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Monte Carlo simulations on marker grouping and ordering

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Abstract Four global algorithms, maximum likelihood (ML), sum of adjacent LOD score (SALOD), sum of adjacent recombinant fractions (SARF) and product of adjacent recombinant fraction (PARF), and one approximation algorithm, seriation (SER), were used to compare the marker ordering efficiencies for correctly given linkage groups based on doubled haploid (DH) populations. The Monte Carlo simulation results indicated the marker ordering powers for the five methods were almost identical. High correlation coefficients were greater than 0.99 between grouping power and ordering power, indicating that all these methods for marker ordering were reliable. Therefore, the main problem for linkage analysis was how to improve the grouping power. Since the SER approach provided the advantage of speed without losing ordering power, this approach was used for detailed simulations. For more generality, multiple linkage groups were employed, and population size, linkage cutoff criterion, marker spacing pattern (even or uneven), and marker spacing distance (close or loose) were considered for obtaining acceptable grouping powers. Simulation results indicated that the grouping power was related to population size, marker spacing distance, and cutoff criterion. Generally, a large population size provided higher grouping power than small population size, and closely linked markers provided higher grouping power than loosely linked markers. The cutoff criterion range for achieving acceptable grouping power and ordering power differed for varying cases; however, combining all situations in this study, a cutoff criterion ranging from 50 cM to 60 cM was recommended for achieving acceptable grouping power and ordering power for different cases.

Keywords Gene mapping · Linkage · Marker order · Genetics · Breeding

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Introduction

The recent development of DNA molecular marker techniques, such as RFLP, AFLP, RAPD, and SSR, has revolutionized quantitative trait locus (QTL) mapping during the last 10 years. By means of specific statistical methods, genes controlling quantitative traits can be searched for at specific positions along linkage groups. Many of the basic inferences and practical applications of genome research rely on accurate marker order. Therefore, marker ordering is a key step for genomic mapping. Apparently, the results will be incorrect even if the QTL mapping methods are appropriate when the markers are poorly grouped or ordered.

The construction of linkage maps among a number of markers includes two important steps. The first is grouping markers into linkage groups and the second is ordering the markers within each linkage group. Linkage grouping consists of placing markers into linkage groups based on their linkage relationships. The parameter used to determine the linkage or non-linkage between two markers is usually chi-square (χ^2) or a recombination value (Doerge 1993). When a higher χ^2 value or a lower recombination frequency is used, more linkage groups will result. There is no specific cutoff criterion used in marker grouping by Doerge (1996); however, a specific cutoff criterion is important since it directly determines the number of linkage groups.

The major goal of marker ordering is to obtain marker order within a linkage group. This ordering problem could utilize the algorithms used for solving the traveling

salesman problem (TSP). Many methods for marker ordering based on the TSP algorithm have been developed; these include minimum sum of adjacent recombination fractions (SARF) (Falk 1989), minimum product of adjacent recombination fractions (PARF) (Wilson 1988), maximum sum of adjacent lod scores (SALOD) (Weeks and Lange 1987), minimum sum of the probability of double recombination (PDR) (Knapp et al. 1989), and maximum likelihood (ML) (Lander and Green 1987). However, these methods require computation of a statistic on each of the $n!/2$ possible marker orders for n markers and therefore, are limited to a small number of loci within a linkage group. Other approaches, such as the stepwise likelihood method (Lathrop et al. 1984; Donis-Keller et al. 1987), seriation (SER) (Buetow and Chakravarti 1987a), and rapid chain delineation (RCD) (Doerge 1996) do not need to consider all possible orders and therefore can be used for ordering large linkage groups.

Before ordering a number of markers, researchers usually do not know the correct order of these markers studied. The effective way to assess performance of an ordering algorithm is to apply it to a set of markers of known orders. The term of the probability of estimated marker orders or percentage of correct gene order (PCO) was introduced to evaluate ordering power (Liu 1998). Buetow and Chakravarti (1987b) applied the Monte Carlo simulation strategy to evaluate their seriation method. Later, Kammerer and MacCluer (1988), Olson and Boehnke (1990), and Doerge (1996) also used simulation to evaluate the efficiency of different ordering methods. PCO can be estimated by the bootstrap approach for practical genomic experiments when repeated experiments are not allowed (Liu 1998); however, the PCO is based on the assumption that the gene order is correct when all genetic markers are used.

The purpose of this paper is to report on a study of the influences of different factors on marker grouping and marker ordering power. Monte Carlo simulations were conducted to evaluate the mapping efficiency taking several factors into consideration, such as ordering approaches, population size, recombination cutoff criteria, marker spacing patterns, and distance between adjacent loci. The results provide precise information on obtaining marker grouping and ordering.

