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A Convolutional Neural Network Using Dinucleotide One-hot Encoder for identifying DNA N6-Methyladenine Sites in the Rice Genome

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ABSTRACT

N6-methyladenine (m^6A) is one of the crucial epigenetic modifications and is related to the control of various DNA processes. Carrying out a genome-wide m^6A analysis via wet experiments is fundamental but takes a long time. As complementary methods, computing tools, especially those based on machine learning, are urgently needed. A new protocol, iRicem6A-CNN, for identifying m^6A sites in the rice genome was developed. This protocol was designed to use dinucleotide one-hot encoding to generate input tensors for predictions by convolutional neutral networks, and achieved five-fold cross-validation and independent testing accuracy values of 93.82% and 96.19%, respectively, performing better than those of other available predictors. The experiment results demonstrates that only the ability of iRicem6A-CNN based on 2-mer one-hot encoding is to display high performance but also to perform more stably and robustly than models using 1-mer one-hot encoding. A webserver is accessible at http://iRicem6A-CNN.aibiochem.net

1. Introduction

As the product of a critical chemical modification of DNA, N6-methyladenine (m^6A) is found ubiquitously in various organisms ranging from eukaryotes to prokaryotes [1] and is evidently involved in DNA replication, DNA repair and transcription regulation [2–5]. Genomic analysis of DNA methylation has emerged as the next-generation sequencing technology, and especially single-molecule real-time (SMRT) sequencing detection has shown increasing application [6–8]. The genome-wide distribution of N6-methyladenine sites has become better characterized, which has led to a better understanding of its biological functions [9–12]. For example, genome-wide m^6A sites studies have revealed different regulatory functions of m^6A in different eukaryotes, and have shown m^6A in prokaryotes functioning as a marker to distinguish invading foreign DNA from host DNA [13].

In 2018, Zhou et al. [13] used SMRT to show that about 0.2% of all adenines in the rice genome are m^6A methylated, and since this discovery, all sorts of machine-learning-based computing methods for m^6A in the rice genome have been springing up. In 2019, Chen et al. [11] developed im6A-Pred, a support vector machine (SVM)-based method, that was trained on a benchmark dataset consisting of 1760 samples and achieved an accuracy of 83.13%. Subsequently, other methods based on the strengths of traditional machine learning algorithms like SVM, random forest (RF) and Markov chain models were developed for identifying m^6A sites in the rice genome; these methods included im6A-DNCP [14], MM-m6Apred [15] , SDM6A [16], iN6-methylat [17] and iDNAm6A-rice [18], and of them, iDNAm6A-rice showed the best accuracy at 91.7%.

Deep learning is a sub-discipline of machine learning and has shown great effectiveness in vision computing, natural language processing and even genomics computational modeling [19–24]. The major difference between deep learning and other machine learning methods is that deep learning does not need to handcraft features before modeling; instead it automatically learns the features embedded in the input data and could discover high-level abstract features to yield end-to-end models itself [25]. Although deep learning can generally achieve a better predictive performance than can the other traditional methods, it is not perfect. Traditional machine learning methods involve direct feature engineering and are easy to interpret and understand. They are also easier to adjust the hyperparameters and change the model design for traditional machine learning [1,26–31]. In contrast, the

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deep learning model is usually a "black box" and is hard to interpret. Moreover, deep learning involves the use of a data-driven model demanding large amounts of input data for training and a relatively high computational capacity [32]. Nevertheless, given the above-described advantages of deep learning, Alipanahi et al. [33] in 2015 set out to demonstrate the application of deep learning to DNA sequence analysis, and were the first to do so successfully. So since then, deep learning has been rapidly and increasingly applied to DNA, RNA and protein data mining [33–47]. In 2019, Tahir et al. [48] used a deep learning approach named iDNAm6A for predicting m^6A sites in the rice genome and obtained an accuracy of ~87%. Then Yu et al. [49] developed another deep-learning-based rice m^6A predictor, SNNRicem6A, and achieved with it a 5-fold cross-validation accuracy of 92.04%, making it one of the top rice m^6A predictors. Both methods adopted a single-nucleotide one-hot encoder and convolution neural network (CNN) for modeling.

