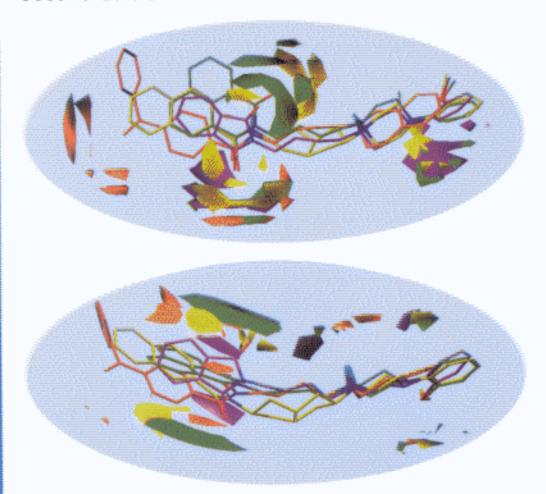


Molecular Modeling

Basic Principles and Applications

Second Edition



Inhalt

Preface 9

1	Introduction 1
1.1	Modern History of Molecular Modeling 2
1.2	Do Today's Molecular Modeling Methods Illustrate only the Lukretian
	World? 3
1.3	What are Models Used for? 4
1.4	Molecular Modeling Uses All Four Types for Model Building 4
1.5	The Final Step is Design 5
1.6	The 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	Sketch Approach 12
2.1.4	Conversion of 2D Structural Data into 3D Form 12
2.2	Computational Tools for Geometry Optimization 15
2.2.1	Force Fields 15
2.2.2	Geometry Optimization 17
2.2.3	Energy-Minimizing Procedures 18
2.2.4	Use of Charges, Solvation Effects 20
2.2.5	Quantum Mechanical Methods 21
2.3	Conformational Analysis 27
2.3.1	Conformational Analysis Using Systematic Search Procedures 29
2.3.2	Conformational Analysis Using Monte Carlo Methods 32
2.3.3	Conformational Analysis Using Molecular Dynamics 33
2.4	Determination of Molecular Interaction Potentials 42
2.4.1	Molecular Electrostatic Potentials (MEPs) 42
2.4.2	Molecular Interaction Fields 50
2.4.3	Display of Properties on a Molecular Surface 56
2.5	Pharmacophore Identification 59
2.5.1	Molecules to be Matched 59

VI	Inhalt	
	2.5.2	Atom-by-Atom Superposition 61
	2.5.3	Superposition of Molecular Fields 63
	2.6	3D QSAR Methods 65
	2.6.1	The CoMFA Method 65
	2.6.2	CoMFA-related Methods 69
	2.6.3	More 3D QSAR Methods 70
	3	A Case Study for Small Molecule Modeling:
		Dopamine D ₃ Receptor Antagonists 173
	3.1	A Pharmacophore Model for Dopamine D ₃ Receptor Antagonists 73
	3.1.1	The Aromatic-Basic Fragment 76
	3.1.2	The Spacer 78
	3.1.3	The Aromatic-Amidic Residue 79
	3.1.4	Resulting Pharmacophore 79
	3.1.5	Molecular Interaction Fields 80
	3.2	3D QSAR Analysis 82
	3.2.1	Variable Reduction and PLS model 82
	3.2.2	Validation of the Method 84
	3.2.3	Prediction of External Ligands 85
	4	Introduction to Comparative Protein Modeling 87
	4.1	Where and How to get Information on Proteins 87
	4.2	Terminology and Principles of Protein Structure 91
	4.2.1	Conformational Properties of Proteins 91
	4.2.2	Types of Secondary Structural Elements 94
	4.2.3	Homologous Proteins 98
	4.3	Comparative Protein Modeling 100
	4.3.1	Procedures for Sequence Alignments 101
	4.3.2	Determination and Generation of Structurally Conserved Regions (SCRs) 106
	4.3.3	Construction of Structurally Variable Regions (SVRs) 108
	4.3.4	Side Chain Modeling 109
	4.3.5	Distance Geometry Approach 111
	4.3.6	Secondary Structure Prediction 111
	4.3.7	Threading Methods 115
	4.4	Optimization Procedures—Model Refinement—Molecular
		Dynamics 119
	4.4.1	Force Fields for Protein Modeling 119
	4.4.2	Geometry Optimization 120
	4.4.3	The Use of Molecular Dynamics Simulations in Model Refinement 121
	4.4.4	Treatment of Solvated Systems 123
	4.4.5	Ligand-Binding Site Complexes 124
	4.5	Validation of Protein Models 126
	4.5.1	Stereochemical Accuracy 127
	4.5.2	Packing Quality 131

