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Description	

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A double classification tree search algorithm for index SNP selection

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Abstract

Background: In population-based studies, it is generally recognized that single nucleotide polymorphism (SNP) markers are not independent. Rather, they are carried by haplotypes, groups of SNPs that tend to be coinherited. It is thus possible to choose a much smaller number of SNPs to use as indices for identifying haplotypes or haplotype blocks in genetic association studies. We refer to these characteristic SNPs as index SNPs. In order to reduce costs and work, a minimum number of index SNPs that can distinguish all SNP and haplotype patterns should be chosen. Unfortunately, this is an NP-complete problem, requiring brute force algorithms that are not feasible for large data sets.

Results: We have developed a double classification tree search algorithm to generate index SNPs that can distinguish all SNP and haplotype patterns. This algorithm runs very rapidly and generates very good, though not necessarily minimum, sets of index SNPs, as is to be expected for such NP-complete problems.

Conclusions: A new algorithm for index SNP selection has been developed. A webserver for index SNP selection is available at

http://cognia.cu-genome.org/cgi-bin/genome/snpIndex.cgi/

Background

Because SNPs are often coinherited as components of a haplotype, they can be highly correlated. Because of this, it is theoretically possible to choose a much smaller number of SNPs to be used as an index set in identifying haplotype or SNP patterns. Johnson and his collaborators [1] have referred to such characteristic SNPs as haplotype tagging SNPs (htSNPs). Bafna et al. [2] refer to them as informative SNPs, using the language of probability theory. We prefer the use of the more general "index SNPs" to indicate not only haplotype but any SNP patterns. The use of index SNPs can reduce the work in SNP-based genotyp-

ing research. Clayton [3] provides computer software for htSNP selection. In his program, he uses five as the default maximum htSNP number and implements a brute force search algorithm to browse over subsets of SNP numbers up to a given maximum, choosing the subset according to predetermined criteria. However, if a large number of index SNPs is required, this algorithm fails. Similarly, Sebastiani and his collaborators [4] have developed a program called BEST (Best Enumeration of SNP Tags); again, use of this program is not feasible with very large sets of SNPs. In the HapScope project, Zhang et al. [5] have developed two programs for selection of index SNPs: BFA,

a brute force algorithm and GPA, a greedy partition algorithm. We have re-formulated the index SNP selection problem and developed a new greedy algorithm for index SNP selection based on a double classification tree search algorithm similar to the double search algorithm we previously developed for physical mapping [6]. This is not an enumeration algorithm. It runs rapidly and generates very reasonable results, though not guaranteeing generation of a minimum set, as is expected by the NP-complete nature of problem. The NP-complete property has been proved by Bafna et al [2]. For the reader's convenience, we have attached a brief proof as an appendix.

Algorithm
Classification tree search algorithm for SNP generation
We use a classification tree for partitioning SNP patterns. We choose SNPs as classifiers in constructing classification trees. For example, assume we have a set of SNP patterns or haplotype patterns (henceforth, we will use the terms "SNP patterns" and "haplotype patterns" interchangeably) as shown in Table 1. Note that these are not stretches of contiguous sequence; only the SNP positions are indicated.

We can generate a classification tree as shown in Figure 1.

Three SNPs (the first, the third, and the fifth) have been chosen as classifiers. The three SNPs can be used to identify the haplotypes. In other words, the three SNPs can be used as index SNPs for the whole set of SNP patterns. In this example, a group of three SNPs is the minimum set of SNPs to distinguish the haplotypes, *i.e.*, the tree has a minimum height of three. It is easy to appreciate that there is no classification tree for the above haplotype set with a height less then three. We propose here a greedy algorithm to generate a classification tree with a "good" height, but no guarantee that it is the minimum height. Our algorithm can be divided into two phases: a greedy phase to choose the classifiers and a tree-building phase to divide the haplotype patterns into the subtrees. A classification tree will be built by recurrently switching from greedy phase to tree building phase until all leaves of the tree have only one haplotype pattern. It is the purpose of our greedy method to choose a classifier from among the SNPs based on its possessing the smallest maximum sized subtree compared to those of the SNPs that have not yet been used as classifiers. If more than one SNP generates smallest maximum subtrees of the same height, we then examine the second maximum subtrees. If they are also the same size, we check the third, and so on. If all classifiers have smallest maximum subtrees of the same size, we can choose any one of them. In the above example, the first SNP has 4 as the maximum size of its subtrees. In contrast, the second SNP has 6 as the maximum size of its subtrees, so it would be rejected. The algorithm is described in Figure 2.

Table 1: A data sample to show the algorithm.

