Reinforced dynamics for enhanced sampling in large atomic and molecular systems.

I. Basic Methodology

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A new approach for efficiently exploring the configuration space and computing the free energy of large atomic and molecular systems is proposed, motivated by an analogy with reinforcement learning. There are two major components in this new approach. Like metadynamics, it allows for an efficient exploration of the configuration space by adding an adaptively computed biasing potential to the original dynamics. Like deep reinforcement learning, this biasing potential is trained on the fly using deep neural networks, with data collected judiciously from the exploration and an uncertainty indicator from the neural network model playing the role of the reward function. Applications to the full-atom, explicit solvent models of alanine dipeptide and tripeptide show some promise for this new approach.

I. INTRODUCTION

Exploring the configuration space of large atomic and molecular systems is a problem of fundamental importance for many applications including protein folding, materials design, and understanding chemical reactions, etc. There are several difficulties associated with these tasks. The first is that the dimensionality of the configuration space is typically very high. The second is that there are often high energy barriers associated with the exploration. Both difficulties can be reduced by the introduction of collective variables (CVs) and the mapping of the problem to the CV space. The problem then becomes finding the free energy surface (FES) associated with the set of CVs, a problem that has attracted a great deal of interest in the last few decades [1–13, 21]. One of the most effective techniques is metadynamics [9], which computes a biasing potential by depositing Gaussian bases along the trajectory in the CV space. It is shown that the biasing potential converges to the inverted free energy at the end of the calculation [10]. Also closely related to our work are the recent papers that propose to use machine learning methods to help parameterizing FES [14,17]. In particular, the deep neural network (DNN) model has shown promise in effectively representing the FES defined on high dimensional CV space [16, 17].

In this work, we take metadynamics and machine learning methods one step further by making an analogy between reinforcement learning [18] and the task of configuration space exploration and FES calculation. Classical reinforcement learning scheme involves a state space, an action space and a reward function. The objective is to find the best policy function, which is a mapping from the state space to the action space, that optimizes the cumulative reward function. Our problem can be thought of as being a multi-scale reinforcement learning problem. We have a micro-state space, the configuration space of the detailed atomic system, and a macro-state space, the space of the CVs. The action space will be represented by the biasing potential in the biased molecular dynamics on the micro-state space. The optimal policy function is the inverted FES, defined on the macro-state space. The FES is parameterized by a carefully designed DNN model. In the absence of an explicit reward function, we introduce an uncertainty indicator that can be used to quantify the accuracy of the FES representation. It is defined as the standard deviation of the predictions from an ensemble of DNN models, which are trained using the same dataset but different initialization of the model parameters. The bias is only adopted in regions where the uncertainty indicator is low, i.e. regions that are sufficiently explored, and the exploration in the insufficiently explored region

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is encouraged. We call this the “reinforced dynamics”, to signal its analogy with reinforcement learning.

Roughly speaking, reinforced dynamics works as follows: The biasing potential, or the action, is initialized at 0 and is expected to converge to the inverted FES as the dynamics proceeds. Each step of the macro iteration involves the following components. First, a biased MD is performed, in which the system is biased only in the regions where the uncertainty indicator is low. The biased simulation is likely to visit the CV regions never visited before or where the FES representation quality is poor. Next, the newly visited CV values in regions where the uncertainty indicator is high are added to the training dataset. A restrained MD is performed to obtain the mean force, or the negative gradient of the FES, at each of the newly added CV values. Finally, the accumulated CV values and the mean forces are used as labels to train several network models, which give the current estimate of the biasing potential and the uncertainty indicator. This process is repeated iteratively until convergence is achieved, when the newly visited CV values all fall in the regions where the uncertainty indicator is low.

In this series of papers, we give a systematic presentation of the theoretical and practical aspects of reinforced dynamics. This first paper will be focused on methodological considerations. We use the classical alanine dipeptide and tripeptide with two and four CVs, respectively, as illustrations due to their intuitive appeal. The solvent effect is explicitly considered in both examples. The FESs constructed by the brute force simulations (5.1 µs for alanine dipeptide and 47.7 µs for tripeptide) to demonstrate the accuracy and efficiency of the method. The second and third papers of this series will be devoted to the details for higher dimensional examples as well as applications to structural optimization.

