

Contents

1	Multiple-Hypothesis Testing Strategy	1
1.1	Multiple-Testing Problems	1
1.1.1	Statistical Hypothesis Testing	1
1.1.2	Sources of Multiplicity	1
1.1.3	Multiple-Testing Taxonomy	3
1.2	Multiple-Testing Approaches	7
1.2.1	Single-Step Procedures	7
1.2.2	Stepwise Procedures	10
1.2.3	Common Gatekeeper Procedure	15
1.2.4	Tree Gatekeeping Procedure	17
1.2.5	Generalized FWER and Partitioning Testing	18
1.2.6	Procedures Controlling False Discovery Rate	21
1.3	Controversies and Challenges	24
1.3.1	Family of Errors	24
1.3.2	Interpretation of Multiple-Testing Results	25
1.3.3	The Spring Water Paradox	25
1.3.4	A Patient's Dilemma with Multiple-Testing	26
1.4	Exercises	27
	Further Readings and References	28
2	Pharmaceutical Decision and Game Theory	31
2.1	Pharmaceutical Decisions	31
2.1.1	Markov Decision Process	31
2.1.2	Dynamic Programming	33
2.1.3	Clinical Development Program	34
2.1.4	R & D Portfolio Optimization	38
2.1.5	Prescription Drug Marketing	40
2.2	Pharmaceutical Games	42
2.2.1	The Game Concept	42
2.2.2	Multiple-Player Game	46
2.2.3	Queuing Game	47

2.2.4	Cooperative Games	49
2.2.5	Sequential Game	50
2.3	Implementation Challenges	53
2.4	Exercises	55
	Further Readings and References	56
3	Noninferiority Trial Design	59
3.1	Concept of Noninferiority Trial	59
3.1.1	Needs for Noninferiority Design	59
3.1.2	Noninferiority Lingo	61
3.1.3	Noninferiority Design Methods	61
3.1.4	Analysis of Noninferiority Trials	65
3.2	Two-Arm Design	66
3.2.1	Fixed-Margin Method	66
3.2.2	λ -Portion Method	69
3.2.3	Synthesis Method	70
3.2.4	Paired Data	74
3.3	Three-Arm Design	75
3.4	The Noninferiority Margin and Regulatory Guidance	77
3.4.1	ICH Guidance	77
3.4.2	FDA Guidance	77
3.4.3	CHMP Guidance	79
3.5	Controversies and Challenges	81
3.5.1	Assay Sensitivity, Constancy and Biocrep	81
3.5.2	Conflicting Noninferiority-Superiority Claims	81
3.5.3	Dilemma of Totality Evidence	82
3.5.4	Superiority-Noninferiority Testing	83
3.5.5	Summary	83
3.6	Exercises	84
	Further Readings and References	85
4	Adaptive Trial Design	87
4.1	Concept of Adaptive Trial Design	87
4.1.1	Reasons for Adaptive Design	87
4.1.2	Hypothesis-Based Adaptive Design	88
4.2	Adaptive Design Methods	92
4.2.1	p -value Weighting Approach	92
4.2.2	Fisher Combination Approach	94
4.2.3	p -value Inversion Approach	95
4.2.4	Error-Spending Approach	96
4.3	Evaluation and Analysis of Adaptive Design	97
4.3.1	Evaluation Matrix	97
4.3.2	Analysis of Adaptive Trial Data	99
4.3.3	Comparison of Adaptive Design Methods	102
4.4	Adaptive Designs in Action	105
4.4.1	Sample Size Reestimation	105

4.4.2	Adaptive Seamless Design	107
4.4.3	Noninferiority-Superiority Adaptive Design	108
4.5	Adaptive Design Debates	109
4.5.1	Sufficiency Principle	109
4.5.2	Minimum Sufficiency Principle and Efficiency	110
4.5.3	Conditionality and Exchangeability Principles.....	110
4.5.4	Equal Weight Principle	111
4.5.5	Consistency of Stagewise Results	111
4.5.6	Adjusted p -value	112
4.5.7	Summary	112
4.6	Exercises	113
	Further Readings and References	114
5	Missing Data Imputation and Analysis	117
5.1	Missing Data Problems	117
5.1.1	Missing Data Issue and Its Impact	117
5.1.2	Missing Data Taxonomy	118
5.2	Analysis Methods for Missing at Random	120
5.2.1	Single Imputation Methods	120
5.2.2	Generalized Linear Mixed Models	120
5.2.3	Expectation-Maximization Algorithm	122
5.2.4	Inverse-Probability Weighting Method	123
5.2.5	Multiple-Imputation Method	125
5.2.6	Weighted Generalized Estimating Equations.....	126
5.3	Analysis Methods for Missing Not at Random	128
5.3.1	Missing Data Frameworks	128
5.3.2	Selection Model	130
5.3.3	Pattern-Mixture Model	131
5.3.4	Shared-Parameter Models	131
5.4	Analysis Examples Using SAS and SOLAS	133
5.4.1	Likelihood Ignorable Analysis	134
5.4.2	Multiple-Imputation Method	134
5.4.3	EM Algorithm Using SAS	136
5.4.4	SOLAS for Missing Data Analysis	136
5.5	Controversies, Challenges, and Recommendations.....	137
5.5.1	Comparisons of Different Methods	137
5.5.2	How to Implement Missingness	138
5.5.3	Regulatory Perspective	139
5.5.4	Recommendations for Clinical Trials.....	140
5.6	Exercises	142
	Further Readings and References	142
6	Multivariate and Multistage Survival Data Modeling.....	145
6.1	Introduction to Survival Data Modeling	145
6.1.1	Basic Terms in Survival Analysis	145
6.1.2	Maximum Likelihood Method	146
6.1.3	Overview of Survival Model	147

