# A comparison of generalized hybrid Monte Carlo methods with and without momentum flip

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## ARTICLE INFO

## ABSTRACT

The generalized hybrid Monte Carlo (GHMC) method combines Metropolis corrected constant energy simulations with a partial random refreshment step in the particle momenta. The standard detailed balance condition requires that momenta are negated upon rejection of a molecular dynamics proposal step. The implication is a trajectory reversal upon rejection, which is undesirable when interpreting GHMC as thermostated molecular dynamics. We show that a modified detailed balance condition can be used to implement GHMC without momentum flips. The same modification can be applied to the generalized shadow hybrid Monte Carlo (GSHMC) method. Numerical results indicate that GHMC/GSHMC implementations with momentum flip display a favorable behavior in terms of sampling efficiency, i.e., the traditional GHMC/GSHMC implementations with momentum flip got the advantage of a higher acceptance rate and faster decorrelation of Monte Carlo samples. The difference is more pronounced for GHMC. We also numerically investigate the behavior of the GHMC method as a Langevin-type thermostat. We find that the GHMC method without momentum flip interferes less with the underlying stochastic molecular dynamics in terms of autocorrelation functions and it to be preferred over the GHMC method with momentum flip. The same finding applies to GSHMC.

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## 1. Introduction

The hybrid Monte Carlo (HMC) method [5] is a popular method to conduct sampling from the constant temperature ensemble for molecular systems [7,17]. The HMC method combines Metropolis corrected constant energy molecular dynamics with a complete replacement of momenta by a random sample from the appropriate Boltzmann distribution at the end of each HMC step. HMC can be combined with other techniques such as parallel tempering [9] and dynamical spatial warping [19] to increase sampling rates in case of high energy barriers between molecular conformations.

HMC has been generalized to allow for partial momentum updates to keep more dynamic information between Monte Carlo steps [11,13]. However, to satisfy a detailed balance condition [17], the generalized hybrid Monte Carlo (GHMC) method requires a momentum flip in case of rejection of the molecular dynamics proposal. This momentum flip implies that the GHMC method essentially reverses its direction upon rejection. In this note, we demonstrate that such a momentum reversal and the implied trajectory reversal upon rejection are, in fact, not necessary in order to satisfy a modified detailed balance condition [8]. Both the standard as well as the modified detailed balance condition guarantee the stationarity of the canonical distribution function [3,17]. We wish to emphasize that the issue of momentum reversal does not arise for the standard

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HMC method since the complete momentum vector is replaced by a new random sample after each constant energy molecular dynamics Monte Carlo step.

The acceptance rate of the HMC method can be increased by using importance sampling with respect to a shadow Hamiltonian as first proposed in [12]. The generalized shadow hybrid Monte Carlo (GSHMC) method [1,2] provides an efficient implementation of shadow Hamiltonians in the context of the GHMC method. As for the standard GHMC method, a momentum flip is required upon rejection of the molecular dynamics proposal. The modified detailed balance condition allows for the elimination of this momentum flip from the GSHMC method.

Our numerical evidence indicates that it is advantageous to run GHMC/GSHMC methods with momentum flips in order to get optimal sampling results. On the other hand, we also demonstrate that elimination of the momentum flip allows for a dynamic interpretation of sampling results in terms of approximations to a second-order stochastic Langevin equation, i.e., in terms of thermostated molecular dynamics, provided the rejection rate is kept sufficiently small.

Another application of the modified detailed balance condition to constant temperature molecular dynamics has recently been provided in [15], where the Nosé–Hoover model [20,10,6] has been put into the framework of Markov chain Monte Carlo (MCMC) methods [17].

The rest of the paper is organized as follows. In Section 2, we derive the modified detailed balance condition for general MCMC methods. The standard GHMC method is described in Section 3, while its generalization to a GHMC method without momentum flip can be found in Section 4. Section 5 outlines the implementation of the GSHMC method without momentum flip. Numerical results for butane and a membrane protein can be found in Section 6.

## 2. Markov chain Monte Carlo (MCMC) methods

Consider a system of $N$ interacting particles with positions $\mathbf{q}_i \in \mathbb{R}^3$, momenta $\mathbf{p}_i \in \mathbb{R}^3$, and masses $m_i$, $i = 1, \ldots, N$. The phase space is $\Omega = \mathbb{R}^{6N}$ and the state variable is given by

$$\Gamma = (\mathbf{q}_1^t, \ldots, \mathbf{q}_N^t, \mathbf{p}_1^t, \ldots, \mathbf{p}_N^t)^t \in \Omega.$$

Here we used the notation that $\mathbf{a}^t$ denotes the transpose of a column vector $\mathbf{a}$. Let us assign a potential energy function $V : \Omega \to \mathbb{R}$ and a total energy

$$E(\Gamma) = \frac{1}{2} \sum_i m_i^{-1} \|\mathbf{p}_i\|^2 + V(\mathbf{q}_1, \ldots, \mathbf{q}_N)$$

to this system. The canonical distribution at temperature $T$ is then given by

$$\rho_{\text{can}}(\Gamma) \propto \exp(-\beta E(\Gamma)), \tag{1}$$

where $\beta = 1/k_B T$ is the inverse temperature.

The energy $E$ is invariant under the involution (momentum flip) $\mathcal{F} : \Omega \to \Omega$ defined by

$$\mathcal{F}\Gamma := (\mathbf{q}_1^t, \ldots, \mathbf{q}_N^t, -\mathbf{p}_1^t, \ldots, -\mathbf{p}_N^t)^t.$$

We obviously also have $\rho_{\text{can}}(\Gamma) = \rho_{\text{can}}(\mathcal{F}\Gamma)$.

