



BIRS Workshop
Mathematical Issues in Molecular Dynamics
June 4–9 2005

MEALS

Breakfast (Continental): 7:00 - 9:00 am, 2nd floor lounge, Corbett Hall, Sunday - Thursday
 *Lunch (Buffet): 11:30 am - 1:30 pm, Donald Cameron Hall, Sunday - Thursday
 *Dinner (Buffet): 5:30 - 7:30 pm, Donald Cameron Hall, Saturday - Wednesday
 Coffee Breaks: As per daily schedule, 2nd floor lounge, Corbett Hall
 *Please remember to scan your meal card at the host/hostess station in the dining room for each lunch and dinner.

MEETING ROOMS

All lectures are held in the main lecture hall, Max Bell 159. Please note that the meeting space designated for BIRS is the lower level of Max Bell, Rooms 155-159. Please respect that all other space has been contracted to other Banff Centre guests, including any Food and Beverage in those areas.

SCHEDULE

	Saturday	Sunday	Monday	Tuesday	Wednesday	Thursday
7:00-9:00		Continental Breakfast, 2nd floor lounge, Corbett Hall				
9:00-9:30		Skeel	Shardlow	Marcia	Bond	discussion
9:30-10:00		Skeel	Kartunnen	Lin	Tupper	discussion
10:00-10:30		Coffee Break, 2nd floor lounge, Corbett Hall				
10:30-11:00		Hayes	Izaguirre	Newman	Reich	discussion
11:00-11:30		Darve	Roland	Tuckerman	Posch	discussion
11:30-11:45				Group Photo ¹		
11:30-13:30		Buffet Lunch, Donald Cameron Hall				
13:00-13:30		Guided Tour ²		free afternoon		
13:30-14:00		Guided Tour	Leimkuhler	free afternoon	Neal	
14:00-14:30		Meerbach	Sweet	free afternoon	Stuart	
14:30-15:00		Chipot	Barth	free afternoon	Tretiakov	
15:00-15:30		Coffee Break, 2nd floor lounge, Corbett Hall (except Tues.)				
15:30-16:00		Ichiye	Hummer	free afternoon	Anitescu	
16:00-16:30		Straub	Negrut	free afternoon	Lubich	
17:30-19:30		Buffet Dinner, Donald Cameron Hall				

¹A group photo will be taken on Tuesday at 11:45 am, directly after the last lecture of the morning. Please meet on the front steps of Corbett Hall.

²A free guided tour of The Banff Centre is offered to all participants and their guests on Sunday starting at 1:00 pm. The tour takes approximately 1 hour. Please meet in the 2nd floor lounge in Corbett Hall.

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ABSTRACTS
(in alphabetic order by speaker surname)

Speaker: **Mihai Anitescu** (Argonne)

Title: *Time stepping schemes with hard constraint subproblems for nonsmooth dynamics simulation*

Abstract: We investigate a set of linear complementarity based time stepping schemes for the simulation of multibody dynamics with contact and friction. We show that these schemes can be interpreted as the limit of implicit approaches for the smoothed dynamics equations. We discuss the complexity of solving the subproblems as well as the convergence properties of the schemes when the time step goes to 0.

Speaker: **Eric Barth** (Kalamazoo)

Title: *Assessing Thermostatting Methods in Biomolecular Dynamics*

Abstract: As models for the coupling of a particle system to a heat bath, extended variable formulations based on the work of Nosé are widely used to produce molecular dynamics trajectories at a fixed average temperature; In principle this class of methods samples from the canonical (NVT) ensemble. We will present results from simulations which show that these methods often achieve the specified average temperature at the expense of correct energy distribution in the system. We also will discuss the sensitivity of this behavior to thermostat parameters and present analysis which leads to a choice of optimal parameter values. We will describe the application of the new Recursive Multiple Thermostat (RMT) method of Sweet and Leimkuhler to biomolecular systems and show that this thermostatting scheme can address the sampling issues discussed here.

