Improving an Exact Solution to the (l,d) Planted Motif Problem

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Introduction

DNA motif finding

- motifs are repeated sub-sequences in DNA that have some biological significance
- DNA motif finding searches for motifs over a set of DNA sequences, allowing for mismatches due to mutation
- known as a difficult problem in computational biology and CS (proven NP-complete)

Introduction

The (l,d) planted motif problem

Find a motif of length l=8 across these 5 DNA sequences, each containing the motif with at most d=2 mismatches.

S_1 atcactcgttctcctctaatgtgtaaagacgtactaccgaccttа
S_2 acgccgaccggtccgatccttgtatagctcctaacgggcatcagc
S_3 tcctgactgcatcgcgatctcggtagtttcctgttcatcatttt
S_4 ggccctcagcatcgtgcgtcctgctaacacattcccatgcagctt
S_5 tgaaaagaatttacggtaaaggatccacatccaatcgtgtgaaag

Planted motif: ccatcgtt

Introduction

Solutions to the (l,d) planted motif problem)

There are two types of methods used by motif search algorithms:

- heuristic methods (ex. probabilistic sampling, projection) perform an iterative local search which is efficient, but not guaranteed to find all motifs
- exact methods (ex. combinatorial search, tree pruning) perform an exhaustive search which will find all possible motifs, at the cost of time/space efficiency

Introduction

l-mers, Hamming distances, and d-neighborhoods

- l-mer
- Hamming distance d_H
- d-neighbor

Introduction

l-mers, Hamming distances, and d-neighborhoods

- l-mer

  - sequence of length l

    $S_1 =$ atcactcgttctcctctaatgtgtaaagacgtactaccgaccttta

- Hamming distance d_H
- d-neighbor

Introduction

l-mers, Hamming distances, and d-neighborhoods

- l-mer
- Hamming distance d_H

  - number of mismatches between l-mers x_1 and x_2

$$x_1 = \texttt{cgatcctt} \qquad d_H(x_1, x_2) = 2$$
$$x_2 = \texttt{ccatcgtt}$$

- d-neighbor

Introduction

l-mers, Hamming distances, and d-neighborhoods

- l-mer
- Hamming distance d_H
- d-neighbor

  - two l-mers x and x' are d-neighbors if $d_H(x, x') \leq d$

  $N($ `ccatcgtt`, 2 $)$ $\rightarrow$ d-neighborhood of `ccatcgtt`, d=2

  $=\{$ `ccatcgtt`,

  `acatcgtt`,`gcatcgtt`,`tcatcgtt`,`caatcgtt`,`cgatcgtt`,`ctatcgtt`,

  ...all l-mers with 1 mismatch

  `aaatcgtt`,`agatcgtt`,`atatcgtt`,`gaatcgtt`,`ggatcgtt`,`gtatcgtt`,

  `taatcgtt`,`tgatcgtt`,`ttatcgtt`,`acctcgtt`,`acgtcgtt`,`acttcgtt`,

  ...all l-mers with 2 mismatches

  $\}$

Introduction

l-mers, Hamming distances, and d-neighborhoods

- l-mer
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EMS-GT

Nabos, 2015

- an exact motif search (EMS) algorithm based on the candidate generate-and-test (GT) principle
- solves any (l,d) planted motif problem instance, $l \leq 17$
- operates on a bit-based representation of the search space

EMS-GT

Generate-and-test approach

EMS-GT proceeds in two steps:

1. Generate the set C of candidate motifs: find the common d-neighbors of the first n' sequences $S_1, S_2, ..., S_{n'}$.

$$C = \mathcal{N}(S_1, d) \cap \mathcal{N}(S_2, d) \cap ... \cap \mathcal{N}(S_{n'}, d), \qquad n' \leq n$$

2. Test every candidate $c \in C$: if a d-neighbor of c appears in each of the remaining sequences $S_{n'+1}, S_{n'+2}, ...S_n$, accept c as a motif.

EMS-GT

Generate-and-test approach

$(l,d) = (8,2)$

S_1 atcactcgttctcctctaatgtgtaaagacgtactaccgaccttа

S_2 acgccgaccggtccgatccttgtatagctcctaacgggcatcagc

S_3 tcctgactgcatcgcgatctcggtagtttcctgttcatcattttt

S_4 ggccctcagcatcgtgcgtcctgctaacacattcccatgcagctt

S_5 tgaaaagaatttacggtaaaggatccacatccaatcgtgtgaaag

EMS-GT

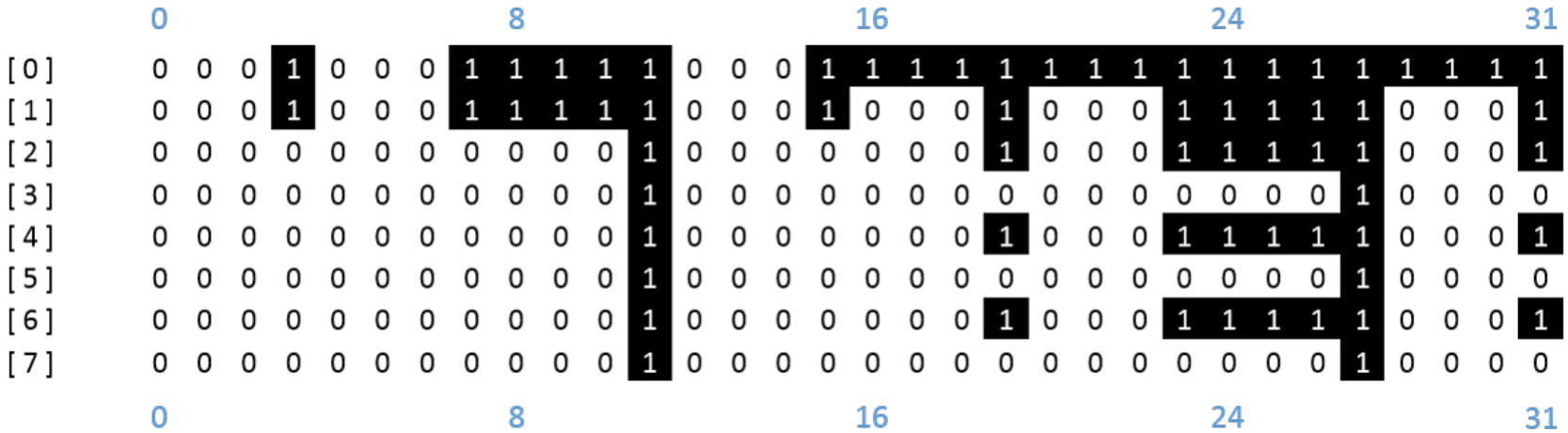
Bit-based representation of the search space

- The search space contains all 4^l possible l-mers that can be formed with $\Sigma = \{\mathtt{a}, \mathtt{c}, \mathtt{g}, \mathtt{t}\}$.
- To represent sets in this space, EMS-GT assigns each of the 4^l l-mers a bit flag, which is 1 if the l-mer is a member of the set, 0 otherwise.
- For efficiency, EMS-GT stores the 4^l bits as $\frac{4^l}{32}$ 32-bit integers.

EMS-GT

Bit-based representation of the search space

- $N($ acgt, 1 $)$: $4^l = 256$, $\frac{4^l}{32} = 8$



EMS-GT

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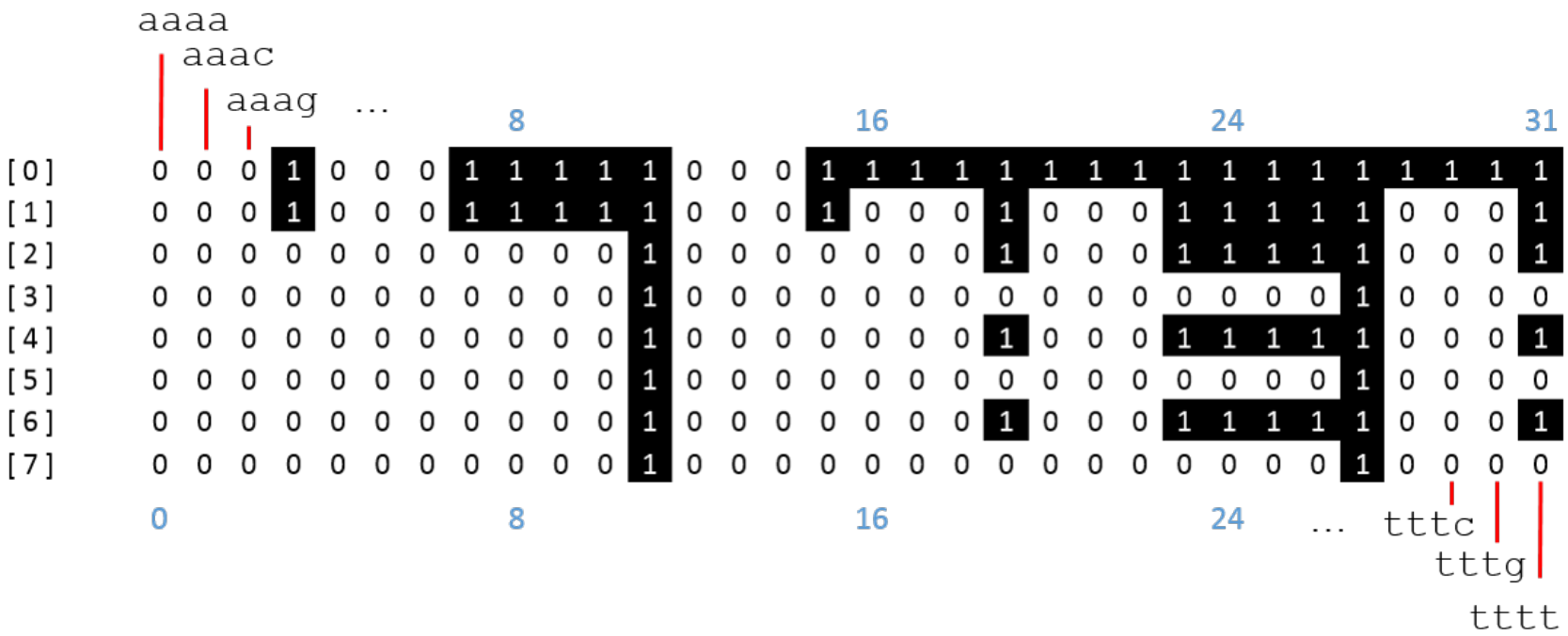

