More Efficient Algorithms for Closest String and Substring Problems

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Abstract. The closest string and substring problems find applications in PCR primer design, genetic probe design, motif finding, and antisense drug design. For their importance, the two problems have been extensively studied recently in computational biology. Unfortunately both problems are NP-complete. Researchers have developed both fixed-parameter algorithms and approximation algorithms for the two problems.

In terms of fixed-parameter, when the radius d is the parameter, the best-known fixed-parameter algorithm for closest string has time complexity $O(nd^{d+1})$, which is still superpolynomial even if $d = O(\log n)$. In this paper we provide an $O\left(n|\Sigma|^{O(d)}\right)$ algorithm where Σ is the alphabet. This gives a polynomial time algorithm when $d = O(\log n)$ and Σ has constant size. Using the same technique, we additionally provide a more efficient subexponential time algorithm for the closest substring problem.

In terms of approximation, both closest string and closest substring problems admit polynomial time approximation schemes (PTAS). The best known time complexity of the PTAS is $O(n^{O(\epsilon^{-2} \log \frac{1}{\epsilon})})$. In this paper we present a PTAS with time complexity $O(n^{O(\epsilon^{-2})})$.

At last, we prove that a restricted version of the closest substring has the same parameterized complexity as closest substring, answering an open question in the literature.

1 Introduction

The closest string and substring problems have been recently studied extensively in computational biology [16,18,22,13,24,12,23,15,7,11,29,4,26,30]. The two problems have a variety of applications in bioinformatics, such as universal PCR primer design [20,16,5,27,12,31], genetic probe design [16], antisense drug design [16,4], finding unbiased consensus of a protein family [2], and motif finding [16,12,30,3,9]. In all these applications, a common task is to design a new DNA or protein sequence that is very similar to (a substring of) each of the given sequences. In the first three applications, the designed DNA sequence can bind to each of the given DNA sequences in order to perform its designated functions. In the last two applications, the designed sequence acts as an unbiased representative of all the given sequences. The common task has been formulated as the closest string problem and the closest substring problem.

Given n length-m strings s_1, s_2, …, s_n, and a radius d, the *closest string* problem seeks for a new length-m string s such that $d(s, s_i) \leq d$. Here $d(\cdot, \cdot)$ is the Hamming distance. The *closest substring* problem seeks for a length L ($L \leq m$) string t such that for every $i = 1, 2, \ldots, n$, there is a substring t_i of s_i with length L such that $d(t, t_i) \leq d$. The problems may also be described as optimization problems where the objectives are to minimize the radius d.

Unfortunately, both of these two problems are NP-complete [10,16]. In addition to many heuristic algorithms without any performance guarantee (for example [19,23,24]), researchers have developed approximation algorithms and fixed-parameter algorithms for the two problems. Approximation algorithms sacrifice the quality of the solution in order to achieve polynomial time [14]. A polynomial time approximation scheme (PTAS) achieves ratio $1 + \epsilon$ in polynomial time for any fixed $\epsilon > 0$. Fixed-parameter algorithms find optimal solutions with time complexity $f(k) \cdot n^c$ for a constant c and any function f [6]. Here k is a parameter naturally associated to the input instance.

For fixed-parameter algorithms, Stojanovic et al. [29] provided a linear time algorithm for $d = 1$. Gramm et al. [13] provided the first fixed-parameter algorithm for closest string with running time $O(nm + nd^{d+1})$. Therefore, for small values of d their algorithm can solve closest string in acceptable time. In this paper we present a novel algorithm that finds the optimal solution of closest string problem with running time $O\left(nm + nd \cdot (16|\Sigma|)^d\right)$. This is exponentially better than the previous fixed-parameter algorithm when the alphabet has constant size.

The closest substring problem appeared to be harder than closest string in terms of parameterized complexity. For unbounded alphabet size, it has been shown that the problem is $W[1]$-hard even if all d, n, L are parameters [8,9]. The $W[1]$-hardness indicates that the problem unlikely has a fixed-parameter polynomial time algorithm [6]. For $|\Sigma|$ being a constant or a parameter, the problem is $W[1]$-hard even if both d and n are parameters [22]. For a more complete review of the parameterized complexities of the closest substring problem, we refer the readers to [9,22,25]. Marx [22] gave a $|\Sigma|^{d(\log d+2)}(nm)^{\log d+O(1)}$ algorithm for the closest substring problem. In this paper we present a new algorithm for closest substring with improved time complexity $O\left((16|\Sigma|)^d \cdot nm^{\lceil \log d \rceil+1}\right)$.

