

Preface

The main purpose of this book was to explain deterministic, age-structured population dynamics models that appear in demography and epidemiology. The first part of this book addresses pure demographic models, while the second part considers epidemic models for infectious diseases.

It should be of essential importance to human beings to know the laws governing their own reproduction and associated results. In fact, the major problems with which we have been confronted relate to population dynamics, as was clearly recognized by Thomas Robert Malthus in the eighteenth century. From the beginning, the main concerns of demography have extended beyond the variations in population size and distribution to the age structure dynamics of the population. The starting point of modern demography was the life table technique developed to measure human life expectancy in the seventeenth century. In the eighteenth century, Euler developed a difference equation model for human populations to show that an age-structured population with constant fertility and mortality will grow geometrically. Moreover, Euler derived relations among demographic indices under this geometrical growth and suggested that these relations could be used to estimate incomplete data. Some 150 years later, Euler's idea was rediscovered by Sharpe and Lotka at 1911, and modern demography was born. As the human vital rates are under conscious control and strongly depend on historical, social, and economic environmental variations, mathematical studies of human populations have developed on the boundary between the social sciences and life sciences under problematic concerns that differ from those of population biology. It should be, however, noted that the basic mathematical tools used in demography (such as life tables, renewal equations, and the basic reproduction number) are universally applicable to the description of any self-renewing aggregates.

In Chap. 1, we introduce the most basic age-dependent population model, called the *stable population model*. We then explain many resulting facets of the Fundamental Theorem of Demography, because the stable population model is a central tenet in the development of modern demography. Indeed, its revision using functional analysis was the prelude to new, more general developments for structured population dynamics from the end of the 1970s. A crucial point of

demographic applications is that the basic demographic indices cannot be interpreted without the stable population model. Although the operator semigroup theory is a powerful tool for studying structured population models, we here mainly adopt the classical integral equation approach, because the scalar integral equation is more elementary and is a most natural expression for the self-reproduction process of any population. Through the renewal equation, we can define the basic reproduction number, which enables the essential relation between individual vital rates and the Malthusian parameter to be established at the population level. The semigroup approach is, however, briefly introduced in Chap. 10.

In Chap. 2, we examine some linear extensions of the stable population model. First, we show that the Fundamental Theorem can be extended to the multistate stable population model, which was developed during the 1970s and the 1980s by various demographers. However, since the 1990s, the mathematical theory of the basic reproduction number has been developed in the context of mathematical epidemiology. Hence, we must reconsider classical results under the light of the modern R_0 theory. Next, we examine linear extensions that can recognize the marital status of individuals. The linear marriage models are mathematically simple, but practically important, because the marriage phenomenon is crucial to understanding the variation of human reproductivity. Subsequently, we consider the non-autonomous case, where the main tool is the *weak ergodicity* theorem. In particular, if the vital rates are time-periodic, the non-autonomous Lotka–McKendrick system has a periodic solution and, as time evolves, the age profile converges to a periodic age profile independent from the initial data, which reflects the strong ergodicity of the non-autonomous system.

In Chap. 3, one-sex nonlinear age-dependent models are examined. In 1974, Gurtin and MacCamy studied a nonlinear age-dependent population model with density dependence, which triggered a huge amount of research into age-structured population dynamics and motivated the functional analytic approach. However, we again use classical, elementary mathematics to examine the existence and uniqueness of the solution, the bifurcation of steady states and their stability and instability. In particular, we take up a cohort control model (the Easterlin model), because it is a unique nonlinear demographic model that has been empirically tested by demographers. Whether the Easterlin mechanism is a feasible explanation for real human population wave remains a controversial topic.

In Chap. 4, we consider demographic pair formation models. The two-sex problem is a fundamental, but difficult challenge in mathematical demography. Indeed, human population reproduction is essentially a result of mating and pair formation, which are nonlinear interactions between both sexes. Moreover, two-sex models are needed to study sexually transmitted diseases. First, we introduce Kendall's pair formation model without age structure and analyze it using homogeneous dynamical system theory. Next, we introduce the age-dependent pair formation models. Different from the age-independent model, we only have limited results on the age-dependent pair formation models. Although we can prove the existence of a Malthusian solution, its uniqueness and stability remain open.

Finally, we introduce a semigroup approach to the Fredrickson's age-structured pair formation model.

