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Integrating immunological and epidemiological models

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Abstract: Disease affects populations in two major and complementary ways: at the individual level, the infected may die or suffer other non-lethal but still undesirable consequences from the disease; at the population level, there may be devastation caused be it by diseases that decimate large numbers of individuals, or by creating endemic situations that are very costly in terms of treatment, prevention or isolation, for example. For many decades mathematical models have been proposed and analyzed to describe the evolution of epidemics through populations. Aside from the simplest ODE-based models that contain only epidemiologically relevant variables, several structural variables have been introduced through the years, such as size, age of disease, chronological age, gender, etc. Separately, in last few decades, several models have been proposed and analyzed for the immunological response at the individual level that is the main determinant of recovery, chronic disease, or death. Even though these types of models naturally beckon modelers to combine them, only very recently has this idea taken strength. We propose a general framework for immuno-epidemiological models that use variables of immunological nature (e.g. viral load and some measure of immune response such as T-cell density) as structure variables of epidemiological models. This results in coupled systems of ordinary and partial differential equations, possibly with nonlocal terms and/or boundary conditions. Under this general framework, we describe a simple such combination in an SIR case, and present a partial analysis of the resulting model, as well as generalizations.

Keywords: *mathematical models, partial differential equations, immunology, epidemiology*

1. INTRODUCTION

Mathematical Modeling has played an important role both in immunology and in epidemiology. It has helped, for example, to develop dosage and timing protocols for treatment of HIV infection (see Jeffrey, 2006, for example), and to forecast prevalence and cohorts of interest as well as vaccination schedules for many diseases (see, for example, the excellent book by Diekmann and Heesterbeek, 2000). These two important areas of research have remained thus far almost non-intersecting, with a large number of publications considering the immune response but not its impact on disease transmission, and many others considering the disease transmission and the passage of individuals from one epidemic class to another (susceptible, exposed, infective, quarantined, and recovered, for example) but not the immune response that leads to such passages.

The main goal of this paper is to describe and analyze a new mathematical model that combines immunology and epidemiology into a unified framework for a research area that will likely continue to evolve and attract research efforts in biology, probably for many years.

We consider the arrival of an infectious disease to a population and the impact it has on the immune system at the individual level, and on the development of an epidemic at the population level. We therefore propose a new epidemiological model based on the classical S-I-R one (Kermack and McKendrick, 1927). In contrast with this model, the infective class is structured in our model not by infection-age but rather by variables of immunological nature that evolve themselves in time according to some prescribed dynamics such as, for example, viral density, uninfected and infected T cell densities in HIV infection (Perelson and Nelson, 1999). We discuss the boundary conditions appropriate for the model and prove the existence and uniqueness of solutions.

Such model will allow, for example, a deeper understanding of the present epidemiological state of the US population concerning re-emerging diseases such as latent tuberculosis infection and how it will spread in the near future, or how the new families of antiviral therapies might impact the annual flu epidemics.

2. A SIMPLE IMMUNOLOGICAL MODEL

A very simple model for viral infection is formed by considering three coupled ordinary differential equations that describe the dynamics of the population of a virus or some other pathogen, that of the defending T-cells, and the infected T-cells in which the virus has injected its RNA to have it replicated with the host cells' DNA (Perelson and Nelson, 1999). Let T, T^*, and V denote, respectively the population size (or density) of naive T-cells, infected T-cells, and virus in an infected individual. The evolution of these populations can be approximately described by the following dynamical system:

$$\begin{aligned} T' &= \Lambda - rT\left[1 - \frac{T + T^*}{L}\right] - \mu T - \beta V T, \\ T^{*\prime} &= \beta V T - \delta T^*, \\ V' &= b\delta T^* - cV. \end{aligned} \tag{1}$$

