

An Uncoupling-Coupling Method  
for Markov Chain Monte Carlo Simulations  
with an Application to Biomolecules

vorgelegt von  
Alexander Fischer

Januar 2003

Zur Erlangung des Grades  
eines Doktors der Naturwissenschaften  
am Fachbereich Mathematik und Informatik  
der Freien Universität Berlin  
eingereichte Dissertation

**Betreuer:**

Prof. Dr. Christof Schütte

Prof. Dr. Dr. h.c. Peter Deuffhard

**Gutachter:**

Prof. Dr. Christof Schütte

Prof. Dr. Eric Vanden-Eijnden

**Datum der Disputation:** 16.07.2003

---

## Contents

<b>1</b>	<b>Introduction</b>	<b>1</b>
<b>2</b>	<b>Simulation of Biomolecules</b>	<b>11</b>
2.1	Hamiltonian Mechanics . . . . .	11
2.2	Molecular Force Fields . . . . .	12
2.3	Molecular Dynamics . . . . .	15
2.4	Canonical Ensemble . . . . .	18
2.5	Sampling Schemes . . . . .	19
2.5.1	Canonical Molecular Dynamics . . . . .	19
2.5.2	Monte Carlo Schemes . . . . .	20
2.6	Metastable Conformations . . . . .	21
<b>3</b>	<b>Markov Chains and Metastability</b>	<b>23</b>
3.1	Classical Limit Theorems . . . . .	24
3.2	Markov Chains on Finite State Spaces . . . . .	27
3.2.1	Pathwise Limit Theorems . . . . .	30
3.2.2	Metastable Sets . . . . .	32
3.2.3	Identification of Metastable Sets . . . . .	34
3.3	Markov Chains on Continuous State Spaces . . . . .	36
3.3.1	Transition Kernel . . . . .	36
3.3.2	The Markov Operator . . . . .	37
3.3.3	Metastable Sets of a Markov Operator . . . . .	39
3.3.4	Dynamical Clustering . . . . .	41
<b>4</b>	<b>Markov Chain Monte Carlo</b>	<b>43</b>
4.1	Metropolis Transition Kernel . . . . .	44
4.2	Metropolis Algorithm . . . . .	46
4.2.1	Examples for Proposal Steps . . . . .	47
4.2.2	Hybrid Monte Carlo . . . . .	49
4.3	Convergence Diagnostics . . . . .	51
4.4	Bridge Distributions . . . . .	53
4.4.1	Reweighting . . . . .	54
4.4.2	Adaptive Temperature HMC . . . . .	55
4.4.3	Potential Scaling HMC . . . . .	58
4.5	Extended MCMC Methods . . . . .	61
4.5.1	Multicanonical Sampling . . . . .	62
4.5.2	Parallel Tempering . . . . .	63

---

<b>5</b>	<b>Uncoupling-Coupling</b>	<b>65</b>
5.1	Bridging the Barrier . . . . .	65
5.2	Uncoupling of Markov Chains . . . . .	69
5.2.1	Restricted Sampling . . . . .	70
5.2.2	Eigenvalue Splitting . . . . .	73
5.2.3	Hierarchical Annealing . . . . .	76
5.3	Coupling Matrix . . . . .	80
5.3.1	Setup and Analysis . . . . .	80
5.3.2	Approximation of the Coupling Matrix . . . . .	83
5.3.3	Reweighting . . . . .	84
5.4	Uncoupling-Coupling Scheme . . . . .	86
<b>6</b>	<b>Numerical Experiments</b>	<b>89</b>
6.1	<i>n</i> -Butane . . . . .	89
6.2	<i>n</i> -Pentane . . . . .	90
6.2.1	Complete Hierarchy . . . . .	92
6.2.2	Essential Hierarchy . . . . .	96
6.3	Epigallocatechin Molecule . . . . .	99
	<b>Conclusion</b>	<b>105</b>
	<b>References</b>	<b>106</b>