Eagle: Making multi-locus association mapping on a genome-wide scale routine

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November 29, 2018

Supplementary Table 1: Implementation and methodology attributes of eight computer programs/packages for genome-wide association mapping.

Attributes	**Eagle**	**bigRR**	**glmnet**	**LMM-Lasso**	**MLMM**	**r2VIM**	**FaST-LMM**	**GEMMA**
Implementation								
Purpose built[a]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Language	R/C++	R	R	Python	R	R	C++ and Python[b]	C++
GUI	Yes	No	No	No	No	No	No	No
Documentation	Videos, user-manuals, website, R help	R help	Vignettes, R help	Readme.txt, test script	Vignette, R help	R help	Videos, website user-manuals,	User-manual, website
Additional fixed effects[c]	Yes	Yes	Yes	No	Yes	No	Yes	Yes
Types of trait data	Cont.	Cont., binary, count	Cont., binary, count	Cont.	Cont.	Cont., binary	Cont.	Cont., binary
Data larger than memory	Yes	No	No	No	No	No	Yes	No
Methodology								
Model [d]	LMM	HEM	GLMM	LMM	LMM	RF	LMM	LMM, mvLMM Bayesian Sparse LMM
SNPs fitted [e]	All/multiple	All	All	All	Multiple	Multiple	Single	Single
Selection type	Model	Variable	Variable	Variable	Model	Variable	Variable	Variable
Threshold free	Yes	No	No	No	Yes	No	No	No

[a] Specifically created for the analysis of GWAS data.

[b] Separate programs, one written in Python, the other C++

[c] Capacity for additional fixed effects (such as age, sex, and/or population structure effects) to be included directly in the model.

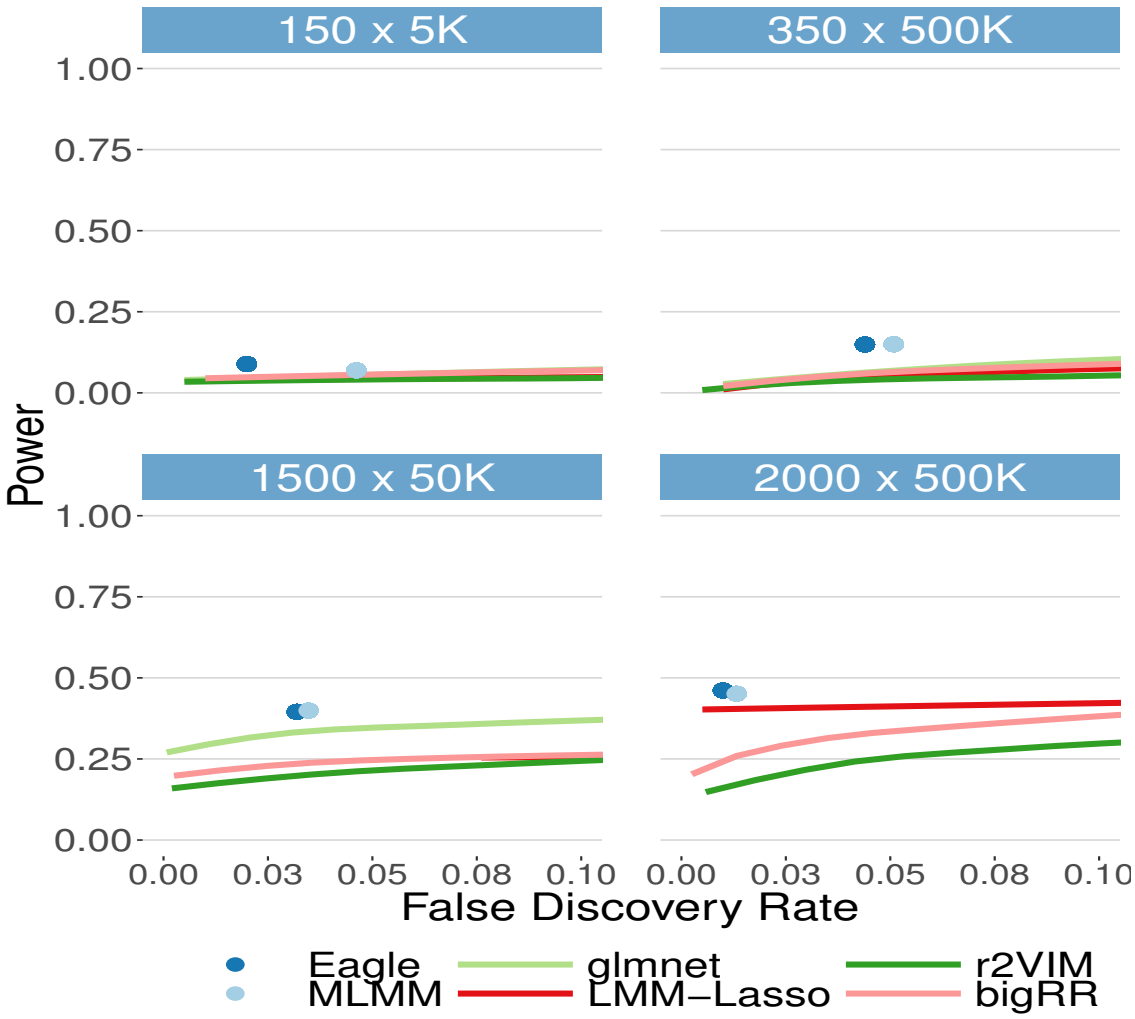
[d] For the different types of model, LMM is linear mixed model. GLM is generalised linear model., GLMM is generalised linear mixed model, and RF is random forests.

