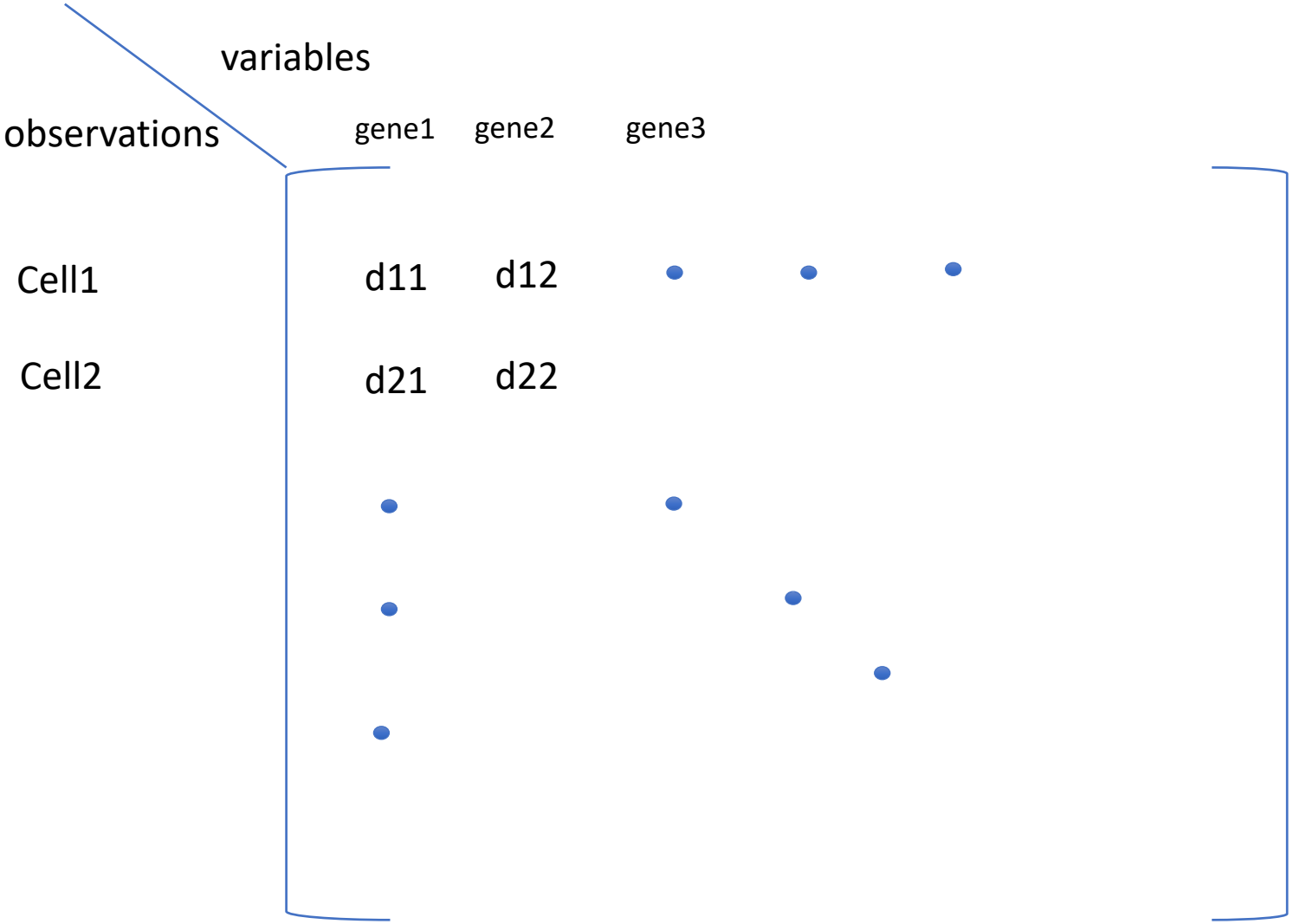
What's the last great TV show or movie you watched?

Day 2: Visualization, Dimensionality Reduction and Manifold Learning

Thinking about high dimensional data

Our Data is a High-dimensional Matrix



Features are dimensions

vector coordinate space

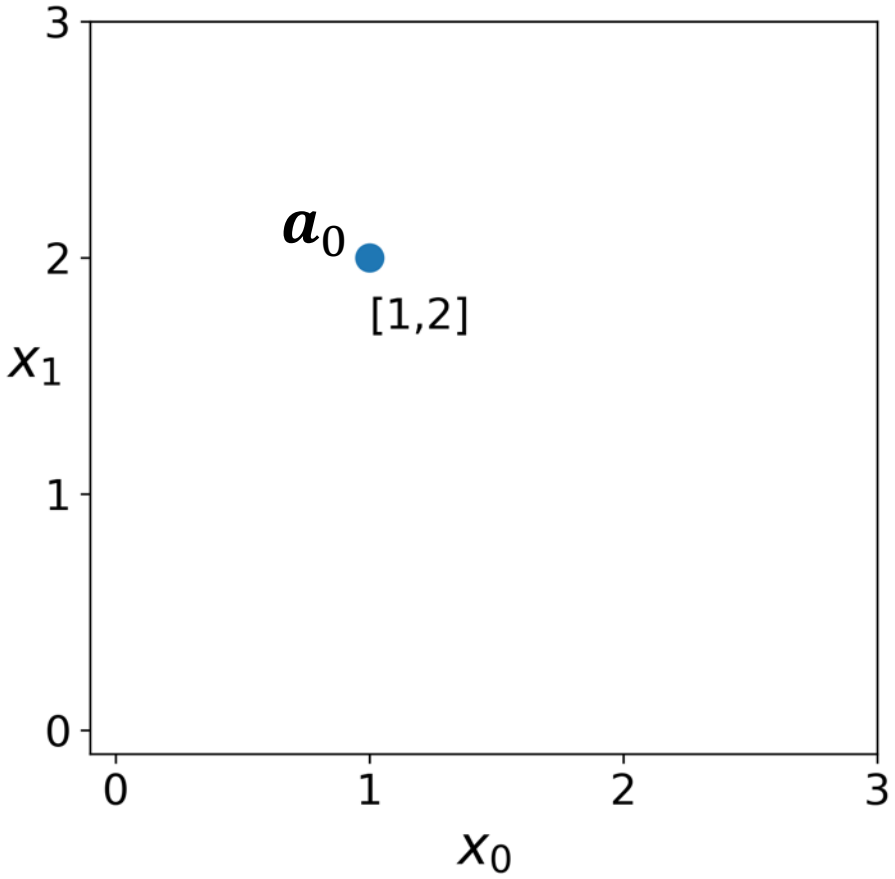
$\boldsymbol{a}_0 \in \mathbb{R}^2$

$\boldsymbol{a}_0 = [1,2]$

x_0 x_1

features

$\mathbb{R}^2$ two-dimensional space



$\boldsymbol{a}_{[:,0]}$

Features are dimensions

$\boldsymbol{a} \in \mathbb{R}^2$

$\boldsymbol{a} = [1,2]$

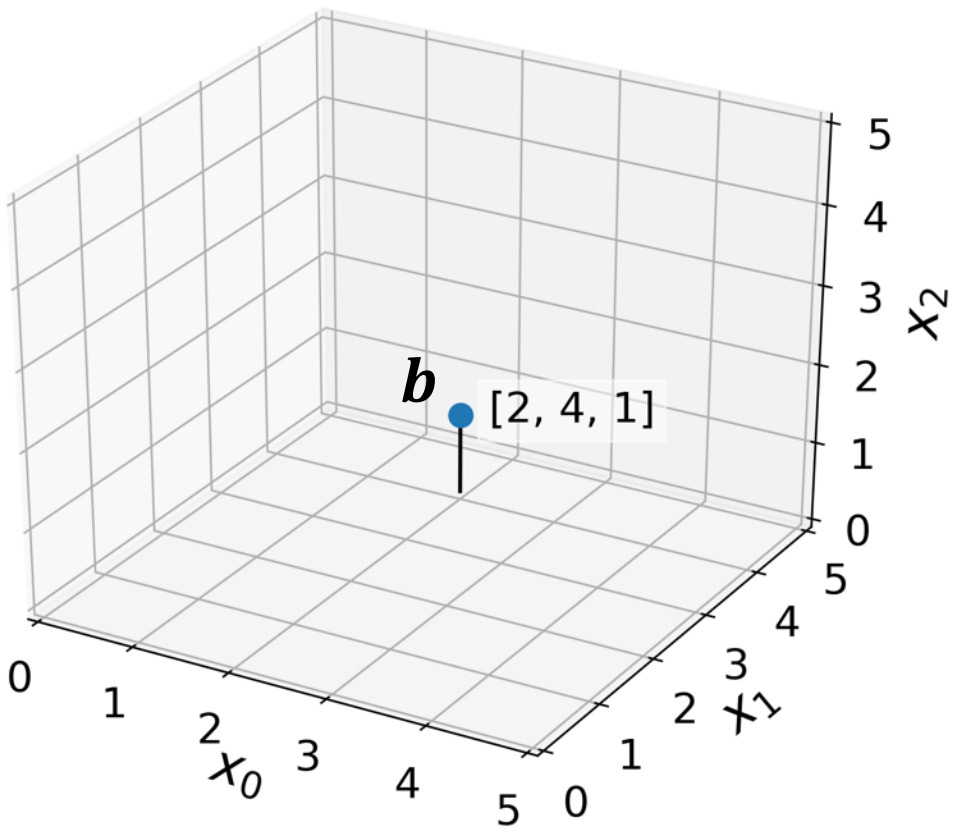
x_0 x_1

$\boldsymbol{b} \in \mathbb{R}^3$

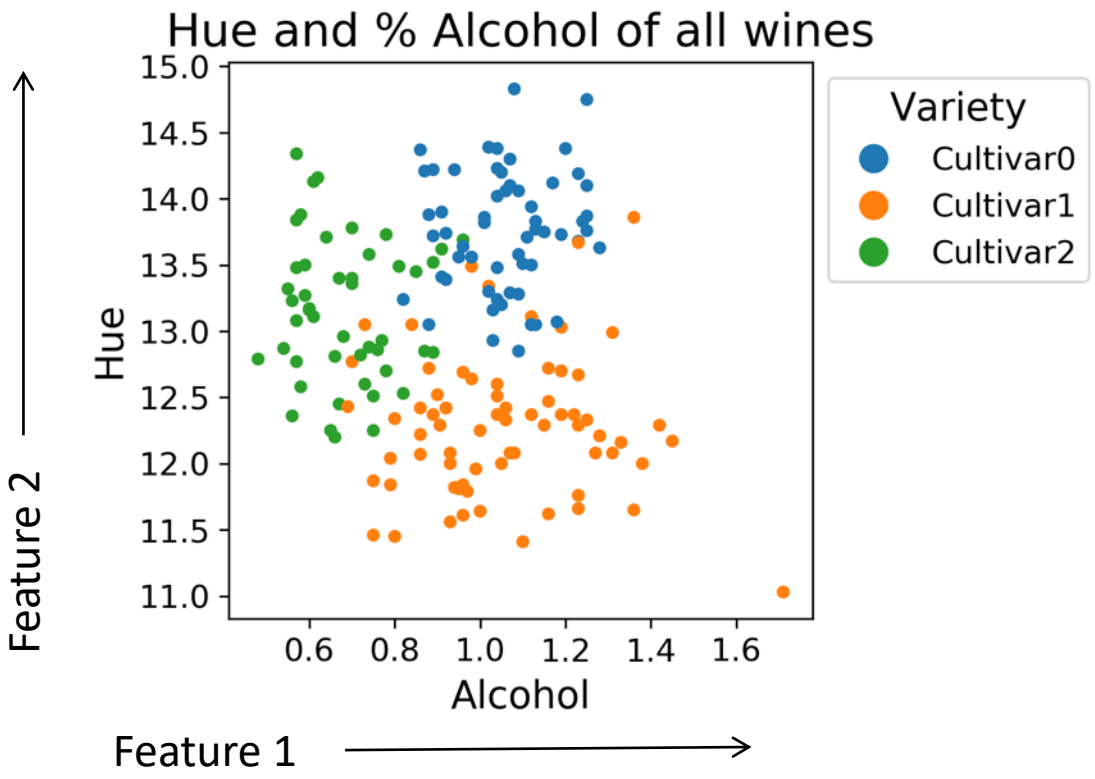
$\boldsymbol{b} = [2,4,1]$

x_0 x_1 x_2

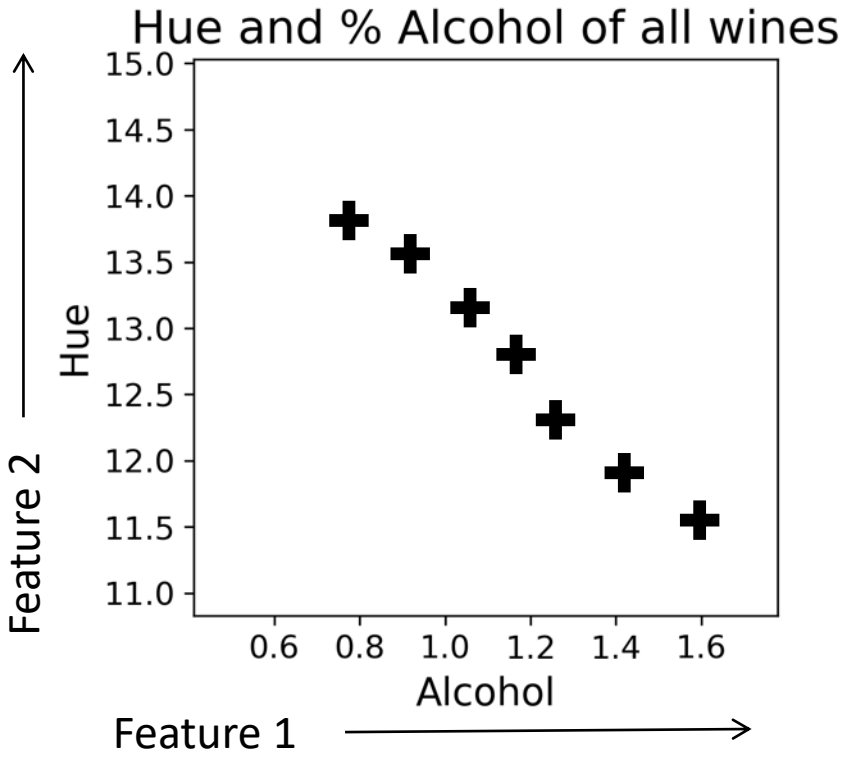
$\mathbb{R}^3$ three-dimensional space



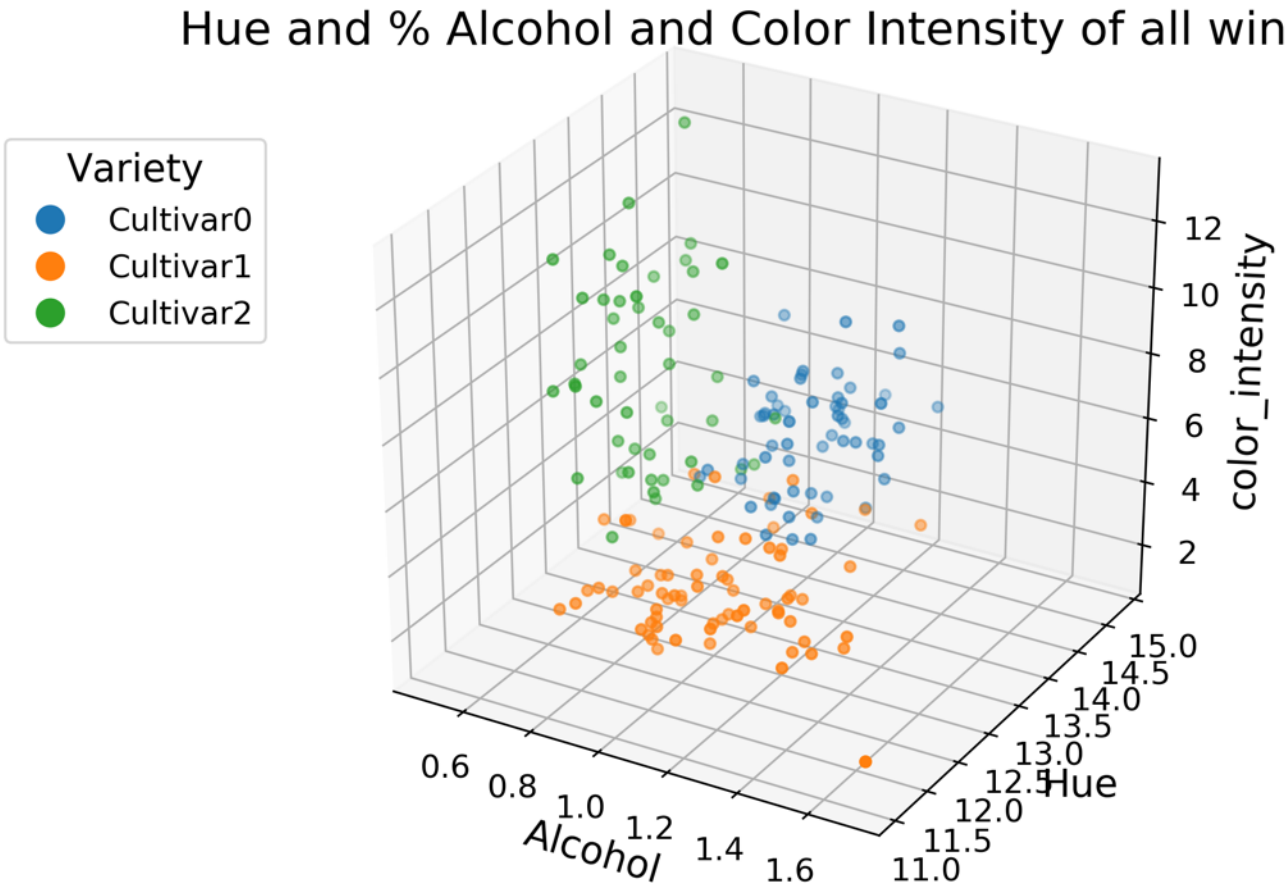
Features reveal structure



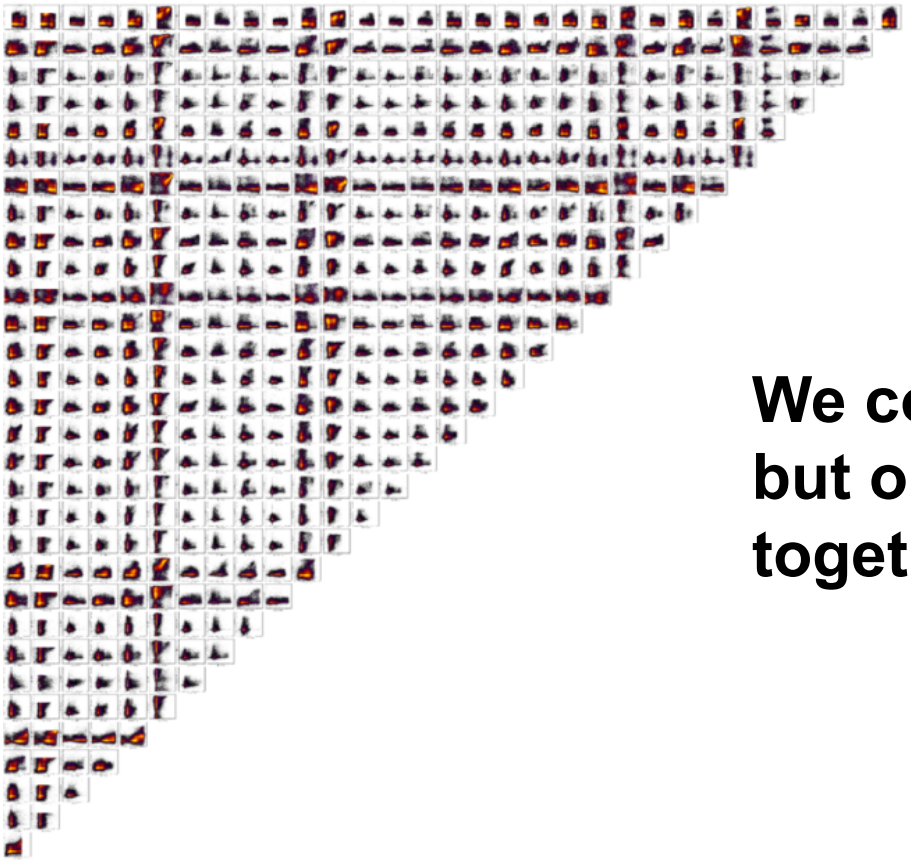
Many types of structure can exist in data



More Dimensions = More Accurate Structure



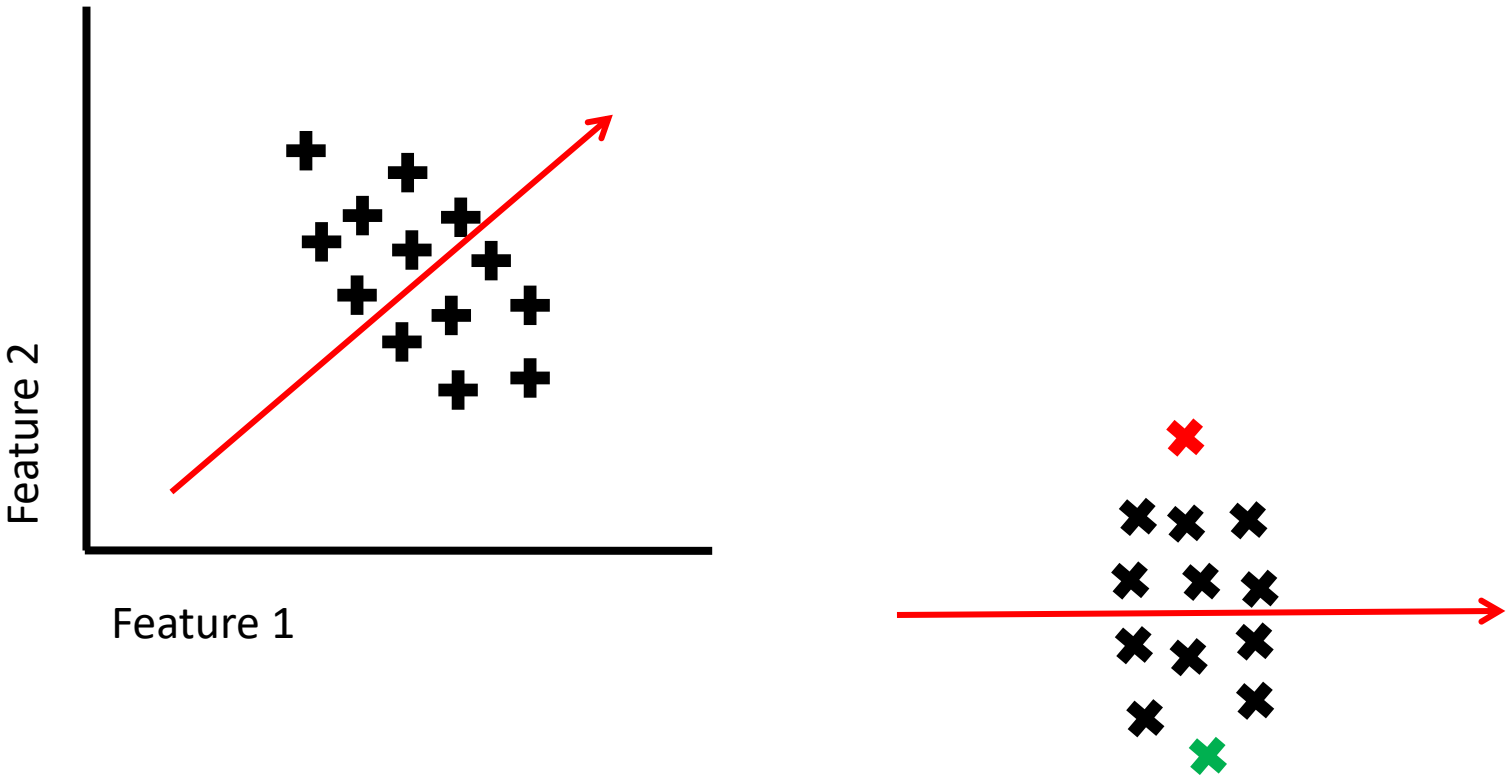
Problem: We can only see in 3D (not 20K D)



