

Workshop

Metastability and Rare Events in Complex Systems

Erwin Schrödinger Institute for Mathematical Physics, Vienna

18-22 February 2008

Organizers: P. G. Bolhuis, C. Dellago, and E. Vanden-Eijnden

From February 18-22, 2008 our workshop “Metastability and rare events in complex systems” funded by the European Science Foundation within the SimBioMa-program took place at the Erwin Schrödinger Institute for Mathematical Physics in Vienna. The Erwin Schrödinger Institute, funded by the Austrian Federal Ministry of Education, Science and Culture and associated with the University of Vienna, is an institution whose mission is to foster development and exchange of ideas in the physics and mathematics communities on an international level. All administrative matters including the reimbursements of the participants, hotel reservations as well as the announcement of the all program activities to the local and international community were handled very expertly by the ESI staff. At the ESI, desks for individual work and separate rooms for discussions in smaller groups were available to all participants.

To organize the workshop and inform the community a webpage was set up that is still available at <http://comp-phys.univie.ac.at/ESI-rare-events>.

The meeting was attended by over 50 scientists from various countries and by numerous people from the local universities. As the ESI provided a per diem to all participants that essentially covered the hotel accommodation, the SimBioMa funds were mainly used to support the travel expenses of a number of participants from SimBioMa member countries.

All participants contributed to the workshop either in form of formal presentations and posters or in informal discussions. A detailed program of the meeting including the titles of the talks is included below. In these talks, several new and promising ideas for rare event algorithms were presented including the single sweep method for free energy calculation discussed by Luca Maragliano and the Green’s function based master equation approach of Gerhard Hummer. The recent progress in the field, as discussed at the present meeting, has been impressive and is reflected in the vigorous discussion after the talks and during the breaks.

It is worth noting that the average age of the speakers was low compared to other meeting of this sort. All workshop participants were offered to bring along students and young collaborators such that they can get in touch with the international community and many colleagues made use of this possibility.

One of the main goals of this workshop was to bring together people working on rare events in a wide range of fields ranging from physics and chemistry to materials science and molecular biology. In particular, the hope was to establish closer links between people engaged in methods development and participants working on their application to large scale systems. In this regard, the workshop was certainly a success as demonstrated by the several new collaborations that were initiated during the meeting. After the event, several participants have suggested that follow-up meetings organized in, say, two-year intervals might help to keep the momentum the community has demonstrated during the workshop.

The following people participated in the workshop:

Speakers

- | | |
|--------------------------|--------------------------------------------------------|
| 1) Allen Rosalind | University Edinburgh |
| 2) Athenes Manuel | CEA Saclay |
| 3) Chandler David | UC Berkeley |
| 4) Chelli Riccardo | U Firenze |
| 5) Chodera John | Stanford University |
| 6) Dinner Aaron | University of Chicago |
| 7) Elber Ron | U Texas at Austin |
| 8) Ensing Bernd | University of Amsterdam |
| 9) Gervasio Francesco | ETH Zürich |
| 10) Grünwald Michael | University of Vienna, Austria |
| 11) Hummer Gerhard | NIH Bethesda MD |
| 12) Kurchan Jorge | ESPCI, France |
| 13) Laio Alessandro | SISSA, Trieste, Italy |
| 14) Maragakis Paul | D. E. Shaw Research, New York |
| 15) Maragliano Luca | Courant Inst. of Mathematical Sciences, New York Univ. |
| 16) Miller Tommy | University of California at Berkeley |
| 17) Mousseau Normand | Université de Montréal |
| 18) Oganov Artem | ETH Zürich and Moscow State University |
| 19) Peters Baron | UCSB |
| 20) Reuter Karsten | Fritz-Haber-Institut, Berlin, Germany |
| 21) Schütte Christof | FU Berlin |
| 22) Valeriani Chantal | U Edinburgh |
| 23) van Erp Titus | CECAM |
| 24) Venturoli Maddalena | NYU, Courant Institute |
| 25) Vuilleumier Rodolphe | U Pierre et Marie Curie, Paris |
| 26) Wiggins Steve | University of Bristol, UK |
| 27) Woolf Tom | Johns Hopkins University |
| 28) Zahn Dirk | MPI Dresden |

Other participants

- | | |
|---------------------------|--------------------------------------------------|
| 1) Barducci Alessandro | ETH Zürich |
| 2) Bonella Sara | Università di Roma "La Sapienza" |
| 3) Boulougouris Georgios | National Technical University of Athens |
| 4) Bucko Tomas | University of Vienna |
| 5) Bussi Giovanni | ETH Zürich |
| 6) Ciccotti Giovanni | University of Rome "La Sapienza" |
| 7) Grazia Cottone | Università di Palermo |
| 8) Delle Site Luigi | Max-Planck-Institute for Polymer Research, Mainz |
| 9) Drechsel-Grau Christof | University of Cambridge |
| 10) Yael Elmatad | University of California at Berkeley |
| 11) Ferrario Mauro | Università di Modena e Reggio Emilia, Italy |
| 12) Hartmann Carsten | FU Berlin |
| 13) Martin Held | FU Berlin |
| 14) Marsili Simone | Università di Firenze |
| 15) Philipp Metzner | Courant Institute, NYU |