We next discuss two detailed balance principles that can be used to derive Markov chain Monte Carlo (MCMC) methods, which sample from the canonical distribution (1). We refer to [17] for an in detail introduction to MCMC methods.

### 2.1. Markov chains and detailed balance

Let us denote the state space of a Markov chain by $\Omega \subset \mathbb{R}^n$, its states by $\Gamma \in \Omega$, and its transition probability kernel by $A(\Gamma'|\Gamma)$. In other words, $A(\Gamma'|\Gamma)$ gives the probability density of going from a state $\Gamma$ to a state $\Gamma'$. A probability density function (PDF) $\rho_{\text{stat}}(\Gamma)$ is stationary under the Markov chain provided

$$\rho_{\text{stat}}(\Gamma') = \int_\Omega A(\Gamma'|\Gamma) \rho_{\text{stat}}(\Gamma) d\Gamma. \tag{2}$$

The detailed balance condition

$$A(\Gamma'|\Gamma) \rho_{\text{stat}}(\Gamma) = A(\Gamma|\Gamma') \rho_{\text{stat}}(\Gamma') \tag{3}$$

provides an easy criterion for the invariance of $\rho_{\text{stat}}$. Of course, condition (3) is not the only criterion to guarantee (2).

Let us consider systems that allow for a linear map (involution) $\mathcal{F} : \Omega \to \Omega$, which satisfies (i) $\mathcal{F} = \mathcal{F}^{-1}$ and (ii) $\rho_{\text{stat}}(\Gamma) = \rho_{\text{stat}}(\mathcal{F}\Gamma)$ for all $\Gamma \in \Omega$. We note that molecular dynamics with the PDF (1), i.e., $\rho_{\text{stat}} = \rho_{\text{can}}$ provides an example.

For such systems, the modified detailed balance condition

$$A(\Gamma'|\Gamma) \rho_{\text{stat}}(\Gamma) = A(\mathcal{F}\Gamma|\mathcal{F}\Gamma') \rho_{\text{stat}}(\mathcal{F}\Gamma') = A(\mathcal{F}\Gamma|\mathcal{F}\Gamma') \rho_{\text{stat}}(\Gamma') \tag{4}$$

can be found in [8] in the context of the Fokker–Planck equation. The modified detailed balance condition (4) also implies (2) since

$$\int_\Omega A(\Gamma'|\Gamma)\rho_{\text{stat}}(\Gamma)d\Gamma = \rho_{\text{stat}}(\Gamma')\int_\Omega A(\mathcal{F}\Gamma|\mathcal{F}\Gamma')d\Gamma = \rho_{\text{stat}}(\Gamma').$$

### 2.2. Metropolis–Hastings acceptance criteria

In this section we generalize the modified detailed balance relation (4) to Markov chain Monte Carlo (MCMC) methods. The MCMC method is to sample from a given PDF $\rho_{\text{stat}}$.

Let $P(\Gamma'|\Gamma)$ denote the proposal distribution of the MCMC method and let us assume that the state space $\Omega$ permits a linear involution $\mathcal{F}$. A proposal state $\Gamma'$ is accepted according to the Metropolis–Hastings criterion $r(\Gamma',\Gamma) \geq \xi$, where $\xi \in [0,1]$ is a uniformly distributed random number and

$$r(\Gamma',\Gamma) = \frac{\delta(\Gamma',\Gamma)}{\rho_{\text{stat}}(\Gamma)P(\Gamma'|\Gamma)}. \tag{5}$$

Here $\delta(\Gamma',\Gamma)$ is any function with

$$\delta(\Gamma',\Gamma) = \delta(\mathcal{F}\Gamma,\mathcal{F}\Gamma')$$

that makes $r(\Gamma',\Gamma) \leqslant 1$.

The probability for the induced Markov chain to make a transition from $\Gamma$ to $\Gamma'$ is now given by

$$A(\Gamma'|\Gamma) := P(\Gamma'|\Gamma)r(\Gamma',\Gamma) = \rho_{\text{stat}}(\Gamma)^{-1}\delta(\Gamma',\Gamma).$$

Similarly,

$$A(\mathcal{F}\Gamma|\mathcal{F}\Gamma') = P(\mathcal{F}\Gamma|\mathcal{F}\Gamma')r(\mathcal{F}\Gamma,\mathcal{F}\Gamma') = \rho_{\text{stat}}(\mathcal{F}\Gamma')^{-1}\delta(\mathcal{F}\Gamma,\mathcal{F}\Gamma') = \rho_{\text{stat}}(\Gamma')^{-1}\delta(\Gamma',\Gamma)$$

and the modified detailed balance relation (4) follows.

One can choose, for example,

$$\delta(\Gamma',\Gamma) := \min\{\rho_{\text{stat}}(\Gamma)P(\Gamma'|\Gamma), \rho_{\text{stat}}(\Gamma')P(\mathcal{F}\Gamma|\mathcal{F}\Gamma')\}$$

and then it follows that

$$r(\Gamma',\Gamma) = \min\left(1, \frac{P(\mathcal{F}\Gamma|\mathcal{F}\Gamma')\rho_{\text{stat}}(\Gamma')}{P(\Gamma'|\Gamma)\rho_{\text{stat}}(\Gamma)}\right). \tag{6}$$

If the proposal distribution satisfies

$$P(\Gamma'|\Gamma) = P(\mathcal{F}\Gamma|\mathcal{F}\Gamma'), \tag{7}$$

then (6) reduces to the familiar Metropolis criterion

$$r(\Gamma',\Gamma) = \min\left(1, \frac{\rho_{\text{stat}}(\Gamma')}{\rho_{\text{stat}}(\Gamma)}\right). \tag{8}$$

On the other hand, the standard detailed balance condition (3) is satisfied by a Markov chain with transition probability kernel $A(\Gamma'|\Gamma) = P(\Gamma'|\Gamma)r(\Gamma',\Gamma)$ if $r(\Gamma',\Gamma)$ is also given by (8) and if the proposal step satisfies

$$P(\Gamma'|\Gamma) = P(\Gamma|\Gamma'). \tag{9}$$

Of course, these conditions are not the only criteria to guarantee the standard detailed balance condition (3). See [17] for details.

