Haplotype Inference Combining Pedigrees and Unrelated Individuals

Ana Graça[1], Inês Lynce[1], João Marques-Silva[2], and Arlindo L. Oliveira[1]

[1] IST/INESC-ID, Technical University of Lisbon, Portugal
{assg,ines}@sat.inesc-id.pt,aml@inesc-id.pt
[2] School of Computer Science and Informatics, University College Dublin, Ireland
jpms@ucd.ie

Abstract. Haplotype inference is a crucial topic in genetic studies and also represents a challenging computational problem. A significant number of combinatorial approaches tackle the haplotype inference problem either for pedigrees or for unrelated individuals. This work integrates two relevant and well-known constraint based haplotyping approaches. The Minimum Recombinant Haplotyping Configuration (MRHC) problem targets the haplotyping solution which minimizes the number of recombinant events within a pedigree. MRHC only takes into consideration the family information. In contrast, the Haplotype Inference by Pure Parsimony (HIPP) problem aims at finding a solution which minimizes the number of distinct haplotypes. The HIPP approach is adequate for phasing unrelated individuals from the same population. This paper proposes a method for inferring haplotypes for individuals of the same population, although organized in different families, thus combining both MRHC and HIPP approaches. This new method can take into account family information and population information, both important in haplotype inference. Experimental results show that the proposed approach is more accurate, both in terms of switch error rate and missing error rate, than the MRHC approach (performed by the PedPhase tool), on sets of families from the same population.

1 Introduction

Genetic association studies with phenotypic variations are only possible with a deep knowledge of the genetic differences between individuals. A very important and challenging task to understand genetic variations consists of inferring haplotypes from genotypes.

Constraint based methods for haplotype inference have been shown to be a practical and relevant alternative to statistical approaches, either for phasing pedigrees [9, 11] or unrelated individuals [4]. Nonetheless, a study comparing the haplotype inference methods using pedigrees and unrelated individuals [12] points out that a new method which takes into consideration both pedigree and population information is necessary. Indeed, existing haplotyping methods for pedigrees ignore the population information, while haplotyping methods for unrelated individuals do not take into account the pedigree information.

The comparison study described in [12] motivated the development of the work presented in this paper. A constraint based model to deal with families and unrelated individuals is proposed. The new method is based in two well-known combinatorial approaches. The Minimum Recombinant Haplotype Configuration (MRHC) approach is used to phase individuals organized in pedigrees, by minimizing the number of recombination events within each pedigree. In general, a significant number of solutions can be obtained using only the minimum recombinant paradigm, especially when several families are considered. Thus, the Haplotype Inference by Pure Parsimony (HIPP) approach is considered to choose a solution

that uses the minimum number of distinct haplotypes, among all the minimum recombinant solutions. The new method for haplotype inference, named PedRPoly, is shown to be more accurate than the method traditionally used for inferring haplotypes on pedigrees using the minimum recombinant approach, performed by the PedPhase tool [11]. In addition, this paper suggests some reductions on the size of the original integer programming MRHC model.

The paper is organized as follows. The next section describes the haplotype inference problem and overviews the MRHC and HIPP approaches. Section 3 details the new proposed model, PedRPoly, which combines MRHC and HIPP formulations. Afterwards experimental results comparing the accuracy of PedPhase and PedRPoly are presented and discussed. Finally, the conclusions are presented in section 5.

2 Haplotype Inference

Single Nucleotide Polymorphisms (SNPs) are the most common variations between human beings, which occur when a nucleotide is mutated into another nucleotide at a single DNA position. Haplotypes correspond to the set of closely linked SNPs, within a single chromosome which tends to be inherited together. However, it is very expensive and time consuming to determine experimentally the haplotypes. Instead, only genotypes, which correspond to the conflated data of two haplotypes on homologous chromosomes are obtained. The haplotype inference problem consists in determining the haplotypes which originate a given genotype.

