Preface

Analysis of repeated measurement data is a recurrent challenge to statisticians engaged in biological and biomedical applications. For example, data from clinical trials are often longitudinal in nature, with repeated measures of response taken over time. In pharmacokinetic studies, serial measurements of drug concentrations are taken from each participant. By definition, growth studies involve repeated measurements over time. In other applications, measurements on experimental units may be repeated across some other dimension, e.g. spatially rather than temporally.

Methods for *linear* modeling of repeated measurement data are well developed and well documented in the statistical literature; recent accounts include those by Crowder and Hand (1990), Lindsey (1993), and Diggle, Liang and Zeger (1994). In many biological applications, such as pharmacokinetic analysis and studies of growth and decay, however, *nonlinear* modeling is required for meaningful analysis. For this type of modeling, statistical approaches are less well understood, and discussion of appropriate methodology is scattered across a wide literature. Recent years have seen more attention to nonlinear repeated measurement data in the statistical literature; however, the economy of style imposed by many journals means that the material is sometimes presented in a manner that does not make it readily accessible to practicing statisticians. The result is that, although nonlinear modeling of repeated measurement data represents an area of some practical importance, it is one that still appears to engender a good deal of confusion among data analysts.

Our purpose in writing this monograph is to provide a clear delineation of currently available modeling approaches and inferential methods for nonlinear repeated measures. The goal is to make the material accessible to a wide audience. The book is targeted mainly to practicing biostatisticians in industry and academia, and to

graduate students in statistics or biostatistics. We have attempted to keep the exposition at an intermediate level, however, so that the majority of the material should also be accessible to pharmacokineticists and to researchers in the clinical and biological sciences.

The model framework that forms the basis for the inferential methods discussed in the book is that of the hierarchical nonlinear model for continuous response data. This may be viewed as an extension of standard nonlinear modeling techniques to accommodate multiple levels of variability (within and among individuals). Alternatively, it may be regarded as a generalization of the hierarchical linear model framework to include models that are nonlinear in parameters of interest. Hierarchical nonlinear modeling may thus be expected to inherit the computational difficulties intrinsic to both nonlinear regression and to hierarchical linear models. We have certainly found this to be true in practice; computational issues can be formidable at times, so that inference within this framework is not an enterprise to be undertaken lightly. We have included several case studies in later chapters; these represent 'real-life' data sets. We have tried to report analyses in sufficient detail to give the reader a realistic sense, not only of the potential scope and utility of the methods discussed, but also of the potential difficulties. Because computational aspects play a key role in the implementation of all the techniques described in this book, we have tried to include some discussion of available software in each of the relevant chapters. Most of the data sets considered in this book will be available on Statlib, together with code to implement model fits discussed in the text using various software packages.

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