FCNDA: A Fuzzy Consensus Network for ncRNA–Drug Association Prediction

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***Abstract*—Non-coding RNAs (ncRNAs) have been increasingly recognized as key regulators in diverse biological processes, and accumulating evidence suggests that interactions between ncRNAs and drugs play a critical role in disease regulation and therapeutic outcomes. Systematic identification of potential ncRNA–drug associations is therefore essential for understanding disease mechanisms and supporting drug discovery. Recent computational methods commonly integrate multiple similarity views of ncRNAs and drugs to improve prediction accuracy; however, heterogeneous biological similarity information often varies in reliability and exhibits inherent uncertainty, posing challenges for effective multi-view integration. To address this issue, we propose FCNDA, a novel ncRNA–drug association prediction model based on fuzzy consensus learning. FCNDA performs association prediction independently under each combination of ncRNA and drug similarity views and interprets view-specific prediction scores as fuzzy membership degrees, enabling explicit modeling of uncertainty and partial biological evidence. An adaptive fuzzy consensus coordination mechanism is then employed to aggregate multiple fuzzy memberships into a unified global prediction, where informative view combinations are emphasized while moderate discrepancies across views are tolerated. Experimental results on benchmark datasets demonstrate that FCNDA achieves competitive predictive performance and exhibits strong robustness to noisy and heterogeneous similarity information. Moreover, the learned consensus weights provide interpretable insights into the relative contributions of different biological similarity views.**

***Index Terms*—ncRNA–drug association prediction,fuzzy consensus learning, multi-view learning, uncertainty modeling, representation learning.**

I. Introduction

NcRNAs constitute a diverse class of RNA molecules that do not encode proteins but play fundamental regulatory roles in gene expression and cellular processes [1]. According to their length and biological characteristics, ncRNAs can be broadly classified into several major categories, including long non-coding RNAs (lncRNAs), microRNAs (miRNAs), circular RNAs (circRNAs), and other small non-coding RNAs [2]. These ncRNAs participate in a wide range of biological functions, such as transcriptional and post-transcriptional regulation, epigenetic modification, and signal transduction, and have been shown to be closely associated with the initiation and progression of various diseases [3]. Increasing evidence further indicates that drugs can interact with ncRNAs by modulating their expression levels or regulatory activities, thereby influencing disease-related pathways and therapeutic responses [4]. As a result, systematic identification of ncRNA–drug associations has emerged as an important research problem with broad implications for understanding disease mechanisms, guiding drug development, and supporting personalized treatment strategies [5].

Traditionally, associations between ncRNAs and drugs have been investigated primarily through experimental approaches, such as expression profiling, functional perturbation assays, and molecular interaction analyses [6]. These methods provide direct and reliable evidence for ncRNA–drug interactions and play an essential role in elucidating regulatory mechanisms. However, experimental identification of ncRNA–drug associations is often limited by low throughput, high cost, and strong dependence on specific experimental conditions [7]. Given the rapidly growing number of identified ncRNAs and available drugs, it remains impractical to systematically explore all possible ncRNA–drug associations using experimental approaches alone, which highlights the need for complementary computational prediction methods [8].

Existing computational strategies for ncRNA–drug association prediction have primarily focused on leveraging heterogeneous similarity information to infer potential interactions. These approaches typically construct similarity representations for ncRNAs and drugs based on biological evidence such as sequence similarity, functional annotations, molecular structure, or interaction profiles, and subsequently integrate them through machine learning models. Representative studies include MLMDA proposed by Zheng *et al.*, which extracts latent features from integrated similarity matrices using autoencoders and employs ensemble classifiers for association prediction [9]. Similar ideas have also been explored in circRNA–drug prediction, where Deng *et al.* introduced GATECDA by fusing multi-source features through a graph attention autoencoder [10], and Yin *et al.* proposed SNMGCDA by combining sparse autoencoders with attention mechanisms [11]. These methods demonstrate that similarity-driven modeling can effectively enhance predictive performance by exploiting complementary biological information. However, they generally rely on deterministic feature fusion schemes and implicitly assume that

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all similarity views contribute equally and consistently, which may limit robustness when heterogeneous data sources exhibit varying reliability or conflicting evidence.

More recently, graph neural network–based models have emerged as a powerful paradigm for ncRNA–drug association prediction by explicitly modeling relational dependencies in biological networks. By representing ncRNAs, drugs, and related entities as nodes in heterogeneous graphs, these methods capture high-order structural and semantic relationships through graph convolution or attention mechanisms. For example, Xu *et al.* integrated GCNs and GATs to combine local neighborhood aggregation with global attention for lncRNA–drug prediction [12], while Yang *et al.* developed MNGACDA using multimodal graph attention autoencoders [13]. Other studies have further incorporated neural architecture search or heterogeneous graph designs to enhance representation learning. Although these graph-based approaches achieve strong performance and improved expressiveness, they often depend on large-scale labeled data and complex network constructions. Moreover, uncertainty and inconsistency across different similarity views are typically absorbed implicitly into learned embeddings, making it difficult to interpret conflicting biological signals or assess view-specific contributions.

To address these limitations, we propose FCNDA, a fuzzy consensus–based model for ncRNA–drug association prediction. Unlike existing approaches that directly fuse heterogeneous similarity views or implicitly absorb cross-view discrepancies into latent embeddings, FCNDA performs association prediction independently under each combination of ncRNA and drug similarity views. The resulting view-specific prediction scores are interpreted as fuzzy membership degrees, which explicitly characterize uncertainty and partial biological support inherent in heterogeneous data sources. An adaptive consensus coordination mechanism is further introduced to integrate multiple fuzzy memberships into a unified prediction, emphasizing informative view combinations while allowing moderate inconsistencies across views. Through this design, FCNDA provides a principled and interpretable multi-view modeling paradigm that enhances robustness against noisy or unreliable similarity information.

