peru and USA. Joshi et al. [17] formulated a model to investigate the effects of information and education campaigns on HIV epidemic in Uganda. Naji and Ahmed [18] proposed and analyzed a mathematical model for infectious diseases with effects of external sources of disease. Feng et al [19] presented a new model that allows the two dynamic processes, i.e. within-host and between-host, to explicitly depend on each other. They showed that new properties can emerge and more complex dynamics may be expected from the coupled system. Ali et al [20] proposed and investigated a mathematical model for HIV-1 infection with multiple delays. Mastahun and Abdurrahman [21] formulated a deterministic model of HIV/AIDS with infective immigration, while this model was then extended to include several control efforts aimed at reducing infection and changing behavior. Recently, Tarfulea [22] proposed an HIV infection and age model that considers virus-to-cell and cell-to-cell infections and immune responses.

Keeping the above in view, this paper proposed and analyzed a mathematical model that describes the spread of AIDS according to two strategies, namely within-host and between-hosts.

2. Modeling Formulation

It is well known that HIV\AIDS type of disease can be transmitted in two stages. The first stage being inside of the body of human by means of direct contact between the healthy cells and virus. While, the second stage is the spread of the disease between the individuals by direct contact , i.e.

sexual transmission, as well as through external sources of infection such as blood and dental and tattoo tools. Hence, the mathematical model of this type of disease can be represented by the seven nonlinear ordinary differential equations described in the following sections along with their related systems.

$$\begin{aligned}
\dot{x} &= \Lambda - \beta x V - mx \\
\dot{y} &= \beta x V - (m+d)y \\
\dot{V} &= eA + py - \eta V - \beta x V \\
\dot{S} &= \psi - \sigma_0 SA - \sigma_1 SC - \sigma_2 S - \mu S \\
\dot{C} &= \sigma_0 SA + \sigma_1 SC + \sigma_2 S - (\mu+\varepsilon)C \\
\dot{I} &= \varepsilon C - (\mu+\gamma)I \\
\dot{A} &= V + \theta I + \rho C - (\mu+\alpha)A
\end{aligned} \tag{1}$$

System (1) can be divided into two subsystems; the first subsystem consists of the first three equations, which represent by system (2). It is called the within-hosts system and can be describe as shown in Figure 1.

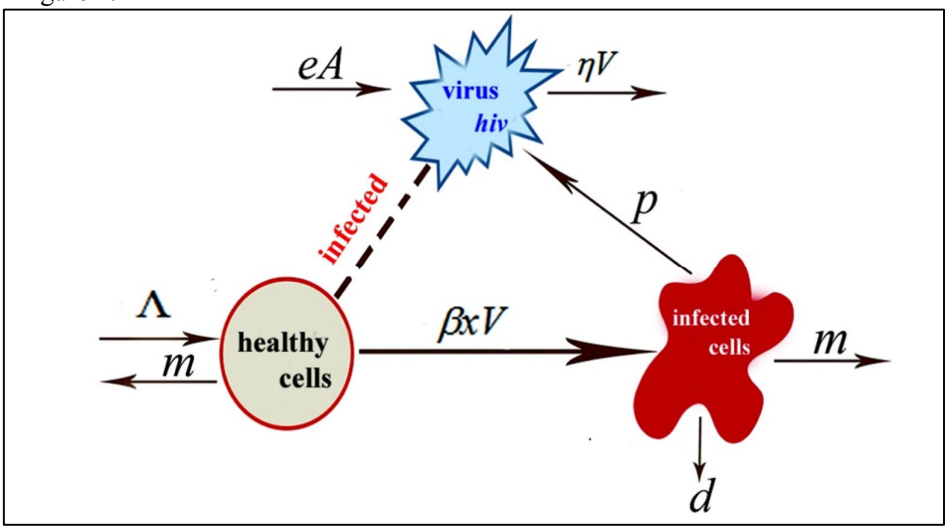


Figure 1: Block diagram of the within host system

Consequently, the following equations can be written to describe the within-host system:

$$\begin{aligned}
\dot{x} &= \Lambda - \beta x V - mx \\
\dot{y} &= \beta x V - (m+d)y \\
\dot{V} &= eA + py - \eta V - \beta x V
\end{aligned} \tag{2}$$

where the variables x, y and V represent the number of healthy cells, infected cells and virus level, respectively. Note that all the parameters of system (2) are positive constants and they stand for the following: Λ is the birth rate of the healthy cells, β is the infection rate by direct contact between healthy cells and virus level so that both the number of healthy cells and the virus level are decreasing[23-25], m is the natural demolition rate for x and y d is the disease related death rate from y, η is disappearance rate of the virus, $p \geq 0$ represents the increase of virus level due to spreading from infected cells, $e \geq 0$ is the production rate of AIDS class A that is assumed to be constant in system (2). On the other hand, the second subsystem of system (1) consists of the last four equations, which represent by system (3). It is called the between host-system and can be represented as shown in the Figure 2.

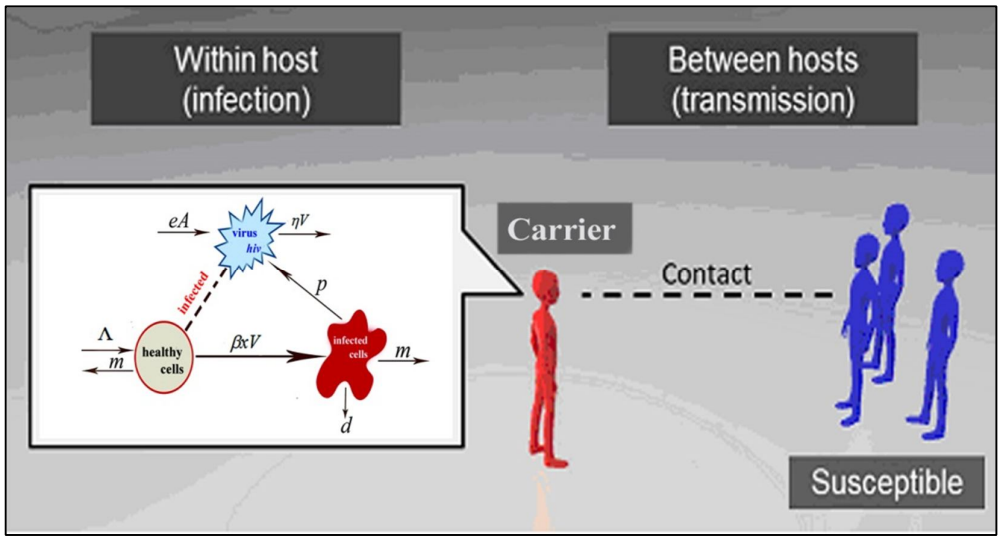


Figure 2: Within-host and between hosts, only considering direct contact between susceptible and carrier individuals

$$\begin{aligned}
\dot{S} &= \psi - \sigma_0 SA - \sigma_1 SC - \sigma_2 S - \mu S \\
\dot{C} &= \sigma_0 SA + \sigma_1 SC + \sigma_2 S - (\mu + \varepsilon) C \\
\dot{I} &= \varepsilon C - (\mu + \gamma) I \\
\dot{A} &= V + \theta I + \rho C - (\mu + \alpha) A
\end{aligned} \tag{3}$$

where the variables *S, C, I* and *A* denote the number of susceptible individuals, carrier individuals, infected individuals and the AIDS class at time *t*, respectively. Here, $\psi > 0$ is the birth rate for susceptible individuals, $\sigma_i > 0, i = 0,1$ represent the infection rate due to contact between the susceptible individuals with AIDS individuals and carrier individuals, $\sigma_2 \geq 0$ is the external source of infection, $\mu > 0$ is the natural death rate, $\varepsilon > 0$ is the transform rate of disease from carrier to infected individuals $\gamma > 0$ is the death rate due to the disease, $V \geq 0$ is the virus level, which is assumed to be constant in system (3), θ and ρ represent the increase of AIDS class due to the infected and carrier individuals, respectively. Finally, $\alpha > 0$ represents the death rate of AIDS class due to the disease. Now, for any point of time t, let the total population be denoted by *N,* such that *N=S+C+I+A,* then due to the biological meaning of the variables *S, C, I* and *A*, system (3) is defined on the region $\Omega = \{(S,C,I,A) : S > 0, C \geq 0, I \geq 0, A \geq 0\}$, which is a positive invariant for the system (3).

