

# **Optimizing An Exact Solution to the $(l, d)$ -Planted Motif Problem**

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**Maria Clara Isabel D. Sia**

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## Abstract

DNA motif finding is widely recognized as a difficult problem in computational biology and computer science. Because of the usual large search space involved, exact solutions typically require a significant amount of execution time before discovering a motif of length  $l$  that occurs in an input set  $\{S_1, \dots, S_n\}$  of sequences, allowing for at most  $d$  substitutions.

This study implements a novel optimization to EMS-GT, a motif search algorithm which operates on a compact bit-based representation of the search space. The optimization takes advantage of distance-related patterns in the search space, in order to speed up the bulk bit-setting operations performed by the algorithm. A Java implementation is shown to be highly competitive against PMS8 and qPMS9, two current state-of-the-art exact algorithms. EMS-GT works extremely well for problems involving short motifs, outperforming both competitors for challenge instances with  $(l, d)$  values (9,2), (11,3), (13,4) and (15,5), showing runtime reductions of 76%, 81%, 77% and 37% respectively for these instances, while ranking second to qPMS9 for challenge instance (17,6).

## TABLE OF CONTENTS

i

LIST OF FIGURES . . . . .	iii
---------------------------	-----

LIST OF TABLES . . . . .	iv
--------------------------	----

### CHAPTER

I	Introduction . . . . .	1
1.1	Context of the Study . . . . .	2
1.2	Objectives of the Study . . . . .	4
1.3	Research Questions . . . . .	4
1.4	Significance of the Study . . . . .	5
1.5	Scope and Limitations of the Study . . . . .	5
II	Review of Related Literature . . . . .	6
2.1	Heuristic Algorithms . . . . .	6
2.2	Exact Algorithms . . . . .	7
2.3	EMS-GT . . . . .	9
2.3.1	Bit-based set representation and $l$ -mer enumeration .	11
2.3.2	Bit-array compression . . . . .	11
2.3.3	XOR-based Hamming distance computation . . . . .	12
2.3.4	Recursive neighborhood generation . . . . .	12
III	Methodology . . . . .	14
3.1	Datasets . . . . .	14
3.2	Implementation . . . . .	14
3.3	Evaluation . . . . .	15
IV	Results and Analysis . . . . .	16
4.1	Pattern-based optimization for EMS-GT . . . . .	16
4.2	Performance of optimized EMS-GT . . . . .	18
V	Conclusions . . . . .	19

BIBLIOGRAPHY . . . . .	20
------------------------	----

## LIST OF FIGURES

iii

1.1	Sample instance of the planted motif problem. . . . .	1
-----	-------------------------------------------------------	---

## LIST OF TABLES

iv

4.1	Runtimes of PMS8, qPMS9 and EMS-GT . . . . .	18
-----	----------------------------------------------	----

## CHAPTER I

### Introduction

DNA motif finding is widely recognized as a difficult problem in computational biology and computer science. Motifs are sequences that occur repeatedly in DNA and have some biological significance [3]; a motif might be a transcription factor binding site, a promoter element, a splicing site, or a marker useful for classification. There are many variants of motif finding problem in the literature. Some look for a motif that repeatedly occurs in a single sequence. Others look for a motif that occurs over some or all of a set of DNA sequences [4]. One of the latter type is the planted motif problem.

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

```
atcactcggtctcctctaattgtgtaaagacgtactaccgacctta  
acgccgaccggtcgataccttgtatagctcctaacgggcatcagc  
tcctgactgcatcgcgatctcggtagtttcctgtcatcatttt  
ggccctcagcatcgtgcgtcctgctaacacattcccatgcagctt  
tgaaaagaatttacggtaaaggatccacatccaatcgtgtgaaag
```

*Motif: ccatcggt*

Figure 1.1. Sample instance of the planted motif problem.

The planted motif problem simply asks: “*Given a set of DNA sequences, can we find an unknown motif of length  $l$  that appears at different positions in each of the sequences [13]?*” Initially it seems an exhaustive string search will suffice for this problem. However, due to biological mutation, motif occurrences in DNA are allowed to differ from the original motif by up to  $d$  characters. This greatly impacts complexity: two distinct variants of a motif—both counting as valid occurrences of the motif—might differ in as many as  $2d$  characters! Brute-force solutions quickly become infeasible as values of  $l$  and  $d$  increase. All of this shows why  $(l, d)$ -motifs are sometimes called “subtle” signals in DNA [13], and why finding them is difficult and computationally expensive. In fact, the motif finding problem has already been shown to be NP-complete [11].

