

Supplementary Information for the article: “Communication-space representation of multicellular tissue organization”

Hui-Sheng Li, Pai Peng, Yu-Ting Tan, Jia-Juan Tu,
Xiao-Fei Zhang, Shou-Feng Shen and Luonan Chen

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1 Supplementary Figures

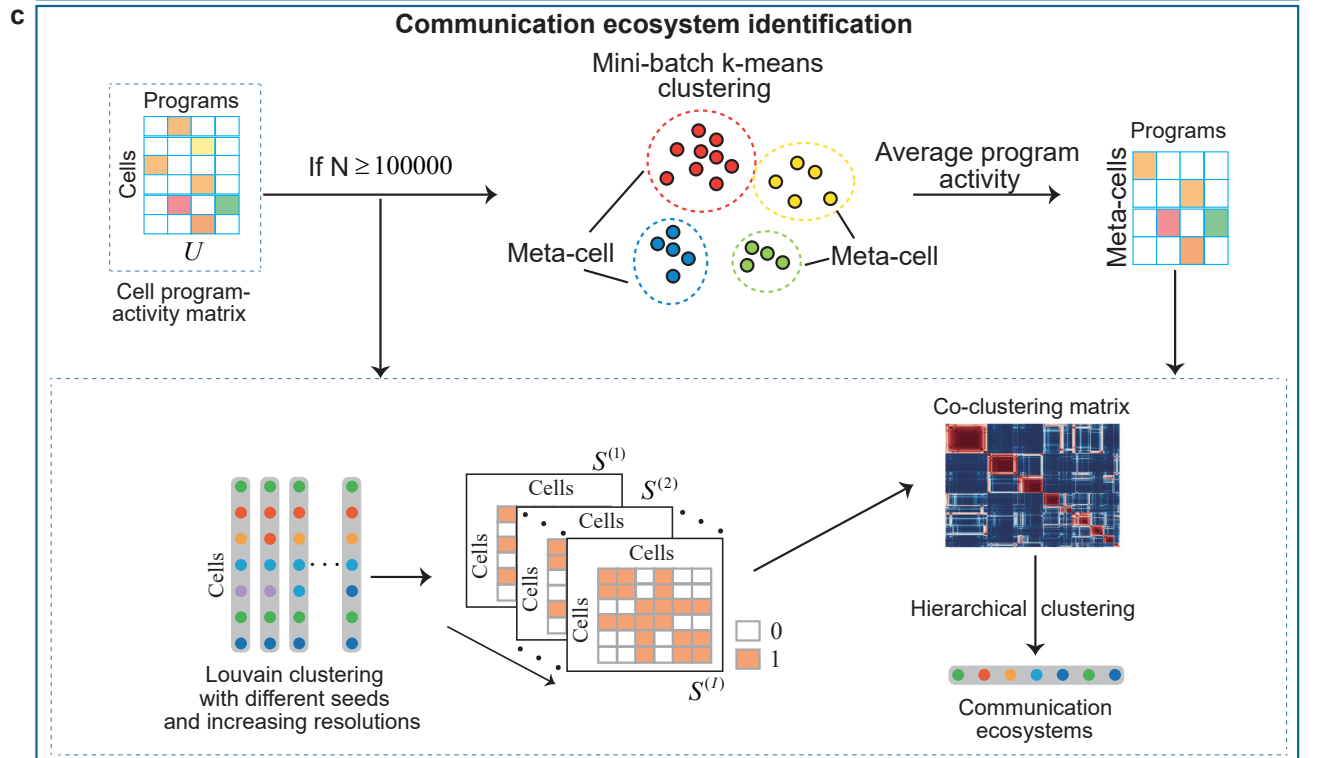
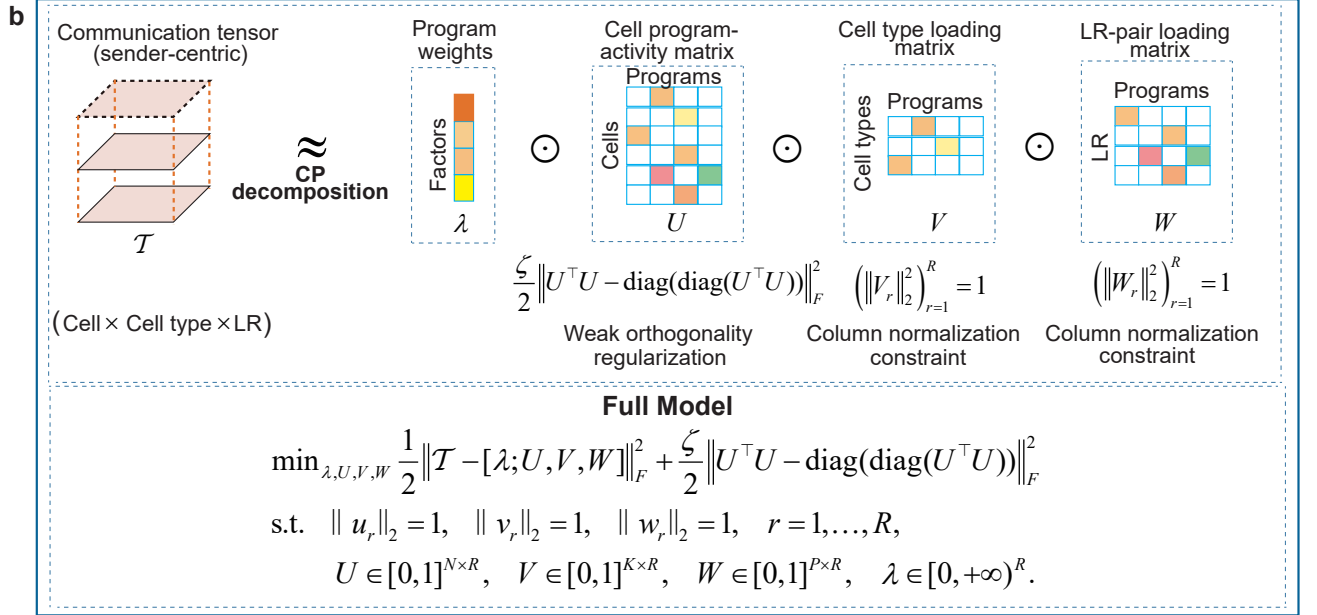
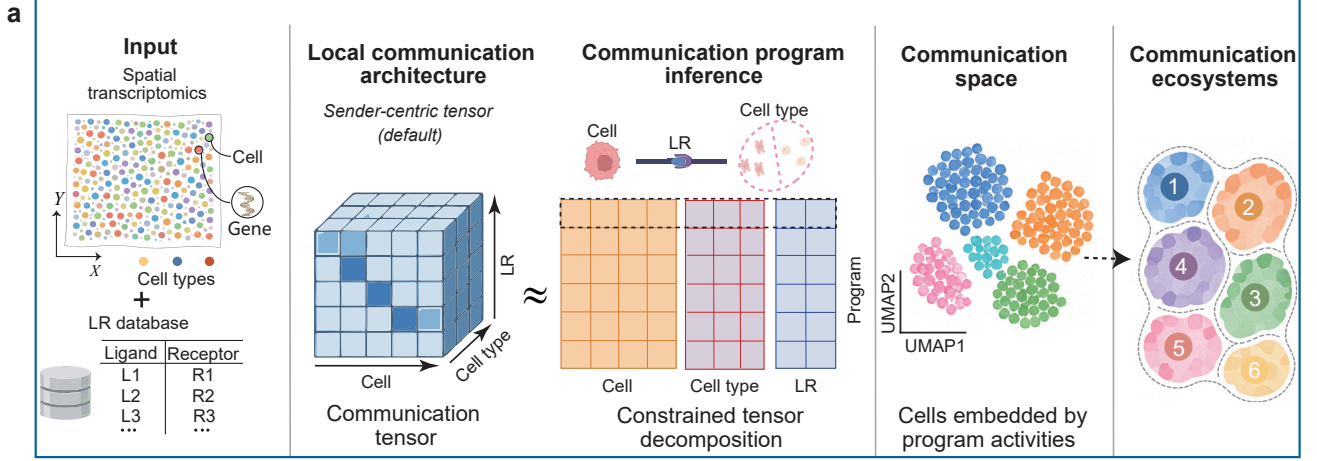


