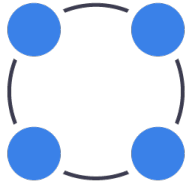

Формальные граммтики и искусственные нейронные сети для анализа вторичной структуры

Студенческий проект на лето 2019

Семён Григорьев

Лаборатория языковых инструментов JetBrains
Санкт-Петербургский государственный университет
Математико-механический факультет

8 июня 2019г.

Кто мы

- Исследовательская группа на Математико-Механическом факультете СПбГУ
- Исследовательская группа в лаборатории языковых инструментов JetBrains Research
- Руководитель группы: Семён Григорьев
  - rsdpisuy@gmail.com
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- Сферы интереснов
  - Теория формальных языков
  - **Применение теории формальных языков для решения прикладных задач**

Анализ вторичной структуры: синтаксический анализ + искусственные нейронные сети

- Формальная граммтика — способ описать особенности вторичной структуры
  - А не смоделировать структуру всей цепочки
  - Используем обыкновенные граммтики, а не вероятностные
- Синтаксический анализ — способ извлечь особенности вторичной структуры
- Искусственная нейронная сеть — вероятностная модель для обработки извлечённых особенностей

Грамматика

```
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 | T s A | C s G | G s C
stem3<s>:                    \\ stem of height exactly 3
      stem1< stem1< stem1<s> > >
stem<s>:                     \\ stem of height 3 or more
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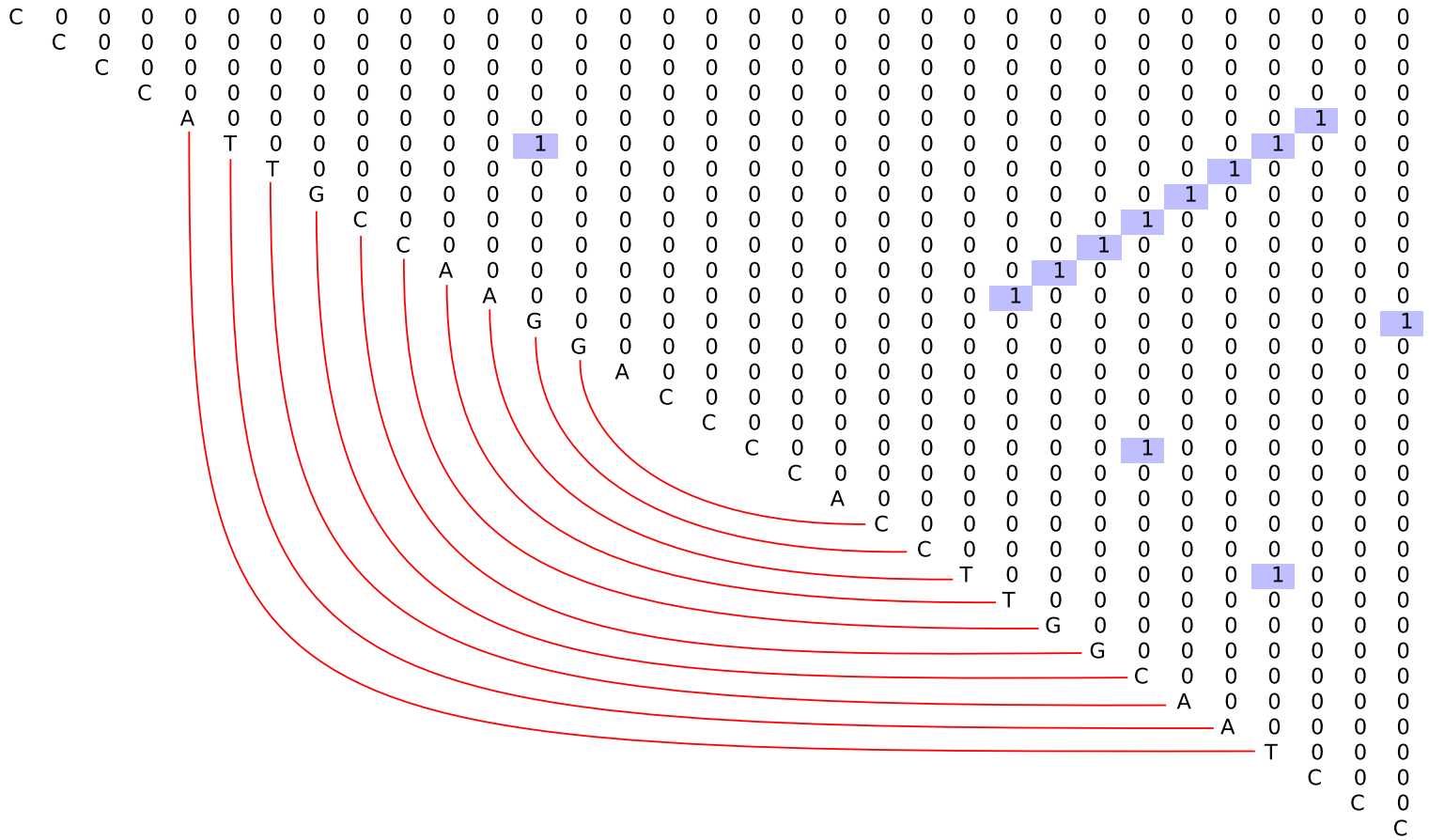

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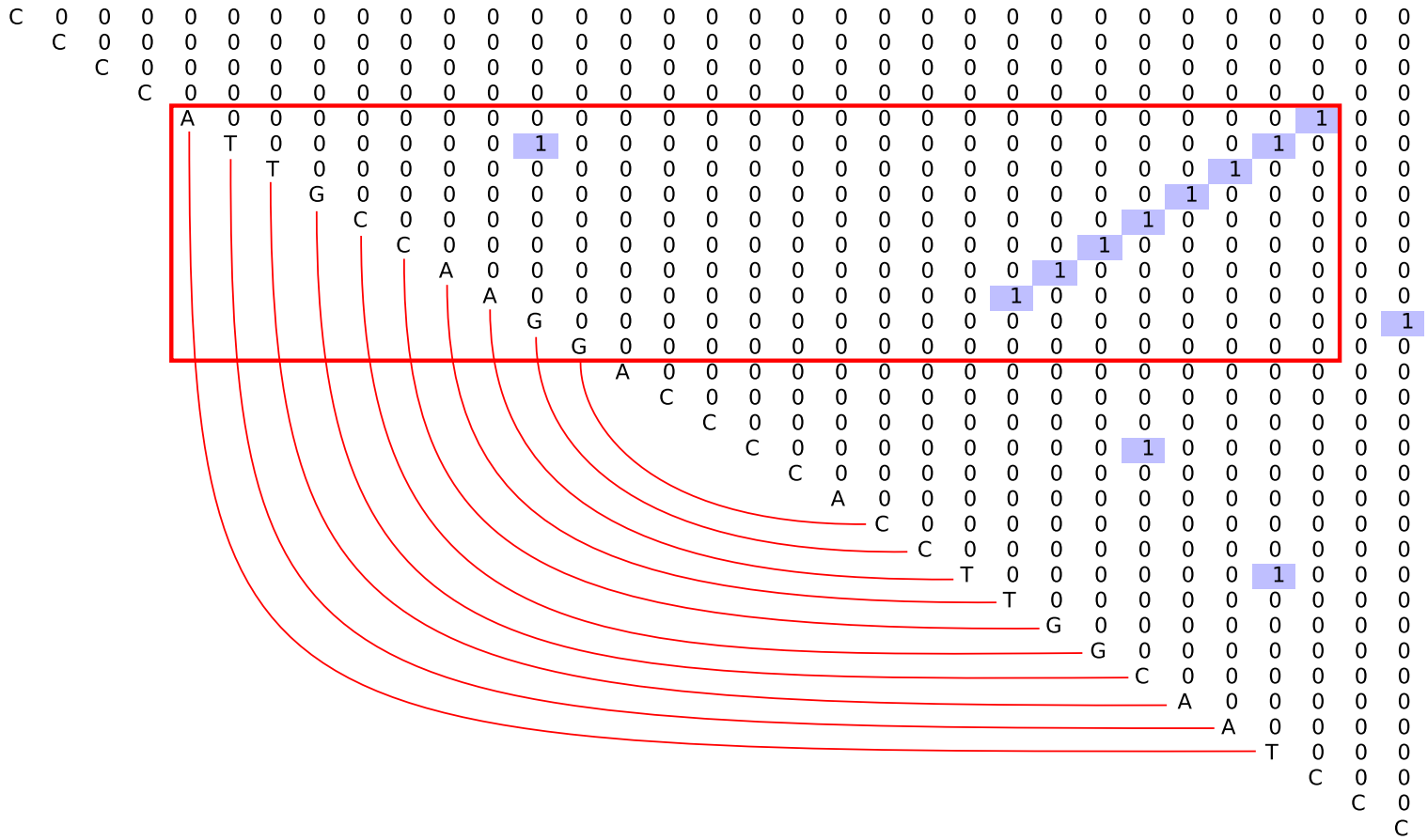

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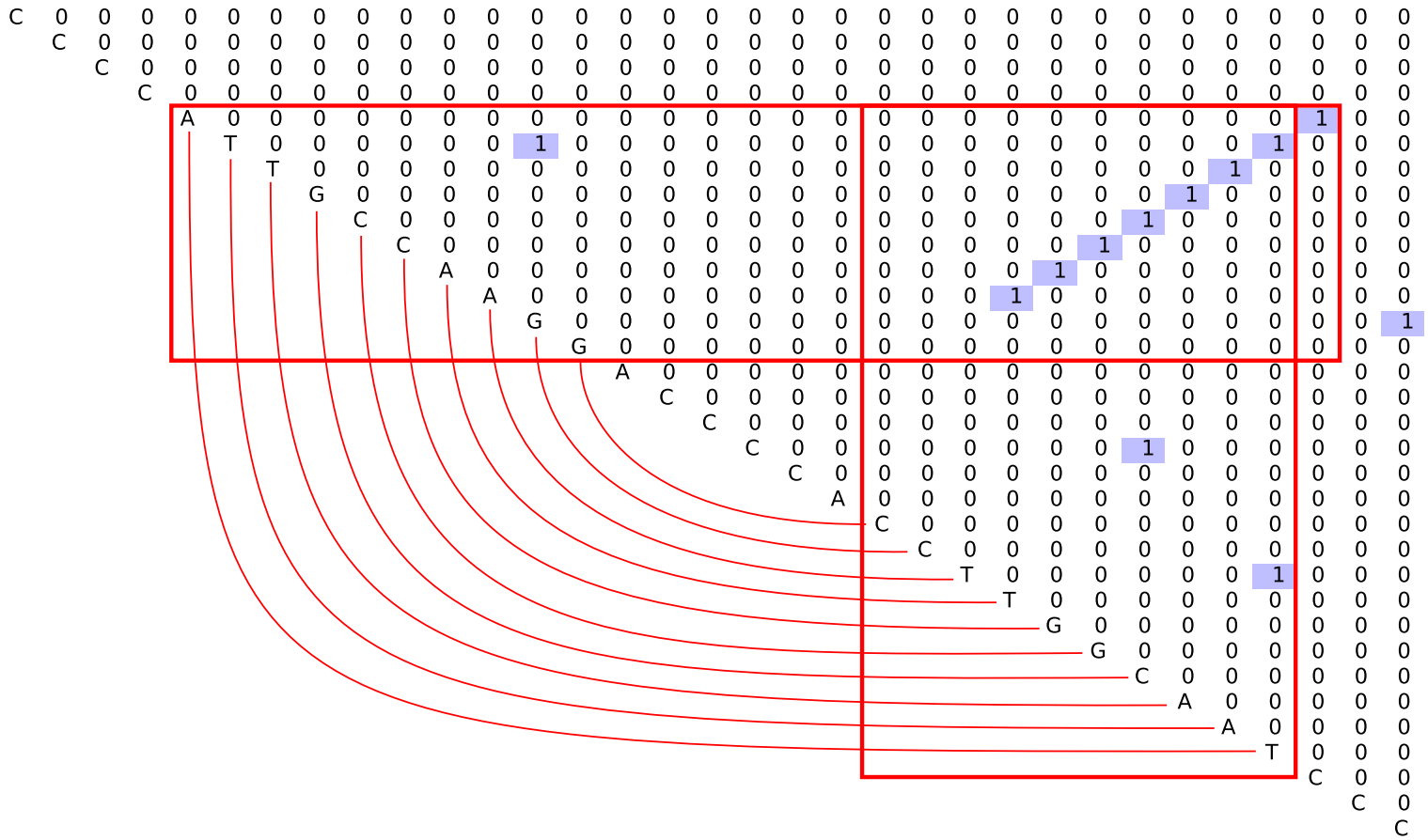
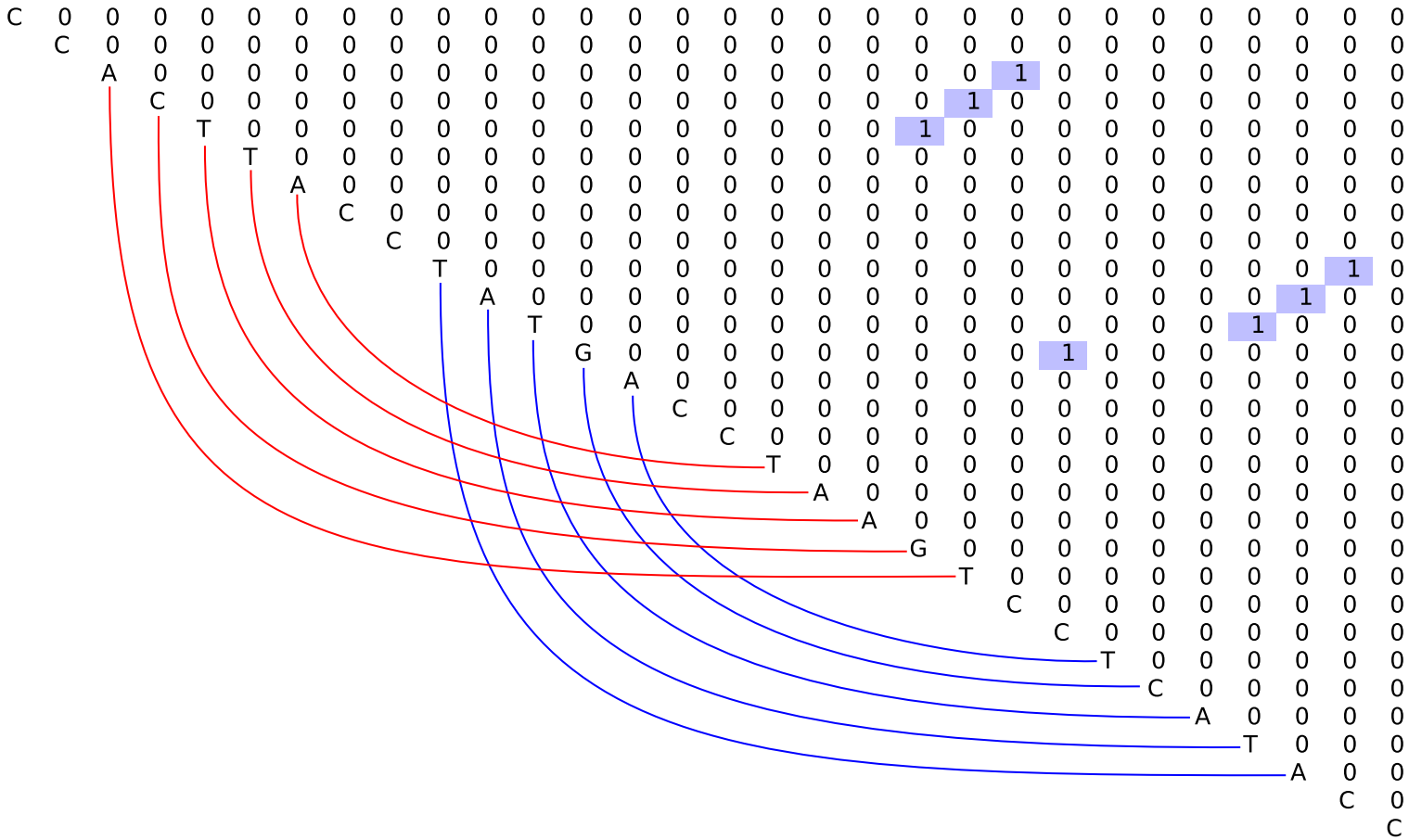


Пример 2: псевдоузел

CCACTTACCTATGACCTAAGTCCTCATACC



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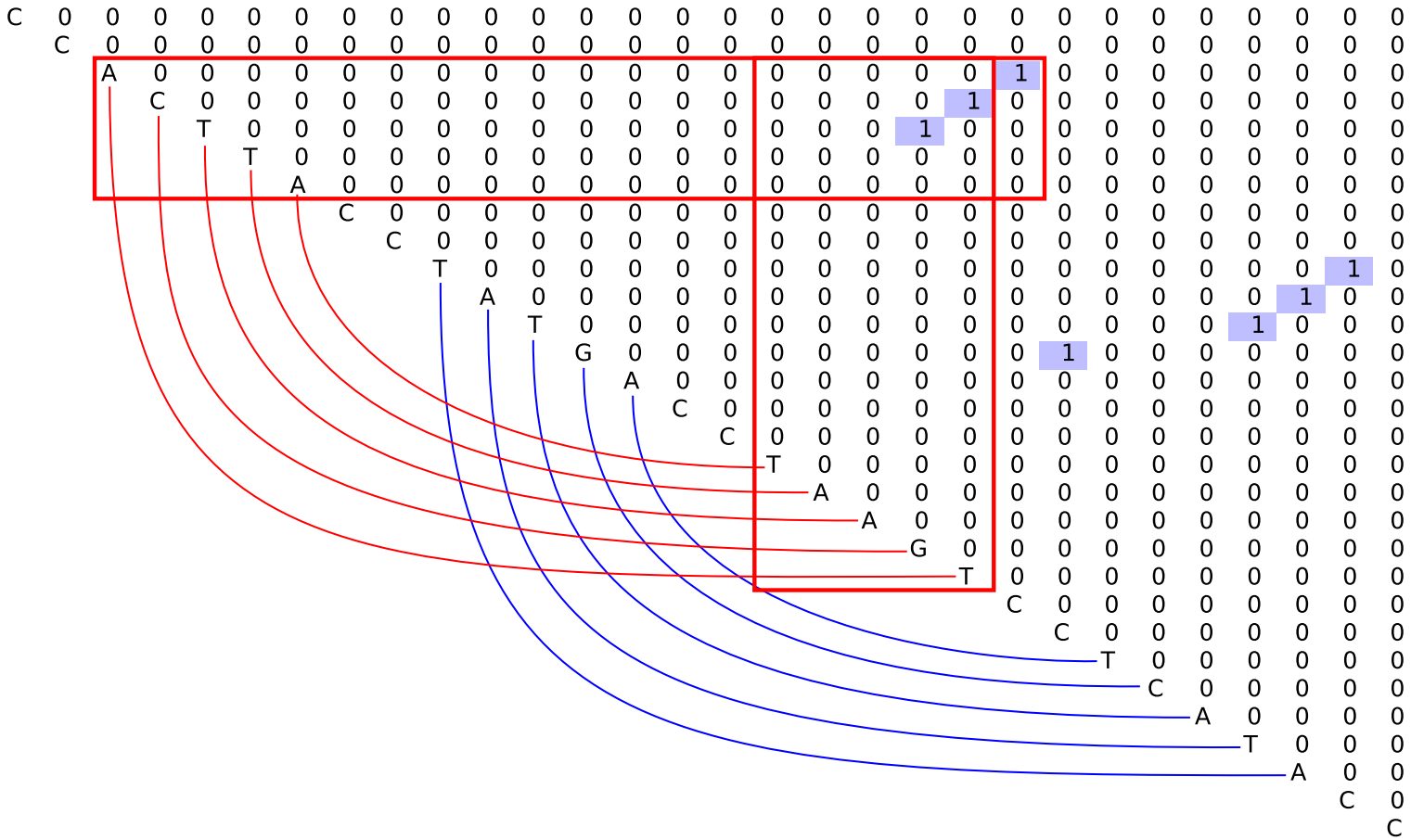

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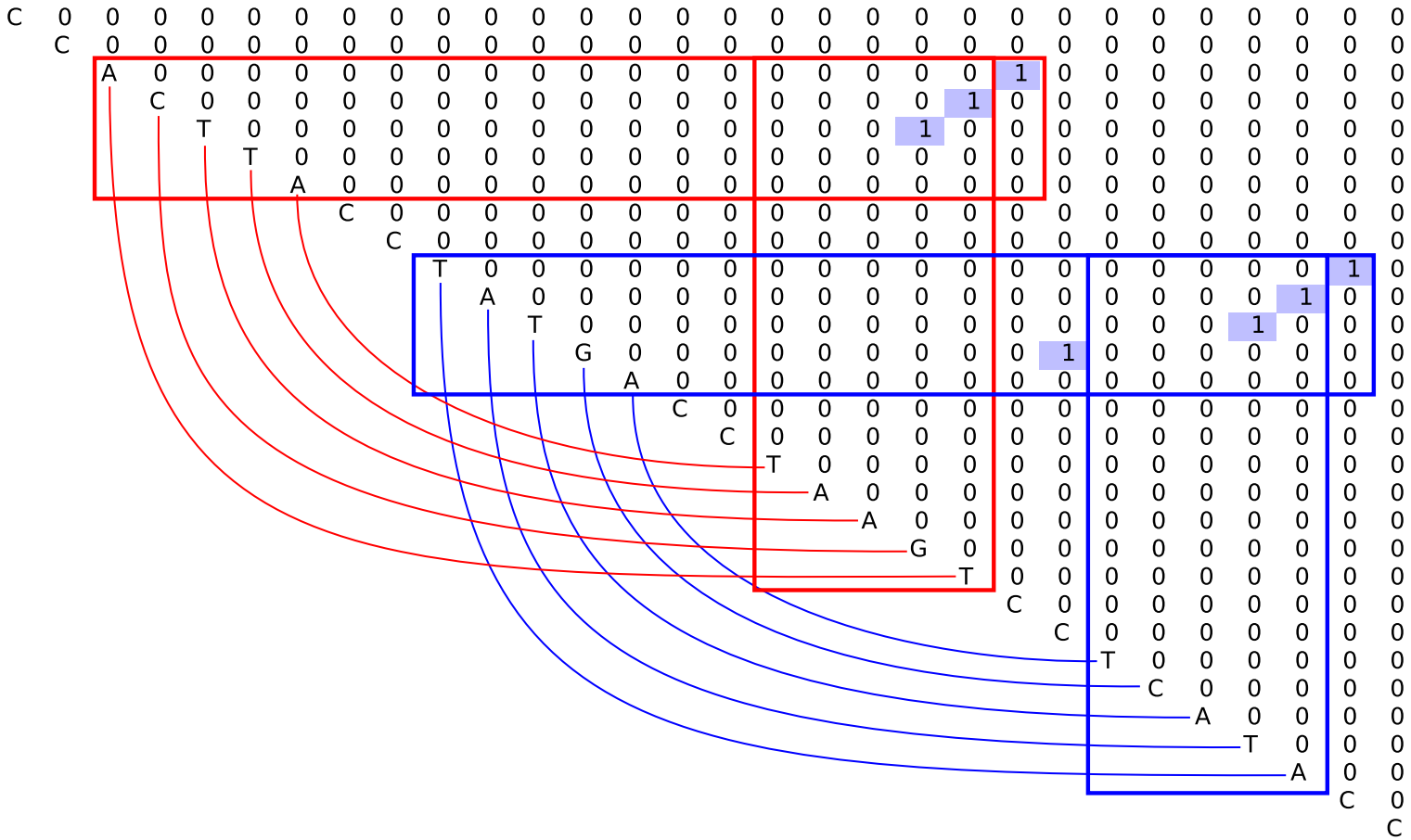

Задачи

- Анализ вторичной структуры РНК-последовательностей
  - Фильтрация химер 16s рРНК
  - Предсказание вторичной структуры цепочек
  - Классификация 16s рРНК

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  - Классификация 16s рРНК
- Анализ вторичной структуры белковых последовательностей
  - Предсказание функций белков

Требования к кандидатам

