C O U R A N T

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24

LECTURE NOTES

Metastability and Markov State Models in Molecular Dynamics

Modeling, Analysis, Algorithmic Approaches

Metastability and
Markov State Models
in Molecular Dynamics

Courant Lecture Notes in Mathematics

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Introduction

This is a book about mathematics. At the same time it is a book about molecular dynamics. Typical books with this combination of topics try to give a mathematical framework for what is done in standard molecular dynamics simulations or consider the temporal discretization schemes used in molecular dynamics. This book will not. Instead it will be concerned with one of the key challenges in molecular dynamics: How can one analyze molecular function if the required simulation timescales are infeasible?

For readers who are not familiar with molecular dynamics a few words explaining this key challenge seem appropriate: Applications in modern biotechnology and molecular medicine require simulation of biomolecular systems in atomic representation with immense length and timescales that are *far* beyond the capacity of computer power currently available. The reason for this is that many of the processes that constitute molecular function are *rare event* processes appearing on timescales that are many orders of magnitude, say 10–15 orders of magnitude, longer than the typical time steps of the numerical simulation. As a consequence, there is an increasing need for reduced models of the dynamical behavior of molecular systems that still allow describing the relevant dynamical properties while at the same time being less complex and thus allowing simulation on longer timescales. However, whether such reduced descriptions reproduce the correct rare event statistics is a question that in principle can only be answered mathematically.

In most molecular systems the biologically interesting and computationally problematic rare events belong to so-called conformation changes. Conformations are *metastable sets* of the dynamical behavior of the molecule, that is, regions of the molecule's state space that are attractive for the dynamics in the sense that typical trajectories remain within such regions for long periods of time before exiting towards other metastable sets. This rough description may already be sufficient for indicating that any mathematical approach to efficient rare event simulation in molecular dynamics should address the issue of metastability of the dynamical behavior of molecular systems. Consequently, this book will be concerned with understanding the origin of metastability and with its mathematical description. This, however, is just the first step. We will see how to exploit the existence of metastable sets for constructing a reduced molecular dynamics model with good approximation properties on the long timescales. In this reduced model, the so-called Markov state model (MSM), the main metastable sets will form the states of a Markov chain or Markov jump process while the transition probabilities or transition rates of the Markov model are given by the transition statistics of the original

molecular dynamics process. Mathematically, the process of reducing the original molecular dynamics process to the MSM process will be a Galerkin discretization of the so-called transfer operator of the molecular dynamics process. Thus, the mathematics of *projected transfer operators* is central for our undertaking.

That is exactly what the book will focus on: metastability, MSMs, and the mathematics of transfer operators that allows the analysis of the relation between one and the other. The rough outline is as follows: We start with a more detailed introduction to the idea behind MSMs in Chapter 1. Next we will outline the different molecular dynamics models and the mathematical framework in which they all can be handled together (Chapter 2). Then we can turn to the mathematical concepts of metastability in Chapter 3 before we introduce transfer operators and the spectral approach to metastability (Chapter 4), and the construction of MSMs via projected transfer operators in Chapter 5. Last, we will investigate how to use an existing MSM to get information on the transition pathways that dominate the transitions from one metastable set into another (Chapter 6).

Recent years have seen an ever increasing publication activity on how to construct MSMs for very different molecular systems ranging from peptides to proteins, from RNA to DNA, and via molecular sensors to molecular aggregation (see the next section for references). Presently, several books are under preparation that will address these practical approaches in all algorithmic detail but not their mathematical background. Therefore, the present book concentrates on the latter.

The material presented in the following has resulted from more than 12 years of research on MSMs and metastability that started with the first publications by the first author and his coworkers in the last millennium; see [**15, 16, 95, 96**]. It has been compiled for mathematicians as well as practical computational scientists interested in modern molecular dynamics.

The book is predominantly addressed to graduate students and researchers wanting to get an overview of the theoretical background of MSMs and associated concepts in molecular dynamics. Therefore the mathematical technicalities have been limited to the level that the authors believe to be accessible for theory-interested nonmathematicians. The text includes many examples and helpful illustrations. Everyone interested in deeper insights into the matter will find comprehensive references to the relevant literature. The authors hope that the present book may help to bridge the still existing gap between mathematical research on molecular dynamics and its practical use for realistic molecular systems by providing readers with tools for performing more in-depth analysis of simulation and data-analysis methods in molecular dynamics.