16) Niezialek Dorota	U Mainz
17) Noe Frank	FU Berlin
18) Noorizadeh Emad	The University of Edinburgh
19) Praprotnik Matej	Max-Planck-Institute for Polymer Research, Mainz
20) Procacci Piero	Università di Firenze, Italy
21) Rogal Jutta	University of Amsterdam, NL
22) Schilling Tanja	Johannes-Gutenberg University, Mainz
23) van Meel Koos	FOM Instituut AMOLF, Amsterdam
24) Jan Wigger	FU Berlin
25) Weare Jonathan	Courant Institute of Mathematical Sciences, NY
26) Willard Adam	University of California at Berkeley

ESI-Workshop
 Metastability and Rare Events in Complex Systems
 18-22 February 2008
 Organizers: Peter G. Bolhuis, Christoph Dellago, and Eric Vanden-Eijnden
Program

Monday, 18 Feb

8:30-8:55	<i>Registration</i>
8:55-9:00	<i>Introductory Remarks</i>
9:00-9:40	Alessandro Laio Folding of small proteins in explicit solvent by the combined use of metadynamics and replica exchange
9:40-10:20	Bernd Ensing Poor man's metadynamics
	<i>Coffee break</i>
10:50 -11:30	Artem Oganov Evolutionary crystal structure prediction: Finding the global energy minima for periodic solids.
11:30 -12:10	Luca Maragliano Single-sweep methods for free energy calculations
	<i>Lunch</i>
14:00-14:40	Karsten Reuter Error-controlled multiscale modeling approaches to surface chemistry and catalysis
	<i>Coffee break</i>
15:10-15:50	Normand Mousseau The dynamical activation-relaxation technique (DART): an on-the-fly kinetic Monte-Carlo algorithm

Tuesday, 19 Feb

9:00-9:40	David Chandler Transition path sampling of large fluctuation functions and non-equilibrium order-disorder transitions
9:40-10:20	Michael Grünwald Precision shooting: sampling diffusive transition pathways
	<i>Coffee break</i>
10:50 -11:30	Thomas Miller Sampling diffusive transition paths
11:30 -12:10	Jorge Kurchan Finding rare trajectories
	<i>Lunch</i>
14:00-14:40	Titus van Erp Efficient path sampling on multiple reaction channels
	<i>Coffee break</i>
15:10-15:50	Giovanni Bussi Well-tempered metadynamics: a smoothly-converging and tunable free energy method
16.00-17:30	<i>Poster Session</i>

Wednesday, 20 Feb

9:00-9:40	Aaron Dinner Umbrella sampling for non-equilibrium processes
9:40-10:20	Riccardo Chelli Calculation of the potential of mean force from nonequilibrium measurements via maximum likelihood estimators
	<i>Coffee break</i>
10:50 -11:30	Manuel Athenes Mapping the equilibrium and non-equilibrium entropy landscapes of metastable systems: the path-sampling approach.
11:30 -12:10	Paul Maragakis A Differential Fluctuation Theorem
	<i>Lunch</i>
14:00-14:40	Rodolphe Vuilleumier Microscopic velocity field around a diffusing particle
	<i>Coffee break</i>
15:10-15:50	Steve Wiggins Recent advances in the high dimensional Hamiltonian dynamics and geometry of reaction dynamics
15:50-16:30	Baron Peters Likelihood Maximization for Obtaining Reaction Coordinates

Thursday, 21 Feb

9:00-9:40	Maddalena Venturoli Kinetics of phase transitions in two dimensional Ising models studied with the string method
9:40-10:20	Ron Elber The recovery stroke of myosin: Atomically detailed simulations by Milestoning
	<i>Coffee break</i>
10:50 -11:30	Christof Schütte New Approaches to Multiscale Modelling of Metastable Systems
11:30 -12:10	Francesco Gervasio The folding mechanism of β -hairpin from PT-metaD and path-based collective variables simulations
	<i>Lunch</i>
14:00-14:40	John Chodera Master equation models of protein folding and dynamics from all-atom molecular dynamics simulations in explicit solvent
	<i>Coffee break</i>
15:10-15:50	Thomas Woolf Dynamic Importance Sampling for Biomolecule Transitions: Progress and the Future
15:50-16:30	Round table discussion
Evening	<i>Conference Dinner</i>

Friday, 22 Feb

9:00-9:40	Dirk Zahn Nucleation Events and Self-Organization
9:40-10:20	Rosalind Allen Homogeneous nucleation under shear in a two-dimensional Ising model
	Coffee break
10:50 -11:30	Chantal Valeriani Evidence for out-of-equilibrium crystal nucleation in suspensions of oppositely charged colloids
11:30 -12:10	Gerhard Hummer Free energies and kinetics of molecular systems from coarse master equations

