Laboratory Note

Genetic Epistasis
VI - Assessing Algorithm SNPHarvester

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Abstract

In this lab note, the algorithm SNPHarvester was presented and tested. This algorithm consists of a stochastic approach that searches relevant SNPs for main effect and epistasis interactions, using a PathSeeker algorithm and revealing relevant results using χ^2 test. The results show that the Power and Type 1 Error Rate of the algorithm is high for main effect and full effect, but shows good results for epistasis detection, with very low error rates. The scalability test of the algorithm shows that this may be a problem for higher data sets.

1 Introduction

SNPHarvester [YHW+09] works as a stochastic algorithm, by generating multiple paths among the many SNPS and these are joined into groups. Significant groups are selected if their scores are above a statistical predetermined threshold. The score function used to measure the association between a k-SNP group, where k is the number of SNPS in epistatic interaction, and the phenotype is χ^2 test.
For this effect, a PathSeeker algorithm was developed to randomly start a new path and for each group tries to increase the score, changing only one SNP in active set at a time, converging to a local minimum, typically converging in two or three iterations. The evaluation is based on the χ^2 value and has a significance threshold of $\alpha = 0.05$ after Bonferroni corrections.
A post processing stage is applied to eliminate k-SNP groups that may be significant due to a sub-group and SNPs that may show a false strong association due to a small marginal effect. An L_2 penalized logistic regression is used to filter out these interactions.

$$L(\beta_0, \beta, \lambda) = -l(\beta_0, \beta) + \frac{\lambda}{2} \|\beta\| \tag{1}$$

where $l(\beta_0, \beta)$ is the binomial log-likelihood and λ is a regularization parameter.
The differences between SNPHarvester and the other algorithms is that SNP focuses on local optima instead of a global optima. Each local optima is significant because there are usually multiple interaction patterns. SNPHarvester also uses a sequential optimization rather than parallel optimization, removing local optima in the search process, becoming a smaller space in later stages. SNPHarvester also uses a model-free approach,randomly creating paths to directly detect significant associations.

1.1 Input files

The input of SNPHarvester consists of the names of each column in the first row, i.e. SNPs and the label phenotype as the last column. The next rows contain the genotypes 0,1,2 as homozygous dominant, heterozygous, and homozygous recessive, respectively. The Label 0,1 is control, case, respectively.

X1,X2,X3,X4,Label
1, 1, 0, 2, 0
1, 1, 2, 1, 1
1, 2, 2, 0, 1

Table 1: An example of the input file containing genotype and phenotype information with 4 SNPs and 3 individuals.

1.2 Output files

The algorithm outputs contain the final extracted single or interacting SNPs, with the χ^2 value of that specific interaction or single SNP, and the running time of the algorithm.

1.3 Parameters

There are two modes: "Threshold-Based" mode, where the program outputs all of the significant SNPs above a user specified significance threshold, and "Top-K Based" mode where the program outputs a specified number of SNP interactions, regardless of their significance level. Both modes have parameters to chose the minimum and maximum number of interacting SNPs to be detected. If the minimum is 1, it will test main effects of SNPs.

2 Experimental Settings

The datasets used in the experiments are characterized in Lab Note 1. The computer used for this experiments used the 64-bit Ubuntu 13.10 operating system, with an Intel(R) Core(TM)2 Quad CPU Q6600 2.40GHz processor and 8,00 GB of RAM memory.
SNPHarvester provides a Java program. The "Threshold-Based" mode was chosen for this analysis, with a significance level of $\alpha = 0.05$. The heap size is set to -Xmx7000M. Main effects and pairwise interactions are tested for this experiment.

3 Results

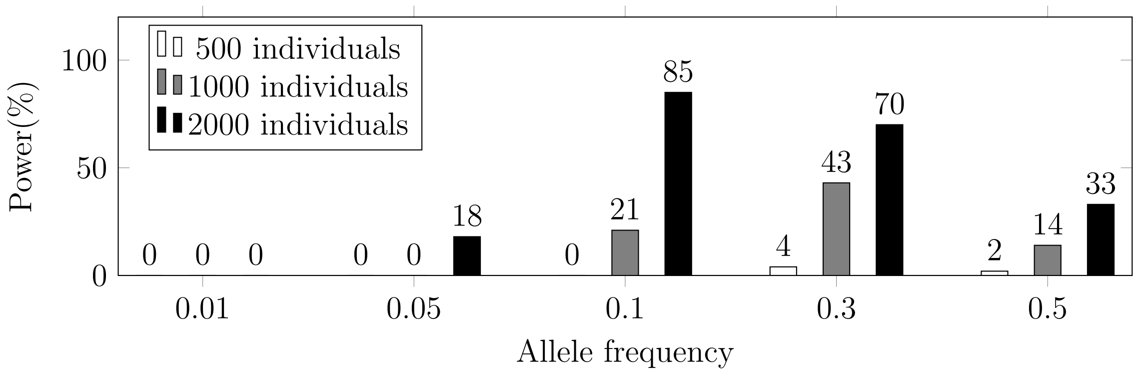
SNPHarvester works in epistasis detection, main effect detection, and full effect detection. All data set configurations were used in this experiment.
Figure 1 shows the Power obtained in relation to allele frequency and population size for epistasis (a), main effect (b) and epistasis + main effect (c). The

results show that the Power is higher in main effect detection than epistasis detection overall, reaching 100% Power in data sets with 0.3 and 0.5 allele frequency. Epistasis detection shows a much lower result, with 0.1 allele frequency and 2000 individuals having the best Power for epistasis detection, with 85%. However, significant results can be seen with allele frequency as low as 0.05%, which is not true for main effect detection. In full effect detection, the results are very similar to main effect detections.

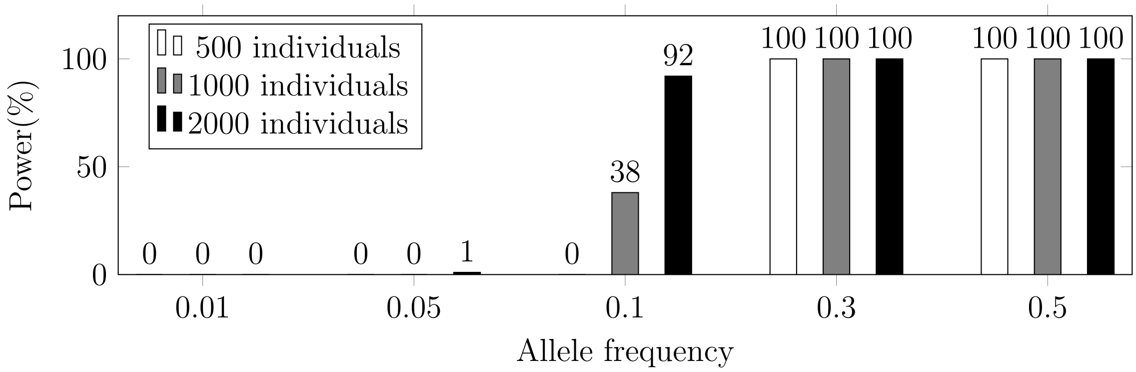
For scalability detection, Figure 2 shows a very significant difference in running time a from the data sets with 500 individuals running for an average of 9.29 seconds, and data sets with 2000 individuals, showing an average of 33 seconds. This somewhat linear growth, together with the slight increase in memory usage (c) reveal a scalability problem. The CPU usage is near 100% across all data set sizes.

Type 1 Error Rates show a concerning increase in main effect and full effect data sets, in relation to epistasis detection. This disproportion is due to the ease in main effect detection, which reveals highly valued ground truths, but also increases the chances of detecting false positives, even if their statistical significance is significantly lower than the ground truth. There is still a higher Power than Type 1 Error Rate in most cases, with the exception of high allele frequencies and high population, which reveal error rates of 100%. This is not true for epistasis detection, having a maximum of 27% error rate with data sets with 2000 individuals with an allele frequency of 0.05. The other configurations show a slight increase of error rate with the increase of data set population size. There is not clear Type 1 Error Rate difference between allele frequencies for epistasis detection.

