

PARASITES AT CENTER STAGE<sup>1,2</sup>J. J. BULL<sup>3</sup> AND DIETER EBERT<sup>4</sup><sup>3</sup>*Section of Integrative Biology, University of Texas, Austin, Texas 78712**E-mail: bull@bull.biosci.utexas.edu*<sup>4</sup>*Ecologie et évolution, Département de biologie, Université de Fribourg, Chemin du Musée 10, CH-1700 Fribourg, Switzerland**E-mail: dieter.ebert@unifr.ch*

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Parasites provide some of the best fodder for evolutionary biologists today. Many parasites have such short generation times that they evolve in real time, allowing direct observation of their adaptations. Large parts of their genomes are easily accessed with molecular methods. And for parasites of humans or pests of agriculture, there is the added bonus of social relevance and the consequent possibility that lots of data are already available and more will be forthcoming. For example, the vast majority of organisms fully sequenced are pathogens. These features have inspired many evolutionary biologists with classical roots to shift or expand careers into the evolutionary biology of parasites, and to encourage their students to work in this area as well. The two books reviewed here contribute to the expanding exploration of parasite evolution. As a pair, they illustrate how rich and broad this landscape is because virtually no overlap exists between them. The book written by Steven Frank addresses the molecular details of pathogen (mostly viral) evolution with its arms race against the vertebrate immune system. The book edited by Dieckmann et al. is a collection of topics loosely connected by the concept of virulence management, spanning from population dynamics and epidemiology to evolution.

*Immunology and Viral Evolution*

Steve Frank is well known as an original theoretician whose papers blend mathematical models with conceptual insights. On the surface, his book divorces this past, as there are essentially no equations or formulae in the book. The first third of the book streamlines a description of properties of the vertebrate immune system, limited to the elements needed to understand what follows in the remainder of the book. Virtually no prior knowledge of the immune system is required to understand these chapters. This part of the book may seem a distraction to the uninitiated, but the effort to follow it is well worth it. The book then dives into a marvellous overview of a few carefully chosen suites of studies on particular viruses, and this overview literally opens a vista into the intricacies of viruses interacting with the immune

system. Special attention is given to foot and mouth virus and influenza, but HIV-1 gets a fair bit of coverage as well.

One attraction of Frank's book is that he picked one area of host-parasite interactions and went into great depth, explaining many biological details of the intriguing way our immune system functions. It becomes quickly clear that one model does not fit all cases. Instead, we need to keep track of the various components of the immune response and acknowledge its complexity and understand the interactions. On the surface, the message here is one of detail. However, the real message is not that the world is complicated, but rather that we are on the verge of reducing the complexity.

A basic understanding of the immune system, as provided in the first few chapters, is needed to navigate the complexity. The immune response has both a chain-like character with various rows of defense one after another, as well as a web-like structure in which information flows through various channels to produce a complex response against pathogens, sometimes with different weapons being launched in parallel. As is well known, there are two arms of the immune system: antibodies and the B-cell response, and the T-cell response, which involves the Major Histocompatibility Complex (MHC) presentation of antigens. Frank's introduction to immunology points out that, especially with respect to the T-cell response, there is a specific sequence of steps in the processing of foreign antigens. With this view of the immune system, the examples in following chapters point out the following: (1) how variation in the human genome (e.g., especially the MHC) can lead different people to respond differently to the same infecting virus, and (2) how viral escape mutations have specific phenotypic effects at one or another step in this sequence of immune system processing. Thus, by understanding the details, we can actually map fitness onto phenotype and onto genotype in viral evolution. All of this relates to one of the biggest questions in host-parasite evolution: What is the role of host and parasite genetic diversity?

One surprise is that Frank does not start from an evolutionary perspective, but rather explains all of this from a mechanistic perspective, placing function in the foreground. In the next step, he tries to understand the function with the eyes of an evolutionary biologist. Each chapter ends with a list of problems that Frank thinks is interesting and worthy of investigation and that also brings the evolutionary perspective clearly into focus. This approach is both refreshing and effective.

The synthesis provided does much to illustrate that genetic details are essential to understanding many aspects of viral

<sup>1</sup> *Immunology and Evolution of Infectious Disease*. Steven A. Frank. 2002. Princeton Univ. Press, Princeton, New Jersey. 348 pp. HB \$75.00, ISBN 0-691-09594-9; PB \$24.95, ISBN 0-691-09595-7.

<sup>2</sup> *Adaptive Dynamics of Infectious Diseases: In pursuit of virulence management*. U. Dieckmann, J.A.J. Metz, M.W. Sabelis, and K. Sigmund, eds. 2002. Cambridge Univ. Press, Cambridge, United Kingdom. 523 pp. HB \$75.00, ISBN 0-521-78165-5.

evolution as they pertain to the immune system. This book is like a set of blueprints that we view for the first time, and which can thus be used to pose new and more general questions about the overall workings of a system. With this understanding, we can begin to ask questions at other levels, such as, what generalities will be found, if viral evolution truly depends on the details of protease cleavage, on MHC binding, and T-cell recognition?; and what prevents ALL viruses from evolving escape from our immune system (e.g., influenza continues evolving so that vaccines need to be updated often, whereas measles and polio viruses have not evolved new antigenic profiles)?

This book should be read by anyone interested in the evolution of infectious disease, as well as by those interested in molecular evolution or in experimental evolution. It is well suited for a semester graduate course in evolutionary biology, with relevance to public health and population biology. The review of the immune system will be unnecessary for many, but there are likely few evolutionary biologists who already appreciate the synthesis that follows. It is refreshing that an accomplished researcher chose to go outside the realm of his previous work, and to synthesize and elevate the work of others. It may be for this reason that the book has such a good balance it will appeal so broadly.

