Latent Space Diffusion Models of Cryo-EM Structures

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Abstract

Cryo-electron microscopy (cryo-EM) is unique among tools in structural biology in its ability to image large, dynamic protein complexes. Key to this ability is image processing algorithms for heterogeneous cryo-EM reconstruction, including recent deep learning-based approaches. The state-of-the-art method cryoDRGN uses a Variational Autoencoder (VAE) framework to learn a continuous distribution of protein structures from single particle cryo-EM imaging data. While cryoDRGN can model complex structural motions, the Gaussian prior distribution of the VAE fails to match the aggregate approximate posterior, which prevents generative sampling of structures especially for multi-modal distributions (e.g. compositional heterogeneity). Here, we train a diffusion model as an expressive, learnable prior in the cryoDRGN framework. Our approach learns a high-quality generative model over molecular conformations directly from cryo-EM imaging data. We show the ability to sample from the model on two synthetic and two real datasets, where samples accurately follow the data distribution unlike samples from the VAE prior distribution. We also demonstrate how the diffusion model prior can be leveraged for fast latent space traversal and interpolation between states of interest. By learning an accurate model of the data distribution, our method unlocks tools in generative modeling, sampling, and distribution analysis for heterogeneous cryo-EM ensembles.

1 Introduction

Single particle cryo-electron microscopy (cryo-EM) is a biological imaging modality capable of visualizing the 3D structure of large biomolecular complexes at (near-)atomic resolution [1]. In this technique, a thin layer of an aqueous sample of the molecule of interest is flash frozen and imaged with a transmission electron microscope. After initial pre-processing of the raw micrographs, the dataset consists of a set of noisy projection images, where each image $x$ contains a 2D projection of a molecular volume $V: \mathbb{R}^3 \to \mathbb{R}$ captured in an unknown pose $(R, t) \in SO(3) \times \mathbb{R}^2$ [2]. Since each image contains a unique molecule, to account for structural variation between the imaged molecules, reconstruction methods introduce a latent variable $z$ to define a conformational space $V(\cdot, z): \mathbb{R}^3 \to \mathbb{R}$ from which volumes $V$ are sampled. Thus, heterogeneous cryo-EM reconstruction amounts to solving the inverse problem of estimating $V$, $z$, and $(R, t)$ from the experimental images $x$. Traditionally, common approaches for heterogeneous reconstruction use a discrete model for $V$ (e.g. a mixture model in 3D classification [3–5]); however, deep generative models have recently been introduced that are designed to capture more complex, continuous distributions of protein conformations [6–10]. CryoDRGN [6] is a state-of-the-art method for heterogeneous reconstruction based on deep generative modeling. In cryoDRGN, a neural field representation of the volume is conditioned on a generic,

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Figure 1: We first train cryo-DRGN with a standard VAE objective (top). Then, we train a diffusion model in its latent space on the embedding distribution (bottom). The diffusion model learns a representation of the conformational space of the molecule. Generating different latents \( z \) corresponds to sampling different molecular configurations (e.g., the blue SARS-CoV-2 spike protein is sampled in receptor binding domain open vs. closed states). (Dataset: Walls et al. [25])

2 Methods

CryoDRGN [6, 26] is designed as a VAE with an MLP encoder neural network that consumes Fourier-space cryo-EM images \( x \) and parametrizes a diagonal Gaussian approximate posterior \( q_\phi(z|x) \) over latent variables \( z \). CryoDRGN’s probabilistic Gaussian decoder \( p_\phi(x|z) \) is parametrized as a neural field [27], also based on an MLP, taking both latent variables \( z \) and Fourier space coordinates \( k = (k_x, k_y, k_z) \) (processed through sinusoidal positional encodings [6, 28]) as inputs. The field outputs the Coulomb scattering potential in Fourier space at \( k \). By the image formation model, 2D central slices of the 3D densities in Fourier space correspond to the input cryo-EM images; During training, a 2D grid of oriented \( k \) are rendered to form a reconstruction loss. However, this requires knowledge of the pose of the molecule, as discussed in Sec. 1. Therefore, cryoDRGN also incorporates an image pose inference step [7]. Specifically, a global search over rotations and translations is performed to find the maximum likelihood pose under the decoder distribution, given the inferred latent variable \( z \). Finally, cryoDRGN is trained with a modified variational lower bound [11, 12] (we omit indicating pose inference here for brevity):

\[
\arg\max_\phi \mathbb{E}_{x \sim p_{\text{data}}(x)} \mathbb{E}_{z \sim q_\phi(z|x)} [\log p_\phi(x|z)] - \beta \text{KL} (q_\phi(z|x) \| p(z)),
\]

