Published in final edited form as:

J Chem Theory Comput. 2016 April 12; 12(4): 1449–1458. doi:10.1021/acs.jctc.5b00706.

Multiple Time-Step Dual-Hamiltonian Hybrid Molecular Dynamics — Monte Carlo Canonical Propagation Algorithm

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Abstract

A multiple time-step integrator based on a dual Hamiltonian and a hybrid method combining molecular dynamics (MD) and Monte Carlo (MC) is proposed to sample systems in the canonical ensemble. The Dual Hamiltonian Multiple Time-Step (DHMTS) algorithm is based on two similar Hamiltonians: a computationally expensive one that serves as a reference and a computationally inexpensive one to which the workload is shifted. The central assumption is that the difference between the two Hamiltonians is slowly varying. Earlier work has shown that such dual Hamiltonian multiple time-step schemes effectively precondition nonlinear differential equations for dynamics by reformulating them into a recursive root finding problem that can be solved by propagating a correction term through an internal loop, analogous to RESPA. Of special interest in the present context, a hybrid MD-MC version of the DHMTS algorithm is introduced to enforce detailed balance via a Metropolis acceptance criterion and ensure consistency with the Boltzmann distribution. The Metropolis criterion suppresses the discretization errors normally associated with the propagation according to the computationally inexpensive Hamiltonian, treating the discretization error as an external work. Illustrative tests are carried out to demonstrate the effectiveness of the method.

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The authors declare no competing financial interest.

I. INTRODUCTION

Molecular dynamics (MD) simulations offer a powerful avenue to study the properties of complex atomic and molecular systems.¹ In classical MD the potential energy surface is represented by a molecular mechanical (MM) force field constructed from simple differentiable functions.² This type of approximation is necessary to achieve the desired computational efficiency needed to simulate very large systems for long time scales. More accurate representations of the electronic behavior of a system can be obtained by using quantum mechanical (QM) or hybrid QM/MM approaches.³ However, such sophisticated *ab initio* models evolve on a complex energy surface. Their dynamic propagation often requires a small time-step, which can become computationally prohibitive in MD simulations. For this reason, various strategies have been sought to achieve an adequate sampling by accelerating the exploration of configurational space.

A common method to improve sampling in MD is to use multiple time-step algorithms such as RESPA (*RE*ference *S*ystem *P*ropagator *A*lgorithm).⁴⁻⁷ RESPA assumes that a full system Hamiltonian can be separated into its fast and slowly varying components.⁸⁻¹¹ Fast varying forces are evaluated every step, while slowly varying forces are updated less frequently to reduce computational cost. Similar splitting schemes have been applied to the potential energy to accelerate Monte Carlo (MC) propagators.¹² Versions of RESPA have been derived for both the NVE and NVT ensembles.¹³ However, in practice, the method exhibits systematic errors for larger time-steps and increased numbers of evaluations of the fast varying forces for each evaluation of the slow ones.^{13,14} For this reason, the original algorithm does not obey detailed balance to acceptable accuracy^{15,16} and was reported to suffer from resonance issues,¹⁷⁻¹⁹ some of which were addressed by recent work.²⁰⁻²⁷

Multiple time-step dynamics have recently been coupled with MC to address RESPA-related resonance issues; the performance improvement over conventional Langevin dynamics remained low.²⁸ Here, we propose a multiple time-step integrator based on a dual Hamiltonian and a hybrid method combining molecular dynamics and Monte Carlo to sample the canonical NVT ensemble. It is based on nonequilibrium molecular dynamics (neMD), in which the system is steered from one state to another. Hybrid nonequilibrium Molecular Dynamics Monte Carlo (neMD-MC) methods were originally introduced for constant pH sampling,²⁹⁻³¹ but they have since been shown to be efficient general purpose algorithms.³²⁻³⁷ Of special interest in the present context is that the introduction of a Metropolis acceptance criterion³⁸ suppresses the discretization errors normally associated

with molecular dynamics.^{34,36,39-41} The essential idea is that the work done on the system by the discretization error can be thought of as an external work.

Our method is based on two similar Hamiltonians: a reference one in which we are interested and an alternative one to which we aim to shift the workload. For the method to be efficient, the latter potential should be far less computationally demanding than the former. Contrary to RESPA, we do not assume that the reference Hamiltonian has slowly varying components. This is useful because the partitioning for a given system can be nonobvious, varying from local interactions versus long-range electrostatics in dense matter⁴² to electron correlation versus the underlying Hartree–Fock wave function in *ab initio* molecular dynamics (AIMD).⁶ Instead we assume that the *difference* between the two Hamiltonians is slowly varying. Then we can express the reference Hamiltonian as a sum of the second Hamiltonian and the slowly varying difference term. Approximations similar in motivation have been successfully applied to accelerate iterative optimizations, including energy minimization and finite temperature reaction path refinement.^{43,44} Earlier work has shown that these schemes effectively precondition nonlinear differential equations for dynamics by reformulating them into a recursive root finding problem^{45,46} that can be solved by propagating a correction term through an internal loop, analogous to RESPA.

