Computational Approaches for Predicting circRNA-Disease Associations: A Comprehensive Review and Integration of Methods

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Circular RNA (circRNA), a class of non-coding RNA, produced through the back-splicing of a pre-mRNA, has emerged as a promising way to understand the complex molecular pathways involved in various diseases. These peculiar non-coding RNAs play diverse roles in regulating gene expression, cellular communication, and protein translation, thereby substantially influencing disease pathogenesis. Their involvement in disease initiation and progression underscores the significance of exploring the associations between circRNAs and particular diseases. Exploring the possibilities of circular RNAs can lead to new strategies for diagnosing and treating newly emerging diseases. In contrast to traditional costly biological experiments for revealing associations between circular RNAs and diseases, novel and more efficient computational approaches are being developed to uncover the complex relationships between circRNAs and diseases. Comprehending these associations offer vital insights into disease mechanisms, that can contribute to disease diagnostic and therapeutic strategies. This paper analyses eleven fundamental studies investigating circRNA-disease associations using advanced computational techniques, including network- based, matrix-based and machine learning methods. Further- more, the study concludes with a comprehensive listing of the Area Under the Curve (AUC) values from each of the studies, providing a quantitative assessment of the predictive performance of the computational models. The findings from these studies lay the groundwork for developing novel diagnostic and therapeutic approaches for a broad spectrum of human diseases that target explicitly specific circular RNAs.

Keywords: CircRNA, Associations, Disease, Matrix- completion, Machine learning, Network analysis.

2024. In Mukesh Saraswat & Rajani Kumari (eds.), *Applied Intelligence and Computing*, 195–208. Computing & Intelligent Systems, SCRS, India. DOI: https://doi.org/10.56155/978-81-955020-9-7-20

1 Introduction

CircRNA, a peculiar type of non-coding RNA, is notable for its circular structure resulting from back splicing [18]. This distinct feature draws attention to the crucial part that circRNA plays in several human diseases [5], [12]. circRNAs are very stable because of their unique structure. Other non-coding RNAs also regulate gene expression and cellular functions, but circRNAs are notable for their stability. The identification of circRNA in pathogens traces back in 1971 [16]. Upon its initial identification in pathogens in the late 1970s, circRNA was commonly perceived as "shear noise" lacking biological relevance [23]. However, the advancements in second-generation sequencing technology, as highlighted by Salzman et al. (2012), have demonstrated the widespread existence of circRNAs in diverse samples, including malignant tissue cells and human embryonic stem cells [26], [2], [20]. These samples comprised human embryonic stem cells, the cervical cancer cell line Hela, and bone marrow from children diagnosed with acute lymphoblastic leukemia. Previous studies have brought attention to the consequential involvement of circular RNA (circRNA) in human diseases [4]. The challenges in prompt and unambiguous human disease detection have emphasized the need for effective computational methods and conventional biological techniques.

The functional significance of circRNA has become more evident, with these circular RNA molecules actively engaging in diverse biological pathways. These roles encompass the regulation of gene expression, intercellular communication, and the translation of proteins. circRNAs exert a substantial influence through their interactions with proteins, microRNAs, and other molecules [15]. circRNA and linear RNAs are both the types of RNA but are different in structure and functions. Linear RNAs have a start and end, forming a straight line, and mainly carry instructions from DNA to make proteins, such as beta-globin mRNA, which helps produce hemoglobin in red blood cells. In contrast, circRNAs form a loop with no start or end, which makes them more stable. They usually don't code for proteins but help in gene expression. An example is CDR1as, a circRNA that binds and inhibits microRNA-7, affecting various cell processes. Operating as "sponges" within cells, they modify the inhibitory effects of circRNAs on target genes. These discoveries have confirmed the critical role of circRNAs in the initiation and progression of various diseases [24], [13]. In a recent study published in 2023, researchers explained that in the case of Alzheimer's disease, circRNAs found in patients' brains could influence the production of proteins involved in the disease by interfering with the standard processing of genetic information, contributing to brain cell damage and memory loss. In gastric cancer, certain circRNAs can act like sponges and absorb the microRNAs that usually prevent the production of proteins that promote cancer growth. The absorption of microRNAs leads to an increase in cancer-promoting proteins, aiding tumor development. Researchers explained this in the journal "Journal of Cancer Research and Clinical Oncology". These are some recent cases which indicates the influence of circRNAs in disease pathogenesis.