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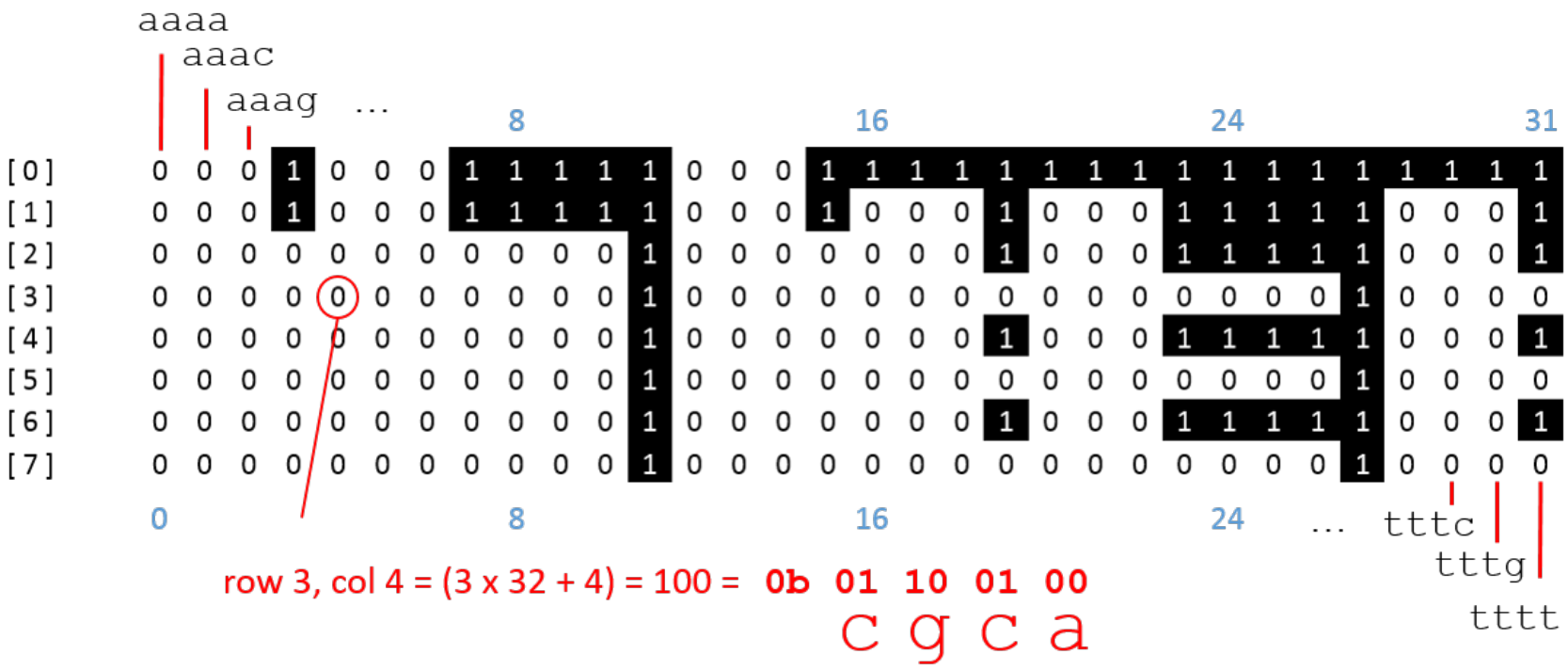

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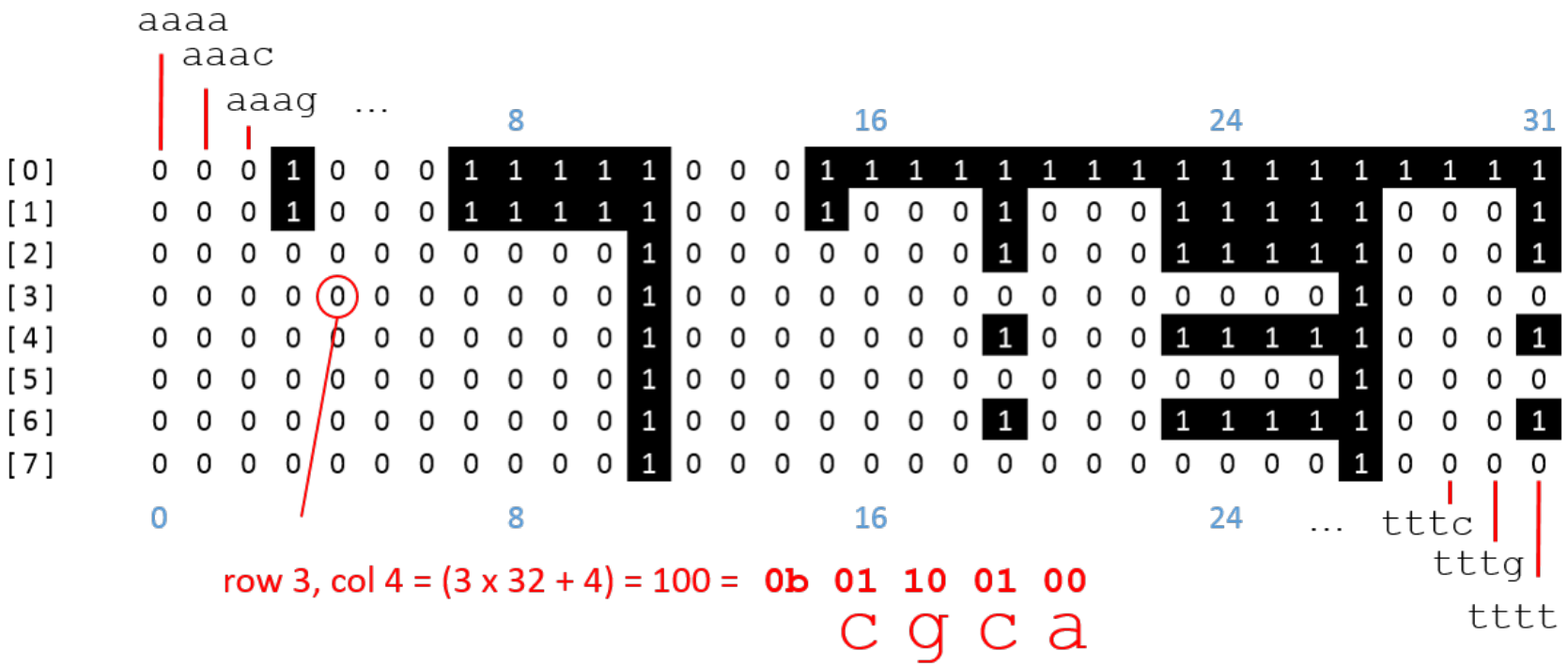
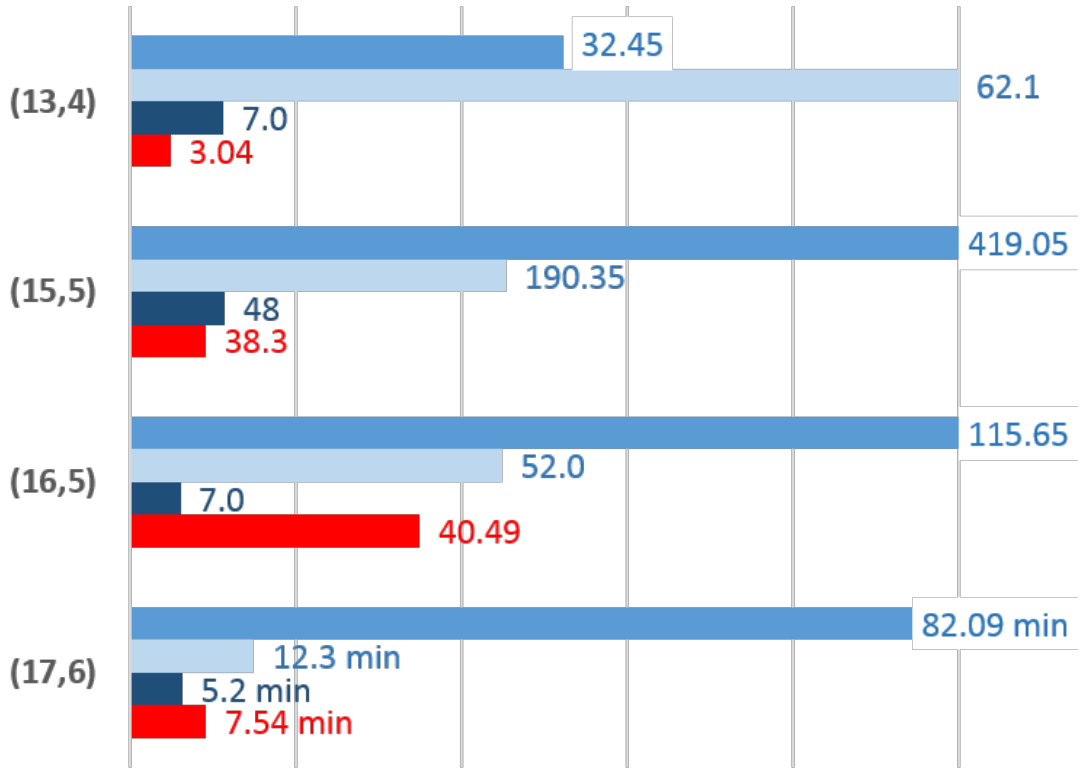


- EMS-GT generates a neighborhood bit-array by generating each individual neighbor, then finding and setting its bit flag.

