Comp790-166: Computational Biology

Lecture 9

February 8, 2023

Announcement

Homework 1 is online and available, here, `https://github.com/natalies-teaching/CompBio2023/tree/main/Homework1_2023`. You can use the LaTeX template I provided or just submit as a PDF by 11:59pm **February 24.**

Today

- Finish the basics of graph signal processing (GSP)
- Low-pass filtering of signals
- Begin differential abundance analysis $\rightarrow$ MELD.

Activity of the Day

Walk around the room, sit in a new seat, introduce yourself to whoever you sit down next to and talk about what you are thinking about

Graph Signal Processing

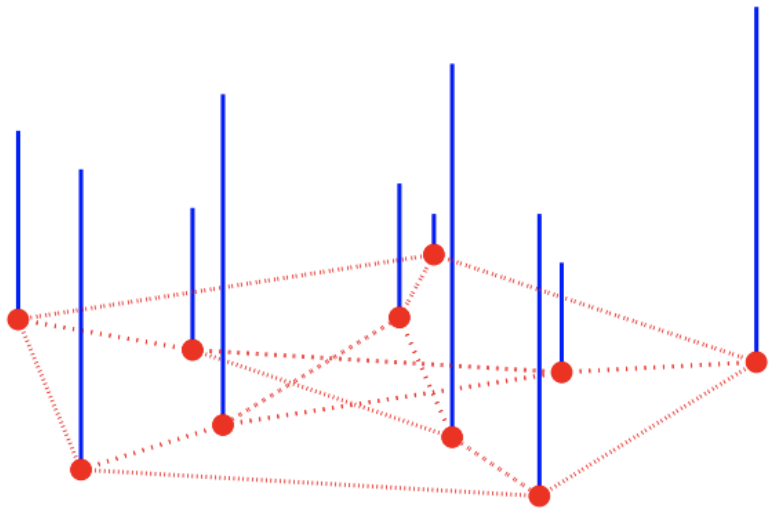


Figure: from Shuman *et al.* ArXiv. The purpose is to study the interplay between some signal and graph connectivity.

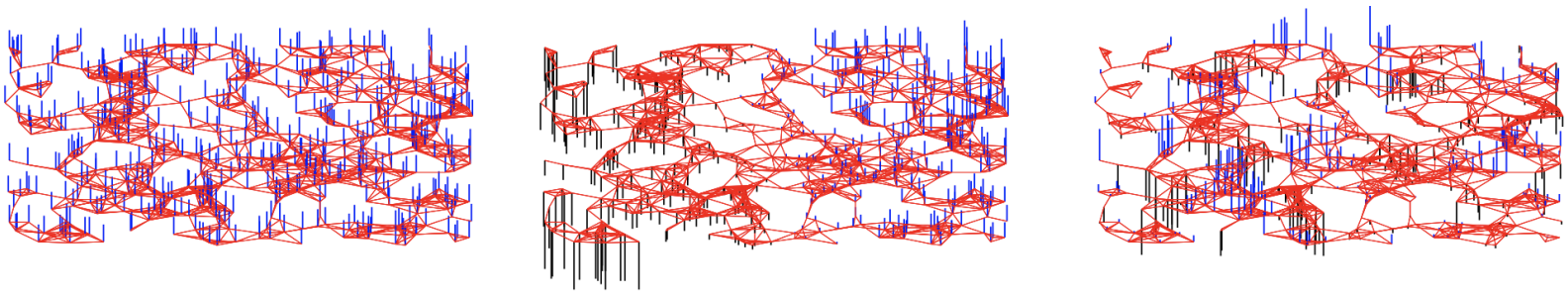
The Interplay Between Signal and Graph Structure

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

- We will use spectra of the graph Laplacian to link signal, $\mathbf{f}$ to graph structure and modulate as necessary. For example $\mathbf{f}$ could be a clinical label of a cell.
  - First re-write $\mathbf{f}$ in terms of eigenvectors of the Laplacian
  - The eigenvectors corresponding to the first *smallest* eigenvalues of $\mathbf{L}$ 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 ($\mathbf{u}_0$,$\mathbf{u}_1$,$\mathbf{u}_{50}$)



