

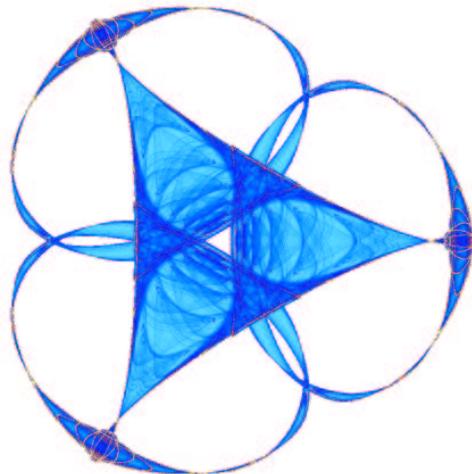
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SOME SAMPLING METHODS FOR MOLECULAR DYNAMICS**

By

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THEORETICAL AND NUMERICAL COMPARISON OF SOME SAMPLING METHODS FOR MOLECULAR DYNAMICS

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Abstract. The purpose of the present article is to compare different phase-space sampling methods, such as purely stochastic methods (Rejection method, Metropolized independence sampler, Importance Sampling), stochastically perturbed Molecular Dynamics (Hybrid Monte Carlo, Langevin Dynamics, Biased Random Walk), and purely deterministic methods (Nosé-Hoover chains, Nosé-Poincaré and Recursive Multiple Thermostats (RMT) methods). After recalling some theoretical convergence properties for the various methods, we provide some new convergence results for the Hybrid Monte Carlo scheme, requiring weaker (and easier to check) conditions than previously known conditions. We then turn to the numerical efficiency of the sampling schemes for a benchmark model of linear alkane molecules. In particular, the numerical distributions that are generated are compared in a systematic way, on the basis of some quantitative convergence indicators.

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Phase-space integrals are widely used in Statistical Physics to relate the macroscopic properties of a system to the elementary phenomena at the microscopic scale [12]. In constant temperature (NVT) molecular simulations, these integrals take the form

$$\langle A \rangle = \int_{T^*\mathcal{M}} A(q, p) d\mu(q, p). \quad (1)$$

In the above expression, \mathcal{M} denotes the position space (also called the *configuration space*), and $T^*\mathcal{M}$ its cotangent space. Typically, $\mathcal{M} = \mathbb{T}^{3N}$ (a torus of dimension $3N$) for simulations with periodic boundary conditions (PBC) and N atoms in the simulation cell. In this case, $T^*\mathcal{M} = \mathbb{T}^{3N} \times \mathbb{R}^{3N}$. Let us note that, for biological systems currently studied, N is typically more than 100,000. A generic element of the position space \mathcal{M} will be denoted by $q = (q_1, \dots, q_N)$ and a generic element of the momentum space \mathbb{R}^{3N} by $p = (p_1, \dots, p_N)$. The so-called canonical probability measure μ appearing in (1) is given by

$$d\mu(q, p) = Z^{-1} \exp(-\beta H(q, p)) dq dp, \quad (2)$$

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where $\beta = 1/k_B T$ (T denotes the temperature and k_B the Boltzmann constant) and where H denotes the Hamiltonian of the molecular system:

$$H(q, p) = \frac{1}{2} p^T M^{-1} p + V(q). \quad (3)$$

In the above expression, $M = \text{Diag}(m_1, \dots, m_N)$ where m_i is the mass of the i -th particle, and V is the potential experienced by the N particles. In simulations with PBC, the potential V takes into account all the particles in the simulated cell, as well as their periodic images.

The constant Z in (2) is the normalization constant defined as

$$Z = \int_{T^* \mathcal{M}} \exp(-\beta H(q, p)) dq dp.$$

Since the Hamiltonian H is separable, the canonical measure is of the form

$$d\mu(q, p) = d\pi(q) d\kappa(p),$$

where

$$d\kappa(p) = \mathcal{P}(p) dp = Z_p^{-1} \exp\left(-\frac{\beta}{2} p^T M^{-1} p\right) dp, \quad (4)$$

and

$$d\pi(q) = f(q) dq = Z_q^{-1} e^{-\beta V(q)} dq. \quad (5)$$

The positive numbers Z_q and $Z_p = (2\pi/\beta)^{3N/2} \prod_{i=1}^N m_i^{3/2}$ are normalization constants. Notice that we implicitly assume that the measures μ and π are probability measures, which is the case when $f \in L^1(\mathcal{M})$. In the case of an isolated system, the potential V is invariant under global translation and rotation of the system, and therefore $f \notin L^1(\mathcal{M})$. It is nevertheless possible to give a sense to (1) by quotienting out rigid body translations.

The function $A(q, p)$ in (1) is an observable, *i.e.* a function on the phase-space related to some physical property of the macroscopic system under consideration. This property can be static, in which case the function A does not depend on time, or dynamical, in which case the function A depends on the time evolution of the system.

Let us present a few examples. For a Lennard-Jones fluid, a classical static quantity is the constant volume specific heat C_V . It is often defined in terms of energy fluctuations, and reads, for a system of N identical particles [39],

$$C_V = \frac{\mathcal{N}_a}{N k_B T^2} (\langle H^2 \rangle - \langle H \rangle^2),$$

where \mathcal{N}_a is the Avogadro number. Another example is the bulk pressure P in a liquid, given by $P = \langle A \rangle$ with

$$A(q, p) = \frac{1}{3|\mathcal{M}|} \sum_{i=1}^N \left(\frac{p_i^2}{m_i} - q_i \cdot \frac{\partial V}{\partial q_i}(q) \right),$$

where $|\mathcal{M}|$ is the volume occupied by the system. Many other static thermodynamical quantities can in fact be computed in the same way. Structural properties such as packing fractions in granular media or radial distribution functions in fluids are also static quantities that are classically considered.

Transport coefficients are examples of dynamical properties. For instance, the self diffusion coefficient in a system of N identical particles of masses m can be computed by the Einstein relation [39]:

$$D = \lim_{t \rightarrow +\infty} \frac{1}{6Nt} \left\langle \sum_{i=1}^N |q_i(t) - q_i(0)|^2 \right\rangle,$$

where $q_i(t)$ is the position of the i -th particle at time t . An alternative expression is the Green-Kubo formula based on the integrated velocity autocorrelation function [39]:

$$D = \frac{1}{3N} \int_0^{+\infty} \left\langle \sum_{i=1}^N \frac{1}{m_i^2} p_i(t) \cdot p_i(0) \right\rangle dt,$$

where $p_i(t)$ is the momentum of the i -th particle at time t . Other classical examples are the shear viscosity of a fluid or its thermal diffusivity [39].

Let us now make precise the way the trajectories $(q(t), p(t))_{t \geq 0}$ are computed in practice. Usually, $(q(t), p(t))$ is taken to be equal to $\Phi_t(q(0), p(0))$ where

$$\begin{aligned} \Phi_t : T^*\mathcal{M} &\rightarrow T^*\mathcal{M} \\ (q, p) &\mapsto \Phi_t(q, p) \end{aligned} \quad (6)$$

is the flow associated with the Hamiltonian (3). In other words, $\Phi_t(q^0, p^0)$ is the solution at time t of the Hamiltonian equations

$$\begin{cases} \frac{dq(t)}{dt} = \frac{\partial H(q(t), p(t))}{\partial p} = M^{-1}p(t) \\ \frac{dp(t)}{dt} = -\frac{\partial H(q(t), p(t))}{\partial q} = -\nabla V(q(t)) \end{cases} \quad (7)$$

with initial conditions $(q(0), p(0)) = (q^0, p^0)$. Choosing NVE (constant energy) trajectories is perfectly justified for computing NVT (constant temperature) dynamical properties for some physical systems such as rarefied gases or molecular beams. The situation is less clear in condensed phase but we can nevertheless remark that this choice is consistent in the sense that the canonical (NVT) measure (2) is invariant under the microcanonical (NVE) dynamics (7). We therefore consider here the following class of time-dependent thermodynamic integrals:

$$\langle B \rangle(t) = \int_{T^*\mathcal{M}} B(\Phi_t(q, p), (q, p)) d\mu, \quad (8)$$

where $B : T^*\mathcal{M} \times T^*\mathcal{M} \rightarrow \mathbb{R}$ is a regular function, Φ_t is defined by (6) and the measure $d\mu$ is given by (2).

An accurate numerical computation of time-dependent thermodynamical integrals asks first for a good sampling of the starting points, distributed according to the canonical distribution. These points should not be too numerous - one must be able to run short Hamiltonian trajectories (one or several) starting from each point with reasonable computer resources. Notice that techniques such as importance sampling do not seem appropriate here since they generate numerous points to sample the canonical measure $d\mu$, many of them with very small weights. As a consequence, when (8) is computed, a lot of time is wasted in computing trajectories with very low weights. Such methods are relevant for the computation of static integrals only. A simple computation confirms these heuristic arguments: the cost of computing a single trajectory over a given physical time interval $[0, T]$ scales as $(\Delta t)^{-1}$. The total cost is of order $O(N(\Delta t)^{-1})$, where N is the number of starting points. Therefore, for a fixed computational cost, there is a trade-off to be made between the accuracy of the sampling of $d\mu$ (scaled by N) and the accuracy of the numerical integration of (7) (given by Δt).

The purpose of this article is twofold: on the one hand, we provide new convergence results on the Hybrid Monte-Carlo sampling scheme (see Section 2.2); on the other hand, we review various numerical methods which are used in molecular simulation to compute integrals such as (1) or (8), and we compare their efficiency on simple alkane molecules. More precisely, we consider the issue of sampling from the canonical measure (2). Since it is straightforward to sample from the momentum distribution (4) (it is a product of independent Gaussian densities), the actual issue is to sample efficiently from the (position space) measure π given by (5).

All the methods considered in this article consist in generating a sequence of points $(q^n)_{n \in \mathbb{N}}$ in the position space. Depending on the method,

Type 1: $(q^n)_{n \in \mathbb{N}}$ is a sequence of independent realizations of a given random variable of density $f(q) = \frac{1}{Z_q} e^{-\beta V(q)}$; this is the case for the standard Rejection and for the Rejection control methods;

Type 2: $(q^n)_{n \in \mathbb{N}}$ is a realization of a continuous state-space Markov chain, for which π is an invariant measure; this is the case for the Metropolized independence sampler and for the Hybrid Monte Carlo method;

Type 3: $(q^n)_{n \in \mathbb{N}}$ is an approximation of $(q_{t_n})_{n \in \mathbb{N}}$ where $(q_t)_{t \geq 0}$ (resp. $(q_t, p_t)_{t \geq 0}$) is a sample path of a stochastic process on \mathcal{M} (resp. on $T^*\mathcal{M}$), for which π (resp. μ) is an invariant measure; this is the case for the biased Random-Walk (resp. for the Langevin dynamics);

Type 4: $(q^n)_{n \in \mathbb{N}}$ is an approximation of $(q(t_n))_{n \in \mathbb{N}}$ where $(q(t), p(t), x(t))_{t \geq 0}$ is a trajectory of a deterministic extended dynamical system (q and p are the physical variables, while x represents some additional variables; see Section 3 for more details); this extended dynamical system is such that it preserves a measure $d\rho$ whose projection on the physical variables q, p is the measure $d\mu$ given by (2); this is the case for Nosé-Hoover, Nosé-Poincaré and Recursive Multiple Thermostat methods.

The first two questions under examination, which are relevant for all the methods mentioned above, are the following:

- **Question 1.** An observable $A(q)$ on \mathcal{M} being given, does the empirical mean $\frac{1}{N} \sum_{n=0}^{N-1} A(q^n)$ converge to the space average $\int_{\mathcal{M}} A(q) d\pi(q)$?
- **Question 2.** If so, can the speed of convergence be estimated?

For methods of Type 1, the answers to Questions 1 and 2 are obviously positive and are direct consequences of the Law of Large Number (LLN) and of the Central Limit Theorem (CLT) for independent identically distributed (i.i.d.) random variables. For the methods of Type 2, Questions 1 and 2 can be positively answered, at least for compact position spaces \mathcal{M} and under some assumptions on the potential V . For Question 1, the point is to check (see Theorem 1 below) that

$$\pi \text{ is an invariant probability measure of the Markov chain,} \quad (9)$$

and that the probability transition kernel $P(q, \cdot)$ of the Markov chain ¹ satisfies the accessibility condition

$$\forall q \in \mathcal{M}, \quad \forall B \in \mathcal{B}(\mathcal{M}), \quad \mu^{\text{Leb}}(B) > 0 \Rightarrow P(q, B) > 0, \quad (10)$$

where $\mathcal{B}(\mathcal{M})$ is the Borel σ -algebra of \mathcal{M} and μ^{Leb} is the Lebesgue measure on \mathcal{M} . Turning to Question 2, a convergence rate of $N^{-1/2}$ can be obtained when the transition kernel P has some regularity properties, and provided some Lyapunov condition holds true (see Theorem 2 and condition (13) below).

For the methods of Type 3, analogous results can be stated at the continuous level (for the underlying Markov processes). In computations, discrete-time approximations are used, and one recovers the case of a Markov chain, and the same kind of results as for methods of Type 2 hold true. For methods of Type 4, no general convergence result is known.

In the case when the sequence $(q^n)_{n \in \mathbb{N}}$ originates from a Markov chain on \mathcal{M} or from a discretized stochastic process on \mathcal{M} or on $T^*\mathcal{M}$ (methods of Types 2 and 3), additional questions arise. Indeed, instead of considering *one* realization starting from a given initial data, it is also possible to generate samples with the same computational cost by considering *several* shorter realizations starting either all from the same point or from different points (which constitute a pre-existing initial distribution). In this case, typical convergence results involve weighted total

¹If $q \in \mathcal{M}$ and B is a Borel set of \mathcal{M} , $P(q, B)$ is the probability for the Markov chain to be in B when starting from q .

variation norms for the probability measures that are generated. In the sequel, we will often refer to this kind of convergence as the "convergence of densities" since, when the n -step probability transition kernel ² $P^n(q, \cdot)$ of the Markov chain and the invariant probability measure both admit densities with respect to the Lebesgue measure, the convergence in total variation norm implies the L^1 convergence of the densities. We can thus formulate the following two questions:

- **Question 3.** Does $\|P^n(q, \cdot) - \pi\|$ converge to zero when n goes to infinity for some (weighted) total variation norm?
- **Question 4.** If so, can the speed of convergence be estimated?

Again, if π is an invariant probability measure and if the accessibility condition (10) holds true, the answer to Question 3 is positive (see Theorems 3 and 4 below). A geometric convergence rate in ρ^N for some $\rho \in (0, 1)$ in some weighted total variation norm can also be obtained when the transition kernel P has some weak regularity properties and provided some Lyapunov condition holds true (namely condition (22) below, see Theorem 8). Let us point out that the Lyapunov condition (22) providing geometric convergence of the densities is not of the same nature as the condition (13) providing a convergence rate of the average along one sample path.