EMS-GT

Performance comparison

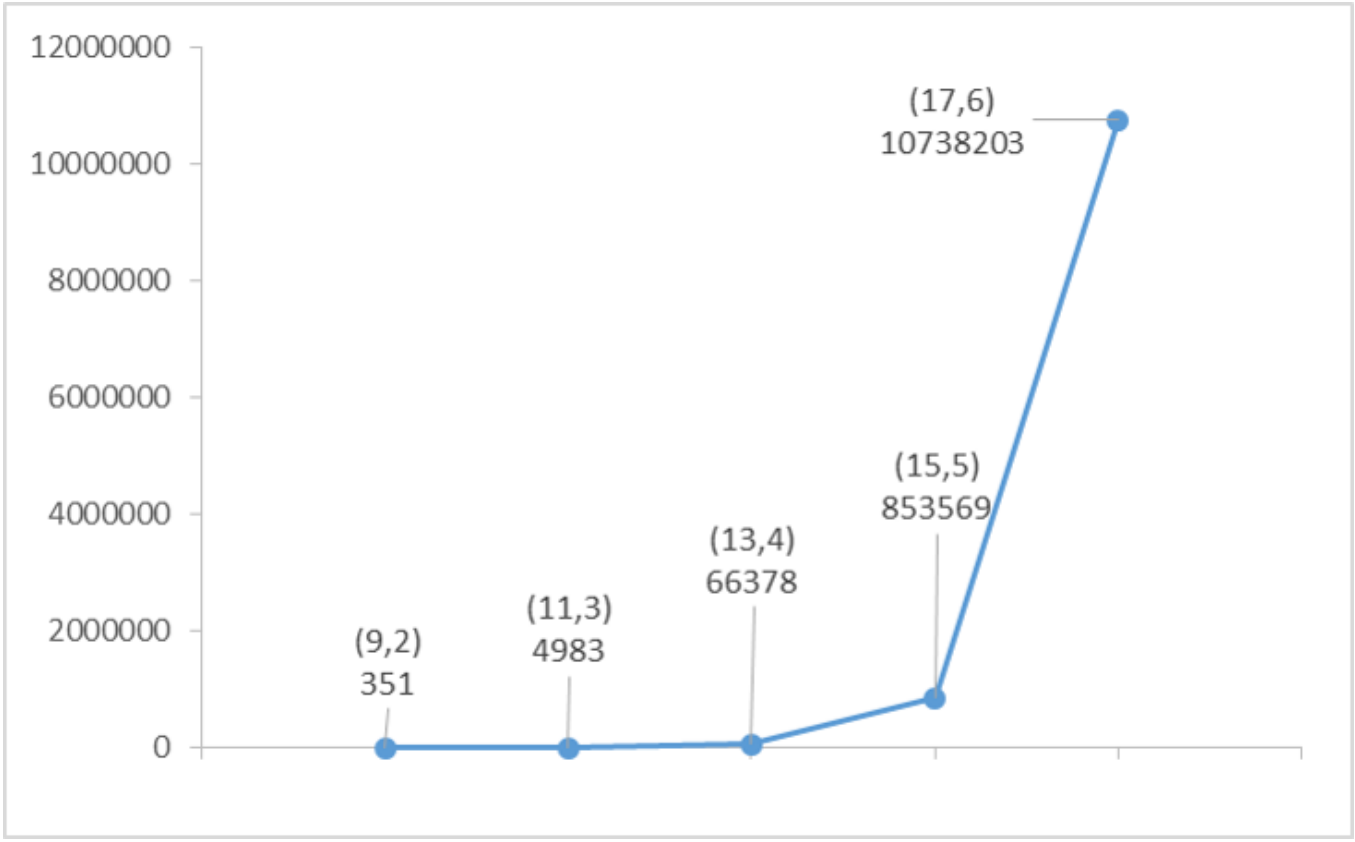
- EMS-GT is competitive against exact motif search algorithms PMSprune, qPMS7 and PMS8; however, for larger (l,d) values, it no longer outperforms the state-of-the-art.



Runtime in seconds, averaged over 20 synthetic datasets per (l,d)

EMS-GT

Neighborhood sizes for challenging (l,d)



- l-mer neighborhoods grow very quickly with (l,d), meaning that EMS-GT must spend more time locating and setting bits.

Research objectives

Improving EMS-GT

The main objectives of this research are:

1. To develop a speedup technique for EMS-GT that takes advantage of distance-related patterns in the search space;
2. To evaluate the speedup technique with regard to improvement in runtime; and
3. To evaluate the improved version of the EMS-GT algorithm against state-of-the-art motif search algorithms.

Speedup technique

Key observation

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- the 4^k l-mers represented in a block all begin with the same prefix (first $l - k$ characters), and will differ only in the k-suffix (last k characters);

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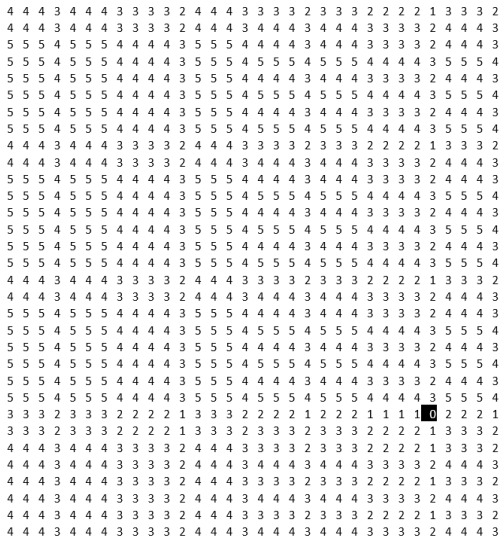
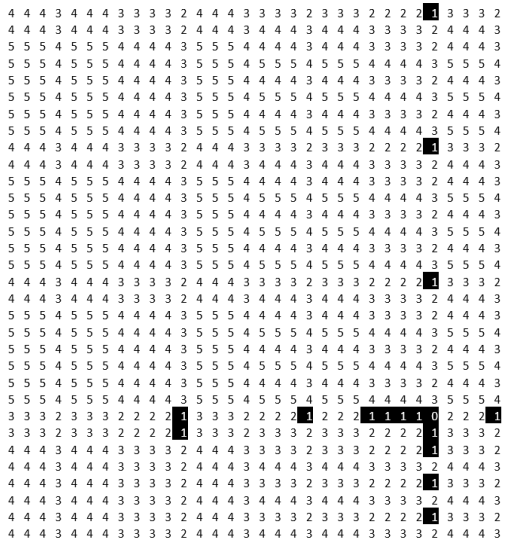
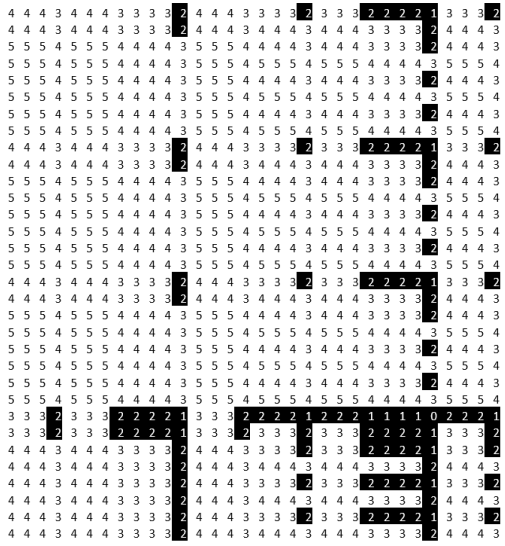
- and each block conforms to one of $(k + 2)$ patterns.

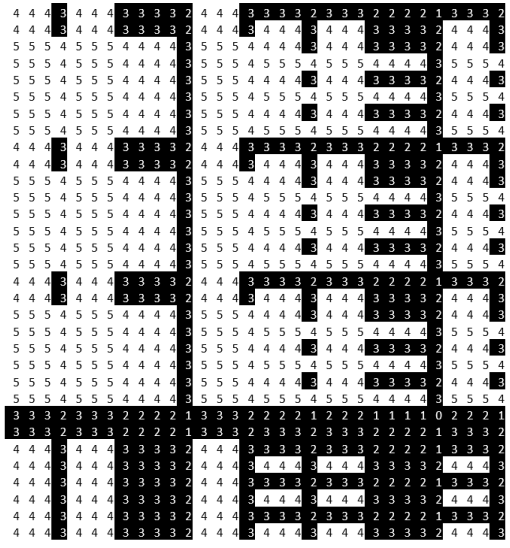
Speedup technique

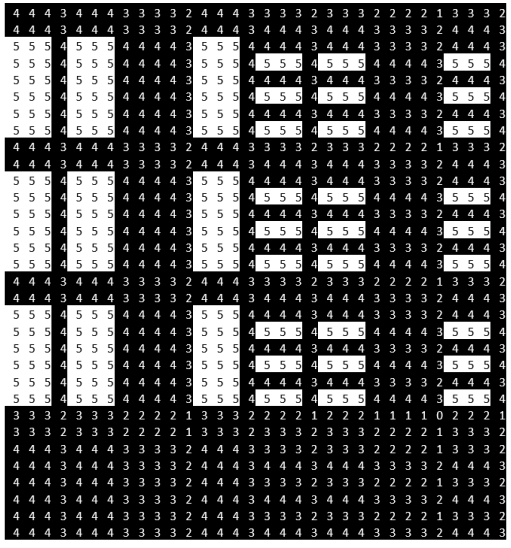
Block patterns in the d-neighborhood of acgtacgtacgt, d=5, k=5

