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E-Synthesis

Acute or Chronic? Within-Host Models with Immune Dynamics, Infection Outcome, and Parasite Evolution

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abstract: There is ample theoretical and experimental evidence that virulence evolution depends on the immune response of the host. In this article, we review a number of recent studies that attempt to explicitly incorporate the dynamics of the immune system (instead of merely representing it by a single black box parameter) in models for the evolution of parasite virulence. A striking observation is that the type of infection (acute or chronic) is invariably considered to be a constraint that model assumptions have to satisfy rather than as a potential outcome of the interaction of the parasite with its host's immune system. We argue that avoiding making assumptions about the type of infection will lead to a better understanding of infectious diseases, even though a number of fundamental and technical problems remain. Dynamical modeling of the immune system opens a wide range of perspectives: for understanding how the immune system eradicates a parasite (which it does for most pathogens but not for all, HIV being a notorious example of a virus that is not completely eliminated), for studying multiple infections through concomitant immunity, for understanding the emergence and evolution of the immune system in animals, and for evolutionary epidemiology in general (e.g., predicting evolutionary consequences of new therapies and public health policies). We conclude by discussing new approaches based on embedded (or nested) models and identify future perspectives for the modeling of infectious diseases.

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The most basic approach in epidemiology, dating from the 1920s, is to track numbers (or densities) of susceptible and infected hosts in a population. This approach assumes that infection is instantaneous, thus simplifying within-host processes, such as establishment of an infection or mounting an immune response, to the extreme. However, it has become clear that for a better understanding of, in particular, the evolutionary aspects of host-parasite interactions, such within-host processes need to be considered in more detail. The first attempts to model the dynamics of the immune system date from the 1970s (Bell et al. 1978; Perelson and Oster 1979), and dynamic models for the interaction between parasites and the immune system, based on the analogy with ecological interactions, followed about a decade later (Nowak et al. 1990; Antia et al. 1994; Sasaki 1994).

By now, a large number of studies of within-host dynamics (WHD) of microparasites have been conducted. Several of these assume that parasites are resource limited, but it is striking that the majority explicitly model dynamics of the immune response of the host. Here, we discuss why this approach, taking into account immunological dynamics, even in a simplified version, can help to better understand disease dynamics.

Within-host dynamics models differ from most studies in the domain of theoretical immunology in that the higher level (demographic events, epidemiology) is explicitly considered, whereas theoretical immunology typically focuses strictly on within-host processes (e.g., De Boer and Perelson 1995). Thus, an important aspect of theoretical immunological models is that hosts do not die, whereas, in contrast, in WHD models it is often the explicit aim to assess the effect of a parasite on its host's mortality (which is one of the standard definitions of virulence). Within-host dynamics models are strongly linked to evolutionary epidemiology (Galvani 2003), and the purpose of this rapidly developing field is to take into account evolution of host-parasite interactions in addition to epidemiological

dynamics. The first developments of this field (Anderson and May 1982) have focused on virulence evolution, but more recently, studies have investigated other parasite traits, such as the periodicity of the disease outbreaks (van Ballegooijen and Boerlijst 2004). The aim of this article is to review how incorporation of the immune system in WHD opens many new perspectives for evolutionary epidemiology.

The literature on models of WHD is so vast that we decided to restrict our approach and focus on specific issues. First, we do not discuss WHD models based on resource exploitation (for reviews, see Smith and Holt 1996; Perelson 2002). Second, we focus on WHD models that have an epidemiological perspective. Finally, we do not address the question of parasite within-host evolution. Throughout this review, we stress a point that, to our knowledge, studies of WHD have failed to make: namely, that such models should be able to predict the outcome of the infection and the type of infectious disease that results.

As we discuss in "On the Importance of Modeling the Immune Response Explicitly," there are many different reasons to build WHD models with the immune system. In spite of this great variety, we show in "Different Types of Within-Host Models" that it is possible to sort existing studies according to the type of infection they model (acute or chronic). Finally, in "Perspectives," we list some of the perspectives opened by these models.

On the Importance of Modeling the Immune Response Explicitly

In some WHD models, parasite growth is limited only by resource availability (Sasaki and Iwasa 1991; Smith and Holt 1996). These models are particularly appropriate for modeling parasites that escape the immune response (at least partially)—for example, *Plasmodium* (malaria; Hoshen et al. 2000)—or to study viral dynamics (Perelson 2002; Gilchrist et al. 2004; Gilchrist and Coombs 2006). However, for many parasites, including the dynamics of the immune system has a pivotal influence for several reasons.

Predicting the Outcome of an Infection

The outcome of an infection depends at least in part on the interaction between the parasite and the immune system of the host. This is what is typically observed in immunocompromised hosts: patients infected with HIV (which destroys the immune system) die from a suite of other so-called opportunistic infections. In mathematical models, this translates into an interaction-dependent mortality (or some other parasite-affected life-history trait). Of course, other ecological processes may be superimposed, such as resource competition. There are grosso modo three possible outcomes for an infection: rapid recovery, rapid death, or persistent infection (if there is neither death nor recovery after a long time). The outcome depends on both the host and the parasite and involves many life-history traits such as parasite growth rate, antigen variation, but also immune strength and immune memory.

