

Contents

Foreword *xvii*

List of Contributors *xxi*

1	Introduction	1
	<i>Thomas Engel and Johann Gasteiger</i>	
1.1	The Rationale for the Books	1
1.2	Development of the Field	2
1.3	The Basis of Chemoinformatics and the Diversity of Applications	3
1.3.1	Databases	3
1.3.2	Fundamental Questions of a Chemist	4
1.3.3	Drug Discovery	5
1.3.4	Additional Fields of Application	6
	Reference	7
2	QSAR/QSPR	9
	<i>Wolfgang Sippl and Dina Robaa</i>	
2.1	Introduction	9
2.2	Data Handling and Curation	13
2.2.1	Structural Data	13
2.2.2	Biological Data	14
2.3	Molecular Descriptors	14
2.3.1	Structural Keys (1D)	15
2.3.2	Topological Descriptors (2D)	16
2.3.3	Geometric Descriptors (3D)	16
2.4	Methods for Data Analysis	17
2.4.1	Overview	17
2.4.2	Unsupervised Learning	17
2.4.3	Supervised Learning	18
2.5	Classification Methods	19
2.5.1	Principal Component Analysis	19
2.5.2	Linear Discriminant Analysis	19
2.5.3	Kohonen Neural Network	19
2.5.4	Other Classification Methods	20
2.6	Methods for Data Modeling	20

2.6.1	Regression-Based QSAR Approaches	20
2.6.2	3D QSAR	22
2.6.3	Nonlinear Models	25
2.7	Summary on Data Analysis Methods	30
2.8	Model Validation	30
2.8.1	Proper Use of Validation Routines	31
2.8.2	Modeling/Validation Workflow	32
2.8.3	Splitting of Datasets	32
2.8.4	Compilation of Modeling, Training, Validation, Test, and External Sets	34
2.8.5	Cross-Validation	36
2.8.6	Bootstrapping	37
2.8.7	Y-Randomization (Y-Scrambling)	38
2.8.8	Goodness of Prediction and Quality Criteria	39
2.8.9	Applicability Domain and Model Acceptability Criteria	41
2.8.10	Scope of External and Internal Validation	43
2.8.11	Validation of Classification Models	45
2.9	Regulatory Use of QSARs	46
	Selected Reading	48
	References	49

3 Prediction of Physicochemical Properties of Compounds

Igor V. Tetko, Aixia Yan, and Johann Gasteiger

3.1	Introduction	53
3.2	Overview of Modeling Approaches to Predict Physicochemical Properties	54
3.2.1	Prediction of Properties Based on Other Properties	55
3.2.2	Prediction of Properties Based on Theoretical Calculations	55
3.2.3	Additivity Schemes for Property Prediction	56
3.2.4	Statistical Quantitative Structure–Property Relationships (QSPRs)	59
3.3	Methods for the Prediction of Individual Properties	59
3.3.1	Mean Molecular Polarizability	59
3.3.2	Thermodynamic Properties	60
3.3.3	Octanol/Water Partition Coefficient (Log <i>P</i>)	63
3.3.4	Octanol/Water Distribution Coefficient (log <i>D</i>)	67
3.3.5	Estimation of Water Solubility (log <i>S</i>)	69
3.3.6	Melting Point (MP)	71
3.3.7	Acid Ionization Constants	73
3.4	Limitations of Statistical Methods	76
3.5	Outlook and Perspectives	76
	Selected Reading	78
	References	78

4	Chemical Reactions	83
4.1	Chemical Reactions – An Introduction	84
	<i>Johann Gasteiger</i>	
	References	85
4.2	Reaction Prediction and Synthesis Design	86
	<i>Jonathan M. Goodman</i>	
4.2.1	Introduction	86
4.2.2	Reaction Prediction	87
4.2.3	Synthesis Design	94
4.2.4	Conclusion	102
	References	103
4.3	Explorations into Biochemical Pathways	106
	<i>Oliver Sacher and Johann Gasteiger</i>	
4.3.1	Introduction	106
4.3.2	The BioPath.Database	110
4.3.3	BioPath.Explore	111
4.3.4	Search Results	112
4.3.5	Exploitation of the Information in BioPath.Database	117
4.3.6	Summary	129
	Selected Reading	130
	References	130
5	Structure–Spectrum Correlations and Computer-Assisted Structure Elucidation	133
	<i>Joao Aires de Sousa</i>	
5.1	Introduction	133
5.2	Molecular Descriptors	135
5.2.1	Fragment-Based Descriptors	135
5.2.2	Topological Structure Codes	135
5.2.3	Three-Dimensional Molecular Descriptors	137
5.3	Infrared Spectra	137
5.3.1	Overview	137
5.3.2	Infrared Spectra Simulation	138
5.4	NMR Spectra	140
5.4.1	Quantum Chemistry Prediction of NMR Properties	142
5.4.2	NMR Spectra Prediction by Database Searching	142
5.4.3	NMR Spectra Prediction by Increment-Based Methods	143
5.4.4	NMR Spectra Prediction by Machine Learning Methods	144
5.5	Mass Spectra	150
5.5.1	Identification of Structures and Interpretation of MS	150
5.5.2	Prediction of MS	151
5.5.3	Metabolomics and Natural Products	151
5.6	Computer-Aided Structure Elucidation (CASE)	153

