On The Closest String and Substring Problems

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Abstract

The problem of finding a center string that is ‘close’ to every given string arises and has many applications in computational molecular biology and coding theory.

This problem has two versions: the Closest String problem and the Closest Substring problem. Assume that we are given a set of strings \( S = \{s_1, s_2, \ldots, s_n\} \) of strings, say, each of length \( m \). The Closest String problem \([1, 2, 4, 5, 11]\) asks for the smallest \( d \) and a string \( s \) of length \( m \) which is within Hamming distance \( d \) to each \( s_i \in S \). This problem comes from coding theory when we are looking for a code not too far away from a given set of codes \([4]\). The problem is NP-hard \([4, 11]\). Berman et al \([2]\) give a polynomial time algorithm for constant \( d \). For super-logarithmic \( d \), Ben-Dor et al \([1]\) give an efficient approximation algorithm using linear program relaxation technique. The best polynomial time approximation has ratio \( \frac{4}{3} \) for all \( d \), given by \([11]\) and \([3]\).

The Closest Substring problem looks for a string \( t \) which is within Hamming distance \( d \) away from a substring of each \( s_i \). This problem only has a \( 2 - \frac{2}{2^{\log_2 d} + 1} \) approximation algorithm previously \([11]\) and is much more elusive than the Closest String problem, but it has many applications in finding conserved regions, genetic drug target identification, and genetic probes in molecular biology \([8, 9, 10, 11, 13, 14, 20, 21, 22, 23, 11]\). Whether there are efficient approximation algorithms for both problems are major open questions in this area.

We present two polynomial time approximation algorithms with approximation ratio \( 1 + \epsilon \) for any small \( \epsilon \) to settle both questions.

*Some of the results in this paper have been presented in Proc. 31st ACM Symp. Theory of Computing, May, 1999 \([12]\), and in Proc. 11th Symp. Combinatorial Pattern Matching, June, 2000, \([4]\).
1 Introduction

Many problems in molecular biology involve finding similar regions common to each sequence in a given set of DNA, RNA, or protein sequences. These problems find applications in locating binding sites and finding conserved regions in unaligned sequences [20, 9, 8, 19], genetic drug target identification [11], designing genetic probes [11], universal PCR primer design [1, 3, 17, 11], and, outside computational biology, in coding theory [4, 5]. Such problems may be considered to be various generalizations of the common substring problem, allowing errors. Many objective functions have been proposed for finding such regions common to every given strings. A popular and most fundamental measure is the Hamming distance. Other measures, like the relative entropy measure used by Stormo and his coauthors [8] may be considered as generalizations of Hamming distance, requires different techniques, and is considered in [13].

Let $s$ and $s'$ be finite strings. Let $d(s,s')$ denote the Hamming distance between $s$ and $s'$. $|s|$ is the length of $s$, $s[i]$ is the $i$-th character of $s$. Thus, $s = s[1]s[2] \ldots s[|s|]$. The following are the problems we study in this paper:

**Closest String:** Given a set $S = \{s_1, s_2, \ldots, s_n\}$ of strings each of length $m$, find a center string $s$ of length $m$ minimizing $d$ such that for every string $s_i \in S$, $d(s,s_i) \leq d$.

**Closest Substring:** Given a set $S = \{s_1, s_2, \ldots, s_n\}$ of strings, and an integer $L$, find a center string $s$ of length $L$ minimizing $d$ such that for each $s_i \in S$ there is a length $L$ substring $t_i$ of $s_i$ with $d(s,t_i) \leq d$.

**Closest String** has been widely and independently studied in different contexts. In the context of coding theory it was shown to be NP-hard [4]. In DNA sequence related topics, [2] gave an exact algorithm when the distance $d$ is a constant. [1, 5] gave near-optimal approximation algorithms only for large $d$ (super-logarithmic in number of sequences); however the straightforward linear programming relaxation technique does not work when $d$ is small because the randomized rounding procedure introduces large errors. This is exactly the reason why [3, 11] analyzed more involved approximation algorithms, and obtained the ratio $\frac{4}{3}$ approximation algorithms. Note that the small $d$ is key in applications such as genetic drug target search where we look for similar regions to which a complementary drug sequence would bind. It is a major open problem [1, 3, 1, 3, 11] to achieve the best approximation ratio for this problem. (Justifications for using Hamming distance can also be found in these references, especially [11].) We present a polynomial approximation scheme (PTAS), settling the problem.

