Beyond the Longest Letter-Duplicated Subsequence Problem

Wenfeng Lai ⊠

College of Computer Science and Technology, Shandong University, Qingdao, China

Adiesha Liyanage ☑

Gianforte School of Computing, Montana State University, Bozeman, MT, USA

Binhai Zhu ☑ 😭

Gianforte School of Computing, Montana State University, Bozeman, MT, USA

Peng Zou ⊠

Gianforte School of Computing, Montana State University, Bozeman, MT, USA

Abstract

Motivated by computing duplication patterns in sequences, a new fundamental problem called the longest letter-duplicated subsequence (LLDS) is proposed. Given a sequence S of length n, a letter-duplicated subsequence is a subsequence of S in the form of $x_1^{d_1} x_2^{d_2} \cdots x_k^{d_k}$ with $x_i \in \Sigma$, $x_j \neq x_{j+1}$ and $d_i \geq 2$ for all i in [k] and j in [k-1]. A linear time algorithm for computing the longest letter-duplicated subsequence (LLDS) of S can be easily obtained. In this paper, we focus on two variants of this problem. We first consider the constrained version when Σ is unbounded, each letter appears in S at least 6 times and all the letters in Σ must appear in the solution. We show that the problem is NP-hard (a further twist indicates that the problem does not admit any polynomial time approximation). The reduction is from possibly the simplest version of SAT that is NP-complete, ($\leq 2, 1, \leq 3$)-SAT, where each variable appears at most twice positively and exact once negatively, and each clause contains at most three literals and some clauses must contain exactly two literals. (We hope that this technique will serve as a general tool to help us proving the NP-hardness for some more tricky sequence problems involving only one sequence – much harder than with at least two input sequences, which we apply successfully at the end of the paper on some extra variations of the LLDS problem.) We then show that when each letter appears in S at most 3 times, then the problem admits a factor $1.5 - O(\frac{1}{n})$ approximation. Finally, we consider the weighted version, where the weight of a block $x_i^{d_i}(d_i \geq 2)$ could be any positive function which might not grow with d_i . We give a non-trivial $O(n^2)$ time dynamic programming algorithm for this version, i.e., computing an LD-subsequence of S whose weight is maximized.

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1 Introduction

In biology, duplication is an important part of evolution. There are two kinds of duplications: arbitrary segmental duplications (i.e., select a segment and paste it somewhere else) and tandem duplications (which is in the form of $X \to XX$, where X is any segment of the input sequence). It is known that the former duplications occur frequently in cancer genomes [16, 12, 3]. On the other hand, the latter are common under different scenarios, for

example, it is known that the tandem duplication of 3 nucleotides CAG is closely related to the Huntington disease [11]. In addition, tandem duplications can occur at the genome level (acrossing different genes) for certain types of cancer [13]. In fact, as early as in 1980, Szostak and Wu provided evidence that gene duplication is the main driving force behind evolution, and the majority of duplications are tandem [17]. Consequently, it was not a surprise that in the first sequenced human genome around 3% of the genetic contents are in the form of tandem repeats [9].

Independently, tandem duplications were also studied in *copying systems* [5]; as well as in formal languages [1, 4, 19]. In 2004, Leupold et al. posed a fundamental question regarding tandem duplications: what is the complexity to compute the minimum tandem duplication distance between two sequences A and B (i.e., the minimum number of tandem duplications to convert A to B). In 2020, Lafond et al. answered this open question by proving that this problem is NP-hard for an unbounded alphabet [7]. In fact, Lafond et al. proved later that the problem is NP-hard even if $|\Sigma| \ge 4$ by encoding each letter in the unbounded alphabet proof with a square-free string over a new alphabet of size 4 (modified from Leech's construction [10]), which covers the case most relevant with biology, i.e., when $\Sigma = \{A, C, G, T\}$ [8]. Independently, Cicalese and Pilati showed that the problem is NP-hard for $|\Sigma| = 5$ using a different encoding method [2].

Motivated by the above applications (especially when some mutations occur after the duplications), some new problems related to duplications are proposed and studied in this paper. Given a sequence S of length n, a letter-duplicated subsequence (LDS) of S is a subsequence of S in the form $x_1^{d_1}x_2^{d_2}\cdots x_k^{d_k}$ with $x_i\in \Sigma$, where $x_j\neq x_{j+1}$ and $d_i\geq 2$ for all i in [k] and j in [k-1]. (Each $x_i^{d_i}$ is called an LD-block.) Naturally, the problem of computing the longest letter-duplicated subsequence (LLDS) of S can be defined, and a simple linear time algorithm can be obtained. (We remark that recently a similar problem called longest run subsequence was studied [15], it differs from our problem in that each letter appears consecutively at most once in the solution and does not have to be repeated, and the goal is the same, i.e., the length of the subsequece is to be maximized.)

