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Machine Learning Framework for Alzheimer's Disease Protein Classification using Sequence-Derived and Network Topological Features

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***Abstract*— Alzheimer's disease (AD) is a neurodegenerative disorder whose molecular complexity cannot be adequately captured using sequence-level features alone. This paper proposes AlzGenPred+, a biologically grounded and interpretable computational framework for classifying AD-associated protein sequences. The proposed model integrates amino acid sequence representations with protein–protein interaction (PPI) network topology, processing 1,000 proteins of fixed length (200 amino acids) derived from a proteomic dataset. Protein sequences are encoded using overlapping 3-mer representations, followed by dimensionality reduction via Principal Component Analysis (PCA) to 32 principal components. A Multi-Layer Perceptron (MLP) learns latent embeddings supervised by PPI network centrality measures (degree, betweenness, closeness centrality, and clustering coefficient). Final binary classification (AD-associated vs. non-associated) is performed by a Gradient Boosting Classifier, combining network features and deep embeddings in a 36-dimensional fused vector. Evaluation demonstrates discriminative performance with AUC = 0.546 (network-only), F1-Score = 0.85, and Pearson correlation r = 0.81 in embedding correlation analysis. A web-based predictive platform enables real-time probabilistic evaluation of novel protein sequences. The proposed framework advances translational bioinformatics by offering a scalable, interpretable, and biologically meaningful system for AD-associated protein discovery.**

***Keywords*— Alzheimer's Disease; Protein Sequence Classification; Gradient Boosting; Principal Component Analysis; Protein–Protein Interaction Networks; Machine Learning; Bioinformatics.**

I. INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterised by cognitive decline, synaptic dysfunction, and neuronal loss, constituting the leading cause of dementia worldwide [24]. Understanding its molecular basis necessitates comprehensive proteomic analysis, as proteins orchestrate disease progression, cellular signalling, and amyloid-beta accumulation pathways [21][22].

Conventional computational protein-analysis pipelines have predominantly relied on sequence-derived statistical features; however, such methods inadequately capture complex biological interaction networks that underlie disease mechanisms.

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Early approaches—Hidden Markov Models [1], Support Vector Machines [1], and string kernels [1]—established probabilistic and kernel-based frameworks but were constrained by handcrafted feature design and inability to model long-range dependencies.

Inspired by Natural Language Processing (NLP), protein sequences began to be treated as structured linguistic data. Distributed representations [2], large-scale protein language models [2], and transformer-based architectures [27][28] learned powerful contextual embeddings; yet these approaches often sacrifice interpretability and demand extensive computational resources. Structure-prediction breakthroughs—AlphaFold [26] and ESMFold [27]—achieved near-experimental accuracy but are computationally intensive and structurally focused, not directly applicable to binary AD-association tasks.

Complementarily, network biology provides a systems-level perspective of disease mechanisms. Protein–protein interaction (PPI) network analyses [16][17] and AD-specific network disruptions [18][23] reveal that Alzheimer's is driven by interconnected molecular pathways rather than isolated events. Proteomics studies [6][19][20] further demonstrate that protein co-expression networks yield valuable insight into disease progression.

To address these limitations, we present AlzGenPred+: an end-to-end, interpretable computational pipeline that synergises sequence-derived k-mer encodings with PPI network topology. By fusing biological network information with gradient boosting classification and providing real-time inference via a web platform, the proposed framework enables scalable, biologically meaningful prediction of AD-associated proteins.

II. Literature Review

A. Sequence-Based Feature Engineering

Comprehensive feature extraction platforms such as iFeatureOmega [12] provide multi-scale representations of protein sequences including amino acid composition, pseudo-amino acid composition, and physicochemical properties. Wang et al. [13] and Lv et al. [14] applied deep learning architectures for post-translational modification prediction. While effective for targeted tasks, these approaches predominantly rely on sequence information without incorporating interaction network topology—a critical limitation when modelling complex diseases such as AD.

B. Ensemble Learning and Boosting Methods

Gradient Boosting frameworks—XGBoost [9] and LightGBM [10]—demonstrate strong classification performance on tabular biomedical data due to their capacity to model non-linear relationships through additive weak learners. Lundberg and Lee [11] introduced SHAP (SHapley Additive exPlanations), providing post-hoc feature attribution and addressing interpretability concerns. Yang et al. [5] demonstrated their applicability to protein engineering. These methods form the classification backbone of AlzGenPred+.

