An Exact Algorithm to Compute the DCJ Distance for Genomes with Duplicate Genes

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Abstract. Computing the edit distance between two genomes is a basic problem in the study of genome evolution. The double-cut-and-join (DCJ) model has formed the basis for most algorithmic research on rearrangements over the last few years. The edit distance under the DCJ model can be computed in linear time for genomes without duplicate genes, while the problem becomes **NP**-hard in the presence of duplicate genes. In this paper, we propose an ILP (integer linear programming) formulation to compute the DCJ distance between two genomes with duplicate genes. We also provide an efficient preprocessing approach to simplify the ILP formulation while preserving optimality. Comparison on simulated genomes demonstrates that our method outperforms MSOAR in computing the edit distance, especially when the genomes contain long duplicated segments. We also apply our method to assign orthologous gene pairs among human, mouse and rat genomes, where once again our method outperforms MSOAR.

Keywords: DCJ distance, adjacency graph, maximum cycle decomposition, orthology assignment.

1 Introduction

The combinatorics and algorithmics of genomic rearrangements have been the subject of much research since the problem was formulated in the 1990s [1]. The advent of whole-genome sequencing has provided us with masses of data on which to study genomic rearrangements. Genomic rearrangements include inversions, transpositions, circularizations, and linearizations, all of which act on a single chromosome, and translocations, fusions, and fissions, which act on two chromosomes. These operations can all be described in terms of the single double-cut-and-join (DCJ) operation [2, 3], which has formed the basis for most algorithmic research on rearrangements over the last few years [4–8]. A DCJ operation makes two cuts in the genome, either in the same chromosome or in two different chromosomes, producing four cut ends, then rejoins the four cut ends in a different order.

A basic problem in genome rearrangements is to compute the edit distance between two genomes, i.e., the minimum number of operations needed to transform one genome into another. Under the inversion model, Hannenhalli and Pevzner gave the first polynomial-time algorithm to compute the edit distance for unichromosomal genomes

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[9], which was later improved to linear time [10]. As for the multichromosomal genomes, the edit distance under the Hannenhalli-Pevzner model (inversions and translocations) has been studied through a series of papers [9, 11–13], culminating in a fairly complex linear-time algorithm [4]. Under the DCJ model, the edit distance can be computed in linear time for two multichromosomal genomes in a simple and elegant way [2].

All of these algorithms assume genomes contain no duplicate genes. However, gene duplications are widespread events and have long been recognized as a major driving force of evolution [14, 15]. For example, in human genomes segmental duplications are hotspots for non-allelic homologous recombination leading to genomic disorders, copy-number polymorphisms, and gene and transcript innovations [16]. The problem of computing the inversion distance for genomes in the presence of duplicate genes has been proved **NP**-hard [17]. Suksawatchon *et al.* proposed a heuristic for this problem using binary integer programming [18], which was later extended to handle gene deletion [19]. Chen *et al.* decomposed this problem into two new optimization problems, called the *minimum common partition* and the *maximum cycle decomposition*, for which efficient heuristics were designed [17]. They packaged the whole algorithms into the SOAR software system, and applied SOAR to assign orthologs on a genome-wide scale. Later, they extended SOAR to unite rearrangements and single-gene duplications as a new software package, called MSOAR, which can be applied to detect inparalogs in addition to orthologs [20]. Recently, they incorporated tandem duplications into their model, and demonstrated that the new system achieved a better sensitivity and specificity than MSOAR [21].

In this paper, we focus on the problem of computing the edit distance for two genomes with duplicate genes under the DCJ model. This problem is also **NP**-hard, which can be proved by a reduction from the **NP**-hard problem of *breakpoint graph decomposition* [22]. We first reduce this problem to the problem of finding the optimal consistent decomposition of the corresponding adjacency graph, then formulate the latter problem as an integer linear program. We also provide an efficient preprocessing approach to reduce the ILP formulation while preserving optimality. Finally, we compare our method with MSOAR on both simulated and biological datasets.

