

Helge Toutenburg

# Statistical Analysis of Designed Experiments

Second Edition

With Contributions by Thomas Nittner



Springer

# Contents

<b>Preface</b>	<b>v</b>
<b>1 Introduction</b>	<b>1</b>
1.1 Data, Variables, and Random Processes . . . . .	1
1.2 Basic Principles of Experimental Design . . . . .	3
1.3 Scaling of Variables . . . . .	5
1.4 Measuring and Scaling in Statistical Medicine . . . . .	7
1.5 Experimental Design in Biotechnology . . . . .	8
1.6 Relative Importance of Effects—The Pareto Principle . .	9
1.7 An Alternative Chart . . . . .	10
1.8 A One-Way Factorial Experiment by Example . . . . .	15
1.9 Exercises and Questions . . . . .	19
<b>2 Comparison of Two Samples</b>	<b>21</b>
2.1 Introduction . . . . .	21
2.2 Paired $t$ -Test and Matched-Pair Design . . . . .	22
2.3 Comparison of Means in Independent Groups . . . . .	25
2.3.1 Two-Sample $t$ -Test . . . . .	25
2.3.2 Testing $H_0 : \sigma_A^2 = \sigma_B^2 = \sigma^2$ . . . . .	25
2.3.3 Comparison of Means in the Case of Un- equal Variances . . . . .	26
2.3.4 Transformations of Data to Assure Homogeneity of Variances . . . . .	27
2.3.5 Necessary Sample Size and Power of the Test . .	27

2.3.6	Comparison of Means without Prior Testing $H_0 : \sigma_A^2 = \sigma_B^2$ ; Cochran–Cox Test for Independent Groups . . . . .	27
2.4	Wilcoxon’s Sign–Rank Test in the Matched–Pair Design . . . . .	29
2.5	Rank Test for Homogeneity of Wilcoxon, Mann and Whitney . . . . .	33
2.6	Comparison of Two Groups with Categorical Response . . . . .	38
2.6.1	McNemar’s Test and Matched–Pair Design . . . . .	38
2.6.2	Fisher’s Exact Test for Two Independent Groups . . . . .	39
2.7	Exercises and Questions . . . . .	41
<b>3</b>	<b>The Linear Regression Model</b> . . . . .	<b>45</b>
3.1	Descriptive Linear Regression . . . . .	45
3.2	The Principle of Ordinary Least Squares . . . . .	47
3.3	Geometric Properties of Ordinary Least Squares Estimation . . . . .	50
3.4	Best Linear Unbiased Estimation . . . . .	51
3.4.1	Linear Estimators . . . . .	52
3.4.2	Mean Square Error . . . . .	53
3.4.3	Best Linear Unbiased Estimation . . . . .	55
3.4.4	Estimation of $\sigma^2$ . . . . .	57
3.5	Multicollinearity . . . . .	60
3.5.1	Extreme Multicollinearity and Estimability . . . . .	60
3.5.2	Estimation within Extreme Multicollinearity . . . . .	61
3.5.3	Weak Multicollinearity . . . . .	63
3.6	Classical Regression under Normal Errors . . . . .	67
3.7	Testing Linear Hypotheses . . . . .	69
3.8	Analysis of Variance and Goodness of Fit . . . . .	73
3.8.1	Bivariate Regression . . . . .	73
3.8.2	Multiple Regression . . . . .	79
3.9	The General Linear Regression Model . . . . .	83
3.9.1	Introduction . . . . .	83
3.9.2	Misspecification of the Covariance Matrix . . . . .	85
3.10	Diagnostic Tools . . . . .	86
3.10.1	Introduction . . . . .	86
3.10.2	Prediction Matrix . . . . .	86
3.10.3	Effect of a Single Observation on the Estimation of Parameters . . . . .	91
3.10.4	Diagnostic Plots for Testing the Model Assumptions . . . . .	96
3.10.5	Measures Based on the Confidence Ellipsoid . . . . .	97
3.10.6	Partial Regression Plots . . . . .	102
3.10.7	Regression Diagnostics by Animating Graphics . . . . .	104

