

# *Contents*

<i>Preface</i>	<i>vii</i>
<i>Acronyms</i>	<i>xxi</i>
<i>1 Introduction</i>	<i>1</i>
<i>1.1 Motivating Longitudinal Data Examples</i>	<i>1</i>
<i>1.1.1 Progesterone Data</i>	<i>2</i>
<i>1.1.2 ACTG 388 Data</i>	<i>4</i>
<i>1.1.3 MACS Data</i>	<i>6</i>
<i>1.2 Mixed-Effects Modeling: from Parametric to Nonparametric</i>	<i>7</i>
<i>1.2.1 Parametric Mixed-Effects Models</i>	<i>7</i>
<i>1.2.2 Nonparametric Regression and Smoothing</i>	<i>8</i>
<i>1.2.3 Nonparametric Mixed-Effects Models</i>	<i>10</i>
<i>1.3 Scope of the Book</i>	<i>11</i>
<i>1.3.1 Building Blocks of the NPME Models</i>	<i>11</i>
<i>1.3.2 Fundamental Development of the NPME Models</i>	<i>12</i>
<i>1.3.3 Further Extensions of the NPME Models</i>	<i>13</i>
<i>1.4 Implementation of Methodologies</i>	<i>14</i>
<i>1.5 Options for Reading This Book</i>	<i>14</i>

1.6	<i>Bibliographical Notes</i>	14
2	<i>Parametric Mixed-Effects Models</i>	17
2.1	<i>Introduction</i>	17
2.2	<i>Linear Mixed-Effects Model</i>	17
2.2.1	<i>Model Specification</i>	17
2.2.2	<i>Estimation of Fixed and Random-Effects</i>	19
2.2.3	<i>Bayesian Interpretation</i>	20
2.2.4	<i>Estimation of Variance Components</i>	22
2.2.5	<i>The EM-Algorithms</i>	23
2.3	<i>Nonlinear Mixed-Effects Model</i>	26
2.3.1	<i>Model Specification</i>	26
2.3.2	<i>Two-Stage Method</i>	26
2.3.3	<i>First-Order Linearization Method</i>	29
2.3.4	<i>Conditional First-Order Linearization Method</i>	31
2.4	<i>Generalized Mixed-Effects Model</i>	32
2.4.1	<i>Generalized Linear Mixed-Effects Model</i>	32
2.4.2	<i>Examples of GLME Model</i>	35
2.4.3	<i>Generalized Nonlinear Mixed-Effects Model</i>	37
2.5	<i>Summary and Bibliographical Notes</i>	37
2.6	<i>Appendix: Proofs</i>	38
3	<i>Nonparametric Regression Smoothers</i>	41
3.1	<i>Introduction</i>	41
3.2	<i>Local Polynomial Kernel Smoother</i>	43
3.2.1	<i>General Degree LPK Smoother</i>	43
3.2.2	<i>Local Constant and Linear Smoothers</i>	45
3.2.3	<i>Kernel Function</i>	46
3.2.4	<i>Bandwidth Selection</i>	47
3.2.5	<i>An Illustrative Example</i>	49
3.3	<i>Regression Splines</i>	50
3.3.1	<i>Truncated Power Basis</i>	51
3.3.2	<i>Regression Spline Smoother</i>	52
3.3.3	<i>Selection of Number and Location of Knots</i>	53
3.3.4	<i>General Basis-Based Smoother</i>	54
3.4	<i>Smoothing Splines</i>	54
3.4.1	<i>Cubic Smoothing Splines</i>	55
3.4.2	<i>General Degree Smoothing Splines</i>	56

