From data to noise to data: mixing physics across temperatures with generative artificial intelligence

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Presented by Connor Blake

Outline

- Problem Framing
- Denoising Diffusion Probabilistic Model (DDPM) Review
- Replica Exchange Molecular Dynamics (REMD) Overview
- Methods
- Results

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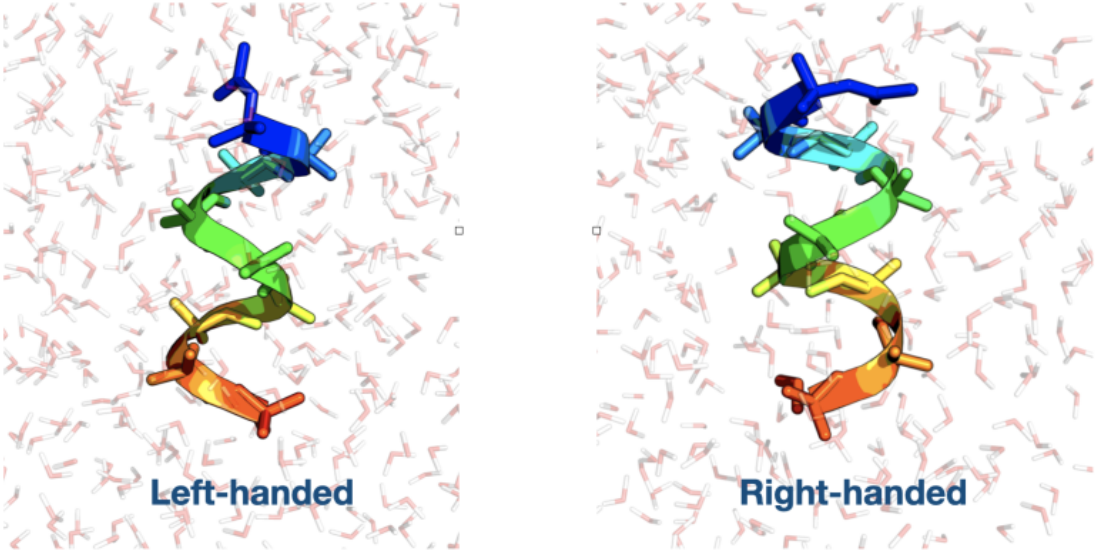


Figure: Aib9 Left and Right Conformations [1]

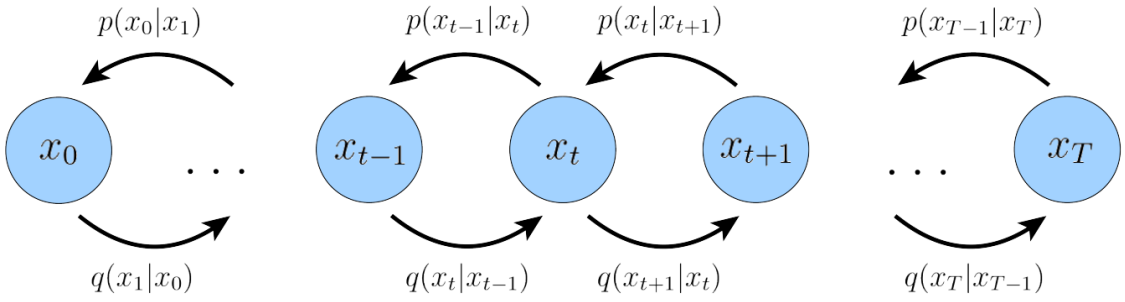
Notation and Motivation

For a typical sample (numbers here for Aib9)

- $N = 4749$ (all-atoms, explicit TIP3P solvation)
- $x = \{q, p\} \in \mathbb{R}^{N \times 2}$
- $s = \{x, \beta\}$
- $x' = R(x)$ (reduced coordinates)
- $N' = 18$

From equilibrium thermodynamics, $\Delta T \propto \frac{1}{\sqrt{N}}$

Review of Denoising Diffusion Probabilistic Model (DDPM)



