Probability Based Enhanced Sampling

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Abstract

Many physical and chemical processes of interest take place on timescales that cannot be explored using standard molecular dynamics simulations. This renders the use of enhanced sampling mandatory. Here we introduce an enhanced sampling method that is based on constructing a model probability density from which a bias potential is derived. The model relies on the fact that in a physical system most of the configurations visited can be grouped into isolated metastable islands. To each island we associate a distribution that is fitted to a Gaussian mixture. The different distributions are combined together with coefficients that are computed on the fly. This results in an efficient method that offers considerable advantages relative to existent approaches. In order to illustrate its applicability two exemplary applications are presented.

In order to overcome this limitation a great variety of methods has been suggested[1]. The first such method has been described in the classic work of Torrie and Valleau[2] in which umbrella sampling was first presented. In this paper a bias potential \( V(\mathbf{R}) \), function of the atomic coordinates \( \mathbf{R} \), was added to the potential \( U(\mathbf{R}) \). The role of \( V(\mathbf{R}) \) was to facilitate transitions from one metastable state to another. The Boltzmann expectation value of any operator \( O(\mathbf{R}) \) was then computed from the biased trajectories using the reweighting formula:

\[
\left\langle O(\mathbf{R}) \right\rangle = \frac{\left\langle O(\mathbf{R}) \, e^{\beta V(\mathbf{R})} \right\rangle_V}{\left\langle e^{\beta V(\mathbf{R})} \right\rangle_V} \quad (1)
\]

where \( \beta \) is the inverse temperature and the suffix \( V \) indicates that the averages are performed over the ensemble biased by \( V(\mathbf{R}) \). Torrie and Valleau suggested to write \( V(\mathbf{R}) \) in the form of \( V(s(\mathbf{R})) \) where \( s(\mathbf{R}) \) is a set of order parameters or collective variables (CVs) that describe the difficult-to-sample degrees of freedom. After Torrie and Valleau many proposals have been put forward on how to build a suitable \( V(s(\mathbf{R})) \). Some of the proposed methods include adaptive umbrella sampling[3], Gaussian mixture umbrella sampling[4], metaboltions[5] and variationally enhanced sampling[6]. Of course, crucial to the success of all these methods, is the use of an appropriate set of CVs. While the process of identifying CVs can be very insightful[7], it can also be time consuming, even if several methods have been proposed to facilitate[8,9] CV construction or to ameliorate existing CVs[10,11,12].

Here we take a different approach that does not require the introduction of a restricted set of CVs and aims at constructing an intrinsically multidimensional bias. However, before discussing the details of our work, a brief preliminary introduction is in order. In umbrella sampling and in several other methods that followed, emphasis has been put on modelling the external bias. Following previous efforts[13,14], we suggest instead that it might be more profitable to focus one’s attention on modelling the probability distribution. Here we follow the same approach and construct a bias starting from a model probability density \( P_m(\mathbf{R}) \) linking it to the bias \( V(\mathbf{R}) \) using the relation:

\[
V(\mathbf{R}) = \frac{1}{\beta} \log P_m(\mathbf{R}) \quad (2)
\]

In order to understand why one establishes such a link, we consider two extreme cases. In the first, \( P_m(\mathbf{R}) \)
such a way that equilibrium configurations belonging to
these configurations to model the probability density
where we have introduced the normalizing constants
In the Gaussian mixture scheme
or the harmonic linear discriminant analysis[5] For instance in the case of a flexible molecule in a non polar solvent these could be all the angles and intramolecular distances that define its conformation or in the case of a chemical reaction all the relevant atomic distances. Identifying a set of useful descriptors is far less challenging than determining a set of CVs. In fact the number of descriptors N_d can be large, while the number of CVs needs to be small since in many methods the computational cost scales exponentially with such numbers. In addition the choice of CVs implies a hypothesis, even if tentative, on the transition mechanism. No such insight is needed here and the d(R) are just a set of variable that can distinguish the different metastable states, in such a way that equilibrium configurations belonging to different metastable states are projected into separate regions of d space.

We then run for each of the M metastable states short trajectories obtaining M sets of configurations. We use these configurations to model the probability density p^i(d) for each metastable state i. Here we choose to approximate p^i(d) by a Gaussian mixture but other choices might also be possible.