II. THEORY

A. Free energy and mean forces

We assume that the system we are studying has $N$ atoms, with their positions denoted by $r = (r_1, \ldots, r_N)$. The potential energy of the system is denoted by $U(r)$. Without loss of generality, we consider the system in a canonical ensemble. Given $M$ predefined CVs, denoted by $s(r) = (s_1(r), \ldots, s_M(r))$, the free energy defined on the CV space is

$$A(s) = -\frac{1}{\beta} \ln p(s), \quad p(s) = \frac{1}{Z} \int e^{-\beta U(r)} \delta(s(r) - s) \, dr,$$

(1)

with $Z = \int e^{-\beta U(r)} \, dr$ being the normalization factor. The brute-force way of computing the free energy \[1\] is to sample the CV space exhaustively and to approximate the probability distribution $p(s)$ by making a histogram of the CVs. This approach may easily become prohibitively expensive. In such a case, an alternative way of constructing the FES is to fit the mean forces acting on the CVs, i.e.,

$$F(s) = -\nabla_s A(s).$$

(2)

Several ways of computing $F(s)$ have been proposed \[12\] \[20\] \[21\]. We will adopt the approach of restrained dynamics proposed in \[21\]. In this formulation, a new term is added to the potential of the system to represent the effect of the spring forces between the configuration variables and the CVs. It can be shown that the mean force is given by

$$F^k(s) = \frac{1}{Z_k(s)} \int k_\alpha(s_\alpha(r) - s_\alpha) e^{-\beta U_k(r,s)} \, dr.$$ \hspace{1em} \hspace{1em} (3)

Here $Z_k(s) = \int e^{-\beta U_k(r,s)} \, dr$ is the normalization factor, $\{k_\alpha | \alpha = 1, \ldots, M\}$ are the spring constants for the harmonic restraining potentials, and $U_k(r,s)$ is defined by

$$U_k(r,s) = U(r) + \sum_{\alpha=1}^{M} \frac{1}{2} k_\alpha (s_\alpha(r) - s_\alpha)^2.$$ \hspace{1em} \hspace{1em} (4)

In practice, the spring constants are chosen to be large enough to guarantee the convergence to the mean forces. The time duration for the restrained dynamics should be longer than the largest relaxation timescale of the fast modes of the system, in order for the ensemble average in Eq. (3) to be approximated adequately by the time average. In the rest of the paper, we do not explicitly distinguish $F$ and $F^k$.

B. Free energy representation

The free energy $A(s)$ will be represented by a deep neural network (DNN) model, in which the input CVs are first preprocessed, then passed through multiple fully connected hidden layers, and, in the end, mapped to the free energy. The structure of the DNN model is schematically illustrated in Fig. [I]. Mathematically, a DNN representation with $N_h$ hidden layers is given by

$$A(s) = L^{\text{out}} \circ L^{N_h} \circ \cdots \circ L^1 \circ P(s)$$

(5)

where “$\circ$” denotes function composition. The differentiable operator $P$ represents the system-dependent pre-processing procedure for the CVs, which will be illustrated by the examples in Sec. [III]. For the $p$-th hidden layer, which has $M_p$ neurons $d_p \in \mathbb{R}^{M_p}$, $L_p$ is the operation that maps $d_{p-1}$ to $d_p$, using:

$$d_p = L_p(d_{p-1}) = \varphi(W_p d_{p-1} + b_p).$$

(6)
The DNN representation of the free energy is obtained by solving the following minimization problem

$$\min_{\{W, b\}} L_D(\{W, b\}).$$

(9)

The loss function $L_D$ is defined by

$$L_D(\{W, b\}) = \frac{1}{|D|} \sum_{s \in D} ||\mathcal{F}(s) - \mathcal{F}(s)||^2,$$

(10)

where $D$ denotes the set of training data and $|D|$ denotes the size of the dataset $D$. Here $\mathcal{F}(s)$ comes from the DNN model, and $\mathcal{F}(s)$ is the collected mean force for the data $s$. Precise ways of collecting the data will be discussed later. It should be noted that at the beginning of the training process, we have no data. Data is collected as the training process proceeds.

