

Contents

List of Contributors XIII

Preface XVII

A Personal Foreword XIX

Part I Binding Thermodynamics 1

1 Statistical Thermodynamics of Binding and Molecular Recognition Models 3

Kim A. Sharp

- 1.1 Introductory Remarks 3
- 1.2 The Binding Constant and Free Energy 3
- 1.3 A Statistical Mechanical Treatment of Binding 4
- 1.3.1 Binding in a Square Well Potential 6
- 1.3.2 Binding in a Harmonic Potential 7
- 1.4 Strategies for Calculating Binding Free Energies 9
- 1.4.1 Direct Association Simulations 9
- 1.4.2 The Quasi-Harmonic Approximation 10
- 1.4.3 Estimation of Entropy Contributions to Binding 11
- 1.4.4 The Molecule Mechanics Poisson–Boltzmann Surface Area Method 13
- 1.4.5 Thermodynamic Work Methods 14
- 1.4.6 Ligand Decoupling 15
- 1.4.7 Linear Interaction Methods 15
- 1.4.8 Salt Effects on Binding 16
- 1.4.9 Statistical Potentials 17
- 1.4.10 Empirical Potentials 18
- References 19

2 Some Practical Rules for the Thermodynamic Optimization of Drug Candidates 23

Ernesto Freire

- 2.1 Engineering Binding Contributions 25
- 2.2 Eliminating Unfavorable Enthalpy 25
- 2.3 Improving Binding Enthalpy 26

2.4	Improving Binding Affinity	27
2.5	Improving Selectivity	28
2.6	Thermodynamic Optimization Plot	28
	Acknowledgments	30
	References	31
3	Enthalpy–Entropy Compensation as Deduced from Measurements of Temperature Dependence	33
	<i>Athel Cornish-Bowden</i>	
3.1	Introduction	33
3.2	The Current Status of Enthalpy–Entropy Compensation	34
3.3	Measurement of the Entropy and Enthalpy of Activation	34
3.4	An Example	35
3.5	The Compensation Temperature	38
3.6	Effect of High Correlation on Estimates of Entropy and Enthalpy	39
3.7	Evolutionary Considerations	40
3.8	Textbooks	40
	References	42
Part II	Learning from Biophysical Experiments	45
4	Interaction Kinetic Data Generated by Surface Plasmon Resonance Biosensors and the Use of Kinetic Rate Constants in Lead Generation and Optimization	47
	<i>U. Helena Danielson</i>	
4.1	Background	47
4.2	SPR Biosensor Technology	48
4.2.1	Principles	48
4.2.2	Sensitivity	49
4.2.3	Kinetic Resolution	50
4.2.4	Performance for Drug Discovery	51
4.3	From Interaction Models to Kinetic Rate Constants and Affinity	53
4.3.1	Determination of Interaction Kinetic Rate Constants	53
4.3.2	Determination of Affinities	54
4.3.3	Steady-State Analysis versus Analysis of Complete Sensorgrams	54
4.4	Affinity versus Kinetic Rate Constants for Evaluation of Interactions	55
4.5	From Models to Mechanisms	56
4.5.1	Irreversible Interactions	57
4.5.2	Induced Fit	57
4.5.3	Conformational Selection	58
4.5.4	Unified Model for Dynamic Targets	58
4.5.5	Heterogeneous Systems/Parallel Reactions	59
4.5.6	Mechanism-Based Inhibitors	60
4.5.7	Multiple Binding Sites and Influence of Cofactors	61
4.6	Structural Information	61

