# Multi-resolution analysis of DTI-derived brain connectivity and the influence of PET-derived Alzheimers disease pathology in a preclinical cohort

Seong Jae Hwang Won Hwa Kim Nagesh Adluru Barbara B. Bendlin Vikas Singh

THE UNIVERSITY of WISCONSIN MADISON

## Background

- Characterizing Alzheimer's disease (AD) at **preclinical stages** is crucial for early diagnosis for effective prevention and treatments.
- **Pittsburgh compound B (PiB)** detects highly potent risk factor known as beta-amyloid.
- Currently, studies treat the connections either locally with individual edges or globally with features such as modularity.
- While sufficient for detecting influence of disease, they severely fall short for detecting effects of preclinical pathology on brain connectivity.

## Problem Statement

- In this study, we investigate the **influence of the amyloid burden**.
- Specifically, **distribution volume ratios (DVR) of PiB** in 16 gray matter regions of interest (ROIs) on brain connectivity.
- **We propose a multi-resolution statistical analysis method for brain connectivity networks.**

## Wavelets in Continuous Space

- Similar to the Fourier transform, but uses wavelet basis function instead of sin() and cos() functions.
- Wavelet transform overcomes the ringing artifacts (i.e., Gibbs phenomenon) caused by infinite duration of basis function in Fourier transform.
- Localized in both time and frequency.
- Behave as *band-pass* filters in the frequency domain.
- The mother wavelet $\psi$ on $x$ is a function of scale $s$ and translation $a$,

$$\psi_{s,a}(x) = \frac{1}{a}\psi\left(\frac{x-a}{s}\right).$$

- The forward wavelet transform is

$$W_f(s,a) = \langle f, \psi \rangle = \frac{1}{s}\int f(x)\psi^*\left(\frac{x-a}{s}\right)\mathrm{d}x,$$

- The inverse wavelet transform is

$$f(x) = \frac{1}{C_\psi}\iint W_f(s,a)\psi_{s,a}(x)\,\mathrm{d}a\,\mathrm{d}s$$

where $C_\psi$ is the admissibility constant.

## Wavelet in the Non-Euclidean Space

- Graph $\mathcal{G}$ is given as $\mathcal{G} = \{V, E, \omega\}$ where $V$ is a vertex set, $E$ is an edge set and $\omega$ is the edge weight.
- Main bottleneck for defining wavelet in the non-Euclidean space, i.e., a graph : What is the notion of scale and translation?
- Key idea: Define scale in the frequency domain and translate by an impulse function (Maggioni, 2007; Hammond 2012).
- Spectral graph theory: Graph Laplacian defined as $\mathbf{L} = \mathbf{D} - \mathbf{A}$ where $\mathbf{D}$ and $\mathbf{A}$ are graph adjacency and degree matrix, and the eigenfunctions $\chi_l$ of $\mathbf{L}$ provide the orthonormal bases for graph Fourier transform.
- Graph Fourier Transform

$$\hat{f}(l) = \langle \chi_l, f \rangle = \sum_{n=1}^{N} \chi_l^*(n) f(n) \quad \text{and} \quad f(n) = \sum_{l=0}^{N-1} \hat{f}(l)\chi_l(n)$$

- Spectral graph wavelet is constructed by applying a band-pass filter $g$ at various scales $s \in S$ and localizing it at $n$ with a impulse function as,

$$\psi_{s,n}(m) = \sum_{l=0}^{N-1} g(s\lambda_l)\chi_l^*(n)\chi_l(m)$$

## Wavelet in the Non-Euclidean Space (continued)

- The wavelet transform of a given function $f(n)$ is derived from graph Fourier transform and yields the wavelet coefficients.

$$W_f(s,n) = \langle \psi_{s,n}, f \rangle = \sum_{l=0}^{N-1} g(s\lambda_l)\hat{f}(l)\chi_l(n)$$