**Closest Substring** is a more general version of the **Closest String** problem. Obviously, it is also NP-hard. In applications such as drug target identification and genetic probes design, the radius $d$ is usually small. Moreover, when the radius $d$ is small, the center
strings can also be used as motifs in repeated-motif methods for multiple sequence alignment problems [7, 11, 16, 18, 21, 22, 23], that repeatedly find motifs and recursively decompose the sequences into shorter sequences. A trivial ratio-2 approximation was given in [11]. We presented the first nontrivial algorithm with approximation ratio $2 - \frac{2}{|\Sigma|+1}$, in [12]. This is a key open problem in search of a potential genetic drug sequence which is “close” to some sequences (of harmful germs) and “far” from some other sequences (of humans). The problem appears to be much more elusive than CLOSEST STRING. We extend the techniques developed for closest string here to design a PTAS for closest substring problem when $d$ is small, i.e., $d \leq O(\log N)$, where $N$ is the input size of the instance. Using a random sampling technique, and combining our methods for CLOSEST STRING, we then design a PTAS for CLOSEST SUBSTRING, for all $d$.

2 Approximating CLOSEST STRING

In this section, we give a PTAS for CLOSEST STRING. We note that a direct application of LP relaxation in [1] does not work when the optimal solution is small. Rather we extend an idea in [11] to do LP relaxation only to a fraction of the bits. Let $S = \{s_1, s_2, \ldots, s_n\}$ be a set of $n$ strings each of length $m$.

The idea is as follows. Let $r$ be a constant. If we choose a subset of $r$ strings from $S$, consider the bits that they all agree. Intuitively, we can replace the corresponding bits in the optimal solution by these bits of the $r$ strings, and this will only slightly worsen the solution. Lemma 1 shows that this is true for at least one subset of $r$ strings. Then all we need to do is to optimize on the positions (bits) where they do not agree, by LP relaxation and randomized rounding.

We first introduce some notations. Let $P = \{j_1, j_2, \ldots, j_k\}$ be a set (multiset) and $1 \leq j_1 \leq j_2 \leq \cdots \leq j_k \leq m$. $P$ is called a position set (multiset). Let $s$ be a string of length $m$, then $s|P$ is the string $s[j_1] s[j_2] \cdots s[j_k]$.

For any $k \geq 2$, let $1 \leq i_1, i_2, \ldots, i_k \leq n$ be $k$ distinct numbers. Let $Q_{i_1, i_2, \ldots, i_k}$ be the set of positions where $s_{i_1}, s_{i_2}, \ldots, s_{i_k}$ agree. Obviously $|Q_{i_1, i_2, \ldots, i_k}| \geq m - kd_{\text{opt}}$. Let $\rho_0 = \max_{1 \leq i, j \leq n} d(s_i, s_j)/d_{\text{opt}}$. The following lemma is the key of our approximation algorithm.

**Lemma 1** If $\rho_0 > 1 + \frac{1}{2r-1}$, then for any constant $r$, there are indices $1 \leq i_1, i_2, \ldots, i_r \leq n$ such that for any $1 \leq l \leq n$,

$$d(s_l|Q_{i_1, i_2, \ldots, i_r}, s_{i_1}|Q_{i_1, i_2, \ldots, i_r}) - d(s_l|Q_{i_1, i_2, \ldots, i_r}, s|Q_{i_1, i_2, \ldots, i_r}) \leq \frac{1}{2r-1}d_{\text{opt}}.$$

**Proof.** Let $p_{i_1, i_2, \ldots, i_k}$ be the number of mismatches between $s_{i_1}$ and $s$ at the positions in $Q_{i_1, i_2, \ldots, i_k}$. Let $\rho_k = \min_{1 \leq i_1, i_2, \ldots, i_k \leq n} p_{i_1, i_2, \ldots, i_k}/d_{\text{opt}}$. First, we prove the following claim.
Claim 2 For any \(k\) such that \(2 \leq k \leq r\), where \(r\) is the constant in the algorithm closest-String, there are indices \(1 \leq i_1, i_2, \ldots, i_r \leq m\) such that for any \(1 \leq l \leq n\).

\[
|\{j \in Q_{i_1,i_2,\ldots,i_r} | s_{i_1}[j] \neq s_l[j] \text{ and } s_{i_1}[j] \neq s[j]\}| \leq (p_k - p_{k+1}) d_{opt}
\]

Proof. Consider indices \(1 \leq i_1, i_2, \ldots, i_k \leq m\) such that \(p_{i_1,i_2,\ldots,i_k} = p_k d_{opt}\). Then for any \(1 \leq i_{k+1}, i_{k+2}, \ldots, i_r \leq m\) and \(1 \leq l \leq n\), we have

\[
|\{j \in Q_{i_1,i_2,\ldots,i_r} | s_{i_1}[j] \neq s_l[j] \text{ and } s_{i_1}[j] \neq s[j]\}| \leq (p_k - p_{k+1}) d_{opt}
\]

where Inequality (1) is from the fact that \(Q_{i_1,i_2,\ldots,i_k} \subseteq Q_{i_1,i_2,\ldots,i_k}\) and Equality (2) is from the fact that \(Q_{i_1,i_2,\ldots,i_k,l} \subseteq Q_{i_1,i_2,\ldots,i_k}\).

