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# Eradication Conditions of Infected Cell Populations in the 7-Order HIV Model with Viral Mutations and Related Results

**Konstantin E. Starkov [1,*,†] and Anatoly N. Kanatnikov [2,†]**

[1] Instituto Politecnico Nacional-CITEDI, Av. de IPN 1310, Nueva Tijuana, Tijuana 22435, Mexico
[2] Department of Mathematical Modeling, Bauman Moscow State Technical University, 105005 Moscow, Russia; skipper@bmstu.ru
* Correspondence: kstarkov@ipn.mx or konstarkov@hotmail.com
† These authors contributed equally to this work.

**Abstract:** In this paper, we study possibilities of eradication of populations at an early stage of a patient's infection in the framework of the seven-order Stengel model with 11 model parameters and four treatment parameters describing the interactions of wild-type and mutant HIV particles with various immune cells. We compute ultimate upper bounds for all model variables that define a polytope containing the attracting set. The theoretical possibility of eradicating HIV-infected populations has been investigated in the case of a therapy aimed only at eliminating wild-type HIV particles. Eradication conditions are expressed via algebraic inequalities imposed on parameters. Under these conditions, the concentrations of wild-type HIV particles, mutant HIV particles, and infected cells asymptotically tend to zero with increasing time. Our study covers the scope of acceptable therapies with constant concentrations and values of model parameters where eradication of infected particles/cells populations is observed. Sets of parameter values for which Stengel performed his research do not satisfy our local asymptotic stability conditions. Therefore, our exploration develops the Stengel results where he investigated using the optimal control theory and numerical dynamics of his model and came to a negative health prognosis for a patient. The biological interpretation of these results is that after a sufficiently long time, the concentrations of wild-type and mutant HIV particles, as well as infected cells will be maintained at a sufficiently low level, which means that the viral load and the concentration of infected cells will be minimized. Thus, our study theoretically confirms the possibility of efficient treatment beginning at the earliest stage of infection. Our approach is based on a combination of the localization method of compact invariant sets and the LaSalle theorem.

**Keywords:** HIV ultimate dynamics; localization; $\omega$-limit set; local stability; global stability; equivalence; invariant plane; LaSalle theorem

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## 1. Introduction

Human immunodeficiency virus (HIV) infection as the cause of AIDS has attracted the attention of many researchers from various fields around the world since the 1980s. In particular, the interest of many scientists has been focused on the elaboration and studies of mathematical models which describe the immunological response to infection with HIV. There are different types of such dynamical models that characterize interactions of HIV with $CD4$-expressing cells including helper $T$ cells, macrophages, and natural killer cells. The basic studies in this area are contained in seminal works of [1–5]. The mentioned researches were continued in papers [6–14] where various dynamical issues related to HIV models are explored, such as positive invariance properties, boundedness of positive half trajectories of this model, stability analysis of equilibrium points, the existence of an orbitally asymptotically stable periodic solution, and bifurcations. These articles did not address the propensity of viral mutations to replicate HIV. Taking HIV mutations into account gives a more realistic picture of the human infectious process. This leads to more

complete and complex models. However, as far as the authors know, HIV models with mutant infection have not been sufficiently studied yet [15–22].

In [16], Stengel constructed the seven-order model of HIV mutant infection and discussed the feasibility and effectiveness of the optimal therapies for his model in which virtual therapies for wild-type infections are incorporated:

$$\begin{cases} \dot{x}_1 = -a_1x_1 - a_2(1-u_2)x_1x_2 + a_3a_4(1-a_{10})(1-u_1)x_4; \\ \dot{x}_2 = \frac{a_5}{1+x_1+x_5} - a_2(1-u_2)(1-u_4)x_1x_2 - a_6x_2 - a_2a_{11}x_2x_5 + a_7(1+u_3)q(x)x_2; \\ \dot{x}_3 = a_2(1-u_2)(1-u_4)x_1x_2 - (a_6+a_9)x_3; \\ \dot{x}_4 = a_9x_3 - a_4x_4; \\ \dot{x}_5 = a_3a_4a_{10}x_4 - a_1x_5 - a_2a_{11}x_2x_5 + a_3a_4x_7; \\ \dot{x}_6 = a_2a_{11}x_2x_5 - (a_6+a_9)x_6; \\ \dot{x}_7 = a_9x_6 - a_4x_7, \end{cases} \tag{1}$$

where the notation

$$q(x) = 1 - \frac{x_2+x_3+x_4+x_6+x_7}{a_8}$$

is utilized. The model (5) has been obtained from 4D equations in [3] by adding equations describing the dynamics of the mutant HIV strain. The four state variables of the initial model of [3] represent concentrations of free, wild-type HIV particles ($x_1$), uninfected Th cells ($x_2$), latently infected Th cells ($x_3$), and productively infected Th cells ($x_4$) in both the periphery and lymphoid organs. Other state variables of (1) represent concentrations of the mutant HIV strain ($x_5$), proviral Th cells infected by the mutant strain ($x_6$), and Th cells productively infected by the new strain ($x_7$).

Parameters have the following biological meanings: $a_1$ is the death rate of free virions; $a_2$ is the rate at which CD4$^+$ T cells become infected by free virions; $a_3$ is the number of free virions produced by $x_4$ cells; $a_4$ is the death rate of the actively infected CD4$^+$ T cell population; $a_5$ is the source term for uninfected CD4$^+$ T cells; $a_6$ is the death rate of the uninfected CD4$^+$ T cell population; $a_7$ is the growth rate for the CD4$^+$ T cell population; $a_8$ is the maximum CD4$^+$ T cell population level; $a_9$ is the rate at which $x_3$ cells convert to actively infected cells; $a_{10}$ is the mutation rate; $a_{11}$ is the fitness of the mutant strain.

In [23], it is indicated that the main damage to the immune system occurs in the first weeks of infection, when the diversity of virions is low. The model in [16] describes the interaction of the HIV-immune system only at an early stage of infection, when wild-type virions and virions of the first mutant strain attack the patient, but new mutant strains have not yet appeared.

Treatment or control parameters $u_i$ are supposed to be constant, $u_i \in [0,1)$, and are defined as follows: they are concentrations of protease inhibitor ($u_1$), fusion inhibitor ($u_2$), Th cell enhancer ($u_3$), and reverse transcription inhibitor ($u_4$). According to Equation (1), applied therapy can affect wild HIV particles, but do not possess direct effects on the mutant HIV strain. Stengel raised the question of whether the complex interactions described in the upper three equations of (1), as well as the presence of the mutant HIV strain variable in the second equation, may have a "good effect" on the patient's health. Based on clinical practice, according to which "HIV infection is never cured, and requires continuous treatment to maintain a state in remission", Stengel studied the possibility of optimal therapy for treating HIV infection at certain parameter values. Mathematically, his research is based on the steepest descent algorithm and Pontryagin's maximum principle.