In this paper, we focus on some important variants around the LLDS problem, focusing on the constrained and weighted cases. The constraint is to demand that all letters in Σ appear in a resulting LDS, which simulates that in a genome with duplicated genes, how to compute the maximum duplicated pattern while including all the genes. Then we have two problems: feasibility testing (FT for short, which decides whether an LDS of S containing all letters in Σ exists) and the problem of maximizing the length of a resulting LDS where all letters in the alphabet appear, which we call LLDS+. It turns out that the status of these two problems change quite a bit when d, the maximum number a letter can appear in S, varies. We denote the corresponding problems as FT(d) and LLDS+(d) respectively. Let |S| = n, we summarize our main results in this paper as follows:

- 1. We show that when $d \ge 6$, both FT(d) and (the decision version of) LLDS+(d) are NP-complete, which implies that LLDS+(d) does not have a polynomial-time approximation algorithm when $d \ge 6$.
- 2. We show that when d=3, FT(d) is decidable in $O(n^2)$ time, which implies that LLDS+(3) admits a factor-1.5 approximation. With an increasing running time, we could improve the factor to $1.5 O(\frac{1}{n})$.
- 3. When a weight of an LD-block is any positive function (i.e., it does not even have to grow with its length), we present a non-trivial $O(n^2)$ time dynamic programming solution for this Weighted-LDS problem.

Note that the parameter d, i.e., the maximum duplication number, is of practical interest in bioinformatics, since in many genomes duplication is a rare event and the number of duplicates is usually a small constant. For example, it is known that plants have undergone up to three rounds of whole genome duplications, resulting in a number of duplicates bounded by 8 [20].

At the end of paper, we will briefly mention two extra variations of the LLDS problem, where in the solution, i.e., a subsequence of S in the form of $x_1^{d_1} x_2^{d_2} \cdots x_k^{d_k}$, each x_i is either a substring or a subsequence of S. The latter is remotely related to computing the longest square subsequence of an input sequence S, for which Kosowski gave an $O(n^2)$ time algorithm [6]. Then, what Kosowski considered is the more restricted version of the latter, i.e., $x_1^{d_1} x_2^{d_1}$, with $x_1 = x_2$ and $d_1 = d_2 = 1$.

This paper is organized as follows. In Section 2 we give necessary definitions. In Section 3 we focus on showing that the LLDS+ and FT problems are NP-complete when $d \geq 6$ and some positive results when d = 3. In Section 4 we give polynomial-time algorithms for Weighted-LDS. We conclude the paper in Section 5.

2 Preliminaries

Let \mathbb{N} be the set of natural numbers. For $q \in \mathbb{N}$, we use [q] to represent the set $\{1, 2, ..., q\}$. Throughout this paper, a sequence S is over a finite alphabet Σ . We use S[i] to denote the i-th letter in S and S[i...j] to denote the substring of S starting and ending with indices i and j respectively. (Sometimes we also use (S[i], S[j]) as an interval representing the substring S[i...j].) With the standard run-length representation, S can be represented as $y_1^{a_1}y_2^{a_2}\cdots y_q^{a_q}$, with $y_i \in \Sigma, y_j \neq y_{j+1}$ and $a_j \geq 1$, for $i \in [q], j \in [q-1]$. If a letter x appears multiple times in S, we could use $x^{(i)}$ to denote the i-th copy of it (reading from left to right). Finally, a subsequence of S is a string obtained by deleting some letters in S.

2.1 The LLDS Problem

A subsequence S' of S is a letter-duplicated subsequence (LDS) of S if it is in the form of $x_1^{d_1}x_2^{d_2}\cdots x_k^{d_k}$, with $x_i\in \Sigma, x_j\neq x_{j+1}$ and $d_i\geq 2$, for $i\in [k], j\in [k-1]$. We call each $x_i^{d_i}$ in S' a letter-duplicated block (LD-block, for short). For instance, let S=abcacabcb, then $S_1=aaabb, S_2=ccbb$ and $S_3=ccc$ are all letter-duplicated subsequences of S, where aaa and bb in S_1 , cc and bb in S_2 , and ccc in S_3 all form the corresponding LD-blocks. Certainly, we are interested in the longest ones – which gives us the longest letter-duplicated subsequence (LLDS) problem.

As a warm-up, we solve this problem by dynamic programming. We first have the following observation.

- ▶ **Observation 1.** Suppose that there is an optimal LLDS solution for a given sequence S of length n, in the form of $x_1^{d_1}x_2^{d_2}\dots x_k^{d_k}$. Then it is possible to decompose it into a generalized LD-subsequence $y_1^{e_1}y_2^{e_2}\dots y_p^{e_p}$, where
- $2 \le e_i \le 3, for i \in [p],$
- $p \geq k$
- y_j does not have to be different from y_{j+1} , for $j \in [p-1]$.

The proof is straightforward: For any natural number $\ell \geq 2$, we can decompose it as $\ell = \ell_1 + \ell_2 + \ldots + \ell_z \geq 3$, such that $2 \leq \ell_j \leq 3$ for $1 \leq j \leq z$. Consequently, for every $d_i > 3$, we could decompose it into a sum of 2's and 3's. Then, clearly, given a generalized LD-subsequence, we could easily obtain the corresponding LD-subsequence by combining $y_i^{e_i} y_{i+1}^{e_{i+1}}$ when $y_i = y_{i+1}$.

We now design a dynamic programming algorithm for LLDS. Let L(i) be the length of the optimal LLDS solution for S[1..i]. The recurrence for L(i) is as follows.

$$\begin{split} L(0) &= 0, \\ L(1) &= 0, \\ L(i) &= \max \begin{cases} L(i-x-1) + 2 & x = \min\{x|S[i-x] = S[i]\}, x \in (0,i-1] \\ L(i-x) + 1 & x = \min\{x|S[i-x] = S[i]\}, x \in (0,i-1] \\ L(i-1) & \text{otherwise.} \end{cases} \end{split}$$

Note that the step involving L(i-x)+1 is essentially a way to handle a generalized LD-subsequence of length 3 (by keeping S[i-x] for the next level computation) and cannot be omitted following the above observation. For instance, if S=dabcdd then without that step we would miss the optimal solution ddd.

