Attention based convolutional neural network for predicting RNA-protein binding sites

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Abstract

RNA-binding proteins (RBPs) play crucial roles in many biological processes, e.g. gene regulation. Computational identification of RBP binding sites on RNAs are urgently needed. In particular, RBPs bind to RNAs by recognizing sequence motifs. Thus, fast locating those motifs on RNA sequences is crucial and time-efficient for determining whether the RNAs interact with the RBPs or not. In this study, we present an attention based convolutional neural network, iDeepA, to predict RNA-protein binding sites from raw RNA sequences. We first encode RNA sequences into one-hot encoding. Next, we design a deep learning model with a convolutional neural network (CNN) and an attention mechanism, which automatically search for important positions, e.g. binding motifs, to learn discriminant high-level features for predicting RBP binding sites. We evaluate iDeepA on publicly gold-standard RBP binding sites derived from CLIP-seq data. The results demonstrate iDeepA achieves comparable performance with other state-of-the-art methods.

1 Introduction

RNA-binding proteins (RBPs) take over about 10% of the eukaryotic proteome and are closely associated with many biological processes [1]. How to identify whether a RNA binds to a RBP is important for further analyzing the RNAs’ functions. Many experimental technologies have been developed, such as CLIP-seq. However, they are still time-consuming and high-cost. Thus, computational identification of RBP binding sites are urgently needed. To this end, many machine learning based methods have been proposed. For example, GraphProt encodes RNA sequences and structures in a graph, which is further fed into support vector machine to classify bound sites from unbound sites [2]. iONMF integrates multiple sources of data to predict RBP binding sites using Orthogonal matrix factorization [3].

Recently, deep learning have been successfully developed to predict RNA binding sites. For example, deepnet-rbp applies deep belief network to integrate k-mer frequency features of sequences and structures to model RBP targets [4]. DeepBind [5] applies a convolutional neural network (CNN) [6] to identify RBP binding sequence specificity. iDeep uses multimodal deep learning to integrate different sources of data to infer RBP binding sites and sequence motifs [7]. iDeepS infers sequence and structure motifs simultaneously using a convolutional neural network and long short temporal network [8]. The core of all the above methods is CNN, which demonstrates high accuracy for identifying RBP binding sites.

It is commonly assumed that a RNA sequence that can be bound by a RBP, which contains at least one binding subsequence (motif) of this RBP. Therefore, it is fairly intuitive to consider putting more attention on this motif subsequence along the RNA sequence. To better model this characteristics...
of RBP binding sites, attention mechanism is introduced [9]. Attention mechanism allows deep learning models to focus selectively on only the important features. Deep models augmented with attention mechanisms have obtained great success on machine translation [9, 10], and computational biology [11].

In this study, we propose an attention-based convolutional neural network model, iDeepA, to predict RBP binding sites from RNA sequences alone. iDeepA combines learned features from CNNs and two levels of attentions to locate important subsequences.

2 Method and Materials

2.1 Dataset

We download RBP binding sites dataset derived from CLIP-seq from GraphProt (http://www.bioinf.uni-freiburg.de/Software/GraphProt) [2]. It contains 24 experiments of 21 RBPs. For each RBP, it has thousands of bound RNA subsequences with variable length, and almost the same number of negative sequences are selected with no evidence showing they are bound to this RBP.

2.2 iDeepA

In this study, we present a CNN based method with attention mechanism to classify RBP bound sites from unbound sites (Figure 1). We first encode RNA sequences into one-hot encoding showing the presence of nucleotide A,C,G,U. Then the one-hot encode matrix is fed into a CNN, which involves convolution, activation, and max-pool operations. The CNN layer preserves the spatial information and output feature maps for subsequent processing. Inspired by [9, 10], we introduce attention mechanism to further attend differentially to related motifs and locate important positions for predicting RBP binding sites. We extract three levels of abstract features: 1) The output feature maps from the CNN. 2) The outputs from attention model 1 for sequence dimension, whose input is one copy of the two-dimensional hidden states from the CNN. 3) The outputs from another attention model 2 for feature map dimension, whose input is transposition of hidden states from the CNN. For both attention models, we use the same structure with a feedforward neural network as decoder to generate a representation vector. The output O from an attention model are:

\[
O = \sum_{t=1}^{T} h_t \ast \alpha_t
\]

where \(h_t\) is hidden state from the CNN and \(\alpha_t\) is the softmax weight of each hidden state \(h_t\):

\[
\alpha_t = \frac{\exp(e_t)}{\sum_{i=1}^{T} e_i}
\]

where \(e_t\) is generated from the hidden state \(h_t\) by a feedforward neural network.

By augmenting with the attention mechanism, it learns a soft transformation between the input and output sequences. Finally, the outputs from CNN layer and two attention models are connected to two fully connected layers. The last layer is the sigmoid layer used to classify the RBP bound sites from unbound sites. We optimize a categorical entropy loss function using RMSProp [12] with number of epochs 30. iDeepA is implemented using Keras 1.1.2 library https://github.com/fchollet/keras.

2.3 Baseline methods

We compare iDeepA with other state-of-the-art methods, GraphProt, deepnet-rbp, Deepbind and MILCNN. A negative sequence has no any binding site, while a positive sequence contains at least one binding sites of this RBP. It is intuitive to consider each sequence as a bag, whose any subsequence is an instance. Inspired by the characteristics, MILCNN first breaks each RNA sequence into multiple overlapping fixed-length subsequence, each subsequence is an instance and each sequence is a bag of instances. Next, MILCNN trains a CNN under the multiple instance learning framework. Multiple instance learning has been used for predicting protein-DNA interactions [14].
Figure 1: The flowchart of iDeepA. iDeepA first encodes the sequence into one-hot matrix, which is fed into a CNN to output feature maps. Next, we input the last hidden states of the CNN to an attention model, and its transposition into another attention model. In the end, the outputs from two attention models and the CNN are combined into two fully connected layers to predict RBP binding sites.

3 Results

GraphProt, deepnet-rbp, MILCNN, DeepBind and iDeepA achieve the average AUC 0.887, 0.902, 0.861, 0.921 and 0.921 across 24 experiments (Figure 2), respectively. iDeepA and DeepBind yield similar average AUC, which is higher than other three methods. In addition, iDeepA improves some RBPs with small training set on that DeepBind does not achieve high AUC. For example, iDeepA obtains an AUC of 0.839 for C17orf85 with only 4000 training samples, which is an increase by 11% compared to an AUC 0.755 of DeepBind. The results indicates introducing attention mechanism can enhance the learning ability on small dataset than DeepBind and it is fast to focus on important subsequences. However, introducing attention mechanism does not improve the performance on those RBPs with large number of training samples, it is possible because feeding more samples into model training can make the model to converge to the same optimum model. In addition, MILCNN yields lower performance than other methods, it maybe because that training RNA sequences are themselves subsequence anchored at the peak center derived from CLIP-seq, breaking them into subsequence may also break the binding sites.

4 Conclusion

In this study, we present an attention-based CNN method to predict RBP binding sites. Our method iDeepA yields comparable performance with other state-of-the-art methods. However, we still do not further investigate whether the attention can be used to identify interpretable motifs. In future work, we expect to obtain more interpretability of iDeepA and comprehensively evaluate iDeepA on larger dataset with more RBPs.

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Figure 2: The AUCs of different methods for predicting RBP binding sites. The AUCs of GraphProt and deepnet-rbp are taken from original papers, other three methods are ran on the same training and testing set with similar CNN network.

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