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Activity: Abstract

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Genetic association models are robust to common population kinship estimation biases.
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Abstract:

Common genetic association studies for structured populations, including Principal Component Analysis (PCA) and Linear Mixed-effects Models (LMM), model the correlation structure between individuals using population kinship matrices, also known as Genetic Relatedness Matrices or "GRMs". However, the most common kinship estimators can have severe biases that were only recently characterized. Here we characterize the effect of these kinship biases on genetic association. We employ a large simulated admixed family and genotypes from the 1000 Genomes Project, both with simulated traits, to evaluate a variety of kinship matrices (every bias type has two locus weight types, and their theoretical limits for the simulation). Remarkably, we find nearly equal association statistics and performance for kinship matrices of different bias types (when all other features are matched). These empirical observations lead us to hypothesize that these association tests are invariant to these kinship biases, which using linear algebra we prove holds exactly for LMM and approximately for PCA. Our constructive proof shows that the intercept and relatedness (PCs in PCA, random effect in LMM) coefficients compensate for the kinship bias, so the result extends to generalized linear models as long as those coefficients are present and are nuisance parameters. Overall, we find that existing association studies are robust to kinship estimation bias, and our theoretical results may help improve association methods by taking advantage of this unexpected robustness, as well as help determine the effects of kinship bias in other settings.

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