A slow-replicating mutant induces synchronized replication rates and oscillatory viral dynamics in an HIV mathematical model

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HIV infection is an incurable disease that leads to the destruction of immunity. Its clinical course is divided into the acute, latency, and acquired immunodeficiency syndrome (AIDS) phases. Nowak and May proposed a simple mathematical model that considered viral mutation and found the parameter condition for the long-term development of AIDS [M. A. Nowak, R. M. May. J. Theor. Biol 159, 329-342 (1992)]. However, the mechanism of the acute and latency phase remains unclear from their study. In the present paper, we consider the same model and investigate its capability to qualitatively reproduce the time course of an actual HIV infection. We find that the three phases robustly appear when there are two viral mutants with quite different replication rates. The viral dynamics have the following two components: the damped oscillation that forms the initial viral peak and the following slow exponential growth that resembles the latency and AIDS phase. We analyze the obtained dynamics utilizing linear stability analysis and subsequently generalize for the many mutants case in which one mutant has a considerably lower replication rate than the others. We demonstrate that (i) all replication rates synchronize to the same value of \( O(\epsilon) \) and (ii) an oscillation appears if the initial value of the slowest-replicating mutant is sufficiently small. In particular, the synchronization of replication rates emphasizes the role of a slow-replicating mutant in maintaining the latency. Our findings explain the pathogenesis of HIV from a mathematical aspect, possibly providing a clue for the cure of HIV infection.

HIV | mathematical model | nonlinear dynamics | oscillation | stability analysis

Significance Statement

HIV infection is an incurable disease that leads to the long-term development of AIDS. We focus on the following three clinical phases of HIV infection: acute, latency, and AIDS phase, and investigate the mechanism of these phases using a simple mathematical model. We find that (i) all replication rates synchronize to the same value of \( O(\epsilon) \) if one mutant has a considerably lower replication rate than the others and (ii) oscillatory viral dynamics, which resemble the acute phase, appear if the initial value of the slowest-replicating mutant is sufficiently small. Our analytical results suggest the importance of a slow-replicating mutant for developing and maintaining three clinical phases, which could help clarify the pathogenesis of HIV.

The authors declare no competing interest.

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viral mutants, numerical simulations suggest that the initial peak and the following slow increase in viral load appear if one viral mutant has a considerably lower replication rate than the other. We perform the existence and linear stability analysis, which is valid even when the viral load is low, and we determine that an oscillation occurs if the initial value of the slow-replicating viral mutant is sufficiently small. In addition, we generalize these results for the \( n \geq 3 \)-mutant case in which one mutant has a considerably lower replication rate \( \varepsilon \) than the others. In particular, we prove that (i) all replication rates synchronize to the same value of \( O(\varepsilon) \) if the parameters of immune strength satisfy a few conditions and that (ii) oscillatory viral dynamics exist if the initial value of the slowest-replicating mutant is sufficiently small. Our findings indicate that the virus can live long with the host by producing a slow-replicating mutant and delaying the onset of AIDS, suggesting a survival strategy for HIV.

**Mathematical model and nondimensionalization**

Our model is based on the one proposed by Nowak and May (11). The dynamics of virus and immune cells are described by the following \( 2n \)-dimensional system:

\[
\begin{align*}
\dot{v}_i &= \frac{d v_i}{dt} = v_i (r_i - p_i x_i), \quad [1a] \\
\dot{x}_i &= \frac{d x_i}{dt} = k v_i - u x_i \sum_{i=1}^{n} v_i, \quad [1b]
\end{align*}
\]

where \( v_i \) denotes the amount of mutant virus \( i \), \( x_i \) is the quantity of strain-specific immune cells attacking the virus \( i \), and \( n \) represents the number of HIV mutant strains \( (1 \leq i \leq n) \). The parameter \( r_i \) is the replication rate of virus \( i \), \( p_i \) represents the strength of the immune attack on virus \( i \), \( k \) is the activation rate of immune cells, and \( u \) represents the strength of the viral attack on immune cells. Note the asymmetric interaction between the virus and immune cells; even though each strain of immune cells \( x_i \) is specific to virus \( i \), virus \( i \) can attack all strains of immune cells. The parameters \( r_i, p_i, k, \) and \( u \) are assumed to be positive constants.

This mathematical model is consistent with the virological evidence that HIV infects and destroys immune cells, especially CD4+ T lymphocytes (15), and that HIV produces numerous mutants in the body (16). It is also known that various viral mutants may have different virulence (17), which is represented by \( r_i \) and \( p_i \) in this model.

We introduce dimensionless quantities \( \alpha_i := \frac{r_i}{r_1}, \tilde{v}_i := \frac{v_i}{v_{10}}, \tilde{x}_i := \frac{x_i}{x_1}, \tau := \frac{r_1 t}{\tilde{r}_1}, \) and \( q_i := \frac{p_i}{r_1 u} \). By renaming \( \tilde{v}_i \rightarrow v_i, \tilde{x}_i \rightarrow x_i, \) and \( \tau \rightarrow \tilde{t} \), we transform Eq. (1) into the following dimensionless system:

\[
\begin{align*}
\dot{v}_i &= \alpha_i v_i (1 - x_i), \quad [2a] \\
\dot{x}_i &= v_i \left( q_i - x_i \sum_{i=1}^{n} \frac{v_i}{v_1} \right). \quad [2b]
\end{align*}
\]

The parameter \( \alpha_i \) is the ratio of replication rates among viral mutants and \( q_i \) represents the immunological strength of \( x_i \) compared with the virulence of \( v_i \). We assume \( 0 < \alpha_n \leq \cdots \leq \alpha_2 \leq \alpha_1 = 1 \) without loss of generality.

**The case of only one viral mutant**

When there is only one viral mutant \( (i.e., n = 1) \), our model is given by

\[
\begin{align*}
\dot{v} &= v(1 - x), \quad [3a] \\
\dot{x} &= v (q - x). \quad [3b]
\end{align*}
\]

Fig. 1 presents the simulation results, where we assume that the initial value of \( x \) is zero \( (i.e., x(0) = 0) \) because virus-specific immunity has not been prepared at the beginning of infection. Then, the viral dynamics are classified into the following two types: (i) for \( q < 1 \), the viral load continues to increase (Figs. 1 (A) and (B)), and (ii) for \( q > 1 \), the viral load initially increases and subsequently decreases, eventually converging to zero (Figs. 1 (C) and (D)). We conclude that three clinical phases in HIV infection cannot be reproduced in the case of \( n = 1 \).

