Bio-Inspired Operations on Formal Languages

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Preliminary Defense of Ph.D Thesis

Outline

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In Molecular Biology

Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA)

- are sequences over $\{A, G, C, T\ (U)\}$,
- has hydrogen bonds with the strongest complementary pairs A-T(U) and G-C.

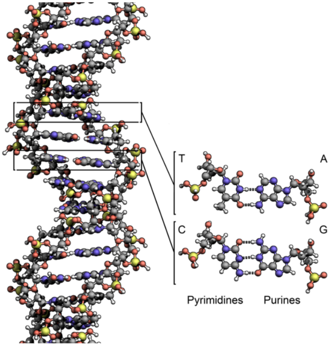

Figure: An example of double-stranded DNA.

DNA Rearrangements

DNA undergoes abnormal rearrangement such as insertion, deletion, inversion, and duplication.

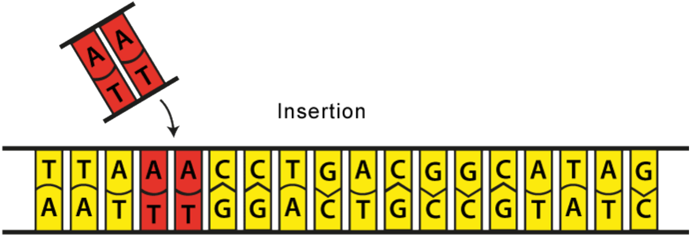

Figure: An example of insertion on a DNA sequence.

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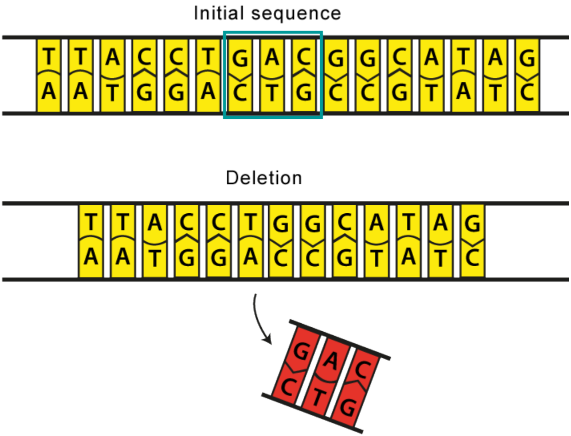


Figure: An example of deletion on a DNA sequence.

DNA Rearrangements

DNA undergoes abnormal rearrangement such as insertion, deletion, inversion, and duplication.

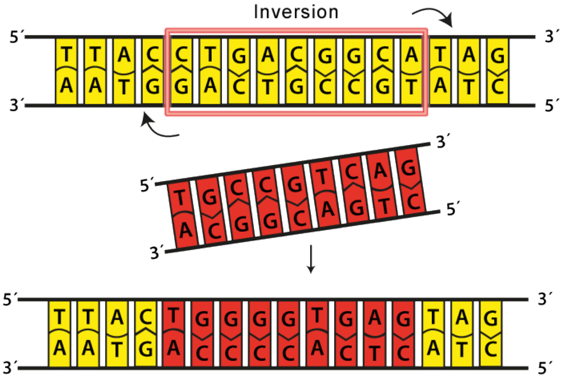
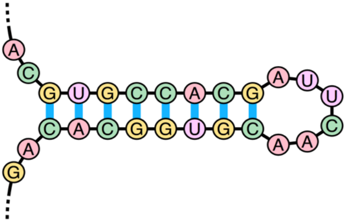


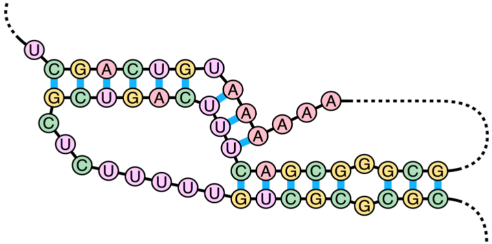
Figure: An example of inversion on a DNA sequence.

Secondary Structure

- An RNA is generated from *DNA transcription*
- The complementary paring *A*-*U* and *G*-*C* leads an RNA to form secondary structures



(a) Hairpin structure



(b) Pseudoknot structure

Figure: An example of RNA secondary structures

Relation between transformation and disease

Abnormal transformations on DNA (or RNA) are closely related to

- several diseases (can be inherited)
- species diversity

Figure: The Cri du chat (Cat-cry) syndrome caused by deletion mutation.

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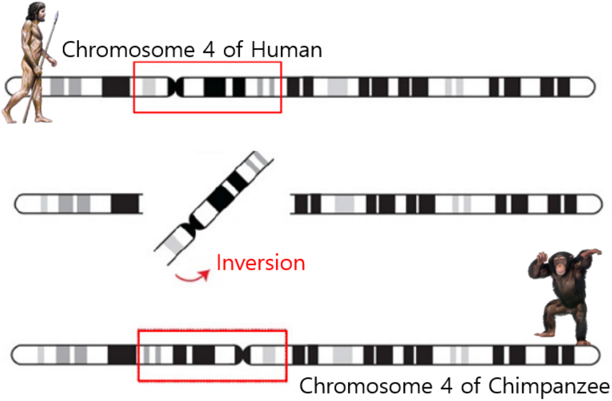

Figure: An inversion occurs on chromosome 4 between human and chimpanzee.

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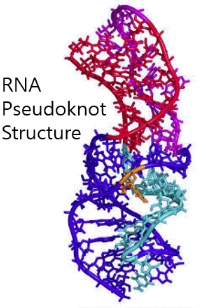

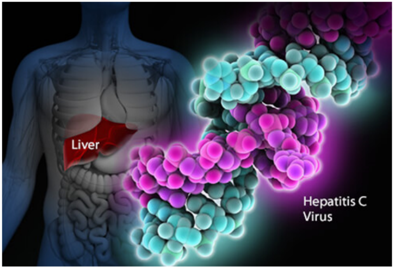

Figure: Pseudoknot structure is related to hepatitis C virus (HCV).

