Analysis of HIV mutation dynamics for a linear mutation tree

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Abstract—This work is focused on modelling HIV mutation and drug resistance. We develop a technique to study viral dynamics in a system of $m$ viral strains including mutation between the different strains. Stability analysis of the nonlinear dynamics involving the free virus and its host cell is provided. For the class of model considered, with “low” mutation rate, we analytically determine all possible equilibria, their local stability and positivity properties. Numerical results show that the model describes the ability of HIV to mutate into drug-resistant variants resulting from its replication process.

I. INTRODUCTION

Among the different types of cells that help to protect our body from infections, Cluster of Differentiation Antigen 4 (CD4) is used as a host by retrovirus Human Immunodeficiency Virus (HIV) to replicate itself. HIV is considered an infection of the immune system since this virus infects and damages CD4 during the viral replication process summarized in the sequel.

The inner-core of HIV (figure 1) is protected by a membrane that includes several receptors used by HIV to attach itself to its host cell before entering to it. The viral core shelters the enzymes Reverse Transcriptase (RT), Integrase (IN) and Protease (PR) required during the HIV replication.

The genetic code of HIV is stored as two identical copies of single-stranded Ribonucleic acid (RNA). To establish infection, the free virus attaches to its host cell by interaction between molecules gp120 on the surface of the virus, CD4 and co-receptor. Following attachment, viral envelope and host cell membrane fuse together to give entry to HIV.

Once HIV is released into the host cell, RT makes a Deoxyribonucleic acid (DNA) copy of the viral RNA genome, which is inserted into the host cell chromosome by IN. During this transcription the provirus may remain dormant and produce few or no new DNA copies, because the infected cells producing new viruses are destroyed either by the immune system or by natural death [1]. When activated, the provirus uses RNA polymerase to encode itself inside a messenger mRNA and create new proteins that are broken by PR enzyme to form the core of the new virus, which is then released by a budding process to infect other CD4 cells.

This work extends a model of HIV infection developed in [2] by describing the relation between different types of HIV strains (Section II) resulting from the viral replication process briefly introduced. Section III considers mutations between strains. Stability analysis provides information related to fitness of resistance mutations (Section IV).

II. MULTI-STRAIN MODEL

We consider the following simplified multi-strain ($m$ strain) model that has been formulated in [3] to study the virus dynamics.

$$
\begin{align*}
\dot{V} &= s_T - d_T T - \sum_{i=1}^{m} r_i \\
\dot{T}_i &= r_i - d_{T_i} T_i, \quad i = 1, \ldots, m \\
\dot{V}_i &= p_i T_i^* - d_{V_i} V_i, \quad i = 1, \ldots, m
\end{align*}
$$

where $r \in \mathbb{R}^m = [r_1, r_2, \ldots, r_m]^T$, with $r_i = T \beta_i V_i$, $i = 1, \ldots, m$ corresponding to infection rates by HIV-1 and mutant type viruses to infected cells. $T$ denotes concentration of uninfected target cells (CD4$^+$ T cells). $T_i^*$, $i = 1, \ldots, m$ denotes the concentration of T cells infected by the viral strain, $V_i$, $p_i T_i^*$, and, $d_{V_i} V_i$, denote viral replication and death respectively. Therefore, there are $m$ virus variants in (1). $\beta_i$ represents the rates at which viral variants infect cells, while $p_i$ denotes the rates of virus production by infected cells.

Uninfected cells are produced by the thymus at rate, $s_T$. Uninfected cells, free virus and infected cells die at rates $d_T$, $d_{T_i}$ and $d_{V_i}$ respectively.

A. Viral infection dynamics without mutation

The mathematical analysis in the sequel is intended to investigate the relation between the different HIV strains without the presence of HIV mutants in (1). That model is extended later in section III to account for mutations between the different strains. We look for the existence of possible equilibria and examine their local stability properties. Similar work involving dynamic models of HIV infection with no mutation is discussed in [4] from a theoretical point of view. The technique developed hereafter is based on the prior work.
B. Stability analysis without mutation

[2] and applied to (1). Stability conditions are determined by evaluating the Jacobian matrix [5] at each equilibrium of (1) in its compact form

\[ \frac{dx}{dt} = Ax + Er + Fs_T \]  

(2)

where \( x \in \mathbb{R}^n = [T, T_1, T_2, \ldots , T_m, V_1, \ldots , V_m]^T \) and \( n = 2m + 1 \) are state variables of (26).

