

# Comp683: Computational Biology

## Lecture 3

January 15, 2025

# Today

- Graph Laplacian
- Building Graphs from Data (k-D trees and random projection trees)
- Graph Representations of Data and Dimension Reduction
- Modularity-Based Graph Partitioning

# Diffusion on Graphs

Suppose we have some quantity that will spread or *diffuse* across a graph, given the graph's connectivity. Suppose there is a quantity of  $\psi_i$  at node  $i$ . Suppose that this quantity flows along the graph from node  $j$  to an adjacent node  $i$  at a rate of  $C(\psi_j - \psi_i)$ . The rate at which  $\psi_i$  is changing is given as,

$$\frac{d\psi_i}{dt} = C \sum_j A_{ij}(\psi_j - \psi_i) \quad (1)$$

Here,  $A_{ij}$  enforces the idea that the only terms in a sum are pairs of nodes connected by an edge.

$$\frac{d\psi_i}{dt} = C \sum_j A_{ij}(\psi_j - \psi_i) \quad (2)$$

Splitting up terms, we can rewrite this as,

$$\frac{d\psi_i}{dt} = C \sum_j A_{ij}\psi_j - C\psi_i \sum_j A_{ij} = C \sum_j A_{ij}\psi_j - C\psi_i k_i \quad (3)$$

- Remember,  $k_i = \sum_j A_{ij}$  is simply the degree of node  $i$

## Diffusion continued

$$\frac{d\psi_i}{dt} = C \sum_j A_{ij} \psi_j - C \psi_i k_i \quad (4)$$

further simplifies to,

$$\frac{d\psi_i}{dt} = C \sum_j (A_{ij} - \delta_{ij} k_j) \psi_j. \quad (5)$$

Here,  $k_i$  is the degree of node  $i$  and  $\delta_{ij} = 1$  if  $i = j$  and is 0 otherwise.

- That was just some massaging so that everything can be written as a  $\sum_j$  to make our next step easier.

# Massaging Explained

In case you were wondering how we reworked  $C\psi_i k_i$  to be written in terms of  $\sum_j$  as,  $C \sum_j \delta_{ij} \psi_j k_j$

- We only need to count it for node  $i$ , so  $\delta_{ij}$  is our indicator for indexing over  $j$  that ensures that we only add a non-zero value when  $i = j$

# Diffusion and Connection with the Graph Laplacian

$$\frac{d\psi_i}{dt} = C \sum_j (A_{ij} - \delta_{ij} k_j) \psi_j. \quad (6)$$

- This simplifies because  $C\psi_i k_i = C \sum_j \delta_{ij} \psi_j k_j$

This can further be expressed in matrix form as,

$$\frac{d\psi}{dt} = C(\mathbf{A} - \mathbf{D})\psi. \quad (7)$$

Here,  $\mathbf{D}$  is an  $N \times N$  diagonal matrix where  $k_i$  is the  $i$ th diagonal element and represents the degree of node  $i$ .

- The **Graph Laplacian** is the matrix  $\mathbf{L} = \mathbf{D} - \mathbf{A}$ , and satisfies  $\frac{d\psi}{dt} + C\mathbf{L}\psi = 0$  (aka the diffusion equation).

# Diffusion on a Bunny Using its Graph Representation

A small amount of signal spreads locally according to specified edges and takes many time steps to spread across the bunny.