From now on, for fixed value of AIDS class (*A*), system (2) is called the fast system and denoted by FS. However, for fixed value of virus level (*V*), system (3) is called the slow system and denoted by SS.

3. Existence and number of equilibrium points

In this section, the existence and boundedness of the solutions of systems (2) and (3) in addition to the existence of equilibrium points are discussed.

3.1 The FS analysis

It is well known that, due to the biological meaning of the variables in the FS, the solution is positive and bounded. Moreover, the FS has the following equilibrium points.

1. If $V = 0$, then the FS has an equilibrium point called the virus free equilibrium point and denoted by $E_0 = \left(\frac{\Lambda}{m}, 0, 0\right)$, which is trivial and hence the analysis around it is omitted.
2. If $V \neq 0$, then the FS has a positive equilibrium point (PEP) that is denoted by $E_1 = (x_1, y_1, V_1)$ where

$$x_1 = \frac{\Lambda}{\beta V_1 + m} \tag{4a}$$

$$y_1 = \frac{\beta \Lambda V_1}{(m+d)(\beta V_1 + m)} \tag{4b}$$

$$V_1 = -\frac{h_2}{2h_1} - \frac{\sqrt{h_2{}^2 - 4h_1 h_3}}{2h_1} \tag{4c}$$

where

$$h_1 = -\eta\beta(m+d) < 0$$

$$h_2 = \beta\, p\Lambda + (m+d)(eA\beta - \eta m - \beta\Lambda)$$

$$h_3 = emA(m+d) > 0$$

Clearly, as the AIDS class A is assumed to be constant in FS, the positive equilibrium point E_1 always exists whenever $V \neq 0$.

3.2 The SS analysis

In this subsection, the existence, uniqueness and boundedness of the solution of SS are investigated. Further, the possible equilibrium points are determined. Now, since the right hand side of the equations of system (3) are continuous and have a continuous partial derivative, the solution of SS exists and unique. Further, the following theorem investigates the boundedness of the solution of SS.

Theorem 1. All solutions of SS with nonnegative initial conditions are bounded if the following sufficient condition holds.

$$\mu > min.\{\rho, \theta - \gamma\} \tag{5}$$

Proof: Let $(S(t), C(t), I(t), A(t))$ be any solutions of SS and let $N = S + C + I + A$, then for any constant value of virus level V we obtain:

$$\dot{N} = \dot{S} + \dot{C} + \dot{I} + \dot{A}$$

$$\dot{N} = \psi - \mu S - (\mu - \rho)C - (\mu + \gamma - \theta)I + V - (\mu + \alpha)A$$

$$\dot{N} + m^* \dot{N} \leq \psi + V$$

To solve the above inequality and by applying the Gronwall lemma we have:

$$\dot{N} \leq \frac{\psi + V}{m^*}$$

where $m^* = min.\{\mu - \rho, \mu + \gamma - \theta\}$

Hence the proof is complete

Now, the existence conditions of all possible equilibrium points of SS are determined. Obviously, SS has two equilibrium points. The 1st point always exists, when $C = 0$ and $A = 0$, that implies that the virus level, which is assumed to be constant in SS, is equal to zero (i.e. $V = 0$). This is called the disease free equilibrium point (DFEP) and denoted by $E_2 = (S_2, 0,0,0) = \left(\frac{\psi}{\mu}, 0, 0, 0\right)$. However, in case $A \neq 0$ and $C \neq 0$, then for any constant value of V, the 2nd point, which is known as an endemic equilibrium point (EEP) and denoted by $E_3 = (S_3, C_3, I_3, A_3)$, is obtained such that S_3, C_3, I_3 and A_3 are given by:

$$C_3 = \frac{k_1 - k_2 S_3}{k_3 S_3} \tag{6a}$$

$$I_3 = \frac{\varepsilon(k_1 - k_2 S_3)}{(\mu+\gamma)k_3 S_3} \tag{6b}$$

$$A_3 = \frac{V(\mu+\gamma)k_3 S_3 + [\theta\varepsilon + \rho(\mu+\gamma)](k_1 - k_2 S_3)}{(\mu+\alpha)(\mu+\gamma)k_3 S_3} \tag{6c}$$

where k_1, k_2 and k_3 are given by:

$$k_1 = \psi(\mu + \alpha)(\mu + \gamma)$$

$$k_2 = (\mu + \gamma)[(\mu + \alpha)(\mu + \sigma_2) - \sigma_0 V]$$

$$k_3 = \sigma_0[\theta\varepsilon + \rho(\mu + \gamma)] + \sigma_1(\mu + \alpha)(\mu + \gamma)$$

While, S_3 is a positive root for the second order equation

$$D_1 S_3^2 + D_2 S_3 + D_3 = 0 \quad (6e)$$

where

$$D_1 = [\sigma_0 V + \sigma_2(\mu+\alpha)](\mu+\gamma)k_3 - [\theta\varepsilon + \rho(\mu+\gamma) + (\mu+\alpha)(\mu+\gamma)]\sigma_1 k_2$$
$$D_2 = [\theta\varepsilon + \rho(\mu+\gamma) + (\mu+\alpha)(\mu+\gamma)]\sigma_1 k_1 + (\mu+\alpha)(\mu+\gamma)(\mu+\varepsilon)k_2$$
$$D_3 = -(\mu+\alpha)(\mu+\gamma)(\mu+\varepsilon)k_1 < 0$$

Consequently, the endemic equilibrium point E_3 exists uniquely in the interior of $\mathbb{R}_+^4$ under the following conditions

$$k_1 > k_2 S_3 \quad (7a)$$
$$[\sigma_0 V + \sigma_2(\mu+\alpha)](\mu+\gamma)k_3 > [\theta\varepsilon + \rho(\mu+\gamma) + (\mu+\alpha)(\mu+\gamma)]\sigma_1 k_2 \quad (7b)$$

4. Local stability analysis of FS and SS

In this section, the local stability analysis of the possible equilibrium points in FS and SS is carried out using the linearization method, as shown the following theorems. Recall that, the method of linearization depends on the calculation of the Jacobian matrix at each point E_i, $i = 1,2,3$ along with their eigenvalues.

