Comp683: Computational Biology

Lecture 10

February 14, 2024

Announcement

Homework 1 is online and available, here, `https://github.com/natalies-teaching/Comp683_CompBio_2024/tree/main/Homework1`. You can use the LaTeX template I provided or just submit as a PDF by 11:59pm **February 27.**

Today

- Data Augmentation for Single-Cell Data : Filling in the gaps across the cellular landscape.
- Start graph signal processing (GSP) - an important tool for the upcoming attraction that is differential abundance analysis.

Do you Remember Questions

- What is the intuition for how MAGIC fixes noise and / or dropout? If given a cell, how would I adjust its features, given the rest of the data?
- What do the potential distances in PHATE do?

Rare + Sparse Cell Populations

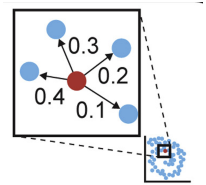


Figure: from MAGIC paper

- ‘Dense‘ cell-populations vs ‘Sparse‘ cell-populations.
- Low-frequency cell-populations and data artifacts can fail to be under-represented and not accurately reflect the underlying biology.
- Are members of a particular cell-type not there or are they just very infrequent?

General Problems with Downstream Tasks from Sparse Data

- Imbalanced classes can affect classification accuracy
- In clustering, imbalanced ‘ground-truth‘ clusters can cause distortion or mis-representation of the clusters in the data
- Too few samples/observations can cause mis-representation of the dependencies or correlations between features.

Welcome SUGAR

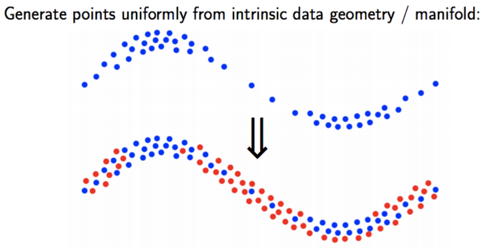


Figure: from Lindenbaum *et al.* NeurIPS. 2018

- Most generative modeling approaches seek to learn and replicate the data density
- SUGAR is a data-generation approach that uses the underlying geometry of the data (e.g. a random walk based approach)

Common Data Generation Approaches

- Older Techniques
    - **Parametric Models :** Specify a model and optimize the parameters through maximum likelihood optimization.
    - Use the learned model to generate new data
    - Use a histogram or kernel to estimate generating distributions
- Newer techniques to generate additional points from complicated data distributions
    - GAN (generative adversarial network) $\rightarrow$ `https://papers.nips.cc/paper/2014/file/5ca3e9b122f61f8f06494c97b1afccf3-Paper.pdf`
    - VAE (variational autoencoders) $\rightarrow$ `https://arxiv.org/abs/1606.05908`

Remembering our Good Friend Gaussian Kernel

For a pair of nodes, i and j, the strength of their connection can be computed as $\mathcal{K}(\mathbf{x}_i, \mathbf{x}_j)$, or

$$K_{ij} = \exp(-\frac{||\mathbf{x}_i - \mathbf{x}_j||^2}{2\sigma^2}) \tag{1}$$

We also remember our row-stochastic markov matrix, **P** computed from **K**.

Measure Based Gaussian Correlation (MGC)

- Given your data, $\mathbf{X}$, define a set of reference points, $\mathbf{r}$ with $r \in \mathbf{X}$.
- Define $\mu(\mathbf{r})$ as some measure over the reference points

Then define a new kernel, $\hat{\mathcal{K}}(\mathbf{x}_i, \mathbf{x}_j)$ as,

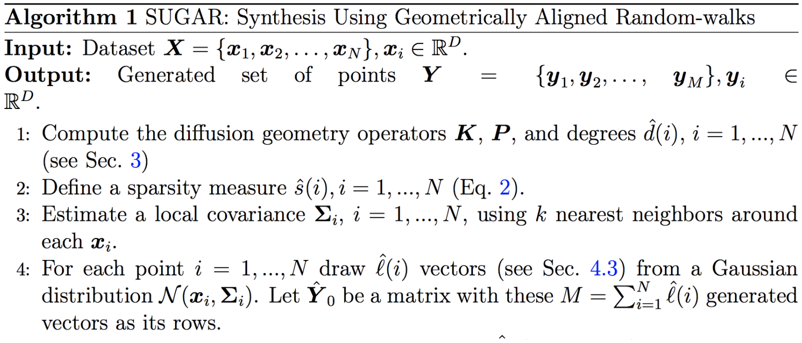
$$\hat{\mathcal{K}}(\mathbf{x}_i, \mathbf{x}_j) = \sum_{\mathbf{r} \in \mathbf{X}} \mathcal{K}(\mathbf{x}_i, \mathbf{r}) \mathcal{K}(\mathbf{x}_j, \mathbf{r}) \mu(\mathbf{r}) \tag{2}$$