Let us mention that, in some applications, integrals such as (1) are sometimes computed using Blue Moon sampling techniques [6, 8, 10]. In this case, integrals over submanifolds (generally hypersurfaces) of $T^*\mathcal{M}$ have to be estimated. For such computations, the theoretical analysis is the same as the one we present in this article. From the numerical viewpoint, algorithms adapted to the constraint of sampling a hypersurface (and not the whole space) have to be used, namely projected algorithms for stochastic dynamics and SHAKE or RATTLE algorithms for deterministic evolutions (see [14, Chap. VII.1.4]). The numerical analysis of the sampling properties of these specific algorithms is out of the scope of this article.

The article is organized as follows. We first describe and compare from a theoretical point of view the most popular methods to sample from the canonical distribution. In Section 1, we consider purely stochastic methods; stochastically perturbed Molecular Dynamics methods and deterministic thermostating methods are presented in Section 2 and 3 respectively. In particular, in Section 2.2, we present some new convergence results for the Hybrid Monte Carlo scheme (see Theorems 7, 9 and 10). A summary of the main known results is presented in Table 1. We refer to the corresponding sections for notations and further explanations.

We then turn to a practical application of those methods in the case of linear alkane molecules in Section 4. The fact that some methods may work better than others, and that this depends on the situation at hand, is commonly accepted. However, these beliefs are usually only based on some qualitative comparisons, or on comparison with experimental data. In the latter case, discrepancies between numerical results and experimental results can come both from numerical and modelling approximations, so it is not easy to draw conclusions specifically on the numerical methods. Comparing the methods in a *quantitative* way is one of the main purposes of this article.

1. PURELY STOCHASTIC METHODS

Purely stochastic methods consist in generating points in the position space according to the measure $d\pi(q) = f(q) dq$ given by (5), without referring to any physical dynamics of the system.

We briefly recall here four methods, the Rejection, Rejection control, Importance sampling, and Metropolized sampling methods. They all make use of a reference positive probability distribution $g(q)$, such that (i) it is easy to generate samples from g , and (ii) g is a "good" approximation of f , in a sense that will be made precise below.

²For $q \in \mathcal{M}$ and B a Borel set of \mathcal{M} , $P^n(q, B)$ is the probability for the Markov chain to be in B when starting from q after exactly n steps. It is inductively defined from P by $P^0(q, B) = \mathbf{1}_B(q)$ and the induction rule

$$P^n(q, B) = \int_{\mathcal{M}} P(q, dq') P^{n-1}(q', B).$$

| Name | Rejection and Rejection control | Metropolized independence sampler (MIS) | Hybrid Monte-Carlo (HMC) | Biased Random-Walk | Langevin dynamics | Deterministic dynamics |
|--------------------------|---------------------------------|---|---|--|---|---|
| Method | Sampling from the true density | MH with independent proposals | MH with MD proposals | Elliptic diffusion | Hypoelliptic diffusion | Extended MD system |
| Type | i.i.d variables | Markov chain | Discrete time Markov chain | Markov process | Markov process | ODE |
| Questions 1,2 | LLN | MC LLN (conditions on the proposal function) | MC LLN (conditions on V) | MP LLN (Lyapunov condition) | MP LLN (Lyapunov condition) | Open question |
| | Any textbook | Section 1.3 and [31] | Section 2.2.2 | Section 2.3.1 | Section 2.4.1 | |
| Questions 3,4 | - | Uniform ergodicity when a bounding function exists Section 1.3 | Ergodicity Section 2.2.2 | Geometric ergodicity (Lyapunov condition) Section 2.3.2 | Geometric ergodicity (Lyapunov condition) Section 2.4.1 | Open question |
| Numerical discretization | - | - | MH with velocity-Verlet Section 2.2.5 | MALA (RW + MH) Section 2.3.3 | BBK algorithm Section 2.4.2 | Operator splitting Section 3 |
| Type | - | - | Discrete time MC | MH with MD proposals | Discrete-time MC | ODE discretization |
| Convergence | - | - | Same techniques and results as for the continuous scheme Section 2.2.5 | Classical MC techniques Section 2.3.3 and [42] | No result for BBK Results for other schemes Section 2.4.2 | Open question |
| Free parameters | Sampling function g | Proposal function g | Time step Δt , Integration time τ | Time step Δt | Time step Δt , Friction coefficient ξ | Number/values of Nosé masses, Time step Δt |
| Rule | g "close to" f | g "close to" f | "Not too much rejection" | Acceptance rate $\simeq 0.5$ | $\xi \Delta t$ "small" (0.01) | |

TABLE 1. Summary of the different sampling methods and their properties. The following shorthands have been used: MH (Metropolis-Hastings scheme), MD (Molecular Dynamics), i.i.d. r.v. (independently and identically distributed random variables), LLN (usual Law of Large Numbers, *i.e.* for random variables), MC LLN (LLN for Markov chains), MP LLN (LLN for Markov processes), RW (Random-Walk).

1.1. Rejection method

The Rejection method [23] requires the knowledge of a probability density g which bounds f from above up to a multiplicative factor $c > 0$:

$$f \leq cg, \quad (11)$$

and from which it is easy to generate samples. For instance, when $\mathcal{M} = \mathbb{T}^{3N}$ (molecular system with periodic boundary conditions) and the potential V is bounded, a uniform density g may be used (but its efficiency is likely to be very poor). A less simple example is dealt with in [50]. The idea of the method is to draw proposals according to the density g and to accept them with probability $f/(cg)$.

Actually, a bound on the (non-normalized) distribution $\tilde{f}(q) = Z_q f(q) = e^{-\beta V(q)}$ is sufficient to run the algorithm. Such a bound reads $\tilde{f} \leq \tilde{c}g$, and is much easier to establish in practice since the normalization constant Z_q is unknown and very difficult to estimate. The proposals are then accepted with probability $\tilde{f}/(\tilde{c}g)$.

Finding a function g such that the constant c appearing in (11) is small is very important. It is indeed well-known [23] that, on average, generating one sample point requires c draws, *i.e.* c evaluations of the potential V , which is by far the most computationally expensive part of the calculation. This constant c is therefore of paramount importance. When the system dimension is small, it is usually possible to find g such that c is not too large, and therefore the method is very efficient. But when c is very large, the method is totally inefficient. In molecular simulation, it is usually very difficult to construct efficient sampling functions g for systems involving more than a few atoms. This can however still be done for some specific systems, such as crystals at low temperature, using Taylor expansions around the equilibrium position, and controlling the relevance of the expansion by Rejection control techniques (see Section 1.2 below). We refer to [50] for some examples of this approach.

Since the points generated by the Rejection algorithm are independent realizations of some random variable, usual convergence results such as the Law of Large Numbers and the Central Limit Theorem apply [13]. Let A be some observable over the position space, $(q^n)_{0 \leq n \leq N-1}$ be the sample generated by the method, and let us set

$$S_N(A) = \sum_{n=0}^{N-1} A(q^n). \quad (12)$$

If $\pi(|A|) < +\infty$, then the Law of Large Numbers applies. It reads

$$\lim_{N \rightarrow \infty} \frac{1}{N} S_N(A) = \int_{\mathcal{M}} A(q) f(q) dq = \int_{\mathcal{M}} A d\pi \quad \text{a.s.}$$

If $\pi(|A|^2) < +\infty$, then the Central Limit Theorem holds true: there exists $\gamma_A > 0$ such the following convergence in law holds:

$$(N\gamma_A)^{-1/2} S_N(\bar{A}) \xrightarrow{N \rightarrow \infty} \mathcal{N}(0, 1),$$

where $\bar{A} = A - \int_{\mathcal{M}} A d\pi$ and $\mathcal{N}(0, 1)$ is the standard Gaussian random variable.

1.2. Rejection control

It is often delicate to find a function g such that (11) is satisfied everywhere in \mathcal{M} . However, it is sometimes possible to find a sampling function g for which (11) is satisfied for most proposals \tilde{q} generated from g . In this case, the Rejection method presented in the previous section can be somewhat modified so that the non-global character of the bound is taken into account.

The Rejection control scheme [7] allows one to handle proposals that violate the inequality (11) by an appropriate *a posteriori* reweighting. Let us just note here that this scheme can be recast [7] as an Importance sampling scheme, a method we will recall in Section 1.4.

1.3. Metropolized independence sampler

When c is large, the Rejection method may require many evaluations of the potential V . As c is unknown in practice, it is difficult to estimate *a priori* the computational efficiency of the method. Therefore, a stochastic method with a fixed computational cost could provide an interesting alternative.

The Metropolized independence sampler (MIS), presented e.g. in [23, Section 5.4.2], is one such method. Basically, it is a Metropolis-Hastings algorithm with i.i.d. proposals. Therefore, the generated sequence of points forms a Markov chain (see [33] for some definitions and properties of continuous state-space Markov chains).

We assume that the potential V is continuous. Considering an everywhere positive probability density g , let us set $w(q) = \frac{f(q)}{g(q)}$. The algorithm is as follows:

Algorithm 1.1 (Metropolized independence sampling). *Consider an initial point q^0 . For $n \geq 1$,*

- (1) *generate a point \tilde{q} in \mathcal{M} from the density g ;*
- (2) *generate a random number $s \sim \mathcal{U}[0, 1]$;*
- (3) *if $s \leq \min \left\{ 1, \frac{w(\tilde{q})}{w(q^n)} \right\}$, set $q^{n+1} = \tilde{q}$, otherwise, set $q^{n+1} = q^n$;*
- (4) *replace n by $n + 1$ and go back to step (1).*

Let us now recall some convergence results for this method. We denote by P the transition kernel of this Markov chain.

1.3.1. Convergence of the average along one sample path

Let us denote by A some observable on the position space and by $(q^n)_{n \in \mathbb{N}}$ one realization of the MIS Markov chain starting from a given q^0 . The question under examination is that of the convergence of the empirical mean $\frac{1}{N} S_N(A)$ toward $\int_{\mathcal{M}} A(q) d\pi(q)$ where π is the canonical measure defined by (5) and $S_N(A)$ is defined by (12).

By construction, π is an invariant measure [23]. Therefore, condition (9) is satisfied. Condition (10) is also trivially satisfied whenever the support of f is a subset of the support of g . This is the case here since we have chosen a function g whose support is the whole position space \mathcal{M} .

Since conditions (9) and (10) are satisfied, a Law of Large Numbers (LLN) holds for almost all starting points, and Question 1 can therefore be answered positively. Indeed, Meyn and Tweedie have proved the following theorem:

Theorem 1 ([33, Theorem 17.1.7]). *Suppose conditions (9) and (10) are satisfied. Then, for any measurable function $A \in L^1(\pi)$,*

$$\lim_{N \rightarrow \infty} \frac{1}{N} S_N(A) = \int_{\mathcal{M}} A d\pi \quad \text{a.s.}$$

for almost all starting points $q^0 \in \mathcal{M}$, where $S_N(A)$ is defined by (12).

To obtain a convergence rate on $S_N(A)$, an additional condition is needed, such as:

$$\begin{aligned} &\text{There exist two measurable functions } L \geq \min\{1, A\} \text{ and } W \geq 0, \text{ a real number } b \\ &\text{and a petite set } C \text{ such that} \\ &\Delta W(q) \leq -L(q) + b \mathbf{1}_C(q), \quad \pi(W^2) < +\infty, \end{aligned} \tag{13}$$

where A is the observable under consideration and $\Delta W(q)$ is defined by

$$\forall q \in \mathcal{M}, \quad \Delta W(q) = (PW)(q) - W(q) = \int_{\mathcal{M}} P(q, dy) W(y) - W(q). \tag{14}$$

The definition of petite sets can be found in [33]. Let us make the following remark, which will be very useful:

Remark 1. *Under some regularity conditions that will always be met here (including the fact that the chain is weak Feller [33, Chap. 6]), all compact subsets of \mathcal{M} are petite sets. As a consequence, when the state space \mathcal{M} is compact, the condition (13) holds true (choose $C = \mathcal{M}$, W and L arbitrary smooth functions and take b large enough).*

Condition (13) allows one to obtain a Central Limit Theorem (CLT). For a given measurable function A such that $\pi(|A|) < \infty$, the function \hat{A} is formally defined by the following Poisson equation:

$$-\Delta \hat{A} = A - \pi(A),$$

where $\Delta \hat{A}$ is defined as in (14). It is not clear in general whether \hat{A} is well-defined. This turns out to be the case when condition (13) is satisfied, and allows to state a CLT:

Theorem 2 ([33, Theorem 17.5.3]). *Assume conditions (9), (10) and (13) hold true, and let A be a function such that $|A| \leq L$. Let $S_N(A)$ be defined by (12). Then the constant $\gamma_A^2 := \pi(\hat{A}^2 - (P\hat{A})^2)$ is well-defined, non-negative and finite. If $\gamma_A^2 > 0$, then, defining $\bar{A} = A - \pi(A)$,*

$$(N\gamma_A^2)^{-1/2} S_N(\bar{A}) \xrightarrow{N \rightarrow \infty} \mathcal{N}(0, 1),$$

this convergence being in law.

Since conditions (9), (10) and (13) are satisfied for the MIS chain, Question 2 can be answered positively for almost all starting points q^0 .

1.3.2. Convergence of the densities

To handle convergence of densities, it is necessary to introduce the total variation norm for a signed Borel measure ν , defined as

$$\|\nu\| = \sup_{h \text{ measurable}, |h| \leq 1} |\nu(h)| = \sup_{A \in \mathcal{B}(\mathcal{M})} \nu(A) - \inf_{A \in \mathcal{B}(\mathcal{M})} \nu(A), \quad (15)$$

and the weighted total variation norm for some non-negative measurable function $W \geq 1$, defined as

$$\|\nu\|_W = \sup_{h \text{ measurable}, |h| \leq W} |\nu(h)|. \quad (16)$$

Notice that convergence in total variation implies weak convergence.

Definition 1. *A chain on \mathcal{M} is ergodic when*

$$\forall q \in \mathcal{M}, \quad \lim_{n \rightarrow \infty} \|P^n(q, \cdot) - \pi\| = 0$$

where π is the invariant measure and P^n is the n -step probability transition kernel.

Recall the following theorem:

Theorem 3 ([33, Theorem 13.3.4]). *If conditions (9) and (10) hold true, then*

$$\|P^n(q, \cdot) - \pi\| \rightarrow 0 \quad \text{as } n \rightarrow \infty$$

for π -almost all starting points q .

The convergence in total variation norm allows one to conclude to convergence of the expectations only for bounded observables A . It is therefore not sufficient in practice. Fortunately, the ergodicity results can be strengthened in a straightforward way. For a given measurable non-negative function $W \geq 1$, let us define the W -total variation norm for a signed Borel measure μ as

$$\|\mu\|_W = \sup_{h \text{ measurable}, |h| \leq W} |\mu(h)|.$$

Then Theorem 3 can be readily extended to π -integrable functions A .