The value of the optimal LLDS solution for S can be found in L(n). For the running time, for each S[x] we just need to scan S to find the closest S[i] such that S[x] = S[i]. With this information, the table L can be filled in linear time. With a simple augmentation, the actual sequence corresponding to L(n) can also be found in linear time. Hence LLDS can be solved in O(n) time.

2.2 The Variants of LLDS

In this paper, we focus on the following variations of the LLDS problem.

▶ **Definition 2** (Constrained Longest Letter-Duplicated Subsequence (*LLDS*+ for short)).

Input: A sequence S with length n over an alphabet Σ and an integer ℓ .

Question: Does S contain a letter-duplicated subsequence S' with length at least ℓ such that all letters in Σ appear in S'?

▶ **Definition 3** (Feasibility Testing (FT for short)).

Input: A sequence S with length n over an alphabet Σ .

Question: Does S contain a letter-duplicated subsequence S'' such that all letters in Σ appear in S''?

For LLDS+ we are really interested in the optimization version, i.e., to maximize ℓ . Note that, though looking similar, FT and the decision version of LLDS+ are different: if there is no feasible solution for FT, certainly there is no solution for LLDS+; but even if there is a feasible solution for FT, computing an optimal solution for LLDS+ could still be non-trivial.

Finally, let d be the maximum number of times a letter in Σ appears in S. Then, we can represent the corresponding versions for LLDS+ and FT as LLDS+(d) and FT(d) respectively.

It turns out that (the decision version of) LLDS+(d) and FT(d) are both NP-complete when $d\geq 6$, while when d=3 the status varies: FT(3) can be decided in $O(n^2)$ time, which immediately implies that LLDS+(3) has a factor-1.5 approximation. (If we are willing to increase the running time – still polynomial but higher than $O(n^2)$, with some simple twist we could improve the approximation factor for LLDS+(3) to $1.5-O(\frac{1}{n})$.) We present the details in the next section. In Section 4, we will consider an extra version of LLDS, Weighted-LDS, where the weight of an LD-block is an arbitrary positive function.

3 Hardness with the full-appearance constraint

3.1 Hardness for LLDS+(d) and FT(d) when $d \ge 6$

We first try to prove the NP-completeness of the (decision version of) LLDS+(d), when $d \ge 6$. In fact, we need a very special version of SAT, which is possibly the simplest version of SAT remaining NP-complete.

Given a 3SAT formula ϕ , which is a conjunction of m disjunctive clauses (over n variable x_i 's), each clause F_j containing exactly 3 literals (i.e., in the form of x_i or \bar{x}_i), the problem is to find whether there is a satisfiable truth assignment for ϕ .

- ▶ **Definition 4.** ($\leq 2, 1, \leq 3$)-SAT: this is a special case of SAT where each variable x_i appears at most twice and \bar{x}_i appears exactly once in ϕ ; moreover, each clause contains either two or three literals (which will be called 2-clause and 3-clause henceforth).
- ▶ Lemma 5. $(\leq 2, 1, \leq 3)$ -SAT is NP-complete.

Proof. We modify the proof by Tovey [18]. Given a 3SAT formula ϕ , without loss of generality, assume that each variable x_i and its complement \bar{x}_i appears in (different clauses of) ϕ . We convert ϕ to ϕ' in the form of ($\leq 2, 1 \leq 3$)-SAT as follows.

- \blacksquare if both x_i and \bar{x}_i appears once in ϕ , do nothing.
- \blacksquare if x_i appears twice and \bar{x}_i appears once in ϕ , do nothing.
- if \bar{x}_i appears twice and x_i appears once in ϕ , replace \bar{x}_i with a new variable z and replace x_i by \bar{z} .
- Otherwise, if the total number of literals of x_i (i.e., x_i and \bar{x}_i) is $k \geq 4$ then introduce k variables $y_{i,1}, y_{i,2}, \dots, y_{i,k}$ replacing the k literals of x_i respectively. Moreover, let $z_{i,j}$ be $y_{i,j}$ if the j-th literal of x_i is \bar{x}_i . Finally, add k 2-clauses as $(z_{i,j} \vee \bar{z}_{i,j+1})$ for j = 1..k 1 and $(z_{i,k} \vee \bar{z}_{i,1})$. (Note that it always holds that $\bar{z} = z$.)

Following [18], when $k \geq 4$, the 2-clauses added will force all $z_{i,j}$'s to have all True values or all False values. (The only difference between our construction and Tovey's is that all literals appearing at least 4 times in the original clauses in ϕ are replaced by positive variables in the form of $y_{i,j}$'s; the negated literal $\bar{y}_{i,j}$ could only occur in the newly created 2-clauses – exactly once for each $y_{i,j}$. On the other hand, each $y_{i,j}$ occur twice – once in the original 3-clauses of ϕ and once in the newly created 2-clauses.) It is obvious to see that ϕ is satisfiable if and only if ϕ' is satisfiable. The transformation obviously takes $O(|\phi|)$ time. Hence the lemma is proven.

