Finding Local Genome Rearrangements[*]

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Abstract

The Double Cut and Join (DCJ) model of genome rearrangement is well studied due to its mathematical simplicity and power to account for the many events that transform genome architecture. These studies have mostly been devoted to the understanding of minimum length scenarios transforming one genome into another. In this paper we search instead for DCJ rearrangement scenarios that minimize the number of rearrangements whose breakpoints are unlikely due to some biological criteria. We establish a link between this Minimum Local Scenario (MLS) problem and the problem of finding a Maximum Edge-disjoint Cycle Packing (MECP) on an undirected graph. This link leads us to a 3/2-approximation for MLS, as well as an exact integer linear program. From a practical perspective, we briefly report on the applicability of our methods and the potential for computation of distances using a more general DCJ cost function.

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1 Overview

The problem of sorting genomes by a prescribed set of biologically plausible rearrangements has been a central problem in comparative genomics for roughly a quarter century. The Double Cut and Join (DCJ) model covers a diverse set of these possible rearrangements while being grounded in a very simple mechanism [15, 2]. An important step forward is the development of methodology to find plausible rearrangement scenarios using biological constraints.

We recently introduced a model for weighting DCJs that is suitable for representing certain biological constraints. The model groups breakpoint regions between adjacent genes (or syntenic blocks) into equivalence classes that are likely to participate in a rearrangement [14]. The 3D spacial proximity of breakpoint regions could be used as such, and the data is becoming increasingly available due to an experiment called Hi-C [9, 13]. (The pertinence of this model is discussed in Section 7.) The model colors adjacencies for use with a binary cost function, where a DCJ acting on adjacencies with the same color is of zero cost while those acting on different colors are of cost one. We showed that the problem of finding – out

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of all minimum length rearrangement scenarios – a scenario that minimizes the number of costly moves, takes polynomial time [14].

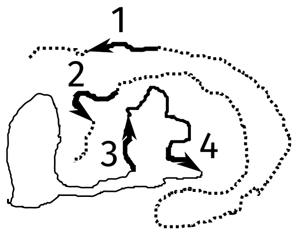
In this paper we disregard the length of the scenario and instead focus solely on the number of costly moves. We show that the Minimum Local Scenario problem is NP-Hard, while admitting a 3/2-approximation. This is done by exploiting a relationship to the Maximum Edge-disjoint Cycle Packing problem, a problem which was first linked to genome rearrangement in a different way by Alberto Caprara (sorting by unsigned reversals is NP-Hard [4]).

In our method, MLS is transformed into an edge elimination problem on a *junction graph*, representing the transitions between colors encountered when traversing the connected components of the adjacency graph. We give an exact formula for the number of costlyy moves based solely on the number of edges and the number of cycles in the MECP of the junction graph. We also propose an exact algorithm for MLS that is exponential in the number of colors and not in the number of genes and discuss an example where this algorithm is computationally feasible. Finally, we show how to bound the number of non-parsimonious moves when using a more general cost function.

The paper is organized as follows. Section 2 introduces basic definitions. In Section 3 our main result, relating MLS to MECP by way of the junction graph, is described in the simplified realm of sets of pairs. In this context, the junction graph is Eulerian. Section 4 extends the results to the general case where the junction graph is not Eulerian. Section 5 presents our algorithmic results. Finally, Section 6 discusses a more general cost function, while Section 7 reports on practical aspects of coloring adjacencies.

2 Genome and DCJ rearrangements

A *genome* consists of *chromosomes* that are linear or circular molecules partitioned into uniquely labeled directed genes (or equivalently *syntenic blocks* of genes) and intergenic regions separating them.



The genome depicted above consists of a linear and a circular chromosome each having two genes. Arrows in the picture indicate the *head extremities* of the genes. We can represent a genome by a set of *adjacencies* between the gene extremities and such a set for a genome from our example is $\{\{1_h\},\{1_t,2_t\},\{2_h\},\{3_h,4_t\},\{4_h,3_t\}\}$. Here 1_h denotes the head extremity of a gene 1. An *adjacency* is either an unordered pair of gene extremities that are adjacent on a chromosome, called *internal* adjacency, or a single gene extremity adjacent to one of the two ends of a linear chromosome, called an *external* adjacency.

▶ **Definition 1** (Double Cut and Join). DCJ move acts on one or two adjacencies as follows:

1. $\{a,b\},\{c,d\} \to \{a,c\},\{b,d\}$ or $\{a,d\},\{b,c\}$
2. $\{a,b\},\{c\} \to \{a,c\},\{b\}$ or $\{b,c\},\{a\}$
3. $\{a,b\} \to \{a\},\{b\}$
4. $\{a\},\{b\} \to \{a,b\}$

We first treat a simplified instance of sets of pairs where all the adjacencies are internal and DCJs can only swap the elements between them in Section 3. Then in Section 4 we show how genomes can be extended to the sets of pairs and use the previously obtained results to solve the Minimum Local Scenario problem.