Relation between transformation and disease

For analyzing and investigating DNA transformations

- predict abnormal transformations (insertion, deletion, inversion, duplication...)
- deliberately introduce a transformation to normal sequence

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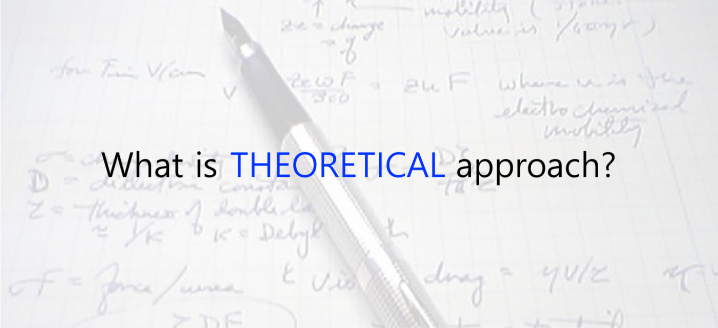

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In Formal Language Theory

Researchers in formal language theory characterize the biological phenomena into OPERATIONS on strings.

- Searls, "The computational linguistics of biological sequences", *Artificial Intelligence and Molecular Biology*, 1993
- Kari and Thierrin, "Contextual insertions/deletions and computability", *Information and Computation*, 1996
- Dassow et al., "Context-free evolutionary grammars and the structural language of nucleic acids", *Biosystems*, 1997
- Dassow et al., "Operations and language generating devices suggested by the genome evolution", *Theoretical Computer Science*, 2002
- Leupold et al., "Formal languages arising from gene repeated duplication", *Theoretical Computer Science*, 2004
- Enaganti et al., "A formal language model of DNA polymerase enzymatic activity", *Fundamenta Informaticae*, 2015

In Formal Language Theory

Researchers in formal language theory characterize the biological phenomena into OPERATIONS on strings.

Why is theoretical research needed?

- Genetic testing can take up to several months to receive the results
- The cost of genetic testing can be over \$2,000[1]
- Errors in genetic testing occur regularly[2]

[1] from U.S. national library of medicine, https://ghr.nlm.nih.gov

[2] Error rates in forensic DNA analysis: definition, numbers, impact and communication, 2014

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- ~~Genetic testing can take up to several months to receive the results~~ Reduce testing time by an efficient algorithm
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How does formal language theory work?

Outline

1. Motivation
   - Background from Molecular Biology
   - Related Works on Bio-Inspired Operations
   - Problems from a Formal Language Viewpoint
2. Main Results
   - Definition of Bio-Inspired Operations
   - Closure Properties of Bio-Inspired Operations
   - Membership Problem for Bio-Inspired Operations
   - Freeness of Bio-Inspired Operation
3. Conclusions
   - Summary
   - Future Works

In Formal Language Theory

Formal language theory can be applied to these problems in practice by

- Modeling biological phenomena as an operation $\clubsuit$
- Solving several theoretical problems
  - Closure: Decide whether or not languages in the Chomsky hierarchy are closed under the operation $\clubsuit$

    $$\text{Given a language } L, \text{ is } \clubsuit(L) \text{ REGULAR?}$$

  - Membership problem: Decide whether or not a given string x belongs to the language $\clubsuit(L)$
  - Freeness: Decide whether or not a given language L contains any string $x \in \clubsuit(L)$

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$$\text{Given } L, L \text{ is } \clubsuit\text{-free if } L \cap \clubsuit(L) = \emptyset$$

Our Goal

The objective of this thesis is to give a theoretical foundation for DNA computing by

- Characterizing realistic biological phenomena
  - The pseudo-inversion operation $\mathbb{PI}$
  - The pseudo-duplication operation $\mathbb{PD}_k$
  - The pseudoknot-generating operation $\mathbb{PK}_{\mathbb{R}}$
  - The site-directed insertion/deletion operations $\mathbb{SDI}, \mathbb{SDD}$
- Solving problems that might be applied to DNA computing in practice

Outline

Bio-Inspired Operation: Pseudo-Inversion

Definition

For a string $w = uxv \in \Sigma^*$, we define pseudo-inversion of w to be

$$\mathbb{PI}(w) = \{v^R x u^R \mid u, x, v \in \Sigma^*, uv \neq \lambda\}.$$

- for a string $w = w_1 w_2 \cdots w_n$, $w^R = w_n w_{n-1} \cdots w_1$
- λ denotes the empty string, and $\mathbb{PI}(\lambda) = \emptyset$
- extend $\mathbb{PI}$ to languages

$$\mathbb{PI}(L) = \bigcup_{w \in L} \mathbb{PI}(w)$$

- define iterated pseudo-inversion $\mathbb{PI}^*(L)$ as

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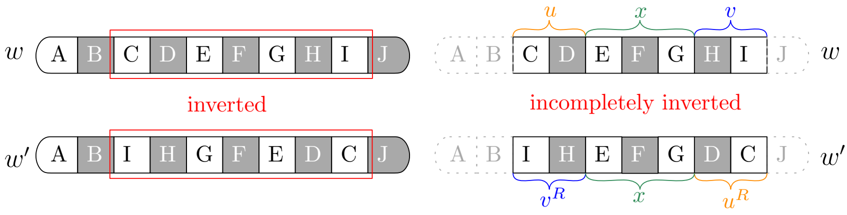