4.7	The Use of Kinetic Rate Constants in Lead Generation and Optimization	62
4.7.1	Structure–Kinetic Relationships	62
4.7.2	Selectivity/Specificity and Resistance	63
4.7.3	Chemodynamics	63
4.7.4	Thermodynamics	64
4.8	Designing Compounds with Optimal Properties	65
4.8.1	Correlation between Kinetic and Thermodynamic Parameters and Pharmacological Efficacy	65
4.8.2	Structural Modeling	66
4.9	Conclusions	67
	Acknowledgments	67
	References	67
5	NMR Methods for the Determination of Protein–Ligand Interactions	71
	<i>Bernd W. Koenig, Sven Schünke, Matthias Stoldt, and Dieter Willbold</i>	
5.1	Experimental Parameters from NMR	72
5.2	Aspects of Protein–Ligand Interactions That Can Be Addressed by NMR	77
5.2.1	Detection and Verification of Ligand Binding	77
5.2.2	Interaction Site Mapping	78
5.2.3	Interaction Models and Binding Affinity	80
5.2.4	Molecular Recognition	81
5.2.5	Structure of Protein–Ligand Complexes	82
5.3	Ligand-Induced Conformational Changes of a Cyclic Nucleotide Binding Domain	84
5.4	Ligand Binding to GABARAP Binding Site and Affinity Mapping	86
5.5	Transient Binding of Peptide Ligands to Membrane Proteins	88
	References	90
Part III	Modeling Protein–Ligand Interactions	99
6	Polarizable Force Fields for Scoring Protein–Ligand Interactions	101
	<i>Jiajing Zhang, Yue Shi, and Pengyu Ren</i>	
6.1	Introduction and Overview	101
6.2	AMOEBA Polarizable Potential Energy Model	102
6.2.1	Bond, Angle, and Cross-Energy Terms	102
6.2.2	Torsional Energy Term	103
6.2.3	Van der Waals Interactions	103
6.2.4	Permanent Electrostatic Interactions	103
6.2.5	Electronic Polarization	104
6.2.6	Polarization Energy	105
6.3	AMOEBA Explicit Water Simulation Applications	106
6.3.1	Small-Molecule Hydration Free Energy Calculations	106
6.3.2	Ion Solvation Thermodynamics	108

6.3.3	Binding Free Energy of Trypsin and Benzamidine Analogs	110
6.4	Implicit Solvent Calculation Using AMOEBA Polarizable Force Field	113
6.5	Conclusions and Future Directions	115
	References	116
7	Quantum Mechanics in Structure-Based Ligand Design	121
	<i>Pär Söderhjelm, Samuel Genheden, and Ulf Ryde</i>	
7.1	Introduction	121
7.2	Three MM-Based Methods	122
7.3	QM-Based Force Fields	123
7.4	QM Calculations of Ligand Binding Sites	125
7.5	QM/MM Calculations	126
7.6	QM Calculations of Entire Proteins	127
7.6.1	Linear Scaling Methods	128
7.6.2	Fragmentation Methods	129
7.7	Concluding Remarks	133
	Acknowledgments	134
	References	134
8	Hydrophobic Association and Volume-Confined Water Molecules	145
	<i>Riccardo Baron, Piotr Setny, and J. Andrew McCammon</i>	
8.1	Introduction	145
8.2	Water as a Whole in Hydrophobic Association	146
8.2.1	Background	146
8.2.2	Computational Modeling of Hydrophobic Association	150
8.2.2.1	Explicit versus Implicit Solvent: Is the Computational Cost Motivated?	152
8.3	Confined Water Molecules in Protein–Ligand Binding	153
8.3.1	Protein Hydration Sites	153
8.3.2	Thermodynamics of Volume-Confined Water Localization	154
8.3.3	Computational Modeling of Volume-Confined Water Molecules	156
8.3.4	Identifying Hydration Sites	158
8.3.5	Water in Protein–Ligand Docking	160
	Acknowledgments	161
	References	161
9	Implicit Solvent Models and Electrostatics in Molecular Recognition	171
	<i>Tyler Luchko and David A. Case</i>	
9.1	Introduction	171
9.2	Poisson–Boltzmann Methods	173
9.3	The Generalized Born Model	175
9.4	Reference Interaction Site Model of Molecular Solvation	176
9.5	Applications	179

- 9.5.1 The “MM-PBSA” Model 180
- 9.5.2 Rescoring Docking Poses 182
- 9.5.3 MM/3D-RISM 182
- Acknowledgments 185
- References 185

- 10 Ligand and Receptor Conformational Energies 191**
Themis Lazaridis
- 10.1 The Treatment of Ligand and Receptor Conformational Energy in Various Theoretical Formulations of Binding 191
- 10.1.1 Double Decoupling Free Energy Calculations 192
- 10.1.2 MM-PB(GB)SA 192
- 10.1.3 Mining Minima 193
- 10.1.4 Free Energy Functional Approach 194
- 10.1.5 Linear Interaction Energy Methods 195
- 10.1.6 Scoring Functions 196
- 10.2 Computational Results on Ligand Conformational Energy 196
- 10.3 Computational Results on Receptor Conformational Energy 198
- 10.4 Concluding Remarks 199
- Acknowledgments 199
- References 199

