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A Pseudo-Boolean Framework for Computing Rearrangement Distances between Genomes with Duplicates

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Abstract

Computing genomic distances between whole genomes is a fundamental problem in comparative genomics. Recent researches have resulted in different genomic distance definitions: number of breakpoints, number of common intervals, number of conserved intervals, Maximum Adjacency Disruption number (MAD), *etc.* Unfortunately, it turns out that, in presence of duplications, most problems are **NP**-hard, and hence several heuristics have been recently proposed. 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. In this paper, we present a novel generic pseudo-boolean approach for computing the exact genomic distance between

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two whole genomes in presence of duplications, and put strong emphasis on common intervals under the maximum matching model. Of particular importance, we show three heuristics which provide very good results on a well-known public dataset of γ -Proteobacteria.

Keywords: pseudo-boolean programming, genome rearrangement, common intervals, duplication, heuristic.

1 Introduction

Due to the increasing amount of completely sequenced genomes, the comparison of gene order is now becoming a standard approach in comparative genomics. A natural way to compare species is to compare their whole genomes, where comparing two genomes is very often realized by determining a measure of similarity (or dissimilarity) between them. Several similarity (or dissimilarity) measures between two whole genomes have been proposed and studied in the past few years, such as the number of breakpoints (Sankoff, 1999; Bryant, 2000; Blin et al., 2004; Goldstein et al., 2004; Chrobak et al., 2005), the number of reversals (Bryant, 2000; El-Mabrouk, 2001; El-Mabrouk, 2002; Marron et al., 2004; Chen et al., 2005; Swenson et al., 2005a; Swenson et al., 2005b; Fu et al., 2006; Kolman and Waleń, 2006; Kolman and Waleń, 2007), the number of conserved intervals (Blin and Rizzi, 2005; Chen et al., 2006a), the number of common intervals (Bourque et al., 2005), the Maximum Adjacency Disruption Number (MAD) (Sankoff and Haque, 2005), *etc.* However, in the presence of duplications and for each of the above measures, one has first to disambiguate the data by inferring homologs, *i.e.*, a non-ambiguous mapping between the genes of the two genomes.

Up to now, two extremal approaches have been considered: the *exemplar* matching model and the *maximum* matching model. In the exemplar matching model (Sankoff, 1999), for all duplicated genes, all but one occurrence in each genome are deleted. In the maximum matching model (Blin et al., 2004; Goldstein et al., 2004; Chrobak et al., 2005; Chen et al., 2005; Fu et al., 2006; Chauve et al., 2006; Kolman and Waleń, 2007), 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**-hard as soon as duplicates are present in genomes (Bryant, 2000; Blin et al., 2004; Blin and Rizzi, 2005; Chauve et al., 2006) ; some inapproximability results are known for some special cases (Thach, 2005; Chen et al., 2006b; Chen et al., 2006a). Therefore, several heuristic methods have been recently devised to obtain (hopefully) good solutions in a reasonable amount of time (Blin et al., 2005; Bourque et al., 2005). 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.

In the present paper, we introduce a novel generic pseudo-boolean programming approach for computing exact solutions. In this first attempt, we focus on the problem of finding the maximum number of common intervals between two genomes under the maximum matching model. From a computational point of view, the problem of computing a matching that maximizes the number of common intervals (together with MAD) is one of the hardest in our pseudo-boolean framework. Moreover, this allows us to present with a single example

the main idea of our approach: a pseudo-boolean program together with reduction rules. We also present three heuristics for solving this problem, and we compare their results to the ones obtained by the pseudo-boolean program on a 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 maximum number of common intervals under the maximum matching model, and give a pseudo-boolean programming approach together with some reduction rules. Section 4 is devoted to experimental results on a dataset of γ -Proteobacteria. In particular, in this section we define three different heuristics and we prove that they provide very good results on our dataset.

2 Preliminaries

Genomes with duplications are usually represented by signed sequences over the alphabet of *gene families*, where every element in a genome is a *gene*. However, in order to simplify notations, and since common intervals do not depend on the sign given to the genes, we will consider only *unsigned* genomes in the rest of the paper. Any gene belongs to a gene family, and two genes belong to the same gene family if they have the same label. In the sequel, we will be extensively concerned with pairs of genomes. Let G_1 and G_2 be two genomes, and let $a \in \{1, 2\}$. The number of genes in genome G_a is always written n_a . We denote the i -th gene of genome G_a by $G_a[i]$. For any $1 \leq i \leq j \leq n_a$, we write $\mathcal{G}_a(i, j)$ for the set $\{G_a[i], G_a[i+1], \dots, G_a[j]\}$ and we let \mathcal{G}_a stand for $\mathcal{G}_a(1, n_a)$. In other words, $\mathcal{G}_a(i, j)$ is the set of all distinct genes between positions i and j in genome G_a , while \mathcal{G}_a is the set of all distinct genes in the whole genome G_a . For any gene $\mathbf{g} \in \mathcal{G}_a$ and any $1 \leq i \leq j \leq n_a$, we denote by $\text{occ}_a(\mathbf{g}, i, j)$ the number of occurrences of gene \mathbf{g} in the sequence $(G_a[i], G_a[i+1], \dots, G_a[j])$.

To simplify notations, we abbreviate $\text{occ}_a(\mathbf{g}, 1, n_a)$ to $\text{occ}_a(\mathbf{g})$.

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, *i.e.*, $G_1[i] = G_2[j]$. Genes of G_1 and G_2 that do not belong to any pair of the matching \mathcal{M} are said to be *unmatched* for \mathcal{M} . A matching \mathcal{M} between G_1 and G_2 is said to be *maximum* if for any gene family f , there are no two genes of f that are unmatched for \mathcal{M} and belong to G_1 and G_2 , respectively. A matching \mathcal{M} between G_1 and G_2 is said to be *exemplar* if for any gene family f , exactly one gene of f is matched by \mathcal{M} between G_1 and G_2 . A matching \mathcal{M} between G_1 and G_2 can be seen as a way to describe a putative assignment of orthologous pairs of genes between G_1 and G_2 (see for example (Chen et al., 2005) ; see also Figure 1 for an illustration of the exemplar and maximum matching concepts).

Let \mathcal{M} be any matching between G_1 and G_2 . By first deleting unmatched 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 permutation of G_1 .