The matrix \( A \) is given by

\[ A = \begin{pmatrix} -d_T & 0_{1 \times m} & 0_{1 \times m} \\ 0_{m \times 1} & -d_T I_{m \times m} & 0_{m \times m} \\ 0_{m \times 1} & diag \{ p_i \} & -d_V I_{m \times m} \end{pmatrix} \]  

(3)

where \( I \) is an identity matrix. The matrix \( E \) has as structure

\[ E \triangleq \begin{bmatrix} -K_{1 \times m} \\ I_{m \times m} \\ 0_{m \times m} \end{bmatrix} \]  

(4)

where \( K = \begin{bmatrix} 1 & 1 & \cdots & 1 \end{bmatrix} \).

The term \( Fs_T \) represents the generation rate of target \( T \) cells produced by the thymus, with \( F \) given by

\[ F = \begin{bmatrix} 1 & 0 & 0 & \cdots & 0 \end{bmatrix}^T. \]  

(5)

Let \( r \in \mathbb{R}^m \) be expressed as follows

\[ r = (F^T x) (W^T x). \]  

(6)

where \( W^T = \begin{bmatrix} 0_{m \times 1} & 0_{m \times m} & diag \{ \beta_i \} \end{bmatrix} \).

From (2) and (6) \( xeq, req \) is an equilibrium point iff:

\[ 0_{(2m+1) \times 1} = Ax + Er + Fs_T \]  

(7)

where the equilibrium is defined as

\[ req \triangleq (F^T xe) (W^T xe). \]  

(8)

**Lemma 1**

\[ F^T xeq = \frac{1}{dt} (-K req + s_T). \]  

(9)

**Lemma 2**

\[ W^T xeq = -\Gamma req \]  

where \( \Gamma \in \mathbb{R}^{m \times m} \) is

\[ \Gamma = -\frac{1}{dt \cdot d_V} diag \{ \beta_i \} diag \{ p_i \} = W^T A^{-1} E. \]  

See proofs in the appendix.

**B. Stability analysis without mutation**

One solution to (45) is obtained by trivial solution \( req = 0 \)

\[ xe = -A^{-1} F s_T = \frac{s_T}{dt} F \]  

which is checked by setting (1) to zero to give rise to

\[ V_i \left( T \beta_i - d_T \frac{dv}{p_i} \right) = 0 \Rightarrow V_i = 0, \quad i = 1, \ldots , m \]  

(10)

corresponding to the uninfected steady state

\[ E_{\text{uninfected}} = \left( \frac{s_T}{dt}, 0, 0, \ldots , 0 \right) \]  

(11)

which means that there is no virus inside the host cell.

All other equilibria can be derived from Lemmas 1 and 2 (45) when \( req \neq 0 \) as follows. In this case \( \Gamma \) as defined in Lemma 2 is:

\[ \Gamma_{m \times m} = \begin{bmatrix} \beta_i p_i \frac{d_T \cdot d_V}{\beta_i p_i} \end{bmatrix}. \]  

(12)

**Assumption 1** \( \Gamma_{m \times m} \) in (12) has disjoint eigenvalues, \( \gamma_i \), that is, \( \gamma_i \neq \gamma_j \) for \( i \neq j \).

The characteristic values of (12) are given by the non-zero entries on its main diagonal, \( \gamma_i = \frac{-\beta_i p_i \frac{d_T \cdot d_V}{\beta_i p_i}}{dt \cdot d_V} \) with associated nonzero eigenvectors, \( v_i \), satisfying the \( n \) equalities

\[ \Gamma v_i = \gamma_i v_i. \]  

(13)

- For distinct eigenvalues, \( \gamma_i \), the only one dimensional invariant subspaces of \( \Gamma \) are the \( n \) subspaces spanned by each eigenvector, \( v_i \), of \( \Gamma \). As all \( \gamma_i \) are distinct, then the corresponding \( v_i \) are independent and form a basis.
- Since \( F^T req \) is scalar value, the only possible solutions to (45) are found when \( req \) belongs to an invariant subspace of \( \Gamma \).

