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Mapping Alzheimer's Complexity with Computational Neurology

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Abstract

Alzheimer's disease is the most common brain disorder causing dementia. It is marked by amyloid-beta plaques, tau tangles, and chronic brain inflammation that damage nerve cells years before symptoms appear. Alzheimer's disease also involves vascular, metabolic, mitochondrial, and immune changes, showing that its biology is more diverse than the amyloid-tau model alone suggests. No treatment currently exists that halts disease progression. This article summarizes the basic biology of Alzheimer's disease and introduces computational neurology that uses bioinformatics, artificial intelligence, and simulation to study neurological disease at a systems level, unlike traditional systems neurology, which focuses more on neural circuits and networks. It describes how three computational approaches are reshaping research, including (i) multi-omics bioinformatics, which combines large genetic and protein datasets to discover disease biomarkers, (ii) Artificial intelligence applied to brain scans for earlier diagnosis, and (iii) *In silico* drug discovery, which uses computer simulations to identify candidate therapies. Together, these tools show that Alzheimer's disease is not just a single disease but a group of molecular subtypes, suggesting a need for personalized treatment strategies. There are certain key challenges, including limited diversity in research datasets, the gap between computational predictions and clinical approval, and ethical concerns, such as algorithmic bias and data privacy that must be addressed as these tools move toward clinical use.

Keywords: Alzheimer's disease, amyloid-beta, artificial intelligence, bioinformatics, biomarkers, computational neurology, drug discovery, neuroinflammation, tau protein

1. Introduction

Alzheimer's disease (AD) accounts for 60-70% of dementia cases worldwide and is rising rapidly as populations age¹. Despite decades of research, no drug can stop or reverse its progression². The disease involves several interacting problems, including abnormal protein build-up, inflammation, and loss of connections between nerve cells, rather than a single defect³. This complexity has pushed scientists toward computational tools capable of studying the disease as a whole system rather than one molecule at a time. This emerging field, often called computational neurology, uses large-scale data analysis, machine learning, and simulation to study neurological diseases. Unlike classical systems neurology, which focuses on neural circuits and behavior, it centers on integrating genomic, imaging, and clinical datasets. In Alzheimer's research, it brings together multi-omics, artificial intelligence (AI)-based imaging, and *in silico* drug discovery within one systems-level framework⁴.

2. Overview of Alzheimer's Disease

Alzheimer's disease typically begins after the age of 65 years, although a rare familial form starts earlier⁵. Amyloid-beta accumulates silently for 15-20 years before mild cognitive impairment and, eventually, dementia develops. Progression rates vary among patients, which has motivated efforts to identify molecular subtypes of AD rather than treating it as a single, uniform condition⁶.

3. Molecular Pathogenesis

Amyloid-beta forms when the amyloid precursor protein (APP) is cut by enzymes called secretases, producing sticky fragments that clump into toxic oligomers and, later, plaques outside nerve cells⁷. Genetic mutations in APP, presenilin 1 (PSEN1), and presenilin 2 (PSEN2) cause early-onset disease, while the apolipoprotein E (APOE4) variant is the strongest risk factor for the common late-onset form⁸.

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Tau is a protein that normally stabilizes the internal scaffolding of nerve cells. In AD, excess phosphate groups attach to tau, which causes it to detach and clump into neurofibrillary tangles within cells. Tangles spread through the brain in a predictable pattern, corresponding with symptom severity, and amyloid and tau accumulation worsen in a vicious cycle⁹.

The brain's immune cells i.e., microglia and astrocytes, become chronically activated in AD. Rather than only clearing waste, they begin releasing inflammatory cytokines that injure nerve cells further, a process called neuroinflammation that is now considered a central driver of disease rather than a side effect¹⁰. Additional damage occurs through breakdown of the blood-brain barrier (BBB) and loss of synapses, both of which correlate closely with cognitive decline¹¹.

Although central, the amyloid-tau model does not explain all aspects of AD. Vascular dysfunction, poor glymphatic clearance, mitochondrial damage, and altered brain metabolism also contribute to disease progression. In some patients, synaptic dysfunction relates more closely with cognitive decline than plaque burden. Differences in microglial activation may also help explain why some people worsen quickly while others decline more slowly.