Claim 3 \(\min\{\rho_0 - 1, \rho_2 - \rho_3, \rho_3 - \rho_4, \ldots, \rho_r - \rho_{r+1}\} \leq \frac{1}{2r-1}\).

Proof. Consider \(1 \leq i, j \leq n\) such that \(d(s_i, s_j) = \rho_0 d_{opt}\). Then among the positions where \(s_i\) mismatches \(s_j\), for at least one of the two strings, say, \(s_i\), the number of mismatches between \(s_i\) and \(s\) is at least \(\rho_0 d_{opt}/2\). Thus, among the positions where \(s_i\) matches \(s_j\), the number of mismatches between \(s_i\) and \(s\) is at most \((1 - \frac{\rho_0}{2}) d_{opt}\). Therefore, \(\rho_2 \leq 1 - \frac{\rho_0}{2}\). So,

\[
\frac{\frac{1}{2} (\rho_0 - 1) + (\rho_2 - \rho_3) + (\rho_3 - \rho_4) + \cdots + (\rho_r - \rho_{r+1})}{r - 1} \leq \frac{\frac{1}{2} \rho_0 + \rho_2 - \frac{1}{2}}{r - 1} \leq \frac{1}{2r - 1}
\]

Thus, at least one of \(\rho_0 - 1, \rho_2 - \rho_3, \rho_3 - \rho_4, \ldots, \rho_r - \rho_{r+1}\) is less than or equal to \(\frac{1}{2r-1}\).

If \(\rho_0 > 1 + \frac{1}{2r-1}\), then from Claim 3, there must be a \(2 \leq k \leq r\) such that \(\rho_k - \rho_{k+1} \leq \frac{1}{2r-1}\). From Claim 3

\[
|\{j \in Q_{i_1,i_2,\ldots,i_r} | s_{i_1}[j] \neq s_l[j] \text{ and } s_{i_1}[j] \neq s[j]\}| \leq \frac{1}{2r-1} d_{opt}
\]

Hence, there are at most \(\frac{1}{2r-1} d_{opt}\) bits in \(Q_{i_1,i_2,\ldots,i_r}\) where \(s_l\) differs from \(s_{i_1}\) while agrees with \(s\). The lemma is proved.

Lemma 1 hints us to select \(r\) strings \(s_{i-1}, s_{i_2}, \ldots, s_{i_r}\) from \(S\) at a time and use the unique letters at the positions in \(Q_{i_1,i_2,\ldots,i_r}\) as an approximation of the optimal center string \(s\). For the positions in \(P_{i_1,i_2,\ldots,i_r} = \{1, 2, \ldots, L\} - Q_{i_1,i_2,\ldots,i_r}\), we use ideas in Lemma 1, i.e., the following two strategies: (1) if \(|P_{i_1,i_2,\ldots,i_r}|\) is small, i.e., \(d \leq O(\log L)\), we can enumerate \(|\Sigma|^{|P_{i_1,i_2,\ldots,i_r}|}\)
possibilities to approximate \( s \); (2) if \(|P_{t_1,i_2,\ldots,i_r}|\) is large, i.e., \( d > O(\log L) \), we use the LP relaxation to approximate \( s \). The details are found in Lemma \ref{lemma:approximation}. Before presenting our main result, we need the following two lemmas, where Lemma \ref{lemma:approximation} is commonly known as Chernoff’s bounds (\cite{Raz01}, Theorem 4.2 and 4.3):

**Lemma 4** \textsuperscript{[15]} Let \( X_1, X_2, \ldots, X_n \) be \( n \) independent random 0-1 variables, where \( X_i \) takes 1 with probability \( p_i \), \( 0 < p_i < 1 \). Let \( X = \sum_{i=1}^{n} X_i \), and \( \mu = E[X] \). Then for any \( \delta > 0 \),

1. \( \Pr(X > (1 + \delta)\mu) \leq \left[ \frac{\exp(\delta)}{(1 + \delta)^{1 + \frac{\delta}{1 + \mu}}} \right]^\mu \),
2. \( \Pr(X < (1 - \delta)\mu) \leq \exp \left( -\frac{\mu}{\delta^2} \right) \).

From Lemma \ref{lemma:approximation}, we can prove the following lemma:

**Lemma 5** Let \( X_i \), \( X \) and \( \mu \) be defined as in Lemma \ref{lemma:approximation}. Then for any \( 0 < \epsilon \leq 1 \),

1. \( \Pr(X > \mu + \epsilon n) < \exp \left( -\frac{n\epsilon^2}{2} \right) \),
2. \( \Pr(X < \mu - \epsilon n) \leq \exp \left( -\frac{n\epsilon^2}{2} \right) \).

