

B. Andresen

Maxwellian velocity distributions in slow time

Abstract:

We extend Maxwellian velocity distributions to long observational timescales in much the same way that short timescale statistical mechanics distributions are averaged to yield normal laboratory timescale thermodynamic distributions. This long timescale view has several novel effects: Fluctuating overall velocities (i.e. "wind") thermalizes into an additional component of temperature, while returning a Maxwellian velocity distribution. However, fluctuating temperature results in a new distribution with a Gaussian core but heavy polynomial tails. The power of the polynomial tail is either  $-3$  or  $-2$  depending on whether the precision of the temperature is allowed to extend to  $\pm\infty$  or is required to remain strictly positive. The distribution is also interesting in the way it remains almost exactly Gaussian up to a certain velocity after which it quickly breaks off to become polynomial. The distributions are carefully analyzed mathematically, and physical consequences are drawn.

Nicolae-Viorel Buchete

**Title:**

Mapping the kinetic folding network of helical and amyloid-forming peptides

**Abstract:**

The formation of secondary and tertiary structure elements in protein folding involves intrinsically complex processes, notoriously difficult to study in a systematic manner. We construct coarse master equations for conformational dynamics of biomolecules, such as helix formation, based on data from atomistic molecular dynamics (MD) simulations with explicit water molecules. By carefully controlling the effects of fast, non-Markovian transitions, on one hand, and the typically limited sampling of slow relaxation processes on the other hand, we probe the underlying network of folding-unfolding transitions between the various configuration states of a protein. This systematic analysis reveals the important conformational states and the associated folding pathways at multiple levels, from atomistic to coarse-grained representations. We validate our approach in several MD studies of shorter helix- and amyloid-forming peptides, and of larger systems such as Cyclosporin A, and the helix-turn-helix subdomain of a viral scaffolding protein.

## ENERGY LANDSCAPES: SAMPLING, ANALYSIS, AND COMPARISON

F. Cazals, Inria Sophia-Antipolis, Algorithms-Biology-Structure

Frederic.Cazals@inria.fr / <http://team.inria.fr/abs>

**Summary:** This talk will revisit three fundamental problems for energy landscapes, in light of recent developments in Computer Science.

First, a hybrid exploration algorithm combining basin hopping and rapidly exploring random trees will be sketched, yielding an enhanced exploration of complex landscapes [RDRC16].

Second, a generic algorithm to analyze a height field i.e. a collection of conformations each endowed with an elevation, will be presented [CDM<sup>+</sup>15]. The algorithm will be used to identify so-called persistent local minima, their attraction basins, and connexions across saddles. The interest of such features will be discussed [CMCW16].

Finally, an algorithm to compare two (sampled) energy landscapes will be outlined [CM14]. The strategy, based on optimal transportation theory, consists of computing a least cost mapping between the basins, compatible with the transition paths known on both landscapes.

Illustrations on various systems whose (frustrated) landscapes have been exhaustively studied in the literature will be presented.

The software implementing the algorithms discussed is made available to the community in the Structural bioinformatics Library at <http://sbl.inria.fr> > Applications > Conformational Analysis.

## References

- [CDM<sup>+</sup>15] F. Cazals, T. Dreyfus, D. Mazauric, A. Roth, and C.H. Robert. Conformational ensembles and sampled energy landscapes: Analysis and comparison. *Journal of Computational Chemistry*, 36(16):1213–1231, 2015.
- [CM14] F. Cazals and D. Mazauric. Mass transportation problems with connectivity constraints, with applications to energy landscape comparison. *Submitted*, 2014. Preprint: Inria tech report 8611.
- [CMCW16] J. Carr, D. Mazauric, F. Cazals, and D.J. Wales. Energy landscapes and persistent minima. *The Journal of Chemical Physics*, 144(5), 2016.
- [RDRC16] A. Roth, T. Dreyfus, C. Robert, and F. Cazals. Hybridizing rapidly growing random trees and basin hopping yields an improved exploration of energy landscapes. *Journal of Computational Chemistry*, NA(NA), 2016.

# Single base flipping mechanisms and kinetics in a DNA duplex: an energy landscape perspective

*Debayan Chakraborty, Kaushik Sen and David J. Wales*

*Department of Chemistry, University of Cambridge, Lensfield Road, CB2 1EW, United Kingdom*

## **ABSTRACT**

Base flipping is an elementary and localized deformation of a DNA fragment, initiated by the rupture of Watson-Crick interactions at a target base-pair, followed by extrusion of one of the bases to an extrahelical position. On extrusion, the genetic information otherwise encoded, becomes accessible to enzymes. In many important cellular processes such as DNA transcription and replication, base flipping constitutes a key step. In addition, there is growing evidence to suggest the importance of base flipping in DNA damage recognition by repair enzymes.

Despite a wealth of experimental and theoretical studies, the microscopic details of base flipping mechanisms and kinetics are not clearly understood. In this work, we employ the Discrete Path Sampling method in conjunction with an all-atom potential and an implicit solvent model to investigate the flipping mechanisms and kinetics of a B-DNA duplex, in terms of its underlying energy landscape. We find that base flipping can occur either via the major or minor grooves, in agreement with previous simulations. Furthermore, the flipping time scales are estimated to be in the millisecond regime, consistent with imino-proton exchange experiments. Our results also demonstrate that even for local deformations such as base-flipping, a perfect structural order parameter may not exist, and therefore highlight the pitfalls of using low-dimensional projections of the energy landscape.

# Molecular dynamics modeling of mechanical loss in amorphous tantala and titania-doped tantala

Hai-Ping Cheng and Jonathan Trinastic  
Department of Physics and Quantum Theory Project,  
University of Florida, Gainesville, Florida, 32611, USA

## Abstract

The mechanical loss ( $Q^{-1}$ ) intrinsic to amorphous oxides that is determined by the energy landscape of the materials. It is the limiting factor for sensitive, high-precision gravitational wave detectors and optical devices. Recent experimental work suggests that doping amorphous tantala with titania reduces  $Q^{-1}$ , however the physical processes underlying this reduction are unknown. Here we calculate  $Q^{-1}$  for pure and titania-doped tantala using numerical methods combined with molecular dynamics simulations that have atomic levels of resolution. Our results match experimental trends that titania doping decreases the magnitude of the low-temperature loss peak characteristic of these materials, with 62% titanium cation doping minimizing  $Q^{-1}$  at low temperature. We provide a microscopic explanation for this reduced loss by examining how doping affects the potential energy landscape, strain coupling constant, relaxation time, and other properties of the amorphous materials within the framework of the double well potential model. We identify the important parameters contributing to  $Q^{-1}$  that are most affected by doping and provide guidance for how to screen for optimal doping combinations to minimize loss in other materials. If time allows, I will also address an interesting problem in silica, a most studied system perhaps.

# How Does Coordination Affect the Low Lying Minima in Inorganic Clusters

Andi Cuko<sup>a</sup>, Monica Calatayud<sup>b</sup>, Stefan T. Bromley<sup>a,c</sup>

<sup>a</sup>The Institute of Theoretical and Computational Chemistry (IQTC)  
& Department of Materials Science & Physical Chemistry, Universitat de Barcelona, Spain

<sup>b</sup>Laboratoire de Chimie Théorique, Université Pierre et Marie Curie, France

<sup>c</sup>Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Spain

The coordination number,  $N_{\text{coord}}(\text{A})$ , of an atom, A, in a crystal is defined as the number of its nearest neighbour atoms. This local order parameter does not uniquely define a crystal type, or polymorph, but its average value,  $\langle N_{\text{coord}} \rangle$  often acts as a guide to important polymorphic changes (e.g. 6- coordinated rocksalt  $\leftrightarrow$  4 coordinated wurtzite). In turn, changes in  $\langle N_{\text{coord}} \rangle$  often signal deeper more physico-chemical changes (e.g. band gaps, hardness). Although the important role of  $\langle N_{\text{coord}} \rangle$  in inorganic crystallography is undoubted, for non-periodic and potentially non-symmetric finite clusters its utility is less clear.

