The Composition of Dense Neural Networks and Formal Grammars for Secondary Structure Analysis

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Sequences Analysis: classification, search...

Problem: high variability of data

- Mutations
- Different kinds of noise
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- Primary structure
- Secondary structure
- Tertiary structure

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We should handle secondary structure

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Probabilistic approach which handles secondary structure

Proposed Solution: Parsing + Artificial Neural Network

- Use parsing to extract features, not to model secondary structure
  - As compared to the classical way of probabilistic CF grammars utilization

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- Use parsing to extract features, not to model secondary structure
  - As compared to the classical way of probabilistic CF grammars utilization
- Formal grammars as secondary structure description
- Parsing as features extraction
- Artificial neural network as probabilistic model for features processing

Solution Structure

Grammar
Fixed formal grammar (not necessarily context-free) describes features of secondary structure and can be tuned to increase the quality of result.

Sequences
Each sequence is treated as a text in $\{A, C, G, T\}$ alphabet.

Result of classification

Parser
Parser extracts features of the given sequence secondary structure. Implementation of parsing algorithm is based on matrix multiplications (Valiant, Okhotin) and utilizes GPGPU.

Matrices

0	1	0	1
0	0	1	0
0	0	0	1
0	0	0	0

Parsing result is (0-1) matrix M which represents secondary structure features for sequence ω:
$M[i,j] = 1 \iff \text{s1} \xrightarrow{*} \omega[i,j],$
and 0 otherwise.

Neural Network
Dense neural network with more than 10 dense layers. Agressive dropout and batch normalization for learning process stabilization. Typical building block:

Dropout	input:	1024
(75%)	output:	1024

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Activation	input:	1024
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$[0,1,0,1,0,1,0,0,1,0] \Rightarrow$
$[84,128]$

Line-by-line compressed matrix representation: sequence of 8 cells (bits) is compressed into a byte. Bottom left triangle of the matrix is always empty, so can be ignored.

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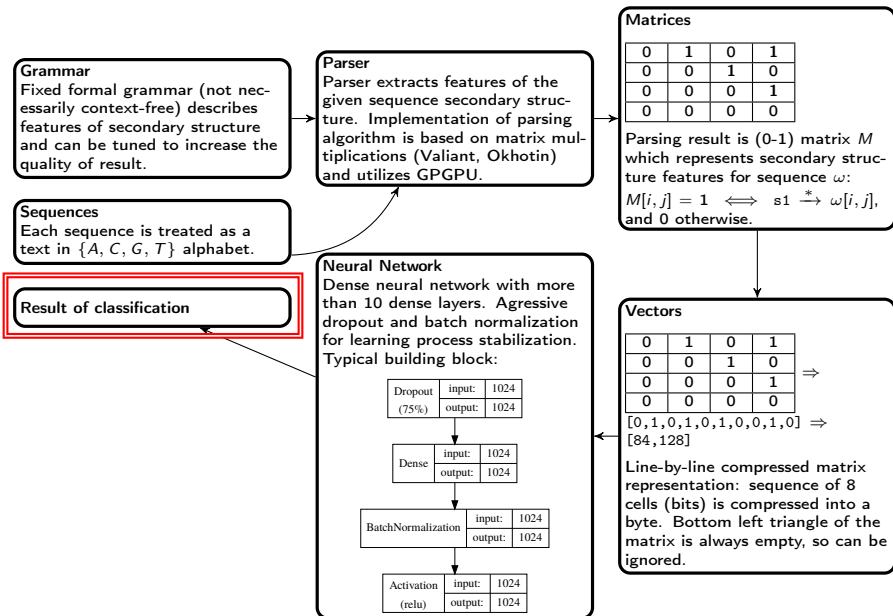$M[i, j] = 1 \iff s1 \xrightarrow{*} \omega[i, j]$, and 0 otherwise.