Speaker: **Stephen Bond** (UIUC)

Title: *Estimating Accuracy in Averages from Molecular Dynamics Simulation*

Abstract: In the context of molecular dynamics, accuracy and efficiency of a numerical method should be measured with respect to statistical averages, rather than deviations from an “exact trajectory”. In this talk I will survey some results from backward error analysis and show how (under certain assumptions) these results can be applied to compute estimates of the error in averages from molecular dynamics simulations. Results from several test problems will be explored including examples from constant temperature molecular dynamics.

Speaker: **Christophe Chipot** (Université Henri Poincaré)

Title: *Overcoming free energy barriers using an average force*

Abstract: Combining unconstrained molecular dynamics and the formalism of thermodynamic integration, potentials of mean force are determined in a rigorous and very effective fashion, without the *a priori* knowledge of the free energy surface to predict the biasing potentials that will help escaping from local free energy minima [1]. This approach relies upon the determination of an average force acting along the reaction coordinate from the individual forces exerted on the ensemble of atoms [2]. Application of this biasing force to the system virtually erases the rugosity of the free energy surface, thereby allowing all values of the reaction coordinate to be sampled with a uniform probability. The mathematical foundation of the method will be described, along with its implementation in the molecular dynamics program NAMD [3]. Next, applications that utilize reaction coordinates of different natures will be presented with a series of guidelines for the optimal performance of the method. Last, the challenging determination of the potential of mean force characterizing the reversible association of two transmembrane α -helices in a membrane mimetic will be discussed from both a methodological and a biological perspective [4].

References

- [1] Hénin, J.; Chipot, C., *J. Chem. Phys.*, **2004**, *121*, 2904–2914.
- [2] Darve, E.; Pohorille, A., *J. Chem. Phys.*, **2001**, *115*, 9169–9183.
- [3] Bhandarkar, M.; Brunner, R.; Chipot, C.; Dalke, A.; Dixit, S.; Grayson, P.; Gullingsrud, J.; Gursoy, A.; Humphrey, W.; Hurwitz, D. Krawetz, N.; Nelson, M.; Phillips, J.; Shinozaki, A.; Zheng, G.; Zhu, F.; *NAMD users guide, version 2.5*; Theoretical biophysics group, University of Illinois and Beckman Institute, 405 North Mathews, Urbana, Illinois 61801, **September 2003**.
- [4] Hénin, J.; Pohorille, A.; Chipot, C. Insights into the recognition and association of transmembrane α -helices. The free energy of α -helix dimerization in glycophorin A. *J. Am. Chem. Soc.* **2005** (submitted).

Speaker: **Eric Darve** (Stanford)

Title: *Adaptive Biasing Force Method for Molecular Dynamics and Monte-Carlo Simulations*

Abstract: I will review recent developments and applications of the Adaptive Biasing Force method (ABF). ABF is a technique to reduce the cost of free energy calculations by improving the sampling of configurational space of the system. It has a minimal statistical error and has been demonstrated to compare favorably to other techniques on several complex bio-molecular systems. I will discuss a new formulation of ABF with time derivatives and compare it with the original ABF formulation. An example will be presented for the insertion of an alpha-helix in a mimetic membrane and the association of two alpha-helices. We also present for the first time an application of ABF to Monte Carlo simulations and compare its efficiency with other fast Monte Carlo sampling techniques.

Speaker: **Wayne Hayes** (UC Irvine)

