

# ParaHaplo Manual

A program for whole genome association study using parallel computing  
Version 3.0

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## Introduction

### The purpose of this program package

Recent advances in high-throughput genotyping technologies have allowed us to test allele frequency differences between case and control populations on a genome-wide scale (1). More than one million single nucleotide polymorphisms (SNPs) for which accurate and complete genotypes have been obtained. Thousands of people are now being genotyped (2,3).

One of the crucial problems in GWAS is correction for multiple comparisons. Usually Bonferroni's correction for the P value is used to account for multiple testing. When SNP loci are in linkage disequilibrium, however, Bonferroni's correction is known to be too conservative and may drop truly significant SNPs (4,5).

To cope with multiple comparison problem in GWAS, Misawa et al. (4) have developed new algorithms to correct for the multiple comparisons at multiple SNP loci in linkage disequilibrium by treating linked loci as one haplotype block. They developed the method to calculate the exact probability of the type I error under the condition that the haplotype frequencies in the population are known and the number of haplotype copies in sample follows a multinomial distribution. The permutation test also can handle this problem (5).

Running time is a problem in calculating the exact probability (4) as well as in performing permutation tests (5). In this study, we developed ParaHaplo (6), parallel computation programs for calculating exact probability (4) as well as for permutation tests (5) for GWAS. ParaHaplo is based on data parallelism, a programming technique for splitting a large data set into small data sets that can be operated on in parallel (7) p44. ParaHaplo is developed based on the Intel Message Passing Interface (MPI) and runs on PC clusters.

To measure the efficiency of ParaHaplo in computational time, difference in haplotype frequency between CHB and JPT hapmap (8) on chromosome 22 is analyzed by using the new program. The result showed that more than 100 times speed up was achieved by ParaHaplo.

## Program overview

ParaHaplo tests the difference in allele frequency between case and control as well as that between two populations. ParaHaplo outputs the Pearson score for chi-square test. The users can make ParaHaplo output  $F_{st}$  by using command line option. ParaHaplo calculates the rates of type I errors of the test on the allele frequency by the exact method (4). The algorithm to calculate asymptotically the type I error rates using a Markov-chain Monte Carlo sampler (4) is also implemented in this program. This program also supports The standard permutation test (SPT) and RAT (5) .

ParaHaplo is implemented in a MPI-C multithreaded package. MPI package allows us to construct parallel computing programs on multiprocessors. The genome-wide polymorphism data is broken into haplotype blocks defined by users. Then, the MPI-Bcast function is used to distribute a single set of haplotype block data into each processor. Then haplotype frequency data of one haplotype block are analyzed by a single-processor. In this step, the probability of local type I error given the significance level at each SNP locus is calculated.

After the analysis on each haplotype block is complete, the results are joined into a single genome-wide data by using the MPI-Gatherv function. Then, the global type I error is obtained from the local type I error by using Bonferroni's correction, because different haplotype blocks are considered to be independent of each other although SNPs within haplotype block are not independent.

ParaHaplo requires an input file of haplotype block boundary, and two data for population data. When data files are provided for each chromosome, ParaHaplo HapMap data format and BioBank Japan data format are supported. ParaHaplo is compatible to OpenMPI version 1.2.5 as well as to MPICH version 1.2.7p1. The users can compile the source by GCC compiler as well as by Intel C compiler. C programs as well as Java programs are also available for single-processor machines. This program package contains the following programs:

- (i) A Markov-chain Monte Carlo (MCMC) algorithm to calculate asymptotically the probability of the type I error (4)
- (ii) Calculation of exact type I error rates (4)
- (iii) Permutation test based on RAT algorithm (5)
- (iv) Standard Permutation test (SPT)
- (v) Data conversion from BioBank Japan format to HapMap format

## Operating systems and platforms

We have tested our program package of parallel and single-processor versions that were coded in C on the following machine.

Machine	PC cluster with 1,024 nodes CPU: Intel Core2Duo 1.5GHz Memory: 2GB HDD: 4GB
OS	Linux OS (CentOS 4.5)
Parallel computing	OpenMPI and MPICH
Compiler	GCC4, Intel C compiler

We also have tested our program package of single-processor versions that were coded in java on the following machine.

