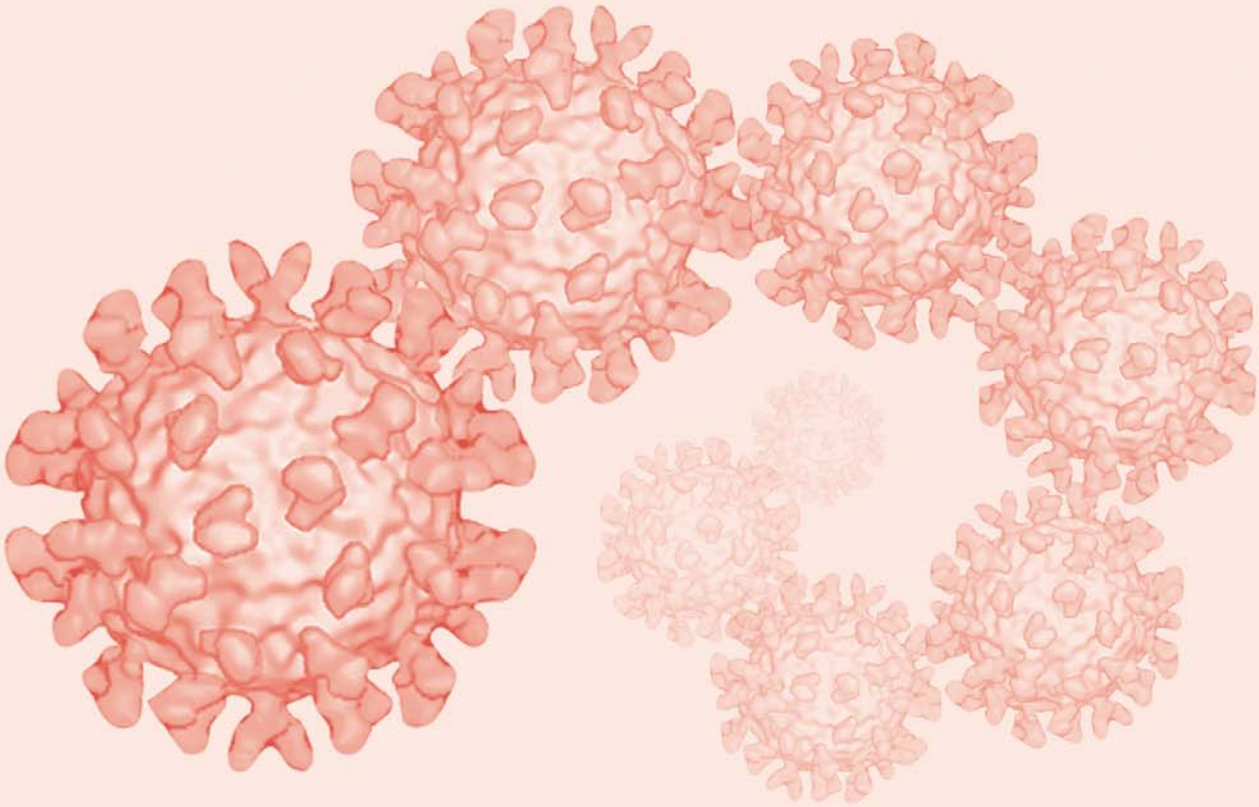
Cambridge Studies in Adaptive Dynamics

Adaptive Dynamics of Infectious Diseases

In Pursuit of Virulence Management



Edited by
U. Dieckmann, J.A.J. Metz, M.W. Sabelis, and K. Sigmund

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List of Boxes

This volume features an integrated series of boxes that systematically introduce the tools needed to analyze virulence evolution and to assess strategies of virulence management. Readers interested in the fundamental concepts and techniques used throughout the book are invited to turn to these boxes. Written in a didactic style, the material listed below also provides convenient points of departure for readers new to the field.

Notational Standards

Few things are as much a distraction as irregular changes of mathematical notation between the individual chapters of a book. While mathematicians have learned to cope with this, such changes pose serious problems for many other readers.

To allow for a better focus on the content of chapters and to highlight their interconnections, we have encouraged all the authors of this volume to adhere to the following notational standards:

S, I, R	Host population sizes or densities of susceptible, infected, and removed individuals
N	Total host population size or density ($N = S + I + R$ or $S + I$)
s, i	Proportion of susceptible and infected hosts ($s = S/N, i = I/N$)
b	Per capita birth rate of hosts
d	Per capita death rate of disease-free hosts
r	Intrinsic growth rate of disease-free hosts ($r = b - d$)
K	Carrying capacity of hosts
B	Population-level rate of host birth or immigration
R_0	Basic reproduction ratio
S_0	Value of S in the absence of infected hosts
N_0	Value of N in the absence of infected hosts
b_0	Value of b at low population density
d_0	Value of d at low population density
r_0	Value of r at low population density
α	Per capita disease-induced death rate of hosts
β	Infection rate constant
γ	Per capita recovery rate of hosts, from infected to removed hosts
θ	Per capita recovery rate of hosts, from infected to susceptible hosts
μ	Per capita removal rate of infected hosts ($\mu = \alpha + d + \gamma + \theta$ or $\alpha + d + \gamma$ or $\alpha + d$)
λ	Force of infection ($\lambda = \beta S$)
U	Population density of uninfected vectors
V	Population density of infected vectors
Z	Total population density of vectors ($Z = U + V$)
v	Proportion of infected vectors ($v = V/Z$)
χ	Per capita bite rate of vectors
F	Population-level rate of vector birth or immigration

f	Fitness in continuous time ($f = 0$ is neutral)
w	Fitness in discrete time ($w = 1$ is neutral)
t	Time
τ	Delay time
T	Duration of time period
a	Age
p	Probability (subscripted if necessary)
c	Cost-related constant
c_0, c_1, c_2	Arbitrary constants
$\cdot_{\text{res}}$	Trait value of resident individuals
$\cdot_{\text{mut}}$	Trait value of mutant individuals
$\cdot'$	Derivative
$\bar{\cdot}$	Average
$\cdot^*$	Equilibrium value

1

Introduction

Karl Sigmund, Maurice W. Sabelis, Ulf Dieckmann, and Johan A.J. Metz

Toward the end of the 1960s, by dint of science and collective efforts, humankind had managed to eradicate smallpox and to land on the moon. Accordingly, some of the best-informed experts felt that the time had come to close the book on infectious diseases, and that the colonization of interplanetary space was about to begin. Today, these predictions seem as quaint as the notion – also quite widespread at the time – that the Age of Aquarius was about to begin.

The subsequent decades have taught us to be less sanguine about the future. In 2001 we do not send out manned spacecraft to meet with extraterrestrials, but instead are shutting down obsolete space accommodation. And far from closing the book on infectious diseases, we find that books on infectious diseases still have to be written. Few experts believe, nowadays, that we are witnessing the beginning of the end of our age-old battle against germs. In 1999, for instance, the World Health Organization (WHO) launched an ambitious program, "Roll Back Malaria" – a battle cry that seems tellingly defensive. In the 1960s, optimists still entertained hopes that malaria could be wiped out altogether. And why not? It had worked for smallpox, after all.

Aside from the disappointments with malaria and other infectious diseases – alarming outbreaks of cholera or foot-and-mouth epidemics, for instance – we had to learn to come to terms with other baffling setbacks. New scourges such as acquired immunodeficiency syndrome (AIDS, which is killing humans by the millions), the prions pandemonium, or the humiliating effectiveness of bacteria in their arms races against pharmaceutical companies are but a few examples.