(a) Inversion (b) Pseudo-inversion

Bio-Inspired Operation: Pseudo-Duplication

Definition

For a string $w = uxv \in \Sigma^*$, we define k-pseudo-duplication $\mathbb{PD}_k$ of w to be

$$\mathbb{PD}_k(w) = \{uxx'v \mid u, x, v \in \Sigma^* \text{ and } d(x, x') \leq k\}.$$

- $d(x, x')$ denotes the smallest number of operations that transform x to x', the *edit-distance* between x and x'

$$d(city, kitty) = 2$$

- $\mathbb{PD}_k(L) = \bigcup_{w \in L} \mathbb{PD}_k(w)$ and $\mathbb{PD}_k^*(L) = \bigcup_{w \in L} \mathbb{PD}_k^*(w)$

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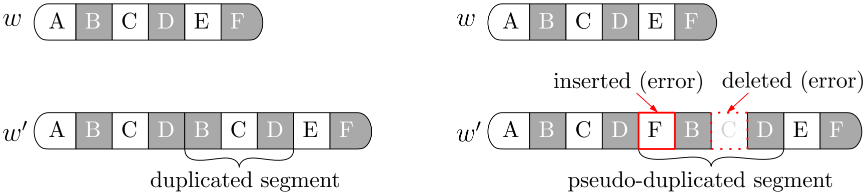


(a) Ordinary duplication

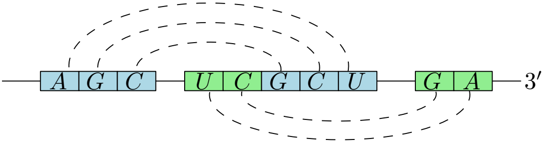
(b) Pseudo-duplication

Bio-Inspired Operation: Pseudoknot-Generating

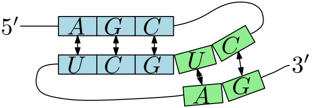
Definition

For a string $w = w_1 w_2 w_3$, we define the pseudoknot-generating operation of w to be

$$\mathbb{PK}_{\mathbb{R}}(w) = \{w_1 w_2 w_3 w_1^R w_4 w_3^R \mid w_1, w_2, w_3, w_4 \in \Sigma^+\}$$



(a) Sequence for pseudoknot



(b) Pseudoknot structure

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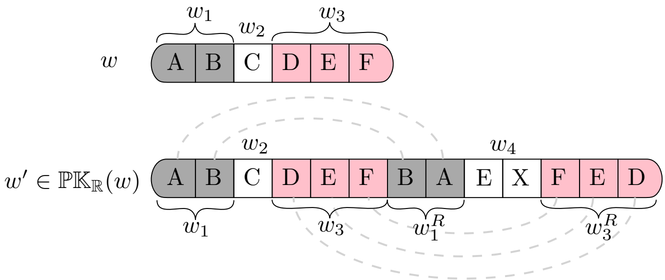

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- extend the pseudoknot-generating operation to languages

$$\mathbb{PK}_{\mathbb{R}}(L) = \bigcup_{w \in L} \mathbb{PK}_{\mathbb{R}}(w)$$

- define iterated $\mathbb{PK}_{\mathbb{R}}$ of w to be

$$\mathbb{PK}_{\mathbb{R}}^*(L) = \bigcup_{w \in L} \mathbb{PK}_{\mathbb{R}}^*(w)$$

Bio-Inspired Operation: Site-Directed Insertion

Definition

Given two strings $x = x_1 uv x_2$ and $y = uwv$, the site-directed insertion of y into x is defined to be

$$x \overset{sdi}{\leftarrow} y = \{x_1 uwvx_2 \mid u \neq \lambda \text{ and } v \neq \lambda\}.$$

- for a string $y = uwv$, we say (u, v) is an outfix of y
- an outfix (u, v) of y is an insertion guide of x if $x \overset{sdi}{\leftarrow} y \neq \emptyset$.
- extend site-directed insertion to languages

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

- site-directed insertion of L is inductively defined as $\mathbb{SDI}^0(L) = L$,

$$\text{and } \mathbb{SDI}^{i+1}(L) = \mathbb{SDI}^i(L) \overset{sdi}{\leftarrow} \mathbb{SDI}^i(L).$$

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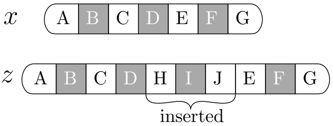
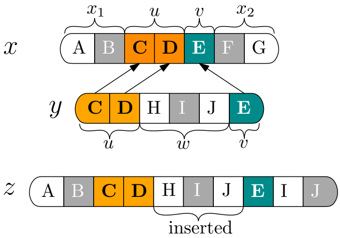


(a) Ordinary insertion on x



(b) Site-directed insertion of x and y

Bio-Inspired Operation: Site-Directed Deletion

Definition

Given two strings $x = x_1 uwv x_2$ and $y = uv$, the site-directed deletion from x by y is defined to be

$$x \overset{sdd}{\leftarrow} y = \{x_1 uv x_2 \mid u \neq \lambda \text{ and } v \neq \lambda\}.$$

- $y = uv$ is a deletion guide of x if $x \overset{sdd}{\leftarrow} y \neq \emptyset$.
- extend site-directed deletion to languages

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

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Bio-Inspired Operation: Site-Directed Deletion

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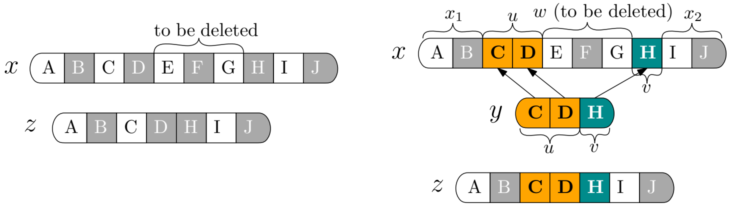

