Multi-scale neighbor topology guided transformer and KAN enhanced feature learning for prediction of disease-related circRNAs

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Abstract

Circular non-coding RNA (circRNA) is closely associated with various human diseases. Identifying disease-related circRNAs can provide deeper insights into the pathogenesis of diseases. Advanced prediction methods for circRNA-disease associations mainly focus on graph learning techniques such as graph convolutional networks and graph attention mechanisms. However, these methods do not fully encode the multi-scale neighbor topology among nodes. We propose a **m**ulti-scale neighbor topology-guided transformer and **K**AN enhanced feature learning-based **c**ircRNA and **d**isease association prediction model (MKCD) to integrate multi-scale neighbor topology, complex relationships among multiple nodes, and the global and local

dependencies of node pair attributes. First, MKCD incorporates an adaptive random walk with restart (ARWR) component, which can generate neighbor topologies covering different scopes of neighbors by random walking on the circRNA-disease-miRNA heterogeneous graph. Second, we design a dynamic multi-scale neighbor topology-guided transformer (DMTT), which leverages the multi-scale neighbor topology to guide the learning of relationships among circRNA, miRNA, and disease nodes. The multi-scale neighbor topology is dynamically evolved, enabling dynamical guidance of the transformer's learning process. Third, we establish a feature gated network (FGN) to access the feature importance of the topological features derived from DMTT and the original features of the nodes. Finally, we develop an adaptive Kolmogorov-Arnold network and convolutional neural networks joint learning strategy to learn the global and local dependencies of features of circRNA and disease node pairs. The comprehensive comparison experiments demonstrate the superior prediction performance of our method over six advanced methods, and ablation experiments further highlight the effectiveness of ARWR, DMTT, FGN, and ACK. Case studies on three diseases further validate the application value of our method in discovering reliable circRNA candidates for diseases of focus.

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. The KATZHCDA and PWCDA models calculate the association scores for each circRNA-disease pair based on the paths connecting them in heterogeneous networks.[12,13] The 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] The 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 (CNN)-based models to predict disease-related circRNAs,[23–25] yet they overlook the neighbor topology structure among multiple circRNA and disease nodes. The Bi-SGTAR proposed by Li et al. employs an encoder with sparse gating to predict the propensity of all circRNA-disease associations.[26] This method also neglects the topology formed by circRNA and disease nodes. Other methods are based on graph convolutional networks[27–29] and graph attention networks,[30] and combinations of both,[31] to learn deep features of 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 circRNA-disease association prediction model, MKCD, aimed at learning the multi-scale neighbor topology, the relationships among circRNA, miRNA, and disease nodes, and the global and local dependencies between features of node pairs. The main contributions of this work are summarized as follows.

First, the circRNA-disease-miRNA heterogeneous graph includes circRNA, disease, and miRNA nodes, along with their association, interaction, and similarity relationships. Each circRNA (disease, miRNA) node in the heterogeneous graph has multi-scale neigh-

bors, with varying degrees of closeness to the node. To differentiate the contributions of different scale neighbor topologies to node feature learning, we propose a strategy based on adaptive random walk with restart (ARWR). This strategy can adaptively determine the importance of each scale neighbor topology and form multi-scale neighbor topology embeddings.

Second, most current transformers focus only on the similarities between node features while neglecting the topological structure among nodes. The proposed dynamic multi-scale neighbor topology-guided transformer (DMTT) encodes the relationships among multiple circRNA, miRNA, and disease nodes. DMTT can generate a dynamically evolving neighbor topology and utilize it to evaluate the importance of all circRNA, miRNA, and disease nodes.

Third, multi-scale neighbor topology-guided node features focus on leveraging information from the topological structure, while the original features of circRNA, miRNA, and disease nodes contain more detail. We design a feature gated network (FGN), which enables discriminating the importance of topological features and original features.

