

Chapter One

Introduction

This book is designed as an introduction to the modeling of infectious diseases. We start with the simplest of mathematical models and show how the inclusion of appropriate elements of biological complexity leads to improved understanding of disease dynamics and control. Throughout, our emphasis is on the development of models, and their use either as predictive tools or as a means of understanding fundamental epidemiological processes. Although many theoretical results can be proved analytically for very simple models, we have generally focused on results obtained by computer simulation, providing analytical results only where they lead to a more generic interpretation of model behavior. Where practical, we have illustrated the general modeling principles with applied examples from the recent literature. We hope this book motivates readers to develop their own models for diseases of interest, expanding on the model frameworks given here.

1.1. TYPES OF DISEASE

The Oxford English Dictionary defines a disease as “a condition of the body, or of some part or organ of the body, in which its functions are disturbed or deranged; a morbid physical condition; a departure from the state of health, especially when caused by structural change.” This definition encompasses a wide range of ailments from AIDS to arthritis, from the common cold to cancer. The fine-scale classification of diseases varies drastically between different scientific disciplines. Medical doctors and veterinary clinicians, for example, are primarily interested in treating human patients or animals and, as such, are most concerned about the infection’s pathophysiology (affecting, for example, the central nervous system) or clinical symptoms (for example, secretory diarrhea). Microbiologists, on the other hand, focus on the natural history of the causative organism: What is the etiological agent (a virus, bacterium, protozoan, fungus, or prion)? and what are the ideal conditions for its growth? Finally, epidemiologists are most interested in features that determine patterns of disease and its transmission.

In general terms, we may organize diseases according to several overlapping classifications (Figure 1.1). Diseases can be either infectious or noninfectious. Infectious diseases (such as influenza) can be passed between individuals, whereas noninfectious diseases (such as arthritis) develop over an individual’s lifespan. The epidemiology of noninfectious diseases is primarily a study of risk factors associated with the chance of developing the disease (for example, the increased risk of lung cancer attributable to smoking). In contrast, the primary risk factor for catching an infectious disease is the presence of infectious cases in the local population—this tenet is reflected in all the mathematical models presented in this book. These two categories, infectious and noninfectious, are not necessarily mutually exclusive. Infection with the human papillomavirus (HPV), for example, is firmly associated with (although not necessary for developing) cervical cancer,

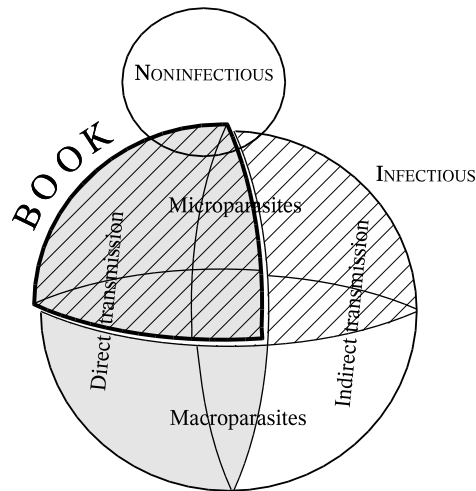


Figure 1.1. A representation of the various types of diseases. The two main groups of infectious and noninfectious diseases are represented by the two circles. The infectious group can be further subdivided into directly transmitted (gray) and indirectly transmitted infections as well as into diseases due to microparasites (hatched) and macroparasites. The focus of this book are the diseases subsumed within the intersection of the hatched and gray areas, which is offset and bounded by a thick black line.

thus bridging the two fields. This book focuses on infectious diseases, where models have great predictive power at the population scale and over relatively short time scales.

Infectious diseases can be further subdivided (Figure 1.1). The infecting pathogen can be either a microparasite (hatched in diagram) or a macroparasite. Microparasites, as the same suggests, are small (usually single-cell organisms) and are either viruses, bacteria, protoza, or prions; macroparasites are any larger form of pathogen and include helminths and flukes. Although the biological distinction between these two groups of organisms is clear, from a modeling perspective the boundaries are less well defined. In general, microparasitic infections develop rapidly from a small number of infecting particles so the internal dynamics of the pathogen within the host can often be safely ignored. As a result, we are not interested in the precise abundance of pathogens within the host; instead we focus on the host's infection status. In contrast, macroparasites such as helminths have a *complex life cycle* within the host which often needs to be modeled explicitly. In addition, the worm burden, or the number of parasites within the host, represents an important contributing factor to pathogenicity and disease transmission. We focus in this book on microparasites, where extensive long-term data and a good mechanistic understanding of the transmission dynamics have led to a wealth of well-parameterized models.

