Comp683: Computational Biology

Lecture 23

April 22, 2024

Today

- Conclude mini convex optimization lecture. See slides 44 and beyond from last time for one last omics approach that uses ADMM for optimization. https://github.com/natalies-teaching/Comp683_CompBio_2024/blob/main/Lectures/Lecture22.pdf
- Technical Writing in Computational Biology
- Conclusion and summary of major themes from the semester.

Important announcements

- Homework 2, due Friday
- Presentations start tomorrow. Please sign up here, https://docs.google.com/spreadsheets/d/1LvzE54589TLroS8McWfQ6uAscSf9uOLs_FXnLyScMw4/edit?usp=sharing
- Final project writeup template available here, https://github.com/natalies-teaching/Comp683_CompBio_2024/blob/main/Project_Proposal/Project_Proposal.tex

Convex Function

A function $f : \mathbb{R}^n \to \mathbb{R}$ is convex, if the domain of f is a convex set and if for all x and y in the domain of f with $0 \leq \theta \leq 1$, we have

$$f(\theta x + (1-\theta)y) \leq \theta f(x) + (1-\theta)f(y)$$

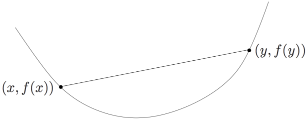


Figure 3.1 Graph of a convex function. The chord (*i.e.*, line segment) between any two points on the graph lies above the graph.

Figure: from the CVX book by Boyd and Vandenberghe. Geometrically, the inequality means that the line segment between $(x, f(x))$ and $(y, f(y))$ lies above f

Dual Problem

Consider a convex equality constrained optimization problem,

$$\begin{array}{ll} \text{minimize} & f(x) \\ \text{subject to} & Ax = b \end{array}$$

We can write the Lagrangian as,

$$L(x, y) = f(x) + y^T(Ax - b)$$

The idea of Lagrangian duality is to take the constraints into account by augmenting the objective function with a weighted sum of the constraints.

Dual Problem Continued

Given the Lagrangian,

$$L(x, y) = f(x) + y^T(Ax - b)$$

we denote the dual function as,

$$g(y) = \inf_x L(x, y)$$

.

We can also consider the dual problem,

$$\max g(y)$$

Finally recover an optimal value, x^* from a dual optimal, y^*,

$$x^* = \arg\ min_x L(x, y^*)$$

Dual Ascent

Use a gradient method for the dual problem,

$$y^{k+1} = y^k + \alpha^k \nabla g\left(y^k\right)$$

In this case, the gradient is,

$$\nabla g\left(y^k\right) = A\tilde{x} - b,$$

where

$$\tilde{x} = \operatorname{argmin}_x L\left(x, y^k\right)$$

So, the dual ascent method is,

$$x^{k+1} := \operatorname{argmin}_x L\left(x, y^k\right) \qquad //x\text{ -minimization}$$

$$y^{k+1} := y^k + \alpha^k\left(Ax^{k+1} - b\right) \qquad //\text{ dual update}$$

Dual Decomposition

Suppose f is separable :

$$f(x) = f_1(x_1) + \cdots + f_N(x_N), \quad x = (x_1, \ldots, x_N)$$

Then L is separable in x :

$$L(x, y,) = L_1(x_1, y) + \cdots + L_N(x_N, y) - y^T b$$

with

$$L_i(x_i, y) = f_i(x_i) + y^T A_i x_i$$

Dual Decomposition, Continued

x-minimization in dual ascent splits into N separate minimizations can be carried out in parallel.

$$x_i^{k+1} := \underset{x_i}{\operatorname{argmin}} L_i\left(x_i, y^k\right)$$

Updates are,

$$\begin{aligned} x_i^{k+1} &:= \operatorname{argmin}_{x_i} L_i\left(x_i, y^k\right), \quad i = 1, \ldots, N \\ y^{k+1} &:= y^k + \alpha^k \left(\sum_{i=1}^N A_i x_i^{k+1} - b\right) \end{aligned}$$

Augmented Lagrangian

For $\rho > 0$, form the augmented Lagrangian,

$$L_\rho(x, y) = f(x) + y^T(Ax - b) + (\rho/2)\|Ax - b\|_2^2$$

- The augmented Lagrangian was developed to in part bring robustness to the dual ascent method, and to encourage convergence without strict assumptions about convexity of f.