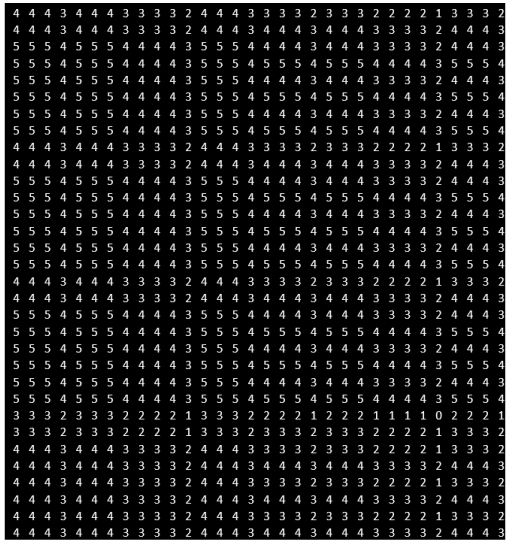












Speedup technique

Key observation

- In a d-neighbor of x, the d allowable mismatches from x are distributed between the prefix and the k-suffix.

$$x = \texttt{acgtacg tacgt}$$
$$x' = \texttt{acgaaaa tccga}$$

- If a block's prefix already has p mismatches from x's prefix, then for an l-mer in the block to be a neighbor of x, it must have a suffix with at most $d - p$ mismatches from x's suffix.

Speedup technique

Key observation

- The $(k+2)$ block patterns thus correspond to $k+2$ cases for the p mismatches between x's prefix and a block's prefix:

prefix mismatches	**suffix mismatches**
more than d	–
d	0
d - 1	0 or 1
d - 2	0, 1, or 2
...	...
d - (k-1)	0, 1, 2, ..., or (k-1)
d - k or less	0, 1, 2, ..., (k-1), or k

