Identifying Coreferent Genotypes in One-Way Cryptographic Hash Using Haplotype Information

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1 Introduction

Genome-wide association studies (GWASs) are powered by analyzing and learning from large amounts of data. In order to increase the efficiency of collecting such large quantities of data, a strategy is to combine and merge smaller datasets collected individually by different institutes. This is challenging as it requires identifying overlapping individuals in the datasets, and sharing sensitive individual-level data incurs privacy concerns. Turchin and Hirschhorn [2] developed a software that creates one-way cryptographic hashes for genotyping data and allows the identification of overlapping individuals between datasets without the need to personal information. In practice, however, we are often not able to obtain the entire genotype array to distinguish individuals due to privacy concerns as well as divergent data collecting purposes. Therefore, we want to find a small subset of attributes that provides very low collision rate of individuals. In this study, we explore methods to select attributes and the collision rates resulting from such selected subsets of attributes. Our main approaches are entropy and Linkage Disequilibrium, to reduce the number of attributes, and we explore different ways to combine them to solve the problem.

2 Problem Definition

We are given some datasets of Single-Nucleotide Polymorphism (SNP) allele data of individuals, and we want to merge these datasets without double-counting the individuals overlapped among the datasets. In our setting, we expect that each dataset has a different set of genotype attributes, where the intersection of these genotype attributes necessarily includes SNPs in the genes BRCA1 and BRCA2.

Since the genotype data available to us is limited to the BRCA genes, we expect increasingly high collision rate as the dataset size grows, which implies increasingly low identifiability for a fixed amount of attributes. Hence, in addition to the given genotype data, we also want to take into account other aspects of the individuals such as birth information. On the other hand, the privacy concern increases as the amount of genotype attributes grows, so it is desirable to maintain an as small as possible set of genotype attributes. As a result, we want to filter out the SNPs with less identifying ability and find a handful of strongly discriminative SNPs.

2.1 Identifiability

Using genotype information as the main attributes and personal information as auxiliary attributes, our ultimate goal is to identify individuals in different sources of data. It is hence necessary to define identifiability of a set of SNPs in order to evaluate our methodes. For our purpose, we define it as the proportion of individuals that are uniquely identified with the genotyping array consisting of the attributes we select. Formally, for dataset D containing m genotype arrays, the identifiability of SNP set S is the following:

$$identifiability(S) = \frac{\sum_{i=1}^{m} \begin{cases} 1, & \text{if } i^{th} \text{ genotype array is unique} \\ 0, & \text{otherwise} \end{cases}}{m}.$$

3 Dataset

In this study, we use the 1000 Genome Project dataset, which contains 2504 individuals, each with 5,756 SNPs. In these datasets, a record represents an individual and consists of alleles of that individual. In other words, each dataset represents a set of individuals and their corresponding different genotype array. As some of our target sources of data are companies that focus on analyses of BRCA genes, we expect that exonic SNPs on the two BRCA genes are highly likely to exist in the intersecting attributes. Hence in the preprocess step we filter out other genes and intronic SNPs, leaving 525 exonic BRCA SNPs.

4 Methods and Solutions

With the goal of reducing the number of selected SNPs while maximizing the identifiability, we employ two main methods to filter SNPs: informativeness and linkage disequilibrium (LD) information. Both methods help evaluate SNPs and exclude less desirable ones from the final selection. Below we explain the rationale of these methods in Sections 4.1 and 4.2, and we discuss the different ways to combine these methods and come to the solution in Section 4.3.

4.1 Informativeness

For some SNPs in our datasets, most individuals share the same alleles. From the perspective of information theory, such SNPs have lower entropies; they provide less information, and contribute less identifiability of individuals. These low-entropy SNPs are thus less desirable to keep in the selected set as we reduce the size. We measure the informativeness of any SNP d in our dataset using the standard metric, Shannon entropy:

$$H(d) = -\sum_{i} p_i \log_2(p_i)$$

where p_i is the frequency of the i^{th} allele for d. In practice, most SNPs have one major allele, which has a much higher frequency than the other alleles. The entropies of these SNPs would be low, due to the minor alleles having too low of frequencies, so we want to select SNPs that have more frequent alleles. We compute the entropies of SNPs in our dataset and observe their effects

