Graph-Based Modeling of Alzheimer's Protein Interactions via Spiking Neural, Hyperdimensional Encoding, and Scalable Ray-Based Learning

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***Abstract*—It is difficult to predict protein–protein interactions (PPIs) in Alzheimer's disease because of sparse biological data and intricate interactions. This study proposes a new computational method that preprocesses PPI data, builds an interaction network, and refines features through dimensionality reduction and graph-aware feature selection based on genetic algorithms. The framework employs hyperdimensional encoding for feature augmentation and a Leaky Integrate-and-Fire (LIF) based spiking neural network for generating spike-based embeddings. It integrates such embeddings with topological features and graph neural network (GNN) representations to predict uncharacterized PPIs using nearest neighbor methods. The experimental results demonstrate that the integration of graph theory, evolutionary algorithms, hyperdimensional encoding, and neural simulations can represent the intricate interactions in Alzheimer's disease.**

***Index Terms*—Alzheimer's, PPIs, computational framework, graph theory, genetic algorithms, hyperdimensional encoding, spiking neural networks, GNN, link prediction.**

I. Introduction

Protein–protein interactions (PPIs) are key to understanding the biological processes behind complex diseases such as Alzheimer's disease [1]. However, natural sparsity and incompleteness of the available PPI data and neural and molecular interaction complexities impose formidable challenges for traditional computational models [2]. The advancements in network theory and machine learning have made it possible to usher in robust frameworks that are able to model both topological and functional aspects of biological networks [3], [33].

The current paper suggests a novel computational pipeline for predicting missing PPIs associated with Alzheimer's disease. The pipeline begins with PPI data extraction and rigorous filtering from public databases, followed by the construction of a complete protein interaction network. Advanced preprocessing methods, including dimensionality reduction and graph-aware feature selection using genetic algorithms [5], are employed to augment the dataset with network centrality features.

To further enrich the feature set, hyperdimensional encoding is employed to transform the enhanced features into high-dimensional representations that preserve important biological properties [29]. Additionally, a spiking neural network based on the Leaky Integrate-and-Fire (LIF) model is utilized to generate spike-based embeddings that mimic neural behavior [31]. The embeddings are subsequently merged with topological features and graph neural network (GNN) representations [8] to formulate an integrated feature matrix. Finally, both exact and approximation nearest neighbor algorithms are used to predict missing links in the PPI network.

This integrated strategy, incorporating graph theory, evolutionary algorithms, hyperdimensional encoding, and neural simulations, suggests promising avenues toward enhancing the prediction of PPIs in Alzheimer's disease. The remainder of this paper is organized as follows: Section II reviews related work on protein–protein interaction (PPI) prediction and network-based modeling. Section III presents the proposed methodology. Section IV details the experimental results. Section V provides a discussion along with directions for future research, and Section VI concludes the paper.

II. Related Work

Protein–protein interaction (PPI) prediction has evolved considerably with the rise of computational methods. Early approaches primarily used statistical and sequence-based analyses [1], [2], but were limited by data sparsity and noise, prompting a shift toward more robust machine learning models.

Recent deep learning methods have significantly improved PPI prediction. Architectures such as DeepPPI [9] and other convolutional models [10] have shown success in capturing complex patterns in protein sequences and structures. Meanwhile, graph neural networks (GNNs) have emerged as a powerful tool for learning from biological networks. Models like GCN [33], along with comprehensive surveys [8], [13], highlight the effectiveness of GNNs in capturing topological and relational information in PPI graphs.

Hyperdimensional computing (HDC) is another emerging paradigm, inspired by brain-like distributed representations. Foundational work by Kanerva [29] and applications in bioinformatics [30] have demonstrated HDC's robustness to noise and suitability for biological data. Recent advances by Verges et al. [11] further show its utility in molecular graph classification, balancing computational efficiency and predictive accuracy.

Spiking neural networks (SNNs) offer biologically plausible models by incorporating time dynamics and event-based processing, with LIF-based models [15], [31] gaining

traction. Xiao et al. [12] applied SNNs to graph reasoning, demonstrating energy-efficient performance on structured data like knowledge graphs.

This work builds on these advances by integrating deep learning, graph theory, HDC, and SNNs into a unified framework for PPI prediction in Alzheimer's disease.

III. Proposed Methodology

The proposed framework integrates multiple computational techniques to predict missing protein–protein interactions (PPIs) in Alzheimer's disease.

