A Graph Theoretic Approach to Multiscale Functional Connectivity Estimation

Motivation: Functional connectivity (FC) in the brain aims to estimate the landscape of cooperation between active brain regions, identifying regions that functionally act together. FC can be estimated at multiple scales to give a more complete picture of functional organization. Whole-brain FC is more extensively studied, but recent papers have investigated joint FC within and outside local neighborhoods of each voxel. These measures can then be combined to compute overlap connectivity (OC)—mapping agreement between LC and DC—or contrasted as preferential connectivity (PC)—whether an area tends to be more locally or distally connected. These studies used Pearson correlation across regions in blood-oxygen-level-dependent (BOLD) fMRI signals to model FC [7]. However, great progress in FC estimation utilizing structural information, Bayesian statistics, and graphical models have been made in the last few years. Such methods model regions of interest as nodes in a graph and use diffusion tensor imaging (DTI) data, encoding the anatomical tracts in the brain, in conjunction with BOLD fMRI signals to estimate FC. Fig 1 compares the power and computational efficiency of current cutting-edge structural connectivity (SC)-informed methods. Structurally informed Gaussian graphical model (siGGM), developed in [2], was improved upon in [8] by utilizing a new notion of SC derived from a graphical ranodm walk and is referred to as siGGM with Diffusion. Neuro-Hotnet was created in [8] as a more scalable alternative to siGGM with Diffusion that still leverages the diffusion formulation of SC. SC Naive refers to the use of only Pearson correlation to model FC, as in [7]. Neuro-Hotnet not only performs on par with other SC-informed methods but also allows strict control on the statistical significance of discoveries, scales much better with high dimensional data, and is able to identify strongly connected subnetworks of maximal interest [8]. It remains to be seen if these advanced models can replace the SC Naive use of Pearson correlation in attempts to model local FC.

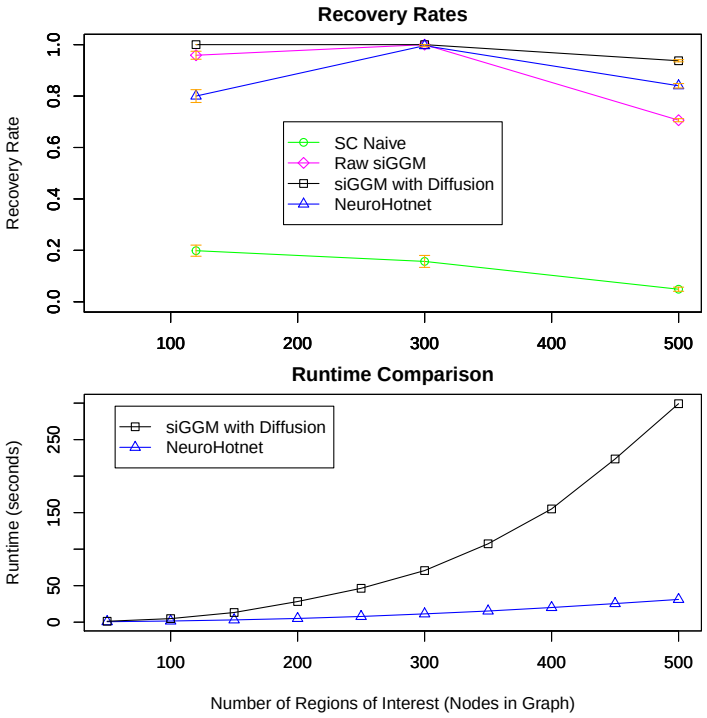

Figure 1: *Top:* Comparison of current methods' average recovery rate for components of randomly generated SC graphs of varying sizes. Orange error bars represent 95% confidence intervals. Rates for each graph are calculated as the proportion of components in the graph that have a match in a method's estimates. *Bottom:* Runtime comparison for the two novel algorithms in [8].

Aim I - Adapt Neuro-Hotnet to local FC: First the notion of SC in [8] must be redefined to work at a smaller scale. DTI data fail to adequately measure short fibers connecting adjacent regions, so at a small enough scale DTI may not be sufficient to define SC. Previous local FC estimation approaches ignore SC and simply use fMRI correlations as a proxy for FC (SC Naive) [7]. However, recent improvements in imaging technology such as diffusion spectrum magnetic resonance imaging (DSI) are able to track intra-voxel crossing fibers and thus map anatomical connectivity between adjacent regions much better [9]. I believe the heat diffusion random walk process previously used on DTI data to define SC in [8] can also be applied to DSI, resulting in a finer grain SC graph appropriate for local FC estimation. See Fig 2 depicting how this process down-weights edges lying in paths with high degree nodes to highlight paths through low degree nodes that are of greater interest and are also more likely to have gone undetected in previous FC estimation approaches.