We remark that ($\leq 2, 1 \leq 3$)-SAT, while seemingly similar to SAT3W (each clause has at most 3 literals and each clause has at most one negated variable [14]), is in fact different from it. (Following the Dichotomy Theorem for SAT by Schaefer [14], SAT3W is in P.) The difference is that in ϕ' we could even have a clause containing 3 negated variables.

Now let ϕ be an instance of $(\leq 2, 1, \leq 3)$ -SAT where either both x_i and \bar{x}_i appear once in ϕ (we call such an x_i a (1,1)-variable), or x_i appears twice and \bar{x}_i appears once in ϕ (we call such an x_i a (2,1)-variable), for i=1..n. (Note that the case when x_i appears once and \bar{x}_i does not appear in ϕ at all, or vice versa, can be easily handled. Hence we can assume that we do not have these kind of "single-appearance" literals in ϕ .) Without loss of generality, we assume $\phi = F_1 \wedge F_2 \wedge \cdots \wedge F_m$ and there are n variables x_1, x_2, \cdots, x_n ; moreover, we assume that F_j cannot contain x_i and \bar{x}_i at the same time. Given F_j we say F_jF_j forms a 2-duplicated clause-string.

Given a (1,1)-sequence T = ACCA over $\{A,C\}$, where A and C both appear twice, it is easy to see that the maximal (longest) LD-subsequences of T are AA or CC. Similarly, given a (2,1)-sequence T = ACABCB over $\{A,B,C\}$, where A,B and C all appear twice, it is easy to verify that the maximal LD-subsequences of T are AABB or CC.

For each (1,1)-variable x_i , i.e., both x_i and \bar{x}_i appear once in ϕ , say x_i in F_j and \bar{x}_i in F_k , we define L_i as a (1,1)-sequence: $F_jF_kF_kF_j$. For each (2,1)-variable x_i , i.e., x_i appears twice and \bar{x}_i appears once in ϕ , say x_i in F_j and F_k , and \bar{x}_i in F_ℓ , we define L_i as a (2,1)-sequence: $F_jF_\ell F_jF_kF_\ell F_k$.

Now we proceed to construct the sequence S from an $(\leq 2, 1, \leq 3)$ -SAT instance ϕ .

$$S = g_1 g_1 L_1 g_2 g_2 \cdots g_i g_i L_i \cdots g_{n-1} g_{n-1} L_{n-1} g_n g_n L_n g_{n+1} g_{n+1}.$$

We claim the following: ϕ is satisfiable if and only if LLDS+ has a solution of length at least $2(n+1)+4K_1+2K_2+2J$, where K_1,K_2 are the number of (2,1)-variables in ϕ which are assigned True and False respectively and J is the number of (1,1)-variables in ϕ .

Proof.

"Only-if part". Suppose that ϕ is satisfiable. If a (1,1)-variable x_i is assigned True, to have a solution for LLDS+, in L_i we select the 2-duplicated clause-string F_jF_j ; likewise, if x_i is assigned False we select F_kF_k instead. Similarly, if a (2,1)-variable x_i is assigned True, to have a solution for LLDS+, in L_i we select two 2-duplicated clause-strings $F_jF_jF_kF_k$; likewise, if x_i is assigned False we select $F_\ell F_\ell$. Since g_ig_i only occurs once in S and T, we must include them in the solution. Clearly we have a solution for LLDS+ with length $2(n+1)+4K_1+2K_2+2J$.

"If part". If LLDS+ has a solution of length at least $2(n+1)+4K_1+2K_2+2J$, by definition, it must contain all g_ig_i 's. To find the truth assignment, we look at the contents between g_ig_i and $g_{i+1}g_{i+1}$ in the solution as well as in S (i.e., L_i). If x_i is a (1,1)-variable, $L_i = F_jF_kF_kF_j$ and in the solution F_jF_j is kept then we assign $x_i \leftarrow \text{True}$; otherwise, we assign $x_i \leftarrow \text{False}$. If x_i is a (2,1)-variable, $L_i = F_jF_\ell F_jF_kF_\ell F_k$ and in the solution either $F_jF_jF_kF_k$, F_jF_j or F_kF_k is kept then we assign $x_i \leftarrow \text{True}$. (When F_jF_j or F_kF_k is kept, then the LLDS+ solution could be longer by augmenting this sub-solution to $F_jF_jF_kF_k$.) If in the solution of LLDS+, clearly ϕ is satisfied.

We comment that $2(n+1)+4K_1+2K_2+2J=2(n+1)+2K_1+2n=4n+2+2K_1$, as $K_1+K_2+J=n$. (Note that K_1 only represents a part of the truth assignment for ϕ and it could be general, i.e., K_1 could be $\Omega(n)$.) But the former makes our arguments more clear. This reduction obviously takes O(m+n) time. Note that each 3-clause F_j appears 6 times in S and each 2-clause F_ℓ appears 4 times in S respectively, while each $g_k, k \in [n+1]$, appears twice in S. Since we could arbitrarily add an LD-block u^j , with $u \notin \Sigma$ and $j \geq 6$, at the end of S, we have the following theorem.

▶ **Theorem 6.** The decision version of LLDS+(d) is NP-complete for $d \ge 6$.

We next present an example for this proof.

