Algorithms for determining transposons in gene sequences

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Abstract

Some genes can change their relative locations in a genome. Thus for different individuals of the same species, the orders of genes might be different. Such jumping genes are called transposons. A practical problem is to determine transposons in given gene sequences. Through an intuitive rule, we transform the biological problem of determining transposons into a rigorous mathematical problem of determining the longest common subsequence. Depending on whether the gene sequence is linear (each sequence has a fixed head and tail) or circular (we can choose any gene as the head, and the previous one is the tail), and whether genes have multiple copies, we classify the problem of determining transposons into four scenarios: (1) linear sequences without duplicated genes; (2) circular sequences without duplicated genes; (3) linear sequences with duplicated genes; (4) circular sequences with duplicated genes. With the help of graph theory, we design fast algorithms for different scenarios. We also derive some results that might be of theoretical interests in combinatorics.

KEY WORDS: transposon, gene sequence, algorithm, graph

1 Introduction

Various genome rearrangement events, such as inversion, insertion, deletion, and duplication, can change the gene sequence. Such rearrangement events lead to the existence of transposons (also called transposable elements or jumping genes), which are DNA sequences that can change their relative locations in a genome.
positions within the genome of a cell. The mechanism of such transpositions can be expressed as a mixture of copy, cut, paste, and invert [1]. Transposons are common in various species. For the human genome, the proportion of transposons is approximately 44% [2]. Transposons can participate in controlling gene expression [3], and they are related to several diseases, such as cancer [4], hemophilia [5], and porphyria [6]. Transposons can drive rapid phenotypic variations, which cause complicated cell behaviors [7, 8, 9, 10, 11]. Transposons can be used to detect cancer drivers [12] and potential therapies [13]. Transposons are also essential for the development of *Oxytricha trifallax* [14], antibiotic resistance of bacteria [15], and the proliferation of various cells [16, 17, 18]. With the presence of transposons, the regulation between genes might be affected, which is a challenge for inferring the structures of gene regulatory networks [19] and general transcriptome analysis [20, 21].

There have been many algorithms developed to determine transposons, such as MELT [22], ERVcaller [23], and TEMP2 [24]. For more details, readers may refer to other papers [25, 26]. However, they aim at targeting transposons (possibly very short, not whole genes) from raw DNA sequencing data. The sequencing data only contain imperfect information about the true DNA sequence, and the data quality depends on some factors that vary across different datasets [27]. Besides, they need a corresponding genome or reference transposon libraries. Therefore, these algorithms focus more on the implementation aspect, not the theoretical aspect of the transposon determination problem.

In this paper, we consider an ideal scenario: We have some accurate sequences of genes (not nucleotides) from different individuals. Since some genes are transposons, these gene sequences are different. The goal is to compare these sequences and determine the transposons.

In the copy-paste (duplication) case and deletion case, we can compare the numbers of copies of genes for different individuals to determine the transposons that have changed their copy numbers. In the inversion case, we can check the direction of genes to determine transposons that have changed their orientations [28]. In the cut-paste (insertion) case, the compositions of gene sequences are the same, but the orders of genes differ. It is not straightforward to uniquely determine which genes have changed their relative locations. Instead, we can consider the complement of transposons, which keep their relative locations and form a common subsequence of gene sequences from different individuals. Notice that genes in a subsequence does not need to be adjacent in the original sequences, different from a substring. We aim at explaining the difference among gene sequences
with minimal transposons, meaning that we want to maximize the length of the complement of transposons. Thus we define the transposons to be the complement of the longest common subsequence.

It is common to use the length of the longest common subsequence as a quantitative score for comparing DNA sequences [29, 30, 31]. The longest common subsequence has also been used to define ultraconserved elements [32] or remove incongruent markers [33].

Determining the longest common subsequence is a classical problem in computer science. In the most commonly studied scenario, there are two sequences with possibly repeated genes, and the sequence length is $n$. The goal is to find the longest common subsequence, where the length is counted by gene copies. This can be solved by dynamic programming with $O(n^2)$ time complexity [34], but $O(n^{2-\epsilon})$ time complexity for any $\epsilon > 0$ is impossible [35]. This also can be solved with $o(n)$ space complexity and $O(n^3)$ time complexity [36]. In another commonly studied scenario, there are $m$ sequences with possibly repeated genes, and the sequence length is $n$. The goal is to find the longest common subsequence, where the length is counted by gene copies. This problem is equivalent to the maximum clique problem in graph theory, which is NP-hard [37]. A standard dynamic programming algorithm has $O(n^m)$ time complexity [38]. There have been other faster algorithms [39, 40, 41]. For more works in these two classical scenarios, readers may refer to more thorough reviews [42, 43, 44].

In this paper, we consider four scenarios that are different from the classical ones. These four scenarios are determined by two factors: whether the gene sequence is linear or circular (since some species have circular DNAs while others not), and whether genes have multiple copies. When genes have multiple copies, we only consider common subsequences that consist of all or none of copies of the same gene. Scenario 1 has linear sequences without duplicated genes; Scenario 2 has circular sequences without duplicated genes; Scenario 3 has linear sequences with duplicated genes; Scenario 4 has circular sequences with duplicated genes. Scenarios 2, 4 have circular sequences, and Scenarios 3, 4 only consider subsequences that consist of all or none copies of the same gene, and calculate the length by genes. As far as we know, these new settings are not studied by other papers, and known methods cannot be directly applied. Thus we need to develop new algorithms, such as Algorithm 3 for Scenario 2. Besides, known methods only aim at finding one longest common subsequence. When the longest common subsequence is not unique, we also need to classify whether a gene appears in all/some/none of the longest common subsequences. Determining all longest common subsequences is too time-consuming, and we develop
corresponding algorithms with polynomial time complexities for Scenarios 1,2 (Algorithms 2,4).

Scenario 1 (except the case with multiple longest common subsequences) is similar to well-studied classical situations, and our method (Algorithm 1) is easily derived from standard algorithms. Scenarios 3,4 are equivalent to maximum clique problems in graphs and hypergraphs, which are NP-hard. These properties are also similar to the classical situations. For these NP-hard scenarios, we design fast heuristic algorithms (Algorithms 5,6) and test them to find that they only fail in rare cases. These heuristic algorithms are similar to those classical algorithms for the maximum clique problem [45].

The author of this paper proposed the idea of using the longest common subsequence to find transposons and Algorithm 1 in a previous paper [46], where other coauthors applied Algorithm 1 to study the “core-gene-defined genome organizational framework” (the complement of transposons) in various bacteria, and found that for different species, the transposon distribution and developmental traits are correlated. This paper considers other situations (especially when the longest common subsequence is not unique), and can be regarded as a theoretical sequel of that previous paper. Algorithm 1 is contained in this paper for the sake of completeness.

In sum, our main contributions are Algorithms 2,3,4 and Proposition 1 that builds the equivalence between Scenario 3 and the maximum clique problem.

We first describe the setup for the problem of determining transposons and transform it into the problem of finding the longest common subsequence. In the following four scenarios, we transform them into corresponding graph theory problems and design algorithms. We finish with some discussions. All the algorithms in this paper have been implemented in Python. See https://github.com/YueWangMathbio/Transposon for the code files.

2 Setup

For some species, the DNA is a line [47]. We can represent this DNA as a linear gene sequence of distinct numbers that represent genes: (1,2,3,4). If some genes change their transcriptional orientations, we can simply detect them and handle the remaining genes. Now a linear DNA naturally has a direction (from 5’ end to 3’ end), thus (1,2,3,4) and (4,3,2,1) are two different gene sequences.