4. Computational Approaches in Alzheimer's Research

Advances in computational science and the availability of large-scale biological datasets have opened new avenues for understanding AD, improving early diagnosis, and accelerating therapeutic development. Multi-omics bioinformatics integrates genomic, transcriptomic, proteomic, metabolomic, and epigenomic data to identify molecular signatures and biomarkers associated with disease onset, progression, and patient heterogeneity. Artificial intelligence and machine-learning algorithms can analyze complex clinical, neuroimaging, genetic, and biochemical datasets to detect subtle patterns, distinguish cognitively normal individuals from those with mild cognitive impairment or AD, and predict disease progression, thereby supporting earlier and more personalized diagnosis. Complementing these approaches, *in silico* drug discovery employs molecular docking, virtual screening, pharmacophore modeling, and molecular dynamics simulations to identify and optimize compounds targeting AD-related molecular pathways. Collectively, these computational strategies provide complementary tools for biomarker discovery, precision diagnosis, and the development of novel therapeutic interventions for AD (Figure 1).

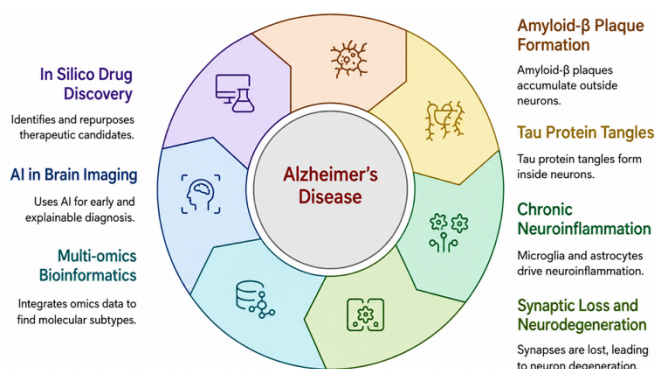


Figure 1: Alzheimer's disease cycle and computational approaches

4.1. Multi-omics bioinformatics for biomarker discovery

The term omics refers to the large-scale study of genes, proteins, RNA, and metabolites. Four omics layers are especially relevant to AD research, including (i) transcriptomics (the complete set of all RNA transcripts produced by the genome), (ii) proteomics (the entire set of

proteins produced by an organism, organ, or cell), (iii) metabolomics (the large-scale study of small-molecule metabolites present in cells, tissues, or biological fluids), and (iv) epigenomics (the global study of the entire set of epigenetic modifications i.e., chemical tags and structural changes, across a cell's entire genetic material). Each layer reveals a different piece of the disease puzzle, and no single layer alone can capture a condition as complex as AD. When these layers of data are brought together through multi-omics integration, they provide a much more complete picture of disease biology than any single molecule can offer alone¹².

In AD research, this approach has helped identify biomarkers in blood, brain tissue, and cerebrospinal fluid that can reflect the presence of disease, its stage, and even its molecular subtype¹³. Large brain-based studies have also revealed that AD is not the same in every patient, with some cases showing stronger immune activity, others showing problems with energy metabolism, and still others showing signs of structural cell damage, suggesting that treatment may need to be tailored to different biological patterns¹⁴. Because these datasets are so large, researchers are now using machine learning methods like random forests and SHAP (SHapley Additive exPlanations) to find patient-specific biomarkers and possible drug targets¹⁵. In the same way, combining p-tau217 (phosphorylated tau at threonine 217) with multi-omics data may improve early detection, but standardizing these methods across laboratories is still difficult, especially in low-resource settings¹⁶.

Techniques like single-cell RNA sequencing (scRNA-seq) and single-nucleus RNA sequencing (snRNA-seq) have transformed the study of AD by capturing gene activity within individual cells rather than averaging signals across whole tissue samples, allowing researchers to distinguish disease-linked microglia from normal ones and reveal subtle molecular shifts that bulk-tissue methods often miss^{17,18}. Therefore, combining these single-cell data with other omics layers (genomics, proteomics, and metabolomics), provides a more complete picture of how microglial states evolve alongside disease progression.

