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Sébastien Angibaud* Guillaume Fertin† Irena Rusu‡

Annelyse Thévenin§ Stéphane Vialette¶

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Abstract

Comparing genomes of different species is a fundamental problem in comparative genomics. Recent research has resulted in the introduction of different measures between pairs of genomes: reversal distance, number of breakpoints, number of common or conserved intervals, etc. However, classical methods used for computing such measures are seriously compromised when genomes have several copies of the same gene

*Laboratoire d'Informatique de Nantes-Atlantique (LINA), UMR CNRS 6241, Université de Nantes, 2 rue de la Houssinière, 44322 Nantes Cedex 3, France, Sebastien.Angibaud@univ-nantes.fr, Phone: (+33) 2 51 12 59 68, Fax: (+33) 2 51 12 58 12

†Laboratoire d'Informatique de Nantes-Atlantique (LINA), UMR CNRS 6241, Université de Nantes, 2 rue de la Houssinière, 44322 Nantes Cedex 3, France, Guillaume.Fertin@univ-nantes.fr, Phone: (+33) 2 51 12 58 14, Fax: (+33) 2 51 12 58 12

‡Laboratoire d'Informatique de Nantes-Atlantique (LINA), UMR CNRS 6241, Université de Nantes, 2 rue de la Houssinière, 44322 Nantes Cedex 3, France, Irena.Rusu@univ-nantes.fr, Phone: (+33) 2 51 12 58 16, Fax: (+33) 2 51 12 58 12

§Laboratoire de Recherche en Informatique (LRI), UMR CNRS 8623, Université Paris-Sud, 91405 Orsay, France, thevenin@lri.fr, Phone: (+33) 1 69 15 70 99, Fax: (+33) 1 69 15 65 86.

¶IGM-LabInfo, UMR CNRS 8049, Université Paris-Est, 5 Bd Descartes 77454 Marne-la-Vallée, France, vialette@univ-mlv.fr, Phone: (+33) 1 60 95 77 49, Fax: (+33) 1 60 95 75 57.

scattered across them. Most approaches to overcome this difficulty are based either on the *exemplar model*, which keeps exactly one copy in each genome of each duplicated gene, or on the *maximum matching model*, which keeps as many copies as possible of each duplicated gene. The goal is to find an exemplar matching, respectively a maximum matching, that optimizes the studied measure. Unfortunately, it turns out that, in presence of duplications, this problem for each above-mentioned measure is **NP**-hard.

In this paper, we propose to compute the minimum number of breakpoints and the maximum number of adjacencies between two genomes in presence of duplications using two different approaches. The first one is a (exact) generic 0–1 linear programming approach, while the second is a collection of three heuristics. Each of these approaches is applied on each problem and for each of the following models: exemplar, maximum matching and *intermediate model*, that we introduce here. All these programs are run on a well-known public benchmark dataset of γ-Proteobacteria, and their performances are discussed.

Keywords: genome rearrangements, number of breakpoints, number of adjacencies, exemplar/matching/intermediate models, 0–1 linear programming

1 Introduction

It is a well-known fact that, between different species, the order of genes in the genomes is not conserved. Hence, it appears natural to exploit this information, in order for instance to infer the phylogenetic relationships between those species. Comparison of gene orders is usually done between pairs of genomes, and can be undertaken in many different ways, which fall into two main categories. The first one consists in defining different types of rearrangement operations, and to find a most parsimonious rearrangement scenario that, using these operations, allows to go from one genome to the other. Probably the most famous example is the *reversal distance* problem, in which only one operation, reversal, is allowed (see for instance (Hannenhalli and Pevzner, 1999)). The second category consists in computing a (dis-)similarity measure between two genomes, that is a number which reflects the proximity (or not) of the two considered genomes. In that case, the measure is computed regardless of any possible rearrangement scenario that would lead from one genome to the other. Several (dis-)similarity measures between two whole genomes have been proposed in the past: number of breakpoints (Watterson et al., 1982), number of common intervals (Uno and Yagiura, 2000), number of conserved intervals (Bergeron and Stoye, 2003), Maximum Adjacency Disruption (MAD) number (Sankoff and Haque, 2005).

In this paper, we will only be interested in the latter category. Moreover, our study focuses on genomes where genes possibly have several copies. When such duplications are present, in order to compute any measure between two genomes, one first needs to disambiguate the data by inferring orthologs, *i.e.*, a non-ambiguous one-to-one mapping between the genes of the two genomes. In order to achieve this, two approaches have been considered recently: the exemplar model and the maximum matching model. In the exemplar model (Sankoff, 1999), for all gene families, all but one occurrence in each genome are deleted. In the maximum matching model (Blin et al., 2004), the goal is to map as many genes as possible. These two models can be considered as the extremal cases of the same generic homolog assignment approach.

Unfortunately, it has been shown that, for each of the above mentioned measures, and for each model (exemplar or maximum matching), the problem of finding the non-ambiguous one-to-one mapping that optimizes the studied (dis-)similarity measure becomes **NP**-hard as soon as duplicates are present in genomes (Bryant, 2000; Blin et al., 2004; Blin and Rizzi, 2005; Blin et al., 2007) ; several inapproximability results are known (Thach, 2005; Chen et al., 2006b; Chen et al., 2006a; Blin et al., 2007; Angibaud et al., 2008), and in some cases, heuristic (hence, not exact) methods have been devised to obtain good solutions in a reasonable amount of time (Blin et al., 2005; Bourque et al., 2005; Angibaud et al., 2007b).

The main goal of this paper is to study two measures, the number of breakpoints and the number of adjacencies, under three different models: the exemplar model, the maximum matching model and a model we introduce here, the *intermediate* model, in which, for all gene families, *at least* one occurrence in each genome is kept. In other words, in this model, one is allowed to modulate the number of conserved copies of each duplicated gene in each genome. Indeed, it seems natural to take this new model into account, because it is a generalization of both the exemplar and maximum matching models. We will actually discuss the interest of the intermediate model later in the paper, according to the results that will be presented.

We will then focus on methods to answer the problems: given two genomes, find the exemplar (respectively intermediate, maximum) matching that maximizes the number of adjacencies (or minimizes the number of breakpoints). Extending research initiated in (Angibaud et al., 2007b), we propose, for each problem, a generic 0–1 linear programming method that exactly (though not always quickly) answers the question. We then provide, for each problem, several heuristics and compare them with results obtained by 0–1 linear programming on a dataset of γ-Proteobacteria. In addition, we show strong evidence that our fast and simple heuristics based on iteratively finding Longest Common Subsequences provide very good results on our dataset.

The paper is organized as follows. In Section 2, we present some preliminaries and definitions. In Section 3, we reduce our study, that we wish to perform for two measures and three models, to only three main problems. In Section 4, for each of these three problems, we provide the corresponding 0–1 linear programming encoding, together with some reduction rules that help speed-up the computation. In Section 5, we present and discuss the results that we have obtained by running our 0–1 linear programming methods on a dataset of γ-Proteobacteria. In Section 6, a collection of three heuristics is proposed and their results are compared to the exact results obtained in Section 5.

2 Preliminaries

From an algorithmic perspective, a *unichromosomal genome* is a signed sequence over a finite alphabet, referred hereafter as the alphabet of *gene families*. Each element of the sequence is called a *gene*. DNA has two strands, and genes on a genome have an orientation that reflects the strand on which the genes lie. We represent the order and orientation of the genes on each genome as a sequence of signed genes, *i.e.*, genes with a sign, "+" or "−". Let G_1 and G_2 be two genomes, and let n_x, $x \in \{1, 2\}$ be the number of genes in genome G_x. For each $x \in \{1, 2\}$, $G_x[i]$ denotes the gene at position i $(1 \leq i \leq n_x)$ in G_x, and $\mathsf{occ}_x(\mathbf{g}, i, j)$ denotes the number of genes $\mathbf{g}$ (and $-\mathbf{g}$) in G_x between positions i and j, $1 \leq i \leq j \leq n_x$. To simplify notations, we abbreviate $\mathsf{occ}_x(\mathbf{g}, 1, n_x)$ to $\mathsf{occ}_x(\mathbf{g})$. As we shall only be concerned here with pairs of genomes (G_1, G_2) having the same gene content, we shall ignore those genes that occur in one genome but not in the other.

In order to deal with the inherent ambiguity of duplicate genes, we now precisely define what is a *matching* between two genomes. Roughly speaking, a matching between two genomes can be seen as a way to describe a putative assignment of orthologous pairs of genes between the two genomes (see for example (Chen et al., 2005)). More formally, a matching $\mathcal{M}$ between genomes G_1 and G_2 is a set of pairwise disjoint pairs $(G_1[i], G_2[j])$, where $G_1[i]$ and $G_2[j]$ belong to the same gene family regardless of the sign, *i.e.*, $|G_1[i]| = |G_2[j]|$. Genes of G_1 and G_2 that belong to a pair of the matching $\mathcal{M}$ are said to be *saturated* by $\mathcal{M}$, or $\mathcal{M}$-saturated for short. The size of a matching $\mathcal{M}$ is noted by $|\mathcal{M}|$. A matching $\mathcal{M}$ between G_1 and G_2 is said to be *maximum* if for any gene family, there are no two genes of this family that are unmatched for $\mathcal{M}$ and belong to G_1 and G_2, respectively.

The above definition allows us a large degree of freedom in the choice of a matching between two genomes. Two types of matchings are usually considered and specify the underlying model to focus on for computing the desired measure. In the *exemplar* model, the matching $\mathcal{M}$ is required to saturate exactly one gene of each gene family ; thus, the size of the matching is the number of gene families. In the *maximum matching* model, the matching $\mathcal{M}$ is required to be maximum, *i.e.*, to saturate as many genes of any gene family as possible. Here again, the size of $\mathcal{M}$ can be easily computed in advance, from the two input genomes. In this paper, we present and study a third model, that we call the *intermediate* model. In this model, the matching $\mathcal{M}$ is required to saturate *at least* one gene of each gene family. In that sense, this new model lies between the two extrema that are the exemplar and the maximum matching models.

Let $\mathcal{M}$ be any matching between G_1 and G_2 that fulfills the requirements of a given model (exemplar, intermediate or maximum matching). By first deleting non-saturated genes and next renaming genes in G_1 and G_2 according to the matching $\mathcal{M}$, we may now assume that both G_1 and G_2 are duplication-free, *i.e.* G_2 is a signed permutation of G_1. We call the resulting genomes $\mathcal{M}$-*pruned*.

Let G_1 and G_2 be two duplication-free genomes of size n. Without loss of generality, we may assume that G_1 is the identity positive permutation, *i.e.*, $G_1 = +1\ +2\ \ldots\ +n$. We say that there is a *breakpoint* after gene $G_1[i]$, $1 \leq i < n-1$, in G_1 if neither $G_1[i]$ and $G_1[i+1]$ nor $-G_1[i+1]$ and $-G_1[i]$ are consecutive genes in G_2, otherwise we say that there is an *adjacency* after gene $G_1[i]$. In order to take into account the breakpoints and/or adjacencies that arise at the extremities of the genomes, we artificially add, for each genome in the studied pair, a unique (*i.e.*, non-duplicated) gene at both extremities. For simplicity, the artificial gene added before the first gene in both genomes will always be $+0$, while the one added after the last gene will always be $+(n+1)$.

For example, if $G_1 = +1\ +2\ +3\ +4\ +5\ +6$ and $G_2 = +1\ -6\ -5\ -4\ +3\ +2$, we modify both genomes in order to obtain: $G'_1 = +0\ +1\ +2\ +3\ +4\ +5\ +6\ +7$ and $G'_2 = +0\ +1\ -6\ -5\ -4\ +3\ +2\ +7$. In this example, we have breakpoints in G'_1 after genes 1, 2, 3 and 6 and hence we have adjacencies in G'_1 after genes 0, 4 and 5. Thus, the number of breakpoints between G_1 and G_2 is equal to 4, while the number of adjacencies between G_1 and G_2 is equal to 3.

3 The problems

Given two genomes G_1 and G_2 and a model (exemplar, intermediate or maximum matching), we wish to find a matching which (1) is appropriate to the model, and (2) yields the optimal number of breakpoints/adjacencies, where *optimal* means *minimum* for breakpoints and *maximum* for adjacencies. Not all of the six resulting problems are essentially different. In fact, only three of them are.

3.1 From six problems to four

Let G_1 and G_2 be two genomes and $\mathcal{M}$ be a matching between G_1 and G_2 under any model (exemplar, intermediate or maximum matching). We define $\texttt{bkp}(\mathcal{M})$ to be the number of breakpoints between the two $\mathcal{M}$-pruned genomes. The number of adjacencies between two $\mathcal{M}$-pruned genomes is denoted by $\texttt{adj}(\mathcal{M})$.

It is easy to see, but important to notice, that for any matching $\mathcal{M}$ between two genomes G_1 and G_2, we have

$$\texttt{adj}(\mathcal{M}) + \texttt{bkp}(\mathcal{M}) = |\mathcal{M}| + 1. \tag{1}$$

Hence, for any given instance, if the size of the matching $\mathcal{M}$ is fixed, then finding the matching which minimizes the number of breakpoints is equivalent to finding the matching that maximizes the number of adjacencies, because of equality (1). As a consequence, we have the following proposition.

