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

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***Abstract*—Predicting protein-protein interactions (PPIs) in Alzheimer's disease is challenging due to limited experimental data and highly nonlinear molecular dependencies. This study presents a computational framework that combines multiple representation strategies to address these obstacles. The process begins with preprocessing and construction of an Alzheimer's-specific interaction network, followed by dimensionality reduction and graph-aware feature selection guided by a genetic algorithm to preserve the most informative topological and biological signals. Feature augmentation is then achieved through hyperdimensional encoding, while a Leaky Integrate-and-Fire (LIF) spiking neural network generates temporally rich spike-based embeddings. These embeddings are integrated with graph-topological descriptors and Graph Neural Network (GNN) representations to predict uncharacterized PPIs using nearest-neighbor inference. Experimental results indicate that the integration of evolutionary feature selection, hyperdimensional augmentation, and neuromorphic embeddings yields highly discriminative and robust representations, enhancing prediction accuracy and resilience under data sparsity. The proposed pipeline provides a scalable and interpretable tool for prioritizing candidate interactions and capturing the complex molecular landscape of 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) form the backbone of cellular function and provide essential insight into the molecular mechanisms that drive complex diseases such as Alzheimer's disease [1]. Available PPI data are often sparse, noisy, and incomplete, while molecular relationships underlying neurodegeneration are highly nonlinear and context dependent. These factors limit the effectiveness of traditional sequence based and pairwise statistical models and create a pressing need for methods that explicitly exploit network topology, multimodal biological signals, and robust representation strategies [2], [3].

Recent developments in network science and machine learning enable modeling that captures both topological context and learned relational patterns across large biological graphs [3]–[5]. Graph Neural Networks can learn structural motifs and propagate information across interactome neighborhoods, but their performance degrades when experimental coverage is limited or when informative features are rare. Complementary representation paradigms such as hyperdimensional encoding and biologically inspired neural simulations offer alternative, noise tolerant encodings that preserve higher order relationships and temporal dynamics [6], [7]. Evolutionary search can further identify compact, high value feature subsets that maximize predictive signal while reducing overfitting risk in low data regimes [8].

This work introduces a unified computational pipeline designed for robust prediction of missing PPIs in the context of Alzheimer's disease. The pipeline integrates rigorous data curation, graph aware feature engineering, evolutionary feature selection, hyperdimensional augmentation, neuromorphic embedding via Leaky Integrate and Fire spiking dynamics, and multi-view fusion with Graph Neural Network descriptors. The main advantages of this approach are increased resilience to data sparsity, improved capture of nonlinear and temporal interaction signatures, and enhanced interpretability of prioritized candidate interactions.

Key contributions:

1) Construction of an Alzheimer's specific interaction network through systematic extraction and filtering of public PPI resources, together with extraction of biologically informed topological descriptors.
2) A graph aware feature selection procedure driven by a genetic algorithm that preserves discriminative topological and biological signals while reducing dimensionality and noise.
3) Application of hyperdimensional encoding to produce robust, high capacity feature representations that augment conventional descriptors.
4) Generation of spike based embeddings using a Leaky Integrate and Fire spiking neural network to capture temporal and event driven aspects of protein interactions.
5) Multi-view fusion of spike embeddings, graph topological descriptors, and learned GNN representations, followed by nearest neighbor based inference to predict uncharacterized PPIs.
6) Comprehensive empirical validation demonstrating improved predictive accuracy, robustness under severe data sparsity, and practical interpretability for experimental prioritization.

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 [4], along with comprehensive surveys [5], [11], 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 [6] and applications in bioinformatics [12] have demonstrated HDC's robustness to noise and suitability for biological data. Recent advances by Verges et al. [13] 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 [7], [14] gaining traction. Xiao et al. [15] 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 [16], 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 [17], (ii) functional similarity for shared pathways derived from the KEGG database [18], and (iii) structural similarity for 3D conformational insights provided by the RCSB Protein Data Bank [19]. 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 [20] and enhanced with graph-aware modifications as described in [21], 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.