3 Minimum Local Scenario for sets of pairs

3.1 Cost of a DCJ scenario

Given two sets of *pairs*:

$$A = \{\{1,2\},\dots,\{2n-1,2n\}\}, \text{ and}$$
$$B = \{\{q_1,q_2\},\dots,\{q_{2n-1},q_{2n}\}\},$$

with *pairs* being unordered and $(q_1,\dots,q_{2n})$ being a permutation of $(1,\dots,2n)$, our goal is to transform A into B with a sequence of DCJ moves $\{a,b\},\{c,d\} \to \{a,c\},\{b,d\}$ and $\{a,b\},\{c,d\} \to \{a,d\},\{b,c\}$.

A *coloring* of a set of pairs A over a set of colors Δ is a function $col : A \to \Delta$ partitioning A into the subsets of different colors. A *coloring* is used to define the *cost* of a DCJ move. A move is *local* and of zero cost if it acts on the pairs with equal colors and it is *non-local* and of cost 1 otherwise. The *cost* of a sequence of DCJ moves, a DCJ *scenario*, is the sum of the costs of its constituent moves.

A DCJ move $A \to A'$ transforming a set of pairs A into A' will also transform col into col', a coloring of A'. This means that a DCJ scenario transforming A into B will transform A's coloring col into B's coloring col_B. For a pair $p \in A$ we use notation $(p, col(p))$ of a *colored pair*. Four different DCJ moves on colored pairs $(\{a,b\},x)$ and $(\{c,d\},y)$ are allowed in our model giving four possible outcomes:

$$(\{a,c\},x),(\{b,d\},y), \text{ or } (\{a,d\},x),(\{b,c\},y), \text{ or}$$
$$(\{a,c\},y),(\{b,d\},x), \text{ or } (\{a,d\},y),(\{b,c\},x).$$

The biological interpretation of this model is that intergenic regions are broken and repaired at their borders with the gene extremities. We discuss the applicability of such a model in Section 7.

In our previous work [14] we have treated the Minimum Local Parsimonious Scenario problem.

▶ **Problem 1** (MLPS). *For two sets of pairs A, B and a coloring of A find a minimum cost scenario among the DCJ scenarios of minimum length transforming A into B.*

We have shown that MLPS takes polynomial time, however the real evolutionary scenario might be non-parsimonious. In this paper we study the Minimum Local Scenario problem which asks for such non-parsimonious scenarios.

▶ **Problem 2** (MLS). *For two sets of pairs A, B and a coloring of A find a minimum cost DCJ scenario transforming A into B.*

MLS has the following combinatorial interpretation. Pairs of uniquely labeled balls (set of pairs A) are partitioned into the bins (coloring of A). Given a partition T of the balls into pairs (set of pairs B), find a minimum length sequence of ball swaps between the bins (DCJ moves) so that for all pairs $\{a,b\} \in T$, a and b end up in the same bin (A is transformed into B).

3.2 Adjacency and junction graphs

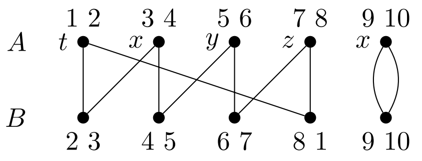
The *Adjacency* graph was introduced in [2] for the study of DCJ rearrangements. We introduce a transformation of the adjacency graph, called a *junction* graph, that incorporates the information on a coloring.

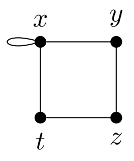
▶ **Definition 2** (Adjacency graph). For two sets of pairs A and B the adjacency graph $AG(A,B)$ is defined as a bipartite multi-graph whose vertices are $A \cup B$ and for each $p \in A$ and $q \in B$ there are exactly $|p \cap q|$ edges joining these two vertices.

▶ **Definition 3** (Junction graph). For two sets of pairs A, B and a coloring col of A over Δ we define a multi-graph $J(A,B,col) = (\Delta, E)$. For every pair $\{a,b\} \in B$ we add an edge (x,y) to E such that x and y are the colors of the pairs of A adjacent to $\{a,b\}$ in $AG(A,B)$.

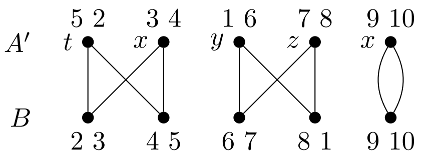
▶ **Example 4.** For two sets of pairs A, B and a coloring col of A we present below $AG(A,B)$ on the left and $J(A,B,col)$ on the right.

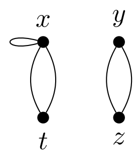
$$A = \{(\{1,2\},t), (\{3,4\},x), (\{5,6\},y), (\{7,8\},z), (\{9,10\},x)\}$$
$$B = \{\{2,3\},\{4,5\},\{6,7\},\{8,1\},\{9,10\}\}$$





A DCJ move $(\{1,2\},t), (\{5,6\},y) \rightarrow (\{5,2\},t), (\{1,6\},y)$ transforming A into A' transforms adjacency and junction graphs as follows.





All connected components of $AG(B,B)$ are cycles of length 2 thus at the end of a DCJ scenario transforming A into B we are left with a junction graph whose edges are all loops, we call such a graph *terminal*.

▶ **Definition 5** (A DCJ move on a graph). Edges (x,y) and (z,t) of a graph are deleted and replaced by either (x,z) and (y,t) or (x,t) and (y,z).

