

Contents

Volume 1

Beginnings

Chapter 1	Personal Perspective	3
	<i>Harold A. Scheraga</i>	
	References	6
Chapter 2	Fashioning NAMD, a History of Risk and Reward: Klaus Schulten Reminisces	8
	<i>Lisa Pollack</i>	
	2.1 Introduction	8
	2.2 Early Influences of Molecular Dynamics	9
	2.3 Building a Parallel Computer	10
	2.4 Transporting a Supercomputer	12
	2.5 Rejection	13
	2.6 Collaborations with Computer Scientists	13
	2.7 Graduate Students Revolt	15
	2.8 Factors that Shaped NAMD	15
	2.9 Continual Evolution of NAMD	16
	2.10 Conclusions	17
	Acknowledgements	18
	References	19

RSC Biomolecular Sciences No. 23

Innovations in Biomolecular Modeling and Simulations: Volume 1

Edited by Tamar Schlick

© Royal Society of Chemistry 2012

Published by the Royal Society of Chemistry, www.rsc.org

Force Fields and Electrostatics

Chapter 3	Towards Biomolecular Simulations with Explicit Inclusion of Polarizability: Development of a CHARMM Polarizable Force Field based on the Classical Drude Oscillator Model	23
	<i>C. M. Baker, E. Darian and A. D. MacKerell Jr</i>	
3.1	Introduction	23
3.2	Polarizable Force Fields	26
3.3	The CHARMM Drude Polarizable Force Field	27
3.3.1	The Model	27
3.3.2	Parametrization Strategy	33
3.3.3	Biomolecular Building Blocks	38
3.3.4	Case Study: The Nucleic Acids	41
3.4	Conclusions	45
	Acknowledgements	46
	References	46
Chapter 4	Integral Equation Theory of Biomolecules and Electrolytes	51
	<i>Tyler Luchko, In Suk Joung and David A. Case</i>	
4.1	Introduction	51
4.1.1	Some History	52
4.2	Integral Equation Theory for Simple Liquids	54
4.2.1	Ornstein-Zernike Equation	54
4.2.2	Closures	55
4.2.3	1D-RISM	56
4.2.4	3D-RISM	58
4.2.5	Long Range Asymptotics	59
4.2.6	Solvation Free Energy	61
4.2.7	Numerical Approaches	62
4.3	Pure Solvent Structure and Thermodynamics	63
4.4	Macromolecules and Other Solutes	69
4.4.1	Ion Binding to Crown Ethers	69
4.4.2	Ion Binding to Proteins	72
4.4.3	Ion Atmosphere Around Duplex DNA	73
4.4.4	Solvent Distributions	75
4.5	Conclusions	76
4.6	Methods	78
4.6.1	Parameters	78
4.6.2	Bulk Electrolytes	79
4.6.3	Crown-ether	79
4.6.4	DNA	79
	Acknowledgements	80
	References	80

Chapter 5	Molecular Simulation in the Energy Biosciences	87
	<i>Xiaolin Cheng, Jerry M. Parks, Loukas Petridis, Benjamin Lindner, Roland Schulz, Hao-Bo Guo, Goundla Srinivas and Jeremy C. Smith</i>	
5.1	Introduction	87
5.2	Methodological Development: An Order N Poisson-Boltzmann Solver	88
5.2.1	A Tree Code-Based Generalized Born (tGB) Method	91
5.2.2	Scaling of a Multimillion-atom Lignocellulose Simulation on a Petascale Supercomputer	95
5.2.3	Comparison of Simulations with Different Electrostatic Methods	96
5.2.4	Scaling	97
5.3	Applications	97
5.3.1	Biofuel Research	97
5.3.2	Bioremediation: Mechanisms of Bacterial Mercury Resistance	104
5.4	Conclusions	111
	Acknowledgements	111
	References	112
	Sampling and Rates	
Chapter 6	Enhancing the Capacity of Molecular Dynamics Simulations with Trajectory Fragments	117
	<i>Alfredo E. Cardenas and Ron Elber</i>	
6.1	Introduction	117
6.2	Trajectory Fragments: General Overview	120
6.3	Challenges in Using Trajectory Fragments	123
6.3.1	Milestoning	123
6.3.2	Forward Flux Sampling (FFS)	126
6.4	Applications of Trajectory Fragments: Equilibrium and Kinetics	129
6.5	Examples	132
6.6	Conclusions	135
	References	136
Chapter 7	Computing Reaction Rates in Bio-molecular Systems Using Discrete Macro-states	138
	<i>Eric Darve and Ernest Ryu</i>	
7.1	Introduction	138
7.2	Transition Path Sampling	144