Finally, the features of circRNA and disease node pairs contain both local and global dependencies. We propose a feature learning strategy for node pairs, ACK, which effectively learns global dependencies among features by the Kolmogorov-Arnold network (KAN)[32] and learns local relationships among features through a multi-layer CNN. Comparative experiments demonstrate MKCD outperforms state-of-the-art methods in predicting circRNA-disease associations, and case studies validate our method can effectively screen potential disease-related circRNA candidates.

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 between circRNA, disease, and miRNA(Figure 1(a)). MKCD consists of three 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 ARWR(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.

Dataset

The dataset utilized in this study is derived from previous work,[33] which comprises two datasets containing circRNA and disease 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 consolidated dataset consists of 989 circRNA-diseas e 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,[34] the circad database,[35] and the circRNADisease database.[36]

CircRNA-disease-miRNA heterogeneous graph

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

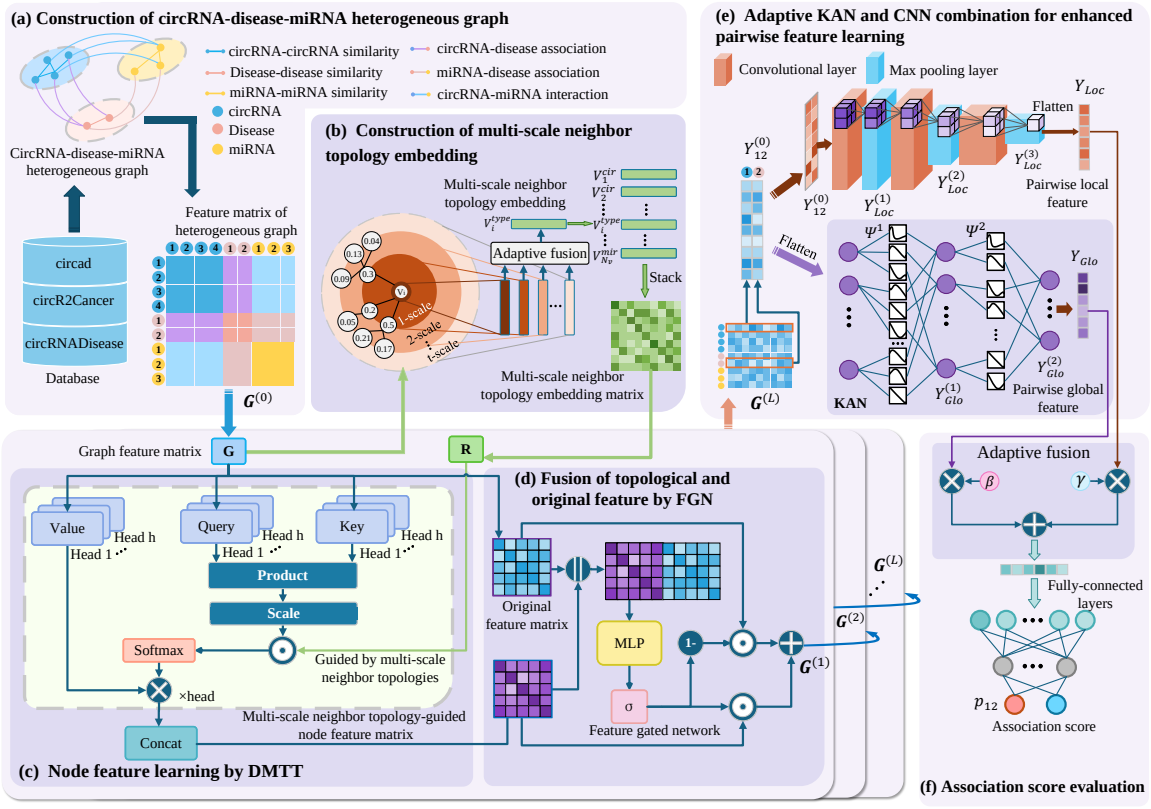

Figure 1: The overall framework of MKCD. **(a)** Construction of the circRNA-disease-miRNA heterogeneous graph. **(b)** Construct multi-scale neighbor topology embeddings through ARWR. **(c)** Learning the complex relationships among circRNA, miRNA, and disease nodes based on DMTT. **(d)** Fuse topological 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.

