Computational inference of heterotypic cell interactions in single cell RNA-seq data

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Single-cell RNA sequencing (scRNA-seq) has become a critical technology for unraveling the complex cellular heterogeneity within a tissue. While droplet-based microfluidics system is currently most widely used among many such methodologies, a typical artifact called 'doublets', where two cells are caught in the same droplet, should be successfully identified and removed in downstream analysis to obtain unbiased results. Conversely, some recent studies utilized the innate interactions between those 'physically interacting cells (PICs)' and obtained spatial information from them. Here, we introduce a computational analysis pipeline to infer potential cell-cell interactions from scRNA-seq data. In this pipeline, for every putative cell-type pair which are forming heterotypic doublets that are computationally detected, the observed rate of doublets comprised of corresponding cell-types is compared to the expected doublet rate of them. This signal-to-noise ratio with confidence-intervals was utilized to infer the interactions between the two cell-types. We evaluated this method over simulated doublets as well as biological samples from fly blood and multiple myeloma patients, detecting immune-cell interactions with a statistical significance in scRNA-seq data. We believe our research can help gain further insight into biologically meaningful cell-cell interactions in diverse conditions and diseases.