ACCURACY OF FOUR HEURISTICS FOR THE FULL SIBSHIP RECONSTRUCTION PROBLEM IN THE PRESENCE OF GENOTYPE ERRORS

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The full sibship reconstruction (FSR) problem is the problem of inferring all groups of full siblings from a given population sample using genetic marker data without parental information. The FSR problem remains a significant challenge for computational biology, since an exact solution for the problem has not been found. The new algorithm, named SIMPSON-assisted Descending Ratio (SDR), is devised combining a new Simpson index based $O(n^2)$ algorithm (MS2) and the existing Descending Ratio (DR) algorithm. The SDR algorithm outperforms the SIMPSON, MS2, and DR algorithms in accuracy and robustness when tested on a variety of sample family structures. The accuracy error is measured as the percentage of incorrectly assigned individuals. The robustness of the FSR algorithms is assessed by simulating a 2% mutation rate per locus (a 1% rate per allele).

1 Introduction

Let population sample N be a collection $(X_1, X_2, ..., X_n)$ of n diploid genotypes

$$X_i = \left((x_{i1}, x'_{i1}), (x_{i2}, x'_{i2}), ..., (x_{iL}, x'_{iL})\right), \quad (1)$$

where each locus l is described by an unordered pair of alleles (x_{il}, x'_{il}) and L is the total number of loci which are assumed to be unlinked. Each locus l is a set of λ_l codominant alleles $\{a_{l1}, ..., a_{l\lambda_l}\}$. The full sibship reconstruction (FSR) problem is the problem of finding the *best* partition B from the set of available partitions $\{P_j\}$, where each P_j represents the partitioning of N into groups of full siblings without the availability of parental information. In order to find partition B, the partitions are ranked by a scoring function which is algorithm specific. Currently there are a number of heuristic FSR algorithms[1-7] employing a variety of scoring functions and techniques for searching the partition space $\{P_j\}$.

Some FSR algorithms[1,5,3] utilize the Mendelian rules of inheritance in determining the full sibling groups. For example, Butler *et al.*[3] devised the so-called SIMPSON algorithm which used the Simpson index

$$S = \frac{1}{n(n-1)} \sum_{k=1}^{r} g_k (g_k - 1) = -\frac{1}{(n-1)} + \frac{1}{n(n-1)} \sum_{k=1}^{r} g_k^2 \quad (2)$$

as the scoring function, where N is partitioned into r sib groups with group k containing g_k individuals. The SIMPSON algorithm is a brute force heuristic which searches for the best partition B by starting from all given genotypes being placed in different groups of size one. The algorithm then searches the available partition space by

randomly moving one individual into a different group if the newly enlarged group passes the Mendelian sibship test. The test is passed if all individuals in the group could be generated from the same pair of parental genotypes strictly obeying the Mendelian rules of inheritance. The number of random moves (iterations) is limited by the algorithm's parameter, $T_n = 100\,000$. The SIMPSON formulation of the FSR problem (FSR-S) has the partition search space at least exponential in n,[8] limiting the applicable range of the SIMPSON algorithm or any other "random-walk" based algorithms for that matter. For example, even a relatively small sample of 10 individuals restricted to being either full siblings or unrelated is estimated to yield $115\,975$ partitions.[6] The estimation is provided by the Bell number and is an upper bound of the actual partition space size.[8]

Another class of algorithms, notably the GRAPH[2] and DR[4] algorithms, use the pairwise likelihoods of Goodnight and Queller[9] in construction and assessment of the sib groups. The important difference between the Mendelian sibship test and likelihood-based tests is the ability of likelihoods to accommodate the presence of genotype errors. Essentially the Mendelian sibship test is likely to fail for a previously valid sib group[3] if even one allele is mutated, while the likelihood-based sibship tests are expected to be more robust.[7] The interest in the errors is not purely academic. The discovery of microsatellite markers revolutionized[10] conservation biology and molecular ecology as well as medical, forensic and population genetics, to name a few. However, markers may suffer from a wide range of error types with drastic consequences: a relatively *"small 1% error rate in allele calling would lead to almost a quarter of 12-locus genotypes containing at least one error".*[11] In the important case of noninvasive genotyping the situation is even more error-prone due to the small amount of target DNA further affecting the reliability of polymerase chain reaction (PCR) to correctly amplify all alleles.[12] In addition, microsatellite markers could be highly susceptible to mutation.[13]

In this study we compare the two existing algorithms; the SIMPSON[3] algorithm representing the class of algorithms based on the Mendelian sibship test and the Descending Ratio[4] (DR) algorithm which is purely likelihood based. We show that the SIMPSON algorithm could be replaced by a more efficient new $O(n^2)$ algorithm, named the Modified SIMPSON (MS2) algorithm. We also present a new algorithm, named the SIMPSON-assisted Descending Ratio (SDR) algorithm, which combines the advantages of the MS2 algorithm when there are no genotype errors with the robustness of DR to the errors.