2 Problem Statement

We model one genome as a set of chromosomes, and each chromosome as a linear or circular list of genes. Homologous genes are grouped into *gene families*. In this paper, we study two genomes with the same gene content: each gene family has the same number of genes in both genomes. Assuming that two genomes G_1 and G_2 have the same gene content, we say a bijection between G_1 and G_2 is *valid* if it specifies n homologous gene pairs, where n is the number of genes in each genome. If G_1 and G_2 contain only singleton gene families (exactly one gene in each family in each genome), then there is a unique valid bijection between G_1 and G_2, and the DCJ distance between G_1 and G_2 can be computed in linear time [2]. If G_1 and G_2 contain gene families with multiple genes in each genome, then there are many valid bijections between G_1 and G_2. Different valid bijections define different one-to-one correspondences between homologous genes, yielding possibly different DCJ distances between

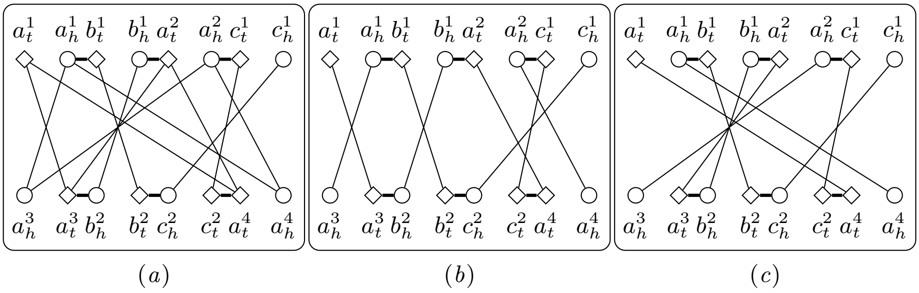

a_t^1 a_h^1 b_t^1 b_h^1 a_t^2 a_h^2 c_t^1 c_h^1
a_h^3 a_t^3 b_h^2 b_t^2 c_h^2 c_t^2 a_t^4 a_h^4
(a)
(b)
(c)

Fig. 1. An example of adjacency graph and its two consistent decompositions. Genome 1 contains one linear chromosome, (a^1, b^1, a^2, c^1), and genome 2 also contains one linear chromosome $(-a^3, -b^2, -c^2, a^4)$. Genes in the same gene family are represented by the same label, and distinguished by different superscripts. All black edges are represented by long thin lines, and all grey edges are represented by short thick lines. (a) The corresponding adjacency graph, in which head extremities are represented by circles, while tail extremities are represented by diamonds. (b) A consistent decomposition with 2 odd-length paths, whose corresponding valid bijection maps a^1 to a^3 and a^2 to a^4. (c) Another consistent decomposition with 2 odd-length paths and 1 cycle, whose corresponding valid bijection maps a^1 to a^4 and a^2 to a^3.

G_1 and G_2. In this paper, we study the following *generalized DCJ distance problem*: given two genomes G_1 and G_2 with the same gene content, find a valid bijection between G_1 and G_2 that minimizes the DCJ distance. We denote the generalized DCJ distance between G_1 and G_2 as $d(G_1, G_2)$.

We use the notation introduced by Bergeron *et al.* [2] for gene orders. The two ends of a gene g are called *extremities*, the head as g_h and the tail as g_t. If genes f and g are homologous, its corresponding extremities (f_h and g_h, f_t and g_t) are also *homologous*. Two consecutive genes a and b can be connected by one *adjacency*, which is represented by a set of two extremities; thus adjacencies come in four types: $\{a_t, b_t\}$, $\{a_h, b_t\}$, $\{a_t, b_h\}$, and $\{a_h, b_h\}$. If gene g lies at one end of a linear chromosome, then this end can be represented by a set of one extremity, $\{g_t\}$ or $\{g_h\}$, called a *telomere*. The set of all extremities of a genome is called the *extremity set*.

Let G_1 and G_2 be two genomes with the same gene content, and let S_1 and S_2 be the extremity sets of G_1 and G_2, respectively. The *adjacency graph* with respect to G_1 and G_2 can be written as $AG = (V, E)$, with $V = S_1 \cup S_2$ and where E is composed of two types of edges, *black edges* and *grey edges*. Two extremities in different extremity sets (one is in S_1 and the other one is in S_2) are connected by one black edge if they are homologous, and two extremities in the same extremity set are connected by one grey edge if they form an existing adjacency. Figure 1a gives an example.