circRNAs with a looped structure act as "sponges," influence disease formation, and are crucial for regulating gene expression. Different diseases will result when there is a disruption in the average balance of gene regulation. Furthermore, circRNAs can interact with proteins, thereby influencing cellular functions and leading to developing diseases like cancer, cardiovascular diseases, and neurological disorders. This comparative study extensively examines the computational methods employed in exploring the circRNA-disease associations. The selected methods include Network-Based, Matrix-based, and Machine Learning-based techniques. The analysis presented here offers a comprehensive overview of the methodologies employed by researchers in identifying novel circRNA-disease relationships. Moreover, the AUC values displayed in Table 1 highlight the predictive performance evaluation of various computational techniques employed across the discussed papers.

2 Computational Models

Circular RNAs (circRNAs) have emerged as a fascinating class of non-coding RNAs that play crucial roles in various biological processes, enticing candidates for therapeutic intervention in multiple diseases [34]. Understanding the complex associations between circRNAs and diseases has become a focal point in biomedical research, as these associations can shed light on disease mechanisms [33]. Efforts to open up the complex regulatory networks involving circRNAs are expected to provide valuable insights into disease progression and offer promising avenues for developing personalized medicine strategies [11]. Investigating circular RNA-disease associations involves integrating network-based, matrix-based, and machine learning with deep-learning methods to uncover potential links between circRNAs and various diseases.

Network-based methods provide a framework for exploring circRNA-disease associations by connecting complex interactions within biological systems as networks. These approaches aims to uncover potential relationships between diseases and circRNAs as a missing edge prediction problem in the constructed heterogenous circRNA-disease association network [25]. These frameworks construct a network representation consisting of two types of nodes: circRNAs and diseases. The intra-edges among circRNAs and diseases represents their similarities and inter-edges represent experimentally confirmed associations between them. The value of an inter-edge is 1 if there exists an experimentally verified association between a circRNA and disease, otherwise, it is 0. The intra-edges among circRNAs and diseases represents the respective similarities as edge weights. Using iterative algorithms, the weights of unknown edges between circRNAs and diseases are updated from 0; the new weights represent the probability of new circRNA-disease associations [10]. These predicted associations are validated using experimental techniques. These methods can easily integrate various types of biological data such as disease data, circRNA data, and their associations. A study on neuroblastoma, a type of cancer, uti-

lized network-based methods to integrate gene expression, protein-protein interactions, and circRNA data into a comprehensive network.

Matrix-based methods are simple and provide computational efficiency when identifying associations between circRNA and disease. These methods efficiently handle large-scale datasets using sparse matrix representations to process and analyze high-throughput data. The matrix-based methods predict circRNA-disease associations by unitizing three matrices; circRNA similarity matrix, disease similarity matrix and circRNA-disease association matrix. circRNA similarity matrix is an adjacency matrix where values represent the similarities between circRNAs. Similarly, disease similarity matrix is an adjacency matrix where the values represent the similarities between diseases. In the circRNA-disease association matrix, circRNAs are represented as rows and diseases are represented as columns. This is a binary matrix where 1 represents experimentally verified circRNA-disease associations and 0 represents unknown associations [35]. The circRNA-disease relationship prediction problem is formulated as predicting the values of each unknown entry in the association matrix. The predicted values represent the probability of association between each circRNA and disease [21], [22]. For example, in a study on hepatocellular carcinoma (HCC), researchers used matrix-based methods such as singular value decomposition (SVD) to reduce the dimensionality of circRNA expression data.

