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Computational Reconstruction of Disease-Associated Networks in Human Alzheimer's Pathogenesis

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Abstract Alzheimer's disease (AD) is a multifactorial neurodegenerative disease characterized by progressive cognitive decline, and understanding its complex molecular mechanisms remains a significant challenge. This review summarizes the application of computational network reconstruction methods to elucidate disease-related molecular interactions in the pathogenesis of AD; it systematically examines genetic, transcriptomic, and proteomic alterations leading to network dysregulation and reviews state-of-the-art algorithms for reconstructing and analyzing biological networks. Disease modules were identified through clustering and functional annotation, prioritizing candidate genes and pathways associated with AD. A case study of late-onset AD demonstrates how integrative network analysis can reveal novel associations between molecular components and clinical phenotypes. Despite these advances, challenges such as data heterogeneity, limited interpretability, and methodological limitations remain significant. This study highlights the powerful role of computational network-based frameworks in revealing the systemic organizational structure of Alzheimer's disease and predicts that future integration of single-cell omics and spatial omics, combined with AI-driven analysis, will provide deeper insights and facilitate the application of precision medicine for Alzheimer's disease.

Keywords Alzheimer’s disease; Computational network reconstruction; Disease modules; Systems biology; Bioinformatics

1 Introduction

Alzheimer's disease (AD) is often noticed by people, but it usually shows obvious memory decline or slow thinking. In fact, its asymptomatic stage can last for many years (Li and Zhang, 2024). By the time cognitive function begins to decline, pathological changes such as beta-amyloid (Aβ) plaques and tau protein tangles in the brain have quietly accumulated in regions such as the default mode network and the medial temporal lobe, and have affected neural connections and coordination between brain regions (Yu et al., 2021). These structural and functional changes are merely superficial. Behind them lies a series of disorders at the molecular, cellular and even genetic levels, interwoven into a disease picture that is difficult to explain from a single perspective.

Although research on AD has been ongoing for many years, the molecular mechanism of sporadic AD has not been truly clarified, which still makes the development of treatment difficult to this day. The progression of diseases is often not as simple as a problem with a single gene or pathway, but rather the result of the superposition of multiple factors at different levels. Some patients show a rapid progression while others do so slowly. This individual difference also suggests that AD does not follow a fixed pathological "path".

Against this backdrop, network-based computing methods have gradually been adopted by more researchers. They attempt to put together data from multiple omics, gene expression and brain connections, no longer focusing only on a single gene, but observing broader interactions. In this way, regulatory factors, molecular pathways or cell types that act as "key nodes" in AD can be identified, and signals that are easily overlooked by traditional analysis can be captured in the dynamic changes of the network (Beckmann et al., 2020; Xu et al., 2020; Merchant et al., 2023). Of course, such methods are not omnipotent, but at least they provide an entry point closer to real biological systems for understanding complex diseases.

This study will focus on these network-based computing strategies, with a particular emphasis on the research progress made in network reconstruction of the molecular mechanisms of human AD in recent years. This study

focuses not only on which molecular drivers or cell-level interactions they reveal, but also on how they help explain the changes in brain networks during disease progression. At the same time, the value of these results in screening potential biomarkers and therapeutic targets was also discussed, hoping to provide some references for promoting precision medicine research in the field of AD.

2 Molecular Basis of Alzheimer's Disease

Many molecular changes in Alzheimer's disease (AD) often start to accumulate before symptoms appear, but people usually become aware of their existence only when cognitive decline or memory problems arise. Aβ plaques and hyperphosphorylated tau protein tangles are still regarded as major markers, as they disrupt communication between neurons, but these are not all. Mitochondrial damage, increased oxidative stress and persistent neuroinflammation are also involved, resulting in a "multi-point imbalance" state at the molecular level of AD (Guo et al., 2020). In recent years, multi-omics studies have continuously expanded this picture. Multiple pathways, including neurotransmitter signaling, the immune system, lipid metabolism, and even cell transport, have all shown varying degrees of disorder, indicating that the progression of AD is not a single route but the result of multiple pathways simultaneously deviating from the normal track.