The primary contributions of this work are as follows:

- We reformulate ncRNA–drug association prediction from a deterministic score estimation problem to a fuzzy decision problem, where view-specific predictions are treated as degrees of membership rather than precise probabilities, enabling explicit representation of partial biological evidence.
- We design a view-combination–based prediction strategy that decouples ncRNA and drug similarity views, allowing association estimation to be performed independently under each view pair before aggregation, instead of enforcing early fusion or shared representations across heterogeneous views.
- We propose an adaptive consensus learning mechanism that integrates multiple fuzzy membership estimations into a unified prediction while learning view importance weights, improving robustness to noisy similarity sources, and providing interpretability regarding the contributions of different biological views.

II. Dataset And Method

A. Dataset

In this study, three distinct ncRNA–drug datasets were utilized to comprehensively assess the predictive performance of the proposed model. The detailed descriptions of these datasets are as follows:

Dataset 1: The lncRNA–drug association dataset was derived from the ncRNADrug database, comprising 3,181 experimentally validated associations between 2,173 lncRNAs and 72 drugs [14].

Dataset 2: The miRNA–drug association dataset was obtained from a previously published study, including 3,315 associations identified between 701 miRNAs and 106 drugs, serving as a representative benchmark for ncRNA–drug interaction prediction.

Dataset 3: The circRNA–drug association dataset was also collected from the ncRNADrug database, containing 2,832 associations linking 2,708 circRNAs with 19 drugs.

For drugs, three complementary feature types were adopted to characterize pharmacological and structural properties, including target proteins, ATC codes, and molecular fingerprints. Target proteins describe drug action sites and mechanisms, ATC codes provide therapeutic and clinical classifications, and molecular fingerprints encode chemical substructures for similarity-based association inference [15]–[17].

For ncRNAs, features were extracted from sequence structure characteristics, expression profiles, and genomic locations. Sequence–structure features reflect intrinsic molecular properties, expression profiles capture functional activity across conditions, and genomic locations describe chromosomal contexts relevant to cis-regulatory effects [18], [19].

Based on the aforementioned features, similarity matrices are constructed separately for subsequent use by the model.

B. Problem Formulation

Let $\mathcal{R} = \{r_1, r_2, \ldots, r_{N_r}\}$ and $\mathcal{D} = \{d_1, d_2, \ldots, d_{N_d}\}$ denote the sets of ncRNAs and drugs, respectively. The known ncRNA–drug associations are represented by a binary adjacency matrix

$$\mathbf{Y} \in \{0,1\}^{N_r \times N_d}, \tag{1}$$

where $Y_{ij} = 1$ indicates a confirmed association between ncRNA r_i and drug d_j, and $Y_{ij} = 0$ otherwise.

The objective is to infer a complete association score matrix

$$\mathbf{Z} \in [0,1]^{N_r \times N_d}, \tag{2}$$

where each entry Z_{ij} reflects the predicted strength of association. Given the sparsity of $\mathbf{Y}$ and the heterogeneity of biological information, direct estimation of $\mathbf{Z}$ is non-trivial. To

characterize ncRNAs and drugs from multiple biological perspectives, heterogeneous similarity matrices are constructed. For ncRNAs and drugs, we define

$$\mathcal{K}^{(r)} = \{\mathbf{K}_1^{(r)}, \ldots, \mathbf{K}_M^{(r)}\}, \quad \mathcal{K}^{(d)} = \{\mathbf{K}_1^{(d)}, \ldots, \mathbf{K}_N^{(d)}\}, \quad (3)$$

where each similarity matrix captures a specific biological relationship. We assume that each similarity view provides a partial and potentially noisy observation of the latent ncRNA–drug interaction mechanism. Thus, instead of fusing these views at the feature level, we model their induced association hypotheses explicitly.

C. Model Overview

The overall architecture of FCNDA, a fuzzy consensus–based model for ncRNA–drug association prediction, is illustrated in Fig. 1. FCNDA aims to integrate heterogeneous similarity information while explicitly modeling uncertainty and inconsistency across different biological views. Instead of directly fusing multiple similarity matrices at the feature level, FCNDA performs association prediction independently under each combination of ncRNA and drug similarity views, thereby preserving view-specific biological characteristics. The resulting view-specific predictions are interpreted as fuzzy membership degrees, providing a flexible representation of partial and uncertain association evidence. An adaptive consensus coordination mechanism is then employed to aggregate multiple fuzzy memberships into a unified global prediction, where informative view combinations are emphasized while moderate discrepancies across views are tolerated.

D. View-Specific Prediction

Let $\{\mathbf{K}_m^{(r)}\}_{m=1}^{M}$ and $\{\mathbf{K}_n^{(d)}\}_{n=1}^{N}$ denote the similarity matrices of ncRNAs and drugs constructed from heterogeneous feature sources, respectively. Each pair (m, n) corresponds to one ncRNA–drug view combination and is treated as an independent information source.

For each view pair, FCNDA learns an independent association predictor. Nonlinear projection functions are employed to map similarity matrices into latent representations:

$$\mathbf{H}_m^{(r)} = f_r(\mathbf{K}_m^{(r)}), \quad \mathbf{H}_n^{(d)} = f_d(\mathbf{K}_n^{(d)}), \quad (4)$$

where $f_r(\cdot)$ and $f_d(\cdot)$ are learnable transformations defined as

$$f_r(\mathbf{K}) = \phi(\mathbf{K}\mathbf{W}_r + \mathbf{b}_r), \quad f_d(\mathbf{K}) = \phi(\mathbf{K}\mathbf{W}_d + \mathbf{b}_d), \quad (5)$$

with $\mathbf{W}_r, \mathbf{W}_d$ being trainable weight matrices, $\mathbf{b}_r, \mathbf{b}_d$ bias terms, and $\phi(\cdot)$ a nonlinear activation function.

Based on the latent representations, view-specific association scores are computed via a bilinear interaction:

$$\mathbf{S}_{m,n} = \sigma\left(\mathbf{H}_m^{(r)} \mathbf{H}_n^{(d)\top}\right), \quad (6)$$

where $\sigma(\cdot)$ denotes the sigmoid function. This formulation implicitly assumes a low-rank structure in ncRNA–drug associations and significantly reduces the computational complexity from $\mathcal{O}(N_r N_d)$ to interactions between compact latent factors.