Materials and methods

Generating marker data

To reduce complexity and enable the comparison of different combinations of several factors (locus spacing patterns, population sizes, cutoff criteria), a single simple pedigree structure was chosen (Olson and Boehnke 1990). Five loci were located evenly or unevenly on single linkage or each of three linkage groups with known linkage distances. Under the assumptions of no interference, codominant marker data from a doubled haploid (DH) population for each combination of different population sizes (100, 150, and 200) and three evenly spacing patterns (5 cM, 10 cM, and 15 cM) and one unevenly spacing pattern were generated.

Estimating pair-wise distance matrix

Let 1, 2, …, l denote l markers available. The following matrices are used to denote the statistics from the two-locus analysis:

$$\mathbf{R} = \lfloor \hat{\theta}_{ij} \rfloor_{ixl},\ \mathbf{Z} = \lfloor \hat{z}_{ij} \rfloor_{ixl},\ \mathbf{D} = \lfloor \hat{d}_{ij} \rfloor_{ixl},$$

and

$$\mathbf{N} = \lfloor n_{ij} \rfloor_{ixl},$$

where

$$\hat{\theta}_{ij}, \hat{z}_{ij}, \hat{d}_{ij},$$

and, n_{ij} are the estimated recombination fraction, lod score, distance and number of informative observations, respectively, between loci i and j (Liu 1998).

An $l \times l$ pairwise recombination frequency matrix could be obtained among l markers (or loci) based on maximum likelihood for the DH population (Liu 1998). Then the distance matrix among l markers could be transformed based on Haldane's (1919) mapping function.

Marker grouping and ordering

Linkage groups were determined by the cutoff criteria ranging from 20 cM to approximately 40 cM for the combinations of three evenly paced distances (5 cM, 10 cM, and 15 cM) and three population sizes (100, 150, and 200) for single linkage group and three linkage groups. For comparing the ordering power of the different methods, four global approaches ML, SARF, PARF, and SALOD, and SER were used for marker ordering within each group. More widely cutoff criteria ranging from 30 cM to approximately 100 cM and the SER method were used for searching the best range for more general cases in this simulation study.

Definitions for grouping power and ordering power

Let n be the total simulation number, g be the number of correct groups for a specific linkage group, and o be the number of correct marker orders for the same linkage group, then the grouping power and ordering power are defined as following,

$$\text{grouping power} = \frac{g}{n} \times 100\%;$$

$$\text{ordering power} = \frac{o}{n} \times 100\%$$

Two hundred simulations were conducted for each case. The standard error for mean grouping power and ordering power were calculated based on the properties of binomial distributions (Weir 1990). Correlation coefficients were calculated between ordering power and grouping power for these ordering methods, respectively. All calculations were run on self-written software in C++ in a personal computer.

Results

Comparisons of ordering powers for five ordering approaches

Ordering powers were almost identical for five methods for the single linkage group case based on different population sizes, marker spacing distances, and cutoff criteria (Table 1). Correlation between ordering power and grouping power was greater than 0.99 (Table 2) for each of five methods, suggesting that if given a correct

Table 1 Comparisons of ordering power[a] for five ordering methods for single and multiple linkage group cases

Ordering method	Ordering power (%)	
	Single linkage group	Three linkage groups
ML	94.67 (0.60)	94.77 (0.33)
SALOD	94.76 (0.59)	94.78 (0.33)
SARF	94.52 (0.60)	94.76 (0.35)
PARF	94.69 (0.60)	94.74 (0.35)
SER	94.57 (0.60)	94.60 (0.35)

[a] Standard error is in parenthesis

marker group, the markers in this group have a probability of greater than 99% of being correctly ordered.

Although increasing cutoff criterion improves the grouping power for a single linkage group, it is not applicable for multiple linkage groups. For more generality, simulations for multiple-linkage cases were also conducted. These five methods also provided similar ordering power based on all conditions (Table 1). The high correlation of greater than 0.99 between grouping power and ordering powers (Table 2) not only indicated that these five methods have very similar ordering powers, but also confirmed that they were reliable and that their ordering powers were highly related to grouping powers. Comparing the grouping power and ordering power of the five methods for single linkage and multiple linkage cases, it is clear that all five methods for marker ordering are powerful and reliable and that they are mainly dependent on the grouping power. Since the simplification and faster computation of the SER algorithm could be used, the following simulations for searching appropriate cutoff criteria were based on this algorithm.

