Bivariate linkage analysis for mapping quantitative trait loci in pedigrees: Comparison of methods and assessment of the test statistics distributions in the NEMO study.

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The use of correlated phenotypes may increase the power to map the underlying quantitiative loci (QTL). One popular approach is the multivariate variance components, a generalization of the univariate variance components method [Amos, 1994; Blangero et al, 1997]. Several issues make the linkage analysis of multiple phenotypes more complicated than those of univariate phenotypes. The asymptotic distributions of the multivariate variance components methods are subtle and nontrivial, mainly because of the dimension reduction of the parameter space under the null hypothesis and the non-negative constraints on some of the linkage components. Existing claims are indeed contradictory [Almasy et al, 1997, de Andrade et al, 1997; Amos et al, 2001] and some might be erroneous [Wang K, 2002; Mangin, personnal communication]. Further, estimation, through simulations, of the null distribution faces the problem of extensive time-consuming computations, especially in extended pedigrees and when using multiple markers. As a consequence, multivariate linkage studies have most often relied on assumed asymptotic distributions rather than on empirical ones. Other approaches, as Principal Component Analysis, permit to reduce the dimensionality of the data. Multivariate linkage test can be computed using the SPC test [Mangin et al, 1998], which is the sum of independent univariate tests of new phenotypes (linear combinations of raw phenotypes). In practice, however, linkage studies using data reduction techniques have often relied on the significance of the best univariate finding and ignored the multi-test problem. Here, we have applied different multivariate linkage tests to detect QTLs for Bone Mineral Density, measured at the lumbar spine and at the femoral Neck, in NEMO data (103 extended pedigrees). Extensive simulation studies were conducted to study the empirical performances of variance-components and PCA-based linkage tests. Efficient estimates of the empirical distributions were obtained by simulating 12,000 replicates of NEMO data under the null hypothesis. Our analyses highlighted the problem of interpreting nominal p-values of bivariate variance-components linkage tests: some of the suggested theoretical distributions resulted to be too liberal while others were found quite conservative. Our results also showed that in the NEMO data both variance components and PCA approaches have similar performances, advocating thus for the use of data-reduction techniques.

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