2.1 Genetic contributors to AD

At the genetic level, the risk of AD is not exactly the same. Some familial cases are caused by mutations in APP, PSEN1 or PSEN2, which lead to deviations in amyloid protein processing. Such patients often develop the disease at an earlier age. However, more people encounter late-onset AD (LOAD), with more scattered and complex influencing factors, among which APOE ε4 is the most prominent one. More than forty risk loci have been identified by GWAS, but the directions they involve are not entirely consistent. Immunity, lipid metabolism, and endocytosis are all related. Rare variations such as TREM2, SORL1, and ABCA7 mostly affect microglia and innate immune function. However, the specific effects of many variations remain unclear and require combined analysis of genetics and transcriptomics to be further clarified (Gao et al., 2025; Han et al., 2025). That is to say, although genetic factors are important, their influence is not linear. Instead, they may present different disease course trajectories due to different individual gene combinations.

2.2 Transcriptomic and proteomic dysregulation

When the focus is extended from the genetic level to the transcriptional and protein levels, it can be seen that the changes that occur in the brain tissue of AD are more diverse. Transcriptome studies have shown that not only immune-related genes change, but also the expression patterns related to synaptic activity and metabolism deviate from normal. With the development of RNA sequencing and single-cell analysis methods, an increasing number of cell type-specific expression changes have been identified, including the contribution of certain alternative splicing events in the disease process. The information provided by proteomics is more intuitive: the protein networks involved in inflammatory responses, complement activation and mitochondrial function are often in an abnormal state, accompanied by some changes in post-translational modifications. Combining these data can more clearly outline the key molecular characteristics related to amyloid deposition and neurodegeneration, and also provide more clues for finding potential biomarkers and therapeutic targets (Figure 1) (Bai et al., 2020; Tijms et al., 2024).

2.3 Cellular and pathway-level dysfunctions

When discussing Alzheimer's disease (AD), the changes at the cellular level are often not caused by a single source. Different types of cells, such as neurons, microglia, astrocytes, and even brain endothelial cells, all have their own ways of being affected. For instance, neurons are more likely to exhibit synaptic reduction, and the phenomenon of enhanced inflammation is usually closely related to the activity of microglia. When the blood-brain barrier becomes fragile, external factors are also more likely to interfere with the internal brain environment, making the problem more complicated. However, these changes do not only occur separately in different cells. Multi-omics studies have shown that pathways such as immune response, oxidative stress, calcium signaling, and cell adhesion molecules are often simultaneously "activated". In addition, with mitochondrial dynamics disorders and weakened autophagy processes, it is naturally more difficult for neurons to maintain

stability in such an environment. All these seemingly independent changes are actually interrelated, forming a mutually pulling network that jointly drives the disease forward (Kodam et al., 2023). This is also why understanding the interactions between these cells and pathways is particularly crucial. Only by clarifying these relationships can we more accurately identify the regulatory nodes that truly affect the course of AD.