For approximation algorithms, Lanctot et al. [16] gave the first polynomial time approximation algorithm with approximation ratio $\frac{4}{3} + o(1)$. Li et al. [17] provided a PTAS for closest string with time complexity $O(mn^{O(\epsilon^{-5})})$. Ma [21] provided a PTAS for closest substring problem. These two PTAS results were collected in [18]. There have been many negative comments regarding the large exponent of the PTAS [9,3,11,13,22]. By using a lemma in [22] and an idea of [17], Andoni et al. [1] proposed a PTAS to obtain a much better time complexity $O(mn^{O(\epsilon^{-2}\log\frac{1}{\epsilon})})$. By combining our new fixed-parameter algorithm, in Section 5 we provide a simpler PTAS with further improved time complexity $O(mn^{O(\epsilon^{-2})})$.

Noticing the hardness of closest substring problem, Moan and Rusu [25] studied a more restricted version of closest substring. They put a diameter constraint on top of the original closest substring problem by further requiring the pairwise distances between substrings in the solution do not exceed a diameter D for some $D < 2d$. They hoped that such a constraint may reduce the parameterized complexity of closest substring when D is close enough to d. The condition for this to happen is left as a main open problem in [25]. In this paper we answer this question by proving that such condition does not exist. That is, for any given $\epsilon > 0$, all parameterized complexity results of closest string preserve in the constrained instances for $D < (1+\epsilon)d$.

2 Preliminaries and Notations

Let Σ be an alphabet with constant size $|\Sigma|$. Suppose s is a string over Σ. $|s|$ denotes the length of s. $s[i]$ denotes the i-th letter of s. Therefore, $s = s[1]s[2]\ldots s[m]$, where m is the length of s. Let s and t be two strings with the same length m, $d(s,t)$ denotes the Hamming distance between s and t. Use $[1,m]$ to denote the set $\{1,2,\ldots,m\}$. For $P = \{i_1,i_2,\ldots,i_k\} \subseteq [1,m]$, define $s|_P = s[i_1]s[i_2]\ldots s[i_k]$ and $d^P(s,t) = d(s|_P, t|_P)$. Let $Q = [1,m] \setminus P$. From the definition of Hamming distance, clearly $d(s,t) = d^P(s,t) + d^Q(s,t)$. Let $Q(s,t)$ denote the set of positions where s and t agree, i.e., $Q(s,t) = \{j \mid s[j] = t[j]\}$. Similarly, for k given strings $s_1, s_2, \ldots, s_k$ of same length, $Q(s_1, s_2, \ldots, s_k)$ denotes the position set where all strings agree. Let $P(s,t)$ denote the position set where s and t disagree.

Let s_1, s_2, ..., s_n be n strings of length m. The *closest string problem* asks for a string center s such that $d = \max_{i=1}^{n} d(s,t_i)$ is minimized. The minimum value of d is called the *radius* of the n input strings. $D = \max_{1\le i,j\le n} d(s_i,s_j)$ is called the *diameter* of the n input strings. Let $L \le m$. The *closest substring problem* asks for a length-L string center s and a length-L substring t_i of each s_i, such that $d = \max_{i=1}^{n} d(s,t_i)$ is minimized.

In this paper we will also study a more generalized version of closest string problem, the *neighbor string problem*: Given n strings s_1, s_2, ..., s_n with length m, and n nonnegative integers d_1, d_2, ..., d_n, the neighbor string problem seeks for a length m string s such that $d(s,s_i) \le d_i$ for every $1 \le i \le n$. An instance of the neighbor string problem is given by $\langle (s_1,d_1),(s_2,d_2),\ldots,(s_n,d_n)\rangle$.

3 $O\left(nm + nd \cdot (16|\Sigma|)^d\right)$ Algorithm for Closest String Problem

Parameterized complexity has been used to tackle NP-hard problems [6]. In principle, a fixed-parameter polynomial time algorithm is a well-structured superpolynomial algorithm such that the superpolynomial factor is only with respect to one parameter of the given instance. Many NP-hard problems have been found to be fixed-parameter tractable, which means that an algorithm with running time $f(k) \cdot n^c$ exists to solve the problem. Here k is a parameter naturally associated with the problem; n is the size of the input and c is a constant. Clearly $f(k)$ must be superpolynomial if $\mathbf{P} \neq \mathbf{NP}$. The hope is that this $f(k)$ will not grow too fast, and parameter k is small for practical instances; and hence the problem can be solved efficiently in practice.

Gramm et al. [13] provided a fixed-parameter polynomial time algorithm for closest string when the radius d is used as the fixed parameter. For a given instance $\{s_1, s_2, \ldots, s_n\}$ and a given value d, their algorithm finds a center string s such that $d(s, s_i) \leq d$ in $O(nm + nd^{d+1})$ time, if such a string exists.

In this section we provide a new algorithm for closest string problem with time complexity $O(nm + nd \cdot (16|\Sigma|)^d)$. When the alphabet size is a constant, our algorithm is exponentially faster than the previous algorithm. In order to design the algorithm for closest string, let us focus on the more generalized neighbor string problem.

