Chapter 1
Introduction

1.1 Epidemiology

Epidemiology is the subject that studies the patterns of health and illness and associated factors at the population level. The word "epidemiology" is derived from the Greek terms *epi*, which means "upon," *demos*, which means " people," and *logos*, which means "study." This etymology implies that the subject of epidemiology applies only to human populations. The role of father of epidemiology is often assigned to the Greek physician Hippocrates (460–377 B.C.E.), who described the connection between disease and environment [83]. The term "epidemiology" appears to have first been used to describe the study of epidemics in 1802 by the Spanish physician de Villalba in *Epidemiologia Espanola* [30]. Until the twentieth century, epidemiological studies were mostly concerned with infectious diseases. Nowadays, the leading causes of deaths worldwide are diseases such as stroke and coronary heart disease [132], positioning diseases that do not transmit from one person to another as a central concern of epidemiology. Among infectious diseases, those that dominate worldwide as a cause of death include lower respiratory infections (such as pneumonia) and HIV. In this book, we will be concerned with mathematical modeling of infectious diseases.

1.2 Classification of Infectious Diseases

An *infectious disease* is a clinically evident illness resulting from the presence of a pathogenic microbial agent. The microbial agent causing the disease can be bacterial, viral, fungal, parasitic, or it can be toxic proteins, called prions. Infectious diseases caused by bacteria include tuberculosis and pneumonia; viral diseases include HIV and influenza; the most widespread fungal diseases are dermatomycoses; parasitic infections are caused by macroparasites such as protozoa, helminths, trematodes, and cestodes. An example of a prion-caused disease is

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Creutzfeldt–Jakob disease. *Communicable diseases* are infectious diseases that can be transmitted from one infectious person to another, directly or indirectly. Often, we do not make a distinction between infectious diseases and communicable diseases, since many of the infectious diseases are in fact communicable diseases. However, there are diseases that are infectious but not communicable. Tetanus is an example of such a disease. *Transmittable diseases* are infectious diseases that can be transmitted from one person to another through unnatural routes. For instance, Creutzfeldt–Jakob disease can be passed from one patient to another through surgical instruments or transplants. Nonetheless, the distinction between infectious diseases, communicable diseases, and transmittable diseases is subtle, and infectious diseases are often called communicable diseases or transmittable diseases because of their potential to be transmitted from one person to another.

Transmission of infectious diseases may occur through a variety of pathways. According to the means of transmission, infectious diseases are classified as follows:

- **Person-to-person transmitted diseases** are diseases that require **direct** or **indirect contact**. Direct contact includes touching or sexual contact. Diseases that are transmitted through sexual contact are called *sexually transmitted diseases*. Sexually transmitted diseases include HIV, gonorrhea, and syphilis. Indirect contact includes exchange of an infected object, blood, or other body fluids. Influenza can be transmitted through indirect contact.
- **Airborne transmission** occurs on inhalation of infected air. Airborne transmitted diseases include influenza, smallpox, measles, chickenpox, and tuberculosis.
- **Food- and waterborne diseases** are transmitted through ingestion of contaminated food or water. Cholera is a waterborne disease. Foodborne diseases include salmonella and stomach flu.
- **Vector-borne diseases** are transmitted by a vector, most often an arthropod such as a mosquito or tick, or a mollusk such as a snail. Examples of vector-borne diseases are malaria, dengue, and West Nile virus, which are transmitted by mosquitoes.
- **Vertical transmission** occurs when a disease is transmitted through the placenta from a mother to a child before or at birth. Examples of such diseases are HIV, hepatitis B, syphilis, rubella, and herpes simplex virus.

For modeling purposes, we distinguish four types of transmission: *direct*, when the causative pathogen is transmitted from one person to another; *vector-transmitted*, when the causative agent is transmitted from a vector to a human; *environmental transmission*, when a human becomes infected through contact with a pathogen present in the environment; and *vertical*, when the pathogen is transmitted from mother to child at birth. Person-to-person and airborne diseases are usually modeled as directly transmitted when transmission occurs through contact between one person and another. What constitutes a "contact" sufficient for transmission in these diseases depends on the specific disease. In sexually transmitted diseases, sexual contact is necessary, while airborne diseases, which are often modeled as directly transmitted, require a certain degree of physical proximity without the necessity of touching. Modeling vector-borne transmission requires the inclusion of the

dynamics of the vector in addition to the dynamics of the infected individuals. Environmentally transmitted diseases are typically modeled by separately modeling the dynamics of the virus in the environment and the transmission that occurs on contact between an individual and the free pathogen.