We say that a cycle (or path) in the adjacency graph is *alternating* if any two adjacent edges in this cycle (or path) consist of one black edge and one grey edge. The *length* of a cycle (or path) is defined as the number of its black edges. A *decomposition* of the adjacency graph is a set of vertex-disjoint alternating cycles and paths that cover all vertices and all grey edges. We say a decomposition is *consistent* if for any two homologous genes f and g, either both (f_h, g_h) and (f_t, g_t) are in this decomposition, or neither of them is in this decomposition. Figure 1b and 1c give two examples of consistent decompositions.

Given two genomes G_1 and G_2 with the same gene content, there is a natural one-to-one correspondence between the set of all possible valid bijections from G_1 to G_2 and the set of all possible consistent decompositions of the adjacency graph with respect to G_1 and G_2. In fact, if one valid bijection is given, which maps gene f in G_1 to a homologous gene g in G_2, then we can keep the black edges (f_h, g_h) and (f_t, g_t) in the decomposition. We do the same thing for every pair of genes specified by this valid bijection; this process culminates in a consistent decomposition. On the other hand, if we are given a consistent decomposition of the corresponding adjacency graph, we can collect all homologous gene pairs (f, g) indicated by black edges (f_h, g_h) and (f_t, g_t), which form a valid bijection from G_1 to G_2. Given a consistent decomposition with c cycles and o odd-length paths, exactly $(|V|/4 - c - o/2)$ DCJ operations are needed to transform G_1 into G_2 [2]. Thus, we can write $d(G_1, G_2) = \min_{D\in\mathcal{D}}(|V|/4 - c_D - o_D/2) = |V|/4 - \max_{D\in\mathcal{D}}(c_D + o_D/2)$, where $\mathcal{D}$ is the space of all consistent decompositions, and c_D and o_D are the numbers of cycles and odd-length paths in a decomposition D, respectively. This formula transforms the generalized DCJ distance problem into the *maximum cycle decomposition problem*, which asks for a consistent decomposition of the adjacency graph such that the number of cycles plus half the number of odd-length paths in this decomposition is maximized.

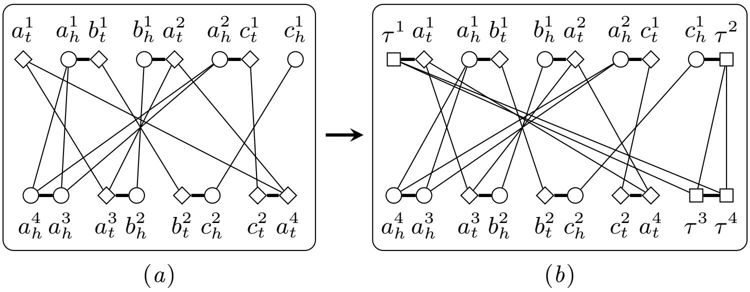
3 ILP for the Maximum Cycle Decomposition Problem

In [23], we described a capping method to remove telomeres by introducing *null extremities*. All null extremities are homologous to each other, but none is homologous to any other extremity. Let $AG = (V = S_1 \cup S_2, E)$ be the adjacency graph with respect to two given genomes G_1 and G_2. Suppose that G_1 and G_2 contain $2 \cdot k_1$ and $2 \cdot k_2$ telomeres respectively. The "telomere removal" proceeds as follows (see Figure 2 for an example). For each extremity $u \in S_1$ coming from each telomere in G_1, we add one null extremity τ to S_1 and add one grey edge to E that connects u and τ. Similarly, for each extremity $v \in S_2$ coming from each telomere in G_2, we add one null extremity τ to S_2 and add one grey edge to E that connects v and τ. If we additionally have $k_1 < k_2$, we then add $(k_2 - k_1)$ pairs of null extremities to S_1, each of which is connected by one more grey edge added to E. We finally add black edges connecting all possible pairs of null extremities between S_1 and S_2. We can prove that this telomere removal process does not change $d(G_1, G_2)$ using the same argument as in [7, 23]. In the following we assume that each vertex is adjacent to exactly one grey edge in the adjacency graph, and that the consistent decompositions consist of only cycles.