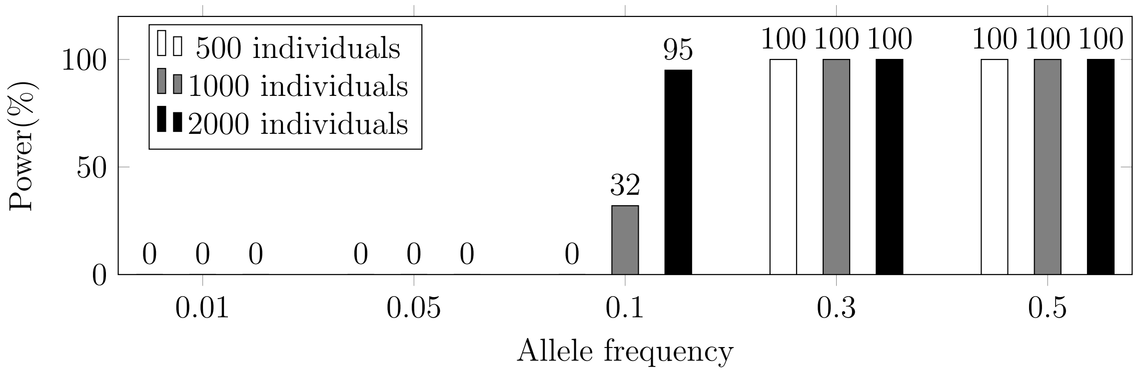
The relation of Power and population and allele frequency is reinforced in Figure 4 and 7. However, the Power by allele frequency in Epistasis detection shows a peak in 0.1 minor allele frequency and a descent for higher allele frequencies. Figure 6 shows a slight but not significant increase of Power with prevalence for epistasis detection and a slight decrease for main and full effect detection. The linear increase in Power shown in Figure 5 by odds ratios is similar to the distribution of Power by population.



(a) Epistasis

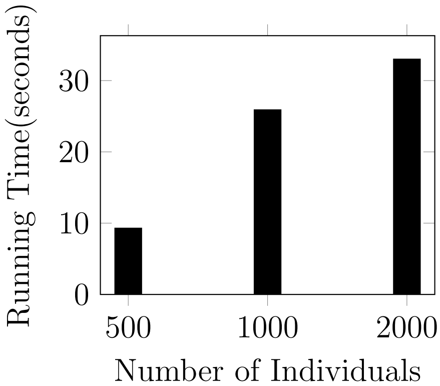


(b) Main Effect

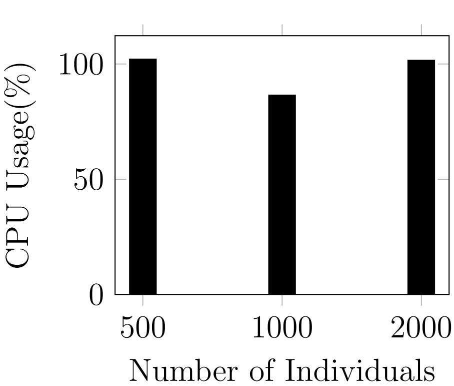


(c) Full Effect

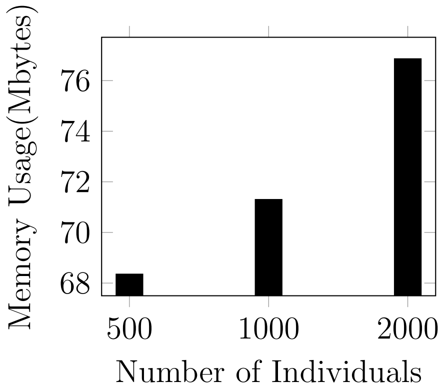
Figure 1: Power by allele frequency. For each frequency, three sizes of data sets were used to measure the Power, with odds ratio of 2.0 and prevalence of 0.02. The Power is measured by the amount of data sets where the ground truth was amongst the most relevant results, out of all 100 data sets. (b), (a), and (c) represent main effect, epistatic and main effect + epistatic interactions.



(a) Average Running time.

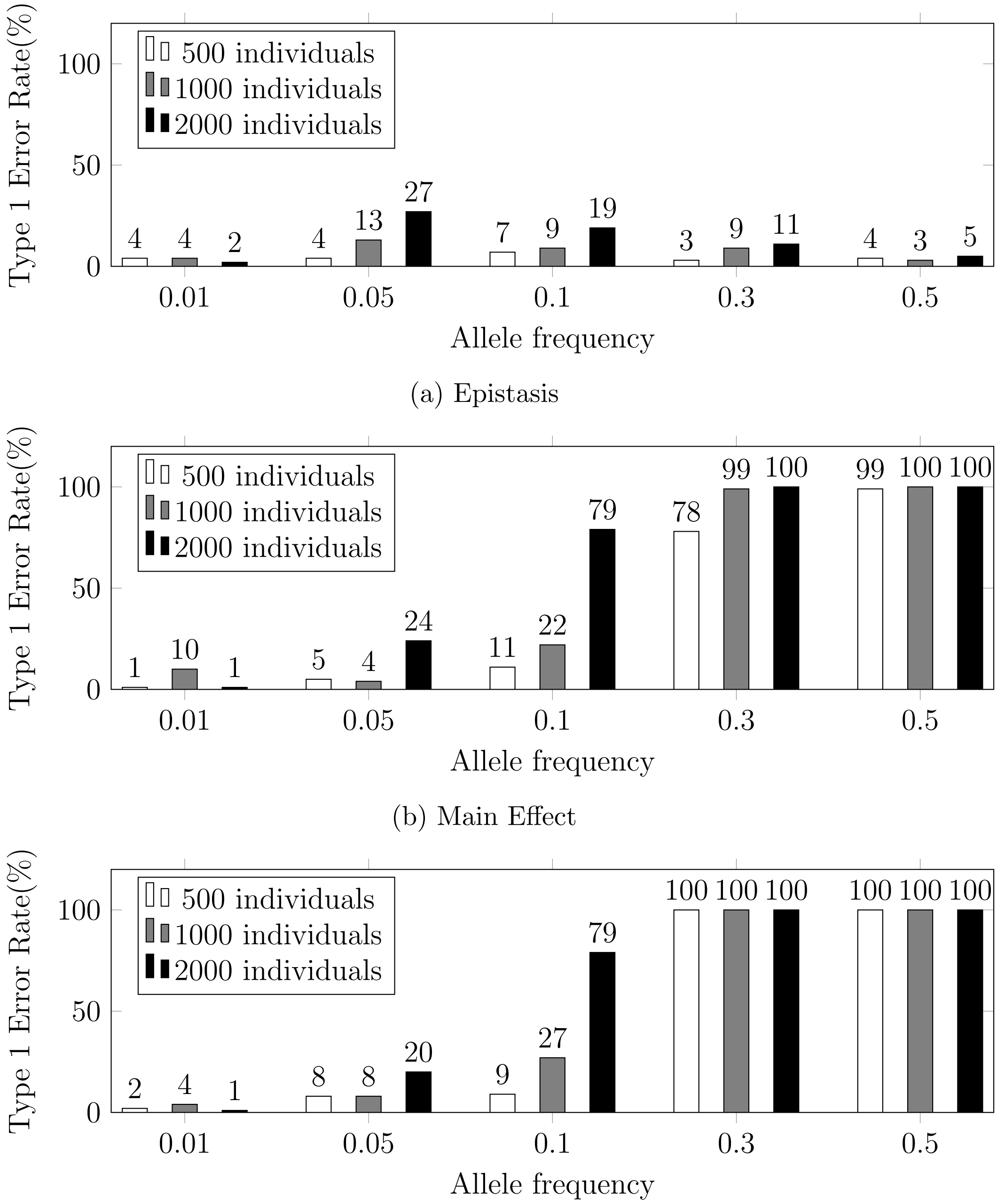


(b) Average CPU usage.



(c) Average Memory usage.

Figure 2: Comparison of scalability measures between different sized data sets. The data sets have a minor allele frequency is 0.5, 2.0 odds ratio, 0.02 prevalence and use the full effect disease model.