**Proof.** (1) Let \( \delta = \frac{\epsilon n}{\mu} \). By Lemma \ref{lemma:approximation},

\[
\Pr(X > \mu + \epsilon n) < \left[ \frac{\exp(\epsilon n)}{(1 + \frac{\epsilon n}{\mu})(1 + \frac{\epsilon n}{\mu})} \right]^{\mu} \leq \left[ \frac{\exp(\epsilon n)}{(1 + \epsilon)^{1 + \frac{\epsilon}{1 + \mu}}} \right]^{\epsilon n},
\]

where the last inequality is because \( \mu \leq n \) and that \( (1 + x)^{(1+\frac{x}{1+x})} \) is increasing for \( x \geq 0 \). It is easy to verify that for \( 0 < \epsilon \leq 1 \), \( \frac{\epsilon}{(1+\epsilon)^{1+\frac{\epsilon}{1+\epsilon}}} \leq \exp \left( -\frac{\epsilon^2}{4} \right) \). Therefore, (1) is proved.

(2) Let \( \delta = \frac{\epsilon n}{\mu} \). By Lemma \ref{lemma:approximation}, (2) is proved. \( \blacksquare \)

Now, we come back to the approximation of \( s \) at the positions in \( P_{t_1,i_2,\ldots,i_r} \).

**Lemma 6** Let \( S = \{s_1, s_2, \ldots, s_n\} \), where \( |s_i| = m \) for all \( i \). Assume that \( s \) is the optimal solution of CLOSEST STRING and \( \max_{1 \leq i \leq n} d(s_i, s) = d_{opt} \). Given a string \( s' \) and a position set \( Q \) of size \( m - O(d_{opt}) \) such that for any \( i = 1, \ldots, n \)

\[
d(s_i|Q, s'|Q) - d(s_i|Q, s|Q) \leq \rho d_{opt},
\]

where \( 0 \leq \rho \leq 1 \), one can obtain a solution with cost at most \( (1 + \rho + \epsilon)d_{opt} \) in polynomial time for any fixed \( \epsilon \geq 0 \).

**Proof.** Let \( P = \{1, 2, \ldots, m\} - Q \). Then, for any two strings \( x \) and \( x' \) of length \( m \), we have \( d(x|P, x'|P) + d(x|Q, x'|Q) = d(x, x') \). Thus for any \( i = 1, 2, \ldots, n \),

\[
d(s_i|P, s'|P) = d(s_i, s) - d(s_i|Q, s|Q) \leq (1 + \rho) d_{opt} - d(s_i|Q, s'|Q).
\]
Therefore, the following optimization problem

\[
\begin{align*}
\min & \ d; \\
\text{s.t.} & \ d(s_i|p, x) \leq d - d(s_i|Q, s'|Q), \ i = 1, \ldots, n; |x| = |P|,
\end{align*}
\]  

has a solution with cost \(d \leq (1 + \rho)d_{\text{opt}}\). Suppose that the optimization problem has an optimal solution \(x\) such that \(d = d_0\). Then

\[
d_0 \leq (1 + \rho)d_{\text{opt}}.
\]  

Now we solve (4) approximately. Similar to \([1, 11]\), we use a 0-1 variable \(a\) for \(d\) to indicate whether \(x[j] = a\). Denote \(\chi(s_i[j], a) = 0\) if \(s_i[j] = a\) and 1 if \(s_i[j] \neq a\). Then (4) can be rewritten as a 0-1 optimization problem as follows:

\[
\begin{align*}
\min & \ d; \\
\text{s.t.} & \ \sum_{a \in \Sigma} x_{j,a} = 1, \ j = 1, 2, \ldots, |P|, \\
& \sum_{i} \sum_{a \in \Sigma} \chi(s_i[j], a) x_{j,a} \leq d - d(s_i|Q, s'|Q), \ i = 1, 2, \ldots, n.
\end{align*}
\]  

Solve (4) by linear programming to get a fractional solution \(\tilde{x}_{j,a}\) with cost \(\bar{d}\). Clearly \(\bar{d} \leq d_0\). Independently for each \(0 \leq j \leq |P|\), with probability \(\tilde{x}_{j,a}\), set \(x_{j,a} = 1\) and \(x_{j,a'} = 0\) for any \(a' \neq a\). Then we get a solution \(x_{j,a}\) for the 0-1 optimization problem, hence a solution \(x\) for (4). It is easy to see that \(\sum_{a \in \Sigma} \chi(s_i[j], a) x_{j,a}\) takes 1 or 0 randomly and independently for different \(j\)'s. Thus \(d(s_i|p, x) = \sum_{1 \leq j \leq |P|} \sum_{a \in \Sigma} \chi(s_i[j], a) x_{j,a}\) is a sum of \(|P|\) independent 0-1 random variables, and

\[
E[d(s_i|p, x)] = \sum_{1 \leq j \leq |P|} \sum_{a \in \Sigma} \chi(s_i[j], a) E[x_{j,a}]
\]

\[
= \sum_{1 \leq j \leq |P|} \sum_{a \in \Sigma} \chi(s_i[j], a) \tilde{x}_{j,a}
\]

\[
\leq \bar{d} - d(s_i|Q, s'|Q) \leq d_0 - d(s_i|Q, s'|Q).
\]  