- Знания в геномике/протеомике: первичная и вторичная структуры, задачи поиска и классификации последовательностей, умение работать с базами соответствующих последовательностей
- Базовые знания теории формальных языков: формальная грамматика, вывод в граммтике, синтаксический анализ
- Хорошие знания в машинном обучении: подготовка и проведение экспериментов, подготовка данных, оценка качества моделей
- Хорошие знания в искусственных нейронных сетях: прикладные пакеты для создания и обучения, принципы построения сетей, смысл параметров и метапараметров

Условия

- 1 месяц, предпочтительно июль
- Можно удалённо, но с регулярным общением с руководителем
- Стипендия

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

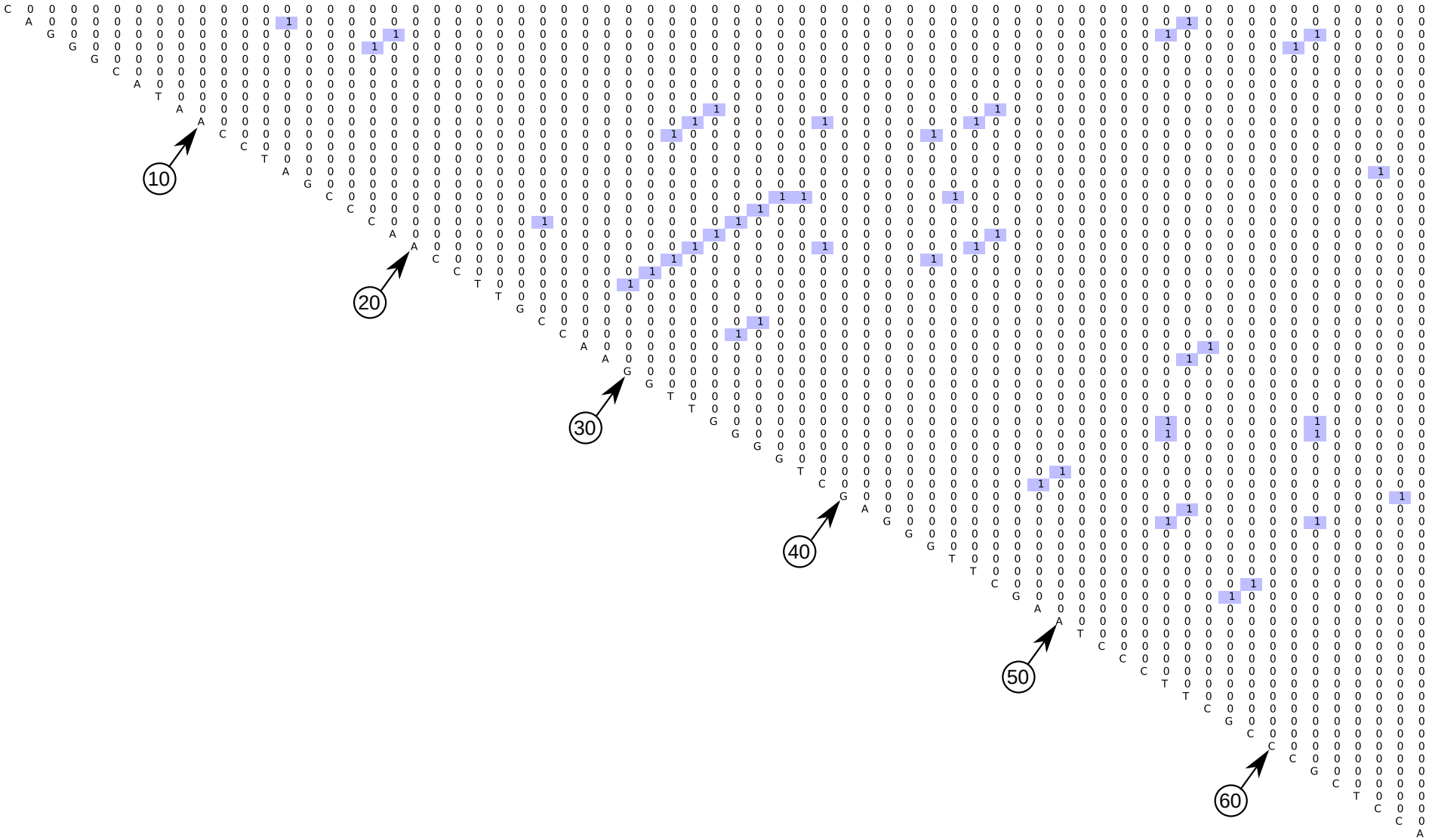
- Training data: 50000 sequences from GtRNADB
- Input data normalization
  - Set the upper bound of sequence length to 220
  - First k symbols of the input are tRNA and the rest $220 - k$ symbols are filled by the special symbol
- Validation set: 217984 sequences for prokaryotes and 62656 sequences for 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

Example 3: real tRNA

