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ML-Based RNA Secondary Structure Prediction Methods: A Survey

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Abstract: The secondary structure of noncoding RNAs (ncRNA) is significantly related to their functions, emphasizing the importance and value of identifying ncRNA secondary structure. Computational prediction methods have been widely used in this field. However, the performance of existing computational methods has plateaued in recent years despite various advancements. Fortunately, the emergence of machine learning, particularly deep learning, has brought new hope to this field. In this review, we present a comprehensive overview of machine learning-based methods for predicting RNA secondary structures, with a particular emphasis on deep learning approaches. Additionally, we discuss the current challenges and prospects in RNA secondary structure prediction.

Keywords: RNA secondary structure prediction; machine learning; deep learning

Supplementary

Table 1. ML-based score scheme

Category	Title	ML Technique	Brief Description	Pros	Cons	Resource
Free energy parameter refining	Thermodynamic Parameters for an Expanded Nearest-Neighbor Model for Formation of RNA Duplexes with Watson-Crick Base Pairs, Xia et al., 1998 [50]	Linear regression	The model extends the INN-HB model by giving special treatment to terminal AU and GC base pairs, combining statistical analysis with physical models of the number of hydrogen bonds to improve RNA structure prediction.	The hydrogen bond model is supported by the physical model.	Model complexity increases.	`https://pubs.acs.org/doi/10.1021/bi9809425`
	Efficient parameter estimation for RNA secondary structure prediction, Andronescu et al., 2007 [63]	Constraint generation	The model presents constraint generation, which is the first computational approach to RNA free energy parameter estimation.	The parameters are compatible with various RNA secondary structure prediction software.	Unable to predict pseudoknots.	`http://www.rnasoft.ca/CG/`
	Computational approaches for RNA energy parameter estimation, Andronescu et al., 2010 [64]	Loss-augmented max-margin constraint generation, Boltzmann-likelihood model	The model combines both CG and BL methods to predict the structure through constraint generation with maximum margin extension and a novel linear Gaussian Bayes network.	Expandability	Limitations of physical modeling	`http://www.cs.ubc.ca/labs/beta/Projects/RNA-Params`
Weighted method	Rich Parameterization Improves RNA Structure Prediction, Zakov et al., 2011 [67]	Discriminative structured prediction, online learning	The model uses a rich parametric machine learning method based on marginal error-driven parameter estimation to predict RNA secondary structure.	Expandability	Limitations of physical modeling	`http://www.cs.bgu.ac.il/~negevcb/contextfold`
	A Max-Margin Training of RNA Secondary Structure Prediction Integrated with the Thermodynamic Model, Akiyama et al., 2018 [68]	SSVM	The model uses thermodynamic parameters and feature scoring parameters from SSVM training, avoiding overfitting via L1 regularization to predict RNA secondary structure.	1.Integrates thermodynamic methods and machine learning to enhance prediction accuracy. 2.Rapid prediction of long RNA sequences using sparse techniques.	High complexity due to large computational resource demands.	`https://github.com/keio-bioinformatics/mxfold`
	RNA secondary structure prediction using deep learning with thermodynamic integration, Sato et al., 2021 [69]	Deep neural network	Combines folding scores from deep neural networks with Turner nearest neighbor free energy parameters, predicting structures via thermodynamic regularization to align folding scores and free energy estimates with true values.	Overfitting is mitigated by thermodynamic regularization. Using deep neural network combined with Zuker-style dynamic programming.	1.Cannot predict pseudoknot structures. 2.High parameter complexity.	`http://www.dna.bio.keio.ac.jp/mxfold2/`
Probabilistic method	Stochastic context-free grammars for tRNA modeling, Sakakibara et al., 1994 [70]	EM method	Based on SCFGs, uses tree syntax EM algorithms to generate multiple syntax rules for effective structure prediction.	High prediction for tRNA secondary structure prediction.	Limited prediction effectiveness; cannot fully adapt to standard secondary structures.	None

