

Preface to the First Edition

This book is written for the pharmacokineticist who performs pharmacokinetic–pharmacodynamic modeling and is occasionally asked to model data that may have nothing to do with pharmacokinetics, but may be important in other areas of drug development. The emphasis of this book is on modeling in drug development since that is my own area of expertise and because ultimately all pharmacokinetic–pharmacodynamic modeling is applied to the therapeutic use of drugs in clinical practice. Throughout this book, pharmacokinetic and pharmacodynamic models will be used without derivation and little in the way of explanation. It is expected that the reader has basic knowledge of pharmacokinetics and simple pharmacodynamic models. If not, the reader is referred to Gibaldi and Perrier (1982), Wagner (1993), or Shargel and Yu (1999) for background material. The reader is also expected to have had a 1-year introductory course in statistics that covers basics of probability, regression, and analysis of variance. A one-semester course in matrix algebra is desired but not needed.

The material in this text begins with a broad overview of modeling, which I call “The Art of Modeling.” This chapter is meant to introduce some of the broad topics associated with modeling, such as model selection criterion, model validation, the importance of good communication, and ethics. The next chapter is “Linear Regression,” which is the foundation for most parametric modeling. From there nonlinear regression is covered, followed by variance models, weighting, and transformations. Lastly, case studies in linear and nonlinear models are presented to illustrate the theory that was presented in the previous chapters. In the material presented to this point, a key assumption is that each subject contributes a single observation to the data set. Next, the book moves to mixed effects models, which allow for multiple observations to be measured on the same individual. The next chapter is “Linear Mixed Effects Models,” which is meant as a brief introduction to the topic. Next is the theory of nonlinear mixed effects models, which form the foundation for population pharmacokinetic–pharmacodynamic modeling. This is followed by a chapter on “Practical Issues in Nonlinear Mixed Effects Modeling,” such as how weight, genetic, or racial information is incorporated into a model. The last chapter in this section presents some case studies

on population pharmacokinetic–pharmacodynamic modeling. A key concept in this book is the inter-relatedness between the materials. For example, nonlinear mixed effects models are simply extensions of linear mixed effects models, which are themselves extensions of linear models, etc. Thus, in order to understand the more complex chapters, it is necessary to understand the foundation material, e.g., what is a variance model and how are they used, how can a linear covariate model be built into a nonlinear mixed effects model, etc.

I wrote this book to be as reader-friendly as possible. Those parts of the book that are nontechnical are written in an almost conversational tone with anecdotes and interesting quotes interspersed throughout. I love quotations and each chapter begins with one I thought especially poignant about the forthcoming material in the chapter. When mathematics is needed, I tried to make those sections self-contained. Variables are defined in each chapter so that the reader does not have to search for “now what is G again?”

John of Salisbury (1115–1180), a twelfth century English philosopher and historian (which was later used by Sir Isaac Newton), once wrote:

We are like dwarves sitting on the shoulders of giants. We see more, and things more distant than they did, not because our sight is superior or because we are taller than they, but because they raise us up, and by their great stature add to ours.

I would like to thank the many giants who helped me understand things I was unclear about during the writing of this text and the reviewers who took the time to read the chapters and offer their opinions on how each could be improved. Without your help I would have been lost in many places. I would like to ask that if you do spot any mistakes or typographical errors to please contact me at peter.bonate@gmail.com.

I would also like to thank my wife, Diana, for her encouragement and my children, Robyn and Ryan, for reminding me that there is indeed more to life than writing “Daddy’s Big Book of Science,” which is what they called this while I was writing it.

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Preface to the Second Edition

I would like to give some thoughts on this second edition and the first edition since its publication. I cannot believe it has been 6 years since the first edition was published. A lot has happened in our field since then. When I first started writing this book in 1999, the word “pharmacometrics” was not in existence. NONMEM was in Version V. There was no pharmacometrics group at the Food and Drug Administration. When the first edition came out, people were using the word but not to any great extent. Pharmacometrics was recognized by the *Journal of Pharmacokinetics and Pharmacodynamics* as a category for manuscript classification but these articles were mostly theoretical. Today, pharmacometrics is recognized as the de facto name for our discipline and encompasses both theoretical and practical modeling and simulation.

It is hard to imagine what will happen between now and the next edition. Whether pharmacometrics becomes just another tool like statistics in the development of drugs or becomes a central basis for drug approval remains to be seen. There is a definite shift in the field toward more difficult, mathematical, and statistically complex analyses. While providing more useful information, they make the entry barrier to our field harder and the methods less accessible to outsiders, which will make communication tougher.

I originally had many names for this book. “Pharmacostatistical Modeling,” “Pharmacometrics,” and “A Heartbreaking Work of Staggering Genius” were all considered, but that last one was already taken. I finally settled on “Pharmacokinetic–Pharmacodynamic Modeling and Simulation” (PKPD-MS) since I thought nobody, except maybe me, used Pharmacostatistical Modeling as a term. Pharmacometrics would be too vague and only people in our field would know what it meant, but even PKPD-MS gave me pause as I thought that even this might be too limiting. Sales for the first edition have proven me wrong in that regard because unless every pharmacokineticist in the world has bought my book then others outside our field are buying copies as well, which can only be positive and increase our discipline’s exposure (no pun intended).

Although I have gotten many compliments on the first edition, there have been complaints. Not enough pharmacodynamic modeling. Nothing on categorical data. Light on simulation aspects. These are valid criticisms. The problem is that the first edition is not the book

I wanted to write, nor is this edition. The second edition is getting close but it is still not there. When I first envisioned the book I wanted to write, it was to be this grand book on models and modeling. But as I started writing I realized the grandiose plans I had made were impractical. There was simply too much material. So I thought I would split it into two editions or volumes. The first edition was what I considered to be the essentials for pharmacokinetic–pharmacodynamic modeling. The second edition, this edition was to cover everything I left out of the first edition. What I did not take into account was burnout and the further maturity of the field. The first edition took me about 5 years to write, as did this edition. Burnout is the beast that is always lurking around the corner and there were times when I could not bear to even open Word to start working. It is surprising how difficult it is to write even this preface, the last thing I do before I send it off to Springer for publishing.

Nevertheless, in writing a book like this, you have to have a cut-off date for writing. I gave myself 5 years to finish what I wanted to include, but it took a year longer, and I still did not get to include everything I wanted: optimal design, a chapter on nonparametric methods like the one on Bayesian methods, and the models themselves. I would like to have written another entire section devoted to models – compartmental, stochastic, physiologically-based, mechanistic, etc. That will be the next edition. For now, the new material tried to cover those topics that exploded over the last few years, like categorical and Bayesian data analysis, and those topics that were not given adequate coverage in the first edition, like simulation. I still tried to follow the guides I set for myself in the first edition: readable, accessible, and useful. I hope I have met these goals and that this will suffice for now.

When I started this book my children, Ryan and Robyn, were toddlers, now they are in their preteens and will be teenagers next year. With the next edition they will be dating and driving. Heaven help me. They do not call it “Daddy’s Big Book of Science” any longer, though I do still get asked why I am always working. I could not have done this without the support of my wife, Diana, bless her heart, who after 25 years together knows how obsessive I can be and helps keep me grounded. I love all of you.

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