(1)

with standard Gaussian prior \( p(z) \sim N(0, I) \). The Kullback Leibler (KL) divergence weighting is chosen to be \( \beta = 1/\dim(z) < 1 \) in cryoDRGN. This effectively reduces the KL regularization and gives more flexibility to the model to learn diverse encodings that translate to accurate reconstructions (however, it also encourages a mismatch between prior and aggregate approximate posterior; see...
VAEs [13, 19, 31], we propose to model cryoDRGN’s latent embedding distribution with an expressive generative model and sample latents \( z \) drawn from the Gaussian prior fail to reproduce the latent embedding distribution. This implies that, between the aggregate approximate posterior and prior distributions. As we show in Sec. 3.2, samples drawn from the Gaussian prior fail to reproduce the latent embedding distribution. This implies that, although cryoDRGN is a state-of-the-art cryo-EM reconstruction approach, we cannot use it as a generative model and sample latents \( z \) according to the modeled distribution of conformational states. Furthermore, prior samples will not necessarily decode into coherent cryo-EM density volumes.

Inspired by recent works on RGB image synthesis that fit diffusion models in the latent space of VAEs [13, 19, 31], we propose to model cryoDRGN’s latent embedding distribution with an expressive generative model. Probability Flow through the numerical simulation of the SDE \([23, 39]\) that effectively samples the same distribution (see App. A.1). Diffusion Models are a novel class of deep generative models that has recently demonstrated state-of-the-art quality in image synthesis \([29–38]\) as well as many other applications. In this work, we use continuous-time diffusion models \([23]\) and follow Karras et al. \([39]\). Let \(x_0 \sim \mathcal{N}(0, \sigma^2_{\text{max}})\) and sequentially denoise \(x_0\) into \(x_i \sim p(x_i; \sigma_i), i \in [0, ..., M]\), with \(\sigma_i < \sigma_{i-1}\) \((\sigma_0 = \sigma_{\text{max}})\). If \(\sigma_M = 0\), then \(x_0\) is distributed according to the data. In practice, the sequential denoising is often implemented through the numerical simulation of the Probability Flow ordinary differential equation (ODE) \([23]\)

\[
dx = -\dot{\sigma}(t)\sigma(t)\nabla_x \log p(x; \sigma(t)) dt, \tag{2}
\]

where \(\nabla_x \log p(x; \sigma)\) is the score function \([40]\). The schedule \(\sigma(t) : [0, 1] \to \mathbb{R}_+\) is user-specified and \(\dot{\sigma}(t)\) denotes the time derivative of \(\sigma(t)\). Alternatively, we may also use a stochastic differential equation (SDE) \([23, 39]\) that effectively samples the same distribution (see App. A.1). Diffusion model training reduces to learning the score model \(s_\theta\). The model can, for example, be parameterized as \(\nabla_x \log p(x; \sigma) \approx s_\theta = (D_\theta(x; \sigma) - x)/\sigma^2\) \([39]\), where \(D_\theta\) is a learnable denoiser that, given a noisy data point \(x + n, x \sim p_{\text{data}}(x), n \sim \mathcal{N}(0, \sigma^2)\) and conditioned on the noise level \(\sigma\), tries to predict the clean \(x\). The denoiser \(D_\theta\) can be trained by minimizing an \(L_2\)-loss \((\lambda(\sigma) : \mathbb{R}_+ \to \mathbb{R}_+\) is a weighting function)

\[
\arg\min_\theta \mathbb{E}_{x \sim p_{\text{data}}(x), \sigma \sim p(\sigma), n \sim \mathcal{N}(0, \sigma^2)} \left[ \lambda(\sigma) \| D_\theta(x + n, \sigma) - x \|^2_2 \right]. \tag{3}
\]