▶ **Example.** Let $\phi = F_1 \wedge F_2 \wedge F_3 \wedge F_4 \wedge F_5 = (x_1 \vee x_2 \vee x_3) \wedge (\bar{x}_1 \vee \bar{x}_2 \vee x_3) \wedge (x_2 \vee \bar{x}_3 \vee x_4) \wedge (x_1 \vee x_4 \vee x_5) \wedge (\bar{x}_4 \vee \bar{x}_5)$. Then

$$S = g_1g_1F_1F_2F_1F_4F_2F_4 \cdot g_2g_2F_1F_2F_1F_3F_2F_3 \cdot g_3g_3F_1F_3F_1F_2F_3F_2 \cdot g_4g_4F_3F_5F_3F_4F_5F_4 \cdot g_5g_5F_4F_5F_5F_4 \cdot g_6g_6,$$

Corresponding to the truth assignment, $x_1, x_4 = \text{True}$ and $x_2, x_3, x_5 = \text{False}$, we have

$$S' = g_1g_1F_1F_1F_4F_4 \cdot g_2g_2F_2F_2 \cdot g_3g_3F_3F_3 \cdot g_4g_4F_3F_3F_4F_4 \cdot g_5g_5F_5F_5 \cdot g_6g_6,$$

which is of length
$$2(5+1) + 4 \times K_1 + 2 \times K_2 + 2 \times 1 = 12 + 4 \times 2 + 2 \times 2 + 2 = 26$$
.

The above theorem implies the following corollary.

▶ Corollary 7. FT(d) is NP-complete for $d \ge 6$.

Proof. The reduction remains the same. We just need to augment the proof in the reverse direction. Suppose there is a feasible solution S'' for S for the feasibility testing problem. Again, all g_ig_i 's must be in S''. We now look at the contents between g_ig_i and $g_{i+1}g_{i+1}$ in S (i.e., L_i) and S''. Corresponding to L_i , if in S'' we have an empty string between g_ig_i and $g_{i+1}g_{i+1}$, then we can assign x_i either as True or False. If $L_i = F_jF_kF_kF_j$, i.e., x_i is a (1,1)-variable, and F_jF_j is kept in S'' then we assign $x_i \leftarrow$ True; otherwise, we assign $x_i \leftarrow$ False. If $L_i = F_jF_\ell F_jF_kF_\ell F_k$, i.e., x_i is a (2,1)-variable, and either $F_jF_jF_kF_k$, F_jF_j or F_kF_k is kept in S'' then we assign $x_i \leftarrow$ True. If in the solution $F_\ell F_\ell$ is kept instead then we assign $x_i \leftarrow$ False. By definition, all clauses must appear in S'' (solution of FT), clearly ϕ is satisfied. It is clear that FT belongs to NP as a solution can be easily checked in polynomial time.

The above corollary essentially implies that the optimization version of LLDS+(d), $d \geq 6$, does not admit any polynomial-time approximation algorithm (regardless of the approximation factor), since any such approximation would have to return a feasible solution. A natural direction to approach LLDS+ is to design a bicriteria approximation for LLDS+, where a factor- (α, β) bicriteria approximation algorithm is a polynomial-time algorithm which returns a solution of length at least OPT/α and includes at least N/β letters, where $N = |\Sigma|$ and OPT is the optimal solution value of LLDS+. We show that obtaining a bicriteria approximation algorithm for LLDS+ is no easier than approximating LLDS+ itself.

▶ Corollary 8. If LLDS+(d), $d \ge 6$, admitted a factor- $(\alpha, N^{1-\epsilon})$ bicriteria approximation for any $\epsilon < 1$, then LLDS+(d), $d \ge 6$, would also admit a factor- α approximation, where N is the alphabet size.

Proof. Suppose that a factor- $(\alpha, N^{1-\epsilon})$ bicriteria approximation algorithm \mathcal{A} exists. We construct an instance S^* for LLDS+(6) as follows. (Recall that S is the sequence we constructed from an $(\leq 2, 1 \leq 3)$ -SAT instance ϕ in the proof of Theorem 1.) In addition to $\{F_i|i=1..m\} \cup \{g_j|j=1..n+1\}$ in the alphabet, we use a set of integers $\{1,2,...,(m+n+1)^x-(m+n+1)\}$, where x is some integer to be determined. Hence,

$$\Sigma = \{F_i | i = 1..m\} \cup \{g_i | j = 1..n + 1\} \cup \{1, 2, ..., (m+n+1)^x - (m+n+1)\}.$$

We now construct S^* as

$$S^* = 1 \cdot 2 \cdot \cdot \cdot ((m+n+1)^x - (m+n+1)) \cdot S \cdot ((m+n+1)^x - (m+n+1)) \cdot ((m+n+1)^x - (m+n+1) - 1) \cdot \cdot \cdot 2 \cdot 1.$$

Clearly, any bicriteria approximation for S^* would return an approximate solution for S as including any number in $\{1, 2, ..., (m+n+1)^x - (m+n+1)\}$ would result in a solution of size only 2.

Notice that we have $N = m + (n+1) + (m+n+1)^x - (m+n+1) = (m+n+1)^x$. In this case, the fraction of letters in Σ that is used to form such an approximate solution satisfies

$$\frac{m+(n+1)}{(m+n+1)^x} \leq \frac{1}{N^{1-\epsilon}},$$

which means it suffices to choose $x \ge \lceil 2 - \epsilon \rceil = 2$.

