Hybrid of Restricted and Penalized Maximum Likelihood Method for Efficient Genome-wide Association Study

Wenlong Ren¹, Zhikai Liang², Shu He¹, Jing Xiao^{1,*}

¹ Department of Epidemiology and Medical Statistics, School of Public Health, Nantong University, Nantong, Jiangsu, China

² Plant and Microbial Biology Department, University of Minnesota, Saint Paul, USA

* Correspondence: Jing Xiao jxiaont@ntu.edu.cn

Supplementary Material

ΟΤΝ	Chr	Desition(hn)	D ²	Effoat		Power (%)				Mean Squared Errors (MSE)			
QIN	211 Chr. Toshton(bp)		N	Effect	HRePML	MLMM	FarmCPU	GEMMA	HRePML	MLMM	FarmCPU	GEMMA	
1	1	404108	0.01	0.4742	12.1	3.4	2.9	0.0	0.0633	0.1841	0.1055	-	
2	1	636788	0.03	0.8213	46.3	54.1	64.7	0.7	0.0311	0.0473	0.0342	0.2322	
3	3	507976	0.03	0.8213	71.1	46.0	18.4	10.1	0.1926	0.1124	0.1223	0.1719	
4	3	931437	0.05	1.0603	88.7	63.5	47.6	43.5	0.0528	0.0265	0.0954	0.0366	
5	4	75898	0.08	1.3412	100.0	99.5	100.0	99.4	0.0490	0.0381	0.0619	0.0345	
6	4	461978	0.01	0.4742	10.1	6.0	10.4	1.0	0.2273	0.4381	0.3674	0.6338	
7	4	607026	0.05	1.0603	74.8	86.9	99.3	92.3	0.0856	0.1720	0.1277	0.2630	
8	5	282008	0.05	1.0603	96.5	97.2	98.1	76.7	0.0390	0.0561	0.0331	0.1158	

Table S1. Comparison of statistical power and mean squared errors (MSE) for each QTN among HRePML, MLMM, FarmCPU and GEMMA methods in the second simulation study^{*}.

* In the second simulation study, the data set consists of 500 individuals and 10,000 SNP markers with 1,000 replicates. And 8 true QTNs are set in each replicate. Then, this dataset can be regarded as having 10,000,000 SNPs and 8,000 true QTNs in total.

Table S2. Comparison of average statistical power, average mean squared errors (MSE) and running time among HRePML, MLMM, FarmCPU and GEMMA methods in the second simulation study^{*}.

Statistical Properties	HRePML	MLMM	FarmCPU	GEMMA
Average power (%)	62.45	57.08	55.18	40.46
Average MSE	0.0926	0.1343	0.1184	0.2125
Running time (Hour)	3.2273	27.4473	4.9198	2.3855

* The data set used in Table S2 are the same with those used in Table S1.

OTN Chy Desition(hu		Desition(hn)	D ²			Number of Markers: Effect					
QIN	QIN CIII.	Position(bp)	K-	500	1000	2000	4000	10000	50000	100000	200000
1	1	404108	0.01	0.4742	0.4340	0.4334	0.4317	0.4742	0.4239	0.4496	0.4551
2	1	636788	0.03	0.8213	0.7584	0.7682	0.7745	0.8213	0.8094	0.8305	0.7479
3	3	507976	0.03	0.8213	0.7526	0.7409	0.7452	0.8213	0.7359	0.7266	0.7554
4	3	931437	0.05	1.0603	0.9883	0.9691	0.9665	1.0603	0.9399	1.0053	0.9856
5	4	75898	0.08	1.3412	1.2113	1.2192	1.2195	1.3412	1.2214	1.2606	1.2071
6	4	461978	0.01	0.4742	0.4263	0.4303	0.4286	0.4742	0.4384	0.4278	0.4195
7	4	607026	0.05	1.0603	0.9816	0.9869	1.0005	1.0603	1.0024	1.0145	0.9966
8	5	282008	0.05	1.0603	0.9691	0.9772	0.9743	1.0603	0.9610	0.9522	1.0145

Table S3. Parameters settings including true effect for each QTN with different sample size in the third simulation study^{*} and true effect for each QTN with different number of markers in the fourth simulation study[#].

* In the third simulation study, there are four data sets consisting of 500, 1,000, 2,000 and 4,000 individuals, respectively, and 10,000 SNP markers, with 100 replicates. And 8 true QTNs are set in each replicate. Then, each dataset can be regarded as having 1,000,000 SNPs and 800 true QTNs in total.