It is easily seen that, by first resorting to a renaming procedure, we can always assume that one of the two genomes, say G_1 , is the identity permutation, *i.e.*, $G_1 = 1\ 2\ \dots\ n_1$ (an illustration is shown in the bottom part of Figure 1).

A *common interval* between G_1 and G_2 is a substring of G_1 , *i.e.*, a sequence of consecutive genes of G_1 , for which the exact same content can be found in a substring of G_2 (see for instance (Uno and Yagiura, 2000; Landau et al., 2005; Bergeron et al., 2005)). For example, let $G_1 = 1\ 2\ 3\ 4\ 5$ and $G_2 = 1\ 5\ 3\ 4\ 2$. Then, the interval $[3 : 5]$ of G_1 is a common interval (because $5\ 3\ 4$ occurs as a substring in G_2). Notice that there exists at least $n + 1$ ($n = n_1 = n_2$) common intervals between G_1 and G_2 since each individual gene is always

a common interval and G_1 itself is also a common interval. This lower bound is tight as shown by $G_1 = 1\ 2\ 3\ 4$ and $G_2 = 2\ 4\ 1\ 3$. Furthermore, if $G_1 = G_2$ the number of common intervals between G_1 and G_2 is $\frac{n(n+1)}{2}$, where $n = n_1 = n_2$, *i.e.*, each possible substring of G_1 is a common interval.

-Figure 1 should go here-

3 An exact algorithm for maximizing the number of common intervals

In this section, we are interested in the following problem: given two genomes that contain duplicates, find a maximum matching that maximizes the number of common intervals. We show how this problem can be transformed into an equivalent pseudo-boolean problem. The section is organized as follows: in Section 3.1, we briefly introduce basic and general notions concerning pseudo-boolean programs. Section 3.2 shows how to transform our initial problem into a pseudo-boolean program, while Section 3.3 shows how this program can be simply modified in order to compute the maximum number of common intervals between two genomes under two other models: the *exemplar matching* model and the *intermediate* model, where at least one gene in each gene family is mapped. Finally, Section 3.4 contains a set of rules which will help speed-up the program by avoiding the generation of a large number of variables and constraints.

3.1 Pseudo-boolean models

A Linear Pseudo-boolean (LPB) program is a linear program (Schrijver, 1998) where all variables are restricted to take values of either 0 or 1. For one, LPB programs are viewed by the linear programming community as just a domain restriction on general linear programming. For another, from a satisfiability (SAT) point of view, pseudo-boolean constraints can be seen as a *generalization* of clauses providing a significant extension of purely propositional constraints (Chai and Kuehlmann, 2003; Eén and Sörensson., 2006).

Conventionally, LPB problems are handled by generic Integer Linear Programming (ILP) solvers. The drawback of such an approach is that generic ILP solvers typically ignore the boolean nature of the variables. Alternatively, LPB decision problems could be encoded as SAT instances in pure CNF (Conjunctive Normal Form), *i.e.*, conjunction of disjunctions of boolean literals, which are then solved by any of the highly specialized SAT approaches. However the number of clauses required for expressing the LPB constraints is prohibitively large. Moreover a pure CNF encoding may prevent the solver from pruning the search space efficiently (Chai and Kuehlmann, 2003). Boolean satisfiability solvers available today are the result of decades of research and are deemed to be among the faster **NP**-hard problem specific solvers. The latest generation of SAT solvers generally have three key features (randomization of variable selection, backtracking search and some form of clause learning) and they usually run in reasonable time (even for very large instances).

A number of generalizations of SAT solvers to LPB solvers have been proposed (**Pueblo** (Sheini and Sakallah, 2006), **Galena** (Chai and Kuehlmann, 2003), **OPBDP** (Barth, 2005) and more). We decided to use for our tests the **minisat+** LPB solver (Eén and Sörensson., 2006) because of its good results during PB evaluation 2005 (special track of the SAT COMPETITION 2005).

3.2 Common intervals in the Maximum Matching Model

We propose in Figure 2 a pseudo-boolean program for computing the maximum number of common intervals between two genomes under the maximum matching model in the presence of duplications (we assume here that each gene $\mathbf{g} \in \mathcal{G}_1 \cup \mathcal{G}_2$ occurs both in G_1 and in G_2 ; if this is not the case, a pre-process of G_1 and G_2 will delete from G_1 and G_2 those genes which appear in only one genome).

-Figure 2 should go here-

Program `Common-Intervals-Matching` is clearly a pseudo-boolean program, *i.e.*, a $(0, 1)$ -linear program. Roughly speaking, the boolean variables are divided in two sets: true setting of variables in C denote possible common intervals between G_1 and G_2 , while true setting of variables in X denote the mapping, *i.e.*, matching, between G_1 and G_2 .

We now turn to describing the constraints. Constraints in (C.01) and in (C.02) deal with consistency of the mapping: each gene of G_1 is mapped to at most one gene of G_2 , and conversely (some genes need indeed to be deleted in case of unbalanced families).

Constraints in (C.03) ensure that each common interval is counted exactly once. The key idea here is to impose an “*active border*” property, *i.e.*, if variable $c_{k,\ell}^{i,j}$ is set to 1 then genes $G_1[i]$ and $G_1[j]$ must match some distinct genes between positions k and ℓ in G_2 , and genes $G_2[k]$ and $G_2[\ell]$ must match some distinct genes between positions i and j in G_1 . More intuitively, this constraint ensures that a common interval will not be counted more than once, by forcing each extremity of a common interval to be matched.

Constraints in (C.04) to (C.07) ensure that if $c_{k,\ell}^{i,j} = 1$ then the interval $[i : j]$ of G_1 and the interval $[k : \ell]$ of G_2 is a common interval according to the mapping induced by the

true setting of X . For example, constraints in (C.04) ensure that each gene in the interval $[i : j]$ of G_1 is either not mapped or is mapped to a gene in the interval $[k : \ell]$ of G_2 (thanks to constraints in (C.01), (C.02) and (C.03), genes at position i and j in G_1 are actually mapped to distinct genes in G_2 if $i < j$ and $c_{k,\ell}^{i,j} = 1$).

Finally, constraints in (C.08) force the mapping to be a maximum matching between G_1 and G_2 .