Now we formulate the maximum cycle decomposition problem as an integer linear program. Let $AG = (V, E)$ be the adjacency graph with respect to two given genomes G_1 and G_2 with the same gene content. For each edge $e \in E$, we create binary variable x_e to indicate whether e will be in the final decomposition. First, we require that all grey edges be in the final decomposition:

$$x_e = 1, \quad \forall e \text{ that are grey}$$

Second, we require that the final decomposition be consistent: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a_h^4 a_h^3 a_t^3 b_h^2 b_t^2 c_h^2 c_t^2 a_t^4
(a)
τ^1 a_t^1 a_h^1 b_t^1 b_h^1 a_t^2 a_h^2 c_t^1 c_h^1 τ^2
a_h^4 a_h^3 a_t^3 b_h^2 b_t^2 c_h^2 c_t^2 a_t^4 τ^3 τ^4
(b)

Fig. 2. An example of the telomere removal. Genome 1 contains one linear chromosome, (a^1, b^1, a^2, c^1), and genome 2 contains one circular chromosome $(-a^3, -b^2, -c^2, a^4)$. (*a*) The corresponding adjacency graph. (*b*) The adjacency graph after the telomere removal, in which null extremities are represented by squares.

$$x_{(f_h,g_h)} = x_{(f_t,g_t)}, \quad \forall f \in G_1 \text{ and } \forall g \in G_2 \text{ that are homologous}$$

Third, we require that for each vertex exactly one adjacent black edge adjacent be chosen:

$$\sum_{(u,v)\in E,\ v\in S_2} x_{(u,v)} = 1, \quad \forall u \in S_1$$
$$\sum_{(u,v)\in E,\ u\in S_1} x_{(u,v)} = 1, \quad \forall v \in S_2$$

These three groups of constraints guarantee that all selected edges form a consistent decomposition.

Now we count the number of cycles. We first index the vertices arbitrarily, $V = \{v_1, v_2, \cdots, v_{|V|}\}$. For each vertex v_i, we create variable y_i to indicate the *label* of v_i. We set a distinct positive bound i for each y_i:

$$0 \le y_i \le i, \quad 1 \le i \le |V|$$

We require that all vertices in the same cycle in the final decomposition have the same label, which can be guaranteed by requiring that, for each selected edge, the two adjacent vertices have the same label:

$$y_i \le y_j + i \cdot (1 - x_e), \quad \forall e = (v_i, v_j) \in E$$
$$y_j \le y_i + j \cdot (1 - x_e), \quad \forall e = (v_i, v_j) \in E$$

Then, for each vertex v_i, we create binary variable z_i to indicate whether y_i is equal to its upper bound i:

$$i \cdot z_i \le y_i, \quad 1 \le i \le |V|$$

Since all vertices in the same cycle have the same label and all upper bounds are distinct, there is exactly one vertex in each cycle whose label can be equal to its upper bound. Finally, we set the objective to

$$\max \sum_{1 \le i \le |V|} z_i,$$

which is equal to the number of cycles.

There are $O(|E|)$ variables and $O(|E|)$ constraints in this ILP formulation.

4 Fixing Cycles of Length Two

A cycle of length two in the adjacency graph indicates one shared adjacency. The following theorem gives a sufficient condition to fix this cycle while preserving optimality, which can be used to narrow the search for an optimal bijection.

Theorem 1. *Given an adjacency graph $AG = (V,E)$, if a length-two cycle C contains some vertex with total degree 2, then there exists an optimal consistent decomposition of AG that contains C.*

Proof. Let $\{a_h^1, b_h^1, a_h^2, b_h^2\}$ be the four vertices of C, where a_h^1 and b_h^1 form an adjacency in G_1 while a_h^2 and b_h^2 form an adjacency in G_2, and (a_h^1, a_h^2) and (b_h^1, b_h^2) are the two black edges of C. Let a_h^1 be the vertex of total degree 2; then the gene family of $\{a^1, a^2\}$ is a singleton family, and thus edge (a_h^1, a_h^2) appears in every consistent decomposition. Now we prove the theorem by contradiction. Suppose that edge (b_h^1, b_h^2) is not in any optimal consistent decomposition. Take any optimal consistent decomposition D, in which b_h^1 is linked to b_h^4 and b_h^2 is linked to b_h^3. Since D is consistent, we know that edges (b_t^1, b_t^4) and (b_t^2, b_t^3) are also in D. We now transform D into a new decomposition D'' that contains edge (b_h^1, b_h^2) by exchanging two pairs of edges. Figure 3 illustrates this process. First, we remove edges (b_h^1, b_h^4) and (b_h^3, b_h^2) from D and add edges (b_h^1, b_h^2) and (b_h^3, b_h^4); denote this inconsistent decomposition by D'. Since in this step one cycle is split into two small cycles, we have that $c_{D'} = c_D + 1$. Now, we remove edges (b_t^1, b_t^4) and (b_t^3, b_t^2) from D' and add edges (b_t^1, b_t^2) and (b_t^3, b_t^4) to obtain the consistent decomposition D''. This step involves at most two cycles of D', and merges these two