Applying dual ascent (also called here method of multipliers),

$$x^{k+1} := \underset{x}{\operatorname{argmin}} L_\rho\left(x, y^k\right)$$
$$y^{k+1} := y^k + \rho\left(Ax^{k+1} - b\right)$$

Alternating Direction Method of Multipliers

The ADMM problem form (where f and g are convex) is,

$$\begin{array}{ll} \text{minimize} & f(x) + g(z) \\ \text{subject to} & Ax + Bz = c \end{array}$$

You can further write down the associated augmented Lagrangian as,

$$L_\rho(x, z, y) = f(x) + g(z) + y^T(Ax + Bz - c) + (\rho/2)\|Ax + Bz - c\|_2^2$$

ADMM will therefore do updates as follows,

$$x^{k+1} := \text{argmin}_x\, L_\rho\left(x, z^k, y^k\right)$$

$$z^{k+1} := \text{argmin}_z\, L_\rho\left(x^{k+1}, z, y^k\right)$$

$$y^{k+1} := y^k + \rho\left(Ax^{k+1} + Bz^{k+1} - c\right)$$

ρ is the particular update step size.

Technical Writing Motivation

- We are all busy. Make your paper clear and easy to understand.
- In Comp Bio we write for two different audiences.
- Notation, figure presentation, publicly available code goes a long way.
- **Communication is Your Job!**
  - Good writing through simple language and organization
  - Well-documented publicly available code

Question

What part of technical writing do you find the most challenging?

Abstract: A Self Contained Story

- An elevator pitch of the main points
- Someone should read this and know exactly what your paper is about.
- Sentence breakdown
  - 1 sentence background
  - 1 sentence about what is still missing
  - 1 sentence about what you did
  - 1 sentence about what results suggest
  - 1 inspirational sentence about how this advances the field.

Introduction

General sections of an introduction.

- Problem motivation- what are we even talking about?
- Description of previous approaches to the problem.
  - Always highlight the work of others in a positive way
- A paragraph where you compare and contrast previous solutions. You can still discuss limitations by spinning them in relation to all of the positive things that the other authors have done.
- Paragraph giving an overview of your contributions. Someone might only read this section of your paper. You need to sell your contribution in a human-readable way.

Methods: First Defining Your Notation

- Notation needs to be clearly defined. There should never be a symbol in an equation that has not been properly defined.
- Keep bolding, italics, upper-case and lower-case consistent
- Dimensions of matrices need to be consistent represented with the same letter (usually p, d, or m)
- Indices should always map the same thing throughout the paper (for example i referring to cells and j referring to a feature of a cell)

Example Defining Notation

We start with some notation. We assume that we have an undirected graph $G = (V, E)$, where there are $n = |V|$ nodes with features on each node represented by a matrix $X \in \mathbb{R}^{n \times p}$. Let A be the adjacency matrix of the graph, D be the diagonal degree matrix, and S be the normalized adjacency matrix $D^{-1/2}AD^{-1/2}$. For the prediction problem, the node set V is split into a disjoint set of unlabeled nodes U and labeled nodes L, which are subsets of the indices $\{1, \ldots, n\}$. We will further split the labeled nodes into a training set L_t and validation set L_v. We represent the labels by a one-hot-encoding matrix $Y \in \mathbb{R}^{n \times c}$, where c is the number of classes (i.e., $Y_{ij} = 1$ if $i \in L$ is known to be in class j, and 0 otherwise, where the ith row of Y is all zero if $i \in U$), Our problem is transductive node classification: assign each node $j \in U$ a label in $\{1, \ldots, c\}$, given G, X, and Y.

Figure: from Huang *et al.* ICLR 2021.

Methods : Problem Formulation

- A section where you mathematically define your problem with the notation you introduced.
- What are your inputs and outputs? What are the dimensions of the inputs and outputs and what do they represent?
- Even if you write out your problem in text format, reference the variables that you defined in the text.

For example: 'For each cell, $\mathbf{x}_i \in \mathbb{R}^d$, we wish to learn its label, y_i through the use of the graph, $\mathcal{G}$.

Tip: Give Reminders

- It is good to keep reminding readers what notations and abstractions represent.
- For example, defining a graph? It doesn't hurt to remind them that nodes are cells and edges represent sufficient similarity between cells.
- Connect problem formulation to 'Figure 1'. In defining the overview of your problem, reference sub-panels of figure 1 of interest.

Example of a Comprehensive Figure 1

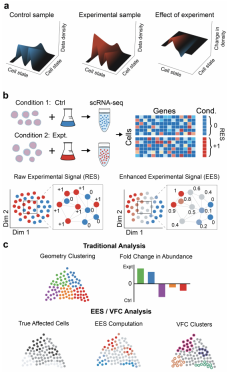


Figure: from Burkhardt *et al.* Nature Biotech. 2021.

Schematic Illustrations

If you draw cells, or patients, make sure these are carried through the entire figure.

