
Contents

Contributors

xi

Preface

xiii

1 The Molecular Modeling Perspective in Drug Design

N. CLAUDE COHEN

I. Definition of Molecular Modeling	1
II. The First Generation of Rational Approaches in Drug Design	3
III. Molecular Modeling: The Second Generation	4
A. Conceptual Frame and Methodology of Molecular Modeling	4
B. The Field Currently Covered	4
C. Importance of the "Bioactive Conformation"	5
IV. Molecular Mimicry and Structural Similarities	6
A. Molecular Mimicry	6
B. Structural Similarities and Superimposition Techniques	7
V. Rational Drug Design and Chemical Intuition	7
A. An Important Key and the Role of the Molecular Modelist	7
B. Limitations of Chemical Intuition	9

VI. Major Milestones and Future Perspectives	16
VII. Conclusion	17
References	17

2 Molecular Graphics and Modeling: Tools of the Trade

RODERICK E. HUBBARD

I. Introduction	19
II. Development of Molecular Graphics Hardware	20
III. Hardware for Graphics and Modeling	23
A. Central Servers	25
B. High Performance Graphics Systems	28
C. Personal Workstations	29
IV. Components of Molecular Graphics Hardware	29
A. Memory/Disk	30
B. Communications	30
C. Data Security	31
D. User Interaction	31
E. Organization	31
F. Visualization	33
G. Hardcopy/Publication	38
H. Standards	39
V. Software Components of a Molecular Graphics and Modeling System	40
A. User Interfaces	40
B. Constructing an Initial Model	41
C. Refining the Model	43
D. Manipulating the Model	45
E. Visualization	46
VI. Future Perspectives	53
References	54

3 Molecular Modeling of Small Molecules

TAMARA GUND

I. Introduction	55
A. History	56
B. Why Do Modeling?	56
C. Who Should Do Modeling?	56
D. Getting Started	57

II. Molecular Modeling Functions	58
A. Structure Generation or Retrieval	58
B. Structure Visualization	59
C. Conformation Generation	60
D. Deriving Bioactive Conformations	64
E. Molecule Superposition and Alignment	64
F. Deriving the Pharmacophoric Pattern	66
G. Receptor Mapping	67
H. Estimating Biological Activities	68
I. Molecular Interactions: Docking	69
J. Calculation of Molecular Properties	70
K. Energy Calculations	71
III. Examples of Small Molecule Modeling Work	76
A. Nicotinic Ligands	76
B. Sigma Ligands	81
C. Antimalarial Agents	84
References	87

4 Computer-Assisted New Lead Design

AKIKO ITAI, MIHO YAMADA MIZUTANI, YOSHIHIKO NISHIBATA, AND
NUBUO TOMIOKA

I. Introduction	93
II. Basic Concepts	95
A. Molecular Recognition by Receptor and Ligand Design	95
B. Active Conformation	95
C. "Function"	96
D. Approaches to Discover New Functions	97
E. Approaches to the Cases with Known and Unknown Receptor Structure	98
III. Docking Problem and Docking Methods	100
A. Program GREEN Grid: Three-Dimensional Description of Binding Site Environment and Energy Calculation	101
B. Automatic Docking Method	103
IV. Three-Dimensional Database Search Approaches	109
V. Automated Structure Construction Methods	113
A. Structure Construction Methods with Known Three-Dimensional Structure of the Receptor	114
B. Structure Construction in the Case of Unknown Receptor Structure	124

VI. Scope and Limitations	129
A. Points for Consideration in Structure Construction Methods	129
B. Handling of X-Ray Structures of Proteins	133
C. Future Perspectives	134
References	135

5 Experimental Techniques and Data Banks

JOHN P. PRIESTLE AND C. GREGORY PARIS

I. Experimental Techniques	139
A. X-Ray Crystallography	139
B. Nuclear Magnetic Resonance (NMR)	150
C. Results of Experimental Structures	158
D. Use of Experimental Structures in Protein Modeling	165
II. Three-Dimensional Structure Databases	166
A. Components of a Chemical Database	167
B. Data and Sources of Data	172
C. Queries and Sources of Queries	180
D. Search Engines	189
E. Successes of Three-Dimensional Database Searching	194
F. In Depth: The Brookhaven PDB	195
G. In Depth: The Cambridge Structural Database	199
III. IUPAC Conventions for Peptides and Nucleic Acids	202
A. Peptides	202
B. Nucleic Acids	207
Appendix	213
References	214

6 Computer-Assisted Drug Discovery

PETER GUND, GERALD MAGGIORA, AND JAMES P. SNYDER

I. The Drug Development Process	219
A. Introduction	219
B. The Discovery and Development Process	220
C. New Lead Discovery Strategies	220
D. Composition of Drug Discovery Teams	222

II. The Practice of Computer-Assisted Drug Discovery (CADD)	222
A. Current Practice of CADD in the Pharmaceutical Industry	222
B. Management Structures of CADD Groups	224
C. Contributions and Achievements of CADD Groups	225
D. The Case for Company Investments in CADD	226
III. Limitations to CADD Support	227
A. Inherent Limitations of CADD Support	227
B. State of Current Computational Models	229
C. Software and Hardware Constraints	229
D. Organizational Issues: The CADD Conundrum	230
IV. Proposals for Maximizing CADD Technology	231
V. Conclusions	232
References	233

7 Modeling Drug–Receptor Interactions

KONRAD F. KOEHLER, SHASHIDHAR N. RAO, AND JAMES P. SNYDER

I. Receptors—Introduction and Definition	235
A. Macromolecular Targets	235
B. Sources of Structural Information	237
C. Ligand—Receptor Interaction	240
II. Receptor Fitting—X ray and Other Explicit Structures	246
A. Utility	246
B. Binding-Site Properties	247
C. Ligand Binding Predictions	252
D. Free Energy and the Elusive Entropy Factor	263
III. Receptor Mapping—Structurally Ill-Defined Biological Receptors	273
A. The Pharmacophore Concept	273
B. Practical Utility	278
C. A Case Study in New Lead Design	279
IV. Pseudoreceptors—A Bridge between Fitting and Mapping	281
A. The Philosophy	281
B. Construction of Reduced Protein Models	281
C. Structural Correlation with Experiment	283
V. Role of Solvent—Models and Limits	284
A. Aqueous and Nonaqueous Solvent Models	284
B. Small Molecule Energetics	289

C. Macromolecular Conformation and Ligand Binding	291
VI. Peptidomimetic Design—Goals and Achievements	293
A. Interplay between Modeling and Bioassay	293
B. General Design Strategies	296
C. A Sampling of Disease Targets	298
D. Prospects for the Future	313
References	315
8 Glossary of Terminology	
J. P. TOLLENAERE	337
Index	357