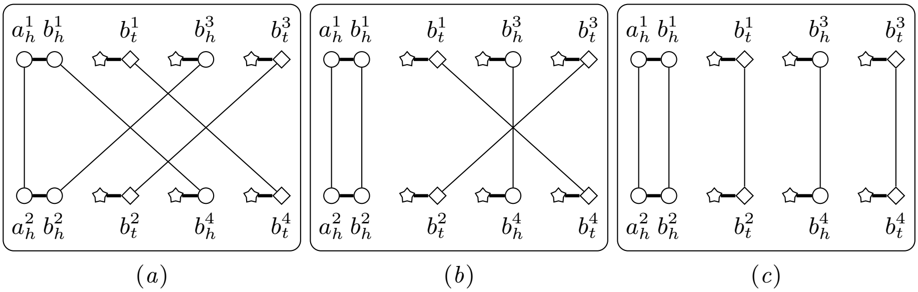


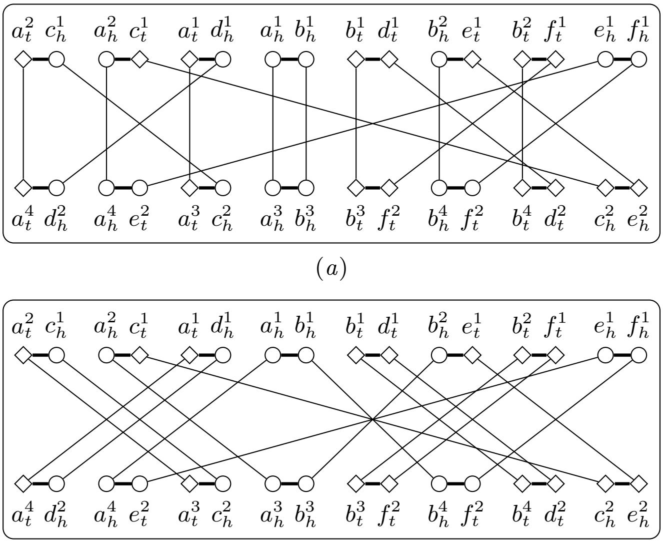
Fig. 3. The process of building a new optimal consistent decomposition that contains edge (b_h^1, b_h^2). (a) One optimal consistent decomposition D without edge (b_h^1, b_h^3). Star represents unrelated extremities. (b) The inconsistent decomposition D'. (c) The consistent decomposition D''.

cycles together in the worst case. Thus, we have $c_{D''} \geq c_{D'} - 1$. Overall, we have that $c_{D''} \geq c_D$, which means D'' is also an optimal consistent decomposition—the desired contradiction. □

If all four vertices in a cycle of length two have degree larger than 2, then it is possible that this cycle is not part of any optimal consistent decomposition. Figure 4 gives such an example. Moreover, this example also shows that if a shared adjacency appears exactly once in each genome, it is still possible that the corresponding cycle of length two is not part of any optimal consistent decomposition.

5 Experimental Results

We compare our method with MSOAR on both simulated and biological datasets. The input for both methods is two genomes with the same gene content, and the output is a bijection between the two genomes, plus the DCJ distance calculated as $n - c - o/2$, where n is the number of genes in each genome, and c and o are the numbers of cycles and odd-length paths in the adjacency graph induced by the bijection. We use both the accuracy of the bijection, which is defined as the percentage of correct gene pairs (compared with a reference bijection), and the deviation from the true evolutionary distances, to evaluate the performance of the two methods.



(a)

(b)

Fig. 4. An example of a cycle of length two that is not part of any optimal consistent decomposition. (*a*) A consistent decomposition with 4 cycles that contains the cycle of length two of $\{a_h^1, b_h^1, a_h^3, b_h^3\}$. (*b*) An optimal consistent decomposition with 5 cycles.

