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Site-Directed Deletion

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Abstract. We introduce a new bio-inspired operation called a *site-directed deletion* motivated from site-directed mutagenesis performed by enzymatic activity of DNA polymerase: Given two strings x and y , a site-directed deletion partially deletes a substring of x guided by the string y that specifies which part of a substring can be deleted. We study a few decision problems with respect to the new operation and examine the closure properties of the (iterated) site-directed deletion operations. We, then, define a site-directed deletion-closed (and -free) language L and investigate its decidability properties when L is regular or context-free.

Keywords: Bio-inspired operations · Site-directed deletion · Closure properties · Decidability · Automata theory

1 Introduction

A deletion operation is one of the well-established operations [4, 5, 10, 12, 14]. We focus on a variant of deletion, *site-directed deletion mutagenesis*, which can be performed *in vitro*, whose goal is to create a deletion on a given gene sequence under enzymatic activities [19]. The activity under DNA polymerase requires a single-stranded DNA segment (called a template) and primers designated to form a partially double-stranded region with the template. In particular, primers complementarily bind to a given template excluding a region to be deleted and extend to the end of the template forming a double-stranded DNA segment.

From the formal language viewpoint, Head et al. [11] and Kari and Kopecki [15] considered a splicing system inspired by DNA recombination under enzymatic

activities. Kari and Thierrin [16] modeled a contextual deletion that occurs in a context sensitive manner: It deletes a string v from a string u only if certain contexts are presented in a given set \mathcal{C} . Furthermore, Daley and McQuillan [3], and Enaganti et al. [6, 7] studied operations inspired by the action of DNA polymerase enzyme that plays a major role in DNA recombination. Recently, Cho et al. [2] studied the site-directed insertion operation⁶ that inserts a string y at a specific position of x according to the matching outfix of x .

We define a new operation called *site-directed deletion* that *partially* deletes a substring from a given string x based on a guide string y that specifies which part of a substring can be deleted. In other words from a biological viewpoint, x is a template and y is a guide primer with information of the region to be deleted. We say that a site-directed deletion occurs on x if a site-directed deletion of x and y partially deletes a substring from x guided by y . This is analogous to the contextual deletion operation studied by Kari and Thierrin [16]. A contextual deletion of a string y from x occurs only if certain contexts exist in a given set \mathcal{C} of contexts. Roughly speaking, contextual deletion specifies y —a string to be deleted—according to a set \mathcal{C} whereas site-directed deletion deletes a substring from x according to y . Fig. 1 illustrates the difference among ordinary, contextual and site-directed deletions.

A site-directed deletion successfully generates a desired DNA sequence *in vitro* if a primer is designed to complementarily interact with a template which can result in the desired DNA sequence. From the formal language viewpoint, we consider a question of deciding whether or not the template and primer interact each other as desired. We show linear time algorithms to determine whether or not the site-directed deletion (SDD) of two strings x and y is not empty and whether or not the site-directed deletion of x and y results in a given string z . We show that regular languages are closed under site-directed deletion, whereas context-free languages are not, and we give a context-free language L which is not closed under iterated site-directed deletion. Finally, we consider decidability for *sdd*-closedness and *sdd*-freeness on a language L .

2 Preliminaries

Let Σ be a finite alphabet of characters and Σ^* be the set of all strings over Σ . The symbol \emptyset denotes the empty language and the symbol λ denotes the empty string. Given a string x , $|x|$ denotes the length of x and x^R denotes the reversal of x . A string $x = x[1]x[2] \cdots x[n] \in \Sigma^n$ is a finite sequence of n symbols. For $1 \leq i \leq j \leq n$, we denote $x[i : j] = x[i]x[i + 1] \cdots x[j]$. Given a string $x = uv$, where $u, v \in \Sigma^*$, we say that u is a *prefix* of x and v is a *suffix* of x . Given a string $y = uvv$, where $u, w, v \in \Sigma^*$, we say that (u, v) is an outfix of y . If $u \neq \lambda$ and $v \neq \lambda$, then we say that (u, v) is a *non-trivial outfix* of y . Sometimes (in particular, when talking about the site-directed deletion operation) we call an outfix (u, v) simply a string uv (when it is known from the context what

⁶ Site-directed insertion has earlier been considered under the name *outfix-guided insertion* [2].