Machine learning-based methods are excellent in capturing complex, non-linear relationships in circRNA data, providing high predictive accuracy in identifying disease associations. These methods can quickly learn relevant features from raw data and handle high-dimensional data. Machine learning methods define circRNA-disease relationship prediction problem as a classification task. These classification approaches compute circRNA, disease similarity measurements and build features from these similarities [6]. The features are then sent to different classifiers to predict novel circRNA-disease associations. Some methods directly send the features to classifiers [using classifier only]. Some other approaches extract relevant features using various feature extraction models like Autoencoders, Convolution Neural Networks, etc., and send the extracted features for classification [29]. In colorectal cancer research, machine learning models were used to analyze circRNA expression profiles, thereby successfully predicting circRNAs that play crucial roles in tumorigenesis.

In all three categories mentioned above, the model performance is assessed by various cross-validation experiments and case studies. Various evaluation measures like AUC, accuracy, specificity, sensitivity, F1-score, etc., are computed, and the model's performance is evaluated [1]. Classification of computational approaches for identifying novel circRNAs associated with diseases is depicted in Figure 1.

2.1 Based on Network

We selected three network-based approaches: PWCDA, NSL2CD, and RWLR.

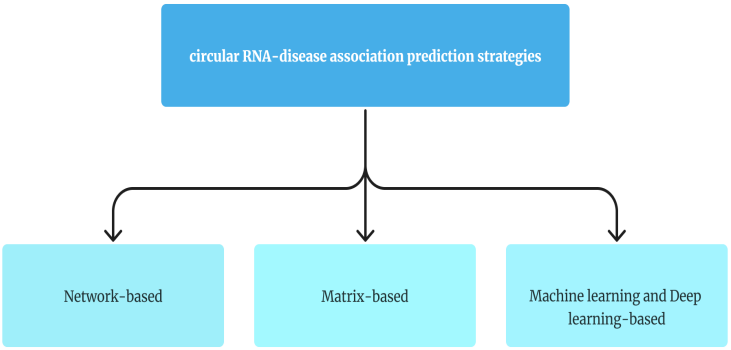

Figure 1: Various strategies for circular RNA-disease association prediction.

PWCDA: This study [17] introduce a novel computational approach, PWCDA, for predicting associations between circular RNAs (circRNAs) and diseases. This method calculates the similarity between diseases and circRNAs based on their related gene sequences. Then, it utilizes Gaussian Interaction Profile (GIP) kernel similarity scores derived from circRNA-disease associations to handle missing scores. They merge these similarity scores to construct a heterogeneous network comprising three sub-networks: disease similarity, circRNA similarity, and circRNA-disease associations. Subsequently, they compute association scores for each circRNA-disease pair by analyzing the paths connecting them within the heterogeneous network, thus determining their potential association. They evaluate the performance of PWCDA using leave-one-out cross-validation (LOOCV) and five-fold cross-validation techniques. They also conduct case studies focusing on three common diseases: Breast, Gastric, and Colorectal Cancer. Their experimental findings demonstrate the reliability of the computational approach in effectively predicting circRNA-disease associations, as evidenced by various validation measures.

NSL2CD: Xiao et al. proposed a new model NSL2CD [31] to discover potential circRNA-disease associations and thus to prioritize the role of circRNAs behind human diseases. The proposed approach initiates by computing the similarities between diseases and circRNAs, then proceeds to extract low-dimensional features from various data domains. Afterward, a model based on network embeddings and adaptive subspace learning is formulated to forecast potential associations between circRNAs and diseases by map-

ping the high-dimensional data spaces into a common subspace. Moreover, this model incorporates graph regularization and sparsity constraint terms to capture latent characteristics and structural insights. The results are plotted using the Receiver Operating Characterization (ROC) curve, and achieved an AUC value 0.926. They used some metrics such as accuracy, recall, precision, and F1-score for the performance comparison.