In the Gaussian mixture scheme p^i(d) is expressed as a linear combination of multivariate Gaussians:

\[ p^i(d) \equiv \sum_{k=1}^{K^i} \pi^i_k N(d; \mu^i_k, \Sigma^i_k) \] (4)

where the mixing coefficients \( \pi^i_k \) satisfy the conditions

\[ 0 \leq \pi^i_k \leq 1 \] and \[ \sum_{k=1}^{K^i} \pi^i_k = 1. \]

Having determined for each metastable state its d space probability density, we then construct \( P_m(R) \) as

\[ P_m(R) = \frac{1}{M} \sum_{i=1}^{M} \frac{p^i(d(R))}{Z^i} \] (5)

where we have introduced the normalizing constants

\[ Z^i = \int dR \, p^i(d(R)). \]

In setting up this density model we have in mind the fact that, as discussed earlier, a physical system spends most of its time visiting only a small part of the configuration space and the regions visited are characterized by the presence of a finite number of metastable states. The descriptors d help one to focalise on a selected part of the configuration space and distinguish between the different relevant states.

The bias is then

\[ V(R) = \frac{1}{\beta} \log \left( \frac{1}{M} \sum_{i=1}^{M} \frac{p^i(d(R))}{Z^i} \right) \] (6)

which can also be rewritten, after dropping irrelevant constants, as:

\[ V(R) = \frac{1}{\beta} \log \left( \sum_{i=1}^{M} \frac{Z^i}{Z^i} \right) \] (7)

The ratios \( Z^i/Z^j \) are not known a priori, but they can be set to an arbitrary value, say one, at the beginning of the calculation and estimated on the fly from

\[ \frac{Z^i}{Z^j} = \frac{\left( \langle p^i(d(R))e^{\beta(U(R)+V(R))} \rangle_v \right)}{\left( \langle p^j(d(R))e^{\beta(U(R)+V(R))} \rangle_v \right)} \] (8)

taking cue from what is done in Integrated Tempering Sampling[17][18]. Alternatively one could use VESAF[19] or its generalization to many states. We note that the introduction of the terms \( Z^i/Z^j \) is crucial for getting a good biasing potential since it provides information on the relative free energy. However, accurately converged values of \( Z^i/Z^j \) are not needed provided that when inserted in Eq. (7) the resulting bias is able to promote efficiently transitions between metastable states. We refer to our method as Gaussian Mixture Based Enhanced Sampling (GAMBES).

We now test our method on the simple but instructive case of alanine dipeptide in vacuum. At room temperature, three different conformational states are accessible to this small peptide, C7eq, C5, and C7ax. The peptide converts easily from C7eq to C5 and much more rarely visits C7ax. Thus we can regard this system as composed of two metastable states in the first one (i = 1), C7eq and C5 are both populated while in the second one (i = 2), only C7ax is visited. We run for each state two unbiased simulations of 2 ps.

The simulations are carried out in the NVT ensemble using a molecular dynamics (MD) timestep of 2 fs and the AMBER99-SB forcefield. The temperature is kept constant at 300K using the stochastic velocity rescaling thermostat[20]. The electrostatic and non-bonded van der Waals interactions are used without any cutoffs, and periodic boundary conditions are not imposed. All simulations are performed using GROMACS2018.4[21] and for the biased simulations, the MD engine is patched with a modified version of the PLUMED2.0 plugin[22]
We use as descriptors the two dihedral angles $d \equiv \{\phi,\psi\}$ and fit the probability distribution for these two angles to two different multivariate Gaussian mixture models. The number of Gaussians for each state is chosen using the Bayes Information Criterion\textsuperscript{23}. The optimal value for state 1 is $K^1 = 3$ while for state 2 it is $K^2 = 2$ (see supporting information).

In order to evaluate the performance of the method, we run 50 independent 10 ns long biased simulations with different initial structures that are selected from an available diffusive trajectory. For reference, we also run 50 independent well-tempered metadynamics simulations with biasfactor $\gamma = 10$.

In figure\textsuperscript{2} the mean and the standard deviation of the free energy differences ($\Delta F$) observed using the set of simulations are shown. In the metadynamics runs $\Delta F$ has been computed using the reweighting scheme proposed by Tiwary and Parrinello\textsuperscript{22} and the initial 2 ns necessary for the metadynamics simulation to reach its asymptotic limit are discarded. In the GAMBES runs, we use the initial 2 ns to estimate the ratio $Z^1/Z^2$ and then keep fix this ratio for the remaining 8 ns, during which we calculate $\Delta F^i$ using a static reweighting (Equation\textsuperscript{1}).

It is reassuring to see that the performance of our method is even slightly better than that of metadynamics. In fact experience has shown that it is difficult to outperform metadynamics when good CVs are used. Such is the case for alanine dipeptide when both $\phi$ and $\psi$ are used as CVs. However, our method offers an even clearer advantage when suboptimal CVs are used. This being the case most encountered in the practice when dealing with real systems.