Not that scientific progress has come to a halt: far from it. But it has led us to a point at which we can see, much more clearly than before, a long and bumpy stretch of road extending before us, probably with many twists and turns hidden from view. Cartographers of yore would have inscribed the warning "there be monsters here". In this book we have tried to be a bit more specific, with the help of some of the most expert scouts in the field. However, infectious diseases are among the relatively uncharted realms in evolutionary biology, offering plenty of drama and scope for adventure – witness, for instance, the efforts to reconstruct the genome of the virus responsible for the 1918 Great Influenza Epidemic: monsters be here indeed!

A generation ago, medical doctors and biologists were brought up on what is nowadays called the "conventional wisdom". It holds that pathogens should evolve toward becoming ever more benign to their hosts, since it is selectively

Box 1.1 Notions of virulence

Virulence describes the detrimental effect of parasitic exploitation on the host (just as resistance characterizes the detrimental effect of host defense on the parasite). Virulence therefore arises from processes through which parasites exploit their host to further their own multiplication and transmission. This general definition is respected throughout the present book.

To unravel alternative, more specific notions of virulence, it is useful to distinguish diseases according to how the process of damage to the hosts unfolds:

- *Killing the host*. For relatively harmful diseases, the exploitation of hosts often results in their death. In such cases, a large part of the parasite's tendency to inflict harm can usually be summarized in terms of the parasite-induced additional mortality rate of the hosts. Many chapters in this book focus on this case and therefore equate virulence with parasite-induced mortality.
- *Impairing other life-history characters*. Other negative consequences of parasite exploitation gain in relative importance if infection only rarely leads to death. Such alternative detrimental impacts of the parasites – ranging from a decrease in host fecundity through a change in its competitive abilities to a mere plunge in its mobility or well-being – are important aspects of parasite virulence in their own right and can impact on its evolution. While changes in mortality and fecundity affect host fitness directly, to understand the contributions of other side-effects of host exploitation to both parasite and host fitness may require an in-depth consideration of relatively subtle mechanisms.
- *Gaining entrance*. Especially in the plant world, the potential of a pathogen to inflict damage often strongly depends on whether or not there is a match between resistance genes in the host and genes in the parasite to overcome that resistance. Often little variation is found in the damage inflicted on hosts by different parasite strains once they have gained entrance to the host. The relative capacity of parasites to enter the host then becomes the key determinant of any detrimental effects. Plant pathologists thus tend to use the term virulence to refer to those capacities. In this book, the term "matching virulence" is used for this; in contrast to this, and when the need arises, the term "aggressive virulence" is used for the detrimental effects of the parasite's exploitation strategy.
- *Local spreading*. When hosts are structured into local populations, the harm that pathogens can bring to these depends on their transmission within the local populations – which, in turn, depends both on the local transmission rate and on the damage inflicted on individual hosts. "Virulent" parasites may then be defined as those that quickly and relentlessly spread throughout a local population. Such a use of the word virulence correlates it with traits that affect the transmissibility of the pathogen.

In an agricultural setting, these last two aspects of virulence tend to be present together (with a farm's crop as the local population), which explains the different terminological tradition in the phytopathological literature compared to, for example, the medical literature. While the last three aspects of virulence listed above may all be attractive for defining virulence for particular systems, the goal of conceptual clarity compelled us, throughout the book, to use them only with further qualification.

advantageous for parasites to have efficient vehicles at hand for their transmission. Thus, the virulence of a pathogen (Box 1.1) was envisaged as an adaptive trait: all pathogens would eventually become avirulent if given enough time to evolve. This Panglossian view has not always been that conventional: indeed, it helped, in its day, to spread the idea that virulence is subject to evolution, very rapid evolution, in fact – and this was quite a revolutionary insight at one time. Of course, it was but a first step. Evolutionary biologists have since learned that constraints within the relationship between transmissibility and virulence can seriously upset the trend toward harmlessness (Box 1.2), and that competition between several strains of a pathogen within one host demand an altogether more complex analysis than the former optimization arguments offered. These insights have prompted the idea that it may be feasible to interfere with or even redirect the evolution of virulence to achieve some desired practical goals – such as low virulence in the parasites of crops, cattle, or humans, and high virulence in the parasites that control weeds and pests. This Darwinian approach gave rise to a new research program on virulence management (Box 1.3) and provides the basis for this book.

Many of the arguments on the adaptive dynamics of virulence have become so involved that they are easier to analyze mathematically rather than verbally. We have nevertheless tried in this book to keep the mathematical techniques down to earth, and to display the modeling techniques in "stand-alone" boxes which, in combination, offer a concise and coherent introduction to the theoretical approaches used in the book (see the overview on page xvi).

Our emphasis is on the connection of this theory with empirical data and experimental set-ups. It turns out, in fact, that the data prove quite hard to interpret without a clear understanding of the actual meaning of basic notions such as virulence and fitness. To a first approximation, fitness is reproductive success and virulence is the additional mortality caused by the pathogen (see Box 1.1). However, in many instances, such as for populations that are not well mixed but distributed in clumps, this first approximation is not adequate. Case studies from infectious diseases in humans, chestnut blight, senescence in fungi, rinderpest, and, of course, the celebrated myxoma virus in rabbits, all show how difficult it is to disentangle rival concepts and to assess different modeling approaches.

Like all good Darwinians, we look toward theory to guide us through the plethora of facts. So in this book the initial chapters set the stage by discussing the impact of alternative transmission modes and ecological feedbacks on the evolution of virulence (Part A). We then proceed systematically to analyze, first, the implications of host population structure for the evolution of virulence (Part B), second, the competition of pathogens within a host (Part C), and, finally, pathogen–host coevolution (Part D) and multilevel selection (Part E). We firmly believe that only when armed with these tools is there a reasonable chance of understanding the long-term effects of vaccines and drugs (Part F) and of successfully addressing the options and problems of virulence management (Part G).

Box 1.2 A simple example of virulence evolution and management

Here we illustrate how evolutionary theory can be used to suggest measures that will help manage the virulence of a pathogen. We start with some conventional assumptions about the disease under consideration.

Single-species assumptions

- Pathogens only survive in living hosts.
- Pathogens can enter disease-free hosts only through contact between these and infected hosts.
- Once in a host, pathogens multiply rapidly, so that the first infection determines the final impact.
- Within the hosts, pathogens compete only with their own offspring.
- The per-host disease-free death rate is constant.

Interaction assumptions

- The rate at which susceptible hosts become infected is proportional to the product of the density of infected and that of susceptible hosts (law of mass action). The proportionality constant, termed per-host disease transmission rate, increases with pathogen replication.
- Pathogen replication occurs at the expense of the host's resources, and this damage to the host, termed virulence, increases the per-host disease-induced death rate.
- The trade-off between the per-host transmission rate and the per-host disease-induced death rate conforms to a law of diminishing returns.

For pathogens to transmit they require living hosts, so pathogen fitness depends on the average survival time of the hosts. Thus too high a virulence is not expected to pay off. As a representative measure of pathogen fitness, we use the number of new infections produced per host over the period it survives and is infectious, known as the pathogen's basic reproduction ratio R_0 (see Box 2.2). As shown in Box 9.1, the pathogen strain with highest R_0 outcompetes all others.