(a) Epistasis

(b) Main Effect

(c) Full Effect

Figure 3: Type 1 Error Rate by allele frequency. For each frequency, three sizes of data sets were used to measure the Power, with odds ratio of 2.0 and prevalence of 0.02. The Type 1 Error Rate is measured by the amount of data sets where the false positives were amongst the most relevant results, out of all 100 data sets. (a), (b), and (c) represent epistatic, main effect, and main effect + epistatic interactions.

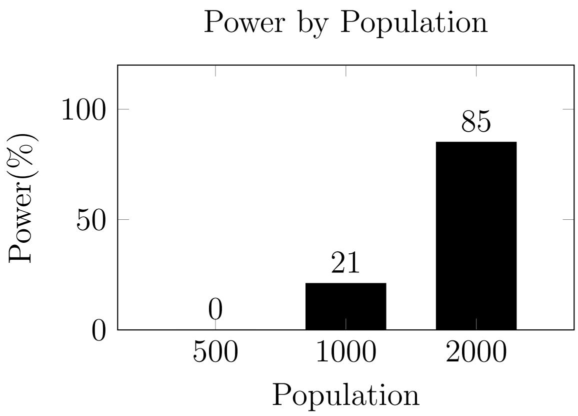
4 Summary

In this experiment, the SNPHarvester was tested using many data sets with significant configuration changes. The results show that the algorithm has a high Power in main effect and full effect detections, but also a high Type 1 Error Rate. For epistasis, the Power is lower but reveals very low Type 1 Error Rate values. There is a linear increase of Power with the number of individuals and odds ratios, and a significant increase with allele frequencies. The algorithm shows scalability problems, due to the high increase in running time, which may be crucial in genome wide studies.

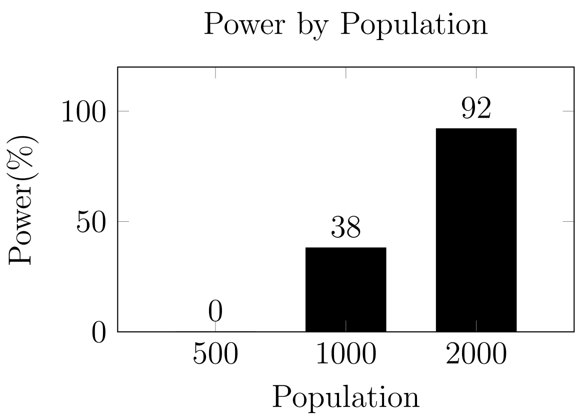
References

[YHW+09] Can Yang, Zengyou He, Xiang Wan, Qiang Yang, Hong Xue, and Weichuan Yu. SNPHarvester: a filtering-based approach for detecting epistatic interactions in genome-wide association studies. *Bioinformatics (Oxford, England)*, 25:504–511, 2009.

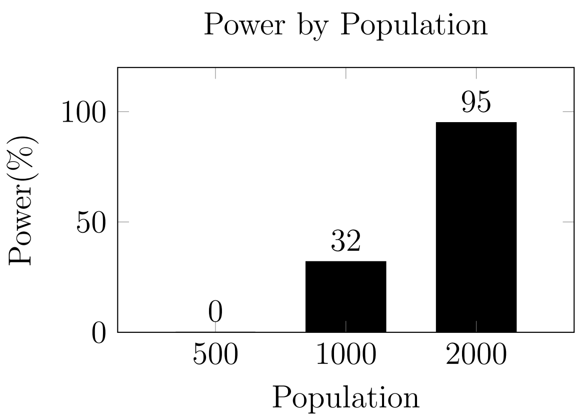
A Bar Graph



(a) Epistasis

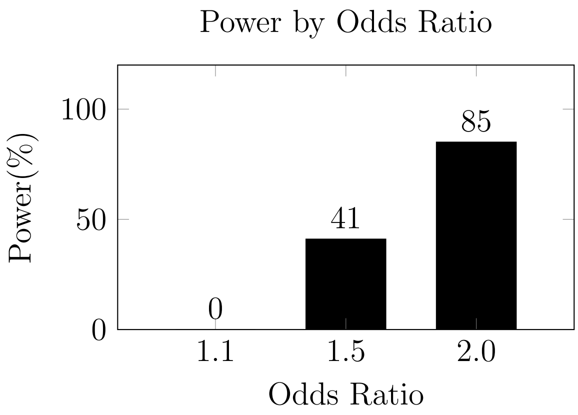


(b) Main Effect

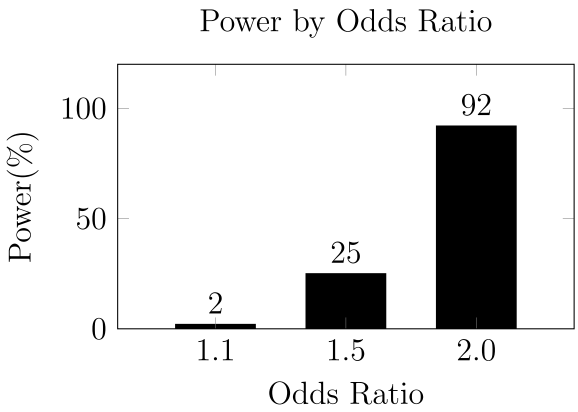


(c) Full Effect

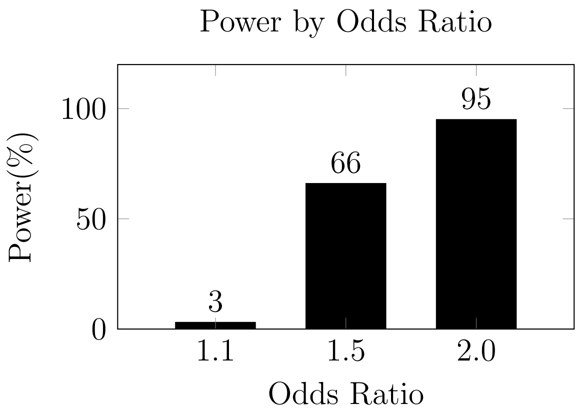
Figure 4: Distribution of the Power by population for all disease models. The allele frequency is 0.1, the odds ratio is 2.0, and the prevalence is 0.02.



(a) Epistasis

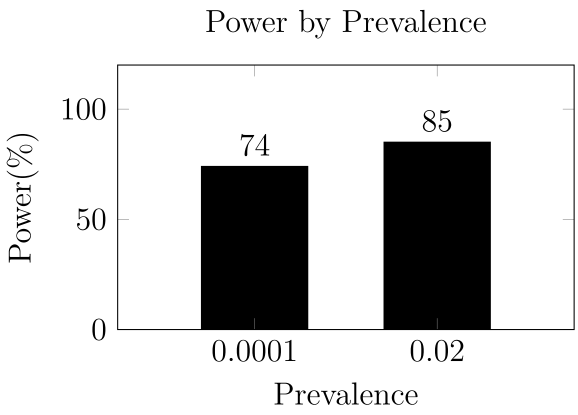


(b) Main Effect

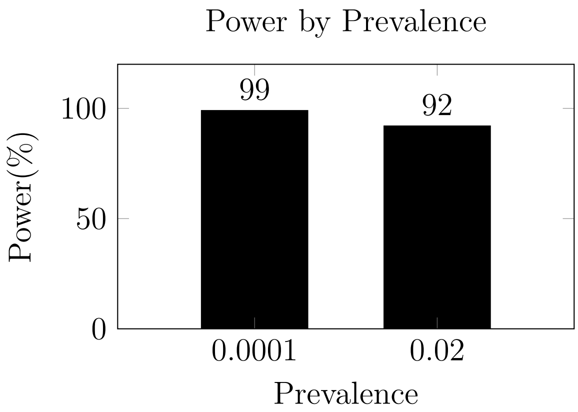


(c) Full Effect

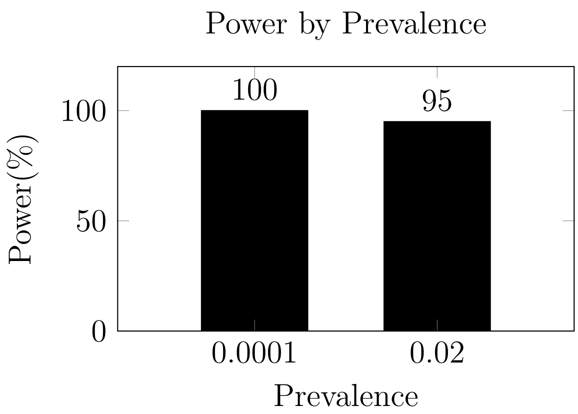
Figure 5: Distribution of the Power by odds ratios for all disease models. The allele frequency is 0.1, the population size is 2000 individuals, and the prevalence is 0.02.



