A175 · SIMBA+: Interpreting GWAS through single-cell multiomic graphs identifies disease-relevant genes and cell states

Presenter: Junxi Feng — University of California, San Diego

Authors: Jayoung Ryu, Junxi Feng, Elizabeth Dorons, Karthik Guruvayurappan, Anatori Prieto, Zixuan Eleanor Zhang, Kushal Dey, Steven Gazal, Martin Jinye Zhang, Luca Pinello

Session: Day 1 · Thu Oct 1, 2026 · 2:15–4:15 PM

Translating genome-wide association study (GWAS) signals into causal variant mechanisms remains a major challenge. We present SIMBA+, a probabilistic graph framework that integrates single-cell multiomic data with GWAS to identify variant target genes and the cellular contexts in which regulatory effects occur. SIMBA+ constructs a unified knowledge graph linking cells, genes, and regulatory elements, learns low-dimensional node representations, and uses metapath-based relationships to score variant–gene–cell associations. This representation jointly captures regulatory connectivity and cellular heterogeneity, enabling genetic associations to be interpreted within specific cell states rather than only at bulk or cell-type-averaged resolution. Applied to atopic dermatitis, SIMBA+ revealed cell-specific regulatory mechanisms, including disease-associated variants linked to CSF2RB in monocytes and NLRP3 in CD14+ populations. Systematic benchmarking showed that SIMBA+ outperformed existing approaches for identifying target genes of variants and regulatory elements in both cell-type-specific and cell-type-agnostic settings, with stronger enrichment for eQTL-supported and CRISPR-validated regulatory links, particularly for distal interactions. Beyond variant-to-gene mapping, SIMBA+ leverages its learned latent factors to decompose trait heritability at single-cell resolution. Applying SIMBA+ to 75 complex traits across three single-cell multiome atlases spanning 19 tissues, including blood and bone marrow, identified disease-relevant cell states among hundreds of cell populations, uncovered trait-associated regulatory programs missed by pseudobulk analyses, and generated single-cell-resolution estimates of heritability. These capabilities enable mechanistic interpretation across scales, from individual variants to complex trait architecture. Together, SIMBA+ provides a unified framework for connecting genetic variation to regulatory mechanisms, target genes, and disease-relevant cellular states, advancing interpretation of GWAS findings at single-cell resolution.