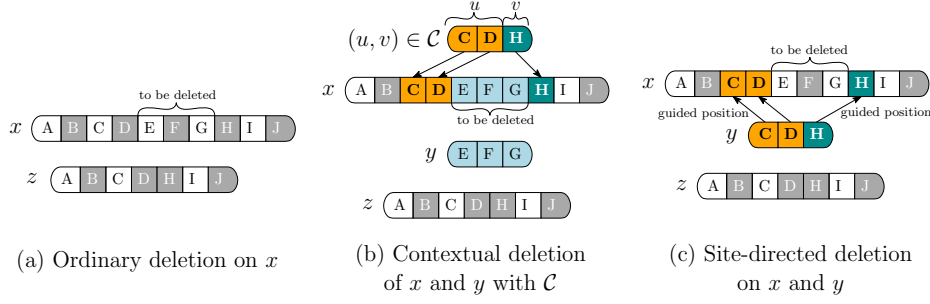


Fig. 1: Examples of ordinary deletion, contextual deletion and site-directed deletion. (a) An ordinary deletion of x results in a string z removing a substring EFG . The resulting string z is one of many possible deletion outputs. (b) A contextual deletion of x and y with a set $\mathcal{C} \subseteq \Sigma^* \times \Sigma$ of contexts results in a string z if there exists an infix uyv of x , where $(u, v) \in \mathcal{C}$, $uv = CDH$ and $y = EFG$. (c) A site-directed deletion of two strings x and y —in other words, a template and a primer, respectively—results in a string z if $y = CDH$ is the catenation of an outfix (CD, H) of a substring $CDEFGH$ of x . The string z is the only possible site-directed deletion output when the guide string is CDH .

the components u and v are). Given a language L , we use \bar{L} to denote the complement of L ; $\bar{L} = \Sigma^* \setminus L$.

A nondeterministic finite automaton (NFA) is a tuple $A = (\Sigma, Q, \delta, q_0, F)$, where Σ is an input alphabet, Q is a finite set of states, $\delta: Q \times \Sigma \rightarrow 2^Q$ is a multivalued transition function, $q_0 \in Q$ is the initial state and $F \subseteq Q$ is a set of final states. In the usual way, δ is extended as a function $Q \times \Sigma^* \rightarrow 2^Q$ and the language recognized by A is $L(A) = \{w \in \Sigma^* \mid \delta(q_0, w) \cap F \neq \emptyset\}$. The automaton A is a deterministic finite automaton (DFA) if δ is a single valued partial function. A sequence q_0, q_1, \dots, q_n of states denotes a *path*. A string w is accepted by A if there is a labeled path from q_0 to $q_n \in F$, and we call this path an *accepting path*.

We now introduce a new operation called a *site-directed deletion* that formalizes an enzymatic reaction called the site-directed deletion mutagenesis.

Definition 1. *The site-directed deletion from a string x by y is*

$$x \xleftarrow{sdd} y = \{x_1uvx_2 \mid x = x_1uvw_2, y = uv, u \neq \lambda \text{ and } v \neq \lambda\}.$$

We say that y is a deletion guide of x if $x \xleftarrow{sdd} y \neq \emptyset$.

We use the notation $x \xrightarrow{[y]} z$ to indicate that z is obtained by $x \xleftarrow{sdd} y$. Note that a string x is obtained from itself by selecting the outfix to be x itself, in other words $x \xrightarrow{[x]} x$, when $|x| \geq 2$. The site-directed deletion operation can be

extended to languages as follows:

$$L_1 \stackrel{sdd}{\leftarrow} L_2 = \bigcup_{w_i \in L_i, i=1,2} w_1 \stackrel{sdd}{\leftarrow} w_2.$$

We define the *iterated site-directed deletion* on a language, which is an iterated version of the site-directed deletion operation.

Definition 2. *Site-directed deletion* SDD of L is inductively defined as

$$\text{SDD}^{(0)}(L) = L, \text{ and } \text{SDD}^{(i+1)}(L) = \text{SDD}^{(i)}(L) \stackrel{sdd}{\leftarrow} \text{SDD}^{(i)}(L), i \geq 0.$$

The *iterated site-directed deletion* SDD^* of L is

$$\text{SDD}^*(L) = \bigcup_{i=0}^{\infty} \text{SDD}^{(i)}(L).$$

3 Decidability of Site-Directed Deletion on Strings

We first consider the question of determining whether or not a string y can be a deletion guide of a string x ; in other words, is $x \stackrel{sdd}{\leftarrow} y \neq \emptyset$? The site-directed deletion mutagenesis deliberately creates mutant DNA sequences using designed DNA sequences—a source DNA sequence to be partially deleted, a DNA sequence that contains the target mutant region and designed primers that indicate a starting point of synthesis. Given two strings x and y , a DNA sequence that contains a target mutant region is a deletion-guide y of a source DNA sequence x . Note that site-directed deletion cannot create a mutant DNA sequence if a DNA sequence containing a mutant region does not interact with a source DNA sequence. Thus, it is important to check whether or not designed DNA sequences can interact each other. We present a linear time algorithm that determines whether or not $x \stackrel{sdd}{\leftarrow} y \neq \emptyset$.