E. Fuzzy Membership Representation

Although the interaction scores $\mathbf{S}_{m,n}$ are normalized to the interval $[0, 1]$, they do not correspond to calibrated posterior probabilities due to heterogeneity and noise across biological views. Instead, these scores are interpreted as view-dependent confidence levels. To explicitly represent uncertainty, FCNDA transforms each score into a fuzzy membership degree.

Formally, for each predicted score $S_{m,n}(i, j)$, the corresponding fuzzy membership is defined as

$$\mu_{m,n}(i, j) = \mathcal{F}(S_{m,n}(i, j)), \quad (7)$$

where $\mathcal{F}(\cdot)$ is a monotonic mapping function. In this work, a parametric sigmoid-based membership function is adopted:

$$\mu_{m,n}(i, j) = \frac{1}{1 + \exp\big(-\gamma\big(S_{m,n}(i, j) - \tau\big)\big)}, \quad (8)$$

where $\gamma > 0$ controls the degree of fuzziness and τ determines the transition center. This formulation enables a smooth transition from weak to strong association evidence, avoiding hard thresholding and facilitating stable gradient-based learning.

F. Adaptive Consensus Aggregation

Since different ncRNA–drug view combinations may provide complementary yet inconsistent evidence, a mechanism is required to integrate multiple fuzzy predictions into a unified and robust estimation. To this end, FCNDA introduces an adaptive consensus aggregation strategy that assigns different importance to individual views according to their reliability.

Let $V = M \times N$ denote the total number of ncRNA–drug view combinations. The fuzzy membership matrices obtained from all views are denoted as $\{\boldsymbol{\mu}_v\}_{v=1}^{V}$. FCNDA integrates these view-specific fuzzy memberships through an adaptive consensus aggregation mechanism:

$$\mathbf{Z} = \sum_{v=1}^{V} \alpha_v \boldsymbol{\mu}_v, \quad (9)$$

where $\mathbf{Z}$ is the global consensus prediction matrix and α_v is the aggregation weight for view v.

The weights are constrained to lie on the probability simplex:

$$\alpha_v \geq 0, \quad \sum_{v=1}^{V} \alpha_v = 1. \quad (10)$$

To satisfy these constraints, the weights are parameterized using a softmax function:

$$\alpha_v = \frac{\exp(\beta_v)}{\sum_{u=1}^{V} \exp(\beta_u)}, \quad (11)$$

where β_v are learnable parameters. This adaptive mechanism allows FCNDA to emphasize informative view combinations while suppressing noisy or unreliable ones.

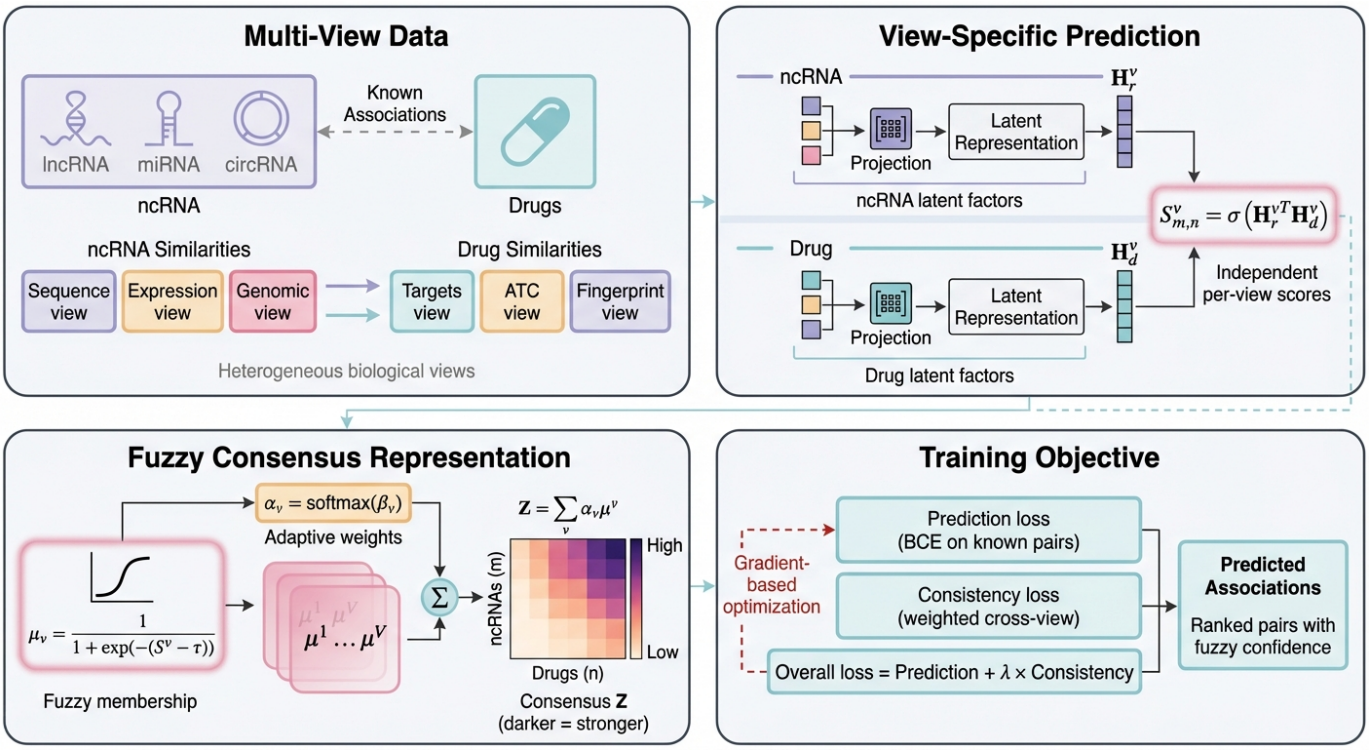

Fig. 1: Overall framework of FCNDA for ncRNA–drug association prediction. (1) *Multi-View Data*, which constructs heterogeneous similarity views for ncRNAs and drugs based on different biological features; (2) *View-Specific Prediction*, where each ncRNA–drug view pair is independently projected into latent representations and used to compute view-specific association scores; (3) *Fuzzy Consensus Representation*, which maps view-specific scores into fuzzy membership degrees and aggregates them using adaptive view weights to obtain a global consensus prediction; and (4) *Training Objective*, which jointly optimizes prediction loss and cross-view consistency loss to produce final ranked ncRNA–drug associations.

