SOBOLEV SAMPLING OF FREE ENERGY LANDSCAPES.

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ABSTRACT

A family of fast sampling methods is introduced here for molecular simulations of systems having rugged free energy landscapes. The methods represent a generalization of a strategy consisting of adjusting a model for the free energy as a function of one- or more collective variables as a simulation proceeds. Such a model is gradually built as a system evolves through phase space from both the frequency of visits to distinct states and generalized force estimates corresponding to such states. A common feature of the methods is that the underlying functional models and their gradients are easily expressed in terms of the same parameters, thereby providing faster and more effective fitting of the model from simulation data than other available sampling techniques. They also eliminate the need to train simultaneously separate neural networks, while retaining the advantage of generating smooth and continuous functional estimates that enable biasing outside the support grid. Implementation of the methods is relatively simple and, more importantly, they are found to provide gains of up to several orders of magnitude in computational efficiency over existing approaches.

Keywords Enhanced sampling · Second keyword · More

1 Introduction

Simulations of systems whose underlying free energy landscape consists of local minima separated by large barriers generally require the use of advanced sampling techniques. The Umbrella Sampling method is perhaps the most widely used example [1], where harmonic restraints are used to coerce the system of interest to visit target states. In order to collect biased statistics, multiple simulations are performed, subject to constraints along one or more collective variables. The results of these calculations are then combined through a weighted histogram analysis approach [2] to arrive at a more comprehensive picture of a particular region of the free energy landscape.

A different class of adaptive techniques, which we refer to as density-of-states (DOS) sampling methods [3] [4], seek to generate a running estimate of the free energy, on the fly, by relying on visits to distinct points in phase space. That estimate allows an algorithm to “push” a system towards high-energy states, which would otherwise by visited with a low probability, and eventually cross a barrier. Examples include the Wang-Landau method [3], or configurational-temperature density-of-states sampling [5] [9], or weighted ensemble methods [6]. Another example...
of such methods is provided by “metadynamics” [7], where the free energy landscape is represented as a sum of Gaussians with weights and widths determined dynamically as a simulation advances. Most of these methods require a certain level of intervention by the user; to improve performance and reduce reliance on user expertise, several newer, “automated” alternatives have been proposed [8–11], including basis function sampling [12], Green’s function sampling [13], variationally enhanced sampling [14], and artificial neural network (ANN) sampling [15, 16] – the latter approach being perhaps the most robust of the methods in this category.

A fundamentally distinct class of sampling methods is based on the Adaptive Biasing Force (ABF) algorithm [17, 18]. In such methods, the free energy landscape of the system is estimated from its derivatives with respect to a set of collective variables. Methods based on ABF tend to exhibit good performance. Working with them, however, can be cumbersome as they usually lack a simple means of computing the free energy. Inspired by the success of ANN sampling, an analogous scheme based on ABF was recently proposed FUNN [19]. A combined strategy that takes advantage of both density-of-states and ABF based methods has also been proposed recently – the so-called combined force frequency cff neural-network-based method [16] offers superior performance by relying on both frequencies and forces.

In this work, we present a set of alternatives to CFF that enable construction of a free energy landscape from force and frequency information, but that are more effective and computationally efficient. We also propose a family of methods that allow one to use more information from any given simulation and facilitate learning the free energy landscape of a system. As shown below, the performance of the proposed methods is better than that of previously available techniques.

2 Methods

We begin with a brief review of the idea behind the CFF method. As mentioned above, CFF is based on the idea of using artificial neural networks to learn the free energy by querying both force and frequency information. It employs two neural networks, one to learn from frequency contributions to the free energy estimate, as described in the original ANN technique, and one to learn from force contributions, as in the FUNN method. More specifically, at every step of a simulation, a generalized force is computed according to

$$\frac{dA}{d\xi} = -\left\langle \frac{d}{dt} (Wp) \right|_\xi \right\rangle$$

where $W$ is an arbitrary vector field that satisfies an orthogonality constraint, as explained in Darve et al.’s original work [17, 18], and $p$ is the matrix of atomic momenta.