Consider two linear gene sequences from different individuals: (1,2,3,4) and (1,4,2,3). We can intuitively detect that gene 4 changes its relative
position, and should be regarded as a transposon. However, changing the
positions of genes 2, 3 can also transform one sequence into the other. The
reason that we think gene 4 (not genes 2, 3) changes its relative position is
that the number of genes we need to move is smaller. However, the number
of genes that change their relative locations is difficult to determine. We can
consider the complement of transposons, i.e., genes that do not change their
relative positions. These fixed genes can be easily defined as the longest
common subsequence of given gene sequences. Here a common subsequence
consists of some genes (not necessarily adjacent, different from a substring)
that keep their relative orders in the original sequences. Thus transposons
are the complement of this longest common subsequence. Notice that the
longest common subsequence might not be unique. We classify genes by
their relations with the longest common subsequence(s). The motivation of
classifying transposons with respect to the intersection and union of longest
common subsequences is similar to defining essential variables with Markov
boundaries in causal inference [48].

**Definition 1.** A gene is a **proper-transposon** if it is not contained in any
longest common subsequence. A gene is a **non-transposon** if it is contained
in every longest common subsequence. A gene is a **quasi-transposon** if it
is contained in some but not all longest common subsequences.

In the example of (1, 2, 3, 4) and (1, 4, 2, 3), the unique longest com-
mon subsequence is (1, 2, 3). Thus 4 is a proper-transposon, and 1, 2, 3 are
non-transposons. In the following, we consider other scenarios, where the
proper/quasi/non-transposons still follow Definition 1 but the definition of
the longest common subsequence differs.

For some species, the DNA is a circle, not a line [49]. A circular DNA
also has a natural direction (from 5’ end to 3’ end), and we use the clock-
wise direction to represent this natural direction. In the circular sequence
scenario, a common subsequence is a circular sequence that can be obtained
from each circular gene sequence by deleting some genes. See Fig. 1 for two
circular gene sequences and their longest common subsequence. Notice that
we can rotate each circular sequence for a better match.

A gene might have multiple copies (duplicated) in a gene sequence [50].
Notice that the definition of the transposon is a gene (specific DNA se-
quence) that has the ability to change its position, not a certain copy of
a gene that changes its position. This means transposons should be de-
defined for genes, not gene copies. Thus we should only consider common
subsequences that consist of all or none copies of the same gene. When
calculating the length of a common subsequence, we should count genes,
not gene copies. Consider two linear sequences \((4,1,2,1,1,3,2,4,1,1)\) and \((4,1,2,3,1,1,2,1,1,4)\). If we consider any subsequences, the longest common subsequence is \((4,1,2,1,1,2,1,1)\); if we only consider subsequences that contain all or none copies of the same gene, but count the length by copies, the longest common subsequence is \((1,2,1,1,2,1,1)\); if we only consider subsequences that contain all or none copies of the same gene, and count the length by genes, the unique longest common subsequence is \((4,2,3,2,4)\), and gene 1 is a proper-transposon.

When we consider circular gene sequences with duplicated genes, we should still only consider subsequences that consist of all or none copies of the same gene, and calculate the length by genes. Notice that circular sequences can be rotated. See Fig. 2 for two circular gene sequences with duplicated genes and their longest common subsequence.

\[
\begin{align*}
\text{Figure 2: Two circular gene sequences with duplicated genes and their longest common subsequence, corresponding to Scenario 4.}
\end{align*}
\]
sequence that is a common subsequence of these $m$ sequences. Here circular sequences can be rotated.

**Scenario 3:** Consider $m$ linear sequences of genes $1, \ldots, n$, where each gene can have multiple copies in each sequence. Determine the longest linear sequence that is a common subsequence of these $m$ sequences. Only consider subsequences that consist of all or none copies of the same gene, and calculate the length by genes.

**Scenario 4:** Consider $m$ circular sequences of genes $1, \ldots, n$, where each gene can have multiple copies in each sequence. Determine the longest circular sequence that is a common subsequence of these $m$ sequences. Only consider subsequences that consist of all or none copies of the same gene, and calculate the length by genes. Here circular sequences can be rotated.

These four scenarios correspond to different algorithms, and will be discussed separately.

## 3 Linear sequences without duplicated genes

In Scenario 1, consider $m$ linear gene sequences, where each sequence contains $n$ genes $1, \ldots, n$. Each gene has only one copy. For such permutations of $1, \ldots, n$, we need to find the longest common subsequence.

### 3.1 A graph representation of the problem

Brute-force searching that tests whether each subsequence appears in all sequences is not applicable, since the time complexity is exponential in $n$. To develop a polynomial algorithm, we first design an auxiliary directed graph $G$.

**Definition 2.** For $m$ linear sequences with $n$ non-duplicated genes, the corresponding **auxiliary graph** $G$ is a directed graph, where each vertex is a gene $g_i$, and there is a directed edge from $g_i$ to $g_j$ if and only if $g_i$ appears before $g_j$ in all $m$ sequences.

A directed path $g_1 \rightarrow g_2 \rightarrow g_3 \rightarrow \cdots \rightarrow g_4 \rightarrow g_5$ in $G$ corresponds to a common subsequence $(g_1, g_2, g_3, \ldots, g_4, g_5)$ of $m$ sequences, and vice versa. We add 0 to the head of each sequence and $n + 1$ to the tail. Then the longest common subsequence must start at 0 and end at $n + 1$. The problem of finding the longest common subsequence becomes finding the longest path from 0 to $n + 1$ in $G$. See Fig. 3 for an example of using the auxiliary graph to determine transposons. This auxiliary graph $G$ has no directed
loop (acyclic). If there exists a loop $g_1 \rightarrow g_2 \rightarrow g_3 \rightarrow \cdots \rightarrow g_4 \rightarrow g_1$, then $g_1$ is prior to $g_4$ and $g_4$ is prior to $g_1$ in all sequences, a contradiction.

![Graph Diagram]

Figure 3: The auxiliary graph $\mathcal{G}$ of two sequences $([0], 1, 2, 3, 4, [5])$ and $([0], 1, 4, 2, 3, [5])$. The unique longest path (double arrows) from 0 to 5 is $0 \rightarrow 1 \rightarrow 2 \rightarrow 3 \rightarrow 5$, meaning that the unique longest common sequence is $([0], 1, 2, 3, [5])$. Thus 1, 2, 3 are non-transposons, and 4 is a proper transposon.

3.2 Find the longest path

Determining the longest path between two vertices in a directed acyclic graph can be solved by a standard dynamic programming algorithm. For a vertex $g_i \in \{0, 1, \ldots, n\}$, consider the longest path from $g_i$ to $n + 1$. Since there exists an edge $g_i \rightarrow n + 1$, and $\mathcal{G}$ is acyclic, this longest path exists. If the longest path is not unique, assign one arbitrarily.

**Definition 3.** Define $F_+(g_i)$ to be the length of the longest path from $g_i$ to $n + 1$ in $\mathcal{G}$, and $H_+(g_i)$ to be the vertex next to $g_i$ in this path.