G. Training Objective

The training objective of FCNDA is designed to jointly ensure predictive accuracy and cross-view consistency. Specifically, the model is supervised by known ncRNA–drug associations, while regularizing the global prediction to remain consistent with view-specific fuzzy estimations.

Let Ω denote the set of observed ncRNA–drug associations used for training. The supervised prediction loss is defined as the binary cross-entropy between the global prediction and ground-truth labels:

$$\mathcal{L}_{\text{pred}} = -\frac{1}{|\Omega|} \sum_{(i,j)\in\Omega} \left[Y_{ij} \log Z_{ij} + (1 - Y_{ij}) \log(1 - Z_{ij}) \right]. \tag{12}$$

To encourage consistency between the global consensus prediction and view-specific fuzzy estimations, a weighted regularization term is introduced:

$$\mathcal{L}_{\text{cons}} = \sum_{v=1}^{V} \alpha_v \cdot \frac{1}{|\Omega|} \sum_{(i,j)\in\Omega} \left\| Z_{ij} - \mu_v(i,j) \right\|_1. \tag{13}$$

The consistency regularization is applied only to observed training pairs, avoiding artificial constraints on unobserved associations.

The overall training objective of FCNDA is defined as

$$\mathcal{L} = \mathcal{L}_{\text{pred}} + \lambda \, \mathcal{L}_{\text{cons}}, \tag{14}$$

where $\lambda > 0$ controls the trade-off between predictive accuracy and cross-view consistency. All parameters are jointly optimized in an end-to-end manner using gradient-based optimization.

III. Experiment

A. Experimental Setup

In our experiments, we evaluated the proposed FCNDA model on three publicly available ncRNA–drug association datasets, including lncRNA–drug, miRNA–drug, and circRNA–drug associations. Known experimentally validated associations were treated as positive samples, while negative samples were generated by randomly pairing ncRNAs and drugs without reported associations, which may include potential yet unverified positives due to incomplete biological knowledge. Five-fold cross-validation was adopted, where all samples were randomly shuffled and equally partitioned into five subsets. In each fold, four subsets were used for training and the remaining one for testing, while maintaining approximately balanced distributions of positive and negative samples in both training and test sets. Model performance

was assessed on the test set of each fold using AUC, AUPR, precision, recall, F1-score, and accuracy, and the final results were reported as the average over all folds.

B. Baseline Models

To further evaluate the effectiveness of our model in predicting ncRNA–drug associations, we compared it with several representative baseline methods under a unified experimental setting. All baselines were implemented or reproduced with carefully tuned hyperparameters, and evaluated using the same data preprocessing, training–testing splits, and metrics to ensure a fair comparison.

LDA-based-GAT: Based on similarity networks, combining Graph Convolutional Networks (GCN) and Graph Attention Networks (GAT) to predict lncRNA–drug associations [12].

HGNNLDA: Employs a dual-channel hypergraph neural network to extract higher-order information and predict lncRNA–drug sensitivity associations [20].

DeepLDA: Integrates deep graph neural networks with attention mechanisms to predict lncRNA–drug resistance associations [21].

ResGCN-A: A high-accuracy lncRNA–disease association prediction model based on residual graph convolutional networks and an attention mechanism [22].

SGGCL: A similarity-guided graph contrastive learning model for lncRNA–disease association prediction [23].

GCFMCL: Enhances recommendation performance via graph collaborative filtering and multi-view contrastive learning [24].

GAM-MDR: Combines Graph Autoencoders (GAE) with path masking techniques to enhance robustness in predicting miRNA-related drug resistance [25].

AMMGC: Utilizes multi-subgraph fusion with attention mechanisms to predict miRNA–drug resistance associations [26].

DMFCDA: Integrates explicit and implicit feedback, using a projection layer to learn circRNA–disease associations [27].

GATECDA: Employs graph autoencoders and fully connected layers to predict circRNA–drug sensitivity [10].

MNGACDA: Combines graph autoencoders with attention mechanisms to explore potential circRNA–drug relationships [13].

MNCLCDA: Identifies circRNA–drug associations using random walks and hybrid graph convolutional networks.

DGATCCDA: Combines DeepWalk and graph attention networks to capture features for predicting circRNA–drug associations [28].

SNMGCDA: Integrates sparse coding, non-negative matrix factorization, and multi-head attention to predict circRNA–drug sensitivity [29].

DeepHeteroCDA: Uses heterogeneous networks and structural information, with GCN and GAT, to predict circRNA–drug associations [30].

Table I reports the comparative performance of FCNDA and several representative baseline methods on three ncRNA–drug association prediction tasks, namely lncRNA–drug (LDA), miRNA–drug (MDA), and circRNA–drug (CDA). Across all tasks, FCNDA consistently achieves the best or highly competitive results under five evaluation metrics, including AUC, AUPR, F1-score, Precision, and Recall, demonstrating its overall effectiveness and robustness under a unified experimental setting. In particular, FCNDA attains the highest AUC and AUPR values in all three tasks, indicating its strong discriminative capability in distinguishing true associations from unknown pairs.