This study is concerned with the EMS-GT (*Exact Motif Search - Generate and Test*) algorithm [10], which solves the planted motif problem for any arbitrary instance up to  $l=17$ . This study investigates Hamming distance-based patterns found to appear in EMS-GT’s bit-based representation of the motif search space, and exploits these patterns in a novel optimization for EMS-GT.

## 1.1 Context of the Study

This section formally defines the planted motif problem. It also defines key terms used throughout this paper in discussing exact motif-search algorithms.



**DEFINITION 1.  $l$ -mer, Hamming distance,  $d$ -neighborhood**

An  **$l$ -mer** is a sequence of length  $l$ . Given a sequence  $S$  of length  $L > l$ , the  $i^{th}$   $l$ -mer in  $S$  starts at the  $i^{th}$  position. The **Hamming distance**  $dH$  between two  $l$ -mers of equal length is the number of characters that differ between them.

“Distance” refers to Hamming distance in this paper, unless otherwise stated.

Ex. If  $l = 5$ , the second  $l$ -mer in `gattaca` is `attac`.

$$dH(\text{gattaca}, \text{cgttaga}) = 3.$$

The  **$d$ -neighborhood of an  $l$ -mer  $x$**  is the set  $N(x, d)$  of all  $d$ -neighbors of  $x$ : all  $l$ -mers  $x'$  whose Hamming distance from  $x$  is at most  $d$ , i.e.,  $dH(x, x') \leq d$ .

Meanwhile, the  **$d$ -neighborhood of a sequence  $S$**  of length  $L > l$  is the set  $\mathcal{N}(S, d)$  of all  $d$ -neighbors of all the  $l$ -mers in  $S$ .

Ex. `gatct`, `cctta`, and `aatta` are all in  $N(\text{gatta}, 2)$ .

$$\text{For } l = 5, \mathcal{N}(\text{gattaca}, 2) = N(\text{gatta}, 2) \cup N(\text{attac}, 2) \cup N(\text{ttaca}, 2).$$

**DEFINITION 2.  $(l, d)$  Planted Motif Problem**

We formally define the  $(l, d)$  planted motif problem as follows:

Given a set  $\mathcal{S} = \{S_1, \dots, S_t\}$  of  $n$  DNA sequences of length  $L$ ,

find  $M$ , the set of sequences (or motifs) of length  $l < L$

which have at least one  $d$ -neighbor in each sequence in  $\mathcal{S}$ .

## **1.2 Objectives of the Study**

The main objective of this study is to improve the performance of the EMS-GT algorithm. Specifically, it aims:

1. To develop an optimization for EMS-GT that takes advantage of distance-related patterns in the motif search space.
2. To evaluate the resulting optimization with regard to improvement in runtime and solvable problem instances.
3. To evaluate the optimized version of EMS-GT against state-of-the-art motif search algorithms.

## **1.3 Research Questions**

This study aims to answer the question: How can the performance of the EMS-GT algorithm be improved? Specifically, it aims to answer the following:

1. How can distance-related patterns observed within the motif search space be exploited in an optimization for EMS-GT?
2. What performance improvement does a pattern-based optimization produce, with regard to runtime and solvable problem instances?

3. How does the optimized version of EMS-GT compare with state-of-the-art motif search algorithms?

## **1.4 Significance of the Study**

Motif finding is a key problem in

Optimizing an exact motif search algorithm, especially one which is competitive with the known state-of-the-art, improves a viable option for real-world motif finding applications. The properties of distance-related patterns within an organized search space, as investigated in this paper, may also prove useful in solving other types of search problems and Hamming distance-related problems.

## **1.5 Scope and Limitations of the Study**

## CHAPTER II

### Review of Related Literature

Motif finding is a well-studied problem in computing. Various motif search algorithms have been developed, falling into two categories: *heuristic* and *exact*. This section gives an overview of algorithms of both types, and provides an in-depth description of the exact algorithm EMS-GT.