Currently, models assume that a disease is either always eventually completely cleared (acute infection) or never cleared (chronic infection) from the host, and models are constructed that satisfy this assumption. We advocate that it is necessary to generate testable predictions about the outcome of the infection by developing approaches that avoid such a priori assumptions. A first alternative approach is to consider the WHD using realistic and consequently complex models. Such an approach can give indications about what parasites will be quickly eliminated and what can persist indefinitely. A second approach is to build more simple models where the immune system is defined by only a few elementary characteristics. The advantage of the latter approach (which we will focus on here) is that it provides a general framework that can be incorporated into more complex models (e.g., with explicit epidemiology).

Ecological Immunology

Models for HIV infections were among the first to include the immune system (Cooper 1986; Nowak et al. 1990; De Boer and Boerlijst 1994). The outcome of this type of interaction, where the "predator" is also a "prey," is not at all immediately obvious and calls for a particular modeling approach in which one needs to model lymphocyte populations explicitly. Several HIV models have developed useful concepts for developing simple immune system models. For instance, Nowak et al. (1990) show that the nonspecific immune response along with antigen variation can have important consequences. Wodarz et al. (2000) show that small differences in modeling immune memory can greatly affect the predictions of the model. The relationship between the immune system and parasites shares many characteristics with the ecological predator-prey interaction, the dynamics of which have been studied extensively. Thus, it is tempting to exploit the analogy in order to understand how the immune system fights infections. For further discussion of the parallel between ecology and immunology, see Wodarz (2006). Here, we will focus on the question of how such models can lead to new insights into the interaction between epidemiology and evolution. We thus include acute infections in our

review, and we also focus on the evolutionary consequences of WHD, in particular, the evolution of virulence.

Immune Response as a Selection Pressure for the Parasite

Many studies suggest that immune responses impose a major selection pressure on the parasite. The potential consequences become apparent when we consider the parallel with antibiotic resistance, which can be seen as an "external" defense (Medley 1996; van Baalen 2002). Antigenic drift, where a parasite keeps changing its antigenic properties, is an obvious example of the result of selection pressures exerted by the immune system (Sasaki 1994; Gupta et al. 1998; Frank 2002). More in the scope of this review, several models suggest that other traits such as virulence may also depend on the level of host defenses (van Baalen 1998; Day and Burns 2003; Alizon and van Baalen 2005).

Experimental and observational evidence support these claims. Jäkel et al. (2001) suggested a possible role of immune defense as a selection pressure on parasite virulence for a protozoan in rats. More recently, Mackinnon and Read (2004) showed that passing *Plasmodium chabaudi* (rodent malaria) through immunized mice selects for higher levels of virulence. These experiments illustrate the fact that it is difficult to study parasite evolution without considering the immune response as a major force that drives this evolution.

Cost of the Immune Response for the Host

Defense against parasites involves different costs. First, several trade-offs between the maintenance of an immune system (i.e., constitutive costs; Harvell 1990) and other life-history traits (fecundity, senescence) have been demonstrated. Such trade-off relationships are central in ecology and evolution (Sheldon and Verhulst 1996; Gemmill and Read 1998; Moret and Schmid-Hempel 2000; Day and Burns 2003; Koella and Boëte 2003; Rolff and Siva-Jothy 2003; Schmid-Hempel and Ebert 2003; Restif and Koella 2004). Hence, investing in the immune system may decrease reproduction or survival. Second, the immune response (i.e., induced defense; Harvell 1990) may have various costs. In particular, the response may contribute to virulence. Indeed, immunopathology is a common phenomenon (Graham et al. 2005); it is often considered as a dysfunctioning of the immune system, but it should be realized that it cannot be clearly separated from parasite virulence (defined as parasite-induced mortality or other detrimental effects). Immune system–mediated virulence occurs in SARS (Nicholls et al. 2003), possibly caused the extreme virulence of the 1918 influenza virus (Kobasa et al. 2007), and is responsible for the virulence of the lymphocytic choriomeningitis virus (Lipsitch and Moxon 1997). Another form of immunopathology may result from concomitant infections. In coinfected hosts, the immune system may be unable to mount conflicting responses, leading to an error in the induced immune response, which leads to immunopathology (Graham 2002).

Different Types of Within-Host Models

Immunity is modeled in a great variety of ways in WHD models, but the dynamics of the parasite are typically modeled by similar equations (often identical to the differential equation describing prey dynamics in a Lotka-Volterra predator-prey system). That is, in models that do not describe parasites with several life-stages (such as *Plasmodium*) and do not include resource competition, changes in parasite density are given by an equation of the type

$$\frac{dx}{dt} = (\varphi - \sigma y)x, \tag{1}$$

where x is the parasite density, y is the immune effector density, φ is the parasite growth rate, and σ is the rate of destruction of the parasites by the immune system (see table 1).

Because the main point of interest is the parasite, the structural complexity of the immune system is very much simplified in models of WHD compared with typical models in theoretical immunology. For instance, WHD models tend not to distinguish between T and B lymphocytes (or other immune components), which illustrates the kind of simplifying assumptions that underlie them. Typically, they assume that there is a population of effector cells attacking the parasite and that these effector cells replicate following infection. The vertebrate immune system seems the most appropriate to fit this definition, but it can also apply to insect immune systems. Instead of attempting to incorporate all specific components of the immune response (as in theoretical immunology), WHD models adopt a

Table 1: List of the notations used

Symbol	Description
x	Parasite density
y	Lymphocyte density
φ	Parasite within-host growth rate
σ	Rate of destruction of parasites by the immune system
c	Lymphocyte proliferation rate
c_0	Lymphocyte baseline production rate
δ	Lymphocyte death rate
Φ	Parasite density that stimulates immune cells to grow at half their maximum rate
D	Lethal density of parasites

more qualitative approach that merely tracks the strength of the immune response. Even if still rather simplified, the resulting models are more realistic than representing the immune system as a single black box parameter.

