A203 · Airqtl dissects cell state-specific causal gene regulatory networks with efficient single-cell eQTL mapping

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Single-cell expression quantitative trait loci (sceQTL) mapping offers a powerful approach for understanding gene regulation and its heterogeneity across cell types and states. It has profound applications in genetics and genomics, particularly causal gene regulatory network (cGRN) inference to unravel the molecular circuits governing cell identity and function. However, computational scalability remains a critical bottleneck for sceQTL mapping, prohibiting thorough benchmarking and optimization of statistical accuracy. We present Airqtl, an efficient method to overcome these challenges through algorithmic advances and efficient implementations of linear mixed models. Airqtl achieves superior time complexity and over 10^8x acceleration, enabling objective method benchmarking and optimization. Airqtl offers de novo inference of robust, experimentally validated cell state-specific cGRNs that reflect perturbation outcomes. Our results dissect the drivers of cGRN heterogeneity and underscore the value of natural genetic variations in primary human cell types for biologically relevant single-cell cGRN inference.

We further extend Airqtl to single-cell chromatin accessibility QTL (sccaQTL) mapping using scATAC-seq data, tailored to a nearly binary read count matrix and extreme data sparsity. Preliminary results demonstrate genome-wide sccaQTL mapping within ten hours on standard GPU hardware, achieving sufficient power to detect thousands of cis- and trans-sccaQTLs with a highly controlled Type I error rate. This framework enables reconstruction of a combined gene and chromatin accessibility network, revealing alternative promoter and enhancer usage together with expression-related changes in global chromatin accessibility.