$F_+$ and $H_+$ can be calculated recursively: For one gene $g_i$, consider all genes $g_j$ with an edge $g_i \rightarrow g_j$ in $\mathcal{G}$. The gene $g_j$ with the largest $F_+(g_j)$ is assigned to be $H_+(g_i)$, and $F_+(g_i) = F_+(g_j) + 1$. If $g_l \rightarrow n + 1$ is the only edge that starts from gene $g_l$, then $F_+(g_l) = 1$, and $H_+(g_l) = n + 1$. In other words,

$$H_+(g_i) = \arg \max_{\{g_j \text{ with } g_i \rightarrow g_j\}} F_+(g_j);$$

$$F_+(g_i) = 1 + F_+[H_+(g_i)].$$
Then $0 \rightarrow H_+(0) \rightarrow H_+^2(0) \rightarrow H_+^3(0) \rightarrow \cdots \rightarrow H_+^{f-1}(0) \rightarrow H_+^f(0) = n + 1$, denoted by $L_0$, is a longest path in $G$. Here $f = F_+(0)$, and $H_+^f$ is the $i$th iteration of $H_+$.

### 3.3 Test the uniqueness of the longest path

To test whether quasi-transposons exist, we need to check the uniqueness of this longest path.

**Definition 4.** For $g_i \in \{1, \ldots, n, n + 1\}$, define $F_-(g_i)$ to be the length of the longest path from 0 to $g_i$ in $G$, and $H_-(g_i)$ to be the vertex prior to $g_i$ in this path.

$F_-$ and $H_-$ can be calculated similar to $F_+$ and $H_+$. We can see that

$$F_+(g_i) + F_-(g_i) = n + 1,$$

a longest path from 0 through $g_i$ to $n + 1$. For $g_i \notin L_0$, if $F_+(g_i) + F_-(g_i) < F_+(0)$, then $g_i$ is a proper-transposon; if $F_+(g_i) + F_-(g_i) = F_+(0)$, then $g_i$ is a quasi-transposon. If every $g_i \notin L_0$ is a proper-transposon, then the longest common subsequence is unique, and all genes in $L_0$ (excluding the auxiliary 0 and $n + 1$) are non-transposons. The procedure of determining transposons stops here. Otherwise, the longest common subsequence is not unique, and we need to find quasi-transposons in $L_0$.

### 3.4 Find quasi-transposons

When determining all quasi-transposons $g_1, \ldots, g_k$ not in $L_0$, as described above, we construct corresponding longest paths $L_1, \ldots, L_k$ from 0 to $n + 1$, where each $L_i$ passes through $g_i$. We claim that a gene $g_j \in L_0$ is a non-transposon if and only if $g_j$ is contained in all $L_1, \ldots, L_k$. To prove this, we need the following lemma.

**Lemma 1.** In Scenario 1 of linear sequences without duplicated genes, each quasi-transposon $g_i$ has a corresponding quasi-transposon $g_j$, so that no longest common subsequence can contain both $g_i$ and $g_j$.

If a gene $g_j \in L_0$ is a non-transposon, then it is contained in all $L_1, \ldots, L_k$. If $g_j \in L_0$ is a quasi-transposon, by Lemma 1, there is a quasi-transposon $g_i \notin L_0$ which is mutual-exclusive with $g_j$, in the sense that $g_i$ and $g_j$ cannot

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appear in the same longest common subsequence. The corresponding longest
path \( L_l \) contains \( g_l \), thus cannot contain \( g_j \). This proves our approach to
determine the quasi-transposons in \( L_0 \).

Proof of Lemma 7. Fix a quasi-transposon \( g_i \). It is contained in a longest
path \( L_i \), which contains all non-transposons. Thus for each non-transposon
\( g^* \), there is an edge between \( g^* \) and \( g_i \) in \( G \). Assume \( g_i \) has no such mutual-
exclusive quasi-transposon \( g_j \). Then there is an edge (direction unknown)
in \( G \) between \( g_i \) and each quasi-transposon \( g_j \). Choose a longest path \( L^* \)
in \( G \) that does not contain \( g_i \). Whether \( g_j \in L^* \) is a non-transposon or a
quasi-transposon, there is an edge between \( g_j \) and \( g_i \). Determine the first
gene \( g_k \) in \( L^* \) that has an edge \( g_i \rightarrow g_k \). Since there is an edge \( g_i \rightarrow n + 1 \),
gk exists. Since there is an edge \( 0 \rightarrow g_i \), \( g_k \neq 0 \). Denote the previous gene
of \( g_k \) in \( L^* \) by \( g_l \), then \( g_l \) exists, and there is an edge \( g_l \rightarrow g_i \). Thus we
construct a path \( 0 \rightarrow \cdots \rightarrow g_l \rightarrow g_i \rightarrow g_k \rightarrow \cdots \rightarrow n + 1 \), which is longer
than the longest path, a contradiction. Thus \( g_i \) has a mutual-exclusive
quasi-transposon \( g_j \).

3.5 Algorithms and complexities

We summarize the above method as Algorithms 1,2. If we have known
that the longest common subsequence is unique, then we just need to apply
Algorithm 1 so that genes in \( L_0 \) are non-transposons, and genes not in \( L_0 \)
are proper-transposons. Algorithm 1 has been briefly reported in a previous
paper, also by the author of this paper [46, 51]. We keep Algorithm 1 here
to make the story complete. Assume we have \( m \) sequences with length
\( n \), and the length of the longest common subsequence is \( n - k \). The time
complexities of Steps 2-5 in Algorithm 1 are \( O(m) \), \( O(mn^2) \), \( O(n) \), \( O(n) \).
The time complexities of Step 2 and Step 3 in Algorithm 2 are \( O(k) \) and
\( O(kn) \). Since \( k \leq n \), the overall time complexity of determining transposons
in Scenario 1 by Algorithms 1,2 is \( O(mn^2) \). The space complexity is trivially
\( O(mn + n^2) \).

4 Circular sequences without duplicated genes

In Scenario 2, consider \( m \) circular gene sequences, where each sequence
contains \( n \) genes \( 1, \ldots, n \). Each gene has only one copy in each sequence. For
such circular permutations of \( 1, \ldots, n \), we need to find the longest common
subsequence. Assume the length of the longest common subsequence is \( n - k \).
1. **Input**

$m$ linear sequences of genes $1, \ldots, n$. No duplicated genes.

2. **Modify** the sequences:

   Add 0 to the head, and $n + 1$ to the tail of each sequence

3. **Construct** the auxiliary graph $G$:

   Vertices of $G$ are all the genes $1, \ldots, n$

   For each pair of genes $g_i, g_j$

   If $g_i$ is prior to $g_j$ in all $m$ sequences

   Add a directed edge $g_i \to g_j$ in $G$

   End of if

   End of for

4. **Calculate** $F_+(\cdot)$ and $H_+(\cdot)$ for each gene $g_i$ in $0, 1, \ldots, n$ recursively;

   **calculate** $F_-(\cdot)$ and $H_-(\cdot)$ for each gene $g_i$ in $1, \ldots, n, n + 1$

   recursively:

   \[ H_+(g_i) = \arg\max_{\{g_j \text{ with } g_i \to g_j\}} F_+(g_j) \]

   \% If $g_j$ with $g_i \to g_j$ that maximizes $F_+(g_j)$ is not unique, choose one randomly

   \[ F_+(g_i) = 1 + F_+[H_+(g_i)] \]

   \[ H_-(g_i) = \arg\max_{\{g_j \text{ with } g_j \to g_i\}} F_-(g_j) \]

   \% If argmax is not unique, choose one randomly

   \[ F_-(g_i) = 1 + F_-[H_-(g_i)] \]

5. **Construct** a longest path $L_0$ from 0 to $n + 1$:

   \[ 0 \to H_+(0) \to H_+^2(0) \to H_+^3(0) \to \cdots \to H_+^{f-1}(0) \to H_+^f(0) = n + 1 \]

