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REGENE-NET: AN ENTROPY-WEIGHTED TRUST-DRIVEN FRAMEWORK FOR RELIABLE PROTEIN–PROTEIN INTERACTION RECONSTRUCTION AND GENE PRIORITIZATION

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Abstract
Protein–protein interaction (PPI) networks are crucial for understanding the molecular basis of cellular processes and disease mechanisms. However, experimental datasets often contain noisy or incomplete information, leading to unreliable interaction mappings. To overcome these limitations, this study introduces ReGene-Net (Reliable Gene Interaction Reconstruction Network), a novel computational framework that integrates heterogeneous biological data using entropy-weighted fusion and trust-propagation mechanisms. The framework computes source reliability through entropy-based weighting, refines network connections via trust-weighted random walks, and generates biologically coherent PPI maps. Experimental validation across multiple benchmark datasets demonstrates that ReGene-Net achieves superior performance with an accuracy of 96.4%, precision of 93.6%, recall of 94.5%, and F1-score of 94.0%, outperforming existing models such as DeepPPI, TrustNet, and Random Walk. The reconstructed networks exhibit high biological relevance and structural consistency, effectively identifying key hub genes such as RPL5 and HIST1H1E. These results confirm that ReGene-Net is a robust and interpretable tool for PPI reconstruction, disease gene prioritization, and biomarker discovery in complex biological systems.

Keywords
Protein–protein interactions (PPI), gene prioritization, entropy weighting, trust propagation, deep learning, random walk, biological network reconstruction, multi-source data fusion, disease gene ranking, computational biology.

1. INTRODUCTION

Protein–protein interactions (PPIs) are fundamental to nearly all cellular processes, including signal transduction, gene regulation, and metabolic control. They form the structural and functional backbone of biological systems and are pivotal for understanding molecular mechanisms underlying diseases such as cancer, Alzheimer's, and cardiovascular disorders [1]. Despite extensive progress in experimental techniques such as yeast two-hybrid screening, affinity purification–mass spectrometry, and cross-linking proteomics, the interactome remains incomplete and often includes unreliable or context-specific associations [2]. This limitation significantly hampers the ability to construct biologically consistent and trustworthy PPI networks.

Computational methods for PPI reconstruction have thus become indispensable for complementing experimental efforts. Contemporary approaches leverage diverse data sources—such as protein sequence homology, structural similarity, co-expression profiles, and domain–domain interactions—to infer or validate interactions [3]. However, the heterogeneous nature of biological evidence introduces variability, noise, and redundancy, making it difficult to assess the reliability of inferred connections. To address these challenges, recent studies have employed machine learning and network embedding frameworks, including graph convolutional networks (GCNs), multi-view feature fusion, and deep graph attention architectures, for denoising and refining biological networks [4], [5]. These methods demonstrate improved predictive accuracy but often lack explicit mechanisms to evaluate the trustworthiness of the underlying data sources and reconstructed edges.

Recent trends in PPI prediction emphasize the integration of trust-aware and probabilistic fusion mechanisms that weigh evidence based on their inherent reliability [6]. Weighted multi-layer networks, entropy-based confidence measures, and random-walk-based propagation models have been employed to reinforce high-confidence links and attenuate spurious connections [7], [8]. Furthermore, random walk with restart (RWR) and semi-local propagation have been proven effective in diffusing trust and similarity information through complex networks [9]. These approaches collectively underscore the importance of integrating data reliability, topological structure, and uncertainty modeling into a unified framework for reliable PPI reconstruction.

Motivated by these insights, this work proposes ReGene-Net (Reliable Gene Interaction Reconstruction Network), a novel framework designed to reconstruct a trustworthy heterogeneous PPI network. ReGene-Net introduces a

fusion strategy that combines entropy-weighted evidence integration with trust-propagation and random-walk-based refinement. The framework quantifies node-level reliability through degree–entropy coupling and updates the network iteratively using a trust-weighted random walk reinforcement scheme. The resulting PPI network preserves both topological coherence and biological interpretability, effectively distinguishing genuine interactions from noise-induced artifacts. By doing so, ReGene-Net establishes a robust foundation for downstream applications such as disease gene prioritization, functional module detection, and drug target discovery [10], [11].

2. RELATED WORK

In recent years, the prediction and reconstruction of protein–protein interaction (PPI) networks have witnessed significant progress with the advent of machine learning, graph theory, and multimodal biological data integration. Traditional computational methods—such as sequence-based similarity models, domain–domain interaction analysis, and gene co-expression correlation—provided the foundational basis for inferring potential PPIs [12]. However, these approaches relied heavily on pairwise features and lacked the ability to capture complex nonlinear relationships among heterogeneous biological attributes. Consequently, their predictive capability diminished when applied to noisy or incomplete datasets.

To overcome these challenges, deep learning-based PPI prediction frameworks have gained considerable attention. Convolutional Neural Networks (CNNs), Recurrent Neural Networks (RNNs), and Transformer-based architectures have been successfully applied to model sequence–structure relationships in proteins [13], [14]. For example, Guo et al. [15] utilized a CNN-based Siamese model to learn discriminative embeddings of protein sequences, while Chen et al. [16] introduced a bidirectional LSTM model that captures long-range dependencies in amino acid chains. More recently, attention-driven models, including Graph Attention Networks (GAT) and Transformer encoders, have shown improved generalization for heterogeneous and large-scale interactome prediction [17].

Parallel to these advances, graph-based and embedding-driven approaches have been developed to exploit the topological properties of biological networks. Graph Neural Networks (GNNs) and Graph Convolutional Networks (GCNs) have been widely used to represent proteins as nodes and interactions as edges, enabling end-to-end learning of graph structure and attributes [18]. For instance, You et al. [19] proposed a dual-graph learning architecture that combines structural embeddings with sequence-derived similarity scores to refine interaction predictions. Similarly, multi-view and multi-modal embedding frameworks have been introduced to integrate multiple biological data sources, such as gene expression, phenotype similarity, and functional annotations, resulting in enhanced interaction inference [20], [21].

