Efficient Bayesian mixed-model analysis increases association power in large cohorts

Loh et al. 2015. Nature Genetics

April 21, 2015

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- LMMs can reduce the false discovery rate by accounting for pseudo-replication
- LMMs can be computationally expensive, $O(MN^2)$ or $O(M^2N)$

Standard LMM

The standard LMM takes the form:

$$y_i = x_i\beta + \sigma_G^2 K + \sigma_E^2 I$$

Where y_i is the phenotype of individual i, xi are the covariates of interest (SNPs, age, etc.), σ_G^2 is the variance due to genetic similarity, K is the *genetic similarity matrix (GSM)*, E is the variance due to environment (chance), and I is the NxN identity matrix.

- The GSM (K) accounts for the hierarchical structure of the data and can be estimated in various ways
- The $\sigma_E^2 I$ term is similar to a typical regression error term

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- Assumes linearity in the parameters (β)

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2. Use score test to compute test statistics for each SNP

$$\chi_1^2 = \frac{\left(x'_{SNP} V^{-1} y\right)^2}{x'_{SNP} V^{-1} x_{SNP}}$$

where V is the $cov(y) = \sigma_G^2 K + \sigma_E^2 I$

(Some models use simultaneous likelihood ratio tests to achieve exact statistics)

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  3. Gaussian mixture extension to accommodate heterogeneous effect sizes
- Not purely Bayesian – actual test statistic is frequentist

Calibration Factor: c_{inf}

The BOLT_LMM statistic (for infinitesimal model)

$$\chi_1^2 = \frac{\left(x'_{SNP} V_{LOCO}^{-1} y\right)^2}{c_{inf}}$$

where,

$$c_{inf} = \frac{\text{mean}\left(x'_{SNP} V_{LOCO}^{-1} y\right)^2}{\text{mean}\chi_1^2}$$

This statistic is similar to others (GRAMMAR-gamma and MASTOR) but avoids proximal contamination via the LOCO approach.

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  - The test statistic uses residuals where other effects have been "conditioned out"
  - Less noise = more power to detect a signal
  - Can manipulate the model producing the residual without changing the test statistic
- The test statistic is still a quasi-likelihood score so is asymptotically χ^2

The Bayesian Part

Assume the effects, β have a distribution:

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- The general (heterogeneous effects) model utilizes a Gaussian mixture:

$$\beta \sim N(0, \sigma_{\beta,1}^2) \text{ with probability } p$$

$$\beta \sim N(0, \sigma_{\beta,2}^2) \text{ with probability } 1 - p$$

  If p is small and $\sigma_{\beta,2}^2$ is much smaller than $\sigma_{\beta,1}^2$ you will get a many βs of small (near 0) effect and a few of large effect.

From Bayesian to Frequentist

The method uses Bayesian model to obtain a frequentist statistic:

- First fit the Bayesian mixture model
- Calculate the posterior mean to obtain the residual
- Use the residual to calculate the χ^2 statistic

Computational Efficiency

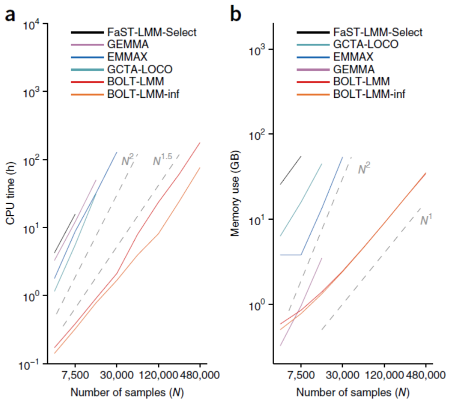
Table 1 Comparison of fast mixed-model association methods that model all SNPs

Method[a]	Requires $O(MN^2)$ time	Avoids proximal contamination	Models non-infinitesimal genetic architecture
EMMAX (ref. 3)	X		
FaST-LMM (ref. 5)	X[b]	X	
FaST-LMM-Select (refs. 9,11,15)	X[b]	X	X[c]
GEMMA (ref. 6)	X		
GRAMMAR-Gamma (ref. 10)	X[d]		
GCTA-LOCO (ref. 12)	X	X	
BOLT-LMM		X	X

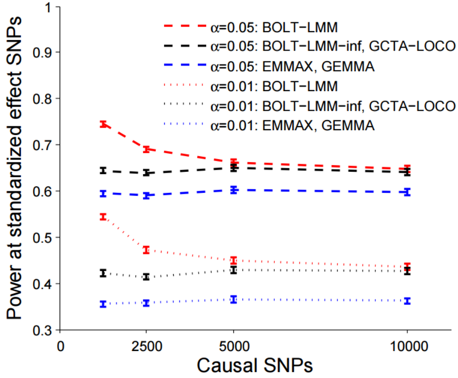
- Computes on $\sim O(MN)$ time
- Avoids proximal contamination by borrowing methods from GCTA-LOCO
- Accommodates non-infinitesimal genetic architecture

Computational Efficiency

- Fastest of the group*
- CPU time scales to $\sim O(MN^{1.5})$
- Memory use scales to $\sim O(MN)$



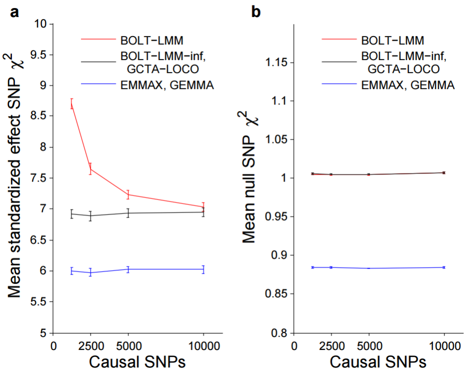
Simulations



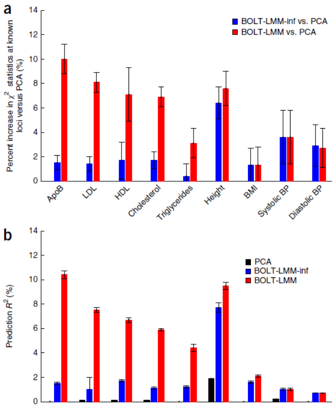
- Increased power especially when the number of causal SNPs is small
- Increased power is stable at various α levels (consistent with theory)
- BOLT-LMM is virtually identical to GCTA-LOCO under infinitesimal architecture assumption

Simulations

- Effective false positive control
- Large gains in power with small number of causal SNPs
- No associated increase in type I error with power increase



Women's Genome Health Study



- Similar increases in power in non-simulated data
- Power increases are not homogeneous (as predicted by theory)
- Substantial increases in predictive ability

Comments from the Peanut Gallery

- Not sure about mixing Bayesian and Frequentist paradigms
- Room to improve the modelling of genetic architecture
- Carry the Bayesian theme through to the test statistic to get a credible interval

Questions?