Deep Mapper: Efficient Visualization of Plausible Conformational Pathways

Ziyad Oulhaj^{a,1}, Yoshiyuki Ishii^b, Kento Ohga^b, Kimihiro Yamazaki^b, Mutsuyo Wada^b, Yuhei Umeda^b, Takashi Katoh^b, Yuichiro Wada^{b,c} and Hiroaki Kurihara^{b,*}

^aNantes Université, École Centrale Nantes, CNRS, Laboratoire de Mathématiques Jean Leray, UMR 6629, France ^bFujitsu Limited, Japan

^cRIKEN Center for Advanced Intelligence Project, Japan

Abstract. Acquiring plausible pathways on high-dimensional structural distributions is beneficial in several domains. For example, in the drug discovery field, a protein conformational pathway, i.e. a highly probable sequence of protein structural changes, is useful to analyze interactions between the protein and the ligands, helping to create new drugs. Recently, a state-of-the-art method in drug discovery was presented, which efficiently computes protein pathways using latent variables obtained from an isometric auto-encoding of the space of 3D density maps associated to protein conformations. However, our preliminary experiments show that there is room to significantly reduce the computing time. In this study, we use the Mapper algorithm, which is a Topological Data Analysis method, and present a novel variant to extract plausible conformational pathways from the isometric latent space with comparatively short running time. The extracted pathways are visualized as paths on the resulting Mapper graph. The methodological novelties are described as follows: firstly, the filter function of the Mapper algorithm is optimized so as to extract the pathways via minimization of an energy loss defined on the Mapper graph itself, while filter functions taken in the classical Mapper algorithm are fixed beforehand. The optimization is with respect to parameters of a deep neural network in the filter. Secondly, the clustering method, which defines the vertices and edges of the Mapper graph, of our algorithm is designed by incorporating domain prior knowledge to assist the extraction. In our numerical experiments, based on an isometric latent space built on the common 50S-ribosomal dataset, the resulting Mapper graph successfully includes all the well-recognized plausible pathways. Moreover, our running time is much shorter than the above state-of-the-art counterpart.

1 Introduction

Acquiring plausible pathways on a high-dimensional structural distribution is beneficial in several domains, such as food [25] and drug discovery [15]. In those domains, the pathway (a.k.a. conformational pathway; see [24]) is expressed by a finite sequence of chemical structures, and the structure is represented by either an allatom model [5] or a 3D density map [24]. The benefit in the food domain is, for example, that the plausible conformational pathways are useful to analyze interactions between antioxidants and proteins, leading to the understanding of functionality or nutritional properties of proteins [25]. Moreover, the benefit in the drug discovery domain is that those pathways are useful to analyze interactions between proteins and ligands, and the analysis can lead to the development of new drugs [15]. Because of this usefulness, several authors have proposed a method to construct such conformational pathways [5, 1, 23, 12, 24].

As a brief review of the studies above, Yamazaki et al. [24] have proposed a protocol in the drug discovery domain for constructing a plausible protein conformational pathway as a sequence of 3D density maps from a set of 2D projection protein images collected via cryo-Electron Microscopy (cryo-EM) [13], based on their autoencoder named cryoTWIN. The auto-encoder is trained by cryo-EM images; the trained auto-encoder predicts the corresponding protein 3D density map from the latent variable. CryoTWIN captures continuous structural change of the target protein via a latent distribution having a closed form. The latent space is theoretically guaranteed to be isometric to the space of 3D density maps, if the training dataset holds the manifold assumption [2]. We note that the isometric latent distribution is efficient, since it is a low-dimensional equivalent expression to a distribution of 3D density maps. In numerical experiments, Yamazaki et al. [24] reproduced four well-recognized 50Sribosomal pathways by Davis et al. [4] using a trained cryoTWIN by the 50S-ribosomal cryo-EM images. The reproducing process consists of the following two steps: (i) generate several paths via their proposed pathway computing algorithm (see [24, Algorithm 1]) using the isometric latent distribution in the trained cryoTWIN, and then aggregate the paths, (ii) evaluate quantitatively and qualitatively whether the aggregated pathway is consistent with one of the four plausible pathways. The plausibility of the four pathways is considered high in [24], since Davis et al. [4] constructed the four pathways with heavy manual labor and standard biological tools; see visualized four pathways in [4, Figure 7]. Yamazaki et al. [24] report that they could construct the plausible conformational pathways with shorter running time compared to the counterpart studies such as Kinman et al. [12].

In our preliminary experiments, following Yamazaki et al. [24], we try to reproduce the four 50S-ribosomal pathways of [4], since the detailed information of the reproduction are not provided. In the experiments, we take 5 hours after training cryoTWIN by the 50S-ribosomal images. The initial 4 hours and the remaining 1 hour are from the above two steps (i) and (ii), respectively. The reason of

^{*} Corresponding Author. Email: h_kurihara@fujitsu.com

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Figure 1. Example of the Mapper graph construction: Firstly, the thirteen points in the input space of \mathbb{R}^d are mapped to \mathbb{R} by the filter function f. In \mathbb{R} , the mapped points are covered by a set of the intervals $(I_s)_{1 \le s \le S}$, S = 6 that overlap consecutively in a certain proportion $r \in (0, 1)$; see the five lime green intervals for the overlaps. Secondly, a clustering algorithm \mathcal{A}_C is applied to each $f^{-1}(I_s)$, where C denotes the the maximum number of clusters, and C = 2. The two green colored groups $C_{2,1}$ and $C_{2,2}$ are the clustering result to $f^{-1}(I_2)$. Thirdly, based on the clustering results, the Mapper graph M is constructed. In M, for example, the vertex $v_{2,1}$ represents the cluster $C_{2,1}$, and there exists an edge between $v_{2,1}$ and $v_{3,1}$

since two clusters $C_{2,1}$ and $C_{3,1}$ share a point in the overlapped region.

the 4 hours in step (i) is that Algorithm 1 of [24] is conducted for all pairs with significant two latent variables (number of the pairs is around 400), while the running time of Algorithm 1 for each pair is not short. We emphasize that our computational environment is the same as [24]. Further details of the preliminary experiments are deferred to Section 4.1. The preliminary experiments imply that there exists an innovation room to make step (i) more efficient in terms of running time.

