Universidad Politécnica de Madrid

Escuela Técnica Superior de Ingenieros Informáticos

Grado en Máster Universitario en Innovación Digital

Complex Data in Health

Studying Alzheimer's Disease

Authors:

Emanuele Alberti
Leandro Duarte
Ottavia Biagi

December 2025

Contents

Introduction

For this assignment, we were assigned to study **Alzheimer's Disease (AD)**. The following identifiers were provided: UMLS CUI `C0002395`, NCIt code `C2866`, recommended protein Apolipoprotein E (UniProt: `P02649`), transcriptome dataset `GSE300079`, and image dataset from OASIS (Kaggle).

1 Medical Terminologies and Semantic Datasets

1.1 Disease General Information

We explored biomedical databases to gather standardized information about Alzheimer's Disease.

NCBI MedGen (UID: 1853) provides the following definition: *"A degenerative disease of the brain that causes dementia, which is a gradual loss of memory, judgment, and ability to function. This disorder usually appears in people older than age 65, but less common forms of the disease appear earlier in adulthood."* The disease is classified as *Disease or Syndrome* with concept ID `C0002395`. The directly associated gene is `APP` (21q21.3), with related genes including `APOE`, `PSEN1`, `PSEN2`, `ABCA7`, `MPO`, and `PLAU` [1].

NCBI MeSH (ID: D000544) describes AD as a degenerative brain disease with insidious onset of dementia, impairment of memory, judgment, and attention span, followed by apraxias and global loss of cognitive abilities. Pathologically, it is marked by senile plaques, neurofibrillary tangles, and neuropil threads [2].

ICD-10 classifies AD under code `G30`, with subtypes: `G30.0` (early onset, before age 65), `G30.1` (late onset, after age 65), `G30.8` (other), and `G30.9` (unspecified) [3].

Orphanet (ORPHA:1020) describes Early-onset autosomal dominant Alzheimer disease (EOAD), representing less than 1% of all AD cases, caused by mutations in `PSEN1` (69%), `APP` (13%), or `PSEN2` (2%) [4].

Table 1 summarizes the disease codifications across vocabularies.

Table 1: Alzheimer's Disease codifications across medical vocabularies [1, 2, 3, 5, 6, 7, 8, 4].

Vocabulary	Code
UMLS CUI	C0002395
MedGen UID	1853
MeSH	D000544
ICD-10	G30
SNOMED CT	26929004
NCIt	C2866
OMIM	104300, 516000
Orphanet	ORPHA:238616, ORPHA:1020
MONDO	MONDO:0004975
HPO	HP:0002511

1.2 SPARQL Query Results

We queried the NCIt SPARQL endpoint (`https://shared.semantics.cancer.gov/sparql`) to retrieve annotation properties for Alzheimer's Disease (code `C2866`) [6]. The query extracted the preferred label, synonyms, definition, semantic type, and UMLS CUI.

Summary of SPARQL Findings: The query retrieved annotation properties for NCIt code C2866. The disease is classified under semantic type "Mental or Behavioral Dysfunction" and maps to UMLS CUI C0002395. Seven synonyms were identified, including "Alzheimer's Dementia", "Alzheimer Disease", and "Alzheimer dementia". The definition describes AD as a progressive neurodegenerative disease characterized by nerve cell death leading to loss of cognitive function such as memory and language.

2 Bioinformatics

2.1 Disease Genes

We identified three main genetic factors linked to Alzheimer's disease from NCBI MedGen [1]: APP and PSEN1, when mutated, can directly cause rare, early-onset familial forms of the disease. APOE primarily affects an individual's risk for the more common late-onset form.

APP (Amyloid Precursor Protein) – NCBI Gene ID: 351, chromosome 21q21.3. The APP gene provides the blueprint for amyloid precursor protein. This protein is cut into smaller fragments, including amyloid-beta (Aβ), which is a key component of the plaques observed in the brains of Alzheimer's patients [9, 10]. Certain APP mutations or extra copies of the gene lead to an overproduction or more "sticky" forms of Aβ, which promotes plaque buildup and can directly cause early-onset familial Alzheimer's disease [9].

