Constructing the Minimum Founder Set from a Set of Recombinant Sequences

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Abstract—Genetic recombination plays an important role in shaping the within-species genetic variations. It has been generally accepted that current-day population evolved from a small number of specific sequences called founders, and the genomic sequences (called recombinants) of individuals within the population are composed of segments from the founders due to recombination. A related computational problem is the so-called Minimum Founder Set problem: construct the minimum founder set from a set of given recombinant sequences so that the minimum fragment length is not less than the given fragment length bound. Ukkonen presented a segmentation based dynamic programming (SDYN) algorithm to solve it. However, the number of reconstructed founders obtained by the SDYN algorithm is restricted by the given fragment length bound in a certain situation. In this paper, a practical constructive heuristic algorithm HMFS is proposed for solving the problem. The HMFS algorithm partitions the sites of founders into three parts and reconstructs them respectively. Experimental results show that the HMFS algorithm can reconstruct a founder set very quickly, and the solutions obtained by the HMFS algorithm are close to or better than those obtained by the SDYN algorithm. In addition, the HMFS algorithm runs much faster than the SDYN algorithm, and it is still efficient for solving large size problems.

Index Terms—bioinformatics, minimum founder set problem, recombinant, founder, reconstruction, heuristic, algorithm

I. INTRODUCTION

In the post-genome era, with the rapid development of DNA sequencing, abundant DNA sequences and haplotyped SNP sequences are available. The investigation on genealogy inference has become one of the main topics in genomics, which is a precondition for dissecting the relationship between genotypes and phenotypes, and discovering the genetic basis of complex diseases. Finding meiotic recombination events is a major difficulty in inferring genealogy, which has become a key problem in bioinformatics [1]–[5]. In most combinatorial models, given a set of sequences from individuals of a population (for example, humans), the population is assumed to descend from a small number of specific sequences called founders. Due to recombination, a genomic sample sequence, called a recombinant, is thus a concatenation of fragments from the founders. When all the recombinants are arranged in aligned rows, they look like a mosaic of fragments from the founders. When all the recombinants are arranged in aligned rows, they look like a mosaic of fragments from the founders.

In Recent years, in order to infer the evolutionary history of the recombinants, researchers try to construct more recombinants from relatively fewer founders. However, the information about the founder sequences is unknown. The founder sequence reconstruction problem, i.e., reconstructing the founder set or recombinant mosaic
pattern from a group of recombinant samples, has received attention in bioinformatics.

Since there are a large number of possible mosaic patterns or founder sets for a set of sample sequences, biologically meaningful models need to be given for inferring breakpoints and founders. In 2002, Ukkonen [3] first proposed an optimization form of the problem based on the mosaic model and parsimony. Two optimization versions were considered: 1. the number of founders (called the Minimum Founder Set problem); 2. the number of recombinations (called the Maximum Fragment Length problem, or the Minimum Mosaic problem).

The recent research works are focusing mainly on minimizing the number of recombinations, i.e., the second optimization problem, which needs to give a bound for the number of founders before inferring the founders. Ukkonen [3] presented a dynamic programming based algorithm for this problem. The algorithm does not scale well when the number of founders or the number/length of the recombinants grows. Wu et al. [5] developed an exact algorithm RECBLOCK based on tree search. RECBLOCK can give a very good solution when the number of founders is small, and does not scale well either with the increase of founder number. In 2009, Roli et al. [7] presented a heuristic algorithm to solve the Maximum Fragment Length problem, and a tabu search algorithm to further optimize the solution obtained by the heuristic one. The tabu search algorithm can get rather good solutions efficiently and scales well while solving problems of large size, and it outperforms the heuristic version of RECBLOCK on large size instances. In 2010, Wu [8] created a new lower bound (called C bound) for the minimum mosaic problem by using integer linear programming, which is more accurate in practice than an existing bound CH [5]. In 2011, Blin et al. [9] put forward an accurate exponential algorithm. When the number of founder sequences increases, the performance of the algorithm still deteriorates.

However, the number of founders is unknown before hand in realistic application, it maybe more important to study the first optimization version, i.e., the Minimum Founder Set problem. To the best of our knowledge, only Ukkonen [3] proposed a segmentation based dynamic programming of time $O(n^3m)$ for solving the model (it is named as SDYN in this paper), where $m$ is the number of recombinants, $n$ is the number of SNP sites. The SDYN algorithm derives the number of reconstructed founders and the corresponding segmentation from a set of recombinants. We observe that the number of reconstructed founders obtained by the SDYN algorithm is restricted by the given fragment length bound, i.e., when the number of SNP sites $n$ can be dividable by the given fragment length bound $L$, the number of reconstructed founders obtained by the SDYN algorithm must not be more than $2^L$. In this paper, a constructed heuristic algorithm HMFS is proposed for solving the problem. The HMFS algorithm partitions the sites of founders into three parts and reconstructs them respectively. The solutions obtained by the HMFS algorithm are close to or better than those obtained by the SDYN algorithm, which is established by a number of experiments. Furthermore, the HMFS algorithm runs much faster than the SDYN algorithm, it is efficient even for solving large size problem.

