Efficient Relative-Entropy Coarse-Graining with Boltzmann Generators

A popular principle for coarse-graining molecular systems is thermodynamic consistency: the coarse-grained and the fine-grained dynamics should have the same equilibrium distribution over the coarse-grained variables. An attractive approach for learning coarse-grained force fields is relative entropy minimization, but this approach is hampered by the fact that during optimization, the equilibrium distribution of the coarse-grained force field needs to be resampled, making the approach computationally expensive and unstable for high-dimensional systems. Here we present a solution for this limitation by developing coarse-graining with Boltzmann Generators. Boltzmann Generators are machine learning models, which can simultaneously represent the coarse-grained force field and efficiently sample from its equilibrium distribution. Boltzmann Generators make relative entropy based coarse-graining efficient and therefore better scalable to larger molecular systems.

I. INTRODUCTION

[**General intro**]

A popular principle for coarse-graining molecular systems is thermodynamic consistency: the coarse-grained and the fine-grained dynamics should have the same equilibrium distribution over the coarse-grained variables. Two popular realizations of this principle rae: multiscale coarse-graining[4,7] – a supervised learning method that is based on minimizing the force-matching error between the coarse-grained and the fine-grained ensemble, and the relative entropy method[9]. These two approaches are connected[8].[**FN: they are obviously connected because they both achieve thermodynamic consistency. Is there a less obvious connection in this paper?**]

These methods have complementary strengths and weaknesses – force matching benefits from being a supervised learning method, but requires the force labels for the training set to be saved when generating the all-atom simulations. Although saving forces during MD simulation is neither difficult nor time-consuming, it is not commonly done unless one generates the dataset specifically for force matching, and therefore most available MD dataset do not have forces available. Relative entropy coarse-graining does not require force labels, but is an unsupervised learning method which is always more difficult than supervised learning. A main technical challenge of relative entropy coarse-graining is that during training, an expectation value over the learned CG ensemble needs to be computed[9]. As the parameters, and thus the learned CG equilibrium distribution change during training, the CG model needs to be resampled while updating its parameters. As most interesting molecular systems have metastable states, this method suffers from the rare event sampling problem during its training. This problem can make the method computationally untractable, and failing to reach a converged sample in every training update can break convergence to the optimal CG force field. Addressing this limitation is important in order to make relative-entropy coarse-graining more scalable.

The recently introduced Boltzmann Generator[6] is a machine learning method to efficiently learn to sample equilibrium states of many-body systems. While Boltzmann Generators have been introduced as methods to sample full (all-atom) configurations for a given energy function, they can also be used to learn a coarse-grained energy function and sample from it. [**continue...**]

II. COARSE-GRAINING WITH BOLTZMANN GENERATORS

A. Thermodynamic consistency

[***This section is copied from the ACS central science paper***]We first define what we mean by coarse-graining and which physical properties shall be preserved in the coarse-grained model.

[**some of this is intro**]The starting point in the design of a molecular model with resolution coarser than atomistic is the definition of the variables. The choice of the coarse coordinates is usually made by replacing a group of atoms by one effective particle. Because of the modularity of a protein backbone or a DNA molecule, popular models coarse-grain a macromolecule to a few interaction sites per residue or nucleotide, e.g., the C_α and C_β atoms for a protein[2,3,5,11]. Alternative schemes have also been proposed for the partitioning of the atoms into coarse-grained coordinates[1,10]. In general, given a high-dimensional atomistic representation of the system $\mathbf{r} \in \mathbb{R}^{3N}$, a CG representation is given by a coordinate transformation to a lower-dimensional space:

$$\mathbf{x} = \xi(\mathbf{r}) \in \mathbb{R}^{3n} \tag{1}$$

with $n < N$. Here we assume that ξ is linear, i.e. there is some coarse-graining matrix $\Xi \in \mathbb{R}^{3n \times 3N}$ that clusters atoms to coarse-grained beads: $\mathbf{x} = \Xi\mathbf{r}$.

