
Contents

Preface	xix
Editors	xxi
List of Contributors	xxiii
I Preliminaries	1
1 Introduction and Preliminaries	3
<i>Garrett M. Fitzmaurice, Michael G. Kenward, Geert Molenberghs, Geert Verbeke, and Anastasios A. Tsiatis</i>	
1.1 Introduction	3
1.2 Notation and Terminology	5
1.3 Missing Data Mechanisms	7
1.3.1 Missing completely at random (MCAR)	7
1.3.2 Missing at random (MAR)	8
1.3.3 Not missing at random (NMAR)	10
1.4 Joint Models for Non-Ignorable Missingness	11
1.4.1 Selection models	12
1.4.2 Pattern-mixture models	13
1.4.3 Contrasting selection and pattern-mixture models	13
1.5 Methods for Handling Missing Data	15
1.5.1 Likelihood and Bayesian methods	15
1.5.2 Weighting methods	16
1.5.3 Multiple imputation methods	18
1.6 Concluding Remarks	18
2 Developments of Methods and Critique of ad hoc Methods	23
<i>James R. Carpenter and Michael G. Kenward</i>	
2.1 Introduction	23
2.2 Stream 1: Computational	25
2.2.1 Direct likelihood	26
2.3 Stream 2: Inferential	28

2.3.1	Rubin's classes	28
2.3.2	Missing at random and the conditional predictive distribution	29
2.3.3	Not missing at random and selection models	30
2.4	Stream 3: Semi-Parametric	31
2.5	Critique of <i>Ad Hoc</i> Methods	33
2.5.1	The Isolde trial	34
2.5.2	Complete records analysis	34
2.5.3	Marginal and conditional mean imputation	35
2.5.4	Last observation carried forward	38
2.6	Discussion	41
II	Likelihood and Bayesian Methods	47
3	Introduction and Overview	49
	<i>Michael G. Kenward, Geert Molenberghs, and Geert Verbeke</i>	
3.1	Likelihood and Bayesian Inference and Ignorability	49
3.2	Joint Models	51
4	Perspective and Historical Overview	53
	<i>Michael G. Kenward and Geert Molenberghs</i>	
4.1	Introduction	53
4.2	Selection Models	55
4.2.1	The Heckman model	55
4.2.2	Models for categorical data	56
4.2.3	Models for continuous data	61
4.3	Pattern-Mixture Models	68
4.3.1	Introduction	68
4.3.2	Identifying restrictions	71
4.3.3	An example	74
4.4	Shared-Parameter Models	77
4.4.1	The simple shared-parameter framework	77
4.4.2	The generalized shared-parameter model	79
4.4.3	An example: Congestive heart failure	81
4.5	Concluding Remarks	84
5	Bayesian Methods	91
	<i>Michael J. Daniels and Joseph W. Hogan</i>	
5.1	Introduction	91
5.2	Primer on Bayesian Inference and Its Importance in Incomplete Data . . .	93

5.2.1	Complete data concepts and prior specification	93
5.2.2	The prior distribution and incomplete data	94
5.3	Importance of Correct Model Specification	95
5.4	Multiple Imputation and Bayesian Ignorability with and without Auxiliary Covariates	97
5.4.1	Bayesian ignorability	97
5.4.2	Connection to multiple imputation	98
5.4.3	Bayesian ignorability with auxiliary covariates	98
5.4.4	Fully Bayesian modeling with auxiliary covariates	99
5.5	Bayesian Non-Ignorability	100
5.5.1	Why mixture models?	101
5.5.2	Identifying restrictions	101
5.5.3	Identification by modeling assumptions	103
5.5.4	Some challenges for mixture models	105
5.6	General Computational Issues with the Posterior Distribution	106
5.7	Non-Parametric Bayesian Inference	109
5.8	Concluding Remarks and Future Directions	110
6	Joint Modeling of Longitudinal and Time-to-Event Data	117
	<i>Dimitris Rizopoulos</i>	
6.1	Introduction	117
6.2	Joint Modeling Framework	118
6.2.1	Estimation	121
6.3	Missing Data Mechanism	123
6.4	Parameterizations for the Association Structure	124
6.4.1	Interaction and lagged effects	125
6.4.2	Time-dependent slopes parameterization	126
6.4.3	Cumulative-effects parameterization	126
6.4.4	Random-effects parameterization	127
6.5	Analysis of the AIDS Data	128
6.6	Discussion and Extensions	131
III	Semi-Parametric Methods	137
7	Introduction and Overview	139
	<i>Garrett M. Fitzmaurice</i>	
7.1	Introduction	139
7.2	Inverse Probability Weighting	140
7.3	Double Robustness	141