**The case of two viral mutants**

For \( n = 2 \), our model is given as

\[
\begin{align*}
\dot{v}_1 &= v_1 (1 - x_1), \quad [4a] \\
\dot{v}_2 &= \alpha_2 v_2 (1 - x_2), \quad [4b] \\
\dot{x}_1 &= v_1 \left( q_1 - x_1 \left( 1 + \frac{v_2}{v_1} \right) \right), \quad [4c] \\
\dot{x}_2 &= v_2 \left( q_2 - x_2 \left( 1 + \frac{v_1}{v_2} \right) \right). \quad [4d]
\end{align*}
\]

**Simulation results.** Fig. 2 demonstrates the simulation results. In Figs. 2 (A) and (B), we consider the situation in which two viral mutants have similar replication rates and the immunity is strong enough to eradicate the virus. Next, we weaken the immunity, or decrease \( q_i \), so that the viral load diverges (Figs. 2 (C) and (D)). Finally, we notably reduce \( \alpha_2 \) to simulate a slow-replicating mutant (Figs. 2 (E) and (F)). Throughout

![Fig. 1](image1.png)

![Fig. 2](image2.png)
these simulations, we use the same initial conditions ($v_1(0) = v_2(0) = 0.01$ and $x_1(0) = x_2(0) = 0$) because it is natural to assume that the amount of virus is very low and virus-specific immunity has not been established at the beginning of the infection.

The dynamics observed in Figs. 2 (A), (B), (C), and (D) are qualitatively the same as those obtained in the previous section. In contrast, Figs. 2 (E) and (F) demonstrate a new pattern with two components, namely, damped oscillation and slow exponential viral growth, which resembles the three clinical phases in HIV infection. We are going to clarify why this pattern was obtained.

**Analysis.** We expect that the dynamics in Figs. 2 (E) and (F) may arise when $\alpha_2 \ll 1$. Thus, we treat $\alpha_2$ as a small parameter and put $\varepsilon = \alpha_2$. The other parameters are assumed to be $O(1)$.

In Figs. 2 (E) and (F), we observe that $x_i(t)$ converges toward a nonzero constant, denoted by $x_i^*$, whereas $v_i$ diverges. Based on Eq. (4), this condition is only possible when $\beta := \frac{w}{q}$ also converges toward a positive constant, represented by $\beta^*$. Assuming the convergence of $\beta$ to $\beta^*$, we obtain the fixed point $x_i^*$ in Eq. (4c) and Eq. (4d), which is given as

$$x_i^* = \frac{q_1}{1 + \beta^*}, \quad x_i^* = \frac{q_2 \beta^*}{1 + \beta^*}. \quad [5]$$

Substituting $x_i = x_i^*$ into $\dot{\beta} = \frac{v_i}{1 + \beta} - \frac{v_i}{q_2}$, we further obtain

$$\beta^* = \frac{q_1 - 1 + \varepsilon}{1 + \varepsilon (q_2 - 1)} = q_1 - 1 + O(\varepsilon). \quad [6]$$

For sufficiently small $\varepsilon$, the condition $\beta^* > 0$ holds when $q_1 > 1$; thus, we assume this inequality below. Substituting $x_i = x_i^*$ and $\beta = \beta^*$ into Eqs. (4a) and (4b), we obtain

$$v_1 = \lambda v_1, \quad \dot{v}_2 = \lambda v_2,$$

where

$$\lambda = \frac{\varepsilon (q_1 + q_2 - q_1 q_2)}{q_1 + \varepsilon q_2} = O(\varepsilon). \quad [7]$$

We also assume $q_1 + q_2 - q_1 q_2 > 0$ so that $\lambda > 0$. Therefore, if $x_i$ and $\beta$ sufficiently approach $x_i^*$ and $\beta^*$, respectively, $v_1$ and $v_2$ exponentially increase with the same time scale $\lambda^{-1}$ of $O(\varepsilon^{-1})$.

We now perform the stability analysis of the obtained solution by invoking the notion of time-scale separation. For convenience, we introduce new variables $w_i(t)$ as $w_i := v_i e^{-\lambda t}$. Then, Eq. (4) is transformed to the following four-dimensional nonautonomous system:

$$\dot{w}_1 = w_1 (1 - \lambda - x_1), \quad [8a]$$

$$\dot{w}_2 = \varepsilon w_2 (1 - \lambda - x_2), \quad [8b]$$

$$\dot{x}_1 = e^{\lambda t} w_1 \left\{ q_1 - x_1 (1 + \frac{w_1}{w_2}) \right\}, \quad [8c]$$

$$\dot{x}_2 = e^{\lambda t} w_2 \left\{ q_2 - x_2 (1 + \frac{w_1}{w_2}) \right\}. \quad [8d]$$

As far as $t = O(1)$, we can safely replace $e^{\lambda t}$ in Eqs. (8c) and (8d) with 1 because $e^{\lambda t} = 1 + O(\lambda t) = 1 + O(\varepsilon)$. Moreover, $w_2$ is a slow variable. Thus, in a good approximation, the dynamics of $w_1, x_1$, and $x_2$ are described by the following three-dimensional autonomous subsystem:

$$\dot{w}_1 = w_1 (1 - \lambda - x_1), \quad [9a]$$

$$\dot{x}_1 = w_1 \left\{ q_1 - x_1 (1 + \frac{w_1}{w_2}) \right\}, \quad [9b]$$

$$\dot{x}_2 = w_2 \left\{ q_2 - x_2 (1 + \frac{w_1}{w_2}) \right\}, \quad [9c]$$

in which $w_2$ is regarded as a constant. This subsystem has a nontrivial fixed point $(w_1^*, x_1^*, x_2^*) = (w_1^*, x_1^*, x_2^*)$, where $w_1^* = \frac{q_1}{1 + \beta^*}$ and $x_1^*$ is given in Eq. (5). The Jacobian matrix at this fixed point is

$$\begin{pmatrix}
0 & -w_1^* & 0 \\
-q_1 - x_1^* & -w_1^* + w_2 & 0 \\
-x_2^* & 0 & -(w_1^* + w_2)
\end{pmatrix},$$

and its eigenvalues are

$$-\frac{(1 + \beta^*) w_2}{\beta^*} \quad \text{and} \quad \frac{-(1 + \beta^*) w_2}{\beta^2} \pm \sqrt{D_0}, \quad [11]$$

where

$$D_0 = \frac{1}{2} \left( \frac{(1 + \beta^*) w_2}{\beta^*} \right)^2.$$
where
\[ D_0 = \frac{(1 + \beta^*)^2w_\alpha^2}{(\beta^*)^2} - \frac{4q_1w_2}{1 + \beta^*}. \]  

Regardless of the sign of \( D_0 \), all eigenvalues have negative real parts. Thus, the fixed point under consideration is asymptotically stable. We also determine that imaginary eigenvalues appear if \( D_0 < 0 \); i.e.,
\[ 0 < w_2 < \frac{4q_1(\beta^*)^2}{(1 + \beta^*)^2} = \frac{4q_1(q_1 - 1 + \varepsilon)^2(1 + \varepsilon(q_2 - 1))}{(q_1 + \varepsilon q_2)^3}. \]

Oscillation arises in this case.

