Multivariate Data Analysis 6th Edition

An introduction to Multivariate Analysis, Process Analytical Technology and Quality by Design

> Kim H. Esbensen and Brad Swarbrick

with contributions from Frank Westad, Pat Whitcombe and Mark Anderson



Contents

Prefa	ace	X	V
Cha	pter	1. Introduction to multivariate analysis	1
1.1	The	world is multivariate	1
1.2	Indir	ect observations and correlations	2
1.3	Data	a must carry useful information	2
1.4	Varia	ance, covariance and correlation	3
1.5	Cau	sality vs correlation	6
1.6	Hido	len data structures—correlations again	6
1.7	Mult	ivariate data analysis vs multivariate statistics	8
		Data description (exploratory data structure modelling) Discrimination and classification	9 9
1.9 1.9		ivariate techniques as geometric projections	
1.10	The	grand overview in multivariate data analysis1	1
1.11	Refe	erences	2
Chap	oter	2: A review of some fundamental statistics 13	3
2.1	Term	ninology13	3
2.2 2.2 2.2 2.2	2.1 2.2 2.3	nitions of some important measurements and concepts 14 The mean 15 The median 16 The mode 17 Variance and standard deviation 17	5 6 7
2.3 2.3		ples and representative sampling	
2.4 2.4		normal distribution and its properties	

2.5	Hypothesis testing	
2.	2.5.1 Significance, risk and power	
	2.5.2 Defining an appropriate risk level	
	2.5.3 A general guideline for applying formal statistical tests	
	2.5.4 A Test for Equivalence of Variances: The <i>F</i> -test	
	2.5.5 Tests for equivalence of means	
2.6	An introduction to time series and control charts	45
2.7	Joint confidence intervals and the need for multivariate analysis	48
2.8	Chapter summary	50
2.9	References	52
Cha	apter 3: Theory of Sampling (TOS)	53
3.1	Chapter overview	54
3.2	Heterogeneity	
3.:	3.2.1 Constitutional heterogeneity (CH)	
3.:	B.2.2 Distributional heterogeneity (DH)	
3.3	Sampling error vs practical sampling	57
3.4	Total Sampling Error (TSE)—Fundamental Sampling Principle (F	SP)58
3.5	Sampling Unit Operations (SUO)	
3.6	Replication experiment—quantifying sampling errors	61
3.7	TOS in relation to multivariate data analysis	62
3.8	Process sampling—variographic analysis	63
3.8	.8.1 Appendix A. Terms and definitions used in the TOS literature	
3.9	References	68
Cha _l 69	apter 4: Fundamentals of principal component analysis ((PCA)
4.1	Representing data as a matrix	69
4.2	The variable space — plotting objects in <i>p</i> -dimensions.2.1Plotting data in 1-d and 2d space.2.2The variable space and dimensions.2.3Visualisation in 3-D (or more)	
4.3	Plotting objects in variable space	71
4.4	Example – plotting raw data (beverage)	
4.4	.4.1 Purpose	
4.4	.4.2 Data set	71