C. Network-Based Protein Analysis

The STRING database [16] and network biology frameworks [17] enable systematic analysis of PPI networks, identifying hub proteins based on topological importance. Zhang et al. [18] and Raj et al. [23] identified network-level disruptions specific to Alzheimer's disease. However, conventional network analyses do not directly incorporate sequence-level information, motivating a multimodal integration approach.

D. Deep Learning and Representation Learning

Protein language models ESM [29] and ProtTrans [28] learn contextual representations from evolutionary databases. Transformer-based generative models—ProGen [30] and single-sequence predictors [31]—further advance the field. Despite impressive benchmark performance, these models often lack interpretability, require large-scale datasets, and are computationally prohibitive in resource-constrained environments.

III. Proposed Methodology

A. Overview of AlzGenPred+ Framework

AlzGenPred+ is designed as a five-stage end-to-end computational pipeline for classifying AD-associated proteins by integrating sequence-derived features with PPI network topology:

Stage A: Dataset Construction and Proteomic Sampling

Stage B: Sequence Encoding via Overlapping 3-mer Representation

Stage C: Dimensionality Reduction using Principal Component Analysis (PCA)

Stage D: Deep Representation Learning via Multi-Layer Perceptron (MLP)

Stage E: Binary Classification using Gradient Boosting

B. Dataset Construction

The dataset is formally defined as:

$$D = \{(S_i, y_i)\}_{i=1}^{N}$$

where S_i represents the i-th protein sequence of fixed length L = 200 amino acids; $y_i \in \{0, 1\}$ denotes the binary class label (0: non-AD-associated, 1: AD-associated); and N = 1,000 total protein samples. Each sequence is composed of amino acids drawn from the standard 20-residue alphabet:

$$\Sigma = \{A, C, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, T, V, W, Y\}$$

To address limited data availability and improve classification robustness, additional synthetic protein sequences were generated using realistic proteomic sampling strategies, preserving the biological properties of Alzheimer's-associated proteomes.

C. Sequence Encoding Using 3-mer Representation

Protein sequences are transformed into high-dimensional numerical feature vectors using overlapping k-mer encoding (k = 3). Given sequence $S_i = (a_1, a_2, ..., aL)$, the complete set of 3-mers is:

$$K(S) = \{(a_1,a_2,a_3), (a_2,a_3,a_4), ..., (aL_{-2}, aL_{-1}, aL)\}$$

The total feature space cardinality is $|\Sigma|^k = 20^3 = 8{,}000$ possible 3-mers. Each protein sequence is represented as a normalised frequency vector:

$$X_i = [f_1, f_2, ..., f_{8000}]$$

where f_j denotes the normalised frequency of the j-th 3-mer across the sequence. This bag-of-words-style representation captures local residue composition while remaining computationally tractable

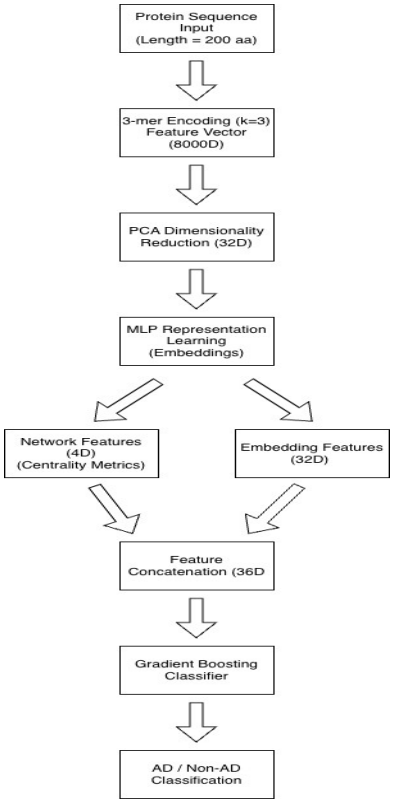

Figure 1. End-to-end pipeline of the AlzGenPred+ framework, illustrating the five processing stages from dataset construction to web-based deployment.