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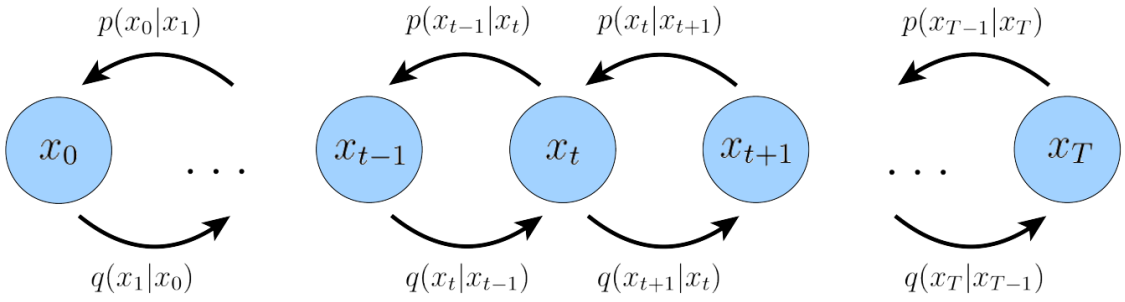

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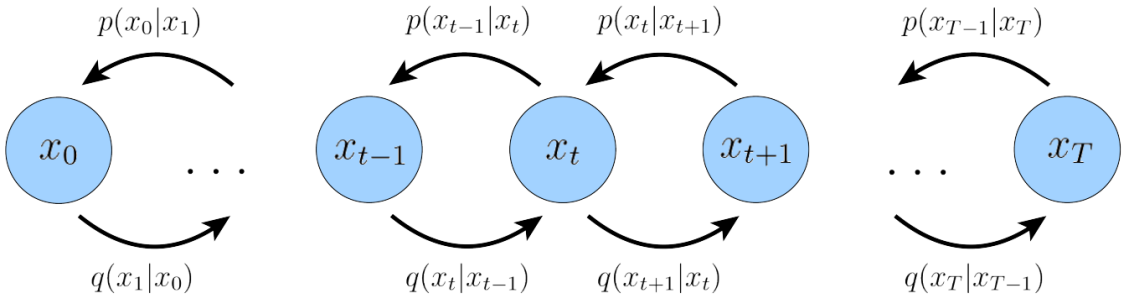

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3. $$p(s_0) = p(s_T) \prod_{t=1}^{T} p_\theta(s_{t-1} \mid s_t), \quad p(s_T) = \mathcal{N}(s_T; 0, I)$$

