Separable Shadow Hybrid Monte Carlo: An efficient propagator for macromolecules.

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The sampling problem

- Molecular dynamics (MD) is an important sampling method for biomolecules as it can easily generate long trajectories in phase-space.
- MD methods introduce a bias which depends on the integration time-step, even when using symplectic methods such as Verlet.
- Markov chain Monte Carlo methods are rigorous sampling methods but generating successive position sets is a challenge for large molecules.
- Hybrid Monte Carlo (HMC) combines these methods to give rigorous sampling and good exploration of phase-space.
- HMC scales poorly with system size.

Hybrid Monte Carlo (HMC) method

Given a separable probability density function, for example a Hamiltonian model sampling from the canonical ensemble

$$\begin{aligned}\rho(X,P) &\propto \exp(-\beta\mathcal{H}) = \exp(-\beta\mathcal{T})\exp(-\beta\mathcal{U}) \\ &\propto \rho_x(X)\rho_p(P)\end{aligned}$$

With mapping $(X',P') = \Psi(X,P)$, the HMC method is:

- MG step: Generate P from ρ_p
- MD step: (a) mapping $(X',P') = \Psi(X,P)$
  (b) Accept with probability
  $\min\{1, \rho(X',P')/\rho(X,P)\}$
  (c) If rejected chose X

The acceptance probability depends on $\sigma^2_{\mathcal{H}} \propto N$.

Shadow Hamiltonians

- Since the acceptance ratio of HMC depends on N it scales poorly with system size, limiting it use for Biomolecules.
- For symplectic methods it can be shown that the MD numerical results are the exact solution for a 'Shadow Hamiltonian'.
- The value of the Shadow Hamiltonian is constant for all phase-space variables and hence the probability of acceptance would be 1.
- The generation of P is now from a probability density which we have no expression for.
- Need to calculate the Shadow Hamiltonian easily.

Shadow momenta/Hamiltonian generation

- By a simple modification to the Hamiltonian the equation $\mathcal{H}_{[2k]}(x(t)) = \frac{1}{2}\dot{x}(t)^T \mathbf{J} x(t)$ can be used to calculate the Shadow Hamiltonian. The $\dot{x}(t)$ term can be calculated using an interpolative scheme to the desired order of accuracy.
- To generate a set of momenta from the probability density function from the Shadow phase-space the following scheme is used:
  Define the new Hamiltonian $\tilde{\mathcal{H}} = \min\{\mathcal{H}, \mathcal{H}_{[2k]} - c\}$
  (a) Generate P from ρ_P
  (b) Accept with probability

$$\min\{1, \exp(-\beta(\mathcal{H}_{[2k]} - c - \mathcal{H}))\}$$

  (c) Repeat until P accepted

Shadow Hybrid Monte Carlo (SHMC)

The Shadow hybrid Monte Carlo method can be defined as:

- MG step: Generate P from $\tilde{\rho}(X,P) \propto \exp(-\beta\tilde{\mathcal{H}})$
- MD step: (a) mapping $(X', P') = \Psi(X,P)$

  (b) Accept with probability

  $$\min\{1, \tilde{\rho}(X',P')/\tilde{\rho}(X,P)\}$$

  (c) If rejected chose X
- Since $\tilde{\mathcal{H}}$ is nearly conserved by the numerical method the acceptance at the MD stage will be very high.
- The acceptance rate of the MG step will be dependent on the constant c.
- Any observable A must be reweighted to obtain the correct canonical distribution so that