To guarantee accuracy for this model, we require that the CV values in $D$ be an adequate sample of the CV space. This is made difficult due to the barriers on the energy landscape. The MD will tend to be stuck at metastable states without being able to escape. To help overcome this problem, we introduce a biased dynamics. Details of that will be discussed in the next subsection.

A key notion for reinforced dynamics is the uncertainty indicator. This quantity is important in the data collection step as well as in the biased dynamics step. Our intuition is that the DNN models should produce a reasonably accurate prediction of the free energy in regions that are adequately covered by $D$, but is much less so in regions that are covered poorly by $D$ (or have not been visited by the MD). To quantify this, we introduce a small ensemble of DNN models, where the only difference between these models is the random weights used to initialize them. We can then define the uncertainty indicator as $\mathcal{E}(s)$, the standard deviation of the force predictions, viz.

$$\mathcal{E}^2(s) = \langle ||\mathcal{F}(s) - \overline{\mathcal{F}(s)}||^2 \rangle, \quad \mathcal{F}(s) = \langle \mathcal{F}(s) \rangle,$$

(11)

where the ensemble average is taken over each ensemble of models. One expects that this ensemble of models gives rise to predictions of the mean forces $\mathcal{F}$ that are close to each other in regions well covered by $D$. In the regions that are covered poorly by $D$, the predictions will scatter much more. This is confirmed by our numerical results.

Finally, it is worth noting that the minimization problem (9) is solved by the stochastic gradient descent (SGD) method combined with the back-propagation algorithm [24]. This has become the de facto standard algorithm for training DNN models. At each training step, the loss function is evaluated on a small batch, or subset $B$ of the training data $D$, i.e.,

$$L = \frac{1}{|B|} \sum_{s \in B} ||\mathcal{F}(s) - \mathcal{F}(s)||^2.$$  

(12)
D. Adaptive biasing

A way of encouraging the MD to overcome the barriers in the energy landscape and escape metastable regions is to add a bias to the potential. The force on the $i$-th atom then becomes:

$$\tilde{f}_i(r) = -\nabla_r U(r) - \nabla_r U_{\text{bias}}(s(r)).$$  \hspace{1cm} (13)

Since the FES is the best approximation of the potential energy in the space of CVs, it is natural to use the current approximation of the FES, with a negative sign added, as the biasing potential, as is done in metadynamics [9, 10]. We will adopt the same strategy but we propose to switch on the biasing potential only in regions where we have low uncertainty on the DNN representation of the FES:

$$\tilde{f}_i(r) = -\nabla_r U(r) + \sigma(E(s(r))) \nabla_r A(s(r)),$$  \hspace{1cm} (14)

where the biasing potential $A(s(r))$ is the mean of the predefined ensemble of DNN models, and $\sigma(\cdot)$ is a smooth switching function defined by

$$\sigma(e) = \begin{cases} 
1, & e < e_0, \\
\frac{1}{2} + \frac{1}{2} \cos \left( \pi \frac{e - e_0}{e_1 - e_0} \right), & e_0 \leq e < e_1, \\
0, & e \geq e_1.
\end{cases}$$  \hspace{1cm} (15)

Here $e_0$ and $e_1$ are two uncertainty levels for the accuracy of the DNN model. In regions where the uncertainty indicator $E(s)$ is smaller than the level $e_0$, the accuracy of the DNN representation of $A(s)$ is adequate, and hence the system will be biased by $A(s)$. In the regions where $E(s)$ is larger than level $e_1$, the accuracy of the DNN representation is inadequate, and the system will follow the original dynamics governed by the potential energy $U(r)$. In between $e_0$ and $e_1$, the DNN model is partially used to bias the system via a rescaled force term $-\sigma(E(s(r))) \nabla_r A(s(r))$.