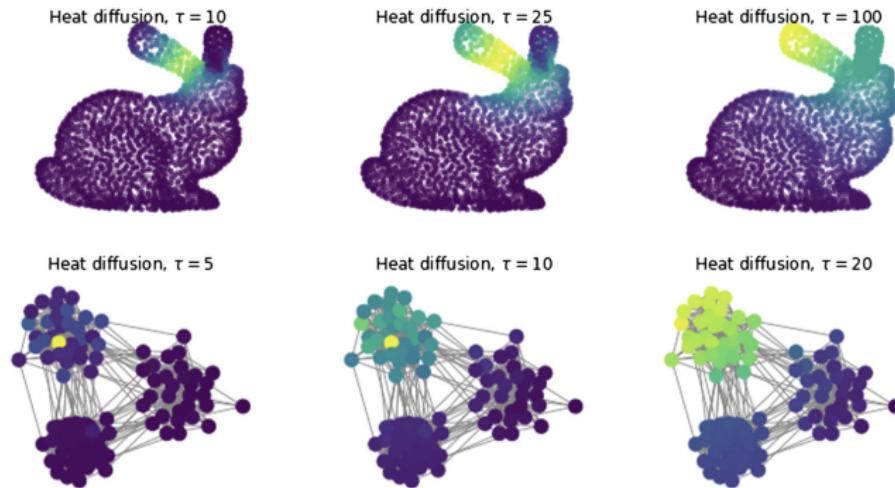


Figure: from <https://www.sciencedirect.com/science/article/pii/S1631070519301094>

# Welcome Graph Laplacian

- Besides describing diffusion, the Graph Laplacian has many other nice properties.
- Notably, properties about **connectivity patterns** in the graph and can be useful for **graph partitioning**.
- We are going to be using the graph Laplacian for **many tasks!**

## Laplacian Matrix in More Detail

The elements of the Laplacian matrix are defined as follows for an undirected, unweighted matrix.

- Remember:  $\mathbf{L} = \mathbf{D} - \mathbf{A}$

$$L_{ij} = \begin{cases} k_i & \text{if } i = j \\ -1 & \text{if } i \neq j \text{ and there is an edge } (i, j) \\ 0 & \text{otherwise} \end{cases}$$

# The Graph Laplacian Has Many Nice Linear Algebraic Properties

- In a network with  $c$  components, the number of zero eigenvalues is equal to the number of components, ( $c$ ).

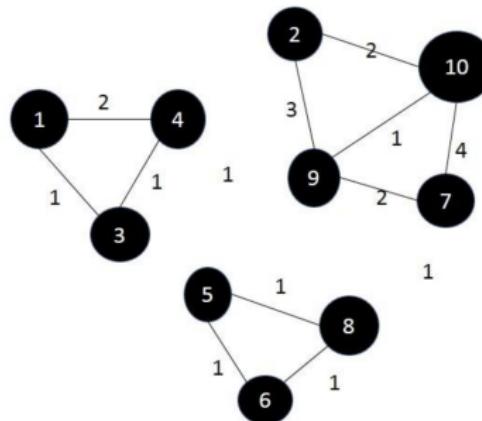


Figure: Each group of nodes makes a component.

# Building graphs from data

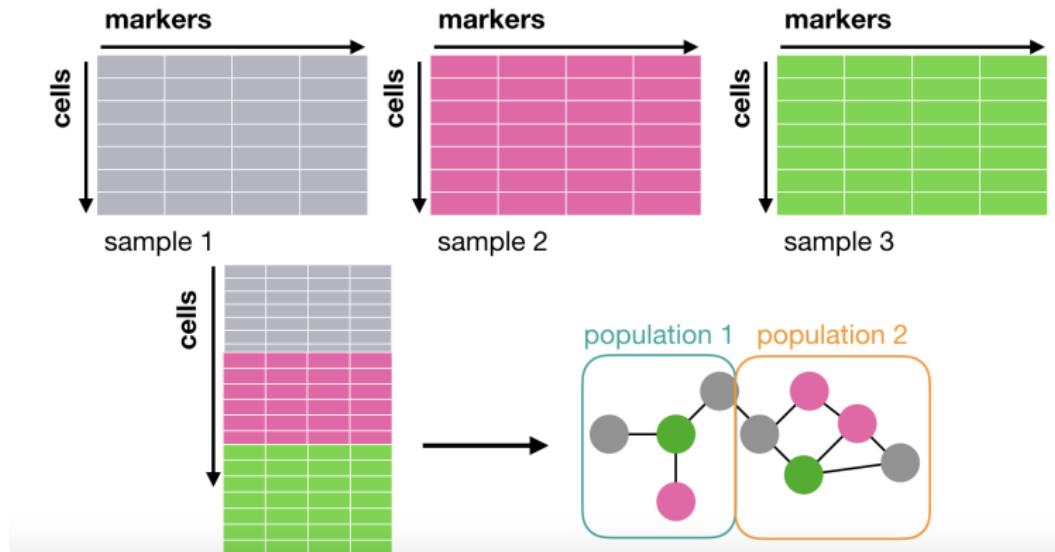


Figure: The task is to compute distances between all pairs of cells, and connect each cell with their nearest neighbors