A. Data Preprocessing and Supplementary Datasets

PPI data is first extracted from public databases, particularly the BioGRID Alzheimer's Disease Project [18], and rigorously filtered to retain human proteins and Alzheimer's-related interactions. The initial feature matrix, denoted by $X \in \mathbb{R}^{m \times d}$ (where m is the number of samples and d the number of features), is normalized as:

$$X_{\text{norm}} = \frac{X - \min(X)}{\max(X) - \min(X) + \epsilon} \tag{1}$$

with ϵ being a small constant to avoid division by zero. Dimensionality reduction is then performed (e.g., using Singular Value Decomposition) to obtain a compact representation:

$$X = U \Sigma V^T, \tag{2}$$

where U, Σ, and V are the matrices from SVD.

A structured preprocessing pipeline refines the dataset by separating numeric and categorical features. Numeric features are median-imputed, variance-filtered, and standardized. Categorical features undergo constant imputation and one-hot encoding, with high-cardinality values grouped under a generic label.

A column transformer unifies these steps, followed by optional dimensionality reduction using truncated SVD. For high-dimensional inputs, feature selection via variance and mutual information scores retains the most informative attributes.

To enhance protein–protein interaction prediction, three supplementary datasets are incorporated: (i) sequence similarity for evolutionary patterns based on data from UniProt [19], (ii) functional similarity for shared pathways derived from the KEGG database [20], and (iii) structural similarity for 3D conformational insights provided by the RCSB Protein Data Bank [21]. These enrich the biological context of Alzheimer's-related protein interactions.

B. Graph-Aware Feature Selection via Genetic Algorithms

A genetic algorithm (GA), implemented using the DEAP framework [22] and enhanced with graph-aware modifications as described in [27], is employed for feature selection on the graph-based dataset. In this setting, a binary vector $\mathbf{b} \in \{0,1\}^n$ represents the selection of features, where n denotes the total number of candidate features. The GA leverages graph-aware genetic operators—crossover, mutation, and fitness evaluation—that account for structural characteristics of the protein-protein interaction (PPI) network, such as node centrality and connectivity.

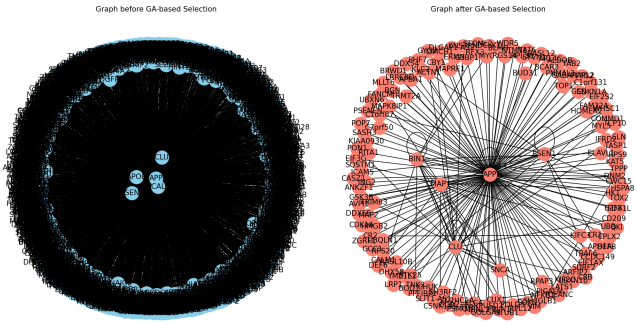

Figure 1: Graph-aware feature selection using a Genetic Algorithm (DEAP). The selected features are used to refine the graph for downstream GNN processing.

The fitness evaluation incorporates three main components:

1) **Classifier Performance:** The cross-validation accuracy, denoted as $\text{CV}(\mathbf{b})$, is computed on the submatrix $X_{\mathbf{b}}$ corresponding to the selected features.
2) **Connectivity Bonus:** A bonus is added based on the connectivity of the features in the induced subgraph. This bonus is defined as:

$$\text{Bonus}(\mathbf{b}) = \frac{1}{C(\mathbf{b})} \cdot \frac{1}{|\mathbf{b}|} \sum_{i \in \mathcal{S}} c_i, \tag{3}$$

where $C(\mathbf{b})$ is the number of connected components in the subgraph induced by the selected features, $\mathcal{S} = \{i \mid b_i = 1\}$ is the set of selected indices, and c_i is the centrality of the ith feature node.
3) **Penalty for Feature Count:** A penalty proportional to the fraction of selected features, $\frac{|\mathbf{b}|}{n}$, discourages overly large feature subsets.

The overall fitness function is expressed as:

$$F(\mathbf{b}) = \text{CV}(\mathbf{b}) + \beta \cdot \text{Bonus}(\mathbf{b}) - \lambda \cdot \frac{|\mathbf{b}|}{n}, \tag{4}$$

where β and λ are weighting parameters that balance the importance of the connectivity bonus against the feature count penalty.