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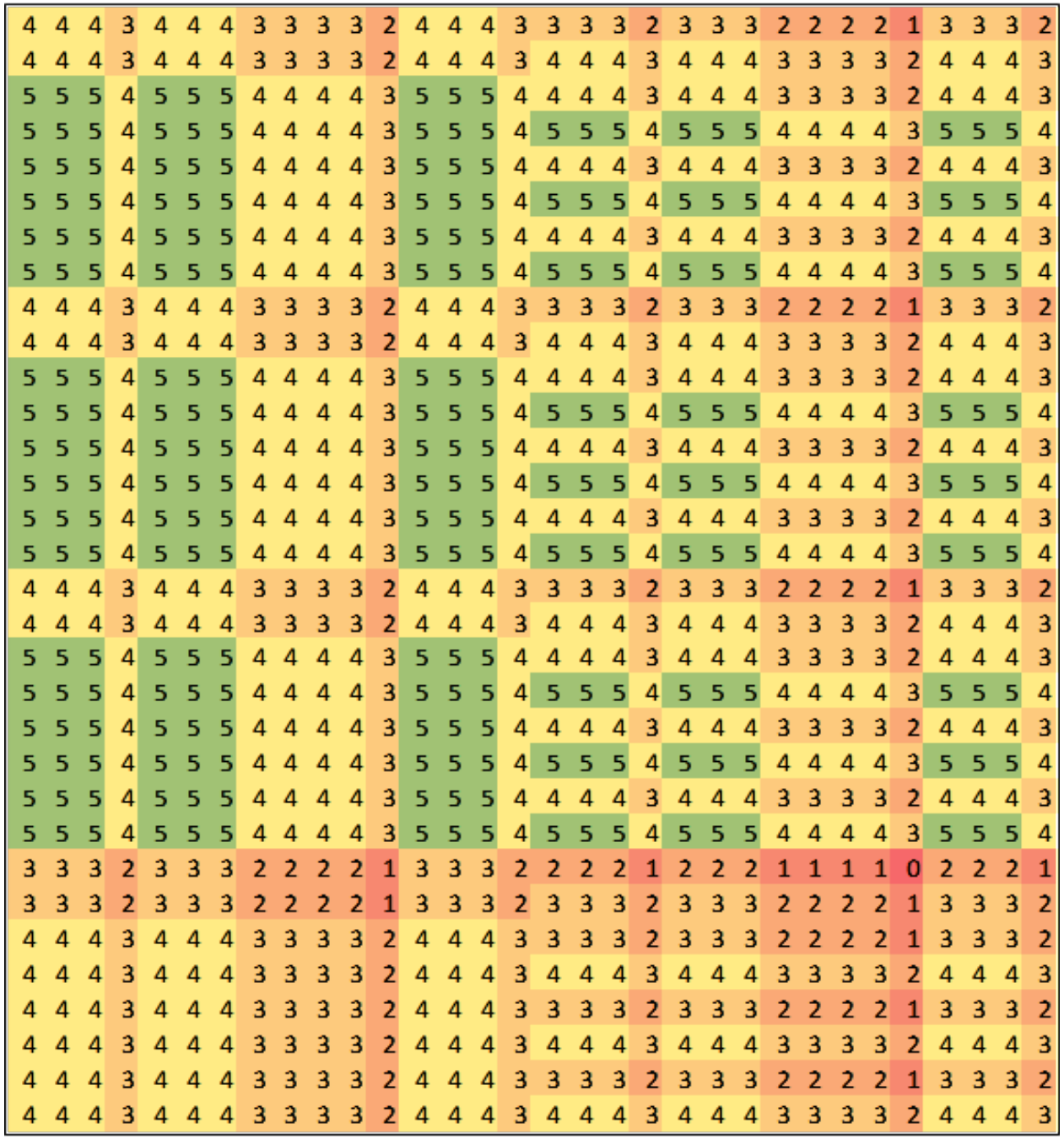
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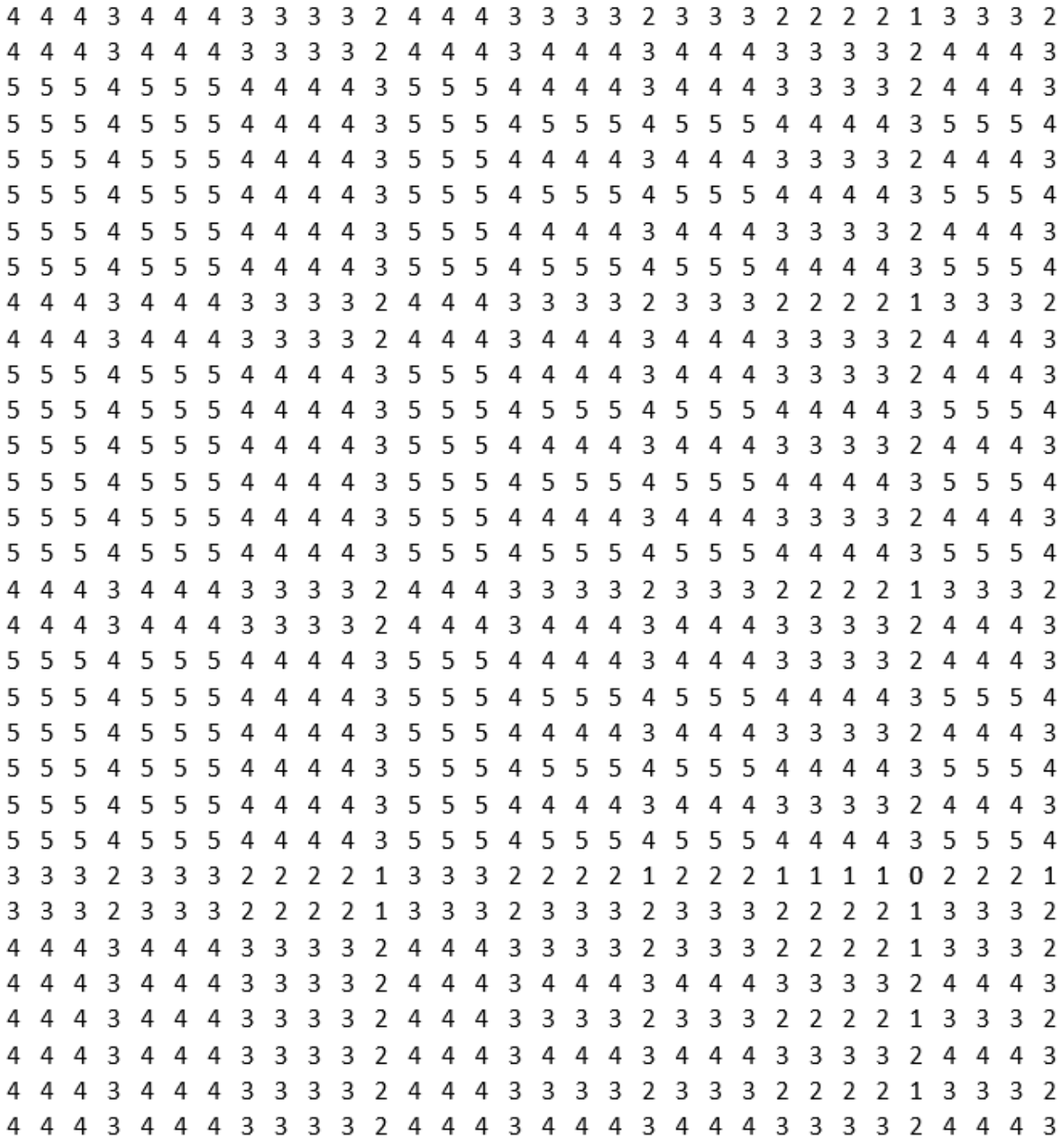
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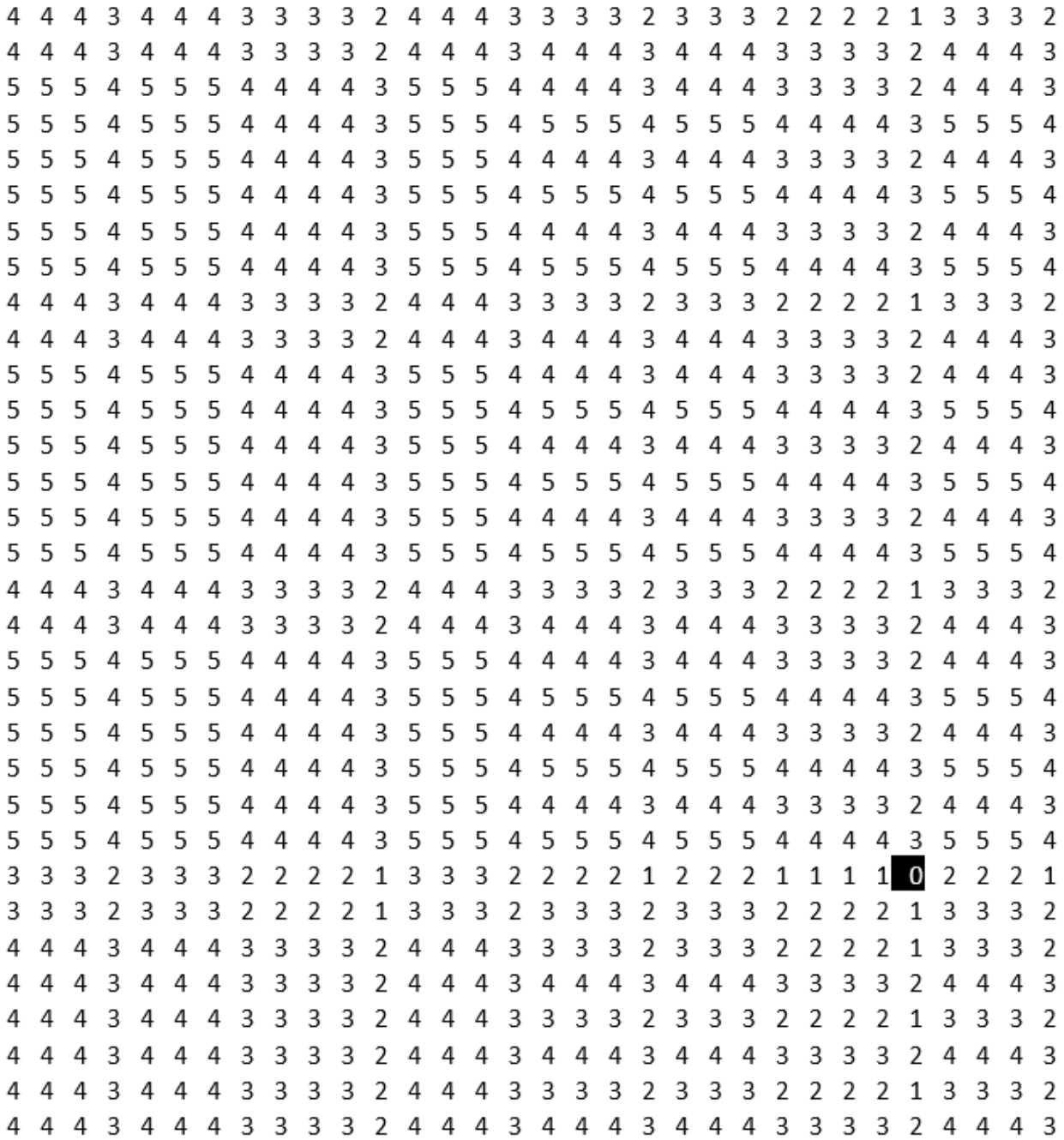
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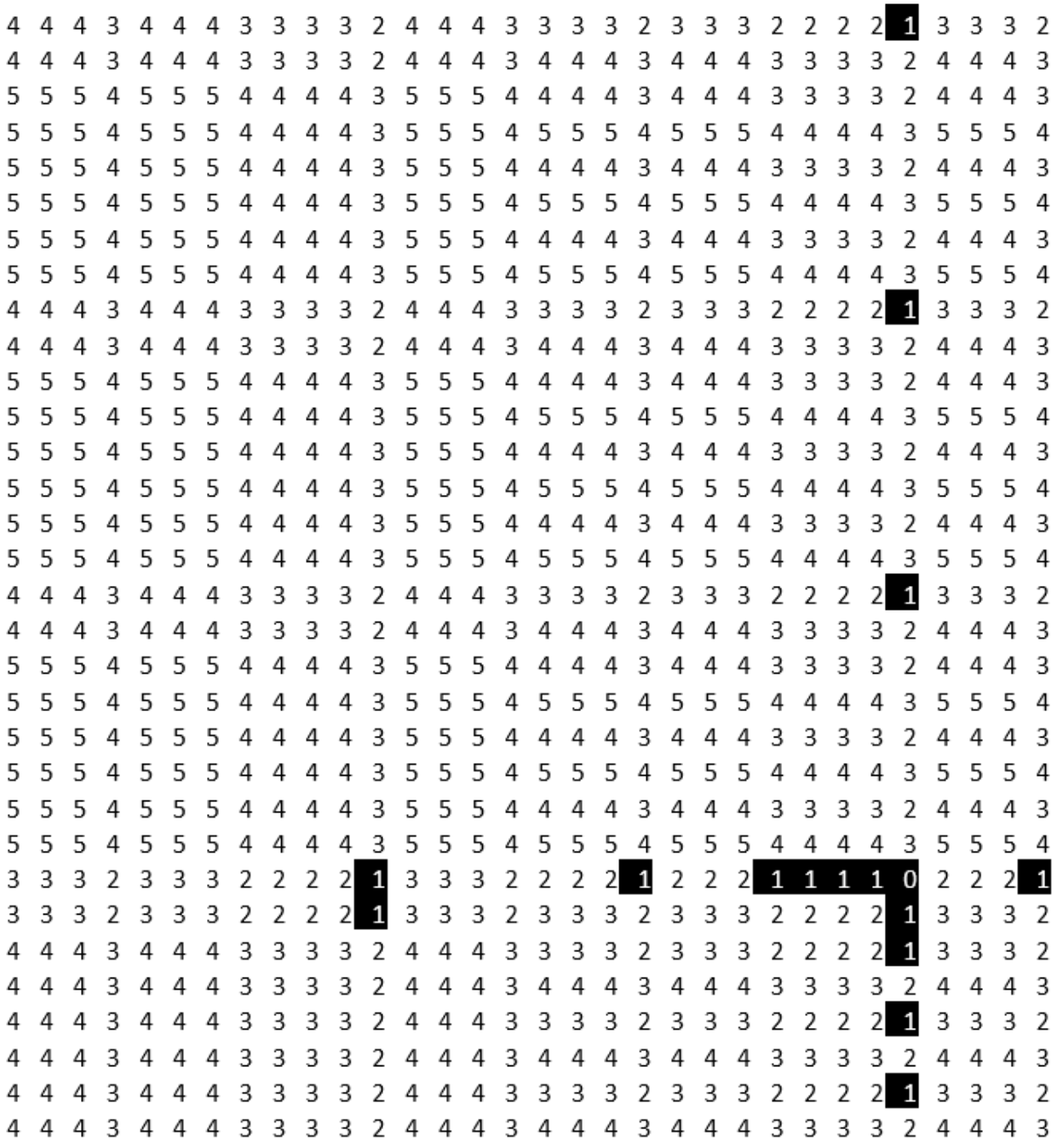