Considering that mutations are rare, we may assume that each SNP can only have two values. Each haplotype is therefore represented by a binary string with size $m \in \mathbb{N}$, where 0 represents the wild type and 1 represents the mutant type. Each site i of the haplotype h_i is represented by $h_{i\,j}$ ($1 \leq j \leq m$). Each genotype is represented by a string, with size m, over the alphabet $\{0, 1, 2\}$, and each site of the genotype g_i is represented by $g_{i\,j}$. Each genotype is explained by two haplotypes. A genotype $g_i \in \mathcal{G}$ is explained by a pair of haplotypes (h_i^a,h_i^b) such that

$$g_{i\,j} = \begin{cases} h_{i\,j}^a \text{ if } h_{i\,j}^a = h_{i\,j}^b \\ 2 \quad \text{if } h_{i\,j}^a \neq h_{i\,j}^b \end{cases} . \tag{1}$$

A genotype site $g_{i\,j}$ with either value 0 or 1 is a homozygous site (the same allele is inherited from both parents), whereas a site with value 2 is a heterozygous site (different alleles are inherited from each parent).

Definition 1. *Given a set $\mathcal{G}$ of n genotypes, each with size m, the haplotype inference problem consists in finding a set of haplotypes $\mathcal{H}$, such that each genotype $g_i \in \mathcal{G}$ is explained by two haplotypes $h_i^a, h_i^b \in \mathcal{H}$.*

For each genotype g with k heterozygous sites, there are 2^{k-1} pairs of haplotypes that can explain g. For example, genotype $g_i = 202$ can be explained either by haplotypes (000,101) or by haplotypes (001,100).

When the considered individuals are organized in pedigrees, additional information may be associated with the haplotype inference problem. Considering the Mendelian law of inheritance, every site in a single haplotype is inherited from a single parent, assuming no mutations within a pedigree. In a pedigree, an individual is a *founder* if he does not have parents on the pedigree (and a non-founder if he has both parents on the pedigree). We assume that haplotype h^a is inherited from the father and h^b is inherited from the mother, thus

breaking a symmetry on the pairs of haplotypes for non-founder individuals. However, a recombination may occur, where the two haplotypes of a parent get shuffled and the shuffled haplotype is passed on to the child. The result of a recombination event is a *recombinant*.

2.1 Minimum Recombinant Haplotype Configuration

Recombination events are rare in DNA regions with high linkage disequilibrium. Therefore, most rule-based haplotype inference methods for pedigrees assume no recombination among SNPs within each pedigree [19, 20, 13]. Although the assumption of no recombination is valid in many cases, this assumption can be violated even for some dense markers [9]. Therefore, the problem of minimizing the number of recombinants was suggested [6, 18]. The Minimum Recombinant Haplotype Configuration problem (MRHC) is a well-known approach to haplotype inference in pedigrees. The MRHC problem is NP-hard [9, 10, 15].

Definition 2. *The Minimum Recombinant Haplotype Configuration (MRHC) problem aims at finding a haplotype inference solution for a pedigree which minimizes the number of required recombinants [6, 18].*

The PedPhase tool [9] implements an Integer Linear Programming (ILP) model for minimum recombinant with missing alleles.

2.2 Haplotype Inference by Pure Parsimony

The Haplotype Inference by Pure Parsimony (HIPP) approach aims at finding a minimum-cardinality set of haplotypes $\mathcal{H}$ that can explain a given set of genotypes $\mathcal{G}$. The idea of searching for the solution with the smallest number of haplotypes is biologically motivated by the fact that individuals from the same population have the same ancestors and mutations do not occur often. Moreover, it is also well-known that the number of haplotypes in a population is much smaller than the number of genotypes. It has been shown that the HIPP problem is NP-hard [7].

Definition 3. *The haplotype inference by pure parsimony (HIPP) problem consists in finding a solution to the haplotype inference problem which minimizes the number of distinct haplotypes [5].*

RPoly [4] is a state-of-the-art HIPP solver implementing a 0-1 ILP model.

3 PedRPoly: Minimum Recombinant Maximum Parsimony

This section describes the PedRPoly model which aims at finding a haplotype inference solution for sets of pedigrees from the same population. The PedRPoly model is a combination of the MRHC PedPhase model [10] and the HIPP RPoly model [4].