A pathogen reservoir is an ecological niche in which a pathogen lives and multiplies. Such a reservoir plays a significant role in the spread of the pathogen. According to their reservoir, the microbial agents are classified as **human**, **animal**, and **environmental**. Human pathogens circulate mostly among humans, and humans play a role in their transmission. Animal pathogens have vertebrate animals as a reservoir, and circulate primarily among animals. Epidemiologically, this is significant, because many such pathogens adapt to infect humans through animal-to-human transmission. Infections that spread from vertebrate animals to humans are called **zoonoses**. Environmental pathogens multiply primarily in the environment (typically water and soil) and spread from there to animal and human populations.

Many infectious diseases have more than one pathway of transmission. For instance, HIV is primarily transmitted through sexual contact, but it can also be transmitted by blood transfusion or needle sharing. Furthermore, HIV can be transmitted vertically at birth from an infected mother to her child. Avian influenza H5N1 is primarily transmitted through direct contact with infected poultry and rarely directly from human to human. However, significant evidence now exists that H5N1 can persist in the environment, and the environmental route of transmission is gaining more importance.

1.3 Basic Definitions in the Epidemiology of Infectious Diseases

There are a number of concepts in epidemiology strictly related to infectious diseases. These concepts play an important role in the construction of mathematical models by adding various features to the model. Some of the most widely used concepts are listed below. Others will be introduced as new models are discussed.

- **Exposed Individuals.** When a healthy individual who is vulnerable to contracting a disease makes a potentially disease-transmitting contact, that individual becomes *exposed*. Exposed individuals may or may not develop the disease. These individuals are typically not infectious. In mathematical models, we often assume that all exposed individuals eventually develop the disease.
- **Infected and Infectious Individuals.** If the pathogen establishes itself in an exposed individual, then that individual becomes *infected*. Infected individuals who can transmit the disease are called *infectious*. Infected individuals may not be infectious during the entire time of being infected.
- **Latent Individuals.** These are individuals that are infected but not yet infectious. The *latent period* is defined as the time from infection to when the host is able to transmit the infectious agent to another individual.
- **Incubation Period.** The incubation period is the period between exposure to an infectious agent and the onset of symptoms of the disease. In infectious diseases, the incubation period is the time required for the infectious agent to multiply

to a threshold necessary to produce symptoms or laboratory evidence of infection. The incubation period does not necessarily coincide with the latent period. For instance, in influenza, individuals become infectious approximately one day *before* they exhibit visible flu symptoms.

- **Incidence.** Incidence is defined as the number of individuals who become ill during a specified interval of time (e.g., one year). Sometimes, incidence is the number of individuals who become ill during a specified interval of time divided by the total population. In most cases, incidence is determined from the number of clinical cases, which underestimates the true incidence, since it ignores the subclinical cases.
- **Prevalence.** The prevalence of a disease is the number of people who have the disease at a specific time. Sometimes, prevalence is defined as the number of people who have the disease at a specific time divided by the total population size.
- **Case Fatality Proportion (CFP).** The case fatality proportion is given as the ratio of people who die of a disease to those who contract it. For instance, as of June 27, 2014, 667 people have been diagnosed with H5N1 avian influenza, and 393 of them have died. The CFP is 0.59.
- **Disease-Induced Mortality.** Disease-induced mortality is the number of people who have died from the disease in one unit of time (e.g., one year) divided by the entire population.

This list is by no means exhaustive. More complete lists of terms used in infectious disease epidemiology can be found in the many excellent books on this subject (e.g., [56]).

1.4 Historical Remarks on Infectious Diseases and Their Modeling

The first significant epidemic described by historians was the plague of Athens, which struck the city of Athens in 430–426 B.C.E. The most precise description of that plague was provided by the scientific historian Thucydides (460–400 B.C.E.) in his *History of the Peloponnesian War*. His description is based on personal experience and includes symptoms, progression of the disease, and numbers of deaths. The causative agent of the plague of Athens is still being debated [131, 134]. Hippocrates (459–337 B.C.E.), in his treatise *Epidemics*, delineates the factors that affected the spread of disease at that time. In 165–180 C.E., the Roman Empire and Egypt were affected by smallpox. Tens of millions of people died [5].

One of the most well documented epidemics that devastated Europe was the Black Death. The Black Death spread throughout the Mediterranean and Europe and is estimated to have killed about 50–100 million people in the years 1348–1350 [5]. Recent DNA evidence from victims in Europe suggests that the pathogen responsible was the *Yersinia pestis* bacterium, which causes several forms of

plague [69]. The Black Death pathogen reappeared in Europe in multiple locations into the nineteenth century. Another disastrous epidemic attacked the Aztec population in the sixteenth century. This smallpox epidemic killed an estimated 35 million people. In the early twentieth century, an influenza pandemic killed an estimated 20 million of the world's population. At present, we still have significant outbreaks of epidemics: The Bombay plague 1905–1906, the 2003 severe acute respiratory syndrome (SARS), and the H1N1 swine flu pandemic of 2009. Threats of epidemics and pandemics exist continually, since viruses mutate very quickly and can jump species barriers, infecting humans, potentially on a mass scale.