The purpose of our work is to investigate some qualitative features of the model (1). Our research provides a positive answer to Stengel's question for certain ranges of parameter values within the broad framework of the rigorous dynamic analysis (1) carried out in this article. With this goal, we find equilibrium points and provide local asymptotic stability (LAS) conditions for the infection-free equilibrium point, prove the existence of the attracting set, and calculate ultimate upper bounds for the polytope containing the attracting set. Further, we show that the dynamics of the model (1) theoretically makes it possible to eradicate the infection by an appropriate choice of treatment parameters if the

model parameters satisfy a number of algebraic inequalities. Namely, we find the curious dynamic property of (1), which is that the LAS conditions of the infection-free equilibrium point imply its global asymptotic stability (GAS) conditions, that is, these GAS conditions cannot be improved. Another interesting issue found here is that these conditions do not depend on controls $u_3$ and $u_4$. Moreover, we describe the case when these conditions do not depend on rest controls $u_1$ and $u_2$ as well.

The ranges of parameters at which the cure is achieved in the studied model can be considered as target ranges for real biomedical problems, as well as when choosing parameter control. The biological feasibility issues of numerical values are not the focus of this study.

Biologically, the global asymptotic eradication of infection (GAS) property means that after a sufficiently long observation period, concentrations of wild and mutant HIV particles and infected cells are maintained at a fairly low level. Thus, the results of our study may be applicable in subsequent studies in the case of early initiation of therapy for the patient, when the time period after infection is short.

Our research is based on the localization method of compact invariant sets (LMCIS) [24], and the LaSalle theorem. It should be noted that earlier, the LMCIS was effectively used in the study of many models taken from chaos theory, see, for example [25], cosmology [26], mathematical oncology [27,28], mathematical inclusions [29], and others.

The structure of this paper is the following. In Section 2 we describe the LMCIS which is utilized in combination with the LaSalle theorem for obtaining conditions for the locations of $\omega$-limit sets in coordinate planes. Section 3 contains preliminary remarks. In Section 4, formulas for equilibrium points and LAS conditions for the infection-free equilibrium point $E_0$ are provided. In Section 5 we derive ultimate upper bounds for all state variables; these bounds define the localization polytope containing the attracting set. Section 6 contains main results of this paper: we present the GAS conditions, and, besides, we concern two other issues of ultimate dynamics of (1). Finally, concluding remarks are given in Section 7.

## 2. On the Localization Problem of Compact Invariant Sets

For the reader's convenience, we give reminders on a few helpful notions. We consider a nonlinear system

$$\dot{x} = F(x), \tag{2}$$

where $x \in \mathbf{R}^n$, $F(x) = (F_1(x), \ldots, F_n(x))^T \in C^1(\mathbf{R}^n)$. Let $h(x) \in C^1(\mathbf{R}^n)$ be a function. This function is used in the solution of the localization problem of compact invariant sets, and is called a localizing function. Suppose that the function $h$ is not the first integral of the system (2). By $h|_U$, we denote the restriction of $h$ on a set $U \subset \mathbf{R}^n$.

By $S(h)$ we denote the set $\{x \in \mathbf{R}^n \mid L_F h(x) = 0\}$, where $L_F h(x)$ is the Lie derivative of $h(x)$ with respect to the vector field $F$. Let us define

$$h_{\inf}(U) := \inf\{h(x) \mid x \in U \cap S(h)\}; \quad h_{\sup}(U) := \sup\{h(x) \mid x \in U \cap S(h)\}.$$

**Assertion 1** (see [24]). *For any $h(x) \in C^1(\mathbf{R}^n)$, all compact invariant sets of the system (2) located in $U$ are contained in the set*

$$K(U;h) = \{x \in U \mid h_{\inf}(U) \le h(x) \le h_{\sup}(U)\}$$

*as well.*

## 3. Preliminary Remarks

The system (1) is defined in

$$\mathbf{R}^7_{+,0} = \{x \in \mathbf{R}^7 \mid x_i \ge 0,\ i = \overline{1,7}\}$$

which is the positively invariant domain.

In order to simplify computations, we introduce the following notations:

$$b_1 = a_2(1-u_2), \quad b_2 = a_2(1-u_2)(1-u_4), \quad b_3 = a_7(1+u_3), \quad b_4 = a_3a_4(1-a_{10})(1-u_1),$$
$$c_1 = a_2a_{11}, \quad c_2 = a_3a_4a_{10}, \quad c_3 = a_3a_4,$$

for which we have

$$b_2 \le b_1, \quad c_2 + b_4 \le c_3. \tag{3}$$

Utilizing these notations, we come to the system

$$\begin{cases} \dot{x}_1 = -a_1x_1 - b_1x_1x_2 + b_4x_4; \\ \dot{x}_2 = \frac{a_5}{1+x_1+x_5} - a_6x_2 - b_2x_1x_2 - c_1x_2x_5 + b_3q(x)x_2; \\ \dot{x}_3 = b_2x_1x_2 - (a_6+a_9)x_3; \\ \dot{x}_4 = a_9x_3 - a_4x_4; \\ \dot{x}_5 = c_2x_4 - a_1x_5 - c_1x_2x_5 + c_3x_7; \\ \dot{x}_6 = c_1x_2x_5 - (a_6+a_9)x_6; \\ \dot{x}_7 = a_9x_6 - a_4x_7. \end{cases} \tag{4}$$

We note that (4) is the extension of the four-dimensional system from [3], in which the resistant virus modification is included. The latter system has the form

$$\begin{cases} \dot{x}_1 = -a_1x_1 - a_2(1-u_2)x_1x_2 + a_3a_4(1-u_1)x_4, \\ \dot{x}_2 = \frac{a_5}{1+x_1} - a_2(1-u_2)(1-u_4)x_1x_2 - a_6x_2 + a_7(1+u_3)\left(1 - \frac{x_2+x_3+x_4}{a_8}\right)x_2, \\ \dot{x}_3 = a_2(1-u_2)(1-u_4)x_1x_2 - (a_6+a_9)x_3, \\ \dot{x}_4 = a_9x_3 - a_4x_4, \end{cases}$$

or after using notations introduced above,

$$\begin{cases} \dot{x}_1 = -a_1x_1 - b_1x_1x_2 + b_4x_4, \\ \dot{x}_2 = \frac{a_5}{1+x_1} - b_2x_1x_2 - a_6x_2 + b_3\left(1 - \frac{x_2+x_3+x_4}{a_8}\right)x_2, \\ \dot{x}_3 = b_2x_1x_2 - (a_6+a_9)x_3, \\ \dot{x}_4 = a_9x_3 - a_4x_4. \end{cases} \tag{5}$$

Below by $f$, we denote the vector field corresponding to (4).