7.2.1	Reactive Flux and Transition State Theory	144
7.2.2	Transition Path Sampling	146
7.2.3	Transition Interface Sampling	148
7.2.4	Forward Flux Sampling	149
7.2.5	Milestoning	151
7.2.6	Milestoning Using Optimal Milestones	152
7.3	Conformation Dynamics and Markov State Models	156
7.3.1	Conformation Dynamics	156
7.3.2	Perron Cluster Cluster Analysis	157
7.3.3	Markov State Models	160
7.4	Non-equilibrium Umbrella Sampling and Reactive Trajectory Sampling	163
7.4.1	Non-equilibrium Umbrella Sampling	163
7.4.2	Reactive Trajectory Sampling	165
7.4.3	Optimal Cells	170
7.4.4	Metastability, Convergence, and the Multi-colored Algorithm	172
7.5	Analysis of Statistical Errors in Markov State Models	174
7.5.1	Eigenvectors and Eigenvalues of the Transition Matrix	175
7.5.2	Sensitivity of Eigenvalues and Systematic Errors	178
7.5.3	Statistical Errors	182
7.6	Some Numerical Benchmarks for Markov State Models and Reactive Trajectory Sampling	186
7.6.1	Set up of Numerical Simulations	186
7.6.2	Numerical Benchmarks	188
7.7	Conclusion	193
7.8	Technical Proofs	195
	Acknowledgements	197
	References	197
Chapter 8	Challenges in Applying Monte Carlo Sampling to Biomolecular Systems	207
	<i>M. Mezei</i>	
8.1	Introduction	207
8.2	Basic Ideas of Monte Carlo Sampling	208
8.3	Why 'Bother' with Monte Carlo?	209
8.4	Correlated Moves	210
8.5	Cooperative Potentials	212
8.6	Long-range Energy Contributions	212
8.7	Parallelization	213
8.8	Conclusion	215
	References	215

Coarse Graining and Multiscale Models

Chapter 9 Coarse-grain Protein Models**219***N. Ceres and R. Lavery*

9.1	Introduction	219
9.2	Coarse-grain Representations	220
9.2.1	All-atom and United-atom Models	220
9.2.2	Bead Models	220
9.2.3	Lattice Models	222
9.2.4	Polymer and Material Models	222
9.3	Formulating the Energy	222
9.3.1	Gō Potentials	222
9.3.2	Elastic Network Models	223
9.3.3	Statistical Potentials	225
9.3.4	Physics-based Potentials	228
9.3.5	Hybrid Potentials	229
9.3.6	Solvent	229
9.4	Applications: From Folding to Function	230
9.4.1	Protein Folding	230
9.4.2	Structure Prediction	232
9.4.3	Mechanical and Dynamical Properties	234
9.4.4	Protein-protein Interactions	235
9.4.5	Large Protein Assemblies	237
9.5	Conclusions	238
	Acknowledgements	239
	References	239

Chapter 10 Generalised Multi-level Coarse-grained Molecular Simulation and its Application to Myosin-V Movement**249***William R. Taylor and Zoe Katsimitsoulia*

