A multi-scale neighbor topology guided transformer and Kolmogorov-Arnold network enhanced feature learning model for disease-related circRNA prediction

Ping Xuan, Haoyuan Li, Hui Cui, Zelong Xu, Toshiya Nakaguchi and Tiangang Zhang *

***Abstract*— As circular non-coding RNA (circRNA) is closely associated with various human diseases, identifying disease-related circRNAs can provide a deeper understanding of the mechanisms underlying disease pathogenesis. Advanced circRNA-disease association prediction methods mainly focus on graph learning techniques such as graph convolutional networks and graph attention networks. However, these methods do not fully encode the multi-scale neighbor topologies of each node, and the dependencies among the pairwise attributes. We propose a multi-scale neighbor topology-guided transformer with Kolmogorov-Arnold network (KAN) enhanced feature learning for circRNA and disease association prediction, termed MKCD. The model integrates multi-scale neighbor topology, complex relationships among multiple nodes, and the global and local dependencies of pairwise attributes. First, MKCD incorporates an adaptive multi-scale neighbor topology embedding construction strategy (AMNE), which generates neighbor topologies covering varying scopes of neighbors by performing random walks on a circRNA-disease-miRNA heterogeneous graph. Second, we design a dynamic multi-scale neighbor topology-guided transformer (DMTT) that leverages the multi-scale neighbor topologies to guide the learning of relationships among circRNA, miRNA, and disease nodes. The multi-scale neighbor topology is dynamically evolved, providing adaptive guidance to the transformer's learning process. Third, we establish a feature-gated network (FGN) to evaluate the importance of topological features derived from DMTT and the original node attributes. Finally, we propose an adaptive joint convolutional neural networks and KAN learning strategy (ACK) to learn the global and local dependencies of circRNA and disease node pair features. Comprehensive comparison experiments demonstrate the superior performance of our method over six state-of-the-art methods, and ablation experiments further validate the effectiveness of AMNE, DMTT, FGN and ACK innovations. Case studies on three diseases further validate the application value of our method in discovering reliable circRNA candidates for diseases of focus.**

***Index Terms*— Multi-scale neighbor topology, neighbor topology-guided transformer, KAN enhanced feature learning, local and global dependencies of pairwise attributes, disease-related circRNA prediction.**

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I. Introduction

CIRCRNA is a class of single-stranded circular non-coding RNA that lacks 5' and 3' polyadenylated tails [1]. Increasing evidence suggests that the abnormal expression of circRNAs is associated with the occurrence of various diseases [2], including cancers [3]–[5], immune system disorders [6], and cardiovascular diseases [7]–[9]. Therefore, identifying the associations between specific diseases and circRNAs can aid in the diagnosis and treatment of these diseases. Computational prediction methods can discover associations between circRNAs and diseases, which can then be used to provide reliable disease-related circRNA candidates for subsequent biological experiments [10], [11].

Existing computational prediction methods can be categorized into three main types. The first type involves establishing network-based models to predict associations between circRNAs and diseases. KATZHCDA and PWCDA models calculate the association scores for each circRNA-disease pair based on the paths connecting them in heterogeneous networks [12], [13]. iCircDA-MF model proposed by Wei *et al.* incorporates gene information to construct a circRNA-gene-disease relationship network and predicts associations using matrix factorization [14]. However, these models suffer from limited association information.

The second category of prediction models is based on machine learning techniques to predict the associations between circRNAs and diseases. A couple of methods combine k-nearest neighbors to predict disease-associated circRNA candidates [15]–[17]. MLCDA model proposed by Wang *et al.* performs predictions using inductive matrix completion

[18]. GBDTCDA and AE-RF are both decision tree-based prediction methods [19], [20], whereas CD-LNLP and RNMFLP calculate the association scores between circRNAs and diseases through label propagation [21], [22]. However, these methods establish superficial prediction models, making it difficult to capture the deep relationships between circRNAs and diseases.

The third category focuses on developing models based on deep learning strategies, improving prediction performance by extracting complex and representative features. Several methods establish convolutional neural network-based models [23]–[25] or attention mechanism-based models [26] to predict disease-related circRNAs, yet they overlook the neighbor topology structure between multiple circRNA and disease nodes. Bi-SGTAR proposed by Li *et al.* employs an encoder with sparse gating to predict the propensity of all circRNA-disease associations [27]. This method also neglects the topology formed by circRNA and disease nodes. Other methods are based on graph convolutional networks [28]–[31] and graph attention networks [32], and combinations of both [33], to learn deep relationships among nodes. However, these methods learn the features of each node from the entire graph, ignoring the global dependency learning of features between individual circRNA and disease node pairs.

We propose a novel association prediction model, **m**ulti-scale neighbor topology-guided transformer with **K**olmogorov-Arnold network enhanced feature learning for **c**ircRNA and **d**isease association prediction (MKCD), to learn multi-scale neighbor topologies, the relationships among circRNA, miRNA, and disease nodes, as well as the global and local dependencies between node pair features. The main contributions of this work are summarized as follows.

- We construct a circRNA-disease-miRNA heterogeneous graph that incorporates circRNA, disease, and miRNA nodes, along with their association, interaction, and similarity relationships. Each circRNA (disease, miRNA) node in this graph has multi-scale neighbors, with varying degrees of closeness to the target node. To effectively differentiate the contributions of neighbor topologies at different scales to node feature learning, we propose an adaptive multi-scale neighbor topology embedding construction strategy (AMNE). This strategy can adaptively determine the importance of each scale-specific neighbor topology and generate multi-scale neighbor topology embeddings.
- Most existing transformer-based models primarily focus on feature similarities between nodes while neglecting the topological structure among them. To address this limitation, we introduce dynamic multi-scale neighbor topology-guided transformer (DMTT), which encodes relationships among multiple circRNA, miRNA, and disease nodes. DMTT dynamically constructs an evolving neighbor topology and utilizes it to assess the importance of all circRNA, miRNA, and disease nodes in the heterogeneous graph.
- Multi-scale neighbor topology-introduced node features capture structural information, whereas the original features of circRNA, miRNA, and disease nodes provide rich biological details. To effectively integrate these complementary feature representations, we design a feature-gated network (FGN), which selectively determines the importance of topological and original features for downstream predictions.
- The features of circRNA and disease node pairs exhibit both local and global dependencies. To capture these dependencies, we propose a feature learning strategy for node pairs, ACK, which leverages Kolmogorov-Arnold network (KAN) [34] to learn global feature relationships and a multi-layer convolutional neural networks (CNNs) to extract local feature dependencies. Comparative experiments demonstrate that MKCD outperforms state-of-the-art methods in predicting circRNA-disease associations. Case studies validate that our method can effectively screen potential disease-related circRNA candidates.

II. Materials and Methods

We propose a novel prediction model, MKCD (Figure 1), for predicting disease-related circRNA candidates. A circRNA-disease-miRNA heterogeneous graph is constructed to integrate the similarities, interactions, and associations among circRNA, disease, and miRNA (Figure 1(a)). MKCD consists of four components, each learning distinct information from the heterogeneous graph. The proposed DMTT encodes the complex relationships among multiple circRNA, disease, and miRNA nodes (Figure 1(c)). It further guides the transformer model's learning process through dynamically constructed multi-scale neighbor topology embeddings via AMNE (Figure 1(b)). To preserve more detailed information from node features, we introduce FGN (Figure 1(d)). The designed ACK is used to learn and fuse both global and local dependencies between the features of circRNA and disease node pairs (Figure 1(e)). These components work together to improve the capability of MKCD in predicting circRNA-disease associations.