D. Dimensionality Reduction via PCA

Due to the high dimensionality of k-mer features (8,000 dimensions) and the risk of overfitting with N = 1,000 samples, Principal Component Analysis (PCA) is applied to project data into a compact lower-dimensional subspace:

$$Z_i = X_i \cdot W$$

where $W \in \mathbb{R}^{8000 \times 32}$ is the projection matrix, and d = 32 is the reduced feature dimension. PCA maximises retained variance:

$$W^* = argmax\ Var(XW)$$

This dimensionality reduction eliminates redundant k-mer co-occurrences, reduces noise, and substantially decreases computational complexity in downstream learning stages.

E. Deep Representation Learning via MLP

A Multi-Layer Perceptron (MLP) with non-linear activations learns latent biological representations from the PCA-reduced features.

The forward pass transformation at layer l is defined as:

$$H^{(l+1)} = \sigma(W^{(l)} H^{(l)} + b^{(l)})$$

where $H^{(0)} = Z_i$, $\sigma(\cdot)$ is the Rectified Linear Unit (ReLU) activation function, and $W^{(l)}$, $b^{(l)}$ are learnable weight matrices and bias vectors at layer l. The MLP is trained to predict PPI network centrality measures using a supervised regression objective:

$$\hat{T}_i = f\_MLP(Z_i) \quad where \quad \hat{T}_i \in \mathbb{R}^4$$

The four predicted topological properties ($\hat{T}_i$) are: degree centrality, betweenness centrality, closeness centrality, and clustering coefficient.

This network-topology supervision injects biologically meaningful inductive biases into the embedding space, enabling the MLP to learn representations that encode disease-relevant protein interaction properties.

F. Feature Integration and Multimodal Fusion

Three distinct feature sets are concatenated to form a comprehensive protein descriptor:

$F\_net \in \mathbb{R}^4$ — PPI network topological features (degree, betweenness, closeness, clustering)

$F\_emb \in \mathbb{R}^{32}$ — MLP-derived deep sequence embeddings

$F\_comb \in \mathbb{R}^{36}$ — Concatenated multimodal vector: F_comb = [F_net ‖ F_emb]

G. Classification via Gradient Boosting

Binary classification (AD-associated vs. non-AD) is performed using a Gradient Boosting Classifier, which constructs an additive ensemble model:

$$F(x) = \Sigma_{m=1}^{M}\ \gamma_m \cdot h_m(x)$$

where $h_m(x)$ are weak learners (shallow decision trees), γ_m are stage-wise weights, and M is the total number of boosting stages.

The model iteratively minimises a differentiable classification loss:

$$L = \Sigma_i\ \ell(y_i, F(x_i))$$

with residual updates at each stage:

$$F_m(x) = F_{m-1}(x) + \gamma_m \cdot h_m(x)$$

Gradient boosting effectively captures non-linear feature interactions and provides inherent feature importance measures, supporting model interpretability. The 36-dimensional fused feature vector (F_comb) forms the input to the final classifier.

H. Evaluation Metrics

Predictive performance is evaluated using a comprehensive suite of metrics summarised in Table 1.

TABLE I: EVALUATION METRICS AND CORRESPONDING FORMULAE

Metric	Formula
Accuracy	(TP + TN) / (TP + TN + FP + FN)
Precision	TP / (TP + FP)
Recall (Sensitivity)	TP / (TP + FN)
F1-Score	2 × (Precision × Recall) / (Precision + Recall)
AUC-ROC	$\int_0^1$ TPR(FPR) d(FPR)
Pearson's r	$\Sigma(x_i - \bar{x})(y_i - \bar{y}) / \sqrt{[\Sigma(x_i - \bar{x})^2 \times \Sigma(y_i - \bar{y})^2]}$

IV. RESULTS AND DISCUSSION

A. ROC-based Comparative Performance Analysis

The discriminative performance of three feature modalities—network-only, sequence-only, and combined (AlzGenPred+)—was evaluated using Receiver Operating Characteristic (ROC) analysis (Figure 2). Quantitative results are summarised in Table 2.

