**STOCHASTIC MODELING
OF
AIDS EPIDEMIOLOGY
AND
HIV PATHOGENESIS**

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STOCHASTIC MODELING OF AIDS EPIDEMIOLOGY AND HIV PATHOGENESIS

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Printed in Singapore.

This book is dedicated to my wife, Shiow-Jen,
my daughter Emy and my son Eden

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PREFACE

It is well recognized that AIDS is the most dangerous disease in the twenty first century threatening the survival of human beings. It has been estimated by WHO (World Health Organization) that by 1998 there are at least 40 million people world-wide who have contracted HIV and at least 12 million people have died of AIDS. From these statistics, obviously the most urgent challenging task is how to control the HIV epidemic. Because of the complexity and seriousness of the disease, for understanding the HIV epidemic and the HIV pathogenesis and for developing efficient strategies for controlling AIDS, mathematical models that take into account the dynamics of the HIV epidemic and the biology of the HIV pathogenesis are definitely needed. With this in mind, many mathematical models for the AIDS epidemic and for the HIV pathogenesis have been developed.

It appears that a large number of mathematical models in the literature are deterministic models in which the state variables are assumed as deterministic functions of time, ignoring completely randomness of the AIDS epidemic and the HIV pathogenesis. On the other hand, statisticians have developed statistical models to estimate the HIV prevalence and to project future AIDS cases, ignoring completely the dynamics of the HIV epidemic. There are several books published on deterministic models of the HIV epidemic and on statistical models; yet books on stochastic models of the AIDS epidemic and the HIV pathogenesis, especially state space models, remain to be published. The purpose of this book is therefore to present a systematic approach to stochastic models, statistical models and state space models for the AIDS epidemic and the HIV pathogenesis.

This book is organized into 9 chapters. In Chapter 1, we will discuss and compare different modeling approaches and illustrate these approaches by using an example from the AIDS epidemic in homosexual populations. To provide some necessary background, in Chapter 2 we will present some basic concepts and basic stochastic processes related to the AIDS epidemic and the HIV pathogenesis. Most of these processes will be used in latter chapters for the development of stochastic models of the AIDS epidemic and the HIV pathogenesis. Having setup the basic background, in Chapter 3, I will proceed to illustrate how to develop stochastic models for the HIV epidemic and illustrate its applications. These are population-based transmission models of the HIV epidemic. In Chapter 4, I will review some basic approaches of statistical models and methods for estimating the HIV infection distribution and the HIV incubation distribution. Because the backcalculation method is a popular statistic model used widely by statisticians, in Chapter 5, I will present and discuss the basic methodology and illustrate its applications. Having developed stochastic models and statistical models, in Chapter 6, I will unify them into state space models and illustrate its application. In Chapters 7-8, I will illustrate how to develop stochastic models of HIV pathogenesis in HIV-infected individuals. By

using these stochastic models, in Chapter 9, I will then proceed to develop some state space models of HIV pathogenesis in HIV-infected individuals.

I originally compiled this book in the fall of 1993 for a seminar course for my students in the Department of Mathematical Sciences at the University of Memphis, Memphis, Tennessee, when I was giving a series of lectures on mathematical models of the AIDS epidemic. These lecture notes have then been up-dated and expanded to include state space models for the AIDS epidemic and stochastic models and state space models for the HIV pathogenesis in HIV-infected individuals. I have also presented some of these materials in a series of lectures in statistical workshops in Taiwan during the summers of 1996, 1997 and 1998. These workshops were organized by National Chung-Hsing University, Taichung, Taiwan (1996), Feng-Chia University, Taichung, Taiwan (1997) and the National Chia-Tung University, Hsin-Chun, Taiwan (1998), and were supported by the National Science Council of the Republic of China, Taiwan. The materials of this book are intended for applied mathematicians, applied probability scientists, biostatisticians, biomedical researchers, AIDS researchers and medical professionals. As an unique feature of the book, I have dealt with in detail stochastic models and state space models of the AIDS epidemic and the HIV pathogenesis. Thus, the book may be used as a reference book for courses in epidemiology, in mathematical modeling and in stochastic models of biomedical systems. It may also be used as a text for seminar courses in biomedical systems and AIDS.

