

A Pseudo-Boolean programming approach for computing the breakpoint distance between two genomes with duplicate genes

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of the most common rearrangement operations is reversals, which reverse the order of a subset of neighboring genes) [11]. The second one consists in computing a (dis-)similarity measure based on the gene order and most common rearrangement operations [15,8,4,1]. We focus in this paper on the latter approach.

Several similarity (or dissimilarity) measures between two whole genomes have been recently proposed, such as the number of breakpoints [15,8,4], the number of reversals [8,11], the number of conserved intervals [6], the number of common intervals [7], the Maximum Adjacency Disruption Number (MAD) [16], *etc.* However, in the presence of duplications and for each of the above measures, one has first to disambiguate the data by inferring orthologs, *i.e.*, a non-ambiguous mapping between the genes of the two genomes. Up to now, two extremal approaches have been considered : the *exemplar* model and the *maximum matching* model. In the *exemplar* model [15], for all gene families, all but one occurrence in each genome is deleted. In the *maximum matching* model [4,10], 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, whatever the considered model (*exemplar* or *maximum matching*), the problem becomes **NP**-complete as soon as duplicates are present in genomes [8,4,6,10] ; a few inapproximability results are known for some special cases. Therefore, several heuristic methods have been recently devised to obtain (hopefully) good solutions in a reasonable amount of time [5,7]. However, while it is relatively easy to compare heuristics between them, until now very little is known about the absolute accuracy of these heuristics. Therefore, there is a great need for algorithmic approaches that compute exact solutions for these genomic distances.

Extending research initiated in [2], we propose in this paper a novel generic pseudo-boolean approach for computing the exact breakpoint distance between two genomes in presence of duplications for both the *exemplar* and *maximum matching* methods. Furthermore, we show strong evidence that a fast and simple heuristic based on iteratively finding longest common subsequences provides very good results on our dataset of γ -Proteobacteria.

This paper is organized as follows. In Section 2, we present some preliminaries and definitions. We focus in Section 3 on the problem of finding the minimum number of breakpoints under the two models and we give a pseudo-boolean program together with some reduction rules. Section 4 is devoted to experimental results on a dataset of γ -Proteobacteria.

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 of the genes. We represent the order and directions of the genes on each genome as a sequence of signed

elements, *i.e.*, elements with signs “+” and “-”. Let G_0 and G_1 be two genomes. For each $x \in \{0, 1\}$, we denote the label at position i in G_x

3 An exact algorithm

3.1 Pseudo-boolean problem

Minimizing the number of breakpoints between two genomes with duplications is an **NP**-hard problem under the *exemplar* model even when $\text{occ}_0(\mathbf{g}) = 1$ for all genes \mathbf{g} in G_0 and $\text{occ}_1(\mathbf{g}) \leq 2$ for all genes \mathbf{g} in G_1 [8]. Consequently, the NP-hardness also holds under the *maximum matching* model.

The exact algorithms we define in this section attempt to take advantage of the existing solvers, and more precisely of the linear pseudo-boolean solvers, which are a generalization of the SAT solvers. To this end, we have to express our problem (with its two variants, according to the *exemplar* or *maximum matching* model) as a linear pseudo-boolean problem (or LPB problem), *i.e.* as a linear program [17] whose variables take 0 or 1 values. A number of generalizations of SAT solvers to LPB solvers have been proposed (Pueblo [18], Galena [9], OPBDP [3] and more). We decided to use for our tests the `minisat+` LPB solver [12] because of its good results during PB evaluation 2005 (special track of the SAT COMPETITION 2005).