$\mathbf{u}_0$ $\mathbf{u}_1$ $\mathbf{u}_{50}$

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

Same Concept Visualized A Bit Differently

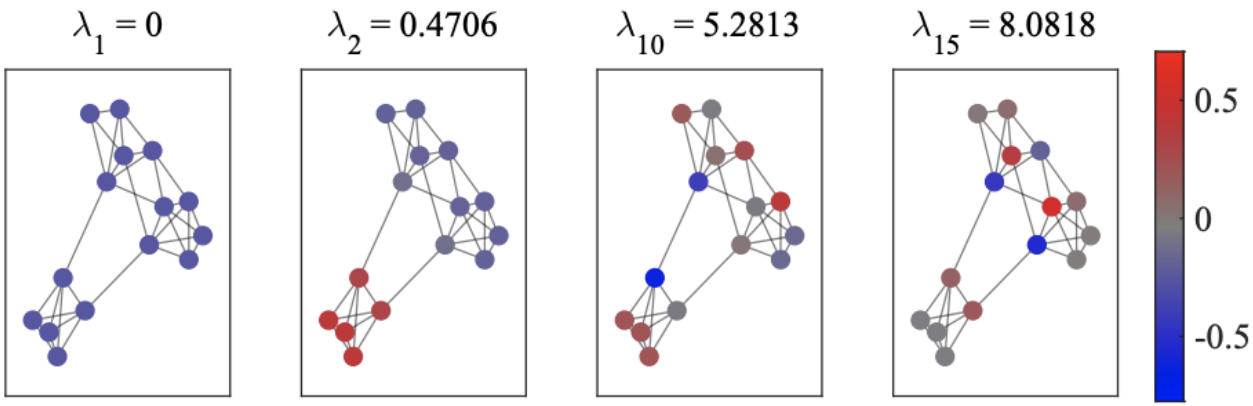


Figure: Notes are colored by their corresponding eigenvector component. From `https://arxiv.org/pdf/2008.01305.pdf`

Similarly

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

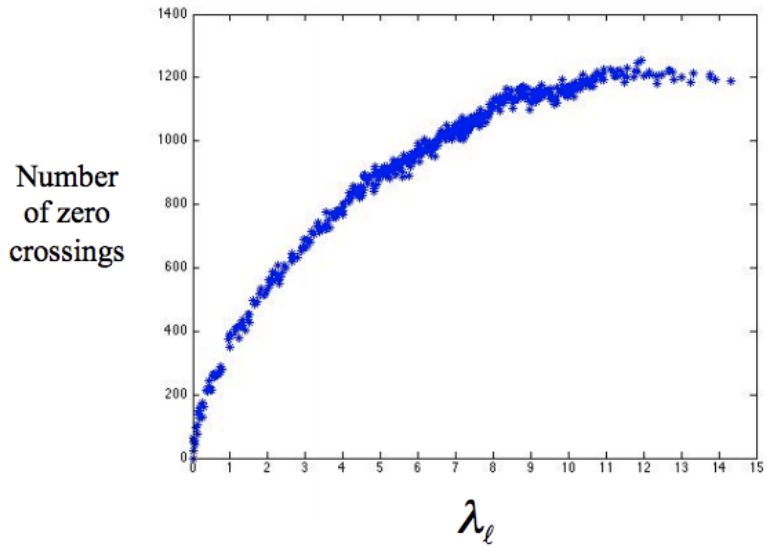


Figure: from GSP Review https://arxiv.org/abs/1211.0053

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,

$$(\mathcal{L}\mathbf{f})(i) = ([\mathbf{D} - \mathbf{A}]\mathbf{f})(i) \tag{1}$$