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 matrices 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 matrices 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.

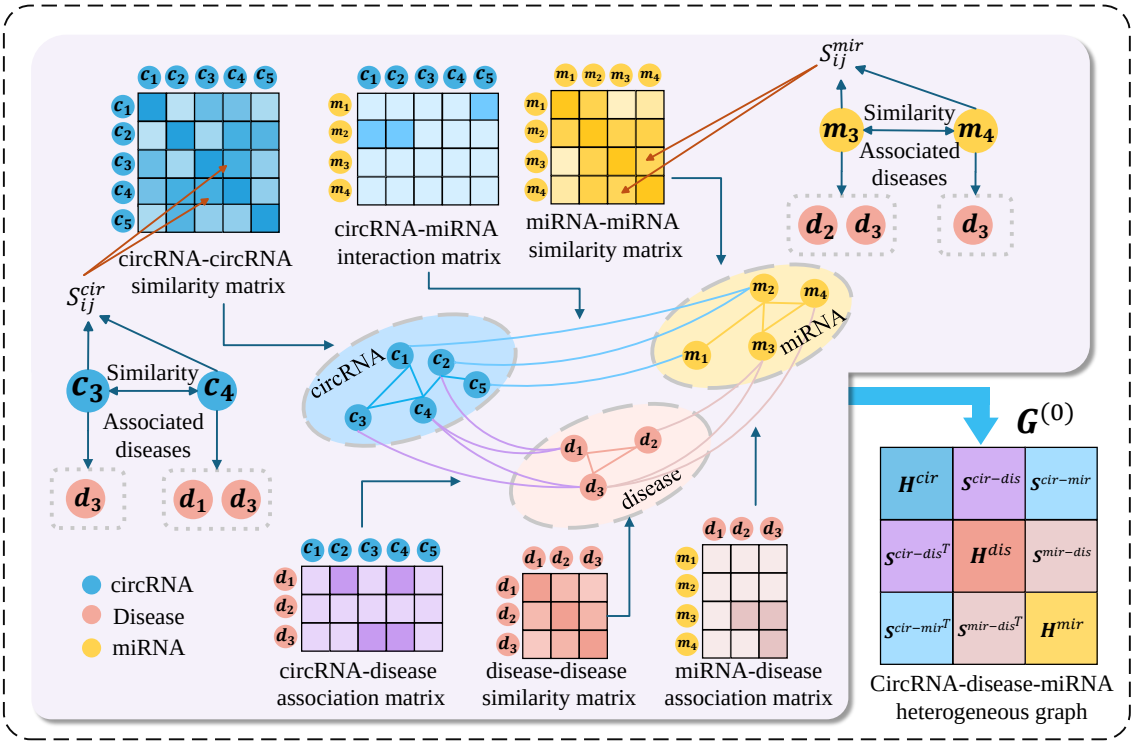

Figure 2: Construction of the circRNA-disease-miRNA heterogeneous graph based on multi-source data.

According to the method proposed by Wang et al.,[37] 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.[37] and Chen et al.,[38] 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_{cir}^i diseases, which forms the set $\Omega_i^{cir} = \{d_{ik} | k = 1, \ldots, N_{cir}^i\}$, and the j-th circRNA node v_j^{cir} is associated with the disease set $\Omega_j^{cir} = \{d_{jl} | l = 1, \ldots, N_{cir}^j\}$. 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,

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

where N_v denotes the total number of circRNAs, miRNAs, and diseases, and $S^{cir-dis^T}$ represents the transpose of the matrix $S^{cir-dis}$. 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.

