Deep Unsupervised Learning (Overview)

Naeemullah Khan
naeemullah.khan@kaust.edu.sa

KAUST Academy
King Abdullah University of Science and Technology

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Supervised ML

x	y

$x \in \mathbb{R}^d$

$y \in \mathbb{R}^k$

Regression problem

x	y

$x \in \mathbb{R}^d$

$y \in \{0, 1 \dots c\}$

classification

$$\hat{y} = f_\theta(x)$$

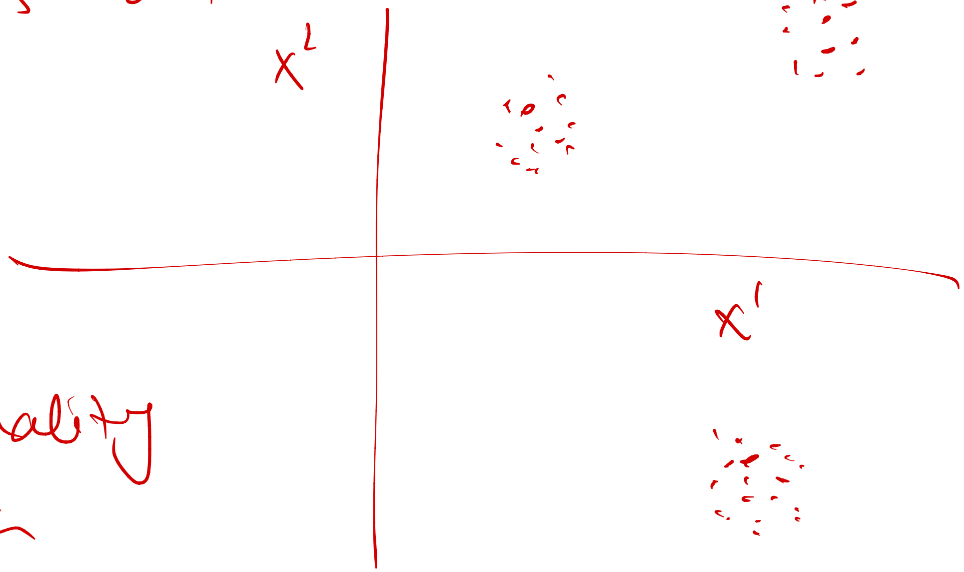
Unsupervised ML

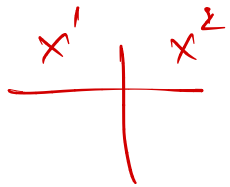
1. pattern detection
2. Generation
3. Compression

X
x_0
⋮
x_N

① Clustering

① measure the "distance" of points and groups points with small distances together





② Compression / Dimensionality Reduction

$\underline{x} \in \mathbb{R}^d$ $\qquad$ $\underline{x}' \in \mathbb{R}^{d'}$

$d' < d$

$x \in \mathbb{R}^3$ $\qquad$ $x' \in \mathbb{R}^2$

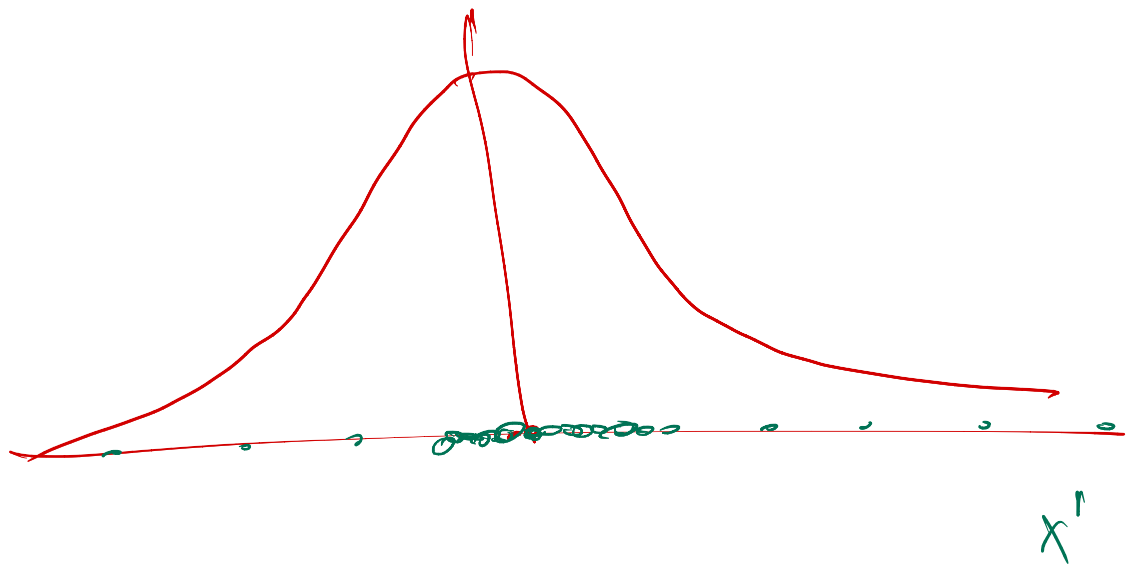
$$x'^1 = \underbrace{f_1}(x^1, x^2, x^3)$$

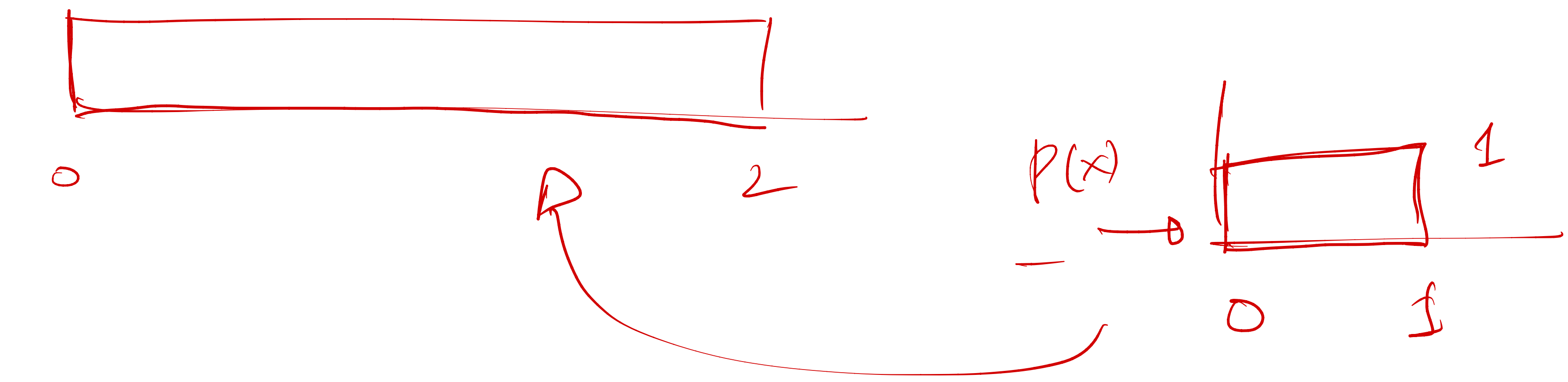
$$x'^2 = \underbrace{f_2}(x^1, x^2, x^3)$$

Generative tools

$X = \{x_1 \ldots \ldots x_N\}$

$x \sim p(x)$





$$z = f(x)$$

$p(z)$

$$z = 2x$$

Gen AI

DNN

$p(x^t = 1 \mid x^{t<})$

$p(x^t = 2 \mid x^{t<})$

$\vdots$

$p(x^t = 255 \mid x^{t<})$

15

Clustering

Metric Similarity / Dissimilarity

$$\underline{d_{ij}} = \sum_{k=1}^{d} \left(x_i^k - x_j^k \right)^2$$

$$= \underbrace{\|x_i - x_j\|_2^2}$$

Dim. Reduction

go from $x \to x'$ without loss of information

$x \in \mathbb{R}^d$

$x' \in \mathbb{R}^{d'}$

Lo information is measured through variance

$d' < d$

$x, \tilde{x} \in \mathbb{R}^d$

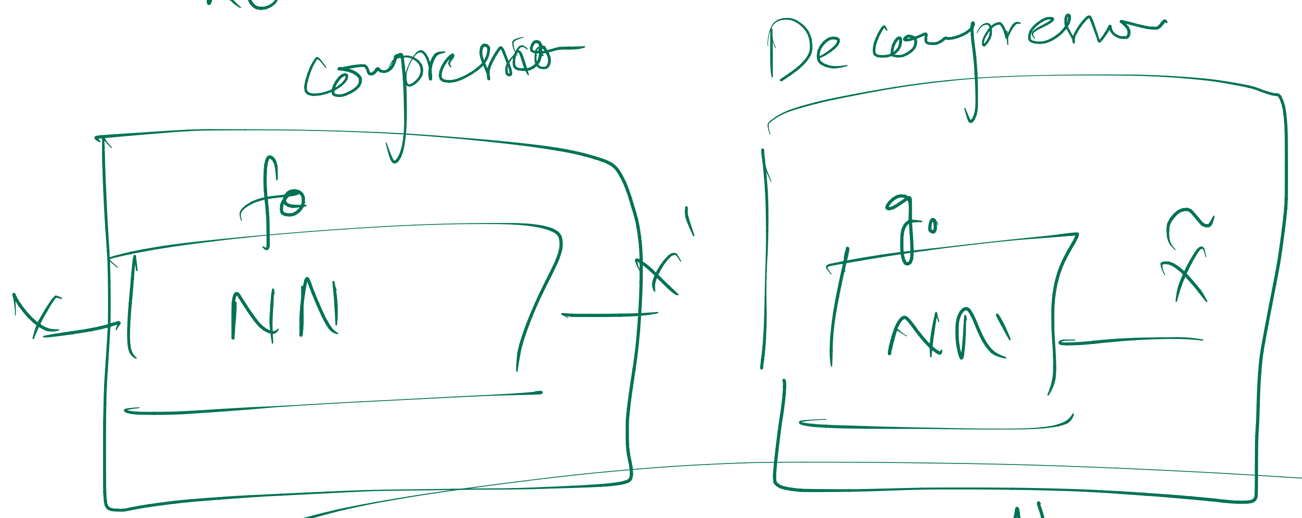
$x' \in \mathbb{R}^{d'}$

$$x \to \boxed{f_\theta(x)} \to x' \to \boxed{g_\phi(x')} \to \hat{x}$$

$d' < d$

$\|x - \tilde{x}\|_2^2$ is small $< \epsilon$

At



$\tilde{x}$	x
$g_\phi(f_\theta x)$	x_1
	$\vdots$
	x_N

$$\arg\min_{\theta\,\phi} \frac{1}{N}\sum_{i=1}^{N} \| x_i - \tilde{x}_i \|_2^2$$

Generative Tools

$$x \sim \underbrace{P_{\theta X}(x)}$$ $\leftarrow \theta$

$$\underbrace{\frac{X}{x_1 \; \vdots \; x_N}}$$

$x_1 - - \quad x_N$

$$P_\theta(x_1, x_2, x_3 \cdots x_N) = \underbrace{P_\theta(x_1) \cdot P_\theta(x_2) \cdots P_\theta(x_N)}_{} - i$$

$$= \prod_{i=1}^{N} P_\theta(x_i)$$

$$\log\left(\prod_{i=1}^{N} P_\theta(x_i)\right)$$

$$\boxed{\arg\max_\theta - \sum_{i=1}^{N} \log P_\theta(x_i)}$$

NLP

$\to \theta$ Gen AI Images

$$p_\theta(x_1 \cdots x_N) = p_\theta(x_1)\, p_\theta(x_2) \cdots p_\theta(x_N)$$

$$= \prod_{i=1}^{N} p_\theta(x_i)$$

$$\boxed{\arg\max_\theta \prod_{i=1}^{N} p_\theta(x_i)} = \arg\max_\theta \log\left(\prod_{i=1}^{N} p_\theta(x_i)\right)$$

$$\arg\min_\theta -\log \prod_{i=1}^{N} p_\theta(x_i) = \arg\min_\theta - \sum_{i=1}^{N} \log(p_\theta(x_i))$$

clustering

K clusters

X

x^1

$\vdots$

x^N

$$\sum_{j \in C_k} \sum_{i \in C_k} d_{ij} = \sum_{j \in C_k} \sum_{i \in C_k} \| x_i - x_j \|_2^2$$

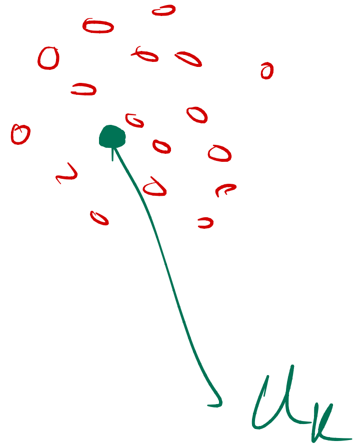
$1, \dots, K$

$$\sum_{k=1}^{K} \sum_{j \in C_k} \sum_{i \in C_k} \| x_i - x_j \|_2^2$$

C_k

K^N

$$\underbrace{\sum_{k=1}^{K} \sum_{j \in C_k} \| x_i - u_k \|_2^2 \frac{1}{N_k}}$$



