

Sorting by Cuts, Joins, and Whole Chromosome Duplications

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ABSTRACT

Genome rearrangement problems have been extensively studied due to their importance in biology. Most studied models assumed a single copy per gene. However, in reality, duplicated genes are common, most notably in cancer. In this study, we make a step toward handling duplicated genes by considering a model that allows the atomic operations of cut, join, and whole chromosome duplication. Given two linear genomes, Γ with one copy per gene and Δ with two copies per gene, we give a linear time algorithm for computing a shortest sequence of operations transforming Γ into Δ such that all intermediate genomes are linear. We also show that computing an optimal sequence with fewest duplications is NP-hard.

Keywords: computational genomics, genome rearrangements, SCJ.

1. INTRODUCTION

GENOME ORGANIZATION EVOLVES OVER TIME by undergoing rearrangement operations. Finding a shortest sequence of operations (also called a sorting scenario) between two genomes is the focus of the field of *genome rearrangements*. Such problems were studied extensively over the last two decades due to their importance in evolution (Fertin et al., 2009).

The combinatorial problems in genome rearrangements depend on the allowed operations. Hannenhalli and Pevzner (1995) showed in their seminal work that finding the minimal number of inversions that transform one signed genome into another is polynomial. Many other models were studied later, allowing one or several types of operations (Hannenhalli and Pevzner, 1995; Christie, 1996; Hannenhalli, 1996; Caprara, 1997; Dias and Meidanis, 2001; Lu et al., 2006; Mira and Meidanis, 2007; Bulteau et al., 2012).

The double cut and join (DCJ) operation (Yancopoulos et al., 2005) models reversals, transpositions, translocations, fusions, fissions, and block-interchanges as variations of one basic operation. A DCJ operation cuts the genome in two places, producing four open ends, and rejoins them in two new pairs. Finding the DCJ distance between two gene permutations can be done in linear time (Bergeron et al., 2006). The single cut or join (SCJ) model (Feijão and Meidanis, 2011) further simplifies the model and allows polynomial solutions to some rearrangement problems that are NP-hard under most formulations. An SCJ operation either cuts a chromosome or joins two chromosome ends. This simple model gives good results in real biological applications (Biller et al., 2013).

Models of genomes that assume a single copy of each gene are too restrictive for many real biological problems. Duplications are frequent in cancer genomes, especially in oncogenic regions (Bayani et al.,

2007). Most plant genomes contain large duplicated segments (Blanc et al., 2000). A major evolutionary event is *whole genome duplication*, wherein all chromosomes are duplicated (Savard et al., 2011).

In spite of their importance, models that allow duplications as rearrangement operations have not been the subject of extensive research to date. Ozery-Flato and Shamir (2009) considered a model that includes certain duplications, deletions, and SCJ operations. Under some simplifying assumptions, they provided a 3-approximation algorithm that performed well on cancer genomes. Bader (2009, 2010) provided a heuristic for sorting by DCJs, duplications, and deletions. Shao et al. (2013) studied sorting genomes using DCJs and segmental duplications and provided an algorithm to improve an initial sorting scenario. The majority of extant models for genomes with multiple gene copies result in NP-hard problems (Tannier et al., 2009; Savard et al., 2011; Shao and Lin, 2012; Shao et al., 2014).

In this article, we present a model that allows the operations, cut, join, and whole chromosome duplication. We call it the *SCJD model*. The model tries to combine the simplicity and applicability of the SCJ model while allowing chromosomal duplications observed in cancer genomes. In fact, aneuploidy (whole chromosome duplication or deletion) is a hallmark of cancer, and how cancer cells can adapt to tolerate aneuploidy remains a key enigma (Gordon et al., 2012; Giam and Rancati, 2015). The SCJD model is applicable for tumor genomes where one copy of each chromosome remains unaffected and the other is duplicated at most once. Thus, we view this model as moving one step closer to a realistic model of cancer genome evolution. Such model should allow multiple gene copies and reversals, translocations, duplications, and deletions.

Given two linear genomes, Γ with one copy per gene and Δ with two copies per gene, we give a linear time algorithm for computing a shortest sequence of operations transforming Γ into Δ , where all intermediate genomes must be linear too. We provide a closed-form formula for that sequence length. In addition, we show that there is an optimal sequence in which all duplications are consecutive.

While cuts or joins are local events, a duplication of an entire chromosome is a more drastic event. We show that our algorithm actually gives an optimal scenario with a maximum number of duplications. On the other hand, we prove that finding a conservative optimal SCJD scenario with fewest duplications is NP-hard.

The structure of this article is as follows. We give computational background in Section 2. In Section 3, we present the SCJD model. Section 4 gives the algorithm for the SCJD sorting problem and Section 5 shows the NP-hardness result. Finally, in Section 6, we present a brief discussion and suggest future directions. A preliminary version of this article appeared in the proceedings of CPM 2015 (Zeira and Shamir, 2015).

2. PRELIMINARIES

2.1. Genome representation

We use the following standard terminology in genome rearrangements (Bergeron et al., 2006). The basic entities are *genes*, denoted by a, b, c etc. Gene a has *extremities*: a *head* a_h and a *tail* a_t . Gene a is assumed to be oriented from its tail to its head and is *positively oriented* if a_t is to the left of a_h . A *negatively oriented* gene a is denoted by $-a$. A *chromosome* is a sequence of oriented genes, for example, $C = ab - c - d$. An *adjacency* in a chromosome is a consecutive pair of extremities from distinct neighboring genes. For example, the adjacencies in C above are $\{a_h, b_t\}$, $\{b_h, c_h\}$, and $\{c_t, d_h\}$. A *telomere* is an extremity that is not adjacent to any other gene, corresponding to the end of a chromosome, for example, $\{a_t\}, \{d_t\}$ in C . Hence, a chromosome can be equivalently represented by its set of adjacencies, where the telomeres are implicit. Note that the set of adjacencies defining a chromosome is identical to that of the reverse chromosome, where order and orientation of genes are inverted (the reverse of C is $-C = dc - b - a$). Hence, a chromosome and its reverse are equivalent.