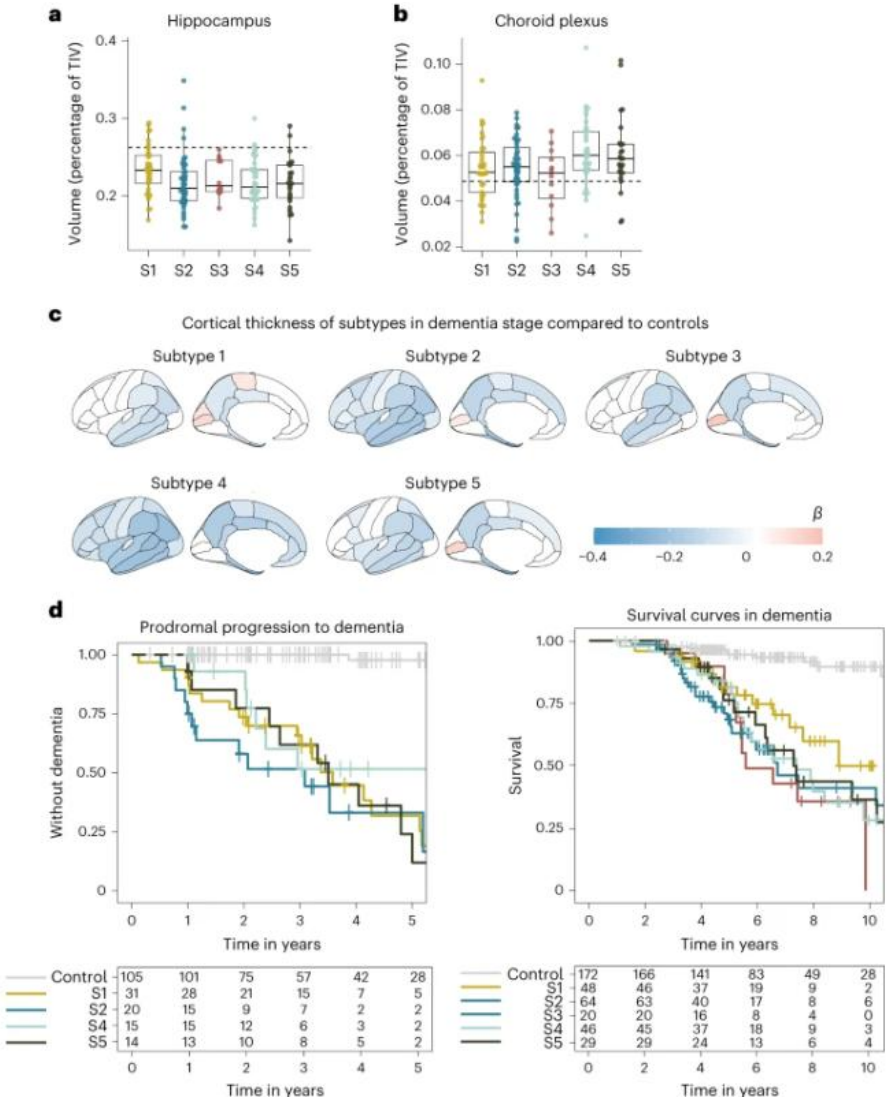

Figure 1 AD subtype comparisons on MRI and clinical outcomes (Adopted from Tijms et al., 2024)

Image caption: a, Median hippocampal volume as the percentage of total intracranial volume (TIV) compared to subtypes in the dementia stage. b, Choroid plexus volume as the percentage of TIV compared to subtypes in the dementia stage. c, Cortical atrophy associated with AD subtypes in the dementia stage compared to controls (n = 160). β indicates mean cortical thickness in mm, averaged over the right and left hemispheres and adjusted for age and sex. d, Clinical progression from MCI to dementia according to subtype (left; excluding subtype 3 due to n = 2) and time from dementia to death according to subtypes (right) (Adopted from Tijms et al., 2024)

3 Principles of Computational Network Reconstruction

When studying diseases like Alzheimer's disease (AD) that involve numerous molecular changes, looking at a single gene or pathway is often insufficient. Therefore, it is necessary to understand these molecular relationships within a "network". The purpose of computational reconstruction is to express these seemingly scattered biological components and their connections, and then use various algorithms to infer the hidden regulatory structures within them. However, the network is not necessarily the more complex the better. How to be rich in details while preventing the model from being distorted due to overfitting is an unavoidable issue for such methods. Therefore, both data integration and network reasoning need to follow certain principles (Peixoto, 2025).

3.1 Types of biological networks

Biological networks are not a single form but are composed of relationships at different levels. The gene regulatory network (GRN) focuses on describing the regulation of target genes by transcription factors. The protein-protein interaction (PPI) network focuses on whether proteins directly "encounter" each other. There are also metabolic networks and signaling networks, which are more inclined to display the chemical reactions and information transmission pathways within cells. Each network alone can reveal some cellular functions, but when it comes to the actual disease mechanism, these networks often need to be used in combination because the molecular changes of AD themselves span multiple levels (Tieri et al., 2019; Liu et al., 2020).

3.2 Data integration and preprocessing

Before reconstructing the network, researchers usually have to deal with data from different sources, of different scales, and even of different qualities. Gene expression, epigenetic modifications, proteomics, and genetic variations all fall under common inputs. To enable them to "speak the same language", normalization, noise reduction and feature selection are often required first. Although multiple datasets are more comprehensive when placed together, they also have more differences. Therefore, batch correction or cross-study learning methods are often used to reduce technical biases. If handled properly, integrated data often capture complementary biological information more effectively than a single data source and also make network inferences more stable (Delgado-Chaves and Gomez-Vela, 2019).

3.3 Inference algorithms and models

After the data is organized, researchers usually face another problem: exactly how to "push" out the network structure. Not all methods are very complicated; some merely look for clues based on the correlations between variables. However, in many cases, researchers will turn to machine learning or Bayesian methods, hoping to uncover more concealed connections. Techniques such as L1 regularization, hierarchical Bayes, and multi-task learning are all attempting to address an old problem: the network should neither be too dense nor lose important relationships due to excessive simplification. Meanwhile, graph neural networks and active learning have also begun to be frequently used in this type of analysis. They can incorporate existing biological knowledge and experimental intervention information into the model, making the network structure inference closer to the actual situation. These methods can usually more stably identify the key nodes or pathways that may be related to AD, providing more evidence for the screening of new mechanism hypotheses or therapeutic targets (Cui et al., 2024).