A. Dataset

The dataset utilized in this study is derived from previous work [35], which comprises two datasets containing circRNA, disease and miRNA information. The first dataset covers 514 circRNAs, 62 diseases, and 564 miRNAs. The second dataset contains associations and interactions among 330 circRNAs, 79 diseases, and 245 miRNAs. We integrated these two datasets to form a new, larger dataset. This merged dataset consists of 989 circRNA-disease associations, 837 miRNA-disease associations, and 902 circRNA-miRNA interactions, covering a total of 834 circRNAs, 138 diseases, and 555 miRNAs. The original associations between circRNAs and diseases are obtained from the circR2Cancer database [36], the circad database [37], and the circRNADisease database [38].

B. CircRNA-disease-miRNA heterogeneous graph

We constructed a three-layer heterogeneous graph $\mathcal{G} = (\mathcal{V}, \mathcal{E})$ using associations, interactions, and similarities among

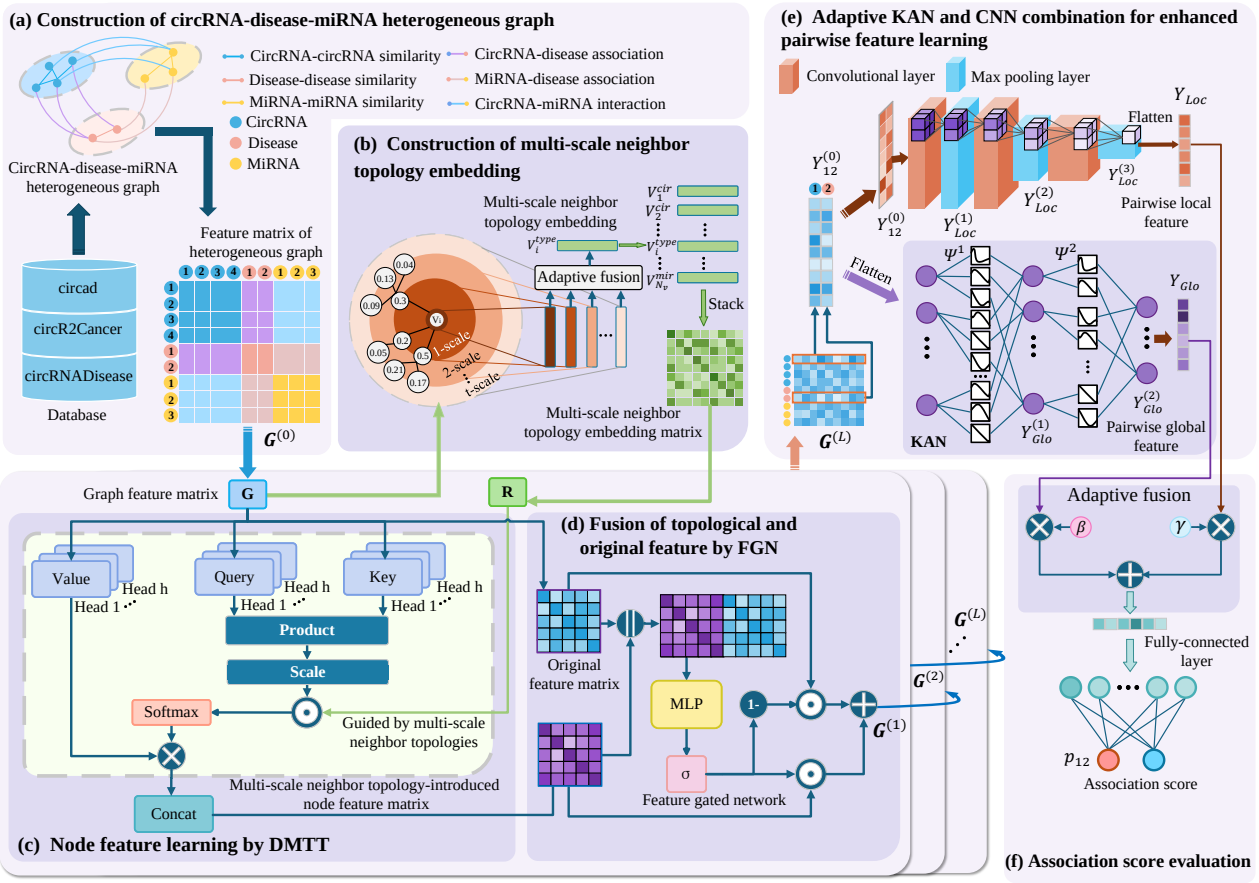

Fig. 1. The overall framework of MKCD. **(a)** Construction of the circRNA-disease-miRNA heterogeneous graph. **(b)** Adaptive multi-scale neighbor topology embedding construction strategy. **(c)** Learn the complex relationships among circRNA, miRNA, and disease nodes based on DMTT. **(d)** Fuse topological features and original node features by FGN. **(e)** Learn local and global dependencies of features of circRNA and disease node pairs based on ACK. **(f)** Adaptively fuse two representations and estimate circRNA-disease association scores.

circRNAs, miRNAs, and diseases (Figure 2). The node set $\mathcal{V} = \{V^{cir} \cup V^{dis} \cup V^{mir}\}$ comprises the set of circRNA nodes V^{cir}, disease nodes set V^{dis}, and miRNA nodes set V^{mir}. An edge $e_{ij} \in \mathcal{E}$ connects a pair of nodes $v_i, v_j \in \mathcal{V}$, represented by the association and interaction matrix H and similarity matrix S.

The association and interaction matrix H among circRNAs, miRNAs, and diseases is defined as follows,

$$H = \begin{cases} H^{cir-dis} \in \mathbb{R}^{N_{cir} \times N_{dis}}, & \text{if } v_i \in V^{cir}, v_j \in V^{dis}; \\ H^{mir-dis} \in \mathbb{R}^{N_{mir} \times N_{dis}}, & \text{if } v_i \in V^{mir}, v_j \in V^{dis}; \\ H^{cir-mir} \in \mathbb{R}^{N_{cir} \times N_{mir}}, & \text{if } v_i \in V^{cir}, v_j \in V^{mir}; \end{cases} \tag{1}$$

where $H^{cir-dis}$, $H^{mir-dis}$, and $H^{cir-mir}$ denote the circRNA-disease association matrix, miRNA-disease association matrix, and circRNA-miRNA interaction matrix, respectively. N_{cir}, N_{dis}, and N_{mir} represent the number of circRNAs, diseases, and miRNAs in the dataset. $H_{ij} \in H^{cir-dis}(H^{mir-dis})$ represents the association between the circRNA (miRNA) node $v_i^{cir}(v_i^{mir})$ and the disease node v_j^{dis}. For a circRNA (miRNA) node v_i^{cir} (v_i^{mir}) and a disease node d_j^{dis}, if $H_{ij}^{cir-dis} = 1$ ($H_{ij}^{mir-dis} = 1$), it indicates the existence of an association between them; conversely, $H_{ij}^{cir-dis} = 0$ ($H_{ij}^{mir-dis} = 0$), no association has been observed. If $H_{ij}^{cir-mir} = 1$, an interaction is present between the circRNA node v_i^{cir} and the miRNA node v_j^{mir}; otherwise, $H_{ij}^{cir-mir} = 0$.