Infectious diseases (both macro- and microparasitic) can also be subdivided into two further categories (Figure 1.1), depending on whether transmission of infection is direct (shaded gray) or indirect. Direct transmission is when infection is caught by close contact with an infectious individual. The great majority of microparasitic diseases, such as influenza, measles, and HIV, are directly transmitted, although there are exceptions such as cholera, which is waterborne. Generally, directly transmitted pathogens do not survive for long outside the host organism. In contrast, indirectly transmitted parasites are passed between hosts via the environment; most macroparasitic diseases, such as those caused

by helminths and schistosomes, are indirectly transmitted, spending part of their life cycle outside of their hosts. In addition, there is a class of diseases where transmission is via a secondary host or vector, usually insects such as mosquitoes, tsetse flies, or ticks. However, this transmission route can be considered as two sequential direct transmission events, from the primary host to the insect and then from the insect to another primary host.

The models and diseases of this book are focused toward the study of directly transmitted, microparasitic infectious diseases. As such, this subset represents only a fraction of the whole field of epidemiological modeling and analysis, but one in which major advances have occurred over recent decades.

Worldwide there are about 1,415 known human pathogens of which 217 (15%) are viruses or prions and 518 (38%) are bacteria or rickettsia; hence around 53% are microparasites (Cleaveland et al. 2001). Of these pathogens, 868 (61%) are zoonotic and can therefore be transmitted from animals to humans. Around 616 pathogens of domestic livestock are known, of which around 18% are viral and 25% bacterial. However, if we restrict our attention to the 70 pathogens listed by the Office International des Epizooties (which contain the most prominent and infectious livestock diseases), we find that 77% are microparasites (Cleaveland et al. 2001). The lower number of known livestock pathogens compared to human pathogens probably reflects to some degree our natural anthropocentric bias. Similarly, very few infectious diseases of wildlife are known or studied in any detail, and yet wildlife reservoirs may be important sources of novel emerging human infections. It is therefore clear that the study of microparasitic infectious diseases encompasses a huge variety of hosts and diseases.

1.2. CHARACTERIZATION OF DISEASES

The progress of an infectious microparasitic disease is defined qualitatively in terms of the level of pathogen within the host, which in turn is determined by the growth rate of the pathogen and the interaction between the pathogen and the host's immune response. Figure 1.2 shows a much simplified infection profile. Initially, the host is *susceptible* to infection: No pathogen is present; just a low-level nonspecific immunity within the host. At time 0, the host encounters an infectious individual and becomes infected with a microparasite; the abundance of the parasite grows over time. During this early phase the individual may exhibit no obvious signs of infection and the abundance of pathogen may be too low to allow further transmission—individuals in this phase are said to be in the *exposed* class. Once the level of parasite is sufficiently large within the host, the potential exists to transmit the infection to other susceptible individuals; the host is *infectious*. Finally, once the individual's immune system has cleared the parasite and the host is therefore no longer infectious, they are referred to as *recovered*.

This fundamental classification (as susceptible, exposed, infectious, or recovered) solely depends on the host's ability to transmit the pathogen. This has two implications. First, the disease status of the host is irrelevant—it is not important whether the individual is showing symptoms; an individual who feels perfectly healthy can be excreting large amounts of pathogen (Figure 1.2). Second, the boundaries between exposed and infectious (and infectious and recovered) are somewhat fuzzy because the ability to transmit does not simply switch on and off. This uncertainty is further complicated by the variability in responses between different individuals and the variability in pathogen levels over the infectious period; it is only with the recent advances in molecular techniques that these

