Secondary Structure Prediction by Combination of Formal Grammars and Neural Networks

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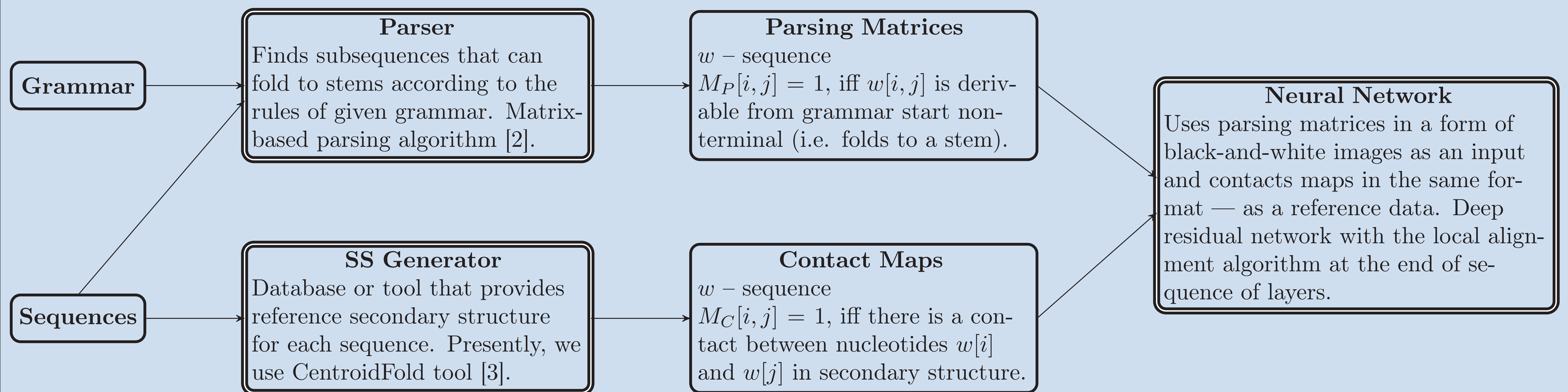
Introduction

Secondary structure is known to have a crucial impact on the RNA molecule functioning, therefore, development of the algorithms for secondary structure modeling and prediction is a fundamental task in computational genomics. An approach for sequences secondary structure analysis by combination of formal grammars and neural networks was proposed in [1]. We encode stems of secondary structure by means of context-free grammar, extract them by parsing algorithm and then process the parsing provided data by neural network. In this work, we apply this approach to RNA secondary structure prediction problem.
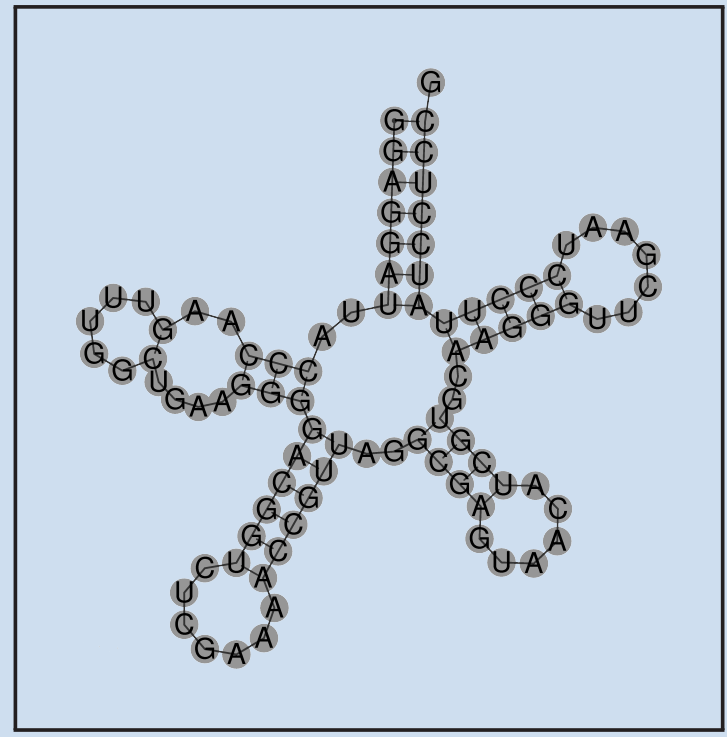
Research Motivation