2 Method

2.1 *Accuracy*

Normally[3] a sample with known sib groups (partition A) is generated by simulation (each such simulation is called a FSR trial). The sample is then presented to an FSR algorithm yielding the *best* (according to the algorithm) partition B. The known partition A and reconstructed partition B are compared and the accuracy measure for

the given trial (and sample structure) is calculated. The accuracy measure is then averaged over a number of trials, as large as one hundred[2] or as small as six[3]. However, the measures of accuracy were defined differently in the published algorithms making them difficult (if not impossible) to compare. For example, the following measures currently exist: the minimum number of moves $\xi(A,B)$ required to convert B into A;[3,2] the percentage of trials where $A=B$;[2] $(S_{fs|fs}-S_{fs|ur})/T_{fs}$, where $S_{fs|fs}$ is the total number of correctly reconstructed full-sib pairs, $S_{fs|ur}$ is the total number of incorrectly reconstructed full-sib pairs, and T_{fs} is the total number of full-sib pairs in A;[6] the number of full-sib families being completely recovered relative to the actual numbers in a sample.[7]

For this study, the *accuracy-error* is adopted as the accuracy measure. The error equals the percentage of incorrectly assigned individuals[14] $\xi=\xi(A,B)/n$ and is equivalent to the partition-distance which has known theoretical properties[15] and could be efficiently calculated via the maximum[15] or minimum[16] assignment problem for bipartite graphs. In addition the accuracy-error is directly comparable[8] to the $\xi(A,B)$ results of GRAPH[2] and the four algorithms studied by Butler *et al.*,[3] i.e. the AF,[1] Full Joint Likelihood (FJL[a]),[5] SC[5] and SIMPSON[3] algorithms. The available measures of accuracy compare the known partition A to the reconstructed partition B, while the ultimate goal of the FSR algorithms is to provide B together with its confidence level[17] for a given population sample with an *unknown* structure. While, at present, the assessment of the confidence levels for the FSR remains unexplored, the accuracy-error could provide consistent initial comparisons between the FSR algorithms.

2.2 *Simulations*

There are a number of sample family structures that are used for testing of the FSR algorithms. For example, while testing their GRAPH algorithm, Beyer and May[2] used four family distributions for the population sample of $n=50$ individuals with the following family sizes: (5×10),[b] (20,10,10,5,5), (30,5,5,5,5) and (40,5,2,2,1). They also used $n=500$ where all family sizes from their $n=50$ testing set were multiplied by 10. Butler *et al.*[3] used the (50×1),[c] (5×10), (25,10,10,4,1) and (45,1,1,1,1) family sizes for $n=50$ and (20×10), (5×40), (100,40,40,16,4) and (196,1,1,1,1) for $n=200$. The JW[7] algorithm was tested on the simulated samples with family sizes following Poisson or negative binomial distributions. The reconstructions of empirical data sets were also carried out to assess or illustrate the accuracy of the algorithms under consideration.[3,5,7] However, any conclusions drawn from what are normally a very limited number of empirical trials are statistically questionable and hence such cases are not considered here.

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[a] denoted by *Likelihood* in [3].
[b] Five families containing 10 full siblings each.
[c] Fifty unrelated individuals.

The fixed family sizes[2,3,5] are not scalable between different values of n while the distribution based[7] sizes may be prone to misinterpretation. Eventually it would be desirable to reach a consensus on family structure benchmarks that are easy to reproduce, exactly defined, and scalable to a wide range of n. The benchmarks could be used in the reporting of an algorithm's accuracy, allowing for consistent comparison between different algorithms. Two such benchmarks are proposed below and used for the testing of the FSR algorithms in this study:

- The *uniform* distribution benchmark (inspired by the $(5\times10)^{3,2}$ and $(50\times1)^3$ distributions) is defined by a partition $U_n(r,g)$, where r is the number of families (sib groups) and g is the size of each family, giving the population size $n = rg$. This benchmark tests how well an FSR algorithm performs as the amount of genetic information is gradually reduced: the number of families r increases maintaining the constant population sample size n and reducing each group size $g = n/r$.