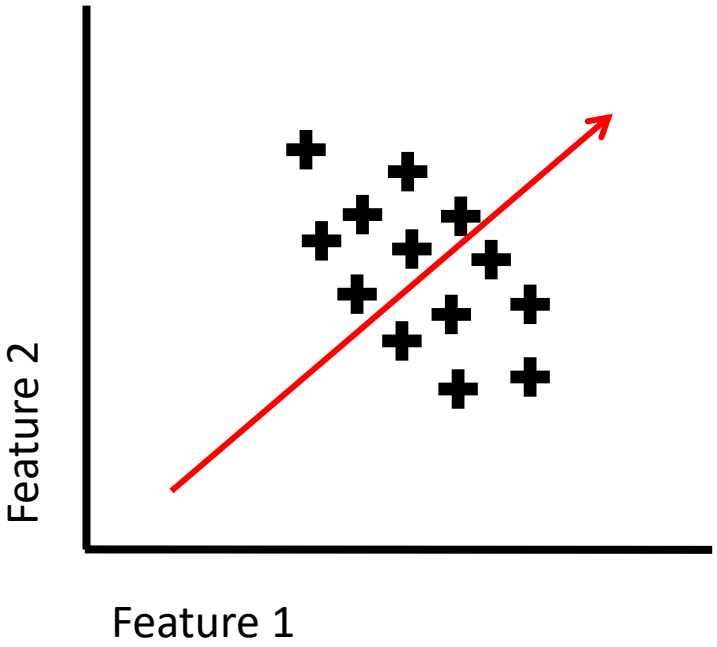
We could try all 2D pairs, but our brains can't put this together

Solution: Dimensionality Reduction

Thought Exercise: Reduce this to 1D

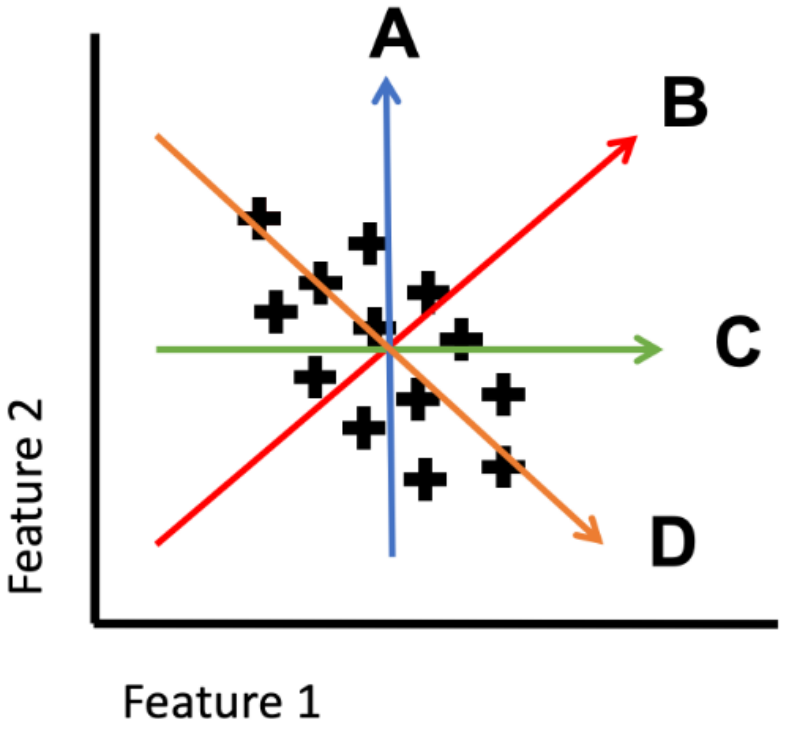


Thought Exercise: Reduce this to 1D



Most distant points on top of each other !

Which line do you think would be the best line to consider the data onto?



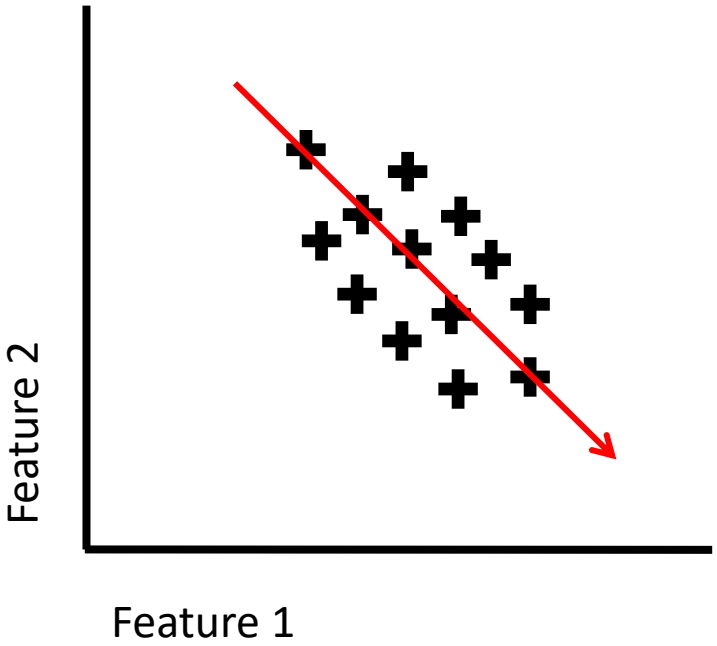
A

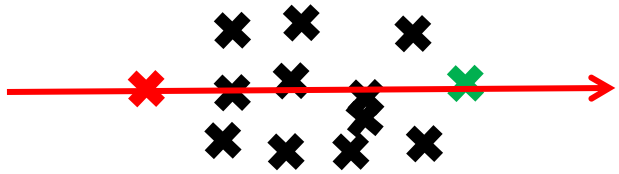
B

C

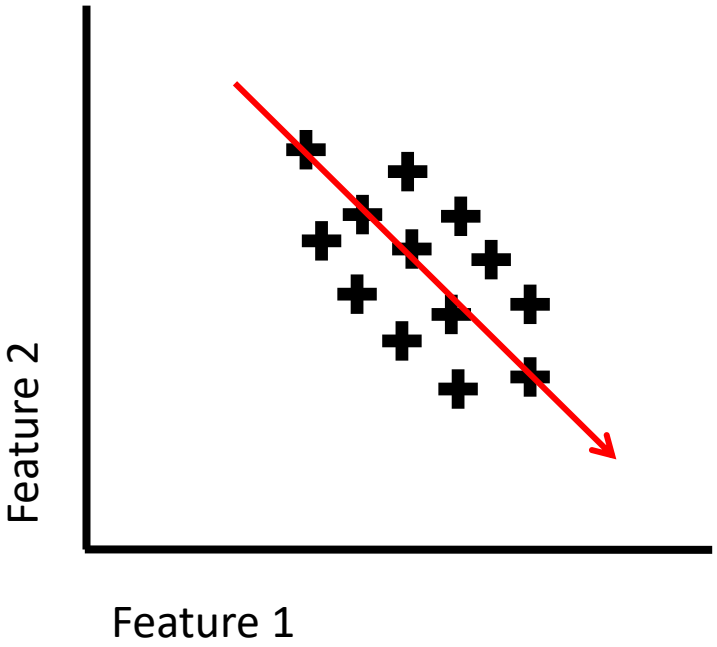
D

Thought Exercise: Reduce this to 1D





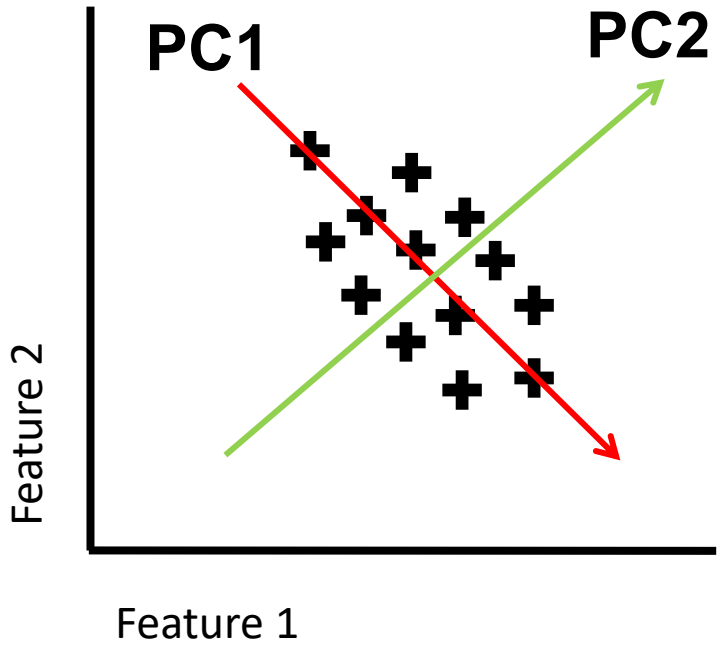
Thought Exercise: Reduce this to 1D



What is special about this line?

It explains most of the variance in the data

Principle Components Analysis



PCA linear directions in the data that explain the most variance

PC1 explains the most

PC2 explains the next most and is orthogonal to PC1

How do we find these directions?

Covariance Matrix

$$\mathbf{X} = (X_1, X_2, \ldots, X_n)^{\mathrm{T}}$$

$$\mathrm{K}_{X_i X_j} = \operatorname{cov}[X_i, X_j] = \mathrm{E}[(X_i - \mathrm{E}[X_i])(X_j - \mathrm{E}[X_j])]$$

$$\mathrm{K}_{\mathbf{XX}} = \begin{bmatrix} \mathrm{E}[(X_1 - \mathrm{E}[X_1])(X_1 - \mathrm{E}[X_1])] & \mathrm{E}[(X_1 - \mathrm{E}[X_1])(X_2 - \mathrm{E}[X_2])] & \cdots & \mathrm{E}[(X_1 - \mathrm{E}[X_1])(X_n - \mathrm{E}[X_n])] \\ \mathrm{E}[(X_2 - \mathrm{E}[X_2])(X_1 - \mathrm{E}[X_1])] & \mathrm{E}[(X_2 - \mathrm{E}[X_2])(X_2 - \mathrm{E}[X_2])] & \cdots & \mathrm{E}[(X_2 - \mathrm{E}[X_2])(X_n - \mathrm{E}[X_n])] \\ \vdots & \vdots & \ddots & \vdots \\ \mathrm{E}[(X_n - \mathrm{E}[X_n])(X_1 - \mathrm{E}[X_1])] & \mathrm{E}[(X_n - \mathrm{E}[X_n])(X_2 - \mathrm{E}[X_2])] & \cdots & \mathrm{E}[(X_n - \mathrm{E}[X_n])(X_n - \mathrm{E}[X_n])] \end{bmatrix}$$

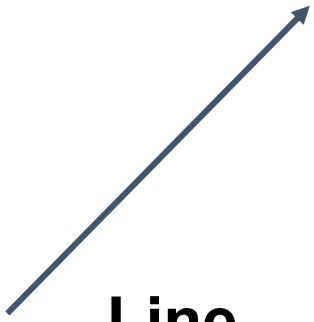
Matrices as Transformations

- Matrices only store data, but can also represent ***transformations***
- Specifically they are linear transformations
- They transform lines by changing their length and angle from origin

$$\begin{bmatrix} \cos(90) & -\sin(90) \\ \sin(90) & \cos(90) \end{bmatrix}$$

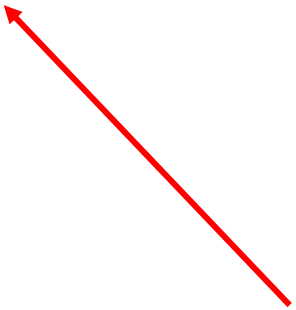
Rotation matrix

*



Line

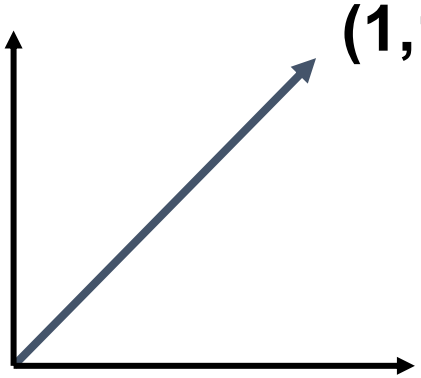
=



Rotated Line

Matrix–Vector Notation

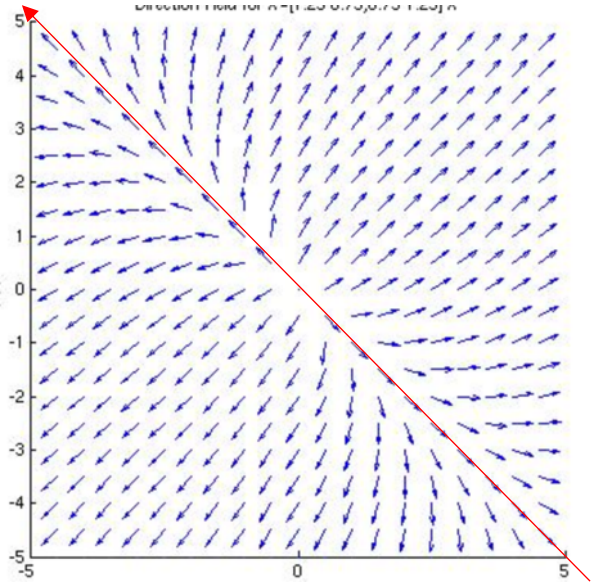
- Lines can be described as vectors from the origin



$$\begin{bmatrix} 1 \\ 1 \end{bmatrix}$$

$$\begin{bmatrix} \cos(90) & -\sin(90) \\ \sin(90) & \cos(90) \end{bmatrix} \begin{bmatrix} 1 \\ 1 \end{bmatrix} = \begin{bmatrix} -1 \\ 1 \end{bmatrix}$$

Eigenvectors



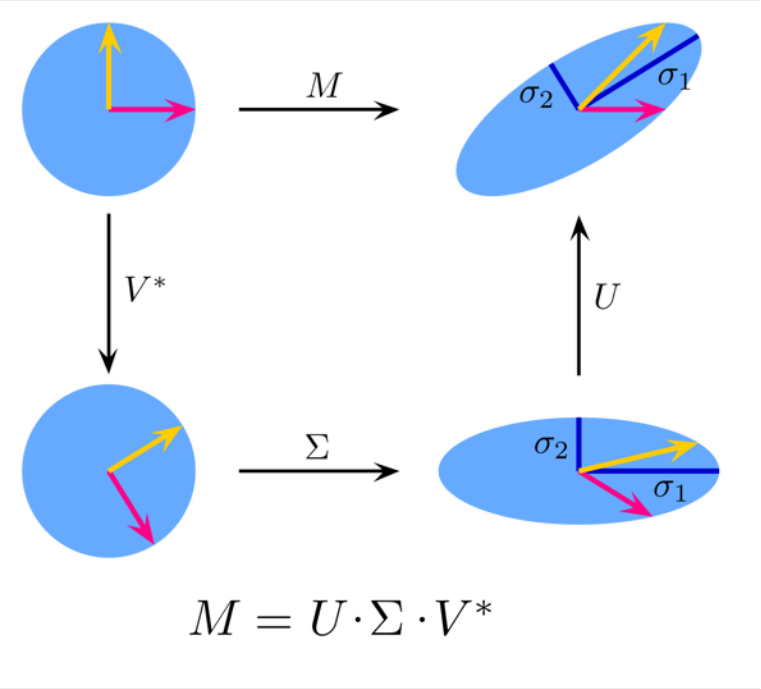
Rotation matrices rotate lines in only one direction

Other matrices can move different lines in different directions

- Such linear transformations have fixed points called *Eigenvectors*
- In other words, the transformation only ***stretches*** the vector and does not rotate it.

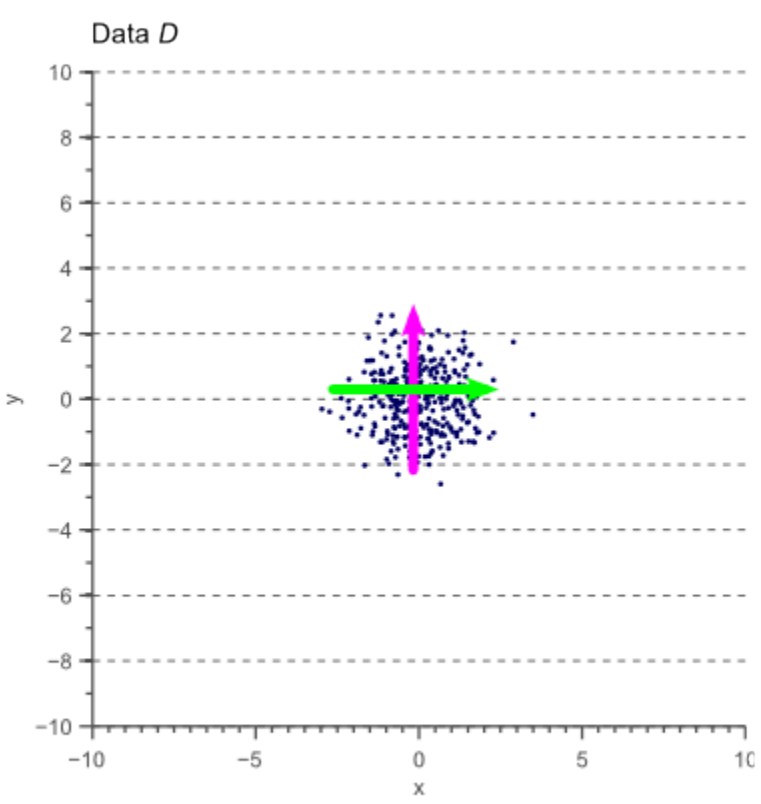
Eigendecomposition

- Eigenvectors can be used to decompose a linear transformation into a rotation + stretch + anti-rotation

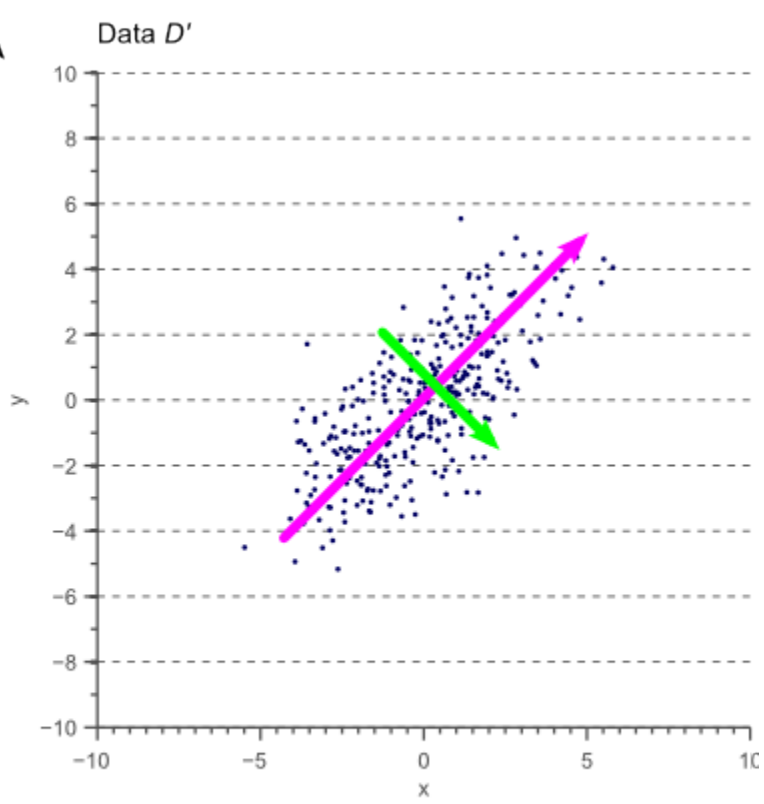


Non-square matrices
have similar OP called
Singular value decomposition

Eigenvectors of Covariance



$$D' = TD = RSD$$

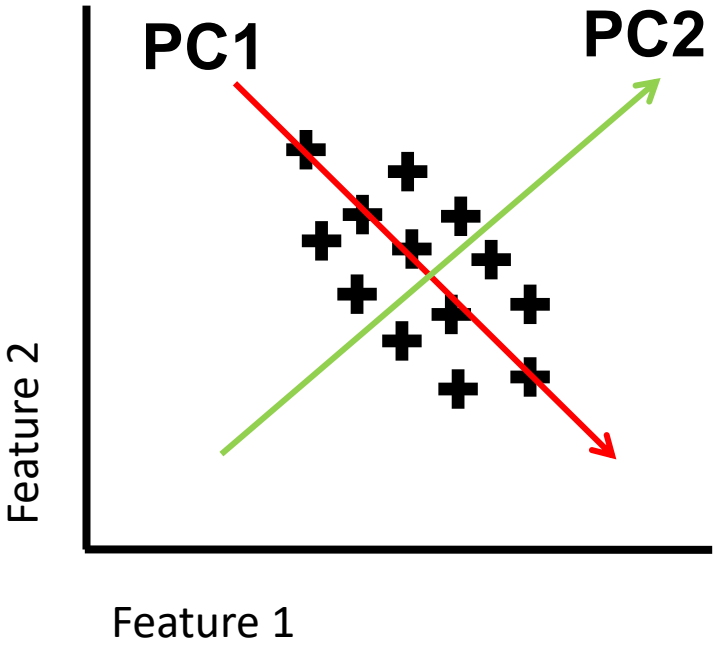


$$\Sigma = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}$$

$$\Sigma' = \begin{bmatrix} 4.25 & 3.10 \\ 3.10 & 4.29 \end{bmatrix} = RSSR^{T}$$

Matrix creates correlation structure of data on unit blob

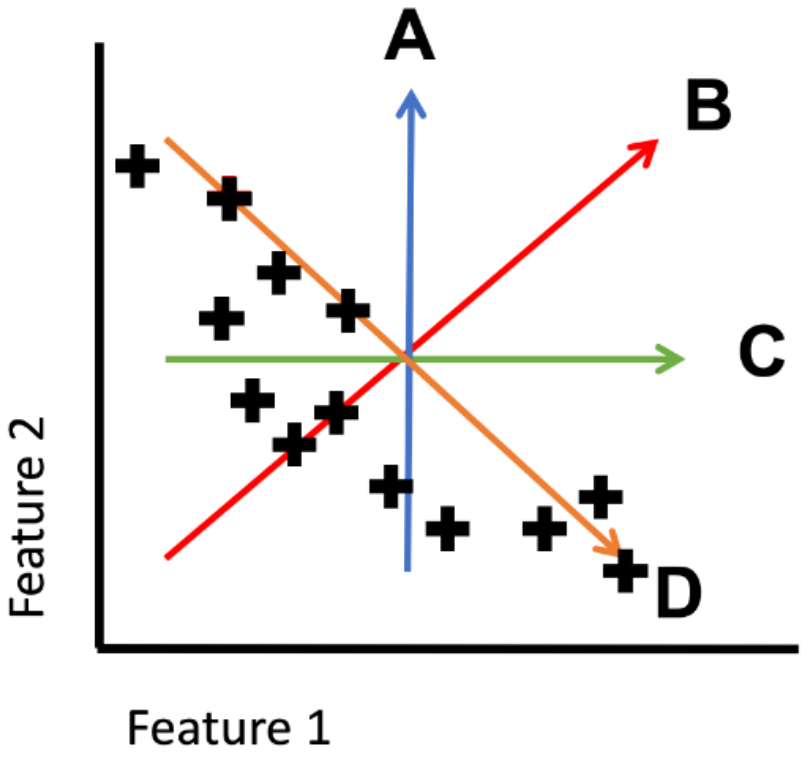
Principle Components Analysis



PC1 is first eigenvector (with Highest eigenvalue)

PC2 is next eigenvector

Which line would be PC1 for the following data?