The disease-induced death rate that maximizes R_0 can be found graphically, the rationale for which is given in Box 5.1. In the figure at the end of this box, the fixed disease-free death rate is plotted to the left of the origin, while the evolutionarily variable disease-induced death rate, or virulence, is plotted to the right. The thick trade-off curve describes the effect of virulence on the disease transmission rate. Figure (a) shows how, by drawing a tangent line from the point on the left to the trade-off curve on the right, the optimal level of virulence is found just below the tangent point. In this simple example, pathogens are therefore expected to evolve toward intermediate levels of virulence.

continued

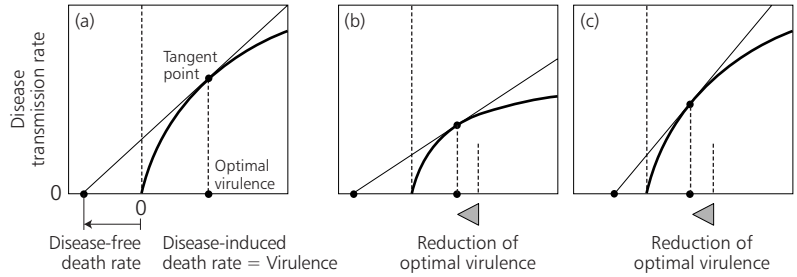
Box 1.2 *continued*

This graphic construction immediately suggests two possible routes to managing virulence:

- Either we change the trade-off curve such that the tangent point shifts to the left, Figure (b);
- Or we decrease the disease-free host death rate and keep the trade-off curve in place, Figure (c).

Both options are expected to result in the evolution of reduced virulence levels. Moreover, the second option generates the interesting hypothesis that investment in host health – so as to promote the life span of the hosts *in the absence of the disease* – creates an environment in which pathogens evolve to become more benign.

Of course the model as discussed above is overly simplistic. The remainder of this book investigates the various intricacies that should be considered to capture a wider range of circumstances.



Whenever public health officials, veterinary epidemiologists, advisory plant pathologists, conservation biologists, or biocontrol workers want to devise strategies to manage the course of infectious diseases, they must bear in mind that they are merely adding one level of strategic action on top of other, age-old layers of strategic interactions. These have been devised through the programming by natural selection of both the pathogens and hosts – organisms that differ widely in scale, generation time, and life history, and that use individual variability and polymorphisms to fuel their arms races. If public health decisions are not based on a sound knowledge of these underlying tugs of war, they risk being counterproductive. Many human interferences, far from managing disease, have helped disease to manage us.

No doubt the next generations will know vastly more than we do now, but we hope that this book will offer no reason for them to deem us naively oversimplistic, as the 1960s appear to us now. To take Einstein's dictum to heart, we and all the contributors to this book have tried to present matters as simply as possible, but not simpler, and have endeavored to approach the complexity of our subject with the appropriate respect.

Box 1.3 A research program on virulence management

As a backbone for further research efforts, we outline a systematic sequence of steps to test hypotheses about virulence evolution and to probe options for virulence management:

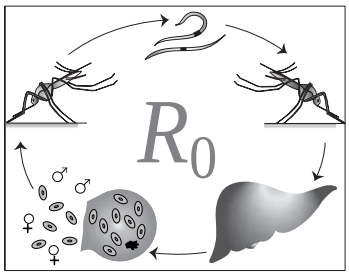
1. Specify how the hosts are affected by the parasite's exploitation (effects of virulence).
2. Assess which of these effects influences parasite transmission (identification of trade-offs).
3. Spell out the ecological setting (e.g., which of the participants interact with each other, and how mixing takes place). Derive suitable representative measures for fitness given the ecological setting (e.g., R_0).
4. Analyze the adaptive dynamics of the ecological and evolutionary feedback processes.
5. Extract model predictions on how selection affects virulence and, in particular, how controllable epidemiologic parameters can be changed to select for reduced virulence.
6. Test these predictions theoretically (e.g., robustness of the model) and empirically.
7. Search for alternative explanations (e.g., multiple instead of single infection) and, if necessary, carry out tests to distinguish between the alternative mechanisms.

The chapters in the book follow this agenda and describe results for particular ecological settings. Given the diversity of relevant scenarios and the empirical uncertainty regarding some of their key components, it is evident that much research remains to be done in pursuit of this program.

Acknowledgments Development of this book took place at the International Institute of Applied Systems Analysis (IIASA), Laxenburg, Austria, where IIASA's former director Gordon J. MacDonald and current director Arne Jernelöv have provided critical support. To achieve as much continuity across the subject areas as possible we organized two workshops in which the authors were brought together to discuss their contributions. The success of a book of this kind depends very much on the cooperation of the authors in dealing with the many points the editors are bound to raise, and we thank our authors for their patience. The book has benefited greatly from the support of the Publications Department at IIASA; we are especially grateful to Anka James, Martina Jöstl, Eryl Maedel, John Ormiston, and Lieselotte Roggenland for the work they have put into preparing the manuscript. Any mistakes that remain are our responsibility.

Part A

Setting the Stage



Introduction to Part A

Investigating options for virulence management is a multidisciplinary endeavor. To identify the most promising avenues, contributions from epidemiology, ecology, microbiology, genetics, and theoretical biology have to be integrated into a common perspective. That goal is an inspiration and challenge for this book as a whole.

Before diving into this complexity, some readers might appreciate a gentle start. Part A therefore introduces the essential ideas and concepts in this book and addresses the following questions:

- Is it realistic to expect measures of virulence management to succeed in practice?
- What are the epidemiological and ecological complexities that virulence management strategies ultimately may have to deal with?
- Which methods are suitable for assessing outcomes of virulence evolution and for predicting consequences of managerial interference?
- Which problems and dilemmas are bound to arise in the context of virulence management efforts?

Chapter 2 provides first suggestions of management options that can successfully influence the virulence of pathogens. Ewald and De Leo emphasize the critical importance of the mode of pathogen transmission for virulence evolution. They propose that, if pathogens can be transmitted from host to host along several routes, public health managers should be concerned primarily with those routes that are least dependent on the host's health. Taking waterborne transmission as an example, a model of diarrheal disease is presented. Maximization of the basic reproduction ratio shows that, when waterborne transmission prevails, evolutionarily stable levels of virulence tend to be high. Narrowing this transmission channel will therefore often select for less virulent pathogens.

Whereas Chapter 2 offers an optimistic view on the feasibility of virulence management for systems in which interventions are relatively easy and data are available, Chapter 3 concentrates on the opposite end of the scale. In their review of wildlife diseases, De Leo, Dobson, and Goodman flag some of the problems that arise from the distinction between micro- and macroparasites, from genetic diversity, and from coevolution. They make the important point that much of theory on the evolution of virulence has been developed for microparasites, even though macroparasites can have a major impact on host dynamics and community structure. The authors also stress that both micro- and macroparasites exert strong selection pressures on the host and that frequency-dependent selection plays an important role in the evolution of virulence. Moreover, they highlight that human

populations expand and thereby come into contact with wildlife and their parasites: this creates the danger of parasites jumping over to humans, which in turn may lead to newly emerging diseases.