- **Wavelet Multiscale Descriptor (WMD)**: multi-resolutional shape descriptor

$$\mathrm{WMD}_f(n) = \{W_f(s,n) | s \in S\}$$

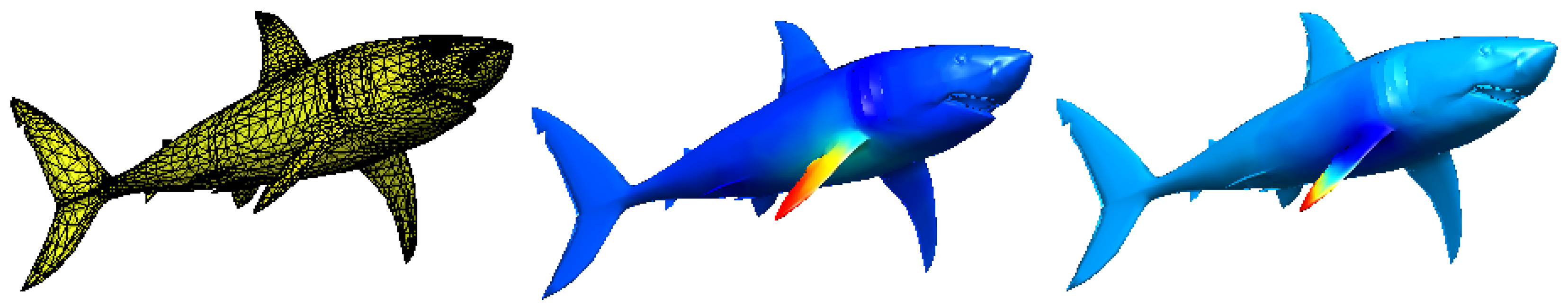

Figure: Shark-shaped mesh domain (left), $\psi_{1,1}$ (center) $\psi_{2,1}$ (right).

## Line Graph (Dual Graph) Transformation

- Line graph $L(\mathcal{G})$ is a dual form of graph $\mathcal{G}$.
- The $L(\mathcal{G})$ is formed by interchanging the roles of $\mathcal{V}$ and $\mathcal{E}$ in $\mathcal{G}$.
- When two edges share a common vertex in $\mathcal{G}$, these edges are connected to each other by the common vertex.
- Let $g_{ij}$ be the elements in the adjacency matrix $\mathbf{A_L}$ of $L(\mathcal{G})$, then

$$g_{ij} = \begin{cases} 1 & \text{if } v \in \mathcal{V},\ v \backsim e_i, e_j \\ 0 & \text{otherwise} \end{cases}$$

where $v$ is a vertex in $\mathcal{V}$ and $e$ is an edge in $\mathcal{E}$.

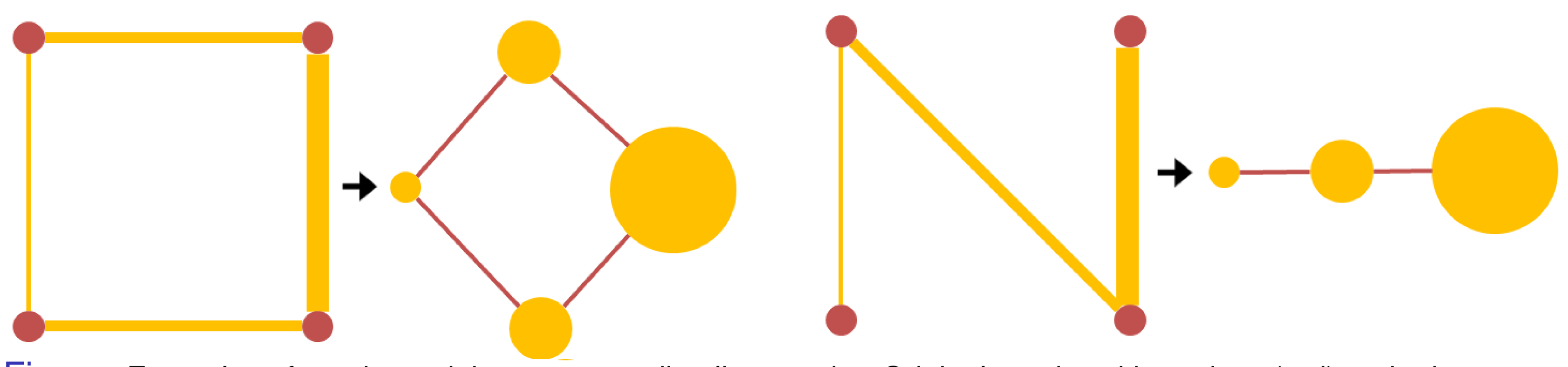

Figure: Examples of graphs and the corresponding line graphs. Original graphs with vertices (red) and edges (yellow) with edge weights (thickness). Line graphs with vertices (yellow) with function (vertex size) and edges (red).

## Network Filtering Process

- In order to filter the network structure, we need to bring the network connectivity information as a signal into another domain.
- Using line graph, we transform our domain $\mathcal{G}$ to $L(\mathcal{G})$, where edge weights are viewed as a signal defined on vertices.

