

# Contents

<b>1</b>	<b>Overview of the Book</b>	1
<b>2</b>	<b>Introduction: Heterogeneity in Medicine</b>	7
2.1	Example: Plasma Concentration of Beta-Carotene	11
2.1.1	Identification of a Latent Structure	11
2.1.2	Including Covariates	13
2.2	Computation	15
2.3	Example: Analysis of Heterogeneity in Drug Development	18
2.3.1	Basic Pharmacokinetic Concepts	18
2.3.2	Pharmacokinetic Parameters	19
2.3.3	First-Order Compartment Models	20
2.3.4	Population Pharmacokinetics	21
2.3.5	Theophylline Pharmacokinetics	22
2.4	A Note of Caution	28
<b>3</b>	<b>Modeling Count Data</b>	29
3.1	Example: Morbidity in Northeast Thailand	29
3.2	Parametric Mixture Models	30
3.3	Finite Mixture Models	33
3.3.1	Diagnostic Plots for Finite Mixture Models	34
3.3.2	A Finite Mixture Model for the Illness Spell Data	34
3.3.3	Estimating the Number of Components	36
3.4	Computation	39
3.4.1	Combination of VEM and EM Algorithms	39
3.4.2	Using the EM Algorithm	41
3.4.3	Estimating the Number of Components	42
3.5	Including Covariates	43
3.5.1	The Ames Test	43
3.5.2	Poisson and Negative Binomial Regression Models	47
3.5.3	Covariate-Adjusted Mixture Model for the Ames Test Data	49

3.6	Computation .....	51
3.6.1	Fitting Poisson and Negative Binomial Regression Models with SAS .....	51
3.6.2	Fitting Poisson and Negative Binomial Regression Models with R .....	52
3.6.3	Fitting Finite Mixture Models with the Package CAMAN ..	53
<b>4</b>	<b>Theory and Algorithms .....</b>	<b>55</b>
4.1	The Likelihood of Finite Mixture Models .....	55
4.2	Convex Geometry and Optimization .....	56
4.2.1	Derivatives and Directional Derivatives of Convex Functions .....	61
4.3	Application to the Flexible Support Size Case .....	64
4.3.1	Geometric Characterization.....	64
4.3.2	Algorithms for Flexible Support Size .....	69
4.3.3	VEM Algorithm: Computation .....	70
4.4	The Fixed Support Size Case .....	72
4.4.1	Fixed Support Size: The Newton–Raphson Algorithm .....	72
4.4.2	A General Description of the EM Algorithm .....	73
4.4.3	The EM Algorithm for Finite Mixture Models .....	74
4.4.4	EM Algorithm: Computation .....	77
4.4.5	A Hybrid Mixture Algorithm .....	79
4.4.6	The EM Algorithm with Gradient Update .....	80
4.5	Estimating the Number of Components .....	82
4.5.1	Graphical Techniques.....	82
4.5.2	Testing for the Number of Components .....	83
4.5.3	The Bootstrap Approach .....	84
4.6	Adjusting for Covariates .....	87
4.6.1	Generalized Linear Models .....	87
4.6.2	The EM Algorithm for Covariate-Adjusted Mixture Models .....	91
4.6.3	Computation: Vitamin A Supplementation Revisited .....	93
4.6.4	An Extension of the EM Algorithm with Gradient Update for Covariate-Adjusted Mixture Models .....	95
4.7	Case Study: EM Algorithm with Gradient Update for Nonlinear Finite Mixture Models .....	97
4.7.1	Introduction.....	97
4.7.2	Example: Dipyrone Pharmacokinetics .....	98
4.7.3	First-Order Compartment Models .....	98
4.7.4	Finite Mixture Model Analysis .....	102
<b>5</b>	<b>Disease Mapping and Cluster Investigations .....</b>	<b>107</b>
5.1	Introduction .....	107
5.2	Investigation of General Clustering .....	109
5.2.1	Traditional Approaches .....	110
5.2.2	The Empirical Bayes Approach .....	112