S represents the similarity matrix related to circRNAs, miRNAs, and diseases,

$$S = \begin{cases} S^{cir} \in \mathbb{R}^{N_{cir} \times N_{cir}}, & \text{if } v_i, v_j \in V^{cir}; \\ S^{dis} \in \mathbb{R}^{N_{dis} \times N_{dis}}, & \text{if } v_i, v_j \in V^{dis}; \\ S^{mir} \in \mathbb{R}^{N_{mir} \times N_{mir}}, & \text{if } v_i, v_j \in V^{mir}; \end{cases} \tag{2}$$

where S^{cir}, S^{dis}, and S^{mir} are the similarity matrix for circRNAs, diseases, and miRNAs, respectively. The values in S^{cir}, S^{dis}, and S^{mir} range from 0 to 1, reflecting similarity between two nodes of the same type, with higher values indicating greater similarity.

According to the method proposed by Wang *et al.* [39], the similarity between two disease nodes $[v_i^{dis}, v_j^{dis}]$ is calculated based on their directed acyclic graph (DAG). The similarities of circRNAs and miRNAs are calculated using the methods proposed by Wang *et al.* [39] and Chen *et al.* [40], respectively, where the similarity of a pair of circRNAs (miRNAs) is derived from the similarity between the two sets of diseases associated with them. For instance, suppose the i-th circRNA node v_i^{cir} is associated with N_i^{cir} diseases, which forms the

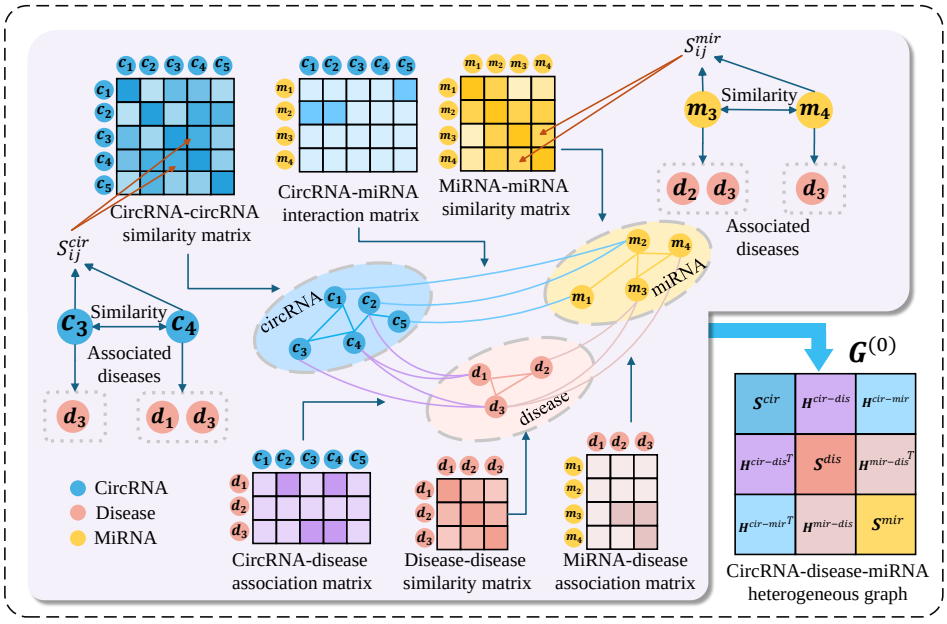

Fig. 2. Construction of the circRNA-disease-miRNA heterogeneous graph based on multi-source data.

set $\Omega_i^{cir} = \{d_{ik} | k = 1, \ldots, N_i^{cir}\}$, and the j-th circRNA node v_j^{cir} is associated with the disease set $\Omega_j^{cir} = \{d_{jl} | l = 1, \ldots, N_j^{cir}\}$. The similarity S_{ij}^{cir} of $[v_i^{cir}, v_j^{cir}]$ is determined by assessing the similarity between Ω_i^{cir} and Ω_j^{cir}. Similarly, we can calculate the similarity S_{ij}^{mir} for $[v_i^{mir}, v_j^{mir}]$.

Based on the constructed association (interaction) matrix H and the similarity matrix S, the original feature matrix of the heterogeneous graph $G^{(0)} \in \mathbb{R}^{N_v \times N_v}$ is defined as follows,

$$G^{(0)} = \begin{bmatrix} S^{cir} & H^{cir-dis} & H^{cir-mir} \\ H^{cir-dis^T} & S^{dis} & H^{mir-dis^T} \\ H^{cir-mir^T} & H^{mir-dis} & S^{mir} \end{bmatrix}, \quad (3)$$

where N_v denotes the total number of circRNAs, miRNAs, and diseases, and $H^{cir-dis^T}$ represents the transpose of the matrix $H^{cir-dis}$. The i-th row g_i of the matrix $G^{(0)}$ represents the node embedding of node $v_i \in \mathcal{V}$, which contains the associations and similarities involving v_i and all circRNAs, diseases, and miRNAs. The set $\{g_i | 0 \leqslant i < N_{cir}\}$ denotes the collection of node embeddings for all circRNAs. Furthermore, the sets $\{g_i | N_{cir} \leqslant i < N_{cir} + N_{dis}\}$ and $\{g_i | N_{cir} + N_{dis} \leqslant i < N_{cir} + N_{dis} + N_{mir}\}$ represent the collections of node embeddings for all diseases and miRNAs, respectively.

C. Adaptive multi-scale neighbor topology embedding construction strategy (AMNE)

In the circRNA-disease-miRNA heterogeneous graph, the node v_i has one-scale neighbors that can be reached in one step, or d-scale neighbors that can be reached in d $(d > 1)$ steps. The multi-scale neighbor topological structure formed by these neighboring nodes can provide important auxiliary information for predicting the associations between circRNAs and diseases. The contributions of low-scale (one-scale) neighbors and high-scale (d-scale) neighbors to the features learned for each node are different, thus, we proposed AMNE, which utilizes random walk with restart (RWR) to establish multi-scale neighbor topology embeddings (Figure 3). Taking v_i as an example, the walker starts from v_i and performs random walks to travel to other nodes in the circRNA-disease-miRNA heterogeneous graph. The probability distribution of reaching all circRNA, disease, and miRNA nodes at time t is given by $\theta_i(t) \in \mathbb{R}^{1 \times N_v}$,

$$\theta_i(t) = (1 - \lambda) O^T \theta_i(t - 1) + \lambda \theta_i(0), \quad (4)$$

where the j-th value of $\theta_i(t)$ denotes the probability that the walker starts from v_i reaches node v_j $(0 \leqslant j < N_v)$ after t steps. $\theta_i(0)$ is the initial one-hot vector, where the i-th position is 1 and all other positions are 0. λ is the probability that the walker restarts from the starting point; a larger value of λ results in a smaller movement range of the walker within the network. $O \in \mathbb{R}^{N_v \times N_v}$ is obtained from the row-normalized matrix of $G^{(0)}$, where $o_{ij} \in O$ represents the transition probability from v_i to v_j. $\theta_i(t)$ can be viewed as the probability distribution of reaching various nodes after t steps from v_i, thus it serves as the t-scale neighbor topology embedding of v_i.