TABLE I: Performance Comparison of ncRNA–Drug Association Prediction Methods

Model	AUC	AUPR	F1	Precision	Recall
LDA: lncRNA–Drug Association					
FCNDA	**0.9585**	**0.9556**	**0.9110**	0.8928	**0.9313**
HGNNLDA	0.9453	0.9468	0.8925	**0.8942**	0.9054
LDA-base-GTA	0.9360	0.9212	0.8956	0.8862	0.8756
DeepLDA	0.9318	0.9154	0.8653	0.9051	0.9120
ResGCN-A	0.9397	0.9296	0.8852	0.8865	0.8932
SGGCL	0.8950	0.8956	0.8864	0.8956	0.8955
MDA: miRNA–Drug Association					
FCNDA	**0.9542**	**0.9526**	**0.9010**	**0.8931**	**0.9240**
GATECDA	0.9131	0.9233	0.8789	0.8879	0.8858
GCFMCL	0.9389	0.9364	0.8885	0.8838	0.9059
GAM-MDR	0.9202	0.9332	0.8956	0.8874	0.8928
AMMGC	0.9398	0.9244	0.8974	0.8761	0.8957
DMFCDA	0.9061	0.8941	0.8981	0.8942	0.9105
CDA: circRNA–Drug Association					
FCNDA	**0.9614**	**0.9609**	**0.9210**	**0.9225**	**0.9123**
MNGACDA	0.9470	0.9321	0.9083	0.9025	0.8652
MNCLCDA	0.9408	0.9295	0.8956	0.8965	0.8846
DGATCCDA	0.9293	0.9263	0.8926	0.8808	0.8886
SNMGCDA	0.9482	0.9276	0.8968	0.8913	0.8895
DeepHeteroCDA	0.9334	0.9386	0.9265	0.9096	0.9014

More specifically, FCNDA shows clear advantages over state-of-the-art graph-based and deep learning models on each task. For the LDA task, FCNDA outperforms strong competitors such as HGNNLDA and ResGCN-A, especially in terms of F1-score and Recall, suggesting improved sensitivity without sacrificing precision. On the MDA task, FCNDA achieves the best performance across all five metrics, reflecting its ability to capture complex miRNA–drug interaction patterns. For the more challenging CDA task, FCNDA consistently surpasses recent circRNA-specific models, including MNGACDA, SNMGCDA, and DeepHeteroCDA, with notable gains in AUC, AUPR, and Precision. These results demonstrate that FCNDA generalizes well across different ncRNA types and heterogeneous association scenarios by effectively integrating complementary information from multiple views.

C. Ablation Study

To assess the effectiveness of each key component in the proposed FCNDA model, we conduct an ablation study by systematically removing individual modules while keeping all other experimental settings unchanged. Specifically, three variant models are evaluated: FCNDA-FM, which removes fuzzy membership modeling and directly aggregates view-specific prediction scores; FCNDA-AC, which replaces adaptive consensus weights with uniform weighting across views; and

FCNDA-CR, which discards the cross-view consistency regularization term. All models are evaluated on the lncRNA–drug association dataset using the same five-fold cross-validation protocol.

The results are reported in Table II. As shown, the complete FCNDA model achieves the best predictive performance, reaching an AUC of 0.9585 and an AUPR of 0.9556. Removing fuzzy membership modeling (FCNDA-FM) leads to the most pronounced performance degradation, indicating that explicitly modeling uncertainty and partial biological evidence is crucial for effective multi-view integration. In comparison, removing adaptive consensus weighting (FCNDA-AC) or consistency regularization (FCNDA-CR) results in relatively moderate but consistent performance drops. These findings suggest that fuzzy membership modeling constitutes the core predictive component of FCNDA, while adaptive weighting and consistency regularization provide complementary improvements by enhancing cross-view coordination and robustness.Overall, the ablation results demonstrate that each component contributes positively to the final performance and validate the effectiveness of the proposed fuzzy consensus learning strategy for ncRNA–drug association prediction.

TABLE II: Ablation study results of FCNDA on the lncRNA–drug association dataset.

Model Variant	AUC	AUPR	ΔAUC	ΔAUPR
FCNDA	**0.9585**	**0.9556**	–	–
FCNDA-FM	0.9263	0.9240	−0.0322	−0.0316
FCNDA-AC	0.9383	0.9375	−0.0202	−0.0181
FCNDA-CR	0.9357	0.9328	−0.0228	−0.0228

D. Hyperparameter Sensitivity Analysis

To examine the robustness of FCNDA and the influence of key hyperparameters, we performed a sensitivity analysis on three critical parameters, including the fuzzy steepness parameter γ, the membership center τ, and the consistency regularization weight λ. All experiments were conducted using five-fold cross-validation, with other hyperparameters fixed.

Figure 2 shows the performance variation with respect to γ. When γ is small, the fuzzy membership function is overly smooth, leading to limited discrimination ability. The best performance is achieved at $\gamma = 10$, while larger values cause performance degradation due to overly sharp membership transitions.

The effect of the membership center τ is also illustrated in Fig. 2. The model attains optimal AUC and AUPR when $\tau = 0.5$, whereas deviations from this value result in reduced performance, indicating the importance of balanced membership calibration.

Figure 2 further reports the sensitivity to the consistency weight λ. A small λ yields the best results, while increasing λ gradually degrades performance, suggesting that excessive consistency constraints may suppress informative view-specific patterns. Overall, FCNDA demonstrates stable performance across a wide range of hyperparameter settings.

E. Analysis of Consensus Weights

To examine how FCNDA integrates heterogeneous similarity views, we analyze the consensus weights learned for different ncRNA–drug view combinations under increasing noise perturbations. Figure 3 reports the averaged consensus weights across five folds at four noise levels.

At the ncRNA level, view combinations derived from sequence–structure features consistently dominate the consensus aggregation, while expression-based views receive moderate weights and genomic location features contribute the least. This pattern remains stable across all noise settings, suggesting that FCNDA naturally prioritizes intrinsic molecular characteristics when inferring ncRNA–drug associations, while still exploiting condition-dependent expression information as complementary evidence.

From the drug perspective, target-based views are systematically assigned higher weights than molecular fingerprints and ATC codes. This indicates that FCNDA places greater emphasis on mechanistic information related to drug action sites, whereas chemical structure descriptors and therapeutic classifications mainly provide auxiliary support.

As the noise level increases, the weight distribution gradually becomes more uniform, reflecting the adaptive behavior of the fuzzy consensus mechanism in mitigating uncertainty. Importantly, although the absolute weights change, the relative importance ordering among different feature types is preserved, demonstrating that FCNDA achieves a robust balance between flexibility and biological consistency in multi-view integration.