In the fourth simulation study, there are four data sets consisting of 10,000, 50,000, 100,000 and 200,000 SNP markers, respectively, and 500 individuals, with 100 replicates. And 8 true QTNs are set in each replicate. Then, four data sets can be regarded as having 1,000,000, 5,000,000, 10,000,000 and 20,000,000 SNPs, respectively, and 800 true QTNs.

Table S4. The numbers of SNPs significantly associated with four development related traits in *Arabidopsis* thaliana and the number of genes around theseSNPs identified by HRePML, MLMM, FarmCPU and GEMMA methods.

Tusit	Number of	SNPs Significa	untly Associated	with Traits	Number of Known Genes Detected				
i ran -	HRePML	MLMM	FarmCPU	GEMMA	HRePML	MLMM	FarmCPU	GEMMA	
FT Duration GH	10	2	5	7	6	1	1	1	-
LC Duration GH	26	31	11	2	11	13	7	0	
LFS GH	23	7	6	5	13	4	4	3	
MT GH	18	3	10	3	11	1	13	1	
Total	77	43	32	17	41	19	25	5	

FT Duration GH: number of days between appearance of the first flower and the senescence of the last flower, LC Duration GH: number of days between germination and plant complete senescence, LFS GH: number of days between germination and senescence of the last flower and MT GH: number of days between last flower senescence and complete plant senescence.

Detected Genes	Associated Trait	Chromosome	Position	Effect Estimate	LOD/P-value	Methods	Reference
AT1G01690	LFS GH	1	252095	-2.906	8.12	HRePML	[1]
AT1G06150	FT Duration GH	1	1876943	1.027	4.07	HRePML	[2]
AT1G06170	FT Duration GH	1	1876943	1.027	4.07	HRePML	[3]
AT1G08410	LC Duration GH	1	2653741	-2.707	7.85	HRePML	[4]
AT1G09100	LC Duration GH	1	2948670	-1.634	3.02	HRePML	[5]
AT1G10745	LC Duration GH	1	3580647	-1.239	9.09E-10	MLMM	[6]
AT1G10747	LC Duration GH	1	3580647	-1.239	9.09E-10	MLMM	[6]
AT1G13590	FT Duration GH	1	4653501	-2.752	7.96E-08	MLMM	[7]
AT1G14280	LC Duration GH	1	4882806	-6.469	9.29E-13	FarmCPU	[8]
AT1G14320	LC Duration GH	1	4882806	-6.469	9.29E-13	FarmCPU	[9]
AT1G14350	LFS GH	1	4912083	2.819	4.67	HRePML	[10]
AT1G14360	LFS GH	1	4912083	2.819	4.67	HRePML	[11]
AT1G18835	MT GH	1	6499060	0.448	4.08	HRePML	[12]
AT1G27135	MT GH	1	9427585	0.526	4.31	HRePML	-
AT1G30000	MT GH	1	10515519	-0.576	6.86	HRePML	[13]
AT1G30010	MT GH	1	10515519	-0.576	6.86	HRePML	[14]
AT1G47200	LC Duration GH	1	17306925	1.116	3.96E-10	MLMM	[15]
AT1G55460	MT GH	1	20709875	-0.298	3.34	HRePML	[16]
AT1G58210	LFS GH	1	21551184	2.483	4.29	HRePML	[17]
AT1G60370	FT Duration GH	1	22248393	-0.927	3.83	HRePML	[18]
AT1G62060	MT GH	1	22945740	0.419	3.26	HRePML	[19]
AT1G62080	MT GH	1	22945740	0.419	3.26	HRePML	-
AT1G62085	MT GH	1	22945740	0.419	3.26	HRePML	-
AT1G62430	LFS GH	1	23112452	-1.836	3.18	HRePML	[20]
AT1G62830	MT GH	1	23267151	-0.510	3.33	HRePML	[21]
AT1G65480	LC Duration GH	1	24341923	-1.873	4.37	HRePML	[22]
AT1G74500	LFS GH	1	28003216	-1.838	3.09	HRePML	[23]
AT2G13540	MT GH	2	5638874	0.412	3.94	HRePML	[24]
AT2G15570	MT GH	2	6787293	-1.041	1.74E-15	FarmCPU	[25]
AT2G16440	LC Duration GH	2	7140030	-5.979	6.54E-22	FarmCPU	[26]
AT2G16440	LFS GH	2	7140030	-7.461, -9.107, -5.16	3.90E-11, 1.28E-17, 9.56E-08	FarmCPU, MLMM, GEMMA	[26]

Table S5. GWAS for four development related traits in Arabidopsis thaliana using HRePML, MLMM, FarmCPU and GEMMA methods.