The fast variables stay in the \( \varepsilon \)-vicinity of the fixed point in the full system after the transient process because the subsystem of the fast variables has a stable fixed point \( (w_1^*, x_1^*, x_2^*) \). Substituting \( x_2 = x_2^* + O(\varepsilon) \) into Eq. \((8b)\) and further using Eqs. \((6)\) and \((7)\), we obtain \( w_2 = O(\varepsilon^2) \), which implies that \( w_2(t) = w_2(0) + O(\varepsilon^2) \) for \( t = O(1) \). Therefore, \( w_2 \) in inequality \((13)\) can be regarded as \( w_2(0) \) in a good approximation. Consequently, we conclude that oscillation inevitably occurs if there is a viral mutant whose replication rate is considerably smaller than the other’s and its initial value is sufficiently small; i.e.,
\[ w_2(0) = w_2(0) < \frac{4q_1(\beta^*)^2}{(1 + \beta^*)^2}. \]

Moreover, both viral mutants share an effective growth rate of \( \lambda = O(\varepsilon) \), namely, the slow mutant entrains the fast mutant. This synchronization underlies the emergence of the latency phase.

By applying the same analysis for the case of three viral mutants (i.e., \( n = 3 \)), we also find that oscillatory viral dynamics and synchronized replication rates are observed if one viral mutant has a considerably lower replication rate than the others and its initial value is sufficiently small. See SI Appendix for more details about the three viral mutants case.

**General case**

We consider the system \((2)\) for the general case of \( n \) mutants. Let \( \Lambda \) be a real number. By introducing new variables \( w_i := n_i e^{-\Lambda t} \), we transform Eq. \((2)\) into the following 2\( n \)-dimensional nonautonomous system:
\[
\begin{align*}
\dot{w}_i &= \alpha_i w_i \left( 1 - \frac{\alpha_i}{\alpha_i} - x_i \right), \\
\dot{x}_i &= e^{\Lambda t} w_i \left( q_i - x_i \sum_{l=1}^{n} \frac{w_l}{w_i} \right),
\end{align*}
\]
for \( 1 \leq i \leq n \). As in the case of two viral mutants, we are particularly concerned with the situation in which one viral mutant has a considerably lower replication rate than the others. Thus, we treat \( \alpha_n \) as a small parameter and put \( \varepsilon := \alpha_n \). The other parameters are assumed to be of \( O(1) \).

We are going to prove that system \((15)\) has at least one internal fixed point (i.e., the coordinates are all positive) if and only if
\[
\Lambda = \frac{\left( \sum_{l=1}^{n} \frac{1}{q_l} \right) - 1}{\sum_{l=1}^{n} \frac{1}{\alpha_l q_l}},
\]
and
\[
\varepsilon \sum_{l=1}^{n} \frac{1}{\alpha_l q_l} > \left( \sum_{l=1}^{n} \frac{1}{q_l} \right) - 1.
\]

**Proof of necessity:** Let \((w_i^*, x_i^*)\) with \( w_i^* > 0 \) and \( x_i^* > 0 \) be the internal fixed point of system \((15)\). Then, \((w_i^*, x_i^*)\) satisfies
\[
x_i^* = 1 - \frac{\Lambda}{\alpha_i},
\]
and
\[
w_i^* q_i - x_i^* \sum_{l=1}^{n} w_l^* = 0.
\]

We rewrite Eq. \((19)\) as
\[
Q_n w^* = 0_n,
\]
where \( Q_n \) is the coefficient matrix given as
\[
Q_n := \begin{pmatrix}
q_1 - x_1^* & -x_1^* & \cdots & -x_1^* \\
-x_2^* & q_2 - x_2^* & \cdots & -x_2^* \\
\vdots & \vdots & \ddots & \vdots \\
-x_n^* & -x_n^* & \cdots & q_n - x_n^*
\end{pmatrix},
\]
and \( 0_n \) denotes the zero vector of order \( n \). On one hand, since we assume \( w^* \neq 0_n \), Eq. \((20)\) has a nontrivial solution; i.e., \( \det Q_n = 0 \). On the other hand, as is shown in SI Appendix, we find
\[
\det Q_n = \left( 1 - \sum_{l=1}^{n} \frac{x_l^*}{q_l} \right) \prod_{k=1}^{n} q_k.
\]
It thus follows that
\[
1 - \sum_{l=1}^{n} \frac{x_l^*}{q_l} = 0.
\]
By substituting Eq. \((18)\) into Eq. \((23)\), we obtain Eq. \((16)\). Moreover, since we assume \( x_n^* = 1 - \frac{\Lambda}{\varepsilon} > 0 \), the inequality \((17)\) follows from Eq. \((16)\).

**Proof of sufficiency:** We set \( x_i^* = 1 - \frac{\Lambda}{\alpha_i} \). Since \( \det Q_n = 0 \) follows from Eq. \((16)\), Eq. \((20)\) has a nontrivial solution, denoted by \( w^* = (w_1^*, w_2^*, \ldots, w_n^*) \neq 0_n \). Recall the inequality \( \alpha_1 \geq \alpha_2 \geq \cdots \geq \alpha_{n-1} \gg \alpha_n \); we have \( x_1^* \geq x_2^* \geq \cdots \geq x_{n-1}^* > x_n^* \) from Eq. \((18)\). Hence, the inequality \((17)\), which is equivalent to \( x_n^* > 0 \), implies that \( x_i^* > 0 \) for all \( i \). It thus follows from Eq. \((19)\) and \( q_i > 0 \) that each \( w_i^* \) has the same sign with \( \sum_{l=1}^{n} w_l^* \). Then, all \( w_i^* \) have the same sign, i.e., \( w_i^* > 0 \) for all \( i \) or \( w_i^* < 0 \) for all \( i \). If \( w_i^* < 0 \) for all \( i \), then \((x_i^*, w_i^*)\) is an internal fixed point of system \((15)\) because \( -w^* = (-w_1^*, -w_2^*, \ldots, -w_n^*) \) is also a nontrivial solution of Eq. \((20)\). Hence, system \((15)\) has at least one internal fixed point.