## 3. Generalized hybrid Monte Carlo (GHMC) method

We now consider a particular MCMC method for systems of interacting particles as introduced in Section 2.

First note that a Markov chain will converge to some distribution of configurations if it is constructed out of Markov chain Monte Carlo (MCMC) updates each of which has the desired distribution as a fixed point, and which taken together are ergodic. The generalized hybrid Monte Carlo (GHMC) algorithm of Horowitz [11] and Kennedy and Pendleton [13] for sampling from the canonical ensemble with PDF (1) is defined as the concatenation of two MCMC steps: a molecular dynamics Monte Carlo (MDMC) and a partial momentum refreshment Monte Carlo (PMMC) step. We describe both steps in detail.

### 3.1. Partial momentum refreshment Monte Carlo (PMMC)

Let us denote the last accepted state vector by $\Gamma^n$, $n \geqslant 1$. Its momenta $\mathbf{p}_i^n$, $i = 1, \ldots, N$, are now mixed with an independent and identically distributed normal (Gaussian) noise vector $\mathbf{u}_i \in \mathbb{R}^3$ and the partial momentum refreshment step is given by

$$\begin{pmatrix} \mathbf{u}_i \\ \mathbf{p}_i \end{pmatrix} = \begin{pmatrix} \cos(\phi) & -\sin(\phi) \\ \sin(\phi) & \cos(\phi) \end{pmatrix} \begin{pmatrix} \mathbf{u}_i^n \\ \mathbf{p}_i^n \end{pmatrix}, \tag{10}$$

where

$$\mathbf{u}_i^n = \beta^{-1/2} m_i^{1/2} \xi_i, \quad \xi_i = (\xi_{i,1}, \xi_{i,2}, \xi_{i,3})^T, \quad \xi_i \sim [N(0,1)]^3$$

and $0 < \phi \leqslant \pi/2$. Here $N(0,1)$ denotes the normal distribution with zero mean and unit variance. Let us denote the new state vector by $\Gamma$.

Note that if $\mathbf{p}_i^n$ and $\mathbf{u}_i^n$ are both distributed according to the same normal (Gaussian) distribution, then so are $\mathbf{p}_i$ and $\mathbf{u}_i$. This special property of Gaussian random variables under an orthogonal transformation (10) makes it possible to conduct the partial momentum refreshment step without a Metropolis accept/reject test.

### 3.2. Molecular dynamics Monte Carlo (MDMC)

This step consists of the following two sub-steps.

(i) *Molecular dynamics* (MD). Hamilton's equations of motion

$$m_i \dot{\mathbf{q}}_i = \mathbf{p}_i,$$
$$\dot{\mathbf{p}}_i = -\nabla_{\mathbf{q}_i} V(\mathbf{q}_1, \ldots, \mathbf{q}_N),$$

$i = 1, \ldots, N$, are integrated numerically with a time-reversible and symplectic method $\Psi_h$ over $L$ steps and step-size $h$. We use the Störmer–Verlet method [3,14] for all experiments in this paper. The resulting time-reversible and symplectic (and hence volume conserving) map from the initial state to the final state is denoted by $U_\tau : \Omega \to \Omega$, $\tau = Lh$. Given the current state $\Gamma$, the proposal state is now defined by $U_\tau(\Gamma)$ followed by a momentum flip $\mathcal{F}$.

(ii) *Monte Carlo* (MC): A Metropolis accept/reject test

$$\Gamma' = \begin{cases} \mathcal{F}U_\tau(\Gamma) & \text{with probability } \min(1, \exp(-\beta\delta E)), \\ \Gamma & \text{otherwise}, \end{cases}$$

with

$$\delta E := E(U_\tau(\Gamma)) - E(\Gamma) = E(\mathcal{F}U_\tau(\Gamma)) - E(\Gamma)$$

is applied.

Note that the time-reversibility of $U_\tau$ is equivalent to $(\mathcal{F}U_\tau) = (\mathcal{F}U_\tau)^{-1}$. Hence the proposal distribution $P(\Gamma'|\Gamma)$, characterized by $\Gamma' = \mathcal{F}U_\tau(\Gamma)$, satisfies (9) and MDMC satisfies the standard detailed balance relation (3).

We finally apply a momentum flip and define the next accepted state vector by $\Gamma^{n+1} = \mathcal{F}\Gamma'$. Hence the momenta are negated upon rejection of a proposal $\Gamma' = U_\tau(\Gamma)$.

This completes a single step of the GHMC algorithm.

## 4. A GHMC method without momentum flip

The momentum flip in the MDMC step upon rejection may lead to a *Zitterbewegung* (going forward and backward) in the molecular trajectories for high rejection rates. It has been argued in [11] that this *Zitterbewegung* is the main obstacle to achieve better sampling efficiency under the GHMC method.