**Latent Space Diffusion Models in cryoDRGN.** Since cryoDRGN is trained in regular VAE-fashion with a standard Gaussian prior, it can suffer from the prior hole problem \([13–21]\), i.e., a mismatch between the aggregate approximate posterior and prior distributions. As we show in Sec. 3.2, samples drawn from the Gaussian prior fail to reproduce the latent embedding distribution. This implies that, although cryoDRGN is a state-of-the-art cryo-EM reconstruction approach, we cannot use it as a generative model and sample latents \(z\) according to the modeled distribution of conformational states. Furthermore, prior samples will not necessarily decode into coherent cryo-EM density volumes.

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diffusion model. We can formulate the training objective of our latent space diffusion model as

$$\arg\min_\theta \mathbb{E}_{x \sim p_{data}(x), z \sim q_\phi(z|x), \sigma \sim p(\sigma), n \sim \mathcal{N}(0, \sigma^2)} \left[ \lambda(\sigma) \| D_\theta(z + n, \sigma) - z \|_2^2 \right],$$

where we extract latent embeddings $z$ from the cryo-EM images $x$ with cryoDRGN’s encoder $q_\phi(z|x)$ and fit the diffusion model to the latent space distribution formed by the latent variables $z$. Note that we are training in a two-stage manner: We first train a cryoDRGN VAE model (with the objective in Eq. (1)), which we then freeze. Next, we train the diffusion model in latent space with the objective in Eq. (4). Sampling from the diffusion model and feeding the synthesized latent variables to cryoDRGN’s neural field decoder allows us to sample conformational states of the modeled protein. Our approach is visualized in Fig. 1. All training details are provided in App. A.1.

### 3 Results

#### 3.1 Datasets

We run experiments on cryoDRGN models trained on a total of four datasets: 2 synthetic datasets, "linear1d" and "circular1d", where ground truth volumes are generated along a continuous 1-dimensional linear or circular reaction coordinate, respectively [6]; "ribosome", a real dataset containing a mixture of assembly intermediates of the E. coli large ribosomal subunit from EMPIAR-10076 [42], and "covid", a real dataset of the SARS-CoV-2 spike protein transitioning between the receptor binding domain (RBD) open and closed conformations [25]. CryoDRGN models were trained with either an 8 or 10 dimensional latent variable model. The sizes of these datasets range from 50k to 277k cryo-EM images. Additional dataset and cryoDRGN training details are provided in App. A.1.

#### 3.2 Generative Model Sampling

We train a diffusion model on latent encodings from cryoDRGN to model the aggregate approximate posterior distribution for several datasets exhibiting different types of heterogeneity. Once trained, we sample 1,000 latent variables $z$ from the diffusion model (sampling details in App. A.1). A visualization of these samples, together with embeddings of the data distribution and VAE prior samples, is shown in Fig. 2. While the diffusion model accurately models the data, samples from the original Gaussian VAE prior fail to model the data distribution; the mismatch is worst for highly structured latent spaces. In Tab. 1, we also show quantitatively that the diffusion model prior captures the distribution of the data’s latent encodings much more accurately than the standard Gaussian prior. Furthermore, in Fig. 3 we visualize corresponding 3D volumes for circular1d. We find that while the diffusion model samples decode into realistic molecular conformations, the VAE prior samples, which are located in an empty region of the latent space, produce incorrect volumes with artifacts in the heterogeneous region. Our experiments verify that the learned diffusion model prior is able to accurately model the latent embedding distribution.