For our purposes, $\mu(\mathbf{r})$ will be some value that relates to sparsity and is the inverse of node r's degree.

Problem Formulation for Data Generation Problem

- Let $\mathcal{M}$ be a *d*-dimensional manifold such that $\mathcal{M} \in \mathbb{R}^d$
- Let $\mathbf{X} \subset \mathcal{M}$ be a subset of points samples from $\mathcal{M}$ with $\{\mathbf{x}_1, \mathbf{x}_2, \ldots \mathbf{x}_N\} \in \mathbf{X}$
- Assuming that instances, $\mathbf{X}$ are unevenly sampled from $\mathcal{M}$, we seek a set of new points, $\mathbf{Y} = \{\mathbf{y}_1, \mathbf{y}_2, \ldots \mathbf{y}_M\}$ that also lie of $\mathcal{M}$ and that $\mathbf{X} \cup \mathbf{Y}$ is uniform.

Synthesis Using Geometrically Aligned Random Walks



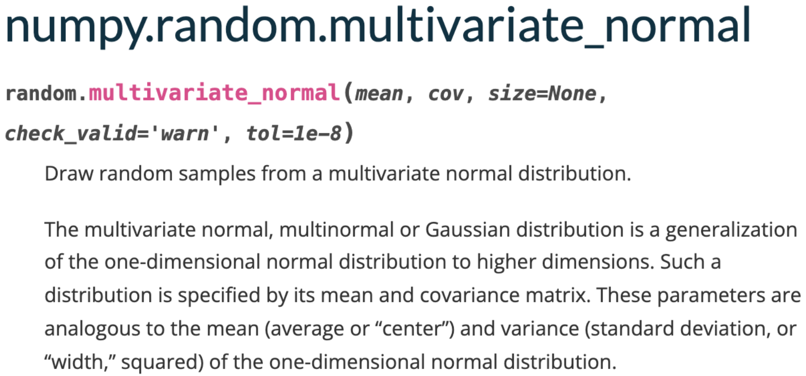
```
Algorithm 1 SUGAR: Synthesis Using Geometrically Aligned Random-walks
Input: Dataset $\boldsymbol{X} = \{\boldsymbol{x}_1, \boldsymbol{x}_2, \dots, \boldsymbol{x}_N\}, \boldsymbol{x}_i \in \mathbb{R}^D$.
Output: Generated set of points $\boldsymbol{Y} = \{\boldsymbol{y}_1, \boldsymbol{y}_2, \dots, \boldsymbol{y}_M\}, \boldsymbol{y}_i \in \mathbb{R}^D$.
1: Compute the diffusion geometry operators $\boldsymbol{K}$, $\boldsymbol{P}$, and degrees $\hat{d}(i)$, $i = 1, ..., N$ (see Sec. 3)
2: Define a sparsity measure $\hat{s}(i), i = 1, ..., N$ (Eq. 2).
3: Estimate a local covariance $\boldsymbol{\Sigma}_i$, $i = 1, ..., N$, using $k$ nearest neighbors around each $\boldsymbol{x}_i$.
4: For each point $i = 1, ..., N$ draw $\hat{\ell}(i)$ vectors (see Sec. 4.3) from a Gaussian distribution $\mathcal{N}(\boldsymbol{x}_i, \boldsymbol{\Sigma}_i)$. Let $\hat{\boldsymbol{Y}}_0$ be a matrix with these $M = \sum_{i=1}^{N} \hat{\ell}(i)$ generated vectors as its rows.
```

Figure: from Lindenbaum *et al.* NeurIPS. 2018. Let's walk through steps 1-4 for now.

