Sampling rare events by constrained motion

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Abstract

A typical problem in statistical mechanics consists in computing equilibrium averages of certain observables. We present a novel hybrid Monte-Carlo algorithm for sampling the Gibbs distribution of a mechanical system that is subject to configuration constraints. Using the ordinary Metropolis-Hastings acceptance rule together with a standard symplectic integrator for constrained systems (e.g., SHAKE or RATTLE) we can prove that the dynamics is ergodic and samples the correct distribution for any stable step size.

The sampling problem

Consider a system assuming states $(x, v) \in T\mathbb{R}^n$ with the energy

$$E(x,v) = \frac{1}{2}|v|^2 + V(x)\,.$$

Typical problems, e.g., in molecular dynamics (MD) or quasi-continuum methods consists in calculating equilibrium averages of an observable $f(x)$ over all configurations,

$$\mathbb{E}f = \int_{\mathbb{R}^n} f\,d\mu\,, \quad d\mu(x) \propto \exp(-\beta V(x))dx\,,$$

where μ denotes the Gibbs measure at temperature $T = 1/\beta$. Now consider the solution of the following initial value problem

$$\ddot{x}(t) = -\nabla V(x(t))\,, \quad x(0) = x\,.$$

We call the *sampling problem* the task of computing the expectation $\mathbb{E}f$ by taking the time average over the trajectory $x(t)$, i.e.,

$$\mathbb{E}f \approx \frac{1}{T}\int_0^T f(x(t))\,dt\,.$$

Rare events

The are various problems with computing ensemble averages from single trajectories:

- the system may contain large energy barriers that obstruct fast sampling (metastability),
- the dynamics $x(t)$ are not ergodic with respect to the Gibbs measure, i.e., trajectories do not sample μ.

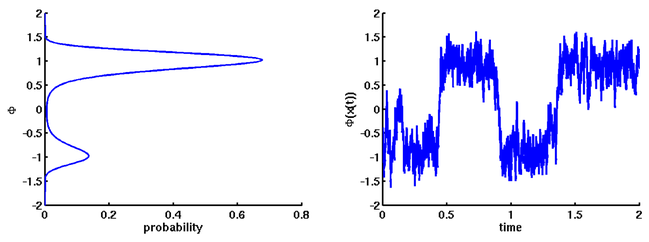
The Gibbs distribution of a typical metastable system is shown in the figure below. Large deviations theory states that the exit from a metastable set is a *rare event* when the dynamics have to overcome a potential barrier, say, ΔV. The asymptotic exit time scales like

$$\tau_{\text{exit}} \propto \exp(-\beta\Delta V) \quad \text{for} \quad \beta \ll 1\,.$$

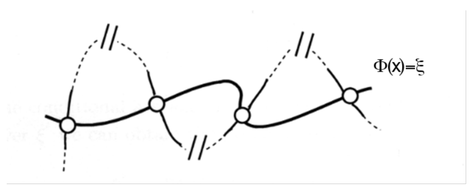
Hence sampling the Gibbs measure requires integrating the system over an exponentially long times. Quantities of interest that assume knowledge of μ are, e.g., free energy differences or transition rates between metastable sets. For these purposes, however, is often sufficient to know μ at certain (improbable) points, e.g., in a local neighbourhood of a transition state in case of which the sampling problem boils down to computing *conditional expectations* of the form

$$\mathbb{E}\left[f|\xi\right] = \frac{1}{Z(\xi)}\int_{\mathbb{R}^n} f(x)\delta(\Phi(x)-\xi)d\mu(x)\,.$$

Here $Z(\xi)$ normalizes the conditional probability to one, and $\Phi\colon \mathbb{R}^n \to \mathbb{R}$ denotes some physical observable (reaction coordinate) that parametrizes, e.g., a transition between metastable sets.



Following Ciccotti *et al.* (1989) we employ constrained simulations to sample conditional probabilities. Given a reaction coordinate Φ, we introduce a constraint as the set of all configurations $x \in \mathbb{R}^n$ for which $\Phi(x) = \xi$ for a regular value ξ of Φ.