We use an empirical potential to describe clusters of type  $(\text{AB}_2)_n$  where A and B are two atoms which tend to bind together to yield  $N_{\text{coord}}(\text{A}) = 4$  and  $N_{\text{coord}}(\text{B}) = 2$ . These systems have a preference for 4-coordinated networks with A atoms at the vertices and B atoms as inter-vertex links and have a widespread important representation in the world of materials (e.g. water ice, silica). Through a transformation of the parameters determining the potential we can vary the coordination propensity to be higher or lower (e.g. 6-coordinated A, 3-coordinated B) (see also [1]). For each choice of potential parameters and for a range of n we perform a global optimization search of the energy landscape using Monte Carlo Basin Hopping [2] and refine the 25 lowest energy minima found using density functional theory (DFT). We choose specific A and B atoms types to statistically sample our results for a range of clusters of real materials such as titanosilicates (A=Si, Ti and B=O) which are widely used for a wide range of industrial applications [3]. In this way we track how  $\langle N_{\text{coord}} \rangle$ ,  $\langle N_{\text{coord}}(\text{A}) \rangle$  and  $\langle N_{\text{coord}}(\text{B}) \rangle$  affect the structure and stability of the resulting low lying minima of  $(\text{AB}_2)_n$  clusters.

The results demonstrate a way in which to generally classify the structural-energetic tendencies of inorganic clusters in a manner analogous to the crystallographic classification of infinite bulk periodic crystals.

[1] B. Hartke, “Morphing Lennard-Jones clusters to TIP4P water clusters: Why do water clusters look like they do?”, *Chem.Phys.* 346 (2008) 286.

[2] D. J. Wales, ” J. P. K. Doye, “Global Optimization by Basin-Hopping and the Lowest Energy Structures of Lennard-Jones Clusters Containing up to 110 Atoms”, *J. Phys. Chem. A*, 101 (1997) 5111.

[3] X. Gao, I. E. Wachs, “Titania-silica as catalysts: molecular structural characteristics and physico-chemical properties”, *Catal Today* 51 (1999) 233

# Exploring the energy landscape of highly-flexible biomolecules with a forest of random trees

A. Estaña<sup>1,2</sup>, K. Molloy<sup>1</sup>, M. Vaisset<sup>1</sup>, T. Siméon<sup>1</sup>, P. Bernadó<sup>2</sup>, J. Cortés<sup>1</sup>

<sup>1</sup> LAAS-CNRS, 7 av. du Colonel-Roche, 31400 Toulouse, France

<sup>2</sup> Centre de Biochimie Structurale, 29 rue de Navacelles, 34090 Montpellier, France

In a previous edition of this workshop, we presented an algorithm, called T-RRT, to explore the energy landscape of small peptides [1]. T-RRT combines ideas of robot motion planning algorithms and methods in statistical physics. It explores the conformational space of a molecular system by incrementally growing a search tree that is intrinsically biased towards unexplored regions. A stochastic transition tests favours the exploration of low-energy areas, and it involves a self-additive parameter that helps the exploration to overcome local minima traps. Our first works demonstrated the ability of the method to efficiently find diverse conformational transition pathways for small peptides. Subsequent improvements of the algorithm together with the implementation of a multiple-tree variant allowed us to tackle medium-size peptides [2]. In order to study larger systems, such as intrinsically disordered proteins, we have developed an hybrid parallel implementation of the Multi-T-RRT algorithm [3]. It combines shared-memory and distributed-memory programming paradigms with the aim of better exploiting the architecture of current computer clusters. In this talk, we will remind the principle of the (Multi-)T-RRT algorithm and we will provide explanations about its parallel implementation, showing near-linear speedup.

## References

- [1] L. Jaillet, F.J. Corcho, J.J. Pérez, J. Cortés (2011) Randomized tree construction algorithm to explore energy landscapes. *Journal of Computational Chemistry*, 32(16):3464-3474.
- [2] D. Devaurs, K. Molloy, M. Vaisset, A. Shehu, T. Siméon, J. Cortés (2015) Characterizing energy landscapes of peptides using a combination of stochastic algorithms. *IEEE Transactions on NanoBioscience*, 14(5):545-552.
- [3] A. Estaña, M. Vaisset, P. Bernadó, J. Cortés (2016) Hybrid parallelization of a multi-tree pathfinding algorithm. *Submitted*.

## Towards Automated Design Of General Catalysts

**Mark Dittner<sup>a</sup> and Bernd Hartke<sup>b</sup>**

*Institute for Physical Chemistry, Christian-Albrechts-University Kiel, Max-Eyth-Strasse 2,  
24118 Kiel, Germany,*

*Email: <sup>a</sup>dittner@pctc.uni-kiel.de, <sup>b</sup>hartke@pctc.uni-kiel.de*

*Molecular design* usually implies an *inverse* strategy, starting from desired properties and inferring molecular systems that realize them. Inverse problems, however, are hard to solve in practice.<sup>[1a]</sup> One feasible approach is to do a forward sampling, starting from many well chosen and chemically meaningful systems, calculating the property in question *directly*, and then selecting the system coming closest to the desired property value. Naive realizations of this forward strategy fail because *chemical compound space*<sup>[2]</sup> is astronomically huge even for small compounds, making complete enumerations and deterministic global optimization impossible. Thus, even in the forward direction, additional ingredients are necessary: (1) unbiased meta-heuristical optimization algorithms that avoid complete enumeration, and (2) additional abstractions in chemical representation, to further shrink and simplify the search landscape. For item (1), we have chosen Evolutionary Algorithms and our general, highly scalable program package OGOLEM,<sup>[3]</sup> which can be coupled to a broad array of energy/gradient backends, ranging from ab-initio wavefunction methods and DFT to semi-empirical methods and to reactive force fields.

In this project, the optimization target is catalysis, in a very general way: For any given reaction, an arrangement of an additional molecular framework around this reaction center is sought, such that the energy barrier is lowered as much as possible, without compromising reactant affinity and product release. Following earlier work on catalytic design which employed charge-based embedding,<sup>[4]</sup> model interaction groups<sup>[5]</sup> and explicit interaction centers,<sup>[1b]</sup> in a first stage for item (2) above, the optimal catalyst is designed as *General Optimal Catalytic Field* (GOCF), an abstract distribution of partial charges, van-der-Waals centers, hydrogen-bond donors/acceptors, etc., of variable strengths and spatial distributions. These additional ingredients and abstractions have been implemented in OGOLEM. As specific distinction to other work, this allows us to aim at an automation of this abstract catalyst design in a fully general and global sense. In a second stage, optimized GOCFs will then be translated into actual molecular realizations. For the first stage of this process, preliminary results of the optimization approach and GOCF-design are shown, providing proof-of-principle demonstrations and first tests for realistic systems.

[1a,b] T. Weymuth, M. Reiher, *Int. J. Quantum Chem.* **2014**, *114*, 823–837, 838–850.

[2] O. A. von Lilienfeld, *Int. J. Quantum Chem.* **2013**, *113*, 1676–1689.