3.11	Exercises and Questions . . . . .	110
<b>4</b>	<b>Single-Factor Experiments with Fixed and Random Effects</b>	<b>111</b>
4.1	Models I and II in the Analysis of Variance . . . . .	111
4.2	One-Way Classification for the Multiple Compari- son of Means . . . . .	112
4.2.1	Representation as a Restrictive Model . . . . .	115
4.2.2	Decomposition of the Error Sum of Squares . . . . .	117
4.2.3	Estimation of $\sigma^2$ by $MS_{\text{ERROR}}$ . . . . .	120
4.3	Comparison of Single Means . . . . .	123
4.3.1	Linear Contrasts . . . . .	123
4.3.2	Contrasts of the Total Response Values in the Balanced Case . . . . .	126
4.4	Multiple Comparisons . . . . .	132
4.4.1	Introduction . . . . .	132
4.4.2	Experimentwise Comparisons . . . . .	132
4.4.3	Select Pairwise Comparisons . . . . .	135
4.5	Regression Analysis of Variance . . . . .	142
4.6	One-Factorial Models with Random Effects . . . . .	145
4.7	Rank Analysis of Variance in the Completely Randomized Design . . . . .	149
4.7.1	Kruskal-Wallis Test . . . . .	149
4.7.2	Multiple Comparisons . . . . .	152
4.8	Exercises and Questions . . . . .	154
<b>5</b>	<b>More Restrictive Designs</b>	<b>157</b>
5.1	Randomized Block Design . . . . .	157
5.2	Latin Squares . . . . .	165
5.2.1	Analysis of Variance . . . . .	167
5.3	Rank Variance Analysis in the Randomized Block Design . . . . .	172
5.3.1	Friedman Test . . . . .	172
5.3.2	Multiple Comparisons . . . . .	175
5.4	Exercises and Questions . . . . .	176
<b>6</b>	<b>Multifactor Experiments</b>	<b>179</b>
6.1	Elementary Definitions and Principles . . . . .	179
6.2	Two-Factor Experiments (Fixed Effects) . . . . .	183
6.3	Two-Factor Experiments in Effect Coding . . . . .	188
6.4	Two-Factorial Experiment with Block Effects . . . . .	196
6.5	Two-Factorial Model with Fixed Effects—Confidence Intervals and Elementary Tests . . . . .	199
6.6	Two-Factorial Model with Random or Mixed Effects . . . . .	203
6.6.1	Model with Random Effects . . . . .	203

	6.6.2	Mixed Model . . . . .	207
6.7		Three-Factorial Designs . . . . .	211
6.8		Split-Plot Design . . . . .	215
6.9		$2^k$ Factorial Design . . . . .	219
	6.9.1	The $2^2$ Design . . . . .	219
	6.9.2	The $2^3$ Design . . . . .	222
6.10		Exercises and Questions . . . . .	225
<b>7</b>		<b>Models for Categorical Response Variables</b>	<b>231</b>
7.1		Generalized Linear Models . . . . .	231
	7.1.1	Extension of the Regression Model . . . . .	231
	7.1.2	Structure of the Generalized Linear Model . . . . .	233
	7.1.3	Score Function and Information Matrix . . . . .	236
	7.1.4	Maximum Likelihood Estimation . . . . .	237
	7.1.5	Testing of Hypotheses and Goodness of Fit . . . . .	240
	7.1.6	Overdispersion . . . . .	241
	7.1.7	Quasi Loglikelihood . . . . .	243
7.2		Contingency Tables . . . . .	245
	7.2.1	Overview . . . . .	245
	7.2.2	Ways of Comparing Proportions . . . . .	246
	7.2.3	Sampling in Two-Way Contingency Tables . . . . .	249
	7.2.4	Likelihood Function and Maximum Likelihood Estimates . . . . .	250
	7.2.5	Testing the Goodness of Fit . . . . .	252
7.3		Generalized Linear Model for Binary Response . . . . .	254
	7.3.1	Logit Models and Logistic Regression . . . . .	254
	7.3.2	Testing the Model . . . . .	257
	7.3.3	Distribution Function as a Link Function . . . . .	258
7.4		Logit Models for Categorical Data . . . . .	258
7.5		Goodness of Fit—Likelihood Ratio Test . . . . .	260
7.6		Loglinear Models for Categorical Variables . . . . .	261
	7.6.1	Two-Way Contingency Tables . . . . .	261
	7.6.2	Three-Way Contingency Tables . . . . .	264
7.7		The Special Case of Binary Response . . . . .	267
7.8		Coding of Categorical Explanatory Variables . . . . .	270
	7.8.1	Dummy and Effect Coding . . . . .	270
	7.8.2	Coding of Response Models . . . . .	273
	7.8.3	Coding of Models for the Hazard Rate . . . . .	274
7.9		Extensions to Dependent Binary Variables . . . . .	277
	7.9.1	Overview . . . . .	277
	7.9.2	Modeling Approaches for Correlated Response . . . . .	279
	7.9.3	Quasi-Likelihood Approach for Correlated Binary Response . . . . .	280
	7.9.4	The Generalized Estimating Equation Method by Liang and Zeger . . . . .	281

7.9.5	Properties of the Generalized Estimating Equation Estimate $\hat{\beta}_G$ . . . . .	283
7.9.6	Efficiency of the Generalized Estimating Equation and Independence Estimating Equation Methods . . . . .	284
7.9.7	Choice of the Quasi-Correlation Matrix $R_i(\alpha)$ . . . . .	285
7.9.8	Bivariate Binary Correlated Response Variables . . . . .	285
7.9.9	The Generalized Estimating Equation Method . . . . .	286
7.9.10	The Independence Estimating Equation Method . . . . .	288
7.9.11	An Example from the Field of Dentistry . . . . .	288
7.9.12	Full Likelihood Approach for Marginal Models . . . . .	293
7.10	Exercises and Questions . . . . .	294