Machine 1	PC cluster with 1,024 nodes CPU: Intel Core2Duo 1.5GHz Memory: 2GB HDD: 4GB
Machine 2	PC with two processors CPU: Intel Xeon 3GHz Memory: 4GB HDD: 400GB
OS	Windows Vista and Linux OS (CentOS 4.5)
Compiler	Java 1.6.0_11

## Install

Download and expand

The source programs and executable binaries are available at

[http://sourceforge.jp/projects/parallelgwas/?\\_sl=1](http://sourceforge.jp/projects/parallelgwas/?_sl=1)

After \*.tar.gz is downloaded, run

```
%> gunzip *.tar.gz
```

```
%> tar xvf *.tar
```

Then this procedure will make the SNP directory that contains the files and directories shown in table 1.

Table 1. Files and directories of statistical software package for haplotype-based association study

Directory name	Contents
SNP	Statistical software package for haplotype-based association study
SNP/bin	Executable binaries of statistical software package for haplotype-based association study
SNP/HaplotypePhasing	The source programs of single processor version as well as MPI version of haplotype phasing (Misawa and Kamatani, unpublished)
SNP/SNP_MultiLocus	The source programs of single-processor version as well as the MPI version of the Markov-chain Monte Carlo (MCMC) algorithm to calculate asymptotically the probability of the type I error (4)
SNP/SNP_Exact	The source programs for single-processor version calculating the exact probability of the type I error (4)
SNP/SNP_RATParallel	The source programs for MPI version of permutation test based on RAT algorithm (5)
SNP/SNP_RAT	The source programs of single-processor version of permutation test based on RAT algorithm (5)
SNP/SNP_PrimitiveParallel	The source programs for MPI version of permutation test based on standard permutation algorithm
SNP/SNP_Primitive	The source programs of single-processor version of permutation test based on standard permutation algorithm

SNP/SNP_LIB	Library of functions
SNP/dSFMT	Source program of random-number generator of Mersenne twister algorithm (*)
SNP/tool	Script and tools of statistical software package for haplotype-based association study
SNP/Java	Java program sources of statistical software package for haplotype-based association study.
SNP/Jar	Java executable binary (jar files) of statistical software package for haplotype-based association study.

(\*) Copyright (c) 2006,2007 Mutsuo Saito, Makoto Matsumoto and Hiroshima University. All rights reserved. Copyright notice of the Mersenne twister algorithm is also included in the same directory

## How to install

To compile the non-parallel version of the programs

```
%> cd SNP
```

```
%> make -f Makefile.linux single
```

To compile the parallel version of the programs

```
%> cd SNP
```

```
%> make -f Makefile.linux parallel
```

To compile tools:

```
%> cd SNP
```

```
%> make -f Makefile.linux tools
```

To compile all programs:

```
%> cd SNP
```

```
%> make -f Makefile.linux all
```

To clean-up working directories:

```
%> cd SNP
```

```
%> make -f Makefile.linux clean
```

After compile, All of executable binaries will be in SNP/bin.

To compile the Java version of the programs, import allTest.jar into Eclipse. allTest.jar is in SNP/jar directory. The main function is in the class ThreeTests.



## Usage of programs in the packages

### Before imputation

MACH (Li and Abecasis 2008) must be installed. Paths for these programs must be appropriately set.

### How to run the MPI version of imputation on PC clusters

To run the parallel version for imputation on PC clusters, use `ImputationParallel.sh`

Usage:

```
%> ImputationParallel.sh $1 $2 $3 $4 $5 $6 $7 $8 $9
```

`ImputationParallel` is in `SNP/bin` directory. When the user runs `s` this script outside of the `SNP/bin`, the path must be set appropriately.

Command-line options are as follows

- \$1: Input file to be imputed (HapMap data format)
- \$2: Reference file (phased hapmap data format)
- \$3: Haplotype block file
- \$4: Recombination file  
If \$8 is 0, recombination will be read from the file.  
If \$8 is larger than 0, recombination rate will be estimated and be written to the file.
- \$5: Error rate file
- \$6: Output file
- \$7: Sample size per one division of pedigree.
- \$8: Sample size for estimating parameters  
(if 0 is set, parameters will not be estimated.)
- \$9: Number of processing units that run in parallel

## How to run the single version of imputation on PC clusters

To run the non-parallel version to for imputation on PC clusters or on PC, use `Imputation.sh`.

Usage:

```
%> Imputation.sh $1 $2 $3 $4 $5 $6 $7 $8
```

`Imputation.sh` is in `SNP/bin` directory. When the user runs this script outside of the `SNP/bin`, the path must be set appropriately.