For our method, given two genomes, we first build the adjacency graph and then employ the telomere removal technique to obtain a new adjacency graph without telomeres. Then we apply Theorem 1 to fix possible cycles of length two, and finally invoke GUROBI [24] to solve the ILP formulation. Since the ILP solver might take a long time, we set a time limit of two hours for each instance in our experiments—the best solution will be returned if the ILP solver does not terminate in two hours. For MSOAR, we run its binary version downloaded from `http://msoar.cs.ucr.edu/`. We compare our method with MSOAR, rather than the latest version MSOAR 2.0, because we focus on genomes with the same gene content, which implicitly requires that, after the speciation event, only DCJ operations are involved. Compared with MSOAR, MSOAR 2.0 aims to identify tandem duplications of genes *after* the speciation. Thus, under our evolutionary model that does not contain postspeciation duplications, MSOAR and MSOAR 2.0 are equivalent.

5.1 Simulation Results

We simulate artificial genomes under an evolutionary model including segmental duplications and DCJs. We introduce duplicated genes through segmental duplications. For each segmental duplication, we uniformly select a position to start duplicating a segment of the genome and place the new copy to a new position. Since the average copy number of each gene in human, mouse and rat genomes, are 1.46, 1.55 and 1.28, respectively, we set the average copy number to 1.5 in our simulation. From a genome of 1,000 distinct genes, we generate an ancestor genome with 1,500 genes, by randomly performing $500/L$ segmental duplications of length L (in terms of the number of genes in the segment). We then simulate two extant genomes from the ancestor by randomly performing N DCJs (in terms of inversions) independently. Thus, the true evolutionary distance between the two extant genomes is $2 \cdot N$. The reference bijection consists of those gene pairs that correspond to the same gene in the ancestor. We test three different lengths for segmental duplications ($L = 1, 2, 5$); results illustrate the trends and capabilities of the two methods in handling genomes with duplicated segments. We also vary the number of DCJs over a broad range ($N = 200, 210, \cdots, 500$) that reaches beyond the saturation point. For each setting, we randomly simulate 5 independent instances, and calculate the average accuracy of the bijection and the average deviation from the true evolutionary distances over these 5 instances for both methods.

Figure 5 shows the deviation from the true evolutionary distances for both methods. The first observation is that saturation starts occurring for a true evolutionary distance of 720: the DCJ distance obtained from the reference bijection is smaller than the true evolutionary distance, and the gap increases along with the increase of the true evolutionary distance. Second, when the true evolutionary distance is less than 720, our method obtains very accurate DCJ distances while MSOAR usually overestimates the DCJ distance. The difference is particularly pronounced for $L \geq 2$: in such cases, there exist identical segments in each genome, a situation that creates problems when MSOAR tries to partition each genome into a minimum number of common segments [17].

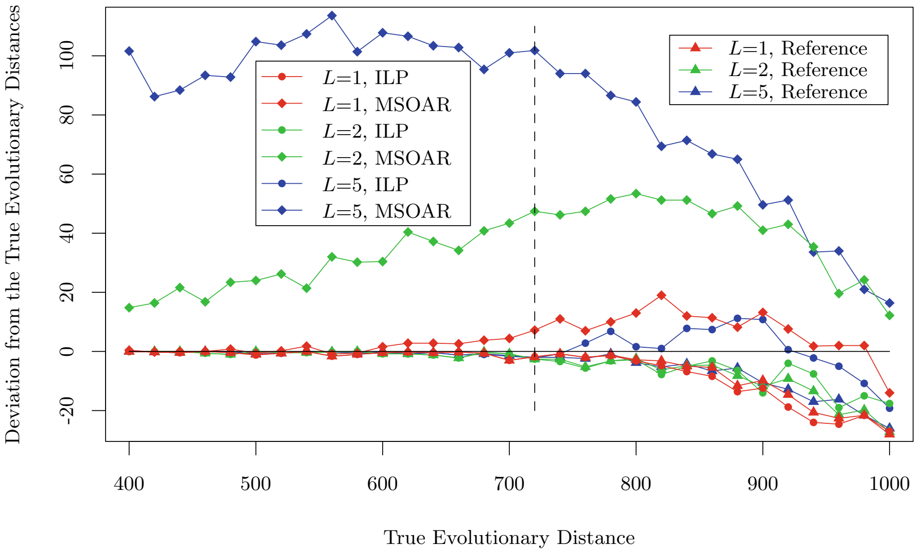


Fig. 5. Deviation from the true evolutionary distances on simulation data. Diamonds track MSOAR, circles track our method, and triangles track the reference bijection.