[3] J. M. Dieterich, B. Hartke, *Mol. Phys.* **2010**, *108*, 279–291.

[4] B. Szeftczyk, A. J. Mulholland, K. E. Ranaghan, W. A. Sokalski, *J. Am. Chem. Soc.* **2004**, *126*, 16148–16159.

[5] X. Zhang, J. DeChancie, H. Gunaydin, A. B. Chowdry, F. R. Clemente, Smith, T. M. Handel, K. N. Houk, *J. Org. Chem.* **2008**, *73*, 889–899.

# Cooperativity in clusters of anisotropic particles

Szilard Fejer<sup>a</sup>, Dwaipayan Chakrabarti<sup>b</sup> and David J. Wales<sup>c</sup>

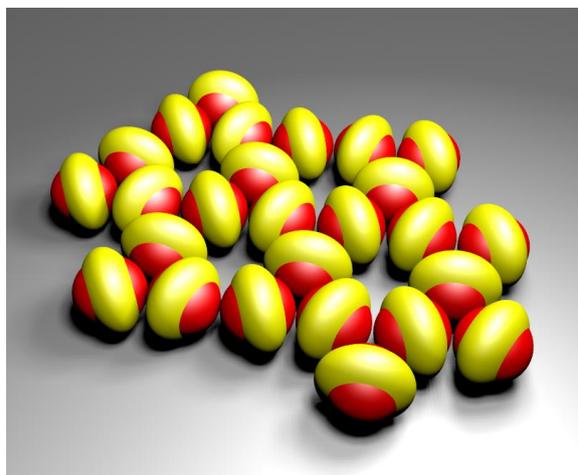
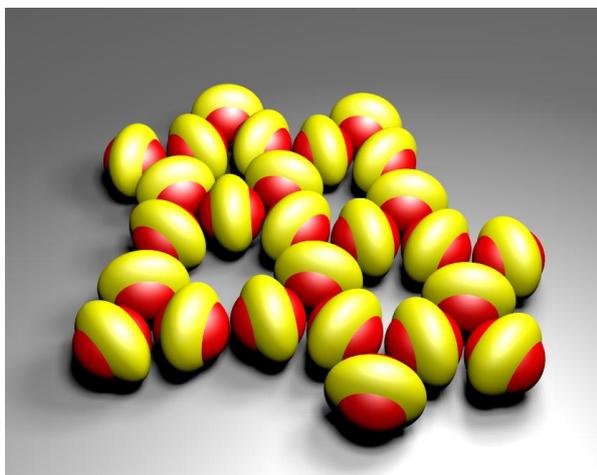
*szilard.fejer@cantab.net*

<sup>a</sup> Provitam Foundation, Cluj-Napoca, Romania

<sup>b</sup> School of Chemistry, University of Birmingham, Edgbaston, Birmingham B15 2TT, United Kingdom

<sup>c</sup> University Chemical Laboratory, Lens\_eld Road, Cambridge CB2 1EW, United Kingdom

The shape and interaction anisotropy of building blocks defines not only the way such particles aggregate, but their dynamical properties as well. The building block anisotropies are therefore of particular importance in the functioning of biological systems and the design of mesoscale structures with well-defined properties. Low-energy aggregates of simple anisotropic building blocks usually interconvert *via* highly cooperative motions that are specific to the system itself. I will present different mechanisms specific to complex structures such as sliding rearrangements in open tubes, hinge-moves in Bernal spirals, string bends in clusters of triblock Janus particles etc. Among these, some can be seen experimentally, but in nanoscale structures such mechanisms are yet to be confirmed. Also, external forces such as gravity can hugely influence the energy landscapes of larger particles, as it will be demonstrated on a model of a self-assembling Kagome lattice. All model systems were created using a simple ellipsoid-based potential, and can be expanded to recreate more complex behaviour, such as hierarchical self-assembly.



## **The potential energy landscape of glass-forming systems: impact of strong external perturbations**

A. Heuer, C.F. Schroer, M. Blank-Burian

Institute for Physical Chemistry, WWU Muenster, Germany

Glass-forming systems display many fascinating properties such as the dramatic increase of relaxation time upon cooling or the presence of dynamic heterogeneities. The potential energy landscape approach (PEL) and in particular the definition of metabasins have proven to be very fruitful to rationalize many of these features. In particular it has turned out that the thermodynamics and the dynamics are strongly interrelated due to the trap-like nature of the PEL.

In this talk I present recent progress in the analysis of the impact of strong external perturbations, going significantly beyond the linear response. In particular microrheological and shear experiments are considered.

In the microrheological case it turns out that the trap-like nature of the PEL and, thus, the strong relation between thermodynamics and dynamics remain valid even far away in the nonlinear regime. This gives rise to the definition of an effective temperature which can be applied in a very large ranges of temperatures and external forces and holds for the description of the thermodynamic as well as the dynamics properties.

For shear experiments a new definition of metabasins of the PEL is introduced which helps to connect the PEL for different degrees of deformation. In this way it is possible, e.g., to map the outcome of the Bauschinger experiment in glasses on the properties of the PEL, i.e. the presence of memory effects under shear reversal is highly correlated to the question whether transitions between these newly defined metabasin have occurred.

In summary, also for strong external perturbations the PEL concept is still very versatile.

# Energy Landscapes of Nano-hydrated Ions and their Relevance to the Hofmeister Series

Roy L. Johnston<sup>a</sup>, John C. Hey<sup>a</sup>, Lewis C. Smeeton<sup>a</sup>, Emily Doyle<sup>a</sup>, Mark T. Oakley<sup>a</sup> and Deepak Sharma<sup>b</sup>

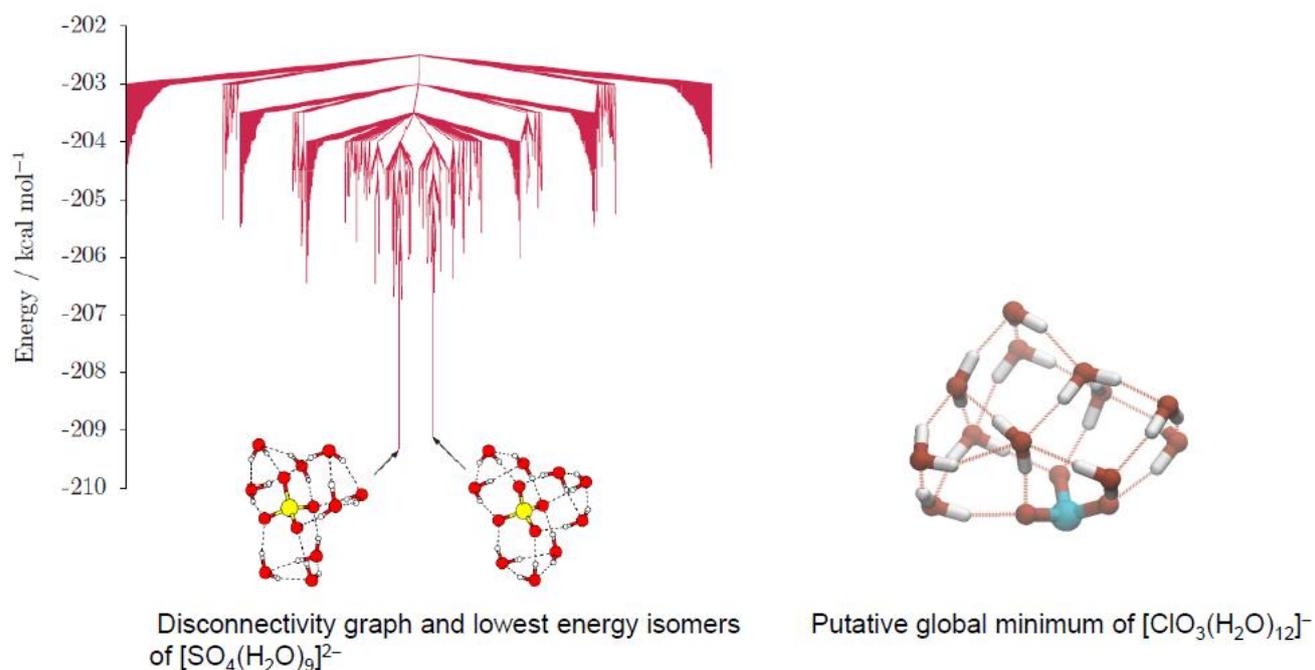
<sup>a</sup> School of Chemistry, University of Birmingham, Edgbaston, Birmingham B15 2TT, United Kingdom