4.5	The	first principal component	73
4	.5.1	Maximum variance directions	73
4	.5.2	The first principal component as a least squares fit	74
4.6	Exte	ension to higher-order principal components	75
4.7	Prine	cipal component models—scores and loadings	76
4	.7.1	Maximum number of principal components	76
4	.7.2	PC model centre	77
4	.7.3	Introducing loadings-relations between X and PCs	77
4	.7.4	Scores-coordinates in PC space	78
4	.7.5	Object residuals	78
4.8	Obje	ectives of PCA	79
4.9	Sco	re plot–object relationships	80
4	.9.1	Interpreting score plots	80
4	.9.2	Choice of score plots	82
4.10) The	loading plot-variable relationships	83
4	.10.1	Correlation loadings	84
4	.10.2	Comparison of scores and loading plots	86
4	.10.3	The 1-dimensional loading plot	87
4.11	I Exar	mple: city temperatures in europe	
	l Exar 11.1	mple: city temperatures in europe Introduction	89
4			89 89
4 4	.11.1	Introduction	89 89 89
4 4 4	.11.1 .11.2 .11.3	Introduction Plotting data and deciding on the validation scheme	89 89 89 90
4 4 4 4.12	.11.1 .11.2 .11.3	Introduction Plotting data and deciding on the validation scheme PCA results and interpretation	89 89 90 93
4 4 4 4.12 4	11.1 11.2 11.3 2 Prine	Introduction Plotting data and deciding on the validation scheme PCA results and interpretation cipal component models	89 89 90 93 93
4 4 4.12 4 4	11.1 11.2 11.3 2 Prind 12.1	Introduction Plotting data and deciding on the validation scheme PCA results and interpretation cipal component models The PC model	89 89 90 93 93 93
4 4 4.12 4 4	11.1 11.2 11.3 2 Prine 12.1 12.2	Introduction Plotting data and deciding on the validation scheme PCA results and interpretation cipal component models The PC model Centring	89 90 90 93 93 93 94
4 4 4.12 4 4 4 4	11.1 11.2 11.3 2 Prind 12.1 12.2 12.3	Introduction Plotting data and deciding on the validation scheme PCA results and interpretation cipal component models The PC model Centring Step by step calculation of PCs	89 89 90 93 93 93 94
4 4 4.12 4 4 4 4 4	11.1 11.2 11.3 2 Prind 12.1 12.2 12.3 12.4	Introduction Plotting data and deciding on the validation scheme PCA results and interpretation cipal component models The PC model Centring Step by step calculation of PCs A preliminary comment on the algorithm: NIPALS Residuals – the E-matrix Residual variance	89 90 93 93 93 93 94 94 95
4 4 4.12 4 4 4 4 4 4	.11.1 .11.2 .11.3 2 Prind .12.1 .12.2 .12.3 .12.4 .12.5	Introduction Plotting data and deciding on the validation scheme PCA results and interpretation cipal component models The PC model Centring Step by step calculation of PCs A preliminary comment on the algorithm: NIPALS Residuals — the E -matrix Residual variance Object residuals	89 90 93 93 93 93 94 94 95 95 96
4 4 4.12 4 4 4 4 4 4 4 4	11.1 11.2 11.3 2 Prind 12.1 12.2 12.3 12.4 12.5 12.6	Introduction Plotting data and deciding on the validation scheme PCA results and interpretation cipal component models The PC model. Centring Step by step calculation of PCs A preliminary comment on the algorithm: NIPALS Residuals — the E -matrix Residual variance Object residuals The total squared object residual	89 90 93 93 93 93 93 93 94 95 95 96
4 4 4.12 4 4 4 4 4 4 4 4	.11.1 .11.2 .11.3 2 Prind .12.1 .12.2 .12.3 .12.4 .12.5 .12.6 .12.7	Introduction Plotting data and deciding on the validation scheme PCA results and interpretation cipal component models The PC model Centring Step by step calculation of PCs A preliminary comment on the algorithm: NIPALS Residuals — the E -matrix Residual variance Object residuals The total squared object residual Explained/residual variance plots	89 90 93 93 93 93 94 94 95 95 96 96
4 4 4.12 4 4 4 4 4 4 4 4 4	.11.1 .11.2 .11.3 2 Prind .12.1 .12.2 .12.3 .12.4 .12.5 .12.6 .12.7 .12.8	Introduction Plotting data and deciding on the validation scheme PCA results and interpretation cipal component models The PC model Centring Step by step calculation of PCs A preliminary comment on the algorithm: NIPALS Residuals — the E -matrix Residual variance Object residuals The total squared object residual Explained/residual variance plots How many PCs to use?	89 90 93 93 93 93 94 94 95 95 95 96 96 96 97
4 4 4.12 4 4 4 4 4 4 4 4 4 4 4 4 4	.11.1 .11.2 .11.3 2 Prind .12.1 .12.2 .12.3 .12.4 .12.5 .12.6 .12.7 .12.8 .12.8 .12.9 .12.10 .12.11	Introduction Plotting data and deciding on the validation scheme	89 90 93 93 93 93 93 93 93 94 95 95 96 96 96 96 97 98
4 4 4.12 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4	.11.1 .11.2 .11.3 2 Prind .12.1 .12.2 .12.3 .12.4 .12.5 .12.6 .12.7 .12.8 .12.9 .12.10 .12.11 .12.12	Introduction Plotting data and deciding on the validation scheme	89 90 93 93 93 93 93 93 93 93 93 94 95 96 96 96 96 98
4 4 4.12 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4	.11.1 .11.2 .11.3 2 Prind .12.1 .12.2 .12.3 .12.4 .12.5 .12.6 .12.7 .12.8 .12.8 .12.9 .12.10 .12.11	Introduction Plotting data and deciding on the validation scheme	89 90 93 93 93 93 93 94 95 95 96 96 96 96 97 98 98 98