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# Grammar

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s1: stem<s0>
any_str: any_smb*[2..10]
any_smb: A | T | C | G
stem1<s>:                    \\ stem of height exactly 1
      A s T | G s C | T s A | C s G
stem2<s>:                    \\ stem of height exactly 2
      stem1< stem1<s> >
stem<s>:                     \\ stem of height 3 or more
      A stem<s> T
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Example 1: Stem

$$\omega_1 = \mathtt{CCCCATTGCCAAGGACCCCACCTTGGCAATCCC}$$
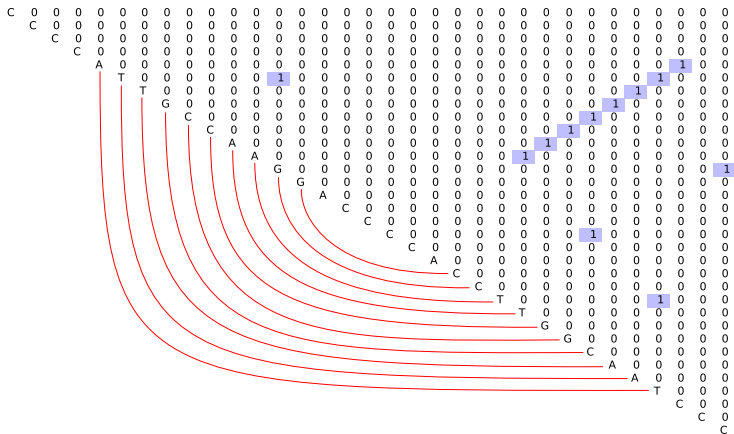
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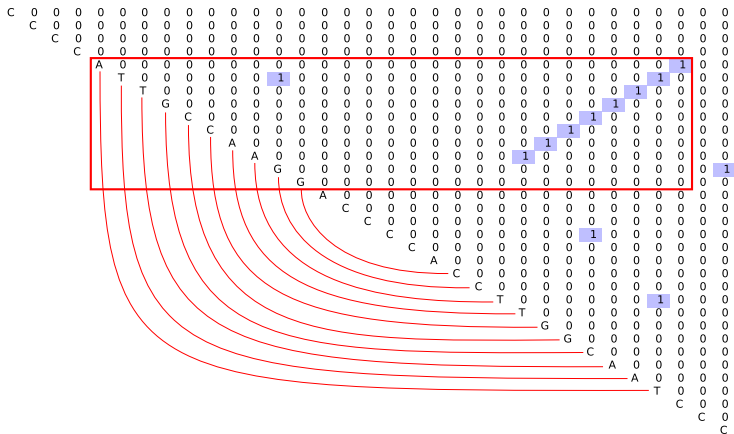
$$\omega_2 = \texttt{CCACTTACCTATGACCTAAGTCCTCATACC}$$
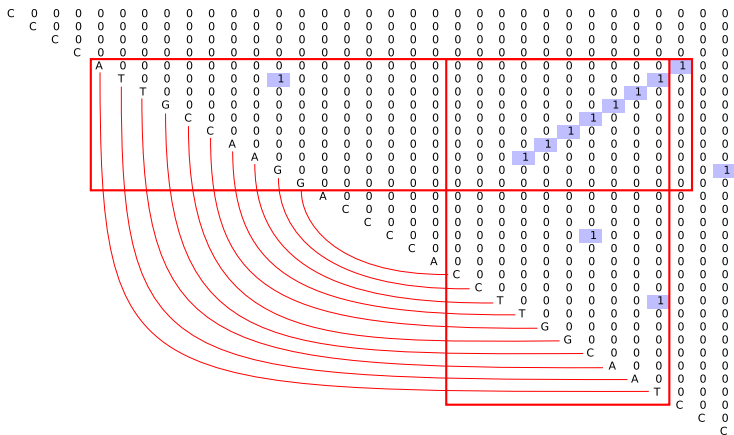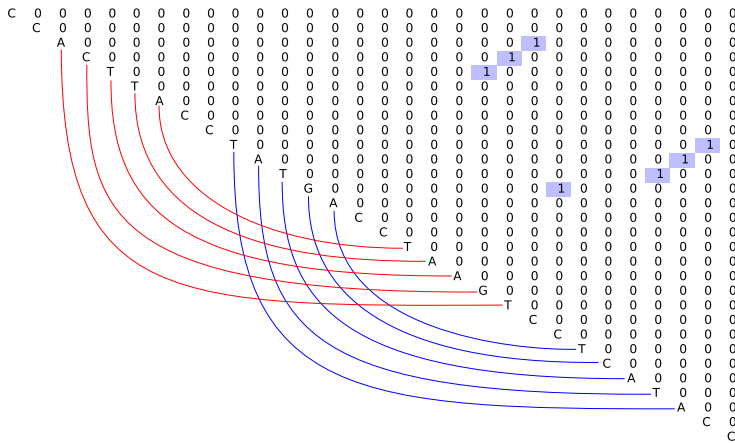
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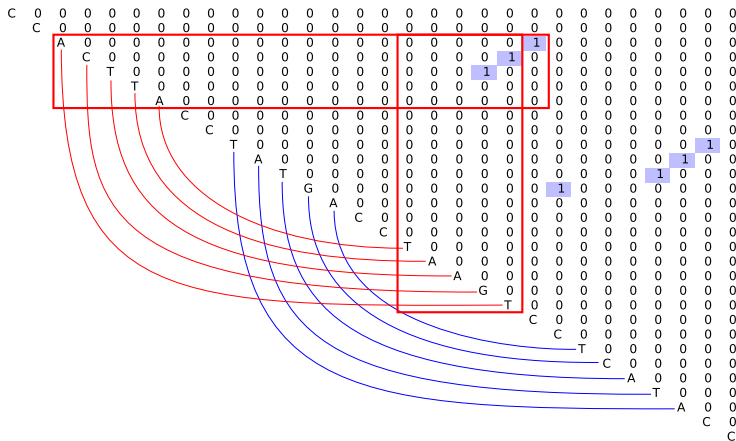
Example 3: real tRNA