A *genome* over gene set \mathcal{G} is a collection of chromosomes. We assume for now that each gene appears once, for example, $\Gamma = \{ab, c - d\}$. Equivalently, it can be defined by a set of adjacencies such that for each gene in \mathcal{G} , each extremity appears at most once. Hence, $\Gamma = \{\{a_h, b_t\}, \{c_h, d_h\}\}$. The *size* of a genome Γ , denoted by $|\Gamma|$, is the number of adjacencies in it. A chromosome is called *linear* if it starts and ends with a telomere and *circular* if it does not contain any telomere, for example, $D = \{\{a_h, b_t\}, \{b_h, a_t\}\}$. For a sequence of genes S , denote by S and (S) the corresponding linear and circular chromosomes, respectively. For example, the linear chromosome $a - b$ is defined by the set of adjacencies $\{\{a_h, b_h\}\}$ and the circular chromosome $(a - b)$ is defined by the set $\{\{a_h, b_h\}, \{b_t, a_t\}\}$. A genome is called *linear* if all its chromosomes are linear.

A gene that has several copies in the genome is called *duplicated*. We *label* different copies of the same gene by superscripts, for example, copies a^1 and a^2 of gene a . A *duplicated genome* has exactly two copies

of each gene. A genome with a single copy of each gene is called *ordinary*. The duplication of an ordinary genome Π creates a special kind of genome (Warren and Sankoff, 2011): each gene and each adjacency in Π is doubled, producing the genome $\Pi \oplus \Pi$. Note that in $\Pi \oplus \Pi$, the two copies of each gene are unlabeled. The set of all possible labeled genomes corresponding to $\Pi \oplus \Pi$ is denoted by 2Π . A genome $\Sigma \in 2\Pi$ is called a *perfectly duplicated genome*. Hence, for Γ above, $\Gamma \oplus \Gamma = \{ab, ab, c-d, c-d\}$ and $\Sigma = \{\{a_h^2, b_i^2\}, \{c_h^2, d_h^1\}, \{a_h^1, b_i^1\}, \{c_h^1, d_h^2\}\} \in 2\Gamma$.

2.2. SCJ distance

A *cut* operation takes an adjacency $\{x, y\}$ and breaks it into two telomeres, $\{x\}$ and $\{y\}$. The reverse operation, called a *join*, combines two telomeres, $\{x\}$ and $\{y\}$, into an adjacency $\{x, y\}$. An SCJ operation is either a cut or a join (Feijão and Meidanis, 2011). Given two ordinary genomes, Π and Γ , on the same gene set, a sequence of SCJ operations that transforms Π into Γ is called a *sorting scenario*. The *SCJ distance*, denoted by $d_{SCJ}(\Pi, \Gamma)$, is the length of a shortest sorting scenario between Π and Γ . Feijão and Meidanis give the following solution for the SCJ distance:

Theorem 1. (Feijão and Meidanis, 2011) $d_{SCJ}(\Pi, \Gamma) = |\Pi \setminus \Gamma| + |\Gamma \setminus \Pi| = |\Pi| + |\Gamma| - 2|\Pi \cap \Gamma|$. $\Pi \setminus \Gamma$ defines the set of cuts and $\Gamma \setminus \Pi$ defines the set of joins in an optimal sorting scenario.

2.3. Double distance

The *SCJ double distance* between an ordinary genome, Γ , and a duplicated genome, Δ , is defined as

$$dd_{SCJ}(\Gamma, \Delta) \equiv \min_{\Sigma \in 2\Gamma} d_{SCJ}(\Sigma, \Delta) \quad (1)$$

Hence, in the *double distance problem*, one seeks a labeling of each gene copy in a perfectly duplicated genome $\Sigma \in 2\Gamma$ that minimizes the SCJ distance to Δ .

For a genome Σ and an adjacency $\alpha = \{x, y\}$, let Σ_α be the set of all adjacencies of the form $\{x^i, y^j\}$ in Σ . Hence, $|\Sigma_\alpha|$ can be 0, 1, or 2 if Σ is duplicated and 0 or 1 if Σ is ordinary. Let $A = \{\alpha = \{x, y\} | x \neq y\}$ be the set of all possible adjacencies with extremities belonging to distinct genes. A solution to the double distance problem is given by the following theorem:

Theorem 2. (Feijão and Meidanis, 2011) *The SCJ double distance between an ordinary genome, Γ , and a duplicated genome, Δ , is*

$$dd_{SCJ}(\Gamma, \Delta) = |\Delta| + 2 \sum_{\alpha \in A} |\Gamma_\alpha| (1 - |\Delta_\alpha|).$$

A perfectly duplicated genome, $\Sigma \in 2\Gamma$, realizing the distance is obtained by taking for each adjacency $\alpha = \{x, y\} \in \Gamma$ (1) the labeled adjacencies of Δ_α and (2) adjacencies $\{x^i, y^j\}$ with arbitrary labeling that do not conflict with (1) or among themselves.

3. THE SCJD MODEL

In this section, we generalize the SCJ model to allow duplications.

A *duplication* operation on a genome, Π , takes a linear chromosome, C , in Π and produces a new genome, Π' , with an additional copy of the chromosome. For example, if $\Pi = \{abcd, efg\}$, then a duplication of the first chromosome will give $\Pi' = \{abcd, abcd, efg\}$. An *SCJD operation* is either an SCJ or a duplication.

Given two linear genomes on the same gene set of size n , an ordinary one, Γ , and a duplicated one, Δ , a sequence of SCJD operations that transforms Γ into Δ is called an *SCJD sorting scenario*. The *SCJD distance*, denoted by $d_{SCJD}(\Gamma, \Delta)$, is the number of operations in a shortest SCJD sorting scenario between Γ and Δ .