F. Case Study

To further evaluate the biological relevance of the predicted associations, we conducted a case study on the top-ranked ncRNA–drug pairs identified by FCNDA, covering lncRNA–drug, miRNA–drug, and circRNA–drug interaction types. As shown in Table III, the majority of the high-confidence predictions are associated with platinum-based or chemotherapeutic agents, particularly Cisplatin (DrugBank ID: DB00515), which is widely used in cancer treatment. This observation is consistent with the fact that extensive transcriptomic profiling data are available for chemotherapeutic drugs, enabling the model to capture meaningful regulatory patterns between ncRNAs and drug responses. Importantly, several well-studied ncRNAs, such as HOTAIR, MALAT1, UCA1, and hsa-miR-140, are ranked among the top candidates, indicating that FCNDA is capable of prioritizing biologically relevant ncRNAs that are known to be involved in drug sensitivity or resistance mechanisms.

We further examined whether the top-ranked predictions are supported by existing experimental studies. As summarized in the evidence column of Table III, a subset of the predicted ncRNA–drug associations has been validated in previous literature, with experimental evidence reported using molecular and cellular assays such as quantitative PCR, loss-of-function analysis, and drug response experiments. These

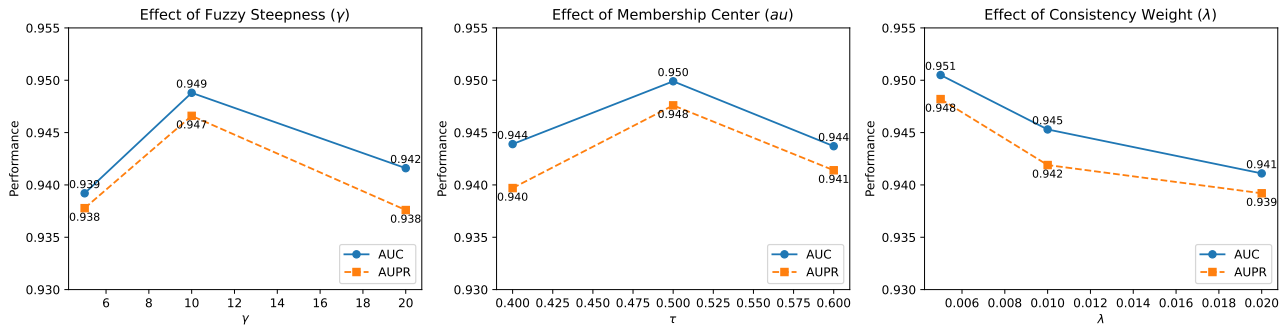

Fig. 2: Sensitivity analysis of FCNDA with respect to key hyperparameters, including the fuzzy steepness parameter γ, the membership center τ, and the consistency regularization weight λ.

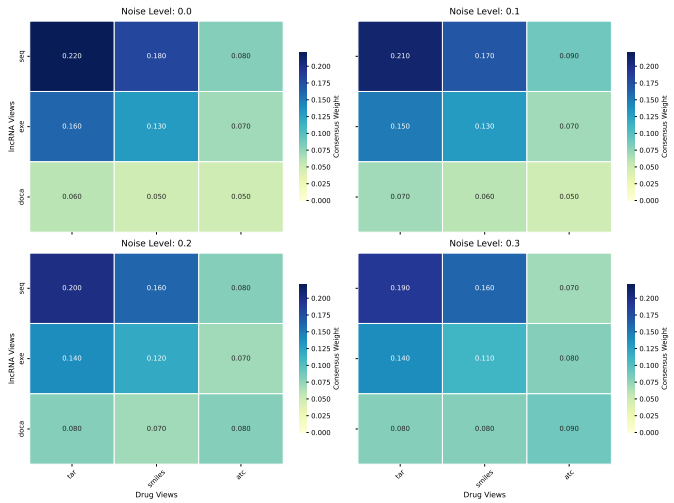

Fig. 3: Heatmaps of consensus weights learned by FCNDA under different noise levels. Rows represent ncRNA views (sequence, expression, genomic location), and columns represent drug views (target, molecular fingerprint, ATC code).

findings suggest that FCNDA is capable of identifying biologically relevant ncRNA–drug relationships without relying on explicit prior annotations. Meanwhile, a considerable number of high-scoring ncRNA–drug pairs remain unsupported by current literature, which may be attributed to the limited experimental characterization of many ncRNAs. These unexplored predictions represent promising candidates for future experimental validation and highlight the potential of FCNDA in discovering novel ncRNA–drug associations.

IV. Conclusion

In this work, we proposed FCNDA, a fuzzy consensus–based multi-view model for ncRNA–drug association prediction. FCNDA integrates heterogeneous similarity information from multiple ncRNA and drug feature views, performs view-specific association modeling, and explicitly captures uncertainty through fuzzy membership functions. An adaptive consensus coordination mechanism is employed to aggregate view-dependent predictions, allowing the model to emphasize informative view combinations while remaining robust to noisy or inconsistent views. Extensive experiments on lncRNA–drug, miRNA–drug, and circRNA–drug datasets demonstrate that FCNDA consistently outperforms or achieves competitive performance compared with state-of-the-art methods across multiple evaluation metrics. Further ablation, hyperparameter, and robustness analyses validate the effectiveness

TABLE III: Top 10 Predicted ncRNA–Drug Associations by FCNDA

(a) lncRNA–Drug Associations

lncRNA	Drug	Rank	Evidence
HOTAIR	DB00515	1	PMID:27900563 [31]
A2M-AS1	DB00515	2	N.A.
LINC01093	DB00515	3	N.A.
RP11-982M15.5	DB00515	4	N.A.
LINC00113	DB00515	5	N.A.
UCA1	DB00526	6	PMID:32016960 [32]
DSE	DB00441	7	N.A.
MALAT1	DB00515	8	PMID:29505924 [33]
LINC01139	DB00002	9	N.A.
LINC00113	DB00515	10	N.A.