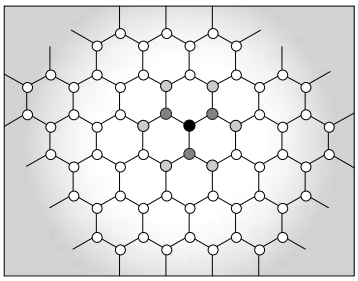
Chapter 4 explains why the traditional approach of predicting evolutionary outcomes by maximizing the basic reproduction ratio of a disease is not always appropriate. Since pathogens tend to affect their host environment in radical ways, selection pressures usually depend on the types of pathogens and hosts that are established in an infected population. In this chapter, Dieckmann outlines the theory of adaptive dynamics as a versatile toolbox for investigating the evolution and coevolution of pathogen–host interactions under conditions of frequency-dependent selection. Examples illustrate how classic methods and the new models presented here result in different predictions about the evolution of infectious diseases.

Decisions on virulence management strategies are fraught with dilemmas, as illustrated by the investigation of a model for the coevolution of virulence and recovery ability in Chapter 5. Van Baalen explains why there can be conflicts of interest between the individual host and the host population as a whole. Since selection tends to favor virulent parasites or those that can overcome host defenses, increased investment in the defense of individual hosts does not necessarily minimize the parasite load for the population as a whole. If more aggressive parasites are favored, hosts play "defense games" against each other, and thereby potentially trigger selection for a further increase of virulence. In the long run, hosts either pay heavily to defend themselves against a rare but extremely virulent parasite or they tolerate the parasite if it stays relatively benign. Human health care managers may thus be confronted with the ethical dilemma of creating either common-but-mild or rare-but-serious diseases.

The four chapters of Part A set the stage for this book by indicating the range of basic issues that have to be considered in the evaluation of strategies of virulence management: transmission routes (direct versus indirect; vertical versus horizontal), distinction between micro- and macroparasites, genetic diversity in host resistance and parasite virulence, frequency-dependent and reciprocal selection, multiplicity of evolutionarily stable virulence levels, and ethical dilemmas in medical epidemiology. Of course, many more aspects must be considered to assess and improve the match between models and epidemiological reality. That is what the remainder of this book is about.

Part B

Host Population Structure



Introduction to Part B

Part B explores the impact of host population structure on the evolution of infectious diseases. While simple models of disease ecology and evolution conveniently ignore this complication, the following three chapters underline its importance. It is shown that host population structure can qualitatively alter expectations for the course and outcome of virulence evolution.

By linking individual-based mechanisms of transmission to the demographic consequences of epidemics in host populations, simple mathematical models offer an essential prerequisite for understanding and influencing the virulence evolution of a disease. Elaborations on such models, accounting for three different types of host heterogeneity, are discussed in this part. First, even in the absence of any spatial structure, a host population may be physiologically structured with respect to certain features of individual hosts. Relevant features could be age and size or could directly relate to epidemiological processes like disease-induced mortality, recovery from an infection, or disease transmission (investigated in Chapter 6). Second, host populations can be viscous in the sense that individual hosts are connected, by spatial proximity or social relations, not to the host population as a whole but to a relatively small number of neighbors. Implications of such connectivity structures are analyzed in Chapter 7. Third, connections between hosts may be organized in a hierarchical way such that infections spread more easily within host groups than between groups. A special case of such a metapopulation structure comprises just two groups of hosts, a large and viable host population (a "source") and a small host population (a "sink") that is prevented from extinction only by the continuous supply of immigrants from the source. As Chapter 8 shows, evolution of virulence or resistance in the sink population can only be understood by considering the impact of the source.

One key implication of host structure may be singled out for special emphasis: such structures often expose virulent pathogens to the detrimental consequences of aggressive host exploitation. Selection in structured host populations can favor pathogens of reduced virulence because those pathogens that exploit their victims excessively may soon run out of susceptible hosts. "Burn-out" phenomena of this sort are much more likely to occur in spatially structured populations; they offer important management opportunities to deliberately select for intermediate levels of virulence.

In Chapter 6, Dwyer, Dushoff, Elkinton, Burand, and Levin improve on basic epidemiological models by taking into account host heterogeneity in susceptibility and host seasonality in reproduction, key features of many insect–pathogen interactions. Their model is calibrated with experimental data on wild-type and genetically modified virus strains that can attack the gypsy moth, a polyphagous forestry pest. To assess the options for the modified virus to act as a biological control agent of the moth, the authors predict the rate of epidemic spread of both viral

types in natural moth populations. They suggest that pathogens that are genetically engineered to have higher virulence may tend to be at a selective disadvantage.

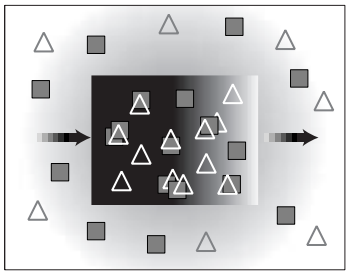
Spatially or socially structured host populations are ubiquitous in nature. Chapter 7 describes how heterogeneity can arise from the local interactions among healthy and infected host individuals. Van Baalen explains why the resulting self-organized patterns of host abundance can lead to levels of pathogen virulence that qualitatively differ from those predicted for spatially unstructured populations. It is shown that increased regularity in the host's social structure selects for diminished virulence and that the same effect results when contacts between hosts become scarce. In general, any management strategy that keeps intact or even strengthens patterns of relatedness among infecting pathogens can be expected to favor the emergence of less virulent strains.

Considering examples of crop and livestock diseases and of hospital infections, Holt and Hochberg illustrate in Chapter 8 that source–sink structures are widespread in epidemiologically important situations. The authors show that virulent pathogens are less likely to conquer a sink habitat if host abundance in the sink is low, mutations have only a small effect, and invasions of benign pathogens (followed by local adaptation toward increased virulence) are rare. Conversely, resistant hosts, having reduced transmission rates for an infection, are more likely to evolve in a sink if host productivity is high, rates of pathogen transmission are low, and infected individuals are short-lived. In both cases, supply of novel genetic material from the source can be both detrimental (by swamping local adaptation) and beneficial (by providing the genetic variation needed to respond to local selection pressures).

Incorporating into a single model all possible aspects of host population structure evidently is impossible. The models considered in this part therefore separately focus on the main different types of host heterogeneity. Investigating interactions between the diverse evolutionary consequences discussed here is a challenge for future research.

Part C

Within-Host Interactions



Introduction to Part C

For a long time, epidemiology essentially dealt with the spread of diseases within a population of susceptible, infected, or recovered hosts. Progress in microbiology and molecular biology has allowed us to study the full life cycle of pathogens: this comprises not only their transmission from one host to the next, but also their population dynamics within individual hosts. It has become clear that within-host interactions between pathogen strains can profoundly influence selection on virulence.

This part therefore concentrates on the ecology and evolution of microparasites within the biosphere presented by a single host. In particular, it focuses on two aspects of utmost importance for understanding the combined effects of mutation and within-host selection. The first aspect is of an ecological nature and relates to competition between different strains for the ecological niche offered by the host. In particular, competitive exclusion among strains can lead to the takeover of the host by the most virulent parasitic strain: this is the case of superinfection. Co-existence of several strains, on the other hand, leads to coinfection. The second aspect of within-host interaction that is crucial for virulence evolution is kin selection; it is based on genetic considerations, in particular on the genetic relatedness of parasites to each other. Very roughly speaking, the two effects pull in opposite directions: competitive exclusion tends to increase the virulence level, whereas kin selection tends to decrease it.

In Chapter 9, Nowak and Sigmund investigate simplified models of multiple infection. The first part of the chapter deals with superinfection: the more virulent strain quickly outcompetes its rivals. The other part deals with coinfection: the rate of new infections produced by one strain is unaffected by the presence of other strains. The two cases differ in expectations for the resultant range of strains within the host population; they are similar in that both predict a considerable increase in virulence. This underscores that mathematical arguments for the evolution of virulence based on optimizing the basic reproduction ratio of the pathogen do not work if several strains of pathogens compete within the host.