The focus in the second part of this book is on deterministic, continuous-time mathematical models for the spread of infectious diseases. It is well known that humans have repeatedly suffered from major outbreaks of infectious diseases, such as the Black Death pandemic in the 1300s, the Great Plague of London in 1665, the "Spanish" Flu of 1918, and the HIV/AIDS pandemic in the 1980s. Indeed, infectious diseases have played a role in changing the historical course of civilization, as we can see from the devastating decline in the native populations of the New World following contact with infectious diseases from the Old World. Corresponding to these considerable challenges, scientists have developed mathematical theories to understand and control epidemic phenomena since the eighteenth century. In 1760, Daniel Bernoulli submitted a paper to the Academy of Sciences in Paris in which the first age-dependent epidemic model was analyzed to calculate the gain in life expectancy after the elimination of a potentially lethal infectious disease. During the late nineteenth century, the earliest expression of a key idea, the basic reproduction number R_0 , appeared in demography and epidemiology. Finally, between World War I and II, a seminal series of papers by Kermack and McKendrick formulated the basic ideas and modeling methods underlying the mathematical theory of infectious diseases.

Until the 1970s, however, very few researchers were interested in mathematical models for infectious diseases, because in developed countries, little attention was paid to infectious diseases as a result of the epidemiological transition in causes of death. There was increasing interest in cancer as well as heart, brain, and other non-communicable diseases. Indeed, in May 1980, smallpox was declared eradicated in the world. That was a very optimistic era: Many people thought that all infectious diseases would disappear in the near future as a result of progress in the medical sciences. The HIV/AIDS pandemic began in the 1980s, which I believe was the starting point for applying infectious disease modeling to policy decisions, and the study of mathematical epidemiology was strongly promoted from practical point of view. In 1990, we had entered a new epoch in mathematical epidemiology, because Diekmann, Heesterbeek, and Metz published a very influential paper about the definition of the basic reproduction number R_0 . The paper gave the first mathematically rigorous definition of the basic reproduction number. Thereafter, the theoretical development of infectious disease epidemiology underwent marked acceleration, and that process was supported by the theory of structured population dynamics. As the 1990s progressed, it was no longer possible to talk about epidemic dynamics except in terms of R_0 .

In Chap. 5, we thus begin by looking at the early Kermack and McKendrick model, from which the basic ideas and ingredients for epidemic modeling are introduced. The crucial insight is that we cannot precisely interpret the basic ideas and indices of infectious disease epidemiology without knowing the underlying nonlinear population dynamics. The early Kermack–McKendrick infection-age-dependent model was revived by Diekmann, Metz, and Thieme from a modern mathematical point of view in the late 1970s. The key idea of analysis in epidemic models is the basic reproduction

number R_0 and its well-known *threshold principle*, that is, the final size of the epidemic is positive no matter how small the initial infected population is if $R_0 > 1$, whereas the final size becomes zero when the initial size of the infected population goes to zero if $R_0 < 1$. We try to show the threshold principle based on the original definition of the final size given by Kermack and McKendrick, although there are slightly different versions of the formulation. Next, we extend the original model to take into account the heterogeneity of individuals and to state a pandemic threshold theorem. Subsequently, we introduce the demography of the host population and prove the endemic threshold theorem, that is, there exists at least one endemic steady state if $R_0 > 1$, whereas there is no endemic steady state if $R_0 < 1$. This principle, however, does not always hold. We provide examples of the existence of subcritical endemic steady states, even when $R_0 < 1$, in the case that reinfection of the recovered individuals can occur, or if the disease is transmitted by vectors. This type of backward bifurcation is again discussed in Chaps. 7 and 8.

In Chap. 6, we introduce the age-structured SIR epidemic model, which is most useful when applied to real age-dependent data of common childhood infectious diseases. A crucial assumption here is that the host demography is not affected by the presence of diseases, so we can assume that the host population has already attained the stable age distribution. This is not the case if we cannot disregard the disease-induced mortality, as in the case of HIV/AIDS. We again establish the endemic threshold principle based on the basic reproduction number, which is defined by the spectral radius of the next-generation operator. Here, we sketch a functional analytic approach to the age-dependent model, because it is a natural way to deal with the infinite-dimensional problem.