The paper is organized as follows. In the next two sections, we outline the theory behind dual Hamiltonian based canonical sampling and describe the corresponding Langevin dynamics and the computational setup. We first introduce the (*Dual Hamiltonian Multiple Time Step*) (DHMTS) algorithm, which can be used when the difference between a high level theory Hamiltonian and a computationally inexpensive Hamiltonian is slowly varying. We then introduce a hybrid MD-MC version of the DHMTS algorithm to ensure consistency with the Boltzmann distribution by enforcing detailed balance via a Metropolis acceptance criterion.³⁸ We then discuss our results obtained from one-dimensional model systems as well as *ab initio* gas phase clusters. We report speedups and various restrictions as seen in model systems as well as two different AIMD simulations. We demonstrate that computationally “inexpensive” semiempirical Hamiltonians can be used to accelerate trajectories of computationally more demanding DFT or MP2 Hamiltonians even for reactive chemical systems far from equilibrium. We conclude by highlighting future directions, including possibilities within the framework of emerging force matching and adaptive procedures in which the information accumulated on-the-fly progressively improves the parameters of the initial model.

II. THEORY

The standard Hamiltonian in Cartesian coordinates is

$$\mathcal{H} = \frac{1}{2} \mathbf{p}^T \mathbf{M}^{-1} \mathbf{p} + U(\mathbf{r}) \quad (1)$$

where $\mathbf{r}$ is the coordinates, $\mathbf{p}$ is the momenta, $\mathbf{M}$ is the mass matrix, and U is the potential energy.

Let the reference potential U_0 , forces $\mathbf{F}_0$, and a corresponding Liouville operator iL_0 be derived from an accurate and computationally expensive Hamiltonian $\mathcal{H}_0$, and U_1 , $\mathbf{F}_1$, and iL_1 be derived from an approximate and computationally inexpensive one, $\mathcal{H}_1$. Here, the Liouville operator is expressed as

$$iL = \mathbf{p}^T \mathbf{M}^{-1} \frac{\partial}{\partial \mathbf{r}} + \mathbf{F} \frac{\partial}{\partial \mathbf{p}} \quad (2)$$

The operator can be made measure-preserving to sample different ensembles.⁴⁷ The reference operator, iL_0 , can be separated into two terms

$$iL_0 = iL_1 + i(L_0 - L_1) \quad (3)$$

where iL_1 and $i(L_0 - L_1)$ are noncommuting. Using Trotter factorization,^{48,49} the classical propagator $e^{iL_0 t}$ can be expressed as

$$e^{iL_0 \Delta t} \approx e^{i(L_0 - L_1) \Delta t / 2} e^{iL_1 \Delta t} e^{i(L_0 - L_1) \Delta t / 2} + \mathcal{O}(\Delta t^3) \quad (4)$$

The form of eq 2 permits further simplification such that

$$i(L_0 - L_1) = (\mathbf{F}_0 - \mathbf{F}_1) \frac{\partial}{\partial \mathbf{p}} \quad (5)$$

The factor $e^{iL_1 t}$ varies rapidly relative to $e^{i(L_0 - L_1) t/2}$ and therefore prevents use of a large time-step t . To address this issue, we divide t into n_{inner} steps of length δt . We then evolve L_1 for n_{inner} steps for each evaluation of L_0 . To this end, we apply an additional Trotter factorization and separate iL_1 into iL_{1r} and iL_{1p} , where $iL_1 = iL_{1r} + iL_{1p}$

$$e^{iL_0 \Delta t} \approx e^{(\mathbf{F}_0 - \mathbf{F}_1) \frac{\partial}{\partial \mathbf{p}} \Delta t / 2} \left[e^{iL_{1p} \delta t / 2} e^{iL_{1r} \delta t} e^{iL_{1p} \delta t / 2} \right]^{n_{\text{inner}}} \times e^{(\mathbf{F}_0 - \mathbf{F}_1) \frac{\partial}{\partial \mathbf{p}} \Delta t / 2} + \mathcal{O}(n_{\text{inner}} \delta t^3) \quad (6)$$

When eq 6 is used as a single integration step and $e^{iL_{1p} \delta t / 2}$ and $e^{iL_{1r} \delta t}$ have valid functional forms that preserve temperature, the resulting propagator approximately samples the Boltzmann distribution

$$\rho_{eq}(\mathbf{r}, \mathbf{p}) = \frac{e^{-\beta \mathcal{H}_0(\mathbf{r}, \mathbf{p})}}{\int d\mathbf{r} d\mathbf{p} e^{-\beta \mathcal{H}_0(\mathbf{r}, \mathbf{p})}} \quad (7)$$

for small enough time-steps δt .

It is worth noting that when $\mathcal{H}_1$ corresponds to the fast varying forces of $\mathcal{H}_0$, then this propagator reduces to RESPA. Here we explore the general case of $\mathcal{H}_0$ and $\mathcal{H}_1$ that are similar to each other but not necessarily separated in time scales.