4.13	Exa	mple: interpreting a PCA model (peas)	
4.	13.1	Purpose	100
4.	13.2	Data set	
4.	13.3	Tasks	100
4.	13.4	How to do it	
4.	13.5	Summary	101
4.14	PC/	A modelling—the NIPALS algorithm	
4.15	Cha	apter summary	
4.16	Ref	erences	
			100
Cha	•	5: Preprocessing	106
5.1	Intro	oduction	106
5.2	Pre	processing of discrete data	
5.	2.1	Variable weighting and scaling	106
5.	2.2	Logarithm transformation	
5.	2.3	Averaging	
5.3	Pre	processing of spectroscopic data	
5.	3.1	Spectroscopic transformations	110
5.	3.2	Smoothing	112
5.	3.3	Normalisation	113
5.	3.4	Baseline correction	114
	3.5	Derivatives	
	3.6	Correcting multiplicative effects in spectra	
5.	3.7	Other general preprocessing methods	125
5.4	Pra	ctical aspects of preprocessing	
	4.1	Scatter effects plot	
5.	4.2	Detailed example: preprocessing gluten-starch mixtures	
5.5	Cha	apter summary	133
5.6	Ref	erences	134
6 P	rinci	oal Component Analysis (PCA)—in practice	135
6.1		PCA overview	
6.2	PC/	A—Step by Step	136
6.3	Inte	rpretation of PCA models	138
6.	3.1	Interpretation of score plots-look for patterns	
6.	3.2	Summary-interpretation of score plots	
6.	3.3	Interpretation of loading plots-look for important variables	

6.4	1 Exa	mple: alcohol in water analysis	141
6.5	5 PCA	A—what can go wrong?	144
	6.5.1	Is there any information in the data set?	
	6.5.2	Too few PCs are used in the model	145
	6.5.3	Too many PCs are used in the model	145
	6.5.4	Outliers which are truly due to erroneous data were not removed	145
	6.5.5	Outliers that contain important information were removed	145
	6.5.6	The score plots were not explored sufficiently	145
	6.5.7	Loadings were interpreted with the wrong number of PCs	145
	6.5.8	Too much reliance on the standard diagnostics in the computer program thinking for yourself	
	6.5.9	The "wrong" data preprocessing was used	145
6.6	6 Out	liers	146
	6.6.1	Hotelling's T ² statistic	
	6.6.2	Leverage	147
	6.6.3	Mahalanobis distance	148
	6.6.4	Influence plots	148
6.7	7 Valio	dation score plot and PCA projection	149
	6.7.1	Multivariate projection	
	6.7.2	Validation scores	150
6.8	B Exe	rcise—detecting outliers (Troodos)	152
	6.8.1	Purpose	
	6.8.2	Data set	152
	6.8.3	Analysis	153
	6.8.4	Summary	156
6.9	9 Sun	nmary: PCA in practice	156
6.1	10 Refe	erences	157
7	N/Lultiv	ariate calibration	158
7.1		tivariate modelling (X, Y) : the calibration stage	
7.2	2 Mul	tivariate modelling (X , Y): the prediction stage	159
7.3	3 Cali	bration set requirements (training set)	160
7.4	1 Intro	oduction to validation	161
-	7.4.1	Test set validation	
	7.4.2	Other validation methods	
	7.4.3	Modelling error	162
7.5	5 Nun	nber of components/factors (model dimensionality)	163
	7.5.1	Minimising the prediction error	