Next, we point to several properties of system dynamics of (4).

(1) Any solution of (5) can be extended on $[0,\infty)$, see Section 6.
(2) This system possesses the invariant plane $x_1 = x_3 = x_4 = 0$; this is the case when there are no wild-type HIV particles and no *Th* cells infected by them. The subsystem defined on this plane is explored in Section 7.
(3) Suppose that $a_5$ is a source term for uninfected CD4$^+$ T cells that is zero, the concentration of uninfected Th cells ($x_2$) is zero as well, and between the death rate and growth rate of the uninfected CD4$^+$ T cell population, the following inequalities are fulfilled: $a_6 > a_7$ and $u_3 < a_6a_7^{-1} - 1$. Then the system (4) becomes a linear asymptotically stable system for which free, wild-type HIV particles and all other cell populations vanish after a sufficiently long observation time.

## 4. Equilibrium Points

Firstly, in order to find equilibrium points, we eliminate variables $x_3$, $x_4$, $x_6$, $x_7$ using equations $f_i(x) = 0, i = 3,4,6,7$. As a result, we get the system:

$$\begin{cases} b_1(d_1-1)x_1x_2 - a_1x_1 = 0, \\ \frac{a_5}{1+x_1+x_5} - (a_6-b_3)x_2 - \frac{b_3}{a_8}x_2^2 - x_2(1+d_3x_2)(b_2x_1+c_1x_5) = 0, \\ c_1(d_2-1)x_2x_5 + \frac{c_2b_1d_1}{b_4}x_1x_2 - a_1x_5 = 0, \end{cases} \tag{6}$$

with

$$d_1 = \frac{a_9 b_4 b_2}{b_1 a_4 (a_6 + a_9)}, \quad d_2 = \frac{a_9 c_3}{a_4 (a_6 + a_9)}, \quad d_3 = \frac{b_3 (a_4 + a_9)}{a_4 a_8 (a_6 + a_9)}. \tag{7}$$

Then we come to two cases: (1) $x_1 = 0$; (2) $x_1 \neq 0$. In the first case, we obtain the system

$$\begin{cases} \frac{a_5}{1+x_5} - (a_6 - b_3)x_2 - \frac{b_3}{a_8}x_2^2 - c_1(1 + d_3 x_2)x_2 x_5 = 0, \\ c_1(d_2 - 1)x_2 x_5 - a_1 x_5 = 0. \end{cases}$$

It follows from the second equation that either $x_5 = 0$ or $x_2 = x_{21} = \frac{a_1}{c_1(d_2-1)}$. If $x_5 = 0$, then

$$a_5 - (a_6 - b_3)x_2 - \frac{b_3}{a_8}x_2^2 = 0,$$

and we obtain the equilibrium point

$$E_0 = (0,\ x_{20},\ 0,\ 0,\ 0,\ 0,\ 0),$$

with

$$x_{20} = \frac{a_8(b_3 - a_6) + \sqrt{a_8^2(b_3 - a_6)^2 + 4a_5 b_3 a_8}}{2b_3} > 0.$$

If $x_5 \neq 0$ then $x_2 = x_{21} = \frac{a_1}{c_1(d_2-1)}$ and we get the equation respecting $x_5$:

$$\frac{a_5}{1 + x_5} = (a_6 - b_3)x_{21} + \frac{b_3}{a_8}x_{21}^2 + c_1(1 + d_3 x_{21})x_{21}x_5.$$

Its maximal root is given by

$$x_{50} = \frac{-(d_5 + d_6) + \sqrt{(d_5 - d_6)^2 + 4d_6 a_5}}{2d_6},$$

where

$$d_5 = (a_6 - b_3)x_{21} + \frac{b_3}{a_8}x_{21}^2, \quad d_6 = c_1(1 + d_3 x_{21})x_{21}.$$

We notice that $x_{50} \geq 0$, provided $a_5 \geq d_5$.

As a result, we come to the equilibrium point $E_1$ given by the formula

$$E_1 = \Big(0,\ \frac{a_1}{c_1(d_2 - 1)},\ 0,\ 0,\ x_{50},\ \frac{a_1 x_{50}}{(d_2 - 1)(a_6 + a_9)},\ \frac{a_1 a_9 x_{50}}{a_4(d_2 - 1)(a_6 + a_9)}\Big);$$

$E_1 \in \mathbf{R}^7_{+,0}$ if $d_2 > 1$ and $a_5 > d_5$.

In the second case $x_1 > 0$, we derive that

$$x_2 = x_{22} = \frac{a_1}{b_1(d_1 - 1)}.$$

In that way, we come to the system of equations

$$\begin{cases} \frac{a_5}{1+x_1+x_5} - (a_6 - b_3)x_{22} - \frac{b_3}{a_8}x_{22}^2 - x_{22}(1 + d_3 x_{22})(b_2 x_1 + c_1 x_5) = 0, \\ c_1(d_2 - 1)x_{22}x_5 - a_1 x_5 + \frac{c_2 b_1 d_1}{b_4}x_1 x_{22} = 0 \end{cases}$$

with respect to $x_1$, $x_5$. Eliminating $x_5$

$$x_5 = r_3 x_1, \qquad r_3 = \frac{c_2 b_1 d_1 x_{22}}{b_4(a_1 - c_1(d_2 - 1)x_{22})}$$

we obtain the first equation in the form

$$\frac{a_5}{1+(1+r_3)x_1} = r_4 + r_5 x_1,$$

where

$$r_4 = (a_6 - b_3)x_{22} + \frac{b_3}{a_8}x_{22}^2, \quad r_5 = (b_2 + c_1 r_3)(1 + d_3 x_{22})x_{22}.$$

We come to the equation

$$(1+r_3)r_5 x_1^2 + \big((1+r_3)r_4 + r_5\big)x_1 - (a_5 - r_4) = 0.$$

This equation has the unique positive root of the form

$$x_{10} = \frac{-(1+r_3)r_4 - r_5 + \sqrt{\big((1+r_3)r_4 - r_5\big)^2 + 4(1+r_3)r_5 a_5}}{2(1+r_3)r_5}.$$

This solution gives us the equilibrium point

$$E_2 = \Big(x_{10},\ x_{22},\ \frac{b_2 x_{10} x_{22}}{a_6 + a_9},\ \frac{a_9 b_2 x_{10} x_{22}}{a_4(a_6 + a_9)},\ r_3 x_{10},\ \frac{c_1 r_3 x_{10}}{a_6 + a_9},\ \frac{c_1 a_9 r_3 x_{10}}{a_4(a_6 + a_9)}\Big).$$

The equilibrium point $E_2 \in \mathbf{R}^7_{+,0}$ if conditions

$$d_1 > 1, \quad d_2 < 1 + \frac{a_1}{c_1 x_{22}}, \quad a_5 \geq (a_6 - b_3)x_{22} + \frac{b_3}{a_8}x_{22}^2$$

are fulfilled.