# k-Nearest Neighbor Graphs

- Suppose our dataset,  $\mathcal{X}$  is defined as  $\mathcal{X} = \{\mathbf{x}_i\}_{i=1\dots N}, \mathbf{x}_i \in \mathbb{R}^d$ .
- The general idea is to connect each node with its  $k$  nearest neighbors
  - Compute all pairwise similarities between all pairs of nodes
  - For a node,  $i$ , find the  $k$  nodes that are closest and draw edges.
- Computing all pairwise distances quickly becomes expensive ( $O(N^2 d)$ ).

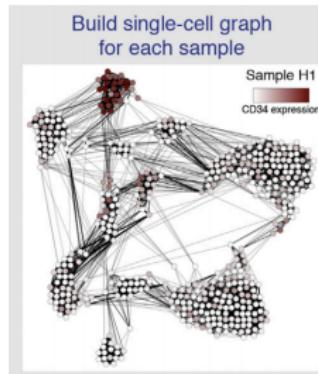


Figure: from Levine *et al.* Cell. 2015. Each cell is connected to its  $k$ -nearest

# A Common way to Calculate Edge Weights in a Graph

For better or for worse, people commonly assume a Gaussian distribution on pairwise similarities between nodes. So, a weight between nodes  $i$  and  $j$  is often computed as,

$$W_{ij} = \exp\left(\frac{-||\mathbf{x}_i - \mathbf{x}_j||^2}{2\sigma^2}\right) \quad (8)$$

# Randomized Trees for Nearest Neighbor Search

People have come up with clever ways to compute  $k$ -NN graphs much faster. A popular approach is  $k$ -d trees and more recently random projection trees.

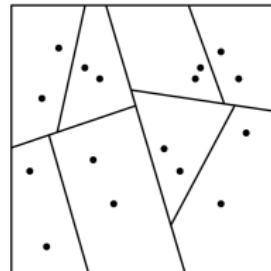
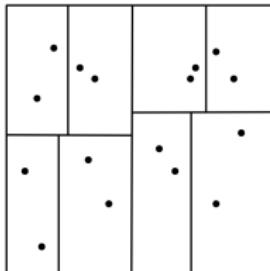


Figure: from Dasgupta *et al.* JMLR. 2013.  $k - d$  tree (left), random projection tree (right).

## $k$ -d tree

This is a partition of  $\mathbb{R}^d$  hyper-rectangular cells based on the datapoints.

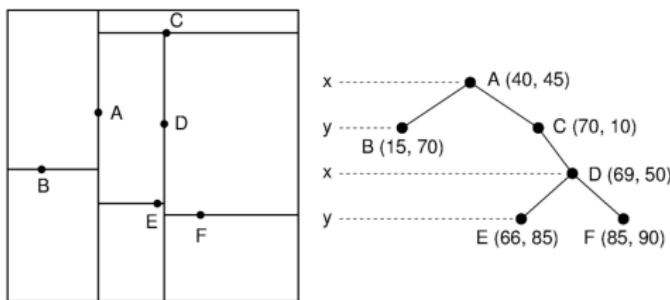


Figure: Alternate between splitting according to the ‘x’ and ‘y’ dimensions. First split according to ‘A’. Based on partition by A, you can split horizontally according to C and B.

# Random Projection Trees

Instead of doing axis parallel splits, split directions and split points are randomly selected.