In this study, we developed a new protocol, called iRicem6A-CNN, to improve the accuracy of predicting rice genome-wide m^6A sites. Distinguishing from reported protocols, our protocol employed a dinucleotide one-hot encoder to transfer DNA sequences into tensors, which were then input into the well-designed CNN for model optimization. It realized a 5-fold cross-validation accuracy of 93.82% and an independent testing accuracy of 96.19%, by values 1.97% and 12.5% better than those of the previously considered the best-performing predictor SNNRicem6A. Evidences indicate iRicem6A-CNN using 2-mer one-hot encoder is more robust and accurate than that utilized 1-mer one-hot encoding. The metrics comparison showed that the better performance of iRicem6A-CNN was not only due to its stable ability to recognize positive samples but also to its more precise identification of negative samples. A webserver for this protocol is available at http://iRicem6A-CNN.aibiochem.net.

2. Methods and materials

2.1. Datasets

Two widely used m^6A benchmark datasets for the rice genome were set up by Chen [11] and by Lv [18] separately, and were labeled as Chen-rice-m6A and Lv-rice-m6A. The Chen-m6A-rice dataset, consisting of 1760 samples with half of them being positive and other samples negative, has been extensively utilized by reported models based on non-deep-learning algorithms. The Lv-m6A-rice dataset was made of 154000 DNA sequences with m^6A sites and 154000 sequences without m6A sites, and has been adopted by Lv for iDNAm6A-rice [18] and by Yu for SNNRicem6A [49]. Sequences in both datasets were chosen to be 41 bp in length and with each having an adenine at the center position. Considering the data-hungry nature of the CNN model, we took the Lv-m6A-rice dataset for model training and the Chen-m6A-rice dataset for independent testing as doing in ref [18] for convenient comparison.

2.2. Data representation

Of the reported methods, some such as iDNAm6A-rice [18], SDM6A [16] and im6A-pred [11] involved the manual conversion of the sequence data into feature vectors via several predefined features, including but not limited to pseudo-nucleic acid composition, accumulated nucleotide frequency, nucleotide chemical property, etc. Instead of requiring prior knowledge of features to be extracted from the sequences, methods based on deep learning such as iDNAm6A [48] and SNNRicem6A [49] could automatically extract features from encoded DNA sequences. iDNAm6A and SNNRicem6A both applied one-hot encoding of A,C,G,T to convert DNA sequences into a matrix for feeding into a following CNN. Generally, the DNA kmer one-hot encoding process is shown in Figure 1 using AATTCAG as instance. Assuming that the length of the DNA sequence is L, and a windows with kmer sliding along with the sequence, then it will get L-k+1 kmer nucleotides and the i^{th} kmer $s_i$will be encoded as following:

$$s_i = [0, \cdots, 0, 1, 0, \cdots, 0] \tag{1}$$

The length of the vector$s_i$is 4^k, and the value of i^{th} position is 1 and values of the other positions are 0. As a result, a DNA sequence converts into a $R^{(L-k+1)\times 2^k}$ matrix composing of vectors like s_i.

As comparison to iDNAm6A and SNNRicem6A, in this study, we used one-hot encoding methods, but here to code dinucleotides (AA, AC, AG, AT, CA, CC, CG, CT, GA, GC, GG, GT, TA, TC, TG and TT). A window two nucleotides long was made to slide along a DNA sequence and each dinucleotide in the window was encoded into a one-hot encoding vector with 16 dimensions, and thus a DNA sequence with 41 nucleotides was transformed into a matrix with 40 rows and 16 columns. Each such matrix was further turned into a tensor fed into the built CNN model for training. The single nucleotides (A, C, G, T) one-hot encoding methods are also used for comparison.

2.3. Model construction

Figure 2 shows the framework of iRicem6A-CNN. First, the input layer is prepared. The DNA sequences were encoded via a 2mer one-hot coding method into matrixes each with 40 rows and 16 columns. Second, the matrixes were fed into a CNN. Here, the CNN consisted of one 1D convolutional layer with 200 filters and a rectified linear unit (ReLU) as the activation function. The filter kernel size was 8. After carrying out the convolution operation, a maxpooling layer was added with a pooling size of 4. A dropout layer was used next to the pooling layer, with a dropout rate of 0.16. Third, the intermediate feature units were flattened to fully connect them to the hidden dense layer. Finally, it is the output layer with 2 units fully connected to the previous layer. The softmax function was used for predicting whether or not a specified DNA sequence would contain a m^6A site: output probabilities greater than and less than a given threshold value were considered to indicate, respectively, the presence and absence of a m^6A site in the input sequence. The given threshold values include 0.5, 0.6, 0.7, 0.8, 0.9, 0.95, and 0.99. When the model was training, it compiled an adaptive moment estimation optimizer with a learning rate of 0.001, and categorical cross-entropy as a loss function.