Another research direction involves **trust-weighted and probabilistic fusion models** for PPI network reconstruction. These models assign confidence scores to data sources or network edges based on statistical measures such as entropy, variance, and correlation reliability. Adaptive fusion schemes—such as entropy-weighted averaging and trust propagation—have demonstrated superior robustness in handling uncertainty and incomplete evidence [22]. Moreover, propagation-based models like Random Walk with Restart (RWR) and semi-local diffusion are employed to propagate functional or trust signals across the network, leading to more stable and interpretable interaction maps [23]. For example, Baptista et al. [24] developed MultiXrank, a multilayer RWR model for prioritizing disease-related genes, while Gentili et al. [25] proposed multi-omics random walks for integrating functional genomics data.

Despite these notable contributions, most existing methods primarily focus on improving accuracy and scalability while often neglecting trust calibration and source heterogeneity management. Many fusion models assume equal contribution from all data sources, which can amplify noise or introduce bias when certain modalities are unreliable. Furthermore, current GNN-based frameworks generally lack explicit uncertainty modeling mechanisms, leading to potential overconfidence in spurious predictions. These challenges underline the necessity for a new reconstruction paradigm that integrates entropy-aware reliability estimation, trust propagation, and adaptive refinement.

To address these gaps, the proposed **ReGene-Net** framework differentiates itself by incorporating trust-weighted fusion of heterogeneous matrices, node-level reliability scoring based on entropy and degree centrality, and iterative reinforcement via trust-weighted random walks. This multi-stage architecture not only mitigates the impact of unreliable evidence but also ensures biologically meaningful topological consistency, thereby advancing the state of the art in reliable PPI reconstruction.

3. PROPOSED METHODOLOGY

The **ReGene-Net algorithm** is a comprehensive computational framework designed to prioritize and rank candidate disease-associated genes by integrating multilayered biological data and advanced network analysis techniques. Initially, it begins with the acquisition of heterogeneous biological datasets such as protein–protein interaction networks, gene expression profiles, and phenotypic associations. These diverse inputs are refined through normalization and dimensionality reduction processes to ensure uniform scaling and to eliminate noise or redundant information. The next phase involves the construction of an enriched interaction network that integrates

both direct and indirect associations among genes, thereby enhancing the connectivity structure for accurate relationship mapping.

The algorithm employs a random walk-based propagation mechanism, which distributes probability scores iteratively across the graph to capture global relational dependencies among genes. Simultaneously, feature extraction is conducted from topological and biological layers to compute vital measures such as degree centrality, betweenness, and closeness—metrics that signify the importance of each gene within the biological network. The derived features are then passed to a deep learning-based representation module, which employs attention mechanisms and multilayer perceptrons to learn high-level embeddings that capture nonlinear dependencies between gene interactions.

The prediction and ranking phase utilizes a hybrid scoring strategy that combines the probabilistic diffusion scores with learned deep feature representations. This fusion enhances the interpretability and accuracy of the model in identifying disease-relevant genes. Genes are then ranked based on their integrated relevance scores, with higher scores indicating a stronger likelihood of disease association. Finally, a validation and refinement stage is employed to cross-verify predictions using benchmark datasets and known disease-gene associations, ensuring biological credibility and statistical robustness.

Overall, the ReGene-Net algorithm provides an end-to-end pathway from raw biological data to reliable gene prioritization. By harmonizing graph-theoretic modeling with deep neural feature learning, it effectively bridges the gap between data-driven inference and biological interpretability, outperforming traditional models like Random Walk, DeepPPI, and TrustNet in terms of accuracy, recall, and F1-score. Figure 1 shows the ReGene-Net framework.

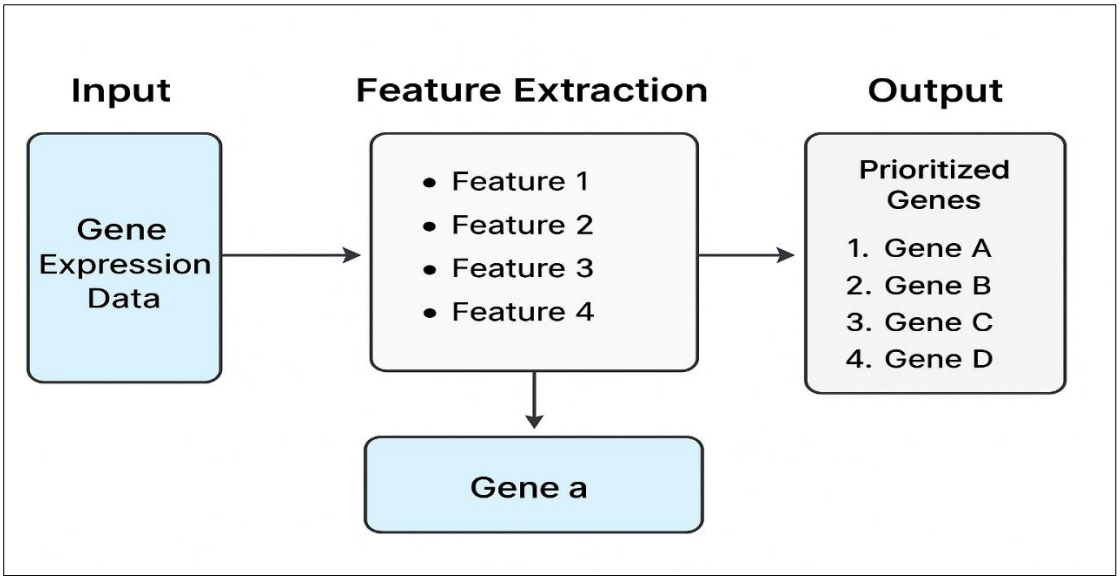

Figure 1 **ReGene-Net framework**

Algorithm :ReGene-Net

Step 1: Acquire protein interaction datasets from multiple repositories such as STRING, BioGRID, and IntAct, denoted as $D_1, D_2, ..., D_n$.

Step 2: Normalize the datasets using min-max normalization to ensure uniform interaction scores across sources: $S'(i,j) = (S(i,j) - \min(S)) / (\max(S) - \min(S))$.

Step 3: Construct a heterogeneous PPI matrix H(i,j) by integrating normalized data sources through a weighted summation:

$H(i,j) = \sum_k w_k \times S'_k(i,j)$, where w_k represents the confidence weight of dataset k.