Instead of directly writing a program that minimizes the number of breakpoints, we chose to write the complementary program which consists in maximizing the number of adjacencies between the two given genomes. There are two reasons for this choice. First, the constraints are simpler and less numerous in this latter case ; moreover, experimental tests moreover showed that the running time of our program is noticeably better by focusing on adjacencies. Second, it is easy to notice that minimizing the number of breakpoints and maximizing the number of adjacencies are equivalent problems under both the *exemplar* and *maximum matching* models. Indeed, according to the above notations, given a matching \mathcal{M} between two genomes G_0 and G_1 we have:

$$B_{\mathcal{M}}(G_0, G_1) + A_{\mathcal{M}}(G_0, G_1) = |\mathcal{M}| - 1. \quad (1)$$

For the *exemplar* and *maximum matching* models, all the matchings \mathcal{M} satisfying the model have the same size, and hence $B_{\mathcal{M}}(G_0, G_1) + A_{\mathcal{M}}(G_0, G_1)$ is a constant. Therefore, maximizing $A_{\mathcal{M}}(G_0, G_1)$ is equivalent to minimizing $B_{\mathcal{M}}(G_0, G_1)$.

3.2 Maximizing the number of adjacencies

The LPB program we propose considers two genomes with duplications and performs an \mathcal{M} -pruning which maximizes the number of adjacencies according to a specified model (*exemplar* or *maximum matching*). As discussed above, the resulting matching also minimizes the number of breakpoints between the two genomes. The LPB program, **Program Breakpoint-Maximum-Matching**, for the *maximum matching* model is given in Figure 1. The *exemplar* variant is easily obtained by performing only a few changes that are discussed subsequently.

Program Breakpoint-Maximum-Matching

Objective :

$$\text{Maximize } \sum_{0 \leq i < n_0} \sum_{i < j \leq n_0} \sum_{0 \leq k < n_1} \sum_{k < \ell \leq n_1} d(i, j, k, \ell)$$

Constraints :

$$(C.01) \quad \forall 1 \leq i \leq n_0, \quad \sum_{\substack{1 \leq k \leq n_1 \\ |G_0[i]| = |G_1[k]|}} a(i, k) = b_0(i)$$

$$\forall 1 \leq k \leq n_1, \quad \sum_{\substack{1 \leq i \leq n_0 \\ |G_0[i]| = |G_1[k]|}} a(i, k) = b_1(k)$$

$$(C.02) \quad \forall 0 \leq x \leq 1, \forall \mathbf{g} \in \mathcal{G}, \quad \sum_{\substack{1 \leq i \leq n_x \\ |G_x[i]| = |\mathbf{g}|}} b_x(i) = \min(\text{occo}(\mathbf{g}), \text{occ}_1(\mathbf{g}))$$

$$(C.03) \quad \forall 0 \leq x \leq 1, \forall 1 \leq i \leq j-1 < n_x, c_x(i, j) + \sum_{i < p < j} b_x(p) \geq 1$$

$$(C.04) \quad \forall 0 \leq x \leq 1, \forall 1 \leq i < p < j \leq n_x, c_x(i, j) + b_x(p) \leq 1$$

$$(C.05) \quad \forall 1 \leq i < j \leq n_0, \forall 1 \leq k < \ell \leq n_1, \\ \text{such that } G_0[i] = G_1[k] \text{ and } G_0[j] = G_1[\ell], \\ a(i, k) + a(j, \ell) + c_0(i, j) + c_1(k, \ell) - d(i, j, k, \ell) \leq 3$$

$$(C.06) \quad \forall 1 \leq i < j \leq n_0, \forall 1 \leq k < \ell \leq n_1, \\ \text{such that } G_0[i] = G_1[k] \text{ and } G_0[j] = G_1[\ell], \\ a(i, k) - d(i, j, k, \ell) \geq 0 \\ a(j, \ell) - d(i, j, k, \ell) \geq 0 \\ c_0(i, j) - d(i, j, k, \ell) \geq 0 \\ c_1(k, \ell) - d(i, j, k, \ell) \geq 0$$

$$(C.07) \quad \forall 1 \leq i < j \leq n_0, \forall 1 \leq k < \ell \leq n_1, \\ \text{such that } G_0[i] = -G_1[\ell] \text{ and } G_0[j] = -G_1[k], \\ a(i, \ell) + a(j, k) + c_0(i, j) + c_1(k, \ell) - d(i, j, k, \ell) \leq 3$$