2.4. Evaluation metrics and methods

Accuracy (ACC), sensitivity (Sn), specificity (Sp) and Matthew's correlation coefficient (MCC) are commonly and generally used valuation metrics for machine learning binary classification models [13,50–71]. These four metrics were calculated using the equations shown in supplementary materials Part 1. The receiver operating characteristic (ROC) curve and the area under ROC (auROC) were also used for model evaluation [72]. Three performance evaluation protocols are commonly applied in evaluating bioinformatics predictors [18,49,73–75]. They are resubstituting test, cross-validation and independent dataset test. K-Fold validation and jackknife test are two types of cross-validation methods. In this paper, we employed the 5-fold cross-validation and independent testing method to test the efficiency of the classification for comparison. The details please see the supplementary materials Part 2.

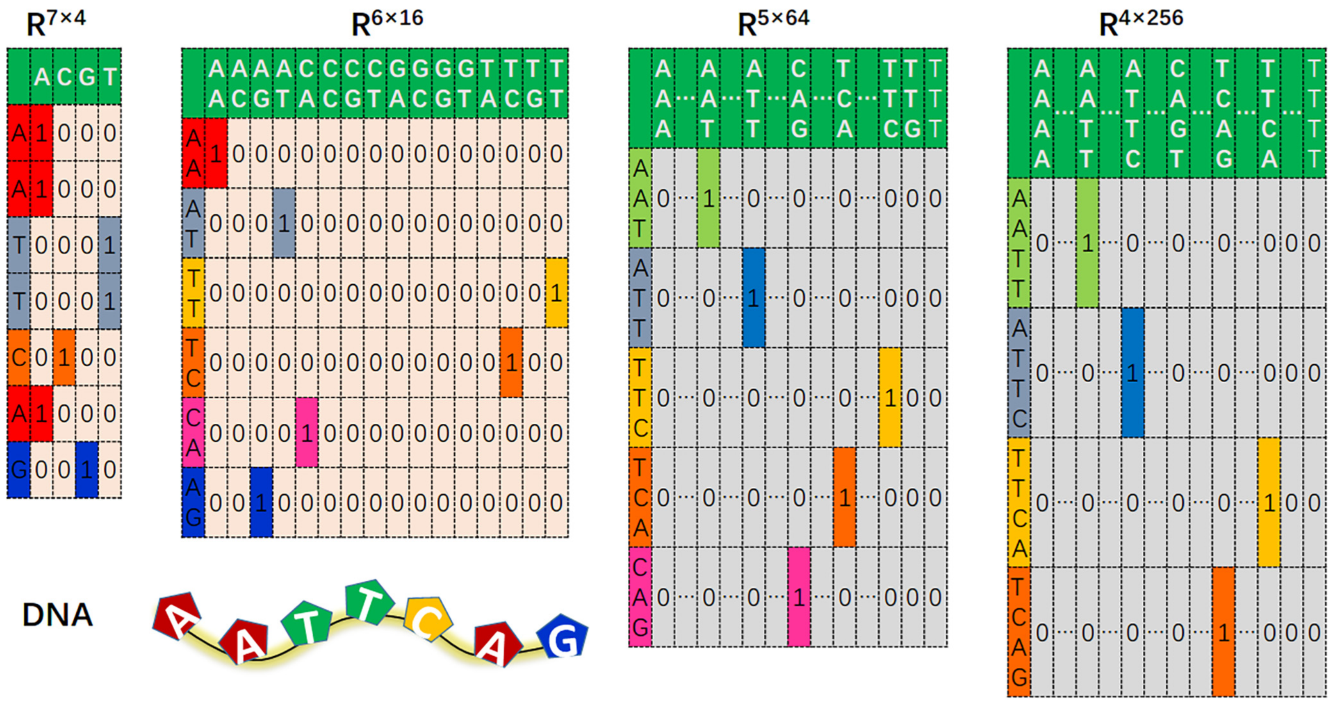


Figure 1. The schematic diagram of 1mer, 2mer, 3mer and 4mer one-hot encoding for the DNA sequence, taking AATTCAG as example. The AATCAG is converted into a 0-1R$^{m\times2^k}$ matrix, while m= sequence length-k+1 and k=1, 2, 3,4.