Searching for the best cutoff criterion for grouping

Because the cutoff criterion determines the number of linkage groups, it is important to search for the best cutoff criterion range for obtaining acceptable grouping power

Table 2 Correlation coefficients between grouping and ordering powers for five methods for single and multiple linkage group cases

Number of linkage groups	Ordering methods				
	ML	PARF	SALOD	SARF	SER
Single	0.994**	0.996**	0.994**	0.993**	0.992**
Three	0.995**	0.995**	0.995**	0.995**	0.994**

** Significant at 0.001 level

Table 3 Marker ordering[a] and grouping powers[a] for DH populations with different population sizes, marker spacing distances, and cutoff criteria

Population size (*n*)	Cutoff criterion (cM)	Marker spacing distances (cM)					
		5		10		15	
		Order	Group	Order	Group	Order	Group
100	30	94.7 (1.8)	100.0 (0.0)	98.5 (1.0)	100.0 (0.0)	98.3 (1.0)	98.5 (1.0)
	40	95.3 (1.7)	100.0 (0.0)	99.0 (0.8)	100.0 (0.0)	99.5 (0.6)	100.0 (0.0)
	50	95.8 (1.6)	99.7 (0.5)	99.0 (0.8)	99.7 (0.5)	98.7 (0.9)	99.0 (0.8)
	60	93.8 (1.9)	99.0 (0.8)	97.7 (1.2)	98.7 (0.9)	98.0 (1.1)	98.7 (0.9)
	70	91.3 (2.3)	95.3 (1.7)	85.5 (2.8)	86.0 (2.8)	86.2 (2.8)	86.8 (2.7)
	80	78.2 (3.3)	81.0 (3.1)	76.2 (3.4)	76.5 (3.4)	71.8 (3.6)	72.2 (3.6)
	90	63.5 (3.8)	67.0 (3.8)	57.5 (3.9)	58.0 (3.9)	42.7 (4.0)	43.0 (4.0)
	100	45.3 (4.0)	47.3 (4.0)	35.7 (3.8)	35.7 (3.8)	23.8 (3.4)	23.7 (3.4)
150	30	99.8 (0.3)	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)	99.5 (0.6)	99.5 (0.6)
	40	99.3 (0.6)	100.0 (0.0)	99.7 (0.5)	100.0 (0.0)	99.8 (0.3)	100.0 (0.0)
	50	98.8 (0.9)	100.0 (0.0)	99.7 (0.5)	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)
	60	98.8 (0.9)	99.7 (0.5)	99.8 (0.3)	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)
	70	97.2 (1.3)	98.2 (1.1)	96.3 (1.5)	96.3 (1.5)	96.0 (1.6)	96.0 (1.6)
	80	93.2 (2.0)	94.0 (1.9)	90.0 (2.4)	90.0 (2.4)	85.2 (2.8)	85.2 (2.8)
	90	78.2 (3.3)	78.3 (3.3)	70.5 (3.6)	70.5 (3.6)	64.0 (3.8)	64.0 (3.8)
	100	62.7 (3.9)	63.3 (3.9)	56.0 (4.0)	56.3 (4.0)	49.2 (4.0)	49.2 (4.0)
200	30	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)
	40	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)
	50	99.8 (0.3)	100.0 (0.0)	99.8 (0.3)	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)
	60	99.8 (0.3)	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)
	70	100.0 (0.0)	100.0 (0.0)	98.3 (1.0)	98.3 (1.0)	99.7 (0.5)	99.7 (0.5)
	80	96.3 (1.5)	96.3 (1.5)	95.0 (1.7)	95.0 (1.7)	95.2 (1.7)	95.3 (1.7)
	90	89.8 (2.4)	90.0 (2.4)	83.3 (3.0)	83.3 (3.0)	78.7 (3.3)	78.7 (3.3)
	100	75.0 (3.5)	75.3 (3.4)	62.8 (3.9)	62.8 (3.9)	58.8 (3.9)	58.8 (3.9)

[a] Standard error is in parenthesis

Table 4 Map distances for three linkage groups (range: 3 cM to approx. 30 cM)

Linkage	Locus				
	1[a]	2[a]	3	4	5
1	0.0a	9.2b	6.7	23.8	26.2
2	0.0	7.3	27.3	27.5	24.7
3	0.0	3.5	6.1	26.6	27.7

[a] Note: a is the position of the first marker in each linkage group, b is the interval distance between two adjacent markers from the beginning side

and ordering power for different cases. A cutoff criterion ranging from 30 cM to approximately 100 cM was used to search for the high grouping power for three different population sizes (100, 150, and 200) and three evenly spaced marker distances (5 cM, 10 cM, and 15 cM). The grouping power and ordering power and their standard errors of 95% are summarized in Table 3.