Proposition 1. *Program Common-Intervals-Matching correctly computes the maximum number of common intervals between G_1 and G_2 under the maximum matching model.*

We briefly discuss here space issues of Program Common-Intervals-Matching. First, it is easily seen that $\#C = \Theta(n_1^2 n_2^2)$ and hence that (C.03) is composed of $\Theta(n_1^2 n_2^2)$ constraints. The number of constraints in (C.04) to (C.07) however does depend on the number of duplications in the two genomes. Second, $\#X = \mathcal{O}(n_1 n_2)$. Clearly, the size of the set X determines the number of constraints in (C.01) and (C.02) and of course strongly depends on the number of duplications in G_1 and G_2 . Not surprisingly, set X turns out to be of moderate size in practice. Finally, the number of constraints in (C.08) is clearly linear in the size of the two genomes. We shall soon describe (section 3.4) how to speed-up the program by reducing the number of variables and constraints. Before that, we show in the following section how to modify the Program Common-Intervals-Matching in order to compute the maximum number of common intervals between two genomes under, respectively, the *exemplar matching* model and the *intermediate model*, where at least one gene in each gene family is mapped.

3.3 Adapting the Program for other Models

In this section, we point out the genericity of the pseudo-boolean framework for computing a matching that maximizes the number of common intervals between two genomes. Indeed, we show here a fast and easy way to modify the Program `Common-Intervals-Matching` in order to compute the maximum number of common intervals between two genomes under two other models: the *exemplar matching* model and the *intermediate* model, where at least one gene in each gene family is mapped.

We observe indeed that replacing constraints in (C.08) by a new set of constraints (C.08') – see below – in Program `Common-Intervals-Matching` results in the pseudo-boolean program `Common-Intervals-Exemplar` that computes the maximum number of common intervals between genomes G_1 and G_2 under the exemplar matching model.

$$(C.08') \quad \forall \mathbf{g} \in \mathcal{G}_1 \cup \mathcal{G}_2, \quad \sum_{\substack{1 \leq i \leq n_1 \\ G_1[i]=\mathbf{g}}} \sum_{\substack{1 \leq k \leq n_2 \\ G_2[k]=\mathbf{g}}} x_k^i = 1$$

Interestingly enough, substituting now the constraints in (C.08) by a new set of constraints (C.08'') – see below – in Program `Common-Intervals-Matching` results in a pseudo-boolean program that computes the maximum number of common intervals between genomes G_1 and G_2 under the following intermediate model: at least one gene in each gene family is mapped. Observe that this model contains both the exemplar matching model and the maximum matching model as special cases.

$$(C.08'') \quad \forall \mathbf{g} \in \mathcal{G}_1 \cup \mathcal{G}_2, \quad \sum_{\substack{1 \leq i \leq n_1 \\ G_1[i]=\mathbf{g}}} \sum_{\substack{1 \leq k \leq n_2 \\ G_2[k]=\mathbf{g}}} x_k^i \geq 1$$

3.4 Speeding-up the program

We give in this section four rules for speeding-up Program `Common-Intervals-Matching`. In theory, a very large instance may be easy to solve and a small instance hard. However, very often, small hard instances turn out to be artificial, *e.g.*, the pigeonhole problem, and hence, in case of practical instances, the running time of a pseudo-boolean solver is most of the time related to the size of the instances. The main idea here is thus to reduce the number of variables and constraints in the program (for ease of exposition, we describe our rules as filters on C). More precisely, we give rules that avoid introducing useless variables $c_{k,\ell}^{i,j}$ in C in such a way that the correctness of Program `Common-Intervals-Matching` is maintained by repeated applications of the rules ; two of these filters however do modify the correct maximum number of common intervals between the two genomes and thus ask for subsequent modifications in order to obtain the correct solution.

[Rule 1] Delete from C all variables $c_{k,k}^{i,i}$, $1 \leq i \leq n_1$ and $1 \leq k \leq n_2$.

Rule 1 does modify the correct number of common intervals between G_1 and G_2 , and hence application of this rule asks for subsequent modifications of the number of common intervals. The key idea of **Rule 1** is simply to discard common intervals of size 1 from the program. Indeed, we can compute in a pre-processing step the numbers d_1 and d_2 of genes that need to be deleted in G_1 and G_2 for obtaining a maximum matching between the two genomes. Therefore, we know that the resulting genomes will consist in $L = n_1 - d_1 = n_2 - d_2$ genes, where

$$L = \sum_{\mathbf{g} \in \mathcal{G}} \min\{\text{occ}_1(\mathbf{g}), \text{occ}_2(\mathbf{g})\}.$$

But each of these genes will contribute for 1 to the number of common intervals between G_1 and G_2 , for any maximum matching. We thus simply delete all these variables and add L to the number of common intervals between G_1 and G_2 found by Program `Common-Intervals-Matching`.

[Rule 2] Delete from C all variables $c_{k,\ell}^{i,j}$ for which any of the following conditions holds true:

1. $(\#\{r : k \leq r \leq \ell \wedge G_1[i] = G_2[r]\} = 0) \vee (\#\{s : k \leq s \leq \ell \wedge G_1[j] = G_2[s]\} = 0)$,
2. $(\#\{r : k \leq r \leq \ell \wedge G_1[i] = G_2[r]\} < 2) \wedge (G_1[i] = G_1[j])$,
3. $(\#\{p : i \leq p \leq j \wedge G_2[k] = G_1[p]\} = 0) \vee (\#\{q : i \leq q \leq j \wedge G_2[\ell] = G_1[q]\} = 0)$,
4. $(\#\{p : i \leq p \leq j \wedge G_2[k] = G_1[p]\} < 2) \wedge (G_2[k] = G_2[\ell])$.

Rule 2 is a quickening for constraints in (C.03). Indeed, these constraints ensure that each common interval is counted exactly once by the program by forcing the border of each common interval to be active in the computed solution, *i.e.*, genes $G_1[i]$ and $G_1[j]$ match some distinct genes between positions k and ℓ in G_2 , and genes $G_2[k]$ and $G_2[\ell]$ match some distinct genes between positions i and j in G_1 . Correctness of **Rule 2** thus follows from the fact that Program `Common-Intervals-Matching` will always set a variable $c_{k,\ell}^{i,j}$ to 0 if the border property cannot be satisfied (it is assumed here that $i < j$ and $k < \ell$).

[Rule 3] Delete from C all variables $c_{k,\ell}^{i,j}$ for which there exists at least one gene $\mathbf{g} \in \mathcal{G}$ such that $|\text{occ}_1(\mathbf{g}, i, j) - \text{occ}_2(\mathbf{g}, k, \ell)| > |\text{occ}_1(\mathbf{g}) - \text{occ}_2(\mathbf{g})|$.