$$\omega_3 = \texttt{CAGGGCATAACCTAGCCCAACCTTGCCAAGG}$$
$$\texttt{TTGGGGTCGAGGGTTCGAATCCCTTCGCCCGCTCCA}$$

- Novosphingobium aromaticivorans DSM 12444
  chr.trna57-GlyGCC(268150-268084) Gly (GCC) 67 bp Sc: 22.9, from
  GtRNAdb
- Predicted secondary structures are given by using the Fold Web Server
  with default settings

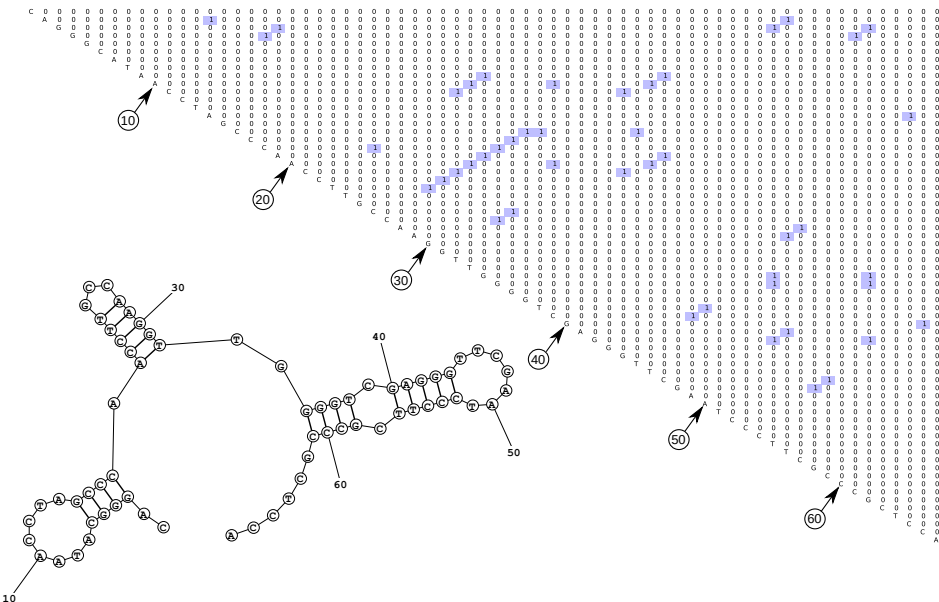# Example 3: real tRNA
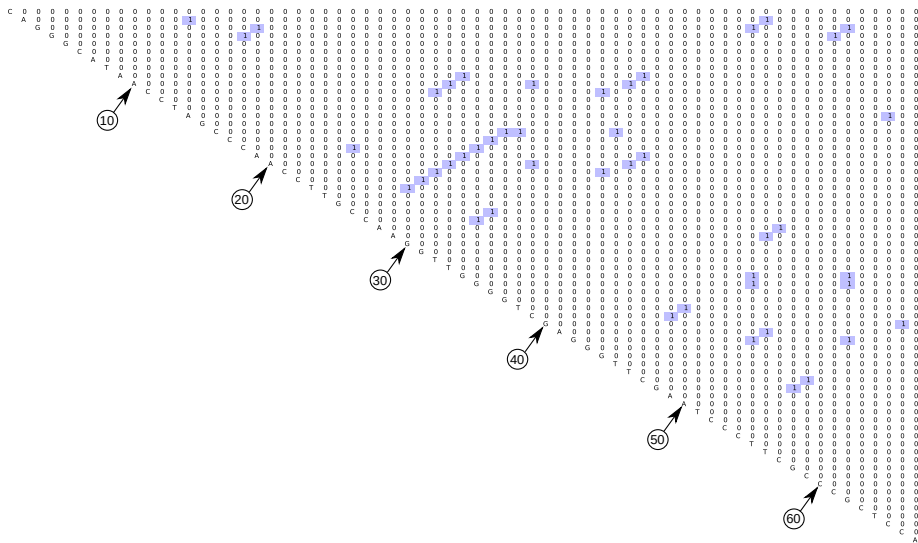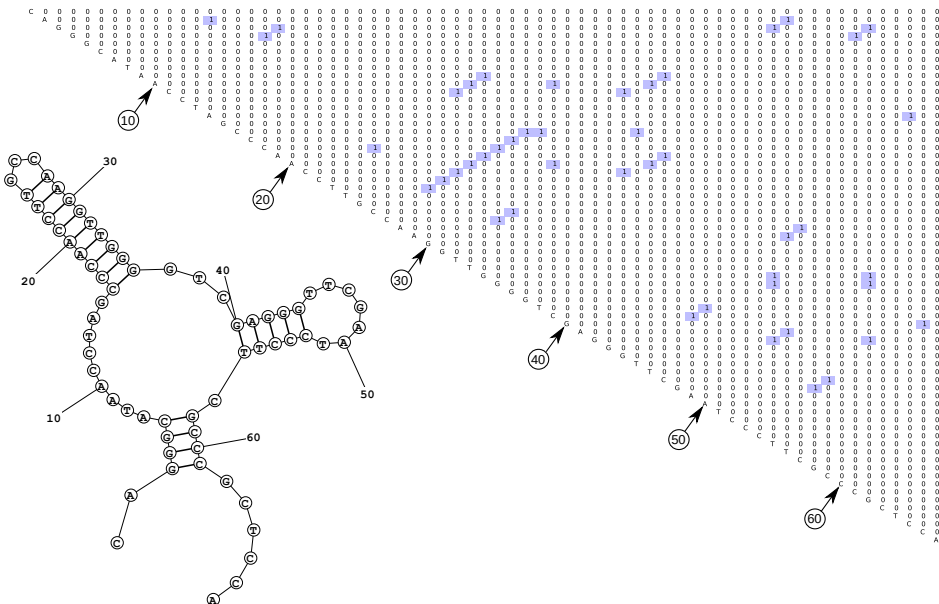