(a) Epistasis

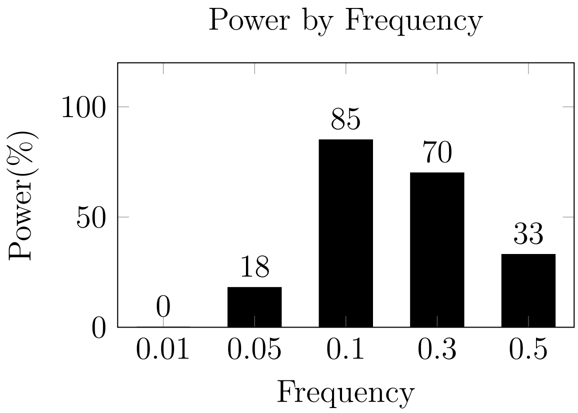


(b) Main Effect

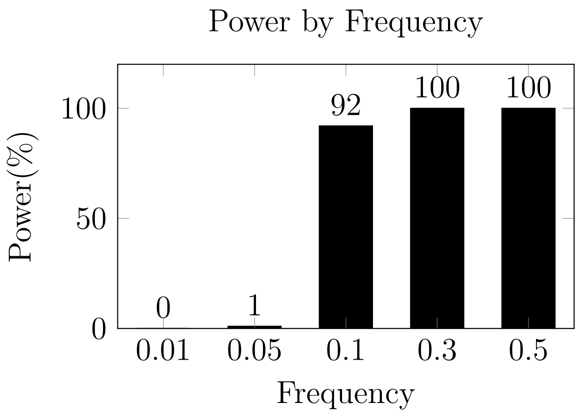


(c) Full Effect

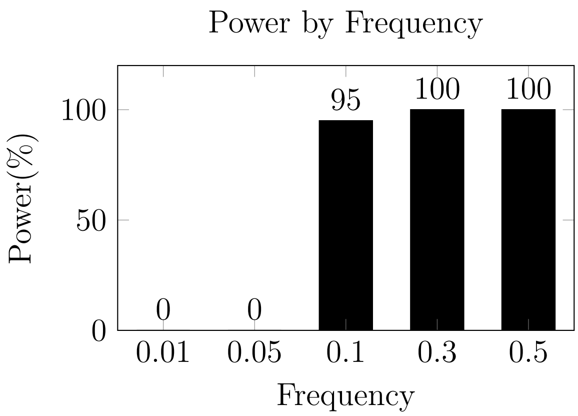
Figure 6: Distribution of the Power by prevalence for all disease models. The allele frequency is 0.1, the odds ratio is 2.0, and the population size is 2000 individuals.



(a) Epistasis



(b) Main Effect



(c) Full Effect

Figure 7: Distribution of the Power by allele frequency for all disease models. The population size is 2000 individuals, the odds ratio is 2.0, and the prevalence is 0.02.

B Table of Results

Table 2: A table containing the percentage of true positives and false positives in each configuration. The first column contains the description of the configuration. The second and third columns contain the number of datasets with true positives and false positives respectively, out of all 100 data sets per configuration.

Configuration*	TP (%)	FP (%)
0.01,500,ME+I,2.0,0.02	0	2
0.01,500,ME+I,2.0,0.0001	0	5
0.01,500,ME+I,1.5,0.02	0	7
0.01,500,ME+I,1.5,0.0001	0	5
0.01,500,ME+I,1.1,0.02	0	1
0.01,500,ME+I,1.1,0.0001	0	6
0.01,500,ME,2.0,0.02	0	1
0.01,500,ME,2.0,0.0001	0	6
0.01,500,ME,1.5,0.02	0	1
0.01,500,ME,1.5,0.0001	0	6
0.01,500,ME,1.1,0.02	0	1
0.01,500,ME,1.1,0.0001	0	6
0.01,500,I,2.0,0.02	0	4
0.01,500,I,2.0,0.0001	0	5
0.01,500,I,1.5,0.02	0	5
0.01,500,I,1.5,0.0001	0	10
0.01,500,I,1.1,0.02	0	3
0.01,500,I,1.1,0.0001	0	6
0.01,2000,ME+I,2.0,0.02	0	1
0.01,2000,ME+I,2.0,0.0001	0	3
0.01,2000,ME+I,1.5,0.02	0	6
0.01,2000,ME+I,1.5,0.0001	0	4
0.01,2000,ME+I,1.1,0.02	0	6
0.01,2000,ME+I,1.1,0.0001	0	6
0.01,2000,ME,2.0,0.02	0	1
0.01,2000,ME,2.0,0.0001	0	3
0.01,2000,ME,1.5,0.02	0	6
0.01,2000,ME,1.5,0.0001	0	4
0.01,2000,ME,1.1,0.02	0	6
0.01,2000,ME,1.1,0.0001	0	4
0.01,2000,I,2.0,0.02	0	2

0.01,2000,I,2.0,0.0001	0	9
0.01,2000,I,1.5,0.02	0	8
0.01,2000,I,1.5,0.0001	0	12
0.01,2000,I,1.1,0.02	0	7
0.01,2000,I,1.1,0.0001	0	6
0.01,1000,ME+I,2.0,0.02	0	4
0.01,1000,ME+I,2.0,0.0001	0	3
0.01,1000,ME+I,1.5,0.02	0	10
0.01,1000,ME+I,1.5,0.0001	0	5
0.01,1000,ME+I,1.1,0.02	0	3
0.01,1000,ME+I,1.1,0.0001	0	5
0.01,1000,ME,2.0,0.02	0	10
0.01,1000,ME,2.0,0.0001	0	5
0.01,1000,ME,1.5,0.02	0	11
0.01,1000,ME,1.5,0.0001	0	5
0.01,1000,ME,1.1,0.02	0	3
0.01,1000,ME,1.1,0.0001	0	5
0.01,1000,I,2.0,0.02	0	4
0.01,1000,I,2.0,0.0001	0	4
0.01,1000,I,1.5,0.02	0	4
0.01,1000,I,1.5,0.0001	0	5
0.01,1000,I,1.1,0.02	0	6
0.01,1000,I,1.1,0.0001	0	5
0.05,500,ME+I,2.0,0.02	0	8
0.05,500,ME+I,2.0,0.0001	0	8
0.05,500,ME+I,1.5,0.02	0	4
0.05,500,ME+I,1.5,0.0001	0	5
0.05,500,ME+I,1.1,0.02	0	3
0.05,500,ME+I,1.1,0.0001	0	7
0.05,500,ME,2.0,0.02	0	5
0.05,500,ME,2.0,0.0001	0	7
0.05,500,ME,1.5,0.02	0	5
0.05,500,ME,1.5,0.0001	0	6
0.05,500,ME,1.1,0.02	0	7
0.05,500,ME,1.1,0.0001	0	4
0.05,500,I,2.0,0.02	0	4
0.05,500,I,2.0,0.0001	0	6
0.05,500,I,1.5,0.02	0	5