Title: *From Butterflies to Galaxies: reliable simulation of chaotic systems*

Abstract: The "Butterfly Effect" refers to the idea that a butterfly flapping its wings in Brazil can affect the weather over L.A. a few weeks later. The Butterfly Effect is an example of "sensitive dependence on small changes", which is exhibited by many nonlinear dynamical systems from integrated circuits to galaxies. When such systems are simulated on a computer, this sensitivity causes small numerical errors to become exponentially magnified, leading some to believe that trajectories of such simulations are the result of nothing but magnified noise. To justify the reliability of such simulations, we turn to the study of "shadowing". A "shadow" is an exact trajectory that stays close to a numerical trajectory for a long time, even in the face of sensitive dependence. From the standpoint of physics, a numerical trajectory that has a shadow can be viewed as an experimental observation of that shadow, which means that the dynamics observed in the simulation are real. This is a very strong statement of simulation reliability. However, verifying the existence of a shadow formally takes time $O(N^3)$, where N is the number of components in the system. In this talk I will outline how I demonstrated the existence of shadows of galaxy simulations in which $N = 10^8$, and discuss the possible application of shadowing to molecular dynamics simulations.

Speaker: **Gerhard Hummer** (NIH)

Title: *From Transition Paths to Transition States and Reaction Coordinates*

Abstract: The molecular mechanism of a reaction in solution is reflected in its transition-state ensemble and transition paths. The phase-space distributions in the equilibrium and transition-path ensembles are related through a Bayesian expression. This relation is used to identify transition states, optimize reaction coordinates, and estimate rate coefficients of rare molecular reactions. The theory is illustrated with applications to protein folding and the dipole reorientation of an ordered water chain inside a solvated carbon nanotube.

Speaker: **Toshiko Ichiye** (Georgetown)

Title: *Soft Sticky Dipole, Quadrupole, Octopole Model of Water*

Abstract: A new model of water based on a multipole expansion of the water potential is presented, which is a revised version of the soft-sticky dipole (SSD) model of water. The interaction potential is modified from a true multipole expansion including quadrupolar and octopolar terms to give a computational fast yet accurate model for liquid water, which is referred to here as the SSDQO model. The new model compares well with the standard three-point models such as SPC/E and TIP4P for thermodynamic and dynamic properties and yet is faster computationally. Moreover, the model is better than the three-point models in representing the tetrahedral structure of water.

Speaker: **Jesus Izaguirre** (Notre Dame)

Title: *Comparison of Multiscale Approaches to Molecular Dynamics and Sampling*

Abstract: I will compare two approaches to include knowledge of reaction or motion coordinates in molecular dynamics: one, using the coarse molecular dynamics approach advocated by W. Gear and collaborators; the second, using a combination of sampling of fast scales and accurate resolution of slow scales. I will present numerical tests on molecules, from alanine dipeptide to larger solvated biomolecules.

Speaker: **Mikko Karttunen** (Helsinki University of Technology)

Title: *Some current issues in coarse graining of soft matter systems*

Abstract: In this talk I will discuss some current issues in coarse graining of soft matter systems. There is currently quite a variety of techniques on the market for various systems, but there is no systematic method that can be applied to all cases. I will focus on combining microscopic MD approach with the Dissipative Particle Dynamics method. The advantages, pitfalls and future developments will be discussed.

Speaker: **Ben Leimkuhler** (Leicester)

Title: *Symplectic variable cell molecular dynamics*

Abstract: Molecular dynamics computations are often performed in a variable cell geometry, for either a constant pressure or constant stress tensor ensemble. The popular Parinello-Rahman technique has been shown to be inappropriate for soft-matter or liquid state simulations due to the possibility of anisotropic spreading or collapse. A variety of enhanced formulations have been proposed which regularize the cell structure, but the existing numerical methods for such formulations are poorly developed. In this article we describe a general symplectic numerical procedure for stable long term integration in the constant stress tensor ensemble.