AT2G16500	LC Duration GH	2	7154976	1.644	3.39	HRePML	[27]
AT2G19690	LC Duration GH	2	8506413	1.213	3.47	HRePML	[28]
AT2G31070	LC Duration GH	2	13226944	3.434	10.91	HRePML	[29]
AT3G01530	LFS GH	3	212444	-4.805	1.22E-08	MLMM	[30]
AT3G03250	LC Duration GH	3	746520	1.947	3.96	HRePML	[31]
AT3G03250	LFS GH	3	746520	2.037	3.08	HRePML	[31]
AT3G07160	LFS GH	3	2280271	-5.934, -8.845	1.16E-07, 9.37E-15	FarmCPU, MLMM	[32]
AT3G22820	LC Duration GH	3	8066094	1.982	3.79	HRePML	[33]
AT3G22840	FT Duration GH	3	8086127	1.154	4.32	HRePML	[34]
AT3G28990	LC Duration GH	3	11006055	2.373	2.74E-24	MLMM	-
AT3G29030	LC Duration GH	3	11006055	2.373	2.74E-24	MLMM	[35]
AT3G47870	MT GH	3	17650250	0.446	3.74	HRePML	[36]
AT3G48610	LC Duration GH	3	18021733	-3.033	4.99E-23	MLMM	[37]
AT3G54280	MT GH	3	20090780	1.002, 1.762	9.90E-13, 5.65E-08	FarmCPU, MLMM	[38]
AT3G56640	LFS GH	3	20981902	1.908	3.23	HRePML	[39]
AT3G62500	LC Duration GH	3	23110632	2.381	1.23E-27	MLMM	-
AT4G00020	MT GH	4	15364	1.136	3.59E-14	FarmCPU	[40]
AT4G00026	MT GH	4	15364	1.136	3.59E-14	FarmCPU	[41]
AT4G00050	MT GH	4	15364	1.136	3.59E-14	FarmCPU	[42]
AT4G00060	MT GH	4	15364	1.136	3.59E-14	FarmCPU	[43]
AT4G00260	LFS GH	4	117376	-3.176	4.63	HRePML	-
AT4G01250	LC Duration GH	4	529409	-3.924	2.29E-14	FarmCPU	[44]
AT4G05410	LFS GH	4	2742918	5.024	9.97	HRePML	[45]
AT4G09960	FT Duration GH	4	6228754	0.822, 1.136	3.74, 3.69E-08	HRePML, FarmCPU	[46]
AT4G31120	LFS GH	4	15126597	-10.514	4.29E-16	MLMM	[47]
AT4G33240	FT Duration GH	4	16028697	1.061	4.47	HRePML	[48]
AT4G33620	LC Duration GH	4	16140068	2.996, 2.540	4.78, 4.29E-29	HRePML, MLMM	[49]
AT4G33620	LFS GH	4	16140068	3.402	5.32	HRePML	[49]
AT5G13690	MT GH	5	4429786	1.702	4.44E-14	FarmCPU	[50]
AT5G13710	MT GH	5	4429786	1.702	4.44E-14	FarmCPU	[51]
AT5G13750	MT GH	5	4429786	1.702	4.44E-14	FarmCPU	[52]
AT5G24240	MT GH	5	8242061	1.426	4.47E-17	FarmCPU	[53]
AT5G27720	LC Duration GH	5	9820126	4.593	1.09E-48	MLMM	[54]
AT5G27740	LC Duration GH	5	9820126	4.593	1.09E-48	MLMM	-

AT5G35600	LC Duration GH	5	13764717	2.627	3.62E-30	MLMM	[55]
AT5G45300	LC Duration GH	5	18355835	-2.236	1.05E-29	MLMM	[56]
AT5G45900, AT5G45940	LC Duration GH	5	18625634, 18625726	-3.707, -6.051	4.78, 2.51E-28	HRePML, FarmCPU	[57]; [58]
AT5G45900, AT5G45940	LFS GH	5	18625634, 18625726, 18625726	-4.318, -5.147, -5.616	5.23, 1.83E-08, 1.05E-07	HRePML, FarmCPU, GEMMA	[57]; [58]
AT5G53360	MT GH	5	21646741	0.236, 0.267	3.05E-14, 1.55E-07	FarmCPU, GEMMA	[59]
AT5G54180	LC Duration GH	5	21982990	-2.129	1.84E-30	MLMM	[60]
AT5G58010	LC Duration GH	5	23476715	-4.708	6.50E-21	FarmCPU	[61]
AT5G59510	FT Duration GH	5	23989818	3.430	4.63E-08	GEMMA	-

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