

# Contents

<b>Preface</b>	<b>xvii</b>
<b>Preface to First Edition</b>	<b>xxi</b>
<b>Acknowledgments</b>	<b>xxv</b>
<b>Part I Introduction to Longitudinal and Clustered Data</b>	
<b>1 Longitudinal and Clustered Data</b>	<b>1</b>
1.1 <i>Introduction</i>	1
1.2 <i>Longitudinal and Clustered Data</i>	2
1.3 <i>Examples</i>	5
1.4 <i>Regression Models for Correlated Responses</i>	13
1.5 <i>Organization of the Book</i>	16
1.6 <i>Further Reading</i>	18
<b>2 Longitudinal Data: Basic Concepts</b>	<b>19</b>
2.1 <i>Introduction</i>	19
2.2 <i>Objectives of Longitudinal Analysis</i>	19
2.3 <i>Defining Features of Longitudinal Data</i>	22
	<b>vii</b>

2.4	<i>Example: Treatment of Lead-Exposed Children Trial</i>	31
2.5	<i>Sources of Correlation in Longitudinal Data</i>	36
2.6	<i>Further Reading</i>	44
	<i>Problems</i>	44

## Part II Linear Models for Longitudinal Continuous Data

<b>3</b>	<b>Overview of Linear Models for Longitudinal Data</b>	<b>49</b>
3.1	<i>Introduction</i>	49
3.2	<i>Notation and Distributional Assumptions</i>	50
3.3	<i>Simple Descriptive Methods of Analysis</i>	62
3.4	<i>Modeling the Mean</i>	72
3.5	<i>Modeling the Covariance</i>	74
3.6	<i>Historical Approaches</i>	76
3.7	<i>Further Reading</i>	86
<b>4</b>	<b>Estimation and Statistical Inference</b>	<b>89</b>
4.1	<i>Introduction</i>	89
4.2	<i>Estimation: Maximum Likelihood</i>	90
4.3	<i>Missing Data Issues</i>	94
4.4	<i>Statistical Inference</i>	96
4.5	<i>Restricted Maximum Likelihood (REML) Estimation</i>	101
4.6	<i>Further Reading</i>	104
<b>5</b>	<b>Modeling the Mean: Analyzing Response Profiles</b>	<b>105</b>
5.1	<i>Introduction</i>	105
5.2	<i>Hypotheses Concerning Response Profiles</i>	107
5.3	<i>General Linear Model Formulation</i>	112
5.4	<i>Case Study</i>	117
5.5	<i>One-Degree-of-Freedom Tests for Group by Time Interaction</i>	120
5.6	<i>Adjustment for Baseline Response</i>	124
5.7	<i>Alternative Methods of Adjusting for Baseline Response*</i>	128

5.8	<i>Strengths and Weaknesses of Analyzing Response Profiles</i>	134
5.9	<i>Computing: Analyzing Response Profiles Using PROC MIXED in SAS</i>	136
5.10	<i>Further Reading</i>	140
	<i>Problems</i>	140
<b>6</b>	<b>Modeling the Mean: Parametric Curves</b>	<b>143</b>
6.1	<i>Introduction</i>	143
6.2	<i>Polynomial Trends in Time</i>	144
6.3	<i>Linear Splines</i>	149
6.4	<i>General Linear Model Formulation</i>	152
6.5	<i>Case Studies</i>	154
6.6	<i>Computing: Fitting Parametric Curves Using PROC MIXED in SAS</i>	161
6.7	<i>Further Reading</i>	162
	<i>Problems</i>	163
<b>7</b>	<b>Modeling the Covariance</b>	<b>165</b>
7.1	<i>Introduction</i>	165
7.2	<i>Implications of Correlation among Longitudinal Data</i>	166
7.3	<i>Unstructured Covariance</i>	168
7.4	<i>Covariance Pattern Models</i>	169
7.5	<i>Choice among Covariance Pattern Models</i>	175
7.6	<i>Case Study</i>	180
7.7	<i>Discussion: Strengths and Weaknesses of Covariance Pattern Models</i>	183
7.8	<i>Computing: Fitting Covariance Pattern Models Using PROC MIXED in SAS</i>	184
7.9	<i>Further Reading</i>	186
	<i>Problems</i>	186
<b>8</b>	<b>Linear Mixed Effects Models</b>	<b>189</b>
8.1	<i>Introduction</i>	189
8.2	<i>Linear Mixed Effects Models</i>	194
8.3	<i>Random Effects Covariance Structure</i>	201
8.4	<i>Two-Stage Random Effects Formulation</i>	203
8.5	<i>Choice among Random Effects Covariance Models</i>	208
8.6	<i>Prediction of Random Effects</i>	209