Since we focus on linear genomes, we will assume from now on that all chromosomes, including intermediate ones, are linear unless specified otherwise. The following simple lemma shows that this can be satisfied when using only SCJ operations:

Lemma 1. *A sequence of SCJ operations transforming one linear genome into another linear genome can be reordered, producing another sequence with the same length such that all intermediate genomes are linear.*

Proof. Let Π and Γ be two ordinary linear genomes and let o_1, \dots, o_d be a sequence of SCJ operations transforming Π into Γ . Suppose there is a join operation, o_i , which creates a circular chromosome C by joining its two telomeres, x and y . Since Γ is linear, there is a cut operation o_i for $i < j$ that breaks C into a linear chromosome by cutting an adjacency $\{w, z\}$. We create a new sequence of the same length by replacing o_i with a cut of $\{w, z\}$ and replacing o_j with a join of x and y . In the new sequence, the chromosome C is linear. By repeating the argument for every intermediate circular chromosome, the lemma holds. ■

The examples below demonstrate SCJ double distances and SCJD sorting scenarios. For simplicity, we drop the braces around genomes from now on.

Example 1. $\Gamma = a$, $\Delta = a - a$; $dd_{SCJ}(\Gamma, \Delta) = 1$; $d_{SCJD}(\Gamma, \Delta) = 2$:

$$\Gamma \xrightarrow[\text{dup}]{} a, a \xrightarrow[\text{join}]{} \Delta$$

Example 2. $\Gamma = ab$, $\Delta = ab, ab$; $dd_{SCJ}(\Gamma, \Delta) = 0$; $d_{SCJD}(\Gamma, \Delta) = 1$:

$$\Gamma \xrightarrow[\text{dup}]{} \Delta$$

Example 3. $\Gamma = a, bc$, $\Delta = ab, abcc$; $dd_{SCJ}(\Gamma, \Delta) = 4$; $d_{SCJD}(\Gamma, \Delta) \leq 4$:

$$\Gamma \xrightarrow[\text{join}]{} abc \xrightarrow[\text{dup}]{} abc, abc \xrightarrow[\text{cut}]{} abc, ab, c \xrightarrow[\text{join}]{} \Delta$$

Example 4. $\Gamma = acb$, $\Delta = abab, cc$; $dd_{SCJ}(\Gamma, \Delta) = 8$; $d_{SCJD}(\Gamma, \Delta) \leq 7$:

$$\Gamma \xrightarrow[\text{cut}]{} a, cb \xrightarrow[\text{cut}]{} a, b, c \xrightarrow[\text{join}]{} ab, c \xrightarrow[\text{dup}]{} ab, ab, c \xrightarrow[\text{dup}]{} ab, ab, c, c \xrightarrow[\text{join}]{} abab, c, c \xrightarrow[\text{join}]{} \Delta$$

Let $\#_c \Pi$ be the number of linear chromosomes in genome Π . Let Γ be an ordinary linear genome and let Δ be a duplicated linear genome on the same gene set. A trivial upper bound for the SCJD distance between Γ and Δ is given by solving the double distance between Δ and Γ . This corresponds to first duplicating each chromosome in Γ and then computing the SCJ distance between Δ and $\Gamma \oplus \Gamma$. We get $d_{SCJD}(\Gamma, \Delta) \leq dd_{SCJ}(\Gamma, \Delta) + \#_c \Gamma$. However, Example 3 shows that this bound is not tight. It is tempting to guess that $dd_{SCJ}(\Gamma, \Delta) \leq d_{SCJD}(\Gamma, \Delta)$. Alas, Example 4 shows this conjecture is incorrect.

4. COMPUTING THE SCJD DISTANCE

In this section, we will solve the SCJD distance problem. The key idea is to show that there is an optimal scenario in which all the duplication operations are performed in sequence, one after the other. Having shown that, the sorting scenario between Γ and Δ can be presented as follows:

1. Transform Γ into another ordinary linear genome, Γ' , using only SCJ operations.
2. Duplicate all the chromosomes of Γ' resulting in a duplicated genome, $\Gamma' \oplus \Gamma'$.
3. Solve the SCJ double distance problem between Γ' and Δ .

Let $O^* = o_1, \dots, o_d$ be an optimal SCJD sorting scenario. Let $\Gamma_0 \equiv \Gamma$ and for every $1 \leq i \leq d$, let $\Gamma_i = o_i(\Gamma_{i-1})$ be the genome resulting from performing o_i on Γ_{i-1} . By definition, $\Gamma_d \equiv \Delta$. Let D_i be the set of duplicated genes in Γ_i . We have $D_0 = \emptyset$ and $D_d = \mathcal{G}$. Given a gene set \mathcal{H} , denote its extremity set by $\mathcal{E}_{\mathcal{H}} = \{a_l | a \in \mathcal{H}\} \cup \{a_h | a \in \mathcal{H}\}$.

Proposition 1. *In an optimal sorting scenario O^* , if o_i is a join operation acting on the two telomeres, x and y , then either both $x, y \in \mathcal{E}_{D_i}$ or both $x, y \notin \mathcal{E}_{D_i}$.*

Proof. Since o_i is not a duplication, we have $D_{i-1} = D_i$. Suppose by contradiction that $x \in \mathcal{E}_{D_i}$, but $y \notin \mathcal{E}_{D_i}$. Let o_j ($i < j$) be the first duplication such that $y \in \mathcal{E}_{D_j}$. The duplication operation must act on a chromosome in which all genes are not yet duplicated. Therefore, there is a cut operation o_k ($i < k < j$) that breaks the adjacency $\{x, y\}$ created by o_i .

Let $O' = o'_1, \dots, o'_{d-2} = o_1, \dots, o_{i-1}, o_{i+1}, \dots, o_{k-1}, o_{k+1}, \dots, o_d$ be an alternative sorting sequence that results from removing o_i and o_k from O^* . Let $\Gamma'_0 \equiv \Gamma$, and denote $\Gamma'_l = o'_l(\Gamma'_{l-1})$. For every l with $1 \leq l \leq i-1$, by definition, $o'_l = o_l$ and therefore $\Gamma'_l = \Gamma_l$.