7.4	Pseudo-Likelihood	143
7.5	Concluding Remarks	145
8	Missing Data Methods: A Semi-Parametric Perspective	149
	<i>Anastasios A. Tsiatis and Marie Davidian</i>	
8.1	Introduction	149
8.2	Semi-Parametric Models and Influence Functions	151
8.3	Review of m -Estimators	153
8.4	Influence Functions and Semi-Parametric Theory	155
8.5	Missing Data and Inverse Probability Weighting of Complete Cases	160
8.6	Density and Likelihood of Missing Data	165
8.7	Geometry of Semi-Parametric Missing Data Models	166
	8.7.1 Observed-data nuisance tangent space	166
	8.7.2 Orthogonal complement of the nuisance tangent space	169
	8.7.3 Augmentation space Λ_2 with two levels of missingness	173
	8.7.4 Augmentation space Λ_2 with monotone missingness	173
8.8	Optimal Observed-Data Estimating Function Associated with Full-Data Estimating Function	174
8.9	Estimating the Missing Data Process	179
8.10	Summary and Concluding Remarks	182
9	Double-Robust Methods	185
	<i>Andrea Rotnitzky and Stijn Vansteelandt</i>	
9.1	Introduction	185
9.2	Data Configuration, Goal of Inference, and Identifying Assumptions	187
9.3	Dimension Reducing Strategies	188
	9.3.1 Regression imputation	188
	9.3.2 Inverse probability weighting	189
9.4	Double-Robust Estimation with Missing-at-Random Data	191
	9.4.1 Double-robust regression imputation estimators	193
	9.4.2 Double-robust sample bounded IPW estimators	195
	9.4.3 Double-robust estimators that are never less efficient than IPW estimators	197
	9.4.4 Double-robust estimators that are efficient over a parametric class of IPWA estimators	199
	9.4.5 Double-robust sample bounded IPW estimators with enhanced efficiency under the missingness model	200
	9.4.6 Double-robust regression imputation estimators with enhanced efficiency under the missingness model	201
9.5	Double-Robust Estimation in Longitudinal Studies with Attrition	202

9.6	Discussion	205
9.6.1	Double-robustness in other data structures	206
9.6.2	Model selection	207
10	Pseudo-Likelihood Methods for Incomplete Data	213
	<i>Geert Molenberghs and Michael G. Kenward</i>	
10.1	Introduction	213
10.2	Notation and Concepts	214
10.3	Pseudo-Likelihood	215
10.3.1	Definition and properties	215
10.3.2	Pairwise pseudo-likelihood	216
10.3.3	Full conditional pseudo-likelihood	216
10.4	Pseudo-Likelihood for Incomplete Data	217
10.4.1	Estimating equations for pairwise likelihood	217
10.4.2	Precision estimation	219
10.4.3	Marginal pseudo-likelihood for binary data	220
10.4.4	The multivariate normal model	222
10.5	Case Studies	224
10.5.1	A clinical trial in onychomycosis	224
10.5.2	Analgesic trial	226
10.6	Concluding Remarks	228
IV	Multiple Imputation	233
11	Introduction	235
	<i>Michael G. Kenward</i>	
11.1	Introduction	235
12	Multiple Imputation: Perspective and Historical Overview	239
	<i>John B. Carlin</i>	
12.1	What Is Multiple Imputation?	239
12.1.1	Introduction	239
12.1.2	A brief overview	240
12.1.3	Illustrative example	242
12.1.4	Early history	246
12.2	Foundations and Basic Theory	247
12.2.1	Multiple imputation as approximate Bayesian inference	248
12.2.2	Proper imputation and repeated sampling properties	250
12.2.3	The role of the missing data model	251

