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FASTCHI: AN EFFICIENT ALGORITHM FOR ANALYZING GENE-GENE INTERACTIONS

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Abstract

Recent advances in high-throughput genotyping have inspired increasing research interests in genome-wide association study for diseases. To understand underlying biological mechanisms of many diseases, we need to consider simultaneously the genetic effects across multiple loci. The large number of SNPs often makes multilocus association study very computationally challenging because it needs to explicitly enumerate all possible SNP combinations at the genome-wide scale. Moreover, with the large number of SNPs correlated, permutation procedure is often needed for properly controlling family-wise error rates. This makes the problem even more computationally demanding, since the test procedure needs to be repeated for each permuted data. In this paper, we present FastChi, an exhaustive yet efficient algorithm for genome-wide two-locus chi-square test. FastChi utilizes an upper bound of the two-locus chi-square test, which can be expressed as the sum of two terms – both are efficient to compute: the first term is based on the single-locus chi-square test for the given phenotype; and the second term only depends on the genotypes and is independent of the phenotype. This upper bound enables the algorithm to only perform the two-locus chi-square test on a small number of candidate SNP pairs without the risk of missing any significant ones. Since the second part of the upper bound only needs to be precomputed once and stored for subsequence uses, the advantage is more prominent in large permutation tests. Extensive experimental results demonstrate that our method is an order of magnitude faster than the brute force alternative.

1. Introduction

Disease association study analyzes genetic variation across a population consisting of diseased and healthy individuals. The most abundant source of genetic variation in mammalian genome is represented by single nucleotide polymorphisms (SNPs), which account for heritable inter-individual differences in complex phenotypes. The allele differences at these single base sites are usually represented as binary variables (e.g. inbred mice) or ternary variables (e.g. human subjects). Recent advancement of the technologies that enable genotyping a vast number of genetic polymorphism has made genome wide association study possible. Initial reports on genome-wide searching for disease associated genes are appearing in the literature 6,10,15.

Most existing analytical methods consider each genetic marker individually 20. In many cases, however, the diseases are complex traits, that is, they are likely due to the interactions among multiple genes 2,17. In order to understand their underlying biological mechanisms, we need to consider simultaneously the joint effects of genotypes across multiple loci. Various machine learning models have been adopted to study the interactions among genes, such as neural networks 3,18 and classification and regression trees (CART)12,22. Under the assumption that the number of SNPs is small, exhaustive algorithms that explicitly enumerate all possible SNP combinations have been developed 7,13. Since these methods

explicitly enumerate all possible SNP combinations, they are not suitable for genome-wide association studies.

The number of SNPs in public datasets ranges from thousands to hundreds of thousands1,21. The computational burden of searching for interactions among the large number of SNPs often makes the complete genome wide association study intractable. SNP tagging 5,16 have been widely used to reduce the number of SNPs to be analyzed. The goal of SNP tagging is to select a subset of SNPs that can be used as proxies for all SNPs in the genome. The tagged SNPs are then used in the association study. These methods are not complete because some important SNPs may not be tagged.

The computational challenge of genome-wide association study is also caused by another problem known as multiple testing problem. It can be described as the potential increase in Type I error when statistical tests are performed multiple times. Let α be the significant level for each independent test. If n independent comparisons are performed, the family-wise error α' is given by $\alpha' = 1 - (1 - \alpha)^n$. For example, if $\alpha = 0.05$ and we test twenty null hypotheses, then we have probability $\alpha' = 1 - 0.95^{20} = 0.64$ to get at least one spurious result. Permutation testing has been the gold standard for assessing significance levels in association studies using multiple markers. However, it is time consuming since the test procedure needs to be repeated for every permutation. To make this process feasible, other correction methods have been proposed 8,9. Some recent work 23 addresses the problem of two-locus quantitative phenotype association mapping when large permutation tests are needed. However, this method focuses on the case where the phenotypes are continuous variables, hence is not readily applicable to case-control study of diseases.