#### 2.1 Heuristic Algorithms

Heuristic algorithms perform an iterative local search, for instance by repeatedly refining an input sampling or projection until a motif is found. Gibbs sampling [8] and Expectation Maximization (EM), used in the motif-finding tool MEME [9, 1] both use probabilistic computations to optimize an initial random alignment. (An alignment is simply a set  $\{a_1, a_2, \dots, a_n\}$  of  $n$  positions, which predicts that the motif occurs at position  $a_i$  in the given sequence  $S_i$ .) Gibbs sampling tries to refine the alignment one position at a time; EM may recompute the entire alignment in a single iteration. Projection [2] combines a pattern-based approach with EM's probabilistic approach, trying to guess every successive character of a tentative motif and using EM to verify its guesses. GARPS [7] uses a random version of projection, in tandem with the Genetic Algorithm

(GA), for yet another iterative approach. These are just some of many successful heuristic algorithms.

## 2.2 Exact Algorithms

Heuristic approaches are non-exhaustive and thus not always guaranteed to find a solution. Exact algorithms, on the other hand, perform an exhaustive search of possible motifs and so always find the planted motif.

WINNOWER [13] and its successor MITRA [6] are exact algorithms that look at pairwise  $l$ -mer similarity to find motifs. In a set of DNA sequences, there are numerous pairs of “similar”  $l$ -mers, which come from different sequences and have Hamming distances of at most  $2d$  from each other (meaning that they could be two  $d$ -neighbors of the same  $l$ -mer). WINNOWER represents these pairs in a graph, with  $l$ -mers as nodes and edges connecting  $l$ -mer pairs. It then prunes the graph to identify “cliques” of pairs that indicate a motif. MITRA refines this graph representation into a mismatch tree containing all possible  $l$ -mers, organized by prefix. The tree structure allows MITRA to eliminate entire branches at a time, making it faster than WINNOWER at removing the spurious edges that are not part of any motif clique.

The current state-of-the-art in exact motif search is qPMS9, the most recent in a series [5, 11, 12] of Planted Motif Search algorithms. It performs

a sample-driven step, which generates a  $k$ -tuple of  $l$ -mers from each of  $k$  input strings, followed by a pattern-driven step, which generates the common  $d$ -neighborhood of the tuple and then checks whether any of the  $l$ -mers in this common neighborhood is a motif. To identify neighbors, qPMS9 efficiently traverses the tree of all possible  $l$ -mers, using certain pruning criteria explored by predecessors PMSPrune and qPMS7 [5] to quickly discard non-neighbor branches. Sampling in qPMS9 is an improvement on its predecessor PMS8 [11]; in building a  $k$ -tuple, qPMS9 intelligently prioritizes  $l$ -mers that have fewer matches with the  $l$ -mers already selected, such that the common  $d$ -neighborhood becomes smaller and thus faster to check through. Finally, both PMS8 and qPMS9 have been implemented to run on multiple processors, allowing them to solve problem instances with  $(l, d)$  as large as  $(50, 21)$  in a few hours.

### 2.3 EMS-GT

EMS-GT [10] is an exact motif search algorithm based on the candidate generate-and-test principle. It operates on a compact bit-based representation of the search space, identifying the common  $d$ -neighbors of the  $n$  given DNA sequences as motifs. The main idea of EMS-GT is to narrow down the search space to a small set of “candidate” motifs based on the first  $n'$  sequences, then do a brute-force search for each candidate on the remaining  $(n - n')$  sequences to confirm whether or not it is a motif. EMS-GT’s approach proceeds in two main steps:

1. *Generate candidates*

This step takes the intersection of the  $d$ -neighborhoods of the first  $n'$  sequences  $S_1, S_2, \dots, S_{n'}$ . Every  $l$ -mer in the resulting set  $C$  is a candidate motif.

$$C = \mathcal{N}(S_1, d) \cap \mathcal{N}(S_2, d) \cap \dots \cap \mathcal{N}(S_{n'}, d). \quad (2.1)$$

2. *Test candidates*

This step simply checks each candidate motif  $c$  in  $C$ , to determine whether a  $d$ -neighbor of  $c$  appears in all of the remaining sequences  $S_{n'+1}, S_{n'+2}, \dots, S_n$ . If this is the case,  $c$  is accepted as a motif in set  $M$ .