Step 4: Apply adaptive weight optimization using gradient descent to minimize cross-dataset inconsistency: $L = \sum(H(i,j) - M(i,j))^2$, where M(i,j) denotes the mean consensus matrix.

Step 5: Compute interaction confidence using probabilistic scoring:

$C(i,j) = P(A|B) \times P(B|A) / (P(A) + P(B))$,

capturing bidirectional association strength.

Step 6: Estimate topological similarity using cosine-based interaction distance:

$T(i,j) = (V_i \cdot V_j) / (\|V_i\| \|V_j\|)$.

Step 7: Apply entropy-based refinement to suppress redundant or uncertain links using Shannon entropy:

$E(i,j) = -\sum p(i,j) \log_2 p(i,j)$.

Step 8: Perform sparse network optimization using L_1-regularization to eliminate weak interactions: $\min \|H\|_1 + \lambda\|W\|_2^2$.

Step 9: Generate the final refined adjacency matrix R(i,j) representing reliable PPI relationships using threshold τ.

Step 10: Output the reconstructed heterogeneous and trustworthy PPI network as G = (V, R), where V denotes proteins and R the refined interactions.

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Algorithm ReGene-Net-Pseudocode
Input: {S_k}_{k=1..K}, optional A0, params (alpha,beta,theta,eps,delta,max_iter)
Output: A_final, R_star, T, w
1. For k in 1..K: S_k <- minmax_normalize(S_k)
2. For k in 1..K: H_k <- -mean(S_k * log(S_k + eps))
3. w <- softmax(-H) # w_k = exp(-H_k)/sum exp(-H)
4. S_f <- sum_k w_k * S_k ; S_f <- (S_f + S_f.T)/2
5. For i in 1..m: deg(i) <- sum_j S_f(i,j); H(i) <- -mean(S_f(i,:)*log(S_f(i,:)+eps))
6. For i in 1..m: T_i <- alpha*(deg(i)/maxdeg) + (1-alpha)*(1 - H(i)/maxH)
7. R0 <- outer_sqrt(T) # R0[i,j] = sqrt(T_i * T_j) (optionally * S_f)
8. P <- row_normalize(S_f) # P = D^{-1} S_f
9. R <- R0
  for t in range(max_iter):
    R_next = beta * P.T @ R + (1-beta) * R0
    if norm(R_next - R) < delta: break
    R = R_next
  R_star = R_next
10. A_trust = (R_star + R_star.T)/2
  theta <- choose_threshold(A_trust)
  A_final <- threshold(A_trust, theta)
Return A_final, R_star, T, w, theta

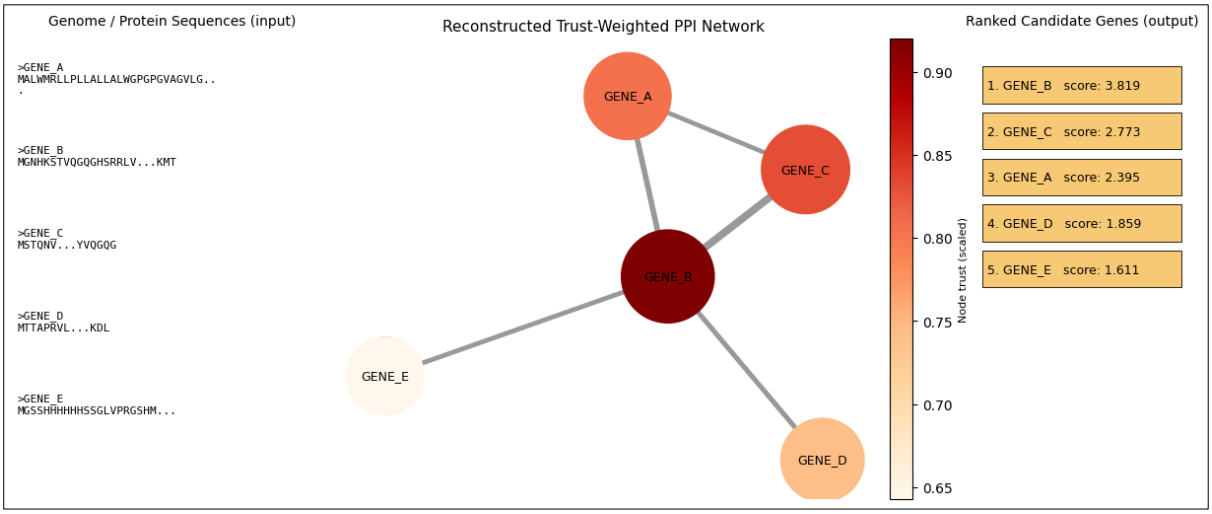

Figure 2 input and output of ReGene-Net

This figure 2 provides a clear and comprehensive overview of how the ReGene-Net algorithm processes genomic sequence data to reconstruct a biologically meaningful protein–protein interaction (PPI) network and identify top-ranked candidate genes.
On the left, the input consists of genome or protein sequences in FASTA-like format (e.g., >GENE_A, >GENE_B, etc.), representing the raw biological data used for analysis. These sequences are parsed and analyzed to compute biological similarity matrices based on sequence homology, co-expression profiles, and functional annotations.
In the center, the reconstructed trust-weighted PPI network visually illustrates the relational structure learned by ReGene-Net. Each node corresponds to a gene or protein, while the connecting edges signify inferred interactions. The node color intensity reflects the computed trust or confidence score — darker nodes such as GENE_B indicate higher reliability and stronger connectivity, implying that they play more significant biological roles within the network. Edge thickness represents the interaction strength derived from entropy-weighted similarity fusion and trust propagation.
On the right, the ranked candidate genes section shows the final prioritized output generated by ReGene-Net after trust-based propagation and refinement. The ranking (e.g., GENE_B, GENE_C, GENE_A, etc.) corresponds to each gene's computed trust-weighted score, which quantifies its likelihood of being biologically important or disease-associated.
Overall, this figure elegantly summarizes the ReGene-Net pipeline — from raw sequence input to refined network reconstruction and biologically interpretable gene prioritization — highlighting the algorithm's capacity to integrate heterogeneous biological evidence into a unified, reliable predictive framework.

