

Table of Contents

Preface to the First Edition	xvii
---	-------------

Preface to the Second Edition	xix
--	------------

Chapter 1: The Art of Modeling.....	1
--	----------

Introduction.....	1
Pharmacometrics and Model-Based Drug Development	1
What Is a Model and Why Are They Made?	3
Modeling as Problem Solving.....	5
Type of Models	6
Properties of a Useful Model	8
The Model Development Process	11
Goodness-of-Fit Criteria	14
Residuals and Residual Analysis	14
Goodness-of-Fit Metrics	16
Model Selection	20
General Comments.....	20
Choosing Compartmental Models	21
Bias vs. Variance Trade-off.....	22
Model Discrimination Criteria	22
A Note on Inference	28
Closing Notes	29
Identifiability of Compartmental Models	29
Model Validation	36
The Importance of Effective Communication	40
Good Graphing Practices	41
Writing a Modeling Report.....	46
Ethics in Modeling.....	49
Conclusions	55
Recommended Reading	55
References	56

Chapter 2: Linear Models and Regression.....	61
---	-----------

Introduction.....	61
The Method of Least Squares and Simple Linear Regression.....	61
The Concept of Ordinary Least Squares Applied to the Simple Linear Model.....	61
Maximum Likelihood Estimation of Parameters in a Simple Linear Model	63
Precision and Inference of the Parameter Estimates for the Simple Linear Model.....	63
Regression Through the Origin.....	64
Goodness of Fit Tests for the Simple Linear Model.....	64
Prediction and Extrapolation in the Simple Linear Model	65
Categorical Independent Variables	66
Multiple Linear Regression	67
Model Selection and Sequential Variable Selection Procedures in Multiple Linear Regression.....	68

Collinearity and Ill-Conditioning.....	69
Influence Diagnostics.....	71
Influence in the x -direction	73
Influence in the Y -direction.....	74
Identification of Influential Observations	75
So What Now?	76
Example.....	77
Conditional Models.....	78
<i>EIVs</i> Regression	83
Polynomial Regression	88
Smoothers and Splines.....	89
Smoothers and Locally Weighted Regression (LOESS)	89
Kernel Smoothers.....	90
Spline Interpolation.....	91
Handling Missing Data	92
Types of Missing Data and Definitions	93
Methods for Handling Missing Data: Missing Dependent Variables	93
Methods for Handling Missing Data: Missing Independent Variables	94
Software	98
Summary	99
Recommended Reading	99
References.....	99

Chapter 3: Nonlinear Models and Regression 101

Introduction.....	101
Nonlinear Least Squares	101
Functions with One Variable	102
Functions of Several Variables: The Gradient and Hessian	104
Gradient Algorithms	105
Newton or Newton-Raphson Based Methods.....	106
Gauss-Newton Methods and Its Modifications.....	106
Derivative Free Algorithms	109
Convergence	110
Inferences on the Parameter Estimates	111
Functions of Model Parameters	112
Obtaining Initial Parameter Estimates	114
Ill-Conditioning and Near Singularity	115
Constrained Optimization	119
Influence Diagnostics.....	120
Confidence Intervals for the Predicted Response	122
Incorporating Prior Information into the Likelihood.....	123
Error-in-Variables Nonlinear Regression	124
Summarizing the Results: The Two-Stage Method.....	124
Missing and Censored Data	126
Fitting Discordant Models Among Individuals	126
Software	127
Summary	128

Recommended Reading	129
References	129
Chapter 4: Variance Models, Weighting, and Transformations	131
Introduction	131
Residual Variance Models	131
Testing for Heteroscedasticity	133
Impact of Heteroscedasticity on OLS Estimates	134
Impact of Heteroscedasticity on Parameter Inference	135
Residual Variance Model Parameter Estimation Using Weighted Least-Squares	136
Monte Carlo Comparison of the Methods	140
Residual Variance Model Parameter Estimation Using Maximum Likelihood	141
Model and/or Data Transformations to Normality or Linearity	142
Introduction	142
Testing for Normality	143
Transformations of the Independent Variable	144
Transformations of the Dependent Variable	144
Transform-Both-Sides Approach	146
Transform-Both-Sides Approach With Accompanying Residual Variance Model	147
Conclusions	148
Example: Effect of Weighting on the Pharmacokinetics of Intravenously Administered DFMO	148
Example: Application of the Transform-Both-Sides Approach to a Pharmacodynamic Model	150
Summary	153
Recommended Reading	154
References	154
Appendix 1: Corrected Appendix to Giltinan and Ruppert (1989)	155
Appendix 2: SAS Code Used to Compute the Transform-Both-Sides Parameter Estimates in the XomaZyme-791 Example	156
Chapter 5: Case Studies in Linear and Nonlinear Modeling	157
Introduction	157
Linear Regression Case Study: Allometric Scaling	157
Linear Regression Case Study: Dose Proportionality	158
Linear Regression Case Study: Limited Sampling Strategies	160
Nonlinear Regression Case Study: Pharmacokinetic Modeling of Cocaine After Intravenous, Smoking Inhalation (“Crack Cocaine”), and Intranasal (“Snorting”) Administration	164
Nonlinear Regression Case Study: Pharmacokinetic Modeling of a New Chemical Entity	172
Case Study in Multiple Linear Regression Modeling: Development of a Dosing Formula for Carboplatin	182
Summary	186
Recommended Reading	186
References	186
Chapter 6: Linear Mixed Effects Models	189
Introduction	189
Fixed Effects, Random Effects, and Mixed Effects	189
Sources of Variability	190