Considering the background, the goal of this study is to design a computationally efficient algorithm that returns a graph, taking as input the latent variables in an isometric latent space to the conformational space, while the graph achieves the following two conditions: (a) the vertex corresponds to a conformation and the edge expresses similarity of two conformations, and (b) a set of paths on the graph includes plausible conformational pathways. In this study, we assume that the latent variables are obtained from an encoder of cryoTWIN taking as input cryo-EM images. Therefore, the conformation is represented by a 3D density map.

To achieve this goal, we focus on the Mapper algorithm, which returns a visualization of topological features of high dimensional datasets in a short running time. In the Mapper graph, vertices and edges express a cluster in the input space and the similarity of two clusters, respectively; see Figure 1 for how to construct the Mapper graph from a set of input data points. Since we employ cryoTWIN, the condition (a) is not challenging: we can identify a representative 3D density map with a vertex on the Mapper graph by applying the isometric decoder to a centroid of the cluster in the latent space. However, the condition (b) is challenging, because it is not trivial what clustering algorithm and filter function make the Mapper graph visualize the plausible pathways. Our other preliminary experiments show that commonly used clustering algorithms and filter functions do not work at all to achieve (b); see details in Section 4.1.

We summarize our two main contributions in this study as follows:

 We propose a variant of the Mapper algorithm, where the clustering algorithm is designed based on the domain prior-knowledge, and the filter function is optimized using input data so as to achieve the condition (b). The filter is parameterized by a deep neural network, and the parameters are optimized via minimizing a MaxFlux-objective-based energy loss on the Mapper graph, which is also parameterized by the neural network; see MaxFlux objective in [7]. Since the minimizers of the original MaxFlux loss are known to be optimal reaction pathways [7], minimization of the energy loss can extract plausible conformatinal pathways from the latent space onto the Mapper graph. To the best of our knowledge, we constitute the first use of a deep neural network as a Mapper filter function, taking advantage of the universal approximation theorem [20, Section 20]. We also theoretically analyze the energy loss, when the size of the input data goes to infinity.

2. We empirically prove the efficiency of our proposed algorithm using the common 50S-ribosomal dataset. The resulting Mapper graph by our method includes all the four plausible conformational pathways by Davis et al. [4], while our running time is much shorter than the counterpart time in the step (i) of [24].

2 Related Work

We review cryoTWIN [24] in Section 2.1, since we employ it as preprocessing technique to obtain latent variables in our numerical experiments. In Section 2.2, we first introduce the Mapper algorithm, and then review existing uses of the Mapper algorithm designed for biological applications.

2.1 CryoTWIN

Yamazaki et al. [24] proposed a method to compute a plausible protein conformational pathway from the single particle cryo-EM images. In their method, first, an isometric latent space to a space of 3D density maps is built via training an auto-encoder named cryoTWIN. Then, a plausible protein conformational pathway is computed as a sequence of 3D protein density maps, utilizing the isometric latent space.

CryoTWIN consists of an encoder h_{ζ} , a decoder g_{ξ} , and a latent distributional model P_{ψ} , where ζ, ξ, ψ are trainable parameters. The encoder outputs the latent variable z as input of a Fourier transformed cryo-EM image x. The latent model is defined as a Gaussian Mixture Model (GMM) $P_{\psi}, \psi = \{(\pi_k, \mu_k, \Sigma_k)\}_{k=1}^K$, where π_k, μ_k , and Σ_k represent k-th Gaussian's weight, mean, and variance, respectively, and $\sum_{k=1}^K w_k = 1 \ \forall k; w_k \ge 0$. Let x_i be a Fourier transformation of *i*-th cryo-EM image. The training objective to obtain the optimized parameters ζ^*, ξ^*, ψ^* is as follows:

$$\arg\min_{\zeta,\xi,\psi} \frac{1}{N} \sum_{i=1}^{N} \mathbb{E}_{\varepsilon} \left[\|W \odot (x_i - \hat{x}_{z_i + \varepsilon})\|_2^2 - \beta \log P_{\psi}(z_i) \right],$$
(1)

where the symbols N, ε, \odot , and β are the number of cryo-EM images, random noise, Hadamard product, and the positive hyperparameter, respectively. In addition, $\hat{x}_{z_i+\varepsilon} = g_{\xi}(z_i + \varepsilon, \hat{R}_i), z_i = h_{\zeta}(x_i), \hat{R}_i$ is the corresponding estimated pose orientation to x_i , and $\hat{x}_{z_i+\varepsilon}$ is the predicted 2D Fourier image in the 3D Fourier volume. The symbol W is a weight matrix for introducing the isometricity; see [24, Appendix A]. CryoTWIN is inspired by another autoencoder namely RaDOGAGA [10], which also builds an isometric latent space to the original space. After the training, for a latent variable z, the corresponding 3D density map \hat{V}_z is reconstructed by the trained decoder g_{ξ^*} .