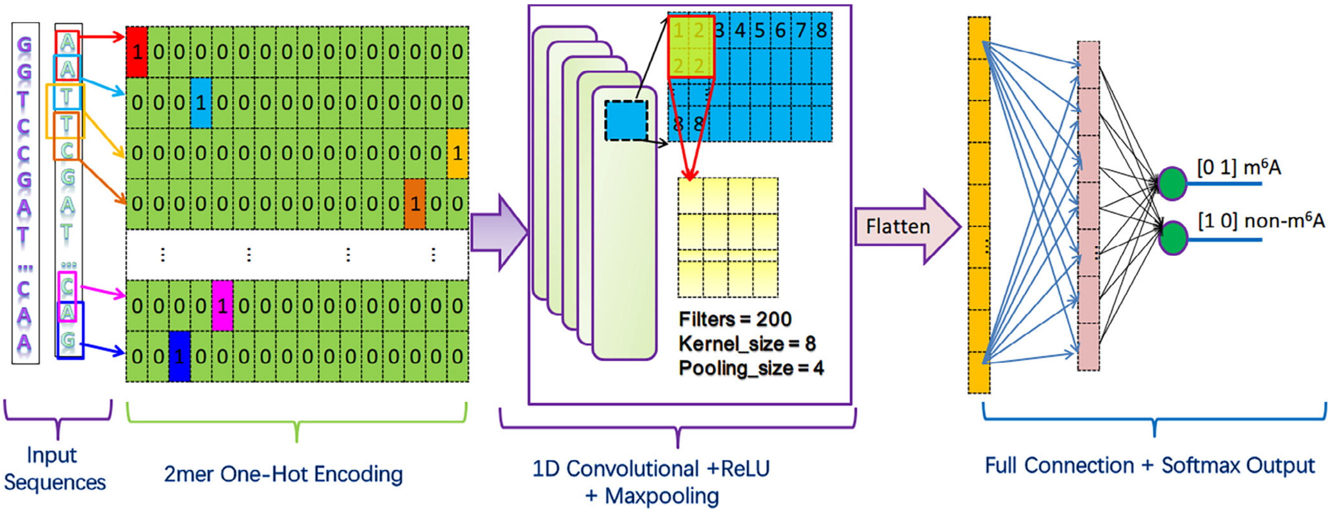


Figure 2. The architecture of the iRicem6A-CNN model used 2mer one-hot encoding.

3. Results and discussion

3.1. Comparison of models based on the different encoder

We constructed two models. One is based on 1-mer encoding, i.e. iRicem6A-CNN (1mer) and the other one is based on 2-mer encoding, i.e. iRicem6A-CNN (2mer). As shown in Figure 3A, the final evaluation results of the 5-fold cross-validation [76–81] for iRicem6A-CNN (1mer) were found to be ACC = 93.41%, MCC = 0.868, auROC = 0.975, Sn = 94.10%, Sp = 92.72%. While the 5-fold cross-validation score of iRicem6A-CNN (2mer) were that ACC = 93.82%, MCC = 0.877, auROC = 0.979, Sn = 94.34%, Sp = 93.31%, which increased by value of 0.4%, 1.0%, 0.4%, 0.3% and 0.6% over those of iRicem6A-CNN (1mer). In the view of model training cross-validation results, iRicem6A-CNN (2mer) has only a slight advantage in performance over the iRicem6A-CNN (1mer). In consideration of independent testing, iRicem6A-CNN (2mer) shows better prediction accuracy and more robustness than iRicem6A-CNN (1mer). For 3mer or 4mer one-hot encoding CNN models, their overall five-fold cross-validation metrics are inferior to iRicem6A-CNN (2mer)(see supplementary materials Figure 1. Also, if kmer≥3, the required memory for computing grew exponentially (supplementary materials Figure 2). Thus it is not a wise strategy to use 3mer or even more for one-hot encoding if not to take steps to reduce memory requirements.