A

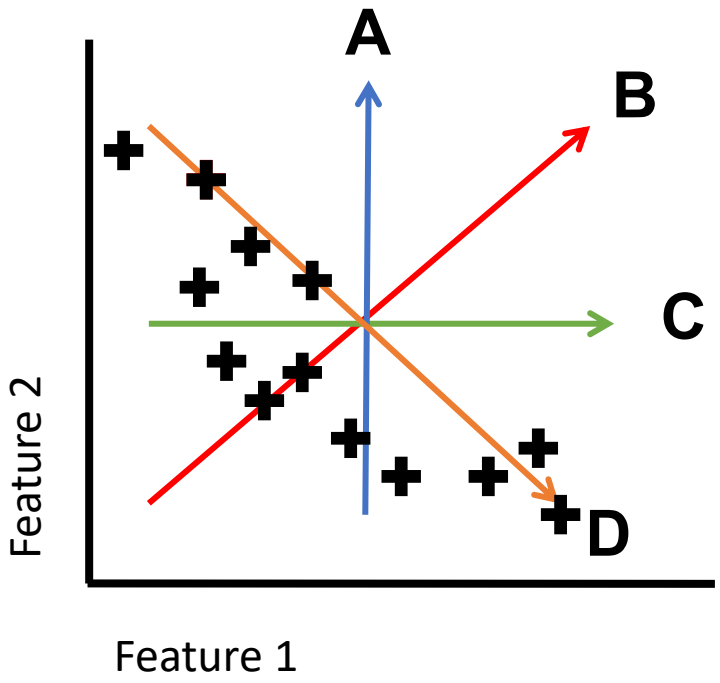
B

C

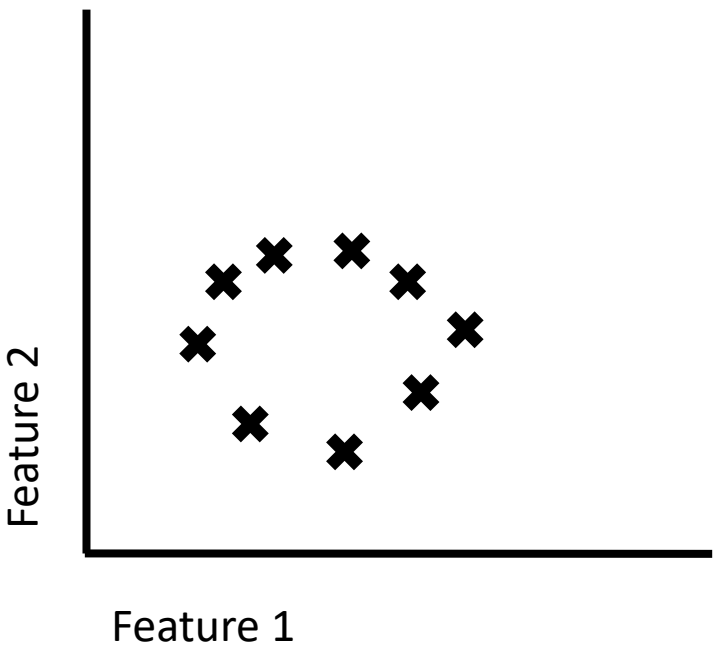
D

Quick quiz

Which line would be PC1 for the following data?



Non-linear structure



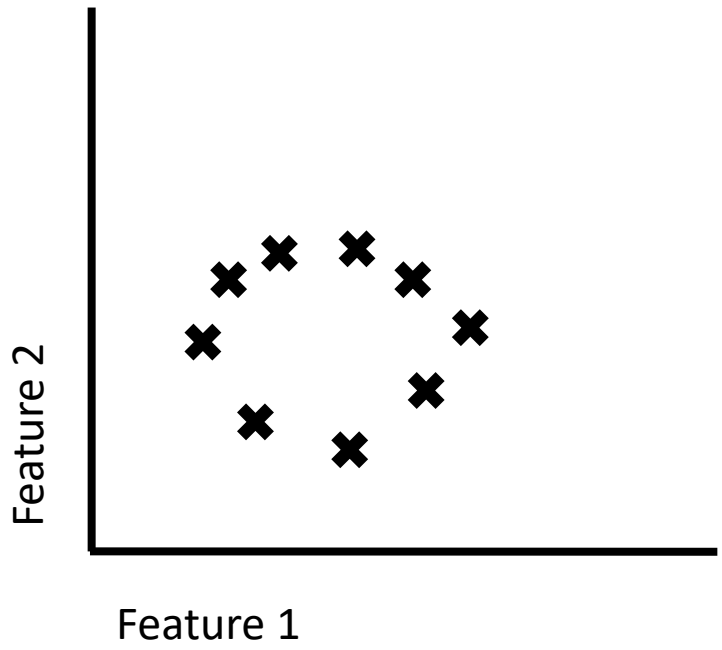
What if the data looked like this?

What line would be good
to project to here?

Non-linear dimensionality reduction

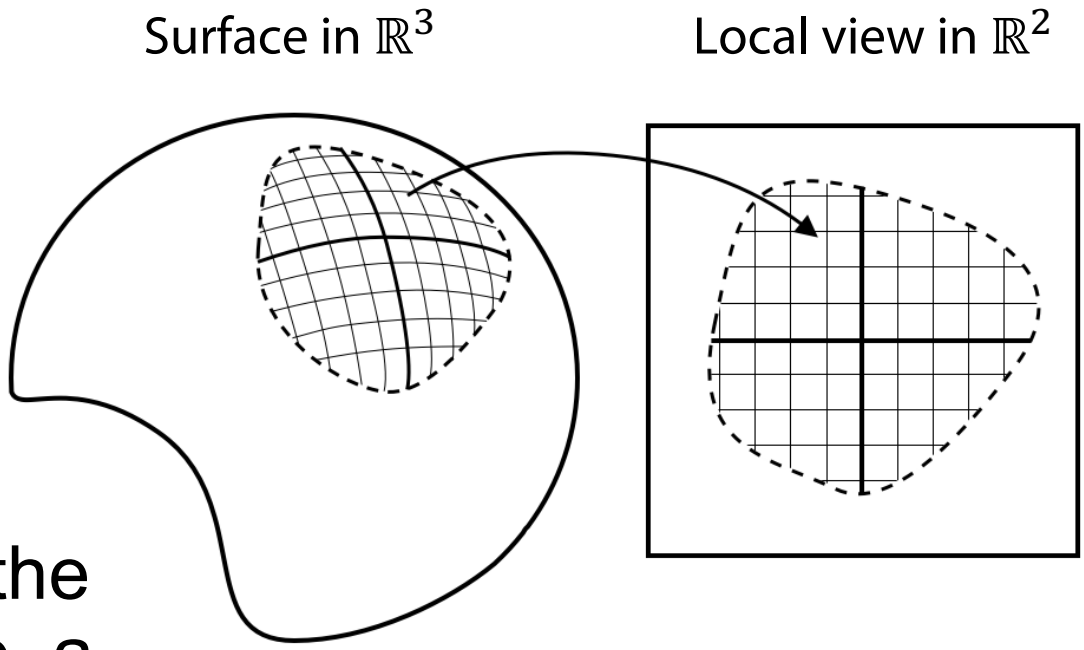
Non-linear dimensions

- To find non-linear or “coiled” dimensions in a dataset we have to understand, and describe the **shape** of the data
- The data can live in lower dimensions
- This can be abstractly called the data “manifold”

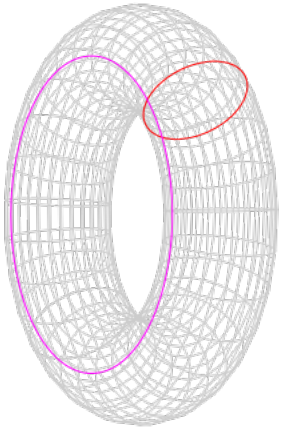


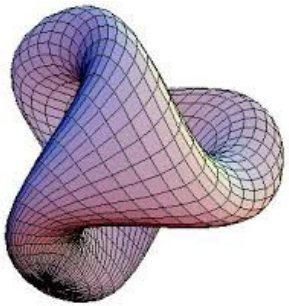
What is a manifold?

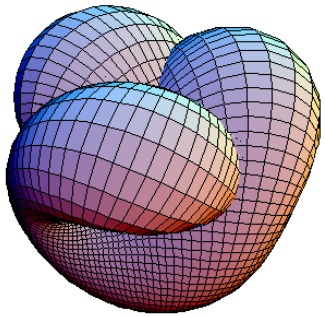
- Locally smooth
- Locally Euclidean
- Generally, lower dimensional than the ambient space (i.e. a subspace)

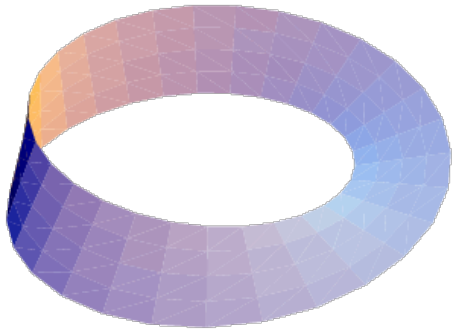


Examples of manifolds

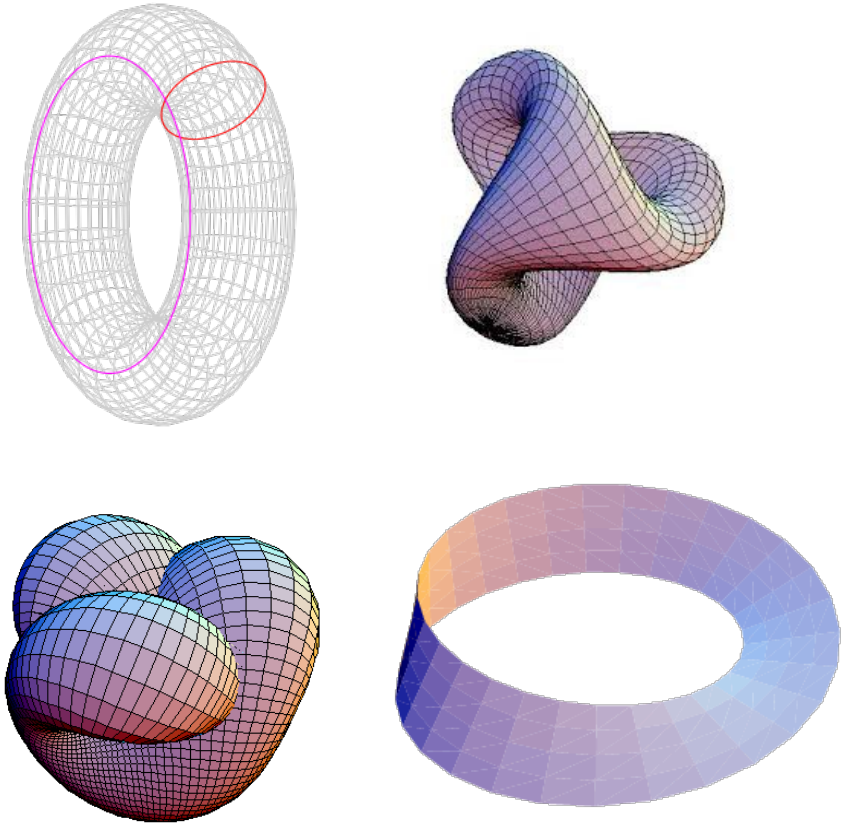




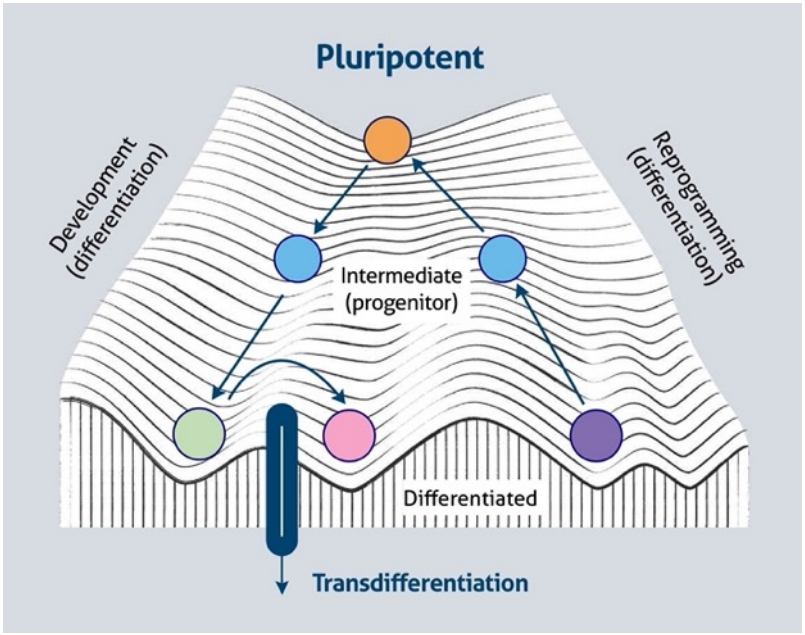




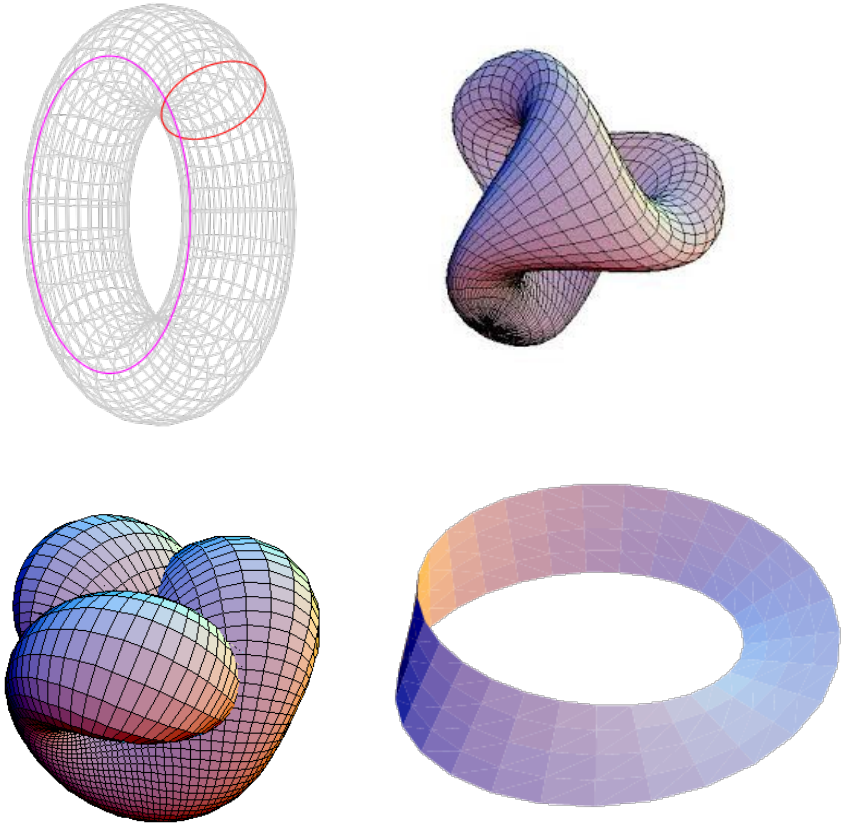
Examples of manifolds



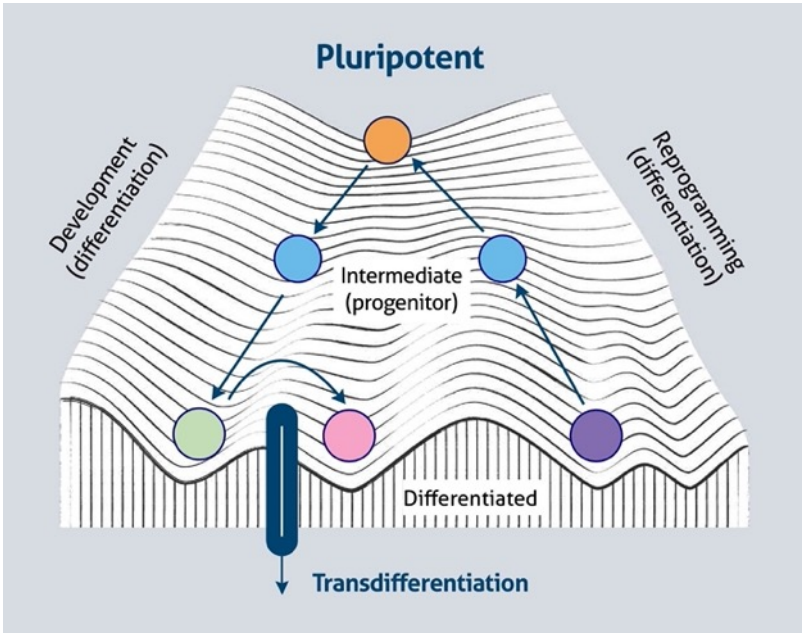
Waddington's landscape



Examples of manifolds

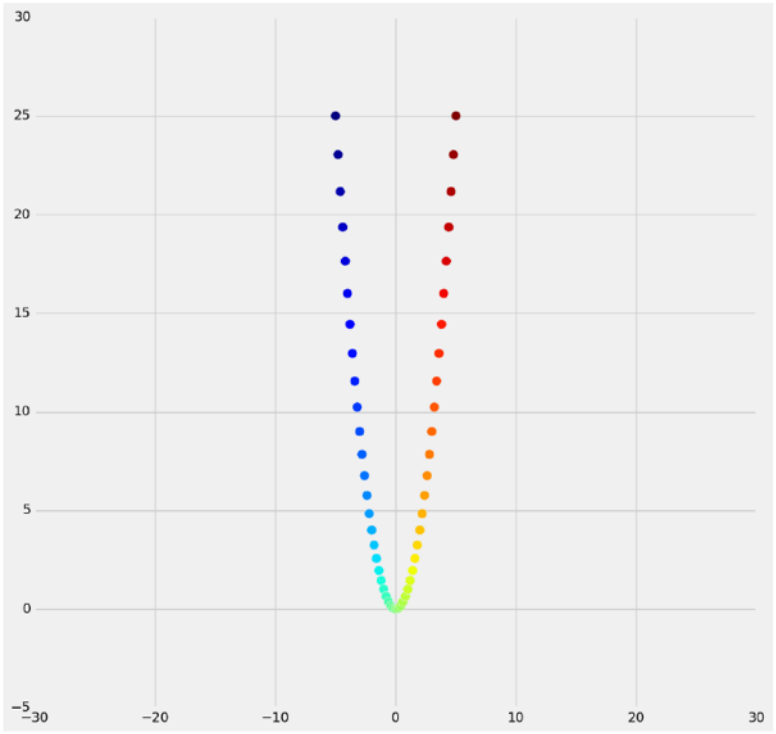


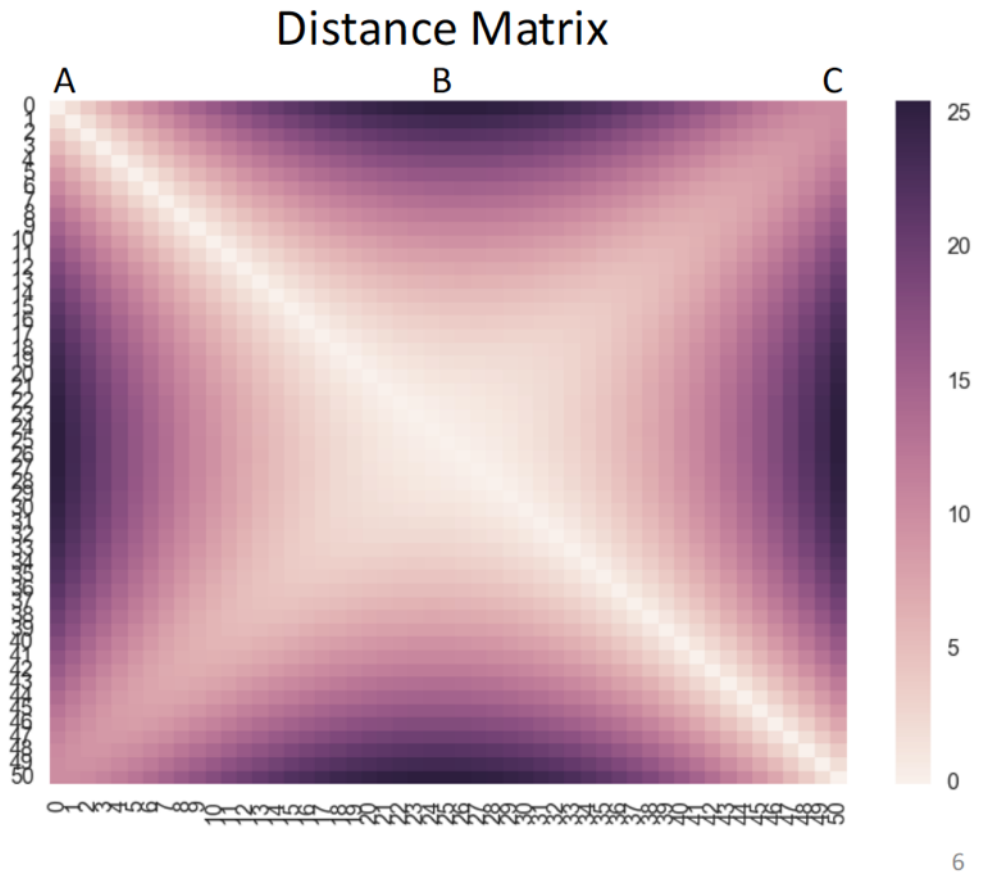
Waddington's landscape



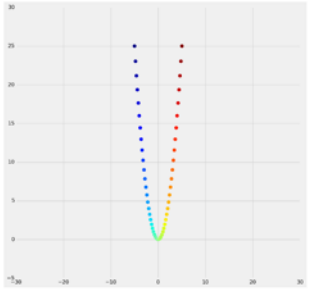
- Smooth transitions between states
- Small changes in gene expression are linear