10.1	Introduction	249
10.2	Implementation	251
10.2.1	Overview	251
10.2.2	Steric Exclusion	252
10.2.3	Polymers and Cross-linking	253
10.2.4	Geometric Regularisation	255
10.2.5	Shape Specification	256
10.2.6	Implementation	256
10.3	Example Application	257
10.3.1	Model Construction	258
10.3.2	Driver Construction	264
10.3.3	Simulation	268

10.4	Conclusions	269
	Acknowledgements	270
	References	270
Chapter 11	Top-down Mesoscale Models and Free Energy Calculations of Multivalent Protein-Protein and Protein-Membrane Interactions in Nanocarrier Adhesion and Receptor Trafficking	272
	<i>Jin Liu, Neeraj J. Agrawal, David M. Eckmann, Portonovo S. Ayyaswamy and Ravi Radhakrishnan</i>	
11.1	Introduction	273
11.2	Mesoscale Model for Functionalized Nanocarrier Targeting to Cells in Drug Delivery	274
11.2.1	Parameter Estimation in the Top-down Modeling Strategy	276
11.2.2	Calculation of the Absolute Binding Free Energy	276
11.2.3	Calculation of Potential of Mean Force (PMF) of NC Binding to EC	278
11.2.4	Comparison with Experiments	279
11.3	Mesoscale Model for Protein-Induced Membrane Curvature	280
11.3.1	Membrane Curvature Model and Conformational Sampling	281
11.3.2	Calculation of Relative Free Energies of Curved Membranes	283
11.3.3	Application to Clathrin-Mediated Endocytosis	285
11.4	Future Outlook	286
	Acknowledgements	287
	References	287
Chapter 12	Studying Proteins and Peptides at Material Surfaces	293
	<i>Jun Feng, Gillian C. Lynch and B. Montgomery Pettitt</i>	
12.1	Introduction	293
12.2	Experimental Surface Chemistry and Immobilization Strategies	295
12.3	Surface Design	297
12.4	Theoretical and Simulation Studies of Proteins at Surfaces	303
12.5	Concluding Remarks	308
	Acknowledgements	308
	References	309

Chapter 13 Multiscale Design: From Theory to Practice	321
<i>J. Fish, V. Filonova and Z. Yuan</i>	
13.1 Introduction	321
13.2 RC ² Formulation	323
13.2.1 Computational Continua	323
13.2.2 Residual-free Computational Unit Cell Problem	324
13.2.3 The Coarse-scale Weak Form	330
13.2.4 Coarse-scale Discretization	332
13.3 Model Verification	333
13.4 Multiscale Characterization	336
13.4.1 Formulation of an Inverse Problem	336
13.4.2 Characterization of Model Parameters in Reduced Order Computational Continua	339
13.4.3 Multistep Model Characterization	340
13.5 Multiscale Design System Architecture	341
13.6 Conclusions	342
Acknowledgements	343
References	343
Subject Index	345

Volume 2

Atomistic Simulations of Nucleic Acids and Nucleic Acid Complexes

Chapter 1 Modelling Nucleic Acid Structure and Flexibility: From Atomic to Mesoscopic Scale	3
<i>Filip Lankaš</i>	
1.1 Introduction	3
1.2 Models Based on Pseudoatoms	4
1.3 Rigid Base and Basepair Models	8
1.3.1 Fitting the Base Frame	11
1.3.2 Internal Coordinates	13
1.3.3 Nonlocal Models	15
1.3.4 Example: DNA A-tract	18
1.3.5 Anharmonic Effects	23
1.4 Coarser Models and Other Approaches	25
1.5 Concluding Remarks	27
Acknowledgements	28
References	28