**x** CONTENTS

8.7	<i>Prediction and Shrinkage*</i>	211
8.8	<i>Case Studies</i>	213
8.9	<i>Computing: Fitting Linear Mixed Effects Models Using PROC MIXED in SAS</i>	234
8.10	<i>Further Reading</i>	237
	<i>Problems</i>	237
<b>9</b>	<b>Fixed Effects versus Random Effects Models</b>	<b>241</b>
9.1	<i>Introduction</i>	241
9.2	<i>Linear Fixed Effects Models</i>	241
9.3	<i>Fixed Effects versus Random Effects: Bias-Variance Trade-off</i>	246
9.4	<i>Resolving the Dilemma of Choosing Between Fixed and Random Effects Models</i>	249
9.5	<i>Longitudinal and Cross-sectional Information</i>	252
9.6	<i>Case Study</i>	255
9.7	<i>Computing: Fitting Linear Fixed Effects Models Using PROC GLM in SAS</i>	258
9.8	<i>Computing: Decomposition of Between-Subject and Within-Subject Effects Using PROC MIXED in SAS</i>	260
9.9	<i>Further Reading</i>	262
	<i>Problems</i>	262
<b>10</b>	<b>Residual Analyses and Diagnostics</b>	<b>265</b>
10.1	<i>Introduction</i>	265
10.2	<i>Residuals</i>	265
10.3	<i>Transformed Residuals</i>	266
10.4	<i>Aggregating Residuals</i>	269
10.5	<i>Semi-Variogram</i>	272
10.6	<i>Case Study</i>	273
10.7	<i>Summary</i>	285
10.8	<i>Further Reading</i>	286
	<i>Problems</i>	287

**Part III Generalized Linear Models for Longitudinal Data**

<b>11 Review of Generalized Linear Models</b>	<b>291</b>
11.1 <i>Introduction</i>	291
11.2 <i>Salient Features of Generalized Linear Models</i>	292
11.3 <i>Illustrative Examples</i>	297
11.4 <i>Ordinal Regression Models</i>	310
11.5 <i>Overdispersion</i>	319
11.6 <i>Computing: Fitting Generalized Linear Models         Using PROC GENMOD in SAS</i>	324
11.7 <i>Overview of Generalized Linear Models*</i>	327
11.8 <i>Further Reading</i>	335
<i>Problems</i>	336
<b>12 Marginal Models: Introduction and Overview</b>	<b>341</b>
12.1 <i>Introduction</i>	341
12.2 <i>Marginal Models for Longitudinal Data</i>	342
12.3 <i>Illustrative Examples of Marginal Models</i>	346
12.4 <i>Distributional Assumptions for Marginal Models*</i>	351
12.5 <i>Further Reading</i>	352
<b>13 Marginal Models: Generalized Estimating Equations (GEE)</b>	<b>353</b>
13.1 <i>Introduction</i>	353
13.2 <i>Estimation of Marginal Models: Generalized         Estimating Equations</i>	354
13.3 <i>Residual Analyses and Diagnostics</i>	361
13.4 <i>Case Studies</i>	364
13.5 <i>Marginal Models and Time-Varying Covariates</i>	381
13.6 <i>Computing: Generalized Estimating Equations         Using PROC GENMOD in SAS</i>	385
13.7 <i>Further Reading</i>	390
<i>Problems</i>	391
<b>14 Generalized Linear Mixed Effects Models</b>	<b>395</b>
14.1 <i>Introduction</i>	395
14.2 <i>Incorporating Random Effects in Generalized         Linear Models</i>	396

14.3	<i>Interpretation of Regression Parameters</i>	402
14.4	<i>Overdispersion</i>	409
14.5	<i>Estimation and Inference</i>	410
14.6	<i>A Note on Conditional Maximum Likelihood</i>	412
14.7	<i>Case Studies</i>	414
14.8	<i>Computing: Fitting Generalized Linear Mixed Models Using PROC GLIMMIX in SAS</i>	429
14.9	<i>Further Reading</i>	433
	<i>Problems</i>	434
<b>15</b>	<b>Generalized Linear Mixed Effects Models: Approximate Methods of Estimation</b>	<b>441</b>
15.1	<i>Introduction</i>	441
15.2	<i>Penalized Quasi-Likelihood</i>	443
15.3	<i>Marginal Quasi-Likelihood</i>	445
15.4	<i>Cautionary Remarks on the Use of PQL and MQL</i>	446
15.5	<i>Case Studies</i>	452
15.6	<i>Computing: Fitting GLMMs Using PROC GLIMMIX in SAS</i>	459
15.7	<i>Basis of PQL and MQL Approximations*</i>	466
15.8	<i>Further Reading</i>	470
	<i>Problems</i>	471
<b>16</b>	<b>Contrasting Marginal and Mixed Effects Models</b>	<b>473</b>
16.1	<i>Introduction</i>	473
16.2	<i>Linear Models: A Special Case</i>	473
16.3	<i>Generalized Linear Models</i>	474
16.4	<i>Simple Numerical Illustration</i>	479
16.5	<i>Case Study</i>	480
16.6	<i>Conclusion</i>	484
16.7	<i>Further Reading</i>	486