4.2. Artificial intelligence for earlier diagnosis

Magnetic resonance imaging (MRI) can pick up shrinkage in memory-related brain areas even before clear symptoms of AD appear. However, reading them manually can be slow and depends a lot on the interpreter. Deep learning models, especially convolutional neural networks (CNN), can now examine large sets of MRI scans and classify the disease stage with high accuracy. Although reported accuracies can be as high as 95%, these figures depend heavily on dataset size, preprocessing pipeline, and validation strategy, and such performance is rarely reproduced when models are tested on independent, external cohorts¹⁹. Newer diagnostic frameworks combine MRI data with speech analysis or blood biomarkers, reflecting the fact that AD affects more than one system of the body. These multimodal approaches have shown better performance than models based on a single dataset type²⁰. One challenge with deep learning is that it often works like a black-box, providing predictions without clear explanations. Explainable AI methods, such as gradient-weighted class activation mapping (Grad-CAM) and SHAP, help address this by showing which brain regions or features have the greatest influence on diagnosis. This increases clinical confidence in these tools²¹.

Despite major progress, very few AI-based diagnostic tools are used routinely in clinics. Models trained in one hospital or population often perform poorly elsewhere because of dataset shift, scanner differences, and demographic variation. Performance may drop further in underrepresented populations, and regulatory approval also requires strong prospective evidence of clinical benefit. So, high accuracy in a research paper is only an early step, not proof of real-world usefulness.

4.3. In silico drug discovery

The *in silico* methods give researchers a fast and cost-effective way to screen large numbers of chemical compounds for possible drug activity

before moving to laboratory testing. Systems biology models help researchers understand how disease pathways are connected and point to new drug targets beyond amyloid and tau, including genes involved in synaptic function and inflammation²². Network pharmacology helps link existing approved drugs with disease-related proteins, offering a quicker path to treatment through drug repurposing rather than starting from scratch with new compounds²³. It has also been used to repurpose drugs from other diseases and to highlight plant-derived natural compounds, including some used in traditional Indian medicine, as promising candidates for AD. In virtual screening studies, AChE (acetylcholinesterase) and BACE1 (beta-site amyloid precursor protein cleaving enzyme 1) are among the most commonly targeted enzymes because of their key roles in neurotransmission and amyloid production, respectively²⁴.

Recent advances are transforming this field. Tools like AlphaFold²⁵ can predict protein structures even without crystal data, expanding the range of targets for computational study. Generative AI and machine learning approaches²⁶, as well as graph neural networks²⁷ are also improving molecule design and prediction of binding and toxicity. These methods can speed up early drug discovery, although many computational leads still fail during experimental and clinical testing²⁸. The above three computational approaches are compared in Table 1.

Table 1: Comparison of computational approaches in Alzheimer's research

Approach	Strength	Weakness	Clinical Readiness
Multi-omics bioinformatics	(i) detects molecular subtypes (ii) identifies novel biomarkers	(i) poor cross-lab standardization (ii) mostly non-European data	Low
AI-based imaging	(i) fast (ii) works with existing clinical data (MRI/PET)	(i) limited generalizability (ii) black-box predictions	Moderate
In silico drug discovery	(i) fast (ii) low-cost	(i) weak correlation with real-world drug efficacy	Low

5. Challenges and Future Directions

Most large AD datasets come from populations of European ancestry, so biomarkers and AI models may not generalize well to Indian or other underrepresented populations. Deep learning models can struggle to perform well when applied to new hospitals or datasets, a limitation often referred to as overfitting. Very few of the drugs that look promising in computer models actually become real medicines for patients, because living bodies are far more complex than any simulation and often react in unexpected ways. Closing this gap will require closer collaboration between computational scientists, laboratory researchers, and clinicians, along with more diverse and longitudinal datasets.

Along with technical challenges, the use of AI in AD research also raises important ethical concerns. Bias can occur when some populations are underrepresented in training data, reducing accuracy for those groups. Privacy and data ownership are also major issues because genomic, imaging, and cognitive data are highly sensitive. In addition, black-box predictions and unclear medico-legal responsibility may limit trust and adoption. These issues must be addressed for responsible clinical use.

Several other technologies are likely to shape the next phase of computational AD research. Wearable sensors can pick up subtle changes in gait, sleep, and activity, years before diagnosis. Blood-based markers like plasma p-tau217 and neurofilament light chain (NfL) are emerging as practical alternatives to positron emission tomography (PET) and lumbar punctures. Large language models (LLMs) are being

explored to summarize clinical notes and aid neurological decision-making, while federated learning lets institutions train shared models without moving sensitive data across borders, thereby easing privacy concerns. Looking ahead, digital twins of a patient's disease trajectory and multimodal foundation models combining imaging, omics, and clinical text may eventually enable integrated precision-medicine pipelines for AD.