Many extraordinarily talented people have contributed to the mathematics of metastable systems in relation to the transfer operator approach, its algorithmic realization, and its applications. We wish to acknowledge the efforts and excellent skill of the following mathematicians: Peter Deuflhard (who has contributed from the very beginnings in the last millennium till today), Eric Vanden-Eijnden, Marcus Weber, and Frank Noe. Their contributions have been invaluable. Furthermore, we want to thank the DFG Research Center MATHEON "Mathematics for

Bibliography

[1] Ahuja, R. K., Magnanti, T. L., and Orlin, J. B. *Network flows*. Prentice Hall, Englewood Cliffs, N.J., 1993.

[2] Beauchamp, K. A., Bowman, G. R., Lane, T. J., Maibaum, L., Haque, I. S., and Pande, V. S. MSMBuilder2: Modeling conformational dynamics at the picosecond to millisecond scale. *J. Chem. Theor. Comput.* 7(10):3412–3419, 2011.

[3] Bolhuis, P. G., Chandler, D., Dellago, C., and Geissler, P. Transition path sampling: throwing ropes over mountain passes, in the dark. *Annu. Rev. Phys. Chem.* 53(1):291–318, 2002.

[4] Bond, S. D., Benedict, B. B. L., and Leimkuhler, J. The Nosé–Poincaré method for constant temperature molecular dynamics. *J. Comput. Phys.* 151(1):114–134, 1999.

[5] Bou-Rabee, N., and Vanden-Eijnden, E. Pathwise accuracy and ergodicity of metropolized integrators for SDEs. *Comm. Pure. Appl. Math.* 63(5):655–696, 2010.

[6] Bovier, A., Eckhoff, M., Gayrard, V., and Klein, M. Metastability and low lying spectra in reversible Markov chains. *Comm. Math. Phys.* 228(2):219–255, 2002.

[7] ———. Metastability in reversible diffusion processes I. Sharp asymptotics for capacities and exit times. *J. Eur. Math. Soc. (JEMS)* 6(4):399–424, 2004.

[8] Bovier, A., Gayrard, V., and Klein, M. Metastability in reversible diffusion processes II. Precise asymptotics for small eigenvalues. *J. Eur. Math. Soc. (JEMS)* 7(1):69–99, 2005.

[9] Bowman, G., Volez, V., and Pande, V. S. Taming the complexity of protein folding. *Current Opinion in Structural Biology* 21(1):4–11, 2011.

[10] Bowman, G. R., Huang, X., and Pande, V. S. Using generalized ensemble simulations and Markov state models to identify conformational states. *Methods* 49(2):197–201, 2009.

[11] Buchete, N.-V., and Hummer, G. Coarse master equations for peptide folding dynamics. *J. Phys. Chem. B* 112(19):6057–6069, 2008.

[12] Chandler, D. Finding transition pathways: throwing ropes over rough mountain passes, in the dark. *Classic and Quantum Dynamics in Condensed Phase Simulations*, 51–66. Singapore: World Scientific, 1998.

[13] Chodera, J. D., Singhal, N., Pande, V. S., Dill, K. A., and Swope, W. C. Automatic discovery of metastable states for the construction of Markov models of macromolecular conformational dynamics. *J. Chem. Phys.* 126(15):155101, 17 pp., 2007.

[14] Dellnitz, M., and Junge, O. On the approximation of complicated dynamical behavior. *SIAM J. Numer. Anal.* 36(2):491–515, 1999.

[15] Deuflhard, P., Dellnitz, M., Junge, O., and Schütte, C. Computation of essential molecular dynamics by subdivision techniques. *Computational Molecular Dynamics: Challenges, Methods, Ideas*, 98–115. Springer, Berlin-Heidelberg, 1999.

[16] Deuflhard, P., Huisinga, W., Fischer, A., and Schütte, C. Identification of almost invariant aggregates in reversible nearly uncoupled Markov chains. *Linear Algebra Appl.* 315(1–3):39–59, 2000.