$$= d(i)\mathbf{f}(i) - \sum_j A_{ij}\mathbf{f}(j) \tag{2}$$

$$= \sum_j A_{ij}(\mathbf{f}(i) - \mathbf{f}(j)) \tag{3}$$

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

$$TV(\mathbf{f}) = \sum_{i,j} A_{ij}(\mathbf{f}(i) - \mathbf{f}(j))^2 \tag{4}$$

$$= \mathbf{f}^T \mathcal{L} \mathbf{f} \tag{5}$$

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

$$\hat{f}_i = \psi_i^T \mathbf{f} \tag{6}$$

The Graph Fourier Transform (GFT) is written as,

$$\hat{\mathbf{f}} = \boldsymbol{\Psi}^T \mathbf{f} \tag{7}$$

Example on Three Different Graphs

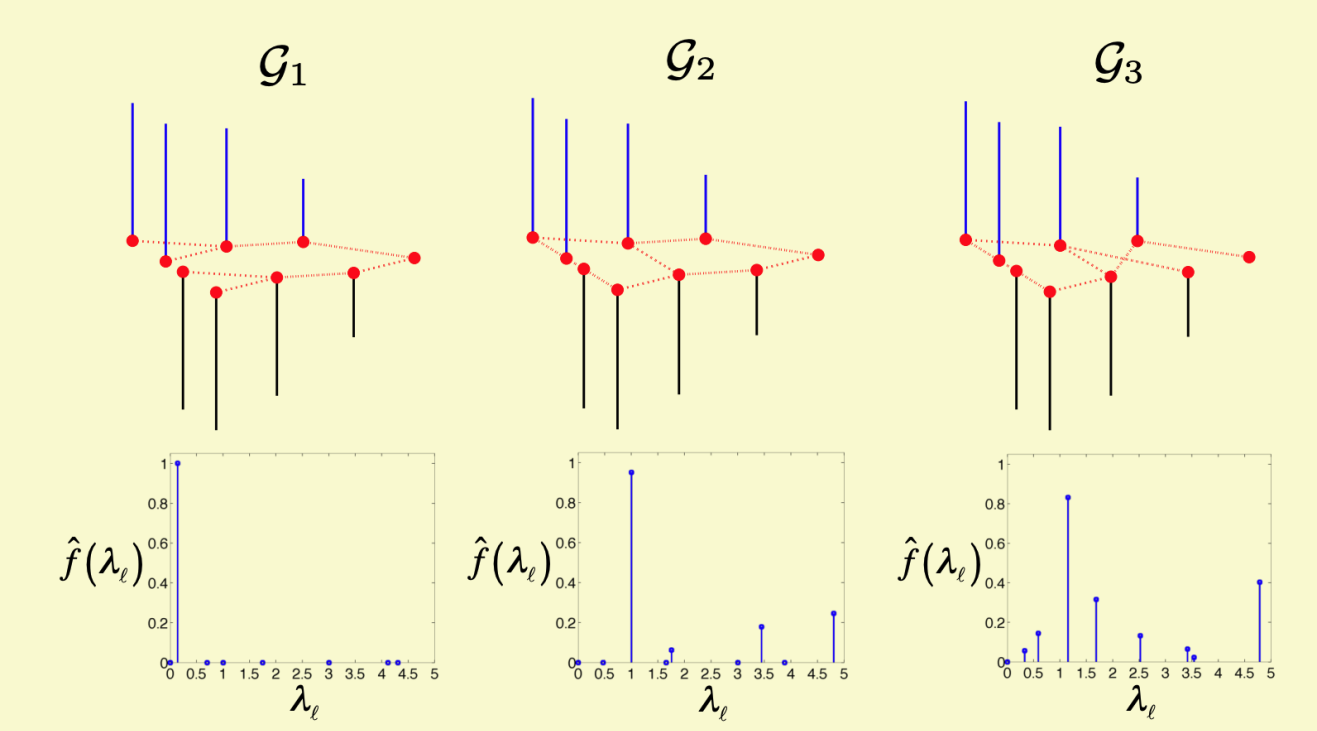


Figure: Recall $\hat{f}(\lambda_l)$ is $\psi_l^T \mathbf{f}$. $\mathcal{G}_1$ has signals corresponding to graph structure and hence highest $\hat{f}(\lambda_l)$ for $l = 0$. The opposite is true for $\mathcal{G}_3$.