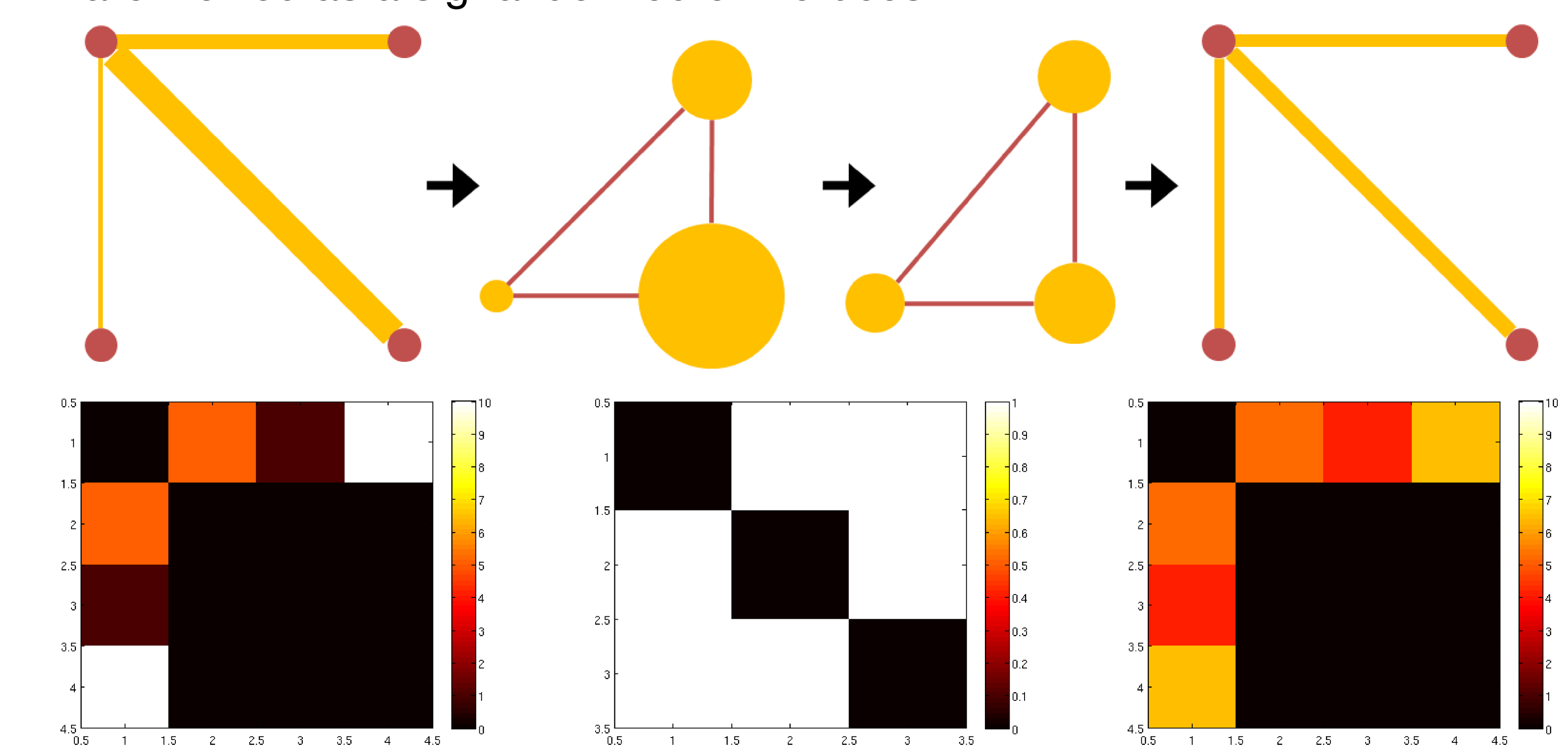

Figure: A toy example of graph structure filtering. The top panel shows the graph filtering steps: (1) Construction of the line graph, (2) filtering the signal on the line graph vertices, (3) reconstructing the filtered graph. The bottom panel shows the corresponding adjacency matrices.

## Dataset

- **140 subjects** (40 male, 100 female) in Wisconsin registry for Alzheimer's prevention (WRAP) cohort.
- Brain connectivity strengths between **162 gray matter regions** from Destrieux atlas were defined as the mean fractional anisotropy (FA) along the tracts of diffusion tensor imaging.
- 5 different scales of the wavelet based multi-resolution connectivity signatures (WaCS) for each connectivity.
- **Pittsburgh compound B (PiB)** distribution volume rations (DVR) of 16 different regions.

## Experimental Result

**Group Analysis**

- Modeled its relationship to mean DVR of PiB for 16 important ROIs.
- Selected 197 edges with mean FA $> 0.01$ for all 140 subjects at all scales.
- We used multivariate general linear model (MGLM) on the WaCS to compute $p$-values.
- For individual scales, we used univariate GLM.

**Results**

- The false discovery rate (FDR) threshold curve is also shown (red).
- The $p$-values for WaCS (blue) for 10 out of the 16 ROIs clearly show the advantage of having multi-resolutional views.
- For 7 out of these 10 ROIs the statistical significance is at the FDR corrected level (blue above red).
- For cingulum regions, the multiple resolutions and individual scales seem to perform similarly at the uncorrected level.