In the following, we classify the different approaches according to the way they assume the immune response is mounted. Of course, many models are difficult to classify this way because of their complexity. For instance, models that include different life stages or antigenic variations (e.g., see Hellriegel 1992; Sasaki 1994; Antia et al. 1996*a*; Anderson 1998) often include more details in the immune response that we cannot describe in detail here.

Models for Persistent Infections

In a way, persistent infections are simpler to model than acute infections because the analysis by its nature focuses on the within-host equilibria so that the transient dynamics (which are much more difficult to study) can be ignored.

Predator-Prey Models. Anderson et al. (1989), Hellriegel (1992), and Anderson (1998) use a classical predator-prey approach to study the particular case of malaria infections. These models differ from the others presented in this review in that several parasite life stages (clonal and sexual) need to be taken into account. Also, they include multiple infections, which raises some specific questions discussed in "Perspectives." With a unique parasite life stage and no multiple infections, the equation for the immune system can be written as follows:

$$\frac{dy}{dt} = c_0 + cxy - \delta y, \tag{2}$$

where c_0 is the lymphocyte baseline production (or proliferation) rate, c is the proliferation rate due to the presence of parasites or their antigens, and δ is the lymphocyte death rate.

A difference with standard predator-prey models is the production term (c_0). This predicts that even in the absence of parasites, there will be a (typically small) standing stock of lymphocytes ready to attack. Without this standing stock, the mounting of an immune response cannot occur.

This model predicts important oscillations (fig. 1*A*), which is consistent with the Lotka-Volterra model. Instantaneous clearance occurs if the parasite's growth rate is very low compared with the immune system's strength. However, this cannot be considered an acute infection because it occurs before the infection: the parasite never really settles in the host. Thus, this model accounts for only persistent infection. Another limitation of this model

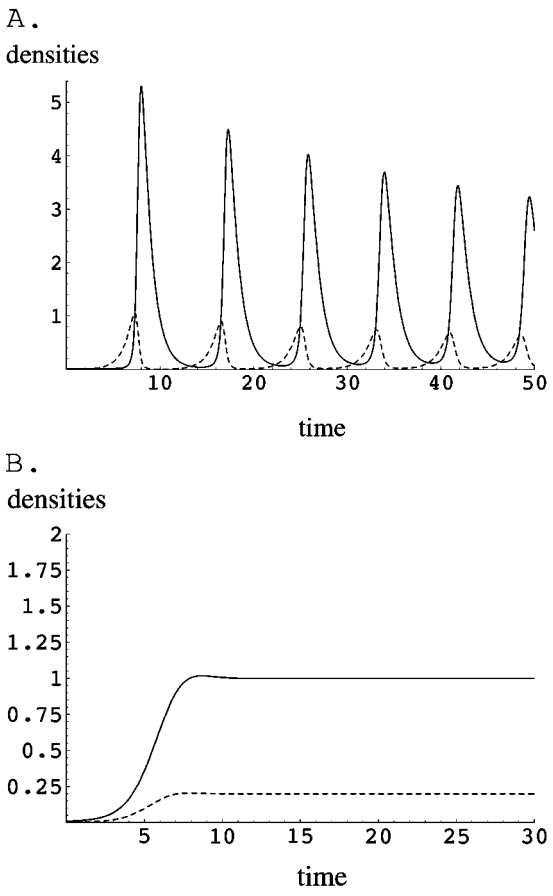

Figure 1: Parasite (*dashed line*) and lymphocyte (*solid line*) densities for persistent infections with a predator-prey model (*A*; eq. [2]) and with a predator-prey-like model (*B*; eq. [3]). Parameter values are $\varphi = 1$, $\sigma = 1$, $c = 5$, $\delta = 1$, and $b = 0.01$.

is that the strong oscillating behavior renders a complete analysis difficult.

Note that in some models (Antia et al. 1996*a*, 1996*b*; Antia and Lipsitch 1997) the activation term is density dependent (see eq. [5] below for a similar case with acute infections). In this case, when the parasite is rare, the model behaves as a predator-prey model (eq. [2]), and when the parasite is abundant, the immune response is independent of the parasite density. This reduces the oscillating behavior and facilitates the analysis of the model.

Finally, Read and Keeling (2006) also use a predator-prey model, but they explicitly model the resource (i.e., the cells) the parasite exploits. The originality of their approach is that they not only embed their within-host model in an epidemiological framework but they also add spatial structure in the host population. They find that a trade-off between recovery and transmission can emerge, depending on the within-host processes.

Predator-Prey-Like Models. Most lymphocytes involved in the specific immune response are not activated after actually meeting the parasite themselves. Instead, there is a complex activation chain with many intermediaries between cells that take information from the parasite (i.e., antigen-presenting cells, such as dendritic cells or macrophages) to those that reproduce clonally and kill parasites (CTL or B lymphocytes). This can be summarized from the following equation:

$$\frac{dy}{dt} = c_0 + cx - \delta y. \tag{3}$$

Bonhoeffer and Nowak (1994), Alizon and van Baalen (2005, 2008*a*), and Fenton et al. (2006) have developed this class of models to account for the fact that the immune response is not a real predator-prey interaction.