From \( req = -\frac{1}{dt} (-K req + s_T) \Gamma req \) in (45) we obtain

\[ I_{m \times m} + \frac{1}{dt} (-K req + s_T) \Gamma req = 0_{m \times 1}. \]  

(14)

Below we show that there are at most \( m \) possible non-zero solutions (14) which we denote by \( req \), namely; Let \( req \neq 0_{m \times 1} \) be defined as

\[ req \triangleq \alpha_i v_i, \quad i = 1, \ldots , m \]  

(15)

for some non-zero scalar, \( \alpha_i \), to be determined. Substituting (15) into (14) gives

\[ \alpha_i v_i = \frac{1}{dt} (-K (\alpha_i v_i) - s_T) \Gamma \alpha_i v_i = \frac{r_{eq}}{r_{eq i}}. \]  

(16)

From (16) we choose \( v_i \) such that \( K v_i = 1 \), which implies

\[ \alpha_i v_i = \frac{1}{dt} (\alpha_i - s_T) \gamma_i \]  

(17)

which after simplification becomes

\[ 1 = \frac{1}{dt} (\alpha_i - s_T) \gamma_i. \]  

(17)

and therefore

\[ \alpha_i = \frac{d_T}{\gamma_i} + s_T = \frac{d_T}{\gamma_i} \frac{d_T \cdot d_V}{\gamma_i} - s_T = -d_T T_{eq i} + s_T. \]  

(18)

Once the equilibrium reaction rates are found, from (10),

\[ xe = -A^{-1} Er - A^{-1} s_T F . \]  

(19)

The equilibria corresponding to (18) are found from (7) as

\[ (T_{eq i}, T^*_i, V_{eq i}) = \left( \frac{d_T \cdot d_V}{\beta_i p_i}, \frac{s_T}{\beta_i p_i} - \frac{d_T \cdot d_V}{\beta_i p_i}, \sqrt{\frac{p_i}{d_T \cdot d_V}} - \frac{d_T}{\beta_i} \right). \]  

(20)
From (18) the infected state defined in (15) is

\[ s_T > \frac{dT}{\gamma_i} \]

if \( s_T > \frac{dT}{\gamma_i} \). Next are examined local stability properties of the equilibria by linearizing (1) about \( x_{eq} = (T_{eq}, T^*, V_{eq}) \) and determined the eigenvalues of the following block partition Jacobian evaluated in the neighborhood of the operating point associated to (1)

\[
Df(x_{eq})|_{\mu=0} = \begin{bmatrix}
-d_T - \sum_{i=1}^{m} \beta_i V_i^0 & 0 & \ldots & -T_{eq,i} B \\
diag \{ \beta_i \} V^T & -d_T \cdot I & \ldots & T_{eq,i} \cdot diag \{ \beta_i \} \\
0 \cdot m \cdot 1 & diag \{ p_i \} & \ldots & -d_T I
\end{bmatrix}
\]

(21)

where \( B = [\beta_1, \beta_2, \ldots, \beta_m] \), \( V = [0, \ldots, V_j^0, \ldots, 0] \in \mathbb{R}^m \) and \( x \in \mathbb{R}^{2m+1} \) represents the state variables \( T, T^* \) and \( V \).

For simplicity we reduce (21) to an upper triangular matrix by permuting the rows and columns. The state variables of (21) represented by

\[
\begin{bmatrix}
T \\
T^* \\
V_j \\
V_{j-1} \\
V_{j-1} \\
V_{j+1} \\
V_m
\end{bmatrix}
\]

leading therefore to the upper triangular Jacobian matrix

\[
Jac_j = \begin{bmatrix}
\Theta_j & \Pi_{j,1} & \Pi_{j,2} & \ldots & \Pi_{j,j-1} & \Pi_{j,j+1} & \ldots & \Pi_{j,m} \\
0 & \Psi_{j,1} & 0 & \ldots & 0 & 0 & \ldots & 0 \\
0 & 0 & \Psi_{j,2} & \ldots & 0 & 0 & \ldots & 0 \\
\ldots & \ldots & \ldots & \ldots & \ldots & \ldots & \ldots & \ldots \\
0 & 0 & 0 & \Psi_{j,j-1} & 0 & 0 & \ldots & 0 \\
0 & 0 & 0 & 0 & \Psi_{j,j+1} & \ldots & 0 & 0 \\
0 & \ldots & \ldots & \ldots & \ldots & \ldots & \ldots & \ldots \\
0 & \ldots & \ldots & \ldots & \ldots & \ldots & \ldots & \ldots \\
\end{bmatrix}
\]