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Poster session, Tuesday, 16 Feb, 16:00-17:30

1	Alessandro Barducci	Well-Tempered Metadynamics: A Smoothly Converging and Tunable Free-Energy Method
2	Georgios Boulougouris	Probing sub-glass relaxation of a-PS, via atomistic simulations (Joint work with D.N. Theodorou)
3	Tomas Bucko	Proton exchange of small hydrocarbons over acidic chabazite: Ab initio study of entropic effects
4	John Chodera	Automatic construction of Markov models of peptide and protein dynamics from simulations in explicit solvent
5	Yael Elmatad	Transition path sampling as a tool for probing dynamical phase transitions in a softened Fredrickson-Andersen model for a structural glass former
6	Carsten Hartmann	Shape-induced effects in conformation dynamics (Joint work with Philipp Metzner)
7	Jürgen Köfinger	Macroscopic order in water pores
8	Wolfgang Lechner	Crystallization in the Gaussian core model
9	Simone Marsili	From instantaneous to reversible replica exchanges
10	Frank Noe	Metastability, Folding pathways and Experimental Observables from Markov Models of Peptide and Protein Dynamics
11	Emad Noorizadeh	An ergodic dynamical sampling method for molecular modeling
12	Baron Peters	Equilibrium path sampling study of methane diffusion in gas hydrates
13	Matej Praprotnik	Concurrent triple-scale simulation of molecular liquids (by Rafael Delgado-Buscalioni, Kurt Kremer, and Matej Praprotnik)
14	Matej Praprotnik	Adaptive resolution simulation of liquid water (by Matej Praprotnik, Luigi Delle Site, Kurt Kremer, Silvina Matysiak, and Cecilia Clementi)
15	Koos van Meel	Crystal nucleation from cold vapor
16	Adam Willard	An aqueous electrolyte at an electrochemical interface - a simulation study

ESI Conference 2008
Metastability and Rare Events in Complex Systems
Titles and Abstracts

Allen Rosalind

Homogeneous nucleation under shear in a two-dimensional Ising model

We have obtained rate constants and transition paths for nucleation under shear in a two-dimensional Ising model with Metropolis Monte Carlo spin flip dynamics using forward flux sampling (FFS) simulations. The nucleation rate shows a nonmonotonic dependence on the shear rate, increasing approximately linearly at low shear rates and decreasing nonlinearly for high shear rates. The physical mechanisms underlying this behaviour were investigated by changing the external field strength, by randomising the shear direction and by performing a committor analysis of the transition path ensemble, as a function of shear rate. We find that the enhancement of nucleation at low shear rate is due partly to shear-enhanced cluster coalescence, while the suppression of nucleation at high shear rates is due to shear-mediated cluster breakup. This indicates that applying shear to the system causes an important change in the nucleation mechanism. This study demonstrates the use of the forward flux sampling method for simulating rare events, including nucleation, in nonequilibrium systems and shows the highly nontrivial effect of shear on nucleation pathways in this model system.

Athenes Manuel

Mapping the equilibrium and non-equilibrium entropy landscapes of metastable systems: the path-sampling approach

Several recent studies have investigated the relevance of computing thermodynamic quantities using non-equilibrium techniques such as path-sampling. We review this approach in the context of free energy calculations. We show the potential advantages of biased path-sampling techniques for computing Landau free energies of systems trapped in rugged energy landscapes. Recent extensions made to these techniques also enable to compute the statistical entropy of systems driven out-of-equilibrium. We present these latest developments and illustrate them by mapping a probability density landscape and estimating its non-equilibrium entropy.

Chandler David

Transition path sampling of large fluctuation functions and non-equilibrium order-disorder transitions

Transition path sampling is an importance sampling of trajectory space that allows the study of barrier crossings where barriers are not already known. But there is more owing to the fact that this sampling is based upon a statistical mechanics of trajectory space. It provides the numerical tool for treating a thermodynamic-like formalism of space-time. Associated partition functions and free energies of space-time as functions of discriminating field variables exhibit singularities at conditions of coexistence between extensively different sub-ensembles of trajectories. In equilibrium statistical mechanics, coexistence can be gleaned numerically from applications of Monte Carlo sampling of micro-states. The corresponding transition path sampling technique allows the study of non-equilibrium order-disorder transitions in general and structural glass transitions in particular.

Chelli Riccardo

Calculation of the potential of mean force from nonequilibrium measurements via maximum likelihood estimators

We present an approach to the estimate of the potential of mean force along a generic reaction coordinate based on maximum likelihood methods and path-ensemble averages in systems

driven far from equilibrium. Following similar arguments, various free energy estimators can be recovered, all providing comparable computational accuracy. The method, applied to the unfolding process of the alpha-helix form of an alanine deca-peptide, gives results in good agreement with thermodynamic integration.