Selected Reading 157
Acknowledgement 157
References 158

6.1 Drug Discovery: An Overview 165

Lothar Terfloth, Simon Spycher, and Johann Gasteiger

- 6.1.1 Introduction 165
- 6.1.2 Definitions of Some Terms Used in Drug Design 167
- 6.1.3 The Drug Discovery Process 167
- 6.1.4 Bio- and Chemoinformatics Tools for Drug Design 168
- 6.1.5 Structure-based and Ligand-Based Drug Design 168
- 6.1.6 Target Identification and Validation 169
- 6.1.7 Lead Finding 171
- 6.1.8 Lead Optimization 182
- 6.1.9 Preclinical and Clinical Trials 188
- 6.1.10 Outlook: Future Perspectives 189
- Selected Reading 191
- References 191

6.2 Bridging Information on Drugs, Targets, and Diseases 195

Andreas Steffen and Bertram Weiss

- 6.2.1 Introduction 195
- 6.2.2 Existing Data Sources 196
- 6.2.3 Drug Discovery Use Cases in Computational Life Sciences 196
- 6.2.4 Discussion and Outlook 201
- Selected Reading 202
- References 202

6.3 Chemoinformatics in Natural Product Research 207

Teresa Kaserer, Daniela Schuster, and Judith M. Rollinger

- 6.3.1 Introduction 207
- 6.3.2 Potential and Challenges 208
- 6.3.3 Access to Software and Data 211
- 6.3.4 *In Silico* Driven Pharmacognosy-Hyphenated Strategies 219
- 6.3.5 Opportunities 220
- 6.3.6 Miscellaneous Applications 228
- 6.3.7 Limits 228
- 6.3.8 Conclusion and Outlook 229
- Selected Reading 231
- References 231

6.4 Chemoinformatics of Chinese Herbal Medicines 237

Jun Xu

- 6.4.1 Introduction 237
- 6.4.2 Type 2 Diabetes: The Western Approach 237
- 6.4.3 Type 2 Diabetes: The Chinese Herbal Medicines Approach 238

6.4.4	Building a Bridge	238
6.4.5	Screening Approach	240
	Selected Reading	244
	References	244
6.5	PubChem	245
	<i>Wolf-D. Ihlenfeldt</i>	
6.5.1	Introduction	245
6.5.2	Objectives	246
6.5.3	Architecture	246
6.5.4	Data Sources	247
6.5.5	Submission Processing and Structure Representation	248
6.5.6	Data Augmentation	249
6.5.7	Preparation for Database Storage	249
6.5.8	Query Data Preparation and Structure Searching	250
6.5.9	Structure Query Input	253
6.5.10	Query Processing	254
6.5.11	Getting Started with PubChem	254
6.5.12	Web Services	255
6.5.13	Conclusion	255
	References	256
6.6	Pharmacophore Perception and Applications	259
	<i>Thomas Seidel, Gerhard Wolber, and Manuela S. Murgueitio</i>	
6.6.1	Introduction	259
6.6.2	Historical Development of the Modern Pharmacophore Concept	260
6.6.3	Representation of Pharmacophores	262
6.6.4	Pharmacophore Modeling	268
6.6.5	Application of Pharmacophores in Drug Design	272
6.6.6	Software for Computer-Aided Pharmacophore Modeling and Screening	278
6.6.7	Summary	278
	Selected Reading	279
	References	280
6.7	Prediction, Analysis, and Comparison of Active Sites	283
	<i>Andrea Volkamer, Mathias M. von Behren, Stefan Bietz, and Matthias Rarey</i>	
6.7.1	Introduction	283
6.7.2	Active Site Prediction Algorithms	284
6.7.3	Target Prioritization: Druggability Prediction	292
6.7.4	Search for Sequentially Homologous Pockets	296
6.7.5	Target Comparison: Virtual Active Site Screening	298
6.7.6	Summary and Outlook	304
	Selected Reading	306
	References	306