0.05,500,I,1.5,0.0001	0	11
0.05,500,I,1.1,0.02	0	5
0.05,500,I,1.1,0.0001	0	3
0.05,2000,ME+I,2.0,0.02	0	20
0.05,2000,ME+I,2.0,0.0001	26	42
0.05,2000,ME+I,1.5,0.02	0	13
0.05,2000,ME+I,1.5,0.0001	1	16
0.05,2000,ME+I,1.1,0.02	0	4
0.05,2000,ME+I,1.1,0.0001	0	9
0.05,2000,ME,2.0,0.02	1	24
0.05,2000,ME,2.0,0.0001	9	30
0.05,2000,ME,1.5,0.02	0	5
0.05,2000,ME,1.5,0.0001	0	15
0.05,2000,ME,1.1,0.02	0	6
0.05,2000,ME,1.1,0.0001	0	8
0.05,2000,I,2.0,0.02	18	27
0.05,2000,I,2.0,0.0001	45	5
0.05,2000,I,1.5,0.02	39	9
0.05,2000,I,1.5,0.0001	40	9
0.05,2000,I,1.1,0.02	0	5
0.05,2000,I,1.1,0.0001	0	6
0.05,1000,ME+I,2.0,0.02	0	8
0.05,1000,ME+I,2.0,0.0001	0	21
0.05,1000,ME+I,1.5,0.02	0	1
0.05,1000,ME+I,1.5,0.0001	0	7
0.05,1000,ME+I,1.1,0.02	0	4
0.05,1000,ME+I,1.1,0.0001	0	5
0.05,1000,ME,2.0,0.02	0	4
0.05,1000,ME,2.0,0.0001	1	26
0.05,1000,ME,1.5,0.02	0	2
0.05,1000,ME,1.5,0.0001	0	6
0.05,1000,ME,1.1,0.02	0	7
0.05,1000,ME,1.1,0.0001	0	4
0.05,1000,I,2.0,0.02	0	13
0.05,1000,I,2.0,0.0001	2	5
0.05,1000,I,1.5,0.02	0	4
0.05,1000,I,1.5,0.0001	1	4
0.05,1000,I,1.1,0.02	0	3

0.05,1000,I,1.1,0.0001	0	11
0.1,500,ME+I,2.0,0.02	0	9
0.1,500,ME+I,2.0,0.0001	41	38
0.1,500,ME+I,1.5,0.02	0	4
0.1,500,ME+I,1.5,0.0001	1	9
0.1,500,ME+I,1.1,0.02	0	3
0.1,500,ME+I,1.1,0.0001	1	4
0.1,500,ME,2.0,0.02	0	11
0.1,500,ME,2.0,0.0001	13	20
0.1,500,ME,1.5,0.02	0	7
0.1,500,ME,1.5,0.0001	0	7
0.1,500,ME,1.1,0.02	0	6
0.1,500,ME,1.1,0.0001	0	6
0.1,500,I,2.0,0.02	0	7
0.1,500,I,2.0,0.0001	1	3
0.1,500,I,1.5,0.02	0	5
0.1,500,I,1.5,0.0001	0	1
0.1,500,I,1.1,0.02	0	5
0.1,500,I,1.1,0.0001	0	7
0.1,2000,ME+I,2.0,0.02	95	79
0.1,2000,ME+I,2.0,0.0001	100	99
0.1,2000,ME+I,1.5,0.02	66	40
0.1,2000,ME+I,1.5,0.0001	61	48
0.1,2000,ME+I,1.1,0.02	3	8
0.1,2000,ME+I,1.1,0.0001	3	17
0.1,2000,ME,2.0,0.02	92	79
0.1,2000,ME,2.0,0.0001	99	88
0.1,2000,ME,1.5,0.02	25	20
0.1,2000,ME,1.5,0.0001	48	41
0.1,2000,ME,1.1,0.02	2	11
0.1,2000,ME,1.1,0.0001	1	7
0.1,2000,I,2.0,0.02	85	19
0.1,2000,I,2.0,0.0001	74	11
0.1,2000,I,1.5,0.02	41	9
0.1,2000,I,1.5,0.0001	23	6
0.1,2000,I,1.1,0.02	0	7
0.1,2000,I,1.1,0.0001	2	9
0.1,1000,ME+I,2.0,0.02	32	27

0.1,1000,ME+I,2.0,0.0001	97	74
0.1,1000,ME+I,1.5,0.02	1	11
0.1,1000,ME+I,1.5,0.0001	13	12
0.1,1000,ME+I,1.1,0.02	0	7
0.1,1000,ME+I,1.1,0.0001	0	8
0.1,1000,ME,2.0,0.02	38	22
0.1,1000,ME,2.0,0.0001	59	43
0.1,1000,ME,1.5,0.02	2	9
0.1,1000,ME,1.5,0.0001	6	12
0.1,1000,ME,1.1,0.02	0	7
0.1,1000,ME,1.1,0.0001	0	12
0.1,1000,I,2.0,0.02	21	9
0.1,1000,I,2.0,0.0001	9	9
0.1,1000,I,1.5,0.02	1	2
0.1,1000,I,1.5,0.0001	1	4
0.1,1000,I,1.1,0.02	0	6
0.1,1000,I,1.1,0.0001	0	12
0.3,500,ME+I,2.0,0.02	100	100
0.3,500,ME+I,2.0,0.0001	100	100
0.3,500,ME+I,1.5,0.02	100	75
0.3,500,ME+I,1.5,0.0001	100	96
0.3,500,ME+I,1.1,0.02	77	21
0.3,500,ME+I,1.1,0.0001	93	28
0.3,500,ME,2.0,0.02	100	78
0.3,500,ME,2.0,0.0001	100	89
0.3,500,ME,1.5,0.02	89	27
0.3,500,ME,1.5,0.0001	89	37
0.3,500,ME,1.1,0.02	25	13
0.3,500,ME,1.1,0.0001	25	9
0.3,500,I,2.0,0.02	4	3
0.3,500,I,2.0,0.0001	20	8
0.3,500,I,1.5,0.02	1	3
0.3,500,I,1.5,0.0001	3	6
0.3,500,I,1.1,0.02	0	3
0.3,500,I,1.1,0.0001	0	6
0.3,2000,ME+I,2.0,0.02	100	100
0.3,2000,ME+I,2.0,0.0001	100	100
0.3,2000,ME+I,1.5,0.02	100	100

0.3,2000,ME+I,1.5,0.0001	100	100
0.3,2000,ME+I,1.1,0.02	100	99
0.3,2000,ME+I,1.1,0.0001	100	100
0.3,2000,ME,2.0,0.02	100	100
0.3,2000,ME,2.0,0.0001	100	100
0.3,2000,ME,1.5,0.02	100	100
0.3,2000,ME,1.5,0.0001	100	100
0.3,2000,ME,1.1,0.02	100	67
0.3,2000,ME,1.1,0.0001	100	62
0.3,2000,I,2.0,0.02	70	11
0.3,2000,I,2.0,0.0001	73	20
0.3,2000,I,1.5,0.02	58	8
0.3,2000,I,1.5,0.0001	53	7
0.3,2000,I,1.1,0.02	1	5
0.3,2000,I,1.1,0.0001	1	8
0.3,1000,ME+I,2.0,0.02	100	100
0.3,1000,ME+I,2.0,0.0001	100	100
0.3,1000,ME+I,1.5,0.02	100	99
0.3,1000,ME+I,1.5,0.0001	100	100
0.3,1000,ME+I,1.1,0.02	100	66
0.3,1000,ME+I,1.1,0.0001	100	69
0.3,1000,ME,2.0,0.02	100	99
0.3,1000,ME,2.0,0.0001	100	100
0.3,1000,ME,1.5,0.02	100	78
0.3,1000,ME,1.5,0.0001	100	75
0.3,1000,ME,1.1,0.02	93	30
0.3,1000,ME,1.1,0.0001	84	33
0.3,1000,I,2.0,0.02	43	9
0.3,1000,I,2.0,0.0001	79	9
0.3,1000,I,1.5,0.02	30	3
0.3,1000,I,1.5,0.0001	27	9
0.3,1000,I,1.1,0.02	0	4
0.3,1000,I,1.1,0.0001	0	5
0.5,500,ME+I,2.0,0.02	100	100
0.5,500,ME+I,2.0,0.0001	100	100
0.5,500,ME+I,1.5,0.02	100	100
0.5,500,ME+I,1.5,0.0001	100	100
0.5,500,ME+I,1.1,0.02	100	79

