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## Multivariate enrichment test for 3D chromatin domain border analysis

Recent advances in genome-wide chromatin interaction mapping have revealed the importance of 3D structure of chromosomes in gene regulation and expression. The next challenge is to identify what are the key molecular drivers of this 3D structure. Several architectural proteins were shown to be enriched at the borders of topological domains, and thus represent good candidates. Simple univariate enrichment approaches such as Fisher's exact or Pearson's chi-squared tests were used for this purpose and there is thus a need for more sophisticated multivariate enrichment methods that could account for potential colocalizations and interactions between architectural proteins. Here we propose a multiple logistic regression model to assess multivariate enrichment of genomic features such as DNA-binding proteins and functional genomic regions at topological domain borders. The proposed method naturally deals with colocalization and interaction. Using simulations, we demonstrate the accuracy of the method to estimate enrichments of marginal features (no interactions) as well as two-way interactions. On real *Drosophila* data, we show the importance of considering all tested genomic features and their potential interactions within the same multivariate framework. Compared with univariate analysis, multivariate analysis reveals huge differences of enrichments among the insulator binding proteins. For instance, multivariate analysis highlights the importance of insulator binding protein Fs(1)h-L whose enrichment is the highest among the IBPs, and that was recently shown to mediate intra- or inter-chromosome interactions. In addition, analysis of interactions between insulator binding proteins and cofactors reveals that they tend to work separately at topological domain borders.

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