



Efficient Algorithms for Multivariate Linear Mixed Models in Genome-wide Association Studies

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(Submitted on 19 May 2013)

Multivariate linear mixed models (mvLMMs) have been widely used in many areas of genetics, and have attracted considerable recent interest in genome-wide association studies (GWASs). However, existing methods for calculating the likelihood ratio test statistics in mvLMMs are time consuming, and, without approximations, cannot be directly applied to analyze even two traits jointly in a typical-size GWAS. Here, we present a novel algorithm for computing parameter estimates and test statistics (Likelihood ratio and Wald) in mvLMMs that i) reduces per-iteration optimization complexity from cubic to linear in the number of samples; and ii) in GWAS analyses, reduces per-marker complexity from cubic to approximately quadratic (or linear if the relatedness matrix is of low rank) in the number of samples. The new method effectively generalizes both the EMMA (Efficient Mixed Model Association) algorithm and the GEMMA (Genome-wide EMMA) algorithm to the multivariate case, making the likelihood ratio tests in GWASs with mvLMM possible, for the first time, for tens of thousands of samples and a moderate number of phenotypes (<10). With real examples, we show that, as expected, the new method is orders of magnitude faster than competing methods in both variance component estimation in a single mvLMM, and in GWAS applications. The method is implemented in the GEMMA software package, freely available at [this http URL](#)

Subjects: **Quantitative Methods (q-bio.QM)**; Applications (stat.AP); Computation (stat.CO)

Cite as: **arXiv:1305.4366 [q-bio.QM]**
(or **arXiv:1305.4366v1 [q-bio.QM]** for this version)

Submission history

From: Xiang Zhou [[view email](#)]
[v1] Sun, 19 May 2013 14:53:48 GMT (307kb,D)

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