

Table S1. Computational methods for analyzing spatial gene expression.

Method	Reference	Effects of neighboring cell type	MIMO system	Descriptions
CCPLS	This study	Consider	Consider	Estimation of highly variable genes influenced by multiple neighboring cell types with PLS regression modeling.
Giotto findICG	Dires et al., 2021b	Consider	Not consider	Estimation of genes influenced by neighboring cell type with spatial permutation test.
Giotto spatCellCellcom	Dires et al., 2021b	Consider	Not consider	Estimation of genes influenced by neighboring cell types with permutation test.
SptialDE	Svensson et al., 2018	Not consider	Not consider	Estimation of spatially variable genes with Gaussian process regression modeling of spatial gene expression.
TrendSceek	Edsgård et al., 2018	Not consider	Not consider	Estimation of spatially variable genes with marked point process modeling of spatial gene expression trends.
SPARK-X	Zhu et al., 2021	Not consider	Not consider	Estimation of spatially variable genes with spatial kernels for non-parametric modeling of spatial gene expression.
Giotto BinSpect	Dries et al., 2021b	Not consider	Not consider	Estimation of spatially variable genes with enrichment analysis of spatially high expression cells after binarization.
Giotto SilhouetteRank	Dries et al., 2021b	Not consider	Not consider	Estimation of spatially variable genes with silhouette score per gene based on spatial distribution of two cells.
SVCA SilhouetteRank	Arnol et al., 2019	Not consider	Not consider	Estimation of spatial variance sources with Gaussian process regression modeling of individual spatial gene expression.
MISTy	Tanevski et al., 2022	Not consider	Not consider	MISTy models marker relationships coming from different spatial views: intrinsic, local niche view, the broader, tissue view, or others.