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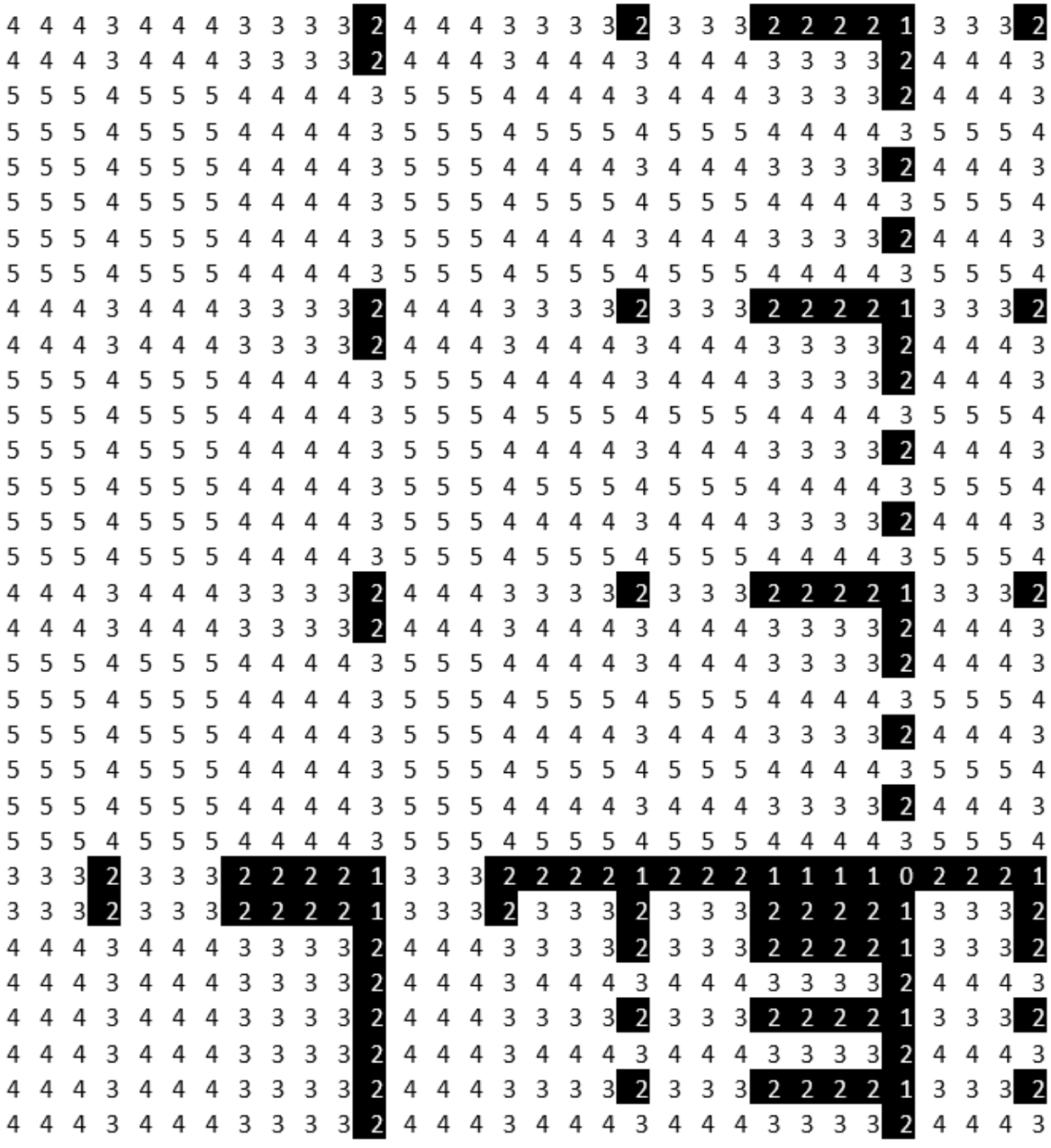

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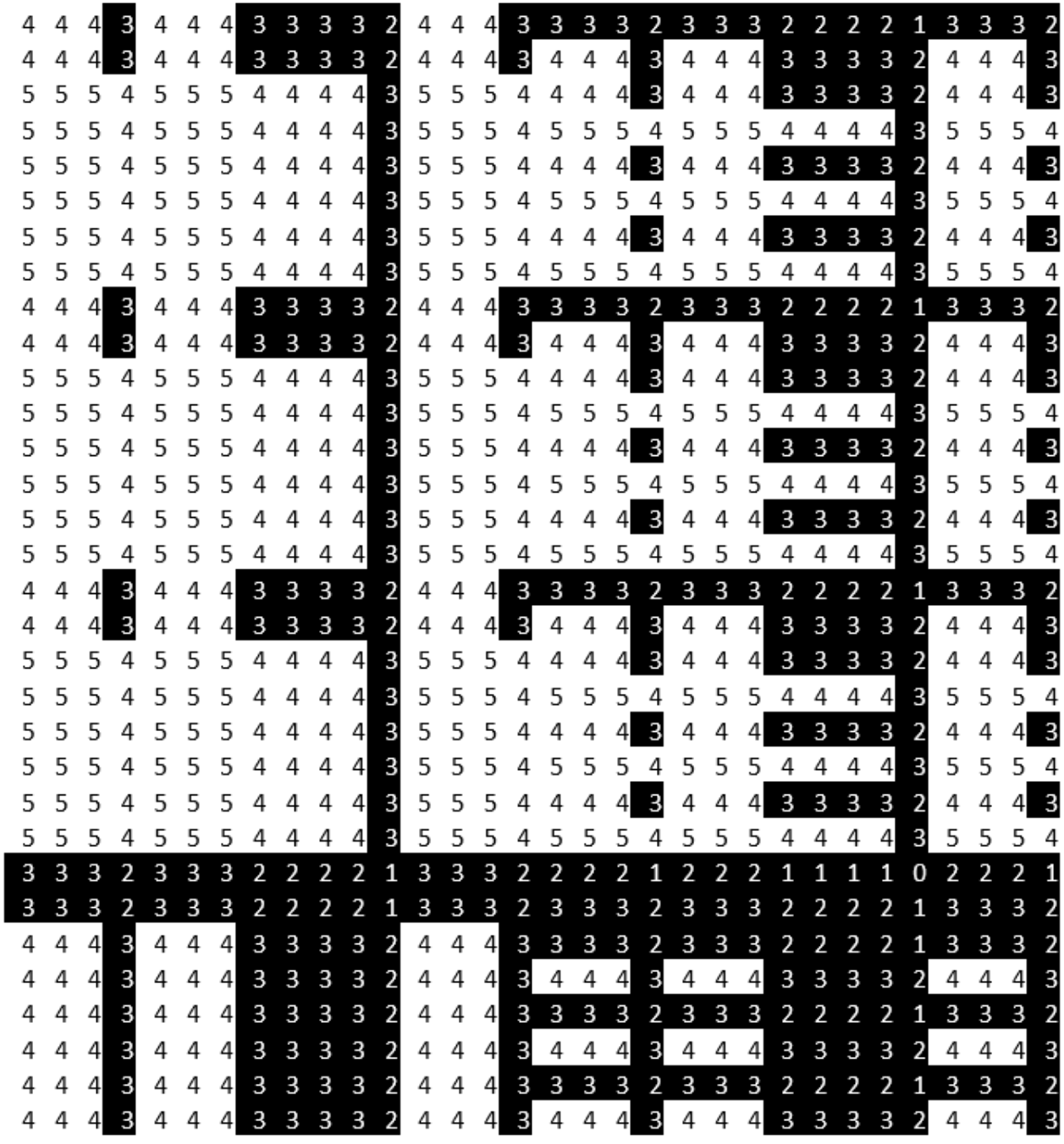

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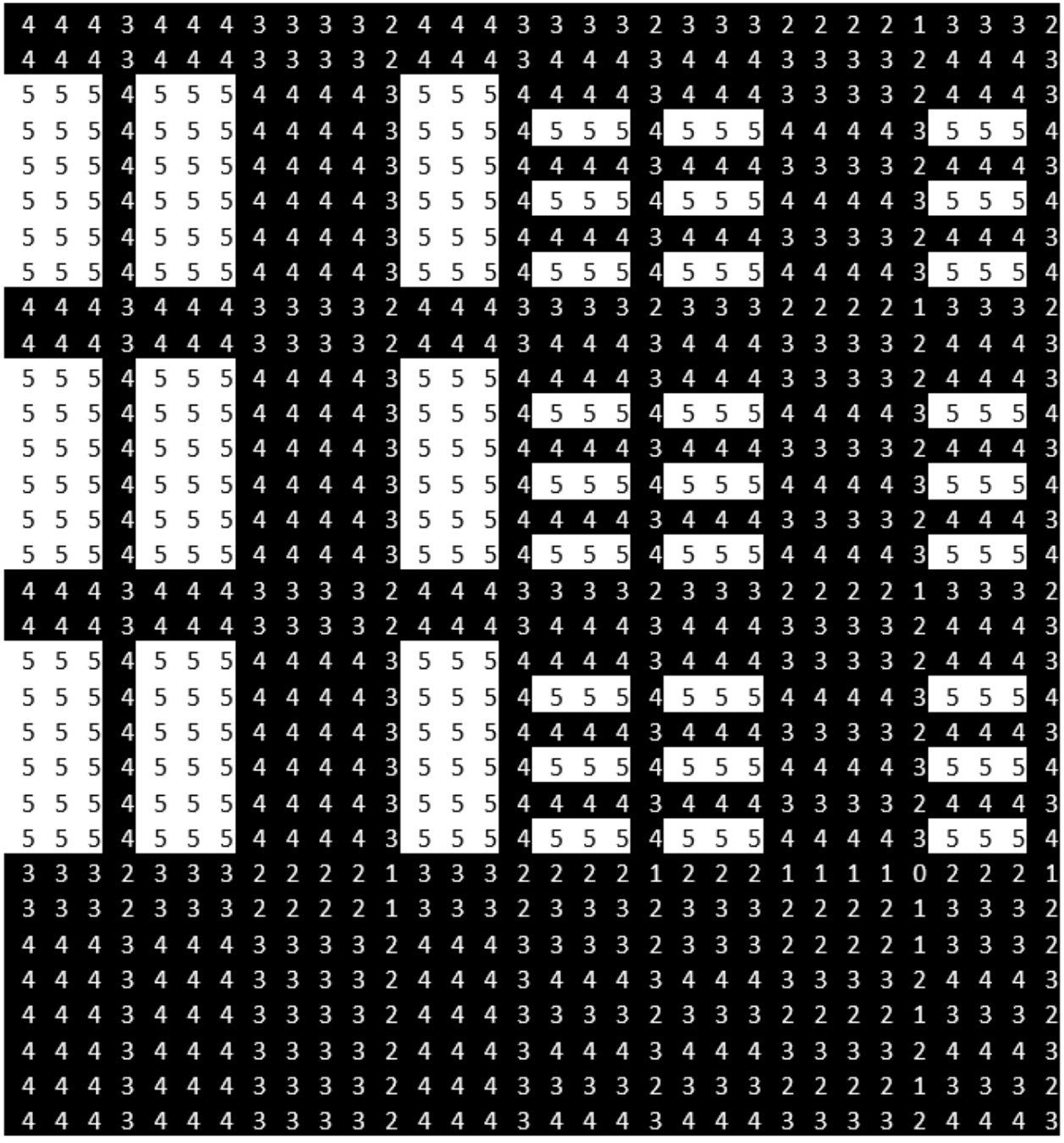

