POEM: Identifying joint additive effects on regulatory circuits

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ABSTRACT

Motivation: Expression Quantitative Trait Locus (eQTL) mapping tackles the problem of identifying variation in DNA sequence that have an effect on the transcriptional regulatory network. Major computational efforts are aimed at characterizing the joint effects of several eQTLs acting in concert to govern the expression of the same genes. Yet, progress towards a comprehensive prediction of such joint effects is limited. For example, existing eQTL methods commonly discover interacting loci affecting the expression levels of a module of co-regulated genes. Such 'modularization' approaches, however, are focused on epistatic relations and thus have limited utility for the case of additive (non-epistatic) effects.

Results: Here we present POEM (Pairwise effect On Expression Modules), a methodology for identifying pairwise eQTL effects on gene modules. POEM is specifically designed to achieve high performance in the case of additive joint effects. We applied POEM to transcription profiles measured in bone marrow-derived dendritic cells across a population of genotyped mice. Our study reveals widespread additive, trans-acting pairwise effects on gene modules, characterizes their organizational principles, and highlights high-order interconnections between modules within the immune signaling network. These analyses elucidate the central role of additive pairwise effect in regulatory circuits, and provide computational tools for future investigations into the interplay between eQTLs.

Availability: The software described in this article is available at csgi.tau.ac.il/POEM/.
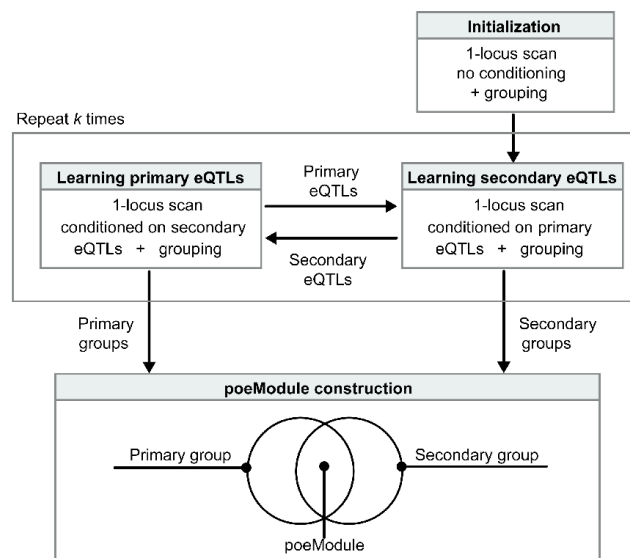
Figure: Overview of the POEM algorithm. POEM takes as input a collection of expression traits from a certain population of genotyped individuals. The procedure is initiated with a non-conditioned scan (top right). The analysis then consists of two iterative stages: learning primary eQTLs after conditioning on the secondary eQTLs and vise versa (middle). The two steps are repeated k times. POEM relies on grouping of the expression traits based on their co-association to the primary and secondary eQTLs. Significant overlaps between the resulting primary and secondary groups are referred to as 'poeModules' (bottom). Such poeModules are interpreted as promising pairwise effects that act on the same group of traits.