

On Model Selection Strategies to Identify Genes Underlying Binary Traits Using Genome-Wide Association Data

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Supplementary Material

1. Genetic Model Incorporating Linkage Disequilibrium

It is possible that the causative loci are not genotyped, but there exists linkage disequilibrium (LD) between the causative loci and genotyped loci. Here we describe the model of incorporating LD into the statistical power calculation for the model selection strategies studied in the article. At the non-observed loci indexed by -1 and -2, the disease-causing alleles are denoted by A_{-1} and A_{-2} . Locus -1 is in LD with the genotyped marker 1; locus -2 is in LD with the genotyped marker 2. The method of calculating the odds of disease at markers 1 and 2 follows Marchini, Donnelly, and Cardon (2005):

$$O = \frac{p(D|g_{A_1}, g_{A_2})}{p(\bar{D}|g_{A_1}, g_{A_2})} = \frac{\sum_{g_{A_{-1}}, g_{A_{-2}}} p(D|g_{A_{-1}}, g_{A_{-2}}) p(g_{A_1}|g_{A_{-1}}) p(g_{A_2}|g_{A_{-2}}) p(g_{A_{-1}}, g_{A_{-2}})}{\sum_{g_{A_{-1}}, g_{A_{-2}}} p(\bar{D}|g_{A_{-1}}, g_{A_{-2}}) p(g_{A_1}|g_{A_{-1}}) p(g_{A_2}|g_{A_{-2}}) p(g_{A_{-1}}, g_{A_{-2}})},$$

where $p(g_{A_1}|g_{A_{-1}})$ (and similarly $p(g_{A_2}|g_{A_{-2}})$) is given by

$$\begin{aligned} p(0_{A_1}|0_{A_{-1}}) &= p(a_1|a_{-1})^2 \\ p(0_{A_1}|1_{A_{-1}}) &= p(a_1|a_{-1})p(a_1|A_{-1}) \\ p(0_{A_1}|2_{A_{-1}}) &= p(a_1|A_{-1})^2 \\ p(1_{A_1}|0_{A_{-1}}) &= 2p(a_1|a_{-1})p(A_1|a_{-1}) \\ p(1_{A_1}|1_{A_{-1}}) &= p(a_1|a_{-1})p(A_1|A_{-1}) + p(a_1|A_{-1})p(A_1|a_{-1}) \\ p(1_{A_1}|2_{A_{-1}}) &= 2p(a_1|A_{-1})p(A_1|A_{-1}) \\ p(2_{A_1}|0_{A_{-1}}) &= p(A_1|a_{-1})^2 \\ p(2_{A_1}|1_{A_{-1}}) &= p(A_1|a_{-1})p(A_1|A_{-1}) \\ p(2_{A_1}|2_{A_{-1}}) &= p(A_1|A_{-1})^2. \end{aligned}$$

The calculation for $p(g_{A_1}|g_{A_{-1}})$ (and similarly for $p(g_{A_2}|g_{A_{-2}})$) is based on the values of $p(A_1|A_{-1})$ and $p(A_1|a_{-1})$, which are obtained by solving an equation of LD under a certain constraint. Specifically, the LD between markers 1 and -1 is measured by the squared correlation coefficient (Pritchard and Przeworski 2001)

$$r_{A_{-1}A_1}^2 = (p(A_1|A_{-1}) - p(A_1|a_{-1}))^2 \frac{p_{A_{-1}}(1 - p_{A_{-1}})}{p_{A_1}(1 - p_{A_1})},$$

where the allele frequency is $p_{A_1} = p(A_{-1}) = \sqrt{p(2_{A_1})}$ with

$$\begin{aligned} p(2_{A_1}) &= p(2_{A_1}|0_{A_{-1}})p(0_{A_{-1}}) + p(2_{A_1}|1_{A_{-1}})p(1_{A_{-1}}) + p(2_{A_1}|2_{A_{-1}})p(2_{A_{-1}}) \\ &= p(A_1|a_{-1})^2(1 - p_{A_{-1}})^2 + p(A_1|a_{-1})p(A_1|A_{-1})2p_{A_{-1}}(1 - p_{A_{-1}}) + p(A_1|A_{-1})^2p_{A_{-1}}^2. \end{aligned}$$

Under any one of the following constraints

$$\text{Constraint 1: } p(A_1|A_{-1}) = q, \quad p(A_1|a_{-1}) = 1 - q,$$

$$\text{Constraint 2: } p(A_1|A_{-1}) = 1, \quad p(A_1|a_{-1}) = q,$$

$$\text{Constraint 3: } p(A_1|A_{-1}) = q, \quad p(A_1|a_{-1}) = 0,$$

$r_{A_{-1}A_1}^2 = f(q)$ becomes a function of q . So for the given values of $p_{A_{-1}}$ and $r_{A_{-1}A_1}^2$, we can solve the equation to get q , then get $p(A_1|A_{-1})$ and $p(A_1|a_{-1})$, and thus get $p(g_{A_1}|g_{A_{-1}})$.

Following this, we obtain the conditional joint genotypic distributions $p(g_{A_1}, g_{A_2}|D)$ and $p(g_{A_1}, g_{A_2}|\bar{D})$ in cases and in controls, respectively. So we can calculate the mean vector and covariance matrix

$$\begin{aligned} \boldsymbol{\theta}_{A_1A_2} &= E(\mathbf{W}_{A_1A_2}) \\ \boldsymbol{\Sigma}_{A_1A_2} &= Var(\mathbf{W}_{A_1A_2}) \end{aligned}$$

involving the genotyped markers 1 and 2. Applying the generalized Delta method given in the article (13) - (15) to the appropriate score test statistics, we can derive the corresponding asymptotic distributions for power calculation.

2. Comparisons of Analytical and Simulation Results

Assume the true genetic model be Model (2) in the article, the following tables give the comparisons between power by simulations (based on score test and log-likelihood ratio test) and by analytical calculations (based on score test). We consider $L = 300$ candidate markers with minor allele frequencies $p_j = 0.3$, $j = 1, \dots, L$. The base line effect $\alpha = 0.007$ corresponds to a disease prevalence approximately 0.01. Two power definitions are considered: (A) the probability of identifying exactly the true genetic model (in marginal search, it is the probability of detecting both targeted markers individually); (B) the probability of detecting either targeted markers. The numbers of cases (n_1) and controls (n_0) and the genotypic effect θ are varied. Tables 1 - 7 are for the statistical power controlled under the Bonferroni corrected genome-wide type I error rate α . Tables 8 - 10 are for statistical power under the control of the discovery number R . The column of $R = 1$ corresponds to $R = 2$ for marginal search under power definition (A).

Table 1: Power under Bonferroni type I error control. $n_1 = n_0 = 1000$, $\theta = 0.2$.

Strategy	Source	$\alpha = \mathbf{0.01}$	$\alpha = \mathbf{0.05}$	$\alpha = \mathbf{0.10}$	$\alpha = \mathbf{0.15}$
<i>Power definition (A)</i>					
Marginal search	Score Simu.	0.00	0.00	0.00	0.00
	LRT Simu.	0.00	0.00	0.00	0.00
	Score Calcu.	0.00	0.00	0.00	0.00
Exhaustive search	Score Simu.	0.00	0.01	0.02	0.02
	LRT Simu.	0.02	0.03	0.03	0.04
	Score Calcu.	0.01	0.01	0.02	0.02
Forward search	Score Simu.	0.00	0.00	0.01	0.01
	LRT Simu.	0.00	0.00	0.01	0.01
	Score Calcu.	0.00	0.00	0.01	0.01
<i>Power definition (B)</i>					
Marginal search	Score Simu.	0.02	0.05	0.07	0.09
	LRT Simu.	0.02	0.05	0.07	0.09
	Score Calcu.	0.02	0.04	0.07	0.09
Exhaustive search	Score Simu.	0.02	0.04	0.06	0.06
	LRT Simu.	0.02	0.04	0.06	0.09
	Score Calcu.	0.01	0.03	0.05	0.06
Forward search	Score Simu.	0.01	0.04	0.06	0.08
	LRT Simu.	0.01	0.04	0.06	0.08
	Score Calcu.	0.01	0.05	0.06	0.08

Table 2: Power under Bonferroni type I error control. $n_1 = n_0 = 1000$, $\theta = 0.3$.