   \% Here $f = F_+(0)$, and $H_+^i$ is the $i$th iteration of $H_+$

6. **Output** $F_+(\cdot), H_+(\cdot), F_-(\cdot), H_-(\cdot), L_0$

**Algorithm 1**: Detailed workflow of determining proper-transposons and quasi-transposons in Scenario 1, preparation stage.
1. **Input**
   \( F_+ (\cdot), H_+ (\cdot), F_- (\cdot), H_- (\cdot), \mathcal{L}_0 \) calculated from Algorithm 1
   
   Denote all genes not in \( \mathcal{L}_0 \) by \( g_1, \ldots, g_k \)

2. **For** each gene \( g_i \) in \( g_1, \ldots, g_k \)
   
   If \( F_+ (g_i) + F_- (g_i) < F_+ (0) \)
   
   **Output** \( g_i \) is a proper-transposon
   
   Else
   
   **Output** \( g_i \) is a quasi-transposon
   
   End of if
   
   End of for

3. **If** all genes in \( g_1, \ldots, g_k \) are proper-transposons
   
   **Output** all genes in \( \mathcal{L}_0 \) are non-transposons

   Else
   
   **For** each gene \( g_i \) in \( g_1, \ldots, g_k \)
   
   Use \( H_+ (\cdot) \) and \( H_- (\cdot) \) to **construct** \( \mathcal{L}_i \), a longest path from 0 to \( n + 1 \) that passes \( g_i \).
   
   End of for
   
   **For** each gene \( g_j \) in \( \mathcal{L}_0 \) (excluding auxiliary 0 and \( n + 1 \))
   
   If \( g_j \) is contained in all \( \mathcal{L}_1, \ldots, \mathcal{L}_k \)
   
   **Output** \( g_j \) is a non-transposon
   
   Else
   
   **Output** \( g_j \) is a quasi-transposon
   
   End of if
   
   End of for
   
   End of if

4. **Output**: whether each gene is a proper/quasi/non-transposon

**Algorithm 2**: Detailed workflow of determining proper-transposons and quasi-transposons in Scenario 1, output stage.
4.1 Find a longest common subsequence

We first randomly choose a gene $g_i$. Cut all circular sequences at $g_i$ and expand them to be linear sequences. For example, the circular sequences in Fig. 1 cut at 1 are correspondingly $(1, 2, 3, 4, 5, 6)$ and $(1, 2, 6, 4, 5, 3)$. Using Algorithm 1 we can find $L_i$ that begins with $g_i$, which is a longest common subsequence of all expanded linear sequences. In the above example, the longest common linear subsequence starting from 1 is $(1, 2, 4, 5)$. If $g_i$ is a non-transposon or a quasi-transposon, then $L_i$ (glued back to a circle) is a longest common circular subsequence. If $g_i$ is a proper-transposon, then $L_i$ is shorter than the longest common circular subsequence. In Fig. 1, gene 1 is a non-transposon, and $(1, 2, 4, 5)$ (glued) is the longest common circular subsequence.

We do not know if $L_i$ (glued) is a longest common subsequence (whether containing $g_i$ or not) for all circular sequences. If there is a longer common subsequence, it should contain genes that are not in $L_i$. Consider four variables $L_i$, $g_i$, $C$, and $S$, whose initial values are $L_i$, $g_i$, the length of $L_i$, and the complement of $L_i$. These variables contain information on the longest common linear subsequence that we have found during this procedure.

Choose a gene $g_j$ in $S$, and cut all circular gene sequences at $g_j$. Apply Algorithm 1 to find $L_j$, which is the longest in common subsequences that contain $g_j$. If the length of $L_j$ is larger than $C$, set $L$ to be $L_j$, set $g$ to be $g_j$, set $C$ to be the length of $L_j$, and set $S$ to be the complement of $L_j$. Otherwise, keep $L$, $g$, $C$, and $S$ still.

Choose another gene $g_l$ in $S$ which has not been chosen before, and repeat this procedure. This procedure terminates when all genes in $S$ have been chosen and cut. Denote the final values of $L$, $g$, $C$, and $S$ by $L_0$, $g_0$, $C_0$, and $S_0$. Here $S_0$ is the complement of $L_0$.

During this procedure, if the current $g$ is a proper-transposon, then $S$ contains a non-transposon or a quasi-transposon, which has not been chosen. Thus $L$, $g$, $C$, $S$ will be further updated. If the current $g$ is a non-transposon or a quasi-transposon, then $C$ has reached its maximum, and $L$, $g$, $C$, $S$ will not be further updated. This means $L_0$ is a longest common circular subsequence, and $C_0$ is the length of the longest common subsequence, $n - k$. Also, the total number of genes being chosen and cut is $k + 1$. All $k$ genes in $S_0$ and $g_0$ are chosen and cut. A gene $g_t$ in $L_0$ (excluding $g_0$) is a non-transposon or a quasi-transposon, and cannot be chosen and cut. The reason is that it cannot be chosen before $g_0$ is chosen (only proper-transposons can be chosen before $g_0$ is chosen), and it cannot be chosen after $g_0$ is chosen ($g_t \notin S_0$).
4.2 Determine quasi-transposons

For each gene \( g_p \in S_0 \), apply Algorithm 1 to calculate \( C_p \), the length of the longest common subsequence that contains \( g_p \). If \( C_p < C_0 \), \( g_p \) is a proper-transposon. Otherwise, \( C_p = C_0 \) means \( g_p \) is a quasi-transposon. We have found all proper-transposons. If all genes in \( S_0 \) are proper-transposons, then all genes in \( L_0 \) are non-transposons, and the procedure terminates.

If \( S_0 \) contains quasi-transposons, then \( L_0 \) also has quasi-transposons. To determine quasi-transposons in \( L_0 \), we need the following lemma.

**Lemma 2.** In Scenario 2, choose a quasi-transposon \( g_p \) and cut the circular sequences at \( g_p \) to obtain linear sequences. A proper-transposon for the circular sequences is also a proper-transposon for the linear sequences; a non-transposon for the circular sequences is also a non-transposon for the linear sequences.

**Proof.** Consider a longest common subsequence \( L_p \) for linear sequences cut at \( g_p \). Since \( g_p \) is a quasi-transposon, the length of \( L_p \) is also \( n - k \), meaning that \( L_p \) is also a longest common subsequence for circular sequences. Now, this lemma is proved by the definition of proper/quasi/non-transposon. \( \square \)

If a gene \( g_r \) in \( L_0 \) is a non-transposon for the circular sequences, then \( g_r \) is a non-transposon for linear sequences cut at each quasi-transposon \( g_q \in S_0 \). If a gene \( g_s \) in \( L_0 \) is a quasi-transposon for the circular sequences, then there is a longest common circular subsequence \( L_t \) that does not contain \( g_s \), meaning that \( L_t \) contains a quasi-transposon \( g_t \) not in \( L_0 \). Then \( g_s \) is a proper/quasi-transposon for linear sequences cut at \( g_t \).

Therefore, we can use the following method to determine quasi-transposons in \( L_0 \). For each quasi-transposon \( g_q \in S_0 \), cut at \( g_q \) and apply Algorithms 1,2 to determine if each gene in \( L_0 \) is a proper/quasi/non-transposon for the linear gene sequences cut at \( g_q \). A gene \( g_r \in L_0 \) is a non-transposon for the circular sequences if and only if it is a non-transposon for linear sequences cut at any quasi-transposon \( g_q \in S_0 \). A gene \( g_s \in L_0 \) is a quasi-transposon for the circular sequences if and only if it is a proper/quasi-transposon for linear sequences cut at some quasi-transposon \( g_q \in S_0 \).