Figure 3B and supplementary materials Table 1 display independent testing scores of both models under various predictions probability threshold. Overall, iRicem6A-CNN (2mer) shows higher scores at every predictions probability threshold. As predictions probability threshold is increased from 0.50 to 0.99, the

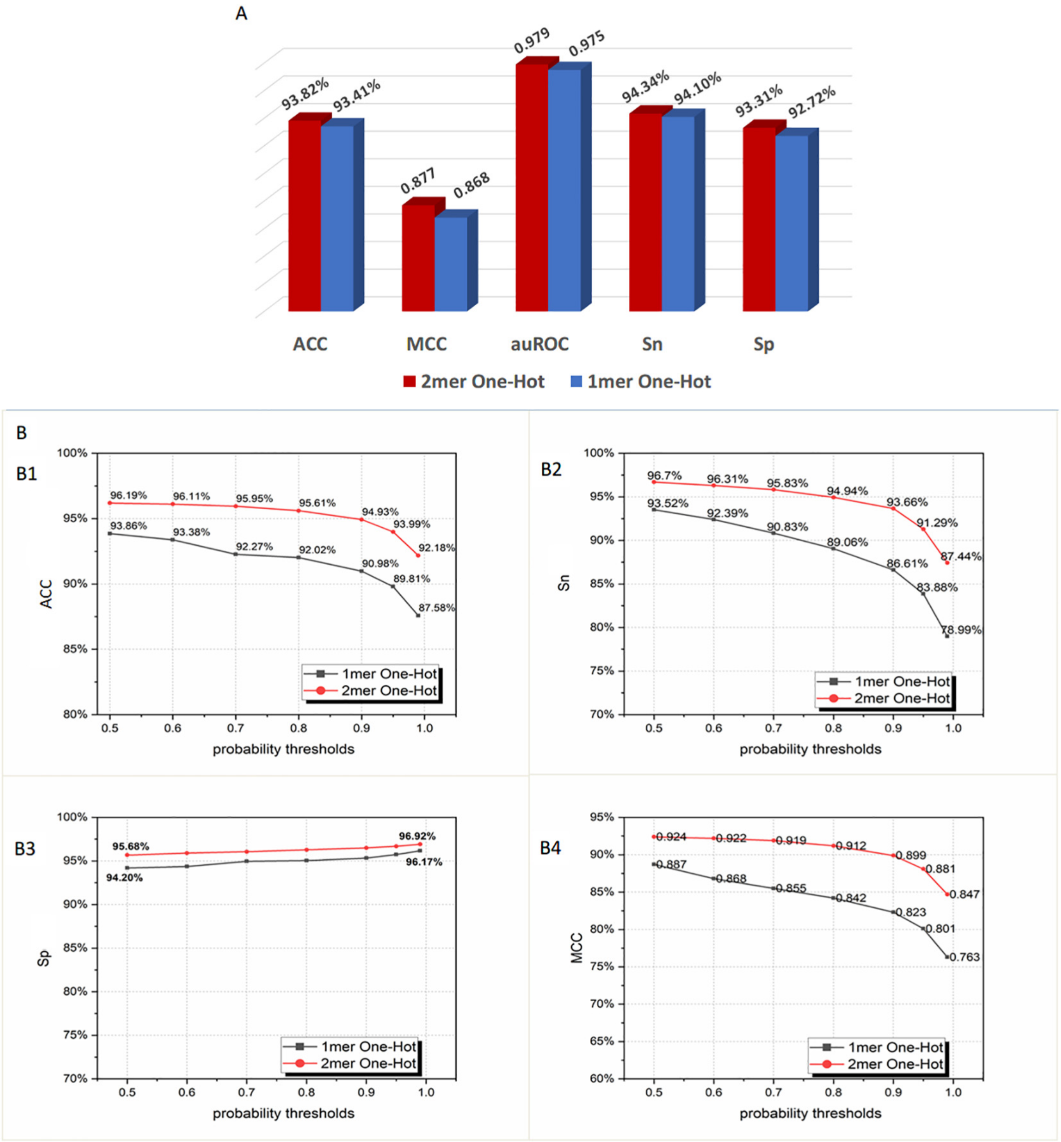


Figure 3. A) Five-fold cross validation and B) Independent testing results for models with different encoding methods under various prediction probability thresholds.