4.5.3	roiding Reliability 133
4.6	Properties of Proteins 138
4.6.1	Electrostatic Potential 138
4.6.2	Interaction Potentials 142
4.6.3	Hydrophobicity 142
5	Protein-based Virtual Screening 145
5.1	Preparation 145
5.1.1	Database Preparation 145
5.1.2	Representation of Proteins and Ligands 147
5.2	Docking Algorithms 149
5.2.1	Incremental Construction Methods 150
5.2.2	Genetic Algorithms 152
5.2.3	Tabu Search 153
5.2.4	Simulated Annealing and Monte Carlo Simulations 154
5.2.5	Shape-fitting Methods 155
5.2.6	Miscellaneous Approaches 155
5.3	Scoring Functions 156
5.3.1	Empirical Scoring Functions 157
5.3.2	Force Field-based Scoring Functions 158
5.3.3	Knowledge-based Scoring Functions 158
5.4	Postfiltering VS Results 159
5.4.1	Filtering by Topological Properties 159
5.4.2	Filtering by Multiple Scoring 159
5.4.3	Filtering by Combining Computational Procedures 160
5.4.4	Filtering by Chemical Diversity 161
5.4.5	Filtering by Visual Inspection 161
5.5	Comparison of Different Docking and Scoring Methods 161
5.6	Examples of Successful Virtual Screening Studies 162
5.7	The Future of Virtual Screening 164
6	Scope and Limits of Molecular Docking 169
6.1	Docking in the Polar Active Site That Contains Water Molecules –
0.1	Viral Thymidine Kinase 170
6.1.1	Setting the Scene 171
6.2	Learning from the Results 172
6.2.1	Water Contribution on dT and ACV Docking 172
6.2.2	In Search of the Binding Constant 175
6.2.3	Application to Virtual Screening 176
7	Example for the Modeling of Protein–Ligand Complexes:
	Antigen Presentation by MHC Class I 179
7.1	Biochemical and Pharmacological Description of the Problem 179
7.1.1	Antigenic Proteins are Presented as Nonapeptides 180
7.1.2	Pharmacological Target: Autoimmune Reactions 180

w [Inhalt	
-	7.2	Molecular Modeling of the Antigenic Complex Between a Viral Peptide and a Class I MHC Glycoprotein 181
	7.2.1	Modeling of the Ligand 181
	7.2.2	Homology Modeling of the MHC Protein 183
	7.3	Molecular Dynamics Studies of MHC-Peptide Complexes 192
	7.3.1	HLA-A2—The Fate of the Complex during Molecular Dynamics Simulations 192
	7.3.2	HLA-B*2705 194
	7.4	Analysis of Models that Emerged from Molecular Dynamics Simulations 199
	7.4.1	Hydrogen Bonding Network 200
	7.4.2	Atomic Fluctuations 200
	7.4.3	Solvent-Accessible Surface Areas 203
	7.4.4	Interaction Energies 204
	7.5	SAR of the Antigenic Peptides from Molecular Dynamics
		Simulations and Design of Non-natural Peptides as
		High-Affinity Ligands for a MHC I Protein 206
	7.5.1	The Design of New Ligands 206
	7.5.2	Experimental Validation of the Designed Ligands 209
	7.6	How Far Does the Model Hold? Studies on Fine Specificity of Antigene Binding to Other MHC Proteins and Mutants 211

The T-Cell Receptor Comes in 211 Some Concluding Remarks 214

Index 217

7.7

7.8