Proposition 1 *Minimizing the number of breakpoints under the exemplar model is equivalent to maximizing the number of adjacencies ; the same result holds for the maximum* *matching model.*

For the intermediate model, the same result does not hold anymore, since the cardinality of the matching cannot be inferred from the input.

3.2 From four problems to three

Another, less straightforward, equivalence holds between two of our remaining problems.

Proposition 2 *Minimizing the number of breakpoints under the exemplar model is equivalent to minimizing the number of breakpoints under the intermediate model.*

Proof. Let G_1 and G_2 be two genomes. Denote by $\texttt{bkp}_E^{\mathbf{opt}}$ and $\texttt{bkp}_I^{\mathbf{opt}}$ the minimum number of breakpoints obtained for G_1 and G_2 under the exemplar and intermediate models, respectively.

Obviously, we have $\texttt{bkp}_E^{\mathbf{opt}} \geq \texttt{bkp}_I^{\mathbf{opt}}$ since any solution for the exemplar model is also a solution for the intermediate problem. What is left is thus to prove $\texttt{bkp}_E^{\mathbf{opt}} \leq \texttt{bkp}_I^{\mathbf{opt}}$.

To this end, consider an optimal solution of the problem for the intermediate model, that is, a matching between genes of G_1 and G_2 yielding $\texttt{bkp}_I^{\mathbf{opt}}$ breakpoints. We then construct a solution (G_1', G_2') for the exemplar model that has at most $\texttt{bkp}_I^{\mathbf{opt}}$ breakpoints. This is done using the following greedy algorithm: while there exists two saturated genes in G_1 that belong to the same gene family (regardless of the sign), delete one of the two genes arbitrarily, together with the corresponding gene in G_2. The above algorithm certainly results in a solution for the exemplar model. We claim that this solution has at most as many breakpoints as the solution for the intermediate model, that is $\texttt{bkp}_I^{\mathbf{opt}}$. To this aim, we consider any iteration of the above algorithm and show that the obtained matching has at most as many breakpoints as the initial one. Four cases need distinct examination. For all genes a, the notation $a_{\blacktriangle}$ denote the presence of a breakpoint after the gene a.

1. $G_1 = \ldots a\ X\ b \ldots$, $G_2 = \ldots a\ X\ b \ldots$ or $G_2 = \ldots -b\ \ -X\ \ -a \ldots$

   Deleting X in both genomes results in genomes $G'_1 = \ldots a\ b \ldots$, $G'_2 = \ldots a\ b \ldots$ or $G'_2 = \ldots -b\ \ -a \ldots$ where no additional breakpoint is introduced.

2. $G_1 = \ldots a_{\blacktriangle} X\ b \ldots$, $G_2 = \ldots c\ X\ b \ldots$ or $G_2 = \ldots -b\ \ -X\ c \ldots$

   Deleting X in both genomes results in genomes $G'_1 = \ldots a_{\blacktriangle} b \ldots$, $G'_2 = \ldots c\ b \ldots$ or $G'_2 = \ldots -b\ c \ldots$ where no additional breakpoint is introduced.

3. $G_1 = \ldots a\ X_{\blacktriangle} b \ldots$, $G_2 = \ldots c\ X\ b \ldots$ or $G_2 = \ldots b\ \ -X\ \ -c \ldots$

   Deleting X in both genomes results in genomes $G'_1 = \ldots a_{\blacktriangle} b \ldots$, $G'_2 = \ldots c\ b \ldots$ or $G'_2 = \ldots b\ \ -c \ldots$ where no additional breakpoint is introduced.

4. $G_1 = \ldots a_{\blacktriangle} X_{\blacktriangle} b \ldots$

   For any arbitrary G_2, deleting X in both genomes induces either genome $G'_1 = \ldots a\, b \ldots$ or genome $G'_1 = \ldots a_{\blacktriangle} b \ldots$. In both cases, the number of breakpoints strictly decreases, which contradicts the optimality of the solution under the intermediate model. Therefore, this case cannot happen.

For each case, deleting X in both genomes induces two genomes where no additional breakpoint is introduced. Therefore, the generated solution cannot admit more breakpoints than $\texttt{bkp}_I^{\textbf{opt}}$, and hence we have $\texttt{bkp}_I^{\textbf{opt}} = \texttt{bkp}_E^{\textbf{opt}}$. □

3.3 The three main problems

We are now in position to formally define the optimization problems we are interested in. As before, G_1 and G_2 are two genomes.

Let $\mathbf{opt}_{\mathrm{E}}$ (respectively $\mathbf{opt}_{\mathrm{M}}$) be the problem of finding an exemplar (respectively maximum) matching $\mathcal{M}$ such that the corresponding $\mathcal{M}$-pruned of G_1 and G_2 has a maximum number of adjacencies. Proposition 1 insures that the same matching $\mathcal{M}$ also minimizes, after $\mathcal{M}$-pruning G_1 and G_2, the number of breakpoints. We denote by $\mathtt{adj}_E^{\mathbf{opt}}$ and $\mathtt{bkp}_E^{\mathbf{opt}}$ (resp. $\mathtt{adj}_M^{\mathbf{opt}}$ and $\mathtt{bkp}_M^{\mathbf{opt}}$) the number of adjacencies and the number of breakpoints in an optimal solution to $\mathbf{opt}_{\mathrm{E}}$ (resp. $\mathbf{opt}_{\mathrm{M}}$).

Let $\mathbf{opt}_{\mathrm{IA}}$ (respectively $\mathbf{opt}_{\mathrm{IB}}$) be the problem of finding an intermediate matching $\mathcal{M}$ such that the corresponding $\mathcal{M}$-pruned of G_1 and G_2 has a maximum number of adjacencies (minimum number of breakpoints, respectively).

According to Proposition 2, as long as we are mainly interested in minimizing the number of breakpoints, we do not need to specifically solve $\mathbf{opt}_{\mathrm{IB}}$, assuming we solve $\mathbf{opt}_{\mathrm{E}}$. We denote by $\mathtt{adj}_I^{\mathbf{opt}}$ and $\mathtt{bkp}_I^{\mathbf{opt}}$ $\mathtt{adj}_I^{\mathbf{opt}}$ and $\mathtt{bkp}_I^{\mathbf{opt}}$ are the number of adjacencies and the number of breakpoints in an optimal solution to $\mathbf{opt}_{\mathrm{IA}}$ and $\mathbf{opt}_{\mathrm{IB}}$, respectively.

4 An exact 0–1 linear programming approach

4.1 Introduction

Minimizing the number of breakpoints between two genomes with duplicated genes is an **NP**-hard problem for the exemplar model, even when $\mathsf{occ}_1(\mathbf{g}) = 1$ for all genes $\mathbf{g}$ in G_1 and $\mathsf{occ}_2(\mathbf{g}) \leq 2$ for all genes $\mathbf{g}$ in G_2 (Bryant, 2000). Consequently, the **NP**-hardness also holds for both the intermediate and the maximum matching models, which means that problems $\mathbf{opt}_{\mathrm{E}}$ (and thus $\mathbf{opt}_{\mathrm{IB}}$, see Proposition 2) and $\mathbf{opt}_{\mathrm{M}}$ are **NP**-hard. Moreover, a recent result (Chen et al., 2007) implies that $\mathbf{opt}_{\mathrm{IA}}$ is **NP**-hard as well.

Aiming at precise evaluations of heuristics, we develop in this section an exact generic approach as initiated in (Angibaud et al., 2007a). More precisely, our approach relies on expressing the different problems as 0–1 linear programs (Schrijver, 1998) and using powerful solvers to obtain optimal solutions.

For ease of exposition, we first present the complete 0–1 linear program for maximizing the number of adjacencies for the maximum matching problem (problem $\mathbf{opt}_{\mathrm{M}}$). Next we give some data reduction rules for reducing the input size, and hence speeding-up the program. Finally, we show how to adapt this program to $\mathbf{opt}_{\mathrm{E}}$ and $\mathbf{opt}_{\mathrm{IA}}$.

4.2 Maximizing the number of adjacencies under the maximum matching model: Problem $\mathbf{opt}_{\mathrm{M}}$

The 0–1 linear program we propose here (referred in the sequel to as Program `Adjacency--Maximum-Matching`) takes as input two genomes with duplicated genes, and solves problem $\mathbf{opt}_{\mathrm{M}}$. We denote by $\mathcal{G}$ the set of all gene families. The program is presented in Figure 1. How to adapt the program for dealing with other problems of interest is deferred to Subsection 4.4.

Here, Figure 1

Program `Adjacency-Maximum-Matching` considers two genomes G_1 and G_2 of respective lengths n_1 and n_2. The objective function, the variables and the constraints involved are now discussed.

Variables:

- Variables $a(i,k)$, $1 \leq i \leq n_1$ and $1 \leq k \leq n_2$, define a matching $\mathcal{M}$: $a_{i,k} = 1$ iff $G_1[i]$ is matched with $G_2[k]$ in $\mathcal{M}$.

- Variables $b_x(i)$, $x \in \{1,2\}$ and $1 \leq i \leq n_x$, represent the $\mathcal{M}$-*saturated* genes: $b_x(i) = 1$ if and only if $G_x[i]$ is saturated by the matching $\mathcal{M}$. Clearly, $\sum_{1 \leq i \leq n_1} b_1(i) = \sum_{1 \leq k \leq n_2} b_2(k)$, and this is precisely the size of $\mathcal{M}$.

- Variables $c_x(i,j)$, $x \in \{1,2\}$ and $1 \leq i < j \leq n_x$, represent *consecutive genes* according to $\mathcal{M}$: $c_x(i,j) = 1$ iff $G_x[i]$ and $G_x[j]$ are both saturated by $\mathcal{M}$ and no gene $G_x[p]$, $i < p < j$, is saturated by $\mathcal{M}$.

- Variables $d(i,j,k,\ell)$, $1 \leq i < j \leq n_1$ and $1 \leq k < \ell \leq n_2$, represent *adjacencies* according to $\mathcal{M}$: $d(i,j,k,\ell) = 1$ iff

  - either $(G_1[i], G_2[k])$ and $(G_1[j], G_2[\ell])$ belong to $\mathcal{M}$, $G_1[i] = G_2[k]$ and $G_1[j] = G_2[\ell]$, or $(G_1[i], G_2[\ell])$ and $(G_1[j], G_2[k])$, and belong to $\mathcal{M}$, $G_1[i] = -G_2[\ell]$ and $G_1[j] = -G_2[k]$, and

– $G_1[i]$ and $G_1[j]$ are consecutive in G_1 according to $\mathcal{M}$, and

– $G_2[k]$ and $G_2[\ell]$ are consecutive in G_2 according to $\mathcal{M}$.

Constraints:

Assume $x \in \{1, 2\}$, $1 \leq i < j \leq n_1$ and $1 \leq k < \ell \leq n_2$.

- Constraint `C.01` ensures that each gene of G_1 and of G_2 is matched at most once, *i.e.*, $b_1(i) = 1$ (respectively $b_2(k) = 1$) iff gene i (respectively k) is matched in G_1 (respectively G_2) ; see Figure 2 for an illustration of this constraint. Observe that in any matching, any two genes that are mapped together necessarily belong to the same gene family, and hence we do not have to explicitly ask for $a(i, k) = 0$ in case $G_1[i]$ and $G_2[k]$ are two genes belonging to different gene families.

- Constraint `C.02` actually defines the considered model (here the maximum matching model). For each gene family $\mathbf{g}$, $\min(\mathsf{occ}_1(\mathbf{g}), \mathsf{occ}_2(\mathbf{g}))$ occurrences of genes belonging to $\mathbf{g}$ must be $\mathcal{M}$-saturated in both G_1 and G_2 (see Figure 2).

- Constraints in `C.03` and `C.04` are concerned with our definition of consecutive genes. Variable $c_x(i, j)$ is equal to 1 iff there exists no p such that $i < p < j$ and $b_x(p) = 1$. It is worth noticing here that, according to these constraints, one may have $c_x(i, j) = 1$ even if one of the genes $G_x[i]$ or $G_x[j]$ is *not* $\mathcal{M}$-saturated.

- Constraints in `C.05` to `C.10` define variables d. In the case where $G_1[i] = G_2[k]$ and $G_1[j] = G_2[\ell]$, Constraints `C.05` and `C.06` ensure that we have $d(i, j, k, \ell) = 1$ if and only if all variables $a(i, k)$, $a(j, \ell)$, $c_1(i, j)$ and $c_2(k, \ell)$ are equal to 1. In the case where $G_1[i] = -G_2[\ell]$ and $G_1[j] = -G_2[k]$, Constraints `C.07` and `C.08` ensure that we have $d(i,j,k,\ell) = 1$ iff all variables $a(i,\ell)$, $a(j,k)$, $c_1(i,j)$ and $c_2(k,\ell)$ are equal to 1. Constraint `C.09` sets variable $d(i,j,k,\ell)$ to 0 if none of the two above cases holds. Finally, thanks to Constraint `C.10`, one must have at most one adjacency for every pair (i,j). See Figure 3 for a simple illustration.