Theorem 2. The positive equilibrium point E_1 of FS is locally asymptotically stable (LAS) if the following condition holds.

$$p < m + d \quad (8a)$$

Proof: The Jacobian matrix of FS at E_1 can be written as:

$$J(E_1) = \begin{pmatrix} -(\beta V_1 + m) & 0 & -\beta x_1 \\ \beta V_1 & -(m+d) & \beta x_1 \\ -\beta V_1 & p & -(\eta + \beta x_1) \end{pmatrix} \quad (8b)$$

Clearly, the characteristic equation of $J(E_1)$ is:

$$\lambda^3 + B_1\lambda^2 + B_2\lambda + B_3 = 0 \quad (8c)$$

where

$$B_1 = \beta(V_1 + x_1) + 2m + d + \eta > 0$$
$$B_2 = (\beta V_1 + m)(m+d) + (\beta V_1 + 2m + d)(\eta + \beta x_1) - \beta x_1(\beta V_1 + p)$$
$$B_3 = \eta(\beta V_1 + m)(m+d) + m\beta x_1(m + d - p)$$

Furthermore, $\Delta = B_1 B_2 - B_3$ can be written as:

$$\Delta = (\beta V_1 + m)(m+d)[\beta V_1 + 2m + d] + [(\beta V_1 + m) + (\eta + \beta x_1)][(\beta V_1 + m)\eta + m\beta x_1] + [(m+d) + (\eta + \beta x_1)][(m+d)\eta + \beta x_1(m + d - p)] + 2(\beta V_1 + m)(m+d)(\eta + \beta x_1) - p\beta^2 x_1 V_1$$

Straightforward computation shows that B_3 and Δ are positive under the condition (8a) and hence by using Routh-Huriwtz criterion, all the eigenvalues of $J(E_1)$ have negative real parts. Thus the positive equilibrium point E_1 of FS is LAS. ■

Theorem 3. The *DFEP* of *SS* that given by $E_2 = (S_2, 0,0,0)$ is *LAS* if the following conditions hold:

$$\sigma_1 S_2 < \mu + \varepsilon \quad (9a)$$
$$\rho\sigma_0 S_2 + (\mu+\alpha)(\mu+\varepsilon) < \sigma_1 S_2(\mu+\alpha) \quad (9b)$$
$$\varepsilon\theta < \rho\sigma_2 \quad (9c)$$
$$\varepsilon\theta\sigma_0(\sigma_2 + \mu) < \sigma_1\sigma_2(\mu+\gamma)(\mu+\alpha) \quad (9d)$$
$$\rho\sigma_0 + \sigma_1(\mu+\varepsilon) < \sigma_1(\sigma_2 + \mu + \sigma_1 S_2) \quad (9e)$$
$$H_1 < H_2 \quad (9f)$$

Proof: The Jacobian matrix of *SS* at *DFEP* can be written as:

$$J(E_2) = (c_{ij})_{4\times 4} \quad (10a)$$

here $c_{11} = -(\sigma_2 + \mu)$, $c_{12} = -\sigma_1 S_2$, $c_{14} = -\sigma_0 S_2$, $c_{21} = \sigma_2$, $c_{22} = \sigma_1 S_2 - (\mu + \varepsilon)$, $c_{24} = \sigma_0 S_2$, $c_{32} = \varepsilon$, $c_{33} = -(\mu+\gamma)$, $c_{42} = \rho$, $c_{43} = \theta$ and $c_{44} = -(\mu+\alpha)$.

Then, we can write the characteristic equation of above matrix in the following format:

$$\lambda^4 + G_1\lambda^3 + G_2\lambda^2 + G_3\lambda + G_4 = 0 \quad (10b)$$

Where

$$G_1 = -(c_{11} + c_{22} + c_{33} + c_{44})$$

$$G_2 = c_{11}(c_{22}+c_{33}+c_{44}) + c_{33}(c_{22}+c_{44}) - c_{12}c_{21} + c_{22}c_{44} - c_{24}c_{42}$$
$$G_3 = -c_{11}c_{33}(c_{22}+c_{44}) + c_{12}c_{21}(c_{33}+c_{44}) - (c_{11}+c_{33})(c_{22}c_{44} - c_{24}c_{42}) - c_{21}c_{42}c_{14} - c_{32}c_{43}c_{24}$$
$$G_4 = c_{11}c_{33}(c_{22}c_{44} - c_{24}c_{42}) + c_{21}c_{14}(c_{33}c_{42} - c_{32}c_{43}) + c_{11}c_{32}c_{24}c_{43} - c_{33}c_{44}c_{12}c_{21}$$

Then

$$G_1G_2 - G_3 = -(c_{11}+c_{22}+c_{33}+c_{44})(c_{22}+c_{44})(c_{11}+c_{33}) - c_{11}c_{33}(c_{11}+c_{33}) - (c_{22}+c_{44})((c_{22}c_{44} - c_{24}c_{42}) + c_{32}c_{43}c_{24} + c_{21}(c_{42}c_{14} + c_{12}c_{11} + c_{12}c_{22})$$

Furthermore

$$\Delta = G_3(G_1G_2 - G_3) - G_1^2G_4 = H_1(H_2 - H_1) + H_3$$

here

$$H_1 = -c_{11}c_{33}(c_{22}+c_{44}) + c_{12}c_{21}(c_{33}+c_{44}) - (c_{11}+c_{33})(c_{22}c_{44} - c_{24}c_{42}) - c_{21}c_{42}c_{14} - c_{32}c_{43}c_{24}$$
$$H_2 = -(c_{11}+c_{22}+c_{33}+c_{44})[c_{11}(c_{22}+c_{33}+c_{44}) + c_{33}(c_{22}+c_{44}) - c_{12}c_{21} + c_{22}c_{44} - c_{24}c_{42}]$$
$$H_3 = (c_{11}+c_{22}+c_{33}+c_{44})^2[c_{11}c_{33}(c_{22}c_{44} - c_{24}c_{42}) + c_{21}c_{14}(c_{33}c_{42} - c_{32}c_{43}) + c_{11}c_{32}c_{43}c_{24} - c_{33}c_{44}c_{12}c_{21}$$

Clearly, it easy to see that, $G_i, i = 1,2,3,4$; $G_1G_2 - G_3$, and Δ are positive under the given conditions. Thus by using Routh-Huriwtz criterion for above characteristic equation, all the eigenvalues of the Jacobian matrix of *SS* at E_2 will be either negative or having negative real parts if and only if the conditions (9a)-(9f) hold. Now we get from above result that, the *DFEP* point of *SS* is *LAS*. ■

Theorem 4. The EEP of SS that is given by $E_3 = (S_3, C_3, I_3, A_3)$ is LAS when the following condition is satisfied:

$$(\mu + \varepsilon) > \sigma_1 S_3 \tag{11a}$$
$$\mu > \max.\{2\sigma_1 S_3 + \rho, \theta - \gamma, 2\sigma_0 S_3 - \alpha\} \tag{11b}$$

Proof: The Jacobian matrix of SS at EEP can be written in the following form:

$$J(E_3) = \begin{pmatrix} e_{11} & e_{12} & 0 & e_{14} \\ e_{21} & e_{22} & 0 & e_{24} \\ 0 & e_{32} & e_{33} & 0 \\ 0 & e_{42} & e_{43} & e_{44} \end{pmatrix}$$

here

$$e_{11} = -(\sigma_0 A_3 + \sigma_1 C_3 + \sigma_2 + \mu)\ ;\ e_{12} = -\sigma_1 S_3\ ;\ e_{14} = -\sigma_0 S_3\ ;$$
$$e_{21} = \sigma_0 A_3 + \sigma_1 C_3 + \sigma_2\ ;\ e_{22} = \sigma_1 S_3 - (\mu + \varepsilon)\ ;\ e_{24} = \sigma_0 S_3\ ;$$
$$e_{32} = \varepsilon\ ;\ e_{33} = -(\mu + \gamma)\ ;\ e_{42} = \rho\ ;\ e_{43} = \theta\ ;\ e_{44} = -(\mu + \alpha)$$

Now, according the *Gershgorin* theorem [26], if the following condition holds:

$$|e_{ii}| > \sum_{\substack{i=1 \\ i \neq j}}^{4} |e_{ij}| = P_i \tag{11c}$$

then, all the eigenvalues of $J(E_3)$ exist in the disc centered at e_{ii} with radius P_i. Thus, if the diagonal elements are negative and the condition (11b) holds, all the eigenvalues will exist in the left half plane and the EEP of SS is LAS. Clearly, conditions (11a)-(11b) guarantee the existence of all eigenvalues in the left half plane, and the proof follows.