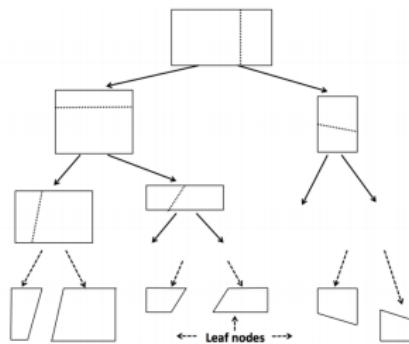


Figure: Random projection tree. (see  
<https://cseweb.ucsd.edu/~dasgupta/papers/exactnn-colt.pdf> for a discussion on randomized partition trees.)

# One Application of $k$ -NN Graph is Visualization (LargeVis)

Using random projection trees, LargeVis creates an embedding for a set of points with a probabilistic model.

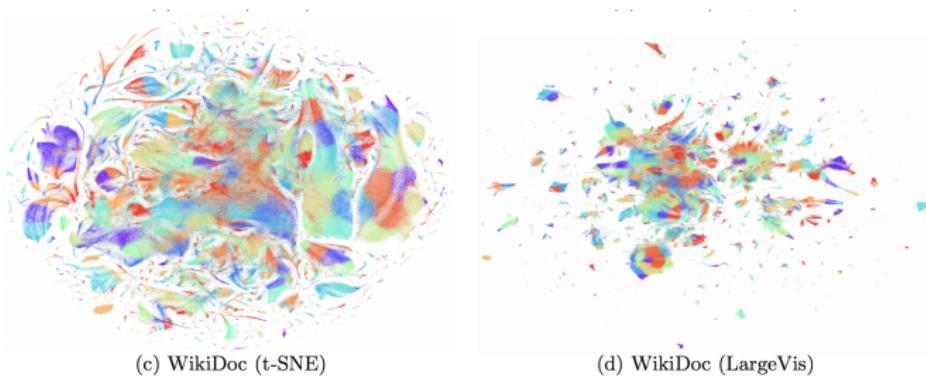


Figure: from Tang *et al.* The Web Conference (WWW). 2016. tSNE and ‘string behavior’ from being designed to preserve super local similarities.

# A Probabilistic Model for Graph Embedding

For some nodes,  $i$  and  $j$ , let  $\mathbf{y}_i$  and  $\mathbf{y}_j$  be their embedding coordinates such that  $\mathbf{y}_i, \mathbf{y}_j \in \mathbb{R}^d$  (for visualization purposes,  $d = 2$ ). We can model the probability that an edge exists between nodes  $i$  and  $j$  as a function ( $f(\cdot)$ ) of their learned embedding coordinates, or,

$$P(e_{ij} = 1) = f(||\mathbf{y}_i - \mathbf{y}_j||) \quad (9)$$

- An important criterion to be satisfied is that  $f(\cdot)$  must ensure a high probability when  $i$  and  $j$  are close, and low otherwise.
- For example:  $f(x) = \frac{1}{1+ax^2}$

## Writing Down the Likelihood of the Observed Graph

The authors define a similarity measure between pairs of nodes where there is an edge, based on the original data,  $\mathbf{x}_i$  and  $\mathbf{x}_j$ . Here,  $\gamma$  being a constant fixed weight for negative edges.

The likelihood of the graph can be written as,

$$\begin{aligned} O &= \prod_{(i,j) \in E} P(e_{ij} = 1) \prod_{(i,j) \in \tilde{E}} (1 - P(e_{ij} = 1))^\gamma \\ &\propto \sum_{(i,j) \in E} \log P(e_{ij} = 1) + \sum_{(i,j) \in \tilde{E}} \gamma \log(1 - P(e_{ij} = 1)) \end{aligned}$$

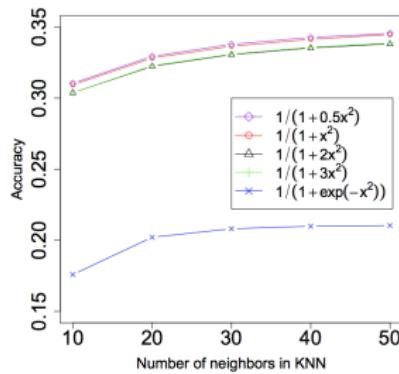
$\tilde{E}$  represents pairs of nodes with no edge.