Kernel functions measure “similarity” or “affinity” on a graph

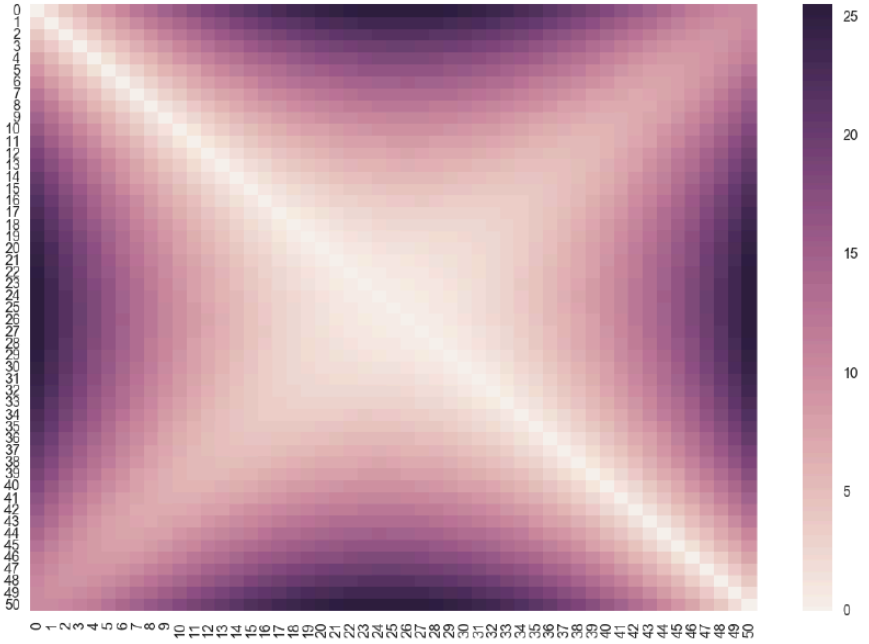




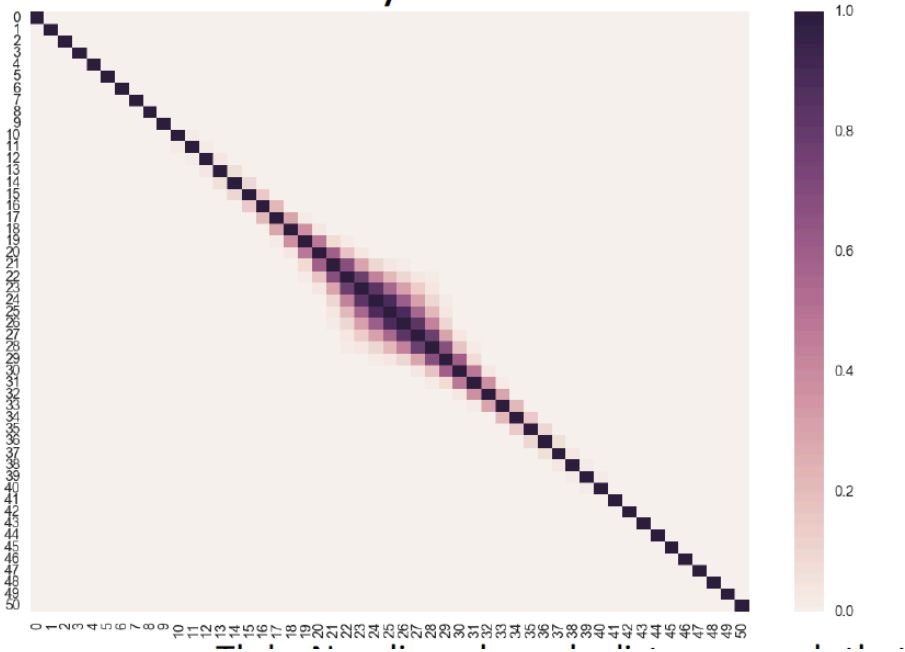
Affinity is the inverse of distance + locality



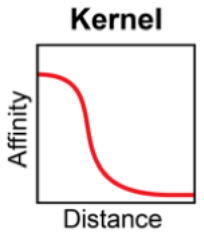
Distance Matrix



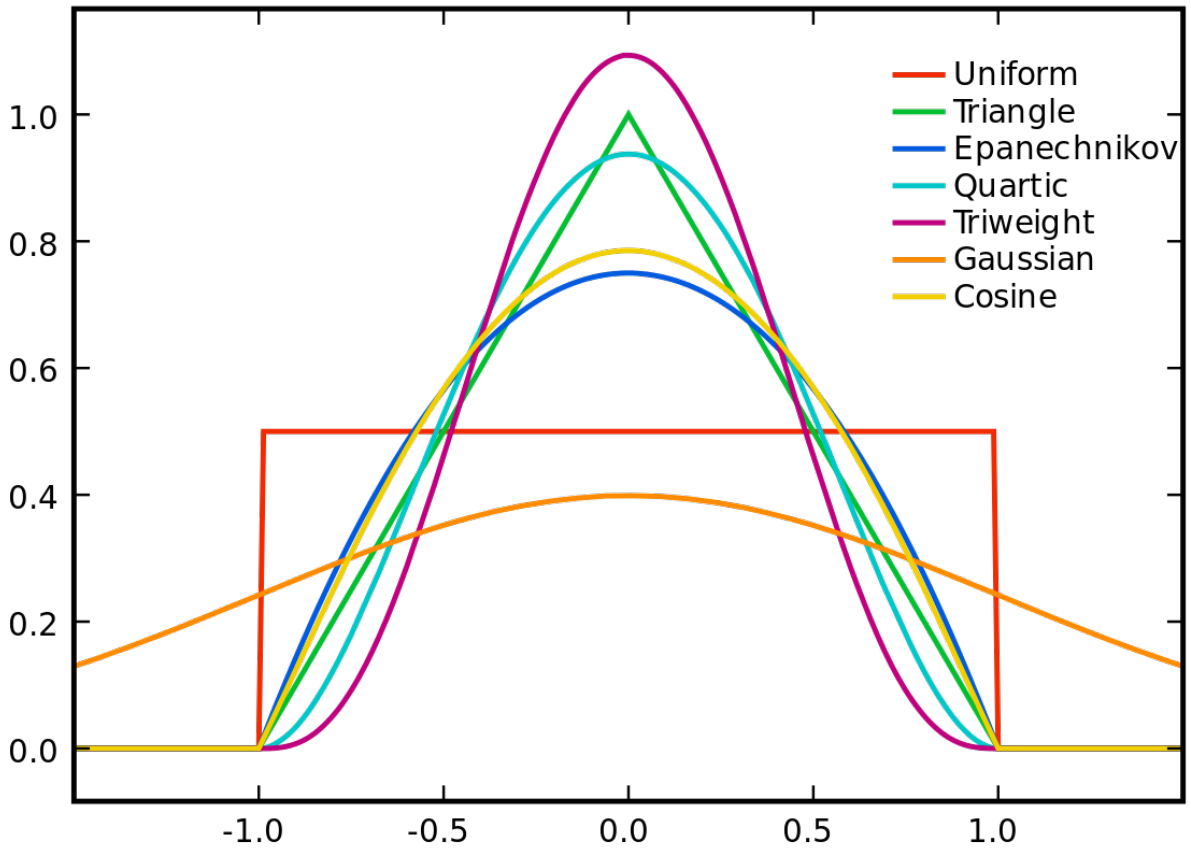
Affinity Matrix



$$Affinity_{i,j} = s_{i,j} = exp\left(-\frac{dist(x_i, x_j)^2}{2\sigma^2}\right)$$



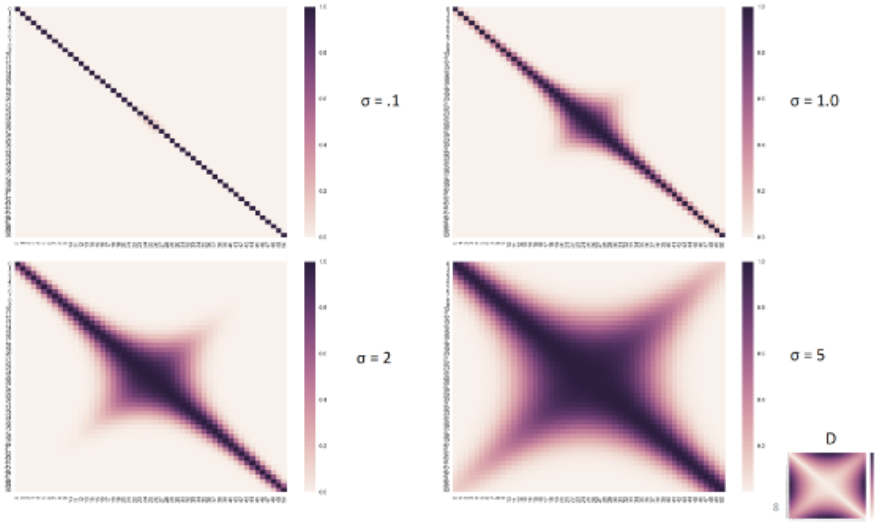
Distance to Affinity via Kernels



Real-valued
Non-negative
Symmetric

Affinities correlations in this hidden hypothetical space

Which value of sigma produces the graph with the least global connectivity



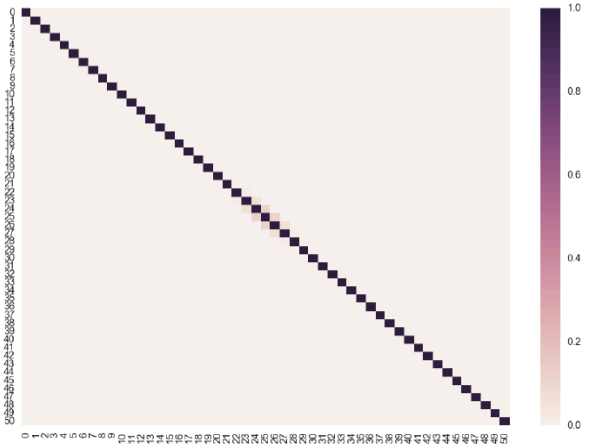
$\sigma = 0.1$

$\sigma = 1$

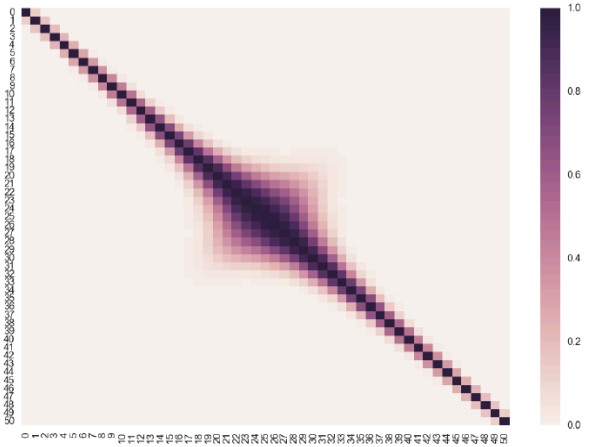
$\sigma = 2$

$\sigma = 5$

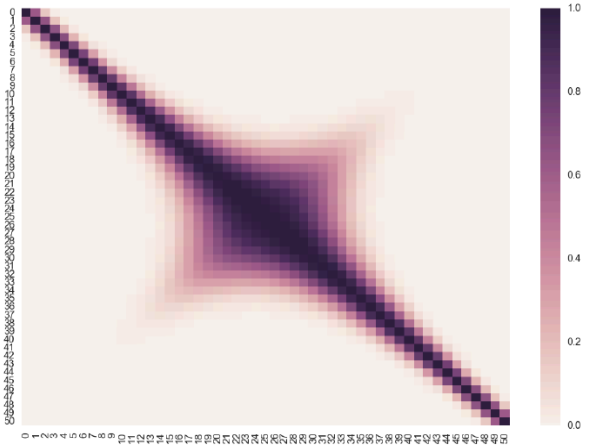
Effect of Changing Kernel Width



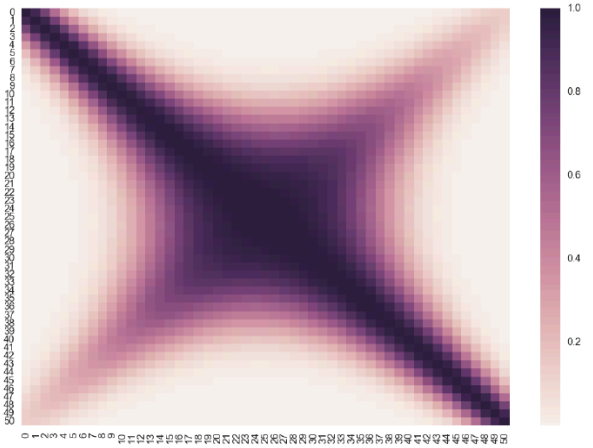
σ = .1



σ = 1.0



σ = 2

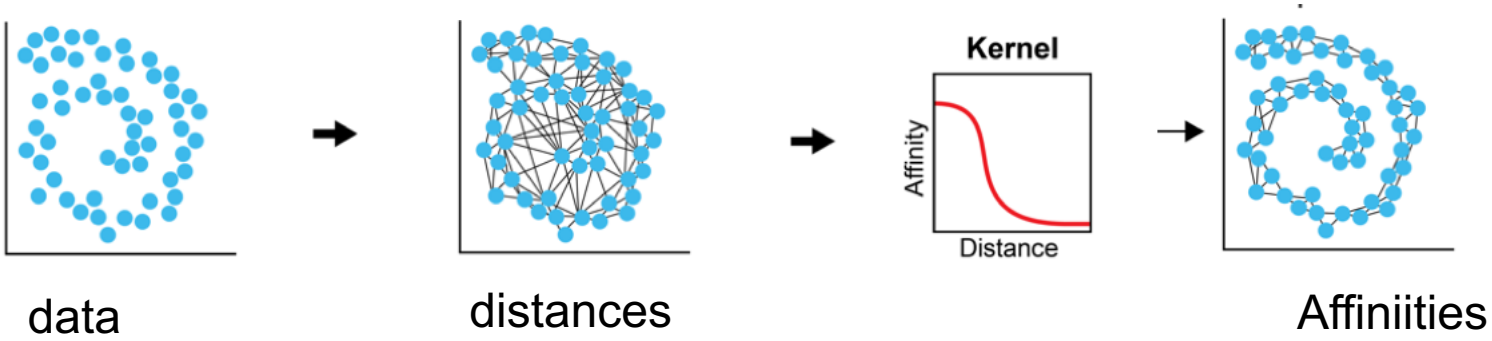


σ = 5

D

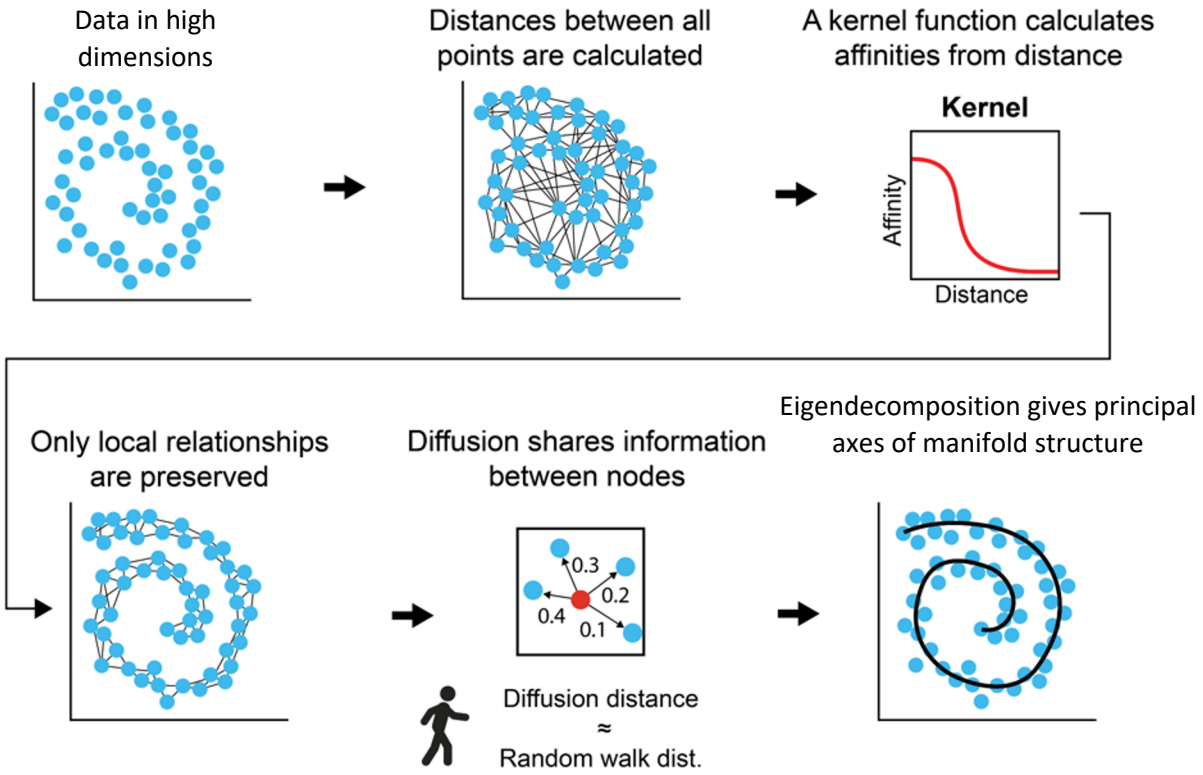
$$s_{i,j} = exp\left(-\frac{dist(x_i, x_j)^2}{2\sigma^2}\right)$$

Kernel PCA

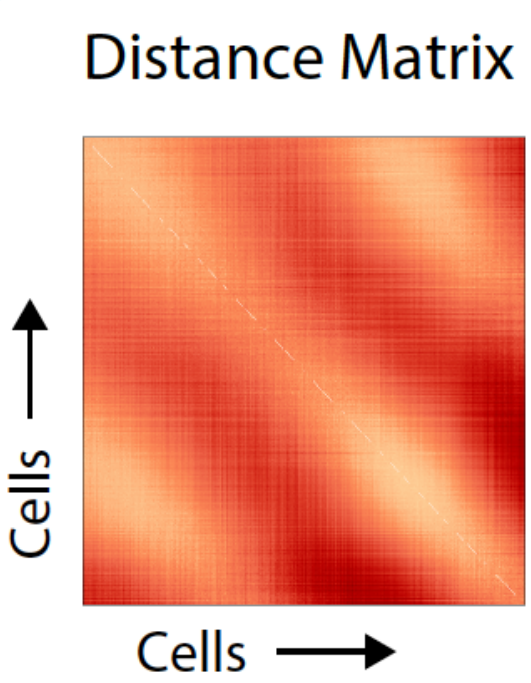


- Use eigenvectors of an **affinity matrix** instead of covariance matrix
- The family of methods called kernel PCA:
- Specific variants include:
  - Laplacian Eigenmaps
  - Diffusion Maps

Diffusion Maps

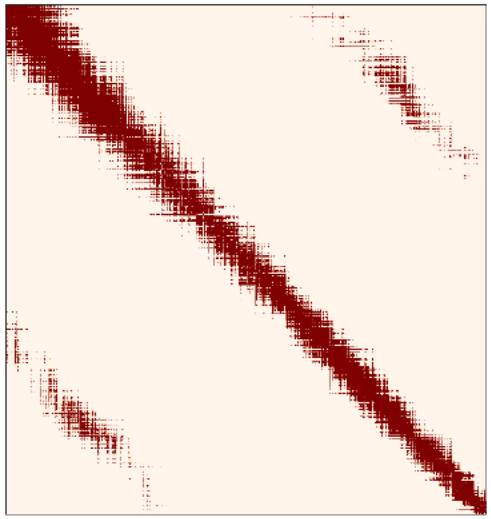


Distance Matrix

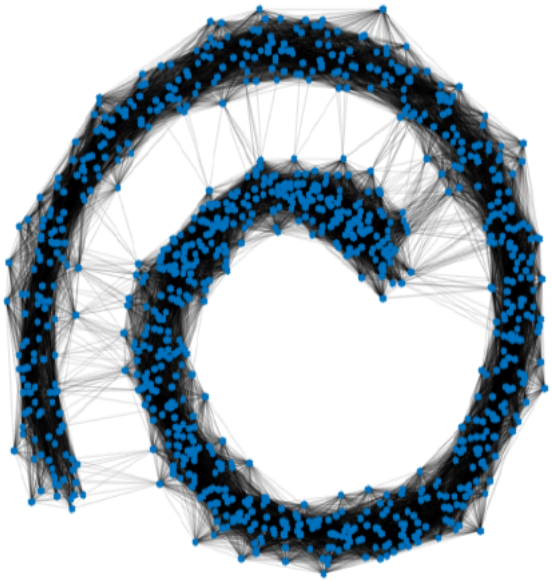


Entries are distances $D(x_i, x_j) = \sqrt{||x_i - x_j||}$

Affinity Matrix



(Gaussian Kernel)