Roughly speaking, **Rule 3** avoids us to delete too many genes in a common interval. Indeed, for one, for any $\mathbf{g} \in \mathcal{G}$, $|\text{occ}_1(\mathbf{g}, i, j) - \text{occ}_2(\mathbf{g}, k, \ell)|$ is clearly the minimum number of occurrences of gene \mathbf{g} that need to be deleted if $c_{k,\ell}^{i,j} = 1$, *i.e.*, $[i : j]$ and $[k : \ell]$ form a common interval between the two genomes. For another, for any $\mathbf{g} \in \mathcal{G}$, $|\text{occ}_1(\mathbf{g}) - \text{occ}_2(\mathbf{g})|$ is the number of occurrences of gene \mathbf{g} that need to be deleted in G_1 and G_2 for finding any maximum matching between the two genomes. Correctness of **Rule 3** thus follows from the fact that we can certainly not delete more than $|\text{occ}_1(\mathbf{g}) - \text{occ}_2(\mathbf{g})|$ occurrences of gene \mathbf{g} .

[Rule 4] Delete from C all variables $c_{k,\ell}^{i,j}$ for which the four following conditions hold true:

1. $\forall \mathbf{g} \in \mathcal{G}_1(i, j), \quad \#\text{occ}_1(\mathbf{g}, 1, i - 1) + \#\text{occ}_1(\mathbf{g}, j + 1, n_1) = 0,$
2. $\forall \mathbf{g} \in \mathcal{G}_2(k, \ell), \quad \#\text{occ}_2(\mathbf{g}, 1, k - 1) + \#\text{occ}_2(\mathbf{g}, \ell + 1, n_2) = 0,$
3. $\#\text{occ}_1(G_1[i]) \leq \#\text{occ}_2(G_1[i]) \wedge \#\text{occ}_1(G_1[j]) \leq \#\text{occ}_2(G_1[j]),$
4. $\#\text{occ}_2(G_2[k]) \leq \#\text{occ}_1(G_2[k]) \wedge \#\text{occ}_2(G_2[\ell]) \leq \#\text{occ}_1(G_2[\ell]).$

We first observe that **Rule 4** does modify the correct number of common intervals between G_1 and G_2 , and hence application of this rule asks for subsequent modifications of the number of common intervals. The rationale of **Rule 4** is that, if the four conditions hold true, then $c_{k,\ell}^{i,j}$ will always be set to 1 by Program `Common-Intervals-Matching`. In other words, for any maximum matching between G_1 and G_2 , $[i : j]$ and $[k : \ell]$ will form a common intervals. We thus simply delete from C all these variables $c_{k,\ell}^{i,j}$ and add the number of deleted variables by **Rule 4** to the number of common intervals between G_1 and G_2 found by Program `Common-Intervals-Matching`. This rule will prove extremely useful for highly conserved regions with localized duplications.

4 Experimental results

As mentioned in the Introduction, the generic pseudo-boolean approach we propose in this paper can be useful for estimating the accuracy of one or several heuristic(s). In that perspective, it is necessary to compute the exact results for different datasets, that could be later used as benchmarks to which confront the results given by any given heuristic algorithm. In this section, we will compare the exact results we have obtained from a given dataset by our pseudo-boolean method to three heuristics, respectively called *ILCS*, *IILCS* and *HYB₂*.

The three heuristics we will study in the following are:

- the heuristic *ILCS*, which is a small variant of the one used in (Blin et al., 2005)
- an improvement we suggest for *ILCS* (that we will denote *IILCS*)
- a hybrid method, called *HYB_k*, that mixes the approach used in the *IILCS* heuristic and the pseudo-boolean approach. We will mainly be interested in the case where parameter k is equal to 2.

We will thus compare the results obtained by the *ILCS*, *IILCS* and *HYB₂* heuristics to the exact results we have obtained via our pseudo-boolean approach. In particular, we will show that *IILCS* and *HYB₂* perform very well on the dataset we used. Before that, we first describe this dataset, and we present each of the three above mentioned heuristics in details.

4.1 Exact Results

We performed the computation of exact results concerning common intervals in the maximum matching model by studying the dataset used in (Blin et al., 2005). This dataset is composed of 12 complete genomes from the 13 γ -Proteobacteria originally studied in (Lerat et al., 2003). 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, this 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 Baphi* (NC_004344).

The computation of a partition of the complete set of genes into gene families, where each family is supposed to represent a group of homologous genes, is taken from (Blin et al., 2005) (this partition was actually provided to these authors by Lerat (Lerat et al., 2003)). The main characteristics (number of genes, number of gene families, percentage of duplicates) of the twelve considered genomes are summarized in Table 1.

-Table 1 should go here-

Despite the fact that the model (maximum matching model) and the measure (number of common intervals) we study are one of the most time consuming, nearly two thirds of the exact results have been computed until now. It is also interesting to note that, for three of the twelve studied genomes (namely, *Buchnera aphidicola*, *Haemophilus influenzae* and

Wigglesworthia glossinidia brevipalpis), we have obtained **all** the exact results that involve those genomes.

These results, though still partial, allow us to go further ; indeed, thanks to the exact results we have obtained, we are now able to confront the results given by three different heuristics to them. Those three heuristics are now presented in details.

4.2 The *ILCS* Heuristic

We first start by describing the heuristic that we will call *ILCS* (Iterative Longest Common Substring). It is actually a small variant of the one used in (Blin et al., 2005). This heuristic is greedy, and works as follows:

1. Compute the Longest Common Substring (*i.e.*, the longest contiguous word) S of the two genomes, up to a complete reversal. If there are several candidates, pick one at random
2. Match all the genes of S accordingly
3. Iterate the process until all possible genes have been matched (*i.e.*, we have obtained a maximum matching)
4. Remove, in each genome, all the genes that have not been matched
5. Compute the number of common intervals that have been obtained in this solution

For instance, suppose that $G_1 = 1\ 2\ 3\ 4\ 5\ 6\ 7$ and $G_2 = 6\ 7\ 4\ 5\ 1\ 6\ 3\ 2\ 1$. Below is a brief description of the running of *ILCS*, where the parts which are underlined represent the Longest Common Substring, and where genes in bold are matched.