**Example 1.** *Let us select the following set of parameters:*

$$a_1 = a_4 = a_5 = a_6 = a_8 = a_9 = 1, \quad b_1 = b_2 = b_3 = 1, \quad b_4 = 5,$$
$$c_1 = 0.4, \quad c_2 = 1, \quad c_3 = 8.$$

*Then the system (6) has three equilibrium points:*

$$E_0 = (0,\ 1,\ 0,\ 0,\ 0,\ 0,\ 0), \quad E_1 = (0,\ 0.5769,\ 0,\ 0,\ 0.4124,\ 0.03172,\ 0.06344),$$
$$E_2 = (0.01018,\ 0.4286,\ 0.001455,\ 0.002909,\ 1.131,\ 0.06465,\ 0.1293).$$

Now we find the stability condition of $E_0$. The Jacobian matrix taken at $E_0$ has the following form:

$$J_0 = \begin{pmatrix} -(a_1 + b_1 x_{20}) & 0 & 0 & b_4 & 0 & 0 & 0 \\ * & (b_3 - a_6) - \frac{2b_3}{a_8}x_{20} & * & * & * & * & * \\ b_2 x_{20} & 0 & -(a_6 + a_9) & 0 & 0 & 0 & 0 \\ 0 & 0 & a_9 & -a_4 & 0 & 0 & 0 \\ 0 & 0 & 0 & c_2 & -(a_1 + c_1 x_{20}) & 0 & c_3 \\ 0 & 0 & 0 & 0 & c_1 x_{20} & -(a_6 + a_9) & 0 \\ 0 & 0 & 0 & 0 & 0 & a_9 & -a_4 \end{pmatrix}$$

where by $*$ we denote non-essential elements of $J_0$.

The spectrum of the matrix $J_0$ contains one evident eigenvalue $\lambda_1 = (b_3 - a_6) - \frac{2b_3}{a_8}x_{20} < 0$ and eigenvalues of the matrix $\hat{J}_0$ which has the block-triangular form:

$$\hat{J}_0 = \begin{pmatrix} -(a_1 + b_1x_{20}) & 0 & b_4 & 0 & 0 & 0 \\ b_2x_{20} & -(a_6 + a_9) & 0 & 0 & 0 & 0 \\ 0 & a_9 & -a_4 & 0 & 0 & 0 \\ 0 & 0 & c_2 & -(a_1 + c_1x_{20}) & 0 & c_3 \\ 0 & 0 & 0 & c_1x_{20} & -(a_6 + a_9) & 0 \\ 0 & 0 & 0 & 0 & a_9 & -a_4 \end{pmatrix}.$$

Therefore, the spectrum of $\hat{J}_0$ is the union of spectra of matrices

$$A_1 = \begin{pmatrix} -(a_1 + b_1x_{20}) & 0 & b_4 \\ b_2x_{20} & -(a_6 + a_9) & 0 \\ 0 & a_9 & -a_4 \end{pmatrix}, \quad A_2 = \begin{pmatrix} -(a_1 + c_1x_{20}) & 0 & c_3 \\ c_1x_{20} & -(a_6 + a_9) & 0 \\ 0 & a_9 & -a_4 \end{pmatrix}.$$

Both matrices $A_1$ and $A_2$ are matrices of the following special type

$$A = \begin{pmatrix} -\alpha_1 & 0 & \beta_3 \\ \beta_1 & -\alpha_2 & 0 \\ 0 & \beta_2 & -\alpha_3 \end{pmatrix},$$

where all $\alpha_i$ and $\beta_i$ are positive. The characteristic polynomial (with an opposite sign) of the matrix $A$ has the form

$$\xi_A(t) = (t + \alpha_1)(t + \alpha_2)(t + \alpha_3) - \beta_1\beta_2\beta_3.$$

One can show (for instance, using the Hurwitz criterion) that roots of $\xi_A(t)$ are negative if, and only if

$$\alpha_1\alpha_2\alpha_3 > \beta_1\beta_2\beta_3. \tag{8}$$

Hence, the condition (8) is the stability condition of the matrix $A$.

Coming back to matrices $A_1$, $A_2$ we write the stability condition of $E_0$ in the form:

$$a_4(a_6 + a_9)(a_1 + b_1x_{20}) > b_2b_4a_9x_{20}, \quad a_4(a_6 + a_9)(a_1 + c_1x_{20}) > c_1c_3a_9x_{20},$$

or in notations (7) we obtain the condition

$$d_1 < 1 + \frac{a_1}{b_1x_{20}}, \quad d_2 < 1 + \frac{a_1}{c_1x_{20}}. \tag{9}$$

In particular, $E_0$ is LAS with $d_1 < 1$, $d_2 < 1$, which means that $E_1$, $E_2$ are contained in the half-space $x_2 < 0$.

## 5. Ultimate Upper Bounds

In this section, we derive upper bounds for the dynamics of the system (4) in non-negative orthant. Upper bounds give us ultimate maximal values for all cell populations involved into the model. We construct a polytope containing all compact invariant sets in $\mathbf{R}^7_{+,0}$. This polytope is a positively invariant set and, therefore, limits biologically significant bounded dynamics. Moreover, the polytope turns out to be globally attractive, so all semi-trajectories are bounded as $t \to +\infty$, and their $\omega$-limit sets are contained in the polytope.

Now we demonstrate that this polytope can be constructed by using linear localizing functions.

