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Introduction

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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

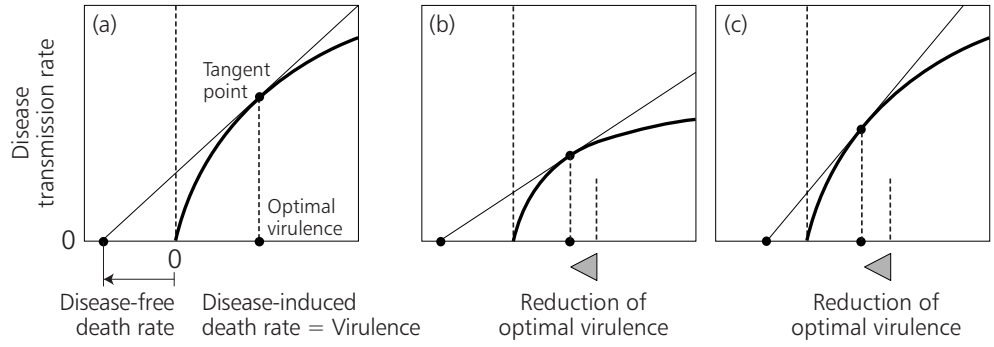
Box 1.2 *continued*

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.

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