Strategy	Source	$\alpha = \mathbf{0.01}$	$\alpha = \mathbf{0.05}$	$\alpha = \mathbf{0.10}$	$\alpha = \mathbf{0.15}$
<i>Power definition (A)</i>					
Marginal search	Score Simu.	0.01	0.02	0.04	0.06
	LRT Simu.	0.01	0.02	0.04	0.06
	Score Calcu.	0.01	0.02	0.04	0.05
Exhaustive search	Score Simu.	0.11	0.17	0.23	0.25
	LRT Simu.	0.14	0.20	0.22	0.25
	Score Calcu.	0.12	0.18	0.22	0.26
Forward search	Score Simu.	0.02	0.06	0.09	0.12
	LRT Simu.	0.02	0.07	0.10	0.12
	Score Calcu.	0.02	0.07	0.10	0.12
<i>Power definition (B)</i>					
Marginal search	Score Simu.	0.15	0.28	0.34	0.38
	LRT Simu.	0.15	0.28	0.34	0.39
	Score Calcu.	0.14	0.26	0.32	0.37
Exhaustive search	Score Simu.	0.14	0.21	0.27	0.32
	LRT Simu.	0.17	0.27	0.31	0.34
	Score Calcu.	0.15	0.25	0.30	0.34
Forward search	Score Simu.	0.14	0.25	0.32	0.37
	LRT Simu.	0.14	0.25	0.32	0.37
	Score Calcu.	0.13	0.25	0.32	0.36

Table 3: Power under Bonferroni type I error control. $n_1 = n_0 = 1000$, $\theta = 0.4$.

Strategy	Source	$\alpha = \mathbf{0.01}$	$\alpha = \mathbf{0.05}$	$\alpha = \mathbf{0.10}$	$\alpha = \mathbf{0.15}$
<i>Power definition (A)</i>					
Marginal search	Score Simu.	0.09	0.20	0.28	0.32
	LRT Simu.	0.10	0.21	0.28	0.32
	Score Calcu.	0.09	0.20	0.27	0.31
Exhaustive search	Score Simu.	0.58	0.71	0.76	0.79
	LRT Simu.	0.58	0.69	0.76	0.77
	Score Calcu.	0.58	0.70	0.74	0.77
Forward search	Score Simu.	0.24	0.42	0.52	0.57
	LRT Simu.	0.26	0.45	0.55	0.59
	Score Calcu.	0.23	0.40	0.49	0.54
<i>Power definition (B)</i>					
Marginal search	Score Simu.	0.48	0.66	0.75	0.78
	LRT Simu.	0.49	0.66	0.75	0.78
	Score Calcu.	0.49	0.66	0.75	0.78
Exhaustive search	Score Simu.	0.61	0.74	0.79	0.81
	LRT Simu.	0.60	0.74	0.81	0.83
	Score Calcu.	0.62	0.74	0.78	0.82
Forward search	Score Simu.	0.49	0.67	0.75	0.78
	LRT Simu.	0.49	0.67	0.75	0.78
	Score Calcu.	0.48	0.66	0.74	0.78

Table 4: Power under Bonferroni type I error control. $n_1 = n_0 = 1000$, $\theta = 0.5$.

Strategy	Source	$\alpha = \mathbf{0.01}$	$\alpha = \mathbf{0.05}$	$\alpha = \mathbf{0.10}$	$\alpha = \mathbf{0.15}$
<i>Power definition (A)</i>					
Marginal search	Score Simu.	0.43	0.61	0.69	0.74
	LRT Simu.	0.43	0.62	0.69	0.74
	Score Calcu.	0.43	0.61	0.69	0.73
Exhaustive search	Score Simu.	0.94	0.97	0.97	0.97
	LRT Simu.	0.91	0.95	0.97	0.98
	Score Calcu.	0.94	0.97	0.98	0.99
Forward search	Score Simu.	0.69	0.83	0.89	0.91
	LRT Simu.	0.71	0.85	0.90	0.92
	Score Calcu.	0.69	0.83	0.87	0.89
<i>Power definition (B)</i>					
Marginal search	Score Simu.	0.84	0.93	0.95	0.96
	LRT Simu.	0.84	0.93	0.95	0.96
	Score Calcu.	0.86	0.94	0.96	0.97
Exhaustive search	Score Simu.	0.95	0.97	0.97	0.98
	LRT Simu.	0.93	0.96	0.97	0.98
	Score Calcu.	0.95	0.98	0.99	0.99
Forward search	Score Simu.	0.87	0.94	0.97	0.98
	LRT Simu.	0.87	0.94	0.97	0.98
	Score Calcu.	0.86	0.94	0.96	0.97

Table 5: Power under Bonferroni type I error control. $n_1 = n_0 = 5000$, $\theta = 0.1$.

Strategy	Source	$\alpha = \mathbf{0.01}$	$\alpha = \mathbf{0.05}$	$\alpha = \mathbf{0.10}$	$\alpha = \mathbf{0.15}$
<i>Power definition (A)</i>					
Marginal search	Score Simu.	0.00	0.00	0.00	0.01
	LRT Simu.	0.00	0.00	0.00	0.01
	Score Calcu.	0.00	0.00	0.00	0.00
Exhaustive search	Score Simu.	0.01	0.03	0.04	0.05
	LRT Simu.	0.01	0.03	0.05	0.05
	Score Calcu.	0.02	0.03	0.04	0.05
Forward search	Score Simu.	0.00	0.01	0.02	0.02
	LRT Simu.	0.00	0.01	0.02	0.02
	Score Calcu.	0.00	0.01	0.01	0.02
<i>Power definition (B)</i>					
Marginal search	Score Simu.	0.03	0.06	0.09	0.11
	LRT Simu.	0.03	0.06	0.09	0.11
	Score Calcu.	0.03	0.07	0.10	0.13
Exhaustive search	Score Simu.	0.02	0.04	0.08	0.09
	LRT Simu.	0.03	0.05	0.08	0.09
	Score Calcu.	0.03	0.06	0.08	0.10
Forward search	Score Simu.	0.03	0.07	0.11	0.13
	LRT Simu.	0.03	0.08	0.11	0.13
	Score Calcu.	0.03	0.07	0.10	0.12

Table 6: Power under Bonferroni type I error control. $n_1 = n_0 = 5000$, $\theta = 0.2$.

Strategy	Source	$\alpha = \mathbf{0.01}$	$\alpha = \mathbf{0.05}$	$\alpha = \mathbf{0.10}$	$\alpha = \mathbf{0.15}$
<i>Power definition (A)</i>					
Marginal search	Score Simu.	0.20	0.37	0.46	0.51
	LRT Simu.	0.20	0.37	0.46	0.51
	Score Calcu.	0.19	0.34	0.42	0.48
Exhaustive search	Score Simu.	0.86	0.92	0.94	0.95
	LRT Simu.	0.87	0.92	0.94	0.95
	Score Calcu.	0.86	0.92	0.93	0.95
Forward search	Score Simu.	0.55	0.73	0.79	0.82
	LRT Simu.	0.56	0.73	0.80	0.83
	Score Calcu.	0.51	0.70	0.76	0.80
<i>Power definition (B)</i>					
Marginal search	Score Simu.	0.68	0.83	0.88	0.91
	LRT Simu.	0.68	0.83	0.88	0.91
	Score Calcu.	0.66	0.82	0.87	0.89
Exhaustive search	Score Simu.	0.87	0.93	0.94	0.96
	LRT Simu.	0.87	0.92	0.94	0.95
	Score Calcu.	0.87	0.93	0.95	0.96
Forward search	Score Simu.	0.69	0.82	0.88	0.89
	LRT Simu.	0.69	0.82	0.88	0.89
	Score Calcu.	0.67	0.82	0.86	0.89

Table 7: Power under Bonferroni type I error control. $n_1 = n_0 = 5000$, $\theta = 0.3$.