3.2 Solving the Feasiblility Testing Version for d=3

For the Feasibility Testing Version, as mentioned earlier, Corollary 1 implies that the problem is NP-complete when $d \ge 6$. We next show that if d = 3, then the problem can be decided in polynomial time.

▶ Lemma 9. Given a string S over Σ such that each letter in S appears at most 3 times, if a feasible solution for FT(3) contains a 3-block then there is a feasible solution for FT(3) which only uses 2-blocks.

Proof. Suppose that $S = \cdots a^{(1)} \cdots a^{(2)} \cdots a^{(3)} \cdots$, and $a^{(1)}a^{(2)}a^{(3)}$ is a 3-block in a feasible solution for FT(3). (Recall that the superscript only indicates the appearance order of letter a.) Then we could replace $a^{(1)}a^{(2)}a^{(3)}$ by either $a^{(1)}a^{(2)}$ or $a^{(2)}a^{(3)}$. The resulting solution is still a feasible solution for FT(3).

Lemma 2 implies that the FT(3) problem can be solved using 2-SAT. For each letter a, we denote the interval $(a^{(1)}, a^{(2)})$ as a variable v_a , and we denote $(a^{(2)}, a^{(3)})$ as \bar{v}_a . (Clearly one cannot select $a^{(1)}a^{(2)}$ and $a^{(2)}a^{(3)}$ as 2-blocks at the same time.) Then, if another interval $(b^{(1)}, b^{(2)})$ overlaps the interval $(a^{(1)}, a^{(2)})$, we have a 2-SAT clause $\overline{v_a \wedge v_b} = (\bar{v}_a \vee \bar{v}_b)$. Forming a 2-SAT instance ϕ'' for all such overlapping intervals and it is clear that we can decide whether ϕ " is satisfiable in $O(n^2)$ time (as we could have $O(n^2)$ pairs of overlapping intervals).

▶ **Theorem 10.** Let S be a string of length n. Whether FT(3) has a solution can be decided in $O(n^2)$ time.

The theorem immediately implies that LLDS+(3) has a factor-1.5 approximation as any feasible solution for FT(3) would be a factor-1.5 approximation for LLDS+(3). In the following, we extend this trivial observation to have a factor- $(1.5 - O(\frac{1}{n}))$ approximation for LLDS+(3).

▶ Corollary 11. Let S be a string of length n such that each letter appears at most 3 times in S. Then LLDS+(3) admits a polynomial-time approximation algorithm with a factor of $1.5 - O(\frac{1}{n})$ if a feasible solution exists.

Proof. First fix some constant (positive integer) D ($D < |\Sigma|$). Then for t=1 to D, we enumerate all the sets which contains letters appearing exactly 3 times in S. For a fixed t, let such a set be $F_t = \{a_1, a_2, ..., a_t\}$. We put the 3-blocks $a_i^{(1)} a_i^{(2)} a_i^{(3)}$, i=1..t, in the solution. (If two such 3-blocks overlap, then we immediately stop to try a different set F_t' ; and if all valid sets of size t have been tried, we increment t to t+1.) The substrings of S, between $a_i^{(1)}$ and $a_i^{(2)}$, and $a_i^{(2)}$ and $a_i^{(3)}$, will then be deleted. Finally, for the remaining letters we use 2-SAT to test whether all together, with the 3-blocks, they form a feasible solution (note that $a_i^{(1)} a_i^{(2)} a_i^{(3)}$ will serve as an obstacle and no valid interval for 2-SAT should contain it), this can be checked in $O(n^2)$ time following Theorem 2. Clearly, with this algorithm, either we compute the optimal solution with at most D 3-blocks, or we obtain an approximate solution of value $2|\Sigma| + D$. Since OPT is at most $3|\Sigma|$, the approximation factor is

$$\frac{3|\Sigma|}{2|\Sigma|+D} = 1.5 - O(\frac{1}{|\Sigma|}),$$

which is $1.5 - O(\frac{1}{n})$, because $|\Sigma|$ is at least $\lceil n/3 \rceil$. The running time of the algorithm is $O(\binom{|Sigma|}{D} \cdot O(n^2)) = O(n^{D+2})$, which is polynomial as long as D is a constant.

In the next section, we show that if the LD-blocks are arbitrarily positively weighted, then the problem can be solved in $O(n^2)$ time. Note that the O(n) time algorithm in Section 2.1 assumes that the weight of any LD-block is its length, which has the property that $\ell(s) = \ell(s_1) + \ell(s_2)$, where $s = s_1 s_2$, s_1 and s_2 are LD-blocks on the same letter x, and $\ell(s)$ is the length of s (or the total number of letters of s in s_1 and s_2).

4 A Dynamic Programming Algorithm for Weighted-LDS

Given the input string S = S[1...n], let $w_x(\ell)$ be the weight of LD-block $x^\ell, x \in \Sigma, 2 \le \ell \le d$, where d is the maximum number of times a letter appears in S. Here, the weight can be thought of as a positive function of x and ℓ and it does not even have to be increasing on ℓ . For example, it could be that $w(aaa) = w_a(3) = 8, w(aaaa) = w_a(4) = 5$. Given $w_x(\ell)$ for all $x \in \Sigma$ and ℓ , we aim to compute the maximum weight letter-duplicated string (Weighted-LDS) using dynamic programming.