7.6	3 Univ	variate regression ($\mathbf{y} \mathbf{x}$) and MLR	164
	7.6.1	Univariate regression (y x)	164
	7.6.2	Multiple linear regression, MLR	165
7.7	7 Colli	nearity	
7.8	B PCF	R—Principal component regression	166
	7.8.1	PCA scores in MLR	
	7.8.2	Are all the possible PCs needed?	
	7.8.3	Example: prediction of multiple components in an alcohol mixture	
	7.8.4	Weaknesses of PCR	
7.9	PIS	-regression (PLSR)	
	7.9.1	PLSR—a powerful alternative to PCR	
	7.9.2	PLSR (X, Y) : initial comparison with PCA (X) , PCA (Y)	
	7.9.3	PLS-NIPALS algorithm	
	7.9.4	PLSR with one or more Y -variables	
	7.9.5	Interpretation of PLS models	
	7.9.6	Loadings (p) and loading weights (w)	176
	7 <i>.</i> 9.7	The PLS1 NIPALS algorithm	177
7.	10 Exar	mple—interpretation of PLS1 (octane in gasoline) part 1: n	nodel
		evelopment	
	7.10.1	Purpose	178
	7.10.2	Data set	178
	7.10.3	Tasks	178
	7.10.4	Initial data considerations	178
	7.10.5	Always perform an initial PCA	181
	7.10.6	Regression analysis	
	7.10.7	Assessment of loadings vs loading weights	
	7.10.8	Assessment of regression coefficients	
	7.10.9	Always use loading weights for model building and understanding	
	7.10.10	Predicted vs reference plot	
	7.10.11	Regression analysis of octane (Part 1) summary	
	7.10.12	A short discourse on model diagnostics	
	7.10.13	Residuals in X	
	7.10.14	Q-residuals	
		F-residuals	
	7.10.16	Hotelling's 7 ² statistic	
	7.10.17	Influence plots for regression models	
		Always check the raw data! Which objects should be removed?	
		Residuals in Y	
	1.10.20		

7.11 Erro	pr measures	192
7.11.1	Calculating the SEL for a reference method	193
7.11.2	Further estimates of model precision	193
7.11.3	X-Y relation outlier plots (T vs U scores)	194
7.11.4	Example — interpretation of PLS1 (octane in gasoline) Part 2: advanced	
	interpretations	
7.11.5	Sample elimination	
7.11.6	Variable elimination	
7.11.7	X-Y relationship outlier plot	198
7.12 Pre	diction using multivariate models	199
7.12.1	Projected scores	202
7.12.2	Prediction influence plots	202
7.12.3	Y-deviation	203
7.12.4	Inlier statistic	203
7.12.5	Example-interpretation of PLS1 (octane in gasoline) Part 3: prediction	203
7.13 Und	certainty estimates, significance and stability—Martens' uncert	ainty
	st	
7.13.1	Uncertainty estimates in regression coefficients, b	206
7.13.2	Rotation of perturbed models	206
7.13.3	Variable selection	206
7.13.4	Model stability	207
7.13.5	An example using data from paper manufacturing	207
7.13.6	Example—gluten in starch calibration	207
7.13.7	Raw data model	209
7.13.8	MSC data model	210
7.13.9	EMSC data model	210
7.13.10	mEMSC data model	211
7.13.11	Comparison of results	211
7.14 PLS	R and PCR multivariate calibration—in practice	212
7.14.1	What is a "good" or "bad" model?	213
7.14.2	Signs of unsatisfactory data models - a useful checklist	214
7.14.3	Possible reasons for bad modelling or validation results	215
7.15 Cha	apter summary	216
	· erences	
8. Princi	oles of Proper Validation (PPV)	218
8.1 Intro	oduction	218
8.2 The	Principles of Validation: overview	219
8.3 Data	a quality—data representativity	220

8.4	Validation objectives	220
8.4	, , , ,	
8.4	,	
8.5	Fallacies and abuse of the central limit theorem	222
8.6	Systematics of cross-validation	222
8.7	Data structure display via <i>t-u</i> plots	223
8.8	Multiple validation approaches	227
8.9	Verdict on training set splitting and many other myths	227
8.10	Cross-validation does have a role-category and model co 232	omparisons
8.11	Cross-validation vs test set validation in practice	234
8.12	Visualisation of validation is everything	234
8.13	Final remark on several test sets	235
8.14	Conclusions	236
8.15	References	237
9. Re 9.1	eplication—replicates—but of what? Introduction	239
9.2	Understanding uncertainty	
9.3	The Replication Experiment (RE)	
9.4	RE consequences for validation	
9.5	Replication applied to analytical method development	
9.6	Analytical vs sampling bias	
9.7	References	
	An introduction to multivariate classification	251
10.1	Supervised or unsupervised, that is the question!	251
	Principles of unsupervised classification and clustering	
10.3	Principles of supervised classification	259
	Graphical interpretation of classification results	
	Partial least squares discriminant analysis (PLS-DA)	