Both neural networks are simultaneously trained to minimize an objective function of the form

$$C = \beta \sum_i \left[ (P_i - Q_i)^2 + (F_i - \dot{Q}_i)^2 \right] + \alpha \sum_j w_j^2$$

where $P_i$ and $F_i$ are the $i$-th estimates of the free energy and its derivative. $Q$ and $\dot{Q}$ are the neural network output and its derivative with respect to the neural network inputs (the collective variable values sampled on its underlying grid). The rightmost term is a regularization term included to prevent over-fitting.

The $m$-th layer of each neural network can be expressed as

$$a_m = \phi_m(a_{m-1}) = f(W_m a_{m-1} + b_m)$$

where $W_m$ and $b_m$ are the layer weights and biases, respectively. The activation function $f$ chosen for the implementation of CFF (as was also done in ANN and FUNN) is the $\tanh$ function, which is applied to all layers except for the output layer, for which a linear activation function is used. The dot after $f$ represents an element-wise application of
the function. The network that trains only on the frequencies of visits to states provides the biasing during the initial stages of the simulation, as there tends to be a significant mismatch between force and frequency based estimates in the early states of a simulation. Training both networks incurs the costs associated with learning the weights of two separate neural networks. In addition, ANN and CFF need tuning by the user to determine the appropriate network size and sweep frequency for a given system. As shown below, these issues can be circumvented by learning a single set of parameters for a simpler model with less user intervention.

2.1 Sirens-based sampling

If the activation function in \( \sin \) is changed from tanh to \( \sin \), one obtains the so-called sinusoidal representation networks, or sirens, which exhibit a series of attractive mathematical properties. For instance, the derivative of a siren is itself a siren. Moreover, the siren that results from differentiating another siren with respect to the network inputs can be evaluated in terms of the same weights and with a shift of \( \pi/2 \) on the biases. For a general overview on the description of sirens we refer readers to the work of Sitzmann, et al. [20]. Specifically, if \( A \) is some \( \mathbb{R}^n \to \mathbb{R} \) function, we represent it as a siren according to:

\[
A(\xi) = W_n (\phi_{n-1} \circ \phi_{n-2} \cdots \circ \phi_0)(\xi) + b_n
\]

with layer \( m \) defined as before:

\[
\phi_m(x) = \sin \left( W_m x + b_i \right).
\]

One can therefore express the gradient of the function \( A \) with respect to the input \( \xi \) as

\[
\nabla_{\xi} A = \left( W_T^0 \phi'(a_0) \right) \cdots \left( W_{n-1}^T \phi'(a_{n-1}) \right) \cdot W_n^T
\]

where \( a_{m-1} \) is the input to the \( m \)-th layer of the siren, and each layer \( \phi'_m \) is the same as \( \phi_m \) but with a phase shift

\[
\phi'_m(a) = \sin \left( W_m a + (b_m + \frac{\pi}{2}) \right).
\]

This permits the evaluation of both a siren and its gradient in a single pass, which is a particularly convenient feature.

These neural architectures can be used to build a wide range of schemes for learning the free energy of a molecular system. The following examples are representative. First, if one sets the same objective function as before, and aims to train the network from both the generalized forces and frequencies, the resulting scheme is similar to CFF, but now the learning proceeds as follows:

1. the unbiased histogram is computed in the same way as for ANN,
2. the network is trained on the generalized forces and frequency of visited states only for a number of initial training sweeps, for example, until all bins for the collective variable grid have been visited at least once,
3. the learning is then switched to train only on generalized forces (this reduces the impact that the training frequency might have).

A second, equally effective variation of the previous procedure (see below), would be to only train the network on the gradients of the forces. This is similar in spirit to the previously reported Funn method, but allows one to compute the free energy directly from the same neural network.

Note that sirens lend themselves to more general problems with cost functions of the form

\[
C \left( \xi, A(\xi), \nabla_{\xi} A(\xi), \nabla^2_{\xi} A(\xi), \ldots \right) = 0.
\]
In principle, one can consider training a model not only using forces and frequencies but, for certain collective variables, with the gradients of the forces, which can be expressed in terms of the local configurational temperature, given by

$$\left\langle \sum_i \nabla \cdot F_i \right\rangle = -\frac{1}{k_B T_{conf}} \left\langle \sum_i F_i^2 \right\rangle$$  \hspace{1cm} (9)

### 2.2 Spectral Sampling

The algorithms outlined in the previous section, specifically Equation (8), without regard for the functional form of $A$, are suggestive of a more general family of sampling methods. Indeed, any function in a Sobolev space for which its values and its derivatives can be conveniently expressed in terms of the same set of parameters could in principle replace the use of sirens.