Theorem 4 ([33, Theorem 14.0.1]). *Suppose that $A \geq 1$ is measurable and $\pi(|A|) < +\infty$. If conditions (9) and (10) hold true, then for π -almost all $q \in \mathcal{M}$,*

$$\|P^n(q, \cdot) - \pi\|_{|A|} \rightarrow 0 \quad \text{as } n \rightarrow \infty.$$

Since conditions (9) and (10) are satisfied, the MIS Markov chain is ergodic and Theorems 3 and 4 hold true. This answers Question 3.

Under an assumption which is reminiscent of the Rejection method setting, a simple uniform convergence rate (independent of the starting point q^0) can be obtained:

Theorem 5 ([31, Theorem 2.1]). *If the probability density g that is used in the metropolized independence sampling scheme is such that*

$$\exists c, \forall q \in \mathcal{M}, \quad f(q) \leq cg(q),$$

then the scheme is geometrically ergodic with a uniform bound. In this case, for all $q^0 \in \mathcal{M}$,

$$\|P^n(q^0, \cdot) - \pi\| \leq (1 - c^{-1})^n.$$

This theorem gives an answer to Question 4. Note that in the particular case when $c = 1$ (that is when $f = g$ since both functions are densities of probability), the convergence is already achieved for $n = 1$. This is actually clear since in this case the MIS scheme samples from the true density!

1.4. Importance sampling

Importance sampling is a well-known general stochastic integration method. The underlying idea is to recast the integral $\mathbb{E}_\pi(A) = \int_{\mathcal{M}} A(q) f(q) dq$ as

$$\mathbb{E}_\pi(A) = \int_{\mathcal{M}} \left(A(q) \frac{f(q)}{g(q)} \right) g(q) dq$$

and to approximate the latter integral through a random sample $(q^n)_{0 \leq n \leq N-1}$ drawn according to the density g (see e.g. [23, Section 2]).

The choice of the trial function g is crucial for the overall efficiency of the method. It should be a good approximation of f or, better, of $f(q)A(q)$. Since f is typically of exponential or Gaussian form, and A is most often bounded by a polynomial, f is usually the most important term in the product $f(q)A(q)$ as far as sampling issues are concerned. Besides, in applications, it is often the case that several integrals have to be computed, with different functions A . So g is often looked for as a good approximation of f .

Let us note that, for the computation of static quantities, the importance sampling method based on a density g outperforms the Rejection method based on the same density g [7].

2. STOCHASTICALLY PERTURBED MOLECULAR DYNAMICS

We first present in Section 2.1 the general framework of deterministic microcanonical (NVE) MD. In Section 2.2, we describe the Hybrid Monte Carlo (HMC) method, from both the theoretical and the numerical viewpoints, and give some new convergence results (see Theorems 7, 9, 10). We then present the biased Random-Walk (BRW) in Section 2.3, and the Langevin dynamics in Section 2.4.

We assume in the sequel that $T^*\mathcal{M}$ is isomorphic to $\mathcal{M} \times \mathbb{R}^{3N}$, and actually identify the two sets for simplicity. We also assume that \mathcal{M} is isomorphic to \mathbb{R}^{3N} in Sections 2.3 and 2.4, and identify the two sets as well. Straightforward modifications allow to handle the other cases (such as systems with periodic boundary conditions or isolated systems parametrized by rigid-body motions and internal coordinates).

2.1. General framework for NVE Molecular Dynamics

The equations of motion (7) associated with the Hamiltonian (3) can be numerically integrated e.g. by the celebrated velocity-Verlet algorithm [57]

$$\begin{cases} p^{n+1/2} = p^n - \frac{\Delta t}{2} \nabla V(q^n) \\ q^{n+1} = q^n + \Delta t M^{-1} p^{n+1/2} \\ p^{n+1} = p^{n+1/2} - \frac{\Delta t}{2} \nabla V(q^{n+1}) \end{cases} \quad (17)$$

where Δt is the time step. The velocity-Verlet scheme is an *explicit* integrator: recall that Statistical Physics often considers systems with a large number of particles, making implicit algorithms untractable. The numerical flow associated to the velocity-Verlet algorithm shares two qualitative properties with the exact flow of (7): it is *time reversible* and *symplectic*, which are very important properties as far as the numerical integration of Hamiltonian dynamics is concerned (see [14, Chap. VIII and IX] and [21]). This algorithm also asks for a unique evaluation of the forces $F = -\nabla V$ per time step. For all these reasons, it is one of the most commonly used algorithm in molecular dynamics.

The dynamics (7) cannot be used to generate points according to the canonical measure, because (3) is preserved by the flow. Hence, the trajectory of the system remains on the submanifold of constant energy

$$T^*\mathcal{M}(E_0) = \{(q, p) \in T^*\mathcal{M}; H(q, p) = E_0\}$$

where $E_0 = H(q_0, p_0)$ is the energy of the initial data. Under some assumptions, the dynamics (7) can be used to compute microcanonical (NVE) ensemble averages, that is averages over $T^*\mathcal{M}(E_0)$. The numerical analysis of this method (in the very simple case of completely integrable systems) can be read in [4, 5, 20]. To generate points according to the canonical measure, there is a need for stochastic perturbations to ensure that different energy levels will be explored, and eventually all of them. These considerations straightforwardly extend to the numerical case since symplectic methods almost preserve energy [14, Chap. IX].

2.2. Hybrid Monte Carlo

2.2.1. Presentation of the method

The Hybrid Monte Carlo method allows one to generate points in the position space distributed according to the canonical measure (5). It aims at combining the advantages of molecular dynamics (that approximates the physical dynamics of the system) and of Monte Carlo methods (that explore the position space more globally). It is in fact a Metropolis-Hastings algorithm, in which proposals are constructed using the NVE Hamiltonian flow of the system. This method has been first introduced by Duane et al. in [9] and partially analyzed from a mathematical viewpoint by Schütte in [47]. It has been used in [48, 49] to identify the metastable conformations of some biological systems. Let us mention that there exist refinements of the standard HMC scheme, see e.g. [34].

In the standard HMC setting, the sequence of generated positions forms a Markov chain of order one defined as follows:

Algorithm 2.1 (Hybrid Monte Carlo). *Consider an initial position $q^0 \in \mathcal{M}$ and $\tau > 0$. For $n \geq 0$,*

- (1) *generate momenta p^n according to the canonical distribution (4) and compute the energy $E^n = H(q^n, p^n)$ of the configuration (q^n, p^n) ;*
- (2) *compute $\Phi_\tau(q^n, p^n) = (q^{n,\tau}, p^{n,\tau})$, i.e. integrate the NVE equations of motion (7) on the time interval $[0, \tau]$ starting from the initial data (q^n, p^n) ;*
- (3) *compute the energy $E^{n,\tau} = H(q^{n,\tau}, p^{n,\tau})$ of the new phase-space configuration. Accept the proposal $q^{n,\tau}$ with probability $p = \min(1, e^{-\beta(E^{n,\tau} - E^n)})$; more precisely, generate a random*

number $\alpha \in [0, 1]$ according to the uniform law, and set $q^{n+1} = q^{n,\tau}$ if $\alpha \leq p$ and $q^{n+1} = q^n$ otherwise;

(4) replace n by $n + 1$ and go back to step (1).

Let us emphasize that the proposal $q^{n,\tau}$ would always be accepted at step (3) if the NVE equations of motion, that are energy conserving, were integrated exactly. In practice, the time-step Δt used in the numerical integrator (17) can be chosen larger than in standard applications of MD since the dynamics of the system used to generate proposals is not constrained to accurately reproduce the physical dynamics of the system. On the other hand, it should not be too large; otherwise, the rejection rate would be large and the efficiency of the method would decrease.

Let us notice that in the standard HMC method, only the end points of the MD trajectories are part of the sample. It is not clear whether taking into account some intermediate points of the generated MD trajectories in the sample would improve the efficiency of the scheme.

2.2.2. Convergence of the average along one realization

As above, let us denote by A some observable on the position space and by $(q^n)_{n \in \mathbb{N}}$ one realization of the HMC Markov chain starting from a given q^0 . Let Π_1 be the first coordinate field of the phase-space: $\Pi_1(q, p) = q$.

Convergence results for the HMC scheme have been published by Schütte in [47]. In this proof, the NVE Hamiltonian flow is assumed to satisfy two conditions:

- (1) a *mixing* condition, which reads as follows (see [47, Assumption 4.27]): for every pair of open subsets $B, C \subset \mathcal{M}$, there exists $n_0 \in \mathbb{N}$ such that

$$\forall n \geq n_0, \int_B T^n \mathbf{1}_C(q) f(q) dq > 0,$$

where f is given by (5) and the function Tu is defined for any function $u : \mathcal{M} \rightarrow \mathbb{R}$ by

$$Tu(q) = \int_{\mathbb{R}^{3N}} u(\Pi_1 \Phi_{-\tau}(q, p)) \mathcal{P}(p) dp, \quad (18)$$

where Φ_τ is defined by (6). This condition amounts to a certain accessibility of the whole position space when starting from any point.

- (2) a so-called *momentum invertibility of the flow* condition (see [47, Definition 4.1]). The flow Φ_τ is called momentum-invertible if the two following conditions hold true:
- for almost every $q \in \mathcal{M}$, there is an open set $M(q) \subset \mathbb{R}^{3N}$ such that the function $y_q : p \mapsto \Pi_1 \Phi_{-\tau}(q, p)$ is locally invertible in $M(q)$, i.e. $\det \nabla_p y_q \neq 0$ for $p \in M(q)$.
 - there is an $\eta > 0$ such that

$$\text{ess-inf}_{q \in \mathcal{M}} \int_{M(q)} \mathcal{P}(p) dp = \eta.$$

This condition states that the transition probabilities are bounded from below in some sense.

The following convergence result is given in [47]:

Theorem 6 ([47, Lemma 4.31 and Theorem A.24]). *Under the assumptions (1) and (2) recalled above, for any measurable function $A \in L^1(\pi)$, it follows*

$$\lim_{N \rightarrow \infty} \frac{1}{N} \sum_{n=0}^{N-1} A(q^n) = \int_{\mathcal{M}} A d\pi \quad \text{a.s.} \quad (19)$$

for almost all starting points $q^0 \in \mathcal{M}$, where $(q^n)_{n \in \mathbb{N}}$ is the sequence of points generated by the HMC Algorithm 2.1 where, at step (2), the NVE equations of motion (7) are exactly integrated.

Note that ergodicity results have also been proved [47, Corollary 4.33], as well as convergence results on the numerical flow [47, p96] (in this latter case, $(q^n)_{n \in \mathbb{N}}$ in (19) is the sequence of points generated by the HMC Algorithm 2.1 where the NVE equations of motion (7) are now numerically integrated).

The conditions (1) and (2) recalled above are difficult to check in practice, and furthermore, it is not clear whether they are necessary. We present here a new convergence result, that does not require these assumptions.

Let us first consider the case when the NVE equations of motion are integrated exactly. The transition kernel P of the HMC Markov chain is defined by

$$\forall (q, B) \in \mathcal{M} \times \mathcal{B}(\mathcal{M}), \quad P(q, B) = \int_{\mathbb{R}^{3N}} \mathbf{1}_{\{\Pi_1 \Phi_\tau(q, p) \in B\}} \mathcal{P}(p) dp, \quad (20)$$

where the density \mathcal{P} is the canonical distribution on the momentum space given by (4).

As the phase-space canonical measure $\mu = \pi \otimes \kappa$ is an invariant measure for Φ_τ , it is clear that the position-space canonical measure π is an invariant measure for the HMC Markov chain (see e.g. [23, Section 9.3] for details). Therefore, condition (9) holds true. In addition, the accessibility condition (10) is satisfied under some assumptions on the potential. This is the result of the following Lemmas.

Lemma 1 (HMC accessibility - exact flow). *Let $\tau > 0$. Assume that V is in $C^1(\mathcal{M})$ and is bounded from above. Then for any $q, q' \in \mathcal{M}$, there exists an open neighborhood \mathcal{V}' of q' such that*

$$P(q, \mathcal{V}') > 0.$$

Proof. The proof is based on the least action principle (LAP). Let us denote by

$$S(\phi) = \int_0^\tau \left(\frac{1}{2} \dot{\phi}^T(t) M \dot{\phi}(t) - V(\phi(t)) \right) dt$$

the action associated with the path $\phi \in \mathcal{H} = \{\phi \in H^1([0, \tau], \mathcal{M}) \mid \phi(0) = q, \phi(\tau) = q'\}$. Since V is bounded from above, there exists E_0 such that $V(q) \leq E_0$ for all $q \in \mathcal{M}$. Thus, S is bounded from below:

$$S(\phi) \geq - \int_0^\tau V(\phi(t)) dt \geq -E_0 \tau.$$

Therefore, there exists a minimizing sequence $(\phi_n)_{n \in \mathbb{N}} \in \mathcal{H}$ such that $S(\phi_n) \rightarrow \inf_{\phi \in \mathcal{H}} S(\phi) = s > -\infty$. Without restriction, it can be assumed that $s \leq S(\phi_n) \leq s + 1$ for all $n \in \mathbb{N}$. Thus,

$$\int_0^\tau \dot{\phi}_n^T(t) M \dot{\phi}_n(t) dt = 2S(\phi_n) + 2 \int_0^\tau V(\phi_n(t)) dt \leq 2S(\phi_n) + 2\tau E_0 \leq 2(s + 1) + 2\tau E_0.$$

Therefore, $(\dot{\phi}_n)_{n \in \mathbb{N}}$ is bounded in $L^2([0, \tau], \mathcal{M})$. The sequence $(\phi_n)_{n \in \mathbb{N}}$ is then bounded in the space $H^1([0, \tau], \mathcal{M})$. Let $\phi \in H^1([0, \tau], \mathcal{M})$ such that (up to an extraction) $\phi_n \rightharpoonup \phi$ in $H^1([0, \tau], \mathcal{M})$ -weak and $\phi_n \rightarrow \phi$ almost everywhere. Since \mathcal{H} is closed in $H^1([0, \tau], \mathcal{M})$, the limit ϕ is actually in \mathcal{H} . Besides, it is easy to check that $\liminf_{n \rightarrow \infty} S(\phi_n) \geq S(\phi)$ (by lower semi-continuity on the kinetic energy and Fatou lemma on the potential energy), and this gives immediately

$$\inf_{\psi \in \mathcal{H}} S(\psi) = \min_{\psi \in \mathcal{H}} S(\psi) = S(\phi).$$

Thus ϕ minimizes S on \mathcal{H} . Therefore, the equation

$$M \ddot{\phi} = -\nabla V(\phi) \quad (21)$$

holds true on $(0, \tau)$ in the distributions sense. By standard regularity results, $\phi \in C^2([0, \tau], \mathcal{M})$ and (21) holds true in the sense of continuous functions. The minimizing function ϕ is simply the solution of the Hamiltonian dynamics with $\phi(0) = q$, $\phi(\tau) = q'$ and initial velocity $\dot{\phi}(0)$.