Chapter 2	Molecular Dynamics and Force Field Based Methods for Studying Quadruplex Nucleic Acids	33
	<i>Shoze M Haider and Stephen Neidle</i>	
2.1	Introduction	33
2.2	Force Fields	35
2.3	Base Stacking/Pairing, Planarity and Backbone Descriptions	36
2.4	Ions in the Central Channel	36
2.5	Long-range Electrostatic Effects	37
2.6	Conformational Sampling	37
2.7	Charge Descriptions	38
2.8	Simulations of Quadruplexes	38
2.8.1	Classical MD	38
2.8.2	Enhanced Sampling Methods	40
2.9	Principal Components Analysis	41
2.10	Modified Bases	42
2.11	Cation Mobility	43
2.12	Quadruplex Folding/Unfolding	43
2.13	Gas-phase Simulations	45
2.14	Free Energy Perturbation, Thermodynamic Integration, PMF and Umbrella Sampling	45
2.15	Continuum Solvent Methods	46
2.16	QM/MM on G-quartets	46
2.17	Simulations of the i-Motif	47
2.18	Conclusions	47
	References	48
Chapter 3	Opposites Attract: Shape and Electrostatic Complementarity in Protein-DNA Complexes	53
	<i>Robert C. Harris, Travis Mackoy, Ana Carolina Dantas Machado, Darui Xu, Remo Rohs and Marcia Oliveira Fenley</i>	
3.1	Introduction	53
3.1.1	Shape and Electrostatic Complementarity	54
3.1.2	Biological Examples for Shape and Electrostatic Complementarity in Protein-DNA Complexes	55
3.1.3	Base and Shape Readout	56
3.2	Electrostatic Features of DNA	56
3.2.1	B-DNA	56
3.2.2	A-DNA	60
3.2.3	Z-DNA	61
3.3	Structural Complementarity in Protein-DNA Complexes	62

3.4	Electrostatic Complementarity at the Interface of Protein-DNA Complexes	63
3.4.1	Complementarity of Electrostatic Potential Surface Maps	63
3.4.2	Approaches using Electrostatic Complementarity in Predictions of Binding free Energy Changes	65
3.4.3	Relationship between Electrostatic Complementarity and Association/Dissociation Constants	67
3.5	Minor Groove Shape Readout in Protein-DNA Complexes	67
3.6	Summary and Outlook	72
3.7	Methods	74
	Acknowledgments	74
	References	74
Chapter 4	Intrinsic Motions of DNA Polymerases Underlie Their Remarkable Specificity and Selectivity and Suggest a Hybrid Substrate Binding Mechanism	81
	<i>Meredith C. Foley, Karunesh Arora and Tamar Schlick</i>	
4.1	Introduction	81
4.2	DNA Polymerase Structure and Function	83
4.3	Methods	85
4.3.1	Molecular Dynamics	85
4.3.2	Principal Component Analysis	86
4.3.3	Correlated Motion Analysis	87
4.4	Results and Discussions	88
4.4.1	Similarities in the Dynamics of X-Family DNA Polymerases and Their Effects on Function and Fidelity	88
4.4.2	PCA Reinforces the Functional Importance of Thumb and DNA Motions	91
4.4.3	Coupled Polymerase/DNA/dNTP Motions Bridge Spatial Gaps and Impact DNA Polymerase Function and Fidelity	93
4.4.4	Hybrid Conformational Selection/Induced-fit Mechanism May Better Account for Intrinsic Polymerase Motions	100
4.4.5	Utilizing the New Hybrid DNA Polymerase Mechanism for Therapeutic Purposes	103
4.5	Conclusion	104
	Acknowledgements	105
	References	105