An important practical advantage of these models is that they predict rapid convergence toward equilibrium (fig. 1*B*), so we can easily assess the consequences of changes in parameter values. In a previous study, we showed that linking WHD to an epidemiological framework leads to a robust convex trade-off curve between transmission and virulence (Alizon and van Baalen 2005). This embedded model allows us to understand how the variation of a within-host parameter affects epidemiological parameters (e.g., virulence and transmission). However, this approach is weakened when the parasite's equilibrium is not a point (e.g., for cycling or chaotic attractors). Also, the restriction of the whole WHD to a unique value that depends on within-host parameters means the loss of many life-history details. This problem can be solved with acute infections.

Models for Acute Infections

For acute infections, the parallel between ecology and immunology is strained because few predators drive their prey to extinction. Nonetheless, many authors model acute infections using approaches inspired by predator-prey models. In this section, the parasite dynamics are still given by equation (1).

Immortal Lymphocytes. One way to ascertain parasite eradication (and thus to produce an acute infection) is to assume that lymphocytes do not die and, instead, accumulate within the host. Sasaki (1994) and Gilchrist and Sasaki (2002) model the immune response by

$$\frac{dy}{dt} = cyx, \tag{4}$$

where c is the lymphocyte proliferation rate.

It is clear that with an immune response that cannot decrease, the immune system will always get rid of an infection (see fig. 2*A*). This is why these models are considered in particular for acute infections. However, it is interesting, and perhaps counterintuitive, that a parasite with a low growth rate would cause a long infection before clearance occurs (Alizon 2008). This underlines the care that must be taken when choosing a mathematical framework to match biological observations (such as the type of an infection).

As shown by Gilchrist and Sasaki (2002), the advantage of this type of model is that it can be nested in an epidemiological framework using an analytical approach, implying that within-host processes and epidemiological processes occur on the same timescale. Contrary to models of persistent infections, it is thus possible to model in more detail the timing of life-history disease events (Day 2003). As Gilchrist and Sasaki (2002) show, this type of embedded model is useful for studying host-parasite coevolution.

Density Dependence. Several models assume, in addition, that lymphocytes react poorly to rare parasites (Antia et al. 1994; Ganusov et al. 2002; Ganusov and Antia 2003). They model the dynamics of the immune response (lymphocyte density) by

$$\frac{dy}{dt} = cy\frac{x}{x + \Phi}, \tag{5}$$

where Φ is the parasite density that stimulates immune cells to grow at half their maximum rate.

In these models, the authors further assume that a host dies if parasites exceed a given threshold density (D; see fig. 2*B*). This class of models predicts that parasites should evolve toward intermediate growth rates so as to transmit maximally without killing the host.

The main problem with these models is that "virulence" is difficult to define: because of the threshold density, there is a discontinuity between 100% virulent strains (that lead to rapid death) and avirulent strains (that lead to rapid recovery). Not only can there be no persistent infections, but also the outcome of the infection is known beforehand from the parasite growth rate. As stated by André et al. (2003), in this model, parasites are expected to evolve toward a zero virulence (i.e., at the optimal growth rate, infections never lead to host death).

However, there are means to overcome this last point. Ganusov et al. (2002) show that host heterogeneity in D (different hosts having different thresholds) strongly affects virulence evolution. Another possibility is to suppose that virulence is not expressed in terms of host death in these models but rather in terms of loss of fecundity and other sublethal effects. In this case, there could still be a

