Title: Identifying topological changes of structural connectome in MCI and AD through persistent homology

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Introduction:

Alzheimer's disease (AD) is the most common form of dementia, an irreversible progressive disease characterized by memory loss followed by deterioration of cognitive function and memory recall. It has been hypothesized to be a disconnection syndrome, characterized by a reduction of efferent and afferent connections between cortical and subcortical regions in AD patients when compared to other subject groups [1]. A contemporary approach to study connectivity is through measuring properties of brain networks, where nodes are defined by regions of interest (ROIs) with edges as relationships derived through structural or functional imaging [2]. However, such measurements are sensitive to thresholding techniques in structural network pipelines, with a lack of consensus on procedure [3]. To circumvent this problem, we may choose to study the networks via persistent homology, which studies homological classes throughout different scales of the network via graph filtration [4]. Using this technique, we study the 0th-homology class (H_0) of AD structural brain networks to investigate changes in topology that may support the hypothesis that AD is a disconnection syndrome.

Methods:

A total of 173 subjects from the ADNI-GO/2 cohort were stratified into three groups: healthy control (HC), mild cognitive impairment (MCI), and Alzheimer's disease (AD) based on their diagnostic group. Fiber density networks were derived from the DTI data, where edge weights are represented by fiber count divided by average volume of the two connected ROIs [5]. These networks were then converted into distance matrices via an inverse radial basis function. The populations' networks were then jackknifed and averaged for persistent homology study. A population of spatial control networks was also created, with edges weighted by Euclidean distance between ROI centroids plus a small amount of random uniform noise [6].

Persistent homology of H_0 in the subject networks was conducted using Ripser [7], studying the presence of connected components as the threshold is increased to accept edges from strongest to weakest via Rips filtration. The primary measurement of this technique is Betti

Number 0 (β_0), which counts the number of connected components [4]. Betti Number Plots (BNPs) were constructed to depict the change of β_0 as the threshold is increased, and its characteristics were quantified with area-under-the-curve (β_0-AUC) obtained through trapezoidal integration. Kruskal-Wallis test was conducted to determine whether β_0-AUC was significantly different among the populations, and Dunn post-hoc test was conducted to observe pairwise population differences.

Results:

From the BNPs (Figure 1), it can be observed that the AD curves are more right-shifted than the HC and MCI curves. The right-shifting is indicative of increased segregation in AD subject brain networks, as weaker edges are required to connect the graph. β_0-AUC measurements were found to be significantly different among the tested groups of HC, MCI, AD, and spatial control (P=1.55e-53) with significant differences between the subject groups found via pairwise tests (P<0.01). AD exhibited significantly higher median β_0-AUC (1.84±2.26e-3), followed by MCI (1.48±1.50e-2), followed by HC (1.10±3.68e-3), reflecting the trend observed in the BNPs.

Conclusions:

Through analysis of H_0, we have identified significant differences among the three subject groups that are indicative of AD being a disconnection syndrome. Increased β_0-AUC is indicative of network segregation, as a more lenient threshold is required to achieve connectivity, with the effect observed to increase monotonically with disease severity. The results found corroborate findings of previous persistent homology studies in AD [8]; however, the methods presented here have found significant differences between all three subject groups, presenting novel evidence of connectivity disruption related to disease.

References (Author Date Format)

1.   Delbeuck, X. (2003), 'Alzheimer's disease as a disconnection syndrome?', *Neuropsychology review*, **vol. 13**, no. 2, pp. 79–92.

2.   Rubinov, M. (2010), 'Complex network measurements of brain connectivity: Uses and interpretations', *NeuroImage*, **vol. 52**, no. 3, pp. 1059-1069.

3.   Caputi, L. (2021), 'Promises and pitfalls of topological data analysis for brain connectivity analysis', *NeuroImage*, **vol. 238**, 118245.

4.   Giusti, C. (2016), 'Two's company, three (or more) is a simplex', *Journal of Computational Neuroscience*, **vol. 41**, no. 1, pp. 1-14.

5.   Li, H. (2017), 'Brain explorer for connectomic analysis'. *Brain Informatics*, **vol. 4,** pp. 253–269.

6.   Sizemore A.E. (2017), 'Cliques and cavities in the human connectome', *Journal of Computational Neuroscience*, **vol. 44**, no. 1, pp. 115-145.

7.   Tralie C. (2018), 'Ripser.py: A lean persistent homology library for python", *The Journal of Open Source Software*, **vol. 3**, no. 29, pp. 925.

8.   Kuang L. (2020), 'White matter brain network research in Alzheimer's disease using persistent features', *Molecules*, **vol. 25**, no. 11, pp. 2472.
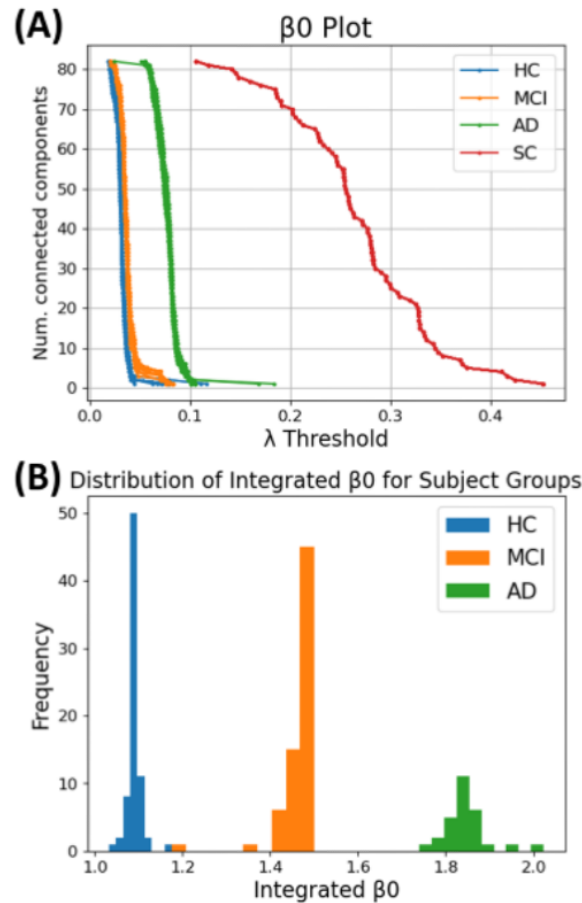
Figure 1. β_0 features were computed using graph filtration and counting the number of connected components at each threshold. **(A)** β_0 BNPs were created for each group. For subject groups (HC, MCI, AD), the population of curves was created by investigating β_0 for each averaged jackknife. For spatial control (SC), the curves were plotted by investigating β_0 for each distance matrix generated with a slight Gaussian noise. It can be observed that the variance of β_0 BNPs is quite small across averaged jackknifes within each group. **(B)** For the subject groups, the distributions of β_0-AUC were plotted, with a bin sizes of 10. SC was omitted, as the median value was a full magnitude larger than the observed subject β_0-AUC values. It can be seen that the subject groups' β_0-AUC differs significantly.