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:

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

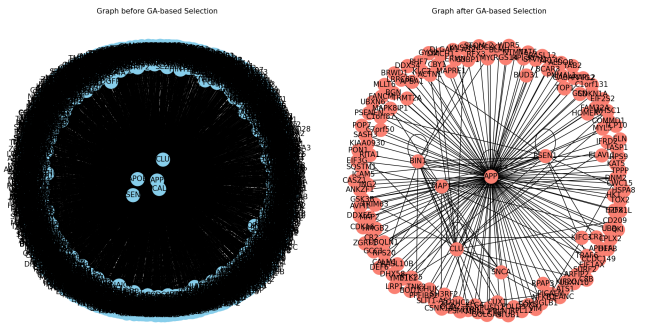

Figure 1: Graph-aware feature selection using a Genetic Algorithm (DEAP). The selected features are used to refine the graph for downstream GNN processing.

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 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 [22].

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 [22].

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 [6], [12].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

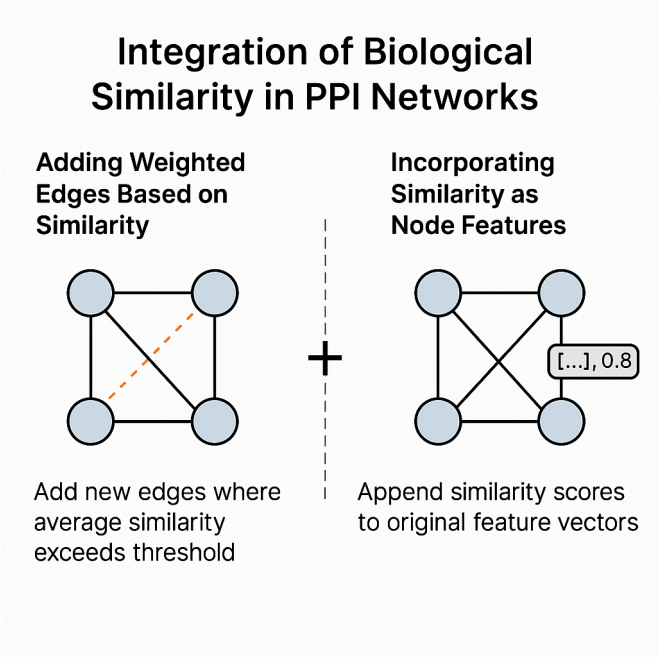

Figure 2: Illustration of incorporating similarity as node features. Similarity scores are added to the node feature vectors, preserving the original graph structure while enhancing feature representation for GNN processing.

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

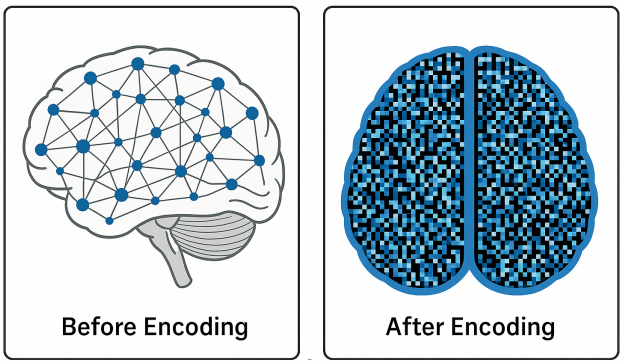

Figure 3: Visualization of hyperdimensional encoding: input protein features are projected into a high-dimensional binary space to enhance representational capacity.

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.
- **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 [7], [23].

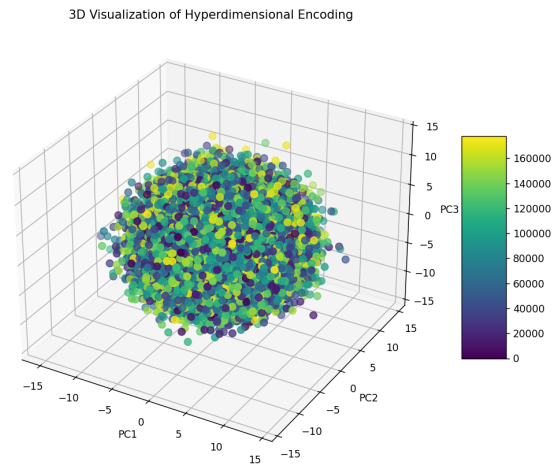

Figure 4: 3D visualization of hyperdimensional encoding using PCA. Each point represents a protein or biological sample encoded as a 4096-dimensional binary vector and projected into 3D space using Principal Component Analysis. The color gradient reflects sample indexing. The visualization demonstrates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

