A061 · An XOR-based framework for detecting mutually exclusive gene modules in single-cell data

Presenter: Irzam Sarfraz — Boston University Chobanian & Avedisian School of Medicine (CAMED), Boston, MA, United States

Authors: Irzam Sarfraz, Joshua D. Campbell

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Objective: Reliable cell-type markers must be specific and sensitive, but standard differential-expression methods often fail to quantify how well markers partition cells into distinct populations. This is especially pronounced in cancers, where clustering is often dominated by patient identity rather than shared biological state. Cells within a cluster remain heterogeneous, and a program of interest, such as a cancer-associated program, may be active in subsets of cells across multiple samples and clusters. Because such programs cut across standard cluster partitioning, our objective is to isolate them independently of predefined cluster boundaries. Methods: We present an XOR-based framework for detecting mutually exclusive gene modules. Given normalized module scores, we apply exclusive-OR logic, which assigns high scores to module pairs active in disjoint sets of cells and low scores to co-occurring modules, directly capturing mutual exclusivity. Mutually exclusive modules are combined iteratively, supported by complementary measures for grouping, gauging strength, and merging while preserving exclusion. Results: Applied to single-cell data, the approach recovers biologically coherent groupings of mutually exclusive programs, distinguishing populations defined by transcriptional activity rather than predefined cluster assignment. Conclusions: The framework offers a cluster-independent means of identifying mutually exclusive gene modules in single-cell data.

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