E. Data collection

After the biased MD, a number of the newly visited CV values that are in the regions with high uncertainty are added to the training dataset $D$. The regions with high uncertainty are defined to be the CV values that give rise to large uncertainty indicator, viz., $E(s) > e_{\text{accept}}$. A reasonable choice of the threshold is $e_{\text{accept}} = e_0$. For each value of the CV in $D$, we use the restrained dynamics to calculate the mean forces $F$ via Eq. (3). These values, together with those computed in previous iterations, are used as the labels for training the next updated model.

F. The reinforced dynamics scheme

Fig. 2 is a flowchart of the reinforced dynamics scheme. Given an initial guess of the FES represented by the DNN, a biased MD, i.e. Eq. (14), is performed to sample the CV space from an arbitrarily chosen starting point. If no a priori information on the FES is available, then a standard MD is carried out. The visited CV values are recorded at a certain time interval and tested by the uncertainty indicator to see whether they belong to a region with high uncertainty in the CV space. If all the newly sampled CV values from the biased MD trajectory belong to the region with low uncertainty, it can be (1) the biased MD is not long enough, so parts of the CV space are not explored, (2) the interval for recording CV values along the biased MD is not small enough, so some visited CV values belonging to the region with high uncertainty are missed, or (3) the DNN representation for FES is fully converged, then the iteration should be stopped and one can output the DNN representation for the FES, namely the mean of the predefined ensemble of models. Case (1) can be excluded by systematically increasing the length of the biased simulation. Case (2) can be excluded by decreasing the recording interval.

If CV values belonging to the region with high uncertainty are discovered, they will be added to the training dataset $D$. The CV values that are already in the training dataset should be retained and serve as training data for later iterations. The mean forces at the added CV values are computed by the restrained dynamics Eq. (3). A new ensemble of DNN models for the FES are then trained, using different random initial guesses for $\{W, b\}$. The standard deviation of the predictions from these models is again used to estimate the uncertainty indicator $E(s)$. [Diagram]
The iteration starts again using the biased MD simulation with the new DNN models.

Finally, it is worth noting that the restrained MD simulations for mean forces, which take over most of the computation time in the reinforced dynamics scheme, are embarrassingly parallelizable. The training of the ensemble of DNN models is also easily parallelizable. Several independent walkers can be set up simultaneously for a parallelized biased simulation, and this provides a more efficient exploration of the FES. These techniques can help accelerate the data collection process and benefit large-scale simulations for complex systems.

III. NUMERICAL EXAMPLES

A. Simulation setup

We investigate the FES of the alanine dipeptide (ACE-ALA-NME) and alanine tripeptide (ACE-ALA-ALA-NME) modeled by the Amber99SB force field [25]. The molecules are dissolved in 342 and 341 TIP3P [26] water molecules, respectively, in a periodic simulation cell. All the MD simulations are performed using the package GROMACS 5.1.4 [27]. The cut-off radius of the van der Waals interaction is 0.9 nm. The dispersion correction due to the finite cut-off radius is applied to both energy and pressure calculations. The Coulomb interaction is treated with smooth particle mesh Ewald method [28] with a real space cut-off 0.9 nm and reciprocal space grid spacing 0.12 nm. The system is integrated with the leap-frog scheme at timestep 2 fs. The temperature of the system is set to 300 K by velocity-rescale thermostat [29] with a relaxation time 0.2 ps. The solute and solvent are coupled to two independent thermostats to avoid the hot-solvent/cold-solute problem [30]. Parrinello-Rahman barostat [31] (GROMACS implementation) with a relaxation timescale 1.5 ps and compressibility $4.5 \times 10^{-5}$ Bar$^{-1}$ is coupled to the system to control the pressure to 1 Bar. For both the alanine dipeptide and tripeptide, any covalent bond that connects a hydrogen atom is constrained by the LINCS algorithm [32]. The H-O bond and H-O-H angle of water molecules are constrained by the SETTLE algorithm [33].