1 2 3 4 5 6 7
 6 7 4 5 1 6 3 2 1
1 2 3 4 5 6 7
 6 7 4 5 1 6 **3 2 1**
1 2 3 4 5 6 7
6 7 4 5 1 6 **3 2 1**
1 2 3 4 5 6 7
6 7 4 5 3 2 1

In this example, the number of Common Intervals we obtain is equal to 19.

The simple idea behind this heuristic algorithm is that a Longest Common Substring (up to complete reversal) of length k contains $\frac{k(k+1)}{2}$ common intervals. Hence, finding such exact copies in both genomes intuitively helps to increase the total number of common intervals.

4.3 The *IILCS* Heuristic: an improvement of *ILCS*

A closer look on the *ILCS* heuristic led us to suggest an improvement to it, in the form of a new heuristic, that we call *IILCS* (Improved Iterative Longest Common Substring). Heuristic *IILCS* works as follows:

1. Compute the Longest Common Substring S of the two genomes, up to a complete reversal. If there are several candidates, pick one at random
2. Match all the genes of S accordingly
3. *Remove from genome G_1 (resp. G_2) the unmatched gene(s) for which there remains no unmatched genes of the same family in G_2 (resp. G_1)*
4. Iterate the process until all possible genes have been matched (*i.e.*, we have obtained a maximum matching)

5. Compute the number of common intervals that have been obtained in this solution

The only difference between *IILCS* and *ILCS* lies in line 3: intuitively, before searching for a Longest Common Substring (up to a complete reversal), we “*tidy*” the two genomes. More precisely, we remove, in each genome and at each iteration, the genes for which we know they will not be matched in the final solution ; such genes are unmatched genes for which there remains no “corresponding” (i.e., of the same family) unmatched gene in the other genome. This process can simply be undertaken by counting, at each iteration, the number of unmatched genes of each gene family in both genomes. This actually allows to find Longest Common Substrings that are possibly longer than the ones found in the *ILCS* heuristic.

For example, let us take the same instance as the one used in the previous section, that is $G_1 = 1\ 2\ 3\ 4\ 5\ 6\ 7$ and $G_2 = 6\ 7\ 4\ 5\ 1\ 6\ 3\ 2\ 1$. Below is a brief description of the running of *IILCS*, where the parts which are underlined represent the Longest Common Substring, genes in italic are genes that are going to be removed (because they have no unmatched gene of the same family in the other genome), and genes in bold are matched.

```

1 2 3 4 5 6 7
6 7 4 5 1 6 3 2 1
1 2 3 4 5 6 7
6 7 4 5 6 3 2 1
1 2 3 4 5 6 7
6 7 4 5 6 3 2 1
1 2 3 4 5 6 7
7 4 5 6 3 2 1
1 2 3 4 5 6 7
7 4 5 6 3 2 1
1 2 3 4 5 6 7
6 7 4 5 3 2 1

```

In this example, the number of Common Intervals we obtain is equal to 20.

4.4 The Hybrid Method HYB_k

Starting from the *IILCS* heuristic, one can think of a further improvement: first, use the *IILCS* method until no Longest Common Substring of size greater than or equal to k exists (where k is a given parameter) ; this will give a partially solved instance, in the sense that some genes are matched while some are not. Second, in order to totally solve the problem, we run our pseudo-boolean program on the partially solved instance.

The HYB_k method can be described as follows:

1. Run the *IILCS* method until no Longest Common Substring of size greater than or equal to k exists
2. Give the partially solved instance obtained above as an input to the pseudo-boolean program `Common-Intervals-Matching`
3. Compute the number of common intervals that have been obtained in this solution

Since the pseudo-boolean program will always output the best (i.e., exact) result, and since before calling the pseudo-boolean program we run the *IILCS* heuristic, we can ensure that HYB_k is at least as good as *IILCS* for any value of k and any given instance (G_1, G_2) . However, the main drawback of HYB_k compared to *IILCS* concerns the running time ; indeed, *IILCS* is a polynomial time algorithm, while there is no guarantee that HYB_k (for any $k \geq 2$) will ever answer, even on a very powerful computer. This is because we are asking for an exact result in the second part of the algorithm, which means that it runs in exponential time. On the other hand, if we choose k sufficiently small, then many genes will

be matched by the *IILCS* part of the heuristic, and one can hope for the exact result to be computed relatively fast. Moreover, the exact part of the $H Y B_k$ heuristic is run through our pseudo-boolean program, which has been designed to speed-up the computation. In that sense, $H Y B_k$ appears as a compromise between the exactness of the results and the computation time.

For our experiments, we will choose the smallest possible value for k , that is $k = 2$. The results we have obtained through our $H Y B_k$ method are at the same time promising and somehow disappointing ; they are promising in terms of quality of the results (more details are provided in Section 4.5), but disappointing in terms of running time. Indeed, even when fixing k as small as possible (that is, $k = 2$), only 46 out of the 66 possible pairwise comparisons were obtained within a few days of computation, that is, only 6 more results than the exact method.

4.5 Results and Discussion

Out of the 66 possible pairwise genome comparisons, 40 results have been obtained within a few days of computation. More precisely, among these 40 values, only 4 of them took several days to be computed (Haein/Pmult, Haein/Xfast, Paeru/Pmult and Paeru/Xfast), while the others took no more than a few minutes.

One of the main interests of our pseudo-boolean approach is that the exact results they provide can be used to test the robustness of some heuristic(s). We have thus confronted the 40 exact results we have obtained to the results given by the three heuristics we have presented in the previous sections.

First, we focus on the three genomes for which we have obtained all the exact results: results

for *Buchnera aphidicola* are summarized in Table 2, results for *Haemophilus influenzae* are summarized in Table 3, while results concerning *Wigglesworthia glossinidia brevipalpis* are summarized in Table 4.

Looking at these results, we can see that, non surprisingly, HYB_2 is always better or as good as $IILCS$, which is itself always better or as good as $ILCS$. In particular, HYB_2 returns the optimal value in **all** the cases for *Buchnera aphidicola*, in 5 out of the 11 cases for *Haemophilus influenzae*, and in 9 out of the 11 cases for *Wigglesworthia glossinidia brevipalpis*.

-Table 2 should go here-

-Table 3 should go here-

-Table 4 should go here-

A more global view at the respective performances of heuristics $ILCS$, $IILCS$ and HYB_2 is given in Table 5. In this table, for each of the 40 exact results we have obtained, and for each heuristic \mathcal{H} , we provide the ratio $\frac{IC(\mathcal{H})}{IC(OPT)}$, where $IC(\mathcal{H})$ is the number of common intervals returned by \mathcal{H} and $IC(OPT)$ is the exact number of common intervals. This ratio is given as a percentage. These results are also illustrated in a graphical form in Figure 3.

