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# DEEP LEARNING-ENHANCED CRISPR/CAS9 GENE EDITING FOR CHRONIC MYELOGENOUS LEUKEMIA: TARGETED THERAPEUTICS AND OFF-TARGET PREDICTION

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**Abstract**
*Chronic Myelogenous Leukemia (CML) is driven by the BCR-ABL1 fusion gene and remains an important model for precision cancer therapy. Although tyrosine kinase inhibitors have substantially improved clinical outcomes, resistance, persistent leukemic stem cells, cumulative toxicity, and long-term treatment requirements continue to motivate investigation of potentially curative strategies. CRISPR/Cas9 offers a direct route for targeting disease-associated genetic alterations, but unintended cleavage remains a major obstacle to safe therapeutic development. This study evaluates sequence-based deep learning methods for predicting CRISPR/Cas9 off-target activity in a CML-oriented setting. The computational framework incorporates one-hot sequence encoding, mismatch profiling, GC-content analysis, normalized genomic features, and ten recurrent, convolutional, feedforward, and attention-based architectures. CRISPR-DIPOFF-LSTM produced the highest reported accuracy (0.985), precision (0.983), recall (0.984), F1-score (0.984), AUROC (0.992), and AUPRC (0.991), with CRISPR-DIPOFF-GRU providing the closest recurrent-model performance. These findings support recurrent sequence modeling as a useful basis for gRNA prioritization, while experimental validation remains necessary before therapeutic application.*

## I. INTRODUCTION

### A. Background

Chronic myelogenous leukemia (CML) is a hematological malignancy characterized by the Philadelphia chromosome and BCR-ABL1 fusion oncogene [1]. Although tyrosine kinase inhibitors have revolutionized the treatment of CML, survival has significantly improved, leukemic stem cells, resistance, cumulative treatment burden, and long-term therapy remain significant clinical challenges [2,3]. These constraints have spurred studies of approaches that directly target genetic abnormalities associated with diseases.

CRISPR/Cas9 provides a programmable tool for DNA cleavage with the help of a guide RNA and the Cas9 nuclease [7, 8]. However, disruption of BCR-ABL related sequences has proven to be effective at abolishing oncogenic phenotypes in cellular and xenograft models [4] and a number of RNA-guided FokI studies have investigated the specificity of editing CML cells [5]. Related work has also considered CRISPR/Cas9 as a platform for targeting cancer-driving genes in CML [6].

These studies establish biological feasibility, but they do not eliminate the risk of unintended cleavage at sequence-similar genomic loci.

Cas9 specificity depends on guide-target complementarity, mismatch identity and position, protospacer-adjacent motif context, and local genomic features [9], [10], [20]. Off-target cleavage can compromise genomic integrity and remains a major safety concern for therapeutic genome editing. Figure 1 provides the hematological context of CML.

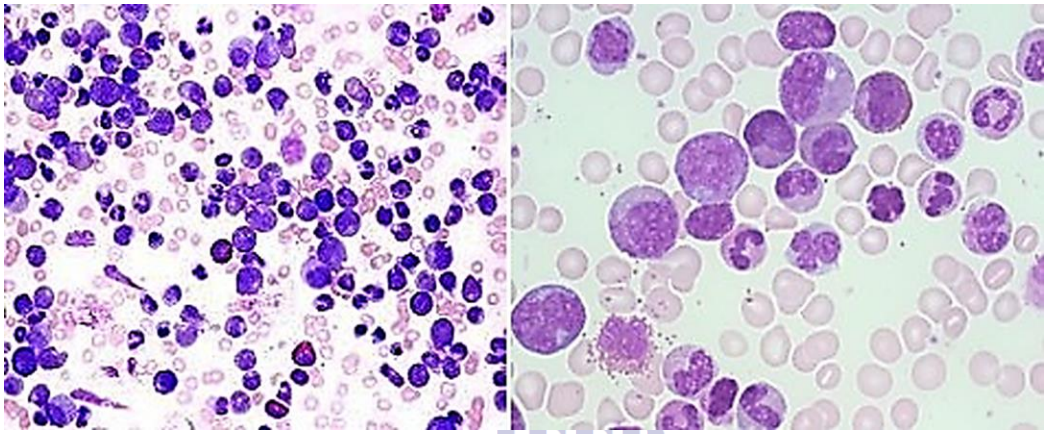

**Fig. 1. Representative hematological microscopy images illustrating the cellular context of CML.**

Statistical scoring systems and early machine-learning models established practical foundations for guide design [20], [21]. More recent methods use convolutional, recurrent, multimodal, and language-model representations to learn complex sequence dependencies [22]-[28]. Their architectures differ substantially in how they encode mismatches and retain positional context. The present study therefore compares recurrent, convolutional, attention-based, transformer-based, and feedforward models under the common reported evaluation setting, with particular attention to the ability of recurrent networks to represent long-range sequence relationships.

