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Global stability and periodic solution of the viral dynamics ☆

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Abstract

It is well known that the mathematical models provide very important information for the research of human immunodeficiency virus-type 1 and hepatitis C virus (HCV). However, the infection rate of almost all mathematical models is linear. The linearity shows the simple interaction between the T cells and the viral particles. In this paper, we consider the classical mathematical model with saturation response of the infection rate. By stability analysis we obtain sufficient conditions on the parameters for the global stability of the infected steady state and the infection-free steady state. We also obtain the conditions for the existence of an orbitally asymptotically stable periodic solution. Numerical simulations are presented to illustrate the results.

Keywords: Periodic solution; Global stability; HIV, HBV and HCV

1. Introduction

Mathematical modelling has been proven to be valuable in understanding the dynamics of HIV, HBV and HCV infection [1–6]. By direct application of models to data obtained from

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experiments in which antiretroviral drugs were given to perturb the dynamical state of infection in HIV-1 infected patients, minimal estimates of the death rate of productively infected cells, the rate of viral clearance and the viral production rate have been obtained [1–6]. Those models gave so accurate depiction of the virus load that they are almost consistent with the actual data. The research of mathematical models is very helpful for the clinical treatment. Especially, the models of combination therapy provide very important meaning for the cure of HIV. However, infection by HIV-1 and HCV has many puzzling quantitative features.

Pathogenesis of chronic infection with HBV, HIV and HCV is characterized by a dynamic equilibrium between viral production and clearance [1,5,7]. The introduction of antiviral therapy can upset this equilibrium by inhibiting virus production and causing a decline in the viral load. Indeed, the rate of decline in the viral load is a measure of the rate of viral clearance and by inference, it must be equivalent to the rate of virus production before therapy [1,5,7]. By using a system of differential equations, mathematical functions describing the level of virus over time can be derived, which predict the fall in serum virus concentration following the introduction of effective antiviral therapy. By using regression analysis one can fit the experimentally derived viral load data and derive quantitative estimates for the various kinetic parameters associated with the viral infection [3]. An essential prerequisite is the ability to accurately quantify the level of serum virus, and so along with the development of potent antiviral agents, the development of sensitive and specific DNA-based methods of viral quantification has been fundamental to the exploration of HIV, HCV and HBV dynamics.

The population dynamics of target cells ($CD4^+$ T cells in case of HIV or hepatic cells in case of HCV and HBV) is not completely understood. Nevertheless, a reasonable model for this population of cells is

$$\frac{dT}{dt} = s - dT + aT(1 - T/T_{\max}), \tag{1.1}$$

where s represents the rate at which new T cells are created from sources within the body, such as the thymus, T cells can also be created by proliferation of existing T cells. Here we represent the proliferation by a logistic function in which a is the maximum proliferation rate of target cells. $T_{\max}$ is the T population density at which proliferation shuts off. d is death rate of the T cells. If the population ever reaches $T_{\max}$, it should decrease; thus we impose the constraint $dT_{\max} > s$. Equation (1.1) has a single stable steady state given by

$$\hat{T} = \frac{T_{\max}}{2a}\big[a - d + \sqrt{(a-d)^2 + 4as/T_{\max}}\,\big]. \tag{1.2}$$

In the presence of virus, T cells become infected. The simplest and most common method of modelling infection is to augment (1.1) with a "mass-action" term in which the rate of infection is given by βVT, with β being the infection rate constant. This type of term is sensible, since virus must meet T cells in order to infect them and the probability of virus encountering a T cell at low concentrations (when V and T motions can be regarded as independent) can be assumed to be proportional to the product of their concentration, which is called linear infection rate. Thus, in what follows, the classical models assume that infected T cells at rate $-\beta VT$ and the generation of infected T cells at rate βVT.

With the simple mass-action infection term, the rates of change of uninfected cells, T, productively infected cells, I, and virus, V, are

$$\dot{T} = s - dT + aT(1 - T/T_{\max}) - \beta TV,$$

$$\dot{I} = \beta TV - \delta I,$$
$$\dot{V} = pI - cV, \tag{1.3}$$

where T is the number of target cells, I is the number of infected cells, V is the viral load of the virion. In model (1.3), δ is the loss rate constant of infective cells, p is the virion production rate for infected cell (p/δ is the total number of virion produced by a productively infected cell during its lifetime) and c is the clearance rate constant of free virion.

Although the rate of infection in most HIV models is bilinear in the virus V and the uninfected target cells T, actual incidence rates are probably not strictly linear in each variable over the entire range of V and T. For example, a less than linear response in V could occur due to saturation at high virus concentration, where the infectious fraction is high so that exposure is very likely. Thus, it is reasonable for us to assume that the infection rate of modelling HIV, HBV and HCV infection in saturated mass action, $\beta TV^p/(1+\alpha V^q)$, where $p, q, \alpha > 0$ are constants.

In this paper, we shall investigate the viral model with saturation response of the infection rate ($p = q = 1$). The model can be written as the following form:

$$\dot{T} = s - dT + aT(1 - T/T_{\max}) - \frac{\beta TV}{1+\alpha V},$$
$$\dot{I} = \frac{\beta TV}{1+\alpha V} - \delta I,$$
$$\dot{V} = pI - cV. \tag{1.4}$$

Standard and simple arguments show that solution of the system (1.4) always exists, and stay positive and bounded.

2. Equilibria, stability and periodic solution of saturation infection

The possible non-negative equilibria of system (1.4) are $E_1(\hat{T}, 0, 0)$, $E_2(\bar{T}, \bar{I}, \bar{V})$, where

$$\bar{T} = \frac{T_{\max}}{2a}\Big[a - d - \beta/\alpha + \sqrt{(a-d-\beta/\alpha)^2 + 4as/T_{\max} + 4ac\delta/(p\alpha T_{\max})}\Big],$$
$$\bar{I} = \frac{c}{p}\bar{V}, \quad \bar{V} = \frac{1}{\alpha c\delta}(p\beta\bar{T} - c\delta).$$

Now, we will begin the analysis of the stability of the equilibria of system (1.4).