Lemma 1.[1] *Let $\langle (s_1, d_1), \ldots, (s_n, d_n) \rangle$ be an instance of the neighbor string problem. If j satisfies $d(s_1, s_j) > d_j$, then for $Q = Q(s_1, s_j)$ and any solution s of the neighbor string problem, $d^Q(s, s_1) < \frac{d_1}{2}$.*

Proof. Let s be a solution, i.e. $d(s, s_i) \leq d_i$ for $i = 1, 2, \ldots, n$. Let $P = [1, m] \setminus Q$. Then

$$d^P(s, s_1) + d^P(s, s_j) \geq d^P(s_1, s_j) = d(s_1, s_j) > d_j. \tag{1}$$

On the other hand,

$$\begin{aligned} & d^P(s, s_1) + d^P(s, s_j) \\ &= \big(d(s, s_1) - d^Q(s, s_1)\big) + \big(d(s, s_j) - d^Q(s, s_j)\big) \\ &= d(s, s_1) + d(s, s_j) - 2\ d^Q(s, s_1) \\ &\leq d_1 + d_j - 2\ d^Q(s, s_1) \end{aligned}$$

The second equation in the above derivation is because $s_1|_Q = s_j|_Q$. Combining with (1), we get $d_1 + d_j - 2\ d^Q(s, s_i) > d_j$. Consequently, $d^Q(s, s_1) < \frac{d_1}{2}$. The lemma is proved. □

Theorem 1. *Let $d = \max_{1 \leq i \leq n} d_i$. If there is a solution s such that $d(s, s_i) \leq d_i$ $(1 \leq i \leq n)$, then algorithm **StringSearch** in Fig. 1 outputs a solution s' such that $d(s', s_i) \leq d_i$ in time $O(mn + nd \cdot T(d, d_1))$, where the size of the search tree*

$$T(d, d_1) \leq \binom{d + d_1}{d_1} (|\Sigma| - 1)^{d_1} \cdot 2^{2d_1}.$$

Proof. First let us prove the correctness of the algorithm. It is easy to verify that when the algorithm returns a non-null string in either line 2 or line 4.3,

[1] Lemma 1 uses a similar idea as Lemma 2.2 in [22]. However the lemma in [22] cannot be directly used in our algorithms.

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Algorithm StringSearch
Input: An instance of neighbor string $\langle(s_1,d_1),(s_2,d_2),\ldots,(s_n,d_n)\rangle$.
Output: String $s$ such that $d(s,s_i)\le d_i$ $(i=1,\ldots,n)$, or NULL if there is no solution.
1. Try to find $i_0$ such that $d(s_1,s_{i_0})>d_{i_0}$.
2. If step 1 fails, return $s_1$.
3. Let $Q=Q(s_1,s_{i_0})$, $P=[1,|s_1|]\setminus Q$.
4. For every possible string $t$ of length $|P|$ such that $d(t,s_1|_P)\le d_1$ and $d(t,s_{i_0}|_P)\le d_{i_0}$
4.1    Let $e_i=d_i-d(t,s_i|_P)$ for $i\ne 1$, and $e_1=\min\{d_1-d(t,s_1|_P),\lceil d_1/2\rceil-1\}$;
4.2    Use StringSearch to find the solution $u$ of $\langle(s_1|_Q,e_1),(s_2|_Q,e_2),\ldots,(s_n|_Q,e_n)\rangle$;
4.3    If $u\ne$ NULL then let $s|_P=t$ and $s|_Q=u$ and return $s$.
5. Return NULL.
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Fig. 1. The algorithm **StringSearch**

the string is a solution of the input instance. Let us prove that when there is a solution of the input instance, then the algorithm can find it. We prove this by using induction on d_1. If $d_1=0$ then clearly the algorithm is correct. When $d_1>0$ and line 1 finds i_0 successfully, by Lemma 1, the Q and P defined in line 3 are such that there is a solution s satisfying $d(s|_Q,s_1|_Q)\le e_1$. Therefore, this s is such that $d(s|_Q,s_i|_Q)\le e_i$ for $1\le i\le n$. As a result, when $t=s|_P$ in line 4, by induction, the recursive call to Algorithm **StringSearch** at line 4.2 will find u such that $d(u,s_i|_Q)\le e_i$ for $1\le i\le n$. Then it is easy to verify that the s returned in line 4.3 is a desired solution.