10.6	Linea	ar Discriminant Analysis (LDA)	275
10.7	Sup	port vector machine classification	277
10.8	Adva	antages of SIMCA over traditional methods and new methods	280
10.9		ication of supervised classification methods to authentication of getable oils using FTIR	
10	.9.1	Data visualisation and pre-processing	. 280
10	.9.2	Exploratory data analysis	. 281
10	.9.3	Developing a SIMCA library and application to a test set	. 282
10	.9.4	SIMCA model diagnostics	. 283
10	.9.5	Developing a PLS-DA method and application to a test set	. 284
10	.9.6	Developing a PCA-LDA method and application to a test set	. 285
10	.9.7	Developing a SVMC method and application to a test set	. 288
10	.9.8	Conclusions from the Vegetable Oil classification	. 288
10.10) Cha	pter summary	290
10.11	l Refe	rences	292

Chapter 11. Introduction to Design of Experiment (DoE) Methodology

293

11.1	Expe	erimental design2	293
11	.1.1	Why is experimental design useful?	293
11	.1.2	The ad hoc approach	293
11	.1.3	The traditional approach - vary one variable at a time	294
11	.1.4	The alternative approach	295
11.2	Expe	erimental design in practice2	296
11	.2.1	Define stage	296
11	.2.2	Design stage	296
11	.2.3	Analyse stage	297
11	.2.4	Improve stage	297
11	.2.5	The concept of factorial designs	297
11	.2.6	Full factorial designs	297
11	.2.7	Naming convention	299
11	.2.8	Calculating effects when there are many experiments	300
11	.2.9	The concept of fractional factorial designs	302
11	.2.10	Confounding	303
11	.2.11	Types of variables encountered in DoE	305
11	.2.12	Ranges of variation for experimental factors	307
11	.2.13	Replicates	308
11	.2.14	Randomisation	308
11	.2.15	Blocking in designed experiments	309