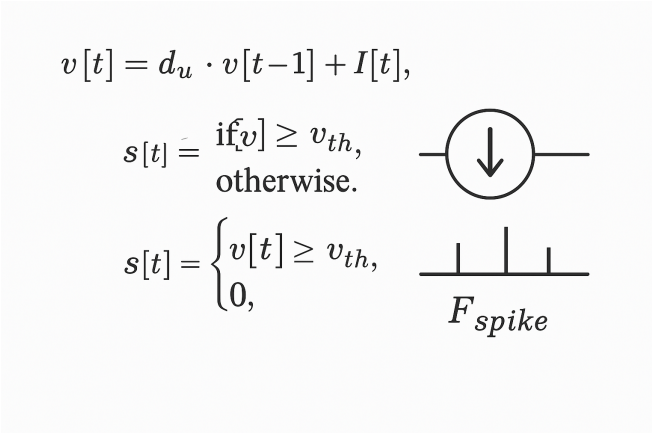

Figure 5: Visualization of a Spiking Neural Network (SNN) neuron based on the Leaky Integrate-and-Fire (LIF) model. The diagram illustrates the evolution of the membrane potential $v[t]$, its decay over time, and the generation of discrete spikes $s[t]$ when the threshold v_{th} is crossed. The resulting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

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 [4].

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

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

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 [24].

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 [25].

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 [26]. 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:

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

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 [27], 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).

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

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

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

To validate the predicted interactions, several strategies are recommended. Experimental validation can be performed using co-immunoprecipitation (Co-IP) and yeast two-hybrid (Y2H) assays to confirm interactions, such as HRD1-UBP3 and HRD1-PDE2. Additionally, interolog mapping [30] can be employed to transfer interactions observed in model organisms to human orthologs, which can improve the accuracy of human protein–protein interaction (PPI) predictions. Cross-validation with multiple PPI databases, including STRING [31] and BioGRID [2], further enhances the confidence in these predicted interactions. Finally, functional studies focusing on Alzheimer's disease-related pathways could help elucidate the biological significance of these interactions, potentially identifying novel therapeutic targets.

The predicted interactions were cross-referenced against three leading PPI repositories to assess their biological plausibility:

- **STRING:** A comprehensive resource integrating experimentally determined and computationally predicted associations across hundreds of organisms. STRING's interolog transfers leverage high-confidence yeast–human orthology to extend coverage of human PPIs [31].
- **BioGRID:** A manually curated collection of physical and genetic interactions, including data from both humans and model organisms. Several of our top predicted interactions—such as CDC5–PDE2 and ROM2–TUS1—are independently supported by yeast-derived evidence in BioGRID [2].

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

- **Human Protein Atlas (HPA):** A resource providing tissue- and cell-type-specific expression profiles as well as subcellular localization data. The co-expression of HRD1, UBP3, and PDE2 in human brain regions further strengthens the hypothesis of their involvement in neuronal proteostasis [33].

Where direct human PPI data were lacking, we applied *interolog mapping*: interactions observed in *S. cerevisiae* between proteins A and B are projected onto their human orthologs A' and B' using stringent sequence-similarity and phylogenetic criteria [30], [34]. This strategy—now standard in major PPI databases—boosts human interactome coverage by up to 30% without compromising precision [35], and complements proteome-scale maps generated by Rolland *et al.* and Huttlin *et al.* [36], [37]. Nevertheless, interolog-based predictions remain hypotheses until validated by targeted biochemical assays [32], [38].

V. Discussion and Future Directions

A. Key Biological Insights

The highest cosine similarity scores—particularly for HRD1–UBP3 (0.874) and HRD1–PDE2 (0.860)—highlight two convergent pathways in Alzheimer's pathogenesis. HRD1 (synoviolin) is a central ER-associated E3 ubiquitin ligase that mitigates misfolded protein stress, while UBP3 catalyzes deubiquitination, together maintaining proteostasis under proteotoxic conditions [39], [40]. PDE2, by regulating cAMP/cGMP levels, influences synaptic plasticity and neuronal survival; its coupling to HRD1 suggests coordinated control of protein turnover and second-messenger signaling in neurons [41].