```
CAGGGCATAACCTAGCCCAACCTTGCCAAGG
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



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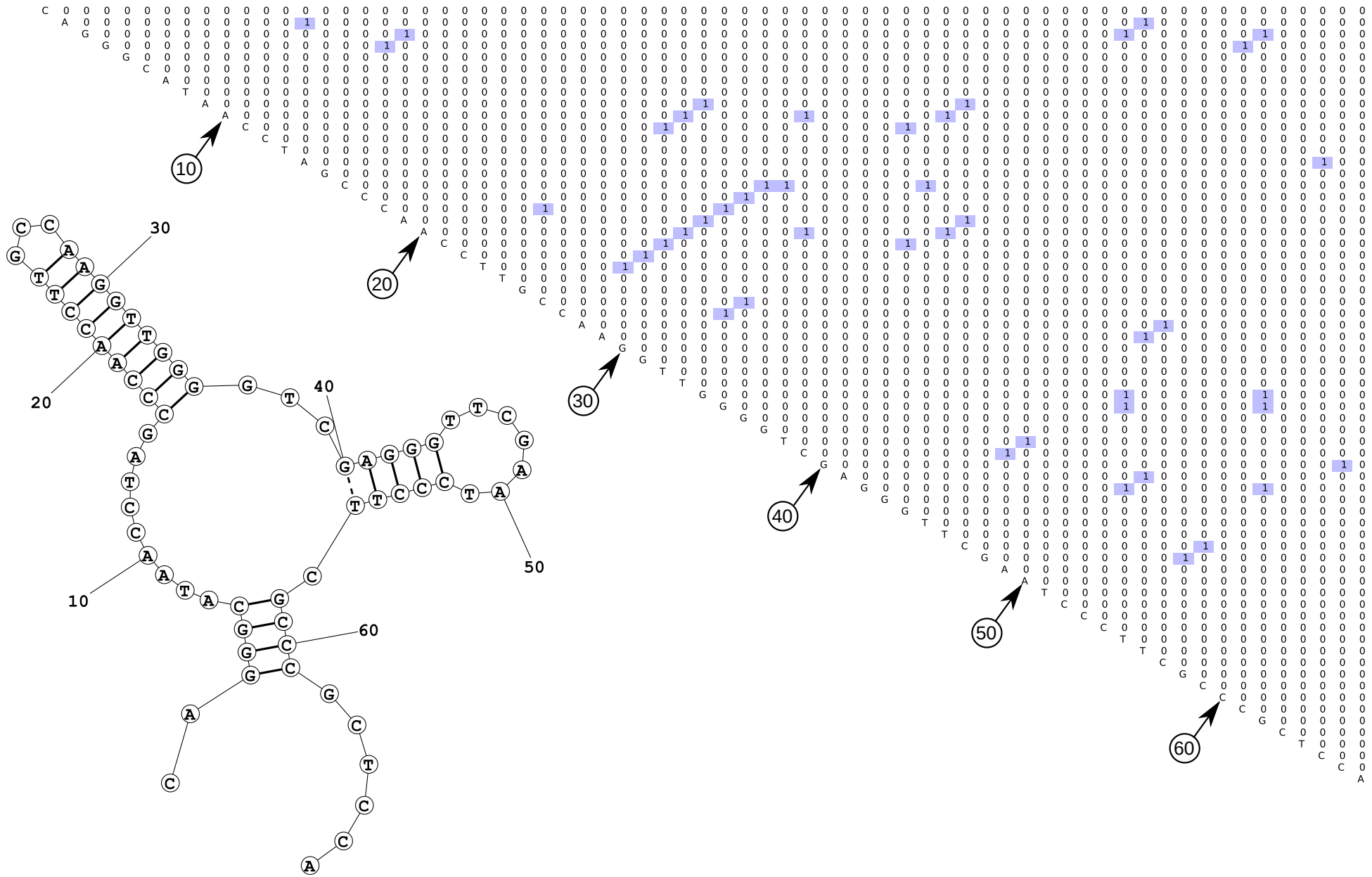