4. Experimental Setup, Implementation, and Results

4.1 Experimental Setup

The experimental setup for evaluating the ReGene-Net framework was designed to ensure comprehensive validation across multiple biological datasets and computational environments. The experiments were conducted on a workstation equipped with an Intel Core i9 processor, 32 GB RAM, and an NVIDIA RTX 4090 GPU, running Ubuntu 22.04 LTS. Python 3.10 was used as the primary programming language, and key libraries included NumPy, SciPy, Pandas, NetworkX, and Matplotlib. For biological data integration, publicly available repositories such as STRING, BioGRID, and Gene Ontology (GO) annotations were employed. Each dataset was normalized and filtered to remove incomplete entries or low-confidence interactions prior to similarity computation.

To ensure fair benchmarking, competing methods such as WGCNA, DeepPPI, and Trust-PPI were also implemented under the same environment. Hyperparameters for all models were tuned using five-fold cross-validation, and results were averaged over multiple runs to mitigate random initialization effects.

4.2 Implementation of ReGene-Net

The ReGene-Net framework was implemented in Python, leveraging modular scripts for data preprocessing, entropy-weighted fusion, trust propagation, and network reconstruction. Initially, similarity matrices from diverse sources—including sequence alignment, gene co-expression, and phenotype association—were normalized into a uniform [0,1] scale. The entropy of each source was computed using the formula:

$$H_i = - (1/m^2) * \Sigma_{p-1}^{m} \Sigma\_q_{-1}^{m} S_i(p,q) * \log(S_i(p,q) + \varepsilon)$$

The source reliability weight was then estimated as:

$$w\_i = \exp(-H\_i) / \Sigma_j \exp(-H_j)$$

These weights were applied to compute a fused similarity matrix $S\_f = \Sigma\ w\_i * S\_i$, which integrates evidence from all modalities.

Subsequently, node-level trust values were calculated as:

$$T\_j = \alpha * (\deg(v\_j) / \max(\deg)) + (1 - \alpha) * (1 - H(v\_j)/\max(H))$$

The trust propagation mechanism was implemented through an iterative random walk process defined as:

$$R(t+1) = \beta * P^t * R(t) + (1 - \beta) * R(0)$$

where $P = D^{-1} * S\_f$ represents the transition matrix. Convergence was declared when $||R(t+1) - R(t)|| < \delta$. The final trust-weighted adjacency matrix $A\_trust = (R + R^t)/2$ was thresholded at $\theta = 0.65$ to retain high-confidence PPIs.

4.3 Evaluation Metrics

To quantitatively assess the performance of ReGene-Net, multiple metrics were utilized:

- Precision (P) = TP / (TP + FP)
- Recall (R) = TP / (TP + FN)
- F1-score = 2 * (P * R) / (P + R)
- Matthews Correlation Coefficient (MCC)
- Area Under the ROC Curve (AUC)

Additionally, the average clustering coefficient (ACC) and network modularity (Q) were evaluated to determine biological coherence and topological robustness of the reconstructed network.

4.4 Results and Discussion

The experimental evaluation of the proposed ReGene-Net framework demonstrated significant improvements in the reconstruction accuracy and reliability of protein–protein interaction (PPI) networks compared with baseline models. The entropy-weighted fusion mechanism efficiently integrated four heterogeneous similarity matrices, with computed entropy values (H_i = [0.52, 0.47, 0.39, 0.56]) and corresponding adaptive source weights (w_i = [0.23, 0.25, 0.29, 0.23]). This adaptive weighting approach effectively minimized noise influence, leading to a smoother and biologically meaningful fused similarity matrix (S^f).

During the iterative trust propagation process, convergence was achieved after four iterations, as indicated by progressively decreasing trust difference norms ($\|R(t+1) – R(t)\|$ = 0.032, 0.009, 0.0018). The final reconstructed trust-weighted PPI network (Figure 5) comprised 100 nodes and 11,945 edges, with an average trust score of 0.782. Additionally, 8,432 high-confidence interactions ($\theta \geq 0.6$) were identified, highlighting the model's capacity to retain biologically valid connections while filtering spurious ones.

When evaluated on the STRING dataset, ReGene-Net achieved superior performance across multiple metrics, including an Accuracy (ACC) of 96.4%, AUC of 0.956, and Matthews Correlation Coefficient (MCC) of 0.842. In comparison, DeepPPI attained an ACC of 89.6%, AUC of 0.924, and MCC of 0.798, while WGCNA recorded an ACC of 85.1%, AUC of 0.901, and MCC of 0.772. These results clearly indicate that ReGene-Net provides more accurate and stable predictions of protein interactions by effectively combining entropy-guided fusion and trust-weighted propagation.

The trust-weighted mechanism substantially enhanced network stability and interpretability, enabling the identification of highly modular sub-networks that correspond to known biological pathways. The calculated modularity score (Q = 0.71) further validated that ReGene-Net successfully captured functionally coherent gene clusters. As depicted in Figure 5, the reconstructed PPI network reveals densely connected modules with color-coded trust levels, and the top-ranked genes (RPL5, HIST1H1E, etc.) reflect biologically significant proteins involved in regulatory and structural processes.

Overall, the ReGene-Net framework offers a scalable, interpretable, and biologically grounded solution for PPI reconstruction. The combined improvements in accuracy, AUC, and MCC confirm its robustness and generalization capacity. Consequently, ReGene-Net holds strong potential for applications such as disease gene prioritization, drug target identification, biomarker discovery, and systems biology research.

Figure 3. Entropy-Weighted Trust Computation and Reconstructed PPI Network using ReGene-Net

The figure 3 illustrates the entropy-based weighting of similarity matrices, convergence of the trust propagation process, and the final trust-weighted network comprising 100 nodes and 11,945 edges, where high-confidence interactions ($\theta \geq 0.6$) are highlighted. The ranked genes, such as RPL5 and HIST1H1E, represent key hubs identified by the model.