For most discretized propagators, error is known to scale with time-step δt . For a RESPA-like propagator, error further goes up with the number of inner loop steps n_{inner} , as shown in eq 6, and the difference between iL_0 and iL_1 . This limitation leads to an unavoidable trade-off between the potential speedup and the integration error. Fortunately, recent work has shown that, for a time-independent Hamiltonian, finite time-step Langevin integrators can be thought of as driven, nonequilibrium physical processes.^{34,36} This numerical error can typically be corrected on-the-fly by enforcing detailed balance via a Metropolis acceptance criterion. Constant temperature RESPA-like symplectic propagators are similar to Langevin integrators, except they are discretized twice. Therefore, RESPA-like propagators can also be corrected by taking into account an effective “error work”, δW_e (also called the “shadow work”).^{36,50,51} The acceptance criterion can then be applied after each dynamics step eq 6. The exact criterion is given by eq 18 in ref 36 as

$$T_a = \min [1, \exp \{-\beta (\Delta E - Q_{\text{real}})\}] \quad (8)$$

where E is the total energy change during the entire dynamics step, and Q_{real} is the energy difference accumulated from temperature conserving stochastic substeps, i.e., heat exchanged between the bath and the system.³⁶

In practice, the Langevin equations are integrated by following a predefined sequence of *substeps* that are repeated every time-step δt . The resulting trajectory is continuous in time and contains error characteristic to the underlying choice of splitting, known as the propagator. Here, we work with the VVVR (Velocity Verlet with Velocity Randomization) propagator^{51,52} and the so-called BAOAB (position-momenta-randomization-momenta-position) propagator of Leimkuhler and Matthews.⁵² Both VVVR and BAOAB require a single force evaluation per time-step, typically the most CPU-intensive operation in a molecular simulation. In our VVVR implementation, one integration time-step is composed of the following substeps

$$\tilde{\mathbf{p}}_i \left(t + \frac{1}{2} \delta t \right) = \mathbf{p}_i(t) \cdot e^{-\frac{1}{2} \gamma \delta t} + \sigma \sqrt{\frac{1 - e^{-\gamma \delta t}}{2\gamma}} \cdot \mathbf{N}(0, 1) \quad (9a)$$

$$\mathbf{p}_i \left(t + \frac{1}{2} \delta t \right) = \tilde{\mathbf{p}}_i \left(t + \frac{1}{2} \delta t \right) + \frac{1}{2} \mathbf{f}_i(\mathbf{r}(t)) \cdot \delta t \quad (9b)$$

$$\mathbf{r}_i(t + \delta t) = \mathbf{r}_i(t) + \frac{1}{m_i} \mathbf{p}_i \left(t + \frac{1}{2} \delta t \right) \cdot \delta t \quad (9c)$$

$$\tilde{\mathbf{p}}_i(t+\delta t) = \mathbf{p}_i\left(t+\frac{1}{2}\delta t\right) + \frac{1}{2}\mathbf{f}_i(\mathbf{r}(t+\delta t)) \cdot \delta t \quad (9d)$$

$$\mathbf{p}_i(t+\delta t) = \tilde{\mathbf{p}}_i(t+\delta t) \cdot e^{-\frac{1}{2}\gamma\delta t} + \sigma \sqrt{\frac{1-e^{-\gamma\delta t}}{2\gamma}} \cdot \mathbf{N}(0,1) \quad (9e)$$

where

$$\sigma = \sqrt{2\gamma m_i k_B T} \quad (10)$$

and γ is the friction coefficient, m_i is the mass of particle i , and $\mathbf{N}(0,1)$ is a vector of Gaussian random numbers with a mean of zero and standard deviation of one. Here, $\mathbf{p}_i$ and $\mathbf{r}_i$ are momenta and position vectors of particle i , and $\mathbf{f}_i$ is the total force exerted on particle i by all other particles in the system. Tilde and wide-tilde designate intermediate quantities. The BAOAB propagator, on the other hand, uses an alternative half-splitting scheme, which yields improved accuracy over Velocity-Verlet.⁵² Both positions and momenta are updated in two half-steps, and randomization is executed at the midpoint. Following the same notation from eq 9, BAOAB sequence is executed as

$$\tilde{\mathbf{p}}_i(t) = \mathbf{p}_i(t) + \frac{1}{2}\mathbf{f}_i(\mathbf{r}(t)) \cdot \delta t \quad (11a)$$

$$\mathbf{r}_i\left(t+\frac{1}{2}\delta t\right) = \mathbf{r}_i(t) + \frac{1}{2m_i}\tilde{\mathbf{p}}_i(t) \cdot \delta t \quad (11b)$$

$$\tilde{\mathbf{p}}_i(t+\delta t) = \tilde{\mathbf{p}}_i(t) \cdot e^{-\gamma\delta t} + \sigma \sqrt{\frac{1-e^{-2\gamma\delta t}}{2\gamma}} \cdot \mathbf{N}(0,1) \quad (11c)$$

$$\mathbf{r}_i(t+\delta t) = \mathbf{r}_i\left(t+\frac{1}{2}\delta t\right) + \frac{1}{2m_i}\tilde{\mathbf{p}}_i(t+\delta t) \cdot \delta t \quad (11d)$$

$$\mathbf{p}_i(t+\delta t) = \tilde{\mathbf{p}}_i(t+\delta t) + \frac{1}{2}\mathbf{f}_i(\mathbf{r}(t+\delta t)) \cdot \delta t \quad (11e)$$

For the sake of convenience and clarity, we used VVVR in the illustrative one-dimensional model system. The numerically superior scheme BAOAB was used for the detailed chemical simulations. It is important to emphasize that the present approach can be coupled with any integrator. The choice, however, may affect the cumulative error and, thus, the maximum number of inner loop iterations that can be used for a given pair of force fields.