The rest of this paper is organized as follows. In Section 2, The Minimum Founder Set problem is formalized. In Section 3, the HMFS algorithm is described. In Section 4, the comparisons between algorithms HMFS and SDYN are given through experimental results. Finally, some conclusions are drawn in Section 5.

II. THE MINIMUM FOUNDER SET PROBLEM

Suppose that we have a set of $m$ recombinants $C=\{C_1,\ldots,C_m\}$, where $C_i=C_{i1}\ldots C_{ik}$ $(i=1,\ldots,m)$ denotes a sequence of length $n$ over a given alphabet $\Sigma$, i.e., $C_i\subset \Sigma$ $(i=1,\ldots,n)$. In this work, a typical biological application is concerned where the recombinants are haplotyped SNP sequences and $\Sigma=\{0,1\}$. The two symbols 0 and 1 encode the two most common alleles of each SNP site. As shown in Fig. 1(a), each row denotes a founder and each column denotes a SNP site. Let $F=\{F_1,\ldots,F_k\}$ denote another set of sequences of length $n$ over the alphabet $\Sigma$, where $F_i=f_{i1}\ldots f_{ik}$ $(f_j\in \Sigma, t=1,\ldots,k; j=1,\ldots,n)$. As shown in Fig. 1(b), each row denotes a founder and each column denotes a SNP site.

If the set of recombinants $C$ can be reconstructed from $F$, $F$ is called a founder set of $C$. This is the case if each $C_i\subset C$ can be decomposed into $p\{(1\leq p\leq n)\}$ nonempty strings (fragments) $F_{d1}, F_{d2},\ldots, F_{dp}$, such that each $F_{dj}$ $(j=1,\ldots,p)$ occurs in at least one sequence of $F$ exactly at the same position as in $C_i$. Take the second recombinant in Fig. 1(a) for example, it can be partitioned into two fragments 10100 and 01 by one breakpoint, such that the two fragments respectively occur in the third and the first founders at the same position as in the second recombinant. In this case, we say $C$ has a parse in terms of $F$. Given all of the fragments $F_{dj}$ $(i=1,2,\ldots,m, j=1,2,\ldots, p_i)$, the minimum fragment length $\lambda_{\text{min}}$ is defined as Formula (1),

$$\lambda_{\text{min}}=\min\{|F_{di}|, i=1,\ldots,m, j=1,\ldots,p_i\}$$  \hspace{1cm} (1)

where $|F_{di}|$ denotes the length of string $F_{di}$.

Based on the above concepts, an important optimization model was proposed by Ukkonen [3] for the sequence reconstruction problem, as follows:

The Minimum Founder Set problem (MFS): Given a set of recombinants $C$ and a fragment length bound $L$ $\{1\leq L\leq n\}$, to construct a smallest possible founder set $F$ such that $C$ has in terms of $F$ a parse for which the minimum fragment length $\lambda_{\text{min}} \geq L$.  

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III. ALGORITHM HMFS

In this section, a constructive heuristic algorithm HMFS is described. In the following some notations and definitions used in HMFS are given first, and the HMFS algorithm is described afterwards.

A. Notations and Definitions

Define an $m \times n$ recombinant matrix. For convenience of description, the recombinant matrix is still denoted by $C$, where each row denotes a recombinant, and each column denotes a SNP site. Similarly, define a $k \times n$ founder matrix $F$, where each row denotes a founder, and each column also denotes a SNP site. The HMFS algorithm constructs founder set $F$ from the first column to the last one. The columns currently being solved are called current column, which is denoted as $f_{\text{col}}$, $f_{\text{col}+l}$, where $f_{\text{col}}$ (resp. $f_{\text{col}+l}+1$) indicates the first (resp. the last) column of current column, and $l$ denotes the number of columns of current column. For each row $C[i,-][i=1, m]$, let $cb(i)$ store the position of the last breakpoint, $c(i)$ store the index of the founder that represents row $i$ after the last breakpoint $cb(i)$, and $c(l)$ store the fragment length between the last breakpoint $cb(l)$ and the last column of current column $f_{\text{col}+l}$. Take the fifth recombinant in Fig. 1(a) for example, assume that current column is the 6th column, i.e., $f_{\text{col}}=6$, $l=1$, then $cb(5)=3$, $c(5)=3$ (represents the third founder), and $c(l)=3$. For each row $F[t,-]$ ($t=1, \ldots, k$), let set $CS(i)$ include the recombinants whose $c(i)$ values are equal to $t$, and $|CS(t)|$ denote the number of recombinants in set $CS(t)$.

