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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 operation<sup>6</sup> 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  $\Sigma$  be a finite alphabet of characters and  $\Sigma^*$  be the set of all strings over  $\Sigma$ . The symbol  $\emptyset$  denotes the empty language and the symbol  $\lambda$  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

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

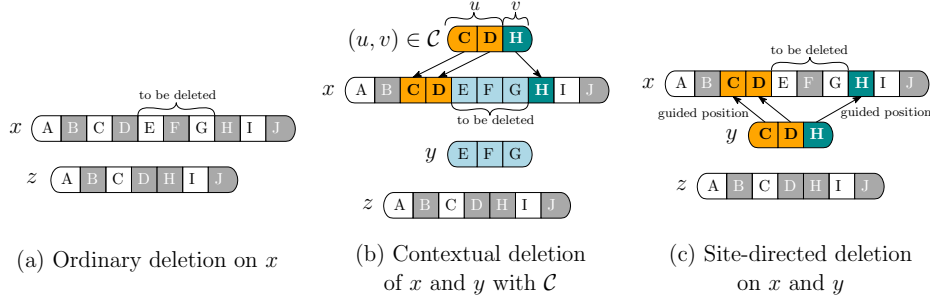


Fig. 1: Examples of ordinary deletion, contextual deletion and site-directed deletion. (a) An ordinary deletion of  $x$  results in a string  $z$  removing a substring  $EFG$ . The resulting string  $z$  is one of many possible deletion outputs. (b) A contextual deletion of  $x$  and  $y$  with a set  $\mathcal{C} \subseteq \Sigma^* \times \Sigma$  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  $\Sigma$  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,  $\delta$  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  $\delta$  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*  $\text{SDD}$  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*  $\text{SDD}^*$  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  $z \in x \xrightarrow{sd} y$ .
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  $L_1 \xrightarrow{sd} L_2$  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  $L_1 \xrightarrow{sd} L_2$ , 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  $\alpha$  be an arbitrary symbol of  $\Sigma$ . We set the following transitions of  $\omega$ :

- (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  $\alpha$  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  $\zeta$ , 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  $\zeta$ , and  $w_2$  does not contain occurrences of  $\zeta$ , in the decomposition of  $w_1$ , the first symbol  $\zeta$  must be in  $x_1$  and the last symbol  $\zeta$  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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