Vector Diffusion Maps and the Connection Laplacian

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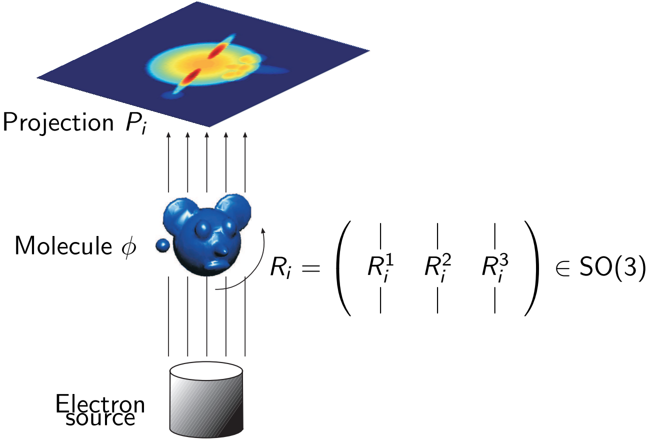
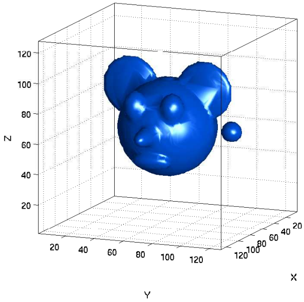
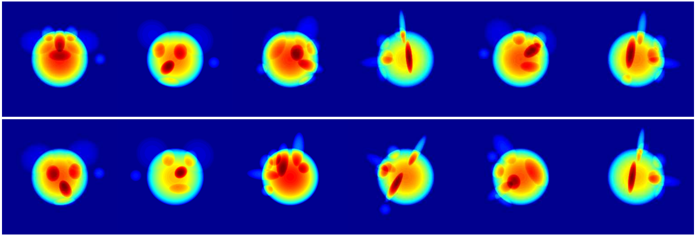
Motivating Problem: Cryo-Electron Microscopy



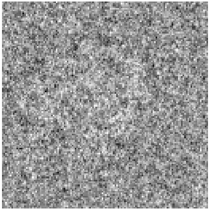
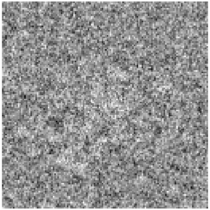
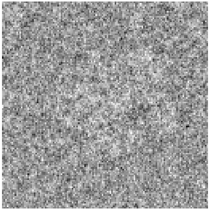
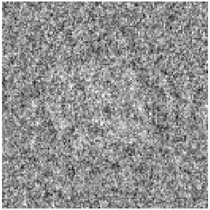
- Projection images $P_i(x,y) = \int_{-\infty}^{\infty} \phi(xR_i^1 + yR_i^2 + zR_i^3)\, dz +$ "noise".
- $\phi : \mathbb{R}^3 \mapsto \mathbb{R}$ is the electric potential of the molecule.
- Cryo-EM problem: Find ϕ and $R_1, \ldots, R_n$ given $P_1, \ldots, P_n$.

Toy Example

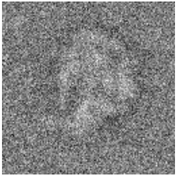


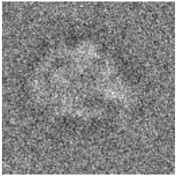


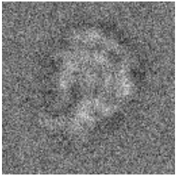
E. coli 50S ribosomal subunit: sample images

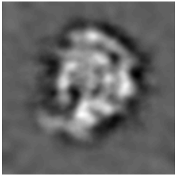





Class Averaging in Cryo-EM: Improve SNR









Current clustering method (Penczek, Zhu, Frank 1996)

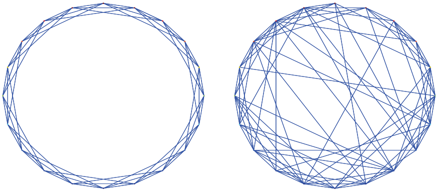
- Projection images $P_1, P_2, \ldots, P_n$ with unknown rotations $R_1, R_2, \ldots, R_n \in SO(3)$
- Rotationally Invariant Distances (RID)

$$d_{RID}(i,j) = \min_{O \in SO(2)} \|P_i - OP_j\|$$

- Cluster the images using K-means.
- Images are not centered; also possible to include translations and to optimize over the special Euclidean group.
- Problem with this approach: outliers.
- At low SNR images with completely different viewing directions may have relatively small d_{RID} (noise aligns well, instead of underlying signal).