[17] Deuflhard, P., and Schütte, C. Molecular conformation dynamics and computational drug design. *Applied mathematics entering the 21st century. Proc. ICIAM (Sydney, 2003)*, 91–119. SIAM, Philadelphia, 2004.

[18] Deuflhard, P., and Weber, M. Robust Perron cluster analysis in conformation dynamics. *Linear Algebra Appl.* 398:161–184, 2005.

[19] Doob, J. L. *Classical potential theory and its probabilistic counterpart*. Grundlehren der mathematischen Wissenschaften, 262. Springer, New York, 1984.

[20] Down, D., Meyn, S. P., and Tweedie, R. L. Exponential and uniform ergodicity of Markov processes. *Ann. Prob.* 23(4):1671–1691, 1995.

[21] Dunford, N., and Schwartz, J. T. *Linear operators*. Part I: General theory, 1–243. Pure and Applied Mathematics. A series of books and monographs, 7. Interscience, New York, 1958.

[22] E, W., Li, T., and Vanden-Eijnden, E. Optimal partition and effective dynamics of complex networks. *Proc. Natl. Acad. Sci. USA* 105(23):7907–7912, 2008.

[23] E, W., Ren, W., and Vanden-Eijnden, E. Probing multiscale energy landscapes using the string method. Preprint, 2002. arXiv:cond-mat/0205528

[24] E, W., and Vanden-Eijnden, E. Metastability, conformation dynamics, and transition pathways in complex systems. *Multiscale modelling and simulation*, 35–68. Lecture Notes in Computational Science and Engineering, 39. Springer, Berlin, 2004.

[25] ———. Towards a theory of transition paths. *J. Stat. Phys.* 123(3):503–523, 2006.

[26] ———. Transition-path theory and path-finding algorithms for the study of rare events. *Annu. Rev. Phys. Chem.* 61:391–420, 2010.

[27] Elber, R., and Karplus, M. Multiple conformational states of proteins: a molecular dynamics analysis of myoglobin. *Science* 235(4786):318–321, 1987.

[28] Eyring, H. The activated complex in chemical reactions. *J. Chem. Phys.* 3:107–115, 1935.

[29] Faradjian, A. K., and Elber, R. Computing time scales from reaction coordinates by milestoning. *J. Chem. Phys.* 120(23):10880, 10 pp., 2004.

[30] Fischer, A., Cordes, F., and Schütte, C. Hybrid Monte Carlo with adaptive temperature in a mixed-canonical ensemble: efficient conformational analysis of RNA. *J. Comput. Chem.* 19(15):1689–1697, 1998.

[31] ———. An uncoupling–coupling technique for Markov chain Monte Carlo methods. Konrad-Zuse-Zentrum für Informationstechnik Berlin (ZIB), Technical report 00-04, 2000.

[32] Fischer, A., Schütte, C., Deuflhard, P., and Cordes, F. Hierarchical uncoupling-coupling of metastable conformations. *Computational methods for macromolecules: challenges and applications (New York, 2000)*, 235–259. Lecture Notes in Computational Science and Engineering, 24. Springer, Berlin, 2002.

[33] Fischer, S., Windshügel, B., Horak, D., Holmes, K. C., and Smith, J. C. Structural mechanism of the recovery stroke in the myosin molecular motor. *Proc. Natl. Acad. Sci. USA* 102(19):6873–6878, 2005.

[34] Frauenfelder, H., and McMahon, B. H. Energy landscape and fluctuations in proteins. *Ann. Phys.* 9(9–10):655–667, 2000.

[35] Frauenfelder, H., Steinbach, P. J., and Young, R. D. Conformational relaxation in proteins. *Chem. Soc. A* 29:145–150, 1989.

[36] Frenkel, D., and Smit, B. *Understanding molecular simulation: from algorithms to applications*. Academic Press, London, 2002.

[37] Fritzsche, D., Mehrmann, V., Szyld, D. B., and Virnik, E. An SVD approach to identifying metastable states of Markov chains. *Electron. Trans. Numer. Anal.* 29:46–69, 2007/2008.