3.4.3	<i>Connection between a Smoothing Spline and a LME Model</i>	57
3.4.4	<i>Connection between a Smoothing Spline and a State-Space Model</i>	58
3.4.5	<i>Choice of Smoothing Parameters</i>	59
3.5	<i>Penalized Splines</i>	60
3.5.1	<i>Penalized Spline Smoother</i>	60
3.5.2	<i>Connection between a Penalized Spline and a LME Model</i>	62
3.5.3	<i>Choice of the Knots and Smoothing Parameter Selection</i>	62
3.5.4	<i>Extension</i>	62
3.6	<i>Linear Smoother</i>	63
3.7	<i>Methods for Smoothing Parameter Selection</i>	63
3.7.1	<i>Goodness of Fit</i>	64
3.7.2	<i>Model Complexity</i>	65
3.7.3	<i>Cross-Validation</i>	65
3.7.4	<i>Generalized Cross-Validation</i>	66
3.7.5	<i>Generalized Maximum Likelihood</i>	67
3.7.6	<i>Akaike Information Criterion</i>	67
3.7.7	<i>Bayesian Information Criterion</i>	68
3.8	<i>Summary and Bibliographical Notes</i>	68
4	<i>Local Polynomial Methods</i>	71
4.1	<i>Introduction</i>	71
4.2	<i>Nonparametric Population Mean Model</i>	72
4.2.1	<i>Naive Local Polynomial Kernel Method</i>	73
4.2.2	<i>Local Polynomial Kernel GEE Method</i>	75
4.2.3	<i>Fan-Zhang's Two-Step Method</i>	77
4.3	<i>Nonparametric Mixed-Effects Model</i>	78
4.4	<i>Local Polynomial Mixed-Effects Modeling</i>	79
4.4.1	<i>Local Polynomial Approximation</i>	79
4.4.2	<i>Local Likelihood Approach</i>	80
4.4.3	<i>Local Marginal Likelihood Estimation</i>	81
4.4.4	<i>Local Joint Likelihood Estimation</i>	82
4.4.5	<i>Component Estimation</i>	84
4.4.6	<i>A Special Case: Local Constant Mixed-Effects Model</i>	85
4.5	<i>Choosing Good Bandwidths</i>	87

4.5.1	<i>Leave-One-Subject-Out Cross-Validation</i>	87
4.5.2	<i>Leave-One-Point-Out Cross-Validation</i>	88
4.5.3	<i>Bandwidth Selection Strategies</i>	88
4.6	<i>LPME Backfitting Algorithm</i>	90
4.7	<i>Asymptotical Properties of the LPME Estimators</i>	92
4.8	<i>Finite Sample Properties of the LPME Estimators</i>	96
4.8.1	<i>Comparison of the LPME Estimators in Section 4.5.3</i>	98
4.8.2	<i>Comparison of Different Smoothing Methods</i>	99
4.8.3	<i>Comparisons of BCHB-Based versus Backfitting-Based LPME Estimators</i>	101
4.9	<i>Application to the Progesterone Data</i>	103
4.10	<i>Summary and Bibliographical Notes</i>	106
4.11	<i>Appendix: Proofs</i>	107
4.11.1	<i>Conditions</i>	107
4.11.2	<i>Proofs</i>	108
5	<i>Regression Spline Methods</i>	117
5.1	<i>Introduction</i>	117
5.2	<i>Naive Regression Splines</i>	117
5.2.1	<i>The NRS Smoother</i>	118
5.2.2	<i>Variability Band Construction</i>	119
5.2.3	<i>Choice of the Bases</i>	120
5.2.4	<i>Knot Locating Methods</i>	121
5.2.5	<i>Selection of the Number of Basis Functions</i>	121
5.2.6	<i>Example and Model Checking</i>	123
5.2.7	<i>Comparing GCV against SCV</i>	125
5.3	<i>Generalized Regression Splines</i>	127
5.3.1	<i>The GRS Smoother</i>	127
5.3.2	<i>Variability Band Construction</i>	128
5.3.3	<i>Selection of the Number of Basis Functions</i>	129
5.3.4	<i>Estimating the Covariance Structure</i>	129
5.4	<i>Mixed-Effects Regression Splines</i>	130
5.4.1	<i>Fits and Smoother Matrices</i>	131
5.4.2	<i>Variability Band Construction</i>	133
5.4.3	<i>No-Effect Test</i>	134
5.4.4	<i>Choice of the Bases</i>	135
5.4.5	<i>Choice of the Number of Basis Functions</i>	135
5.4.6	<i>Example and Model Checking</i>	139