$$(C.08) \quad \forall 1 \leq i < j \leq n_0, \forall 1 \leq k < \ell \leq n_1, \\ \text{such that } G_0[i] = -G_1[\ell] \text{ and } G_0[j] = -G_1[k], \\ a(i, \ell) - d(i, j, k, \ell) \geq 0 \\ a(j, k) - d(i, j, k, \ell) \geq 0 \\ c_0(i, j) - d(i, j, k, \ell) \geq 0 \\ c_1(k, \ell) - d(i, j, k, \ell) \geq 0$$

$$(C.09) \quad \forall 1 \leq i < j \leq n_0, \forall 1 \leq k < \ell \leq n_1, \\ \text{such that } \{|G_0[i]|, |G_0[j]|\} \neq \{|G_1[k]|, |G_1[\ell]|\} \text{ or } G_0[i] - G_0[j] \neq G_1[k] - G_1[\ell], \\ d(i, j, k, \ell) = 0$$

$$(C.10) \quad \forall 1 \leq i < j \leq n_0, \\ \sum_{1 \leq k < n_1} \sum_{k < \ell \leq n_1} d(i, j, k, \ell) \leq 1$$

Domains :

$$\forall x \in \{0, 1\}, \forall 1 \leq i < j \leq n_0, \forall 1 \leq k < \ell \leq n_1, \\ a(i, k), b_x(i), c_x(i, k), d(i, j, k, \ell) \in \{0, 1\}$$

Fig. 1. Program Breakpoint-Maximum-Matching for finding the maximum number of adjacencies between two genomes under the *maximum matching* model.

Program **Breakpoint-Maximum-Matching** considers two genomes G_0 and G_1 of respective lengths n_0 and n_1 . The objective function, the variables and the constraints are briefly discussed hereafter.

Variables:

- Variables $a(i, k)$, $1 \leq i \leq n_0$ and $1 \leq k \leq n_1$, define a matching \mathcal{M} : $a_{i,k} = 1$ if and only if the gene at position i in G_0 is matched with the gene at position k in G_1 in \mathcal{M} .
- Variables $b_x(i)$, $x \in \{0, 1\}$ and $1 \leq i \leq n_x$, represent the \mathcal{M} -saturated genes: $b_x(i) = 1$ if and only if the gene at position i in G_x is saturated by the matching \mathcal{M} . Clearly, $\sum_{1 \leq i \leq n_0} b_0(i) = \sum_{1 \leq k \leq n_1} b_1(k)$, and this is precisely the size of the matching \mathcal{M} .
- Variables $c_x(i, j)$, $x \in \{0, 1\}$ and $1 \leq i < j \leq n_x$, represent *consecutive genes* according to the matching \mathcal{M} : $c_x(i, j) = 1$ if and only if the genes at positions i, j in G_x are saturated by \mathcal{M} and no gene at position p , $i < p < j$, is saturated by \mathcal{M} .
- Variables $d(i, j, k, \ell)$, $1 \leq i < j \leq n_0$ and $1 \leq k < \ell \leq n_1$, represent *adjacencies* according to the matching \mathcal{M} : $d(i, j, k, \ell) = 1$ if and only if (i) either $(G_0[i], G_1[k])$ and $(G_0[j], G_1[\ell])$ are two edges of \mathcal{M} , or $(G_0[i], G_1[\ell])$ and $(G_0[j], G_1[k])$ are two edges of \mathcal{M} , (ii) $G_0[i]$ and $G_0[j]$ are consecutive in G_0 according to \mathcal{M} , (iii) $G_1[k]$ and $G_1[\ell]$ are consecutive in G_1 according to \mathcal{M} .

Objective function:

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

Constraints:

Assume $x \in \{0, 1\}$, $1 \leq i < j \leq n_0$ and $1 \leq k < \ell \leq n_1$.