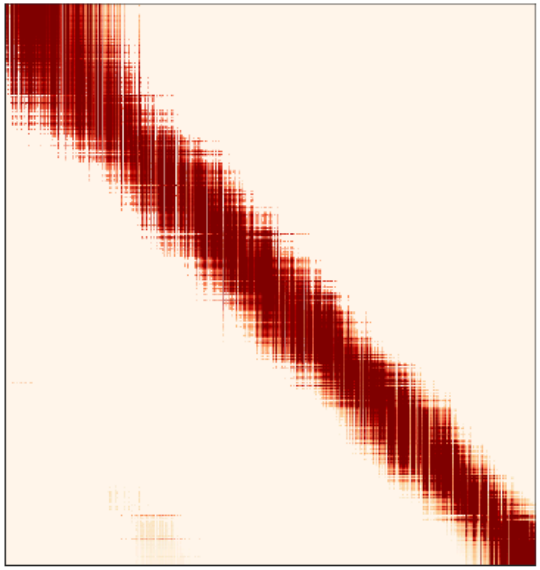
Graph Representation

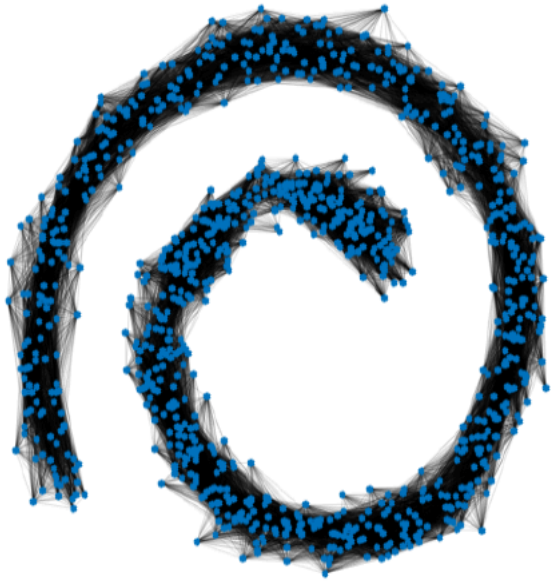
Entries are affinities

$$A(x_i, x_j) = \exp(-\frac{D(x_i,x_j)^2}{\sigma})$$

Powered Markov Matrix

Powered Markov Matrix

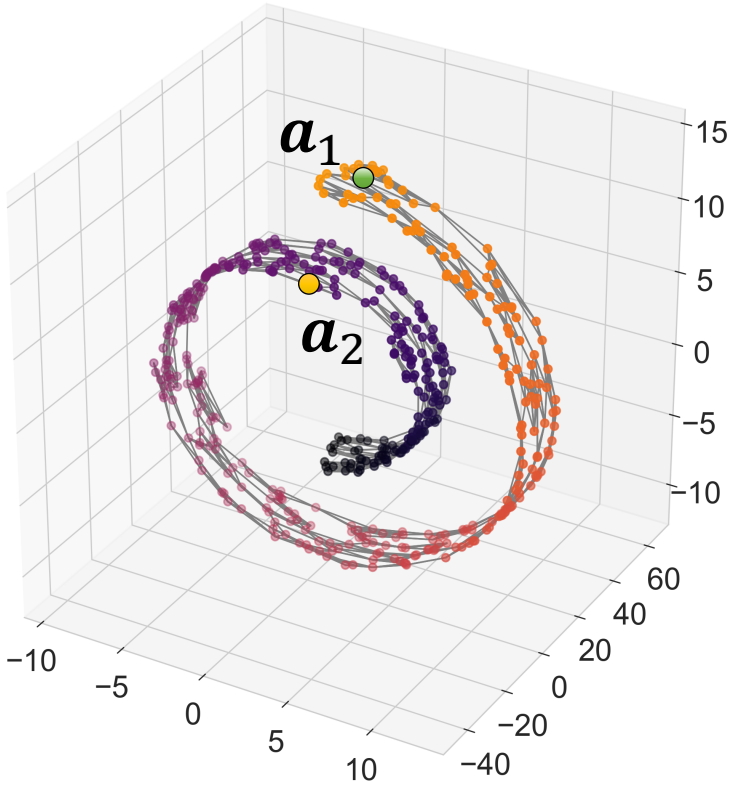




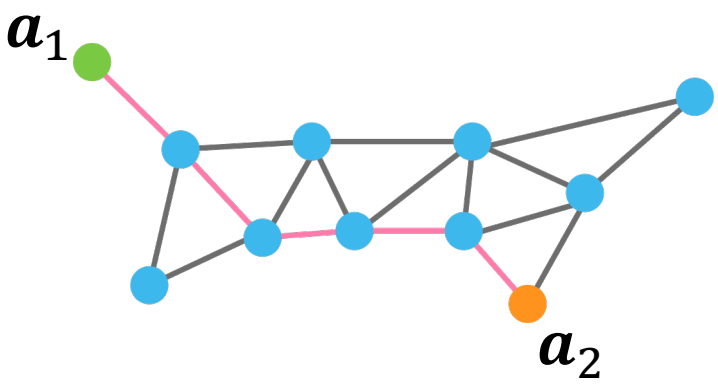
Entries are row normalized affinities

$$M(x_i, x_j) = \frac{A(x_i, x_j)}{\sum_j A(x_i, x_j)}$$

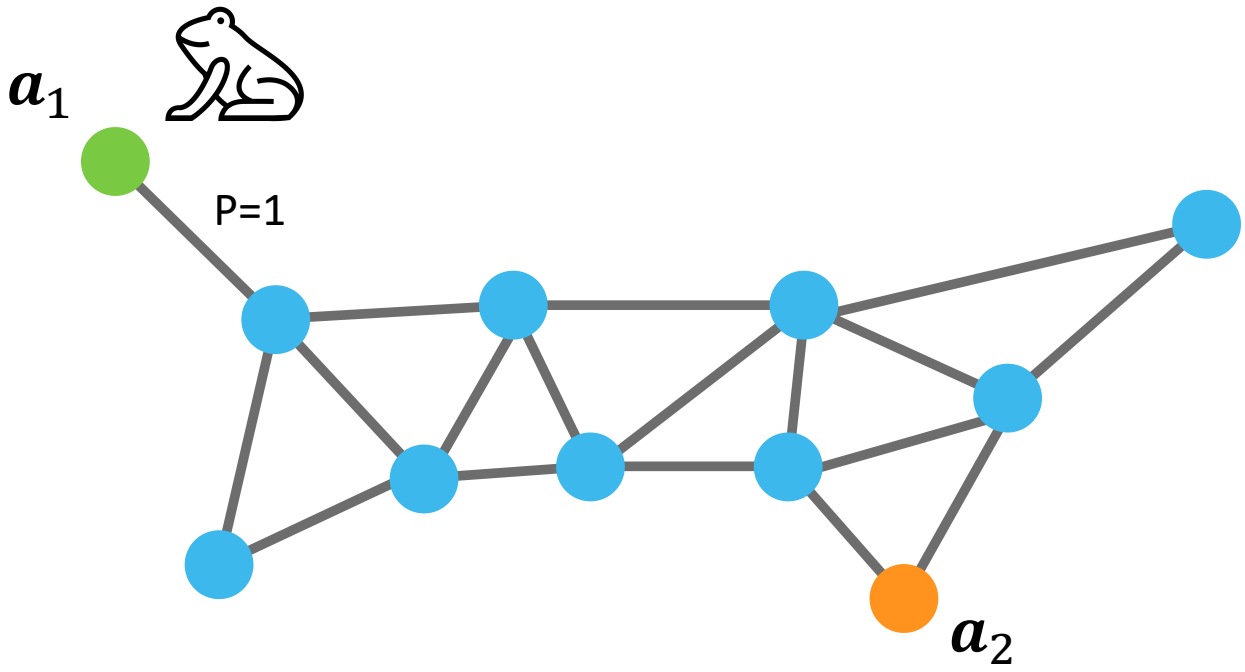
Powering or “walks” on data graphs reveal dominant data manifold directions



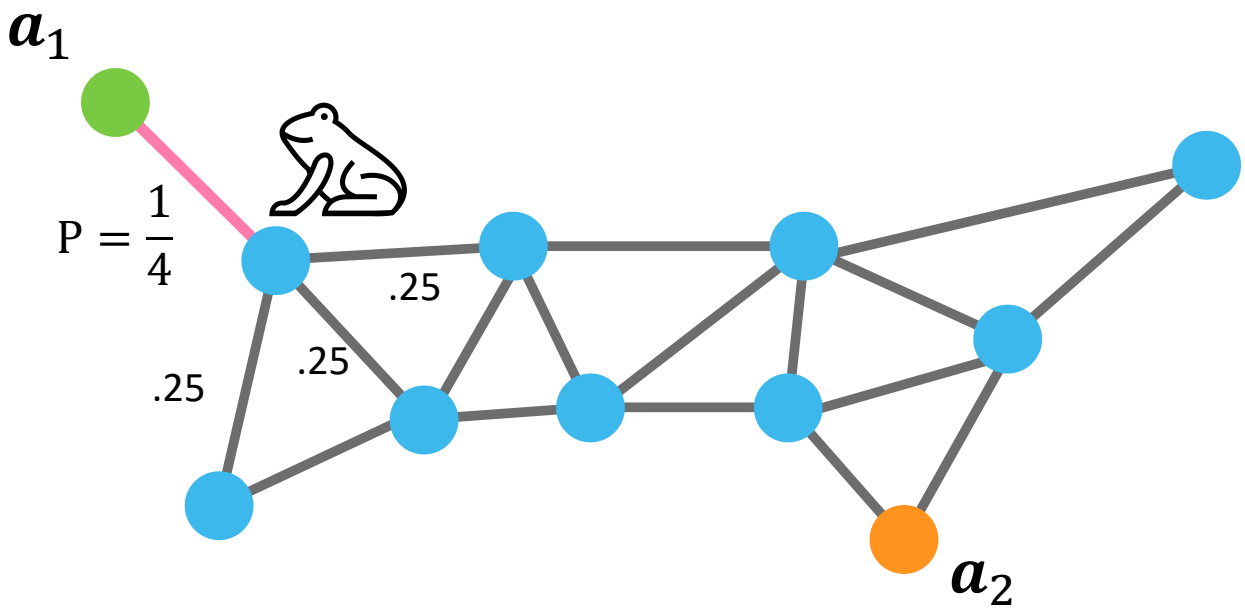
Shortest path between points



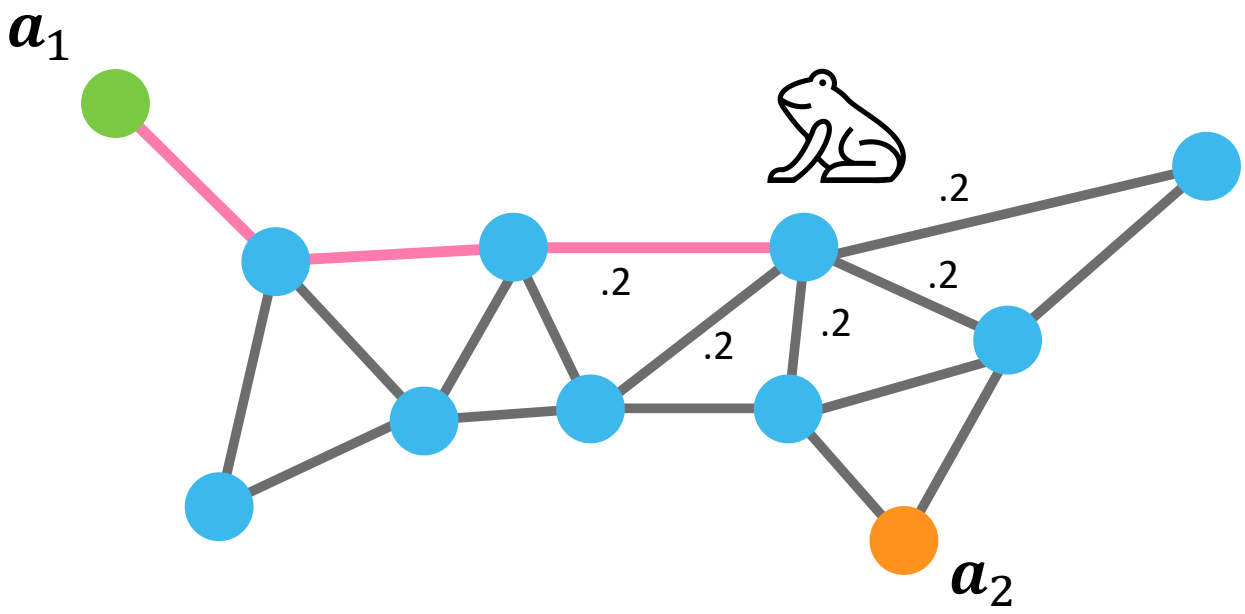
Paths or “walks” on graphs reveal dominant data manifold directions



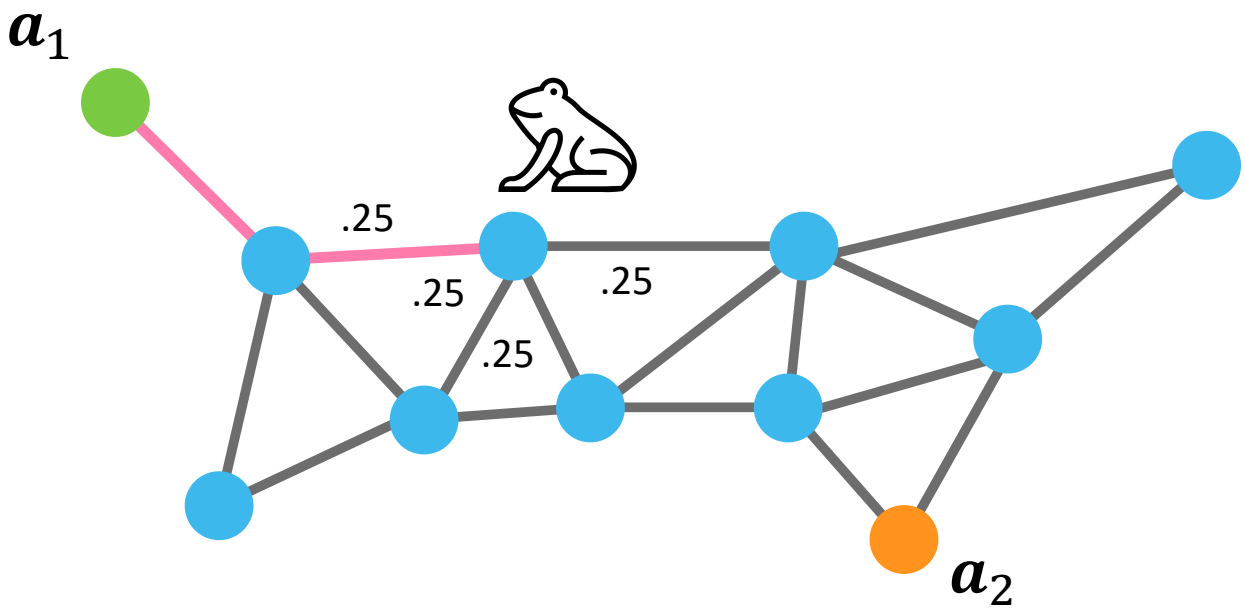
Paths or “walks” on graphs reveal dominant data manifold directions



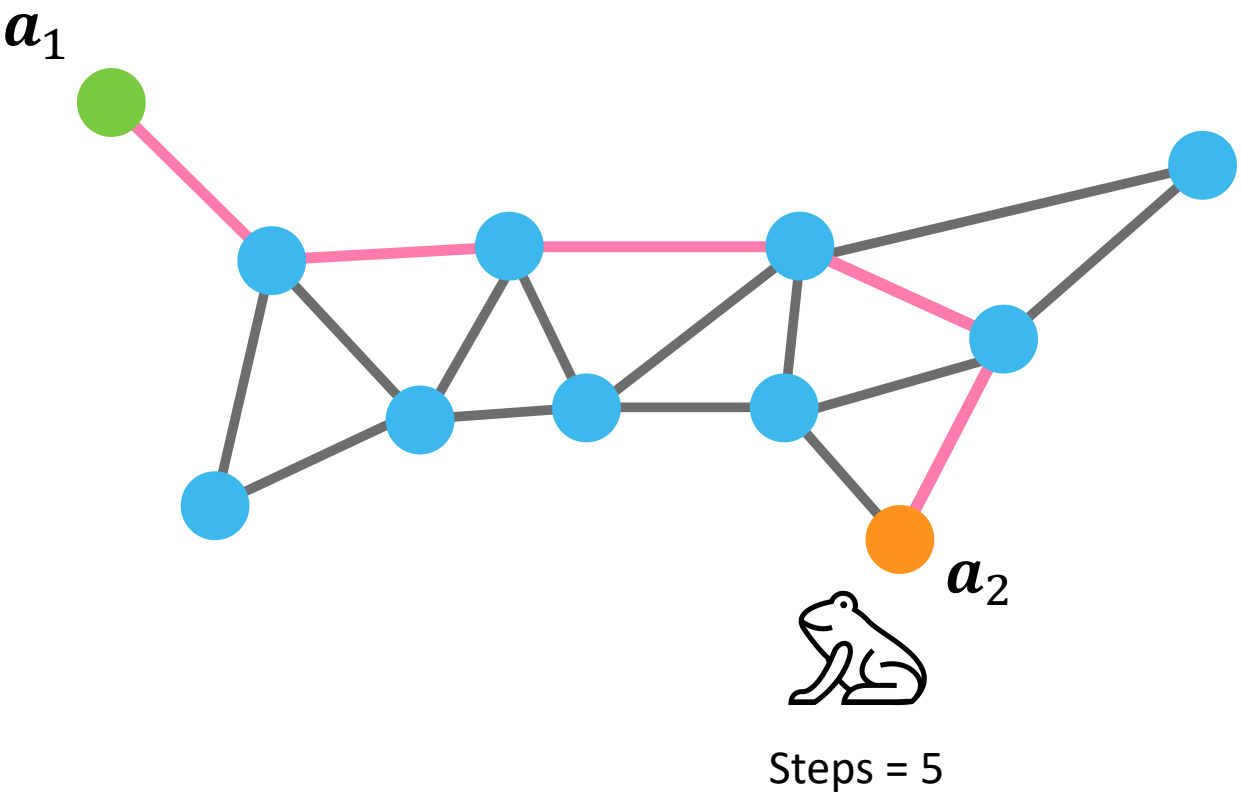
Paths or “walks” on graphs reveal dominant data manifold directions

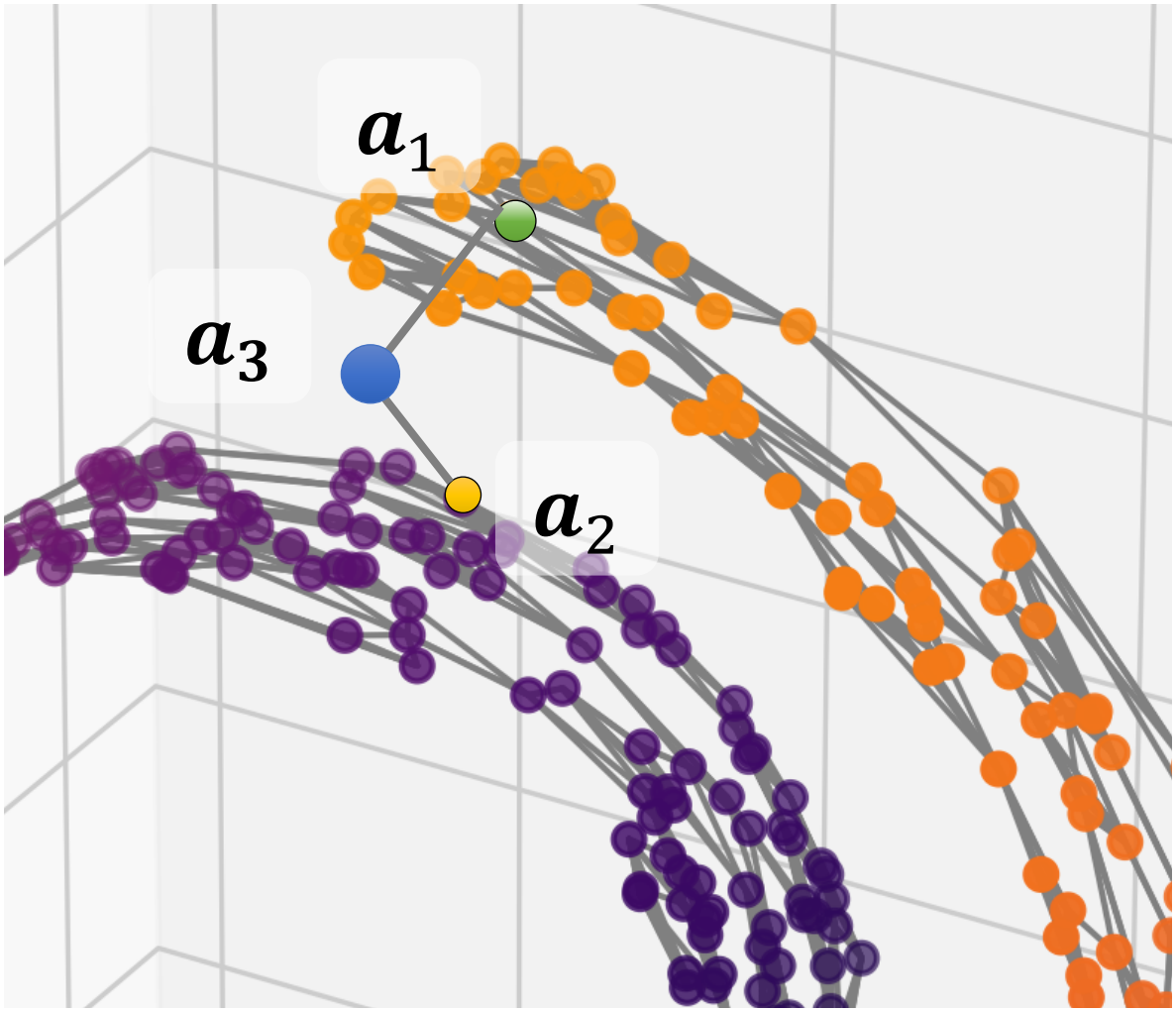


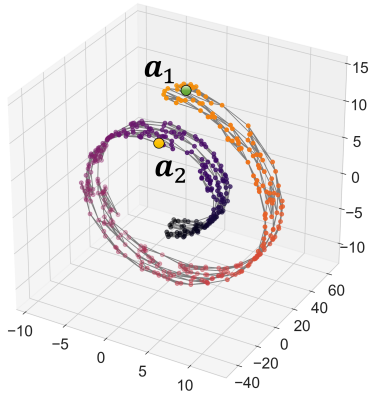
Paths or “walks” on graphs reveal dominant data manifold directions