Construction of multi-scale neighbor topology embedding

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 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 employ ARWR (adaptive random walk with restart) 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 $\theta_i(t) \in \mathbb{R}^{1 \times N_v}$,

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

where the j-th value of $\theta_i(t)$ denotes the probability that the walker starts from v_i reaches node v_j after t steps ($0 \leqslant j < N_v$). $\theta_i(0)$ 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 probability of the walker traveling from v_i to node 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,

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

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

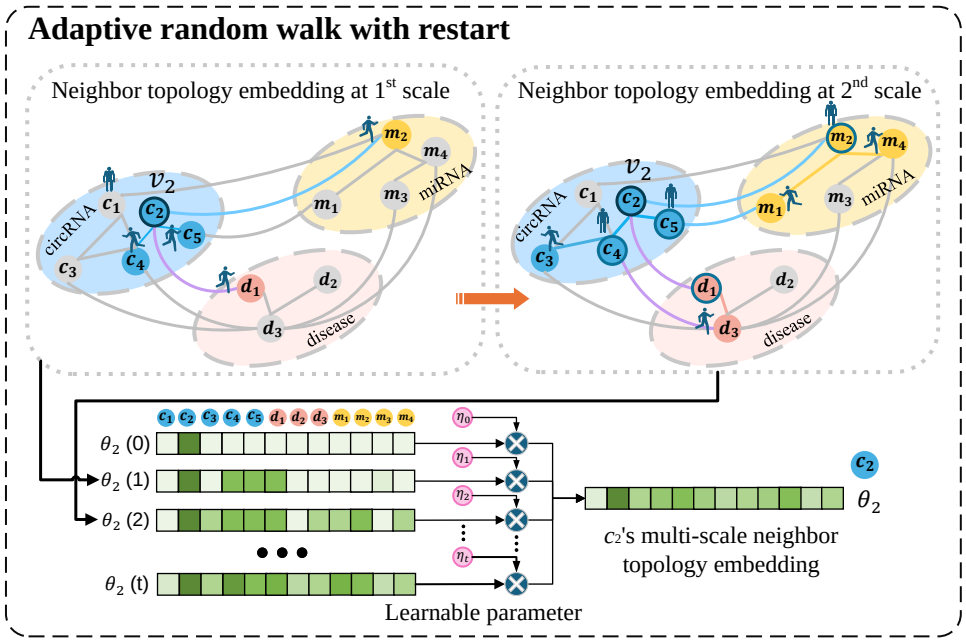

Figure 3: Process of constructing multi-scale neighbor topology embeddings with ARWR, illustrated by node c_2

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

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

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.,[39] we introduce a DMTT (dynamic multi-scale neighbor topology-guided transformer) mechanism that utilizes the multi-scale neighbor topology embeddings established by ARWR 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 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 $R^{(l)}$ for each node is reconstructed through ARWR 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 self-attention encoding. We perform a Hadamard product operation between the i-th row of $R^{(l)}$ and the i-th row of $S_m^{(l)}$. This approach allows the multi-scale neighbor topology embeddings to guide the learning of attention scores. We establish the multi-scale neighbor topology-guided attention score matrix $\widetilde{S}_m^{(l)} \in \mathbb{R}^{N_v \times N_v}$ as follows,

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

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

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

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

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 a FGN (feature

gate network) in 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.

Adaptive KAN and CNN combination enhanced pairwise feature learning

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

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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,

$$Y_{Glo}^{(l)} = KAN^{(l)}(Y_{Glo}^{(l-1)}) = \Psi^{(l)}(Y_{Glo}^{(l-1)}), \tag{16}$$

where $KAN^{(l)}$ denotes the l-th KAN layer. When $l = 1$, $Y_{Glo}^{(0)}$ represents 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,

$$\Psi^{(l)} = \begin{pmatrix} \psi_{1,1} & \psi_{1,2} & \cdots & \psi_{1,n^{(l-1)}} \\ \psi_{2,1} & \psi_{2,2} & \cdots & \psi_{2,n^{(l-1)}} \\ \vdots & \vdots & \ddots & \vdots \\ \psi_{n^{(l)},1} & \psi_{n^{(l)},2} & \cdots & \psi_{n^{(l)},n^{(l-1)}} \end{pmatrix}, \tag{17}$$

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-th layer to the j-th neuron in the $(l-1)$-th layer. The $\psi_{i,j}$ is composed of a basis function and a B-spline function,

$$\psi_{i,j} = \omega_b b(x) + \omega_s spline(x), \tag{18}$$

$$spline(x) = \sum_{k=1}^{n_{grid}} c_k B_k, \tag{19}$$

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.