- Constraint **(C.01)** ensures that each gene of G_0 and of G_1 is matched at most once, *i.e.*, $b_0(i) = 1$ (resp. $b_1(k) = 1$) if and only if gene i (resp. k) is matched in G_0 (resp. G_1); see Figure 2 for an illustration. Moreover, the matching is possible only between genes in the same family. It is worth noticing here that we do not specifically ask that $a(i, k) = 0$ when i and k concern genes belonging to different families. This is simply not necessary.
- Constraint **(C.02)** defines the model (*i.e.* the *maximum matching* model, in this case). For each gene family \mathbf{g} , one must have a single matched gene for the *exemplar* model and $\min(\text{OCC}_0(\mathbf{g}), \text{OCC}_1(\mathbf{g}))$ matched genes for the *maximum matching* model (see Figure 2).
- Constraints in **(C.03)** and **(C.04)** express the definition of consecutive genes, thus fixing the values of the variables c_x . The variable $c_x(i, j)$ is equal to 1 if and only if there exists no p such that $i < p < j$ and $b_x(p) = 1$. Again, it is worth noticing that the constraints do not force the variables $c_x(i, j)$ to have exactly the values we intuitively wish according to the abovementioned

interpretation. Here, we accept that $c_x(i, j) = 1$ even if the gene at position i or j is *not* matched. However, this will pose no problem in the sequel.

- Constraints in **(C.05)** to **(C.10)** define variables d . In the case where $G_0[i] = G_1[k]$ and $G_0[j] = G_1[\ell]$, constraints **(C.05)** and **(C.06)** ensure that we have $d(i, j, k, \ell) = 1$ if and only if all variables $a(i, k)$, $a(j, \ell)$, $c_0(i, j)$ and $c_1(k, \ell)$ are equal to 1. In the case where $G_0[i] = -G_1[\ell]$ and $G_0[j] = -G_1[k]$, constraints **(C.07)** and **(C.08)** ensure that we have $d(i, j, k, \ell) = 1$ if and only if all variables $a(i, \ell)$, $a(j, k)$, $c_0(i, j)$ and $c_1(k, \ell)$ are equal to 1. Constraint **(C.09)** fixes the variable $d(i, j, k, \ell)$ to 0 if none of the two cases above holds. Constraint **(C.10)** requires to have at most one adjacency for every pair (i, j) . See Figure 3 for a simple illustration.