<sup>b</sup> Department of Chemistry, Indian Institute of Technology Bombay, Powai, Mumbai 400 076, India

[r.l.johnston@bham.ac.uk](mailto:r.l.johnston@bham.ac.uk)

The Hofmeister series is an ordering given to solutions of ions based on properties such as their ability to desolvate or “salt-out” proteins or their specific ion effects.<sup>1,2</sup> This effect was first reported in 1888 by Lewith and Hofmeister based on their work on protein solubilities.<sup>3</sup> The Hofmeister series is separated into kosmotropes (order-making) and chaotropes (disorder-making). Ions at opposite ends of the Hofmeister series have different effects on species in solution.<sup>3</sup> Kosmotropes generally increase the solubility of proteins whilst chaotropes decrease their solubility.<sup>1</sup> Understanding the Hofmeister series is important because its effects can be seen in many different systems including industrial processes and atmospheric chemistry as well as in biology.

I will present recent results<sup>4,5</sup> of global optimisation (using basin hopping) and energy-landscape mapping of nano-hydrates of several ions from different regions of the Hofmeister series (with up to around 50 water molecules). The nano-hydrates are modelled using empirical potentials and Density Functional calculations. Systems will include sulfate (a highly kosmotropic ion), perchlorate (a highly chaotropic ion), chlorate, thiocyanate and hexacyano-iron(II) and –iron(III) complex ions. I will talk about the effects of ionic charge and symmetry and will make comparisons with experimental studies of finite ion-water clusters, where available.



- (1) Xie, W. J.; Gao, Y. Q. A Simple Theory for the Hofmeister Series. *J. Phys. Chem. Lett.* **2013**, 4 (24), 4247–4252.
- (2) O'Brien, J. T.; Prell, J. S.; Bush, M. F.; Williams, E. R. Sulfate Ion Patterns Water at Long Distance. *J. Am. Chem. Soc.* **2010**, 132 (24), 8248–8249.
- (3) Cacace, M. G.; Landau, E. M.; Ramsden, J. J. The Hofmeister Series: Salt and Solvent Effects on Interfacial Phenomena. *Q. Rev. Biophys.* **1997**, 30, 241–277.
- (4) Smeeton, L. C.; Farrell, J. D.; Oakley, M. T.; Wales, D. J.; Johnston, R. L. Structures and Energy Landscapes of Hydrated Sulfate Clusters. *J. Chem. Theory Comput.* **2015**, 11 (5), 2377–2384.
- (5) Hey, J. C., Smeeton, L. C.; Oakley, M. T.; Johnston, R. L. An Empirical Study into the Conformations and Energy Landscapes of  $\text{ClO}_4^-(\text{H}_2\text{O})_N$  for  $3 \leq N \leq 50$ . (Submitted.)

# A kinetic disconnectivity graph to decode timescale hierarchy buried in reaction networks

Tamiki Komatsuzaki

Research Institute for Electronic Science, Hokkaido University,  
Kita 20 Nishi 10, Kita-Ku, Sapporo 001-0020 Japan  
E-mail: tamiki@es.hokudai.ac.jp

**Keywords:** Disconnectivity graph, Multiple timescales, Reaction network, single molecules biology

Energy landscapes are one of the most pervasive concepts in understanding dynamics and functions in complex chemical systems such as proteins. One of the intriguing subjects in energy landscape is how to infer energy landscapes and/or reaction networks from experiments such as single molecule experiments for complex chemical systems [1-3]. Another is how to define states of the reactants and products and the dividing surfaces (transition states) under the existence of multiple basins and multiple intermingled pathways in networks [4]. In my talk I present our time series analysis [1-3] and then present the so-called kinetic disconnectivity graph, that is, a new energy landscape reconstruction scheme [5], from the underlying (conformation) state network that decodes the information of hierarchical structure of multiple timescales with a demonstration of Claisen rearrangement reaction.

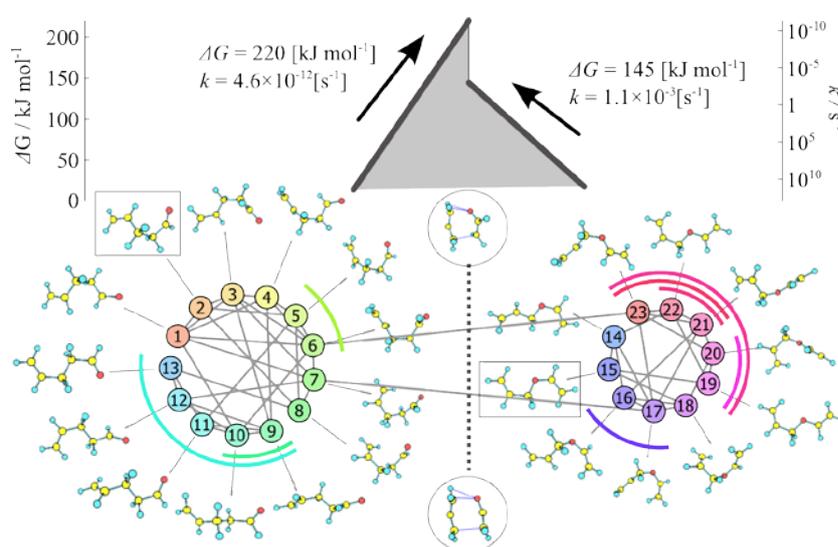


Figure 1: Reaction network and our kinetic disconnectivity graph of Claisen rearrangement.

- [1] J.N. Taylor, C.-B. Li, D.R. Cooper, C.F. Landes, and T. Komatsuzaki, *Scientific Reports* **5**, 9174-1-9174-9 (2015)
- [2] A. Baba, T. Komatsuzaki, *PNAS* **104**, 19297-19302 (2007)
- [3] A. Baba, T. Komatsuzaki, *Phys. Chem. Chem. Phys.* **13**, 1395-1406 (2011)
- [4] S.V. Krivov and M. Karplus *PNAS*, **101**, 14766-14770 (2004)
- [5] Y. Nagahata, S. Maeda, H. Teramoto, T. Horiyama, T. Taketsugu, T. Komatsuzaki *JPCB* in press.