Here Λ represents the production rate of T cells from the bone marrow, r is their net reproduction rate, L the equilibrium density in uninfected individuals, β is the per capita infection rate, μ is the natural mortality rate (apoptosis) of T cells, δ is the burst rate of infected cells, b the amplification factor, and c the virus clearance rate. The dynamics of systems like this one has been studied and applied by several groups, for example A. Perelson et al. at Los Alamos. It is not difficult to establish the existence of a threshold above which the virus remains in the host and below which it is driven to extinction by the immune response (Perelson and Nelson, 1999). As the authors point out, equations (1) imply that for V and T* to be in quasi-steady state, the relation $b\beta T_0 = c$ must hold. This equation implies, for example, that individuals with different quasi-steady state T cell counts must have differences in one of the parameters b, β, or c. It also suggests that "disease progression, characterized by a lowering in the $CD4^+$ T cell count, should occur if b or β increase with time" (Perelson and Nelson, 1999). The authors then examine the situation in which T = constant = T_0, but T^* and V vary according to equations (1) and so they analyze the system

$$\begin{aligned} T^{*\prime} &= \beta V T - \delta T^*, \\ V' &= b\delta T^* - cV. \end{aligned} \tag{2}$$

The null-clines for this reduced system are the straight lines

$$V = \frac{\delta}{\beta T_0} T^*, \qquad V = \frac{b\delta}{c} T^*, \tag{3}$$

that coincide when $c = b\beta T_0$, or otherwise intersect at the origin. When $c \neq b\beta T_0$, the origin is a stable equilibrium if $c > b\beta T_0$ and a saddle point when $c < b\beta T_0$ (Perelson and Nelson, 1999). The characteristic equation is a quadratic polynomial with one negative root and one positive when $c < b\beta T_0$ and the viral density grows without bound. When $c > b\beta T_0$ the other root is also negative and the virus will eventually becomes extinct. As pointed out by the authors, the condition $c > b\beta T_0$ can be interpreted as saying that the rate of clearance of the virus is greater than its rate of production. At the time of initial infection it is reasonable to assume that T = constant. Thus, if one is infected with a virus with parameters $b\beta$ such that $c > b\beta T_0$, the virus is ultimately eliminated.

3. A SIMPLE EPIDEMIOLOGICAL MODEL

The simplest model for the dynamics of an epidemic for a disease that imparts immunity also consists of a system of three ordinary differential equations that describe the evolution of the three epidemiological classes of *susceptible*, *infected*, and *recovered* individuals. The classical SIR model (Kermack and McKendrick, 1927), without infection-age structure, is given by

$$\begin{aligned} S' &= \xi(S + I + R) - mS - \rho SI, \\ I' &= \rho SI - mI - \gamma I, \\ R' &= \gamma I - mR. \end{aligned} \tag{4}$$

Here ξ is the fertility rate, m the mortality rate, ρ the effective per capita infection rate, and γ the per capita recovery rate. When demography is ignored (i.e. $\xi = m = 0$) this simple model admits only the disease-free equilibrium points (S^*,0,R^*), where S^*, $R^* > 0$\$. The epidemic always dies out due to the depletion of the susceptible population, and there is an outbreak —that is an increase in the number of infected individuals— if, and only if the *infection reproductive number* exceeds unity:

$$\mathcal{R}_0 = \frac{\rho S(0)}{\gamma} > 1. \tag{5}$$

Solutions corresponding to non-negative (respectively, positive) initial data are non-negative (respectively, positive) for all time, Dulac's criterion excludes the possibility of periodic solutions and, for a given situation with initial conditions $S(0) = S_0$, $I(0) = I_0$, $R(0) = R_0$, it is always the case that

$$\lim_{t \to \infty} (S(t), I(t), R(t)) = (S^*, 0, R^*), \tag{6}$$

where $S^* + R^* = S_0 + I_0 + R_0$ and S^*, R^* are uniquely determined by the initial conditions and parameters of the model. Many extensions and variations of this model have been proposed and analyzed, including other epidemic classes (e.g. exposed or latently infected, quarantined), other independent variables (e.g. chronological age, infection-age, etc.). However, the role of the immune system on the values and change in the parameters ρ and γ has largely remained unaddressed in such studies.