Strategy	Source	$\alpha = \mathbf{0.01}$	$\alpha = \mathbf{0.05}$	$\alpha = \mathbf{0.10}$	$\alpha = \mathbf{0.15}$
<i>Power definition (A)</i>					
Marginal search	Score Simu.	0.94	0.97	0.98	0.98
	LRT Simu.	0.94	0.97	0.98	0.98
	Score Calcu.	0.94	0.97	0.99	0.99
Exhaustive search	Score Simu.	1.00	1.00	1.00	1.00
	LRT Simu.	1.00	1.00	1.00	1.00
	Score Calcu.	1.00	1.00	1.00	1.00
Forward search	Score Simu.	1.00	1.00	1.00	1.00
	LRT Simu.	1.00	1.00	1.00	1.00
	Score Calcu.	1.00	1.00	1.00	1.00
<i>Power definition (B)</i>					
Marginal search	Score Simu.	1.00	1.00	1.00	1.00
	LRT Simu.	1.00	1.00	1.00	1.00
	Score Calcu.	1.00	1.00	1.00	1.00
Exhaustive search	Score Simu.	1.00	1.00	1.00	1.00
	LRT Simu.	1.00	1.00	1.00	1.00
	Score Calcu.	1.00	1.00	1.00	1.00
Forward search	Score Simu.	1.00	1.00	1.00	1.00
	LRT Simu.	1.00	1.00	1.00	1.00
	Score Calcu.	1.00	1.00	1.00	1.00

Table 8: Power under false discovery number control. $n_1 = n_0 = 1000$, $\theta = 0.2$. (* $R = 2$ in marginal search under power definition (A).)

Strategy	Source	$R = 1^*$	$R = 5$	$R = 10$	$R = 15$	$R = 20$	$R = 30$
<i>Power definition (A)</i>							
Marginal search	Score Simu.	0.02	0.08	0.13	0.18	0.22	0.28
	LRT Simu.	0.02	0.08	0.13	0.18	0.22	0.28
	Score Calcu.	0.01	0.07	0.13	0.18	0.23	0.31
Exhaustive search	Score Simu.	0.02	0.08	0.12	0.15	0.17	0.20
	LRT Simu.	0.05	0.11	0.14	0.16	0.18	0.20
	Score Calcu.	0.03	0.09	0.13	0.10	0.15	0.20
Forward search	Score Simu.	0.04	0.08	0.10	0.11	0.11	0.13
	LRT Simu.	0.04	0.08	0.10	0.11	0.11	0.13
	Score Calcu.	0.04	0.07	0.09	0.10	0.10	0.12
<i>Power definition (B)</i>							
Marginal search	Score Simu.	0.20	0.43	0.55	0.63	0.68	0.76
	LRT Simu.	0.20	0.43	0.55	0.63	0.68	0.76
	Score Calcu.	0.16	0.44	0.58	0.66	0.71	0.79
Exhaustive search	Score Simu.	0.16	0.38	0.50	0.60	0.65	0.72
	LRT Simu.	0.19	0.43	0.54	0.60	0.66	0.73
	Score Calcu.	0.23	0.36	0.48	0.55	0.61	0.70
Forward search	Score Simu.	0.23	0.35	0.46	0.54	0.59	0.69
	LRT Simu.	0.22	0.34	0.46	0.54	0.59	0.69
	Score Calcu.	0.23	0.36	0.48	0.55	0.61	0.70

Table 9: Power under false discovery number control. $n_1 = n_0 = 1000$, $\theta = 0.4$. (* $R = 2$ in marginal search under power definition (A).)

Strategy	Source	$R = 1^*$	$R = 5$	$R = 10$	$R = 15$	$R = 20$	$R = 30$
<i>Power definition (A)</i>							
Marginal search	Score Simu.	0.48	0.77	0.85	0.89	0.92	0.95
	LRT Simu.	0.48	0.77	0.85	0.89	0.92	0.95
	Score Calcu.	0.47	0.78	0.86	0.90	0.92	0.95
Exhaustive search	Score Simu.	0.79	0.90	0.94	0.94	0.95	0.96
	LRT Simu.	0.77	0.91	0.93	0.95	0.96	0.97
	Score Calcu.	0.74	0.87	0.90	0.92	0.94	0.95
Forward search	Score Simu.	0.72	0.82	0.85	0.85	0.85	0.86
	LRT Simu.	0.73	0.83	0.85	0.85	0.85	0.86
	Score Calcu.	0.69	0.80	0.83	0.84	0.85	0.85
<i>Power definition (B)</i>							
Marginal search	Score Simu.	0.88	0.99	0.99	1.00	1.00	1.00
	LRT Simu.	0.88	0.99	0.99	1.00	1.00	1.00
	Score Calcu.	0.89	0.98	0.99	1.00	1.00	1.00
Exhaustive search	Score Simu.	0.90	0.98	0.99	0.99	0.99	1.00
	LRT Simu.	0.92	0.98	0.99	0.99	0.99	0.99
	Score Calcu.	0.94	0.97	0.99	0.99	0.99	1.00
Forward search	Score Simu.	0.90	0.96	0.98	0.99	0.99	1.00
	LRT Simu.	0.90	0.96	0.98	0.99	0.99	1.00
	Score Calcu.	0.90	0.95	0.98	0.99	0.99	1.00

Table 10: Power under false discovery number control. $n_1 = n_0 = 1000$, $\theta = 0.5$. (* $R = 2$ in marginal search under power definition (A).)

Strategy	Source	$R = 1^*$	$R = 5$	$R = 10$	$R = 15$	$R = 20$	$R = 30$
<i>Power definition (A)</i>							
Marginal search	Score Simu.	0.84	0.95	0.98	0.99	0.99	1.00
	LRT Simu.	0.84	0.95	0.98	0.99	0.99	1.00
	Score Calcu.	0.85	0.97	0.98	0.99	0.99	1.00
Exhaustive search	Score Simu.	0.98	0.99	0.99	0.99	1.00	1.00
	LRT Simu.	0.96	1.00	1.00	1.00	1.00	1.00
	Score Calcu.	0.95	0.98	0.99	0.99	0.99	1.00
Forward search	Score Simu.	0.95	0.98	0.98	0.98	0.98	0.98
	LRT Simu.	0.95	0.98	0.98	0.98	0.98	0.98
	Score Calcu.	0.94	0.97	0.98	0.98	0.98	0.98
<i>Power definition (B)</i>							
Marginal search	Score Simu.	0.98	1.00	1.00	1.00	1.00	1.00
	LRT Simu.	0.98	1.00	1.00	1.00	1.00	1.00
	Score Calcu.	0.99	1.00	1.00	1.00	1.00	1.00
Exhaustive search	Score Simu.	0.99	1.00	1.00	1.00	1.00	1.00
	LRT Simu.	1.00	1.00	1.00	1.00	1.00	1.00
	Score Calcu.	1.00	1.00	1.00	1.00	1.00	1.00
Forward search	Score Simu.	0.99	1.00	1.00	1.00	1.00	1.00
	LRT Simu.	0.99	1.00	1.00	1.00	1.00	1.00
	Score Calcu.	0.99	1.00	1.00	1.00	1.00	1.00

3 Graphs for Power Comparisons

The following power comparisons assume the true genetic model is from a logistic model defined in article (4):

$$\log(O(g_1, g_2)) = b_0 + b_1g_1 + b_2g_2 + b_3g_1g_2,$$

where $b_0 = \log(0.007) = -4.96$. The allele frequencies for all SNPs are $p_j = 0.3$, $j = 1, \dots, p$. This model is consistent with a classic setup in the literature (Marchini, Donnelly, and Cardon 2005).

3.1 Under Discovery Number Control

Over a grid combinations of main effects ($b_1 = b_2$ vary from -1 to 1) and interaction effect (b_3 varies from -1 to 1), we can see how the epistases influence the pattern of the relative merit of different marker selection procedures. Figures 1 - 4 demonstrate the power differences among model selection methods under discovery number control R . Row 1 illustrates power definition (A), row 2 illustrates power definition (B). Left column: marginal search vs. exhaustive search; middle column: forward search vs. exhaustive search; right column: marginal search vs. forward search. Green areas indicate the positive values of difference, and red areas indicate the negative values of difference.

