

A Bayesian framework for generalized linear mixed modeling identifies new loci for late-onset Alzheimer's disease

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Methods

Overview of the statistical models

Bayes-GLMM implemented generalized linear mixed models in the Bayesian framework. Bayesian models are defined by two parts: (1) a likelihood function that describes the data-generating process, and (2) the prior distributions of model parameters. Bayes-GLMM took linear regression model (LM), logistic regression model (logit-LM), and ordered logistic regression model (ordered-logit-LM) as likelihoods functions of numerical, binary, and categorical traits respectively.

Linear mixed models

In LM, the numerical response variable Y_i was modeled in the linear mixed model scheme.

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$$Y = \mathbf{X}\beta + g\beta_0 + u + e \quad (1)$$

$$u \sim mvN(0, \sigma K) \quad (2)$$

$$e \sim N(0, \sigma_e I) \quad (3)$$

$$\beta \sim N(0, 1) \quad (4)$$

$$\beta_0 \sim N(0, 1) \quad (5)$$

$$\sigma \sim inv_gamma(2, 1) \quad (6)$$

$$\sigma_e \sim inv_gamma(2, 1) \quad (7)$$

In the above equations, X was a n by m covariate matrix with n the sample size and m the number of conditional variables. β was the corresponding parameter vector in length m . g was the numerical genotype of a variant with 0 to 2 representing homozygous reference alleletype, heterozygous, and homozygous alternative alleletype. β_0 was the variant's effect size. A standard normal, $N(0, 1)$, was used for β_0 of variants with no known effects. Further, β followed $N(0, 1)$ in prior, σ and σ_e followed inverse gamma distribution in priors.

To model the sample relatedness, u was included as a random term that followed a multivariate normal distribution, $mvN(0, \sigma K)$ in prior, with expected mean vector 0 and covariance matrix σK . σ was the variance component. K was the kinship matrix of the samples. $mvN(0, K)$ was parameterized by the Cholesky factoring of K and n independent standard normal distributions.

$$u = L * z \quad (8)$$

$$L = Chol(K) \quad (9)$$

$$z \sim mvN(0, \sigma I) \quad (10)$$

Generalized linear mixed models for binary variables

In logit-LM, the 0/1 response variable Y_i followed a binomial distribution with a scalar parameter π representing the probability that Y_i equaled 1. π was further transformed by the logit function and modeled in the linear model scheme.

$$\pi = P(Y_i = 1) \quad (11)$$

$$\text{logit}(\pi) = \mathbf{X}\beta + g\beta_0 + u \quad (12)$$

$$\beta \sim N(0, 1) \quad (13)$$

$$\beta_0 \sim N(0, 1) \quad (14)$$

$$u \sim mvN(0, \sigma K) \quad (15)$$

$$\sigma \sim inv_gamma(2, 1) \quad (16)$$

Generalized linear mixed models for ordered-categorical variables

In ordered-logit-LM, the ordered categorical response variable Y_i with J levels followed a multinomial distribution with a vector of parameters π , where π_{ij} represents the probability that the i th observation falls in response category j . Cumulative distribution of π was logit-transformed and modeled in the linear model scheme.

$$P(Y_i \leq j) = \pi_{i1} + \dots + \pi_{ij} \quad (17)$$

$$\text{logit}(P(Y_i \leq j)) = \theta_j - \mathbf{X}\beta - g\beta_0 + u \quad j = 1, \dots, J - 1 \quad (18)$$

$$\theta = 10 * cumsum(\theta_0) \quad (19)$$

$$\theta_0 \sim dirichlet(1) \quad (20)$$

$$\beta \sim N(0, 1) \quad (21)$$

$$\beta_0 \sim N(0, 1) \quad (22)$$

$$u \sim mvN(0, \sigma K) \quad (23)$$

$$\sigma \sim inv_gamma(2, 1) \quad (24)$$

θ_j modeled the distances between the categories by providing each category an unique intercept. θ was defined as ten times the cumulative sum of a multivariate variable θ_0 , where θ_0 followed a $J - 1$ dimension Dirichlet distribution in prior.