(a) Ordinary deletion on x (b) Site-directed deletion of x and y

Summary

- Pseudo-inversion $\mathbb{PI}$ of $w = uxv$:

$$\mathbb{PI}(w) = \{v^R x u^R \mid u, x, v \in \Sigma^* \text{ and } uv \neq \lambda\}$$

- Pseudo-duplication $\mathbb{PD}_k$ of $w = uxv$:

$$\mathbb{PD}_k(w) = \{uxx'v \mid u, x, v \in \Sigma^* \text{ and } d(x, x') \leq k\}$$

- Pseudoknot-generating $\mathbb{PK}_\mathbb{R}$ of $w = w_1 w_2 w_3$:

$$\mathbb{PK}_\mathbb{R}(w) = \{w_1 w_2 w_3 w_1^R w_4 w_3^R \mid w_1, w_2, w_3, w_4 \in \Sigma^+\}$$

- Site-directed insertion of y into x:

$$x \overset{sdi}{\leftarrow} y = \{x_1 uwv x_2 \mid x = x_1 uv x_2, y = uwv, u \neq \lambda \text{ and } v \neq \lambda\}$$

- Site-directed deletion from x by y:

$$x \overset{sdd}{\leftarrow} y = \{x_1 uv x_2 \mid x = x_1 uwv x_2, y = uv, u \neq \lambda \text{ and } v \neq \lambda\}$$

Outline

Closure Properties of Pseudo-Inversion

Definition

$\mathbb{PI}(w) = \{v^R x u^R \mid w = uxv, u, x, v \in \Sigma^*$ and $uv \neq \lambda\}$

Theorem

Regular languages are closed under the pseudo-inversion operation.

Closure Properties of Pseudo-Inversion

Theorem

Regular languages are closed under the pseudo-inversion operation.

Given an NFA $A = (Q, \Sigma, \delta, q_0, F)$ recognizing a language L, we construct a λ-NFA $B = (P, \Sigma, \gamma, p_0, F_B)$ recognizing $\mathbb{PI}(L)$.

- Q is a finite set of states
- Σ is the alphabet
- $\delta : Q \times (\Sigma \cup \lambda) \to 2^Q$
- $q_0 \in Q$ is the initial state
- $F \subseteq Q$ is the set of final states

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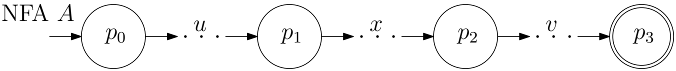

Closure Properties of Pseudo-Inversion

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λ-NFA $B = (P, \Sigma, \gamma, p_0, F_B)$ recognizing $\mathbb{PI}(L)$

- $P = Q \cup \tilde{Q} \cup (Q \times Q \times Q)$
- $F_B = \{q_0, \tilde{q}_0\}$
- γ is defined as follows:
  1. for all $p, q \in Q, a \in \Sigma$ and $p \in \delta(q, a)$, $q \in \gamma(p, a)$ and $\tilde{q} \in \gamma(\tilde{p}, a)$
  2. for all $p, q \in Q$, $(q, q, p) \in \gamma(p, \lambda)$, where $p \neq q_f$ or $q \notin F_B$
  3. for all $q, p, r_1, r_2 \in Q, a \in \Sigma$ and $r_2 \in \delta(r_1, a)$, $(q, r_2, p) \in \gamma((q, r_1, p), a)$
  4. for all $p, q \in Q$, $\tilde{q} \in \gamma((q, p, p), \lambda)$

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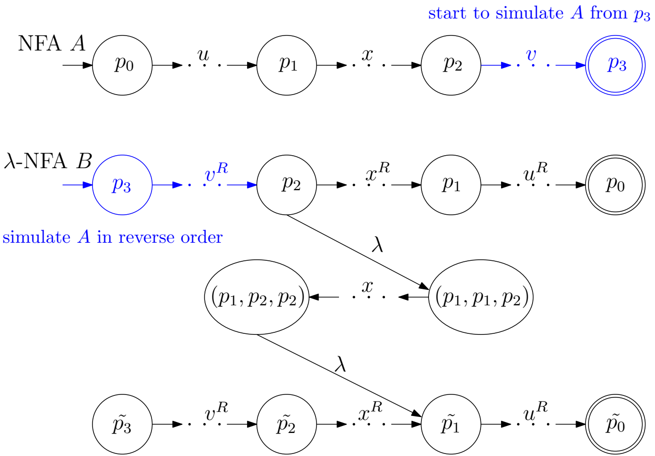

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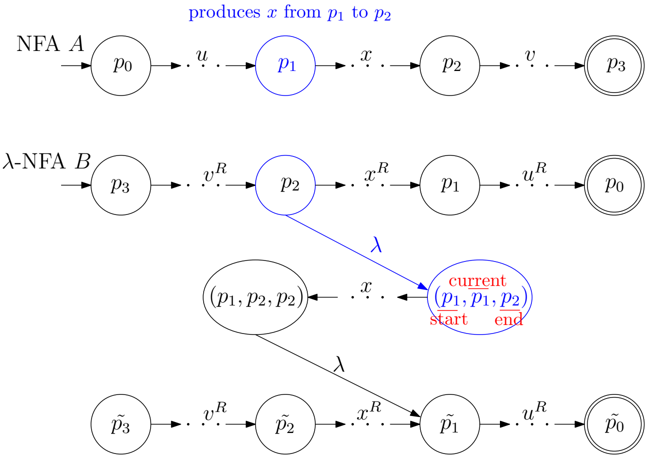