These results confirm that HYB_2 is always better (or as good as) $IILCS$, which is always better (or as good as) $ILCS$: more precisely, on average, $IILCS$ improves by 2.66% the performances of $ILCS$, while HYB_2 improves by a further 0.98% the performances of $IILCS$.

What is even more striking is that both heuristics $IILCS$ and HYB_2 appear to be *very*

good on the dataset we studied. Indeed, out of the 40 instances for which we have computed the exact results, *IILCS* returns the *optimal result* in 7 cases, and returns a number of common intervals that is more than 99% of the optimal number for 22 other cases. The “worse” result that *IILCS* provides is 93.18% away from the optimal (Xfast/Ypest-CO92). On average, over the 40 pairwise comparisons for which we have exact results, *IILCS* gives a number of common intervals that is 98.9% of the optimal number.

Concerning heuristic *HYB₂*, out of the 40 instances for which we have computed the exact results, it returns the *optimal result* in 23 cases, and returns a number of common intervals that is more than 99% of the optimal number for the remaining 17 other cases. The “worse” result that *HYB₂* provides is 99.22% away from the optimal (Pmult/Ypest-KIM). On average, over the 40 pairwise comparisons for which we have exact results, *HYB₂* gives a number of common intervals that is 99.88% of the optimal number.

-Table 5 should go here-

-Figure 3 should go here-

These results come as a surprise, because, despite being extremely simple and fast, *IILCS* appears to be extremely good on this dataset. *HYB₂* works even better on this dataset, but its main drawback is that we have no guarantee on its execution time. Hence, this strongly suggests that computing common intervals in the maximum matching model can simply be undertaken using either *IILCS* or *HYB₂* (depending on the execution time of *HYB₂*), while remaining accurate, thus validating these heuristics.

5 Conclusion

In this paper, we have introduced a novel and original method that helps speeding-up computations of exact results for comparing whole genomes containing duplicates. This method makes use of pseudo-boolean programming. Our approach is very general, and can handle several (dis)similarity measures (breakpoints, common intervals, conserved intervals, MAD, *etc.*) under several possible models (exemplar matching model, maximum matching model, but also most models within those two extrema).

An example of such an approach (common intervals under the maximum matching model) has been developed, in order to illustrate the main ideas of the pseudo-boolean transformation framework that we suggest. Experiments have also been undertaken on a dataset of γ -Proteobacteria, showing the validity of our approach, since 40 results (out of 66) have been obtained in a limited amount of time. Moreover, these preliminary results have allowed us to state that, in particular, both the *IILCS* and the *HYB₂* heuristics provide excellent results on this dataset, hence showing their validity and robustness (though there is no guarantee on the execution time of *HYB₂*). On the whole, these preliminary results are very encouraging.

Our approach is in fact more ambitious. Our long term goal is indeed to develop a generic pseudo-boolean approach for the exact computation of various genome distances (number of breakpoints, number of common intervals, number of conserved intervals, MAD, *etc.*) under both the exemplar and the maximum matching models, and use this generic approach on different datasets. The rationale of this approach is threefold:

1. There is a crucial need for new algorithmic solutions providing exact genome distances under both the exemplar and the maximum matching models in order to estimate

the accuracy of existing heuristics and to design new efficient biologically relevant heuristics.

2. Very little is known about the relations between the various genome distances that have been defined so far (number of breakpoints, number of common intervals, number of conserved intervals, MAD, *etc.*). We thus propose to extensively compare all these genome distances under both models with a generic pseudo-boolean framework on several datasets.
3. We also plan to further investigate the relations between the exemplar and the maximum matching models. We strongly believe here that, in the light of these comparisons, some biologically relevant *intermediate* model between these two extrema could be defined.

There is still a great amount of work to be done, and some of it is being undertaken by the authors at the moment. Among other things, one can cite:

- Implementing and testing all the possible above mentioned models, for all the possible above mentioned (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.

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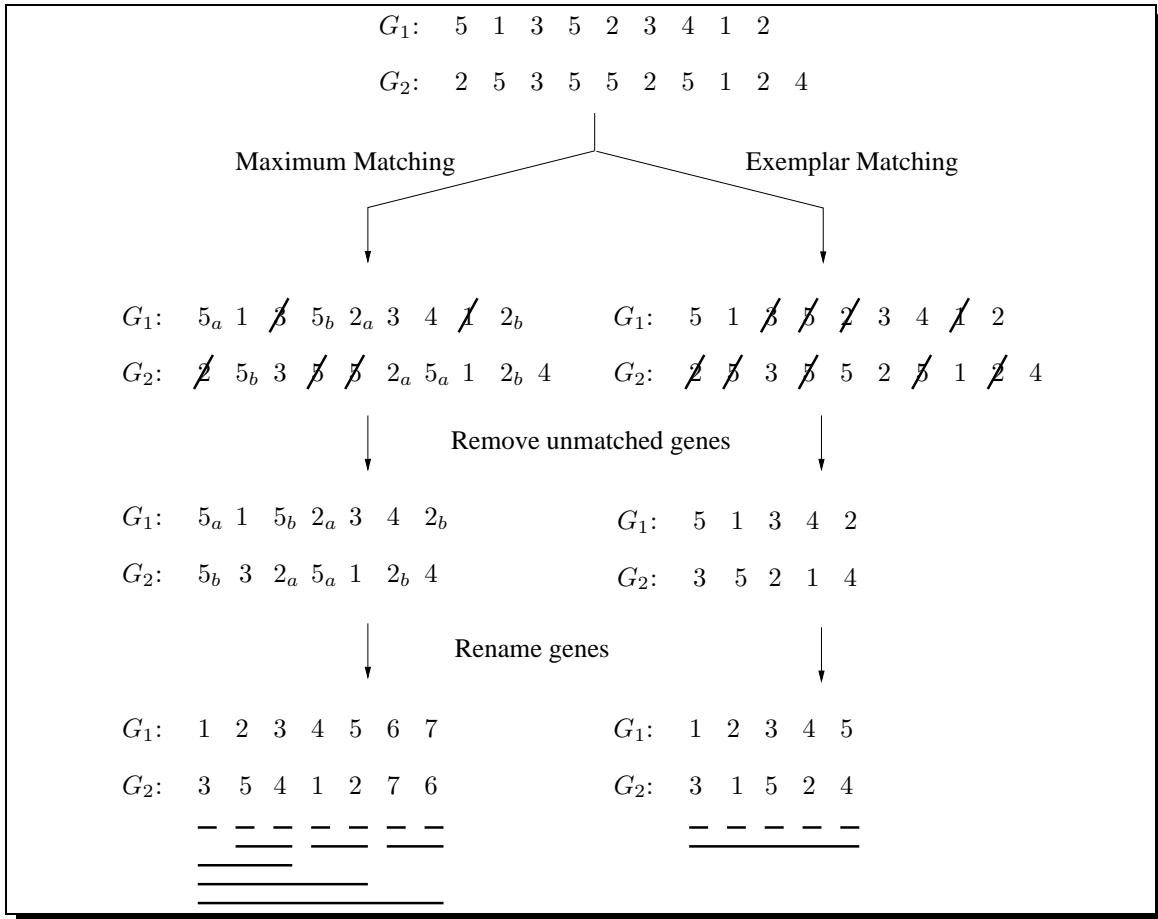


