A MODEL OF THE ROLE OF COFACTORS IN THE INITIATION AND DEVELOPMENT OF AIDS

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ABSTRACT. Understanding the process by which the Human Immunodeficiency Virus (HIV) infects cells in a new host and initiates the steps leading to AIDS requires that both the nature of the initial infection and interactions of the virus and the host be delineated. Factors which must be considered include the nature of the strain of the infecting virus, the state of the host at the time of infection, and the immune response of the host to the virus. The state of the host certainly includes the general "health" and immunological status. In this paper, the role of "cofactors" as seen through antigen load at the time of infection is explored. The motivation for construction of a mathematical model is given by epidemiological observations and laboratory findings suggesting that chronic infections of particular types may make a host more susceptible to an HIV infection. In addition, these "cofactors" may also modulate the rate of disease progression and the clinical nature of the disease itself. What might modulate the susceptibility of the host to HIV infection is a primary question here. The behavior of model solutions suggest that certain individuals may not be susceptible to an HIV infection if exposed to a small dose. And, that an early infection may be aborted by an appropriate change in host parameters. This suggests that identifying and treating the underlying cofactors may be of therapeutic value in early stages of HIV infection.

1. Introduction. The means by which HIV infects cells of a host and puts into motion a process which results in AIDS are complex. The complexity is due in part to the very long time periods involved, the ability of the virus to mutate in response to drugs and the host's immune response, and the nature of the immune response itself. This complexity suggests a mathematical approach to these problems, and a number of modeling efforts have been carried out, e.g., [3, 6, 7, 8]. In these investigations, generally, the population dynamics of the process have been a primary concern. Delineating the interaction between the virus and the primary host, CD4+ T lymphocytes, has been the primary goal. An aspect of these studies which has been recognized by several...
investigators is that an HIV infection in the body is an "epidemic," with CD4+ T lymphocytes playing the role of susceptible individuals and infected macrophages the role of asymptomatic carriers. In terms of this "epidemic in the body" analogy, this paper investigates the question of susceptibility of a population to an epidemic if a few infected individuals are introduced.

The suggestion that individuals may differ with respect to their receptiveness to HIV is not new [9]. The reason for the "biologic variation" identified by Peterman, et al. in 1988 would certainly include the nature of the strains of the infecting virus, mode of introduction of the infectious material, and various host factors. One aspect of the host factors is the presence and quantity of other infectious pathogens at the time of infection. Many common infectious agents have been implicated as "cofactors"—modulators of some aspect of HIV infection—through epidemiological observations or through in vitro investigations. These include herpes simplex types 2 and 6, cytomegalovirus, Epstein-Barr virus and microplasmas. In addition to the specific identified pathogens, any material able to be responded to by the immune response, i.e., an antigen, is a potential cofactor. This expanded view of cofactors is possible due to the role of activated T lymphocytes in HIV infection and replication. The possibility that the initial antigen load, the totality of the immunologically active material present before HIV exposure, is an HIV-infection cofactor is examined through a mathematical model in this paper. A more complete discussion of the biologic motivation for this work is presented in [10].

2. The model. A simple mathematical model, consisting of a system of four nonlinear differential equations, was constructed for the purpose of exploring the effect of cofactors on the natural history of an HIV infection. The definition of cofactor used was, operationally, any non-HIV substance which would result in an increase in the activation of the immune response, and through it, increased activation of the predominant host of HIV, CD4+ T lymphocytes (T-cells). Activation of T-cells seems to be required for complete integration of HIV after the virus has bound and successfully entered the cell [4, 12]. Activation of infected T-cells also marks the beginning of HIV replication [11, 13]. In assigning immune activation a central role, we are, in spirit, following Ascher and Sheppard [1, 2] where the idea of viewing AIDS as a disease
of immune activation was explored—although in that discussion, a central role for stimulatory cofactors was not directly considered.

The model is designed to first describe the pre-HIV exposure state and its dependence on antigen load. With that in hand, the response of the system to a perturbation which mimics a low-level introduction of HIV is described as well as how this response depends on host parameters.

Explorations of the roles of cofactors which altered the immune response to HIV directly would require knowledge of the particular nature of the three-way interaction between the factor, HIV, and the immune response—information not generally available. This has dictated that the investigation here involve this general family of potential cofactors which modulate the fraction of stimulated T-cells. Although the model here is simple, one would expect behavior similar to the type described below even if further complexities were added. In this sense, this model may be the simplest description in which the potential role of stimulatory agents may be observed. As most of the parameters as they appear here have not been measured and many will vary from individual to individual, the behavior of the model solutions will be presented in a way that gives general results—true for all reasonable parameter values.