Theoretically well studied, the chi-square test has been widely used in association studies 11. In this paper, we examine the ***computational aspect*** of the chi-square test. We present an efficient algorithm, FastChi, and show that the standard chi-square test can be applied in the genome-wide scale for two-locus association study even when large permutation tests are performed. Different from the algorithms applying heuristics, tagging SNPs, or adopting other correction methods, FastChi is an *exhaustive* algorithm. It guarantees to find the optimal solution. Yet, FastChi does not need to explicitly compute the chi-square value for every SNP pair. It utilizes an upper bound of the two-locus chi-square test value, which is the sum of two terms: one based on the single-locus chi-square test, and the other based on the pair-wise SNP genotypes. Using this bound, a large portion of the SNP-pairs are pruned without performing the tests. Due to space limitation, in this paper, we mainly focus on the case where the SNPs are binary variables which are encoded using {0, 1}. We also have similar results for the case where the SNPs are ternary variables, which will be discussed in Section 5.

2. Problem Definition

Let $\{X_1, X_2, \cdots, X_N\}$ be the set of all biallelic SNPs , and Y be the binary phenotype of interest (e.g., disease or non-disease). For any SNP X_i $(1 \le i \le N)$, we represent its chi-square test value with Y as $\chi^2(X_i, Y)$. For any SNP-pair X_i and X_j, the chi-square test value is denoted as $\chi^2(X_iX_j, Y)$. We formalize the problem as follows. Given the set of N SNPs and a phenotype Y for a set of M individuals, let $Y' = \{Y_1, Y_2, \cdots Y_K\}$ be the set of K permutations of Y. There are two possible cases:

(1) For a single pass association study, i.e., no permutation correction needed: find all SNP-pairs (X_iX_j) such that $\chi^2(X_iX_j, Y) \ge \theta$.

(2) If there are multiple phenotype permutations: for each $Y_k \in Y'$, find all SNP-pairs (X_iX_j) such that $\chi^2(X_iX_j, Y_k) \ge \theta, (1 \le k \le K)$.

Our problem formalization can also be applied in other problem settings. For example, it is easy to modify this problem definition to find the top-k SNP-pairs that have the largest chi-square test values among all SNP-pairs. In this scenario, θ would be a dynamic value, i.e., the k-th largest chi-square test value identified by the algorithm so far.

3. The FastChi Algorithm

We first present the upper bound of the two-locus chi-square test value in Section 3.1. Then we show how our algorithm FastChi utilizes the upper bound to achieve efficient two-locus chi-square testing. In Section 3.2, we describe the method for a single phenotype Y. In Section 3.3, we discuss how FastChi performs under permutation procedure.

3.1. The Upper Bound

Let A, B, C, D represent the following events respectively: $Y = 0 \wedge X_i = 0$; $Y = 0 \wedge X_i = 1$; $Y = 1 \wedge X_i = 0$; $Y = 1 \wedge X_i = 1$. Let E_{event} and O_{event} denote the expected value and observed value of an event. T_1, T_2, S_1, S_2, $\mathscr{R}_1$, and $\mathscr{R}_2$ represent the formulas shown in Table 1. We have the upper bound of $\chi^2(X_iX_j, Y)$ stated in Theorem 3.1. The derivation of the upper bound is omitted due to space limitation.

Theorem 3.1.—*(Upper bound of $\chi^2(X_iX_j, Y)$)*

$$\chi^2\left(X_iX_j, Y\right) \leq \chi^2(X_i, Y) + T_1S_1\mathscr{R}_1 + T_2S_2\mathscr{R}_2.$$

3.2. A Single Phenotype

It is obvious that, if the upper bound of $\chi^2(X_iX_j, Y)$ is less than θ, there is no need to calculate the exact value of $\chi^2(X_iX_j, Y)$, which is guaranteed to be smaller than θ. We now discuss this idea in further detail.

For every X_i $(1 \leq i \leq N)$, let $AP(X_i) = \{(X_iX_j) | i+1 \leq j \leq N\}$ be the SNP-pairs with X_i being the SNP of lower index value. For all SNP-pairs in $AP(X_i)$, the phenotype Y and SNP X_i do not vary, thus O_A, O_B, O_C and O_D are constants for all SNP-pairs in $AP(X_i)$. The number of individuals, M, is also a constant. Thus, in the upper bound, T_1S_1 and T_2S_2 are constants. Moreover, $\chi^2(X_i, Y)$ is a constant for a given X_i, and θ is given too. Therefore, $\mathscr{R}_1$ and $\mathscr{R}_2$ are the only variables that depend on X_j and may vary for different SNP-pairs $(X_iX_j) \in AP(X_i)$. Thus for a given X_i, we can treat equation $\chi^2(X_i, Y) + T_1S_1\mathscr{R}_2 + T_2S_2\mathscr{R}_2 = \theta$ as a *straight line* in the 2-D space of $\mathscr{R}_1$ and $\mathscr{R}_2$.