**8 Repeated Measures Model 295**

8.1	The Fundamental Model for One Population . . . . .	295
8.2	The Repeated Measures Model for Two Populations . . . . .	298
8.3	Univariate and Multivariate Analysis . . . . .	301
8.3.1	The Univariate One-Sample Case . . . . .	301
8.3.2	The Multivariate One-Sample Case . . . . .	301
8.4	The Univariate Two-Sample Case . . . . .	306
8.5	The Multivariate Two-Sample Case . . . . .	307
8.6	Testing of $H_0 : \Sigma_x = \Sigma_y$ . . . . .	308
8.7	Univariate Analysis of Variance in the Repeated Measures Model . . . . .	309
8.7.1	Testing of Hypotheses in the Case of Compound Symmetry . . . . .	309
8.7.2	Testing of Hypotheses in the Case of Sphericity . . . . .	311
8.7.3	The Problem of Nonsphericity . . . . .	315
8.7.4	Application of Univariate Modified Approaches in the Case of Nonsphericity . . . . .	316
8.7.5	Multiple Tests . . . . .	317
8.7.6	Examples . . . . .	318
8.8	Multivariate Rank Tests in the Repeated Measures Model . . . . .	324
8.9	Categorical Regression for the Repeated Binary Response Data . . . . .	329
8.9.1	Logit Models for the Repeated Binary Response for the Comparison of Therapies . . . . .	329
8.9.2	First-Order Markov Chain Models . . . . .	330
8.9.3	Multinomial Sampling and Loglinear Models for a Global Comparison of Therapies . . . . .	332
8.10	Exercises and Questions . . . . .	339

**9 Cross-Over Design 341**

9.1	Introduction . . . . .	341
9.2	Linear Model and Notations . . . . .	342

9.3	$2 \times 2$ Cross-Over (Classical Approach) . . . . .	343
9.3.1	Analysis Using $t$ -Tests . . . . .	344
9.3.2	Analysis of Variance . . . . .	348
9.3.3	Residual Analysis and Plotting the Data . . . . .	352
9.3.4	Alternative Parametrizations in $2 \times 2$ Cross- Over . . . . .	356
9.3.5	Cross-Over Analysis Using Rank Tests . . . . .	368
9.4	$2 \times 2$ Cross-Over and Categorical (Binary) Response . .	368
9.4.1	Introduction . . . . .	368
9.4.2	Loglinear and Logit Models . . . . .	372
9.5	Exercises and Questions . . . . .	384
<b>10</b>	<b>Statistical Analysis of Incomplete Data</b>	<b>385</b>
10.1	Introduction . . . . .	385
10.2	Missing Data in the Response . . . . .	390
10.2.1	Least Squares Analysis for Complete Data . . . . .	390
10.2.2	Least Squares Analysis for Filled-Up Data . . . . .	391
10.2.3	Analysis of Covariance—Bartlett's Method . . . . .	392
10.3	Missing Values in the $X$ -Matrix . . . . .	393
10.3.1	Missing Values and Loss of Efficiency . . . . .	394
10.3.2	Standard Methods for Incomplete $X$ -Matrices . . . . .	397
10.4	Adjusting for Missing Data in $2 \times 2$ Cross-Over Designs	400
10.4.1	Notation . . . . .	400
10.4.2	Maximum Likelihood Estimator (Rao, 1956) . . . . .	402
10.4.3	Test Procedures . . . . .	403
10.5	Missing Categorical Data . . . . .	407
10.5.1	Introduction . . . . .	407
10.5.2	Maximum Likelihood Estimation in the Complete Data Case . . . . .	408
10.5.3	Ad-Hoc Methods . . . . .	409
10.5.4	Model-Based Methods . . . . .	410
10.6	Exercises and Questions . . . . .	412
<b>A</b>	<b>Matrix Algebra</b>	<b>415</b>
A.1	Introduction . . . . .	415
A.2	Trace of a Matrix . . . . .	418
A.3	Determinant of a Matrix . . . . .	418
A.4	Inverse of a Matrix . . . . .	420
A.5	Orthogonal Matrices . . . . .	421
A.6	Rank of a Matrix . . . . .	422
A.7	Range and Null Space . . . . .	422
A.8	Eigenvalues and Eigenvectors . . . . .	423
A.9	Decomposition of Matrices . . . . .	425
A.10	Definite Matrices and Quadratic Forms . . . . .	427
A.11	Idempotent Matrices . . . . .	433

A.12	Generalized Inverse . . . . .	434
A.13	Projections . . . . .	442
A.14	Functions of Normally Distributed Variables . . . . .	443
A.15	Differentiation of Scalar Functions of Matrices . . . . .	446
A.16	Miscellaneous Results, Stochastic Convergence . . . . .	449
<b>B</b>	<b>Theoretical Proofs</b>	<b>453</b>
B.1	The Linear Regression Model . . . . .	453
B.2	Single-Factor Experiments with Fixed and Random Effects	475
<b>C</b>	<b>Distributions and Tables</b>	<b>479</b>
	<b>References</b>	<b>487</b>
	<b>Index</b>	<b>497</b>