Genetics and population analysis

Inference of missing SNPs and information quantity measurements for haplotype blocks

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ABSTRACT

Motivation: Missing data in genotyping single nucleotide polymorphism (SNP) spots are common. High-throughput genotyping methods usually have a high rate of missing data. For example, the published human chromosome 21 data by Patil et al. contains about 20% missing SNPs. Inferring missing SNPs using the haplotype block structure is promising but difficult because the haplotype block boundaries are not well defined. Here we propose a global algorithm to overcome this difficulty.

Results: First, we propose to use entropy as a measure of haplotype diversity. We show that the entropy measure combined with a dynamic programming algorithm produces better haplotype block partitions than other measures. Second, based on the entropy measure, we propose a two-step iterative partition-inference algorithm for the inference of missing SNPs. At the first step, we apply the dynamic programming algorithm to partition haplotypes into blocks. At the second step, we use an iterative process similar to the expectation-maximization algorithm to infer missing SNPs in each haplotype block so as to minimize the block entropy. The algorithm iterates these two steps until the total block entropy is minimized. We test our algorithm in several experimental data sets. The results show that the global approach significantly improves the accuracy of the inference.

Availability: Upon request.

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1 INTRODUCTION

The study based on the single nucleotide polymorphism (SNP) has drawn wide attraction from the public. An SNP is considered to be a mutation at a single nucleotide position, and it keeps record through heredity thereafter. Human SNP data are very useful for the study of various subjects in human genetics and diseases. Moreover, it is known that SNPs are highly abundant across the entire human genome.

Human chromosomes appear in pairs. A haplotype is an observed sequence of SNPs in one chromosome, and a pair of haplotypes are called a genotype. It has been observed that human haplotypes have a block structure (Daly et al., 2001). Within a block, haplotypes have low diversity. Recombination hotspots are considered to be a source of perturbation of the block patterns—which can also be caused by the population structure. However, these boundaries are not well defined and finding them is itself a challenging task. The study of haplotype block partitioning was pioneered by Daly et al. (2001) and Patil et al. (2001), each offering a human haplotype data set. Systematic partitioning using a dynamic programming (DP) algorithm was first proposed by Zhang et al. (2002). Later, the objective function in the algorithm was replaced with minimum description length (MDL) measurements (Koivisto et al., 2003; Anderson and Novembre, 2003). These two methods produce different results, depending upon how the MDL describes the data set and how it treats missing data.

Missing data are common in haplotype data sets. The data set in Daly et al. (2001) has around 10% missing SNPs, and the data set in Patil et al. (2001) has around 20% missing SNPs. The missing SNPs will cause ambiguities in haplotypes and thus seriously affect many SNP-based applications such as disease mapping. In previous works, missing SNPs were either inferred with some simple methods or just ignored.

The problem of the inference of missing SNPs is associated with the problem of haplotype inference, where given a set of observed genotypes, we are asked to estimate the frequencies of all haplotypes. Statistical solutions for the problem of haplotype inference include those by Excoffier and Slatkin (1995), Niu et al. (2002), Qin et al. (2002), Lin et al. (2002), Stephens et al. (2001) and Stephens and Donnelly (2003). In general, there are two approaches: expectation-maximization (EM) algorithms and Gibbs sampling algorithms. Two kinds of priors were used: Dirichlet prior and approximate coalescent prior. Based on the estimated frequencies of haplotypes, we can assign values to missing SNPs. The challenge of applying these methods directly to infer missing SNPs is the identification of haplotype block boundaries, which is a difficult task.

In this study, we propose to measure haplotype diversity within a block using an information quantity measure called entropy. We develop a dynamic programming algorithm to partition the SNP data into haplotype blocks so as to minimize the total block entropy. Also, we show that the haplotype block structure produced by this measure is closer to the manually generated block structure suggested in Daly et al. (2001) than other measures. Given this haplotype block partition, we develop an EM-like iterative process to infer values of missing SNPs within each block. Combining these two steps, we propose a new algorithm, called the iterative partition-inference (IPI), to infer missing SNPs jointly with haplotype block partitioning. In the first step, we apply a dynamic programming algorithm to partition haplotypes into blocks. In the second step, we use the
iterative process to infer missing SNPs in each haplotype block so as to minimize the block entropy. The algorithm iterates these two steps until the total block entropy is minimized. We test our algorithm in several experimental data sets. The results show that the global approach significantly improves the accuracy of the inference.