The aim is to learn a coarse-grained energy function $U(\mathbf{x}; \boldsymbol{\theta})$ that will be used in conjunction with a dynamical model, e.g., Langevin dynamics, to simulate the CG molecule. $\boldsymbol{\theta}$ are the parameters of the coarse-grained model – in classical CG approaches these are parameters of the potential energy function, such as force constants and partial charges, while here they denote the weights of the neural network.

A common objective in coarse-graining methods is to preserve the equilibrium distribution, i.e. the equilibrium distribution of the coarse-grained model shall be as close

as possible to the equilibrium distribution of the atomistic model when mapped to the CG coordinates. We will be using a simulation algorithm for the dynamics such that the system's equilibrium distribution is identical to the Boltzmann distribution of the employed potential U; therefore this objective can be achieved by enforcing the thermodynamic consistency:

$$U(\mathbf{x};\boldsymbol{\theta}) \equiv -k_B T \ln p^{CG}(\mathbf{x}) + \text{const}, \tag{2}$$

where $k_B T$ is the thermal energy with Boltzmann constant k_B and temperature T, and the probability distribution $p^{CG}(\mathbf{x})$ is the equilibrium distribution of the atomistic model, mapped to the CG coordinates:

$$p^{CG}(\mathbf{x}) = \frac{\int \mu(\mathbf{r})\delta\left(\mathbf{x} - \xi(\mathbf{r})\right) d\mathbf{r}}{\int \mu(\mathbf{r}) d\mathbf{r}} \tag{3}$$

and $\mu(\mathbf{r}) = \exp\left(-V(\mathbf{r})/k_B T\right)$ is the Boltzmann weight associated with the atomistic energy model $V(\mathbf{r})$. Note that the additive constant in (2) can be chosen arbitrarily. Therefore this constant will be omitted in the expressions below, which means that it will absorb normalization constants that are not affecting the CG procedure, such as the logarithm of the partition function.

B. Relative entropy

Coarse-graining with relative entropy was introduced to molecular simulation by Shell[9]. It is based on minimizing the Kullback-Leibler divergence between the two distributions:

$$\begin{aligned} S_{\text{rel}} &= \int \mu(\mathbf{r}) \log \frac{\mu(\mathbf{r})}{p^{CG}(\xi(\mathbf{r}))} \mathrm{d}\mathbf{r} \\ S_{\text{rel}} &= \int \mu(\mathbf{r}) \log \mu(\mathbf{r}) \mathrm{d}\mathbf{r} - \int \mu(\mathbf{r}) \log p^{CG}(\xi(\mathbf{r})) \mathrm{d}\mathbf{r} \\ &= S^{AA} + \mathbb{E}_{\mathbf{r}}\left[-\log p^{CG}(\xi(\mathbf{r}))\right] \end{aligned}$$

where we denote the entropy of the all-atom distribution S^{AA}. This quantity is hard to compute, but irrelevant for our purposes as it is a constant.

C. Boltzmann Generator

We define $\mathbf{x} = \xi(\mathbf{r})$ to be the output of a Boltzmann Generator. We train the Boltzmann Generator to sample from $p^{CG}(\mathbf{x})$ by feeding $\mathbf{x} \to \mathbf{z}$ and optimizing the latent distribution. For this we using the change of variables formula, to rewrite:

$$S_{\text{rel}} = S^{AA} + \mathbb{E}_{\mathbf{r}}\left[-\log p_Z(F_{xz}(\mathbf{x})) - \log R_{xz}(\mathbf{x})\right]$$

We use a Gaussian prior in Z:

$$\mu_Z(\mathbf{z}) = \mathcal{N}(\mathbf{0}, \sigma^2 \mathbf{I}) = Z_Z^{-1} \mathrm{e}^{-\frac{1}{2}\|\mathbf{z}\|^2/\sigma^2}$$

where

$$\sigma^2 = T/T_0$$

is proportional to the temperature. Inserting into S_{rel} results in:

$$\begin{aligned} S_{\text{rel}} &= S^{AA} + \mathbb{E}_{\mathbf{r}}\left[-\log Z_Z^{-1} + \frac{1}{2\sigma^2}\left\|F_{xz}(\mathbf{x})\right\|^2 - \log R_{xz}(\mathbf{x})\right] \\ &= \mathbb{E}_{\mathbf{r}}\left[\frac{1}{2\sigma^2}\left\|F_{xz}(\mathbf{x})\right\|^2 - \log R_{xz}(\mathbf{x})\right] + \text{const} \end{aligned}$$

Which is equivalent to training a Boltzmann Generator with the maximum likelihood approach[6]. Note that we can simultaneously train a set of temperatures in order to obtain a CG potential predicting different temperatures.

