Unraveling Lesion Heterogeneity in Alzheimer's: A Comparative Analysis of Clustering Methods on Intra-Lesional DTI Metrics

Edgar A. Toscano-Flores
Department of Translational Bioengineering, University of Guadalajara, Jalisco, Mexico
Mario A. Mireles-Ramírez
Neurosciences Division, Western Biomedical Research Center, Mexican Institute of Social Security, Guadalajara, Mexico
Francisco A. Alvarez-Padilla*
Department of Translational Bioengineering, University of Guadalajara, Jalisco, Mexico

Abstract:
White matter integrity is fundamental for cognitive function and is progressively disrupted in Alzheimer's Disease. Diffusion Tensor Imaging have validated that this degeneration follows a retrogenesis pattern, where early-myelinating projection pathways remain relatively preserved. Although metodologies have evolved from comparing broad lobar regions to high/dimensional segmentations and specific tract profiling, traditional analyses typically rely on regional averaging. This approach implicitly assumes tissue homogeneity, potentially masking "preserved" fibers embedded within radiologically defined lesions. This study investigates intra-lesional heterogeneity in AD using unsupervised machine learning on DTI data from 53 subjects. We aimed to identify preserved tracts within lesions, using the Internal Capsule of the Corticospinal Tract as a healthy control reference. We compared five clustering algorithms (K-Means, GMM, Agglomerative, Spectral, DBSCAN) and an adaptive threshold method. Performance was validated by calculating the Euclidean distance between the centroids of the cluster identified as "preserved" and the healthy control centroid. Results showed that the Adaptive Thresholding method achieved the highest similarity to healthy tissue (mean distance=0.268). Among the unsupervised algorithms, Spectral clustering emerged as the superior method (mean distance=0.834), successfully isolating fibers with healthy microstructural profiles. In contrast, partitioning methods such as K-Means and Agglomerative clustering failed to sufficiently distinguish preserved from damaged tissue (Distance=0.994). Our results demonstrate that Adaptive Thresholding and Spectral Clustering effectively resolve intra-lesional heterogeneity, revealing preserved anatomical structures often overlooked by global averaging and providing quantitative evidence that supports the retrogenesis hypothesis.

Keywords:
Alzheimer, DTI, MRI, clustering, retrogenesis, preserved tracts.