5. Global stability analysis of FS and SS

In this section, the global asymptotic stability (GAS) of all equilibrium points $E_i, i=1,2,3$ in the FS and SS is investigated. The conditions that satisfy the global stability are determined in the following theorems by utilizing Lypunov function (Lyp. fun.).

Theorem 5. Let PEP that is denoted by E_1 of FS be LAS, then it is GAS if the following sufficient conditions hold.

$$(\beta V_1)^2 < (\beta V_1 + m)(m + d) \quad (12a)$$

$$(\beta x + p)^2 < (m + d)(\beta x + \eta) \quad (12b)$$

$$[\beta(x - V_1)]^2 < (\beta V_1 + m)(\beta x + \eta) \quad (12c)$$

Proof: Consider the following positive definite function:

$$F_1 = \frac{(x - x_1)^2}{2} + \frac{(y - y_1)^2}{2} + \frac{(V - V_1)^2}{2}$$

Clearly, $F_1 : R_+^3 \to R$ is a continuously differentiable function such that $F_1(x_1, y_1, V_1) = 0$ and $F_1(x, y, V) > 0$, for all $(x, y, V) \neq (x_1, y_1, V_1)$. Then we have

$$\begin{aligned}\dot{F}_1 &= (x - x_1)\dot{x} + (y - y_1)\dot{y} + (V - V_1)\dot{V} \\ &= -\frac{1}{2}(\beta V_1 + m)(x - x_1)^2 + \beta V_1 (x - x_1)(y - y_1) - \frac{1}{2}(m + d)(y - y_1)^2 \\ &\quad -\frac{1}{2}(\beta V_1 + m)(x - x_1)^2 - \beta(x - V_1)(x - x_1)(V - V_1) - \frac{1}{2}(\beta x + \eta)(V - V_1)^2 \\ &\quad -\frac{1}{2}(m + d)(y - y_1)^2 + (\beta x + p)(y - y_1)(V - V_1) - \frac{1}{2}(\beta x + \eta)(V - V_1)^2\end{aligned}$$

$$\begin{aligned}\dot{F}_1 \leq &-\left[\sqrt{\frac{\beta V_1 + m}{2}}(x - x_1) - \sqrt{\frac{m + d}{2}}(y - y_1)\right]^2 \\ &-\left[\sqrt{\frac{\beta V_1 + m}{2}}(x - x_1) + \sqrt{\frac{\beta x + \eta}{2}}(V - V_1)\right]^2 \\ &-\left[\sqrt{\frac{m + d}{2}}(y - y_1) - \sqrt{\frac{\beta x + \eta}{2}}(V - V_1)\right]^2\end{aligned}$$

Therefore, $\dot{F}_1 < 0$, and then F_1 is (Lyp. fun.) with respect to E_1 of FS. Hence, this point is a GAS, provided that the conditions (12a-12c) hold.

Theorem 6. Let the DFEP that is denoted by E_2 of SS is LAS, then it is a GAS, if the below sufficient conditions are satisfied.

$$\mu > \max\{\sigma_0 S_2 - \alpha, \rho + \sigma_1 S_2, \theta - \gamma\} \quad (13a)$$

$$\tfrac{\mu}{S}(S - S_2)^2 > \sigma_2 S_2 + V \quad (13b)$$

Proof: Consider the following positive definite function:

$$F_2 = \left(S - S_2 - S_2 \ln \frac{S}{S_2}\right) + C + I + A$$

Now, $F_2 : R_+^4 \to R,$ is a continuously differentiable function such that $F_2(S_2, 0, 0, 0) = 0$ with $F_2(S, C, I, A) > 0$, for all $(S, C, I, A) \neq (S_2, 0, 0, 0)$. Then by the derivation of F_2 with respect to time, we have

$$\begin{aligned}\dot{F}_2 \leq &-\tfrac{\mu}{S}(S - S_2)^2 - (\mu + \alpha - \sigma_0 S_2)A - (\mu - \rho - \sigma_1 S_2)C \\ &-(\mu + \gamma - \theta)I + \sigma_2 S_2 + V\end{aligned}$$

here V represents any constant value of virus level in SS, which is bounded due to boundedness of FS. Therefore, $\dot{F}_2 \leq 0$ under the given conditions and hence F_2 is (Lyp. fun.) with respect to DFEP of SS under the sufficient conditions (13a)-(13b). Hence, the DFEP is a GAS, and the proof is complete.

Theorem 7. Let the EEP that is denoted by E_3 of SS is LAS, then it is a GAS if the following sufficient conditions hold.

$$\sigma_1 S < \mu + \varepsilon \tag{14a}$$

$$(\sigma_0 A_3 + \sigma_1 C_3 + \sigma_2 - \sigma_1 S)^2 < \frac{2}{3}(\sigma_0 A_3 + \sigma_1 C_3 + \sigma_2 + \mu)(\mu + \varepsilon - \sigma_1 S) \tag{14b}$$

$$\varepsilon^2 < \frac{2}{3}(\mu + \varepsilon - \sigma_1 S)(\mu + \gamma) \tag{14c}$$

$$(\sigma_0 S + \rho)^2 < \frac{4}{9}(\mu + \varepsilon - \sigma_1 S)(\mu + \alpha) \tag{14d}$$

$$\theta^2 < \frac{2}{3}(\mu + \gamma)(\mu + \alpha) \tag{14e}$$

$$(\sigma_0 S)^2 < \frac{2}{3}(\sigma_0 A_3 + \sigma_1 C_3 + \sigma_2 + \mu)(\mu + \alpha) \tag{14f}$$

Proof: Consider the following positive definite function:

$$F_3 = \frac{(S - S_3)^2}{2} + \frac{(C - C_3)^2}{2} + \frac{(I - I_3)^2}{2} + \frac{(A - A_3)^2}{2}$$

Clearly, $F_3 : R_+^4 \to R,$ is a continuously differentiable function such that $F_3(S_3, C_3, I_3, A_3) = 0$ and $F_3(S, C, I, A) > 0$, for all $(S, C, I, A) \neq (S_3, C_3, I_3, A_3)$. Clearly, the derivation of F_3 with respect to time shows that:

$$\dot{F}_3 = (S - S_3)\dot{S} + (C - C_3)\dot{C} + (I - I_3)\dot{I} + (A - A_3)\dot{A}$$

Therefore, using SS equations gives that:

$$\begin{aligned}
\dot{F}_3 = &-\frac{1}{2}k_{11}(S - S_3)^2 + k_{12}(S - S_3)(C - C_3) - \frac{1}{3}k_{22}(C - C_3)^2 \\
&-\frac{1}{3}k_{22}(C - C_3)^2 + k_{23}(C - C_3)(I - I_3) - \frac{1}{2}k_{33}(I - I_3)^2 \\
&-\frac{1}{3}k_{22}(C - C_3)^2 + k_{24}(C - C_3)(A - A_3) - \frac{1}{3}k_{44}(A - A_3)^2 \\
&-\frac{1}{2}k_{33}(I - I_3)^2 + k_{34}(I - I_3)(A - A_3) - \frac{1}{3}k_{44}(A - A_3)^2 \\
&-\frac{1}{2}k_{11}(S - S_3)^2 - k_{14}(S - S_3)(A - A_3) - \frac{1}{3}k_{44}(A - A_3)^2
\end{aligned}$$

