

# Contents

|   |     |
|---|-----|
| <b>Preface</b>  | V   |
| <b>A Personal Foreword</b>  | VII |
| <b>1 Introduction</b>   | 1   |
| 1.1 Modern History of Molecular Modeling  | 2   |
| 1.2 Do Today's Molecular Modeling Methods Illustrate<br>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 <i>Design</i>   | 4   |
| 1.6 The Scope of the Book   | 5   |
| <b>2 Small Molecules</b>  | 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  |
| 2.2 Computational Tools for Geometry Optimization                                 | 13  |
| 2.2.1 Force Fields  | 13  |
| 2.2.2 Geometry Optimization   | 15  |
| 2.2.3 Energy-Minimizing Procedures  | 16  |
| 2.2.3.1 Steepest Descent Minimizer  | 17  |
| 2.2.3.2 Conjugate Gradient Method   | 17  |
| 2.2.3.3 Newton-Raphson Minimizer  | 17  |
| 2.2.4 Use of Charges, Solvation Effects   | 18  |
| 2.2.5 Quantum Mechanical Methods  | 19  |
| 2.2.5.1 Ab initio Methods   | 19  |
| 2.2.5.2 Semiempirical Molecular Orbital Methods                                   | 21  |
| 2.3 Conformational Analysis   | 23  |
| 2.3.1 Conformational Analysis Using Systematic Search Procedures                  | 25  |
| 2.3.2 Conformational Analysis Using Monte Carlo Methods                           | 29  |
| 2.3.3 Conformational Analysis Using Molecular Dynamics                            | 29  |

|          |  |           |
|----------|--|-----------|
| 2.4      | Determination of Molecular Interaction Potentials . . . . .                          | 37        |
| 2.4.1    | Molecular Electrostatic Potentials (MEPs) . . . . .                                  | 37        |
| 2.4.1.1  | Methods for Calculating Atomic Point Charges . . . . .                               | 38        |
| 2.4.1.2  | Methods for Generating MEPs . . . . .  | 42        |
| 2.4.2    | Molecular Interaction Fields . . . . .   | 43        |
| 2.4.2.1  | Calculation of GRID Fields . . . . .   | 45        |
| 2.4.2.2  | How GRID Fields can be Exploited . . . . .   | 47        |
| 2.4.2.3  | Use of Chemometrics: The CoMFA Method . . . . .                                      | 49        |
| 2.4.3    | Hydrophobic Interactions . . . . .   | 49        |
| 2.4.3.1  | Log <i>P</i> as a Measure of Lipophilicity . . . . .                                 | 50        |
| 2.4.3.2  | The Hydrophathic Field . . . . .   | 50        |
| 2.4.3.3  | Display of Properties on a Molecular Surface . . . . .                               | 51        |
| 2.5      | Pharmacophore Identification . . . . .   | 55        |
| 2.5.1    | Molecules to be Matched . . . . .  | 55        |
| 2.5.2    | Atom-by-Atom Superposition . . . . .   | 56        |
| 2.5.3    | Superposition of Molecular Fields . . . . .  | 58        |
| 2.6      | The Use of Data Bants . . . . .  | 60        |
| 2.6.1    | Conversion of 2D Structural Data into 3D Form . . . . .                              | 60        |
| 2.6.2    | 3D Searching . . . . .   | 61        |
| <b>3</b> | <b>Example for Small Molecule Modeling:<br/>Serotonin Receptor Ligands . . . . .</b> | <b>65</b> |
| 3.1      | Definition of the Serotonergic Pharmacophore . . . . .                               | 65        |
| 3.2      | The Molecular Interaction Field . . . . .  | 69        |
| 3.3      | Construction of a 5-HT <sub>2a</sub> Receptor Binding Site Model . . . . .           | 71        |
| 3.4      | Calculation of Interaction Energies . . . . .  | 73        |
| 3.5      | Validation of the Model . . . . .  | 74        |
| <b>4</b> | <b>Introduction to Protein Modeling . . . . .</b>                                    | <b>77</b> |
| 4.1      | Where and How to get Information on Proteins . . . . .                               | 77        |
| 4.2      | Terminology and Principles of Protein Structure . . . . .                            | 81        |
| 4.2.1    | Conformational Properties of Proteins . . . . .                                      | 81        |
| 4.2.2    | Types of Secondary Structural Elements . . . . .                                     | 84        |
| 4.2.2.1  | The $\alpha$ -Helix . . . . .  | 84        |
| 4.2.2.2  | The $\beta$ -Sheet . . . . .   | 85        |
| 4.2.2.3  | Turns . . . . .  | 87        |
| 4.2.3    | Homologous Proteins . . . . .  | 88        |
| 4.3      | Knowledge-Based Protein Modeling . . . . .   | 91        |
| 4.3.1    | Procedures for Sequence Alignments . . . . .   | 92        |
| 4.3.2    | Determination and Generation of Structurally Conserved Regions (SCRs) . . . . .      | 96        |
| 4.3.3    | Construction of Structurally Variable Regions (SVRs) . . . . .                       | 98        |
| 4.3.4    | Side Chain Modeling . . . . .  | 99        |