The power comparisons are also studied when the marginal signal at both associated markers and the disease prevalence are fixed. We assume the marginal association, which is represented by the heterozygote odds ratio at each causative marker $\lambda = 1.5$, the disease prevalence $p(D) = 0.01$, the number of cases and controls $n_1 = n_0 = 1000$, the minor allele frequencies $p_j = 0.05, 0.1, 0.2$, and 0.5 , the LD strength $r^2 = 0.5, 0.7$, and 1 , the LD constraint $p(A_i|A_{-i}) = 1$ and $p(A_i|a_{-i}) = q$, $i = 1, 2$, where A_{-i} is the minor disease-causing allele at the unobserved locus indexed by $-i$, A_i is the minor allele at the genotyped locus of marker i , which is in LD with the causative locus $-i$. Under the discovery number control $R = 5$, Figure 5 shows the power comparisons for finding the joint association, under power definition (A). Figure 11 shows the power comparisons for finding either associated marker under power definition (B).

3.2 Under Bonferroni Type I Error Rate Control

Using the similar setups as above, we study the power performance under Bonferroni Type I error rate controls. With the same parameters for Figures 1 - 4, Figures 7 - 9 show the power differences among model selection methods under Bonferroni corrected type I error rate control with family-wise significance level $\alpha = 0.01, 0.1$, and 0.15 . Row 1 illustrates power definition (A), row 2 illustrates power definition (B). Left column: marginal search vs. exhaustive search; middle column: forward search vs. exhaustive search; right column: marginal search vs. forward search. Green areas indicate the positive values of difference, and red areas indicate the negative values of difference. With the same setups for Figures 5 and 11, Figures 10 and 11 demonstrate

the power comparisons under Bonferroni type I error rate $\alpha = 0.05$ for finding both and either associated markers, respectively.

References

Marchini, J., Donnelly, P., and Cardon, L. R. (2005). Genome-wide strategies for detecting multiple loci that influence complex diseases. *Nat Genet* **37**, 413–417.

Pritchard, J. K. and Przeworski, M. (2001). Linkage disequilibrium in humans: models and data. *Am J Hum Genet.* **69**,1-14.

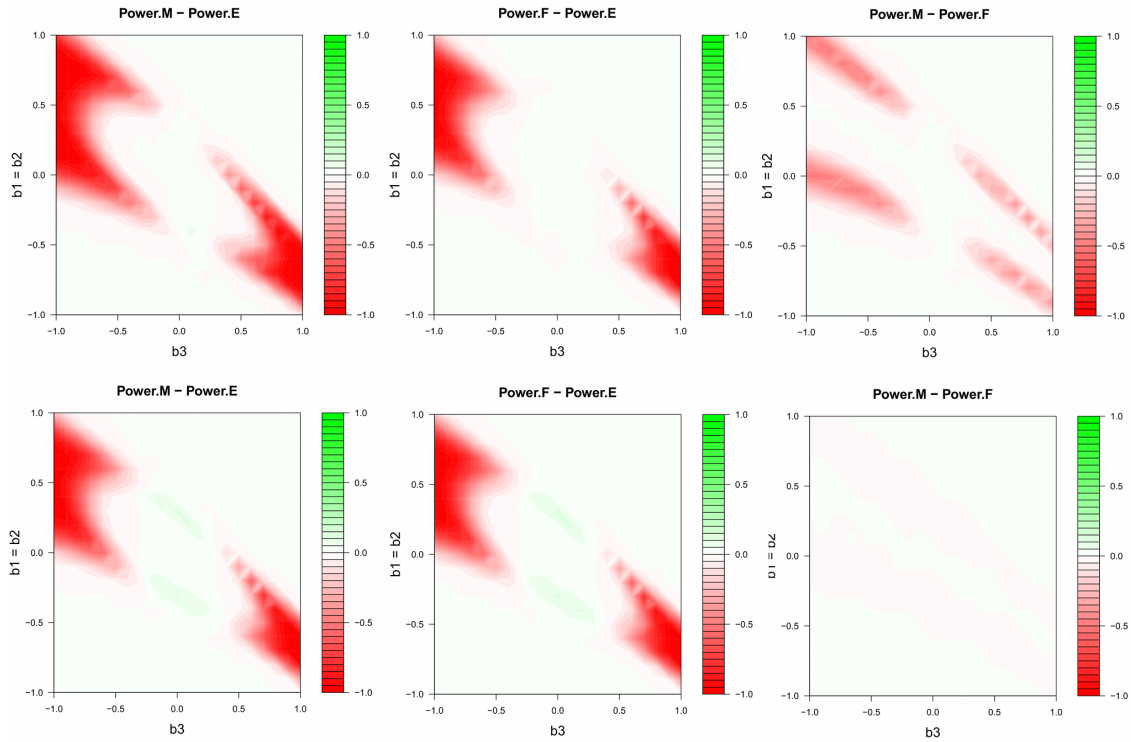


Figure 1: Power differences with varying main and interaction effects with discovery number $R = 1$ (or, $R = 2$ for marginal selection in finding both true SNPs). Row 1 illustrates power definition (A), row 2 illustrates power definition (B). Left column: marginal search vs. exhaustive search; middle column: forward search vs. exhaustive search; right column: marginal search vs. forward search. Green areas indicate positive values of difference, red areas indicate negative values. Main effect $b_1 = b_2$ and epistatic effect b_3 , both vary from -1 to 1, the allele frequency $p_j = 0.3$, $j = 1, \dots, L$.

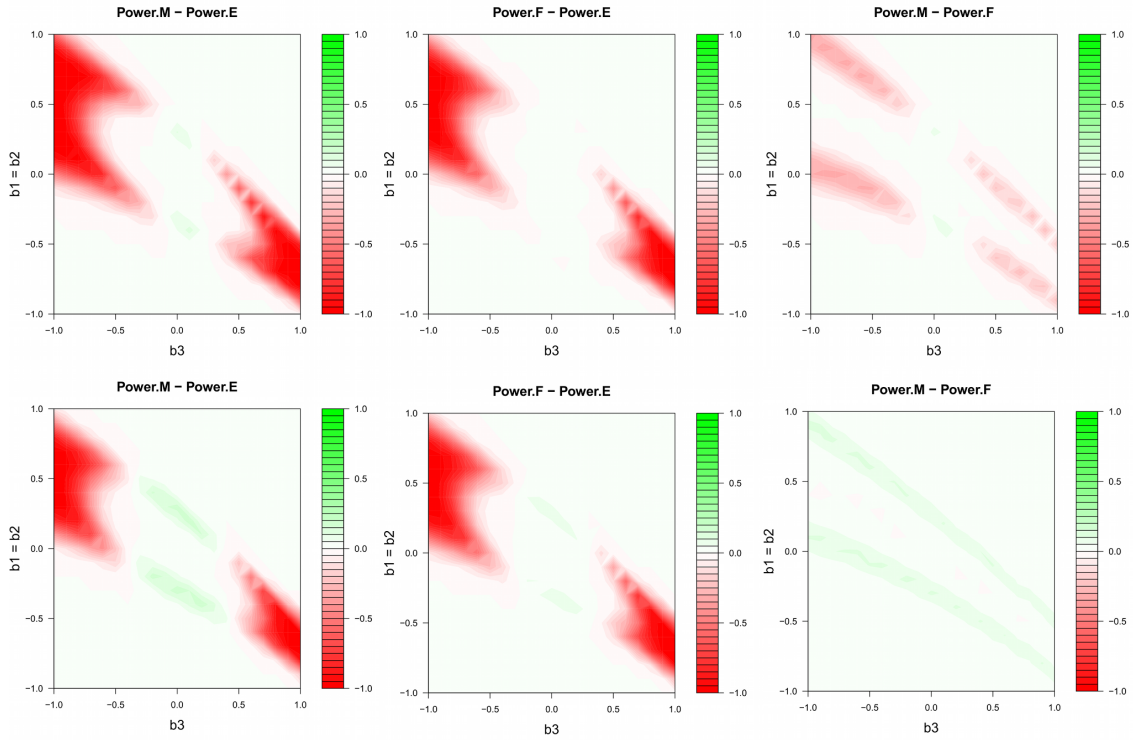


Figure 2: Power differences with varying main and interaction effects with discovery number $R = 5$. Row 1 illustrates power definition (A), row 2 illustrates power definition (B). Left column: marginal search vs. exhaustive search; middle column: forward search vs. exhaustive search; right column: marginal search vs. forward search. Green areas indicate positive values of difference, red areas indicate negative values. Main effect $b_1 = b_2$ and epistatic effect b_3 , both vary from -1 to 1, the allele frequency $p_j = 0.3$, $j = 1, \dots, L$.