- The *skewed* distribution is defined by $S_n(r,q)$, where q is the skewing factor such that group k contains $g_k = g_1 + q(k-1)$ full siblings and the size of the first group is given by $g_1 = n/r - q(r-1)/2$. This benchmark is essential since the accuracy of some FSR algorithms deteriorates as the skewing increases, e.g. GRAPH,[2] SC,[3] and FJL.[3]

Any allelic mutation in an individual genotype (Eq. 1) may lead to misclassification of that individual and is referred to as the *genotype error*. The error could be due to a variety of factors, e.g. mutation, plain human error,[18] PCR missprinting[11,7] and allelic dropout (null allele).[12] Most of the existing sources of error manifest themselves on the per allele basis, making it natural to specify the errors as the error rate per allele or locus.[7,11] In this study the following error model is used capturing the majority of the biologically occurring errors in one parameter, the locus error rate ε. The error is applied by collecting all available loci from all the individuals from a given sample, obtaining nL loci. Next, εnL different loci are randomly selected and one allele at each of the loci is mutated into a randomly chosen *different* (change into itself is prohibited) allele from the same locus. Since a common misprinting error is relatively small (between 0.3% and 11% per allele)[12] the mutation of both alleles at the same locus is omitted from consideration.

3 Algorithms

3.1 *The Modified SIMPSON (MS2) Algorithm*

Let $d_l(X,Y)$ be the number of alleles in an individual X which are not present in an individual Y at locus l. The locus $D_l(X,Y)$ and genotype $D(X,Y)$ distances could be defined by $D_l(X,Y) = \max\left(d_l(X,Y), d_l(Y,X)\right)$,

$D(X,Y) = \min D_l(X,Y)$, respectively.[8] The Modified SIMPSON (MS) algorithm significantly improved the SIMPSON[3] heuristic in speed while maintaining low accuracy-error using the genotype distances and achieving $O(n^3)$ running time.[8] The following $O(n^2)$ algorithm, named MS2, is derived from the original MS algorithm utilizing the local-minimum property of the Simpson index. The MS steps (1-4) remain unchanged:[8] steps (1) and (2) - calculate and sort the list of genotype distances in ascending order; step (3) - create a pool of unassigned individuals; step (4) – repeat this and the following steps; select the next unassigned individual from the list of distances until all individuals are assigned. The new MS2 steps: step (5) - place the next individual into the first group that passes the sibship test;[d] step (6) - sort the available sib groups in the descending order of their sizes.

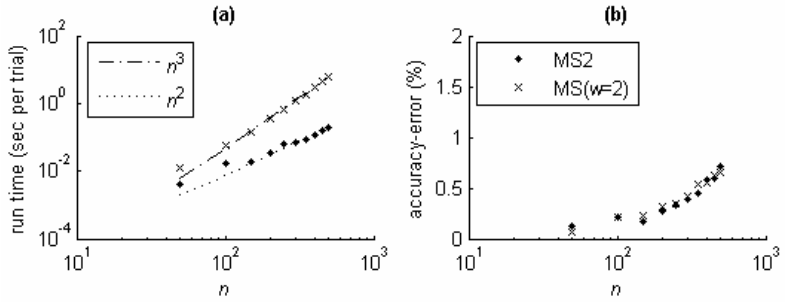

Figure 1. Runtime efficiency (in seconds per trial on a 3GHz PC) and the accuracy-error (%) of the MS (×) and MS2 (●) algorithms. Each FSR trial is performed on a freshly generated population sample genotyped for L=5 loci, each locus containing N_A=10 equifrequent alleles. The sample consists of r groups each containing 5 full siblings, giving the population size n=5r. The MS results are obtained with the window parameter w=2. The cubic and square powers of n are denoted by the dash-dot and dotted lines in the subfigure (a), respectively.