For low dimensional problems (one or two collective variables), one might adopt a generalized approach based on Basis Functions Sampling [12], and model both forces and the free energy as expansions (or tensor product expansions) in an appropriate set of bases.

To illustrate this idea, consider approximating the free energy as a function of a single periodic collective variable using a truncated Fourier series

$$A(\xi) \approx c_0 + \text{Re} \sum_{k=1}^{n} c_k z^k = \sum_{k=1}^{n} a_k \text{Re} z^k - b_k \text{Im} z^k$$  \hspace{1cm} (10)

where $z = e^{ik\xi}$. It follows that the forces can be expressed as

$$- F(\xi) = \frac{\partial A(\xi)}{\partial \xi} \approx \text{Re} \sum_{k=1}^{n} i k c_k z^k = - \sum_{k=1}^{n} k a_k \text{Im} z^k + k b_k \text{Re} z^k.$$  \hspace{1cm} (11)

If we collect partial statistics of the forces, as is done in ABF, we can fit the coefficients of the expansion by means of an alternate matrix for the $m$ support points of the helper histogram

$$- \text{Im} \begin{pmatrix} z_1 & 2z_1^2 & \ldots & n z_1^n \\ z_2 & 2z_2^2 & \ldots & n z_2^n \\ \vdots & \vdots & \ddots & \vdots \\ z_m & 2z_m^2 & \ldots & n z_m^n \end{pmatrix} \begin{pmatrix} a_1 \\ \vdots \\ a_n \end{pmatrix} - \text{Re} \begin{pmatrix} z_1 & 2z_1^2 & \ldots & n z_1^n \\ z_2 & 2z_2^2 & \ldots & n z_2^n \\ \vdots & \vdots & \ddots & \vdots \\ z_m & 2z_m^2 & \ldots & n z_m^n \end{pmatrix} \begin{pmatrix} b_1 \\ \vdots \\ b_n \end{pmatrix} \approx \begin{pmatrix} F_1 \\ \vdots \\ F_m \end{pmatrix}.$$  \hspace{1cm} (12)

and, for example, solve the latter expression as a least squares problem.

Since the coefficients are the same for the expansion of the energy and the approximation of the force (except for the $c_0$), one also obtains an expression for the free energy up to an additive constant. What we have just described is in reality an alternative to the funn sampling method that uses basis expansions instead of a neural network, and the idea can be generalized to parallel the CFF approach as well. Consider the following Vandermonde and diagonal matrices

$$M = \begin{pmatrix} z_1 & z_1^2 & \ldots & z_1^n \\ z_2 & z_2^2 & \ldots & z_2^n \\ \vdots & \vdots & \ddots & \vdots \\ z_m & z_m^2 & \ldots & z_m^n \end{pmatrix}, \quad D = \begin{pmatrix} 1 & 0 & \ldots & 0 \\ 0 & 2 & \ldots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \ldots & n \end{pmatrix}.$$  \hspace{1cm} (13)
By also collecting the frequencies, as in \textit{cFF}, and estimating the free energy \( \{ A_1, \ldots, A_n \} \) from the corresponding re-weighted histogram, as in \textit{ANN}, we can now solve

\[
\begin{pmatrix}
1 & \text{Re}(M) \\
0 & -\text{Im}(DM)
\end{pmatrix}
\begin{pmatrix}
c_0 \\
a_1 \\
\vdots \\
a_n
\end{pmatrix}
- \begin{pmatrix}
\text{Im}(M) \\
\text{Re}(DM)
\end{pmatrix}
\begin{pmatrix}
b_1 \\
\vdots \\
b_n
\end{pmatrix}
\approx \begin{pmatrix}
A_1 \\
\vdots \\
A_m \\
F_1 \\
\vdots \\
F_m
\end{pmatrix}
\tag{14}
\]

Note that the spectral approach just described will not scale as easily to a large number of CVs as the neural network approaches but, given the abundance of systems where only one or two CVs are important, this method should yield faster sampling convergence, because the costs of fitting the spectral approximation should in general be lower than the computational work required to train neural networks for low-dimensional collective variable spaces.

