

Coarse-Grained Boltzmann Generators

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*Equal Contribution

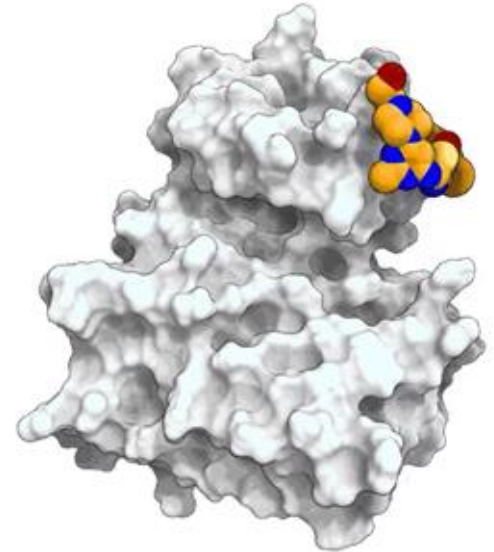


Why Molecular Sampling Matters

- What conformational states can a protein adopt?
- How likely are these conformational and binding states?
- How do these probabilities determine observables such as free energies, affinities, and functional mechanisms?

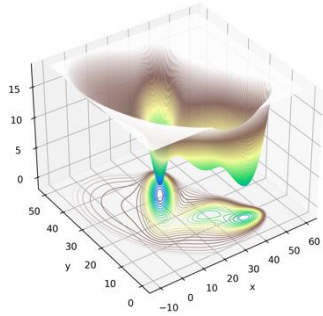
$$p(\mathbf{r}) = \frac{e^{-\beta u(\mathbf{r})}}{Z}$$

$$\mathbb{E}_p[\mathcal{O}] = \int \mathcal{O}(\mathbf{r})p(\mathbf{r})d\mathbf{r}$$

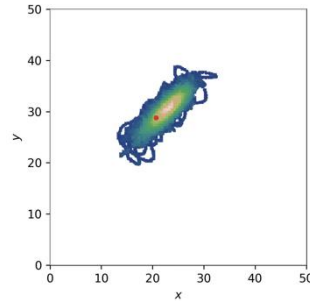


Simulation of a drug binding to a protein.

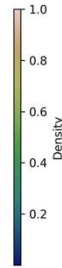
The Sampling Problem



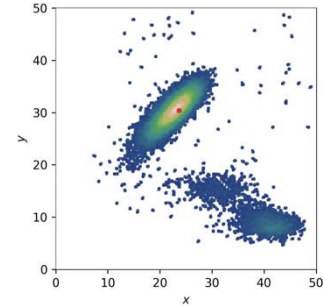
Müller-Brown Potential



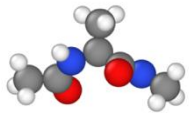
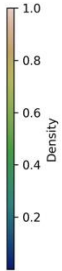
1×10^5 steps