4 Disease Module Identification in AD

When studying Alzheimer's disease (AD), it is found that a single gene often fails to explain the complexity of the disease. Therefore, it is often necessary to further "divide" the related genes or proteins into several smaller sub-networks, which are known as disease modules. The purpose of doing this is to group together those pathologically interrelated components so as to see more clearly the biological processes they are involved in together. In recent years, some methods combining graph representation learning and unsupervised clustering have been applied to multi-omics AD data, which can extract functional modules strongly related to diseases from large networks. Evaluations like the DREAM Challenge for disease module recognition also show that well-performing algorithms typically retrieve core modules related to multiple traits, and these modules often correspond to key disease pathways or potential therapeutic targets. Therefore, when building an AD network, choosing an appropriate clustering strategy is often more important than it seems.

4.1 Network clustering and module detection

When dealing with AD networks, researchers usually encounter many clustering methods. MCL, MCODE, or various community detection algorithms can all be used, but they do not aim for the same result. Some methods prefer compact small modules with clear boundaries, which are suitable for directly corresponding to a certain type of disease-related subnetwork. There are also some methods that produce modules that are relatively large and have a loose structure. Although they are not as "neat", they can cover a wider range of functional areas. To make these modules more closely related to the actual situation of AD, researchers often incorporate known AD risk genes and their adjacent genes into the analysis. This approach of adding a "prior" generally makes the

modules more relevant. However, as many genes are multi-functional and often participate in multiple processes simultaneously, overlapping community detection is particularly important as it can more truly reflect the multi-layered structure of the AD network itself. The evaluation of GWAS data also shows that these improved methods can indeed identify the modules highly enriched with AD genetic signals (Zhou et al., 2021).

4.2 Prioritizing candidate genes

After the module is identified, the next common question is: Which genes are more worthy of attention? Priority ranking usually combines information on network structure, multi-omics evidence and gene function to determine its potential role in AD. For instance, machine learning methods such as semi-supervised non-negative matrix factorization take into account factors like the relationships and proximity within modules. Even if the network data is incomplete, they can still enhance the accuracy of candidate gene screening. Online scoring does not merely look at the evidence of a single gene, but simultaneously assesses its relationship with functionally similar genes. This approach makes it easier to identify the molecules that may truly influence disease progression. After combining the information of genetic association, expression changes and protein interactions, researchers successfully screened out a variety of genes closely related to AD, such as *PSEN1*, *APP*, *ABCA7*, etc. (Yang et al., 2021).

4.3 Functional annotation of modules

After identifying the modules, the next step is usually to figure out exactly what these modules are "doing". Functional annotations mainly determine the biological processes or pathways involved in the module through enrichment analysis. Modules related to AD often focus on neurogenesis, synaptic signaling, immune responses or metabolism, all of which are consistent with the known characteristics of the disease. Functional annotations can not only help researchers associate modules with specific AD phenotypes, but also provide new hypotheses for subsequent experimental verification. In recent years, some multilayer methods that combine ontological terms with network inference results have been proven to improve the consistency of annotations and be more helpful in identifying hub genes that may become key regulatory points or drug targets of AD (Jha et al., 2020).

5 Case Study: Network-Based Insights into Late-Onset AD

Research on late-onset Alzheimer's disease (LOAD) is often difficult to understand from a single perspective, as the influences of genetics, epigenetics, metabolism and living environment are often mixed together. To gain a more comprehensive understanding of how these factors interact, researchers usually incorporate multi-level data into network models rather than merely focusing on a single gene or image. Network analysis can categorize disease-related functional modules at the system level, making it easier to detect some hidden pathways or potential targets (Figure 2) (Sarma and Chatterjee, 2024). This type of method may not solve all problems, but it does offer a different perspective on observing the molecular basis of LOAD.