How Does This Relate to Quadratic Form

Recall quadratic form is $\mathbf{f}^T\mathbf{L}\mathbf{f}$

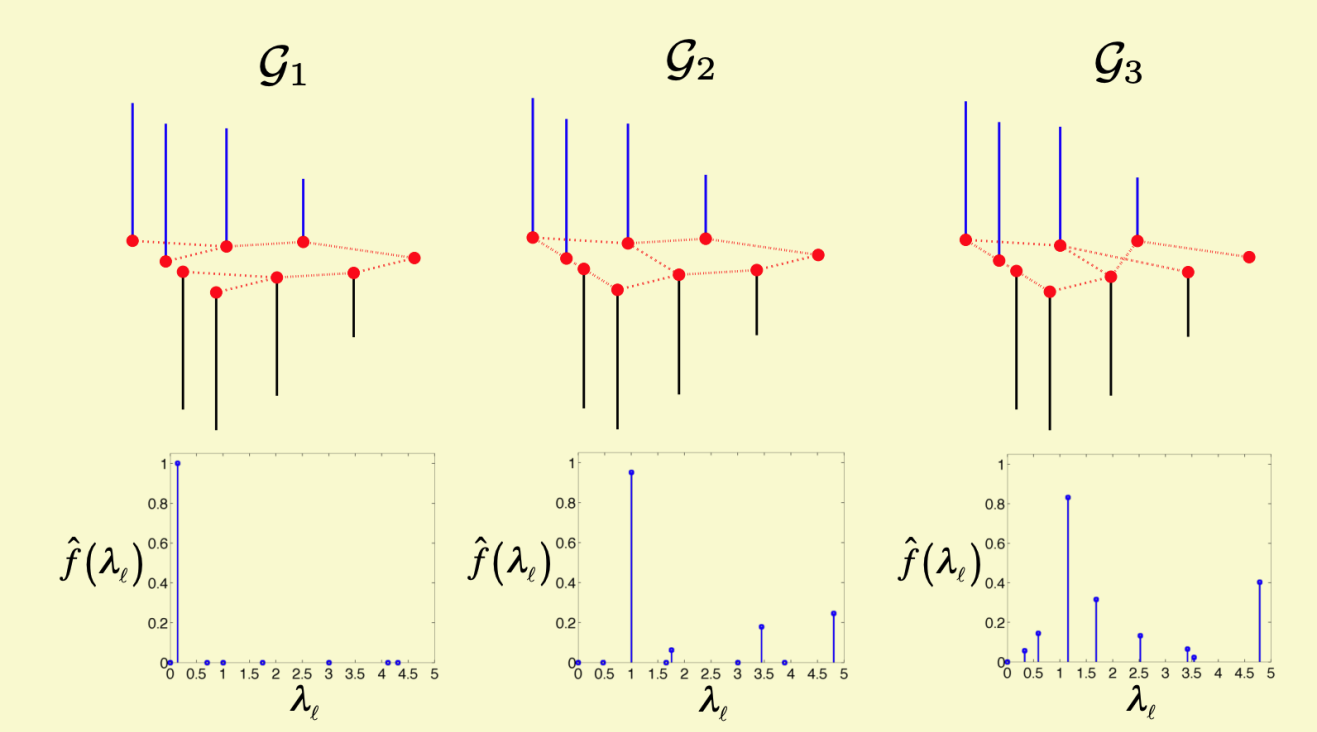


Figure: Here, $\mathbf{f}^T\mathbf{L}_1\mathbf{f} = 0.14$, $\mathbf{f}^T\mathbf{L}_2\mathbf{f} = 1.31$, $\mathbf{f}^T\mathbf{L}_3\mathbf{f} = 1.81$