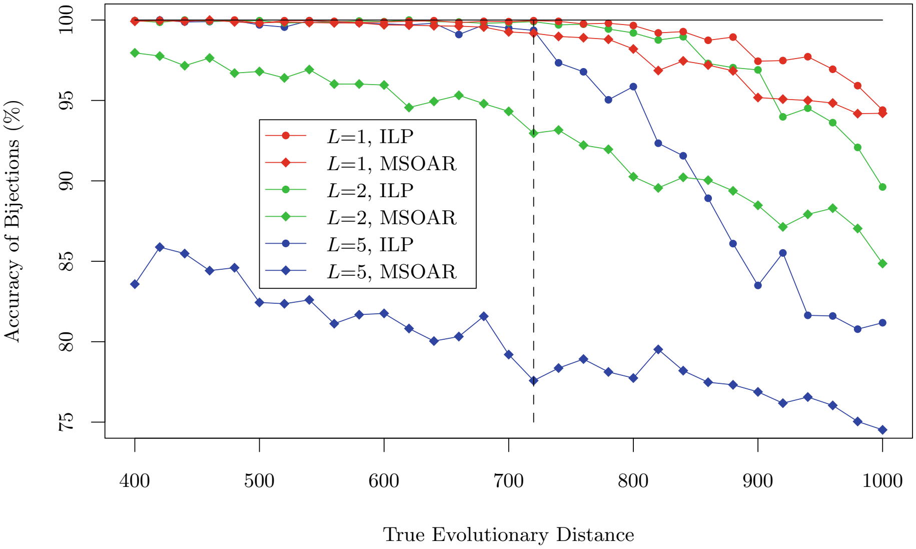


Fig. 6. The accuracy of the bijections on simulation data. Diamonds track MSOAR, while circles track our method.

Figure 6 shows the the accuracy of the bijections for both methods. For $L = 1$, both methods can correctly identify most gene pairs. For $L \geq 2$, our method significantly outperforms MSOAR. For large L, the accuracy of our method decreases rapidly beyond saturation, but continues to dominate MSOAR.

The running time of MSOAR grows slowly as the the true evolutionary distance increases. For the most complicated case of $L = 5$ and the true evolutionary distance is 1000, MSOAR can finish in less than 2000 seconds. Regarding our method, when the true evolutionary distance is relatively small (≤ 640 when $L = 5$, ≤ 740 when $L = 2$, and ≤ 820 when $L = 1$), the preprocessing method can fix a considerable portion of the adjacency graph, leaving a small ILP instance that can be solved very quickly (even faster than MSOAR). When the true evolutionary distance is relatively large, the ILP solver cannot terminate in two hours and a sub-optimal solution is obtained. Usually, this solution is equal or very close to the optimal solution, because the ILP solver can find the optimal solution very quickly, but must spend more time to verify that it is optimal. This observation is also verified by the very high accuracy before the saturation point shown in Figure 6.

5.2 Application to Orthology Assignment

Under a parsimonious evolutionary scenario, the optimal valid bijection between two genomes with the same gene content minimizes the number of DCJs after speciation, and thus infers the orthologous gene pairs [17]. We test both methods for assigning orthologous genes between pairs of genomes. Human, mouse, and rat genomes are well annotated, so we chose them to evaluate the performance of the two methods. For each species, we downloaded the information for all protein-coding genes from Ensembl (`http://www.ensembl.org`), including gene family names, positions on the chromosomes and gene symbols. If a gene has multiple alternative products, we keep its longest isoform. Two genes are considered homologous if they have the same Ensembl gene family name; they are considered orthologous if they have the same gene symbol. (Note that two orthologous genes are necessarily homologous, but two homologous genes need not be orthologous.) For a pair of genomes, we keep only orthologous gene pairs, thereby obtaining two genomes with the same gene content; our reference bijection is then defined by these orthologous gene pairs. For both methods, we use gene family and position information to infer orthologous relationships and compare them to the reference bijection.