▶ **Lemma 6.** *For a DCJ scenario of cost w transforming A into B there exists a DCJ scenario of length at most w transforming $J(A,B,col)$ into a* terminal *graph and vice versa.*

Proof. From Example 4 it should be clear that for every DCJ move $A \rightarrow A'$ we have that a transformation $J(A,B,col)$ to $J(A',B,col')$ is a DCJ move on a graph. If a DCJ move $A \rightarrow A'$ is of zero cost, then $J(A,B,col) = J(A',B,col')$ and such moves will be omitted from a DCJ scenario on a graph. This means that a DCJ scenario of cost w transforming A (and its coloring col) into (B and its coloring col_B) provides us with a DCJ scenario of length at most w on a graph transforming $J(A,B,col)$ into a terminal graph $J(B,B,col_B)$. On the other hand for every DCJ move on a graph $J \rightarrow J'$ a DCJ move $A \rightarrow A'$ can be found such that $J(A',B,col') = J'$. For any DCJ scenario on a graph of length w transforming

$J(A, B, col)$ into a terminal graph we obtain a DCJ scenario of length w, thus of cost at most w, transforming A and its coloring *col* into C and its coloring col_C such that $J(C, B, col_C)$ is terminal. This means that C's pairs belonging to the same connected component of $AG(C, B)$ are of the same color. A DCJ scenario transforming C into B and only acting on the pairs belonging to the same connected components of an adjacency graph can be easily found. Such a scenario is of zero cost and at the end we obtain a DCJ scenario transforming A into B of cost at most w. ◀

3.3 Linking DCJ scenarios and Maximum Edge-disjoint Cycle Packings

Using Lemma 6 we can shift our attention from a DCJ scenario on a set of pairs to a DCJ scenario on a junction graph J. From now on we will shorten "DCJ move on a graph" to "DCJ move".

▶ **Definition 7** (Maximum Edge-disjoint Cycle Packing (MECP)). Maximum Edge-disjoint Cycle Packing of a graph G is a largest set of edge-disjoint cycles in G.

For a graph $G = (V, E)$ we note $E(G) = |E|$ and $c(G)$ the size of its MECP. For a junction graph J we write $w(J)$ to indicate the minimum length of a DCJ scenario transforming J into a *terminal* graph.

▶ **Theorem 8.** *For a junction graph J we have $w(J) = E(J) - c(J)$.*

Proof. It is easy to transform a cycle of length $n > 1$ into n loops in $n-1$ DCJ moves. Given a cycle packing C of J we construct a DCJ scenario transforming J into a terminal graph while transforming all of its cycles separately. The length of such a scenario is $E(J) - |C|$, and if we take a Maximum Edge-disjoint Cycle Packing we obtain $w(J) \leq E(J) - c(J)$.

Now take a scenario of m DCJ moves transforming $J = J_0$ into a terminal graph J_m, with J_k being the junction graph after $k \geq 0$ moves of the scenario. We enumerate J's edges $E = \{e_1, \ldots, e_{E(J)}\}$ and define their partition into singletons $P_0 = \{\{1\}, \ldots, \{E(J)\}\}$. A move k of a scenario acts on two edges e_i and e_j of J_{k-1}, deleting them and introducing two new edges to give J_k. We call one of these edges e_i and another e_j, preserving the enumeration of the edges of J_k. Let S^i and S^j be the subsets of a partition P_{k-1} including e_i and e_j respectively. We define a partition P_k of $\{e_1, \ldots, e_{E(J)}\}$ obtained from P_{k-1} by merging S^i and S^j into $S^i \cup S^j$. At the end we obtain a partition P_m of cardinality at least $E(J) - m$ as there were at most m merges on the way. We will show that P_m is a cycle packing of J.

For J's vertices V, a subset $S \subset \{e_1, \ldots, e_{E(J)}\}$ and $k \in \{0, \ldots, m\}$, we define $S_{J_k} = (V, S)$ a subgraph of J_k. For any graph G and its vertex v we denote $d_G(v)$ the degree of v in G.

▶ **Lemma 9.** *For $k \in \{0, \ldots m\}$, a subset S in a partition P_k, and a vertex v of J we have*

$$d_{S_J}(v) = d_{S_{J_k}}(v).$$

Proof. $J_0 = J$, thus the equality is true for $k = 0$. We suppose that equality is true for every S and v with $k-1$ and proceed by induction on k. We fix a vertex v and a subset $S \in P_k$. The k-th move of a scenario acts on the edges e_i and e_j that by construction belongs to the same subset $S' \in P_k$. There are three possibilities:

1. ($S' \neq S$) In this case $S \in P_{k-1}$ and $S_{J_k} = S_{J_{k-1}}$, as the edges in S are unaffected by a DCJ move. Using the inductive hypothesis we obtain

$$d_{S_{J_k}}(v) = d_{S_{J_{k-1}}}(v) = d_{S_J}(v)\,.$$

2. ($S' = S$ and $S = S^i \cup S^j$ with S^i and S^j being the different subsets in P_{k-1} including e_i and e_j respectively) S_{J_k} is obtained from $S_{J_{k-1}}$ via a DCJ move and, as a DCJ move does not affect the degrees of the vertices we obtain, we use the inductive hypothesis and the fact that $S = S^i \cup S^j$ to get

$$d_{S_{J_k}}(v) = d_{S_{J_{k-1}}}(v) = d_{S^i_{J_{k-1}}}(v) + d_{S^j_{J_{k-1}}}(v) = d_{S^i_J}(v) + d_{S^j_J}(v) = d_{S_J}(v)\,.$$

