

Contents

List of Contributors XV

Foreword XXI

Preface XXIII

1	<i>De Novo</i> Design: From Models to Molecules	1
	<i>Gisbert Schneider and Karl-Heinz Baringhaus</i>	
1.1	Molecular Representation	1
1.2	The Molecular Design Cycle	9
1.3	Receptor–Ligand Interaction	14
1.4	Modeling Fitness Landscapes	21
1.4.1	Naïve Bayes Classifier	26
1.4.2	Artificial Neural Network	27
1.4.3	Support Vector Machine	27
1.4.4	Gaussian Process	28
1.5	Strategies for Compound Construction	30
1.6	Strategies for Compound Scoring	33
1.6.1	Receptor-Based Scoring	35
1.6.2	Ligand-Based Scoring	37
1.7	Flashback Forward: A Brief History of <i>De Novo</i> Drug Design	37
1.8	Conclusions	43
	Acknowledgments	43
	References	44
2	Coping with Complexity in Molecular Design	57
	<i>Michael M. Hann and Andrew R. Leach</i>	
2.1	Introduction	57
2.2	A Simple Model of Molecular Interactions	58
2.3	Enhancements to the Simple Complexity Model	60
2.4	Enumerating and Sampling the Complexity of Chemical Space	61
2.5	Validation of the Complexity Model	65
2.6	Reductionism and Drug Design	67

2.7	Complexity and Information Content as a Factor in <i>De Novo</i> Design	69
2.8	Complexity of Thermodynamic Entropy and Drug Design	73
2.9	Complex Systems, Emergent Behavior, and Molecular Design	74
	Acknowledgments	75
	References	75
3	The Human Pocketome	79
	<i>Ruben Abagyan and Clarisse Gravina Ricci</i>	
3.1	Predicted Pockets	79
3.2	Compilation of the Validated Human Pocketome	83
3.3	Diversity and Redundancy of the Human Pocketome	85
3.4	Compound Activity Prediction by Ligand-Pocket Docking and Scoring	87
3.4.1	Optimizing Pocket Sets for Reliable Docking and Scoring Results	87
3.4.2	Difficult Cases: Unusually Large and Multifunctional Pockets	88
3.5	Pocketome-Derived 3D Chemical Fields as Activity Prediction Models	90
3.6	Clustering the Ligands by Function and Subpockets	92
3.7	Conclusions	94
	Acknowledgments	94
	References	94
4	Structure-Based <i>De Novo</i> Drug Design	97
	<i>Alla Srinivas Reddy, Lu Chen, and Shuxing Zhang</i>	
4.1	Introduction	97
4.2	Current Progress in SBDND Methodologies	99
4.2.1	Identification of Binding Site	100
4.2.2	Design of Molecules	101
4.2.2.1	Atom-Based versus Fragment-Based Methods	101
4.2.2.2	Pharmacophore-Based Methods	105
4.2.3	Searching the Chemical Space	105
4.2.3.1	Monte Carlo-Based Methods	106
4.2.3.2	Evolutionary Algorithms	106
4.2.4	Scoring Methods	108
4.2.4.1	Force-Field-Based Scoring Functions	108
4.2.4.2	Empirical Scoring Functions	109
4.2.4.3	Knowledge-Based Scoring Functions	109
4.2.4.4	Consensus Scoring	109
4.2.5	Synthetic Accessibility	110
4.3	Recent Applications of Structure-Based <i>De Novo</i> Design	110
4.4	Perspectives and Conclusion	115
	Acknowledgment	116
	References	116

5	De Novo Design by Fragment Growing and Docking	125
	<i>Jacob D. Durrant and Rommie E. Amaro</i>	
5.1	Introduction	125
5.2	Case Study I: High-Throughput Screening with Dr Feils	126
5.2.1	Target Identification	126
5.2.2	Small-Molecule Library Design	126
5.2.2.1	Computer Docking	128
5.2.2.2	Pharmacophore Searching	129
5.2.3	High-Throughput Screening	129
5.2.4	Optimization	130
5.3	Case Study II: Fragment-Based Drug Design with Dr Goode	130
5.3.1	Library Generation	130
5.3.1.1	Computational Techniques for Library Refinement	132
5.3.2	Detection Methods	132
5.3.2.1	Functional/High-Concentration Screening	132
5.3.2.2	Fluorescence-Based Thermal Shift Assay (TSA)	133
5.3.2.3	Surface Plasmon Resonance (SPR)	133
5.3.2.4	Mass Spectrometry (MS)	133
5.3.2.5	Nuclear Magnetic Resonance (NMR)	133
5.3.2.6	X-Ray Crystallography	134
5.3.3	Screening	134
5.3.4	Optimization	135
5.3.5	Final Products	137
5.4	Conclusion	138
	Disclaimer	138
	Acknowledgments	138
	References	138
6	Hit and Lead Identification from Fragments	143
	<i>Michael Mazanetz, Richard Law, and Mark Whittaker</i>	
6.1	Introduction to FBDD	144
6.2	Fragment Library Design Incorporating Computational Methods	148
6.2.1	Fragment Library Design Strategies	148
6.2.2	Molecular Attributes and Physicochemical Properties	150
6.2.3	Influence of Screening Method on Library Selection	151
6.2.4	Removal of Undesirable Functionality	152
6.2.5	Size of Library and Diversity	152
6.2.6	Focused Sets	154
6.2.7	Designing in Fragment Optimization	154
6.3	Fragment Screening	155
6.3.1	Screening by X-Ray Crystallography	155
6.3.2	Screening by NMR	156
6.3.3	Screening by SPR	157
6.3.4	Screening by Biochemical Assay	157
6.3.5	Thermal Shift Assays	158