Chapter 5	Molecular Dynamics Structure Prediction of a Novel Protein-DNA Complex: Two HU Proteins with a DNA Four-way Junction	111
	<i>Elizabeth G. Wheatley, Susan N. Pieniazek, Iulia Vitoc, Ishita Mukerji and D.L. Beveridge</i>	
5.1	Introduction	111
5.2	Background	112
5.2.1	DNA Four-way Junctions (4WJ)	112
5.2.2	Protein HU-DNA Complexes	113
5.2.3	Molecular Dynamics (MD) Simulations	114
5.3	Calculations	115
5.4	Results	115
5.4.1	MD on Unbound 4WJ: d(CCGGTACCGG) ₄ and J3 Sequences	115
5.4.2	MD on the Protein HU	117
5.4.3	Structure Prediction: 2 HU + J3 4WJ	119
5.5	Summary and Conclusions	124
	Acknowledgments	124
	References	124
Chapter 6	Molecular Dynamics Simulations of RNA Molecules	129
	<i>J. Šponer, M. Otyepka, P. Banáš, K. Réblová and N. G. Walter</i>	
6.1	Molecular Simulations of RNA: General Considerations	129
6.2	The General Scope and Limitations of MD Simulations	130
6.3	Refinement of the Cornell <i>et al.</i> Force Field for Nucleic Acids: From Parm94 to Parmbsc0 and ParmOL	135
6.4	MD Simulations and the Starting Structure	140
6.5	What Specific Questions Can MD Simulations of RNA Currently Address?	143
6.5.1	Resolving Experimental Artifacts	143
6.5.2	Flexibility of RNA Building Blocks	144
6.5.3	Revealing Solvent and Ion Dynamics	146
6.5.4	Probing the Structural Effects of Base Substitutions and Ionizations	147
6.6	What General Scope and Limitations Do Quantum Mechanical Calculations Have?	148
6.7	What Can QM/MM Reveal About the Chemical Change Catalyzed by Ribozymes?	149
6.8	Conclusion	150
	Acknowledgments	150
	References	151

Chapter 7	The Structure and Folding of Helical Junctions in RNA	156
	<i>David M. J. Lilley</i>	
7.1	The Occurrence of Helical Junctions in RNA	156
7.2	Some Basic Structural Principles of Junctions	158
7.3	The Four-way Junction in DNA	159
7.4	Three-way Junctions in RNA	162
7.5	The Four-way RNA Junction	164
7.6	Elaborated Four-way Junctions	169
7.7	Higher-order Helical Junctions in RNA	171
7.7.1	The General Principles	172
	Acknowledgements	173
	References	173
	DNA Folding, Knotting, Sliding and Hopping	
Chapter 8	Structure and Dynamics of Supercoiled DNA Knots and Catenanes	179
	<i>Guillaume Witz and Andrzej Stasiak</i>	
8.1	Introduction	179
8.2	DNA Topology	180
8.2.1	Topological Concepts	180
8.2.2	DNA Topology <i>In Vitro</i> and <i>In Vivo</i>	181
8.3	Model Description	184
8.3.1	Monte-Carlo Metropolis (MC)	184
8.3.2	Brownian Dynamics (BD)	184
8.3.3	Measuring Topology of Knots and Catenanes	185
8.4	Conformation of Supercoiled Knots and Catenanes	185
8.4.1	Structure of Supercoiled DNA Catenanes	186
8.4.2	Electrophoretic Migration of Supercoiled DNA Catenanes	189
8.4.3	Biological Implications	191
8.4.4	Structure of Supercoiled DNA Knots and their Electrophoretic Migration	191
8.4.5	Biological Implications	195
8.5	Conclusion	195
	Acknowledgements	196
	References	196
Chapter 9	Monte Carlo Simulations of Nucleosome Chains to Identify Factors that Control DNA Compaction and Access	198
	<i>Karsten Rippe, Rene Stehr and Gero Wedemann</i>	
9.1	Introduction	198