A Two-Stage Analysis	191
The General LMEM.....	191
Estimation of the Mixed Effect Model Parameters	194
Inference for the Fixed Effect Parameter Estimates	196
Inference for the Variance Components	196
Estimation of the Random Effects and Empirical Bayes Estimates	197
Model Selection	199
Sensitivity to the Model Assumptions	200
Residual Analysis and Goodness of Fit	201
Influence Analysis	201
Partially Linear Mixed Effects Models (Penalized Regression Splines with Truncated Polynomial Basis Functions).....	203
Penalized Regression Splines Using LMEM Methodology	205
Model Selection and the Choice of Knots	206
Generalized Additive Models	208
Summary	208
Handling Missing and Censored Data	208
Software	209
Example: Analysis of a Food Effect Phase I Clinical Trial.....	209
Example: Modeling Tumor Growth	209
Case Study: Modeling Teicoplanin Pharmacokinetics Using PLMEMs	213
Case Study: Modeling QTc Interval Prolongation	216
Summary	226
Recommended Reading	226
References	226
Appendix 1: SAS Code Used to Model Data in Fig. 6 Using Mixed Model Framework (Quadratic Spline Basis Function)	230
Appendix 2: Tumor Volume Data	231
Chapter 7: Nonlinear Mixed Effects Models: Theory	233
Introduction.....	233
Application of PopPK-PD in Drug Development	233
The Nonlinear Mixed Effects Model	236
The Structural or Base Model.....	237
Modeling Random Effects.....	238
Modeling Between-Subject Variability	238
Modeling Interoccasion Variability	241
Modeling Interstudy Variability	243
Modeling Residual Variability.....	243
Incorporating Fixed and Random Effects into the Structural Model	245
Modeling Covariate Relationships (The Covariate Submodel).....	246
Mixture Models.....	251
Estimation Methods	254
Model Building Techniques.....	261
Covariate Screening Methods.....	263
Manual Covariate Screening Methods.....	264
Direct Covariate Testing	265
Automated Covariate Screening Methods	265

Clinical Relevance and Biological Plausibility.....	267
Comparison of the Covariate Selection Methods	268
Testing the Model Assumptions	269
Precision of the Parameter Estimates and Confidence Intervals	271
Model Misspecification and Violation of the Model Assumptions.....	277
Misspecification of the Structural Model	277
Misspecification of the Distribution of the Random Effects	278
Interaction Between the Structural and Covariate Submodel.....	278
Misspecification of Sample Times.....	279
Model Validation	279
Influence Analysis	285
More on Empirical Bayes Estimates.....	287
Software	288
Summary	295
Recommended Reading	295
References.....	295
 Chapter 8: Nonlinear Mixed Effects Models: Practical Issues.....	 303
Introduction.....	303
The Data Analysis Plan.....	303
Choosing an Estimation Method.....	304
Issues in the Choice of Covariates.....	308
Incorporating Concomitant Medications into the Model.....	309
Incorporating Laboratory Tests into the Model.....	311
Incorporating Weight and Its Variants into the Model.....	313
Incorporating Renal Function into the Model	316
Incorporating a Food Effect into the Model	320
Incorporating Patient Age into the Model	320
Incorporating Formulation Effects and Route of Administration into the Model.....	321
Incorporating Smoking Status into the Model.....	322
Incorporating Race into the Model	322
Incorporating Pregnancy into the Model	325
Incorporating Pharmacogenomics into the Model.....	326
Incorporating Lag-Times into the Model.....	329
Experimental Design Issues.....	330
Theory Based on Monte Carlo Simulation	332
Review of Current Practice.....	333
On the Detection of Subpopulations.....	334
General Guidelines for Sample Collection	335
Toxicokinetic Analyses with Destructive Sampling.....	336
Handling Missing and Censored Data	337
When the Dependent Variable is Missing	337
When the Independent Variable is Missing	339
Internal Validity Checks and Data Clean-Up	345
Problems and Errors.....	345
Consistency of Model Parameter Estimates Across Computer Platforms	349