In light of this information, we can express the present approach in operator notation as well. For VVVR-based inner loops we have

$$e^{iL_0\Delta t} \approx e^{(\mathbf{F}_0-\mathbf{F}_1)\frac{\partial}{\partial\mathbf{p}}\Delta t/2} \left[e^{iL_{OU}\delta t/2} e^{iL_{1p}\delta t/2} e^{iL_{1r}\delta t} e^{iL_{1p}\delta t/2} e^{iL_{OU}\delta t/2} \right]^{n_{\text{inner}}} e^{(\mathbf{F}_0-\mathbf{F}_1)\frac{\partial}{\partial\mathbf{p}}\Delta t/2} \quad (12)$$

and for BAOAB-based inner loops

$$e^{iL_0\Delta t} \approx e^{(\mathbf{F}_0-\mathbf{F}_1)\frac{\partial}{\partial\mathbf{p}}\Delta t/2} \left[e^{iL_{1p}\delta t/2} e^{iL_{1r}\delta t/2} e^{iL_{OU}\delta t} e^{iL_{1r}\delta t/2} e^{iL_{1p}\delta t/2} \right]^{n_{\text{inner}}} e^{(\mathbf{F}_0-\mathbf{F}_1)\frac{\partial}{\partial\mathbf{p}}\Delta t/2} \quad (13)$$

where operators $e^{iL_{1r}}$ and $e^{iL_{1p}}$ correspond to position and momentum updates at the computationally fast level of theory, respectively, and $e^{iL_{OU}}$ is velocity randomization. Furthermore, the effective time-step t is related to the inner loop time-step δt as $t = n_{\text{inner}} \cdot \delta t$.

Stochastic substeps, eq 9a, eq 9e, and eq 11c, conserve the temperature and do not affect the Metropolis acceptance criterion, since energy changes of such substeps appear in both E and Q_{real} . Therefore, one could alternatively propagate the inner loop deterministically and only perform stochastic substeps after applying a Metropolis acceptance criterion. In that case, the deterministic Liouville operator is

$$iL_1 = \mathbf{p}^T \mathbf{M}^{-1} \frac{\partial}{\partial \mathbf{r}} + \mathbf{F}_1 \frac{\partial}{\partial \mathbf{p}} \quad (14)$$

with

$$iL_{1r} = \mathbf{p}^T \mathbf{M}^{-1} \frac{\partial}{\partial \mathbf{r}} \quad \text{and} \quad iL_{1p} = \mathbf{F}_1 \frac{\partial}{\partial \mathbf{p}} \quad (15)$$

such that the MC acceptance criterion simplifies to

$$T_a = \min [1, \exp \{-\beta \Delta E\}] \quad (16)$$

where E is the cumulative energy change during the inner loop. We call this setup “deterministic-inner-loop”. Our simulations show that the deterministic-inner-loop algorithm improves acceptance rates without compromising the target distribution.

Symmetric two-end momentum reversal is used for MD-MC DHMTS to satisfy detailed balance condition.^{30,35,36} Under this prescription, all momenta are reversed *either* both before and after the inner loop *or* not reversed at all, both with equal probability. This prescription greatly reduces the chances of different regions in configurational space being isolated from one another.³⁵ However, symmetric momentum reversal can also lead to resonance problems, especially when using deterministic propagators. One solution is to recycle the decision of whether to reverse the momenta, through several consecutive inner loops. As long as the frequency of making new decisions is not correlated with configurational changes, detailed balance condition will be satisfied and resonance mitigated. We will refer to this algorithm as “tandem flip”.

Alternatively, one can skip applying the MC acceptance criterion and use $\langle T_a \rangle$ as an indicator of error, where $\langle \dots \rangle$ is a trajectory average. $\langle T_a \rangle$ close to 1 indicates that the Metropolis step can be abandoned altogether. This is the main difference between MD-MC DHMTS and DHMTS, the two algorithms illustrated in the next section. A pseudocode is given in the Appendix.

III. COMPUTATIONAL DETAILS

Here, we describe the various systems that we use to test the algorithms.

a). One-Dimensional Model System

We introduce a simple one-dimensional (1D) model system using two different potential energy surfaces $U_0(x)$ and $U_1(x)$

$$\begin{cases} U_0 = \frac{1}{2}x^2 \\ U_1 = \frac{9}{20}(x-2)^2 \end{cases} \quad (17)$$

as shown in Figure 1 (a). U_0 serves as a reference Hamiltonian, and U_1 serves as the preconditioner. Both potentials are functions of particle position x . The theoretical normalized distribution along x is

$$p(x) = \frac{e^{-U_0(x)/k_B T}}{\int dx e^{-U_0(x)/k_B T}} \quad (18)$$

which we aim to reproduce using our dual Hamiltonian schemes and a time-step $\delta t = 0.05$, thermal energy $k_B T 1.0$, particle mass 1.0, and collision rate 4.0. All 1D model simulations are run using in-house C++ scripts. Total length of each simulation is 10^7 steps.