Define T(n) as the value of the optimal solution of S[1...n] which contains the character S[n]. Define w[i,j] as the maximum weight LD-block $S[j]^{\ell}$ ($\ell \geq 2$) starting at position i and ending at position j; if such an LD-block does not exist, then w[i,j] = 0. Notice that $S[j]^{\ell}$ does not necessarily have to contain S[i] but it must contain S[j]. We have the following recurrence relation.

$$T(0) = 0,$$

$$T(i) = \max_{S[y] \neq S[i]} \begin{cases} T(y) + w[y+1, i] & \text{if } w[y+1, i] > 0, \\ 0 & \text{otherwise.} \end{cases}$$

The final solution value is $\max_{n} T(n)$. This algorithm clearly takes $O(n^2)$ time, assuming w[i,j] is given. We compute the table w[-,-] next.

1. For each pair of ℓ (bounded by d, the maximum number of times a letter appears in S) and letter x, compute

$$w_x'(\ell) = \max \begin{cases} w_x'(\ell-1) \\ w_x(\ell) \end{cases} ,$$

with $w'_x(1) = w_x(1)$. This can be done in $O(d|\Sigma|) = O(n^2)$ time.

2. Compute the number of occurrence of S[j] in the range of [i,j], N[i,j]. Notice that $i \leq j$ and for the base case we have $S[0] = \emptyset$.

$$N(0,0) = 0$$

$$N(0,j) = N(0,k) + 1, \quad k = \max \begin{cases} \{y | s[y] = s[j], 1 \le y < j\} \\ 0 \end{cases}$$

Table 1 Input table for $w_x(\ell)$, with S = ababbaca and d = 4.

$x \setminus \ell$	1	2	3	4
a	5	10	20	15
b	4	16	8	3
c	1	3	5	7

Table 2 Table $w'_x(\ell)$, with S = ababbaca and d = 4.

$x \setminus \ell$	1	2	3	4
a	5	10	20	20
b	4	16	16	16
c	1	3	5	7

And,

$$N(i,j) = \begin{cases} N(i-1,j), & \text{if } s[i-1] \neq s[j] \\ N(i-1,j) - 1, & \text{if } s[i-1] = [j] \end{cases}$$

This step takes $O(n^2)$ time.

3. Finally, we compute

$$w[i,j] = \begin{cases} w_{s[j]}'(N(i,j)), & if \ N(i,j) \geq 2 \\ 0, & else \end{cases}$$

This step also takes $O(n^2)$ time. We thus have the following theorem.

▶ Theorem 12. Let S be a string of length n over an alphabet Σ and d be the maximum number of times a letter appears in S. Given the weight function $w_x(\ell)$ for $x \in \Sigma$ and $\ell \leq d$, the maximum weight letter-duplicated subsequence (Weighted-LDS) of S can be computed in $O(n^2)$ time.

We can run a simple example as follows. Let S = ababbaca. Suppose the table $w_x(\ell)$ is given as Table 1. At the first step, $w_x'(\ell)$ is the maximum weight of a LD-block made with x and of length at most ℓ . The corresponding table $w_x'(\ell)$ can be computed as Table 2. At the end of the second step, we have Table 3 computed. From Table 3, the table w[-,-] can be easily computed and we omit the details. For instance, w[1,-] = [0,0,10,16,16,20,0,20]. With that, the optimal solution value can be computed as T(8) = 36, which corresponds to the optimal solution aabbaa.

Table 3 Part of the table N[i, j], with S = ababbaca and d = 4.

$i \backslash j$	1	2	3	4	5	6	7	8
8	0	0	0	0	0	0	0	1
3	0	0	1	1	2	2	1	3
2	0	1	1	2	3	2	1	3
1	1	1	2	2	3	3	1	4

d	LLDS+(d)	FT(d)	Approximability of $LLDS+(d)$
$d \ge 6$	NP-hard	NP-complete	No approximation
d = 3	?	P	$1.5 - O(\frac{1}{n})$

?

Table 4 Summary of results on LLDS+ and FT, the? indicates that the problem is still open.

5 Concluding Remarks

d = 4, 5

We consider the constrained longest letter-duplicated subsequence (LLDS+) and the corresponding feasibility testing (FT) problems in this paper, where all letters in the alphabet must occur in the solutions. We parameterize the problems with d, which is the maximum number of times a letter appears in the input sequence. For convenience, we summarize the results one more time in the following table. Obviously, we have many open problems.

We also consider the weighted version (without the "full-appearance" constraint), for which we give a non-trivial $O(n^2)$ time dynamic programming solution.

If we stick with the "full-appearance" constraint, one direction is to consider two additional variants of the problem where the solutions must be a subsequence of S, in the form of $x_1^{d_1}x_2^{d_2}\cdots x_k^{d_k}$ with x_i being a substring (resp. subsequence) of S with length at least 2, $x_j\neq x_{j+1}$ and $d_i\geq 2$ for all i in [k] and j in [k-1]. Intuitively, for many cases these variants could better capture the duplicated patterns in S. At this point, the NP-completeness results (similar to Theorem 1 and Corollary 1) would still hold with minor modifications to the proofs. (This reduction is still from $(\leq 2,1,\leq 3)$ -SAT and is additionally based on the following fact: given a (2,1)-sequence T=ABCCAB over $\{A,B,C\}$, where A,B and C all appear twice, the corresponding maximal "substring-duplicated-subsequences" or "subsequence-duplicated-subsequences" of T are $ABAB=(AB)^2$ or CC.) But whether these extensions allow us to design good approximation algorithms needs further study. Note that, without the "full-appearance" constraint, when x_i is a subsequence of S, the problem is a generalization of Kosowski's longest square subsequence problem [6] and can certainly be solved in polynomial time.