2.1. Model description. The total quantity of stimulatory agents present will be considered the “non-HIV antigen load” or simply “antigen load.” The antigen load at time $t$, $F(t)$, is actually a weighted sum of concentration of all stimulatory agents present. A weighted sum is necessary as not all agents are necessarily equal in their ability to assist the progression of the HIV infection through stimulation. One of the simplifications is to assume that changes in the antigen load as a function of $t$ can be described through a single dynamic equation as opposed to a quantity requiring tracking each of the factors individually. $F(t)$ can also be thought of as a stimulatory or activation index, with physiologic quantities which measure the level of immune activity used to indirectly measure $F$. Potential measurable quantities include sedimentation rate of white blood cells, serum neopterin levels and measures of the activity of the response to panels of common antigens.

Other quantities in the model are $U(t)$, the number of unstimulated (and HIV uninfected) CD4$^+$ T-cells per ml, $S(t)$, the number of
stimulated (and HIV uninfected) CD4$^+$ T-cells per ml, and $I(t)$, the number of HIV-infected CD4$^+$ T-cells per ml. The meaning of the parameters follows the equations below. The system (1)–(4) involves four nonlinear differential equations involving ten different positive parameters:

(1) \[ F''(t) = c - (c_1 + c_2 S(t)) F(t) \]
(2) \[ U''(t) = c_3 - c_4 F(t) U(t) - c_5 U(t) + c_6 S(t) \]
(3) \[ S'(t) = c_4 F(t) U(t) - c_6' S(t) - c_7 S(t) (F(t) I(t)) \]
(4) \[ I'(t) = -c_4 F(t) I(t) - c_5 I(t) + c_7 S(t) (F(t) I(t)) \]

In the first equation, the parameters $c$ and $c_1$ involve the rate at which the antigen load enters from the external world and is removed by nonspecific means, generally though immune scavenger cells (macrophages, monocytes and polymorphonuclear cells). Depending on the cofactor, this nonspecific removal could also be through the action of the kidney, liver or blood serum components (such as the complement system). The parameter $c_2$ describes the removal of antigen through specific means (rate of removal being proportional to the level of activation of the immune system). To be true to the physical system, the parameter $c$ should be a random quantity changing in time to reflect the changing and random nature of antigen exposure. Usually the behavior of such stochastic systems is best approximated by a deterministic system using the time-average of that random term. This is the formal justification for the constant antigen-load source.

The second equation describes the population dynamics of the unstimulated mature CD4$^+$ T-cells. There is a source of these cells (from bone marrow and periphery) at rate $c_3$. The unstimulated cells die at rate $c_5$ and expand their population as stimulated cells lose that stimulate at rate $c_6$. The rate at which unstimulated cells become stimulated (and leave the unstimulated population) is proportional to the level of the antigen load and the number of unstimulated cells (with constant of proportionality $c_4$). Instead of using a “source” to maintain this unstimulated population, studies were also done using the division of peripheral cells as the primary source. The basic results were the same, illustrating that only the equilibrium value before HIV introduction was critical (data not shown). For this reason, the algebraically simpler constant source term is used here.
The stimulated T cell population has input from the unstimulated population (the first term) and loses population as cells revert back to unstimulated small T cells (rate $c_6$), die, or enter a terminal differentiation state. Stimulated T-cells can also divide. We have included the base line reproduction rate in the parameter $c_3$, so that the rate included below is that part of the reproduction rate that exceeds the base line reproduction rate. The parameter $c'_6$, then, includes the following aspects

$$c'_6 = c_6 + \text{[death rate + (terminal differentiation rate) - excess reproduction rate]}.\]

It will be assumed in all of the theorems that the sum of the rates in brackets above is nonnegative, that is, that $c'_6 \geq c_6$.

The last term in this equation has a somewhat unusual form, involving the product of $F$ and $I$. This product is proportional to the rate at which infected cells are "stimulated" and begin producing virus. As the infective half-life in serum is relatively short [5], this product is also (approximately) proportional to the infective free virus concentration at time $t$. The triple product in last term, then, is proportional to (with constant of proportionality $c_7$) the rate at which stimulated cells interact with free virus and become infected.

