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Applications Note

Genetics and population analysis

bWGR: Bayesian whole-genome regression

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Abstract

Motivation: Whole-genome regressions methods represent a key framework for genome-wide prediction, cross-validation studies and association analysis. The bWGR offers a compendium of Bayesian methods with various priors available, allowing users to predict complex traits with different genetic architectures.

Results: Here we introduce bWGR, an R package that enables users to efficient fit and cross-validate Bayesian and likelihood whole-genome regression methods. It implements a series of methods referred to as the Bayesian alphabet under the traditional Gibbs sampling and optimized expectation-maximization. The package also enables fitting efficient multivariate models and complex hierarchical models. The package is user-friendly and computational efficient.

Availability and implementation: bWGR is an R package available in the CRAN repository. It can be installed in R by typing: `install.packages('bWGR')`.

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Supplementary information: Supplementary data are available at *Bioinformatics* online.

1 Introduction

Genome-wide markers have been increasingly deployed for the prediction of complex traits since the concept of genomic prediction was introduced (Meuwissen *et al.*, 2001). Whole-genome regression (WGR) methods predict traits as a linear combination of marker effects that capture quantitative trait loci and the relationship among individuals (Habier *et al.*, 2007). A large variety of models exist, each with different prior assumptions that are optimized for a specific genetic architecture (de los Campos *et al.*, 2013). Evaluating the parameterizations of genomic information in prediction models to suit different genetic architectures can enhance prediction accuracy.

Few statistical packages enable genome-wide prediction, including rrBLUP, BGLR and VIGoR (Endelman, 2011; Onogi and Iwata, 2016; Pérez and de los Campos, 2014). Genome-wide models are sensitive to the algorithm implementation, such that two implementations of the same model often lead to reasonably different results (Gianola *et al.*, 2009; Lehermeier *et al.*, 2013). In a user-friendly framework, the bWGR package implements a compendium of likelihood and Bayesian methods, via expectation-maximization (EM) and Markov Chain Monte Carlo (MCMC), at univariate and multivariate level (see Supplementary Material for details). It also implements a mixed model solver that enables modeling replicated observations, computing marker effects using link functions and accounting for nuisance parameters (Fig. 1).

2 MCMC methods

MCMC methods constitute the most popular set of WGR (Gianola, 2013). These include Bayesian Ridge Regression, BayesA, BayesB (Meuwissen *et al.*, 2001), BayesC, BayesCpi, BayesDpi (Habier *et al.*, 2011), Bayesian LASSO (Park and Casella, 2008) and Reproducing Kernel Hilbert Spaces (RKHS) regression (de los Campos *et al.*, 2010). The variable selection of BayesB and BayesC was implemented through Gibbs Sampling unconditional prior (Kuo and Mallick, 1998) and Metropolis-Hasting for BayesCpi and BayesDpi. In our models, the prior specifications are similar but not identical to the BGLR package (Pérez and de los Campos, 2014). We kept the models less hierarchical like those originally proposed by Meuwissen *et al.* (2001), with restricted Bayesian learning (Lehermeier *et al.*, 2013) to avoid under- and over-regularization. These methods can be performed either from bWGR's generalized function 'wgr' or by their standalone implementation written entirely in C++ (Eddelbuettel *et al.*, 2011). The generalized function 'wgr' enable users to combine a WGR with a kernel method, such as combining BayesB and RKHS. It also has an exclusive feature as it enables the subsampling of Markov chains to save time and computational power (Xavier *et al.*, 2017).

3 EM methods

EM methods provide an elegant and efficient way to reduce the computation time due to MCMC iterations (Shepherd *et al.*, 2010). Iterative procedures may replace Gibbs sampling by updating parameters with the expectation as opposed to sampling and averaging the posteriors. This algorithmic variation of the traditional MCMC solver of the Bayesian methods was proposed by Meuwissen *et al.* (2009). These EM Bayesian methods can calibrate WGR without loss in accuracy (Lopez *et al.*, 2019). From the Bayesian alphabet implemented via EM, the package provides