Synthesis Using Geometrically Aligned Random Walks

- **Specify Kernel:** Initialized by forming a Gaussian Kernel over the input data, $\mathbf{X}$, $\mathbf{G_x}$.
  - Use $\mathbf{G_x}$ to estimate the degree of each node i, $d(i)$.
  - The sparsity of each point, $s(i)$ is defined as the inverse degree of node i or $s(i) = 1/d(i)$.
- **Sample According to Each Point** Next, sample $\ell(i)$ points, $\mathbf{h}_j \in \mathbf{H}_i$ for $j = 1 \ldots \ell_i$ around each $\mathbf{x}_i \in \mathbf{X}$ from a localized gaussian distribution (e.g. k-nearest points around i).
  - $G_i = \mathcal{N}(\mathbf{x}_i, \Sigma_i)$

Practical : Sampling from MV Gaussians



numpy.random.multivariate_normal

```
random.multivariate_normal(mean, cov, size=None,
check_valid='warn', tol=1e-8)
```

Draw random samples from a multivariate normal distribution.

The multivariate normal, multinormal or Gaussian distribution is a generalization of the one-dimensional normal distribution to higher dimensions. Such a distribution is specified by its mean and covariance matrix. These parameters are analogous to the mean (average or “center”) and variance (standard deviation, or “width,” squared) of the one-dimensional normal distribution.

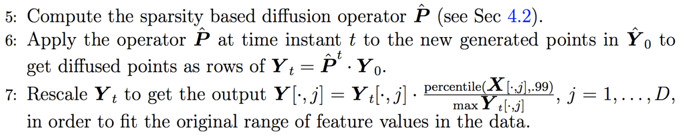
Back to SUGAR

- Let $\mathbf{Y}_0$ be the set of all new $M = \sum_i \ell(i)$ points generated around each i, with $\mathbf{Y}_0 = \{\mathbf{y}_1, \mathbf{y}_2, \ldots, \mathbf{y}_M\}$
- **MGC Kernel:** Now use affinities between points in $\mathbf{X}$ and $\mathbf{Y}_0$. Here, points in $\mathbf{X}$ are used as reference.

$$\hat{\mathcal{K}}(\mathbf{y}_i, \mathbf{y}_j) = \sum_r \mathcal{K}(\mathbf{y}_i, \mathbf{x}_r)\mathcal{K}(\mathbf{x}_r, \mathbf{y}_j)s(r) \tag{3}$$

Pulling $\mathbf{Y}_0$ towards sparser regions of $\mathcal{M}$

Pasted psuedo code for the second part of SUGAR



```
5: Compute the sparsity based diffusion operator $\hat{\boldsymbol{P}}$ (see Sec 4.2).
6: Apply the operator $\hat{\boldsymbol{P}}$ at time instant $t$ to the new generated points in $\hat{\boldsymbol{Y}}_0$ to
   get diffused points as rows of $\boldsymbol{Y}_t = \hat{\boldsymbol{P}}^t \cdot \boldsymbol{Y}_0$.
7: Rescale $\boldsymbol{Y}_t$ to get the output $\boldsymbol{Y}[\cdot, j] = \boldsymbol{Y}_t[\cdot, j] \cdot \frac{\text{percentile}(\boldsymbol{X}[\cdot,j],.99)}{\max \boldsymbol{Y}_t[\cdot,j]}$, $j = 1, \ldots, D$,
   in order to fit the original range of feature values in the data.
```

Figure: from Lindenbaum *et al.* NeurIPS. 2018.

Diffusion Operator Again

- Take affinities from $\hat{\mathcal{K}}$ and convert them to $\mathbf{P}$, the row-normalized Markov matrix.
- This will allow us to correct points in $\mathbf{Y}_0$ according to neighborhood regions

As you will all recognize, powering $\mathbf{P}$ as $\mathbf{P}^t$ estimates the probability of successfully traveling between nodes with t steps. The transformed matrix, $\mathbf{Y}_t$ is computed as