In the following discussion, we set \( \Lambda \) as Eq. \((16)\) and assume the inequality \((17)\). We also assume
\[
\sum_{l=1}^{n} \frac{1}{q_l} > 1,
\]
so that \( \Lambda > 0 \). It follows from Eq. \((16)\) and the assumption \( \varepsilon \ll 1 \) that
\[
\Lambda = \frac{\left( \sum_{l=1}^{n} \frac{1}{q_l} \right) - 1}{\frac{1}{\varepsilon} + \varepsilon \sum_{l=1}^{n-1} \frac{1}{\alpha_l q_l}} = O(\varepsilon).
\]
Next, we perform the stability analysis assuming time-scale separation. As far as $t = O(1)$, we can safely replace $e^{\lambda t}$ in Eq. (15b) with 1 because $e^{\lambda t} = 1 + O(\lambda t) = 1 + O(\epsilon)$. We also see that $w_n$ is a slow variable and $w_1, \ldots, w_{n-1}, x_1, \ldots, x_{n-1}$, and $x_n$ are fast variables. Thus, in a good approximation, the dynamics of these fast variables are described by the following $(2n - 1)$-dimensional autonomous subsystem:

$$w_j = \alpha_j w_j(1 - \frac{\Lambda}{\alpha_j} - x_j),$$

$$x_i = w_i \left( q_i - x_i \sum_{l=1}^{n} w_l \right),$$

for $1 \leq j \leq n - 1$ and $1 \leq i \leq n$. Note that $w_n$ is regarded as a constant.

As is shown in SI Appendix, this subsystem (26) has the unique fixed point $(w^*_j, x^*_i)$ that satisfies $w^*_j > 0$ and $x^*_i > 0$. They are given as

$$x^*_i = 1 - \frac{\Lambda}{\alpha_i},$$

and

$$w^*_i = w_n R^{-1} \begin{pmatrix} x^*_1 \\ x^*_2 \\ \vdots \\ x^*_n \end{pmatrix},$$

where

$$R := \begin{pmatrix} q_1 - x^*_1 & -x^*_1 & \cdots & -x^*_1 \\ -x^*_2 & q_2 - x^*_2 & \cdots & -x^*_2 \\ \vdots & \vdots & \ddots & \vdots \\ -x^*_n & -x^*_n & \cdots & q_n \cdots -x^*_n \end{pmatrix}.$$  

Note that $R$ is a regular matrix (see SI Appendix for the proof). From Eqs. (27), (28), and (29), we determine that $x^*_i$ and $w^*_i$ are independent of $w_n$. Let $J$ be the Jacobian matrix at the fixed point $(w^*_j, x^*_i)$ of system (26). Then, $J$ is written as

$$J = \begin{pmatrix} O_{n-1,n-1} & A_{n-1} & 0_{n-1} \\ R & B_{n-1} & 0_{n-1} \\ i w_n & 0_{n-1} & -b w_n \end{pmatrix},$$

where

$$A := -w_n \text{diag}(a_1, a_2, \ldots, a_{n-1}), \quad B := -b w_n I_{n-1},$$

$$x^*_i := -\left( x^*_1 \quad x^*_2 \quad \cdots \quad x^*_i \right),$$

and $\alpha_j := \frac{a_j w^*_j}{w_n}$, $b := \left( \sum_{l=1}^{n-1} w_l \right) / w_n$.

$O_{m,n}$ denotes the $m \times n$ zero matrix, and $I_{n-1}$ is the identity matrix of order $n - 1$. Note that $A$ and $b$ do not depend on $w_n$. Our purpose is to show that (i) the fixed point $(w^*_j, x^*_i)$ is asymptotically stable and (ii) the Jacobian matrix $J$ has at least one imaginary eigenvalue if $w_n$ is sufficiently small.

We let $f(z)$ be the characteristic polynomial of $J$. Then,

$$f(z) = (z + b w_n) \det \begin{pmatrix} zI_{n-1} & -A \\ -R & (z + b w_n) I_{n-1} \end{pmatrix}.$$  

Recall the next formula (18); if $S, T, U, V$ are square matrices and if $SU = US$, then

$$\det \begin{pmatrix} S & T \\ U & V \end{pmatrix} = \det(SV - UT).$$

It follows from Eqs. (31) and (32) that

$$f(z) = (z + b w_n) \left( 1 - \sum_{l=1}^{n-1} \frac{a_l x^*_l w_n}{z^2 + b w_n z + a_l q_l w_n} \right) \times \prod_{k=1}^{n-1} \left( z^2 + b w_n z + a_k q_k w_n \right).$$

See SI Appendix for the derivation of Eq. (33). We introduce a new variable $X$ and function $g(X)$ given as

$$X := \frac{z^2 + b w_n z}{w_n},$$

and

$$g(X) := \left( 1 - \sum_{l=1}^{n-1} \frac{a_l x^*_l}{X + a_l q_l} \right) \prod_{k=1}^{n-1} (X + a_k q_k).$$

From Eq. (33), it follows that

$$f(z) = (w_n)^{n-1}(z + b w_n)g(X).$$

Note that $g(X)$ is a polynomial of degree $n - 1$. As shown in SI Appendix, we see that the solutions of $g(X) = 0$ are all negative real numbers. Therefore, there exist positive real numbers given as $\xi_k$ ($1 \leq k \leq n - 1$) such that $\xi_1 \leq \xi_2 \leq \cdots \leq \xi_{n-1}$ and

$$g(X) = \prod_{k=1}^{n-1} (X + \xi_k).$$

From Eq. (35), $-\xi_k$ (i.e., the solutions of $g(X) = 0$) do not depend on $w_n$. Substituting Eqs. (37) and (34) into Eq. (36), we have

$$f(z) = (z + b w_n) \prod_{k=1}^{n-1} \left( z^2 + b w_n z + \xi_k w_n \right).$$

From $b w_n > 0$ and $\xi_k w_n > 0$, we now find that the real parts of the solutions of $f(z) = 0$ are all negative. Thus, the fixed point $(w^*_j, x^*_i)$ is asymptotically stable. We also see that the Jacobian matrix $J$ has at least one imaginary eigenvalue if

$$0 < w_n < \frac{4\xi_{n-1}}{b^2}.$$  

Based on the same argument as in the previous section, the dynamics of slow variable $w_n$ is obtained as $w_n = O(\epsilon^2)$, which implies that $w_n(t) = w_n(0) + O(\epsilon^2)$ for $t = O(1)$. Thus, from inequality (39), we conclude that oscillation occurs if

$$w_n(0) = w_n(0) < \frac{4\xi_{n-1}}{b^2}.$$  

In summary, assuming a few parameter conditions (i.e., the inequalities (17) and (21)), we have shown that (i) all of the viral mutants have a shared effective growth rate of $\lambda = O(\epsilon)$ if one mutant has a considerably lower replication rate than the others and (ii) oscillatory viral dynamics occur if the initial value of the slowest-replicating mutant is sufficiently small. These findings are the generalization of those obtained in the previous section.
Discussion

Oscillatory viral dynamics were previously observed but not analyzed (10, 11). According to our results, the initial viral peak or oscillation appears when the initial value of the slowest-replicating mutant is assumed to be sufficiently small. Such an assumption is appropriate because the viral mutation is believed to be caused due to a replication error (19).