5.5	<i>Comparing MERS against NRS</i>	142
5.5.1	<i>Comparison via the ACTG 388 Data</i>	142
5.5.2	<i>Comparison via Simulations</i>	143
5.6	<i>Summary and Bibliographical Notes</i>	145
5.7	<i>Appendix: Proofs</i>	146
6	<i>Smoothing Splines Methods</i>	149
6.1	<i>Introduction</i>	149
6.2	<i>Naive Smoothing Splines</i>	149
6.2.1	<i>The NSS Estimator</i>	150
6.2.2	<i>Cubic NSS Estimator</i>	150
6.2.3	<i>Cubic NSS Estimator for Panel Data</i>	152
6.2.4	<i>Variability Band Construction</i>	153
6.2.5	<i>Choice of the Smoothing Parameter</i>	153
6.2.6	<i>NSS Fit as BLUP of a LME Model</i>	155
6.2.7	<i>Model Checking</i>	156
6.3	<i>Generalized Smoothing Splines</i>	157
6.3.1	<i>Constructing a Cubic GSS Estimator</i>	157
6.3.2	<i>Variability Band Construction</i>	158
6.3.3	<i>Choice of the Smoothing Parameter</i>	158
6.3.4	<i>Covariance Matrix Estimation</i>	159
6.3.5	<i>GSS Fit as BLUP of a LME Model</i>	159
6.4	<i>Extended Smoothing Splines</i>	159
6.4.1	<i>Subject-Specific Curve Fitting</i>	159
6.4.2	<i>The ESS Estimators</i>	160
6.4.3	<i>ESS Fits as BLUPs of a LME Model</i>	161
6.4.4	<i>Reduction of the Number of Fixed-Effects Parameters</i>	164
6.5	<i>Mixed-Effects Smoothing Splines</i>	164
6.5.1	<i>The Cubic MESS Estimators</i>	165
6.5.2	<i>Bayesian Interpretation</i>	167
6.5.3	<i>Variance Components Estimation</i>	168
6.5.4	<i>Fits and Smoother Matrices</i>	170
6.5.5	<i>Variability Band Construction</i>	171
6.5.6	<i>Choice of the Smoothing Parameters</i>	172
6.5.7	<i>Application to the Conceptive Progesterone Data</i>	174
6.6	<i>General Degree Smoothing Splines</i>	177
6.6.1	<i>General Degree NSS</i>	177

6.6.2	<i>General Degree GSS</i>	178
6.6.3	<i>General Degree ESS</i>	178
6.6.4	<i>General Degree MESS</i>	181
6.6.5	<i>Choice of the Bases</i>	182
6.7	<i>Summary and Bibliographical Notes</i>	182
6.8	<i>Appendix: Proofs</i>	183
7	<i>Penalized Spline Methods</i>	189
7.1	<i>Introduction</i>	189
7.2	<i>Naive P-Splines</i>	189
7.2.1	<i>The NPS Smoother</i>	190
7.2.2	<i>NPS Fits and Smoother Matrix</i>	192
7.2.3	<i>Variability Band Construction</i>	193
7.2.4	<i>Degrees of Freedom</i>	193
7.2.5	<i>Smoothing Parameter Selection</i>	194
7.2.6	<i>Choice of the Number of Knots</i>	195
7.2.7	<i>NPS Fit as BLUP of a LME Model</i>	202
7.3	<i>Generalized P-Splines</i>	203
7.3.1	<i>Constructing the GPS Smoother</i>	203
7.3.2	<i>Degrees of Freedom</i>	203
7.3.3	<i>Variability Band Construction</i>	204
7.3.4	<i>Smoothing Parameter Selection</i>	204
7.3.5	<i>Choice of the Number of Knots</i>	204
7.3.6	<i>GPS Fit as BLUP of a LME Model</i>	204
7.3.7	<i>Estimating the Covariance Structure</i>	205
7.4	<i>Extended P-Splines</i>	205
7.4.1	<i>Subject-Specific Curve Fitting</i>	205
7.4.2	<i>Challenges for Computing the EPS Smoothers</i>	207
7.4.3	<i>EPS Fits as BLUPs of a LME Model</i>	207
7.5	<i>Mixed-Effects P-Splines</i>	209
7.5.1	<i>The MEPS Smoothers</i>	210
7.5.2	<i>Bayesian Interpretation</i>	212
7.5.3	<i>Variance Components Estimation</i>	214
7.5.4	<i>Fits and Smoother Matrices</i>	216
7.5.5	<i>Variability Band Construction</i>	216
7.5.6	<i>Choice of the Smoothing Parameters</i>	217
7.5.7	<i>Choosing the Numbers of Knots</i>	221
7.6	<i>Summary and Bibliographical Notes</i>	226