11.2.16	Types of experimental design	309
11.2.17	Which optimisation design to choose in practice	315
11.2.18	Important effects	316
11.2.19	Hierarchy of effects	318
11.2.20	Model significance	318
11.2.21	Total sum of squares (SS _{total})	319
11.2.22	Sum of squares regression (SS _{Feg})	320
11.2.23	Residual sum of squares (SS _{Errc})	
11.2.24	Model degrees of freedom ($ u$)	
11.2.25	Example: building the ANOVA table for a 2 ³ full factorial design	
11.2.26		
11.2.27		
11.2.28	Graphical tools used for assessing designed experiments	
11.2.29	Model interpretation plots	
11.2.30		
11.2.31	An introduction to constrained designs	
11.3 Cha	apter summary	
11.4 Refe	erences	
introduct	12. Factor rotation and multivariate curve resoluti- tion to multivariate data analysis, tier ll	387
introduct		387
introduct 12.1 Sim	tion to multivariate data analysis, tier ll	387 387
introduct 12.1 Sim 12.2 PC/	tion to multivariate data analysis, tier II ple structure A rotation	387 387 387
introduct 12.1 Sim 12.2 PC/	tion to multivariate data analysis, tier II ple structure	387 387 387 389
introduct 12.1 Sim 12.2 PC/ 12.3 Orth	tion to multivariate data analysis, tier II ple structure A rotation nogonal rotation methods	387 387 387 389 389
introduct 12.1 Sim 12.2 PC/ 12.3 Orth 12.3.1	tion to multivariate data analysis, tier II ple structure A rotation nogonal rotation methods Varimax rotation	387 387 387 389 389 389 389
introduct 12.1 Sim 12.2 PC/ 12.3 Orth 12.3.1 12.3.2	tion to multivariate data analysis, tier II ple structure A rotation nogonal rotation methods Varimax rotation Quartimax rotation	387 387 387 389 389 389 390
introduct 12.1 Sim 12.2 PC/ 12.3 Orth 12.3.1 12.3.2 12.3.3 12.3.4	tion to multivariate data analysis, tier II nple structure nogonal rotation methods. Varimax rotation Quartimax rotation Parsimax rotation	387 387 387 389 389 389 390 390
introduct 12.1 Sim 12.2 PC/ 12.3 Orth 12.3.1 12.3.2 12.3.3 12.3.4	tion to multivariate data analysis, tier II ple structure A rotation nogonal rotation methods Varimax rotation Quartimax rotation Equimax rotation	387 387 387 389 389 390 390 390
introduct 12.1 Sim 12.2 PC/ 12.3 Orth 12.3.1 12.3.2 12.3.3 12.3.4 12.4 Inte 12.4.1	tion to multivariate data analysis, tier II ple structure A rotation Nogonal rotation methods Varimax rotation Quartimax rotation Equimax rotation Parsimax rotation rpretation of rotated PCA results	387 387 387 389 389 389 390 390 390 390
introduct 12.1 Sim 12.2 PC/ 12.3 Orth 12.3.1 12.3.2 12.3.3 12.3.4 12.4 Inte 12.4.1	tion to multivariate data analysis, tier II ple structure A rotation Nogonal rotation methods Varimax rotation Quartimax rotation Equimax rotation Parsimax rotation Proretation of rotated PCA results PCA rotation applied to NIR data of fish samples	387 387 387 389 389 390 390 390 394
introduct 12.1 Sim 12.2 PC/ 12.3 Orth 12.3.1 12.3.2 12.3.3 12.3.4 12.4 Inte 12.4.1 12.5 An i	tion to multivariate data analysis, tier II ple structure A rotation Nogonal rotation methods Varimax rotation Quartimax rotation Equimax rotation Parsimax rotation Pretation of rotated PCA results PCA rotation applied to NIR data of fish samples introduction to multivariate curve resolution (MCR)	387 387 387 389 389 390 390 390 390 394 394
introduct 12.1 Sim 12.2 PC/ 12.3 Orth 12.3.1 12.3.2 12.3.3 12.3.4 12.4 Inte 12.4.1 12.5 An i 12.5.1	tion to multivariate data analysis, tier II ple structure A rotation hogonal rotation methods Varimax rotation Quartimax rotation Equimax rotation Parsimax rotation Protation of rotated PCA results PCA rotation applied to NIR data of fish samples introduction to multivariate curve resolution (MCR) What is multivariate curve resolution?	387 387 387 389 389 390 390 390 390 390 390 394 394 395
introduct 12.1 Sim 12.2 PC/ 12.3 Orth 12.3.1 12.3.2 12.3.3 12.3.4 12.4 Inte 12.4.1 12.5 An 12.5.1 12.5.2 12.5.3	tion to multivariate data analysis, tier II ple structure	387 387 387 389 389 390 390 390 390 390 390 394 394 395 395
introduct 12.1 Sim 12.2 PC/ 12.3 Orth 12.3.1 12.3.2 12.3.3 12.3.4 12.4 Inte 12.4.1 12.5 An 12.5.1 12.5.2 12.5.3	tion to multivariate data analysis, tier II ple structure A rotation hogonal rotation methods Varimax rotation Quartimax rotation Equimax rotation Parsimax rotation Protectation of rotated PCA results PCA rotation applied to NIR data of fish samples introduction to multivariate curve resolution (MCR) What is multivariate curve resolution? How multivariate curve resolution works Data types suitable for MCR	387 387 387 389 389 390 390 390 390 394 395 395 396
introduct 12.1 Sim 12.2 PC/ 12.3 Orth 12.3.1 12.3.2 12.3.3 12.3.4 12.4 Inte 12.4.1 12.5.1 12.5.2 12.5.3 12.6 Cor	tion to multivariate data analysis, tier II ple structure	387 387 387 389 389 390 390 390 390 390 394 395 395 396 397
introduct 12.1 Sim 12.2 PC/ 12.3 Orth 12.3.1 12.3.2 12.3.3 12.3.4 12.4 Inte 12.4.1 12.5.1 12.5.2 12.5.3 12.6 Cor 12.6.1	tion to multivariate data analysis, tier II ple structure	387 387 387 389 389 390 390 390 390 390 390 390 391 395 395 396 397