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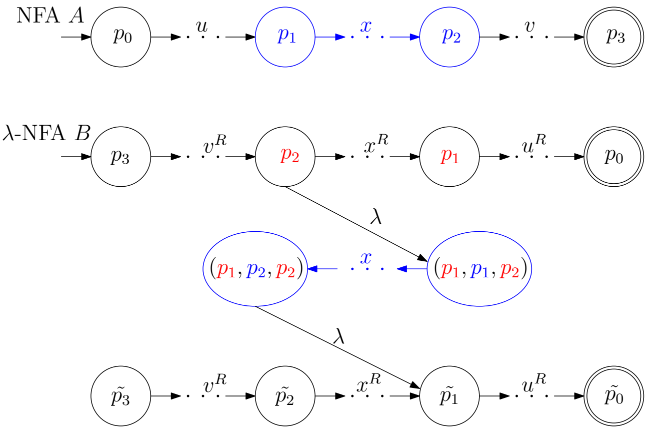

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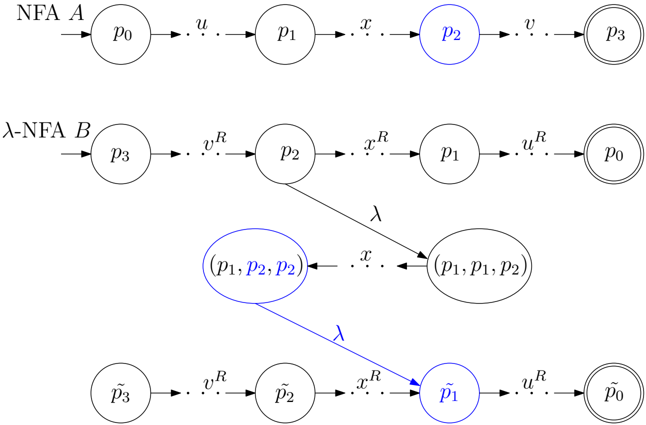

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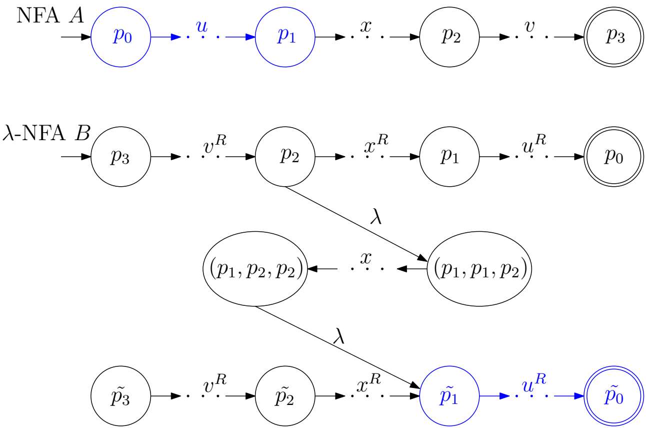

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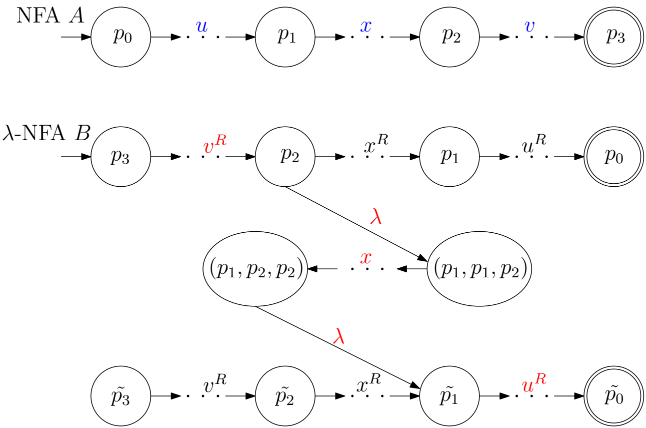


Closure Properties of Pseudo-Duplication

Definition

$\mathbb{PD}_k(w) = \{uxx'v \mid w = uxv, u, x, v \in \Sigma^* \text{ and } d(x, x') \leq k\}$

Theorem

Regular languages are not closed under the k-pseudo-duplication operation.

Closure Properties of Pseudo-Duplication

Theorem

Regular languages are not closed under the k-pseudo-duplication operation.

Let $L = L(a^*)$ over $\Sigma = \{a, b\}$. We show that

$$L(a^*b^*) \cap \mathbb{PD}_k(L) = \{a^ib^j \mid i \geq j\} \text{ is not regular.}$$

- $\{a^ib^j \mid i \geq j\}$ is not regular by the *pumping lemma* for regular languages
- Since $\underbrace{L(a^*b^*)}_{regular} \cap \mathbb{PD}_k(L) = \underbrace{\{a^ib^j \mid i \geq j\}}_{not\ regular}$,

$$\mathbb{PD}_k(L) \text{ is not regular!}$$

Summary of Closure Properties

- For $\mathbb{PI}$, Closed (regular), Not closed (context-free)
- For $\mathbb{PD}_k$, Not closed (regular, context-free), Closed (context-sensitive)
- For $\mathbb{PK}_{\mathbb{R}}$, Not closed (regular, context-free)
- For $L_1 \overset{sdi}{\leftarrow} L_2$, Closed (regular), Not closed (context-free)
- For $L_1 \overset{sdd}{\leftarrow} L_2$, Closed (regular), Not closed (context-free)

Outline

Membership Problem for Site-Directed Deletion

Definition

Site-directed deletion from x by y:

$$x \overset{sdd}{\leftarrow} y = \{x_1 uv x_2 \mid x = x_1 {\color{blue}u}{\color{red}w}{\color{blue}v} x_2, y = {\color{blue}uv}, u \neq \lambda \text{ and } v \neq \lambda\}$$

Problem

Given three strings x, y, and z, where $|x| \geq |z| \geq |y| \geq 2$, can we determine whether or not

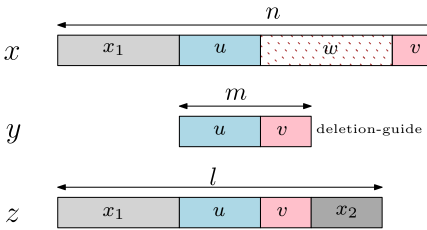
$$z \in x \overset{sdd}{\leftarrow} y?$$

Membership Problem of Site-Directed Deletion

Theorem

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

Suppose that there exist x, y, and z such that $z \in x \overset{sdd}{\leftarrow} y$.