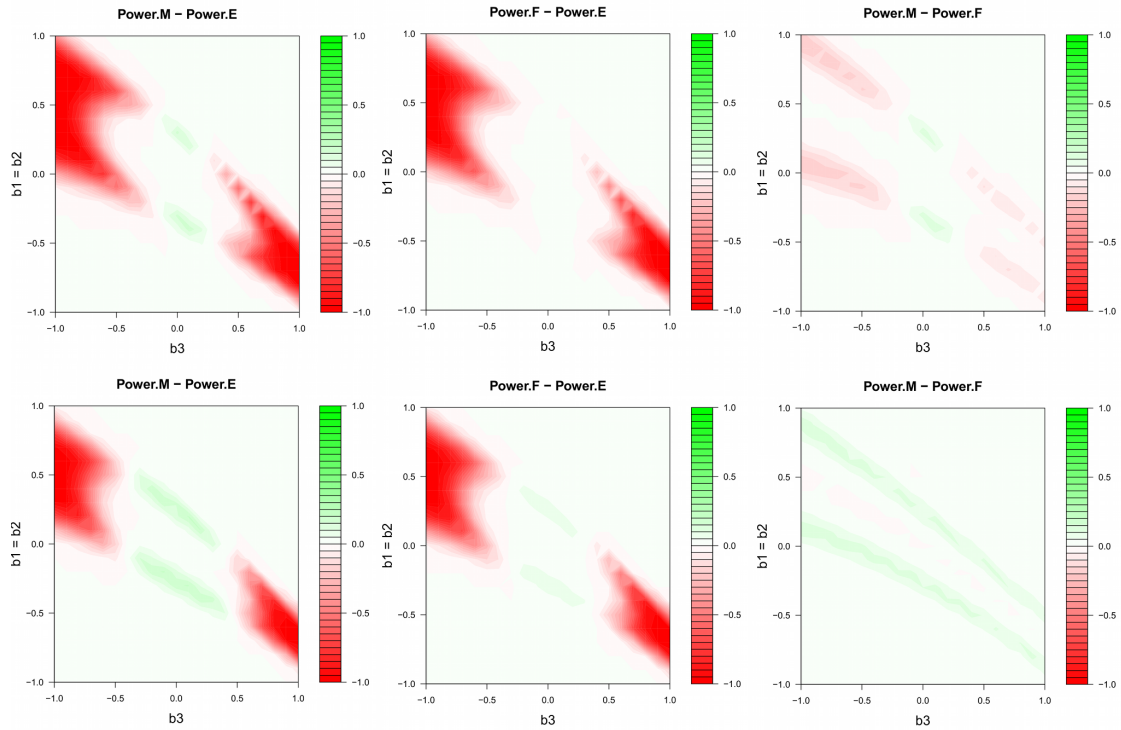


Figure 3: Power differences with varying main and interaction effects with discovery number $R = 20$. Row 1 illustrates power definition (A), row 2 illustrates power definition (B). Left column: marginal search vs. exhaustive search; middle column: forward search vs. exhaustive search; right column: marginal search vs. forward search. Green areas indicate positive values of difference, red areas indicate negative values. Main effect $b_1 = b_2$ and epistatic effect b_3 , both vary from -1 to 1, the allele frequency $p_j = 0.3$, $j = 1, \dots, L$.

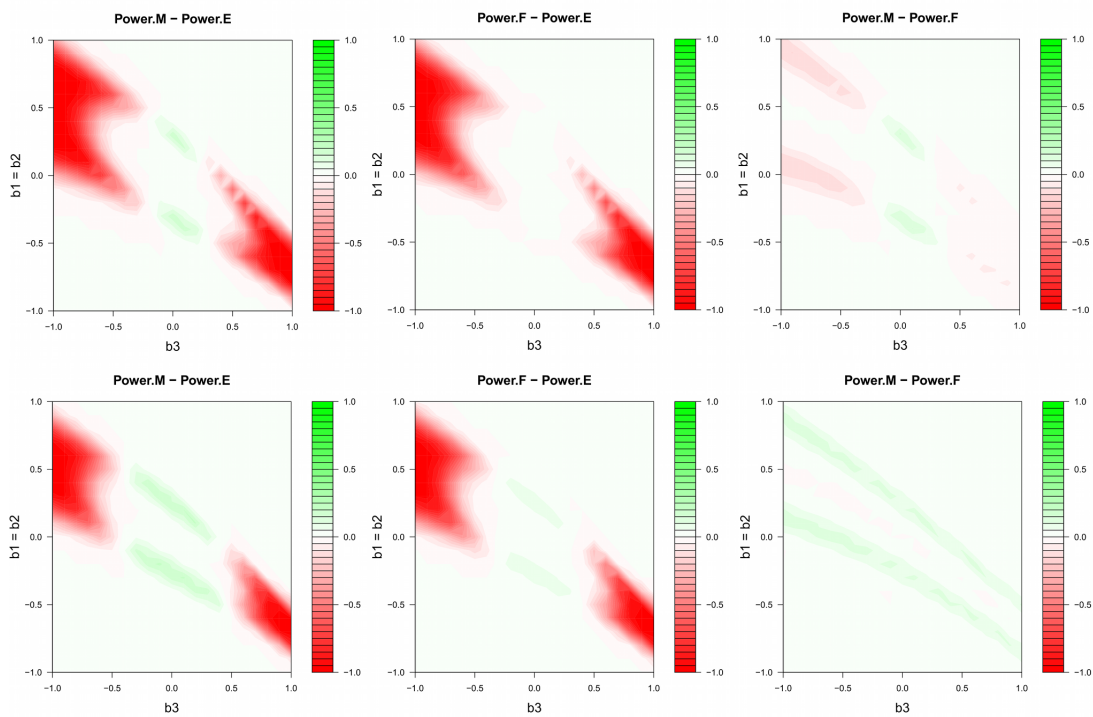


Figure 4: Power differences with varying main and interaction effects with discovery number $R = 30$. Row 1 illustrates power definition (A), row 2 illustrates power definition (B). Left column: marginal search vs. exhaustive search; middle column: forward search vs. exhaustive search; right column: marginal search vs. forward search. Green areas indicate positive values of difference, red areas indicate negative values. Main effect $b_1 = b_2$ and epistatic effect b_3 , both vary from -1 to 1, the allele frequency $p_j = 0.3$, $j = 1, \dots, L$.