The isometricity to a space of 3D density maps enables us to compute plausible conformational pathways via the trained GMM P_{ψ^*} using the decoder g_{ξ^*} . In [24], the pathway computation algorithm is proposed; see also Algorithm 1 of [24]. This algorithm requires two means μ_i^* and μ_i^* as start and end points of the pathway. Then, a MaxFlux path [7] on P_{ψ^*} between μ_i^* and μ_j^* is approximately computed using greedy optimization technique. The following minimization problem is used in the greedy optimization at t + 1-th iteration to compute the t + 1-th latent variable $z^{i \rightarrow j}(t + 1)$:

$$z^{i \to j}(t+1) = \arg\min_{\{\mathbf{z}\}} \frac{\|\mathbf{z} - z^{i \to j}(t)\|_2}{P_{\psi^*}(\mathbf{z})},$$
(2)

where $\{z\}$ is a set of the candidate latent variables. The path on P_{ψ^*} is expressed as a sequence of the latent variables: $(\mu_i^*, \ldots, z^{i \to j}(t), \ldots, \mu_j^*)$. Thereafter, by decoding each element in the sequence $(\mu_i^*, \ldots, z^{i \to j}(t), \ldots, \mu_j^*)$ using g_{ξ^*} , the algorithm outputs a sequence of 3D density maps $(\hat{V}_{\mu_i^*}, \ldots, \hat{V}_{z^{i \to j}(t)}, \ldots, \hat{V}_{\mu_j^*})$.

2.2 Mapper Algorithm

Definition of the Mapper algorithm: Let X be a topological space and let $f: X \to \mathbb{R}$ be a continuous function called a *filter function*. We define an equivalence relation between two elements x and y in X by $x \sim_f y$ if and only if x and y are in the same connected component of $f^{-1}(a)$ for some a in f(X). Then the *Reeb graph* $\mathcal{R}_f(X)$ of a topological space X computed with a filter function f is defined to be the quotient space X/\sim_f . The *Mapper graph*, introduced in [21], is a statistical version of the Reeb graph consisting of a computable approximation. It is discrete in the sense that it is computed on a finite metric space $(\mathbb{X}_n = \{x_0, \ldots, x_n\} \subseteq X, d_X)$ with a continuous filter function f, where d_X is a metric on X.

The procedure to compute a Mapper graph M is the following three steps [3]

- Step 1: Cover the range of values $f(\mathbb{X}_n)$ with a set of intervals $(I_s)_{1 \le s \le S}$ that overlap consecutively in a certain proportion $r \in (0, 1)$.
- Step 2: Apply a clustering algorithm \mathcal{A}_C to each pre-image $f^{-1}(I_s), s \in \{1, \ldots, S\}$, where C is the maximum number of clusters. This produces the *pullback cover* \mathscr{C} of \mathbb{X}_n , where $\mathscr{C} = \{\mathcal{C}_{1,1}, \ldots, \mathcal{C}_{1,C_1}, \ldots, \mathcal{C}_{s,1}, \ldots, \mathcal{C}_{s,C_s}, \ldots, \mathcal{C}_{S,1}, \ldots, \mathcal{C}_{S,C_S}\}$ and $C_s \leq C$ for any s, and $\mathcal{C}_{s,c}$ denotes the c-th cluster of $f^{-1}(I_s)$.
- Step 3: The Mapper graph M is the 1-skeleton of the nerve complex of \mathscr{C} . It is a graph with a vertex $v_{s,c}$ for each $\mathcal{C}_{s,c}$, and an edge between two vertices $v_{s,c}$ and $v_{s',c'}$ if and only if $\mathcal{C}_{s,c} \cap \mathcal{C}_{s',c'} \neq \emptyset$.

See Figure 1 for illustration of the three steps. In Appendix A of the arXiv version [18], we provide complementary information.

Review of Mapper algorithms in biology applications: The Mapper graph can capture various topological features in data which has a complicated structure. It is also known that the Mapper algorithm is more robust to the distance compared to non-linear dimension reduction or geometric embedding methods; see [26]. As examples of applications of the Mapper, Yao et al. [26] applied the Mapper algorithm to characterize transient intermediates or transition states which are quite crucial for the description of biomolecular folding pathways. In [16], a Disease-Specific Genomic Analysis is first performed on a breast cancer dataset to produce measures of deviation between tumor and normal tissue. This information is then introduced to the Mapper algorithm as a filter function. Due to its ability to conserve topological information in the dataset, the resulting graph reveals a region that corresponds to a unique mutational profile, that is otherwise scattered across different clusters in a regular clustering analysis.

Algorithm 1: Deep Mapper graph

Input:

- 1. $\{z_i\}_{i=1}^N$: Set of latent variables in \mathbb{R}^d from an isometric auto-encoder to the structural space,
- 2. $P_{\psi}(z)$: The latent distribution model by GMM, where ψ is the GMM parameters,
- 3. \overline{K} : Number of significant Gaussian components,
- 4. κ : Number of neighbors,
- 5. S and $r \in (0, 1)$: Number of intervals and the overlap rate,
- 6. C: Maximum number of clusters,
- 7. λ : Positive fixed value,
- 8. g: Isometric decoder from a latent variable to the structure.

Output: Optimized Mapper graph with structures.