For the alanine dipeptide, two torsion angles $\varphi$ (C, N, C$_{\alpha}$, C) and $\psi$ (N, C$_{\alpha}$, C, N), are chosen as CVs for this system, i.e. $s = (\varphi, \psi)$. While for the alanine tripeptide, the same torsion angles associated with the first and second C$_{\alpha}$s, denoted by $\varphi_0$, $\varphi_0$, and $\varphi_1$, $\varphi_1$, respectively, are used as CVs for the system, i.e. $s = (\varphi_0, \varphi_0, \varphi_1, \varphi_1)$. The GROMACS source code is modified and linked to PLUMED 2.4b [34] to carry out the biased and restrained simulations. The PLUMED package is modified to compute the DNN biasing force, viz., Eq. (14). The DNN models used in both examples contain three hidden layers of size $(M_1, M_2, M_3) = (48, 24, 12)$. The preprocessing operator for the alanine dipeptide is taken as $P(\varphi, \psi) = (\cos(\varphi), \sin(\varphi), \cos(\psi), \sin(\psi))$, so the periodic condition of the FES is guaranteed. Similarly, the preprocessing operator for the alanine tripeptide is $P(\varphi_0, \psi_0, \varphi_1, \psi_1) = (P(\varphi_0, \psi_0), P(\varphi_1, \psi_1))$. Model training is carried out under the deep learning framework TensorFlow [35], using the Adam stochastic gradient descent algorithm [36] with a batch size of $|B| = 20$. The learning rate is 0.001 in the beginning and decays exponentially according to $r(t) = r(0) \times d_s^{t/d_r}$, where $t$ is the training step, $d_s = 0.96$ is the decay rate, and $d_s = 50 \times |D|/|B|$ is the decay step. In each reinforced dynamics step, four DNN models with independent random initialization are trained in the same way to compute the uncertainty indicator. The biased MD simulations of alanine dipeptide and tripeptide last for 100 ps and 140 ps, respectively. The CV values along the MD trajectories are computed and recorded in every 0.2 ps. We assume no a priori information regarding the FES, so a brute-force simulation is performed for the first iteration step (iteration 0). In each iteration at most 50 recorded CV values in the region with high uncertainty are added to the training dataset $D$. Restrained MD simulations with spring constant 500 kJ/mol/rad$^2$ are performed to estimate the mean forces by Eq. (3). Each restrained MD simulation is 100 ps and 140 ps long for the alanine dipeptide and tripeptide, respectively. The CV values are recorded in every 0.01 ps along the restrained MD trajectory to estimate the mean forces. Both of the alanine dipeptide and tripeptide examples are carried out on a Lenovo X1 carbon laptop computer with an Intel i6-6200U CPU and 8GB memory.

B. Free energy surface construction

The FES of the alanine dipeptide on the $\varphi$-$\psi$ plane (known as the Ramachandran plot) is reported in Fig. 3. We perform 6 independent brute-force MD simulations, with each ~ 860 ns long, thus in total 5.1 $\mu$s MD trajectories are used to estimate the FES and compare with the reinforced dynamics result. The system has 5 metastable states $\alpha_R$, $C_5$, $P_{II}$, $\alpha_L$, and $C_7$, as noted in Fig. 3 (a). The $C_5$, $P_{II}$ regions correspond to the dihedral angles observed in the $\beta$-strands conformations. The $\alpha_R$ and $\alpha_L$ regions correspond to the dihedral angles of right- and left-handed $\alpha$-helix conformations, respectively. The transition between the $P_{II}$ and $\alpha_L$ has to go over an energy barrier of ~25 kJ/mol, or equivalently ~10$\text{kJ}$$^2$/rad$^2$. The mean first passage time from the state $P_{II}$ to $\alpha_L$ is shown to be 43 ns for the same model [37].