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,

$$h : [0, \max(\mathbf{\Lambda})] \rightarrow [0, 1] \tag{8}$$

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,

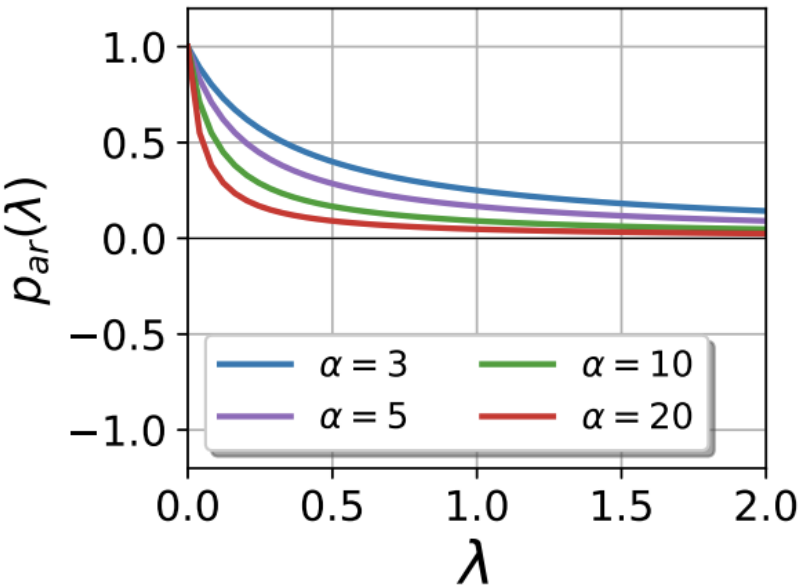
$$\hat{\mathbf{f}}_{filt} = h(\mathbf{\Lambda})\hat{\mathbf{f}} \tag{9}$$

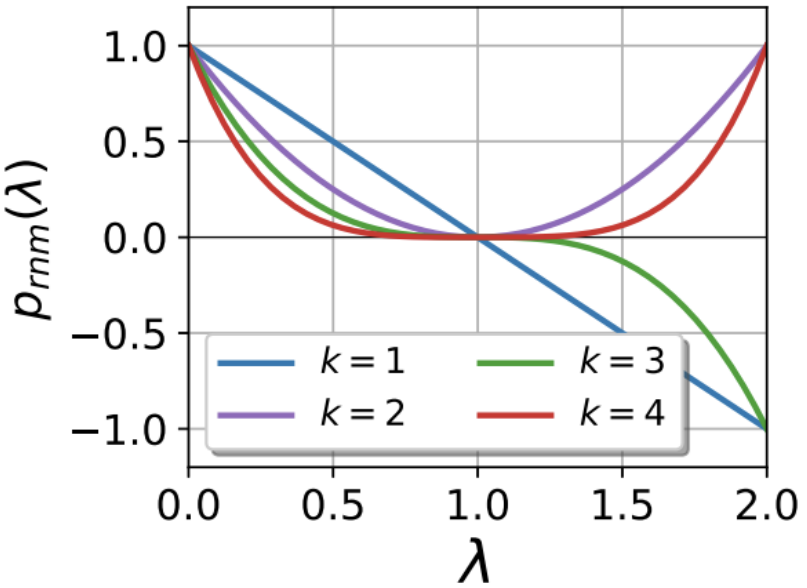
Applying a Filter in General

In general, you can filter an original signal, $\mathbf{f}$ in general as,

$$\underbrace{\boldsymbol{\Psi}(\mathbf{I} + \alpha\boldsymbol{\Lambda})^{-1}\boldsymbol{\Psi}^T}_{\text{Filtered Graph Laplacian}} \mathbf{f}. \tag{10}$$

Example Filters





(a) $p_{\text{ar}}(\lambda) = (1 + \alpha\lambda)^{-1}$ (b) $p_{\text{rnm}}(\lambda) = (1 - \lambda)^{k}$

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

Example in PyGSP

- Access PyGSP here, `https://pygsp.readthedocs.io/en/stable/tutorials/intro.html`

$$g(x) = \frac{1}{1+\tau x},$$

let's define and plot that low-pass filter:

```
>>> tau = 1
>>> def g(x):
...     return 1. / (1. + tau * x)
>>> g = filters.Filter(G, g)
>>>
>>> fig, ax = plt.subplots()
>>> g.plot(plot_eigenvalues=True, ax=ax)
>>> _ = ax.set_title('Filter frequency response')
```