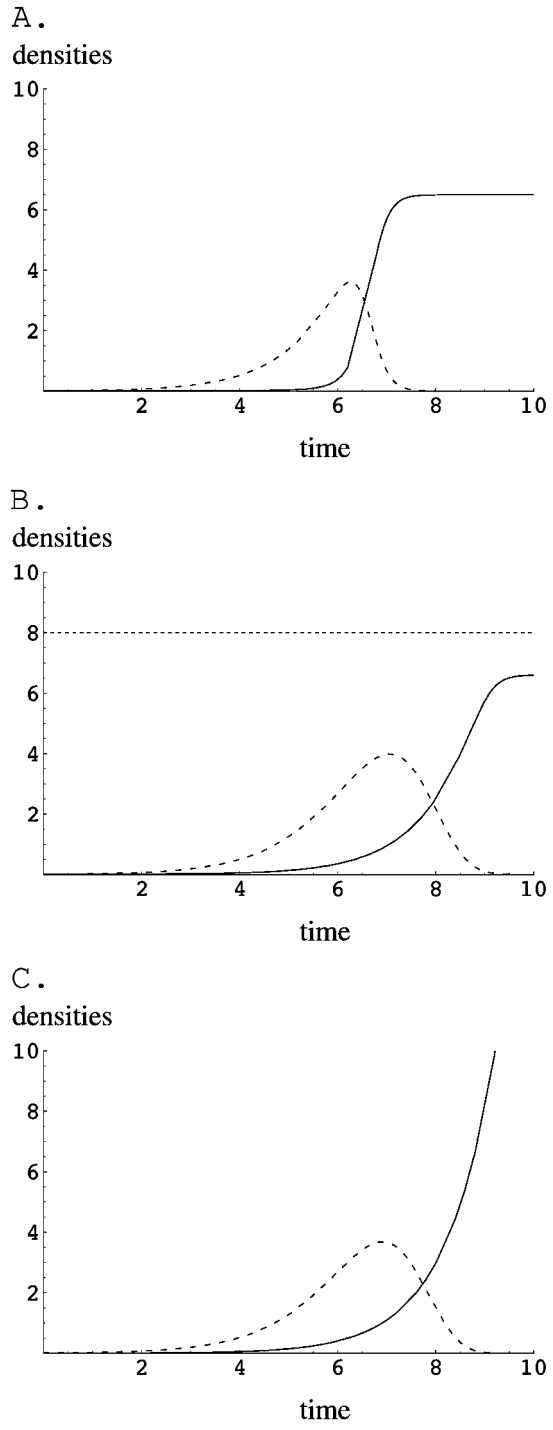

Figure 2: Parasite (*dashed line*) and lymphocyte (*solid line*) densities for acute infections with a classical model (*A*; eq. [4]), with a density-dependent model (*B*; eq. [5]), and with a milker-killer-type model (*C*; eq. [6]). The dotted horizontal line in *B* represents the threshold density (D) above which the parasite kills its host. Parameter values are $\varphi = 1$, $\sigma = 1$, $c = 1$, $D = 8$, and $\Phi = 0.1$.

gradation in parasite deleterious effects, depending on parasite within-host growth rate.

The Milker-Killer Hypothesis. It is even possible to simplify equation (4) by using what is known in ecology as the milker-killer hypothesis (van Baalen and Sabelis 1995*b*). This states that if the prey density is much greater than the predator density, then the predator growth rate is always maximal and is not limited by the prey at all. Here, it means that lymphocytes have a dynamics of their own that does not depend on parasite density. André et al. (2003) apply this approach to host-parasite interactions. Parasite dynamics are still given by equation (1), and the equation for the immune effector is

$$\frac{dy}{dt} = cy. \tag{6}$$

Note that this is equation (5) with $\Phi = 0$.

This model makes a strong simplifying assumption by neglecting the low activation stages, but it allows a more thorough analytical approach through the integration of equations (1) and (6). Knowing the solutions $x(t)$ and $y(t)$ allows one to derive instantaneous virulence and instantaneous transmission rate at any time t of the infection. André et al. (2003) use it to show that it leads to the emergence of a trade-off between virulence and other epidemiological parameters (such as transmission or recovery). They also study the influence of the host's immune strength on the trade-off.

Milker-killer models assume that lymphocyte growth is uncoupled from parasite density. This is reinforced by experimental results, which show that certain immune cells (CD8+) exhibit a "preprogrammed" proliferation activity whenever they encounter a parasite antigen (Antia et al. 2003). Such a behavior justifies the assumption of lymphocyte independent growth and also explains how the host gets rid of the parasite.

In terms of evolution, this hypothesis raises several problems. One of these is, how does this system avoid launching unnecessary immune responses? Unless there exists a means to stop this response once launched (but then, would it still be preprogrammed?), the immune system would be an extremely costly defense. These issues are discussed by Graham et al. (2005), and theoretical approaches may help us to understand how such a mechanism may evolve. Also, a drawback of this model is that the absence of limitation to lymphocyte growth (fig. 2*C*) makes it difficult to follow epidemiological dynamics once the parasite has been eradicated (contrarily to models based on eq. [2], where lymphocyte density stabilizes after host recovery). Finally, as in the two previous models, this model cannot account for persistent infections. Moreover,

in "Delays in the Immune Response," we will see that apparent, complex preprogrammed responses may actually emerge from a simple dynamical model.

Models for Multiple Infections

Multiple infection is a widespread phenomenon that is known to affect the evolution of virulence (Read and Taylor 2001). Most models incorporating multiple infections assume persistent infections because the longer the infection lasts, the higher is the probability of receiving additional infections. Here, we discuss some of the problems that multiple infections raise concerning the modeling of the immune system.

Among models of multiple infections, one can distinguish those that study antigenic variations of a given strain from those that study coinfections by different strains (or species). The main difference between these two approaches is that the former usually includes many variants (with mutations from one variant to another) while the latter usually focuses on only two strains. However, these models raise the same question in terms of immune modeling: how to link the population dynamics of the different variants/strains?

A first possibility is to use a framework for single infection, where each variant/strain elicits a purely specific immune response, and to add an equation for the nonspecific immune response, which targets any parasite indiscriminately (Nowak et al. 1990; Antia et al. 1996*a*; Anderson 1998). This approach has the advantage of being simple; however, it gives an advantage to any close mutant of a resident strain, which is free from any existing immune response specific to the resident.

The second possibility is more in accordance with experimental and theoretical studies suggesting that cross-reactivity often occurs (Alizon and van Baalen 2008*b*). In this case, one can assume that a lymphocyte has the ability to recognize and destroy any parasite but with different efficiencies. This necessitates modeling the interaction between a receptor trait of the immune cells and an antigenic trait of the parasites (Perelson and Oster 1979; Alizon and van Baalen 2008*b*).

In both these cases, the outcome of the infection and the evolutionary consequences for the parasite strongly depend on the strength of the apparent competition among the variants/strains, which itself depends on the proximity of their antigens (Read and Taylor 2001). This idea that competition between coinfecting parasites is affected by the immune system of the host is supported by experimental evidence (Taylor et al. 1997; Davies et al. 2002; Hodgson et al. 2004; Mackinnon and Read 2004; Råberg et al. 2006).

