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# Machine Learning Approaches for RNA Editing Prediction

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## Abstract

RNA editing is a major post-transcriptional modification that contributes significantly to transcriptomic diversity and regulation of cellular processes. Exactly how cis-regulatory elements control RNA editing appears to be highly complex and remains largely unknown. However, with the improvement of computational methods for detecting and quantifying RNA editing from large-scale RNA-seq data, it has become possible to build computational models of RNA editing. Here we report our attempts to develop machine learning models for A-to-I editing prediction in human by training on a large number of highly confident RNA editing sites supported by observational RNA-seq data. Our models achieved good performance on held-out test evaluations. Furthermore, our deep convolutional model also generalizes well to a controlled study dataset.

## 1 Introduction

RNA editing is a post-transcriptional process where the nucleotide sequence of RNA transcripts is modified from its template DNA sequence by substitution, insertion, or deletion[1]. In animals, the most prevalent type of RNA editing is the conversion of adenosine (A) into inosine (I), also known as A-to-I editing[2]. This is catalyzed by the adenosine deaminase acting on RNA (ADAR) family of proteins, which binds co-transcriptionally to double-stranded regions of RNA (dsRNA)[2]. ADAR proteins stochastically edit adenosines and the editing frequencies are determined by cis-acting elements (RNA sequence and structures) and trans-acting cellular states[3]. A-to-I editing is involved in the regulation of many other cellular processes, such as RNA splicing[4], mRNA stability[5], and innate immune response against dsRNAs[6]. Additionally, A-to-I editing increases transcriptomic diversity, through recoding of the resulting amino acids[2] and altering microRNA processing[7]. Aberrant editing can result in cancer[8] and diseases in neurological[9], cardiovascular[5], and autoimmune systems[6].

In spite of its prevalence in humans, our understanding of the exact mechanism and regulation of A-to-I editing is still very limited[10]. The editing occurs in dsRNA regions and the two bases immediately next to the ‘A’ influence the activity of ADAR proteins[11]. Although it is proposed that A-to-I editing is regulated by both the sequence and structural context, there are no simple ‘motifs’ that can explain the editing[3, 10]. Therefore, there has yet been any ‘editing codes’ that can predict A-to-I editing sites given an RNA sequence[10], which is in contrast to other RNA processes where computational codes have been in active development, such as splicing[12–15], RNA protein binding[16–19], and alternative polyadenylation[20, 21]. Recently, there has been an increased interest in A-to-I ‘editing codes’ because of their potential to help with our understanding of RNA editing and applications in diagnostics[10] and RNA therapeutics[22, 23].

Most of the previous computational methods in studying RNA editing focused on the accurate detection of editing events from experimental data. This problem is challenging due to sequencing errors, technical artifacts and false positives from single-nucleotide polymorphisms (SNP)[24]. Conventional detection methods use series of filters to identify RNA editing sites from RNA-seq[25–31]. Recently, there have been several attempts to use machine learning approaches for more accurate detection of RNA editing[32–34].

Meanwhile, few groups studied the prediction problem with carefully designed experiments to probe the editing profile under different sequence contexts[11, 35]. Most recently, Liu et al. [35] designed experiments to study A-to-I editing by introducing point mutations in the vicinity of three known A-to-I editing sites via CRISPR/Cas-9. The resulting mutagenesis data was used to train editing site-specific gradient boosted trees to predict RNA editing frequencies from the sequence and secondary structures computed by RNAfold[36]. The site-specific prediction models showed good

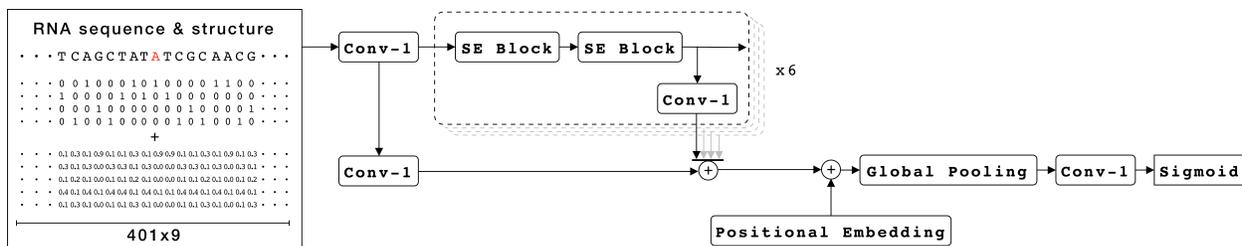


Figure 1: An overview of the deep convolutional model.

performance over variants around the same editing site, but did not generalize across different editing sites, potentially due to the small dataset size. Nevertheless, this study demonstrated the potential of machine learning approaches in learning regulatory features of A-to-I editing.