0.5,500,ME+I,1.1,0.0001	100	89
0.5,500,ME,2.0,0.02	100	99
0.5,500,ME,2.0,0.0001	100	97
0.5,500,ME,1.5,0.02	100	63
0.5,500,ME,1.5,0.0001	100	62
0.5,500,ME,1.1,0.02	80	27
0.5,500,ME,1.1,0.0001	79	28
0.5,500,I,2.0,0.02	2	4
0.5,500,I,2.0,0.0001	4	5
0.5,500,I,1.5,0.02	1	4
0.5,500,I,1.5,0.0001	0	7
0.5,500,I,1.1,0.02	0	1
0.5,500,I,1.1,0.0001	0	8
0.5,2000,ME+I,2.0,0.02	100	100
0.5,2000,ME+I,2.0,0.0001	99	99
0.5,2000,ME+I,1.5,0.02	100	100
0.5,2000,ME+I,1.5,0.0001	100	100
0.5,2000,ME+I,1.1,0.02	100	100
0.5,2000,ME+I,1.1,0.0001	100	100
0.5,2000,ME,2.0,0.02	100	100
0.5,2000,ME,2.0,0.0001	100	100
0.5,2000,ME,1.5,0.02	100	100
0.5,2000,ME,1.5,0.0001	100	100
0.5,2000,ME,1.1,0.02	100	100
0.5,2000,ME,1.1,0.0001	100	98
0.5,2000,I,2.0,0.02	33	5
0.5,2000,I,2.0,0.0001	78	9
0.5,2000,I,1.5,0.02	65	2
0.5,2000,I,1.5,0.0001	21	2
0.5,2000,I,1.1,0.02	7	8
0.5,2000,I,1.1,0.0001	2	7
0.5,1000,ME+I,2.0,0.02	100	100
0.5,1000,ME+I,2.0,0.0001	100	100
0.5,1000,ME+I,1.5,0.02	100	100
0.5,1000,ME+I,1.5,0.0001	100	100
0.5,1000,ME+I,1.1,0.02	100	100
0.5,1000,ME+I,1.1,0.0001	100	100
0.5,1000,ME,2.0,0.02	100	100

0.5,1000,ME,2.0,0.0001	100	100
0.5,1000,ME,1.5,0.02	100	100
0.5,1000,ME,1.5,0.0001	100	97
0.5,1000,ME,1.1,0.02	100	64
0.5,1000,ME,1.1,0.0001	100	69
0.5,1000,I,2.0,0.02	14	3
0.5,1000,I,2.0,0.0001	52	6
0.5,1000,I,1.5,0.02	28	5
0.5,1000,I,1.5,0.0001	1	5
0.5,1000,I,1.1,0.02	0	3
0.5,1000,I,1.1,0.0001	0	9

*MAF,POP,MOD,OR,PREV where MAF represents the minor allele frequency, POP is the number of individuals, MOD is the used model (with or without main effect and with or without epistasis effect), OR is the odds ratio and PREV is the prevalence of the disease.

Table 3: A table containing the running time, cpu usage and memory usage in each configuration.

Configuration*	Running Time (s)	CPU Usage (%)	Memory Usage (KB)
0.5,500,ME+I,2.0,0.02	0	75.44	8975.12
0.5,500,ME+I,2.0,0.0001	0	76.83	8975.00
0.5,500,ME+I,1.5,0.02	0.07	73.91	9593.72
0.5,500,ME+I,1.5,0.0001	0	74.17	8975.28
0.5,500,ME+I,1.1,0.02	0	78.78	8975.20
0.5,500,ME+I,1.1,0.0001	0	76.66	8974.80
0.5,500,ME,2.0,0.02	0	77.81	8974.84
0.5,500,ME,2.0,0.0001	0	77.69	8975.60
0.5,500,ME,1.5,0.02	0	78.18	8975.36
0.5,500,ME,1.5,0.0001	0	76.23	8975.16
0.5,500,ME,1.1,0.02	0	80.54	8975.24
0.5,500,ME,1.1,0.0001	0	78.98	8975.04
0.5,500,I,2.0,0.02	0	76.74	8975.16
0.5,500,I,2.0,0.0001	0	75.78	8974.76
0.5,500,I,1.5,0.02	0	77.19	8975.40
0.5,500,I,1.5,0.0001	0	78.27	8974.64
0.5,500,I,1.1,0.02	0	78.71	8975.20
0.5,500,I,1.1,0.0001	0	78.75	8975.00

0.5,2000,ME+I,2.0,0.02	1.03	84.06	11814.04
0.5,2000,ME+I,2.0,0.0001	35.91	100.13	76053.20
0.5,2000,ME+I,1.5,0.02	45.54	99.68	77689.64
0.5,2000,ME+I,1.5,0.0001	47.30	99.04	78211.72
0.5,2000,ME+I,1.1,0.02	53.11	99.33	78391.92
0.5,2000,ME+I,1.1,0.0001	51.93	98.62	79691.56
0.5,2000,ME,2.0,0.02	54.63	100.05	77422.96
0.5,2000,ME,2.0,0.0001	54.31	99.80	79153.36
0.5,2000,ME,1.5,0.02	44.44	101.10	76040.16
0.5,2000,ME,1.5,0.0001	39.89	101.33	75383.84
0.5,2000,ME,1.1,0.02	20.10	100.50	72422.88
0.5,2000,ME,1.1,0.0001	18.37	101.77	72461.68
0.5,2000,I,2.0,0.02	13.30	101.99	71876.44
0.5,2000,I,2.0,0.0001	14.32	101.73	70963.00
0.5,2000,I,1.5,0.02	14.52	102.26	70528.40
0.5,2000,I,1.5,0.0001	12.63	102.34	71372.92
0.5,2000,I,1.1,0.02	12.16	102.54	73187.88
0.5,2000,I,1.1,0.0001	11.82	101.52	71635.04
0.5,1000,ME+I,2.0,0.02	25.89	86.51	73035.92
0.5,1000,ME+I,2.0,0.0001	26.33	89.30	73462.04
0.5,1000,ME+I,1.5,0.02	26.16	98.22	73189.12
0.5,1000,ME+I,1.5,0.0001	25.22	100.91	73075.68
0.5,1000,ME+I,1.1,0.02	14.21	103.72	71475.92
0.5,1000,ME+I,1.1,0.0001	12.89	104.18	71463.92
0.5,1000,ME,2.0,0.02	19.63	102.59	72507.32
0.5,1000,ME,2.0,0.0001	17.44	103.13	72036.12
0.5,1000,ME,1.5,0.02	10.19	105.15	70972.68
0.5,1000,ME,1.5,0.0001	9.25	105.96	70377.84
0.5,1000,ME,1.1,0.02	6.62	107.41	69163.76
0.5,1000,ME,1.1,0.0001	6.88	109.39	69143.72
0.5,1000,I,2.0,0.02	6.60	108.50	69107.64
0.5,1000,I,2.0,0.0001	7.38	108.82	68815.08
0.5,1000,I,1.5,0.02	7.03	100.62	68200.44
0.5,1000,I,1.5,0.0001	6.38	101.91	67529.52
0.5,1000,I,1.1,0.02	6.47	102.15	68962.80
0.5,1000,I,1.1,0.0001	6.54	102.20	68464.08
0.3,500,ME+I,2.0,0.02	6.26	104.90	68340.96
0.3,500,ME+I,2.0,0.0001	12.21	102.21	70501.56

