

A Mathematical Study on Immune Activation and Related Dynamics in HIV Infection

Zhan Shu, Esteban A. Hernandez-Vargas, and Richard H. Middleton

Abstract—Over decades, mathematical models have been applied successfully to the investigation of HIV dynamics. However, few of these investigations are able to explain the observation that host (CD4+ T) cell counts reduce, while viral load increases as the infection progresses. Various clinical studies of HIV infection have suggested that high T-cell activation levels are positively correlated with rapid disease development in untreated patients. This activation might be a major reason for the depletion of CD4+ T cells observed in most cases of long term untreated HIV infection. In this paper, we use a simple mathematical model to investigate immune activation and its role in HIV infection. Under reasonable assumptions relating to various HIV infection constants, we show that enhanced activation and reduced reversion in the immune system do result in depleted CD4+ T cell count. We further show that this process is robust to parameter variations. An extended model including viral dynamics illustrates the effects of immune activation on viral persistence and immune response. Simulations are given to verify the theoretical analysis.

I. INTRODUCTION

Although it is well-known that human immunodeficiency virus (HIV) is the pathogen that causes acquired immunodeficiency syndrome (AIDS), the intricate mechanisms that link HIV infection to the onset of immunodeficiency remain unclear. Cytopathic effects cannot fully account for the massive loss of CD4+ T cells, since productively infected cells occupy a small fraction of total CD4+ T cells (typically of the order of 0.02% to 0.2% [1]).

On the other hand, various clinical studies of HIV infection have linked the massive depletion of CD4+ T cells to the wide and persistent immune activation ([1], [2]), which seemed to increase with duration of HIV-1 infection ([3]). Rhesus macaques, which suffer progressive CD4+ T cell depletion and develop to AIDS, have strong T cell activation, compared with SIV-infected sooty mangabeys and African green monkeys, the natural host of SIV, which maintain minimal T cell activation despite evident viral replication ([4]). A study with a mouse model has also revealed that immune activation is closely related to T cell immunodeficiency ([5]). These observations motivate the present study of immune activation in HIV infection.

In this paper, we use a simple two-compartmental model to investigate immune activation and its role in HIV infection, and show that enhanced activation and reduced reversion would cause a downward shift of homeostasis if the death

rate of the activated cells is sufficiently large, and this process is quite robust with respect to parameter variations. The model is then extended to a four-compartmental one including viral dynamics. The extended model further illustrates the relationships among immune activation, viral persistence, and immune response. The theoretical results are verified by numerical simulations. As for control of HIV dynamics, we refer readers to [6] and references therein.

II. A BASIC TWO-COMPARTMENTAL MODEL

A. Model Description

We divide the whole CD4+ T cell pool into two compartments: CD4+ resting T cells (R) and activated CD4+ T cells (A) (Fig. 1). Newly generated CD4+ T cells from thymus, bone marrows, or other sources enter the resting cell pool with a constant rate λ . Resting cells are activated with rate a , and activated cells revert to the resting pool with rate r . Activated cells undergo a self-renewal (proliferation) with rate $p(A)$. Resting and activated cells die with rates d_R and d_A , respectively. These processes can be described by the following ordinary differential equations:

$$\begin{cases} \dot{R} = \lambda + rA - aR - d_R R, \\ \dot{A} = aR + p(A)A - rA - d_A A. \end{cases} \quad (1)$$

Here, the proliferation rate $p(A)$ is a density dependent function, which reflects the regulation of division signals. Although the detailed regulation mechanisms have not been fully understood, it is known that this process may involve competition for homeostatic resources such as cytokines and TCR-self-peptide/MHC interactions ([7], [8]). Higher density usually means less chance to receive division signals, and thus we make the following assumption on $p(A)$

Assumption 1: $p(\cdot)$ is a non-negative continuously differentiable decreasing function on the positive reals.

It is noted that slightly modified linearized variants of (1) have been used to fit data in D-Glucose and BrdU labeling experiments ([9], [10]).

B. Equilibrium and Its Shift by Activation¹

Regarding the existence of equilibrium, we have the following result.

Proposition 1: (1), subject to Assumption 1, has at most one equilibrium in the first orthant. If, in addition,

$$p(0) < d_A + \frac{d_R r}{a\theta}, \quad (2)$$

¹All proofs in this section are available in Appendix I.

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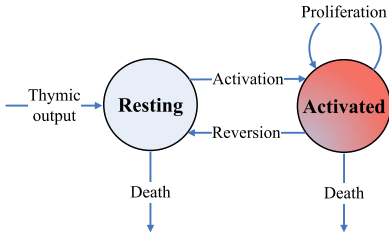


Fig. 1: A basic two compartmental model of immune activation.

where $\theta \triangleq 1 + \frac{d_R}{a}$, then it has a unique equilibrium in the first orthant.