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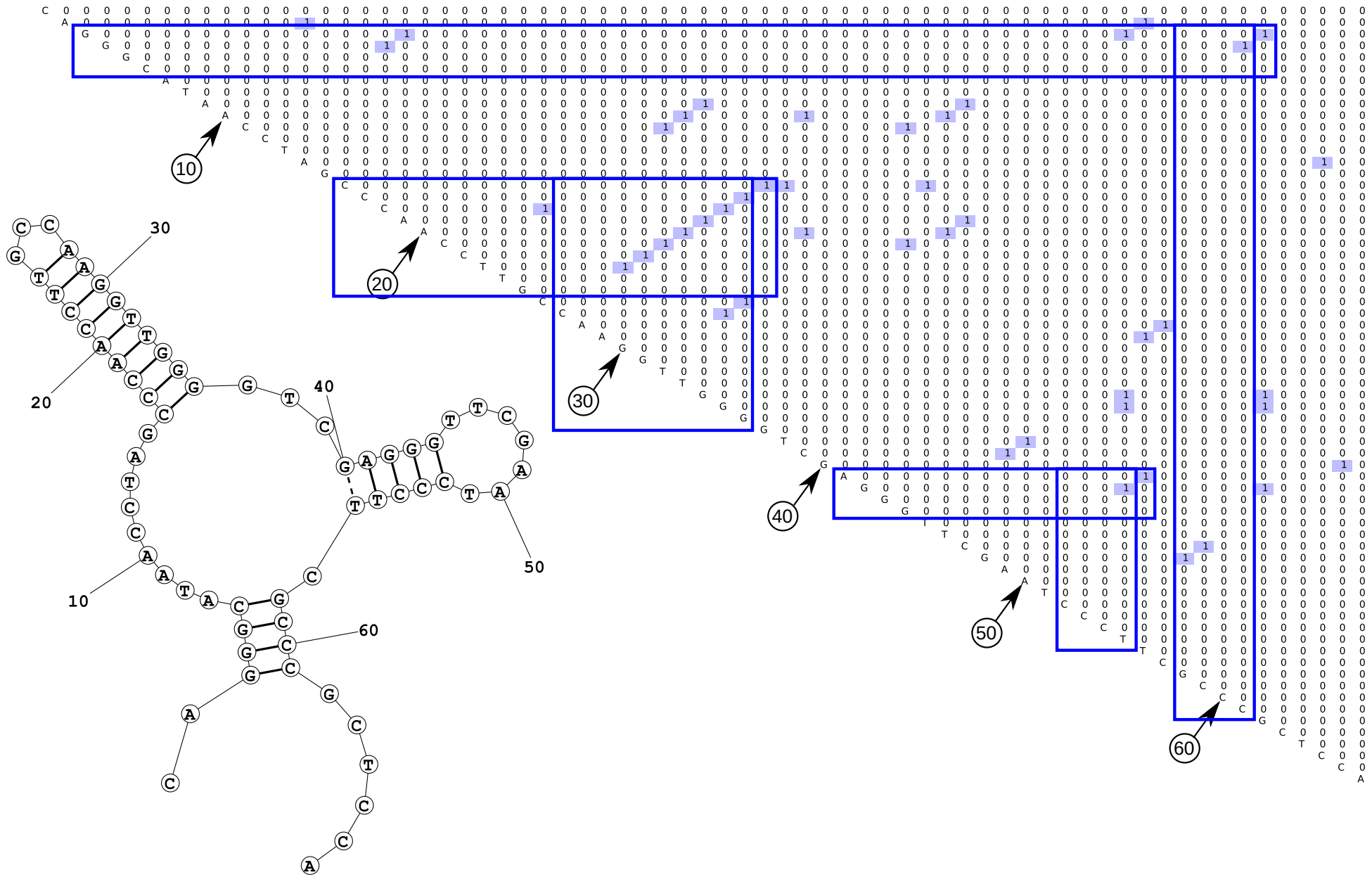