3. ($S' = S$ and e_i, e_j already present in the same subset S of P_{k-1}) S_{J_k} is obtained from $S_{J_{k-1}}$ via a DCJ move which does not affect the degrees of the vertices and thus we obtain (using inductive hypothesis)

$$d_{S_{J_k}}(v) = d_{S_{J_{k-1}}}(v) = d_{S_J}(v)\,.$$

As equality is preserved by a DCJ move and true for $k = 0$ we obtain the result by induction. ◀

All edges of J_m are loops, thus for every subset S in P_m and vertex v of J, $d_{S_{J_m}}(v)$ is even and so, using Lemma 9, we know that $d_{S_J}(v)$ is even as well. This means that the connected components of S_J are Eulerian and thus S is a union of J's cycles. As P_m contains at least $E(J) - m$ subsets, we know that it partitions the edges of J into at least $E(J) - m$ cycles. If we take a scenario of length $w(J)$ we obtain the inequality $c(J) \geq E(J) - w(J)$, which ends the proof of Theorem 8. ◀

4 Minimum Local Scenario for genomes

4.1 Cost of a DCJ scenario

Given two genomes with enumerated extremities

$$A = \big\{\{1,2\}, \ldots, \{2n-1, 2n\}, \{2n+1\}, \ldots, \{2n+2m\}\big\},$$
$$B = \big\{\{q_1, q_2\}, \ldots, \{q_{2l-1}, q_{2l}\}, \{q_{2l+1}\}, \ldots, \{q_{2n+2m}\}\big\},$$

and $(q_1, \ldots, q_{2n+2m})$ being a permutation of $(1, \ldots, 2n+2m)$. Our goal is to transform A into B using DCJ moves defined in Definition 1. As in the case of pairs-only, we define a coloring $col : A \to \Delta$ which is transformed by DCJ moves as follows:

1. $(\{a,b\},x), (\{c,d\},y) \to (\{a,c\},x), (\{b,d\},y)$ or $(\{a,d\},x), (\{b,c\},y)$ or $(\{a,c\},y), (\{b,d\},x)$ or $(\{a,d\},y), (\{b,c\},x)$
2. $(\{a,b\},x), (\{c\},y) \to (\{a,c\},x), (\{b\},y)$ or $(\{a,c\},y), (\{b\},x)$ or $(\{b,c\},x), (\{a\},y)$ or $(\{b,c\},y), (\{a\},x)$
3. $(\{a,b\},x) \to (\{a\},x), (\{b\},z)$ or $(\{a\},z), (\{b\},x)$ with any color z
4. $(\{a\},x), (\{b\},y) \to (\{a,b\},x)$ or $(\{a,b\},y)$

The cost of a DCJ move is equal to 0 if $z = x$ or $x = y$, 1 otherwise.

4.2 Genome extensions

A genome can be extended into a set of pairs by adding artificial gene extremities that represent *telomeres* marking the ends of each linear chromosome.

▶ **Definition 10** (Genome extensions)**.** For a genome A we define a set A_+ of the sets of pairs that are *genome extensions* of A. $\hat{A} \in A_+$ is of a form:

$$\{\{1,2\},\ldots,\{2n-1,2n\},\{2n+1,\circ_1\},\ldots,\{2n+2m,\circ_{2m}\},$$
$$\{\circ_{2m+1},\circ_{2m+2}\},\ldots,\{\circ_{2m+2l-1},\circ_{2m+2l}\}\}$$

with $l \in \mathbb{N}$ and $(\circ_1,\ldots,\circ_{2m+2l})$ being a permutation of $(2n+2m+1,\ldots,2n+4m+2l)$.

A pair $\{i,j\}$ with $i,j > 2n+2m$ will be called a *telomeric* pair. By construction, adjacencies of a genome and non-telomeric pairs of a genome extension can be mapped one to one as internal adjacencies of a genome are present in the genome extension, and external adjacencies are simply complemented by an artificial gene extremity. A coloring *col* of A can be trivially extended to a coloring $\hat{col}$ of $\hat{A} \in A_+$ by keeping the same colors for the non-telomeric pairs and choosing any colors for the telomeric ones. For every DCJ move $A \to A'$ acting on two adjacencies of a genome there is an *induced* DCJ move $\hat{A} \to \hat{A}'$ of the same cost with $\hat{A}' \in A'_+$ acting on the corresponding pairs of a genome extension. For example $(\{a\},x),(\{b\},y) \to (\{a,b\},x)$ induces $(\{a,\circ_1\},x),(\{b,\circ_2\},y) \to (\{a,b\},x),(\{\circ_1,\circ_2\},y)$ and $(\{a,b\},x)(\{c\},y) \to (\{a,c\},x),(\{b\},y)$ induces $(\{a,b\},x),(\{c,\circ_1\},y) \to (\{a,c\},x),(\{b,\circ_1\},y)$. A DCJ move of the form $(\{a,b\},x) \to (\{a\},x),(\{b\},z)$ or $(\{a\},z),(\{b\},x)$ acting on a single adjacency is different, as in this case we need a telomeric adjacency of color z to be present in a genome extension. For example $(\{a,b\},x) \to (\{a\},x),(\{b\},z)$ induces $(\{a,b\},x),(\{\circ_1,\circ_2\},z) \to (\{a,\circ_1\},x),(\{b,\circ_2\},z)$ on a genome extension including $(\{\circ_1,\circ_2\},z)$.