Let $E^*(T^*, I^*, V^*)$ be any arbitrary equilibrium. Then the characteristic equation about E^* is given by

$$\begin{vmatrix} a - d - 2aT^*/T_{\max} - \frac{\beta V^*}{1+\alpha V^*} - \lambda & 0 & -\frac{\beta T^*}{(1+\alpha V^*)^2} \\ \frac{\beta V^*}{1+\alpha V^*} & -\delta - \lambda & \frac{\beta T^*}{(1+\alpha V^*)^2} \\ 0 & p & -c - \lambda \end{vmatrix} = 0. \tag{2.1}$$

For equilibrium $E_1(\hat{T}, 0, 0)$, (2.1) reduces to

$$(a - d - 2a\hat{T}/T_{\max} - \lambda)\big(\lambda^2 + (c+\delta)\lambda + c\delta - p\beta\hat{T}\big) = 0. \tag{2.2}$$

Hence, $E_1(\hat{T}, 0, 0)$ is asymptotically stable for $\hat{T} < c\delta/p\beta$, is a saddle with $\dim W^s(E_1) = 2$, $\dim W^u(E_1) = 1$ for $\hat{T} > c\delta/p\beta$.

Since $\hat{T}$ and $\bar{T}$ satisfy

$$
\begin{aligned}
&s + (a-d)\hat{T} - (a/T_{\max})\hat{T}^2 = 0,\\
&s + (a-d)\bar{T} - (a/T_{\max})\bar{T}^2 = \frac{1}{p\alpha}(p\beta\bar{T} - c\delta),\\
&\bar{T} > c\delta/p\beta \quad \Rightarrow \quad s + (a-d)\bar{T} - (a/T_{\max})\bar{T}^2 > 0 \quad \Rightarrow \quad \hat{T} > \bar{T},\\
&\bar{T} < c\delta/p\beta \quad \Rightarrow \quad s + (a-d)\bar{T} - (a/T_{\max})\bar{T}^2 < 0 \quad \Rightarrow \quad \hat{T} < \bar{T}.
\end{aligned}
$$

Hence, if $\bar{T} > c\delta/p\beta$, then $\hat{T} > \bar{T} > c\delta/p\beta$, and $E_1(\hat{T}, 0, 0)$ is unstable, at the same time, the positive equilibrium $E_2(\bar{T}, \bar{I}, \bar{V})$ exists. Further, if $\bar{T} < c\delta/p\beta$, then $\hat{T} < \bar{T} < c\delta/p\beta$, and $E_1(\hat{T}, 0, 0)$ is locally asymptotically stable, meanwhile, the positive equilibrium $E_2(\bar{T}, \bar{I}, \bar{V})$ ($\bar{I} < 0, \bar{V} < 0$) is not feasible.

Let

$$R_0 = \left(\frac{p\beta}{c\delta}\right)\bar{T}.$$

We can see that R_0 is a bifurcation parameter. When $R_0 < 1$, the uninfected steady state E_1 is stable and the infected steady state E_2 does not exist (unphysical). When $R_0 > 1$, E_1 becomes unstable and E_2 exists.

It is well known that the value, R_0, which is called the basic reproductive ratio of system (1.4), is very important (see [8]). Thus, the basic reproductive ratio, R_0 determines the dynamical properties of system (1.4) over a long period of time.

For system (1.3), it is known that the basic reproductive ratio is given by

$$R_{01} = \left(\frac{p\beta}{c\delta}\right)\hat{T}.$$

Obviously, there are very large differences of the basic reproductive ratio between the linear infection rate and saturation infection rate. If $\alpha \to 0$, then $\bar{T} \to (c\delta)/(p\beta)$, $R_0 \to 1$; if $\alpha \to \infty$, then $\bar{T} \to \hat{T}$, $R_0 \to R_{01}$.

For equilibrium $E_2(\bar{T}, \bar{I}, \bar{V})$, (2.1) reduces to

$$\lambda^3 + b_1\lambda^2 + b_2\lambda + b_3 = 0, \tag{2.3}$$

where

$$
\begin{aligned}
b_1 &= s/\bar{T} + a\bar{T}/T_{\max} + c + \delta > 0,\\
b_2 &= c\delta + (c+\delta)(s/\bar{T} + a\bar{T}/T_{\max}) - \frac{p\beta\bar{T}}{R_0^2}\\
&= \frac{1}{R_0}c\delta(R_0 - 1) + (c+\delta)(s/\bar{T} + a\bar{T}/T_{\max})\\
&> 0,\\
b_3 &= c\delta(s/\bar{T} + a\bar{T}/T_{\max}) + \frac{p\beta\bar{T}}{R_0^2}\left(\frac{\beta\bar{V}}{R_0} - \frac{s}{\bar{T}} - \frac{a\bar{T}}{T_{\max}}\right)\\
&= \frac{1}{R_0^2}(s/\bar{T} + a\bar{T}/T_{\max})c\delta R_0(R_0 - 1) + \frac{p\beta^2\bar{T}\bar{V}}{R_0^3}\\
&> 0.
\end{aligned}
$$

We also have

$$b_1b_2 - b_3 = \frac{c+\delta}{R_0^2}\left[c\delta R_0(R_0-1) + R_0^2(s/\bar{T} + a\bar{T}/T_{\max})(s/\bar{T} + a\bar{T}/T_{\max} + c + \delta) - \frac{\beta c\delta \bar{V}}{c+\delta}\right].$$

By Routh–Hurwitz criterion, we have the following Theorem 2.1.

Theorem 2.1. *Suppose that*

(i) $R_0 > 1$,
(ii) $c\delta R_0(R_0-1) + R_0^2(s/\bar{T} + a\bar{T}/T_{\max})(s/\bar{T} + a\bar{T}/T_{\max} + c + \delta) > \frac{\beta c\delta \bar{V}}{c+\delta}$.

Then the positive equilibrium $E_2(\bar{T}, \bar{I}, \bar{V})$ is asymptotically stable.

For the parameter values $T_0 = 1000$, $I_0 = 0$, $V_0 = 10^{-3}$, $d = 0.01$, $\delta = 0.5$, $c = 9$, $a = 7$, $T_{\max} = 1300$, $s = 5$, $\beta = 2 \times 10^{-4}$, $\alpha = 10^{-6}$. The number of infectious viruses released, p, varies in the literature. We first take $p = 1000$, then the conditions of Theorem 2.1 are satisfied. The infected steady state $E_2 = (23.32558428, 330.2337120, 36692.63466)$ is asymptotically stable. Numerical simulations show that trajectories of system (1.4) approach to the steady state. Increasing the p value will decrease the numbers of uninfected $CD4^+$ T-cells and infected cells and increasing the number of virus, but will not change the stability of the steady state. When $p = 2000$, the steady state becomes $E_2(11.67952500, 171.8100000, 38180.00000)$, which is asymptotically stable.