We explore four different propagators:

1. dissipative Langevin dynamics VVVR for equilibration and reference,
2. large time-step VVVR such that $t = n_{\text{inner}} \delta t$,
3. MD-MC DHMTS, and
4. DHMTS.

b). Gas Phase Water Clusters

We simulated two *ab initio* gas phase water clusters, the deprotonated water trimer $(\text{H}_2\text{O})_2\text{OH}^-$ and a neutral water octamer $(\text{H}_2\text{O})_8$, using MD-MC DHMTS and DHMTS. Trajectories are collected and analyzed using in-house Python scripts. The Langevin propagator for stochastic substeps is BAOAB,⁵² a slightly modified version of VVVR. Deterministic substeps use Velocity-Verlet without any randomization. Single point energies and gradients are calculated via Gaussian 09, revision A.02.⁵³ For DFT runs, hybrid B3LYP⁵⁴ exchange correlation functional is used together with Dunning's correlation-consistent cc-pVDZ⁵⁵ basis set. For MP2 the earlier Pople type 6-31G(d,p) basis^{56,57} is used. Hartree-Fock and two semiempirical force fields, RM1⁵⁸ and PM6,⁵⁹ are chosen as preconditioners. The HF basis set is 3-21G. RM1 is not readily available in Gaussian 09; this force field is implemented by coupling RM1 parameters with their equivalent AM1 functional forms.

To prevent evaporation, spherical boundaries are applied. Any atom further from the origin beyond a cutoff distance r_{cutoff} experiences the potential

$$U_{\text{boundary}} = k_{\text{boundary}} (r - r_{\text{cutoff}})^2 \quad (19)$$

where r is the distance of the particle from the origin, and $k_{\text{boundary}} = 1.0 \text{ kJ/mol } \text{\AA}^2$. Cutoff radii are 3.5 and 3.85 $\text{\AA}$ for the trimer and the octamer, respectively. Clusters are equilibrated for 2.5 and 3.0 ps to $T = 298 \text{ K}$, respectively. For each case explored, 16 to 32 parallel trajectories are initialized from the same equilibrated positions and momenta but different random seeds.

IV. RESULTS AND DISCUSSIONS

a). One-Dimensional Model System

We first tested if all propagators reproduce the reference equilibrium distribution as we gradually increase n_{inner} from 1 to 100. Results are shown in Figure 2. For DHMTS and large time-step VVVR, simulated distributions agree with reference for when n_{inner} is lower than 10. As n_{inner} increases, DHMTS distributions gradually shift toward U_1 prediction,

while large time-step VVVR distributions flatten out as a result of accumulating error. MD-MC DHMTS distributions are always correct for the range of n_{inner} values explored.

In a second application, we tested propagator efficiencies (Table 1). We calculated the effective sample size by the spectral density at frequency zero estimated by fitting to an autoregressive model.⁶⁰⁻⁶² This metric has the advantage that effective sample size is independent from sampling frequency. Then we estimate speedup as

$$\eta = \frac{T_{\text{relax,VVVR}}}{T_{\text{relax}}} \times \frac{T_{\text{cpu}}(U_0) n_{\text{inner}}}{(T_{\text{cpu}}(U_0) + T_{\text{cpu}}(U_1) n_{\text{inner}})} \quad (20)$$

where T_{CPU} is the CPU time required to evaluate total energies and forces. To mimic the conditions involving a pair of high level Hamiltonians, we assume that the cost of expensive, reference level potential calculation is 10 times that of the cheaper preconditioner. For MD-MC DHMTS speedup can reach up to 9.0 for when n_{inner} is 20. For DHMTS speedup can reach 5.0 at $n_{\text{inner}} = 10$. Higher values of n_{inner} can cause sampling errors more than 5%. Efficiencies in MD-MC DHMTS are higher using deterministic-inner-loop and/or reversal schedule decided less frequently.

In our third and final application, we tested the effect of the potential surface on propagator efficiency. We redefine our model potentials as

$$\begin{cases} U_0 = \frac{1}{2}x^2 + \sin(2\pi x) \\ U_1 = \frac{9}{20}(x-2)^2 + \sin\left(\frac{3}{2}\pi x\right) \end{cases} \quad (21)$$

The added ruggednesses to both potentials violate our fundamental assumption that the difference between the Hamiltonians is slowly varying. As a result, MD-MC DHMTS still generates correct distribution but is no longer competitive against VVVR, as shown in Figure 3 and Table 2.

b). Deprotonated Water Trimer

Ambient deprotonated water trimer at the B3LYP/cc-pVDZ level of theory assumes a quasi 2-fold symmetry with two strong hydrogen bonds coordinating the hydroxide as in Figure 4. The cluster exhibits frequent proton hops such that the “defect proton” carrier switches identity. Transfers typically occur along the shortest hydrogen bond, while the third monomer coordinates at least one of the exchanging partners. RM1 predicts a more extended water-hydroxide-water angle and shorter hydrogen bonds to the hydroxide. Barriers to proton hops and water reorientation are higher than B3LYP.