12.	6.5	Ambiguities and constraints in MCR	. 400
12.7	Algo	rithms used in multivariate curve resolution	401
	7.1	Evolving factor analysis (EFA)	
12.	7.2	Multivariate curve resolution-alternating least squares (MCR-ALS)	
12.	7.3	Initial estimates for MCR-ALS.	
12.	7.4	Computational parameters of MCR-ALS	. 403
12.	7.5	Tuning the sensitivity of the analysis to pure components	. 404
12.8	Mair	n results of MCR	404
12.		Residuals	
12.	8.2	Estimated concentrations	. 405
12.	8.3	Estimated spectra	. 405
12.	8.4	Practical use of estimated concentrations and spectra and quality checks	. 405
12.	8.5	Outliers and noisy variables in MCR	. 405
12.9	MCF	R applied to fat analysis of fish	406
12.10	Cha	pter summary	409
	•	rences	
Chap	oter [·]	13. Process analytical technology (PAT) and its role in	the
•			413
13.1	Intro	duction	413
		duction Quality by Design (QbD) initiative	
13.2	The	Quality by Design (QbD) initiative	414
13.2 13.	The 2.1	Quality by Design (QbD) initiative The International Conference on Harmonisation (ICH) guidance	414 . 415
1 3.2 13. 13.	The 2.1 2.2	Quality by Design (QbD) initiative The International Conference on Harmonisation (ICH) guidance US FDA process validation guidance	414 . 415 . 416
13.2 13. 13. 13.	The 2.1 2.2 Proc	Quality by Design (QbD) initiative The International Conference on Harmonisation (ICH) guidance US FDA process validation guidance ess analytical technology (PAT)	414 . 415 . 416 417
13.2 13. 13. 13.3 13.3	The 2.1 2.2 Proc 3.1	Quality by Design (QbD) initiative The International Conference on Harmonisation (ICH) guidance US FDA process validation guidance cess analytical technology (PAT) At-line, online, inline or offline: what is the difference?	414 . 415 . 416 417 . 417
13.2 13. 13. 13.3 13. 13.	The 2.1 2.2 Proc 3.1 3.2	Quality by Design (QbD) initiative The International Conference on Harmonisation (ICH) guidance US FDA process validation guidance vess analytical technology (PAT) At-line, online, inline or offline: what is the difference? Enablers of PAT	414 . 415 . 416 417 . 417 . 419
13.2 13. 13. 13.3 13. 13. 13.4	The 2.1 2.2 Proc 3.1 3.2 The	Quality by Design (QbD) initiative The International Conference on Harmonisation (ICH) guidance US FDA process validation guidance ess analytical technology (PAT) At-line, online, inline or offline: what is the difference? Enablers of PAT link between QbD and PAT	414 . 415 . 416 417 . 417 . 419 425
13.2 13. 13. 13.3 13. 13. 13.4	The 2.1 2.2 Proc 3.1 3.2 The	Quality by Design (QbD) initiative The International Conference on Harmonisation (ICH) guidance US FDA process validation guidance ess analytical technology (PAT) At-line, online, inline or offline: what is the difference? Enablers of PAT link between QbD and PAT mometrics: the glue that holds QbD and PAT together	414 . 415 . 416 417 . 417 . 419 425 427
13.2 13. 13.3 13.3 13. 13.4 13.5 13.5	The 2.1 2.2 Proc 3.1 3.2 The Chei 5.1	Quality by Design (QbD) initiative The International Conference on Harmonisation (ICH) guidance US FDA process validation guidance eess analytical technology (PAT) At-line, online, inline or offline: what is the difference? Enablers of PAT link between QbD and PAT mometrics: the glue that holds QbD and PAT together A new approach to batch process understanding: relative time modelling	414 . 415 . 416 417 . 417 . 419 425 427 . 428