The existence of an open neighborhood \mathcal{V}' of q' such that $P(q, \mathcal{V}') > 0$ is a straightforward consequence of the continuity of the solutions of (21) with respect to the initial velocity $\dot{\phi}(0)$. \square

Lemma 1 gives accessibility from any point to any *open* set. It is therefore not enough for condition (10) to hold true since it requires accessibility from one point to any arbitrary Borel set of positive Lebesgue measure. This asks for some regularity of the transition kernel, and in fact, some regularity of the dynamics, inferred from stronger assumptions on the potential V . More precisely, we have the following lemma:

Lemma 2 (HMC irreducibility - exact flow). *Assume that $V \in C^1(\mathcal{M})$ is bounded from above and ∇V is globally Lipschitz. Then the transition kernel of the HMC Markov chain satisfies*

$$\forall q \in \mathcal{M}, \forall B \in \mathcal{B}(\mathcal{M}), \quad \mu^{\text{Leb}}(B) > 0 \Rightarrow P(q, B) > 0.$$

Proof. Consider $B \in \mathcal{B}(\mathcal{M})$ such that $\mu^{\text{Leb}}(B) > 0$, and $q \in \mathcal{M}$. We want to show that $P(q, B) > 0$ for P defined by (20). For the sake of simplicity, we assume here that all particle masses are equal to 1.

The proof is based on volume conservation in the phase space: any Borel set of final positions of strictly positive measure can be reached from a set of momenta of strictly positive measure. Denote $I_B(q) = \{p \in \mathbb{R}^{3N} \mid \Pi_1 \Phi_\tau(q, p) \in B\}$, and consider the function $\theta : I_B(q) \mapsto B$ such that $\theta(p) = \Pi_1 \Phi_\tau(q, p)$. This function is surjective according to the proof of the accessibility Lemma 1, so that $\theta(I_B(q)) = B$. Moreover, $P(q, B) = \int_{I_B(q)} \mathcal{P}(p) dp$. Therefore, since \mathcal{P} is positive and continuous, it is enough to show that $\mu^{\text{Leb}}(I_B(q)) > 0$ in order to get $P(q, B) > 0$.

We proceed by contradiction. Suppose $\mu^{\text{Leb}}(I_B(q)) = 0$. We first note that θ is Lipschitz (of constant $\text{Lip}(\theta)$) since ∇V is continuous and globally Lipschitz by assumption, and $\tau > 0$ is fixed. Indeed, denote C the Lipschitz constant of ∇V and note that a solution of the equations of motion can be written as

$$q(\tau) = q + p\tau - \int_0^\tau (\tau - s) \nabla V(q(s)) ds.$$

For two different initial momenta p_1 and p_2 , we have

$$|q_1(t) - q_2(t)| \leq |p_1 - p_2|t + C \int_0^t (t - s) |q_1(s) - q_2(s)| ds.$$

By Gronwall lemma, there exists $c_\tau < \infty$ such that

$$|q_1(\tau) - q_2(\tau)| \leq c_\tau |p_1 - p_2|,$$

hence θ is Lipschitz.

Since the Lebesgue measure and the Hausdorff measure \mathcal{H}^{3N} agree on \mathbb{R}^{3N} (see [11, Section 2.2, Theorem 2]), and since the behavior of the Hausdorff measure under Lipschitz mappings is known [11, Section 2.4, Theorem 1], we obtain

$$\mu^{\text{Leb}}(B) = \mu^{\text{Leb}}(\theta(I_B(q))) = \mathcal{H}^{3N}(\theta(I_B(q))) \leq \text{Lip}(\theta)^{3N} \mathcal{H}^{3N}(I_B(q)) = \text{Lip}(\theta)^{3N} \mu^{\text{Leb}}(I_B(q)) = 0.$$

This gives $\mu^{\text{Leb}}(B) = 0$, in contradiction with the assumption $\mu^{\text{Leb}}(B) > 0$. \square

Since conditions (9) and (10) are satisfied, a Law of Large Numbers (LLN) holds true for almost all starting points (see Theorem 1). We can therefore answer positively to Question 1:

Theorem 7. *Assume that $V \in C^1(\mathcal{M})$ is bounded from above and ∇V is globally Lipschitz. Let $(q^n)_{n \in \mathbb{N}}$ be the sequence of points generated by the HMC Algorithm 2.1 where, at step (2), the NVE equations of motion (7) are exactly integrated. Then*

$$\frac{1}{N} \sum_{n=0}^{N-1} A(q^n) \rightarrow \int_{\mathcal{M}} A(q) d\pi \quad \text{a.s.}$$

for almost all starting points $q^0 \in \mathcal{M}$.

When the potential does not satisfy the conditions of Lemma 2, a proof of convergence may still be carried out in some cases using specific arguments (see [50] for the case of a singular central potential).

2.2.3. Convergence of the densities

Since condition (9) is satisfied, and condition (10) holds true under the above assumptions on the potential (V is C^1 , bounded from above and ∇V is globally Lipschitz), the HMC Markov chain is ergodic (see Theorem 3). In particular,

$$\|P^n(q^0, \cdot) - \pi\| \rightarrow 0$$

for almost all starting points $q^0 \in \mathcal{M}$, where $\|\cdot\|$ denotes the total variation norm (15). We also get convergence in the $|A|$ -total variation norm (16) provided $\pi(|A|) < +\infty$ and $|A| \geq 1$ (see Theorem 4). This answers Question 3.

2.2.4. Convergence rates

We have not been able to state more sophisticated convergence results (Central Limit Theorem, geometric ergodicity) in the general HMC framework since they require stronger results on the Markov chain such as a drift condition (13) or a Lyapunov condition such as

$$\begin{aligned} &\text{There exist a measurable function } W \geq 1, \text{ real numbers } c > 0 \text{ and } b, \\ &\text{and a petite set } C \text{ such that} \\ &\forall q \in \mathcal{M}, \Delta W(q) \leq -cW(q) + b\mathbf{1}_C, \end{aligned} \tag{22}$$

where $\Delta W(q)$ is defined by (14). Let us make the following remark:

Remark 2. *Under some regularity conditions that will always be met here (including the fact that the chain is weak Feller [33, Chap. 6]), and when \mathcal{M} is compact, condition (22) is straightforwardly satisfied with the choice $C = \mathcal{M}$ (in view of Remark 1, \mathcal{M} is a petite set) for any arbitrary smooth function W (taking b large enough).*

When the state space is compact, conditions (13) and (22) hold true (in view of Remarks 1 and 2). We thus obtain a positive answer to Question 2 (see Theorem 2). We also obtain a positive answer to Question 4, in view of the following theorem:

Theorem 8 ([33, Theorem 15.0.1]). *Assume conditions (9), (10) and (22) hold true. Then there exist $\rho < 1$ and $R < +\infty$ such that, for all q satisfying $W(q) < +\infty$,*

$$\|P^n(q, \cdot) - \pi\|_W \leq RW(q)\rho^n,$$

where P^n is the n -step probability transition kernel and $\|\cdot\|_W$ is the norm defined by (16).

2.2.5. Numerical implementation: Method and convergence results

It is standard to use the velocity-Verlet scheme (17) to integrate numerically the trajectories over times $\tau = k\Delta t$ for some integer k . Let us point out that the acceptance/rejection step (3) in Algorithm 2.1 ensures that the HMC Markov chain correctly samples the canonical measure π , so that no bias is introduced by inappropriate numerical discretizations (especially when the integration time-step is large). We denote by $P_{\Delta t}$ the transition kernel of the Markov chain using the velocity-Verlet integrator (17) with time-step Δt .

The theoretical proof of convergence for the numerical version of HMC follows the same lines as the proof of convergence for the exact version using the Hamiltonian flow. The only difference lies in the additional acceptance/rejection step which does not modify the structure of the chain (for it does not change the accessibility properties of the chain). We only precise here the changes that have to be considered for the accessibility Lemma.

Lemma 3 (HMC accessibility - numerical flow). *Let $\tau > 0$. Assume that V is in $C^1(\mathcal{M})$ and is bounded from above on \mathcal{M} , and consider the numerical discretization scheme (17). Then for any $q, q' \in \mathcal{M}$, there exists an open neighborhood \mathcal{V}' of q' such that*

$$P_{\Delta t}(q, \mathcal{V}') > 0.$$

Proof. The proof of Lemma 1 is based on the minimization of the action S over some space \mathcal{H} . Here, we extend this proof to the discretized case using a convenient approximation of this variational problem. There are several ways to discretize this variational problem, leading to different numerical schemes. In particular, the velocity-Verlet algorithm can be derived by minimizing the discretized action [25]

$$S_{\Delta t}(\Phi) = \Delta t \sum_{i=0}^{k-1} \frac{1}{2} \left(\frac{q^{i+1} - q^i}{\Delta t} \right)^2 - \frac{V(q^{i+1}) + V(q^i)}{2}, \quad (23)$$

where $\tau = k\Delta t$ (we again assumed here that all particle masses are equal to 1).

The minimization is performed on the sequences $\Phi = \{q^0, q^1, \dots, q^k\}$ with the constraints $q^0 = q$ and $q^k = q'$. The quantity $S_{\Delta t}$ is still bounded from below for a potential bounded from above. Hence, there exists a minimizing sequence $(\Phi_n)_{n \in \mathbb{N}} = (\{q^{0,n}, q^{1,n}, \dots, q^{k,n}\})_{n \in \mathbb{N}}$. Each difference $q^{i+1,n} - q^{i,n}$ is easily seen to be bounded, thus each component $q^{i,n}$ is in fact bounded. Upon extraction, we can consider $\bar{\Phi} = (\bar{q}^0, \dots, \bar{q}^k)$ such that $q^{i,n} \rightarrow \bar{q}^i$ when $n \rightarrow \infty$ for each i . Moreover, $S(\bar{\Phi}) = \min_{\Phi} S(\Phi)$. The optimality conditions then read

$$\bar{q}^{i+1} = 2\bar{q}^i - \bar{q}^{i-1} - \Delta t^2 \nabla V(\bar{q}^i)$$

for $1 \leq i \leq k-1$. We recognize the Verlet scheme. As in addition $\bar{q}^0 = q$ and $\bar{q}^k = q'$, this shows that given two points q, q' , there is a path connecting them using a numerical velocity-Verlet trajectory with initial velocity $\bar{p}^0 = \frac{\bar{q}^1 - \bar{q}^0}{\Delta t} + \frac{\Delta t}{2} \nabla V(\bar{q}^0)$. By continuity, for initial velocities close to \bar{p}^0 , the endpoint of the resulting trajectory remains in a neighborhood of q' . The proof is complete. \square

We can now state a Law of Large Number theorem (see Theorem 1):

Theorem 9. *Assume that $V \in C^1(\mathcal{M})$ is bounded from above and ∇V is globally Lipschitz. Let $(q^n)_{n \in \mathbb{N}}$ be the sequence of points generated by the HMC Algorithm 2.1 where, at step (2), the NVE equations of motion (7) are integrated by (17). Then*

$$\frac{1}{N} \sum_{n=0}^{N-1} A(q^n) \rightarrow \int_{\mathcal{M}} A(q) d\pi \quad \text{a.s.}$$

for almost all starting points $q^0 \in \mathcal{M}$.

2.2.6. Random Time Hybrid Monte Carlo

When the potential is not bounded from above, the classical HMC scheme does not converge in some cases, even the most simple ones! Consider for example a one-dimensional particle ($\mathcal{M} = \mathbb{R}$) of mass $m = 1$ subjected to the potential $V(q) = \frac{1}{2}q^2$. Then the solution $q(t)$ starting from q^0 with momentum p^0 is given by

$$q(t) = q^0 \cos(t) + p^0 \sin(t).$$

As already noticed by Mackenze in [24], taking $\tau = 2\pi$ leads to $q(\tau) = q^0$ whatever the choice of p^0 . The chain is therefore clearly not ergodic. Of course this spurious effect only arises for special choices of τ . A solution to eliminate such resonance effects was proposed in [24]; it consists in

transforming the fixed parameter τ into a random variable, distributed with a density $\mathcal{T}(\tau)$. This ensures that resonance effects are avoided. We call this scheme "Random Time Hybrid Monte Carlo" (RTHMC).

The only property required on \mathcal{T} is that \mathcal{T} is continuous and positive on \mathbb{R}_+ . The corresponding Markov transition kernel reads, for $q \in \mathcal{M}$ and $B \in \mathcal{B}(\mathcal{M})$,

$$P(q, B) = \int_{\mathbb{R}^{3N} \times \mathbb{R}_+} \mathbf{1}_{\{\Pi_1 \Phi_\tau(q, p) \in B\}} \mathcal{P}(p) \mathcal{T}(\tau) dp d\tau. \quad (24)$$

Notice that π is still an invariant probability measure for this Markov chain, so condition (9) holds true. Therefore, to get convergence results, we only need to show condition (10). This is done in two steps, as for the classical HMC scheme.

The first lemma states that there is a positive probability to go from one state q to a neighborhood of any state q' in one RTHMC iteration.

Lemma 4 (RTHMC accessibility). *Assume that $V \in C^1(\mathcal{M})$. Then for any $q, q' \in \mathcal{M}$, there exists an open neighborhood \mathcal{V}' of q' such that*

$$P(q, \mathcal{V}') > 0,$$

where P is given by (24).

The detailed proof can be found in [50]; we just give here the outline.

Proof. A similar idea is used in [47] in a slightly different context. If V is identically equal to zero, then going from q to q' is possible through the choice of (say) the initial momenta $p^* = M(q' - q)$ and the evolution time $\tau^* = 1$. Considering then the rescaled equation

$$M\ddot{q}_\epsilon(t) = -\epsilon \nabla V(q_\epsilon(t)) \quad (25)$$

with initial conditions $q_\epsilon(0) = q$ and $\dot{q}_\epsilon(0) = M^{-1}p^*$, $q_\epsilon(\tau^*)$ is still close from q' for ϵ small enough. This gives the expected result since, as can be seen by a change of variables, $q_\epsilon(\tau^*)$ is the solution of the Newton equations of motion (7) at time $\epsilon\tau^*$ starting from the position q with momentum $\epsilon^{-1}p^*$. \square

Condition (10) can then be obtained in the same way as for the classical HMC scheme. To this end, we need stronger conditions on the potential V , namely a L^∞ bound on $\nabla^2 V$.

Lemma 5 (RTHMC irreducibility). *Provided that $V \in C^2(\mathcal{M})$ and $\nabla^2 V \in L^\infty(\mathcal{M})$, the transition kernel (24) of the RTHMC Markov chain satisfies condition (10).*

The detailed proof can also be found in [50]; we just give here the outline, assuming that particle masses are equal to 1.

