
Contents

Preface	xiii
1 Introduction	1
1.1 Motivating examples	2
1.1.1 Pharmacokinetics of cefamandole	2
1.1.2 Population pharmacokinetics of quinidine	3
1.1.3 Growth analysis for soybean plants	7
1.1.4 Bioassay for relaxin by RIA	8
1.2 Model specification	10
1.3 Outline of this book	13
2 Nonlinear regression models for individual data	17
2.1 Introduction	17
2.2 Model specification	19
2.2.1 Basic nonlinear regression model	20
2.2.2 Classical assumptions	20
2.2.3 Generalizations of the classical framework	21
2.3 Inference	26
2.3.1 Ordinary least squares	27
2.3.2 Generalized least squares	28
2.3.3 Variance function estimation	31
2.3.4 General covariance structures	34
2.3.5 Confidence intervals and hypothesis testing	36
2.4 Computational aspects	43
2.4.1 Least squares estimation	43
2.4.2 Variance function estimation	46
2.4.3 General covariance structures	47
2.5 Examples	48
2.6 Related approaches	55
2.6.1 Generalized linear models	55

2.6.2 Generalized estimating equations	56
2.7 Discussion	57
2.8 Bibliographic notes	61
3 Hierarchical linear models	63
3.1 Introduction	63
3.2 Model specification	64
3.2.1 Examples	64
3.2.2 General linear mixed effects model	67
3.2.3 Bayesian model specification	70
3.3 Inference	72
3.3.1 One-way classification with random effects	72
3.3.2 General linear mixed effects model	76
3.3.3 Bayesian inference	80
3.4 Computational aspects	85
3.4.1 EM algorithm	85
3.4.2 Newton–Raphson and the method of scoring	89
3.4.3 Software implementation	90
3.4.4 Examples revisited	90
3.5 Limitations of the normal hierarchical linear model	92
3.6 Bibliographic notes	95
4 Hierarchical nonlinear models	97
4.1 Introduction	97
4.2 General hierarchical nonlinear model	98
4.2.1 Basic model	98
4.2.2 Intra-individual variation	100
4.2.3 Inter-individual variation	101
4.2.4 Summary	108
4.2.5 Time-dependent covariates	109
4.2.6 Accommodation of multiple responses	110
4.3 Model specification	113
4.3.1 Fully parametric model specification	113
4.3.2 Nonparametric model specification	114
4.3.3 Semiparametric model specification	115
4.3.4 Bayesian model specification	117
4.4 Discussion	118
5 Inference based on individual estimates	125
5.1 Introduction	125
5.2 Construction of individual estimates	126
5.2.1 Generalized least squares	126

5.2.2	Pooled estimation of covariance parameters	127
5.2.3	Confidence regions for covariance parameters	128
5.2.4	Examples	129
5.3	Estimation of population parameters	136
5.3.1	Standard two-stage method	137
5.3.2	Global two-stage method	138
5.3.3	Bayesian method	142
5.3.4	General inter-individual models	142
5.3.5	Choice of individual estimates	144
5.4	Computational aspects	144
5.5	Example	145
5.6	Discussion	147
5.7	Bibliographic notes	150
6	Inference based on linearization	151
6.1	Introduction	151
6.2	First-order linearization	152
6.2.1	Approximate model specification	152
6.2.2	Maximum likelihood	154
6.2.3	Generalized least squares	157
6.2.4	Connection with generalized estimating equations	163
6.3	Conditional first-order linearization	164
6.3.1	Approximate model specification	165
6.3.2	Generalized least squares	166
6.3.3	Alternative derivations and methods	173
6.4	Software implementation	174
6.5	Graphical approaches to model selection	175
6.6	Examples	176
6.7	Discussion	186
6.8	Bibliographic notes	190
7	Nonparametric and semiparametric inference	191
7.1	Introduction	191
7.2	Nonparametric maximum likelihood (NPML)	192
7.2.1	Basic ideas	192
7.2.2	Algorithms for finding the maximum likelihood estimate	196
7.2.3	Incorporation of covariates	198
7.3	Smooth nonparametric maximum likelihood (SNP)	200
7.3.1	Estimation	200
7.3.2	Confidence intervals and hypothesis testing	206

7.4	Other approaches	208
7.5	Software implementation	209
7.6	Example	209
7.7	Discussion	214
8	Bayesian inference	217
8.1	Introduction	217
8.2	Model framework	218
8.2.1	General three-stage hierarchical model	218
8.2.2	Simple examples	219
8.3	Inference	220
8.3.1	Inference for the general hierarchical model	220
8.3.2	Conditional distributions	221
8.3.3	From conditionals to marginals: the Gibbs sampler	222
8.3.4	Sampling from conditional distributions	224
8.4	Description of the Gibbs sampler	225
8.4.1	Bivariate case	225
8.4.2	More than two variables	228
8.4.3	Sampling from conditional distributions	229
8.4.4	Convergence and implementation	230
8.5	More complex models	231
8.6	Software implementation	235
8.7	Discussion	235
9	Pharmacokinetic and pharmacodynamic analysis	237
9.1	Introduction	237
9.2	Background	238
9.2.1	Population pharmacokinetics	238
9.2.2	Pharmacodynamic modeling	239
9.3	Population pharmacokinetics of quinidine	242
9.4	Pharmacokinetics of IGF-I in trauma patients	253
9.5	Dose escalation study of argatroban	262
9.6	Discussion	272
10	Analysis of assay data	275
10.1	Introduction	275
10.2	Background on assay methods	276
10.2.1	Radioimmunoassay	276
10.2.2	Enzyme-linked immunosorbent assay	277
10.3	Model framework	278
10.3.1	Model for the mean response	278

10.3.2 Modeling intra-assay response variation	280
10.4 Assessing intra-assay precision	281
10.4.1 Estimation of variance parameters	281
10.4.2 Intra-assay precision profiles	282
10.5 Assay sensitivity and detection limits	288
10.6 Confidence intervals for unknown concentrations	290
10.6.1 Methods of forming confidence intervals	290
10.6.2 Examples	291
10.6.3 Simulation studies	294
10.7 Bayesian calibration	294
10.8 Discussion	297
10.9 Bibliographic notes	298
11 Further applications	299
11.1 Introduction	299
11.2 Comparison of soybean growth patterns	299
11.3 Prediction of bole volume of sweetgum trees	310
11.4 Prediction of strong motion of earthquakes	319
12 Open problems and discussion	327
References	333
Author index	349
Subject index	355