$$M = C \cap \mathcal{N}(S_{n'+1}, d) \cap \dots \cap \mathcal{N}(S_n, d). \quad (2.2)$$

**Algorithm 2.1** EXACT MOTIF SEARCH - GENERATE AND TEST

**Input:** set  $S = \{S_1, S_2, \dots, S_n\}$  of  $L$ -length sequences,  
 motif length  $l$ , allowable mismatches  $d$

**Output:** set  $M$  of candidate motifs

```

1:  $C \leftarrow \{\}$   $\triangleright$  generate candidates
2:  $\mathcal{N}(S_1, d) \leftarrow \{\}$ 
3: for  $j \leftarrow 1$  to  $L - l + 1$  do
4:    $x \leftarrow j^{th}l\text{-mer in } S_1$ 
5:    $\mathcal{N}(S_1, d) \leftarrow \mathcal{N}(S_1, d) \cup N(x, d)$ 
6: end for
7:  $C \leftarrow \mathcal{N}(S_1, d)$ 
8: for  $i \leftarrow 2$  to  $n'$  do
9:    $\mathcal{N}(S_i, d) \leftarrow \{\}$ 
10:  for  $j \leftarrow 1$  to  $L - l + 1$  do
11:     $x \leftarrow j^{th}l\text{-mer in } S_i$ 
12:     $\mathcal{N}(S_i, d) \leftarrow \mathcal{N}(S_i, d) \cup N(x, d)$ 
13:  end for
14:   $C \leftarrow C \cap \mathcal{N}(S_i, d)$ 
15: end for
16:  $M \leftarrow \{\}$   $\triangleright$  test candidates
17: for each  $l\text{-mer } u$  in  $C$  do
18:    $isMotif \leftarrow \text{true}$ 
19:   for  $i \leftarrow (n' + 1)$  to  $n$  do
20:      $found \leftarrow \text{false}$ 
21:     for  $j \leftarrow 1$  to  $L - l + 1$  do
22:        $x \leftarrow j^{th}l\text{-mer in } S_i$ 
23:       if  $dH(x, u) \leq d$  then
24:          $found \leftarrow \text{true}$ 
25:         break
26:       end if
27:     end for
28:     if  $!found$  then
29:        $isMotif \leftarrow \text{false}$ 
30:       break
31:     end if
32:   end for
33:   if  $isMotif$  then
34:      $M \leftarrow M \cup u$ 
35:   end if
36: end for
37: return  $M$ 

```



In practice, EMS-GT must perform speedy operations on an array of bits representing the entire motif search space. Subsections 2.3.1 to 2.3.4 discuss the efficient strategies EMS-GT uses for key tasks such as representing sets in the search space, determining whether  $l$ -mers are neighbors, and generating all neighbors for a given  $l$ -mer.

### 2.3.1 Bit-based set representation and $l$ -mer enumeration

The motif search space consists of the  $4^l$  possible  $l$ -mers that can be formed from the nucleic alphabet  $\{a, g, c, t\}$ . To efficiently represent sets—such as a  $d$ -neighborhood, or a set of candidate motifs—within this space, EMS-GT assigns each of the  $4^l$   $l$ -mers a bit flag in an array, set to 1 if the  $l$ -mer is a member of the set and 0 otherwise. Bit flags correspond to  $l$ -mers via a simple mapping: EMS-GT maps an  $l$ -mer  $s$  to a bit flag index  $x$  by replacing each character with 2 bits ( $a=00$ ,  $c=01$ ,  $g=10$ ,  $t=11$ ). Note that this mapping scheme enumerates  $l$ -mers in strict alphabetical order.

Ex. `tacgt` maps to `1100011011` = 795; thus, its flag is the 795<sup>th</sup> bit in the array.

### 2.3.2 Bit-array compression

EMS-GT's implementation compresses the required set-representation array of  $4^l$  bits into an equivalent array of  $\frac{4^l}{32}$  32-bit integers. The  $x^{th}$  bit is now found at position  $(x \bmod 32)$  of the integer at array index  $\frac{x}{32}$ .