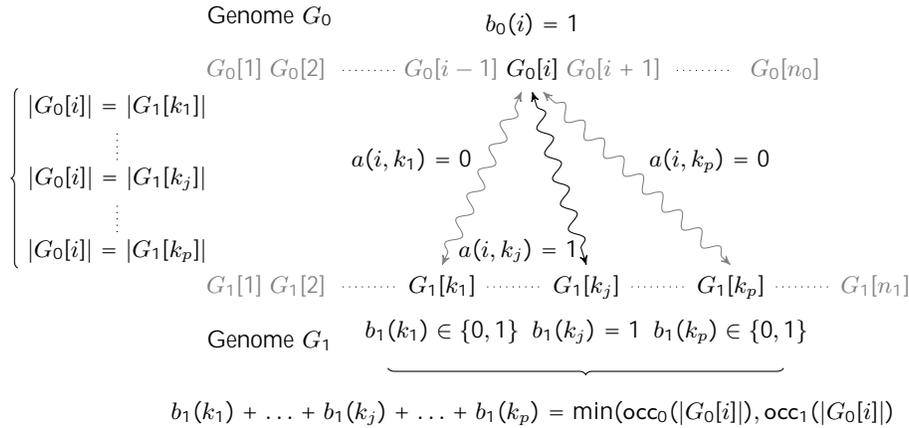


Fig. 2. Illustration of the constraints on variable $b_0(i)$, $1 \leq i \leq n_0$. If gene $G_0[i]$ appears in positions $k_1 < k_2 < \dots < k_p$ in G_1 and gene $G_0[i]$ is mapped to gene $G_1[k_j]$ in the solution mapping, then (i) $a(i, k_j) = 1$, *i.e.*, gene $G_0[i]$ is mapped to gene $G_1[k_j]$, (ii) $a(i, k_q) = 0$ for $1 \leq q \leq p$ and $q \neq j$, *i.e.*, gene $G_0[i]$ is mapped to only one gene in G_1 , (iii) $b_0(i) = 1$, *i.e.*, gene $G_0[i]$ is mapped to a gene of G_1 and (iv) $b_1(k_j) = 1$, *i.e.*, gene $G_1[k_j]$ is mapped to a gene of G_0 . Observe that one may have in addition $b_1(k_q) = 1$ for some $1 \leq q \leq p$ and $q \neq j$ if $\min(\text{occ}_0(|G_0[i]|), \text{occ}_1(|G_0[i]|)) \geq 1$ (this observation is however no longer valid for the *exemplar* model).

Program **Breakpoint-Maximum-Matching** has $O((n_0 n_1)^2)$ constraints and $O((n_0 n_1)^2)$ variables, which could result in a time-consuming computation. Several simple rules have been used in order to speed-up the execution, some of which help to reduce the number of variables and constraints. They are discussed in the next subsection.

$$d(i, j, k, \ell) = 1$$

Genome G_0

$G_0[1] \dots G_0[k-1] \mathbf{G_0[i] G_0[i+1] \dots G_0[j-1] G_0[j]} G_0[j+1] \dots G_0[n_0]$

$G_1[1] \dots G_1[k-1] \mathbf{G_1[k] G_1[k+1] \dots G_1[\ell-1] G_1[\ell]} G_1[\ell+1] \dots G_1[n_1]$

Genome G_1

we must have exactly one occurrence of each gene in each genome, and hence if the same gene occurs, say in G_0 , at positions i and j , then the corresponding variable $d()$ is set directly to 0 and the related constraints are discarded. If for two genes, say occurring at positions i and j in G_0 and k and ℓ in G_1 , at least one gene occurring between position i and j in G_0 or k and ℓ in G_1 must be saturated in any matching \mathcal{M} , then the corresponding variable $d(i, j, k, \ell)$ is set directly to 0 and the related constraints are discarded (details omitted).

Adding redundancy. While adding redundancy to a pseudo-boolean program is certainly useless from a correctness point of view, it can however have a major impact on the practical performance of the programs. For example, Program **Breakpoint-Maximum-Matching** contains some redundant constraints ((**C.06**), (**C.08**) and (**C.10**)) that significantly improved the running time of the program.

4 Experimental results

Thanks to the LPB program discussed previously, as well as formula (1), we are now able to determine the minimum number of breakpoints between pairs of genomes that contain duplicates. This minimum number of breakpoints will be computed according to the two above mentioned models, i.e. the *exemplar* and *maximum matching* models.

To this end, we used a dataset of γ -proteobacteria genomes, originally studied in [13], and exploited several times since then. This dataset is composed of twelve complete linear genomes of γ -Proteobacteria out of the thirteen originally studied in [13]. 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 genomes of the following species:

- *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_003902),
- *Xylella fastidiosa* 9a5c (**Xfast**, NC_002488),
- *Yersinia pestis* CO_92 (**Ypest-C092**, NC_003143),
- *Yersinia pestis* KIM5 P12 (**Ypest-KIM**, NC_004088) and
- *Wigglesworthia glossinidia brevipalpis* (**Wglos**, NC_004344).

should be noted that in average, 11% of duplicated genes are present in these genomes.

The LPB engine is powered by `minisat+` [12]. Computations were carried out on a Quadri Intel(R) Xeon(TM) CPU 3.00 GHz with 16Gb of memory running under Linux. Under the *maximum matching* model, `minisat+` runs our program `Breakpoint-Maximum-Matching` (implemented using the speeding-up rules described in Section 3.3) in less than 10s for 56 out of the 66 possible pairs of genomes, and in several minutes for the remaining 10 pairs. The results are provided in Table 1.