Hence, there is a need for a deep learning-based approach to accurately predict CRISPR/Cas9 off-target cleavage in CML because conventional rule-based methods cannot adequately capture the complex effects of mismatch position, PAM context, sequence composition, and genomic context. Therefore, this study aims to develop and compare deep learning models for predicting off-target cleavage and prioritizing CML-targeting gRNAs with high predicted specificity and low off-target risk, supporting safer CRISPR/Cas9-based therapeutic strategies.

Rule-based sequence matching does not fully capture the interacting effects of nucleotide substitutions, mismatch position, PAM proximity, sequence composition, and broader genomic context. An effective computational model must therefore learn position-dependent relationships within guide-target pairs and distinguish candidate off-target sites from non-cleaved sequences. Such predictions can support gRNA screening by prioritizing candidates with lower predicted off-target risk.

### B. Contributions

The main contributions of this study are:

- A deep-learning framework for CRISPR/Cas9 off-target prediction in a CML-oriented context, using one-hot encoding, mismatch profiles, GC-content analysis, and normalized sequence features;
- A comparative evaluation of ten deep learning architectures using accuracy, precision, recall, F1-score, AUROC, and AUPRC;
- An analysis of recurrent, convolutional, feedforward, and attention-based architectures for modeling guide-target sequence dependencies; and
- Identification of CRISPR-DIPOFF-LSTM as the model with the highest reported values in the evaluated setting, providing a computational basis

for subsequent gRNA screening and experimental testing.

## II. RELATED WORK

Computational CRISPR guide design has progressed from empirical scoring functions to deep neural representations. Doench et al. developed sequence-based rules for balancing activity and off-target effects [20], while Elevation provided an end-to-end framework for guide design and off-target prediction [21]. Cas-OFFinder, CRISPOR, and CRISPRitz remain useful for high-throughput candidate enumeration and variant-aware screening [17]-[19].

DeepCRISPR combined sequence and epigenetic information through deep representation learning [22]. CnnCrispr integrated sequence embeddings, bidirectional recurrence, and convolution [23], whereas CRISPR-Net explicitly modeled mismatch and indel patterns [24]. CRISPR-IP emphasized information-preserving sequence encoding [25]. CRISPR-DIPOFF compared recurrent, LSTM, and GRU configurations and incorporated interpretability analysis [26]. In recent years, multi-view models [27], the RNA language-model off-the-shelf predictor (CCLMoff) [28] and a multi-branch transformer fusion model [30] were developed. These developments call for comparison of the different families directly addressed by the current study: the recurrent, the convolutional, the feedforward, and the attention-oriented families.

Experimental mapping methods provide complementary evidence that computational predictions alone cannot supply. GUIDE-seq [11], Digenome-seq [12], SITE-seq [13], CIRCLE-seq [14], DISCOVER-Seq [15], and CHANGE-seq [16] identify off-target cleavage through distinct in vitro or cellular measurement strategies. There are also several applications of deep learning to the design of high fidelity Cas9 guides [35] and prediction of guide activity in Cpf1 [34]. These studies provide a basis for using computational screening as a prioritization step to be followed by a full-scale genome-wide validation experiment.

## III. PROBLEM FORMULATION

### A. Learning Objective

Let the study data comprise N biological sequence pairs:

$$\mathcal{D} = \{(X_i, y_i)\}_{i=1}^{N}.$$

Here, $X_i$ represents the relationship between a guide sequence and a candidate sequence together with the relevant contextual features, while $y_i \in \{0, 1\}$ denotes the absence or presence of off-target cleavage. The task is to learn a nonlinear mapping

$$f_\theta: X_i \rightarrow P(y_i = 1 \mid X_i).$$

that estimates the probability of off-target cleavage. The predicted probability for the i-th sequence pair is

$$\hat{y}_i = f_\theta(X_i).$$

The optimal parameters are obtained by minimizing the mean binary cross-entropy loss. Equivalently,

$$\theta^* = \arg\min_\theta \mathcal{L}(\theta).$$

where

$$\mathcal{L}(\theta) = \frac{1}{N}\sum_{i=1}^{N}[-y_i \log \hat{y}_i - (1 - y_i)\log(1 - \hat{y}_i)].$$

This objective requires the model to learn position-dependent, sequence-specific, and contextual relationships rather than rely only on rule-based sequence matching.