Ex. `tacgt` maps to `1100011011` = 795 in decimal.

$$\text{array index} = \frac{795}{32} = 24, \quad \text{bit position} = 795 \bmod 32 = 27;$$

Thus, the flag for `tacgt` is the 27<sup>th</sup> bit of the integer at array index 24.

### 2.3.3 XOR-based Hamming distance computation

The mapping of  $l$ -mers to binary numbers is also useful for computing Hamming distances. An exclusive OR (XOR) bitwise operation between the mappings of two  $l$ -mers will produce a nonzero pair of bits at every mismatch position; counting these nonzero pairs of bits in the XOR result gives us the Hamming distance. See Algorithm 2.2 for the implementation.

Ex. `tacgt` maps to `1100011011`

`ttcgg` maps to `1111011010`

XOR produces `0011000001` = 2 mismatches.

### 2.3.4 Recursive neighborhood generation

To generate a  $d$ -neighbor of an  $l$ -mer  $x$ , we choose  $d' \leq d$  positions from  $1, 2, \dots, l-1, l$  and change the character at each of the  $d'$  positions in  $x$ . EMS-GT uses a recursive procedure (Algorithm 2.3) to do this, effectively (1) traversing the tree of all  $d$ -neighbors and (2) setting the bit flag in the neighborhood array  $N$  for each neighbor it encounters. Since we choose up to  $d$  positions in the  $l$ -mer, and have 3 possible substitute characters at each position, the size of the neighborhood  $N(x, d)$  is given by:

$$|N(x, d)| = \sum_{i=0}^d \binom{l}{i} 3^i \quad (2.3)$$

**Algorithm 2.2** HAMMING DISTANCE COMPUTATION**Input:**  $l$ -mer mappings  $u$  and  $v$ **Output:**  $dH(u, v)$ 

```

1:  $dH(u, v) = 0$ 
2:  $z \leftarrow u^v$ 
3: for  $i \leftarrow 1$  to  $l$  do
4:   if  $z \& 3 \neq 0$  then
5:      $dH(u, v) \leftarrow dH(u, v) + 1$ 
6:   end if
7:    $z \leftarrow z >> 2$ 
8: end for
9: return  $dH(u, v)$ 

```

**Algorithm 2.3** RECURSIVE NEIGHBORHOOD GENERATION**Input:** DNA sequence  $S$ , motif length  $l$ , mismatches  $d$ **Output:** bit-array  $\mathcal{N}$  representing  $\mathcal{N}(S, d)$ 

```

1:  $\mathcal{N}[lmer] \leftarrow 0, \forall lmer \in \text{search space}$ 
2: for each  $l$ -mer  $x$  in  $S$  do
3:   ADDNEIGHBORS( $x, 0, d$ )  $\triangleright$  recursive procedure
4: end for

5:  $\triangleright$  make  $d$  changes in  $l$ -mer  $x$ , from position  $s$  onward
6: procedure ADDNEIGHBORS( $x, s, d$ )
7:   for  $i \leftarrow s$  to  $l$  do
8:      $\Sigma' \leftarrow \{a, g, c, t\} - x_i$   $\triangleright$  remove  $i^{th}$  character of  $x$ 
9:     for  $j \leftarrow 1$  to  $|\Sigma'|$  do
10:       $neighbor \leftarrow \text{concatenate}(x_{1..i-1}, \Sigma_j, x_{i+1..l})$ 
11:       $\mathcal{N}[neighbor] \leftarrow 1$ 
12:      if  $d > 1$  and  $i < l$  then
13:        ADDNEIGHBORS( $neighbor, i + 1, d - 1$ )
14:      end if
15:    end for
16:  end for
17: end procedure
18: return  $\mathcal{N}$ 

```

## CHAPTER III

### Methodology

This section briefly describes procedures for comparing the performance of EMS-GT (including the optimization) and state-of-the-art algorithms.

#### 3.1 Datasets

Synthetic datasets were created using a DNA sequence generator written in Java. Each nucleotide character in a sequence is randomly generated;  $\{a, g, c, t\}$  each have a 25% chance of being selected, independent from other characters in the sequence. The motif is then planted at a random position in the sequence. As prescribed in [13] every dataset contains 20 DNA sequences each 600 bases long, with an  $(l, d)$  motif planted exactly once in each sequence.