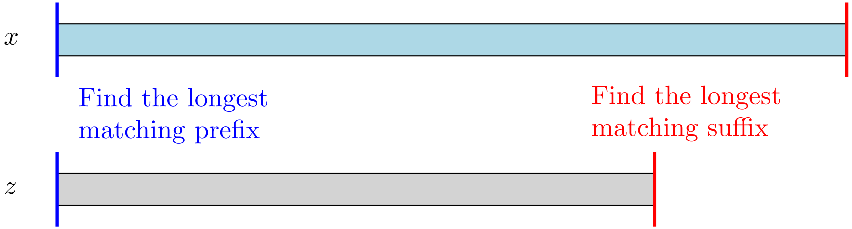


Membership Problem of Site-Directed Deletion

Theorem

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

Scan both ends of x and z until a mismatch occurs.



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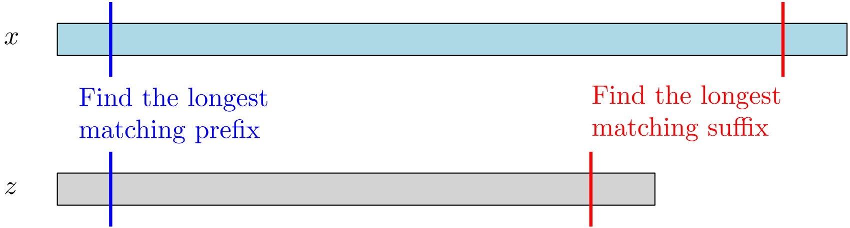

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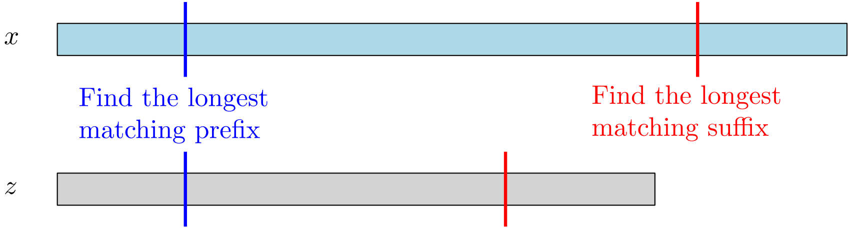
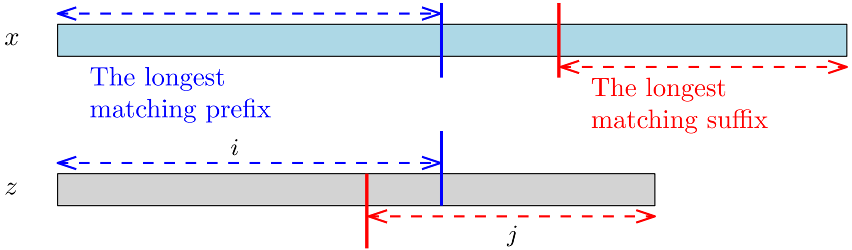


Membership Problem of Site-Directed Deletion

Theorem

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

$x[1:i] = z[1:i]$ and $x[n-j+1:n] = z[l-j+1:l]$



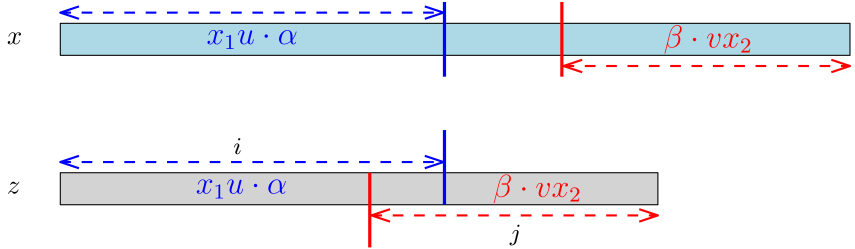
Membership Problem of Site-Directed Deletion

Theorem

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

If $z[1 : i]$ and $z[l{-}j{+}1]$ do not overlap ($\alpha, \beta = \lambda$),

$$z[1 : i] \cdot z[l{-}j{+}1 : l] = x_1 uvx_2.$$



Membership Problem of Site-Directed Deletion

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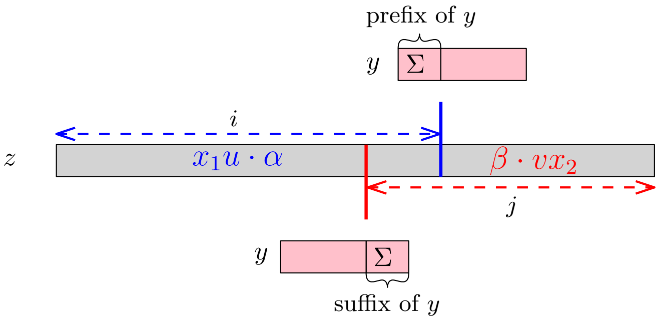
Given three strings x, y, and z, we can determine whether or not $z \in x \overset{sdd}{\leftarrow} y$ in $O(n)$ time, where $n = |x|$ and $|x| \geq |z| \geq |y| \geq 2$.

We check whether or not $y = uv$ is a substring of z.