With this notion of SC adapted for the local setting, either of the two algorithms developed in [8] can be used to obtain local estimates. The Bayesian siGGM has the benefits of handling smaller components better and dealing with an even lower signal-to-noise ratio that may result from working with a small subset of the data. On the other hand the simpler and more scalable Neuro-Hotnet may be much more practical when dealing with voxel-level granularity and thus very large graphs.

Previous work on small-scale FC suggests that there is promise in considering the dynamics of local FC over time, especially in studying the heterogeneity of structures at different scales [3][7]. To address this, the cross-

regional Pearson correlation over all time points previously used in [8] could be replaced with either a sliding-window approach or by modelling time points as layers in a multi-layer graph. The former consists of fixing a temporal window of fixed length, calculating correlations using just those time points, shifting the window by a fixed step size, and repeating [3]. This has been used extensively as a simple method of attaining FC metrics over time. The multi-layer graph approach on the other hand has not been tried to my knowledge. Layers could represent activated regions and edges between layers could be weighted by Pearson correlation. This model could open up the use of graphical algorithms and lead to a lot of theoretical work involving causal inference and is a paper in its own right. With either approach, Neuro-Hotnet could be used at each time-chunk to obtain better estimates and should be quite efficient as the structural influences calculated with diffusion do not vary with time and only need to be computed once.

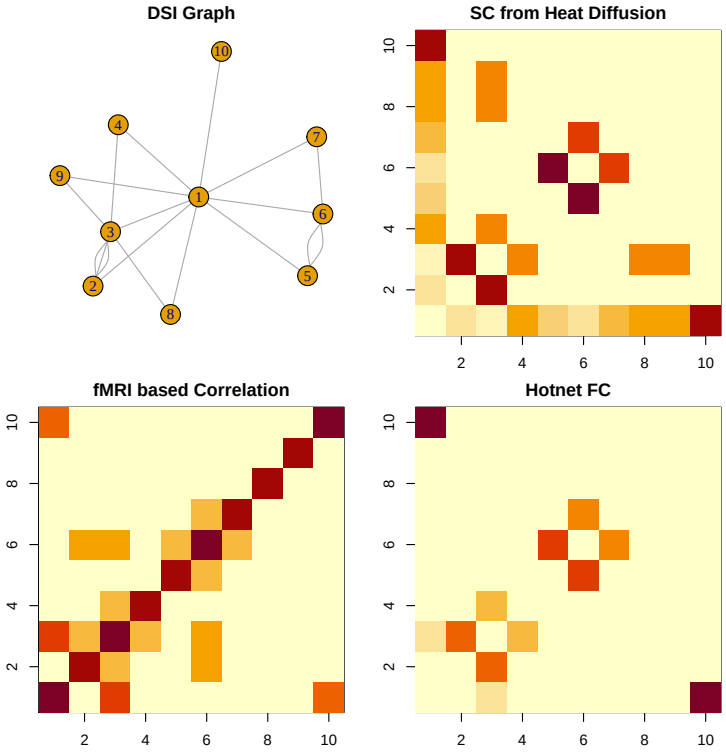

Figure 2: The heat diffusion process was run on the example DSI graph. Note the impact of edges on SC heatmap values and consequently final FC estimates.

Aim II - Update existing multiscale framework: Using the adapted Neuro-Hotnet approach, FC can first be estimated at the whole-brain level. Past definitions of local connectivity (LC) and distant connectivity (DC) can then be computed from this graph. Given voxels v and x, let $d(v,x)$ be the distance (typically Euclidean) between them and N_{vx} the weight of edge $v \leftrightarrow x$ in the Neuro-Hotnet FC estimate. Then

$$LC_r^\delta(v) = \sum_{x:d(v,x)\leq r} \mathbb{1}_{\{N_{vx}>\delta\}}$$

$$DC_r^\delta(v) = \sum_{x:d(v,x)>r} \mathbb{1}_{\{N_{vx}>\delta\}}$$

gives an LC and DC value for each voxel, creating two maps. The distance function $d(\cdot,\cdot)$ and radius r together define locality and δ is a threshold parameter that eliminates weaker edges arising from noise. Finally all values are standardized by Z-score transformation for ease of comparison across subjects. Then $PC = LC - DC$ (difference of Z-scores) and $OC = \min(LC, DC)$, as in [7]. Other normalization and aggregation schemes should be tested since the landscape of the Z-scores may be different with Neuro-Hotnet estimates, as long as they preserve the core idea that PC distinguishes between LC and DC and that OC is some measure of their synchrony. PC, OC, LC, and DC can then be compared to make novel discoveries regarding functional organization [7].