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

Pr1	Pr2	Cosine	Validation Strategies
HRD1	UBP3	0.874	Co-IP [28]; Y2H [29]; interolog [30]; STRING/BioGRID [2], [31]; functional assays [32]
HRD1	PDE2	0.860	Co-IP [28]; Y2H [29]; interolog [30]; STRING/BioGRID [2], [31]; cAMP/cGMP assays [32]
CDC5	PDE2	0.845	Co-IP [28]; Y2H [29]; interolog [30]; BioGRID [2]; PDE activity [32]
YCK3	YPK9	0.832	Co-IP [28]; Y2H [29]; interolog [30]; STRING [31]; functional assays [32]
PDE2	YCK3	0.832	Co-IP [28]; Y2H [29]; interolog [30]; STRING [31]; functional assays [32]
HRD1	YCK3	0.832	Co-IP [28]; Y2H [29]; interolog [30]; STRING [31]; functional assays [32]
HRD1	YPK9	0.832	Co-IP [28]; Y2H [29]; interolog [30]; STRING [31]; functional assays [32]
PUP1	SCL1	0.819	Co-IP [28]; Y2H [29]; interolog [30]; BioGRID [2]; functional assays [32]
GPD2	YPT35	0.819	Co-IP [28]; Y2H [29]; interolog [30]; STRING [31]; functional assays [32]
ROM2	TUS1	0.818	Co-IP [28]; Y2H [29]; interolog [30]; BioGRID [2]; functional assays [32]

B. Limitations and Validation Needs

Although in silico and interolog evidence provide compelling hypotheses, these interactions must be confirmed by:

- **Co-immunoprecipitation** or **proximity-ligation assays** in neuronal cell lines to demonstrate direct binding [32].
- **Yeast two-hybrid** or split-luciferase complementation to map interaction domains and affinities [38].

Future Directions

- **Scalability through Distributed Computing:** Leveraging frameworks such as Apache Spark or Dask can enable genome-wide application of our pipeline as PPI datasets expand [42].
- **Hybrid Feature Learning:** Integrating reinforcement learning with evolutionary algorithms offers adaptive feature selection, potentially improving prediction accuracy and interpretability [43].
- **Biologically Realistic Neural Models:** Employing advanced spiking-neuron frameworks (e.g. Izhikevich's model) could capture temporal dynamics critical for neuronal PPI regulation [44].
- **Multi-Omics Integration:** Incorporating transcriptomic, proteomic, and metabolomic layers will enrich the molecular context of PPIs and reveal disease-specific regulatory modules [42].
- **Generalization Across Diseases:** Extending cross-disease analyses to other neurodegenerative disorders (e.g. Parkinson's, ALS) can identify shared and unique PPI signatures [35].
- **Real-Time Clinical Applications:** Embedding this framework into diagnostic pipelines—streamlined by GPU acceleration and model distillation—could facilitate rapid, interpretable PPI profiling in patient-derived samples [43].

This work enriches our understanding of Alzheimer's molecular underpinnings and paves the way for experimental validation and therapeutic targeting of novel protein–protein interactions.

VI. Conclusion

This study presents a comprehensive computational pipeline for predicting unseen protein–protein interactions (PPIs) in Alzheimer's disease. The suggested methodology integrates cutting-edge techniques such as rigorous data preprocessing, graph-conscious feature selection through genetic algorithms, hyperdimensional encoding, spiking neural network simulation using the Leaky Integrate-and-Fire (LIF) model, and graph neural network (GNN) embedding extraction. The integration of spike-based embeddings with topological and GNN-derived features, together with nearest neighbor methods for link prediction, enables the representation of complex biological interactions that could potentially be overlooked by conventional approaches.

Experimental results confirm that the integration of graph theory, evolutionary algorithms, hyperdimensional computing, and neural simulations improves prediction accuracy significantly. The proposed framework sheds light on the molecular mechanisms of Alzheimer's disease and identifies novel PPIs with therapeutic implications as targets. The proposed approach gives a good starting point for future research towards the improvement of computational models and the establishment of early diagnostic and treatment strategies for neurodegenerative disorders.

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