Assume that $S(s, l)_{n,r}$ is a set of $d$ sequences of length $n$ over $\Sigma$, and $r$ is a $l$-length ($l=1, L$) binary string. Define $n_j(S, j) (j=L+1, \ldots, n-L+1)$ as the number of rows $i'$ in $S$ with $s_{i', l}=r$. Let $p_{j}(S, j) (j=L+1, \ldots, n-L+1)$ be the proportion of $r$ strings in the non null strings of columns $(j, \ldots, j+l-1)$ in matrix $S$, as shown in Formula (2):

$$\begin{align*}
p_{j}(S, j) &= \frac{n_j(S, j)}{\sum_{r \in \mathbb{R}} n_j(S, j)} \text{, if } \sum_{r \in \mathbb{R}} n_j(S, j) \neq 0, \\
&= 0, \text{ otherwise},
\end{align*}$$

where $\mathbb{R}$ denotes the $l$-length binary string of the decimal integer $x$. Given matrices $C$ and $F$, $w_{j}(F, j) (j=L+1, \ldots, n-L+1)$ is defined as the ratio between $p_{j}(F, j)$ and $p_{j}(C, j)$:

$$w_{j}(F, j) = \frac{p_{j}(F, j)}{p_{j}(C, j)}, \quad j = L+1, \ldots, n-L+1. \quad (3)$$

Take the recombinant and founder matrices in Fig. 1(a) and (b) for example (here we also call them as $C$ and $F$), assume that $L=2$ and $n=11$, then $n_{2,11}(C, 6)=2$, $n_{2,11}(F, 6)=1$, $p_{2,11}(C, 6)=0.4$, $p_{2,11}(F, 6)=0.3$, $w_{2,11}(6) = 0.75$.

B. Heuristic Algorithm HMFS

HMFS, a constructive heuristic algorithm, is presented here. The input is an $m \times n$ recombinant matrix $C$ and a fragment length bound $L (\lambda_{\text{min}} \leq L)$. The output is a founder matrix $F$. The HMFS algorithm is based on the intuition that there can not be any breakpoints among the first (resp. the last) $L$ columns under the constraint of $\lambda_{\text{min}} \geq L$. It partitions the $n$ sites of founders into three parts and reconstructs them respectively. In the following, some key steps in designing the HMFS algorithm are described.

1) Creating the Initial Founder Matrix: The HMFS algorithm starts with creating the initial founder matrix $F$, which is depicted as follows.

Let $k=1$, and set $F[k, j] = C[1, j]$ ($j=1, \ldots, L$). For every row $C[i,-][i=2, \ldots, m]$ of matrix $C$, if there does not exist such an $F[t,-][t=1, \ldots, k]$ that $C[i, j] = F[t,j]$ ($j=1, \ldots, L$), insert a new row $F[k+1,-]$ into matrix $F$ and set $F[k+1, j] = C[i, j]$ ($j=1, \ldots, L$), $k=k+1$. After creating the initial founder matrix $F$, the first $L$ columns of row $F[t,-][t=1, \ldots, k]$ are assigned values, and the variables $cb(i)$, $c(i)$ and $c(l)$ ($i=1, \ldots, m$) are initialized. In particular, $cb(i)=0$, $c(i)=L$ ($i=1, \ldots, m$).

2) Computing the Middle Columns: The middle $n-2L$ columns of matrix $F$, i.e., columns $F[-L+1, \ldots, F[-n-L]$ are constructed as follows.

Firstly, the rows of matrix $F$ are sorted according to their $|CS(i)|$ values. A row $F[t, -]$ ($t=1, \ldots, k$) whose $|CS(t)|$ value is odd is sorted before the row $F[t, L]$ whose $|CS(t)|$ value is even, for $F[t, -]$ with odd $|CS(t)|$ value is easier to be ascertained than $F[t, -]$ with an even $|CS(t)|$. If $|CS(t)|$ has the same parity as $|CS(t)|$ (i.e., are both even or both odd), the two rows $F[t, -]$ and $F[t, L]$ are sorted by their $|CS(i)|$ values in ascending order. Let $r_{1, \ldots, L}$ denote the row order so obtained.

Secondly, the rows of matrix $F$ are processed in the sorted order, i.e., $F[r_{t, L}][t=1, \ldots, m]$ is computed using the following two steps:

(a) If $n_{1,1}(CS(r_{t, L}))$ is greater (resp. less) than $n_{1,1}(CS(r_{t, L}))$, $F[r_{t, L}]$ is set to 0 (resp. 1), otherwise go to Step (b).

(b) If $w_{1,1}(F, j)$ is less (resp. greater) than $w_{1,1}(F, j)$, $F[r_{t, L}]$ is set to 0 (resp. 1), otherwise it is set to $C[j, j]$, here recombinant $h$ has the maximum $c(i)$ among the recombinants of set $CS(r_{t, L})$ (i.e., $h, g \in CS(r_{t, L})$, $c(h) > c(g)$).

After column $F[-j][j=1, \ldots, n-L]$ is constructed, some adjustments need to be made to let the proportion of 0 (resp. 1) entries of column $j$ in matrix $F$ approximate what it is in matrix $C$. That is to say if $p_{1,1}(F, j)$ is less than $p_{1,1}(C, j)$ (resp. $p_{1,1}(F, j)$ is less than $p_{1,1}(C, j)$), we should try to find such a row $F[t, -]$ ($t=1, \ldots, k$) of $F$ with $F[t, j]=1$ (resp. 0) and a row $C[i, -][i=1, \ldots, m]$ of $C$ with $C[i, j]=0$ (resp. 1) that $c(i)=t$, then set $F[t, j]=0$ (resp. 1) to improve the proportion of 0 (resp. 1) entries of column $j$ in matrix $F$.