Although epidemiology itself has a long history, the mathematical study of diseases and their spread is only about 350 years old. The first statistical study of infectious diseases is attributed to John Graunt (1620–1674), whose 1663 book *Natural and Political Observations Made upon the Bills of Mortality* was concerned with methods of public health statistics. A century later, Daniel Bernoulli used mathematical methods to analyze mortality from smallpox. In 1766, he published what is now considered the first epidemiological model (reviewed in [22]). Bernoulli argued that inoculation with live virus obtained from a mild case of smallpox would reduce the death rate and thereby increase the population, even if the inoculation itself might occasionally be fatal. A contemporary reformulation of Bernoulli's approach in terms of differential equations is given in [55].

In the mid nineteenth century, Louis Pasteur made remarkable breakthroughs in the causes and prevention of disease. He reduced mortality from puerperal fever and created the first vaccines for rabies and anthrax. His medical discoveries provided direct support for the germ theory of disease. Around the same time, the founder of modern bacteriology, Robert Koch, identified the specific causative agents of tuberculosis, cholera, and anthrax, thus giving experimental support to the concept of infectious disease. He was also famous for the development of Koch's postulates. In the late 1800s, science could finally explain the mechanism of how one becomes ill. The concept of passing a bacterial disease through contact between an infected individual and a healthy one became known. This paved the way for the mathematical modeling of infectious diseases.

Mathematical modeling of infectious diseases made significant strides with the work of William Hamer, in the early twentieth century. He was looking for an explanation of the recurrence of measles. It appears that Hamer was the first to use the mass action law in modeling infectious diseases. But it is Sir Ronald Ross who is considered the father of modern mathematical epidemiology. He did pioneering work on malaria and discovered that it is transmitted between humans and mosquitoes. For his work on malaria, Ross received the Nobel Prize in 1902. Sir Ronald Ross was concerned with prevention of malaria. Despite his contributions, he could not convince his contemporaries that malaria could be eradicated simply by reducing the number of mosquitoes. In the second edition of his book *The Prevention of Malaria*, published in 1911, he developed mathematical models of malaria transmission and derived a threshold quantity, nowadays known as the basic reproduction number. In Ross's time, mathematical modeling of infectious diseases was

not well accepted. Nonetheless, Ross was a supporter of the use of mathematical tools in epidemiology. A British Medical Journal quotes him as follows [71]:

> As a matter of fact all epidemiology, concerned as it is with the variation of disease from time to time or from place to place, must be considered mathematically, however many variables are implicated, if it is to be considered scientifically at all. To say that a disease depends upon certain factors is not to say much, until we can also form an estimate as to how largely each factor influences the whole result. And the mathematical method of treatment is really nothing but the application of careful reasoning to the problems at issue.

Mathematical epidemiology was raised to a new level by the model of the spread of infectious diseases, published by Kermack and McKendrick in 1927. In their joint article "A contribution to the mathematical theory of epidemics" [84], Kermack and McKendrick published for the first time a deterministic epidemic model that included susceptible, infected, and removed individuals, much like the one we will discuss in Chap. 2. In fact, their model is an age-since-infection model, whose contemporary version is discussed in Chap. 13. Their model does not include natural birth and death rates and, consequently, models only disease outbreaks. To capture epidemic modeling of diseases that can become established in a population and persist, Kermack and McKendrick published Part II and Part III of their "A contribution to the mathematical theory of epidemics" in 1932 and 1933 respectively. Because of their seminal importance to mathematical epidemiology, the Kermack–McKendrick fundamental trilogy of papers was reprinted in 1991 [85, 86, 87].

Mathematical modeling of infectious diseases gained importance in the 1980s with the advent of the HIV epidemics. Since then, a very large number of models have been created, analyzed, and employed to study the spread of infectious disease. Today, mathematical epidemiology has a steady presence in the research literature, and mathematical modeling is making significant contributions to mathematics and public health [74, 75, 162].

1.5 General Approach to Modeling

A mathematical model is a description of a system using mathematical tools and language. The process of developing mathematical models is called mathematical modeling. We will be concerned with modeling infectious diseases and their spread in populations, but in principle, mathematical modeling can be applied to any system, biological or otherwise. Mathematical models are developed to help explain a system, to study the effects of its various components, and to make predictions about their behavior.