If (2) is not satisfied, (1) has either an equilibrium or no equilibrium in the first orthant, depending on the detailed form of $p(\cdot)$. For the sake of simplicity, we will be mainly concerned with the case that (2) is satisfied. The following theorem shows the global stability of the equilibrium.

Theorem 1: If (2) holds, then the equilibrium (\bar{R}, \bar{A}) is regional stable with the attraction set $\{(R, A) \mid R \geq 0, A \geq 0\}$.

The following theorem establishes the relationship between equilibrium shift and $a(r)$.

Theorem 2: If (2) holds and

$$p(\bar{A}) < d_A - d_R \quad (3)$$

then $\bar{R} + \bar{A}$ is a decreasing (an increasing) function with respect to $a(r)$.

The theoretical results may provide a route to explain how HIV infection results in the massive depletion of CD4+ T cells. On one hand, HIV may destroy the infected CD4+ T cells by various direct or indirect ways, thus causing an increase in the death rate of activated cells. For example, HIV can induce direct apoptosis of infected CD4+ T cells and kills them by a Fas-independent mechanism ([11]). In addition, infected CD4+ T cells may be removed by CTL response or antibody-dependent cell-mediated cytotoxicity induced by HIV.

On the other hand, the activation levels of CD4+ T cells may be enhanced in HIV infection through direct or indirect pathways. It has been observed that the envelope protein gp120 of HIV may induce activation of healthy CD4+ T cells, even in absence of direct antigenic stimulation, through binding to CD4 and related co-receptors ([12], [13]). The accessory protein Nef may be also responsible for lymphocyte activation through various pathways ([14], [15]), even including the indirect infection of macrophages ([16]). In some labeling experiments, it is revealed that less activated CD4+ T cells revert to the resting pool in HIV infection ([9]). In addition, dendritic cells may facilitate the transmission of HIV from tissue and blood to lymphnode, where most CD4+ T cells reside, resulting in further infection and activation.

Therefore, with these observations and the two theorems mentioned above, we may infer that (3) would be satisfied due to the enhancement of d_A , and thus stronger activation and weaker reversion may result in a downward shift of homeostasis, which eventually leads to the massive depletion of CD4+ T cells.

III. EXTENDED MODEL INCLUDING VIRAL DYNAMICS

A. Model Description

We extend (1) to include viral dynamics in the following equation:

$$\begin{cases} \dot{R} = \lambda + rA - aR - d_R R \\ \dot{A} = aR + p(A)A - rA - d_A A - \mu V A \\ \dot{T}^* = \mu V A - d_T [1 + \delta(R + A)] T^* \\ \dot{V} = \rho T^* - d_V V \end{cases} \quad (4)$$

where T^* and V represent the concentration of productively infected CD4+ T cells and virus, respectively. d_V is the clearance rate of free virus. ρ is the rate of virus production by infected cells. In this model, it is assumed that productively infected CD4+ T cells are mainly generated from infected activated CD4+ T cells, described by the term $\mu V A$, and latent infections to resting CD4+ T cells are not considered here. The death rate of productively infected cells is assumed to be helper-dependent, and has a form $d_T [1 + \delta(R + A)]$, where $\delta(\cdot)$ is a density-dependent function with respect to $R + A$. Here, we make the following assumption on $\delta(\cdot)$.

Assumption 2: $\delta(\cdot)$ is a non-negative continuously differentiable increasing function, and satisfies the sector bounded condition on an underlying interval: $\eta_l |x - y| \leq |\delta(x) - \delta(y)| \leq \eta_r |x - y|$, where $\eta_l, \eta_r \geq 0$.

The biological justification for this helper-dependent killing is that both generation and maintenance of effective CTL response, which plays a major role in killing infected cells, rely on the substantial help from CD4+ cells, and the magnitude of CTL response is proportional to that of help signals. In addition, we use a single parameter a to reflect the whole activation effect, since there are various factors that may contribute to the widespread immune activation in HIV infection and modeling them explicitly would complicate the analysis.

B. Equilibrium and Its Shift by Activation²

The following proposition gives the existence of equilibrium of (4).