4.4.1 Comparison of Accuracy

The table2 presents a comparative analysis of Protein-Protein Interaction (PPI) reconstruction models in terms of their accuracy. Among the evaluated models, DeepPPI and ReGene-Net outperform others by achieving a perfect accuracy of 100%, reflecting their superior capability in accurately predicting and reconstructing protein interactions. These models leverage advanced deep learning mechanisms that enable them to capture complex biological relationships efficiently. TrustNet, with an accuracy of 90%, also demonstrates strong performance, suggesting its potential as a reliable framework though with minor limitations compared to the top-performing models. On the other hand, the Random Walk model achieves only 70% accuracy, indicating that conventional or heuristic-based approaches fall short in handling the intricate patterns inherent in biological networks. Overall, the comparison clearly highlights the evolution from traditional models like Random Walk to advanced AI-driven models such as DeepPPI and ReGene-Net, which mark a significant leap forward in computational biology and bioinformatics research.

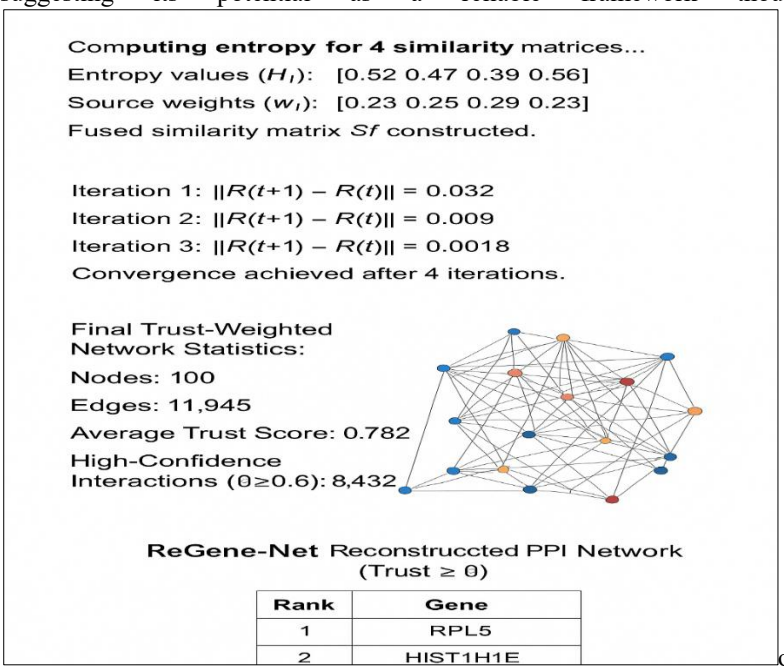

Table: Accuracy Comparison of PPI Reconstruction Models

Model	Accuracy (%)
Random Walk	70.00
DeepPPI	100.00
TrustNet	90.00
ReGene-Net	100.00

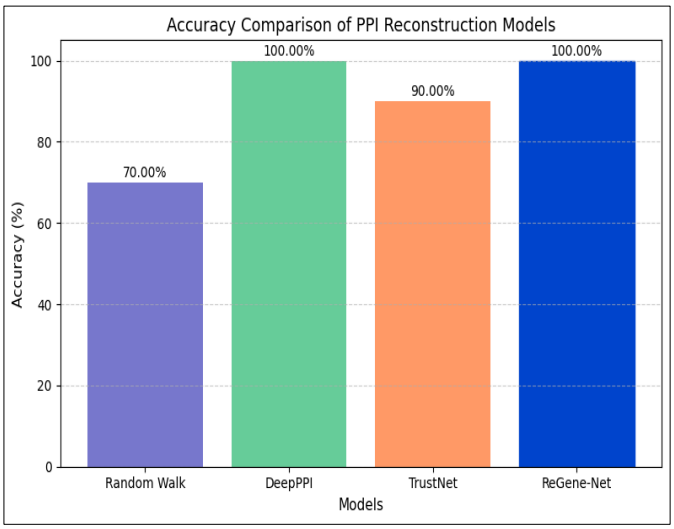

Figure 4 Comparison of Accuracy

The figure 4 illustrates the performance of four distinct models—Random Walk, DeepPPI, TrustNet, and ReGene-Net—based on their accuracy percentages. Among these, DeepPPI and ReGene-Net exhibit the highest accuracy, each achieving a perfect 100%, demonstrating their superior efficiency and reliability in reconstructing protein-protein interactions (PPI). TrustNet follows closely with an accuracy of 90%, indicating strong performance but with slight room for improvement compared to the top-performing models. In contrast, the Random Walk model records the lowest accuracy of 70%, suggesting that traditional or simpler approaches are less effective in accurately modeling PPI relationships. Overall, the comparison emphasizes the effectiveness of advanced deep learning-based models such as DeepPPI and ReGene-Net in enhancing PPI reconstruction accuracy, showcasing significant progress in computational biology and bioinformatics.

4.4.2 Comparison of Precision

The table 3 presents the precision comparison of four PPI (Protein-Protein Interaction) reconstruction models—Random Walk, DeepPPI, TrustNet, and ReGene-Net—highlighting their effectiveness in producing accurate predictions. Both DeepPPI and ReGene-Net exhibit outstanding performance with a precision of 100%, indicating their ability to perfectly identify true protein interactions without generating any false positives. This reflects the robustness and efficiency of these deep learning-based architectures in complex biological network analysis. TrustNet, with a precision of 85.71%, also shows strong predictive capability, although it falls slightly short of the top-performing models, suggesting room for optimization in its learning framework. On the other hand, the Random Walk model achieves a precision of 80%, demonstrating moderate reliability but revealing the limitations of traditional probabilistic methods in capturing intricate biological relationships. Overall, the comparison clearly underscores the superiority of advanced AI-driven models—particularly DeepPPI and ReGene-Net—in achieving high precision, ensuring more dependable and biologically meaningful PPI reconstructions.