- 11 Free Energy Calculations in Drug Lead Optimization 207**
Thomas Steinbrecher
- 11.1 Modern Drug Design 207
- 11.1.1 *In Silico* Drug Design 210
- 11.2 Free Energy Calculations 212
- 11.2.1 Considerations for Accurate and Precise Results 215
- 11.3 Example Protocols and Applications 217
- 11.3.1 Example 1: Disappearing an Ion 219
- 11.3.2 Example 2: Relative Ligand Binding Strengths 221
- 11.3.3 Applications 223
- 11.4 Discussion 226
- References 227

- 12 Scoring Functions for Protein–Ligand Interactions 237**
Christoph Sotriffer
- 12.1 Introduction 237
- 12.2 Scoring Protein–Ligand Interactions: What for and How to? 237
- 12.2.1 Knowledge-Based Scoring Functions 238
- 12.2.2 Force Field-Based Methods 240
- 12.2.3 Empirical Scoring Functions 242
- 12.2.4 Further Approaches 244
- 12.3 Application of Scoring Functions: What Is Possible and What Is Not? 246

12.4	Thermodynamic Contributions and Intermolecular Interactions: Which Are Accounted for and Which Are Not? 248
12.5	Conclusions or What Remains to be Done and What Can be Expected? 254
	Acknowledgments 255
	References 255
Part IV	Challenges in Molecular Recognition 265
13	Druggability Prediction 267
	<i>Daniel Alvarez-Garcia, Jesus Seco, Peter Schmidtke, and Xavier Barril</i>
13.1	Introduction 267
13.2	Druggability: Ligand Properties 267
13.3	Druggability: Ligand Binding 268
13.4	Druggability Prediction by Protein Class 270
13.5	Druggability Predictions: Experimental Methods 270
13.5.1	High-Throughput Screening 270
13.5.2	Fragment Screening 271
13.5.3	Multiple Solvent Crystallographic Screening 272
13.6	Druggability Predictions: Computational Methods 272
13.6.1	Cavity Detection Algorithms 272
13.6.2	Empirical Models 273
13.6.2.1	Training Sets 273
13.6.2.2	Applicability and Prediction Performance 274
13.6.3	Physical Chemistry Predictions 275
13.7	A Test Case: PTP1B 276
13.8	Outlook and Concluding Remarks 278
	References 278
14	Embracing Protein Plasticity in Ligand Docking 283
	<i>Manuel Rueda and Ruben Abagyan</i>
14.1	Introduction 283
14.2	Docking by Sampling Internal Coordinates 284
14.3	Fast Docking to Multiple Receptor Conformations 285
14.4	Single Receptor Conformation 285
14.5	Multiple Receptor Conformations 286
14.5.1	Exploiting Existing Experimental Conformational Diversity 286
14.5.2	Selecting "Important" Conformations 288
14.5.3	Generating <i>In Silico</i> Models 288
14.6	Improving Poor Homology Models of the Binding Pocket 289
14.7	State of the Art: GPCR Dock 2010 Modeling and Docking Assessment 290
14.8	Conclusions and Outlook 290
	Acknowledgments 292
	References 292

15	Prospects of Modulating Protein–Protein Interactions	295
	<i>Shijun Zhong, Taiji Oashi, Wenbo Yu, Paul Shapiro, and Alexander D. MacKerell Jr.</i>	
15.1	Introduction	295
15.2	Thermodynamics of Protein–Protein Interactions	297
15.3	CADD Methods for the Identification and Optimization of Small-Molecule Inhibitors of PPIs	298
15.3.1	Identifying Inhibitors of PPIs Using SBDD	299
15.3.1.1	Protein Structure Preparation	299
15.3.1.2	Binding Site Identification	300
15.3.1.3	Virtual Chemical Database	302
15.3.1.4	Virtual Screening of Compound Database	302
15.3.1.5	Rescoring	304
15.3.1.6	Final Selection of Ligands for Experimental Assay	306
15.3.2	Lead Optimization	307
15.3.2.1	Ligand-Based Optimization	307
15.3.2.2	Computation of Binding Free Energy	308
15.4	Examples of CADD Applied to PPIs	308
15.4.1	ERK	309
15.4.2	BCL6	311
15.4.3	S100B	313
15.4.4	p56Lck Kinase SH2 Domain	313
15.5	Summary	315
	Acknowledgments	315
	References	315
	Index	331