Secondary structure can be described as composition of stems having different heights and loop sizes. We use context-free grammar to encode the most common kinds of stems and parsing algorithm to find the subsequences of sequence that should fold to such stems. Parsing matrix represents all the theoretically possible stems in some sequence in terms of grammar, but the real secondary structure is more complex than that. Therefore, parsing matrices require further processing and we propose using neural network to handle them in order to generate an actual secondary structure.
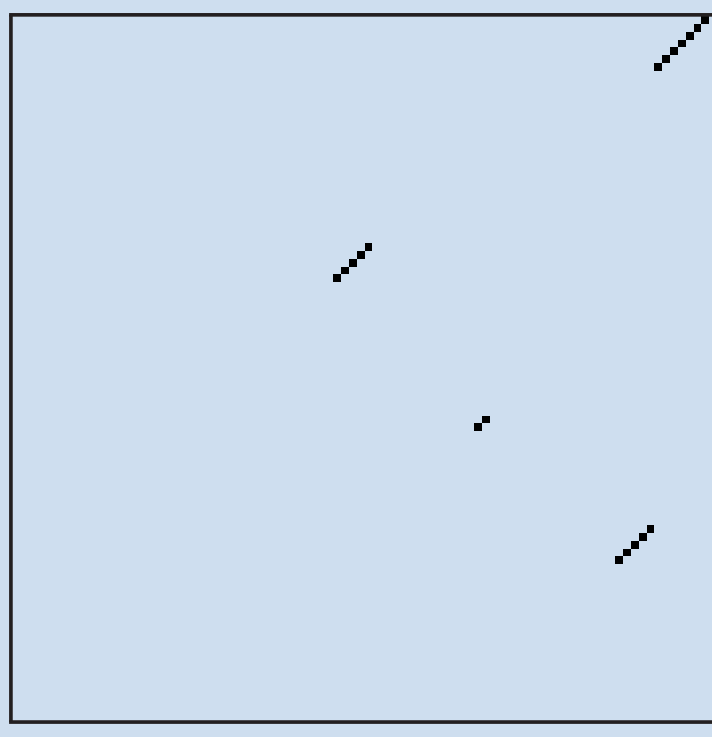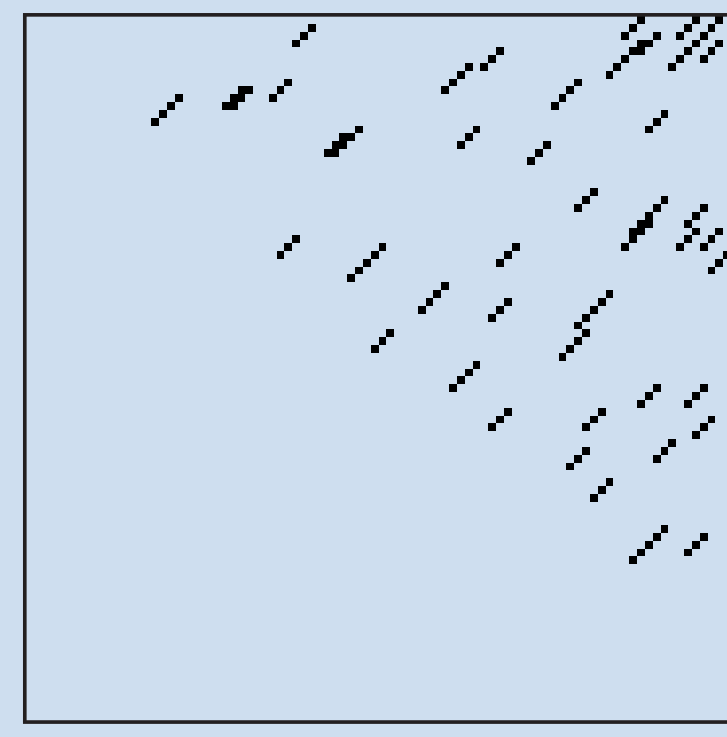
Solution Overview

Grammar → **Parser**
Finds subsequences that can fold to stems according to the rules of given grammar. Matrix-based parsing algorithm [2].

→ **Parsing Matrices**
w – sequence
$M_P[i, j] = 1$, iff $w[i, j]$ is derivable from grammar start non-terminal (i.e. folds to a stem).

Sequences → **SS Generator**
Database or tool that provides reference secondary structure for each sequence. Presently, we use CentroidFold tool [3].

→ **Contact Maps**
w – sequence
$M_C[i, j] = 1$, iff there is a contact between nucleotides $w[i]$ and $w[j]$ in secondary structure.

Neural Network
Uses parsing matrices in a form of black-and-white images as an input and contacts maps in the same format — as a reference data. Deep residual network with the local alignment algorithm at the end of sequence of layers.

Example

Secondary structure

Contact map

Parsing matrix

Metrics

Consider TW (true white), TB (true black), FW (false white) and FB (false black) as amounts of correctly and incorrectly predicted pixels of each color for all images.

- $Precision = \frac{TW}{TW+FW}$

- $Recall = \frac{TW}{TW+FB}$

- $F1\ score = 2 * \frac{Precision*Recall}{Precision+Recall}$

Results

We took sequences from RnaCentral [4] database with 70%:10%:20% split and trained models on several datasets with fixed sequences length interval with and without alignment.

Length	Samples	Alignment	Precision	Recall	F1 score
90	26511	✗	67%	75%	68%
		✓	80%	66%	70%
88-90	77976	✗	66%	78%	69%
		✓	81%	62%	68%
50-90	141835	✗	60%	72%	63%
		✓	71%	61%	63%

We can make the following conclusions.

- The smaller the window size, the more accurate the model.

- Alignment significantly improves precision of neural networks due to removing the contacts that break the secondary structure.

- From the other hand, it decreases recall, probably because it also removes a part of necessary information.

- So, our approach is applicable to secondary structure analysis problem, but further research is required.

Future Research

- Improvement of prediction accuracy.

- Experiments on structures with pseudoknots and corresponding adaptation of the alignment algorithm.

- Building a model that predicts secondary structure for sequences of arbitrary length.

- More accurate choice of the reference data source.

References

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[3] Michiaki Hamada, Hisanori Kiryu, Kengo Sato, Toutai Mituyama, and Kiyoshi Asai. Prediction of rna secondary structure using generalized centroid estimators. *Bioinformatics*, 25(4):465–473, 2009.

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Information

https://github.com/LuninaPolina/SecondaryStructureAnalyzer.
https://github.com/SacredArrow/Secondary_structure_public.

Acknowledgments