According to Eq.(4), we can build neighbor topology embeddings from scale 0 to scale t. These scale neighbor topology embeddings are adaptively fused to obtain the multi-scale neighbor topology embedding θ_i for v_i,

$$\theta_i = \eta_0 \theta_i(0) + \eta_1 \theta_i(1) + \cdots + \eta_k \theta_i(k) + \cdots + \eta_t \theta_i(t), \quad (5)$$

where $\eta_k \in (0, 1)$ are randomly initialized learnable parameters, and $\sum_{k=0}^{t} \eta_k = 1$.

After applying AMNE for each $v_i (0 \leqslant i < N_v)$, we can obtain the multi-scale neighbor embedding for all nodes. These embeddings are stacked vertically to form the embedding matrix $R \in \mathbb{R}^{N_v \times N_v}$,

$$R = \begin{bmatrix} \theta_0 \\ \theta_1 \\ \vdots \\ \theta_{N_v - 1} \end{bmatrix}. \quad (6)$$

D. Node feature learning based on DMTT

Typically, multiple circRNAs and miRNAs form interactions and collaboratively participate in the processes of various diseases. Therefore, there are close relationships among the features of multiple circRNAs, miRNAs, and disease nodes, making it necessary to establish a self-attention mechanism to capture these relationships. Traditional transformer focus solely on the similarities between node features and do not fully exploit the topological structures formed between nodes, especially the multi-scale neighbor topological structures. Inspired by the transformer proposed by Vaswani *et al.* [41], we introduce a DMTT (dynamic multi-scale neighbor topology-guided transformer) mechanism (Figure 4) that utilizes the multi-scale neighbor topology embeddings established by AMNE to guide the learning of attention scores.

We incorporate a multi-head attention mechanism to overcome the problem of single-head attention easily falling into local optima during the training process, thereby reducing bias in the learning process. For the m-th attention head, we first establish the query matrix $Q_m^{(l)} \in \mathbb{R}^{N_v \times \frac{N_v}{h}}$, the key matrix $K_m^{(l)} \in \mathbb{R}^{N_v \times \frac{N_v}{h}}$, and the value matrix $V_m^{(l)} \in \mathbb{R}^{N_v \times \frac{N_v}{h}}$ as follows,

$$\begin{aligned} Q_m^{(l)} &= G^{(l-1)} W_m^{Q(l)} \\ K_m^{(l)} &= G^{(l-1)} W_m^{K(l)}, \\ V_m^{(l)} &= G^{(l-1)} W_m^{V(l)} \end{aligned} \tag{7}$$

where $G^{(l-1)} \in \mathbb{R}^{N_v \times N_v}$ is the feature matrix of the graph nodes that are input at layer l $(1 \leqslant l \leqslant L)$. When $l = 1$, $G^{(0)}$ represents the original feature matrix, and h is the number of attention heads. $Q_m^{(l)}$, $K_m^{(l)}$, and $V_m^{(l)}$ are obtained from $G^{(l-1)}$ through different linear projections, with $W_m^{Q(l)}$, $W_m^{K(l)}$, and $W_m^{V(l)} \in \mathbb{R}^{N_v \times \frac{N_v}{h}}$ being the corresponding weight matrices for the linear projections. Then, we perform a dot product operation on $Q_m^{(l)}$ and ${K_m^{(l)}}^T$ to obtain the attention score matrix $S_m^{(l)} \in \mathbb{R}^{N_v \times N_v}$,

$$S_m^{(l)} = \frac{Q_m^{(l)} {K_m^{(l)}}^T}{\sqrt{d}}, \tag{8}$$

where $d = \frac{N_v}{h}$ and $\sqrt{d}$ is a scaling factor used to adjust the magnitude of the attention scores to enhance numerical stability during the training process. The i-th row of $S_m^{(l)}$ records the attention scores from all circRNA, disease, and miRNA nodes to v_i.

After the $(l-1)$-th layer DMTT, the topology among the nodes changes, and a new multi-scale neighbor topology embedding matrix $R^{(l)}$ for each node is reconstructed through AMNE based on $G^{(l-1)}$. The i-th row of $R^{(l)}$ records the neighbor topology of v_i with all other circRNA, disease, and miRNA nodes after the $(l-1)$-th layer transformer encoding. We perform a Hadamard product operation between $R^{(l)}$ and $S_m^{(l)}$. This approach allows the multi-scale neighbor topology embeddings to guide the learning of attention scores. We establish the multi-scale neighbor topology-introduced attention score matrix $\widetilde{S}_m^{(l)} \in \mathbb{R}^{N_v \times N_v}$ as follows,

$$\widetilde{S}_m^{(l)} = S_m^{(l)} \odot R^{(l)}, \tag{9}$$

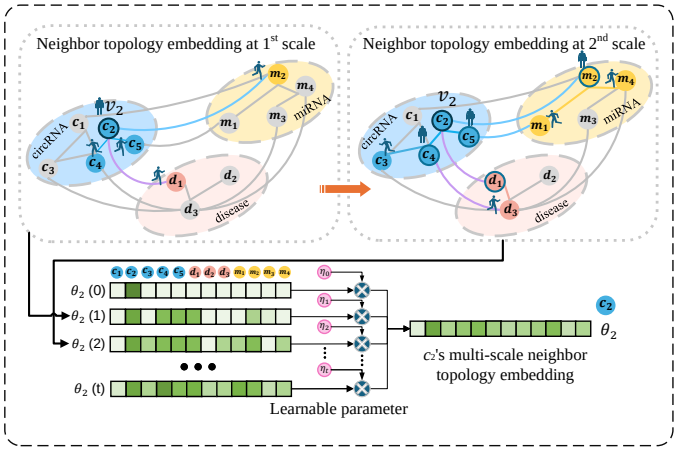

Fig. 3. Process of adaptively constructing multi-scale neighbor topology embeddings with RWR, illustrated by node c_2.

where $\odot$ denotes the Hadamard product operation. Multiplying $\widetilde{S}_m^{(l)}$ with $V_m^{(l)}$ produces the node features $Z_m^{(l)} \in \mathbb{R}^{N_v \times \frac{N_v}{h}}$ learned by the m-th attention head,

$$Z_m^{(l)} = softmax(\widetilde{S}_m^{(l)}) V_m^{(l)}. \tag{10}$$

Finally, by concatenating the node features learned by all h attention heads, we obtain the multi-scale neighbor topology-introduced node feature matrix $\hat{G}^{(l)} \in \mathbb{R}^{N_v \times N_v}$ for layer l,

$$\hat{G}^{(l)} = \Big\|_{m \in [1,h]} Z_m^{(l)}, \tag{11}$$

where $\|$ denotes the concatenation operation. The i-th row of $\hat{G}^{(l)}$ records the features of v_i learned at layer l.

E. Fusion of multiple types of features based on FGN

In DMTT, the feature matrix $G^{(l-1)}$ that is input at layer l contains more detailed information about each node, while the feature matrix $\hat{G}^{(l)}$ learned based on DMTT places greater emphasis on the information guided by multi-scale neighbor topology embedding. Therefore, it is necessary to incorporate $G^{(l-1)}$ into the feature learning process at layer l. To integrate the information contained in $\hat{G}^{(l)}$ and $G^{(l-1)}$, we establish an FGN (feature gate network) after DMTT at layer l, with the weight matrix denoted as $\alpha^{(l)}$,

$$\alpha^{(l)} = \sigma(W^{gate(l)}(\hat{G}^{(l)} \| G^{(l-1)}) + b^{gate(l)}), \tag{12}$$

where $W^{gate(l)}$ and $b^{gate(l)}$ are learnable weight matrices and bias, and σ is the Sigmoid activation function. All parameters of the FGN are randomly initialized and are learnable during the training process, allowing it to discern the more significant features in $\hat{G}^{(l)}$ and $G^{(l-1)}$.