From now on, we use $\mathscr{R}_1(X_iX_j)$ and $\mathscr{R}_2(X_iX_j)$ to represent the specific values of $\mathscr{R}_1$ and $\mathscr{R}_2$ for the SNP-pair (X_iX_j). The following proposition specifies the values that $\mathscr{R}_1(X_iX_j)$ and $\mathscr{R}_2(X_iX_j)$ can take.

Proposition 3.1.—*If there are m 0's and $(M-m)$ 1's in X_i, then for any $(X_iX_j) \in AP(X_i)$, the possible values that $\mathscr{R}_1(X_iX_j)$ can take are: $\left\{\frac{0}{m}, \frac{1}{m-1}, \frac{2}{m-2}, \cdots, \frac{\lfloor m/2 \rfloor}{\lceil m/2 \rceil}\right\}$. The possible values that $\mathscr{R}_2(X_iX_j)$ can take are: $\left\{\frac{0}{M-m}, \frac{1}{M-m-1}, \frac{2}{M-m-2}, \cdots, \frac{\lfloor (M-m)/2 \rfloor}{\lceil (M-m)/2 \rceil}\right\}$.*

Therefore, for all $(X_iX_j) \in AP(X_i)$, in the 2-D space of $\mathscr{R}_1$ and $\mathscr{R}_2$, $(\mathscr{R}_1(X_iX_j), \mathscr{R}_2(X_iX_j))$ falls in the region $[0, 1] \times [0, 1]$. The line $\chi^2(X_i, Y) + T_1S_1\mathscr{R}_1 + T_2S_2\mathscr{R}_2 = \theta$ divides this region into two parts: one above the line and one below it. Among the SNP-pairs in $AP(X_i)$, we only need to perform the test for those ones whose $(\mathscr{R}_1(X_iX_j), \mathscr{R}_2(X_iX_j))$ values are

above the line, i.e., whose upper bounds are greater than the threshold θ. We refer to such SNP-pairs as *candidate* SNP-pairs.

Example 3.1—Suppose that there are 32 individuals, half alleles of X_i are 0's, and half are 1's. Thus, for the SNP-pairs in $AP(X_i)$, the possible values of $\mathcal{R}_1(X_iX_j)$ (and $\mathcal{R}_2(X_iX_j)$) are $\left\{\frac{0}{16}, \frac{1}{15}, \frac{2}{14}, \frac{3}{13}, \frac{4}{12}, \frac{5}{11}, \frac{6}{10}, \frac{7}{9}, \frac{8}{8}\right\}$. Figure 1(a) shows the 2-D space of $\mathcal{R}_1$ and $\mathcal{R}_2$. The blue stars represent the values that $(\mathcal{R}_1(X_iX_j),\mathcal{R}_2(X_iX_j))$ can take. The line $\chi^2(X_i, Y) + T_1S_1\mathcal{R}_1 + T_2S_2\mathcal{R}_2 = \theta$ is also plotted in the figure. The candidate SNP-pairs are those whose $(\mathcal{R}_1(X_iX_j),\mathcal{R}_2(X_iX_j))$ values are in the shaded region. The ones whose $(\mathcal{R}_1(X_iX_j),\mathcal{R}_2(X_iX_j))$ values fall below the line can be pruned without any further test.

To efficiently retrieve the candidates, SNP-pairs (X_iX_j) in $AP(X_i)$ are grouped by their $(\mathcal{R}_1(X_iX_j),\mathcal{R}_2(X_iX_j))$ values and indexed in a 2D array, referred to as $Array(X_i)$.

Example 3.2—Following Example 3.1, Figure 1(b) shows the 9 × 9 array, $Array(X_i)$, whose entries represent the possible values of $(\mathcal{R}_1(X_iX_j),\mathcal{R}_2(X_iX_j))$ for SNP-pairs $(X_iX_j) \in AP(X_i)$. The $\mathcal{R}_1(X_iX_j)$ ($\mathcal{R}_2(X_iX_j)$) value of each column (row) is noted beneath (left to) each column (row). Each entry of the array is a pointer to the SNP-pairs having the corresponding $(\mathcal{R}_1(X_iX_j),\mathcal{R}_2(X_iX_j))$ values.