Next let us examine the time complexity of the algorithm **StringSearch**. We estimate the size (number of leaves) of the search tree first. In line 4, assume t is an eligible string and $d(t,s_1|_P)=k$. Then $|P|=d(s_1|_P,s_{i_0}|_P)\le d(t|_P,s_1|_P)+d(t|_P,s_{i_0}|_P)\le d_{i_0}+k\le d+k$. Therefore, there are at most $\binom{|P|}{k}(|\Sigma|-1)^k\le\binom{d+k}{k}(|\Sigma|-1)^k$ such strings t. For each of them, the size of the subtree rooted at t of the search tree is bounded by $T(d,\min\{d_1-k,\lceil d_1/2\rceil-1\})$. k can take values from 0 to d_1. Therefore, the search tree size satisfies

$$\begin{aligned}T(d,d_1)&\le\sum_{k=\lfloor d_1/2\rfloor+1}^{d_1}\binom{d+k}{k}(|\Sigma|-1)^kT(d,d_1-k)\\&\quad+\sum_{k=0}^{\lfloor d_1/2\rfloor}\binom{d+k}{k}(|\Sigma|-1)^kT(d,\lceil d_1/2\rceil-1) \qquad (2)\\&=I_1+I_2 \qquad (3)\end{aligned}$$

Clearly $T(d,0)=1$ because in this case s_1 is the solution. We prove by induction that for $\tilde{d}\ge 1$,

$$T(d,\tilde{d})\le 2^{2\tilde{d}}\binom{d+\tilde{d}}{\tilde{d}}(|\Sigma|-1)^{\tilde{d}}. \qquad (4)$$

It is easy to verify that when $\tilde{d} = 1$, $T(d, 1) \le (d+1)(|\Sigma|-1)+1$, the statement is true. When $\tilde{d} = 2$, because of (2), $T(d, 2) \le \binom{d+2}{2}(|\Sigma| - 1)^2 + (d + 1)(|\Sigma| - 1) + 1 \le 2\binom{d+2}{2}(|\Sigma| - 1)^2$, the statement is also true. Next we suppose $d_1 > 2$ and eq. (4) is true for $0 \le \tilde{d} < d_1$. We bound the two terms of (3) separately. Let $k_0 = \lfloor d_1/2 \rfloor + 1$.

$$\begin{aligned}
I_1 &= \sum_{k=k_0}^{d_1} \binom{d+k}{k}(|\Sigma| - 1)^k T(d, d_1 - k) \\
&\le \sum_{k=k_0}^{d_1} \binom{d+d_1}{k}(|\Sigma| - 1)^k T(d, d_1 - k) \\
&\le \sum_{k=k_0}^{d_1} \binom{d+d_1}{k}(|\Sigma| - 1)^k \cdot \binom{d+d_1-k}{d_1-k}(|\Sigma| - 1)^{d_1-k} \cdot 2^{2(d_1-k)} \\
&= \binom{d+d_1}{d_1}(|\Sigma| - 1)^{d_1} \sum_{k=k_0}^{d_1} \binom{d_1}{k} \cdot 2^{2(d_1-k)} \\
&\le \binom{d+d_1}{d_1}(|\Sigma| - 1)^{d_1} \cdot 2^{d_1-1} \sum_{k=k_0}^{d_1} \binom{d_1}{k} \\
&\le \binom{d+d_1}{d_1}(|\Sigma| - 1)^{d_1} \cdot 2^{2d_1-2}.
\end{aligned} \tag{5}$$

The rest is to bound I_2 by $3\binom{d+d_1}{d_1}(|\Sigma| - 1)^{d_1} \cdot 2^{2d_1-2}$.

$$\begin{aligned}
I_2 &= \sum_{k=0}^{k_0-1} \binom{d+k}{k}(|\Sigma| - 1)^{k_0} T(d, d_1 - k_0) \\
&\le \sum_{k=0}^{k_0-1} \binom{d+k}{k}(|\Sigma| - 1)^{k_0} \cdot \binom{d+d_1-k_0}{d_1-k_0}(|\Sigma| - 1)^{d_1-k_0} \cdot 2^{2(d_1-k_0)} \\
&= \binom{d+d_1-k_0}{d_1-k_0}(|\Sigma| - 1)^{d_1} \cdot 2^{2(d_1-k_0)} \sum_{k=0}^{k_0-1} \binom{d+k}{k} \\
&\le \binom{d+d_1-k_0}{d_1-k_0}(|\Sigma| - 1)^{d_1} \cdot 2^{2(d_1-k_0)} \binom{d+k_0}{k_0}.
\end{aligned}$$

So we only need to prove

$$\binom{d+d_1-k_0}{d_1-k_0}\binom{d+k_0}{k_0}2^{-2k_0} \le \frac{3}{4} \cdot \binom{d+d_1}{d_1},$$

or equivalently,

$$\binom{d+d_1-k_0}{d_1-k_0}\binom{d_1}{k_0} \le \frac{3}{4} \cdot 2^{2k_0}\binom{d+d_1}{d_1-k_0}. \tag{6}$$

(6) is true because

$$\binom{d+d_1-k_0}{d_1-k_0} \le \binom{d+d_1}{d_1-k_0}, \quad \binom{d_1}{k_0} \le \frac{1}{2}\cdot 2^{d_1+1} < \frac{3}{4}\cdot 2^{2k_0}.$$

Hence (4) is correct.