Indeed, for system (1.4), we have

$$\lim_{t\to+\infty} \sup T(t) \leqslant \hat{T} = \frac{T_{\max}}{2a}\left[a - d + \sqrt{(a-d)^2 + 4as/T_{\max}}\right].$$

Then there is $t_1 > 0$ such that for any sufficiently small $\epsilon > 0$, we have

$$T(t) \leqslant \hat{T} + \epsilon, \quad \text{for } t > t_1.$$

Theorem 2.2. *There is $M > 0$ such that, for any positive solution $(T(t), I(t), V(t))$ of system* (1.4)*,*

$$I(t) < M, \quad V(t) < M, \quad \textit{for all large } t.$$

Proof. Set

$$V_1(t) = T(t) + I(t).$$

Calculating the derivative of V_1 along the solutions of system (1.4), we find

$$\begin{aligned}\dot{V}_1(t) &= s - dT(t) + aT(t)\big(1 - T(t)/T_{\max}\big) - \delta I(t)\\ &= -dT(t) - \delta I(t) + aT(t) - a/T_{\max}T^2(t) + s\\ &= -dT(t) - \delta I(t) - a/T_{\max}(T - T_{\max}/2)^2 + (aT_{\max} + 4s)/4\\ &\leqslant -hV_1(t) + (aT_{\max} + 4s)/4.\end{aligned}$$

We have $\dot{V}_1(t) + hV_1(t) \leqslant M_0$, where $M_0 = (aT_{\max} + 4s)/4$, $h = \min(d, \delta)$. Further

$$V_1(t) < \frac{M_0}{h} + \left(V_1(0) - \frac{M_0}{h}\right)e^{-ht}.$$

Hence, we obtain the boundedness of $V_1(t)$, that is, there exist $t_2 > 0$ and $M_1 > 0$, such that $V_1(t) < M_1$, for $t > t_2$. Then $I(t)$ has an ultimately above bound. It follows from the third equation of Eq. (1.4) that $V(t)$ has an ultimately above bound, say, their maximum is an M. Then the assertion of Theorem 2.2 now follows and the proof is complete. This shows that system (1.4) is dissipative. □

Define

$$\Omega = \big\{(T, I, V)\colon\ 0 \leqslant T \leqslant \hat{T},\ 0 \leqslant I,\ V \leqslant M\big\}.$$

It is easy to see that, for system (1.4),

$$\dot{T} \geqslant s - dT + aT(1 - T/T_{\max}) - (\beta/\alpha)T,$$

which implies that

$$\liminf_{t\to\infty} T(t) \geqslant \frac{T_{\max}}{2a}\big[a - d - \beta/\alpha + \sqrt{(a - d - \beta/\alpha)^2 + 4as/T_{\max}}\,\big] \triangleq m.$$

Theorem 2.3. *If $R_0 < 1$, then $E_1(\hat{T}, 0, 0)$ is globally asymptotically stable.*

Proof. From the last two equations of Eq. (1.4), for $t > t_1$, we have

$$\begin{aligned} \dot{I} &\leqslant \beta\hat{T}V - \delta I, \\ \dot{V} &= pI - cV. \end{aligned} \tag{2.4}$$

We consider the comparison equations

$$\begin{aligned} \dot{z}_1 &= \beta\hat{T}z_2 - \delta z_1, \\ \dot{z}_2 &= pz_1 - cz_2. \end{aligned} \tag{2.5}$$

Since $R_0 < 1$, we have $p\beta\hat{T} < p\beta\bar{T} < c\delta$. It is easy to show that if $p\beta\hat{T} < c\delta$ for any solution of (2.5) with non-negative initial values we have $\lim_{t\to\infty} z_i(t) = 0$, $i = 1, 2$. Let $0 < I(0) \leqslant z_1(0)$, $0 < V(0) \leqslant z_2(0)$. If $(z_1(t), z_2(t))$ is a solution of system (2.5) with initial value $(z_1(0), z_2(0))$, then by the comparison theorem [9], we have $I(t) \leqslant z_1(t)$, $V(t) \leqslant z_2(t)$ for all $t > t_1$. Hence, $\lim_{t\to\infty} I(t) = 0$ and $\lim_{t\to\infty} V(t) = 0$. Moreover, $\lim_{t\to\infty} \inf T(t) \geqslant m$.

For $\epsilon \in (0, 1)$ sufficiently small, there exists $t_2 = t_2(\epsilon)$ such that, for $t > t_2$,

$$s + (a - d - \beta\epsilon)T - (a/T_{\max})T^2 \leqslant \dot{T}(t) \leqslant s + (a - d)T - (a/T_{\max})T^2.$$

This clearly shows that $\lim_{t\to\infty} T(t) = \hat{T}$. This proves the theorem. □

Theorem 2.4. *If $R_0 > 1$, then system* (1.4) *is permanent.*

Proof. If $R_0 > 1$, we have $\hat{T}\,p\beta > \bar{T}\,p\beta > c\delta$. We begin by verifying weak persistence of (1.4). If it is not weakly persistent, it follows from the proof of Theorem 2.2 that there is a positive orbit $(T(t), I(t), V(t))$ of (1.4) such that

$$\lim_{t\to+\infty} T(t) = \hat{T}, \qquad \lim_{t\to+\infty} I(t) = 0, \qquad \lim_{t\to+\infty} V(t) = 0.$$

Since $\hat{T} > (c\delta)/(p\beta)$, we can choose $\epsilon > 0$ small enough such that

$$\frac{\hat{T}-\epsilon}{1+\alpha\epsilon} > \frac{c\delta}{p\beta}. \tag{2.6}$$

Since $\lim_{t\to+\infty} T(t) = \hat{T}$, $\lim_{t\to+\infty} V(t) = 0$, for this ϵ, we can choose $t_0 > 0$ large enough such that if $t > t_0$, we have

$$T(t) > \hat{T} - \epsilon, \qquad V(t) < \epsilon,$$

and

$$\begin{aligned} \dot{I}(t) &= \frac{\beta T(t)}{1+\alpha V(t)} V(t) - \delta I(t) \geqslant \frac{\beta(\hat{T}-\epsilon)}{1+\alpha\epsilon} V(t) - \delta I(t), \\ \dot{V}(t) &= pI(t) - cV(t), \quad \text{for } t > t_0. \end{aligned} \tag{2.7}$$

Let us consider the matrix A_ϵ defined by

$$A_\epsilon = \begin{pmatrix} -\delta & \frac{\beta(\hat{T}-\epsilon)}{1+\alpha\epsilon} \\ p & -c \end{pmatrix}.$$

Since A_ϵ admits positive off-diagonal element, the Perron–Frobenius theorem implies that there is positive eigenvector $v = (v_1, v_2)$ for the maximum eigenvalue α_1 of A_ϵ. Moreover, by (2.6), we see that the maximum eigenvalue α_1 is positive.