The FGN-enhanced node feature representation is denoted as $G^{(l)} \in \mathbb{R}^{N_v \times N_v}$,

$$G^{(l)} = \alpha^{(l)} \odot \hat{G}^{(l)} + (1 - \alpha^{(l)}) \odot G^{(l-1)}. \tag{13}$$

When $l \neq L$, $G^{(l)}$ will serve as the input for the next layer of DMTT, where $l = L$, $G^{(L)}$ represents the final node feature representation matrix.

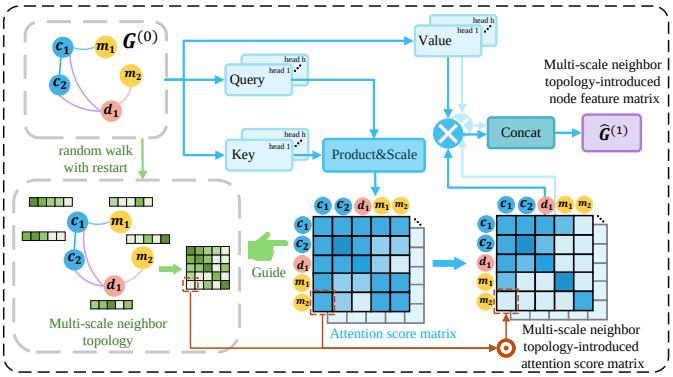

Fig. 4. Illustration of node feature learning process guided by multi-scale neighbor topology, using $\boldsymbol{G^{(0)}}$ as an example.

F. Adaptive joint CNNs and KAN enhanced pairwise feature learning strategy

If the circRNA node v_i^{cir} and the disease node d_j^{dis} have similarities, associations, or interactions with the same circRNAs, diseases, and miRNAs, then the node pair $[v_i^{cir}, d_j^{dis}]$ is more likely to be associated. Based on this biological premise, we vertically stack the feature representations obtained from the FGN-enhanced DMTT for both circRNA and disease nodes, forming a node pair-level feature representation $Y_{ij}^{(0)} \in \mathbb{R}^{2\times N_v}$,

$$Y_{ij}^{(0)} = \begin{bmatrix} G_i^{(L)} \\ G_j^{(L)} \end{bmatrix}, \tag{14}$$

where the sets $\{G_i^{(L)}|0 \leqslant i < N_{cir}\}$ and $\{G_j^{(L)}|N_{cir} \leqslant j < N_{cir}+N_{dis}\}$ represent the node feature representations of all circRNAs and diseases in $G^{(L)}$, respectively.

The ACK (adaptive joint CNNs and KAN learning strategy) we designed will further extract the information within the circRNA-disease node pairs. The KAN module we established learns the pairwise node representations from a global perspective, while the CNN module focuses more on extracting local information of the pairwise node representations.

1) Pairwise global feature learning based on KAN: Compared to the multi-layer perceptron (MLP), KAN replaces weight parameters and activation functions with learnable functions to adaptively learn the weights of the connections between neurons. This learnable function is typically composed of multiple stacked spline functions, enabling the KAN network to better capture the complex relationships among the features in $Y_{ij}^{(0)}$. Through multiple layers of the KAN network, a feature representation of the node pair $[v_i^{cir}, d_j^{dis}]$ is learned from a global perspective. The input feature representation of the node pair at the l-th layer $Y_{Glo}^{(l-1)}$ is transformed into the pairwise global feature representation $Y_{Glo}^{(l)}$ after passing through the l-th layer of the global feature learning module based on the KAN network,

$$Y_{Glo}^{(l)} = KAN^{(l)}(Y_{Glo}^{(l-1)}) = \Psi^{(l)}(Y_{Glo}^{(l-1)}), \tag{15}$$

where $KAN^{(l)}$ denotes the l-th KAN layer. When $l=1$, $Y_{Glo}^{(0)}$ is obtain by flattening the original circRNA-disease node pair-level feature representation $Y_{ij}^{(0)}$. When $l=L$, $Y_{Glo}^{(L)}$ represents the final pairwise global feature representation $Y_{Glo} \in \mathbb{R}^{1\times f}$, where f is the feature dimension. The matrix $\Psi^{(l)}$ is composed of learnable functions for the l-th KAN layer, containing a total of $n^{(l-1)} \times n^{(l)}$ learnable functions. Therefore, $\Psi^{(l)}$ is defined as,

$$\Psi^{(l)} = \begin{pmatrix} \psi_{1,1} & \psi_{1,2} & \cdots & \psi_{1,n^{(l)}} \\ \psi_{2,1} & \psi_{2,2} & \cdots & \psi_{2,n^{(l)}} \\ \vdots & \vdots & \ddots & \vdots \\ \psi_{n^{(l-1)},1} & \psi_{n^{(l-1)},2} & \cdots & \psi_{n^{(l-1)},n^{(l)}} \end{pmatrix}, \tag{16}$$

where $n^{(l-1)}$ and $n^{(l)}$ represent the number of neurons in the $(l-1)$-th and l-th layers, respectively. The $\psi_{i,j}$ corresponds to the learnable function of the edge connecting the i-th neuron in the $(l-1)$-th layer to the j-th neuron in the l-th layer. The $\psi_{i,j}$ is composed of a basis function and a B-spline function,

$$\psi_{i,j} = \omega_b b(x) + \omega_s spline(x), \tag{17}$$

$$spline(x) = \sum_{k=1}^{n_{grid}} c_k B_k, \tag{18}$$

where $b(x)$ is the basis function $SiLU$, and ω_b and ω_s are learnable weight parameters. The B-spline function $spline(x)$ is obtained by stacking n_{grid} B-spline basis functions B_k, where c_k is the learnable parameter for each B_k.

2) Pairwise local feature learning based on CNNs: We have established CNNs to learn the local features of circRNA-disease node pairs. In the CNNs, each block consists of a convolution layer followed by a pooling layer. In the l-th block $(1 \leqslant l \leqslant D)$, given the feature representation of a circRNA-disease node pair $Y_{Loc}^{(l-1)}$, we use the convolution and pooling operations to extract its pairwise local features $Y_{Loc}^{(l)}$,

$$Y_{Loc}^{(l)} = max(\tau(W_{conv}^{(l)} * Y_{Loc}^{(l-1)} + b_{conv}^{(l)})), \tag{19}$$

where * denotes the convolution operation, $W_{conv}^{(l)}$ and $b_{conv}^{(l)}$ are the sets of convolution kernels and bias, respectively, τ is the Leaky ReLU activation function, and max represents the max pooling operation. $Y_{Loc}^{(0)}$ is the original feature representation of the circRNA-disease node pair $Y_{ij}^{(0)}$. When $l=D$, the dimension of $Y_{Loc}^{(D)}$ is reduced and flattened to obtain the final pairwise local feature representation $Y_{Loc} \in \mathbb{R}^{1\times f}$.