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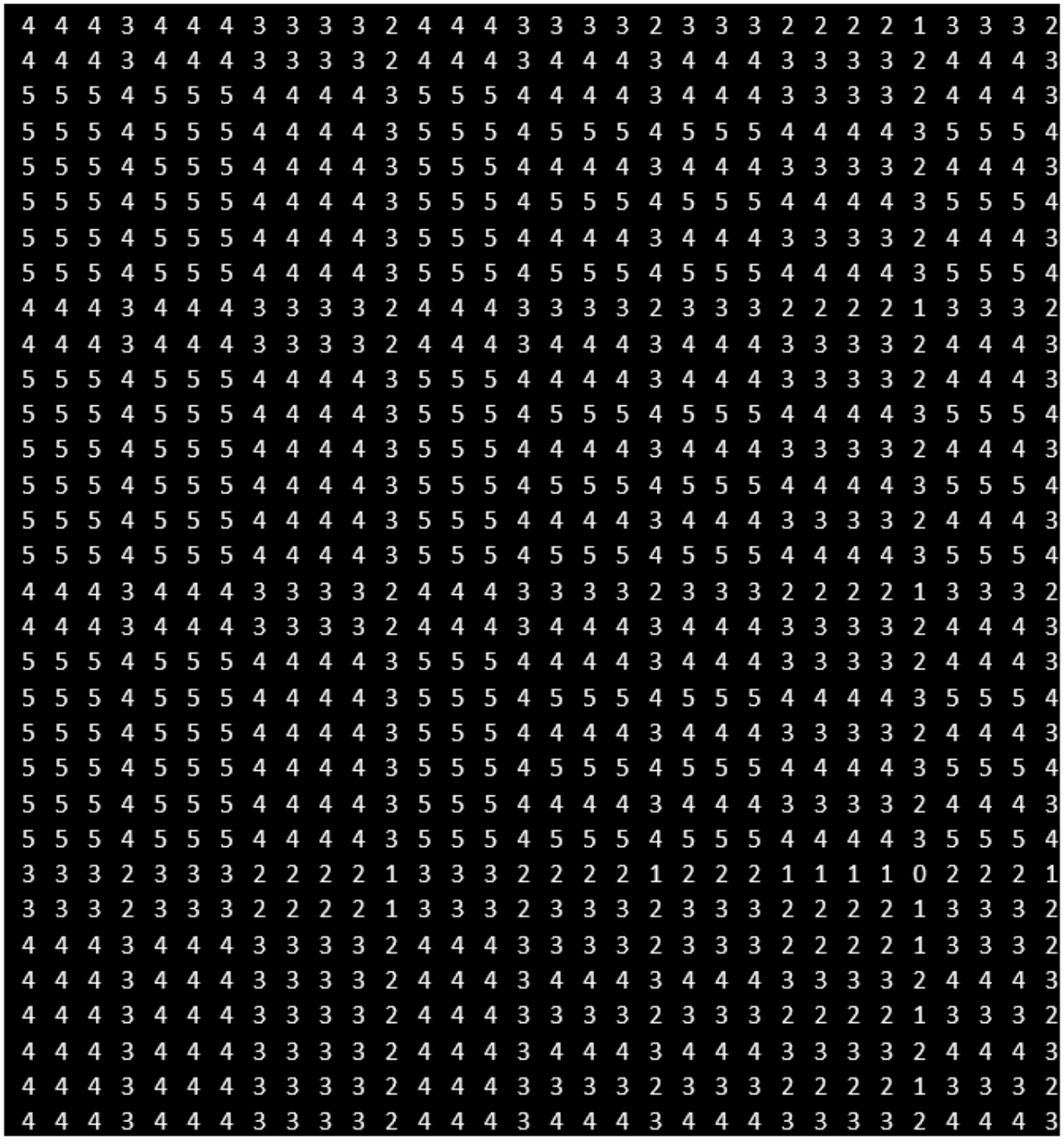
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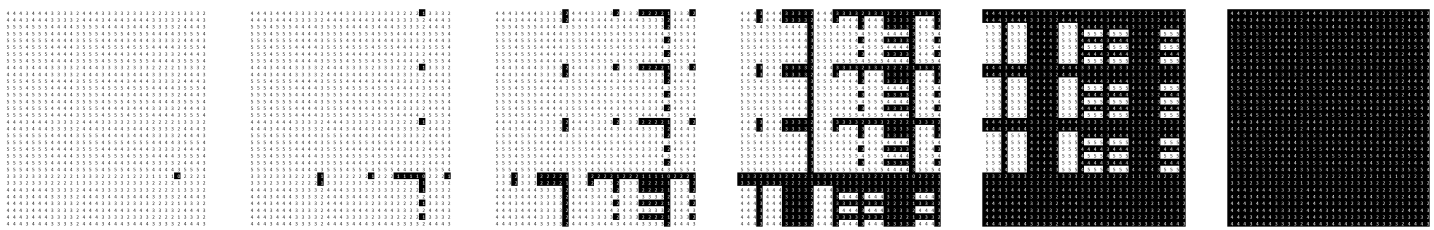
Speedup technique

Generate and apply patterns

To generate N_x for $x = yz$, we perform two steps:

1. From x's suffix z, generate P, the set of block patterns.



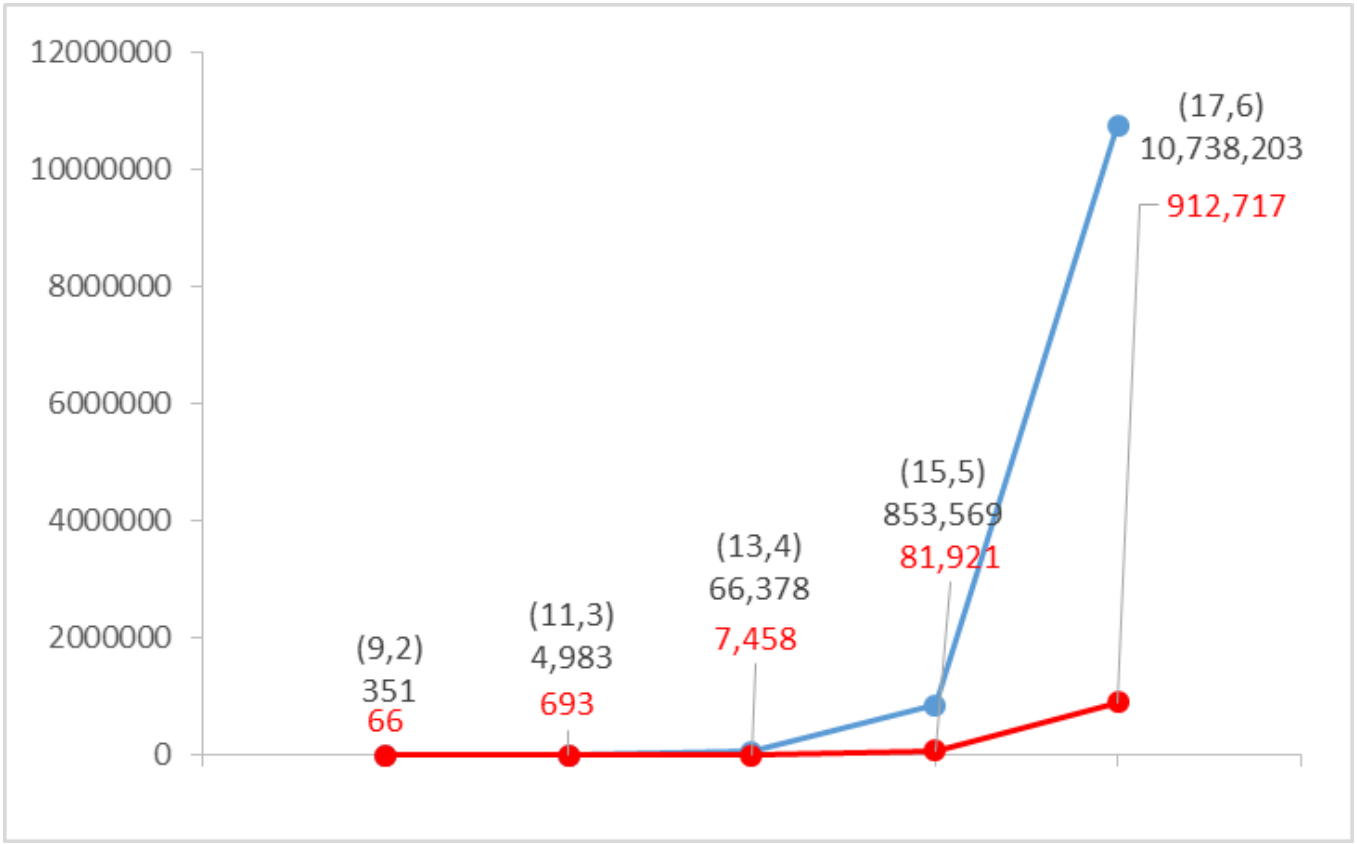
P_0 P_1 P_2 P_3 P_4 P_5

2. From x's prefix y, recursively generate each d-neighbor y', and apply $P_{(d-d_H(y,y'))}$ to the block whose prefix is y'.

	acgtaca	P_4	acgtaga	P_3
acgtacg	atttaca	P_2	atttaga	P_1
	attcaga	P_0		

Results

Reduction in recursive neighbor generation



- We still generate individual d-neighbors, but for x's prefix y; if we set k=5, y's neighborhood is only 10-20% the size of x's.