Command-line options are as follows

- \$1: Input file to be imputed (HapMap data format)
- \$2: Reference file (phased hapmap data format)
- \$3: Haplotype block file
- \$4: Recombination file
  - If \$8 is 0, recombination will be read from the file.
  - If \$8 is larger than 0, recombination rate will be estimated and written to the file.
- \$5: Error rate file
- \$6: Output file
- \$7: Sample size per one division of pedigree.
- \$8: Sample size for estimating parameters
  - (if 0 is set, parameters will not be estimated.)

## Before using haplotype phasing

PHASE 2.1 (9) and SNPHAP 1.3.1 (9,10) must be installed. Paths for these programs must be appropriately set.

## How to run the MPI version of haplotype phasing on PC clusters

To run the parallel version to calculate the probability haplotype phasing on PC clusters, use `HaplotypePhasingParallel.sh`

Usage:

```
%> HaplotypePhasingParallel.sh $1 $2 $3 $4 $5 $6
```

`HaplotypePhasingParallel.sh` is in `SNP/bin` directory. When the user runs this script outside of the `SNP/bin`, the path must be set appropriately.

Command-line options are as follows

- \$1 : Input file (HapMap data format)
- \$2 : Haplotype block file
- \$3 : Output file
- \$4 : Option for phasing program
  - 0: Use SNPHAP 1.3
  - 1: Use PHASE 2.1
- \$5 : Upper bound of the number of SNPs
- \$6: Number of processing units that run in parallel

## How to run the single version of haplotype phasing

To run the non-parallel version to calculate the probability haplotype phasing on PC clusters or on PC, use `HaplotypePhasing.sh`

Usage:

```
%> HaplotypePhasing.sh $1 $2 $3 $4 $5
```

`HaplotypePhasing.sh` is in `SNP/bin` directory. When the user runs this script outside of the `SNP/bin`, the path must be set appropriately.

Command-line options are as follows

- \$1 : Input file (HapMap data format)
- \$2 : Haplotype block file
- \$3 : Output file
- \$4 : Option for phasing program
  - 0: Use SNPHAP 1.3
  - 1: Use PHASE 2.1
- \$5 : Upper bound of the number of SNPs

## Calculation of type I error rates by using MCMC method

To run the non-parallel version to calculate the probability of type I errors asymptotically by using MCMC method, there are three versions: (i) parallel version in C, (ii) non-parallel version in C, and (iii) non-parallel version in Java..

## How to run the MPI version in parallel on PC clusters in C

To run the non-parallel version to calculate the probability of type I errors asymptotically by using MCMC method, use `TypeIParallel.sh`.

Usage:

```
%> TypeIParallel.sh $1 $2 $3 $4 $5 $6 $7 $8 $9 $10
```

`TypeIParallel.sh` is in `SNP/bin` directory. When the user runs this script outside of the `SNP/bin`, the path must be set appropriately.

Command-line options are as follows

- \$1 : The first data file, as the case population
- \$2 : The second data file, as the control population
- \$3 : Output file
- \$4 : Haplotype block option
  - 0: Haplotype blocks defined by user
  - 1: Blocks with equal number of SNPs
- \$5 : Haplotype block file
- \$6 : Output score
  - 0: Pearson score
  - 1: Fst
- \$7: Number of repeats
- \$8 : Number of MCMC generations
- \$9 : Input data format
  - 0: HapMap data
  - 1: Haplotype data
  - 2: Phased HapMap data
- \$10 : Number of processing units that run in parallel

## How to run the non-parallel version in C

To run the non-parallel version to calculate the probability of type I errors asymptotically by using MCMC method, use `TypeI.sh`.

Usage:

```
%> TypeI.sh $1 $2 $3 $4 $5 $6 $7 $8 $9
```

`TypeI.sh` is located in `SNP/bin` directory. When the user runs this script outside of the `SNP/bin`, the path must be set appropriately.

### Command-line options

- \$1 : The first data file, as the case population
- \$2 : The second data file, as the control population
- \$3 : Output file
- \$4 : Haplotype block option
  - 0: Haplotype blocks defined by user
  - 1: Blocks with equal number of SNPs
- \$5 : Haplotype block file
- \$6 : Output score
  - 0: Pearson score
  - 1: Fst
- \$7: Number of repeats
- \$8 : Number of MCMC generations
- \$9 : Input data format
  - 0: HapMap data
  - 1: Haplotype data
  - 2: Phased HapMap data

## Exact Calculation of type I error rates

### How to run the version in C

To run the non-parallel version to calculate the exact probability of type I errors, use `Exact.sh`. `Exact.sh` is in `SNP/bin` directory.