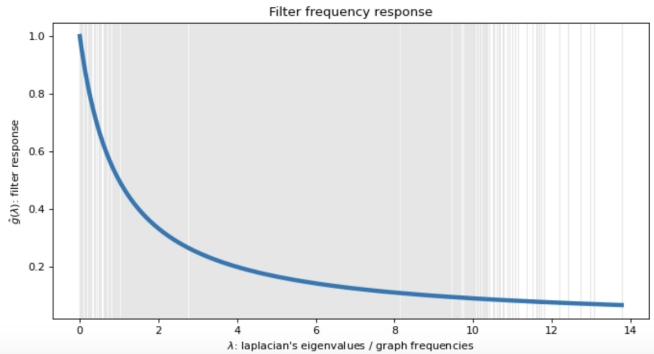
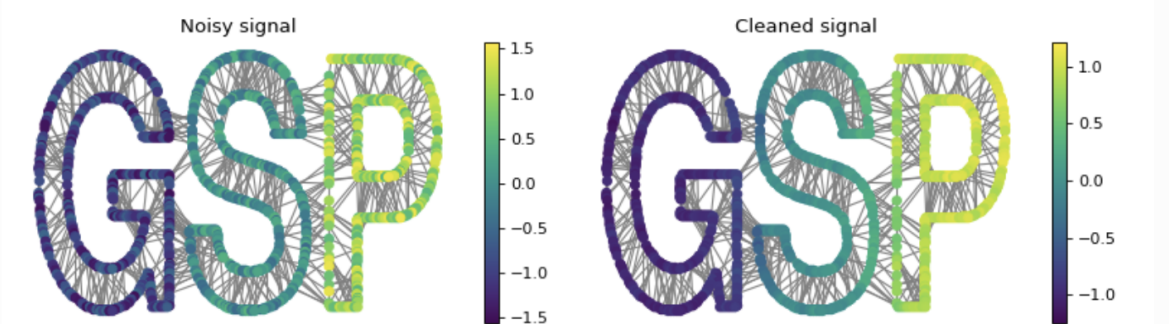


Figure: A simple filter for eigenvalues of **L**

Low-Pass Filtering a Noisy SIgnal

```
>>> s2 = g.filter(s)
>>>
>>> fig, axes = plt.subplots(1, 2, figsize=(10, 3))
>>> G.plot_signal(s, vertex_size=30, ax=axes[0])
>>> _ = axes[0].set_title('Noisy signal')
>>> axes[0].set_axis_off()
>>> G.plot_signal(s2, vertex_size=30, ax=axes[1])
>>> _ = axes[1].set_title('Cleaned signal')
>>> axes[1].set_axis_off()
>>> fig.tight_layout()
```



Linking Single Cell Data to External Information

A Question for You

If you were just given a bunch of cells and someone told you to find 200 cells that were associated with an experiment or a condition of interest, how would you choose those cells? What would cause you to trust that a particular cell was indeed representative of the experimental label?

Treatment as a Signal on a Graph

After creating a graph of cells, an indicator of treatment or control can be viewed as the signal on the graph. Interpretations of ‘signal‘ in relation to graph structure should help to inform treatment associated relative likelihood.

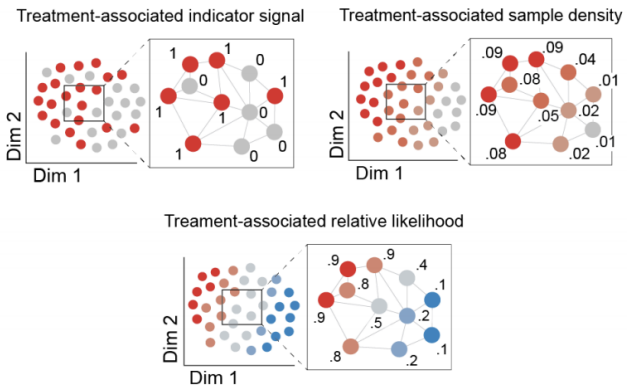


Figure: Burkhardt *et al.*, Nature Biotechnology. 2021.

What on Earth is a Cell-State

We have seen cell states already!

- Frequency $\rightarrow$ how many of a particular cell-type are there in a sample?
- Function $\rightarrow$ Which proteins are activated in a particular cell-type?

General Overview of the Steps of MELD

- Build a graph between cells based on gene or protein expression measurements
- **Graph Signals:** Experimental label (a binary indicator) is used to label each cell according to experimental condition
- Using GSP techniques, MELD filters biological and technical noise to look at how much the experimental signal of a cell matches the true experimental label. This quantifies how prototypical each cell is in its condition.
- Relate back to cell-types and features that differ between experimental conditions

RES vs EES

EES represents the enhanced experimental signal, in comparison to RES, which was the raw, binary signal.

