

Comp790-166: Computational Biology

Lecture 19

April 13, 2021

Announcements

- Homework 2 is online. Due April 23. <https://github.com/stanley/Cmp790-166-Cmp-Bio/tree/main/Homework2>
- Project signup sheet by Thursday but the dates will be April 27, April 29, May 4.
- Comments on projects? How are they going?

Today

- Studying brain connectivity
- Chronnectome : a dynamic view of brain connectivity.
- fMRI + edge communities
- Identifying predictive edges of some phenotype of interest.

Human Connectome Project

An effort to understand the details of neural connectivity. Specifically, within and between individuals.

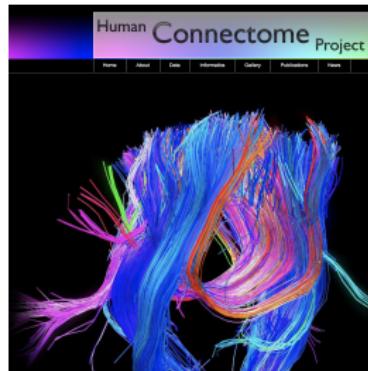


Figure: from <http://www.humanconnectomeproject.org/>

Structural vs Functional Connectivity

- **Structural:** Anatomical white matter fibers connecting brain regions.
- **Functional:** A measure of the covariation between brain activity (e.g. blood flow) at different locations and depends on the time window considered.

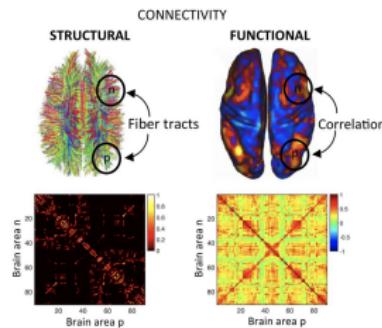


Figure: from Carbral *et al.* *NeuroImage*. 2017. (left: proportion of fiber tracts between brain region) (right: correlation of brain activity between regions over time)

General Pipeline

For our purposes today, we will only be operating on the level of the graph
(are you surprised?)

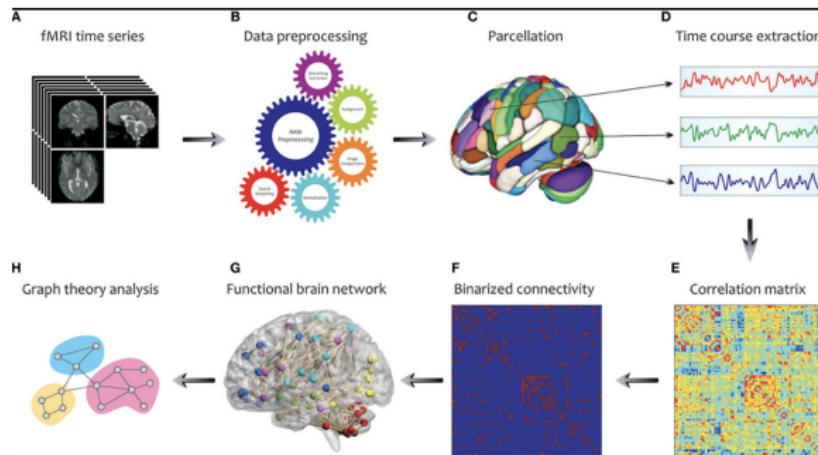


Figure: from Farahani *et al.* Frontiers in Neuroscience. 2019.

Why Study This?

- How does disease impact the healthy connectome?
- In particular, can we derive characteristic signatures of changes in connectivity that are specific to certain brain illnesses.
- For example, given an adjacency matrix (e.g. brain connectivity network) of multiple subjects, can you somehow phenotype these subjects based on either their fMRI or DTI data?

A Practical Problem

- You are going to have an $N \times N$ matrix for each patient.
- Potentially each entry of each patient's matrix is important!
- How do you quickly zoom in on the subset of nodes and edges that are important?
- These matrices are dense! Do we threshold for downstream analysis?