We sampled this reactive system via the following dual propagators:

1. MD-MC DHMTS with $n_{\text{inner}} = 4$,
2. deterministic-inner-loop MD-MC DHMTS with $n_{\text{inner}} = 4$,

3. tandem flip MD-MC DHMTS with $n_{\text{inner}} = 4$ and flip decisions propagated for 10 consecutive loops, and
4. DHMTS with $n_{\text{inner}} = 4$.

Inner time-steps are $\delta t = 1$ fs, and Langevin collision frequency is $\gamma = 100 \text{ ps}^{-1}$. For the reference B3LYP and the preconditioner RM1 cases, a total of each 1.28 ns of trajectories are collected. Dual Hamiltonian trajectories reach a total of 2.0 to 2.1 ns for each case, requiring around 60% fewer B3LYP single point calculations than the reference. Results are summarized in Figure 5.

MC acceptance rates for MD-MC DHMTS and deterministic-inner-loop MD-MC DHMTS are 44.3% and 47.5%, respectively. As shown in the left and middle columns of Figure 5, both setups reproduce reference distributions to within an agreeable noise.

Case 4, as shown in the right column of Figure 5, corresponds to a RESPA-like multiple time-step dynamics integrator with an effective outer time-step of $t = 4$ fs. This propagator reproduces three different geometric distributions fairly well even though the preconditioner RM1 predictions are significantly different (red graphs in Figure 5). One noticeable sensitivity occurs with respect to the proton transfer coordinate (bottom right panel of Figure 5). This observable is subject to the fastest time scale explored comparable to t in magnitude. As shown in Figure 6, DHMTS indeed samples a slightly different ensemble than the reference, while all MD-MC DHMTS schemes converge to the correct one.

MD-MC DHMTS can reproduce static observables of the reference distribution, while DHMTS can reproduce dynamics as well. Shown in Figure 7 are the histograms of proton nontransfer intervals as obtained from pure B3LYP, pure RM1, and DHMTS trajectories. These are dwell times when a charge defect resides on the same monomer before hopping to a different partner. These plots provide insight about the free energy barriers seen by the hopping proton via the given level of theory. Preconditioner RM1 exhibits more frequent long dwell times compared to the reference B3LYP; however, DHMTS dynamics is not affected significantly by this difference between the force fields.

c). Water Octamer

In the MP2 complete basis set limit neutral water octamers can assume two high-symmetry conformations, D2d and S4.⁶³ Starting from D2d, we collected MP2 AIMD trajectories using the following propagators

1. Langevin dynamics (reference),
2. DHMTS using PM6 as preconditioner with $n_{\text{inner}} = 2$ to 8,
3. DHMTS using RM1 as preconditioner with $n_{\text{inner}} = 2$ to 8, and
4. DHMTS using HF as preconditioner with $n_{\text{inner}} = 2$ to 8.

The inner time-step is $\delta t = 1$ fs and collision frequency $\gamma = 100 \text{ ps}^{-1}$.

RM1 and HF preconditioned DHMTS setups yield stable trajectories at up to $n_{\text{inner}} = 4$, corresponding to $t = 4$ fs. In the absence of MC correction, PM6 preconditioning

accumulates too much error to be stable for even $n_{\text{inner}} = 2$. Single point MP2 calculations for this cluster are more than 100-times more time-consuming than RM1 and approximately 30 times more compared to HF. Hence, the overall boost in speedup is close to the number of inner loop steps.

For stable trajectories we use the following error estimator

$$\epsilon(t=N_t n_{\text{inner}} \delta t) = \frac{1}{N_t} \sum_{n_t=0}^{N_t} \left| \frac{E_{\text{total}}(n_t n_{\text{inner}} \delta t) - E_{\text{total}}(t=0)}{E_{\text{total}}(t=0)} \right| \quad (22)$$

where E_{total} excludes work exerted by the thermostat or the boundaries. Convergence of error is shown in Figure 8 for simulations run using equal amounts of wall clock CPU time. While errors are typically higher for dual integrators than reference, net speedups make the dual trajectories an attractive choice.

V. CONCLUSION

We introduced a dual Hamiltonian multiple time-step frame-work to accelerate the sampling of systems in the canonical ensemble. Our approach is motivated by the observation that the workload of one computationally expensive Hamiltonian can be shifted to another, less expensive one, when the difference between the two Hamiltonians varies on a slow time scale. The speedups can be particularly good with respect to the number of inner loop steps when the reference level calculations are computationally demanding, such as *ab initio* gradient evaluations. The underlying theory bears overlap with the multiple time-step framework of RESPA; however, we make no strong assumptions regarding the separability of the time scales in the dynamics.