For this reason we explore the performance of our method in a case in which the CVs are suboptimal\textsuperscript{19}. This is the case of a modified Wolfe Quapp potential\textsuperscript{19} (figure\textsuperscript{3}) in which the x coordinate is used as CV.

We run two unbiased $10^4$ steps long simulations from the two basins (figure\textsuperscript{1}). The simulations are performed using the MD engine implemented in the VES module of PLUMED\textsuperscript{2.0} and using natural units. A friction for the Langevin thermostat of 10, a constant temperature of 1 and a time step of 0.002 are used. We then fit the two distributions to two Gaussian mixtures with $K^1 = 2$ and $K^2 = 2$ where 1 is the state centered at $(-1.9, 0.78)$. Similar to the previous case, we run two sets of 50 independent simulations from different initial positions using our method and well-tempered metadynamics. In the GAMBES case, we obtain an estimate of the ratio $Z^1/Z^2$ from the initial $10^5$ steps and then use the static bias for a longer run. This equilibration part is discarded and a static reweighting is used to estimate $\Delta F$. Similarly, for the well-tempered simulations the initial $10^5$ steps are discarded and the Tiwary and Parrinello rescaling\textsuperscript{22} is employed to calculate $\Delta F$. The free energy differences averaged over the 50 simulations and their standard deviation are shown in figure\textsuperscript{6} for the two sets of simulations. In figure\textsuperscript{5} we show the time evolution of $Z^1/Z^2$ for a representative simulation. From figures\textsuperscript{5} and\textsuperscript{6} we can see that the ratio $Z^1/Z^2$ reaches convergence after $10^5$ steps and a good estimate for $\Delta F$ is obtained after $5 \times 10^5$ steps. This is to be compared with well-tempered metadynamics that still after $10^6$ steps has not yet reached its converged value.

In conclusion we have presented a sampling method that falls in the family of the umbrella sampling approach and it is based on modelling the probability distribution rather than the bias itself, making it closer in spirit to adaptive umbrella sampling. Besides providing an alternative point of view on the sampling problem,
the method appears to be highly competitive with respect to other well-established methods. Relative to other approaches it offers distinctive advantages. One can use a large number of descriptors as long as it is possible to extract a model $p^i(d)$. Different states can be modeled with different descriptors. One could also use the method in an explorative fashion. That is one starts with an initial assumption on the possible metastable states and then as new states are discovered their Gaussian mixture model can be added to $P_m(R)$. An area in which this procedure appears to hold great promise is that of the study of multi-step chemical reactions.

In this first paper we have been conservative in the use of machine learning techniques, that are here confined only to use as a model for the probability densities $p^i(d)$ Gaussian mixture density. Recent developments in deep neural networks both in the search for appropriate descriptors and more advanced probability density models promise to bring our approach to an even higher level of efficiency, further enhancing its power.

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Supporting Information Available

The following files are available free of charge.

The free energy differences were calculated using the following equation:

$$\Delta F = \frac{1}{\beta} \log \frac{\int_A ds \; e^{-\beta F(s)}}{\int_B ds \; e^{-\beta F(s)}}$$

where $s$ denotes the CVs, $F(s)$ is the free energy and
A and B denote the states being considered.

Alanine Dipeptide

The Gaussian fits obtained for the two basins are shown in figure 7a and 7b. The Gaussians are plotted as contours with contour levels at $\sigma$, $2\sigma$, $3\sigma$ and the intensity of their colors adjusted according to the weights assigned by the mixture model to each Gaussian. In figure 8, the time evolution of $Z^1/Z^2$ is shown during a 10 ns trajectory. It is clear from the figure that the value changes little after 2 ns.

(a) The Gaussian fit for 3000 data points (600 ps) at the C7eq and C5 basin.

(b) The Gaussian fit for 3000 data points (600 ps) at the C7ax basin.

Figure 7: Gaussian mixture fitted to unbiased alanine dipeptide data

Wolfe-Quapp potential

In figure 9, it is shown that the $Z^1/Z^2$ values do converge during a long run even for suboptimal CVs. However, we stop the equilibration when the value is sufficient to drive transitions efficiently and use this value to construct a static bias for longer runs. This also allows one to use umbrella-like reweighting for obtaining the quantities of interest.

Figure 8: The time evolution of $Z^1/Z^2$ for one of the simulations of alanine dipeptide. Notice that the values converge very fast and the fluctuations after 2 ns make insignificant changes to the bias potential.

Figure 9: The time evolution of $Z^1/Z^2$ for representative modified Wolfe-Quapp simulation.

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