3) Computing the Last L Columns: The last $L$ columns are constructed together.

Firstly, the founders of matrix $F$ are partitioned into two sets $G_1$ and $G_2$. Given a founder $F[t, -][t=1, \ldots, k]$, if there exists at least one recombinant $i$ of $CS(t)$ such that $c(i)$ is less than $L$, $F[t, -]$ is classed into $G_1$, otherwise it
is classed into \( G_2 \).

Secondly, the founders of set \( G_2(d=1,2) \) are sorted by their \( |\text{CS}(i)| \) values in ascending mode, let \( r_{1}, \ldots, r_{|G_2|} \) denote the founders ordering so obtained.

Finally, the two sets \( G_1 \) and \( G_2 \) are processed in turn. The founders \( F[t\sim] \) \((r=1, \ldots, |G_2|, d=1, 2) \) of set \( G_2 \) are computed in the sorted order with the following three steps:

(a) If \( n_{L\sim}(\text{CS}(r), n-L+1) > n_{L\sim}(\text{CS}(r), n-L+1) \) is set to \( (r', r) \in \{c_{\sim i L+1} \cdots c_{\sim i L} \in \text{CS}(r), \ r' \neq r \} \), \((F[r,n-L+1] \cdots F[r, n]) \) is set to \( r' \), otherwise go to Step (b).

(b) Let set \( S_S \) store the strings \( r' \) with \( n_{L\sim}(\text{CS}(r), n-L+1) \geq n_{L\sim}(\text{CS}(r), n-L+1) \) \((r', r) \in \{c_{\sim i L+1} \cdots c_{\sim i L} \in \text{CS}(r), \ r' \neq r \} \). If \( n_{L\sim}(n-L+1) \) is less than \( n_{L\sim}(n-L+1) \), \((F[r,n-L+1] \cdots F[r, n]) \) is set to \( r' \), otherwise go to Step (c).

(c) Let set \( S_S \) store the strings \( r' \) with \( n_{L\sim}(n-L+1) \leq n_{L\sim}(n-L+1) \) \((r', r) \in \{c_{\sim i L+1} \cdots c_{\sim i L} \in \text{CS}(r), \ r' \neq r \} \). \((F[r,n-L+1] \cdots F[r, n]) \) is set to \( (C[h, n-L+1] \cdots C[h, n]) \), where recombinant \( h \) has the maximum \( c(i) \) among the recombinants of set \( \{c_{\sim i L+1} \cdots c_{\sim i L} \in \text{CS}(r), \ c_{\sim i L+1} \cdots c_{\sim i L} \in \text{SS} \} \), \((i.e., \ \ h, g \in \{c_{\sim i L+1} \cdots c_{\sim i L} \in \text{CS}(r), \ c_{\sim i L+1} \cdots c_{\sim i L} \in \text{SS} \}, \ cl(h) \geq cl(g), \ h \neq g) \). In addition, if \( F[r,n-L+1] \in G_1 \), the HMF algorithm still requires that \( cl(h) \) and \( cl(g) \) are all less than \( L \).

After the last \( L \) columns of matrix \( F \) are constructed, some adjustments are also made to let the proportion of \( r \) \((r \in \{C[i, n-L+1] \cdots C[i, n], i=1, \ldots, m \}) \) strings of columns \((n-L+1, \ldots, n) \) in matrix \( F \) approximate what it is in matrix \( C \). For a given \( r \) value, if \( p_{L\sim}(F[r,n-L+1]) \) is less than \( p_{L\sim}(C[n-L+1]) \), we should try to find such a founder \( F[t\sim] \) of \( F \) with \( (F[t,n-L+1] \cdots F[t, n]) \) and a recombinant \( C[\sim i] \) of \( C \) with \( (C[i, n-L+1] \cdots C[i, n]) \) that \( cl(i)=t \), then set \((F[t,n-L+1] \cdots F[t, n])=r \).

4) Reassigning Founders: After computing current column \((f_{col}, f_{col}+1) \), some recombinants \( C[\sim i] \) \((i=1, \ldots, m) \), which cannot be represented anymore by their current representatives (founders) \( F[\sim i] \) \((i.e., \ C[i, f_{col}] \cdots C[i, f_{col}+1]) \), need to be reassigned representatives as follows:

(a) Search for a founder \( F[t\sim] \) \((r=1, \ldots, k) \) that can equally represent \( C[\sim i] \) starting from breakpoint \( ch(i) \), i.e., \( C[i, f_{col}] \cdots C[i, f_{col}+1] \). If such a founder can be found, set \( cl(i)=cl(i)+1 \), otherwise go to Step (b).