Example: Developing Infants

What are the differences in the modules or highly connected brain regions between newborns, 1 year olds, and 2 year olds? Which are specific to a particular age vs which are common across all ages?

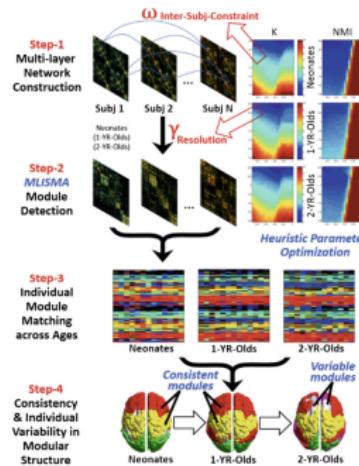


Figure: from Zhang et al. MICCAI. 2018.

Example: Clinical Phenotyping

What is different in terms of functional connectivity between healthy patients and those with schizophrenia?

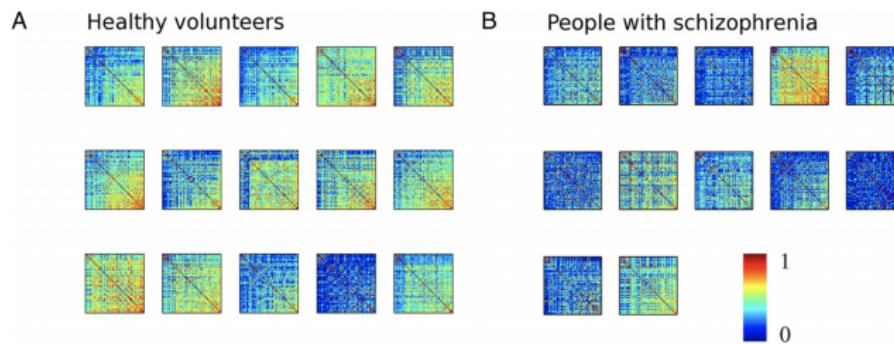


Figure: from Lynall *et al.* Journal of Neuroscience. 2010. Shown here is functional connectivity.

Everything is more fun with a time axis

- **Chronnectome:** A focus on identifying time-varying, but reoccurring patterns of coupling among brain regions.
- So, a model of the brain in which nodal activity and connectivity patterns are changing in fundamental ways through time.
- Each region itself will have variability but analysis of the chronnectome involves the dynamics of the coupling between two or more regions.

Studying Nodes vs Studying Edges

- **Traditional Brain Representation:** Neural elements and pairwise interactions are represented by nodes and edges, respectively.
- Why not consider relationships between edges?

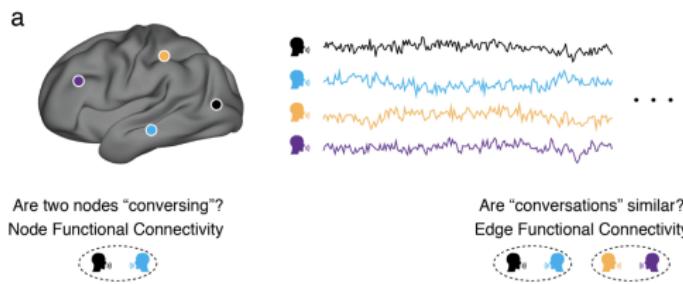


Figure: from Faskowitz *et al.* Nature Neuroscience. 2020. Node-level : the extent to which regions converse. Edge-level: Dynamics of conversation and similarity between conversations.

Example: Each Region of the Brain Can Be Associated with Multiple Sub Networks

Using an overlapping clustering approach, some nodes might belong to multiple subnetworks. For example, regions associated with cognitive processing show a lot of overlap, in contrast to regions associated with motor cortex or visual lobe.