[38] Galliat, T., Deuflhard, P., Roitzsch, R., and Cordes, F. Automatic identification of metastable conformations via self-organized neural networks. *Computational methods for macromolecules: challenges and applications (New York, 2000)*, 260–284. Lecture Notes in Computational Science and Engineering, 24. Springer, Berlin, 2002.

[39] Hastings, W. K. Monte Carlo sampling methods using Markov chains and their applications. *Biometrika* 57(1):97–109, 1970.

[40] Hérau, F., Hitrik, M., and Sjöstrand, J. Tunnel effect and symmetries for Kramers-Fokker-Planck type operators. *J. Inst. Math. Jussieu* 10(3):567–634, 2011.

[41] Heuser, H. *Funktionalanalysis*. Second edition. Mathematische Leitfäden. Teubner, Stuttgart, 1986.

[42] Horenko, I., Dittmer, E., Lankas, F., Maddocks, J., Metzner, P., and Schütte, C. Macroscopic dynamics of complex metastable systems: theory, algorithms, and application to B-DNA. *SIAM J. Appl. Dyn. Syst.* 7(2):532–560, 2008.

[43] Huang, X., Yao, Y., Bowman, G. R., Sun, J., Guibas, L. J., Carlsson, G., and Pande, V. S. Constructing multi-resolution Markov state models (MSMs) to elucidate RNA hairpin folding mechanisms. *Pac. Symp. Biocomput.* 15:228–39, 2010.

[44] Huisinga, W. Metastability of Markovian systems: a transfer operator approach in application to molecular dynamics. Doctoral dissertation, Free University Berlin, 2001.

[45] Huisinga, W., Best, C., Roitzsch, R., Schütte, C., and Cordes, F. From simulation data to conformational ensembles: structure and dynamics based methods. *J. Comp. Chem.* 20(16):1760–1774, 1999.

[46] Huisinga, W., Meyn, S., and Schütte, C. Phase transitions and metastability in Markovian and molecular systems. *Ann. Appl. Probab.* 14(1):419–458, 2004.

[47] Huisinga, W., and Schmidt, B. Metastability and dominant eigenvalues of transfer operators. *New algorithms for macromolecular simulation*, 167–182. Lecture Notes in Computational Science and Engineering, 49. Springer, Berlin, 2006.

[48] Jäger, M., Zhang, Y., Bieschke, J., Nguyen, H., Dendle, M., Bowman, M. E., Noel, J. P., Gruebele, M., and Kelly, J. W. Structure-function-folding relationship in a WW domain. *Proc. Natl. Acad. Sci. USA* 103(28):10648–10653, 2006.

[49] Karatzas, I., and Shreve, S. E. *Brownian motion and stochastic calculus*. Second edition. Graduate Texts in Mathematics, 113. Springer, New York, 1991.

[50] Kato, T. *Perturbation theory for linear operators*. Classics in Mathematics. Springer, Berlin, 1995.

[51] Keller, B. G., Prinz, J.-H., and Noé, F. Markov models and dynamical fingerprints: unraveling the complexity of molecular kinetics. *Chem. Phys.* 396:92–107, 2012.

[52] Knyazev, A. V., and Argentati, M. E. Rayleigh-Ritz majorization error bounds with applications to FEM. *SIAM J. Matrix Anal. Appl.* 31(3):1521–1537, 2009.

[53] Kobitski, A. Y., Nierth, A., Helm, M., Jäschke, A., and Nienhaus, G. U. Mg2+ dependent folding of a Diels-Alderase ribozyme probed by single-molecule FRET analysis. *Nucleic Acids Research* 35(6):2047–2059, 2007.

[54] Kontoyiannis, I., and Meyn, S. P. Spectral theory and limit theorems for geometrically ergodic Markov processes. *Ann. Appl. Probab.* 13(1):304–362, 2003.

[55] ———. Geometric ergodicity and the spectral gap of non-reversible Markov chains. *Probab. Theory Related Fields* 154(1–2):327–339, 2012.

[56] Krivov, S. V., and Karplus, M. Hidden complexity of free energy surfaces for peptide (protein) folding. *Proc. Natl. Acad. Sci. USA* 101(41):14766–14770, 2004.