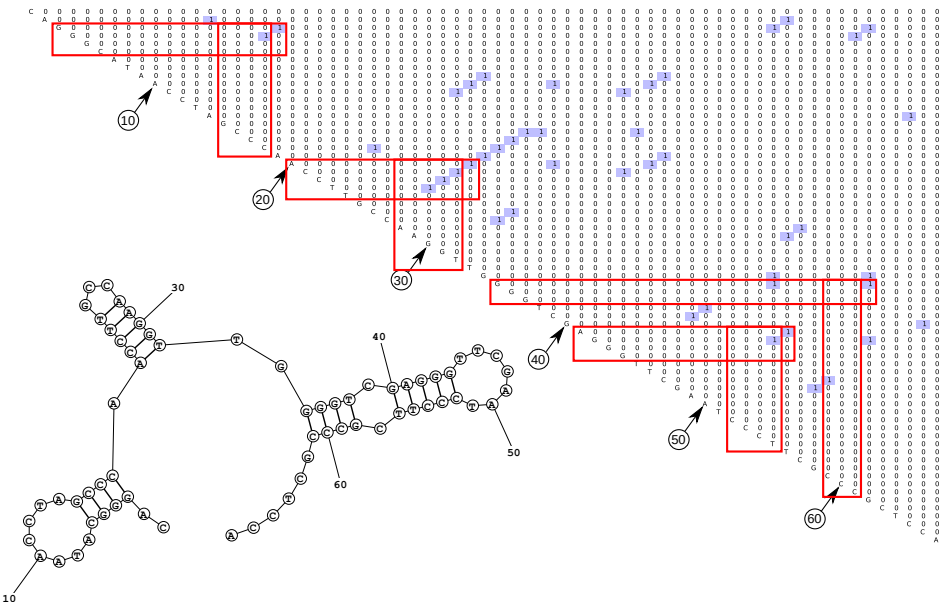# Example 3: real tRNA
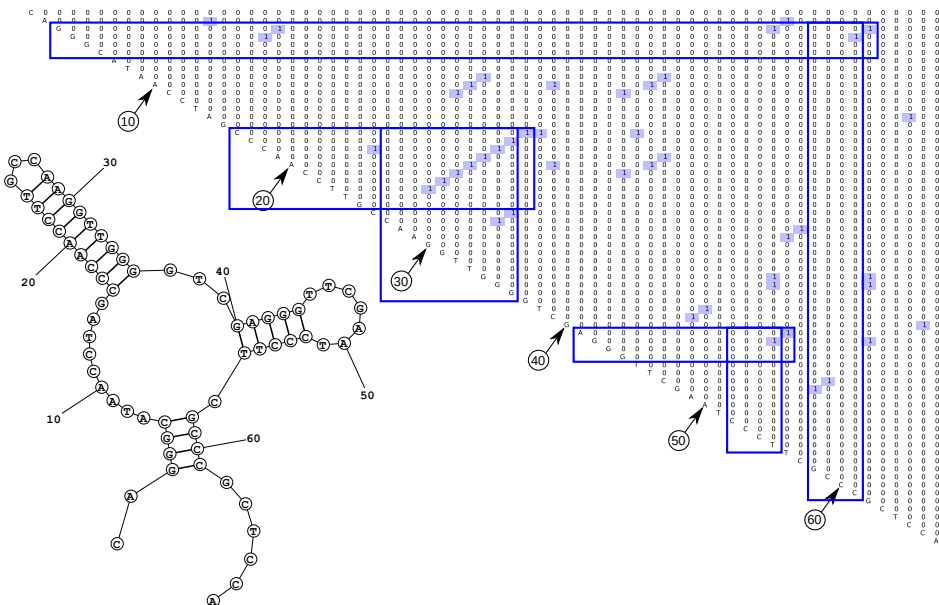
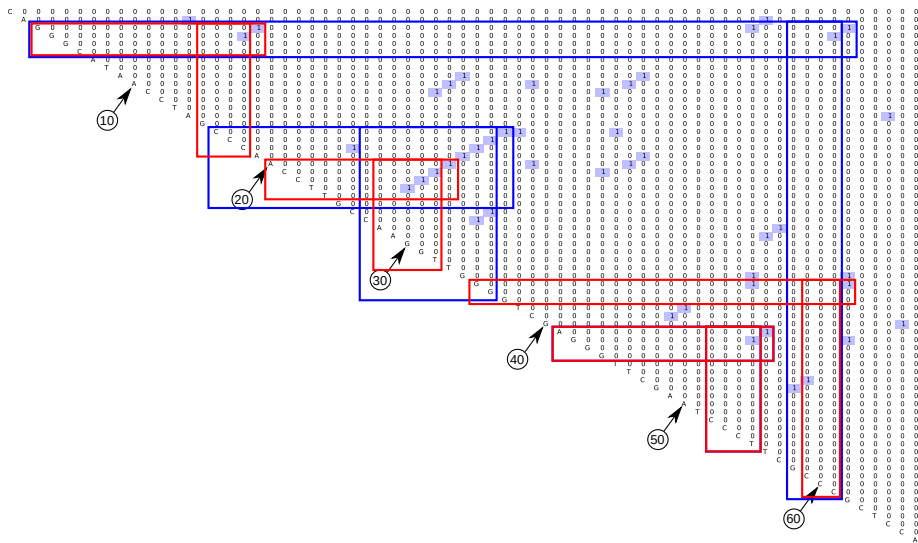# Example 3: real tRNA
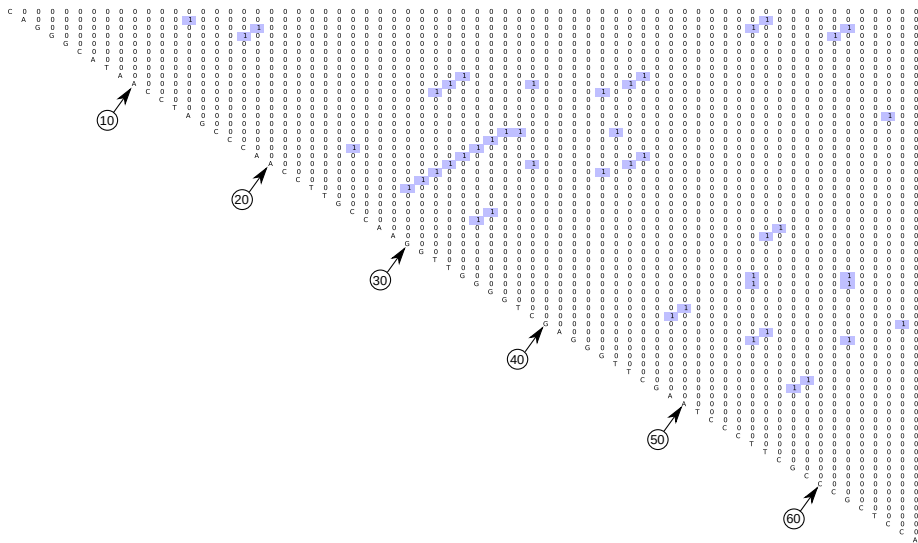
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Summary