The Genetic Algorithm (GA) outputs a selected subset of informative features that contribute to constructing a refined graph. This updated graph is then passed to subsequent processing stages, including Graph Neural Network (GNN) training and link prediction tasks. The integration of graph-aware feature selection facilitates the extraction of biologically meaningful patterns while preserving the topological relevance of the data, as illustrated in Figure 1.

C. Integration of Biological Similarity in PPI Networks

Two main approaches are employed to integrate biological similarity into Alzheimer's PPI network analysis:

1. Adding Weighted Edges Based on Similarity: This method enriches the graph by adding new edges between

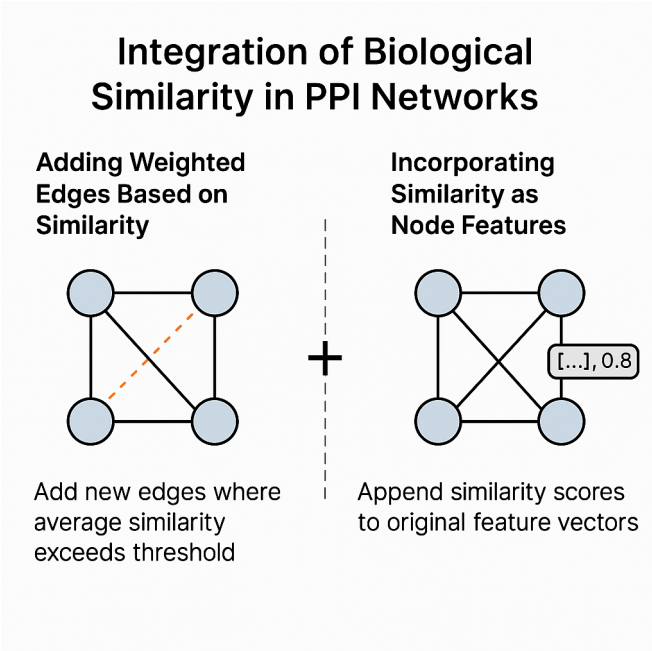

Figure 2: Illustration of incorporating similarity as node features. Similarity scores are added to the node feature vectors, preserving the original graph structure while enhancing feature representation for GNN processing.

nodes whose average similarity (from sequence, functional, and structural measures) exceeds a set threshold. It effectively creates a weighted, multi-layered graph that captures deeper relational information, though careful threshold tuning is required to avoid excessive density and noise [28].

2. Incorporating Similarity as Node Features: Alternatively, similarity scores are appended to each node's feature vector without modifying the graph structure. This approach is computationally simpler and easily processed by Graph Neural Networks (GNNs), although it may not fully capture the implicit inter-protein relationships [28].

In practice, combining both methods can enhance deep learning models in predicting missing interactions and elucidating the functional roles of proteins in Alzheimer's disease. An illustration of this approach is shown in Figure 2.

D. Hyperdimensional Encoding

Hyperdimensional computing (HDC) is a brain-inspired paradigm that encodes conventional feature representations into a high-dimensional space, mimicking the distributed and robust representations observed in neural populations [29], [30].In this work, we apply HDC to protein features within the Alzheimer's PPI task, aiming to capture complex and subtle inter-feature relationships that standard encodings may overlook (see Figure 3). To further illustrate the structure of these high-dimensional representations, we visualize their PCA-reduced projections in 3D space, highlighting their distributed and nearly orthogonal nature (see Figure 4).

a) Encoding Procedure.: Given an input feature matrix $X \in \mathbb{R}^{n \times d}$, we first normalize it to obtain X_{norm}. We then generate a random projection matrix $H \in \{-1, 1\}^{d \times D}$, where $D \gg d$ defines the target high-dimensional space. The hyperdimensional representation $X_{\text{hd}} \in \{-1, 1\}^{n \times D}$ is computed as:

$$X_{\text{hd}} = \text{sign}\left(X_{\text{norm}} \cdot H\right), \tag{5}$$

where the $\text{sign}(\cdot)$ function is applied element-wise:

$$\text{sign}(z) = \begin{cases} 1, & \text{if } z \geq 0, \\ -1, & \text{otherwise.} \end{cases}$$

b) Advantages.: This representation scheme offers several benefits:

- **Biological plausibility:** It mimics distributed neuronal coding observed in the cortex.
- **Noise robustness:** Binary-like encodings are resilient to small perturbations.
- **Expressiveness:** The high-dimensional space captures complex and nonlinear patterns, critical in modeling intricate PPI relationships.