John Chodera

Master equation models of protein folding and dynamics from all-atom molecular dynamics simulations in explicit solvent

To extract insight and make comparisons between simulations of biomolecular conformational dynamics (such as protein folding) and single-molecule or ensemble experiments, we investigate the construction of discrete-state, continuous-time master equation models to describe statistical dynamics. We describe our efforts to efficiently and adaptively construct these models using all-atom molecular dynamics simulations in explicit solvent, determine the range of timescales over which the models faithfully describe dynamics, assess the uncertainties in computed properties, and extract insight about long-timescale processes. Recent results from application to peptide and protein folding datasets from Folding@Home and the IBM Blue Gene project will be presented.

Dinner Aaron

Umbrella sampling for non-equilibrium processes

Many systems of significant fundamental and applied interest are microscopically irreversible. For theoretical studies of such systems, the steady-state distribution is of central importance because it enables calculation of static averages of observables for comparison to experimental measurements. For systems at equilibrium, low probability states can be explored efficiently in simulations with umbrella sampling methods, in which biasing potentials that are functions of one or more order parameters are used to enhance sampling of selected regions of phase space. What complicates extending umbrella sampling to simulations of non-equilibrium processes is that, by definition, they do not obey detailed balance (microscopic reversibility). As such, one must account for the fact that the steady-state probability of observing particular values of the order parameters can be determined by a balance of flows in phase space through different possible transitions. In this talk, I will describe an algorithm for enforcing equal sampling of different regions of phase space in an ergodic system arbitrarily far from equilibrium. This enables determination of the corresponding steady-state probability distribution with high accuracy despite a lack of a priori knowledge of that function. Applications and extensions of the method will be discussed.

Elber Ron

The recovery stroke of myosin: Atomically detailed simulations by Milestoning

Milestoning is a technique to significantly extend the time scale of Molecular Dynamics simulations. It computes explicitly the time evolution of the system even if the process is not activated and exponential in time. The calculation is done in two steps. First, short time trajectories are used to compute Local First Passage Time Distributions (LFPTD) between nearby "Milestones" along a reaction coordinate. In the second step a stochastic non-Markovian integral equation that uses the LFPTD computes the overall time course of the reaction.

I will briefly describe the technique and focus on an application for the recovery stroke in myosin. Myosin is a molecular machine that provides a power stroke in muscles at the cost of an ATP. Once the power stroke is completed the molecule recovers to its pre-stroke state. The relaxation step is called the recovery stroke. The recovery stroke does not require the investment of biological energy and is spontaneous and reasonably rapid in the presence of ATP.

We computed a reaction coordinate for this process using a functional optimization that provides the minimum energy path. For a molecular machine that is designed for efficiency and minimal

energy loss it might be expected that the process will follow a single well-focused reaction coordinate. Indeed the Milestoning calculation that uses the computed reaction coordinate (but included all degrees of freedom of an atomic and fully solvated myosin molecule) reproduces the time scale and the expected features of the free energy surface well.

Joined work with Anthony West

Ensing Bernd

Poor man's metadynamics

Concerted chemical reactions (as well as a range of other phenomena) are processes that are usually well described by a small set of order parameters, or collective variables, but for which a good reaction coordinate is not known a priori. When the set of collective variables, for example the lengths of the bonds that are being broken and formed in the reaction, is small enough, the multidimensional free energy surface (FES) of the reaction can be computed, for instance using the metadynamics simulation technique. The lowest free energy pathway, connecting the stable reaction and product states, is a good estimate for the reaction coordinate. However, even converging a 3-dimensional FES can be very computationally demanding using metadynamics in combination with ab initio molecular dynamics. Previously, we have shown that it can be a good idea to use metadynamics only in a first stage to probe the multidimensional FES with limited accuracy, and then, in a second stage, efficiently converge the one-dimensional free energy profile along the lowest free energy pathway, for example using umbrella sampling. In this presentation, I will discuss our attempts to combine metadynamics, with ideas from path finding techniques (such as the string method, the nudge elastic band method, the dimer method, etc) to compute simultaneously the one-dimensional free energy profile and find the lowest free energy pathway as a function of a small set of collective variables in a single metadynamics simulation.