3) Adaptive fusion of pairwise local features and global features: The pairwise local feature representation Y_{Loc} and global feature representation Y_{Glo} hold varying degrees of importance for the feature representation learning of each circRNA (disease) node. We assign a learnable weight parameter s_β for Y_{Glo} and s_γ for Y_{Loc}, and after normalization, we obtain β and γ,

$$\beta = \frac{e^{s_\beta}}{e^{s_\beta}+e^{s_\gamma}}, \quad \gamma = \frac{e^{s_\gamma}}{e^{s_\beta}+e^{s_\gamma}}. \tag{20}$$

The final feature representation of the circRNA-disease node pair is defined as $Y_F \in \mathbb{R}^{1\times f}$,

$$Y_F = \beta \cdot Y_{Glo} + \gamma \cdot Y_{Loc}, \tag{21}$$

where $\cdot$ denotes scalar multiplication.

G. Association score evaluation and optimization

We utilize a fully connected layer to derive the association prediction score vector $p_{ij} \in \mathbb{R}^{1\times 2}$ for the node pair $[v_i^{cir}, d_j^{dis}]$,

$$p_{ij} = softmax(W_{Fin}Y_F + b_{Fin}), \tag{22}$$

where W_{Fin} and b_{Fin} are the weight matrix and bias of the fully connected layer, respectively. The vector $p_{ij} = [p_{pos}, p_{neg}]$ represents the probabilities that v_i^{cir} is associated with d_j^{dis} or not, denoted as p_{pos} and p_{neg}, respectively.

During the training process, we employ the AdamW algorithm and back propagation to optimize our model. We use the cross-entropy function to estimate the model's loss,

$$loss = -\sum_{(i,j)\in N} \left[y_{ij}\log(p_{pos}) + (1-y_{ij})\log(p_{neg})\right], \tag{23}$$

where N denotes the sample set of all circRNA-disease node pairs. y_{ij} represents the true association label between the circRNA node v_i^{cir} and the disease node d_j^{dis}. When there is an association between v_i^{cir} and d_j^{dis}, $y_{ij} = 1$; otherwise, $y_{ij} = 0$.

III. Experimental Evaluations and Discussions

A. Parameter settings

In the AMNE module, we utilize the 0 to 2-scale neighbor topology to construct multi-scale neighbor topology embeddings, with the restart probability λ for random walk set to 0.7. For the DMTT module, the number of layers L is set to 2, and in each layer of the DMTT, the number of attention heads h is set to 4. In the pairwise local feature learning module, we employ three blocks, where the convolution kernel sizes of the first two blocks are 2×2, and the convolution kernel of the third block is 1×2. The pooling layer of the first block uses a window size of 2×2, while the pooling windows for the remaining two blocks are both set to 1×7. In the pairwise global feature learning module, we establish a 2-layer KAN network with the number of neurons set to 1024 and 256, respectively, and the number of n_{grid} for the B-spline function is set to 5. We train MKCD using an Nvidia GeForce RTX 4060, utilizing the PyTorch framework and optimizing using the AdamW algorithm. The training process consisted of 40 epochs, with a batch size of 32, a learning rate of 0.001, and a weight decay of 0.0001.

B. Evaluation metrics

We employ five-fold cross-validation to evaluate the predictive performance of MKCD and other comparative methods. All known circRNA-disease associations are treated as positive samples and randomly divided into five equal parts, while all unobserved circRNA-disease associations are considered as negative samples. In each fold, we use four parts of positive samples and an equal number of randomly selected negative samples as the training set, while the remaining positive samples and all unselected negative samples constitute the test set.

We select the area under the receiver operating characteristic curve (AUC) [42] and the area under the precision-recall curve (AUPR) [43] as evaluation metrics. AUC and AUPR are calculated separately for each fold, and the averages of these five folds result in the final AUC and AUPR scores. Furthermore, considering that biologists typically choose candidates from the top of the ranked list for further validation, we calculate the recall rate of the top k disease-related circRNAs.

TABLE I
Results of Ablation Experiments of MKCD.

AMNE	DMTT	FGN	ACK	Average AUC	Average AUPR
✗	✓	✓	✓	0.913	0.203
✓	✗	✗	✓	0.909	0.195
✓	✓	✗	✓	0.923	0.221
✓	✓	✓	✗	0.931	0.240
✓	✓	✓	✓	**0.946**	**0.267**

C. Ablation experiments

To validate the effectiveness of AMNE (adaptive multi-scale neighbor topology embedding construction strategy), DMTT (dynamic multi-scale neighbor topology-guided transformer), FGN (feature gate network), and ACK (adaptive joint CNNs and KAN learning strategy), we conducted a series of ablation experiments (Table I). We sequentially removed the AMNE, DMTT, FGN, and ACK modules from MKCD and calculated the corresponding AUC and AUPR. We observed that when all modules were retained, the complete model MKCD achieved the best predictive performance, with AUC and AUPR values of 0.946 and 0.267, respectively. When the AMNE module was removed, the AUC and AUPR decreased by 3.3% and 6.4%, respectively, indicating that the introduction of multi-scale neighbor topology embedding plays a crucial role in enhancing the accuracy of circRNA and disease association predictions. The removal of DMTT and FGN resulted in a 3.7% drop in AUC and a 7.2% drop in AUPR, confirming the necessity of utilizing the multi-scale neighbor topology formed by circRNA, disease, and miRNA nodes to learn node feature representations. The complete model improved AUC and AUPR by 2.3% and 4.6%, respectively, compared to when FGN was ignored, suggesting that the incorporation of detailed features benefits the learning of node features. Finally, the removal of ACK led to a decrease of 1.5% in AUC and 2.7% in AUPR, demonstrating the effectiveness of the adaptive fusion of pairwise local features and global features in enhancing circRNA-disease association prediction performance.

The results of the ablation experiments indicate that DMTT contributes the most to circRNA-disease association prediction, primarily because DMTT encodes the relationships among multiple features of circRNA, disease, and miRNA nodes. AMNE contributes the second largest to the prediction results, as AMNE effectively introduces multi-scale neighbor topology embedding into node feature learning.

D. Comparison with other methods

We compared MKCD with six advanced methods for predicting circRNA-disease associations, including SGFCCD [28], MLNGCF [32], MDGF-MCEC [30], Bi-SGTAR [27], GraphCDA [33], and MPCLCDA [29]. Each method was