RWLR: In this study [8], the researchers developed a computational model termed RWLR (Random Walk with Logistic Regression) to predict circRNA-disease associations. Initially, they constructed a network depicts the similarities between circRNAs by assessing their functional characteristics based on circRNA-related genes. Later, they applied a random walk with a restart algorithm on this network to traverse through the circRNA similarity space. By analyzing the outcomes of this random walk and the circRNA-disease association matrix, they extracted features for each circRNA-disease pair. Additionally, they employ a logistic regression model to forecast potential circRNA-disease associations. They used leave-one-out cross-validation (LOOCV), five-fold cross-validation (5CV), and ten-fold cross-validation (10CV) methodologies to evaluate its predictive performance. They compared this proposed method against two contemporary approaches, namely PWCDA [17] and DWNN-RLS [32]. The findings indicated that RWLR consistently yields higher AUC values than the abovementioned methods.

2.2 Based on Matrix

We selected three matrix-based approaches: SIMCCDA, iCircDA-MF, and DMCCDA.

SIMCCDA: In the work [19], researchers introduce a new method called SIMCCDA (Speedup Inductive Matrix Completion for circRNA-Disease Associations prediction) for predicting associations between circRNAs and diseases. They use important information of known circRNA-disease associations, similarities in circRNA and disease sequences, and a mathematical calculation called Gaussian interaction profile kernel similarity. Then, they apply a speedup inductive matrix completion technique to build the prediction model. SIMCCDA is tested using leave-one-out cross-validation on a dataset that combined three different databases and found that the method achieved an Area Under the ROC curve (AUC) value of 0.8465. The method outperforms other advanced models in predicting circRNA-disease associations. Additionally, they performed case studies on breast cancer, stomach cancer, and colorectal cancer to evaluate its performance further. Overall, the results demonstrate that SIMCCDA reliably predicts circRNA-disease associations.

iCircDA-MF: In the study [30], Wei and Liu introduced a technique to predict circRNA-disease associations. The method begins by extracting circRNA and disease similarities by using disease semantic data and establishing associations between gene-disease, circRNA-gene, and circRNA-disease. Based on these similarities, circRNA-disease associations are computed. In the subsequent phase, the interaction profiles of circRNA-disease pairs are updated. circRNA-disease association predictions are made by applying matrix

factorization to the revised circRNA-disease interaction profiles. Finally, a comparison is made between the proposed method and other methods, revealing that iCircDA-MF showed superior performance by achieving an AUC value of 0.9178.

DMCCDA: In order to obtain an efficient, reliable method for predicting potential circRNA-disease associations, Zuo et al. introduced a novel technique named the Double Matrix Completion method (DMCCDA) [36]. Its initial step involved creating a similarity matrix derived from circRNA sequences and semantic disease data, and the matrix was updated through matrix multiplication with corresponding similarity values. Additionally, Zuo devised a Gaussian interaction profile similarity matrix, obtained from experimentally confirmed associations between circRNAs and diseases.

Furthermore, matrix completion techniques were applied to refine specific blocks, resulted from combining the previously derived association matrix with the corresponding Gaussian similarity matrix. The objective was to enhance the overall completeness of the matrix, considering both circRNA and disease perspectives. As a result, the method achieved an impressive AUC value of 0.9623.

2.3 Based on Machine Learning and Deep Learning

We selected five methods that employed machine learning and deep learning techniques for circRNA-disease association prediction, SGANRDA, AE-RF, RGCNCDA, GATNNCDA and XGBCDA.

SGANRDA: Wang et al. explored the development of a semi-supervised deep learning model called SGANRDA, which considers circRNA sequence information to predict disease-associated circRNAs [28]. Initially, they transformed the circRNA sequence into natural language and applied some techniques to extract relevant features. The fusion feature set was constructed by combining disease semantic features with disease and circRNA GIP kernel features. The pre-training phase involved Generative Adversarial Networks (GANs) with features from all circRNA-disease pairs, and the model parameters were fine-tuned. Following pre-training, the GAN underwent further refinement using an equal number of labeled positive and negative samples. For precise identification of associations between circRNA and disease, an extreme learning machine (ELM) classifier was employed. SGANRDA demonstrated notable results, achieving an AUC of 0.9411 in Leave-One-Out Cross-Validation (LOOCV) and 0.9223 in 5-fold cross-validation.