(b) If \( ch(i) \notin L \) and there exists a founder \( F[t\sim] \) \((r=1, \ldots, k) \) that has the same value as \( C[\sim i] \) on current column, i.e., \( F[t\sim] \) \((f_{col}, f_{col}+1) \), a new breakpoint is added to recombinant \( C[\sim i] \), and set \( ch(i)=f_{col}+1 \), \( cl(i)=cl(i)+1 \), otherwise go to Step (c).

(c) Create a new founder \( F[k+1, L]=C[i, f_{col}] \cdots C[i, f_{col}+1] \), and set \( ch(i)=0, cl(i)=k+1, cl(i)=f_{col}+1, k=k+1 \). Based on the above mentioned steps, the HMF algorithm for reconstructing the minimum founder set is summarized in Fig. 2.

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**Algorithm 1: HMF algorithm**

**Input:** an \( m \times n \) recombinant matrix \( C \), a fragment length bound \( L (1 \leq L \leq n) \)

**Output:** a founder matrix \( F \)

1. \( k=1, F[1, j]=C[1, j] (j=1, \ldots, L) \)
2. for \( i=2 \) to \( m \)
3. if there is not an \( F[t\sim] \) \((r=1, \ldots, k) \) to meet \( C[i, j]=F[t, j] (j=1, \ldots, L) \) then
4. \( F[k+1, j]=C[i, j], k=k+1 \)
5. initialize \( ch(i), cl(i), cl(i) (i=1, \ldots, m) \)
6. for \( j=1 \) to \( n-L \)
7. sort the rows in \( F \) according to \( |\text{CS}(i)| \), and \( r_{1}, \ldots, r_{k} \) denote the sorted order
8. for \( i=1 \) to \( k \)
9. if \( n_{L\sim}(CS(r), n-L+1) \geq n_{L\sim}(CS(r), n-L+1) \) then \( F[r, j]=0 \)
10. else if \( n_{L\sim}(CS(r), n-L+1) < n_{L\sim}(CS(r), n-L+1) \) then \( F[r, j]=1 \)
11. else if \( w_{L\sim}(r, j) < w_{L\sim}(i, j) \) then \( F[r, j]=0 \)
12. else if \( w_{L\sim}(r, j) < w_{L\sim}(i, j) \) then \( F[r, j]=1 \)
13. else \( F[r, j]=C[h, j] (h, g \in C[\sim i], cl(h) \geq cl(g), h \neq g) \)
14. adjust the proportion of \( 0 \) (resp. \( 1 \) ) entries of column \( j \) in matrix \( F \)
15. reassigning founders
16. partition the rows of \( F \) into two sets \( G_1 \) and \( G_2 \)
17. sort the founders in set \( G_\# (d=1,2) \) according to \( |\text{CS}(i)| \), and \( r_{1}, \ldots, r_{|G_\#|} \) denote the sorted order
18. for \( d=1 \) to \( 2 \)
19. for \( e=1 \) to \( |G_\#| \)
20. if \( n_{L\sim}(CS(r), n-L+1) \geq n_{L\sim}(CS(r), n-L+1) \) \((r', r) \in \{c_{\sim i L+1} \cdots c_{\sim i L} \in \text{CS}(r), \ r' \neq r \} \) then \( F[r', n-L+1] \cdots F[r, n])=r' \)
21. else if \( n_{L\sim}(n-L+1) < n_{L\sim}(n-L+1) \) \((r', r) \in \{c_{\sim i L+1} \cdots c_{\sim i L} \in \text{CS}(r), \ r' \neq r \} \) then \( F[r,n-L+1] \cdots F[r, n])=r' \)
22. adjust \( r \) \((r \in \{C[i, n-L+1] \cdots C[i, n]) \) strings of columns \((n-L+1, \ldots, n) \) in matrix \( F \)
24. reassigning founders

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**Figure 2. HMF Algorithm.**
Algorithm HMFS tries to delegate more recombinants with the existing founders during the process of reconstruction. Under the constraint of $\lambda_{\min} \geq L$, there can not be any breakpoints among the first $L$ columns, therefore they are firstly created together in step 1. Next, the middle $(n-2L)$ columns are computed one by one. It is regarded that the entry value (0 or 1) with larger proportion in column $j$ of sequence set $CS(r)$ should be assigned to $F[r, j]$, and the proportion of 0 (resp. 1) entries of column $j$ in matrix $F$ should be close to what it is in matrix $C$. Finally, the last $L$ columns are also computed together under the constraint of $\lambda_{\min} \geq L$. The string $r$ ($r \in \{ B^L_1, \ldots, B^L_n \}$) with largest proportion in columns $(n-L+1, \ldots, n)$ of sequence set $CS(r)$ should be assigned to $F[r, n-L+1\ldots, n]$, and the proportion of string $r$ of columns $(n-L+1, \ldots, n)$ in matrix $F$ should also be close to what it is in matrix $C$.