At each leaf, the time complexity of line 1 is $O(nm)$. By carefully remembering the previous distances and only update the $O(d)$ positions changed, this can be done in $O(nd)$ time. The total running time is dominated by the leaves. Therefore, the time complexity of the algorithm is $O(nm + nd \cdot T(d, d_1))$. □

Corollary 1. ***StringSearch*** *solves the closest string problem in time*

$$O\left(nm + nd \cdot 2^{4d}(|\Sigma| - 1)^d\right).$$

4 More Efficient Algorithm For Closest Substring

In [22], a $|\Sigma|^{d(\log_2 d+2)} N^{\log_2 d + O(1)}$ algorithm is given, where N is the total length of the input strings. In this section we improve it to $O\left(n|\Sigma|^{O(d)} m^{\lceil \log_2 d\rceil + 1}\right)$. That is, the $\log_2 d$ factor at the exponent of $|\Sigma|^{d(\log_2 d+2)}$ is removed. Moreover, the total length N is replaced by the length m of the longest input string.

Again, in order to develop an algorithm for closest substring, we attempt to solve a more generalized version of closest substring. For convenience, we call the new problem *partial knowledge closest substring.* An instance of the partial knowledge closest substring problem is given by $\langle\{s_1, s_2, \ldots, s_n\}, d, d_1, L, O, \tilde{t}\rangle$, where $O \subset [1, L]$ and $\tilde{t}$ is a string of length $|O|$. The problem is to find a string t of length L, such that $t|_O = \tilde{t}$, $d^{[1,L]\setminus O}(t, s_1) \le d_1$, and for every i, $d(t, t_i) \le d$ for at least one substring t_i of s_i.

Theorem 2. *Algorithm* ***SubstringTry*** *in Fig. 2 finds a solution for closest substring with time complexity*

$$O\left((nL + nd \cdot 2^{4d}|\Sigma|^d \cdot m^{\lceil \log_2 d\rceil + 1}\right).$$

Sketch of Proof. When all the input strings have the same length L, a careful comparison between Algorithm **SubstringSearch** and the previous Algorithm **StringSearch** can see that the two algorithms are equivalent. The only difference is made when $|s_i| > L$. Then the "guess" operation in line 4 requires the algorithm to try all possible substrings of s_{i_0}. This expands the search tree size by a factor of at most m. Because of Lemma 1, the recursion of Algorithm **SubstringSearch** is at most $\lceil \log_2 d\rceil$ levels. This increases the search tree size by a factor of $m^{\lceil \log_2 d\rceil}$. Combining with Corollary 1, the theorem is proved. □

5 More Efficient PTAS for Closest String

In [17,18], a PTAS for closest string problem was given. To achieve approximation ratio $1 + \epsilon$, the running time of the algorithm was $O\left(mn^{O(\epsilon^{-5})}\right)$. Apparently

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Algorithm SubstringSearch
Input: $\langle\{s_1, s_2, \ldots, s_n\}, d, L, O, \tilde{t}\rangle$ such that $|s_1| = L$.
Output: A solution $t$ of the partial knowledge closest substring, or NULL if there is no solution.
1. Let $O' = [1..L] \setminus O$. Let $s$ be a string such that $s|_O = \tilde{t}$ and $s|_{O'} = s_1|_{O'}$.
2. Try to find $i_0$ such that $d(s, t_{i_0}) > d_{i_0}$ for every substring $t_{i_0}$ of $s_{i_0}$.
3. If line 1 fails, return $s$.
4. Guess a substring $t_{i_0}$ of $s_{i_0}$.
5. Let $P = P(s_1, t_{i_0}) \setminus O$.
6. For every possible string $t$ of length $|P|$ such that $d(t, s_1|_P) \le d_1$ and $d(t, t_{i_0}|_P) \le d - d(\tilde{t}, t_{i_0}|_O)$
6.1     Let $t'$ be a string such that $t'|_O = \tilde{t}$ and $t'|_P = t$.
6.2     Let $e_1 = \min\{d_1 - d(t, s_1|_P), \lceil d_1/2 \rceil - 1\}$.
6.3     Use SubstringSearch to find solution $u$ of $\langle\{s_1, s_2, \ldots, s_n\}, d, e_1, L, O \cup P, t'|_{O\cup P}\rangle$.
6.4     If 6.3 is successful then return $u$.
7. Return NULL.
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Algorithm SubstringTry
Input: $\langle\{s_1, s_2, \ldots, s_n\}, d, L\rangle$.
1. for every length $L$ substring $t_1$ of $s_1$,
1.1   call SubstringSearch with $\langle\{t_1, s_2, \ldots, s_n\}, d, d, L, \emptyset, e\rangle$.
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Fig. 2. The algorithms **SubstringSearch** and **SubstringTry**