Proposition 2: (4), subject to Assumptions 1 and 2, has two possible non-negative equilibrium if (2) holds and $\mathcal{R} > \mathcal{R}_c$, where $\mathcal{R} \triangleq \frac{\rho\mu}{d_T d_V}$ and $\mathcal{R}_c \triangleq \eta_r \left[1 + \max \left\{ \frac{r}{a\theta}, \frac{r+d_A-p(\bar{A})}{a} \right\} \right]$:

- 1) (Uninfected equilibrium) $\bar{R}_0 = \frac{\lambda+r\bar{A}}{a\theta}$, $\bar{A}_0 = \frac{\lambda}{r+d_A-p(\bar{A}_0)\theta-r}$, $\bar{T}_0^* = \bar{V}_0 = 0$.
- 2) (Infected equilibrium)

$$\bar{R} = \frac{\lambda + r\bar{A}}{a\theta}, \quad \bar{A} = \frac{1 + \delta(\bar{R} + \bar{A})}{\mathcal{R}}, \quad \bar{T}^* = \frac{d_V \bar{V}}{\rho}, \quad (5)$$

$$\bar{V} = \frac{1}{\mu} \left[\frac{1}{\theta} \left(\frac{\lambda}{\bar{A}} + r \right) + p(\bar{A}) - r - d_A \right]. \quad (6)$$

²All proofs in this section are available in Appendix II.

Parameter	Value	Taken From
λ	0.46	[17]
ρ	2000	[18]
μ	2.4×10^{-4}	[19] (Slightly Modified)
d_A	0.057	[9]
d_R	0.00014	[20]
d_T	0.057	[9]
d_V	3.1	[21]
δ_0	16.8	Fitted
K	300	-
n	Varied	-
p_0	0.065	Estimated
A_{\max}	1000	-
r_0	0.201	Estimated
a_0	0.002	[9]
b_r	Varied	-
b_a	Varied	-

TABLE I: Parameter values for simulation

where $\theta \triangleq 1 + \frac{d_R}{a}$.

Before we investigate the equilibrium shift by activation, let us first establish stability properties of these two possible equilibrium.

Theorem 3: If (2) holds and $\mathcal{R} < \mathcal{R}_{c0}$, where $\mathcal{R}_{c0} \triangleq \eta_l \left(1 + \frac{r+d_A-p(\bar{A}_0)}{a} \right)$ then the uninfected equilibrium is locally stable. If (2) holds and $\mathcal{R} > \mathcal{R}_c$, then the infected equilibrium is locally stable.

Global stability may no longer hold generally for this model, but this would not change the result significantly, since for practical initial conditions the local stability holds.

Theorem 4: If (2) holds and $\mathcal{R} > \mathcal{R}_c$, then, \bar{A} and \bar{R} are decreasing (increasing) function with respect to a (r), and \bar{T}^* is an increasing (decreasing) with respect to a (r).

From these two theorems we may infer that enhanced (wide spectrum) activation would deplete the healthy CD4+ T cells, and increase viral load and productively infected T cell counts. This gradual process would eventually lead to the collapse of the whole immune systems and the onset of AIDS. Apart from the effect on disease development, enhanced activation also poses a severe problem to treatment. It can be shown readily that if $\mathcal{R} < \eta_l \left[1 + \max \left\{ \frac{r}{a\theta}, \frac{r+d_A-p(\bar{A})}{a} \right\} \right]$, then there is no non-negative infected equilibrium. Since $1 + \max \left\{ \frac{r}{a\theta}, \frac{r+d_A-p(\bar{A})}{a} \right\}$ is a decreasing function in a , enhanced activation, in order to remove virus, would require a smaller \mathcal{R} , which means a higher drug efficacy and a stronger CTL response. This observation suggests that blocking inappropriate T cell activation or decreasing the manifestations of generalized cytokine might be beneficial to ordinary antiviral treatments

IV. SIMULATIONS

To describe enhanced activation and reduced reversion in HIV infection, r and a are chosen as slow time-varying processes:

$$r = r_0 - b_r t, \quad a = a_0 + b_a t,$$

where $b_r \ll r_0$ and $b_a \ll a_0$. Resting cells are quite long-lived, and thus d_R is quite small. In our simulation, it is

assumed that $d_R = 0.00014$ ([20]). The thymic output is assumed to be $\lambda = 0.46$. It is shown that, using Ki67 as the activation marker, 0.1% – 1% CD4+ cells are activated in lymphoid tissue of HIV-negative individuals ([22]). Based on this observation, the initial condition is taken as $R(0) = 995/mm^3$, $A(0) = 8/mm^3$, $T(0) = 0/mm^3$, $V(0) = 50/mm^3$. It is also assumed that $d_A = 0.057$ and $p(\cdot)$ has a logistic form: $p(A) = p_0 \left(1 - \frac{A}{A_{\max}} \right)$, where $A_{\max} = 1000$. With these data and formula, r and p_0 can be estimated. As for $\delta(\cdot)$, we choose

$$\delta(R + A) = \delta_0 \frac{(R + A)^n}{(R + A)^n + K^n},$$

where δ_0 is the maximum value of $\delta(\cdot)$ and is fitted such that the viral load during the asymptotic period is around $10^2 - 10^3$, K is half-saturation coefficient, and n is the Hill coefficient that determines the steepness of the response. Detailed parameter values are listed in Table I.