Speaker: **Florence Lin** (USC)

Title: *Rotational motion in the dynamics of polyatomic molecules and proteins: an application of geometric mechanics and computation*

Abstract: By changing its shape while conserving angular momentum, a polyatomic molecule can return to its initial shape with a different orientation (as a somersaulting gymnast or a diver can do). Examples where this motion has been observed include the dynamics of protein molecules and the dynamics of a rotary molecular motor. Computational biophysicists have observed the overall rotation of a protein molecule at zero angular momentum due to the molecule's flexibility. A counter-rotary motion has been observed in the rotary F_o motor of ATP synthase. Using geometric mechanics, the net angle of overall rotation is explicitly described as the sum of a dynamic phase and a geometric phase. This extends to polyatomic and protein molecules. This is applied first to an atom-diatom molecule van der Waals complex in terms of Jacobi coordinates and then to polyatomic molecules in terms of more general coordinates. A computational result is obtained for an atom-diatom molecule complex using Hamilton's equations and a potential energy surface determined from experimental spectroscopic data. After taking the solvent effects into account either explicitly or by using the Langevin equation, potential applications of these results would include computational studies of biological macromolecules in solution.

Speaker: **Christian Lubich** (Tübingen)

Title: *A Poisson integrator for Gaussian wavepacket dynamics*

Abstract: The variational approximation of wavefunctions by Gaussian wavepackets is a widely used model to include quantum effects in molecular dynamics simulations. The corresponding finite-dimensional dynamical system inherits a Poisson (or non-canonically symplectic) structure from the Schrödinger equation by its construction via the Dirac-Frenkel variational principle. The variational splitting between kinetic and potential energy turns out to yield an explicit, easily implemented numerical scheme. This method is a time-reversible Poisson integrator, which also preserves the L^2 norm and linear and angular momentum. Using backward error analysis, we show long-time energy conservation for this splitting scheme. In the semi-classical limit the numerical approximations to position and momentum converge to those obtained by applying the Störmer-Verlet method to the classical limit system. Numerical experiments illustrate the theoretical results.

Speaker: **Roummel Marcia** (Wisconsin)

Title: *Predicting protein interactions using the Docking Mesh Evaluator*

Abstract: The Docking Mesh Evaluator (DoME) is a software package for protein docking and energy evaluation. It uses fast energy evaluation methods and an optimization scheme to predict the docked configurations of proteins with DNA, ligand, and other macromolecules. Its energy model uses van der Waals energy terms, Yukawa potentials to describe electrostatic energy, hydrogen bonds, and desolvation energy terms. Global optimization energy methods were developed to determine the lowest function value of this energy model. In particular, the General Convex Quadratic Approximation method constructs a sequence of convex underestimators to a collection of local minima to predict possible areas of low energies. Initial scanning of the energy landscape for favorable configurations as initial seeds for underestimation is used to improve algorithm performance. This coupled use of scanning and optimizing has been shown to be more effective in determining points of low energy values than scanning or optimizing alone. We present some results from a standard benchmarking set for testing protein-protein docking algorithms.

Speaker: **Eike Meerbach** (Berlin)

Title: *TBA*

Speaker: **Dan Negrut** (Argonne)

Title: *On an Iterative Parallel Algorithm for Implicit Numerical Integration in Molecular Dynamics: a Cartesian Approach*

Abstract: There are two schools of thought when it comes to the formulation framework in which the Molecular Dynamics problem is set. One favors the Cartesian representation of the problem, while the second embraces the internal-coordinates, or torsion-angle dynamics representation. The approaches based on internal coordinates have gained momentum in recent years due to a reduced number of equations that it leads to. If the well established (more than three decades by now) mechanical system simulation field is to indicate which direction should be pursued, the outcome is inconclusive. The two largest mechanical system virtual prototyping companies both use the Cartesian formulation by now for more than 30, and 20 years, respectively. The number three and four companies in the business (revenue ranked) are newer companies and use the internal-coordinates representation. While there are certain classes of problems where the latter companies have an edge, the jury is still out in so far which approach should be embraced.

Within the Cartesian formulation framework, the talk starts by briefly outlining an implicit integration scheme for A-stable variable step numerical integration of the MD problem. The focus moves on to the linear algebra component that is essential for an efficient implementation of the integrator. The proposed iterative method leverages structure (topology) information for fast linear algebra computation. A preconditioned parallel sparse iterative algorithm is considered for computing the Lagrange multipliers and resolving the associated constraints. The topology of the system is showed to play an important role in the numerical solution as it induces parallel computational threads that start in the equation formulation and continue

through the numerical algorithms. In spite of using a Cartesian formulation framework, the linear algebra algorithm results in order $O(b)$ effort, where b is the number of bonds (distance and angle) constrained in the problem. This performance is on par with the effort required in the internal-coordinates representation, the caveat being that the latter is significantly more challenging to formulate, implement, and maintain.