The objective of Program `Adjacency-Maximum-Matching` is to maximize the number of adjacencies between the two considered genomes. According to the above, this objective thus reduces in our model to maximizing the sum of all variables $d(i,j,k,\ell)$.

Here, Figure 2

Here, Figure 3

4.3 Speeding-up the program

Program `Adjacency-Maximum-Matching` has $O((n_1 \cdot n_2)^2)$ variables and $O((n_1 \cdot n_2)^2)$ constraints. Aiming at speeding-up the execution of the program, we present here some simple rules for reducing the number of variables and constraints involved.

Pre-processing the genomes. The genomes are pairwise pre-processed to delete all genes that do not appear in both genomes. For instance, for the γ-Proteobacteria benchmark set studied in Section 5, the average size of a genome reduces from 3000 to 1300.

Reducing the number of variables and constraints. For non-duplicated genes, *i.e.*, genes g for which $\mathtt{occ}_1(g) = \mathtt{occ}_2(g) = 1$, the corresponding variable $a_{i,k}$ is set directly to 1, as well as the two variables $b_1(i)$ and $b_2(k)$. Also, if two non-duplicated genes occur consecutively or in reverse order with opposite signs, the corresponding variable d is set directly to 1 and the related constraints are discarded. If for two genes, say occurring at positions i and j in G_1, at least one gene occurring between position i and j in G_1 must be saturated in any matching $\mathcal{M}$ (for example if one family has all occurrences between i and j in G_1), then the corresponding variable $c_1(i,j)$ and the variable $d(i,j,k,\ell)$ for all $1 \le k < \ell \le n_2$ are set directly to 0 and the related constraints are discarded. We can use the same reasoning for two positions k and ℓ in G_2 and the variables $c_2(k,\ell)$ and $d(i,j,k,\ell)$ for all $1 \le i < j \le n_1$.

4.4 Dealing with other measures and models

Program `Adjacency-Maximum-Matching` allows us to solve problem $\mathbf{opt}_{\mathrm{M}}$. We describe here how to adapt this 0–1 linear program for dealing with the two remaining problems, namely $\mathbf{opt}_{\mathrm{E}}$ and $\mathbf{opt}_{\mathrm{IA}}$. As we shall see, only a few modifications are needed.

Exemplar Model (Problem $\mathbf{opt}_{\mathbf{E}}$). As observed before, Constraint `C.02` explicits the model under consideration. For the exemplar model, exactly one occurrence in each gene family must be saturated. Therefore, Constraint `C.02` should be rewritten as follows.

$$\mathtt{C.02} \quad \forall\, x \in \{1,2\}, \forall\, \mathtt{g} \in \mathcal{G}, \sum_{\substack{1 \le i \le n_x \\ |G_x[i]| = |\mathtt{g}|}} b_x(i) = 1$$

Moreover, for efficiency, a simple additional rule can be considered for simplifying the program. Indeed, we must have exactly one occurrence of each gene in each genome. Therefore, for all $0 \leq i < j \leq n_x$, $x \in \{1, 2\}$, if $|G_x[i]| = |G_x[j]|$ then $c_x(i, j) = 0$. The corresponding variables d are set directly to 0 and the related constraints are discarded.

Intermediate Model (Problem $\mathbf{opt_{IA}}$). Again, we are here concerned with Constraint `C.02`. For the intermediate model, at least one gene of each gene family must be saturated. This simply reduces in rewriting Constraint `C.02` as follows.

$$\texttt{C.02} \quad \forall\, x \in \{1, 2\}, \forall\, \mathtt{g} \in \mathcal{G}, \sum_{\substack{1 \leq i \leq n_x \\ |G_x[i]| = |\mathtt{g}|}} b_x(i) \geq 1$$

As seen in the previous section, computing the minimum number of breakpoints or the maximum number of adjacencies are not equivalent problems in the intermediate model. To compute the minimum number of breakpoints (problem $\mathbf{opt}_{\mathrm{IB}}$), the objective must be modified as follows (correctness follows from relation (1)).

$$\texttt{Minimize} \sum_{0 \leq i < n_1} b_1(i) - \sum_{0 \leq i < n_1} \sum_{i < j \leq n_1} \sum_{0 \leq k < n_2} \sum_{k < \ell \leq n_2} d(i, j, k, \ell) - 1$$

One may argue that this latter 0–1 linear program is useless since $\mathbf{opt}_{\mathrm{IB}}$ and $\mathbf{opt}_{\mathrm{E}}$ have been shown to be equivalent problems (see Proposition 2). However, as we shall see in Section 5, the intermediate model gives us the opportunity, for the same minimum number of breakpoints as in the exemplar model, to obtain more adjacencies. As a simple illustration of this point, consider the two genomes $G_1 = +0\ +1\ -4\ +2\ -1\ +2\ -3\ +4$ and $G_2 = +0\ +3\ +1\ +2\ -1\ -3\ +4$. We have $\mathtt{bkp}_E^{\mathbf{opt}} = 0$ as shown by the exemplarization

$G'_1 = G'_2 = +0\ +1\ +2\ -3\ +4$; this solution yields 4 adjacencies. However, the solution under the intermediate model $G''_1 = G''_2 = +0\ +1\ +2\ -1\ -3\ +4$ still induces 0 breakpoint, but yields 5 adjacencies.

5 Experimental results

Based on our generic 0–1 linear programming approach (see Section 4), we present in this section a computation campaign for obtaining almost all results for problems $\mathbf{opt}_{\mathrm{M}}$, $\mathbf{opt}_{\mathrm{IA}}$ and $\mathbf{opt}_{\mathrm{E}}$ (note that problem $\mathbf{opt}_{\mathrm{IB}}$ will also be discussed for reasons developed at the end of the previous section). The rationale of this is threefold. First, we aim at testing the relevance of our generic 0–1 linear programming approach on real biological data. In particular, we are interested in identifying non-artificial hard to solve instances, and more generally in estimating the intrinsic limits of the proposed approach. Second, we seek at comparing on a real biological dataset the three problems $\mathbf{opt}_{\mathrm{M}}$, $\mathbf{opt}_{\mathrm{IA}}$ and $\mathbf{opt}_{\mathrm{E}}$, and at comparing the three models. Finally, in order to evaluate heuristics (see Section 6), we provide here an almost complete set of exact results to which we can refer to, and we also believe these results could be of interest for the community in the design of new heuristic approaches.

Our linear program solver engine is powered by `CPLEX`[1]. All computations were carried out on a Quadri Intel(R) Xeon(TM) CPU 3.00 GHz with 16Gb of memory running under Linux.

5.1 Dataset

We conducted our computation campaign on a dataset of γ-Proteobacteria genomes, originally studied in (Lerat et al., 2003). For one, this dataset is becoming a standard reference dataset in comparative genomics (Lerat et al., 2005; Blin et al., 2005; Angibaud et al., 2007b). For another, this dataset is composed of genomes of moderate sizes, and hence is a good candidate for intensive time consuming computations. More precisely, our reference

[1] `http://www.ilog.com/products/cplex/`

dataset is composed of twelve complete genomes of γ-Proteobacteria out of the thirteen originally studied in (Lerat et al., 2003). Indeed, the thirteenth genome (*V.cholerae*) was not considered, since it is composed of two chromosomes, and hence does not fit in the model we considered here for representing genomes. More precisely, the dataset is composed of the following genomes:

- *Buchnera aphidicola APS* (`Baphi`, Genbank accession number NC_002528),
- *Escherichia coli K12* (`Ecoli`, NC_000913),
- *Haemophilus influenzae Rd* (`Haein`, NC_000907),
- *Pseudomonas aeruginosa PA01* (`Paeru`, NC_002516),
- *Pasteurella multocida Pm70* (`Pmult`, NC_002663),
- *Salmonella typhimurium LT2* (`Salty`, NC_003197),
- *Xanthomonas axonopodis pv. citri 306* (`Xaxon`, NC_003919),
- *Xanthomonas campestris* (`Xcamp`, NC_0 03902),
- *Xylella fastidiosa 9a5c* (`Xfast`, NC_002488),
- *Yersinia pestis CO_92* (`Ypest-CO92`, NC_003143),
- *Yersinia pestis KIM5 P12* (`Ypest-KIM`, NC_004088) and
- *Wigglesworthia glossinidia brevipalpis* (`Wglos`, NC_004344).

The determination of the gene families, where each family is supposed to represent a group of homologous genes, is taken from (Blin et al., 2005) and hence, although a crucial preliminary step, will not be further discussed here. Initially, the sizes of the genomes range from 565 to 5474 genes (see Table 1). Moreover, 8% of the gene families are, on average, duplicated (these duplications cover, on average, 20% of the genes of a genome).

Here, Table 1

5.2 Results

After the pre-processing step (see Section 4.3), 8% of the gene families are, on average, duplicated and these duplications cover, on average, 26% of the genes of a genome. Furthermore, pre-processing the dataset by pairs of genomes drastically reduces the size of the genomes. For example, focusing on comparing `Baphi` and `Ecoli`, their size reduces from 565 and 4119 genes to 531 and 721, respectively. Table 2 gives all reduced sizes for pairwise comparisons for the exemplar model and Table 3 gives all reduced sizes for pairwise comparisons for the maximum matching model. Notice that this latter table also gives all reduced sizes for pairwise comparisons for the intermediate model (indeed, concerning the pre-processing step, a maximum matching can be seen as the "worst" case over all possible intermediate matchings).

Here, Table 2

Here, Table 3

The computation campaign, in which all 0–1 linear programs have been extended with speed-up rules as described in 4.3, has given the results presented in Table 4 (symbol `X` denotes unsolved instances).

Here, Table 4

Maximum matching model. Recall first that computing the minimum number of breakpoints and the maximum number of adjacencies for the maximum matching model are equivalent problems (see Proposition 1). This problem turned out out to be the easiest case for our γ-Proteobacteria dataset. The `CPLEX` engine indeed computed *all* pairwise distances (Table 4) in less than 2 minutes (1.7 second, on average, per pairwise genome comparison).

Exemplar model. Again, recall here that computing the minimum number of breakpoints and the maximum number of adjacencies are equivalent problems for the exemplar model (see Proposition 1). However, oppositely to the maximum matching model, we were not able to compute all pairwise distances. More precisely, 61 out of 66 results (see Table 4) have been obtained thanks to our 0–1 linear programming program in less than 1 minute, except for two cases, for which several hours of computation were necessary. Our attempts for computing the remaining 5 last cases resulted in `CPLEX` memory exhausted crashes. We note that a similar combinatorial explosion was observed in (Angibaud et al., 2007b) in the context of maximizing the number of *common intervals* between two genomes by means of a 0–1 linear program. Unfortunately, we still have no formal explanation for this surprising and counter-intuitive situation. However, we believe this fact to be not related to the `CPLEX` engine - seen as a black box here.The only obvious observation that can be made for these 5 unsolved cases is that they always take as input two genomes of relatively large sizes (roughly, between 2500 and 3500 genes in each case). However, this is not a sufficient explanation since there are pairs of genomes that have more or less the same size and that went through our program (see for instance `Salty/Ypest-KIM`). This is why we strongly suspect the structure of the genomes to play a role concerning this problem.

Intermediate model. Recall first that minimizing the number of breakpoints and maximizing the number of adjacencies are *not* equivalent problems for the intermediate model. Concerning the problem of maximizing the number of adjacencies, 63 out of 66 results have been obtained in about 3 minutes. As for minimizing the number of breakpoints, 59 out of 66 results have been obtained in less than two minutes.

A justification should be given here for having computed the minimum number of breakpoints for the intermediate model (problem $\mathbf{opt}_{\mathrm{IB}}$). Indeed, minimizing the number of breakpoints for the exemplar and the intermediate models were shown to be equivalent problems in Section 3 (see Proposition 2), and thus the rightmost column of Table 4 might appear just superfluous ; indeed it might be verified in Table 4 that column $\mathtt{bkp}(\mathcal{M})$ (exemplar model $\mathbf{opt}_{\mathrm{E}}$) and column $\mathtt{bkp}(\mathcal{M})$ (intermediate model $\mathbf{opt}_{\mathrm{IB}}$) are always equal. The main reason for having presented both results is to draw the attention of the reader to the fact that, although obtaining the same minimum number of breakpoints as the exemplar model, a matching minimizing the number of breakpoints for the intermediate model might result in a solution with more adjacencies (see the example at the end of Section 4 for a simple illustration). This could be helpful for obtaining a solution that achieves a double objective: minimizing the number of breakpoints (primary objective) and, among those optimal solutions, maximizing the number of adjacencies (secondary objective). This latter goal should be, however, modulated here since the secondary objective is not explicitly stated in the 0–1 linear program, *i.e.*, there is no guarantee that the maximum number of adjacencies is achieved.