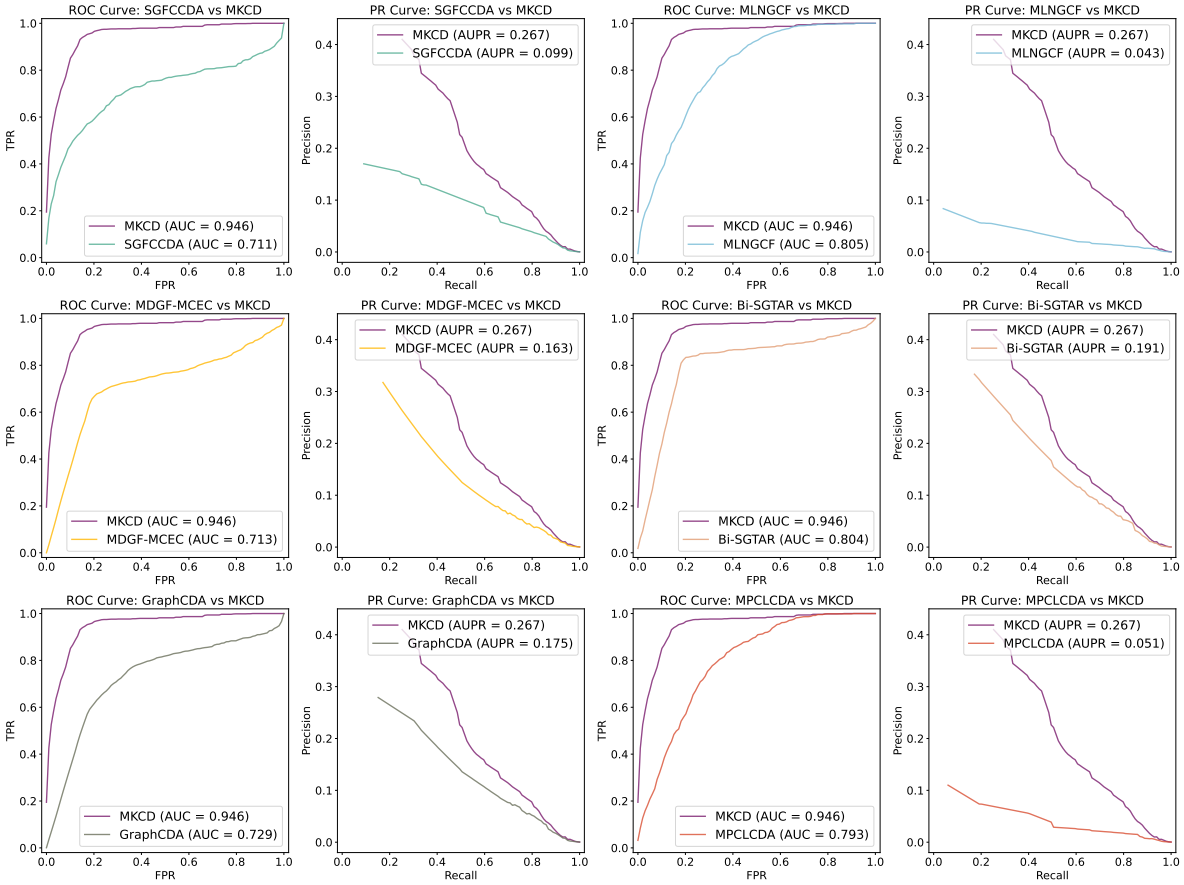

Fig. 5. ROC and PR curves of MKCD and other comparative methods.

TABLE II
RESULTS OF THE PAIRED WILCOXON TEST COMPARING MKCD WITH ALL OTHER METHODS.

p-value	SGFCCDA	MLNGCF	MDGF-MCEC	Bi-SGTAR	GraphCDA	MPCLCDA
AUC	2.71e-111	7.20e-58	2.13e-109	3.27e-60	6.06e-108	1.22e-76
AUPR	6.02e-109	6.60e-115	1.18e-41	1.96e-09	2.86e-26	1.29e-113

trained using the optimal parameters provided in their original papers, and the same training and testing datasets were utilized in cross-validation to ensure fairness.

SGFCCDA: This model constructs a circRNA-disease heterogeneous graph and predicts potential circRNA-disease associations through scale graph convolutional networks and convolutional neural networks.

MLNGCF: In this model, various similarities between circRNAs and diseases are utilized to estimate the association scores based on a multilayer attention neural network.

MDGF-MCEC: This method establishes relationship graphs for circRNAs and diseases based on their respective similarities and learns node features through a multi-view dual attention graph convolution network.

Bi-SGTAR: The adjacency matrix of the circRNA-disease heterogeneous graph is decomposed into two views, and an encoder with sparse gating is employed to identify all circRNA-disease associations.

GraphCDA: This approach constructs separate similarity networks for circRNAs and diseases, utilizing a hybrid graph embedding model that combines graph convolutional networks and graph attention networks to simultaneously learn feature representations for circRNAs and diseases.

MPCLCDA: It automatically selects meta-paths for constructing meta-path graphs and employs graph convolutional networks and contrastive learning to learn node features for circRNAs and diseases.

Figure 5 illustrates the ROC and PR curves for MKCD and the other methods. From the figure, it is evident that MKCD achieved the highest average AUC of 0.946, surpassing SGFCCDA by 23.5%, MLNGCF by 14.1%, MDGF-MCEC by 23.3%, Bi-SGTAR by 14.2%, GraphCDA by 21.7%, and MPCLCDA by 15.3%. The average AUPR of MKCD was 0.267, which is higher than SGFCCDA, MLNGCF, MDGF-MCEC, Bi-SGTAR, GraphCDA, and MPCLCDA by 16.8%, 22.4%, 10.4%, 7.6%, 9.2%, and 21.6%, respectively. Both MLNGCF and MPCLCDA employ graph neural networks, focusing solely on integrating the topology and node features of the circRNA-disease heterogeneous graph. In contrast to these two methods, SGFCCDA utilizes scale graph convolutional networks to address the issue of feature mixing between different channels caused by the linear layer structure of graph convolutional networks. MDGF-MCEC and GraphCDA primarily focus on learning from multiple similarity views, while

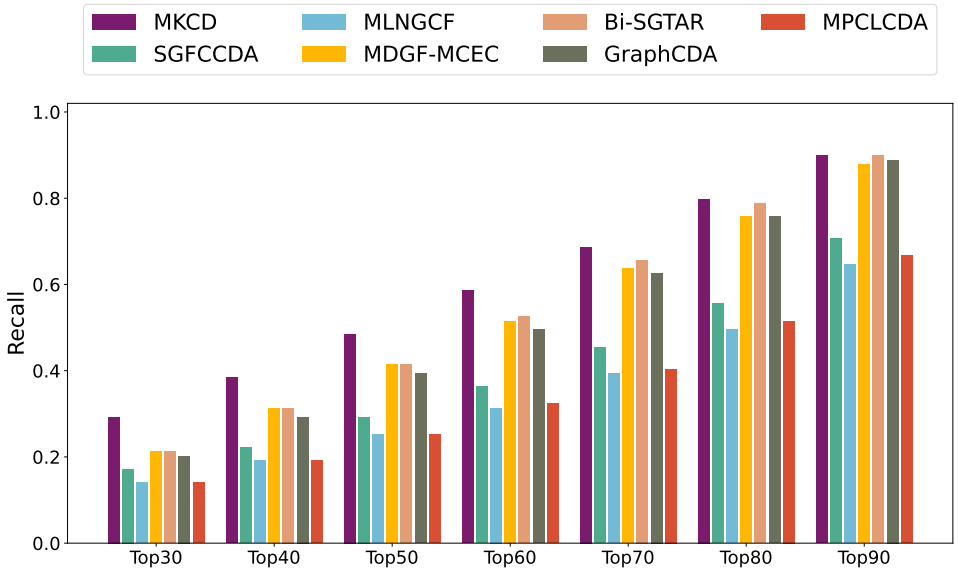

Fig. 6. Recall rates of diseases at multiple top k cutoffs.

Bi-SGTAR emphasizes learning from multiple heterogeneous graph views, which contributes to their higher AUPR. Our method outperforms these six methods mainly due to the embedding of multi-scale neighbor topology and the encoding of relationships among multiple features of circRNA, disease, and miRNA nodes.

For the prediction results of all 138 diseases, we employed the Paired Wilcoxon test to evaluate whether our method outperforms the other six methods significantly. According to the results in Table II, all p-values are below 0.05, indicating that MKCD significantly outperforms SGFCCDA, MLNGCF, MDGF-MCEC, Bi-SGTAR, GraphCDA, and MPCLCDA with respect to AUC and AUPR.

