

# Contents

Acknowledgments	i
Abstract	iii
Contents	v
Symbols	ix
<b>1 Introduction</b>	<b>1</b>
1.1 Motivation	1
1.2 Theory and State of the Art in Molecular Mechanics	3
1.2.1 Molecular Dynamics (MD)	3
1.2.2 Coarse-Graining in Space and Time	8
1.2.3 Other Derivatives and Related Methods: From Monte Carlo to Machine Learning	13
1.2.4 Scope of this Work	15
1.3 Model Systems	16
1.3.1 Alginate Gelation	17
1.3.2 Hepatitis B Core Antigen (HBcAg)	19
1.3.3 Pyruvate Dehydrogenase Complex (PDC)	20
1.4 Outline	23
<b>2 Model Framework</b>	<b>25</b>
2.1 Introduction and Framework Overview	25
2.2 MDEM Implementation	28
2.3 Molecular Reference Structures	30
<b>3 Diffusion and Thermodynamics</b>	<b>33</b>
3.1 Introduction	33
3.2 Model Description	34
3.2.1 Overview	34
3.2.2 Background	35
3.2.3 Simplification for Isotropic Diffusion	36
3.3 Parameterization	36
3.3.1 Approaches	36
3.3.2 Parameterization through Molecular Dynamics	37
3.4 Convergence	38
3.4.1 Critical Time Step	39

3.4.2	Thermal Equilibration Speed . . . . .	40
3.4.3	Diffusion Coefficient . . . . .	40
3.4.4	Kinetic Energy . . . . .	41
3.5	Comparison with Molecular Dynamics Data . . . . .	44
3.6	Enhanced Sampling of the Conformation Space through Simulated Annealing . . . . .	46
<b>4</b>	<b>Intermolecular Interaction</b>	<b>47</b>
4.1	Introduction . . . . .	47
4.2	Probabilistic Interaction Model for Calcium Mediated Alginate Gelation Based on Literature and Theory . . . . .	49
4.2.1	Interaction Model . . . . .	50
4.2.2	Ion Model . . . . .	51
4.2.3	Critical Time Step . . . . .	54
4.3	Data-Driven Interaction Potential Fields Based on MD . . . . .	55
4.3.1	Molecular Dynamics Setup and Potential Groups . . . . .	57
4.3.2	Spatial Descriptors . . . . .	59
4.3.3	Basic Functions for Trend and Variogram Modeling . . . . .	61
4.3.4	Multi-Variant Field Interpolation using Universal Kriging . . . . .	63
4.3.4.1	Method . . . . .	63
4.3.4.2	Grid Design . . . . .	67
4.3.4.3	Initial Sampling and Iterative Refinement . . . . .	69
4.3.4.4	2D Example . . . . .	71
4.3.5	Biased MD and Insertion of Empirical Data . . . . .	72
4.3.6	Molecular Collisions . . . . .	75
4.3.7	Method Summary and Uncertainties . . . . .	77
4.4	Derivation of Interaction Forces and Torques From Potential Fields . . . . .	78
4.4.1	Direct Usage of Potential Field . . . . .	79
4.4.2	Alternative Representations and Simplifications . . . . .	80
4.5	Critical Time Step . . . . .	81
<b>5</b>	<b>Bonded Interaction</b>	<b>83</b>
5.1	Introduction . . . . .	83
5.2	Pairwise Elastic Bond Model (incl. Orientation) . . . . .	84
5.2.1	Model Description . . . . .	84
5.2.2	Bond Contact Point . . . . .	87
5.2.3	Critical Time Step . . . . .	87
5.3	Fiber Bond Model . . . . .	88
5.3.1	Model Description . . . . .	88
5.3.2	Critical Time Step . . . . .	90
<b>6</b>	<b>Results: Alginate System</b>	<b>93</b>
6.1	Model Parameters . . . . .	93
6.1.1	Structural Model . . . . .	93
6.1.2	Functional Model . . . . .	96
6.1.2.1	Diffusion and Thermodynamics . . . . .	96
6.1.2.2	Intermolecular Interaction . . . . .	97
6.1.2.3	Bonded Interaction . . . . .	101