# GPU-Accelerated Exploration of Biomolecular Energy Landscapes

Rosemary G. Mantell\* and David J. Wales

*Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB2  
1EW, United Kingdom*

E-mail: rgm38@cam.ac.uk

## Abstract

We present GPU-accelerated versions of two methods for characterising energy landscapes: basin-hopping global optimization<sup>1,2</sup> and a transition state search algorithm combining the doubly-nudged elastic band method<sup>3</sup> and hybrid eigenvector-following.<sup>4</sup> Both methods are interfaced with the AMBER 12 potential for GPU<sup>5</sup> and support a general formulation for treating rigid bodies.<sup>6</sup> Significant speed ups are obtained, opening up the study of biomolecules that were previously inaccessible.

## References

- (1) Li, Z.; Scheraga, H. A. *Proc. Natl. Acad. Sci.* **1987**, *84*, 6611–6615.
- (2) Wales, D. J.; Doye, J. P. K. *J. Phys. Chem. A* **1997**, *101*, 5111–5116.
- (3) Trygubenko, S. A.; Wales, D. J. *J. Chem. Phys.* **2004**, *120*, 2082–2094.
- (4) Kumeda, Y.; Wales, D. J.; Munro, L. J. *Chem. Phys. Lett.* **2001**, *341*, 185 – 194.
- (5) Götz, A. W.; Williamson, M. J.; Xu, D.; Poole, D.; Le Grand, S.; Walker, R. C. *J. Chem. Theory Comput.* **2012**, *8*, 1542–1555.
- (6) Kusumaatmaja, H.; Whittleston, C. S.; Wales, D. J. *J. Chem. Theory Comput.* **2012**, *8*, 5159–5165.

The coarse-grained model HiRE-RNA can predict complex structures for large RNA molecules, given only their sequence. I will show how this model has been coupled to SAXS experimental data, mainly aiming at a faster convergence to the conformation corresponding to the data. SAXS intensity profiles for coarse-grained systems are constructed integrating the atomistic form factors, and they are shown to be characterized by a mean correction, with periodicity related to the coarse-grain scale. On the one hand, the SAXS bias is introduced at the level of the energy, through a scoring function comparing the coarse-grained profile to the target profile (experimental or theoretical). On the other hand, a force is derived from the SAXS energy term, and is applied to the molecule to drive it towards the target structure. I will present the results for molecules of different sizes (including applications to bistable molecules, for which conformations of similar energies but different shapes are present, making them particularly interesting as benchmarks). At a preliminary level, comparison between SAXS-biased and unbiased simulations shows that the bias toward a specific conformation favors its formation. Moreover, I will illustrate a tool developed in order to analyse coarse-grained structures and molecular dynamics simulations trajectories considering their 2D structure and topology. This tool allows for the systematic network graph representation of 2D structures clusters, making the 2D and topological properties of the structures present in a molecular dynamic simulation or in any set (e.g. obtained from path sampling methods) easy to read.

# Network Properties of Atomic Clusters

John W. R. Morgan<sup>a</sup>, Dhagash Mehta<sup>b</sup> and David J. Wales<sup>a</sup>

*jwrm2@cam.ac.uk*

<sup>a</sup>University Chemical Laboratories, University of Cambridge, Cambridge CB1 2EW

<sup>b</sup>Department of Applied and Computational Mathematics and Statistics, University of Notre Dame,  
Notre Dame, IN 46556, USA

**Abstract:** A database of minima and transition states is a network in which the minima represent nodes and transition states correspond to edges between the pairs of minima they directly connect. We have constructed such networks for small atomic clusters bound by the Morse potential with hundreds to thousands of minima at a variety of physically relevant ranges, in both two and three dimensions. The properties of the networks are analysed with particular reference to two features: whether the networks are small-world, that is a network in which most nodes are not directly connected, but the shortest path between pairs involves only a small number of edges; and whether the networks are scale-free, having a degree distribution that follows a power-law. The networks are shown to be small-world and to be consistent with having a power-law degree distribution. However, statistical tests show there are other distributions which also fit the data.

**Abstract:**

Polymorphism, the ability of a molecule to crystallize in more than one structure, is vitally important to understand and predict as various polymorphs exhibit different physicochemical properties. To this end, the tools of computational Crystal Structure Prediction (CSP) have proved to be extremely useful. It can become a valuable ally and a cheaper alternative for expensive experimental procedures employed to screen polymorphs of pharmaceutical drugs. Two new polymorphs of the anti-fungal drug, Griseofulvin, were recently reported and their crystal structure remain unsolved. Here, we describe the use of global optimisation methods to solve the crystal structure of these novel polymorphs through a CSP approach. A comparison is made with the single-crystal X-Ray diffraction patterns reported in literature.

# Energy Landscape Explored by Generalized-Ensemble Algorithms

Yuko Okamoto

*Department of Physics, Nagoya University, Nagoya, Aichi 464-8602, Japan*  
*E-mail: okamoto@phys.nagoya-u.ac.jp*

Conventional Monte Carlo and molecular dynamics simulations are greatly hampered by the multiple-minima problem, where the simulations tend to get trapped in some of astronomically large number of local-minimum energy states. In order to overcome this difficulty, we have been advocating the uses of generalized-ensemble algorithms which are based on non-Boltzmann weight factors (for reviews, see, e.g., Refs. [1-8] and for our recent algorithm developments and their applications, see, e.g., Refs. [9-17]). With these algorithms we can explore a wide range of the conformational space. The advantage of generalized-ensemble algorithms such as multicanonical algorithm and replica-exchange method (or, parallel tempering) lies in the fact that from only one simulation run, one can obtain various thermodynamic quantities as functions of temperature and other physical parameters by the reweighting techniques. In this talk, I will present the latest results of various applications of generalized-ensemble simulations to energy landscape analyses.

## References

- [1] U. H. E. Hansmann and Y. Okamoto, *Current Opinion in Structural Biology* **9**, 177-183 (1999).
- [2] A. Mitsutake, Y. Sugita, and Y. Okamoto, *Biopolymers* **60**, 96-123 (2001).
- [3] Y. Okamoto, *Journal of Molecular Graphics & Modelling* **22**, 425-439 (2004).
- [4] Y. Sugita, A. Mitsutake, and Y. Okamoto, in *Lecture Notes in Physics, Rugged Free Energy Landscapes: Common Computational Approaches in Spin Glasses, Structural Glasses and Biological Macromolecules*, W. Janke (ed.), (Springer-Verlag, Berlin, 2008) pp. 369-407.
- [5] Y. Okamoto, In *Water and Biomolecules: Physical Chemistry of Life Phenomena*, K. Kuwajima, Y. Goto, F. Hirata, M. Kataoka, and M. Terazima (eds.), (Springer-Verlag, Berlin, 2009) pp. 61-95.
- [6] H. Okumura, S.G. Itoh, and Y. Okamoto, in *Practical Aspects of Computational Chemistry II*, J. Leszczynski and M.K. Shukla (eds.) (Springer, Dordrecht, 2012) pp. 69-101.
- [7] A. Mitsutake, Y. Mori, and Y. Okamoto, in *Biomolecular Simulations: Methods and Protocols*, L. Monticelli and E. Salonen (eds.) (Humana Press, New York, 2012) pp. 153-195.
- [8] H. Kokubo, T. Tanaka, and Y. Okamoto, in *Advances in Protein Chem. and Struct. Biology*, Vol. 92, T. Karabencheva-Christova (ed.) (Academic Press, Burlington, 2013) pp. 63-91.
- [9] A. Mitsutake and Y. Okamoto, *Physical Review E* **79**, 047701 (4 pages) (2009).
- [10] A. Mitsutake and Y. Okamoto, *Journal of Chemical Physics* **130**, 214105 (14 pages) (2009).
- [11] S.G. Itoh, H. Okumura, and Y. Okamoto, *Journal of Chemical Physics* **132**, 134105 (8 pages) (2010).
- [12] Y. Mori and Y. Okamoto, *Journal of Physical Society of Japan* (2010) **79**, 074003 (5 pages) (2010).
- [13] T. Nagai and Y. Okamoto, *Physical Review E* **86**, 056705 (12 pages) (2012).
- [14] T. Nagai, Y. Okamoto, and W. Janke, *Journal of Statistical Mechanics: Theory and Experiment* **2013**, P02039 (21 pages) (2013).
- [15] T. Yoda, Y. Sugita, and Y. Okamoto, *Proteins* **82**, 933-943 (2014).
- [16] Y. Sakae, T. Hiroyasu, M. Miki, K. Ishii, and Y. Okamoto, *Journal of Physics: Conference Series* **487**, 012003 (5 pages) (2014).
- [17] Y. Okamoto, H. Kokubo, and T. Tanaka, *Journal of Chemical Theory and Computation* **10**, 3563-3569 (2014).