K means Algorithm

input K

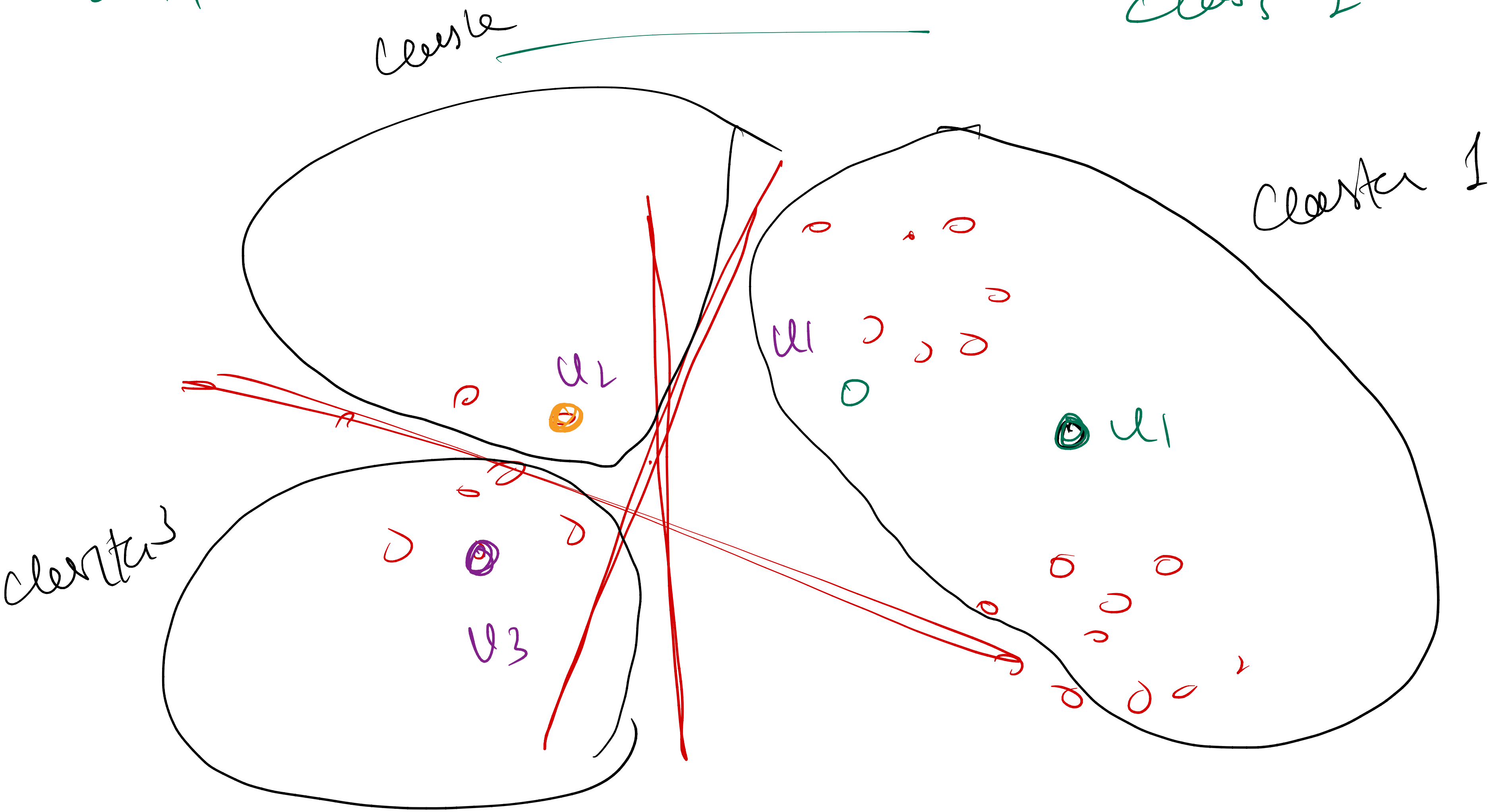
initialize K centroids

$d_1 < d_2$

class 2

$d_2 > d_1$

class 1



Motivation

- **Supervised learning** requires large labeled datasets, which are often unavailable in real-world scenarios.
- **Deep Unsupervised Learning** enables discovery of hidden structures, patterns, and representations in data **without labeled outputs**.
- Systems can learn autonomously from vast amounts of raw, unstructured data.
- Understanding unsupervised methods (clustering, dimensionality reduction, anomaly detection) helps:
  - Unlock insights missed by supervised approaches
  - Reduce dependency on human annotation

Learning Outcomes

By the end of this presentation, you will be able to:

1. **Define** deep unsupervised learning and **differentiate** it from supervised and semi-supervised approaches.
2. **Understand** the importance and real-world applications of unsupervised learning in:
   - Natural language processing
   - Computer vision
   - Fraud detection
3. **Identify** key challenges in unsupervised learning:
   - Model evaluation
   - Lack of labeled ground truth

Learning Outcomes (cont.)

4. **Classify** main types of unsupervised learning tasks:
   - Clustering
   - Dimensionality reduction
   - Anomaly detection
5. **Explain** core dimensionality reduction techniques:
   - Principal Component Analysis (PCA)
   - t-Distributed Stochastic Neighbor Embedding (t-SNE)
   - Uniform Manifold Approximation and Projection (UMAP)
6. **Appreciate** the role of deep learning in enhancing traditional unsupervised methods through representation learning.

Unsupervised Learning - Definition

- We have a dataset without labels. Out goal is to learn something interesting about the underlying structure of the data:
  - Clusters hidden in the dataset.
  - Outliers: particularly unusual and/or interesting data points.
  - Useful signals hidden in the noise, e.g., human speech over a noisy background.

Components of Unsupervised Learning

- **Data**: Unlabeled data, e.g., images, text, or sensor readings.
- **Model**: A mathematical representation of the data, e.g., a mixture model or a neural network.
- **Objective function**: A measure of how well the model fits the data, e.g., likelihood or reconstruction error.
- **Optimization algorithm**: An algorithm to minimize the objective function, e.g., gradient descent or expectation-maximization.
- **Evaluation metrics**: Measures to assess the quality of the learned model, e.g., silhouette score or clustering accuracy.
- **Applications**: Use cases for unsupervised learning, e.g., clustering, dimensionality reduction, or anomaly detection.

Aspect	Supervised Learning	Unsupervised Learning
Objective	Learn a function f from labeled input–output pairs.	Discover structure or representations in unlabeled data.
Evaluation	Accuracy, precision/recall on held-out labels.	Clustering validity indices (e.g. silhouette), reconstruction error.
Cost	Methods range from $\mathcal{O}(n)$ to $\mathcal{O}(n^3)$ per fit.	k-means $\mathcal{O}(nkd)$, hierarchical $\mathcal{O}(n^2)$, PCA $\mathcal{O}(nd^2)$.
Labels/Clusters	Fixed, known set of classes.	Number of clusters unknown; must be chosen or inferred.
Output	Classifier or regressor for new inputs.	Cluster assignments, embeddings, density models, or generative samples.

Table 1: Key differences between Supervised and Unsupervised Learning

Unsupervised Learning - Applications

Unsupervised learning is used in various fields and applications, including:

- **Visualisation**: Identifying and making accessiblge useful hidden structures in the data.
- **Anomaly Detection**: Identifying factory components that are likely to break soon.
- **Signal denoising**: Extracting human speech from a noisy recording.
- **Generative Models**: Learning to generate new data points similar to the training data.
- **Feature Learning**: Automatically discovering useful representations of the data.
- **Data Preprocessing**: Cleaning and transforming data for better performance in supervised learning tasks.

Application: Discovering Structure in Digits

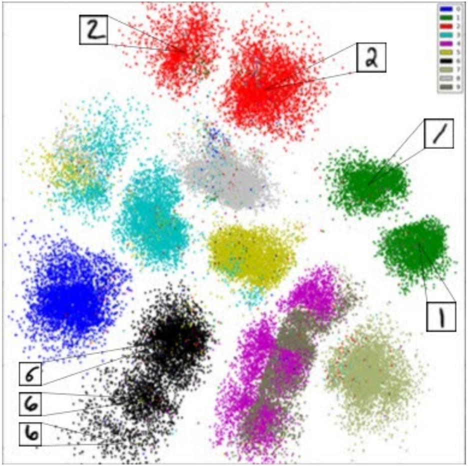


Figure 2: Unsupervised learning can discover structure in digits without any labels.

Application: DNA Analysis

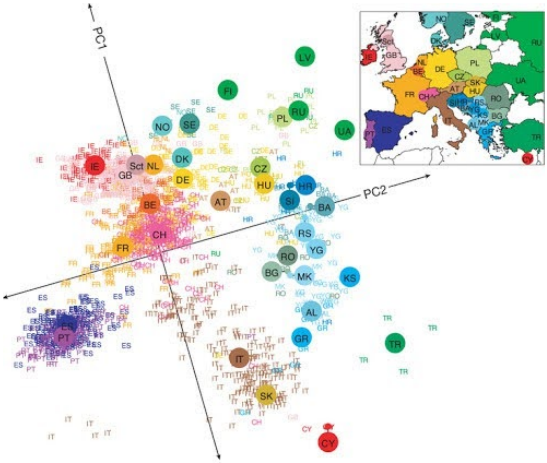


Figure 3: Dimensionality reduction applied to DNA reveal the geography of European countries.

What is Deep Unsupervised Learning?

- Capturing rich patterns in raw data with deep networks in a label-free way.

What is Deep Unsupervised Learning? (cont.)

- Capturing rich patterns in raw data with deep networks in a label-free way.
  - **Generative Models**: Recreate raw data distribution.

Unsupervised Learning - Challenges

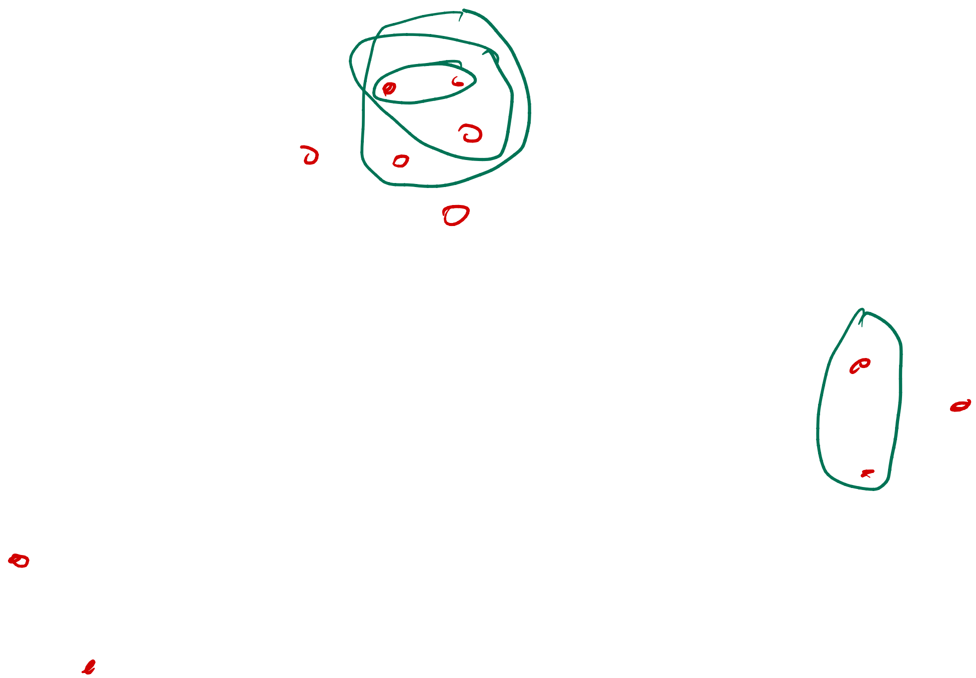
Why is unsupervised learning challenging?

- **Exploratory data analysis**: Unsupervised learning is often used for exploratory data analysis, where the goal is to discover patterns or structures in the data without any prior knowledge of the labels.
- **Difficult to assess performance**: Evaluating the performance of unsupervised learning algorithms can be challenging, as there are no ground truth labels to compare against ("right answer" unknown).
- **Sensitivity to noise**: Unsupervised learning algorithms can be sensitive to noise and outliers in the data, which can lead to misleading results.
- **Curse of dimensionality**: As the number of features increases, the data becomes sparse, making it difficult to find meaningful patterns.