PSEN1 (Presenilin 1) – NCBI Gene ID: 5663, chromosome 14q24.2. PSEN1 encodes presenilin-1, which is the catalytic core of the γ-secretase enzyme. This enzyme performs the final cut of APP to release Aβ. Mutations in PSEN1 typically alter this cutting process, leading to the production of more of the longer, aggregation-prone Aβ peptides. This makes PSEN1 the most common genetic cause of autosomal-dominant early-onset Alzheimer's, with symptoms often beginning before age 65, and sometimes even before 40 [11, 12].

APOE (Apolipoprotein E) – NCBI Gene ID: 348, chromosome 19q13.32. APOE produces apolipoprotein E, a protein that assists in transporting fats and cholesterol within the body and brain [13]. Its common variants (ε2, ε3, ε4) differ in how they manage Aβ and brain lipid metabolism. Carrying the ε4 form increases the risk of late-onset Alzheimer's in a dose-dependent manner, while the ε2 variant tends to lower this risk. APOE primarily acts as a risk modifier; individuals with the ε4 allele may never develop Alzheimer's, and conversely, those without it can still develop the disease [13, 14].

Gene Sequence: Following the assignment recommendation, the APOE mRNA FASTA sequence (RefSeq: `NM_000041.4`) is provided in Appendix A [15].

2.2 Proteins

We analyzed Apolipoprotein E (APOE), the recommended protein for this assignment, using UniProt accession `P02649` [16].

Function: APOE is an apolipoprotein that associates with lipid particles and transports lipids between organs via plasma and interstitial fluids. It is a core component of plasma lipoproteins (chylomicrons, VLDL, IDL, HDL) and participates in their production, conversion, and clearance. APOE binds to cellular receptors (LDLR, LRP1, LRP2, LRP8, VLDLR) that mediate uptake of APOE-containing lipoprotein particles. The protein plays a role in cholesterol homeostasis through reverse cholesterol transport and regulates lipid transport in the central nervous system, affecting neuron survival and sprouting [16].

Role in Alzheimer's Disease: The APOE*4 allele is associated with late-onset familial and sporadic Alzheimer disease. Risk for AD increases from 20% to 90% and mean age at onset decreases

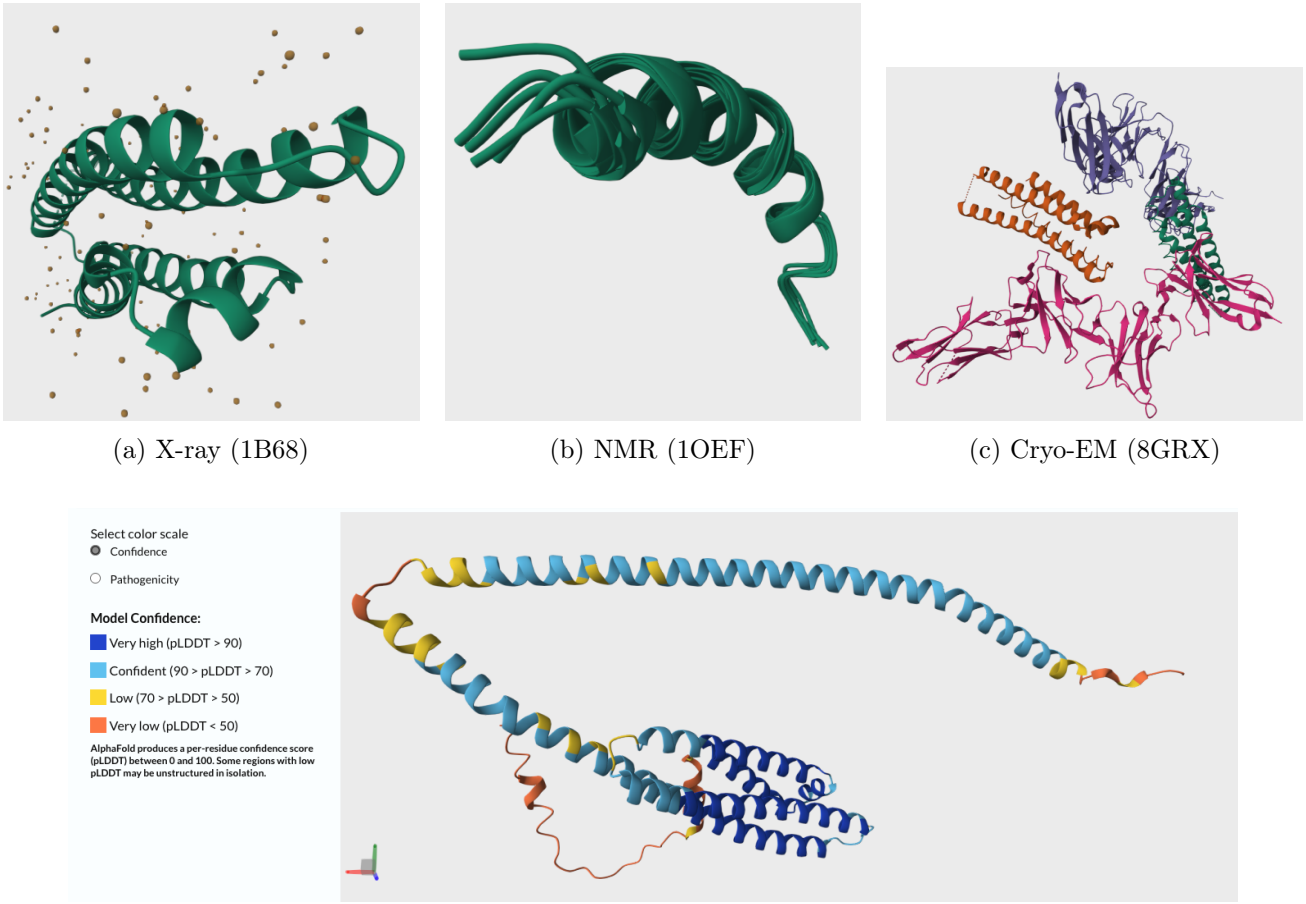
from 84 to 68 years with increasing number of APOE*4 alleles. [16].