Key references:

- [1] Bernd Ensing, Alessandro Laio, Michele Parrinello and Michael L. Klein, A recipe for the computation of the free energy barrier and the lowest free energy path of concerted reactions. *J. Phys. Chem. B* 109 6676 (2005)
- [2] Bernd Ensing, Alessandro Laio, Francesco L. Gervasio, Michele Parrinello and Michael L. Klein, Minimum Free Energy Reaction Path for the E₂ Reaction between Fluoro Ethane and a Fluoride Ion. *J. Am. Chem. Soc.* 126 9492 (2004)
- [3] Bernd Ensing and Michael L. Klein, Perspective of the reactions between F⁻ and CH₃CH₂F: the free energy landscape of the E₂ and SN₂ reaction channels. *Proc. Natl. Acad. Sci. USA* 102 6755 (2005)
- [4] Bernd Ensing, Marco De Vivo, Zhiwei Liu, Preston Moore, and Michael L. Klein, Metadynamics as a tool for exploring the free energy landscape of chemical reactions. *Acc. Chem. Res.* 39 (2006), 73-81

Gervasio Francesco

The folding mechanism of β -hairpin from PT-metaD and path-based collective variables simulations (F. L. Gervasio, M. Bonomi, D. Branduardi, M. Parrinello)

Recently we have developed, in the context of fully atomistic molecular dynamics, two methods to study rare events and reconstruct free energies and reactive trajectories at finite temperature. PTmetaD is based on the combination of parallel tempering and metadynamics and greatly improves the performance of both methods [1]. The path-based collective variables (S and Z) are 2 collective variables that describe the position of a point in configurational/conformational space relative to a pre assigned path. With the help of these two variables the method combines features of approaches like metadynamics or umbrella sampling with those of path based methods. This allows global searches in the space of paths to be performed and a new variational principle for determination of reactive paths to be established [2]. We have applied

both approaches to study the free energy landscape for β -hairpin folding. In this talk we compare the two approaches and discuss the mechanism of folding of β -hairpin in the light of our findings.

[1] Bussi, G.; Gervasio, F. L.; Laio, A.; Parrinello, M. J., *Am. Chem. Soc.* **128**, 13435-13441 (2006).

[2] Branduardi, D., Gervasio, F. L., Parrinello, M. J. *Chem. Phys.* **126** 054103 (2006)

Grünwald Michael

Precision shooting: sampling diffusive transition pathways

Transition path sampling simulations of systems involving long, flat free energy barriers are frequently plagued by a low acceptance of shooting moves, caused by the finite precision of computer floating point numbers. We address this problem by introducing a new shooting algorithm based on the linear short-term behavior of small disturbances in phase space. Using the precision shooting algorithm, arbitrarily small disturbances can be implemented and any desired acceptance ratio of shooting moves can be obtained. We demonstrate the method on a simple diffusive process in a dense liquid of soft sphere particles and also discuss its applicability to barrier crossing events involving metastable states.

Hummer Gerhard

Free energies and kinetics of molecular systems from coarse master equations

Coarse master equations and diffusion models provide powerful frameworks to study the equilibrium and non-equilibrium properties of molecular systems. Maximum likelihood and Bayesian approaches have been used successfully to construct such models from the observed dynamics projected onto discrete and continuous low-dimensional sub-spaces. By using a Green's-function based formalism, issues arising from fast non-Markovian dynamics can be circumvented. The general formalism for the construction of coarse master equations will be illustrated with examples ranging from molecular fluids to protein folding.

Kurchan Jorge

Finding rare trajectories

I shall describe a method to find efficiently trajectories with atypical stability properties of a dynamical system. It can be used to find reaction currents between metastable states, to find soliton and breather configurations and to detect stability islands in chaotic systems.

Laio Alessandro

Folding of small proteins in explicit solvent by the combined use of metadynamics and replica exchange

We recently developed a method [1,2] that combines replica exchange [3] with metadynamics [4] and allows, with a moderate computational effort, the simultaneous reconstruction of the free energy as a function of a large number of variables. This allows simulating very complex reactions, like protein folding, in which the reaction coordinate is totally unknown. We will discuss applications of the methodology to the folding in explicit solvent of the TRP cage miniprotein and of the advillin headpiece C-terminal domain (cHP) and its Pro62Ala mutant. Our calculations allow, for these small proteins, the ab initio prediction of the folded state. For the advillin headpiece we find that the Pro62Ala mutation does not change the overall stability of the native state but it significantly alters the entropic contribution to the folding free energy. Therefore, the mutant is still folded at room temperature but is characterized by a lower unfolding temperature. This prediction was subsequently validated by NMR and CD experiments [5].

[1] G. Bussi et al. *JACS* **128**, 13435 (2006).

[2] S. Piana and A. Laio, *J. Phys. Chem. B* **111**, 4553 (2007).

[3] Y. Sugita and Y. Okamoto, *Chem. Phys. Lett.* **314**, 141 (1999).

[4] A. Laio and M. Parrinello, *Proc Natl. Acad. Sci. USA* **99**, 12562 (2002).

[5] S. Piana et al. J. Mol. Biol., 375, 460 (2008).