In order to find the candidates SNP-pairs whose upper bounds are greater than θ, we start from the right most column of the array, i.e., the entries having the largest $\mathcal{R}_1(X_iX_j)$ value. We scan this column from the top (entries with larger $\mathcal{R}_2(X_iX_j)$ values) towards the bottom (entries with smaller $\mathcal{R}_2(X_iX_j)$ values). If an entry satisfies the inequality $\chi^2(X_i, Y) + T_1S_1\mathcal{R}_1 + T_2S_2\mathcal{R}_2 \geq \theta$, then the SNP-pairs indexed by it are the candidates subject to the chi-square tests. Once we reach an entry violating the inequality, we stop searching the current column, since the remaining entries in the column will not satisfy the inequality. We then move to the top entry of the column left to it and repeat the same scanning process. This whole process terminates when (1) we finish examining all columns or (2) we reach a column whose top entry does not satisfy the inequality.

Example 3.3—Continuing with Examples 3.1 and 3.2, the entries numbered from 1 to 14 in Figure 1(b) are the ones visited by the scanning process. The numbers show the order in which the entries are visited. Only the SNP-pairs indexed by shaded entries need to be evaluated by chi-square tests. The SNP-pairs indexed by the blank entries, including the entries on the boundary can be safely pruned.

3.3. Permuting the Phenotype

Let $Y' = \{Y_1, Y_2, \cdots, Y_K\}$ be the K permutations of the phenotype Y. The upper bound in Theorem 3.1 can be easily incorporated in the algorithm to handle the permutations: For any $(X_iX_j) \in AP(X_i)$, its $(\mathcal{R}_1(X_iX_j),\mathcal{R}_2(X_iX_j))$ value does not change over different permutations. That is, for every SNP X_i, the indexing structure $Array(X_i)$ is *independent* of permutations in Y'. Thus, for each X_i, once we get $Array(X_i)$, it can be reused in all permutations.

The FastChi algorithm is described in Algorithm 1. For each X_i, FastChi first indexes $(X_iX_j) \in AP(X_i)$ using $Array(X_i)$. Then it finds the set of candidate SNP-pairs $Cand(X_i, Y_k)$ by accessing $Array(X_i)$ for every phenotype permutation Y_k. The candidates in $Cand(X_i, Y_k)$ are then evaluated for their chi-square test values. The candidates whose chi-square test values are greater than or equal to θ are reported by the algorithm.

Input: SNPs $X' = \{X_1, X_2, \cdots, X_N\}$, phenotype permutations $Y' = \{Y_1, Y_2, \cdots, Y_K\}$, and input parameter θ
Output: for every $Y_k \in Y'$, find the set of SNP-pairs $Result(Y_k) = \{(X_iX_j) | \chi^2(X_iX_j, Y_k) \geq \theta, 1 \leq i < j \leq N\}$

```
for every X_i ∈ X', do
    index (X_iX_j) ∈ AP(X_i) by Array(X_i);
    for every Y_k ∈ Y', do
        access Array(X_i) to find the candidate SNP-pairs and store them in Cand(X_i, Y_k);
        for every (X_iX_j) ∈ Cand(X_i, Y_k) do
            if χ²(X_iX_j, Y_k) ≥ θ then
                Result(Y_k) ← (X_iX_j);
            end
        end
    end
end
Return Result(Y_k) for all Y_k ∈ Y'.
```

Algorithm 1.
FastChi1

Time complexity—The complexity to build the indexing structure for all SNPs is $O(N^2M)$. The worst case for accessing all $Array(X_i)$ for all permutations is $O(KNM^2)$. Let $C = \sigma_{i,k} |Cand(X_i, Y_k)|$ be the total number of candidates. The time complexity of FastChi is $O(N^2M+KNM^2+CM)$. Note that the time complexity of the brute force approach is $O(KN^2M)$. The number of SNPs N is the dominant factor here.

Space complexity—The dataset size is $O((N+K)M)$. The size of the $Array(X_i)$ is $O(M^2 + N)$. For each X_i, once the evaluation process is over for all permutations, $Array(X_i)$ can be cleared from the memory. Therefore, the space complexity of FastChi is $O((N+K)M) + O(M^2 + N)$. Since M is usually much smaller than N, this space complexity is linear to the dataset size.

4. Experimental Results

We present extensive experimental results on evaluating the performance of FastChi. FastChi is implemented in C++. The experiments are performed on a 2.4 GHz PC with 1G memory running WindowsXP system.