Protein Sequence: The APOE protein sequence (317 amino acids) was retrieved from UniProt and is provided in Appendix B.

Molecular Interactions: APOE does not interact with DNA or RNA. The protein primarily interacts with lipids through its C-terminal domain (residues 222-299), which binds phospholipids and cholesterol in lipoprotein particles. The N-terminal domain (residues 1-191) contains the LDLR-binding region (residues 134-150) that mediates receptor-mediated cellular uptake of lipoproteins. APOE also binds heparin and heparan sulfate proteoglycans on cell surfaces through its N-terminal domain [16].

Protein Structures: We obtained protein structures from classical experimental methods and computational prediction.

Figure 1 shows the four structures obtained from classical methods and AlphaFold prediction.



(a) X-ray (1B68) (b) NMR (1OEF) (c) Cryo-EM (8GRX)

(d) AlphaFold prediction (AF-P02649-F1)

Figure 1: APOE protein structures from different determination methods [17, 18, 19, 20].

Structural Comparison: The X-ray structure displays a static, well-defined conformation typical of crystallographic methods, capturing residues 19-209. Crystallography freezes the protein in a single state, producing a clean ribbon structure. The NMR structure shows multiple overlapping conformations (appearing as a bundle of strands), representing an ensemble of solution-state structures for residues 281-304. NMR captures protein dynamics in solution, resulting in multiple overlaid structures. The Cryo-EM structure presents a complete assembly (residues 41-180), revealing protein organization in a near-native frozen state. AlphaFold predicts the full-length structure (1-317), displayed as a single ribbon colored by confidence: blue indicates high confidence, cyan for confident regions, yellow for low confidence, and orange for very low confidence. Classical methods provide fragmented views of specific domains, while AlphaFold offers a complete structure prediction across the entire sequence.

Cavity Detection: We used CB-Dock2 [21] to identify potential binding pockets on the AlphaFold predicted structure. CB-Dock2 is a web-based tool for blind protein-ligand docking that combines geometry-based cavity detection with template information. The analysis identified 5 potential binding pockets (Table 2). Cavities are grooves or holes in the protein surface where other molecules (lipids, cholesterol, or drugs) can bind.

Table 2: Binding pockets detected by CB-Dock2 on APOE AlphaFold structure.