independent accuracy value of iRicem6A-CNN (2mer) declines from 96.19% to 92.18%, decreasing by 4.16%, while the value of iRicem6A-CNN (1mer) goes down from 93.86% to 87.58%, reducing by 6.69%. The sharper reduction of independent testing accuracy of iRicem6A-CNN (1mer) is mainly due to its lower positive samples identification ability as predictions probability threshold rising as displayed in Figure 3**B**. For instance, when predictions probability threshold increases from 0.5 to 0.99, the 15.5% declining magnitude of Sn for iRicem6A-CNN(1mer) is nearly 1.62 times of the Sn value (9.57%) of iRicem6A-CNN(2mer). These results provided evidence for not only the ability of iRicem6A-CNN(2mer) to display high performance but also to perform stably and robustly. It means that convolution neutral network using 2-mer one-hot encoding in rice DNA m6A analysis could automatically learn more effective latent features for positive samples than that based 1-mer one-hot encoding.

3.2. Comparison with previously reported models

Multiple predictors for rice DNA m^{6}A sites have been implemented and their cross-validation scores and independent testing results are **listed in supplementary materials Table 2 and 3** respectively. The predictions probability threshold is 0.5, which is widely used in reported predictors.

As shown in Figure 4A, in comparison to the previously considered best-performing predictor, i.e., SNNRicem6A, iRicem6A-CNN showed increased values of the ACC, MCC, auROC and Sp metrics, by 1.93%, 4.40%, 0.92% and 3.97%, respectively. With almost the same value of Sn, the Sp improvement showed that iRicem6A-CNN could predict negative samples more correctly than that SNNRicem6A did, which led to better accuracy performance of iRicem6A-CNN.

As shown in Figure 4B, we further comparatively analyzed the independent testing scores of three models trained on the Lv-m6A-rice dataset. The scores of iDNAm6A-rice were obtained from reference [18]. The data for SNNRicem6A were obtained from the model yielding the largest auROC value of the five cross-validation models according to reference [49], the values of which were computed via the source code offered in reference [49]. Evidently, although the cross-validation results of SNNRicem6A were not found to be significantly different from the accuracy of iRicem6A-CNN, the independent testing metrics values of iRicem6A-CNN were found to be considerably greater than those of SNNRicem6A. The ACC, MCC, auROC, Sn and Sp values for