In Chap. 7, we study structured population models for the HIV/AIDS epidemic. Since the 1980s, the HIV/AIDS epidemic has become a worldwide pandemic. This had a big impact on the developments of modern mathematical epidemiology for infectious diseases, because it was the first pandemic of a newly emerging virus since the 1970s—a time when people were very optimistic about the future control of infectious diseases—and it attacked the most scientifically developed countries. HIV/AIDS has a very long incubation period, so we have to take into account the demography of the host population. There also exists a true interaction between demography and epidemiology, because the disease-induced death rate is high and cannot be neglected. First, we summarize the epidemiological features of the HIV/AIDS epidemic and examine mathematical models for the initial invasion phase. We show that the invasion phase of HIV can be described by the stable population model, which can be used to estimate the size of the HIV-infected population based on the observable data. Next, we consider the age-duration-structured HIV epidemic model in a homosexual community and show that there can exist backwardly bifurcated endemic steady states even when $R_0 < 1$, which is a result of the homogeneous force of infection and the disease-induced death rate. Finally, we briefly sketch an age-structured model of in vivo HIV infection, by which we can show that the age-dependent model is a useful framework for studying the infection phenomena at the cell population level and considering effective treatments.

In Chap. 8, we take up three interesting epidemic models that suggest future extensions of classical epidemic models. It is now widely recognized that dynamic changes in host susceptibility due to evolutionary changes in infectious agents and changes in the host immunity distribution due to waning, boosting, or vaccination play important roles in the spread of infectious diseases. In fact, even for traditional common SIR-type childhood diseases such as measles, the natural decay of host immunity can be observed if the environmental virus disappears and the booster effect is lost. First, we consider the Pease model for type A influenza epidemic, which was the first attempt to account for the decay of host immunity due to antigenic changes in the virus population. A remarkable feature is that, for realistic parameter values, the antigenic drift of a dominant virus is a possible mechanism for recurrent outbreaks. Next, we formulate the Kermack–McKendrick reinfection model using the standard age-dependent population dynamics model and examine its basic properties. The potential importance of the Kermack–McKendrick reinfection model is that it can account for variable susceptibility and reinfection, so it is a useful starting point for considering the epidemiological life cycle of individuals. We show that the *reinfection threshold* is given as a threshold number of the fully vaccinated (by incomplete vaccine) system, so the disease cannot be controlled if R_0 exceeds the reinfection threshold. Moreover, subcritical endemic steady states may be created by a backward bifurcation. We show some realistic examples of the *reproductivity enhancement* that can create the backward bifurcation. Finally, we introduce the Aron model for acquired immunity boosted by exposure to infection. This was originally developed to understand the functional relation between the force of infection and the reversion rate and the age prevalence curve of malaria; however, our purpose here is not to give a realistic view of the malaria epidemic, but to show that the age-dependent model is a useful tool for describing the boosting mechanism.

In Chap. 9, we discuss a general theory for the basic reproduction number in heterogeneous environments. The basic reproduction number R_0 plays a central role in structured population dynamics. Although some roots of R_0 can be traced back to the nineteenth century, the specific concept was introduced to the demography literature in 1925. It took a further half century for this number to mature as a key concept in mathematical epidemiology, and it is only recently that the stable population theory has become a popular tool in the field. However, the progress of mathematical epidemiology over the past two decades has been remarkable, and the basic concept and applications of R_0 are now better developed in epidemiology than in demography. In particular, the successful introduction of a general definition of the basic reproduction number for structured populations in the context of epidemic models gave rise to a new epoch in our understanding. Since then, the theory of the basic reproduction number has been developed as a central tenet of both infectious disease epidemiology and general population dynamics. Recently, this basic idea has evolved considerably to allow its application to time-heterogeneous environments. In this chapter, first we formulate a general definition for the basic reproduction number R_0 of structured populations in time-heterogeneous environments. Based on the *generation evolution operator*, we show that the basic

reproduction number can be calculated as the spectral radius of the *next-generation operator* in a constant environment or in a periodic environment. It is stressed that a biological reproduction process is described by a renewal equation, and its basic reproduction number should be uniquely determined. Subsequently, we define the *type-reproduction number* in a time-heterogeneous environment and examine some applications in demography and epidemiology. Finally, we discuss some methods to estimate R_0 from the available data.

In Chap. 10, we explain some mathematical tools commonly applied to demographic and epidemiological population models. As stated above, innovative functional analytic approaches have played a central role in modern developments of structured population dynamics. First, we explain a semigroup approach to consider the stable population model. Using the semigroup setting, the idea of strong ergodicity is extended as the *asynchronous exponential growth* of the semigroup, which can be applied to certain nonlinear problems. We then briefly discuss functional analytic methods for nonlinear population problems. Next, we introduce some results of the positive operator theory, which are useful for studying infinite-dimensional population dynamics. Finally, we summarize some basic results about the Laplace transformation and Volterra integral equation that are used in the previous chapters.

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