When we have determined all quasi-transposons in \( S_0 \), it might be tempting to apply a simpler approach to determine quasi-transposons in \( L_0 \): For each quasi-transposon \( g_q \in S_0 \), cut at \( g_q \) and apply Algorithm 1 to find a longest common subsequence \( L_q \). A gene in \( L_0 \) is a non-transposon if and only if it appears in all such \( L_q \). This approach is valid only if the following conjecture holds, which is similar to Lemma 1:

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Conjecture 1. In Scenario 2 of circular sequences without duplicated genes, each quasi-transposon \( g_i \) has a corresponding quasi-transposon \( g_j \), so that no longest common subsequence can contain both \( g_i \) and \( g_j \).

However, Conjecture 1 does not hold. See Fig. 4 for a counterexample. All genes are quasi-transposons. Any two quasi-transposons are contained in a longest common subsequence (length 3). Thus the simplified approach above does not work.

![Figure 4: A counterexample with three circular sequences that fails Conjecture 1.](image)

We summarize the above method as Algorithms 3, 4. If we have known that the longest common subsequence is unique, then we just need to apply Algorithm 3, so that genes in \( S_0 \) are proper-transposons, and genes not in \( S_0 \) are non-transposons. Assume we have \( m \) sequences with length \( n \), and the length of the longest common subsequence is \( n - k \). The time complexities of Step 2 and Step 3 in Algorithm 3 are \( O(mn^2) \) and \( O(kmn^2) \). The time complexities of Step 2 in Algorithm 4 is \( O(kmn^2) \). The overall time complexity of determining transposons in Scenario 2 by Algorithms 3, 4 is \( O(kmn^2) \). The space complexity is trivially \( O(mn + n^2) \).

5 Linear sequences with duplicated genes

In Scenario 3, consider \( m \) linear gene sequences, where each sequence contains different numbers of copies of \( n \) genes \( 1, \ldots, n \). We need to find the longest common subsequence. Here we only consider common subsequences that consist of all or none copies of the same gene, and the subsequence length is calculated by genes, not gene copies.
1. **Input**
   
m circular sequences of genes 1, . . . , n, where each gene has only one copy in each sequence

2. **Choose** a gene $g_i$ randomly
   
   Cut all circular sequences at $g_i$ and expand them to be linear sequences
   
   Apply Algorithm 1 to find $L_i$, a longest common subsequence in the expanded linear sequences
   
   Set $C$ to be the length of $L_i$, and set $S$ to be the complement of $L_i$

3. **While** $S$ has a gene $g_j$ that has not been chosen and cut
   
   Cut all circular sequences at $g_j$ and apply Algorithm 1 to find $L_j$
   
   Denote the length of $L_j$ by $C_j$
   
   If $C_j > C$
     
     Update $C$ to be $C_j$, and update $S$ to be the complement of $L_j$
   
   End of if
   
   End of while

Denote the final $C$ by $C_0$, and denote the final $S$ by $S_0$

4. **Output** $C_0$ and $S_0$

**Algorithm 3:** Detailed workflow of determining proper-transposons and quasi-transposons in Scenario 2, preparation stage.
1. **Input**

   $m$ circular sequences of genes $1, \ldots, n$, where each gene has only one copy in each sequence; $C_0$ and $S_0$ calculated from Algorithm 3

2. **For** each gene $g_l \in S_0$

   - **Cut** all circular sequences at $g_l$ and expand them to be linear sequences
   - **Apply** Algorithm 1 to find $L_l$, a longest common subsequence in the expanded linear sequences.
   - **Denote** the length of $L_l$ by $C_l$
   - **If** $C_l < C_0$
     - **Output** $g_l$ is a proper-transposon
   - **Else**
     - **Output** $g_l$ is a quasi-transposon
     - **Cut** all circular sequences at $g_l$ and **apply** Algorithms 1, 2 to find all proper/quasi-transposons for linear gene sequences starting at $g_l$
     - **Output** genes not in $S_0$ but being proper/quasi-transposons for such linear sequences are quasi-transposons for circular sequences
   - **End** of if
   - **End** of for
   - **Output** other genes that have not been determined to be proper/quasi-transposons are all non-transposons

3. **Output**: whether each gene is a proper/quasi/non-transposon

**Algorithm 4:** Detailed workflow of determining proper-transposons and quasi-transposons in Scenario 2, output stage.
5.1 A graph representation of the problem

Similar to Scenario 1, we construct an auxiliary graph $G$, where each vertex is a gene (not a copy of a gene). However, in this case, the auxiliary graph is undirected: There is an undirected edge between gene $g_i$ and gene $g_j$ if and only if all the copies of $g_i$ and $g_j$ keep their relative locations in all sequences. For example, consider two sequences $(1, 2, 3, 2, 3, 4, 5)$ and $(2, 1, 3, 3, 2, 4, 5)$. For gene pair $1, 3$, the corresponding sequences are $(1, 3, 3)$ and $(1, 3, 3)$, meaning that there is an edge between 1 and 3. For gene pair 1, 2, the corresponding sequences are $(1, 2, 2)$ and $(2, 1, 2)$, meaning that there is no edge between 1 and 2. See Fig. 5 for the auxiliary graph in this case.

![Figure 5: The auxiliary graph $G$ of two sequences (1, 2, 3, 2, 3, 4, 5) and (2, 1, 3, 3, 2, 4, 5). The unique largest complete subgraph is $\{1, 3, 4, 5\}$, meaning that the unique longest common sequence is $(1, 3, 3, 4, 5)$. Thus $1, 3, 4, 5$ are non-transposons, and 2 is a proper-transposon.]

Definition 5. A subgraph of $G$ consists of some genes $g_1, \ldots, g_l$ and the edges between them. In a subgraph, if there is an edge between any two genes, this subgraph is called a complete subgraph (also called a clique).

If all copies of genes $g_1, \ldots, g_l$ keep their relative locations in all linear sequences, we say that $g_1, \ldots, g_l$ form a common subsequence. In this case, there is an edge in $G$ between any two genes in $g_1, \ldots, g_l$, meaning that they form a complete subgraph. The following Lemma 3 shows that the inverse also holds. Therefore, there is a bijection between common subsequences and complete subgraphs. The problem of determining the longest common subsequence now becomes determining the largest complete subgraph of $G$.

Lemma 3. In Scenario 3, if $g_1, \ldots, g_k$ form a complete subgraph in $G$, then $g_1, \ldots, g_k$ form a common subsequence.

Proof. Only consider copies of $g_1, \ldots, g_k$ in these sequences. If $g_1, \ldots, g_k$ do not form a common subsequence, find the first digit that such sequences
differ. Assume $g_p$ and $g_q$ can both appear in this digit. Then $g_p, g_q$ cannot form a common subsequence, and there is no edge between $g_p$ and $g_q$.

We illustrate this proof with Fig. 5: For genes 2, 3, 4, the sequences are $(2, 3, 2, 3, 4)$ and $(2, 3, 3, 2, 4)$. The third digit is different, where 2 and 3 can both appear. Then the sequences for genes 2, 3, $(2, 3, 2, 3)$ and $(2, 3, 3, 2)$, cannot match, and there is no edge between 2 and 3.

5.2 A heuristic algorithm

The above discussion shows that given gene sequences, we can construct an undirected graph $G$, so that there is a bijection between common subsequences and complete subgraphs. The inverse also holds: We can construct corresponding gene sequences for a graph.

**Lemma 4.** Given an undirected graph $G$, we can construct two gene sequences, so that there is a bijection between common subsequences and complete subgraphs.