2 METHODS

2.1 Entropy map

Conventionally, the linkage disequilibrium (LD) can be measured in a pairwise manner. The widely used Lewontin’s $D'$ is simple and powerful in measuring the LD (Hedrick, 1987). However, the LD measurements are usually too noisy for measuring haplotype blocks.

Low diversity is a common feature of haplotype blocks. Here we use entropy as a measure of haplotype diversity within a block: low entropy indicates low diversity. We define the haplotype block entropy as follows. Let $(i, j)$ denote the SNPs from the $i$th SNP to the $j$th SNP. Let $\Phi(i, j)$ denote the set of haplotypes collected. The block entropy is then defined as

$$E(i, j) = \sum_{\Phi(i, j)} P_\theta \log \frac{1}{P_\theta}$$

This block entropy measurement has an important property of consistency: $E(k, m) \geq E(i, j)$ if $k \leq i \leq j \leq m$. In a region of interest, we can draw entropy contours for better visualization. Figure 1 shows an entropy contour plot for Daly’s data. In the plot, a contour connects all of the $(i, j)$ pairs with same $E(i, j)$. We call this contour plot an entropy map. Since the entropy map is symmetric, we only show the lower triangle of the map.

Entropy has been used as a measure to enhance the conventional LD. Nothnagel et al. (2003) used a sliding window of pre-selected sizes to cumulate entropy-based statistics. In this study, we use information quantities to measure the whole haplotype data through block partitioning.

The information quantity measurement has some advantages over the conventional LD measurement in that it can measure not only the diversity within a block, but also the pairwise relationship between two blocks. For example, the mutual information between two blocks, $(i, j)$ and $(k, m)$, is defined as $I((i, j), (k, m)) = E(i, j) + E(k, m) - E((i, j), (k, m))$, where $E((i, j), (k, m))$ is calculated over all combinations of haplotypes across two blocks $(i, j)$ and $(k, m)$. The mutual information increases as LD increases. When there is no linkage between the two blocks, which means that the two blocks are independent, $D' = 0$, and the mutual information is zero as well. On the other side, when there is full linkage between the two blocks, $D' = 1$, and the mutual information is maximum. The mutual information is an un-normalized measurement, so the maximum value varies.

The $\alpha$-value proposed in Zhang et al. (2002), defined as the percentage of the unambiguous haplotypes in the block that appear more than once, is another normalized measurement of block diversity. Higher $\alpha$-values indicate lower diversity. Figure 2 shows the plot of the $\alpha$ map. By definition, the $\alpha$ value bears the consistency property mentioned above. Therefore, the $\alpha$ map has contours similar to those of the entropy map. However, the $\alpha$-value is not a precise measurement of diversity; it measures the portion of singleton haplotypes in a block.

In conclusion, the information quantities have good properties and yield better measurements of diversity and linkage. We will apply them to the haplotype block partitioning problem.

2.2 Haplotype block partitioning

In general, the haplotype block structure has the following properties that can be measured by information quantities:

(1) Low intra-block diversity, which can be measured by entropy;
(2) High inter-block diversity, which can be measured by joint entropy;
(3) Low inter-block dependency, which can be measured by mutual information.

We use an entropy threshold $T$ to define a block ($\leq T$). A proper $T$-value can be selected with the help of the entropy map. We assume the haplotype blocks are consecutive along chromosomes. Based on the three properties of the haplotype block structure, we employ three different cost functions to partition haplotypes into blocks.

The minimum entropy (ME) method. The ME method is to minimize the total block entropy. Denote $B(j)$ as the minimum total block entropy from the first SNP to the $j$th SNP. Let $e(j)$ be the beginning SNP of the last block of the partition that yields $B(j)$. Then we have the DP structure as

$$B(j) = \min_{1 \leq i \leq j} \{ B(i - 1) + E(i, j) \}; \text{ for } E(i, j) \leq T \}.$$  

The condition $E(i, j) \leq T$ in Equation (2) defines a block.