We first show that for every l with $i \leq l \leq k-2$, $\Gamma'_l = \Gamma_{l+1} \setminus \{\{x, y\}\}$. Since o_i creates the adjacency $\{x, y\}$, we have $\Gamma_i = \Gamma_{i-1} \cup \{\{x, y\}\}$. For every such l , $o'_l = o_{l+1}$ and since none of these operations creates a new copy of y , we have $\Gamma'_l = \Gamma_{l+1} \setminus \{\{x, y\}\}$.

Next, we show that for every l with $k-1 \leq l \leq d-2$, $\Gamma'_l = \Gamma_{l+2}$. From the previous result and the fact that $\Gamma_k = \Gamma_{k-1} \setminus \{\{x, y\}\}$, we have $\Gamma'_{k-2} = \Gamma_k$. Now, for every such l , $o'_l = o_{l+2}$ and therefore $\Gamma'_l = \Gamma_{l+2}$.

We have established that O' is an SCJD sorting sequence of length, $d-2$, contradicting the optimality of O^* . \blacksquare

Proposition 2. *In an optimal sorting scenario O^* , if o_i is a cut operation acting on the adjacency $\{x, y\}$, then either $x, y \in \mathcal{E}_{D_i}$ or $x, y \notin \mathcal{E}_{D_i}$.*

Proof. Suppose by contradiction, $x \in \mathcal{E}_{D_i}$, but $y \notin \mathcal{E}_{D_i}$. Let o_j ($j < i$) be the first duplication such that $x \in \mathcal{E}_{D_j}$. Since x was duplicated as part of a chromosome that did not contain y , there is subsequently a join operation o_k ($j < k < i$) that creates the adjacency $\{x, y\}$. Defining $O' = o'_1, \dots, o'_{d-2} = o_1, \dots, o_{k-1}, o_{k+1}, \dots, o_{i-1}, o_{i+1}, \dots, o_d$, we can get a shorter SCJD sorting scenario in a similar manner as the proof of Proposition 1. \blacksquare

Corollary 1. *In an optimal sequence of SCJD operations, at the time of a cut or a join operation on the two extremities, x and y , either the genes corresponding to both x and y have already been duplicated or none of them have.* \blacksquare

We say that a join operation in a sorting scenario is *valid* only if the two extremities it joins are not already part of any other adjacency. Similarly, a cut operation is *valid* only if the adjacency it breaks exists. A duplication operation is *valid* only if it duplicates a linear chromosome such that all its genes were not previously duplicated. A sorting scenario is *valid* if all its operations are valid.

Let $S = s_1, \dots, s_m$ be a valid SCJD sorting scenario between Γ and Δ . We say the operation, s_{i+1} , can *preempt* the operation, s_i , if the sequence, $S' = s_1, \dots, s_{i+1}, s_i, \dots, s_m$, is also a valid SCJD sorting scenario between Γ and Δ .

Proposition 3. *In a valid SCJD scenario, S transforming Γ into Δ , if s_{i+1} is an SCJ operation acting on two extremities x, y that were not duplicated and s_i is a duplication, then s_{i+1} can preempt s_i .*

Proof. Suppose s_i duplicates the linear chromosome C and produces another copy of it C' . Since s_{i+1} operates on genes that are not duplicated yet, none of those genes belong to C or C' . Therefore, the sequence, $s_1, \dots, s_{i-1}, s_{i+1}$, is valid. Any operation that creates an adjacency or a telomere of C must precede s_i . Hence, $s_1, \dots, s_{i-1}, s_{i+1}, s_i$ is valid. Finally, any s_j for $j > i+1$ that requires the results of s_i or s_{i+1} is still valid. Thus, $S' = s_1, \dots, s_{i-1}, s_{i+1}, s_i, s_{i+2}, \dots, s_m$ is a valid sequence.

To conclude the proof, we need to show that $\Gamma_{i+1} \equiv \Gamma'_{i+1}$. Indeed, s_{i+1} does not alter any of the adjacencies or telomeres of C or C' , and therefore, $\Gamma_{i+1} = s_{i+1}(\Gamma_{i-1} \cup C') \equiv s_{i+1}(\Gamma_{i-1}) \cup C' = \Gamma'_{i+1}$. \blacksquare

Proposition 4. *In a valid SCJD scenario, S transforming Γ into Δ , if s_{i+1} is a duplication and s_i is a cut or join acting on two duplicated extremities, then s_{i+1} can preempt s_i .*

Proof. Suppose s_i is an SCJ operation acting on the two extremities, x and y , such that the genes corresponding have both already been duplicated. Let s_{i+1} be a duplication operation that takes the linear chromosome, C , and produces another copy of it, C' .

Since S is a valid sorting sequence, duplication operations that act on the genes corresponding to x and y must precede s_i . In addition, none of these genes are in C . Thus, the sequence, $s_1, \dots, s_{i-1}, s_{i+1}, s_i$, is still valid. Any subsequent operation has its required set of adjacencies and telomeres and thus the sequence $S' = s_1, \dots, s_{i-1}, s_{i+1}, s_i, s_{i+2}, \dots, s_m$ is valid. In addition, for the same reasons, $\Gamma_{i+1} = s_i(\Gamma_{i-1}) \cup C' \equiv s_i(\Gamma_{i-1} \cup C') = \Gamma'_{i+1}$. \blacksquare

Proposition 5. *In a valid SCJD scenario, S transforming Γ into Δ , if s_{i+1} is an SCJ acting on two extremities that were not duplicated yet and s_i is an SCJ acting on two duplicated extremities, then s_{i+1} can preempt s_i .*

Proof. If $\alpha \in \Gamma$, then $\alpha' \notin \Gamma$ since Γ is an ordinary genome. In addition, since $\eta(\alpha) > 0$, $|\Delta_\alpha| > 0$, therefore $|\Delta_{\alpha'}| < 2$. Thus, $\eta(\alpha') \leq 0$. If $\alpha \notin \Gamma$, then to achieve $\eta(\alpha) > 0$, we must have $|\Delta_\alpha| = 2$, so in particular $|\Delta_{\alpha'}| = 0$ and therefore $\eta(\alpha') \leq 0$. ■

For a sequence of SCJ operations, S , let S^D (\overline{S}^D , respectively) be the subsequence of operations that act on two extremities of genes that have (have not, respectively) already been duplicated at the time of the operation. By Corollary 1, for optimal S , \overline{S}^D is indeed the complement of S^D .