**Part IV Missing Data and Dropout**

<b>17 Missing Data and Dropout: Overview of Concepts and Methods</b>	<b>489</b>
17.1 <i>Introduction</i>	489
17.2 <i>Hierarchy of Missing Data Mechanisms</i>	491
17.3 <i>Implications for Longitudinal Analysis</i>	499
17.4 <i>Dropout</i>	500
17.5 <i>Common Approaches for Handling Dropout</i>	506
17.6 <i>Bias of Last Value Carried Forward Imputation*</i>	511
17.7 <i>Further Reading</i>	513
<b>18 Missing Data and Dropout: Multiple Imputation and Weighting Methods</b>	<b>515</b>
18.1 <i>Introduction</i>	515
18.2 <i>Multiple Imputation</i>	516
18.3 <i>Inverse Probability Weighted Methods</i>	526
18.4 <i>Case Studies</i>	531
18.5 <i>“Sandwich” Variance Estimator Adjusting for Estimation of Weights*</i>	541
18.6 <i>Computing: Multiple Imputation Using PROC MI in SAS</i>	542
18.7 <i>Computing: Inverse Probability Weighted (IPW) Methods in SAS</i>	547
18.8 <i>Further Reading</i>	550

**Part V Advanced Topics for Longitudinal and Clustered Data**

<b>19 Smoothing Longitudinal Data: Semiparametric Regression Models</b>	<b>553</b>
19.1 <i>Introduction</i>	553
19.2 <i>Penalized Splines for a Univariate Response</i>	554
19.3 <i>Case Study</i>	558
19.4 <i>Penalized Splines for Longitudinal Data</i>	563
19.5 <i>Case Study</i>	565

19.6	<i>Fitting Smooth Curves to Individual Longitudinal Data</i>	570
19.7	<i>Case Study</i>	572
19.8	<i>Computing: Fitting Smooth Curves Using PROC MIXED in SAS</i>	576
19.9	<i>Further Reading</i>	579
<b>20</b>	<b>Sample Size and Power</b>	<b>581</b>
20.1	<i>Introduction</i>	581
20.2	<i>Sample Size for a Univariate Continuous Response</i>	582
20.3	<i>Sample Size for a Longitudinal Continuous Response</i>	584
20.4	<i>Sample Size for a Longitudinal Binary Response</i>	598
20.5	<i>Summary</i>	604
20.6	<i>Computing: Sample Size Calculation Using Pseudo-Data</i>	605
20.7	<i>Further Reading</i>	609
<b>21</b>	<b>Repeated Measures and Related Designs</b>	<b>611</b>
21.1	<i>Introduction</i>	611
21.2	<i>Repeated Measures Designs</i>	612
21.3	<i>Multiple Source Data</i>	616
21.4	<i>Case Study 1: Repeated Measures Experiment</i>	617
21.5	<i>Case Study 2: Multiple Source Data</i>	620
21.6	<i>Summary</i>	625
21.7	<i>Further Reading</i>	626
<b>22</b>	<b>Multilevel Models</b>	<b>627</b>
22.1	<i>Introduction</i>	627
22.2	<i>Multilevel Data</i>	628
22.3	<i>Multilevel Linear Models</i>	630
22.4	<i>Multilevel Generalized Linear Models</i>	641
22.5	<i>Summary</i>	651
22.6	<i>Further Reading</i>	652

<b>Appendix A</b>	<b>Gentle Introduction to Vectors and Matrices</b>	<b>655</b>
<b>Appendix B</b>	<b>Properties of Expectations and Variances</b>	<b>665</b>
<b>Appendix C</b>	<b>Critical Points for a 50:50 Mixture of Chi-Squared Distributions</b>	<b>669</b>
<b>References</b>		<b>671</b>
<b>Index</b>		<b>695</b>