1. Firstly, we apply the function $h_1(x) = x_2$. Then

$$L_fh_1 = \frac{a_5}{1 + x_1 + x_5} - a_6x_2 - b_2x_1x_2 - c_1x_2x_5 + b_3x_2\Big(1 - \frac{x_2 + x_3 + x_4 + x_6 + x_7}{a_8}\Big)$$

(we recall that $L_f h$ is the Lie derivative of $h$ with respect to $f$) and the set $S(h_1)$ is defined by

$$\frac{a_5}{1+x_1+x_5} - a_6x_2 - b_2x_1x_2 - c_1x_2x_5 + b_3x_2\Big(1 - \frac{x_2+x_3+x_4+x_6+x_7}{a_8}\Big) = 0.$$

The last formula can be rewritten as

$$\frac{a_5}{1+x_1+x_5} - q_0x_2 - \frac{b_3}{a_8}x_2^2 = 0, \tag{10}$$

where

$$q_0 = (a_6 - b_3) + b_2x_1 + c_1x_5 + \frac{b_3}{a_8}(x_3+x_4+x_6+x_7).$$

The Equation (10) is quadratic, respecting $x_2$, and its larger root increases while $q_0$ decreases and the left summand increases. Thus,

$$h_{1,\sup} = x_{2,\max} = x_{20} = \frac{a_8(b_3-a_6) + \sqrt{a_8^2(b_3-a_6)^2 + 4a_5b_3a_8}}{2b_3}. \tag{11}$$

The value of $h_{1,\inf}$ is reached at the maximum values of the variables $x_1$, $x_3$, $x_4$, $x_5$, $x_6$, $x_7$. We see that $h_{1,\inf} = 0$. Thus, we get the localizing set $\{x \in \mathbf{R}^n \mid 0 \le x_2 \le x_{2,\max}\}$.

2. Let us take the next function $h_2(x) = x_2 + x_3$. Then

$$L_f h_2 = \frac{a_5}{1+x_1+x_5} - a_6x_2 - c_1x_2x_5 + b_3x_2\Big(1 - \frac{x_2+x_3+x_4+x_6+x_7}{a_8}\Big) - (a_6+a_9)x_3.$$

Applying the change $x_3 = h_2 - x_2$ in the equation $L_f h_2 = 0$, describing the set $S(h_1)$, we get that

$$\frac{a_5}{1+x_1+x_5} - (a_6-b_3)x_2 - c_1x_2x_5 - \frac{b_3}{a_8}x_2(x_4+x_6+x_7) - \frac{b_3}{a_8}x_2h_2 - (a_6+a_9)(h_2-x_2) = 0.$$

Solving this linear equation respecting $h_2$, we obtain that

$$h_2 = \frac{\frac{a_5}{1+x_1+x_5} - q_2x_2}{a_6+a_9+r_3x_2}, \tag{12}$$

with

$$q_2 = c_1x_5 + r_3(x_4+x_6+x_7) - b_3 - a_9, \quad r_3 = \frac{b_3}{a_8}.$$

It follows from (12) that $h_{2,\inf} = 0$ and

$$h_{2,\sup} = \max_{x_2} \frac{a_5 + (b_3+a_9)x_2}{a_6+a_9+r_3x_2}. \tag{13}$$

The fractional linear function (13) is monotonic within $(0,\infty)$ and we derive that

$$h_{2,\sup} = \max\Big\{\frac{a_5}{a_6+a_9}, \frac{(b_3+a_9)a_8}{b_3}\Big\}.$$

This estimate can be improved if we use the value $x_{2\max}$ in (13) instead of $x_2 \to +\infty$.

Thus, we get the localization set $\{x \in \mathbf{R}^n \mid x_2 + x_3 \le h_{2,\sup}\}$. Therefore, we come to the estimate

$$x_3 \le x_{3,\max} = h_{2,\sup}.$$

3. Let us apply the localization function $h_3(x) = x_4$. In this case, the set $S(h_3)$ is given by

$$a_9x_3 - a_4x_4 = 0,$$

that entails

$$h_3 = x_4 = \frac{a_9}{a_4} x_3.$$

Hence, we obtain the localization set defined by

$$0 \le x_4 \le x_{4,\max} = \frac{a_9}{a_4} x_{3,\max}.$$

4. Let us employ the localization function $h_4(x) = x_1$. The set $S(h_4)$ is defined by

$$x_1 = \frac{b_4 x_4}{a_1 + b_1 x_2}.$$

Thus, we obtain the localization set defined by

$$0 \le x_1 \le x_{1,\max} = \frac{b_4}{a_1} x_{4,\max} = \frac{b_4 a_9}{a_1 a_4} h_{2,\sup}.$$

5. Next, let us utilize the localization function $h_5(x) = x_2 + x_6$. Then

$$L_f h_5 = \frac{a_5}{1 + x_1 + x_5} - a_6 x_2 - b_2 x_1 x_2 + b_3 x_2 \Big(1 - \frac{x_2 + x_3 + x_4 + x_6 + x_7}{a_8}\Big) - (a_6 + a_9) x_6.$$

The set $S(h_5)$ is defined by

$$\frac{a_5}{1 + x_1 + x_5} - q_3 x_2 - h_5(a_6 + a_9 + r_3 x_2) = 0,$$

where

$$q_3 = b_2 x_1 + r_3(x_3 + x_4 + x_7) - b_3 - a_9.$$

Consequently, we have on $S(h_5)$ that

$$h_5 = \frac{\frac{a_5}{1+x_1+x_5} - q_3 x_2}{a_6 + a_9 + r_3 x_2}.$$

As a result, we derive that

$$h_{5,\inf} = 0, \quad h_{5,\sup} = \max_{x_2} \frac{a_5 + (b_3 + a_9) x_2}{a_6 + a_9 + r_3 x_2} = \max\Big\{ \frac{a_5}{a_6 + a_9}, \frac{(b_3 + a_9) a_8}{b_3} \Big\} = h_{2,\sup}.$$

Therefore, we have the localization set $\{x \in \mathbf{R}^n \mid x_2 + x_6 \le h_{5,\sup}\}$ which provides the bound for $x_6$:

$$x_6 \le x_{6,\max} = h_{5,\sup}.$$

6. Now we take the localization function $h_6(x) = x_7$. Then the set $S(h_6)$ is given by

$$a_9 x_6 - a_4 x_7 = 0.$$

Taking into account the bound for $x_6$, we get that

$$x_7 \le x_{7,\max} = \frac{a_9}{a_4} h_{5,\sup}.$$

7. Now we take the localization function $h_7(x) = x_5$. The set $S(h_7)$ is defined by the equation

$$h_7 = x_5 = \frac{c_2 x_4 + c_3 x_7}{a_1 + c_1 x_2}.$$

Using bounds $x_{4,\max}$; $x_{7,\max}$, we get the localizing set

$$x_5 \le x_{5,\max} = \frac{c_2}{a_1} x_{4,\max} + \frac{c_3}{a_1} x_{7,\max} = \frac{a_9 c_2}{a_4 a_1} h_{2,\sup} + \frac{a_9 c_3}{a_4 a_1} h_{5,\sup}.$$