Proof. The proof relies on the fact that, for $\tau > 0$ small enough, the mapping $p \mapsto \Pi_1 \Phi_\tau(q, p)$ is invertible for a given q . Denote $J_B(q) = \{(p, \tau) \in \mathbb{R}^{3N} \times \mathbb{R}_+ \mid \Pi_1 \Phi_\tau(q, p) \in B\}$, and consider $\psi : J_B(q) \mapsto B$ such that $\psi(\tau, p) = \Pi_1 \Phi_\tau(q, p)$. Then, $P(q, B) = \int_{J_B(q)} \mathcal{P}(p) \mathcal{T}(\tau) dp d\tau$. We first show that $p \mapsto \psi(\tau, p) = \Pi_1 \Phi_\tau(q, p)$ is invertible for $\tau > 0$ small enough when $\nabla^2 V \in L^\infty(\mathcal{M})$. From the equations of motion,

$$\psi(\tau, p) = q + p\tau - \int_0^\tau (\tau - s) \nabla V(\psi(s, p)) ds.$$

Then

$$\nabla_p \psi(\tau, p) = \tau \text{Id} - \int_0^\tau (\tau - s) \nabla^2 V(\psi(s, p)) \cdot \nabla_p \psi(s, p) ds. \quad (26)$$

Set $\alpha(s) = \sup\{\|\nabla_p \psi(s, p) - s\text{Id}\|_\infty, p \in \mathbb{R}^{3N}\}$. It follows

$$\alpha(\tau) \leq C \left(\int_0^\tau (\tau - s) \alpha(s) ds + \frac{\tau^3}{6} \right)$$

for some $C > 0$. Therefore, $\alpha(\tau) \leq \frac{\tau}{2}$ for $0 < \tau \leq \tau_c$ with $\tau_c < C^{-1/2}$. Now,

$$\begin{aligned} (\psi(\tau, p_1) - \psi(\tau, p_2)) \cdot (p_1 - p_2) &= \int_0^1 (p_1 - p_2) \cdot \nabla_p \psi(\tau, p_1 + s(p_1 - p_2)) \cdot (p_1 - p_2) ds \\ &= \int_0^1 (p_1 - p_2) \cdot (\nabla_p \psi(\tau, p_1 + s(p_1 - p_2)) - \tau \text{Id}) \cdot (p_1 - p_2) ds \\ &\quad + \tau |p_1 - p_2|^2 \end{aligned}$$

Let us suppose that $\psi(\tau, p_1) = \psi(\tau, p_2)$. Then

$$\tau |p_1 - p_2|^2 \leq \alpha(\tau) |p_1 - p_2|^2 \leq \frac{\tau}{2} |p_1 - p_2|^2$$

and we obtain $p_1 = p_2$. Hence, the mapping $\psi(\tau, \cdot)^{-1}(B) \ni p \mapsto q(\tau, p) \in B$ is one-to-one. Using (26), we also have $\text{Det}(\nabla_p \psi(\tau, p)) = \tau^{3N}(1 + o(1))$. The mapping $\psi_\tau = \psi(\tau, \cdot)$ is then invertible and $\text{Det}(\nabla_p \psi_\tau^{-1}(q)) = \tau^{-3N}(1 + o(1))$.

If $P(q, B) = 0$, then $\int_{\mathbb{R}^{3N}} \mathbf{1}_{\{\Pi_1 \Phi_\tau(x, p) \in B\}} \mathcal{P}(p) dp = 0$ for almost all τ by Fubini's theorem. Therefore, a change of variable for $0 < \tau < \tau_c$ shows that

$$\int_B \mathcal{P}(\psi_\tau^{-1}(q)) |\text{Jac}(\psi_\tau^{-1}(q))| dq = 0.$$

This is however not possible since \mathcal{P} is continuous and positive, $\mu^{\text{Leb}}(B) > 0$, and $|\text{Jac}(\psi_\tau^{-1}(q))| \sim \tau^{-3N}$ when $\tau \rightarrow 0$ so that $|\text{Jac}(\psi_\tau^{-1}(q))| > 0$ for τ small enough. \square

We then get convergence of the average along a sample path (see Theorem 1):

Theorem 10. *Assume that $V \in C^2(\mathcal{M})$ and $\nabla^2 V \in L^\infty(\mathcal{M})$. Let $(q^n)_{n \in \mathbb{N}}$ be the sequence of points generated by the RTHMC algorithm where the NVE equations of motion (7) are exactly integrated. Then*

$$\frac{1}{N} \sum_{n=0}^{N-1} A(q^n) \rightarrow \int_{\mathcal{M}} A(q) d\pi \quad \text{a.s.}$$

for almost all starting points $q^0 \in \mathcal{M}$.

We also obtain ergodicity and convergence of the densities as for the classical HMC scheme under the assumptions of Lemma 5 (see Theorem 3).

For the numerical discretization, we have to consider times $\tau_n = n\Delta t$, and a probability \mathcal{T} on \mathbb{N} such that $\mathcal{T}(n) > 0$ for all n (a Poisson law for instance). The time-step Δt has to be chosen small enough such that no resonance effect can appear.

2.3. Biased Random-Walk

The so-called biased Random-Walk, also known as the Brownian dynamics, or the overdamped Langevin dynamics, is defined by the fictitious dynamics

$$dq_t = -\nabla V(q_t) dt + \sigma dW_t, \tag{27}$$

where $(W_t)_{t \geq 0}$ is a d dimensional standard Wiener process and $\sigma = (2/\beta)^{1/2}$. The term ‘‘biased’’ refers to the fact that the brownian trajectories are affected by the drift term $-\nabla V$ which tends

to draw them toward the local minima of V . The infinitesimal generator \mathcal{A} associated with the biased Random-Walk (27) is defined by

$$\mathcal{A}g = -\nabla V \cdot \nabla g + \frac{\sigma^2}{2} \Delta g, \quad (28)$$

for $g \in C^2(\mathbb{R}^{3N})$. We denote by P^t the Markov semigroup associated with (27). Trajectorial existence and uniqueness for (27) is classical for globally Lipschitz force-fields [15, Theorem III.3.2], namely for potentials V satisfying for some positive constant L

$$\forall(x, y) \in \mathbb{R}^{3N} \times \mathbb{R}^{3N}, \quad |\nabla V(x) - \nabla V(y)| \leq L|x - y|. \quad (29)$$

When this condition is not satisfied, it is possible to conclude to trajectorial existence and uniqueness for locally Lipschitz force-fields under the following hypothesis (see [15, Theorem III.4.1]): there exist a function $W(q) \in C^2(\mathbb{R}^{3N})$ that goes to infinity at infinity and a positive constant c such that

$$\mathcal{A}W \leq cW. \quad (30)$$

Besides, under assumption (29) or (30), one can prove that the Markov process (27) is Feller [32].

From the Fokker-Planck equation associated with (27), it is easy to check that

$$\pi \text{ is an invariant probability measure of (27),} \quad (31)$$

where π is the canonical position space distribution (5).

2.3.1. Convergence of the time average along one sample path

Let us consider the time average

$$S_T(A) = \frac{1}{T} \int_0^T A(q_t^x) dt, \quad (32)$$

where q_t^x is the solution of (27) with the deterministic initial condition $q_0 = x$. Convergence results analogous to the results obtained for Markov chains can be extended to Markov processes, with an average (32) still taken only over one realization of the process (see [52] for a seminal contribution (that also considers discretization issues), [53, 54] for improvements and refinements, and [38] for a recent review).

To obtain an almost sure convergence of $S_T(A)$ to the state space average (and thus a positive answer to Question 1), the following theorem can be used:

Theorem 11 ([32, Theorem 8.1]). *Assume that the process q_t defined by (27) is Feller, that condition (31) holds true as well as the following condition:*

$$\text{for all } t, \text{ for all } q \in \mathbb{R}^{3N} \text{ and all open set } \mathcal{O} \subset \mathbb{R}^{3N}, \quad P^t(q, \mathcal{O}) > 0. \quad (33)$$

Then, for π -almost every $q \in \mathbb{R}^{3N}$ and for any $A \in L^1(\pi)$,

$$\lim_{T \rightarrow \infty} S_T(A) = \int_{\mathbb{R}^{3N}} A(q) d\pi \quad \text{a.s.}$$

If ∇V is globally Lipschitz, then (33) holds true by standard results [44]. In other cases, a simple way to check condition (33) is to use a controllability argument inspired from [29, Lemma 3.4]. Central Limit Theorems (which would provide a convergence rate of $S_T(A)$ towards its limit and thus provide an answer to Question 2) can also be stated. However, the setting is not as clear as in the discrete time case (the latter has been addressed in Theorem 2). We refer for example to [17].

2.3.2. Convergence of the densities

Ergodicity holds true whenever conditions (31) and (33) are satisfied (see [32, Theorem 6.1]). Question 3 can therefore be answered positively. To get an exponential convergence rate (in the W -total variation norm (16)), that is to answer Question 4, one needs to show the stronger condition

$$\mathcal{A}W(q) \leq -cW(q) + b\mathbf{1}_C(q), \quad (34)$$

where $W \geq 1$ is a measurable function going to infinity at infinity, $c > 0$, $b \in \mathbb{R}$ and C is a compact set. We do not address this question in the present article (see [29, 53, 54] for examples of such studies).

2.3.3. Numerical implementation

The Euler-Maruyama numerical scheme associated to (27) reads, when taking integration steps $h = \Delta t^2/2$:

$$q^{n+1} = q^n - \frac{\Delta t^2}{2} \nabla V(q^n) + \beta^{-1/2} \Delta t R^n, \quad (35)$$

where $(R^n)_{n \in \mathbb{N}}$ is a sequence of i.i.d. $3N$ -dimensional standard Gaussian random vectors.

For globally Lipschitz force-fields, the Euler-Maruyama scheme (35) converges [55]: if the process q_t defined by (27) is ergodic, then the numerical Markov chain is ergodic and its invariant measure is close to the invariant measure of the original process (for Δt small enough).

However, for non-globally Lipschitz force-fields, it is not sufficient to consider the discretization (35) of the diffusion process alone. Indeed, examples of non-globally Lipschitz force-fields are known for which the Euler-Maruyama scheme fails [29, 42]. There are two ways out of this situation. First, discretizations of (35) using some implicit integration can be used, such as the so-called split-step backward Euler method [29]: with a time step $h = \Delta t^2/2$, this algorithm reads

$$\begin{cases} q^* = q^n - \frac{\Delta t^2}{2} \nabla V(q^*) \\ q^{n+1} = q^* + \beta^{-1/2} \Delta t R^n \end{cases} \quad (36)$$

where $(R^n)_{n \in \mathbb{N}}$ is a sequence of d -dimensional i.i.d. Gaussian random vectors. This numerical scheme converges under some assumptions on the potential V , the limit measure converging to the canonical measure when $\Delta t \rightarrow 0$ [29]. However, implicit methods become untractable for large systems. Another approach may then be considered, the so-called ‘‘Metropolis-adjusted Langevin³ algorithm’’ (MALA), proposed by Roberts and Tweedie in [42], which corrects the Euler-Maruyama discretization (35) by an additional acceptance/rejection step. It consists in generating proposal steps using (35), and accepting or rejecting them according to a Metropolis-Hastings rule. Note that choosing the time step h of the MALA algorithm such that $h = \Delta t^2/2$ makes the comparison between the MALA algorithm and the Hybrid Monte Carlo methods easier (see [50] for further details).

In the case of the MALA algorithm, using a potential $V \in C^1(\mathbb{R}^{3N})$ is enough to satisfy condition (10). Since π is by construction an invariant probability measure (and therefore condition (9) holds true), the Markov chain formalizing the algorithm is ergodic for almost all starting points, and the convergence results stated in Theorems 1 and 3 apply. On the other hand, conditions ensuring the Central Limit Theorem and geometric ergodicity (conditions (13) and (22), see Theorems 2 and 8) are not easy to check. We refer to [42, 43] for such studies.

The only adjustable parameter of the algorithm is the time-step Δt . The rejection rate is a good indicator of efficiency. It is indeed well-known that a good sampling is a trade-off between decorrelation (to this end, larger time-steps are required) and acceptance rate (the larger the time-step, the larger the rejection rate). We refer for example to [41] where it is shown that, for tensorized distributions, the asymptotical optimal acceptance rate, when the dimension of

³The term ‘‘Langevin’’ does not refer here to the Langevin dynamics as known in the Physics literature (see Section 2.4). In the Probability and Statistics fields, it is, for some authors, the name for the biased Random-Walk.

the position space \mathcal{M} goes to infinity, is 0.574. This theoretical result does not extend to more complicated situations, but numerical results seem to show that it is quite robust.

In Section 4, we present numerical results obtained both with the Euler-Maruyama scheme and with the MALA scheme.

2.4. Langevin dynamics

The paradigm of Langevin dynamics is to introduce in the Newton equations of motion some fictitious brownian forces modelling fluctuations, balanced by viscous damping forces modelling dissipation. More precisely, the equations of motion read here

$$\begin{cases} dq_t = M^{-1}p_t dt \\ dp_t = -\nabla V(q_t) dt - \xi M^{-1}p_t dt + \sigma dW_t \end{cases} \quad (37)$$

where $(W_t)_{t \geq 0}$ is a $3N$ -dimensional Wiener process. The parameters ξ and σ represent the magnitude of the fluctuations and of the dissipation respectively, and are linked by the fluctuation-dissipation relation:

$$\sigma = (2\xi/\beta)^{1/2}, \quad (38)$$

where $\beta = 1/k_B T$. Therefore, there remains one adjustable parameter in the model. Let us remark that the biased Random-Walk (27) is obtained from the Langevin dynamics (37) by letting the mass matrix M go to zero and by setting $\xi = 1$, which amounts here to rescaling the time.

The proof of trajectorial existence and uniqueness follows the same lines as for the biased Random-Walk case, with the same kind of assumptions (global Lipschitz force fields ∇V or a Lyapunov condition analogous to (30)). It is straightforward to show that the canonical probability measure (2) is a steady state of the Fokker-Planck equation associated with (37).

2.4.1. Convergence results

The same results hold true for the Langevin process as the ones stated in Sections 2.3.1 and 2.3.2 for the biased Random-Walk, the proofs following the same lines. We refer to [29] for further details concerning condition (33) (where \mathbb{R}^{3N} is to be replaced by $\mathbb{R}^{3N} \times \mathbb{R}^{3N}$ and P^t is now the Markov semigroup associated with the Langevin dynamics).

Questions 1 and 3 can therefore be answered positively. Question 4 can also be answered positively when a convenient drift condition can be stated (condition (34) where \mathcal{A} is now the infinitesimal generator associated to (37)). As for the biased Random-Walk, there is no clear answer to Question 2 to our knowledge.