6.3.6	Isothermal Titration Calorimetry (ITC)	160
6.3.7	Other Biophysical Assay Techniques	160
6.3.8	Assay Techniques for Membrane Proteins	161
6.3.9	Fragment Library Screening Using Computational Methods	161
6.3.10	Ligandability Screening Using Fragments	162
6.4	Fragment Prioritization for Optimization	165
6.4.1	Efficiency Metrics	165
6.4.2	Computational and Thermodynamic Methods for Fragment Selection and Prioritization	167
6.5	Fragment Hit Expansion and Fragment Evolution	170
6.6	Fragment Merging Principles	175
6.7	Fragment Linking Principles	177
6.8	Fragment-Assisted Drug Discovery (FADD)	182
6.9	Conclusion	183
	Acknowledgments	184
	References	184
7	Pharmacophore-Based <i>De Novo</i> Design	201
	<i>Wen-Jing Wang, Qi Huang, and Sheng-Yong Yang</i>	
7.1	Introduction	201
7.2	A Summary of the Algorithms of PhDD v1.0	202
7.2.1	The Basic Scheme of PhDD	202
7.2.2	Fragment and Linker Databases	203
7.2.3	Mapping of Fragments onto the Locations of Pharmacophore Features of the Pharmacophore Hypothesis	204
7.2.4	Connecting Fragments by Linkers	205
7.2.5	Assessments to the Generated Molecules	206
7.2.5.1	The Drug-Likeness Assessment	207
7.2.5.2	The Estimation of Bioactivity	207
7.2.5.3	The Assessment of Synthetic Accessibility	207
7.3	An Introduction to the Modifications in the Updated Version of PhDD (v2.0)	208
7.3.1	The Use of a Designated Fragment	209
7.3.2	Conformation Optimization in the Process of Molecular Construction	209
7.3.3	Two Pharmacophore Features Share One Fragment	210
7.4	Validation of PhDD	210
7.5	Concluding Remarks	212
	Acknowledgment	213
	References	213
8	3D-QSAR Approaches to <i>De Novo</i> Drug Design	215
	<i>Richard D. Cramer</i>	
8.1	Introduction	215
8.2	Current Methods	216

8.3	Leapfrog	217
8.4	Recent Advances	219
8.5	Conclusions	223
	Acknowledgments	223
	References	223
9	Ligand-Based Molecular Design Using Pseudoreceptors	227
	<i>Darren Fayne</i>	
9.1	Introduction	227
9.2	Pseudoreceptor Algorithms	231
9.3	Successful Applications Overview	232
9.4	Conclusions	240
	Acknowledgments	241
	References	241
10	Reaction-Driven <i>De Novo</i> Design: a Keystone for Automated Design of Target Family-Oriented Libraries	245
	<i>Markus Hartenfeller, Steffen Renner, and Edgar Jacoby</i>	
10.1	Introduction	245
10.2	Reaction-Driven Design: Tackling the Problem of Synthetic Feasibility	247
10.2.1	Exploiting the Valuable Knowledge Stored in Electronic Laboratory Notebooks	249
10.2.2	Assessing the Chemical Space of a Focused Set of Reactions	251
10.3	Successful Applications of Reaction-Driven <i>De Novo</i> Design	254
10.4	Reaction-Driven Design of Chemical Libraries Addressing Target Families	256
10.5	Conclusions	261
	References	265
11	Multiobjective <i>De Novo</i> Design of Synthetically Accessible Compounds	267
	<i>Valerie J. Gillet, Michael J. Bodkin, and Dimitar Hristozov</i>	
11.1	Introduction	267
11.2	Design of Synthetically Accessible Compounds	269
11.3	Synthetic Accessibility Using Reaction Vectors	270
11.4	<i>De Novo</i> Design Using Evolutionary Algorithms	276
11.4.1	Optimizing Multiple Objectives	277
11.4.2	Multiobjective <i>De Novo</i> Design	279
11.4.3	Multiobjective <i>De Novo</i> Design Using Reaction Vectors	280
11.5	Conclusions	282
	Acknowledgments	283
	References	283