12.2.4	Further technical aspects of multiple imputation inference	251
12.2.5	How many imputations?	253
12.3	Imputation Methods	254
12.3.1	Regression-based imputation	254
12.3.2	Imputation under a joint model	256
12.3.3	Imputation using fully conditional specification	257
12.3.4	General principles for building imputation models	258
12.4	Multiple Imputation in Practice	258
12.4.1	Early applications: Expert imputation of large-scale survey data and other tailored applications	259
12.4.2	Multiple imputation enters the toolkit for practical data analysis . .	260
12.4.3	New applications and outstanding problems	261
13	Fully Conditional Specification	267
	<i>Stef van Buuren</i>	
13.1	Introduction	267
13.1.1	Overview	267
13.1.2	Notation	268
13.2	Practical Problems in Multivariate Imputation	268
13.3	Missing Data Patterns	270
13.3.1	Overview	270
13.3.2	Ways to quantify the linkage pattern	271
13.4	Multivariate Imputation Models	273
13.4.1	Overview	273
13.4.2	Imputation of monotone missing data	274
13.4.3	Imputation by joint modeling	274
13.5	Fully Conditional Specification (FCS)	275
13.5.1	Overview	275
13.5.2	Chained equations: The MICE algorithm	276
13.5.3	Properties	276
13.5.4	Compatibility	277
13.5.5	Number of iterations	279
13.5.6	Performance	279
13.6	Modeling in FCS	280
13.6.1	Overview	280
13.6.2	MAR or NMAR?	281
13.6.3	Model form	282
13.6.4	Predictors	283

13.6.5	Derived variables	285
13.6.6	Visit sequence	287
13.7	Diagnostics	288
13.8	Conclusion	289
14	Multilevel Multiple Imputation	295
	<i>Harvey Goldstein and James R. Carpenter</i>	
14.1	Introduction	295
14.2	Multilevel MI with Mixed Response Types	296
14.2.1	Congeniality	298
14.2.2	Conditioning on fully observed variables in imputation	299
14.2.3	Choice of auxiliary variables	299
14.3	Imputing Mixed Response Types	299
14.3.1	Some comments	302
14.4	Interactions and General Functions of Covariates	303
14.5	Coarsened Data	305
14.6	Record Linkage	307
14.7	Applications	309
14.7.1	Modelling class size data with missing values	309
14.7.2	Individual patient data meta-analysis	311
14.8	Conclusions and Software	313
V	Sensitivity Analysis	317
15	Introduction and Overview	319
	<i>Geert Molenberghs, Geert Verbeke, and Michael G. Kenward</i>	
15.1	Sensitivity	319
15.2	Sensitivity Analysis	320
15.3	Sensitivity Analysis for Parametric Models	320
15.4	Sensitivity Analysis in a Semi-Parametric Setting	322
16	A Likelihood-Based Perspective	325
	<i>Geert Verbeke, Geert Molenberghs, and Michael G. Kenward</i>	
16.1	Introduction	326
16.2	Motivating Examples	327
16.2.1	The orthodontic growth data	327
16.2.2	The Slovenian Public Opinion Survey	328
16.2.3	The rat data	331
16.2.4	A clinical trial in onychomycosis	332