where $k_{11} = \sigma_\circ A_3 + \sigma_1 C_3 + \sigma_2 + \mu$, $k_{12} = \sigma_\circ A_3 + \sigma_1 C_3 + \sigma_2 - \sigma_1 S$, $k_{22} = \mu + \varepsilon - \sigma_1 S$, $k_{23} = \varepsilon$, $k_{24} = \sigma_\circ S + \rho$, $k_{33} = \mu + \gamma$, $k_{34} = \theta$, $k_{14} = \sigma_\circ S$ and $k_{44} = \mu + \alpha$. Hence

$$\begin{aligned}
\dot{F}_3 \leq &-\frac{1}{2}\left[\sqrt{k_{11}}(S - S_3) - \sqrt{\frac{2k_{22}}{3}}(C - C_3)\right]^2 - \frac{1}{2}\left[\sqrt{\frac{2k_{22}}{3}}(C - C_3) - \sqrt{k_{33}}(I - I_3)\right]^2 \\
&-\frac{1}{2}\left[\sqrt{\frac{2k_{22}}{3}}(C - C_3) - \sqrt{\frac{2k_{44}}{3}}(A - A_3)\right]^2 - \frac{1}{2}\left[\sqrt{\frac{k_{33}}{2}}(I - I_3) - \sqrt{\frac{k_{44}}{3}}(A - A_3)\right]^2 \\
&-\frac{1}{2}\left[\sqrt{k_{11}}(S - S_3) + \sqrt{\frac{2k_{44}}{3}}(A - A_3)\right]^2
\end{aligned}$$

Therefore, $\dot{F}_3 < 0$, and hence F_3 is (Lyp. fun.) with respect to E_3 of SS. Hence, this point is a GAS, provided that the conditions (14a-14f) hold.

6. Optimal control strategy of the SS

Based on the above outcomes, AIDS epidemic will become a serious problem that threatens the lives of human beings population in the absence of any controlling measures. Clearly, the idea here from the controlling strategies is trying to reduce the outbreak of the epidemic, which will be achieved through the proposal of some solutions by adding special variables for the proposed system (i.e. SS). In this section, the handy tool of optimal control, described in a previous work [27], is used for controlling the spread of an epidemic through adding two control variables to the SS. The first variable represents the government potential that plans to prevent the spread of the disease, denoted by $u_1(t) \in [0,1]$, which is a Lebesque integrable control function. Moreover, the media will be a second Lebesque integrable control function, denoted by $u_2(t) \in [0,1]$, and its role is mainly increasing the awareness of the population. Taking into account the extensions made above, $(1-u_1), (1-u_2)$ will be still out of control for government potential and awareness of population, respectively. System (3) is modified to an optimal control system as described in the following system:

$$\begin{aligned}
\dot{S} &= \psi - \sigma_0(1-u_1)SA - \sigma_1(1-u_1)SC - \sigma_2(1-u_2)S - \mu S \\
\dot{C} &= \sigma_0(1-u_1)SA + \sigma_1(1-u_1)SC + \sigma_2(1-u_2)S - (\mu+\varepsilon)C \\
\dot{I} &= \varepsilon C - (\mu+\gamma)I \\
\dot{A} &= V + \theta I + \rho C - (\mu+\alpha)A
\end{aligned} \tag{15a}$$

Our goal is minimizing the number of people who become infected by sexual contact or any external source, along with minimizing the effort provided by the government potential and awareness of population as well. For this end, we try to minimize the objective (cost) function which is given as:

$$C_T(u_1,u_2) = \int_0^{t_f} \left[r_0 C(t) + r_1 I(t) + r_2 A(t) + \frac{r_3}{2}u_1^2(t) + \frac{r_4}{2}u_2^2(t) \right] dt \tag{15b}$$

where t_f is the maximum of time interval for computing the objective function. The constants r_0, r_1 and r_2 are positive weight constants to establish a balance in size of carriers, infected individuals, and AIDS class, respectively. However, the constants r_3 and r_4 are the cost weights associated with the controls u_1 and u_2, respectively. According to system (15a), a linear function for the costs arising from the carriers, infected individuals, and AIDS classes is selected. However the relationship between these interventions (government potential and media awareness of population) and their corresponding costs is assumed to be nonlinear and hence a quadratic cost on the controls is chosen. Consequently, we need to find the optimal control variables u_1^* and u_2^* such that:

$$C_T(u_1^*,u_2^*) = \min\{C_T(u_1,u_2)\} \tag{15c}$$

with the admissible control set

$$\Omega = \left\{ (u_1,u_2) \in \left(L^\infty(0,t_f)\right) \middle| 0 \le u_1(t) \le u_{1\max}, 0 \le u_2(t) \le u_{2\max}, t \in [0,t_f] \right\} \tag{15d}$$

Then to derive the optimality conditions for the SS, the following Hamiltonian function with respect to control variables is used:

$$H = L + \sum_{i=1}^{4} \lambda_i g_i \tag{15e}$$

where L is the Lagrangian given by

$$L = r_0 C(t) + r_1 I(t) + r_2 A(t) + \frac{1}{2}[r_3 u_1^2 + r_4 u_2^2]$$

and

$$g_1 = \dot{S}, g_2 = \dot{C}, g_3 = \dot{I}, g_1 = \dot{A}$$

Now, we rewrite Eq. (15e) in the following format:

$$H = r_0 C(t) + r_1 I(t) + r_2 A(t) + \frac{r_3}{2}u_1^2(t) + \frac{r_4}{2}u_2^2(t) + \lambda_1 \dot{S} + \lambda_2 \dot{C} + \lambda_3 \dot{I} + \lambda_4 \dot{A} \tag{15f}$$

Therefore, to derive the necessary conditions for the optimal problem, the Portraying Maximum Principle to the Hamiltonian that is given in Eq. (15f) is used, so that if (Z^*, u_i^*) for $i = 1,2$ is an optimal solution of an optimal control problem (15a), then there exists a non-trivial vector function $\lambda(t) = (\lambda_1(t), \lambda_2(t), \lambda_3(t), \lambda_4(t))^T$ satisfying the following conditions:

$$\begin{aligned} \dot{Z} &= \frac{\partial H(t,Z,u,\lambda)}{\partial \lambda} \\ 0 &= \frac{\partial H(t,Z,u,\lambda)}{\partial u} \\ \dot{\lambda} &= -\frac{\partial H(t,Z,u,\lambda)}{\partial Z} \end{aligned} \tag{15g}$$

where $Z = (S, C, I, A)^T$ and $u = (u_1, u_2)^T$. Now, by applying the Pontryagin's Maximum Principle, the optimization problem described above is converted to the problem of finding the point-wise minimum relative to u_1 and u_2 of the Hamiltonian given in Eq. (15f), as shown in the following theorem.