Though defined in terms of Φ, the set of admissible configurations is intrinsically defined by the hypersurface $\Sigma = \Phi^{-1}(\xi)$. Accordingly, the constrained Gibbs measure is obtained by restriction, i.e.,

$$d\pi(x) \propto \exp(-\beta V(\sigma(x)))\,d\sigma(x)$$

where $d\sigma$ denotes the surface element of $\Sigma \subset \mathbb{R}^n$. Federer's co-area formula implies that the conditional expectation can be recast as

$$\mathbb{E}\left[f|\xi\right] = \left(\int_\Sigma |\nabla\Phi|^{-1}\,d\pi\right)^{-1}\int_\Sigma f|\nabla\Phi|^{-1}\,d\pi\,.$$

Sampling by constrained motion

The co-area formula is an assertion about how to reweight the constrained Gibbs measure the respective conditional probability measure. As yet, we haven't made any reference to dynamics; so any (constrained) dynamical system that samples π will do the job.
We consider the constrained version of our original initial value problem and confine our attention to Hamiltonian systems

$$\begin{aligned}\dot{x} &= \frac{\partial H}{\partial p}\\ \dot{p} &= -\frac{\partial H}{\partial x} - \lambda\frac{\partial\Phi}{\partial x}, \quad \Phi(x) = \xi\,,\end{aligned}$$

with $H\colon T^*\mathbb{R}^n \to \mathbb{R}$ being the system's Hamiltonian

$$H(x,p) = \frac{1}{2}|p|^2 + V(x)\,, \quad p = \dot{x}\,.$$

Stochastic Hamiltonian systems

Hamiltonian systems admit infinitely many invariant probability measures none of which is ergodic in general. But we may enforce ergodicity by adding suitable random perturbations to the dynamics: given the exact Hamiltonian flow Ψ^τ at time $\tau > 0$, we introduce a *stochastic Hamiltonian flow* as iterates of the map

$$x_{n+1} = (\Pi\circ\Psi^\tau)(x_n, p_n)\,, \quad p_n \sim \rho(x_n,\cdot)\,,$$

where $\Pi\colon T^*\Sigma \to \Sigma$, $(x,p) \mapsto x$ and $\rho \propto \exp(-\beta H|_{T^*\Sigma})$. Iterating the thus defined map yields a series of configurations

$$\{x_0, x_1, \ldots\} \subset \Sigma\,.$$

Symplecticness and energy-conservation of Ψ^τ entail ergodicity with respect to π, i.e., the law of large numbers

$$\frac{1}{N}\sum_{k=0}^{N-1} f(x_k) \to \int_\Sigma f\,d\pi \quad \text{as} \quad N\to\infty$$

holds for almost all initial conditions $x_0 \in \Sigma$. If we replace the exact flow by its numerical discretization, $\hat{\Psi}^\tau$, however, π is no longer preserved under the discrete flow. Hence ergodicity gets lost, primarily due to the energy error of the discretization.

Metropolized stochastic Hamiltonian systems

We may adopt appropriate Monte-Carlo strategies to enforce the desired target distribution thereby accounting for the energy error of the numerical flow. We have the following law of large numbers:

Theorem (H. 2007)**.** *Given $\tau > 0$ sufficiently small, let the numerical flow $\hat{\Psi}^\tau$ be symmetric and symplectic. Then*

$$\begin{aligned} q_{n+1} &= (\Pi\circ\Psi^\tau)(x_n,p_n)\,, \quad p_n \sim \rho(x_n,\cdot)\\ \mathbb{P}\left[x_{n+1} = q_{n+1}\right] &= \min\{1, \exp(-\beta\Delta H_{n+1})\}\end{aligned}$$

defines an irreducible Markov process $\{x_0, x_1, \ldots\} \subset \Sigma$ with unique invariant probability measure π and the property

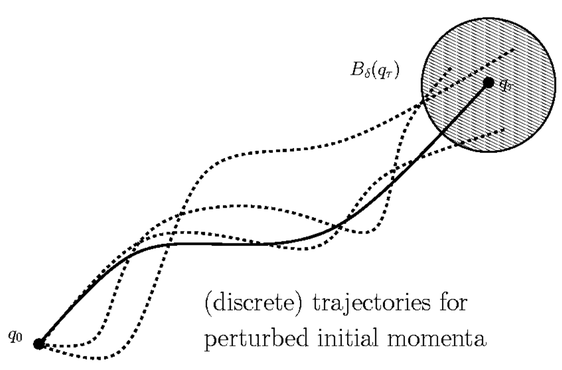
$$\frac{1}{N}\sum_{k=0}^{N-1} f(x_k) \to \int_\Sigma f\,d\pi \quad \textit{as} \quad N\to\infty$$

almost surely and for almost all initial conditions $x_0 \in \Sigma$.

