Preface

A PLANET OF VIRUSES

Viruses have a nasty reputation as killers, at worst, and annoyances, at best. This reputation is deserved, at least in part. The viruses that cause HIV/AIDS, smallpox, and Ebola virus disease infect human cells, damage cells and tissue, and lead—in many instances—to the death of the infected individual. Other viruses, such as rhinoviruses, also infect human cells but are eventually cleared by the immune system, with only mild to moderate effects—for example, the sniffling, sneezing, and fatigue referred to in ubiquitous commercials for common-cold remedies. These viruses are very much the minority on Earth in one obvious respect: most viruses do not infect humans; rather, they infect all manner of life, from animals, plants, insects, to microbes. For example, even if everyone on Earth had a case of the common cold, the number of cold viruses inside humans would likely be billions of times smaller than the number of viruses circulating in the global oceans! Viruses such as those that cause Ebola may also be the minority in another, more subtle, respect: what viruses "do" is not confined to killing cells or individuals. There are, in fact, "good" viruses, that is, those that help their hosts, as well as many viruses that affect their hosts in a way that may not fit into the simple categories good or bad.

This broad view of viruses is laid out in *Planet of Viruses*, a pithy, highly readable book by Carl Zimmer that illustrates through a series of vignettes the diversity of places and hosts that viruses affect (Zimmer 2012). We, the scientific community interested in environmental viruses, still know far less than we would like about the direct effects of viruses on the living organisms they encounter and, by extension, the indirect effects of viruses on the environment. Scientific studies of the interface between living organisms and the "environment" is what many scientists categorize as *ecology*. In that sense, the present book sets out to explore the ecology of viruses from a quantitative perspective. The central objective is to act as a guide for students and scientists who are interested in the many ways that viruses affect their (indeed, our) environment. There are many ways to facilitate such a goal. In thinking about this book, I turned to others who have set strong precedents in advancing the study of virus-host interactions.

One landmark work is Martin Nowak and Robert May's book, *Virus Dynamics: Mathematical Principles of Immunology and Virology* (Nowak and May 2000). This monograph set out to explain and interpret simple models of the interaction between the human immune system and viruses that compromise it, with a focus on HIV and hepatitis B. *Virus Dynamics* was inspired by collaborations between mathematical biologists—including the authors—and virologists who wanted to characterize and control the postinfection dynamics of viruses inside infected patients. This work was seminal both in its contributions to modeling—inferring mechanisms from data—and in demonstrating that modeling should be considered an essential component of what is considered first-rate virology. This view, although not universally adopted, is no longer heretical nor confined to the obscurity of technical journals. However, I contend that a similar book on environmental viruses would be challenging. HIV and hepatitis B virus have clearly identified negative effects on human health. In both cases, the infection of a human host begins with a single or a highly limited number of viral genotypes. Moreover, an enormous amount of structural, biochemical, and immunological information is available on the relationship between these viruses and the human host. When considering environmental viruses of microbes, we would be hard pressed to decide which environmental virus is archetypal or which virus or viruses should be the subject of a book. The answer is likely to be, many!

And so instead of developing the mathematics involved in modeling each virus, I have, instead, turned for inspiration to the volume *Bacteriophage Ecology*, edited by Stephen Abedon (2008). This book focuses on a type of virus—the bacteriophage—that exclusively infects bacteria. *Bacteriophage* means "bacteria eater"; the word *phage* has its etymological roots in the Greek word *phagos*, "to devour." Of course, bacteriophage (or phage, for short) do not devour their hosts. Bacteriophage, like all viruses, depend on host replication machinery to multiply, a process explained in greater detail in Chapter 1. Bacteriophage ecology might seem like an obscure topic in the academic hinterlands. To the contrary, studies of phage have had major influences on the foundations of molecular biology, were an early and now recurring theme in efforts to develop antibacterial therapeutics, and are now a central theme in emerging studies of the microbial world and its impressive genetic and functional complexity. *Bacteriophage Ecology* anticipates many of these areas, addressing, largely in empirical terms, many of the topics essential to a deeper understanding of the effects of viruses in the environment. However, *Bacteriophage Ecology* also focuses on the interaction of a single or small number of phage genotypes with their hosts, whereas, viruses are diverse at genetic, functional, and taxonomic levels. Even more challenging is the fact that many of the viruses that are important in shaping the environment are not yet culturable. Canonical methods must be adapted specifically to the diversity of the viral world and its relative recalcitrance to traditional culture-based approaches. Moreover, both canonical and new methods must be placed in context—linking models to data whenever possible. This is what I have tried to do here.