Let us consider

$$\begin{aligned} \dot{z}_1 &= \frac{\beta(\hat{T}-\epsilon)}{1+\alpha\epsilon} z_2 - \delta z_1, \\ \dot{z}_2 &= pz_1 - cz_2. \end{aligned} \tag{2.8}$$

Let $z(t) = (z_1(t), z_2(t))$ be a solution of (2.8) through (lv_1, lv_2) at $t = t_0$, where $l > 0$ satisfies $lv_1 < I(t_0)$, $lv_2 < V(t_0)$. Since the semiflow of (2.8) is monotone and $A_\epsilon v > 0$, it follows that $z_i(t)$ is strictly increasing and $z_i(t) \to +\infty$, as $t \to +\infty$, contradicting the eventual boundedness of positive solution of (1.4). Thus, no positive orbit of (1.4) tends to $(\hat{T}, 0, 0)$ as t tends to infinity. This shows that (1.4) is weakly persistent. Then an application of the techniques given in [10] concludes the permanence of (1.4). The proof of Theorem 2.4 is complete. □

M. Hirsch [9], H.R. Zhu and H.L. Smith [11] and H.L. Smith and H. Thieme [12] proved that three-dimensional competitive systems that live in convex sets have the Poincaré–Bendixson property; that is, any non-empty compact omega limit set that contains no equilibria must be a closed orbit.

Theorem 2.5. *Assume D is convex and bounded. Suppose system*

$$\dot{X} = F(X), \quad X \in D, \tag{2.9}$$

is competitive and permanent and has the property of stability of periodic orbit. If $\bar{X}_0$ is the only equilibrium point in int D *and if it is locally asymptotically stable, then it is globally asymptotically stable in* int D.

By looking at its Jacobian matrix and choosing the matrix H as

$$H = \begin{pmatrix} 1 & 0 & 0 \\ 0 & -1 & 0 \\ 0 & 0 & 1 \end{pmatrix},$$

we see that system (1.4) is competitive in Ω, with respect to the partial order defined by the orthant $K_1 = \{(T, I, V) \in R^3 \colon T \geqslant 0,\ I \leqslant 0,\ V \geqslant 0\}$.

Theorem 2.6. *Suppose that*

(i) $R_0 > 1$,
(ii) $c\delta R_0(R_0 - 1) + R_0^2(s/\bar{T} + a\bar{T}/T_{\max})(s/\bar{T} + a\bar{T}/T_{\max} + c + \delta) > \frac{\beta c\delta \bar{V}}{c+\delta}$.

Then the positive equilibrium E_2 of Eq. (1.4) *is globally asymptotically stable provided that one of the following two assumptions holds*:

(iii) $T_{\max}(a - d)/(2a) < m < \hat{T} < T_{\max}(a - d + \delta)/(2a)$,
(iv) $m > T_{\max}(a - d + \delta)/(2a)$.

The proof of this theorem is the same as those of Theorems 2.1 and 4.2 in [9]. Since system (1.4) is competitive and permanent, and E_2 is locally asymptotically stable if (i) and (ii) hold. Furthermore, in accordance with Theorem 2.5 (where we can choose $D = \Omega$), Theorem 2.6 would be established if we show that system (1.4) has the property of stability of periodic orbits. In the following, we prove it.

Proposition 2.1. *Assume condition* (iii) *or* (iv) *of Theorem* 2.6 *hold true. Then system* (1.4) *has the property of stability of periodic orbits.*

Proof. Let $P(t) = (T(t), I(t), V(t))$ be a periodic solution whose orbit Γ is contained in $\operatorname{int}\Omega$. In accordance with the criterion given by Muldowney in [13], for the asymptotic orbital stability of a periodic orbit of a general autonomous system, it is sufficient to prove that the linear non-autonomous system

$$\dot{W}(t) = \big(DF^{[2]}\big(P(t)\big)\big)W(t) \tag{2.10}$$

is asymptotically stable, where $DF^{[2]}$ is the second additive compound matrix of the Jacobian DF (see Appendix A).

The Jacobian of Eq. (1.4) is given by

$$DF = \begin{pmatrix} a - d - \frac{2a}{T_{\max}}T - \frac{\beta V}{1+\alpha V} & 0 & -\frac{\beta T}{(1+\alpha V)^2} \\ \frac{\beta V}{1+\alpha V} & -\delta & \frac{\beta T}{(1+\alpha V)^2} \\ 0 & p & -c \end{pmatrix}.$$

For the solution $P(t)$, Eq. (2.10) becomes

$$\begin{aligned} \dot{W}_1 &= -\left(\delta - a + d + \frac{2a}{T_{\max}}T + \frac{\beta V}{1+\alpha V}\right)W_1 + \frac{\beta T}{(1+\alpha V)^2}(W_2 + W_3), \\ \dot{W}_2 &= pW_1 + \left(a - d - \frac{2a}{T_{\max}}T - \frac{\beta V}{1+\alpha V} - c\right)W_2, \\ \dot{W}_3 &= \frac{\beta V}{1+\alpha V}W_2 - (c+\delta)W_3. \end{aligned} \tag{2.11}$$

To prove that Eq. (2.11) is asymptotically stable, we shall use the following Lyapunov function, which is similar to the one found in [14] for the SEIR model,

$$L\big(W_1(t), W_2(t), W_3(t), T(t), I(t), V(t)\big) = \left\| \left(W_1(t), \frac{I(t)}{V(t)} W_2(t), \frac{I(t)}{V(t)} W_3(t) \right) \right\|,$$

where $\|\cdot\|$ is the norm in R^3 defined by

$$\big\|(W_1, W_2, W_3)\big\| = \sup\big\{|W_1|, |W_2| + |W_3|\big\}.$$

From Theorem 2.4, we obtain that the orbit of $P(t)$ remains at a positive distance from the boundary of Ω. Therefore

$$I(t) \geqslant \eta, \quad V(t) \geqslant \eta, \quad \eta = \min\{\underline{I}, \underline{V}\} \text{ for all large } t.$$