Results in Table 3 indicated that grouping power and ordering power were influenced by population size, marker spacing distance, and cutoff criterion. A large population size achieved relatively higher grouping power and ordering power compared to a small population size for a given condition. Closely linked loci achieved higher grouping power but did not guarantee higher ordering power than loosely linked loci, especially when a small population size (100) was used. For example, for the population size of 100, the grouping powers for three marker spacing distances expressed no significant differences when a cutoff criterion ranging from 40 cM to approximately 60 cM was applied; however, the corresponding ordering powers for a marker spacing distance of 5 cM were significantly less than that for marker spacing distances of 10 cM and 15 cM. The results suggested that the estimated recombination fraction for closely linked markers for small population size could be biased so that they resulted in inverted marker orders. The significant differences between grouping power and ordering power disappeared for the large population size. For a specific population size and a specific marker spacing distance, the cutoff criterion can have a very large effect on grouping power and its corresponding ordering power. A cutoff criterion of greater than 80 cM usually provided undesirable grouping or ordering powers for all cases in this study since unlinked markers often had a high possibility of being classified into one linkage group when a large cutoff criterion was used.

A cutoff criterion ranging from 30 cM to approximately 60 cM achieved desirable grouping power ($\geq$95%) and ordering power ($\geq$95%) for a small population size (100) for various marker spacing distances (Table 3). A slightly wider cutoff criterion range resulted in desirable grouping power for a large population size for various marker spacing distances. A correlation of greater than 0.99 between grouping power and ordering power suggested that desirable ordering power could be obtained once high grouping power was achieved.

For more general cases, an unevenly spaced marker pattern (5 cM to approx. 30 cM) was used for searching for the best cutoff criteria for different population sizes. The linkage map distances of three linkage groups are presented in Table 4. Criteria ranging from 30 cM to approximately 100 cM were used for estimating the grouping power and ordering power for different population sizes (100, 150, and 200). Results again showed that grouping powers and ordering powers increased with an increase of the population size (Table 5). These results were similar to those for evenly spaced markers. Correlations ($\geq$0.99) were also detected between grouping power and ordering power, which indicated that improving the ordering power directly depended on grouping power. For marker spacing distances ranging from 5 cM to approximately 30 cM, cutoff criterion ranging from 50 cM to approximately 60 cM was used to obtain acceptable grouping power and ordering power for the three population sizes, therby providing higher and more acceptable grouping powers than other cutoff criteria used. When criteria greater than 70 cM were used, both grouping power and ordering power began significantly decreasing for all population sizes (Table 5).

Discussion

Constructing linkage groups from a large number of molecular markers is critical for both gene mapping and QTL mapping. Linkage mapping consists of different

Table 5 Marker ordering[a] and grouping powers[a] for unevenly spaced markers

Cutoff criterion (cM)	Population sizes(n)					
	100		150		200	
	Order	Group	Order	Group	Order	Group
30	42.5 (3.9)	44.8 (3.9)	43.3 (3.9)	43.7 (3.9)	56.7 (3.8)	57.3 (3.8)
40	85.3 (2.8)	89.8 (2.4)	94.8 (1.8)	96.7 (1.4)	97.5 (1.2)	98.0 (1.1)
50	93.8 (1.9)	98.3 (1.0)	98.2 (1.1)	100.0 (0.0)	99.5 (0.6)	100.0 (0.0)
60	94.0 (1.9)	97.7 (1.2)	98.0 (1.1)	99.7 (0.5)	99.8 (0.3)	100.0 (0.0)
70	82.5 (3.0)	86.0 (2.8)	95.7 (1.6)	97.3 (1.3)	98.5 (1.0)	99.3 (0.7)
80	66.3 (3.8)	68.3 (3.7)	85.0 (2.9)	86.0 (2.8)	92.7 (2.1)	93.7 (1.9)
90	38.8 (3.9)	40.7 (3.9)	63.5 (3.9)	64.7 (3.8)	74.2 (3.5)	75.0 (3.5)
100	16.3 (2.9)	16.8 (3.0)	39.2 (3.9)	39.3 (3.9)	56.8 (4.0)	56.8 (4.0)

[a] Standard error is in parenthesis

Table 6 Marker ordering[a] and grouping powers[a] for F_2 populations with different marker types (cutoff = 60 cM)