Here, we take a different approach by training on a larger dataset consisting of highly confident editing sites that are observed across many RNA-seq experiments. Due to the challenges in accurate quantification of RNA editing frequencies, we focused on binary classification models to predict whether a given ‘A’ is likely to be edited or not based on its surrounding sequence and structural contexts. To test if meaningful features can be learned from the observational data without controlled experiments, we also evaluated whether our models can generalize to the mutagenesis dataset from Liu et al. [35].

## 2 Methods

### 2.1 Dataset Construction

In order to train predictive models to classify whether a given ‘A’ is edited or not, a balanced dataset consisting of edited and non-edited ‘A’s was created. High quality editing sites were curated by REDIPortal[37], which contains 4,668,125 A-to-I editing sites previously reported in the literature. Due to the challenges associated with RNA editing detection[24], REDIPortal still contains many false positives. Therefore, Genotype-Tissue Expression (GTEx)[38] was used to select highly confident editing sites that were supported by: 1) at least 1,000 RNA-seq experiments (out of 2,642 with matching whole genome sequencing), and 2) at least 50 body sites (out of 55 in GTEx). With these two filtering criteria, there were 25,212 edited ‘A’s that were well supported across many tissues and experiments.

For each of the curated editing sites, a negative example was sampled uniformly from the non-edited ‘A’s in the vicinity of 400bp. The size of the sampling window was chosen to ensure that the negative set included a good mixture of: 1) examples close to the editing sites, which could be challenging for models to distinguish as they share most of genomic context, and 2) examples at a distance to help the models generalize to regions outside of the editing sites. Each of the sampled ‘A’s were checked to make sure that they had not been reported to be editing sites in the literature. To mitigate the risk of learning spurious features, additional analysis was performed to check if the distribution of non-editing sites were similar to the editing sites across different 1) genomic regions (e.g. introns, UTRs, and coding regions), and 2) repeated elements (e.g. Alu, non-Alu, and non-repeat). The final dataset consists of 50,424 examples.

### 2.2 Computing RNA secondary structure

Although the features controlling A-to-I editing is mostly unknown, it is assumed that dsRNA regions and structural features, such as bulges or loops, influenced the ADAR activity[10]. To compute structural features, we used RNAplfold[36] with a wrapper, created by the authors of RNAcontext[39]. The wrapper produces per-base probabilities of it being in 5 different types of structures: paired, hairpin loop, inner loop, multi-loop, or external region. RNAplfold was run with the options ‘-W 240 -L 160 -u 1’.

### 2.3 Models

We tried four different types of machine learning models to classify whether a given ‘A’ is edited or not: logistic regression (LR), support vector machines (SVM), gradient boosting (GB), and deep convolutional neural network (CNN).

For LR, SVM, and GB models, input features were derived from 42bp region around a given ‘A’. We empirically observed that context larger than 42bp did not improve the performance of the models. The inputs consisted of three

Table 1: Performance of the models on the held-out chromosomes

Models	Accuracy	auROC	F1-score
LR	0.853	0.924	0.852
SVM	0.880	0.941	0.878
GB	0.885	0.946	0.882
CNN	0.914	0.965	0.913

sets of features: 1) the two bases neighbouring ‘A’, 2) identities of 14 non-overlapping 3-mers within the 42bp region, and 3) computed structures represented by per-base probabilities. Features 1) and 2) were one-hot encoded.

For the deep convolutional network, an overview of the model architecture is shown in Figure 1. The model employs a stack of 1D convolutional blocks with residual and skip connections[40, 41], which have been successful on tasks in language modelling[42], speech recognition[43], and computational biology[15]. The model uses sequence context and the computed structures to predict how likely a given ‘A’ would be edited. The input to the model is a concatenation of one-hot encoded RNA sequence and per-base probabilities, computed from RNAplfold as described in section 2.2. The input is convolved by 12 residual blocks with skip connections every 2 blocks. Each residual block includes a Squeeze-Excitation (SE) operation[44] which explicitly models the interdependence between the channels to help the CNN model focus on the most relevant cis-regulatory features. After the last residual block, a sinusoidal positional embedding[45] is added to the feature map which was then summarized via global pooling over sequence positions. The combination of the positional embedding with global pooling allows the model to be used with variable input sizes. We empirically found that, unlike the other three models, larger context up to 400bp improved the performance of the CNN model. All inputs during training were 400bp in length.

One major advantage of the CNN model is data driven feature discovery, removing the need for manual feature engineering based on our limited knowledge of RNA editing. Furthermore, the CNN architectures have shown to be more efficient in modelling long range interactions compared to the competing architectures. Lastly, the CNN model with global pooling and positional embedding can handle flexible input sizes without much change in the number of parameters, while the number of parameters for the other three models scale linearly with the input size. This could be important for the future development of the model, as A-to-I editing can be influenced by long range interactions up to 10,000bp[46].

### 3 Results

#### 3.1 Evaluation on held-out dataset

The models were evaluated on 20 percent held-out data from chromosomes 2, 14, 15, and 17, for reasons to be explained in section 3.3. The results are summarized in Table 1<sup>1</sup>. All of the models achieved good performance, with the CNN model outperforming the other three.