D. Sampling

Sampling from the CG model is simple, efficient and free of rare events:

$$\begin{aligned} \mathbf{z} &\sim \mathcal{N}(\mathbf{0}, \sigma^2 \mathbf{I}) \\ \mathbf{x} &= F_{zx}(\mathbf{z}) \end{aligned}$$

In particular, each such sample does not only generate $\mathbf{x}$ but also a probability density and thus a CG potential value for $\mathbf{x}$:

$$\begin{aligned} p_X(\mathbf{x}) &= p_Z(\mathbf{z}) R_{zx}^{-1}(\mathbf{z}) \\ u^{CG}(\mathbf{x}) = -\log p_X(\mathbf{x}) &= \frac{1}{2\sigma^2}\left\|F_{xz}(\mathbf{x})\right\|^2 - \log R_{xz}(\mathbf{x}) + \text{const} \\ &= \frac{1}{2\sigma^2}\left\|\mathbf{z}\right\|^2 + \log R_{zx}(\mathbf{z}) + \text{const} \end{aligned}$$

Although we can efficiently sample the CG distribution, we may be interested to perform coarse-grained MD simulations with local steps if we have some reason to believe that the kinetics and mechanisms of MD on the CG potential is realistic. Then we are interested in computing gradients of the CG potential:

$$\nabla_x u^{CG}(\mathbf{x}) = \frac{1}{2\sigma^2}\nabla_x \left\|F_{xz}(\mathbf{x})\right\|^2 - \nabla_x \log R_{xz}(\mathbf{x})$$

These gradients can be easily calculated with tensorflow (already implemented).

III. RESULTS

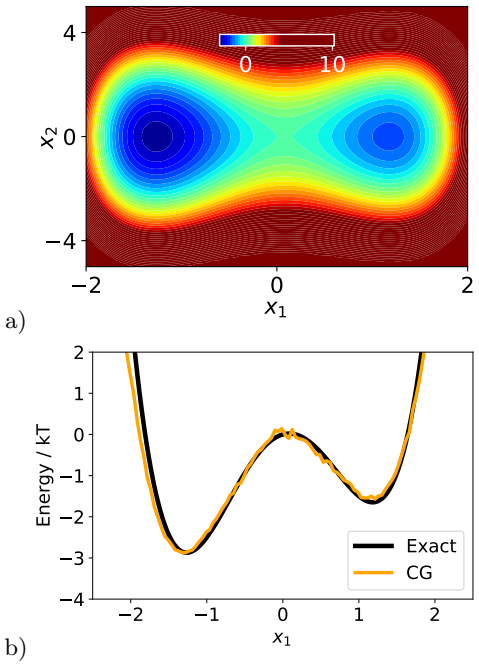

FIG. 1. **BG-Coarsegraining of double well**. The 2-dimensional double-well system is coarse-grained onto the slow coordinate x_1. **a**) Two-dimensional potential energy surface. **b**) Free energy along x_1 from direct integration (black) and BG-coarsegraining (orange).