Pairwise local feature learning based on CNN

We have established a CNN module to learn the local features of circRNA-disease node pairs. In the CNN, 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 $Y_{Loc}^{(l)}$,

$$Y_{Loc}^{(l)} = max(\tau(W_{conv}^{(l)} * Y_{Loc}^{(l-1)} + b_{conv}^{(l)})), \tag{20}$$

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 $Y_{Loc} \in \mathbb{R}^{1 \times f}$.

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,

$$\beta = \frac{e^{s_\beta}}{e^{s_\beta} + e^{s_\gamma}} \ , \quad \gamma = \frac{e^{s_\gamma}}{e^{s_\beta} + e^{s_\gamma}} \ . \tag{21}$$

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

$$Y_F = \beta \cdot Y_{Loc} + \gamma \cdot Y_{Glo} \ \ , \tag{22}$$

where $\cdot$ denotes scalar multiplication.

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 $[v_i^{cir}, d_j^{dis}]$,

$$p_{ij} = softmax(W_{Fin} Y_F + b_{Fin}), \tag{23}$$

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,

$$loss = -\sum_{(i,j)\in N} \left[y_{ij} \log(p_{pos}) + (1 - y_{ij}) \log(p_{neg}) \right], \tag{24}$$

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, $y_{ij} = 0$.

Experimental evaluations and discussions

Parameter settings

In the ARWR module, we utilize the 0 to 2-scale neighbor topology to construct multi-scale neighbor topology embeddings, with the restart probability λ for random walks 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.

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)[40] and the area under the precision-recall curve (AUPR)[41] as evaluation metrics. AUC and AUPR are calculated separately for each fold, and the averages of these five folds yields 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.

Ablation experiments

To validate the effectiveness of MARWR (multi-scale neighbor topology embedding based on adaptive random walk with restart), DMTT (dynamic multi-scale neighbor topology-guided transformer), FGN (feature gate network), and ACK (adaptive KAN and CNN combination learning), we conducted a series of ablation experiments (Table 1). We sequentially removed the MARWR, 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 0.947 and 0.271, respectively. When the MARWR module was removed, the AUC and AUPR decreased by 3.4% and 6.8%, 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 3.8% drop in AUC and a 7.6% 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 2.4% and 5.0%, 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 1.6% in AUC and 3.1% 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. MARWR contributes the second largest to the prediction results, as MARWR effectively introduces multi-scale neighbor topology embedding into node feature learning.

Table 1: Results of ablation experiments of MKCD.

MARWR	DMTT	FGN	ACK	Average AUC	Average AUPR
✗	✓	✓	✓	0.913	0.203
✓	✗	✗	✓	0.909	0.195
✓	✓	✗	✓	0.923	0.221
✓	✓	✓	✗	0.931	0.240
✓	✓	✓	✓	**0.947**	**0.271**