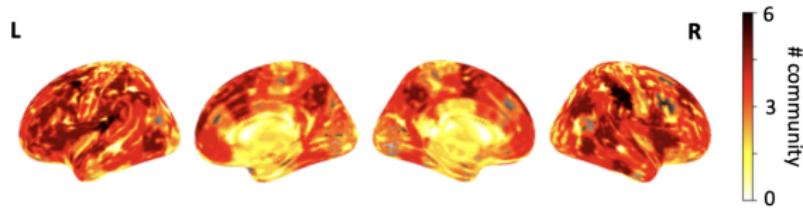


Figure: from Gao *et al.* MICCAI. 2020

Pre-processing fMRI

- Images are parcellated into regions of the brain
- The time-series matrix across subjects are further averaged to a single matrix for downstream analysis.

Edge Graph Construction

- Let $\mathbf{x}_i = [x_i(1), \dots, x_i(T)]$ and $\mathbf{x}_j = [x_j(1), \dots, x_j(T)]$ be the time series recorded at voxels i and j , respectively.

Given voxels of the brain, i and j , calculate their correlation over some time-series as follows:

- z-score each time-series, so, $\mathbf{z}_i = \frac{\mathbf{x}_i - \mu_i}{\sigma_i}$
- Calculate correlation between i and j as $r_{ij} = \frac{1}{T-1} \sum_t [z_i(t) \cdot z_j(t)]$

Edge Functional Connectivity (eFC)

- Consider the following edge pairs between nodes i and j and between nodes u and v .
- Let $c_{ij} = [z_i(1) \cdot z_j(1), \dots, z_i(T) \cdot z_j(T)]$
- Similarly, let, $c_{uv} = [z_u(1) \cdot z_v(1), \dots, z_u(T) \cdot z_v(T)]$

Then eFC between $\{i, j\}$ and $\{u, v\}$ is calculated as,

$$eFC_{ij,uv} = \frac{\sum_t c_{ij}(t) \cdot c_{uv}(t)}{\sqrt{\sum_t c_{ij}(t)^2} \sqrt{\sum_t c_{uv}(t)^2}}$$

A 'Dual' Network

Based on the eFC matrix, a new graph can be constructed/plotted, where each node is the edge pair and edges encode similarity between edge pairs.

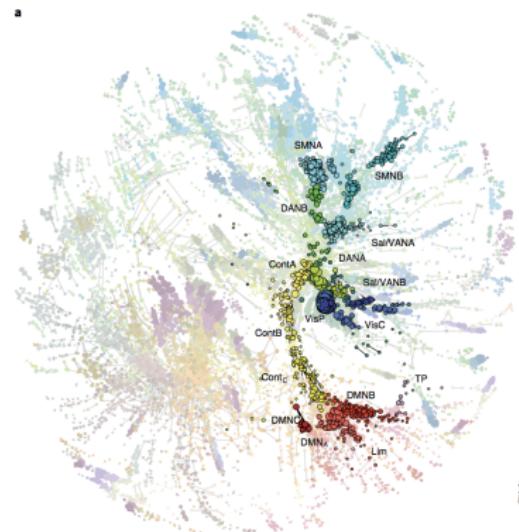


Figure: from Fig. 2 (Faskowitz et al. Nature Neuroscience. 2020.)

Concerns for Clustering

- eFC matrices are much bigger than nFC (node functional connectivity) matrices.
- They made the problem smaller by first doing an eigendecomposition on the eFC matrix and using the top 50 eigenvectors.
- Define clusters based on k -means on the top 50 eigenvectors of the eFC matrix.

Participation of each node in each community

- Each edge was assigned to one of k clusters.
- Further, each node appeared in the edgelist $N - 1$ times.

Therefore, you can calculate the participation of a node i in a cluster c as,

$$p_{ic} = \frac{1}{N - 1} \sum_{j \neq i} \delta(g_{ij}, c)$$

Note that for each node, i , this yields a length- c vector, p_i giving a probability of participation in each cluster.