AE-RF: Deepthi and Jereesh [7] presented an ensemble method based on an autoencoder and a random forest classifier to determine the association between circRNA and diseases. This approach combines multiple sources of information, such as circRNA functional similarity, disease semantic similarity, and Gaussian interaction kernel similarities between circRNAs and diseases, to construct features. The model trains a deep autoencoder using these features to capture complex biological patterns. The resultant reduced-dimensional features are fed to a random forest classifier, which helps to identify new circRNA-disease associations. Predicted results with probabilities above a certain thresh-

old are considered potential circRNA-disease relationships and are subjected to further experiments. In experiments, the proposed approach achieved high performance with AUC values 0.9486 in five-fold cross-validation and 0.9522 in ten-fold cross-validation.

RGCNCDA: Chen et al. [3] introduced a novel approach known as RGCNCDA (Relational Graph Convolutional Network for Improved Prediction of circRNA-Disease Associations) based on Relational Graph Convolutional network (R-GCN). In the initial step, a comprehensive network is established by combining three biological entity networks: circRNA similarity, miRNA similarity, and disease similarity, and by capturing various interactions and associations among these entities. Subsequently, structural information is extracted from the network using the Random Walk with Restart (RWR) and Principal Component Analysis (PCA) models. Finally, a prediction model is constructed using an encoder and decoder to predict potential circRNA-disease associations. RGCNCDA outperforms six other computational methods, which is evidenced in its high AUC scores of 0.9491 and 0.9441 in fivefold cross-validation experiments based on the circR2Disease dataset and the circRNA-disease dataset, respectively.

GATNNCDA: Ji et al. developed a novel methodology [14], for inferring disease-related circRNAs by combining a Graph Attention Network (GAT) with a multi-layer neural network. This approach integrates disease semantic, circRNA functional and Gaussian Interaction Profile (GIP) kernel similarities. These combined similarities served as initial node features in their model. A graph attention framework was applied to extract more informative features from the differentiated circRNA-disease graph. This framework selectively focuses on relevant information and enhances feature extraction capabilities. For prediction purposes, a multi-layer neural network-based classifier was introduced. A 5-fold cross-validation was applied for the evaluation purpose of this model. The results showed that the proposed method, GATNNCDA, attained an average AUC value of 0.9613 and an AUPR (Area Under the Precision-Recall curve) value of 0.9433 on the CircR2Disease dataset. The superior performance of these findings highlights the effective role of GATNNCDA in identifying disease-associated circRNAs.

XGBCDA: To develop a novel model for predicting associations between circRNAs and diseases, Shen et al. introduced XGBCDA [27]. The method systematically computes associations by extracting primary features- including statistical and graph theory features—from the integrated circRNA similarity network, disease similarity network, and circRNA-disease association network. Subsequently, these original features are put into an XGBoost classifier to derive latent features. The XGBoost model undergoes a learning process, constructs a tree and assigns each instance to a specific leaf, and the method combine latent features derived from the XGBoost model with the original features.

This combined feature set trains the final predictive model, enabling effective predictions of associations between circRNAs and diseases. Fivefold cross-validation was conducted to assess the performance of this approach. Through the calculation of AUC,

impressive values of 0.9935, 0.9913, 0.9996, 0.9968, and 0.9660 were obtained for each respective fold. On average, the AUC across all folds was found to be 0.9861. These results highlight the robust predictive capability of this method in identifying the relationships between circRNAs and diseases.