Proposition 6. *There exists an optimal sorting scenario in which all duplication events are consecutive.*

Proof. Let o_{i_1}, \dots, o_{i_p} be the duplication events in an optimal sorting scenario. Denote by S_{i_j} the sequence of SCJ operations occurring between the duplications, o_{i_j} and $o_{i_{j+1}}$. In addition, denote by S_{i_0} and S_{i_p} the sequence of SCJ operations before the first duplication and after the last duplication, respectively.

Given an optimal scenario, $O^* = S_{i_0}, o_{i_1}, S_{i_1}, o_{i_2}, S_{i_2}, \dots, S_{i_{p-1}}, o_{i_p}, S_{i_p}$, we modify it into a new sorting scenario O' as follows: using Propositions 3 and 5, preempt SCJ operations acting on unduplicated genes. Using Proposition 4, preempt duplication events. These steps are iterated until no preemption is possible. We get that $O' = S_{i_0}, \overline{S}_{i_1}^D, \dots, \overline{S}_{i_p}^D, o_{i_1}, \dots, o_{i_p}, S_{i_1}^D, \dots, S_{i_{p-1}}^D, S_{i_p}$ is a valid SCJD optimal sequence in which all duplications are consecutive. ■

Corollary 2. *There exists an optimal SCJD sorting scenario, consisting, in this order, of (1) SCJ operations on single-copy genes, (2) duplications, and (3) SCJ operations acting on duplicated genes.* ■

Denote by Γ' the intermediate (ordinary) genome after step (1). Then, we can conclude the following:

Theorem 3. $d_{SCJD}(\Gamma, \Delta) = \min_{\Gamma'} (d_{SCJ}(\Gamma, \Gamma') + \#_c \Gamma' + dd_{SCJ}(\Gamma', \Delta))$ ■

Recall that n is the number of genes in Γ . Using Theorems 1 and 2 and the fact that $\#_c \Pi = n - |\Pi|$, the distance formula can be simplified as follows:

$$\begin{aligned} d_{SCJD} &= \min_{\Gamma'} \left(|\Gamma| + |\Gamma'| - 2|\Gamma \cap \Gamma'| + n - |\Gamma'| + |\Delta| + 2 \sum_{\alpha \in A} |\Gamma'_\alpha| (1 - |\Delta_\alpha|) \right) \\ &= n + |\Delta| + |\Gamma| - 2 \max_{\Gamma'} \left(|\Gamma \cap \Gamma'| + \sum_{\alpha \in A} |\Gamma'_\alpha| (|\Delta_\alpha| - 1) \right) \\ &= n + |\Delta| + |\Gamma| - 2 \max_{\Gamma'} \sum_{\alpha \in \Gamma'} (|\Gamma_\alpha| + |\Delta_\alpha| - 1) \\ &= n + |\Delta| + |\Gamma| - 2 \max_{\Gamma'} \sum_{\alpha \in \Gamma'} \eta(\alpha) = n + |\Delta| + |\Gamma| - 2 \max_{\Gamma'} H(\Gamma') \end{aligned} \quad (2)$$

where $\eta(\alpha) = \eta(\alpha, \Gamma, \Delta) = |\Gamma_\alpha| + |\Delta_\alpha| - 1$ and $H(\Gamma') = \sum_{\alpha \in \Gamma'} \eta(\alpha)$. Intuitively, $H(\Gamma')$ measures the similarity of Γ' to Γ and Δ in terms of adjacencies. Since we want to maximize $H(\Gamma')$, we will focus on adjacencies with positive contribution in Equation (2).

Lemma 2. *Let $\alpha = \{x, y\}$ be an adjacency such that $\eta(\alpha) > 0$. Then, for every extremity $z \neq y$, the conflicting adjacency $\alpha' = \{x, z\}$ has $\eta(\alpha') \leq 0$.*

Proof. If $\alpha \in \Gamma$, then $\alpha' \notin \Gamma$ since Γ is an ordinary genome. In addition, since $\eta(\alpha) > 0$, $|\Delta_\alpha| > 0$, therefore $|\Delta_{\alpha'}| < 2$. Thus, $\eta(\alpha') \leq 0$. If $\alpha \notin \Gamma$, then to achieve $\eta(\alpha) > 0$, we must have $|\Delta_\alpha| = 2$, so in particular $|\Delta_{\alpha'}| = 0$ and therefore $\eta(\alpha') \leq 0$. ■

Combining Lemma 2 and Theorem 3, we get a closed formula for the SCJD distance:

Theorem 4. *The genome $\Gamma' = \{\alpha = \{x, y\} | \eta(\alpha) > 0\}$ minimizes Equation (2). If Γ' is a linear genome, then the SCJD distance is given by $d_{SCJD}(\Gamma, \Delta) = n + |\Delta| + |\Gamma| - 2H(\Gamma')$.* ■

Let us return to the examples in Section 3:

- Example 1: $n = 1$, $|\Delta| = 1$, $|\Gamma| = 0$, $\Gamma' = \emptyset$, $H(\Gamma') = 0 \rightarrow d = 1 + 1 + 0 - 2 * 0 = 2$
- Example 2: $n = 2$, $|\Delta| = 2$, $|\Gamma| = 1$, $\Gamma' = \{\{a_h, b_r\}\}$, $H(\Gamma') = 2 \rightarrow d = 2 + 2 + 1 - 2 * 2 = 1$
- Example 3: $n = 3$, $|\Delta| = 4$, $|\Gamma| = 1$, $\Gamma' = \{\{a_h, b_r\}, \{b_h, c_r\}\}$, $H(\Gamma') = 1 + 1 \rightarrow d = 3 + 4 + 1 - 2 * 2 = 4$
- Example 4: $n = 3$, $|\Delta| = 4$, $|\Gamma| = 2$, $\Gamma' = \{\{a_h, b_r\}\}$, $H(\Gamma') = 1 \rightarrow d = 3 + 4 + 2 - 2 * 1 = 7$