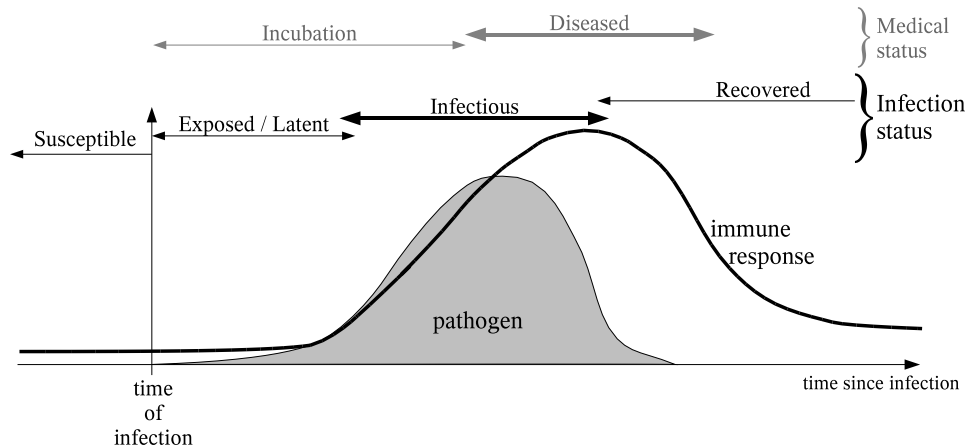


Figure 1.2. A caricature of the time-line of infection, showing the dynamics of the pathogen (gray area) and the host immune response (black line) as well as labeling the various infection classes: susceptible, exposed, infectious, and recovered. Note that the diseased period, when symptoms are experienced, is not necessarily correlated with any particular infection class.

within-host individual-level details are beginning to emerge. Our classification of hosts as susceptible, exposed, infectious, or recovered can therefore be compared to the ecological concept of a metapopulation (Levins 1969; Hanski and Gilpin 1991), in which the within-host density of the pathogen is ignored and each host is simply classified as being in one of a limited number of categories.

Although Figure 1.2 shows an example of a disease profile that might be modeled as *SEIR* (susceptible-exposed-infectious-recovered), other within-host profiles are also common. Often, it is mathematically simpler and justifiable at the population scale to ignore the exposed class, reducing the number of equations by one and leading to *SIR* dynamics. Some infections, especially of plants, are more appropriately described by the *SI* (susceptible-infectious) paradigm; for such diseases, the host is infectious soon after it is infected, such that the exposed period can be safely ignored, and remains infectious until its death. Other infectious diseases, in particular sexually transmitted infections (such as gonorrhoea), are better described by an *SIS* (susceptible-infectious-susceptible) framework, because once recovered (or following treatment) the host is once again susceptible to infection. In the majority of cases this renewed susceptibility is due to the vast antigenic variation associated with sexually transmitted diseases. Finally, many diseases have profiles that are individualistic and require specific model formulation. Smallpox has a definite short prodromal period before the symptoms emerge when the infected individual is mobile and can widely disseminate the virus but infectiousness has not reached its peak. Hepatitis B has a carrier state such that some infected individuals do not fully recover but transmit at a low level for the rest of their lives. Chlamydia (and many other sexually transmitted diseases) may be asymptomatic, such that some infected individuals do not suffer from the disease even though they are able to transmit infection. Similarly, infections such as meningitis or MRSA (methicillin resistant streptococcus aureus) are widespread in the general population and usually benign, with only occasional symptomatic outbreaks. All of these more complex epidemiological behaviors require

greater subdivision of the population and therefore models that deal explicitly with these extra classes.

Although such qualitative descriptions of disease dynamics allow us to understand the behavior of infection within an individual and may even shed some light on potential transmission, if we are to extrapolate from the individual-level dynamics to the population-scale epidemic, numerical values are required for many of the key parameters. Two fundamental quantities govern the population-level epidemic dynamics: the basic reproductive ratio, R_0 , and the timescale of infection, which is measured by the infectious period for *SIS* and *SIR* infections or by a mixture of exposed and infectious periods in diseases with *SEIR* dynamics (for details, see Chapter 2). The basic reproductive ratio is one of the most critical epidemiological parameters because it defines the average number of secondary cases an average primary case produces in a totally susceptible population. Among other things, this single parameter allows us to determine whether a disease can successfully invade or not, the threshold level of vaccination required for eradication, and the long-term proportion of susceptible individuals when the infection is endemic.

One of the key features of epidemiological modeling is the huge variability in infection profiles, parameter values, and timescales. Many childhood infectious diseases (such as measles, rubella, or chickenpox) follow the classic *SEIR* profile, have high basic reproductive ratios ($R_0 \approx 17$ for both measles and whooping cough in England and Wales from 1945 to 1965), and short infected periods (of less than one month). In contrast, diseases such as HIV have a much more complex infection profile with transmission rates varying as a function of time since infection, R_0 is crucially dependent on sexual behavior ($R_0 \approx 4$ for the homosexual population in the United Kingdom, whereas $R_0 \approx 11$ for female prostitutes in Kenya), and infection is lifelong. Between these two extremes lies a vast array of other infectious diseases, with their own particular characteristics and parameters.