The set of methods described in this section can also be viewed as applications of different techniques from approximation theory \cite{21}. For instance, if the chosen bases are ultra-spherical polynomials, the scheme would be closely related to the well-conditioned spectral method by Olver and Townsend \cite{22} for approximating functions and solving ordinary differential equations \cite{23}. A useful result is that a least-squares polynomial approximant of degree \( n \) that satisfies \( n \leq \frac{1}{2} \sqrt{m} \) \cite{24}, \( m \) being a number of equally spaced sampling points, provides weak guarantees on the stability of extrapolations near the sampling domain boundaries. We take this as a guiding principle to automatically choose the polynomial order from the number of points of a user-defined grid for the collective variable.

### 3 Results

In all simulations we followed the same overall strategy to evaluate our approximate model for the free energy as in previous neural network-based sampling methods. We train or fit the model every \( N \) time steps of a simulation, and use the smooth continuous function represented by the selected model to provide an estimate of the forces to bias the simulation. Unless stated otherwise, all methods were implemented and ran with the \textsc{pysages} (Python Software Suite for Advanced General Ensemble Simulations) software package, which is a Python implementation of the \textsc{ssages} library \cite{25} designed for advanced sampling simulations on GPUs.

#### 3.1 Alanine Dipeptide in Water

To examine the performance of the algorithms introduced above we start with one of the canonical examples that is used to benchmark enhanced sampling methods, namely the alanine dipeptide (Figure 1) in explicit water. For this system, simulations were performed using OpenMM 7.5 \cite{26} as a back-end for \textsc{pysages} with the Amber99sb force field and 750 TIP3P water molecules, in a box of size \( 3 \text{ nm} \times 3 \text{ nm} \times 3 \text{ nm} \). Simulations were performed at \( T = 298.15 \text{ K} \). The equations of motion were integrated using a Langevin thermostat with a friction coefficient of \( 1 \text{ ps}^{-1} \) and a 2 fs time step.

In what follows we compare the following sampling methods:

1. A \textsc{siren} network with a single inner layer with 14 nodes, trained with forces and frequencies on a collective variable grid of \( 32 \times 32 \),
2. a tensor-product Fourier expansion fitted on the forces, and
3. a tensor-product Fourier expansion fitted on both frequencies and forces.
Figure 1: Dihedral angles used as canonical CVs to describe alanine dipeptides

For both spectral (Fourier) sampling methods, we sample over a $64 \times 64$ grid. In addition we use as a reference a $100$ ns ABF sampling run and a $(12-8)$ CFF network run with sSAGES and Gromacs [27], as described in the original CFF publication.

Analysis of the convergence of the sIRENS-based CFF and spectral sampling methods reveals the same overall behaviour. This suggests that the general underlying strategy of relying on a single parametric model, and computing its parameters using frequency and forces estimates, leads to comparable explorations of the CV space. At $2.5$ ns all methods recover with good accuracy the full energy landscape (Figure 2). However, all methods proposed here converge faster than CFF (Figure 3). In particular, we believe that the global nature of the spectral approximations results in better bias estimates across the full sampling domain, whereas activated neural network approaches can lead to improvements closer to that of visited sites during a training sweep and the previous one.

Another important advantage of the sIREN method presented here over CFF, and of all spectral methods over neural based approaches, is the reduced computational cost. For instance, training sIRENS was found to be at least 5 times faster than training tanh-based networks of the same size. Even more striking is that a mere 14-node single layer perceptron was able to learn the free energy landscape for this example.

For both spectral methods, fitting every 500 integration steps leads to simulations of around 850 TPS on a single Nvidia GeForce RTX 2070 Super GPU, whereas the sIREN runs with training every 5000 steps proceeded at nearly 150 TPS. The spectral approach generates a converged free energy landscape for the alanine dipeptide in water after approximately 15 minutes on the above hardware.

3.2 One-Dimensional Rugged Free Energy Landscape

To further illustrate the robustness and convergence of the methods proposed here, we now consider a one-dimensional, artificial rugged free energy landscape constructed by adding 100 Gaussians. This landscape can be viewed as representative of that of a protein folding funnel or a glassy system. It is worth noting that this is a more complex surface than the one previously used to evaluate both the Green-Function Sampling and the ANN methods, where the sum of 50 Gaussians was used.