2.4.2. Numerical implementation

There are several ways to compute numerically an invariant distribution using a Langevin dynamics: with a Metropolized scheme as for the biased Random-Walk case (see [50] for further details); with convenient discretizations and a step-size Δt sufficiently small ensuring the sampling from an invariant measure close to the canonical measure (2); or by extending usual NVE schemes used in deterministic MD simulations to the case of the Langevin dynamics. The latter way is the most convenient in many applications. Unfortunately, to our knowledge, there is no theoretical proof of convergence for the resulting scheme. Let us now detail successively the last two approaches.

General results of error analysis hold true for the numerical discretization of the Langevin equation for globally Lipschitz force fields [29]. In this case, the resulting numerical Markov chain is ergodic for usual discretization schemes (including the Euler-Maruyama discretization) and their invariant measures are close to the invariant measure of the original process (for Δt small enough).

The results are not the same for only locally Lipschitz force fields. Some classes of discretized schemes however behave properly under additional assumptions on the potential. This is the case

for the so-called split-step Backward Euler-method [29], already discussed for the biased Random-Walk method (see (36)). Applied to the Langevin equation (37), this algorithm reads

$$\begin{cases} q^{n+1} = q^n + \Delta t M^{-1} p^* \\ p^* = p^n - \xi \Delta t M^{-1} p^* - \Delta t \nabla V(q^{n+1}) \\ p^{n+1} = p^* + \sigma \sqrt{\Delta t} R^n \end{cases} \quad (39)$$

where $(R^n)_{n \in \mathbb{N}}$ is a sequence of d -dimensional i.i.d. Gaussian random vectors. Unfortunately, this method is implicit (see the first two equations, to be solved for (q^{n+1}, p^*)), therefore not convenient for MD simulations of large systems. The following *explicit* scheme is therefore preferred

$$\begin{cases} p^* = p^n - \xi \Delta t M^{-1} p^* - \Delta t \nabla V(q^n) \\ q^{n+1} = q^n + \Delta t M^{-1} p^* \\ p^{n+1} = p^* + \sigma \sqrt{\Delta t} R^n \end{cases} \quad (40)$$

where $(R^n)_{n \in \mathbb{N}}$ is a sequence of d -dimensional i.i.d. Gaussian random vectors. The above algorithm is an extension of the symplectic Euler scheme to the stochastic setting.

We now turn to the numerical analysis of (40). Let us denote by \mathcal{F}_n the σ -algebra of events up to and including the n -th iteration. We need to prove condition (9) and condition (10) to state a Law of Large Number theorem (see Theorem 1). The accessibility condition (10) is easily seen to be satisfied (by arguments similar to those of Section 2.3.1 in this time discrete case). We now prove condition (9), that is the existence of an invariant probability measure. For this purpose, we need to make some assumptions on the potential V , similar to those of [29], to state a Lyapunov inequality for the discretized process. Indeed, we want to make use of the following theorem:

Theorem 12 ([29, Theorem 2.5]). *Denote by P the transition kernel associated to the Markov chain formalizing (40), assumed to be Feller. Assume that (10) is satisfied and that there exist a function $W_{\Delta t}(q, p) \geq 1$, going to infinity at infinity, and two real numbers $b \in (0, 1)$ and $c > 0$ such that*

$$\mathbb{E}(W_{\Delta t}(q^{n+1}, p^{n+1}) | \mathcal{F}_n) \leq b \mathbb{E}(W_{\Delta t}(q^n, p^n)) + c, \quad (41)$$

where (q^n, p^n) is the discrete trajectory given by (40). Then there exists an invariant probability measure $\mu_{\Delta t}$, and condition (9) holds true.

The numerical scheme then converges (the limit being $\int_{\mathbb{R}^{3N} \times \mathbb{R}^{3N}} A(q) d\mu_{\Delta t}$) in the sense of Questions 1 to 4. The question of estimating the distance between $\mu_{\Delta t}$ and the canonical measure μ has been addressed in e.g. [29, 54].

Let us now find $W_{\Delta t}$, b and c satisfying (41). We assume that the potential V is in $C^2(\mathbb{R}^{3N})$ and satisfies a one-sided Lipschitz condition: there exists $C > 0$ such that

$$\forall a, b \in \mathbb{R}^{3N}, (\nabla V(a) - \nabla V(b)) \cdot (a - b) \leq C|a - b|^2. \quad (42)$$

We also assume that there exist $A, B > 0$ such that

$$\forall q \in \mathbb{R}^{3N}, -\nabla V(q) \cdot M^{-1} q \leq A - B \left(V(q) + \frac{\xi^2}{4} q^T M^{-1} q \right). \quad (43)$$

These conditions are satisfied for example for potentials growing quadratically at infinity. The following result, strongly inspired from [29], can then be stated:

Lemma 6. *Let (q^n, p^n) be the discrete trajectory given by (40). Let us assume that V is bounded from below and let us set $m = \max \{m_1, \dots, m_N\}$,*

$$W(q, p) = 1 + \frac{1}{2} p^T M^{-1} p + \frac{\xi^2}{4} q^T M^{-1} q + V(q) - \inf V + \frac{\xi}{2} p^T M^{-1} q \quad (44)$$

and $W_{\Delta t}(q, p) = W(q, p) + \frac{\xi}{4m^2}\Delta t|p|^2$. Let us assume that (42) and (43) are satisfied, and that

$$0 \leq \Delta t \leq \frac{\xi}{\xi^2/m + 4C}. \quad (45)$$

Then $W_{\Delta t}$ satisfies (41) for some $c > 0$, $0 < b < 1$.

We just give here the outline of the proof, and refer to [50] for further details.

Proof. Consider the numerical scheme (40). Some computations give

$$\begin{aligned} W(q^{n+1}, p^*) - W(q^n, p^n) &\leq -\frac{\xi\Delta t}{2m^2} \left(1 - \frac{\xi\Delta t}{2m}\right) |p^*|^2 - \frac{\xi\Delta t}{2} \nabla V(q^n) \cdot M^{-1}q^n \\ &\quad + V(q^n + \Delta t M^{-1}p^*) - V(q^n) - \Delta t \nabla V(q^n) \cdot M^{-1}p^*. \end{aligned}$$

The one-sided Lipschitz condition (42) allows to handle the term $V(q^n + \Delta t M^{-1}p^*) - V(q^n) - \Delta t \nabla V(q^n) \cdot M^{-1}p^*$. The condition (43) allows to handle the term $-\frac{\xi\Delta t}{2} \nabla V(q^n) \cdot M^{-1}q^n$. When (45) is satisfied, it then follows

$$W(q^{n+1}, p^*) - W(q^n, p^n) \leq A \frac{\xi\Delta t}{2} - B \frac{\xi\Delta t}{2} \left(V(q^n) + \frac{\xi^2}{4} q^n \cdot M^{-1}q^n \right) - \frac{\xi}{4m^2} \Delta t |p^*|^2. \quad (46)$$

Recalling $W_{\Delta t}(q, p) = W(q, p) + \frac{\xi}{4m^2}\Delta t|p|^2$, we obtain

$$\begin{aligned} W_{\Delta t}(q^{n+1}, p^*) - W_{\Delta t}(q^n, p^n) &\leq A \frac{\xi\Delta t}{2} - B \frac{\xi\Delta t}{2} \left(V(q^n) + \frac{\xi^2}{4} q^n \cdot M^{-1}q^n \right) - \frac{\xi}{4m^2} \Delta t |p^n|^2 \\ &\leq A \frac{\xi\Delta t}{2} - B' W_{\Delta t}(q^n, p^n) \end{aligned}$$

for some $B' > 0$. The final step $p^{n+1} = p^* + \sigma\sqrt{\Delta t}R^n$ leads to

$$\mathbb{E}(W_{\Delta t}(q^{n+1}, p^{n+1}) \mid \mathcal{F}_n) = \mathbb{E}(W_{\Delta t}(q^{n+1}, p^*)) + \mathbb{E}|\sigma\sqrt{\Delta t}R^n|^2,$$

so that

$$\mathbb{E}(W_{\Delta t}(q^{n+1}, p^{n+1}) \mid \mathcal{F}_n) \leq b \mathbb{E}(W_{\Delta t}(q^n, p^n)) + c \quad (47)$$

for some $c > 0$, $0 < b < 1$. \square

Let us now turn to the last approach. We have not been able to show convergence results for algorithms generalizing the Verlet algorithm. One such algorithm is the BBK algorithm, proposed by Brünger, Brooks and Karplus [3].

It is a modification of the usual velocity-Verlet scheme obtained by adding a term $-\xi \frac{p_i}{m_i} + \frac{\sigma_i}{\sqrt{\Delta t}} R_i^n$ to the force f_i exerted on particle i (the relation between ξ and σ_i will be made precise below). This may explain its popularity since it only asks for slight modifications of standard MD codes. The random forcing terms R_i^n ($i \in \{1, \dots, N\}$) is the label of the particles, n is the iteration index) are standard i.i.d. Gaussian random variables. The scheme reads:

$$\left\{ \begin{array}{l} p_i^{n+1/2} = p_i^n + \frac{\Delta t}{2} \left(-\nabla_{q_i} V(q^n) - \xi \frac{p_i^n}{m_i} + \frac{\sigma_i}{\sqrt{\Delta t}} R_i^n \right) \\ q_i^{n+1} = q_i^n + \Delta t \frac{p_i^{n+1/2}}{m_i} \\ p_i^{n+1} = \frac{1}{1 + \frac{\xi\Delta t}{2m_i}} \left(p_i^{n+1/2} - \frac{\Delta t}{2} \nabla_{q_i} V(q^{n+1}) + \sigma_i \frac{\sqrt{\Delta t}}{2} R_i^{n+1} \right) \end{array} \right. \quad (48)$$

The BBK algorithm is well-suited only for small values of ξ [30] (for large values of ξ other methods have to be used, as described in [18, 58] for example). Let us note that there exist many other integration schemes for the Langevin equation, and that it is not completely understood which integration scheme is the most efficient [18, 30, 58], especially because the comparison benchmarks vary from one field to another. We refer to [46] for examples of other numerical schemes for the integration of (37). Let us emphasize that, to our knowledge, and in contradiction with the two previous discretization strategies for the Langevin dynamics, no convergence result (in the sense of Markov chains theory) is known for the algorithm (48) presented here.

We now make precise the relation between ξ and σ_i by considering the case when there are no forces. When $\nabla V = 0$, the BBK algorithm reads

$$\left(1 + \frac{\xi}{2m_i}\Delta t\right) p_i^{n+1} = \left(1 - \frac{\xi}{2m_i}\Delta t\right) p_i^n + \sigma_i \frac{\sqrt{\Delta t}}{2} (R_i^n + R_i^{n+1}). \quad (49)$$

We see that, if $\mathbb{E}(p_i^n) = 0$, then $\mathbb{E}(p_i^{n+1}) = 0$. Choosing p_i^0 such that $\mathbb{E}(p_i^0) = 0$, we have $\mathbb{E}(p_i^n) = 0$ for all n . Let us now denote by $K_i^n = \mathbb{E}((p_i^n)^2)$ the variance of p_i^n . Setting $\gamma_i = \frac{\xi\Delta t}{2m_i}$, one has

$$(1 + \gamma_i)^2 K_i^{n+1} = (1 - \gamma_i)^2 K_i^n + \frac{3\sigma_i^2}{2}\Delta t + \sigma_i(1 - \gamma_i)\sqrt{\Delta t}\mathbb{E}(p_i^n \cdot R_i^n) \quad (50)$$

since p_i^n is independent of R_i^{n+1} . The last expectation can be computed using (49), leading to

$$(1 + \gamma_i)^2 K_i^{n+1} = (1 - \gamma_i)^2 K_i^n + \frac{3\sigma_i^2}{2}\Delta t + (1 - \gamma_i)(1 + \gamma_i)^{-1} \frac{3\sigma_i^2\Delta t}{2}.$$

Thus

$$K_i^{n+1} = \left(\frac{1 - \gamma_i}{1 + \gamma_i}\right)^2 K_i^n + \frac{3\sigma_i^2\Delta t}{(1 + \gamma_i)^3}.$$

The previous recursion is of the general form $x_{n+1} = ax_n + b$, and has a fixed point provided $a < 1$, which is always the case here since $\gamma_i > 0$. This fixed point K_i^∞ is such that

$$\frac{1}{m_i} K_i^\infty = \frac{3\sigma_i^2}{2\xi(1 + \gamma_i)}.$$

Setting σ_i to the value

$$\sigma_i^{\Delta t} = \sqrt{\frac{2\xi(1 + \gamma_i)}{\beta}}, \quad (51)$$

we see that $K_i^\infty = \frac{3m_i}{\beta}$, which is indeed the expected value (the kinetic temperature is correct).

Note that (51) gives the magnitude of the random forcing that should be used in numerical simulations, which is close to the value (38) used for the SDE (37) only when γ_i is small. Note also that this magnitude depends on the particle mass, so that it may be different from one particle to another one. The simulation results of Section 4 have been obtained with the value $\sigma^{\Delta t}$ given by (51). Note that it can be observed in numerical simulations [50] that if σ is chosen according to (38) instead of (51), then the kinetic temperature is lower than the target temperature T , as predicted by the above theoretical study.

3. DETERMINISTIC MOLECULAR DYNAMICS SAMPLING

We now turn in this Section to purely deterministic methods. These methods rely on the following idea: a system in the canonical ensemble can be considered as a system interacting with an external heat bath, the interaction being such that, at equilibrium, the physical system variables are distributed according to the canonical measure. Thus, the idea is to consider an

extended system composed of the physical variables and some additional variables modelling the bath. Various dynamics have been proposed in this vein.

In this Section, we first consider the Nosé-Hoover dynamics and its generalization to the Nosé-Hoover chains [16, 27, 37, 56]. Then, we consider the Nosé-Poincaré method [2] and the Recursive Multiple Thermostats (RMT) method, which has been recently proposed in [22].