6.2	Frailty Model	151
6.2.1	Univariate Frailty Models	151
6.2.2	Multivariate Frailty Models	152
6.2.3	The Shared Frailty Copula	152
6.2.4	The Correlated Frailty Copula	153
6.3	First-Hitting-Time Model	153
6.3.1	Wiener Process and First Hitting Time	153
6.3.2	Covariates and Link Function	154
6.3.3	Parameter Estimation and Inference	155
6.3.4	Applications of First-Hitting-Time Model	156
6.3.5	Multivariate Model with Biomarkers	157
6.4	Multistage Model.....	159
6.4.1	General Framework of Multistage Model	159
6.4.2	Covariates and Treatment Switching	161
6.4.3	Latent Process and Competing Risks	163
6.4.4	Competing Risks in Progressive Disease	167
6.4.5	Longitudinal Multivariate Model	169
6.5	Challenges and Controversies	170
6.6	Exercises	172
	Further Readings and References	172
7	Meta-Analysis	175
7.1	Concept of Meta-Analysis	175
7.1.1	The Art and Science of Meta-Analysis	175
7.1.2	Study Endpoints	176
7.1.3	Basic Methods	179
7.2	Subject-Based Meta-Analysis	180
7.3	Study-Based Meta-Analysis	180
7.3.1	The Fixed-Effect Model	180
7.3.2	Assessing Heterogeneity	184
7.3.3	Random-Effect Model	184
7.3.4	Mixture Model for Relative Risk	186
7.4	Meta-Analysis in Complex Settings	190
7.4.1	Individual and Aggregate Data Mixtures	190
7.4.2	Mixture of Matched and Unmatched Pairs	193
7.4.3	p -value Combination Approaches	194
7.4.4	Cumulative Meta-Analysis	195
7.5	Graphical Presentations	197
7.5.1	Funnel Plots	197
7.6	Controversies and Challenges	198
7.6.1	Inclusion of Studies	198
7.6.2	Inclusion, Analysis, and Reporting Bias.....	199
7.6.3	Inconsistency in Weight Selection	200
7.7	Exercises	201
	Further Readings and References	202

8	Data Mining and Signal Detection	205
8.1	Common Data Mining Methods	205
8.1.1	Supervised, Unsupervised, and Reinforcement Learning	205
8.1.2	Link Analysis	206
8.1.3	Nearest-Neighbors Method	208
8.1.4	Kernel Method	209
8.1.5	Support Vector Machine	209
8.1.6	Tree Methods	210
8.1.7	Artificial Neural Network	213
8.1.8	Unsupervised to Supervised Learning	215
8.1.9	K-Means Algorithm	216
8.1.10	Genetic Programming	217
8.1.11	Cellular Automata Method	217
8.1.12	Agent-Based Models	218
8.2	Signal Detection and Analysis	219
8.2.1	Pharmacovigilance	219
8.2.2	Traditional Hypothesis Test	220
8.2.3	Sequential Probability Ratio Test	221
8.2.4	Disproportional Analysis	223
8.2.5	Group Sequential Method	226
8.2.6	Data Mining Approach	226
8.3	Challenges	227
8.4	Exercises	229
	Further Readings and References	229
9	Monte Carlo Simulation	233
9.1	Random Number Generation	233
9.1.1	Inverse c.d.f Method	233
9.1.2	Acceptance-Rejection Methods	234
9.1.3	Markov Chain Monte Carlo	235
9.2	Clinical Trial Simulation	236
9.2.1	Adaptive Trial Simulation	236
9.2.2	Dynamic Drug Supply	238
9.2.3	Bootstrapping Methods	240
9.3	Molecular Design and Simulation	242
9.3.1	The Landscape of Molecular Design	242
9.3.2	The Drug-Likeness Concept	243
9.3.3	Molecular Docking	245
9.4	Biological Pathway Simulation	248
9.4.1	Biology Pathways	248
9.4.2	Petri Nets	249
9.4.3	Biological Pathway Simulations	251
9.5	PK and PD Modeling and Simulation	252
9.5.1	Pharmacokinetic Simulation	252
9.5.2	Pharmacodynamic Simulation	255

9.6	Implementation Challenges	257
9.7	Exercises	258
	Further Readings and References	259
10	Bayesian Methods and Applications	261
10.1	Bayesian Paradigm	261
10.1.1	Bayesian Inference	261
10.1.2	Model Selection	266
10.1.3	Hierarchical Model	267
10.1.4	Bayesian Decision-Making	268
10.1.5	Bayesian Approach to Multiplicity	269
10.1.6	Bayesian Computation	272
10.2	Applications of Bayesian Methods	275
10.2.1	Clinical Trial Design	275
10.2.2	Bayesian Adaptive Trial	276
10.2.3	Safety Signal Detection	279
10.2.4	Missing-Data Handling	281
10.2.5	Meta-Analysis	281
10.2.6	Noninferiority Design	282
10.2.7	Disease Mapping	284
10.3	Controversies and Debates	284
10.3.1	Internal Consistency	285
10.3.2	Subjectivity	287
10.4	Exercises	287
	Further Readings and References	288
Index	291