9.2	Experimentally Determined Features of the Nucleosome Chain	201
9.2.1	Experimental Systems	201
9.2.2	Nucleosome Repeat Length	202
9.2.3	Variations in Protein Composition of Nucleosome Chains	203
9.3	Protein-protein and Protein-DNA Interactions in the Nucleosome Chain	205
9.3.1	Nucleosome-nucleosome Interactions	205
9.3.2	DNA Interactions with the Histone Octamer Protein Core	205
9.4	Chromatin Fiber Conformations	206
9.4.1	Solenoid Fibers	206
9.4.2	Crossed-linker Fibers	207
9.5	Coarse-grained Representations of the Nucleosome Chain	209
9.5.1	Coarse Graining	210
9.5.2	Interactions	211
9.6	MC simulations of Nucleosome Chains	214
9.6.1	General Considerations	214
9.6.2	Monte Carlo Moves	214
9.6.3	Reaching Thermodynamic Equilibrium in the MC Simulations	216
9.7	Effect of Protein-protein and Protein-DNA Interactions on the Folding of the Nucleosome Chain	216
9.7.1	Orientation Dependence and Shape of Nucleosome-nucleosome Interactions	216
9.7.2	The Strength of Nucleosome-nucleosome Interactions	217
9.7.3	Contributions of Histone Tails to Nucleosome-nucleosome Interactions	218
9.7.4	Salt Dependence	218
9.8	The Effect of Nucleosome Positioning and Local Geometry on Chain Conformation	219
9.8.1	Effect of DNA Linker Length on the Chromatin Fiber Conformation	219
9.8.2	Transitions between Fiber Conformation	220
9.8.3	Systematically Exploring the Conformation Space with MC Simulated Phase Diagrams	222
9.8.4	Resolution of the Chromatin Fiber Structure	223
9.9	Perspectives	223
	Acknowledgements	225
	References	225

Chapter 10 Sliding Dynamics Along DNA: A Molecular Perspective **236**

Amir Marcovitz and Yaakov Levy

10.1	Introduction	236
10.2	A Computational Model for Nonspecific Protein–DNA Interactions	238
10.2.1	A Coarse-grained Model for Simulations of Protein Search along DNA	238
10.2.2	Structural Classification of Protein Sliding, Hopping, and 3D Diffusion	240
10.2.3	DNA Bead Radius Parameterization: The Effect of the Major Groove Width on Sliding	241
10.3	Results and Discussion	244
10.3.1	Structural Characterization of Protein during Sliding and Hopping on DNA	244
10.3.2	DNA Search Efficiency: Combining 1D and 3D Search Modes Enhances DNA Scanning	247
10.3.3	Protein Dynamics during Target Search: Influence of Helical Sliding and Hopping on 1D Diffusion Coefficient	253
10.4	Concluding Remarks	259
	References	260

Drug Design

Chapter 11 Structure-based Design Technology CONTOUR and its Application to Drug Discovery **265**

Zhijie Liu, Peter Lindblom, David A. Claremon and Suresh B. Singh

11.1	Introduction	265
11.2	Theory and Technology	267
11.2.1	Growth Algorithm	267
11.2.2	CONTOUR Scoring Function	271
11.2.3	Training and Validation	272
11.2.4	Computational Infrastructure	273
11.3	Applications	273
11.3.1	Testing and Validation of Scoring Function	273
11.3.2	Design of 11 β HSD1 Inhibitors	275
11.4	Summary	278
	Acknowledgements	278
	References	278

Chapter 12 Molecular Simulation in Computer-aided Drug Design: Algorithms and Applications	281
<i>Robert V. Swift and Rommie E. Amaro</i>	
12.1 Introduction	281
12.2 Molecular Simulation to Investigate Drug Targets	284
12.2.1 Refinement and Exploration of Target Structures	284
12.2.2 Exploration of New Binding Sites	285
12.3 Molecular Simulation in Virtual Screening Experiments to Identify Initial Hits	291
12.3.1 Dynamic Pharmacophore Method	292
12.3.2 Ensemble-Based Virtual Screening	293
12.3.3 Emerging Non-Equilibrium Approaches	295
12.4 Using Molecular Simulation to Estimate and Enhance Binding Free Energies, and as a Tool in Lead Discovery and Optimization	297
12.4.1 End-Point Free Energy Methods	298
12.4.2 Alchemical Relative Binding Free Energy Methods	303
12.5 Conclusions and Future Prospects	309
References	309
Chapter 13 Computer-aided Drug Discovery: Two Antiviral Drugs for HIV/AIDS	316
<i>J. Andrew McCammon</i>	
13.1 Introduction	316
13.2 Nelfinavir	317
13.3 Raltegravir	317
Acknowledgements	319
References	319
Subject Index	320