(22)

where the block matrices \( \Theta_j \) and \( \Psi_{j,i} \) have the structure

\[
\Theta_j = \begin{bmatrix}
-d_T - \beta_j V_j^0 & 0 & -T_{eq,j} \beta_j \\
\beta_j V_j^0 & -d_T \cdot V_j & T_{eq,j} \beta_j \\
0 & p_j & -d_V
\end{bmatrix};
\]

\[
\Psi_{j,i} = \begin{bmatrix}
-d_T & -T_{eq,i} \beta_i \\
p_i & -d_V
\end{bmatrix};
\]

(23)

with \( i = 1, \ldots, j - 1, j + 1, \ldots, m \).

The local behavior of (26) around equilibrium \( x_{eq} \) is studied via linear stability by analyzing the diagonal blocks of (22) evaluated at \( x_{eq} \). The analysis of the upper 3×3 block is based on the coefficients of \( p\Theta_j(\lambda) \) which is obtained by expanding the determinant (23) as follows

\[
p\Theta_j(\lambda) = \lambda^3 + (d_T + d_T + d_V + \beta_j V_j^0) \lambda^2 +
\]

\[
(d_T d_T + d_T + d_T + \beta_j V_j^0 d_T + T_{eq,j} \beta_j + \beta_j V_j^0 d_T) \lambda
\]

\[
+ d_T d_T d_T + \beta_j V_j^0 d_T d_T + T_{eq,j} \beta_j d_T d_T
\]

(24)

Note that at the \( j \)th equilibrium \( d_T + \beta_j V_j^0 = s_T \beta_i V_i^0 \) and \( T_{eq,j} \beta_j p_j = d_T d_V \). Therefore, (24) becomes

\[
p\Theta_j(\gamma) = \lambda^3 + a_1^2 \lambda + a_2 \lambda + a_3
\]

where \( I \) is a 3-by-3 identity matrix and \( \lambda \) are the zeros of the characteristic polynomial \( p\Theta_j(\lambda) \) which is obtained by expanding the determinant (23) as follows

\[
\begin{bmatrix}
\lambda + d_T + \beta_j V_j^0 & 0 & T_{eq,j} \beta_j \\
-\beta_j V_j^0 & \lambda + d_T & T_{eq,j} \beta_j \\
0 & -p_j & \lambda + d_V
\end{bmatrix}
\]

(25)

Therefore we only need to check \( a_3 > 0 \) to assure stability. In order to complete the analysis, the stability of each lower 2×2 blocks \( \Psi_{j,i} \), \( i = 1, \ldots, j - 1, j + 1, \ldots, m \) on the diagonal of (22) must be considered. The requirement for \( \Psi_{j,i} \) to be stable is \( d_T - d_V > p_i T_{eq,i} \beta_i \). Note that from (18) \( T_{eq,j} = \frac{dT - d_T}{\beta_j p_j} \). Therefore, \( \Psi_{j,i} \) is Hurwitz if and only if \( \beta_j p_i < \beta_j p_j \), i.e., variant “i” is less fit than variant “j”.

III. VIRAL DYNAMICS WITH MUTATION

One major problem with HIV infection is that genetic variations or mutations occur when the viral RNA is reverse transcribed to DNA. These variations in the nucleotide sequence of HIV are usually referred to as mutations and they result in a high amount of viral diversity in the virus populations.

These mutations are changes in the nucleotide sequence of the genetic material of this virus and they are not captured by (1). We therefore modify (1) including a parameter, \( \mu \), to denote the probability of mutation between the different strains, similarly to [7]. However, in [7] the authors considered mutation only from drug-sensitive wild-type virus to mutant virus. Our model below (26) also permits reverse mutations, i.e., a change in a nucleotide pair, in a mutated gene, that restores the original sequence and hence the original genotype. Although this reverse mutation does not
always regenerate the original wild-type sequence, it may occur in some cases (see for example [8]). Model (26) allows numerical simulation of the dynamics of individual infections where new viral variants are continuously created. For simplicity, we consider a linear genetic mutation tree, whilst more realistic models (e.g. [14]) would consider a more complex viral genetic “tree”.