Therefore, for any fixed \(\epsilon' > 0\), by Lemma 3

\[
\Pr \ (d(s_i|p, x) \geq d_0 + \epsilon'|P| - d(s_i|Q, s'|Q)) \leq \exp \left( -\frac{1}{3} \epsilon'^2 |P| \right).
\]  

Considering all sequences, we have

\[
\Pr \ (d(s_i|p, x) \geq d_0 + \epsilon'|P| - d(s_i|Q, s'|Q) \text{ for at least one } i) \leq n \times \exp \left( -\frac{1}{3} \epsilon'^2 |P| \right).
\]  

If \(|P| \geq (4 \ln n)/\epsilon'^2\), then \(n \times \exp \left( -\frac{1}{3} \epsilon'^2 |P| \right) \leq n^{-\frac{1}{4}}\). Thus we obtain a randomized algorithm to find a solution for (4) with cost at most \(d_0 + \epsilon'|P|\) with probability at least \(1 - n^{-\frac{1}{4}}\). The above randomized algorithm can be derandomized by standard method of conditional probabilities [15].

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If \( |P| < (4 \ln n)/\epsilon^2 \), \( |\Sigma|^{|P|} < n^{(4 \ln |\Sigma|)/\epsilon^2} \) is a polynomial of \( n \). So, we can enumerate all strings in \( \Sigma^{|P|} \) to find an optimal solution for (3). Thus, in both cases, we can obtain a solution \( x \) for the optimization problem (3) with cost at most \( d_0 + \epsilon' |P| \) in polynomial time. Since \( |P| = O(d_{opt}) \), \( |P| \leq c \times d_{opt} \) for a constant \( c \). Let \( \epsilon' = \frac{\epsilon}{c} \) and \( s^* = R(s', x, P) \). From Formula (4),

\[
\begin{align*}
    d(s_i, s^*) &= d(s_i|_P, s^*|_P) + d(s_i|_Q, s^*|_Q) \\
               &= d(s_i|_P, x) + d(s_i|_Q, s'|_Q) \\
               &\leq d_0 + \epsilon' |P| \leq (1 + \rho) d_{opt} + \epsilon d_{opt},
\end{align*}
\]

where the last inequality is from Formula (5). This proves the lemma. \( \square \)

Now we describe the complete algorithm in Figure 1.

---

**Algorithm closestString**

**Input** \( s_1, s_2, \ldots, s_n \in \Sigma^m \).

**Output** a center string \( s \in \Sigma^m \).

1. **for** each \( r \)-element subset \( \{s_{i_1}, s_{i_2}, \ldots, s_{i_r}\} \) of the \( n \) input strings **do**
   (a) \( Q = \{1 \leq j \leq m \mid s_{i_1}[j] = s_{i_2}[j] = \ldots = s_{i_r}[j]\} \), \( P = \{1, 2, \ldots, m\} - Q \).
   (b) Solve the optimization problem defined by Formula (4) as described in the proof of Lemma 3 to get an approximate solution \( x \) of length \( |P| \).
   (c) Let \( s' \) be a string such that \( s'|_Q = s_{i_1}|_Q \) and \( s'|_P = x \). Calculate the cost of \( s' \) as the center string.
2. **for** \( i = 1, 2, \ldots, n \) **do**
   calculate the cost of \( s_i \) as the center string.
3. **Output** the best solution of the above two steps.

---

**Figure 1**: Algorithm for Closest String

**Theorem 7** The algorithm closestString is a PTAS for Closest String.

**Proof.** Given an instance of Closest String, suppose \( s \) is an optimal solution and the optimal cost is \( d_{opt} \), i.e. \( d(s, s_i) \leq d_{opt} \) for all \( i \). Let \( P \) be defined as step 1(a) of Algorithm closestString. Since for every position in \( P \), at least one of the \( r \) strings \( s_{i_1}, s_{i_2}, \ldots, s_{i_r} \) conflict the optimal center string \( s \), so we have \( |P| \leq r \times d_{opt} \). As far as \( r \) is a constant, step 1(b) can be done in polynomial time by Lemma 3. Obviously the other steps of Algorithm closestString runs in polynomial time, with \( r \) as a constant.
If $\rho_0 - 1 \leq \frac{1}{2r-1}$, then by the definition of $\rho_0$, it is easy to see that the algorithm finds a solution with cost at most $\rho_0 d_{\text{opt}} \leq (1 + \frac{1}{2r-1}) d_{\text{opt}}$ in step 2.

If $\rho_0 > 1 + \frac{1}{2r-1}$, then from Lemma 1 and Lemma 2, the algorithm finds a solution with cost at most $(1 + \frac{1}{2r-1} + \epsilon) d_{\text{opt}}$. This proves the theorem.  