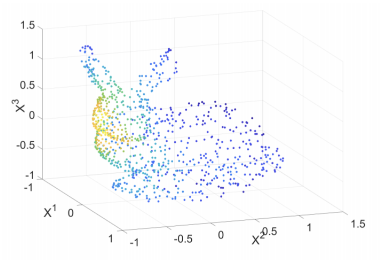
$$\mathbf{Y}_t = \mathbf{P}^t \times \mathbf{Y}_o \tag{4}$$

Same Story Regarding t

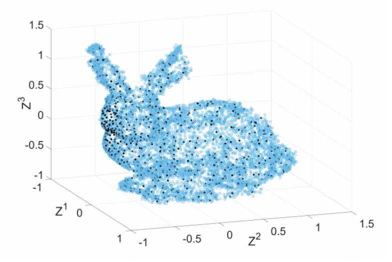
Remember in PHATE, t was chosen according to the knee point of the Von-Neumann entropy of the normalized eigenvalues of $\mathbf{P}^t$.

Experiments : Synthetic and Biological

Stanford Bunny



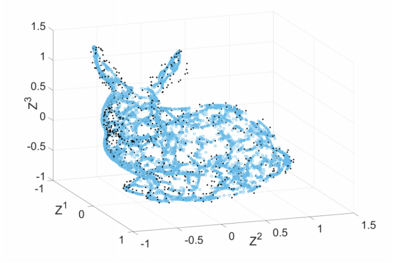
(a)



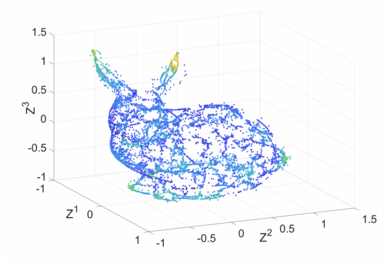
(b)

Figure: from Lindenbaum *et al.* NeurIPS. 2018. (**a**). The original set, $\mathbf{X}$ of points, colored by node degree. (**b**) $\mathbf{Y}_0$ are generated points (blue) and original points, $\mathbf{X}$ (black).

Stanford Bunny Part II



(c)



(d)

Figure: from Lindenbaum *et al.* NeurIPS. 2018. (**c**). Original and generated points, before MGC diffusion. (**d**) Generated points (**Y**) after MGC diffusion. Points are colored by degree.

Application : Augmented Clustering

SUGAR was used to generate additional data points to improve the quality of clusters identified with *k*-means.

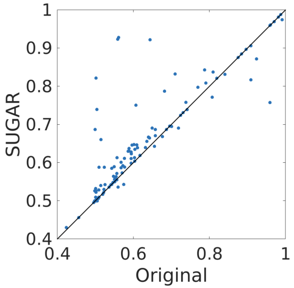
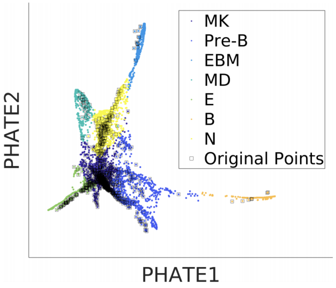


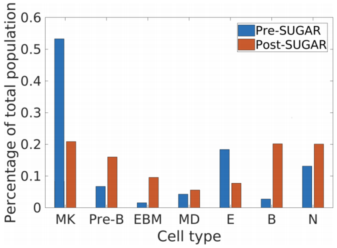
Figure: from Lindenbaum *et al.* NeurIPS. 2018. In 119 datasets, the data were augmented with additional datapoints using sugar. Adjusted Rand Index was computed for the original data vs data + SUGAR.

SUGAR on Single-Cell

SUGAR was using to augment cells in a single-cell RNAseq dataset.



(a)

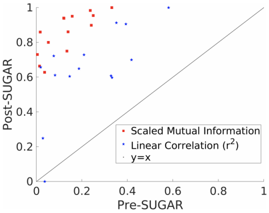


(b)

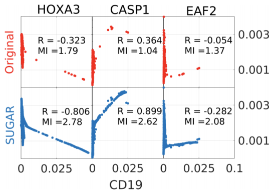
Figure: from Lindenbaum *et al.* NeurIPS. 2018

Maintaining Intra-Module Marker Co-Expression

Among cells assigned to the same module or cluster, after SUGAR led to higher intra-module between-marker correlation.