We now turn to comparing the results for the different models. First, the following two (average) ratios can be computed from Table 4:

$$\frac{\mathtt{bkp}_E^{\mathbf{opt}}}{\mathtt{bkp}_M^{\mathbf{opt}}} = 0.89 \qquad \text{and} \qquad \frac{\mathtt{adj}_E^{\mathbf{opt}}}{\mathtt{adj}_M^{\mathbf{opt}}} = 0.92.$$

These two ratios illustrate the fact that (i) the minimum number of breakpoints for the exemplar and the maximum matching models differ in about 10%, and (ii) the maximum number of adjacencies for the exemplar and the maximum matching models also differ in about 10%. In the light of these factual ratios, it should thus be emphasized here that, for most practical applications, the choice of the model (exemplar or maximum matching) to focus on should not be underestimated, since noticeable differences might result from this decision.

As for the intermediate model, we already showed that $\mathtt{bkp}_E^{\mathbf{opt}} = \mathtt{bkp}_I^{\mathbf{opt}}$. We compare in Table 5 the results for the intermediate model with the results for the two other models. To complement Table 5, we indicate in Table 6 how often the same optimal measure (number of breakpoints or number of adjacencies) is found for the intermediate model and for another model (exemplar or maximum matching). It should be noticed here that, for most cases, we obtain more adjacencies using the intermediate model. The situation is more contrasted when considering the number of breakpoints: for one, we have $\texttt{bkp}_E^{\textbf{opt}} = \texttt{bkp}_I^{\textbf{opt}}$ (denoted by 100% in Table 6), and for another, for 1/3 of the comparisons, we obtain the same number of breakpoints when maximizing the number of adjacencies for the intermediate model as we obtain for the exemplar model.

Here, Table 5

Here, Table 6

To compare $\texttt{adj}_I^{\textbf{opt}}$ and $\texttt{bkp}_I^{\textbf{opt}}$, the two following (average) ratios can be computed (see Table 5):

$$\frac{\texttt{adj}(\mathcal{M}_{I,\texttt{bkp}}^{\textbf{opt}})}{\texttt{adj}_I^{\textbf{opt}}} = 0.94 \qquad \text{and} \qquad \frac{\texttt{bkp}_I^{\textbf{opt}}}{\texttt{bkp}(\mathcal{M}_{I,\texttt{adj}}^{\textbf{opt}})} = 0.97.$$

The intermediate model gives us opportunity to drive the computation with a double objective (minimum number of breakpoints and maximum number of adjacencies). According to the above, one may be tempted to argue that, for the intermediate model, maximizing the number of adjacencies is better than minimizing the number of breakpoints since the obtained solution certainly maximizes the number of adjacencies yet giving about $1/0.97 \approx 103\%$ of the minimum number of breakpoints (minimizing the number of breakpoints gives about

94% of the maximum number of adjacencies). We however do think that the two ratios are too close to draw any definitive conclusion here on the «$\texttt{adj}_I^{\mathbf{opt}}$ *versus* $\texttt{bkp}_I^{\mathbf{opt}}$» question.

6 Heuristic algorithms

Though our 0–1 linear programming approach presented in Section 4 allows us to obtain almost all the expected exact results in the exemplar, intermediate and maximum matching models on the studied set of γ-Proteobacteria (see Section 5), it should be said that the limits of this method have been attained. Indeed, especially in the intermediate model, some results could not be obtained in reasonable time using this method, and one of the reasons for this is that the sizes of the genomes were too large for the 0–1 linear programming method to be able to handle it. In other words, while this method seems to be promising for "small" genomes (*i.e.* genomes which, after pre-processing, do not exceed, roughly, two thousand genes), there is a crucial need for faster (and thus not necessarily exact) algorithms in case genomes are of substantially larger sizes ; of course, these heuristic algorithms should provide results of high quality, that is as close as possible from the exact results. In that sense, thanks to the results presented in the previous section, we will be able to compare several heuristics to the exact results and to validate the accuracy of the heuristics provided in this section.

In the following, altogether nine heuristics will be presented and studied (three for each model) ; each of these heuristics fall into one of the two following categories: (i) heuristics based on finding iteratively the *Longest Common Subsequence* (or *LCS*, for short) of two genomes, and (ii) heuristics which are a hybrid between category (i) above and the 0–1 linear programming method.

6.1 Description of the Heuristics

Before describing in detail our heuristics, we recall that under the intermediate model, two different problems exist: either we wish to find a matching that maximizes the number of adjacencies, or one that minimizes the number of breakpoints. However, we have seen that minimizing the number of breakpoints in the intermediate model is equivalent to minimizing the number of breakpoints in the exemplar model (see Proposition 2). Thus any heuristic that aims at minimizing the number of breakpoints in the exemplar model will of course apply for minimizing the number of breakpoints in the intermediate model. Consequently, when we turn to the intermediate model, we will only focus on heuristics that aim at maximizing the number of adjacencies.

6.1.1 IILCS heuristics

We first describe here the main ideas that lie behind heuristics based on finding iteratively the *Longest Common Subsequence* (or LCS, for short), that we have called *IILCS* heuristics. Let G_1 and G_2 be two genomes: an *LCS* of (G_1, G_2) is a longest common word S of G_1 and G_2, up to a complete reversal. The idea here is to match, at each iteration, *all the genes* that are present in an *LCS*, until the desired matching is obtained.

We note that this idea is not new: it has already been used, for instance, in (Marron et al., 2004). In (Angibaud et al., 2007b), this heuristic has been improved in the following way: at each iteration, not only we match all the genes that are contained in an *LCS* (**Rule 1**), but we also remove each unmatched gene of a genome for which there is no unmatched gene of same family in the other genome (**Rule 2**).

The three heuristics that we are going to present use the two above mentioned rules.

Since the difference between the problems lies in the matching that we wish to obtain, our three heuristics will differ on that specific point.

Maximum matching model. We apply iteratively **Rule 1** and **Rule 2** until the algorithm stops. By definition of **Rule 1** and **Rule 2**, this implies that the resulting matching is maximum. We call this heuristic `IILCS_M`.

Intermediate model. We also apply iteratively **Rule 1** and **Rule 2**. The difference here is the stop condition: the algorithm stops as soon as each gene family has been matched at least once. We call this heuristic `IILCS_IA`.

Exemplar model. We apply iteratively **Rule 1** and **Rule 2** again, but we apply extra deletions of genes at each iteration. Indeed, we need to make sure that only *one gene* from each family is matched on each genome. In that case, at each iteration, for the duplicate genes which are contained in the current *LCS*, we arbitrarily keep (and match) the first occurrence ; while for those genes **g** who are outside *LCS*, we apply the following rule: if **g** is present in the *LCS* (and thus kept in the matching), then we remove all the other occurrences of **g** in the rest of both genomes. When this heuristic stops, we are thus guaranteed to obtain an exemplar matching. We call this heuristic `IILCS_E`.

Remark that, for each of those three heuristics, at each iteration, there might exist several *LCS* ; in that case, we have decided to randomly choose one of them. Due to this, if one runs `IILCS_M` (respectively `IILCS_IA`, `IILCS_E`) several times on the same instance, it could result in different matchings, and thus the number of breakpoints and adjacencies may vary.

Hence, for each pair of genomes, we have decided to run ten times the heuristics IILCS_M, IILCS_IA and IILCS_E and to keep the best result.

6.1.2 Hybrid method

Let us now describe the other category of heuristics we propose for solving our problems in the three models: this method is a hybrid method using the appropriate IILCS heuristic, followed by the 0–1 linear programming algorithm. The principle is to compute a part of the matching by iterating of the appropriate heuristic IILCS until the size of the LCS is strictly smaller than a given parameter k. Once this is done, we complete the matching by invoking the appropriate 0–1 linear programming algorithm. This heuristic is called HYB_M(k) (respectively HYB_IA(k), HYB_E(k)) in the maximum matching (respectively intermediate, exemplar) model.

For each of the three models, we have tested the hybrid heuristic described above for two different values of k, namely $k = 2$ and $k = 3$. We deliberately chose small values of k, because when k gets bigger, invoking the exact algorithm for completing the partial matching might take too long, which is something we want to avoid. Moreover, we will see in the next section that the results obtained with $k = 2$ and $k = 3$ are already extremely good.

6.2 Non-exact results

Each of the nine heuristics has been tested on the dataset of γ-Proteobacteria described in Section 5.1. A synthesis of all these results is given in Table 7, where we show, for the nine heuristics, how close they lie to the exact results on average, at worse and at best.

The complete set of results is given in Tables 8, 9 and 10 for problems $\mathbf{opt}_{\mathrm{M}}$, $\mathbf{opt}_{\mathrm{IA}}$ and $\mathbf{opt}_{\mathrm{E}}$, respectively. A graphical representation showing, for each problem, how each heuristic compares to the exact results is provided in Figures 4, 5 and 6 (note that, in each figure, the results are presented in the same arbitrary order than Tables 8, 9 and 10).

Concerning heuristics based on *IILCS*, their running time is approximately 40 minutes for each of the three problems (we recall that, for each pair of genomes, any given heuristic of this type is run 10 times, thus it takes approximately 4 minutes for each heuristic to achieve all the 66 pairwise comparisons).

As said before, concerning the heuristics based on the hybrid method, we have run them, for each of the three models (i) with parameter k set to 2 and (ii) with parameter k set to 3. The running time, for each of those six heuristics, is roughly five minutes.

Here, Table 7

Here, Figure 4

Here, Figure 5

Here, Figure 6

Here, Table 8

Here, Table 9

Here, Table 10

6.3 Discussion

Globally, the nine heuristics that we have proposed perform very well on our dataset. For each of the three problems, the appropriate `IILCS` heuristic returns results that are on average at least 90% of the optimal value. It can be seen that `IILCS_IA` is relatively less effective than `IILCS_E` and `IILCS_M`: `IILCS_IA` returns on average results that are 90.56% of the optimal value, while `IILCS_E` (respectively `IILCS_M`) reaches 99.36% (respectively 99%). This can be explained by the fact that `IILCS_IA`, which relies on iteratively finding and matching the genes of a Longest Common Subsequence, is in fact well-fitted for minimizing the number of breakpoints, but not necessarily for maximizing the number of adjacencies. Still, its performances, though not as good as the ones of `IILCS_E` and `IILCS_M`, remain satisfying.

Non surprisingly, our hybrid methods, with parameter $k = 2$, give better results than their corresponding IILCS heuristics (we are on average 99.48% close to the optimal values for the less effective heuristic). Non surprisingly again, when we set parameter k to 3, the hybrid methods get even better (we are on average 99.82% close to the optimal values for the less effective heuristic). In each case, we are on average closer to the optimal values, and much more exact values are obtained.

There are two main conclusions that can be drawn from this set of results.

First, any of the nine presented heuristics is good on the studied dataset, and in that sense they are all validated. Of course, when possible, better results should be obtained using the hybrid method HYB(3), or HYB(2). However, even after having computed a partial matching by running IILCS down to $k = 3$ or $k = 2$, we cannot obtain in reasonable time all results with the 0–1 linear program. In particular, this situation might occur when genomes are of very large sizes. In that case, the good performances of the IILCS heuristics show that they still can be used to obtain fast and accurate results.

Second, these results show that the rather intuitive idea consisting of iteratively finding and matching the genes of a Longest Common Subsequence is very effective for both measures (number of breakpoints and number of adjacencies) and for the three models. It should be said that the same conclusion was drawn in (Angibaud et al., 2007b) concerning the measure "number of *common intervals*" under the maximum matching model. In that sense, it tends to prove that comparing gene orders should probably, in the future, be studied under this angle.

7 Discussion and future works

This paper developed out of an attempt to build more accurate models for comparative genomics and to design accurate and fast heuristics for breakpoints and adjacencies based measures.

In that sense, the results we have obtained are very satisfying: for one, virtually all the results have been obtained through our 0–1 linear programming approach (though it seems hard to push it further for genomes of larger sizes). For the other, all the heuristics we have proposed perform very well on our dataset.

Another aspect of our work was to focus on the intermediate model. Indeed, our main motivation for this lies on the fact that both the exemplar and the maximum matching might be too restrictive for practical applications. More precisely, if both the exemplar and the maximum matching models provide a clear and simple algorithmic framework, we believe the intermediate model to be well-suited and more accurate for comparative genomics. From this point of view, one of our goals was to observe whether this new model would give very different results from the exemplar and maximum matching models. It turns out that the results are not conclusive: (i) $\mathbf{opt}_{\mathrm{IB}}$ is equivalent to $\mathbf{opt}_{\mathrm{E}}$ (see Proposition 2), and (ii) solving $\mathbf{opt}_{\mathrm{IA}}$ returns results which, in terms of adjacencies, are relatively close to both $\mathbf{opt}_{\mathrm{E}}$ and $\mathbf{opt}_{\mathrm{M}}$ (see Tables 5 and 6). Hence, studying the pertinence of the intermediate model on our dataset and for our measures would require a deeper study, and in particular a study of the structure of the output genomes (how many genes of each family are kept and what are their locations, for instance). This specific study is one that we will undertake in the next future.