Marker type[b]	Population size	Marker spacing distance (cM)			
		5		10	
		Order	Group	Order	Group
DDR	100	3.2 (1.4)	39.5 (3.9)	9.2 (2.2)	37.5 (3.9)
	200	8.5 (2.1)	60.8 (3.8)	31.0 (3.2)	75.8 (3.4)
	300	16.5 (2.8)	70.0 (3.6)	45.0 (3.0)	83.5 (2.9)
	400	22.7 (3.0)	73.2 (3.5)	51.5 (2.7)	90.5 (2.3)
CD	100	79.0 (3.3)	86.2 (2.8)	77.2 (3.4)	79.7 (3.2)
	200	98.7 (0.9)	99.7 (0.5)	99.0 (0.8)	99.0 (0.8)
	300	99.8 (0.3)	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)
	400	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)
CC	100	97.8 (1.2)	98.3 (1.0)	95.7 (1.6)	95.7 (1.6)
	200	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)
	300	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)
	400	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)
DDC	100	79.2 (3.2)	83.0 (3.0)	73.5 (3.5)	75.7 (3.4)
	200	98.3 (1.0)	99.3 (0.7)	98.5 (1.0)	98.5 (1.0)
	300	99.8 (0.3)	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)
	400	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)

[a] Standard error is in parenthesis
[b] CC, Codominant/codominant; CD, codominant/dominant; DDC, dominant/dominant with coupling phase; DDR, dominant/dominant with repulsion phase

steps, and each step plays its own important role in gene mapping and QTL mapping; however, this study mainly addressed grouping and ordering powers taking the effects of several different factors into consideration.

When a number of molecular markers are available, researchers usually do not know the exact number of linkage groups. The most important task is to group markers into different linkage groups. However, most of the researchers in the past considered mainly the single linkage group. In this study, we set a general case with several linkage groups. Also, different ordering methods may result in different ordering powers. In this study several commonly used global algorithms and one approximation algorithm were considered for comparing the ordering efficiency. An appropriate way to evaluate the marker mapping efficiency is to compare the known linkage groups and marker orders. This evaluation strategy can be effectively conducted by the Monte Carlo simulation technique (Olson and Boehnke 1990; Doerge 1996). In this study, DH populations with different population sizes, cutoff criteria, and marker spacing patterns were used for simulations. Our results showed that the ordering power for the SER method was very similar to that for four other global methods that were time-consuming and computationally intensive. More importantly, the ordering power was found to be highly dependent on the grouping power for all five methods.

Our study shows that cutoff criterion play a critical role in grouping power and, correspondingly, in ordering power. Different cutoff criteria may result in very different mapping powers. Too high or low cutoff criteria are not desirable for achieving acceptable grouping and ordering powers. The appropriate cutoff range may differ for various cases. Therefore, one of the important concerns relative to linkage mapping is the determination of the appropriate cutoff criterion for obtaining desirable mapping powers. A wider criterion range could be used for a large population size or closely linked markers, while a narrower criterion range could be appropriate for a small population size or loosely linked loci. However, a cutoff criterion ranging from 50 cM to approximately 60 cM is desirable for obtaining acceptable mapping powers in most cases.

Tightly linked markers may result in the inversion of markers for small population sizes and subsequently decrease the ordering power. On the other hand, loosely linked markers may result in low grouping power and a corresponding ordering power; thus, a more narrow range of cutoff criteria is applicable to achieving acceptable grouping power and ordering power. That is why the uneven marker spacing pattern generally had low mapping powers when the cutoff criterion used was too small or large. For unevenly spaced markers, a large population size was required to obtain desirable mapping powers.

This simulation study was based on a DH population. However, population types may have different mapping powers. Our other simulations indicated that DH, single-seed descent, and backcross populations were similar with respect to grouping power and ordering power (results not presented); however, marker types in an F_2 population gave different mapping powers. Codominant/codominant, codominant/dominant, and dominant/dominant with coupling phase marker types had desirable and similar mapping powers, but dominant/dominant with repulsion phase (DDR) marker type provided much lower mapping powers (Table 6). This is because biased estimations are obtained for recombination frequency with the DDR marker type for the F_2 population (Liu 1998). Simulations for F_2 populations with DDR marker types showed that a large population size (400) still resulted in undesirable

mapping powers (Table 6). The results suggest that codominant DNA markers (i.e. SSR and RFLP markers) should be preferred to obtain desirable linkage mapping powers in F_2 populations.

Segregation ratio distortion due to sampling, biological selection, or lethal genes affects the estimation power for recombination fraction and decrease mapping power (Liu 1998). Commonly used computer software for linkage analysis and genomic map construction like MAPMAKER (Lander and Green 1987) and JOINMAP (Stam 1993) cannot properly analyze distorted data. The development of software which will properly analyze data with distorted segregation remains a challenge.

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