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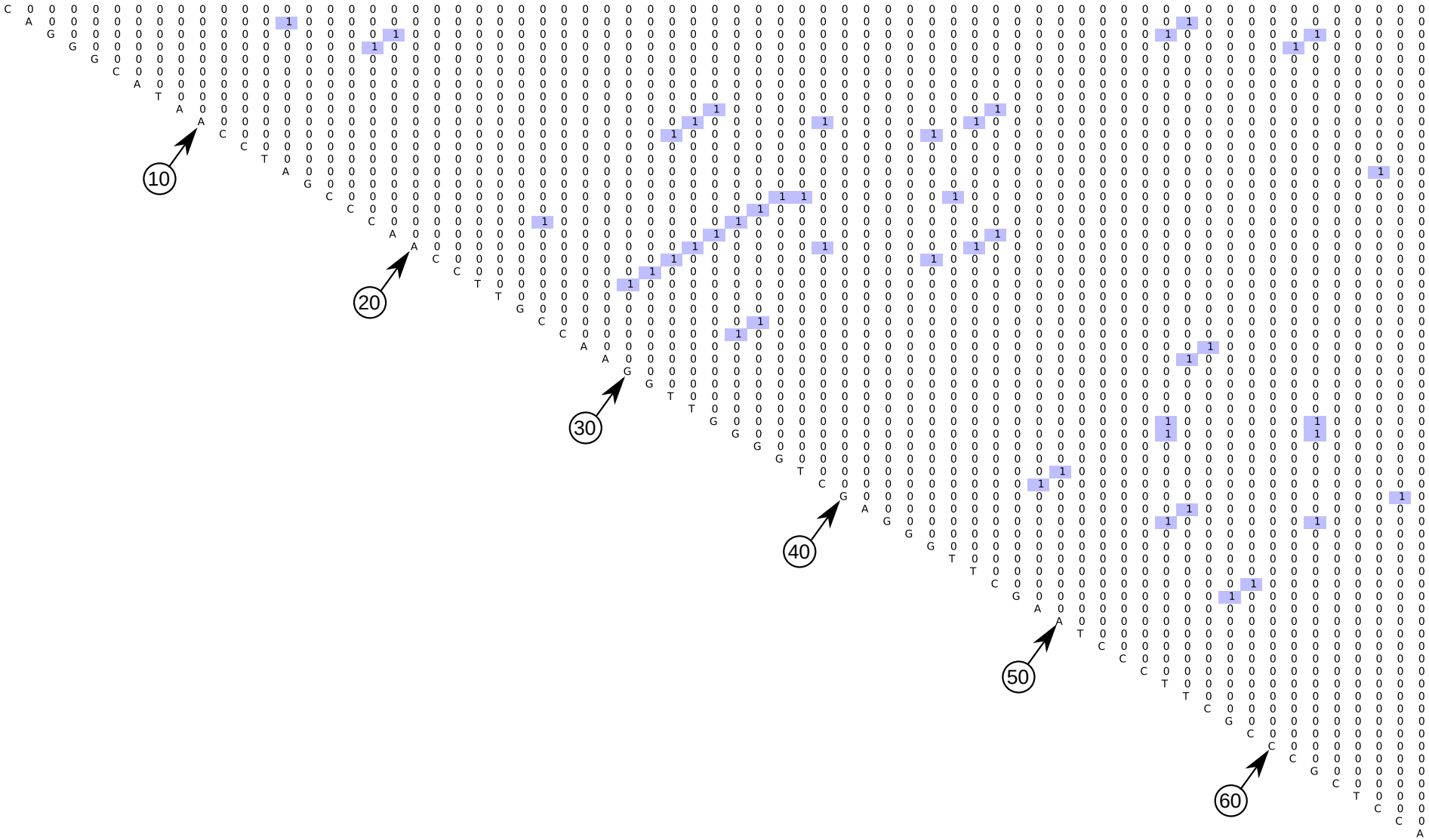