Comparison with other methods

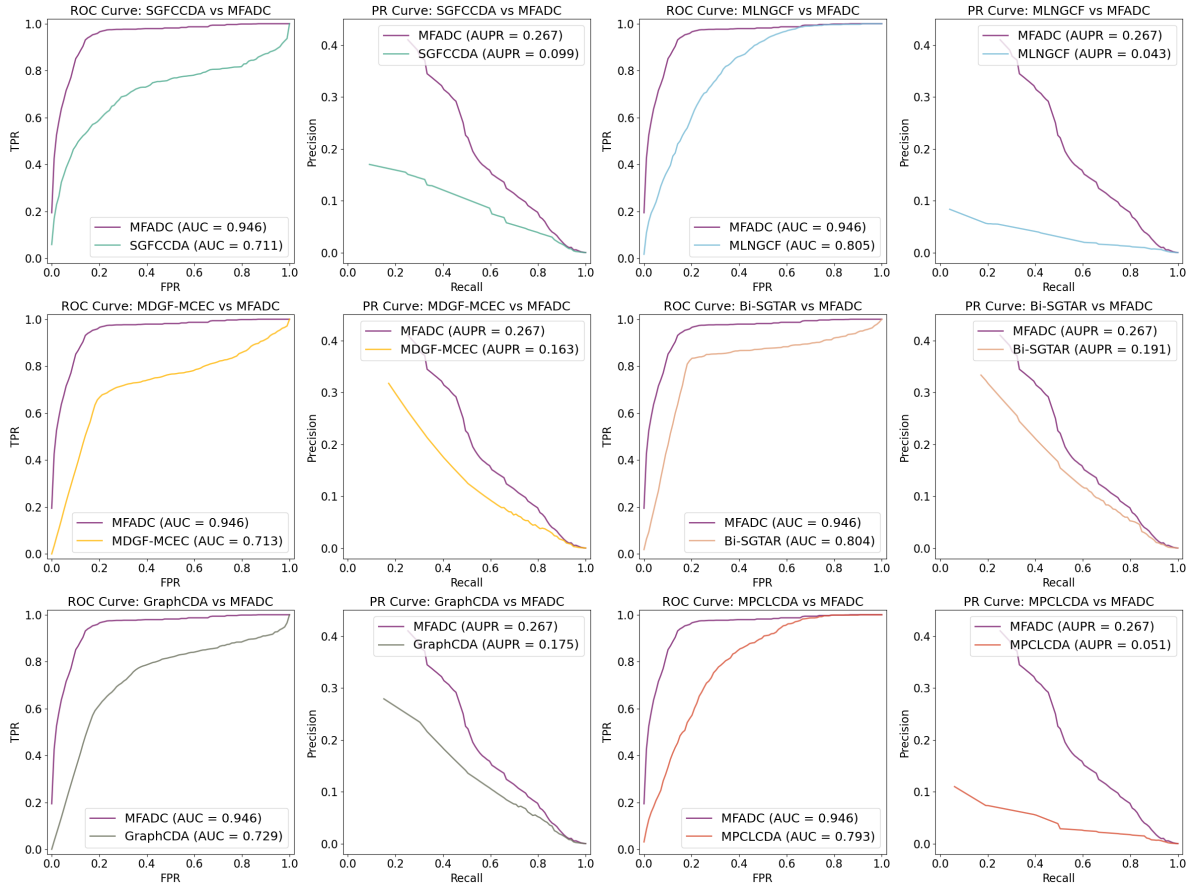

Figure 4: ROC and PR curves of MKCD and other comparative methods.

Table 2: 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

We compared MKCD with six advanced methods for predicting circRNA-disease associations, including SGFCCD,[27] MLNGCF,[30] MDGF-MCEC,[29] Bi-SGTAR,[26] GraphCDA,[31] and MPCLCDA.[28] Each method was 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 4 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 0.947, 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 0.271, which is higher than SGFCCDA, MLNGCF, MDGF-MCEC, Bi-SGTAR, GraphCDA, and MPCLCDA by 17.2%, 22.8%, 10.8%, 8.0%, 9.6%, and 22.0%, 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 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