Hence, the function $L(t)$ is well defined along $P(t)$ and

$$L(W_1, W_2, W_3; T, I, V) \geqslant \frac{\eta}{M} \big\|(W_1, W_2, W_3)\big\|. \tag{2.12}$$

Along a solution (W_1, W_2, W_3) of the system (2.11), $L(t)$ becomes

$$L(t) = \sup\left\{ \big|W_1(t)\big|, \frac{I(t)}{V(t)} \big(\big|W_2(t)\big| + \big|W_3(t)\big| \big) \right\}.$$

Then we have the following inequalities:

$$\begin{aligned}
D_+\big|W_1(t)\big| &\leqslant -\left(\delta - a + d + \frac{2a}{T_{\max}} T + \frac{\beta V}{1+\alpha V} \right) \big|W_1(t)\big| \\
&\quad + \frac{\beta T}{(1+\alpha V)^2} \big(\big|W_2(t)\big| + \big|W_3(t)\big| \big), \\
D_+\big|W_2(t)\big| &\leqslant -\left(c - a + d + \frac{2a}{T_{\max}} T + \frac{\beta V}{1+\alpha V} \right) \big|W_2(t)\big| + p\big|W_1(t)\big|, \\
D_+\big|W_3(t)\big| &\leqslant -(c+\delta)\big|W_3(t)\big| + \frac{\beta V}{1+\alpha V} \big|W_2(t)\big|.
\end{aligned} \tag{2.13}$$

From (2.13), we get

$$\begin{aligned}
D_+ \frac{I}{V} \big(|W_2| + |W_3| \big) &= \left(\frac{\dot I}{V} - \frac{I\dot V}{V^2} \right) \big(|W_2| + |W_3| \big) + \frac{I}{V} D_+ \big(|W_2| + |W_3| \big) \\
&\leqslant \left(\frac{\dot I}{I} - \frac{\dot V}{V} \right) \frac{I}{V} \big(|W_2| + |W_3| \big) + \frac{pI}{V} |W_1| \\
&\quad - \left(c - a + d + \frac{2a}{T_{\max}} T \right) \frac{I}{V} |W_2| - (c+\delta) \frac{I}{V} |W_3|.
\end{aligned}$$

Thus, we can obtain

$$D_+ L(t) \leqslant \sup\big\{ g_1(t), g_2(t) \big\} L(t), \tag{2.14}$$

where

$$\begin{aligned}
g_1(t) &= -\delta + a - d - \frac{2a}{T_{\max}} T - \frac{\beta V}{1+\alpha V} + \frac{\beta T V}{I(1+\alpha V)^2}, \\
g_2(t) &= \frac{pI}{V} + \frac{\dot I}{I} - \frac{\dot V}{V} - G_1, \\
G_1 &= \min\{ c - a + d + 2aT/T_{\max}, c + \delta \}.
\end{aligned}$$

From the second equation of system (1.4), we have

$$\begin{aligned} g_1(t) &= -\delta + a - d - \frac{2a}{T_{\max}}T - \frac{\beta V}{1+\alpha V} + \frac{\beta T V}{I(1+\alpha V)^2} \\ &\leqslant -\delta + a - d - \frac{2a}{T_{\max}}T - \frac{\beta V}{1+\alpha V} + \frac{\beta T V}{I(1+\alpha V)} \\ &= a - d - \frac{2a}{T_{\max}}T - \frac{\beta V}{1+\alpha V} + \frac{\dot{I}}{I}. \end{aligned}$$

If (iii) holds, then $-\delta < a - d - 2aT/T_{\max} < 0$, that is, $G_1 = c - a + d + 2aT/T_{\max}$. Then we get

$$g_2(t) = a - d - \frac{2a}{T_{\max}}T + \frac{\dot{I}}{I}.$$

Hence,

$$\sup\{g_1(t), g_2(t)\} \leqslant a - d - \frac{2a}{T_{\max}}T + \frac{\dot{I}}{I} \leqslant -\mu + \frac{\dot{I}}{I}, \tag{2.15}$$

where $\mu > 0$ is such that $a - d - 2aT/T_{\max} \leqslant -\mu < 0$.

If (iv) holds, then $a - d - 2aT/T_{\max} \leqslant -\delta$, that is $G_1 = c + \delta$. Then we get

$$g_2(t) = c - c - \delta + \frac{\dot{I}}{I} = \frac{\dot{I}}{I} - \delta.$$

Hence,

$$\sup\{g_1(t), g_2(t)\} \leqslant \frac{\dot{I}}{I} - \delta. \tag{2.16}$$

Let $\mu_1 = \min\{\mu, \delta\}$. Then, from (2.15) and (2.16), we have

$$\sup\{g_1(t), g_2(t)\} \leqslant -\mu_1 + \frac{\dot{I}}{I}. \tag{2.17}$$

Therefore, from (2.14) and Gronwall's inequality, we obtain

$$L(t) \leqslant L(0)I(t)e^{-\mu_1 t} \leqslant L(0)Me^{-\mu_1 t},$$

which implies that $L(t) \to 0$ as $t \to +\infty$. By (2.12) it turns out that

$$\big(W_1(t), W_2(t), W_3(t)\big) \to 0, \quad \text{as } t \to +\infty.$$

This implies that the linear system equation (2.11) is asymptotically stable and therefore the periodic solution is asymptotically orbitally stable. This proves Proposition 2.1. □

As noted before, this result proves Theorem 2.6.

Theorem 2.7. *Suppose that*

(i) $R_0 > 1$,
(ii) $c\delta R_0(R_0 - 1) + R_0^2(s/\bar{T} + a\bar{T}/T_{\max})(s/\bar{T} + a\bar{T}/T_{\max} + c + \delta) < \frac{\beta c\delta \bar{V}}{c+\delta}$.