Though we were not able to clearly distinguish, using the number of breakpoints or the number of adjacencies, whether the intermediate model radically differs from the others, we still believe this model to be of interest. First, giving more freedom in the structure of the solution is certainly an advantage for practical applications. Second, as illustrated in Table 4, the intermediate model actually gives rise to two combinatorial problems (minimizing the number of breakpoints *and* maximizing the number of adjacencies). A complementary line of research is thus to develop a 0–1 linear based program for achieving such a double objective. Note that such a program could be obtained by the following procedure: compute the minimum number of breakpoints for the intermediate model, transform this objective into an additional constraint to obtain a modified linear program, and finally compute the maximum number of adjacencies according to the modified 0–1 linear program. Conversely, we can add a constraint to obtain the maximum number of adjacencies, then compute the minimum of breakpoints. These approaches would give us more precise results for the intermediate model than those in Table 4 but its time computation should be more important.

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Program `Adjacency-Maximum-Matching`

Objective :

Maximize $\sum_{0\le i<n_1} \sum_{i<j\le n_1} \sum_{0\le k<n_2} \sum_{k<\ell\le n_2} d(i,j,k,\ell)$

Constraints :

C.01 $\forall\ 1 \le i \le n_1, \quad \sum_{\substack{1\le k\le n_2\\ |G_1[i]|=|G_2[k]|}} a(i,k) = b_1(i)$

$\forall\ 1 \le k \le n_2, \quad \sum_{\substack{1\le i\le n_1\\ |G_1[i]|=|G_2[k]|}} a(i,k) = b_2(k)$

C.02 $\forall\ x \in \{1,2\}, \forall\ \mathtt{g} \in \mathcal{G}, \quad \sum_{\substack{1\le i\le n_x\\ |G_x[i]|=|\mathtt{g}|}} b_x(i) = \min(\mathsf{occ}_1(\mathbf{g}), \mathsf{occ}_2(\mathbf{g}))$

C.03 $\forall\ x \in \{1,2\}, \forall\ 1 \le i \le j-1 < n_x,\ c_x(i,j) + \sum_{i<p<j} b_x(p) \ge 1$

C.04 $\forall\ x \in \{1,2\}, \forall\ 1 \le i < p < j \le n_x,\ c_x(i,j) + b_x(p) \le 1$

C.05 $\forall\ 1 \le i < j \le n_1, \forall\ 1 \le k < \ell \le n_2$,
such that $G_1[i] = G_2[k]$ and $G_1[j] = G_2[\ell]$,
$a(i,k) + a(j,\ell) + c_1(i,j) + c_2(k,\ell) - d(i,j,k,\ell) \le 3$

C.06 $\forall\ 1 \le i < j \le n_1, \forall\ 1 \le k < \ell \le n_2$,
such that $G_1[i] = G_2[k]$ and $G_1[j] = G_2[\ell]$,
$a(i,k) - d(i,j,k,\ell) \ge 0$
$a(j,\ell) - d(i,j,k,\ell) \ge 0$
$c_1(i,j) - d(i,j,k,\ell) \ge 0$
$c_2(k,\ell) - d(i,j,k,\ell) \ge 0$

C.07 $\forall\ 1 \le i < j \le n_1, \forall\ 1 \le k < \ell \le n_2$,
such that $G_1[i] = -G_2[\ell]$ and $G_1[j] = -G_2[k]$,
$a(i,\ell) + a(j,k) + c_1(i,j) + c_2(k,\ell) - d(i,j,k,\ell) \le 3$

C.08 $\forall\ 1 \le i < j \le n_1,\ \forall\ 1 \le k < \ell \le n_2$,
such that $G_1[i] = -G_2[\ell]$ and $G_1[j] = -G_2[k]$,
$a(i,\ell) - d(i,j,k,\ell) \ge 0$
$a(j,k) - d(i,j,k,\ell) \ge 0$
$c_1(i,j) - d(i,j,k,\ell) \ge 0$
$c_2(k,\ell) - d(i,j,k,\ell) \ge 0$

C.09 $\forall\ 1 \le i < j \le n_1,\ \forall\ 1 \le k < \ell \le n_2$,
such that $\{|G_1[i]|, |G_1[j]|\} \ne \{|G_2[k]|, |G_2[\ell]|\}$ or $G_1[i] - G_1[j] \ne G_2[k] - G_2[\ell]$,
$d(i,j,k,\ell) = 0$

C.10 $\forall\ 1 \le i < j \le n_1$,
$\sum_{1\le k<n_2} \sum_{k<\ell\le n_2} d(i,j,k,\ell) \le 1$

Domains :

$\forall\ x \in \{1,2\}, \forall\ 1 \le i < j \le n_1, \forall\ 1 \le k < \ell \le n_2$,
$a(i,k),\ b_x(i),\ c_x(i,k),\ d(i,j,k,\ell) \in \{0,1\}$

Figure 1: Program `Adjacency-Maximum-Matching` for finding the maximum number of adjacencies between two genomes under the maximum matching model.

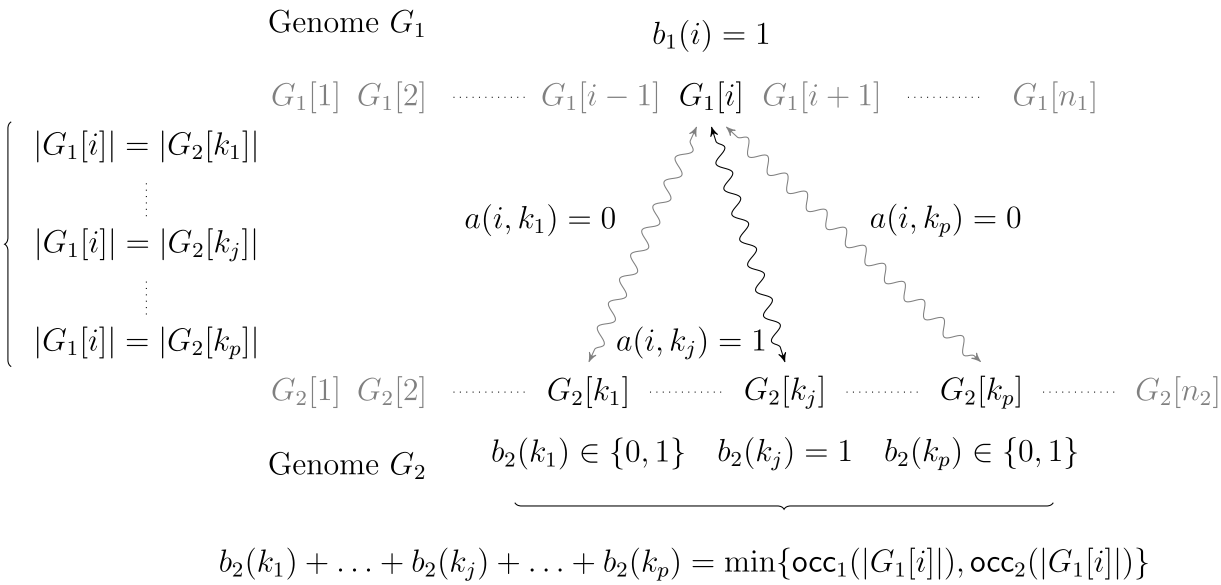


Figure 2: Illustration of the constraints on variable $b_1(i)$, $1 \leq i \leq n_1$. If gene $G_1[i]$ appears in positions $k_1 < k_2 < \ldots < k_p$ in G_2 and gene $G_1[i]$ is mapped to gene $G_2[k_j]$ in the solution matching, then (i) $a(i, k_j) = 1$, *i.e.*, gene $G_1[i]$ is mapped to gene $G_2[k_j]$, (ii) $a(i, k_q) = 0$ for $1 \leq q \leq p$ and $q \neq j$, *i.e.*, gene $G_1[i]$ is mapped to only one gene in G_2, (iii) $b_1(i) = 1$, *i.e.*, gene $G_1[i]$ is mapped to a gene of G_2 and (iv) $b_2(k_j) = 1$, *i.e.*, gene $G_2[k_j]$ is mapped to a gene of G_1. Observe that one may have in addition $b_2(k_q) = 1$ for some $1 \leq q \leq p$ and $q \neq j$ if $\min(\mathsf{occ}_1(|G_1[i]|), \mathsf{occ}_2(|G_1[i]|) \geq 1$ (this observation is however no longer valid for the exemplar model).

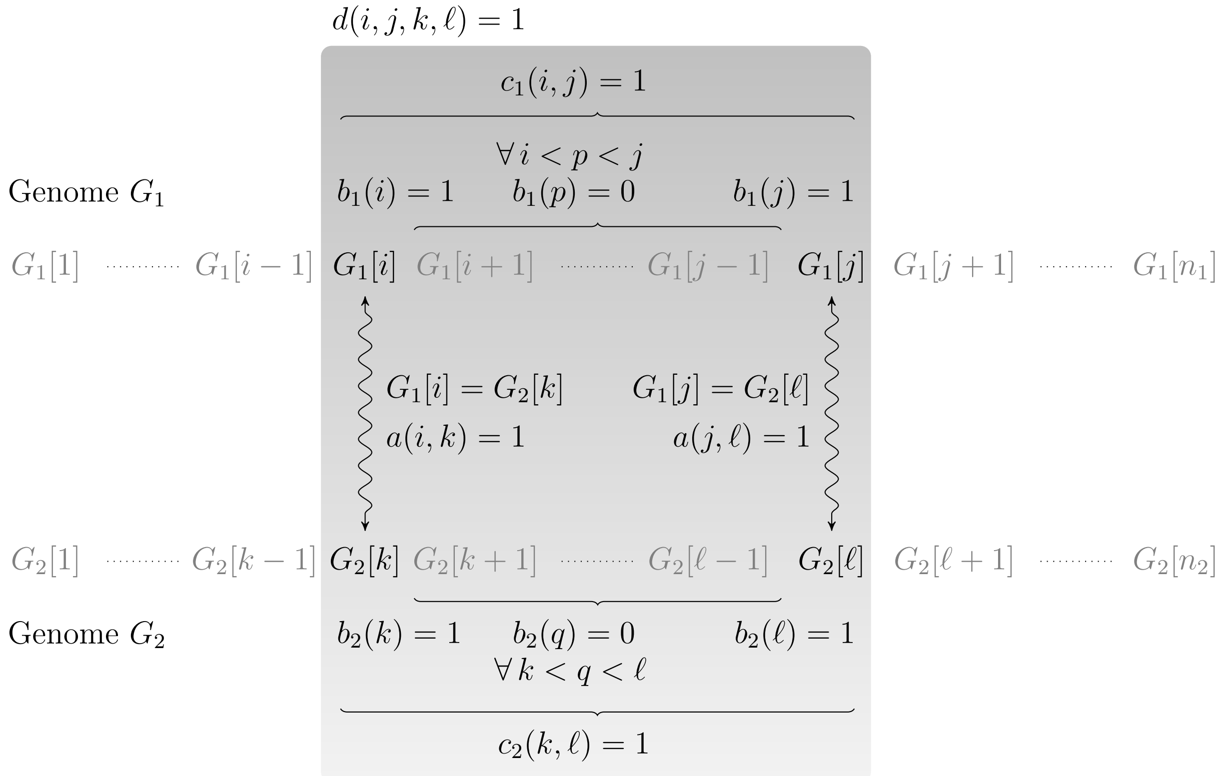
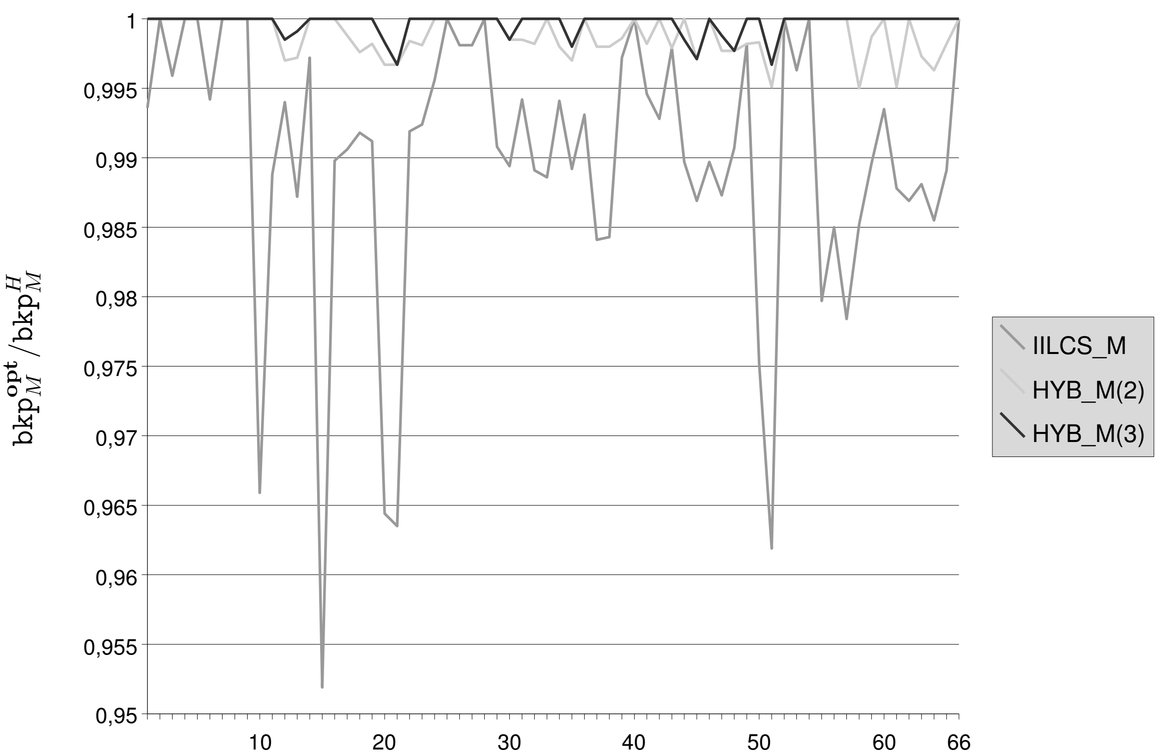