Haplotype1	ACAGATG
Haplotype2	ACGAATG
Haplotype3	ATGGGTG
Haplotype4	GTAAGTG
Haplotype5	GTGGGCA
Haplotype6	GTAGACA
Haplotype7	ATAAGCA
Haplotype8	GTGGACA

This algorithm runs very fast. Let the number of SNPs be N and the number of haplotype patterns be M. The major calculation is on the loop of step 2 and step 3. Since the loop can run no more than the number of SNPs: N, step 2 needs less than $O(NM)$ operations. Step 3 needs less than $O(NM)$ operations also. The total complexity of this algorithm is below the order of $O(N^2M)$.

Properties of classifiers
We outline some fundamental properties for a set of classifiers. We denote a set of classifiers as a **complete set** if and only if the set of classifiers can distinguish haplotypes. If no proper subset of a complete set is a complete set, we will call it **minimal complete set**. The smallest minimal complete set will be called the **minimum complete set**.

(1) The whole SNP set for the group of haplotypes is a complete set.

(2) For SNPs with only two variations (the major and the minor), the size of a complete set of classifiers cannot be less than $\log_2 N$ where N is the number of haplotypes.

(3) Any complete set of classifiers can be used to build up a classification tree. If the complete set is a minimal set, the height of the tree is equal to the number of classifiers in the set.

(4) The classification tree algorithm generates a complete set.

A double classification tree search algorithm
Our goal is to generate a minimum index SNP set. But one run of the above greedy classification tree search algorithm is insufficient to attain this objective. This can be demonstrated by examining the set of SNP data presented in Table 2.

Using the previously described classification tree search algorithm:

SNP 1 splits the 12 patterns into groups of 6 and 6;
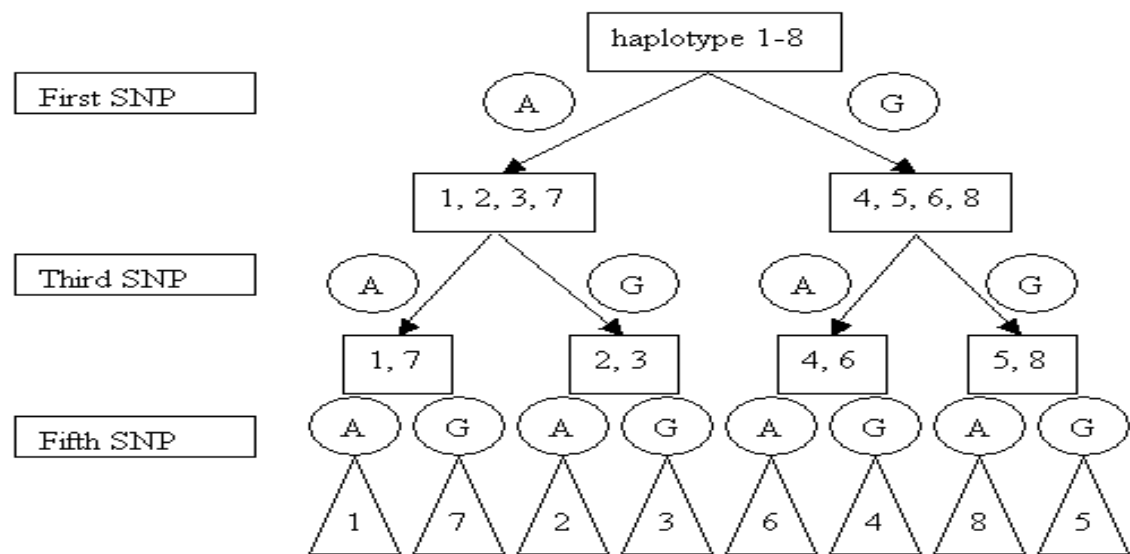
Figure 1
Classification tree search algorithm for the data in Table 1.

SNP 2 splits the 12 patterns into groups of 8 and 4;

SNP 3 splits the 12 patterns into groups of 7 and 5;

SNP 4 splits the 12 patterns into groups of 7 and 5;

SNP 5 splits the 12 patterns into groups of 7 and 5.

Based on the algorithm, we choose SNP 1 first as classifier. But no set of four SNPs containing SNP 1 suffice to distinguish all 12 patterns:

SNPs 1, 2, 3, 4 cannot distinguish A from B;

SNPs 1, 2, 3, 5 cannot distinguish A from C;

SNPs 1, 2, 4, 5 cannot distinguish A from E;

SNPs 1, 3, 4, 5 cannot distinguish A from I.

Hence, the algorithm will have to choose all five SNPs to distinguish all the patterns. But SNPs 2, 3, 4, 5 will distinguish these patterns, and clearly that is a minimal set. We have been trapped by SNP 1. In order to avoid such a trap, a second round tree search is needed. For the second round search, we force the last classifier of the first round

Table 2: A data sample to show the second round search is needed.