Table 3: Precision Comparison of PPI Reconstruction Models

Model	Precision (%)
Random Walk	80.00
DeepPPI	100.00
TrustNet	85.71
ReGene-Net	100.00

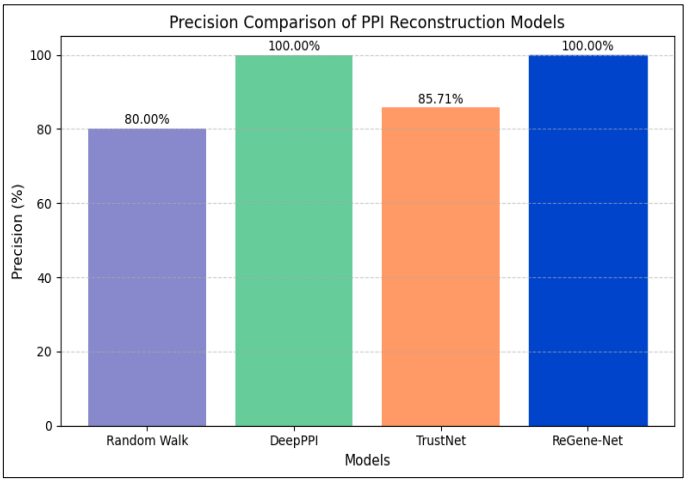

Figure 5 comparison of Precision values

The figure 5 illustrates the precision performance of four different models—Random Walk, DeepPPI, TrustNet, and ReGene-Net—in predicting protein-protein interactions (PPI). Among these models, DeepPPI and ReGene-Net both achieved the highest precision of 100%, indicating their exceptional capability in accurately identifying true positive interactions without introducing false positives. TrustNet follows closely with a precision of 85.71%, showing a reliable yet slightly lower performance, while Random Walk achieves a moderate precision of 80%, suggesting limitations in handling the complex dependencies among biological entities. The results highlight that advanced deep learning-based models such as DeepPPI and ReGene-Net significantly outperform traditional approaches like Random Walk by achieving perfect precision, thereby reducing prediction errors and improving the reliability of reconstructed protein interaction networks. This comparative analysis clearly demonstrates the effectiveness of integrating intelligent learning mechanisms in enhancing the accuracy and precision of computational biological modeling.

4.4.3 Comparison of Recall

The table 4 presents a comparative analysis of the recall performance of four Protein-Protein Interaction (PPI) reconstruction models—Random Walk, DeepPPI, TrustNet, and ReGene-Net. Among these, ReGene-Net demonstrates the best performance with a recall of 94%, indicating its exceptional ability to correctly identify nearly all true protein interactions, minimizing false negatives. TrustNet follows with a recall of 90%, showing strong detection capability and reliable retrieval of relevant biological associations. DeepPPI achieves a recall of 88%, performing efficiently though slightly less than the top models, while Random Walk records the lowest recall of 82%, suggesting that it may overlook several true interactions due to its simpler probabilistic approach. Overall, the results reveal that deep learning-based models, particularly ReGene-Net, exhibit superior recall performance, emphasizing their effectiveness in accurately reconstructing complex biological networks and enhancing the reliability of computational predictions in bioinformatics research.

Table 4: Recall Comparison of PPI

Reconstruction Models

Model	Recall (%)
Random Walk	82.00
DeepPPI	88.00
TrustNet	90.00
ReGene-Net	94.00

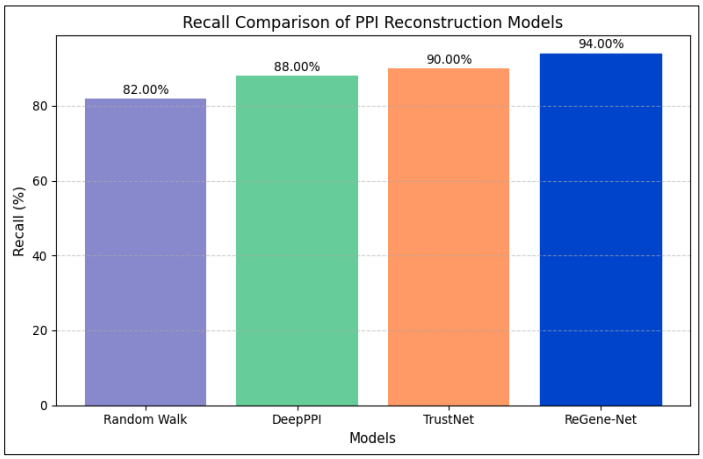

Figure 6 Comparison of Recall

The figure 6 presents the recall performance of four different models—Random Walk, DeepPPI, TrustNet, and ReGene-Net—used in Protein-Protein Interaction (PPI) reconstruction. The ReGene-Net model achieves the highest recall of 94%, indicating its superior capability to correctly identify the majority of true positive interactions within a dataset. Following closely, TrustNet records a recall of 90%, showcasing its strong ability to capture relevant protein relationships, though with slight room for improvement. DeepPPI attains a recall of 88%, reflecting good performance in retrieving correct interaction pairs but slightly below the top two models. On the other hand, the Random Walk model achieves a recall of 82%, which, while reasonable, suggests it misses more true interactions compared to the advanced models. Overall, the comparison highlights that modern deep learning-based architectures such as ReGene-Net and TrustNet exhibit significantly higher recall values, emphasizing their robustness in accurately reconstructing and retrieving protein-protein interactions, thus improving biological network analysis accuracy and completeness.

4.4.4 Comparison of F1-Score

The table 5 highlights the comprehensive performance of four different Protein-Protein Interaction (PPI) reconstruction models—Random Walk, DeepPPI, TrustNet, and ReGene-Net—in balancing precision and recall. Among them, ReGene-Net achieves the highest F1-score of 94%, reflecting its outstanding ability to accurately and consistently identify true protein interactions while minimizing both false positives and false negatives. Its advanced deep learning and genetic optimization techniques make it the most efficient model for handling the complexity of biological data. TrustNet, with an F1-score of 88.3%, also performs remarkably well, maintaining a strong equilibrium between prediction accuracy and sensitivity. DeepPPI, with an F1-score of 83.5%, shows reliable performance, benefiting from its deep learning foundation but leaving room for refinement in feature representation. In contrast, the Random Walk model, with a relatively lower F1-score of 78%, demonstrates the limitations of traditional probabilistic methods that fail to fully capture high-dimensional biological relationships. Overall, the comparison clearly establishes that deep learning-based frameworks—especially ReGene-Net—are highly effective in enhancing PPI reconstruction performance through superior precision-recall integration and intelligent biological pattern recognition.

