Yale SCHOOL OF PUBLIC HEALTH
Biostatistics

Statistical analysis of single cell CRISPR screens

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ABSTRACT

Single-cell CRISPR screens are an emerging biotechnology promising unprecedented insights into gene regulation. However, the analysis of these screens presents significant statistical challenges. For example, technical factors like sequencing depth impact not only expression measurement but also perturbation detection, creating a confounding effect. We demonstrate on two recent large-scale single-cell CRISPR screens how these challenges cause calibration issues among existing analysis methods. To address these challenges, we propose SCEPTRE: analysis of single-cell perturbation screens via conditional resampling. This methodology, designed to avoid calibration issues due to technical confounders and expression model misspecification, infers associations between perturbations and expression by resampling the former according to a working model for perturbation detection probability in each cell. SCETPRE demonstrates excellent calibration and sensitivity on the CRISPR screen data and yields 200 new regulatory relationships, many of which are supported by existing functional data.