# Brief Overview of Optimization of Parameters

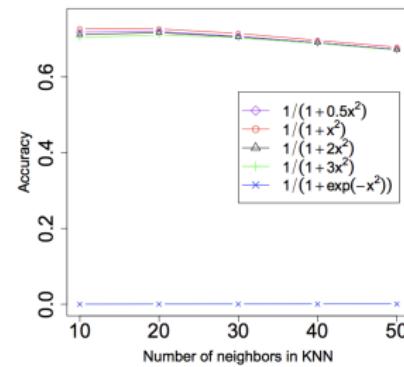
- Since these graphs are very sparse, there are a lot of ‘negative edges’ or edges  $\in \tilde{E}$ . So the authors used a smart negative sampling approach to only consider a subset of negative node pairs
  - For each node,  $i$ , consider sample some ‘negative’ pair nodes.
  - A node,  $j$  from the negative pair set to pair with  $i$  as a negative example is sampled with probability  $\propto d_j^{0.75}$ . Here  $d_j$  is the degree of node  $j$ .
  - Optimize parameters with asynchronous stochastic gradient descent (<https://papers.nips.cc/paper/2011/file/218a0aef1d1a4be65601cc6ddc1520e-Paper.pdf>)

# Choice of $f(\cdot)$

The authors tested how choice of  $f(\cdot)$  affected the quality of their embedding. Looks like there is one bad choice, but overall, does not make a huge difference.



(a) WikiDoc



(b) LiveJournal

Figure: from Tang *et al.* The Web Conference (WWW). 2016.

# More Practical Reasons to Use LargeVis: Scales better than tSNE

Nothing would ever be as fast as PCA. But, if you need to understand more local types of similarities between data points, perhaps it's worth the wait....

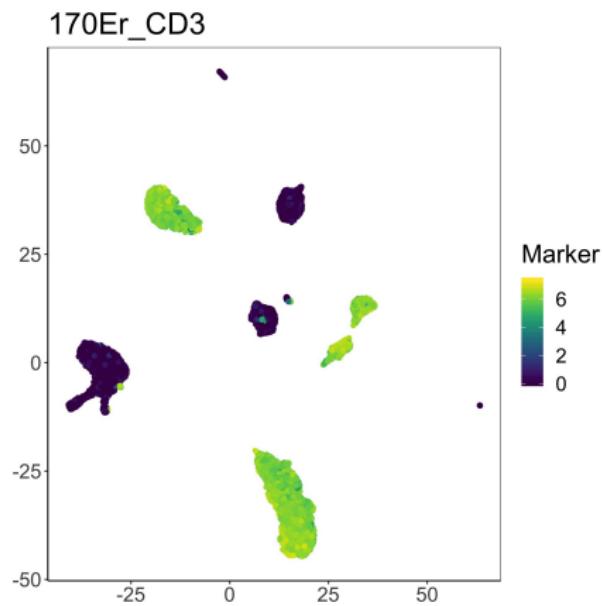
Table 2: Comparison of running time (hours) in graph visualization between the t-SNE and LargeVis.

Algorithm	20NG	MNIST	WikiWord	WikiDoc	LiveJournal	CSAuthor	DBLPaper
t-SNE	0.12	0.41	9.82	45.01	70.35	28.33	18.73
LargeVis	0.14	0.23	2.01	5.60	9.26	4.24	3.19
Speedup Rate	0	0.7	3.9	7	6.6	5.7	4.9

Figure: from Tang *et al.* The Web Conference (WWW). 2016. Comparison in run-time between tSNE and LargeVis.

## Example Use Case- Single Cell Data!

Your input,  $\mathbf{X}$  is the cells  $\times$  marker matrix. Not only do you get the graph out, but we can easily find T-cells and different T-cell subsets!