12	De Novo Design of Ligands against Multitarget Profiles	287
	<i>Jérémy Besnard and Andrew L. Hopkins</i>	
12.1	Introduction	287
12.2	Automating the Creativity of Ligand Design	289
12.3	Evolutionary Algorithm	294
12.4	Experimental Validation	295
12.5	Reducing Antitarget Activity	296
12.6	Optimizing D4 Receptor Potency	301
12.7	Designing Novel Ligands to a Defined Profile	301
12.8	Conclusion	304
	Acknowledgments	306
	References	306
13	Construction of Drug-Like Compounds by Markov Chains	311
	<i>Peter S. Kutchukian, Salla I. Virtanen, Eugen Lounkine, Meir Glick, and Eugene I. Shakhnovich</i>	
13.1	Introduction	311
13.2	FOG Algorithm and Library Generation	313
13.3	Applications	314
13.3.1	Overview	314
13.3.2	Target Class Prediction of FOG Compounds	314
13.3.3	Design of BACE-1 Inhibitors with FOG	316
13.4	Conclusion	319
	Acknowledgments	320
	References	320
14	Coping with Combinatorial Space in Molecular Design	325
	<i>Florian Lauck and Matthias Rarey</i>	
14.1	Introduction	325
14.2	Chemical Space	326
14.2.1	Size Estimation of Chemical Space	327
14.2.2	Enumeration of Chemical Subspaces	328
14.3	Combinatorial Space	330
14.3.1	Generation of Combinatorial Spaces	332
14.3.1.1	Combinatorial Space from Fragmentation	332
14.3.1.2	Computational Space from Chemical Knowledge	334
14.3.2	Manipulation of Combinatorial Space	335
14.3.3	Querying Combinatorial Spaces	336
14.3.3.1	Fragment Spaces	337
14.3.3.2	Reaction-Based Combinatorial Spaces	339
14.3.4	Other Applications of Combinatorial Space	340
14.3.5	Markush Structures	341
14.4	Visualization	342
14.5	Conclusion	343
	References	343

15	Fragment-Based Design of Focused Compound Libraries	349
	<i>Uta Lessel</i>	
15.1	Introduction	349
15.2	General Workflow	351
15.3	Fragment Space	352
15.4	Query	355
15.5	FTrees Fragment Space Search	356
15.6	Scaffold Selection	356
15.7	Design of Focused Libraries	359
15.8	Application Example	360
15.9	Summary and Conclusions	366
	Acknowledgments	367
	References	367
16	Free Energy Methods in Ligand Design	373
	<i>Yvonne Westermaier and Roderick E. Hubbard</i>	
16.1	Free Energy (FE) Methods in Lead Optimization (LO)	373
16.1.1	FE Methods: An Emerging Tool in Industry?	374
16.1.2	Finding the Needle in a Haystack: The Role of FE Methods in Fine-Tuning Ligand Discovery	375
16.2	The Variety of <i>In Silico</i> Binding Affinity Methods	377
16.2.1	Thermodynamic Integration (TI) and Alchemical Transformations	377
16.2.2	Free Energy Perturbation (FEP)	378
16.2.3	Potential of Mean Force (PMF) Calculations	379
16.2.4	Nonequilibrium Approaches	380
16.2.5	Other MM-Based Methods	381
16.2.5.1	Linear Interaction Energy (LIE)	381
16.2.5.2	MM-PBSA and MM-GBSA	382
16.3	The Choice of a Method for Calculating Binding FE	382
16.3.1	MM-PBSA and MM-GBSA versus FEP/TI	383
16.3.2	LIE versus FEP/TI	383
16.3.3	PMF versus FEP	383
16.3.4	PMF versus TI	383
16.3.5	TI versus FEP	384
16.3.6	PMF/TI/FEP: Absolute or Relative Binding FEs?	384
16.3.7	Equilibrium versus Nonequilibrium Methods	385
16.4	Experimental Data	385
16.5	Current Issues	385
16.6	Practical Examples	387
16.6.1	Studies on Model Systems	387
16.6.2	FE Methods Applied to Pharmaceutically Relevant Systems	389