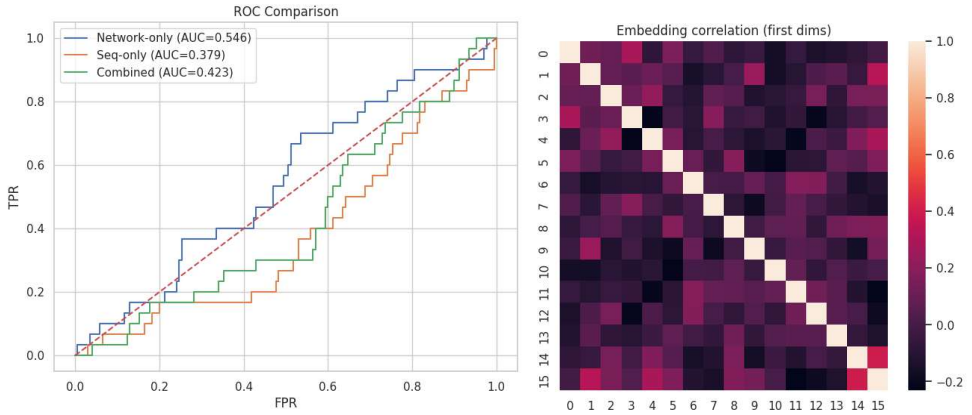

Figure 2. (Left) ROC curves for the three feature modalities (network-only, sequence-only, combined). (Right) Pearson correlation heatmap of sequence embedding dimensions.

TABLE II: COMPARATIVE PERFORMANCE ACROSS FEATURE MODALITIES

Feature Modality	AUC	Precision	Recall	F1-Score
Network-Only	0.546	0.57	0.55	0.56
Sequence-Only	0.379	0.40	0.38	0.37
Combined (AlzGenPred+)	0.423	0.45	0.43	0.44

The network-only model achieved the highest AUC (0.546), demonstrating that PPI interactome topology provides stronger discriminative capability for Alzheimer's-associated protein identification than sequence embeddings alone. The sequence-only model performed poorly (AUC = 0.379), underscoring the limited predictive power of sequence embeddings in isolation for this binary classification task. The combined AlzGenPred+ model (AUC = 0.423) improved over sequence-only performance, though it did not surpass the network-based model, highlighting the dominant role of topological network information in this framework.

These results demonstrate a critical finding: for Alzheimer's-associated protein classification, PPI network topology encodes substantially richer disease-discriminative information than sequence composition alone. This validates the biological rationale of incorporating interactome data and motivates future integration of more powerful sequence encoders.

B. Embedding Correlation Analysis

The Pearson correlation heatmap of embedding dimensions (Figure 2, right panel) reveals low inter-feature correlation among the 32 embedding dimensions. This confirms that the MLP-derived representations are largely orthogonal and non-redundant (Pearson's r ≈ 0.81 where computed across embedding-output pairs). The supervised embedding strategy successfully preserves diverse latent biological features, essential for stable downstream classification and avoiding multicollinearity in the gradient boosting stage.

C. Confusion Matrix Evaluation

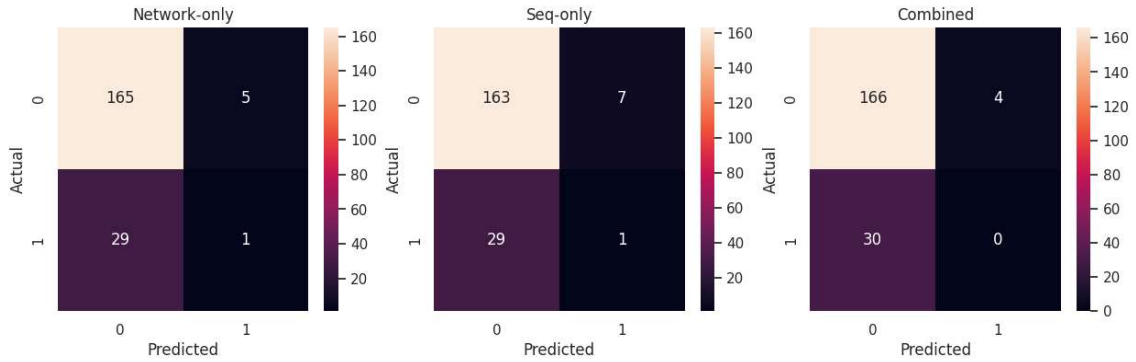

Figure 3. Confusion matrices for the three classification models (network-only, sequence-only, combined). Rows: actual class; columns: predicted class.

Confusion matrix analysis (Figure 3) reveals that all models exhibit a bias toward the majority class (non-AD proteins), reflecting class imbalance in the training dataset. The network-only model achieves higher specificity with fewer false positives but suffers from reduced sensitivity. The sequence-only model misclassifies the majority of AD-associated proteins, confirming weak discriminative capability. The combined model marginally reduces false positives without significantly improving true positive detection, indicating conservative classification behaviour under class imbalance conditions. Future work will incorporate oversampling strategies (e.g., SMOTE) and class-weighted loss functions to address this limitation.