Entropy for Each Node Based on Edge Communities

From a particular p_i , you can calculate entropy over all of the communities as,

$$h_i = - \sum_c p_{ic} \log_2 p_{ic}.$$

Some brain regions are prone to higher entropy.

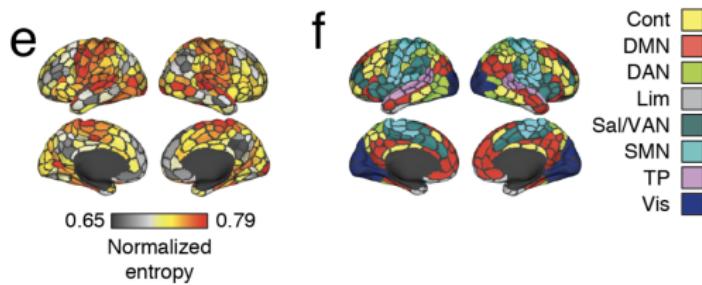


Figure: from <https://www.biorxiv.org/content/10.1101/2020.05.05.067777v1.full.pdf>

Mapping Edge Communities Back to Brain Regions

From each community determined through eFC, check the edges assigned there. Collect the stubs of these edges, and for each node, count the number of edges assigned to that community that it was a stub of.

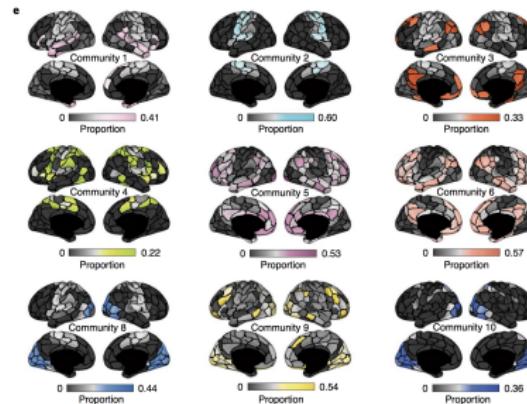


Figure: from Fig. 4 Faskowitz *et al.* Nature Neuroscience. 2020. The edge communities resemble known intrinsic connectivity networks. There is also a notion of overlapping communities.

Participation Coefficient

The idea of community entropy on the node level is usually measured with a participation coefficient as,

$$pc_i = 1 - \sum \left(\frac{k_{is}}{k_i} \right)^2$$

- k_i is the sum of edgeweights incident on node i
- k_{is} is the total weight of node i in community s .

Comm Entropy and Participation Coefficient

The community entropy via edge based clustering and the participation coefficient via node clustering are related but not the same. This shows that these techniques can offer complementary as well as overlapping perspectives.

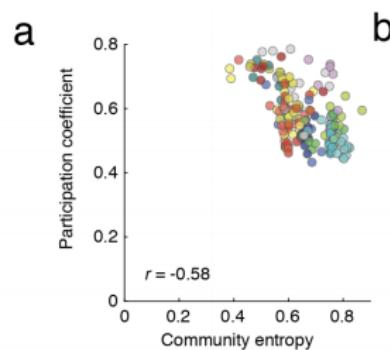


Figure: from Supp. Fig. 16 Faskowitz *et al.* Nature Neuroscience. 2020.

Multi-relational Connectivity Information

- Combining rest + task functional connectivity measurements
- Multiple measurements of structural connection weights

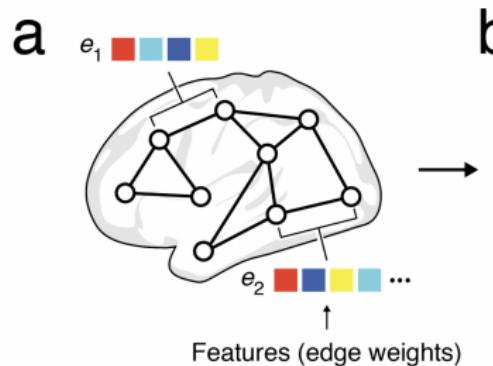


Figure: from <https://www.biorxiv.org/content/10.1101/2021.01.07.425450v1.full.pdf>