▶ **Lemma 11.** *For a DCJ scenario transforming genome A into B and a coloring of A there exist genome extensions $\hat{A} \in A_+$, $\hat{B} \in B_+$ and a scenario of the same cost transforming $\hat{A}$ into $\hat{B}$.*

Proof. In a DCJ scenario there is a certain number l of the DCJ moves acting on a single adjacency. We take a genome extension $\hat{A} \in A_+$ with l telomeric pairs. Every DCJ move $(\{a,b\},x) \to (\{a\},x),(\{b\},z)$ or $(\{a\},z),(\{b\},x)$ will induce a move acting on a different telomeric pair of a genome extension and its color will be a color z required by that DCJ move on a genome. In this way every DCJ move on a genome will induce a move on a genome extension and after a scenario of cost w we will end up with $\hat{B}$, an extension of genome B. ◀

▶ **Lemma 12.** *For a DCJ scenario transforming $\hat{A} \in A_+$ into $\hat{B} \in B_+$ and a coloring of A there exists a DCJ scenario of the same cost or smaller transforming A into B.*

Proof. We start with a couple $(A,\hat{A})$ and apply a scenario transforming $\hat{A}$ into $\hat{B}$ step by step, transforming A on the way. After the first k moves of a scenario whose cost is w_k we get a couple $(A^k,\hat{A}^k)$ with $\hat{A}^k \in A^k_+$ and A^k obtainable from A by a scenario of cost at most w_k. A couple $(A^{k+1},\hat{A}^{k+1})$ is constructed as follows. The $k+1$st move of a scenario is $\hat{A}^k \to \hat{A}^{k+1}$.

1. If $\hat{A}^{k+1} \in A^k_+$, then output $(A^k,\hat{A}^{k+1})$.
2. If $\hat{A}^{k+1} \notin A^k_+$, then we can easily find a genome C such that $\hat{A}^{k+1} \in C_+$ and there is a DCJ move $A^k \to C$ of the same cost as $\hat{A}^k \to \hat{A}^{k+1}$. Output $(C,\hat{A}^{k+1})$.

Now $\hat{A}^{k+1} \in A^{k+1}_+$ and the scenario transforming A into A^{k+1} is of cost at most w_{k+1}. We continue until we obtain $(B,\hat{B})$ with a scenario transforming A into B of cost at most w. ◀

▶ **Definition 13** (Adjacency graph)**.** For two genomes A and B the adjacency graph $AG(A,B)$ is defined as a bipartite multi-graph whose vertices are $A \cup B$ and for each $p \in A$ and $q \in B$ there are exactly $|p \cap q|$ edges joining these two vertices.

▶ **Definition 14** (Junction graph). For two genomes A, B and a coloring col of A over Δ we define a multi-graph $J(A, B, col) = (\Delta, E)$. For every internal adjacency $\{a, b\} \in B$ we add an edge (x, y) to E such that x and y are the colors of the pairs of A adjacent to $\{a, b\}$ in $AG(A, B)$.

We define an *Eulerian extension* of a graph to be an Eulerian graph obtained from the initial one by adding some edges. By construction $J(\hat{A}, \hat{B}, \hat{col})$ is an Eulerian extension of $J(A, B, col)$. We close this section by relating Eulerian extensions of $J(A, B, col)$ to the junction graphs of genome extensions, the proof is provided in the appendix.

▶ **Lemma 15.** *For every Eulerian extension J' of $J(A, B, col)$ there exists genome extensions $\hat{A} \in A_+$ and $\hat{B} \in B_+$ such that $J(\hat{A}, \hat{B}, \hat{col})$ and J' have exactly the same non-loop edges. We say that such graphs are* loop-equal*.*

4.3 Minimum Local Scenario

▶ **Theorem 16.** *The minimum cost w of a DCJ scenario transforming genome A into B is $E(J) - c(J)$ with $J = J(A, B, col)$.*

Proof. For a cycle packing C of J of cardinality $c(J)$ we define an Eulerian extension J' with every edge of J not belonging to C duplicated, we denote the number of such edges by k. A union of C and k cycles of length 2 created by the added edges will be a cycle packing C' of J'. Using Theorem 8 we obtain a DCJ scenario of length $E(J') - |C'| = E(J) + k - c(J) - k = E(J) - c(J)$ transforming J' into a terminal graph. Using Lemma 15 we obtain the sets of pairs $\hat{A} \in A_+$ and $\hat{B} \in B_+$ such that $J(\hat{A}, \hat{B}, \hat{col})$ is loop-equal to J'. Using Lemma 6 we obtain a DCJ scenario of cost at most $E(J) - c(J)$ transforming $\hat{A}$ into $\hat{B}$ from which we obtain a DCJ scenario of cost at most $E(J) - c(J)$ transforming A into B while using Lemma 12, meaning that $w \leq E(J) - c(J)$.