4. NEW IMMUNO-EPIDEMIOLOGICAL MODELS

The new system we propose to study is a SIR epidemiological model structured by the immunological variables T, T^*, and V rather than by the infection-age considered in (Kermack and McKendrick, 1927). We introduce the variable $\mathbf{X} = (T, T^*, V)$, and we consider the infected individuals in the population structured by this variable,

$$\eta = \eta(t, \mathbf{X}).$$

Based on (Perelson and Nelson, 1999), we shall assume that T is constant and that T^* and V evolve according to the reduced immunological ODE system (2). If we consider parameter ranges where the roots of the characteristic equation for (2) are both negative, i.e. $c > b\beta T_0$, it follows that all solutions of (2) are bounded

by (T^*_{max}, V_{max}) say. The natural domain for **X** thus seems to be

$$\Omega = \{\mathbf{X} = (T,T^*,V): T = T_0,\ 0 \le T^* \le T^*_{max},\ 0 \le V \le V_{max}\}.$$

The total number of infected is given by

$$I(t) = \int \eta(t, \mathbf{X})\, d\mathbf{X}. \tag{7}$$

The immunologically structured SIR model is given by

$$\begin{aligned} S' &= \xi(S + I + R) - mS - \rho SI, \\ \frac{\partial \eta}{\partial X} &= -grad(\eta)\cdot\frac{\partial \mathbf{X}}{\partial t} - m(\mathbf{X})\eta - \gamma(\mathbf{X})\eta, \quad \mathbf{X} \in \Omega, \\ R' &= \gamma I - mR. \end{aligned} \tag{8}$$

The system must be complemented with appropriate boundary conditions. The one that might seem reasonable at first glance to account for new infections,

$$\eta(t, \mathbf{X}) = \rho S(t) I(t), \tag{9}$$

is actually incompatible with continuous solutions for positive values for V since $\overline{\mathbf{X}} = (\overline{T}, 0, 0)$ is a steady state of the immunological system of ODEs (1) for any $\overline{T} > 0$ and, therefore, no virus or infected T cells will ever exist if none are initially present. One way to circumvent this problem is by assuming every individual in the population to have some positive density of virus, of at least $\varepsilon > 0$ say.

Then we consider

$$\Omega = \{\mathbf{X} = (T,T^*,V): T = \overline{T},\ 0 \le T^* \le T^*_{max},\ \varepsilon \le V \le V_{max}\}.$$

and the susceptible are those individuals whose viral density is at the threshold $\varepsilon > 0$.
The Dirichlet boundary condition (9) may be better replaced by a Neumann one, since it is really the flux into the infected class that is given by the mass action term describing new infections. For this model, therefore, we consider the boundary conditions for both T* and V as Neumann:

$$\frac{\partial \eta}{\partial T^*}(t,(\overline{T},0,V)) = 0, \quad \frac{\partial \eta}{\partial V}(t,(\overline{T},T^*,\varepsilon)) = \rho S(t) I(t), \tag{10}$$

and complete the system with initial conditions that are compatible with them, $S(0) = S_0 > 0$ and $\eta(0, \mathbf{X}) = \eta(0, (\overline{T},0,0)) = \eta_0(\mathbf{X})$, such that

$$\frac{\partial \eta_0}{\partial T^*}(\overline{T},0,V) = 0, \quad \frac{\partial \eta_0}{\partial V}(\overline{T},T^*,\varepsilon) = \rho S_0 \int_\Omega \eta_0(X)\, dX. \tag{11}$$

5. WELL-POSEDNESS OF THE NEW IMMUNO-EPIDEMIOLOGICAL MODEL

Since we are considering the hyperplane of Ω defined by $T = \overline{T}$, we need not consider triples (T, T^*, V) ∈ Ω but rather pairs (T^*, V) ∈ $\Omega \cap \{T = \overline{T}\}$, i.e. $0 \le T^* \le T^*_{max}$, $\varepsilon \le V \le V_{max}$.

We introduce the solution operator for the initial value problem (2) with initial condition $\mathbf{X}(t_0) = \mathbf{X}_0$ and denote it by $G(\sigma; \mathbf{X}_0, t_0)$; that is,

$$\mathbf{X}(\sigma) = G(\sigma; \mathbf{X}_0, t_0) \tag{12}$$

denotes the integral curve of (2) that passes through the triple (t_0, T_0^*,V_0).