# Graph Partitioning Illustrated

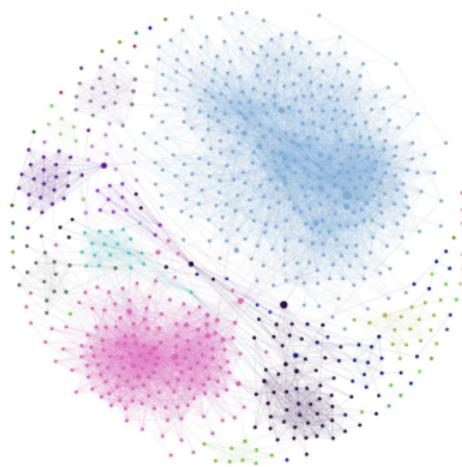


Figure: The high-level goal is to partition nodes into coherent node-subsets (communities), such that nodes within a group have on average more within group edges than between-group edges.

# Graph Partitioning is just Clustering

- Instead of your standard clustering problem in a matrix of  $N$  objects with  $P$  features, our input here is an adjacency matrix,  $\mathbf{A}$ , where we want to cluster nodes based on similarities in their connectivity patterns.
- Most graph partitioning optimization problems seek a hard partition (each node assigned to a single cluster)
- There are some variants that learn a soft partition, or a propensity or probability that each node is assigned to each community.
- Optimization for this problem can come in many flavors

# Optimization Approaches

- Quality Function with a Null Model + Heuristic for Optimization ←
  - A null model describes a graph with no structure, for example, nodes connected randomly.
- Probabilistic and Likelihood Optimization ←
- Spectral Clustering Methods (Partition based on graph Laplacian)
- Most recently: graph embedding + clustering on embedding
  - We will touch on this briefly Thursday with node2vec

# Why Partition a Graph?

Build a graph between cells based on marker expression and partition into cell-populations. Members of a cell-population should be phenotypically similar and therefore express the same markers.

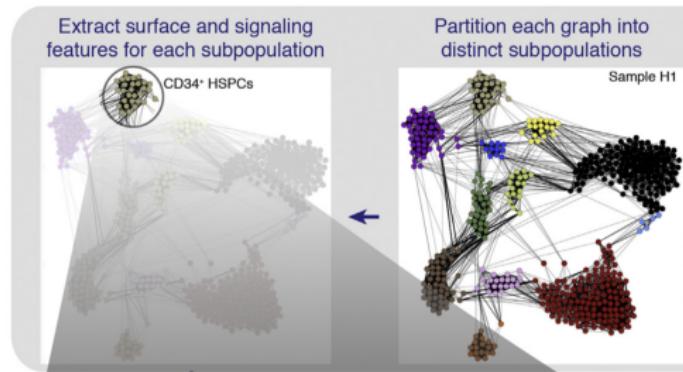


Figure: from Levine *et al.* Cell. 2015. This is the PhenoGraph algorithm.

# PhenoGraph Uses Modularity Based Maximization

- **Intuition:** We first specify a null model of a network with no structure about the probability of two nodes being connected. Then we find the partition that is maximally different from this null model.
- **A Simple Null Model:** An easy way to think about the probability of two edges being connected is based on some function of their degree.
  - Consider the null model,  $\frac{k_i k_j}{2M}$
  - $k_i$  and  $k_j$  give the degrees of nodes  $i$  and  $j$
  - $M$  (as always in our notation) is the total number of edges, or the sum of all edge weights.
- **Configuration Model:** This is known as the configuration model, or fixing the degree sequence and connecting nodes at random.

## Modularity Defined

$$Q = \frac{1}{2M} \sum_{i,j} [A_{ij} - \gamma \frac{k_i k_j}{2M}] \delta(c_i, c_j) \quad (10)$$

- $A_{ij}$  is the adjacency matrix entry for node pair  $(i, j)$  (can be weighted and not just binary)
- $\delta(c_i, c_j)$  is an indicator function for whether or not nodes  $i$  and  $j$  were assigned to the same community.
- We need an algorithm to help us determine node-to-community assignments for all nodes  $i$ , such that  $Q$  is as large as possible.
- $\gamma$  is a resolution parameter controlling the size of communities

# Louvain: A Simple Algorithm that Makes a lot of Sense

Merge (if modularity increases), agglomerate, repeat until modularity doesn't increase anymore.