Outliers: Small World Graph on S^2

- Define graph $G = (V, E)$ by $\{i, j\} \in E \iff d_{RID}(i, j) \leq \varepsilon$.



- Optimal rotation angles

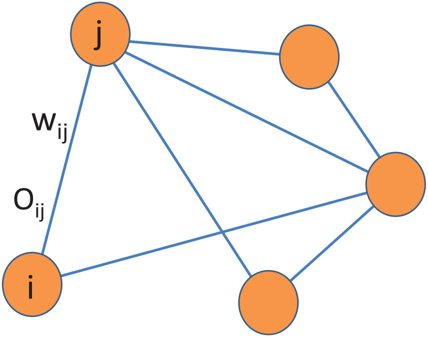
$$O_{ij} = \underset{O \in SO(2)}{\operatorname{argmin}} \|P_i - OP_j\|, \quad i, j = 1, \ldots, n.$$

- Triplet consistency relation – good triangles

$$O_{ij} O_{jk} O_{ki} \approx Id.$$

- How to use information of optimal rotations in a systematic way? Vector Diffusion Maps

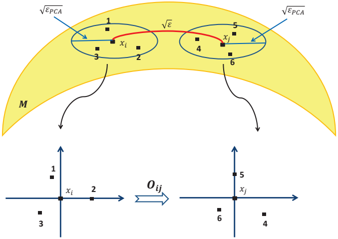
Vector Diffusion Maps: Setup

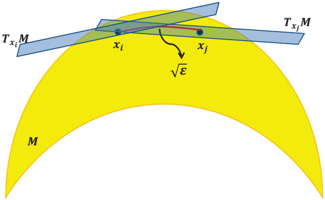


In VDM, the relationships between data points (e.g., cryo-EM images) are represented as a weighted graph, where the weights w_{ij} describing affinities between data points are accompanied by linear orthogonal transformations O_{ij}.

Manifold Learning: Point cloud in $\mathbb{R}^p$

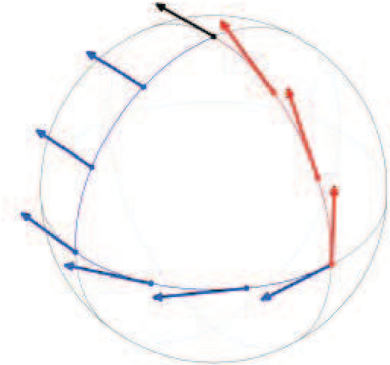
- $x_1, x_2, \dots, x_n \in \mathbb{R}^p$.
- Manifold assumption: $x_1, \dots, x_n \in \mathcal{M}^d$, with $d \ll p$.
- Local Principal Component Analysis (PCA) gives an approximate orthonormal basis O_i for the tangent space $T_{x_i}\mathcal{M}$.
- O_i is a $p \times d$ matrix with orthonormal columns: $O_i^T O_i = I_{d \times d}$.
- Alignment: $O_{ij} = \operatorname{argmin}_{O \in O(d)} \|O - O_i^T O_j\|_{HS}$ (computed through the singular value decomposition of $O_i^T O_j$).





Parallel Transport

- O_{ij} approximates the parallel transport operator $P_{x_i,x_j} : T_{x_j}\mathcal{M} \to T_{x_i}\mathcal{M}$



Vector diffusion mapping: S and D

- Symmetric $nd \times nd$ matrix S:

$$S(i,j) = \begin{cases} w_{ij} O_{ij} & (i,j) \in E, \\ 0_{d \times d} & (i,j) \notin E. \end{cases}$$

  $n \times n$ blocks, each of which is of size $d \times d$.

- Diagonal matrix D of the same size, where the diagonal $d \times d$ blocks are scalar matrices with the weighted degrees:

$$D(i,i) = \deg(i) I_{d \times d},$$

  and

$$\deg(i) = \sum_{j:(i,j) \in E} w_{ij}$$

$D^{-1}S$ as an averaging operator for vector fields

- The matrix $D^{-1}S$ can be applied to vectors v of length nd, which we regard as n vectors of length d, such that $v(i)$ is a vector in $\mathbb{R}^d$ viewed as a vector in $T_{x_i}\mathcal{M}$. The matrix $D^{-1}S$ is an averaging operator for vector fields, since

$$(D^{-1}Sv)(i) = \frac{1}{\deg(i)} \sum_{j:(i,j)\in E} w_{ij} O_{ij} v(j).$$

  This implies that the operator $D^{-1}S$ transport vectors from the tangent spaces $T_{x_j}\mathcal{M}$ (that are nearby to $T_{x_i}\mathcal{M}$) to $T_{x_i}\mathcal{M}$ and then averages the transported vectors in $T_{x_i}\mathcal{M}$.