The maximum joint entropy (MJE) method. Given a haplotype block partition, the total joint entropy is the sum of the joint entropies of adjacent blocks. Let
Inference of missing SNPs

$C(j, k)$ denote the maximum total joint entropy from the first SNP to the $k$th SNP, with the last block beginning at the $j$th SNP. Then, the maximum total joint entropy can be computed by a two-dimensional DP algorithm using the following recursion:

$$C(j, k) = \max_{i \leq j \leq k} \{C(i, j) + E(i, j - 1) + E(j, k)\}$$

for $E(j, k) \leq T$ and $E(i, k) \geq T$. (3)

The minimum mutual information (MMI) method. Given a haplotype block partition, the total mutual information is the sum of the mutual informations of adjacent blocks. Let $D(j, k)$ denote the minimum total mutual information from the first SNP to the $k$th SNP, with the last block beginning at the $j$th SNP. Then, the minimum total mutual information can be computed by a two-dimensional DP algorithm using the following recursion:

$$D(j, k) = \min_{i \leq j \leq k} \{D(i, j) + I((i, j - 1), (j, k))\}$$

for $E(j, k) \leq T$ and $E(i, j - 1) \leq T$. (4)

Information quantities serve as criteria in all of our three methods. The DP algorithms proposed above can produce partitions which yield the optimal information quantities. However, the resulting partitions are sensitive to the threshold $T$. In Section 4, we will discuss how to choose $T$.

2.3 Inference of missing SNPs

In this study, we use entropy as the measure for haplotype blocks. Since haplotype blocks lack diversity, the value of a missing SNP can be inferred so as to lower the block entropy. However, there may be multiple missing SNPs within a block, so they have to be assigned jointly to yield the lowest block entropy of that block. Assuming that there are $m$ missing SNPs within a block, let $X = x_1, \ldots, x_m$ be the random variables of these missing SNPs, each of which can be assigned 0 or 1 representing the wild type or the mutant type, respectively. Our goal is to find

$$X = \arg \min_{X} \sum_{i} \min_{x} E(X),$$

where $E(\cdot)$ is the entropy of the block. Note that the number of possible assignments for $X$ can be as large as $2^m - 1$. A brute force search would be impractical because $m$ is generally large. Thus, we develop an EM-like iterative process as follows. In each run of the iterative process, we fix $m - 1$ missing SNPs, and update the frequency of the remaining missing SNP according to the frequencies of the current haplotypes within the block. Gradually, the updating process organizes the haplotype content within a block into lower diversity.

We start with the $i$th missing SNP $x_i$. Define $H_{-i}$ to be the set of haplotypes excluding $h(x_i)$. Similarly, define $X_{-i}$ as the set of missing SNPs excluding $x_i$. The conditional probability for $x_i$ being the majority ($x_i = 0$) is $P(x_i = 0|X_{-i})$. Let $\mathbb{D}$ be the non-missing SNPs in this block. Then, in the first step (similar to the E-step in EM) of the iterative process, we estimate the frequency of haplotype $h(x_i)$ for $x_i = 0$,

$$f_0 = P(h(x_i = 0)|H_{-i}, \mathbb{D}),$$

and the frequency of haplotype $h$ for $x_i = 1$,

$$f_1 = P(h(x_i = 1)|H_{-i}, \mathbb{D}).$$

In the second step (similar to the M-step in EM), we assign $x_i = 0$ if the new conditional majority probability

$$P(x_i = 0|X_{-i}) = \frac{f_0}{f_0 + f_1} \geq 0.5,$$

and $x_i = 1$ otherwise.

The haplotypes within a block can be organized into clusters within which haplotypes are identical. The block entropy is measured by the size of each cluster and the number of clusters. Thus, each run of the iterative process incurs a cluster movement of the following:

- **Death**: current haplotype $h(x_i)$ itself, a cluster, merges into another haplotype cluster, or
- **Migration**: current haplotype $h(x_i)$ moves from a smaller-sized cluster to a larger-sized cluster, or
- **Keep**: current haplotype does not move anywhere.