Example 5. $\Gamma = abc$ and $\Delta = cab, bca$. According to Theorem 4, we get $\Gamma' = (abc)$ because $\eta(\{a_h, b_t\}) = \eta(\{b_h, c_t\}) = \eta(\{c_h, a_t\}) = 1$. The corresponding distance is $d = 3$, providing the following invalid sorting scenario:

$$\Gamma \xrightarrow{\text{join}} (abc) \xrightarrow{\text{dup}^*} (abc), (abc) \xrightarrow{\text{cut}} cab, (abc) \xrightarrow{\text{cut}} \Delta$$

dup^* indicates a duplication of a circular chromosome, an operation that is not allowed in the SCJD model (and has no cost). It is not difficult to verify that there is no valid sorting scenario with $d \leq 3$.

The reason for the discrepancy in Example 5 is that $\#_c(\Gamma') = n - |\Gamma'| = 0$ is not equal to the number of duplications if there are circular chromosomes. Therefore, to minimize the SCJD distance given by Equation (2), we need to maximize $H(\Gamma')$ under the constraint that Γ' is a linear genome, that is, $H(\Gamma') \geq H(\tilde{\Gamma})$ for every linear genome $\tilde{\Gamma}$. Lemma 3 shows that we can do so simply by removing one adjacency with $\eta = 1$ from each circular chromosome in Γ' and that such adjacency must exist.

Lemma 3. *Let $\Gamma' = \{\alpha = \{x, y\} \mid \eta(\alpha) > 0\}$ and let Γ'' be a genome obtained by removing one adjacency α with $\eta(\alpha) = 1$ from each circular chromosome in Γ' . Then, Γ'' is a linear genome that maximizes $H(\cdot)$ and the SCJD distance is given by $d_{\text{SCJD}}(\Delta, \Gamma) = n + |\Delta| + |\Gamma| - 2H(\Gamma'')$.*

Proof. Let Π be an ordinary linear genome maximizing $H(\Pi)$. From the maximality of $H(\Pi)$, we may assume w.l.o.g. that Π does not contain adjacencies with $\eta(\alpha) \leq 0$. By the definition of Γ' and from Lemma 2, we have that $\forall \alpha \in \Pi$ if $\eta(\alpha) > 0$, then $\alpha \in \Gamma'$. It follows that $\Pi \subseteq \Gamma'$. Therefore, every linear chromosome in Γ' is also in Π .

Since $\Pi \subseteq \Gamma'$, any linear chromosome C in Π that is not in Γ'' must be fully contained in a circular chromosome C' of Γ' . From the maximality of Π , C must contain all adjacencies in C' except for one adjacency α with minimum $\eta(\alpha)$.

Since Γ' contains only adjacencies with $\eta(\alpha) = 1$ or 2, the minimal value is an adjacency with $\eta(\alpha) = 1$ if one exists. If C' contains only adjacencies with $\eta(\alpha) = 2$, it follows that $|\Gamma_\alpha| = 1$ for every $\alpha \in C'$, so Γ contains the circular chromosome C' , contradicting the linearity of Γ . Hence, C' must contain at least one adjacency with $\eta(\alpha) = 1$. ■

Applying Lemma 3 to Example 5, we get $\Gamma'' = abc$ and $d = 5$:

$$\Gamma \xrightarrow{\text{dup}} abc, abc \xrightarrow{\text{cut}} a, bc, abc \xrightarrow{\text{join}} bca, abc \xrightarrow{\text{cut}} bca, ab, c \xrightarrow{\text{join}} \Delta$$

Instead, we can choose $\Gamma'' = cab$, which gives a different optimal sorting scenario:

$$\Gamma \xrightarrow{\text{cut}} ab, c \xrightarrow{\text{join}} cab \xrightarrow{\text{dup}} cab, cab \xrightarrow{\text{cut}} cab, a, bc \xrightarrow{\text{join}} \Delta$$

Algorithm 1 gives the full procedure for solving the SCJD distance and sorting problems. Each step of the algorithm takes $O(|\Gamma| + |\Delta|)$ time. In conclusion:

Algorithm 1 SCJD distance.

Input: An ordinary genome, Γ , and a duplicated genome, Δ , (both linear) on the same gene set.

Output: The SCJD distance, $d_{\text{SCJD}}(\Gamma, \Delta)$, and an optimal sorting scenario, o_1, \dots, o_d , in which all intermediate genomes are linear.

- 1: $\Gamma' \leftarrow \{\alpha = \{x, y\} \mid \eta(\alpha) > 0\}$ (Theorem 4)
 - 2: Create a linear genome, Γ'' , by removing one adjacency, α , with $\eta(\alpha) = 1$ from each circular chromosome in Γ' (Lemma 3)
 - 3: $d_{\text{SCJD}}(\Gamma, \Delta) \leftarrow n + |\Delta| + |\Gamma| - 2H(\Gamma'')$ (Theorem 4, Lemma 3)
 - 4: $o_1, \dots, o_i \leftarrow$ Sort Γ into Γ'' (Theorem 1, Lemma 1)
 - 5: $o_{i+1}, \dots, o_j \leftarrow$ Duplicate all chromosomes in Γ'' .
 - 6: $o_{j+1}, \dots, o_d \leftarrow$ Sort $2\Gamma''$ into Δ (Theorem 2, Lemma 1).
 - 7: **return** d, \vec{o}
-

Theorem 5. *Algorithm 1 computes the SCJD distance in linear time.* ■

5. CONTROLLING THE NUMBER OF DUPLICATIONS

In this section, we discuss how to control the number of duplications in an optimal SCJD sequence. Since the number of duplications is $n - |G''|$, selecting different intermediate genomes G'' that preserve the SCJD distance can produce scenarios with different number of duplications.

An optimal SCJD scenario with fewer duplications can be viewed as more conservative. The assumption behind this is that duplications are more radical events than breakage (cut) or fusion (join), which are local events.