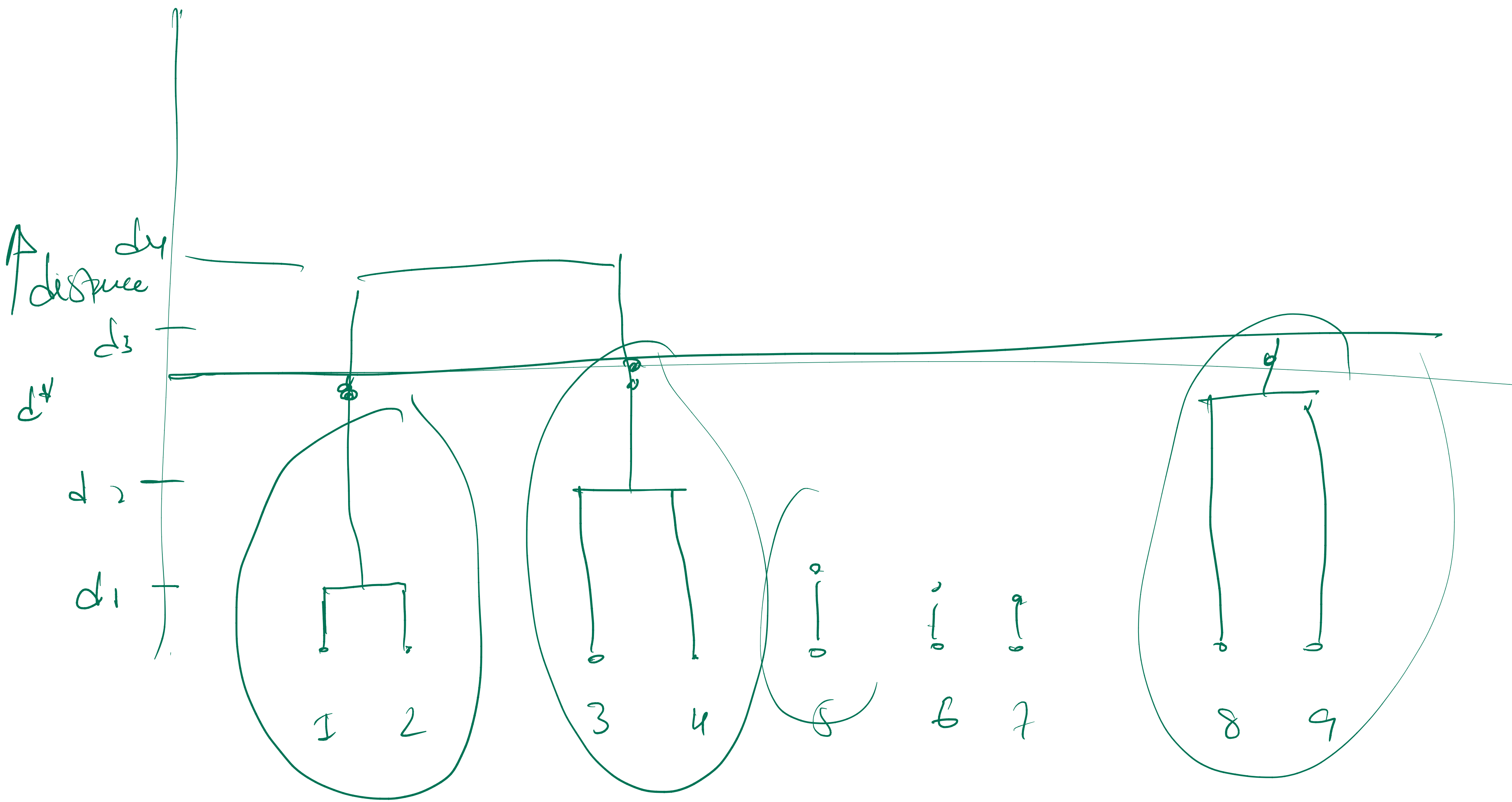
Unsupervised Learning - Types

- **Cluster Analysis**:
  - For identifying homogenous subgroups of samples.
  - **Examples**: K-means, hierarchical clustering, DBSCAN.
- **Dimensionality Reduction**:
  - For finding a low-dimensional representation to characterize and visualize the data.
  - Reducing the number of features in a dataset while preserving important information.
  - **Examples**: PCA, t-SNE, UMAP.
- **Anomaly Detection**:
  - **Finding outliers in the dataset**: Identifying unusual (rare items, events, or observations) data points that do not conform to expected patterns.
  - **Examples**: Isolation Forest, One-Class SVM, Autoencoders.

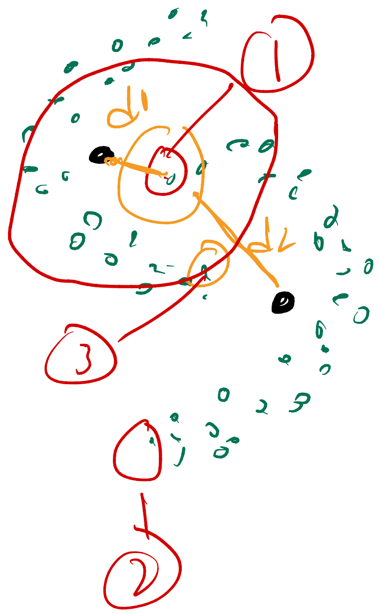
Clustering Review

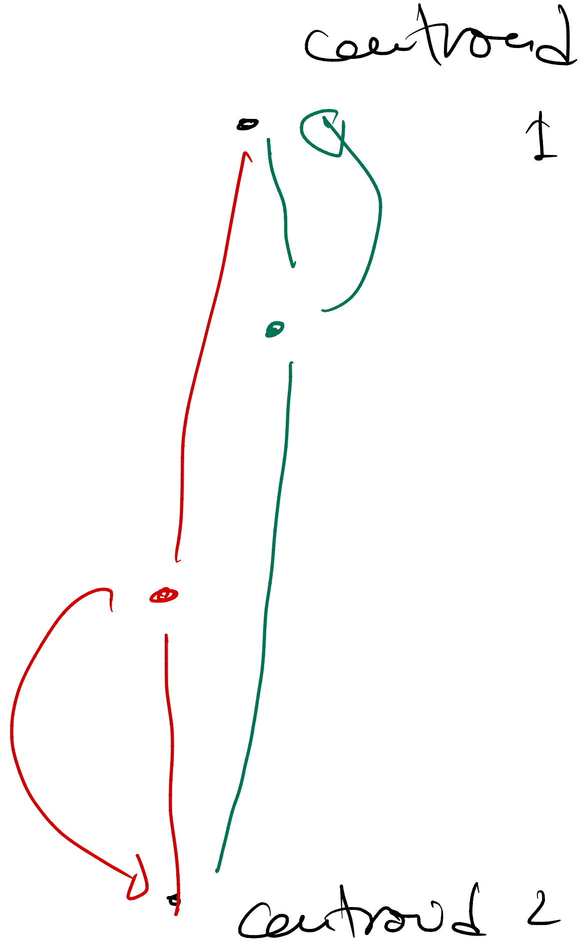


Hieravchical clustering



DBSCAN





1 eps — 0.1

2 Num of neighbour — 3

hierarchical cluster

Clustering

A set of methods for finding subgroups within the dataset.

- Observations should share common characteristics within the same group, but differ across groups.
- Groupings are determined from attributes of the data itself — differs from classification.

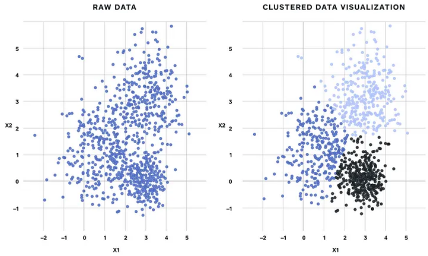


Figure 4: Taking a 2 dimensional dataset and separating it into 3 distinct clusters. [Source]

Input: Dataset $D = \{x_1, x_2, \ldots, x_n\}$, number of clusters k
Output: Cluster assignments for each data point

Initialization: Randomly initialize k cluster centroids or seeds;

repeat

Assignment Step: Assign each data point x_i to the nearest cluster based on a distance metric;

Update Step: Recompute cluster centroids using current assignments;

until *convergence or maximum iterations reached*;

return Final cluster assignments;

Algorithm: Generic Clustering Algorithm

Clustering Vs Classification

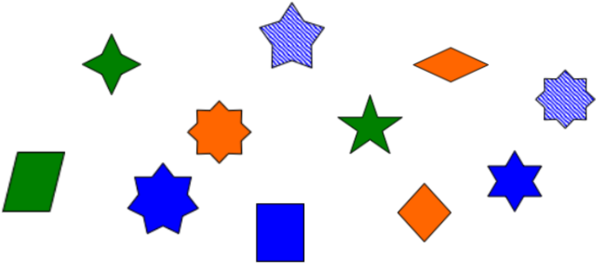


Figure 5: Sample data points.

Classification

- Labels available
- Assigning to known classes
- Supervised

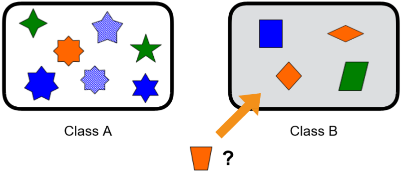


Figure 6: Classification result.

Clustering

- No labels
- Grouping based on similarity
- Unsupervised

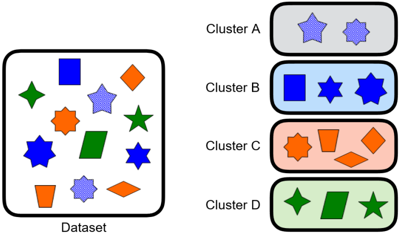


Figure 7: Clustering result.

Clustering: Types

- **Centroid-Based Clustering**: Groups data points based on their proximity to a central point, such as K-means or K-medoids.
- **Hierarchical Clustering**: Builds a hierarchy of clusters using either agglomerative (bottom-up) or divisive (top-down) approaches.
- **Model-Based Clustering**:
  - Each cluster is represented by a parametric distribution.
  - Dataset is a mixture of distributions.
  - Assumes a probabilistic model for the data and uses statistical methods to identify clusters, such as Gaussian Mixture Models (GMM).
- **Hard Clustering**:
  - Each data point is assigned exclusively to exactly one cluster.
  - **Example algorithms**: K-means, Hierarchical clustering.

  - **interpretation**: No ambiguity — clusters are crisp and non-overlapping.

- **Soft/Fuzzy Clustering**:
  - Each data point can belong to multiple clusters simultaneously with varying degrees of membership (probabilities or weights).
  - **Example algorithms**: Gaussian Mixture Models (GMM), Fuzzy C-means.
  - **interpretation**: Reflects uncertainty or mixed membership — clusters can overlap.

Groups data into K clusters that satisfy two properties.

1. Each observation belongs to at least one of the K clusters.
2. Clusters are non-overlapping. No observation belongs to more than one cluster.

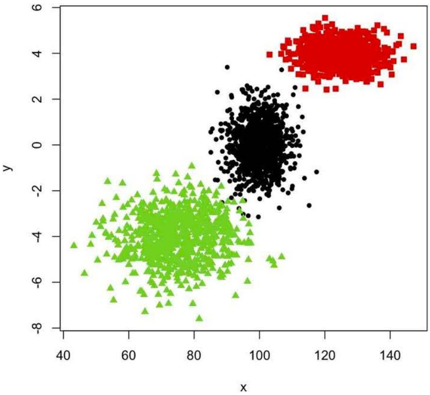


Figure 8: Clusters.

A good clustering is one for which the *within-cluster variation* is as small as possible.

Denote each cluster by C_k, and let $W(C_k)$ be a measure of the within-cluster variation.

K-means aims to solve the following optimization problem:

$$\underset{C_1,\ldots,C_k}{\text{minimise}} \left\{ \sum_{k=1}^{K} W(C_k) \right\} \tag{1}$$

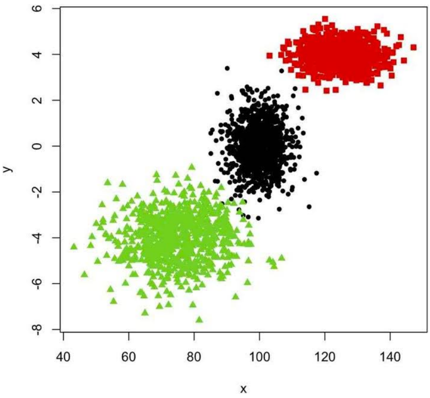


Figure 9: Clusters.

Clustering - K-means (cont.)

How to measure within-cluster variation?

The most common choice is squared Euclidean distance:

$$W(C_k) = \frac{1}{|C_k|} \sum_{i,i' \in C_k} \sum_{j=1}^{p} (x_{ij} - x_{i'j})^2 \qquad (2)$$

where $|C_k|$ is the number of points in cluster C_k and x_{ij} is the j^{th} feature of the i^{th} point.

Which means overall we solve:

$$\underset{C_1,\ldots,C_k}{\text{minimise}} \left\{ \sum_{k=1}^{K} \frac{1}{|C_k|} \sum_{i,i' \in C_k} \sum_{j=1}^{p} (x_{ij} - x_{i'j})^2 \right\} \qquad (3)$$

Clustering - K-means (cont.)

- It turns out that this optimization problem is difficult to solve, as it is discrete and there are nearly K^n ways to split n samples into K clusters.
- In practice, use an iterative algorithm that finds a local minimum to this optimization.

Input: Dataset $D = \{x_1, x_2, \ldots, x_n\}$, number of clusters k
Output: Cluster assignments for each data point

Initialization: Randomly initialize k cluster centroids or seeds;

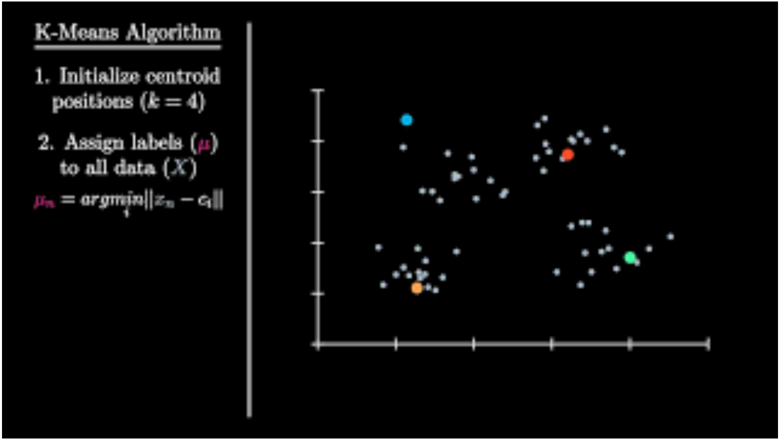
Repeat until convergence:

- **Assignment Step:** Assign each data point x_i to the nearest cluster based on a distance metric;
- **Update Step:** Recompute cluster centroids using current assignments;
- **Convergence Check:** Check if cluster assignments have changed or if centroids have stabilized;

Return: Final cluster assignments and centroids;

Algorithm: K-means Clustering Algorithm

Watch the K-means clustering algorithm in action:



Clustering - K-means (cont.)

1. It can be shown that the value of the objective function will never increase at each iteration of k-means.
2. Since the algorithm finds local minima, however, it will result in different clusters with different initializations.

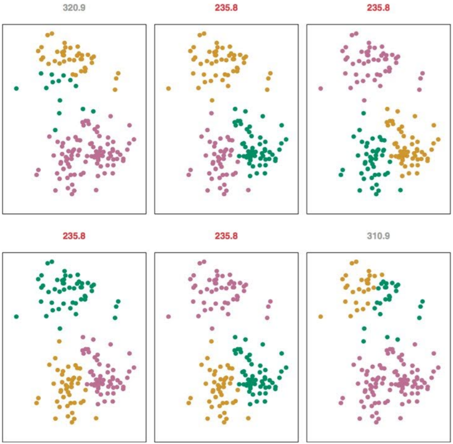


Figure 10: Different initializations of K-means.