However, using the modified detailed balance relation (4) in the MCMC part of GHMC, one can now eliminate the need for the additional momentum flip in the MDMC step and, hence, the source for the *Zitterbewegung* upon high rejection rates. The key observation is that a proposal $\Gamma' = U_\tau(\Gamma)$ leads to a proposal distribution $P(\Gamma'|\Gamma)$ satisfying (7). Hence, following Section 2.2, we can implement the MDMC part of GHMC without a momentum flip while still using the same Metropolis acceptance criterion.

### 4.1. Algorithmic summary

Since the momentum refreshment PMMC step remains unchanged, we only state the modified MDMC step.

(i) *Molecular dynamics* (MD): The updated momentum vectors and the current particle positions give rise to a new state $\Gamma$, which is now propagated under the map $U_\tau = [\Psi_h]^L$ as discussed in Section 3.

(ii) *Monte Carlo* (MC): a standard Metropolis accept/reject test

$$\Gamma' = \begin{cases} U_\tau(\Gamma) & \text{with probability } \min(1, \exp(-\beta\delta E)) \\ \Gamma & \text{otherwise} \end{cases} \tag{11}$$

with

$$\delta E := E(U_\tau(\Gamma)) - E(\Gamma)$$

is applied and we set $\Gamma^{n+1} = \Gamma'$.

### 4.2. Special cases of GHMC

We now discuss two special cases which arise from different choices for $\phi$, $h$, and $L$ in the GHMC algorithm.

- The standard hybrid Monte Carlo (HMC) algorithm [5] is obtained by setting $\phi = \pi/2$. In this case $\mathbf{p}_i = \mathbf{u}_i^n$ in (10) and the previous value of $\mathbf{p}_i^n$ is entirely discarded.
  Let us now also set $L = 1$ (single molecular dynamics time-step) and let us assume that $\Psi_h$ corresponds to the Störmer–Verlet method. Then we can interpret the hybrid Monte Carlo method as a single Brownian dynamics [3] time step

$$\mathbf{q}_i = \mathbf{q}_i^n - \frac{\Delta t}{m_i}\nabla_{\mathbf{q}_i}V(\mathbf{q}_1^n,\dots,\mathbf{q}_N^n) + \sqrt{\frac{2\Delta t}{m_i^2}}\mathbf{u}_i^n, \quad i = 1,\dots,N, \tag{12}$$

  with time-step $\Delta t = h^2/2$ followed by the Metropolis acceptance criterion (11). Hence we also need to define a momentum proposal to evaluate $\delta E$ in (11). This momentum proposal is given by

$$\mathbf{p}_i = \mathbf{u}_i^n - \sqrt{\frac{\Delta t}{2}}(\nabla_{\mathbf{q}_i}V(\mathbf{q}_1^n,\dots,\mathbf{q}_N^n) + \nabla_{\mathbf{q}_i}V(\mathbf{q}_1^{n+1},\dots,\mathbf{q}_N^{n+1})), \quad i = 1,\dots,N$$

  in case of the Störmer–Verlet method. Recall that $\mathbf{u}_i^n = \sqrt{m_i k_B T}\xi_i$, $\xi_i \sim [N(0,1)]^3$ and, hence, (12) can be rephrased in the more familiar formulation

$$\mathbf{q}_i = \mathbf{q}_i^n - \frac{\Delta t}{m_i}\nabla_{\mathbf{q}_i}V(\mathbf{q}_1^n,\dots,\mathbf{q}_N^n) + \sqrt{\frac{2k_B T\Delta t}{m_i}}\xi_i, \quad i = 1,\dots,N.$$

  Note that this Metropolis corrected single time-step Brownian dynamics scheme is equivalent to the Metropolis adjusted Langevin algorithm (MALA) [21].
- The Langevin Monte Carlo algorithm of Horowitz [11] corresponds to a generalized hybrid Monte Carlo method as described in Section 3 with $L = 1$, i.e., a MCMC method with momentum flip. Because of the momentum flips in case of rejection, a dynamic interpretation of the Langevin Monte Carlo algorithm is difficult to make. On the other hand, a single GHMC step with $L = 1$ and with all MD proposals being accepted can be interpreted as a particular time discretization of stochastic Langevin dynamics

$$m_i\dot{\mathbf{q}}_i = \mathbf{p}_i, \quad \dot{\mathbf{p}}_i = -\nabla_{\mathbf{q}_i}V(\mathbf{q}_1,\dots,\mathbf{q}_N) - \gamma\mathbf{p}_i + \sigma_i\dot{\mathbf{W}}_i, \quad i = 1,\dots,N \tag{13}$$

  with time-step $\Delta t = h$ provided that $\phi = \sqrt{2\gamma h} \ll 1$. Here $\gamma > 0$ is a constant, $\mathbf{W}_i(t)$ are i.i.d. 3-dimensional Wiener processes, and $\sigma_i = \sqrt{2\gamma m_i k_B T}$. Indeed, we find that Taylor expansion of (10) in $\phi = \sqrt{2\gamma h} \ll 1$ reduces to

$$\mathbf{p}_i \approx (1 - \gamma\Delta t)\mathbf{p}_i^n + (2\gamma m_i k_B T\Delta t)^{1/2}\xi_i, \quad i = 1,\dots,N$$

  for $\Delta t = h$ and $\xi_i \sim [N(0,1)]^3$. An interesting question is how the introduction of a Metropolis acceptance criterion (either with or without momentum flip) will modify the underlying Langevin dynamics. We expect convergence of all three approaches (no rejections, Metropolis with and without momentum flip) as $h = \Delta t \to 0$. We will investigate finite time-step effects in Section 6.