IV. EXPERIMENTAL RESULTS

In this section, both real biological data and simulation data were used to compare the performance of the algorithm HMFS with algorithm SDYN designed by Ukkonen [3]. The experiments were implemented on an Intel Pentium IV 2.0GHz with a 1GB RAM. The operating system was Windows XP Professional and the compiler was Microsoft Visual C++ 6.0. In our experiments, we used the following measurements to evaluate the two algorithms:

1. Reconstruction rate $RR$, the accuracy of the reconstructed founder set. Assume that $Fo_0 = \{ Fo_1, \ldots, Fo_{10} \}$ is the original founder set with $|Fo|$ $n$-length founders, and $Fr_0 = \{ Fr_1, \ldots, Fr_{10} \}$ is the reconstructed founder set with $|Fr|$ $n$-length founders. The proportion $RR$ of nucleotides that are reconstructed correctly is defined as follows:

$$RR = \left(1 - \frac{\sum_{i=1}^{n} \min \{ r_{ij} \mid j = 1, \ldots, n, |Fr| \}}{|Fo| \times n}\right) \times 100,$$

(4) $r_{ij} = \sum_{i=1}^{m} (Fo_{mi} \oplus Fr_{pi}), i = 1, \ldots, [|Fo|], j = 1, \ldots, |Fr|,$

(5)

where $\oplus$ denotes the logical XOR operator.

2. $|Fr|$, the number of founders in the reconstructed founder set $Fr$.

3. $|Fr| - |Fo|$, the difference in the number of founders between sets $Fr$ and $Fo$.

4. $\#BP$, the sum of the number of breakpoints across all recombinant sequences, as defined in Formula (6):

$$\#BP = \sum_{1 \leq i \leq m} p_i - m$$

(6)

5. $f_{r, \text{avg}}$, the fragment length corresponding to the reconstructed founder set $Fr$, as defined in Formula (7):

$$f_{r, \text{avg}} = \frac{\sum_{1 \leq i \leq m} \sum_{j \leq \text{mp}} Fd_{ij}}{m \times \sum_{1 \leq i \leq m} p_i}$$

(7)

6. The running time (Time).

Since the original founder set $Fo$ is unknown, measurements (2), (4), (5) and (6) are adopted in the experiments performed on real biological data, while measurements (1), (3) and (6) are used in the experiments performed on simulation data.

A. Experiments on Kreitman’s ADH Data

The alcohol dehydrogenase (ADH) data of Kreitman [11] consist of 11 haplotypes over 43 polymorphic sites of the ADH locus of fruit fly, Drosophila melanogaster. Among these 11 haplotypes, there are three identical ones. After removing the duplicate sequences, there are 9 haplotypes left.

Table I shows the experimental results on ADH data, where ten sets of parameters were set in dealing with the minimum fragment length bound $L$. From this table, we can see that the number of reconstructed founders $|Fr|$ of the two algorithms are both increased with the augmentation of $L$, and $|Fr|$ obtained by the HMFS algorithm is close to that obtained by the SDYN algorithm. However, the HMFS algorithm can generate much fewer breakpoints than the SDYN algorithm, that is to say that the average fragment length $f_{r, \text{avg}}$ obtained by the HMFS algorithm is much longer than that obtained by the SDYN algorithm. The running speed of the HMFS algorithm is much faster than the SDYN algorithm.

| $L$ | $|Fr|$ | $\#BP$ | $f_{r, \text{avg}}$ | Time(s) | $|Fr|$ | $\#BP$ | $f_{r, \text{avg}}$ | Time(s) |
|-----|-------|-------|---------------|--------|-------|-------|---------------|--------|
| 1   | 2     | 122   | 3.2           | 0.0002 | 2     | 270   | 1.4           | 0.0018 |
| 2   | 4     | 26    | 14.9          | 0.0001 | 4     | 90    | 4.3           | 0.0017 |
| 3   | 4     | 34    | 11.4          | 0.0001 | 4     | 72    | 5.4           | 0.0016 |
| 4   | 6     | 13    | 29.8          | 0.0001 | 5     | 54    | 7.2           | 0.0014 |
| 5   | 6     | 13    | 29.8          | 0.0001 | 5     | 45    | 8.6           | 0.0012 |
| 6   | 7     | 5     | 77.4          | 0.0001 | 5     | 45    | 8.6           | 0.0011 |
| 7   | 7     | 5     | 77.4          | 0.0001 | 6     | 27    | 14.3          | 0.0010 |
| 8   | 7     | 5     | 77.4          | 0.0001 | 6     | 27    | 14.3          | 0.0009 |
| 9   | 7     | 2     | 193.5         | 0.0001 | 7     | 18    | 21.5          | 0.0008 |
| 10  | 7     | 2     | 193.5         | 0.0001 | 7     | 18    | 21.5          | 0.0007 |

TABLE I. RESULTS FOR KREITMAN’S ADH DATA.
B. Experiments on Simulation Data

In this subsection, simulation data were used to evaluate algorithms HMFS and SDYN. Firstly, the original founder set $F_0$ was generated randomly. Secondly, $m$ recombinants were generated by randomly patching up $n_{\text{seg}}$ random segments from the original founders. We evaluated the performance of the two algorithms by varying the number of the original founders $|F_0|$, the fragment length bound $L$, the number of recombinants $m$, the number of sites $n$, and the original average fragment length $f_{\text{avg}}$, which is equal to $\frac{n}{n_{\text{seg}}}$.