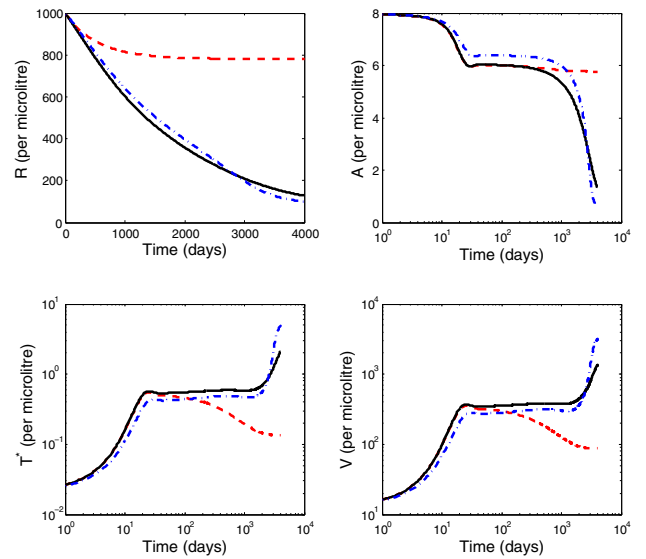


Fig. 2: Time course of HIV infection. Red dashed line: $n = 2$ and no enhanced activation and reduced reversion, i.e., $b_r = b_a = 0$; Black solid line: $n = 2$, $b_r = b_a = 10^{-6}$; Blue dashdot line: $n = 3$, $b_r = b_a = 10^{-6}$.

Time evolution of (4) is depicted in Fig. 2. After around three weeks transient process, HIV infected patients would experience an asymptotic period, which lasts for nearly 2500 days. During this time, viral load and the number of infected cells and activated cells are maintained at a relatively narrow range, while resting cells deplete gradually due to enhanced activation and reduced reversion. After this time, the patients would undergo a rapid growth in viral load and infected cells, since the low CD4+ level cannot maintain an effective immune response, and finally progress to AIDS. Fig. 3 gives the time evolution of infection fraction and activation fraction. During the asymptotic period, the infection fraction is around 0.1%, which is consistent with the observation in [1], and the activation fraction varies from 1% – 2%, which is also consistent with the observation in [22].

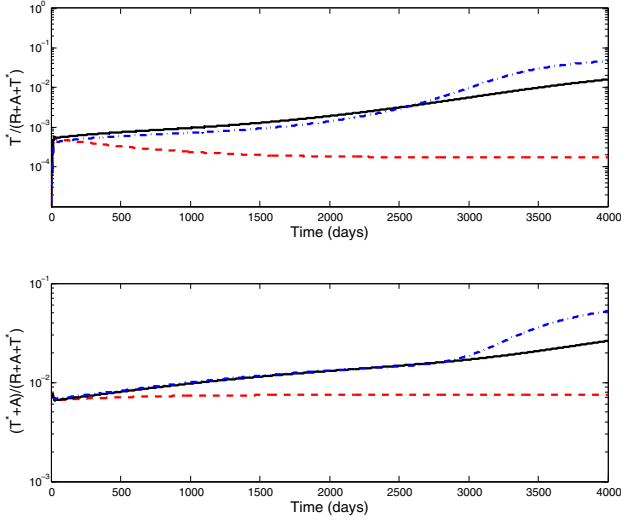


Fig. 3: Time course of activation fraction and infection fraction. Red dashed line: $n = 2$ and no enhanced activation and reduced reversion, i.e., $b_r = b_a = 0$; Black solid line: $n = 2$, $b_r = b_a = 10^{-6}$; Blue dashdot line: $n = 3$, $b_r = b_a = 10^{-6}$.

V. CONCLUSIONS

Immune activation and its role in HIV infection have been studied by using mathematical models. It is revealed with a two-compartmental model that enhanced activation and reduced reversion would deplete the CD4+ T cell pool if the death rate of activated cells is sufficiently large, which is very likely to be true in HIV infection, and the depletion process is quite robust to parameter variations. An extended model further elucidates the relationship among immune activation, viral persistence, and immune response. Strong activation and weak reversion cause an increase in viral load and a downward shift of healthy CD4+ T cell count, which impairs the antiviral immune responses. This process leads to the final onset of AIDS. Simulations have verified the theoretical analysis. Further investigations would include detailed modeling on immune activation, and implications to development of new immunological therapies.