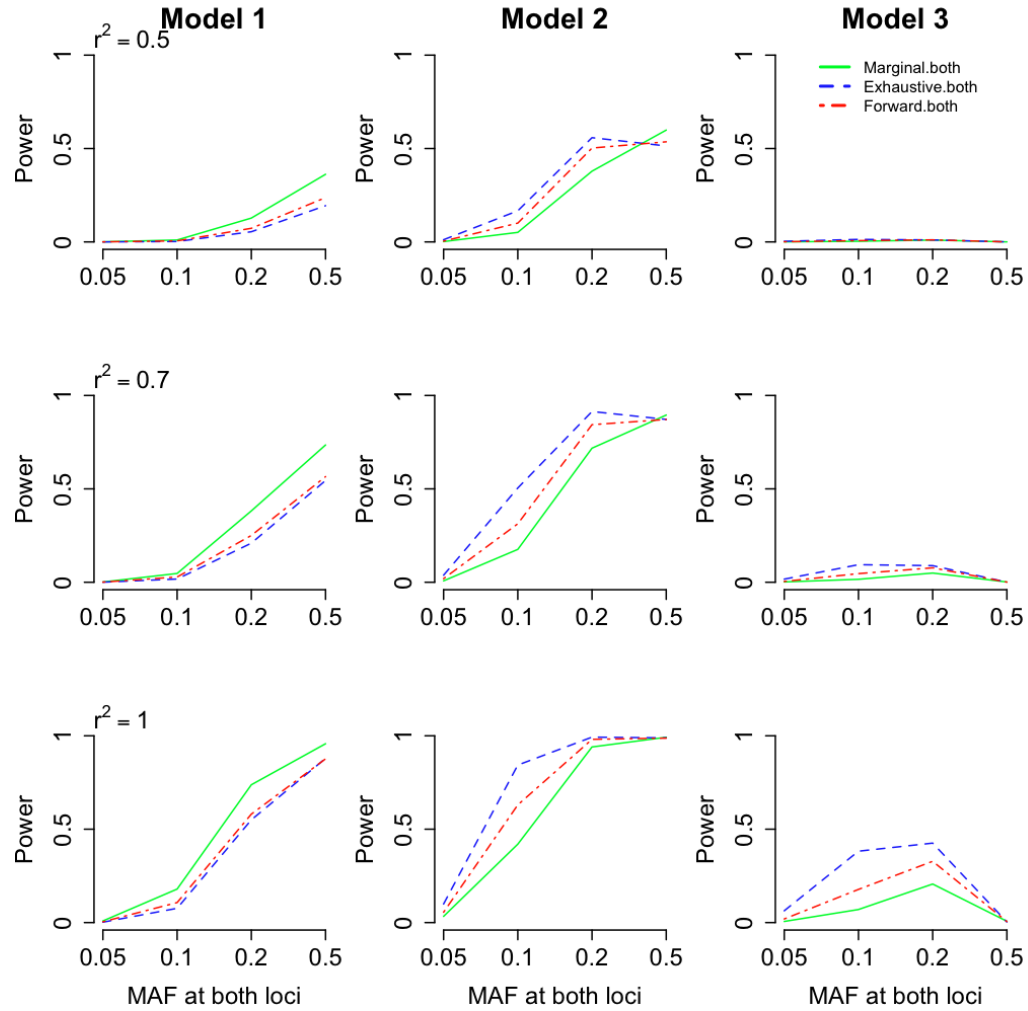


Figure 5: Power of finding joint association with the discovery number $R = 5$. The case and control numbers are both 1000, marginal odds ratio at both loci is 1.5, disease prevalence is 0.01. Green lines, marginal search; blue dashed lines, exhaustive search; red dot-dashed lines, forward search. Columns of panels show genetic Models (1), (2), and (3) in the article, respectively; rows show LD strength $r^2 = 0.5, 0.7,$ and 1 . The minor allele frequencies are 0.05, 0.1, 0.2, and 0.5 on the x-axis of each panel.

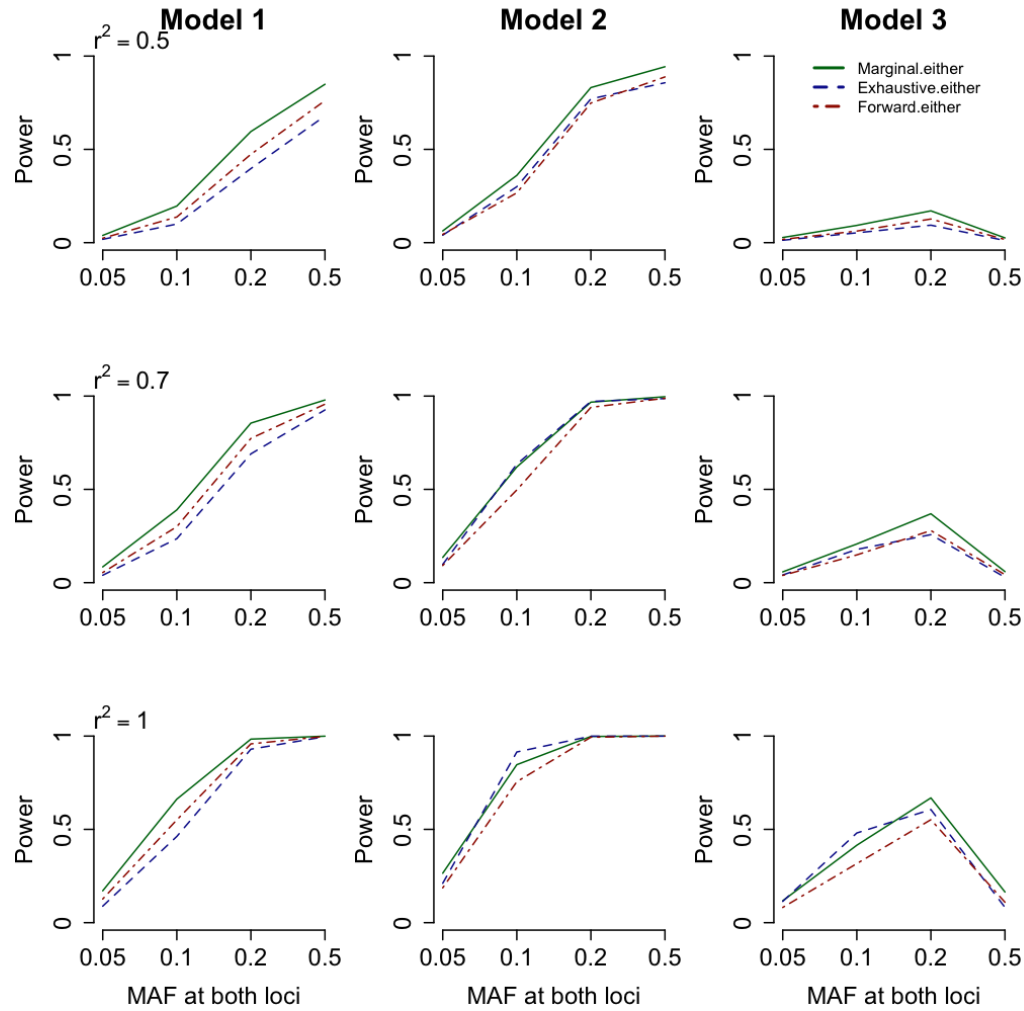


Figure 6: Power of finding either associated marker with discovery number $R = 5$. The case and control numbers are both 1000, marginal odds ratio at both loci is 1.5, disease prevalence is 0.01. Green lines, marginal search; blue dashed lines, exhaustive search; red dot-dashed lines, forward search. Columns of panels show genetic Models (1), (2), and (3) in the article, respectively; rows show LD strength $r^2 = 0.5, 0.7$, and 1. The minor allele frequencies are 0.05, 0.1, 0.2, and 0.5 on the x-axis of each panel.