7.7	<i>Appendix: Proofs</i>	227
8	<i>Semiparametric Models</i>	229
8.1	<i>Introduction</i>	229
8.2	<i>Semiparametric Population Mean Model</i>	230
8.2.1	<i>Model Specification</i>	230
8.2.2	<i>Local Polynomial Method</i>	231
8.2.3	<i>Regression Spline Method</i>	234
8.2.4	<i>Penalized Spline Method</i>	234
8.2.5	<i>Smoothing Spline Method</i>	237
8.2.6	<i>Methods Involving No Smoothing</i>	239
8.2.7	<i>MACS Data</i>	241
8.3	<i>Semiparametric Mixed-Effects Model</i>	244
8.3.1	<i>Model Specification</i>	244
8.3.2	<i>Local Polynomial Method</i>	247
8.3.3	<i>Regression Spline Method</i>	250
8.3.4	<i>Penalized Spline Method</i>	251
8.3.5	<i>Smoothing Spline Method</i>	253
8.3.6	<i>ACTG 388 Data Revisited</i>	257
8.3.7	<i>MACS Data Revisted</i>	259
8.4	<i>Semiparametric Nonlinear Mixed-Effects Model</i>	264
8.4.1	<i>Model Specification</i>	264
8.4.2	<i>Wu and Zhang's Approach</i>	265
8.4.3	<i>Ke and Wang's Approach</i>	267
8.4.4	<i>Generalizations of Ke and Wang's Approach</i>	270
8.5	<i>Summary and Bibliographical Notes</i>	271
9	<i>Time-Varying Coefficient Models</i>	275
9.1	<i>Introduction</i>	275
9.2	<i>Time-Varying Coefficient NPM Model</i>	276
9.2.1	<i>Local Polynomial Kernel Method</i>	277
9.2.2	<i>Regression Spline Method</i>	279
9.2.3	<i>Penalized Spline Method</i>	281
9.2.4	<i>Smoothing Spline Method</i>	282
9.2.5	<i>Smoothing Parameter Selection</i>	286
9.2.6	<i>Backfitting Algorithm</i>	287
9.2.7	<i>Two-Step Method</i>	288
9.2.8	<i>TVC-NPM Models with Time-Independent Covariates</i>	289

9.2.9	<i>MACS Data</i>	290
9.2.10	<i>Progesterone Data</i>	292
9.3	<i>Time-Varying Coefficient SPM Model</i>	293
9.4	<i>Time-Varying Coefficient NPME Model</i>	295
9.4.1	<i>Local Polynomial Method</i>	296
9.4.2	<i>Regression Spline Method</i>	298
9.4.3	<i>Penalized Spline Method</i>	300
9.4.4	<i>Smoothing Spline Method</i>	303
9.4.5	<i>Backfitting Algorithms</i>	305
9.4.6	<i>MACS Data Revisted</i>	307
9.4.7	<i>Progesterone Data Revisted</i>	309
9.5	<i>Time-Varying Coefficient SPME Model</i>	312
9.5.1	<i>Backfitting Algorithm</i>	312
9.5.2	<i>Regression Spline Method</i>	313
9.6	<i>Summary and Bibliographical Notes</i>	313
10	<i>Discrete Longitudinal Data</i>	315
10.1	<i>Introduction</i>	315
10.2	<i>Generalized NPM Model</i>	316
10.3	<i>Generalized SPM Model</i>	318
10.4	<i>Generalized NPME Model</i>	321
10.4.1	<i>Penalized Local Polynomial Estimation</i>	322
10.4.2	<i>Bandwidth Selection</i>	325
10.4.3	<i>Implementation</i>	327
10.4.4	<i>Asymptotic Theory</i>	328
10.4.5	<i>Application to an AIDS Clinical Study</i>	331
10.5	<i>Generalized TVC-NPME Model</i>	334
10.6	<i>Generalized SAME Model</i>	336
10.7	<i>Summary and Bibliographical Notes</i>	341
10.8	<i>Appendix: Proofs</i>	342
<i>References</i>		347
<i>Index</i>		362