#### 3.2 Evaluation on dataset without the weak motif

Although there is no well established sequence motifs for ADAR proteins, it is observed that they prefer editing sites without 5’G and with 3’G. Even though this is a very weak motif, since every 3 out of 16 non-editing sites can have this feature by chance, it could still be important information for the models to rely on, which was evidenced by the large weights on these features in the LR model. Therefore, editing events without these features could serve as more challenging subsets for testing.

The held-out testset was further split into three groups: 1) sites without 5’ G, 2) sites with 3’ G, and 3) sites without 5’ G and with 3’ G. The results are summarized in Table 2. Interestingly, all models achieved comparable performances with or without the weak motif 3.1.

#### 3.3 Evaluation on the mutagenesis dataset

To evaluate if the models can generalize beyond the observational dataset used in training, the mutagenesis dataset created by Liu et al. [35] was used. The study generated 200-300 single and double point mutations for each of the three ADAR editing sites (NEIL1, TTYH2, and AJUBA) from chromosomes 14, 15, and 17, which the models were

<sup>1</sup>We calculated accuracy and f1-scores using the optimal threshold that maximizes accuracy.

Table 2: Performance of the models on the three subsets of the held-out chromosomes

Models	Without 5'G			With 3'G			Without 5'G and With 3'G		
	Accuracy	auROC	F1-score	Accuracy	auROC	F1-score	Accuracy	auROC	F1-score
LR	0.851	0.923	0.850	0.852	0.924	0.852	0.851	0.926	0.851
SVM	0.877	0.941	0.875	0.883	0.943	0.881	0.879	0.944	0.878
GB	0.882	0.944	0.878	0.891	0.946	0.888	0.891	0.947	0.889
CNN	0.912	0.964	0.911	0.915	0.967	0.914	0.916	0.967	0.915

Table 3: Performance of the CNN model on the mutagenesis dataset

Editing substrate	Accuracy	auROC	F1-score
NEIL1	0.841 ( $\pm 0.028$ )	0.881 ( $\pm 0.030$ )	0.844 ( $\pm 0.030$ )
TTYH2	0.876 ( $\pm 0.029$ )	0.917 ( $\pm 0.028$ )	0.875 ( $\pm 0.031$ )
AJUBA	0.752 ( $\pm 0.047$ )	0.742 ( $\pm 0.060$ )	0.788 ( $\pm 0.048$ )

not trained on. For each mutated sequence, the dataset reported the measured RNA-editing frequency. We further processed this dataset by only selecting samples with high or low editing frequencies and assigning positive or negative labels, respectively. The processed set is roughly balanced and contains 161, 122, and 83 samples from NEIL1, TTYH2, and AJUBA, respectively. Even though our models were not trained on classifying editing sites by frequencies, we hypothesized that because editing sites with higher editing frequencies would have ‘stronger’ editing features, our models should be able to generalize to this new task of distinguishing between the two extreme editing frequencies. Table 3 summarizes the results<sup>2</sup> from only the CNN model, as the other three models performed only slightly better than random. This demonstrated that while the other three models failed to generalize, the CNN model learned features that could be used across different datasets and tasks. This could be attributed to using large dataset to train an expressive CNN model and discover features in a data-driven way.

Performance of the CNN model is slightly worse than on the held-out dataset. This is to be expected because the model was trained on normal tissue samples from GTEx whereas HEK293T cell line was used to generate the mutagenesis dataset. Additionally, classifying sites by editing frequencies is different from the task that the model was trained on. For AJUBA, the editing frequency gap between the lowest positive and the highest negative is small (0.003, in contrast to 0.45 and 0.302 for NEIL1 and TTYH2), so it is more challenging for the CNN model to distinguish.

## 4 Discussion

We presented new machine learning approaches to predict human A-to-I editing from RNA sequences and structures. We trained our models on a much larger dataset comprised of editing sites highly supported by GTEx RNA-seq data, augmented by sampled non-editing sites. Our CNN model not only achieved good performance on the held-out evaluation, but also generalized to a more challenging task on a mutagenesis dataset. This shows that our model can learn general cis-regulatory features of A-to-I editing from the observational dataset alone.

One major limitation of our models is that we focused only on binary ‘editing codes’ with some ability to distinguish the highly edited sites from lowly edited ones. A more complete ‘editing code’ in the future should be able to predict the editing frequency, and constructing high quality training dataset for this task will require accurate quantification of editing frequency from noisy RNA-seq. Additionally, our models did not take into account the differences in tissue types, so modelling both cis- and trans-regulatory features could be an interesting future work. Another direction is to focus on understanding the features that the models learned, which can help with our understanding of the editing mechanism and regulation. With a more complete ‘editing code’, there are many interesting applications that could be explored, such as identifying disease causing variants and RNA therapies using site-directed RNA editing.

<sup>2</sup>Due to the small number of samples, we used bootstrapping with 1000 samples to estimate means and uncertainties of the reported metrics.

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