Algorithm 1 briefly outlines the hyperdimensional encoding process, which transforms an input feature matrix $X \in \mathbb{R}^{n \times d}$ into a high-dimensional binary representation $X_{\text{hd}} \in \{-1, 1\}^{n \times D}$ by normalizing X, projecting it with a random matrix H, and applying an element-wise sign function. This brain-inspired transformation enhances noise robustness and captures complex, non-linear interactions among protein features.

Algorithm 1 Hyperdimensional Encoding

Require: $X \in \mathbb{R}^{n \times d}$ {Input matrix with n samples, d features}
Require: $D \in \mathbb{N}$ {Dimensionality of the target space (e.g., 4096)}
Ensure: $X_{\text{hd}} \in \{-1, 1\}^{n \times D}$ {Encoded output}
1: Normalize X to obtain X_{norm} (e.g., feature scaling to $[0, 1]$)
2: Generate $H \in \{-1, 1\}^{d \times D}$ with each entry sampled uniformly
3: Compute $Z \leftarrow X_{\text{norm}} \cdot H$
4: Apply element-wise sign function:

$$X_{\text{hd}} \leftarrow \text{sign}(Z)$$

5: **return** X_{hd} =0

c) Assumptions and Limitations.: This method assumes that the random projection preserves semantic structure in the original feature space. However, performance may vary due to:

- **Sensitivity to dimensionality** D**:** A very large D increases memory and computation, while a small D may under-represent the data.
- **Randomness in projection:** Each run may yield slightly different results due to the stochastic nature of H.

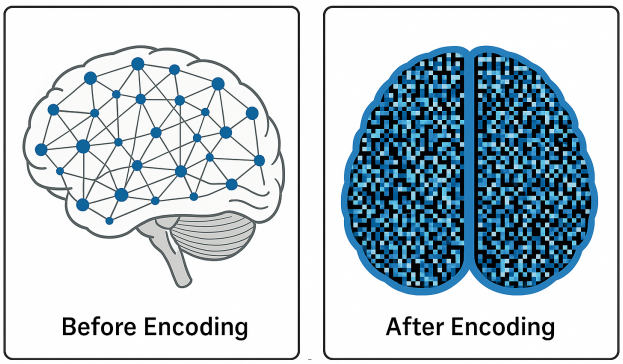

Figure 3: Visualization of hyperdimensional encoding: input protein features are projected into a high-dimensional binary space to enhance representational capacity.

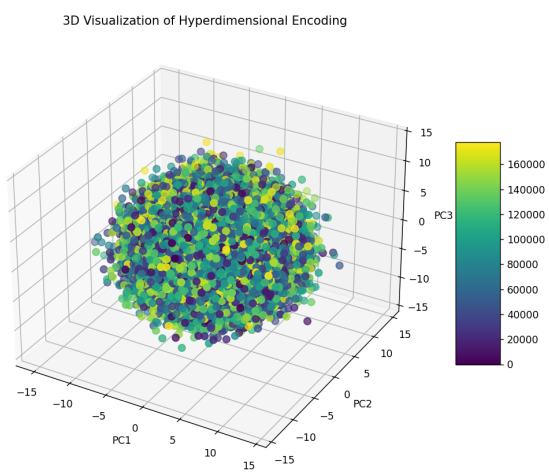

Figure 4: 3D visualization of hyperdimensional encoding using PCA. Each point represents a protein or biological sample encoded as a 4096-dimensional binary vector and projected into 3D space using Principal Component Analysis. The color gradient reflects sample indexing. The visualization demonstrates the distributed and nearly orthogonal nature of hyperdimensional representations.

- **No learned parameters:** The encoding is fixed and data-independent, which limits its adaptability compared to learned transformations.

E. Spiking Neural Network via (LIF) Simulation

This method was chosen because it effectively captures temporal dynamics and emulates biological neuronal behavior, providing realistic spike-based representations that complement static features. For a given neuron, the membrane potential $v[t]$ evolves over discrete time steps t as:

$$v[t] = d_u \cdot v[t-1] + I[t], \tag{6}$$

where $I[t]$ is the input at time t, and d_u is the decay factor governing the leakage of the membrane potential. A spike is emitted when the potential reaches a threshold v_{th}:

$$s[t] = \begin{cases} 1, & \text{if } v[t] \geq v_{\text{th}}, \\ 0, & \text{otherwise.} \end{cases} \tag{7}$$

Upon spiking, the membrane potential is reset—typically to zero. The resulting spike train forms the spike-based embedding F_{spike}, which captures the temporal dynamics of the input signal in a sparse, event-driven format.