\[ \dot{T} = sT - dT - \sum_{i=1}^{m} r_i \]
\[ \dot{T}^*_i = (1 - \mu) r_i + \mu r_2 - dT \cdot T^*_i \]
\[ \dot{T}^*_i = \mu r_{i-1} + (1 - 2\mu) r_i + \mu r_{i+1} - dT \cdot T^*_i, \quad i = 2, \ldots, m - 1 \]
\[ T^*_m = \mu r_{m-1} + (1 - \mu) r_m - dT \cdot T^*_m \]
\[ V_i = p_i T^*_i - d_i V_i, \quad i = 1, \ldots, m \]  

(26)

The analysis proposed in [2] made possible to determine possible equilibria, to study local stability properties and to prove that generically, there exists a locally unstable fixed point corresponding to an uninfected state and a locally stable equilibrium corresponding to the infected steady state. However, [2] considered only HIV models with a single point mutation in the wild type (HIV-1), i.e., a type of mutation that causes the replacement of a single base nucleotide with another nucleotide. Throughout this section we use (26) to show that [2] can be extended to multi-strain models accounting for possible mutations between the m strains.

Equation (26) describes the interaction among uninfected cells, the concentration of HIV RNA in plasma (which is related to the rate of viral replication) and infected cells (CD4 cells contaminated with HIV). Assuming viral mutation progressing along a string (one type of virus mutates into two adjacent types), then the viral evolution following this trajectory of mutations along the genome is captured by redefining (4) as

\[ E_{\mu} = \begin{bmatrix} -K_{1 \times m} & T_{m \times m} \\ I_{m \times m} & 0_{m \times m} \end{bmatrix} + \mu \begin{bmatrix} 0_{1 \times m} \\ 0_{m \times m} \end{bmatrix} \]  

(27)

where the T is a tridiagonal m × m matrix

\[ T = \begin{bmatrix} -1 & 1 & 0 & \cdots & 0 \\ 1 & -2 & 1 & \ddots & \vdots \\ 0 & \ddots & \ddots & \ddots & 0 \\ \vdots & \ddots & \ddots & \ddots & \ddots \\ 0 & \cdots & 0 & 1 & -1 \end{bmatrix} \]

Consequently, the structure of (42) becomes \( \Gamma |_{\mu > 0} \), namely

\[ \Gamma |_{\mu > 0} \in \mathbb{R}^{m \times m} = \begin{bmatrix} -\text{diag} \{ \beta_m \} & \frac{1}{\sigma_{P1}} \text{diag} \{ p_m \} \end{bmatrix} (I + \mu T)_{m \times m} \]  

(28)

A. Stability analysis with mutation (\( \mu > 0 \))

Stability analysis in subsection II-B assumes no HIV mutation. Next we investigate viral fitness mutations by assessing the viral replication potential under the presence of HIV mutants in (26).

Assumption 2 \( \mu > 0 \) with mutation rate, \( \mu \ll 1 \), i.e., existence of mutations between the multiple strains.

Since the eigenvalues of a matrix are continuous functions of elements of the matrix for sufficiently small mutation, \( \mu \ll 1 \), the stability of the equilibria are not altered (unless one or more of the eigenvalues are marginally stable). However, all of the equilibria are at the boundary of the positive orthant and therefore higher order terms need to be examined to check whether positivity of the equilibria is maintained for small \( \mu > 0 \). We perform an eigendecomposition in which \( A_{m \times m} \triangleq \text{diag} \{ \lambda_1, \ldots, \lambda_m \} \) and \( V = [v_1, \ldots, v_m]_{m \times m} \) is a matrix of eigenvectors.

\[ \Gamma V = V \Lambda \]  

(29)

where \( \Lambda \) is now given by its new structure (28).

Taking Taylor expansion of (29) we approximate \( \Gamma, V, \Lambda \)

\[ \Gamma(\mu) = \Gamma^{(0)} + \mu \Gamma^{(1)} \\ V(\mu) = V^{(0)} + \mu V^{(1)} + \ldots \\ \Lambda(\mu) = \Lambda^{(0)} + \mu \Lambda^{(1)} + \ldots \]  

(30)

We take \( \Lambda^{(0)} = \Gamma^{(0)} \) and \( V^{(0)} = I \), where I is the identity matrix. Then, (29) can be approximated as

\[ \begin{bmatrix} \Gamma^{(0)} + \mu \Gamma^{(1)} \\ I + \mu V^{(1)} \end{bmatrix} = \begin{bmatrix} \Gamma V \\ V \Lambda \end{bmatrix} \]  

