

Contents

	Preface to the Third Edition	X
1	Introduction	1
1.1	Modern History of Molecular Modeling	2
1.2	Do Today's Molecular Modeling Methods Only Make Pictures of the Lukretian World or Do They Make Anything More?	3
1.3	What are Models Used For?	4
1.4	Molecular Modeling Uses all Four Kinds for Model Building	5
1.5	The Final Step Is <i>Design</i>	5
1.6	Scope of the Book	6
2	Small Molecules	9
2.1	Generation of 3D Coordinates	9
2.1.1	Crystal Data	9
2.1.2	Fragment Libraries	10
2.1.3	Conversion of 2D Structural Data into 3D Form	12
	References	15
2.2	Computational Tools for Geometry Optimization	16
2.2.1	Force Fields	16
2.2.2	Geometry Optimization	19
2.2.3	Energy-minimizing Procedures	21
2.2.4	Use of Charges, Solvation Effects	23
2.2.5	Quantum Mechanical Methods	24
	References	29
2.3	Conformational Analysis	32
2.3.1	Conformational Analysis Using Systematic Search Procedures	34
2.3.2	Conformational Analysis Using Monte Carlo Methods	37
2.3.3	Conformational Analysis Using Molecular Dynamics	39
2.3.4	Which Is the Method of Choice?	44
	References	46

2.4	Determination of Molecular Interaction Potentials	50
2.4.1	Molecular Electrostatic Potentials (MEPs)	50
2.4.2	Molecular Interaction Fields	57
2.4.3	Display of Properties on a Molecular Surface	66
	References	66
	Further Reading	69
2.5	Pharmacophore Identification	70
2.5.1	Molecules to be Matched	70
2.5.2	Atom-by-atom Superposition	72
2.5.3	Superposition of Molecular Fields	74
	References	75
2.6	3D QSAR Methods	77
2.6.1	The CoMFA Method	77
2.6.2	Other CoMFA-related Methods	81
2.6.3	More 3D QSAR Methods	83
2.6.4	Receptor-based 3D QSAR	84
2.6.5	Reliability of 3D QSAR Models	86
	References	87
	Further Reading	91
3	A Case Study for Small Molecule Modeling: Dopamine D₃ Receptor Antagonists	93
3.1	A Pharmacophore Model for Dopamine D ₃ Receptor Antagonists	93
3.1.1	The Aromatic–Basic Fragment	99
3.1.2	The Spacer	100
3.1.3	The Aromatic–Amidic Residue	101
3.1.4	Resulting Pharmacophore	102
3.1.5	Molecular Interaction Fields	102
3.2	3D QSAR Analysis	104
3.2.1	Variable Reduction and PLS Model	104
3.2.2	Validation of the Model	107
3.2.3	Prediction of External Ligands	108
	References	110
4	Introduction to Comparative Protein Modeling	111
4.1	Where and How to Get Information on Proteins	111
	References	115
4.2	Terminology and Principles of Protein Structure	116
4.2.1	Conformational Properties of Proteins	116
4.2.2	Types of Secondary Structural Elements	119
4.2.3	Homologous Proteins	122
	References	124

4.3	Comparative Protein Modeling	126
4.3.1	Procedures for Sequence Alignments	127
4.3.2	Determination and Generation of Structurally Conserved Regions (SCRs)	133
4.3.3	Construction of Structurally Variable Regions (SVRs)	135
4.3.4	Side-Chain Modeling	136
4.3.5	Distance Geometry Approach	138
4.3.6	Secondary Structure Prediction	139
4.3.7	Threading Methods	141
	References	144
4.4	Optimization Procedures – Model Refinement – Molecular Dynamics	149
4.4.1	Force Fields for Protein Modeling	149
4.4.2	Geometry Optimization	150
4.4.3	The Use of Molecular Dynamics Simulations in Model Refinement	151
4.4.4	Treatment of Solvated Systems	153
4.4.5	Ligand-binding Site Complexes	155
	References	155
4.5	Validation of Protein Models	158
4.5.1	Stereochemical Accuracy	158
4.5.2	Packing Quality	164
4.5.3	Folding Reliability	166
	References	169
4.6	Properties of Proteins	173
4.6.1	Electrostatic Potential	173
4.6.2	Interaction Potentials	177
4.6.3	Hydrophobicity	177
	References	178
5	Virtual Screening and Docking	181
5.1	Preparation of the Partners	181
5.1.1	Preparation of the Compound Library	181
5.1.2	Representation of Proteins and Ligands	186
5.2	Docking Algorithms	189
5.2.1	Incremental Construction Methods	189
5.2.2	Genetic Algorithms	191
5.2.3	Tabu Search	192
5.2.4	Simulated Annealing and Monte Carlo Simulations	194
5.2.5	Shape-fitting Methods	195
5.2.6	Miscellaneous Approaches	195
5.3	Scoring Functions	196
5.3.1	Empirical Scoring Functions	196