Then system (1.4) *has an orbitally asymptotically stable periodic solution.*

Proof. A change of variables $z_1 = -T$, $z_2 = I$ and $z_3 = -V$ transforms (1.4) as

$$\begin{aligned}
\dot{z}_1 &= -s - dz_1 + az_1(1 + z_1/T_{\max}) + \frac{\beta z_1 z_3}{1 - \alpha z_3},\\
\dot{z}_2 &= \frac{\beta z_1 z_3}{1 - \alpha z_3} - \delta z_2,\\
\dot{z}_3 &= -pz_2 - cz_3.
\end{aligned} \tag{2.18}$$

If we write this system as $\dot{z} = f(z)$, the Jacobian matrix of f at z is given by

$$J(z) = \begin{pmatrix}
-d + a + 2az_1/T_{\max} + \frac{\beta z_3}{1-\alpha z_3} & 0 & \frac{\beta z_1}{(1-\alpha z_3)^2}\\
\frac{\beta z_3}{1-\alpha z_3} & -\delta & \frac{\beta z_1}{(1-\alpha z_3)^2}\\
0 & -p & -c
\end{pmatrix}.$$

Define set E by

$$E = \big\{(z_1, z_2, z_3)\colon\ z_1 \leqslant 0,\ z_2 \geqslant 0,\ z_3 \leqslant 0\big\}.$$

Since $J(z)$ has non-positive off-diagonal elements at each point of E, (2.18) is competitive at E. Set $z^* = (-T^*, I^*, -V^*)$. It is easy to see that z^* is unstable and $\det J(z^*) < 0$. Furthermore, it follows from Theorem 2.4 that there exists a compact set B in the interior of E such that for each $z_0 \in \operatorname{int} E$, there exists $T(z_0) > 0$ such that $z(t, z_0) \in B$ for all $t > T(z_0)$. Consequently, by Theorem 1.2 of [11], the system has an orbitally asymptotically stable periodic solution. The proof of Theorem 2.7 is complete. □

3. The drug effectiveness under the saturation infection

We consider the following model

$$\begin{aligned}
\dot{T} &= s - dT + aT(1 - T/T_{\max}) - (1 - \eta)\beta\frac{TV}{1 + \alpha V},\\
\dot{I} &= (1 - \eta)\beta\frac{TV}{1 + \alpha V} - \delta I,\\
\dot{V} &= (1 - \epsilon)pI - cV,
\end{aligned} \tag{3.1}$$

where $\eta =$ efficiency of drug therapy in preventing new infections; $\epsilon =$ efficiency of drug therapy in inhibiting viral production; and the other parameters are defined as in Eq. (1.4). Before IFN therapy, $\epsilon = \eta = 0$. Once therapy is initiated, $0 < \epsilon < 1$ or $0 < \eta < 1$ or both.

In this section, we are following the approach of Perelson and Nelson [6]. Before therapy begins, viral loads are relatively constant. Thus $dV/dt = 0$, which implies

$$(1 - \epsilon)pI_0 = cV_0, \quad \epsilon = \eta = 0, \tag{3.2}$$

where the subscript 0 is used to denote a pretreatment quasi-steady state value. Because V is relatively constant for weeks before therapy, this implies that I must also be relatively constant (assuming that the various model parameters ϵ, p and c are also constant). For I to be constant, we assume $dI/dt = 0$ on this same time scale, and thus

$$(1 - \eta)\beta T_0 V_0 = \delta I_0(1 + \alpha V_0), \quad \epsilon = \eta = 0. \tag{3.3}$$

Generally, the concentration of productively infected cells, I, is not measured in patients. However, T cell counts and viral loads are monitored, and it is reasonable to assume that the $CD4^+$

T cell concentration and the viral load are known. The vast majority of cells susceptible to HIV infection are CD4$^+$ T cells [15], and we shall assume that T_0 is equal to the CD4$^+$ T count at the start of therapy. Using Eq. (3.3) one can then determine I_0. Thus, for patients in quasi-steady state before antiretroviral therapy begins, V_0, T_0 and I_0 provide initial conditions for Eq. (3.1).

The T cell count changes in HIV-1 infected patients, but on a time scale of years. If we assume that on a scale of weeks the T cell count as well as V and I do not change, we can compute a full pretreatment steady state. Equations (3.2) and (3.3) imply that for I_0 and T_0 to be in quasi-steady state,

$$I_0 = \frac{cV_0}{(1-\epsilon)p}, \quad T_0 = \frac{c\delta + c\delta\alpha V_0}{(1-\eta)\beta(1-\epsilon)p}, \quad \epsilon = \eta = 0.$$

V_0 satisfies the following equality:

$$s - dT_0 + aT_0(1 - T_0/T_{\max}) - (1-\eta)\beta\frac{T_0V_0}{1+\alpha V_0} = 0, \quad \epsilon = \eta = 0.$$

If we assume that for a short period after therapy is initiated, $T = \text{constant} = T_0$, $\epsilon > 0$ or $\eta > 0$ or both, I and V vary according to the last two equations of system (3.1), then the system (3.1) becomes the following system:

$$\begin{aligned} \dot{I} &= (1-\eta)\beta T_0\frac{V}{1+\alpha V} - \delta I, \\ \dot{V} &= (1-\epsilon)pI - cV. \end{aligned} \tag{3.4}$$

The possible non-negative equilibria of system (3.4) are $O(0,0)$, $E(I^*, V^*)$, where

$$I^* = \frac{(1-\epsilon)p(1-\eta)\beta T_0 - c\delta}{\alpha\delta(1-\epsilon)p}, \qquad V^* = \frac{(1-\epsilon)p}{c}I^*.$$

The characteristic equation of equilibrium $O(0,0)$ is

$$\lambda^2 + (c+\delta)\lambda + c\delta - (1-\epsilon)p(1-\eta)\beta T_0 = 0.$$

In the general case, when $c\delta \neq (1-\epsilon)p(1-\eta)\beta T_0$, the $O(0,0)$ is a stable fixed point if $c\delta > (1-\epsilon)p(1-\eta)\beta T_0$ and a saddle point if $c\delta < (1-\epsilon)p(1-\eta)\beta T_0$.

The characteristic equation of equilibrium $E(I^*, V^*)$ is

$$\lambda^2 + (c+\delta)\lambda + c\delta\frac{(1-\epsilon)p(1-\eta)\beta T_0 - c\delta}{(1-\epsilon)p(1-\eta)\beta T_0} = 0.$$

Hence, the $E(I^*, V^*)$ is a stable fixed point if $c\delta < (1-\epsilon)p(1-\eta)\beta T_0$ and the $E(I^*, V^*)$ does not exist if $c\delta > (1-\epsilon)p(1-\eta)\beta T_0$.