Pros

- Simple and easy to implement
- Efficient for large datasets
- Works well with spherical clusters
- Scalable to large datasets

Cons

- Not robust to data perturbations and different initializations
- Sensitive to initial centroid placement
- Assumes spherical clusters
- Requires specifying the number 'K' of clusters in advance
- Sensitive to outliers
- May converge to local minima
- Not suitable for non-convex shapes

Cluster based on distances between observations.

Represented as a tree hierarchy (*dendrogram*) rather than a partition of data.

Does not require committing to a choice of K.

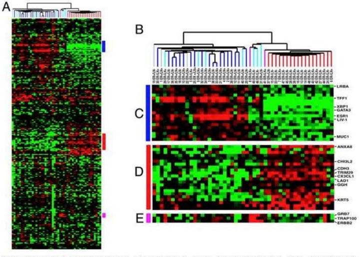


Figure 11: Sørlie, Therese, et al. (2003) "Repeated observation of breast tumor subtypes in independent gene expression data sets," PNAS.

Clustering - Hierarchical: Dendrograms

- Each leaf in a dendrogram is a sample/ observation.
- As we move up the dendrogram, observations that are similar to each other begin to fuse into branches.
- Branches then fuse into bigger branches.
- Observations that fuse later (near the top of the tree, or root) are more different than observations that fuse earlier (near the leaves).

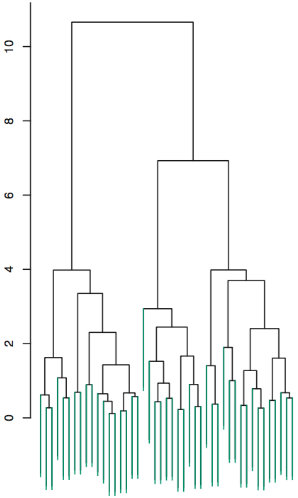


Figure 12: ISL (8th printing 2017)

Note that the horizontal distance between observations on a dendrogram is not the appropriate assessment of observation similarity. Instead, look at vertical axis where branches are first fused.

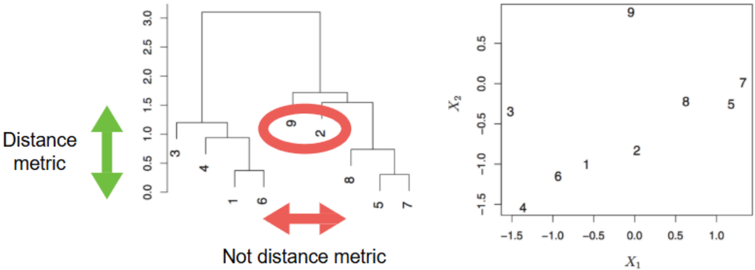


Figure 13: ISL (8th printing 2017)

Clusters are created by making a horizontal cut across the dendrogram. Clusters are the separate trees below the cut.

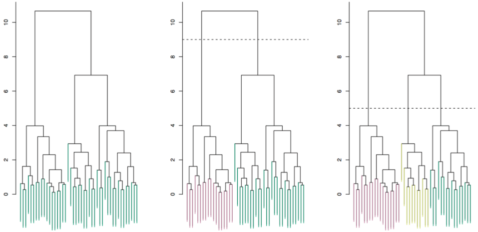


Figure 14: ISL (8th printing 2017)

Building a Dendrogram

A dendrogram is most commonly built using a bottom-up or agglomerative algorithm.

We start at the leaves and group observations until we reach the root containing the entire dataset.

Like in k-means, we need a measure of similarity. Again, the most common is Euclidean distance.

- Compute the distance between each pair of observations.
- Merge the two closest observations into a cluster.
- Compute the distance between the new cluster and all other observations.
- Repeat until all observations are in one cluster.
- The distance between clusters is computed using a linkage method.

Input: Dataset $D = \{x_1, x_2, \ldots, x_n\}$
Output: Dendrogram representing the hierarchical structure of clusters
Initialization: Treat each data point as a separate cluster;
Compute distance matrix: Calculate pairwise distances between all clusters;
Repeat until only one cluster remains:

- Find the two closest clusters based on the distance matrix;
- Merge the two clusters into a new cluster;
- Update the distance matrix to reflect the new cluster;
- Recompute distances between the new cluster and all other clusters using a linkage method;

Return: Dendrogram representing the hierarchical structure of clusters;

Algorithm: Hierarchical Clustering Algorithm

w3schools: Codes and Playground

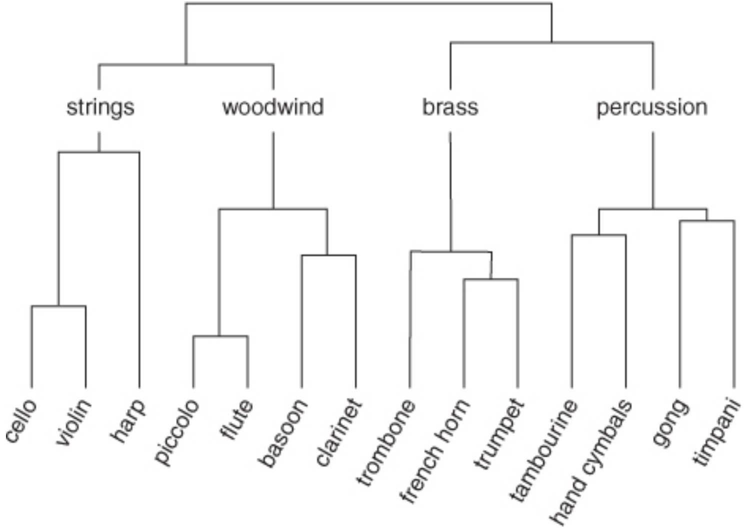


Figure 15: Dendrogram interpretation.

Distance between groups

It's easy to compute Euclidean distance between two observations. What is the distance or similarity between two groups or clusters of observations?

Linkage: defines the dissimilarity between two groups of observations. Most common types are *complete*, *average*, *single*, and *centroid*.

- **Single Linkage**: Distance between two clusters is the minimum distance between any two points in the clusters.
- **Complete Linkage**: Distance between two clusters is the maximum distance between any two points in the clusters.
- **Average Linkage**: Distance between two clusters is the average distance between all pairs of points in the clusters.
- **Centroid Linkage**: Distance between two clusters is the distance between their centroids.
- **Ward's Linkage**: Distance between two clusters is the increase in variance when the two clusters are merged.

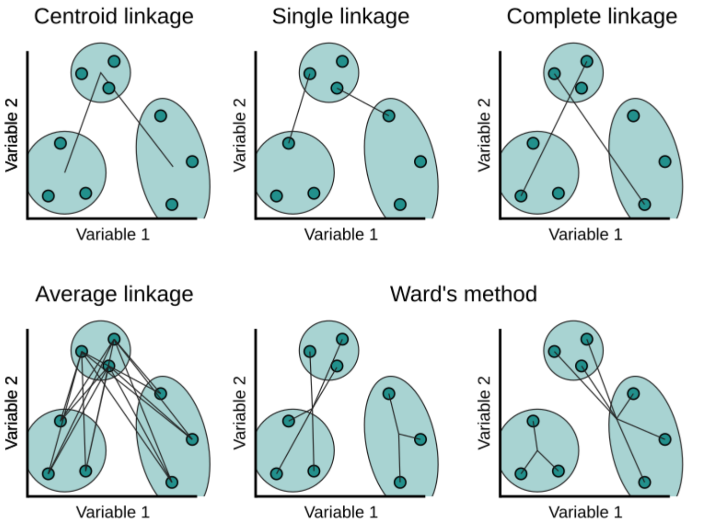


Figure 16: Linkage methods.

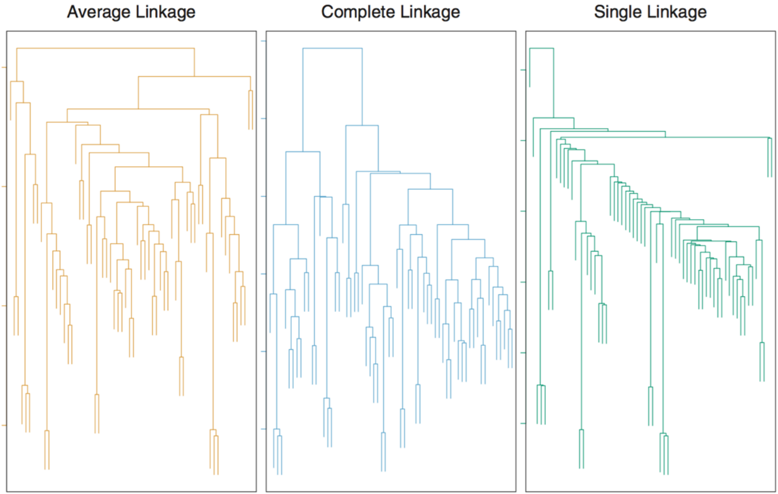


Figure 17: Dendrogram with different linkage types.

Clustering - Hierarchical: Pros and Cons

Pros

- No need to specify the number of clusters K in advance.
- Dendrograms provide a visual representation of the clustering process.
- Can capture complex cluster shapes and relationships.

Cons

- Computationally expensive for large datasets.
- Do have to pick where to cut the dendrogram to obtain clusters
- Sensitive to similarity measure and type of linkage used.
- Sensitive to noise and outliers.
- Difficult to interpret and choose the optimal number of clusters.

Clustering - Density-Based Methods

- Clustering based on density (local cluster criterion), such as density-connected points or based on an explicitly constructed density function.
- **Major features**:
  - Discover clusters of arbitrary shape
  - Handle noise
  - One scan
  - Need density parameters

- **Major algorithms**:
  - DBSCAN (Density-Based Spatial Clustering of Applications with Noise): Ester, et al. (KDD'96)
  - OPTICS (Ordering Points to Identify the Clustering Structure): Ankerst, et al. (SIGMOD'99)
  - HDBSCAN (Hierarchical Density-Based Spatial Clustering of Applications with Noise): Campello, et al. (ACM TIST'15)
  - DENCLUE (DENsity-based CLUstEring): Hinneburg and Gabriel (KDD'97)
  - CLIQUE (CLustering In QUEst): Karypis, Han, and Kumar (SIGMOD'98)

- **DBSCAN** (Density-Based Spatial Clustering of Applications with Noise):
  - Density = number of points within a specified radius ϵ.
  - A point is a core point if it has more than a specified number of points (MinPts) within ϵ. These are points that are at the interior of a cluster.
  - A border point has fewer than MinPts within ϵ, but is in the neighborhood of a core point
  - A noise point is any point that is not a core point or a border point.
  - Groups together points that are closely packed together, marking as outliers points that lie alone in low-density regions.
  - Parameters:
    - ϵ: Maximum distance between two points for them to be considered as in the same neighborhood.
    - MinPts: Minimum number of points required to form a dense region.

Clustering - DBSCAN (cont.)

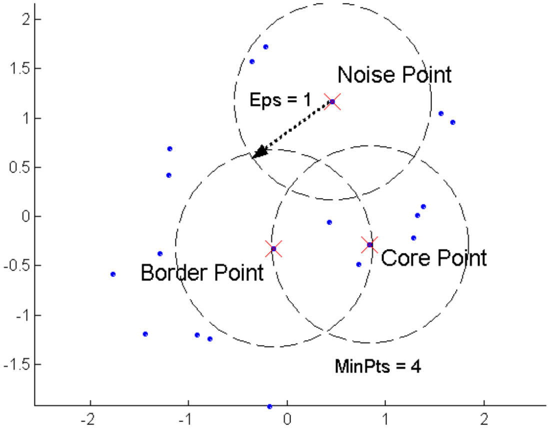


Figure 18: DBSCAN features: Core, Border, and Noise Points

Input: Set of points P, distance threshold ε, minimum number of points *minPts*

Output: A set of clusters

Construct a directed graph $G = (V, E)$ where each node in V corresponds to a point in P;

foreach *point* $c \in P$ **do**

  if *c is a core point (i.e., $|\mathcal{N}_\varepsilon(c)| \geq minPts$)* **then**

    foreach *point* $p \in \mathcal{N}_\varepsilon(c)$ **do**

      Add a directed edge $(c \to p)$ to E;

    end

  end

end

$N \leftarrow V$;

while *there exists a core point $c \in N$* **do**

  Let X be the set of nodes reachable from c via directed edges in G;

  Form a cluster $C = X \cup \{c\}$;

  Remove all nodes in C from N;

end

Figure 19: Original Points

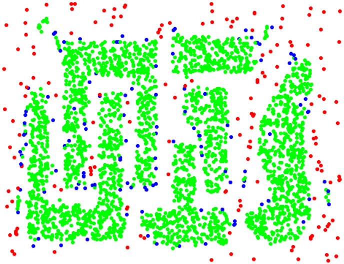


Figure 20: Point types: Core, Border, and Noise Points

Eps = 10, MinPts = 4

Figure 21: Original Points

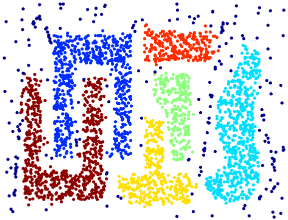


Figure 22: Clusters identified by DBSCAN

DBSCAN works well when:

- Clusters are of varying shapes and sizes.
- There is a clear distinction between dense and sparse regions.
- The data contains noise or outliers.