(c)



(d)

Figure: from Lindenbaum *et al.* NeurIPS. 2018

Graph Signal Processing

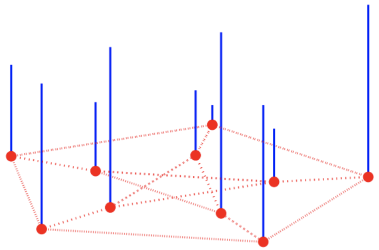
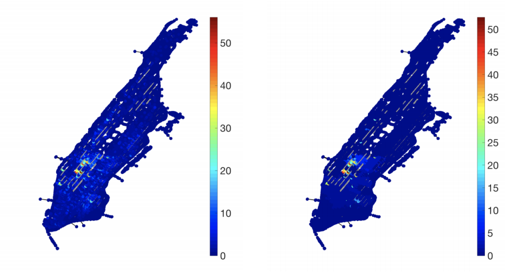


Figure: from Shuman *et al.* ArXiv. The purpose is to study the interplay between some signal and graph connectivity.

Piecewise Smooth Assumption

Translation: Nodes that are close (in terms of geodesic distance) on the graph should have similar signals. You can approximate the signal of a node, based on its neighbors.



(a) Actual data (b) Approximation

Figure: from `https://arxiv.org/abs/1712.00468`. Here the graph is street intersections in Manhattan and the signal is taxi pickups.

How Localized is the Signal?

Remember, our friend Graph Laplacian ($\mathbf{L} = \mathbf{D} - \mathbf{A}$),

- Some very nice theory falls out about based on the spectra of the Laplacian matrix, relating to how 'localized' a graph signal, **f**, is. For example **f** could be an expression of some protein.
    - First re-write **f** in terms of eigenvectors of the Laplacian
    - The eigenvectors corresponding to the first *smallest* eigenvalues of **L** are considered **low frequency**, and hence entries of the eigenvector entries corresponding to nodes that are connected should be similar
    - For higher **high frequencies** corresponding to larger eigenvalues, the values of the eigenvectors of adjacent nodes will be more different.

Signal Specificity

Here we visualize eigenvector entries at nodes ($\mathbf{u}_0$,$\mathbf{u}_1$,$\mathbf{u}_{50}$)

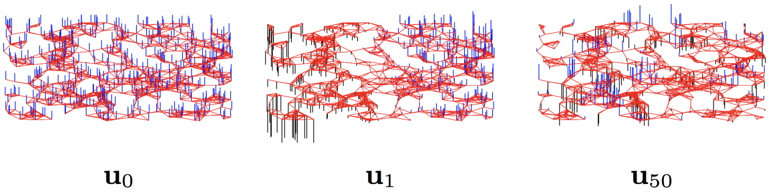


Figure: from GSP Review https://arxiv.org/abs/1211.0053

Similarly

Zero crossings mean that eigenvector entries are neighboring nodes will be different.

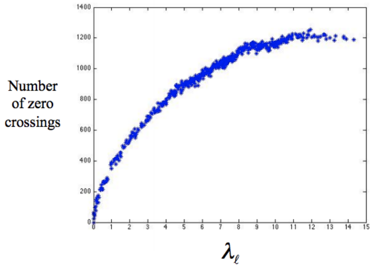


Figure: from GSP Review https://arxiv.org/abs/1211.0053

What is Graph Fourier Transform (on a high level?)

- Explain frequency content of the graph signal (e.g. experimental measurements/labels/etc) as a weighted sum of the eigenvectors of the Graph Laplacian
- The eigenvectors of the Graph Laplacian comprise the **Graph Fourier Basis and can help to decouple high and low frequency signals**

Local Variation of a Signal

The local variation of a signal or the sum of differences around a node can be written as,

$$
\begin{aligned}
(\mathcal{L}\mathbf{f})(i) &= ([\mathbf{D} - \mathbf{A}]\mathbf{f})(i) && (5)\\
&= d(i)\mathbf{f}(i) - \sum_j A_{ij}\mathbf{f}(j) && (6)\\
&= \sum_j A_{ij}(\mathbf{f}(i) - \mathbf{f}(j)) && (7)
\end{aligned}
$$