Definition 4. *The Minimum Recombinant Maximum Parsimony model aims at finding a haplotype inference solution which minimizes the number of recombinants within pedigrees and the number of distinct haplotypes used.*

Table 1. The PedRPoly Model: Minimum Recombinant Maximum Parsimony.

minimize:	$(2n+1) \times \sum_{non-founder\ i} \sum_{j=1}^{m-1} (r^1_{i\,j} + r^2_{i\,j}) + \sum_{i=1}^{n} (u^a_i + u^b_i)$	
subject to:		
Equation	Constraint	Indexes
	Mendelian Law of Inheritance rules (Table 2)	
(2)	$-r^l_{i\,j} + g^l_{i\,j} - g^l_{i\,j+1} \leq 0$ $-r^l_{i\,j} - g^l_{i\,j} + g^l_{i\,j+1} \leq 0$	$l = 1,\ 2$ $1 \leq i \leq n$, i non-founder $1 \leq j \leq m$
(3)	$\neg(R \Leftrightarrow S) \Rightarrow x^{p\,q}_{i\,k}$ (Table 3)	$p, q \in \{a, b\}$ $1 \leq k < i \leq n$
(4)	$\sum_{k<i\,;\,q\in\{a,b\}} x^{p\,q}_{i\,k} - u^p_i \leq 2i - 3$	$1 < i \leq n$ $p \in \{a, b\}$

Example 1. Consider two trios (father, mother and child), from two families A and B, with the following genotypes: $g_A^{father} = 102$, $g_A^{mother} = 222$, $g_A^{child} = 202$, $g_B^{father} = 211$, $g_B^{mother} = 102$ and $g_B^{child} = 222$. Family A has two possible MRHC solutions (with 0 recombinants). Solution 1: $h_A^{father} = (100, 101)$, $h_A^{mother} = (001, 110)$, $h_A^{child} = (100, 001)$. Solution 2: $h_A^{father} = (100, 101)$, $h_A^{mother} = (000, 111)$ and $h_A^{child} = (101, 000)$. Family B has only one possible MRHC solution (with 0 recombinants): $h_B^{father} = (111, 011)$, $h_B^{mother} = (100, 101)$ and $h_B^{child} = (011, 100)$. Therefore, when considering both families, there are two possible MRHC solutions. Nonetheless, taking into consideration the number of haplotypes that each solution uses, solution 2 is preferred. Indeed, solution 1 uses 6 distinct haplotypes $(100, 101, 001, 110, 111, 011)$ while solution 2 uses only 5 distinct haplotypes $(100, 101, 000, 111, 011)$.

PedRPoly is a 0-1 ILP model which combines the ILP PedPhase model and the RPoly model. Constraints are detailed in Table 1. Following the RPoly model, the PedRPoly model associates two haplotypes, h_i^a and h_i^b, with each genotype g_i, and these haplotypes are required to explain g_i. Moreover, PedRPoly associates a variable $t_{i\,j}$ with each heterozygous site $g_{i\,j}$, such that $t_{i\,j} = 1$ indicates that $h^a_{i\,j} = 1$ and $h^b_{i\,j} = 0$, whereas $t_{i\,j} = 0$ indicates that $h^a_{i\,j} = 0$ and $h^b_{i\,j} = 1$. The values of h_i^a and h_i^b at homozygous sites are implicitly assumed.

To analyze the recombination events within pedigrees, not only the paternal and maternal haplotypes are considered, but also the grand-paternal and grand-maternal origin of each allele in the haplotypes. Following the PedPhase MRHC model, for each non-founder individual i and site j, two variables are defined: $g^1_{i\,j}$ and $g^2_{i\,j}$. $g^1_{i\,j} = 0$ ($g^1_{i\,j} = 1$) represents that the paternal allele of individual i at site j comes from the paternal grandfather (grandmother). In a similar way, $g^2_{i\,j} = 0$ ($g^2_{i\,j} = 1$) represents that the maternal allele of individual i at site j comes from the maternal grandfather (grandmother). Constraints to ensure that the Mendelian law of inheritance is satisfied are defined in Table 2. Note that PedRPoly only associates variables with heterozygous sites (inspired by RPoly), while PedPhase associates variables with both homozygous and heterozygous sites. The new definition of variables associated with sites requires the redefinition of the constraints related with Mendelian laws.

Table 2. Mendelian Law of Inheritance Rules (regarding variables g^1_{ij}). The constraints involving variables g^2_{ij} are defined similarly ($1 \leq i \leq n$, i non-founder, $1 \leq j \leq m$).$f(i)$ corresponds to the father of i.