In Fig. 3, the FES of alanine dipeptide sampled by the brute-force MD (a) is compared with the one constructed by reinforced dynamics (b) with uncertainty levels $e_0 = 3.0$ kJ/mol/rad and $e_1 = 3.5$ kJ/mol/rad. At the 9th iteration for (b), the biased simulation does not produce any CV value that belongs to the region with the...
**FIG. 3:** The free energy of alanine dipeptide on the $\phi$-$\psi$ plane. The plots are obtained by (a) making log-scaled histogram of the CV values from brute-force MD simulations; (b)–(c) using the reinforced dynamics with uncertainty levels $e_0 = 3.0$, $e_1 = 3.5$ kJ/mol/rad. (b) plots the FES, and (c) plots the error compared with the brute force MD. (d)–(e) using the reinforced dynamics with uncertainty levels $e_0 = 1.5$, $e_1 = 2.0$ kJ/mol/rad. (d) plots the FES, and (e) plots the error compared with the brute force MD. The contour lines in (a), (b) and (d) are plotted from 0 kJ/mol to 30 kJ/mol with an interval of 5 kJ/mol. The red regions in (a), (c) and (d) are the CV values that are never been visited by the MD trajectories.

In this case, the biased MD simulation does not generate CV values belonging to the region with high uncertainty at the 21st iteration. In total (from the 0th to the 20th iteration) 303 CV values are added to the training dataset $D$ to construct the FES. The error of FES at all metastable states and transition regions is uniformly below 0.5 kJ/mol. The total biased MD simulation time is $22 \times 0.1 \text{ ns} = 2.2 \text{ ns}$. The total restrained MD simulation time is $303 \times 0.1 \text{ ns} = 30.3 \text{ ns}$. Thus the total MD simulation time is $32.5 \text{ ns}$, which is 50 % longer than the reinforced dynamics with higher uncertainty levels ($e_0 = 3.0$ kJ/mol/rad and $e_1 = 3.5$ kJ/mol/rad), but still shorter than the mean first passage time from $P_{II}$ to $\alpha_L$ of the brute-force simulation (43 ns).

The information of the four-dimensional FES of the
alanine tripeptide constructed by brute-force MD sampling and the reinforced dynamics is presented in Fig. 4 by projecting on the \((\varphi_0, \psi_0), (\varphi_1, \psi_1)\) and \((\varphi_1, \psi_0)\) planes. For example, the projection onto the \((\varphi_0, \psi_0)\) variables is defined by

\[
A(\varphi_0, \psi_0) = -\frac{1}{\beta} \ln \int d\varphi_1 d\psi_1 e^{-\beta A(\varphi_0, \psi_0; \varphi_1, \psi_1)} + C,
\]

(16)

where \(C\) is a constant that is chosen to normalize the minimum value of \(A(\varphi_0, \psi_0)\) to zero. Projected free energies \(A(\varphi_1, \psi_1)\) and \(A(\varphi_1, \psi_0)\) are defined analogously. The uncertainty levels of the reinforced dynamics are set to \(e_0 = 3.0 \text{ kJ/mol/rad}\) and \(e_1 = 3.5 \text{ kJ/mol/rad}\). The biased MD simulation of iteration 72 does not find any CV value belonging to the region with high uncertainty, so the process stops. From the 0th to the 71st iteration, 1363 CV values are added to the training dataset. The total biased MD simulation time is \(73 \times 0.14 = 10.22\) ns, while the total restrained MD simulation time is \(1363 \times 0.14 = 190.82\) ns. For comparison, we carried out 18 independent brute-force MD simulations, each of which is \(2.65\) \(\mu s\) long, so the total length of brute-force MD trajectories is \(47.7\) \(\mu s\). Fig. 4 shows that the reinforced dynamics is able to reproduce the FES with satisfactory accuracy on all the projected planes. It is noted that the projected FESs on both the \((\varphi_0, \psi_0)\) and \((\varphi_1, \psi_1)\) variables are different from the FES of alanine dipeptide, which indicates the correlation of backbone atoms.