The first conclusion that can be drawn from these results is the following: the pseudo-boolean approach we have considered here is a good approach for computing the minimum number of breakpoints for the *maximum matching* model, since *all* the results have been obtained within a few minutes. However, as already observed in [1] for maximizing the number of *common intervals* between two genomes, we notice that the *exemplar* model is the main bottleneck of our approach. Indeed, for the *exemplar* model, only 49 out of 66 (that is about 74%) results have been obtained within a few minutes (we stopped the computation of the 17 remaining cases after a few days). We still have no formal explanation for this surprising and counter-intuitive fact. The 49 results we have obtained are given in Table 2.

Besides the fact that computing the minimum number of breakpoints under the *maximum matching* model proves to be feasible under our pseudo-boolean approach, we find interesting to note that we have a sufficient number of results in both the *maximum matching* and the *exemplar* models to test the absolute accuracy of possible heuristics for these two problems. Indeed, if one wishes to obtain fast (though not optimal) results by using a given heuristic, it is relevant to know how tight this heuristic is. We carried out this study, focusing on two heuristics (one for the *maximum matching* model, the other for the *exemplar* model), that are both based on iteratively choosing a Longest Common Substring (LCS).

Maximum Matching Model. In [14], the authors introduced an heuristic that aimed at computing a matching between two genomes. This heuristic is a greedy algorithm based on the notion of *LCS*. Let G_0 and G_1 be two genomes: an *LCS* of (G_0, G_1) is a longest common word S of G_0 and G_1 , up to a complete reversal. The idea of the greedy algorithm is to match, at each iteration, all the genes that are in an *LCS*. If there are several *LCS*, one is chosen arbitrarily. In [1], we improved this heuristic in the following way: at each iteration, not only we match an *LCS*, but we also remove each unmatched gene of a genome, for which there is no unmatched gene of same family in the other genome. These rules imply that the resulting matching is a maximum matching. We call this heuristic `IILCS_MM`.

Exemplar Model. For the *exemplar* model, we use the same strategy (iteratively match the genes of an *LCS*), except that in this case we must make sure that only *one gene* from each family is matched on each genome. Therefore, at each

iteration, and for each gene \mathbf{g} present in the LCS (and thus kept in the matching), we remove all the other occurrences of \mathbf{g} in both genomes. Let us call this heuristic IILCS_EX.

We have tested both IILCS_MM and IILCS_EX under, respectively, the *maximum matching* and *exemplar* models. Current results are given in Tables 1 to 4 (see http://www.lri.fr/~thevenin/Breakpoint/#Some_results for up-to-date results). The two heuristics are quite fast and one can obtain all results for IILCS_MM and IILCS_EX within 20 minutes on a regular desktop computer. For the *maximum matching* model, Heuristic IILCS_MM provides results that are on average 99.11% of the optimal number of breakpoints, ranging from 95.51% to 100%. We actually note that in 14 out of the 66 cases, IILCS_MM returns the optimal value. Concerning IILCS_EX, the average, obtained over the 49 instances for which we know the optimal result, is 96.88%, ranging from 94.38% to 99.10%.

Genomes	Number of Breakpoints (<i>maximum matching</i> model)										
Ecoli	156										
Haein	270	665									
Paeru	240	1082	615								
Pmult	259	703	525	681							
Salty	158	277	676	1091	704						
Wglos	170	194	277	260	270	192					
Xaxon	226	842	533	1016	557	854	269				
Xcamp	226	845	530	1012	555	854	268	181			
Xfast	236	564	468	572	481	569	272	400	404		
Ypest-co92	170	596	649	990	671	591	193	760	755	542	
Ypest-kim	176	607	653	1004	676	606	197	760	749	545	59

Table 1. Exact number of breakpoints for the *maximum matching* model

We thus conclude that both heuristics IILCS_MM and IILCS_EX, despite being extremely simple and fast, appear to be very good on the dataset we studied. In particular, for the *exemplar* model, since our pseudo-boolean approach seems to reach its limits for some instances, it could be convenient to compute those remaining instances using Heuristic IILCS_EX.