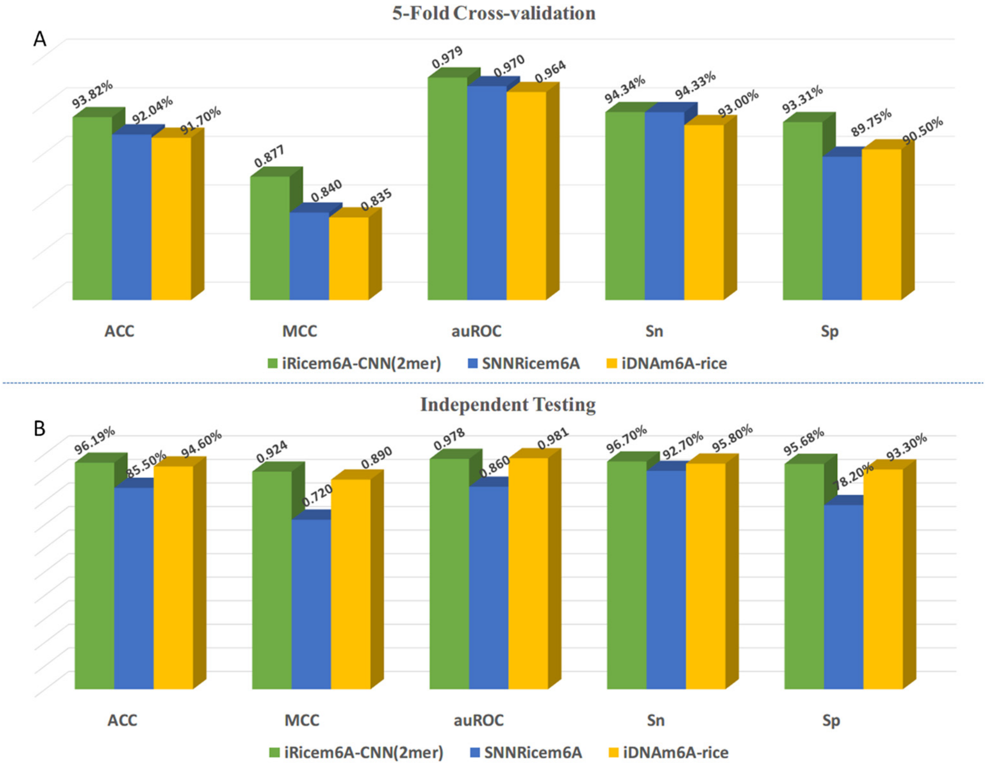
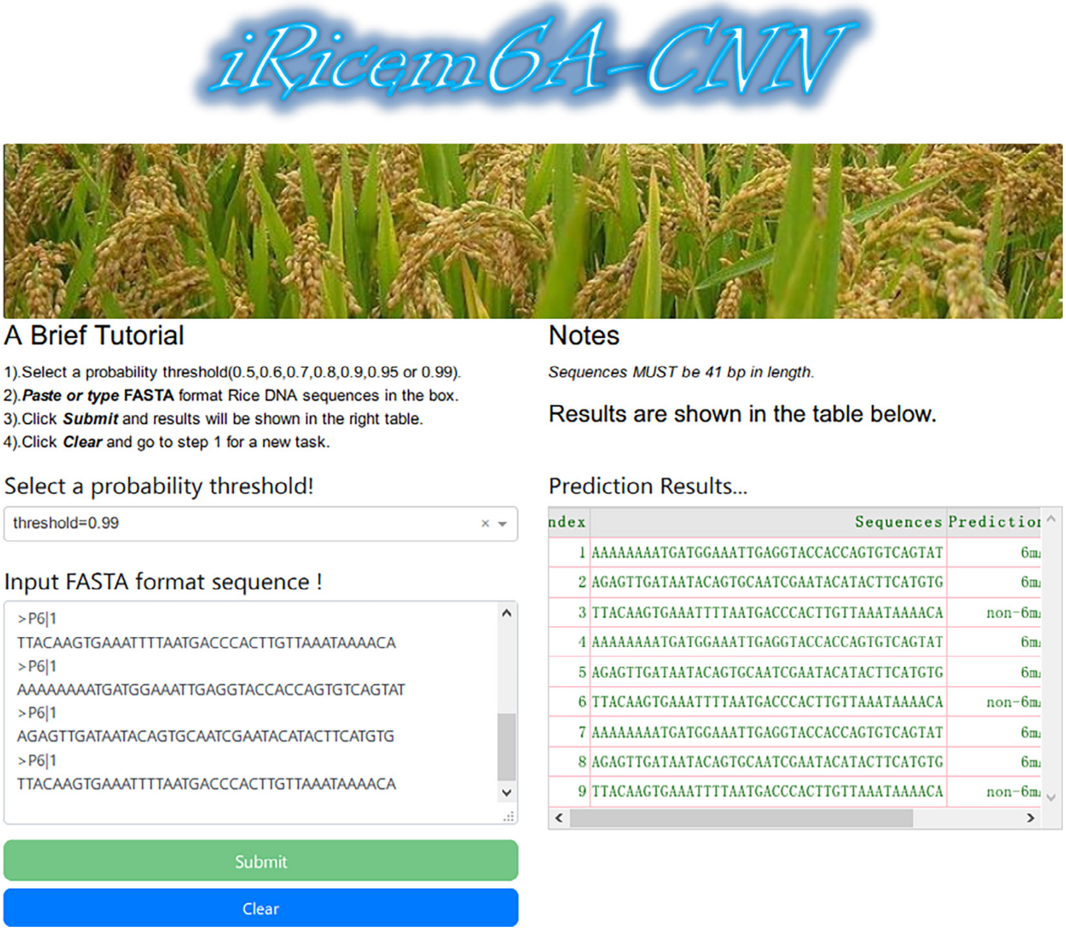


Figure 4. A) Five-fold Cross-validation scores of iRicem6A-CNN and the other two state-of-the-art models based on Lv-rice-m6A training dataset (probability threshold=0.50) and B) independent testing scores for iRicem6A-CNN and other models based on Chen-rice-m6A dataset.



A Brief Tutorial

1).Select a probability threshold(0.5,0.6,0.7,0.8,0.9,0.95 or 0.99).
2).***Paste or type*** **FASTA** format Rice DNA sequences in the box.
3).Click ***Submit*** and results will be shown in the right table.
4).Click ***Clear*** and go to step 1 for a new task.