Maragakis Paul

A Differential Fluctuation Theorem

I present a new non-equilibrium thermodynamics identity ("A Differential Fluctuation Theorem", Maragakis, Spichty, and Karplus, J Phys Chem B 2008, in press). This identity follows from a general symmetry relation between averages over non-equilibrium forward and backward path functions that was derived by Crooks [Crooks, G. E. Phys Rev E 2000, 61, 2361-2366]. The identity provides the proper reweighting of the Crooks fluctuation theorem when the work data are restricted to measurements between two subsets a and b of the full states A and B. Several existing non-equilibrium thermodynamic identities follow directly from this differential fluctuation theorem. I will demonstrate its applicability to the analysis of molecular dynamics simulations by estimating the free energy difference between two conformers of the standard alanine dipeptide model system. I anticipate that these developments can be applied to the analysis of laboratory experiments.

Maragliano Luca

Single-sweep methods for free energy calculations

A simple, efficient and accurate method is proposed to map multi-dimensional free energy landscapes. The method combines the temperature-accelerated Molecular Dynamics (TAMD) proposed in [Maragliano & Vanden-Eijnden (2006) Chem. Phys. Lett. 426, 168-175] with a variational reconstruction method using radial-basis functions for the representation of the free energy. TAMD is used to rapidly sweep through the important regions of the free energy landscape and compute the gradient of the free energy (i.e. the mean force) locally at points in these regions. The variational method is then used to reconstruct the free energy globally from the mean force at these points. The method will be illustrated on numerical and Molecular Dynamics examples.

Miller Tommy

Sampling diffusive transition paths

With the goal of simulating soft matter dynamics on long timescales, we address the problem of sampling diffusive transition paths. The transition path ensemble is expressed as a path integral distribution, and a convenient path weight functional is obtained by symmetrizing the Onsager-Machlup action. Upon discretization, the path weights are accurate to second order in the trajectory timestep, and they can be evaluated using only first derivatives of the potential energy function. Recently developed path integral Monte Carlo techniques are employed to sample the transition paths. Using the Markov property, different segments of the transition paths can be sampled independently, which leads to a low-communication scheme in which the molecular dynamics is parallelized in time. It is shown that thousands of parallel computer processors can be efficiently used to access long dynamical timescales. Several applications are considered.

Mousseau Normand

The dynamical activation-relaxation technique (DART): an on-the-fly kinetic Monte-Carlo algorithm

We present DART, the dynamical activation-relaxation technique, that combines the activation-relaxation technique (ART nouveau) with a non-lattice KMC method that allows on-the-fly identification of barriers and the full treatment of lattice deformations. Most KMC schemes rely on the use of a fixed list of events and barriers, which are drawn with the proper weight during the simulation. While this works well with a number of problems, such as metal-on-metal growth, the standard KMC cannot be used for processes where the type of events changes with time. DART presents a solution to this limitation. ART nouveau has been used extensively for the

study of activated mechanisms in different materials both within an empirical and ab-initio description of the systems (references). In DART, KMC moves are made based on a catalog of events constructed using ART. After each KMC move, this catalog is updated to take into account new environments, when needed. A topological description of the system structure at each moment allows the method to identify rapidly these new environments and to move forward efficiently.

This work was done mostly by Fedwa El-Mellouhi in collaboration with Michel Côté and Laurent J. Lewis.

Oganov Artem

Evolutionary crystal structure prediction: Finding the global energy minima for periodic solids

(Artem R. Oganov, Andriy Lyakhov, Yanming Ma)

Crystal structure prediction on the basis of just the chemical formula has long been considered a formidable or even insoluble problem. Being able to solve this problem would open the possibilities to find new phases of planetary materials at extreme conditions [1,2], to solve structures where experimental data are insufficient, and to design new materials entirely on the computer (once the structure is known, it is relatively easy to predict many of its properties – e.g., [3]). This problem is equivalent to finding the global minimum of the free energy with respect to structural parameters. For a periodic solid, there are $3(N-1)+3$ degrees of freedom (where N is the number of atoms in the unit cell). To solve this multidimensional global optimization problem, we recently developed a new method based on a specifically devised and carefully tuned *ab initio* evolutionary algorithm, implemented in the USPEX code (Universal Structure Predictor: Evolutionary Xtallography, [4-6]). Key ingredients of this method (selection, variation operators, redundancy control) and its current developments will be discussed. Some of the important applications (high-pressure phases of hydrogen, oxygen, boron, hydrocarbons and some technologically interesting materials) will be presented.

[1] Oganov A.R., Ono S. (2004). Theoretical and experimental evidence for a post-perovskite phase of MgSiO_3 in Earth's D" layer. *Nature* **430**, 445-448.

[2] Oganov A.R., Ono S. (2005). The high pressure phase of alumina and implications for Earth's D" layer. *Proc. Natl. Acad. Sci.* **102**, 10828-10831.

[3] Oganov A.R., Brodholt J.P., Price G.D. (2001). The elastic constants of MgSiO_3 perovskite at pressures and temperatures of the Earth's mantle. *Nature* **411**, 934-937.