Results

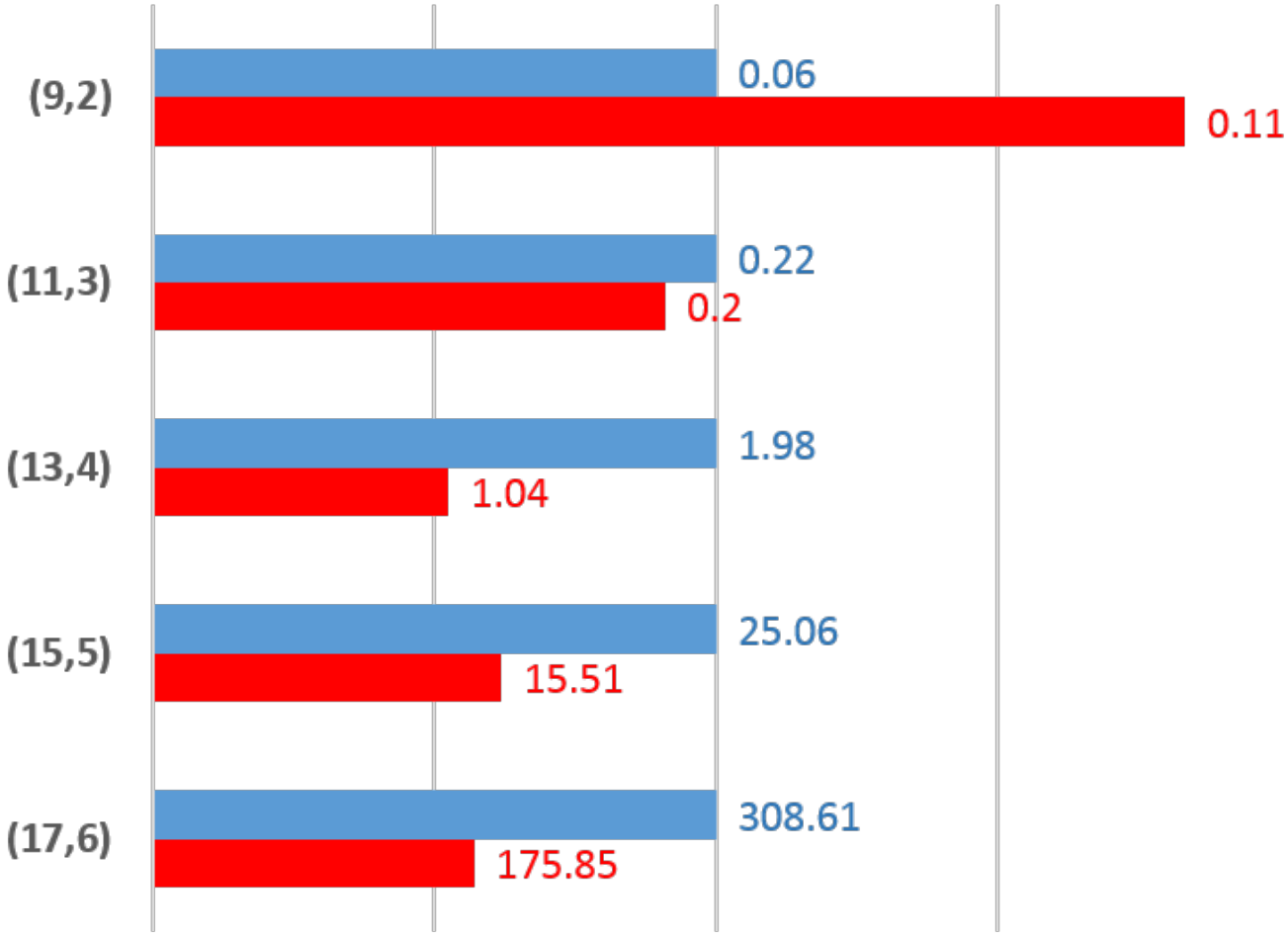
Runtime comparison of PMS8, qPMS9, and EMS-GT

(l, d)	**PMS8**	**qPMS9**	**EMS-GT**	**EMS-GT with speedup**
9,2	0.74 s	0.47 s	**0.06** s	0.11 s
11,3	1.58 s	1.06 s	0.22 s	**0.20 s**
13,4	5.39 s	4.52 s	1.98 s	**1.04 s**
15,5	36.45 s	24.63 s	25.06 s	**15.51 s**
17,6	3.91 min	**1.96 min**	5.14 min	*2.93 min*

Average runtime over 20 synthetic datasets per (l,d)
on Intel Xeon 2.10 GHz processor (single core execution).

Results

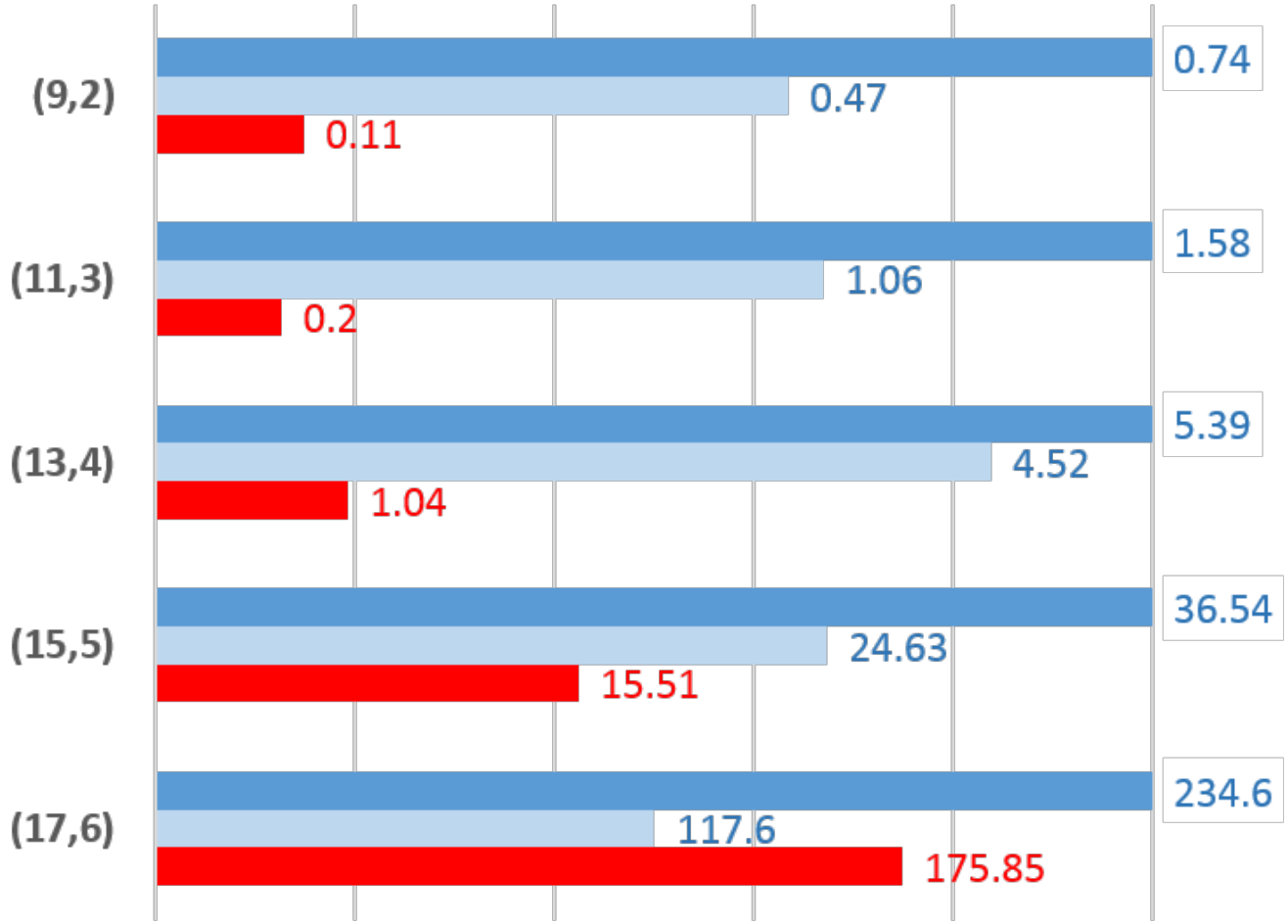
EMS-GT without vs. **with** the speedup technique



Runtime in seconds, averaged over 20 synthetic datasets per (l,d)

Results

PMS8 vs. **qPMS9** vs. **EMS-GT with speedup technique**



Runtime in seconds, averaged over 20 synthetic datasets per (l,d)

Conclusions

- We introduced a novel speedup technique for the EMS-GT algorithm, which takes advantage of suffix-related patterns in EMS-GT's bit-based representation of the motif search space.

Conclusions

- Our speedup technique reduces EMS-GT's runtime for most instances; however, for some (l,d) values our technique increases runtime due to overhead.

$(l,\ d)$	**(9,2)**	**(11,3)**	**(13,4)**	**(15,5)**	**(17,6)**
Runtime reduction	–	6.7%	47.5%	38.1%	43.0%

Conclusions

- EMS-GT with the speedup technique is highly competitive with the state-of-the-art: for all tested (l,d), it is faster than PMS8, and faster than qPMS9 except for (17,6).

(l, d)	**(9,2)**	**(11,3)**	**(13,4)**	**(15,5)**	**(17,6)**
RR from qPMS9	76.6%	81.1%	77.0%	37.0%	–
RR from PMS8	85.1%	87.3%	80.7%	57.6%	25.0%