## Predicting and exploring complex nucleic acids architectures through a coarse-grained model

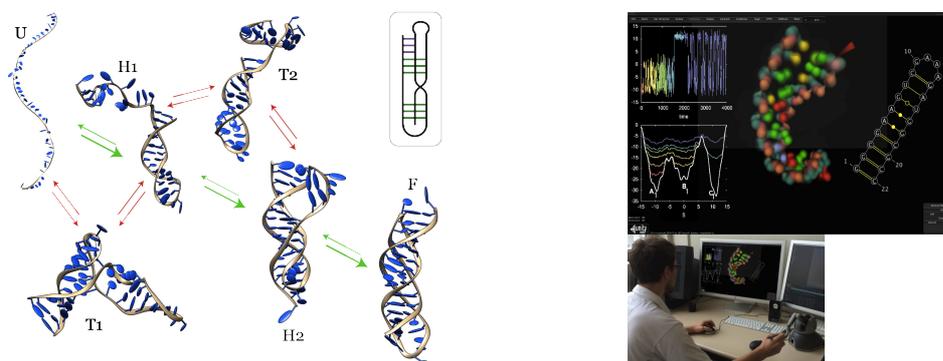
T. Cragolini, S. Doutréline, M. Baaden, P. Derreumaux, L. Mazzanti, S. Pasquali  
Laboratoire de Biochimie Théorique – IBPC, UPR CNRS 9080 et Université Paris Diderot  
Paris, France 75005

Ph: +33-1-58 41 51 69    Fx: +33-1-58 41 51 74    Email: samuela.pasquali@ibpc.fr

Simulation of large biomolecules and biomolecular complexes is still an open challenge especially when interested large scale and long time phenomena such as the folding of proteins and RNA. Atomistic simulations are limited to small systems and to short time scales even when adopting the most advanced computer technologies and sampling strategies.

We have developed two coarse-grained models, OPEP for proteins and HiRE-RNA for nucleic acids, that have proven effective to study folding, aggregation and assembly of peptides, RNA and DNA. I will briefly present the models explaining the key features of their force-fields, discussing in particular the new, ongoing, developments on integrating ions and pH effects as well as coupling proteins and nucleic acids.

When available, integrating experimental data into the simulation protocol greatly reduces the conformational space to be explored and leads to faster convergence to data-compatible structures. I will discuss how we can integrate various sources of experimental data into our models and I will conclude with the presentation of our most recent work on an interactive simulations software explicitly designed for the use by experimentalists.



### References:

1. S. Pasquali, P. Derreumaux, HiRE-RNA: a high resolution coarse-grained energy model for RNA, *J Phys Chem B.*, 114, 11957-11966 (2010)
2. F. Sterpone, ..., S. Pasquali, P. Derreumaux, The OPEP coarse-grained protein model: from single molecules, amyloid formation, role of macromolecular crowding and hydrodynamics to RNA/DNA complexes, *Chem Soc Reviews*, 43, 4871-4893 (2014)
3. T. Cragolini, Y. Laurin, P. Derreumaux, S. Pasquali, Coarse-Grained HiRE-RNA Model for ab Initio RNA Folding beyond Simple Molecules, Including Noncanonical and Multiple Base Pairings, *J. Chem. Theory Comput.*, 2015, 11 (7), pp 3510–3522
4. S. Doutréline, C. Gageat, T. Cragolini, A. Taly, S. Pasquali, P. Dereumaux, M. Baaden, UnityMol: interactive and ludic visual manipulation of coarse-grained RNA and other biomolecules, *Virtual and Augmented Reality for Molecular Science (VARMS@IEEEVR)*, 2015 IEEE 1st International Workshop on

# **Empirical Potential Ternary Cluster Structure Prediction**

Alvaro Posada-Amarillas

Departamento de Investigación en Física, Universidad de Sonora

## **Abstract**

The importance of monoatomic and binary clusters has been broadly demonstrated in applications mainly related to catalysis, being currently an intense research topic. In this work, an extension to predict ternary cluster structures is presented. A thorough exploration of the potential energy surface of trimetallic clusters is performed using the basin-hopping method, coupled to the semi-empirical Gupta many-body potential for modeling interatomic interactions. Geometric structures of noble-metal ternary clusters are analyzed, focusing on all composition of hexanuclear clusters and the most representative structures of 38-atom ternary clusters.

Nonequilibrium thermodynamic theory has much to offer in explaining the observations of biological evolution. Formalizing evolution in terms of thermodynamic parameters reveals that the generation of natural organization and complexity is an emergent property of exergy flux and entropy production in dissipative systems. As such, evolutionary systems have a tendency to maximize power in their early stages while tending to minimize dissipation and thus, maximize yield efficiency over longer time scales. Understanding the interplay between thermodynamics and evolution would provide key insights into prebiotic evolution, mutational and recombinational frequency bias, astrobiology, and trophic dynamics. We employ a stochastic mathematical model of biological evolution, the Tangled Nature Model (TNM), to explore the dynamic nature of the environment and the emergence of structure that is so crucial to biology. More specifically, we utilize Landsberg's (1984) decoupling of disorder and entropy to explore the emergent properties of entropy production in biological systems using the TNM. We find that the punctuated equilibria successively generated by the model's dynamics have increasing entropies, and that this leads to emergent order, organization, and complexity. Furthermore, we present experimental and field based data supporting the hypothesis that nonequilibrium thermodynamics is an underlying mechanism in the succession and evolution of biological systems.

# Heme incorporation into artificial four-helix bundles

Charles H. Robert

CNRS Laboratoire de Biochimie Thorique, Institut de Biologie Physico-Chimique (IBPC), 75005 Paris

Helix bundle architectures have been exploited in a variety of natural proteins, including DNA binding motifs, cytochromes, and many others. Man-made helical bundles have also been engineered from what can be called first principles, starting with the work of DeGrado [Regan and DeGrado, 1988]. The “maquette” proteins conceived by Dutton et al. [Farid et al., 2013] explore cofactor binding to designed four-helix bundle architectures, leading to progress towards artificial oxygen transporters and photosynthetic proteins, among other targets. I will present preliminary work towards the analysis of conformational heterogeneity in one of these systems and the influence of heme binding leading to a structured *holo*-state.