[4] Glass C.W., Oganov A.R. & Hansen N. (2006). USPEX - evolutionary crystal structure prediction. *Comp. Phys. Comm., in press.*

[5] Oganov A.R. & Glass C.W. (2006). Crystal Structure Prediction using *ab initio* evolutionary techniques: principles and applications. *J. Chem. Phys* **124**, art. 244704.

[6] Oganov A.R., Glass C.W., Ono S. (2005). High-pressure phases of CaCO_3 : crystal structure prediction and experiment. *Earth Planet. Sci. Lett.* **241**, 95-103.

Peters Baron

Obtaining reaction coordinates with likelihood maximization

The presentation introduces the likelihood maximization approach for obtaining accurate reaction coordinates, the "Aimless Shooting" version of transition path sampling, and a quantitative extension of committor probability analysis for assessing reaction coordinate accuracy. Examples that will be discussed include barrier crossing in a model free energy landscape, a comparison to the earlier "Genetic Neural Network" approach, nucleation in the Ising model, and nucleation of the Form I to Form II polymorph transformation in terephthalic acid crystals.

Reuter Karsten

Error-controlled multiscale modeling approaches to surface chemistry and catalysis

A materials science modeling that is based on understanding, predictive, and applicable to a wide range of realistic conditions requires to cover a wide range of length and time scales. Electronic structure theory deals with the finest scale and is thus the base for such a multiscale modeling of materials properties and functions. First-principles statistical mechanics and continuum mechanics techniques represent the next levels that build on this basis. Using examples from heterogeneous catalysis I will demonstrate the approach using density-functional theory, kinetic Monte Carlo and rate equation theory to treat the electronic, statistical and continuum levels, respectively. I will discuss the need for error-controlled links between the levels, e.g. using sensitivity analyses, as well as an approach to address binding interactions that challenge present-day exchange-correlation functionals.

Schütte Christof

New Approaches to Multiscale Modelling of Metastable Systems

We will present a novel approach to the identification of metastable states like biomolecular conformations via the optimal statistical representations of transition kernels of the underlying dynamics. Compared to other approaches this approach scales favorably with the size of the system and allows to derive some of the alternative approaches from some fundamental principles.

Valeriani Chantal

Evidence for out-of-equilibrium crystal nucleation in suspensions of oppositely charged colloids

We report a numerical study of the rate of crystal nucleation in a binary suspension of oppositely charged colloids. Two different crystal structures compete in the thermodynamic conditions under study. We find that the crystal phase that nucleates is metastable and, more surprisingly, its nucleation free energy barrier is not the lowest one. This implies that, during nucleation, there is insufficient time for sub-critical nuclei to relax to their lowest free-energy structure. Such behavior is in direct contradiction with the common assumption that the phase that crystallizes most readily is the one with the lowest free-energy barrier for nucleation. The phenomenon that we describe should be relevant for crystallization experiments where competing solid structures are not connected by an easy transformation. In my talk I will discuss possible implications of these findings when sampling nucleation pathways.

van Erp Titus

Efficient path sampling on multiple reaction channels

Due to the time scale problem, rare events are not accessible by straightforward molecular dynamics. The presence of multiple reaction channels complicates the problem even further. The feasibility of the standard free energy based methods relies strongly on the success in finding a proper reaction coordinate. This can be very difficult task in high-dimensional complex systems and even more if several distinct reaction channels exist. Even if a proper reaction coordinate can be found, ergodic sampling will be a challenge. In this article, we discuss the recent advancements of path sampling methods to tackle this problem. We argue why the path sampling methods, via the transition interface sampling technique, is less sensitive to the choice of reaction coordinate. Moreover, we review a new algorithm, parallel path swapping, that can dramatically improve the ergodic sampling of trajectories for the multiple reaction channel systems.

Venturoli Maddalena

Kinetics of phase transitions in two dimensional Ising models studied with the string method

We present the kinetics of phase transitions in the two dimensional Ising model under different conditions studied using the string method. The key idea is to work in collective variables, consisting of block of spins, which allow for a continuous approximation of the collective

variables state-space. The string method computes the minimum free energy path (MFEP) in this collective variables space, which is shown to explain the mechanism of the phase transformation (in particular, an approximation of its committor function, its free energy and its transition state). The theoretical background of the technique as well as its computational aspects are discussed in detail. The string method is then used to analyze phase transition in the Ising model with imposed boundary conditions and in a periodic system under an external field of increasing magnitude. In each case, the mechanism of the phase transformation is elucidated.

Joint work with Eric Vanden-Eijnden and Giovanni Ciccotti

Vuilleumier Rodolphe

Microscopic velocity field around a diffusing particle

The fundamental model for diffusion is the Stokes-Einstein approach. It relates the diffusion coefficient to the friction coefficient which is in turn extracted from the hydrodynamic friction felt by a moving sphere in a liquid environment. The hydrodynamic flow around the sphere, commonly called Stokes flow, depends on the boundary conditions on the sphere. Two boundary conditions are usually considered: stick boundary conditions (no velocity at contact), as in the original approach, or slip boundary conditions (finite tangential velocity). As these two boundary conditions lead to different diffusion coefficient as a function of particle size, the usual way to investigate these from numerical simulations has been to compute the diffusion coefficient as a function of particle size. This leads for diffusion of Lennard-Jones particles to the suggestion of slip boundary conditions.