ORIGINS OF THIS MONOGRAPH

In early 2003, Hyman Hartman stopped by on one of his regular visits to the graduate student offices of Daniel Rothman's group at MIT. Daniel Rothman, a geophysicist by training and a geobiologist in practice, was my PhD adviser. Hyman is a biochemist with expertise in the origins of life who, for many years, has challenged colleagues with questions, sometimes insisting that they take an entirely new look at a problem. Hyman had heard I was close to finishing my PhD and was considering new directions for my postdoctoral research. I described my plans to study the relationship between the structure of plant vascular networks and their function. His paraphrased reaction: "Forget plants. You need to work on the problem of viruses in the ocean." In the course of our discussion, Hyman insisted that ocean viruses were abundant and diverse. And, importantly, that their abundance and diversity belie laboratory studies and theories suggesting that viruses of microbes could be easily eliminated in culture. I was intrigued, but not quite convinced.

A few months later, just weeks before I graduated, I discovered colleagues at the forefront of ocean virus research working just steps away, in the Parsons Laboratory at MIT. One of them, Matthew Sullivan—then a PhD candidate working under the supervision of Penny Chisholm—agreed to meet for coffee. We chatted about our mutual interests, including the role of theory in biology. Matt gave me a preview of some of the new discoveries coming out of the study of ocean virus ecology, enabled, in part, by advances in technology that could allow scientists to see and characterize a previously hidden world. We agreed to keep in touch, particularly if I ended up focusing on viral ecology. A few months later, in August 2003, Matt, Penny, and John Waterbury published a seminal paper characterizing a suite of novel phage isolates that could infect cyanobacteria that were ubiquitous in the surface ocean (Sullivan et al. 2003). I was behind, that was evident, but so was nearly everyone else. And, more important, this was an area entering a new age of discovery.

Whenever one enters a new field, it takes time to orient oneself. What are the central ideas and outstanding problems? Who are those that founded the field and who are currently pushing it forward? And, crucially, what can I do to make a difference? More than 10 years have elapsed since my conversation with Hyman. I did, in my own way, follow his advice—not to forget plants but to think about the problems of viruses in the ocean. The problem, as it turns out, was not singular. Why are there so many viruses, both in terms of number and in terms of diversity? Whom do viruses infect? How do viruses modify the fate of infected cells? How do viruses and microbes coevolve? How do viruses shape the structure of microbial communities? And, finally, how can theory help deepen our understanding of the ecological role of the viruses of microbes? This book reflects my attempt to shed light on each of these questions, and perhaps even a few more. I have tried to do so by synthesizing field and lab studies of virus-host interactions via the lens of theory and models. Its origins reside in conversations at the end of my PhD program, but its structure and, indeed, its subject require some elaboration. I did not formally begin to write this monograph until I entered my new sabbatical offices at the University of Arizona, in fall 2013, just steps away, once again, from Matt Sullivan.

IDEAS AND TOPICS COVERED

The term *quantitative viral ecology* can and will mean different things to different readers. Here, the focus is on the dynamics at multiple scales that ensue as a result of the interaction between viruses and their *microbial* hosts. There are many excellent books and monographs on the population biology of infectious diseases, of which viral diseases may form one part. In such texts, the hosts are usually human, animal, or plant, which implies different timescales and issues of concern. Here, I have not drawn a firm line in the sand as to what constitutes a microbe—in practice, this book focuses on the viruses of bacteria and, to a lesser extent, those of archaea and microeukaryotes. Nonetheless, it is my hope that the models and concepts herein may prove useful to those working at other scales, or perhaps where virus-microbe interactions take place on the surface of or inside a larger organism, as is the case in animal-associated microbiomes.

This monograph on quantitative viral ecology has seven core chapters, motivated by three major questions: (i) what are viruses of microbes and what do they do to their hosts? (ii) how do interactions of a single host-viral pair affect the number and traits of hosts and virus populations? (iii) what do viruses of microbes do in natural environments, when interactions take place between many viruses and many hosts? Throughout, I have tried to emphasize the ways in which theory and models can provide insights into all these questions and provide a cohesive framework to the study of the ecology of viruses of microorganisms, that is, quantitative viral ecology.