[57] Lafon, S., and Lee, A. B. Diffusion maps and coarse-graining: a unified framework for dimensionality reduction, graph partitioning, and data set parameterization. *IEEE Transactions on Pattern Analysis and Machine Intelligence* 28(9):1393–1403, 2006.

[58] Lasota, A., and Mackey, M. C. *Chaos, Fractals and Noise*. Second edition. Applied Mathematical Sciences, 97. Springer, New York, 1994.

[59] Lau, K. F., and Dill, K. A. A lattice statistical mechanics model of the conformational and sequence spaces of proteins. *Macromolecules* 22(10):3986–3997, 1989.

[60] Lebow, A., and Schechter, M. Semigroups of operators and measures of noncompactness. *J. Functional Analysis*, 7:1–26, 1971.

[61] Liu, J. S. *Monte Carlo strategies in scientific computing*. Springer Series in Statistics. Springer, New York, 2008.

[62] Mangasarian, O. Perron-Frobenius properties for $Ax - \lambda Bx$. *J. Math. Anal. Appl.* 36(1):86–102, 1971.

[63] Mattingly, J. C., Stuart, A. M., and Higham, D. J. Ergodicity for SDEs and approximations: locally Lipschitz vector fields and degenerate noise. *Stochastic Process Appl.* 101 (2):185–232, 2002.

[64] Meerbach, E., Schütte, C., and Fischer, A. Eigenvalue bounds on restrictions of reversible nearly uncoupled Markov chains. *Linear Algebra Appl.* 398:141–160, 2005.

[65] Metzner, P. *Transition path theory for Markov processes: application to molecular dynamics.* Doctoral dissertation, Free University Berlin, 2007.

[66] Metzner, P., Noé, F., and Schütte, C. Estimating the sampling error: distribution of transition matrices and functions of transition matrices for given trajectory data. *Phys. Rev. E* 80(2):021106, 13 pp., 2008.

[67] Metzner, P., Schütte, C., and Vanden-Eijnden, E. Illustration of transition path theory on a collection of simple examples. *J. Chem. Phys.* 125(8): 084110, 17 pp., 2006. 084110.

[68] ———. Transition path theory for Markov jump processes. *Multiscale Model. Simul.* 7(3):1192–1219, 2008.

[69] Meyer, C. D. Stochastic complementation, uncoupling Markov chains, and the theory of nearly reducible systems. *SIAM Rev.* 31(2):240–272, 1989.

[70] Meyn, S. P., and Tweedie, R. L. *Markov chains and stochastic stability.* Communications and Control Engineering Series. Springer, London, 1993.

[71] Muff, S., and Caflisch, A. Kinetic analysis of molecular dynamics simulations reveals changes in the denatured state and switch of folding pathways upon single-point mutation of a β-sheet miniprotein. *Proteins: structure, function, and bioinformatics* 70(4):1185–1195, 2007.

[72] Nienhaus, G. U., Mourant, J. R., and Frauenfelder, H. Spectroscopic evidence for conformational relaxation in myoglobin. *Proc. Natl. Acad. Sci.* 89(7):2902–2906, 1992.

[73] Noé, F., and Fischer, S. Transition networks for modeling the kinetics of conformational change in macromolecules. *Current Opinion in Structural Biology* 18(2):154–162, 2008.

[74] Noé, F., Horenko, I., Schütte, C., and Smith, J. C. Hierarchical analysis of conformational dynamics in biomolecules: transition networks of metastable states. *J. Chem. Phys.* 126(15):155102, 17 pp., 2007.

[75] Noé, F., Krachtus, D., Smith, J. C., and Fischer, S. Transition networks for the comprehensive characterization of complex conformational change in proteins. *J. Chem. Theory Comput.* 2(3):840–857, 2006.

[76] Noé, F., Schütte, C., Vanden-Eijnden, E., Reich, L., and Weikl, T. Constructing the full ensemble of folding pathways from short off-equilibrium trajectories. *Proc. Natl. Acad. Sci. USA* 106(45):19011–19016, 2009.

[77] Olender, R., and Elber, R. Calculation of classical trajectories with a very large time step: formalism and numerical examples. *J. Chem. Phys.* 105(20):9299–9315, 1996.