When DBSCAN Doesn't Works Well

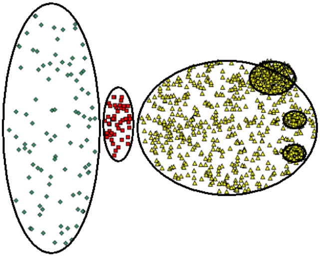


Figure 23: Original Points

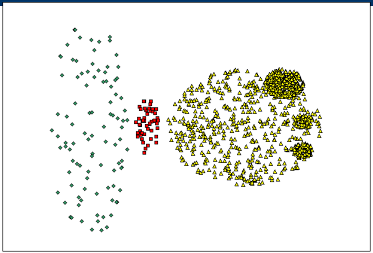


Figure 24: MinPts=4, ϵ=9.75

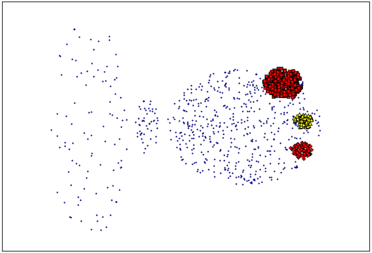


Figure 25: MinPts=4, ϵ=9.92

DBSCAN does not work well when:

- Clusters are of varying densities.
- The data has varying scales or dimensions.
- There are overlapping clusters.
- The choice of ϵ and MinPts is not suitable for the data distribution.

DBSCAN: Determining ϵ and MinPts

- A common approach to determine ϵ is to use a k-distance graph:
  - For each point, compute the distance to its k-th nearest neighbor.
  - Plot these distances in ascending order.
  - Look for a "knee" in the plot, which indicates a suitable value for ϵ.
- MinPts is often set based on domain knowledge or heuristics:
  - A common rule of thumb is to set MinPts to at least the dimensionality of the data plus one (e.g., for 2D data, MinPts $= 3$).
  - Higher values of MinPts can lead to fewer clusters and more noise points.

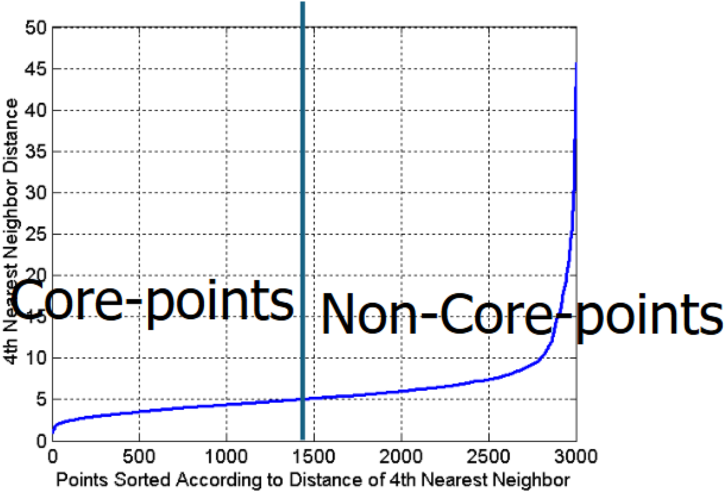


Figure 26: Run K-means for Minp=4 and not fixed ϵ

DBSCAN: Complexity and Limitations

- **Complexity**:
  - The time complexity of DBSCAN is $O(n \log n)$ for spatial data structures like KD-trees or R-trees, where n is the number of points.
  - Without spatial indexing, the complexity can degrade to $O(n^2)$.
  - Space complexity is $O(n)$, as it needs to store the points and their cluster assignments.
- **Limitations**:
  - Sensitive to the choice of ϵ and MinPts parameters.
  - Struggles with clusters of varying densities.
  - Not suitable for high-dimensional data due to the curse of dimensionality.
  - Cannot handle clusters that are not well-separated in terms of density.

- **Good**:
  - Can discover clusters of arbitrary shape.
  - Effectively handles noise and outliers.
  - Requires only one scan of the data.
  - Suitable for datasets with varying densities.
  - Does not require prior knowledge of the number of clusters.
- **Bad**:
  - Does not work well in high-dimensional datasets.
  - Parameter selection is tricky.
  - Has problems identifying clusters of varying densities ($\rightarrow$ SSN algorithm).
  - Density estimation is simplistic ($\rightarrow$ does not create a real density function, but rather a graph of density-connected points).

$current\_cluster\_label \leftarrow 1$
for all core points **do**
  if the core point has no cluster label **then**
    $current\_cluster\_label \leftarrow current\_cluster\_label + 1$
    Label the current core point with cluster label $current\_cluster\_label$
  end if
  for all points in the Eps-neighborhood, except i^{th} the point itself **do**
    if the point does not have a cluster label **then**
      Label the point with cluster label $current\_cluster\_label$
    end if
  end for
end for

Figure 27: DBSCAN Algorithm Steps

Where are we heading?

Gene	Description	Cell 1	Cell 2	Cell 3	Cell 4	Cell 5
Inpp5d	inositol polyphosphate-5-phosphatase D	7.00	5.45	5.89	6.03	5.75
Aim2	absent in melanoma 2	3.01	4.37	4.59	4.38	4.18
Gldn	gliomedin	3.48	3.63	4.61	4.70	4.74
Frem2	Fras1 related extracellular matrix protein 2	4.75	4.66	3.46	3.74	3.45
Rps3a1	ribosomal protein S3A1	6.10	7.23	7.44	7.36	7.34
Slc38a3	solute carrier family 38, member 3	1.90	3.16	3.52	3.61	3.19
Mt1	metallothionein 1	5.07	6.49	6.46	6.04	6.05
C1s1	complement component 1, s subcomponent 1	2.74	3.02	3.86	4.10	4.10
Cds1	CDP-diacylglycerol synthase 1	4.55	4.22	3.80	3.16	3.12
Ifi44	interferon-induced protein 44	4.82	4.52	3.87	3.42	3.59
Lefty2	left-right determination factor 2	6.95	6.28	5.88	5.60	5.61
Fmr1nb	fragile X mental retardation 1 neighbor	4.28	2.78	3.10	3.25	2.57
Tagln	transgelin	7.93	7.91	7.20	7.02	6.68

Figure 28: Original Points

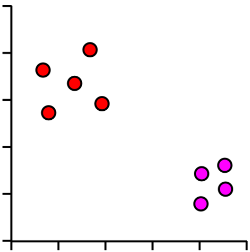
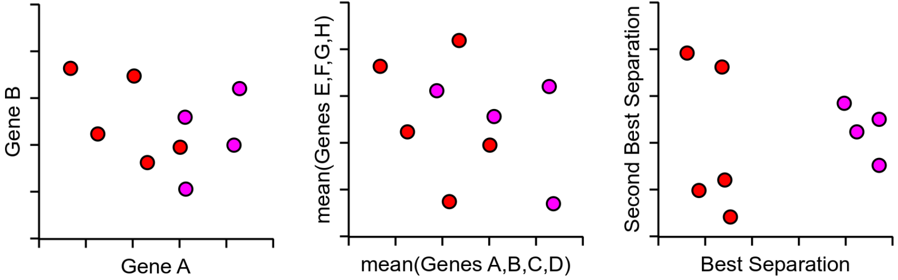


Figure 29: Clusters identified by DBSCAN

- Each dot is a cell.
- Groups of dots are similar cells.
- Separation of groups could be interesting biology.

- 5000 cells and 2500 measured genes
- Realistically only 2 dimensions we can plot (x, y)



Principal Component Analysis (PCA)

- Principal Component Analysis (PCA) is a method for optimally summarizing large, multi-dimensional datasets.
- PCA identifies a smaller number of dimensions (ideally 2) that retain most of the useful information present in the original data.
- The technique constructs a set of new variables, called Principal Components (PCs), which are linear combinations of the original variables.
- Each Principal Component represents a specific weighted sum of the original features. For example:

$$\text{PC} = (10\times\text{GeneA}) + (3\times\text{GeneB}) + (-4\times\text{GeneC}) + (-20\times\text{GeneD}) + \ldots$$

- By projecting the data onto these principal components, PCA reduces dimensionality while preserving as much variance (information) as possible.

Principal Component Analysis (PCA) (cont.)

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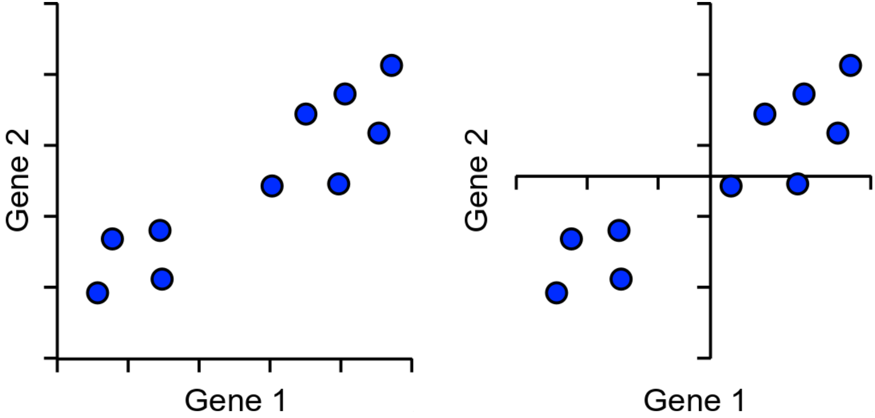
Simple example using 2 genes and 10 cells

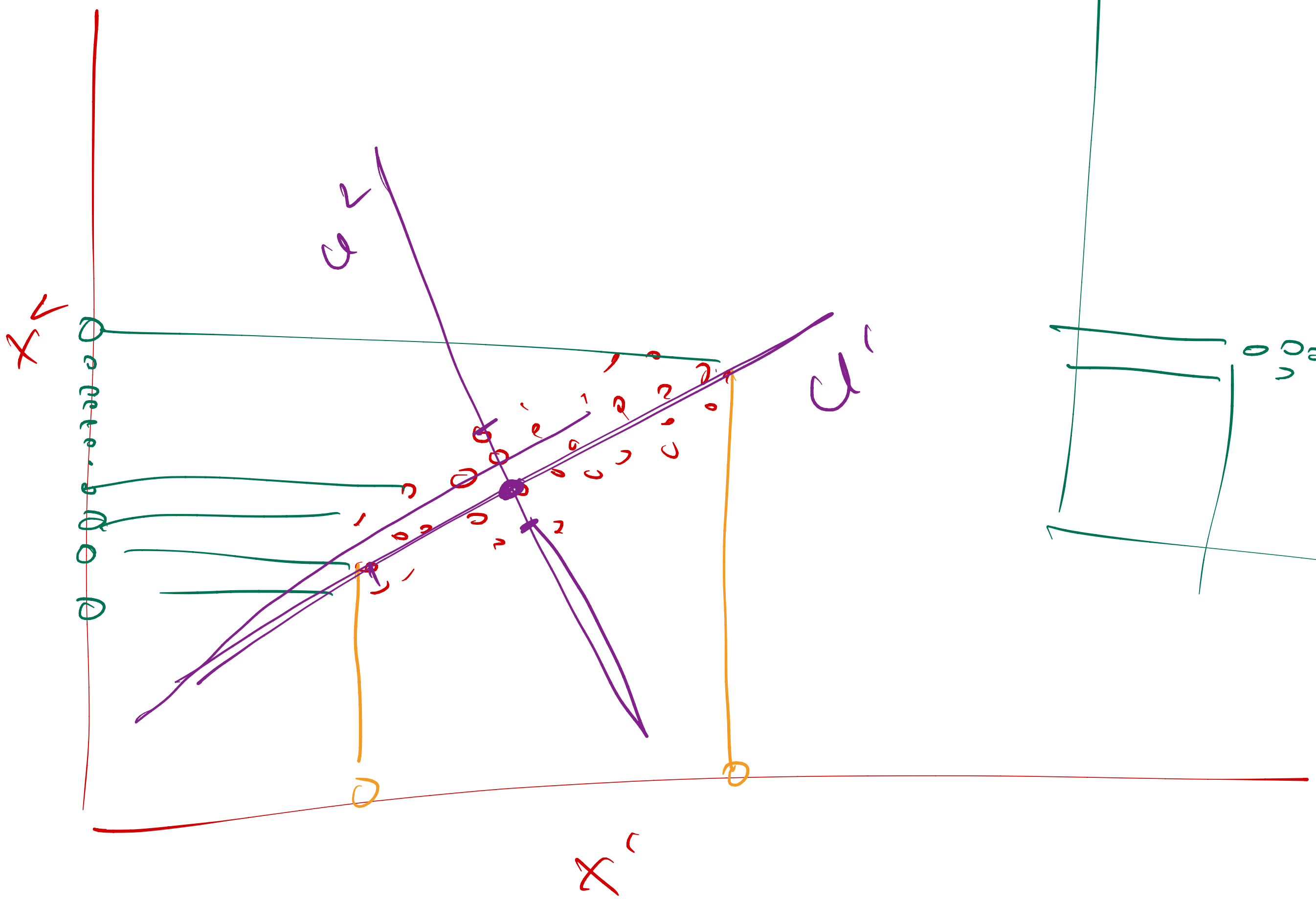
Simple example using 2 genes and 10 cells