We consider now a triple (t,T^*,V) ∈ $(0,t_{max}) \times (0,T^*_{max}) \times (\varepsilon,V_{max})$ and track it back to the "initial-boundary" that consists of the three planes $t = 0$ ("initial"), $T^* = 0$ ("T^*-boundary"), and $V = \varepsilon$ ("V-boundary"). Next we

integrate the partial differential equation in (8) along the characteristic curve, from the "initial-boundary" to the point (t,T^*,V). There are three different possibilities according to the plane on which the integration (i.e. the characteristic) originates. Let us consider the first case, namely the one where the characteristic originates on the "initial" plane $t = 0$: $\mathbf{X}_0 = G(-t; \mathbf{X}, t)$ or, equivalently,

$$(T^*,V) = G\big(t; (T_0^*,V_0),0\big), \quad \mathbf{X}_0 = (T_0^*,V_0). \tag{13}$$

Then, we obtain

$$\eta(t,X) = \eta_o(t,X_0)\exp\Big(-\int_0^t \alpha\big(G(\sigma;X_0)d\sigma\Big), \tag{14}$$

where $\alpha = \mu + \gamma$.

Considering the second case, namely the one where the characteristic originates on the "T*-boundary" $T^* = 0$, we have $(0,V_0) = G(t_0\text{-}t,(T^*,V),t)$ or, equivalently,

$$(T^*,V) = G(t;(0,V_0),t_0). \tag{15}$$

Then, we obtain

$$\eta(t,T^*,V) = \eta_o(t_0,0,V_0)\exp\Big(-\int_0^t \alpha\big(G(\sigma;(0,V_0),t_0)d\sigma\big)\Big). \tag{16}$$

The relation (16) needs to be differentiated in T^* and then evaluated at $T^* = 0$ to use the vanishing boundary condition on that plane. Finally, repeating the procedure for points $\mathbf{X}$ whose characteristic curve originates on the plane $V = \varepsilon$, one arrives at an expression for the solution η on Ω in terms of S. Then, integrating the ODE for S in terms of $I(t) = \int_\Omega \eta(t,\mathbf{X})d\mathbf{X}$\$, we can substitute the resulting S into the expression for η to obtain an implicit representation

$$\eta(t,\mathbf{X}) = F(\eta). \tag{17}$$

Finally, we can define an operator Φ: $C\big([0,t_{max}] \times \Omega\big) \to C\big([0,t_{max}] \times \Omega\big)$ as $\Phi(g)=F(g)$, $g \in C\big([0,t_{max}] \times \Omega\big)$, where F is the functional in (15). The contraction mapping theorem can then be applied to the operator Φ on the Banach space $C\big([0,t_{max}] \times \Omega\big)$ to show the existence of a unique solution. $\Phi(g)$ can be shown to be continuous from the compatibility conditions of the initial and boundary conditions (11), proving that Φ is well defined.

6. DISCUSSION AND CONCLUSIONS

We proposed a first epidemiological model of S-I-R type that is structured by immunological variables. The description of the boundary conditions is essential for the biological significance and applicability of the model.

We established the existence and uniqueness of solutions for the initial-boundary value problem the model consists of. It is still necessary to prove that solutions originating from non-negative initial data remain non-negative for as long as they exist. Moreover, the continuous dependence of solutions on model parameters needs to be established to complete the well-posedness. These two results are quite straightforward to obtain.

Further study is needed to determine the asymptotic behavior of solutions, as well as possible equilibria and their stability and instability, and thresholds that separate disease extinction from persistence.

Numerical simulations need to be performed for a wide range of model parameters in order to see different behaviors that may occur in the transient path to steady states. This may not be simple to do because the structure of the model will tend to make any numerical method based on characteristics degenerate as time evolves en the solution of (\ref{imm}) approaches its equilibrium.

REFERENCES

Diekmann, O., and J.A.P. Heesterbeek (2000), Mathematical Epidemiology of Infectious Diseases, Model Building, Analysis and Interpretation, Wiley Series in Mathematical and Computational Biology.

Jeffrey, A.M. (2006), Control theoretic approach to HIV/AIDS drug dosage design and timing the initiation of therapy, Ph.D. dissertation, University of Pretoria.

Kermack, W.O. and McKendrick, A.G. (1927), A contribution to the mathematical theory of epidemics, *Proc. Roy. Soc. A* 115, 700-721.

Perelson, A.S., and P.W. Nelson (1999), Mathematical analysis of HIV-1 dynamics in vivo, *SIAM Journal of Applied Mathematics* 41, 3-44.