## 5. Generalized shadow hybrid Monte Carlo (GSHMC) method

The generalized shadow hybrid Monte Carlo (GSHMC) method [1,2] makes use of the fact that a symplectic method $\Psi_h$ can be viewed as a highly accurate approximation to a modified Hamiltonian system with energy $\widehat{E}_h$ [14]. Since the method $\Psi_h$ is also assumed to be time-reversible, it follows that the modified Hamiltonian satisfies

$$\widehat{E}_h(\Gamma) = \widehat{E}_h(\mathcal{F}\Gamma)$$

and the modified detailed balance relation (4) also holds with $\rho_{\text{stat}}$ being replaced by the modified canonical density

$$\widehat{\rho}_{\text{can}}(\Gamma) \propto \exp(-\beta\widehat{E}_h(\Gamma)).$$

In exactly the same manner as the modified detailed balance condition (4) allows us to eliminate the momentum flip $\mathcal{F}$ from the GHMC method, we can now also modify the GSHMC method. Again the only significant change is a modified acceptance criterion in the MDMC part of GSHMC which becomes

$$\Gamma' = \begin{cases} U_\tau(\Gamma) & \text{with probability } \min(1, \exp(-\beta\delta\widehat{E})) \\ \Gamma & \text{otherwise} \end{cases} \tag{14}$$

with

$$\delta\widehat{E} := \widehat{E}_h(U_\tau(\Gamma)) - \widehat{E}_h(\Gamma)$$

in terms of the notations introduced in Section 4.1.

The partial momentum update step of GSHMC, as described in [2], remains unaffected except for the removal of the initial momentum flip.

We remind the reader that the modified energy $\widehat{E}_h$ leads to a significantly increased acceptance rate in the MDMC part of the GSHMC method. At the same time, the momentum refreshment step itself becomes subject to a Metropolis acceptance criterion. The acceptance rate can be adjusted by selecting the angle $\phi$ in (10) appropriately.

Finally, since we sample with respect to a modified canonical density $\hat{\rho}_{\mathrm{can}}$, a reweighting of simulation data for computing averages is necessary.

## 6. Numerical results

We present numerical results from two model systems. We first simulate a single butane molecule using GHMC/GSHMC methods with and without momentum flip. This system contains $N = 4$ particles. We also provide results from simulations of a membrane protein system. This system has been investigated in [23] using GSHMC with momentum flips and results were compared to a molecular dynamics simulation with a standard Berendsen thermostat [3].

### 6.1. Butane

We perform two sets of experiments. The first set is to test GHMC/GSHMC with and without momentum flip as a sampling tool. In this context we wish to achieve a high degree of decorrelation between samples. In the second test we are interested in the behavior of GHMC with and without momentum flip as a Metropolis corrected Langevin thermostat (see Section 4.2). In this case, we wish to preserve the autocorrelation in a molecular model as much as possible. We assume that the molecular model is given by second-order Langevin dynamics (13) with an appropriate damping coefficient $\gamma$.

#### 6.1.1. Sampling

All Monte Carlo simulations are performed with a step-size of $h = 6$ fs and trajectory length $\tau = h L = 600$ fs, i.e, $L = 100$, in the MDMC part. The angle in (10) is set to $\phi = \pi/10$. A total of 1.9e+5 Monte Carlo steps are performed with target temperature $T = 300$ K. Each experiment is repeated five times and we compute the mean value of the torsion potential energy, the mean kinetic energy, and the acceptance rate (AR) in the MDMC part. The results are displayed in Table 1, where computed quantities are stated in terms of the mean and standard deviation over the five independent experiments. The exact mean value for the torsion potential energy has been taken from [12]. We find that GHMC without momentum flips leads to a reduced acceptance rate and that the deviations in the computed expectation values are larger. In case of the GSHMC method (with a fourth order modified energy) no significant difference between implementations with and without momentum flips can be detected. This is very likely due to the high acceptance rate in the MDMC part. We will come back to this issue in a more demanding membrane protein test case.

#### 6.1.2. Metropolis corrected Langevin thermostat

We compare the GHMC method with and without momentum flip to a GHMC implementation with all proposal steps in the MDMC part being accepted. Such an implementation samples no longer exactly from the canonical distribution (and, in fact, is no longer a MCMC method) but it provides a consistent discretization of the underlying Langvin equations (13) for $L = 1$, i.e., $\tau = h$ in the MDMC part of GHMC.

All three simulations are performed with $L = 1$, $\phi = \sqrt{2\gamma h}$ in (10), $\gamma = 0.5$ ps$^{-1}$ in (13), and target temperature $T = 150$ K. We used three different step-sizes $h$ (1fs, 2fs, 4fs) and simulated over a constant time-interval $T_{\mathrm{total}} = N_{MC} h = 40$ ps with the number of time/Monte Carlo steps $N_{MC}$ appropriately adjusted.

**Table 1**
Simulation results for butane with $h = 6$ fs and $\tau = h L = 600$ fs. All energy values are stated in kJ mol$^{-1}$. Simulations are run at $T = 300$ K. The acceptance rates (AR) are stated for the molecular dynamics Monte Carlo (MDMC) step.