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Category	Title	ML Technique	Brief Description	Pros	Cons	Resource
	RNA secondary structure prediction using stochastic context-free grammars and evolutionary history, Knudsen and Hein, 1999 [**?**]	EM method	Combines SCFGs with evolutionary history using phylogenetic trees to capture mutation patterns in RNA sequences. Employs maximum a posteriori estimation to enhance RNA secondary structure prediction using structural and evolutionary information.	Use mutation patterns to provide additional structural information. Incorporate evolutionary history into RNA secondary structure prediction.	High computational complexity.	None
	Pfold: RNA secondary structure prediction using stochastic context-free grammars, Knudsen and Hein, 2003 [72]	EM method	Based on explicit evolutionary and probabilistic models, Pfold improves upon previous algorithms.	1.Suitable for related RNA sequences with conserved structures. 2.Improves speed, robustness, and prediction accuracy of multiple sequence alignment. 3. Capable of handling large-scale data.	Relies on comparison quality. 2.Limited capability in processing complex structures.	`http://www.daimi.au.dk/~compbio/pfold`
	A Non-Parametric Bayesian Approach for Predicting RNA Secondary Structures, Sato et al., 2010 [75]	Non-parametric Bayesian methods	Based on non-parametric Bayesian methods, HDP-SCFGs accurately capture the complex relationship between RNA sequences and their secondary structures through adaptive mechanisms for structure prediction.	1.Adaptive and can automatically infer appropriate parameters, enhancing flexibility and prediction accuracy. 2.HDP-SCFGs outperform MFE-based models.	Relatively slow computational efficiency.	None
	A semi-supervised learning approach for RNA secondary structure prediction, Yonemoto et al., 2015 [76]	Semi-supervised learning algorithm	Combines SCFG and CRF to propose a semi-supervised learning method for training probabilistic models to predict RNA secondary structures.	Make use of unlabeled data.	Less accurate than free energy-based methods.	None
	CONTRA-fold: RNA secondary structure prediction without physics-based models, Do et al., 2006 [77]	Conditional log-linear models (CLLM)	Uses CLLM, which generalizes SCFGs by employing discriminative training and feature-rich scoring to learn and estimate the probabilistic parameters of RNA structures. It distinguishes between correct and incorrect structures by maximizing conditional log-likelihood, ultimately selecting the most probable RNA structure.	1.Higher accuracy than traditional physics and probability-based models. 2.CLLM is flexible. 3. Data-driven and independent of physical models.	1.CLLM is computationally slow. 2.Fewer structural constraints may generate incorrect structures. 3.Lacks biological explanation.	`http://contra.stanford.edu/contrafold/`

Table 2. ML-based preprocessing and postprocessing

Category	Title	ML Technique	Brief Description	Pros	Cons	Resource
Pre-processing method	A tool preference choice method for RNA secondary structure prediction by SVM with statistical tests, Hor et al., 2013 [78]	SVM	A SVM-based model which extracts features in RNA sequences and uses information theory methods to select features. Then, it selects the most appropriate model from three tools (pknotsRG, RNA structure, and NUPACK) for RNA secondary structure prediction.	Feature selection and fusion strategies enhance prediction accuracy.	Semi-automatic selection of the number of features.	None
	Research on folding diversity in statistical learning methods for RNA secondary structure prediction, Zhu et al., 2018 [79]	Statistical context-free grammar model	Based on SCFG, the model identifies the most likely folding rules of RNA sequences before the prediction process.	Simplifying the folding rules of RNA sequences improves the universality and applicability of prediction.	Finiteness of syntactic rules of SCFG model.	None
	RNA independent fragment partition method based on deep learning for RNA secondary structure prediction, Zhao et al., 2023 [**?**]	CNN, Bi-LSTM, ResNet, transfer learning	RNA-Par combines CNN, Bi-LSTM, ResNet, and other modules to preprocess long RNA sequences into multiple shorter fragments, enhancing the processing capacity of long RNA sequences through transfer learning.	1.Suitable for long RNA sequences. 2.High time efficiency.	1.Difficult to handle long-distance interactions and integrity between fragments. 2.Performance is limited when processing short RNA sequences.	`https://github.com/mianfei71/RNAPar`
Post-processing method	Using a neural network to identify secondary RNA structures quantified by graphical invariants, Haynes et al., 2008 [81]	MLP	Based on graph theory, trained neural networks identify the graph invariants that quantitatively describe the structures of RNA to determine whether it is a RNA secondary structure or not.	1.Innovative graph theory method that does not rely on the traditional minimum free energy model. 2.Efficient structure identification.	Inadequate treatment of complex RNA structures.	None
	A predictive model for secondary RNA structure using graph theory and a neural network, Koessler et al., 2010 [82]	MLP	The model uses vertex merges to create larger RNA secondary structures by combining graph theory operations with neural networks. It can be used to verify known RNA classifications and make structural predictions on unknown RNA trees.	1.Simulate the RNA binding process to improve accuracy. 2.Innovative graph theory applications. 3.Applicable for prediction of both known RNA structures and unclassified RNA trees.	1.Strong data dependence. 2.Only seven, eight, nine vertices of the RNA tree were verified.	None