Modeling multiple infections raises all the problems already detailed for single infections but sometimes in different ways. For instance, there are more possible outcomes of the infection: rapid host death, rapid recovery, superinfection (i.e., that one parasite strain ousts the other), persistent coinfection, short-term coinfection, and so on. Also, multiple infections may confuse the immune system, which can lead to immunopathology (Graham 2002; de Roode et al. 2004; Hughes and Boomsma 2004). Finally, several studies have shown that parasites can cooperate, which may affect the overall virulence value (Brown et al. 2002). However, modeling the immune response and cross-immunity in a case with parasite cooperation remains an open question.

Toward a Unifying Model

Models are designed to reflect biological observations. However, it is striking that the type of infection (acute or chronic) is typically considered as a constraint that model assumptions have to satisfy rather than as something that needs to be explained. Consensus about how to build general models that have both persistent and acute infections as potential outcomes is still lacking, though some studies have already, albeit often indirectly, identified important aspects, which we will review here.

Antigen Turnover and Parasite Persistence. To obtain a general model, a first possibility is to modify a model for acute infections to allow some infections to become persistent. Nowak et al. (1990) do this for HIV by introducing many parasite strains with different antigens. Their model is similar to an acute infection version of the milker-killer type. The novel aspect of their approach is that they introduce a virus-dependent mortality for the lymphocytes and allow for new parasite mutants to occur. They show that acute infections may become persistent if antigenic diversity is continuously created. Because antigens are continually changing, the immune system is always one step late and thus cannot clear the infection. In other words, this model shows that parasite diversity allows long-term coexistence (and thus persistent infection).

However, Nowak et al.'s (1990) model cannot be generally applied because it is specially tailored to study HIV, which has a high mutation rate and which is able to destroy immune cells. Moreover, the conditions that lead either to an acute infection or to a persistent infection are complicated to derive (mainly because the aim of the authors is to understand HIV dynamics, particularly the final viremia peak).

Delays in the Immune Response. Recently, Fenton et al. (2006) showed that obtaining both chronic and acute infections could be achieved by introducing a delay between

parasite growth and immune response. They define the delay as the time between parasite detection and immune growth. This introduces a great variability in the population dynamics. In a simplified version, the lymphocyte dynamics can be given by

$$\frac{dy}{dt} = cx_{t-\tau} - \delta y, \tag{7}$$

where τ is the time delay.

If the delay between parasite detection and immune activation (τ) decreases, dynamics tend to become stable, typically resulting in chronic infections. Of course, the values of the parasite growth rate φ and of the lymphocyte activation rate c also influence the infection outcome. Fenton et al. (2006) show how this delay influences virulence evolution: the greater the delay, the lower the optimal virulence.

A limitation of this study lies in the modeling of the time delay between parasite and lymphocyte dynamics. For the sake of simplicity, we did not show here all the complexity of the model because, in addition to the immune delay, Fenton et al. (2006) also incorporate a degree of complexity in the immune response (defined as the number of stages required before obtaining efficient killer lymphocytes). This renders the delay definition less clear and could be an obstacle for further experimental studies.

Immune Memory and Parasite Clearance. What distinguishes persistent from acute infections is linked to the question of how to clear a persistent infection. This is similar to the ecological question of how a predator can drive its prey to extinction. In the absence of an alternative prey, a population of specialist predators, when too efficient, will become extinct for want of prey, and thus the last prey will eventually escape. In a similar fashion, when lymphocytes are successful, they remove the very factor that stimulates their production. What is necessary for elimination, therefore, is a mechanism that enables the immune response to persist (long enough) in the absence of a stimulus. Wodarz et al. (2000) show that immune memory can account for parasite clearance by stimulating other immune cells. According to these authors, immune systems with long-term memory are likely to have evolved out of precursor systems that tried to eradicate infections using a more short-term memory. This has been applied by Heffernan and Keeling (2008) to study WHD and the epidemiology of measles.

The underlying mechanism is based on autostimulation (for a more in-depth analysis, see Chaui-Berlinck et al. 2004). The idea is that, once activated, some of the lymphocytes become stimulating lymphocytes (or memory lymphocytes) instead of becoming killer lymphocytes. The two properties required to obtain immune clearance are that stimulating lymphocytes must be able to activate new lymphocytes and must have a lower death rate than killer lymphocytes. This idea is similar to the proliferation program evoked above in that once a parasite has stimulated some lymphocytes, there will be sustained lymphocyte activation. The duration of the activation depends on the death rate of the stimulating lymphocytes. This model is simple and does not require a complex "program" to orchestrate the immune response.

However, this approach is still rather limited. Even if memory lymphocytes allow for the sustained production of new lymphocytes when the parasite has reached very low densities, there is still a problem with the parameter values that lead to a clear bifurcation in the parasite density equilibrium values. To observe a shift from a nonzero density to a null equilibrium density, one must choose parameter values that lead to an "explosion" of the immune system (S. Alizon and M. van Baalen, unpublished data). This means that once the parasite is cleared, lymphocytes continue to grow exponentially and reach huge densities (as in the "milker-killer" approach). This problem is ignored because authors assume a minimum density threshold that allows for parameter values that do not lead to an explosion. Density thresholds often make sense biologically but not always, as we will see for some viral infections. Also, the problem of the immune system's behavior after parasite clearance is often ignored because of the tendency to use the host as a system boundary. To study both host dynamics and WHD, it is essential to tackle this question.