[e] Association is assessed a SNP at a time (single), for multiple SNPs (multiple), or for all SNPs (all). Eagle fits all SNPs but also identifies multiple SNPs (All/multiple) in association with the trait.

Supplementary Table 2: New findings for the analysis of the mouse data. Given is the trait for which the new SNP-trait association was found (Trait), the chromosome (Chrm) and map position in megabases (Position) for the SNP, and the list of other traits for which this SNP is known to be in association (Known Associations).

Method	Trait	Chrm	Position (Mb)	Known Associations
Eagle^{alt}	Bioch.HDL	6	17.53	Muscles.Sol.g Muscles.TA.g Muscles.Plant.g Muscles.EDL.g Muscles.Gast.g SPPI.ln.pa Bioch.Calcium Bioch.Tot.Cholesterol Bioch.Tot.Protein Bioch.Albumin
	Bioch.LDL	6	17.53	Muscles.Sol.g Muscles.TA.g Muscles.Plant.g Muscles.EDL.g Muscles.Gast.g SPPI.ln.pa Bioch.Calcium Bioch.Tot.Cholesterol Bioch.Tot.Protein Bioch.Albumin
Eagle^{optimal}	Bioch.Tot.Cholesterol	4	134.58	FACS.CD3posCD44posCD4CD8Ratio
	Bioch.HDL	4	134.58	FACS.CD3posCD44posCD4CD8Ratio
		6	17.53	Muscles.Sol.g Muscles.TA.g Muscles.Plant.g Muscles.EDL.g Muscles.Gast.g SPPI.ln.pa Bioch.Calcium Bioch.Tot.Cholesterol Bioch.Tot.Protein Bioch.Albumin
	BMC.Mean	15	86.57	BMC.Median
	BMC.Mean.N	5	24.64	BMC.Mean BMC.StdDev BMC.StdDev.N BMC.Max.N BMC.Median BMC.Kurt BMC.Max BMC.Kurt.N
	BMC.Max.N	15	86.57	BMC.Median
	Bioch.LDL	6	17.53	Muscles.Sol.g Muscles.TA.g Muscles.Plant.g Muscles.EDL.g Muscles.Gast.g SPPI.ln.pa Bioch.Calcium Bioch.Tot.Cholesterol Bioch.Tot.Protein Bioch.Albumin

Supplementary Figure 1: Power verse false discovery rates for Eagle and the multi-locus methods. Plots for only those simulation scenarios where all multi-locus methods could be implemented are shown. Eagle has the highest power across the four scenarios but MLMM also performs well. A false discovery rate of greater than 10% is typically not employed in GWASs so the upper limit of the x-axis is 0.1.



Supplementary Figure 2: Memory usage (in gigabytes) of Eagle and the other association mapping programs/packages across the six simulation scenarios. The maximum amount of memory on the computer is 128 gigabytes. The x-axis is on the log scale. GEMMA, a single-locus implementation, had the lowest memory usage. Of the multi-locus implementations, Eagle had the lowest memory usage. Also, it was the only multi-locus implementation able to produce results for data under scenario 10000 x 1.5M. This is due to its ability to handle data larger than the available memory of a computer. FaST-LMM was run where all the SNP data are used to estimate the relationship matrix (FaST-LMM^{all}) and where genotype data from every five-hundredth SNP are used to estimate the relationship matrix (FaST-LMM^{few})

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