The book begins with an introduction to the fundamentals of virology, albeit from an ecologist's perspective. Chapters 1–2 are therefore highly complementary to the introduction to viral biology found in molecular biology and virology textbooks. Both of these chapters make evident one of the central themes of this book: that viruses differ not only in which hosts they infect but also in the functions—qualitative and quantitative—that they carry out. These preliminary chapters enable the book to function as a stand-alone text for those readers new to the field, either from a biology or modeling perspective. In doing so, I have also tried to synthesize many analyses of viral diversity in the hope of providing new connections and directions for future research on the physical and chemical basis for viral traits.

With this foundation in place, Chapters 3–5 form the theoretical core of the book, results and insights of which are of value in their own right but will prove useful in efforts to characterize complex communities. These chapters introduce core models to address how virus-host interactions affect population dynamics (Chapter 3), evolutionary dynamics (Chapter 4), and coevolutionary dynamics (Chapter 5). These chapters focus on relatively low diversity communities, showing how a combination of physical and mathematical models can provide insights into how viruses shape microbial populations and potentially stimulate diversity. The data relevant here spans more than 70 years—from the earliest days of molecular biology to the origins of the modern study of microbial population biology and, finally, to ongoing studies of eco-evolutionary dynamics of viruses and hosts. In this theoretical core, I have tried to communicate how much there is to learn from studies and models of the interactions of populations of viruses and hosts, often grown from a single isolate.

However, the complexity in the natural world demands new methods and new perspectives. I move in this direction in the final chapters by building upon the results of the theoretical core. In doing so, I chose to focus on the ecological role of viruses in a particular type of environment: marine surface waters. This choice reflects, in part, my involvement in the analysis of ocean virus dynamics. More important, it reflects the fact that many of the seminal findings of viral effects on ecological processes stem from the study of marine viruses. Moreover, the methodology for examining viruses of marine microbes is, for now, better developed than methods for examining viruses of microbes in alternative contexts, for example, in soils, hot springs, or microbiomes.

Chapter 6 begins this final part, by introducing quantitative methods to infer the abundance and diversity of viruses as well as the network of interactions with potential hosts. These methods are then applied to datasets from the oceans, largely from the marine surface. As I will explain, there are likely more than 10^{29} viruses in the marine surface waters—what they do to the global Earth system is a topic of both foundational and practical concern.

Finally, Chapter 7 extends the core models to examine the basis for viral effects in marine surface waters. This complexity includes new types of interactions, like the regeneration of organic matter by viral-induced lysis of hosts, and new trophic complexity, like the effect of predators on the very hosts that viruses infect. These two chapters lead naturally to the conclusion, in Chapter 8, in which I present a perspective on the types of developments, both technical and theoretical, that are forthcoming and the influence they are likely to have in shaping our view of the diversity and functions of environmental viruses. While ocean viruses may provide a model for discovery, they are unlikely to be the only source of surprises and discoveries on the diverse role of viruses in shaping the environment—whether in the oceans or inside us.

As a whole, this monograph includes analysis of models, synthesis of laboratory manipulations of cultured host-virus systems, as well as inferences of viral effects when culturing is not possible. All these necessitate the use of many different kinds of theoretical and modeling approaches. In this sense, I have tried to embrace an approach to be more like the fox who, according to Archilochus, knows many things, and less like a hedgehog who knows one big thing. The benefit of this approach is that there are very few prerequisites to understand the theoretical concepts discussed herein. A reader with physics, mathematics, computer science, or engineering training need not have any background in virology to understand the material. The text does expect familiarity with probability and statistics and some recollection of differential equations—increasingly a part of the standard training in the biological sciences. To the extent that methods begin to stretch beyond a core competency in modeling and analysis, I have included appendixes linked to each chapter that explain methods when they first appear and are used in the text.

A final note before beginning—the working title I had in my mind while writing the book began slightly differently:

an invitation to

Quantitative Viral Ecology

The lowercase preamble captures my intention throughout this book, that is, to draw in readers who may want to engage in this field in a meaningful way, and to accelerate the pace at which theory can be connected to empirical studies of virus-host interactions. This working title also captures an important feature of my perspective on the field, which is that many, if not most, of the important problems are not yet identified, to say nothing of being solved! The study of the viruses of microbes is at its infancy when viewed in an ecological and evolutionary perspective. I view this book as an opening salvo—the beginning of something that will require a mix of theorists and empiricists.