### C. Illustration of the adaptive feature

To highlight the adaptive feature of the reinforced dynamics, we take the alanine dipeptide as an example, and illustrate in Fig. 5 the CV values visited in each biased MD simulation and those iteratively added to the training dataset \(D\). The uncertainty levels are \(e_0 = 3.0\), \(e_1 = 3.5 \text{ kJ/mol/rad}\), and the reinforced dynamics stops at the 9th iteration. In the 0th iteration, no \textit{a priori} information of the FES is available, so the MD simulation is not biased. The starting state of the simulation is \(P_{\text{II}}\), and the system spontaneously transforms to states \(C_3\) and \(\alpha_R\) in the 0.1 ns simulation [38], thus the visited CV values cover \(P_{\text{II}}, C_3\) and \(\alpha_R\), and 50 of them are randomly chosen as training data. The first DNN representation of FES is trained by these CV values, and is used to bias the system at the 1st iteration. Since the first DNN representation is of good quality at states \(P_{\text{II}}, C_3\) and \(\alpha_R\), the system diffuses out of \(P_{\text{II}}, C_3\) and \(\alpha_R\), and is trapped by a new metastable state \(\alpha_L\). Only the visited CV values that sample the metastable state \(\alpha_L\) are added to the training dataset. The DNN representation trained by the updated dataset is of good quality at states \(P_{\text{II}}, C_3, \alpha_R\) and \(\alpha_L\).

Following this observation, in the 2nd iteration, although the visited CV values cover a wide region including the metastable states \(P_{\text{II}}, C_5, \alpha_R\) and \(\alpha_L\), only those in the transition regions between \(P_{\text{II}}\) and \(\alpha_R\), and between \(\alpha_L\) and \(P_{\text{II}}/C_5\) are added to the training set. The CV values added in the 3rd iteration are those that sample the metastable state \(C_5^{\text{ax}}\) and the transition region between \(C_7^{\text{ax}}\) and \(\alpha_L\). The CV values added in the 4th iteration are those that sample the transition region between \(C_7^{\text{ax}}\) and \(\alpha_R\).

From the 5th to the 8th iteration, the DNN representation of the FES is of relatively good quality. The CV values added to the training dataset are those that sample the border of high energy peaks at \(\varphi \approx 2\) rad and \(\varphi \approx -0.5\) rad. At iteration 9, no CV value belonging to regions with high uncertainty is found because the pushing-back events happen so quickly that the CV values are not recorded by the biased MD trajectory with the 0.2 ps recording interval. However, if we reduce the CV recording interval from 0.2 ps to 0.04 ps, 19 CV values can still be identified to be in the regions with high uncertainty and used to start the next biasing-and-training iteration. Since the construction of high energy FES peaks is of less interest, for the sake of computational cost, we do not use the smaller recording interval in our result. This means that the we ignore the FES regions with sharp gradient so that the biased system can only stay for a time scale that is much shorter than the recording interval. Better stopping criteria that guarantee the representation quality of the important structures of FES and excludes the irrelevant energy peaks are left for future studies.

![Fig. 5: The CV values visited by the biased MD simulations (thin green dots) and those added to the training dataset (thick black dots) in each reinforced dynamics step. The uncertainty levels of the reinforced dynamics are set to \(e_0 = 3.0\) and \(e_1 = 3.5 \text{ kJ/mol/rad}\). The color scale is the same as plot (b) of Fig. 3.](image-url)
IV. CONCLUSION AND PERSPECTIVE

In summary, reinforced dynamics is a promising tool for exploring the configuration space and calculating the free energy of atomistic systems. Even though we only presented two examples of bio-molecules, it should be clear that the same strategy should also be useful for condensed systems. In particular, due to the ability of the deep neural network in representing high dimensional functions [17, 22], we expect the reinforced dynamics to be particularly powerful when the dimensionality of the CV space is high. In addition, one should be able to couple it with optimization algorithms in order to perform structural optimization.

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