Lemma 4. *Algorithm 1 gives an optimal sorting scenario with a maximum number of duplications.*

Proof. Observe first that for any sorting scenario (optimal or suboptimal) transforming G into Δ , we can assume w.l.o.g. that all duplications are consecutive without affecting the number of operations (Corollary 2). Call the genome right before the duplications the *last ordinary genome*. Denote by $d(G, \Pi, \Delta)$ the shortest scenario transforming G into Δ given that the last ordinary genome is Π . The proof of Theorem 3 implies that $d(G, \Pi, \Delta) = n + |\Delta| + |G| - 2H(\Pi)$.

Let G' be the last ordinary genome produced by the algorithm. Consider an optimal scenario O with a maximum number of duplications and let \tilde{G} be the last ordinary linear genome in O . Since O is optimal, $H(\tilde{G})$ must be maximal. Hence, \tilde{G} cannot contain adjacencies with $\eta < 0$. Moreover, it cannot contain adjacencies with $\eta = 0$ as such adjacencies increase $|\tilde{G}|$ and thus decrease the number of duplications in O . Therefore, $\tilde{G} \subseteq G'$.

We now show that $\forall \alpha \in G' \setminus \tilde{G}, \eta(\alpha) = 1$. Suppose by contradiction that there is an adjacency $\alpha \in G' \setminus \tilde{G}$ with $\eta(\alpha) > 1$ and let $\Pi = \tilde{G} \cup \{\alpha\}$. If Π is a linear genome, $d(G, \Pi, \Delta) < d(G, \tilde{G}, \Delta)$, contradicting the optimality of O . Otherwise, Π contains a circular chromosome and by Lemma 3, there is an adjacency $\beta \in \tilde{G}$ with $\eta(\beta) = 1$ such that $\Pi \setminus \{\beta\}$ is a linear genome with $H(\Pi \setminus \{\beta\}) > H(\tilde{G})$, again contradicting the optimality of O . Thus, $|G' \setminus \tilde{G}| = |G'| - |\tilde{G}| = H(G') - H(\tilde{G})$.

G' may contain circular chromosomes. By Lemma 3, G'' is produced by removing one adjacency with $\eta = 1$ from each circular chromosome in G' . Hence, $|G' \setminus G''| = |G'| - |G''| = H(G') - H(G'')$.

Since both \tilde{G} and G'' are last ordinary genomes, in optimal SCJD scenarios, $H(\tilde{G}) = H(G'')$. Thus, $|G' \setminus \tilde{G}| = H(G') - H(\tilde{G}) = H(G') - H(G'') = |G'| - |G''|$, which implies that $|\tilde{G}| = |G''|$. ■

One can decrease the number of duplications in an optimal SCJD scenario by adding adjacencies with $\eta(\alpha) = 0$ to G'' . However, we need to make sure that the resulting genome is still linear. Consider the following example:

Example 6: $G = a, b, c, \Delta = abccba$. From Theorem 4, we have that $G' = G$ and so the SCJD distance is 8. The scenario produced by Algorithm 1 will first duplicate the three chromosomes of G and then perform five joins to create Δ . An alternative optimal sorting scenario is as follows:

$$G \xrightarrow{JJ} abc \xrightarrow{D} abc, abc \xrightarrow{CC} abc, a, b, c \xrightarrow{JJJ} \Delta$$

Here, since each adjacency $\alpha \in \Delta$ has $\eta(\alpha) = 0$, we chose $G'' = abc$ and obtained an optimal scenario with a single duplication. In contrast, if we add to G'' the adjacencies $\{b_h, c_t\}$ and $\{c_h, b_t\}$ (which also have $\eta = 0$), we create a circular chromosome and an invalid SCJD sorting scenario.

To minimize the number of duplications, we must add to G'' a maximum set of adjacencies with $\eta = 0$ such that the resulting genome is still linear. Here, we show that this problem is NP-hard using a reduction similar to (Kováč, 2014).

Theorem 6. *Given an ordinary linear genome, G , a duplicated linear genome, Δ , on the same gene set, and an integer, k , the problem of finding an optimal SCJD scenario with at most k duplications is NP-hard.*

Proof. Call a directed graph in which all in- and out-degrees are 2 a *2-digraph*. Deciding if a 2-digraph contains a Hamiltonian cycle is NP-hard (Plesnik, 1979; Kováč, 2014). This implies that the following variant is also NP-hard: given a 2-digraph, G , with an edge, (x, y) , decide if there is a Hamiltonian path from y to x in G .

Let $G=(V, E)$ be a 2-digraph with an edge (x, y) as above. We may assume w.l.o.g. that G is strongly connected since otherwise it would not contain a Hamiltonian path from y to x . Notice that $G \setminus (x, y)$ contains an Eulerian path from y to x (Cormen et al., 2001). Denote it by $P=e_1, e_2, \dots, e_m$.

We construct a duplicated genome Σ as follows: for each $e_q=(u, v) \in P$, add the adjacency, $\{u_h^i, v_t^j\}$, where $i=2$ if there is an edge $e_l=(u, v')$ with $l < q$ and $i=1$ otherwise. Similarly, $j=2$ if there is an edge $e_m=(u', v)$ with $m < q$ and $j=1$ otherwise. The result is a linear chromosome created by traversing P and numbering the first occurrence of each vertex v in P as the gene copy v^1 and the second occurrence as v^2 . Denote by $\overset{P}{\rightsquigarrow}$ the sequence of genes along the path P . In addition, we add two new genes w, z and the adjacencies $\{w_h^1, y_t^1\}, \{x_h^2, z_t^1\}$. Thus, Σ has three linear chromosomes: $w^1 y^1 \overset{P}{\rightsquigarrow} x^2 z^1, w^2$ and z^2 . Let $\Pi = \{\{w_h, y_t\}, \{x_h, z_t\}\}$ be an ordinary genome with n chromosomes over the same set of genes. (Note that every vertex in $V \setminus \{x, y\}$ corresponds to a separate chromosome in Π).