Theorem 1. *Given two strings x and y , we can determine whether or not $x \stackrel{sdd}{\leftarrow} y \neq \emptyset$ in $O(n)$ time, where $|x| = n$, $|y| = m$ and $m \leq n$.*

Proof. Our goal is to determine whether or not there exist two substrings u, v of x such that $y = uv$. In other words, we look for a pentuple (g, h, i, j, k) that satisfies the following conditions:

1. $y[1 : g] = x[j-g+1 : j]$
2. $y[m-h+1 : m] = x[k : k+h-1]$
3. $j - g + i \leq k + h - m + i$
4. $i \leq g$
5. $m - i \leq h$

Suppose there exists a pentuple (g, h, i, j, k) that satisfies all five conditions. Also suppose that there exists g' such that $y[1 : g'] = x[j-g'+1 : j]$ and $g' < g$. If $i \leq g'$, then $i \leq g$ and (g, h, i, j, k) also satisfies the five conditions. Therefore, for each index in x , we need to find the longest prefix of y that ends at j and the longest suffix of y that starts from k . We check the required conditions using a modified Aho-Corasick algorithm [1].

Using all prefixes of y and y^R as two dictionaries, we construct two Aho-Corasick automata \mathcal{A}_P and \mathcal{A}_S where the output function from a state directs to the longest matching pattern. Since we use prefixes of a string as a dictionary, it is straightforward that these modified automata can be built in $O(m)$ time using $O(m)$ space. The result is two lists of pairs $(j, g), (k, h)$ of indices from \mathcal{A}_P and \mathcal{A}_S , where the first element indicates the ending (starting, respectively) index and the second elements indicates the length of the longest matched pattern.

In condition 3, the inequality indicates that $m \leq (g - j) + (k + h)$. From conditions 4 and 5, we know that $m \leq g + h$. On the other hand, if two conditions $m \leq (g - j) + (k + h)$ and $m \leq g + h$ are satisfied, then we can find $i = g$ that satisfies conditions 3, 4 and 5.

We store j and k using g and h as indices respectively. Moreover, to check the condition $m \leq (g - j) + (k + h)$, we only need to keep the smallest j and the largest k for same g and h , respectively. Constructing such two arrays $j[g]$ and $k[h]$ requires $O(n)$ time and $O(m)$ space. Note that we have $k[h] > k[h+1]$, since an occurrence of $y[m-h+2 : m]$ that starts at index k guarantees an occurrence of $y[m-h+1 : m]$ that starts at index $k+1$. Then we start from $g = 1$ and $h = m$, and check if $j[g] \leq k[h] + 1$. If the condition is satisfied, we know that $m \leq g + h$ and $m \leq g - j[g] + k[h] + h$. If the condition is not satisfied, we increase g and decrease h by 1 continuously and check the condition. The runtime to compare arrays is $O(m)$, and the total runtime becomes $O(n)$. \square

We next consider a problem of determining whether or not $z \in x \stackrel{sdd}{\leftarrow} y$ for given strings x, y and z . The biological implication of $z \in x \stackrel{sdd}{\leftarrow} y$ is that a site-directed deletion mutagenesis by PCR (Polymerase Chain Reaction) successfully generates a desired DNA sequence, which is denoted by z . We show that the problem can be solved in linear time.

Theorem 2. *Given three strings $x, y, z \in \Sigma^*$, we can determine whether or not $z \in x \stackrel{sdd}{\leftarrow} y$ in $O(n)$ time, where $n = |x|$ and $|x| \geq |z| \geq |y| \geq 2$.*

Proof. Suppose that there exist three strings $x[1 : n], y[1 : m]$ and $z[1 : l]$ such that $z \in x \stackrel{sdd}{\leftarrow} y$, where $n, m, l \geq 2$. Then there are decompositions of strings $x = x_1 u v v x_2, y = u v$ and $z = x_1 u v x_2$, where $x_1, x_2, w \in \Sigma^*$ and $u, v \neq \lambda$. We decide whether or not $z \in x \stackrel{sdd}{\leftarrow} y$ as follows:

1. **Scanning x and z for finding common prefix $x_1 u$ and suffix $v x_2$:**
 We scan both ends of x and z until a mismatch occurs—in other words, we find the longest matching prefix and suffix between $x[1 : n]$ and $z[1 : l]$. Let $z[1 : i] = x[1 : i]$ be the longest matching prefix, and $z[l-j+1 :$

$m] = x[n-j+1 : n]$ be the longest matching suffix, where $i, j > 1$. When $i+1 = l-j+1$, we show that the catenation of the longest matching prefix and suffix $z[1 : i] \cdot z[l-j+1 : l]$ equals to $z = x_1uvx_2$.