6.8	Structure-Based Virtual Screening	313
	<i>Adrian Kolodzik, Nadine Schneider, and Matthias Rarey</i>	
6.8.1	Introduction	313
6.8.2	Docking Algorithms	315
6.8.3	Scoring	317
6.8.4	Structure-Based Virtual Screening Workflow	321
6.8.5	Protein-Based Pharmacophoric Filters	323
6.8.6	Validation	323
6.8.7	Summary and Outlook	326
	Selected Reading	328
	References	328
6.9	Prediction of ADME Properties	333
	<i>Aixia Yan</i>	
6.9.1	Introduction	333
6.9.2	General Consideration on SPR/QSPR Models	334
6.9.3	Estimation of Aqueous Solubility (log <i>S</i>)	336
6.9.4	Estimation of Blood–Brain Barrier Permeability (log <i>BB</i>)	342
6.9.5	Estimation of Human Intestinal Absorption (HIA)	346
6.9.6	Other ADME Properties	349
6.9.7	Summary	354
	Selected Reading	355
	References	355
6.10	Prediction of Xenobiotic Metabolism	359
	<i>Anthony Long and Ernest Murray</i>	
6.10.1	Introduction: The Importance of Xenobiotic Biotransformation in the Life Sciences	359
6.10.2	Biotransformation Types	362
6.10.3	Brief Review of Methods	364
6.10.4	User Needs: Scientists Use Metabolism Information in Different Ways	370
6.10.5	Case Studies	372
	Selected Reading	382
	References	383
6.11	Cheminformatics at the CADD Group of the National Cancer Institute	385
	<i>Megan L. Peach and Marc C. Nicklaus</i>	
6.11.1	Introduction and History	385
6.11.2	Chemical Information Services	386
6.11.3	Tools and Software	388
6.11.4	Synthesis and Activity Predictions	391
6.11.5	Downloadable Datasets	391
	References	392

6.12	Uncommon Data Sources for QSAR Modeling	395
	<i>Alexander Tropsha</i>	
6.12.1	Introduction	395
6.12.2	Observational Metadata and QSAR Modeling	397
6.12.3	Pharmacovigilance and QSAR	398
6.12.4	Conclusions	401
	Selected Reading	402
	References	402
6.13	Future Perspectives of Computational Drug Design	405
	<i>Gisbert Schneider</i>	
6.13.1	Where Do the Medicines of the Future Come from?	405
6.13.2	Integrating Design, Synthesis, and Testing	408
6.13.3	Toward Precision Medicine	409
6.13.4	Learning from Nature: From Complex Templates to Simple Designs	411
6.13.5	Conclusions	413
	Selected Reading	414
	References	414
7	Computational Approaches in Agricultural Research	417
	<i>Klaus-Jürgen Schleifer</i>	
7.1	Introduction	417
7.2	Research Strategies	418
7.2.1	Ligand-Based Approaches	419
7.2.2	Structure-Based Approaches	422
7.3	Estimation of Adverse Effects	429
7.3.1	<i>In Silico</i> Toxicology	429
7.3.2	Programs and Databases	430
7.3.3	<i>In Silico</i> Toxicology Models	432
7.4	Conclusion	435
	Selected Reading	436
	References	436
8	Cheminformatics in Modern Regulatory Science	439
	<i>Chihae Yang, James F. Rathman, Aleksey Tarkhov, Oliver Sacher, Thomas Kleinoeder, Jie Liu, Thomas Magdziarz, Aleksandra Mostraq, Joerg Marusczyk, Darshan Mehta, Christof Schwab, and Bruno Bienfait</i>	
8.1	Introduction	439
8.1.1	Science and Technology Progress	439
8.1.2	Regulatory Science in Twenty-First Century	440
8.2	Data Gap Filling Methods in Risk Assessment	441
8.2.1	QSAR and Structural Knowledge	442
8.2.2	Threshold of Toxicological Concern (TTC)	443
8.2.3	Read-Across (RA)	445
8.3	Database and Knowledge Base	448
8.3.1	Architecture of Structure-Searchable Toxicity Database	448