100 data sets were generated for each parameter setting. The average over 100 runs at each parameter setting was calculated and presented.

Fig. 3 shows $RR$ and $|F_r|-|F_0|$ obtained by the HMFS algorithm with different $m$ and $n$, where $L=2$, $|F_0|=10$ and $n_{\text{seg}}=10$. In Fig. 3(a), when $m=300$, 500 and 800, the HMFS algorithm gets relatively high reconstruction rates, and $RR$ varies between a very narrow range for each $n$ setting. In addition, as shown in Fig. 3(b), the HMFS algorithm also gets relatively small $|F_r|-|F_0|$ when $m=300$. Therefore, $m$ was set to 300 in the following experiments for the trade-off among $RR$, $|F_r|-|F_0|$ and running time.

In Table II, nine sets of parameters were set in dealing with the number of original founders $|F_0|$, and $L=2$, $m=300$, $n=600$, $n_{\text{seg}}=4$.

With the increase of $|F_0|$, $|F_r|-|F_0|$ obtained by the HMFS algorithm varies from 1.6 to 3.5, while $|F_r|-|F_0|$ obtained by the SDYN algorithm varies from -6 to 2. It is apparent that when $|F_r|-|F_0|$ is a negative, there must exist certain founders of set $F_0$ not being reconstructed in set $F_r$, hence the HMFS algorithm is superior to the SDYN algorithm in reconstructing founder set.

The running time of the HMFS algorithm is much shorter than that of the SDYN algorithm. When $|F_0|$ is 10, the running time of algorithm SDYN is 550.7405 seconds, while the HMFS algorithm only uses 0.0230 seconds. Therefore, algorithm HMFS is still efficient for solving the instances with large $m$ and $n$.

The SDYN algorithm obtains the number of reconstructed founders and the corresponding segmentation from a set of recombinants [3]. Since it is possible to construct many founder sets from a kind of segmentation, and there is not a concrete construction method described in reference [3], we only computed $RR$ for the HMFS algorithm in our experiments. From Table II, we can see that algorithm HMFS gets relatively high reconstruction rates in every $|F_0|$ setting, and $RR$ decreases with the increase of $|F_0|$.

Given a fixed number of recombinants $m$, the increase of $|F_0|$ decreases the recombinant coverage, which is the number of recombinants covering a SNP site of the original founders. As shown in Table II, when $|F_0|$ changes from 2 to 10, the recombinant coverage decreases from 150 to 30. This is disadvantage for...
In Table III, nine sets of parameters were set in dealing with the fragment length bound $L$, and $|F_o|=6$, $m=300$, $n=600$, $n_{seg}=4$.

From this table we can see that $|F_r|-|F_o|$ obtained by the two algorithms are all increased with the augment of $L$, and the increment speed of the HMFS algorithm is slower than that of the SDYN algorithm. When parameter $L$ increases, the probability of a recombinant event occurring decreases, which is disadvantageous for constructing the minimum founder set, hence $|F_r|-|F_o|$ increases accordingly.

The running speed of the HMFS algorithm is more than 3000 times faster than that of the SDYN algorithm, the running time of the HMFS algorithm changes from 0.0202 to 0.0218 seconds, while the running time of the SDYN algorithm changes from 709.9364 to 745.2394 seconds. In every $L$ setting, algorithm HMFS is able to get relatively high reconstruction rates, and RR decreases slightly with the increase of $L$.

Table IV shows the experimental results for different $f_{o_{avg}}$ settings. For each $f_{o_{avg}}$, three sets of parameters were set in dealing with $n$ and $n_{seg}$, and $L=2$, $|F_o|=6$, $m=300$.

In our experiments, it has been noticed that when the number of SNP sites $n$ can be dividable by the given fragment length bound $L$, the obtained number of reconstructed founders by the SDYN algorithm must not be more than $2^L$. Since in the following experiments with $L=2$, $|F_r|-|F_o|$ obtained by the SDYN algorithm must be between $-5$ and $-2$, we only show the experimental results obtained by the HMFS algorithm. It can be seen from Table IV that with the increase of parameter $f_{o_{avg}}$, the performance of the HMFS algorithm improves gradually. Take $n=3000$ for example, when $f_{o_{avg}}$ changes from 15 to 150, RR increases from 62.621 to 95.879, $|F_r|-|F_o|$ decreases from 29.4 to 2.2, and the running time decreases from 0.2749 to 0.0987 seconds. The HMFS algorithm is still efficient for reconstructing long founders.