#### *Adaptive Dynamics and Virulence Management*

The book edited by Dieckmann et al. is a collection of chapters by different authors on many aspects of infectious diseases. One theme throughout the book is that humans can affect pathogen evolution intentionally or unintentionally by how they alter pathogen transmission—the concept of “management” refers to the use of intentionally channelling parasite evolution to our benefit. The management issues includes virulence management, drug- and vaccine-resistance management, and how the use of vaccines may alter the composition of circulating strains. The question is worthy: how can we alter the course of infectious disease evolution through our practices that affect the transmission and other fitness consequences for the parasite? The question remaining is how much we can actually accomplish.

The field of host-parasite evolution is dichotomous in its distribution of empirical and theoretical approaches. For within-host processes of host-parasite interactions, we have many data, mainly about the molecular and mechanistic aspects of the vertebrate immune system (as Frank's book shows) to go along with a rather poor quantitative understanding of them. In contrast, at the level of between-host processes (epidemiology), we have substantial mathematical insights, but relatively few data to support those models. A deep-rooted tradition in epidemiology focuses on quantitative aspects of diseases, especially the mode and rate of transmission and the abundance of susceptible, infected, and resistant hosts. Most of our current understanding of epidemiology and of the evolution of infectious diseases is due to these mathematical analyses.

What the epidemiological models have told us, and this is apparent in many places throughout the Dieckmann et al. book (as well as the Frank book), is that a thorough quantitative understanding of the way hosts and parasite populations in-

teract is essential for predicting epidemics and the evolution of infectious diseases—intuition often fails. A simple illustration is the increase in polio virulence during the early 1900s, as improved hygiene led to a reduced incidence of infection. (By standard evolution of virulence arguments, virulence should have evolved to lower levels under these conditions.) This unintuitive increase in virulence is explained by the fact that improved hygiene reduced the spread of the virus (lowered  $R_0$ ) and led to an increase in the average age of infection. Polio is more virulent when infecting older people, as compared to infants, and the different levels of virulence have nothing to do with evolution. This relationship cannot be understood with a knowledge of individual infections only, rather population studies are needed. This example is typical of several cases regarding the evolution of infectious diseases. Understanding the evolution of virulence hinges critically on a thorough understanding of population processes.

The basic formulation of epidemiological models has come from simple observations, but apart from a few classical studies, epidemiology has largely lacked a footing in experimental hypothesis testing. The reason for this omission may be that ethical reasons preclude the experimental study of human diseases, yet the paucity is nonetheless puzzling because there is a plethora of nonhuman model parasite systems that could be used for experimentation. Furthermore, epidemiology is a field in which generalizations across systems are widely accepted (which is the best justification for investment into a model system) because of the belief that transmission is key and that patterns of modes and rates of transmission can be compared across taxa.

This aloofness from experimental systems is diminishing today, and some of the leading researchers are heavily entrenched in empiricism mixed with modeling. But it remains true that the field has a large excess of mathematical models. Thus, one rarely encounters a level of empirical detail in the Dieckmann et al. book even approaching that in the Frank book. Instead, much of this book lies within the vein of current infectious disease epidemiology and evolution, with an emphasis on mathematical models. A lack of empirical foundation is certainly excusable for approaches that attempt to capture only the most elementary (and general) dynamical aspects of a system. However, current generations of mathematical models reach a frightening level of complexity, building on a few, often poorly supported key assumptions. A good example is the prominence of the trade-off model for the evolution of virulence. It is based on the idea that killing the host is bad for the parasite, but this cost is offset by the benefit of increased transmission rates while the host remains alive. This trade-off model underlies many models found in different chapters of the Dieckmann et al. book, and is otherwise widely accepted in the evolution of infectious disease literature. Yet, its generality and the applications to which it is being applied are far from demonstrated and are even suspect (Ebert and Bull 2003).

By virtue of being an edited book, the chapters cover a range of topics, but also span a range of quality and novelty. As a general book on the evolution (adaptation) of infectious diseases, we think it incorporates too little biology, but some chapters do indeed bring both biology and evolution together

in a fine manner. In addition, we do think this is a good book for a mathematical and technical perspective, as these aspects are well explained in many chapters. As is to be expected in an edited volume, many sections are not new, but rather reiterate previously published work. Typical for the entire field, and clearly noticeable in this book, is the dominance of a few overworked examples, such as the evolution of myxoma virus and its rabbit host. However, you will definitely find good chapters with new and interesting material and synthesis. Our personal preference is for those chapters on specific aspects of infectious disease, such as the MHC, strain population structure, sexual selection, apoptosis, antibiotic resistance, chestnut blight, Pox mutant of mitochondria, malaria, vaccine escape, and other consequences of vaccine use. Overall, this book should be a useful guide to much of the landscape in the epidemiology and evolution of infectious diseases, but the beginner may have difficulty in sorting out which chapters are most worthy of study.

There is no shortage of exciting research in evolutionary biology today. These books stand out because they address

problems of direct social relevance—infectious disease. There seems to be little disadvantage in choosing to work on these applied problems because, if anything, a higher quality of research is possible with parasites than with other organisms due to parasite abundance and accessibility with molecular techniques. For someone choosing a career path or career change, these books should provide inspiration. For those concerned about jobs and research funding, these books may provide some insight as to why Britain's research community in population and evolutionary biology went heavily into infectious disease over a decade ago, and why the U.S. National Institutes of Health have started funding evolutionary biology and are even proposing to establish a grant review panel for evolutionary studies.

#### LITERATURE CITED

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