16.2.5	A depression trial	333
16.3	Notation and Concepts	333
16.4	What Is Different When Data Are Incomplete?	334
16.4.1	Problems with model selection and assessment with incomplete data	334
16.4.2	The BRD family of models	335
16.4.3	Model selection and assessment with incomplete data	337
16.4.4	Model assessment for the orthodontic growth data	339
16.4.5	Model assessment for the Slovenian Public Opinion Survey	340
16.5	Interval of Ignorance, Global Influence, and Local Influence	343
16.5.1	Interval of ignorance	344
16.5.2	Global influence	345
16.5.3	Local influence	346
16.5.4	How sensitive is the proportion of “Yes” voters?	350
16.5.5	Local influence for Gaussian data	352
16.5.6	Analysis and sensitivity analysis of the rat data	354
16.5.7	Local influence methods and their behavior	355
16.6	A Sensitivity Analysis for Shared-Parameter Models	357
16.6.1	An extended shared-parameter model	358
16.6.2	SPM models for the onychomycosis data	359
16.6.3	A sensitivity analysis in the shared-parameter framework	362
16.7	A Latent-Class Mixture Model for Incomplete Longitudinal Gaussian Data	364
16.7.1	Classification	366
16.7.2	Analysis of the depression trial	367
16.7.3	A sensitivity analysis for the depression trial	370
16.8	Further Methods	370
16.9	Concluding Remarks	372
17	A Semi-Parametric Perspective	379
	<i>Stijn Vansteelandt</i>	
17.1	Why Semi-Parametric Sensitivity Analyses?	379
17.2	Non-Parametric Identification	381
17.2.1	Why non-parametric identification?	383
17.2.2	The curse of dimensionality	384
17.3	Case Study on Non-Monotone Missing Follow-Up Data	386
17.3.1	International Breast Cancer Study Group, Trial VI	386
17.3.2	Missing data assumptions	387
17.3.3	Estimation	390
17.3.4	Sensitivity analysis with a scalar sensitivity parameter	393

17.3.5	Summarizing the sensitivity analysis results	394
17.3.6	Sensitivity analysis with a vector of sensitivity parameters	396
17.4	Discussion	398
18	Bayesian Sensitivity Analysis	405
	<i>Joseph W. Hogan, Michael J. Daniels, and Liangyuan Hu</i>	
18.1	Introduction	405
18.2	Notation and Definitions	406
18.2.1	Outcome variables, covariates, and response indicators	406
18.2.2	Distributions and models	407
18.2.3	Missing data mechanisms	408
18.3	Inference from Under-Identified Models	409
18.3.1	Overview	409
18.3.2	Assessing veracity of modeling assumptions	410
18.3.3	Non-parametric (non-)identifiability	411
18.3.4	Parametric identification	412
18.3.5	Summary	413
18.4	Sensitivity Analysis from a Bayesian Perspective	414
18.4.1	Likelihood parameterization	414
18.4.2	Sensitivity parameters	415
18.4.3	Priors	417
18.4.4	Summary	418
18.5	Empirical Illustrations	419
18.5.1	Overview	419
18.5.2	Inference about proportions	419
18.5.3	Inference about continuous bivariate distribution	427
18.5.4	Summary	431
18.6	Summary and Discussion	431
19	Sensitivity Analysis with Multiple Imputation	435
	<i>James R. Carpenter and Michael G. Kenward</i>	
19.1	Introduction	435
19.2	Review of NMAR Modelling	437
19.3	Pattern-Mixture Modelling with Multiple Imputation	438
19.3.1	Modifying the MAR imputation distribution	439
19.3.2	Missing covariates	442
19.3.3	Application to survival analysis	444
19.4	Longitudinal Clinical Trial Data	447