### B. Risk-Based Candidate Prioritization

For each guide-candidate pair, the predicted probability serves as an off-target risk score. These scores are used to distinguish positive and negative cases and to rank candidate sequences for downstream gRNA prioritization. Candidates with lower predicted off-target risk are preferred for CML-oriented screening and are then advanced to the experimental validation described in the research framework.

## IV. MATERIALS AND METHODS

### A. Research Framework

Figure 2 presents the seven-stage sequence-based deep learning workflow used in this study. CML-oriented inputs are cleaned and labeled, transformed into sequence and mismatch-aware features, evaluated across ten architectures, trained with threshold selection, interpreted using complementary performance and attribution

analyses, and converted into off-target probability scores for gRNA prioritization. The stages are described below in the same order as the framework.

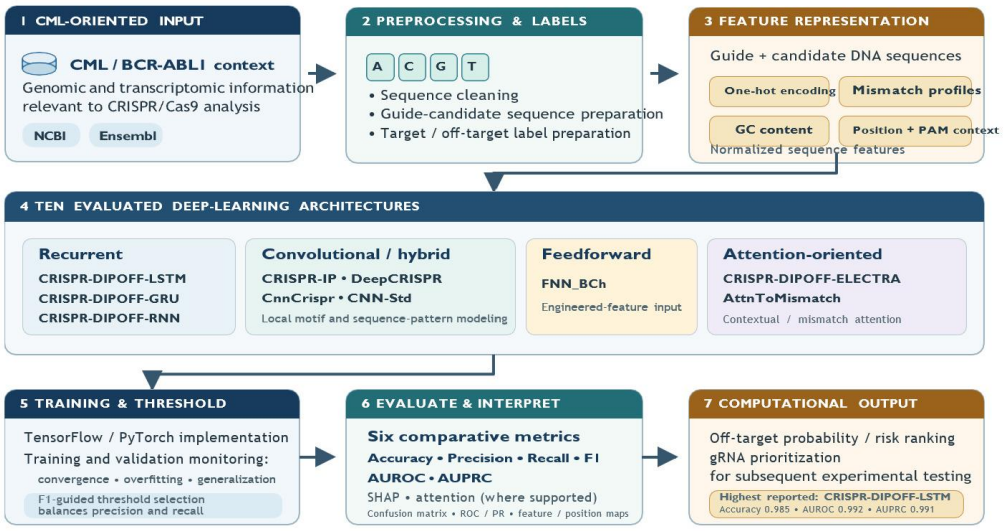


**Fig. 2. Seven-stage research framework for CML-oriented CRISPR/Cas9 off-target prediction and gRNA prioritization.**

### B. CML-Oriented Input

At Step 1, genomic and transcriptomic information relevant to CML and CRISPR/Cas9 analysis was obtained from NCBI [36] and Ensembl [37]. These resources provide the CML/BCR-ABL1 context and the guide and candidate sequence information that enters the computational pipeline.

### C. Preprocessing and Label Preparation

Step 2 converts the collected sequences into consistent model inputs through sequence cleaning, guide-candidate pair preparation, and target/off-target label assignment. Preprocessing preserves biologically meaningful nucleotide information while standardizing the input format. Because off-target datasets may contain unequal numbers of positive and negative examples, class distribution is considered during label preparation and subsequent evaluation.

### D. Feature Representation

At Step 3, guide and candidate DNA sequences are represented numerically using one-hot encoding. Mismatch profiles encode differences within each guide-target pair, GC content summarizes sequence composition, and position-aware PAM-context features retain the distinction between PAM-proximal and PAM-distal mismatches [9], [20]. The resulting sequence features are normalized to comparable scales, consistent with established deep CRISPR representations [22]-[26].

### E. Evaluated Deep Learning Architectures

Step 4 evaluates ten architectures. The recurrent group comprises CRISPR-DIPOFF-LSTM, CRISPR-DIPOFF-GRU, and CRISPR-DIPOFF-RNN; the convolutional or hybrid group comprises CRISPR-IP, DeepCRISPR, CnnCrispr, and CNN-Std; FNN_BCh represents the feedforward group; and CRISPR-DIPOFF-ELECTRA and AttnToMismatch form the attention-oriented group. This organization follows the model families shown in Figure 2 and supports comparison of sequence-context modeling strategies.