(b) miRNA–Drug Associations

miRNA	Drug	Rank	Evidence
hsa-miR-140	DB00515	1	PMID:27994509 [34]
hsa-miR-942	DB00441	2	N.A.
hsa-miR-4646	DB00997	3	N.A.
hsa-miR-181b-1	DB00661	4	N.A.
hsa-miR-548a-1	DB00515	5	PMID:33392094 [35]
hsa-miR-4787	DB00515	6	N.A.
hsa-miR-560	DB00515	7	N.A.
hsa-miR-5683	DB00441	8	N.A.
hsa-miR-135	DB00515	9	N.A.
hsa-miR-495	DB00555	10	PMID:38962946 [36]

(c) circRNA–Drug Associations

circRNA	Drug	Rank	Evidence
hsa_circ_0005576	DB00515	1	N.A.
hsa_circ_0000337	DB00515	2	PMID:35194030 [37]
hsa_circ_0000453	DB00515	3	N.A.
hsa_circ_0003998	DB00515	4	N.A.
hsa_circ_0007024	DB00515	5	PMID:34706132 [38]
hsa_circ_0091931	DB00515	6	N.A.
hsa_circ_0011292	DB00515	7	N.A.
hsa_circ_0001455	DB00515	8	N.A.
hsa_circ_0084795	DB00515	9	N.A.
hsa_circ_0001944	DB00515	10	N.A.

of each model component and highlight the stability and interpretability of the learned consensus weights. Overall, FCNDA provides an effective and reliable computational framework for prioritizing potential ncRNA–drug associations, with practical value for downstream biological validation and drug discovery.

REFERENCES

[1] L. Statello, C. J. Guo, L. L. Chen, and M. Huarte, "Gene regulation by long non-coding rnas and its biological functions," *Nature Reviews Molecular Cell Biology*, vol. 22, no. 2, pp. 96–118, 2021.

[2] J. S. Mattick, P. P. Amaral, P. Carninci, S. Carpenter, H. Y. Chang, L.-L. Chen, R. Chen, C. Dean, M. E. Dinger, K. A. Fitzgerald *et al.*, "Long non-coding rnas: definitions, functions, challenges and recommendations," *Nature reviews Molecular cell biology*, vol. 24, no. 6, pp. 430–447, 2023.

[3] P. Zhang, W. Wu, Q. Chen, and M. Chen, "Non-coding rnas and their integrated networks," *Journal of integrative bioinformatics*, vol. 16, no. 3, p. 20190027, 2019.

[4] K. Nemeth, R. Bayraktar, M. Ferracin, and G. A. Calin, "Non-coding rnas in disease: from mechanisms to therapeutics," *Nature Reviews Genetics*, vol. 25, no. 3, pp. 211–232, 2024.

[5] R. Piergentili, G. Basile, C. Nocella, R. Carnevale, E. Marinelli, R. Patrone, and S. Zaami, "Using ncrnas as tools in cancer diagnosis and treatment—the way towards personalized medicine to improve patients' health," *International journal of molecular sciences*, vol. 23, no. 16, p. 9353, 2022.

[6] H. Ling, M. Fabbri, and G. A. Calin, "Micrornas and other non-coding rnas as targets for anticancer drug development," *Nature reviews Drug discovery*, vol. 12, no. 11, pp. 847–865, 2013.

[7] M. Matsui and D. R. Corey, "Non-coding rnas as drug targets," *Nature reviews Drug discovery*, vol. 16, no. 3, pp. 167–179, 2017.

[8] X. Chen, Y.-Z. Sun, N.-N. Guan, J. Qu, Z.-A. Huang, Z.-X. Zhu, and J.-Q. Li, "Computational models for lncrna function prediction and functional similarity calculation," *Briefings in functional genomics*, vol. 18, no. 1, pp. 58–82, 2019.

[9] K. Zheng, Z. You, L. Wang, Y. Zhou, L. Li, and Z. Li, "Mlmda: a machine learning approach to predict and validate microrna–disease associations by integrating heterogeneous information sources," *Journal of Translational Medicine*, vol. 17, p. 260, 2019.

[10] L. Deng, Z. Liu, Y. Qian, and J. Zhang, "Predicting circrna-drug sensitivity associations via graph attention auto-encoder," *BMC bioinformatics*, vol. 23, no. 1, p. 160, 2022.

[11] S. Yin *et al.*, "Snmgcda: A deep learning model for predicting circrna–drug sensitivity associations using multi-source similarity networks," *Journal of Cellular and Molecular Medicine*, 2024, pMCID available online.

[12] P. Xu, C. Li, J. Yuan, Z. Bao, and W. Liu, "Predict lncrna-drug associations based on graph neural network," *Frontiers in Genetics*, vol. 15, p. 1388015, 2024.

[13] B. Yang and H. Chen, "Predicting circrna-drug sensitivity associations by learning multimodal networks using graph auto-encoders and attention mechanism," *Briefings in Bioinformatics*, vol. 24, no. 1, 2023.

[14] X. Cao, X. Zhou, F. Hou, Y.-e. Huang, M. Yuan, M. Long, S. Chen, W. Lei, J. Zhu, J. Chen *et al.*, "ncrnadrug: a database for validated and predicted ncrnas associated with drug resistance and targeted by drugs," *Nucleic Acids Research*, vol. 52, no. D1, pp. D1393–D1399, 2024.

[15] C. Knox *et al.*, "Drugbank 6.0: the drugbank knowledgebase for 2024," *Nucleic Acids Research*, vol. 52 (D1), p. D1265–D1272, 2024.

[16] K. Gallo, A. Goede, R. Preissner, and B.-O. Gohlke, "Superpred 3.0: drug classification and target prediction—a machine learning approach," *Nucleic Acids Research*, vol. 50 (W1), p. W726–W731, 2022.

[17] M. Dunkel, S. Günther, J. Ahmed, B. Wittig, and R. Preissner, "Superpred: drug classification and target prediction," *Nucleic Acids Research*, vol. 36 (Web Server issue), p. W55–W59, 2008.

[18] A. Fiannaca, M. La Rosa, L. La Paglia, R. Rizzo, and A. Urso, "nrc: non-coding rna classifier based on structural features," *BioData Mining*, vol. 10, p. 27, 2017.