APPENDIX I PROOFS OF THE RESULTS IN SECTION II

Proof: [Proof of Proposition 1] Setting the left side of (1) to zero yields that $R = \frac{\lambda+rA}{a+d_R}$ and $aR = [(r+d_A) - p(A)]A$. With this two equations, we have that (1) has an equilibrium in the first orthant if and only if the equation $f_l(A) = f_r(A)$ has a non-negative solution, where $f_l(A) = \frac{a\lambda}{a+d_R} \frac{1}{A}$ and $f_r(A) = (r+d_A) - p(A) - \frac{ar}{a+d_R}$. $f_l(A) > 0$ and $f_r(A)$ are decreasing and increasing function in A , respectively. Therefore, the only possible solutions are where $f_r(A)$ is non-negative and finite. If (2) holds, we have $f_r(0) > 0$ and $f_l(A)$ and $f_r(A)$ have a unique intersection point in the first orthant. If $p(0) \geq d_A + \frac{d_{RR}r}{a+d_R}$, we have two cases.

- 1) $\lim_{A \rightarrow \infty} p(A) \geq d_A + \frac{d_{RR}r}{a+d_R}$. Then, $f_r(A) \leq 0$, and $f_l(A) = f_r(A)$ has no non-negative solution.
- 2) $\lim_{A \rightarrow \infty} p(A) < d_A + \frac{d_{RR}r}{a+d_R}$. Then, there exists a $\xi > 0$ such that $f_r(A) > 0$, and $f_l(A) = f_r(A)$ has a unique non-negative solution. ■

Proof: [Proof of Theorem 1] Shifting the equilibrium to zero by defining $R_e \triangleq R - \bar{R}$ and $A_e \triangleq A - \bar{A}$ yields that

$$\begin{cases} \dot{R}_e = rA_e - aR_e - d_R R_e, \\ \dot{A}_e = aR_e + p(A_e + \bar{A})A_e - rA_e - d_A A_e \\ \quad + [p(A_e + \bar{A}) - p(\bar{A})]\bar{A}. \end{cases}$$

It is easy to show that a forward-invariant set of this system is $\{(R_e, A_e) \mid R_e \geq -\bar{R}, A_e \geq -\bar{A}\}$, and hence $R(0) \geq 0$ and $T(0) \geq 0$ ensure that $R_e(t) \geq -\bar{R}$ and $A_e(t) \geq -\bar{A}$ for all $t > 0$. Construct a Lyapunov function as $W \triangleq \frac{1}{2}(aR_e^2 + rA_e^2)$. Then, the derivative is evaluated as

$$\begin{aligned} \dot{W} &= aR_e(rA_e - aR_e - d_R R_e) \\ &\quad + rA_e[aR_e + p(A_e + \bar{A})A_e - rA_e - d_A A_e] \\ &\quad + rA_e[p(A_e + \bar{A}) - p(\bar{A})]\bar{A}. \end{aligned}$$

Noting that

$$\begin{aligned} p(A_e + \bar{A}) - p(\bar{A}) &\leq 0, \quad A_e \geq 0, \\ p(A_e + \bar{A}) - p(\bar{A}) &> 0, \quad -\bar{A} \leq A_e < 0, \end{aligned}$$

we have that $\dot{W} \leq aR_e(rA_e - aR_e - d_R R_e) + rA_e[aR_e + p(A_e + \bar{A})A_e - rA_e - d_A A_e] = x^T M x$, where $x = [R_e \ A_e]^T$ and

$$M = \begin{bmatrix} -a(a+d_R) & ar \\ ar & -r(r+d_A - p(A_e + \bar{A})) \end{bmatrix}.$$

On one hand, with (2) and Assumption 1, it is easy to verify that $-r(r+d_A - p(A_e + \bar{A})) < 0$. On the other hand,

$$\begin{aligned} &(a+d_R)(r+d_A - p(A_e + \bar{A})) - ar \\ &= (a+d_R) \left[d_A + \frac{d_{RR}r}{a\theta} - p(A_e + \bar{A}) \right] \\ &> 0 \end{aligned}$$

which implies that the Schur complement $-a(a+d_R) + \frac{(ar)^2}{r(r+d_A - p(A_e + \bar{A}))}$ is negative. Therefore, M is negative definite, and the regional stability follows from the Lyapunov theory. ■

Proof: [Proof of Theorem 2] Define $c \triangleq r + d_A - p(\bar{A})$. It is easy to verify that $c > 0$ and $\bar{R} + \bar{A} = \frac{\lambda}{a\theta} + (\frac{r}{a\theta} + 1) \frac{\lambda}{c\theta - r}$. We first show $\frac{d\bar{A}}{da} > 0$. Define $F(\bar{A}, a) = \frac{\lambda}{[r+d_A - p(\bar{A})]^\theta - r} - \bar{A} = \frac{\lambda}{c\theta - r} - \bar{A}$. Then, simple calculations give $\frac{\partial F}{\partial a} = -\frac{\lambda c \dot{c}_a}{(c\theta - r)^2}$, $\frac{\partial F}{\partial \bar{A}} = -\frac{\lambda \theta (-\dot{p}(\bar{A}))}{(c\theta - r)^2} - 1$, and thus $\frac{d\bar{A}}{da} = -\frac{\frac{\partial F}{\partial a}}{\frac{\partial F}{\partial \bar{A}}} = \frac{\lambda c d_R / a^2}{\lambda \theta (-\dot{p}(\bar{A})) + (c\theta - r)^2} > 0$, where Assumption 1 is used. With this, the derivative of $\bar{R} + \bar{A}$ with respect to a can be evaluated as