**Remark 1.** *The formula $x_{2\max} = x_{20}$ provides the best upper bound for the concentration of uninfected Th cells. Indeed, it was established that $x_{20} = h_{1,\sup}$ and, at the same time, $x_{20}$ is the coordinate of an equilibrium point. We see that the bound $h_{1,\sup}$ is not refinable.*

To summarize all these results, we arrive at:

**Theorem 1.** *All compact invariant sets of the system (4) located in $\mathbf{R}^7_{+,0}$ are contained in the polytope*

$$\Pi = [0,\, x_{1,\max}] \times [0,\, x_{2,\max}] \times [0,\, x_{3,\max}] \times [0,\, x_{4,\max}] \times [0,\, x_{5,\max}] \times [0,\, x_{6,\max}] \times [0,\, x_{7,\max}],$$

*as well. Here,*

$$x_{2,\max} = \frac{a_8(b_3 - a_6) + \sqrt{a_8^2(b_3 - a_6)^2 + 4a_5 b_3 a_8}}{2b_3},$$

$$x_{3,\max} = x_{6,\max} = \max\left\{\frac{a_5}{a_6 + a_9}, \frac{(b_3 + a_9)a_8}{b_3}\right\}, \quad x_{1,\max} = \frac{b_4 a_9}{a_1 a_4} x_{3,\max},$$

$$x_{4,\max} = \frac{a_9}{a_4} x_{3,\max}, \quad x_{5,\max} = \frac{c_2 a_9}{a_4 a_1} x_{3,\max} + \frac{c_3 a_9}{a_4 a_1} x_{6,\max}, \quad x_{7,\max} = \frac{a_9}{a_4} x_{6,\max}.$$

**Remark 2.** *Based on this theorem, we obtain the lower bound for $x_2$:*

$$x_{2,\min} = \frac{1}{2b_3}\left(-a_8 q_{\max} + \sqrt{q_{\max}^2 a_8^2 + \frac{4b_3 a_5 a_8}{1 + x_{1,\max} + x_{5,\max}}}\right)$$

*with*

$$q_{\max} = a_6 - b_3 + b_2 x_{1,\max} + c_1 x_{5,\max} + \frac{b_3}{a_8}\left(x_{3,\max} + x_{4,\max} + x_{6,\max} + x_{7,\max}\right).$$

## 6. On the Location of $\omega$-Limit Sets

It follows from Theorem 1 that all $\omega$-limit sets are located in $\Pi$. Generally speaking, this polytope is not a positive invariant domain. Let us take a smaller polytope $\Pi_0$ defined by

$$\begin{cases} 0 \le x_1 \le x_{1,\max}, \\ 0 \le x_2 \le x_{2,\max}, \\ 0 \le x_2 + x_3 \le x_{3,\max}, \\ 0 \le x_4 \le x_{4,\max}, \\ 0 \le x_5 \le x_{5,\max}, \\ 0 \le x_2 + x_6 \le x_{6,\max}, \\ 0 \le x_7 \le x_{7,\max}. \end{cases}$$

We recall that this polytope is the localization set obtained as a result of applying the iterative procedure using localizing functions $h_1, \ldots, h_7$. Herewith, we note that $L_f h_i(x) < 0$, with $x$ taken from the domain $h_i(x) > h_{i,\sup}$ and other inequalities are satisfied. Indeed, $L_f h_i(x)$ in this domain keeps its sign, and one can verify that for large values of $h_i(x)$, the Lie derivative $L_f h_i(x)$ is negative. This conclusion means that the vector field $f$ is directed inward $\Pi_0$ on the boundary of $\Pi_0$, and this polytope is positively invariant.

Actually, one can prove a stronger assertion. Arguing as above, we conclude that for any $C > 0$, the polytope $\Pi_0(C)$ defined by inequalities

$$\begin{cases} 0 \le x_1 \le x_{1,\max} + C, \\ 0 \le x_2 \le x_{2,\max} + C, \\ 0 \le x_2 + x_3 \le x_{3,\max} + C, \\ 0 \le x_4 \le x_{4,\max} + C, \\ 0 \le x_5 \le x_{5,\max} + C, \\ 0 \le x_2 + x_6 \le x_{6,\max} + C, \\ 0 \le x_7 \le x_{7,\max} + C, \end{cases}$$

is positively invariant. It follows from this fact that a trajectory exiting a point $M_0 \in \mathbf{R}^7_{+,0}$, remains in the polytope $\Pi_0(C)$ for sufficiently large $C$. However, $\Pi_0(C)$ is a compact set. Therefore, the $\omega$-limit set of the trajectory is a compact set belonging to $\Pi_0$. We conclude that $\Pi_0$ is a globally attracting set.

**Theorem 2.** *If conditions (9) hold for the system (4), then the equilibrium point $E_0$ attracts all trajectories in $\mathbf{R}^7_{+,0}$.*

**Proof.** Let us take the function

$$h_8(x) = \eta_1 x_1 + \eta_2 x_3 + x_4 + \eta_3 x_5 + \eta_4 x_6 + \eta_5 x_7$$

with positive parameters $\eta_i$, $i = 1, \ldots, 5$. Then we compute that

$$\begin{aligned} L_f h_8(x) = {} & [-\eta_1 a_1 - \eta_1 b_1 x_2 + \eta_2 b_2 x_2] x_1 + [-\eta_2 (a_6 + a_9) + a_9] x_3 + \\ & + [\eta_1 b_4 - a_4 + \eta_3 c_2] x_4 + [-\eta_3 a_1 - \eta_3 c_1 x_2 + \eta_4 c_1 x_2] x_5 + \\ & + [-\eta_4 (a_6 + a_9) + \eta_5 a_9] x_6 + [\eta_3 c_3 - \eta_5 a_4] x_7. \end{aligned}$$

The condition $L_f h_8(x) \le 0$ holds if the system of inequalities

$$\begin{cases} \eta_2 b_2 x_2 < \eta_1 (a_1 + b_1 x_2), \\ \eta_2 (a_6 + a_9) > a_9, \\ \eta_1 b_4 + \eta_3 c_2 < a_4, \\ \eta_4 c_1 x_2 < \eta_3 (a_1 + c_1 x_2), \\ \eta_5 a_9 < \eta_4 (a_6 + a_9), \\ \eta_3 c_3 < \eta_5 a_4 \end{cases} \tag{14}$$

holds in this polytope, that is, under the condition $0 \le x_2 \le x_{2,\max} = x_{20}$.