Figure 1(a) verifies that the complexity of the MS2 algorithm is $O(n^2)$, further improving the MS's $O(n^3)$. By the definition of the MS2 algorithm, the lower bound of its accuracy-error is the accuracy-error of the original MS algorithm when the MS's window parameter is $w = 1$. Figure 1(b) indicates that any potential loss of accuracy could be insignificant. The efficiency improvement is due to the Simpson index (Eq. 2) which is maximized on the local scale by increasing the largest group. To illustrate that, let two available groups have sizes g and $g-1$. Assuming that the next individual could be added to both groups, the Simpson index is maximized by placing the individual into the g-group since $(g+1)^2 + (g-1)^2 > 2g^2$. However the greedy method is still only a heuristic even on the local scale since two or more largest groups may have the same size. On the global scale this greedy approach has no guarantee in achieving the maximum value of the index, e.g. the partition with the group sizes (8,3,2) has a smaller index than the partition with (7,6) sizes.

[d] The sibship test is performed on the newly created group containing the next individual and the existing group.

Figure 1(b) verifies that the MS2 algorithm is as accurate as the MS algorithm However the MS2 algorithm is superior in run-time efficiency, e.g. Figure 1(a) shows that MS2 takes the same amount of computer time to reconstruct 500 individuals as for MS to reconstruct 150 individuals. The absolute terms, MS2 requires only a fraction of a second to perform the full sibship reconstruction of 500 individuals on a 3GHz Pentium 4 PC.

3.2 *The SIMPSON-assisted Descending Ratio (SDR) Algorithm*

Figure 2 compares the DR,[4] SIMPSON[3] and MS2 algorithms. Figure 2(a) for 50 unrelated individuals stands out as a reminder that the Simpson index based formulation (FSR-S) is still only an approximation of the FSR problem. The MS2 correctly finds the partition with the largest Simpson index (as does SIMSPON) by placing the individuals in groups of size two or larger (any two individuals always pass the sibship test). While the Simpson index as the scoring function is biologically incorrect in this instance, the likelihood based DR algorithm makes sense biologically by becoming more accurate as the amount of genetic information increases (larger L). The DR results are obtained with the *null* and *primary* hypotheses[e] being the unrelated and diploid full-sibling relationships, respectively.

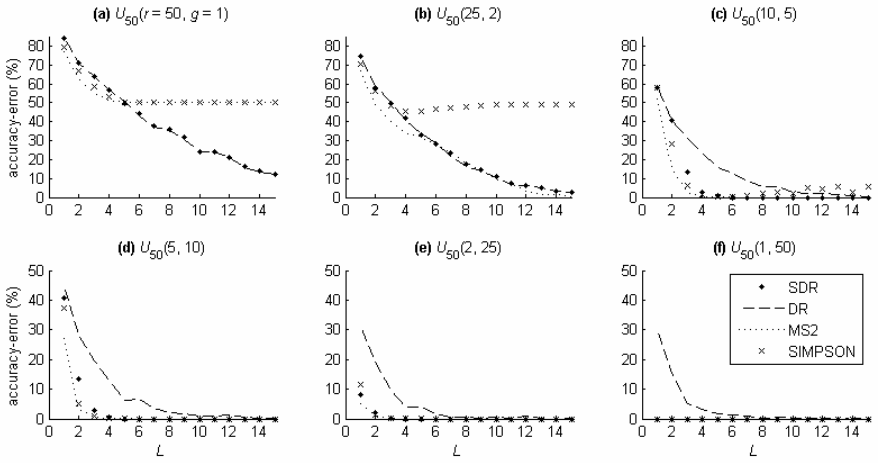

Figure 2. The accuracy-error of the SDR (●), DR (dashed line), MS2 (dotted line) and SIMPSON (×) algorithms as the function of the number of loci L and family structure in the absence of genotype errors. The subfigures are titled by the uniform distribution $U_n(r,g)$, e.g. the subfigure (a) displays the FSR results for 50 unrelated individuals.

Figure 3(c-f) verifies that the Mendelian sibship test based MS2 and SIMPSON algorithms are not robust to the presence of a realistic[12] error rate of 2% per locus or 1% per allele confirming the serious concern raised by Hoffman and Amos[11] who criticized

[e] *null* and *primary* are from the terminology of the KINSHIP [9] and KINGROUP [4] programs

the current common practice of reporting genotype inferred results without the error analysis. However in the absence of errors the MS2 and SIMPSON algorithms are more accurate than DR (Figure 2).

The MS2 accuracy in the absence of genotype errors and the DR robustness to the errors prompts the following SIMPSON-assisted Descending Ratio (SDR) algorithm: step (1) - perform the reconstruction using MS2 algorithm; step (2) - retain one largest group with size 3 or larger; step (3) - assign the remaining unassigned individuals as per the DR[4] algorithm. Only one largest group is retained in step (2) since the MS2 (and hence MS and SIMPSON) algorithm tends to break up a true sib group into a number of smaller sib groups in the presence of mutated alleles.