Genomes	Number of Breakpoints (<i>exemplar</i> model)											
Ecoli	152											
Haein	265	610										
Paeru	232		550									
Pmult	254	622		592								
Salty	154		612		622							
Wglos	168	183	267	248	262	181						
Xaxon	222	675	473		495	684	261					
Xcamp	222	678	473		495		260					
Xfast	231	491	424	499	436	497	264					
Ypest-co92	166		597		597		182	624	620	473		
Ypest-kim	172		598		601		186	624	618	477		

Baphi Ecoli Haein Paeru Pmult Salty Wglos Xaxon Xcamp Xfast Ypest-co92

Table 2. Exact number of breakpoints for the *exemplar* model (49 instances out of 66)

Genomes	Number of Breakpoints (<i>maximum matching</i> model) for Heuristic IILCS_MM											
Ecoli	157											
Haein	270	670										
Paeru	241	1097	619									
Pmult	259	705	529	684								
Salty	158	290	680	1101	708							
Wglos	171	195	277	262	270	193						
Xaxon	226	848	533	1023	560	863	269					
Xcamp	226	851	532	1023	559	860	269	185				
Xfast	236	569	468	575	481	571	272	406	408			
Ypest-co92	173	618	655	1007	678	609	195	767	766	549		
Ypest-kim	178	628	660	1019	684	626	198	766	758	550	59	

Baphi Ecoli Haein Paeru Pmult Salty Wglos Xaxon Xcamp Xfast Ypest-co92

Table 3. Number of breakpoints for the *maximum matching* model by IILCS_MM

5 Conclusion

In this paper, we presented a method that helps speeding-up computations of exact results for comparing whole genomes containing duplicates. This method,

Genomes	Number of Breakpoints (<i>exemplar</i> model) for Heuristic IILCS_EX										
Ecoli	155										
Haein	268	636									
Paeru	238	888	571								
Pmult	258	657	509	619							
Salty	156	175	641	908	659						
Wglos	170	189	272	254	266	188					
Xaxon	224	712	494	844	516	722	264				
Xcamp	224	716	492	841	516	720	263	126			
Xfast	234	511	443	517	456	514	268	384	383		
Ypest-co92	171	482	619	829	620	491	188	650	648	490	
Ypest-kim	176	485	624	827	623	492	191	649	644	495	34

Table 4. Number of breakpoints for the *exemplar* model by IILCS_EX

which makes use of pseudo-boolean programming, has been introduced in [1] for computing the maximum number of common intervals between two genomes, and can be used for several (dis)similarity measures. In this paper, we used this method for computing the minimum number of breakpoints between two genomes, and developed pseudo-boolean programs for both the *maximum matching* and *exemplar* models. Experiments were undertaken on a dataset of γ -Proteobacteria, showing the validity of our approach, since all the results (resp. 49 results out of 66) have been obtained in a limited amount of time in the *maximum matching* model (resp. *exemplar* model). Moreover, these results allow us to state that both the IILCS_MM and the IILCS_EX heuristics provide excellent results on this dataset, hence showing their validity and robustness. On the whole, these preliminary results are very encouraging.

There is still a great amount of work to be done. For instance:

- Implementing and testing the *maximum matching* and the *exemplar* models, for several other (dis)similarity measures,
- For each case, determining strong and relevant rules for speeding-up the process by avoiding the generation of a large number clauses and variables (a pre-processing step that should not be underestimated),
- Obtaining exact results for each of these models and measures, and for different datasets, that could be later used as benchmarks in order to validate (or not) possible heuristics, and
- Implementing and testing an intermediate model between the *maximum matching* and the *exemplar* models, in which one must match *at least one* gene of each family in each genome.

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