Table 1: Total Variation Distance in PC1 marginal space between data embedding distribution and diffusion prior as well as Gaussian VAE prior distributions.

| Dataset    | Latent Diffusion Model Prior | Standard Gaussian VAE Prior |
|------------|-----------------------------|-----------------------------|
| circular1d | 0.015                       | 0.82                        |
| linear1d   | 0.015                       | 0.86                        |
| covid      | 0.005                       | 0.19                        |
| ribosome   | 0.015                       | 0.58                        |
3.3 Diffusion Model Interpolations

We may be interested in modeling transitions between structures by interpolating between their corresponding encodings in latent space. However, as discussed, the latent space distribution can be complex and multi-modal and a linear interpolation directly in latent space between different encodings may pass through prior holes, i.e., “empty” regions in latent space, which may produce artifacts. However, our diffusion model effectively maps all states into its own Gaussian prior distribution \( x_0 \sim \mathcal{N}(0, \sigma_{\text{max}}^2) \), see Sec. 2, and interpolating within this Gaussian space is, in fact, valid. In particular, there are no prior holes in this space, because the diffusion model’s forward diffusion process converges to this distribution by construction. Using the deterministic Probability Flow ODE (Eq. (2)), we encode states \( z_A \) and \( z_B \) in the diffusion model’s own prior (see App. A.1 for details). Denoting the resulting encodings as \( \tilde{z}_A \) and \( \tilde{z}_B \), respectively, we then linearly interpolate \( \tilde{z}_{AB}(y) = (1-y)\tilde{z}_A + y\tilde{z}_B \), where \( y \in [0,1] \) is an interpolation parameter (more sophisticated interpolations, such as spherical, are possible, but we did not observe any benefits). Again using the Probability Flow ODE, we decode states \( \tilde{z}_{AB}(y) \) along the interpolation back to \( z_{AB}(y) \) in cryoDRGN’s original latent space.

In Fig. 5, we visualize such an interpolation trajectory between the open and closed conformations of the SARS-CoV-2 spike protein and we observe a smooth transition. We use cryoDRGN’s decoder to generate corresponding molecular volumes. We also show the latent space trajectory for an interpolation between two far-apart states in linear1d, a challenging case due to its highly structured latent space (Fig. 4). We performed equidistant steps in the diffusion model’s Gaussian prior and observe a “jump” behavior. This is expected, as it merely implies that the diffusion model has learned a sharp transition in its Probability Flow ODE. Importantly, no samples are generated in the empty region during the jump.

3.4 Efficient Latent Space Traversal and Sampling

The diffusion model’s Probability Flow ODE can be interpreted as an instance of a continuous Normalizing Flow [43, 44]. Previous work has leveraged Normalizing Flows [45] and other invertible mappings [46] to accelerate Markov Chain Monte Carlo (MCMC) algorithms such as Hamiltonian Monte Carlo and Langevin dynamics [47]: The MCMC chain is run in the Gaussian prior of the invertible mapping, where no barriers are present, while the Flow non-linearly transforms the samples along the sampling path such that they effectively jump between states and efficiently traverse the complex distribution of interest at the output of the Flow (cryoDRGN’s latent space distribution in our case). In Fig. 6, we demonstrate that running Langevin dynamics in the Gaussian prior space of our latent diffusion model allows us to very efficiently traverse the molecular manifold, making large jumps between distant states. Note that sampling with an iterative sampler like Langevin dynamics can be advantageous, because it would allow us to trivially incorporate additional potential energy terms, which can be more difficult in regular diffusion model sampling.

4 Future Directions

We have shown that a diffusion model incorporated in cryoDRGN’s latent space has learned an accurate representation of the conformational state space of the imaged proteins, directly from cryo-EM imaging data. We envision that we can leverage this as a promising tool for relevant and novel
applications in generative modeling, accelerated sampling, and distribution analysis in cryo-EM and molecular modeling.

**Conditional Generative Modeling.** We have demonstrated that random samples from the diffusion model accurately reproduce the molecular manifold. But one may also be able to perform conditional generation: For instance, we envision applications where molecular conformations are sampled from the latent diffusion model based on guidance from auxiliary scoring algorithms or classifiers to fulfill certain properties, like high binding affinity to a ligand. Methodologically, one could build on classifier- and classifier-free guidance techniques from the literature on diffusion models [23, 30, 48]. Moreover, since we have learned a smooth continuous latent manifold of the data that we can traverse easily, as we demonstrated, we can also employ gradient-based optimization techniques in latent space to optimize the corresponding conformational states according to different criteria [49].