Theorem 8. Given the optimal control variables (u_1^*, u_2^*) and the corresponding solution of system (15a), that are denoted by (S^*, C^*, I^*, A^*), that minimize the objective function (15b) over the admissible control set Ω, then there exist adjoint functions λ_i for $i = 1,2,3,4$ satisfying:

$$\begin{aligned} \dot{\lambda}_1 &= \lambda_1\mu + (\lambda_1 - \lambda_2)\sigma_0(1-u_1)A^* + (\lambda_1 - \lambda_2)\sigma_1(1-u_1)C^* + (\lambda_1 - \lambda_2)\sigma_2(1-u_2) \\ \dot{\lambda}_2 &= -r_0 + \lambda_2(\mu + \varepsilon) + \lambda_1\sigma_1(1-u_1)S^* - \lambda_3\varepsilon - \lambda_4\rho \\ \dot{\lambda}_3 &= -r_1 + \lambda_3(\mu + \gamma) - \lambda_4\theta \\ \dot{\lambda}_4 &= -r_2 + \lambda_4(\mu + \alpha) + (\lambda_1 - \lambda_2)\sigma_0(1-u_1)S^* \end{aligned} \tag{15h}$$

with transversality conditions $\lambda_i(t_f) = 0$ for $i = 1,2,3,4$. Moreover, the optimal control pair is given by the continuous functions

$$\begin{aligned} u_1^*(t) &= \min\left\{u_{1max}, \max\left\{0, \frac{(\lambda_2-\lambda_1)\sigma_0 S^* A^* + (\lambda_2-\lambda_1)\sigma_1 S^* C^*}{r_3}\right\}\right\} \\ u_2^*(t) &= \min\left\{u_{2max}, \max\left\{0, \frac{(\lambda_2-\lambda_1)\sigma_2 S^*}{r_4}\right\}\right\} \end{aligned} \tag{15i}$$

Proof: The existence of an optimal control was confirmed by Fleming and Rishel [28]. Moreover, to obtain the adjoint equations (15h) as well as their transversality conditions, we differentiate the Hamiltonian that is given by Eq. (15f), with respect to $S(t), C(t), I(t)$ and $A(t)$, respectively, then substitute that $S(t) = S^*$, $C(t) = C^*$, $I(t) = I^*$ and $A(t) = A^*$. While, by solving $\frac{\partial H}{\partial u_1} = 0$ and $\frac{\partial H}{\partial u_2} = 0$ on the interior of the admissible control set and using the property of the control space, we get:

$$\begin{aligned} u_1^*(t) &= \frac{(\lambda_2-\lambda_1)\sigma_0 S^* A^* + (\lambda_2-\lambda_1)\sigma_1 S^* C^*}{r_3} \\ u_2^*(t) &= \frac{(\lambda_2-\lambda_1)\sigma_2 S^*}{r_4} \end{aligned} \tag{15j}$$

Thus the proof is complete.

8. Numerical simulation

In this section, numerical simulations are carried out in order to confirm our obtained results and understand the effects of varying parameter values on the dynamics of the systems. The following set of hypothetical parameter values is used, and then the systems are solved numerically starting from different sets of initial data. The obtained trajectories are drawn using Matlab version 8.

$$\begin{aligned} &\Lambda = 750\ ,\ \beta = 0.001\ ,\ m = 0.01\ ,\ p = 0.1\ ,\ d = 0.1\ ,\ \eta = 0.1 \\ &e = 0.13\ ,\ A = 900 \end{aligned} \tag{16a}$$

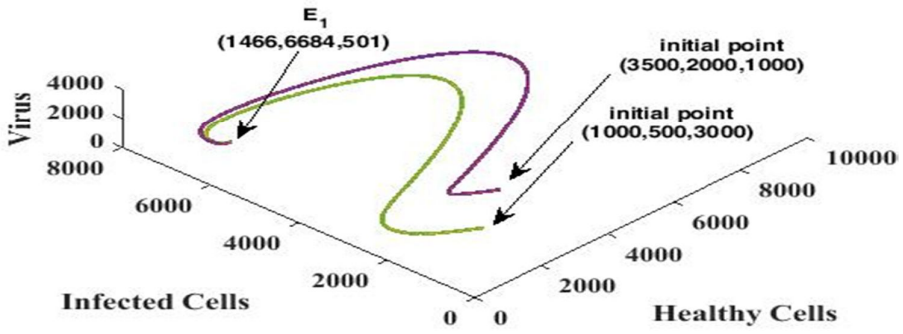


Figure 3: Phase plot of the trajectory of FS for the data given by Equation (16a). The trajectory approaches asymptotically to PEP in the FS starting from two different initial points.

Obviously, the phase plot illustrated in Figure 3 shows that the PEP of the FS that is given by $E_1 = (1466, 6684, 501)$ is globally asymptotically stable, which confirms our obtained analytical results.

Now, for the following set of data, it is observed that the SS has a globally asymptotically stable DFEP given by $E_2 = (10000, 0, 0, 0)$.

$$\psi = 1000\ ,\ \sigma_0 = 0.00001\ ,\ \sigma_1 = 0.0001\ ,\ \sigma_2 = 0\ ,\ \mu = 0.1\ ,\ \varepsilon = 1$$
$$\gamma = 0.1\ ,\ \theta = 0.0001\ ,\ \rho = 0.0001\ ,\ \alpha = 0.1\ ,\ V = 0 \qquad (16b)$$

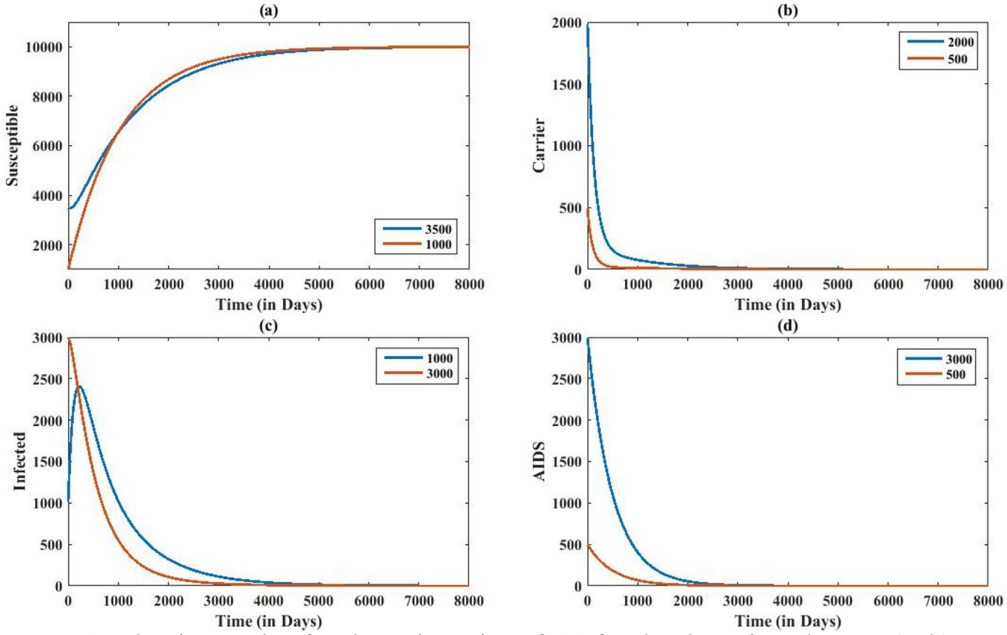


Figure 4: The time series for the trajectories of SS for the data given by Eq. (16b) starting from different initial points: (3500, 2000, 1000, 3000) and (1000, 500, 3000, 500) (a) Trajectories of S(t). (b) Trajectories of C(t), (c) Trajectories of I(t), (d) Trajectories of A(t).