We also find that all replication rates synchronize to the same value of $O(\varepsilon)$, suggesting the mechanism of the latency phase. In other words, by producing an extremely slow-replicating mutant, the total viral load increases as slowly as the slowest-replicating mutant. Thus, the virus can delay the onset of AIDS and survive for a long time with the host. The role of different replication rates in the latency phase was previously studied (20, 21). It is assumed that there are two states of HIV transcription; one with a high transcriptional rate and one with a low rate (20). These two states are determined stochastically, and the stochastic process could lead to latency (20).

The inequality (24) represents the same result as in previous studies (11, 22) and it is the parameter condition in which the viral load eventually diverges. Our study reveals that this condition is valid even without assuming fast dynamics of immune cells. We also find that the inequality (17) is the condition for the synchronization of replication rates. Obviously, the following inequality

$$\sum_{i=1}^{n-1} \frac{1}{q_i} < 1,$$  \hspace{1cm} [41]

is a sufficient condition for the inequality (17). Note that the parameter $1/q_i := \frac{\nu_i}{\nu_n}$ characterizes the strength of the $i$-th viral mutant compared with immunity. Then, the inequality (41) suggests that synchronized replication rates are observed when the total virulence of $v_1, \ldots, v_{n-2}$, and $v_{n-1}$ is insufficiently high to cause AIDS.

This study has several possible extensions. It is known that the amount of immune cells decreases as the disease progresses (3). In contrast, $x_i$ converges to $x_i^*$ > 0 in our model. One of the reasons why this property arises is that the activation rate of immune cells, given as $kv_i$ in Eq. (1b), increases indefinitely as $v_i$ increases; however, in reality, the activation should have an upper limit. Therefore, it would be more appropriate to replace the term $kv_i$ by a nonlinear term, such as $\frac{kv_i}{\nu_i + k}$, with some positive constant $\nu_i$. Another possible extension is to divide the group of immune cells into infected and uninfected cells, which is a characteristic of HIV infection. Such a mathematical model was already proposed by Nowak and Bangham (12). Iwami et al. performed the linear stability analysis of the model for the case of one viral mutant with an assumption that viral dynamics are sufficiently fast (13). Thus, it is worth applying our method to the model. Finally, the global stability of the fixed point $(w_0^*, x_0^*)$ in the subsystem (26) is an open problem in this study. As previously reported in (23), constructing the Lyapunov function, if possible, is expected to solve this problem.

In conclusion, we use a simple mathematical model to examine the mechanism of three clinical phases in HIV infection. We find that the viral load initially oscillates and then slowly increases if the parameters and initial values satisfy a few conditions. Our results suggest that all viral mutants can grow as slowly as the slowest-replicating mutant and survive for a long time with the patient. Even now, it is still quite challenging to cure HIV infection even though there are many efficacious drugs. Our study suggests the survival strategy of HIV and is expected to provide a clue for the cure of HIV infection. A further mathematical study is projected to contribute to a complete understanding of HIV pathogenesis.

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Supplementary Information for

A slow-replicating mutant induces synchronized replication rates and oscillatory viral dynamics in an HIV mathematical model

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The case of three viral mutants

We consider the following system:

\[
\begin{align*}
\dot{v}_1 &= v_1(1-x_1), \\
\dot{v}_2 &= \alpha_2 v_2(1-x_2), \\
\dot{v}_3 &= \alpha_3 v_3(1-x_3), \\
\dot{x}_1 &= v_1 \left\{ q_1 - x_1 (1 + \frac{v_2}{v_1} + \frac{v_3}{v_1}) \right\}, \\
\dot{x}_2 &= v_2 \left\{ q_2 - x_2 (1 + \frac{v_1}{v_2} + \frac{v_3}{v_2}) \right\}, \\
\dot{x}_3 &= v_3 \left\{ q_3 - x_3 (1 + \frac{v_1}{v_3} + \frac{v_2}{v_3}) \right\}.
\end{align*}
\]

We treat \( \alpha_3 \) as a small parameter (i.e., \( \alpha_3 \ll 1 \)) and put \( \varepsilon := \alpha_3 \). The other parameters are assumed to be \( O(1) \). As in the case of two viral mutants, we introduce new variables \( \beta := \frac{v_2}{v_1} \) and \( \gamma := \frac{v_3}{v_2} \). Assuming the convergence of \( \beta \) and \( \gamma \) to positive constants \( \beta^* \) and \( \gamma^* \), respectively, we see that

\[
x^*_1 = \frac{q_1}{1 + \beta^* + \gamma^*}, \quad x^*_2 = \frac{\beta^* q_2}{1 + \beta^* + \gamma^*}, \quad \text{and} \quad x^*_3 = \frac{\gamma^* q_3}{1 + \beta^* + \gamma^*},
\]

are fixed points of the subsystem given by Eqs. (1d), (1e), and (1f). Substituting \( x_i = x_i^* \) into the equations \( \dot{\beta} = \frac{\delta_{i1} q_{i2} - \delta_{i2} q_{i1}}{v_1^2} = 0 \) and \( \gamma = \frac{\delta_{i3} q_{i2} - \delta_{i2} q_{i3}}{v_2^2} = 0 \), we obtain the following

\[
\beta^* = \frac{\alpha_2 q_1 + \varepsilon(q_1 q_2 - q_1 - q_2) + \alpha_2 \varepsilon q_3}{\alpha_2 q_2 + \varepsilon q_3 + \alpha_2 \varepsilon (q_2 q_3 - q_2 - q_3)} = \frac{q_1}{q_2} + O(\varepsilon),
\]

and

\[
\gamma^* = \frac{\alpha_2 (q_1 q_2 - q_1 - q_2) + \varepsilon q_1 + \alpha_2 \varepsilon q_2}{\alpha_2 q_2 + \varepsilon q_3 + \alpha_2 \varepsilon (q_2 q_3 - q_2 - q_3)} = \frac{q_1 q_2 - q_1 - q_2}{q_2} + O(\varepsilon).
\]

For sufficiently small \( \varepsilon \), the conditions \( \beta^* > 0 \) and \( \gamma^* > 0 \) hold if

\[
q_1 q_2 - q_1 - q_2 > 0.
\]

We assume this inequality (5) for the following argument.