Figure S1: Expanded technical schematic of communication-space construction and scalable communication ecosystem identification in CommuSpace. **(a)** Schematic overview of CommuSpace. Spatial transcriptomic data, cell-type annotations and ligand–receptor pairs are integrated to construct local communication tensors that encode sender-, receiver- and sender–receiver-associated interactions. Constrained tensor decomposition identifies recurrent communication programs, which embed cells into communication space according to their signaling activities. Stable regions within this space are subsequently summarized as communication ecosystems. **(b)** Detailed schematic of the sender-centric communication tensor and its constrained non-negative CP decomposition, expanding the overview shown in Figure 1. The communication tensor links focal cells, interacting cellular populations, and LR signaling channels. Decomposition identifies latent communication programs represented by cell-level program activities, interacting-population loadings, LR-channel loadings, and program weights. Non-negativity, column-normalization, and soft-orthogonality constraints are used to improve interpretability, resolve scale ambiguity, and encourage distinct communication programs. Cell-level program activities define the communication-space representation of cells. **(c)** Scalable procedure for identifying communication ecosystems from communication space. For large datasets, cells are first grouped into fine-grained micro-clusters in communication space, and each micro-cluster is represented by the mean communication embedding of its member cells. Louvain clustering is then performed across multiple resolutions and random initializations, and the resulting partitions are integrated into a consensus co-assignment structure. Final communication ecosystems are obtained as stable regions of communication space and propagated back to individual cells when micro-clustering is used.