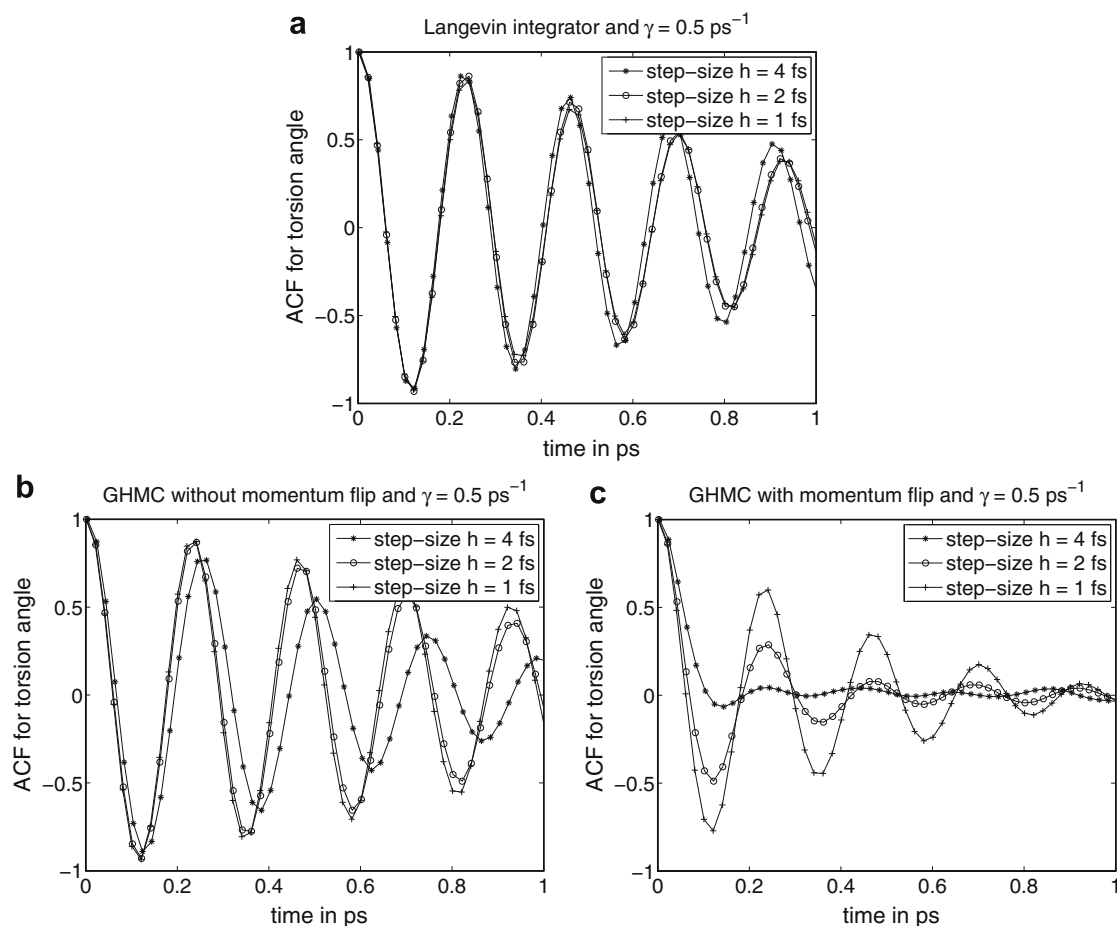| Method | Flip | Numerical $\langle V_{\mathrm{tors}}\rangle$ | Exact $\langle V_{\mathrm{tors}}\rangle$ | Numerical $\langle E_{\mathrm{kinetic}}\rangle$ | Exact $\langle E_{\mathrm{kinetic}}\rangle$ | AR (%) |
|--------|------|---------------------------------------|-----------------------------------|----------------------------------------|--------------------------------------|--------|
| GHMC | Yes | 2.6720 ± 0.1135 | 2.6313 | 14.9894 ± 0.0210 | 14.9663 | 78 |
| GHMC | No | 2.6136 ± 0.1874 | 2.6313 | 15.0028 ± 0.0674 | 14.9663 | 74 |
| GSHMC | Yes | 2.5845 ± 0.1298 | 2.6313 | 15.0142 ± 0.0652 | 14.9663 | 99 |
| GSHMC | No | 2.5754 ± 0.1276 | 2.6313 | 14.9579 ± 0.0598 | 14.9663 | 99 |

**Fig. 1.** Autocorrelation functions (ACFs) for torsion angle of a single butane molecular at $T = 150$ K. Displayed are results from GHMC simulations with (c) and without (b) momentum flip. These results are compared to a Langevin dynamics simulation (a) of the same system. It is found that GHMC without momentum flip reproduces the ACF from Langevin dynamics well for $h = 1$ fs as well as $h = 2$ fs. GHMC with momentum flip, on the other hand, leads to a dramatic reduction in the autocorrelation, which would be desirable for sampling purposes but is not appropriate for thermostated molecular dynamics.

**Table 2**
Acceptance rates in the molecular dynamics Monte Carlo (MDMC) steps for GHMC with and without momentum flip for $\tau = h$ and $\phi = (2\gamma h)^{/12}$ in (10), $\gamma = 0.5$ ps$^{-1}$.

| Method | $h = 1$ fs | $h = 2$ fs | $h = 4$ fs |
|---|---|---|---|
| GHMC without momentum flip | 99.8% | 98.7% | 90.3% |
| GHMC with momentum flip | 99.8% | 98.9% | 91.0% |

**Table 3**
Acceptance rates (AR) in the molecular dynamics Monte Carlo (MDMC) and partial momentum Monte Carlo (PMMC) steps of GSHMC simulations of membrane protein implemented with and without momentum flip and run with different values of molecular dynamics step-size $h$.