**Proof.** Assume the graph has $n$ genes. We start with two sequences $(1, 2, \ldots, n)$ and $(1, 2, \ldots, n)$. For each pair of genes $g_i, g_j$, if there is no edge between them in $G$, add $g_i, g_j$ to the end of the first sequence, and $g_j, g_i$ to the end of the second sequence. Then $g_i, g_j$ cannot both appear in a common subsequence, and this operation does not affect other gene pairs.

For example, corresponding to Fig. 5, we start with $(1, 2, 3, 4, 5)$ and $(1, 2, 3, 4, 5)$. Since there is no edge between 1, 2, we add them to have $(1, 2, 3, 4, 5, 1, 2)$ and $(1, 2, 3, 4, 5, 2, 1)$. Since there is no edge between 2, 3, we add them to have $(1, 2, 3, 4, 5, 1, 2, 2, 3)$ and $(1, 2, 3, 4, 5, 2, 1, 3, 2)$. These two sequences corresponds to Fig. 5.

Combining Lemma 3 and Lemma 4, we obtain the following result:

**Proposition 1.** Finding the longest common sequence in Scenario 3 is NP-hard.

**Proof.** For an undirected graph, we can use Lemma 4 to construct corresponding sequences. If we have the solution of finding the longest common sequence in Scenario 3, then we can find the largest complete subgraph in an extra polynomial time.

For gene sequences in Scenario 3, we can construct corresponding auxiliary graph. If we have the solution of finding the largest complete subgraph, then we can use Lemma 3 to find the longest common sequence in Scenario 3 in an extra polynomial time.
Therefore, finding the longest common sequence in Scenario 3 and finding the largest complete subgraph are equivalent. The problem of determining the largest complete subgraph is just the maximum clique problem, which is NP-hard [52]. Thus finding the longest common sequence in Scenario 3 is also NP-hard. This means it is not likely to design an algorithm that always correctly determines the longest common subsequence in polynomial time.

We still determine transposons by finding the largest complete subgraph in $G$, and we can design a greedy heuristic algorithm that only fails in rare cases. Readers may refer to a review for more details about the maximum clique problem [45].

**Definition 6.** In graph $G$, the degree of a gene $g$ is the number of edges linking $g$. In a complete graph of $p$ genes, where any two genes have an edge in between, each gene has degree $p - 1$.

The idea is simple: In the auxiliary graph $G$, repeatedly abandon the gene with the smallest degree (and also edges linking this gene) until the remaining genes form a complete subgraph. See Algorithm 5 for the details of this greedy heuristic method.

We test Algorithm 5 on random graphs. Construct a random graph with $n$ genes, and any two genes have probability 0.5 to have an edge in between. Use brute-force search to find the maximum clique, and compare its size with the result of Algorithm 5. For each $n \leq 15$, we repeat this for 10000 times, and every time Algorithm 5 returns the correct result. Therefore, we can claim that Algorithm 5 is a good heuristic algorithm that fails with a very small probability. Since finding the true maximum clique requires exponentially slow brute-force search, we do not test on very large graphs.

Nevertheless, Algorithm 5 does not always produce the correct result. See Fig. 6 for a counterexample. Here genes 1, 2, 3, 4, 5, 6 have degree 4, while genes 7, 8, 9, 10 have degree 3. When applying Algorithm 5 genes 7, 8, 9, 10 are first abandoned, and the final result just has three genes, such as 1, 3, 5. However, the largest complete graph is 7, 8, 9, 10. Besides, Algorithm 5 can only determine one (possibly longest) common subsequence. Thus we cannot determine the existence of quasi-transposons.

Assume we have $m$ sequences with $n$ genes. In general, the copy number of a gene is small, and we can assume the length of each sequence is $O(n)$. The time complexities of Step 2 and Step 3 in Algorithm 5 are $O(mn^2)$ and $O(n^2)$, and the overall time complexity is $O(mn^2)$. The space complexity is trivially $O(mn + n^2)$.
1. **Input**
   
   $m$ linear sequences of genes $1, \ldots, n$, where each gene can have multiple copies

2. **Construct** the auxiliary graph $G$:
   
   Vertices of $G$ are all the genes $1, \ldots, n$ (not their copies)
   
   **For** each pair of genes $g_i, g_j$
   
   **If** all copies of $g_i$ and $g_j$ keep their relative locations in all $m$ sequences
   
   **Add** an undirected edge between $g_i$ and $g_j$ in $G$

   **End** of if

   **End** of for

   **Calculate** the degree for each gene in $G$

3. **While** true
   
   **Find** a gene $g_i$ with the smallest degree $d_i$ in $G$
   
   % If the minimal $g_i$ is not unique, choose one randomly
   
   **If** $d_i + 1$ is smaller than the number of genes in $G$
   
   **Delete** $g_i$ and edges linking $g_i$ in $G$

   **Update** the degrees of other genes

   **Else**
   
   % The remaining genes form a complete subgraph

   **Break** the while loop

   **End** of if

   **End** of while

   % The final $G$ is a complete subgraph of the original $G$, and it is likely to be the largest one

4. **Output** genes in the final $G$ are not transposons, and genes not in the final $G$ are transposons

**Algorithm 5**: A heuristic method for detecting transposons in Scenario 3.
Figure 6: The auxiliary graph $G$ of linear sequences $(7,8,9,10,1,1,2,3,3,4,5,5,6)$ and $(1,2,1,3,4,3,5,6,5,7,8,9,10)$. This counterexample fails Algorithm 5.

6 Circular sequences with duplicated genes

In Scenario 4, consider $m$ circular gene sequences, where each sequence contains different numbers of copies of $n$ genes $1, \ldots, n$. We need to find the longest common subsequence. Here we only consider common subsequences that consist of all or none copies of the same gene, and the subsequence length is calculated by genes, not gene copies.

In this scenario, Lemma 3 does not hold. For example, we can consider a circular sequence $(1,2,3)$ and its mirror symmetry. These two sequences are different, but any two genes form a common subsequence. However, inspired by Lemma 3, we have the following conjecture.

**Conjecture 2.** In Scenario 4, if any three genes $g_i, g_j, g_k$ in $g_1, \ldots, g_k$ form a common subsequence, then $g_1, \ldots, g_k$ form a common subsequence.

For now, we do not know if Conjecture 2 is correct or not. If it is valid, then we can try to find a group of genes, where any three of them form a common subsequence. This group of genes forms a common subsequence.

Construct a 3-uniform hypergraph $G$ as following [53]: vertices are genes $1, \ldots, n$; there is a 3-hyperedge (undirected) that links genes $g_i, g_j, g_k$ if and only if they form a common subsequence. The longest common subsequence corresponds to the largest complete subgraph (any three genes are linked by a 3-hyperedge). The maximum clique problem for 3-uniform hypergraphs is NP-hard [45]. Similar to the proof of Proposition 1, we can prove that finding the longest common subsequence in Scenario 4 is also NP-hard.

We have a simple idea: Repeatedly delete the gene that has the smallest degree, until we have a complete subgraph that any three genes have a 3-hyperedge that links them. We summarize this greedy heuristic method as Algorithm 6.

We test Algorithm 6 on random graphs. Construct a random graph with $n$ genes, and any two genes have probability 0.5 to have an edge in between.
Use brute-force search to find the maximum clique, and compare its size with the result of Algorithm 6. For each \( n \leq 15 \), we repeat this for 10000 times, and every time Algorithm 6 returns the correct result. Therefore, we can claim that Algorithm 6 is a good heuristic algorithm that fails with a very small probability. Since finding the true maximum clique requires exponentially slow brute-force search, we do not test on very large graphs.