Figure 3: Illustration of the constraints on variable $d(i,j,k,\ell)$, $1 \leq i < j \leq n_1$ and $1 \leq k < \ell \leq n_2$, for $G_1[i] = G_2[k]$ and $G_1[j] = G_2[\ell]$. The two genes $G_1[i]$ and $G_1[j]$ are adjacent according to a solution matching if there exist two genes $G_2[k]$ and $G_2[\ell]$, $G_1[i] = G_2[k]$ and $G_1[j] = G_2[\ell]$, such that (i) $G_1[i]$ is mapped to $G_2[k]$, *i.e.*, $a(i,k) = 1$, (ii) $G_1[j]$ is mapped to $G_2[\ell]$, *i.e.*, $a(j,\ell) = 1$, (iii) no gene between $G_1[i]$ and $G_1[j]$ is mapped to a gene of G_2, *i.e.*, $c_1(i,j) = 1$ and (iv) no gene between $G_2[k]$ and $G_2[\ell]$ is mapped to a gene of G_2, *i.e.*, $c_2(k,\ell) = 1$. The above situation reduces in our model to $d(i,j,k,\ell) = 1$.



66 runs

Figure 4: Graphical representation of ratio $\mathtt{bkp}_M^{\mathbf{opt}}/\mathtt{bkp}_M^H$ under the maximum matching model, for each of the 66 exact results that we have obtained. H is the studied heuristic (*i.e.*, either IILCS_M, HYB_M(2) or HYB_M(3)), $\mathtt{bkp}_M^H$ is the number of breakpoints computed by H and $\mathtt{bkp}_M^{\mathbf{opt}}$ is the minimum number of breakpoints under the maximum matching model.

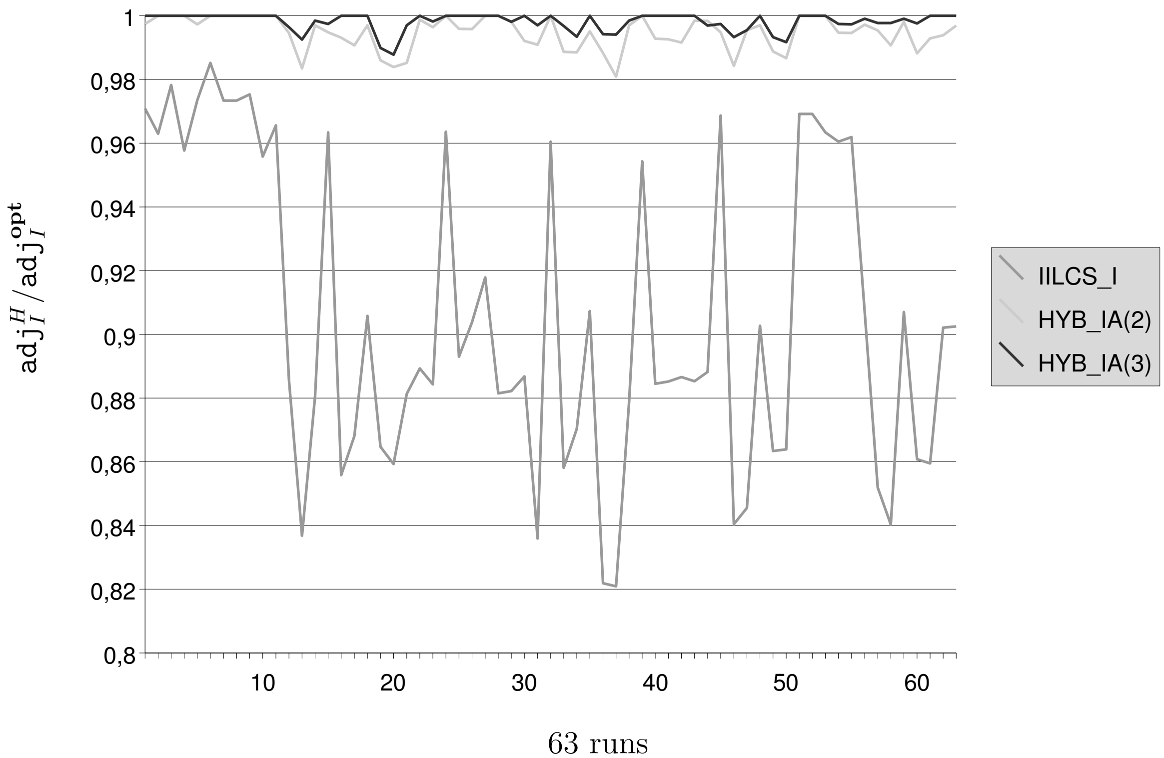


Figure 5: Graphical representation of ratio $\mathtt{adj}_I^H/\mathtt{adj}_I^{\mathbf{opt}}$ under the intermediate model, for each of the 63 exact results that we have obtained. H is the studied heuristic (*i.e.*, either IILCS_IA, HYB_IA(2) or HYB_IA(3)), $\mathtt{adj}_I^H$ is the number of adjacencies computed by H and and $\mathtt{adj}_I^{\mathbf{opt}}$ is the maximum number of adjacencies under the intermediate model.

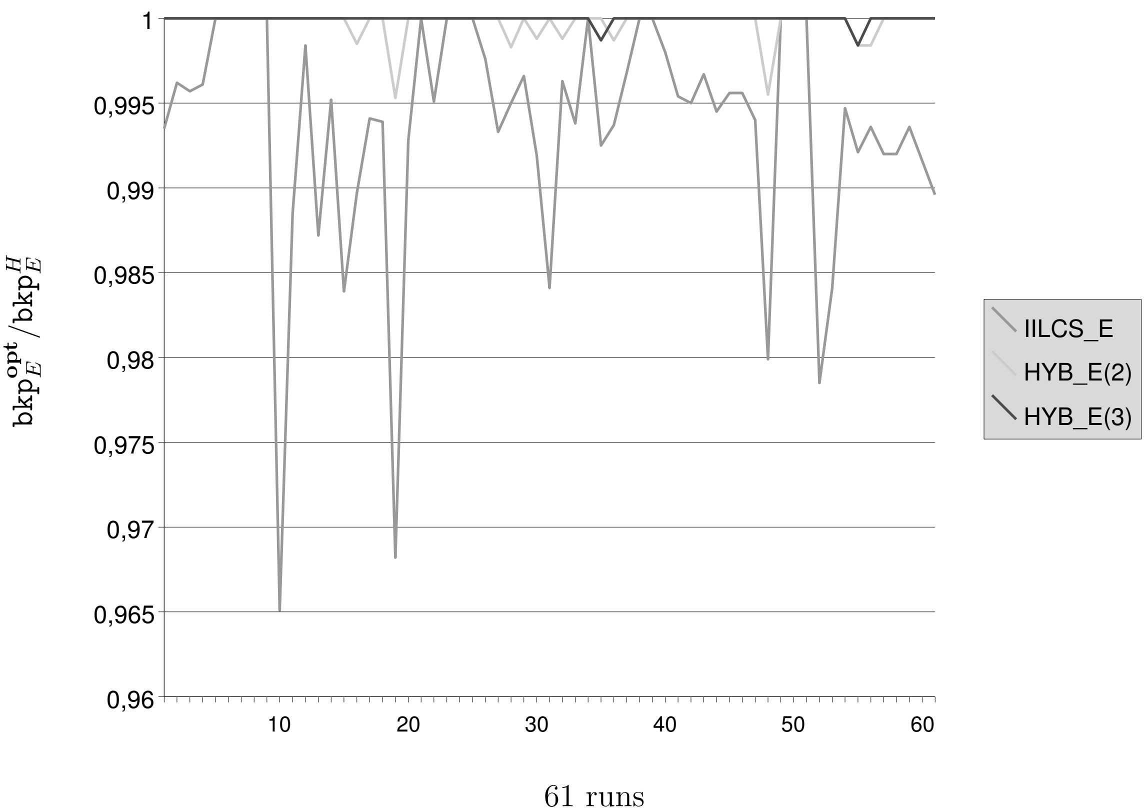


Figure 6: Graphical representation of ratio $\mathtt{bkp}_E^{\mathbf{opt}}/\mathtt{bkp}_E^H$ under the exemplar model, for each of the 61 exact results that we have obtained. H is the studied heuristic (*i.e.*, either `IILCS_E`, `HYB_E(2)` or `HYB_E(3)`), $\mathtt{bkp}_E^H$ is the number of breakpoints computed by H and $\mathtt{bkp}_E^{\mathbf{opt}}$ is the minimum number of breakpoints under the exemplar model.

Genome	Baphi	Ecoli	Haein	Paeru	Pmult	Salty	Wglos	Xaxon	Xcamp	Xfast	Ypest-CO92	Ypest-KIM
Size	565	4119	1975	5474	1981	4157	642	4105	3939	2631	3540	3788

Table 1: Size of genomes before pre-processing

	Baphi	Ecoli	Haein	Paeru	Pmult	Salty	Wglos	Xaxon	Xcamp	Xfast	Ypest-CO92	Ypest-KIM
BAPHI		721	498	709	525	723	382	545	540	460	721	718
ECOLI	531		1227	2088	1370	3279	570	1365	1355	908	2427	2452
HAEIN	434	1490		1307	1403	1514	440	924	900	718	1384	1399
PAERU	470	1889	969		1078	1912	510	1675	1665	984	1776	1785
PMULT	448	1637	1390	1382		1660	465	967	945	748	1517	1537
SALTY	533	3253	1233	2066	1373		569	1365	1352	913	2448	2476
WGLOS	380	769	497	769	533	779		610	603	496	765	763
XAXON	416	1435	794	2005	860	1467	465		3445	1488	1328	1343
XCAMP	416	1437	791	2022	854	1470	464	3455		1470	1308	1321
XFAST	400	1096	711	1289	754	1117	437	1645	1623		1041	1050
Ypest-CO92	530	2536	1189	2014	1327	2566	537	1290	1268	881		3388
Ypest-KIM	523	2537	1185	2011	1323	2574	558	1286	1262	882	3362	

Table 2: Reduced sizes of the genomes for pairwise comparisons under the *exemplar* model. As an illustration, pre-processing the data for comparing `Baphi` with `Ecoli` reduces in two genomes of size 531 (`Baphi`) and 721 (`Ecoli`).

	Baphi	Ecoli	Haein	Paeru	Pmult	Salty	Wglos	Xaxon	Xcamp	Xfast	Ypest-CO92	Ypest-KIM
BAPHI		745	504	733	533	738	389	564	559	465	745	748
ECOLI	535		1254	2129	1395	3320	582	1411	1398	927	2470	2525
HAEIN	437	1529		1338	1431	1540	451	964	939	734	1422	1455
PAERU	473	1931	987		1098	1942	522	1726	1711	1007	1815	1848
PMULT	451	1675	1426	1414		1688	477	1008	985	773	1556	1595
SALTY	537	3310	1263	2107	1399		581	1413	1395	931	2490	2547
WGLOS	381	791	508	800	542	794		639	631	502	792	799
XAXON	419	1476	809	2044	878	1495	477		3539	1522	1364	1395
XCAMP	419	1473	803	2057	869	1494	476	3541		1499	1339	1366
XFAST	403	1122	723	1316	769	1135	449	1697	1679		1073	1091
Ypest-CO92	534	2584	1220	2052	1353	2607	579	1333	1311	901		3473
Ypest-KIM	527	2587	1216	2048	1349	2613	570	1329	1305	902	3422	

Table 3: Reduced sizes of the genomes for pairwise comparisons under the *maximum matching* and *intermediate* models. As an illustration, pre-processing the data for comparing `Baphi` with `Ecoli` reduces in two genomes of size 535 (`Baphi`) and 745 (`Ecoli`).

