

# Contents

<b>Preface</b>	<b>xi</b>
<b>1 Basic Concepts</b>	<b>1</b>
1.1 Introduction	1
1.2 Examples	3
1.2.1 NHANES 2011–2014 Accelerometry Data	3
1.2.2 COVID-19 US Mortality Data	7
1.2.3 CD4 Counts Data	12
1.2.4 The CONTENT Child Growth Study	15
1.3 Notation and Methodological Challenges	19
1.4 R Data Structures for Functional Observations	20
1.5 Notation	23
<b>2 Key Methodological Concepts</b>	<b>25</b>
2.1 Dimension Reduction	25
2.1.1 The Linear Algebra of SVD	26
2.1.2 The Link between SVD and PCA	27
2.1.3 SVD and PCA for High-Dimensional FDA	28
2.1.4 SVD for US Excess Mortality	29
2.2 Gaussian Processes	34
2.3 Semiparametric Smoothing	36
2.3.1 Regression Splines	37
2.3.1.1 Univariate Regression Splines	37
2.3.1.2 Regression Splines with Multiple Covariates	38
2.3.1.3 Multivariate Regression Splines	39
2.3.2 Penalized Splines	40
2.3.3 Smoothing as Mixed Effects Modeling	43
2.3.4 Penalized Spline Smoothing in NHANES	44
2.3.4.1 Mean PA among Deceased and Alive Individuals	44
2.3.4.2 Regression of Mean PA	46
2.4 Correlation and Multiplicity Adjusted (CMA) Confidence Intervals and Testing	47
2.4.1 CMA Confidence Intervals Based on Multivariate Normality	48
2.4.2 CMA Confidence Intervals Based on Parameter Simulations	50
2.4.3 CMA Confidence Intervals Based on the Nonparametric Bootstrap of the Max Absolute Statistic	51
2.4.4 Pointwise and Global Correlation and Multiplicity Adjusted (CMA) p-values	52
2.4.5 The Origins of CMA Inference Ideas in this Book	53
2.5 Covariance Smoothing	54
2.5.1 Types of Covariance Smoothing	55
2.5.1.1 Covariance Smoothing for Dense Functional Data	56

2.5.1.2	Covariance Smoothing for Sparse Functional Data . . . . .	57
2.5.2	Covariance Smoothing in NHANES . . . . .	58
2.5.3	Covariance Smoothing for CD4 Counts . . . . .	60
<b>3</b>	<b>Functional Principal Components Analysis</b>	<b>65</b>
3.1	Defining FPCA and Connections to PCA . . . . .	65
3.1.1	A Simulated Example . . . . .	66
3.1.1.1	Code for Generating Data . . . . .	67
3.1.1.2	Data Visualization . . . . .	68
3.1.1.3	Raw PCA versus FPCA Results . . . . .	69
3.1.1.4	Functional PCA with Missing Data . . . . .	73
3.1.2	Application to NHANES . . . . .	74
3.1.2.1	Data Description . . . . .	74
3.1.2.2	Results . . . . .	75
3.2	Generalized FPCA for Non-Gaussian Functional Data . . . . .	76
3.2.1	Conceptual Framework . . . . .	78
3.2.2	Fast GFPCA Using Local Mixed Effects . . . . .	80
3.2.3	Binary PCA Using Exact EM . . . . .	83
3.2.4	Functional Additive Mixed Models . . . . .	84
3.2.5	Comparison of Approaches . . . . .	86
3.2.6	Recommendations . . . . .	87
3.3	Sparse/Irregular FPCA . . . . .	88
3.3.1	CONTENT Child Growth Data . . . . .	88
3.3.2	Data Structure . . . . .	90
3.3.3	Implementation . . . . .	91
3.3.4	About the Methodology for Fast Sparse FPCA . . . . .	96
3.4	When PCA Fails . . . . .	96
<b>4</b>	<b>Scalar-on-Function Regression</b>	<b>101</b>
4.1	Motivation and EDA . . . . .	102
4.2	“Simple” Linear Scalar-on-Function Regression . . . . .	106
4.2.1	Model Specification and Interpretation . . . . .	107
4.2.2	Parametric Estimation of the Coefficient Function . . . . .	108
4.2.3	Penalized Spline Estimation . . . . .	113
4.2.4	Data-Driven Basis Expansion . . . . .	118
4.3	Inference in “Simple” Linear Scalar-on-Function Regression . . . . .	123
4.3.1	Unadjusted Inference for Functional Predictors . . . . .	123
4.4	Extensions of Scalar-on-Function Regression . . . . .	126
4.4.1	Adding Scalar Covariates . . . . .	126
4.4.2	Multiple Functional Coefficients . . . . .	127
4.4.3	Exponential Family Outcomes . . . . .	129
4.4.4	Other Scalar-on-Function Regression Models . . . . .	129
4.5	Estimation and Inference Using mgcv . . . . .	130
4.5.1	Unadjusted Pointwise Inference for SoFR Using mgcv . . . . .	132
4.5.2	Correlation and Multiplicity Adjusted (CMA) Inference for SoFR . . . . .	134
<b>5</b>	<b>Function-on-Scalar Regression</b>	<b>143</b>
5.1	Motivation and Exploratory Analysis of MIMS Profiles . . . . .	144
5.1.1	Regressions Using Binned Data . . . . .	145
5.2	Linear Function-on-Scalar Regression . . . . .	151
5.2.1	Estimation of Fixed Effects . . . . .	153