References

- Daniel P. Bovet and Stefano Varricchio. On the regularity of languages on a binary alphabet generated by copying systems. *Information Processing Letters*, 44(3):119–123, 1992.
- 2 Ferdinando Cicalese and Nicolo Pilati. The tandem duplication distance problem is hard over bounded alphabets. In Paola Flocchini and Lucia Moura, editors, Combinatorial Algorithms 21st International Workshop, IWOCA 2021, Ottawa, Canada, July 5-7, 2021, volume 12757 of Lecture Notes in Computer Science, pages 179–193. Springer, 2021.
- 3 Giovanni Ciriello, Martin L Miller, Bülent Arman Aksoy, Yasin Senbabaoglu, Nikolaus Schultz, and Chris Sander. Emerging landscape of oncogenic signatures across human cancers. *Nature Genetics*, 45:1127–1133, 2013.
- 4 Juegen Dassow, Victor Mitrana, and Gheorghe Paun. On the regularity of the duplication closure. *Bulletin of the EATCS*, 69:133–136, 1999.
- 5 Andrzej Ehrenfeucht and Grzegorz Rozenberg. On regularity of languages generated by copying systems. *Discrete Applied Mathematics*, 8(3):313–317, 1984.
- 6 Adrian Kosowski. An efficient algorithm for the longest tandem scattered subsequence problem. In Alberto Apostolico and Massimo Melucci, editors, String Processing and Information Retrieval, 11th International Conference, SPIRE 2004, Padova, Italy, October 5-8, 2004, Proceedings, volume 3246 of Lecture Notes in Computer Science, pages 93–100. Springer, 2004.

- 7 Manuel Lafond, Binhai Zhu, and Peng Zou. The tandem duplication distance is NP-hard. In Christophe Paul and Markus Bläser, editors, 37th International Symposium on Theoretical Aspects of Computer Science, STACS 2020, March 10-13, 2020, Montpellier, France, volume 154 of LIPIcs, pages 15:1–15:15. Schloss Dagstuhl Leibniz-Zentrum für Informatik, 2020.
- 8 Manuel Lafond, Binhai Zhu, and Peng Zou. Computing the tandem duplication distance is NP-hard. SIAM J. Discrete Mathematics, 36(1):64–91, 2022.
- 9 E.S. Lander, et al., and International Human Genome Sequencing Consortium. Initial sequencing and analysis of the human genome. *Nature*, 409(6822):860–921, 2001.
- 10 John Leech. A problem on strings of beads. The Mathematical Gazette, 41(338):277-278, 1957.
- Marcy Macdonald, et al., and Peter S. Harper. A novel gene containing a trinucleotide repeat that is expanded and unstable on huntington's disease. *Cell*, 72(6):971–983, 1993.
- 12 The Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. Nature, 474:609–615, 2011.
- Layla Oesper, Anna M. Ritz, Sarah J. Aerni, Ryan Drebin, and Benjamin J. Raphael. Reconstructing cancer genomes from paired-end sequencing data. BMC Bioinformatics, 13(Suppl 6):S10, 2012.
- Thomas J. Schaefer. The complexity of satisfiability problems. In Richard J. Lipton, Walter A. Burkhard, Walter J. Savitch, Emily P. Friedman, and Alfred V. Aho, editors, Proceedings of the 10th Annual ACM Symposium on Theory of Computing, May 1-3, 1978, San Diego, California, USA, pages 216–226. ACM, 1978.
- Sven Schrinner, Manish Goel, Michael Wulfert, Philipp Spohr, Korbinian Schneeberger, and Gunnar W. Klau. The longest run subsequence problem. In Carl Kingsford and Nadia Pisanti, editors, 20th International Workshop on Algorithms in Bioinformatics, WABI 2020, September 7-9, 2020, Pisa, Italy (Virtual Conference), volume 172 of LIPIcs, pages 6:1–6:13. Schloss Dagstuhl Leibniz-Zentrum für Informatik, 2020.
- Andrew J. Sharp, et al., and Even E. Eichler. Segmental duplications and copy-number variation in the human genome. *The American J. of Human Genetics*, 77(1):78–88, 2005.
- 17 Jack W. Szostak and Ray Wu. Unequal crossing over in the ribosomal dna of saccharomyces cerevisiae. *Nature*, 284:426–430, 1980.
- 18 Craig A. Tovey. A simplified np-complete satisfiability problem. Discret. Appl. Math., 8(1):85–89, 1984.
- 19 Ming-Wei Wang. On the irregularity of the duplication closure. *Bulletin of the EATCS*, 70:162–163, 2000.
- 20 Chunfang Zheng, P Kerr Wall, James Leebens-Mack, Claude de Pamphilis, Victor A Albert, and David Sankoff. Gene loss under neighborhood selection following whole genome duplication and the reconstruction of the ancestral populus genome. *Journal of Bioinformatics and Computational Biology*, 7(03):499–520, 2009.