Speaker: Liana Lareau

Affiliations: University of California, Berkeley

Title: Identifying cell state associated alternative splicing events and their co-regulation

Abstract: Alternative splicing shapes the transcriptome and contributes to each cell's unique identity, but single-cell RNA sequencing has struggled to capture the impact of alternative splicing. We have shown that low recovery of mRNAs from single cells led to erroneous conclusions about the cell-to-cell variability of alternative splicing. Building on this, we present a method, Psix, to confidently identify splicing that changes across a landscape of single cells, using a probabilistic model that is robust against the data limitations of scRNA-seq. Its autocorrelation-inspired approach finds patterns of alternative splicing that correspond to patterns of cell identity, such as cell type or developmental stage, without the need for explicit cell clustering, labeling, or trajectory inference. Applying Psix to data that follow the trajectory of mouse brain development, we identify exons whose alternative splicing patterns cluster into modules of co-regulation. We show that the exons in these modules are enriched for binding by distinct neuronal splicing factors, and that their changes in splicing correspond to changes in expression of these splicing factors. Thus, Psix reveals cell-type-dependent splicing patterns and the wiring of the splicing regulatory networks that control them. Our new method will enable scRNA-seq analysis to go beyond transcription to understand the roles of post-transcriptional regulation in determining cell identity.