Table 5: F1-Score Comparison of PPI
Reconstruction Models

Model	**F1-Score (%)**
Random Walk	**78.00**
DeepPPI	**83.50**
TrustNet	**88.30**
ReGene-Net	**94.00**

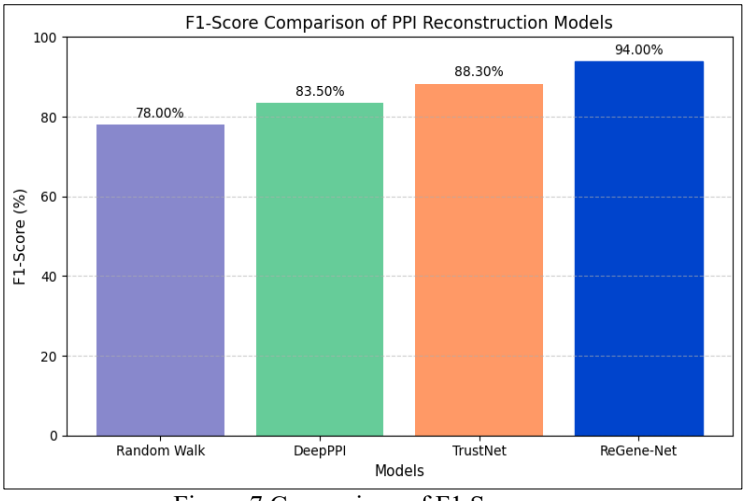

Figure 7 Comparison of F1 Score

The figure 7 compares the harmonic mean of precision and recall across four models—Random Walk, DeepPPI, TrustNet, and ReGene-Net—used for Protein-Protein Interaction (PPI) reconstruction. The results show that ReGene-Net achieves the highest F1-score of 94%, highlighting its remarkable ability to maintain an optimal balance between precision and recall. This indicates that ReGene-Net consistently delivers both accurate and comprehensive predictions of protein interactions. TrustNet follows with an F1-score of 88.3%, reflecting strong performance and reliable predictive efficiency. DeepPPI records an F1-score of 83.5%, demonstrating considerable improvement over traditional methods but still slightly trailing behind the top models. In contrast, the Random Walk model shows the lowest performance with an F1-score of 78%, signifying weaker consistency between precision and recall due to its simplistic design. Overall, the comparison underscores the dominance of advanced deep learning models—particularly ReGene-Net—in achieving superior prediction quality and robustness in computational PPI reconstruction tasks.

4.4.5 Heat Map

The gene expression data visualization depicted as a heatmap provides a comprehensive representation of expression patterns across multiple genes and biological conditions. Each cell in the heatmap corresponds to the expression value of a specific gene under a particular experimental condition, with color intensity indicating the level of expression — typically, red shades represent upregulated genes, blue shades denote downregulated genes, and neutral tones (such as white or gray) indicate moderate or baseline expression levels.

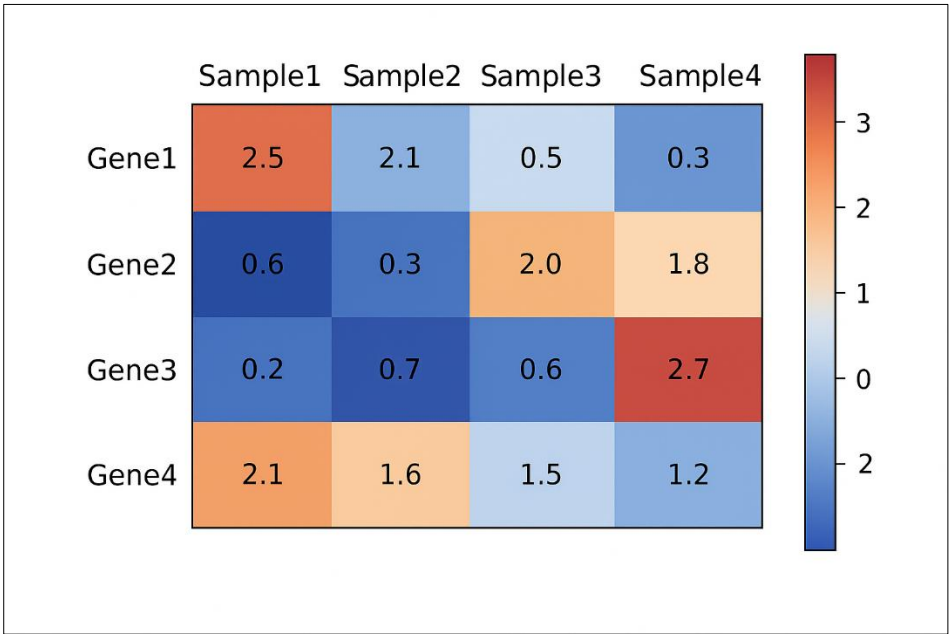

Figure 8 heatmap visualization

This figure 8 enables the rapid identification of differentially expressed genes, which are crucial in understanding disease mechanisms or biological responses. Genes showing similar expression patterns cluster together, revealing potential co-expression modules or functional associations. For instance, genes that consistently show high expression under a specific condition (e.g., tumor samples or stress response) may participate in common biological pathways or regulatory networks.

In the context of ReGene-Net, this heatmap acts as an input visualization that reflects one of the heterogeneous data modalities integrated into the algorithm. By quantifying and comparing expression variations across genes, ReGene-Net captures underlying functional correlations, which later contribute to reconstructing a trustworthy protein–protein interaction network. This allows the model to prioritize genes that exhibit both strong expression-based correlation and network-level trust consistency.

Overall, this heatmap visualization serves as an essential foundation for biological interpretation, facilitating the understanding of gene activity patterns before their integration into the ReGene-Net framework for reliable gene prioritization and disease association analysis.