DDPM Architecture Used Here

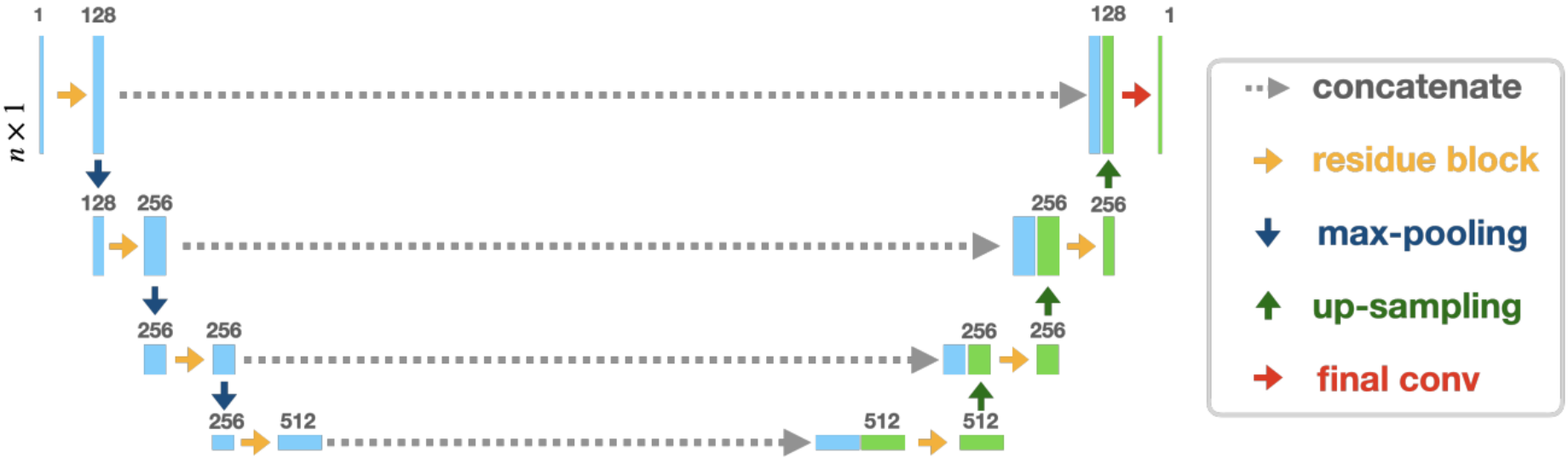

Figure: U-Net Convolutional Architecture for p_θ denoising layers [1]

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7. Repeat steps 2–6 until simulation is done

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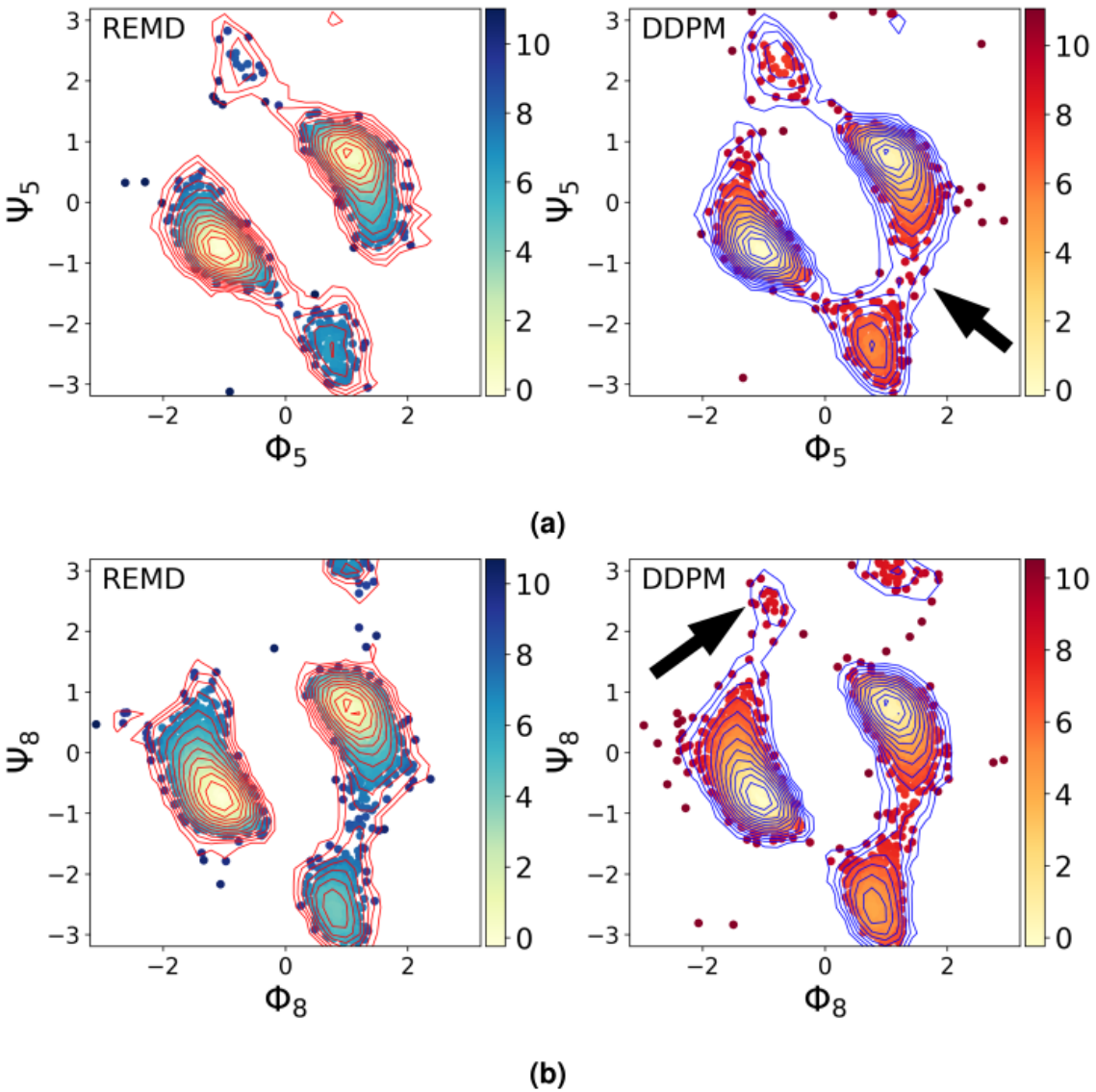
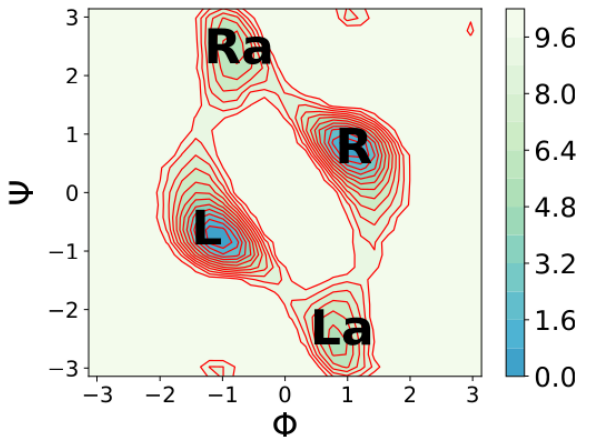
- Function to learn: joint PDF $p(s) \equiv p(x, \beta)$ via DDPM diffusion model
- Training Data: REMD trajectories in reduced coordinates
- Benchmarks: Unbiased long-time MD, pure REMD
- Metrics: Can it better-identify transition and metastable states and their free energies? Can it be used to interpolate and extrapolate free energies at temperatures outside $\{T_m\}_{m=1}^{M}$?