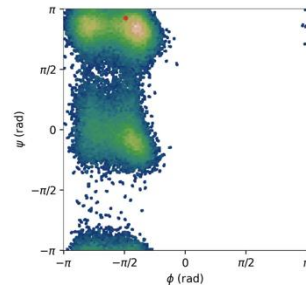
$50 \times$



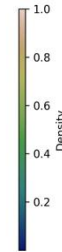
5×10^6 steps



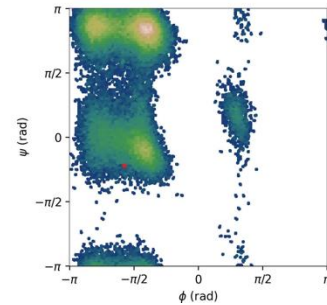
Alanine Dipeptide



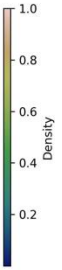
10 ns $\sim 2 \times 10^7$ steps



$50 \times$

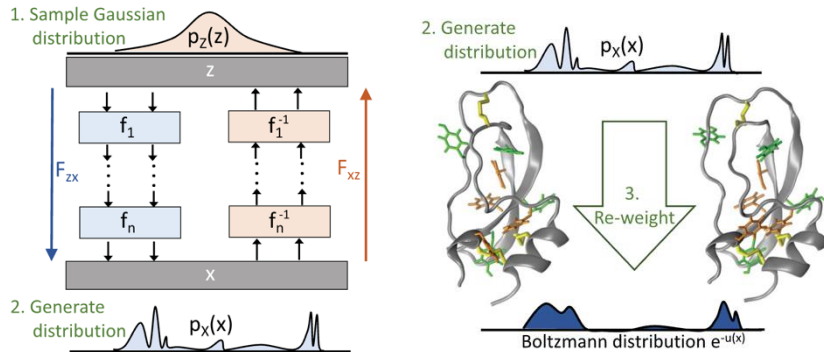


500 ns $\sim 1 \times 10^9$ steps



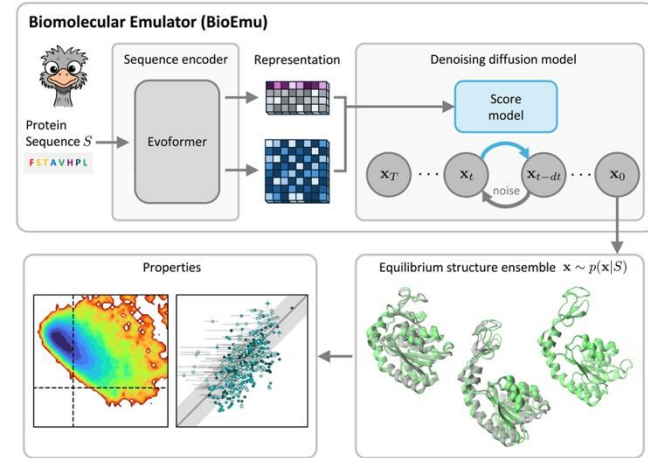
Deep Generative Sampling

Boltzmann Generators



- Exact-likelihood generative model
- Reweight samples using target energy
- Bottleneck: hard to scale in atomistic space

Boltzmann Emulators

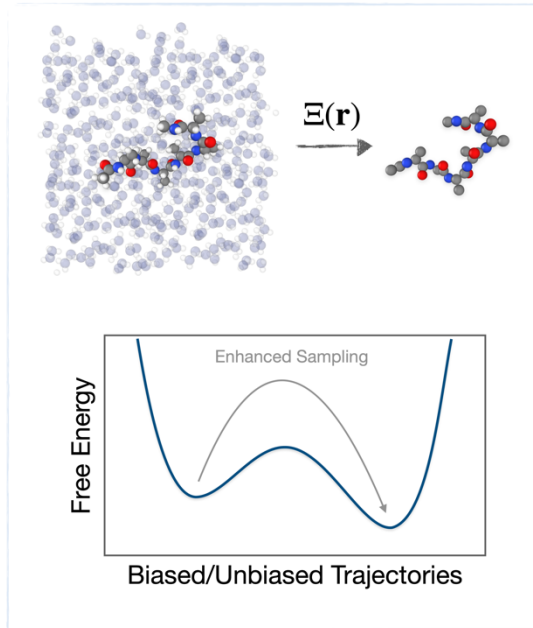


- Generate in coarse-grained space
- No target energy for reweighting
- Risk: biased samples if training data are biased

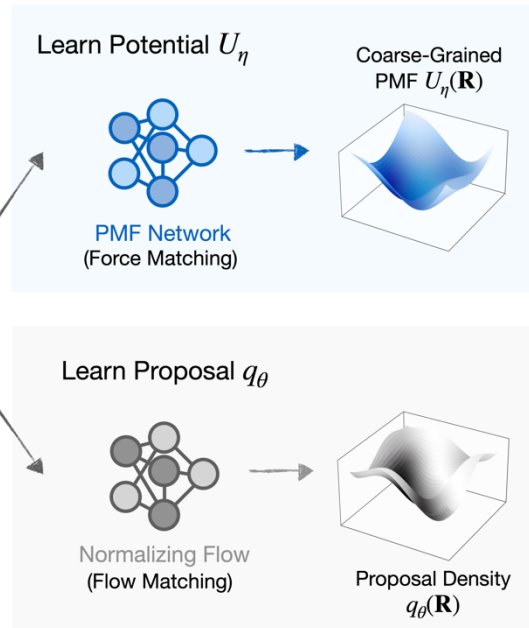
Can we keep the scalability of coarse-grained emulators, while bringing back the reweighting capability of Boltzmann Generators?