3.1. The Nosé-Hoover and Nosé-Hoover chains methods

The Nosé-Hoover (NH) method, proposed by Hoover, consists in describing the heat bath by two scalar variables, its “position” η and its “momentum” ξ , and to *postulate* the following dynamics for the extended set of variables [16, 37]:

$$\begin{cases} \frac{dq_i}{dt} = \frac{p_i}{m_i} \\ \frac{dp_i}{dt} = -\nabla_{q_i} V - \frac{p_i \xi}{Q} \\ \frac{d\eta}{dt} = \frac{\xi}{Q} \\ \frac{d\xi}{dt} = \sum_{i=1}^N \frac{p_i^2}{m_i} - dNk_B T \end{cases} \quad (52)$$

where V is the potential energy of the system, d is the dimension of the physical space (3 in realistic MD simulations), N is the number of particles and T is the target temperature. The parameter Q represents the mass of the thermostat; it is a free parameter that the user has to choose. The quantity

$$\tilde{H}_{\text{NH}} = \sum_{i=1}^N \frac{p_i^2}{2m_i} + V(q) + \frac{\xi^2}{2Q} + dNk_B T \eta \quad (53)$$

is an invariant of the dynamics (52), which also preserves the measure

$$d\mu_{\text{NH}} = \exp(dN\eta) dq dp d\eta d\xi. \quad (54)$$

We refer to [12] for details on the origin of this dynamics. Let us just note here that (52) is not a Hamiltonian dynamics⁴. Since the dynamics preserves (53), it cannot be ergodic with respect to $d\mu_{\text{NH}}$. Let us introduce the manifold $\mathcal{M}_{\text{NH}}(E_0) = \left\{ (q, p, \eta, \xi) \in \mathbb{R}^{6N+2} \mid \tilde{H}_{\text{NH}}(q, p, \eta, \xi) = E_0 \right\}$ (we have taken $d = 3$) and the measure

$$d\rho_{\text{NH}} = \frac{d\sigma_{\text{NH}}}{\|\nabla \tilde{H}_{\text{NH}}\|_2}, \quad (55)$$

where $d\sigma_{\text{NH}}$ is the measure induced on $\mathcal{M}_{\text{NH}}(E_0)$ by the measure (54), $\nabla \tilde{H}_{\text{NH}}$ is the gradient of (53) with respect to all variables and $\|\cdot\|_2$ is the euclidian norm. Then $d\rho_{\text{NH}}$ is an invariant measure for the Nosé-Hoover dynamics (52).

An easy computation (see [56]) shows that, if the dynamics is ergodic with respect to $d\rho_{\text{NH}}$ (note that this implies that \tilde{H}_{NH} is the unique invariant of (52)), then the dynamics $(q(t), p(t))$ is ergodic with respect to the canonical measure (2), and thus provides a sampling of the phase space according to the canonical measure (at least before numerical discretization).

We emphasize the fact that, to the best of the authors knowledge, there is no rigorous proof in the literature showing that (52) is ergodic with respect to $d\rho_{\text{NH}}$. Furthermore, it has been numerically observed that, for systems as simple as a 1D harmonic oscillator, the dynamics $(q(t), p(t))$ does not seem to sample the phase space according to the canonical measure. It is actually observed

⁴The Nosé-Hoover dynamics can be recast, after changing variables and time, as a Hamiltonian dynamics, the so-called Nosé dynamics [36]. However, the time of this dynamics does not correspond anymore to the physical time.

that the trajectory stays in a ring, namely that there exist $c, C > 0$ such that $c \leq q^2(t) + p^2(t) \leq C$ for all t (see [27, 56]).

To circumvent this difficulty, a generalization of the Nosé-Hoover dynamics (52) has been proposed by Martyna et al. in [27]. The idea consists in coupling the physical variables with a first thermostat as in (52), and to couple this thermostat with a second one, which can be coupled to a third one, and so on. The variables now include $2M$ additional scalar variables η_j and ξ_j , $j = 1, \dots, M$, where the number M of thermostats is arbitrary. The corresponding dynamics is the so-called Nosé-Hoover chain dynamics (NHC) [27], in which there are M free parameters, Q_1, \dots, Q_M , representing the masses of the M thermostats. The dynamics preserves an invariant \tilde{H}_{NHC} and a measure $d\mu_{\text{NHC}}$ (which are the generalization of (53) and (54)).

As for the Nosé-Hoover dynamics, if the NHC dynamics is ergodic with respect to a measure $d\rho_{\text{NHC}}$ built in the same way as $d\rho_{\text{NH}}$, then the dynamics $(q(t), p(t))$ is ergodic with respect to the canonical measure. Provided that the number M of thermostats is large enough ($M \geq 3$ or 4 in practice), numerical simulations seem to show that this dynamics samples the phase space according to the canonical measure, even for systems such as the harmonic oscillator. Again, there is no rigorous proof showing that the NHC dynamics is *actually* ergodic with respect to $d\rho_{\text{NHC}}$.

Regarding numerical integration, it seems interesting to work with algorithms that reproduce the qualitative structure of the dynamics, that is *time reversibility* and *measure preservation*. Reversible-in-time and measure-preserving algorithms have been proposed in [28] (let us just mention here that they are based on a splitting of the dynamics). Simulation results discussed in Section 4 have been obtained with these algorithms.

3.2. The Nosé-Poincaré and the Recursive Multiple Thermostat methods

Both the Nosé-Hoover and the Nosé-Hoover chain dynamics suffer from not being Hamiltonian dynamics. As a consequence, the quasi-conservation of the invariants \tilde{H}_{NH} and \tilde{H}_{NHC} is not guaranteed. On the contrary, when working with a Hamiltonian dynamics, it is known that the energy can be preserved over very long times, provided symplectic algorithms are used (see [14, Chap. IX] and [40]). Another problem with Nosé-Hoover chains is the choice of the number of thermostats as well as their masses Q_j , which seem to have an influence on the results.

The Recursive Multiple Thermostat method has been recently proposed by Leimkuhler and Sweet [22] to solve the difficulties that have just been highlighted. It is a Hamiltonian dynamics which, like the Nosé-Hoover or Nosé-Hoover chains dynamics, couples the physical variables with a heat bath. This dynamics is a generalization of the Nosé-Poincaré method [2], which is also a Hamiltonian method. The Nosé-Poincaré method consists in adding a single thermostat, whereas the RMT method consists in adding an arbitrary number M of thermostats, which are all coupled together and to the physical particles. This is not the case in the Nosé-Hoover chain dynamics, where only the first thermostat is coupled to the physical particles (and not the other thermostats).

The Nosé-Poincaré method is based on the following Hamiltonian:

$$H_{\text{NP}}(q, p, \eta, \xi) = \eta \left(H \left(q, \frac{p}{\eta} \right) + \frac{\xi^2}{2Q} + dNk_{\text{B}}T \ln \eta - H_0 \right),$$

where H is given by (3), H_0 is chosen such that $H_{\text{NP}} = 0$ for the initial conditions, and where Q is some free parameter. Sampling properties and numerical algorithms are discussed in [2].

The motivation for introducing the RMT method is the numerical observation that results depend much less on the thermostat masses (which are user-chosen parameters) than with the Nosé-Poincaré method (see [22, 51]).

The numerical results that are presented in Section 4 have been computed with the algorithms proposed in [22]. Let us note that the implementation of the method may have a consequence on its numerical stability and so on its ability to adequately sample the phase space with a trajectory of a given number of time steps. A new implementation of the RMT dynamics has been proposed in [1].

4. NUMERICAL ILLUSTRATIONS

The different methods presented above can be used to compute numerical approximations of phase space integrals. In some cases, theoretical convergence rates can be obtained. Typically, when a CLT holds true, the error is bounded by $Cn^{-1/2}$ (where n is the number of evaluations of the potential and/or of the forces; see the Central Limit Theorem 2) for some unknown prefactor C , depending on both the system and the observable A . An important issue is the value of the prefactor in numerical computations, which can greatly vary from one method to another one.

However, since this prefactor depends on A , it is not easy to compare the different methods in a general way. After a brief description of the alkane model in Section 4.1, we present in Section 4.2 an abstract criterion defined without any explicit dependence on an observable A . The criterion measures the deviation between the empirical distributions and the canonical distribution. This comparison can be performed for a fixed sample size [50] (bearing in mind the computation of autocorrelation functions with a fixed computational cost for example), or, more fairly, at a fixed computational cost. Some improvements can also be achieved when combining different sampling techniques, or when resorting to strategies different from the computation of a single trajectory. This is made precise in Section 4.3.

4.1. Description of the linear alkane molecule

Linear alkanes are chemical compounds of the form $\text{CH}_3\text{-(CH}_2\text{)}_n\text{-CH}_3$. In this study, the so-called united-atom model [45] is used, in which the conformation of the molecule is completely characterized by the positions of the Carbon atoms. The presence of the Hydrogen atom is implicitly taken into account in the definition of the interaction potential the Carbon atoms are subjected to. The Carbon atoms of the linear alkane molecule are indexed from 1 to N , and their positions are described by the vector $q = (q_1, \dots, q_N) \in (\mathbb{R}^3)^N$. We set $r_{i,j} = q_j - q_i$ and we denote by $d_{i,j} = |r_{i,j}|$ the distance between the Carbon atoms i and j .

In the model presented here, the interatomic potential involves two-, three-, and four-body interactions :

- two Carbon atoms connected by a covalent bond interact *via* a harmonic potential

$$V_2(d) = \frac{1}{2}k_0(d - d_0)^2. \quad (56)$$

- two Carbon atoms that are separated by more than 3 covalent bonds interact *via* a Lennard-Jones potential

$$V_{\text{LJ}}(d) = 4\epsilon \left(\frac{1}{2} \left(\frac{\sigma}{d} \right)^{12} - \left(\frac{\sigma}{d} \right)^6 \right).$$

Notice that for the linear pentane molecule, only the two extremal Carbon atoms (labeled 1 and 5) experience a Lennard-Jones interaction.

- three consecutive Carbon atoms $C_i\text{-}C_{i+1}\text{-}C_{i+2}$ interact *via* the three-body interaction potential

$$V_3(\theta_i) = \frac{1}{2}k_\theta(\theta_i - \theta_0)^2, \quad (57)$$

where

$$\theta_i = \arccos \left(\frac{r_{i,i+1} \cdot r_{i+1,i+2}}{|r_{i,i+1}| \cdot |r_{i+1,i+2}|} \right) \quad (58)$$

is the bending angle of the $C_i\text{-}C_{i+1}\text{-}C_{i+2}$ chain.

- lastly, four consecutive Carbon atoms $C_i\text{-}C_{i+1}\text{-}C_{i+2}\text{-}C_{i+3}$ experience the four-body interaction potential

$$V_4(\phi_i) = u_{\text{tors}}(\cos \phi_i), \quad (59)$$

where ϕ_i is the dihedral angle defined by

$$\cos \phi_i = -\frac{(r_{i,i+1} \times r_{i+1,i+2}) \cdot (r_{i+1,i+2} \times r_{i+2,i+3})}{|(r_{i,i+1} \times r_{i+1,i+2})| \cdot |(r_{i+1,i+2} \times r_{i+2,i+3})|} \quad (60)$$

and where the function u_{tors} is given by

$$u_{\text{tors}}(x) = c_1(1 - x) + 2c_2(1 - x^2) + c_3(1 + 3x - 4x^3).$$

The potential energy of the linear alkane molecule eventually reads

$$V(q) = \sum_{i=1}^{N-1} V_2(d_{i+1,i}) + \sum_{i=1}^{N-2} V_3(\theta_i) + \sum_{i=1}^{N-3} V_4(\phi_i) + \sum_{i=1}^{N-4} \sum_{j=i+4}^N V_{\text{LJ}}(d_{i,j}). \quad (61)$$

The values of the parameters d_0 , ϵ , σ , k_θ , θ_0 , c_1 , c_2 and c_3 are taken from [26]. In the system of units where the length unit is $l_0 = 1.53 \cdot 10^{-10}$ m and the energy unit is such that $k_B T = 1$ at $T = 300$ K, the numerical values of these parameters are $d_0 = 1$, $\epsilon = 0.29$, $\sigma = 2.55$, $k_\theta = 208 \text{ rad}^{-2}$, $\theta_0 = 1.187 \text{ rad}$, $c_1 = 1.18$, $c_2 = -0.23$ and $c_3 = 2.64$. Notice that for these values of the parameters c_i , the function u_{tors} has a unique global minimum (at $\phi = 0$) and two local non-global minima. As far as the parameter k_0 is concerned, we set $k_0 = 1000$ (another possibility [26] is to constrain the C-C covalent bond length to be equal to d_0). We set the unit of mass such that the mass of each particle is equal to 1.

The linear pentane is the shortest linear alkane for which a two-body Lennard-Jones interaction (coupling the variables $d_{i,i+1}$, θ_i and ϕ_i all together) has to be taken into account. In addition, it involves only two dihedral angles and these two angles essentially determine the conformation of the molecule. Indeed, the covalent stretching and bending potentials are stiff and consequently the bond lengths and bending angles are statistically close to their equilibrium values at room temperature. Therefore, the linear pentane molecule is a good test case for it allows a simple reduced representation of the conformation while being a non-trivial model in which the internal degrees of freedom are coupled all together. For completeness, tests on longer molecules are performed in order to investigate the robustness of the numerical methods with respect to increasing configurational space dimensions.

Some reference empirical densities for the dihedral angles obtained through Importance sampling techniques are presented in Figure 1. They correspond to pentane, with $N = 10^9$ sample points.



FIGURE 1. Empirical probability distribution of the dihedral angles (ϕ_1, ϕ_2) of the pentane molecule generated with Importance sampling, for $\beta = 1$ (Left) and $\beta = 2$ (Right), with sample size $N = 10^9$.

4.2. Discrepancy of sample points

In order to quantitatively assess the quality of the samples generated by the various methods described above, we use a discrepancy criterion. Recall that the discrepancy D_n of a sequence $x = \{x_m\}_{0 \leq m \leq n-1}$ with values in $[0, 1]^d$ is defined as (see [19])

$$D_n(x) = \sup_{y \in [0, 1]^d} \left| \frac{1}{n} \sum_{m=0}^{n-1} \mathbf{1}_{\{x_m \in [0, y]\}} - \text{Volume}([0, y]) \right|, \quad (62)$$

where, for d -dimensional vectors y, z , we write $y \leq z$ when $y_i \leq z_i$ for all $1 \leq i \leq d$, and note $[0, y] = \{z \in [0, 1]^d, z \leq y\}$. The fact that $D_n(x) \rightarrow 0$ when $n \rightarrow \infty$ is equivalent (see [19, p.15]) to the fact that, for any Riemann integrable function A defined on $[0, 1]^d$,

$$\lim_{n \rightarrow \infty} \frac{1}{n} \sum_{m=0}^{n-1} A(x_m) = \int_{[0, 1]^d} A(x) dx.$$

In addition, for functions A which have bounded variations $V_{\text{HK}}(A)$ in the sense of Hardy and Krause [35], the following error estimate holds true:

$$\left| \frac{1}{n} \sum_{m=0}^{n-1} A(x_m) - \int_{[0, 1]^d} A(x) dx \right| \leq V_{\text{HK}}(A) D_n(x). \quad (63)$$

If $A \in C^d([0, 1]^d)$, then its variation $V_{\text{HK}}(A)$ has a simple expression:

$$V_{\text{HK}}(A) = \sum_{k=1}^d \sum_{1 \leq i_1 < \dots < i_k \leq d} \int_{[0, 1]^d} \left| \frac{\partial^k A}{\partial x_{i_1} \dots \partial x_{i_k}} \right| dx.$$

As a consequence of (63), the convergence of $D_n(x)$ toward 0 implies the law of large numbers, and the rate of convergence of $D_n(x)$ gives information about the convergence rate of the observable average.

