IMMUNOLOGICAL MODELS OF EPIDEMICS

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Abstract: Mathematical models for analyzing the spread of a disease are usually epidemiological or immunological. The former are mostly ODE-based models that use classes like susceptibles, recovered, infectives, latently infected, etc to describe the evolution of an epidemic in a population. Some of them also use structure variables, such as size or age. The latter describe the evolution of the immune system/pathogen in the infected host—usually resulting in death, recovery or chronic infection. There is valuable insight to be gained from combining these two types of models, as that may lead to a better understanding of the severity of an epidemic. In this article we propose a new type of model that combines the two by using variables of immunological nature as structure variables for epidemiological models. We then describe a practical application of the model to HIV infection.

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1 INTRODUCTION

In almost all epidemiological models, the death rates and the recovery rates are either constant or dependent on chronological age or age of infection. However, what ultimately decides whether an individual recovers from an infection (with or without immunity), endures it as a chronic disease or dies because of it, is how the immune system of that individual protects her/him from the disease [1]. With HIV, for example, the depletion of CD4+ T cells, not age, is the best indicator of an individual’s state of health and prognosis [7]. Therefore, a model that takes into account the immune status of individuals in the population seems reasonable and desirable.

A similar philosophy of nesting one model inside another was used in [5]. The authors presented a framework for modeling host-parasite coevolution using nested modeling, and illustrated it by analyzing a simple host-parasite system. [2] and [4] considered models similar to the one presented in this paper, although their approach was geared more towards understanding the evolution of virulence and natural selection. [6] presented a model of viral spread in a population that embeds an immune response model in an epidemic network model.

2 A GENERAL IMMUNOLOGICAL SIR-TYPE MODEL

We present the general form of our model resembling so-called size-structured models, and then present a model that is specific to HIV. We will allow any number of structure variables that will be represented by a vector, and assume the total population is undergoing logistic growth through linearly increasing mortality but no reduction in fertility. The goal of this model is to provide detailed immunological information about individuals in a population suffering from an epidemic of a viral disease for the purpose of informed public health planning.

Consider a vector $\mathbf{Y}$ that has as components the immunological variables that will be used as structure variables for the epidemiological model, which evolve according to a system of ODEs, for example $\mathbf{Y} = (T, T^*, V)$ and

\[
\begin{array}{l}
\frac{dT}{dt} = s + pT \left(1 - \frac{T + T^*}{T_{\text{max}}}\right) - d_T T - kVT, \\
\frac{dT^*}{dt} = kVT - \delta T^*, \\
\frac{dV}{dt} = b\delta T^* - cV,
\end{array}
\]

(1)

where $T$, $T^*$ and $V$ are, respectively, the densities of CD4+ T cells, infected CD4+ T cells and virus in the plasma of an individual. The model parameters in this model have the following meaning and approximate values [3]:
$s =$ rate of supply of CD4+ T cells from precursors $= 10 \text{day}^{-1}\text{mm}^{-3}$

$p =$ rate of growth for the CD4+ cell population $= 0.03 \text{day}^{-1}$

$T_{\text{max}} =$ maximum CD4+ cell population level $= 1500 \text{mm}^{-3}$

$\alpha_T =$ the death rate of uninfected (healthy) T cells $= 0.02 \text{day}^{-1}$

$\delta =$ the death rate of infected T cells $= 0.24 \text{day}^{-1}$

$c =$ the death rate of free virus $= 2.4 \text{day}^{-1}$

$k =$ the rate at which CD4+ cells become infected by free virus $= 2.4 \times 10^{-5} \text{mm}^3 \text{day}^{-1}$

$b =$ "burst size" = lifelong number of virions produced by an actively infected T cell $= 50-1000$, see [10].

We then denote the density of infected individuals in the population with respect to $Y$ and the total infected population as

$i = i(t, Y), \quad I(t) = \int i(t, Y) dY,$

where the integral is computed over the entire domain of the structure variables. The immunologically structured SIR model is now given by

$$
\begin{align*}
\frac{\partial S}{\partial t} &= -\nabla Y(i) \cdot \frac{\partial Y}{\partial t} - \gamma(Y)i - \mu(Y)i, \\
\frac{\partial I}{\partial t} &= \beta N - (\mu + aN)N, \\
\frac{\partial N}{\partial t} &= S + I + R,
\end{align*}
$$

(2)

where, $S$, $I$ and $R$ represent, respectively, the numbers of susceptible, infective, and recovered individuals, $N$ is the total population, $\gamma$ is the recovery rate, $\mu$ is the natural mortality rate, $\beta$ is the birth rate, $a$ is a (very small) coefficient representing the per capita increase in mortality over baseline that ensures logistic behavior, and $\rho$ is the per capita infection rate.