	1	2	3	4	5
A	1	1	1	1	1
B	1	1	1	1	0
C	1	1	1	0	1
D	0	1	1	0	0
E	1	1	0	1	1
F	1	1	0	1	0
G	0	1	0	0	1
H	0	1	0	0	0
I	1	0	1	1	1
J	0	0	1	1	0
K	0	0	1	0	1
L	0	0	0	1	1

to be used as the first classifier in the second round. The same rule is followed for choosing the second classifier, and so on. By the double search algorithm, in the first search we may generate classifiers in the order: SNP1, SNP5, SNP3, SNP4, and SNP2; in the second search we will generate in order: SNP2, SNP3, SNP4, and SNP5.
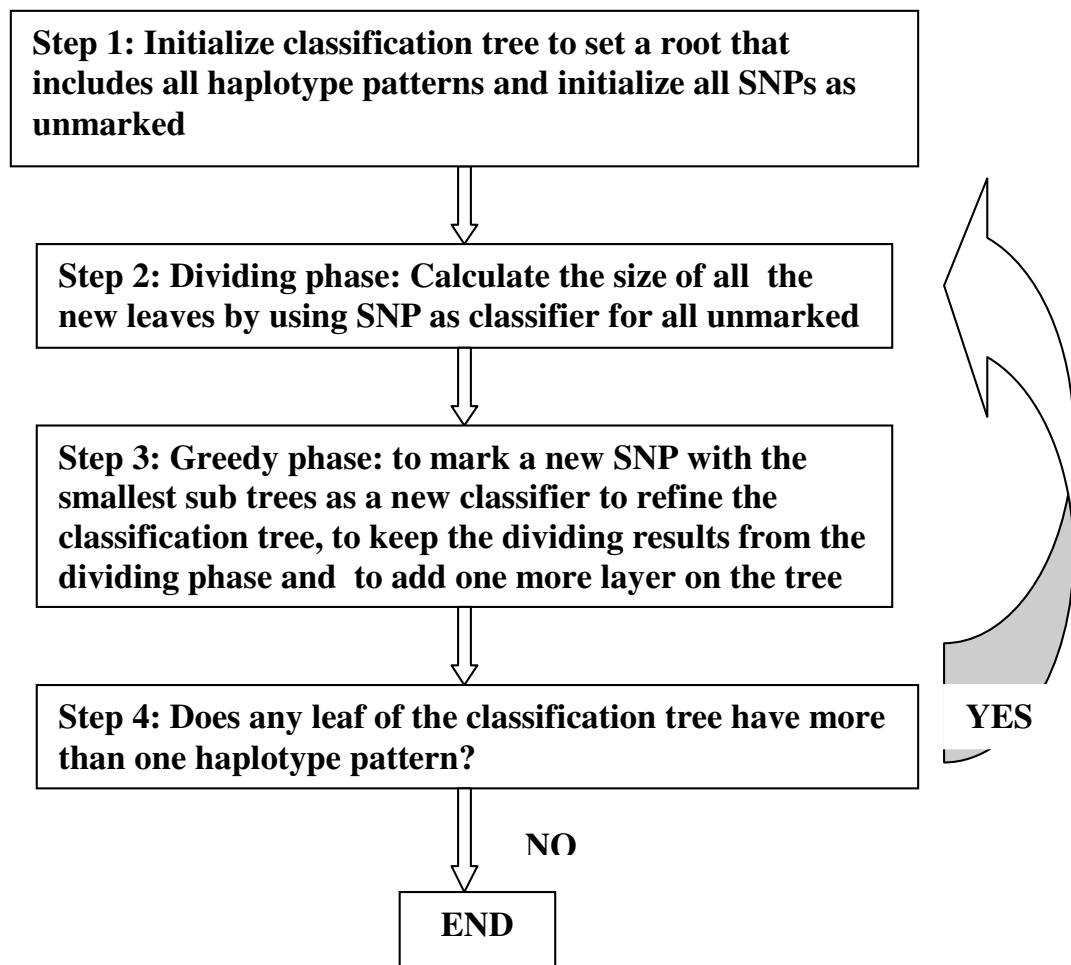
Figure 2
Flow chart of the algorithm.

Index SNP selection with constraints

Sometimes it is necessary to select some important and interesting SNPs as the index SNPs. In that case, we can use those SNPs as classifiers first in building up the trees. Then the greedy algorithm is used to choose additional classifiers. On our webserver, the user can provide a list for those SNPs that definitely should be included.

Discussion

The index SNP selection problem is a very important and practical problem. Since it is an NP-complete problem, there is no polynomial algorithm so far for an exact solution. Brute force algorithms have been developed that are useful for small sets of data. In contrast, the double search

algorithm is good for both small and large data sets. This algorithm gives a quite reasonable solution but is not guaranteed to generate the minimum index set. Given the NP-complete nature of the problem, it may be possible to develop different approximation algorithms in the future.