Pocket ID	**Volume (Å^3)**	**Center (x, y, z)**	**Size (x, y, z)**
C1	1123	(10, -3, 10)	(12, 16, 16)
C2	287	(48, 27, -33)	(8, 13, 8)
C3	134	(-6, -13, 7)	(11, 6, 5)
C4	97	(20, -2, -15)	(7, 8, 9)
C5	93	(1, 1, -7)	(8, 8, 7)

Cavity C1 has the largest volume (1123 Å^3), which is 4 times larger than the second pocket. This indicates C1 is the primary binding site where lipids or potential therapeutic ligands would bind. The remaining pockets (C2-C5) are smaller and represent secondary binding sites.

A APOE Gene FASTA Sequence

>NM_000041.4 Homo sapiens apolipoprotein E (APOE), transcript variant 2, mRNA
CTACTCAGCCCCAGCGGAGGTGAAGGACGTCCTTCCCCAGGAGCCGACTGGCCAATCACAGGCAGGAAGA
TGAAGGTTCTGTGGGCTGCGTTGCTGGTCACATTCCTGGCAGGATGCCAGGCCAAGGTGGAGCAAGCGGT
GGAGACAGAGCCGGAGCCCGAGCTGCGCCAGCAGACCGAGTGGCAGAGCGGCCAGCGCTGGGAACTGGCA
CTGGGTCGCTTTTGGGATTACCTGCGCTGGGTGCAGACACTGTCTGAGCAGGTGCAGGAGGAGCTGCTCA
GCTCCCAGGTCACCCAGGAACTGAGGGCGCTGATGGACGAGACCATGAAGGAGTTGAAGGCCTACAAATC
GGAACTGGAGGAACAACTGACCCCGGTGGCGGAGGAGACGCGGGCACGGCTGTCCAAGGAGCTGCAGGCG
GCGCAGGCCCGGCTGGGCGCGGACATGGAGGACGTGTGCGGCCGCCTGGTGCAGTACCGCGGCGAGGTGC
AGGCCATGCTCGGCCAGAGCACCGAGGAGCTGCGGGTGCGCCTCGCCTCCCACCTGCGCAAGCTGCGTAA
GCGGCTCCTCCGCGATGCCGATGACCTGCAGAAGCGCCTGGCAGTGTACCAGGCCGGGGCCCGCGAGGGC
GCCGAGCGCGGCCTCAGCGCCATCCGCGAGCGCCTGGGGCCCCTGGTGGAACAGGGCCGCGTGCGGGCCG
CCACTGTGGGCTCCCTGGCCGGCCAGCCGCTACAGGAGCGGGCCCAGGCCTGGGGCGAGCGGCTGCGCGC
GCGGATGGAGGAGATGGGCAGCCGGACCCGCGACCGCCTGGACGAGGTGAAGGAGCAGGTGGCGGAGGTG
CGCGCCAAGCTGGAGGAGCAGGCCCAGCAGATACGCCTGCAGGCCGAGGCCTTCCAGGCCCGCCTCAAGA
GCTGGTTCGAGCCCCTGGTGGAAGACATGCAGCGCCAGTGGGCCGGGCTGGTGGAGAAGGTGCAGGCTGC
CGTGGGCACCAGCGCCGCCCCTGTGCCCAGCGACAATCACTGAACGCCGAAGCCTGCAGCCATGCGACCC
CACGCCACCCCGTGCCTCCTGCCTCCGCGCAGCCTGCAGCGGGAGACCCTGTCCCCGCCCCAGCCGTCCT
CCTGGGGTGGACCCTAGTTTAATAAAGATTCACCAAGTTTCACGCA

B Apolipoprotein E FASTA Sequence

>sp|P02649|APOE_HUMAN Apolipoprotein E OS=Homo sapiens OX=9606 GN=APOE PE=1 SV=1
MKVLWAALLVTFLAGCQAKVEQAVETEPEPELRQQTEWQSGQRWELALGRFWDYLRWVQT
LSEQVQEELLSSQVTQELRALMDETMKELKAYKSELEEQLTPVAEETRARLSKELQAAQA
RLGADMEDVCGRLVQYRGEVQAMLGQSTEELRVRLASHLRKLRKRLLRDADDLQKRLAVY
QAGAREGAERGLSAIRERLGPLVEQGRVRAATVGSLAGQPLQERAQAWGERLRARMEEMG
SRTRDRLDEVKEQVAEVRAKLEEQAQQIRLQAEAFQARLKSWFEPLVEDMQRQWAGLVEK
VQAAVGTSAAPVPSDNH

References

[1] NCBI. *MedGen UID 1853: Alzheimer's Disease*. https://www.ncbi.nlm.nih.gov/medgen/1853.