3 Approximating Closest Substring when $d$ is small

In some applications such as drug target identification, genetic probe design, the radius $d$ is often small. As a direct application of Lemma 1, we now present a PTAS for Closest String when the radius $d$ is small, i.e., $d < O(\log N)$, where $N$ stands for the input size of the instance. Again, we focus on the construction of the center string. The basic idea is to choose $r$ substrings $t_{i_1}, t_{i_2}, \ldots, t_{i_r}$ of length $L$ from the strings in $S$, keep the letters at the positions where $t_{i_1}, t_{i_2}, \ldots, t_{i_r}$ all agree, and try all possibilities for the rest of the positions. The complete algorithm is described in Figure 2:

![Algorithm](image)

**Theorem 8** Algorithm smallSubstring is a PTAS for Closest Substring when the radius $d$ is small, i.e., $d \leq O(\log N)$, where $N$ is the input size.

**Proof.** Obviously, the size of $P$ in Step 1 is at most $O(r \times \log N)$. Step 1 takes $O((mn)^r \times \Sigma^{O(r \times \log N)} \times mnL) = O(N^{r+1} \times N^{O(r \times \log |\Sigma|)}) = O(N^{O(r \times \log |\Sigma|)})$ time. Other steps take less than that time. Thus, the total time required is $O(N^{O(r \times \log |\Sigma|)})$, which is polynomial in term of input size for any constant $r$.  

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From Lemma 1, the performance ratio of the algorithm is $1 + \frac{1}{2r-1}$.

\section{A PTAS For Closest Substring}

In this section, we further extend the algorithms for Closest String to a PTAS for Closest Substring, making use of a random sampling strategy. Note that Algorithm smallSubstring runs in exponential time for general radius $d$. And Algorithm closestString does not work for Closest Substring since we do not know how to construct an optimal problem similar to (4) — The construction of (4) requires us to know all the $n$ strings (substrings) in an optimal solution of Closest String (Closest Substring). It is easy to see that the choice of a “good” substring from every string $s_i$ is the only obstacle on the way to the solution. We use random sampling to handle this.

Now let us outline the main ideas. Let $\langle S = \{s_1, s_2, \ldots, s_n\}, L \rangle$ be an instance of Closest Substring, where $s_i$ is of length $m$. Suppose that $s$ is its optimal center string and $t_i$ is a length $L$ substring of $s_i$ which is the closest to $s$ ($i = 1, 2, \ldots, n$). Let $d_{opt} = \max_{i=1}^{n} d(s, t_i)$. By trying all possibilities, we can assume that $t_{i_1}, t_{i_2}, \ldots, t_{i_r}$ are the $r$ substrings $t_{ij}$ that satisfy Lemma 1 by replacing $s_i$ by $t_i$ and $s_{ij}$ by $t_{ij}$. Let $Q$ be the set of positions where $t_{i_1}, t_{i_2}, \ldots, t_{i_r}$ agree and $P = \{1, 2, \ldots, L\} - Q$. By Lemma 1, $t_{i_1}|Q$ is a good approximation to $s|Q$. We want to approximate $s|P$ by the solution $x$ of the following optimization problem (8), where $t'_i$ is a substring of $s_i$ and is up to us to choose.

$$\begin{align*}
\min & \; d; \\
& \; d(t'_i|P, x) \leq d - d(t'_i|Q, t_{i_1}|Q), \; i = 1, \ldots, n; |x| = |P|.
\end{align*}$$

(8)

The ideal choice is $t'_i = t_i$, i.e., $t'_i$ is the closest to $s$ among all substrings of $s_i$. However, we only approximately know $s$ in $Q$ and know nothing about $s$ in $P$ so far. So, we randomly pick $O(\log(mn))$ positions from $P$. Suppose the multiset of these random positions is $R$. By trying all possibilities, we can assume that we know $s$ at these $|R|$ positions. We then find the substring $t'_i$ from $s$ such that $d(s|R, t'_i|R) \times \frac{|P|}{|R|} + d(t_{i_1}|Q, t'_i|Q)$ is minimized. Then $t'_i$ potentially belongs to the substrings which are the closest to $s$.

Then we solve (8) approximately by the method provided in the proof of Lemma 9 and combine the solution $x$ at $P$ and $t_{i_1}$ at $Q$, the resulting string should be a good approximation to $s$. The detailed algorithm (Algorithm closestSubstring) is given in Figure 3. We prove Theorem 9 in the rest of the section.

**Theorem 9** Algorithm closestSubstring is a PTAS for the closest substring problem.

**Proof.** Let $s$ be an optimal center string and $t_i$ be the length-$L$ substring of $s_i$ that is the closest to $s$. Let $d_{opt} = \max d(s, t_i)$. Let $\epsilon$ be any small positive number and $r \geq 2$ be
Algorithm closestSubstring

Input  \( n \) sequences \( \{s_1, s_2, \ldots, s_n\} \subseteq \Sigma^m \), integer \( L \).
Output  the center string \( s \).