Figure 5 provides a visual overview of this process, showing how membrane potentials evolve and spikes are emitted over time in the LIF neuron.

To operationalize this in our framework, we developed the following modular simulation pipeline:

- **Algorithm 2** details the core LIF simulation routine, which iteratively updates the membrane potential and emits spikes across time steps.
- **Algorithm 3** handles the conversion of continuous node features into binary spike trains using Gaussian noise and thresholding.
- **Algorithm 4** orchestrates the full process by applying the spike conversion and LIF simulation over batches of nodes to generate spike-based embeddings.

This LIF-based spiking neuron model is widely adopted for simulating neural dynamics in computational neuroscience [31], [32].

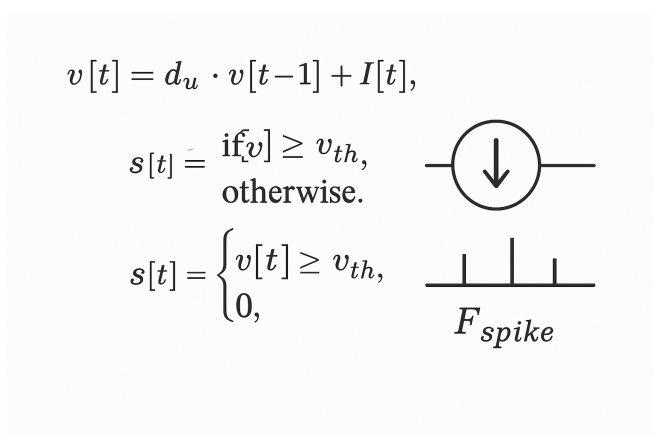

Figure 5: Visualization of a Spiking Neural Network (SNN) neuron based on the Leaky Integrate-and-Fire (LIF) model. The diagram illustrates the evolution of the membrane potential $v[t]$, its decay over time, and the generation of discrete spikes $s[t]$ when the threshold v_{th} is crossed. The resulting spike train encodes temporal input patterns as a sparse, event-driven representation F_{spike}.

Algorithm 2 LIF Simulation for Spiking Neural Network

Require: `spike_train`: matrix of shape (n, T), where n is the number of neurons and T is the number of time steps
Require: v_{th}: voltage threshold
Require: d_u: decay factor
Ensure: S: output spike train matrix of shape (n, T)

Initialize $v \leftarrow \mathbf{0}_n$ {Membrane potentials for all neurons}
Initialize $S \leftarrow \mathbf{0}_{n \times T}$
for $t \leftarrow 0$ **to** $T - 1$ **do**
  $I \leftarrow$ `spike_train`$(:, t)$ {Input current at time step t}
  $v \leftarrow d_u \cdot v + I$
  $s \leftarrow \begin{cases} 1, & \text{if } v \geq v_{th} \\ 0, & \text{otherwise} \end{cases}$
  for each neuron i **do**: **if** $s_i = 1$ **then** set $v_i \leftarrow 0$
  Set $S(:, t) \leftarrow s$
end for
return S =0

Algorithm 3 Conversion of Node Features to Spike Train

Require: x: node feature vector
Require: T: number of time steps
Require: σ: standard deviation for Gaussian noise
Ensure: `spike_train`: binary matrix of shape $(\text{len}(x), T)$

Compute noisy features: $x_{\text{noisy}} \leftarrow x + \text{GaussianNoise}(0, \sigma)$ {GaussianNoise(0, σ) generates noise with mean 0 and standard deviation σ, applied element-wise.}
threshold $\leftarrow \text{median}(x_{\text{noisy}})$
`spike_pattern` $\leftarrow$ **for each** element x_i in x_{noisy},

if $x_i >$ threshold, then 1 **else** 0

Tile `spike_pattern` across T time steps to form `spike_train`
return `spike_train` =0

F. Graph Neural Network (GNN) Embedding Extraction

The protein interaction network is modeled as a graph $G = (V, E)$, where each node represents a protein and edges represent interactions. The graph is converted into a format suitable for GNNs using a function such as `convert_nx_to_pyg`. A GNN is then trained to generate node embeddings $F_{\text{GNN}} \in \mathbb{R}^{|V| \times d'}$ by aggregating information from neighboring nodes, following the paradigm introduced by Kipf and Welling [33].