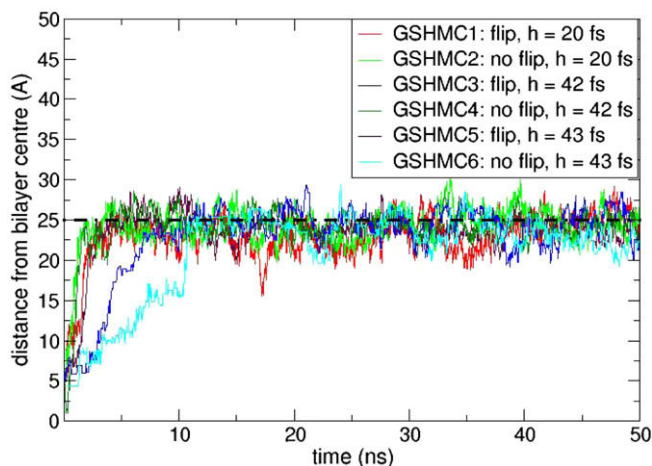| Method | length (ns) | step-size (fs) | flip | AR in MDMC (%) | AR in PMMC (%) |
|---|---|---|---|---|---|
| GSHMC1 | 50 | 20 | Yes | 99.8 | 99.9 |
| GSHMC2 | 50 | 20 | No | 99.9 | 99.7 |
| GSHMC3 | 50 | 42 | Yes | 98.2 | 27.2 |
| GSHMC4 | 50 | 42 | No | 98.1 | 27.2 |
| GSHMC5 | 50 | 43 | Yes | 65.6 | 48.1 |
| GSHMC6 | 50 | 43 | No | 51.8 | 18.2 |

**Fig. 2.** Time evolution of the distance $d$ between the centre of mass (c.o.m.) of the toxin and the c.o.m. of the bilayer along the bilayer normal under GSHMC1–GSHMC6. The dotted horizontal line corresponds to the average of $d$ obtained from a control MD simulation (averaged over 15–200 ns). The lower Metropolis acceptance rates for GSHMC5/GSHMC6 lead to a slower convergence of the toxin to its preferred interfacial position.
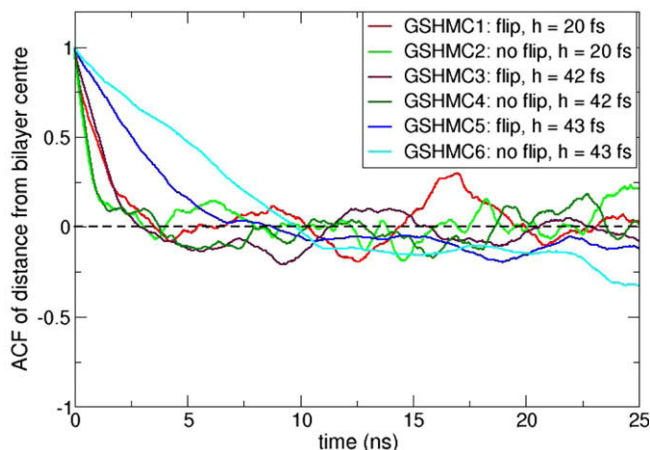


**Fig. 3.** Autocorrelation functions (ACF) for the time series displayed in Fig. 3. No significant difference between implementations with and without momentum flips can be observed for step-sizes of 20 fs and 42 fs. However, the large time-step simulations GSHMC5/GSHMC6 display a longer correlation due to lower Metropolis acceptance rates. This effect is more pronounced for the method without momentum flip (GSHMC6). Despite of this, the toxin has converged to the correct interfacial position after a simulation interval of 50 ns for all implementations GSHMC1–GSHMC6. See also Fig. 2.

In Fig. 1 we display the computed autocorrelation functions (ACFs) [3] for the torsion angle. We find that GHMC with momentum flip leads to a rapid decay of correlation even for relatively modest rejection rates (see Tabel 2). The ACFs obtained from the discretization of the Langevin equations (13) are, on the contrary, well reproduced by the GHMC method without momentum flip for $h = 1$ fs and $h = 2$ fs. A rejection rate of nearly 10% (see Table 2) leads to significant distortions in the ACFs for both GHMC implementations. Note from Table 2 that the rejection rates with and without momentum flips are nearly identical in this simulation regime.

### 6.2. Membrane protein

To investigate the sampling performance of the GSHMC method with and without momentum flips, we chose the previously studied [23] gating-modifier peptide toxin VST×1 from spider venom in a palmitoyl-oleoyl-phosphatidyl choline (POPC) membrane environment as a test application.

We implemented GSHMC in combination with a CG force-field [18,4] where four "heavy" particles on average were represented as one CG particle. The details of the molecular model are same as described in [23]. The toxin was initially buried in the hydrophobic core of a POPC bilayer and we measured the rate of drift of the toxin along the bilayer normal (which corresponds to the $z$-axis) to an interfacial location. The initial orientation of the toxin in the bilayer was such that its hydrophilic face pointed towards the headgroup region of the upper leaflet of the bilayer.