2. **Identifying search-range of z with respect to y :** For the case $i > l-j+1$, which implies that a suffix of $z[1 : i]$ is a prefix of $z[l-j+1 : l]$, we check an occurrence of y within $z[l-(j+m)+2 : i+m-1]$. We call the range from $l-(j+m)+2$ to $i+m-1$ a *search-range* on z . The search-range is calculated from the assumption that the longest prefix $z[1 : i]$ contains u as an infix, and the longest suffix $z[l-j+1 : l]$ contains v as an infix, where the catenation of u and v becomes y for $|u|, |v| \geq 1$. We consider a case where y matches with $z[l-j-m+2 : i+m-1]$. Suppose $y = z[l-j-m+2 : l-j+1]$. Then, $z[l-j+1 : l] = x[n-j+1 : n]$ denotes vx_2 and there exists a corresponding prefix $x[1 : l-j]$, which denotes x_1u , and we show that $z \in x \xrightarrow{sdd} y$.
3. **Finding y from search-range of z :** We can prove for all the other cases when y appears within the search-range using a similar argument. We check the existence of y within the search-range in $O(m)$ time using the KMP algorithm [17]. Thus, the total runtime is $O(n)$.

□

4 Closure Properties and Decidability on Languages

4.1 Closure Properties of Site-Directed Deletion on Languages

We show that regular languages are closed under the site-directed deletion, whereas context-free languages are not. Context-free languages are closed under site-directed deletion with regular languages. We give a context-free language L such that $\text{SDD}^*(L)$ is not context-free.

Theorem 3. *If L_1 and L_2 are regular, then $L_1 \xrightarrow{sdd} L_2$ is regular.*

Proof. Let L_1 be recognized by an NFA $A = (Q_A, \Sigma, \delta, q_0, F_A)$ and L_2 be recognized by an NFA $B = (Q_B, \Sigma, \gamma, p_0, F_B)$. Let $\widetilde{Q}_A = \{\widetilde{q} \mid q \in Q_A\}$ such that Q_A is disjoint with \widetilde{Q}_A . We construct an NFA $C = (Q_C, \Sigma, \omega, s, F_C)$ recognizing all strings of $L_1 \xrightarrow{sdd} L_2$, where $Q_C = Q_A \times (\{\clubsuit, \heartsuit\} \cup Q_B) \cup \widetilde{Q}_A \times Q_B$, $s = (q_0, \clubsuit)$ and $F = \{(q, \heartsuit) \mid q \in F_A\} \cup \{(\widetilde{q}, p) \mid q \in F_A, p \in F_B\}$. Let α be an arbitrary symbol of Σ . We set the following transitions of ω :

- (i) for $q \in Q_A$, $\omega((q, \clubsuit), \alpha) = \{(q', \clubsuit) \mid q' \in \delta(q, \alpha)\} \cup \{(q', p') \mid q' \in \delta(q, \alpha) \text{ and } p' \in \gamma(p_0, \alpha)\}$,
- (ii) for $q \in Q_A$ and $p \in Q_B$, $\omega((q, p), \alpha) \in \{(q', p') \mid q' \in \delta(q, \alpha) \text{ and } p' \in \gamma(p, \alpha)\} \cup \{(\widetilde{q}'', p') \mid q' \in \delta(q, \alpha), q'' \in \delta(q', \lambda), p' \in \gamma(p, \alpha) \text{ and } \widetilde{q}'' \in \widetilde{Q}_A\}$,
- (iii) for $\widetilde{q} \in \widetilde{Q}_A$ and $p \in Q_B$, $\omega((\widetilde{q}, p), \alpha) \in \{(q', p') \mid q' \in \delta(q, \alpha) \text{ and } p' \in \gamma(p, \alpha)\} \cup Z_q$, where

$$Z_q = \begin{cases} \{(q', \heartsuit) \mid q' \in \delta(q, \alpha)\} & \text{if } p \in F_B, \\ \emptyset & \text{if } p \notin F_B, \end{cases}$$

(iv) for $q \in Q_A$, $\omega((q, \heartsuit), \alpha) = \{(q', \heartsuit) \mid q' \in \delta(q, \alpha)\}$.