1.3. CONTROL OF INFECTIOUS DISEASES

One of the primary reasons for studying infectious diseases is to improve control and ultimately to eradicate the infection from the population. Models can be a powerful tool in this approach, allowing us to optimize the use of limited resources or simply to target control measures more efficiently. Several forms of control measure exist; all operate by reducing the average amount of transmission between infectious and susceptible individuals. Which control strategy (or mixture of strategies) is used will depend on the disease, the hosts, and the scale of the epidemic.

The practice of vaccination began with Edward Jenner in 1796 who developed a vaccine against smallpox—which remains the only disease to date that has been eradicated world-wide. Vaccination acts by stimulating a host immune response, such that immunized individuals are protected against infection. Vaccination is generally applied prophylactically to a large proportion of the population, so as to greatly reduce the number of susceptible individuals. Such prophylactic vaccination campaigns have successfully reduced the incidence of many childhood infections in the developed world by vaccinating the vast majority of young children and infants. In 1988, the World Health Organization (WHO) resolved to use similar campaigns to eradicate polio worldwide by 2005—this is still ongoing work although much progress has been made to date.

Although vaccination offers a very powerful method of disease control, there are many associated difficulties. Generally, vaccines are not 100% effective, and therefore only a proportion of vaccinated individuals are protected. Some vaccines can have adverse side effects; the vaccine against smallpox can be harmful (sometimes fatal) to those with eczema, asthma, or are immuno-suppressed, and may even cause cases of smallpox. Some vaccines provide only limited immunity, whether this is due to the natural waning of immunity in the host or to antigenic variation in the pathogen. Finally, in the face of a novel (or unexpected) epidemic, reactive vaccination may prove to be too slow to prevent a large outbreak. Therefore, in many situations, alternative control measures are necessary.

Vaccination operates by reducing the number of susceptible individuals in the population.



Quarantine, or the isolation of known or suspected infectious individuals, is one of the oldest known forms of disease control. During the fifteenth and sixteenth century, Venice, Italy, practiced a policy of quarantine against all ships arriving from areas infected with plague, and in 1665 the village of Eyam in Derbyshire, UK, famously quarantined themselves in an effort to prevent the plague spreading to neighboring villages. Today quarantining is still a powerful control measure; was used to combat SARS in 2003, and it is a rapid first response against many invading pathogens. Quarantining essentially operates by preventing infectious individuals from mixing with susceptible individuals, hence stopping transmission. The primary advantage of quarantining is that it is simple and generic; quarantining is effective even when the causative agent is unknown. However, quarantining can be applied only once an infectious individual is identified, by which time the individual may have been transmitting infection for many days. In addition, unless the number of cases is small, quarantining can be a prohibitive drain on resources.

Quarantining operates by reducing the number of infected individuals freely mixing in the population.



Culling acts by depleting the host population by killing hosts. From recent years, there are three clear examples of culling as a means of control. During the 2001 foot-and-mouth epidemic in the United Kingdom, culling was used as a fast and effective control measure. Ring culling, removing all citrus trees within, 1900 feet of identified infected trees, is currently being used to control Citrus Canker disease (caused by the *Xanthomonas axonopodis* pv. *citri* bacterium) in Florida. For this disease, proximity was judged to be the main risk factor, with around 95% of inoculum dispersal being within 1,900 feet. Finally, large-scale field trials in the United Kingdom and Ireland have examined the effect of culling badger populations on the spread of bovine tuberculosis in cattle—based on the assumption that badgers act as a reservoir of infection.

Obviously culling is applicable only to animal and plant diseases, and even then it is used only against harmful, rapidly spreading, pathogens when other control measures are ineffective. Culling is usually indiscriminate, killing both infected and susceptible hosts and thereby reducing transmission in two distinct ways. However, culling is often locally targeted such that this severe action is limited to regions of high risk. It is vitally important that culling measures are highly targeted and tightly controlled—there is a clear trade-off between sufficient culling to control the epidemic and excess culling that could be more detrimental than an uncontrolled epidemic. Models can be extremely powerful tools of discrimination in such situations.

Culling operates by reducing both the number of infected and susceptible individuals in the population.

Contact tracing, although not a control measure in itself, is an important tool in efficiently targeting other control measures and therefore limiting disease spread. Contact tracing operates by questioning infected individuals about their behavior, identifying potential transmission contacts, and therefore finding individuals who are likely to be infected but are not yet symptomatic. The individuals identified by contact tracing can then be vaccinated, quarantined, or hospitalized, depending on the nature of the infection.