Condition	Constraint
$g_{ij} = 0 \wedge g_{f(i)j} = 2$	$t_{f(i)j} \Leftrightarrow g^1_{ij}$
$g_{ij} = 0 \wedge g_{f(i)j} = ?$	$(g^1_{ij} \vee \neg h^a_{f(i)j}) \wedge (\neg g^1_{ij} \vee \neg h^b_{f(i)j})$
$g_{ij} = 1 \wedge g_{f(i)j} = 2$	$t_{f(i)j} \Leftrightarrow \neg g^1_{ij}$
$g_{ij} = 1 \wedge g_{f(i)j} = ?$	$(g^1_{ij} \vee h^a_{f(i)j}) \wedge (\neg g^1_{ij} \vee h^b_{f(i)j})$
$g_{ij} = 2 \wedge g_{f(i)j} = 0$	$\neg t_{ij}$
$g_{ij} = 2 \wedge g_{f(i)j} = 1$	t_{ij}
$g_{ij} = 2 \wedge g_{f(i)j} = 2$	$(g^1_{ij} \vee t_{ij} \vee \neg t_{f(i)j}) \wedge (g^1_{ij} \vee \neg t_{ij} \vee t_{f(i)j}) \wedge$ $(\neg g^1_{ij} \vee t_{ij} \vee t_{f(i)j}) \wedge (\neg g^1_{ij} \vee \neg t_{ij} \vee \neg t_{f(i)j})$
$g_{ij} = 2 \wedge g_{f(i)j} = ?$	$(g^1_{ij} \vee t_{ij} \vee \neg h^a_{f(i)j}) \wedge (g^1_{ij} \vee \neg t_{ij} \vee h^a_{f(i)j}) \wedge$ $(\neg g^1_{ij} \vee t_{ij} \vee \neg h^b_{f(i)j}) \wedge (\neg g^1_{ij} \vee \neg t_{ij} \vee h^b_{f(i)j})$
$g_{ij} = ? \wedge g_{f(i)j} = 0$	$\neg h^a_{ij}$
$g_{ij} = ? \wedge g_{f(i)j} = 1$	h^a_{ij}
$g_{ij} = ? \wedge g_{f(i)j} = 2$	$(g^1_{ij} \vee h^a_{ij} \vee \neg t_{f(i)j}) \wedge (g^1_{ij} \vee \neg h^a_{ij} \vee t_{f(i)j}) \wedge$ $(\neg g^1_{ij} \vee h^a_{ij} \vee t_{f(i)j}) \wedge (\neg g^1_{ij} \vee \neg h^a_{ij} \vee \neg t_{f(i)j})$
$g_{ij} = ? \wedge g_{f(i)j} = ?$	$(g^1_{ij} \vee h^a_{ij} \vee \neg h^a_{f(i)j}) \wedge (g^1_{ij} \vee \neg h^a_{ij} \vee h^a_{f(i)j}) \wedge$ $(\neg g^1_{ij} \vee h^a_{ij} \vee \neg h^b_{f(i)j}) \wedge (\neg g^1_{ij} \vee \neg h^a_{ij} \vee \neg h^b_{f(i)j})$

Table 3. Definition of predicates R and S, accordingly to index values.

Condition	Constraint
$g_{ij} \neq 2 \wedge g_{kj} = 2$	$R = (g_{ij} \Leftrightarrow (q \Leftrightarrow a))$ and $S = t_{kj}$
$g_{kj} \neq 2 \wedge g_{ij} = 2$	$R = (g_{kj} \Leftrightarrow (p \Leftrightarrow a))$ and $S = t_{ij}$
$g_{ij} = 2 \wedge g_{kj} = 2$	$R = (p \Leftrightarrow q)$ and $S = (t_{ij} \Leftrightarrow t_{kj})$
$g_{ij} = ? \wedge g_{kj} \notin \{2, ?\}$	$R = t^p_{ij}$ and $S = g_{kj}$
$g_{kj} = ? \wedge g_{ij} \notin \{2, ?\}$	$R = t^q_{kj}$ and $S = g_{ij}$
$g_{ij} = ? \wedge g_{kj} = 2$	$R = (q \Leftrightarrow a)$ and $S = (t^p_{ij} \Leftrightarrow t_{kj})$
$g_{kj} = ? \wedge g_{ij} = 2$	$R = (p \Leftrightarrow a)$ and $S = (t^q_{kj} \Leftrightarrow t_{ij})$
$g_{ij} = ? \wedge g_{kj} = ?$	$R = t^p_{ij}$ and $S = t^q_{kj}$