The SNP dataset used in the experiments is extracted from a set of combined SNPs from the 140k Broad/MIT mouse dataset 21 and 10k GNF 1 mouse dataset. This merged dataset has 156,525 SNPs for 71 mouse strains. The missing values in the dataset are imputed using NPUTE 14. The default setting of the experiments are as follows: the phenotypes are random permutations of binary variable with half 0's and half 1's, #individuals = 32, #SNPs=8k, #permutations=20. There are 60,970 unique SNPs for these 32 mice strains. To find the appropriate threshold value, we permute the phenotypes 1000 times. Figure 2 shows the distribution of the maximum chi-square test values of the 1000 permutations. Using a critical significance level of 1%, we set the default threshold value of θ to be 32.

Note that these experimental settings are chosen to demonstrate the performance gain and enhanced scalability offered by FastChi over the brute force approach. In real utility, one may use larger SNP panels and/or more permutation tests. The performance of FastChi is expected to follow the same trends presented in the remainder of this section.

FastChi v.s. the brute force approach

As far as we know, FastChi is the first algorithm addressing the problem of how to scale up the complete two-locus Chi-square test involving large permutation test. For comparison, we

show the runtime of FastChi versus the runtime of the brute force approach. The implementation of the brute force approach includes the computation of two-locus chi-square test for every SNP pairs. Figures 3(a) to 3(d) show the running time comparison under various parameter settings. The numbers below the runtime line of FastChi indicate the ratio of the runtime of the brute force approach and the runtime of FastChi. Figure 3(a) shows that the runtime of FastChi dramatically decreases as θ increases. FastChi offers 3.9 fold speedup when $\theta = 26$ and 16.3 fold speedup when $\theta = 34$. Figure 3(b) shows that FastChi is an order of magnitude faster than the brute force approach. Figure 3(c) shows that the runtime of FastChi increases as the number of individuals increases. This is because more SNPs-pairs are expected to have larger chi-square values when the number of individuals increases. Their upper bounds will also increase accordingly. In practice, it is reasonable to set higher threshold values for the datasets containing more individuals. Figure 3(d) shows that FastChi is consistently an order of magnitude faster than the brute force approach in permutation tests.

Pruning effect of the upper bound

Figure 4(a) shows the fraction of SNP-pairs pruned under different thresholds. The pruning ratio is averaged over 20 random phenotype permutations. The datasets contain half cases (diseased individuals) and half controls (healthy individuals). A large portion of the SNP-pairs are pruned even when the threshold is low. Figure 4(b) show the pruning ratio of the SNP-pairs when the case/control ratio varies, while the total number of individuals is fixed. Clearly, the pruning effect reaches the maximum power when there are 16 cases and 16 controls, which demonstrates that FastChi is more suitable for balanced study.

Computational cost of each component of FastChi

FastChi has three major components: building the indexing structure $Array(X_i)$ for every SNP X_i, accessing $Array(X_i)$ to find the candidate SNP-pairs whose upper bounds are greater or equal to the threshold, and performing chi-square tests on these candidates. Figure 5 shows the runtime of these three components when the number of SNPs increases. We also plot the runtime of the brute force approach for reference, which is the top line. Note that the runtimes in this figure are for a single permutation. As we can see, the most time consuming component of FastChi is building the index structures. Yet, its runtime is about 1/5 of the time required to perform the two-locus chi-square tests on all SNP pairs in one permutation. Note that when the number of permutations is large, the cost on building the index structures is negligible since they only need to be built once and can be reused in all permutations. Thus the performance gain of FastChi is more prominent for large permutation tests.

5. Discussion

In this paper, we present the FastChi algorithm for genome-wide two-locus chi-square test. FastChi is an exhaustive method which guarantees to find the optimal solution. It utilizes an upper bound of the two-locus chi-square test value to prune a majority of the SNP-pairs. The upper bound developed in this paper can be easily incorporated in the algorithm for SNP-pair pruning and candidates retrieval. By eliminating redundant computation of the invariant units in each permutation, FastChi is even more effective than the brute force method in large permutation tests.

So far, we have described the method for given θ. The main goal of permutation test is to find threshold θ for a given family-wise error α'. FastChi can be easily modified for this task: For each permutation Y_k, we use a parameter θ_k (initially 0) to track the largest chi-

square value identified so far by the algorithm. The non-decreasing θ_k is then used as the threshold to prune the search space when the remaining SNP-pairs are examined.