$$\begin{aligned}
& \frac{d(\bar{R} + \bar{A})}{da} \\
&= \frac{-\lambda(c\theta - r)^2 - \lambda r(c\theta - r) + a\theta[r + a\theta](-\lambda c\dot{\theta}_a)}{(a\theta)^2(c\theta - r)^2} \\
&+ \left(\frac{r}{a\theta} + 1\right) \frac{\lambda\dot{p}(\bar{A})}{(c\theta - r)^2} \frac{d\bar{A}}{da} \\
&= -\lambda c \frac{(c - d_R - r)}{a^2(c\theta - r)^2} + \left(\frac{r}{a\theta} + 1\right) \frac{\lambda\dot{p}(\bar{A})}{(c\theta - r)^2} \frac{d\bar{A}}{da} \\
&= -\lambda c \frac{d_A - p(\bar{A}) - d_R}{a^2(c\theta - r)^2} + \left(\frac{r}{a\theta} + 1\right) \frac{\lambda\dot{p}(\bar{A})}{(c\theta - r)^2} \frac{d\bar{A}}{da} \\
&< 0
\end{aligned}$$

Similarly, we can show $\frac{d\bar{A}}{dr} < 0$, and thus

$$\begin{aligned}
\frac{d(\bar{R} + \bar{A})}{dr} &= \lambda \frac{[d_A - d_R - p(\bar{A})] + (r + a\theta)\dot{p}(\bar{A})}{a(c\theta - r)^2} \frac{d\bar{A}}{dr} \\
&> 0.
\end{aligned}$$

This completes the proof. \blacksquare

APPENDIX II

PROOFS OF THE RESULTS IN SECTION III

Proof: [Proof of Proposition 2] The proof for uninfected equilibrium is similar to that of Proposition 1, and thus omitted here. As for infected equilibrium, it is easy to show that $\mathcal{R} > \mathcal{R}_c$ implies the positivity of \bar{V} provided that $\bar{A} \geq 0$. Hence, it suffices to prove that \bar{A} exists and is non-negative. To this end, consider the equation $y(A) \triangleq \frac{1 + \delta(\frac{\lambda + rA}{a\theta} + A)}{\mathcal{R}} - A = 0$. From $\mathcal{R} > \mathcal{R}_c$, it follows that $\frac{\eta_r}{\mathcal{R}} < \frac{a\theta}{r + a\theta}$. With this and $\dot{\delta} \leq \eta_r$ (Assumption 2), we have that $\frac{dy(A)}{dA} < 0$. In addition, $y(0) = \frac{1 + \delta(\lambda/a\theta)}{\mathcal{R}} > 0$. Therefore, $y(A) = 0$ has a unique non-negative solution \bar{A} . This completes the proof. \blacksquare

Proof: [Proof of Theorem 3] Computing the Jacobian matrix at uninfected equilibrium yields that

$$J_0 = \begin{bmatrix} J_{01} & * \\ 0 & J_{02} \end{bmatrix},$$

where $J_{01} = \begin{bmatrix} -a - d_R & r \\ a & p(\bar{A}_0) - r - d_A + \dot{p}(\bar{A}_0)\bar{A}_0 \end{bmatrix}$, $J_{02} = \begin{bmatrix} -d_T [1 + \delta(\bar{R}_0 + \bar{A}_0)] & \mu_A \bar{A}_0 \\ \rho & -d_V \end{bmatrix}$, and $*$ is unrelated to stability. If (2) holds, it is easy to show by using Routh-criterion that J_{01} is Hurwitz. As for block J_{02} , simple algebraic manipulations together with Routh criterion yields that it is Hurwitz if and only if

$$d_T \delta (\bar{R}_0 + \bar{A}_0) + d_V > 0, \quad (7)$$

$$d_T [1 + \delta(\bar{R}_0 + \bar{A}_0)] d_V - \rho \mu \bar{A}_0 > 0. \quad (8)$$

(7) is always true. (8) holds if $\mathcal{R} < \mathcal{R}_{c0}$. This can be shown by noting $\bar{A}_0 = \frac{\lambda}{(r + d_A - p(\bar{A}_0))^{\theta - r}}$ and $\frac{1 + \delta(\bar{R}_0 + \bar{A}_0)}{\bar{A}_0} >$