(31)

Equation (31) in terms of \( O(\mu) \) is given by

\[ \mu \Gamma^{(1)} I + \mu \Gamma^{(0)} V^{(1)} = \mu V^{(1)} \Gamma^{(0)} + \mu I \Lambda^{(1)} \]  

(32)

Since \( \Gamma^{(0)} \) is diagonal and without loss of generality we can scale \( V(\mu) \) such that \( \text{diag} \{ V^{(1)} \} = 0 \). Then from (32)

\[ \left( \Gamma^{(1)} \right)_{(i,j)} + \left( \Gamma^{(0)} \right)_{(i,j)} V^{(1)}_{(i,j)} = \left( V^{(1)} \right)_{(i,j)} \left( \Gamma^{(0)} \right)_{(i,j)} + \left( \Lambda^{(1)} \right)_{(i,j)} \]  

(33)

Since in (33) the matrix \( \left( \Lambda^{(1)} \right)_{(i,j)} = 0 \), for \( i \neq j \), then \( \Lambda^{(1)} |_{\mu > 0} \) has the following structure

\[ \Lambda^{(1)} |_{\mu > 0} = \text{diag} \{ \beta_{m} \} = \begin{bmatrix} \frac{1}{\sigma_{P1}} \beta_{m} & 0 & 0 & \cdots & 0 \\ 0 & -\frac{1}{\sigma_{P1}} \beta_{m} p_{m} & 0 & \cdots & 0 \\ \vdots & \ddots & \ddots & \ddots & \ddots \\ 0 & \cdots & 0 & -\frac{1}{\sigma_{P1}} \beta_{m} p_{m} & 0 \\ 0 & \cdots & 0 & \cdots & -\frac{1}{\sigma_{P1}} \beta_{m} p_{m} \end{bmatrix} \]  

(34)

Assuming all diagonal elements of \( V^{(1)} \) are zero, i.e., \( \text{diag} \{ V^{(1)} \} = 0 \) and recalling that \( \left( \Lambda^{(1)} \right)_{(i,j)} = 0 \) for \( i \neq j \), then the factor of \( \left( V^{(1)} \right)_{(i,j)} \) in (33) leads to

\[ \left( \Gamma^{(1)} \right)_{(i,j)} = \left( V^{(1)} \right)_{(i,j)} \left( \Gamma^{(0)} \right)_{(j,j)} - \left( \Gamma^{(0)} \right)_{(i,j)} \]  

(35)
from which we obtain the entries that lie in the \( i-th \) row and the \( j-th \) column of \( V^{(1)} \)

\[
\left( V^{(1)} \right)_{(i,j)} = \frac{(\Gamma^{(1)})_{(i,j)} - (\Gamma^{(0)})_{(i,j)}}{(\Gamma^{(0)})_{(j,j)} - (\Gamma^{(0)})_{(i,i)}}, \quad i \neq j.
\]

(36)

From (12) we have

\[
\left( \Gamma^{(0)} \right)_{(j,j)} = -\frac{\beta_i p_j}{d_T d_V},
\]

(37)

while from (28) the matrix \( (\Gamma^{(1)})_{(i,j)} \) has all its off-diagonal elements equal to zero except for the first superdiagonal, \( (\Gamma^{(1)})_{(i,i+1)} \) and first subdiagonal \( (\Gamma^{(1)})_{(i,i-1)} \), namely

\[
(\Gamma^{(1)})_{\mu>0} = \begin{pmatrix}
-\frac{\beta_i p_i}{d_T d_V} & 0 & \cdots \\
\frac{\beta_{i-1} p_{i}}{dp_T d_V} & -2 \frac{\beta_{i-1} p_{i}}{d_T d_V} & \cdots \\
\vdots & \ddots & \ddots \\
-\text{diag}\{\beta_i\}_{1} & \cdots & -\text{diag}\{p_i\}2_{m \times m} \\
\end{pmatrix}.
\]

As \( \text{diag}\{V^{(1)}\} = 0 \), then from (36) we obtain an approximation for the super diagonal elements of \( V^{(1)} \)

\[
(V^{(1)})_{(i,i+1)} = \frac{\beta_i p_i}{\beta_{i+1} p_{i+1} - \beta_i}
\]