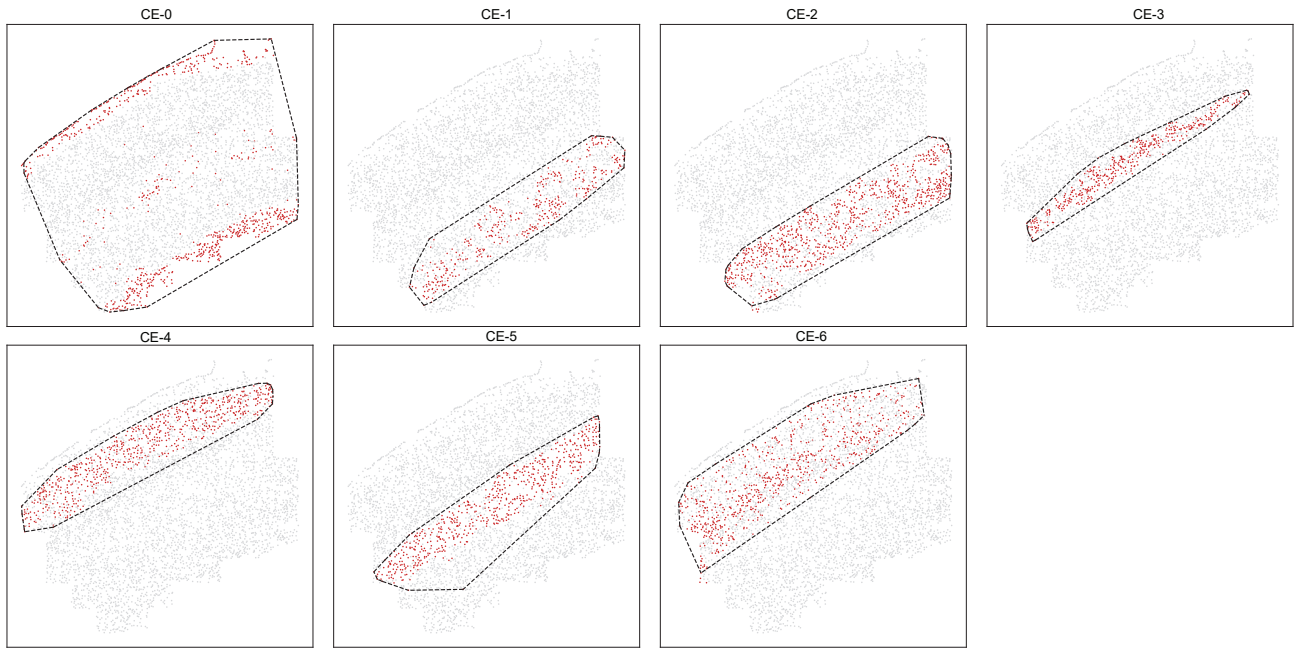


Figure S2: Spatial distributions of communication ecosystems in the mouse primary motor cortex. Cells belonging to each communication ecosystem (CE) are highlighted in red, while all other cells are shown in gray for spatial context. Dashed outlines indicate the spatial extent of each CE.