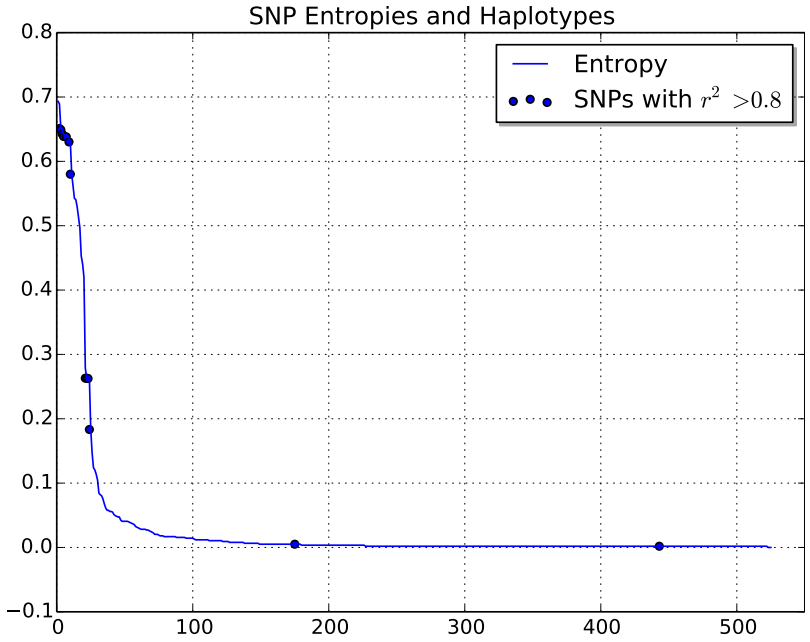


Figure 1: Entropies of exonic SNPs on BRCA1 and BRCA2 genes, marked with the high-r^2 SNPs.

on identifiability, and we plot their entropies in descending order in Figure 1. We observe that only 7% of the exonic SNPs have entropy values greater than 0.1, suggesting that there are many that we may be able to exclude from the final selection.

4.2 Linkage Disequilibrium

Studies have found that some SNPs, typically those that locate closely with each other on the genotyping array, tend to be inherited together. This implies that these SNPs have very similar variability and provide very similar information in terms of identifiability, and they can hence be considered redundant to all have as our attributes. Such highly correlated sets of SNPs are termed haplotypes, and a standard measure of the correlation between SNPs is the correlation coefficient r^2, defined based on the coefficient of D. For alleles A and B with frequencies being p_A and p_B, and the frequency of co-occurrence being p_{AB},

$$D_{AB} = p_A p_B - p_{AB}$$

$$r_{AB}{}^2 = \frac{D_{AB}{}^2}{p_A(1-p_A)p_B(1-p_B)}$$

We use SNP Annotation and Proxy Search (SNAP) [1] to obtain pairwise LD information between SNPs in our dataset and SNPs in their dataset. Using the pairwise correlation r^2, we identify the haplotypes in our dataset, plotted in Figure 1. According to data from SNAP, our dataset has 3 haplotypes: one haplotype is located around the 5^{th} SNP, one around the 22^{nd} and the other on the 176^{th} and the 444^{th} SNPs.

With the haplotypes determined, we select SNPs in a greedy fashion. Having the SNPs ranked in an descending order of entropy and iterating from the highest-entropy SNP to the lowest, we select a SNP only if it is not highly correlated with any already selected SNP, and otherwise we discard it. This greedy algorithm of SNP selection based on LD allows us to exclude SNPs optimally with respect to information, as all SNPs solely selected from its haplotype is the one that gives us the most value among all SNPs in that haplotype.

4.3 Solutions

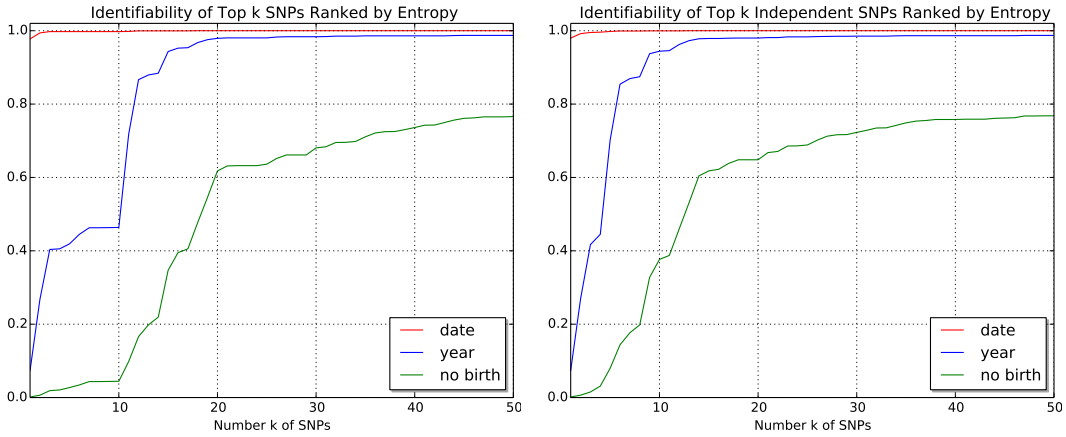
We propose two solutions to combine the two methods discussed. One is the simple composition of the two methods, by first removing high-r^2 SNPs and then removing low-entropy SNPs. We apply the two methods in this order so we are able to vary the size of the final selection set and observe the resulted identifiabilities. We will refer to this solution as the Composition Solution.
The other solution is to regard this problem as a combinatorial optimization problem: We want to minimize the size of the selected set of SNPs, to maximize the informativeness of the set of SNPs, and also to reduce the correlation between selected SNPs. Formally, for a set of n SNPs, where the i^{th} has weight w_i and value v_i and is selected $x_i \in 0, 1$ times, the maximum weight of the selection is restricted to be $\leq W$, and the number of items selected is exactly C:

$$\begin{aligned} \text{maximize} & \sum_{i=1}^{n} v_i x_i \\ \text{subject to} & \sum_{i=1}^{n} w_i x_i \leq W, \\ & \sum_{i=1}^{n} x_i = C, \text{ and} \\ & x_i \in 0, 1 \end{aligned}$$

It is hence an instance of the Knapsack Problem, and we can solve it using the dynamic programming solution. The weight and value functions are not obvious in our case, but we can define them basing on the entropoy and LD functions. Below we define $w(d)$ the weight function of a SNP d and $v(d)$ the value function of d,

$$\begin{aligned} w(d) &= \frac{\sum_{p \in \Pi_d} r^2(d, p)}{n} \\ v(d) &= H(d) \end{aligned}$$

where Π_d is the set of proxies of SNP d according to LD data from SNAP, and it depends on the r^2 threshold picked. Note that the weight function is the fraction of SNPs in the dataset that are in a haplotype of size > 1, weighted by the correlation measured in r^2, and thus it is normalized to be always between 0 and 1. And the value function is simply the entropy, as we prefer a SNP more if it has higher entropy. We will refer to this solution as the Knapsack Solution.



(a) Without high-r^2 SNPs removed

(b) With high-r^2 SNPs removed

Figure 2: Identifiability of top k SNPs selected using the Composition Solution. The rate of increase of identifiability reaches the maximum more quickly when high-r^2 SNPs have been removed first.

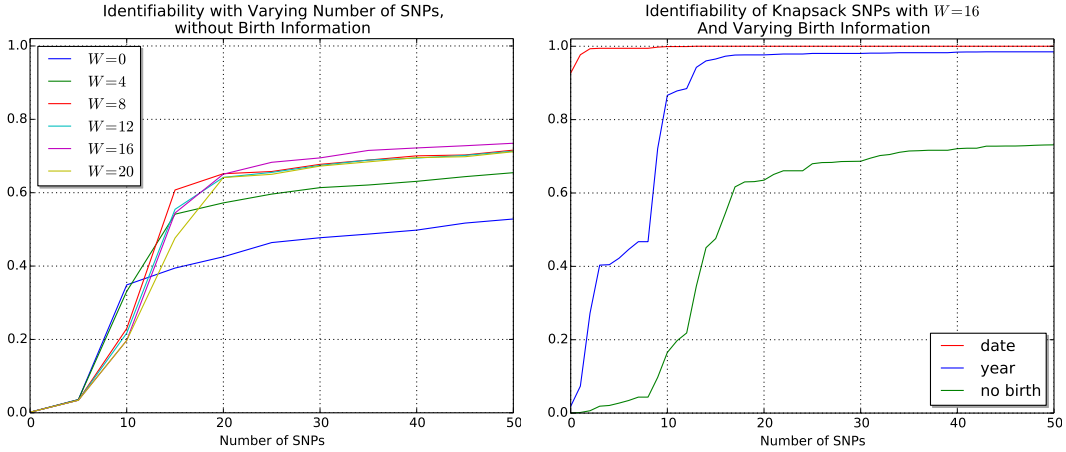
5 Evaluation

In this section we present the experiment results of solving the problem using methods and solutions discussed in Section 4.

5.1 Composition Solution

In Figure 2 we show the identifiability of top k SNPs ranked by entropy, where k varies from 1 to 50, as well as the identifiability of low-r^2 (we chose 0.8 as the r^2 threshold) SNPs that is ranked and selected in the same fashion. We also compare the effects of different types of birth information being added in the attributes. Since we do not have access to the true birth information of the individuals in the 1000 Genome dataset, we generate synthetic birth information uniformly at random instead. Naturally, no birth information gives the lowest identifiability, birth year gives better identifiability, and birth date gives the highest. In particular, we can see that the birth year information is sufficient to give very high identifiability, at 98%, using only 20 SNPs without the removal of high-r^2 SNPs in Figure 2a.