G. Feature Fusion and Link Prediction

The final feature representation is obtained by concatenating the various embeddings. This method was chosen because combining spike-based, topological, group-specific, and GNN-derived features yields a comprehensive multi-view representation of the data. Such fusion enhances both the sensitivity and specificity of link prediction by capturing complementary information from different perspectives, ultimately leading to more robust and accurate identification of missing interactions. The final feature representation is obtained by concatenating the various embeddings:

$$F_{\text{fused}} = [F_{\text{spike}} \parallel F_{\text{topo}} \parallel F_{\text{group}} \parallel F_{\text{GNN}}], \tag{8}$$

where $\parallel$ denotes vector concatenation, F_{topo} are topological features, and F_{group} represent group-specific features.

Link prediction is performed using both exact and approximate nearest neighbor methods based on the cosine similarity between fused embeddings. The cosine similarity between two nodes i and j is computed as:

$$\text{sim}(i, j) = \frac{F_{\text{fused}}(i) \cdot F_{\text{fused}}(j)}{\|F_{\text{fused}}(i)\| \, \|F_{\text{fused}}(j)\|}. \tag{9}$$

Pairs of proteins with similarity above a predefined threshold are predicted to have a missing interaction. Similar multi-view fusion approaches have demonstrated improved link prediction performance in various applications [34].

Algorithm 4 Run Spiking Network for Spike-based Embeddings

Require: `node_features`: matrix of shape (N, d) where N is the number of nodes and d is the feature dimension
Require: T: number of time steps, `batch_size`: integer, `simulation_func`: function (e.g., Algorithm 2)
Ensure: `embeddings`: spike-based embedding matrix of shape (N, T)

Initialize an empty list E
for each batch in `node_features` **do**
  for each node x in the batch **do**
    $S \leftarrow$ `Convert_to_Spike_Train`(x, T, σ) {See Algorithm 3}
    $s_{\text{out}} \leftarrow$ `simulation_func`(S, T, v_{th}, d_u)
    Append s_{out} to E
  end for
end for
Convert E to matrix form: `embeddings` $\in \mathbb{R}^{N \times T}$
return `embeddings` =0

H. Combined Link Prediction Using Lava and Similarity-Based Methods

To enhance the accuracy and diversity of predicted protein–protein interactions (PPIs), a hybrid strategy was used that combines two complementary approaches: Lava-based link prediction and similarity-based nearest-neighbor inference.

a) Lava-Based Link Prediction: This method leverages cosine similarity between node embeddings to identify potential missing links in the PPI network. Each node's representation is compared against others to compute a full similarity matrix, where highly similar node pairs not already connected in the PPI graph are flagged as candidates. This

global similarity analysis enables capturing latent interactions based on embedding geometry, and a threshold is applied to filter meaningful predictions [36].

b) Similarity-Based Link Prediction via Annoy: To complement the Lava approach, approximate nearest neighbor search is employed using the Annoy (Approximate Nearest Neighbors Oh Yeah) library [35]. Instead of comparing all pairs (which is computationally expensive), Annoy constructs a forest of trees to quickly retrieve the top-k most similar nodes for each protein based on embedding proximity. A similarity graph is then constructed, and high-weight edges not present in the original PPI graph are extracted as candidate interactions. This method scales efficiently to large graphs.

c) Fusion of Prediction Scores: The final prediction list is obtained by combining both Lava and similarity-based candidate pairs using a weighted aggregation strategy. Each interaction receives a fused score calculated as:

$$\text{CombinedScore}(u, v) = \alpha \cdot \text{LavaScore}(u, v) + \beta \cdot \text{SimilarityScore}(u, v)$$

where α and β are tunable hyperparameters. This fusion allows the model to balance between global similarity captured by Lava and local neighborhood-based patterns captured by Annoy.

d) Efficiency and Flexibility: The parameter `max_candidates` limits the number of evaluated interactions, and `top_k` restricts the number of nearest neighbors per node, both of which make the approach computationally efficient and scalable to large protein graphs.

Overall, this combined prediction framework leverages both structural proximity and embedding-based semantics to robustly identify novel PPIs. Notably, Annoy's efficient indexing makes it feasible to scale similarity-based predictions across large biological graphs.