However, for the following data set, it is observed that the trajectory of SS approaches asymptotically to the EEP given by $E_3 = (378, 2405, 3608, 1386)$, starting from different initial points: *(3500, 2000, 1000, 3000) and (1000, 500, 3000, 500).*

$$\psi = 1000\ ,\ \sigma_0 = 0.0001\ ,\ \sigma_1 = 0.001\ ,\ \sigma_2 = 0.0001$$
$$\mu = 0.1\ ,\ \varepsilon = 0.3\ ,\ \gamma = 0.1\ ,\ \theta = 0.01\ ,\ \rho = 0.01\ ,\ \alpha = 0.1\ ,\ V = 0.6 \tag{16c}$$

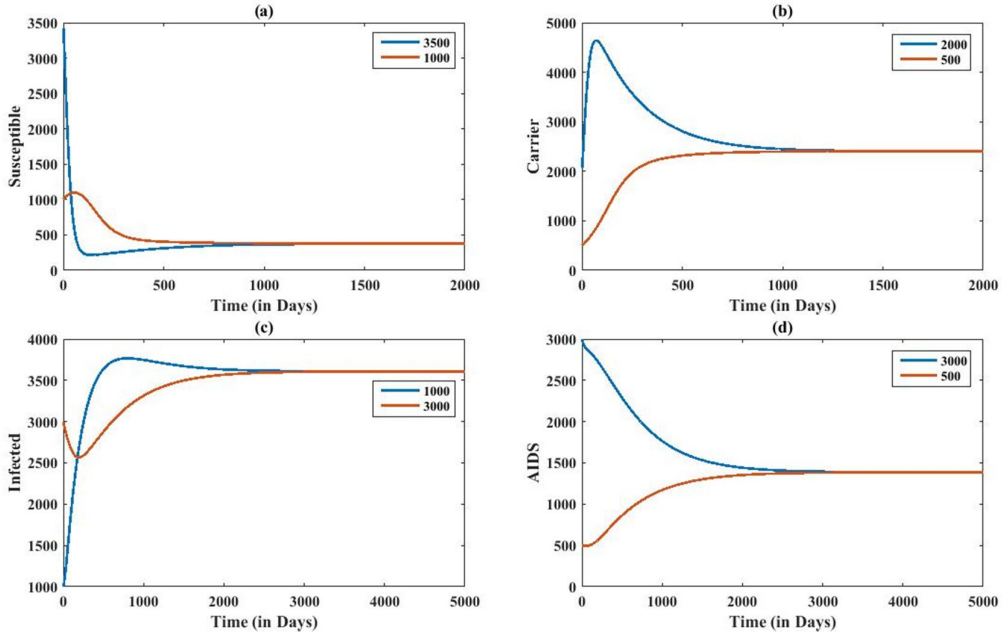
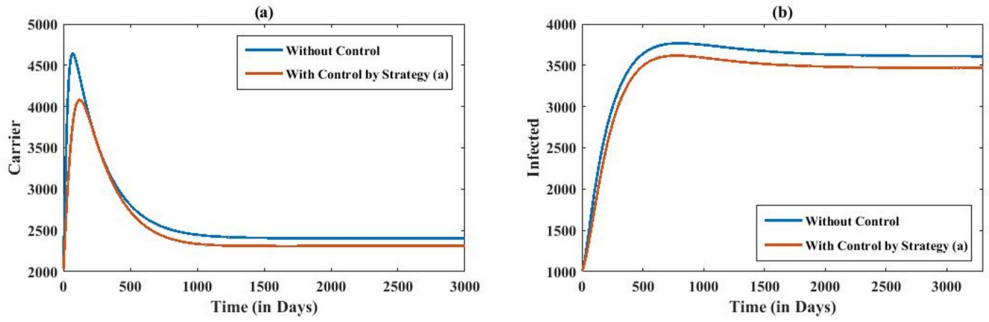


Figure 5: The time series for the trajectories of SS for the data given by Eq. (16c) starting from different initial points: (3500, 2000, 1000, 3000) and (1000, 500, 3000, 500) (a) Trajectories of S(t). (b) Trajectories of C(t), (c) Trajectories of I(t), (d) Trajectories of A(t).

Now, the effect of the control variables is discussed, using three types of strategies: the first is given by the control of the government only, which is called strategy (a) (i.e. $u_2 = 0$), the second is the control by the media only and called strategy (b) (i.e. $u_1 = 0$), and the third strategy is the control by both government and media, which is termed strategy (c).



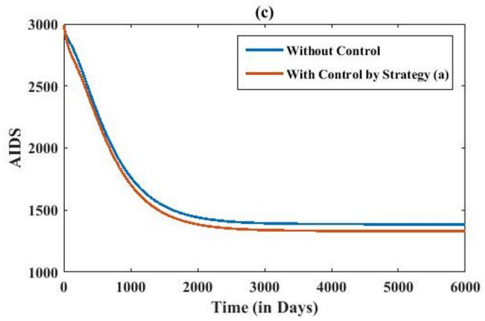


Figure 6: The time series for the trajectories of SS with control strategy of type (a) using data given by Eq. (16c) with $u_1 = 0.5$ (a) Trajectories of C(t), (b) Trajectories of I(t), (c) Trajectories of A(t).

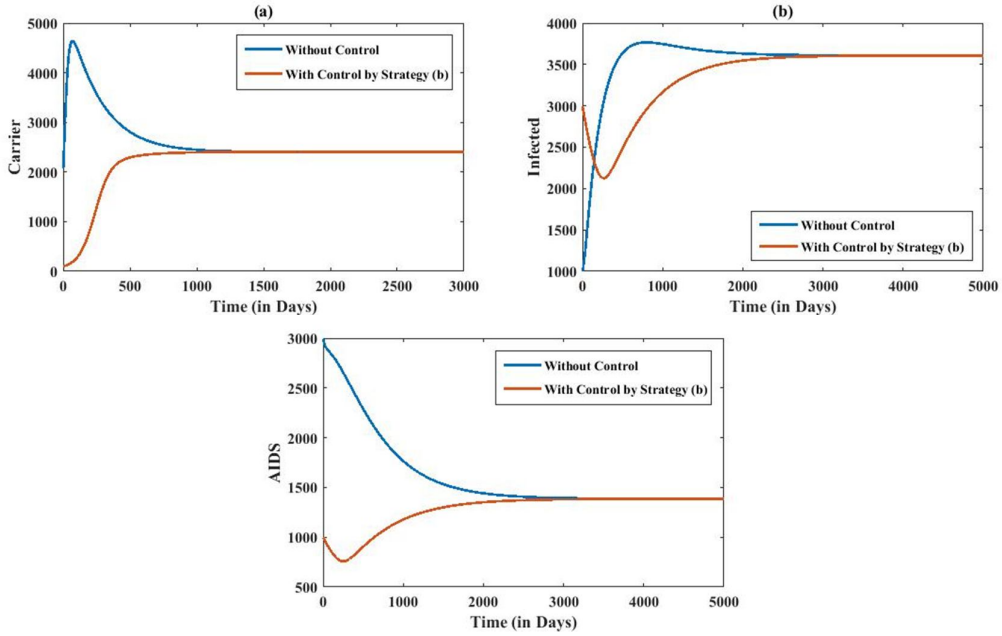
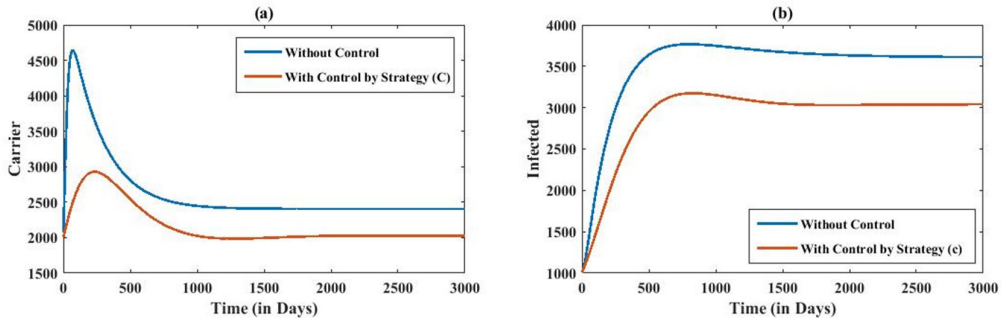


Figure 7: The time series for the trajectories of SS with control strategy of type (b) using data given by Eq. (16c) with $u_2 = 0.9$ (a) Trajectories of C(t), (b) Trajectories of I(t), (c) Trajectories of A(t).