13.2 13. 13.3 13. 13. 13.4 13.5 13. 13.	The 2.1 2.2 Proc 3.1 3.2 The Chei 5.1 5.2	Quality by Design (QbD) initiative The International Conference on Harmonisation (ICH) guidance US FDA process validation guidance ess analytical technology (PAT) At-line, online, inline or offline: what is the difference? Enablers of PAT link between QbD and PAT mometrics: the glue that holds QbD and PAT together A new approach to batch process understanding: relative time modelling Hierarchical modelling	414 . 415 . 416 417 . 417 . 419 425 427 . 428 . 434
13.2 13. 13.3 13.3 13.4 13.5 13. 13. 13.	The 2.1 2.2 Proc 3.1 3.2 The Chei 5.1 5.2 5.3	Quality by Design (QbD) initiative The International Conference on Harmonisation (ICH) guidance US FDA process validation guidance vess analytical technology (PAT) At-line, online, inline or offline: what is the difference? Enablers of PAT Ink between QbD and PAT mometrics: the glue that holds QbD and PAT together A new approach to batch process understanding: relative time modelling Hierarchical modelling Classification–classification hierarchies	414 . 415 . 416 417 . 417 . 419 425 427 . 428 . 434
13.2 13. 13.3 13. 13.4 13.5 13. 13. 13. 13. 13.	The 2.1 2.2 Proc 3.1 3.2 The Cher 5.1 5.2 5.3 5.4	Quality by Design (QbD) initiative The International Conference on Harmonisation (ICH) guidance US FDA process validation guidance cess analytical technology (PAT) At-line, online, inline or offline: what is the difference? Enablers of PAT link between QbD and PAT mometrics: the glue that holds QbD and PAT together A new approach to batch process understanding: relative time modelling Hierarchical modelling Classification–classification hierarchies	414 . 415 . 416 417 . 417 . 419 425 427 . 428 . 434 . 434 . 435
13.2 13. 13.3 13. 13. 13. 13. 13. 13. 13. 13	The 2.1 2.2 Proc 3.1 3.2 The Chei 5.1 5.2 5.3 5.4 5.5	Quality by Design (QbD) initiative	414 . 415 . 416 417 . 417 . 419 425 427 . 428 . 434 . 434 . 435 . 437
13.2 13. 13.3 13.3 13.4 13.4 13.5 13. 13. 13. 13. 13. 13.	The 2.1 2.2 Proc 3.1 3.2 The Chei 5.1 5.2 5.3 5.4 5.5 5.6	Quality by Design (QbD) initiative The International Conference on Harmonisation (ICH) guidance US FDA process validation guidance vess analytical technology (PAT) At-line, online, inline or offline: what is the difference? Enablers of PAT link between QbD and PAT mometrics: the glue that holds QbD and PAT together A new approach to batch process understanding: relative time modelling Hierarchical modelling Classification–classification hierarchies Prediction–prediction hierarchies Continuous pharmaceutical manufacturing: the embodiment of QbD and PAT	414 . 415 . 416 417 . 417 . 419 425 427 . 428 . 428 . 434 . 434 . 435 . 437
13.2 13. 13.3 13.3 13.4 13.4 13.5 13. 13. 13. 13. 13. 13.	The 2.1 2.2 Proc 3.1 3.2 The Chei 5.1 5.2 5.3 5.4 5.5 5.6	Quality by Design (QbD) initiative	414 . 415 . 416 417 . 417 . 419 425 427 . 428 . 428 . 434 . 434 . 435 . 437 [438 440
13.2 13. 13.3 13.3 13.4 13.4 13.5 13. 13. 13. 13. 13. 13.	The 2.1 2.2 Proc 3.1 3.2 The Cher 5.1 5.2 5.3 5.4 5.5 5.6 An ir	Quality by Design (QbD) initiative	414 . 415 . 416 417 . 417 . 419 425 427 . 428 . 434 . 434 . 435 . 437 F 438 440 . 441
13.2 13. 13.3 13.3 13.4 13.5 13. 13. 13. 13. 13. 13.6 13. 13.	The 2.1 2.2 Proc 3.1 3.2 The Cher 5.1 5.2 5.3 5.4 5.5 5.6 An ir	Quality by Design (QbD) initiative	414 . 415 . 416 417 . 417 . 419 425 427 . 428 . 434 . 434 . 435 . 437 F 438 440 . 441 . 443

13.7	Mod	lel lifecycle management	445
13.	.7.1	The iterative model building cycle	446
13	.7.2	A general procedure for model updating	448
13	.7.3	Summary of model lifecycle management	449
13.8	Cha	pter summary	449
13.9	Refe	erences	452

.