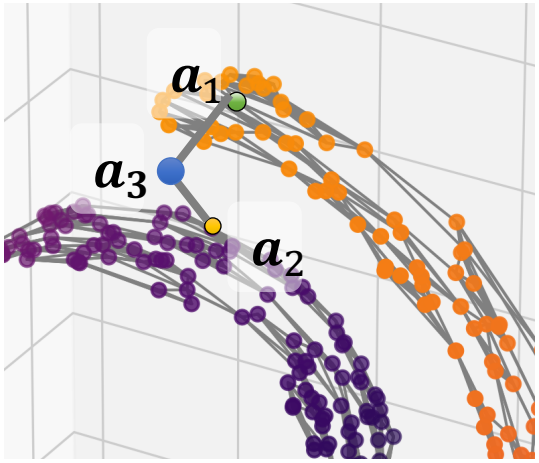


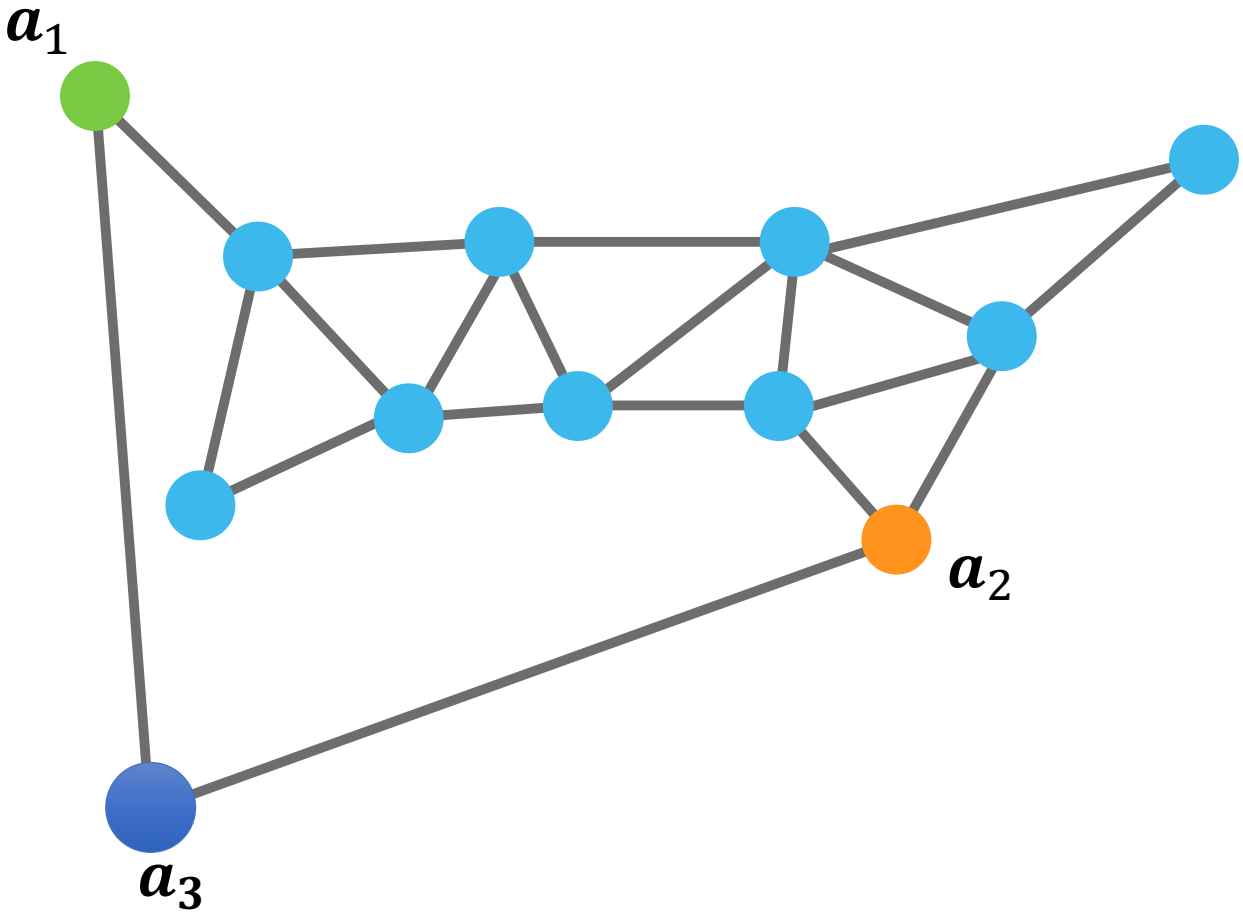
Paths or “walks” on graphs reveal dominant data manifold directions

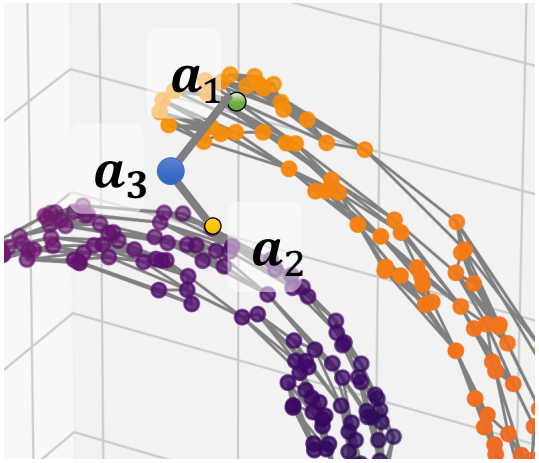


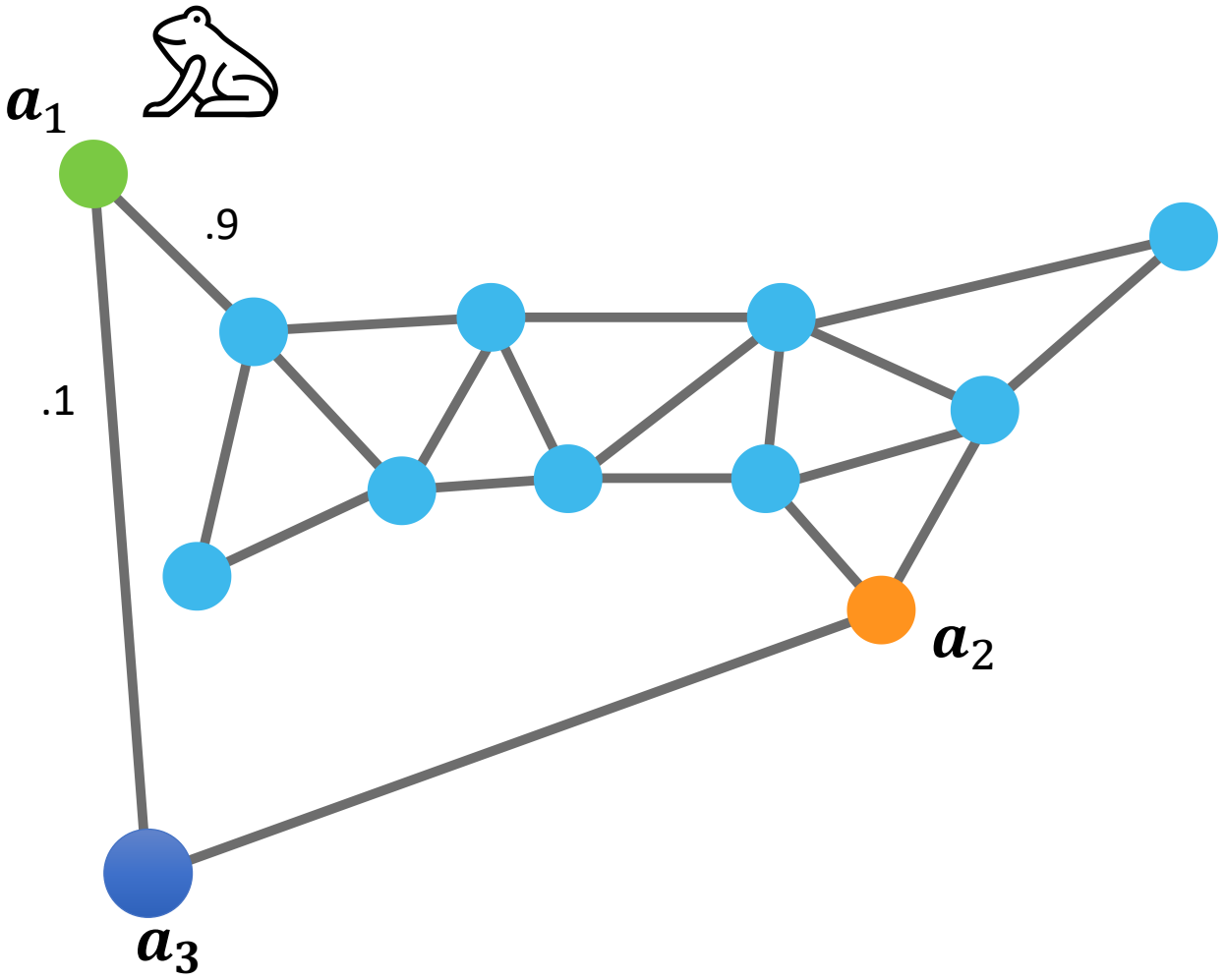

a_1
a_3
a_2


a_1
a_2
15
10
5
0
−5
−10
60
40
20
0
−20
−40
−10
−5
0
5
10


a_1
a_3
a_2

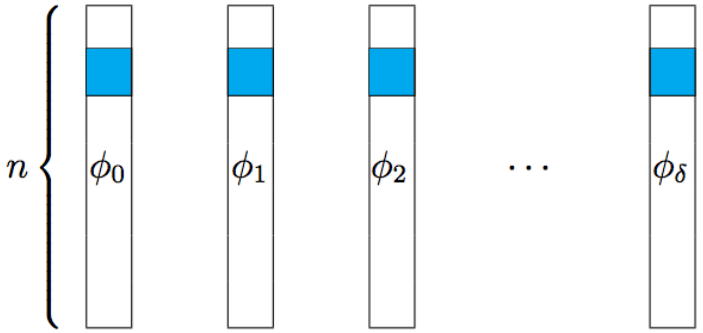

a_1
a_2
a_3


a_1
a_3
a_2


a_1
.9
.1
a_2
a_3

Eigendecomposition of Diffusion Operator = DMs

$$1 = \boxed{\lambda_0} \geq \boxed{\lambda_1} \geq \boxed{\lambda_2} \geq \cdots \geq \boxed{\lambda_\delta} > 0$$



$$x \mapsto \Phi(x) \triangleq [\lambda_0\phi_0(x)\,,\ \lambda_1\phi_1(x)\,,\ \lambda_2\phi_2(x)\,,\ \ldots\,,\ \lambda_\delta\phi_\delta(x)]^T$$

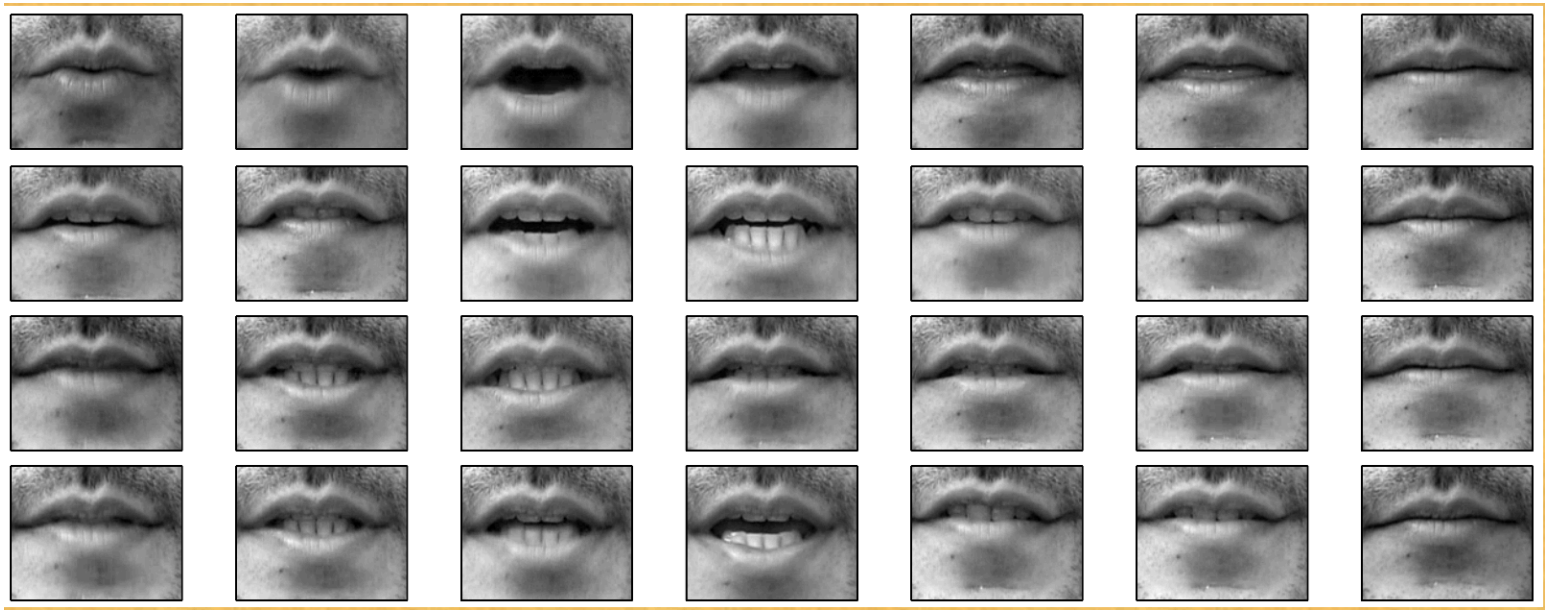
[Coifman, Lafon, ACHA 2006]

Uncoiling the space

First non-trivial eigenvector DM1 tracks the most prominent non-linear path

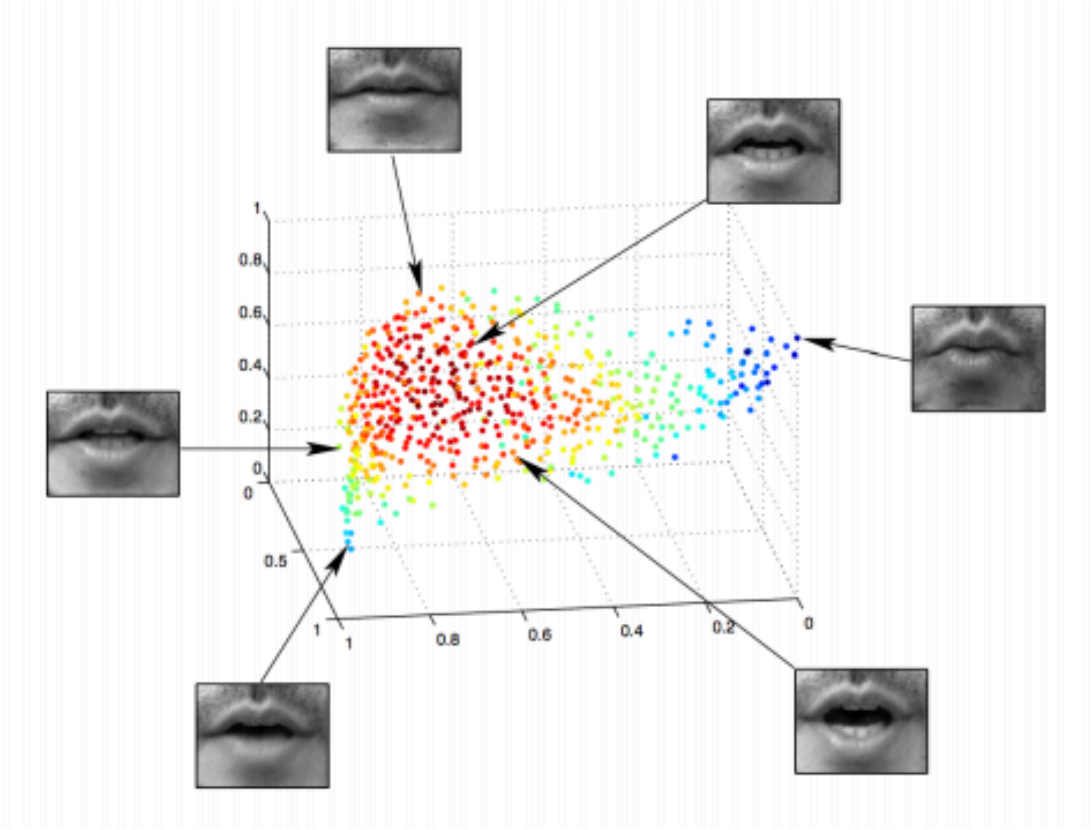
Lips Dataset: Spoken Digits

ONE



[3]S. Lafon, Y. Keller, and R. R. Coifman. Data Fusion and Multi-Cue Data Matching by Diffusion Maps. *IEEE Transactions on Pattern Analysis and Machine Intelligence*, volume 28, pages 1784-1797, 2006.

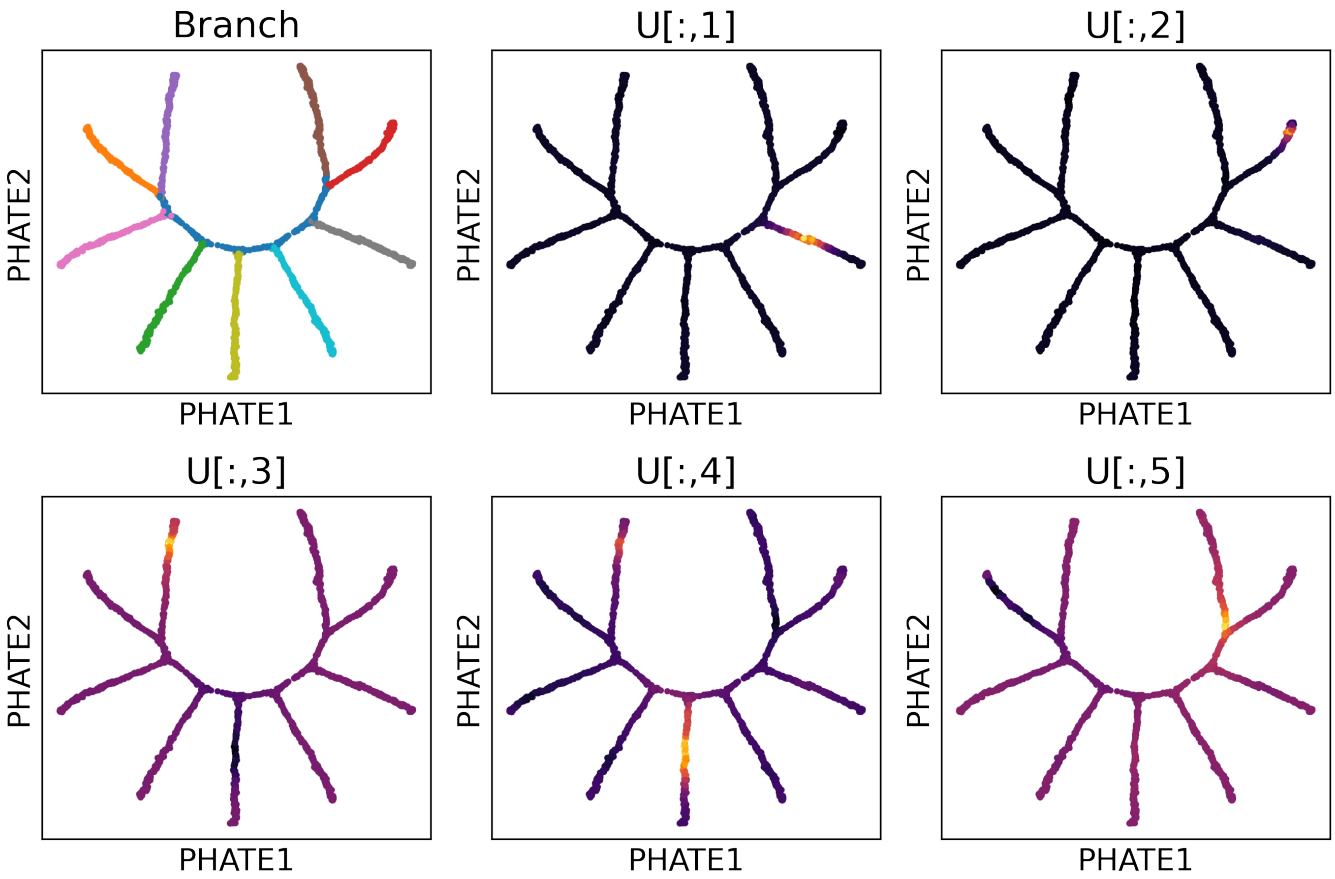
Lips Manifold



Opening of mouth

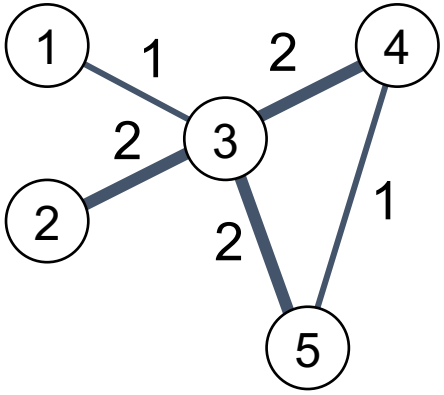
portion of teeth visible

Disentangling effect of DMs



The graph Laplacian is a matrix representation of a graph

G



A adjacency matrix

$$\mathbf{A} = \begin{vmatrix} 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 2 & 0 & 0 \\ 1 & 2 & 0 & 2 & 2 \\ 0 & 0 & 2 & 0 & 1 \\ 0 & 0 & 2 & 1 & 0 \end{vmatrix}$$

D degree matrix

$$\mathbf{D} = \begin{vmatrix} 1 & 0 & 0 & 0 & 0 \\ 0 & 2 & 0 & 0 & 0 \\ 0 & 0 & 7 & 0 & 0 \\ 0 & 0 & 0 & 3 & 0 \\ 0 & 0 & 0 & 0 & 3 \end{vmatrix}$$

Laplacian matrix

$$\mathcal{L} = \mathbf{D} - \mathbf{A} = \begin{vmatrix} 1 & 0 & -1 & 0 & 0 \\ 0 & 2 & -2 & 0 & 0 \\ -1 & -2 & 7 & -2 & -2 \\ 0 & 0 & -2 & 3 & -1 \\ 0 & 0 & -2 & -1 & 3 \end{vmatrix}$$

Laplacian Eigenmaps

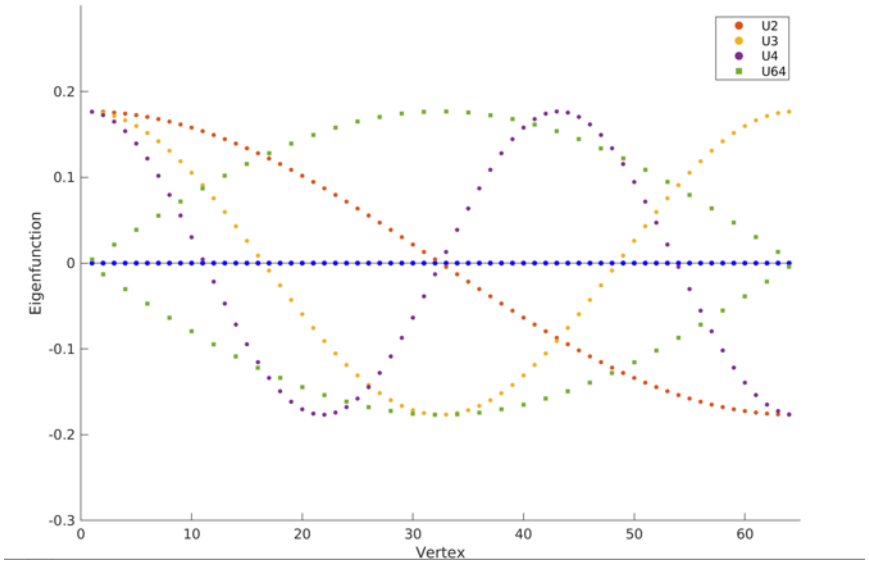
$$\mathcal{L} = \mathbf{D} - \mathbf{A} = \begin{vmatrix} 1 & 0 & -1 & 0 & 0 \\ 0 & 2 & -2 & 0 & 0 \\ -1 & -2 & 7 & -2 & -2 \\ 0 & 0 & -2 & 3 & -1 \\ 0 & 0 & -2 & -1 & 3 \end{vmatrix}$$