$\eta_l \left(1 + \frac{\bar{R}_0}{\bar{A}_0}\right) = \eta_l \left(1 + \frac{\lambda}{a\theta \bar{A}_0} + \frac{r}{a\theta}\right) = \mathcal{R}_{c0}$. To probe the stability of infected equilibrium, we define some variables for later use.

$$\begin{aligned}
c &\triangleq r + d_A - p(\bar{A}) - \dot{p}(\bar{A})\bar{A}, \\
m &\triangleq \left(1 - \frac{1}{\theta}\right) r + d_A - p(\bar{A}) - \dot{p}(\bar{A})\bar{A}, \\
f &\triangleq -\dot{p}(\bar{A})\bar{A} + \frac{\lambda}{\theta \bar{A}}, \quad \bar{d}_T \triangleq d_T [1 + \delta(\bar{R} + \bar{A})], \\
k_f &\triangleq f + \frac{r}{\theta} + a\theta, \quad k_m \triangleq m + \frac{r}{\theta} + a\theta, \\
q &\triangleq a\theta(\mathcal{R} - \delta_d) - r\delta_d, \quad \delta_d \triangleq \dot{\delta}(\bar{R} + \bar{A}).
\end{aligned}$$

If (2) holds, these variables are all *positive*. Then, the characteristic polynomial at the equilibrium can be computed as

$$\begin{aligned}
|J| &= \begin{vmatrix} \varepsilon + a + d_R & -r & 0 & 0 \\ -a & \varepsilon + c + \mu\bar{V} & 0 & \mu\bar{A} \\ d_T \delta_d \bar{T}^* & -\mu\bar{V} + d_T \delta_d \bar{T}^* & \varepsilon + \bar{d}_T & -\mu\bar{A} \\ 0 & 0 & -\rho & \varepsilon + d_V \end{vmatrix} \\
&= b_4 \varepsilon^4 + b_3 \varepsilon^3 + b_2 \varepsilon^2 + b_1 \varepsilon + b_0,
\end{aligned}$$

where $b_4 = 1$, $b_3 = \bar{d}_T + d_V + c + \mu\bar{V} + a + d_R$, $b_2 = (\bar{d}_T + d_V)(c + \mu\bar{V}) + (a + d_R)(\bar{d}_T + d_V + c + \mu\bar{V}) - ar$, $b_1 = \mu\bar{V}(\bar{d}_T - \delta_d d_T \bar{A})d_V - ar(\bar{d}_T + d_V) + (a + d_R)(c + \mu\bar{V})(\bar{d}_T + d_V)$, $b_0 = \mu\bar{V}d_T d_V q \bar{A}$. Applying Routh criterion yields that the equilibrium is stable if and only if

- 1) $b_0 > 0, b_1 > 0, b_2 > 0, b_3 > 0, b_4 > 0$.
- 2) $b_2 b_3 - b_1 b_4 > 0$.
- 3) $b_1(b_2 b_3 - b_1 b_4) - b_0 b_3^2 > 0$.

Let us now verify whether these conditions are satisfied. Before proceeding, we need to establish several relationships:

$$\begin{aligned}
c + \mu\bar{V} &= f + \frac{r}{\theta}, \\
(a + d_R)(c + \mu\bar{V}) - ar &= a\theta f, \\
\mu\bar{V} &= f - m > 0, \\
\bar{d}_T - \delta_d d_T \bar{A} &= (\mathcal{R} - \delta_d)\bar{A}d_T > 0, \\
q &> 0,
\end{aligned}$$

where Assumption 2 is employed.

- 1) $b_4 > 0, b_3 = \bar{d}_T + d_V + k_f > 0, b_2 = (\bar{d}_T + d_V)k_f + a\theta f > 0, b_1 = (f - m)(\mathcal{R} - \delta_d)\bar{A}d_T d_V + a\theta f(\bar{d}_T + d_V) > 0, b_0 > 0$.
- 2)

$$\begin{aligned}
b_2 b_3 - b_1 b_4 &= (\bar{d}_T + d_V)^2 k_f + (\bar{d}_T + d_V) k_f^2 \\
&+ a\theta f k_f - (f - m)(\mathcal{R} - \delta_d)\bar{A}d_T d_V \\
&= (\bar{d}_T^2 + d_V^2 + \bar{d}_T d_V) k_f + (\bar{d}_T + d_V) k_f^2 \\
&+ a\theta f k_f + \bar{d}_T d_V \left(\frac{r}{\theta} + a\theta\right) \\
&+ m(\mathcal{R} - \delta_d)\bar{A}d_T d_V + \delta_d d_T d_V f \bar{A} \\
&> 0.
\end{aligned}$$