### F. Model Training and Threshold Selection

At Step 5, the models were implemented in TensorFlow [32] and PyTorch [33] using sequence representations appropriate to each architecture. The outcomes of training and validation behavior

were made to be monitored for convergence, overfitting and generalization. The operating threshold was chosen to maximize the F1 score, neither assuming 0.5 was the optimum threshold nor relying on precision vs. recall.

### G. Evaluation and Model Interpretation

Evaluation of discrimination in Step 6 is based on accuracy, precision, recall, F1-score, AUROC and AUPRC. The introduction of precision-recall measures mitigates the potential for overemphasis on the high accuracy and the possibility of missing on-target events of biological relevance, if they exist, when the class distributions are unequal. Model behavior is explored further through SHAP-based feature attribution [31] and plots of attention (when supported), confusion matrices, ROC and precision-recall curves, feature-importance plots, and sequence-position maps.

### H. Computational Output and gRNA Prioritization

The final step transforms each model prediction into an off-target probability score for risk ranking. Predicted off-target profiles of candidate gRNAs are used to rank the candidates, and the model that has been most reported is used as the basis for subsequent screening. These rankings may be used to select candidates for experimental validation, they cannot be used in place of cell or genome-wide validation.

## V. RESULTS

### A. Overall Model Performance

The comparative evaluation showed clear differences among the ten architectures. CRISPR-DIPOFF-LSTM achieved the highest reported accuracy of 0.985, followed by CRISPR-DIPOFF-GRU at 0.982 and CRISPR-IP at 0.979. The CNN-based models also performed strongly, while the feedforward and attention-oriented configurations produced lower accuracy. Table I summarizes the complete accuracy comparison.

**TABLE I. OVERALL ACCURACY OF THE EVALUATED MODELS**

| Model | Accuracy | Category |
|---|---|---|
| AttnToMismatch | 0.880 | Fair |
| CRISPR-DIPOFF-ELECTRA | 0.912 | Good |
| FNN_BCh | 0.935 | Good |
| CRISPR-DIPOFF-RNN | 0.940 | Good |
| CNN-Std | 0.971 | Excellent |
| CnnCrispr | 0.977 | Excellent |
| DeepCRISPR | 0.978 | Excellent |
| CRISPR-IP | 0.979 | Excellent |
| CRISPR-DIPOFF-GRU | 0.982 | Excellent |
| CRISPR-DIPOFF-LSTM | 0.985 | Excellent |

### B. Precision, Recall, and F1-Score

Table II shows that CRISPR-DIPOFF-LSTM produced the highest reported precision (0.983), recall (0.984), and F1-score (0.984). CRISPR-DIPOFF-GRU followed closely, with precision 0.980, recall 0.981, and F1-score 0.981. Figure 3 presents the same comparison graphically and shows the consistent ranking of the two recurrent models across all three measures.

TABLE II. PRECISION, RECALL, AND F1-SCORE

| Model | Precision | Recall | F1 |
|---|---|---|---|
| **CRISPR-DIPOFF-LSTM** | **0.983** | **0.984** | **0.984** |
| CRISPR-DIPOFF-GRU | 0.980 | 0.981 | 0.981 |
| CRISPR-IP | 0.977 | 0.978 | 0.978 |
| DeepCRISPR | 0.976 | 0.977 | 0.977 |
| CnnCrispr | 0.975 | 0.976 | 0.976 |
| CNN-Std | 0.968 | 0.969 | 0.969 |
| CRISPR-DIPOFF-RNN | 0.937 | 0.938 | 0.938 |
| FNN_BCh | 0.932 | 0.933 | 0.933 |
| CRISPR-DIPOFF-ELECTRA | 0.908 | 0.909 | 0.909 |
| AttnToMismatch | 0.875 | 0.876 | 0.876 |