Adler and Mosquera Losada in Chapter 10 offer a considerably more detailed picture of multiple-infection processes. These authors investigate the full range of infection patterns possible for two strains of pathogen, ranging from coinfection to superinfection. In particular, they take into consideration the order of infection. Their mathematical analysis highlights some usually neglected subtleties of super- and coinfection processes that depend on the relation between virulence of strains, their ability to infect a susceptible or singly infected host, and their impact on the coexistence patterns of competing strains.

When pathogens replicate inside their hosts, their relatedness tends to be high and kin selection prevails. In Chapter 11, Gandon and Michalakis analyze how the coefficient of pathogen relatedness is influenced by four ecological parameters:

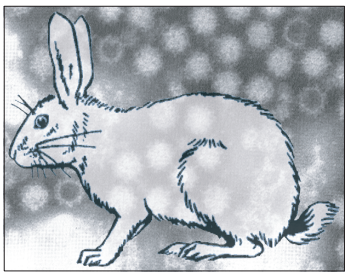
population size, pathogen dispersal rate, cost of dispersal, and transmission mode. On this basis, they investigate how the separate and joint evolution of pathogen virulence and dispersal rate is affected by these parameters. Applying these findings to identify options for virulence management, the authors conclude that in the presence of multiple infections long-term benefits arise from sanitation and vaccination that would otherwise be absent.

In Chapter 12, Read, Mackinnon, Anwar, and Taylor evaluate the relevance of kin-selection models for malaria epidemiology, and critically assess data on the influence of genetic relatedness among parasites on the outcome of the disease. Correlations observed in the field and laboratory experiments support the conclusion that plausible mathematical models may rely on wrong assumptions about the effects of within-host competition on between-host transmission. This strikes a cautionary note and stresses that, at present, the models serve to suggest further experiments.

Resolving the many open questions that surround within-host interactions may be the most important milestone on the road toward consolidating existent models of disease ecology and evolution. Much empirical testing has to be carried out before the current thicket of within-host models that has sprung up in recent years gives way to harvestable cultures – an intermediate slash-and-burn stage seems inevitable.

Part D

Pathogen–Host Coevolution



Introduction to Part D

Virulence is not a property of the parasite, but of the interaction between host and parasite. Accordingly, the evolution of virulence is the result of a coevolutionary process and to understand it we have to account for both sides. As a result of their generation time, which is usually much shorter than that of the host, microparasites seem to be at a huge advantage. However, sexual reproduction allows host organisms to present a moving target (while at the same time inevitably offering opportunities for parasites to use sexual contacts between hosts to infect new susceptibles). In particular, genetic recombination helps to preserve heterozygosity and leads to a wide diversity of immune responses. But there are many other examples of the intricate struggles between parasite and host and of the trade-offs imposed on them.

Part D explores how reciprocal selection between host and parasite populations influences the evolution of host resistance and parasite virulence. Chapters 13 and 14 deal with parasite–host interactions in which investments in resistance and/or virulence incur a cost. The question here is how the resultant trade-offs influence the coevolutionary process. In Chapters 15 to 17 trade-offs play no role. In these, coevolution acts on the ability of the host to recognize the parasite and discriminate it against cells and tissue of its own, while, at the same time, parasites attempt to bypass recognition by the host. In its simplest form this leads to gene-for-gene coevolution. The question posed in these chapters is whether this process can explain the great diversity in resistance and virulence genes observed in parasite–host systems. Chapter 18 focuses on the role of sexual selection for parasite-free or parasite-resistant mates and its consequences for the health of the offspring. The final chapter of Part D, Chapter 19, is devoted to phylogenetic techniques that help to glean coevolutionary trends from historical reconstructions of species-branching patterns.

In Chapter 13, Krakauer models the coevolution of pathogens and host cells to identify the conditions under which we should expect apoptosis, that is, programmed cell death, to be induced by the host, the virus, or by both. Apoptosis is commonly thought of as a host strategy to create "scorched earth" around a virus-infected cell, thereby hampering progress of the disease. The obvious response of the virus is to inhibit apoptosis and to shift an infection to a more persistent latent form while gaining net productivity. Some viruses, however, can even stimulate apoptosis to promote virus extrusion to surrounding cells. These intricate trade-off mechanisms suggest various routes for intervention to protect the host.

In Chapter 14, Hochberg and Holt explore patterns of virulence and resistance in coevolving parasite–host systems along a gradient of habitat suitability. Their model predicts the parasite's virulence and the hosts' resistance to rise with increasing host productivity along the gradient. However, this prediction critically hinges on the assumption that cost functions of attack and defense do not depend

on the habitat. If this does not hold, as can easily be the case because of some inherent trade-off, the trend can even be reversed. Model predictions are thus extremely sensitive to the underlying assumptions. Hochberg and Holt discuss the consequences of their findings for selecting suitable natural enemies for biological pest control.

In Chapter 15, Beltman, Borghans, and de Boer critically assess the common belief that heterozygote advantage is sufficient to explain the widespread polymorphism in molecules of the major histocompatibility complex (MHC). They show that the evolutionary response of the pathogens involves a frequency-dependent selection, which leads to a much higher diversity in MHC molecules than results from selection for host heterozygosity alone. This illustrates that, if defense is subject to genetic constraints, parasite–host coevolution may well contribute to the diversity in host defense and parasite virulence genes. The implication for virulence management is that health in the host population may decrease whenever possibilities for host evolution are limited, as is the case, for instance, in breeding programs for endangered species and in livestock production.

Chapter 16 studies the genetic response of the host population to parasite onslaught. An understanding of this response is crucial to assess the long-term impact of measures of virulence management. Andreasen investigates classic one-locus, two-allele models, both in discrete and in continuous time. Fitness of host genotypes depends on differential susceptibilities and hence on the prevalence of the disease, which in turn depends on the genetic composition of the host population. This relation can be used to assess the consequences of virulence management measures on polymorphic equilibria in the host population, for example, in the context of malaria-induced sickle-cell polymorphism.

In Chapter 17, Sasaki analyzes the coevolution of virulence and resistance in plant–pathogen systems by using a class of mathematical models that incorporate the genetic composition of both the host and the parasite population. This leads to coevolutionary dynamics with a high degree of instability based on complex cycles in genotype frequencies and in genetic polymorphism, which reflects an endless arms race between the interacting populations. A consequence of potential relevance to virulence management is that the analysis allows an estimation of the number of resistant host varieties necessary to protect a host population from disease.

Gene-for-gene interactions may play an important role in the evolution of sexual reproduction. This is highlighted by the Red Queen hypothesis, which emphasizes that there is a continual arms race between parasite and host. In particular, hosts (and parasites too) can benefit from outbreeding because the mere random recombination of host genes already acts to forestall the optimal adaptation of parasites to their host. In Chapter 18, Wedekind explains how sexual selection may play a role in parasite–host arms races. Sexual selection in the host population can act in two ways – on the one hand through uniform preferences for healthy and vigorous mates, and on the other hand through active preferences for complementary genes, especially for loci of the MHC (a crucial component of host–parasite interactions).