The modeling process, schematically depicted in Fig. 1.1, requires translation of a biological scenario into a mathematical problem. The modeling process typically begins with a clear description of the processes based on the scientist's understanding of the system. The translation into mathematical equations should be made with a specific goal or biological question in mind. Then the verbal description of the system is encoded in mathematical equations. The model should incorporate only

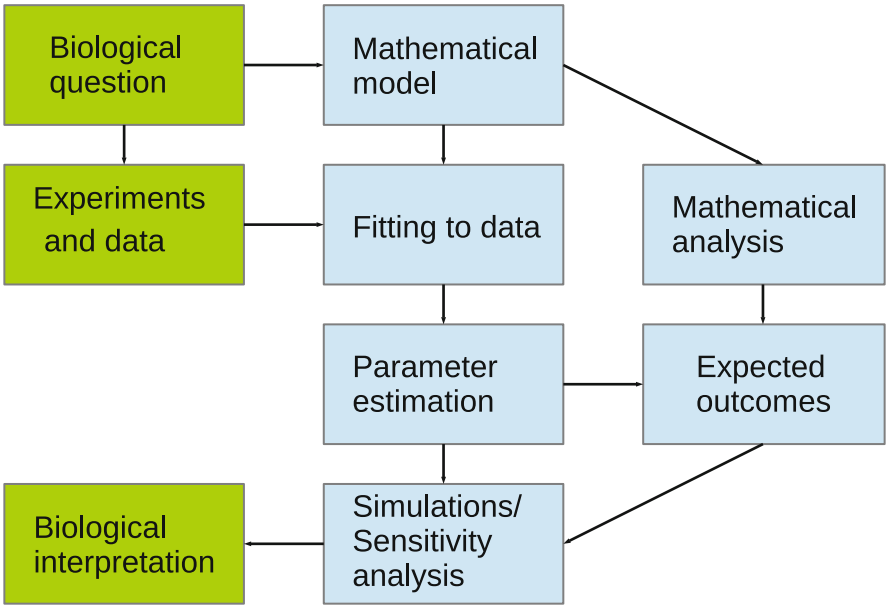

Fig. 1.1 Modeling diagram

those features that are relevant to the specific goal or biological question in mind. Once the model is formulated, it can be investigated with a number of mathematical tools:

- it may be analyzed to produce critical quantities that govern the overall behavior of the solutions;
- it may be fitted to available data or used to stimulate experiments that can produce data;
- parameters of the model may be estimated;
- it may be simulated to understand how important each parameter is to the solution.

After the model has been understood, we must interpret its results in the light of the biological scenario considered and potentially seek the answer of the biological question that was set forth at the beginning. At the very least we must address these questions: What did we learn about the real world from the model? Is our model's message supported by the information about the system?

Mathematical models usually consist of parameters and variables that are connected by relationships. Variables are abstractions of the system's properties that can be quantified or measured. Models can be classified in multiple ways:

- **Linear/nonlinear**. A model is classified as nonlinear if it contains a nonlinear dependence on the variables (e.g., a product of variables). Otherwise, it is classified as linear. The models we will construct and use in this book will be nonlinear.

- **Static/dynamic**. A dynamic model accounts for time-dependent changes in the state of the system, while a static model calculates system quantities assuming that it does not change in time and thus is time-invariant. Dynamic models typically employ differential equations or difference equations. The models that we will consider in this book will be dynamic models.
- **Discrete/continuous**. Discrete models treat time or system states as discrete. Continuous models incorporate time and system states as continuous.
- **Deterministic/stochastic**. A deterministic model is one in which every set of variable states is uniquely determined by the parameters in the model and the initial state of the variables. Stochastic models are characterized by randomness, and variable states are described by probability distributions. The models that we will consider in this book will be deterministic models, although stochastic epidemic models have also been developed and used in the literature.

In this book we will primarily use differential equation models to model the distribution of infectious diseases in a population. The main modeling tool will be ordinary differential equations, but we will introduce epidemic models of delay-differential equations, age-since-infection structured partial differential equations, age-structured partial differential equations, and diffusion partial differential equations. We will also discuss discrete epidemic models. Several types of models used for epidemic modeling will be left out, primarily stochastic epidemic models and network models. For these, you may consult some excellent books and book chapters on the subject (e.g., [7, 124]).

Mathematical models are of great importance in the natural sciences, including biology and epidemiology. They help us to gain new understanding about a system, organize and make sense of biological data, obtain the response behavior of the system, seek optimal performance and intervention strategies, and make predictions about the system. Mathematical models of infectious diseases are the focal point of this book.