Excluding parameters $\eta_2$, $\eta_5$, we come to the system

$$\begin{cases} \dfrac{a_9}{a_6 + a_9} < \eta_1 \dfrac{b_1}{b_2} \left(1 + \dfrac{a_1}{b_1 x_{20}}\right), \\ \eta_1 b_4 + \eta_3 c_2 < a_4, \\ \eta_4 c_1 x_2 < \eta_3 (a_1 + c_1 x_2), \\ \eta_3 \dfrac{c_3}{a_4} < \eta_4 \dfrac{a_6 + a_9}{a_9}. \end{cases} \tag{15}$$

Next, we exclude $\eta_4$:

$$\begin{cases} \dfrac{a_9}{a_6 + a_9} < \eta_1 \dfrac{b_1}{b_2} \left(1 + \dfrac{a_1}{b_1 x_{20}}\right), \\ \eta_1 b_4 + \eta_3 c_2 < a_4, \\ \dfrac{a_9 c_3}{a_4 (a_6 + a_9)} < \left(1 + \dfrac{a_1}{c_1 x_{20}}\right). \end{cases} \tag{16}$$

Finally, we come to the inequalities

$$\frac{a_9}{a_6+a_9} < \frac{a_4}{b_4}\frac{b_1}{b_2}\Big(1+\frac{a_1}{b_1x_{20}}\Big), \quad \frac{a_9c_3}{a_4(a_6+a_9)} < 1+\frac{a_1}{c_1x_{20}},$$

which are equivalent to inequalities (9).

Thus, if inequalities (9) hold, then the system (14) has a solution $\eta_i^*$, $i = 1, \ldots, 5$. Taking these values, we have $L_f h_8(x) \le 0$ in polytope $\Pi_1$ and $h_8(x) = 0$ if

$$x_1 = x_3 = x_4 = x_5 = x_6 = x_7 = 0,$$

that is, on the axis $Ox_2$. The unique compact invariant contained in the half axis $Ox_2$ is the equilibrium point $E_0$. Now our assertion is followed from the LaSalle theorem. □

**Remark 3.**

1. *Conditions of Theorem 2 do not depend on controls $u_3$ and $u_4$.*
2. *If the condition $d_2 < 1$ holds, then Theorem 2 is true. Indeed, taking into account (3), we get that this condition implies the condition $d_1 < 1$ and, consequently, conditions (9). Note that the condition $d_2 < 1$ does not depend on controls, that is, it is satisfied with zero values of controls.*

**Theorem 3.** *Suppose that*

$$d_1 < 1 + \frac{a_1}{b_1 x_{2,\max}}. \tag{17}$$

*Then all $\omega$-limit sets in $\mathbf{R}^7_{+,0}$ are located in the invariant plane $x_1 = x_3 = x_4 = 0$.*

**Proof.** We take $h_{10} = \eta_1 x_1 + \eta_2 x_3 + x_4$. Then

$$L_f h_{10} = (-\eta_1 a_1 - \eta_1 b_1 x_2 + \eta_2 b_2 x_2)x_1 + (-\eta_2(a_6+a_9)+a_9)x_3 + (\eta_1 b_4 - a_4)x_4.$$

We obtain $L_f h_{10} \le 0$ in $\Pi_1$ if the following conditions hold:

$$(\eta_2 b_2 - \eta_1 b_1)x_2 < \eta_1 a_1, \quad \eta_2 > \frac{a_9}{a_6+a_9}, \quad \eta_1 < \frac{a_4}{b_4}.$$

These inequalities have a solution with respect to $\eta_1$, $\eta_2$ if the following condition holds:

$$\frac{a_9}{a_6+a_9} < \frac{a_4 b_1}{b_2 b_4}\Big(1+\frac{a_1}{b_1 x_{2,\max}}\Big).$$

Since the last inequality is satisfied in virtue of (17), then for the corresponding choice of parameters $\eta_1$, $\eta_2$, we have that $L_f h_{10} \le 0$ in $\Pi_1$ and $L_f h_{10} = 0$ if $x_1 = x_3 = x_4 = 0$. Similarly, arguing as in the previous result, we get the desirable conclusion. □

**Theorem 4.** *If $d_2 > 1$, then*

$$0 < x_{2,\min} \le \frac{a_1}{c_2(d_2-1)}. \tag{18}$$

**Proof.** Let us suppose that

$$x_{2,\min} > \frac{a_1}{c_2(d_2-1)} \tag{19}$$

and take the localizing function $h_9 = \eta_1 x_4 + \eta_2 x_5 + \eta_3 x_6 + \eta_4 x_7$ with some positive parameters $\eta_i$, $i = 1, 2, 3, 4$. We calculate that

$$\begin{aligned} L_f h_9 \;=\; & \eta_1 b_4 x_3 + x_4[-\eta_1 a_4 + \eta_2 c_3)] + x_5(-\eta_2 a_1 - \eta_2 c_2 x_2 + \eta_3 c_2 x_2) \\ & + x_6(\eta_4 a_9 - \eta_3(a_6+a_9)) + x_7(\eta_2 c_4 - \eta_4 a_4) \end{aligned}$$

and estimate this expression within the positively invariant set $\Pi_1 = \{x_2 \geq x_{2\min}\} \cap \Pi_0$. In order to have $L_f h_6 \geq 0$ in $\Pi_1$, we should claim that

$$\begin{aligned} &\eta_1 > 0; \\ &-\eta_1 a_4 + \eta_2 c_3 > 0; \\ &\eta_3 c_2 x_{2,\min} > \eta_2 (a_1 + c_2 x_{2,\min}); \\ &\eta_4 a_9 - \eta_3 (a_6 + a_9) > 0; \\ &\eta_2 c_4 - \eta_4 a_4 > 0. \end{aligned} \tag{20}$$

Conditions (20) are met with the appropriate choice of $\eta_i$ if the condition (19) is true. Therefore, choosing the proper parameters $\eta_i$, we have that $L_f h_9 \geq 0$ within $\Pi_1$ and $L_f h_6 = 0$ if $x_3 = x_4 = x_5 = x_6 = x_7 = 0$ therein. Next, all trajectories eventually go into $\Pi_1$ and remain there. Utilizing the LaSalle theorem with respect to the domain $\Pi_1$, we get that all $\omega$-limit sets of the system trajectories lie in the plane $x_1 x_2$.

However, there is only one compact invariant set in the plane $x_1 x_2$—the equilibrium point $E_0$. We conclude that this point is GAS. However, this condition contradicts the condition (9) of LAS of $E_0$. This means that the assumption (19) is not true, and we have the condition (18). □

## 7. Concluding Remarks

In this work, we carry out an analysis of ultimate dynamics of the seven-order Stengel model as mentioned below:

- Calculate equilibrium points;
- Present local stability conditions;
- Find ultimate upper bounds for all variables of this model that define the polytope containing all $\omega$-limit sets.