Membership Problem of Site-Directed Deletion

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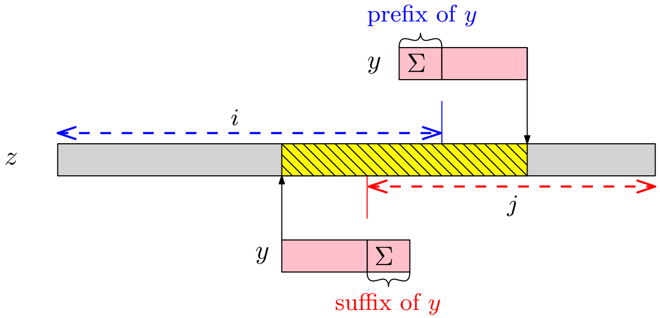
Given three strings x, y, and z, we can determine whether or not $z \in x \overset{sdd}{\leftarrow} y$ in $O(n)$ time, where $n = |x|$ and $|x| \geq |z| \geq |y| \geq 2$.

A prefix of y should be a suffix of the longest matching prefix of z,
A suffix of y should be a prefix of the longest matching suffix of z.

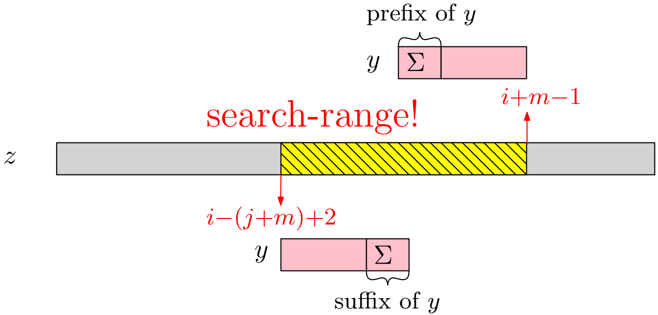


Membership Problem of Site-Directed Deletion

Theorem

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

We check for an occurrence of y within $z[l-(j+m)+2 : i+m-1]$.

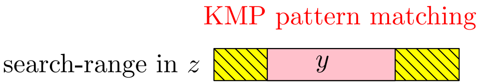


Membership Problem of Site-Directed Deletion

Theorem

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

KMP algorithm returns 1 if y occurs in the search-range.



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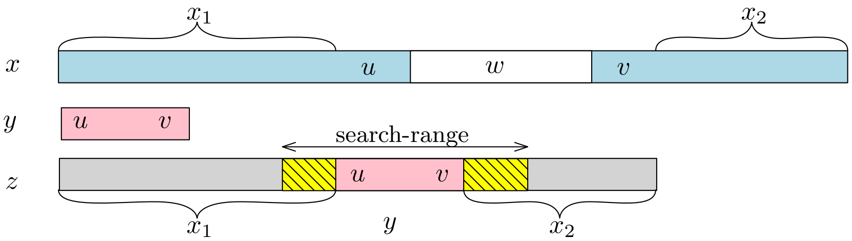

Summary

- Given two strings u and v of length n, we can determine whether or not $v \in \mathbb{PI}(u)$ (and, $v \in \mathbb{PI}^*(u)$) in $O(n)$ time

- Given a string w and an FA A,

$$w \in \mathbb{PK}_{\mathbb{R}}(L(A)) \text{ iff } I_{pk}(w) \cap I_p(w, A) \neq \emptyset$$

- Given two strings x and y, we can determine whether or not $x \overset{sdi}{\leftarrow} y \neq \emptyset$ in $O(n+m)$ time, where $|x| = n$ and $|y| = m$

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

Outline

Freeness of Pseudoknot-Generating

Definition

$\mathbb{PK}_{\mathbb{R}}(w) = \{w_1 w_2 w_3 w_1^R w_4 w_3^R \mid w = w_1 w_2 w_3 \text{ and } w_1, w_2, w_3, w_4 \in \Sigma^+\}$

Theorem

For a given context-free language L, it is undecidable to determine whether or not L is $\mathbb{PK}_{\mathbb{R}}$-free.

A language L is $\mathbb{PK}_{\mathbb{R}}$-free if $L \cap \mathbb{PK}_{\mathbb{R}}(L) = \emptyset$.

Example

The language $L = \{computer, computeroccret\}$ is not $\mathbb{PK}_{\mathbb{R}}$-free since

$$computeroccret \in \mathbb{PK}_{\mathbb{R}}(computer).$$

Freeness of Pseudoknot-Generating

Theorem

For a given context-free language L, it is undecidable to determine whether or not L is $\mathbb{PK}_{\mathbb{R}}$-free.

We use a reduction from the *Post Correspondence Problem* (PCP)

- Let $((u_1, u_2, \ldots, u_n), (v_1, v_2, \ldots, v_n))$ be an instance of PCP, where $u_i, v_i \in \Sigma^*$ and $1 \leq i \leq n$
- A solution of the PCP instance is $i_1, \ldots, i_k \in \{1, \ldots, n\}$ such that

$$u_{i_1} \cdots u_{i_k} = v_{i_1} \cdots v_{i_k}$$

Freeness of Pseudoknot-Generating

Theorem

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We use a reduction from the *Post Correspondence Problem* (PCP)

Example

Let $I_{PCP} = ((\underbrace{ab}_{u_1}, \underbrace{bbb}_{u_2}, \underbrace{a}_{u_3})(\underbrace{ab}_{v_1}, \underbrace{b}_{v_2}, \underbrace{bba}_{v_3}))$.

The solution is $2, 3, 1$ since

$$u_2 u_3 u_1 = v_2 v_3 v_1 = bbbaab.$$

Freeness of Pseudoknot-Generating

Theorem

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We use a reduction from the *Post Correspondence Problem* (PCP)

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- A solution of this instance is $i_1, \ldots, i_k \in \{1, \ldots, n\}$ such that

$$u_{i_1} \cdots u_{i_k} = v_{i_1} \cdots v_{i_k}$$

- PCP is undecidable!