We have compared our algorithm with other methods for a set of real data downloaded from UW-FHCRC Variation Discovery Resource (SeattleSNPs) [8]. There are 40 SNPs in this data set (see Figure 3). By our program, 10 index SNPs were selected from left to right numbered 1, 10, 13, 14, 15, 20, 21, 27, 29, and 36. This is a minimum index SNP set. We tried to run Best [4]. After one night, we cancelled the process without any results.

```
               3612222334567799111111111111112222222222
               1861277199804837001222346669990223456777
               037345674841251062789320790675246357334
               265992782931648165072554826397453 06222
                         7461648039109436978 00231
hap1      0000001000000010001000010001000001000000 1087
hap3      0000001000000010001000010000000000000000 652
hap16     1101100000000010001000011101000001000000 217
hap111    0000001000001010001000010000011000000000 217
hap15     1101100000000010001000011101000001010000 217
hap157    0000001000011100000000010000010100000110 217
hap100    0000001000001000100100000000001000000000 217
hap12     0000001000001010100100011100010000010000 217
hap2      1101100000000000000000000000000000000000 870
hap19     0000001000000000000111000000000000001100 652
hap7      1101100110010100010000111010000010 10000 217
hap5      1101000000010101011000111010110010 00000 217
hap11     1101100110011100010000111010000010 10000 217
hap587    0000001001101010100100100000101000000000 217
hap9      0010010011010000100000000000010000000000 217
hap14     1101100010000000000000110000000000000000 217
hap4      0010010011010010010000000000000010000001 435
hap10     0010010011011010011000111010000110 10001 217
hap979    0010000110000010101010100000100100 00000 217
hap6      0010010011010100000000000000000010000001 217
hap43     1101100000000000001000000000100000000110 217
hap17     1101100110001110110011100011000011 00001 217
hap2006   0010000110000010100001000101001000000000 217
hap13     1101100101100000010100000000100000000110 217
hap27     0010000011100111011001111101100001110001 217
hap31     0010010011010001010001000001000001 00001 217
hap175    1101100101001001110100000000000000000000 217
hap85     1101100100000010100000000101000001 00011 217
hap18     1101100110100000100011000001000100 00000 217
hap39     0010000100001001010000000101101101 00011 217
hap2717   0010010011110100000011000000000010001110 217
hap60     1101100101100000000100000100001000001110 217
hap8      0010000011101001110001100000111010000000 217
hap68     1101100000001001011000000101101101 00011 217
```

Figure 3
A test data set was downloaded from UW-FHCRC Variation Discovery Resource (SeattleSNPs). On the top of this table are the locations of the SNPs. For example, the first SNP is located on the 31st base. The last figure on every haplotype is the frequency. For example haplotype one (hap1) has frequency 1087. By our program, 10 index SNPs were selected from left to right numbered 1, 10, 13, 14, 15, 20, 21, 27, 29, and 36. The locations are in bold type. This is a minimum index SNP set. We tried to run the Best program. After one night, we cancelled the process without any results.

This program is designed for haplotype data. It can be extended for genotype data. It is our strategy to select a minimum set of index SNPs after a small set of data has been genotyped and haplotypes have been generated. Then the selected minimum index SNPs will be used to genotype the whole sample set.

This program is limited to deal with biallelic SNP. The non-biallelic case and the missing data case can be developed using a SNP pattern extension.

Authors' contributions
PZ developed the new double search algorithms. HS implemented the web-server. RU provided a brief proof for the NP-completeness. All authors read and approved the final manuscript.

Appendix: A brief proof of the N-P completeness
We reduce the following NP-complete problem known as the minimum test set problem [7] to the minimum index SNP set problem:

Input
Collection C of subsets of a finite set S, positive integer k $\leq C$.

Question
Is there a subcollection $C' \subseteq C$ with $C' \leq k$ such that for each pair of distinct elements u, v $\in S$, there is some set **c** $\in C'$ that contains exactly one of u and v?

Let $C = \{c_1, ..., c_n\}$ and $S = \{s_1, ..., s_m\}$. We then construct a set of SNPs as follows;

(1) the number of SNPs is n (the number of the size of C),

(2) the number of SNP patterns is m (the number of the size of S),

(3) the ith letter of the jth SNP pattern is '1' if $s_j \in c_i$, otherwise '0'.

Intuitively, the jth SNP pattern describes if the element s_j $\in S$ is in each subset c_i or not.

The reduction can be done in linear time, and the solution of the minimum index SNP set problem directly gives the solution of the minimum test set problem.

Acknowledgements

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