Table 3. ML-based predicting process

Category	Title	ML Technique	Brief Description	Pros	Cons	Resource
End-to-end approach	An Hopfield Neural Network-Based Algorithm for RNA Secondary Structure Prediction, Liu et al., 2006 [85]	Hopfield networks	Uses HNN to find the approximate maximum independent set of adjacent plots composed of RNA base pairs, dynamically adjusts the inhibition and encouragement terms between base pairs to predict the structure.	Higher sensitivity and specificity compared with Nussinov and Zuker algorithm.	Highly dependent on biological knowledge.	None
	Secondary Structure Prediction of RNA using Machine Learning Method, Qasim et al., 2011 [84]	MLP	Finds the approximate maximum independent set in the circle graph and uses statistical probability distribution to predict optimal structure.	Low time complexity.	Limited applicability.	None
	Neural Networks, Adaptive Optimization, and RNA Secondary Structure Prediction, Steeg, 1993 [87]	MFT network	The RNA secondary structure prediction problem is formalized as an optimization problem and mapped to Hopfield network. Using MFT and weight sharing improves learning efficiency and reduces computational complexity.	MFT avoids local minimum problems.	Small experimental data with 35 tRNA sequences.	None
	RNA secondary structure prediction by MFT neural networks, Apolloni et al., 2003 [86]	MFT network with mean field approximation	Models receive one-hot encoding sequences into MFT networks coupled with an objective function and biological constraints to identify the optimal structure.	Introduces biological constraints into neural network to ensure the correct structure.	Limited to predicting tRNA sequences of 75-77 nts.	None
	RNA secondary structure prediction using an ensemble of two-dimensional deep neural networks and transfer learning, Singh et al., 2019 [?]	Compound deep neural networks, transfer learning	Utilizes a compound deep neural network architecture combining ResNets and LSTM networks. Additionally, transfer learning with high-resolution RNA structures is employed to further enhance prediction accuracy.	1.The first end-to-end deep learning model for RNA secondary structure prediction. 2.Transfer learning improves the performance of the model. 3.Can predict the base pairs related to tertiary interactions, including pseudoknots, solitary base pairs, and non-classical base pairs.	1.Due to data noise, the precision of the preliminary training model is limited. 2.For RNA strands longer than 500 nts, the predictive performance is insufficient.	`https://sparks-lab.org/server/spot-rna/`

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Category	Title	ML Technique	Brief Description	Pros	Cons	Resource
	Improved RNA secondary structure and tertiary base-pairing prediction using evolutionary profile, mutational coupling and two-dimensional transfer learning, Singh et al., 2021 [88]	Dilated convolutional network, transfer learning	One-hot encoding and LinearPartition algorithm are used to generate single-sequence-based features, and PSSM and DCA are used to generate two evolutionary-based features. Both features are input into the dilated convolutional network and use transfer learning to improve performance.	Using evolutionarily derived sequence profiles and mutation coupling, the prediction accuracy is significantly improved.	1.Limited to sequences less than 1000 nts. 2.Depends on homologous sequences and artificial sequences.	`https://github.com/jaswindersingh2/SPOT-RNA2`
	UFold: fast and accurate RNA secondary structure prediction with deep learning, Fu et al., 2022 [89]	FCN	Views sequences as images and uses U-Net to get the score matrix and applies hard constraints post-processing to obtain structures.	1.The network is fully convolutional with fast computing speed. 2.Converting sequences into ”images” that explicitly model all possible base pairings between nucleotides. 3.Uses U-net which is capable of handling images-like data.	Data-dependent.	`https://github.com/uci-cbcl/UFold`
	RNA secondary structure prediction by learning unrolled algorithms, Chen et al., 2020 [90]	Compound deep neural networks	Employs a transformer-based deep model to encode the sequence information, and then uses a multilayer network to filter the output.	1.Being Able to process longer RNA sequences. 2.Captures non-local interactions in the sequence.	Severe overfitting and limited generalization on unseen RNAs.	`https://github.com/ml4bio/e2efold`
	Machine learning a model for RNA structure prediction, Calonaci et al., 2020 [91]	CNN, MLP	The network combines thermodynamic parameters, chemical probing data (DMS and SHAPE), and co-evolution data to predict the secondary structure.	1.Multiple information sources improve the accuracy of structure prediction. 2.Flexible architecture and strong adaptability. 3.Automated training and optimization.	1.High computational complexity. 2.Due to thermodynamic parameters, pseudoknots cannot be predicted.	None