|          |   |            |
|----------|---|------------|
| 4.3.5    | Distance Geometry Approach . . . . .                                    | 101        |
| 4.3.6    | Secondary Structure Prediction . . . . .                                | 101        |
| 4.3.7    | Energy-Based Modeling Methods . . . . .                                 | 103        |
| 4.4      | Optimization Procedures — Model Refinement — Molecular Dynamics . . .   | 109        |
| 4.4.1    | Force Fields for Protein Modeling . . . . .                             | 109        |
| 4.4.2    | Geometry Optimization . . . . .   | 110        |
| 4.4.3    | The Use of Molecular Dynamics Simulations in Model Refinement . . . . . | 111        |
| 4.4.4    | Treatment of Solvated Systems . . . . .                                 | 113        |
| 4.4.5    | Ligand-Binding Site Complexes . . . . .                                 | 113        |
| 4.5      | Validation of Protein Models . . . . .                                  | 115        |
| 4.5.1    | Stereochemical Accuracy . . . . .                                       | 116        |
| 4.5.2    | Packing Quality . . . . .   | 120        |
| 4.5.3    | Folding Reliability . . . . .   | 122        |
| 4.6      | Properties of Proteins . . . . .  | 127        |
| 4.6.1    | Electrostatic Potential . . . . .                                       | 127        |
| 4.6.2    | Interaction Potentials . . . . .  | 130        |
| 4.6.3    | Hydrophobicity . . . . .  | 130        |
| <b>5</b> | <b>Example for the Modeling of Protein–Ligand Complexes:</b>            |            |
|          | <b>Antigen Presentation by MHC Class I . . . . .</b>                    | <b>133</b> |
| 5.1      | Biochemical and Pharmacological Description of the Problem . . . . .    | 133        |
| 5.1.1    | Antigenic Proteins are Presented as Nonapeptides . . . . .              | 134        |
| 5.1.2    | Pharmacological Target: Autoimmune Reactions . . . . .                  | 134        |
| 5.2      | Molecular Modeling of the Antigenic Complex                             |            |
|          | Between a Viral Peptide and a Class I MHC Glycoprotein . . . . .        | 135        |
| 5.2.1    | Modeling of the Ligand . . . . .  | 135        |
| 5.2.2    | Homology Modeling of the MHC Protein . . . . .                          | 136        |
| 5.2.2.1  | Preparation of the Coordinates . . . . .                                | 137        |
| 5.2.2.2  | Building the H-2L <sup>d</sup> Molecule . . . . .                       | 137        |
| 5.3      | Molecular Dynamics Studies of MHC–Peptide Complexes . . . . .           | 146        |
| 5.3.1    | HLA-A2 — The Fate of the Complex during                                 |            |
|          | Molecular Dynamics Simulations . . . . .                                | 146        |
| 5.3.2    | HLS-B*2705 . . . . .  | 148        |
| 5.3.2.1  | The Fate of the Complex during Molecular Dynamics Simulations . . . . . | 150        |
| 5.4      | Analysis of Models that Emerged from                                    |            |
|          | Molecular Dynamics Simulations . . . . .                                | 153        |
| 5.4.1    | Hydrogen Bonding Network . . . . .                                      | 153        |
| 5.4.2    | Atomic Fluctuations . . . . .   | 154        |
| 5.4.3    | Solvent-Accessible Surface Areas . . . . .                              | 157        |
| 5.4.4    | Interaction Energies . . . . .  | 158        |
| 5.5      | SAR of the Antigenic Peptides from Molecular                            |            |
|          | Dynamics Simulations and Design of Non-natural Peptides                 |            |
|          | as High-Affinity Ligands for a MHC I Protein . . . . .                  | 160        |

XII *Contents*

|                   |  |     |
|-------------------|--|-----|
| 5.5.1             | The Design of New Ligands . . . . .                      | 160 |
| 5.5.2             | Experimental Validation of the Designed Ligand . . . . . | 163 |
| 5.6               | Summary and Conclusion . . . . .                         | 164 |
| <b>Appendices</b> | . . . . .  | 165 |
| <b>Index</b>      | . . . . .  | 177 |