Modeling the prior information of variant effects

To integrate prior information of variant effects, Bayes-GLMM implemented an approach that allowed priors to only modulate information of the data under study. In this method, prior distribution of variant effect was modeled by a hierarchical model, $\beta_0 \sim N(t * \sigma_0, \sigma_0)$, in which t represented prior information of the given variant. t was further modeled by a normal distribution with expected mean the standardized effect size *prior* and unit deviation. *prior* was defined by the

variant's prior effect size divided by its standard error, which was often reported by published GWAS. A standard normal, $N(0, 1)$, was used for β_0 of variants with no known effects. Further, β followed $N(0, 1)$ in prior.

$$\beta_0 \sim N(t * \sigma_0, \sigma_0) \quad (25)$$

$$t \sim N(\text{prior}, 1) \quad (26)$$

$$\sigma_0 \sim \text{inv_gamma}(2, 1) \quad (27)$$

We found this method of using priors appealing in three aspects: (1) it standardized the different interpretations of effect size from different statistical models; (2) it took information on both effect size and its standard error; (3) it softened the strong weight of priors from big studies.

Model estimations

Our models were built under Stan, which provides a flexible and efficient programming environment for statistical modeling. Inherited from Stan, Bayes-GLMM supported two methods for parameter estimation, L-BFGS maximal likelihood estimation (MLE) and Hamilton Markov chain Monte Carlo (HMC) sampling. MLE method made a point estimation for each parameter that maximized the joint posterior of model parameters, whereas MCMC sampling method captured a full posterior distribution for each parameter by iterative sampling. Significance of the estimated effect size β_0 can be accessed by combining β_0 and its standard error $SE(\beta_0)$. Standard errors of MLE were computed as the inverse of the square root of the diagonal elements of the observed Fisher Information matrix (Pawitan, 2001). In MCMC sampling, $SE(\beta_0)$ was computed directly from the samples. A standardized z value was computed as $\beta_0/SE(\beta_0)$, which led to a P-value that quantified the probability of obtaining the β_0 by chance.

$$SE(\hat{\theta}_{ML}) = \frac{1}{\sqrt{I(\hat{\theta}_{ML})}} \quad (28)$$

$$I(\theta) = -\frac{\partial^2}{\partial \theta_i \partial \theta_j} l(\theta) \quad 1 \leq i, j \leq p \quad (29)$$

$\hat{\theta}_{ML}$ was MLE of model parameters. $I(\theta)$ was the Fisher Information matrix. p was the number of parameters.

In genetic association studies, comparing the two nested null and full models was a widely used method to estimate the significance of a variant. The full models were the same as described above whereas the null models ignored the variant, g , as a linear predictor. In MLE, the null to full model improvements was quantified by LRT, which equals two times the log likelihood difference between the full and null models using the MLE estimation of model parameters.

$$LRT = -2 \cdot (\log(P(data|\theta_p^n)) - \log(P(data|\theta_p^f))) \quad (30)$$

θ_p^n and θ_p^f were the MLE of the parameter spaces under the null and full models, respectively.

Kinship matrix

We used u as a random term to account for the sample relatedness. u follows $mvNormal(0, \sigma K)$, where K was the kinship matrix of the samples. For each K entry, genotype-based relatedness for the sample pair, or IBS coefficient, was computed using the full spectrum of genomic variants in the ADSP samples. PLINK was used for fast kinship estimation on the massive genotype data.

$$k_{i,j} = \frac{1}{M} \sum_{m=1}^M (g_{m,i} \cdot g_{m,j} + (1 - g_{m,i}) \cdot (1 - g_{m,j})) \quad (31)$$

$k_{i,j}$ is the IBS relatedness between sample i and j . M is the variant number. $g_{m,i}$ and $g_{m,j}$ is the genotype of variant m in sample i and j , respectively.

Linear mixed models in the frequentist scheme

To compare the performances of our method to that of a LMM in the frequentist scheme in analyzing the ADSP dataset, we built a LMM as follow:

$$y_i = \mathbf{X}_i \beta + u + e \quad (32)$$

$$u \sim mvN(0, \delta_g^2 K) \quad (33)$$

$$e \sim N(0, \delta_e^2 I) \quad (34)$$

y_i was the numerical transformation of the AD categories: no/0, possible/0.25, probable/0.5, definite/1. X was the covariate matrix including age and sex. u was the random term. e was the model residual. The LMM model was estimated with QTLRel in R (Cheng et al., 2011).

Code availability

We deployed Bayes-GLMM as a GitHub repository for public use (<https://github.com/xulong82/bayes.glmm>).