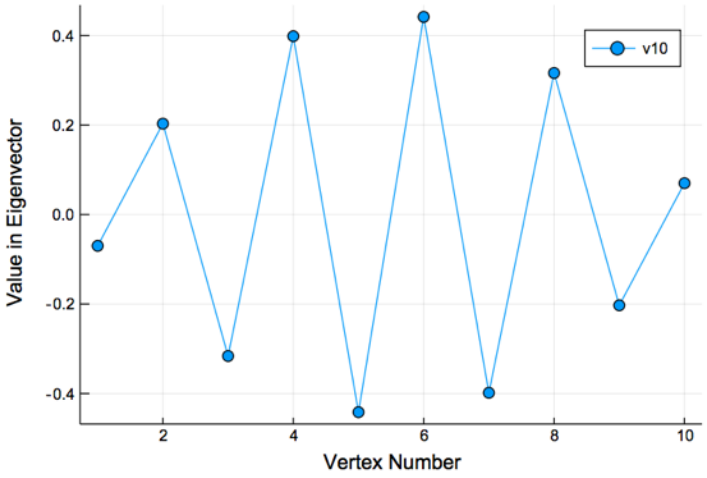
Eigenvectors of Laplacian matrix form Laplacian Eigenmaps

Graph Laplacian

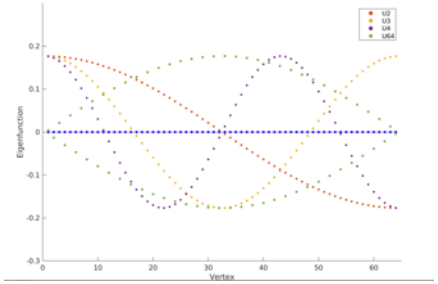
- A difference operator based on the graph adjacency matrix A.
- (unnormalized Laplacian)$L = D - A$
  - Degree matrix: $D_{ii} = \sum_j A_{ij}$, 0 everywhere else
- (normalized Laplacian) $L = I - D^{-1/2} A D^{-1/2}$
  - I is identity
  - Measures how similar a point is to its neighbors
- (random walk Laplacian) $L = I - D^{-1} A = I - M$
  - Related to Markovian matrix

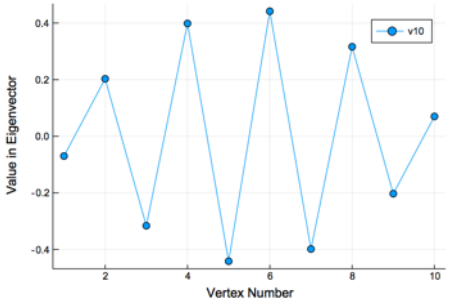
Eigenvectors form a Graph Spectrum

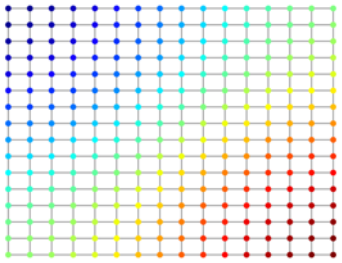




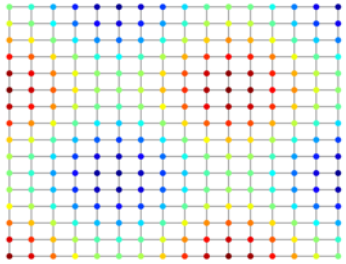
Eigenvectors are frequency harmonics



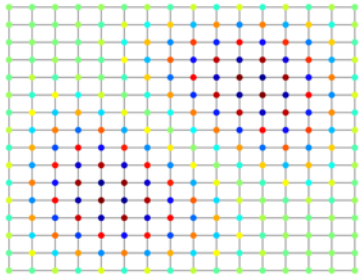




2nd Eigenvector



10th Eigenvector

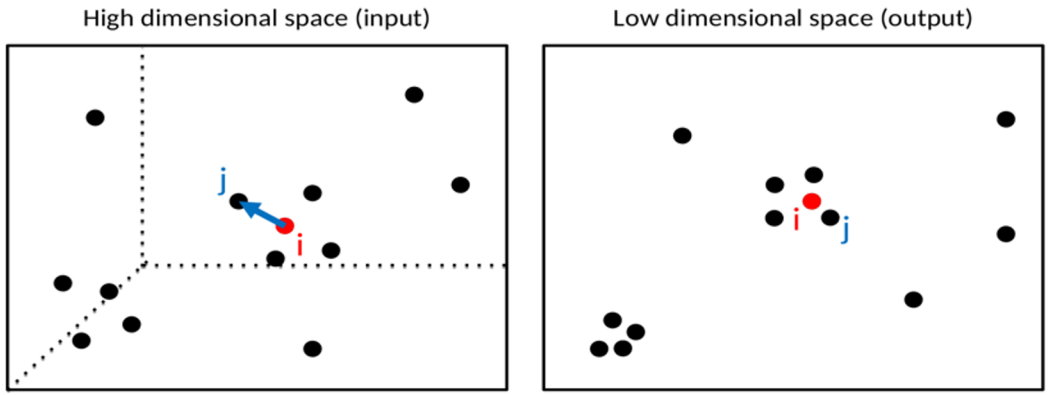


2nd to last eigenvector

2D Dimensionality Reductions

- These methods preserve information from an affinity matrix in 2-3 dimensions exactly
- There are as many eigenvectors as datapoints, so taking only the top 2 misses information
  - **tSNE/UMAP:** greedy method for preserving near neighbors in 2D
  - **PHATE:** creates a new distance matrix from a distance between diffusion probabilities of points and squeezes that variation into 2D

tSNE



Goal: Maintain the local neighborhood of each cell

Steps: 1. Place points randomly in a 2D plane
2. Move points to locally optimal location via gradient descent

$$\frac{\delta C}{\delta y_i} = 2\sum_j (p_{j|i} - q_{j|i} + p_{i|j} - q_{i|j})(y_i - y_j).$$

tSNE Penalty

$$KL(P||Q) = \sum_{i \neq j} p_{ij} \log \frac{p_{ij}}{q_{ij}}$$

Neighbors in high dimensions

Neighbors in low dimensions

What happens when the p_{ij} is SMALL?

No effective penalty for placement of points that are not close

Combination of attraction and repulsion

$$KL(P||Q) = \sum_{i \neq j} p_{ij} \log \frac{p_{ij}}{q_{ij}}$$

Neighbors in high dimensions

High probabilities to some neighbors have to be counteracted by some low probabilities to other points (sum has to be 1)

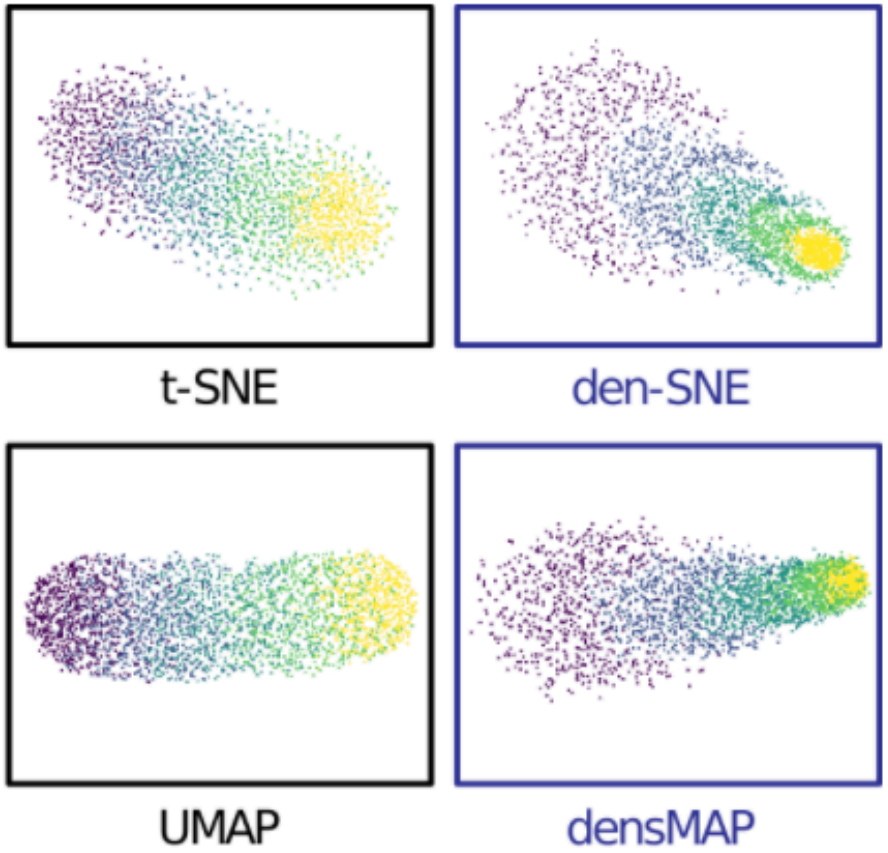
To fit close neighbors together have to repel far points. This is what leads to a “explosion”-like embedding

UMAP

- Very similar to tSNE (but its NOT published!)
- What about the “uniform manifold approximation?”
  - This is actually saying that UMAP approximates a uniform manifold from your data
  - In other words tSNE/UMAP plots have even density throughout

- Why uniform density?
  - They use a Markov matrix where the bandwidth is set to the Kth nearest neighbor, so each point is placed near its K-nearest neighbors no matter how near or far they are
  - **Advantage** of this is that you can see how many points are in each cluster
  - **Disadvantage** is you don’t get an idea of the real (even local) density

Local density inducing variant



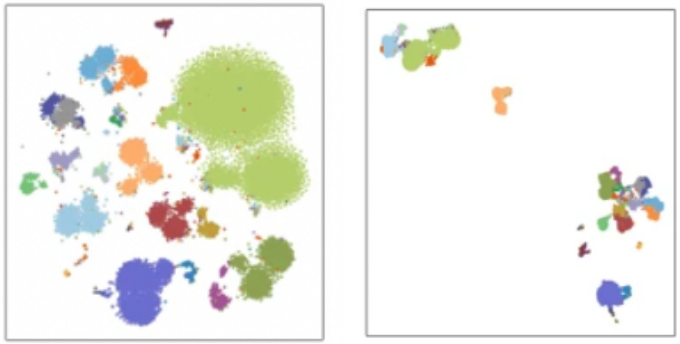
http://cb.csail.mit.edu/cb/densvis/

Differences from tSNE

- Initialized with a Laplacian eigenmap, stronger start to a greedy method

- Noise-contrastive estimation in the implementation
  - UMAP uses an un-normalized matrix (probabilities don't sum to 1)
  - Instead some points are sampled and if they are far away they have to be repelled
  - All nearest neighbors have to be put close
  - This decreases the repulsion

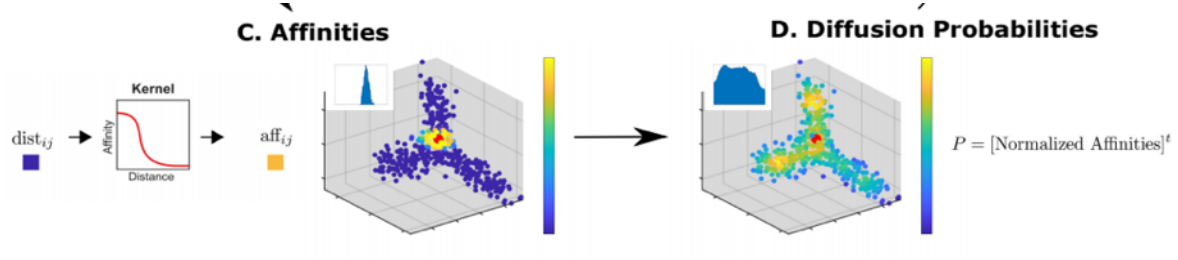
- Less "explosive looking"



tSNE **UMAP**

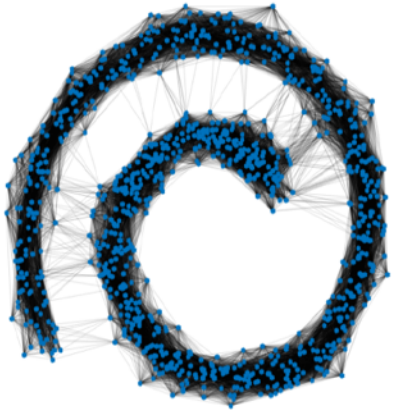
PHATE:

- Goal: to preserve manifold structure
- Step 1. Each cell is represented as a t-step diffusion probability to other cells

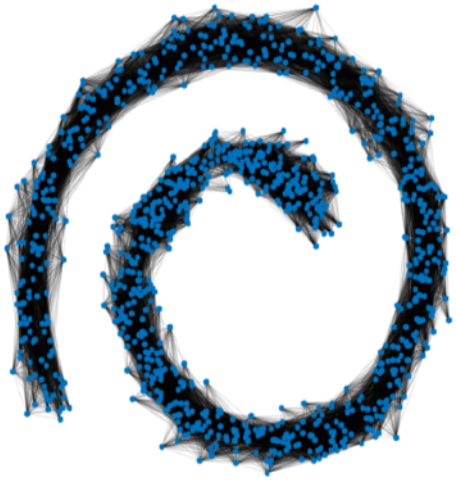


- Diffusion induces global connectivity and denoises paths
- PHATE uses an adaptive Markov matrix too! But using it for diffusion is very different from using it to match neighbors directly

Diffusion in PHATE denoises



Connectivity
without diffusion



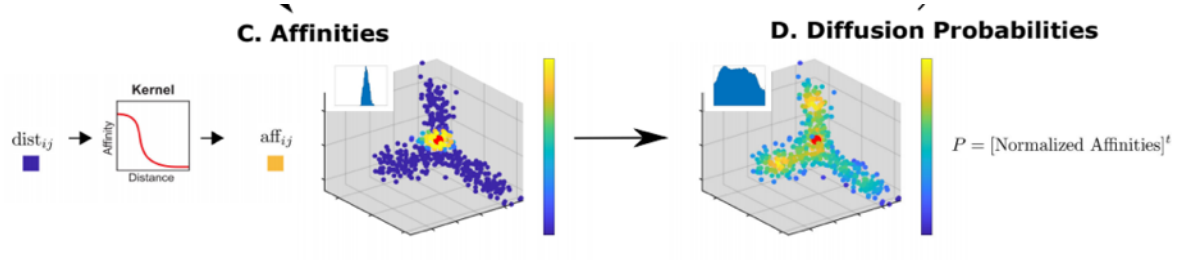
Connectivity after
t-steps of diffusion

Adaptive Alpha-decay kernel

- Adaptive kernel in PHATE separate geometry from density
- If there are density variations in the initial Markov matrix creation then paths tend to drift towards dense regions and it DISTORTS geometry
- Adaptive kernel (bandwidth set to Kth nearest neighbor) reveals geometry

PHATE:

- Goal: to preserve manifold structure
- Step 1. Each cell is represented as a t-step diffusion probability to other cells



- Step 2: Re-represent each point by its diffusion probabilities to all other points

$C_1 = [\ p_{11}\ p_{12}\ \ldots\ldots p_{1n}]$
$C_2 = [\ p_{21}\ p_{22}\ \ldots\ldots p_{2n}]$
...
$C_n = [\ p_{n1}\ p_{n2}\ \ldots\ldots p_{nn}]$

- Step 3. Define a new distance between points with this new representation

$C_1 = [\, p_{11}\ p_{12}\ \ldots\ldots p_{1n}]$

……

$C_i = [\, p_{i1}\ p_{i2}\ \ldots\ldots p_{in}]$

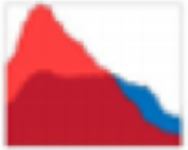
…

$C_j = [\, p_{j1}\ p_{j2}\ \ldots\ldots p_{jn}]$

…

$C_n = [\, p_{n1}\ p_{n2}\ \ldots\ldots p_{nn}]$

$$\mathrm{dist}_{ij} = \sqrt{\| \log P_i - \log P_j \|^2}$$

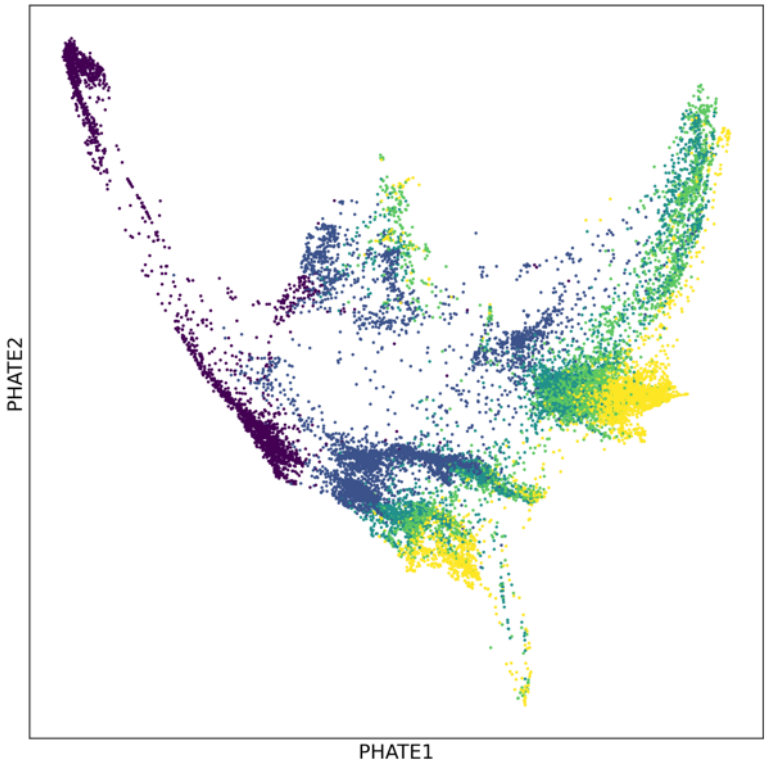


- Step 4: Embed with multidimensional scaling

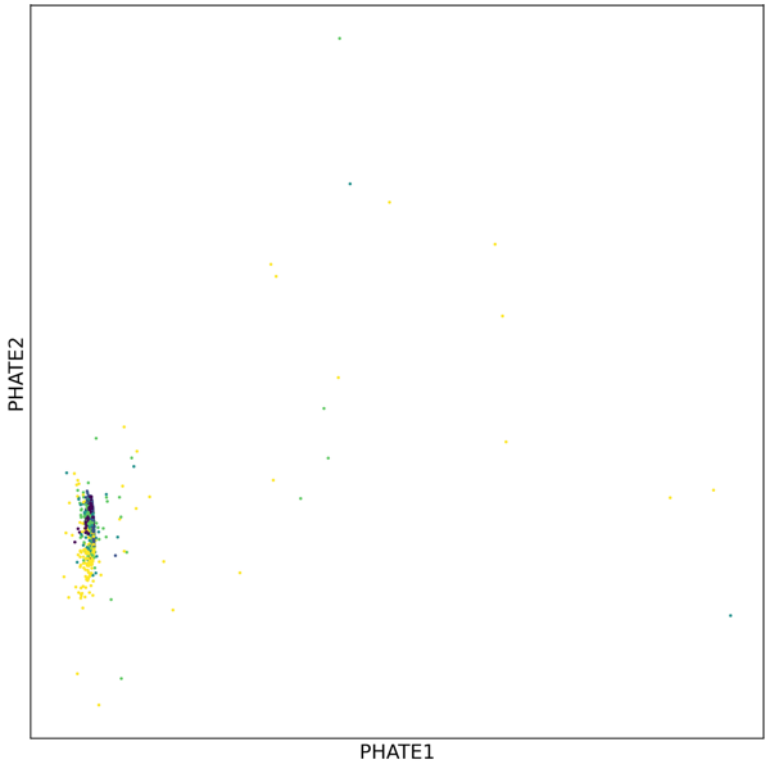
- This reorganizes information in a diffusion map into 2D