8.3.2	Data Model for Chemistry-Centered Toxicity Database	449
8.3.3	Inventories	452
8.4	New Approach Descriptors	453
8.4.1	ToxPrint Chemotypes	453
8.4.2	Liver BioPath Chemotypes	458
8.4.3	Dynamic Generation of Annotated Linear Paths	459
8.4.4	Other Examples of Descriptors	461
8.5	Chemical Space Analysis	462
8.5.1	Principal Component Analysis	462
8.6	Summary	464
	Selected Reading	466
	References	466

9 Chemometrics in Analytical Chemistry 471

Anita Rácz, Dávid Bajusz, and Károly Héberger

9.1	Introduction	471
9.2	Sources of Data: Data Preprocessing	472
9.3	Data Analysis Methods	475
9.3.1	Qualitative Methods	475
9.3.2	Quantitative Methods	483
9.4	Validation	488
9.5	Applications	492
9.6	Outlook and Prospects	492
	Selected Reading	496
	References	496

10 Chemoinformatics in Food Science 501

Andrea Peña-Castillo, Oscar Méndez-Lucio, John R. Owen, Karina Martínez-Mayorga, and José L. Medina-Franco

10.1	Introduction	501
10.2	Scope of Chemoinformatics in Food Chemistry	502
10.3	Molecular Databases of Food Chemicals	503
10.4	Chemical Space of Food Chemicals	506
10.4.1	General Considerations	506
10.4.2	Chemical Space Analysis of Food Chemical Databases	508
10.5	Structure–Property Relationships	510
10.5.1	Structure–Flavor Relationships and Flavor Cliffs	511
10.5.2	Quantitative Structure–Odor Relationships	512
10.6	Computational Screening and Data Mining of Food Chemicals Libraries	513
10.6.1	Anticonvulsant Effect of Sweeteners and Pharmaceutical and Food Preservatives	514
10.6.2	Mining Food Chemicals as Potential Epigenetic Modulators	516
10.7	Conclusion	521
	Selected Reading	522
	References	523

11	Computational Approaches to Cosmetics Products	
	Discovery	527
	<i>Soheila Anzali, Frank Pflücker, Lilia Heider, and Alfred Jonczyk</i>	
11.1	Introduction: Cosmetics Demands on Computational Approaches	527
11.2	Case I: The Multifunctional Role of Ectoine as a Natural Cell Protectant (Product: Ectoine, "Cell Protection Factor", and Moisturizer)	528
11.2.1	Molecular Dynamics (MD) Simulations	530
11.2.2	Results and Discussion: Ectoine Retains the Power of Water	531
11.3	Case II: A Smart Cyclopeptide Mimics the RGD Containing Cell Adhesion Proteins at the Right Site (Product: Cyclopeptide-5: Antiaging)	533
11.3.1	Methods	536
11.3.2	Results and Discussion	536
11.4	Conclusions: Cases I and II	542
	References	545
12	Applications in Materials Science	547
	<i>Tu C. Le, and David A. Winkler</i>	
12.1	Introduction	547
12.2	Why Materials Are Harder to Model than Molecules	548
12.3	Why Are Chemoinformatics Methods Important Now?	548
12.4	How Do You Describe Materials Mathematically?	549
12.5	How Well do Chemoinformatics Methods Work on Materials?	551
12.6	What Are the Pitfalls when Modeling Materials?	551
12.7	How Do You Make Good Models and Avoid the Pitfalls?	553
12.8	Materials Examples	554
12.8.1	Inorganic Materials and Nanomaterials	554
12.8.2	Polymers	557
12.8.3	Catalysts	558
12.8.4	Metal–Organic Frameworks (MOFs)	560
12.9	Biomaterials Examples	561
12.9.1	Bioactive Polymers	561
12.9.2	Microarrays	564
12.10	Perspectives	566
	Selected Reading	567
	References	567
13	Process Control and Soft Sensors	571
	<i>Kimito Funatsu</i>	
13.1	Introduction	571
13.2	Roles of Soft Sensors	573
13.3	Problems with Soft Sensors	574
13.4	Adaptive Soft Sensors	576

13.5	Database Monitoring for Soft Sensors	578
13.6	Efficient Process Control Using Soft Sensors	581
13.7	Conclusions	582
	Selected Readings	583
	References	583
14	Future Directions	585
	<i>Johann Gasteiger</i>	
14.1	Well-Established Fields of Application	585
14.2	Emerging Fields of Application	586
14.3	Renaissance of Some Fields	587
14.4	Combined Use of Chemoinformatics Methods	588
14.5	Impact on Chemical Research	589
	Index	591