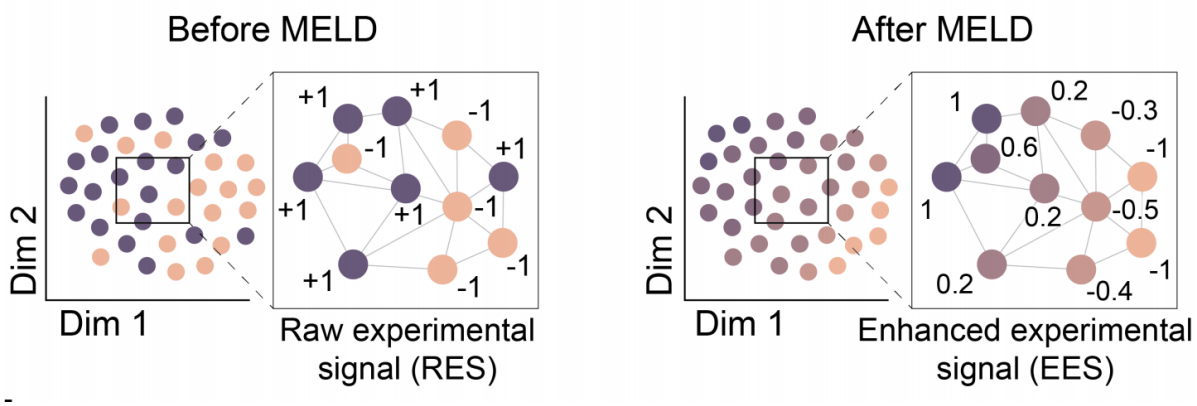


Figure: from Burkhardt *et al.*, Nature Biotechnology. 2021

Sources of Noise

- Cells with similar feature measurements are said to be in the same state (biologically)
- **High Frequency Noise** : High frequency noise is when the labels of neighboring cells are rapidly fluctuating.
- **Graph Fourier Transform** is used to study the frequency of a signal over an irregular domain, like a graph.

Incorporating these ideas into meld

- Define a latent variable $\mathbf{z}$ that gives a score for how prototypical a cell is for a specific experimental or clinical condition.
- $\mathbf{z}$ will be computed using low-pass graph filters.
- Defining more specific variables
  - $\mathbf{x}$ is the vector of original labels (RES) for each cell
  - $\mathbf{z}$ is the vector of enhanced experimental signals (EES) for each cell.

Visualizing **x** and **z**

The left is RES (**x**) and the right is EES (**z**). **z** is what is being optimized.

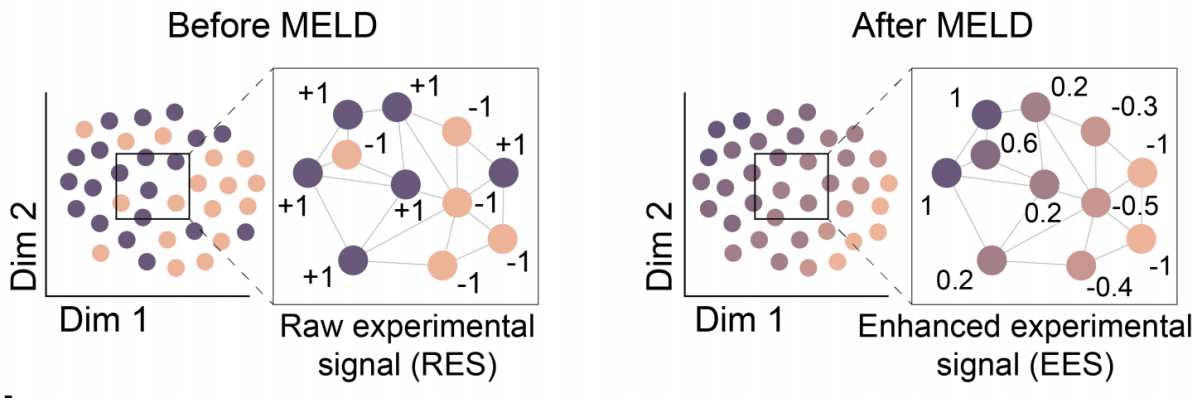


Figure: from Burkhardt *et al.*, Nature Biotechnology. 2021

MELD Optimization Problem

To find an appropriate $\mathbf{z}$, an optimization problem can be defined as,

$$\mathbf{y} = \underset{\mathbf{z}}{\operatorname{argmin}} \underbrace{\|\mathbf{x} - \mathbf{z}\|_2^2}_{\mathbf{a}} + \underbrace{\beta \mathbf{z}^T \mathcal{L} \mathbf{z}}_{\mathbf{b}} \tag{11}$$