this PTAS has only theoretical value as the degree of the polynomial grows very fast when ϵ gets small. By using the Lemma 2.2 in [22] and an idea of [17,18], Andoni et al. [1] proposed a PTAS in [17] to get much better time complexity $O(mn^{O(\epsilon^{-2}\log\frac{1}{\epsilon})})$. The proof in [1] argued that when $d = \Omega(n/\epsilon^2)$, a standard linear programming relaxation method can solve the closest string problem with good approximation ratio. When $d = O(n/\epsilon^2)$, one can exhaustively enumerate all the possibilities of positions in the solution where r of the input strings do not agree. However, by using Lemma 2.2 of [22], r can be reduced from the original $O(\frac{1}{\epsilon})$ in [18] to $O(\log\frac{1}{\epsilon})$.

With our new fixed-parameter algorithm that runs $O\left(mn + nd \cdot (16|\Sigma|^d)\right)$ time, we can further reduce the time complexity by the following algorithm: Use the fixed-parameter algorithm to solve $d = O(n/\epsilon^2)$, and use the standard linear programming relaxation to solve the case $d = \Omega(n/\epsilon^2)$. It is easy to verify that this provides a simple $O(m \cdot n^{O(\epsilon^{-2})})$ PTAS.

Theorem 3. *Closest string has a PTAS that achieves approximation ratio* $1+\epsilon$ *with time* $O(m \cdot n^{O(\epsilon^{-2})})$.

6 Hardness Result

Together with the development of fixed-parameter polynomial time algorithms, W-hierarchy has been developed to prove fixed-parameter intractability [6]. The

W[1]-hardness results reviewed in Section 1 indicate that the closest substring problem unlikely has fixed-parameter polynomial time algorithms even if both d and n are fixed-parameters. More parameterized complexity results about the closest substring problem can be found in [9,22,25].

Moan and Rusu [25] studied a variant of the closest substring problem by adding a constraint on the diameter of the solution, and hoped that the constraint can help reduce the parameterized complexity of the problem. The constraint is called the bounded Hamming distance (BHD) constraint in their paper. Then the *BHD-constrained closest substring (BCCS)* problem is defined as follows.

BCCS Given a set of n strings $s_1, s_2, \ldots, s_n$, substring length L, radius d, and diameter D. Find length-L substring t_i of each s_i, $i = 1, 2, \ldots, n$, and a new length-L string t, such that $d(t_i, t_j) \leq D$, and $d(t, t_i) \leq d$.

Clearly, $d \leq D \leq 2d$. For any $c \geq \frac{4}{3}$, Moan and Rusu proved that the diameter constraint $D \leq c \cdot d$ does not reduce the complexity of closest substring problem. More precisely, with any $c \geq \frac{4}{3}$, all parameterized complexity results for closest substring preserve for BCCS when using any non-empty subset of the following values as parameters: the radius d, the alphabet size $|\Sigma|$, the number of input strings n, the length of desired substrings L.

However, Moan and Rusu pointed out that in computational biology, D is usually significantly smaller than $2d$. Therefore, they hoped that when $\frac{D}{d}$ is very close to 1, the BCCS problem might become easier than the original closest substring problem. If this is true, BCCS can be used to solve the practical closest substring problems. The finding of the necessary condition for that BCCS problem becomes easier is left as the "main open question" of the paper [25]. In this section, we answer this question negatively with the following theorem.

Theorem 4. *For any constant $\epsilon > 0$, with the diameter constraint $D \leq (1+\epsilon)d$, all parameterized complexity (W[l]-hardness) results for closest substring preserve for BCCS when using any non-empty subset of the following values as parameters: the radius d, the alphabet size $|\Sigma|$, the number of input strings n, the length of desired substrings L.*

Proof. The proof is done in three steps: First, we construct an instance of closest string with radius $\tilde{d}$ and diameter $\tilde{D} = (1 + o(1))\tilde{d}$. Then, we show that an instance of closest substring with radius d and diameter D can be "merged" with an instance of the closest string with radius $\tilde{d}$ and diameter $\tilde{D}$, so that the new instance has radius $d+\tilde{d}$ and diameter $D+\tilde{D}$. Thirdly, by letting $\tilde{d} \gg d$ and $\tilde{D} \gg D$, we get an instance such that the diameter is very close to the radius. Thus, we reduce the closest substring problem to BCCS, and hence prove the theorem. The detailed proof can be found in the appendix. □

7 Discussion

The closest string and closest substring are two problems motivated and well-studied in computational biology. We proposed a novel technique that leads to more efficient fixed-parameter algorithm for closest string. This is also the first polynomial algorithm for the problem when $d = O(\log n)$. The same technique is then used to give a more efficient algorithm for closest substring. As a consequence of the fixed-parameter algorithm, we presented a more efficient PTAS of the closest string problem. At last, we showed that a restricted version of the closest substring problem has the same parameterized complexity as the original closest substring problem. This answers an open question raised in [25].