All transitions not listed above are undefined. We show that $L(A) \stackrel{sdd}{\leftarrow} L(B) \subseteq L(C)$. Let $x_1 u v v x_2 \in L(A)$ and $u v \in L(B)$, where $x_1, x_2, w \in \Sigma^*$ and $u, v \in \Sigma^+$. The construction is based on the idea that C uses the states (q, \clubsuit) of C to process the prefix x_1 , the states (q, p) to process the following substring u , the states (\tilde{q}, p) to process the substring v and the states (q, \heartsuit) to process the following substring x_2 . Let $\mathcal{P}_A(x)$ be an accepting path $q_0, \dots, q_{x_1}, \dots, q_u, \dots, q_w, \dots, q_u, \dots, q_{x_2}$ of $x \in L(A)$ and $\mathcal{P}_B(y)$ be an accepting path $p_0, \dots, p_u, \dots, p_v$ of $y \in L(B)$. From the initial state (q_0, \clubsuit) of C the transition rule (i) allows C to simulate the path q_0, \dots, q_{x_1} of $\mathcal{P}_A(x_1 u v v x_2)$ reaching a state (q_{x_1}, \clubsuit) . When the first symbol α of u appears, the transition rule (ii) allows C to simulate both paths q_{x_1}, \dots, q_u of \mathcal{P}_A and p_0, \dots, p_u of \mathcal{P}_B . Note that the transition (ii) allows C to nondeterministically enter the state (\tilde{q}_w, p_u) which shows that C simulates the path q_u, \dots, q_w of \mathcal{P}_A reading w . Then, the transition (iii) allows C to simulate both paths q_w, \dots, q_v of \mathcal{P}_A and p_u, \dots, p_v of \mathcal{P}_B , and C enter the state (\tilde{q}_v, p_v) . Note that C enter the state (q_v, \heartsuit) if $p_v \in F_B$. The transition (iv) allows C to simulate the remaining path q_v, \dots, q_{x_2} of \mathcal{P}_A , and simulation ends in an accepting state (q_{x_2}, \heartsuit) , where $q_{x_2} \in F_A$.

We now show that if C recognizes a string $x_1 u v v x_2$, then A recognizes a string $x_1 u v v x_2$ and B recognizes a string $u v$, in other words; $L(C) \subseteq L(A) \stackrel{sdd}{\leftarrow} L(B)$. We decompose an accepting path $(q_0, \clubsuit), \dots, (q_{x_2}, \heartsuit)$ for a string $z = x_1 u v v x_2 \in L(C)$ into four paths $\mathcal{P}_1, \mathcal{P}_2, \mathcal{P}_3$ and \mathcal{P}_4 such that

$$\underbrace{(q_0, \clubsuit), \dots, (q_{x_1}, \clubsuit)}_{\mathcal{P}_1}, \underbrace{(q_{x_1}, p_s), \dots, (q_u, p_u)}_{\mathcal{P}_2},$$

$$\underbrace{(\tilde{q}_w, p_u), \dots, (\tilde{q}_v, p_v)}_{\mathcal{P}_3}, \text{ and } \underbrace{(q_v, \heartsuit), \dots, (q_{x_2}, \heartsuit)}_{\mathcal{P}_4}.$$

Path \mathcal{P}_1 shows that there is a path q_0, \dots, q_{x_2} in \mathcal{P}_A that recognizes a string x_1 . Path \mathcal{P}_2 shows that there exist paths q_{x_1}, \dots, q_u of \mathcal{P}_A and p_0, \dots, p_u of \mathcal{P}_B that recognize a string u , and path \mathcal{P}_3 shows that there exist paths $\tilde{q}_u, \dots, \tilde{q}_v$ of \mathcal{P}_A and p_u, \dots, p_v of \mathcal{P}_B that recognize a string v . Note that based on the transitions (ii), C nondeterministically enters a state (\tilde{q}, p_u) from (q_u, p_u) , then, C simulates a path q, \dots, q_w of \mathcal{P}_A reaching (\tilde{q}_w, p_u) . Path \mathcal{P}_4 shows that C only simulates a path q_v, \dots, q_{x_2} of \mathcal{P}_A , and the simulation ends on the final state (q_{x_2}, \heartsuit) . It implies that if C accepts a string $x_1 u v v x_2$, then there exist accepting paths on A and B that recognize strings $x_1 u v v x_2$ and $u v$. \square

Theorem 4. *There exist context-free languages L_1 and L_2 such that $L_1 \stackrel{sdd}{\leftarrow} L_2$ is not context-free.*

Proof. Consider two context-free languages $L_1 = \{a^n b^n c^m \# \mid n, m \geq 1\}$ and $L_2 = \{b^n c^n \# \mid n \geq 1\}$. Then, the language $(L_1 \stackrel{sdd}{\leftarrow} L_2) \cap (a^* b^* c^* \#) = \{a^n b^n c^n \# \mid n \geq 1\}$ is not context-free. \square

The proof of Theorem 5 is omitted due to the limitation on the number of pages.