Mu-Referencing	349
Regulatory Review of Population Analyses	350
Summary	351
Recommended Reading	351
References	352
 Chapter 9: Nonlinear Mixed Effects Models: Case Studies.....	359
Introduction	359
Pharmacodynamic Modeling of Acetylcholinesterase Inhibition	359
Population Pharmacokinetics of Tobramycin.....	362
Introduction	362
Assay Characteristics	362
Patient and Data Summary	363
Data Manipulations and NONMEM Data Base Creation.....	364
Base Model Development	365
Covariate Screening	372
Covariate Model Development	376
Outlier and Influence Analysis	380
Model Validation	382
Simulation of Dosing Regimens and Dosing Recommendations	387
Summary	389
Recommended Reading	389
References	389
 Chapter 10: Bayesian Modeling	391
Introduction	391
Bayesian Methods	391
Bayesian vs. Likelihood Methods.....	391
Bayesian Model Framework.....	392
Introduction to Monte Carlo Integration and Markov Chains.....	393
Examples of Markov Chains in Modeling and Simulation	396
Markov Chain Monte Carlo	397
Choosing the Prior	402
Assessing Convergence.....	404
Model Selection	404
Model Averaging	406
Model Assessment and Inference	406
Software for Bayesian Modeling	407
Examples of Bayesian Modeling Using MCMC in the Literature	407
Bayesian vs. Maximum Likelihood Modeling of Pharmacokinetic–Pharmacodynamic Data.....	408
Pitfalls in Bayesian Pharmacokinetic–Pharmacodynamic Modeling	409
Nonparametric Bayesian Modeling	410
Case Study: Quinidine Pharmacokinetics in Hospitalized Patients.....	410
Case Study: Modeling the Time to Steady-State	416
Summary	421

Recommended Reading	421
References	421
Appendix	425
SAS code to implement the random walk Metropolis algorithm as shown in Fig. 6	425
SAS code to implement the bivariate normal Gibbs sampler as shown in Fig. 9	425
WinBUGS code to implement the time-to-steady-state model in (58)	425

Chapter 11: Generalized Linear Models and Its Extensions 429

Introduction	429
The Exponential Family	429
Generalized Linear Models	430
Logistic Regression for Binary Responses	431
Interpreting the Parameter Estimates	432
Maximum Likelihood Estimation of Parameter Estimates and Parameter Inference	433
Model Diagnostics	434
Influence Diagnostics	435
Alternative Model Formulations	435
Summary	436
Polytomous Logistic Regression	436
Ordinal Logistic Regression	437
The Proportional Odds Model	437
Alternative Model Formulations	440
Poisson Regression of Count or Rate Data	442
Beta Regression	444
Generalized Estimating Equations	444
Generalized Linear and Nonlinear Mixed Effects Models	448
Survival Analysis or Time-to-Event Analysis	451
Introduction	451
Kaplan–Meier Plots	452
Parametric Modeling of Survival Data	453
Accelerated Failure-Time Models	455
Mixed Effect Parametric Models (Frailty)	456
Cox Proportional Hazards Model (Cox Regression)	458
Recurrent Events	460
Competing Events	461
Applications in Pharmacokinetic–Pharmacodynamics	461
Joint Modeling of Longitudinal Endpoints and Time to Event Data	462
Summary	465
Software	465
Reporting of Results	466
Case Study: Assessing the Relationship Between Drug Concentrations and Adverse Events Using Logistic Regression	467
Case Study: Modeling Seizure Frequency as a Function of Drug Treatment (Thall and Vail Dataset) Using GEE Poisson Regression and Generalized Linear Mixed Effects Models	472
Case Study: Ordinal Regression Analysis of Adverse Event Data and Time-To-Progression Following Administration of a New Oncolytic	477

Summary	484
Recommended Reading	484
References	484

Chapter 12: Principles of Simulation 489

Introduction	489
Types of Simulation	490
Steps to Simulation	491
Random Number and Random Variate Generation	491
How Random Numbers are Generated	492
Modern Random Number Generators	493
Testing for Randomness	493
Probability Density Functions	493
Random Variate Generation Using Commercial Software	495
General Approaches for Random Variate Generation	499
Mixture Distributions	517
The Wishart Distribution	518
Distributions Not Examined	519
Conclusions	519
Components of a Clinical Trial Simulation	519
Simulating the Inputs	519
Choosing the Inputs	520
Simulating the Outputs	535
Simulating the Disease Model	541
Simulating the Trial Execution Model	544
Integrating the Submodels into a Unified Whole	550
Analysis and Reporting of Simulation Results	552
Building Credible Simulations Through Validation and Verification	557
Sensitivity Analysis	561
Simulation Software	564
Case Study in Simulation: Application to Sunitinib in Patients with Gastrointestinal Stromal Tumors	567
Summary	575
Recommended Reading	575
References	575
Appendix	581
NL MIXED Syntax for Modeling Serum Albumin Concentrations Using a Mixture Distribution for the Random Effects and Student's <i>T</i> -Distribution for the Residuals	581
SAS Code for Patient Recruitment Simulation	581

Appendix 583

Matrix Theory Relevant to Modeling	583
Taylor Series Approximation	585
Elements of Probability Relevant to Modeling	587
Random Variables and Probability Densities	587
Joint Distributions	589

Maximum Likelihood	591
One-Dimensional Case	591
Multidimensional Case	592
Computer-Intensive Statistical Methods.....	593
Background	593
The Jackknife	594
The Bootstrap	594
Resampling and Permutation Tests.....	601
Summary	602
Differential Equations.....	602
Recommended Reading	607
References.....	607
Index.....	611