

# Contents

<b>1. Introduction</b>	<b>1</b>
<b>2. Theory: Time-continuous Markov Processes</b>	<b>9</b>
2.1. Markov Diffusion Processes . . . . .	9
2.1.1. Markov Processes . . . . .	9
2.1.2. The Infinitesimal Operator . . . . .	10
2.1.3. Diffusion Processes . . . . .	11
2.1.4. Reversed-time Diffusion Process . . . . .	12
2.1.5. Backward and Forward Equations . . . . .	13
2.1.6. Partial Differential Operators . . . . .	14
2.1.7. Relation between $\mathcal{L}_{bw}$ and $\mathcal{L}_{fw}$ . . . . .	15
2.1.8. Stochastic Representation of Solutions of Boundary Value Problems . . . . .	16
2.1.9. Adjoint Boundary Condition . . . . .	17
2.1.10. Langevin and Smoluchowski Dynamics . . . . .	18
2.2. Markov Jump Processes . . . . .	20
<b>3. Transition Path Theory for Diffusion Processes</b>	<b>25</b>
3.1. Theory: Transition Path Theory . . . . .	25
3.1.1. Ensemble of Reactive Trajectories . . . . .	25
3.1.2. Committor Function . . . . .	26
3.1.3. Probability Density Function of Reactive Trajectories . . . . .	28
3.1.4. Probability Current and Transition Rate . . . . .	28
3.1.5. Transition Tubes . . . . .	30
3.2. TPT in the Smoluchowski Case . . . . .	30
3.3. TPT in the Langevin Case . . . . .	31
3.4. Numerical Aspects . . . . .	33
3.5. Diffusion in the Double-Well Potential . . . . .	34
3.5.1. Committor Function . . . . .	35
3.5.2. Probability Density Function of Reactive Trajectories . . . . .	35
3.5.3. Probability Current of Reactive Trajectories and its Streamlines	37
3.5.4. Reaction Rate . . . . .	37
3.6. Entropic Barriers: Pure Diffusion . . . . .	38
3.7. Entropic Switching . . . . .	40
3.7.1. Diffusion in a Three-Hole Potential . . . . .	40
3.7.2. Diffusion in a Rough Three-Hole Potential . . . . .	44
3.8. Different Time-Scales: Fast-Slow Diffusion in a Double-Well Potential	47
3.9. Langevin Dynamics . . . . .	50
3.9.1. High Friction Case, $\gamma = 10$ . . . . .	51
3.9.2. Medium Friction Case, $\gamma = 1$ . . . . .	53

## Contents

3.9.3. Low Friction Case, $\gamma = 0.001$ . . . . .	54
3.9.4. Rough Potential Landscape . . . . .	54
<b>4. Transition Path Theory for Markov Jump Processes</b>	<b>59</b>
4.1. Theoretical Aspects . . . . .	60
4.1.1. Preliminaries: Notations and Assumptions . . . . .	60
4.1.2. Reactive Trajectories . . . . .	60
4.1.3. Probability Distribution of Reactive Trajectories . . . . .	62
4.1.4. Discrete Committor Equations . . . . .	63
4.1.5. Probability Current of Reactive Trajectories . . . . .	65
4.1.6. Transition Rate and Effective Current . . . . .	67
4.1.7. Relations with Electrical Resistor Networks . . . . .	68
4.1.8. Dynamical Bottlenecks and Reaction Pathways . . . . .	69
4.1.9. Relation with Laplacian Eigenmaps and Diffusion Maps . . . . .	72
4.2. Algorithmic Aspects . . . . .	73
4.2.1. Computation of Dynamical Bottlenecks and Representative Dominant Reaction Pathways . . . . .	73
4.3. Illustrative Examples . . . . .	75
4.3.1. Discrete Analog of a Diffusion in a Potential Landscape . . . . .	75
4.3.2. Molecular Dynamics : Glycine . . . . .	79
4.3.3. Chemical Kinetics . . . . .	87
<b>5. Generator Estimation of Markov Jump Processes</b>	<b>91</b>
5.1. The Embedding Problem . . . . .	91
5.2. The Maximum Likelihood Method . . . . .	92
5.2.1. Continuous and Discrete Likelihood Functions . . . . .	92
5.2.2. Likelihood Approach Revisited . . . . .	94
5.2.3. Enhanced Computation of the Maximum Likelihood Estimator	96
5.2.4. Reversible Case . . . . .	98
5.2.5. Scaling . . . . .	100
5.2.6. Enhanced MLE-Method vs. MLE-Method . . . . .	100
5.3. An Alternative Approach: The Quadratic Optimization Method . . . . .	101
5.4. Numerical Examples for Equidistant Observation Times . . . . .	102
5.4.1. Preparatory Considerations . . . . .	102
5.4.2. Transition Matrix with Underlying Generator . . . . .	104
5.4.3. Transition Matrix without Underlying Generator . . . . .	106
5.4.4. Transition Matrix with Exact Generator under Perturbation	107
5.4.5. Application to a Time Series from Molecular Dynamics . . . . .	109
5.5. Numerical Examples for Non-Equidistant Observation Times . . . . .	110
5.5.1. Test Example . . . . .	112
5.5.2. Application to a Genetic Toggle Switch Model . . . . .	112
<b>6. Detecting Reaction Pathways via Shortest Paths in Graphs</b>	<b>117</b>
6.1. Shortest Path in Graphs . . . . .	117
6.1.1. Dijkstra Algorithm . . . . .	117
6.1.2. Bidirectional Dijkstra Algorithm . . . . .	118
6.2. Choice of Edge Weights . . . . .	120
6.2.1. Likelihood Approach . . . . .	120

6.2.2. Free Energy Approach . . . . .	121
6.3. Numerical Experiments . . . . .	123
<b>7. Variance of the Committor Function</b>	<b>127</b>
7.1. The Discrete Committor Function . . . . .	127
7.2. Metropolis Markov Chain Monte Carlo . . . . .	128
7.3. Ensemble of Transition Matrices via MCMC . . . . .	130
7.3.1. Dynamics on the Transition Matrix Space . . . . .	130
7.3.2. MCMC on the Frequency Matrix Space . . . . .	130
7.3.3. Proof of Correctness . . . . .	132
7.4. Numerical Experiments . . . . .	134
7.4.1. Dirichlet Distribution . . . . .	134
7.4.2. Small Example . . . . .	135
7.4.3. Glycine . . . . .	139
<b>8. Summary and Conclusion</b>	<b>143</b>
<b>A. Appendix</b>	<b>145</b>
A.1. Discretization of the Committor Equation . . . . .	145
A.1.1. Discretization via Finite Differences . . . . .	146
A.1.2. Finite Difference Discretization of the Smoluchowski Committor Equation . . . . .	148
A.1.3. Finite Difference Discretization of the Langevin Committor Equation . . . . .	153
A.2. Weak Formulation for the Elliptic Mixed-Boundary Value Problem .	159
A.2.1. Existence of a Weak Solution . . . . .	162
A.2.2. Classical Solution vs. Weak Solution . . . . .	163
A.3. Approximation of Diffusion Processes via Markov Jump Processes .	164
A.4. Proofs . . . . .	165
A.4.1. Proof for the Representation of the Probability Current of Reactive Trajectories . . . . .	165
A.4.2. Proof for the Representation of the Transition Rate via a Volume Integral . . . . .	167
A.5. Short Account to Free Energy . . . . .	168
A.6. Definitions and Theorems . . . . .	169