In this framework, we intend for example to characterize the repartition of sample points in the subset $[-\pi, \pi]^2$ of the (ϕ_i, ϕ_j) -plane for two of the dihedral angles ϕ_i, ϕ_j . This can be achieved by considering the marginal ν_{ij} of the canonical density π with respect to the other degrees of freedom. Unfortunately, there is no simple exact expression of this marginal. We therefore consider the situation when $\epsilon = 0$ (*i.e.* when the Lennard-Jones interaction is turned off), in which case the marginal has the simple expression

$$d\nu_{ij}(\phi_i, \phi_j) = Z_\phi^{-2} e^{-\beta V_4(\phi_i)} e^{-\beta V_4(\phi_j)} d\phi_i d\phi_j, \quad (64)$$

with V_4 given by (59).

We then introduce the discrepancy criterion

$$D_n(\{q^m\}) = \sup_{(\phi_i, \phi_j) \in [-\pi, \pi]^2} \left| \frac{1}{n} \sum_{m=0}^{n-1} \mathbf{1}_{\{\phi_i^m \leq \phi_i, \phi_j^m \leq \phi_j\}} - \int_{\{\psi_i \leq \phi_i, \psi_j \leq \phi_j\}} d\nu_{ij}(\psi_i, \psi_j) \right|, \quad (65)$$

which provides a bound on the L^∞ distance between the empirical distribution functions and the exact ones. Notice that the second integral factorizes as

$$\int_{\{\psi_i \leq \phi_i, \psi_j \leq \phi_j\}} d\nu_{ij}(\psi_i, \psi_j) = Z_\phi^{-2} \int_{\psi_i \leq \phi_i} e^{-\beta V_4(\psi_i)} d\psi_i \int_{\psi_j \leq \phi_j} e^{-\beta V_4(\psi_j)} d\psi_j,$$

and can therefore be computed using standard numerical techniques.

Numerically, we compute an approximate value of D_n as follows. Suppose that we have partitioned the (ϕ_i, ϕ_j) -plane into K^2 boxes $B_{kl} = [\Phi_k, \Phi_{k+1}[\times [\Phi_l, \Phi_{l+1}[$ with $\Phi_k = -\pi + \frac{2k\pi}{K}$ for $0 \leq k \leq K-1$. The supremum in (65) is now taken over a finite set of elements:

$$D_n^K(q) = \sup_{1 \leq k, l \leq K} \left| \frac{1}{n} \sum_{m=0}^{n-1} \mathbf{1}_{\{\phi_i^m \leq \Phi_k, \phi_j^m \leq \Phi_l\}} - \int_{\{\psi_i \leq \Phi_k, \psi_j \leq \Phi_l\}} d\nu_{ij}(\psi_i, \psi_j) \right|. \quad (66)$$

We then compute the discrepancies for the sample points obtained by different methods with a fixed computational cost. The computational cost measures here the number of force or energy evaluations. Implementation details, optimal choice of parameters and algorithmic costs are discussed more precisely in [50]. The results are presented in Tables 2 to 4. For each method, 10 different simulations have been performed, and we give in the Tables the mean and the square-root of the variance (in brackets) of the 10 different results. For the three purely stochastic methods, the sampling function g is built upon the quadratic potentials V_2 and V_3 given by (56) and (57). Indeed, when working with the internal degrees of freedom, g is then a gaussian probability density (see [50] for more details).

One can see that purely stochastic methods are very efficient for small alkane chains, but rapidly loose their efficiency when the length of the chain increases. The Langevin, the HMC and the BRW (with Euler-Maruyama algorithm) methods keep the same efficiency whatever the length of the chain, while the efficiency of the biased Random-Walk (with the MALA algorithm) decreases when the chain length increases. It seems that the efficiency of the purely deterministic methods increases when the chain gets longer. Choosing parameters for the RMT method happened to be more difficult than for the NHC method, so the fact that the RMT method is less efficient than the NHC method may be due to a bad choice of parameters. We have also observed that, for given thermostat masses and a given time step, the accuracy in the conservation of the NHC invariant \tilde{H}_{NHC} is stable with respect to the length of the chain, while, for the RMT method, this accuracy decreases when the length of the chain increases. Note that increasing the time step from 0.001 to 0.0025 does not change the results of the RMT method. We see that, for short chains, the biased Random-Walk (MALA) is more efficient than the NHC method. However, for chains of 9 and 12 particules, the NHC method is more efficient. The biased Random-Walk with the Euler-Maruyama algorithm always seems to be a little more efficient than the biased Random-Walk with the MALA algorithm.

TABLE 2. Numerical results for the discrepancy (66) for the pentane (ϕ_1, ϕ_2) distribution in the case $\beta = 1$ and $K = 100$.

| Method | Parameters | Discrepancy | |
|----------------------|---|------------------------|----------------------------------|
| | | for 10^6 evaluations | for 10^7 evaluations |
| Importance sampling | - | 0.00428 (0.00114) | 0.00115 (1.60.10 ⁻⁴) |
| Rejection | - | 0.00856 (0.00204) | 0.00256 (4.98.10 ⁻⁴) |
| MIS | - | 0.0228 (0.00416) | 0.0225 (7.75.10 ⁻⁴) |
| HMC | $\tau = 10\Delta t, \Delta t = 0.025$ | 0.0389 (0.0183) | 0.0119 (4.87.10 ⁻⁴) |
| BRW (Euler-Maruyama) | $\Delta t = 0.028$ | 0.0791 (0.0265) | 0.0231 (0.00619) |
| BRW (MALA) | $\Delta t = 0.028$ | 0.104 (0.0446) | 0.0343 (0.0139) |
| Langevin | $\Delta t = 0.02, \xi = 1$ | 0.0339 (0.0142) | 0.0157 (0.00393) |
| NHC | $Q_1 = Q_2 = 0.1, \Delta t = 0.0025$ | 0.121 (0.0363) | 0.0425 (0.0142) |
| RMT | $Q_1 = 4.5, Q_2 = 0.3, \Delta t = 0.001$ | 0.393 (0.0499) | 0.225 (0.0943) |
| RMT | $Q_1 = 4.5, Q_2 = 0.3, \Delta t = 0.0025$ | 0.404 (0.150) | 0.337 (0.0856) |

4.3. Improvement of the convergence rates

4.3.1. Convergence rate improvements using several shorter realizations

We already mentioned that, instead of running a single long trajectory, it might be more efficient, for a given computational cost, to run several shorter trajectories. This can be done

TABLE 3. Numerical results for the discrepancy (66) for the (ϕ_1, ϕ_3) distribution for C_9H_{20} in the case $\beta = 1$ and $K = 100$. The computational cost is fixed to 10^7 force or energy evaluations.

| Method | Parameters | Discrepancy |
|----------------------|---|------------------|
| Importance sampling | - | 0.0205 (0.00544) |
| Rejection | - | 0.192 (0.0379) |
| MIS | - | 0.521 (0.0151) |
| HMC | $\tau = 10\Delta t, \Delta t = 0.02$ | 0.0261 (0.00846) |
| BRW (Euler-Maruyama) | $\Delta t = 0.025$ | 0.0402 (0.0229) |
| BRW (MALA) | $\Delta t = 0.025$ | 0.0477 (0.0129) |
| Langevin | $\Delta t = 0.025, \xi = 1$ | 0.0144 (0.00544) |
| NHC | $Q_1 = 0.15, Q_2 = 0.01, \Delta t = 0.0025$ | 0.0369 (0.00979) |
| RMT | $Q_1 = 4.5, Q_2 = 0.3, \Delta t = 0.001$ | 0.162 (0.120) |
| RMT | $Q_1 = 4.5, Q_2 = 0.3, \Delta t = 0.0025$ | 0.197 (0.0864) |

TABLE 4. Numerical results for the discrepancy (66) for the (ϕ_1, ϕ_3) distribution for $C_{12}H_{26}$ in the case $\beta = 1$ and $K = 100$. The computational cost is fixed to 10^7 force or energy evaluations.

| Method | Parameters | Discrepancy |
|----------------------|---|------------------|
| Importance sampling | - | 0.102 (0.0436) |
| Rejection | - | 1.0 (0.0) |
| MIS | - | 0.493 (0.222) |
| HMC | $\tau = 10\Delta t, \Delta t = 0.02$ | 0.0207 (0.00730) |
| BRW (Euler-Maruyama) | $\Delta t = 0.023$ | 0.0312 (0.0102) |
| BRW (MALA) | $\Delta t = 0.023$ | 0.0610 (0.0201) |
| Langevin | $\Delta t = 0.025, \xi = 1$ | 0.0173 (0.00726) |
| NHC | $Q_1 = 0.15, Q_2 = 0.01, \Delta t = 0.0025$ | 0.0373 (0.0137) |
| RMT | $Q_1 = 4.5, Q_2 = 0.3, \Delta t = 0.001$ | 0.167 (0.0797) |
| RMT | $Q_1 = 4.5, Q_2 = 0.3, \Delta t = 0.0025$ | 0.201 (0.0833) |

for methods of Type 2 to 4. For methods of Type 2 and 3, this strategy relies on the following numerical approximation. Assuming that the methods are ergodic, it follows

$$\mathbb{E}_x(A(q^{N_1})) \rightarrow \int_{\mathcal{M}} A(q) d\pi \quad (67)$$

when $N_1 \rightarrow +\infty$. In some cases, this convergence is exponentially fast. The term $\mathbb{E}_x(A(q^{N_1}))$ is the expectation of the realizations of the chain conditioned at starting from $x \in \mathcal{M}$. It can be approximated by N_2 independent realizations of the Markov chain. Each realization is labelled by an index $k \in \{1, \dots, N_2\}$, and the associated sample path is $(q^{0,k}, \dots, q^{N_1-1,k})$. Notice that, for all samples, $q^{0,k} = x$. An approximation of $\mathbb{E}_x(A(q^{N_1}))$ is then obtained as

$$\mathbb{E}_x(A(q^{N_1})) \simeq I_{N_2}^{N_1}(x) = \frac{1}{N_2} \sum_{k=1}^{N_2} A(q^{N_1,k}). \quad (68)$$

Notice that we expect the error between $I_{N_2}^{N_1}(x)$ and the space average $\int_{\mathcal{M}} A(q) d\pi$ to be of the form $C(x)\rho^{N_1} + C(x, N_1)N_2^{-1/2}$ for some $0 < \rho < 1$.

When a short trajectory of length N_1 is computed for N_2 realizations starting from a given initial point x , we can also consider the following approximation of the state average

$$\int_{\mathcal{M}} A(q) d\pi \simeq \frac{1}{N_1} \sum_{m=0}^{N_1-1} I_{N_2}^m(x), \quad (69)$$

where the right hand side is the Cesaro average of (68).

The results are presented in Table 5 in the case of a Langevin sampling for the pentane molecule at $\beta = 1$. As can be seen, there is a slight improvement when generating several shorter trajectories, provided these trajectories remain long enough. Note however that such an improvement is not always observed. But we emphasize that there is no degradation of the results either. This is an interesting point since it allows a straightforward parallelization of the method.

TABLE 5. Numerical results for the discrepancy (66) for the pentane (ϕ_1, ϕ_2) distribution in the case $\beta = 1$ and $K = 100$, using a Langevin method with $\xi = 1$ and $\Delta t = 0.02$. The discrepancy has been computed with all points appearing in (69) (i.e. all points of the N_2 trajectories of length N_1), with a computational cost fixed to 10^7 force or energy evaluations.

| Number N_2 of realizations | Discrepancy |
|------------------------------|------------------|
| 1 | 0.0157 (0.00393) |
| 5 | 0.0117 (0.00388) |
| 10 | 0.0132 (0.00210) |
| 20 | 0.0149 (0.00701) |
| 50 | 0.0120 (0.00330) |
| 100 | 0.0112 (0.00263) |
| 200 | 0.0130 (0.00419) |
| 500 | 0.0308 (0.00834) |
| 1000 | 0.0528 (0.00740) |

4.3.2. Convergence rate improvements at fixed computational cost, using an appropriate initial distribution

Another improvement is as follows. Instead of considering a fixed initial point, we can make a first approximation of the canonical distribution. Let us denote by π^{N_3} the following approximation of π :

$$\pi^{N_3} = \frac{1}{N_3} \sum_{i=1}^{N_3} \delta_{x^i}.$$

For each initial point x^i ($1 \leq i \leq N_3$), an approximation (69) can be computed, for N_2 realizations of the Markov chain with trajectories of length N_1 . The total number of points generated in this way is therefore $N_1 N_2 N_3$. The important issue is then to optimize the choices of N_1 , N_2 and N_3 in order to have the best accuracy for a given total cost.

For the method to be efficient, the empirical measure π^{N_3} has to be a good approximation of π . To this end, the points x^i are chosen as follows. We first generate N^{tot} points $(y^1, \dots, y^{N^{\text{tot}}})$ with weights $(w_1, \dots, w_{N^{\text{tot}}})$, using (say) an Importance sampling method. We then generate N_3 points from this list with replacement with probabilities $(\frac{w_1}{W}, \dots, \frac{w_{N^{\text{tot}}}}{W})$ where $W = \sum_{i=1}^{N^{\text{tot}}} w_i$, and run one or several trajectories for each starting point. This can improve the rate of convergence of some methods. An example is the biased Random Walk at $\beta = 1$ with $\Delta t = 0.028$ for 10^6 operations. We consider $N^{\text{tot}} = 10^4$, $N_3 = 99$, $N_1 = 10^4$ and $N_2 = 1$. The discrepancy is lowered from 0.104 (0.0446) (with $N_1 = 10^6$, $N_2 = 1$ and $N_3 = 1$, see Table 2) to 0.0430 (0.0144). In general, it is observed that convergence occurs faster when starting from an approximate distribution.

4.3.3. Effect of undersampling

As a final improvement, we can test the influence of a systematic undersampling, which consists in picking only some of the points generated instead of considering all of them. Indeed, some techniques generate points (q^0, \dots, q^{N-1}) that may be very much correlated, and it can happen that the sequence $(q^0, q^r, \dots, q^{sr})$, the undersampling rate r being such that $N - 1 = rs$, is better distributed than the original sequence.

The results are presented in Table 6 in the case of a Langevin sampling for pentane at $\beta = 1$. As can be seen, the efficiency of the method remains stable when undersampling the data. This is particularly interesting when computing autocorrelation functions or time-dependent integrals of the form (8) since a NVE trajectory has to be computed for each starting point generated from the canonical distribution.

TABLE 6. Numerical results for the discrepancy (66) for the pentane (ϕ_1, ϕ_2) distribution in the case $\beta = 1$ and $K = 100$, using a Langevin method with $\xi = 1$ and $\Delta t = 0.02$. The computational cost is fixed to 10^6 force or energy evaluations.

| Undersampling rate | Discrepancy |
|--------------------|------------------|
| 1 | 0.0339 (0.0142) |
| 5 | 0.0369 (0.0121) |
| 10 | 0.0350 (0.00996) |
| 50 | 0.0391 (0.0194) |
| 100 | 0.0385 (0.0169) |
| 500 | 0.0343 (0.0102) |
| 1000 | 0.0539 (0.0173) |

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