- 1 Using κ , build a kNN graph $G = (\mathcal{V}, \mathcal{E})$ on $\{z_i\}_{i=1}^N$, where $\mathcal{V} = \{z_i\}_{i=1}^N$ and \mathcal{E} is the set of the edges.
- 2 Select the significant Gaussian components in $P_{\psi}(z)$. Then, using the significant components and C, define a clustering algorithm \mathcal{A}_C to each pre-image $f_{\theta}^{-1}(I_s)$, where I_s is the *s*-th $(1 \le s \le S)$ interval in \mathbb{R} ; see the interval in *Step 1* of Section 2.2. The clustering algorithm is designed to provide a representative variable to each cluster. Also, based on the selected components, define the filter function $f_{\theta} : \mathbb{R}^d \to \mathbb{R}$, which is parameterized by trainable parameters θ in a deep neural network. See further details in Section 3.1.
- 3 for each epoch do
- 4 Following Step 1 to Step 3 in Section 2.2, construct a Mapper graph M_{θ} on $\{z_i\}_{i=1}^N$ by using S, r, f_{θ} , and \mathcal{A}_C .
- 5 Compute the energy loss L_{θ} on M_{θ} using P_{ψ} ; see Section 3.2.
- 6 Compute a regularization term $\operatorname{Reg}_{\theta}(G) := \lambda \sum_{(i,j) \in \mathcal{E}} (f_{\theta}(z_i) - f_{\theta}(z_j))^2 \text{ on } G.$
- 7 $L_{\theta} \leftarrow L_{\theta} + \operatorname{Reg}_{\theta}(G)$, and then minimize L_{θ} with respect to the parameters θ .
- 8 For each representative latent variable in the optimized Mapper graph, compute the corresponding structure using the decoder g. See Section 3.1 for the representative latent variables.
- **9 return** M_{θ} with the structures.

In the context of single-cell RNA sequencing data analysis, Wang et al. [22] proposed a Mapper algorithm, whose filter function is designed via gene co-expression network analysis. As a result, the Mapper graph not only preserved the continuous nature in gene expression profiles, but also successfully separated different cell types. In [8], the authors adopted the Mapper algorithm to data with velocity, and associated flow on edges of the resulting Mapper graph. They applied their method to single-cell gene expression and combined their method with the Hodge decomposition on a graph to enhance the interpretation of the flow on the Mapper graph.

A relaxed and more general version of the Mapper graph, that enjoys improved stratification properties, is introduced in [17]. It is then used to optimize parameterized filter functions for regular Mapper graphs, with respect to a topological risk based on persistent homology. This is shown to produce quality Mapper graphs for 3-dimensional shapes and single cell RNA-sequencing data.

3 Proposed Algorithm

Our proposed algorithm is shown in Algorithm 1. Assuming that the original dataset holds the manifold assumption in a high-dimensional structural space, this algorithm requires a set of latent variables $\{z_i\}_{i=1}^N$, where z_i is the encoding of the *i*-th original data point with an isometric auto-encoder. Thanks to this isometric auto-encoder such as cryoTWIN [24], we can use the low-dimensional latent space, which is equivalent to the high-dimensional structural space. Using $\{z_i\}_{i=1}^N$, our algorithm extracts plausible conformational pathways from the latent space, and visualizes them on the resulting Mapper graph. The extraction is achieved by an optimized filter function f_{θ} and our designed clustering algorithm \mathcal{A}_C . The optimization is via minimization of a MaxFlux objective [7] inspired energy loss L_{θ} defined on the parameterized Mapper graph M_{θ} .

Remark 1. As mentioned at the fourth paragraph of Section 1, in this study, we assume cryoTWIN [24] to prepare the first and ninth inputs of Algorithm 1. However, any isometric auto-encoders to the original structural space are applicable as long as they enable us to prepare those inputs from a set of original data. Furthermore, once the latent variables are obtained from the isometric auto-encoder, we can fit a Gaussian mixture model to those variables by [20, Section 24.4.2], and then we can prepare the second input.

The definitions of our clustering algorithm A_C and the filter function f_{θ} are given in Section 3.1, while that of the energy loss is described in Section 3.2. Thereafter, we theoretically analyze Algorithm 1 in Section 3.3.

3.1 The Clustering Algorithm and Filter Function

As the second input to Algorithm 1, let us consider a trained GMM $P_{\psi}(z) = \sum_{k=1}^{K} \pi_k \mathcal{N}(z; \mu_k, \Sigma_k)$ obtained from cryoTWIN (see Section 2.1), where \mathcal{N} expresses a Gaussian distribution. Inspired by Expt2 in [24], we select the significant Gaussian components: we find top \bar{K} largest weight values $\pi_k, k = 1, \ldots, K$, and define the corresponding Gaussian indexes as k_j $(j = 1, \ldots, \bar{K})$, where $\pi_{k_j} \leq \pi_{k_{j+1}}$.

able to each cluster by the mean vector of μ_k , where $k \in \mathcal{K}$ denotes the estimated cluster label.

In the first step, we compute Q_k for k-th Gaussian component to measure how much the component is related to the pre-image $f_{\theta}^{-1}(I_s)$ using the density of the joint distribution $\pi_k \mathcal{N}(z; \mu_k, \Sigma_k)$. In the second step, we pick the most related C components to define the set "Candidates". In the third step, we use Bayes' theorem (see [20, Section 24.5]) to estimate cluster label of z from "Candidates". Note that we can compute an associated structure to each cluster via decoding μ_k by the eighth input g in Algorithm 1; see the decoding in Section 2.1. Additionally, we use the prior knowledge to design the clustering: a set of conformations obtained by decoding mean vectors of significant Gaussian components in cryoTWIN is empirically almost equivalent to a set of important conformations. Next, the filter function is given by a neural network that acts on a feature transform of the latent space. Specifically, the filter function has the form of $f_{\theta}(z) = DNN_{\theta}(T(z))$. The symbol DNN_{θ} is a deep neural network with trainable parameters θ . In addition, T(z) is a vector via the map $T : \mathbb{R}^d \to \mathbb{R}^{|\bar{K}|}$, and for $j = 1, \ldots, \bar{K}$, the *j*-th element of T(z) is defined by $(z - \mu_{k_j})^\top \Sigma_{k_j}^{-1}(z - \mu_{k_j}), k_j \in \mathcal{K}$, i.e., the map T is a characterization of z by the top \bar{K} significant Gaussian components with Mahalanobis' distance [14].