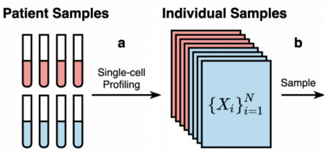


Figure: from Haidong Yi. `https://www.biorxiv.org/content/biorxiv/early/2021/04/14/2021.04.13.439702.full.pdf`

Pseudo-Code

Writing good pseudo code is extremely helpful. It can often by more helpful than the entire methods section.

Algorithm 2 xNetMF $(G_1, G_2, p, K, \gamma_s, \gamma_a)$

================ **STEP 1. Node Identity Extraction** ================
for node u in $\mathcal{V}_1 \cup \mathcal{V}_2$ **do**
    for hop k up to K **do** ▹ counts of node degrees of k-hop neighbors of u
        $\mathbf{d}_u^k$ = CountDegreeDistributions$(\mathcal{R}_u^k)$ ▹ $1 \leq K \leq$ graph diameter
    end for
    $\mathbf{d}_u = \sum_{k=1}^{K} \delta^{k-1} \mathbf{d}_u^k$ ▹ discount factor $\delta \in (0, 1]$
end for
========= **STEP 2. Efficient Similarity-based Representation** =========
========== **STEP 2a. Reduced $n \times p$ Similarity Computation** ==========
$\mathcal{L}$ = ChooseLandmarks(G_1, G_2, p) ▹ choose p nodes from G_1, G_2
for node u in $\mathcal{V}$ **do**
    for node v in $\mathcal{L}$ **do**
        $c_{uv} = e^{-\gamma_s \cdot \|\mathbf{d}_u - \mathbf{d}_v\|_2^2 - \gamma_a \cdot \mathrm{dist}(\mathbf{f}_u, \mathbf{f}_v)}$
    end for
end for ▹ Used in low-rank approx. of similarity graph (not constructed)
=========== **STEP 2b. From Similarity to Representation** ============
$\mathbf{W} = \mathbf{C}[\mathcal{L}, \mathcal{L}]$ ▹ Rows of $\mathbf{C}$ corresponding to landmark nodes
$[\mathbf{U}, \Sigma, \mathbf{V}] = \mathrm{SVD}(\mathbf{W}^\dagger)$
$\tilde{\mathbf{Y}} = \mathbf{C}\mathbf{U}\Sigma^{-\frac{1}{2}}$ ▹ **Embedding**: *implicit* factorization of similarity graph
$\tilde{\mathbf{Y}} = Normalize(\tilde{\mathbf{Y}})$ ▹ **Postprocessing**: make embeddings have magnitude 1
$\tilde{\mathbf{Y}}_1, \tilde{\mathbf{Y}}_2$ = Split$(\tilde{\mathbf{Y}})$ ▹ **Separate** representations for nodes in G_1, G_2
return $\tilde{\mathbf{Y}}_1, \tilde{\mathbf{Y}}_2$

Figure: from `https://arxiv.org/pdf/1802.06257.pdf`

Results

- Figure/table legends should be self-contained. For example, if there is some kind of confidence interval around your curve, tell us what it represents
- Plotting: try to choose appropriate axis to capture all of the datapoints. Don't just plot for example between 0 and 1 on the y-axis by default.
- Make sure that each panel of your results figures are clearly referenced in the text.
- Avoid sloppiness. Don't let a table flow over the margin. Try to avoid different fonts and font sizes between figures.
- Colors: choose them well. Try changing default colors and removing grids from plots, etc.

Information to Include in Results

- **Baselines:** How were the baseline methods used? Did you use default parameters?
- (In real life...) you should be testing your method on several datasets (3 in biology is good).
- **Dataset description:** Describe these datasets, any pre-processing you did, and where the information can be accessed.
- **Description of Experiments:** Experiments need to be clearly described, including small details like the number of times you repeated such experiment. Always reference the figure or table where the results appear wrt a given experiment.

Discussion

- Recap what you have done with an overall summary
- Explain how your work complements or addresses some unmet need in the field
- Summarize your results again
- Discuss limitations and future work
- **Inspirational Parting Thought:** What is the main reason people should care and why does your work advance the field?

Publishing in Comp Bio

- Conferences
  - ISMB
  - RECOMB
  - ACM BCB
- Journals
  - Bioinformatics
  - Cell Systems
  - Nature Journals (Nature Methods, Nature Biotech, Nature Communications)

Writing a Conference Paper

- Self-contained, well-structured, making it easy to read and write
- Much faster in terms of review, revision
- Appealing to CS audience.