Substituting \( x_i = x_i^* \) and \( (\beta, \gamma) = (\beta^*, \gamma^*) \) into Eqs. (1a), (1b), and (1c), we acquire the following equation

\[
\dot{w}_i = \lambda w_i,
\]

where

\[
\lambda = \frac{\alpha_2 \varepsilon (q_1 q_2 + q_2 q_3 + q_3 q_1 - q_1 q_2 q_3)}{\alpha_2 q_2 + \varepsilon q_3 + \alpha_2 \varepsilon (q_2 q_3 - q_2 - q_3)} = O(\varepsilon).
\]

We also assume \( q_1 q_2 + q_2 q_3 + q_3 q_1 - q_1 q_2 q_3 > 0 \) so that \( \lambda > 0 \).

Next we perform the linear stability analysis. By introducing new variables \( w_i := v_i e^{-\lambda t} \), we transform Eq. (1) into the following six-dimensional nonautonomous system:

\[
\begin{align*}
\dot{w}_1 &= w_1 (1 - \lambda - x_1), \\
\dot{w}_2 &= \alpha_2 w_2 (1 - \frac{\lambda}{\alpha_2} - x_2), \\
\dot{w}_3 &= \varepsilon w_3 (1 - \frac{\lambda}{\varepsilon} - x_3), \\
\dot{x}_1 &= e^\lambda w_1 \left\{ q_1 - x_1 (1 + \frac{w_2}{w_1} + \frac{w_3}{w_1}) \right\}, \\
\dot{x}_2 &= e^\lambda w_2 \left\{ q_2 - x_2 (1 + \frac{w_1}{w_2} + \frac{w_3}{w_2}) \right\}, \\
\dot{x}_3 &= e^\lambda w_3 \left\{ q_3 - x_3 (1 + \frac{w_1}{w_3} + \frac{w_2}{w_3}) \right\}.
\end{align*}
\]
As far as \( t = O(1) \), we can safely replace \( e^{\lambda t} \) in Eq. (7) with 1 from \( e^{O(t)} = 1 + O(t) = 1 + O(\varepsilon) \). Moreover, it is obvious that \( w_3 \) is a slow variable and \( w_1, w_2, x_1, x_2, \) and \( x_3 \) are fast variables. Thus, in a good approximation, the dynamics of these fast variables are described by the five-dimensional autonomous subsystem as below:

\[
\dot{w}_1 = w_1 (1 - \lambda - x_1), \\
\dot{w}_2 = \alpha_2 w_2 (1 - \frac{\lambda}{\alpha_2} - x_2), \\
\dot{x}_1 = w_3 \left\{ q_1 - x_1 (1 + \frac{w_2}{w_1} + \frac{w_3}{w_3}) \right\}, \\
\dot{x}_2 = w_2 \left\{ q_2 - x_2 (1 + \frac{w_2}{w_2} + \frac{w_2}{w_2}) \right\}, \\
\dot{x}_3 = w_3 \left\{ q_3 - x_3 (1 + \frac{w_3}{w_3} + \frac{w_3}{w_3}) \right\},
\]

in which \( w_3 \) is regarded as a constant. The nontrivial fixed point of this subsystem (8) is

\[
(w_1, w_2, x_1, x_2, x_3) = \left( \frac{w_3}{\gamma^*}, \frac{\beta^* w_3}{1 + \beta^* + \gamma^*}, \frac{\beta^* q_1}{1 + \beta^* + \gamma^*}, \frac{\gamma^* q_1}{1 + \beta^* + \gamma^*} \right),
\]

and the Jacobian matrix at this fixed point is

\[
\begin{pmatrix}
0 & 0 & -\frac{w_3}{\gamma^*} & 0 & 0 \\
0 & 0 & (1 + \beta^* + \gamma^*) w_3 & 0 & 0 \\
-\frac{q_1 (1 + \beta^* + \gamma^*)}{1 + \beta^* + \gamma^*} & -\frac{q_1}{1 + \beta^* + \gamma^*} & 0 & -\frac{\alpha_2 \beta^* w_2}{\gamma^*} & 0 \\
-\frac{q_2 \beta^*}{1 + \beta^* + \gamma^*} & 0 & 0 & 0 & 0 \\
-\frac{q_3 \gamma^*}{1 + \beta^* + \gamma^*} & 0 & 0 & 0 & (1 + \beta^* + \gamma^*) w_3
\end{pmatrix}.
\]

We rewrite this matrix (10) as

\[
\begin{pmatrix}
e_1 & 0 & -e_1 & 0 & 0 \\
0 & e_2 & 0 & -e_2 & 0 \\
e_3 & -e_4 & e_5 & 0 & 0 \\
e_6 & -e_7 & 0 & 0 & -e_8
\end{pmatrix},
\]

where \( e_1, \ldots, e_8 \) are positive constants given by

\[
e_1 = \frac{w_3}{\gamma^*}, \quad e_2 = \frac{\alpha_2 \beta^* w_3}{\gamma^*}, \quad e_3 = \frac{q_1 (1 + \beta^* + \gamma^*)}{1 + \beta^* + \gamma^*}, \quad e_4 = \frac{q_1}{1 + \beta^* + \gamma^*}, \\
e_5 = \frac{q_2 \beta^*}{1 + \beta^* + \gamma^*}, \quad e_6 = \frac{q_2 (1 + \gamma^*)}{1 + \beta^* + \gamma^*}, \quad e_7 = \frac{q_3 \gamma^*}{1 + \beta^* + \gamma^*}, \quad \text{and} \quad e_8 = \frac{1 + \beta^* + \gamma^*}{\gamma^*} w_3.
\]

Then, the eigenvalues of matrix (11) are given as

\[
-\frac{e_8}{2} + \frac{1}{2} \sqrt{e_8^2 - 2(e_1 e_3 + e_2 e_6) \pm 2 \sqrt{(e_1 e_3 - e_2 e_6)^2 + 4 e_1 e_2 e_4 e_5}},
\]

and

\[
-\frac{e_8}{2} + \frac{1}{2} \sqrt{e_8^2 - 2(e_1 e_3 + e_2 e_6) \pm 2 \sqrt{(e_1 e_3 - e_2 e_6)^2 + 4 e_1 e_2 e_4 e_5}}.
\]

From \( e_3 e_6 > e_4 e_5 \), we conclude that the real parts of these eigenvalues are all negative, which implies that the fixed point (9) is asymptotically stable. Moreover, imaginary eigenvalues appear if

\[
-2(e_1, e_3, e_2) e_6 - 2 \sqrt{(e_1 e_3 - e_2 e_6)^2 + 4 e_1 e_2 e_4 e_5} < 0.
\]