The idea of irreducibility is essentially that the probability to reach any point in configuration space is nonzero, i.e.,

$$\mathbb{P}\left[x_{n+1} \in B(q_\tau)\,\middle|\,x_n = q_0\right] > 0$$

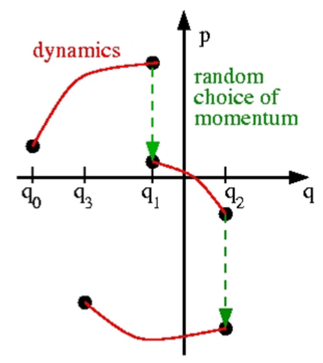
holds true for all $q_0, q_\tau \in \Sigma$ and any Borel set $B \in \mathcal{B}(\Sigma)$, where the connecting paths can be constructed as stationary solutions of a discrete action principle. The discrete Euler-Lagrange equations then yield a numerical flow map that is both symmetric and symplectic; employing, e.g., trapezoidal rule for discretizing the action integral yields the well-known SHAKE/RATTLE algorithm.



Since the energy error ΔH_{n+1} in each step is bounded, we can reach any point $x_{n+1} \in B(q_\tau)$ with non-zero probability by perturbing the initial momenta (the set of admissible momenta is nonempty).
The law of large numbers guarantees that any realization of the "metropolized" stochastic Hamiltonian flow eventually samples the constrained Gibbs measure without bias and independent of the stable step size of the integrator. Yet the rate of convergence may depend on how τ or the internal step size of the integrator is chosen.

Hybrid Monte-Carlo

For the algorithmic realization of the constrained stochastic Hamiltonian system we employ an appropriately adapted hybrid Monte-Carlo (HMC) scheme. Given a numerical integrator the idea of HMC is to reject those moves that have too large energy fluctuations.



The algorithm is as follows.

1. Set $q_k = x_k$ with $\Phi(q_k) = \xi$.
2. Pick a random momentum $\zeta \sim \mathcal{N}(0, \beta^{-1}\mathrm{Id})$.
3. Project onto the hidden constraint

$$p_k = P(q_k)\zeta \quad\Longrightarrow\quad p_k \sim \rho(q_k,\cdot)\,.$$

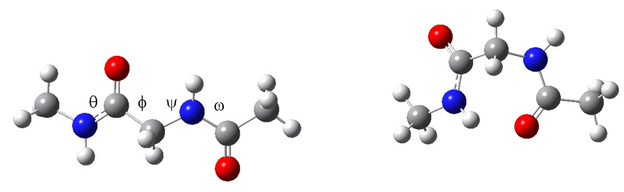
4. Integrate $(q_{k+1}, p_{k+1}) = \hat{\Psi}_\tau(q_k, p_k)$.
5. Accept, $x_{k+1} = q_{k+1}$ with probability

$$\min(1, \exp(-\beta\Delta H_{k+1})$$

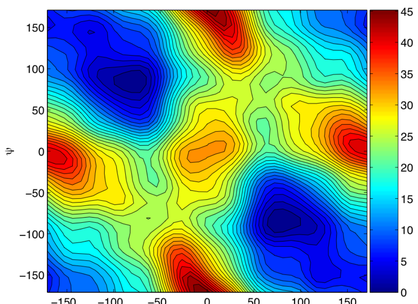
   or reject, i.e, $x_{k+1} = x_k$.
6. Repeat.

Application: free energy calculation

In order to illustrate the applicability of the proposed HMC algorithm we have computed the free energy profile or *potential of mean force* of the glycine dipeptide as a function of its two central torsion angles. At $T = 300K$, the most pronounced metastable conformations of the dipeptide, the extended C5 conformation and the ring-like C7 conformation, are separated by large potential barriers (see below).



The constrained simulations were carried out on a 36×36 grid using the GROMOS96 force field and the RATTLE algorithm with a step size $h = 2fs$. Each grid point $\Phi_1 = \phi$ and $\Phi_2 = \psi$ represents a combination of the two dihedral angles (ϕ,ψ). The HMC integration interval was chosen to be $\tau = 100fs$ and each conditional expectation was taken over $N = 10\,000$ points; with the thus set parameters the acceptance rate of the HMC algorithm was about 90% (typically the acceptance rate decreases as the number of particles grows).
For each grid point (ϕ,ψ), we computed the conditional expectation of the total force acting on the two angles. Eventually the corresponding free energy profile is obtained upon numerically integrating the resulting 2-dimensional vector field.



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References

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