Freeness of Pseudoknot-Generating

Theorem

For a given context-free language L, it is undecidable to determine whether or not L is $\mathbb{PK}_{\mathbb{R}}$-free.

Let $L = L_1 \cup L_2$, where

$$L_1 = \{\$ i_k i_{k-1} \cdots i_1 \$' \% \# u_{i_1} u_{i_2} \cdots u_{i_k} \#' \$' j_1 j_2 \cdots j_l \$ \% \#' v_{j_l}^R v_{j_{l-1}}^R \cdots v_{j_1}^R \#\},$$

$$L_2 = \{\$ i_k i_{k-1} \cdots i_1 \$' \% \# u_{i_1} u_{i_2} \cdots u_{i_k} \#'\},$$

for $k, l \geq 1, 1 \leq i_1, \ldots, i_k, j_1, \ldots, j_l \in \{1, \ldots, k\}$.

Freeness of Pseudoknot-Generating

Theorem

For a given context-free language L, it is undecidable to determine whether or not L is $\mathbb{PK}_{\mathbb{R}}$-free.

If there is a solution $i_1 i_2 \cdots i_k = j_1 j_2 \cdots j_l$ such that

$$u_{i_1} u_{i_2} \cdots u_{i_k} = v_{j_1} v_{j_2} \cdots v_{j_l},$$

L is not $\mathbb{PK}_{\mathbb{R}}$-free.

$$x \in L_2 \quad \overbrace{\$ \; i_k i_{k-1} \cdots i_1 \; \$'}^{w_1} \; \overbrace{\%}^{w_2} \; \overbrace{\# \; u_{i_1} u_{i_2} \cdots u_{i_k} \; \#'}^{w_3}$$

$$y \in L_1 \quad \underbrace{\$ \; i_k i_{k-1} \cdots i_1 \; \$'}_{w_1} \; \underbrace{\%}_{w_2} \; \underbrace{\# \; u_{i_1} u_{i_2} \cdots u_{i_k} \; \#'}_{w_3} \; \underbrace{\$' \; j_1 j_2 \cdots j_l \; \$}_{w_1^R} \; \underbrace{\%}_{w_4} \; \underbrace{\#' \; v_{j_1}^R v_{l-1}^R \cdots v_{j_1}^R \; \#}_{w_3^R}$$

Freeness of Pseudoknot-Generating

Theorem

For a given context-free language L, it is undecidable to determine whether or not L is $\mathbb{PK}_{\mathbb{R}}$-free.

If there is a solution $i_1 i_2 \cdots i_k = j_1 j_2 \cdots j_l$ such that

$$u_{i_1} u_{i_2} \cdots u_{i_k} = v_{j_1} v_{j_2} \cdots v_{j_l},$$

L is not $\mathbb{PK}_{\mathbb{R}}$-free.

PCP is undecidable, thus, it is undecidable!

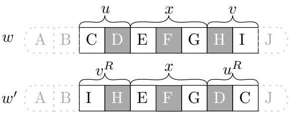
Summary of Freeness

- A given language L is $\underline{\mathbb{PI}\text{-free}}$ if $(\Sigma^* \cdot \mathbb{PI}(L) \cdot \Sigma^*) \cap L = \emptyset$.
  - Regular language L: Decidable in polynomial time
  - Context-free language L: Undecidable
- A given language L is $\underline{\mathbb{PK}_{\mathbb{R}}\text{-free}}$ if $L \cup \mathbb{PK}_{\mathbb{R}}(L) = \emptyset$.
  - Regular language L: Decidable in polynomial time
  - Context-free language L: Undecidable
- A given language L is $\underline{\mathbb{SDI}\text{-closed}}$ if $(L \overset{sdi}{\leftarrow} L) \subseteq L$.
  - Regular language L: Decidable in polynomial time
  - Context-free language L: Undecidable
- A given language L is $\underline{\mathbb{SDD}\text{-closed}}$ if $(L \overset{sdd}{\leftarrow} L) \subseteq L$.
  - Regular language L: Decidable in polynomial time
  - Context-free language L: Undecidable
- A given language L is $\underline{\mathbb{SDD}\text{-free}}$ if $x \overset{sdd}{\leftarrow} y = \emptyset$, where $x, y \in L$.
  - Regular language L: Decidable in polynomial time
  - Context-free language L: Undecidable

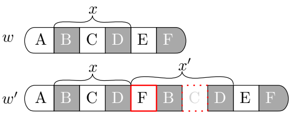
Outline

Summary of Thesis

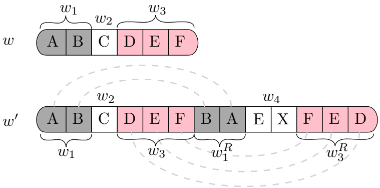
We have studied bio-inspired operations and their properties.



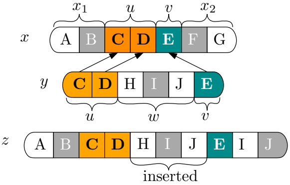
Pseudo-Inversion: Closure Properties and Decidability
in *Natural Computing*, 2016



Duplications and Pseudo-Duplications
in *International Journal of Unconventional Computing*, 2016



Pseudoknot-Generating Operation
in *Theoretical Computer Science*, 2017



Site-Directed Insertion
in *Theoretical Computer Science*, 2017

Outline

Future Works

Closure properties for iterated bio-inspired operations:

- For a bio-inspired operation ♣, iterated ♣ closure is not easy
- Finding a counter example to or a construction for iterated ♣

Bio-inspired operation on finite tree automata and tree grammars:

- Tree automata accept tree structures, while FA accept strings
- Tree automata were introduced in the 1900s to solve certain decision problems in logic
- Tree automata and tree grammars can be used to characterize structural properties of DNA (RNA)

Thank you for your attention!