Usage:

```
%> Exact.sh $1 $2 $3 $4 $5 $6 $7
```

`Exact.sh` is in `SNP/bin` When the user runs this script outside of the `SNP/bin`, the path must be set appropriately.

### Command-line options

- \$1 : The first data file, as the case population
- \$2 : The second data file, as the control population
- \$3 : Output file
- \$4 : Haplotype block option
  - 0: Haplotype blocks defined by user
  - 1: Blocks with equal number of SNPs
- \$5 : Haplotype block file
- \$6 : Output score
  - 0: Pearson score
  - 1: Fst
- \$7 : Input data format
  - 0: HapMap data
  - 1: Haplotype data
  - 2: Phased HapMap data

## Permutation test based on RAT algorithm (5)

### How to run the MPI version in parallel on PC clusters in C

To run the non-parallel version to calculate the P value by using the RAT algorithm, use RatParallel.sh. RatParallel.sh is in SNP/bin directory.

Usage:

```
%> RatParallel.sh $1 $2 $3 $4 $5 $6 $7 $8 $9 $10
```

RatParallel.sh is in SNP/bin directory. When the user runs this script outside of the SNP/bin, the path must be set appropriately.

### Command-line options

- \$1 : The first data file, as the case population
- \$2 : The second data file, as the control population
- \$3 : Output file
- \$4 : Haplotype block option
  - 0: Haplotype blocks defined by user
  - 1: Blocks with equal number of SNPs
- \$5 : Haplotype block file
- \$6 : Output score
  - 0: Pearson score
  - 1: Fst
- \$7 : Number of MCMC generations
- \$8 : Number of burnin generations
- \$9 : Input data format
  - 0: HapMap data
  - 1: Haplotype data
  - 2: Phased HapMap data
- \$10 : Number of processing units that run in parallel



## How to run the non-parallel version in C

To run the non-parallel version to calculate the P value by using the RAT algorithm, use Rat.sh.

Usage:

```
%> Rat.sh $1 $2 $3 $4 $5 $6 $7 $8 $9
```

Rat.sh is in SNP/bin directory. When the user runs this script outside of the SNP/bin, the path must be set appropriately.

### Command-line options

- \$1 : The first data file, as the case population
- \$2 : The second data file, as the control population
- \$3 : Output file
- \$4 : Haplotype block option
  - 0: Haplotype blocks defined by user
  - 1: Blocks with equal number of SNPs
- \$5 : Haplotype block file
- \$6 : Output score
  - 0: Pearson score
  - 1: Fst
- \$7 : Number of MCMC generations
- \$8: Number of burnin generations
- \$9 : Input data format
  - 0: HapMap data
  - 1: Haplotype data
  - 2: Phased HapMap data

## Standard Permutation test (SPT)

### How to run the MPI version in parallel on PC clusters in C

To run the non-parallel version to calculate the P value by standard permutation algorithm, use PrimitiveParallel.sh. PrimitiveParallel.sh is in SNP/bin directory.

Usage:

```
%> PrimitiveParallel.sh $1 $2 $3 $4 $5 $6 $7 $8 $9
```

PrimitiveParallel.sh is in SNP/bin directory. When the user runs this script outside of the SNP/bin, the path must be set appropriately.

### Command-line options

- \$1 : The first data file, as the case population
- \$2 : The second data file, as the control population
- \$3 : Output file
- \$4 : Haplotype block option
  - 0: Haplotype blocks defined by user
  - 1: Blocks with equal number of SNPs
- \$5 : Haplotype block file
- \$6 : Output score
  - 0: Pearson score
  - 1: Fst
- \$7: Number of repeats
- \$8 : Input data format
  - 0: HapMap data
  - 1: Haplotype data
  - 2: Phased HapMap data
- \$9 : Number of processing units that run in parallel

## How to run the non-parallel version in C

To run the non-parallel version to calculate the exact probability of type I errors, use `Primitive.sh`. `Primitive.sh` is in `SNP/bin` directory.