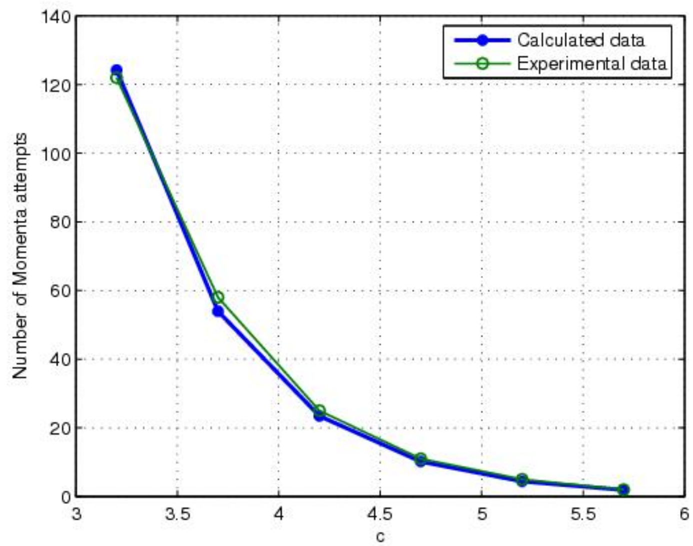
  $$\langle A \rangle = \sum_i \omega_i A_i / \sum_i \omega_i, \;\; \omega_i = \exp(-\beta(\mathcal{H} - \tilde{\mathcal{H}}))$$

Selection of 'c' parameter for MG stage

The acceptance ratio R_{MG} at the MG stage will increase for large *c* and we can show

$$R_{MG} \approx \exp\left(\frac{1}{2}\beta(2c + \beta\sigma^2_{\Delta\mathcal{H}} - 2\mu_{\Delta\mathcal{H}})\right)$$

This will be a significant factor as it takes several MD steps to calculate the Shadow Hamiltonian.



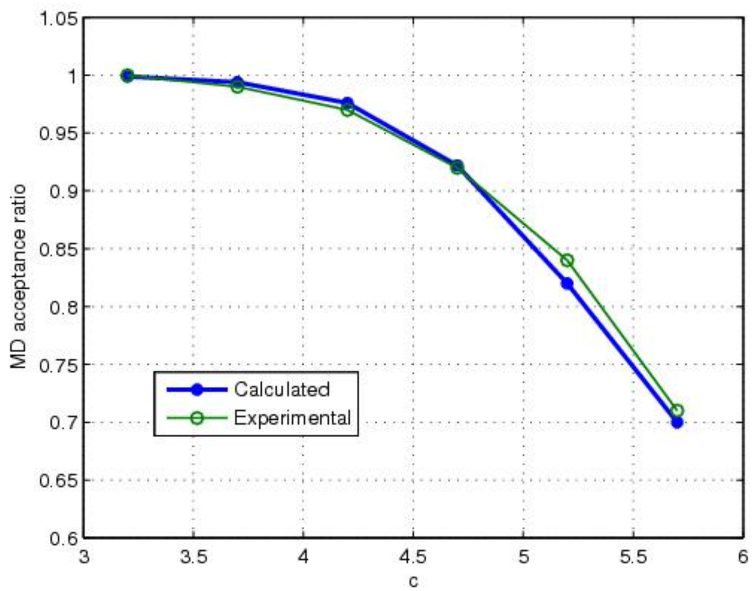
Selection of 'c' parameter for MD stage

The acceptance ratio R_{MD} at the MG stage will degrease for large *c* and we can show

$$R_{MD} = (1 - S_H) + 0.5 S_H^2$$

Where

$$S_H = \frac{1}{2} - \frac{1}{2}\mathrm{erf}\left(\frac{\mu_{\Delta\mathcal{G}} - c}{\sqrt{2}\sigma_{\Delta\mathcal{G}}}\right)$$