Furthermore, variables are defined to count the number of recombinations. For each non-founder individual i, variable r^1_{ij} (r^2_{ij}) is assigned value 1 if there was recombination at site j, to create the paternal (maternal) haplotype of individual i. Thus, $r^l_{ij} = 1$ if $g^l_{ij} \neq g^l_{ij+1}$, for $l = 1, 2$ and $1 \leq j \leq m-1$, which is ensured by constraints (2). Here, a simplification to the original MRHC is considered. Actually, in the original model, $r^l_{ij} = 1$ *if and only if* $g^l_{ij} \neq g^l_{ij+1}$. Observe that an implication, instead of an equivalence, is sufficient for correctness and reduces in half the number of these constraints.

Once more following the RPoly model, let x^{pq}_{ik}, with $p, q \in \{a, b\}$ and $1 \leq k < i \leq n$, be 1 if haplotype p of genotype g_i and haplotype q of genotype g_k are different. The conditions on the x^{pq}_{ik} variables are based on the values of variables t_{ij} and t_{kj} for heterozygous sites, and are described by equations (3).

In addition, the model uses variables u to denote when one of the haplotypes, associated with a given genotype, is different from all previous haplotypes. Hence, u^p_i, with $p \in \{a, b\}$ and $1 \leq i \leq n$, is 1 if haplotype p of genotype g_i is different from all previous haplotypes. Then, the conditions on the u^p_i variables are based on the conditions for the x^{pq}_{ik} variables, with $1 \leq k < i$ and $q \in \{a, b\}$ and correspond to equation (4).

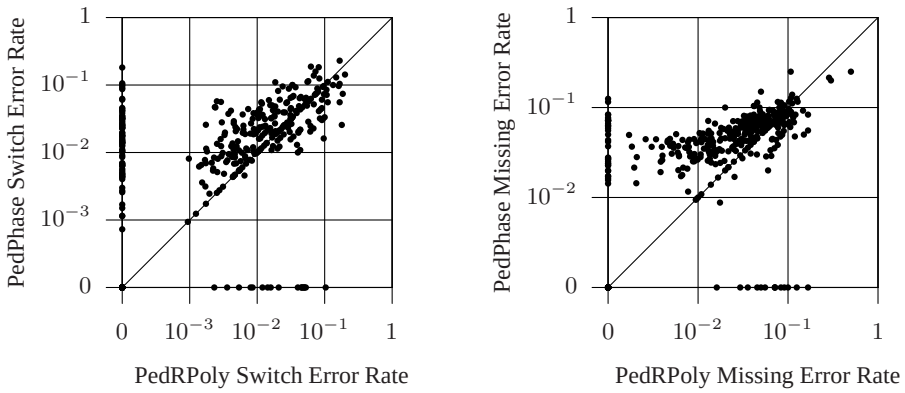

Fig. 1. Comparison of PedRPoly and PedPhase error rates

Finally, the cost function minimizes the number of recombination events, which is given by the sum of variables r, and the number of distinct haplotypes used on the solution, which is given by the sum of variables u. Nonetheless a larger weight is given to the number of recombinants, because we want to guarantee that a minimum recombinant solution is chosen. (Note that $2n$ is a trivial upper bound on the number of haplotypes on the solution.)

4 Experimental Results

The experimental data was simulated using the SimPed program [8]. SimPed generates haplotypes for families, given the pedigree structure, as well as the haplotypes and their frequencies for founders. Three different sets of haplotypes were considered. These sets of haplotypes are real data for which haplotypes have been experimentally identified [1, 17], and correspond to the A, B and C data sets used in [2]. Haplotypes in set A have 9 SNPs, haplotypes in set B have 5 SNPs and haplotypes in set C have 17 SNPs. Three different pedigree structures, taken from [10], were considered: pedigree 1 with 15 members, pedigree 2 with 29 individuals and pedigree 3 with 17 individuals (with a mating loop). Each simulated instance consists of 10 replicates of the given pedigree, simulating 10 different families from the same population. Recombination events between alleles were considered with probabilities 0.1%, 0.5% and 1%. Three variations on missing rates were considered: 1%, 10% and 20%. For each parameters combination, 5 independent replicates were selected, resulting in a total of 405 ($= 3^4 \times 5$) input trials. MiniSat+ [3] was used as a 0-1 ILP tool to solve the PedRPoly model.