Affinity between nodes based on consistency of transformations

- In the VDM framework, we define the affinity between i and j by considering all paths of length t connecting them, but instead of just summing the weights of all paths, we *sum the transformations*.
- Every path from j to i may result in a different transformation (like parallel transport due to curvature).
- When adding transformations of different paths, cancelations may happen.
- We define the affinity between i and j as the consistency between these transformations.
- $D^{-1}S$ is similar to the symmetric matrix $\tilde{S}$

$$\tilde{S} = D^{-1/2} S D^{-1/2}$$

- We define the affinity between i and j as

$$\|\tilde{S}^{2t}(i,j)\|_{HS}^2 = \frac{\deg(i)}{\deg(j)} \|(D^{-1}S)^{2t}(i,j)\|_{HS}^2.$$

Embedding into a Hilbert Space

- Since $\tilde{S}$ is symmetric, it has a complete set of eigenvectors $\{v_l\}_{l=1}^{nd}$ and eigenvalues $\{\lambda_i\}_{l=1}^{nd}$ (ordered as $|\lambda_1| \geq |\lambda_2| \geq \ldots \geq |\lambda_{nd}|$).
- Spectral decompositions of $\tilde{S}$ and $\tilde{S}^{2t}$:

$$\tilde{S}(i,j) = \sum_{l=1}^{nd} \lambda_l v_l(i) v_l(j)^T, \quad \text{and} \quad \tilde{S}^{2t}(i,j) = \sum_{l=1}^{nd} \lambda_l^{2t} v_l(i) v_l(j)^T,$$

  where $v_l(i) \in \mathbb{R}^d$ for $i = 1, \ldots, n$ and $l = 1, \ldots, nd$.
- The HS norm of $\tilde{S}^{2t}(i,j)$ is calculated using the trace:

$$\|\tilde{S}^{2t}(i,j)\|_{HS}^2 = \sum_{l,r=1}^{nd} (\lambda_l \lambda_r)^{2t} \langle v_l(i), v_r(i) \rangle \langle v_l(j), v_r(j) \rangle.$$

- The affinity $\|\tilde{S}^{2t}(i,j)\|_{HS}^2 = \langle V_t(i), V_t(j) \rangle$ is an inner product for the finite dimensional Hilbert space $\mathbb{R}^{(nd)^2}$ via the mapping V_t:

$$V_t : i \mapsto \left((\lambda_l \lambda_r)^t \langle v_l(i), v_r(i) \rangle \right)_{l,r=1}^{nd}.$$

Vector Diffusion Distance

- The vector diffusion mapping is defined as

$$V_t : i \mapsto \left((\lambda_l \lambda_r)^t \langle v_l(i), v_r(i) \rangle \right)_{l,r=1}^{nd}.$$

- The vector diffusion distance between nodes i and j is denoted $d_{\text{VDM},t}(i,j)$ and is defined as

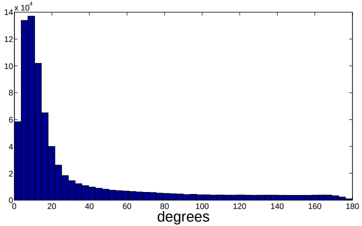
$$d^2_{\text{VDM},t}(i,j) = \langle V_t(i), V_t(i) \rangle + \langle V_t(j), V_t(j) \rangle - 2\langle V_t(i), V_t(j) \rangle.$$

- Other normalizations of the matrix S are possible and lead to slightly different embeddings and distances (similar to diffusion maps).
- The matrices $I - \tilde{S}$ and $I + \tilde{S}$ are positive semidefinite, because

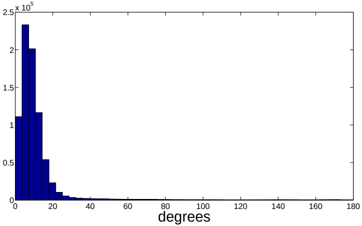
$$v^T(I \pm D^{-1/2} S D^{-1/2})v = \sum_{(i,j)\in E} \left\| \frac{v(i)}{\sqrt{\deg(i)}} \pm \frac{w_{ij} O_{ij} v(j)}{\sqrt{\deg(j)}} \right\|^2 \geq 0,$$

for any $v \in \mathbb{R}^{nd}$. Therefore, $\lambda_l \in [-1, 1]$. As a result, the vector diffusion mapping and distances can be well approximated by using only the few largest eigenvalues and their corresponding eigenvectors.