There are two impossible movements: **Birth** and **Migration from larger cluster to smaller cluster**. For all of the possible movements, we show the increase of block entropy $\Delta E \leq 0$. The proof is shown in supplementary data. Whenever there is a cluster movement, the block entropy will decrease. The movement will eventually stop as the block entropy reaches its local minimum.

2.4 Iterative partition and inference

The aforementioned haplotype block partitioning and inference of missing SNPs can be combined together to reduce the diversity in all blocks. Thus, we propose the IPI scheme shown in Figure 3. In the haplotype partitioning module, we choose the **ME method**, which computes the partition to minimize the total block entropy. In the inference module, we employ the iterative process to minimize the entropy locally within a block. The whole system will converge to a locally minimal block entropy and a locally minimal error rate of the inference, given the current parameters in the partitioning step. We can further feed the inference performance back to the partitioning step. Thus the parameters can be adjusted dynamically so that the total block entropy reduces.

3 RESULTS

3.1 Data sources

We use two data sets for testing, one from Daly et al. (2001), and the other from Patil et al. (2001). Here we use 0 and 1 to denote the majority value (wild type) and the minority value (mutant) of an SNP, and we introduce 2 for the missing SNP. The data set in Daly et al. (2001) contains 387 samples of 103 SNPs in genotype format. To create a ground truth haplotype data set for testing, we pre-process the data set in Daly et al. (2011) as follows. Every heterozygous allele is inferred through trios (father, mother and child). If it cannot be determined, we assume it as missing. These originally missing SNPs are assigned to the majority value at their loci. This haplotype data set will serve as the ground truth for the test of the inference error rate. The data set in Patil et al. (2001) contains 20 samples of 24,047 SNPs in haplotype format. Thus, no reduction needs to be made on it. However, the quality varies across its 24,047 SNPs. We select a high-quality region (8461–8720) in our test. This data set contains 683 missing SNPs (13%) among the total of 5200 SNPs. Similarly, these missing SNPs are assigned to the majority value at their loci. Both data sets are used in the following experiments.

3.2 Haplotype block partitioning

We compare the three information quantity-based measures with those proposed by Daly et al. (2001), Koivisto et al. (2003), Anderson and Novembre (2003) and Zhang et al. (2002), using the data set offered by Daly et al. (2001). All except Daly et al. (2001) used dynamic programming techniques to optimize different objective functions. The dynamic programming methods assume blocks to be consecutive, while the partition proposed by Daly et al. (2001)}
In conclusion, we show that (1) the lower the diversity is within a block, the more powerful the inference can be, and (2) the intra-block entropy measure is a better measure than others in terms of defining the block structure. In addition, the inferred missing SNP then can be used to generate better haplotype block partition, and this process can iterate. Among all measurements, only the ME method fits into this iterative scheme due to its focus on minimizing block entropy, which matches the goal of the inference of missing SNPs.

3.3 Inference of missing SNPs

First we randomly generate missing SNPs on the preprocessed haplotype data set. We partition the haplotypes into blocks and infer every missing SNP locally within the block. We run the EM-like iterative process on the entire data set. At each run, we choose a missing SNP, identify the block it is located in, calculate its probability of being a majority, and update its value. Then the error rate is computed according to the original data set.

With 1% missing rate on Daly’s data and given partitions, the error rate is 9.98% for Daly et al. (2001), 9.60% for Koivisto et al. (2003) and 6.03% for the ME method. It should be noted that the error rate for Anderson’s partition is 5.65%, lower than the three methods. It is because the MDL method contains a step to infer missing SNPs jointly with the block partition. The results show that the block partition obtained by the ME method yields the lowest overall error rate. In conclusion, we show that (1) the lower the diversity is within a block, the more powerful the inference can be, and (2) the intra-block entropy measure is a better measure than others in terms of defining the block structure. In addition, the inferred missing SNP then can be used to generate better haplotype block partition, and this process can iterate. Among all measurements, only the ME method fits into this iterative scheme due to its focus on minimizing block entropy, which matches the goal of the inference of missing SNPs.