The final equation involves the (eventual) death of infected cells as they are stimulated (rate $c'_4$) and the natural death of infected cells (not directly due to HIV)—rate $c_5$. The last term again describes the rate of infection of stimulated T cells. We have used the rate coefficients with the primes to indicate parameters with the same kinetic role as the unprimed version. The relationship between $c_4$ and $c'_4$ depends on whether infected and uninfected T cells are stimulated at the same rate when presented with the same stimuli.

Initial conditions at time $t = 0$ are to be always nonnegative. The infected population at $t = 0$, $I(0)$, will be taken to be 0 when the pre-HIV state is investigated.

2.2. Model behavior. The properties of the solutions of system (1)–(4) with nonnegative initial conditions of interest in this application are given in the following theorems. The first deals with the solutions staying nonnegative and bounded.
Theorem 2.1. For system (1)–(4) with all parameters positive and $c'_6 \geq c_6$, all solutions with nonnegative initial conditions at time $t = 0$.

1. Exist for all $t > 0$ and

2. Remain bounded for all $t > 0$. Moreover, if there are no HIV-infected cells at time 0 (and, as a result, the rate of infection by HIV is zero), $I(0) = 0$, then $I(t) = 0$ for all $t > 0$.

Proof. Existence of unique solutions to every initial condition follows directly from the Picard existence theorem. Showing that solutions starting in the nonnegative orthant stay bounded will also establish (1). First, we show that the nonnegative orthant is positively invariant. As

$$F'(t) = c - (c_1 + c_2 S(t))F(t),$$

when $F$ is 0, $F' = c > 0$. As a result, no solution, $(F(t), U(t), S(t), I(t))$, can cross the $F = 0$ hyperplane as $t$ increases. Also, note that as

$$I'(t) = (-c_4 F(t) - c_5 + c_7 S(t)F(t))I(t),$$

the $I = 0$ hyperplane is invariant. By uniqueness, no solution can cross this hyperplane. When $S = 0$,

$$S'(t) = c_4 F(t)U(t) \geq 0$$

for $F$ and $U$ in the nonnegative orthant. As $S''$ when $S' = 0$ and $S = 0$ is given by

$$S'' = c_4 F' U + c_4 FU'$$

$$= c_4(c_1 - F')U + c_4 F(c_3 - c_4 FU - c_5 U)$$

if either $F$ or $U$ is zero,

$$S'' = c_4(cU + c_3 F).$$

This second derivative is positive ($S(t)$ has a local min) if either $U$ or $F$ is not zero. If both are zero, examining $S'''$ at that point, we find

$$S''' = 2c_4 c_3 > 0.$$
From that evidence, if \( S, F \) and \( U \) are simultaneously zero, \( S \) will be increasing. Finally, if \( U = 0 \) in the nonnegative orthant,

\[
U' = c_3 + c_6 S > 0.
\]

Thus, no solution can leave the nonnegative orthant, and it is positively invariant.

The boundedness of all solutions is established by showing that all solutions starting in the positive orthant eventually enter a globally attracting set. Let

\[
b_1 = \frac{c}{c_1}, \quad b_2 = \frac{c_3}{\min(c_5, c_6' - c_6)}, \quad b_3 = \frac{c_4 b_1 b_2}{\min(c_5, c_6')};
\]

then the following set \( A \) attracts all solutions in the nonnegative orthant:

\[
A = \{(F, U, S, I) \mid 0 \leq F \leq b_1; 0 \leq U \leq b_2; 0 \leq S \leq b_2; 0 \leq I \leq b_3\}.
\]

This is established through a series of differential inequalities which hold in the nonnegative orthant:

\[
F' \leq c - c_1 F \\
(S + U)' \leq c_3 - (\min(c_5, c_6' - c_6))(S + U) \\
(I + S)' \leq c_4 b_1 b_2 - (\min(c_5, c_6'))(I + S).
\]

The existence of such a region implies both that all solutions stay bounded and exist for all \( t > 0 \), establishing the theorem.

The second result concerns the natural or "virgin" equilibrium between the quantities describing antigen load, unstimulated cells, and stimulated cells prior to HIV exposure. This result also describes the relationship between the equilibrium value of the stimulated population and the value of \( c \), the rate of introduction of new antigen. It suggests that the equilibrium number of stimulated cells per ml will be larger if the rate at which the cofactor enters the system is larger.
Theorem 2.2. System (1)–(4) with all parameters positive has a unique equilibrium having $I$ coordinate zero, $(F_0, U_0, S_0, 0)$, in the nonnegative orthant. As a function of the parameter $c$ (the rate of new antigen exposure), $S_0$, the equilibrium value of the stimulated cell population, is an increasing function.