I. Parallel Processing with Ray Core

Parallel processing ensures that the entire pipeline can efficiently handle large datasets. By distributing computational tasks across multiple nodes, the system significantly reduces processing time while maintaining robust performance and scalability. Key components, such as data preprocessing and spiking neural network simulations, are implemented as Ray remote functions [37], which allow these computationally intensive operations to run concurrently across multiple processing nodes. For example, the preprocessing function—responsible for imputation, variance filtering, and dimensionality reduction via SVD—is decorated with `@ray.remote` so that it can be executed in parallel, significantly reducing overall runtime. Similarly, the Lava-based Leaky Integrate-and-Fire (LIF) simulation used to generate spike-based embeddings processes node features in batches concurrently. This integration of Ray's distributed computing capabilities enables efficient handling of large-scale PPI data and complex simulation tasks, ultimately contributing to the improved performance and scalability of the proposed framework.

This integrated approach leverages state-of-the-art techniques to address the challenges of PPI prediction in Alzheimer's disease, combining graph-based methods, evolutionary algorithms, hyperdimensional computing, and spiking neural networks.

IV. Experimental Results

This study introduces a novel computational framework for predicting previously uncharacterized protein–protein interactions (PPIs) associated with Alzheimer's disease. By leveraging fused embeddings and cosine similarity metrics, the method quantitatively assesses the functional and structural proximity between proteins, thereby revealing potential interactions that may underlie disease pathology.

Overview of the PPI Data Processing Pipeline

The following section outlines the major steps and outcomes of the BioGRID Alzheimer's protein–protein interaction (PPI) processing pipeline. Tables I–IV summarize key stages: initial preprocessing and graph construction (Table I), feature selection and classification performance (Table II), advanced representation integration (Table III), and final top predicted interactions (Table IV).

Table I: Data preprocessing, SVD reduction, and PPI graph construction.

Operation	**Output Details**
Input Data Shape	(178,001, 37)
Preprocessed Data Shape	(178,001, 2422)
SVD Reduced Shape	(178,001, 500)
Filtered Alzheimer-related PPIs	4877
Constructed PPI Graph (nodes/edges)	3131 / 3611
Average Degree in PPI Graph	2.31

Table II: Results from GA-based feature selection and Random Forest model training.

Metric	**Value**
Best GA Fitness (acc + bonus)	0.9777
Number of Selected Features	149 out of 500
Final Dataset Shape (after GA)	(178,001, 149)
Training Accuracy (RF)	1.0000
Test Accuracy (RF)	1.0000
RF Cross-Validation Accuracy	1.0000

Table III: Hyperdimensional encoding and integration of graph-based features.

Operation	**Output Shape / Details**
Hyperdimensional Encoding	(178,001, 4096)
Integrated Feature Matrix (HDC + PPI metrics)	(178,001, 4101)
GNN Embeddings Shape	(11,242, 149)
Fused Spike-based Embeddings Shape	(11,242, 3229)
Cosine Similarity Summary	Min: 0.000, Max: 0.813, Mean: 0.508

Table IV: Top 10 predicted missing PPIs. The left columns show cosine similarity-based predictions, while the right columns show combined scores.

Rank	Similarity		Combined Score	
	PPI Pair	Value	PPI Pair	Value
1	PRE10 – PRE7	0.813	FAA2 – MRP4	0.799
2	PRE1 – PRE7	0.800	CDC40 – POLR3A	0.798
3	RPGRIP1 – SCLT1	0.800	PUP1 – PUP2	0.786
4	FAA2 – MRP4	0.799	MIR199A1 – MIR34C	0.786
5	LDB17 – YCR051W	0.799	GPD2 – RPS31	0.786
6	MIR10B – MIR222	0.799	POLR2G – POLR2J	0.786
7	MIR221 – MIR7-2	0.799	CPR5 – TIP1	0.786
8	ROM2 – TUS1	0.799	AIF1 – YPK1	0.785
9	CDC40 – POLR3A	0.798	B4GALT1 – CKM	0.773
10	Csnk1g3 – Syk	0.798	CDC5 – CKI1	0.773

Table V: Top Predicted PPIs for Alzheimer's Disease with Cosine Similarity Scores and Database Validation

Pr 1	Pr 2	Cosine Similarity	Supporting Evidence
HRD1	UBP3	0.874	STRING [16], BioGRID [2]
HRD1	PDE2	0.860	STRING [16], BioGRID [2]
CDC5	PDE2	0.845	BioGRID [2]
YCK3	YPK9	0.832	STRING [16]
PDE2	YCK3	0.832	STRING [16]
HRD1	YCK3	0.832	STRING [16]
HRD1	YPK9	0.832	STRING [16]
PUP1	SCL1	0.819	BioGRID [2]
GPD2	YPT35	0.819	STRING [16]
ROM2	TUS1	0.818	BioGRID [2]