The results of comparing these three genomes are shown in Table 1. Both methods mostly agree with annotation, indicating that the parsimonious model is appropriate

Table 1. Comparison of human, mouse and rat genomes

species pairs	gene pairs	accuracy of bijection (%)		DCJ distance	
		MSOAR	our method	MSOAR	our method
human mouse	14876	98.63	99.18	933	894
human rat	12971	98.79	99.28	1320	1294
mouse rat	13525	98.60	99.26	968	916

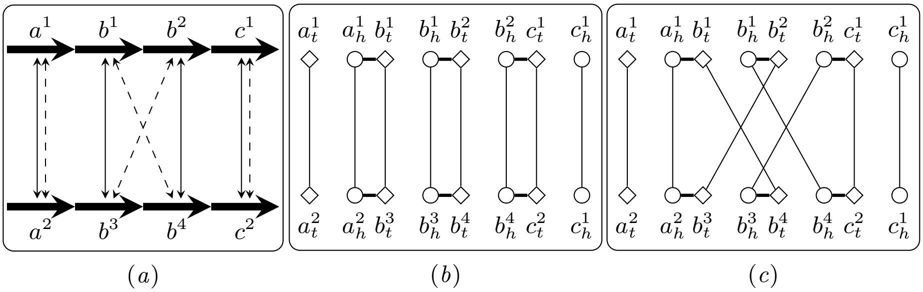

a^1 b^1 b^2 c^1
a^2 b^3 b^4 c^2
a_t^1 $a_h^1\ b_t^1$ $b_h^1\ b_t^2$ $b_h^2\ c_t^1$ c_h^1
a_t^2 $a_h^2\ b_t^3$ $b_h^3\ b_t^4$ $b_h^4\ c_t^2$ c_h^1
a_t^1 $a_h^1\ b_t^1$ $b_h^1\ b_t^2$ $b_h^2\ c_t^1$ c_h^1
a_t^2 $a_h^2\ b_t^3$ $b_h^3\ b_t^4$ $b_h^4\ c_t^2$ c_h^1
(a)
(b)
(c)

Fig. 7. Comparison of the reference bijection with our bijection. (a) Two identical segments. Our bijection is shown by solid lines while reference bijection is shown by dashed lines. (b) The adjacency graph corresponding to the our bijection, in which there are 3 cycles. (c) The adjacency graph corresponding to the reference bijection, in which there is only 1 cycle.

when comparing these genomes; our method obtains slightly better accuracy. On human and mouse for example, our bijection has 122 different gene pairs compared with the reference bijection. Among these pairs, 34 of them can be explained by a simple structure, illustrated in Figure 7. For two identical segments, our method outputs a sequential bijection for which no DCJ operation is needed, while the reference bijection contains a crossover, for which at least two DCJ operations are needed. The other 87 pairs can be explained by 32 pairs of segments, for each of which our bijection needs fewer DCJ operations than the reference bijection. On the comparison of the DCJ distance, our method gets fewer DCJ operations than MSOAR in all three pairs of genomes.

6 Conclusion

We formulated the maximum cycle decomposition problem as an integer linear program. We proved a theorem that can be used to reduce the complexity while preserving optimality. The combination of the two gives a practical method to compute the exact DCJ distance for genomes with duplicate genes. Such a method is crucial for comparative genomics, since duplicate genes are commonly observed in most species.

The ILP formulation can be extended in various ways. First, we can use the relaxed LP (linear programming) techniques to design possible approximation algorithms. Second, when we apply it to do orthology assignment, we can also take the sequence similarity information into account, by adding a term of the form $\sum_{e \in E} w_e \cdot x_e$ to the objective function, where w_e can be set to the similarity of the two genes. How to combine sequence similarity and DCJ distances remains an unexplored problem, but our ILP formulation provides a first step by allowing us to study linear combinations of the two.

We assumed that, after a speciation event, only DCJ operations are involved. This assumption is clearly unrealistic—it was made to simplify the problem and enable us to devise a first exact solution. However, now that our ILP method has proved successful, we can combine it with our previous work [23] to include single-gene deletion and single-gene insertion in the model.

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