Here, we want to present a direct calculation of the microscopic velocity field around a diffusing particle from numerical simulations. This allow for comparison between the atomic model and the hydrodynamics approach. It is first demonstrated that the hydrodynamics flow is well recovered after only a few atomic radius from the tagged particle. However, two effects of the velocity fluctuations of the diffusing particle are evidenced. The boundary conditions are shown to include a finite normal velocity at contact, which would seem at first in contradiction with the non-penetrability of the particles but is an effect of fluctuations. Then, the flux of momentum in the flow is not determined solely by viscosity but also from the diffusion of the tagged particle.

This gives new insight in the diffusion process in liquids and in particular on the role of fluctuations at the atomic level. We will also try to show how this method could be also used in order to provide a more mechanistic description of the diffusion processes, in terms similar to reaction paths and transition states.

Wiggins Steve

Recent advances in the high dimensional Hamiltonian dynamics and geometry of reaction dynamics

In the early development of applied dynamical systems theory it was hoped that the complexity exhibited by low dimensional nonlinear systems might somehow lead to ways of understanding the complex dynamics of high dimensional systems. Unfortunately, there has not been great progress in this area. The availability of high performance computing resources has led to many computational studies of high dimensional systems. But even under these circumstances, the problem of high dimensionality often forces one to make severe assumptions on the dynamics in order to derive physically relevant quantities from the model, e.g., ergodicity assumptions may be necessary in order to deduce a reaction rate from a computation. We approach the problem of high dimensionality from the other direction. Our interest is in the exact Hamiltonian dynamics of high dimensional systems. As applied dynamical systems theory developed and expanded throughout the 70's and 80's there was much effort in applying global, geometrical concepts and techniques to problems related to the dynamics of molecules. In the early 90's this effort began to die out in the chemistry community because the approach did not appear to apply to problems

with more than two degrees-of-freedom. New concepts were required. In the past few years there has been much progress along these lines. We will discuss these recent developments and their application to the understanding of a variety of issues related to the dynamics of molecules. Theoretically, we have constructed a dynamically exact *phase space* transition state theory, for which we can rigorously construct a "surface of (locally) no return" through which all reacting trajectories must pass. It can also be shown that the flux across the surface we construct is minimal. Central to this construction is a normally hyperbolic invariant manifold (NHIM) whose stable and unstable manifolds enclose the phase space conduits of all reacting trajectories. They enable us to determine the volume of trajectories that can escape from a potential well (the "reactive volume"), which is a central quantity in any reaction rate, and to construct a "dynamical" reaction path. Moreover, we show that the NHIM is the mathematical manifestation of the chemist's notion of the "activated complex".

The application of these ideas to concrete problems relies on the computational realisation of these structures. These can be realized locally through the Poincare- Birkhoff normal form, and then globalised. Recent advances in computational techniques enable one to carry out this procedure for systems with a large number of degrees of freedom. A similar set of techniques can be developed to deal with the corresponding quantum mechanical system. In particular a quantum normal form is used to determine quantum mechanical resonances and reaction rates with high precision. In this talk we describe the theory, applications, and computations that make this possible. We will use HCN isomerization and the Muller-Brown potential to illustrate the ideas and methods and point out a number of areas where more close collaborations between chemists and applied mathematicians could prove fruitful. For example, "rare events" from a dynamical systems point of view are homoclinic and heteroclinic trajectories. Are they related, and do they provide insight, into the "rare events" observed in reaction dynamics?

Woolf Tom

Dynamic Importance Sampling for Biomolecule Transitions: Progress and the Future

This talk will review progress in our implementation and use of dynamic importance sampling applied to biomolecules. We continue to be interested in membrane proteins and one long-term goal of this work is the ability to comment on gating and pumping mechanisms for ion channels and transporters. In addition we believe that the time is appropriate to start asking questions of how computed kinetic pathways can be tested and used within an experimental setting. Thus, within the spirit of the workshop, we will present ideas for new algorithms, a review of progress, and our estimate for where the simulation methods need to end up to be maximally useful to the experimental community.

Zahn Dirk

Nucleation Events and Self-Organization

This talk discusses possible approaches to the crossing of nucleation barriers in molecular dynamics simulations. The wide scope of the transition path sampling method is demonstrated by a series of phase transition and phase separation studies. Accessible insights range from nucleation mechanisms, coalescence/competition of multiple nuclei during phase growth to the interplay of separation processes with nucleation and growth. The limitations of transition path sampling are illustrated at the example of crystal nucleation from solution. For studying diffusion-controlled aggregate formation I will present a recently developed method and discuss potential applications.