5.1 Dataset selection and preprocessing

When conducting LOAD network analysis, the commonly used datasets mostly come from queues that have been tracked for a long time, such as ROSMAP or ADNI. These data sets integrate genomic, epigenomic, proteomic, imaging and clinical manifestation information, but often require a lot of processing before use. Normalization, noise filtering and feature selection are the basic steps, mainly to enable data from different sources to run within the same analytical framework. Recent studies have also particularly reminded that choosing samples with sufficient information and reducing technical differences through batch correction can make the final constructed network more stable and better interpretable (Cruz et al., 2025; Zhou et al., 2025).

5.2 Construction and analysis of AD networks

When studying late-onset AD (LOAD), the construction of the network usually does not start from a single type of data. Researchers often need to incorporate gene co-expression, protein interaction, and the connection conditions between different brain regions into the analytical framework; otherwise, it is very easy to overlook key details. As methods such as single-sample network inference and dynamic collaborative indicators gradually mature, the changes that occur at different stages of LOAD have become easier to capture, such as functional disorders in certain brain regions at an early stage, or the transmission paths of tau protein in different regions are not the same.

These analyses often draw attention to several fixed brain regions, such as the entorhinal cortex and the parahippocampal gyrus, which are more like hubs in the network, and any slight fluctuation will affect the surrounding structures. Looking further down at the results at the module level, many familiar pathways can be seen: neurodegeneration, synaptic related signals, immune responses... These are all core processes that repeatedly occur in LOAD (Lee et al., 2022; Zhang et al., 2025).

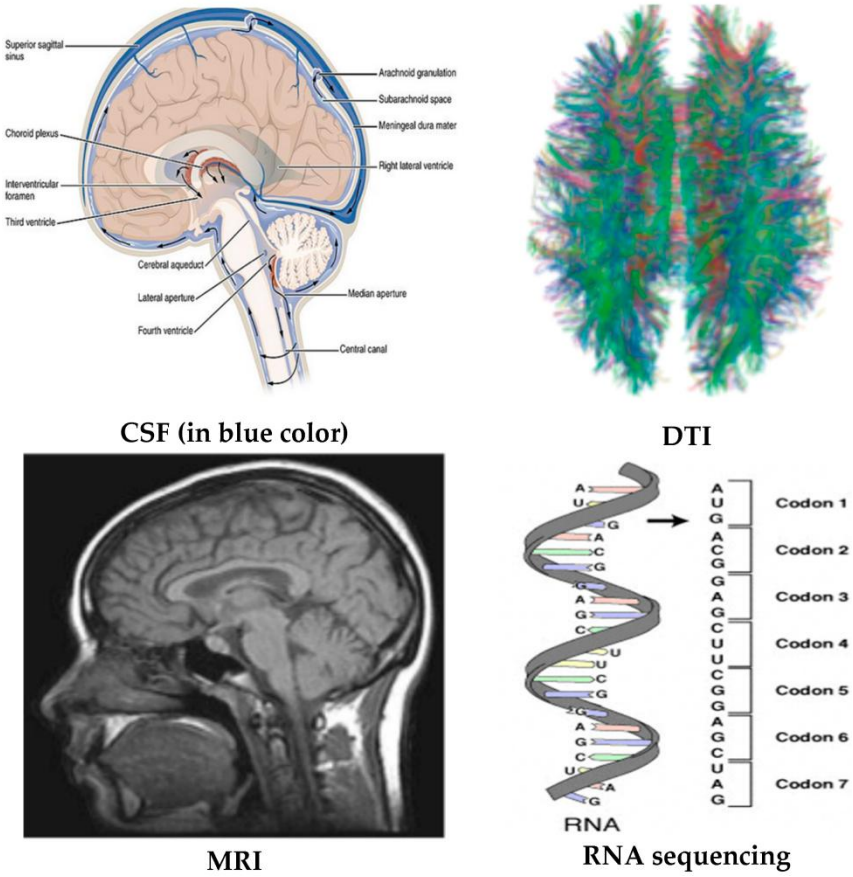

Figure 2 AD biomarkers (Adopted from Sarma and Chatterjee, 2024)

5.3 Biological and clinical interpretation

After the network construction is completed, a common problem is how to map these molecular-level clues to clinical manifestations. The network of LOAD often reflects the combined influence of multiple risk factors, such as APOE genotype, age or lifestyle, which can make the brain regions responsible for memory, sensory integration or emotion regulation more vulnerable to damage. Machine learning models trained on these networks can usually make more accurate diagnoses or disease course staging than single indicators, and are also more suitable for individualized prediction. In more cases, this online information can also help explain why LOAD behaves divergenously and provide references for formulating more precise intervention strategies (Venugopalan et al., 2021; Winter et al., 2024).