3.2 The Energy Loss and Minimization

Let $M_{\theta} = (\tilde{\mathcal{V}}_{\theta}, \tilde{\mathcal{E}}_{\theta})$ denote the resulting Mapper graph after line 4 of Algorithm 1. Here, $\tilde{\mathcal{V}}_{\theta}$ is a set of vertexes with the Mapper graph, and $\tilde{\mathcal{E}}_{\theta}$ is a set of the edges. Since the vertex set can be identified with a set of clusters $\{\mathcal{C}\}$ defined by \mathcal{A}_{C} , we express the edge by $(\mathcal{C}, \mathcal{C}') \in \tilde{\mathcal{E}}_{\theta}$.

For computing the energy loss L_{θ} on the Mapper graph M_{θ} , set L_{θ} and B to zero and a natural number, respectively. Then, for each edge $(\mathcal{C}, \mathcal{C}') \in \tilde{\mathcal{E}}_{\theta}$, compute the edge-wise energy loss $\ell_{\theta}(\mathcal{C}, \mathcal{C}')$ by the following three steps. Firstly, sort the latent variables in $\mathcal{C} \cup \mathcal{C}'$ based on the filter value in ascending order. Secondly, for $b = 1, \ldots, B$, let $\iota(b) \in \{1, \ldots, N\}$ denote an index of the $\lfloor \frac{b(|\mathcal{C} \cup \mathcal{C}'| - 1)}{B} \rfloor$ -th latent variable in the order. Thirdly, the edge-wise energy loss is given by $\sum_{b=1}^{B-1} \text{LDA}(z_{\iota(b)}, z_{\iota(b+1)}, f_{\theta}, \nabla f_{\theta}(z_{\iota(b)})) / P_{\psi}\left(\frac{z_{\iota(b)} + z_{\iota(b+1)}}{2}\right)$. At last, the energy loss L_{θ} is defined by $L_{\theta} = \sum_{(\mathcal{C}, \mathcal{C}') \in \tilde{\mathcal{E}}_{\theta}} \ell_{\theta}(\mathcal{C}, \mathcal{C}')$.

The LDA stands for *Local Distance Approximation*. As the name suggests, the value of LDA $(z, z', f, \nabla f(z))$ is an approximation to the distance $||z' - z||_2$. The motivation to introduce LDA is to make $\ell_{\theta}(\mathcal{C}, \mathcal{C}')$ differentiable w.r.t. θ . Let us assume $z \approx z'$, and let z_i denote the *i*-th element in *z*. Additionally, we define a *d*-dimensional vector of z_{-i} by replacing the *i*-th element in *z* with z'_i . By the definitions, LDA $(z, z', f, \nabla f(z))$ is given by $\left\| \left(\frac{f(z_{-1}) - f(z)}{\nabla f(z)_1}, \ldots, \frac{f(z_{-i}) - f(z)}{\nabla f(z)_i}, \ldots, \frac{f(z_{-d}) - f(z)}{\nabla f(z)_d} \right) \right\|_2$, where $\nabla f(z)_i$ is the *i*-th element in the gradient of *f* at *z*; see details of LDA in Appendix B.1 of the arXiv version [18].

From the definition of LDA, the energy loss L_{θ} is approximately equal to $\sum_{(\mathcal{C},\mathcal{C}')\in \tilde{\mathcal{E}}_{\theta}} \sum_{b=1}^{B-1} ||z_{\iota(b+1)} - z_{\iota(b)}||_2 / P_{\psi}\left(\frac{z_{\iota(b)} + z_{\iota(b+1)}}{2}\right)$. Thus, minimization of L_{θ} w.r.t. θ can be considered as the MaxFlux objective on the Mapper graph M_{θ} ; see [7, Equation (17)] for the original objective. Since the minimizers of the original MaxFlux objective are known to be optimal chemical reaction pathways [7], i.e., a kind of plausible conformational pathways on a chemical structural distribution, the minimization of L_{θ} has a potential to extract the plausible pathways from the latent distribution P_{ψ} , leading to visualization of the pathways on M_{θ} .

Note that only the LDA related parts are parameterized by θ in $\ell_{\theta}(\mathcal{C}, \mathcal{C}')$, whereas P_{ψ} related parts are not. Indeed, it is natural to also parameterize the latter parts by θ since they are components in the original MaxFlux objective. However, since the way of the parameterization is not trivial, we only parameterize the former parts in this study.

As line 7 of Algorithm 1 shows, we add a regularization term $\operatorname{Reg}_{\theta}(G)$ to L_{θ} in practice, where the regularizer is computed on a k-Nearest Neighbor (kNN) graph of $\{z_i\}_{i=1}^N$; see [20, Section 19.1] for kNN graph. In this study, we compute the exact kNN graph with brute-force search, whose time and memory complexities are $O(dN^2)$ and $O(\kappa N)$, respectively. To reduce the time complexity, the approximation method of [27], whose time complexity is $O(dN \log N)$, is available. The minimization of $\operatorname{Reg}_{\theta}(G)$ helps the

filter function to preserve the data manifolds of $\{z_i\}_{i=1}^N$ onto the filter space. The final loss in the line 7 is minimized using Adam optimizer [11] with He initialization [6].

