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## Preface

This book builds on two previous books on the same topic by the same set of authors (plus one). We feel it is important, right from the start, to make clear how the new book and the old books are related. Both the previous books appeared more than 10 years ago: *Mathematical Epidemiology of Infectious Diseases: model building, analysis and interpretation*, Diekmann and Heesterbeek, John Wiley & Sons, 2000; and: *Stochastic Epidemic Models and their Statistical Analysis*, H. Andersson and Britton Springer-Verlag, 2000. The first took a textbook approach to predominantly deterministic modeling — at least deterministic at the population level, but allowing for stochasticity at the level of individuals. The second had more a monograph-like approach to predominantly mathematical and statistical analysis of stochastic epidemic systems — concentrating on analysis, rather than model building. The present book is based on these two earlier volumes, and in fact makes both of them obsolete. It replaces them with a textbook in the spirit of ‘Diekmann and Heesterbeek,’ and the result is, in our (admittedly biased, but humble) opinion, more valuable than the sum of its parts. The new book integrates the deterministic and stochastic theory and approaches, rather than merely merging the old versions, treating both deterministic and stochastic modeling and analysis of infectious disease dynamics. New topics have been added, and for most topics already treated in one of the predecessors the text has been updated, or revised to improve exposition or integration.

We do not see our book as a mathematics monograph in the sense of instilling in the reader the beauty of the mathematical subject and prove theorems. The value of our book, in our view, is not in doing rigorous mathematics in ‘theorem-proof style,’ and also not in highlighting ‘deep problems’ from a mathematical point of view. The value of the book lies in showing how to be very precise in modeling phenomena in infectious disease dynamics, using mathematical reasoning and analysis. Mathematics is the tool, not the aim. We feel that for our aim the narrative style of doing mathematics is much more efficient in getting the message across. Our aim is to be very rigorous in the *modeling*. If we are being ‘missionary’ at all, it is in trying to get across what (often hidden) assumptions lie behind choices and concepts in modeling, what the consequences are of these choices, and how superficially different concepts are related. The book is about *translating* assumptions concerning biological (behavioral, immunological, demographical, medical) aspects into mathematics, about mathematical *analysis* of certain classes of equations aided by interpretation, about inference from data (measurements, observations), and finally about the *drawing of conclusions* where results from the mathematical and statistical analysis are translated back into biology. We try to offer insight into the relation between assumed mechanisms at the individual level and the resulting phenomena at the population level, both for ‘small’ and ‘large’ populations, and the grey area that lies in between.

Some books offer wisdom. They can be read at leisure in an armchair near a fireplace, provided one pauses every now and then for contemplation. This is not such a book. This book has a zillion exercises and begs to be read with pencil and paper at hand (or perhaps, in a more modern way, using a computer with a program for symbolic manipulation). Some of the exercises one may want to read simply to see what statements they concern. This reading is essential, since usually the exercises are an integral part of the exposition. For many exercises, however, mere reading is not enough: one actually needs to do them. Learning to translate, model, analyze and interpret involves training. Some exercises are ridiculously simple since we have tried not to omit arguments or to tire the reader with details that interrupt the exposition too much; where other writers would state ‘one easily sees’ or ‘a simple argument shows,’ etc., we have inserted an exercise. Other exercises, however, are difficult and elaborate. Many exercises point the reader to caveats, pitfalls, and to similarities and differences in concepts. We anticipate that our readers will feel at times frustrated or even irritated. We therefore provide complete elaborations of all exercises, even of the ‘ridiculously simple ones,’ as an integral part of the book. When a specific exercise seems beyond reach, we advise the reader to only glance at the elaboration as a kind of hint and then try again.

The authors are not sadists who like to pester their readers with exercises, even though it may sometimes feel like that. We are convinced that the reward is enormous. In literally working through this book the reader acquires modeling skills that are also valuable outside of epidemiology, certainly within population dynamics, but even beyond that. The reader receives training in mathematical argumentation, deterministic and stochastic modeling, analysis and inference.

Our hope is that the applied mathematicians learn to see i) the subtleties of model assumptions; ii) that continuous-time models not necessarily take the form of a system of ordinary differential equations; and iii) that often biological interpretation suggests how to proceed with the mathematical analysis.