FastChi can also benefit the two-stage genome-wide association study. The idea of the two-stage approache 4,19 is to first select a subset of important SNPs according to some criteria. Then in the second step, an exhaustive search is performed to find the interactions among the selected SNPs. FastChi can dramatically speed up the interaction analysis procedure in the second step. A much larger number of SNPs can now be selected in the first step for the subsequent interaction analysis.

In this paper, we mainly focus on the biallelic SNPs. For the heterozygous case (where SNPs are encoded using {0, 1, 2}), we can also derive a similar upper bound. Let *A, B, E, C, D, F* represent the following events respectively: $Y = 0 \wedge X_i = 0$; $Y = 0 \wedge X_i = 1$; $Y = 0 \wedge X_i = 2$; $Y = 1 \wedge X_i = 0$; $Y = 1 \wedge X_i = 1$; $Y = 1 \wedge X_i = 2$. The upper bound for $\chi^2(X_iX_j, Y)$ is: $\chi^2(X_iX_j, Y) \leq \chi^2(X_i, Y) + T_1S_1\mathcal{R}_0 + T_2S_2\mathcal{R}_1 + T_3S_3\mathcal{R}_2$. In the upper bound, $\mathcal{R}_a = \left\{\left[\min\left\{\frac{O_{X_j=1}}{O_{X_j=0}}, \frac{O_{X_j=0}}{O_{X_j=1}}\right\} + \min\left\{\frac{O_{X_j=2}}{O_{X_j=0}}, \frac{O_{X_j=0}}{O_{X_j=2}}\right\} + \min\left\{\frac{O_{X_j=2}}{O_{X_j=1}}, \frac{O_{X_j=1}}{O_{X_j=2}}\right\}\right] | X_i = a\right\}$, where $a \in \{0, 1, 2\}$, $T_1 = L/(O_A + O_C)$, T2 = $L/(O_B + O_D)$, $T_3 = L/(O_E + O_F)$, (where $L = M^2/[(O_A + O_B + O_E)(O_C + O_D + O_F)]$), $S_1 = \max\left\{O_A^2, O_C^2\right\}$ $S_2 = \max\left\{O_B^2, O_D^2\right\}$ $S_3 = \max\left\{O_E^2, O_F^2\right\}$.

In our future work, we will investigate association study involving more than two SNPs following the same principle discussed in this paper.

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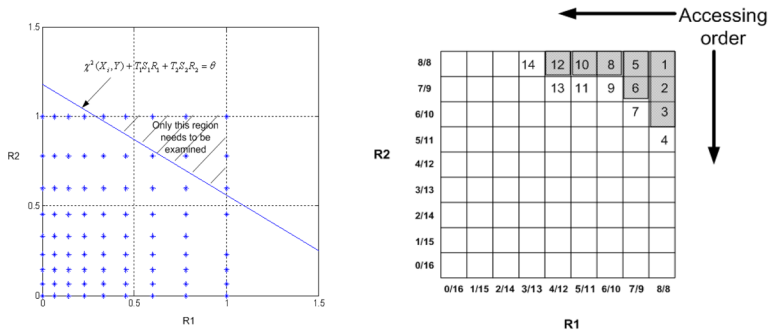