5.3	Computation .....	117
5.4	A Note on Autocorrelation Versus Heterogeneity .....	119
5.4.1	Heterogeneity .....	119
5.4.2	Autocorrelation.....	121
5.5	Focused Clustering .....	124
5.5.1	The Score Test for Focused Clustering .....	124
5.5.2	The Score Test Adjusted for Heterogeneity .....	128
5.5.3	The Score Test Based on the Negative Binomial Distribution .....	129
5.5.4	Estimation of $\alpha$ and $v$ .....	130
5.6	Case Study: Leukemia in Adults in the Vicinity of Krümmel .....	132
5.6.1	Background .....	133
5.6.2	The Retrospective Incidence Study Elbmarsch .....	134
5.6.3	Focused Analysis .....	135
5.6.4	Disease Mapping and Model-Based Methods .....	136
5.7	Mathematical Details of the Score Test .....	138
5.7.1	Expectation and Variance of the Score .....	138
5.7.2	The Score Test .....	139
<b>6</b>	<b>Modeling Heterogeneity in Psychophysiology .....</b>	<b>143</b>
6.1	The Electroencephalogram.....	143
6.1.1	Digitization .....	143
6.2	Modeling Spatial Heterogeneity Using Generalized Linear Mixed Models .....	144
6.2.1	The Periodogram and its Distributional Properties .....	144
6.3	Connection to Generalized Linear Models .....	148
6.3.1	Covariate-Adjusted Finite Mixture Models for the EEG Data .....	149
<b>7</b>	<b>Investigating and Analyzing Heterogeneity in Meta-analysis .....</b>	<b>153</b>
7.1	Introduction .....	153
7.1.1	Different Types of Overviews .....	154
7.2	Basic Statistical Analysis .....	155
7.2.1	Single Study Results .....	155
7.2.2	Publication Bias .....	157
7.2.3	Estimation of a Summary Effect.....	160
7.3	Analysis of Heterogeneity .....	162
7.3.1	The DerSimonian–Laird Approach .....	164
7.3.2	Maximum Likelihood Estimation of the Heterogeneity Variance $\tau^2$ .....	166
7.3.3	Another Estimator of $\tau^2$ : The Simple Heterogeneity Variance Estimator .....	168
7.3.4	A Comment on Summary Estimates Under Heterogeneity ..	169
7.3.5	The Finite Mixture Model Approach .....	169
7.4	A Simulation Study Comparing Four Estimators of $\tau^2$ .....	171
7.4.1	Design of the Simulation Study .....	171

7.4.2	Simulation Results .....	173
7.4.3	Discussion .....	173
7.5	Metaregression .....	176
7.5.1	Finite Mixture Models Adjusted for Covariates .....	177
7.6	Interpretation of the Results of Meta-analysis of Observational Studies .....	180
7.6.1	Bias .....	181
7.6.2	Confounding .....	181
7.6.3	Heterogeneity .....	182
7.7	Case Study: Aspirin Use and Breast Cancer Risk – A Meta-analysis and Metaregression of Observational Studies from 2001 to 2007 .....	183
7.7.1	Introduction .....	183
7.7.2	Literature Search and Data Extraction .....	184
7.7.3	Study Characteristics .....	184
7.7.4	Publication Bias .....	185
7.7.5	Results .....	186
7.7.6	Results of a Metaregression .....	186
7.7.7	Modeling Dose Response .....	187
7.7.8	A Metaregression Model for Dose-Response Analysis .....	190
7.7.9	Discussion .....	191
7.8	Computation .....	192
7.8.1	“Standard Meta-analysis” .....	192
7.8.2	Meta-analysis with SAS .....	194
7.8.3	Finite Mixture Models .....	196
7.8.4	Metaregression .....	197
8	<b>Analysis of Gene Expression Data .....</b>	201
8.1	DNA Microarrays .....	201
8.2	The Analysis of Differential Gene Expression .....	202
8.2.1	Analysis Based on Simultaneous Hypothesis Testing .....	202
8.2.2	A Mixture Model Approach .....	206
8.2.3	Computation .....	209
8.3	A Change of Perspective: Applying Methods from Meta-analysis .....	210
8.4	Case Study: Identification of a Gene Signature for Breast Cancer Prognosis .....	213
8.4.1	Introduction .....	213
8.4.2	Application of the Meta-analytic Mixture Model to the Breast Cancer Data .....	214
8.4.3	Validation of Results .....	215
	<b>References .....</b>	219
	<b>Subject Index .....</b>	237
	<b>Author Index .....</b>	243