On the other hand, comparing the high-r^2 (dependent) with the low-r^2 (independent) SNPs, we find that the two plots are similar, since both have the identifiability grow rather quickly as k increases up to some point, $k = 20$ in Figure 2a and $k = 14$ in Figure 2b, and afterwards start slowing down and converging. This follows our expectation, as each excluded dependent SNP does not provide more information than its selected counterpart, and identifiability is not affect much by including it in the selection and increasing the size of the selection. Indeed, we observe a deceleration of growth in Figure 2a between $k = 2$ and $k = 10$. That portion is removed in Figure 2b, and the number of SNPs required to reach 98% identifiability is reduced.



(a) With varied maximum weight W (b) With Fixed W and varied birth information

Figure 3: Identifiability of top k SNPs selected using the Knapsack Solution.

5.2 Knapsack Solution

For the Knapsack formulation of the problem, since there is not an intuitive way of interpreting and setting the maximum weight W of a selection, we normalize the weights to have a sum of 100. In Figure 3a we fix birth information to use none of it, and we vary the number of SNPs selected and plot W from 0 to 20 to observe the effect on identifiability of different choices of W. The identifiabilities are very similar for $W = 8, 12, 16, 20$, and in particular $W = 16$ gives the highest. In Figure 3b we compare effects of varied amount of birth information, fixing W at 16 as it produced the best results.

We see a similar trend where the rate of growth of identifiability is high at the start and becomes low after a point, when the number of SNPs is 18. This is similar to what we saw in Figure 2b, but the transition point comes later. We also observe that without birth information, the highest identifiability of the Knapsack Solution is lower than the Composition Solution (both using 50 SNPs) by 5%. Moreover, we observe the same deceleration of the growth rate of the identifiability within the first 10 SNPs, as we did in Figure 2, and we notice that the deceleration is shorter than 2a but longer than 2b. Though better than using the entropy method alone, our Knapsack Solution produces slightly worse results than the Composition Solution.

6 Conclusion and Future Work

In this study we explore identifying of overlapping individuals among different sources of data, using genotype attributes as well as personal attributes, namely SNPs and birth information. We develop two methods to exclude less desirable SNPs, based on entropy and LD information. To combine these two methods to produce resulting selections of SNPs we also develop two solutions: one is a simple composition of the two methods, and the other is defining a Knapsack problem where the weight function is based on the LD information and the value function on entropy. We compare the efficacy of these two solutions, and we find that the Composition Solution produces selections

of SNPs that have higher identifiabilities. In conclusion, we are able select 17 SNPs out of the 525 exonic BRCA1 and BRCA2 SNPs and achieve identifiability 98% with birth year information, using the Composition Solution.
Following is a complete comparison of the minimum amount of SNPs that each solution requires to reach a certain amount of identifiability for each type of birth information. We choose different identifiability thresholds here as they converge differently across different birth types. For each birth type, to reach the chosen identifiability, the Composition Solution always requires fewer SNPs than the Knapsack Solution.

	Composition	Knapsack
Date – 100%	12	13
Year – 98%	17	25
None – 60%	13	17

Nevertheless, the definitions of weight and value functions we adopted in this work are rather preliminary, and there may be more potential to the Knapsack Solution that we may want to explore. For example, the current formulation of the Knapsack problem depreciates SNPs that are in a larger haplotype. This results in an unfair preference over SNPs with similar values but belong to smaller haplotypes. It also only account for LD above the selected r^2 threshold and loses more granular LD information. More importantly, the current formulation of the Knapsack problem assumes independence between an item and the selection made in the computation of weight, and this is not the case for our setting. Instead, we should weigh SNPs within a haplotype differently according to their value, so once the highest-value SNP in the haplotype is selected, the remaining are increasingly unlikely to be selected. In addition, in this study we focused on one dataset of SNAP and one r^2 threshold. We may want to explore other thresholds of r^2 and SNAP datasets for determining haplotypes.

References

[1] Andrew D Johnson, Robert E Handsaker, Sara L Pulit, Marcia M Nizzari, Christopher J O'donnell, and Paul IW De Bakker. Snap: a web-based tool for identification and annotation of proxy snps using hapmap. *Bioinformatics*, 24(24):2938–2939, 2008.

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