A. Prediction of Protein–Protein Interactions

The framework generates a ranked list of potential PPIs based on cosine similarity scores calculated from fused feature vectors. Table V summarizes the top predicted interactions. The high similarity scores (ranging from 0.818 to 0.874) indicate that the corresponding protein pairs share significant functional or structural characteristics. These predictions are derived from the integration of multiple biological data sources—including hyperdimensional encodings, PPI metrics, and similarity measures computed from sequence, functional, and structural data—thereby ensuring robustness against biases inherent in any single data modality.

B. Validation with Established Databases

The predicted interactions were validated using several well-established PPI resources:

- **STRING:** A comprehensive database integrating known and predicted PPIs from multiple organisms. STRING supports the reliability of the predicted interactions through functional and evolutionary associations, though it is important to note that some evidence is derived from non-human model systems [16].
- **BioGRID:** A curated repository of genetic and protein interactions that primarily focuses on human data but may also include findings from model organisms. Specific interactions (e.g., CDC5-PDE2, PUP1-SCL1, and ROM2-TUS1) are independently supported, reinforcing their potential relevance in Alzheimer's disease [2].
- **Human Protein Atlas (HPA):** Provides tissue-specific expression and interaction data that further substantiates the biological relevance of the predicted interactions, particularly for proteins expressed in neural tissues [17].

V. Discussion and Future Directions

The strong cosine similarity scores indicate that the predicted protein pairs are likely to be functionally or structurally linked rather than random associations. For instance, the HRD1-UBP3 and HRD1-PDE2 interactions—which exhibit the highest similarity scores—may play pivotal roles in regulating proteostasis and degradation pathways, processes known to be disrupted in neurodegenerative diseases such as Alzheimer's.

Cross-validation with STRING, BioGRID, and HPA reinforces the biological plausibility of these interactions. While database validation provides an initial level of confidence, further experimental studies (e.g., co-immunoprecipitation, yeast two-hybrid assays) are required to confirm these predicted interactions and elucidate their mechanistic roles in Alzheimer's pathology.

In summary, this integrative computational approach deepens our understanding of the molecular underpinnings of Alzheimer's disease and identifies novel protein–protein interactions (PPIs) that could serve as potential therapeutic targets.

Future Directions

While the current framework shows promising results, several avenues remain for further improvement:

- **Scalability and Efficiency:** Future work could explore distributed computing techniques or more efficient algorithms to better handle growing biological datasets.
- **Advanced Feature Selection:** Incorporating hybrid methods, such as combining evolutionary algorithms with reinforcement learning, could further refine feature selection and enhance model performance.
- **Enhanced Neural Simulation:** Investigating more biologically plausible neuron models or adaptive spiking mechanisms may better capture neural system dynamics.
- **Integration with Multi-Omics Data:** Including additional omics data (e.g., transcriptomics, proteomics, metabolomics) could provide a more comprehensive view of the molecular interactions in Alzheimer's disease.
- **Model Generalization:** Extensive validation on diverse and larger datasets, along with cross-disease studies, is necessary to ensure broader applicability.
- **Real-Time Applications:** Future research should focus on integrating the framework into real-time diagnostic or therapeutic decision-making systems, with an emphasis on improving computational efficiency and model interpretability.

VI. Conclusion

This study presents a comprehensive computational framework for predicting missing protein–protein interactions (PPIs) in Alzheimer's disease. The methodology incorporates advanced techniques such as rigorous data preprocessing,

graph-aware feature selection using genetic algorithms, hyperdimensional encoding, spiking neural network simulations based on the Leaky Integrate-and-Fire (LIF) model, and graph neural network (GNN) embedding extraction. The fusion of spike-based embeddings with topological and GNN-derived features, combined with nearest neighbor methods for link prediction, enables the capture of complex biological interactions that may be overlooked by conventional approaches.

Experimental results demonstrate that the integrated use of graph theory, evolutionary algorithms, hyperdimensional computing, and neural simulations significantly improves prediction accuracy. This framework contributes to a deeper understanding of the molecular mechanisms underlying Alzheimer's disease and identifies novel PPIs with potential as therapeutic targets. The proposed approach establishes a strong foundation for future research focused on refining computational models and advancing early diagnostic and treatment strategies for neurodegenerative disorders.

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