6 Challenges and Limitations

When attempting to reconstruct the network related to Alzheimer's disease (AD) using computational methods, researchers often encounter problems with the data itself first. Although various omics, imaging and clinical information are all important, the noise, missing values and batch differences among them are often inconsistent, which makes network inference particularly tricky. Due to different sample sources, processing procedures, and the inherent diversity of the population, these factors can easily "drown out" the true disease signals, resulting in low repeatability. Even if the situation is improved through standardization, batch correction or more advanced methods, the residual heterogeneity is still difficult to be completely eliminated, which also makes the construction of stable and reliable network models more challenging (Wang et al., 2022).

6.1 Data quality and heterogeneity

The problem with AD data is not only the technical differences, but more intractable is its inherent biological complexity. The disease stage, genetic background and whether there are comorbidities of different patients may all affect the pattern of the data. In addition, due to the generally small sample size and limited longitudinal data, the accuracy of statistical analysis will also decline accordingly. Although multi-omics integration sounds more comprehensive, when data from different scales and with different sources of error are placed together, the problem of heterogeneity becomes even more prominent. Some methods proposed in recent years, such as fuzzy hypergraph models or contrast learning, can reduce noise to a certain extent and capture more complex correlations. However, the extent of improvement ultimately achieved is still limited by the quality of the original data (Bi et al., 2025; Koksalmis et al., 2025).

6.2 Methodological constraints

Whether a network can be successfully inferred largely depends on the selected algorithm and its parameters. However, many methods are based on some default assumptions, such as the stability of the network topology or the interaction mode between genes, and these assumptions may not hold true in multifactorial diseases like AD. Although deep learning or graph neural networks are powerful, the problem of poor interpretability has always existed. Meanwhile, overfitting is also common. Once the data scale is too small or the samples are biased, the model's performance on external data often declines rapidly. Furthermore, integrating heterogeneous data itself brings computational and statistical challenges. How to balance sensitivity and specificity simultaneously remains a difficulty for current methods (Khatami et al., 2020; Raza et al., 2025).

6.3 Biological interpretation

Although the Internet can be built, it is actually not easy to truly explain and interpret these results into biologically significant content. The pathological mechanism of AD has not been fully understood yet. Coupled with the complex structure and diverse cell types of the brain, many things cannot be accurately presented by a static model. The identified modules or genes often lack clear functional annotations and are difficult to directly correspond to clinical manifestations, which also makes the experimental verification progress relatively slow. Furthermore, the development of AD does not progress linearly. Different cells will undergo different changes at different stages, and these differences can be easily "flattened" in a static network. Current research is attempting to enhance the interpretability of models through more detailed annotation methods or by more closely pairing network results with clinical phenotypes. Even so, there is still a considerable gap between computational prediction and actual biological understanding that needs to be gradually narrowed (Huang et al., 2025).

7 Future Directions in Network Reconstruction for AD

In recent years, the progress of Alzheimer's disease (AD) network reconstruction has increasingly relied on data of a finer scale. Especially single-cell and spatial omics, they can present the state and tissue structure of cells from different perspectives, allowing researchers to see details that were difficult to observe in the past. Single-cell multi-omics can record transcriptional, epigenetic and protein information at the single-cell level, while spatial omics fills in the gap in the location and neighborhood relationships of cells in brain tissue. To handle these complex "irregular" data, computational methods such as graph neural networks (GNNS) are increasingly adopted, and they have shown considerable potential in reconstructing the gene regulation and signal networks related to AD (Efremova and Teichmann, 2020).

7.1 Integration of single-cell and spatial omics

In future research, the combination of single-cell omics and spatial omics is almost regarded as an inevitable trend, because the pathology of AD does not occur uniformly throughout the brain but is highly dependent on the vulnerability of specific brain regions. Combining the molecular state and spatial position for analysis can more directly reveal which cells and which regions undergo changes first during the disease process. In recent years, deep learning frameworks such as contrastive learning and domain adaptive models have been helping to align different datasets and reduce batch differences. Methods such as GraphCellNet and NicheTrans demonstrate how the combination of the two types of data can more clearly depict the spatial features in AD, from spatial domains

to intercellular communication. It also provides new ideas for discovering potential biomarkers or drug action sites at specific locations (Wang et al., 2024).