- Parser is only a features extractor
- Parsing result contains all possible foldings (w.r.t. grammar) including impossible in practice
- Grammar is a parameter: one can add a `G-T` pair, change minimal height of the stem, etc
- It is possible to detect features which are not expressible in the language class in use

Artificial Neural Networks

- Dense neural network
  - About 10 dense layers
  - `Relu` activation function
- Problem: input size is fixed, but the length of sequences is variable

ACACAC		ACACAC$$
CGTACGCT	$\Rightarrow$	CGTACGCT
GCT		GCT$$$$$

- Agressive dropout (up to 90% after each layer) and batch normalization (after each layer) for learning stabilization

Evaluation: 16s rRNA detection

- Training data
  - All sequences are 512 symbols in length
  - Totally up to 310000 sequences
  - Positive: random subsequences of 16s rRNA sequences from the Green Genes database
  - Negative: random subsequences of full genes from the NCBI database
- Validation set: up to 81000 sequences
- Accuracy is 90% after training

Evaluation: tRNA classification

- Training data: 50000 sequences from GtRNADB
- Input data normalization
    - Set the upper bound of sequence length to 220
    - First k symbols of the input are tRNA and the rest $220 - k$ symbols are filled by the special symbol
- Validation set: 217984 sequences for prokaryotes and 62656 sequences for eukaryotes from tRNADB-CE 3
- Accuracy is 97% after training
    - 3276 of eukaryotes (5.23% of all eukaryotes in the validation set) are classified as prokaryotes
    - 4373 of prokaryotes (2.01% of all prokaryotes in the validation set) are classified as eukaryotes

Future work

- Create DNN which does not requre input parsing
  - Create a training set of matrices using parsing
  - Train the network NN_1 which can handle vectorized matrices
  - Create network NN_2 by extending NN_1 with a set of layers which convert the sequence to input for NN_1
  - Train NN_2, weights of layers from NN_1 are fixed
- Try to use other types of neural networks: bitwise networks, convolutional networks
- Do more evaluation
- Perform comparison with other tools

Conclusion

- We propose the approach to handle secondary structure of sequences
- This approach can be applied for real data processing
- This approach can be extended to more expressive classes of formal languages
  - ▶ Conjunctive and boolean grammars
  - ▶ Multiple context-free grammars

Contact Information

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  - ▶ Semen.Grigorev@jetbrains.com
- Polina Lunina:
  - ▶ lunina_polina@mail.ru
- Trained models: https://github.com/YaccConstructor/YC.Bio

Thanks!