Setup

- We have n brain regions (e.g. nodes)
- $\mathbf{W} \in \mathbb{R}^{n \times n}$ is the matrix of edgeweights between regions
- There are potentially n_w total ways of weighting according to the multiple modalities, so define, $\mathbf{W}_{ij} = [W_{ij}^1, \dots, W_{ij}^{n_w}]$

Edge Covariance Network

Assuming there are m edges, the features for each edge can be represented in matrix format as,

$$\Psi = [\mathbf{W}_{e_1}, \dots, \mathbf{W}_{e_m}]^\top.$$

Then, you can calculate an edge covariance matrix, Ω as,

$$\Omega = \frac{1}{n_W - 1} \Psi \times \Psi^\top$$

Fingerprint per Cluster per Condition

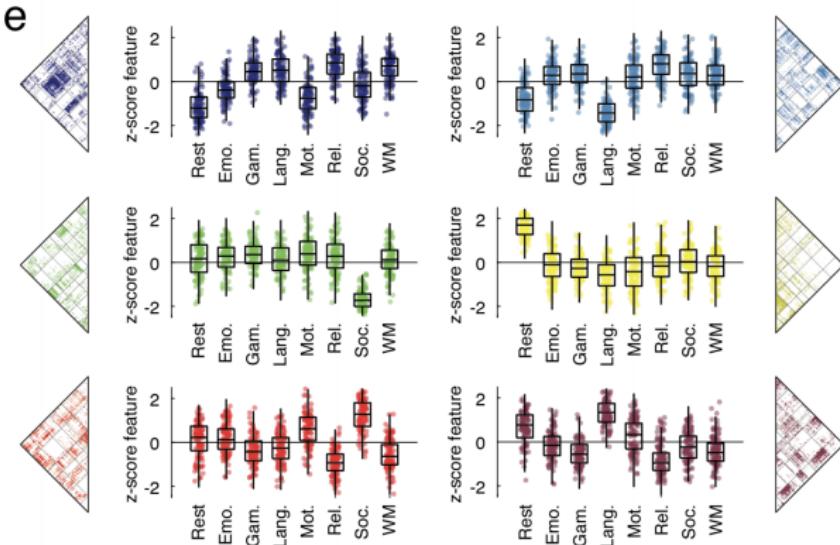


Figure: from <https://www.biorxiv.org/content/10.1101/2021.01.07.425450v1.full.pdf>.

Here, the distributions of edgeweights per community and per task are visualized.

What do we think of this? These are not big networks, but overall, this all seems a bit dense.

Transition: Finding Predictive Subnetworks

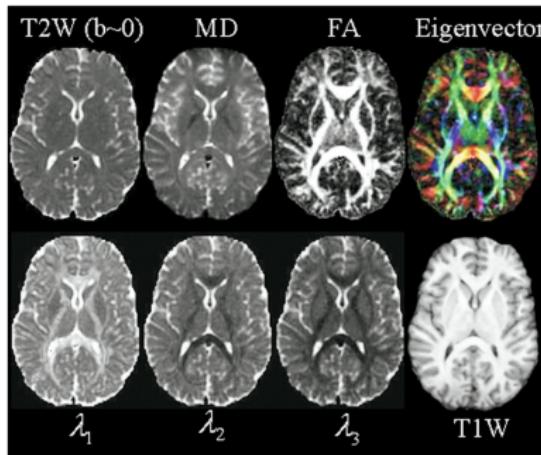


Figure: from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2041910/>
DTI is tracking diffusion of molecules between regions of the brain.

Switching Gears + Still Studying Edges

- Imagine a cohort of patients with structural connectivity measurements between N nodes
- Imagine you want to know which of those ' N choose 2' total possible edge pairs are predictive of some clinical outcome
- Also imagine you want to integrate prior knowledge about which regions of the brain are likely to be connected.

