

## Contents

### List of Contributors XI

<b>1</b>	<b>Detection in Capillary Electrophoresis – An Introduction</b>	<b>1</b>
	<i>Gerhardus de Jong</i>	
1.1	UV Absorption	2
1.2	Fluorescence	2
1.3	Conductivity	3
1.4	Mass Spectrometry	4
	References	4
<b>2</b>	<b>Electrospray Ionization Interface Development for Capillary Electrophoresis–Mass Spectrometry</b>	<b>7</b>
	<i>Jessica M. Risley, Caitlyn A.G. De Jong, and David D.Y. Chen</i>	
2.1	A Brief Introduction to the Development of CE-MS	7
2.2	Fundamentals of ESI and Electrochemical Reactions in CE-MS	8
2.2.1	Principles of ESI: Converting Solvated Ions into Gaseous Ions	8
2.2.2	Considerations and Conditions for CE-ESI-MS Methods	9
2.2.3	Electrochemical Considerations in CE-MS	10
2.3	Interface Designs	11
2.3.1	Sheath-Flow Interfaces	11
2.3.1.1	Flow-Through Microvial Interface	12
2.3.1.2	Nanospray Sheath-Flow Interfaces	13
2.3.1.3	Electrokinetically Pumped Sheath-Flow Nanospray Interface	13
2.3.2	Sheathless Interfaces	15
2.3.2.1	Porous-Tip Nanospray Sheathless Interface/CESI 8000	15
2.3.2.2	Sheathless Porous Emitter NanoESI Interface	16
2.3.3	Interface Applications/CE Mode of Separation	17
2.4	Specific Interface Applications	18
2.4.1	Capillary Isoelectric Focusing	18
2.4.2	Glycan Analysis by CE-ESI-MS	19
2.5	Conclusion	20
	Abbreviations	32

	Acknowledgments	32
	References	32
<b>3</b>	<b>Sheath Liquids in CE-MS: Role, Parameters, and Optimization</b>	<b>41</b>
	<i>Christian W. Klampfl and Markus Himmelsbach</i>	
3.1	Introduction	41
3.2	Sheath-Liquid Functions and Sheath-Flow Interface Design	42
3.2.1	Coaxial Sheath-Flow Interface	42
3.2.2	Liquid Junction Interface	44
3.3	Sheath-Liquid-Related Parameters and their Selection	46
3.3.1	Sheath-Liquid Composition	46
3.3.2	Effect of Sheath-Liquid Composition on Molecular Structures	51
3.3.3	Sheath-Liquid Flow Rates and their Optimization	51
3.4	Sheath Liquids for Non-ESI CE-MS Interfaces	53
3.4.1	APCI and APPI	53
3.5	Sheath-Flow Chemistry	57
3.6	Conclusions	59
	References	61
<b>4</b>	<b>Recent Developments of Microchip Capillary Electrophoresis Coupled with Mass Spectrometry</b>	<b>67</b>
	<i>Gerard Rozing</i>	
4.1	Introduction	67
4.2	Microchip Capillary Electrophoresis	68
4.2.1	Brief Retrospective	68
4.2.2	Principle of Operation of MCE	69
4.2.3	Preparation and Availability of Microfluidic Chips for Capillary Electrophoresis	71
4.3	Reviews on MCE and MCE-MS	72
4.4	Principal Requirements for MCE-MS	74
4.4.1	Electrospray Ionization	74
4.4.2	Principle Layout of MCE-MS Devices	76
4.5	MCEMS by Direct Off-Chip Spraying	77
4.6	MCE-MS with Connected Sprayer	78
4.7	MCE-MS Devices with Integrated Sprayer	83
4.8	Multidimensional MCE-MS Devices	90
4.9	Conclusions and Perspectives	91
	References	96
<b>5</b>	<b>On-Line Electrophoretic, Electrochromatographic, and Chromatographic Sample Concentration in CE-MS</b>	<b>103</b>
	<i>Joselito P. Quirino</i>	
5.1	Introduction	103
5.2	Electrophoretic and Electrochromatographic Sample Concentration or Stacking	104