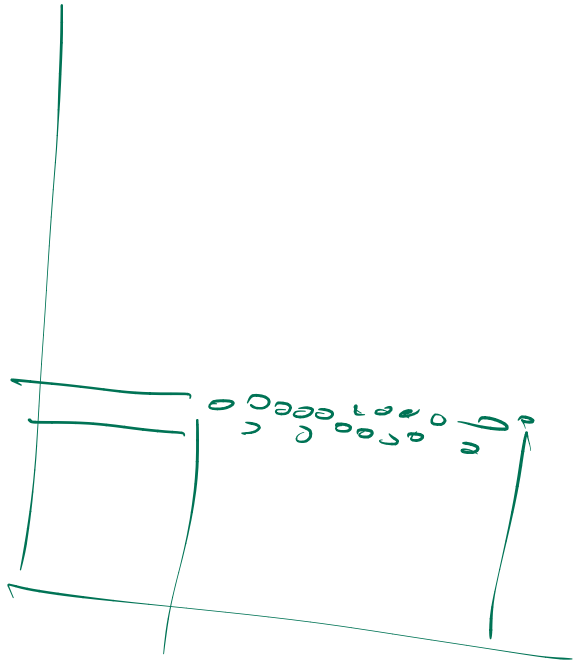


Dimensionality Reduction

$$x^1 + x^2$$
$$\shortparallel$$

x^1	x^2	x^3
1	1	2
0	1	1
1	1	1
3	2	5
0	2	2
1	1	2





t-SNE / UMAP

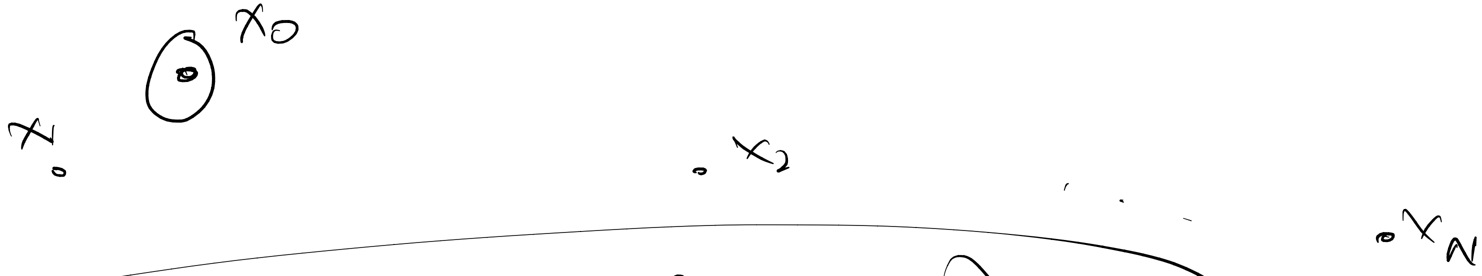
$p(x_i | x_0)$

probability

$d_{x_i x_0}$
1
.9
3
8

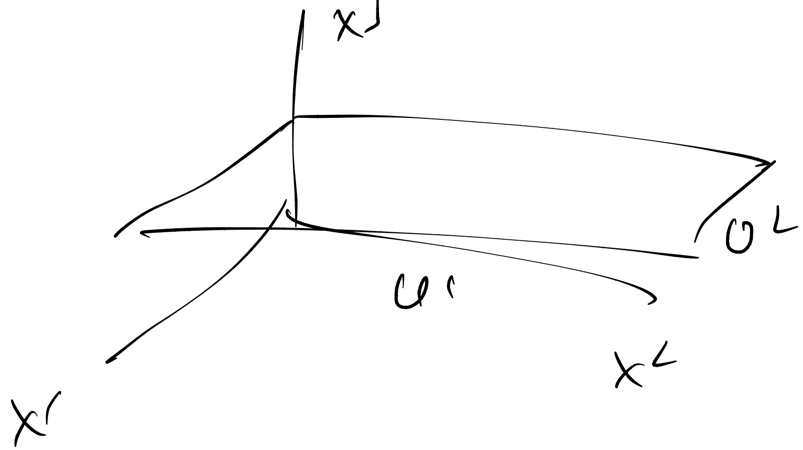
tSNE

$\propto \exp^{-d_{x_i x_0}}$



$$\boxed{p(x_i | x_0) = \frac{\exp(-d_{x_i, x_0})}{\sum_{j=1}^{N} \exp(-d_{x_j, x_0})}}$$

$$p(u^i \mid u^0) = \frac{\exp(-d_{u^i,u^0})}{\sum_j \exp(-d_{u^j,u^0})}$$



$$\min_{u^i} \; KL\left(p(x \mid x^0) \,\|\, p(u \mid u^0) \right)$$

$$\tilde{X} = (X - \mu)$$

$$\begin{array}{c|}
x^1 \quad x^2 \\
\hline
x_1 \\
x_2 \\
\vdots \\
x_N
\end{array}$$

$$\mu = \frac{1}{N} \sum_{i=1}^{N} x$$

$$cov = \underbrace{X^T X}$$

eigen value

eigen vector

$$\boxed{Av = \lambda v}$$

v is an eigen vector

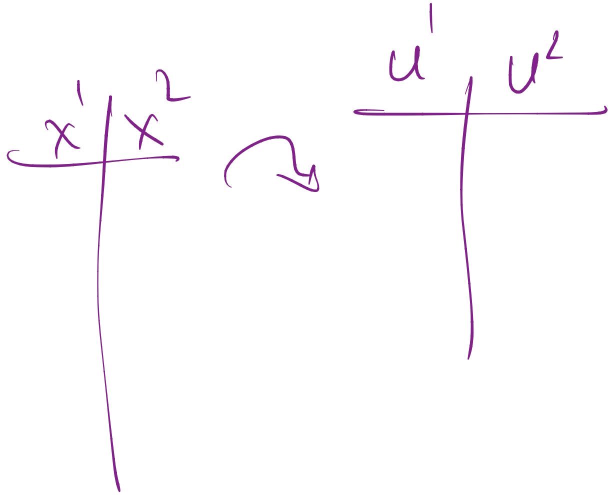
$\underbrace{\lambda}$ is an eigen value

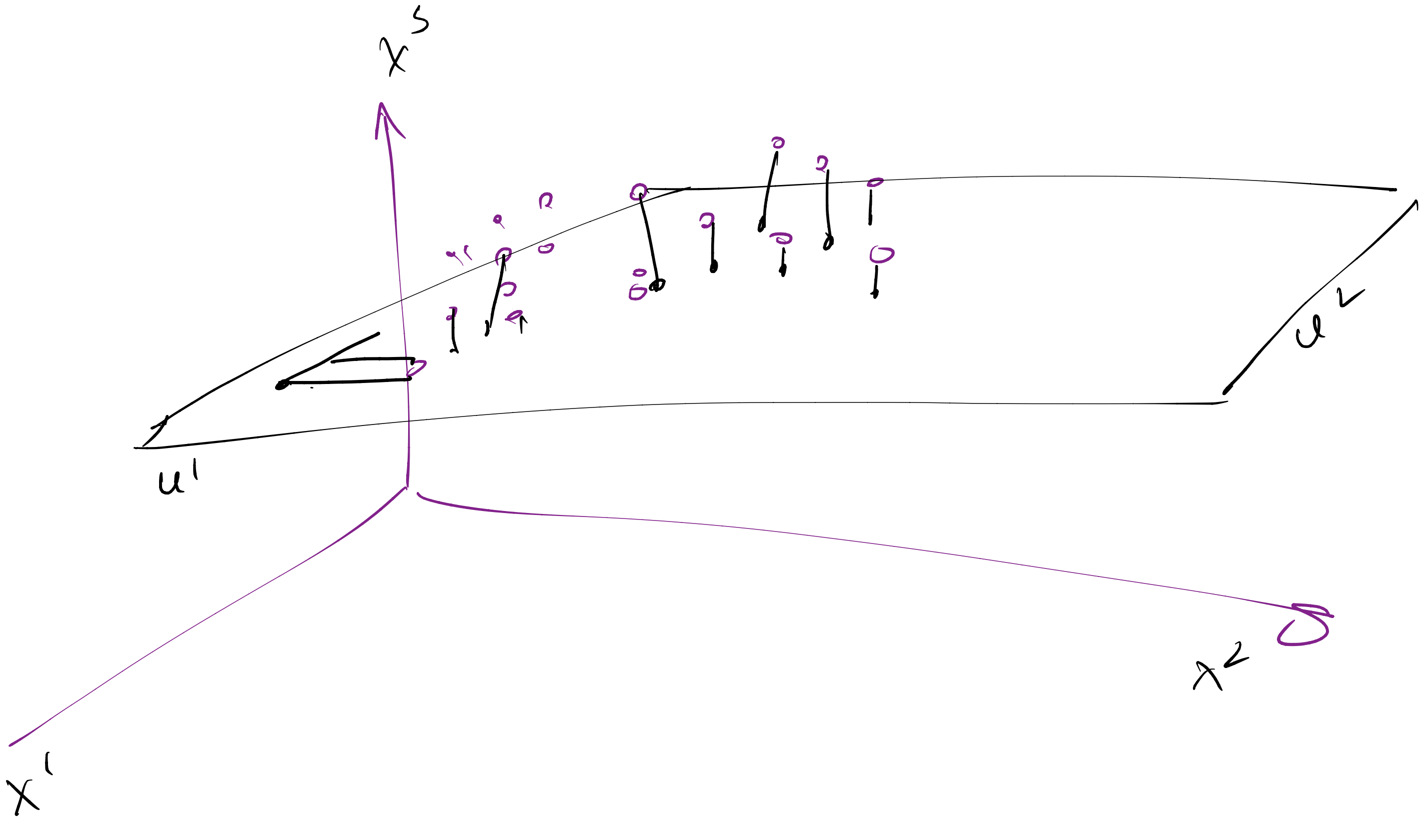
variance along principle component

$u^1 = x^1 + x^2$

$$\underbrace{\begin{bmatrix} 1 \\ 1 \end{bmatrix}} \qquad \underbrace{10}$$

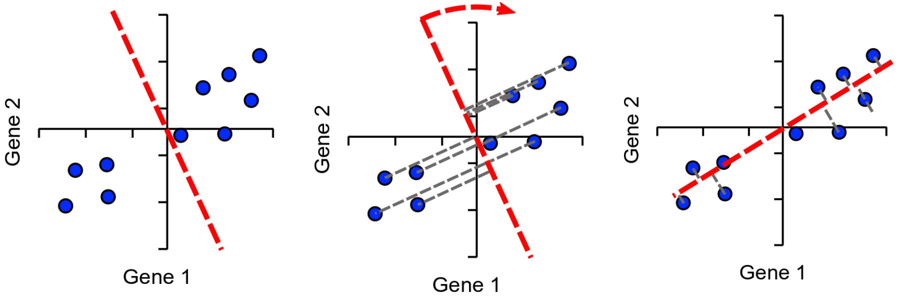
$$\underbrace{\begin{bmatrix} -1 \\ 1 \end{bmatrix}} \qquad \underbrace{1}$$



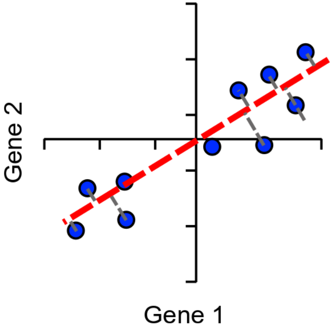


x^3
x^1
x^2
u^1
u^2

Find line of best fit, passing through the origin



Assigning Loadings to Genes



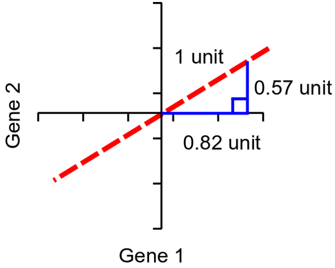
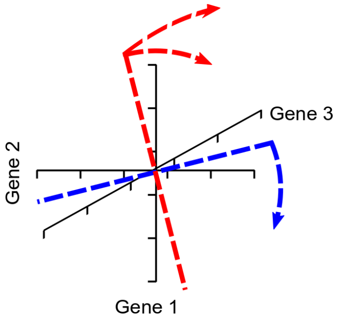


Figure 30: **Eigenvector** or Single Vector

- **Loadings** represent the contribution of each gene to the principal component.
- For this example using 2 genes and 10 cells:
  - Gene1 loading: 0.82
  - Gene2 loading: 0.57
- A higher loading means the gene has a greater influence on the principal component.

More Dimensions

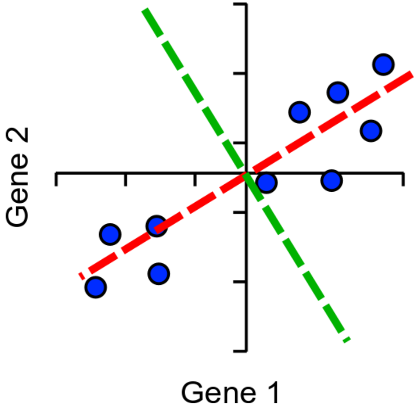


- The same idea extends to datasets with more dimensions (n genes).
- The first principal component (PC1) finds the direction of maximum variance, rotating in $(n - 1)$ dimensions.
- The next principal component (PC2) is perpendicular to PC1 and rotates in the remaining $(n - 2)$ dimensions.
- Each subsequent principal component is always perpendicular to the previous ones, capturing the next largest variance.
- The last principal component is the only remaining perpendicular direction.
- The number of principal components always equals the number of original genes (features).

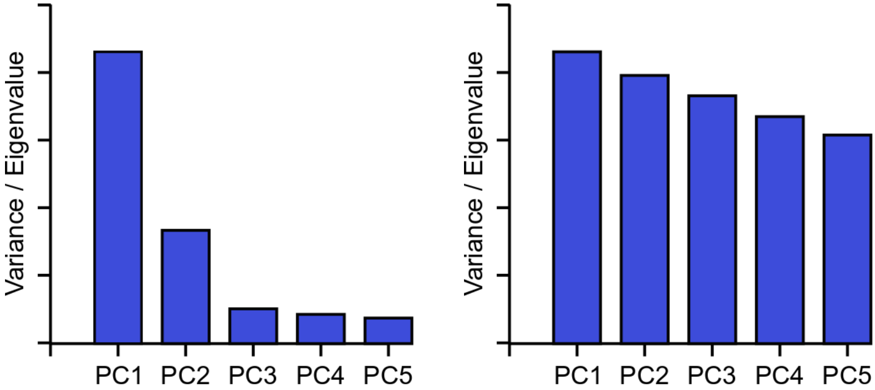
Explaining Variance

- Each principal component (PC) explains a certain proportion of the total variance in the data. Together, all PCs account for 100% of the variance.
- PC1 always explains the largest amount of variance.
- PC2 explains the next largest amount, and so on for subsequent PCs.
- Since we typically plot only 2 dimensions (PC1 and PC2), it's important to check how much of the total variance these two PCs explain.
- **How do we calculate this?**

Explaining Variance (cont.)