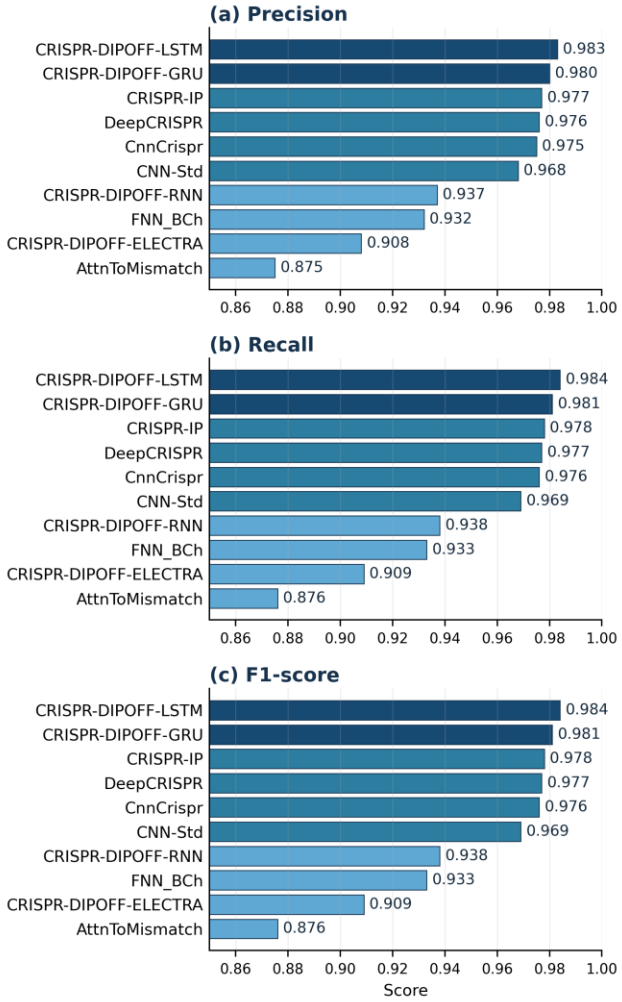


**Fig. 3. Precision, recall, and F1-score for the ten evaluated architectures.**

### C. AUROC and AUPRC

AUROC summarizes discrimination across classification thresholds, whereas AUPRC emphasizes positive-class retrieval. CRISPR-DIPOFF-LSTM obtained an AUROC of 0.992 and an AUPRC of 0.991. CRISPR-DIPOFF-GRU obtained 0.990 and 0.989, respectively. The complete values are reported in Table III and visualized in Figure 4.

**TABLE III. AUROC AND AUPRC OF THE EVALUATED MODELS**

| Model | AUROC | AUPRC |
|---|---|---|
| **CRISPR-DIPOFF-LSTM** | **0.992** | **0.991** |
| CRISPR-DIPOFF-GRU | 0.990 | 0.989 |
| CRISPR-IP | 0.989 | 0.988 |
| DeepCRISPR | 0.988 | 0.987 |
| CnnCrispr | 0.988 | 0.987 |
| CNN-Std | 0.985 | 0.984 |
| CRISPR-DIPOFF-RNN | 0.975 | 0.974 |

| Model | AUROC | AUPRC |
|---|---|---|
| FNN_BCh | 0.970 | 0.969 |
| CRISPR-DIPOFF-ELECTRA | 0.955 | 0.953 |
| AttnToMismatch | 0.930 | 0.928 |

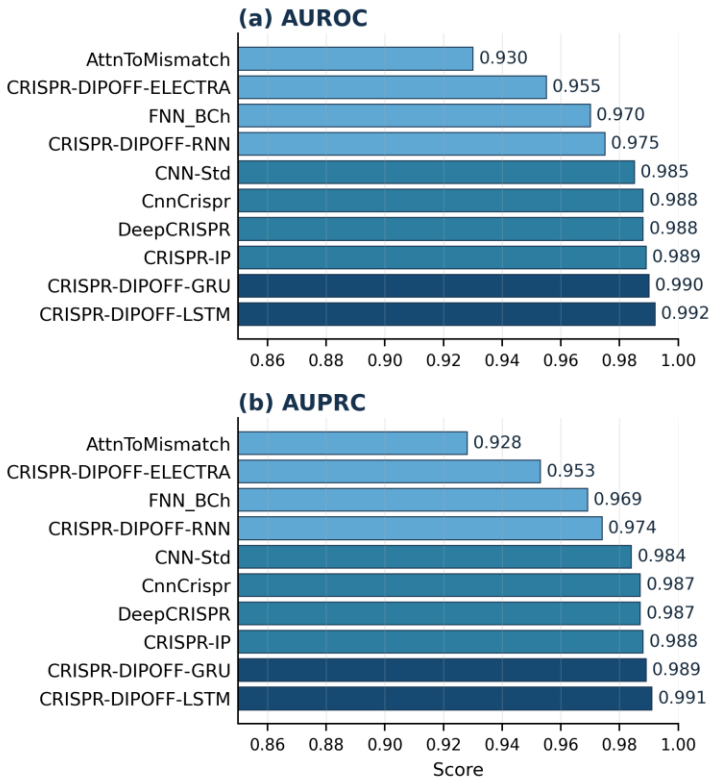


**Fig. 4. AUROC and AUPRC comparison for the ten evaluated architectures.**

### D. Training Stability and Convergence

Qualitative training assessment showed that LSTM and GRU had convergence that was fast, overfitting risk was low and stability was high. The CNN-based models exhibited moderate convergence with negligible overfitting risk, and high stability. Vanilla RNNs were rated as moderate on these dimensions while feedforward and attention were less stable and slower to converge. Table IV reports these observations.