19.4.1	Estimands	447
19.4.2	Deviations	449
19.4.3	Change in slope post-deviation: The ‘ Δ -method’	449
19.4.4	Example: Asthma Study	450
19.4.5	Reference-based imputation	452
19.4.6	Constructing joint distributions of pre- and post-deviation data	453
19.4.7	Technical details	454
19.4.8	Example: Asthma Study	456
19.4.9	Distinguishing two types of sensitivity analysis	459
19.5	Approximating a Selection Model by Importance Weighting	460
19.5.1	Algorithm for approximate sensitivity analysis by re-weighting	462
19.5.2	Reliability of the approximation	462
19.5.3	Further developments	465
19.6	Discussion	466
20	The Elicitation and Use of Expert Opinion	471
	<i>Ian R. White</i>	
20.1	Introduction	471
20.2	Background on Elicitation	472
20.3	How to Parameterise a Model to Elicit Expert Opinion	473
20.3.1	Pattern-mixture model	473
20.3.2	Prior	474
20.3.3	Estimation: Sensitivity analysis	474
20.3.4	Estimation: Bayesian analysis	475
20.4	Eliciting Expert Opinion about a Single Sensitivity Parameter	475
20.4.1	The peer review trial	475
20.4.2	Elicitation	477
20.4.3	Analysis	477
20.5	A Spreadsheet to Elicit Expert Opinion about Two Sensitivity Parameters	478
20.5.1	The Down Your Drink (DYD) Trial	478
20.5.2	Spreadsheet for each arm	479
20.5.3	Spreadsheet for the correlation	480
20.5.4	Use of the elicited values	481
20.6	Practicalities	481
20.6.1	Choice of experts	481
20.6.2	Format of elicitation	482
20.6.3	Feedback	482
20.6.4	Pooling experts	484

20.6.5	When to elicit	484
20.7	Discussion	485
VI	Special Topics	491
21	Introduction and Overview	493
	<i>Geert Molenberghs</i>	
21.1	Introduction	493
21.2	Missing Data in Clinical Trials	493
21.3	Missing Data in Surveys	495
21.4	Model Diagnostics	495
22	Missing Data in Clinical Trials	499
	<i>Craig Mallinckrodt</i>	
22.1	Introduction	499
22.1.1	Clinical trials	499
22.1.2	History	501
22.1.3	National Research Council recommendations	502
22.2	Preventing Missing Data	502
22.3	Estimands	504
22.4	Analyses	506
22.4.1	Primary analysis	506
22.4.2	Model diagnostics	507
22.4.3	Sensitivity analyses	508
22.5	Example	512
22.5.1	Data	512
22.5.2	Primary analyses	512
22.5.3	Model diagnostics	513
22.5.4	Sensitivity analyses	515
22.6	Discussion	521
23	Missing Data in Sample Surveys	525
	<i>Thomas R. Belin and Juwon Song</i>	
23.1	Design-Based versus Model-Based Inference	526
23.2	Design-Based versus Model-Based Perspectives on Missing-Data Uncertainty in Estimation of Census Undercount Rates	526
23.3	Weighting and Imputation as Strategies for Unit and Item Nonresponse	528
23.4	Strategies for Producing Imputations	529
23.5	Imputation Based on an Explicit Bayesian Model	529

23.6	Hot-Deck Imputation	531
23.6.1	Hot-deck imputation within adjustment cells	531
23.6.2	Hot-deck imputation using distance metrics	532
23.6.3	Maintaining relationships between variables in multivariate data	533
23.7	Sampling Weights	534
23.8	Multiple Imputation	535
23.9	When the Imputer's Model Differs from the Analyst's Model	536
23.9.1	When the analyst considers fewer variables than the imputer	536
23.9.2	When the imputer assumes more than the analyst	536
23.10	Variance Estimation with Imputed Data	537
23.10.1	Applying explicit variance formulae	537
23.10.2	Resampling methods	538
23.10.3	Multiple imputation	539
23.11	Discussion	539
24	Model Diagnostics	547
	<i>Dimitris Rizopoulos, Geert Molenberghs, and Geert Verbeke</i>	
24.1	Introduction	547
24.2	Multivariate Models	548
24.2.1	Marginal and mixed-effects models	548
24.2.2	Analysis of the AIDS and PBC datasets	550
24.3	Residuals for Mixed-Effects and Marginal Models	551
24.3.1	Definitions	551
24.3.2	Residuals for the AIDS and PBC datasets	552
24.3.3	Dropout and residuals	552
24.4	Multiple Imputation Residuals	555
24.4.1	Fixed visit times	555
24.4.2	Random visit times	557
24.5	Discussion and Extensions	561
	Index	565