(39)

while for the sub diagonal elements of \( V^{(1)} \) we have

\[
(V^{(1)})_{(i,i-1)} = \frac{\beta_i p_i}{\beta_{i-1} p_{i-1} - \beta_{i-1} p_{i-1}}.
\]

(40)

Conditions for positivity of (36) are therefore \( \beta_{i+1} p_{i+1} > \beta_{i-1} p_{i-1} \) in (39) and \( \beta_i p_i > \beta_{i-1} p_{i-1} \) in (40), i.e., mutant “\( i \)” is fitter than its neighbors “\( i-1 \)” and “\( i+1 \)”. Therefore we note that positivity of the “\( i-th \)” is maintained in the \( O(\mu) \) model if and only if the mutant is fitter than its both neighbors.

B. Numerical simulation of viral dynamics with mutation

Mutations hidden in previously ignored parts of the HIV genome may contribute to the development of drug resistance in AIDS patients [9]. Then, multi-drug Highly Active Antiretroviral Therapy is recommended to inhibit HIV replication as well as to delay or prevent further infection and subsequent deterioration of the immune system. The effect of RT and PI inhibitors used in combination to combat the HIV replication are assessed by representing them in (26) as external input, replacing \( \beta_i \) with \( (1-u_{RT}) \beta_i \) and \( p_i \) with \( (1-u_{PI})p_i \), where \( (u_{RT}, u_{PI}) \in [0,1] \) denotes the effect of RT in inhibiting T cell infection and PI denotes the effect in producing non-infective virions. \( u_{RT} = 1 \) and \( u_{PI} = 1 \) correspond to 100% treatment efficacy. The efficiency of therapy is assessed by evaluation of the Jacobian at each of the equilibrium of (26) and also through the qualitative behavior in figure 2, obtained with Matlab© considering drug efficiency, \( u_{RT_1}=u_{RT_2}=u_{RT_3}=u_{PI_1}=u_{PI_2}=u_{PI_3}=70\% \),

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( s_T )</td>
<td>10 mm&lt;sup&gt;-1&lt;/sup&gt;day&lt;sup&gt;-1&lt;/sup&gt;</td>
</tr>
<tr>
<td>( d_T )</td>
<td>0.02 day&lt;sup&gt;-1&lt;/sup&gt;</td>
</tr>
<tr>
<td>( \beta_i )</td>
<td>infection rate ( 2.4e^{-6}, 1.8e^{-6}, 1.2e^{-6}, 0.6e^{-6} )</td>
</tr>
<tr>
<td>( d_{RT} )</td>
<td>( T ) cell death rate ( 0.24 ) day&lt;sup&gt;-1&lt;/sup&gt;</td>
</tr>
<tr>
<td>( p_i )</td>
<td>viral production rate ( 100, 75, 50, 25 )</td>
</tr>
<tr>
<td>( m )</td>
<td>number of mutants ( 4 )</td>
</tr>
<tr>
<td>( \mu )</td>
<td>mutation rate ( 0.0001 )</td>
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</tbody>
</table>

\( u_{RT}=0.70\% \) and \( d_V = 0.24 \). Note that HIV-1 dominates the population before treatment in \( t = 200 \), causing an initial improvement in T-cell count. Parallely, a new resistant mutant subpopulation develops, culminating in a transition to a new equilibrium, \( E_{\text{infected}} \), by day 917, when there is a shift between HIV-1 and mutant \( m_1 \), which is favored and less sensitive to therapy. If the resistant HIV makes enough copies of itself, it could eventually become the dominant type. This indicates that the development of multidrug-resistant HIV-1 variants may compromise the efficacy of the antiretroviral therapy, which in turn could limit therapeutic options among patients.

Numerical solution of \( T, T_1, T_2, T_3, T_4, V_1, V_2, V_3, V_4 \) obtained via xppaut [11], parameters from Table I, numerical method cvode, relative tolerance 0.001, step size = 0.5, absolute tolerance 0.001, \( d_V = 3 \), and initial conditions: \( T = 955, V_1 = 325 \) and zeros to all other state variables confirms the existence of two equilibria:

**Uninfected state:** \( E_{\text{uninfected}} = (500, 0, 0, 0, 0, 0, 0, 0, 0) \).

**Infected state:** \( E_{\text{infected}}: (300.03, 16.65, 0.00951, 2.3543e^{-6}, 3.3047e^{-6}, 555.16, 0.2854, 6.278e^{-5}, 7.7109e^{-9}) \).