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Category	Title	ML Technique	Brief Description	Pros	Cons	Resource
Hybrid approach	RNA secondary structure prediction from sequence alignments using a network of k-nearest neighbor classifiers, Bindewald et al., 2006 [42]	Hierarchical network of k-nearest neighbor model	Based on a hierarchical network of k-nearest neighbor classifiers to predict the shared RNA secondary structure by RNA sequence alignment.	Combining thermodynamic information and complementary information to predict RNA secondary structure, able to predict pseudoknot interactions.	1.Noise problem in mutual information and complementary nucleotide fraction matrix. 2.Model performs poorly with too high or too low sequence homology.	None
	Developing parallel ant colonies filtered by deep learned constraints for predicting RNA secondary structure with pseudoknots, Quan et al., 2020 [94]	Bi-LSTM	DpacoRNA uses a parallel ant colony optimization algorithm to predict RNA secondary structure. Additionally, uses bidirectional LSTM recurrent neural network to learn base pairing constraints and optimize the final prediction results.	1. The effectiveness of multi-objective optimization design and DL constraint can predict the pseudoknot structure. 2. SHOP parallel strategy increases efficiency.	1. The MCC value still has room for improvement. 2. DL is loosely coupled to pacoRNA and is only adjusted during the pacoRNA output phase. 3. Depends on the quality of the objective function.	None
	RNA Secondary Structure Prediction Based on Long Short-Term Memory Model, Wu et al., 2018 [92]	Bi-LSTM	An LSTM-based method converting the problem of predicting RNA secondary structure into the problem of classifying base pairs in sequences.	The complexity of the prediction problem is simplified and the computational efficiency is improved.	LSTM network requires a lot of computation and takes a long time to train.	None
	Predicting RNA secondary structure via adaptive deep recurrent neural networks with energy-based filter, Lu et al., 2019 [93]	Bi-LSTM	The DL model automatically adapts to sequence length and incorporates an energy-based filter to remove overfitting base pairs.	1.Solves the problem of sequence length variability. 2.Dynamic weighting algorithm to deal with data imbalance. 3.Energy-based filter to improve accuracy.	The ability to generalize is not sufficiently verified.	`http://eie.usts.edu.cn/prj/AdaptiveLSTMRNA/index.html`
	LTP Constraint: A Transfer Learning Based End-to-End Method for RNA Secondary Structure Prediction, Fei et al., 2022 [95]	Bi-LSTM, Transformer, U-Net	Composed of a global semantic extraction module, local feature extraction module, and filter network, applying transfer learning to improve the prediction accuracy.	Combines the advantages of each substructure.	High training costs and large demand for high-quality data.	`https://github.com/jluF/LTPConstraint`

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Category	Title	ML Technique	Brief Description	Pros	Cons	Resource
	RNA secondary structure prediction with convolutional neural networks, Booy et al., 2022 [99]	CNN	Uses three-dimensional tensors to represent RNA sequences and convolutional neural networks to predict two-dimensional mappings of base pairing relationships.	Consists only of CNN model and does not rely on any other energy model.	Cannot apply to data from completely new families compared to the training set.	https://github.com/mehdi1902/RNA-secondary-structure-prediction-using-CNN
	A New Method of RNA Secondary Structure Prediction Based on Convolutional Neural Network and Dynamic Programming, Zhang et al., 2019 [100]	CNN	Utilizes the convolutional neural network to learn the hidden features of RNA structure and the dynamic programming method to generate the optimal RNA secondary structure according to the predicted base pairing probability.	Novel combination of CNN with DP improves accuracy.	The issue of G-U wobble pairing remains, and pseudoknots cannot be predicted accurately.	None
	DMfold: A Novel Method to Predict RNA Secondary Structure with Pseudoknots Based on Deep Learning and Improved Base Pair Maximization Principle, Wang et al., 2019 [**?**]	Bi-LSTM	Combining DL and IBPMP to predict RNA structures with pseudoknots.	Takes full advantage of the two main methods.	The prediction accuracy of long RNA sequences needs to improve.	https://github.com/linyuwangPHD/RNA-Secondary-Structure-Database
	Improving RNA secondary structure prediction via state inference with deep recurrent neural networks, Willmott et al., 2020 [102]	Bi-LSTM	Predicts RNA state through deep bidirectional LSTM to generate synthetic SHAPE data, and combines these data into NNTM for prediction of RNA secondary structure.	Achieved significant improvement over undirected NNTM.	Directed NNTM is difficult to generate high-precision MFE structures for some sequences.	`https://github.com/dwillmott/rna-state-inf`
	REDfold: accurate RNA secondary structure prediction using residual encoder-decoder network, Chen et al., 2023 [103]	CNN	An encoder-decoder network based on convolutional neural network (CNN) is used to learn short and long-range dependencies in RNA sequences, and the network output is post-processed by constraint optimization.	1.Uses constrained optimization instead of DP to find the best structure,so the structures predicted are not limited to nested folding structures. 2.Able to predict RNA structures with pseudoknots efficiently and accurately.	High data dependence, long training time, and vast computational cost.	`https://github.com/aky3100/REDfold`

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