Welcome 'Predictive Subnetwork Extraction with Structural Priors for Infant Connectomes' (MICCAI 2016).

Biomedical Problem

- Pre-term dataset of 168 scans of 115 preterm infants born between 24 and 32 weeks
- Cognitive and neuromotor function of each infant was assessed at 19 months.

Problem: Find the subnetwork (e.g. collection of edges) that can predict these child outcomes. Make sure that the edges chosen are anatomically possible.

Notation

- The matrix of N subjects $\times M$ edge weights is given by $\mathbf{X} \in \mathbb{R}^{N \times M}$.
- The cognitive scores for each of the N infants is given by $\mathbf{y} \in \mathbb{R}^{N \times 1}$.

Specifying a Backbone Prior Network

Pairs of edges are given if they represent a connectivity between regions that are anatomically unlikely.

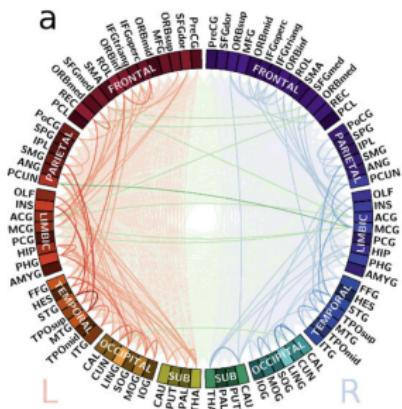


Figure: from Fig. 1 in Brown *et al.* MICCAI. 2016.

SNR to Penalty

Compute the signal to noise ratio in samples that are healthy and in those with adverse outcomes and define,

$$B_{j,j} = \begin{cases} 1, & \text{if } \text{SNR}(X_{H,j}) \leq 1 \text{ and } \text{SNR}(X_{U,j}) \leq 1 \\ 0, & \text{otherwise.} \end{cases}$$

A penalty term, $\mathbf{w}^T \mathbf{B} \mathbf{w}$ only penalizes edges that do not pass SNR threshold (so, noise more than signal)

The Objective Function to Identify Useful Edges

To find the optimal subnetwork or the set of edges that can best help to predict the outcomes in \mathbf{y} ,

$$\mathbf{w}^* = \underset{\mathbf{w}}{\operatorname{argmin}} \|\mathbf{y} - \mathbf{X}\mathbf{w}\|^2 + \lambda_{L1} \|\mathbf{w}\|_1 + \lambda_B (\mathbf{w}^T \mathbf{B}\mathbf{w}) + \lambda_C (\mathbf{w}^T \mathbf{C}\mathbf{w})$$

such that $\mathbf{w} \geq 0$

- The $\mathbf{w}^T \mathbf{C}\mathbf{w}$ encourages for edges to be returned that are connected to similar hubs (e.g. part of a similar sub-network of the brain)

Adding Additional Penalty Terms Improves Performance

Method	Motor			Cognitive		
	r	AOC	acc.	r	AOC	acc.
Zhu et al. [8]	0.1586	27.3904	45.10	0.02055	28.0529	49.65
Elastic-Net [7]	0.2703	24.575	58.75	0.2074	24.8292	54.75
Brown et al. [6]	-	-	62.85	-	-	52.55
Linear regression	0.2696	24.777	58.75	0.2445	24.72	55.15
+ L1 regularization	0.3136	18.5451	64.00	0.2443	24.7514	55.2
+ Non-neg. constraint	0.4327	14.5326	68.80	0.3171	17.7255	57.65
+ Backbone prior	0.4355	14.474	68.55	0.3271	17.8184	58.45
+ Connectivity prior (Ours)	0.4423	14.253	70.80	0.3432	17.3768	59.50

Figure: from Table 1 in Brown *et al.* MICCAI. 2016.

Conclusion

- Studying edges seems to have a complementary perspective than studying nodes.
- Here we saw example for how edges were clustered, giving an image of overlapping community
- We also saw a penalized regression approach for predicting clinical outcomes from structural connectivity data.