5.2.1	Electrophoretic Stacking Techniques	104
5.2.1.1	Transient Isotachopheresis or t-ITP	105
5.2.1.2	Field-Amplified/Enhanced Stacking	107
5.2.1.3	Dynamic pH Junction	110
5.2.2	Electrochromatographic Sample Concentration	113
5.2.2.1	Sweeping	113
5.2.2.2	Analyte Focusing by Micelle Collapse or AFMC	114
5.2.2.3	Micelle to Solvent Stacking or MSS	115
5.3	On-line/In-line SPE with CE-MS	115
5.3.1	On-line SPE	116
5.3.2	In-line SPE	117
5.4	Conclusion	121
	Acknowledgment	122
	References	122
<b>6</b>	<b>CE-MS in Drug Analysis and Bioanalysis</b>	<b>129</b>
	<i>Julie Schappler, Víctor González-Ruiz, and Serge Rudaz</i>	
6.1	Introduction	129
6.2	CE-MS in Drug Analysis	132
6.2.1	Impurity Profiling	134
6.2.2	Chiral Analysis	135
6.2.3	Determination of Drugs' Physicochemical Properties	136
6.2.3.1	$pK_a$ and $\log P$	137
6.2.3.2	Plasma Protein Binding	140
6.3	CE-MS in Bioanalysis	141
6.3.1	Selectivity Issues and Matrix Effects	142
6.3.2	Sample Preparation	144
6.4	CE-MS in Drug Metabolism Studies	145
6.4.1	Electrophoretically Mediated Microanalysis	146
6.4.2	Targeted <i>in vitro</i> Metabolism Assays	147
6.5	Quantitative Aspects in CE-MS	148
6.5.1	Instrumental Aspects	148
6.5.2	Methodological Aspects	149
6.6	Conclusions	151
	Abbreviations	151
	References	152
<b>7</b>	<b>CE-MS for the analysis of intact proteins</b>	<b>159</b>
	<i>Rob Haselberg and Govert W. Somsen</i>	
7.1	Introduction	159
7.2	CE of Intact Proteins	161
7.2.1	CE Modes	161
7.2.2	Preventing Protein Adsorption	161
7.3	MS Detection of Intact Proteins	164
7.3.1	Ionization Modes	164

- 7.3.2 Mass Analyzers 167
- 7.4 Applications of Intact Protein CE-MS 168
  - 7.4.1 Biopharmaceuticals 168
  - 7.4.2 Glycoproteins 174
  - 7.4.3 Protein–Ligand Interactions 177
  - 7.4.4 Metalloproteins 180
  - 7.4.5 Top-Down Protein Analysis 182
  - 7.4.6 Other Selected Applications 184
- 7.5 Conclusions 186
- Abbreviations 187
- References 188
  
- 8 CE-MS in Food Analysis and Foodomics 193**  
*Tanize Acunha, Clara Ibáñez, Virginia García-Cañas, Alejandro Cifuentes, and Carolina Simó*
  - 8.1 Introduction: CE-MS, Food Analysis, and Foodomics 193
    - 8.1.1 CE-MS and Food Safety 194
    - 8.1.2 CE-MS in Food Quality and Authenticity 201
    - 8.1.3 CE-MS and Foodomics 204
  - 8.2 Concluding Remarks 209
  - Acknowledgments 209
  - References 210
  