Unpacking

z is the EES or Enhanced Experimental Signal

$$\mathbf{y} = \underset{\mathbf{z}}{\operatorname{argmin}} \underbrace{\|\mathbf{x} - \mathbf{z}\|_2^2}_{\mathbf{a}} + \underbrace{\beta \mathbf{z}^T \mathcal{L} \mathbf{z}}_{\mathbf{b}} \tag{12}$$

- The Laplacian Regularization (term b) initially encourages smoothness for an input graph signal, **x**
- (**a**) Term a represents reconstruction between **x** and **z**
- (**b**) Term b represents Laplacian regularization or a measure of smoothness on the graph. Recall this looks a lot like total variation.

$$\beta \mathbf{z}^T \mathcal{L} \mathbf{z} = \beta \sum_{i,j} A_{ij} (\mathbf{z}(i) - \mathbf{z}(j))^2 \tag{13}$$

Introducing the MELD Filter

They adjust the filer a bit as follows. The following allows also for a flexible notion of figure order, ρ,

$$\begin{aligned} \mathbf{y} &= \underset{z}{\text{argmin}} \|\mathbf{x} - \mathbf{z}\|_2^2 + \mathbf{z}^T \mathcal{L}_* \mathbf{z} \\ \text{where } \mathcal{L}_* &= [\beta \mathcal{L} - \alpha \mathbf{I}]^\rho \end{aligned} \tag{14}$$

Takeaway

They show that their Laplacian Regularization is a filter with the following frequency response,

$$h_{\mathrm{MELD}}(\lambda) = \frac{1}{1 + (\beta\lambda - \alpha)^{\rho}} \tag{15}$$

This was a lot to unpack. I recommend staring at the details (if you are interested) in
`https://www.biorxiv.org/content/10.1101/532846v1.full.pdf`

Filter Variety

Here are some experiments showing what parameters on the MELD filter will do to the frequency response, $h(\lambda)$.

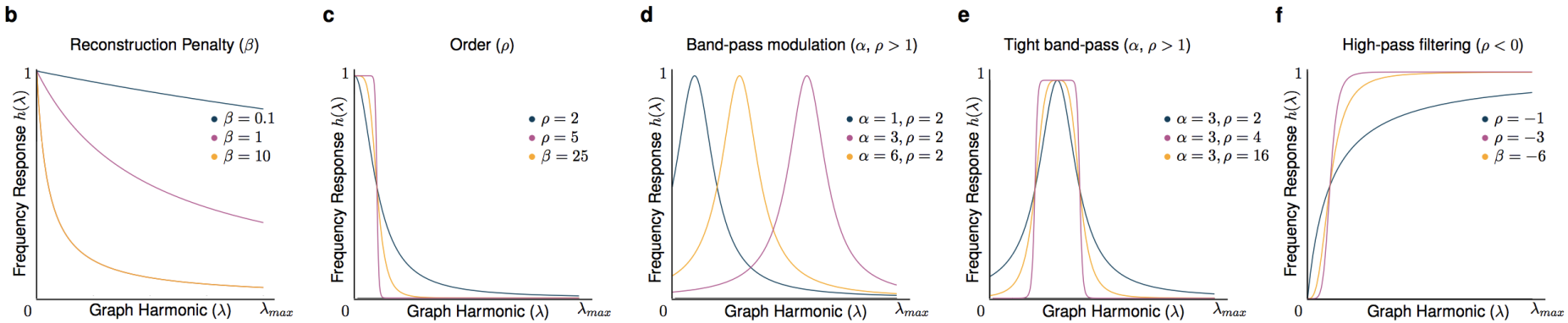


Figure: from Burkhardt *et al.*, Nature Biotechnology. 2021. Negative values of ρ, for example, can produce a high-pass filter.