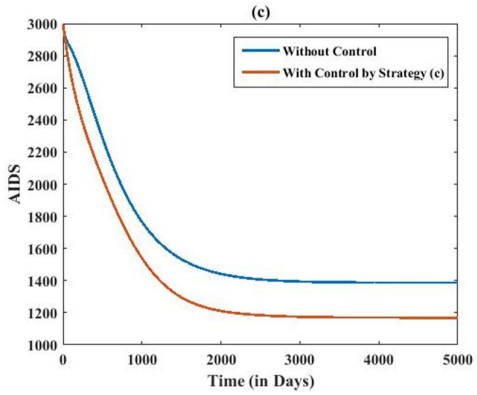


Figure 8: The time series for the trajectories of SS with control strategy of type (c) using data given by Eq. (16c) with $u_1 = 0.6$ and $u_2 = 1$ (a) Trajectories of C(t), (b) Trajectories of I(t), (c) Trajectories of A(t).

According to the above three Figures (6-8), the control given by strategy (a) reduces the outbreak of the epidemic, as shown in Fig. (6). However the control given by strategy (b) has a small effect on the outbreak of the epidemic, as shown in Figure-7. Finally, the control given by strategy (c) reduces the outbreak of the epidemic more than that happened in strategy (a), as shown in Figure-8.

Furthermore, in order to discuss the effect of varying the infection rate due to contact with AIDS on the dynamical behavior of system SS. we solved it for different values of infection rates $\sigma_0 = 0.000001, 0.003$ respectively, keeping other parameters fixed as given in Eq. (16c). Then the solution of SS was drawn in Figures (9a)-(9b), without applying control measures respectively. However, Fig. (9c) shows the effect of the control parameter $u_1$with the same value of σ_0 .

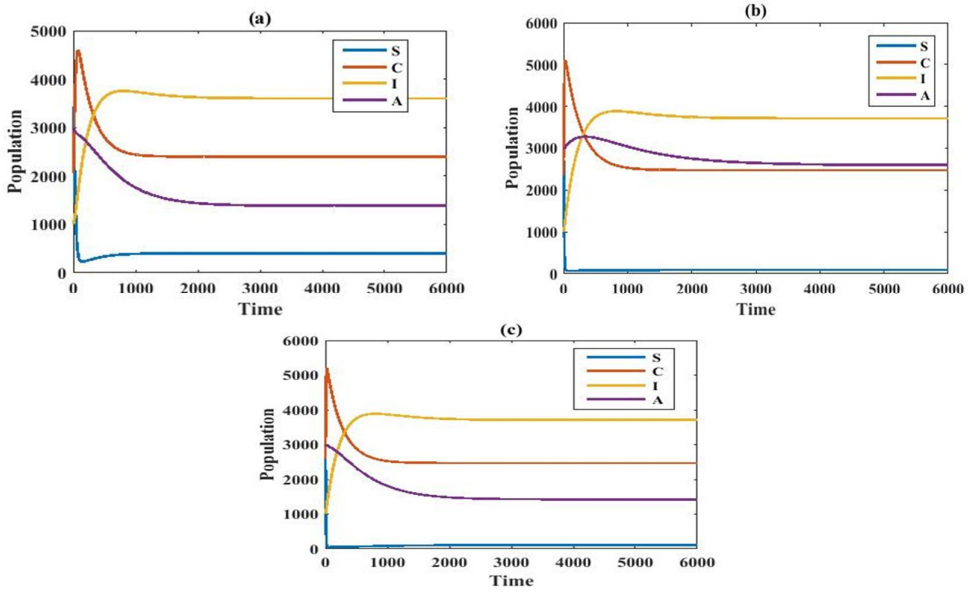


Figure 9: The time series for the trajectories of SS using data given by Eq. (16c). (a)The trajectories with $\sigma_0 = 0.000001$, (b) The trajectories with $\sigma_0 = 0.003$, (c) The trajectories with $\sigma_0 = 0.003$ and $u_1 = 0.9$.

Similarly, the effect of infection rate due to contact between susceptible individuals and carrier individuals on the dynamical behavior of system SS is investigated. The SS is solved numerically for different values of infection rates $\sigma_1 = 0.00001, 0.002$ respectively, and the obtained trajectory is drawn in Figs. (10a)-(10b), without applying control. However, Figure (10c) shows the effect of the control parameter $u_1$with the value of $\sigma_1 = 0.002$.

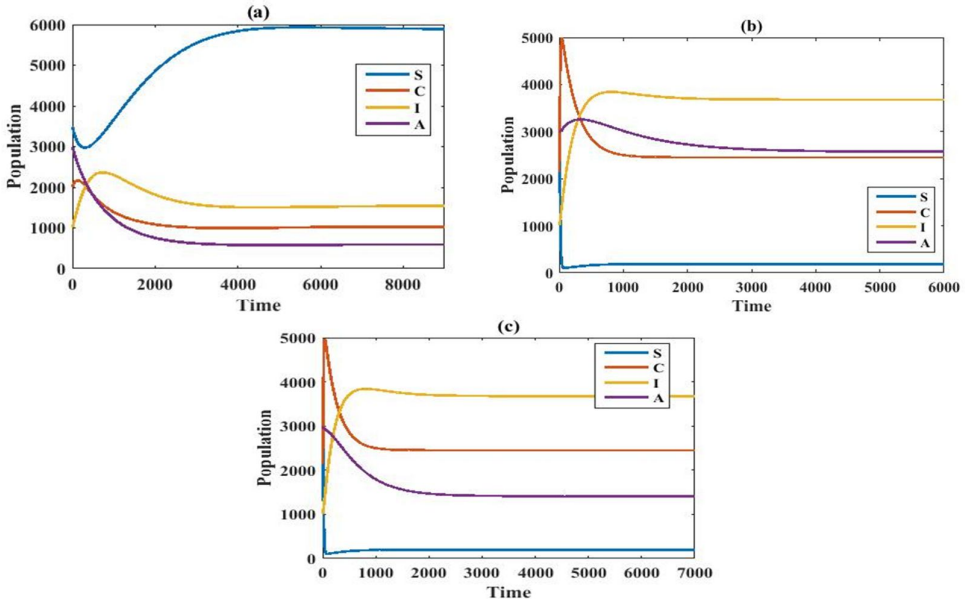


Figure 10: The time series for the trajectories of SS using data given by Eq. (16c). (a) The trajectories with $\sigma_1 = 0.00001$, (b) The trajectories with $\sigma_1 = 0.002$, (c) The trajectories with $\sigma_1 = 0.002$ and $\mu_1 = 0.8$.

9. Discussion and Conclusions

In this article, a mathematical model that describes the spread of the human immunodeficiency virus (HIV) or the AIDS epidemic is proposed and studied. It is assumed that the disease is spreading through two stages. The first stage takes place inside the body due to contact of the healthy cells with free virus, and it is called the within-host stage. While, in the second stage, the disease spreads among the individuals by direct contact and external sources of infection. For the simplifying the study of the proposed model, the system is divided into two systems. The first system, which is called the within-host body system or Fast system (FS) is obtained when we assume that the AIDS class is constant. While the second system which is called the between-host or slow system (SS) is obtained when the virus level is assumed to be constant. The existence, uniqueness and boundedness of the solutions of these models are discussed. The possible equilibrium points in both systems are determined. The local stability analysis of these systems is studied. The sufficient conditions for the global stability of these systems are obtained. In order to control the outbreak of such disease, two different optimal control variables (the effort of government potential and awareness of population) are determined analytically with the help of Pontryagin's Maximum Principle. Finally, numerical simulations were used to illustrate the effects of varying the parameters set on the dynamical behavior of the FS and SS in two cases when there is no control and in the case of the existence of constant control values. It is observed that the existence of constant control value causes reduction in the AIDs class.

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