Substituting Eq. (12) into inequality (14), we have

\[
\left( \frac{1 + \beta^* + \gamma^*}{\gamma^*} \right)^2 - 2w_3 \left[ \frac{q_1 (1 + \gamma^*) + \alpha_2 q_2 \beta^* (1 + \gamma^*) + \sqrt{(q_1 (1 + \gamma^*) - \alpha_2 q_2 \beta^* (1 + \gamma^*) + 2} + 4 \alpha_2 q_1 q_2 (1 + \gamma^*))^2} \gamma^*(1 + \beta^* + \gamma^*) \right] < 0
\]

\[
\iff 0 < w_3 < \frac{2\gamma^* (q_1 (1 + \gamma^*) + \alpha_2 q_2 \beta^* (1 + \gamma^*) + \sqrt{(q_1 (1 + \gamma^*) - \alpha_2 q_2 \beta^* (1 + \gamma^*))^2 + 4 \alpha_2 q_1 q_2 (1 + \gamma^*))^2}}{(1 + \beta^* + \gamma^*)^3}.
\]

The fast variables stay in the vicinity of the fixed point in the full system after the transient process because the subsystem of the fast variables has the stable fixed point (9). Substituting \( x_3 = x_3^* + O(\varepsilon) \) into Eq. (7c) and further using Eqs. (3), (4), and (6), we obtain \( \dot{w}_3 = O(\varepsilon^2) \), which implies that \( w_3(t) = w_3(0) + O(\varepsilon^2) \) for \( t = O(1) \). Therefore, \( w_3 \) in inequality (15) can be regarded as \( w_3(0) \) in a good approximation. Thus, we conclude that oscillatory viral dynamics occur if there is a viral strain whose replication rate is considerably lower than the others and its initial value is sufficiently small. We also find that all viral mutants have the following shared effective growth rate: \( \lambda = O(\varepsilon) \). Note that these findings are the same as those obtained in the case of two viral mutants.
We demonstrate the following equation

\[
\text{det} Q_n = \left(1 - \sum_{l=1}^{n} \frac{x_l^+}{q_l}\right) \prod_{k=1}^{n} q_k,
\]

with mathematical induction. Obviously, Eq. (17) holds when \( n = 2 \). We assume that Eq. (17) is true when \( n = m \). Then,

\[
\text{det} Q_{m+1} = \begin{vmatrix}
q_1 - x_1^+ & -x_2^+ & \cdots & -x_m^+ & -x_{m+1}^+ \\
-x_2^+ & q_2 - x_2^+ & \cdots & -x_m^+ & -x_{m+1}^+ \\
\vdots & \vdots & \ddots & \vdots & \vdots \\
-x_m^+ & -x_m^+ & \cdots & q_m - x_m^+ & -x_{m+1}^+ \\
-x_{m+1}^+ & -x_{m+1}^+ & \cdots & -x_{m+1}^+ & q_{m+1} - x_{m+1}^+
\end{vmatrix}
\]

\[
= q_{m+1} \text{det} Q_m + \begin{vmatrix}
q_1 & 0 & \cdots & 0 & -x_1^+ \\
-1 & q_2 & \cdots & 0 & -x_2^+ \\
\vdots & \vdots & \ddots & \vdots & \vdots \\
-1 & -1 & \cdots & q_m & -x_m^+ \\
-1 & -1 & \cdots & -1 & q_{m+1} - x_{m+1}^+
\end{vmatrix}
\]

\[
= q_{m+1} \left(1 - \sum_{l=1}^{m} \frac{x_l^+}{q_l}\right) \left(\prod_{k=1}^{m} q_k\right) - q_1 q_2 \cdots q_m x_{m+1}^+ = \left(1 - \sum_{l=1}^{m+1} \frac{x_l^+}{q_l}\right) \prod_{k=1}^{m+1} q_k.
\]

Thus we have shown Eq. (17).

**Derivation of the fixed point \((w_j^*, x_i^*)\) of the subsystem.**

The subsystem of fast variables is as follows:

\[
w_j = \alpha_j w_j \left(1 - \frac{\Lambda}{\alpha_j} - x_j\right), \quad [18a]
\]

\[
x_i = w_i \left(q_i - x_i \frac{\sum_{l=1}^{n} w_l}{w_i}\right), \quad [18b]
\]

for \( 1 \leq j \leq n - 1 \) and \( 1 \leq i \leq n \). We regard \( w_n \) as a constant in this subsystem. Note that we set \( \Lambda \) as

\[
\Lambda = \frac{\left(\sum_{l=1}^{n} \frac{1}{q_l}\right) - 1}{\sum_{l=1}^{n} \frac{1}{\alpha_l q_l}}, \quad [19]
\]

and assume that

\[
\varepsilon \sum_{l=1}^{n} \frac{1}{\alpha_l q_l} > \left(\sum_{l=1}^{n} \frac{1}{q_l}\right) - 1, \quad [20]
\]

and

\[
\sum_{l=1}^{n} \frac{1}{q_l} > 1.
\]
We put
\[ x_i^* = 1 - \frac{A}{\alpha_i}, \]
so that we have \( w_j = 0 \) if \( x_j = x_j^* \). Obviously,
\[ x_1^* \geq x_2^* \geq \cdots \geq x_{n-1}^* > x_n^* = \frac{1}{\varepsilon} \left( \frac{1}{\sum_{l=1}^{n-1} \frac{1}{q_l}} + \varepsilon \sum_{l=1}^{n-1} \frac{1}{\alpha_l q_l} \right) > 0, \]
from \( \alpha_1 \geq \alpha_2 \geq \cdots \geq \alpha_{n-1} \gg \alpha_n \) and inequality (20). It also follows from Eq. (19) that
\[ 1 - \sum_{l=1}^{n-1} \frac{x^*_l}{q_l} = 1 - \sum_{l=1}^{n} \frac{1 - \varepsilon \alpha_l}{q_l} = 0. \]
Next, we let \( w^*_j (1 \leq j \leq n - 1) \) be the set of solutions for the following equations:
\[ w^*_j q_j - x^*_j (w_n + \sum_{l=1}^{n-1} w^*_l) = 0 \]
for \( 1 \leq j \leq n - 1 \). As shown below, the set of solutions \( w^*_j \) uniquely exists: Eq. (23) can be rewritten as
\[ R \begin{pmatrix} w^*_1 \\ w^*_2 \\ \vdots \\ w^*_{n-1} \end{pmatrix} = w_n \begin{pmatrix} x^*_1 \\ x^*_2 \\ \vdots \\ x^*_{n-1} \end{pmatrix}, \]
where
\[ R := \begin{pmatrix} q_1 - x^*_1 & \cdots & -x^*_1 \\ \vdots & \ddots & \vdots \\ -x^*_{n-1} & \cdots & q_n - x^*_n \end{pmatrix}. \]
According to Eqs. (17) and (22),
\[ \det R = \left( 1 - \sum_{l=1}^{n-1} \frac{x^*_l}{q_l} \right) \prod_{k=1}^{n-1} q_k = \frac{x_n^* \prod_{k=1}^{n-1} q_k}{q_n} > 0. \]
Therefore, we determine that \( R \) is a regular matrix, and we solve Eq. (24) as
\[ \begin{pmatrix} w^*_1 \\ w^*_2 \\ \vdots \\ w^*_{n-1} \end{pmatrix} = w_n R^{-1} \begin{pmatrix} x^*_1 \\ x^*_2 \\ \vdots \\ x^*_{n-1} \end{pmatrix}. \]
Finally, we demonstrate that the equations \( w_j = w^*_j \) and \( x_i = x_i^* \) satisfy \( \dot{x}_n = 0 \) in Eq. (18b). From Eq. (23), we have
\[ w^*_j = \left( w_n + \sum_{l=1}^{n-1} w^*_l \right) \frac{x^*_j}{q_j}. \]
Then,
\[ \sum_{j=1}^{n-1} w^*_j = \left( w_n + \sum_{l=1}^{n-1} w^*_l \right) \sum_{j=1}^{n-1} \frac{x^*_j}{q_j} \leqslant \sum_{j=1}^{n-1} w^*_i = \frac{w_n \sum_{j=1}^{n-1} \frac{x^*_j}{q_j}}{1 - \sum_{j=1}^{n-1} \frac{x^*_j}{q_j}}, \]
which implies that
\[ \dot{x}_n = w_n q_n - x_n^* \left( w_n + \sum_{l=1}^{n-1} w^*_l \right) = w_n \left( q_n - \frac{x_n^*}{1 - \sum_{j=1}^{n-1} \frac{x^*_j}{q_j}} \right) = 0. \]
We used \( 1 - \sum_{l=1}^{n-1} \frac{x^*_j}{q_i} = \frac{x^*_n}{q_n} \) from Eq. (22). According to Eq. (28) and \( w_n > 0 \), we also see that
\[ \sum_{l=1}^{n-1} w^*_l = \frac{w_n \sum_{j=1}^{n-1} \frac{x^*_j}{q_j}}{q_n} > 0. \]
Then, \( w^*_j > 0 \) from Eq. (27). Thus, we have proved that the system (18) has the unique fixed point \( (w^*_j, x^*_i) \) that satisfies \( w^*_j > 0 \) and \( x^*_i > 0 \).
Derivation of the characteristic polynomial $f(z)$ of Jacobian matrix $J$.