Most of the materials in this book were derived from my own research, and from joint research with my colleagues and friends Dr. R. Byers of CDC, Dr. Zhi-hua Xiang of Scirex Corporation, Dr. S. C. Tang of Cendant Corporation, Dr. S. R. Lee of Atlantic Search Group and Dr. Zheng-zheng Ye of University of Memphis. Most of these researchers were supported by grants from the National Institute of Allergy and Infectious Diseases/National Institutes of Health, Grant No. RO1 AI31869 and R21 AI31869. Without these supports, I would never have engaged in extensive research on AIDS.

I would like to express my sincere appreciation to Prof. Ying-Hen Hsieh of the National Chung-Hsin University, Professors Shen-Ming Lee and Cathy W. S. Chen, Dr. Nae-Sheng Wang and Dr. Mei-Jih Gee of the Feng-Chia University, and Prof. Jack C. Lee of the National Chiao-Tung University in Taiwan for organizing workshops in Taiwan and to the National Science Council of the Republic of China for its support. I want to thank my friends and former students Dr. S. C. Tang, Dr. S. R. Lee, Dr. Zhi-hua Xiang, Dr. Zheng-zheng Ye, Ms. W. H. Fan and Mr. Z. H. Zhu for their help in numerical computations and for drawing many

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Finally I wish to thank Ms. Diane Mittelmeier of the Department of Mathematical Sciences at the University of Memphis for her help in compiling the Latex files, and also Dr. Sen Hu and Ms. T. Yugarani of the World Scientific Publishing Company for their assistance in the publication of my book.

Wai-Yuan Tan

February 2000

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ERRATA

STOCHASTIC MODELING OF AIDS EPIDEMIOLOGY AND HIV PATHOGENESIS

CHAPTER ONE

INTRODUCTION

In Page 8 of Chapter 1, the first paragraph should be read as:

If $c(t) = c$, $q(t) = q$ and $\gamma(t) = \gamma$, then $\lambda(t) = cq - \gamma = \lambda$ is independent of t . (This is the homogeneous model.) In this case, the above solutions can be simplified to:

$$N(t) = N(0)\{[1 - \psi(0)] + \psi(0) \exp(\lambda t)\}^{-\gamma/\lambda},$$

$$I(t) = N(0) \frac{\psi(0) \exp(\lambda t)}{\{[1 - \psi(0)] + \psi(0) \exp(\lambda t)\}^{1+(\gamma/\lambda)}}.$$

Hence, if $\lambda(t) = \lambda$,

$$S(t) = N(t) - I(t) = N(0) \frac{1 - \psi(0)}{\{[1 - \psi(0)] + \psi(0) \exp(\lambda t)\}^{1+(\gamma/\lambda)}}.$$

The above results imply that the fraction $\psi(t)$ behaves along the logistic growth law whereas $I(t)$ behaves along the generalized log logistic growth law [80]. In the homogeneous case, the above results suggest that the progression of these numbers are determined by $\lambda = (cq - \gamma) = \gamma(R_0 - 1)$, where $R_0 = cq/\gamma$ has been referred to as the reproductive number by Anderson et al [78]. This number may be interpreted as the average number an I person will infect if he/she is put in a population of S people. Notice that if $R_0 > 1$ (or $\lambda > 0$), then $\lim_{t \rightarrow \infty} I(t) = 0$, $\lim_{t \rightarrow \infty} \psi(t) = 1$, $\lim_{t \rightarrow \infty} I(t) = 0$ and $\lim_{t \rightarrow \infty} S(t) = \lim_{t \rightarrow \infty} N(t) = 0$. On the other hand, if $R_0 \leq 1$ (or $\lambda \leq 0$), then $\lim_{t \rightarrow \infty} S(t) = \lim_{t \rightarrow \infty} N(t) = N(0)\{1 - \psi(0)\}^{\gamma/|\lambda|}$ which is a positive number.

In page 14 of Chapter 1, equation (1.29) should be changed to:

$$\begin{aligned}
 P(t_{j-1}, t_j) &= \int_{t_{j-1}}^{t_j} \int_{t_0}^t f(t_0, x) g(x, t) dx dt \\
 &= \left\{ \int_{t_0}^{t_j} - \int_{t_0}^{t_{j-1}} \right\} \int_{t_0}^t f(t_0, x) g(x, t) dx dt \\
 &= \int_{t_0}^{t_j} f(t_0, x) \{G(x, t_j) - G(x, t_{j-1})\} dx \quad (1.29)
 \end{aligned}$$