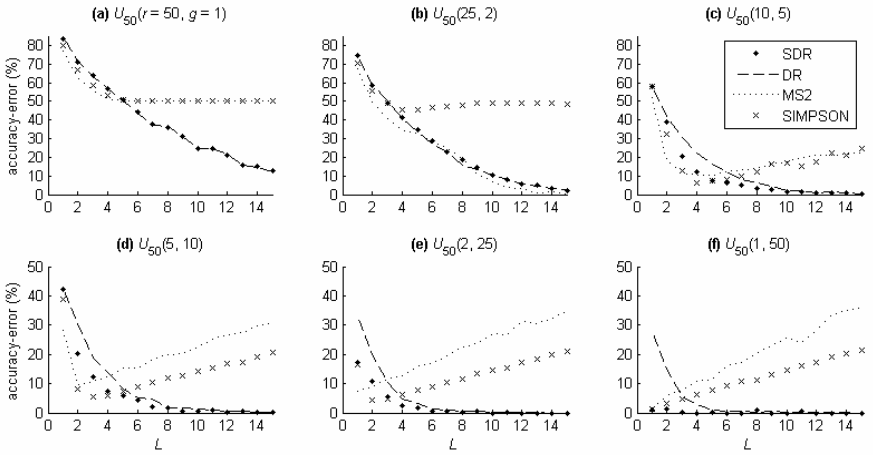

Figure 3. The same as in Figure 2 but with a 2% locus (1% allele) error rate applied to the generated population samples.

4 Results and Discussion

For this study the genotypes (Eq. 1) are considered with the same number of equifrequent alleles $\lambda_l = N_A = 10$ at each of the L loci. The number of loci L is chosen as a varying parameter since biologists would normally have a choice in the number of loci (e.g. microsatellite markers) but not their heterozygosity. Already having L as a parameter the variations in the number of alleles N_A are not considered since it is well understood that the increase in either N_A, L or both improves the accuracy of an FSR algorithm.[2,3] The SIMPSON results are calculated with $100\,000$ iterations. All presented results are averaged over 100 trials.

Figure 2 and Table 1 demonstrate that with 10 equifrequent alleles and in the absence of genotype errors: the SDR algorithm is as accurate as MS2 and SIMPSON from about $L = 5$ loci onwards; the MS2 and SIMPSON algorithms are essentially identical in accuracy. Figure 2(b) shows, however, that in the case of 25 families of two full siblings each, the MS2 algorithm is as accurate as DR while SIMPSON fails to distinguish correct sib groups.

In the presence of a 2% locus (1% allele) error rate (Figure 3): both MS2 and SIMPSON fail to deal with the errors, effectively arriving at proportionally worse partitions as the absolute number of errors increases with the increase of L; SDR is more accurate than the MS2, SIMPSON and DR algorithms, starting from about $L = 6$ loci; the SDR algorithm outperforms DR for all considered number of loci and family structures verifying the value of the MS2 preprocessing. The $O(n^2)$ cost of the MS2 preprocessing is negligible in comparison to the $O(n^3)$ cost[8] of the DR algorithm making SDR run in $O(n^3)$ and be feasible for practical applications.

Since SDR retains the largest sib group reconstructed by MS2, it may be expected that the effect of just one sib group should be proportionally small when a large number of groups is present, as in the case of 10 groups of 5 individuals each, see Figure 2(c). Surprisingly, Figure 2(c) demonstrates that the accuracy-error is reduced disproportionally, showing that the DR algorithm works significantly better if at least one "seed" sib group is supplied. This suggests a new approach which has a potential to resolve the current problem with the widely used KINSHIP[9] program. Using simulations, the program determines the pairwise likelihood ratios (the same ratios are used in the DR algorithm) for the given significance levels but then it is up to the user to manually assign individuals into sib groups based on their pairwise ratios. The problem arises when the same individual is significantly likely to be in the full sibling relationship with a number of individuals from different sib groups.[19] An algorithm similar to the SDR algorithm could accept all sib groups reconstructed by KINSHIP without conflict and then complete the reconstruction using the DR algorithm which, as shown here, becomes significantly more accurate once at least one seed group is supplied.