- 9 CE-MS in Forensic Sciences with Focus on Forensic Toxicology 217**  
*Nadia Porpiglia, Elena Giacomazzi, Rossella Gottardo, and Franco Tagliaro*
  - 9.1 Introduction 217
  - 9.2 Sample Preparation of Forensically Relevant Matrices 218
    - 9.2.1 Blood 219
    - 9.2.2 Urine 221
    - 9.2.3 Hair 223
    - 9.2.4 Saliva 224
  - 9.3 Separation Modes and Analytical Conditions 225
    - 9.3.1 Capillary Zone Electrophoresis 225
    - 9.3.2 Capillary Isotachopheresis 226
    - 9.3.3 Micellar Electrokinetic Chromatography 227
    - 9.3.4 Capillary Electrochromatography 228
    - 9.3.5 Capillary Gel Electrophoresis 228
    - 9.3.6 Chiral Separation 228
    - 9.3.7 Analytical Conditions 231
  - 9.4 Applications 234
    - 9.4.1 Forensic Toxicology 234
      - 9.4.1.1 Drugs of Abuse 235
      - 9.4.1.2 Alcohol Abuse Biomarkers 247

- 9.4.1.3 Doping 251
- 9.4.2 Trace Evidence Analysis 257
  - 9.4.2.1 Gunshot Residues, Explosives, and Chemical Weapons 259
  - 9.4.2.2 Inks 264
  - 9.4.2.3 Dyes 265
  - 9.4.2.4 Textile Fibers 268
- 9.4.3 Forensic DNA 269
- 9.4.4 Occupational and Environmental Health 272
  - 9.4.4.1 Toxins 274
  - 9.4.4.2 Venoms 275
  - 9.4.4.3 Pesticides 276
- 9.5 Conclusions 278
- References 280
  
- 10 CE-MS in Metabolomics 293**  
*Akiyoshi Hirayama and Tomoyoshi Soga*
  - 10.1 Introduction 293
  - 10.2 Sample Preparation and MS Systems 294
  - 10.3 Application 297
    - 10.3.1 Blood 298
    - 10.3.2 Urine 302
    - 10.3.3 Other Biofluids 303
    - 10.3.4 Cell Cultures 304
    - 10.3.5 Tissue 305
    - 10.3.6 Plants 308
  - 10.4 Conclusions 308
  - Acknowledgments 310
  - References 310
  
- 11 CE-MS for Clinical Proteomics and Metabolomics: Strategies and Applications 315**  
*Rawi Ramautar and Philip Britz-McKibbin*
  - 11.1 Introduction 315
  - 11.2 Clinical Proteomics 317
    - 11.2.1 Sample Pretreatment 317
    - 11.2.2 Separation Conditions 319
    - 11.2.3 Data Analysis and Validation 322
    - 11.2.4 Comparison of CE-MS with Other Techniques 325
  - 11.3 Clinical Metabolomics 328
    - 11.3.1 CE-MS Strategies for Clinical Metabolomics 328
    - 11.3.2 Data Analysis and Clinical Validation 335
    - 11.3.3 Comparison of CE-MS with Other Techniques 337
  - 11.4 Conclusions and Perspectives 339

Abbreviations 339  
 Acknowledgments 340  
 References 340

**Index 345**

10 CE-MS in Metabolomics 361  
 10.1 Introduction 362  
 10.2 Sample Preparation and MS/MS Acquisition 363  
 10.3 Application 365  
 10.3.1 Blood 366  
 10.3.2 Urine 367  
 10.3.3 Other Biofluids 368  
 10.3.4 Cell Culture 369  
 10.3.5 Other 370  
 10.4 Conclusions 370  
 10.5 Acknowledgments 371  
 10.6 References 371  
 11 CE-MS for Clinical Proteomics and Metabolomics: Strategies and Applications 372  
 11.1 Introduction 372  
 11.2 Clinical Proteomics 372  
 11.3 Sample Preparation 373  
 11.4 Separation Conditions 374  
 11.5 Data Analysis and Validation 375  
 11.6 Comparison of CE-MS with Other Technologies 376  
 11.7 Clinical Metabolomics 377  
 11.8 CE-MS Strategies for Clinical Proteomics 378  
 11.9 Data Analysis and Clinical Validation 379  
 11.10 Comparison of CE-MS with Other Technologies 380  
 11.11 Conclusions and Perspectives 381