Local Variation Leads to Total Variation

The total variation of a signal on a graph is defined as follows and is also known as the Laplacian Quadratic Form

$$TV(\mathbf{f}) = \sum_{i,j} A_{ij}(\mathbf{f}(i) - \mathbf{f}(j))^2 \tag{8}$$

$$= \mathbf{f}^T \mathcal{L} \mathbf{f} \tag{9}$$

- Note here I have been assuming that we have an unweighted graph, but you could certainly substitute A_{ij} with a weighted version, W_{ij}

Getting to Graph Fourier Basis

- Start with the eigendecomposition of of $\mathbf{L}$ as $\mathbf{L} = \mathbf{\Psi \Lambda \Psi}^T$
- We can look at eigenvectors, $\mathbf{\Psi} = [\psi_1, \psi_2, \ldots, \psi_N]$ of $\mathcal{L}$
- and eigenvalues, $\mathbf{\Lambda} = [0 = \lambda_1 \leq \cdots \leq \lambda_N]$ of $\mathcal{L}$

The Graph Fourier Transform of a Signal

The *i*th frequency component of a signal, $\mathbf{f}$ is the inner product between $\boldsymbol{\psi}_i$ and $\mathbf{f}$ and can be written as,

$$\hat{f}_i = \psi_i^T \mathbf{f} \tag{10}$$

The Graph Fourier Transform (GFT) is written as,

$$\hat{\mathbf{f}} = \mathbf{\Psi}^T \mathbf{f} \tag{11}$$

GFT Will Be Used to Filter

- A filter on the graph will take in a signal and attenuate it according to a frequency response function.
- **Low-Pass Filter:** We filter or preserve only frequencies corresponding to eigenvalues below some threshold, λ_k. So, consider frequencies λ_b, with $\lambda_b < \lambda_k$
- **High-Pass Filters**: Preserve only frequencies corresponding to eigenvalues above some threshold, λ_k. So, consider frequencies λ_b, with $\lambda_b \geq \lambda_{k+1}$

A Simple Low-Pass Filter

Define some filter h as,

$$h : [0, \max(\mathbf{\Lambda})] \to [0, 1] \tag{12}$$

Assuming the cutoff is λ_k,
$h(x) > 0$, for $x < \lambda_k$ and $h(x) = 0$, otherwise

Defining Notation and Applying Filter to GFT

Define $h(\mathbf{\Lambda})$ as a diagonal matrix of eigenvalues with the filter applied. Based on what we computed with GFT, the filtered signal, $\hat{\mathbf{f}_{filt}}$ can be computed as,

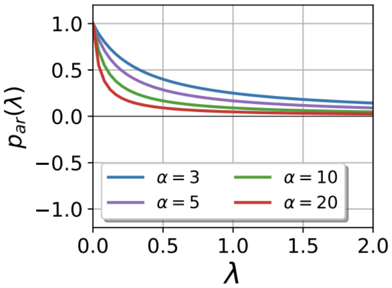
$$\hat{\mathbf{f}}_{filt} = h(\mathbf{\Lambda})\hat{\mathbf{f}} \tag{13}$$

Applying a Filter in General

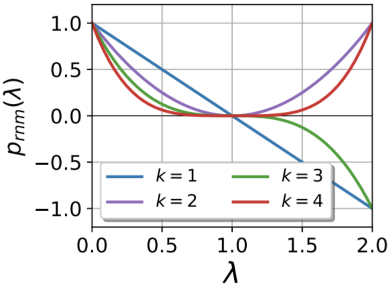
In general, you can filter an original signal, **f** in general as,

$$\underbrace{\boldsymbol{\Psi}(\mathbf{I} + \alpha\boldsymbol{\Lambda})^{-1}\boldsymbol{\Psi}^{T}}_{\text{Filtered Graph Laplacian}} \ \mathbf{f}. \tag{14}$$

Example Filters



(a) $p_{\mathrm{ar}}(\lambda) = (1 + \alpha\lambda)^{-1}$



(b) $p_{\mathrm{rnm}}(\lambda) = (1 - \lambda)^k$

Figure: from `https://openaccess.thecvf.com/content_CVPR_2019/papers/Li_Label_Efficient_Semi-Supervised_Learning_via_Graph_Filtering_CVPR_2019_paper.pdf`