Contact tracing operates by refining the targeting of other control measures.**1.4. WHAT ARE MATHEMATICAL MODELS?**

Recent years have seen an increasing trend in the number of publications, both in high-profile journals and more generally, that utilize mathematical models (Figure 1.3). This is associated with an increased understanding of what models can offer in terms of prediction and insight. Any model can be typically thought of as a conceptual tool that explains how an object (or system of objects) will behave. A mathematical model uses the language of mathematics to produce a more refined and precise description of the system. In epidemiology, models allow us to translate between behavior at various scales, or extrapolate from a known set of conditions to another. As such, models allow us to predict the population-level epidemic dynamics from an individual-level knowledge of epidemiological factors, the long-term behavior from the early invasion dynamics, or the impact of vaccination on the spread of infection.

Models come in a variety of forms—from highly complex models that (like jet aircraft) need a range of experts to create and maintain them, to simple “toy” models that (like bicycles) can be easily understood, modified, and adapted. The decision whether to travel by bike or aircraft depends on several factors, such as time, distance, and cost. Similarly, which sort of model is the most appropriate depends on the precision or generality required, the available data, and the time frame in which results are needed. By definition, all models are “wrong,” in the sense that even the most complex will make some simplifying assumptions. It is, therefore, difficult to express definitively which model is “right,” though naturally we are interested in developing models that capture the essential features of a system. Ultimately, we are faced with a rather subjective measure of the *usefulness* of any model.

Formulating a model for a particular problem is a trade-off between three important and often conflicting elements: accuracy, transparency, and flexibility. *Accuracy*, the ability to reproduce the observed data and reliably predict future dynamics, is clearly vital, but whether a qualitative or quantitative fit is necessary depends on the details of the problem. A qualitative fit may be sufficient to gain insights into the dynamics of an infectious disease, but a good quantitative fit is generally necessary if the model is used to advise on future control policies. Accuracy generally improves with increasing model complexity and the inclusion of more heterogeneities and relevant biological detail. Clearly, the feasibility of model complexity is compromised by computational power, the mechanistic understanding of disease natural history, and the availability of necessary parameters. Consequently, the accuracy of any model is always limited. *Transparency* comes from being able to understand (either analytically or more often numerically) how the various

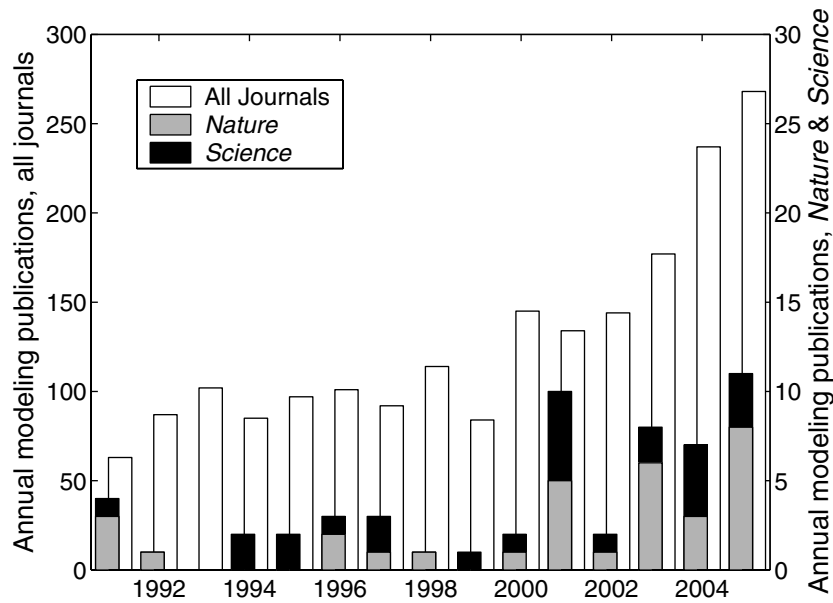


Figure 1.3. An indication of the increasing importance and use of mathematical models in the epidemiological literature. White bars show the approximate number of publications in the entire scientific literature that utilize models of infectious diseases. (Data are obtained from ISI Web of Science, and include all publications that contain in their title or abstract the words “epidemic,” and “infect*,” and either “model*” or “simulat*.”) The gray and black bars show the number of these publications to be found in *Nature* and *Science* respectively, providing some indication of the high impact of such work. (These papers were identified from their title and abstract.) Note the different scales for general papers and those in *Nature* or *Science*.

model components influence the dynamics and interact. This is usually achieved by successively adding or removing components and building upon general intuitions from simpler models. As the number of model components increases, it becomes more difficult to assess the role of each component and its interactions with the whole. Transparency is, therefore, often in direct opposition to accuracy. *Flexibility* measures the ease with which the model can be adapted to new situations; this is vital if the model is to evaluate control policies or predict future disease levels in an ever-changing environment. Most mechanistic models (such as those within this book) are based on well-understood disease transmission principles and are therefore highly flexible, whereas “black-box” time-series tools (such as neural nets) that may be able to accurately reproduce a given time series of reported cases are less amenable to modification.