## References

- [Regan and DeGrado, 1988] Regan, L. and DeGrado, W. F. (1988) *Science* **241**(4868), 976–978
- [Farid et al., 2013] Farid, T. A., Kodali, G., Solomon, L. A., Lichtenstein, B. R., Sheehan, M. M., Fry, B. A., Bialas, C., Ennist, N. M., Siedlecki, J. A., Zhao, Z., Stetz, M. A., Valentine, K. G., Anderson, J. L. R., Wand, A. J., Discher, B. M., Moser, C. C., and Dutton, P. L. (2013) *Nat Chem Biol* **9**(12), 826–833

# Kinetics of Molecular Diffusion and Self-Assembly: Glycine on Cu{110}

**Judith B. Rommel**

*Department of Chemistry, University of Cambridge,  
Lensfield Road, Cambridge, CB2 1EW,  
United Kingdom  
Email: jbr36@cam.ac.uk*

Nano-fabrication plays an important role in various industries including microelectronics and health care, e.g. biosensors to measure blood sugar levels. The functionality of biosensors reacting with different chemical structures depends on its electrode coating. Self-assembled monolayers (SAM) of organic molecules provide efficient coatings. Understanding the fundamentals of spontaneous SAM growth is therefore important to optimize the assembly for increased efficiency. Glycine (GLY) adsorbed on Cu{110} provides a good model with a rich phenomenological space to explore and to understand the self-assembly of more complex amino acids, since GLY constitutes the same chiral footprint as alanine and proline on the same surface.

We investigated the energy landscape of adsorbed GLY conformers including energy barriers (DFT), reaction pathways, and transition rates. Based on these results we used a newly developed stochastic discrete event algorithm ( $\tau$ -leaping) to study (a) the dynamics exhibited by GLY when diffusing on the surface and (b) the chemical kinetics of how GLY molecules form clusters, networks, and islands.

We found substantial energy barriers for the diffusion of GLY molecules parallel or across the Cu{110} steps. Moreover, heterochiral islands (see Fig. 1) are significantly more stable than homochiral islands which means that using a heterochiral mixture will enhance the formation of strong and long-lasting SAMs.

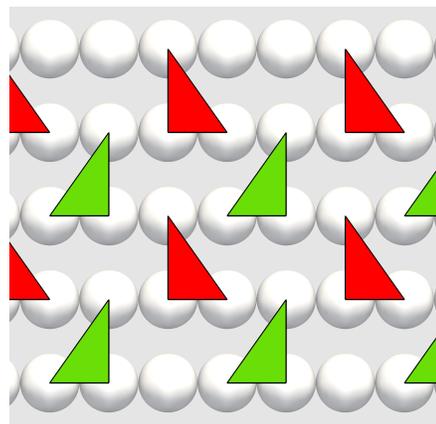


Figure 1: Glycine bound by hydrogen bonds in (3×2) heterochiral domains.

# Asymmetric activation of RAF Kinase Dimers

Edina Rosta

Department of Chemistry, King's College London

RAF kinases are key participants in the MAPK/ERK pathway, fundamental in the regulation of many cellular processes related to cell growth and division. Their mutations, such as V600E for BRAF, are present in melanomas, colorectal, ovarian, and thyroid cancer. In RAF protein dimers, an activator protomer forms a binary molecular complex with a receiver protomer, and thus significantly enhances RAF catalytic activity. Here, we present atomistic molecular dynamics simulation results,<sup>1,2</sup> a novel Markov model-based kinetic analysis,<sup>3</sup> and experimental mutational studies providing structural insights for the RAF activation mechanism.<sup>1,2</sup> Our results offer new prospective pathways in rational drug design for overcoming dimerization-related drug resistance.

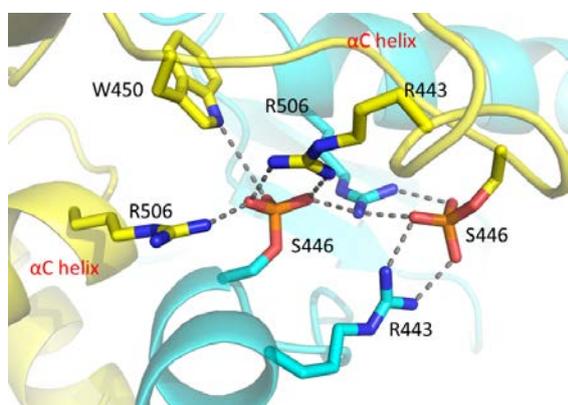


Figure 1. Inter-protomer salt bridges formed in phosphorylated BRAF dimers.

## References

1. P. G. Jambrina, O. Bohuszewicz, N.-V. Buchete, W. Kolch and E. Rosta, *Biochemical Society Transactions*, 2014, **42**, 784-790.
2. P. G. Jambrina, N. Rauch, R. Pilkington, K. Rybakova, L. Nguyen, K. B. N., N.-V. Buchete, W. Kolch and E. Rosta, *Angew. Chem., Int. Ed.*, 2015, **Accepted**.
3. E. Rosta and G. Hummer, *Journal of Chemical Theory and Computation*, 2014, **11**, 276-285.

Energy Landscapes 2015, Porquerolles

The Landscape of a Quantum Optimal Control Problem

Peter Salamon

Controlling a collection of harmonic oscillator by varying the shared frequency to minimize the time to reach the minimum accessible energy is a remarkably difficult problem with a surprisingly rich landscape. The talk will describe the problem, its simple solutions, and the region of parameter space where the global minimum solutions become difficult to find even for very low dimensional examples.

# Energy landscape explorations in two-dimensional chemical systems

C. Schoen

## **Abstract**

While the energy landscape of three-dimensional chemical systems such as crystals or glasses, and of quasi-one-dimensional systems such as clusters of molecules, have been studied successfully in the past three decades, the ones of two-dimensional systems have only rarely been explored. In this presentation, we present results for metastable polymorphs of two-dimensional Si/C-monolayers and for new metastable polymorphs of MgO-monolayers on a sapphire substrate, and discuss the special methodological aspects involved in the exploration of such two-dimensional chemical systems.

# Thermodynamics and kinetics of protein aggregation from atomistic simulations

Birgit Strodel

Computational Biochemistry Group  
ICS-6: Structural Biochemistry, Jülich Research Centre

A major cause for cellular toxicity involved in the onset of several neurodegenerative diseases is the aberrant aggregation of proteins into oligomers and eventually fibrils. In the case of Alzheimer's disease, the main aggregating protein is the amyloid  $\beta$ -protein ( $A\beta$ ). Recently, a secondary nucleation mechanism in the presence of fibrils has been proposed to produce toxic  $A\beta$  oligomers that might have different conformation than oligomers formed in the absence of fibrils.[1] To explore the aggregation mechanisms and differences in the oligomeric conformations we follow the aggregation of  $A\beta$  from isolated monomers in solution [2] as well as in the presence of  $A\beta$  fibrils. We use all-atom molecular dynamics simulations to explore the aggregation process and describe the thermodynamics and kinetics of aggregation using transition networks.[3] Furthermore, we present our very first results from the application of Markov state models to peptide aggregation.

## References:

- [1] Cohen et al. *Proliferation of amyloid- $\beta$ 42 aggregates occurs through a secondary nucleation mechanism*, Proc. Nat. Acad. Sci., 110, 9758–9763 (2013)
- [2] B. Barz, O. Olubiyi, and B. Strodel. *Early amyloid  $\beta$ -protein aggregation precedes conformational change*, Chem. Commun., 50, 5373-5375 (2014)
- [3] B. Barz, D. J. Wales, and B. Strodel. *A kinetic approach to the sequence–aggregation relationship in disease-related protein assembly*, J. Phys. Chem. B, 118, 1003-1011 (2014)

# Time series analysis using wavelet for molecular dynamics simulation of proteins

Mikito Toda

*Physics Department, Faculty of Science,  
Nara Women's University, Nara, Japan*

A new method to extract nonstationary features of coarse grained motions is presented for time series data of molecular dynamics simulation of proteins. We use the wavelet transformation together with the singular value decomposition (SVD). The wavelet analysis enables us to characterize time varying features of the dynamics and SVD enables us to reduce the degrees of freedom of the data. We apply our method to time series data obtained by molecular dynamics simulation for proteins.