Experiment 1: Aib9



Aib9 ϕ, ψ angles on the 5,8 residues from REMD, REMD+DDPM at 400K. [1]



Unbiased 4μs MD, 400K free energy profile for residue 5. All units (both plots) in $k_B T$.

Experiment 1: Aib9 (cont.)

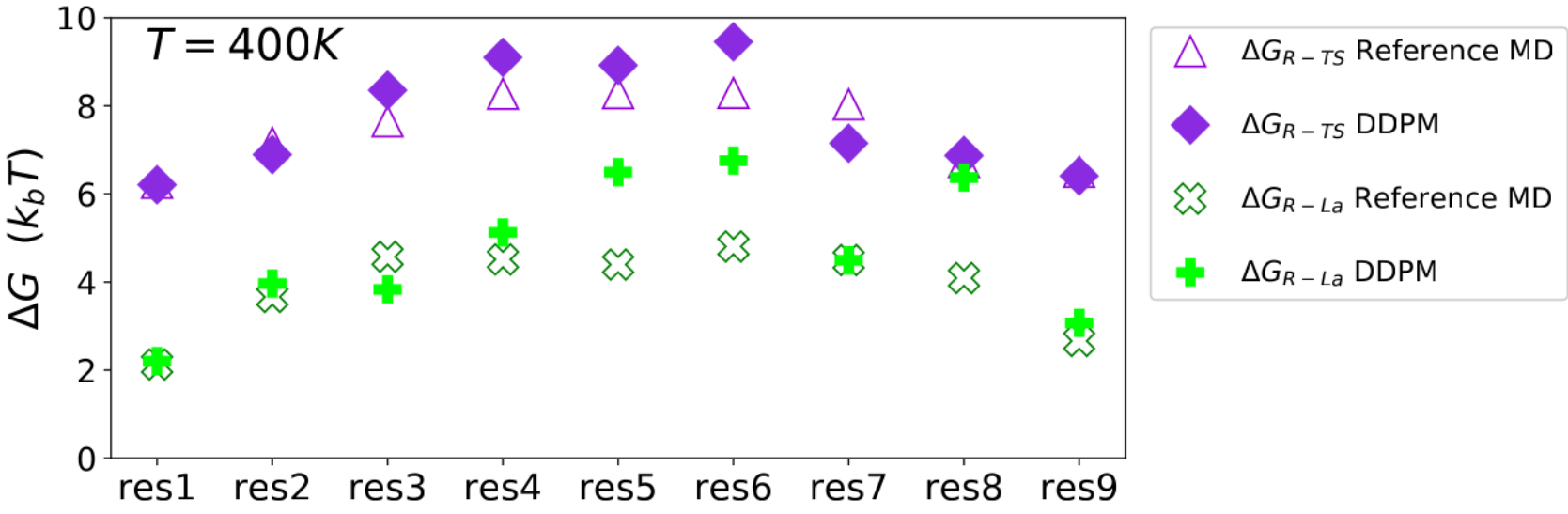


Figure: Extrapolation free energy predictions still work.[1]