As we discussed in the main article,

$$f(z) = (z + bw_n) \det \begin{pmatrix} zI_{n-1} & -A \\ -R & (z + bw_n)I_{n-1} \end{pmatrix}. \tag{29}$$

where

$$A := -w_n \text{diag}(a_1, a_2, \ldots, a_{n-1})$$

and $R$ is given in Eq. (25). $I_{n-1}$ denotes the identity matrix of order $n - 1$. We employ the subsequent formula (1): if $S, T, U, V$ are square matrices and if $SU = US$, then

$$\det \begin{pmatrix} S & T \\ U & V \end{pmatrix} = \det(SV - UT). \tag{30}$$

We have

$$\det \begin{pmatrix} zI_{n-1} & -A \\ -R & (z + bw_n)I_{n-1} \end{pmatrix} = \det \begin{pmatrix} a_1(x_1^* - q_1) & a_2x_1^* & \cdots & a_{n-2}x_1^* & a_{n-1}x_1^* \\ a_1x_2 & a_2(x_2^* - q_2) & \cdots & a_{n-2}x_2 & a_{n-1}x_2 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ a_1x_{n-2} & \cdots & \cdots & -w_n & a_{n-2}x_{n-2} \\ a_1x_{n-1} & \cdots & \cdots & \cdots & \cdots & -w_n \end{pmatrix}$$

$$= \begin{vmatrix} z^2 + bw_n z + w_n a_1(q_1 - x_1^*) & -w_n a_2x_1^* & \cdots & -w_n a_{n-2}x_1^* & -w_n a_{n-1}x_1^* \\ -w_n a_2x_2 & z^2 + bw_n z + w_n a_2(q_2 - x_2^*) & \cdots & -w_n a_{n-2}x_2 & -w_n a_{n-1}x_2 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ -w_n a_{n-2}x_{n-2} & \cdots & \cdots & z^2 + bw_n z + w_n a_{n-2}(q_n - x_{n-2}) & -w_n a_{n-1}x_{n-2} \\ -w_n a_{n-1}x_{n-1} & \cdots & \cdots & \cdots & \cdots & \cdots & -w_n x_{n-1} \\ a_1 & a_2 & \cdots & a_{n-2} & a_{n-1} \end{vmatrix}.$$"
where $\delta_i$, $\eta_i$, and $\theta_i$ satisfy the following conditions for $1 \leq i \leq m$:

$$
\prod_{k=1}^{n-1} (X + a_kq_k) = \prod_{i=1}^m (X + \delta_i)^{\theta_i},
$$

$$
\delta_k < \delta_l \text{ if } k < l,
$$

and

$$
\sum_{l=1}^{n-1} \frac{a_l x_l^*}{X + a_l q_l} = \sum_{j=1}^m \frac{\eta_j}{X + \delta_j}.
$$

Obviously, $\delta_i > 0$, $\eta_i > 0$, $\theta_i > 0$ and $\sum_{i=1}^m \theta_i = n - 1$. We introduce a new function $h(X)$, which is a polynomial of degree $m$, as

$$
h(X) := \left(1 - \sum_{j=1}^m \frac{\eta_j}{X + \delta_j}\right) \prod_{i=1}^m (X + \delta_i).
$$

Then, from Eq. (34),

$$
g(X) = h(X) \prod_{i=1}^m (X + \delta_i)^{\theta_i-1}.
$$

From Eqs. (22) and (33), it follows that

$$
g(0) = \left(1 - \sum_{l=1}^{n-1} \frac{x_l^*}{q_l}\right) \prod_{k=1}^{n-1} (a_kq_k) = \frac{x_n^*}{q_n} \prod_{k=1}^{n-1} (a_kq_k) > 0.
$$

Thus, $h(0) > 0$ from Eq. (35). We also have

$$
h(-\delta_i) = -\eta_i \left| \prod_{l=1}^m \frac{(X + \delta_l)}{X + \delta_i}\right|_{X=-\delta_i}.
$$

It follows from $\eta_i > 0$ that

$$
\text{sgn } h(-\delta_i) = (-1)^i.
$$

We put $\delta_0 := 0$. Then, by the intermediate value theorem, $h(X)$ has a root in each interval $(-\delta_i, -\delta_{i-1})$ for $1 \leq i \leq m$. Therefore, $h(X)$ has $m$ negative roots. From Eq. (35), we have shown that the roots of $g(X)$ are all negative real numbers.

References

1. D Serre, *Matrices: Theory and Applications*. (Springer, New York, NY), Second edition, pp. 40–41,61 (2010).