3.4 Iterative partition and inference

We use the data sets in both Daly et al. (2001) and Patil et al. (2001) to test the IPI system. The iteration begins as we assume every missing SNP to be the majority at its location. This assignment is again employed for partitioning. We compare the performance of the iterative system in Tables 2 and 3, each with 1% missing rate and five rounds of iteration.
Inference of missing SNPs

Both results show a significant improvement due to the iteration. Since the data set in Patil et al. (2001) has a much smaller number of samples (20), its error rate is notably higher than that in Daly et al. (2001). It should also be noted that 5.08% error rate for Daly’s data is lower than the 5.85% error rate obtained through the partition by Anderson and Novembre (2003). In addition, we test our algorithm for different missing rates, 1, 5, and 10%, on the data sets in Daly et al. (2001) and Patil et al. (2001). The results are shown in Tables 4 and 5. It is obvious that the inference becomes more difficult as there are more missing SNPs.

Table 2. IPI for Daly’s data, with 1% missing rate (majority assignment error rate: 16.95%)

<table>
<thead>
<tr>
<th>Round</th>
<th>Error rate (%)</th>
<th>Number of blocks</th>
<th>Total block entropy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.02</td>
<td>11</td>
<td>33.05</td>
</tr>
<tr>
<td>2</td>
<td>5.08</td>
<td>11</td>
<td>32.37</td>
</tr>
<tr>
<td>3</td>
<td>5.08</td>
<td>11</td>
<td>32.12</td>
</tr>
<tr>
<td>4</td>
<td>5.08</td>
<td>11</td>
<td>32.12</td>
</tr>
<tr>
<td>5</td>
<td>5.08</td>
<td>11</td>
<td>32.12</td>
</tr>
</tbody>
</table>

Table 3. IPI for the selected region (8461–8720) in Patil’s data, with 1% missing rate (majority assignment error rate: 19.23%)

<table>
<thead>
<tr>
<th>Round</th>
<th>Error rate (%)</th>
<th>Number of blocks</th>
<th>Total block entropy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9.61</td>
<td>42</td>
<td>68.49</td>
</tr>
<tr>
<td>2</td>
<td>7.69</td>
<td>41</td>
<td>66.71</td>
</tr>
<tr>
<td>3</td>
<td>7.69</td>
<td>40</td>
<td>66.25</td>
</tr>
<tr>
<td>4</td>
<td>7.69</td>
<td>40</td>
<td>66.25</td>
</tr>
<tr>
<td>5</td>
<td>7.69</td>
<td>40</td>
<td>66.25</td>
</tr>
</tbody>
</table>

Table 4. Error rates for the inference of missing SNPs according to different missing rates, using full data in Daly et al. (2001)

<table>
<thead>
<tr>
<th>Missing rates</th>
<th>1%</th>
<th>5%</th>
<th>10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Majority assignment error rates</td>
<td>16.95%</td>
<td>19.01%</td>
<td>19.35%</td>
</tr>
<tr>
<td>1st round</td>
<td>6.02%</td>
<td>8.51%</td>
<td>8.73%</td>
</tr>
<tr>
<td>2nd round</td>
<td>5.08%</td>
<td>7.75%</td>
<td>8.02%</td>
</tr>
<tr>
<td>3rd round</td>
<td>5.08%</td>
<td>7.38%</td>
<td>8.02%</td>
</tr>
<tr>
<td>4th round</td>
<td>5.08%</td>
<td>7.34%</td>
<td>7.98%</td>
</tr>
<tr>
<td>5th round</td>
<td>5.08%</td>
<td>7.34%</td>
<td>7.98%</td>
</tr>
</tbody>
</table>

Table 5. Error rates for the inference of missing SNPs according to different missing rates, using region 8461–8720 in Patil et al. (2001)

<table>
<thead>
<tr>
<th>Missing rates</th>
<th>1%</th>
<th>5%</th>
<th>10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Majority assignment error rates</td>
<td>19.23%</td>
<td>20.38%</td>
<td>23.08%</td>
</tr>
<tr>
<td>1st round</td>
<td>9.61%</td>
<td>10.38%</td>
<td>9.81%</td>
</tr>
<tr>
<td>2nd round</td>
<td>7.69%</td>
<td>9.62%</td>
<td>9.62%</td>
</tr>
<tr>
<td>3rd round</td>
<td>7.69%</td>
<td>9.23%</td>
<td>9.42%</td>
</tr>
<tr>
<td>4th round</td>
<td>7.69%</td>
<td>9.23%</td>
<td>9.42%</td>
</tr>
</tbody>
</table>