For this example, simulations were carried out with pySAGES using HOOMD-blue 2.9.6 [28] as the back-end. A single 1 amu particle restrained to one dimension in a simulation box of 10 nm was integrated using Langevin dynamics with $dt = 0.0005$ and $kT = 1$. The external potential consists of the sum of 100 Gaussians with heights, widths and centers randomly chosen from the distributions $\mathcal{U}(-20, 5)$, $\mathcal{U}(1/1000, 1/\sqrt{20})$, and $\mathcal{U}(-4, 4)$, respectively.

The potential was sampled with a two-layer sIREN network with two hidden layers of eight nodes each $(8, 8)$ at a training frequency of 5000 integration steps. As a means to assess the performance of the method, we use a FUNN network with the same architecture. We can observe (Figure 4) that after 20 training sweeps, the sIRENS sampling scheme is able to basically recover the full potential. In contrast, after 100 training sweeps, the FUNN method has
Figure 2: Comparison of the free energy landscape of alanine dipeptide as a function of the dihedral angles from Fig. 1 for the methods introduced in this work. A 100 ns run of ABF is plotted for reference.

Figure 3: Root mean square error of the free energy estimates for both methods
qualitatively learned all of the landscape features, but it still fails to match the heights of most of the hills by about $3 kT$.

![Matching the sum of 100 gaussians with SIREN and FUNN](image)

**Figure 4:** Matching the sum of 100 gaussians with **SIREN** and **FUNN**

### 3.3 Stretching of Deca-alanine

As a final example, we compare the spectral method proposed here to other recent methods from the literature that also try to combine learning from frequencies and forces, such as the GaWTM–eABF hybrid method \[29\], which combines Well-tempered Metadynamics with the extended ABF method and Gaussian-accelerated molecular dynamics strategies. To do this, we consider the stretching of deca-alanine reported in the GaWTM–eABF work. All simulations were again performed with **PYSAGES** and OpenMM 7.5 as back-end. All bonded and non-bonded interactions were modeled with the **CHARMM22** force field \[30\]. The temperature was set to 300 K and the system was evolved using a Langevin integrator ($dt = 0.5$ fs) after a standard energy minimization step.
The collective variable used to bias the simulation was the same as for the GaWTM–eABF work, namely the distance between the first and the last $\alpha$-carbon atoms of the peptide. For this, the CV domain (4 nm–32 nm) was split into two Chebyshev-distributed sets of points 4 nm–13 nm and 13 nm–32 nm (256 points per region) that we used for binning both forces and frequencies. The free energy is then modeled as the two piece-wise sets of polynomial expansions.

After a single 50 ns simulation we are able to recover the free-energy profile shown in Figure 5. This free-energy profile portrays all the features of the one obtained by a multiwalker 200 $\mu$s ABF simulation, and exhibits greater fidelity than the GaWTM–eABF strategy, which mixes three different generally robust sampling methods to bias the system. Furthermore, our proposed approach does not need the a-priori calibration of the method to set any user-facing parameters (other than the size and distribution of the sampling grid).

Figure 5: Free energy of stretching deca alanine as a function of the distance between terminal $\alpha$ carbons

4 Conclusions

A new family of fast and globally convergent enhanced sampling methods had been proposed. First, building on the idea of learning free energy surfaces by training neural networks on both frequency of visits to CV states as well as on generalized forces, we introduced the use of siren neural networks with periodic activation functions that provide a better description of a function and its gradients. The proposed siren are shown to be more stable and efficient than networks that rely on other activation functions. Going beyond siren sampling, we also proposed two methods that follow the same fitting strategy, but that are inspired by previously proposed algorithms based on basis-function sampling. We refer to such methods as Spectral sampling.

The effectiveness of the proposed new algorithms was established through a series of examples. In all cases the performances of sirens and Spectral methods surpass those of all other methods considered here, not only in terms
of convergence, but also from a computational perspective, even for extremely rugged free-energy landscapes. All the methods proposed have been implemented in the publicly available \textsc{pysages} software suite.

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