Select a probability threshold!

threshold=0.99

Input FASTA format sequence !

```
>P6|1
TTACAAGTGAAATTTTAATGACCCACTTGTTAAATAAAACA
>P6|1
AAAAAAAATGATGGAAATTGAGGTACCACCAGTGTCAGTAT
>P6|1
AGAGTTGATAATACAGTGCAATCGAATACATACTTCATGTG
>P6|1
TTACAAGTGAAATTTTAATGACCCACTTGTTAAATAAAACA
```

Notes

Sequences MUST be 41 bp in length.

Results are shown in the table below.

Prediction Results...

ndex	Sequences	Predictio
1	AAAAAAAATGATGGAAATTGAGGTACCACCAGTGTCAGTAT	6m
2	AGAGTTGATAATACAGTGCAATCGAATACATACTTCATGTG	6m
3	TTACAAGTGAAATTTTAATGACCCACTTGTTAAATAAAACA	non-6m
4	AAAAAAAATGATGGAAATTGAGGTACCACCAGTGTCAGTAT	6m
5	AGAGTTGATAATACAGTGCAATCGAATACATACTTCATGTG	6m
6	TTACAAGTGAAATTTTAATGACCCACTTGTTAAATAAAACA	non-6m
7	AAAAAAAATGATGGAAATTGAGGTACCACCAGTGTCAGTAT	6m
8	AGAGTTGATAATACAGTGCAATCGAATACATACTTCATGTG	6m
9	TTACAAGTGAAATTTTAATGACCCACTTGTTAAATAAAACA	non-6m

Figure 5. Webserver interface.

iRicem6A-CNN all outperformed those of SNNRicem6A, by 12.5%, 28.3%, 13.7%, 4.3% and 22.3% respectively. Particularly, the remarkable difference between their Sp values indicated a greater ability of iRicem6A-CNN than of SNNRicem6A to accurately distinguish negative samples from positive samples, and hence indicated a better general performance of iRicem6A-CNN for rice-gnome m^6A sites discrimination. Compared with iDNAm6A-rice based on the random forest method, iRicem6A-CNN showed improvements of 1.68%, 3.82%, 0.94% and 2.55% in ACC, MCC, Sn and Sp respectively, with the other two metrics with tiny decline (0.30% of auROC). The better Sp and means its better recognition of negative and positive samples for iRicem6A-CNN compared to those of iDNAm6A-rice, which led to the greater ACC and MCC values for iRicem6A-CNN.

3.3. Webserver implementation

A webserver for iRicem6A-CNN is easily accessed at http://iRicem6A-CNN.aibiochem.net. The user firstly select a probability threshold (e.g. threshold = 0.99) and just needs to type or paste the DNA sequence in FASTA format into the text box as shown in the webpage (Figure 5) and then click the submit button for a prediction. After allowing a while for computing, the prediction results are displayed in a tabular format. To start a new query task, clicking the clear button resets the model, and repeating the above-mentioned operation allows iRicem6A-CNN to automatically handle the new query task.

4. Conclusions

Here, a new deep-learning-based protocol for m^6A sites in the rice genome, iRicem6A-CNN, was developed. The iRicem6A-CNN model was designed with a special feature, involving DNA sequences fed into the model becoming first converted into a 2-mer one-hot encoding tensor. The experiment results shown that model with 2-mer one-hot encoding outperforms model with 1-mer one-hot encoding and demonstrates more robust under various prediction probability threshold values. Application of the model showed a good 5-fold cross-validation accuracy (93.82%) and independent testing accuracy (96.19%), making it one of the best predictors of the m^6A site in the rice genome. Our analysis and comparisons showed iRicem6A-CNN to be capable of not only accurately predicting m^6A-positive samples but also reducing the error rate of negative sample identification, and our results indicated it to run better than the state-of-the-art predictors. Moreover, a user-friendly webserver for iRicem6A-CNN has been made available. We expect iRicem6A-CNN to become a useful tool for computationally discerning m6A sites. Note, moreover, that with regards to iRicem6A-CNN, there remains room for improvement: we expect new methods such as Gen2Vec [82], auto encoder [83], MOEA [84,85] or long- and short-term memory networks [86] to be explored for the purpose of further optimizing the model.

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CRediT authorship contribution statement

Zhibin Lv: Conceptualization, Methodology, Data curation. **Hui Ding:** Investigation. **Lei Wang:** Visualization, Investigation. **Quan Zou:** Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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