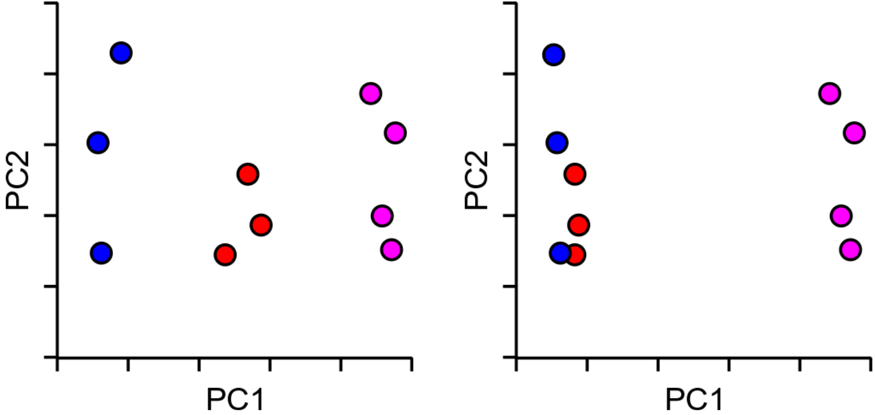


- Project each data point onto the principal component (PC).
- Calculate the distance of each projected point to the origin.
- Compute the sum of squared differences (SSD) from the origin.
- This SSD is a measure of variance, called the *eigenvalue*.
- Divide the SSD by (number of points − 1) to obtain the actual variance explained by the PC.


Variance / Eigenvalue
PC1
PC2
PC3
PC4
PC5
Variance / Eigenvalue
PC1
PC2
PC3
PC4
PC5

So PCA is great then?

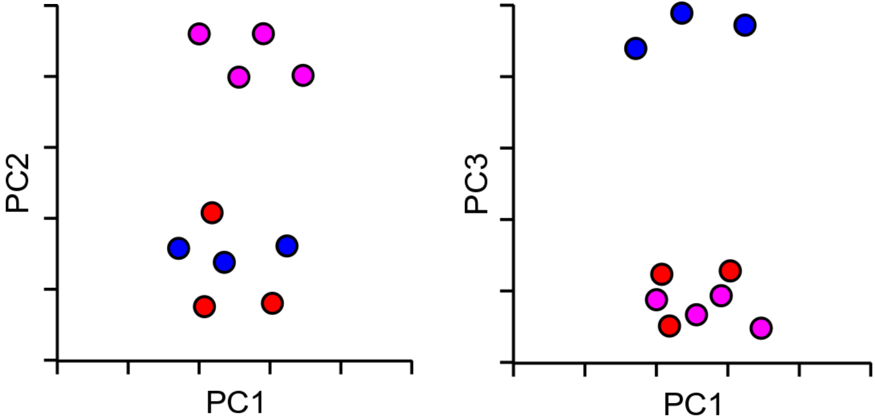
Kind of...



Non-linear separation of values

So PCA is great then? (cont.)

Kind of. . .



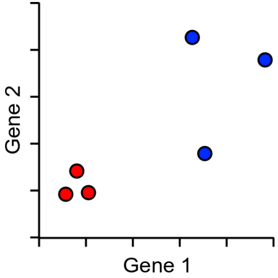
Not optimised for 2-dimensions

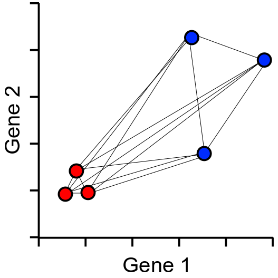
tSNE to the rescue. . .

- T-Distributed Stochastic Neighbour Embedding
- Aims to solve the problems of PCA
- Non-linear scaling to represent changes at different levels
- Optimal separation in 2-dimensions

tSNE: How does it work?

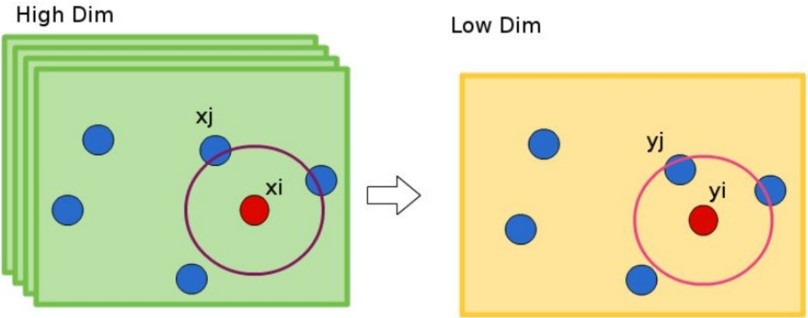
- Based around all-vs-all table of pairwise cell to cell distances
- Each cell is represented as a point in a high-dimensional space
- The pairwise distances are converted into probabilities



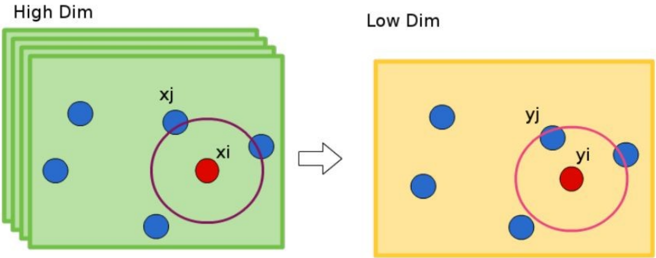


	0	10	10	295	158	153
	9	0	1	217	227	213
	1	8	0	154	225	238
	205	189	260	0	23	45
	248	227	246	44	0	54
	233	176	184	41	36	0

tSNE: Underlying idea



Measure pairwise similarities between high-dimensional and low-dimensonal objects



$$p_{j|i} = \frac{exp(-||x_i - x_j||^2/2\sigma_i^2)}{\sum_{k\neq i} exp(-||x_i - x_k||^2/2\sigma_i^2)}$$

tSNE: Stochastic Neighbor Embedding (cont.)

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KAUST ACADEMY

Converting the high-dimensional Euclidean distances into conditional probabilities that represent similarities

- Similarity of datapoints in High Dimension

$$p_{j|i} = \frac{exp(-||x_i - x_j||^2/2\sigma_i^2)}{\sum_{k\neq i} exp(-||x_i - x_k||^2/2\sigma_i^2)}$$

- Similarity of datapoints in Low Dimension

$$q_{j|i} = \frac{exp(-||y_i - y_j||^2)}{\sum_{k\neq i} exp(-||y_i - y_k||^2)}$$

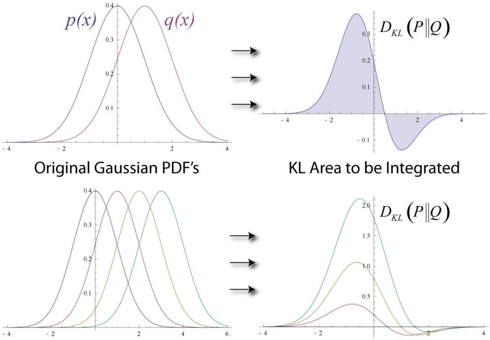
- Cost function

$$C = \sum_i KL(P_i||Q_i) = \sum_i \sum_j p_{j|i} log \frac{p_{j|i}}{q_{j|i}}$$

KL Divergence

Measures the similarity between two probability distributions it is asymmetric.

$$D_{\mathrm{KL}}(P\|Q) = \sum_i P(i) \log \frac{P(i)}{Q(i)}.$$



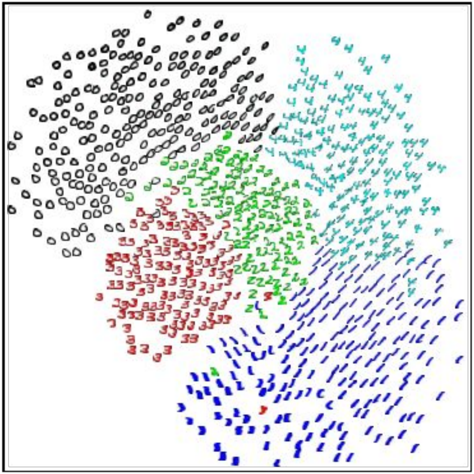
Gradient has a surprisingly simple form

$$\frac{\partial C}{\partial y_i} = \sum_{j \neq i} (p_{j|i} - q_{j|i} + p_{i|j} - q_{i|j})(y_i - y_j)$$

The gradient update with momentum term is given by

$$Y^{(t)} = Y^{(t-1)} + \eta \frac{\partial C}{\partial y_i} + \beta(t)(Y^{(t-1)} - Y^{(t-2)})$$

- The result of running the SNE algorithm on 3000 256-dimensional grayscale images of handwritten digits.
- The classes are quite well separated even though SNE had no information about class labels.
- Furthermore, within each class, properties like orientation, skew, and stroke thickness tend to vary smoothly across the space.



Symmetric SNE

Such that $p_{ij} = p_{ji}, q_{ij} = q_{ji}$, the main advantage is simplifing the gradient

$$\frac{\partial C}{\partial y_i} = 2\sum_j (p_{ij} - q_{ij})(y_i - y_j)$$

However, in practice we symmetrize (or average) the conditionals

$$p_{ij} = \frac{p_{j|i} + p_{i|j}}{2N}$$

Set the bandwidth σ_i such that the conditional has a fixed perplexity (effective number of neighbors) $Perp(P_i) = 2^{H(P_i)}$, typical value is about 5 to 50

t-Distribution

Use heavier tail distribution than Gaussian in low-dim space, we choose

$$q_{ij} \propto (1 + ||y_i - y_j||^2)^{-1}$$

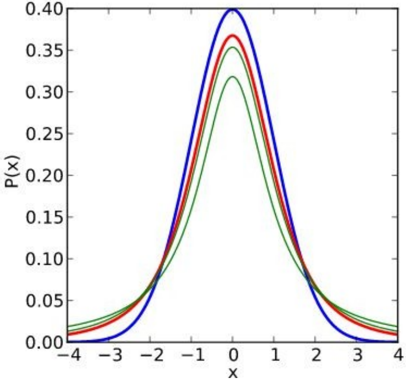
Then the gradient could be

$$\frac{\partial C}{\partial y_i} = 4 \sum_{j \neq i} (p_{ij} - q_{ij})(1 + ||y_i - y_j||^2)^{-1}(y_i - y_j)$$

- Why do we define map similarities as:

$$q_{ij} = \frac{(1 + \|y_i - y_j\|^2)^{-1}}{\sum_{k \neq l}(1 + \|y_k - y_l\|^2)^{-1}}$$

- Suppose data is intrinsically high dimensional
- We try to model the local structure of this data in the map
- Result: Dissimilar points have to be modeled as too far apart in the map!



- Similarity of datapoints in High Dimension

$$p_{ij} = \frac{exp(-||x_i - x_j||^2/2\sigma^2)}{\sum_{k \neq l} exp(-||x_l - x_k||^2/2\sigma^2)}$$

- Similarity of datapoints in Low Dimension

$$q_{ij} = \frac{(1 + ||y_i - y_j||^2)^{-1}}{\sum_{k \neq l}(1 + ||y_k - y_l||^2)^{-1}}$$

- Cost function

$$C = KL(P||Q) = \sum_i \sum_j p_{ij} log \frac{p_{ij}}{q_{ij}}$$

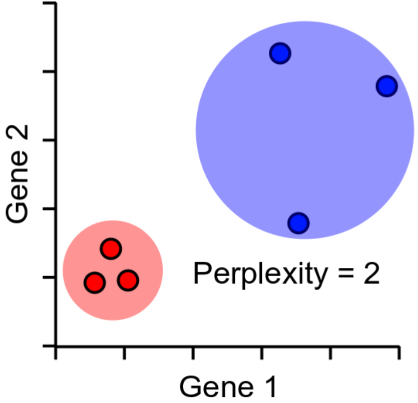
  - Large p_{ij} modeled by small q_{ij}: Large penalty
  - Small p_{ij} modeled by large q_{ij}: Small penalty
  - t-SNE mainly preserves local similarity structure of the data

- Gradient

$$\frac{\partial C}{\partial y_i} = 4 \sum_{j \neq i} (p_{ij} - q_{ij})(1 + ||y_i - y_j||^2)^{-1}(y_i - y_j)$$

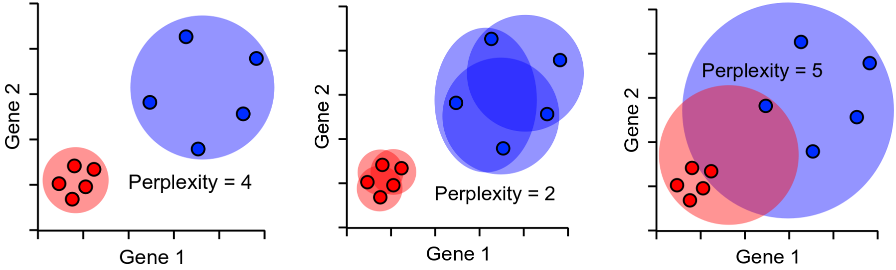
Distance scaling and perplexity

- Perplexity = expected number of neighbours within a cluster
- Distances scaled relative to perplexity neighbours