Adaptive vs fixed bandwidth kernel

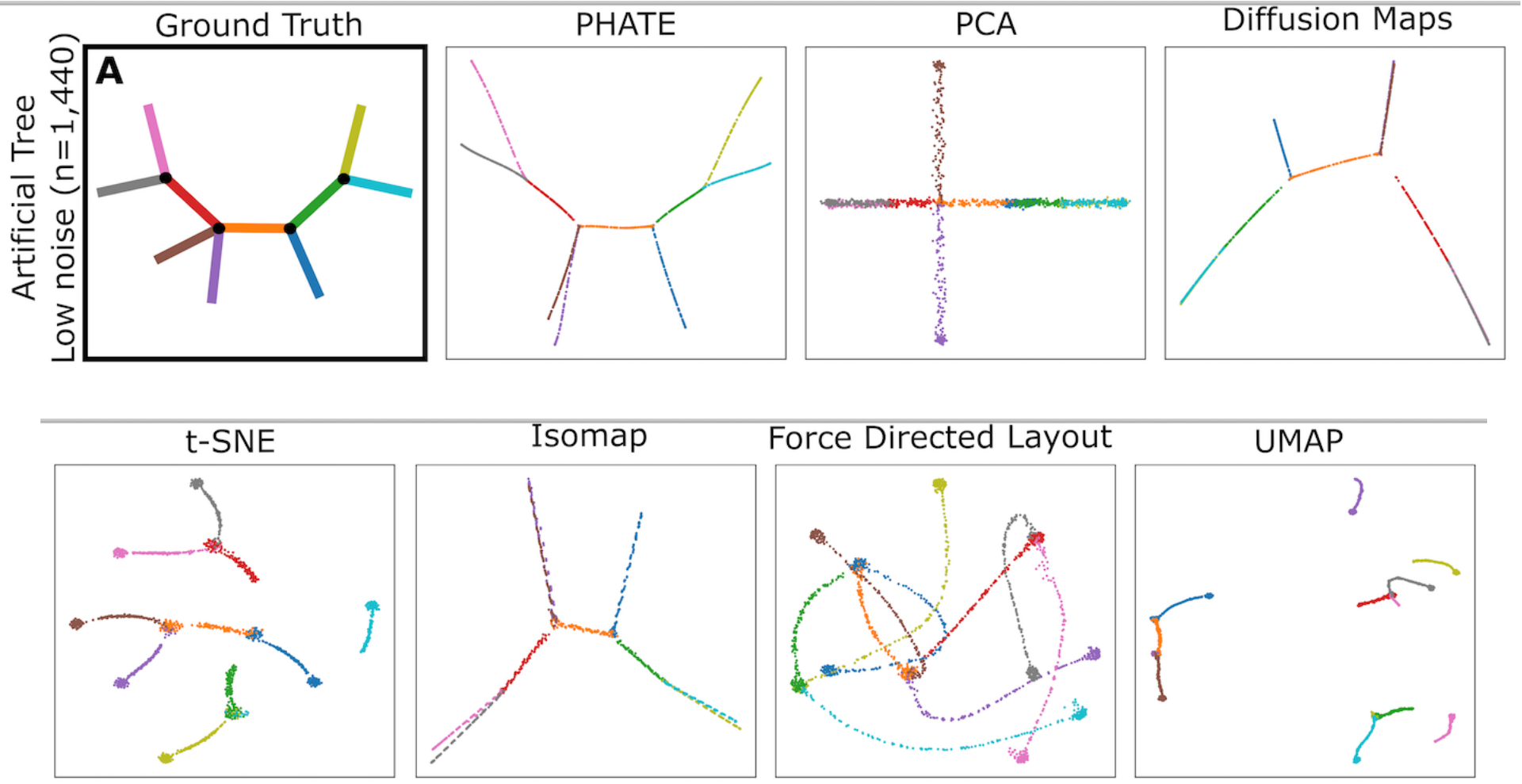
Adaptive



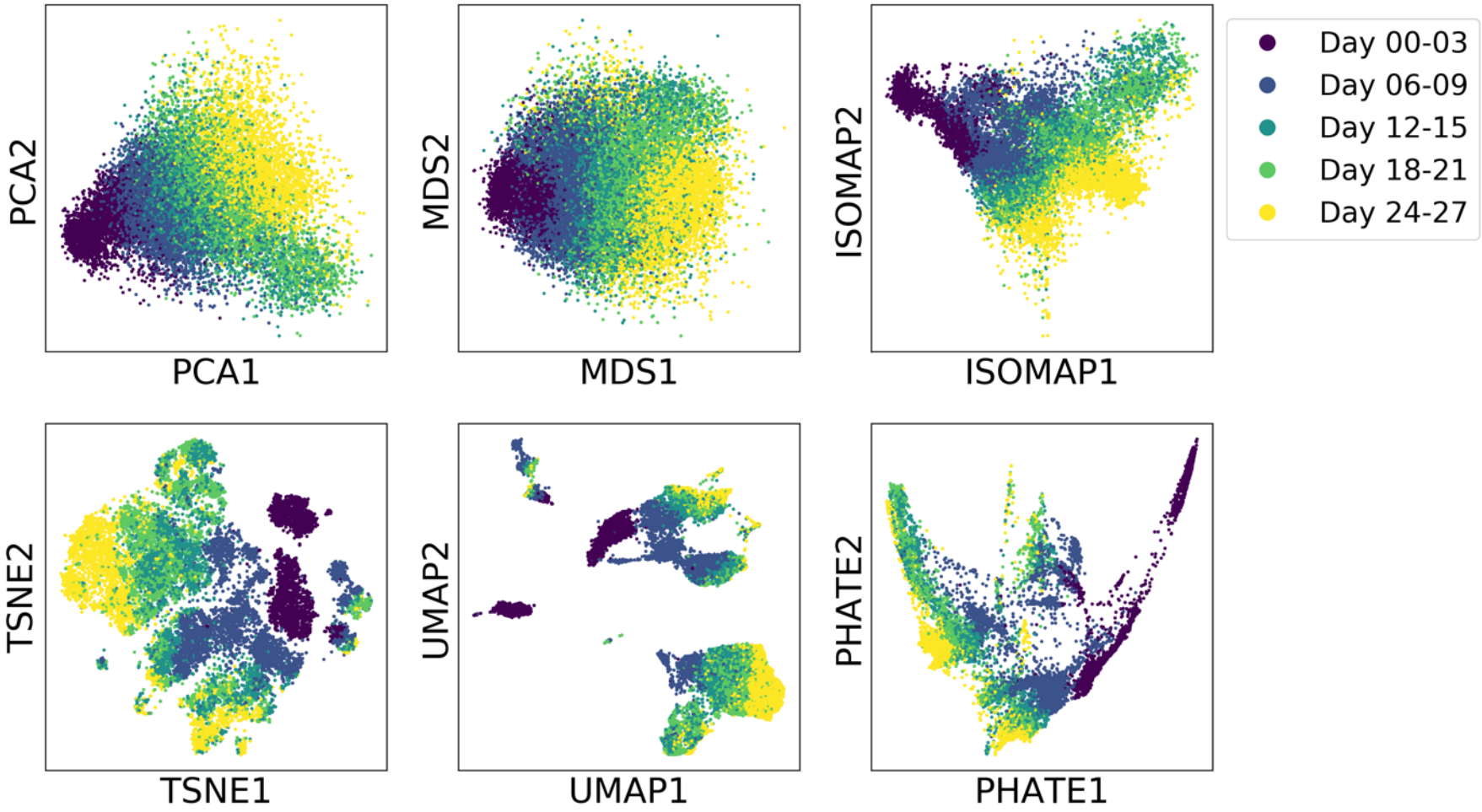
Fixed

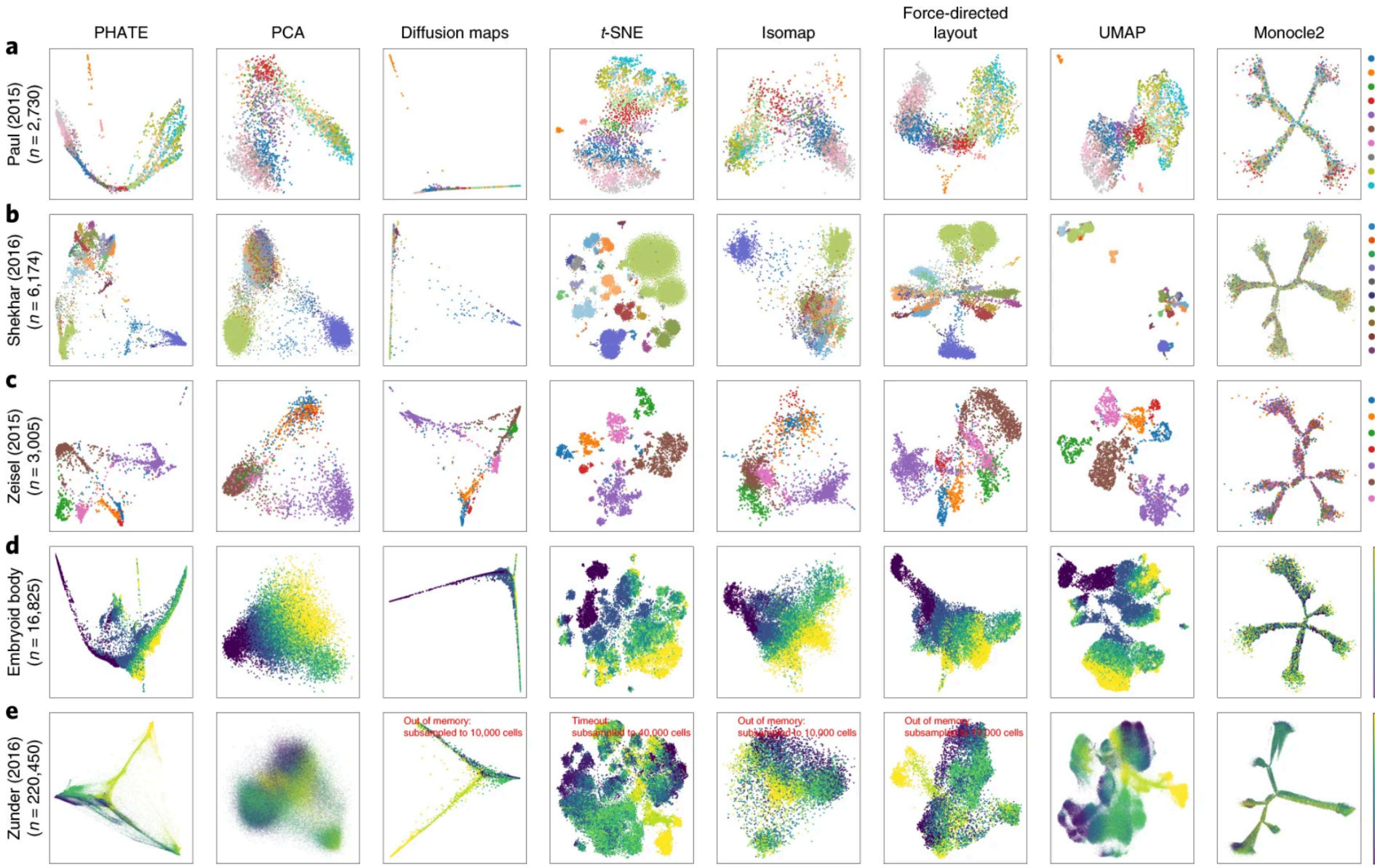


Comparing Artificial Case

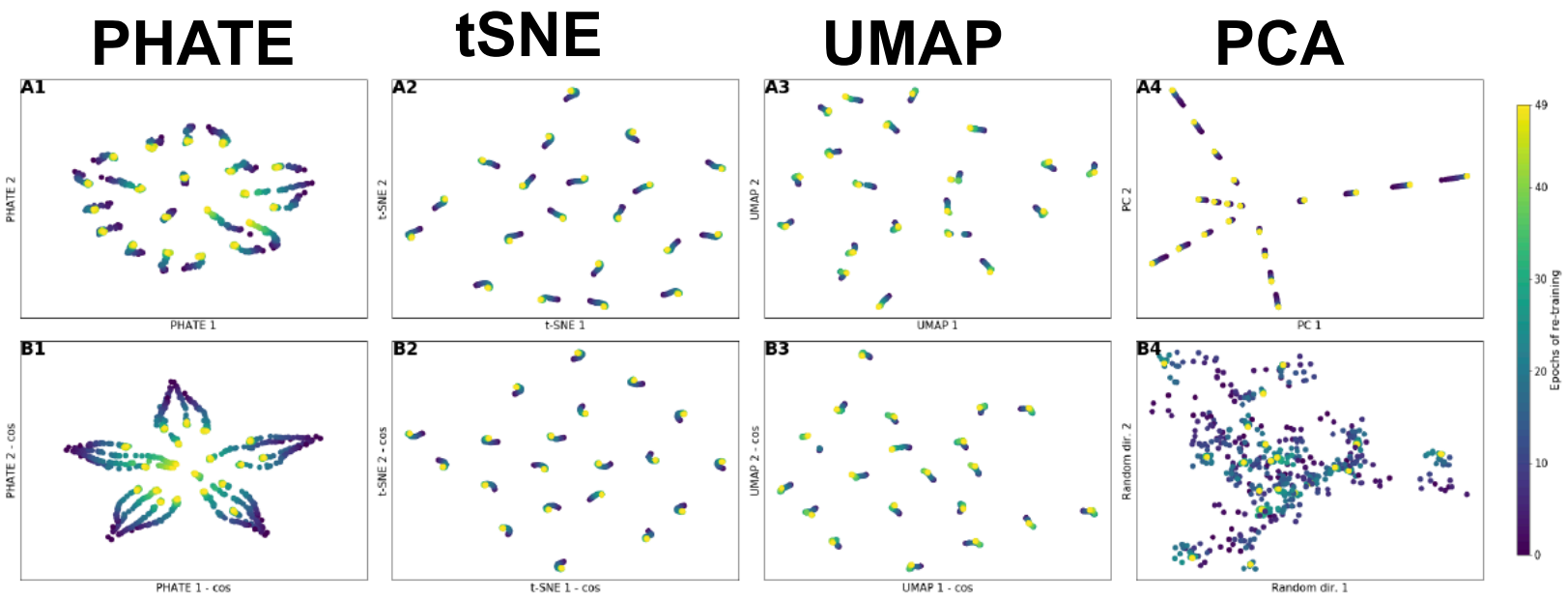


Comparing visualization algorithms on single-cell data



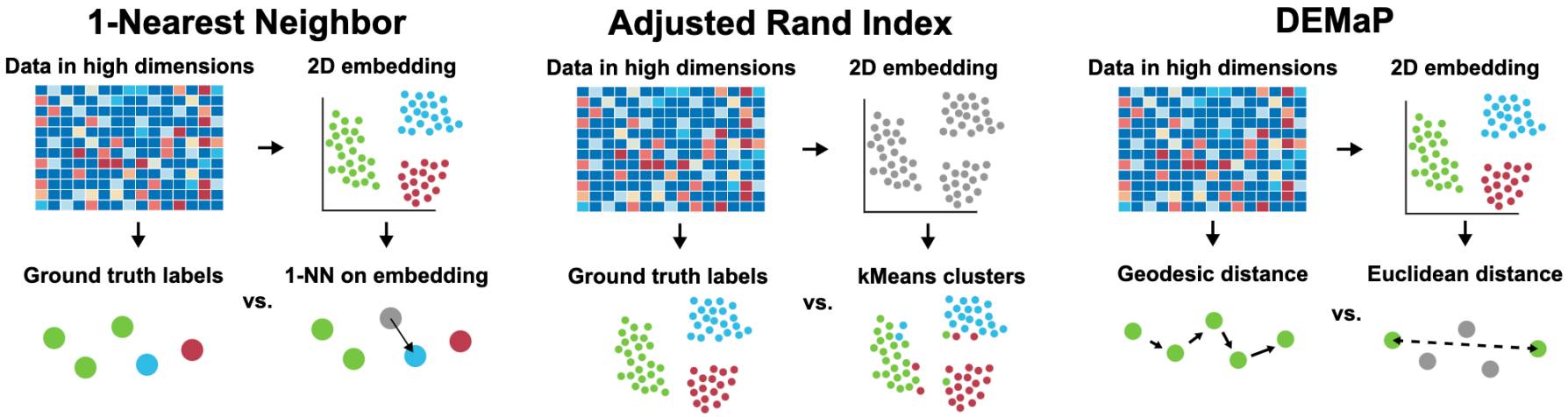

PHATE
PCA
Diffusion maps
t-SNE
Isomap
Force-directed layout
UMAP
Monocle2
a
Paul (2015) (n = 2,730)
b
Shekhar (2016) (n = 6,174)
c
Zeisel (2015) (n = 3,005)
d
Embryoid body (n = 16,825)
e
Zunder (2016) (n = 220,450)
Out of memory: subsampled to 10,000 cells
Timeout: subsampled to 40,000 cells
Out of memory: subsampled to 10,000 cells
Out of memory: subsampled to 10,000 cells

Data agnostic: Neural network loss landscapes

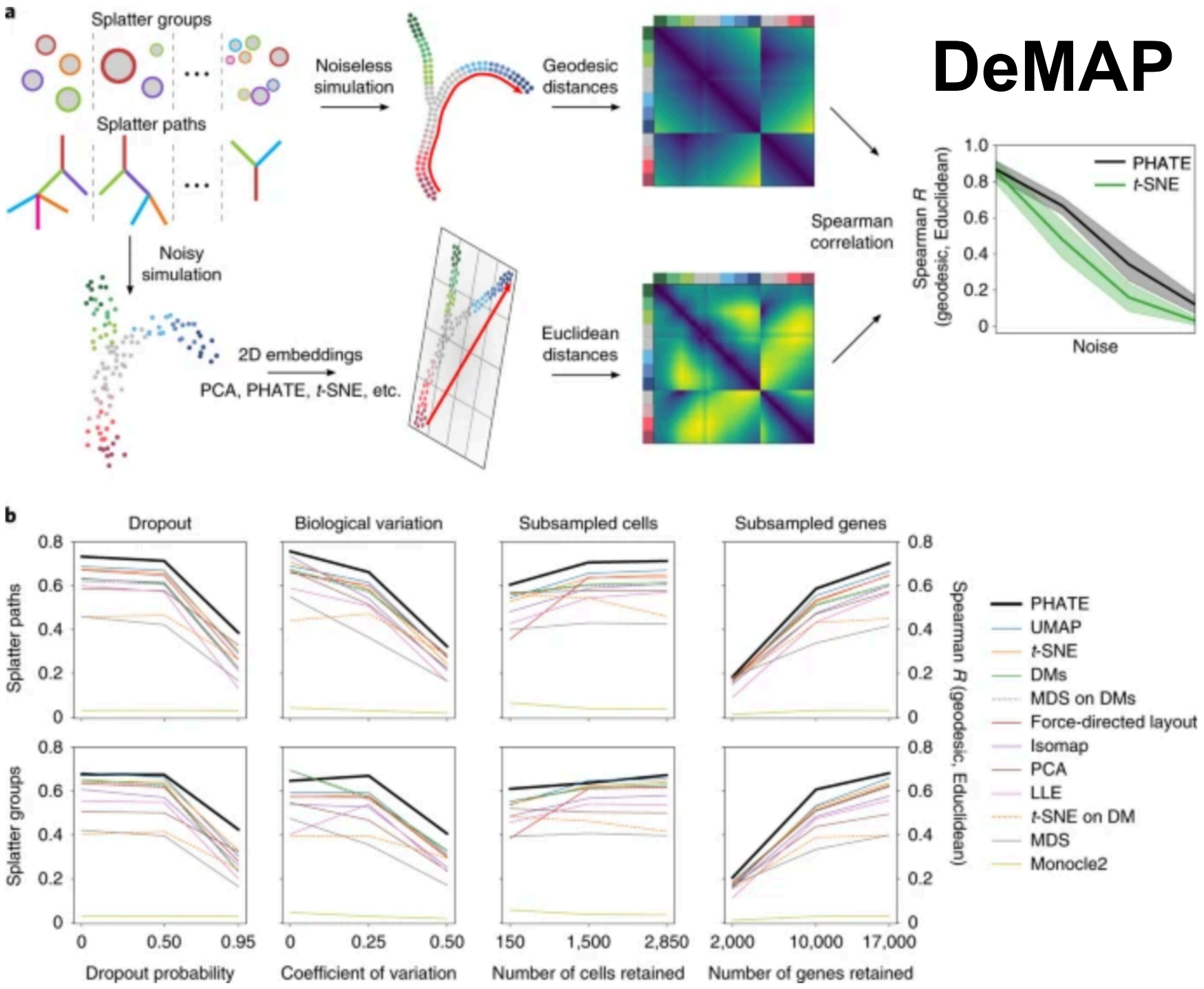


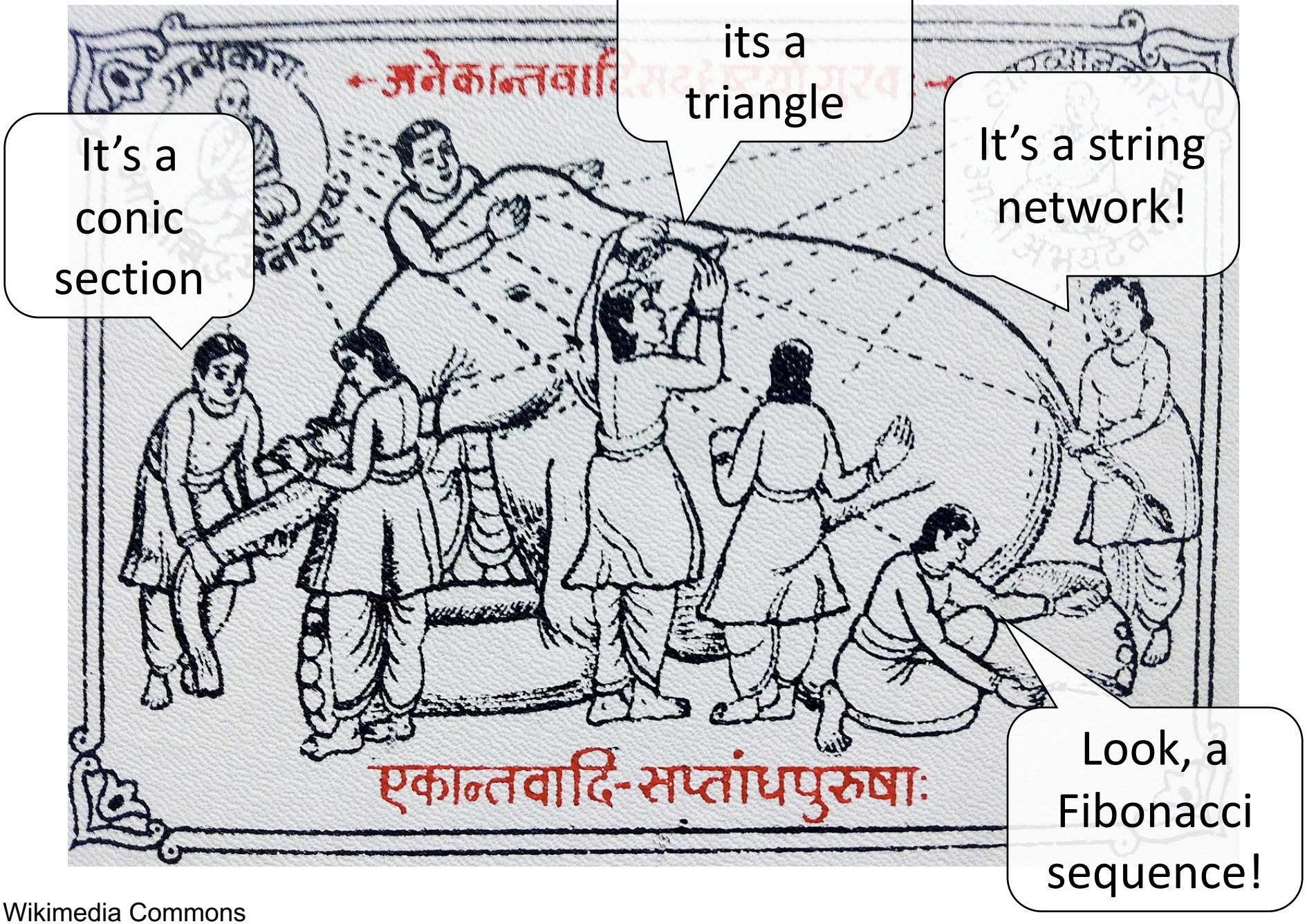
[Horoi et al. 2020]

Quantative Comparisons



DeMAP


a
Splatter groups
Splatter paths
Noiseless simulation
Geodesic distances
Noisy simulation
2D embeddings
PCA, PHATE, t-SNE, etc.
Euclidean distances
Spearman correlation
Spearman R (geodesic, Euclidean)
PHATE
t-SNE
Noise
b
Dropout
Biological variation
Subsampled cells
Subsampled genes
Splatter paths
Splatter groups
Spearman R (geodesic, Euclidean)
PHATE
UMAP
t-SNE
DMs
MDS on DMs
Force-directed layout
Isomap
PCA
LLE
t-SNE on DM
MDS
Monocle2
Dropout probability
Coefficient of variation
Number of cells retained
Number of genes retained



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Conclusions

- Dimensionality reduction and visualization helps to identify structure in data
- PCA uses eigenvectors to identify linear combinations of features that explain maximum variance
- Manifold learning identifies non-linear patterns and structure
- Graphs can be used to approximate manifolds and are helpful for modelling single cell data
- Laplacian Eigenmaps and diffusion maps visualize data using dominant non-linear directions in data manifold
- PHATE summarizes manifold information in 2D
- UMAP, tSNE are non-linear methods focused on preserving local neighborhoods in 2D

What questions do you have about today's lecture material?

Top