5.3.2	Force-field-based Scoring Functions	198
5.3.3	Knowledge-based Scoring Functions	198
5.3.4	Critical Overview of Fast Scoring Functions	199
5.4	Postfiltering Virtual Screening Results	200
5.4.1	Filtering by Topological Properties	200
5.4.2	Filtering by Consensus Mining Approaches	200
5.4.3	Filtering by Combining Computational Procedures	201
5.4.4	Filtering by Chemical Diversity	201
5.4.5	Filtering by Visual Inspection	202
5.5	Comparison of Different Docking and Scoring Methods	202
5.6	Examples of Successful Virtual Screening Studies	203
5.7	Outlook	206
	References	207
6	Scope and Limits of Molecular Docking	217
6.1	Docking in the Polar Active Site that Contains Water Molecules	218
6.2	Including Cofactor in Docking ²	225
6.3	Impact of Tautomerism on Docking	227
	References	229
	Further Reading	231
7	Chemogenomic Approaches to Rational Drug Design	233
7.1	Description of Ligand and Target Spaces	235
7.1.1	Ligand Space	236
7.1.2	Target Space	238
7.1.3	Protein–Ligand Space	240
7.2	Ligand-based Chemogenomic Approaches	242
7.2.1	Annotating Ligand Libraries	242
7.2.2	Privileged Structures	244
7.2.3	Ligand-based <i>In silico</i> Screening	246
7.3	Target-based Chemogenomic Approaches	249
7.3.1	Sequence-based Comparisons	249
7.3.2	Structure-based Comparisons	251
7.4	Target-Ligand-based Chemogenomic Approaches	254
7.4.1	Chemical Annotation of Target Binding Sites	254
7.4.2	Two-dimensional Searches	256
7.4.3	Three-dimensional Searches	256
7.5	Concluding Remarks	258
	References	258

8	A Case Study for Protein Modeling: the Nuclear Hormone Receptor CAR as an Example for Comparative Modeling and the Analysis of Protein-Ligand Complexes	265
8.1	The Biochemical and Pharmacological Description of the Problem	265
8.1.1	Nuclear Hormone Receptor Superfamily	265
8.1.2	Molecular Architecture and Activation Mechanisms of Nuclear Hormone Receptors	265
8.1.3	The Human Constitutive Active Androstan Receptor (CAR)	267
8.1.4	CAR Ligands	267
8.2	Comparative Modeling of the Human Nuclear Hormone Receptor CAR	268
8.2.1	Choosing Appropriate Template Structures	269
8.2.2	Homology Modeling of the Human CAR	271
8.2.3	Setting up the System for the Molecular Dynamics Simulations	271
8.3	Analysis of the Models that Emerged from MD Simulations	272
8.3.1	Atomic Fluctuations	272
8.3.2	AF-2 Interaction Domain	275
8.3.3	Deciphering the Structural Basis for Constitutive Activity of Human CAR	276
8.3.4	Coactivator Binding	278
8.4	Analysis of CAR Mutants	279
8.4.1	Identifying Important Amino Acids for CAR Activation	279
8.4.2	MD Simulations of Selected CAR Mutants	282
8.5	Modeling of CAR-Ligand Complexes	284
8.6	The CAR X-ray Structure Comes into Play	286
8.6.1	How Accurate is the Generated CAR Model?	286
8.6.2	Docking Studies Using the CAR X-ray Structure	288
8.6.3	The Basis for Constitutive Activity Revisited	289
8.7	Virtual Screening for Novel CAR Activators	292
8.8	Concluding Remarks	295
	References	296
	Index	299