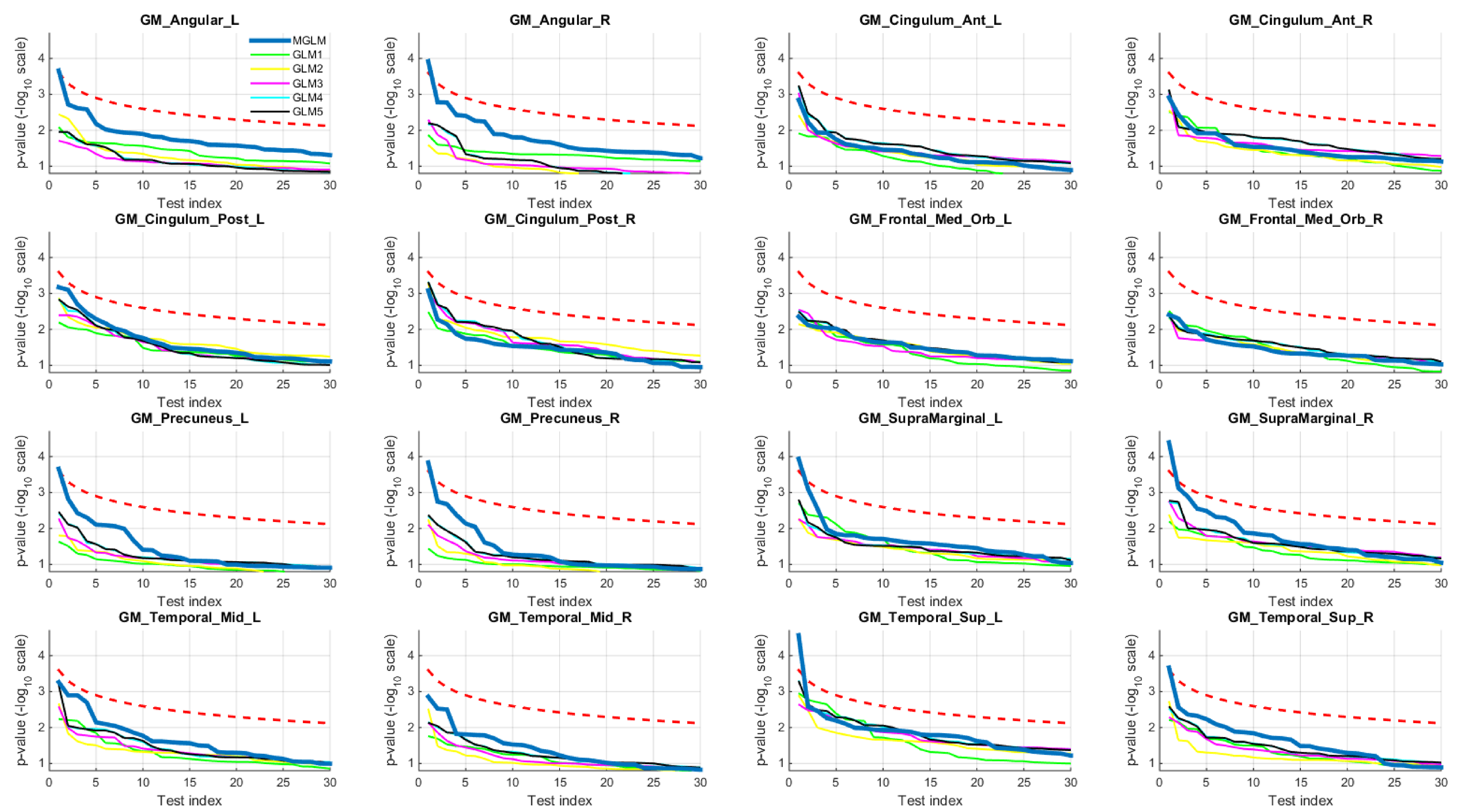


Figure: Comparisons of sorted $p$-values of 16 ROIs using MGLM (blue) and GLMs (other straight lines) and FDR (red) in -log10 scale.

## Conclusion

- We presented a unique multi-resolutional statistical analysis to study the influence of amyloid burden on structural brain connectivity.
- In almost all the regions implicated as important in Alzheimer's disease the multiple resolutions tend to improve the distribution of the $p$-values.

## Acknowledgment

SJH was supported by a University of Wisconsin CIBM fellowship (5T15LM007359-14). We acknowledge support from NIH R01 AG040396 (VS), NIH R01 AG027161 (SCJ), NIH R01 AG37639 (BBB), NSF CCF 1320755 (VS), NSF CAREER award 1252725 (VS), UW ADRC AG033514, UW ICTR 1UL1RR025011, Waisman Core grant P30 HD003352-45 and UW CPCP AI117924.