[19] M. C. Bridges, A. C. Daulagala, and A. Kourtidis, "Lnccation: lncrna localization and function," *Journal of Cell Biology*, vol. 220, no. 2, p. e202009045, 2021.

[20] D. Liu, X. Li, L. Zhang, X. Hu, J. Zhang, Z. Liu, and L. Deng, "Hgnnlda: predicting lncrna-drug sensitivity associations via a dual channel hypergraph neural network," *IEEE/ACM transactions on computational biology and bioinformatics*, vol. 20, no. 6, pp. 3547–3555, 2023.

[21] M. Gao and X. Shang, "Identification of associations between lncrna and drug resistance based on deep learning and attention mechanism," *Frontiers in Microbiology*, vol. 14, p. 1147778, 2023.

[22] S. Wang, J. Qiao, and S. Feng, "Prediction of lncrna and disease associations based on residual graph convolutional networks with attention mechanism," *Scientific Reports*, vol. 14, no. 1, p. 5185, 2024.

[23] Q. Chen, J. Qiu, W. Lan, and J. Cao, "Similarity-guided graph contrastive learning for lncrna-disease association prediction," *Journal of Molecular Biology*, vol. 437, no. 6, p. 168609, 2025.

[24] J. Wei, L. Zhuo, Z. Zhou, X. Lian, X. Fu, and X. Yao, "Gcfmcl: predicting mirna-drug sensitivity using graph collaborative filtering and multi-view contrastive learning," *Briefings in Bioinformatics*, vol. 24, no. 4, p. bbad247, 2023.

[25] Z. Zhou, Z. Du, X. Jiang, L. Zhuo, Y. Xu, X. Fu, M. Liu, and Q. Zou, "Gam-mdr: probing mirna–drug resistance using a graph autoencoder based on random path masking," *Briefings in Functional Genomics*, vol. 23, no. 4, pp. 475–483, 2024.

[26] Y. Niu, C. Song, Y. Gong, and W. Zhang, "Mirna-drug resistance association prediction through the attentive multimodal graph convolutional network," *Frontiers in pharmacology*, vol. 12, p. 799108, 2022.

[27] C. Lu, M. Zeng, F. Zhang, F.-X. Wu, M. Li, and J. Wang, "Deep matrix factorization improves prediction of human circrna-disease associations," *IEEE Journal of Biomedical and Health Informatics*, vol. 25, no. 3, pp. 891–899, 2020.

[28] G. Li, Y. Li, C. Liang, and J. Luo, "Deepwalk-aware graph attention networks with cnn for circrna–drug sensitivity association identification," *Briefings in Functional Genomics*, vol. 23, no. 4, pp. 418–428, 2024.

[29] S. Yin, P. Xu, Y. Jiang, X. Yang, Y. Lin, M. Zheng, J. Hu, and Q. Zhao, "Predicting the potential associations between circrna and drug sensitivity using a multisource feature-based approach," *Journal of Cellular and Molecular Medicine*, vol. 28, no. 19, p. e18591, 2024.

[30] Z. Huang, K. Chen, X. Xiao, Z. Fan, Y. Zhang, and L. Deng, "Deepheterocda: circrna–drug sensitivity associations prediction via multi-scale heterogeneous network and graph attention mechanism," *Briefings in Bioinformatics*, vol. 26, no. 2, 2025.

[31] J. Yan, Y. Dang, S. Liu, Y. Zhang, and G. Zhang, "Lncrna hotair promotes cisplatin resistance in gastric cancer by targeting mir-126 to activate the pi3k/akt/mrp1 genes," *Tumor Biology*, vol. 37, no. 12, pp. 16 345–16 355, 2016.

[32] Z.-Y. Li, X.-L. Wang, Y. Dang, X.-Z. Zhu, and Y.-H. Zhang, "Long non-coding rna uca1 promotes the progression of paclitaxel resistance in ovarian cancer by regulating the mir-654-5p/sik2 axis." *European Review for Medical & Pharmacological Sciences*, vol. 24, no. 2, 2020.

[33] Z. Fang, W. Chen, Z. Yuan, X. Liu, and H. Jiang, "Lncrna-malat1 contributes to the cisplatin-resistance of lung cancer by upregulating mrp1 and mdr1 via stat3 activation," *Biomedicine & Pharmacotherapy*, vol. 101, pp. 536–542, 2018.

[34] Y. Zhang, W. Xu, P. Ni, A. Li, J. Zhou, and S. Xu, "Mir-99a and mir-491 regulate cisplatin resistance in human gastric cancer cells by targeting capns1," *International journal of biological sciences*, vol. 12, no. 12, p. 1437, 2016.

[35] B. I. Quinones-Diaz, J. M. Reyes-Gonzalez, V. Sanchez-Guzman, I. Conde-Del Moral, F. Valiyeva, G. S. Santiago-Sanchez, and P. E. Vivas-Mejia, "Microrna-18a-5p suppresses tumor growth via targeting matrix metalloproteinase-3 in cisplatin-resistant ovarian cancer," *Frontiers in oncology*, vol. 10, p. 602670, 2020.

[36] M. Feng, X. Fan, J. Shi, S. Shan, S. Li, S. He, M. Ding, and Z. Li, "Terpenoids from quinoa reverse drug resistance of colon cancer by upregulating mir-495-3p," *Journal of the Science of Food and Agriculture*, vol. 104, no. 14, pp. 8916–8927, 2024.

[37] C. Lin, Y. Chen, F. Zhang, B. Liu, C. Xie, and Y. Song, "Encoding gene rab3b exists in linear chromosomal and circular extrachromosomal dna and contributes to cisplatin resistance of hypopharyngeal squamous cell carcinoma via inducing autophagy," *Cell death & disease*, vol. 13, no. 2, p. 171, 2022.

[38] S. Liu, Z. Jiang, P. Xiao, X. Li, Y. Chen, H. Tang, Y. Chai, Y. Liu, Z. Zhu, Q. Xie *et al.*, "Hsa_circ_0005576 promotes osimertinib resistance through the mir-512-5p/igf1r axis in lung adenocarcinoma cells," *Cancer Science*, vol. 113, no. 1, pp. 79–90, 2022.