1. for every \( r \) length-\( L \) substrings \( t_{i_1}, t_{i_2}, \ldots, t_{i_r} \) (allowing repeats, but if \( t_{i_j} \) and \( t_{i_k} \) are both chosen from the same \( s_i \) then \( t_{i_j} = t_{i_k} \)) of \( s_1, \ldots, s_n \) do
   (a) \( Q = \{1 \leq j \leq L \mid t_{i_1}[j] = t_{i_2}[j] = \ldots = t_{i_r}[j]\} \), \( P = \{1, 2, \ldots, L\} - Q \).
   (b) Let \( R \) be a multiset containing \( \lceil \frac{1}{2r} \log(nm) \rceil \) uniformly random positions from \( P \).
   (c) for every string \( y \) of length \( |R| \) do
      (i) for \( i \) from 1 to \( n \) do
          Let \( t'_i \) be a length-\( L \) substring of \( s_i \) minimizing \( d(y, t'_i|_R) \times \frac{|P|}{|R|} + d(t_{i_1}|_Q, t'_i|_Q) \).
      (ii) Using the method provided in the proof of Lemma 3, solve the optimization problem defined by Formula (5) approximately. Let \( x \) be the approximate solution within error \( \epsilon |P| \).
      (iii) Let \( s' \) be the string such that \( s'|_P = x \) and \( s'|_Q = t_{i_1}|_Q \). Let \( c = \max_{i=1}^n \min \{t_i \text{ is a substring of } s_i\} d(s', t_i) \).
   2. for every length-\( L \) substring \( s' \) of \( s_1 \) do
      Let \( c = \max_{i=1}^n \min \{t_i \text{ is a substring of } s_i\} d(s', t_i) \).
   3. Output the \( s' \) with minimum \( c \) in step 1(c)(iii) and step 2.

Figure 3: The PTAS for the closest substring problem.

For any fixed integer. Let \( \rho_0 = \max_{1 \leq i, j \leq n} d(t_i, t_j)/d_{\text{opt}} \). If \( \rho_0 \leq 1 + \frac{1}{2r-1} \), then clearly we can find a solution \( s' \) within ratio \( \rho_0 \) in step 2. So, we assume that \( \rho_0 \geq 1 + \frac{1}{2r-1} \) from now on.

By Lemma 5, Algorithm closestSubstring picks a group of \( t_{i_1}, t_{i_2}, \ldots, t_{i_r} \) in step 1 at some point such that

**Fact 1** For any \( 1 \leq l \leq n \), \(|\{j \in Q \mid t_{i_1}[j] \neq t_{i_2}[j] \text{ and } t_{i_1}[j] \neq s[j]\} \) \( \leq \frac{1}{2r-1} d_{\text{opt}} \).

Obviously, the algorithm takes \( y \) as \( s|R \) for at some point in step 1(c). Let \( y = s|R \) and \( t_{i_1}, t_{i_2}, \ldots, t_{i_r} \) satisfy Fact 1. Let \( t'_i \) be defined as in step 1(c)(i). Let \( s^* \) be a string such that \( s^*|_P = s|_P \) and \( s^*|_Q = t_{i_1}|_Q \). Then we claim:

**Fact 2** With high probability, \( d(s^*, t'_i) \leq d(s^*, t_i) + 2\epsilon |P| \) for all \( 1 \leq i \leq n \).

**Proof.** For convenience, for any position multiset \( T \), we denote \( d^T(t_1, t_2) = d(t_1|_T, t_2|_T) \) for any two strings \( t_1 \) and \( t_2 \). Let \( \rho = \frac{|P|}{|R|} \). Consider any length-\( L \) substring \( t' \) of \( s_i \) satisfying

\[
\sum_{i=1}^n \min_{t_i \text{ is a substring of } s_i} d(s^*, t'_i) \geq d(s^*, t_i) + 2\epsilon |P|.
\]
It is easy to see that \( \rho d^R(s^*, t') + d^Q(t_{i_1}, t') \leq \rho d^R(s^*, t_i) + d^Q(t_{i_1}, t_i) \) implies either \( \rho d^R(s^*, t') + d^Q(s^*, t') \leq d(s^*, t') - \epsilon|P| \) or \( \rho d^R(s^*, t_i) + d^Q(s^*, t_i) \geq d(s^*, t_i) + \epsilon|P| \). Thus, we have the following inequality:

\[
\Pr \left( \rho d^R(s^*, t'_i) + d^Q(t_{i_1}, t') \leq \rho d^R(s^*, t_i) + d^Q(t_{i_1}, t_i) \right) \\
\leq \Pr \left( \rho d^R(s^*, t') + d^Q(s^*, t') \leq d(s^*, t') - \epsilon|P| \right) + \\
\Pr \left( \rho d^R(s^*, t_i) + d^Q(s^*, t_i) \geq d(s^*, t_i) + \epsilon|P| \right). 
\]  