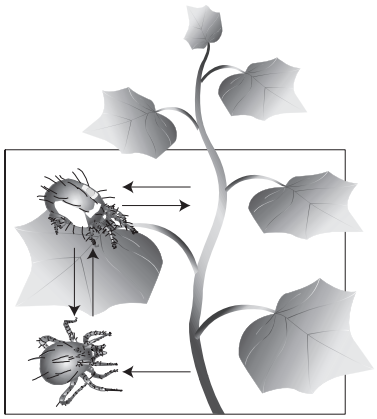
Such sexual preferences for dissimilar types have been observed in mites, mice, and man. Since free natural mate choice may well be important for the health of host populations, Wedekind points out the dangers of assisted reproductive technology in humans and breeding programs for endangered species; in both cases, possibilities for mate choice are limited.

The models for the evolution of diseases presented in this book eventually have to be gauged against field data. These data can be observations of genetic changes in response to various selection pressures, but also historical reconstructions of the origin of various diseases, as well as comparative data. To assess the effect of different selective environments the latter have to be considered against the background of historical relatedness. In Chapter 19, Rannala presents techniques to reconstruct phylogenetic trees and applies these to a number of case studies to demonstrate the insights that phylogenetic analyses provide in virulence evolution.

Arms races between hosts and parasites offer some of the most dramatic and intriguing examples of coevolutionary dynamics. They not only add excitement to theoretical modeling, but also lead to testable predictions and, indeed, suggest promising opportunities for virulence management.

Part E

Multilevel Selection



Introduction to Part E

The implications of multilevel selection for virulence evolution deserve closer attention, especially where selection leads to conflicts of interest between organisms at different organizational levels. In pathogen–host interactions this conflict is self-evident, but in numerous cases parasites have evolved to act as commensalists or even as mutualists. The latter case, however, does not imply that interests exactly match.

In Chapter 20, Hoekstra and Debets consider mutants of mitochondria that slow down the growth of their host, a bread mold fungus. In spite of this apparent disadvantage, these mutants outcompete normal mitochondria in crosses between fungi that contain wild-type and mutant mitochondria. If such crosses occur frequently enough in nature, the resultant intragenomic conflict may lead to the interesting phenomenon that, through the lower-level selection process, fungal hosts with relatively slow growth can increase in frequency in the population. Similar processes can occur via mitochondrial plasmids that cause senescence, a phenomenon normally absent in fungi. The persistence of these obviously harmful plasmids is striking in some genera of fungi; the key to understanding this observation is probably the existence of horizontal transmission by anastomosis between different fungal units. Hoekstra and Debets suggest that, once horizontal transfer is open to manipulation, the performance of fungal diseases could be changed through intragenomic conflict.

Chapter 21 describes the evolutionary dynamics of the tritrophic interaction between chestnut trees, a blight fungus, and a double-stranded RNA virus. Whereas the fungus infects the chestnut trees and greatly reduces their growth, the virus infects the fungi and greatly reduces their virulence. The virus is transmitted vertically, but also horizontally by anastomosis between fungi infesting the same tree. So, even though the virus more or less debilitates its host, the infected fungi do not necessarily lose the competition with other fungi within a tree through horizontal transmission. The virus therefore appears to be a potential candidate for the natural biological control of chestnut blight. However, Taylor shows in this chapter that only a careful analysis of the various trade-offs, of the rates of horizontal and vertical transmission, and of feedbacks involved in this system can explain why, despite the presence of the virus, chestnut blight continues to be such a devastating disease in the USA, whereas it is controlled by the virus in Southern Europe.

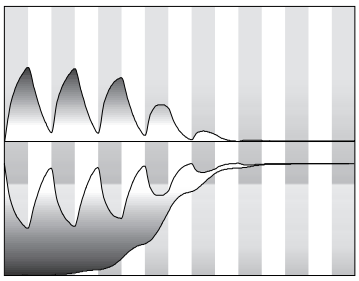
Multilevel selection not only has the potential to generate conflict of interest, but also forms of “conspiracy” may arise. This can happen when organisms are hierarchically organized in more than two trophic levels in a linear food chain: species at different trophic levels can then join forces against those sandwiched between them.

In Chapter 22, Sabelis, Van Baalen, Pels, Egas, and Janssen analyze how plants and predators evolved to conspire against herbivores. Plants invest in attracting, retaining, feeding, and protecting the herbivore's enemies; as this occurs in so many plant species it may help explain why herbivores are predator-controlled, and why, therefore, "the world is green." The authors ask why plant–predator mutualisms are ubiquitous and model the tritrophic interaction as a series of games: defensive allocations among neighboring plants, avoidance of plant defense and predation risk among herbivores, and resource exploitation among herbivores and among predators. They predict low-cost plant defenses when herbivores and predators are sufficiently mobile, and prudent (imprudent) exploitation strategies when single (multiple) strains exploit the same resource: what matters is the degree to which a strain monopolizes exploitation of a resource. The model needs extension to include population dynamics, and the outcome of such a model is not at all self-evident – plant–predator mutualisms therefore do not simply evolve because "it is both in the interest of plants to be rid of the herbivores and in the interest of the predators to find herbivores as prey."

Multilevel selection inevitably plays an important role in molding organismal traits in a way that we would not be able to understand by considering one-level selection only. In this sense multilevel selection poses a challenge to the experimental biologist to identify those biological levels at which relevant selection pressures may operate. Indeed, most organisms may harbor influential "passengers," and one may wonder which organisms are actually passenger-free. Moreover, organisms are part of a food web, so selection within the population of one organism influences that of others in the food web and vice versa. Theoreticians can help to predict phenomena from first principles (i.e., natural selection); when these predictions are not compatible with biological observations, possible causes and alternative mechanisms have to be identified. Multilevel selection is a likely candidate to help achieve this.

Part F

Vaccines and Drugs



Introduction to Part F

Evolutionary virulence management necessarily takes a long-term perspective and concentrates on population-level characteristics. Yet, in practice we also have to interfere with diseases on a short-term basis and, especially in the case of humans, the welfare of individual patients is an additional concern. This establishes the need to evaluate the longer-term effects of short-term protection measures. Only on this basis can we understand which compromises can be made or, even better, whether it is possible to devise practices that allow both satisfactory short-term and long-term disease control.

The main individual-level protection measures are drug treatment and vaccination. Both have consequences for public health by affecting the population dynamics of the disease, though in different manners: the former by shortening the infectious period, the latter by changing the inflow of fresh susceptible hosts. And both tend to have evolutionary consequences in terms of resistance evolution and vaccine escape.

After drug resistance develops, we are basically back at square one in terms of the control effort, since resistant types have at best a very slightly reduced fitness. If the drug-based selective regime is maintained long enough, resistant and nonresistant types even tend to become equally fit in a drug-free environment because of the incorporation of genetic modifiers.

In the case of drug resistance we appear to be rapidly running out of alternative options, whereas the prospects are considerably better for vaccination as, in principle, we can keep adapting the vaccine type. In addition, vaccine-escape mutants tend to have a lower basic reproduction ratio as they do not gain a foothold before implementation of the vaccination scheme.

Chapter 23 discusses the problems that arise from the rapid evolution of antibiotic resistance. Bonhoeffer addresses this issue by means of a mathematical model for the dynamics of infection that tackles the question of how to use existing antibiotics with maximal effect for the treatment of bacterial infections, while simultaneously delaying, and possibly even reversing, the emergence of resistance. Within this framework he assesses the effects of different strategies, like cycling antibiotic therapy, combination therapy, and others. The chapter also comments on how to define optimal treatment policies, and, in this context, how to weigh long-term against short-term benefits.