In order to analyze the accuracy of the methods, two different errors were considered. The *switch error rate* measures the percentage of possible switches in haplotype orientation, used to recover the correct phase in an individual [14]. Missing alleles are not considered for computing the switch error. The *missing error rate* is the percentage of incorrectly inferred missing data [16].

Figure 1 presents two scatter plots comparing the switch error and missing error rates for PedRPoly and PedPhase. Each problem instance corresponds to a point in the plot, where the x-axis represents the error rate of the PedRPoly approach and the y-axis represents the error rate of the ILP PedPhase approach.

The switch error rate of the methods is compared in the left plot of Figure 1. The switch error of PedRPoly is smaller than the switch error of PedPhase for 55.3% of the problem instances. The switch error of PedRPoly is larger than the switch error of PedPhase for

Table 4. Switch Error Rate and Missing Error Rate for PedRPoly and PedPhase in sets of instances with different parameters (n is the number of genotypes of the instance, with n=$10 \cdot f$ where f is the size of each pedigree, and m is the number of sites of each genotype).

		Error Rate			
Set		**Switch Error Rate**		**Missing Error Rate**	
		PedRPoly	**PedPhase**	**PedRPoly**	**PedPhase**
Missing Rate	1%	0.0115	0.0143	0.0361	0.0411
	10%	0.0190	0.0232	0.0382	0.0488
	20%	0.0304	0.0437	0.0456	0.0625
Recombination Rate	0.1%	0.0157	0.0221	0.0393	0.0472
	0.5%	0.0212	0.0267	0.0398	0.0506
	1%	0.0240	0.0324	0.0407	0.0546
Pedigree	Ped1 (n=150)	0.0194	0.0245	0.0428	0.0469
	Ped2 (n=290)	0.0199	0.0284	0.0355	0.0471
	Ped3 (n=170)	0.0217	0.0283	0.0415	0.0584
Population	A (m=9)	0.0116	0.0210	0.0428	0.0469
	B (m=5)	0.0450	0.0482	0.0355	0.0471
	C (m=17)	0.0044	0.0120	0.0415	0.0584

16.8% of the problem instances, and for the remaining 27.9% the error is the same for both methods.

With respect to the missing error rate (right plot of Figure 1), it is clear that PedRPoly is more accurate than PedPhase. Indeed, the missing error of PedRPoly is smaller than the missing error of PedPhase for 64.7% of the problem instances. The missing error of PedRPoly is larger than the missing error of PedPhase for 18% of the problem instances, and for the remaining 17.3% instances the error is the same for both methods.

Table 4 presents the accuracy results organized by parameter value. Each value is the average of the missing error for the 135 instances generated with the correspondent parameter value. We conclude that PedRPoly has a smaller error rate on every class of instances.

Finally, we have compared the number of distinct haplotypes in the PedRPoly solution and the PedPhase solution with the number of haplotypes in the real solution. PedRPoly has the same number of haplotypes than the real solution for 64.7% of the instances and for 96.8% of the instances the number of haplotypes in the PedRPoly solution differs in less than 3 haplotypes from the number in the real solution. PedPhase solutions have less similarity with the real solutions with respect to the number of distinct haplotypes. For 23.7% of the instances, the number of haplotypes in the PedPhase solution is equal to the number of haplotypes in the real solution, and for 50% of the instances, the number of haplotypes in the PedRPoly solution differs in more than 2 haplotypes from the real solution.

Regarding the efficiency of PedRPoly and PedPhase methods, while PedPhase is able to solve each instance in a few seconds, PedRPoly can take a few hours. Improving the efficiency of PedRPoly is the main short term goal.

5 Conclusions and Future Work

This paper presents a new method for inferring haplotypes from genotype data of families from the same population. The proposed method (called PedRPoly) integrates the minimum recombinant and the pure parsimony principles, two relevant constraint based haplotyping approaches. Thus, PedRPoly can take into account both the family information and the

population information. Experimental results show that PedRPoly is actually more accurate than PedPhase which only uses the minimum recombinant principle.

Future work directions include improving the efficiency of the PedRPoly method and testing the method in larger and real data sets.

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