(10)

It is easy to see that \( d^R(s^*, t') \) is the sum of \( |R| \) independent random 0-1 variables \( \sum_{i=1}^{|R|} X_i \), where \( X_i = 1 \) indicates a mismatch between \( s^* \) and \( t' \) at the \( i \)-th position in \( R \). Let \( \mu = E[d^R(s^*, t')] \). Obviously, \( \mu = d^P(s^*, t')/\rho \). Therefore, by Lemma 3 (2),

\[
\Pr \left( \rho d^R(s^*, t') + d^Q(s^*, t') \leq d(s^*, t') - \epsilon|P| \right) \\
= \Pr \left( d^R(s^*, t') \leq (d(s^*, t') - d^Q(s^*, t'))/\rho - \epsilon|R| \right) \\
= \Pr \left( d^R(s^*, t') \leq d^P(s^*, t')/\rho - \epsilon|R| \right) \\
= \Pr \left( d^R(s^*, t') \leq \mu - \epsilon|R| \right) \leq \exp \left( -\frac{1}{2} \epsilon^2 |R| \right) \leq (nm)^{-2},
\]

(11)

where the last inequality is due to the setting \( |R| = \lceil \frac{1}{\epsilon^2} \log(nm) \rceil \) in step 1(b) of the algorithm. Similarly, using Lemma 3 (1) we have

\[
\Pr \left( \rho d^R(s^*, t_i) + d^Q(s^*, t_i) \geq d(s^*, t_i) + \epsilon|P| \right) \leq (nm)^{-\frac{4}{3}}.
\]

(12)

Combining Formula (10), (11), (12), we know that for any \( t' \) that satisfies Formula (3),

\[
\Pr \left( \rho d^R(s^*, t') + d^Q(t_{i_1}, t') \leq \rho d^R(s^*, t_i) + d^Q(t_{i_1}, t_i) \right) \leq 2(nm)^{-\frac{4}{3}}.
\]

(13)

For any fixed \( 1 \leq i \leq n \), there are less than \( m \) substrings \( t' \) that satisfies Formula (3). Thus, from Formula (13) and the definition of \( t'_i \),

\[
\Pr \left( d(s^*, t'_i) \geq d(s^*, t_i) + 2\epsilon|P| \right) \leq 2n^{-\frac{4}{3}}m^{-\frac{4}{3}}.
\]

(14)

Summing up all \( i \in [1, n] \), we know that with probability at least \( 1 - 2 (nm)^{-\frac{4}{3}} \), \( d(s^*, t'_i) \leq d(s^*, t_i) + 2\epsilon|P| \) for all \( i \).

From Fact 1, \( d(s^*, t_i) = d^P(s, t_i) + d^Q(t_{i_1}, t_i) \leq d(s, t_i) + \frac{1}{2r-1}d_{opt} \). Combining with Fact 2 and \( |P| \leq r d_{opt} \), we get

\[
d(s^*, t'_i) \leq (1 + \frac{1}{2r-1} + 2\epsilon r)d_{opt}.
\]

(15)

By the definition of \( s^* \), the optimization problem defined by Formula (3) has a solution \( s|P \) such that \( d \leq (1 + \frac{1}{2r-1} + 2\epsilon r)d_{opt} \). We can solve the optimization problem within error
\[ \epsilon|P| \] by the method in the proof of Lemma 6. Let \( x \) be the solution of the optimization problem. Then by Formula (8), for any \( 1 \leq i \leq n \),

\[
    d(t_i'|P, x) \leq (1 + \frac{1}{2r - 1} + 2\epsilon r)\text{d}_{\text{opt}} - d(t_i'|Q, t_i|Q) + \epsilon|P|.
\]

(16)

Let \( s' \) be defined in step 1(c)(iii), then by Formula (16),

\[
    d(s', t_i') = d(x, t_i'|P) + d(t_i|Q, t_i'|Q)
    \leq (1 + \frac{1}{2r - 1} + 2\epsilon r)\text{d}_{\text{opt}} + \epsilon|P|
    \leq (1 + \frac{1}{2r - 1} + 3\epsilon r)\text{d}_{\text{opt}}.
\]

It is easy to see that the algorithm runs in polynomial time for any fixed positive \( r \) and \( \epsilon \). For any \( \delta > 0 \), by properly setting \( r \) and \( \epsilon \) such that \( \frac{1}{2r - 1} + 3\epsilon r \leq \delta \), with high probability, the algorithm outputs in polynomial time a solution \( s' \) such that \( d(t_i', s') \) is no more than \( (1 + \delta)d_{\text{opt}} \) for every \( 1 \leq i \leq n \), where \( t_i' \) is a substring of \( s_i \). The algorithm can be derandomized by standard methods [15].

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