If $c\delta > (1-\epsilon)p(1-\eta)\beta T_0$, then $O(0,0)$ is asymptotically stable, and the solution of one order linear approximation equation of system (3.4), with T constant, is

$$V(t) = V_0\big[Ae^{-\lambda_1(t-t_0)} + (1-A)e^{-\lambda_2(t-t_0)}\big], \quad t > t_0,$$

where

$$\begin{aligned} \lambda_{1,2} &= \frac{(c+\delta) \pm \sqrt{(c+\delta)^2 + 4[(1-\eta)\beta(1-\epsilon)pT_0 - c\delta]}}{2} \\ &= \frac{(c+\delta) \pm \sqrt{(c-\delta)^2 + 4(1-\eta)\beta(1-\epsilon)pT_0}}{2}. \end{aligned}$$

For example, we choose $T_0 = \frac{c\delta}{(1-\eta)\beta p} < \frac{c\delta}{(1-\epsilon)p(1-\eta)\beta}$, the origin is a stable point, and according to

$$V(t=t_0) = V_0, \qquad \left.\frac{dV}{dt}\right|_{t=t_0} = -\epsilon c V_0.$$

We can obtain

$$\lambda_{1,2} = \frac{(c+\delta) \pm \sqrt{(c-\delta)^2 + 4(1-\epsilon)c\delta}}{2}, \qquad A = (\epsilon c - \lambda_2)/(\lambda_1 - \lambda_2).$$

From the above discussion, we can obtain the threshold value parameter

$$R_{02} = \frac{(1-\epsilon)p(1-\eta)\beta T_0}{c\delta}.$$

If $R_{02} < 1$, the virus is cleared and the disease dies out; if $R_{02} > 1$, then virus persists in the host.

4. Discussion

In this paper, we consider the classical mathematical model with saturation response of the infection rate. By stability analysis we obtain sufficient conditions on the parameters for the global stability of the infected steady state and the infection-free steady-state. We also show that periodic oscillations in the viral load and T cell populations are possible. Biologically, it implies that some of the parameter values can cause the cell and virus population to fluctuate.

Our analysis establishes that the global dynamics of T cells are completely determined by a basic reproductive ratio R_0. If $R_0 < 1$, the virus is cleared and the disease dies out. If $R_0 > 1$, then virus persists in the host, solutions approaching either a chronic disease steady state E_2 or a periodic orbit.

For system (1.3) with the simple mass-action infection term, it is known that the basic reproductive ratio is given by R_{01}. Obviously, there are very large differences of the basic reproductive ratio between the linear infection rate and saturation infection rate. If $\alpha \to 0$, then $\bar{T} \to (c\delta)/(p\beta)$, $R_0 \to 1$; if $\alpha \to \infty$, then $\bar{T} \to \hat{T}$, $R_0 \to R_{01}$. Hence, the system (1.3) with the simple mass-action infection term is an extreme case of the HIV model (1.4) in this paper.

Let $(\bar{T}_1, \bar{I}_1, \bar{V}_1)$ be the infected steady-state of system (1.3) when $R_{01} > 1$, where

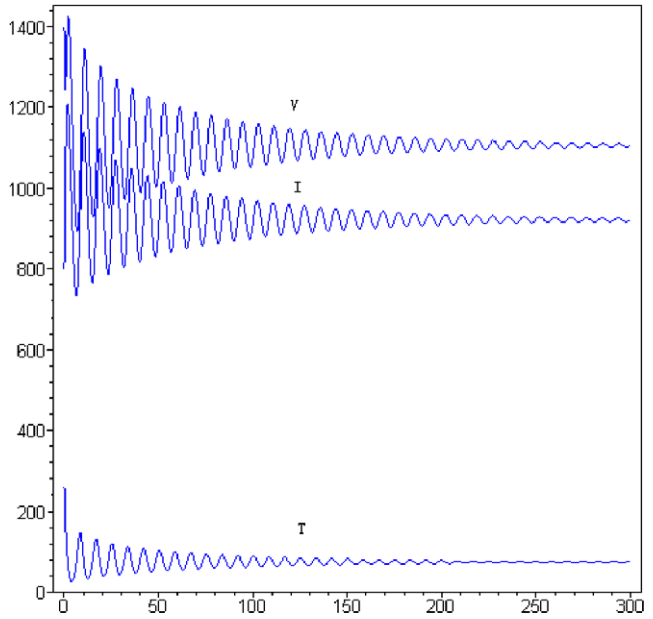
$$\bar{T}_1 = \frac{c\delta}{p\beta}, \qquad \bar{I}_1 = \frac{1}{\delta}\big[s - d\bar{T}_1 + a\bar{T}_1(1 - \bar{T}_1/T_{\max})\big],$$
$$\bar{V}_1 = \frac{p}{c\delta}\big[s - d\bar{T}_1 + a\bar{T}_1(1 - \bar{T}_1/T_{\max})\big].$$

We have $\bar{T} > \bar{T}_1$, $\bar{V} < \bar{V}_1$, $R_0 < R_{01}$. Thus, although the threshold behavior and dynamic behavior of system (1.4) in this paper are similar to those of system (1.3), the basic reproductive ratio R_0 of system (1.4) is less than R_{01}, the virus level of the endemic equilibrium state is less than those of (1.3).

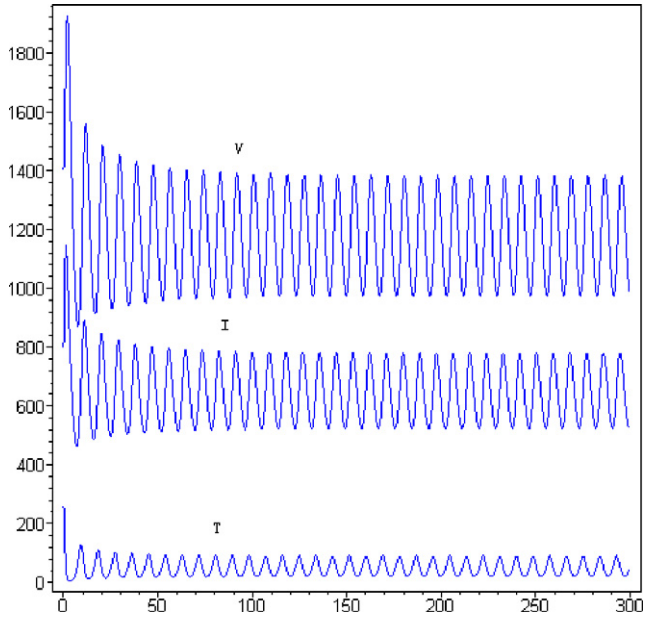
In the range of parameters that was found to be realistic, we find with model (1.4) the next behaviors (1)–(4).