6. Conclusion

Alzheimer's disease results from multiple interacting problems, including abnormal protein accumulation, chronic inflammation, and neuronal loss. Computational approaches, ranging from multi-omics bioinformatics and AI-driven imaging, to *in silico* drug discovery, are helping researchers better understand this complexity, enable earlier detection, and uncover new therapeutic candidates. Even though there are still real hurdles, such as ensuring the data represent people from all backgrounds and translating research findings into safe treatments, these new methods offer hope that, in the future, each person with AD can receive care better tailored to their body and needs.

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Disclosure of AI Use

No generative AI tools, such as ChatGPT, Gemini, or Claude were used for writing the manuscript. The AI tool, Napkin AI was used for creating the figure.

References

- Xu L, Wang Z, Li M, Li Q. Global incidence trends and projections of Alzheimer disease and other dementias: an age-period-cohort analysis 2021. J Glob Health. 2025;15:04156. DOI: 10.7189/jogh.15.04156.
- Ivanova AV, Kutuzova AD, Kuzmichev IA, Abakumov MA. Alzheimer's disease: from molecular mechanisms to promising therapeutic strategies. Int J Mol Sci. 2025;26(19):9444. DOI: 10.3390/ijms26199444.
- Arnsten AFT, Del Tredici K, Barthélemy NR, Gabitto M, van Dyck CH, Lein E, et al. An integrated view of the relationships between amyloid, tau, and inflammatory pathophysiology in Alzheimer's disease. Alzheimers Dement. 2025;21(8):e70404. DOI: 10.1002/alz.70404.
- Yang Y, Diao Y, Jiang L, Li F, Chen L, Ni M, et al. A computational medicine framework integrating multi-omics, systems biology, and artificial neural networks for Alzheimer's disease therapeutic discovery. Acta Pharm Sin B. 2025;15(9):4411-26. DOI: 10.1016/j.apsb.2025.07.018.
- Wu L, Rosa-Neto P, Hsiung GYR, Sadovnik AD, Masellis M, Black SE, et al. Early-onset familial Alzheimer's disease (EOFAD). Can J Neurol Sci. 2012;39(4):436-45. DOI: 10.1017/S0317167100013949.
- Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM. Towards defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging - Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):280-92. DOI: 10.1016/j.jalz.2011.03.003.
- Ahmadi S, Khaleedi S, Ahmadi K, Hassanzadeh K. Amyloid beta in Alzheimer's disease: mechanisms, biomarker potential, and