Aim III - A novel multiscale FC model: While accomplishing aim II would be a significant contribution in itself, it does not take full advantage of what Neuro-Hotnet has to offer. I want to explore running the graphical random walk used to define SC (Fig 1) on local subgraphs to isolate regions of interest. First a full discretization of the brain into desired local regions must be defined. With B the set of all voxels in the brain let $\{b_1, b_2, \dots, b_n : b_i \cap b_j = \emptyset, \forall i \neq j\}$ be a collection of disjoint local regions such that $B = \bigcup_{i=1}^n b_i$. Then DSI subgraphs can be defined for each b_i by simply taking all voxels in b_i as nodes and including all edges connecting any two nodes in b_i. The adapted Neuro-Hotnet can then be run with each subgraph being used to define SC for its corresponding b_i, giving LC estimates $l_1, \dots, l_n$. A single Neuro-Hotnet run can be done, as in aim II, for a whole-brain FC estimate N. Then all edges in each l_i and N are standardized by Z-score transformation. A PC graph can now be defined as $\left(\bigcup_{i=1}^n l_i\right) - N$ and OC graph as $\min(\bigcup_{i=1}^n l_i, N)$, with graph operations being done for the values on each edge.

With this approach, identifying optimal discretizations of the brain becomes a question in itself. Ubiquitous divisions such as into the commonly defined lobes can be tested as well as various atlases such as Automated Anatomical Labeling (as used in Neuro-Hotnet), Brodmann areas, Harvard-Oxford Atlas, or others appearing in

literature. There may be merit in considering more data-driven approaches that create tailored discretizations on the fly. Given any metric of connectivity between voxels, clustering algorithms could be used to create any number of voxel groups k. Each pair of a specific connectivity metric and fixed k would result in a unique discretization and could be thought of as an additional parameter in this mulstiscale model. Between experimenting with different metrics and varying k's there is a wide range of combinations to compare and likely much nuance in this consideration.

Contribution: Aim II and III, both incorporating aim I, address an expressed need for better multiscale estimation methods: "The heterogeneity of nodes and their pairwise dynamics within networks highlight the importance of considering the hierarchy and scale in which they are embedded" [3]. Aim II does this by generally improving local FC estimates, and aim III by accommodating arbitrary discretizations and finding connected components in a way existing multiscale estimation approaches cannot.

Specifically, from the paper that aim II builds off of: "It is possible, although not explicitly tested here, that local functional coupling may provide a powerful approach for identifying task-activated regions including for brief epochs of task performance" [7]. Aim III directly addresses this call to action and in general confers two major advantages. First, it allows for precise choice of local regions of interest and leverages an isolated random walk process to define SC tailored to that region. Second, it results in graph representations of FC, allowing for the identification of functionally coupled subnetworks as in [8]. Aim II produces heat maps of connectivity but loses all information on the coupling between any two specific voxels in its definition of PC and OC. Aim III retains this information and thus may be much more discerning.

Relevance to Society and the DoD: This proposal aims to address the call for research in Biomathematics, more specifically Neuromathematics, in the ARO BAA. The BAA expresses interest in brain-related disorders, and some of the most highly cited studies in FC are those that show its numerous clinical applications from identifying consistent group differences in diseases like Alzheimer's and Schizophrenia to their diagnosis and prognosis [1][6]. Specifically relevant to this proposal is a study showing proportional local and distant FC reduction in autism spectrum disorders [4]. Because improving local FC estimates and rethinking how they are compared with distant FC is the explicit focus of this proposal, I am hopeful this novel approach may lead to significant advancements in our understanding of autism spectrum and related disorders.

Of particular interest to the DoD is the proven ability of FC estimation to distinguish between healthy subjects and those afflicted with post-traumatic stress disorder (PTSD). Significant FC differences were even found between subjects with a dissociative PTSD response versus a flashback response, suggesting that FC may hold the answer to very fundamental questions regarding the disorder [5]. Further advancements in FC estimation will lead to a better understanding of functional changes underlying PTSD and very likely consequent improvements in treatment. In the long run this will lead to improved soldier performance and a healthier post-service life for warfighters.

Within the broader category of Biomathematics, this proposal directly addresses the multiscale modeling research thrust. The thrust describes the important problem of creating models at different scales and synchronizing their connections, while simultaneously capturing the heterogeneity of individual elements. Aim III does all of these things, as it models individual regions differently through isolated instances of the diffusion random walk process and synchronizes estimates for all of them in new notions of LC and DC. The thrust also calls for the application of traditionally "pure" mathematical fields to Biomathematics. The original Neuro-Hotnet, as well as the locally adapted version in aim I, explores this through techniques in graph theory for social networks and also utilizes the Bayesian siGGM. I hope to continue using rigorous mathematical theory and pulling from traditionally pure fields—particularly graph theory, Bayesian methods, probability, and theoretical machine learning—to carry out this proposal and further work on multiscale connectivity in the brain.