The PDE (2.1) for the density of infected individuals reflects the changes in immunological state of the individuals as the pathogen-immune system evolves as described by (1). It has to be complemented by appropriate boundary conditions, and this is not a trivial issue. In particular, for the case motivated in the previous section, $Y = (V, T, T^*)$, it is obvious that individuals who have not been infected should have initial values $V_0 = T^*_0 = 0$, but such conditions on the structure variables at any time force $V(t) = T^*(t) = 0$ for all future times $t$ and, therefore, new infections may not be reflected as Dirichlet boundary conditions on $V$. Thus we are led to the following boundary conditions for $i$:

$$
\begin{align*}
i(0, T, T^*) &= 0, & T \geq 0, & T^* > 0, \\
i(V, 0, T^*) &= 0, & V, T^* \geq 0, \\
i((V, T, 0) &= 0, & V > 0, & T \geq 0, \\
\frac{\partial i}{\partial N}(0, T, 0) &= \frac{1}{T_{\text{max}}} \rho \frac{SI}{N}, & T > 0.
\end{align*}
$$

(3)

The first 3 conditions in (3) reflect, respectively, the fact that no individual can have no virus if (s)he has infected CD4+ T cells, that nobody may have no healthy T cells, and that nobody can have no infected T cells in the presence of virus. The last condition in (3) gives the flow of newly infected individuals—who prior to infection had $V = T^* = 0$—into the correct domain for $Y = (V, T, T^*)$, where $T$ can have any allowable value (i.e. whatever it was prior to infection), and $V = T^* = 0$ with $V$ increasing at the rate that accounts for all new infections from (2.iii) when integrated in $T$.

The analysis of the general model (1)–(3) is very complex and remains an open problem.

3 Results from Numerical Simulations

Simulations based on the full model (1)–(3) require a 4-dimensional domain for the structure variables $T, V, T^*, t$ creating a serious computer memory problem to run our numerical method. Therefore, we do not take into account the variable $T$ in the simulations, using the following reduction suggested in [9]: since the T cell levels generally change very slowly within any one individual, we hold $T = T_0$ constant though
not necessarily satisfying the parameter constraint \( c = bkT_0 \) resulting from \( V \) and \( T^* \) being at equilibrium. We use this reduced model with representative values \( T = T_0 = \) taking the values 100 (AIDS), 400 (HIV+, non-AIDS), and 1000 (healthy). Our numerical method is a finite difference method of characteristics.

We measure time in days since that is a good scale for the pathogen-immune response model. The per capita death rate and birth rate per day are \( \mu = 0.000035396843 \) and \( \beta = 0.00003863122 \) [12]. To estimate \( \rho \) we used data from [11] reporting the number of new cases for every year from 2004 to 2008 (respectively, 639, 518, 520, 518, and 434), suggesting \( \rho \approx 0.000095 \pm 0.000025 \) per day.

We performed several simulations with our numerical method in order to show the behavior of the model in different situations. As explained in the previous subsection, in order to avoid RAM problems we use a bidimensional grid for \( V \) and \( T^* \), and we select several values of \( T \) and \( b \).

The computational (and immunological) domain for \((V, T^*)\) increases with the value of \( T \), as we see comparing the left two regions in figure 2 and decreases with the value of \( b \), as we see comparing the right two regions in figure 2. Note that \( T = 400 \) to infected immuno-compromised individuals, and \( T = 1000 \) to healthy.

\[ \text{Figure 1: Evolution of infected individuals. Left plot: } T = 400 \ b = 150. \text{ Right plot: } T = 1000 \text{ and } b = 100. \]

In these plots we see that the total number of infected individuals decreases slowly for \( T = 1000 \) and \( b = 100 \), and it increases quickly for \( T = 400 \), \( b = 150 \).

\[ \text{Figure 2: Domain of } V \times T^*: b = 50, T = 400 \text{ (left); } b = 50, T = 1000 \text{ (middle); } b = 100, T = 1000 \text{ (right).} \]
This last figure shows the negative impact that larger burst size has on the epidemic, reflected in larger densities and larger range for $T^*$.

4 SUMMARY

We described a general model of epidemics of SIR type structured by immunological variables representing densities of uninfected and infected T cells, and of the virus responsible for the epidemic.

We use a numerical algorithm based on the finite difference of characteristics to approximate solutions of a population subject to real life demographic and epidemiological parameters and see clear evidence that the prevalence of infection is intimately related to the density of uninfected T cells as well as to the burst size of infected T cells.

For healthy individuals, with a density of uninfected T cells of one thousand per milliliter of blood, a mild infection slowly decays to extinction, while for immunocompromised individuals with a density of uninfected T cells of four hundred per milliliter of blood the viral load increases quite rapidly.

We see that the computational domain corresponding to the same final time changes a lot with both the density of uninfected T cells and with burst size—increasing with the former and decreasing with the latter.

Refinements of the numerical method are necessary to accommodate the situations of smaller values of $T$ or larger values of $b$ since the small size of the computational $(V, T^*)$-domain makes the characteristics approach each other sooner leading to increased errors in the approximation.

REFERENCES