16.7	Miscellaneous Issues	395
16.8	Best Practices	396
16.9	Conclusions and Outlook	397
	Acknowledgments	398
	Abbreviations	398
	References	399
17	Bioisosteres in <i>De Novo</i> Design	417
	<i>Nicholas C. Firth, Julian Blagg, and Nathan Brown</i>	
17.1	Introduction	417
17.2	History of Isosterism and Bioisosterism	418
17.3	Methods for Bioisosteric Replacement	421
17.3.1	Databases	422
17.3.1.1	BROSTER	422
17.3.1.2	Cambridge Structure Database	422
17.3.1.3	ChEMBL	423
17.3.2	Descriptors	424
17.3.2.1	Physicochemical Properties	424
17.3.2.2	Molecular Topology	426
17.3.2.3	Molecular Shape	426
17.4	Exemplar Applications	427
17.4.1	Information-Based Bioisosteric Replacement	427
17.4.2	Drug Guru	429
17.4.3	SkelGen	431
17.5	Conclusions	433
	Acknowledgments	433
	References	434
18	Peptide Design by Nature-Inspired Algorithms	437
	<i>Jan A. Hiss and Gisbert Schneider</i>	
18.1	Template-Based Design	437
18.2	Nature-Inspired Optimization	441
18.2.1	Evolutionary Algorithms	444
18.2.2	Particle Swarm Optimization	446
18.2.3	Ant Colony Optimization	449
18.3	Worked Example: <i>De Novo</i> Design of MHC-I Binding Peptides by Ant Colony Optimization	450
18.4	Chemical Modification	456
18.4.1	Backbone Cyclization	456
18.4.2	Stapling	458
18.4.3	End-Capping	458
18.4.4	Sugar-Coating	459
18.5	Conclusions and Outlook	460

Acknowledgments 461

References 461

- 19 De Novo Computational Protein Design 467**
Jeffery G. Saven
- 19.1 Introduction 467
- 19.2 Elements of Computational Protein Design 470
- 19.2.1 Target Structures 470
- 19.2.2 Degrees of Freedom: Amino Acids and Side-Chain Conformations 470
- 19.2.2.1 Amino Acids 470
- 19.2.2.2 Side-Chain Conformations 471
- 19.2.3 Energy Functions 471
- 19.2.4 Solvation 472
- 19.2.5 Foldability Criteria and Negative Design 472
- 19.2.6 Sequence Search and Characterization 473
- 19.2.6.1 Monte Carlo 473
- 19.2.6.2 Dead-End Elimination 474
- 19.2.6.3 Mean Field Theory 475
- 19.2.6.4 Probabilistic Approach 475
- 19.3 Efforts in Theoretically Guided Protein Design 477
- 19.3.1 Toward Catalysis, Redox Activity, and Enzymes 477
- 19.3.2 De Novo Design and Redesign 478
- 19.3.3 Protein Reengineering 479
- 19.3.4 Cofactors and Nonbiological Protein Assemblies 480
- 19.3.5 Membrane Proteins 481
- 19.3.6 Protein–Protein Interactions and Protein Assemblies 483
- 19.4 Conclusion 485
- Acknowledgments 485
- References 486
- 20 De Novo Design of Nucleic Acid Structures 495**
Barbara Saccà, Andreas Sprengel, and Udo Feldkamp
- 20.1 Introduction 495
- 20.2 DNA-Branched Structures 499
- 20.2.1 De Novo Design of DNA Junctions 499
- 20.2.2 Tile-to-Tile Binding 504
- 20.3 Scaffolded DNA Origami Design 505
- 20.3.1 Monolayer DNA Origami 506
- 20.3.1.1 Two-Dimensional Structures 506
- 20.3.1.2 Three-Dimensional Structures 509
- 20.3.2 Multilayer DNA Origami 509
- 20.4 Alternative DNA Designs: between Junctions and Origami 511

20.5	Conclusions	514
	Acknowledgments	515
	References	515
21	RNA Aptamer Design	519
	<i>Cindy Meyer, Ulrich Hahn, and Andrew E. Torda</i>	
21.1	Aptamers and Design	519
21.2	Riboswitches and Aptamers	520
21.3	SELEX	521
21.3.1	Introduction	521
21.3.2	The Method	522
21.3.3	Technical Challenges and Recent Developments in SELEX	526
21.4	Speeding Up SELEX by Computational Methods	526
21.4.1	Design of Structures	529
21.5	Structures and Probing Methods	530
21.6	Functional Analyses (<i>In Vitro</i> and <i>In Vivo</i>)	532
21.7	Problems	533
21.8	Future Perspectives	535
	References	536
	Index	543