Theorem 5. *Given a context-free language L_1 and a regular language L_2 , $L_1 \xleftarrow{sdd} L_2$ and $L_2 \xleftarrow{sdd} L_1$ are context-free.*

Theorem 6. *There exists a context-free language L such that $\text{SDD}^*(L)$ is not context-free.*

Proof. Let $\Sigma = \{a, b, c, \$, \%, \#\}$ and define $L = L_1 \cup L_2$, where $L_1 = \{\#a^n b^n \%c^m \# \mid n, m \geq 1\}$ and $L_2 = \{\$b^n \$c^n \# \mid n \geq 1\}$. Denote $M_1 = \#a^+ \$b^+ \%c^+ \#$, $M'_1 = \#a^+ \$b^+ \$c^+ \#$ and $M_2 = \$b^+ \$c^+ \#$ (and thus $L_1 \subseteq M_1$ and $L_2 \subseteq M_2$). We observe the following properties:

- (i) It is not possible to use a string $y \in M_1 \cup M'_1$ as a deletion guide for a string $x \in M_2$ (because strings of M_2 contain only one occurrence of $\#$).
- (ii) Using a string in $M_1 \cup M'_1$ as a deletion guide for a string in $M_1 \cup M'_1$ can be done only in a trivial deletion step (that produces the original deletion guide).
- (iii) Using a string in M_2 as a deletion guide for a string in M_2 can be done only in a trivial deletion step.
- (iv) Using a string in M_2 as a deletion guide for strings of $M_1 \cup M'_1$ always produces a string in M'_1 .

We explain observation (iv) below. The first three observations follow directly from the definition of site-directed deletion.

Consider $z \in x \xleftarrow{sdd} y$ where $x \in M_1 \cup M'_1$ and $y \in M_2$. The end-marker $\#$ of y must be matched with the last symbol of x and the two occurrences of $\$$ in y must be matched with the two occurrences of $\$$ in the string x . This means that z must be the result of deleting from $x \in M_1$ the symbol $\%$ and zero or more symbols c and, if $x \in M'_1$, z must be the result of deleting from x zero or more symbols c . Not all c 's can be deleted because the string $y \in M_2$ contains at least one c . Thus, in both cases $z \in M'_1$.

Since trivial deletion steps produce only the original deletion guide, observations (i)–(iv) imply that

$$L \cup \text{SDD}^{(1)}(L) = L_1 \cup L_2 \cup (L_1 \xleftarrow{sdd} L_2),$$

and in particular,

$$L \cup \text{SDD}^{(1)}(L) = L_1 \cup L_2 \cup \{\#a^n \$b^n \$c^n \# \mid n \geq 1\}. \quad (1)$$

The last equality is verified as in the proof of Theorem 4. Note that our current construction is a modification of the construction used in the proof of Theorem 4.

Now $L_1 \xleftarrow{sdd} L_2 \subseteq M'_1$ and none of the deletion steps (i)–(iv) produces new strings of M_2 (the steps (ii) and (iii) must use a trivial deletion step). This means that using induction on k and the observations (i)–(iv), we get that

$$\bigcup_{i=0}^{k+1} \text{SDD}^{(i)}(L) = L_1 \cup L_2 \cup (\text{SDD}^{(k)}(L) \xleftarrow{sdd} L_2),$$

and, thus, $\text{SDD}^*(L)$ consists of L and strings obtained from L by iterated deletions that all use a string in L_2 as a guide.

When using a string $y \in L_2$ as a deletion guide for a string $x \in \{\#a^n b^n c^n \# \mid n \geq 1\}$, the only possibility is to match y with a suffix of x , because the string x has the same number of b 's and c 's and the string y has the same property. When y is matched with a suffix of x , the result of the deletion is just x . This means that iterating the deletions does not produce anything new and $\text{SDD}^*(L) = L \cup \text{SDD}^{(1)}(L)$ and from equation (1) we get that $\text{SDD}^*(L) \cap \#a^+ b^+ c^+ \# = \{\#a^n b^n c^n \# \mid n \geq 1\}$ which is not context-free. \square

Closure of regular languages under iterated site-directed deletion remains open.

4.2 Decidability of *sdd*-closed and *sdd*-free Languages

A language L is *sdd*-closed if $L \stackrel{sdd}{\leftarrow} L \subseteq L$, which implies that L does not generate a string that is not in L under the site-directed deletion operation. A language L is *sdd*-free if $x \stackrel{sdd}{\leftarrow} y = \emptyset$, where $x, y \in L$ and $x \neq y$. Note that a string in L is obtained only from itself by site-directed deletion if L is *sdd*-free.

We show that it is decidable whether or not a given language L is *sdd*-closed when L is regular and is undecidable when L is context-free.