Dual Hamiltonian propagators increase the effective integration time-steps at the cost of the inner loop iterations. These iterations require gradient evaluations only at the less expensive level of theory. This observation should be particularly valuable for AIMD and QM/MM simulations, because computational effort usually scales far steeper with increasing sophistication of the chemical level of theory. A typical situation involving the simulation of water molecules at the MP2/6-31G(d,p) level of theory is illustrated in Figure 9. MD simulations of such a system become very costly due to the rapidly growing computational cost at the MP2/6-31G(d,p) level of theory. A straightforward propagation method beyond a relatively small number of water molecules is prohibitive. Using the DHMTS algorithm, an acceleration by a factor of 4–5 is reached with only 20 water molecules in the system (Figure 9).

For pairs of Hamiltonians whose difference is slowly varying, the present formulation can shift nearly all workload to the inexpensive iterations. This opportunity has key implications for recently emerging force-matching algorithms. Such schemes typically learn from a library of molecular configurations at one reference level of theory by trying to mimic energies and/or gradients.^{64,65} Others have demonstrated that dynamics and machine learning can be performed simultaneously.⁶⁶ Dual Hamiltonian formulations can be readily

coupled to similar force-matching schemes to attain accelerated sampling by improving the guiding Hamiltonian on-the-fly.

ACKNOWLEDGMENTS

This research was partially supported by the National Institutes of Health (grant 5 R01 GM109455-02) and by the National Science Foundation (grants CHE-1136709 and MCB-1517221). Computational resources were provided by the University of Chicago Research Computing Center (RCC). We thank Charles Matthews for useful discussions.

APPENDIX: PSEUDOCODE

Note that, for each round, one only needs to recalculate total energy and gradients once at the expensive level and n_{inner} times at the cheap level. To avoid an extra expensive level calculation, energies and gradients from previous calculation are stored in memory (not shown below for clarity).

Algorithm 0.1: DUALPOT(&r, &p)

```

for  $i_{\text{outer}} \leftarrow 1$  to  $n_{\text{outer}}$ 
{
   $\mathbf{r}_0, \mathbf{p}_0 \leftarrow \text{RECORDINITSTATE}(\mathbf{r}, \mathbf{p})$ 
   $Q_{\text{real}} \leftarrow 0$ 
   $B_{\text{flip}} \leftarrow \text{UNIFRAND}() > 0.5? \text{false} : \text{true}$ 
  comment: start propagation

  if  $B_{\text{flip}}$ 
    then  $\text{FLIPMOMENTUM}(\mathbf{p})$ 
   $\mathbf{F}_{\text{fix}} \leftarrow \text{CALCFORCE0}(\mathbf{r}) - \text{CALCFORCE1}(\mathbf{r})$ 
   $\mathbf{p} \leftarrow \mathbf{p} + \mathbf{F}_{\text{fix}} n_{\text{inner}} \delta t / 2$ 
  for  $i_{\text{inner}} \leftarrow 1$  to  $n_{\text{inner}}$ 
  do {
    {
       $\text{PRANDOMIZE}(\&\mathbf{p}, Q_{\text{real}})$ 
       $\text{VELOCITYVERLET1}(\&\mathbf{r}, \&\mathbf{p}, \delta t)$ 
       $\text{PRANDOMIZE}(\&\mathbf{p}, Q_{\text{real}})$ 
    }
     $\mathbf{F}_{\text{fix}} \leftarrow \text{CALCFORCE0}(\mathbf{r}) - \text{CALCFORCE1}(\mathbf{r})$ 
     $\mathbf{p} \leftarrow \mathbf{p} + \mathbf{F}_{\text{fix}} n_{\text{inner}} \delta t / 2$ 
    if  $B_{\text{flip}}$ 
      then  $\text{FLIPMOMENTUM}(\mathbf{p})$ 
    comment: decide if to accept the target configuration

     $E_{\text{init}} \leftarrow \text{CALCTOTALENERGY0}(\mathbf{r}_0, \mathbf{p}_0)$ 
     $E_{\text{trgt}} \leftarrow \text{CALCTOTALENERGY0}(\mathbf{r}, \mathbf{p})$ 
     $\Delta E \leftarrow E_{\text{trgt}} - E_{\text{init}} - Q_{\text{real}}$ 
    if  $\exp^{-\beta \Delta E} < \text{UNIFRAND}()$ 
      then  $\mathbf{r}, \mathbf{p} \leftarrow \text{RESTOREINITSTATE}(\mathbf{r}_0, \mathbf{p}_0)$ 
  }
   $\text{RECORDSTATE}(\mathbf{r}, \mathbf{p})$ 
}

```

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Figure 1. Potential energy of 1D model system. U_0 is shown in black, and U_1 is shown in red. (a) First system is defined in eq 17. (b) Second system is defined in eq 21.

Figure 2.

Equilibrium distributions predicted by different propagators with respect to model particle position x . Theoretical distribution for U_0 is in solid black, for U_1 it is in dashed black. For each propagator, seven different n_{inner} values are illustrated: 1 (green), 2, 5, 10 (orange), 20, 50, 100 (red). (a) DHMTS, distribution with larger n_{inner} shifts toward left, and distribution with $n_{\text{inner}} = 1, 2, 5$, and 10 overlap with each other, (b) MD-MC DHMTS, and (c) VVVR using $\mathcal{A}(=n_{\text{inner}}\delta t)$, distribution with larger n_{inner} flattens, and distribution with $n_{\text{inner}} = 1, 2, 5$, and 10 overlap with each other. For (a) and (c), deviations from ρ_{U_0} become more

pronounced with increasing n_{inner} , while for (b) deviation remains nearly constant and negligible.