3.5 Hard and soft decisions in iterations

As described in the previous section, the inference of each missing SNP is stored as the probability of being the majority at its location. This is called a soft decision, because the decision is in probability format and not yet finalized. When we partition the haplotypes into blocks, we have to make a hard decision for the missing SNPs, claiming each of them to be either the majority or the minority. Upon making the hard decision, we can define a threshold to cut-off. Let $T_h$ denote this threshold. If the probability of being the majority for a missing SNP is $\geq T_h$, we assign it to the majority. Similarly, if it is $<1-T_h$, we assign it to the minority. In our previous tests, $T_h$ was set to 0.5, and every missing SNP had an assignment. During the iteration, we perform the hard decision for two purposes: partition and inference, separately. At the partition, every missing SNP is assigned a value; if we fail to assign a missing SNP a value using the current $T_h$, we use 0.5 as the threshold instead for this particular SNP. Finally, when we calculate the error rate, we only consider the
Fig. 6. The error rate of the inference of missing SNPs converges after runs of the iterative process that minimize the entropy using different $T$-values on Daly’s data set. Different $T$ values result in different error rates converged.

missing SNPs with assigned values according to the $T_h$ while keeping the un-assigned SNPs out of the assignment coverage.

In Figure 5, we compare the majority assignment and our IPI system on Daly’s data set with 1% missing rate. In the upper plot of Figure 5(a), we see that both the majority and the IPI assignments improve as $T_h$ increases. The majority assignment yields a lower error rate when $T_h \geq 0.95$. However, in the lower plot we can also observe that this low error rate has a very poor coverage, $<10\%$, whereas the IPI assignment has more than 95% coverage in all $T_h$’s. The hard decision behavior of both assignments can be concluded in Figure 5(b). The $T_h$ can serve as an index for the confidence level. Our IPI assignment covers 98% of the missing SNPs to a confidence level of 0.999, at an error rate of approximately 3%. At the same error rate, there are only 10% of the missing SNPs covered for the majority assignment, with a confidence level of 0.95.

4 DISCUSSION

Our three information quantity-based partitioning methods are targeted to minimize the total block entropy, to maximize the total joint diversity, or to minimize the total mutual information. Although all the three properties reflect some dimensions of haplotype blocks, they are not equally important. If we assume that the partition in Daly et al. (2001) is true, the partition by the ME method is closer to it than the two others. This suggests that the property of low intra-block diversity is a better measure of a haplotype block. In a future study, the two other properties of haplotype blocks can be applied to either synthesize a new cost function, or shape the inter-block requirement for the ME method.

The $T$-value is the maximum entropy allowed within a block. The selection of the $T$-values affects the resulting partitions, which in turn affects the accuracy of the inference of missing SNPs. An example is shown in Figure 6 using the data set in Daly et al. (2001) with 1% missing SNPs. We run the iterative process on the entire data set. At each run, we choose a missing SNP, identify the block it is located in, calculate its probability of being a majority, and update its value.

Figure 6 shows the convergence of the error rate after runs of the iterative process, according to different entropy thresholds $T$.

The preprocessed data set in Daly et al. (2001) has an entropy of 8.71261. We test the range $1 \leq T \leq 7$ on a 1% missing rate, with five IPI iterations. The corresponding error rates and the number of haplotype blocks are shown in Figure 7. When $T$ is too small, the data set is partitioned into many small blocks. In this case, not enough neighboring information is employed to infer missing SNPs. However, when $T$ is too large, the data set is partitioned into too few blocks. Thus, distant neighboring information may be involved in the inference. Normally, the proper $T$ can be selected with the help of an entropy map. In this case, $2.2 \leq T \leq 3.8$ is a suitable range.

ACKNOWLEDGEMENTS

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SUPPLEMENTARY DATA

Supplementary data for this paper are available on Bioinformatics online.

REFERENCES


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