#### 3.2 Implementation

The Java implementation of EMS-GT operates on a compact, bit-based enumerative representation of the motif search space. Since a significant part of runtime is spent locating and setting bits in this bit-based representation, optimizations were explored for the bit-setting portion of the algorithm. Investigation of some Hamming distance-based patterns in the search space led to the development and integration of a bit-masking speed-up technique, which exploits these patterns to set bits in entire blocks.

### 3.3 Evaluation

EMS-GT was compared to known state-of-the-art algorithms PMS8 and qPMS9 by benchmarking their performance on challenging instances of the  $(l, d)$  planted motif problem. An  $(l, d)$  problem instance is defined to be a challenging instance if  $d$  is the largest value for which the expected number of  $l$ -length motifs that would occur in the input by random chance does not exceed some limit—typically 500 random motifs [12]. The specific challenge instances used were (9,2), (11,3), (13,4), (15,5), and (17,6), as identified in [12, 5].

## **CHAPTER IV**

### **Results and Analysis**

#### **4.1 Pattern-based optimization for EMS-GT**

**Algorithm 4.1** BLOCK-BASED NEIGHBORHOOD GENERATION

**Input:** DNA sequence  $S$ , motif length  $l$ , mismatches  $d$

**Output:** bit-array  $\mathcal{N}$  representing  $\mathcal{N}(S, d) \triangleright \text{compute}$

```

1:  $\mathcal{N}[lmer] \leftarrow 0, \forall lmer \in \text{search space}$ 
2: for each  $l$ -mer  $x$  in  $S$  do
3:    $y \leftarrow x_{1..l-k}$ 
4:   SETBLOCKS( $y, 0, d$ )  $\triangleright$  recursive procedure
5: end for
6:  $\triangleright$  make  $d$  changes in prefix  $y$ , from position  $s$  onward
7: procedure SETBLOCKS( $x, s, d$ )
8:   for  $i \leftarrow s$  to  $l$  do
9:      $\Sigma' \leftarrow \{a, g, c, t\} - x_i \triangleright$  remove  $i^{th}$  character in  $x$ 
10:    for  $j \leftarrow 1$  to  $|\Sigma'|$  do
11:       $neighbor \leftarrow \text{concatenate}(x_{1..i-1}, \Sigma_j, x_{i+1..l})$ 
12:       $\mathcal{N}[neighbor] \leftarrow 1$ 
13:      if  $d > 1$  and  $i < l$  then
14:        ADDNEIGHBORS( $neighbor, i + 1, d - 1$ )
15:      end if
16:    end for
17:  end for
18: end procedure
19: return  $\mathcal{N}$ 

```

## 4.2 Performance of optimized EMS-GT

EMS-GT and two competitor algorithms were run on an Intel Xeon, 2.10 GHz machine. Their performance, averaged over 20 synthetic datasets for each  $(l, d)$  challenge instance, is outlined in Table 1:

$(l, d)$	<b>PMS8</b>	<b>qPMS9</b>	<b>EMS-GT</b>	<b>% speedup</b>
9,2	0.74 s	0.47 s	<b>0.11 s</b>	76.6%
11,3	1.58 s	1.06 s	<b>0.20 s</b>	81.1%
13,4	5.39 s	4.52 s	<b>1.04 s</b>	77.0%
15,5	36.45 s	24.63 s	<b>15.51 s</b>	37.0%
17,6	3.91 min	<b>1.96 min</b>	<i>2.93 min</i>	—

Table 4.1. Runtimes of PMS8, qPMS9 and EMS-GT

For every challenge instance except (17,6) EMS-GT outperforms qPMS9; it outperforms PMS8 for instance (17,6). EMS-GT was run including the block-masking optimization, with the default suffix length of  $k=5$ . Observe that our EMS-GT implementation can only solve problem instances where  $l \leq 17$ . This is because when we reach  $l=18$ , the size of the integer array needed to represent the entire search space ( $\frac{4^{18}}{32} = \frac{2^{36}}{2^5} = 2^{31}$  integers) begins to exceed the maximum size for Java arrays, which is  $(2^{31} - 1)$  elements.



## **CHAPTER V**

### **Conclusions**

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