For a DCJ scenario of cost w transforming A into B we use Lemma 11 to obtain the sets of pairs $\hat{A} \in A_+$ and $\hat{B} \in B_+$, and a scenario of cost w transforming $\hat{A}$ into $\hat{B}$. This leads to a DCJ scenario transforming $J' = J(\hat{A}, \hat{B}, \hat{col})$ into a terminal graph in at most w moves using Lemma 6. Theorem 8 gives us a cycle packing C' of J' such that $w \geq E(J') - |C'|$. We then define C to be the union of the cycles in C' consisting entirely of the edges of $J = J(A, B, col_A)$. While counting edges and cycles we obtain

$$w \geq E(J') - |C'| = E(J) - |C| + E(J') - E(J) - |C' \setminus C|.$$

Due to the construction of C every cycle in $C' \setminus C$ admits at least one edge from J' not belonging to J and thus $E(J') - E(J) \geq |C' \setminus C|$. So we have inequality $w \geq E(J) - |C| \geq E(J) - c(J)$, which ends the proof. ◀

5 Algorithms for MLS

5.1 NP-completeness of MLS

▶ **Theorem 17.** *The decision version of* Minimum Local Scenario *is NP-complete.*

Proof. The decision version of MLS is clearly in NP. We reduce the decision version of MECP on Eulerian graphs, which is NP-hard [7] (and APX-hard [5]), to MLS. Without loss of generality, take an instance $G = (V, E)$ and a bound k of MECP, where G is Eulerian and connected. Consider an Eulerian cycle $u_1, u_2, \ldots, u_n, u_1$ of G and construct genomes

$$A = \big\{\{1,2\},\{3,4\},\ldots,\{2n-1,2n\}\big\}, \text{and}$$
$$B = \big\{\{2,3\},\{4,5\},\ldots,\{2n,1\}\big\},$$

and a coloring *col* over the set V such that $col\big(\{2i-1,2i\}\big) = u_i$ for all $i \in \{1,\ldots,n\}$ to obtain $J(A,B,col) = G$. Theorem 16 says that an optimal solution to MLS of cost $w(G)$ implies the existence of a cycle packing of size $E(G) - w(G)$. Thus there is an MECP of size k if and only if $E(G) - w(G) \geq k$. ◀

5.2 3/2-approximation for MLS

For a graph G we denote the number of edges by $E(G)$, the number length one and two cycles by $L(G)$ and $B(G)$ respectively. A simple counting argument leads to the following theorem proved in the appendix.

▶ **Theorem 18.** *For genomes A, B and a coloring col of A, the cost w_{MLS} of a* MLS *transforming A into B respects*

$$w_{\text{MLS}} \geq \frac{2}{3}E(J) - \frac{1}{3}B(J) - \frac{2}{3}L(J), \textit{where } J = J(A,B,col).$$

In Theorem 16 we have shown how a cycle packing C of $J = J(A,B,col)$ gives a DCJ scenario of cost $w \leq E(J) - |C|$ transforming A into B. If we take C consisting of $B(J)$ pairwise edge-disjoint cycles of length two and $L(J)$ loops, we obtain a scenario of cost $w \leq E(J) - B(J) - L(J) = w'$. Using Theorem 18 we have

$$w_{\text{MLS}} \geq \frac{2}{3}E(J) - \frac{1}{3}B(J) - \frac{2}{3}L(J) = \frac{2}{3}(w' + \frac{1}{2}B(J))$$

and obtain

$$\alpha = \frac{w}{w_{\text{MLS}}} \leq \frac{3}{2}\frac{w}{w' + \frac{1}{2}B(J)} \leq \frac{3}{2}.$$

5.3 An exact algorithm for MLS

Consider a junction graph J with $L(J)$ loops and $B(J)$ length two cycles. A simple observation that there exists a MECP of J that includes all of these cycles allows us to simplify the problem by removing them from J. This leaves us with a simple graph $\bar{J}$ such that the cost of MLS is equal to $E(J) - L(J) - B(J) - c(\bar{J})$. A straightforward way to compute $c(\bar{J})$ is to take all of $\bar{J}$'s simple cycles and solve the Maximum Set Packing problem on their sets of edges formulated as an integer linear program. The number of simple cycles might be exponential, but it depends on the size of a simple graph $\bar{J}$ having $|\Delta|$ vertices and not the number of genes. We see in Section 7 that our algorithm solves MLS on instances between *drosophila melanogaster* and *yakuba*.

6 Towards a more general cost function

Our work opens the door to the development of a more general model for genome rearrangements with positional constraints, where local moves are attributed nonzero cost. In such a model the costs of local and non-local moves would be respectively ω_L and ω_N with $0 < \omega_L < \omega_N$. For any DCJ scenario ρ we will denote $\omega(\rho)$, $N(\rho)$ and $L(\rho)$ as its cost, its number of non-local, and local moves respectively. We categorize the different DCJ problems based on the cost pair (ω_L, ω_N) with $0 \leq \omega_L \leq \omega_N$ where we look for a ρ that minimizes the cost function $\omega(\rho) = \omega_L L(\rho) + \omega_N N(\rho)$:

- $(0, 1)$ is the Minimum Local Scenario problem,
- $(1, 1)$ is the traditional Double Cut and Join problem,
- (ω_L, ω_N) with $\frac{\omega_L}{\omega_N - \omega_L} > n$, where n is the number of adjacencies, is the Minimum Local Parsimonious Scenario problem,
- (ω_L, ω_N) with $0 < \omega_L < \omega_N$ is the problem that we consider in this section.

