3. Network Medicine Analysis

3.1 Disease Module Identification for Alzheimer's Disease (AD)

To identify the disease module associated with Alzheimer's Disease (AD), curated disease–gene associations were integrated with the human protein–protein interactome. A total of 101 AD-associated genes (identifier C0002395) were extracted from the dataset. After mapping these onto the interactome, 91 genes were found to be present. The AD-specific subgraph induced on these genes was generated, and its Largest Connected Component (LCC) was selected as the final AD disease module.

The AD disease module contains:
- 46 genes (nodes)
- 132 raw interactions (edges)
- 87 cleaned interactions (after removing 45 self-loops)

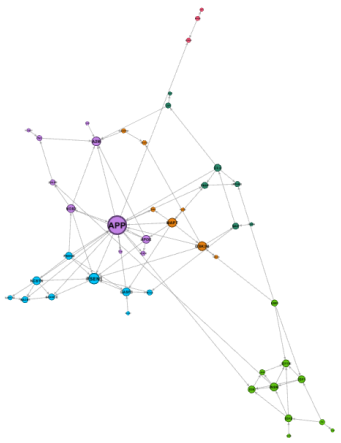

Figure: Gephi visualization of the AD module.

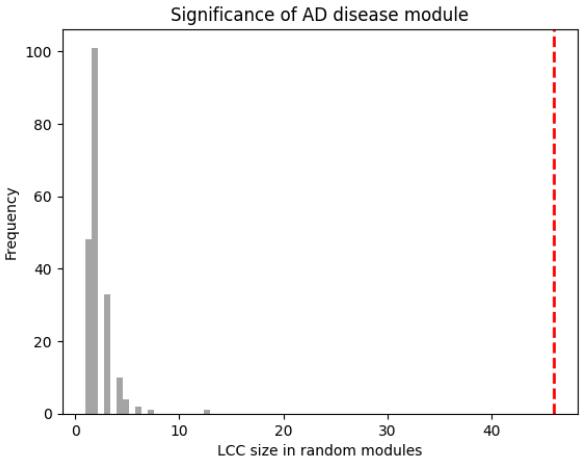

Figure: Histogram of random LCC sizes vs AD LCC.

The Gephi visualization highlights the topological organization of the AD module. Nodes are sized by degree centrality, emphasizing key hub genes such as APP, MAPT, and PSEN1. These nodes form a dense central core, while peripheral nodes connect through short paths, forming modular communities corresponding to known AD-related biological pathways.

To evaluate the statistical significance of this module, its LCC size was compared against 200 random modules of equal size (46 nodes). Random LCC sizes followed a distribution with mean = 2.21 and SD = 1.28, whereas the AD module exhibited an LCC size of 46, far outside the random distribution. This yields a z-score of approximately 34.19 and an empirical p-value of 0.0, indicating extreme statistical significance.

3.2 Disease Separation Analysis

To assess molecular relationships between AD and other conditions, two additional diseases were considered: Presenile Dementia (CUI: C0011265), which is biologically close to AD, and Liver Fibrosis (CUI: C0239946), a distant disease affecting a separate organ system. Gene-level comparison revealed that AD and Presenile Dementia share 89 genes, whereas AD and Liver Fibrosis share only 4, suggesting substantial molecular proximity for the former and minimal overlap for the latter.

Using the disease separation metric by Menche et al. (2015), the following results were obtained:

- AD vs Presenile Dementia: s = 0.0 (complete overlap)
- AD vs Liver Fibrosis: s = 0.0709 (small but positive separation)

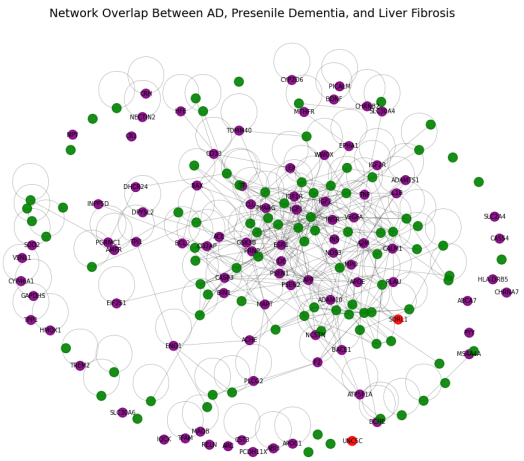

Figure: Network overlap between AD, Presenile Dementia, and Liver Fibrosis

The visualization of the overlap network shows a dense purple region representing genes shared between AD and Presenile Dementia, demonstrating that the two diseases occupy the same molecular neighborhood. In contrast, Liver Fibrosis genes (green) appear peripheral and sparsely connected, reflecting their distinct biological pathways. These results confirm that AD and Presenile Dementia share significant mechanistic foundations, while Liver Fibrosis is molecularly distant.

3.3 Disease–Drug Proximity and Repurposing Opportunities

To explore drug repurposing opportunities, drug targets from drug_target.csv were mapped to the interactome. Drugs with existing indications for Alzheimer's Disease or dementia were removed to obtain a conservative set of candidates. Network proximity between each drug and the AD module was computed as the average shortest-path distance between drug targets and AD module genes.

Drugs with proximity = 0.0 directly target genes inside the AD module; drugs with small positive proximity target first-neighbor nodes of the module, suggesting potential mechanistic relevance. The highest-ranking repurposing candidates based on proximity include compounds targeting ENO1, GAPDHS, TPI1, ESR1, INS, CALM1, TF, CYP2D6, BCHE, and PPARG. These targets lie directly within the AD module and therefore may influence key pathways implicated in Alzheimer's pathology.

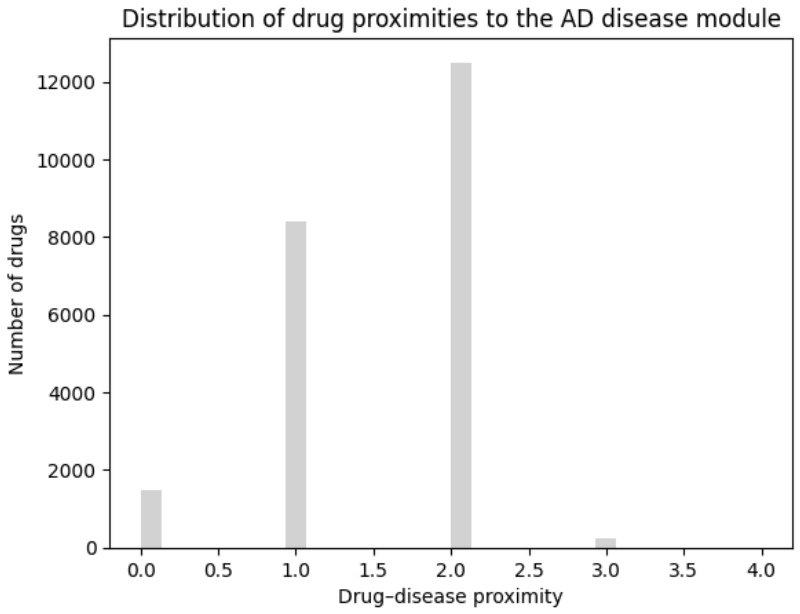

Figure: Distribution of drug proximities

The distribution of drug proximities shows three characteristic clusters: a small group at proximity = 0 representing drugs whose targets lie directly inside the AD module; a dominant peak near proximity ≈ 1 representing drugs whose targets lie in the module's immediate neighborhood; and a broader distribution near proximity ≈ 2 representing drugs acting in more distant regions of the interactome. Drugs with proximity = 0 or very close to 0 represent promising mechanistic repurposing opportunities.