1.5. WHAT MODELS CAN DO

Models have two distinct roles, *prediction* and *understanding*, which are related to the model properties of accuracy and transparency, and therefore can often be in conflict. We usually require a high degree of accuracy from any predictive model, whereas transparency is a more important quality of models used to improve our understanding.

Prediction is the most obvious use of models. It requires that the model is as accurate as possible and therefore includes all of the known complexities and population-level heterogeneities. Predictive models can have great power in specific situations, guiding difficult policy decisions where a trade-off between two (or more) alternative control strategies exists. It is interesting to contrast how models were used during the 2001 UK foot-and-mouth epidemic to how models were used to investigate the control of potential bio-terrorist releases of smallpox. Both of these scenarios called for detailed, accurate predictive modeling. Chapter 8 provides a comprehensive description of the types of models that could be used to tackle these two problems.

During the UK foot-and-mouth epidemic in 2001, two primary questions were addressed using models: first, was the epidemic “under control” and second, whether additional targeted culling would lead to a reduction in the total loss of livestock. Three distinct models were used, based on different judgements of the known dynamical complexity. Each of these models had their own advantages and problems, but fortunately—due to the robustness of the problem—all three models provided similar advice: A large-scale epidemic was predicted and additional, locally targeted culling would reduce the overall loss of livestock by dramatically reducing the number of cases (Keeling 2005).

Smallpox is a potential bio-terrorist weapon given the high mortality rate and the large number of susceptible individuals in the population. Here the main question focused on the best method of control, mass-vaccination or targeted measures. Mass-vaccination is obviously most effective against a large-scale outbreak, but due to side effects of the vaccine, a large-scale vaccination campaign could cause more health problems than a small-scale epidemic. Again a variety of models were used, ranging from the very simple (Meltzer et al. 2001) to highly complex (Halloran et al. 2002). However, these models provided conflicting advice, in part due to uncertainties in the epidemiological parameters and to the different underlying assumptions. It is still an open problem to determine under what conditions it is optimal to mass-vaccinate against smallpox.

Accurate predictive models can have an additional use as a statistical tool. The failure to accurately predict epidemic behavior in a particular area can act as a diagnostic warning that underlying parameters and behavior may be different from the norm. For example, whereas isolated cases of meningitis may be the norm, several clustered cases can signify the start of a localized epidemic; accurate models should be able to predict a threshold number of cases above which prompt action is required (Stollenwerk and Jansen 2003). Similarly, during an eradication campaign, regions that do not respond as rapidly as the models predict could be detected and targeted for more intensive control measures. Finally, detailed modeling and robust statistical analysis of reported and hospitalized cases may be able to identify the early emergence of an epidemic.

Models can also be used to understand how an infectious disease spreads in the real world, and how various complexities affect the dynamics. In essence, models provide epidemiologists with a ideal world in which individual factors can be examined in isolation and where every facet of the disease spread is recorded in perfect detail. With such tools we can examine, in a fairly robust and generic framework, a range of issues such as the effects of variable numbers of partners on the spread of sexually transmitted diseases, the effects of increased transmission between children during school terms, or the effects of localized spread of infection.

It might seem that such modeling approaches are driven purely by scientific curiosity with little relevance to practical matters or particular infections. However, the insights gained from such modeling are often robust and generic, and therefore can be applied

to a wide variety of particular problems. Moreover, the understanding gained can help us to develop more sophisticated predictive models and gather more relevant epidemiological data, allowing us to decide which elements are important and which can be neglected. Finally, it is only by developing an intuition for infection patterns, building from simple models to more complex ones, that we can begin to understand all the rich complexities and dynamics that are observed in the real world.

Although some of the model examples given in this book are predictive in nature, because they are accurate characterizations of reality, the majority of this book is devoted to obtaining a deeper understanding of epidemiological patterns. However, the techniques can be utilized to build more complex predictive models.