**Coupling with Atomic Models.** Future versions of cryoDRGN might perform direct atomic model reconstruction, a direction also explored by Zhong et al. [8], Rosenbaum et al. [50]. In general, directly inferring an accurate atomic model from cryo-EM imaging data is an extraordinarily challenging problem without any additional inductive biases or priors. However, recently diffusion models have also been used for atomic small molecule and protein generation [51–59]. Such models can potentially serve as powerful priors for cryo-EM-based atomic protein structure prediction. Combined with an appropriate decoder neural network that operates in atom coordinates, our latent diffusion model would then effectively be a generative model not only over 3D density volumes, but also their underlying atomic structures.

**Molecular Simulation.** Here, we demonstrated that we can interpolate between different protein states and efficiently traverse the latent space using diffusion model-enhanced MCMC techniques. In fact, MCMC methods like Langevin dynamics are widely used in statistical mechanics and molecular dynamics [60, 61] to sample molecular conformations. When combined with atomic coordinate outputs, future work could explore leveraging our latent diffusion model for accelerated molecular dynamics simulations as well as for free energy calculations between relevant protein states.

**End-to-end Training and Hierarchical Models.** There are also promising technical extensions: For instance, end-to-end training of cryoDRGN together with the latent diffusion model, similarly to Vahdat et al. [13], may allow cryoDRGN to learn better embeddings and perform better reconstruction by offering more flexibility to cryoDRGN in how to distribute encodings in latent space. Moreover, deep hierarchical VAEs are often used to improve model expressivity in RGB image synthesis tasks [17, 62]. CryoDRGN would likely benefit from similar hierarchical architectures. Such models can sometimes even learn a semantic disentanglement of different features of the data [63]—exploring this in the context of protein structure modeling would be highly interesting. For instance, we might learn one diffusion model that captures the main data clusters, i.e., main conformational states, and another one to model intra-cluster variation. These directions will be particularly relevant when modeling large-scale, complex and heterogeneous protein data.

In conclusion, we believe that combining state-of-the-art cryo-EM reconstruction methods such as cryoDRGN with modern deep generative learning approaches such as diffusion models has the potential to lead to powerful new tools and promising applications both in cryo-EM reconstruction and in biomolecular modeling more generally.

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A Appendix

A.1 Implementation and Training Details

CryoDRGN. All cryoDRGN models are trained as in Zhong et al. [26]. Dataset and training details summarized in Table 2. Synthetic datasets are generated from atomic models as described in Zhong et al. [6] and with poses sampled uniformly from SO(3) for rotations and $[-10, 10]^2$ pixels for translations. CryoDRGN models for linear1d and circular1d used positional encodings with geometrically spaced wavelengths between 1 and the Nyquist frequency and leaky ReLU activations. The cryoDRGN model for ribosome was downloaded from Zenodo [64]. All other settings unless otherwise specified were at their default values for cryoDRGN software version 1.0.

Table 2: Summary of the synthetic and experimental datasets and cryoDRGN training details. $D$ is the resolution of the images, in pixels. $N$ is the dataset size. Architecture is denoted as the width $\times$ depth of the encoder and decoder MLPs.

| Dataset       | $D$ | $N$   | $\text{Å/pix.}$ | $|z|$ | Architecture   | Epochs |
|---------------|-----|-------|------------------|------|----------------|--------|
| Linear1d      | 128 | 50k   | 6                | 8    | 256 $\times$ 3 | 25     |
| Circular1d    | 128 | 100k  | 6                | 8    | 256 $\times$ 3 | 25     |
| Ribosome (EMPIAR-10076) [42] | 256 | 87,328 | 1.6375        | 10   | 1024 $\times$ 3 | 50     |
| Covid (Walls et al. [25]) | 256 | 276,549 | 1.640625   | 8    | 1024 $\times$ 3 | 25     |

Diffusion Model. Our latent space diffusion models follow the framework proposed in Karras et al. [39]. We set $\sigma_{\text{data}}$ to the standard deviation of the training dataset. Our model parametrization, including the loss weighting $\lambda(\sigma)$, follows their setup (see column 4 in Table 2 in Karras et al. [39]). The neural network backbone of our diffusion models consists of a simple ResNet architecture with 16 hidden layers, using 128 hidden dimensions per layer. We train all models using Adam with a learning rate $3 \cdot 10^{-4}$ and batch size 1024. We set the EMA rate to 0.999.