Figure 1: Illustration of the *maximum matching* and the *exemplar matching* concepts. Common intervals, in each of the two cases, are shown with bold lines in the bottom part of the figure

Program Common-Intervals-Matching

objective:

$$\text{maximize } \sum_{c_{k,\ell}^{i,j} \in C} c_{k,\ell}^{i,j}$$

variables:

$$C = \{c_{k,\ell}^{i,j} : 1 \leq i \leq j \leq n_1 \wedge 1 \leq k \leq \ell \leq n_2\}$$

$$X = \{x_k^i : 1 \leq i \leq n_1 \wedge 1 \leq k \leq n_2 \wedge G_1[i] = G_2[k]\}$$

subject to:

$$(C.01) \quad \forall i = 1, 2, \dots, n_1, \quad \sum_{\substack{1 \leq k \leq n_2 \\ G_1[i]=G_2[k]}} x_k^i \leq 1$$

$$(C.02) \quad \forall k = 1, 2, \dots, n_2, \quad \sum_{\substack{1 \leq i \leq n_1 \\ G_1[i]=G_2[k]}} x_k^i \leq 1$$

$$(C.03) \quad \forall c_{k,\ell}^{i,j} \in C, \quad 4c_{k,\ell}^{i,j} - \sum_{\substack{k \leq r \leq \ell \\ G_1[i]=G_2[r]}} x_r^i - \sum_{\substack{k \leq s \leq \ell \\ G_1[j]=G_2[s]}} x_s^j - \sum_{\substack{i \leq p \leq j \\ G_1[p]=G_2[k]}} x_k^p - \sum_{\substack{i \leq q \leq j \\ G_1[q]=G_2[\ell]}} x_\ell^q \leq 0$$

$$(C.04) \quad \forall c_{k,\ell}^{i,j} \in C, \quad \forall i < p < j, \quad \forall 1 \leq r < k, \quad G_1[p] = G_2[r], \quad c_{k,\ell}^{i,j} + x_r^p \leq 1$$

$$(C.05) \quad \forall c_{k,\ell}^{i,j} \in C, \quad \forall i < p < j, \quad \forall \ell < r \leq n_2, \quad G_1[p] = G_2[r], \quad c_{k,\ell}^{i,j} + x_r^p \leq 1$$

$$(C.06) \quad \forall c_{k,\ell}^{i,j} \in C, \quad \forall k < r < \ell, \quad \forall 1 \leq p < i, \quad G_1[p] = G_2[r], \quad c_{k,\ell}^{i,j} + x_r^p \leq 1$$

$$(C.07) \quad \forall c_{k,\ell}^{i,j} \in C, \quad \forall k < r < \ell, \quad \forall j < p \leq n_1, \quad G_1[p] = G_2[r], \quad c_{k,\ell}^{i,j} + x_r^p \leq 1$$

$$(C.08) \quad \forall \mathbf{g} \in \mathcal{G}_1 \cup \mathcal{G}_2, \quad \sum_{\substack{1 \leq i \leq n_1 \\ G_1[i]=\mathbf{g}}} \sum_{\substack{1 \leq k \leq n_2 \\ G_2[k]=\mathbf{g}}} x_k^i = \min\{\text{occ}_1(\mathbf{g}), \text{occ}_2(\mathbf{g})\}$$

domains:

$$\forall x_k^i \in X, \quad x_k^i \in \{0, 1\}$$

$$\forall c_{k,\ell}^{i,j} \in C, \quad c_{k,\ell}^{i,j} \in \{0, 1\}$$

Figure 2: Program Common-Intervals-Matching for finding the maximum number of common intervals between two genomes under the maximum matching model

Main characteristics			
Genome	Number of genes	Number of gene families	Percentage of duplications
Baphi	564	549	2.66
Ecoli	4183	3423	18.17
Haein	1709	1531	10.42
Paeru	5540	4500	18.77
Pmult	2015	1811	10.12
Salty	4203	3456	17.77
Wglos	653	627	3.98
Xaxon	4192	3634	13.31
Xcamp	4029	3468	13.92
Xfast	2680	2346	12.46
Ypest-CO92	3599	3021	16.06
Ypest-KIM	3879	3236	16.58

Table 1: Main characteristics of the twelve considered γ -Proteobacteria genomes

Baphi vs				
	<i>ILCS</i>	<i>IILCS</i>	<i>HYB₂</i>	Exact
Ecoli	2605	2869	2882	2882
Haein	1103	1109	1109	1109
Paeru	1492	1518	1524	1524
Pmult	1216	1224	1224	1224
Salty	2641	2849	2849	2849
Wglos	1261	1267	1275	1275
Xaxon	1127	1183	1183	1183
Xcamp	1147	1183	1183	1183
Xfast	975	979	979	979
Ypest-CO92	2387	2541	2585	2585
Ypest-KIM	1965	2124	2141	2141