[78] Ostermann, A., Waschipky, R., Parak, F. G., and Nienhaus, U. G. Ligand binding and conformational motions in myoglobin. *Nature* 404(6774):205–208, 2000.

[79] Pande, V. S., Beauchamp, K., and Bowman, G. R. Everything you wanted to know about Markov state models but were afraid to ask. *Methods* 52(1):99–105, 2010.

[80] Pavliotis, G. A., and Stuart, A. M. *Multiscale methods: averaging and homogenization.* Texts in Applied Mathematics, 53. Springer, New York, 2008.

[81] Prinz, J.-H. *Improved estimation methods for Markov models and projected Markov models.* Doctoral dissertation, Free University Berlin, 2012.

[82] Prinz, J.-H., Chodera, J. D., Pande, V. S., Swope, W. C., Smith, J. C., and Noé, F. Optimal use of data in parallel tempering simulations for the construction of discrete-state Markov models of biomolecular dynamics. *J. Chem. Phys.* 134(24):244108, 14 pp., 2011.

[83] Prinz, J.-H., Keller, B., and Noé, F. Probing molecular kinetics with Markov models: metastable states, transition pathways and spectroscopic observables. *Phys. Chem. Chem. Phys.* 13(38):16912–16927, 2011.

[84] Prinz, J.-H., Wu, H., Sarich, M., Keller, B., Senne, M., Held, M., Chodera, J. D., Schütte, C., and Noé, F. Markov models of molecular kinetics: generation and validation. *J. Chem. Phys.* 134(17):174105, 23 pp., 2011.

[85] Rao, F., and Caflisch, A. The protein folding network. *Journal of Molecular Biology* 342(1):299–306, 2004.

[86] Revuz, D. *Markov chains*. North-Holland Mathematical Library, vol. 11. North-Holland, Amsterdam-Oxford; American Elsevier, New York, 1975.

[87] Risken, H. *The Fokker-Planck equation*. Second edition. Springer, New York, 1996.

[88] Roberts, G. O., and Rosenthal, J. S. Geometric ergodicity and hybrid Markov chains. *Electron. Comm. Probab.* 2(2):13–25, 1997.

[89] Roeblitz, S. *Statistical error estimation and grid-free hierarchical refinement in conformation dynamics*. Doctoral dissertation, Free University Berlin, 2008.

[90] Sarich, M. *Projected transfer operators: discretization of Markov processes in high-dimensional state spaces*. Doctoral dissertation, Free University Berlin, 2011.

[91] Sarich, M., Noé, F., and Schütte, C. On the approximation quality of Markov state models. *Multiscale Model. Simul.* 8(4):1154–1177, 2010.

[92] Sarich, M., and Schütte, C. Approximating selected non-dominant timescales by Markov state models. *Comm. Math. Sci.* 10(3):1001–1013, 2012.

[93] Scharkoi, O., Fackeldey, K., Merkulow, I., Andrae, K., Weber, M., Nehls, I., Siegel, D. Conformational analysis of alternariol on the quantum level. *Journal of Molecular Modeling*, 19(6):2567–2572, 2013.

[94] Schultheis, V., Hirschberger, T., Carstens, H., and Tavan, P. Extracting Markov models of peptide conformational dynamics from simulation data. *J. Chem. Theory Comput.* 1(4):515–526, 2005.

[95] Schütte, C. Conformational dynamics: modelling, theory, algorithm, and application to biomolecules. Habilitation dissertation, Free University Berlin, 1998.

[96] Schütte, Ch., Fischer, A., Huisinga, W., and Deuflhard, P. A direct approach to conformational dynamics based on hybrid Monte Carlo. *J. Comput. Phys.* 151(1):146–168, 1999.

[97] Schütte, Ch., and Huisinga, W. On conformational dynamics induced by Langevin processes. *Equadiff 99*, vol. 2, 1247–1262. World Scientific, Singapore, 2000.

[98] _____. Biomolecular conformations can be identified as metastable sets of molecular dynamics. *Handbook of numerical analysis*, vol. X, 699–744. North-Holland, Amsterdam, 2003.

[99] Schütte, Ch., Huisinga, W., and Deuflhard, P. Transfer operator approach to conformational dynamics in biomolecular systems. *Ergodic theory, analysis, and efficient simulation of dynamical systems*, 191–223. Springer, Berlin, 2001.