Nevertheless, Algorithm 6 does not always produce the correct result. See Fig. 7 for a counterexample. Here each gene in 1, 2, 3, 4, 5, 6 has degree 4, while each gene in 7, 8, 9, 10 has degree 3. When applying Algorithm 6, genes 7, 8, 9, 10 are first deleted, and the final result just has three genes, such as (1, 3, 5). However, the longest common subsequence (7, 8, 9, 10) has four genes.

Assume we have \( m \) sequences with \( n \) genes. In general, the copy number of a gene is small, and we can assume the length of each sequence is \( O(n) \). The time complexities of Step 2 and Step 3 in Algorithm 6 are \( O(mn^3) \) and \( O(n^3) \), and the overall time complexity is \( O(mn^3) \). The space complexity is trivially \( O(mn + n^3) \).

![Figure 7: Four circular sequences. The longest common subsequence is (7, 8, 9, 10). This counterexample fails Algorithm 6.](image)

### 7 Discussion

In this paper, we study the problem of determining transposons in gene sequences. Depending on whether the gene sequences are linear or circular, and whether genes have multiple copies, we classify the problem into four scenarios. We first transform the problems of determining transposons into finding the longest common subsequences, and then transform them into...
1. **Input**
   
   $m$ circular sequences of genes $1, \ldots, n$, where each gene can have multiple copies

2. **Construct** the auxiliary graph $\mathcal{G}$:
   
   Vertices of $\mathcal{G}$ are all the genes $1, \ldots, n$ (not their copies)
   
   For each gene triple $g_i, g_j, g_k$
   
   If all copies of $g_i, g_j, g_k$ keep their relative locations in all $m$ sequences
   
   Add a 3-hyperedge that links $g_i, g_j, g_k$ in $\mathcal{G}$

   End of if

   End of for

3. **While** there exist three genes that do not share a 3-hyperedge
   
   Calculate the degree for each gene in $\mathcal{G}$
   
   Delete the gene with the smallest degree and 3-hyperedges that links this gene
   
   % If there are multiple genes with the smallest degree, delete one randomly

   End of while

   % After this while loop, any three genes form a common subsequence

   % If Conjecture 2 holds, the remaining genes form a common subsequence

4. **Output** remaining genes are not transposons, and other genes are transposons

**Algorithm 6**: A heuristic method for detecting transposons in Scenario 4.
graph theory problems. For the first two scenarios without duplicated genes, we develop complete algorithms with polynomial complexities. For the latter two scenarios with duplicated genes, the problems are NP-hard, and we develop fast algorithms that only fail in rare cases. We also propose some unresolved conjectures in discrete mathematics.

In Scenario 1 and Scenario 2 (linear/circular sequences without duplicated genes), if each sequence has $n$ genes, and the longest common subsequence has length $n-k$, then there are at most $k$ proper-transposons. About quasi-transposons, inspired by Lemma 1, we have the following guess.

**Conjecture 3.** Consider $m$ linear/circular sequences with $n$ genes without multiple copies. Assume the length of the longest common subsequence is $n-k$, and there are $l$ proper-transposons. Then the number of quasi-transposons is no larger than $2(k-l)$.

When $l + 2(k-l) \leq n$, in both linear and circular scenarios, we can find examples with $2(k-l)$ quasi-transposons.

When transposons have been determined, we can use them to compare the genomes of different species, and such comparisons can be combined with other measurements between species, such as metrics on developmental trees [54]. Such comparisons can be also extended to different tissues to help with the prediction of tissue transplantation experiments [55]. Besides, for some species, cells at different positions have different gene expression patterns, which might be related to transposons [56].

A gene $g_i$ might be missing in some sequences. Since $g_i$ is not in any longest common subsequence, it should be a proper-transposon. This gene can be directly removed before applying corresponding algorithms.

We can adopt a stricter definition of transposons to exclude a gene which only changes its relative position in a few (no more than $l$, where $l$ is small enough) sequences. Then we should consider the longest sequence which is a common subsequence of at least $m-l$ sequences. We can run the corresponding algorithm for every $m-l$ sequences. Thus the total time complexity will be multiplied by a factor of $m!$.

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References

[1] Ivics Z, Izsvák Z. The expanding universe of transposon technologies for gene and cell engineering. Mob DNA. 2010;1(1):1–15.

[2] Mills RE, Bennett EA, Iskow RC, Devine SE. Which transposable elements are active in the human genome? Trends Genet. 2007;23(4):183–191.

[3] Zhou W, Liang G, Molloy PL, Jones PA. DNA methylation enables transposable element-driven genome expansion. Proc Natl Acad Sci USA. 2020;117(32):19359–19366.

[4] DeNicola GM, Karreth FA, Adams DJ, Wong CC. The utility of transposon mutagenesis for cancer studies in the era of genome editing. Genome Biol. 2015;16(1):1–15.

[5] Kazazian HH, Wong C, Youssoufian H, Scott AF, Phillips DG, Antonarakis SE. Haemophilia A resulting from de novo insertion of L1 sequences represents a novel mechanism for mutation in man. Nature. 1988;332(6160):164–166.

[6] Mustajoki S, Ahola H, Mustajoki P, Kauppinen R. Insertion of Alu element responsible for acute intermittent porphyria. Hum Mutat. 1999;13(6):431–438.

[7] Zhou D, Wang Y, Wu B. A multi-phenotypic cancer model with cell plasticity. J Theor Biol. 2014;357:35–45.

[8] Niu Y, Wang Y, Zhou D. The phenotypic equilibrium of cancer cells: From average-level stability to path-wise convergence. J Theor Biol. 2015;386:7–17.

[9] Niu XM, Xu YC, Li ZW, Bian YT, Hou XII, Chen JF, et al. Transposable elements drive rapid phenotypic variation in Capsella rubella. Proc Natl Acad Sci USA. 2019;116(14):6908–6913.

[10] Chen X, Wang Y, Feng T, Yi M, Zhang X, Zhou D. The overshoot and phenotypic equilibrium in characterizing cancer dynamics of reversible phenotypic plasticity. J Theor Biol. 2016;390:40–49.

[11] Jiang DQ, Wang Y, Zhou D. Phenotypic equilibrium as probabilistic convergence in multi-phenotype cell population dynamics. PLOS ONE. 2017;12(2):e0170916.
[12] Noorani I, Bradley A, de la Rosa J. CRISPR and transposon in vivo screens for cancer drivers and therapeutic targets. Genome Biol. 2020;21(1):1–22.

[13] Angelini E, Wang Y, Zhou JX, Qian H, Huang S. A model for the intrinsic limit of cancer therapy: Duality of treatment-induced cell death and treatment-induced stemness. PLOS Comput Biol. 2022;18(7):e1010319.

[14] Nowacki M, Higgins BP, Maquilan GM, Swart EC, Doak TG, Landweber LF. A functional role for transposases in a large eukaryotic genome. Science. 2009;324(5929):935–938.

[15] Babakhani S, Oloomi M. Transposons: the agents of antibiotic resistance in bacteria. J Basic Microbiol. 2018;58(11):905–917.

[16] Rahrmann EP, Collier LS, Knutson TP, Doyal ME, Kuslak SL, Green LE, et al. Identification of PDE4D as a proliferation promoting factor in prostate cancer using a Sleeping Beauty transposon-based somatic mutagenesis screen. Cancer Res. 2009;69(10):4388–4397.

[17] Xia M, Greenman CD, Chou T. PDE models of adder mechanisms in cellular proliferation. SIAM J Appl Math. 2020;80(3):1307–1335.

