A134 · ProtScape: A molecular structure and energy-aware representation for protein conformation generation

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Session: Day 1 · Thu Oct 1, 2026 · 2:15–4:15 PM

Molecular dynamics simulations are a principled but computationally expensive approach for studying protein conformational variability, making it challenging to generate large ensembles of structures or to characterize transitions between metastable conformations. AI methods for upsampling MD simulations have been developed in recent years, but struggle due to difficulties of sampling complex, high-dimensional molecular distributions. One avenue that these methods overlook is to learn a latent space in which such sampling becomes easier. In order to address this, we introduce ProtScape, a generative geometric deep learning framework that learns structure and energy-aware representations of protein conformational landscapes from MD simulations. ProtScape represents protein conformations using an equivariant graph neural network and a multiscale, deep wavelet transform that captures both local geometric interactions and nonlocal, collective motions. This latent representation of the model is dual-organized: 1) by the structure captured by wavelet transform, 2) by energy using a Laplacian energy smoothness penalty. This structured latent space enables meaningful generation and exploration of protein conformations. ProtScape supports multiple generative modes including 1) ensemble generation, which upsamples ensembles given limited MD trajectories flow matching from noise to the organized manifold of conformations, 2) minimum-energy path generation between two high energy conformations, which is guided by energy using a nudged elastic band formulation, and 3) energy-descent, which generates trajectories towards lower energies from a high-energy conformation using gradient descent, thereby hypothesizing folding or other stabilizing trajectories. Across multiple protein systems, ProtScape produces conformational ensembles and transition pathways with favorable structural properties, demonstrating that learning a multiscale, energy-aligned representation of protein conformational landscapes enables both accurate modeling and physically meaningful generation of protein dynamics.

PROTSCAPE: A molecular structure and energy-aware representation for protein conformation generation

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Protein function does not arise from a single static structure, but from a collection of conformations and the ability to move between them [1, 2]. Molecular Dynamics (MD) simulations provide a physically grounded way to model these motions by integrating Newton's equations on an atomistic energy landscape [3]. In practice, however, MD simulations are severely limited by computational cost. As a result, MD often undersamples the conformational landscape and rarely observes transitions between metastable states without extensive simulation time. In this work, we introduce **ProtScape**, a geometric deep learning framework that learns a structured, energy-regularized latent representation of protein conformational landscapes from MD trajectories. ProtScape combines an SE(3)-equivariant graph neural network with deep graph wavelet transforms to capture both local geometric features and nonlocal collective motions, while an energy-based smoothness penalty aligns the latent space with the underlying potential energy landscape. This unified representation supports three complementary generative modes: latent diffusion for ensemble upsampling, latent energy-descent for generating relaxation trajectories toward lower-energy states, and a latent-space Nudged Elastic Band (NEB) method for minimum-energy path estimation between metastable conformations. We demonstrate ProtScape on proteins from the ATLAS dataset [4], showing that it scales beyond short peptides and supports both conformational generation and interpolation for real-world protein systems.

ProtScape is trained as an autoencoder framework that learns latent representations of protein conformations jointly organized by molecular structure and physical energy. In parallel, we regularize the latent manifold using molecular energy computations so that nearby latent representations correspond to energetically similar conformations. We therefore introduce an energy-based regularization that reorganizes the latent space according to potential energy. For each protein conformation, we compute the potential energy E_i using OpenMM with the AMBER force field [5]. This loss encourages nearby latent representations to correspond to conformations with similar energies, producing a smoother and more physically organized conformational manifold.

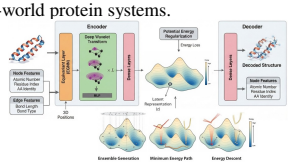

Figure 1: Overview of the ProtScape framework.

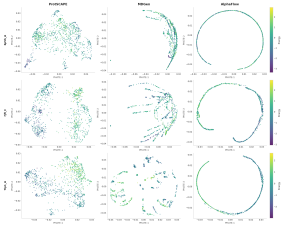

Figure 2: PHATE embeddings of conformational ensembles colored by potential energy.

We evaluated ProtScape on molecular dynamics trajectories from the ATLAS dataset [4], first analyzing the structure and organization of the learned latent manifold, and subsequently evaluating three downstream generative modeling tasks: (i) ensemble generation, (ii) energy-descent, and (iii) minimum energy path interpolation using NEB. Across nearly all proteins and metrics, ProtScape achieves substantially lower errors than AlphaFlow and MDGen, indicating closer agreement with the reference conformational distributions. Across all proteins, ProtScape produces substantially lower Ramachandran outlier percentages, clash scores, MolProbity scores [6], and consecutive-frame RMSD values than MDGen, indicating smoother and more physically realistic conformational transitions. Together, these results suggest that explicitly learning structured latent conformational landscapes provides a promising direction for scalable and physically meaningful modeling of protein dynamics.

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