Diffusion Model Sampling. For deterministic sampling, we use an adaptive step-size Runge–Kutta (RK) 4(5) solver [23, 65] for the Probability Flow ODE (Eq. (2)), with $\sigma(t) = t$. To embed points in the latent space of the diffusion model, we run the solver from $\sigma_{\text{min}} = 0.002$ to $\sigma_{\text{max}} = 80$. On the other hand, for usual sampling (decoding), we run the solver (or sampler) from $\sigma_{\text{max}} = 80$ to $\sigma_{\text{min}} = 0.002$.

To synthesize regular diffusion model samples, as visualized in Fig. 2, we apply the Euler–Maruyama method [66] to the sum of the Probability Flow ODE and a Langevin diffusion SDE [23, 39]

$$
\frac{d\mathbf{x}}{dt} = -\sigma(t)\nabla_x \log p(x; \sigma(t)) - \beta(t)\sigma^2(t)\nabla_x \log p(x; \sigma(t)) + \sqrt{2\beta(t)\sigma(t)} \, d\mathbf{\omega}_t,
$$

where $d\mathbf{\omega}_t$ is the standard Wiener process, $\beta(t) = \dot{\sigma}(t)/\sigma(t)$, and $\sigma(t) = t$. We use the sampling schedule proposed in Karras et al. [39]; in particular:

$$
\sigma_i = \left( \frac{\sigma_{\text{max}}^{1/\rho}}{M-1} \right)^{\rho} \left( \sigma_{\text{min}}^{1/\rho} - \sigma_{\text{max}}^{1/\rho} \right), \quad i \in \{0, \ldots, M-1\},
$$

with $\rho = 7.0$. We set the number of function evaluations to $M = 1,000$.

Langevin Dynamics. In Sec. 3.4, we run regular Langevin dynamics:

$$
\hat{z}_{n+1} = \hat{z}_n - \frac{\hat{z}_n}{2} \Delta t + \sqrt{\Delta t} \mathcal{N}(0, I),
$$

using step size $\Delta t = 0.1$. The sequence $\{\hat{z}_n\}$ is then decoded using the RK solver (see above).

Latent Interpolations. For latent interpolations, we first encode points into the latent space of the diffusion model using the RK solver. We then perform linear interpolation in the diffusion model’s latent space. Subsequently, these points are decoded using the RK solver. We generally interpolate using 100 equidistant steps.
Figure 7: Marginal distributions by projecting samples along the first two principal components of the latent embeddings. Latent embeddings of the data are shown in blue; sampled latent variables from the diffusion model prior or VAE prior are shown in orange or red, respectively. Note that the data marginals are plotted with a (blue) dashed line, which ends up lying directly on top of the orange curves for the diffusion model samples. From these plots we can observe that the marginal distributions for samples from the diffusion model priors are consistent with those of the data’s latent embeddings.

A.2 Additional Plots

In Fig. 7, we show 1-dimensional marginal distributions of the principal components for all datasets in addition to the samples themselves.

In Fig. 8, we show a conformational state interpolation for circular1d. Leveraging the diffusion model prior, we see that the interpolation proceeds along the data manifold.

In Fig. 9, we show fast Langevin dynamics sampling leveraging the diffusion model prior for all four datasets.
Figure 8: Latent interpolation in the diffusion model prior visualized using PCA (as in fig. 7); data latent embeddings are shown in blue. Starting and end points are shown in orange. Zoom in for details.
Figure 9: Langevin dynamics in the diffusion model prior visualized using PCA (as in Fig. 7). Data latent embeddings are shown in blue. The color-coding indicates the sampling path—color changes smoothly as the Langevin dynamics proceed. Zoom in for details.