0.3,500,ME+I,1.5,0.02	4.13	106.37	66912.32
0.3,500,ME+I,1.5,0.0001	5.38	105.98	68096.64
0.3,500,ME+I,1.1,0.02	3.74	105.94	65277.00
0.3,500,ME+I,1.1,0.0001	3.82	105.86	65443.96
0.3,500,ME,2.0,0.02	4.08	106.11	65608.68
0.3,500,ME,2.0,0.0001	4.43	106.19	67463.80
0.3,500,ME,1.5,0.02	3.73	106.90	65098.52
0.3,500,ME,1.5,0.0001	3.80	109.81	65059.36
0.3,500,ME,1.1,0.02	3.67	109.74	64770.44
0.3,500,ME,1.1,0.0001	3.73	105.00	65267.44
0.3,500,I,2.0,0.02	3.79	102.17	65143.80
0.3,500,I,2.0,0.0001	3.90	105.07	65876.56
0.3,500,I,1.5,0.02	3.68	105.09	65198.44
0.3,500,I,1.5,0.0001	3.70	100.02	65044.64
0.3,500,I,1.1,0.02	3.67	105.56	64918.80
0.3,500,I,1.1,0.0001	3.75	103.87	65366.36
0.3,2000,ME+I,2.0,0.02	52.54	97.45	78867.88
0.3,2000,ME+I,2.0,0.0001	33.90	101.81	75939.52
0.3,2000,ME+I,1.5,0.02	50.68	100.31	76332.04
0.3,2000,ME+I,1.5,0.0001	54.60	101.14	75759.68
0.3,2000,ME+I,1.1,0.02	18.08	104.45	71770.00
0.3,2000,ME+I,1.1,0.0001	22.20	103.66	72230.52
0.3,2000,ME,2.0,0.02	47.70	101.73	76081.80
0.3,2000,ME,2.0,0.0001	51.00	98.52	77481.44
0.3,2000,ME,1.5,0.02	23.96	98.85	73314.16
0.3,2000,ME,1.5,0.0001	23.65	99.04	72820.92
0.3,2000,ME,1.1,0.02	13.11	96.47	71377.16
0.3,2000,ME,1.1,0.0001	12.94	100.18	72271.40
0.3,2000,I,2.0,0.02	14.49	99.58	70987.12
0.3,2000,I,2.0,0.0001	13.89	100.05	70761.04
0.3,2000,I,1.5,0.02	14.63	102.00	71405.12
0.3,2000,I,1.5,0.0001	14.30	99.79	71175.52
0.3,2000,I,1.1,0.02	11.88	100.25	72587.36
0.3,2000,I,1.1,0.0001	12.30	100.42	72231.52
0.3,1000,ME+I,2.0,0.02	24.07	99.29	72695.04
0.3,1000,ME+I,2.0,0.0001	25.39	99.83	72831.76
0.3,1000,ME+I,1.5,0.02	18.57	98.83	71546.72
0.3,1000,ME+I,1.5,0.0001	24.64	98.82	72522.36

0.3,1000,ME+I,1.1,0.02	11.58	98.75	71113.48
0.3,1000,ME+I,1.1,0.0001	11.98	98.73	71254.12
0.3,1000,ME,2.0,0.02	16.77	98.95	71090.84
0.3,1000,ME,2.0,0.0001	19.44	98.35	71731.32
0.3,1000,ME,1.5,0.02	12.06	98.94	71088.80
0.3,1000,ME,1.5,0.0001	12.44	98.89	70971.28
0.3,1000,ME,1.1,0.02	11.00	98.78	71013.08
0.3,1000,ME,1.1,0.0001	11.27	98.53	70955.92
0.3,1000,I,2.0,0.02	12.35	98.54	71127.96
0.3,1000,I,2.0,0.0001	13.31	98.89	70009.72
0.3,1000,I,1.5,0.02	12.28	98.94	71714.48
0.3,1000,I,1.5,0.0001	12.17	98.91	71538.40
0.3,1000,I,1.1,0.02	11.20	98.96	71779.92
0.3,1000,I,1.1,0.0001	11.12	98.62	71854.36
0.1,500,ME+I,2.0,0.02	6.07	99.82	70315.16
0.1,500,ME+I,2.0,0.0001	6.13	99.08	69049.48
0.1,500,ME+I,1.5,0.02	6.06	99.41	70168.84
0.1,500,ME+I,1.5,0.0001	6.12	98.96	69809.04
0.1,500,ME+I,1.1,0.02	6.13	99.57	70186.84
0.1,500,ME+I,1.1,0.0001	6.14	99.51	70018.72
0.1,500,ME,2.0,0.02	6.12	99.33	70033.16
0.1,500,ME,2.0,0.0001	6.15	99.98	69367.68
0.1,500,ME,1.5,0.02	6.16	99.87	70112.36
0.1,500,ME,1.5,0.0001	6.16	99.11	70216.16
0.1,500,ME,1.1,0.02	6.12	99.47	70135.28
0.1,500,ME,1.1,0.0001	6.13	99.55	70127.36
0.1,500,I,2.0,0.02	6.11	99.21	70007.60
0.1,500,I,2.0,0.0001	6.11	98.95	70187.96
0.1,500,I,1.5,0.02	6.16	98.99	70377.76
0.1,500,I,1.5,0.0001	6.08	99.29	70226.68
0.1,500,I,1.1,0.02	6.11	98.84	70228.80
0.1,500,I,1.1,0.0001	6.15	99.60	70123.92
0.1,2000,ME+I,2.0,0.02	24.39	98.80	72612.80
0.1,2000,ME+I,2.0,0.0001	35.63	98.93	74894.12
0.1,2000,ME+I,1.5,0.02	21.49	98.70	72437.88
0.1,2000,ME+I,1.5,0.0001	22.66	98.90	72547.36
0.1,2000,ME+I,1.1,0.02	20.98	98.79	73179.28
0.1,2000,ME+I,1.1,0.0001	21.20	98.72	73060.00

0.1,2000,ME,2.0,0.02	23.49	98.81	72854.64
0.1,2000,ME,2.0,0.0001	27.55	98.84	73112.76
0.1,2000,ME,1.5,0.02	20.96	98.65	72501.96
0.1,2000,ME,1.5,0.0001	22.40	98.84	72125.24
0.1,2000,ME,1.1,0.02	20.94	98.07	73506.48
0.1,2000,ME,1.1,0.0001	21.46	99.20	73131.60
0.1,2000,I,2.0,0.02	24.99	98.67	71017.84
0.1,2000,I,2.0,0.0001	25.33	98.95	71315.96
0.1,2000,I,1.5,0.02	24.72	99.68	72858.24
0.1,2000,I,1.5,0.0001	23.07	99.88	72926.08
0.1,2000,I,1.1,0.02	21.07	101.62	73633.20
0.1,2000,I,1.1,0.0001	21.58	101.93	73469.88
0.1,1000,ME+I,2.0,0.02	11.19	104.18	71543.48
0.1,1000,ME+I,2.0,0.0001	13.23	103.98	71146.12
0.1,1000,ME+I,1.5,0.02	11.13	104.34	71897.60
0.1,1000,ME+I,1.5,0.0001	11.32	104.25	71671.52
0.1,1000,ME+I,1.1,0.02	11.01	104.52	72502.08
0.1,1000,ME+I,1.1,0.0001	11.26	104.54	72783.76
0.1,1000,ME,2.0,0.02	11.10	104.39	71333.52
0.1,1000,ME,2.0,0.0001	11.59	104.16	71271.44
0.1,1000,ME,1.5,0.02	11.11	104.37	71968.00
0.1,1000,ME,1.5,0.0001	11.11	104.28	71837.24
0.1,1000,ME,1.1,0.02	11.00	104.53	72532.48
0.1,1000,ME,1.1,0.0001	11.18	104.47	72076.52
0.1,1000,I,2.0,0.02	11.52	104.40	71641.20
0.1,1000,I,2.0,0.0001	11.29	104.52	72135.84
0.1,1000,I,1.5,0.02	11.12	104.56	72310.20
0.1,1000,I,1.5,0.0001	11.12	104.58	72486.12
0.1,1000,I,1.1,0.02	11.11	104.71	72571.52
0.1,1000,I,1.1,0.0001	11.16	104.38	72365.84
0.05,500,ME+I,2.0,0.02	6.23	108.59	69799.12
0.05,500,ME+I,2.0,0.0001	6.14	108.27	69907.08
0.05,500,ME+I,1.5,0.02	6.13	108.57	70177.28
0.05,500,ME+I,1.5,0.0001	6.15	108.44	70259.12
0.05,500,ME+I,1.1,0.02	6.20	108.71	70280.92
0.05,500,ME+I,1.1,0.0001	6.13	108.78	69942.24
0.05,500,ME,2.0,0.02	6.19	108.97	70123.56
0.05,500,ME,2.0,0.0001	6.13	108.19	69865.56