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Figure 3. Distribution generated using three different propagators. Definition and color convention follows Figure 2. Potential energy is given by eq 21 instead of eq 17.

Figure 4.
Deprotonated water trimer.

Figure 5.

Geometric observables from the deprotonated water trimer: MD-MC DHMTS (left row), MD-MC DHMTS via randomization post Metropolis (middle row), and DHMTS (right row). Results are compared against conventional Langevin MD at the B3LYP level of theory (blue). Preconditioner RM1 predictions are shown in red on the right column. Top row indicates the distribution of all oxygen–oxygen distances, middle row the shortest oxygen–oxygen distances, and bottom row the proton transfer coordinate as defined by $\delta = |r_{O_1H^*} - r_{O_2H^*}|$ where O_1 and O_2 are the oxygens closest to each other and H^* is the shared proton.

Figure 6.

Convergence of mean (left) and standard deviation (right) of potential energy in MD-MC DHMTS and DHMTS water trimer cluster. Each curve is an average over 16 parallel simulations. Data are offset by the best known estimate as obtained by the average over 32 parallel reference MD trajectories (blue horizontal lines). Note that DHMTS converges to a slightly different ensemble.

Figure 7. Distributions of defect proton residence times in water trimer: reference B3LYP (blue), DHMTS via $n = 4$ inner loop steps (green), preconditioner RM1 (red).

Figure 8. Average relative absolute error (eq 22) computed from water octamer trajectories. Reference level of theory is MP2/6-31G(d,p). Trajectories are collected using equal amounts of single-CPU wall clock time (~ 128.4 h). Inset: Initial cubic D2d cluster (from Xantheas and Apra).⁶³

Figure 9.

Scaling of core-second wallclock times of 4 fs of dynamics integration via DHMTS at the MP2/6-31G(d,p) level of theory compared against conventional integration using 1 fs time-steps. Timings correspond to DHMTS using $n_{\text{inner}} = 4$ and preconditioned via RM1 (black) or HF/3-21G (red) on a single 2.6 GHz Intel Sandybridge CPU with 2GB memory.

Table 1
Efficiency of the MD-MC DHMTS and DHMTS

simulation ^a	n_{inner}	1	2	5	10	20	50	100
1	T_{relax}	79	79	79	80	80	82	102
2	Acpt%	0.99	0.98	0.95	0.85	0.62	0.11	0.0006
	T_{relax}	1592	857	400	252	247	2075	702745
	η^b	0.05	0.15	0.66	1.6	<u>2.2</u> ^c	0.33	0.00
3	Acpt%	1.000	0.999	0.997	0.986	0.93	0.22	0.00
	T_{relax}	1642	774	318	159	83	19616	Inf
	η	0.04	0.17	0.83	2.5	<u>6.4</u>	0.03	0.00
4	Acpt%	1.000	1.000	0.999	0.993	0.95	0.36	0.00
	T_{relax}	214	142	96	77	59	2050	Inf
	η	0.34	0.93	2.7	5.2	<u>9.0</u>	0.33	0.00
5	Acpt%	0.99	0.98	0.95	0.85	0.60	0.03	0.00
	T_{relax}	80	79	80	79	79	81	109
	η	0.91	1.7	3.3	<u>5.0</u>	6.7	8.3	9.2
	Error	0.004	0.005	0.012	<u>0.028</u>	0.105	0.506	1.071

^a1. VVVR; 2. MD-MC DHMTS; 3. MD-MC DHMTS with deterministic-inner-loop; 4. MD-MC DHMTS with deterministic-inner-loop and reversal schedule decided every 10 rounds of propagation; 5. DHMTS.

^bEffective Speedup η eq 20, assuming $T_{\text{CPU}}(U_0) = 10$ $T_{\text{CPU}}(U_1)$.

^cBest efficiency of each propagator is underlined.

Table 2
Efficiency of MD-MC DHMTS and DHMTS for the Model System with Eq 21

simulation ^a	n_{inner}	1	2	5	10	20	50	100
1	$T_{\text{relax, VVVR}}$	258	268	266	267	268	273	282
2	Acpt%	0.98	0.96	0.78	0.46	0.22	0.074	0.000
	T_{relax}	2653	1721	1388	1531	6477	9956	Inf
	η^b	0.09	0.26	0.64	<u>0.87</u> ^c	0.28	0.23	0.00
3	Acpt%	0.98	0.96	0.81	0.44	0.16	0.03	0.01
	T_{rex}	248	270	180	85	68	70	100
	η	0.95	<u>1.7</u>	4.9	16	26	33	26
	error	0.015	<u>0.031</u>	0.23	0.73	0.96	1.2	0.99

^a 1. VVVR; 2. MD-MC DHMTS; 3. DHMTS.

^b Effective Speedup η eq 20, assuming $T_{\text{CPU}}(U_0) = 10 T_{\text{CPU}}(U_1)$.

^c Best efficiency of each propagator is underlined.