Table 2: Comparison of the results - *Buchnera aphidicola*

Haein vs				
	<i>ILCS</i>	<i>IILCS</i>	<i>HYB₂</i>	Exact
Baphi	1103	1109	1109	1109
Ecoli	2758	2774	2783	2784
Paeru	1980	2016	2026	2036
Pmult	3901	3910	3911	3936
Salty	2794	2809	2819	2820
Wglos	1077	1085	1085	1085
Xaxon	1446	1468	1469	1471
Xcamp	1441	1455	1458	1458
Xfast	1285	1293	1295	1295
Ypest-CO92	2668	2686	2694	2694
Ypest-KIM	2458	2487	2499	2500

Table 3: Comparison of the results - *Haemophilus influenzae*

Wglos vs				
	<i>ILCS</i>	<i>IILCS</i>	<i>HYB₂</i>	Exact
Baphi	1261	1267	1275	1275
Ecoli	2102	2184	2328	2328
Haein	1077	1085	1085	1085
Paeru	1496	1506	1552	1558
Pmult	1204	1211	1214	1214
Salty	2083	2274	2331	2335
Xaxon	1120	1198	1225	1225
Xcamp	1151	1196	1223	1223
Xfast	963	973	994	994
Ypest-CO92	2037	2301	2318	2318
Ypest-KIM	1833	2086	2093	2093

Table 4: Comparison of the results - *Wigglesworthia glossinidia brevipalpis*

Genome 1	Genome 2	ILCS	IILCS	HYB2	Genome 1	Genome 2	ILCS	IILCS	HYB2
Baphi	Ecoli	90.39	99.55	100	Haein	Xcamp	98.83	99.79	100
Baphi	Haein	99.46	100	100	Haein	Xfast	99.23	99.85	100
Baphi	Paeru	97.9	99.61	100	Haein	Ypest-CO92	99.03	99.7	100
Baphi	Pmult	99.35	100	100	Haein	Ypest-KIM	98.32	99.48	99.96
Baphi	Salty	92.7	100	100	Paeru	Pmult	97.48	99.32	99.74
Baphi	Wglos	98.9	99.37	100	Paeru	Wglos	96.02	96.66	99.61
Baphi	Xaxon	95.27	100	100	Paeru	Xfast	98.11	99.5	99.71
Baphi	Xcamp	96.96	100	100	Pmult	Salty	98.16	99.23	99.56
Baphi	Xfast	99.59	100	100	Pmult	Wglos	99.18	99.75	100
Baphi	Ypest-CO92	92.34	98.3	100	Pmult	Ypest-CO92	98.15	99.03	99.42
Baphi	Ypest-KIM	91.78	99.21	100	Pmult	Ypest-KIM	97.83	98.19	99.22
Ecoli	Haein	99.07	99.64	99.96	Salty	Wglos	89.21	97.39	99.83
Ecoli	Pmult	98.65	99.61	99.97	Salty	Xfast	98.74	99.44	99.9
Ecoli	Wglos	90.29	93.81	100	Wglos	Xaxon	91.43	97.8	100
Ecoli	Xfast	97.39	98.4	99.79	Wglos	Xcamp	94.11	97.79	100
Haein	Paeru	97.25	99.02	99.51	Wglos	Xfast	96.88	97.89	100
Haein	Pmult	99.11	99.34	99.36	Wglos	Ypest-CO92	87.88	99.27	100
Haein	Salty	99.08	99.61	99.96	Wglos	Ypest-KIM	87.58	99.67	100
Haein	Wglos	99.26	100	100	Xfast	Ypest-CO92	92.2	93.18	100
Haein	Xaxon	98.3	99.8	99.86	Xfast	Ypest-KIM	98.04	98.31	99.89
Heuristic				ILCS		IILCS		HYB2	
Average performance				96.24		98.9		99.88	

Table 5: Performances of each of the three heuristics compared to the exact result (40 instances)

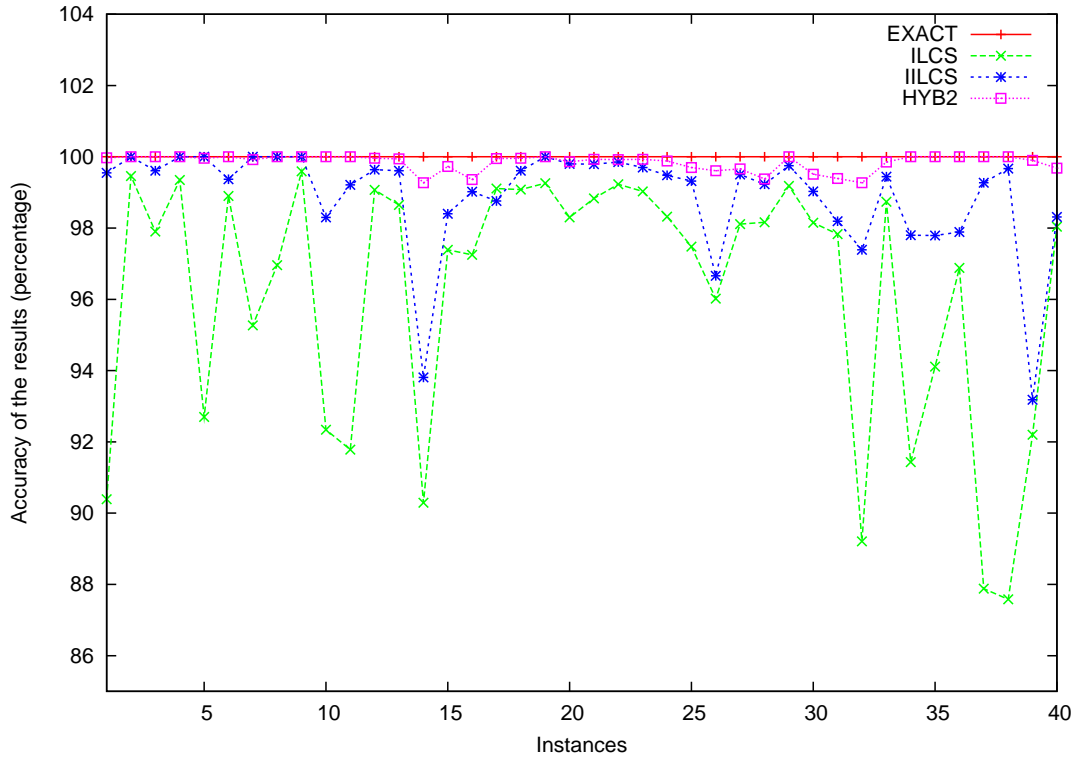


Figure 3: Graphical comparison of the exact results (100%) with the three heuristics *ILCS*, *IILCS* and *HYB₂*