---

6.1.2.4	Critical Time Step . . . . .	102
6.2	Simulation Setup and Procedure . . . . .	102
6.3	Analysis and Postprocessing . . . . .	103
6.4	Results . . . . .	104
6.4.1	Base Case . . . . .	106
6.4.2	Case Studies . . . . .	109
6.4.2.1	Constant Temperature (No Annealing) . . . . .	109
6.4.2.2	Annealing Procedure (AN2) . . . . .	114
6.5	Comparison with Literature and Collaborator Data . . . . .	117
<b>7</b>	<b>Results: HBcAg System</b>	<b>125</b>
7.1	Model Parameters . . . . .	125
7.1.1	Structural Model . . . . .	125
7.1.2	Functional Model . . . . .	126
7.1.2.1	Diffusion and Thermodynamics . . . . .	126
7.1.2.2	Intermolecular Interaction . . . . .	126
7.1.2.3	Bonded Interaction . . . . .	127
7.1.2.4	Critical Time Step . . . . .	128
7.2	Simulation Setup and Procedure . . . . .	128
7.3	Analysis and Postprocessing . . . . .	129
7.4	Results . . . . .	130
7.4.1	Intermolecular Interaction Potential and VLP Stability . . . . .	131
7.4.1.1	Pure MD-Based Interaction Potential . . . . .	131
7.4.1.2	Biased MD-Based Interaction Potential . . . . .	135
7.4.1.3	MD-Based Interaction Potential with Empirical Data . . . . .	136
7.4.2	VLP Self-Assembly . . . . .	138
<b>8</b>	<b>Results: PDC System</b>	<b>151</b>
8.1	Model Parameters . . . . .	151
8.1.1	Structural Model . . . . .	151
8.1.2	Functional Model . . . . .	152
8.1.2.1	Diffusion and Thermodynamics . . . . .	152
8.1.2.2	Intermolecular Interaction . . . . .	152
8.1.2.3	Bonded Interaction . . . . .	155
8.1.2.4	Critical Time Step . . . . .	155
8.2	Simulation Setup and Procedure . . . . .	156
8.3	Analysis and Postprocessing . . . . .	156
8.4	Results . . . . .	158
8.4.1	Intermolecular Interaction Potentials . . . . .	158
8.4.2	PDC Self-Assembly . . . . .	164
8.4.2.1	Pure E2 System . . . . .	164
8.4.2.2	Full Component PDC System . . . . .	170
<b>9</b>	<b>Conclusions</b>	<b>177</b>

---

<b>A</b>	<b>General Appendix</b>	<b>181</b>
A.1	Euler Angle Definition . . . . .	181
A.2	Detailed Framework Overview . . . . .	182
A.3	Hydrodynamic Interaction . . . . .	183
<b>B</b>	<b>Diffusion Model Comparison with Molecular Dynamics Data</b>	<b>185</b>
<b>C</b>	<b>Kriging Algorithm Components</b>	<b>187</b>
C.1	Variogram Binning Algorithm . . . . .	187
C.2	Kriging Neighborhood Search and Convergence . . . . .	188
C.3	Objective Function For Quantitative Structural Stability . . . . .	190
C.4	MD Quality Criteria . . . . .	191
<b>D</b>	<b>HBcAg Results Supplementary</b>	<b>193</b>
D.1	Spatial Descriptors . . . . .	194
D.2	Biased MD-Based Interaction Potential . . . . .	195
D.3	Kriging Statistical Data . . . . .	195
<b>E</b>	<b>PDC Results Supplementary</b>	<b>201</b>
E.1	Binding Locations . . . . .	202
E.2	Pure MD-Based Interaction Potentials . . . . .	205
E.3	Repulsive-Only Interaction Potentials . . . . .	206
E.4	Kriging Statistical Data . . . . .	208
E.5	PDC Self-Assembly . . . . .	221
E.5.1	Pure E2 System . . . . .	221
E.5.2	Full Component PDC System . . . . .	224
E.5.3	Enhanced E2 – E2 Arm Interaction . . . . .	231
	<b>Bibliography</b>	<b>239</b>