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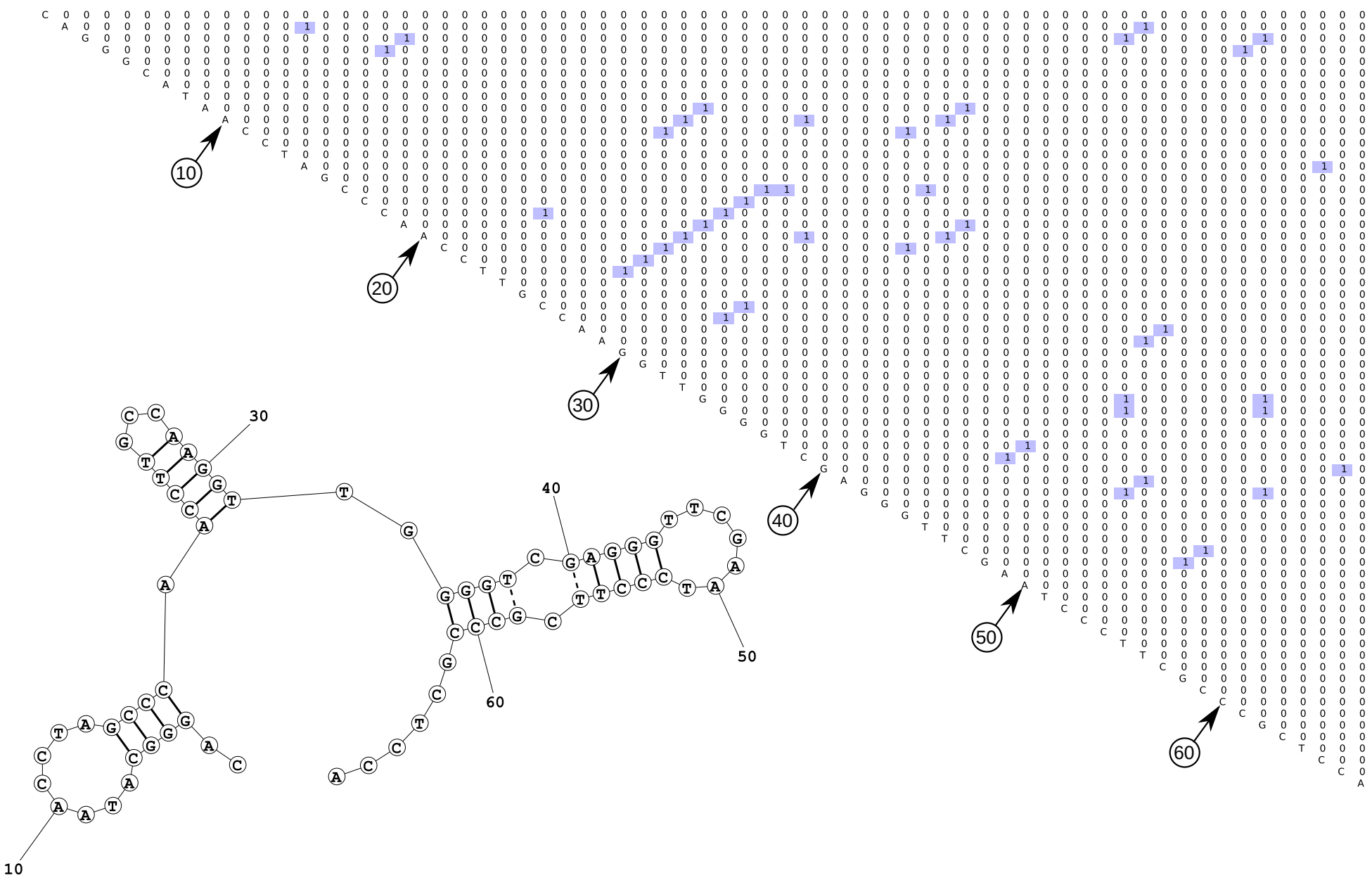

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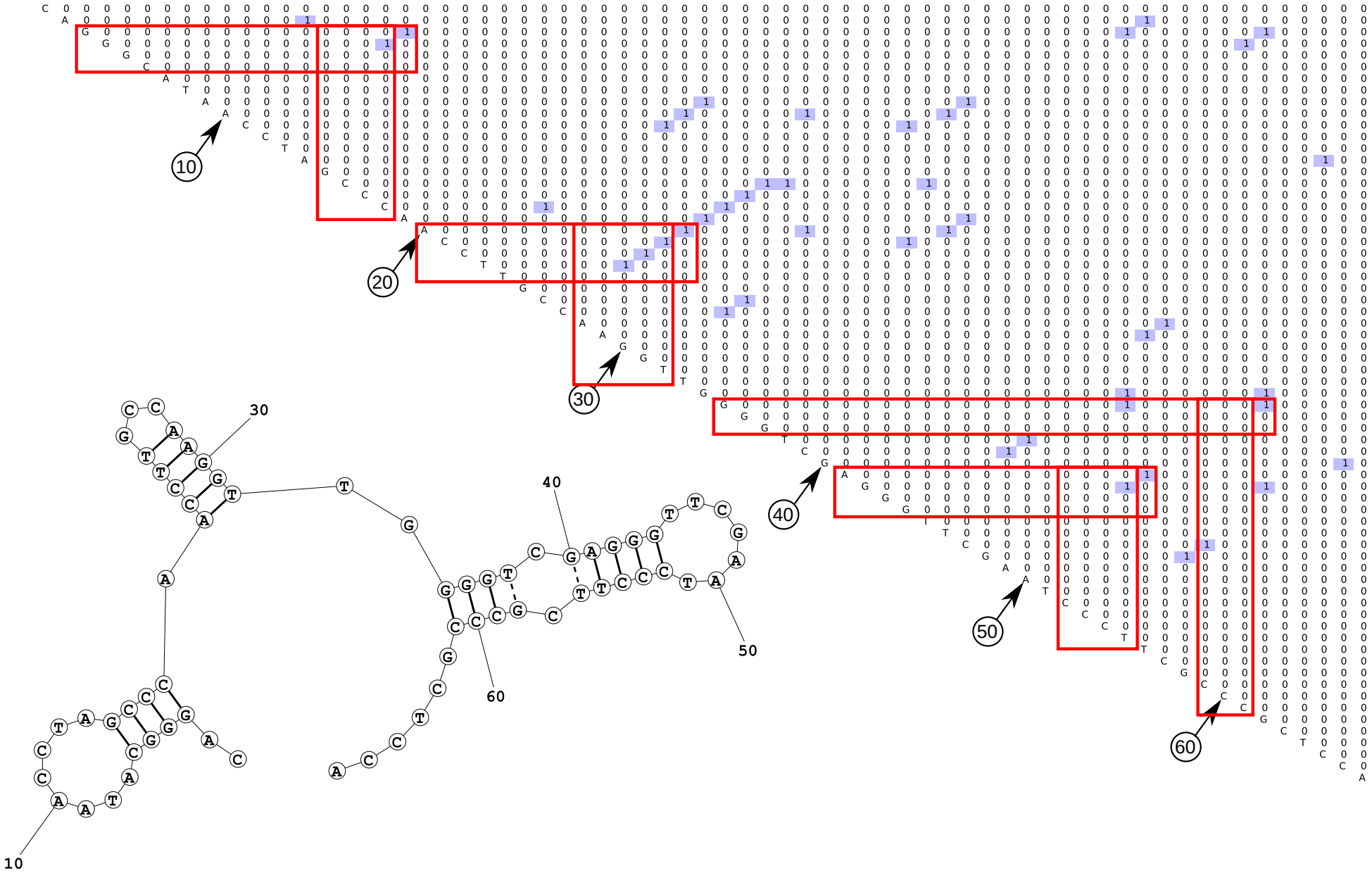