0.05,500,ME,1.5,0.02	6.14	109.00	70221.36
0.05,500,ME,1.5,0.0001	6.14	108.88	69994.16
0.05,500,ME,1.1,0.02	6.12	108.32	69700.40
0.05,500,ME,1.1,0.0001	6.11	108.61	70141.16
0.05,500,I,2.0,0.02	6.14	108.80	70028.96
0.05,500,I,2.0,0.0001	6.16	108.74	70185.16
0.05,500,I,1.5,0.02	6.09	108.90	69967.76
0.05,500,I,1.5,0.0001	6.18	108.73	69698.04
0.05,500,I,1.1,0.02	6.22	107.68	69844.80
0.05,500,I,1.1,0.0001	6.21	101.49	69872.32
0.05,2000,ME+I,2.0,0.02	21.74	96.81	72821.72
0.05,2000,ME+I,2.0,0.0001	22.90	92.35	72652.16
0.05,2000,ME+I,1.5,0.02	21.44	97.61	73224.84
0.05,2000,ME+I,1.5,0.0001	21.35	97.65	73010.56
0.05,2000,ME+I,1.1,0.02	21.32	100.62	73583.24
0.05,2000,ME+I,1.1,0.0001	21.79	100.34	73084.72
0.05,2000,ME,2.0,0.02	21.33	102.42	72800.80
0.05,2000,ME,2.0,0.0001	22.45	100.06	72805.60
0.05,2000,ME,1.5,0.02	22.20	97.06	73334.84
0.05,2000,ME,1.5,0.0001	21.67	101.75	73099.68
0.05,2000,ME,1.1,0.02	21.64	102.07	73360.48
0.05,2000,ME,1.1,0.0001	21.36	102.47	73394.80
0.05,2000,I,2.0,0.02	21.75	101.65	72672.52
0.05,2000,I,2.0,0.0001	24.67	99.33	72954.52
0.05,2000,I,1.5,0.02	23.76	99.50	72027.12
0.05,2000,I,1.5,0.0001	24.41	99.04	72224.64
0.05,2000,I,1.1,0.02	21.99	98.53	73594.44
0.05,2000,I,1.1,0.0001	21.83	99.55	73442.16
0.05,1000,ME+I,2.0,0.02	11.21	102.98	71934.28
0.05,1000,ME+I,2.0,0.0001	11.22	102.77	71696.96
0.05,1000,ME+I,1.5,0.02	11.07	103.08	72868.56
0.05,1000,ME+I,1.5,0.0001	11.12	101.16	72054.76
0.05,1000,ME+I,1.1,0.02	10.98	103.88	72243.88
0.05,1000,ME+I,1.1,0.0001	11.04	105.79	71986.88
0.05,1000,ME,2.0,0.02	10.99	105.88	72255.96
0.05,1000,ME,2.0,0.0001	11.11	105.82	71831.64
0.05,1000,ME,1.5,0.02	10.91	105.93	72275.60
0.05,1000,ME,1.5,0.0001	11.01	105.99	72655.04

0.05,1000,ME,1.1,0.02	10.91	106.09	72631.16
0.05,1000,ME,1.1,0.0001	10.88	106.08	72100.20
0.05,1000,I,2.0,0.02	10.89	105.87	72380.60
0.05,1000,I,2.0,0.0001	10.98	105.90	72264.56
0.05,1000,I,1.5,0.02	11.06	105.79	72350.44
0.05,1000,I,1.5,0.0001	11.02	106.11	72392.64
0.05,1000,I,1.1,0.02	11.07	105.81	72310.56
0.05,1000,I,1.1,0.0001	11.17	105.82	72267.92
0.01,500,ME+I,2.0,0.02	6.10	110.76	70623.48
0.01,500,ME+I,2.0,0.0001	6.19	100.90	70173.60
0.01,500,ME+I,1.5,0.02	6.23	88.83	70297.80
0.01,500,ME+I,1.5,0.0001	6.19	92.12	70435.84
0.01,500,ME+I,1.1,0.02	6.21	95.10	70178.08
0.01,500,ME+I,1.1,0.0001	6.18	94.75	69908.24
0.01,500,ME,2.0,0.02	6.17	100.01	70107.48
0.01,500,ME,2.0,0.0001	6.20	98.25	70174.40
0.01,500,ME,1.5,0.02	6.20	96.74	70149.52
0.01,500,ME,1.5,0.0001	6.20	97.67	69945.92
0.01,500,ME,1.1,0.02	6.21	100.55	70039.24
0.01,500,ME,1.1,0.0001	6.24	91.17	69905.40
0.01,500,I,2.0,0.02	6.23	102.47	70315.16
0.01,500,I,2.0,0.0001	6.17	103.53	70046.48
0.01,500,I,1.5,0.02	6.25	101.20	69696.88
0.01,500,I,1.5,0.0001	6.18	101.27	69886.68
0.01,500,I,1.1,0.02	6.30	99.65	70166.36
0.01,500,I,1.1,0.0001	6.27	99.71	70019.80
0.01,2000,ME+I,2.0,0.02	21.61	99.05	73708.60
0.01,2000,ME+I,2.0,0.0001	21.65	98.32	73273.96
0.01,2000,ME+I,1.5,0.02	21.57	99.21	73551.20
0.01,2000,ME+I,1.5,0.0001	21.52	98.94	73723.64
0.01,2000,ME+I,1.1,0.02	21.20	99.76	73592.64
0.01,2000,ME+I,1.1,0.0001	21.51	96.31	73391.08
0.01,2000,ME,2.0,0.02	21.70	92.67	73853.88
0.01,2000,ME,2.0,0.0001	21.51	99.72	73350.92
0.01,2000,ME,1.5,0.02	21.44	99.98	73758.00
0.01,2000,ME,1.5,0.0001	21.44	99.25	73351.20
0.01,2000,ME,1.1,0.02	21.53	97.16	73346.52
0.01,2000,ME,1.1,0.0001	21.16	101.37	73605.40

0.01,2000,I,2.0,0.02	21.07	101.02	73651.60
0.01,2000,I,2.0,0.0001	21.55	100.96	73217.44
0.01,2000,I,1.5,0.02	21.19	100.46	73303.00
0.01,2000,I,1.5,0.0001	21.60	99.60	73325.36
0.01,2000,I,1.1,0.02	21.43	100.51	73260.24
0.01,2000,I,1.1,0.0001	21.91	97.81	73582.96
0.01,1000,ME+I,2.0,0.02	11.24	98.26	71785.68
0.01,1000,ME+I,2.0,0.0001	11.18	97.90	72111.08
0.01,1000,ME+I,1.5,0.02	11.29	98.82	71760.68
0.01,1000,ME+I,1.5,0.0001	11.29	99.32	71912.76
0.01,1000,ME+I,1.1,0.02	11.19	98.55	71999.88
0.01,1000,ME+I,1.1,0.0001	11.28	98.35	72015.68
0.01,1000,ME,2.0,0.02	11.34	97.87	71920.68
0.01,1000,ME,2.0,0.0001	11.35	99.01	72120.60
0.01,1000,ME,1.5,0.02	11.34	95.71	71681.44
0.01,1000,ME,1.5,0.0001	11.39	96.87	71781.12
0.01,1000,ME,1.1,0.02	11.21	99.33	71747.48
0.01,1000,ME,1.1,0.0001	11.35	98.86	71964.16
0.01,1000,I,2.0,0.02	11.19	98.84	71847.96
0.01,1000,I,2.0,0.0001	11.36	97.89	71583.32
0.01,1000,I,1.5,0.02	11.25	97.67	72072.00
0.01,1000,I,1.5,0.0001	11.29	96.01	71814.48
0.01,1000,I,1.1,0.02	11.28	97.48	71709.20
0.01,1000,I,1.1,0.0001	11.36	97.21	71803.64

*MAF,POP,MOD,OR,PREV where MAF represents the minor allele frequency, POP is the number of individuals, MOD is the used model (with or without main effect and with or without epistasis effect), OR is the odds ratio and PREV is the prevalence of the disease.