Writing a Journal Article

- The main text is selling an algorithm to a broad audience.
- Heavily relies on supplemental text to get all of the relevant details.
- Very slow process. From initial submission to publication can take 1 year.
- Not as appealing to a CS audience.
- More appealing to biology audience.
- Very expensive to publish

Providing Code

- It is good to provide code with your paper starting at the time of submission
- Repository should contain a pre-processed version of the data and instructions about how to run code on these data.

From the Point of View of a Paper Consumer

- It is great to publish in fancy interdisciplinary journals
- It becomes less valuable to us on the CS side if the method is scattered over 100 pages of supplement
- Writing a version of your paper with all of the technical details for ArXiv is very good practice.

A Word of Advice for Being a PhD Student in Comp Bio

Protect your expertise and your time. You are not a core facility.

- Prioritize collaborations that are mutually beneficial
- Make sure you publish your own papers without too many distractions of analyzing random datasets.
- Check where your potential collaborators put their comp bio people in the author list.

Communicating Between Fields

- People will care about different things, between biology and computer science- tailor your details accordingly.
- You need to translate your complex model to a series of steps that don't involve mathematical phrases that we all take for granted. For example, don't say phrases like 'L1 penalty'

Choosing What to Work On

Inspired by the talk of Quaid Morris
`https://www.youtube.com/watch?v=xueh6WnpRDQ`

- Don't be the state-of-the-art, be the benchmark (aka ask a new question)
- Choose hard problems rooted in biology that other people wouldn't have thought to ask because they don't read the biological literature.
- Watch the superstars who speak both languages. Watch how they publish and what they choose to work on.

Transitioning and Summarizing What we Have Covered

We have focused on representing data as graphs and using the graphs to help us to answer questions.

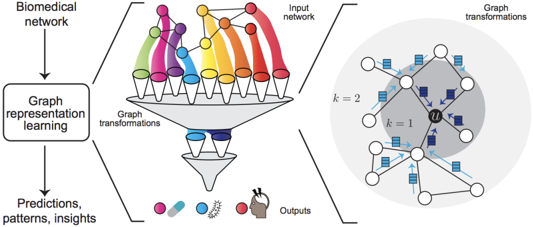
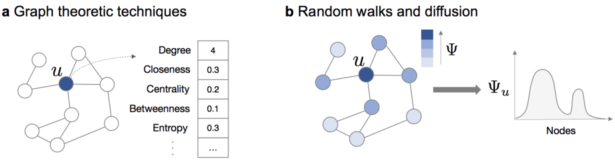


Figure: From `https://arxiv.org/abs/2104.04883`. For example. Assigning proteins to groups or people to outcomes.

Class 1: Graph Summary Statistics and Diffusion

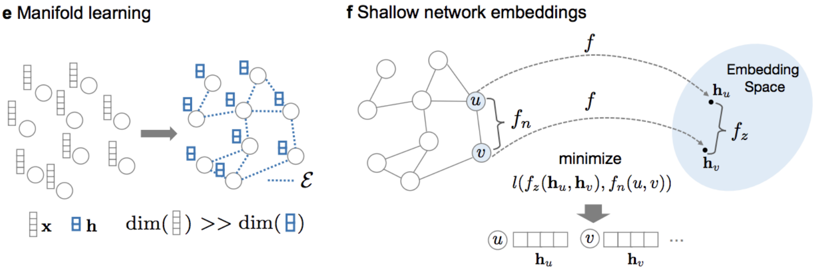
Summary statistics and diffusion can describe patterns in the graph, importance of nodes,



Graph Structure and Diffusion and Papers

- **PhenoGraph:** Partition cells to cell clusters
- **BigClam:** For overlapping clustering
- **MAGIC:** for imputation in single cell data.
- **MELD:** for predicting the specificity of each cell to each condition.
- **Conos:** Combining multiple single cell datasets
- **REGAL:** graph alignment based on structural properties

Node Embedding Theme



Class 2: Node Embedding Theme

- Node2Vec for node embedding (embedding)
- SUGAR for data augmentation in single-cell analysis (manifold)
- SLICER for trajectory inference (manifold)
- Grassmann Embedding for combining multiple datasets (manifold)
- Mashup for embedding nodes according to multiple relational definitions (embedding)

Class 3: Machine Learning on Graphs

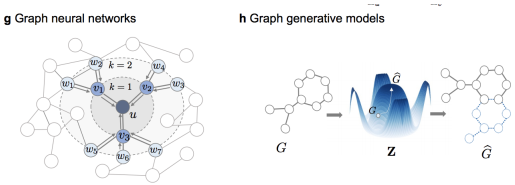


Figure: We haven't seen so much here.....

Seen in ML on Graphs

- Correct and Smooth for predicting labels of nodes based on simple base predictor for node features.
- More next year.....