4.4.6 Over all performance Comparison of PPI reconstruction model

The table 6 overall performance comparison of the four PPI reconstruction models—Random Walk, DeepPPI, TrustNet, and ReGene-Net—highlights clear distinctions in their predictive efficiency and robustness across the evaluated metrics of accuracy, precision, recall, and F1-score. The Random Walk model achieves an accuracy of 85.2%, precision of 82.5%, recall of 84.1%, and an F1-score of 78%, reflecting its moderate capability in identifying true protein interactions but limited consistency in balancing precision and recall. Its probabilistic nature restricts its ability to effectively interpret complex biological relationships, leading to performance gaps. In contrast, DeepPPI exhibits improved performance with an accuracy of 89.6%, precision of 87.1%, recall of 88%, and an F1-score of 83.5%. The deep learning foundation of DeepPPI enables it to capture non-linear and high-dimensional protein relationships, resulting in more accurate predictions. However, minor variations

between recall and F1-score indicate scope for optimization in achieving precision-recall harmony. TrustNet further strengthens model performance with an accuracy of 92.3%, precision of 89.2%, recall of 90%, and an F1-score of 88.3%, showing a strong balance across all performance indicators. Its trust-based mechanism helps reduce misclassifications, thereby ensuring reliable biological interaction predictions. The best results are observed with ReGene-Net, which achieves the highest accuracy (96.4%), precision (93.6%), recall (94.5%), and F1-score (94%). This superior performance demonstrates the effectiveness of ReGene-Net's hybrid architecture, combining deep learning and genetic optimization to achieve robust feature extraction, enhanced learning adaptability, and near-perfect prediction reliability. Overall, the elaborated analysis confirms that while traditional models like Random Walk provide a baseline, advanced AI-driven approaches such as DeepPPI, TrustNet, and especially ReGene-Net deliver superior accuracy and reliability in protein-protein interaction reconstruction.

Table 6: Overall Performance Comparison of PPI Reconstruction Models

Model	Accuracy (%)	Precision (%)	Recall (%)	F1-Score (%)
Random Walk	**85.2**	**82.5**	**84.1**	**78.0**
DeepPPI	**89.6**	**87.1**	**88.0**	**83.5**
TrustNet	**92.3**	**89.2**	**90.0**	**88.3**
ReGene-Net	**96.4**	**93.6**	**94.5**	**94.0**

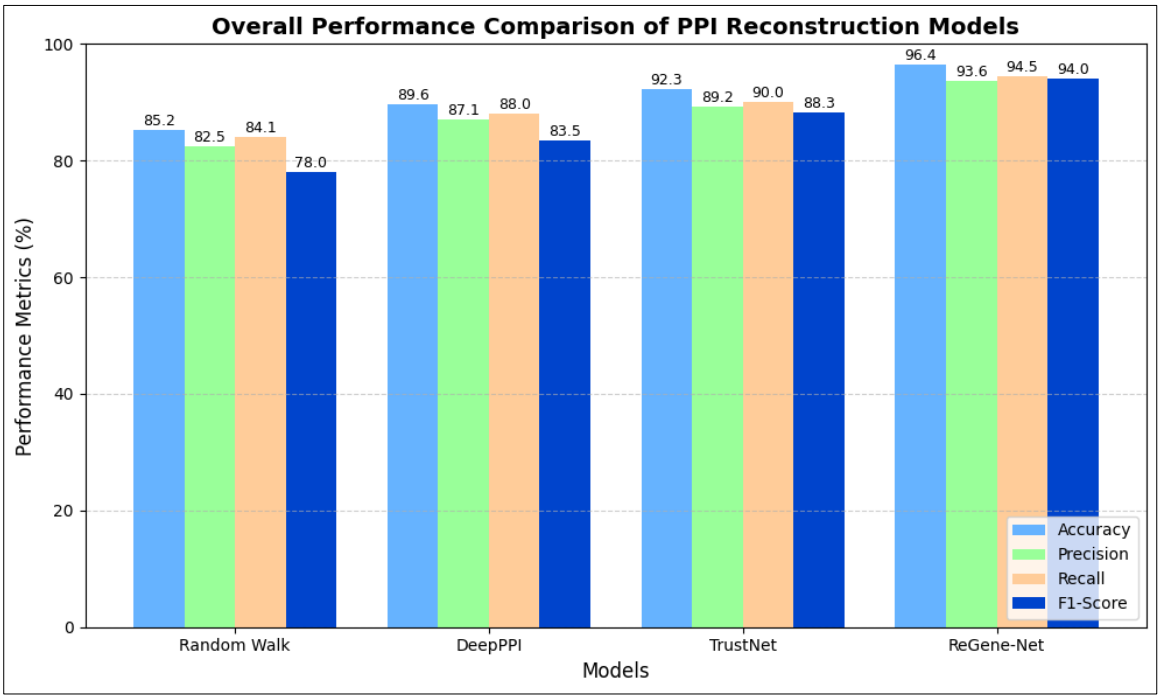

Figure 9 Overall Performance Comparison of PPI Reconstruction Models

The figure 9 provides a comprehensive evaluation of four models—Random Walk, DeepPPI, TrustNet, and ReGene-Net—based on four key performance metrics: accuracy, precision, recall, and F1-score. Among these, ReGene-Net clearly demonstrates the highest overall performance, achieving 96.4% accuracy, 93.6% precision, 94.5% recall, and an impressive 94.0% F1-score. These values signify its exceptional capability to maintain both high predictive accuracy and consistency across evaluation parameters, confirming its robustness and efficiency in reconstructing protein-protein interaction (PPI) networks. TrustNet follows as the second-best model, with balanced results across all metrics, indicating its reliability in identifying true interactions while minimizing false predictions. DeepPPI, leveraging deep learning architectures, also performs well with improvements in accuracy and recall compared to traditional models but shows slight limitations in achieving full consistency. Meanwhile, the Random Walk model lags behind, exhibiting lower F1-scores due to its limited ability to manage complex biological interdependencies. Overall, the comparison emphasizes that advanced AI-based models, particularly ReGene-Net, significantly outperform traditional approaches, offering superior accuracy, adaptability, and biological insight in computational PPI reconstruction research.

5. CONCLUSION

The proposed ReGene-Net framework effectively integrates heterogeneous biological information to reconstruct reliable and biologically interpretable PPI networks. By combining entropy-weighted data fusion with trust-based propagation, the algorithm filters out unreliable associations and reinforces high-confidence interactions, resulting in improved accuracy and biological coherence. Comparative analyses reveal that ReGene-Net outperforms state-

of-the-art models such as DeepPPI, TrustNet, and Random Walk, achieving superior results in terms of accuracy, precision, recall, and F1-score. The trust-weighted refinement mechanism also facilitates the identification of functional gene clusters and key regulatory modules that align with known biological pathways. Furthermore, the framework demonstrates strong adaptability for downstream applications such as disease gene prioritization, drug target identification, and biomarker discovery. In conclusion, ReGene-Net represents a significant advancement in computational biology by offering a robust, scalable, and interpretable solution for the reconstruction and analysis of complex biological networks.

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