	OPT_E		OPT_M		OPT_{IA}		OPT_{IB}	
$G_1 - G_2$	adj($\mathcal{M}$)	bkp($\mathcal{M}$)	adj($\mathcal{M}$)	bkp($\mathcal{M}$)	adj($\mathcal{M}$)	bkp($\mathcal{M}$)	adj($\mathcal{M}$)	bkp($\mathcal{M}$)
BAPHI-ECOLI	368	152	377	156	378	154	372	152
BAPHI-HAEIN	157	265	161	270	162	267	158	265
BAPHI-PAERU	226	232	229	240	230	237	227	232
BAPHI-PMULT	182	254	188	259	189	256	184	254
BAPHI-SALTY	367	154	376	158	377	155	372	154
BAPHI-WGLOS	201	168	203	170	203	168	201	168
BAPHI-XAXON	183	222	188	226	188	223	184	222
BAPHI-XCAMP	183	222	188	226	188	223	183	222
BAPHI-XFAST	158	231	162	236	162	234	158	231
BAPHI-YPEST-CO92	352	166	361	170	362	167	355	166
BAPHI-YPEST-KIM	339	172	348	176	349	172	343	172
ECOLI-HAEIN	489	610	550	665	551	624	507	610
ECOLI-PAERU	570	847	651	1082	668	906	597	847
ECOLI-PMULT	593	622	662	703	670	647	612	622
ECOLI-SALTY	X	X	2875	277	X	X	X	X
ECOLI-WGLOS	371	183	379	194	382	187	374	183
ECOLI-XAXON	380	675	425	842	437	718	390	675
ECOLI-XCAMP	378	678	420	845	432	717	386	678
ECOLI-XFAST	301	491	324	564	329	503	308	491
ECOLI-YPEST-CO92	1559	426	1744	596	1789	463	X	426
ECOLI-YPEST-KIM	X	X	1747	607	1798	464	X	X
HAEIN-PAERU	301	550	333	615	337	567	309	550
HAEIN-PMULT	755	497	849	525	849	509	794	497
HAEIN-SALTY	492	612	550	676	553	635	515	612
HAEIN-WGLOS	159	267	165	277	165	271	163	267
HAEIN-XAXON	217	473	241	533	243	482	221	473
HAEIN-XCAMP	216	473	238	530	239	485	218	473
HAEIN-XFAST	191	424	205	468	207	440	194	424
HAEIN-YPEST-CO92	465	597	522	649	523	617	481	597
HAEIN-YPEST-KIM	460	598	517	653	518	622	479	598
PAERU-PMULT	340	592	373	681	380	627	347	592
PAERU-SALTY	559	862	644	1091	658	918	585	862
PAERU-WGLOS	246	248	251	260	253	249	249	248
PAERU-XAXON	536	802	610	1016	620	863	562	802
PAERU-XCAMP	536	801	597	1012	609	847	557	801
PAERU-XFAST	372	499	406	572	410	522	389	499
PAERU-YPEST-CO92	571	790	671	990	685	853	604	790
PAERU-YPEST-KIM	566	786	662	1004	681	855	598	786
PMULT-SALTY	597	622	670	704	677	650	620	622
PMULT-WGLOS	188	262	197	270	197	265	190	262
PMULT-XAXON	245	495	274	557	277	506	248	495
PMULT-XCAMP	241	495	267	555	270	507	245	495
PMULT-XFAST	213	436	234	481	238	451	221	436
PMULT-YPEST-CO92	582	597	648	671	654	621	602	597
PMULT-YPEST-KIM	574	601	639	676	644	631	588	601
SALTY-WGLOS	372	181	380	192	383	185	376	181
SALTY-XAXON	375	684	434	854	445	718	391	684
SALTY-XCAMP	375	684	427	854	440	716	389	684
SALTY-XFAST	300	497	325	569	329	509	310	497
SALTY-YPEST-CO92	1560	439	1758	591	1793	483	X	439
SALTY-YPEST-KIM	X	X	1761	606	1800	477	X	X
WGLOS-XAXON	189	261	194	269	195	266	189	261
WGLOS-XCAMP	189	260	194	268	195	266	189	260
WGLOS-XFAST	158	264	163	272	164	267	160	264
WGLOS-YPEST-CO92	369	182	377	193	380	186	373	182
WGLOS-YPEST-KIM	356	186	364	197	367	187	361	186
XAXON-XCAMP	X	X	3257	181	X	X	X	X
XAXON-XFAST	980	375	1076	400	1077	380	1026	375
XAXON-YPEST-CO92	372	624	420	760	432	654	386	624
XAXON-YPEST-KIM	368	624	422	760	432	661	385	624
XCAMP-XFAST	969	373	1061	404	1065	383	1005	373
XCAMP-YPEST-CO92	369	620	412	755	424	644	380	620
XCAMP-YPEST-KIM	365	618	412	749	420	655	379	618
XFAST-YPEST-CO92	298	473	323	542	327	485	306	473
XFAST-YPEST-KIM	292	477	315	545	318	487	298	477
YPEST-CO92-YPEST-KIM	X	X	3328	59	X	X	X	X

Table 4: Number of adjacencies $\mathtt{adj}(\mathcal{M})$ and number of breakpoints $\mathtt{bkp}(\mathcal{M})$ for problems $\mathbf{opt}_{\mathrm{E}}$, $\mathbf{opt}_{\mathrm{M}}$, $\mathbf{opt}_{\mathrm{IA}}$ and $\mathbf{opt}_{\mathrm{IB}}$. $\mathcal{M}$ always denotes the returned solution and X stands for the unsolved cases.

	$\mathtt{adj}_I^{\mathbf{opt}}$	$\mathtt{adj}(\mathcal{M}_{I,\mathtt{bkp}}^{\mathbf{opt}})$	$\mathtt{bkp}(\mathcal{M}_{I,\mathtt{adj}}^{\mathbf{opt}})$	$\mathtt{bkp}_I^{\mathbf{opt}}$
$\mathtt{adj}_E^{\mathbf{opt}}$	**1.10**	**1.02**	-	-
$\mathtt{adj}_M^{\mathbf{opt}}$	**1.01**	0.95	-	-
$\mathtt{bkp}_E^{\mathbf{opt}}$	-	-	1.03	**1.00**
$\mathtt{bkp}_M^{\mathbf{opt}}$	-	-	**0.92**	**0.90**

Table 5: Comparison of the results for $\mathtt{adj}_I^{\mathbf{opt}}$: maximum number of adjacencies for the intermediate model, $\mathtt{adj}(\mathcal{M}_{I,\mathtt{bkp}}^{\mathbf{opt}})$: number of adjacencies induced by a matching $\mathcal{M}_{I,\mathtt{bkp}}^{\mathbf{opt}}$ yielding the minimum number of breakpoints for the intermediate model, $\mathtt{bkp}(\mathcal{M}_{I,\mathtt{adj}}^{\mathbf{opt}})$: number of breakpoints induced by a matching $\mathcal{M}_{I,\mathtt{adj}}^{\mathbf{opt}}$ yielding the maximum number of adjacencies for the intermediate model, $\mathtt{bkp}_I^{\mathbf{opt}}$: minimum number of breakpoints the intermediate model, $\mathtt{adj}_E^{\mathbf{opt}}$: maximum number of adjacencies for the exemplar model, $\mathtt{adj}_M^{\mathbf{opt}}$: maximum number of adjacencies for the maximum matching model, $\mathtt{bkp}_E^{\mathbf{opt}}$: minimum number of breakpoints for the exemplar model, $\mathtt{bkp}_M^{\mathbf{opt}}$: minimum number of breakpoints for the maximum matching model. Bold values indicate cases where the intermediate model performs better than the exemplar or maximum matching model. Shown here are the average ratios, *e.g.*, $\frac{\mathtt{adj}_I^{\mathbf{opt}}}{\mathtt{adj}_E^{\mathbf{opt}}} = 1.10$, and hence, on average, the number of adjacencies for the exemplar model is about $1/1.10 = 90\%$ of the number of adjacencies achieved by the intermediate model.

	$\mathtt{adj}_I^{\mathbf{opt}}$	$\mathtt{adj}(\mathcal{M}_{I,\mathtt{bkp}}^{\mathbf{opt}})$	$\mathtt{bkp}(\mathcal{M}_{I,\mathtt{adj}}^{\mathbf{opt}})$	$\mathtt{bkp}_I^{\mathbf{opt}}$
$\mathtt{adj}_E^{\mathbf{opt}}$	0%	9%	-	-
$\mathtt{adj}_M^{\mathbf{opt}}$	11%	0%	-	-
$\mathtt{bkp}_E^{\mathbf{opt}}$	-	-	3%	100%
$\mathtt{bkp}_M^{\mathbf{opt}}$	-	-	0%	0%

Table 6: Shown here is the percentage that the same optimal measure (maximum number of adjacencies and minimum number of breakpoints) is found for the intermediate models and the two other models (exemplar and maximum matching). For example, for 5 out of 58 pairs of genomes *i.e.*, 9%, it holds that $\mathtt{adj}_E^{\mathbf{opt}} = \mathtt{adj}(\mathcal{M}_{I,\mathtt{bkp}}^{\mathbf{opt}})$ (see Table 5).

	Exemplar - $\texttt{adj}_E^{\texttt{opt}}$			Intermediate - $\texttt{adj}_I^{\texttt{opt}}$			Maximum matching - $\texttt{adj}_M^{\texttt{opt}}$		
Heuristic	IILCS_E	HYB_E(2)	HYB_E(3)	IILCS_IA	HYB_IA(2)	HYB_IA(3)	IILCS_M	HYB_M(2)	HYB_M(3)
Average	99.36%	99.97%	99.99%	90.56%	99.48%	99.82%	99.00%	99.89%	99.97%
Worst case	96.51%	99.53%	99.84%	82.09%	98.09%	98.78%	95.19%	99.50%	99.67%
Best case	100%	100%	100%	98.52%	100%	100%	100%	100%	100%
Number of instances for which the exact result is obtained	15	52 (out of 66)	59	0	17 (out of 63)	35	12	35 (out of 61)	55

Table 7: Summary of the results for the nine studied heuristics and comparison to the exact results. As an illustration, in the intermediate model, HYB_IA(2) provides results that are on average 99.48% of the optimal number of breakpoints, ranging from 98.09% to 100%. Moreover, in 17 out 63 of the cases solved by our 0–1 linear program, HYB_IA(2) returns the optimal value.

	OPT$_M$		IILCS_M		HYB_M(2)		HYB_M(3)	
$G_1 - G_2$	adj($\mathcal{M}$)	bkp($\mathcal{M}$)	adj($\mathcal{M}$)	bkp($\mathcal{M}$)	adj($\mathcal{M}$)	bkp($\mathcal{M}$)	adj($\mathcal{M}$)	bkp($\mathcal{M}$)
BAPHI-ECOLI	377	156	376	157	377	156	377	156
BAPHI-HAEIN	161	270	161	270	161	270	161	270
BAPHI-PAERU	229	240	228	241	229	240	229	240
BAPHI-PMULT	188	259	188	259	188	259	188	259
BAPHI-SALTY	376	158	376	158	376	158	376	158
BAPHI-WGLOS	203	170	202	171	203	170	203	170
BAPHI-XAXON	188	226	188	226	188	226	188	226
BAPHI-XCAMP	188	226	188	226	188	226	188	226
BAPHI-XFAST	162	236	162	236	162	236	162	236
BAPHI-YPEST-CO92	361	170	355	176	361	170	361	170
BAPHI-YPEST-KIM	348	176	346	178	348	176	348	176
ECOLI-HAEIN	550	665	546	669	548	667	549	666
ECOLI-PAERU	651	1082	637	1096	648	1085	650	1083
ECOLI-PMULT	662	703	660	705	662	703	662	703
ECOLI-SALTY	2875	277	2861	291	2875	277	2875	277
ECOLI-WGLOS	379	194	377	196	379	194	379	194
ECOLI-XAXON	425	842	417	850	424	843	425	842
ECOLI-XCAMP	420	845	413	852	418	847	420	845
ECOLI-XFAST	324	564	319	569	323	565	324	564
ECOLI-YPEST-CO92	1744	596	1722	618	1742	598	1743	597
ECOLI-YPEST-KIM	1747	607	1724	630	1745	609	1745	609
HAEIN-PAERU	333	615	328	620	332	616	333	615
HAEIN-PMULT	849	525	845	529	848	526	849	525
HAEIN-SALTY	550	676	547	679	550	676	550	676
HAEIN-WGLOS	165	277	165	277	165	277	165	277
HAEIN-XAXON	241	533	240	534	241	533	241	533
HAEIN-XCAMP	238	530	237	531	238	530	238	530
HAEIN-XFAST	205	468	205	468	205	468	205	468
HAEIN-YPEST-CO92	522	649	516	655	522	649	522	649
HAEIN-YPEST-KIM	517	653	510	660	516	654	516	654
PAERU-PMULT	373	681	369	685	372	682	373	681
PAERU-SALTY	644	1091	632	1103	642	1093	644	1091
PAERU-WGLOS	251	260	248	263	251	260	251	260
PAERU-XAXON	610	1016	604	1022	608	1018	610	1016
PAERU-XCAMP	597	1012	586	1023	594	1015	595	1014
PAERU-XFAST	406	572	402	576	406	572	406	572
PAERU-YPEST-CO92	671	990	655	1006	669	992	671	990
PAERU-YPEST-KIM	662	1004	646	1020	660	1006	662	1004
PMULT-SALTY	670	704	668	706	669	705	670	704
PMULT-WGLOS	197	270	197	270	197	270	197	270
PMULT-XAXON	274	557	271	560	273	558	274	557
PMULT-XCAMP	267	555	263	559	267	555	267	555
PMULT-XFAST	234	481	233	482	233	482	234	481
PMULT-YPEST-CO92	648	671	641	678	648	671	647	672
PMULT-YPEST-KIM	639	676	630	685	637	678	637	678
SALTY-WGLOS	380	192	378	194	380	192	380	192
SALTY-XAXON	434	854	423	865	432	856	433	855
SALTY-XCAMP	427	854	419	862	425	856	425	856
SALTY-XFAST	325	569	324	570	324	570	325	569
SALTY-YPEST-CO92	1758	591	1743	606	1757	592	1758	591
SALTY-YPEST-KIM	1761	606	1737	630	1758	609	1759	608
WGLOS-XAXON	194	269	194	269	194	269	194	269
WGLOS-XCAMP	194	268	193	269	194	268	194	268
WGLOS-XFAST	163	272	163	272	163	272	163	272
WGLOS-YPEST-CO92	377	193	373	197	377	193	377	193
WGLOS-YPEST-KIM	364	197	361	200	364	197	364	197
XAXON-XCAMP	3257	181	3253	185	3257	181	3257	181
XAXON-XFAST	1076	400	1070	406	1074	402	1076	400
XAXON-YPEST-CO92	420	760	412	768	419	761	420	760
XAXON-YPEST-KIM	422	760	417	765	422	760	422	760
XCAMP-XFAST	1061	404	1056	409	1059	406	1061	404
XCAMP-YPEST-CO92	412	755	402	765	412	755	412	755
XCAMP-YPEST-KIM	412	749	403	758	410	751	412	749
XFAST-YPEST-CO92	323	542	315	550	321	544	323	542
XFAST-YPEST-KIM	315	545	309	551	314	546	315	545
YPEST-CO92-YPEST-KIM	3328	59	3328	59	3328	59	3328	59