[18] Dessalles R, Pan Y, Xia M, Maestrini D, D'Orsogna MR, Chou T. How Naive T-Cell Clone Counts Are Shaped By Heterogeneous Thymic Output and Homeostatic Proliferation. Front Immunol. 2021;12.

[19] Wang Y, Wang Z. Inference on the structure of gene regulatory networks. J Theor Biol. 2022;539:111055.

[20] Sha Y, Wang S, Zhou P, Nie Q. Inference and multiscale model of epithelial-to-mesenchymal transition via single-cell transcriptomic data. Nucleic Acids Res. 2020;48(17):9505–9520.

[21] Zhou P, Wang S, Li T, Nie Q. Dissecting transition cells from single-cell transcriptome data through multiscale stochastic dynamics. Nat Commun. 2021;12(1):1–15.

[22] Gardner EJ, Lam VK, Harris DN, Chuang NT, Scott EC, Pittard WS, et al. The Mobile Element Locator Tool (MELT): population-scale mobile element discovery and biology. Genome Res. 2017;27(11):1916–1929.
[23] Chen X, Li D. ERVcaller: identifying polymorphic endogenous retrovirus and other transposable element insertions using whole-genome sequencing data. Bioinformatics. 2019;35(20):3913–3922.

[24] Yu T, Huang X, Dou S, Tang X, Luo S, Theurkauf WE, et al. A benchmark and an algorithm for detecting germline transposon insertions and measuring de novo transposon insertion frequencies. Nucleic Acids Res. 2021;49(8):e44–e44.

[25] Orozco-Arias S, Piña JS, Tabares-Soto R, Castillo-Ossa LF, Guyot R, Isaza G. Measuring performance metrics of machine learning algorithms for detecting and classifying transposable elements. Processes. 2020;8(6):638.

[26] Goubert C, Craig RJ, Bilat AF, Peona V, Vogan AA, Protasio AV. A beginner’s guide to manual curation of transposable elements. Mob DNA. 2022;13(1):1–19.

[27] Evrony GD, Hinch AG, Luo C. Applications of single-cell DNA sequencing. Annu Rev Genomics Hum Genet. 2021;22:171.

[28] Lin CH, Lian CY, Hsiung CA, Chen FC; BioMed Central. Changes in transcriptional orientation are associated with increases in evolutionary rates of enterobacterial genes. BMC Bioinform. 2011;12(9):1–8.

[29] Chen ZZ, Gao Y, Lin G, Niewiadomski R, Wang Y, Wu J. A space-efficient algorithm for sequence alignment with inversions and reversals. Theor Comput Sci. 2004;325(3):361–372.

[30] Imbeault M, Helleboid PY, Trono D. KRAB zinc-finger proteins contribute to the evolution of gene regulatory networks. Nature. 2017;543(7646):550–554.

[31] Zimin AV, Puig D, Luo MC, Zhu T, Koren S, Marçais G, et al. Hybrid assembly of the large and highly repetitive genome of Aegilops tauschii, a progenitor of bread wheat, with the MaSuRCA mega-reads algorithm. Genome Res. 2017;27(5):787–792.

[32] Reneker J, Lyons E, Conant GC, Pires JC, Freeling M, Shyu CR, et al. Long identical multispecies elements in plant and animal genomes. Proc Natl Acad Sci USA. 2012;109(19):E1183–E1191.
[33] Diop SI, Subotic O, Giraldo-Fonseca A, Waller M, Kirbis A, Neubauer A, et al. A pseudomolecule-scale genome assembly of the liverwort Marchantia polymorpha. Plant J. 2020;101(6):1378–1396.

[34] Hirschberg DS. A linear space algorithm for computing maximal common subsequences. Commun ACM. 1975;18(6):341–343.

[35] Backurs A, Indyk P. Edit distance cannot be computed in strongly subquadratic time (unless SETH is false). In: Proceedings of the Forty-Seventh Annual ACM Symposium on Theory of Computing; 2015. p. 51–58.

[36] Kiyomi M, Horiyama T, Otachi Y. Longest common subsequence in sublinear space. Inf Process Lett. 2021;168:106084.

[37] Maier D. The complexity of some problems on subsequences and supersequences. J ACM. 1978;25(2):322–336.

[38] Blum C, Djujanovic M, Santini A, Jiang H, Li CM, Manyà F, et al. Solving longest common subsequence problems via a transformation to the maximum clique problem. Comput Oper Res. 2021;125:105089.

[39] Wang Q, Korkin D, Shang Y. A fast multiple longest common subsequence (MLCS) algorithm. IEEE Trans Knowl Data Eng. 2010;23(3):321–334.

[40] Mousavi SR, Tabataba F. An improved algorithm for the longest common subsequence problem. Comput Oper Res. 2012;39(3):512–520.

[41] Islam M, Saifullah C, Asha ZT, Ahamed R, et al. Chemical reaction optimization for solving longest common subsequence problem for multiple string. Soft Comput. 2019;23(14):5485–5509.

[42] Bergroth L, Hakonen H, Raita T. A survey of longest common subsequence algorithms. In: Proceedings Seventh International Symposium on String Processing and Information Retrieval. SPIRE 2000. IEEE; 2000. p. 39–48.

[43] Huang K, Yang CB, Tseng KT, et al. Fast algorithms for finding the common subsequences of multiple sequences. In: Proceedings of the International Computer Symposium. Citeseer; 2004. p. 1006–1011.

[44] Wei S, Wang Y, Yang Y, Liu S. A path recorder algorithm for Multiple Longest Common Subsequences (MLCS) problems. Bioinformatics. 2020;36(10):3035–3042.
[45] Wu Q, Hao JK. A review on algorithms for maximum clique problems. Eur J Oper Res. 2015;242(3):693–709.

[46] Kang Y, Gu C, Yuan L, Wang Y, Zhu Y, Li X, et al. Flexibility and symmetry of prokaryotic genome rearrangement reveal lineage-associated core-gene-defined genome organizational frameworks. mBio. 2014;5(6):e01867–14.

[47] Rowley MJ, Corces VG. Organizational principles of 3D genome architecture. Nat Rev Genet. 2018;19(12):789–800.

[48] Wang Y, Wang L. Causal inference in degenerate systems: An impossibility result. In: International Conference on Artificial Intelligence and Statistics. PMLR; 2020. p. 3383–3392.

[49] Verma SC, Qian Z, Adhya SL. Architecture of the Escherichia coli nucleoid. PLOS Genet. 2019;15(12):e1008456.

[50] Ibal JC, Pham HQ, Park CE, Shin JH. Information about variations in multiple copies of bacterial 16S rRNA genes may aid in species identification. PLOS ONE. 2019;14(2):e0212090.

[51] Wang Y. Some Problems in Stochastic Dynamics and Statistical Analysis of Single-Cell Biology of Cancer [Ph.D. thesis]. University of Washington; 2018.

[52] Valiente G. Algorithms on Trees and Graphs. Berlin: Springer; 2002.

[53] Diestel R. Graph Theory. 5th ed. Berlin: Springer; 2017.

[54] Wang Y. Two metrics on rooted unordered trees with labels. Algorithms Mol Biol. 2022;17(1):1–17.

[55] Wang Y, Zhang B, Kropp J, Morozova N. Inference on tissue transplantation experiments. J Theor Biol. 2021;520:110645.

[56] Wang Y, Kropp J, Morozova N. Biological notion of positional information/value in morphogenesis theory. Int J Dev Biol. 2020;64(10-11-12):453–463.