1.6. WHAT MODELS CANNOT DO

Models also have their limitations. It is impossible to build a fully accurate model; there will always be some element of the host behavior or quirk of the disease that is unknown or even unknowable. Consider trying to make an accurate model for a human airborne infection (say influenza); such a model would need to account for variations in transmission with temperature and climate, capture the day-to-day movement and interaction of individuals, and encompass the variability in susceptibility due to genetic factors or past infections. Even if such a model could be built, the chance nature of transmission would still prevent perfect prediction. We will never be able to predict the precise course of an epidemic, or which people will be infected. The best that we can hope for is models that provide confidence intervals on the epidemic behavior and determine the risk of infection for various groups of hosts.

1.7. WHAT IS A GOOD MODEL?

It is clear from what has already been said that no model is perfect, and no model can accurately predict the detailed outcome of an infection process. However, two key points define a good model. First, a model should be *suited to its purpose*—that is, it should be as simple as possible, but no simpler—having an appropriate balance of accuracy, transparency, and flexibility. A model that is designed to help us understand the behavior of an infectious disease should concentrate on the characteristics that are of interest while simplifying all others. A model built for accurate prediction should provide a comprehensive picture of the full dynamics, and include all the relevant features of the disease and host, although determining which factors are relevant and which may be safely ignored is a complex and skilled process. Second, the model should be *parameterizable* (where necessary) *from available data*. Thus, although a predictive model requires the inclusion of many features, it is important that they can all be parameterized from available data. Hence, in many situations—such as at the start of an emerging (novel) epidemic—it may be impossible to produce a good predictive model. In contrast, if we are interested only in understanding an epidemic pattern, there is far less need for a model to accurately represent a particular scenario, and so parameterization and availability of data are less important. Therefore, it is clear that what constitutes a good model is context dependent. Throughout this book we have attempted to use only examples of good modeling practice.

1.8. LAYOUT OF THIS BOOK

This book is divided into seven major chapters (plus this introduction), which deal with different characteristic patterns of epidemics and the models that can be used to understand and capture their behavior. Each chapter can be further subdivided into methods and applications or case studies: Methods explain the underlying principles of models, and applications show how this type of model has been used in understanding specific disease dynamics in human and animal populations. Finally, to help with a rapid understanding of each chapter, crucial synopsis of the main points are highlighted throughout the chapter as follows:

This sentence is an important summary of this section.



The chapters are as follows:

1. Introduction

This chapter introduces the basic concepts and ideas of modeling, as well as providing a brief overview of epidemiological characteristics and behavior.

2. Introduction to Simple Epidemic

This first true chapter reviews the basic building blocks of most epidemiological models: the compartmental *SIS* and *SIR* models. For these models it is possible to develop some analytical results, which are useful in the understanding of simple epidemics and in our interpretation of more complex scenarios. Therefore, although much of the analytical detail of this chapter has been considered elsewhere in far greater depth, this work is included to provide a firm foundation to further developments. In addition, we discuss the dynamics of other compartmental models, such as those with exposed or carrier classes.

3. Host Heterogeneities

Almost all populations (with the exception of large clonal agricultures) can be sub-divided into different groups, depending upon characteristics that may influence the risk of catching and transmitting an infection. For example, an individual's pattern of sexual behavior clearly determines the likelihood of catching sexually transmitted diseases. Models that include such heterogeneities, therefore, are a better representation of reality in such cases. Other important population-level heterogeneities include age, gender, behavior, and even generic susceptibility, although this may be difficult to ascertain. Understanding how such heterogeneities influence transmission allows us to determine which individuals in a population are most at risk and the most effective means of targeting control.

4. Multi-Pathogen Multi-Host Models

Many diseases can be caught and transmitted by numerous hosts (e.g., most livestock species are susceptible to foot-and-mouth disease); other diseases require an obligatory second host species to complete the transmission cycle (e.g., vector-borne diseases such as malaria). These are all examples of multi-host single-pathogen systems. The converse situation, single-host multi-pathogen, occurs if we are interested in the competition between two strains that are to some degree cross-reactive. The dynamics of many diseases can be fully explained only as the interaction of many cross-reactive strains. The prediction

of future worldwide influenza strains and the possibility of pandemics are based on such models.

5. Temporally Forced Models

Many diseases undergo periodic forcing from some external environmental factor. Examples include the opening and closing of school terms for childhood diseases, climatic variations affecting the transmission of diseases by arthropod vectors, or the annual planting and harvesting of agricultural crops. Such simple periodic perturbations to the basic models can have dramatic consequences, driving regular multi-year epidemic cycles or even complex/chaotic dynamics. Much of this dynamical behavior is illustrated for measles infection, where there is a rich history in studying the seasonal behavior observed in major cities in Europe and the United States. The concept of a bifurcation diagram is introduced, which provides a powerful and intuitive visualization of epidemic patterns because a key parameter is varied.