Speaker: **Radford Neal** (Toronto)

Title: *Hamiltonian Importance Sampling*

Abstract: Importance sampling uses points drawn with probability density $q(x)$ to estimate expectations with respect to the distribution with density $p(x)$ using a weighted average, with weights proportional to $p(x)/q(x)$. This technique typically fails for high-dimensional problems, because it is too hard to find an easily-sampled $q(x)$ that is close enough to $p(x)$, and for which the density $q(x)$ can easily be computed. I will show how this problem can be overcome using a $q(x)$ that is defined in terms of Hamiltonian dynamics. For a molecular system, we sample particle positions uniformly over some (wrapped-around) region, and also sample momenta for these particles from their distribution at a high temperature. We then simulate Hamiltonian dynamics for this system, while periodically multiplying the momenta by some factor slightly less than one, which eventually cools the system to whatever temperature, T , we are interested in. This procedure defines a distribution $q(x)$, which can be used to estimate expectations with respect to $p(x)$, the canonical distribution at temperature T . Crucially, for each sampled x , we can compute $q(x)$, and hence the appropriate weight to attach to this point in the average: The density of the initial point sampled from the high-temperature distribution is easily calculated; since Hamiltonian dynamics conserves phase space volume, the density of a point found after simulating Hamiltonian dynamics for some time is the same as that of the original point; and finally, multiplying a momentum variable by a factor less than one simply increases the probability density of the resulting point by the same factor. I explain some elaborations needed to apply this idea in practice, and demonstrate its use to find canonical expectations and the partition function for a system of Lennard-Jones particles.

Speaker: **William Newman** (UCLA)

Title: *Brouwer's Law: Optimal Multistep Integrators for Celestial Mechanics*

Abstract: The integration of Newton's equations of motion for self-gravitating systems, particularly in the context of our Solar System's evolution, remains a paradigm for complex dynamics. We implement Störmer's multistep method in backward difference, summed form and perform arithmetic according to what we call "significance ordered computation." We achieve results where the truncation error of our 13th order integrator resides below machine (double) precision and roundoff error accumulation is strictly random and not systematic. Our integrations of the outer Solar System are such that the positions of the major planets are known with an estimate error of no more than 2° error after 10^9 years, a precision unmatched by earlier investigations. Further, we show the outer Solar System is not chaotic, as has previously been reported, but rather computational errors in positions grow no faster than $t^{3/2}$ conforming with existing models for stochastic error growth in an otherwise well-behaved ordinary differential equation system.

Speaker: **Harald Posch** (Vienna)

Title: *Lyapunov Modes and Phase-Space Fractals for Particle Systems*

Abstract: Exponentially-growing tangent-space perturbation associated with the small positive Lyapunov exponents of many-particle systems exhibit coherent stationary patterns in physical space, to which we refer as "Lyapunov modes". They were first observed for hard-disk fluids in one, two and three dimensions. Using refined Fourier-transformation methods, we demonstrate that they exist also in soft-disk systems. We discuss the symmetry properties and the dynamics of the modes. In addition, we study many-particle systems in stationary nonequilibrium states and review some recent results on the entropy production and the associated phase-space fractals. Both dynamical and stochastic thermostats are considered.

Speaker: **Sebastian Reich** (Potsdam)

Title: *The Targeted Shadowing Hybrid Monte Carlo (TSHMC) Method*

Abstract: Following recent publications by Izaguirre & Hampton and Attard as well as work of one of the authors on dissipative particle dynamics and modified equations, we suggest a modified Metropolis criterion and a more flexible momentum update to improve the acceptance rate and the flexibility of the thermal coupling in standard hybrid Monte Carlo simulations.