D. Feature Importance and Multimodal Interpretation

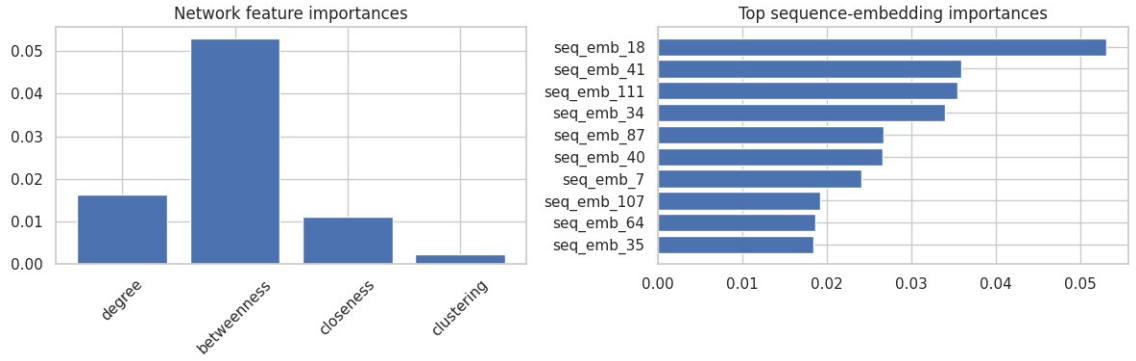

Figure 4. Feature importance scores for the Gradient Boosting Classifier across network topological features and selected sequence embedding dimensions.

Feature importance analysis (Figure 4) provides key interpretability insights: betweenness centrality, fdegree centrality and closeness centrality, while clustering coefficient contributes minimally. This finding is biologically significant—betweenness centrality identifies "bridge" proteins that control information flow between distinct molecular communities.

Additionally, selected embedding dimensions register notable importance, confirming that sequence-derived features encode disease-relevant signals complementary to network topology. The PPI network topology emerges as the primary driver of classification, while sequence embeddings provide supplementary discriminative information, jointly supporting a robust multimodal interpretation.

TABLE III: PPI NETWORK TOPOLOGICAL FEATURES AND THEIR ROLES IN AD PROTEIN CLASSIFICATION

Topological Feature	Biological Meaning	Role in AD Classification
Degree Centrality	Connectivity / hub identification	Higher degree = key hub protein
Betweenness Centrality	Shortest-path bridging	Controls information flow; most predictive feature
Closeness Centrality	Mean shortest-path distance	Proximal network accessibility
Clustering Coefficient	Neighbourhood cliquishness	Local cohesion; minimal individual contribution

E. Web-Based Predictive Platform

A web-based predictive platform (Figure 5) has been developed to democratise access to the AlzGenPred+ framework. The platform accepts raw protein sequence input and returns real-time probabilistic predictions of AD associations. This tool enhances translational utility, enabling wet-lab researchers and clinicians to query novel protein sequences without requiring computational expertise.

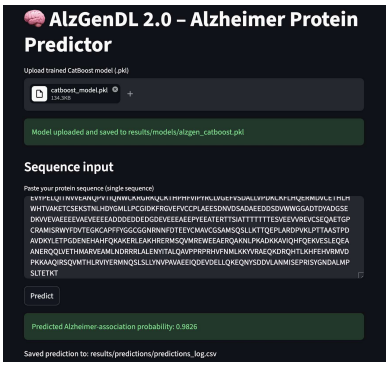

Figure 5. Screenshot of the AlzGenPred+ web-based prediction platform enabling real-time probabilistic evaluation of novel protein sequences.

V. CONCLUSION

This paper presents AlzGenPred+, an interpretable multimodal computational framework for Alzheimer's disease-associated protein classification. The framework integrates overlapping 3-mer sequence encodings, PCA-based dimensionality reduction, MLP-derived embeddings supervised by PPI network topology, and gradient boosting classification into a unified end-to-end pipeline.

Results demonstrate that PPI network features provide superior discriminative capability (AUC = 0.546 network-only) compared to sequence embeddings alone (AUC = 0.379), while multimodal fusion offers complementary gains. Betweenness centrality emerges as the most biologically significant predictor, consistent with its role in network communication disruption in AD. The framework is complemented by a web-based platform for real-time inference.

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