- therapeutic targets. *CNS Neurosci Ther.* 2025;31(12):e70688. DOI: 10.1002/cns.70688.
8. Pires M, Rego AC. Apoe4 and Alzheimer's disease pathogenesis – mitochondrial deregulation and targeted therapeutic strategies. *Int J Mol Sci.* 2023;24(1):778. DOI: 10.3390/ijms24010778.
 9. Dahiya M, Yadav M, Kumar A, Goyal C. Tau pathology in Alzheimer's disease: bridging molecular mechanisms and targeted therapies. *CNS Neurol Disord Drug Targets.* 2025 July 9. DOI: 10.2174/0118715273376581250626003322. Online ahead of print.
 10. Ebrahimi R, Bordbar S, Azad G, Davoody S, Mahmoudi M, Esmaeilpour K. Beyond neuroinflammation: microglia at the crossroads of amyloid, tau, and neurodegeneration in Alzheimer's disease. *Neurol Sci.* 2025;46(11):5591-605. DOI: 10.1007/s10072-025-08403-4.
 11. Tao QQ, Lin RR, Chen YH, Wu ZY. Discerning the role of blood brain barrier dysfunction in Alzheimer's disease. *Aging Dis.* 2022;13(5):1391-404. DOI: 10.14336/AD.2022.0130-1.
 12. Ceballos MWG, Sy FFA, Akbar A, Taofiq A. Multi-omics integration in disease research. *Prog Brain Res.* 2025;297:155-89. DOI: 10.1016/bs.pbr.2025.08.012.
 13. Aerqin Q, Wang ZT, Wu KM, He XY, Dong Q, Yu JT. Omics-based biomarkers discovery for Alzheimer's disease. *Cell Mol Life Sci.* 2022;79(12):585. DOI: 10.1007/s00018-022-04614-6.
 14. Latifi-Navid H, Mokhtari S, Taghizadeh S, Moradi F, Poostforoush-Fard D, Alijanpour S, et al. AI-assisted multi-omics analysis reveals new markers for the prediction of AD. *Biochim Biophys Acta Mol Basis Dis.* 2025;1871(7):167925. DOI: 10.1016/j.bbadis.2025.167925.
 15. Ren F, Wei J, Chen Q, Hu M, Yu L, Mi J, et al. Artificial intelligence-driven multi-omics approaches in Alzheimer's disease: progress, challenges, and future directions. *Acta Pharm Sin B.* 2025;15(9):4327-85. DOI: 10.1016/j.apsb.2025.07.030.
 16. Khasanov S, Tolibov M, Daminova N. Bridging the gaps in Alzheimer's disease biomarker research: from multi-omics integration to point-of-care diagnostics, a comprehensive review. *Clin Chim Acta.* 2026;589:121046. DOI: 10.1016/j.cca.2026.121046.
 17. Mathys H, Davila-Velderrain J, Peng Z, Gao F, Mohammadi S, Young JZ, et al. Single-cell transcriptomic analysis of Alzheimer's disease. *Nature.* 2019;570(7761):332-7. DOI: 10.1038/s41586-019-1195-2.
 18. Olah M, Menon V, Habib N, Taga MF, Ma Y, Yung CJ, et al. Single cell RNA sequencing of human microglia uncovers a subset associated with Alzheimer's disease. *Nat Commun.* 2020;11(1):6129. DOI: 10.1038/s41467-020-19737-2.
 19. Mousavi SM, Moulaei K, Ahmadian L. Classifying and diagnosing Alzheimer's disease with deep learning using 6735 brain MRI images. *Sci Rep.* 2025;15(1):22721. DOI: 10.1038/s41598-025-08092-1.
 20. Christodoulou RC, Woodward A, Pitsillos R, Ibrahim R, Georgiou MF. Artificial intelligence in Alzheimer's disease diagnosis and prognosis using PET-MRI: a narrative review of high-impact literature post-tauvid approval. *J Clin Med.* 2025;14(16):5913. DOI: 10.3390/jcm14165913.
 21. Vlontzou ME, Athanasiou M, Dalakleidi KV, Skampardon I, Davatzikos C, Nikita K. A comprehensive interpretable machine learning framework for mild cognitive impairment and Alzheimer's disease diagnosis. *Sci Rep.* 2025;15(1):8410. DOI: 10.1038/s41598-025-92577-6.
 22. Azmal M, Paul JK, Shohan MNH, Haque ANMSNB, Mrinmoy M, Talukder OF, et al. Evaluating computational and experimental approaches in early-stage Alzheimer's drug discovery: a systematic review. *J Comput Aided Mol Des.* 2025;39(1):27. DOI: 10.1007/s10822-025-00610-7.
 23. Akgüller O, Balci MA, Cioca G. Network-medicine-guided drug repurposing for Alzheimer's disease: a multi-dimensional systems pharmacology approach. *Int J Mol Sci.* 2025;26(20):10003. DOI: 10.3390/ijms262010003.
 24. Alkhamash A, Alotaibi G, Algethami A, Alqarni M. Decoding apoptosis-associated pathways in inflammatory and neurodegenerative diseases: a network pharmacology-based drug discovery approach. *Eur J Pharmacol.* 2025;1007:178231. DOI: 10.1016/j.ejphar.2025.178231.
 25. Jumper J, Evans R, Pritzel A, Green T, Figurnov M, Ronneberger O, et al. Highly accurate protein structure prediction with AlphaFold. *Nature.* 2021;596:583-9. DOI: 10.1038/s41586-021-03819-2.
 26. Du Y, Jamasb AR, Guo J, Fu T, Harris C, Wang Y, et al. Machine learning-aided generative molecular design. *Nat Mach Intell.* 2024;6:589-604. DOI: 10.1038/s42256-024-00843-5.
 27. Corso G, Stark H, Jegelka S, Jaakkola T, Barzilay R. Graph neural networks. *Nat Rev Methods Primers.* 2024;4:17. DOI: 10.1038/s43586-024-00294-7.
 28. Mullard A. When can AI deliver the drug discovery hits? *Nat Rev Drug Discov.* 2024;23:159-61. DOI: 10.1038/d41573-024-00036-0.