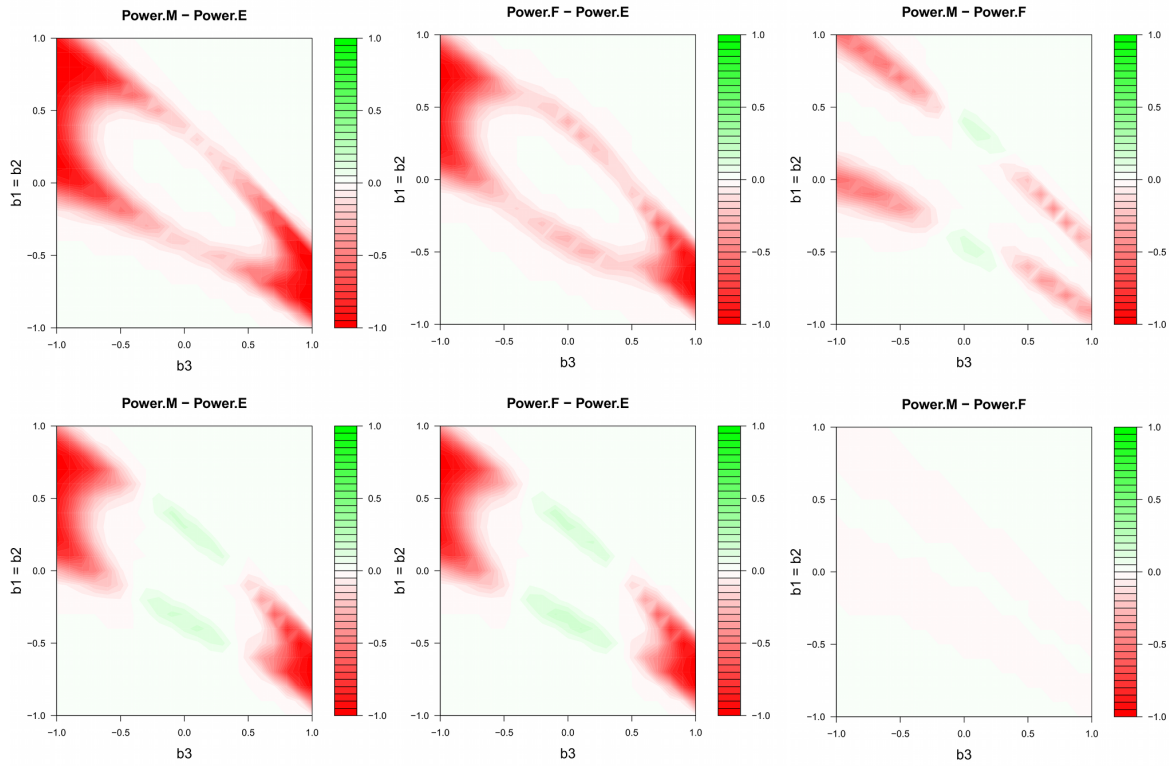


Figure 7: Power differences with varying main and interaction effects with Bonferroni type I error rate $\alpha = 0.05$. Power definition (A) is applied in row 1 and (B) is used in row 2. Left column: marginal search vs. exhaustive search; middle column: forward search vs. exhaustive search; right column: marginal search vs. forward search. Green areas indicate positive values of difference, red areas indicate negative values. Main effects $b_1 = b_2$ varies from -1 to 1, epistatic effect b_3 varies from -1 to 1, the allele frequency $p_j = 0.3$, $j = 1, \dots, L$.

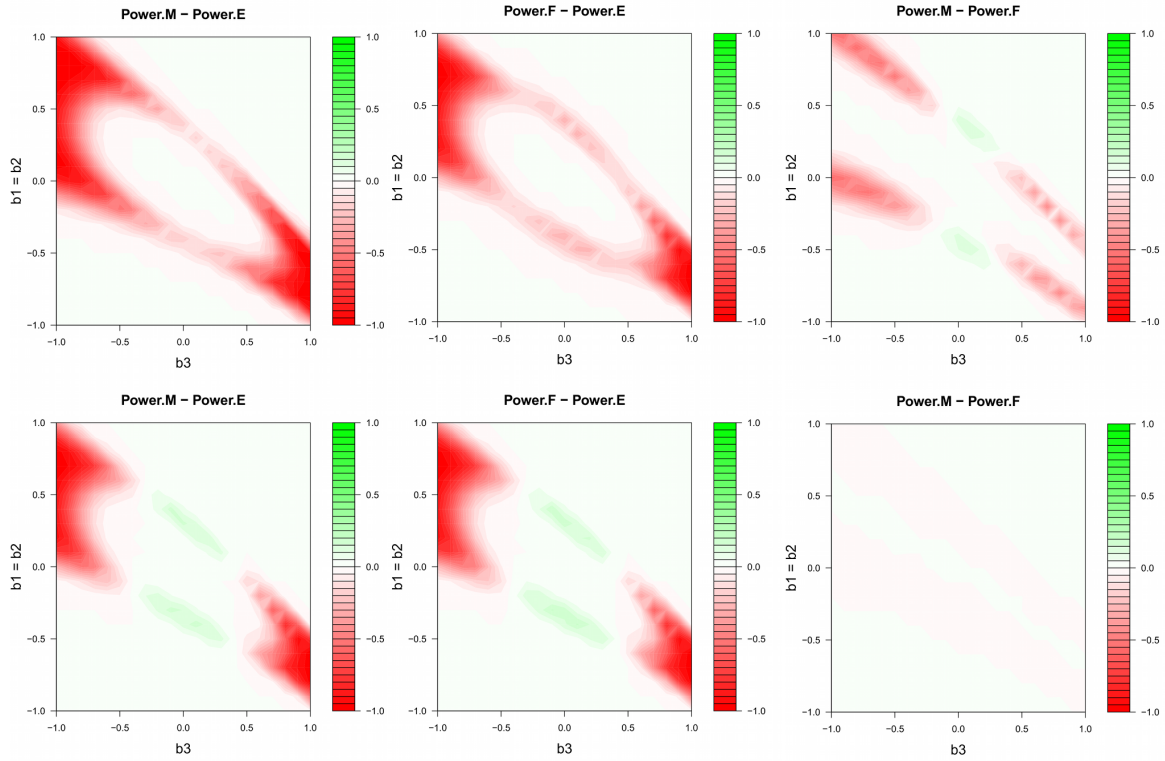


Figure 8: Power differences with varying main and interaction effects with Bonferroni type I error rate $\alpha = 0.1$. Power definition (A) is applied in row 1 and (B) is used in row 2. Left column: marginal search vs. exhaustive search; middle column: forward search vs. exhaustive search; right column: marginal search vs. forward search. Green areas indicate positive values of difference, red areas indicate negative values. Main effects $b_1 = b_2$ varies from -1 to 1, epistatic effect b_3 varies from -1 to 1, the allele frequency $p_j = 0.3$, $j = 1, \dots, L$.

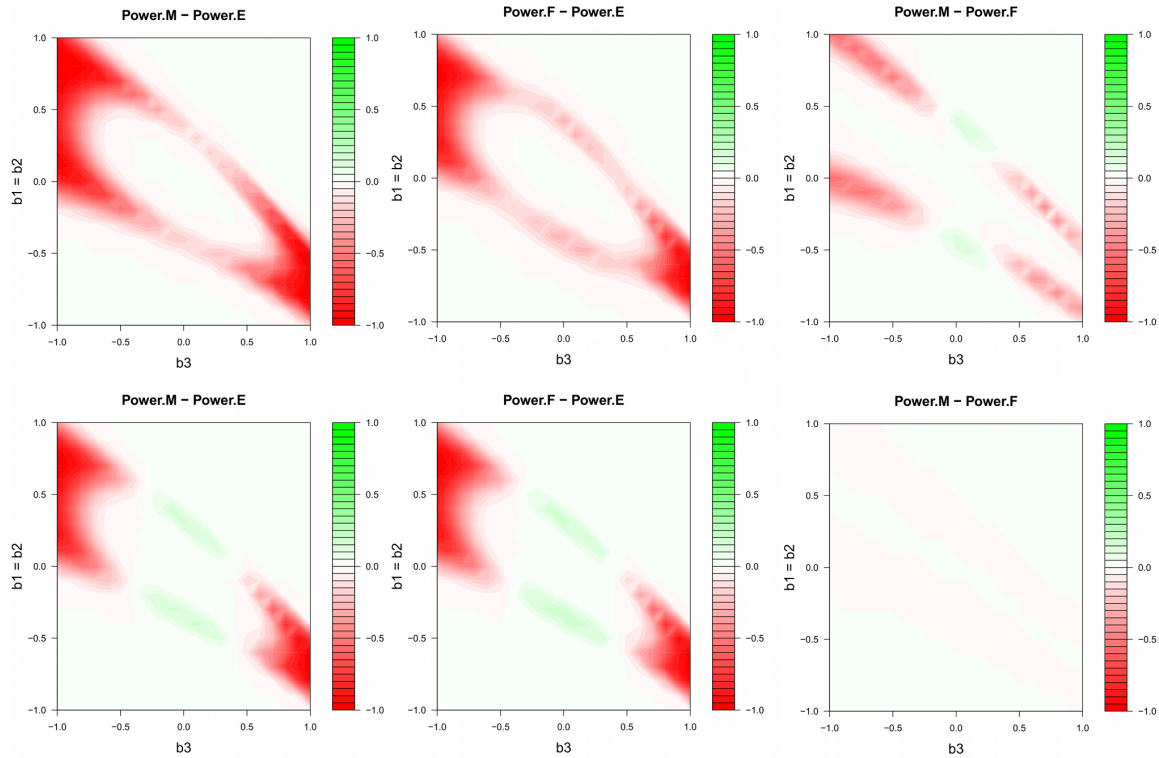


Figure 9: Power differences with varying main and interaction effects with Bonferroni type I error rate $\alpha = 0.15$. Power definition (A) is applied in row 1 and (B) is used in row 2. Left column: marginal search vs. exhaustive search; middle column: forward search vs. exhaustive search; right column: marginal search vs. forward search. Green areas indicate positive values of difference, red areas indicate negative values. Main effect $b_1 = b_2$ varies from -1 to 1, epistatic effect b_3 varies from -1 to 1, the allele frequency $p_j = 0.3$, $j = 1, \dots, L$.