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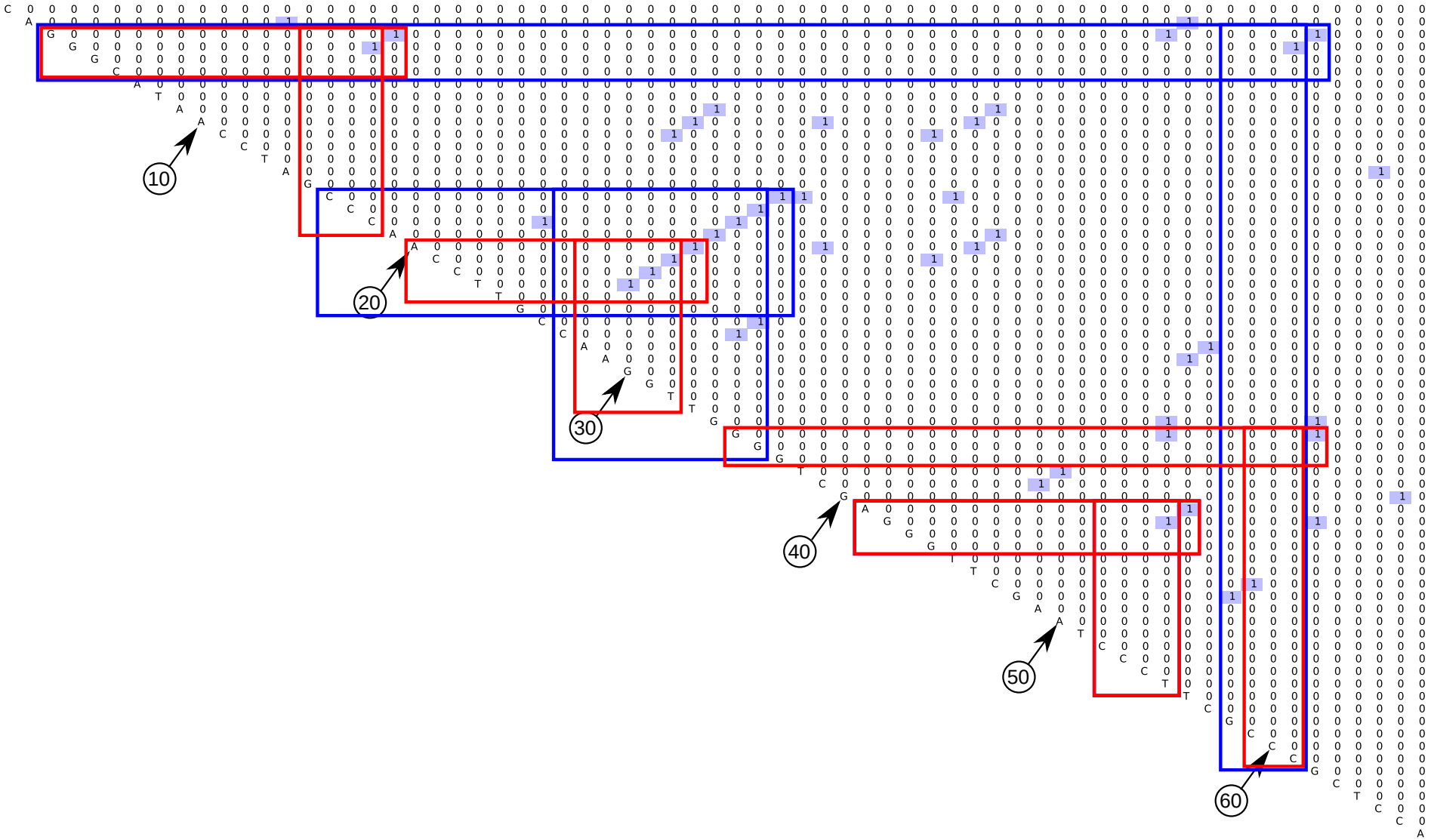

Solution Structure

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

$$\begin{pmatrix} 0 & 1 & 0 & 1 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

Parsing result is (0-1) matrix M which represents secondary structure features for sequence ω:
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Vectors

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$\Downarrow$

`[0,1,0,1,0,1,0,0,1,0]`

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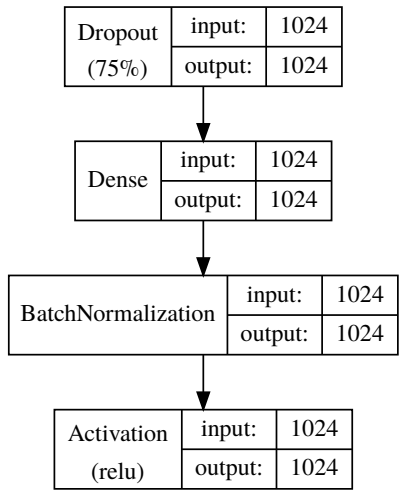
`[84,128]`

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.

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



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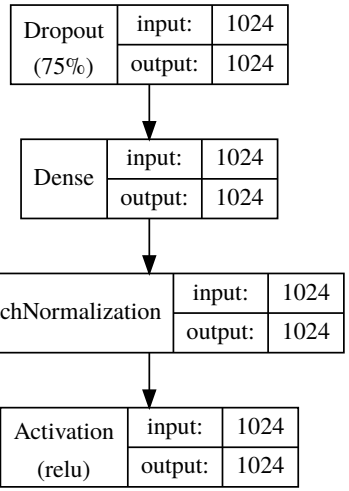

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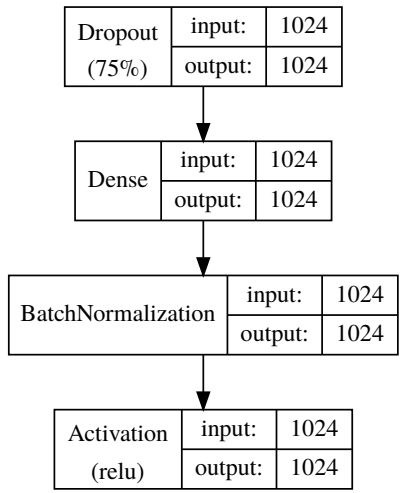

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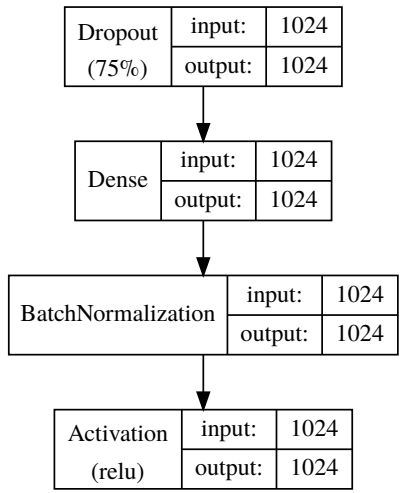

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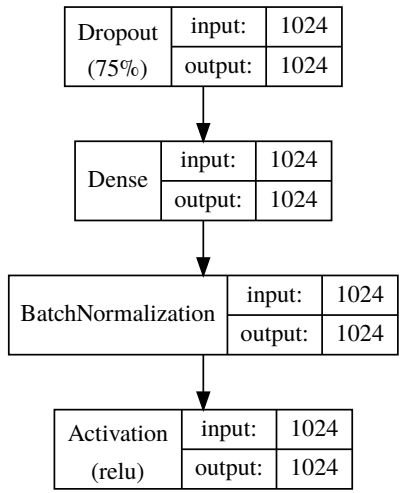

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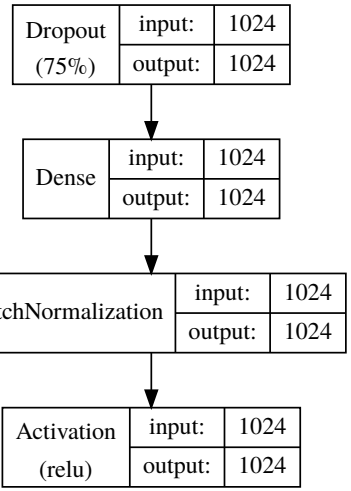

Vectors

$$\begin{pmatrix} 0 & 1 & 0 & 1 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

$\Downarrow$

`[0,1,0,1,0,1,0,0,1,0]`

$\Downarrow$

`[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.

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

$$\begin{pmatrix} 0 & 1 & 0 & 1 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

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

Vectors

$$\begin{pmatrix} 0 & 1 & 0 & 1 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

$\Downarrow$

`[0,1,0,1,0,1,0,0,1,0]`

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