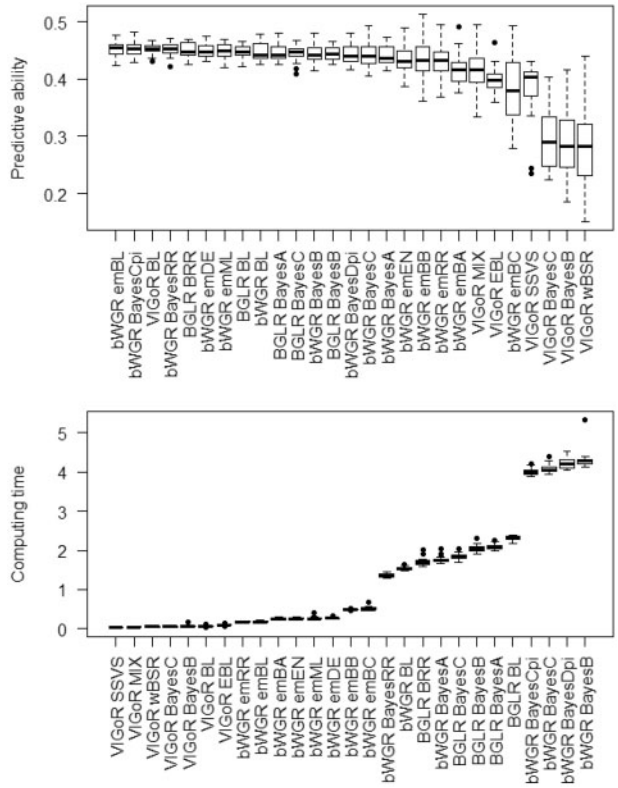

Fig. 1. Comparison between bWGR, BGLR and VIGoR packages. Predictive ability (top) as the correlation between predicted and observed values and computing time (bottom) in seconds to fit a WGR, 5-fold cross-validation repeated 20× on the wheat dataset available on the BGLR package

implementations of BayesA ('emBA'), BayesB ('emBB'), BayesC ('emBC') and Bayesian Lasso ('emBL'). The package also includes a Gaussian maximum likelihood ('emML') and an elastic-net ('emEN') and the fast Laplace model ('emDE'; Xavier, 2019).

To facilitate cross-validation studies, the bWGR implements 'emCV' and 'mcmcCV' which allow k-fold cross-validations and leave-a-level-out cross-validation, where the cross-validations are performed on the phenotypes or true breeding values, if provided.

4 Multivariate methods

The package provides a ridge-type ('mrr') and kernel-type ('mkr') function for multivariate regressions that enable simultaneous modeling of two or more response variables. Both implementations were based on an efficient Gauss-Seidel (Legarra and Misztal, 2008) paired with an efficient first-derivative estimation of EM-REML like variance components (Schaeffer, 1986) written in C++. These implementations are fast and memory efficient by avoiding explicit matrix inversion or Kronecker products, also robust to a relatively large number of traits and accept missing values. The multivariate regression functions do not offer the modeling flexibility of other packages but the computation time to fit the model is ~8% of those fit with REML implementations (Gilmour *et al.*, 1995; Covarrubias-Parazan, 2016) and without the burden of MCMC methods (Hadfield, 2010; Montesinos-López *et al.*, 2019).

5 Hierarchical mixed models

The functions implemented via MCMC and EM enable simple models with one or two random effects. For more complex models, the function 'mixed' enables fitting models with multiple fixed and random effects, with or without marker information through link functions.

Design to be a multi-purpose function, users can use the 'mixed' function to run a wide range of models, from phenotypic analysis to single-step models. The function can estimate best linear unbiased predictors (BLUPs), marker effects and variance components, while accounting for environmental factors and other nuisance parameters.

6 Additional tools

The bWGR package is a self-coined toolbox for genetic analysis. In this section we will briefly describe some of the key additional functions.

6.1 Relationship matrices

'GRM' creates the genomic relationship described by VanRaden (2008) and 'GAU' generates a Gaussian kernel often deployed for RKHS regression (de los Campos *et al.*, 2010).

6.2 Genotyping imputation

'markov' implements a forward Markov model that accounts for the linkage disequilibrium among neighbor markers, and 'IMP' imputes missing values with the expected value of the marker (marker average).

6.3 Spatial analysis

Providing field coordinates and phenotype, the spatial covariate function 'SPC' creates covariates on neighbor plots (Lado *et al.*, 2013). The 'SPM' function generates a design matrix for spatial adjustment (Gilmour *et al.*, 1995; Muir, 2005).

6.4 Miscellaneous

'CNT' centralizes markers for a better blending a posteriori and unbiasedness. 'SibZ' creates a WGR-compatible matrix from pedigree. 'emGWA' runs a ridge regression coupled with genome-wide association studies that outputs values for prediction and inference.

6.5 Two random effects

Hybrid breeding models often fit two random terms, such as Additive-Dominance and Parent1-Parent2. Besides the function 'mixed', simpler stand-alone functions that can handle two random effects include: 'BayesA2', 'BayesB2', 'BayesRR2', 'emML2', 'mrr2X' and 'mkr2X'.

7 Conclusions

The bWGR package has implemented a series of WGR methods in Bayesian framework that covers a variety of priors to enable accurate genome-wide prediction of complex traits across various genetic architectures. Implementations are available in the traditional MCMC framework as well as efficient EM methods. The package also enables efficient multivariate and hierarchical modeling. The package focuses on statistically sound methodologies implemented for high computational performance and prediction accuracy.

Conflict of Interest: none declared.

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