In Chapter 24 McLean develops a simple model framework to evaluate the effect of vaccination schedules on the emergence of vaccine-escape mutants. The depression of a competitively superior strain by a vaccine that confers little cross-immunity may change the competitive balance, setting off an outbreak of an earlier, competitively inferior strain. An unexpected finding is that such effects take much longer to occur than might be guessed naively. The message to virulence managers is that we should not allow ourselves to be lulled into a false feeling of

security. The good news is that the escaping strain should have a smaller basic reproduction ratio than the one that dominated earlier on.

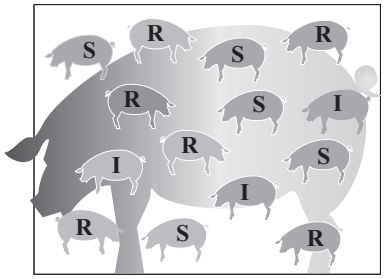
Chapter 25 considers pathogen populations that exhibit a vast diversity in antigen types from the start. These are maintained by immune selection as a stable, discrete set of independently transmitted types without overlap in antigenic repertoires. Gupta argues that when antigenic types can provide cross-protection, the dynamics of each antigenic type may change dramatically, and so will the dynamics of pathogen virulence. Therefore, to understand changes in pathogen virulence in the absence or presence of interventions such as vaccination, one should consider the underlying composition of the pathogen population.

Chapter 26 takes the argument in Chapter 25 a step further. One move in the combat against the diversity of circulating antigenic types has been the development of conjugate vaccines that simultaneously offer protection against several serotypes of the pathogen. With the increased use of such vaccines the concern now is that these vaccinations vacate niches for other serotypes. Lipsitch critically reviews the empirical data sets that have been used to identify serotype replacement, outlines better ways of tracing such processes, and argues that serotype replacement can be, but is not necessarily always, bad. This is because serotype replacement may augment the effectiveness of a vaccination program in a community when nonvaccine serotypes outcompete vaccine serotypes.

Taken together, the chapters in Part F give an overview of the current scientific insight into the potential evolutionary implications of the major measures of short-term disease control.

Part G

Perspectives for Virulence Management



Introduction to Part G

The authors of this book have been encouraged by the editors to stick their necks out and dream up strategies for virulence management, phrased as concretely as possible. As editors, we believe that good science proceeds by making definite predictions so that they can be rigorously put to the test. Phrasing predictions in the form of recommendations forces a healthy definitiveness; no one is allowed to hide under a slightly woolly phrasing. It must nevertheless be understood that not all the recommendations outlined here can as yet be taken at face value; many of the issues raised require additional theoretical and experimental research.

The stress on management aspects is the defining feature of this last part of the book. Whereas earlier parts review particular mechanisms of virulence evolution with a perspective on potentially ensuing options for virulence management, for this part of the book the authors were invited to focus on the following questions:

- For which specific empirical settings can the various possible options of virulence management strategies be expected to apply?
- For each given context, which options appear to be particularly promising?
- What are the open research questions that have to be addressed before measures of virulence management can be recommended for implementation?

After an introductory chapter that is meant to summarize what has been achieved so far, each chapter in this part covers one of the main potential arenas for virulence management: human, wildlife, and livestock diseases, crop protection, and pest control.

Given the variety of these arenas we must recall the range of virulence concepts highlighted in the Introduction – the common denominator is the damage wrought to individual health, to Darwinian fitness, to economic return, or to the pest to be controlled. In particular, the notion of virulence considered in the chapters on human and animal diseases captures various forms of damage to host individuals. In the plant pathology chapter, virulence refers to a pathogen's ability to obtain access to host individuals, a type of virulence that is of great practical importance in plant disease control. The chapter on pest control focuses on the ability of a disease to spread between host populations and thus to produce differential damage at the metapopulation level.

Chapter 27 sets the stage for the later chapters by placing the theory developed in the previous parts in a wider context, with an emphasis on the interface between the theoretical and experimental literature. After giving a methodologically oriented overview of the field, stressing restrictions and caveats, Sabelis and Metz attempt to summarize the main results on virulence evolution gleaned from the previous chapters and the literature. From that perspective the authors identify what they see as gaps in our current knowledge that need to be filled to transform the study of virulence evolution and management into a mature science.

Chapter 28 considers those opportunities for virulence management of human diseases that result from influencing the modes of pathogen transmission from one host to another. After reviewing the available evidence for a diarrheal disease (cholera) and a vectorborne disease (malaria), Ewald concludes that the predicted effects of transmission route manipulation are broadly, although preliminarily, corroborated by comparative studies. For cholera the evidence stems from water purification efforts in South America, and for malaria from mosquito-proofing measures in the USA. Such practices offer short-term as well as long-term benefits, appear ethically uncontroversial, achieve high levels of cost effectiveness, and are expected to be evolutionarily stable – they therefore constitute prime candidates for virulence management initiatives.

In Chapter 29, De Leo and Dobson point out that the goal of preserving charismatic wildlife biodiversity in our human-dominated world makes virulence management of feral populations an issue. Since the time it takes for drug resistance to develop tends to be very short and containment is absent, drug treatments are generally not advisable. There is a dearth of empirical data at the population level, which is especially problematic because wildlife systems are far less controllable than systems in other arenas of virulence management. One strategy to overcome this difficulty is to estimate the disease-induced reduction in host population density from the relative prevalence of the disease in corpses and live animals to gauge where efforts can be invested most usefully. At present, realistic measures aim at the containment of potential disease sources; these options are of two types. First, uncontrolled "spill-overs" from reservoir populations to endangered populations must be minimized. Owing to their higher densities, the former populations can harbor more virulent strains. Second, we should try to reduce the risks of disease transport in controlled wildlife translocations.

Chapter 30 considers livestock that are kept under such controlled conditions and for which diseases are so costly that there is a strong incentive to go beyond the simplifications made in more generally applicable models. It is against this background that de Jong and Janss discuss a verbal model, in which the body of an animal is subdivided into two compartments by the action of the evolving immune system: one in which the virus multiplies and from which it spreads, and one in which it rarely enters but is at its most harmful. Their considerations lead to a number of recommendations for stocking schemes that enable an infection to be stamped out quickly and, at the same time, prevent the disease evolving to escape from the standard control measures.

Whereas Chapter 30 focuses on effects of the host defense system, it is the total absence of systemic defenses in plants that underlies the analysis by Jarosz in Chapter 31. In such a setting, the relative rate of increase of a plant disease depends mainly on the available amount of free tissue. This engenders a dominant impact of seasonality through the dramatic changes in amount of leaf tissue, which lead to different selective pressures the year round. In particular, in winter the amount of leaf tissue is so small that stochastic and metapopulation effects

may kick in. The resultant mechanisms affect the genetic structure of the populations in different manners and therefore open up different avenues for virulence management. Inferring the relative importance of these mechanisms from the observed genetic structure of a population makes it possible to devise management strategies accordingly.

Chapter 32 considers biological pest control from a metapopulation perspective. From this vantage point it becomes mandatory to distinguish the virulence of a biocontrol agent (pathogen, parasitoid, or predator) toward its individual victim (individual-level virulence) from its virulence toward local populations of its victim (patch-level virulence). Whenever the aim is to achieve establishment, spread, and long-term persistence of the biocontrol agent over a large geographical area, it becomes important to consider whether the biocontrol agent exploits local pest populations so as to maximize the number of dispersers. That aim is not necessarily best achieved by a high rate of killing of pest organisms. Elliot, Sabelis, and Adler argue that the key to understanding changes in patch-level virulence is to assess the degree to which biocontrol agents monopolize exploitation of local pest populations. Thus, any means by which this monopoly can be broken will increase the virulence of the biocontrol agent. This results in a suite of measures that can be taken to increase the effectiveness (i.e., the patch-level virulence) of biocontrol agents.