**TABLE IV. TRAINING STABILITY AND CONVERGENCE BEHAVIOR**

| Model family | Convergence | Overfitting risk | Stability |
|---|---|---|---|
| **LSTM / GRU** | **Fast** | **Low** | **High** |
| CNN-based | Moderate | Low | High |
| Vanilla RNN | Moderate | Medium | Moderate |
| FNN / Attention | Slow | Medium | Low |

## VI. DISCUSSION

### A. Recurrent Versus Convolutional Architectures

The results reported show that LSTM and GRU models perform well for the sequence-prediction task evaluated. They have well-developed recurrent memory mechanisms suitable for the storage of ordered information over a guide-target pair [29]. CNNs are good at capturing motifs at local level while recurrent units can capture the relationship over a longer distance of the sequence. This separation is a plausible reason why the scores of the CRISPR-DIPOFF-LSTM and CRISPR-DIPOFF-GRU models are higher.

### B. Biological Interpretation

There are other factors affecting the specificity of CRISPR/Cas9. The cleavage behavior can vary depending on mismatch position, nucleotide identity and proximity to the PAM [9, 10, 20]. The positional information is preserved through the sequence so that patterns consistent with known mechanisms of specificity can be learned. The findings indicate that the sequential memory function is useful for these relationships, but the overall quantities do not indicate a biological mechanism.

### C. Comparison With Other Model Families

The next strongest group comprises CNN-Std, CnnCrispr, DeepCRISPR, and CRISPR-IP, with accuracy values from 0.971 to 0.979. These results reinforce the importance of sequence representation in off-target prediction. CRISPR-DIPOFF-RNN achieved 0.940 accuracy, while FNN_BCh, CRISPR-DIPOFF-ELECTRA, and AttnToMismatch produced lower values in the evaluated setting. The comparison should be interpreted within this experiment; it does not imply that an architecture family is universally superior across datasets or assays.

### D. Implications for gRNA Design

Off-target prediction can support gRNA screening by ranking candidate sequences according to predicted risk. Precision is important because excessive false positives may reject useful guides, whereas recall is critical because missed off-target sites can have serious biological consequences. The reported precision and recall of CRISPR-DIPOFF-LSTM provide a balanced computational basis for prioritizing candidates for subsequent experimental testing. Genome-wide assays such as GUIDE-seq, CIRCLE-seq, SITE-seq, DISCOVER-Seq, or CHANGE-seq remain necessary to evaluate cleavage experimentally [11]-[16].

### E. Limitations

The findings should be interpreted within the scope of a computational evaluation. Off-target activity is influenced by chromatin accessibility, cellular state, DNA structure, repair processes, and assay conditions in addition to sequence composition. The reported predictions therefore do not constitute experimental evidence of safe or effective gene editing. Validation in K562 and other hematopoietic cell systems, followed by genome-wide off-target assays, is required before drawing therapeutic conclusions. Integrating multi-omics and chromatin-context features may also improve biological coverage.

### F. Future Directions

Future work should evaluate larger and more diverse genomic datasets, integrate multi-omics and chromatin-context information, and examine transformer architectures with genomic or RNA-specific pretraining [28], [30]. Experimental testing of highly ranked predictions is also required. Extensions to prime editing and base editing represent additional opportunities for AI-assisted safety assessment in next-generation genome-editing systems.

## VII. CONCLUSION

This study evaluated ten deep learning architectures for CRISPR/Cas9 off-target prediction in a CML-oriented computational setting. CRISPR-DIPOFF-LSTM produced the highest reported accuracy (0.985), precision (0.983), recall (0.984), F1-score (0.984), AUROC (0.992), and AUPRC (0.991), with CRISPR-DIPOFF-GRU providing the closest performance. The findings indicate that recurrent sequence models can effectively represent position-dependent guide-target relationships and support

computational gRNA prioritization. The study does not demonstrate therapeutic editing; cellular and genome-wide experimental validation remains essential before the approach can inform CML-directed gene-editing studies.

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