The figure 2 describes step-by-step processes in identifying potential circRNA-disease associations. The initial phase involves obtaining data from various databases, primarily the circR2Disease database [9]. Using the data obtained, the circRNA-circRNA and disease-disease similarities are computed. Then, one of the techniques among network-based, matrix-based or machine learning and deep learning-based is applied to derive associations within circRNA-disease relationships. Finally, the acquired findings are assessed based on their AUC values. Table 1 describes the techniques applied and their corresponding AUC values.

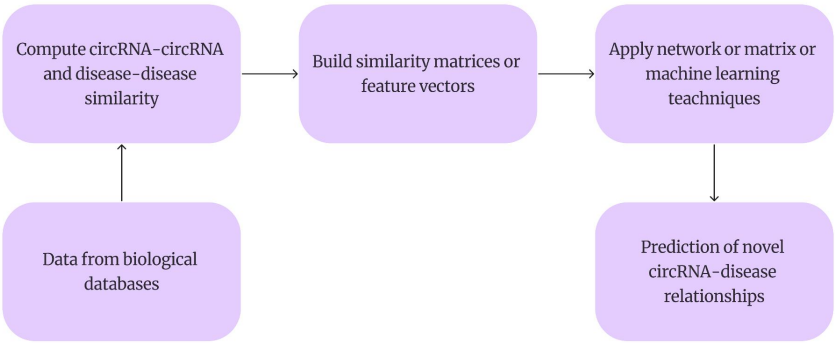

Figure 2: Workflow diagram of circRNA-disease association prediction

3 Conclusion

Recently, circular RNAs (circRNAs) have acquired significant attention due to their significant role in various disease processes. This paper comprehensively explored the interactions between circRNAs and disease pathogenesis, emphasizing the critical importance of computational techniques in identifying these novel relationships. Advanced computational methods, including network-based, matrix-based, machine learning and deep learning analysis, have proven its role in uncovering the associations between circRNAs and specific diseases. By integrating data from various sources, including the circR2Disease database, researchers have made significant achievements in predicting and validating circRNA-disease associations.

Table 1: Techniques applied and their corresponding AUC values

Computational Approach	Study	Technique	Result (AUC)
Network based	Lei et al. [17]	Path weighted method	0.884
	Xiao et al. [31]	Network embedding & subspace learning	0.926
	Ding et al. [8]	Random walk and Logistic regression model	0.960
Matrix based	Li et al. [19]	Inductive matrix completion	0.8465
	Wei & Liu [30]	Matrix factorization	0.9178
	Zuo et al. [36]	Double matrix completion	0.9623
Machine Learning and Deep Learning based	Wang et al. [28]	Semi-supervised generative adversarial network	0.9223
	Deepthi & Jereesh [7]	Deep Autoencoder-based classification	0.9486
	Chen et al. [3]	Relational graph convolutional network	0.9491
	Ji et al. [14]	Graph attention & multi-layer neural network	0.9613
	Shen et al. [27]	Multiple heterogeneous network	0.9861

The findings from the eleven studies discussed in this study provide insight into the efficiency and reliability of different computational models in predicting circRNA-disease associations. Additionally, the network-based methods have proven effective in inferring disease-related circRNAs and revealing essential relationships within the circRNA-disease network. Notably, research utilizing matrices has demonstrated superior performance to several novel approaches. These methods have shown remarkable accuracy and efficiency in predicting circRNA-disease associations. The machine learning and deep learning-based approaches have exhibited substantial promise in exploring various biological data types to predict potential circRNA-disease associations accurately. These models have demonstrated robust performance and high predictive power, providing insightful information on the regulatory processes that underlie the links between circRNAs and diseases.

Overall, the comprehensive analysis offered in this study serves as a valuable resource for researchers dedicated to identifying the novel mechanisms behind the onset and progression of disease. The insights gained from these studies could pave the way for developing innovative diagnostic and therapeutic strategies, ultimately leading to improved outcomes for patients suffering from diverse human diseases. As the field of circRNA research continues to evolve, the integration of advanced computational techniques will undoubtedly play a pivotal role in furthering our understanding of the complex interplay between circRNAs and disease parthenogenesis.

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