(1) For the following parameter values, $d = 0.002$, $\delta = 0.24$, $c = 2.0$, $a = 3$, $T_{\max} = 1500$, $s = 10$, $\beta = 0.0027$, $\alpha = 0.000001$, $p = 2.4$, the conditions (i), (ii) of Theorem 2.1 are satisfied. Then the positive equilibrium E_2 of Eq. (1.4) is locally asymptotically stable (see Fig. 1(a)).

(2) For the following parameter values, $d = 0.002$, $\delta = 0.24$, $c = 1.32$, $a = 3$, $T_{\max} = 1500$, $s = 10$, $\beta = 0.0027$, $\alpha = 0.000001$, $p = 2.4$, the conditions (i), (ii) of Theorem 2.7 are satisfied. Then the system (1.4) has an orbitally asymptotically stable periodic solution (see Fig. 1(b)).

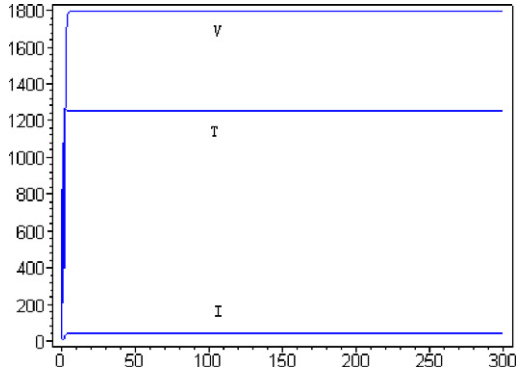


(a)

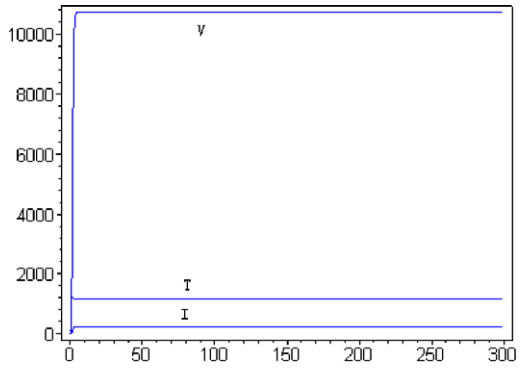


(b)

Fig. 1.



(a)



(b)

Fig. 2.

(3) For the following parameter values, $d = 0.01$, $\delta = 4$, $c = 9$, $a = 4$, $T_{\max} = 1300$, $s = 4$, $\beta = 0.0002$, $\alpha = 0.001$, $p = 400$, the conditions (i)–(iii) of Theorem 2.6 are satisfied. Then the positive equilibrium E_2 of Eq. (1.4) is globally asymptotically stable (see Fig. 2(a)).

(4) For the following parameter values, $d = 0.01$, $\delta = 5$, $c = 9$, $a = 10$, $T_{\max} = 1300$, $s = 5$, $\beta = 0.0002$, $\alpha = 0.0001$, $p = 400$, the conditions (i), (ii) and (iv) of Theorem 2.6 are satisfied. Then the positive equilibrium E_2 of Eq. (1.4) is globally asymptotically stable (see Fig.2(b)).

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Appendix A

In this appendix, we shall give the definition of an additive compound matrix. A survey of properties of additive compound matrices together with their connections to differential equations may be found in [13,14].

We start by recalling the definition of a kth exterior power or multiplicative compound of a matrix.

Definition A.1. Let A be an $n \times m$ matrix of real or complex numbers. Let $a_{i_1,\dots,i_k,j_1,\dots,j_k}$ be the minor of A determined by the rows $(i_1,\dots,i_k)$ and the columns $(j_1,\dots,j_k)$, $1 \leqslant i_1 < i_2 < \cdots < i_k \leqslant n$, $1 \leqslant j_1 < j_2 < \cdots < j_k \leqslant m$. The kth multiplicative compound matrix $A^{(k)}$ of A is the $\binom{n}{k} \times \binom{m}{k}$ matrix whose entries, written in lexicographic order, are $a_{i_1,\dots,i_k,j_1,\dots,j_k}$.

In particular, when A is an $n \times k$ matrix with columns $a_1, a_2, \dots, a_k$, $A^{(k)}$ is the exterior product $a_1 \wedge a_2 \wedge \cdots \wedge a_k$.

In the case $m = n$, the additive compound matrices are defined in the following way.

Definition A.2. Let A be an $n \times n$ matrix. The kth additive compound $A^{[k]}$ of A is the $\binom{n}{k} \times \binom{m}{k}$ matrix given by

$$A^{[k]} = D(I + hA)^{(k)}\big|_{h=0}. \tag{A.1}$$

If $B = A^{[k]}$, then the following formula for $b_{i,j}$ can be deduced from Eq. (A.1). For any integer $i = 1,\dots,\binom{n}{k}$, let $(i) = (i_1, i_2, \dots, i_k)$ be the ith member in the lexicographic ordering of all k-tuples of integers such that $1 \leqslant i_1 < i_2 < \cdots < i_k \leqslant n$. Then

$$b_{i,j} = \begin{cases} a_{i_1,i_1} + \cdots + a_{i_k,i+k} & \text{if } (i) = (j), \\ (-1)^{r+s} a_{i_s,j_r} & \text{if exactly one entry } i_s \text{ in } (i) \text{ does not occur in } (j) \\ & \quad \text{and } j_r \text{ does not occur in } (i), \\ 0 & \text{if } (i) \text{ differs from } (j) \text{ in two or more entries.} \end{cases}$$

In the extreme cases when $k = 1$ and $k = n$, we have $A^{[1]} = A$ and $A^{[n]} = \operatorname{tr}(A)$. For $n = 3$, the matrices $A^{[k]}$ are as follows:

$$A^{[1]} = A, \qquad A^{[2]} = \begin{pmatrix} a_{11} + a_{22} & a_{23} & -a_{13} \\ a_{32} & a_{11} + a_{33} & a_{12} \\ -a_{31} & a_{21} & a_{22} + a_{33} \end{pmatrix}, \qquad A^{[3]} = a_{11} + a_{22} + a_{33}.$$

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