For each disease, we calculated the recall rates of circRNA candidates at various top k values (Figure 6). When $k = 30$, MKCD achieved a recall rate of 29.3%, surpassing SGFCCDA by 12.1%, MLNGCF by 15.2%, MDGF-MCEC by 8.1%, Bi-SGTAR by 8.0%, GraphCDA by 9.1%, and MPCLCDA by 15.1%. When $k = 50$, 70, and 90, MKCD maintained its leading position with recall rates of 48.5%, 68.6%, and 90.1%, respectively. Bi-SGTAR (41.3%, 65.7%, 89.8%), MDGF-MCEC (41.3%, 63.6%, 87.9%), and GraphCDA (39.4%, 62.5%, 88.8%) also achieved decent performance. In contrast, SGFCCDA (29.3%, 45.5%, 70.6%), MLNGCF (25.2%, 39.4%, 64.6%), and MPCLCDA (25.3%, 40.5%, 66.7%) showed inferior performance.

E. Case studies on three diseases

We conducted case studies on glioma, systemic lupus erythematosus, and glioblastoma to further validate MKCD's ability to mine potential circRNA candidates associated with these diseases. Glioma and glioblastoma are two types of primary brain tumors [44], [45], while systemic lupus erythematosus is a systemic autoimmune disease, primarily affecting women [46]. For each disease, the circRNA candidates were ranked in descending order based on their association scores, and the top 15 circRNAs were selected as candidates. Tables III, IV, and V show the top 15 circRNA candidates for glioma, systemic lupus erythematosus, and glioblastoma, respectively. The circRNADisease v2.0 database provides validated associations between circRNAs and various diseases, covering 4246 circRNAs and 330 diseases [47]. This database, along with relevant bioinformatics literature, was used to validate the predictions of circRNA-disease associations.

Using glioma as an example (Table III), all 15 circRNAs are validated in the literature, with 14 of them have been identified in circRNADisease v2.0. For instance, the top-ranked circ_002136 was found by He *et al.* [48] to inhibit the viability, migration, and tube formation of U87 glioma-exposed endothelial cells (GECs). Li *et al.* [49] found that the expression levels of hsa_circ_0061868 were upregulated in glioma cells.

All 15 circRNA candidates associated with systemic lupus erythematosus (SLE) (Table IV) are confirmed in the literature and have been included in circRNADisease v2.0. For example, Li *et al.* [50] identified hsa_circ_0046599 as a potential biomarker for systemic lupus erythematosus. Hsa_circ_0000479 was confirmed by Guo *et al.* [51] to be upregulated in peripheral blood mononuclear cells of patients with SLE.

For glioblastoma, 11 of the top 15 circRNA candidates (Table V) are validated in recent literature and documented in circRNADisease v2.0. For example, the study by Wang *et al.* [52] demonstrated that circNT5E exhibits tumor suppressor-like features in glioblastoma. Additionally, circMMP9 has been shown by Wang *et al.* [53] to promote the proliferation, migration, and invasion of glioblastoma multiforme cells.

F. Prediction of novel circRNA-disease associations

We utilized all known associations between circRNAs and diseases, and randomly selected an equal number of negative examples to train MKCD to predict circRNA candidates for 138 diseases. The top 15 circRNA candidates predicted by MKCD for each disease are listed in Supplementary File SF1.

TABLE III
TOP 15 PREDICTED RESULTS OF GLIOMA-RELATED CIRCRNAS BASED ON MKCD.

Rank	CircRNA name	Evidence	Rank	CircRNA name	Evidence
1	circ_002136	L^a, PMID:30736838	9	hsa_circ_0079593	L^a, PMID:31148222
2	hsa_circ_0061868	PMID:30341906	10	circSMO742	L^a, PMID:31895689
3	circPTN	L^a, PMID:31511040	11	hsa_circ_0012129	L^a, PMID:29686222
4	circ-TTBK2	L^a, PMID:32196629	12	hsa_circ_0088732	L^a, PMID:32154171
5	circ-EZH2	L^a, PMID:31669648	13	circNFIX	L^a, PMID:30072869
6	hsa_circ_0000594	L^a, PMID:28219405	14	circ-PTPRZ1	L^a, PMID:31364003
7	hsa_circ_0005198	L^a, PMID:31038801	15	hsa_circ_0014359	L^a, PMID:30745107
8	hsa_circ_0000177	L^a, PMID:30010402			

L^a: circRNADisease v2.0.

TABLE IV
TOP 15 PREDICTED RESULTS OF SYSTEMIC LUPUS ERYTHEMATOSUS-RELATED CIRCRNAS BASED ON MKCD.

Rank	CircRNA name	Evidence	Rank	CircRNA name	Evidence
1	hsa_circ_0046599	L^a, PMID:29360436	9	hsa_circ_0008615	L^a, PMID:29360436
2	hsa_circ_0001866	L^a, PMID:29360436	10	hsa_circ_0021549	L^a, PMID:29360436
3	hsa_circ_0034398	L^a, PMID:29360436	11	has_circ_0049220	L^a, PMID:29606700
4	hsa_circ_0003146	L^a, PMID:29360436	12	hsa_circ_0092374	L^a, PMID:29360436
5	hsa_circ_0000479	L^a, PMID:31608065	13	hsa_circ_0040705	L^a, PMID:29360436
6	hsa_circ_0057762	L^a, PMID:30628013	14	hsa_circ_0012919	L^a, PMID:30237316
7	circPTPN22	L^a, PMID:30871426	15	hsa_circ_0049224	L^a, PMID:29606700
8	hsa_circ_0045272	L^a, PMID:29700819			

L^a: circRNADisease v2.0.

TABLE V
TOP 15 PREDICTED RESULTS OF GLIOBLASTOMA-RELATED CIRCRNAS BASED ON MKCD.

Rank	CircRNA name	Evidence	Rank	CircRNA name	Evidence
1	hsa_circ_0001801	L^a, PMID:31858556	9	circMTO1	L^a, PMID:31456594
2	circNT5E	L^a, PMID:29967262	10	circ-AKT3	L^a, PMID:31470874
3	circ-PITX1	L^a, PMID:31493405	11	circPVT1	unknown
4	hsa_circ_0043949	L^a, PMID:31823158	12	circPTN	L^a, PMID:31511040
5	hsa_circ_0074027	L^a, PMID:30738578	13	hsa_circ_101996	unknown
6	circMMP9	L^a, PMID:30470262	14	hsa_circ_100242	unknown
7	circ-Foxo3	L^a, PMID:31802888	15	hsa_circ_0003855	unknown
8	hsa_circ_0001946	L^a, PMID:31599076			

L^a: circRNADisease v2.0.

IV. CONCLUSIONS

This paper presents a novel approach for encoding the relationships among circRNA, miRNA, and disease node features, while effectively learning and integrating both global and local features of node pairs to predict disease-related circRNAs. By adjusting the walking range of random walkers in the circRNA-disease-miRNA heterogeneous graph, multi-scale neighbor topologies are constructed, and the importance of each scale-specific neighbor topology is adaptively determined. The proposed multi-scale neighbor topology-guided transformer dynamically updates the neighbor topology and captures the evolving relationships between the features of circRNA, miRNA, and disease nodes. The FGN assigns higher weights to topological and original features based on their importance. The ACK encodes the features of circRNA-disease node pairs, facilitating the identification of local and global dependencies among pairwise attributes. The comparison results demonstrate that our model outperform other SOTA methods in terms of AUC and AUPR. The recall rate of top-ranked circRNA candidates and case studies over three diseases further prove that MKCD is capable of providing reliable disease-related circRNA candidates.

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