Experiment 2: rGACC

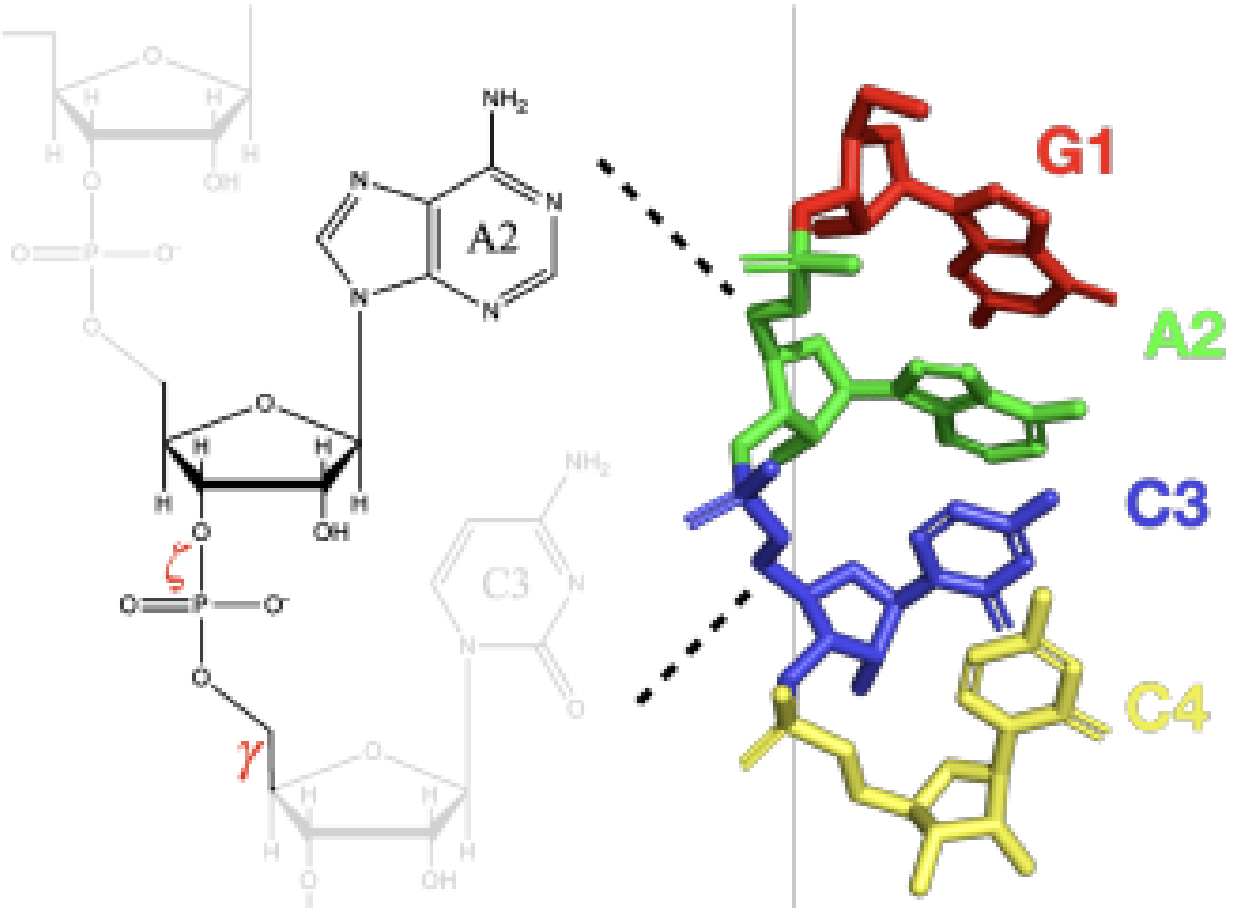
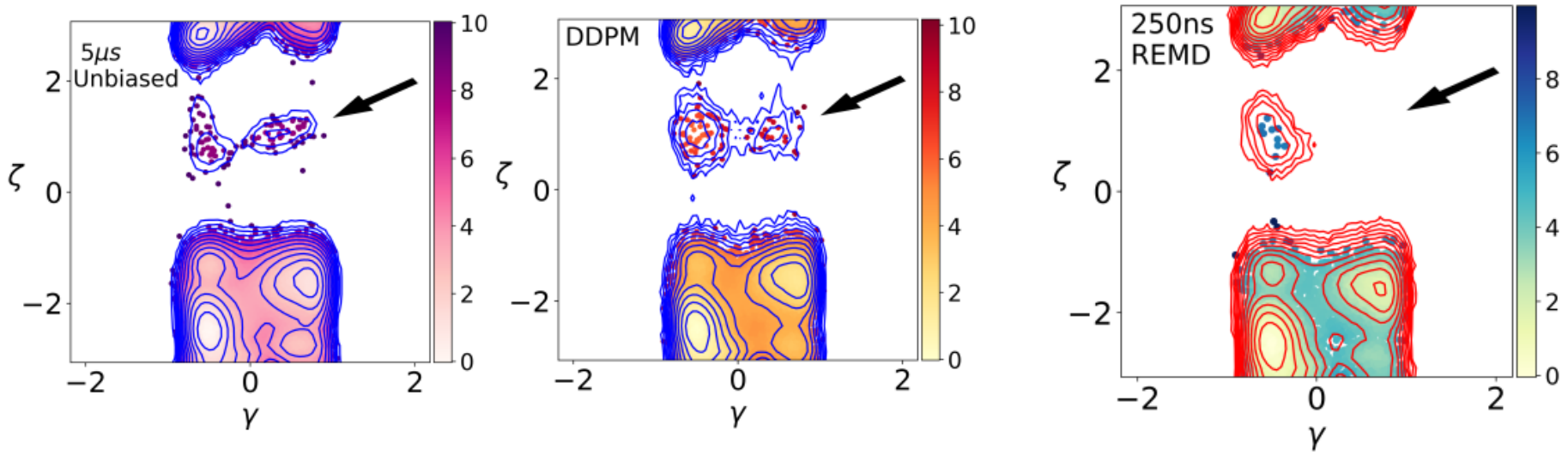


Figure: [1]

Experiment 2: rGACC (cont.)



rGACC ζ, γ angles on the A2 from unbiased MD, REMD+DDPM, REMD at 325K. [1]

Comparison with Boltzmann Generators

This Paper [1]

Boltzmann Generators (Tommy+Joshua) [4]

Similarities

- trying to efficiently construct equilibrium distribution including transition/metastable states
- comparable MD costs in training

Differences

- stochastic map (more expressive) $z \to x$
- generates reduced coordinate structures in explicit solvents

- deterministic map $z \to x$
- generates all-atom structures in implicit solvents
- reaction coordinates easy to generate

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- key insight: treats T as an observation, not control variable (will work for any ensemble)
- allows explicit solvation
- highly expressive stochastic mappings
- Drawbacks: currently must use reduced coordinates, internal sidechain coordinates not addressed

Questions?

References I


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