Application to the class averaging problem in Cryo-EM



(a) Neighbors are identified using d_{RID}



(b) Neighbors are identified using $d_{\mathrm{VDM},t=2}$

Figure: SNR=1/64: Histogram of the angles (x-axis, in degrees) between the viewing directions of each image (out of 40000) and it 40 neighboring images. Left: neighbors are identified using the original rotationally invariant distances d_{RID}. Right: neighbors are post identified using vector diffusion distances.

The Hairy Ball Theorem

- There is no non-vanishing continuous tangent vector field on the sphere.
- Cannot find O_i such that $O_{ij} = O_i O_j^{-1}$.
- No global rotational alignment of all images.

Convergence Theorem to the Connection-Laplacian

Let $\iota : \mathcal{M} \hookrightarrow \mathbb{R}^p$ be a smooth d-dim closed Riemannian manifold embedded in $\mathbb{R}^p$, with metric g induced from the canonical metric on $\mathbb{R}^p$, and the data set $\{x_i\}_{i=1,\ldots,n}$ is independently uniformly distributed over $\mathcal{M}$. Let $K \in C^2(\mathbb{R}^+)$ be a positive kernel function decaying exponentially, that is, there exist $T > 0$ and $C > 0$ such that $K(t) \leq Ce^{-t}$ when $t > T$. For $\epsilon > 0$, let $K_\epsilon(x_i, x_j) = K\left(\frac{\|\iota(x_i)-\iota(x_j)\|_{\mathbb{R}^p}}{\sqrt{\epsilon}}\right)$. Then, for $X \in C^3(T\mathcal{M})$ and for all x_i almost surely we have

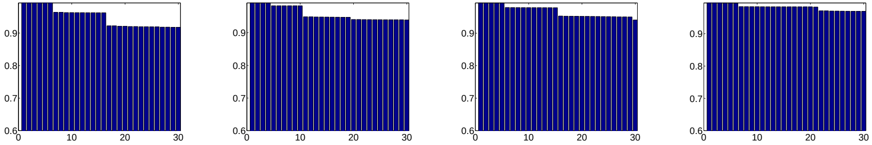
$$\lim_{\epsilon\to 0}\lim_{n\to\infty}\frac{1}{\epsilon}\left[\frac{\sum_{j=1}^n K_\epsilon(x_i,x_j)\,O_{ij}X_j}{\sum_{j=1}^n K_\epsilon(x_i,x_j)} - X_i\right] = \frac{m_2}{2dm_0}\left(\langle \iota_*\nabla^2 X(x_i), e_l\rangle\right)_{l=1}^d,$$

where ∇^2 is the connection Laplacian, $X_i \equiv (\langle \iota_* X(x_i), e_l\rangle)_{l=1}^d \in \mathbb{R}^d$ for all i, $\{e_l(x_i)\}_{l=1,\ldots,d}$ is an orthonormal basis of $\iota_* T_{x_i}\mathcal{M}$, $m_l = \int_{\mathbb{R}^d} \|x\|^l K(\|x\|)\mathrm{d}x$, and O_{ij} is the optimal orthogonal transformation determined by the algorithm in the alignment step.

Example: Connection-Laplacian for S^d embedded in $\mathbb{R}^{d+1}$

The connection-Laplacian commutes with rotations and the eigenvalues and eigen-vector-fields are calculated using representation theory:

$$S^2 : 6, 10, 14, \ldots.$$
$$S^3 : 4, 6, 9, 16, 16, \ldots.$$
$$S^4 : 5, 10, 14, \ldots.$$
$$S^5 : 6, 15, 20, \ldots.$$



(a) S^2 (b) S^3 (c) S^4 (d) S^5

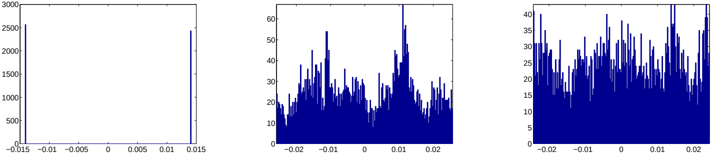
Figure: Bar plots of the largest 30 eigenvalues of $D^{-1}S$ for $n = 8000$ points uniformly distributed over spheres of different dimensions.