IV. CONCLUSIONS

We generalized to multiple virus variants the technique proposed in [2] to study HIV infection with one single mutant. Our analysis suggests that the ability of HIV to become drug resistant and proliferaters could be related to viral diversity (figure 2). We observed the existence of two valid equilibria around which the local behavior of (26) is:

i) Uninfected state (locally unstable equilibrium) and;

ii) Infected state (possibly equilibria), where only one (corresponding to the fittest strain) is locally stable.

Section II extended [2] by expressing in a general form a mathematical analysis that yields a complete description of all possible equilibrium and their local stability properties of a model without virus mutation. Stability conditions for (26) are \( a_3 > 0 \) and \( \beta_j p_j < \beta_j p_0 \) in absence of mutants and two inequalities: \( \beta_i p_i > \beta_{i+1} p_{i+1} \) in (39) and \( \beta_{i-1} p_{i-1} \) in (40) when \( 0 < \mu << 1 \) under assumption 2.

Since viral fitness refers to the virus’ ability to replicate and cause disease, then our findings regarding the number and stability of the equilibria could give indications of the causes leading to HIV mutations that become resistant to the effects of the medications. A more comprehensive study based on the mathematical models should allow the assessment of the factors that could explain different resistant patterns to the drugs that treat the disease; for instance the
type and amount of antiretroviral drugs as observed in the clinical study [12]. The analysis represents however a first step for understanding the local interactions that may occur between virions and adaptive immune cells [13].

Because the classification of strains is changes as new scientific discoveries are made and considering that more strains may appear in the future (e.g., by recombinants), then the assumption of viral mutation progressing along a line is not sufficient to describe viral evolution along the HIV genome. Therefore, we consider to express (26) on lattice space [14][15], so that more realistic scenarios in which all different types of HIV-1 mutation are possible.

APPENDIX

Proof lemma 1. Multiplying both sides of (7) by $A^{-1}$ gives

$$0 = x_{eq} + A^{-1} E r_{eq} + A^{-1} F S_T.$$ 

Then multiplying on the left by $F^T$ gives the result, since

$$F^T A^{-1} = -\frac{1}{d_F} F^T$$
and $F^T E = -K$. □

Proof lemma 2. Multiplying both sides of (7) by $-W^T A^{-1}$ implies

$$W^T x_{eq} = -W^T A^{-1} E r_{eq} - W^T A^{-1} F S_T$$

(41)

where $W^T A^{-1} E r_{eq}$ is given by

$$W^T = \begin{bmatrix} 0_{m \times 1} & 0_{m \times m} & \text{diag} \{ \beta_i \} \end{bmatrix} \times (2m+1)$$

and

$$A^{-1} = \begin{bmatrix} -\frac{1}{d_T} I_{m \times m} & -\frac{1}{d_T} \text{diag} \{ p_i \} & -\frac{1}{d_T} \text{diag} \{ p_i \} \\ 0_{m \times 1} & 0_{m \times m} \end{bmatrix} \times (2m+1)$$

Then, by defining $\Gamma_{m \times m} \triangleq W^T A^{-1} E$ we have

$$\Gamma_{m \times m} = \begin{bmatrix} -\text{diag} \{ \beta_i \} & -\text{diag} \{ p_i \} & -\text{diag} \{ p_i \} \\ 0_{m \times m} & 0_{m \times m} \end{bmatrix} \times (2m+1)$$

Since in (41) $W^T A^{-1} F S_T = 0$ then

$$W^T x_{eq} = -\Gamma_{m \times m} \begin{bmatrix} r_{eq_1} \\ \vdots \\ r_{eq_m} \end{bmatrix}$$

(43)

leads to

$$W^T x_{eq} = -\Gamma r_{eq}.$$  

(44)

Substituting (9) and (44) in (8) results

$$r_{eq} = -\frac{1}{d_T} \left[ W^T x_{eq} \right] \Gamma r_{eq} - \frac{1}{d_T} \left[ W^T x_{eq} \right] \Gamma r_{eq}$$

which can be rewritten as

$$r_{eq} = -\frac{\left[ W^T x_{eq} \right] \Gamma r_{eq} + s T}{d_T d_T d_T} [\text{diag} \{ \beta_i p_i \}] r_{eq}.$$  

(45)

REFERENCES