Usage:

```
%> Primitive.sh $1 $2 $3 $4 $5 $6 $7 $8
```

`Primitive.sh` is in `SNP/bin` directory. When the user runs this script outside of the `SNP/bin`, the path must be set appropriately.

### Command-line options

- \$1 : The first data file, as the case population
- \$2 : The second data file, as the control population
- \$3 : Output file
- \$4 : Haplotype block option
  - 0: Haplotype blocks defined by user
  - 1: Blocks with equal number of SNPs
- \$5 : Haplotype block file
- \$6 : Output score
  - 0: Pearson score
  - 1: Fst
- \$7 : Number of repeats
- \$8 : Input data format
  - 0: HapMap data
  - 1: Haplotype data
  - 2: Phased HapMap data

## Data formats of input and output files

ParaHaplo supports data format of the HapMap (8) and that of BioBank Japan (2). The example data are included in SNP/data.

### Data conversion from BioBank Japan format to HapMap format

To convert genotype file in format of BioBank Japan to HapMap format, use `illumina2hapmap.exe`.

Usage:

```
%> illumina2hapmap.exe $1 $2 $3
```

`illumina2hapmap.exe` is in `SNP/tools/illumina2hapmap` directory. When the user runs this script outside of this directory, the path must be set appropriately.

### Command-line options

- \$1: Data file in BioBank Japan style.
- \$2: Information file of SNPs
- \$3: Output data file in HapMap format

## Haplotype block file

In this program package, users can specify the haplotype-block file; Haplotype blocks defined by user or sliding window method.

## Haplotype blocks defined by user

When haplotype blocks defined by user are used, users must list the boundaries of haplotype blocks in the haplotype-block file. The last line must be empty. When this option is used, haplotype blocks are not overlapping. The following is an example of the haplotype-block file.

```
14000000
15000000
16000000
17000000

48000000
49000000
50000000
```

## Sliding window method

When sliding window method is used, users must write the window size and the step size in the haplotype-block file. The first line of the haplotype block file must be the window size, and the second line must be the step size. Both of the window size and the step size are measured by the number of SNPs. When the step size is smaller than the window size, each window is overlapping. When the step size is larger than the window size, SNPs between windows are ignored. If each SNP is need to be analyzed separately, Both of window size and step size must be set to 1. The third line must be empty. The following is an example of the haplotype-block file.

```
100
200
```

## Output file

The programs within the program package output the result of analyses in the similar format. The output files consist of two parts; the header part and the result part. The difference among the output files of different programs is in the header part.

### The header part

The first and second lines show the names of case and control data file. The first column shows the range of the haplotype block on the chromosomes. The second column shows the number of SNPs in the haplotype block. The third line shows the number of runs of the MCMC chains. The fourth line shows the number of generations of the MCMC chains. The fifth line is the headline. All lines after the headline are result lines.

### The result part

The result lines show the result of the analyses. The third column and the fourth column show the rs number and the position on the chromosome of the SNP that has the highest score, respectively. The fifth column shows the highest score. The sixth score shows the P value. When there is no polymorphic site in the haplotype block, the program outputs “NoData.”

The first column shows the range of the haplotype block on the chromosomes. The second column shows the number of SNPs in the haplotype block. The third column shows the rs number of the SNP that has highest score. The fourth and fifth columns show the position and the score of the SNP that has highest score, respectively. The sixth column shows the type I error.

```
CaseData      = /phased/JPT/chr22.txt
ControlData   = /phased/CHB/chr22.txt
Repeat        = 4
Generation    = 100000
BlockArea     SNPNum  rsNumber Position  Score          Type I error
14657412-14893245  100  rsxxxxx1  14870204  7.9158529679  0.0161200000
14976512-16148952  100  rsxxxxx2  15853229  10.0341711103 0.4292800000
16485214-17065485  100  rsxxxxx3  16643268  16.3205869262 0.0189700000
17165489-18221578  100  NoData
18345862-19147853  100  rsxxxxx5  18582729  28.5802577195 0.0000000000
19348562-19965482  100  rsxxxxx6  19660266  14.2802131465 0.0318300000
```

## Calculating the global P value

Usually the data files for case and control populations are separated into chromosomes. Thus, the users must calculate the global P value by gathering the results from all chromosomes. To calculate the global P value, use global.awk. global.awk is in SNP/Tools.

Usage:

```
%> gawk -f global.awk datafile1.txt datafile2.txt ... >all.txt
```

## Acknowledgment

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