Our hope is that the theoretical biologists and epidemiologists i) enlarge their tool kit considerably; ii) conclude that sometimes abstraction may actually make things simpler and more transparent; and iii) are inspired by the book to delve deeper into the mathematical tools used.

Our ideal reader feels attracted by these educational aims.

## A BRIEF OUTLINE OF THE BOOK

This book is divided into four parts and 18 chapters. In Part I, we shall introduce the key questions, basic ideas, fundamental concepts and mathematical arguments in as simple a context as possible. This entails in particular that we treat all host individuals as identical with respect to behavior and physiology and that we deal with such concepts as thresholds, final sizes for epidemics, repeated outbreaks, the endemic state and population regulation, aimed both at small and large populations. In this simplest setting we also introduce methods to relate the simple models to data for inference.

When the host population is heterogeneous, we need more advanced mathematics, both for small and large populations. To describe the initial phase of epidemic spread, we can restrict attention to linear mathematics and a systematic approach is possible. The theory, with many examples, is presented in Part II. In addition we

pay some (but not much) attention to nonlinear aspects in a general setting. We shall pay more attention to age structure and spatial structure in separate chapters, because these are particularly relevant for understanding of the population dynamics of many infective agents. To analyze nonlinear structured models one is often forced to make debatable simplifying assumptions. Even then, one needs to resort to tricks, for lack of a powerful general theory. We therefore do not forage deeply into nonlinear theory. For most of the examples in the book we have those infective agents in mind that are usually collectively called ‘microparasites,’ but in Chapter 11 we briefly touch upon some aspects where ‘macroparasites’ differ from ‘microparasites’ (and where they do not), and concentrate on the consequences that these differences and agreements have for the mathematical treatment of invasion. In the final chapter of Part II we pay attention to one of the fundamental and conceptually most difficult aspects of epidemic theory: the myriad ways in which one can model contacts between individuals (Chapter 12).

Part III consists of three chapters. Chapter 13 presents a selection of methods to estimate a value of the basic reproduction number  $R_0$  from a variety of available data. Chapter 14 is a case study and shows in detail how to model the dynamics of a pathogen in a very small dynamic population (nosocomial infections in an Intensive Care Unit of a hospital) based on the type of data that will be routinely available. In Chapter 15 we briefly review computer-intensive statistical methods, that go beyond the methods of inference treated earlier in the book.

Part IV consists, as a consequence of our educational ‘philosophy,’ of complete elaborations for all exercises in three chapters, one for each Part of the book. These elaborations are detailed and sometimes lengthy, and in this way often serve as an extension of the main text. This makes the elaborations an integral part of the book.

It is good to point out that, as another consequence of our educational aim, this book is not an easy reference book in the sense that it can be used to quickly look up certain concepts and definitions or specific results. We have tried to help the reader somewhat in finding relevant information on specific topics of interest by providing a detailed index and by reiterating some concepts and notation in various places.

A final remark concerns our way of referring to the literature. The literature of epidemic theory is extensive and growing steadily. It would be very difficult, bordering on the impossible, to do justice to all valuable contributions to the literature. We have deliberately chosen to write a textbook and not a review of state-of-the-art epidemic theory. As a consequence we have two types of references: local specialist literature (mostly papers) and global general texts for further reading (books). The local literature is included in places where it is necessary for the exposition at that point and is given in footnotes. The global references are given in a short bibliography near the end of the book. They are ordered thematically and include background mathematical reading. To a large extent the choices of books we recommend for background are personal; in the current age we feel that a first impression of an unfamiliar mathematical concept or method can be obtained reliably from the internet, where notably Wikipedia is a good initial source.

The spirit of our view of modeling is captured by the following quote attributed to Picasso:

“Art is the lie that helps us to discover the truth.”

Much, if not all, of our insight has been derived from reading the rich literature and notably from collaborations and discussions with many excellent scientists, colleagues and students over a period of many years. We cannot possibly list them all. We specifically want to mention (in no particular order): Hans Metz, Martin Bootsma, Mick Roberts, Håkan Andersson, Mirjam Kretzschmar, Karl Haderer, Fred Brauer, Mart de Jong, Marc Bonten and Barbara Boldin. In addition, we want to thank the University of Utrecht, Stockholm University, the Netherlands Organization for Scientific Research (NWO) and the Swedish Research Council for financial support during the many years it took us to complete this book.