An interesting observation is that the approximation and fixed-parameter strategies work complementarily for different d values. For smaller $d < \log_2 n$ and binary strings, our fixed-parameter algorithm has time complexity $O(nm + nd \cdot 2^{4d}) = O(nm + n^5 \log_2 n)$. For larger $d > c \ln n/\epsilon^2$ for some constant c, the linear programming relaxation's time complexity is dominated by the time to solve a linear programming of m variables and nm coefficients, which is again a low-degree polynomial. This scenario can be intuitively explained as follows. When d is small and n is large, each input string puts a strong constraint on the solution, and consequently removes a large portion of the search space in a fixed-parameter algorithm. Therefore, it is easier to design a fixed-parameter algorithm. Conversely, when d is large and n is small, the constraint superimposed by each input string is weaker and there are fewer constraints. Therefore, it is easier to find an approximate solution to roughly satisfy those constraints.

But when d falls in between $\log_2 n$ and $c \ln n/\epsilon^2$, the polynomial will have high degree for the fixed-parameter algorithm, and the approximation ratio of the linear programming relaxation may exceed $1 + \epsilon$. The instances with d in this range seem to be the "hardest" instances of the closest string problem. However, because the fixed-parameter algorithm has polynomial (although with high degree) running time on these instances, a proof for the "hardness" of these instances seem to be difficult too. We leave the finding of more efficient (approximation) algorithm for $\log_2 n < d < c \ln n/\epsilon^2$ as an open problem.

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Appendix - Proof of Theorem 4

Step I

First let us construct an instance $\mathcal{I}_1$ of the closest string problem with very close radius and diameter. Let k be an even number. Examine the instance with k binary strings $x_1, x_2, \ldots, x_k$. Each x_i has length $\tilde{L} = \binom{k}{k/2}$. For each column j, exactly half of $x_1[j], x_2[j], \ldots, x_k[j]$ take value 0 and the other half take value 1. Hence there are in total $\binom{k}{k/2}$ ways to assign values to a column. Each of the $\binom{k}{k/2}$ columns takes a distinct way.

Claim 1. The radius of the constructed instance is $\tilde{d} = \tilde{L}/2$.

Proof. Because of the construction, each string has half of the $\tilde{L}$ letters as 0. Therefore, $d(0^{\tilde{L}}, x_i) = \tilde{L}/2$ for every x_i. Therefore, the radius is at most $\tilde{L}/2$.

On the other hand, for any center string x, at each column, the total number of differences between x_i $(i = 1, 2, \ldots, k)$ and the center string is exactly $k/2$. Therefore, $\sum_{i=1}^{k} d(x, x_i) = k\tilde{L}/2$. Consequently, $\max_{i=1}^{k} d(x, x_i) \geq \tilde{L}/2$. The claim is proved. □

Now let us examine the diameter of the constructed instance. For every two strings x_i and x_j, the Hamming distance is the number of columns such that x_i and x_j take different values. This is equivalent to the number of ways to split k elements into two equal-sized subsets, ensuring that elements i and j are separated. With simple combinatorics, this number is $2\binom{k-2}{\frac{k}{2}-1}$. Therefore,

$$\frac{\tilde{D}}{\tilde{d}} = \frac{2\binom{k-2}{\frac{k}{2}-1}}{\tilde{L}/2} = \frac{4\binom{k-2}{\frac{k}{2}-1}}{\binom{k}{k/2}} = \frac{k}{k-1}$$

In order to avoid the exponential growth of $\tilde{D}$ and $\tilde{d}$ with respect to k, we note that $\tilde{D}$ and $\tilde{d}$ can be enlarged while keeping the same ratio $\frac{\tilde{D}}{\tilde{d}}$ by replacing each x_i by $\underbrace{x_i x_i \ldots x_i}_{K}$, i.e., the concatenation of K copies of x_i. In the rest of the proof we consider $\mathcal{I}_1$ as such an enlarged instance, and the value K is to be determined later. The notations diameter $\tilde{D}$, radius $\tilde{d}$, input string x_i, and string length $\tilde{L}$ all correspond to the enlarged instance.

Step II
Let $\mathcal{I} = \langle \{s_1, \ldots, s_n\}, L, d\rangle$ be an instance of the closest substring. We construct a new instance in the following.