3.3 Theoretical Analysis

We study the properties of the energy loss L_{θ} , when B and N of Section 3.2 go to infinity. In the following paragraphs, we prove two properties below: firstly, the discretized edge-wise energy loss $\ell_{\theta}(\mathcal{C}, \mathcal{C}')$ converges to the continuous counterpart when $B \to \infty$ (see Equation (3) in Theorem 1), and secondly, the discretized energy loss of L_{θ} converges to the continuous MaxFlux loss in the Mapper graph when $B, N \to \infty$; see Equation (4) in Theorem 1. For the original continuous MaxFlux loss, see [7, Equation (6)].

Consider the case that we are interested in an optimal conformational path between two protein conformation representations z_0 and z_{∞} , where $z_0, z_{\infty} \in \mathbb{R}^d$ $(d \in \mathbb{N})$. We also assume that we know a closed form $P_{\psi} : \mathbb{R}^d \to [0, +\infty)$ for the probability density of the protein conformation representations, and $P_{\psi}(\mathbb{R}^d)$ is connected.

We denote by $\mathrm{PC}^0([0,1],\mathbb{R}^d)$ the set of piecewise continuous functions $f:[0,1] \to \mathbb{R}^d$ that satisfy $f(0) = z_0$ and $f(1) = z_\infty$. A map $f \in \mathrm{PC}^0([0,1],\mathbb{R}^d)$ will be called a *conformational path* between z_0 and z_∞ . For $f \in \mathrm{PC}^0([0,1],\mathbb{R}^d)$, we define its energy loss I_f , which is defined as the Riemann integral, as $I_f = \int_0^1 1/P_{\psi}(f(t))\mathrm{d}f(t) := \lim_{n\to\infty} \sum_{i=0}^{n-1} ||f(\frac{i+1}{n}) - f(\frac{i}{n}))||_2/P_{\psi}((f(\frac{i}{n}) + f(\frac{i+1}{n}))/2)$. The optimal energy loss for all possible conformational paths is defined as $S^* := \inf_{f \in \mathrm{PC}^0([0,1],\mathbb{R}^d)} I_f$. We here remark the following two: first, the notation f used in this section is different from a filter function f appeared in Section 3.1, and second, I_f can be interpreted as the energy loss on the Mapper graph if a map f defines a path on the graph.

In our work, we wish to approach the optimal energy loss by using a finite N samples $\{z_j\}_{j=1}^N$ of conformations, that independently follow a distribution of density P_{ψ} . We then discretize the energy loss using l steps; the symbol l corresponds to B in Section 3.2. Precisely, we define the *stochastic loss* with l steps associated to $\{z_j\}_{j=1}^N$ as $S_l^{(N)} := \min_{\{z_i\}_{i=1}^{l-1} \subseteq \{z_j\}_{j=1}^N} \sum_{i=0}^{l-1} ||z_{i+1} - z_i||_2 / P_{\psi}\left(\frac{z_i + z_{i+1}}{2}\right)$, with the convention $z_l = z_{\infty}$, where $\{z_j\}_{j=1}^N \subseteq \mathbb{R}^d$ is a random sample drawn independently from a distribution of density P_{ψ} and $l \in \mathbb{N}$ such that l > 2.

The theoretical part of our work aims at proving that $S_l^{(N)}$ gets arbitrarily close to S^* when N and l go to infinity. In order to properly define this property in terms of real sequence convergence and random variable sequence convergence, we define the *discrete optimal energy loss* with l steps as $S_l := \inf_{\{z_i\}_{i=1}^{l-1} \subseteq \mathbb{R}^d} \sum_{i=0}^{l-1} ||z_{i+1} - z_i||_2 / P_{\psi}\left(\frac{z_i + z_{i+1}}{2}\right)$, with the same convention $z_l = z_{\infty}$, where $l \in \mathbb{N}$ such that l > 2. We then have the following result regarding the different losses that we defined above.

Theorem 1. We have

$$S_l \xrightarrow[l \to \infty]{} S^*.$$
 (3)

Moreover, for every $l \in \mathbb{N}$ such that l > 2, assuming that (i) the density P is continuously differentiable, (ii) the density P is strictly positive almost everywhere, and (iii) we now only consider discrete paths $\{z_i\}_{i=1}^{l-1} \subseteq \mathbb{R}^d$ such that $\forall i \in \{0, \ldots, l-1\}$ $z_{i+1} \neq z_i$. Then we have

$$S_l^{(N)} \xrightarrow[N \to \infty]{a.s} S_l. \tag{4}$$

The proof of this theorem is given in Appendix B.2 and B.3 of the arXiv version [18].

4 Numerical Experiments

In this section, we introduce our numerical experiments. In Section 4.1, we describe our setting and result. Then, we discuss the result in Section 4.2. Thereafter, we describe both ablation and robustness studies against our method in Section 4.3 and 4.4, respectively.

4.1 Setting and Result

Through all experiments, we use a set of the latent variables $\{z_i\}_{i=1}^N$, which are the encoding results of cryoTWIN [24] as input of 50S-ribosomal cryo-EM images from EMPIAR-10076; see [9] for what EMPIAR is.

In the following, we first describe the preprocessing for our experiments. Then, we introduce 1st and 2nd preliminary experiments, which motivate us to propose the deep Mapper shown in Algorithm 1. Finally, we explain our main experiment.