5.2.1.1	Estimation Using Ordinary Least Squares . . . . .	153
5.2.1.2	Estimation Using Smoothness Penalties . . . . .	155
5.2.2	Accounting for Error Correlation . . . . .	159
5.2.2.1	Modeling Residuals Using FPCA . . . . .	161
5.2.2.2	Modeling Residuals Using Splines . . . . .	166
5.2.2.3	A Bayesian Perspective on Model Fitting . . . . .	168
5.3	A Scalable Approach Based on Epoch-Level Regressions . . . . .	170
<b>6</b>	<b>Function-on-Function Regression</b>	<b>175</b>
6.1	Examples . . . . .	176
6.1.1	Association between Patterns of Excess Mortality . . . . .	176
6.1.2	Predicting Future Growth of Children from Past Observations . . . . .	176
6.2	Linear Function-on-Function Regression . . . . .	176
6.2.1	Penalized Spline Estimation of FoFR . . . . .	178
6.2.2	Model Fit and Prediction Using FoFR . . . . .	180
6.2.3	Missing and Sparse Data . . . . .	181
6.3	Fitting FoFR Using <code>pffr</code> in <code>refund</code> . . . . .	181
6.3.1	Model Fit . . . . .	185
6.3.2	Additional Features of <code>pffr</code> . . . . .	187
6.3.3	An Example of <code>pffr</code> in the CONTENT Study . . . . .	190
6.4	Fitting FoFR Using <code>mgcv</code> . . . . .	194
6.5	Inference for FoFR . . . . .	198
6.5.1	Unadjusted Pointwise Inference for FoFR . . . . .	199
6.5.2	Correlation and Multiplicity Adjusted Inference for FoFR . . . . .	201
<b>7</b>	<b>Survival Analysis with Functional Predictors</b>	<b>211</b>
7.1	Introduction to Survival Analysis . . . . .	212
7.2	Exploratory Data Analysis of the Survival Data in NHANES . . . . .	213
7.2.1	Data Structure . . . . .	213
7.2.1.1	Traditional Survival Analysis . . . . .	213
7.2.1.2	Survival Analysis with Functional Predictors . . . . .	215
7.2.2	Kaplan-Meier Estimators . . . . .	217
7.2.3	Results for the Standard Cox Models . . . . .	218
7.3	Cox Regression with Baseline Functional Predictors . . . . .	220
7.3.1	Linear Functional Cox Model . . . . .	220
7.3.1.1	Estimation . . . . .	221
7.3.1.2	Inference on the Functional Coefficient . . . . .	224
7.3.1.3	Survival Curve Prediction . . . . .	232
7.3.2	Smooth Effects of Traditional and Functional Predictors . . . . .	234
7.3.3	Additive Functional Cox Model . . . . .	236
7.4	Simulating Survival Data with Functional Predictors . . . . .	239
<b>8</b>	<b>Multilevel Functional Data Analysis</b>	<b>243</b>
8.1	Data Structure in NHANES . . . . .	244
8.2	Multilevel Functional Principal Component Analysis . . . . .	245
8.2.1	Two-Level Functional Principal Component Analysis . . . . .	245
8.2.1.1	Two-Level FPCA Model . . . . .	246
8.2.1.2	Estimation of the Two-Level FPCA Model . . . . .	246
8.2.1.3	Implementation in R . . . . .	248
8.2.1.4	NHANES Application Results . . . . .	249
8.2.2	Structured Functional PCA . . . . .	252

8.2.2.1	Two-Way Crossed Design . . . . .	253
8.2.2.2	Three-Way Nested Design . . . . .	254
8.3	Multilevel Functional Mixed Models . . . . .	255
8.3.1	Functional Additive Mixed Models . . . . .	258
8.3.2	Fast Univariate Inference . . . . .	259
8.3.3	NHANES Case Study . . . . .	260
8.4	Multilevel Scalar-on-Function Regression . . . . .	262
8.4.1	Generalized Multilevel Functional Regression . . . . .	262
8.4.2	Longitudinal Penalized Functional Regression . . . . .	263
<b>9</b>	<b>Clustering of Functional Data</b> . . . . .	<b>265</b>
9.1	Basic Concepts and Examples . . . . .	265
9.2	Some Clustering Approaches . . . . .	268
9.2.1	K-means . . . . .	268
9.2.1.1	Clustering States Using K-means . . . . .	268
9.2.1.2	Background on K-means . . . . .	271
9.2.2	Hierarchical Clustering . . . . .	271
9.2.2.1	Hierarchical Clustering of States . . . . .	271
9.2.2.2	Background on Hierarchical Clustering . . . . .	274
9.2.3	Distributional Clustering . . . . .	276
9.2.3.1	Distributional Clustering of States . . . . .	276
9.2.3.2	Background on Distributional Clustering . . . . .	276
9.3	Smoothing and Clustering . . . . .	280
9.3.1	FPCA Smoothing and Clustering . . . . .	280
9.3.2	FPCA Smoothing and Clustering with Noisy Data . . . . .	285
9.3.3	FPCA Smoothing and Clustering with Sparse Data . . . . .	287
9.3.4	Clustering NHANES Data . . . . .	289
	<b>Bibliography</b> . . . . .	<b>291</b>
	<b>Index</b> . . . . .	<b>313</b>