[100] Schütte, C., Huisinga, W., and Meyn, S. Metastability of diffusion processes. *IUTAM Symposium on Nonlinear Stochastic Dynamics*, 71–81. Solid Mechanics and Its Applications, 110. Kluwer, Dordrecht, 2003.

[101] Schütte, C., Noé, F., Lu, J., Sarich, M., and Vanden-Eijnden, E. Markov state models based on milestoning. *J. Chem. Phys.* 134(20):204105, 15 pp., 2011.

[102] Schütte, C., Noe, F., Meerbach, E., Metzner, P., and Hartmann, C. Conformation dynamics. *ICIAM 07–6th International Congress on Industrial and Applied Mathematics*, 297–335. European Mathematical Society, Zürich, 2009.

[103] Schütte, C., Sarich, M., and Djurdjevac, N. On Markov state models for metastable processes. *Proceedings of the International Congress of Mathematicians, 2010 (ICM 2010)*, 3105–3131. doi:10.1142/9789814324359_0182

[104] Senne, M., Trendelkamp-Schroer, B., Mey, A., Schütte, C., and Noé, F. EMMA: A software package for Markov model building and analysis. *J. Chem. Theory Comput.* 8(7):2223–2238, 2012.

[105] Singhal, N., and Pande, V. S. Error analysis in Markovian state models for protein folding. *J. Chem. Phys.*, 123:204909, 13 pp., 2005.

[106] Singleton, G. Asymptotically exact estimates for metastable Markov semigroups. *Quart. J. Math. Oxford Ser. (2)* 35(139):321–329, 1984.

[107] Ueda, Y., Taketomi, H., and Gō, N. Studies on protein folding, unfolding and fluctuations by computer simulation. II. A. Three-dimensional lattice model of lysozyme. *Biopolymers*, 17(6):1531–1548, 1978.

[108] Wales, D. J. *Energy landscapes: applications to clusters, biomolecules and glasses*. Cambridge University Press, Cambridge, 2003.

[109] ———— . Energy landscapes and properties of biomolecules. *Phys. Biol.* 2(4):S86–S93, 2005.

[110] Walters, P. *An introduction to ergodic theory*. Springer, 2000.

[111] Weber, M. Improved Perron cluster analysis. Konrad-Zuse-Zentrum für Informationstechnik Berlin (ZIB) Report, 03-04, 2003.

[112] ———— . *A subspace approach to molecular Markov state models via a new infinitesimal generator*. Habilitation dissertation, Free University Berlin, 2012.

[113] Weber, M., Bujotzek, A., and Haag, R. Quantifying the rebinding effect in multivalent chemical ligand-receptor systems. *J. Chem. Phys.* 137(5):054111, 10 pp., 2012.

[114] Weber, M., and Fackeldey, K. Computing the minimal rebinding effect included in a given kinetics. *Multiscale Model. Simul.*, submitted.

[115] Werner, D. *Funktionalanalysis*. Second edition. Springer, Berlin, 1997.

[116] Wigner, E. The transition state method. *Trans. Faraday Soc.*, 34:29–41, 1938.

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Metastability and Markov State Models in Molecular Dynamics

CHRISTOF SCHÜTTE AND MARCO SARICH

Applications in modern biotechnology and molecular medicine often require simulation of biomolecular systems in atomic representation with immense length and timescales that are far beyond the capacity of computer power currently available. As a consequence, there is an increasing need for reduced models that describe the relevant dynamical properties while at the same time being less complex. In this book the authors exploit the existence of metastable sets for constructing such a reduced molecular dynamics model, the so-called Markov state model (MSM), with good approximation properties on the long timescales.

With its many examples and illustrations, this book is addressed to graduate students, mathematicians, and practical computational scientists wanting an overview of the mathematical background for the ever-increasing research activity on how to construct MSMs for very different molecular systems ranging from peptides to proteins, from RNA to DNA, and via molecular sensors to molecular aggregation. This book bridges the gap between mathematical research on molecular dynamics and its practical use for realistic molecular systems by providing readers with tools for performing in-depth analysis of simulation and data-analysis methods.

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