Theorem 7. *Given a regular language L , it is decidable in polynomial time whether or not L is *sdd*-closed.*

Theorem 8. *For a given context-free language L , determining whether or not L is *sdd*-closed is undecidable.*

Proof. Let $((u_1, \dots, u_n), (v_1, \dots, v_n))$ be an instance of the *Post's Correspondence Problem* (PCP) [18], where $u_i, v_i \in \Sigma^*$ and $1 \leq i \leq n$. A solution for the instance is a sequence of integers (i_1, \dots, i_k) , $i_j \in \{1, \dots, n\}$, $j = 1, \dots, k$ such that $u_{i_1} \cdots u_{i_k} = v_{i_1} \cdots v_{i_k}$. It is well known that the PCP is undecidable [18]. Let $\Sigma' = \Sigma \cup \{\#, \%, \check{\cdot}\}$.

We consider a context-free language $L = L_1 \cup L_2$, where

$$L_1 = \{\check{\cdot} \$ i_1 i_2 \cdots i_r \# u_{i_r}^R u_{i_{r-1}}^R \cdots u_{i_1}^R \# \% \# v_{j_1} v_{j_2} \cdots v_{j_s} \# j_s j_{s-1} \cdots j_1 \$ \check{\cdot}\} \text{ and}$$

$$L_2 = \{\$ i_1 i_2 \cdots i_r \# w \# w^R \# i_r i_{r-1} \cdots i_1 \$\}$$

for $w \in \Sigma^*$, $1 \leq r, s$, and $1 \leq i_r, j_s \leq n$. Then, L has two types of string

$$w_1 = \check{\cdot} \$ i_1 i_2 \cdots i_r \# u_{i_r}^R u_{i_{r-1}}^R \cdots u_{i_1}^R \# \% \# v_{i_1} v_{i_2} \cdots v_{i_r} \# i_r i_{r-1} \cdots i_1 \$ \check{\cdot} \in L_1, \text{ and}$$

$$w_2 = \$ i_1 i_2 \cdots i_r \# u_{i_r}^R u_{i_{r-1}}^R \cdots u_{i_1}^R \# \# u_{i_1} u_{i_2} \cdots u_{i_r} \# i_r i_{r-1} \cdots i_1 \$ \in L_2.$$

Here, $w = u_{i_r}^R u_{i_{r-1}}^R \cdots u_{i_1}^R$ and it follows $w^R = u_{i_1} u_{i_2} \cdots u_{i_r}$. We claim that the PCP has a solution if and only if L is not *sdd*-closed, and we prove both implications of the claim.

- “If the PCP has a solution, then L is not sdd -closed”: Suppose that (i_1, \dots, i_r) is a solution for the PCP, which implies $u_{i_1}u_{i_2} \cdots u_{i_r} = v_{i_1}v_{i_2} \cdots v_{i_r}$. We decompose $w_1 = x_1uwx_2$ and $w_2 = uv$, where $x_1, x_2 = \zeta, w = \%$, and

$$u = \$i_1i_2 \cdots i_r \# u_{i_r}^R u_{i_{r-1}}^R \cdots u_{i_1}^R \#, v = \#u_{i_1}u_{i_2} \cdots u_{i_{r-1}} \# i_r i_{r-1} \cdots i_1 \$.$$

Then, the claim holds that L is not sdd -closed since

$$w_1 \xleftarrow{sdd} w_2 = \zeta \$i_1i_2 \cdots i_r \# w \# w^R \# i_r i_{r-1} \cdots i_1 \$ \zeta,$$

which is not in L —there is no string contains all occurrences of symbols $\zeta, \$$ and $\#$ without the symbol $\%$.

- “If the PCP has no solution, then L is sdd -closed”: We consider two strings

$$w_1 = \zeta \$i_1i_2 \cdots i_r \# u_{i_r}^R u_{i_{r-1}}^R \cdots u_{i_1}^R \# \% \# v_{j_1}v_{j_2} \cdots v_{j_s} \# j_s j_{s-1} \cdots j_1 \$ \zeta \in L_1 \text{ and}$$

$$w_2 = \$i_1i_2 \cdots i_r \# u_{i_r}^R u_{i_{r-1}}^R \cdots u_{i_1}^R \# \# u_{i_1}u_{i_2} \cdots u_{i_r} \# i_r i_{r-1} \cdots i_1 \$ \in L_2.$$

We consider the following four possible cases of $L \xleftarrow{sdd} L$, and show that there is a contradiction of the assumption.