Perspectives

Predicting the Outcome of an Infection

Predicting the outcome of an infection is arguably one of the most important roles of within-host models. Following common practice, we distinguish between models of acute and chronic infections, but it is worth pointing out that even in an acute infection model, a parasite with a low replication rate may persist for a long time. Thus, it does not suffice to just define the type of infection (acute or chronic); in addition, the conditions leading to important biological processes such as host death or recovery must be understood. The ability of the immune system to clear a parasite depends on several variables, such as the parasite growth rate and the strength of the immune system. All of the models explored in this review predict that if this growth rate is too low compared with the strength of the immune system, the parasite will not be able to cause an infection. In addition to this process of immediate clearance, there may be a more complex relationship between

parasite growth rate and host recovery. As underlined in another study (Alizon 2008), when a virus increases its replication rate, it is likely to become easier prey for the immune system. This may lead to a negative relationship between the rate of exploitation by the parasite and the duration of the infection.

The second obvious variable that will influence the outcome of an infection is the strength of the host immune response: different antigenic and nutritional environments among hosts lead to differences in their specific immune responses following infection (Woolhouse et al. 1997; Ganusov et al. 2002). Moreover, it is well known that previous exposure to an antigen has a strong influence on the clearance rate because of immune memory. Without getting into all the details of immune memory, it is possible to show that introducing a particular long-lived lymphocyte population that is able to activate "classical" lymphocytes is enough to observe parasite clearance. This is why Wodarz et al. (2000) suggest that immune memory originally evolved as a by-product of a mechanism to ensure complete clearance of the infection.

The outcome of the infection may also depend on the parasite infection dose because parasites with large initial population sizes can establish persistent infection more easily, as some experiments suggest (Brunner et al. 2005). Contrary to what is usually assumed, the initial dose could be an important factor in pathogenesis for microparasites (Schmid-Hempel and Frank 2007). More generally, it is important to notice that some host characteristics—such as the age on infection, the nutrition, or the genetical background—could be as important as parasite life-history traits to explain parasite clearance.

For certain parasites, antigen dynamics may have to be taken into account in order to predict the outcome of an infection. For instance, according to Nowak et al. (1990), antigenic variation is the mechanism that allows HIV (modeled as a series of acute infections) to persist in its human host (for a recent discussion on this issue, see Rambaut et al. 2004). Insights could be gained from ecology here: evolutionary processes have a key role in explaining the persistence of preys in predator-prey systems (for a review, see Abrams 2000).

Finally, to our knowledge, the framework developed by Fenton et al. (2006) is the only one where the type of infection (acute or chronic) is not an a priori assumption of the model and where both outcomes may occur. In this model, clearance depends on three things: the relative importance of parasite growth rate compared with immune efficiency, the time delay between parasite growth and immune activation, and the complexity of the immune system. Even though their model is a first step, it clearly shows how simple models can be useful for understanding the determinants of infection outcomes. In particular, consideration of ecological models involving discrete-time processes or delayed life-history effects (Beckerman et al. 2002) could provide inspiration.

Modeling Clearance

Even when a host's immune system is able to suppress a parasite to low densities, it remains an important challenge to completely clear it. Consideration of demographic stochasticity becomes elemental when studying clearance: extinction never occurs in models derived from ecological differential equations (except maybe in certain special cases, such as in the milker-killer model). The potential role of stochasticity is linked with the verbal theory that predicts that the greater the fluctuations in parasite density, the higher the probability that parasites become extinct.

Most studies incorporating clearance assume a density threshold below which the parasite cannot survive in the host. Though this assumption often makes sense biologically (particularly if one thinks of WHD as predator-prey dynamics), there are cases where it is likely to be an oversimplification, particularly for viruses. Viremia curves of patients infected with HIV (or hepatitis C) reveal that after a first peak, the immune system is able to decrease parasite density to very low levels but not to clear it completely.

If we interpret acute infections as infections where the immune system manages to drive the parasite density below this extinction threshold, two explanations may account for persistence of viruses such as HIV. Either this threshold is very low and unreachable (i.e., the virus is able to survive at exceptionally low densities) or the threshold is reached but the virus is not cleared from the host because a nonhomogeneous distribution within the host allows it to exploit refuges from the action of the immune system.

It has been shown that HIV's population structure within a single patient is similar to what is termed a "metapopulation" in ecology (Frost et al. 2001; Achaz et al. 2004; Funk et al. 2005). Thus, it could be that the reason why HIV is not cleared after the first peak is that some reservoir populations (termed "source" in ecology) are not reached by the immune system (Funk et al. 2005). Such refuges are a problem since clearing the virus from the blood compartment is not enough to eliminate it (Cavert et al. 1997). If this metapopulation structure is true, insights from conservation biology may be useful for developing treatment strategies for HIV infections. Indeed, conservation biology studies have identified ecological patterns influencing animal extinction in metapopulations (Ferrière et al. 2004). The problem is similar but the goal inverted: instead of species conservation, the goal is parasite extinction. This example highlights some of the issues raised in this review: Under what conditions is there im-

mune clearance? Is there a well-defined threshold density? This question might concern not only the specific case of HIV, since other viruses, such as hepatitis C, seem to exhibit similar survival at low densities. Modeling WHD as a spatial process using metapopulation approaches could thus lead to new insights.