7.2 AI and deep learning approaches

When dealing with multi-omics data, researchers are increasingly relying on artificial intelligence, especially deep learning. However, the reason is not that traditional methods are completely unusable, but that when high-dimensional, sparse, and disordered data are analyzed together, the old methods often seem inadequate. Deep learning architectures such as graph convolutional networks and generative models are actually more capable of integrating different types of data into the same framework, making the model's judgment on cell states or disease phenotypes more stable. These methods also have a feature: they can simulate responses under different disturbances, thus giving researchers the opportunity to speculate on deeper mechanisms, which is particularly helpful when dealing with the high heterogeneity of AD. Of course, the improvement of interpretability is also very important. After all, no matter how strong a model is, if it cannot clearly explain "why", its credibility in clinical or biological terms will be greatly reduced. The development of explainable artificial intelligence in recent years is gradually improving this, making the conclusions of network inference more acceptable (Ji et al., 2021; Ge et al., 2024).

7.3 Translational applications

At the application level, web-based analysis is mainly used to identify biomarkers, distinguish patient subtypes, and locate potential therapeutic targets. By integrating multi-omics data, spatial information and clinical phenotypes through artificial intelligence models, there is a chance to make the early diagnosis of AD more accurate and it is also easier to formulate individualized treatment strategies. Meanwhile, the network model can point to those key nodes that truly drive pathological changes, providing direction for experimental verification and drug development. As these computing tools gradually mature, the possibility of their being incorporated into clinical processes is also increasing, which is expected to promote the further implementation of precision medicine in the field of AD (Kim et al., 2023; Ballard et al., 2024).

8 Concluding Remarks

In recent years, if we look back at the research on Alzheimer's disease (AD) from the perspective of network reconstruction, we will find that many molecular clues that were previously difficult to detect have gradually been pieced together. The addition of multi-omics data continuously brings new candidate genes and pathways. Familiar pathways such as immune signals and neuroinflammation have once again been brought to the forefront, all seemingly promoting the disease process to varying degrees. However, the conclusions drawn by network models do not always revolve around those "most prominent" genes. Many peripheral genes play a key role at certain stages, which also makes the traditional assumptions about gene centrality seem less solid. These results to some extent highlight the variability and regional specificity of AD pathology, and also remind us that a static and coarse-grained perspective is difficult to truly understand the hierarchical structure of AD. Without higher-resolution data and computational methods that can flexibly handle complex relationships, these dynamic changes would have been very easy to be overlooked.

Web-based analysis has also brought about several particularly notable results. For instance, regional functional disorders presented at different disease stages, the emergence of major regulatory factors such as JMJD6 and VGF, as well as the stable inflammation-related molecular network between microglia and astrocytes. These clues become clearer when combined with single-cell and batch transcriptome data, and the graph diffusion and causal inference methods further enhance the robustness of network reconstruction. It is precisely these advancements that have made it more realistic to search for biomarkers and potential therapeutic targets that can reflect the multi-factor characteristics of AD.

To truly understand the complexity of AD, interdisciplinary cooperation is still indispensable. Computational biology can only provide one entry point. When combined with the results of neurogenetics, clinical research and experimental verification, the biological significance of the network model will be more reliable. Analyzing large-scale genetic data, imaging materials and clinical phenotypes together can help enhance the translational

value of the model. In addition, introducing analyses of different populations, including rare variations, can also help make up for the current deficiencies in understanding the genetic structure of AD. For network prediction to truly play a role in the future, the closed loop between computational research and experimental verification is of vital importance.

Looking ahead, researchers have set their sights on spatial omics and explainable artificial intelligence, and these two types of technologies seem likely to open up new breakthroughs. Their value does not lie in "replacing" existing methods, but in being able to fill in many details that were previously unclear from the spatiotemporal dimension, making the trajectory of AD pathological changes more definite. Of course, the integration framework is still being improved, but as the coordination among data types increases, the factors that truly drive diseases may be identified more accurately, and the direction of drug reuse will also become clearer accordingly. However, no matter how powerful the computational model is, it cannot do without the coordination of experimental results and clinical observations. If these types of information can eventually be linked together, the diagnosis, prognosis and even treatment strategies of AD will mostly develop towards individualized routes that better reflect the heterogeneity of the disease.

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Conflict of Interest Disclosure

The author affirms that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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