Figure 4 verifies that the SDR algorithm is robust to the mutation errors for skewed family structures. In particular, the accuracy-error SDR results in Figure 3(d) for 5 uniform groups are very similar to the results in Figure 4(b) for 5 skewed groups.

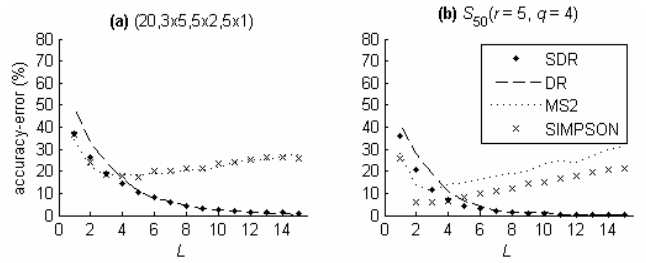

Figure 4. The same as in Figure 3 but for skewed family distributions: (a) 50 individuals distributed in 14 sib groups with (20, 5, 5, 5, 2, 2, 2, 2, 2, 1, 1, 1, 1, 1) sizes; (b) 50 individuals distributed in 5 sib groups with (2, 6, 10, 14, 18) sizes.

In conclusion, given a population sample without genotype errors and in the absence of unrelated individuals, the new MS2 $O(n^2)$ algorithm solves the FSR problem to the near-optimal level in speed and accuracy. On the other hand, the presented preliminary

results suggest that the new SDR $O(n^3)$ algorithm could solve the FSR problem to a high level of accuracy even in the presence of unrelated individuals and genotype errors.

Table 1. The accuracy-error (percentage of incorrectly classified individuals) achieved by the DR, MS2, SDR and SIMPSON algorithms for 50 individuals uniformly distributed in r groups of g size each. The family distributions are denoted by (r, g). Each of the L loci is simulated with 10 equifrequent alleles.

Algorithm	$U_{50}(r,g)$	L=1	2	3	4	5	6	8	10	12	14
DR	(50,1)	84.6	71.2	63.8	57	50.7	43.3	35.6	23.9	20.9	13.6
DR	(25,2)	74.8	59.2	50.2	40.9	33.6	28.8	16.4	10.6	6	3.3
DR	(10,5)	58.5	40.6	31	23.7	16	12.5	5.4	2.9	1.9	1
DR	(5,10)	44.9	28.2	19.5	13.2	6.4	6.5	2.2	0.9	1.2	0.2
DR	(2,25)	31.1	19.2	9.7	3.9	4	1.6	0.6	0.4	1	0
DR	(1,50)	30	15.4	5.1	3.2	1.8	1.5	0.2	0.2	0.1	0
MS2	(50,1)	77	62.9	54.9	51.3	50.1	50	50	50	50	50
MS2	(25,2)	67	49.2	40.3	34.3	31.8	27.6	18.4	9.2	3.2	1.2
MS2	(10,5)	52.2	15	2.6	0.4	0.1	0	0	0	0	0
MS2	(5,10)	27.2	3.2	0.5	0	0	0	0	0	0	0
MS2	(2,25)	5	0.8	0.1	0	0	0	0	0	0	0
MS2	(1,50)	0	0	0	0	0	0	0	0	0	0
SDR	(50,1)	83.9	71.2	63.7	56.7	49.7	44.2	36.2	24.3	21.2	14
SDR	(25,2)	74.4	58.2	49.9	41.8	32.8	28	17.6	10.7	6.3	3.2
SDR	(10,5)	57.7	40.7	13.4	2.6	0.7	0	0	0	0	0
SDR	(5,10)	40.8	13.5	2.8	0.5	0	0	0	0	0	0
SDR	(2,25)	8.3	2.1	0.1	0	0	0	0	0	0	0
SDR	(1,50)	0	0	0	0	0	0	0	0	0	0
SIMPS	(50,1)	79.6	67.1	58.4	53.4	50.3	50	50	50	50	50
SIMPS	(25,2)	70.4	56.5	48.6	45.6	45.7	46.7	48	48.9	48.8	48.9
SIMPS	(10,5)	58	28.3	6.2	1.2	0.3	0	2.4	2.3	4.6	2.4
SIMPS	(5,10)	37.4	5	0.9	0.1	0	0	0	0	0	0
SIMPS	(2,25)	11.4	1.3	0	0	0	0	0	0	0	0
SIMPS	(1,50)	0	0	0	0	0	0	0	0	0	0

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