[2] NCBI. *MeSH D000544: Alzheimer Disease*. https://www.ncbi.nlm.nih.gov/mesh/68000544.

[3] WHO. *ICD-10 G30: Alzheimer's Disease*. https://icd.who.int/browse10/2019/en#G30.

[4] Orphanet. *Orphanet 1020: Early-onset autosomal dominant Alzheimer disease*. https://www.orpha.net/en/disease/detail/1020.

[5] NCBI. *SNOMED CT 26929004: Alzheimer disease*. https://vsac.nlm.nih.gov/context/cs/codesystem/SNOMEDCT/version/2021-09/code/26929004/info.

[6] NCI. *NCIt C2866: Alzheimer's Disease*. https://evsexplore.semantics.cancer.gov/evsexplore/concept/ncit/C2866.

[7] Monarch Initiative. *MONDO:0004975 Alzheimer disease*. https://monarchinitiative.org/MONDO:0004975.

[8] MSeqDR. *HPO HP:0002511 Dementia*. https://mseqdr.com/hpo_browser.php?2511.

[9] NCBI. *APP amyloid beta precursor protein [Homo sapiens (human)]*. https://www.ncbi.nlm.nih.gov/datasets/gene/351/. Gene ID: 351.

[10] Julia TCW and Alison M Goate. "Genetics of -Amyloid Precursor Protein in Alzheimer's Disease". In: *Cold Spring Harbor Perspectives in Medicine* (2017). DOI: 10.1101/cshperspect.a024539.

[11] NCBI. *PSEN1 presenilin 1 [Homo sapiens (human)]*. https://www.ncbi.nlm.nih.gov/datasets/gene/5663/. Gene ID: 5663.

[12] Jaya Bagaria, Eva Bagyinszky, and Seong Soo A An. "Genetics, Functions, and Clinical Impact of Presenilin-1 (PSEN1) Gene". In: *International Journal of Molecular Sciences* (2022). DOI: 10.3390/ijms231810970.

[13] NCBI. *APOE apolipoprotein E [Homo sapiens (human)]*. https://www.ncbi.nlm.nih.gov/datasets/gene/348/. Gene ID: 348.

[14] Amy C Raulin, Symone V Doss, Zachary A Trottier, Tadafumi C Ikezu, Guojun Bu, and Chia-Chen Liu. "APOE and Alzheimer's disease: advances in genetics, pathophysiology, and therapeutic approaches". In: *Molecular Neurodegeneration* (2022). DOI: 10.1186/s13024-022-00574-4.

[15] NCBI. *NM_000041.4 Homo sapiens apolipoprotein E (APOE), transcript variant 2, mRNA*. https://www.ncbi.nlm.nih.gov/nuccore/NM_000041.4?report=fasta.

[16] UniProt. *P02649 · APOE_HUMAN - Apolipoprotein E*. https://www.uniprot.org/uniprotkb/P02649/entry.

[17] RCSB PDB. *PDB 1B68 - Apolipoprotein E4, 22K Fragment*. https://www.rcsb.org/structure/1B68. X-ray, 2.00 Å, residues 19-209.

[18] RCSB PDB. *PDB 1OEF - Apolipoprotein E C-terminal domain*. https://www.rcsb.org/structure/1OEF. NMR, residues 281-304.

[19] RCSB PDB. *PDB 8GRX - Apolipoprotein E structure*. https://www.rcsb.org/structure/8GRX. Cryo-EM, 3.00 Å, residues 41-180.

[20] AlphaFold DB. *AlphaFold Structure Prediction for P02649*. https://alphafold.ebi.ac.uk/entry/P02649. Predicted structure, residues 1-317.

[21] Yang Liu, Xiaocong Yang, Jianhong Gan, Shuo Chen, Zhixiang Xiao, and Yang Cao. *CB-Dock2: improved protein-ligand blind docking by integrating cavity detection, docking and homologous template fitting.* `https://cadd.labshare.cn/cb-dock2/index.php`. 2022.