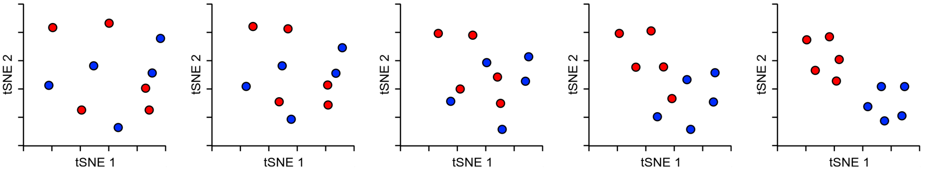
	0	4	6	586	657	836
	4	0	4	815	527	776
	9	3	0	752	656	732
	31	28	29	0	4	7
	31	24	25	4	0	7
	40	37	32	8	8	0

Perplexity Robustness

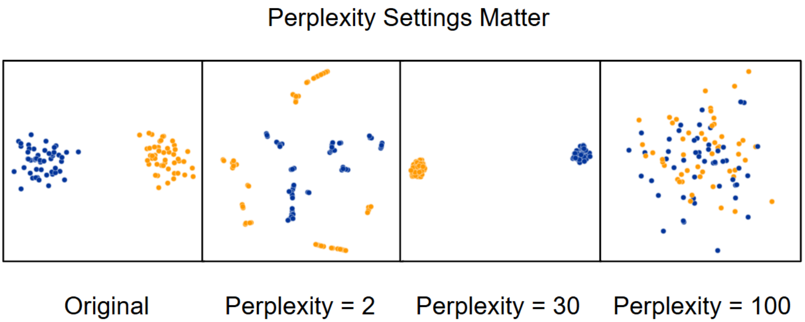


tSNE Projection

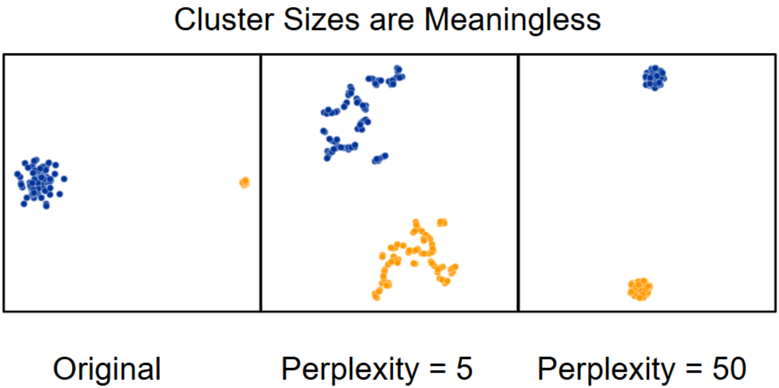
- Randomly scatter all points within the space (normally 2D)
- Start a simulation
  - Aim is to make the point distances match the distance matrix
  - Shuffle points based on how well they match
  - Stop after fixed number of iterations, or
  - Stop after distances have converged

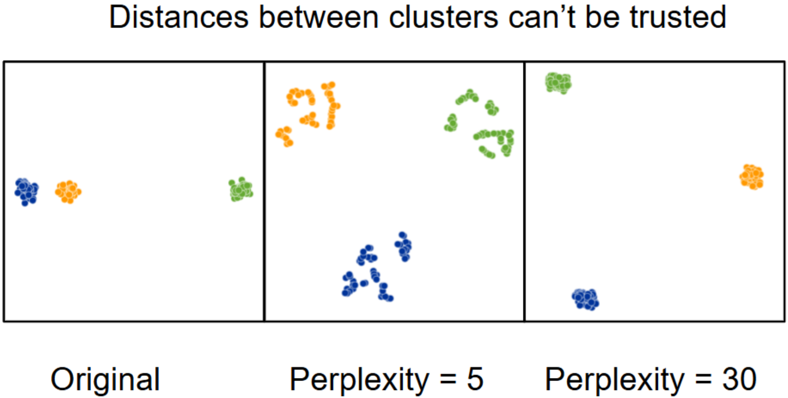


- X and Y don't mean anything (unlike PCA)
- Distance doesn't mean anything (unlike PCA)
- Close proximity is highly informative
- Distant proximity isn't very interesting
- Can't rationalise distances, or add in more data


Perplexity Settings Matter
Original
Perplexity = 2
Perplexity = 30
Perplexity = 100

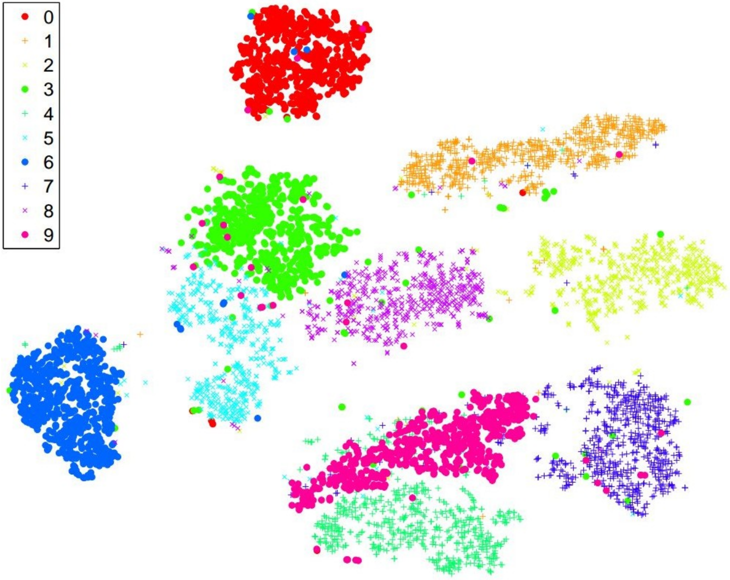
tSNE: Practical Examples (cont.)




Distances between clusters can't be trusted
Original
Perplexity = 5
Perplexity = 30

tSNE: Results on MNIST

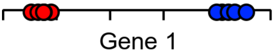
tSNE: Results on MNIST (cont.)



So tSNE is great then?

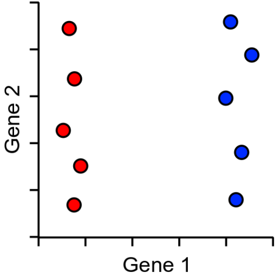
Kind of. . .

Imagine a dataset with only one super informative gene



Distance within cluster = low

Distance between clusters = high



Distance within cluster = higher

Distance between clusters = lower

- First - 3 genes
- Second - 3,000 genes
- Everything is the same distance from everything

So there is no clear solution?

PCA:

- Requires more than 2 dimensions
- Expects linear relationships

tSNE:

- Can't cope with noisy data
- Loses the ability to cluster

So there is no clear solution? (cont.)

PCA:
- Requires more than 2 dimensions
- Expects linear relationships

tSNE:
- Can't cope with noisy data
- Loses the ability to cluster

Answer: Combine the two methods, get the best of both worlds!

PCA:
- Good at extracting signal from noise
- Extracts informative dimensions

tSNE:
- Can reduce to 2D well
- Can cope with non-linear scaling

This is what many pipelines do in their default analysis!

So PCA + tSNE is great then?

Kind of...

- tSNE is slow—this is its biggest drawdown.
  - tSNE does not scale well to large datasets (10,000+ samples).
- tSNE provides reliable information only about the closest neighbors; large distance information is mostly irrelevant.

UMAP to the rescue!

- UMAP is a replacement for t-SNE, designed to fulfill the same role in dimensionality reduction.
- It is conceptually very similar to t-SNE, but introduces several relevant (and somewhat technical) changes.
- In practice, UMAP offers several advantages:
  - UMAP is significantly faster than t-SNE.
  - It can preserve more global structure compared to t-SNE.[1]
  - UMAP can operate directly on raw data without requiring PCA preprocessing.[2]
  - It allows new data points to be added to an existing projection, enabling incremental updates.

[1] Preservation of global structure may depend on the dataset and parameter choices.

[2] Although PCA preprocessing can still be beneficial in some cases.

UMAP differences

- Unlike t-SNE, which uses a single perplexity parameter, UMAP introduces two key parameters:
  - **Number of Nearest Neighbours:** Specifies how many nearest neighbours are considered for each point. This is conceptually similar to perplexity in t-SNE and controls the balance between local and global structure in the embedding.
  - **Minimum Distance:** Determines how closely UMAP packs points together in the low-dimensional space. Lower values allow points to be closer, resulting in more compact clusters, while higher values spread points apart.
- The **nearest neighbours** parameter influences the trade-off between preserving local versus global structure in the data.
- The **minimum distance** parameter affects the density and compactness of clusters in the resulting visualization.
- Together, these parameters provide more flexibility and control over the embedding compared to t-SNE's single perplexity value.

UMAP differences (cont.)

Structure preservation – mostly in the 2D projection scoring

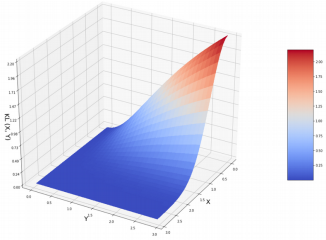


Figure 31: t-SNE

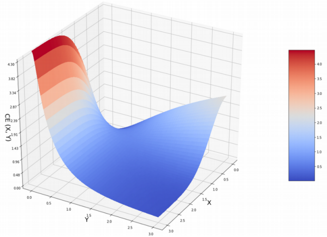
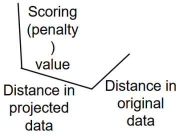
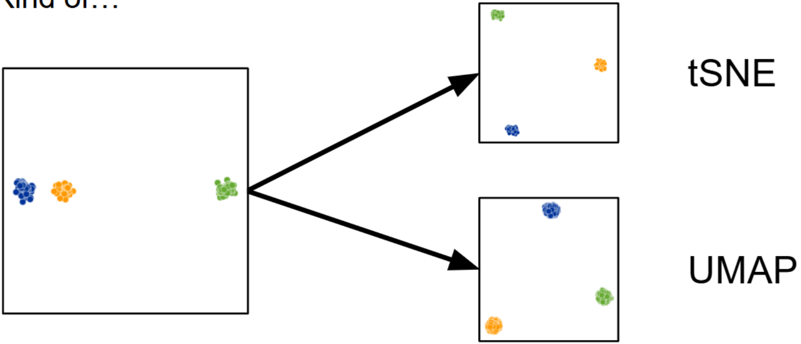


Figure 32: UMAP



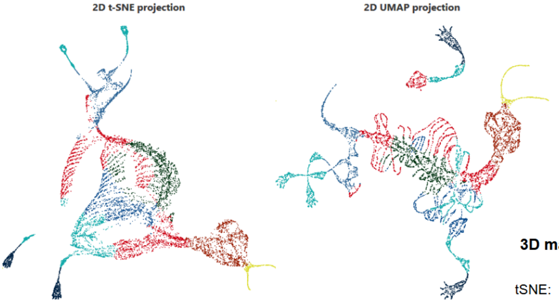
So UMAP is great then?

Kind of...



So UMAP is all hype then?

No, it really does better for some datasets…



https://pair-code.github.io/understanding-umap/

3D mammoth skeleton projected into 2D

tSNE:	Perplexity 2000	2h 5min
UMAP:	Neigh 200, mindist 0.25,	3min

Practical approach PCA + tSNE/UMAP

- **Filter the data:**
  - Remove poorly behaving cells to ensure data quality.
  - Select only expressed genes for further analysis.
  - Identify and retain variable genes to focus on informative features.
- **Apply PCA (Principal Component Analysis):**
  - Extract the most interesting and informative signals from the data.
  - Select the top principal components (PCs) to reduce dimensionality, but do not reduce directly to 2 dimensions.
- **Run t-SNE or UMAP:**
  - Calculate distances between samples using the PCA projections.
  - Scale these distances appropriately.
  - Project the data into 2 dimensions for visualization using t-SNE or UMAP.

- Kind of... as long as you only have one dataset.
  - In 10X experiments, each library is considered a **batch**.
  - Over time or distance, additional biases can be introduced.
  - These biases make direct comparisons between datasets challenging.
  - To enable meaningful comparisons, it is necessary to align the datasets and correct for batch effects.

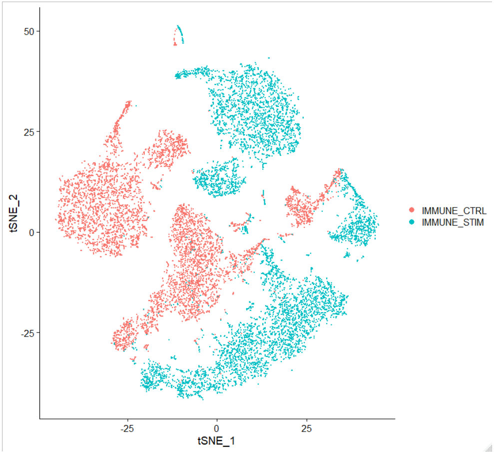


Figure 33: UMAP

- Sherrie Wang, CME 250: Introduction to Machine Learning, Stanford University. https://web.stanford.edu/class/cme250/
- Volodymyr Kuleshov, CS 5785: Applied Machine Learning, Cornell University. https://www.cs.cmu.edu/~arielpro/15381f16/slides/NLP_guest_lecture.pdf
- Aykut Erdem, COMP547: Deep Unsupervised Learning, Koç University. https://aykuterdem.github.io/classes/comp547.s24/
- Christoph F. Eick, Machine Learning, University of Houston. http://www2.cs.uh.edu/~ceick/ML/Topic9.ppt
- Zaur Fataliyev, Seoul AI. https://seoulai.com/presentations/t-SNE.pdf
- Simon Andrews, "Dimensionality Reduction", Babraham Bioinformatics. https://www.bioinformatics.babraham.ac.uk/training/10XRNASeq/Dimension%20Reduction.pptx

Credits

Dr. Prashant Aparajeya

Computer Vision Scientist — Director(AISimply Ltd)

p.aparajeya@aisimply.uk

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