Coarse-Grained Boltzmann Generators

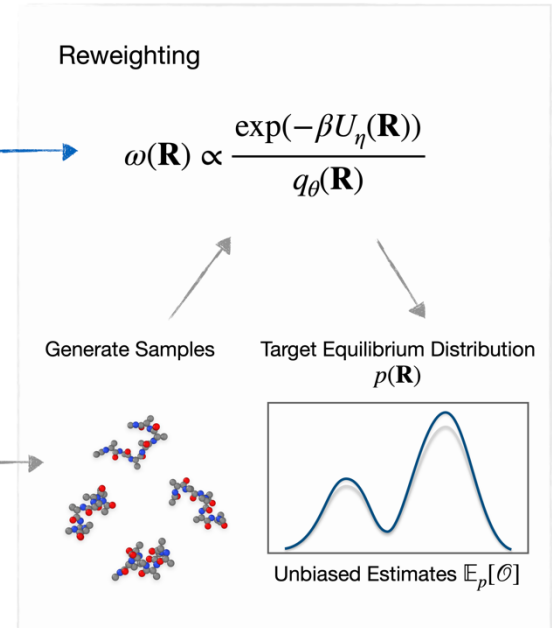
1. Coarse-Graining & Data Generation



2. Parallel Learning (PMF & Flow)

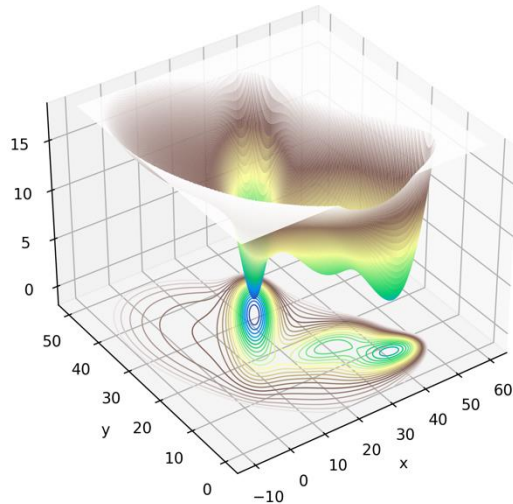


3. Asymptotically Exact Sampling



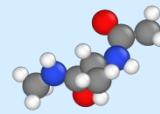
Experiments

Müller-Brown Potential

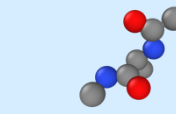


Alanine Peptides

ALA2



All Atom

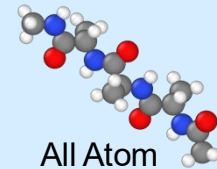


Heavy Atom

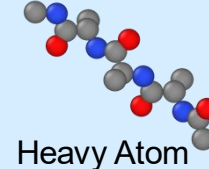


Core Beta

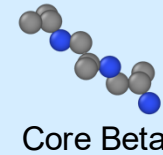
ALA3



All Atom

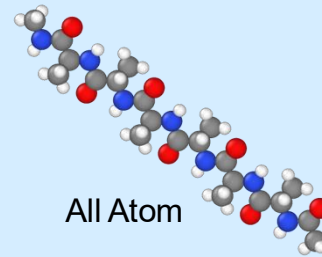


Heavy Atom

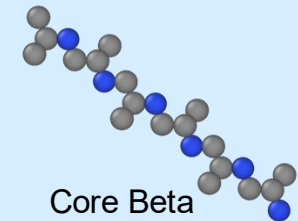


Core Beta

ALA6

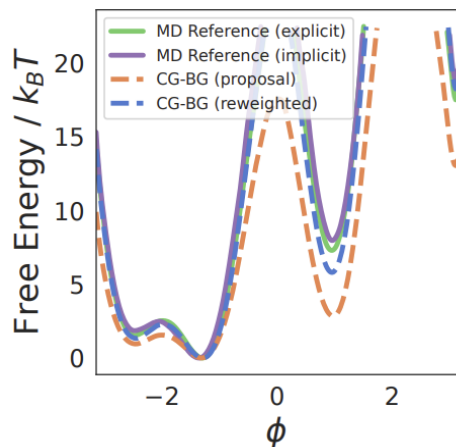
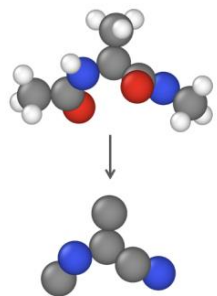


All Atom



Core Beta

Results



Stage	Core Beta	Heavy Atom	All Atom
Training	0.45h	0.80h	2.55h
Inference	0.95min	3.78min	14.91min
Total	0.47h	0.86h	2.80h

Model	Alanine Tripeptide			Alanine Hexapeptide		
	JS (\downarrow)	PMF (\downarrow)	ESS (\uparrow)	JS (\downarrow)	PMF (\downarrow)	ESS (\uparrow)
Core Beta	0.0060(1)	0.2112(51)	0.4212(5)	0.0100(1)	0.3646(81)	0.1231(3)
Heavy Atom	0.0056(1)	0.1957(52)	0.3201(4)	—	—	—
Implicit Solvent Baselines						
GB (OBC2)	0.0932(3)	1.0274(65)	—	0.1652(3)	1.8401(70)	—

Coarse-Grained Boltzmann Generators

arXiv 2602.10637 License MIT Environment Pixi

Boltzmann Generators for exact equilibrium sampling in coarse-grained representations, powered by JAX.



Paper Link

Overview

This repository provides the official implementation of **Coarse-Grained Boltzmann Generators (CG-BGs)**. Unlike traditional BGs that operate in all-atom space, CG-BGs act directly in a **coarse-grained coordinate space**. By leveraging Conditional Flow Matching and [Enhanced Sampling Force Matching](#), this method enables exact equilibrium sampling and reweighting for CG molecular systems.

Check out on GitHub:
github.com/tummmfm/cg-bg



Code Link