Leapfrog Method Shadow Hamiltonian

The ‘truncated’ shadow Hamiltonian for the Leapfrog method is

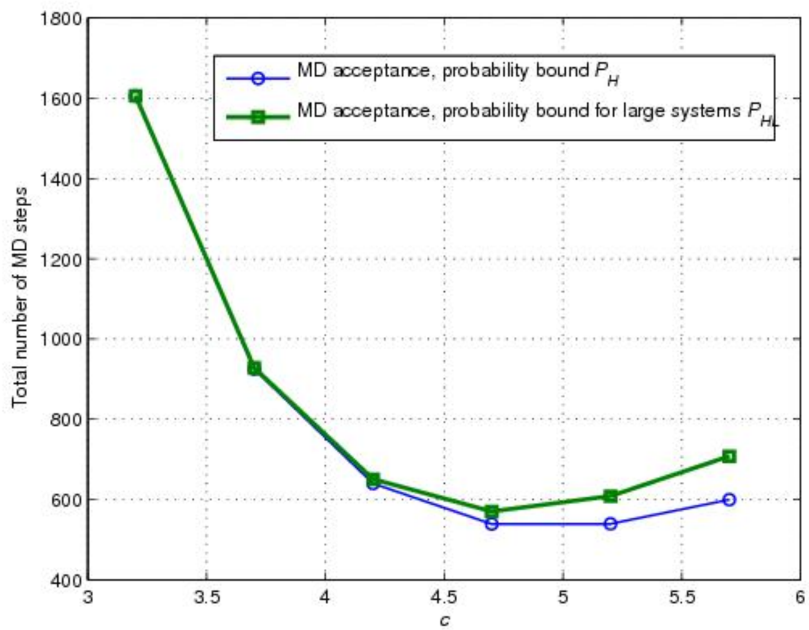
TexPoint Display

Conclusions

- SHMC can be used for efficient sampling of biomolecules without introducing the bias associated with MD.
- SHMC can be used for systems which are orders of magnitude larger than HMC can achieve, typically over 20,000 atoms.
- The *c* parameter introduced by SHMC can be calculated explicitly with data from some additional MG stages.
- The increase in variance observed when re-weighting observables from SHMC can be controlled easily by selecting the step-size, a fourth order relationship for Verlet.

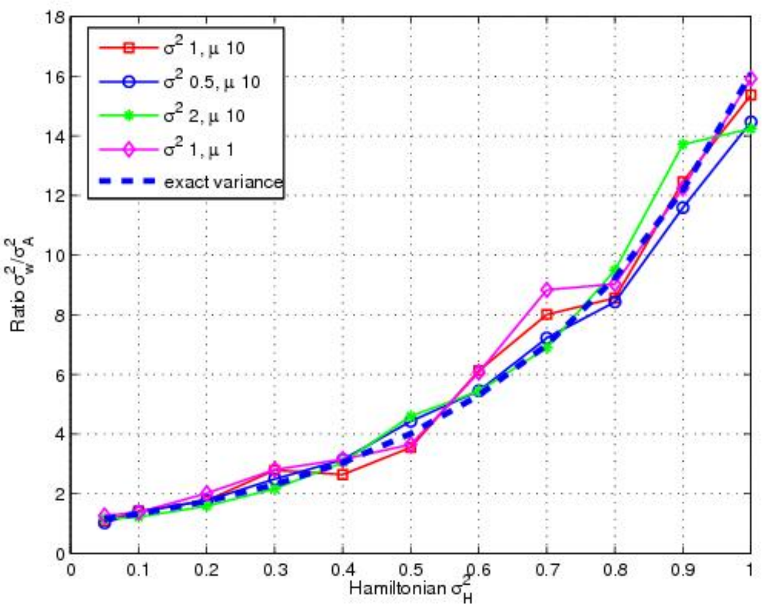
Optimum 'c' parameter

Since the choice of *c* is a compromise we can find an optimum depending on the number of MD steps n_{MD} and MG steps n_{MG} and the variance of the Hamiltonian $\sigma^2_{\Delta\mathcal{H}}$ to give the total steps $n_s = \frac{n_{MG}}{R_{MG}} + \frac{n_{MD}}{R_{MD}}$



Variance of observables for SHMC

The reweighting stage of the SHMC method can be shown to increase the variance of the observable σ_ω^2 according to $\sigma_\omega^2 = \exp(\beta^2\sigma_{\mathcal{H}}^2)\sigma_A^2$ where σ_A^2 is the original variance and $\sigma_{\mathcal{H}}^2$ the variance of the Hamiltonian as seen in the figure below.



We can control $\sigma_{\mathcal{H}}^2$ by changing the step-size according to

$$\Delta t_T = \Delta t_H \sqrt{\frac{\sigma_T}{\sigma_{\mathcal{H}}}}$$

SHMC compared to HMC for large N

We can now compare the efficiency of the SHMC and HMC methods for different *N*, assuming $\sigma^2_{\Delta\mathcal{H}} \propto N$, compared to the Hamiltonian variance for a box of 216 water molecules.