Table 8: Number of adjacencies adj($\mathcal{M}$) and number of breakpoints bkp($\mathcal{M}$) under the maximum matching model: exact results and results obtained by heuristics IILCS_M, HYB_M(2) and HYB_M(3). $\mathcal{M}$ is a maximum matching between the genomes G_1 and G_2.

	OPT_{IA}		IILCS_IA		HYB_IA(2)		HYB_IA(3)	
$G_1 - G_2$	adj($\mathcal{M}$)	bkp($\mathcal{M}$)	adj($\mathcal{M}$)	bkp($\mathcal{M}$)	adj($\mathcal{M}$)	bkp($\mathcal{M}$)	adj($\mathcal{M}$)	bkp($\mathcal{M}$)
BAPHI-ECOLI	378	154	367	153	377	156	378	154
BAPHI-HAEIN	162	267	156	266	162	268	162	266
BAPHI-PAERU	230	237	225	233	230	235	230	237
BAPHI-PMULT	189	256	181	255	189	257	189	255
BAPHI-SALTY	377	155	367	154	376	158	377	156
BAPHI-WGLOS	203	168	200	169	203	169	203	169
BAPHI-XAXON	188	223	183	222	188	225	188	224
BAPHI-XCAMP	188	223	183	222	188	225	188	223
BAPHI-XFAST	162	234	158	231	162	235	162	234
BAPHI-YPEST-CO92	362	167	346	172	362	168	362	168
BAPHI-YPEST-KIM	349	172	337	174	349	173	349	174
ECOLI-HAEIN	551	624	488	611	548	644	549	645
ECOLI-PAERU	668	906	559	858	657	911	663	913
ECOLI-PMULT	670	647	590	625	668	664	669	651
ECOLI-SALTY	X	X	2464	154	2882	247	2889	240
ECOLI-WGLOS	382	187	368	186	380	191	381	190
ECOLI-XAXON	437	718	374	681	434	723	437	715
ECOLI-XCAMP	432	717	375	681	428	720	432	724
ECOLI-XFAST	329	503	298	494	328	511	329	508
ECOLI-YPEST-CO92	1789	463	1547	438	1764	518	1771	506
ECOLI-YPEST-KIM	1798	464	1545	437	1769	523	1776	503
HAEIN-PAERU	337	567	297	554	332	575	336	571
HAEIN-PMULT	849	509	755	497	848	517	849	515
HAEIN-SALTY	553	635	489	615	551	648	552	649
HAEIN-WGLOS	165	271	159	267	165	273	165	272
HAEIN-XAXON	243	482	217	473	242	488	243	505
HAEIN-XCAMP	239	485	216	473	238	488	239	502
HAEIN-XFAST	207	440	190	425	207	436	207	438
HAEIN-YPEST-CO92	523	617	461	601	523	627	523	633
HAEIN-YPEST-KIM	518	622	457	601	517	628	517	620
PAERU-PMULT	380	627	337	595	377	620	380	620
PAERU-SALTY	658	918	550	871	652	931	656	922
PAERU-WGLOS	253	249	243	251	253	251	253	251
PAERU-XAXON	620	863	532	806	613	876	618	866
PAERU-XCAMP	609	847	530	807	602	864	605	861
PAERU-XFAST	410	522	372	499	408	524	410	515
PAERU-YPEST-CO92	685	853	563	798	677	854	681	857
PAERU-YPEST-KIM	681	855	559	793	668	850	677	846
PMULT-SALTY	677	650	595	624	675	665	676	664
PMULT-WGLOS	197	265	188	262	197	267	197	267
PMULT-XAXON	277	506	245	495	275	514	277	523
PMULT-XCAMP	270	507	239	497	268	511	270	531
PMULT-XFAST	238	451	211	438	236	447	238	453
PMULT-YPEST-CO92	654	621	579	600	653	635	654	646
PMULT-YPEST-KIM	644	631	572	603	643	641	642	630
SALTY-WGLOS	383	185	371	182	381	189	382	188
SALTY-XAXON	445	718	374	686	438	726	442	724
SALTY-XCAMP	440	716	372	687	438	724	438	715
SALTY-XFAST	329	509	297	500	328	516	329	511
SALTY-YPEST-CO92	1793	483	1548	451	1773	526	1781	512
SALTY-YPEST-KIM	1800	477	1555	446	1776	528	1785	515
WGLOS-XAXON	195	266	189	261	195	263	195	265
WGLOS-XCAMP	195	266	189	260	195	262	195	265
WGLOS-XFAST	164	267	158	264	164	267	164	266
WGLOS-YPEST-CO92	380	186	365	186	378	190	379	188
WGLOS-YPEST-KIM	367	187	353	189	365	194	366	192
XAXON-XCAMP	X	X	2877	117	3270	157	3271	154
XAXON-XFAST	1077	380	977	378	1074	394	1076	396
XAXON-YPEST-CO92	432	654	368	628	430	664	431	661
XAXON-YPEST-KIM	432	661	363	629	428	667	431	664
XCAMP-XFAST	1065	383	966	376	1063	393	1064	394
XCAMP-YPEST-CO92	424	644	365	624	419	657	423	651
XCAMP-YPEST-KIM	420	655	361	622	417	656	420	655
XFAST-YPEST-CO92	327	485	295	476	325	489	327	491
XFAST-YPEST-KIM	318	487	287	482	317	494	318	495
YPEST-CO92-YPEST-KIM	X	X	2815	32	3330	56	3330	56

Table 9: Number of adjacencies adj($\mathcal{M}$) and number of breakpoints bkp($\mathcal{M}$) under the intermediate model: exact results when we maximize the number of adjacencies and results obtained by heuristics IILCS_IA, HYB_IA(2) and HYB_IA(3). $\mathcal{M}$ is an intermediate matching between the genomes G_1 and G_2. X stands for the unsolved cases.

	OPT_E		IILCS_E		HYB_E(2)		HYB_E(3)	
$G_1 - G_2$	adj($\mathcal{M}$)	bkp($\mathcal{M}$)	adj($\mathcal{M}$)	bkp($\mathcal{M}$)	adj($\mathcal{M}$)	bkp($\mathcal{M}$)	adj($\mathcal{M}$)	bkp($\mathcal{M}$)
BAPHI-ECOLI	368	152	367	153	368	152	368	152
BAPHI-HAEIN	157	265	156	266	157	265	157	265
BAPHI-PAERU	226	232	225	233	226	232	226	232
BAPHI-PMULT	182	254	181	255	182	254	182	254
BAPHI-SALTY	367	154	367	154	367	154	367	154
BAPHI-WGLOS	201	168	201	168	201	168	201	168
BAPHI-XAXON	183	222	183	222	183	222	183	222
BAPHI-XCAMP	183	222	183	222	183	222	183	222
BAPHI-XFAST	158	231	158	231	158	231	158	231
BAPHI-YPEST-CO92	352	166	346	172	352	166	352	166
BAPHI-YPEST-KIM	339	172	337	174	339	172	339	172
ECOLI-HAEIN	489	610	488	611	489	610	489	610
ECOLI-PAERU	570	847	559	858	570	847	570	847
ECOLI-PMULT	593	622	590	625	593	622	593	622
ECOLI-SALTY	X	X	2464	154	2465	153	2465	153
ECOLI-WGLOS	371	183	368	186	371	183	371	183
ECOLI-XAXON	380	675	373	682	379	676	380	675
ECOLI-XCAMP	378	678	374	682	378	678	378	678
ECOLI-XFAST	301	491	298	494	301	491	301	491
ECOLI-YPEST-CO92	1559	426	1545	440	1557	428	1559	426
ECOLI-YPEST-KIM	X	X	1543	439	1559	423	1560	422
HAEIN-PAERU	301	550	297	554	301	550	301	550
HAEIN-PMULT	755	497	755	497	755	497	755	497
HAEIN-SALTY	492	612	489	615	492	612	492	612
HAEIN-WGLOS	159	267	159	267	159	267	159	267
HAEIN-XAXON	217	473	217	473	217	473	217	473
HAEIN-XCAMP	216	473	216	473	216	473	216	473
HAEIN-XFAST	191	424	190	425	191	424	191	424
HAEIN-YPEST-CO92	465	597	461	601	465	597	465	597
HAEIN-YPEST-KIM	460	598	457	601	459	599	460	598
PAERU-PMULT	340	592	338	594	340	592	340	592
PAERU-SALTY	559	862	552	869	558	863	559	862
PAERU-WGLOS	246	248	242	252	246	248	246	248
PAERU-XAXON	536	802	533	805	535	803	536	802
PAERU-XCAMP	536	801	531	806	536	801	536	801
PAERU-XFAST	372	499	372	499	372	499	372	499
PAERU-YPEST-CO92	571	790	565	796	571	790	570	791
PAERU-YPEST-KIM	566	786	561	791	565	787	566	786
PMULT-SALTY	597	622	595	624	597	622	597	622
PMULT-WGLOS	188	262	188	262	188	262	188	262
PMULT-XAXON	245	495	245	495	245	495	245	495
PMULT-XCAMP	241	495	240	496	241	495	241	495
PMULT-XFAST	213	436	211	438	213	436	213	436
PMULT-YPEST-CO92	582	597	579	600	582	597	582	597
PMULT-YPEST-KIM	574	601	572	603	574	601	574	601
SALTY-WGLOS	372	181	371	182	372	181	372	181
SALTY-XAXON	375	684	373	687	376	684	376	684
SALTY-XCAMP	375	684	372	687	375	684	375	684
SALTY-XFAST	300	497	297	500	300	497	300	497
SALTY-YPEST-CO92	1560	439	1551	448	1558	441	1560	439
SALTY-YPEST-KIM	X	X	1553	448	1561	440	1562	439
WGLOS-XAXON	189	261	189	261	189	261	189	261
WGLOS-XCAMP	189	260	189	260	189	260	189	260
WGLOS-XFAST	158	264	158	264	158	264	158	264
WGLOS-YPEST-CO92	369	182	365	186	369	182	369	182
WGLOS-YPEST-KIM	356	186	353	189	356	186	356	186
XAXON-XCAMP	X	X	2878	116	2879	115	2879	115
XAXON-XFAST	980	375	978	377	980	375	980	375
XAXON-YPEST-CO92	372	624	367	629	371	625	371	625
XAXON-YPEST-KIM	368	624	364	628	367	625	368	624
XCAMP-XFAST	969	373	966	376	969	373	969	373
XCAMP-YPEST-CO92	369	620	364	625	369	620	369	620
XCAMP-YPEST-KIM	365	618	361	622	365	618	365	618
XFAST-YPEST-CO92	298	473	294	477	298	473	298	473
XFAST-YPEST-KIM	292	477	287	482	292	477	292	477
YPEST-CO92-YPEST-KIM	X	X	2815	32	2815	32	2815	32

Table 10: Number of adjacencies adj($\mathcal{M}$) and number of breakpoints bkp($\mathcal{M}$) under the exemplar model: exact results and results obtained by heuristics IILCS_E, HYB_E(2) and HYB_E(3). $\mathcal{M}$ is an exemplar matching between the genomes G_1 and G_2. X stands for the unsolved cases.