Let X be an i.i.d. random binary string with length $7(L+\tilde{L})$. Then by using Chernoff's bound, it is easy to verify that with positive probability,

$$d(X[1..j], X[|X|-j+1, |X|]) + d(X[j+1..|X|], X[1..|X|-j]) > 3(L+\tilde{L}) \text{ for } j \neq 0 \text{ and} |X|. \quad (7)$$

By using the standard derandomization techniques such as conditional probability [28], we can easily design a polynomial time deterministic procedure to construct the binary string X satisfying (7). Here we omit the detail.

For each s_i $(i = 1, \ldots, n)$ and each x_j $(j = 1, \ldots, k)$, let

$$s_{ij} = X\ s_i[1..L]x_j\ XX\ s_i[2..L+1]x_j\ XX\ \ldots\ XX\ s_i[m-L+1..m]x_j\ X$$

The new instance is then

$$\mathcal{I}_2 = \langle \{s_{ij} | i = 1, \ldots, n, j = 1, \ldots, k\}, 15(L+\tilde{L}), d+\tilde{d}\rangle.$$

Claim 2. $\mathcal{I}$ has a solution with radius $\leq d$ and diameter $\leq D$ if and only if $\mathcal{I}_2$ has a solution with radius $\leq d+\tilde{d}$ and diameter $\leq D+\tilde{D}$.

Proof. Suppose $\mathcal{I}$ has a solution $s_i[l_i..l_i+L-1]$, $i = 1, \ldots, n$ with radius d and diameter D. Then the substrings $Xs_i[l_i..l_i+L-1]x_jX$, $i = 1, \ldots, n$, $j = 1, \ldots, k$ are a solution of $\mathcal{I}_2$. It is easy to verify that the radius and diameter are bounded by $d+\tilde{d}$ and $D+\tilde{D}$, respectively.

Now we prove the other direction. We first show that the solution of $\mathcal{I}_2$ is such that X from different strings are aligned exactly together. Otherwise, because of 7, the inexact overlaps between X from two input strings will cause at least $3(L+\tilde{L})$ minus two times of the length of $s_i[k..k+L]x_j$. This gives a diameter at least $L+\tilde{L} > D+\tilde{D}$, contradicting the condition.

Further, without making the solution worse, we can easily modify the solution by "sliding" so that every substring has the form $Xs_i[l_i..l_i+L-1]x_jX$ for some l_i. Next we show that $s_i[l_i..l_i+L-1]$ $(i = 1, 2, \ldots, n)$ is the desired solution for $\mathcal{I}$.

Let $Xs\tilde{s}X$ be the center of $Xs_i[l_i..l_i+L-1]x_jX$ with radius $d+\tilde{d}$. Because $\tilde{d}$ is the radius of $\mathcal{I}_1$, there is j_0 such that $d(\tilde{s}, x_{j_0}) = \tilde{d}$. Therefore, $d(Xs\tilde{s}X, Xs_i[l_i..l_i+L-1]x_{j_0}X) \le d+\tilde{d}$ derives that $d(s, s_i[l_i..l_i+L-1]) \le d$ for every i.

Similarly, there are j_0 and j_1 such that $d(x_{j_0}, x_{j_1}) = \tilde{D}$. Therefore, $d(Xs_i[l_i..l_i+L-1]x_{j_0}X, Xs_{i'}[l_{i'}..l_{i'}+L-1]x_{j_0}X) \le D+\tilde{D}$ derives that $d(s_i[l_i..l_i+L-1], s_{i'}[l_{i'}..l_{i'}+L-1]) \le D$ for every i and i'.

The claim is proved. □

Step III

For any $\epsilon > 0$, we let $k = \lceil \frac{2}{\epsilon} + 1 \rceil$ and $K = \left\lceil \frac{4D}{\binom{k}{k/2}\epsilon} \right\rceil$ in the construction of $\mathcal{I}_1$. Then $\tilde{d} = \frac{K}{2} \cdot \binom{k}{k/2} \ge \frac{2D}{\epsilon}$. Then in instance $\mathcal{I}_2$, the ratio between the diameter and radius is

$$\frac{D+\tilde{D}}{d+\tilde{d}} \le \frac{D}{\tilde{d}} + \frac{\tilde{D}}{\tilde{d}} \le \frac{\epsilon}{2} + \frac{k}{k-1} \le 1+\epsilon$$

Thus, we successfully reduce the closest substring problem to the closest substring problem with the constraint that the diameter is within $1+\epsilon$ times the radius. The number n, length m of the input strings are increased only by a constant factor determined by ϵ. The new length L and radius d of the substrings are polynomials of the old L and d. Therefore, all the W-complexities of the closest substring problem still hold with the diameter constraint $D \le (1+\epsilon)d$ for any small $\epsilon > 0$. The theorem is proved. □