### Table III

**Performance of different $L$ with $|F_o|=6$, $m=300$, $n=600$, $n_{seg}=4$**

| $L$ | HMFS $RR$ | $|F_r|-|F_o|$ | Time(s) | SDYN $|F_r|-|F_o|$ | Time(s) |
|-----|-----------|---------------|---------|------------------|---------|
| 2   | 98.44     | 3.4           | 0.0202  | -2               | 709.9364|
| 3   | 98.18     | 7.1           | 0.0205  | 2.8              | 750.4958|
| 4   | 96.99     | 11.2          | 0.0204  | 9.3              | 727.6994|
| 5   | 96.25     | 14.7          | 0.0208  | 10.5             | 742.7943|
| 6   | 96.14     | 17.0          | 0.0202  | 18.3             | 776.4991|
| 7   | 95.71     | 22.1          | 0.0206  | 26.4             | 732.3794|
| 8   | 95.32     | 22.9          | 0.0207  | 33.6             | 733.5970|
| 9   | 94.58     | 25.0          | 0.0209  | 36.5             | 718.7402|
| 10  | 94.52     | 28.3          | 0.0218  | 37.2             | 745.2394|

### Table IV

**Performance of different $f_{o_{avg}}$ and $n$ with $L=2$, $|F_o|=6$, $m=300$**

| $f_{o_{avg}}$ | $n$ | $n_{seg}$ | RR | $|F_r|-|F_o|$ | Time(s) |
|---------------|-----|-----------|----|---------------|---------|
| 15            | 300 | 20        | 79.32 | 5.1 | 0.0167 |
|               | 1500| 100       | 64.905 | 17.8 | 0.1334 |
|               | 3000| 200       | 62.621 | 29.4 | 0.2749 |
| 20            | 300 | 15        | 85.53 | 3.6 | 0.0144 |
|               | 1500| 75        | 67.227 | 11.6 | 0.1272 |
|               | 3000| 150       | 64.015 | 20.9 | 0.2129 |
| 25            | 300 | 12        | 90.98 | 2.9 | 0.0140 |
|               | 1500| 60        | 70.732 | 8.4 | 0.1141 |
|               | 3000| 120       | 65.456 | 14.9 | 0.1842 |
| 30            | 300 | 10        | 94.01 | 2.3 | 0.0139 |
|               | 1500| 50        | 75.130 | 6.5 | 0.1023 |
|               | 3000| 100       | 66.871 | 11.9 | 0.1692 |
| 50            | 300 | 6         | 95.74 | 1.9 | 0.0137 |
|               | 1500| 30        | 87.523 | 3.3 | 0.0956 |
|               | 3000| 60        | 76.625 | 5.9 | 0.1426 |
| 75            | 300 | 4         | 96.31 | 1.9 | 0.0136 |
|               | 1500| 20        | 89.648 | 2.8 | 0.0825 |
|               | 3000| 40        | 84.049 | 4.1 | 0.1235 |
| 100           | 300 | 3         | 96.92 | 1.9 | 0.0134 |
|               | 1500| 15        | 94.234 | 2.2 | 0.0666 |
|               | 3000| 30        | 88.414 | 3.2 | 0.1137 |
| 150           | 300 | 2         | 97.52 | 1.8 | 0.0133 |
|               | 1500| 10        | 97.945 | 2.1 | 0.0482 |
|               | 3000| 20        | 95.879 | 2.2 | 0.0987 |
It has been reported that one centimorgan, which is a unit of measure of recombination frequency, is equivalent to one million base pairs on average in human beings [10]. Since there is about one SNP per 1000 bases, the number of SNP sites covered by one centimorgan is about 1000. As shown in Fig. 4, further experiments were conducted to test the performance of the HMFS algorithm in dealing with parameters $f_{o, avg}$ and $n$. When $f_{o, avg}$ ranges between 200 and 1000, HMFS can get very high reconstruction rate, and the number of reconstructed founders $|Fr|$ is very close to that of the original founders $|Fo|$. 

![Graph](image)

**Figure 4.** RR and $|Fr|-|Fo|$ of different $f_{o, avg}$ and $n$ with $L=2$, $|Fo|=6$, $m=300$. (a) RR; (b) $|Fr|-|Fo|$.

V. CONCLUSIONS

During meiosis, genetic recombination generates a mosaic structure of the genome, and each resulting haplotype consists of fragments from different ancestral sequences. In this paper, we study the Minimum Founder Set problem, which is an important computational model for inferring breakpoints and founders.

A novel constructive heuristic algorithm HMFS is presented for finding the minimum founder set. The HMFS algorithm partitions the sites of founders into three parts and reconstructs them respectively. Comparing with the SDYN algorithm, algorithm HMFS can get close or better solution with much shorter running time, which was tested by a number of experiments. Furthermore, the HMFS algorithm has high efficiency and is intended to reconstruct long founders. In conclusion, algorithm HMFS is a practical method for solving the Minimum Founder Set problem.

ACKNOWLEDGMENT

The authors are grateful to Professor Yufeng Wu for his kindly providing the ADH sample data, and Professor Qi Zhang for bringing the minimum mosaic problem to our attention. This research was supported in part by Guangxi Natural Science Foundation under Grant No. 2011GXNSFBO18068, No. 2011GXNSFBO18070 and No. 2012GXNSFAA053219, the National Natural Science Foundation of China under Grant No. 61165009, and “Bagui Scholar” Project Special Funds.

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