Proof. Setting the righthand side of each equation (1)–(3) to zero and setting $I$ to be zero in each gives us equations that any equilibrium in the $I = 0$ hyperplane must satisfy.

(5) \[ c - (c_1 + c_2 S_0) F_0 = 0 \]
(6) \[ c_3 - c_4 F_0 U_0 - c_5 U_0 + c_6 S_0 = 0 \]
(7) \[ c_4 F_0 U_0 - c'_6 S_0 = 0 \]

For any equilibrium $(F_0, U_0, S_0, 0)$, we have from (5) that

(8) \[ F_0 = \frac{c}{c_1 + c_2 S_0}. \]

Using (8) in (6) gives

\[ c_3 - c_4 \frac{c}{c_1 + c_2 S_0} U_0 - c_5 U_0 + c_6 S_0 = 0, \]

an equation which can be solved for $U_0$ in terms of $S_0$,

(9) \[ U_0 = \frac{(c_3 + c_6 S_0)(c_1 + c_2 S_0)}{cc_4 + c_5 (c_1 + c_2 S_0)}. \]

Finally, substituting the results of (8) and (9) into (7), we have a single equation for $S_0$,

\[ c_4 \frac{c}{c_1 + c_2 S_0} \frac{(c_3 + c_6 S_0)(c_1 + c_2 S_0)}{cc_4 + c_5 (c_1 + c_2 S_0)} - c'_6 S_0 = 0, \]

or

(10) \[ cc_4 (c_3 + c_6 S_0) - c'_6 S_0 (cc_4 + c_5 (c_1 + c_2 S_0)) = 0. \]

Equation (10) is a quadratic equation for $S_0$ which has one positive root and one negative root for all positive parameter values. The positive
root, along with (8) and (9) generates the unique equilibrium in the region of interest.

The relationship between $S_0$ and the parameter $c$ is seen through implicitly differentiating (10). With all other parameters positive and constant, $S_0 = S_0(c)$, and

$$\frac{\partial S_0}{\partial c} = \frac{c_4[(c_3 + c_6 S_0) - c'_6 S_0]}{cc_4(c'_6 - c_6) + c'_6 c_1 c_5 + 2c'_6 S_0 c_2 c_5}.$$

With $c'_6 - c_6 > 0$, the denominator of this expression is positive. The numerator is also positive since, from (7) and (8),

$$c'_6 S_0 = cc_4 \frac{c_3 + c_6 S_0}{c_4 + c_5(c_1 + c_2 S_0)}.$$

As a result,

$$(c_3 + c_6 S_0) - c'_6 S_0 = c_3 + c_6 S_0 - cc_4 \left( \frac{c_3 + c_6 S_0}{c_4 + c_5(c_1 + c_2 S_0)} \right)$$

$$= \left( c_3 - \frac{c_3}{1 + c_5(c_1 + c_2 S_0)/(cc_4)} \right)$$

$$+ \left( c'_6 S_0 - \frac{c'_6 S_0}{1 + c_5(c_1 + c_2 S_0)/(cc_4)} \right)$$

$$> 0. \quad \square$$

In order to describe the susceptibility of the system under study to an exposure of HIV, we determine the stability of this equilibrium to a perturbation in the $I$ direction. The eigenvalue $\lambda_0$ corresponding to that direction provides the relative decay or growth rate depending on the sign. An asymptotically stable equilibrium ($\lambda_0 < 0$) would indicate that a small number of infected cells would be eliminated over time. An unstable equilibrium ($\lambda_0 > 0$) will indicate that a small number of infected cells would be expected to grow in numbers and not be eliminated.

**Theorem 2.3.** The equilibrium $(F_0, U_0, S_0, 0)$ of system (1)–(4) with $c'_6 \geq c_6$ has at least a three-dimensional stable manifold contained in
\{(F, U, S, I) \mid I = 0\} \text{ for all nonnegative parameter choices. Moreover, this equilibrium is asymptotically stable if}

\[ \lambda_0 = -c'_4 F_0 - c_5 + c_7 S_0 F_0 < 0 \]

and unstable if \( \lambda_0 > 0 \).