Embedded Models

According to Tauber and Podolsky (1994) the main aim of early studies in theoretical immunology (starting with the work of Burnett in the 1940s) was to explain how the immune system distinguishes between self and nonself. These early approaches were very much based on physiological models, but in the 1970s, Bell et al. (1978) drew attention to the analogy with ecological systems, arguing that the immune system can be understood as a miniature ecosystem with predation, competition, resources, and so on. However, in these approaches, survival of the host is taken for granted. Recently, Pradeu and Carosella (2006) argued that immune system dynamics cannot be understood in isolation because within-host processes interact in many ways with the environment of the host. This theory can find some support in embedded (or "nested") models (Ganusov et al. 2002; Gilchrist and Sasaki 2002; André et al. 2003; Alizon and van Baalen 2005; Gilchrist and Coombs 2006) that link WHD to an epidemiological framework (the "environment" of the host).

Embedded models constitute a promising perspective for simple models of WHD. In "Different Types of Within-Host Models," we showed some of the applications of embedded models, particularly the idea that they allow one to vary a within-host parameter and study the consequences on epidemiological parameters (Ganusov and Antia 2003; Alizon and van Baalen 2005; Heffernan and Keeling 2008). However, there are other question that have not been addressed or that deserve further investigation.

The framework of embedded models is essential for understanding the evolutionary consequences of multiple infections. Multiple infection will modify selective pressure on parasites because it engenders a conflict between parasites at different levels; that is, at the host level, a definite level of virulence is optimal, but competition among strains favors increased virulence (Nowak and May 1994; van Baalen and Sabelis 1995*a*). However, the models on which these conclusions are based are characterized by quite severe simplifying assumptions. In particular, within-host competitive processes are assumed to be instantaneous with respect to epidemiological timescales. In reality, within-host competition between different strains of parasites is likely to occur at timescales comparable to those of the epidemiology; for instance, the replacement of one strain by another may be a slow process that lasts a host's lifetime. A better understanding therefore requires explicit modeling of both within- and between-host dynamics and thus necessitates an embedded approach.

Embedded models will also be useful for improving our understanding of the evolutionary consequences of cooperation among parasites. Recently, it has been suggested that parasites often need to cooperate to successfully exploit their hosts (Brown et al. 2002; André and Godelle 2005). However, existing models (and experimental approaches) are restricted to within-host levels (Brown et al. 2002). Modeling the dynamics at these two levels explicitly can help to better understand virulence evolution (Coombs et al. 2007; Alizon and van Baalen 2008*b*; Boldin and Diekmann 2008).

The study of the evolution of the immune system should also benefit from the use of embedded models. As we discussed above, immunopathology is a constitutive aspect of the immune system, yet few studies take it into account (Graham et al. 2005; Day et al. 2007). A possible means for studying the origin and evolution of the immune system would be to consider this defense mechanism as a "dangerous liaison" (van Baalen and Jansen 2001) between the individual and its immune system. In the absence of parasites, the immune system has a cost for the host (i.e., maintenance, risk of immunopathology) and thus behaves as a parasite itself. When the host is infected, the immune system will eliminate the disease and can then be classified as mutualistic. Of course, other ecological factors may affect the outcome of this interaction (e.g., the fact that some parasites may provoke an autoimmune response). Using embedded models may help to develop the necessary integrative approach.

Finally, the most appealing application of embedded models has to do with the study of the consequences of antiparasite treatments. Treatments (vaccines, antibiotic treatments) can be considered as an external part of the immune system (Medley 1996; van Baalen 2002). With this approach, theoretical studies show that antipathogen therapies, in addition to selecting for resistance, might even select for higher levels of parasite virulence (Gandon et al. 2001; van Baalen 2002; Bell and Gouyon 2003; Alizon and van Baalen 2005). Embedded models with host vaccination (André and Gandon 2006; Ganusov and Antia 2006) are particularly useful because they take into account the fact that all the epidemiological parameters (virulence, transmission, and clearance) are linked through within-host processes. Thus, a treatment that affects clearance can have unexpected effects on virulence. In a way, this was understood long ago: in ancient Greek, *pharmakon* (*φαρμάκον*) meant "treatment" as well as "poison."

Conclusion

Simple models of WHD can be very useful for studying parasite evolution. Embedded models have led to interesting insights in evolutionary epidemiology, and we argue that a future use of these models could be to understand the outcome of an infection. Another promising area of modeling concerns parasite within-host evolution. This has already raised some interest for rapidly mutating viruses, but studies have focused more on the changes in viral diversity per se rather than in the evolution of viral quantitative traits, such as replication rate (but see Gilchrist et al. 2004; Iwasa et al. 2005; Ball et al. 2007). These models could offer the opportunity to test different simple immune response functions against experimental data because the evolution of the virus is easier to follow than the precise dynamics of the immune response.

More generally, one of the main challenges for models of WHD is to incorporate experimental data. There has been some success in this area in the case of HIV (Perelson 2002), and a recent approach introduces the notion of maximum likelihood in model selection to find the most parsimonious model to explain malaria dynamics within a mouse (Mideo et al. 2008). However, all these models are based on resource exploitation, and there is no immune response. Finding a way to combine simplicity in the modeling of the immune response and interpretation of experimental data is still an open question.

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