6. Stochastic Dynamics

All diseases are subject to stochasticity in terms of the chance nature of transmission, and so, in principle, a stochastic model is always more realistic than a deterministic one. However, the relative magnitude of stochastic fluctuations reduces as the number of cases increases; therefore, in large populations, with a high level of disease incidence, a deterministic model may be a good approximation. However, when the population is small or the disease is rare (for example, due to vaccination or early during an epidemic), stochasticity can have a major impact. In particular, stochasticity can have three major effects: It pushes the system away from the deterministic attractor such that transients may play a significant role, it can cause chance extinctions of the disease, and finally it introduces variances and co-variances that can influence the deterministic behavior. Hence, if we are interested in eradication of a disease, or if irregular epidemics are observed, stochastic modeling is generally necessary.

7. Spatial Models

Spatial heterogeneities occur at a range of scales, although it is the two extremes that are most commonly studied. At the local scale, strong correlations emerge between the infectious status of interacting individuals, such that infected hosts are spatially aggregated and patches of susceptibles exist. It is with such individual-based models that we can capture the wavelike spread of invading diseases through populations. At the other extreme, there are the heterogeneities between distinct populations, such as different towns and cities, or different geographic regions. Models for such scenarios act at a much larger scale, and are generally concerned with the correlation between the populations and the effects of the transmission between them. This chapter provides a comprehensive review of a large range of model types that are used to capture the spatial spread of infection.

8. Controlling Infectious Diseases

The final chapter deals with the applied issue of control, and as such focuses on issues that are of public health and veterinary importance. In particular it discusses how the models and understanding gained in the previous chapters can be used to optimally target control measures so as to minimize the impact of infection. Vaccination, quarantining, culling, and contact tracing are all together, as well as detailed studies of smallpox, foot-and-mouth disease, and swine fever virus.

1.8.1. Accompanying Software

Given that much of the focus in this book is on understanding epidemiological problems that are analytically intractable, a variety of programs are available at the Web page:

<http://press.princeton.edu/titles/8459.html>

The purpose of these programs is to help those interested in further exploring the models presented and to aid in the development of new models. For each model, four different versions of the program are included: a *Java* program that allows parameters to be adjusted and the dynamics to be inspected graphically, and programs in *C*, *Fortran* and *Matlab* that can be freely adapted and tailored to suit a given situation. These programs serve to ease and facilitate the use of models in epidemiological problems—they are not intended as a programming guide and are not necessarily the most refined or efficient programming approach.

1.9. WHAT ELSE SHOULD YOU KNOW?

An epidemiological modeler requires a wide arsenal of tools and techniques in addition to an understanding of disease behavior and the ability to construct models (which is the focus of this book). Here we give a brief summary of potentially useful additional techniques and disciplines, and point the reader to general texts that provide an introduction to the subject matter.

In much of this book, we go about modeling by first considering the underlying assumptions about the processes involved and how these scale the number of infected and susceptible individuals. We then proceed to express these assumptions in terms of mathematical equations, which are then analyzed. The actual process of analysis usually involves computing the solution numerically, because the models are often analytically intractable. A variety of off-the-shelf software may be used to solve ordinary differential equations. Examples include *ModelMaker* and *Stella*. Numerous scientific computing packages also permit quite sophisticated modeling, such as *Mathematica*, *Maple*, *R*, *Mathcad*, and *Matlab*. Our personal preference is to carry out (nearly) all model analyses in code written in a low-level computing language, such as *C* or *Fortran*. Almost all the figures in this book were generated by first simulating the equations using *C*-code, followed by analyses of these computer-generated data in *Matlab*, which has the additional advantage of superb graphics capabilities.

A sound knowledge of *statistics* is obviously an essential asset, allowing us to link models with available data, and providing a framework for analyzing the results of model simulations. Statistics therefore has three main purposes in epidemiological modeling. First, it allows us to analyze any data that are available and to use this information to derive parameters (and associated confidence intervals) for our model. Second, statistics provides a powerful set of tools to compare model output with available data, with the general aim of showing that the model is a good fit. Finally, statistics can be used to compare the results of multiple model simulations, and so elucidate the differences between them—this is particularly important if the models are stochastic. Statistics itself is a very diverse subject area and no single publication could possibly cover the entire discipline. However, *Statistics in Theory and Practise* by Robert Lupton (1993) or *Introductory Statistics* by Ronald and Thomas Wonnacott (1990) provide a good introduction to the basics, whereas