**Table 4**
Average ± standard deviation of observable $\Omega$ ($\Omega = d$, $LJ_{pb}$, and $LJ_{pw}$). $d$ is the distance between the centre of mass (c.o.m.) of the toxin and the c.o.m. of the bilayer along the bilayer normal, $LJ_{pb}$ is the Lennard-Jones (LJ) interaction energy between the toxin and the bilayer and $LJ_{pw}$ is the LJ interaction energy between the toxin and water. Averages are taken from 20 to 50 ns, except for control MD simulation [23], where averages are taken from 15 to 200 ns.

| Method | length (ns) | step-size (fs) | flip | $d$ (Å) | $LJ_{pb}$ (kJ mol$^{-1}$) | $LJ_{pw}$ (kJ mol$^{-1}$) |
|--------|-------------|----------------|------|---------|---------------------------|---------------------------|
| MD | 200 | 20 | N/A | 24.8 ± 1.8 | −697.9 ± 62.6 | −620.1 ± 65.7 |
| GSHMC1 | 50 | 20 | Yes | 23.8 ± 2.0 | −760.3 ± 66.8 | −545.6 ± 72.1 |
| GSHMC2 | 50 | 20 | No | 24.7 ± 1.7 | −719.2 ± 52.4 | −614.2 ± 53.7 |
| GSHMC3 | 50 | 42 | Yes | 23.4 ± 0.9 | −667.3 ± 44.8 | −561.6 ± 59.2 |
| GSHMC4 | 50 | 42 | No | 24.6 ± 0.9 | −718.0 ± 45.4 | −619.2 ± 38.7 |
| GSHMC5 | 50 | 43 | Yes | 26.2 ± 0.5 | −697.3 ± 20.3 | −590.7 ± 22.8 |
| GSHMC6 | 50 | 43 | No | 24.2 ± 0.1 | −728.7 ± 31.5 | −540.7 ± 52.1 |

We performed six GSHMC simulations (GSHMC1–GSHMC6) for three different values of the molecular dynamics times-step $h$ (20 fs, 42 fs, and 43 fs) with and without momentum flips. Note that the smallest step-size of 20 fs has also been used in the study [23]. The two larger step-sizes have been chosen such that we can demonstrate the difference between high and low acceptance rates in the MDMC part of GSHMC. In fact, a time-step of 43 fs is close to the stability limit of the Störmer–Verlet method for this problem.

Each simulation was run for 50 ns. The MD stage of GSHMC was performed using a modified version of GROMACS 3.2.1 [16]. The simulations were run at a temperature of 310 K.

The number of MD steps between Monte Carlo steps was set to $L = 1000$, the angle in (10) was chosen to be $\phi = 0.18$ and the order of a modified Hamiltonian was assigned to 6th order [2]. We calculated the acceptance rates in both MDMC and PMMC steps for each simulation and found that the smaller step-sizes lead to similar acceptance in the GSHMC implementations with momentum flip (GSHMC1/GSHMC3) and without momentum flip (GSHMC2/GSHMC4). The MDMC acceptance rates are kept high in these four simulations. The acceptance rates deteriorate for the larger step-size of 43 fs in both GSHMC implementations though GSHMC with momentum flip (GSHMC5) allows for significantly higher acceptance rate than in the simulation without momentum flip (GSHMC6). The acceptance rates for all simulations can be found in Table 3.

To probe our simulations further, we monitored the time evolution of the distance $d$ of the centre of mass (c.o.m.) of the toxin with respect to the c.o.m. of the bilayer along the bilayer normal. See Fig. 2 for the time evolution of $d$ under GSHMC1–GSHMC6 and Fig. 3 for the associated autocorrelation functions (ACF) [17,23], where the ACF is computed over data from 0 to 50 ns. No significant differences in behavior of $d$ between GSHMC with and without momentum flip can be observed for step-sizes of 20 and 42 fs. A visibly slower decay of the ACF can be observed for GSHMC without momentum flip at the large step-size of 43 fs (GSHMC6) compared to GSHMC5.

In all simulations, the toxin drifts towards the headgroup/water interface of the bilayer. To make this statement more precise, we examined sample averages for the distance $d$, the Lennard-Jones (LJ) interaction energy between the toxin and the bilayer ($LJ_{pb}$), and the LJ interaction energy between the toxin and water ($LJ_{pw}$). We found the averages in Table 4 in good agreement with the previously obtained simulation data for all GSHMC methods. See Table 4 in [23]. The values from the control MD simulation, as displayed in Table 4, are reproduced from [23].

## 7. Summary and discussion

We have made use of a modified detailed balance condition to propose an implementation of the generalized hybrid Monte Carlo (GHMC) method without momentum flip. Numerical evidence indicates, however, that the standard GHMC method with momentum flip leads to higher acceptance rates and more efficient sampling. The same effect is observed for the generalized shadow hybrid Monte Carlo (GSHMC) method. These findings are also in line with a similar observation made in [22] for Metropolis corrected second-order Langevin dynamics.

An intuitive explanation for the reduced acceptance rates of the GHMC/GSHMC methods without momentum flip can be provided for small values of the angle $\phi$ in the partial momentum update (10) and a small number $L$ of molecular dynamics time-steps. In that case, rejection of the molecular dynamics proposal step will lead to an almost identical molecular dynamics proposal under the next GHMC iteration and the probability of rejection will remain high. If, on the other hand, the momenta are negated, then the subsequent molecular dynamics proposal will lead back close to a previously accepted state and the acceptance rate will be high. We note that this does not yet explain the observed higher sampling efficiency of the GHMC/GSHMC methods with momentum flips.

GHMC without momentum flip is a viable option for thermostated molecular dynamics since it interferes less with the natural autocorrelation functions of the underlying (stochastic) molecular dynamics model. We explicitly demonstrated this effect for a single butane molecule and observed that momentum flips reduce the correlation quite dramatically while GHMC without momentum flip reproduces the autocorrelation function in the torsion angle well provided the rejection rate is kept below 10%.

GSHMC offers the possibility to run the MDMC part at a very high acceptance rate by using a high order shadow Hamiltonian [2]. Combining this property with a sufficiently small angle $\phi$ in (10) allows for the interpretation of GSHMC as a

thermostated molecular dynamics simulation method. In this context, an implementation without momentum flip is advisable.

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