It is clear that for positive k the cost pairs (ω_L, ω_N) and $(k\omega_L, k\omega_N)$ define the same minimum scenarios, thus for $0 < \omega_L < \omega_N$ it suffices to treat the normalized pair $(1, 1 + \alpha)$ with a positive α. For a scenario ρ we denote $\delta(\rho) = N(\rho) + L(\rho) - d_{DCJ}$ the difference of its length and the length of a parsimonious DCJ scenario. If δ were small we would have an algorithmic tool in the search for the genomic distances. For $(\omega_L, \omega_N) = (1, 1 + \alpha)$, we have

$$\omega(\rho) = L(\rho) + N(\rho) + N(\rho)\alpha = \delta(\rho) + d_{DCJ} + N(\rho)\alpha,$$

By d_{MLPS} and d_{MLS} we denote the numbers of non-local moves in Minimum Local Parsimonious Scenario and Minimum Local Scenario respectively. For a scenario ρ^* minimizing the cost $L(\rho) + (1 + \alpha)N(\rho)$ we have $d_{DCJ} + d_{MLPS}\alpha \geq \omega(\rho*)$ as $d_{DCJ} + d_{MLPS}\alpha$ is the cost of a MLPS and subtracting d_{DCJ} we obtain $d_{MLPS}\alpha \geq \delta(\rho*) + N(\rho^*)\alpha$. By definition $N(\rho^*) \geq d_{MLS}$ and thus we obtain

$$(d_{MLPS} - d_{MLS})\alpha \geq \delta(\rho^*).$$

In general $d_{MLPS} - d_{MLS}$ can be large. For the experiments in Section 7, however, it was found to be smaller than 0.8 on average. This means that finding a scenario of minimum cost among those with a small δ, for example $\delta = 1$, might be of interest in practice.

7 The practice of coloring adjacencies

In this section we address the applicability of our model that colors adjacencies. We summarize our experimental results on *drosophila melanogaster* and *yakuba* reported in [12].

We use the Hi-C data for *drosophila* as a similarity function on the pairs of the adjacencies of a genome. We generate colorings using a centroid-based clustering [10]; the adjacencies are clustered based on Hi-C similarity, and two adjacencies get the same color if they are in the same cluster. Weights are assigned to the colorings based on how well they respect the within-clusters similarity. MLS is then computed on the colorings.

The first positive result reported in [12] is that, despite the NP-hardness of the Minimum Local Scenario problem, it can be computed exactly (using our algorithms from Section 5.3) for all of the colorings encountered between *drosophila melanogaster* and *yakuba* (the DCJ distance being roughly 90).

We find that colorings created uniformly at random have high MLS cost, while colorings created using the Hi-C data have low MLS cost. As we introduce randomness to the good colorings, a significant correlation between MLS and the weights of the colorings is observed no matter how many clusters are created. Indeed, the Pearson's correlation is better than 0.77 for all reasonable k, and is as high as 0.92 in some cases.

A significant correlation is also found between the differences $d_{MLPS} - d_{MLS}$, and the weights of the colorings. Further, for the colorings that were optimized on the similarity function this difference never exceeded 4, and no matter the number of colors assigned, it is less than 0.8 on average for both species. The implication is that in many cases MLPS is an optimal solution for both MLS and the problem considered in Section 6. In all cases $\bar{J}$ has less than 25 simple cycles on average, and never more than 300. The hope is that MLS will remain tractable for the more distant genomes.

8 Conclusion and further work

Aside from problems that consider rearrangement length, little is known about weighted rearrangement problems [3, 11, 8, 1, 6]. In [14], we showed that with a simple cost function based on a partition of the adjacencies of one of the genomes into equivalence classes, one can choose – from the exponentially large set of shortest scenarios – a scenario that minimizes the number of moves acting across classes. In this paper we showed that the genome rearrangement problem with an objective function based solely on the cost of DCJs is NP-Hard, even for a simple binary cost function. We gave a 3/2-approximation derived from bounds on the sizes of cycles in a cycle packing of the junction graph. We also presented an exact algorithm and found that an exact solution can be computed between *drosophila*.

This work opens the door to the development of more complex models of genome rearrangement with positional constraints, where local moves would be attributed nonzero cost. To this end we established a useful link between the weighted distance, and the difference between Minimum Local Parsimonious Scenario and Minimum Local Scenario. Experimental results indicate that a problem of finding a minimum cost scenario among those of length only slightly greater than that of a parsimonious scenario might be of practical interest, however further experiments must be conducted to confirm this.