(a) Pruning SNP-pairs in $AP(X_i)$ (b) Candidate retrieval from $Array(X_i)$

Figure 1.
Applying the upper bound

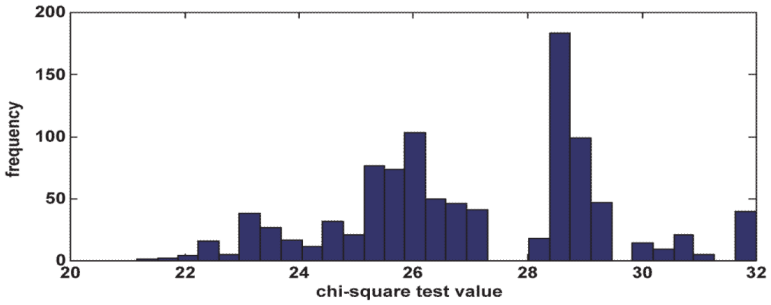


Figure 2.
Distribution of the maximum chi-square test values

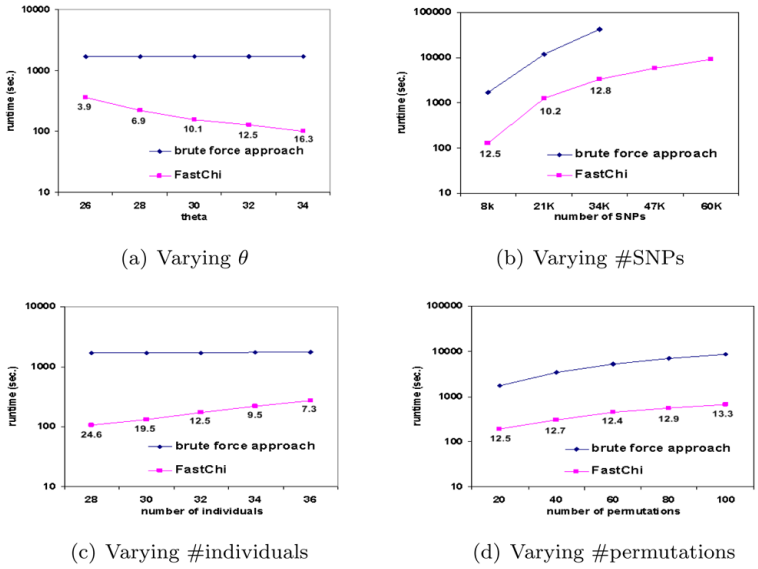
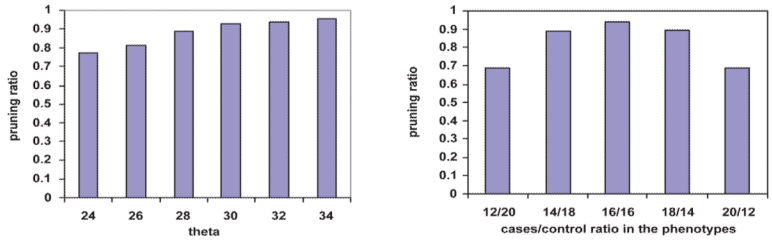


Figure 3.
Comparisons between FastChi and the brute force approach



(a) Varying threshold values (b) Varing case/control ratios

Figure 4.
Pruning effect of the upper bound

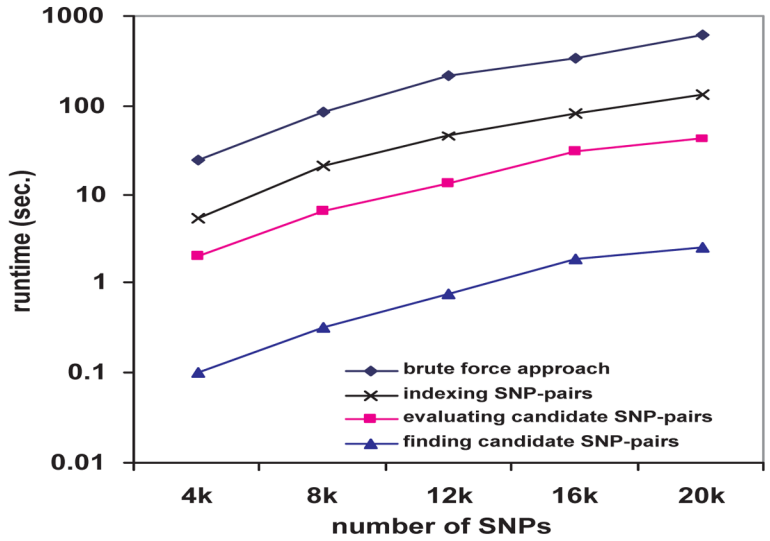


Figure 5.
Computational cost of each component of FastChi

Table 1

Notations used in the upper bound

Symbols	Formulas
T_1	$\frac{M^2}{(O_A + O_B)(O_A + O_C)(O_C + O_D)}$
S_1	$\max\{O_A^2, O_C^2\}$
$\mathcal{R}_1$	$\min\left\{\left[\frac{O_{X_j=1}}{O_{X_j=0}} \mid X_i = 0\right], \left[\frac{O_{X_j=0}}{O_{X_j=1}} \mid X_i = 0\right]\right\}$
T_2	$\frac{M^2}{(O_A + O_B)(O_B + O_D)(O_C + O_D)}$
S_2	$\max\{O_B^2, O_D^2\}$
$\mathcal{R}_2$	$\min\left\{\left[\frac{O_{X_j=1}}{O_{X_j=0}} \mid X_i = 1\right], \left[\frac{O_{X_j=0}}{O_{X_j=1}} \mid X_i = 1\right]\right\}$