More applications of VDM: Orientability from a point cloud

Encode the information about reflections in a symmetric $n \times n$ matrix Z with entries

$$Z_{ij} = \begin{cases} \det O_{ij} & (i,j) \in E, \\ 0 & (i,j) \notin E. \end{cases}$$

That is, $Z_{ij} = 1$ if no reflection is needed, $Z_{ij} = -1$ if a reflection is needed, and $Z_{ij} = 0$ if the points are not nearby. Normalize Z by the node degrees.



(a) S^2 (b) Klein bottle (c) $\mathbb{R}P^2$

Figure: Histogram of the values of the top eigenvector of $D^{-1}Z$.

Orientable Double Covering

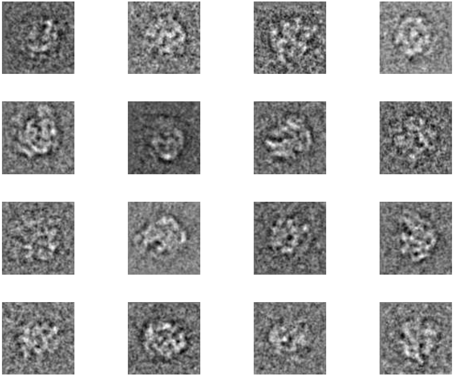
Embedding obtained using the eigenvectors of the (normalized) matrix

$$\begin{bmatrix} Z & -Z \\ -Z & Z \end{bmatrix} = \begin{pmatrix} 1 & -1 \\ -1 & 1 \end{pmatrix} \otimes Z,$$

Figure: Left: the orientable double covering of $\mathbb{R}P(2)$, which is S^2; Middle: the orientable double covering of the Klein bottle, which is T^2; Right: the orientable double covering of the Möbius strip, which is a cylinder.

3D Reconstruction (not optimal)

- 27000 images of the 50S ribosomal subunit were class averaged into 3000 classes using available software (Imagic).



3D Reconstruction (not optimal)

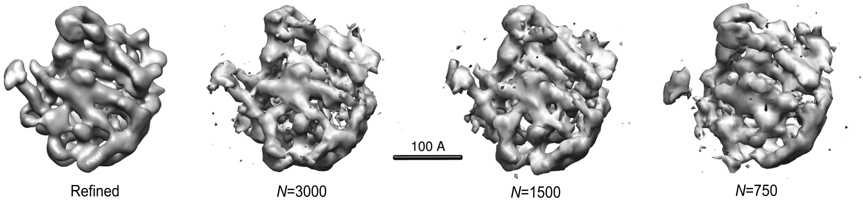


Figure: The refined model is from an Imagic reference-based alignment of the 27,000 particle data set used in this study and refined to 15Å resolution (0.5 Fourier shell correlation threshold criteria). The structures were also flipped about the z-axis such that their handedness is consistent with the X-ray structure of T. Steitz.

Ongoing Research in cryo-EM

- Molecules with symmetries
- Heterogeneity problem
- Signal/Image processing

Summary and Outlook

- VDM is a generalization of diffusion maps: from functions to vector fields
- A way to globally connect local PCAs.
- Vector diffusion distance: a new metric for data points
- Noise robustness: random matrix theory
  (noise model – orthogonal transformations average to 0).
- Other higher order Laplacians from point clouds (e.g., the Hodge Laplacian).
- Revealing the topology of the data (e.g., orientability).
- Diffusion on orbit spaces $\mathcal{M}/G$.
- More applications

References

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- A. Singer, H.-T. Wu, "Orientability and Diffusion Maps", *Applied and Computational Harmonic Analysis*, *Applied and Computational Harmonic Analysis*, **31** (1), pp. 44–58 (2011).
- A. Singer, Z. Zhao, Y. Shkolnisky, R. Hadani, "Viewing Angle Classification of Cryo-Electron Microscopy Images using Eigenvectors", *SIAM Journal on Imaging Sciences*, **4** (2), pp. 723–759 (2011).

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