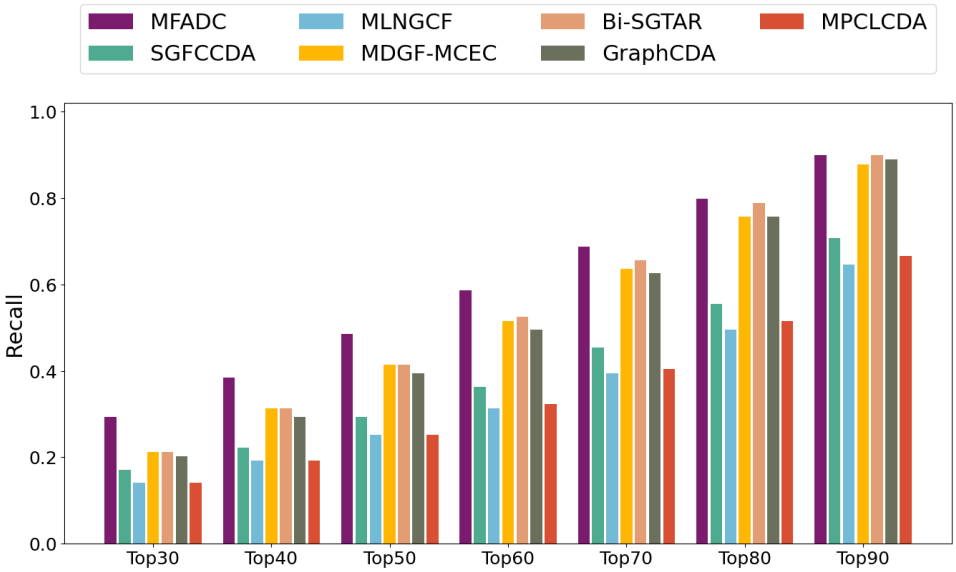

Figure 5: Recall rates of diseases at multiple top k cutoffs.

evaluate whether our method outperforms the other six methods significantly. According to the results in Table 2, 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 5). 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.

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,[42,43] while systemic lupus erythematosus is a systemic autoimmune disease, primarily affecting women.[44] 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 3, 4, and 5 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.[45] This database, along with relevant bioinformatics literature, was used to validate the predictions of circRNA-disease associations.

Table 3: 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 4: 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.

Using glioma as an example (Table 3), all 15 circRNAs are validated in the literature, with 14 of them have been identified in circRNADisease v2.0. For instance, the top-ranked hsa_circ_002136 was found by He et al.[46] to inhibit the viability, migration, and tube formation of U87 glioma-exposed endothelial cells (GECs). Li et al.[47] 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 4) are confirmed in the literature and have been included in circRNADisease v2.0. For example, Li et al.[48] identified hsa_circ_0046599 as a potential biomarker for systemic

Table 5: Top 15 predicted results of systemic lupus erythematosus-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.

lupus erythematosus. Hsa_circ_0000479 was confirmed by Guo et al.[49] to be upregulated in peripheral blood mononuclear cells of patients with SLE.

For glioblastoma, 11 of the top 15 circRNA candidates (Table 5) are validated in recent literature and documented in circRNADisease v2.0. For example, the study by Wang et al.[50] demonstrated that circNT5E exhibits tumor suppressor-like features in glioblastoma. Additionally, circMMP9 has been shown by Wang et al.[51] to promote the proliferation, migration, and invasion of glioblastoma multiforme cells.

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 S1.

Conclusions

This paper introduces a novel approach for encoding the relationships among circRNA, miRNA, and disease node features, as well as learning and integrating the 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 neighbor topology is adaptively determined. The designed multi-scale neighbor topology-guided transformer can dynamically update the neighbor topology and learn the dynamic relationships between the features of circRNA, miRNA, and disease nodes. A feature-level gated network

is established to assign higher weights to topological and original features based on their importance. The proposed ACK encodes the features of circRNA-disease node pairs, which helps to reveal the local and global dependencies between pairwise attributes. The results of five-fold cross-validation experiments demonstrate that the AUC and AUPR of MKCD are higher than those of six comparative methods. The recall rate of top-ranked circRNA candidates and case studies on three diseases indicate that MKCD is capable of providing reliable disease-related circRNA candidates.

Data and Software Availability

The source codes and datasets are freely available at https://github.com/pingxuan-hlju/MKCD.

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Supporting Information Available

The authors declare no competing financial interest.

- The top 15 circRNA candidates predicted by MKCD for each disease are listed in Supplementary File S1.

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