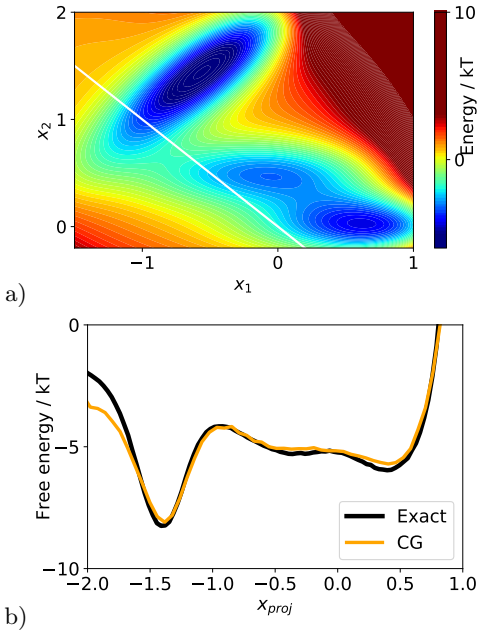

FIG. 2. **BG-Coarsegraining of Mueller potential**. The 2-dimensional Mueller potential is coarse-grained onto x_{proj} (white line). **a**) Two-dimensional potential energy surface. **b**) Free energy along x_{proj} from direct integration (black) and BG-coarsegraining (green).

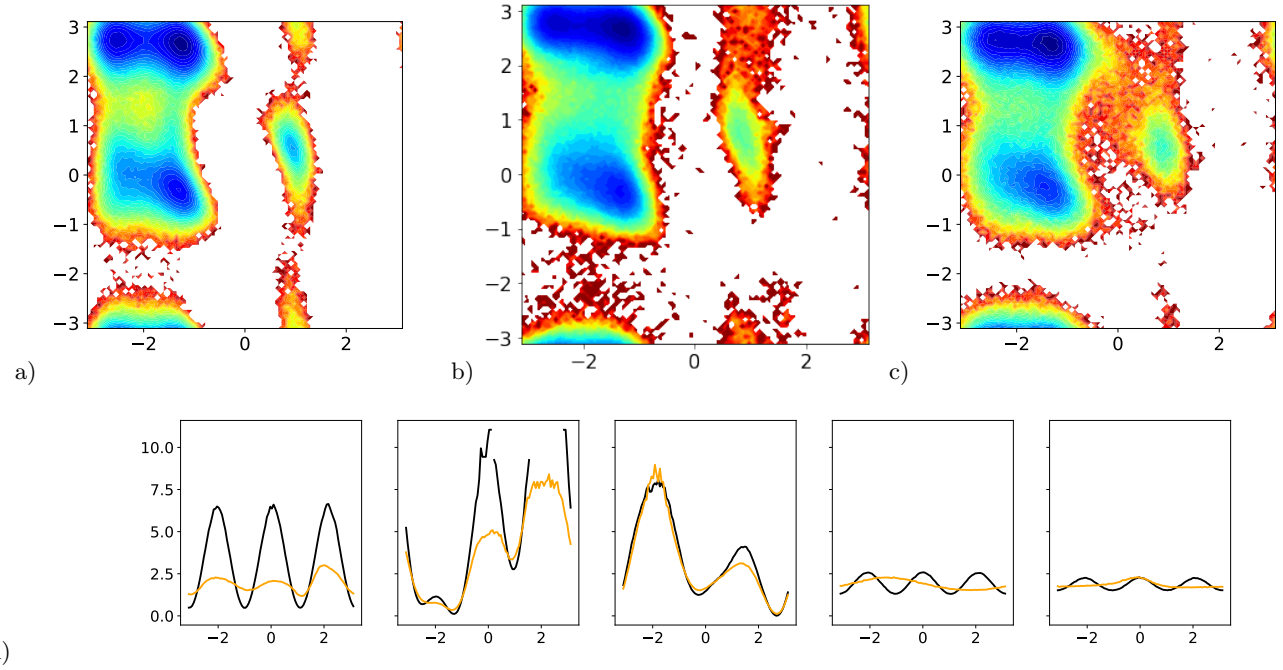

FIG. 3. **BG-Coarsegraining of alanine dipeptide**. The explicit-solvent all-atom system is coarse-grained to an implicit solvent model with all solute atoms resolved. **a-c**) Relative free energy $-\log p(\phi, \psi)$ of backbone torsions ϕ, ψ. **a**) From histograming ϕ, ψ of atomistic trajectory. **b**) BG with 6 central atoms (C,N,C_α,C_β,C,N) in Cartesian and remaining atoms in internal coordinates. **c**) BG with 4 central atoms (N,C_α,C_β,C) in Cartesian and remaining atoms in internal coordinates. **d**) Free energy profiles of individual flexible torsions (black: from histogramming all-atom, orange: BG from panel c).

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