Our principal contribution is the exploration of wild-type and the possibility of mutant HIV particle eradication, as well as infected cells in the model (1) at the early stage of HIV infection provided the treatment affects only wild-type HIV viruses.

In particular, we establish that the LAS condition to the infection-free equilibrium point $E_0$ implies the GAS condition to $E_0$. These conditions do not depend on control parameters $u_3$, $u_4$ and under the additional assumption that $d_2 < 1$, the GAS conditions to $E_0$ do not depend on controls $u_i$, $i = 1, \ldots, 4$, thus, they can be chosen as equal to zero.

To summarize, the system (4) may possess complex behaviour only when conditions (9) are violated. In this case, the location of the attracting set is described in Theorem 1. However, analysis of other features of ultimate dynamics of (4) remains a very difficult task.

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## References

1. Perelson, A.S.; Kirschner, D.E.; De Boer, R. Dynamics of HIV infection of $CD4^+$ T cells. *Math. Biosci.* **1993**, *114*, 81–125. [CrossRef]
2. Perelson, A.S.; Nelson, P.W. Mathematical Analysis of HIV-1 Dynamics in Vivo. *SIAM Rev.* **1999**, *41*, 3–44. [CrossRef]
3. Kirschner, D.; Lenhart, S.; Serbin, S. Optimal control of the chemotherapy of HIV. *J. Math. Biol.* **1997**, *35*, 775–792. [CrossRef] [PubMed]
4. De Leenheer, P.; Smith, H.L. Virus dynamics: A global analysis. *SIAM J. Appl. Math.* **2003**, *63*, 1313–1327.

5. Nowak, M.; May, R.M. *Virus Dynamics: Mathematical Principles of Immunology and Virology*; Oxford University Press: Oxford, UK, 2000.
6. Dehghan, M.; Nasri, M.; Razvan, M.R. Global stability of a deterministic model for HIV infection in vivo. *Chaos Solitons Fractals* **2007**, *34*, 1225–1238. [CrossRef]
7. Hadjiandreou, M.; Conejeros, R.; Vassiliadis, V.S. Towards a long-term model construction for the dynamic simulation of HIV infection. *Math. Biosci. Eng.* **2007**, *4*, 489–504. [PubMed]
8. Elaiw, A.M. Global properties of a class of HIV models. *Nonlinear Anal. Real World Appl.* **2010**, *11*, 2253–2263. [CrossRef]
9. Hernandez-Vargas, E.A.; Middleton, R.H. Modeling the three stages in HIV infection. *J. Theor. Biol.* **2013**, *320*, 33–40. [CrossRef] [PubMed]
10. Korobeinikov, A. Global properties of basic virus dynamics models. *Bull. Math. Biol.* **2004**, *66*, 879–883. [CrossRef]
11. Song, X.; Neumann, A.U. Global stability and periodic solution of the viral dynamics. *J. Math. Anal. Appl.* **2007**, *329*, 281–297. [CrossRef]
12. Li, M.Y.; Wang, L. Backward bifurcation in a mathematical model for HIV infection in vivo with anti-retroviral treatment. *Nonlinear Anal. Real World Appl.* **2014**, *17*, 147–160. [CrossRef]
13. Luo, J.; Wang, W.; Chen, H.; Fu, R. Bifurcations of a mathematical model for HIV dynamics. *J. Math. Anal. Appl.* **2016**, *434*, 837–857 [CrossRef]
14. Wang, X.; Liu, X.; Xie, W.C.; Xu, W.; Xu, Y. Global stability and persistence of HIV models with switching parameters and pulse control. *Math. Comput. Simul.* **2016**, *123*, 53–67. [CrossRef]
15. Stengel, R.F. Mutation and control of the human immunodeficiency virus. In Proceedings of the 13th Yale Workshop on Adaptive and Learning Systems, New Haven, CT, USA, 30 May–1 June 2005.
16. Stengel, R.F. Mutation and control of the human immunodeficiency virus. *Math. Biosci.* **2008**, *213*, 93–102. [CrossRef]
17. Vergu, E.; Mallet, A.; Golmard, J. A modeling approach to the impact of HIV mutations on the immune system. *Comput. Biol. Med.* **2005**, *35*, 1–24. [CrossRef]
18. Alizon, S.; Magnus, C. Modelling the course of an HIV infection: Insights from ecology and evolution. *Viruses* **2012**, *4*, 1984–2013. [CrossRef] [PubMed]
19. Pankavich, S. The effects of latent infection on the dynamics of HIV. *Differ. Equ. Dyn. Syst.* **2016**, *24*, 281–303. [CrossRef]
20. Pankavich, S.; Shutt, D. An in-host model of HIV incorporating latent infection and viral mutation. *arXiv* **2015**, arXiv:1508.07616.
21. Hattaf, K.; Dutta, H. Modeling the dynamics of viral infections in presence of latently infected cells. *Chaos Solitons Fractals* **2020**, *136*, 109916. [CrossRef] [PubMed]
22. Hadjiandreou, M.M.; Conejeros, R.; Wilson, I. HIV treatment planning on a case-by-case basis. *Int. J. Biol. Life Sci.* **2011**, *7*, 148–157
23. Douek, D.C.; Picker, L.J.; Koup, R.A. T cell dynamics in HIV-1 infection. *Annu. Rev. Immunol.* **2003**, *21*, 265–304. [CrossRef] [PubMed]
24. Krishchenko, A.P. Localization of invariant compact sets of dynamical systems. *Differ. Equ.* **2005**, *41*, 1669–1676. [CrossRef]
25. Krishchenko, A.P.; Starkov, K.E. Localization of compact invariant sets of the Lorenz system. *Phys. Lett. A* **2006**, *353*, 383–388. [CrossRef]
26. Starkov, K.E. Unbounded dynamics and compact invariant sets of one Hamiltonian system defined by the minimally coupled field. *Phys. Lett. A* **2015**, *379*, 1012–1016. [CrossRef]
27. Starkov, K.E.; Krishchenko, A.P. Ultimate dynamics of the Kirschner–Panetta model: Tumor eradication and related problems. *Phys. Lett. A.* **2017**, *381*, 3409–3416. [CrossRef]
28. Starkov, K.E. On dynamic tumor eradication conditions under combined chemical/anti-angiogenic therapies. *Phys. Lett. A* **2018**, *382*, 387–393. [CrossRef]
29. Kanatnikov, A.N. Localization of invariant compact sets in differential inclusions. *Differ. Equ.* **2015**, *51*, 1425–1431. [CrossRef]