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A Proof of Lemma 15

Proof. We will demonstrate with a help of an example how to obtain such $\hat{A} \in A_+$ and $\hat{B} \in B_+$. We will augment $AG(A, B)$ with adjacencies to obtain a graph AG' which at the end will turn out to be $AG(\hat{A}, \hat{B})$. Our working example will consist of the following graphs:

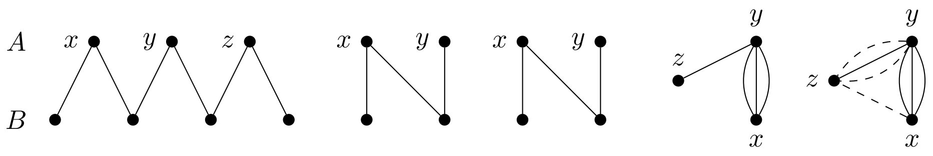
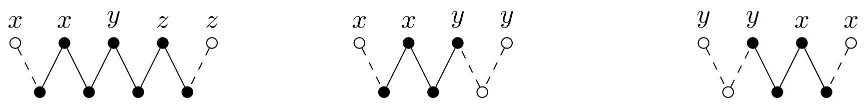
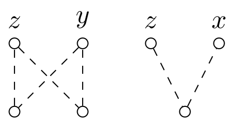


Figure 1 $AG(A, B)$, $J(A, B, col) = J$ and J'.

We first include into AG' every cycle of $AG(A, B)$. Other connected components of $AG(A, B)$ are paths and to these we add new adjacencies at their end points copying their colors to obtain the paths for AG'. In our example $AG(A, B)$ has no cycles and its three paths give paths for AG'



For graphs $G' = (V, E \cup E')$ and $G = (V, E)$ we will note $G' - G = (V, E')$. We take an Eulerian subgraph H of $J' - J$ such that $F = (J' - J) - H$ is a forest. For H we create a union of cycles in AG' giving H as its junction graph. F can be partitioned into paths joining the vertices of an odd degree and for each path in F we create a path consisting of new adjacencies of corresponding colors in AG'. In our example H is a cycle (z, y, z) and F has a single path (z, x) and these add a cycle and a path to AG'.



The vertices of J' have even degrees as it is an Eulerian graph. This guarantees that for every color the number of the pairs added at the ends of the paths in AG' is even. We can group these pairs at the ends of the paths into monochromatic couples and merging these couples we obtain an AG' which is an Eulerian extension of $AG(A, B)$ giving a junction graph loop-equal to J'. A possible grouping of the added end points into monochromatic couples and their merge leads to AG'

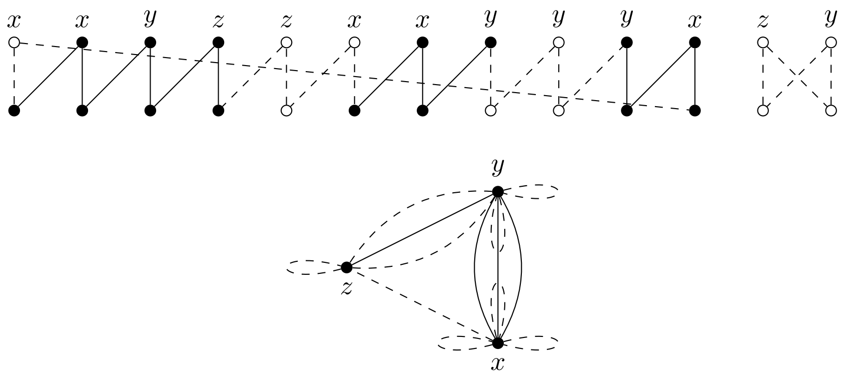


Figure 2 A junction graph obtained from AG' is loop-equal to J'.

Now it is easy to reconstruct $\hat{B} \in B_+$, $\hat{A} \in A_+$ and its coloring $\hat{col}$ such that $AG' = AG(\hat{A}, \hat{B}, \hat{col})$, which guarantees that $J(\hat{A}, \hat{B}, \hat{col})$ is loop-equal to J'. ◀

B Proof of Theorem 18

Proof. For a cycle packing C, we denote the number of loops in it by $L(C)$, the number of the cycles of length 2 by $B(C)$ and the number of longer cycles by $R(C)$. We start by proving Lemma 19

▶ **Lemma 19.** *For every Eulerian graph G*

$$w(G) \geq \frac{2}{3}E(G) - \frac{1}{3}B(G) - \frac{2}{3}L(G).$$

Proof. Using Theorem 8 we obtain a cycle packing C of G such that $w(G) = E(G) - |C|$. We have $|C| = L(C) + B(C) + R(C)$ and $E(G) \geq L(C) + 2B(C) + 3R(C)$ and from this we get

$$w(G) - \frac{2}{3}E(G) = \frac{1}{3}E(G) - |C| \geq -\frac{1}{3}B(C) - \frac{2}{3}L(C), \text{ so}$$
$$w(G) \geq \frac{2}{3}E(G) - \frac{1}{3}B(C) - \frac{2}{3}L(C) \geq \frac{2}{3}E(G) - \frac{1}{3}B(G) - \frac{2}{3}L(G).$$ ◀

Now we take a MECP C of J. It covers an Eulerian subgraph J' of J. Using Theorem 16 we have $w_{\text{MLS}} = E(J) - |C|$ and by counting edges and using Theorem 8 we obtain

$$w_{\text{MLS}} = E(J) - |C| = E(J') - |C| + E(J) - E(J') = w(J') + E(J) - E(J')$$

from which using Lemma 19 and a simple counting argument we obtain

$$w_{\text{MLS}} \geq \frac{2}{3}E(J') - \frac{1}{3}B(J') - \frac{2}{3}L(J') + E(J) - E(J') \geq \frac{2}{3}E(J) - \frac{1}{3}B(J) - \frac{2}{3}L(J).$$ ◀