Speaker: **Christopher Roland** (NCSU)

Title: *Distributed Multipole Methods for Accurate Electrostatics in Large-Scale Biomolecular Simulations*

Abstract: An accurate and numerically efficient treatment of electrostatics is essential for biomolecular simulations, in particular, when a smooth interface to quantum chemical descriptions is needed. Force fields used in biomolecular simulations such as AMBER and CHARMM assign “partial charges” to every atom in a simulation in order to model the interatomic electrostatic forces. The respective charge values are obtained via least-squares fitting to the Coulombic potential produced by quantum chemical procedures. Unfortunately, the fitting procedure for large, conformationally flexible molecules is under-determined, which is a major source of errors. There are two main problems associated with the treatment of classical electrostatics: (i) how does one eliminate artifacts associated with the point charges as used in force fields, and thereby improve the electrostatic potentials in a physically meaningful way?; (ii) how does one efficiently simulate the very costly long-range electrostatic interactions? Here, we present results on a recently developed distributed multipole method. This formalism which is based either on the Particle-Mesh Ewald summation method or on a multigrid method can treat interactions between electrostatic multipoles up to hexadecapoles without prohibitive additional computational costs. The required multipoles may be effectively computed via a new formalism based on maximally localized Wannier functions. The importance of these methods for large scale biomolecular simulations will be discussed.

Speaker: **Tony Shardlow** (Manchester)

Title: *Dissipative Particle Dynamics*

Abstract: Dissipative Particle Dynamics is a system of stochastic differential equations (SDEs) used to model multi phase fluids at a mesoscopic level, introduced originally by researchers at Shell. We will discuss the numerical solution and ergodicity of this and related systems of SDEs.

Speaker: **Robert Skeel** (Purdue)

Title: *What Makes Molecular Dynamics Work?*

Abstract: Temporal discretization of deterministic molecular dynamics (MD) is problematic due to the long simulation times and lack of dissipation. A general treatment for MD must be based on randomness in the initial values and the concept of weak convergence from stochastic differential equations. Weak convergence requires that expectations be accurately computed for smooth distributions of initial values. In this setting it is plausible that accurate solutions can be obtained for very long intervals of time. There remain questions concerning the accuracy of different numerical integrators in this weak sense, and these questions are explored. In the case of ergodic Hamiltonian systems, evidence suggests that consistent integrators give convergent results on very long intervals if the integrator nearly conserves energy on very long intervals and conserves volume in phase space. However, for certain practical reasons it seems that the stronger property of being symplectic is needed, and this is explained.

Speaker: **John Straub** (Boston)

Title: *Vibrational energy relaxation in proteins*

Abstract: When a protein is excited by ligand binding, ATP attachment, or laser pulses, there occurs vibrational energy relaxation (VER). Energy initially “injected” into a localized region flows to the rest of the protein and surrounding solvent. VER in large molecules (including proteins) itself is an important problem for chemical physics. Even more significant is the challenge to relate VER to fundamental reaction processes, such as a conformational change or electron transfer of a protein, associated with protein function. The development of an accurate understanding of VER in proteins is an essential step toward the goal of controlling protein dynamics.

Here VER of a selected mode in cytochrome c is studied using two theoretical approaches. One is the equilibrium simulation approach, with quantum correction factors, and the other is the reduced model approach, which describes the protein as an ensemble of normal modes interacting through nonlinear coupling elements. Both methods result in similar estimates of the VER time (sub picosecond) for a CD stretching mode in the protein at room temperature. The theoretical predictions are in accord with the experimental data of Romesberg's group. A perspective on future directions for the detailed study of time scales and mechanisms for VER in proteins is presented.