A few of the recommendations in this part have already passed more or less rigorous tests so that they indeed are entering the realm of practical application. Other practical measures suggested here appear to have a good chance of surviving further empirical testing. Generally speaking, however, we are dealing with the very initial stages of a fascinating and hopefully, in the long run, practical science. The following chapters are meant to provide a sense of direction.

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Epilogue

Ulf Dieckmann, Karl Sigmund, Maurice W. Sabelis, and Johan A.J. Metz

Far from conquering infectious diseases through good sanitation, vaccines, and antimicrobial agents, populations of humans – as well as those of other animals and plants – continue to be harassed by an onslaught of pathogens. Complex processes of host–pathogen adaptation are responsible for the perennial persistence of this threat.

To develop sustainable control strategies, it is important to ask which new selective pressures on virulence will thus be created, and how resistance against control measures can be slowed, prevented, or even reversed. On the one hand, population growth, increased mobility, and climate change create new opportunities for diseases, while on the other hand adaptations allow disease agents to overcome the current transmission barriers.

Can epidemiological changes be steered in the desired directions and can they be prevented from veering off course in detrimental ways? That is what this book is about. Its aims are

- To show how evolutionary epidemiology as a science can profit from modeling techniques that take both population dynamics and natural selection into account;
- To explore the design of strategies for virulence management based on models of the evolutionary dynamics of pathogen–host systems;
- To highlight important unresolved research questions that need to be addressed before evolutionary predictions and management options are to be trusted; and
- To foster the dialogue between theorists and empiricists in the field of evolutionary epidemiology.

What are the general predictions regarding the evolution of virulence traits, as they have emerged throughout this book? An overarching principle appears to be the following: the more control the pathogen has over the host, the smaller the likelihood that the pathogen will become virulent. The basis for this prediction is that whenever exploitation by a pathogen cannot be interfered with by other pathogens or environmental causes, the well-being of the host is in the evolutionary interest of the parasite. However, under unclear conditions of "ownership", restrained exploitation is less likely. This can best be viewed as an instance of the Tragedy of the Commons. Whenever the resource (the host) is not safely monopolized, consideration of long-term benefits loses importance. The following points can be viewed as special cases of this principle.

- Under conditions of guaranteed transmission, selection favors the strains that replicate faster. This highlights why it is important to analyze alternative transmission modes, be they actual or potential.
- Under vertical (horizontal) transmission, low (high) virulence is favored. A vertically transmitted pathogen is generally much more closely tied to the host than an invader can ever be. There are relatively few theoretical analyses on this aspect, but it is likely to play an essential role in long-term evolution.
- The larger the multiplicity of infections, the higher the virulence. This is the result of arguments based on game theory (rather than optimization arguments) and the core of the Tragedy of the Commons: the more players, the less interest each has in safeguarding the common resource.
- Compared with well-mixed systems, in socially or spatially structured systems less virulent parasites are favored.

From these considerations, important options for virulence management emerge. We list them succinctly, with cross-references to the corresponding chapters for the essential caveats.

- Evolutionary optimality principles should be used with caution when managing virulence evolution under frequency-dependent selection (Chapter 4).
- In the presence of multiple infections, the evolutionary stability of biological control strategies must be assessed in the light of multiple levels of selection (Chapters 9 to 12, 22, and 32).
- Routes of pathogen transmission that function independently of host health, or that even intensify for sick hosts, should be at the very focus of management measures (Chapters 2 and 28).
- Altering transmission networks so that virulent pathogens are exposed to the detrimental consequences of their aggressive exploitation strategy selects for decreased virulence (Chapter 7).
- In animal husbandry and crop management, enhancing the relatedness of infected hosts is expected to select for decreased virulence (Chapters 7 and 11).
- Influencing the likelihood of horizontal versus vertical transmission can select for decreased virulence (Chapters 20 and 21).
- Models based on subdividing the host organism into compartments may help us to prevent the disease from escaping standard control measures (Chapter 30).
- By preventing hosts from acquiring multiple infections, decreased virulence can be selected for (Chapters 9 to 11).
- In the presence of multiple infections, long-term benefits arise from sanitation and vaccination that would otherwise be absent (Chapter 11).
- Tolerating relatively benign parasites, rather than trying to eliminate them, may often be advisable from an evolutionary perspective (Chapter 5).
- Strengthening the “conspiracy” between plants and arthropod predators in tritrophic interactions can improve the prospects for controlling the herbivores sandwiched in between (Chapter 22).

- In the context of biological control efforts, it must be kept in mind that pathogens genetically engineered to have a high virulence may be at a selective disadvantage (Chapters 6 and 32).
- Management-induced supply of novel genetic material from source to sink populations provides the genetic variation needed for local responses in the sink, but can also swamp the local adaptation of pathogens and hosts (Chapter 8).
- Uncontrolled spillover of pathogens from reservoir populations to endangered populations must be minimized, since the former pathogens tend to be more virulent than those in the latter populations (Chapter 29).
- By fostering host evolution and mate choice, it is possible to diminish disease losses in breeding programs for endangered species and livestock production (Chapters 15 and 18).
- To keep virulence at bay in systems with gene-for-gene interactions between parasites and their hosts, fostering the genetic diversity of hosts is essential (Chapter 17).
- If gene-for-gene interactions prevail, breeding schemes can be devised to select for hosts that have simultaneous resistance against multiple pathogen strains (Chapter 31).
- If more than one antibiotic is available to treat a bacterial infection, they should be administered, in a population-wide campaign, to individual hosts through combination therapy (Chapter 23).
- The suppression of a competitively superior pathogen strain by a vaccine that confers little cross-immunity may set off outbreaks of earlier, competitively inferior strains (Chapter 24).
- When nonvaccine serotypes outcompete vaccine serotypes, serotype replacement may augment the effectiveness of a vaccination program in a community (Chapter 26).

It hardly needs to be emphasized that many theoretical and empirical questions remain still unanswered. As with all good engineering, the development of techniques for virulence management requires a process of stepwise scaling up from small-scale predictions and controlled experiments toward applications of realistic complexity. In this context, our impression is that the following problems need to be addressed most urgently.

- A deeper understanding of the genetic basis of virulence traits is needed to better predict virulence evolution in the short term.
- More information is needed on the evolution of mutation rates.
- More experimental clues to the mechanisms of intraspecific competition of pathogens within hosts are needed.
- Actual patterns of competitive and cooperative interactions between different pathogenic strains need to be better understood.
- The existence of alternative transmission routes and their evolutionary implications should be explored in greater depth, both empirically and theoretically.
- Evolutionary implications of spatial structure are as yet imperfectly understood.

- The role of ecological networks in shaping pathogen–host interactions is still largely unexplored, especially if the hosts harbor several pathogen species and parasites can use multiple hosts.
- The richness of patterns in pathogen–host coevolution driven by reciprocal selection warrants further analysis.

If readers feel that this leaves them with more unanswered questions than they had before, the editors will be perfectly satisfied. The main goal of this book is to set a research program for evolutionary virulence management firmly on the road.