Preprocessing: We download the 50S-ribosomal cryo-EM images with their estimated pose orientations from GitHub URL of [29]. The image size is 128×128 . We train cryoTWIN by the downloaded dataset with the training objective in Equation (1). For the training, we employ the same hyperparameter values and computational resource (i.e., four NVIDIA V100 GPU accelerators with two Intel Xeon Gold 6148 processors) as Yamazaki et al. [24]. After the training, we prepare the latent variable set $\{z_i\}_{i=1}^N$ by the encoder, where N = 131899 and $\forall i; z_i \in \mathbb{R}^8$. Then, following [24, Expt2], we evaluate whether we can observe the structural labels defined by Davis et al. [4] (e.g., B, C2, D1, E5,... etc) in the corresponding 3D density maps of the mean vectors of significant Gaussian components. The evaluation is based on PyMOL [19] and Fourier Shell Correlation (FSC) metric; see FSC in [28, 3rd footnote]. In this preprocessing, we observe almost all important structural labels; see details of the quantitative evaluations by FSC in Appendix D of the arXiv version [18].

1st preliminary experiment: The aim of this experiment is to measure the running time in reproducing the four pathways of [4], based on the above trained cryoTWIN via the protocol shown in [24, Expt2]. To do so, we only focus on the mean vectors of top 30 significant Gaussian components out of 100, since the decodings of the remaining 70 mean vectors are not necessarily consistent with wellrecognized structures by Davis et al. [4]. Note that we measure the significance based on the Gaussian weight π , as Yamazaki et al. [24] do. Then, (i) we generate the ribosomal path by applying the pathway computing algorithm of Algorithm 1 in [24] to a pair of the significant mean vectors; see Equation (2) for how to generate the path. For Algorithm 1 of [24], we use exactly the same hyperparameter values as [24]. Since the number of pairs is 435, we conduct parallel computing for the pairs using the same computers in the preprocessing. At last, (ii) we aggregate the paths, and evaluate whether the aggregated path is consistent with one of the four pathways. The running time in step (i) is around 240 minutes, while the time in step (ii) is around 60 minutes.

2nd preliminary experiment: The aim of this experiment is to qualitatively evaluate whether the resulting Mapper graph, which is obtained via applying a classical Mapper algorithm to the set of latent



Figure 2. Left and right graphs: Resulting Mapper graphs of 2nd preliminary and main experiments, respectively. In both graphs, each color of nodes corresponds to the average value over the filtered values in each cluster. The labels such as B on the graphs are the 50S-ribosomal structural label defined by Davis et al. [4]. The red and orange arrows in the right graph are two of four well-recognized conformatinal pathways defined also in [4].

variables $\{z_i\}_{i=1}^N$ from the preprocessing, can contain the four wellrecognized 50S-ribosomal conformational pathways of Davis et al. [4, Figure 7]. Following Steps 1 to 3 in Section 2.2, we employ f_{mean} and k-means [20, Section 22.2] for the filter function and the clustering algorithm in the classical algorithm, respectively. Here, f_{mean} returns the average value over d-elements in d-dimensional vector, and the number of clusters in k-means is 3. Additionally, the numbers of intervals S and overlap rate r are S = 20 and r = 0.25, respectively. Moreover, we introduce a representative latent variable for each cluster as follows. Let $\{\mu_{k_j}\}_{j=1}^{25}$ denote a set of mean vectors related to the top 25-significant Gaussian components, and let q denote the cluster centroid given by k-means. The definition of the significance is the same as in the 1st preliminary experiment. Then, the representative latent variable is defined by $\arg \min_{\{\mu_{k_j}\}_{j=1}^{25}} \|\mu_{k_j} - q\|_2$. Note that the structural labels corresponding to the top 25 Gaussian mean vectors do not correspond to junk structures. The resulting Mapper graph with the labels is shown in the left-hand side of Figure 2. The running time is less than one minute using Apple M1 16 GB 8 cores.

Main experiment: We apply our deep Mapper of Algorithm 1 to the set of latent variable $\{z_i\}_{i=1}^N$ using the trained GMM P_{ψ} from the preprocessing. The aim of this experiment is not only to evaluate whether the resulting Mapper graph can contain the four plausible pathways, but also to measure the running time. We set $(\bar{K}, \kappa, S, r, C, \lambda)$ of Algorithm 1 to (25, 15, 25, 0.25, 5, 0.01). Additionally, we set *B* of Section 3.2 to 100. For the filter function f_{θ} , we employ a single layer neural network with rectifier activation function. We optimize the loss L_{θ} of line 7 in Algorithm 1 w.r.t. θ in 300 epochs, where we use full-batch, and the learning rate of Adam optimizer is 0.001. The computational environment is Apple M1 16 GB 8 cores. The resulting Mapper graph with the labels by Davis et al. [4] is shown in the right-hand side of Figure 2. The running time is around 40 minutes.

For above experiments including the preprocessing, we choose hyperparameter values, which return the best result.

4.2 Analysis of Results

The running time of our method (40 min) is sufficiently shorter than our main counterpart time of Yamazaki et al. [24] (240 min), although our computer (Apple M1 16 GB 8 cores) is less powerful than [24] (four NVIDIA V100 GPU accelerators with two Intel Xeon Gold 6148 processors). However, in comparison with the classical Mapper algorithm, our method is much slower (40 min vs. 1 min), since ours optimizes the filter function.

As for the extraction of plausible pathways, from Figure 2, we can observe that our Mapper graph contains all the four plausible 50S-ribosomal conformational pathways of [4, Figure 7], which are the following p_1 to p_4 :

p_1 :	$B \rightarrow D1 \rightarrow D2 \rightarrow D3 \rightarrow D4 \rightarrow E5$; see the red arrows,
p_2 :	$B \rightarrow D1 \rightarrow E1 \rightarrow E2 \rightarrow E4 \rightarrow E5,$
p_3 :	$B \rightarrow C2 \rightarrow E1 \rightarrow E2 \rightarrow E4 \rightarrow E5$; see the orange arrows
p_4 :	$B \rightarrow C2 \rightarrow C3 \rightarrow C1 \rightarrow E2 \rightarrow E4 \rightarrow E5,$

whereas the counterpart result by the classical method contains none of the four. In the pathway p_1 , the structural label E3 is absent, because the label does not correspond to one of the top 25-significant Gaussian components in the preprocessing.