3) On one hand,

$$\begin{aligned} b_0 b_3^2 &= q\bar{A}(f-m)d_T d_V (\bar{d}_T + d_V)^2 \\ &+ q\bar{A}(f-m)d_T d_V k_f^2 \\ &+ 2q\bar{A}(f-m)d_T d_V (\bar{d}_T + d_V) k_f \\ &\leq h_1 + h_2 + h_3, \end{aligned}$$

where

$$\begin{aligned} h_1 &= 2q\bar{A}f d_T d_V (\bar{d}_T + d_V) k_f, \\ h_2 &= q\bar{A}f d_T d_V k_f^2, \\ h_3 &= q\bar{A}(f-m)d_T d_V (\bar{d}_T + d_V)^2. \end{aligned}$$

On the other hand,

$$b_1(b_2 b_3 - b_1 b_4) = g_1 + g_2 + g_3 + g_4 + *,$$

where $* > 0$ represents an irrelevant term. and

$$\begin{aligned} g_1 &= a\theta f (\bar{d}_T + d_V) (\bar{d}_T^2 + d_V^2 + \bar{d}_T d_V) k_f, \\ g_2 &= a\theta f (\bar{d}_T + d_V)^2 k_f^2, \\ g_3 &= (f-m)(\mathcal{R} - \delta_d) \bar{A} \\ &\quad \times d_T d_V (\bar{d}_T^2 + d_V^2 + \bar{d}_T d_V) k_f, \\ g_4 &= (f-m)(\mathcal{R} - \delta_d) \bar{A} \\ &\quad \times d_T d_V (\bar{d}_T d_V) k_m. \end{aligned}$$

Noting that $a\theta\mathcal{R} > q$, $a\theta(\mathcal{R} - \delta_d) > q$, and $k_f > k_m > a\theta$, we have that

$$\begin{aligned} g_1 &> 2a\theta\mathcal{R}\bar{A}d_T d_V f (\bar{d}_T + d_V) k_f > h_1, \\ g_2 &> a\theta\mathcal{R}\bar{A}f d_T d_V k_f^2 > h_2, \end{aligned}$$

and

$$\begin{aligned} &g_3 + g_4 \\ &> (f-m)(\mathcal{R} - \delta_d) \bar{A}d_T d_V (\bar{d}_T^2 + d_V^2 + \bar{d}_T d_V) k_m \\ &\quad + (f-m)(\mathcal{R} - \delta_d) \bar{A}d_T d_V (\bar{d}_T d_V) k_m \\ &= (f-m)(\mathcal{R} - \delta_d) \bar{A}d_T d_V (\bar{d}_T + d_V)^2 k_m \\ &> a\theta(\mathcal{R} - \delta_d) \bar{A}(f-m)d_T d_V (\bar{d}_T + d_V)^2 \\ &> h_3, \end{aligned}$$

and thus $b_1(b_2 b_3 - b_1 b_4) - b_0 b_3^2 > 0$.

Therefore, the result follows immediately. \blacksquare

Proof: [Proof of Theorem 4] Define $\delta_d \triangleq \dot{\delta}(\bar{R} + \bar{A})$ and $F(\bar{A}) = \frac{1+\delta(\bar{R}+\bar{A})}{\mathcal{R}} - \bar{A}$. Then, following a similar line as used in the proof of Theorem 2, we have that $\frac{d\bar{A}}{da} = -\frac{\frac{\partial F}{\partial a}}{\frac{\partial F}{\partial \bar{A}}} = \frac{\delta_d(\lambda+r\bar{A})/[\delta_d(\frac{r}{a\theta}+1)-\mathcal{R}]}{a^2\theta^2}$. From $\mathcal{R} > \mathcal{R}_c$ and Assumption 2 it follows that $0 \leq \delta_d \leq \eta_r < \mathcal{R}/(\frac{r}{a\theta}+1)$, and thus $\frac{d\bar{A}}{da} \leq 0$. Since $\bar{R} = (\lambda+r\bar{A})/(a+d_R)$, $\frac{d\bar{R}}{da} \leq 0$. Similarly, $\frac{d\bar{T}^*}{da} = \frac{d_v}{\rho} \frac{d\bar{V}}{da} \geq 0$, which can be proved by noting that $d\frac{1}{\theta}(\frac{\lambda}{A}+r)/da \geq 0$ and $\dot{p}(\bar{A}) \frac{d\bar{A}}{da} \geq 0$. Likewise, we can show that $\frac{d\bar{A}}{dr} \geq 0$, $\frac{d\bar{R}}{dr} \geq 0$, and $\frac{d\bar{T}^*}{dr} = \frac{d_v}{\rho} \frac{d\bar{V}}{dr} \leq 0$. \blacksquare

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