For Adenylate Kinase from *Escherichia coli* (AKE), we show that the first singular vector alone can describe main features of the collective motions. Moreover, time dependence of the first singular vector reveals transient features of slow collective motions both in space and frequency. Introducing quantities which characterize similarity of such transient features, we have identified several types of collective motions. As for the space, the most typical types exhibit collective movement of the domains, and the boundaries of these collective oscillations coincide with the hinges identified previously. However, more complicated features of slow motions are also revealed, which indicates that some parts of the domains exhibit separate slow oscillations. As for the frequency, we have noticed that peaks of the spectra vary as time evolves. Such time-dependence of the spectra implies importance of nonlinear effects which result in energy transfer among collective motions.

For the case of *Thermomyces lanuginosa* lipase (TLL), by introducing indexes to characterize collective motion of the protein, we have obtained the following two results. First, time evolution of the collective motion involves not only the dynamics within a single potential well but takes place wandering around multiple conformations. Second, correlation of the collective motion between secondary structures shows that collective motion exists involving multiple secondary structures. We discuss future prospects of our study involving “disordered proteins”.

## References

Kamada M, Toda M, Sekijima M, Takada M and Joe K 2011 *Chem. Phys. Lett.* **502** 241

# Materials Beyond the Periodic Table: A High-Throughput Structure Prediction Study

Martin Uhrin, Nicola Marzari, and Chris J. Pickard

École polytechnique fédérale de Lausanne

## Abstract

The properties of any material are, on some level, a function of its internal structure making an understanding of structure key to the discovery process. We use the Lennard-Jones potential as a convenient proxy to describe the features common to many bulk forming systems: Long range attraction and short range repulsion. We see varying the potential parameters of interaction strength and particle size as sweeping through a simple, continuous, periodic table. Given just these ‘knobs’ and stoichiometry we ask: What are all the binary crystal structures that can form?

Structure prediction is used to populate a schemaless database with over 20M structures, many more than current databases populated from experiment or electronic structure calculations. We discuss some challenges of performing local and global analysis over such a large dataset. Some fascinating finds are highlighted including structures reported for the first time. Furthermore our model allows us to break free from the constraints imposed by the periodic table such as the range of atom sizes and binding energies and explore structures that lie beyond atomic crystals. We make a connection to self assembly and show that it may be possible to realize these structures using artificial superatoms.

# A computational toolbox for the structure determination of porous hybrid solids

Mohammad Wahiduzzaman<sup>a</sup>, Ben Sikora<sup>a</sup>, Sujing Wang<sup>b</sup>, Christian Serre<sup>b</sup>, and Guillaume Maurin<sup>a</sup>

<sup>a</sup>*Institut Charles Gerhardt Montpellier, UMR 5253 CNRS, Université Montpellier, Montpellier, France*

<sup>b</sup>*Institut Lavoisier Versailles, UMR 8180 CNRS, Université Versailles Saint Quentin en Yvelines, France.*

Metal-organic frameworks and such materials often present an arduous challenge for structure determination due to their relatively poor crystallinity, low symmetry and large unit cell volumes that make the indexation of their powder X-ray patterns very complex. Inspired by the concept of molecular building units[1], we developed a software for such structure solution based on a revisited version of the AASBU (**Automated Assembly of Structure Building Units**) method[2]. In order to make a significant leap forward in this field, we implemented a series of extensions of the existing methodology in terms of program development and incorporation of experimental data. This includes the consideration of (i) sophisticated semi-empirical cost functions to control the arrangement of molecular blocks which are based on information gained from various experimental techniques (NMR, PDF,...), (ii) more accurate force fields to describe the intra- and inter-molecular interactions and (iii) more efficient energy minimization algorithms. As a first step, this computational tool has been thoroughly validated on a series of experimentally-known MOF structures. The software has been further able to successfully predict some recently synthesized novel Zr-based MOFs characterized by the SBU present in the widely-studied UiO-66(Zr) MOF[3]. As the software is under active development, we are confident that in the near future we will present a mature version of the software which will allow the determination and *in silico* anticipation of novel structures that are created by more advanced and complex organic linkers, metal corners, and hybrid clusters.

## References

- [1] M. Eddaoudi, D. B. Moler, H. Li, B. Chen, T. M. Reineke, M. O'Keeffe, and O. M. Yaghi, *Acc. Chem. Res.*, vol. 34, no. 4, pp. 319–330, Apr. 2001.
- [2] C. Mellot-Draznieks, J. Dutour, and G. Férey, *Angew. Chemie - Int. Ed.*, vol. 43, no. 46, pp. 6290–6296, 2004.
- [3] Q. Yang, S. Vaesen, F. Ragon, A. D. Wiersum, D. Wu, A. Lago, T. Devic, C. Martineau, F. Taulelle, P. L. Llewellyn, H. Jobic, C. Zhong, C. Serre, G. De Weireld, and G. Maurin, *Angew. Chemie Int. Ed.*, vol. 52, no. 39, pp. 10316–10320, Sep. 2013.

# Energy landscape investigation of ZnO using the threshold algorithm method

D. Zagorac<sup>1,2\*</sup>, J. C. Schön<sup>2</sup>, J. Zagorac<sup>1,2</sup>, M. Rosic<sup>1</sup>, B. Matovic<sup>1</sup>

<sup>1</sup>Institute of Nuclear Sciences Vinča, Materials Science Laboratory, Belgrade University, Belgrade, Serbia

<sup>2</sup>Max Planck Institute for Solid State Research, Stuttgart, Germany

\*corresponding author: dzagorac@vinca.rs

In order to investigate the energy landscape of zinc oxide, we have performed several sets of calculations using different approaches. First, we have performed several global optimizations using empirical potentials followed by local optimizations on *ab initio* level, using different number of atoms, temperatures and/or pressures within the calculations [1,2]. Full analysis of the landscape was performed and important minima were identified. Very important aspect beyond the identification of local minima is the analysis of the barrier structure of the landscape surrounding the minima, and of the possible transition paths connecting the major locally ergodic regions. Therefore, in the next step we have performed threshold algorithm (TA) calculations for different numbers of formula units of ZnO.

A particular focus is the dependence of the shape of the landscape on the number of atoms per simulation cell, and the structural equivalence of local minima due to the periodicity of the system. Structure candidates which we had obtained after *ab initio* local optimization were used as starting points for the threshold runs. Then, the complete energy landscape was analyzed lid by lid, for each specific structure. In addition, we have performed the TA runs for different shapes of the primitive cell for a given structure. With a new lid-by-lid analysis, we have gained new insights into the influence of atom increase in the simulation cell on the energy landscape of a periodic system.

[1] D. Zagorac, J. C. Schön, J. Zagorac, and M. Jansen: *Prediction of structure candidates for zinc oxide as a function of pressure and investigation of their electronic properties*. Phys. Rev. B **89**, 075201 (2014).

[2] D. Zagorac, J. C. Schön, J. Zagorac, and M. Jansen: *Theoretical investigations of novel zinc oxide polytypes and in-depth study of their electronic properties*, RSC Advances, **5**, 25929 (2015).