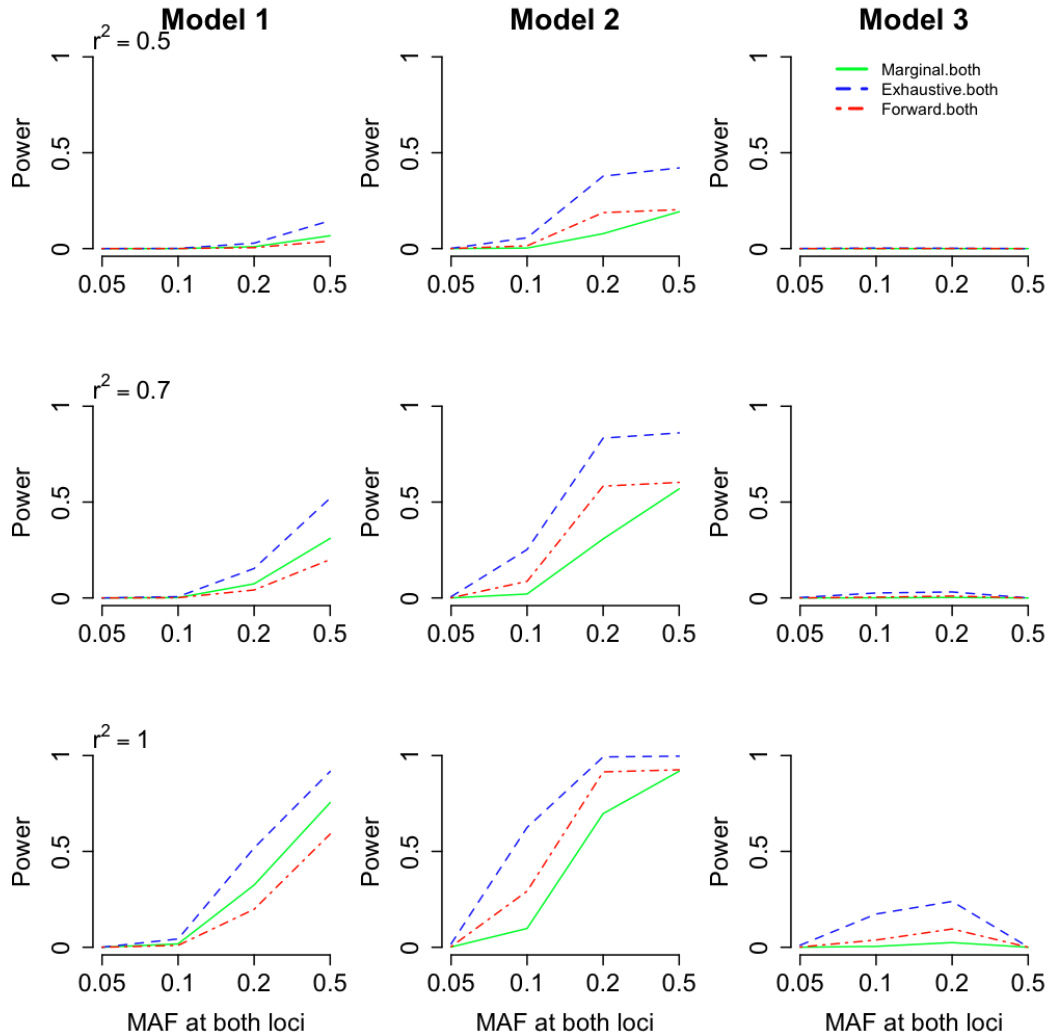


Figure 10: Power of finding joint association with Bonferroni type I error rate $\alpha = 0.05$. The case and control numbers are both 1000, marginal odds ratio at both loci is 1.5, disease prevalence is 0.01. Green lines, marginal search; blue dashed lines, exhaustive search; red dot-dashed lines, forward search. Columns of panels show genetic Models (1), (2), and (3) in the article, respectively; rows show LD strength $r^2 = 0.5, 0.7, \text{ and } 1$. The minor allele frequencies are 0.05, 0.1, 0.2, and 0.5 on the x-axis of each panel.

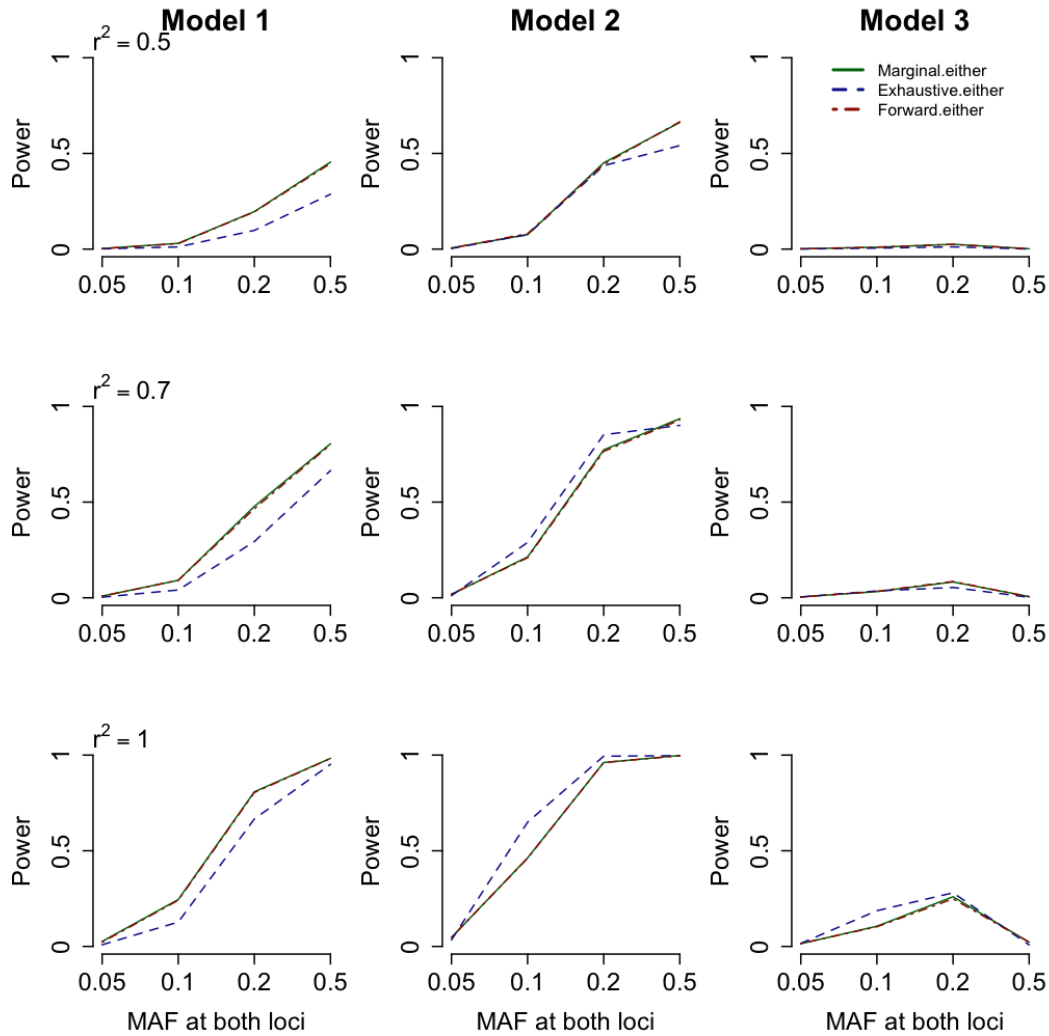


Figure 11: Power of finding either association with Bonferroni type I error rate $\alpha = 0.05$. The case and control numbers are both 1000, marginal odds ratio at both loci is 1.5, disease prevalence is 0.01. Green lines, marginal search; blue dashed lines, exhaustive search; red dot-dashed lines, forward search. Columns of panels show genetic Models (1), (2), and (3) in the article, respectively; rows show LD strength $r^2 = 0.5, 0.7, \text{ and } 1$. The minor allele frequencies are 0.05, 0.1, 0.2, and 0.5 on the x-axis of each panel.