- (i) $L_1 \xleftarrow{sdd} L_1$: A string $w_1 \in L_1$ itself is a deletion guide of w_1 , which is obtained by $w_1 \xrightarrow{[w_1]} w_1$, and the claim holds that $L \xleftarrow{sdd} L \subseteq L$.
- (ii) $L_2 \xleftarrow{sdd} L_2$: Similarly, a string $w_2 \in L_2$ is obtained by $w_2 \xrightarrow{[w_2]} w_2$, and it implies that $L \xleftarrow{sdd} L \subseteq L$.
- (iii) $L_2 \xleftarrow{sdd} L_1$: A string $w_1 \in L_1$ begins and ends with the symbol ζ , which does not occur in $w_2 \in L_2$, and it also implies that $L \xleftarrow{sdd} L \subseteq L$.
- (iv) $L_1 \xleftarrow{sdd} L_2$: Suppose that $w_2 \in L_2$ is a deletion guide of $w_1 \in L_1$ such that $w_1 = x_1uwx_2$ and $w_2 = uv$, where $u, n \neq \lambda$. Since w_1 begins and ends with ζ , and w_2 does not contain occurrences of ζ , in the decomposition of w_1 , the first symbol ζ must be in x_1 and the last symbol ζ must be in x_2 . Similarly, in the decomposition of w_1 , $\%$ must be in w since w_2 does not contain $\%$. As an outfix (u, v) of a substring of w_1 should be $w_2 = uv$ when w_2 is a deletion-guide of w_1 , it follows that

$$u = \$i_1i_2 \cdots i_r \# u_{i_r}^R u_{i_{r-1}}^R \cdots u_{i_1}^R \# \text{ and } v = \#v_{j_1}v_{j_2} \cdots v_{j_s} \# j_s j_{s-1} \cdots j_1 \$,$$

$$\text{where } r = s, i_r = j_r \text{ and } v_{j_1}v_{j_2} \cdots v_{j_s} = u_{i_1}u_{i_2} \cdots u_{i_{r-1}} = (u_{i_r}^R u_{i_{r-1}}^R \cdots u_{i_1}^R)^R.$$

Thus, (i_1, \dots, i_r) is a solution for the PCP—a contradiction.

Therefore, it is undecidable whether or not L is sdd -closed since the PCP is undecidable. \square

We also show that it is decidable whether or not L is sdd -free in polynomial time when L is regular, and it is undecidable when L is context-free. The insertion of y into x in an arbitrary place in x is defined as the set of strings $x \xleftarrow{ins} y = \{x_1yx_2 \mid x = x_1x_2 \text{ and } x_1, x_2 \in \Sigma^*\}$ [9, 13]. We use the closure property of regular languages under the insertion operation.

Lemma 1. *Consider $L \subseteq \Sigma^*$. Then L is sdd -free if and only if*

$$L \cap [\Sigma^+(L \stackrel{ins}{\leftarrow} \Sigma^*)\Sigma^* \cup \Sigma^*(L \stackrel{ins}{\leftarrow} \Sigma^+)\Sigma^* \cup \Sigma^*(L \stackrel{ins}{\leftarrow} \Sigma^*)\Sigma^+] = \emptyset.$$

When L is regular the language on the left-side of the equation of Lemma 1 is regular. Theorem 9 is proved using Lemma 1.

Theorem 9. *Given an NFA A , we can decide in polynomial time whether or not $L(A)$ is sdd -free.*

Theorem 10. *It is undecidable whether or not a context-free language L is sdd -free.*

We now consider the question of determining whether or not sdd -closed and sdd -free languages preserve their properties. We establish the following results which characterize sdd -closed and sdd -free languages with respect to basic operations such as intersection, union, catenation and complement. Notice that the basic operations are widely used in molecular biology, biochemistry and pharmacology, for instance, a complement under enzymatic activities inhibits an enzymatic activation that causes a disease or inflammation [8].

Theorem 11. *sdd -closed languages are closed under intersection and complement but not closed under union and catenation.*

Theorem 12. *sdd -free languages are closed under intersection but not closed under union, complement and catenation.*

5 Conclusions

From a site-directed deletion mutagenesis under enzymatic activities, we have introduced the site-directed deletion operation. We have designed linear time algorithms for determining whether or not $x \stackrel{sdd}{\leftarrow} y = \emptyset$ and $z \in x \stackrel{sdd}{\leftarrow} y$. We have shown that $L_1 \stackrel{sdd}{\leftarrow} L_2$ is regular when L_1 and L_2 are regular, however, $L_1 \stackrel{sdd}{\leftarrow} L_2$ may not be context-free when L_1 and L_2 are context-free. Given a context-free language L_1 and a regular language L_2 , both $L_1 \stackrel{sdd}{\leftarrow} L_2$ and $L_2 \stackrel{sdd}{\leftarrow} L_1$ are context-free. In addition, we have established that it is decidable whether or not a regular language L is sdd -closed and sdd -free in polynomial time, and it is undecidable whether or not a context-free language is sdd -closed and sdd -free.

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