Our Mapper graph moreover captures the important character of [4, Figure 7]: the labels C and D are well-separated overall in the graph. On the other hand, with two pairs (D2, E1) and (D4, E4), two labels in each pair are connected in our graph, while they should not according to [4, Figure 7].

Remark 2. We are interested in a protein dataset that satisfies the following four conditions. First, the experts already have constructed the conformational pathway from the dataset, and the plausibility was well evaluated. Second, the pathway includes intermediate structures, whose occurrence probabilities are low. Third, the conformational diversity within the pathway is high. Fourth, the dataset is collected from cryo-EM; recall that we assume cryoTWIN for Algorithm 1 in this study. Note that analyzing such assembly pathways in a short running time is valuable, as ordinary methods (e.g., molecular dynamics) often struggle with the analysis. To the best of our knowledge, one of the few datasets that satisfy the four conditions is the 50S-ribosomal dataset from EMPIAR-10076.

4.3 Ablation Study

We evaluate our algorithm's performance in the three cases, using the latent variable set from the preprocessing. The first case is that



Figure 3. Three resulting Mapper graphs in ablation study. Left: The graph built on our clustering algorithm A_C in Section 3.1 and the fixed filter function f_{mean} . Middle: The graph build on k-means and our parameterized filter function f_{θ} . Right: The graph by Algorithm 1 with $\lambda = 0$.



Figure 4. Four resulting Mapper graphs in robustness study. From right to left: The graphs constructed by Algorithm 1 with (S, C) = (24, 5), (S, C) = (26, 5), (25, 4), and (25, 6), respectively.

we only replace the filter function f_{θ} in our algorithm with a fixed one. We consider the four fixed filter functions: f_i , f_{\min} , f_{\max} , and f_{mean} . The filter f_i is a projection from \mathbb{R}^8 to \mathbb{R} which maps z to z_i , where z_i denotes the *i*-th entry of z. The filter functions f_{\min} , f_{\max} , and f_{mean} map $z \mapsto \min\{z_1, \ldots, z_8\}, z \mapsto \max\{z_1, \ldots, z_8\}$, and $z \mapsto \max\{z_1, \ldots, z_8\}$, respectively. The second case is that we only replace the clustering algorithm \mathcal{A}_C in our algorithm with kmeans. We set the number of clusters in k-means to 2. The last case is that we remove the kNN regularizer from our algorithm, i.e., we set λ in Algorithm 1 to 0.

In the first case, among the eleven resulting Mapper graphs, we obtain Mapper graphs which contain three of the four plausible conformational pathways in [4] at the best. One such the graph is shown on the left-hand side in Figure 3. For the second and third cases, none of the four conformational pathways is contained in the Mapper graph; see results of the second and third cases in the middle and right-hand side graphs of Figure 3, respectively. From those results, both the kNN regularizer $\text{Reg}_{\theta}(G)$ and our designed clustering algorithm \mathcal{A}_C in Algorithm 1 are important factors to extract the pathways from the latent distribution P_{ψ} , while the parameterized filter function f_{θ} also contributes to the extraction.

4.4 Robustness Study

We conduct a robustness study against the change of hyperparameters in Algorithm 1. In this study, we focus on the following two important hyperparameters of the Mapper algorithm: the number of intervals S and the maximum number of clusters C; see S and Cin Algorithm 1. Firstly, we change S in {24, 25, 26}, while fixing the other hyperparameters in Algorithm 1 to the values described in the main experiment paragraph in Section 4.1. See the results with S = 24 and 26 at the first and second graphs from the left in Figure 4, respectively. Secondly, we change C in $\{4, 5, 6\}$, while fixing the other hyperparameters to the values used in the main experiment. See the results with C = 4 and 6 at the third and fourth graphs from the left in Figure 4, respectively.

In the first graph of Figure 4, one pathway $B \rightarrow C2 \rightarrow C3 \rightarrow C1 \rightarrow E2 \rightarrow E4 \rightarrow E5$ is contained in the graph. In the second, two pathways $B \rightarrow C2 \rightarrow E1 \rightarrow E2 \rightarrow E4 \rightarrow E5$ and $B \rightarrow C2 \rightarrow C3 \rightarrow C1 \rightarrow E2 \rightarrow E4 \rightarrow E5$ are contained in the graph. In the third, one pathway $B \rightarrow D1 \rightarrow E1 \rightarrow E2 \rightarrow E4 \rightarrow E5$ is contained in the graph. In the fourth, no complete pathway is contained in the graph, but two partial pathways $B \rightarrow D1 \rightarrow D2 \rightarrow D4 \rightarrow E5$ and $B \rightarrow C2 \rightarrow C3 \rightarrow C1 \rightarrow E2 \rightarrow C3 \rightarrow C1 \rightarrow E2$ and $B \rightarrow C2 \rightarrow C3 \rightarrow C1 \rightarrow E2 \rightarrow E5$ are contained in the graph. From those analyses, our Mapper algorithm proves to be fairly sensitive to the change of hyperparameters.

5 Conclusion and Future Work

We propose a deep Mapper algorithm to extract plausible conformational pathways from the isometric latent distribution of cryoTWIN in short running time. In our numerical experiments, our method successfully extracts the well-recognized 50S-ribosomal pathways in shorter running time than the state-of-the-art method.

One of our future work is to make our method to be more robust against change of the hyperparameters. Another future work is to apply our method to other datasets, and evaluate the results.

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