Speaker: **Andrew Stuart** (Warwick)

Title: *Infinite Dimensional MCMC Methods*

Abstract: There are a wide variety of sampling problems which are infinite dimensional in character. Examples include transition path sampling in chemistry and nonlinear filtering in signal processing. In both these examples the object to sample is a path in time, and is hence infinite dimensional. We describe an abstract MCMC method for sampling such problems, based on generalizing the Metropolis adjusted Langevin algorithms to infinite dimensions. This leads naturally to the study of stochastic reaction-diffusion equations which, in their invariant measure, sample from the required distribution. Furthermore, the study of preconditioning in this context leads to some interesting new infinite dimensional semilinear evolution equations, which are not generated by an analytic semigroup possessing a smoothing property.

Speaker: **Christopher Sweet** (Leicester)

Title: *TBA*

Speaker: **Michael Tretyakov** (Leicester)

Title: *Computing ergodic limits for Langevin equations*

Abstract: We develop an approach to computing averages with respect to the invariant law for Langevin-type equations. To evaluate ergodic limits for Langevin-type equations, one faces with two essential computational difficulties. The first one is connected with the necessity to integrate Langevin equations over long time intervals, especially when dissipation is small. The second difficulty is caused by the fact that in cases of physical interest Langevin equations have nonglobal Lipschitz coefficients; this can imply an explosive behavior of approximate trajectories. The first difficulty is overcome by using quasi-symplectic integrators which preserve some important structural properties of Langevin equations. To avoid the second difficulty, we exploit the concept of rejecting explosive trajectories which does not require from numerical methods to be ergodic and even convergent in the nonglobal Lipschitz case. The developed approach together with quasi-symplectic integrators gives a powerful tool for computing ergodic limits for Langevin-type equations. A special attention is paid to the case when the invariant measure is known (e.g., when this measure is Gibbsian). Some computer experiments with three model problems (Van der Pol's equation with additive noise, one-dimensional arrays of oscillators in thermal equilibrium, and a physical pendulum with linear friction and additive noise) are presented. The talk is based on a joint paper with G. N. Milstein.

Speaker: **Mark E. Tuckerman** (NYU)

Title: *Molecular dynamics with long time steps: Analysis and design of non-Hamiltonian dynamical systems*

Abstract: Biological macromolecules are characterized by a wide range of time scales ranging over 12-15 orders of magnitude from a few tens of femtoseconds, representing, for example, C-H and N-H bond stretching to the millisecond-second time scale for the formation of biologically active folded structures in proteins and nucleic acids. Bridging these time scales is a major challenge in the theoretical modeling of biological systems. Currently, molecular dynamics calculations, one of the most widely used approaches, are fundamentally limited in their time discretization parameter or time step to a few femtoseconds by so called resonance phenomena that arise when multiple time scale integration techniques are employed. In this talk, it will be shown how non-Hamiltonian equations of motion can be employed to overcome

resonance problems, thereby allowing time steps as large as 100 fs or more to be used in simulations based on all-atom force fields. In the course of this talk, techniques for analyzing the phase space distribution generated by non-Hamiltonian dynamical systems will be reviewed and applied to show that, despite the large time steps employed, the correct distribution is obtained. Applications to flexible water models and large proteins in vacuo will be presented.

Speaker: **Paul Tupper** (McGill)

Title: *The Shadow Hamiltonian in Molecular Dynamics*

Abstract: When the Verlet method is used to perform Molecular Dynamics simulations, the trajectory of the original Hamiltonian system is not, of course, computed exactly. However, we can formally write the numerical method as exactly solving a modified system with a perturbed Hamiltonian function which is known as the *Shadow Hamiltonian*. Unfortunately, the Shadow Hamiltonian is only expressed as a non-convergent asymptotic series. Until recently it was expected that the Shadow Hamiltonian series could be truncated at a particular optimal point, and that adding successive terms would soon cause explosively bad approximations. Suprisingly, recent work by Skeel et al. suggest instead that even though the asymptotic series does not converge, neither does it diverge to infinity. Rather, the addition of successive terms appears to maintain a good approximation for arbitrarily many terms. I will discuss this evidence and the open problems that it suggests.