Let $\Sigma_{(i)}$ and $\Pi_{(i)}$ be genomes in which every gene $v \in V$ is renamed $v_{(i)}$. We define $\Delta = \bigcup_{i=1}^k \Sigma_{(i)}$ and $\Gamma = \bigcup_{i=1}^k \Pi_{(i)}$ to be the disjoint union of k different copies of Σ and Π , respectively. This completes the reduction, which is clearly polynomial. We will show that there is an optimal SCJD scenario between Γ and Δ with at most k duplications if G admits a Hamiltonian path from y to x .

For each edge $e=(u, v) \in E$ and every i , the corresponding adjacency $\alpha = \{(u_{(i)})_h^j, (v_{(i)})_t^l\}$ has $\eta(\alpha)=1$ if there are two parallel edges from u to v and $\eta(\alpha)=0$ otherwise. In addition, for every i , $\eta(\{(w_{(i)})_h, (y_{(i)})_t\}) = \eta(\{(x_{(i)})_h, (z_{(i)})_t\}) = 1$, and every other adjacency of $w_{(i)}, z_{(i)}$ has $\eta < 0$.

Suppose G contains a Hamiltonian path S from y to x . Let Γ' be the genome formed by the set of adjacencies $\{\{(w_{(i)})_h, (y_{(i)})_t\}, \{(x_{(i)})_h, (z_{(i)})_t\} | i=1 \dots k\} \cup \{\{(u_{(i)})_h, (v_{(i)})_t\} | (u, v) \in S, i=1 \dots k\}$. Since S is a Hamiltonian path, Γ' is a valid ordinary linear genome with k chromosomes of the form $w_{(i)} y_{(i)} \overset{S}{\rightsquigarrow} x_{(i)} z_{(i)}$. To prove that Γ' maximizes $H(\cdot)$, we need to show it contains every adjacency with $\eta=1$ and no adjacency with $\eta < 0$. Indeed (suppressing the copy index i for clarity), the only adjacencies α with $\eta(\alpha)=1$ are $\{w_h, y_t\}, \{x_h, z_t\}$ ($|\Delta_\alpha|=|\Gamma_\alpha|=1$) and parallel edges in G ($|\Delta_\alpha|=2, |\Gamma_\alpha|=0$), one copy of which must be included in S . All other adjacencies in Γ' have $|\Delta_\alpha|=1, |\Gamma_\alpha|=0$ and $\eta(\alpha)=0$. We conclude that Γ' is part of an optimal scenario with k duplications.

Conversely, suppose there is an optimal scenario O^* with at most k duplications and let $\tilde{\Gamma}$ be the last ordinary genome in O^* . Let $\Gamma' = \{\alpha | \eta(\alpha) > 0\}$ be a genome that minimizes the SCJD distance according to Theorem 4. First, notice that Γ' is indeed a linear genome. Otherwise, a circular chromosome of adjacencies with $\eta(\alpha)=1$ would imply a strongly connected component without the vertices x, y , contradicting the strong connectivity of G . It follows that $\Gamma' \subseteq \tilde{\Gamma}$, $H(\Gamma')=H(\tilde{\Gamma})$, and $\#_c \tilde{\Gamma} \leq k$.

Since $\Sigma_{(i)}$ and $\Sigma_{(j)}$ for $i \neq j$ contain different genes, an adjacency between a gene in $\Sigma_{(i)}$ and a gene $\Sigma_{(j)}$ has negative η . Therefore, $\tilde{\Gamma}$ contains no such adjacencies. Since $\tilde{\Gamma}$ has at most k linear chromosomes, it must contain exactly k linear chromosomes, each containing all the genes of $\Sigma_{(i)}$ for one i .

Let $C=w_{(1)} y_{(1)} \dots x_{(1)} z_{(1)}$ be the linear chromosome in $\tilde{\Gamma}$ that contains all the genes of $\Sigma_{(1)}$. Define an edge set S in G by taking for each adjacency $\{(u_{(1)})_h, (v_{(1)})_t\} \in C \setminus \{\{(w_{(1)})_h, (y_{(1)})_t\}, \{(x_{(1)})_h, (z_{(1)})_t\}\}$ the edge (u, v) . Since C is an ordinary linear chromosome containing all the genes of $\Sigma_{(1)}$, S is a Hamiltonian path in G from y to x . ■

6. DISCUSSION

In this article, we presented the SCJD rearrangement model, which allows the operations, cut, join, and whole chromosome duplication. We analyzed the problem of finding the minimum number of SCJD operations that transform an ordinary linear genome into a duplicated linear genome and provided a linear time algorithm for it. Furthermore, we showed that this algorithm gives an optimal scenario with a maximum number of duplications and that finding one with fewest duplications is NP-hard.

In the analysis, we focused on the SCJD sorting problem, which restricts the target genome to have exactly two copies of each gene. However, it is not difficult to generalize our algorithm to address the more general situation where each gene in the target genome has *at most* two copies. One can show that in this case too, an optimal solution in which all duplications are consecutive exists. In addition, each adjacency in the original genome between a gene that has two copies and a gene that has one copy in the target genome must first be cut. This is true because duplications are defined over linear chromosomes in which every gene is unduplicated.

Our algorithm relies on the property that all duplications in the optimal solution can be clustered (Corollary 2). In this sense, the problem we study is similar to the SCJ Guided Genome Halving problem (Feijão and Meidanis, 2011). In that model, the whole genome is duplicated at once, while in ours, there is one duplication per chromosome, and accounting for these duplications is part of the optimization challenge.

Many aspects in the analysis of the SCJD model require further research: How can we address the problem if there are more than two copies of each gene? Can we find the SCJD distance between two arbitrary genomes—each containing single copy and multiple copy genes? How does removing the requirement of linearity affect various SCJD problems? Moreover, duplications may be defined differently, for example, tandem duplications (Bader, 2009) and segmental duplications (Shao et al., 2013). Finally, developing a rigorous model that will allow both duplications and deletions is needed to analyze the full complexity of real biological data such as cancer samples.

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