**Proof.** Linearizing (1)–(4) about the unique equilibrium in the nonnegative orthant with \( I_0 = 0 \), the Jacobian matrix becomes

\[
J = \begin{bmatrix}
-(c_1 + c_2 S_0) & 0 & -c_2 F_0 & 0 \\
-c_4 U_0 & -c_4 F_0 - c_5 & c_6 & 0 \\
c_4 U_0 & c_4 F_0 & -c'_6 & -c_7 S_0 F_0 \\
0 & 0 & 0 & -c'_4 F_0 - c_5 + c_7 S_0 F_0
\end{bmatrix}.
\]

One eigenvalue is clearly \( \lambda_0 = -c'_4 F_0 - c_5 + c_7 S_0 F_0 \). The other three eigenvalues come from the \( 3 \times 3 \) submatrix

\[
\begin{bmatrix}
-(c_1 + c_2 S_0) & 0 & -c_2 F_0 \\
-c_4 U_0 & -c_4 F_0 - c_5 & c_6 \\
c_4 U_0 & c_4 F_0 & -c'_6
\end{bmatrix}.
\]

The characteristic polynomial of this matrix is

\[
\lambda^3 + (c'_6 + c_2 S_0 + c_4 F_0 + c_5 + c_1)\lambda^2 \\
+ [c_4 F_0(c'_6 - c_6) + c_2 c'_6 S_0 + c_2 c_4 S_0 F_0 \\
+ c_1 c'_6 + c_1 c_4 F_0 \\
+ c_1 c_5 + c_2 c_5 S_0 + c_5 c'_6 + c_2 c_4 U_0 F_0] \lambda \\
+ [c_2 c_4 S_0 F_0(c'_6 - c_6) + c_1 c_5 c'_6 \\
+ c_1 c_4 F_0(c'_6 - c_6) + c_2 c_5 c'_6 S_0 + c_2 c_4 c_5 U_0 F_0] = 0.
\]

All roots of this polynomial have negative real part by the Routh-Hurwitz criteria. As a result, this equilibrium point always has at least a three-dimensional stable manifold (which is inside the \( I = 0 \) hyperplane). The final eigenvalue (whose eigenvector points out of the \( I = 0 \) hyperplane) determines the stability of this equilibrium in the full four-dimensional space. □

The final result establishes the conditions under which one is or is not susceptible to an HIV infection through a small initial dose in
terms of the parameter $c$, the rate of introduction of the cofactor, the rate of virus production from stimulated infected cells, $c_7$, the specific elimination rate of the cofactor, $c_2$, and the death rate of unstimulated cells, $c_5$. Asymptotic stability of the equilibrium means biologically that one is not susceptible to an introduction of a small number of infected cells. If one is susceptible to infection after introduction of a small number of infected cells, the equilibrium will be unstable. Biologically, this implies that in that case, a small number of infected cells will establish a chronic HIV infection.

**Theorem 2.4.** If $cc_7 - c_5c_2 \leq 0$, the equilibrium $(F_0, U_0, S_0, 0)$ is always asymptotically stable. Moreover, for $c$ sufficiently large and $c_3/(c_6' - c_6) > c_4'/c_7$, $(F_0, U_0, S_0, 0)$ is unstable.

**Proof.** We need only look to see how the critical eigenvalue $\lambda_0$ varies with the parameters

$$
\lambda_0 = \frac{(-c_4' + c_7S_0)F_0 - c_5}{c_4' + c_7S_0}
\frac{c}{c_1 + c_2S_0} - c_5
= \frac{-cc_4' - c_5c_1 + (cc_7 - c_5c_2)S_0}{c_1 + c_2S_0}.
$$

If the quantity $cc_7 - c_5c_2 \leq 0$, then $\lambda_0 < 0$. For the last part, from (10), dividing through by $c$ we see that $S_0 \to c_3/(c_6' - c_6)$ as $c \to \infty$. Also, $\lambda_0 = 0$ when

$$
(11) \quad S_0 = \frac{cc_4' + c_1c_5}{cc_7 - c_5c_2}.
$$

As we know that $S_0$ is an increasing function of $c$, it must cross the graph of the righthand side of (11) when $c > c_2c_5/c_7$ if $c_3/(c_6' - c_6) > c_4'/c_7$. □

The parameter $c$ is the rate at which cofactors (as measured through antigen load) enter. This last theorem gives evidence that susceptibility to HIV infection may be determined by antigen load. With a sufficiently small parameter $c$, infection a small dose of HIV is not possible. Under a certain condition of the parameter values, with a larger $c$, the individual
becomes susceptible to HIV infection. The righthand side of that condition, \( c_4/c_7 \), depends on the nature of the particular "cofactors" present.

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