A055 · HyperCom: a hypergraph based method to infer cell-resolved cell-cell communication

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Cell-cell communication underlies many pathologies including heart disease and infection; however current methods tend to aggregate signals by cell type annotations. These annotations may introduce bias especially in cases where there are continuous cell types or non cell type specific responses. To address these issues, we developed HyperCom, a hypergraph based method to infer cell-resolved cell-cell communication from single cell transcriptomics data. HyperCom constructs a hypergraph by combining known ligand-receptor interactions with the expression of those ligands and receptors in individual cells. HyperCom uses graph diffusion on this hypergraph to calculate a global influence matrix which provides the basis of two functionalities: per cell "LR Score" and dataset wide per-condition "LR Priority". "LR Score" scores cells on a continuous spectrum from sender to receiver for a given LR pair, while "LR Pair Priority" ranks each LR pair in a dataset by its communication in each condition, timepoint, or other supplied metadata. We validate HyperCom's performance against current tools, detect up and down regulated LR pairs agnostic of a user specified control condition, demonstrate its ability to capture signals from experimentally measured physical cell-to-cell contact, identify key biomarkers in lowly expressed spatial transcriptomic data, and distinguish between subtle expression differences in a multicondition datasets.

HyperCom: a hypergraph based method to infer cell-resolved cell-cell communication

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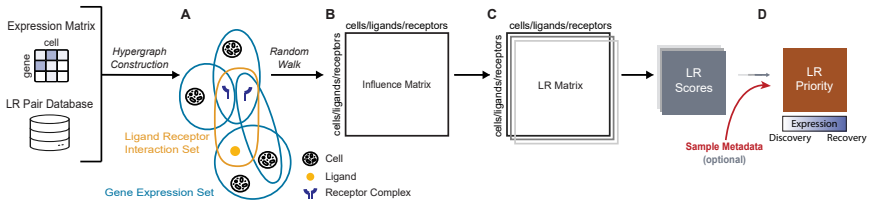
Cell-cell communication underlies many pathologies including heart disease and infection; however current methods tend to aggregate signals by cell type annotations. These annotations may introduce bias, especially in cases where there are continuous cell types or non cell type specific responses. To address these issues, we developed HyperCom, a hypergraph based method to infer cell-resolved cell-cell communication from single cell transcriptomics data. HyperCom provides two main functionalities: “LR Score”, which scores cells continuously from sender to receiver for a given ligand receptor (LR) pair, and “LR priority” which ranks each LR pair in a dataset by its communication in each condition, timepoint, or other supplied metadata.

HyperCom constructs a heterogeneous hypergraph where nodes represent cells, ligand genes, or receptor genes, and hyperedges represent the relationships between these nodes. Hyperedges, unlike the pairwise edges in a regular graph, encode sets that can contain multiple nodes. HyperCom uses hyperedges to capture two different relationships: gene expression by cells, and LR pair interactions between genes. Each gene expression hyperedge contains a gene node and all cells that express that gene to link genes for ligands and receptors to cells. LR pair hyperedges contain the genes of a given LR pair to capture the interaction between a ligand and its receptor or receptor complex. Together these nodes and hyperedges form the HyperCom hypergraph, the basis of all downstream analysis. Although this hypergraph includes observed and known direct relationships between ligands, receptors, and cells, it does not encode the global connectivity of nodes in the network. The network does not inherently capture multistep communications, and due to the sparsity of scRNA-seq, may have missing edges. To address this, HyperCom performs a random walk with restart on the hypergraph to produce an influence matrix. The influence matrix quantifies the communication from all nodes to all nodes rather than just direct neighbors. A given entry in this influence matrix represents the probability of a walk starting at a row node and then ending at a column node, for example from a ligand to a cell or from a cell to another cell. After generating the influence matrix, HyperCom can score individual cells per LR pair using “LR Scores.” To compute an LR score, an LR matrix is generated as the product of the ligand row and receptor column for the given ligand and receptor. Although many LR pairs may be expressed in a dataset, only a small subset of those pairs are expected to exhibit high communication or condition specificity. To identify these LR pairs “LR priority” weighs condition purity and communication in two modes. “Discovery Mode” prioritizes highly communicative but lowly expressed LR pairs like interaction between rare cell populations which are generally missed by expression-based methods. Conversely, “Recovery Mode,” prioritizes highly expressed LR pairs and gives similar results to expression based methods.

We validate HyperCom’s performance against current tools, detect up and down regulated LR pairs agnostic of a user specified control condition, demonstrate its ability to capture signals from experimentally measured physical cell-to-cell contact, identify key biomarkers in lowly expressed spatial transcriptomic data, and distinguish between subtle expression differences in a multicondition datasets.



Overview of HyperCom. A. HyperCom takes a cell by gene expression matrix and LR pair database as input to construct a hypergraph. **B**. This hypergraph is used to calculate the influence matrix using a random walk. **C**. Subsequently an LR matrix can be calculated using the influence matrix for any LR pair from which a per cell LR score is derived. **D**. LR priority can be tuned to weigh gene expression highly for Recovery Mode or lowly for Discovery Mode.