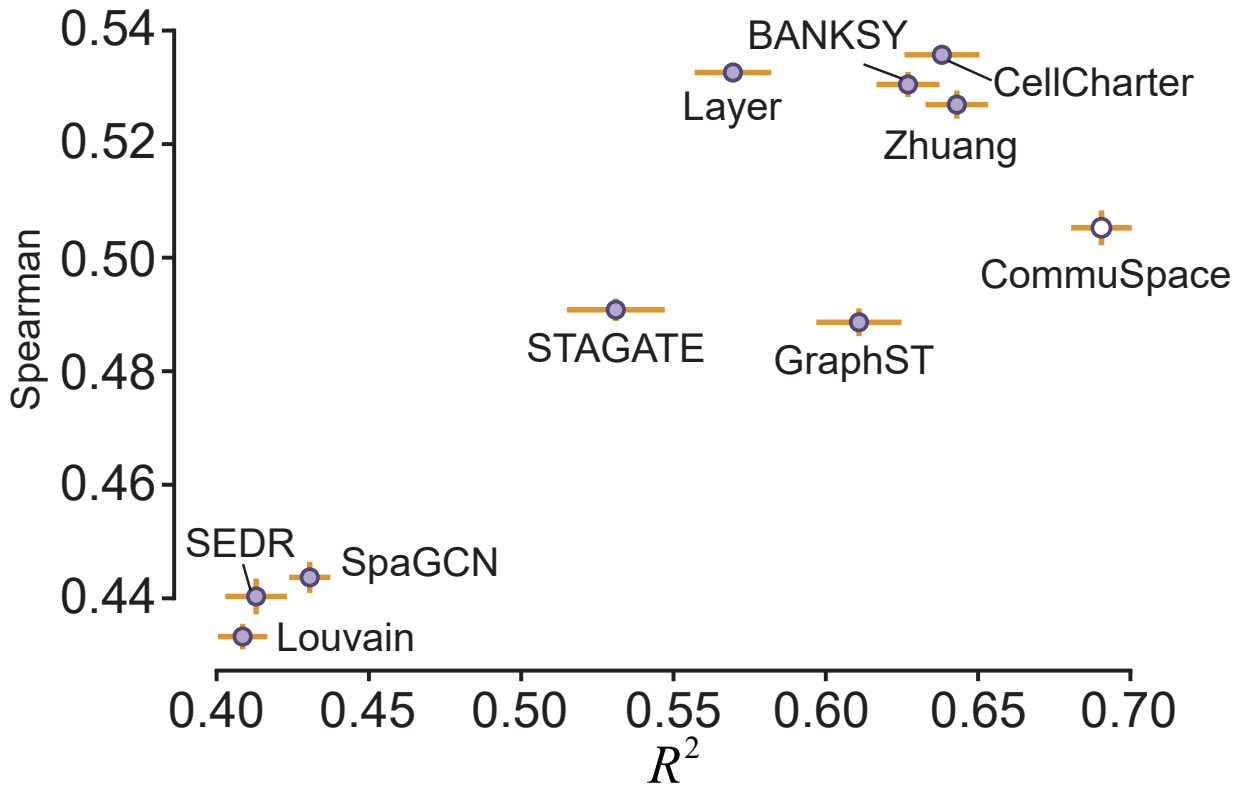
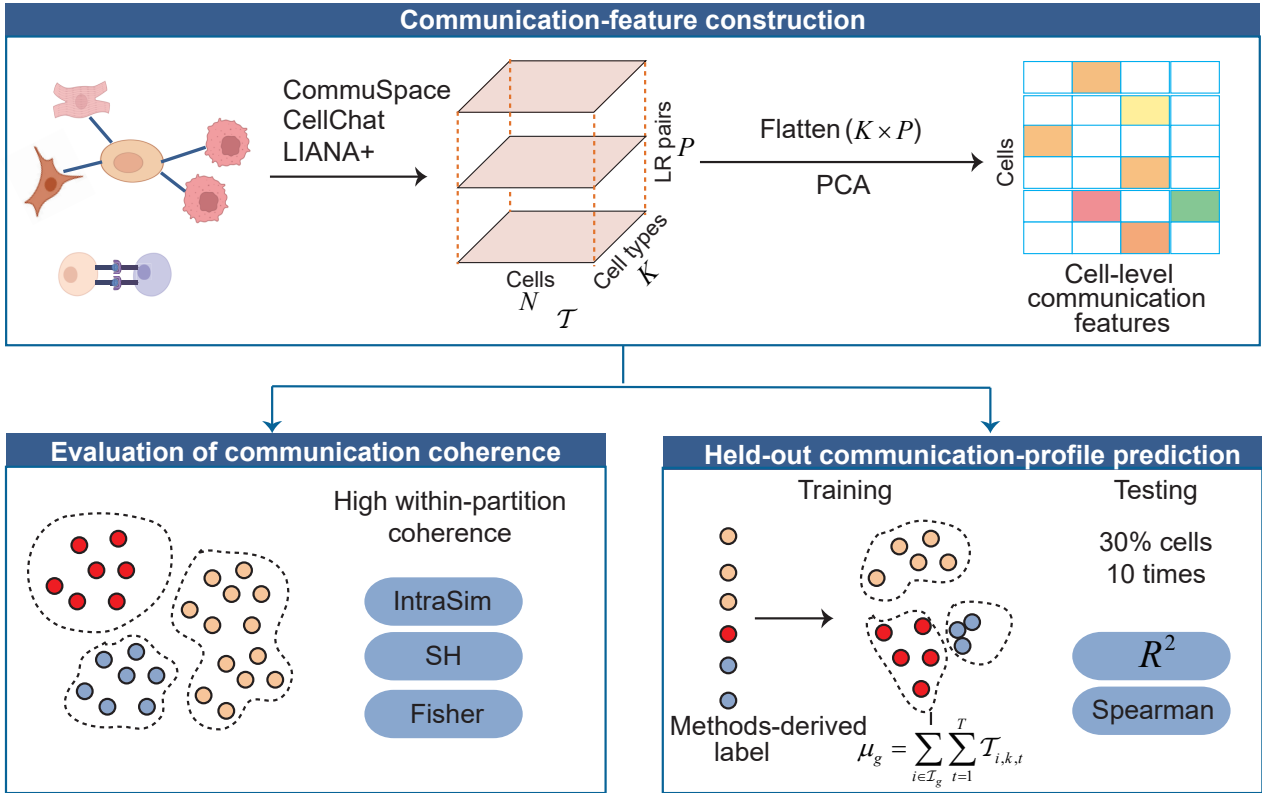
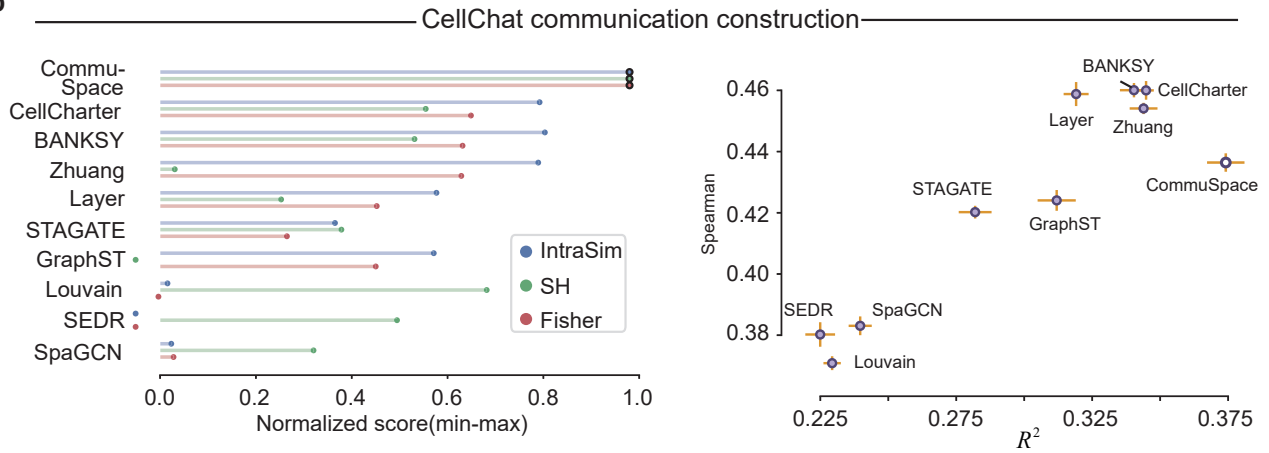


Figure S3: **Quantitative comparison of communication-profile prediction accuracy.** Prediction of held-out communication profiles across methods is evaluated using Spearman correlation and R^2 . Each point represents one method. Higher values indicate better recovery of local communication architecture.

a



b



c

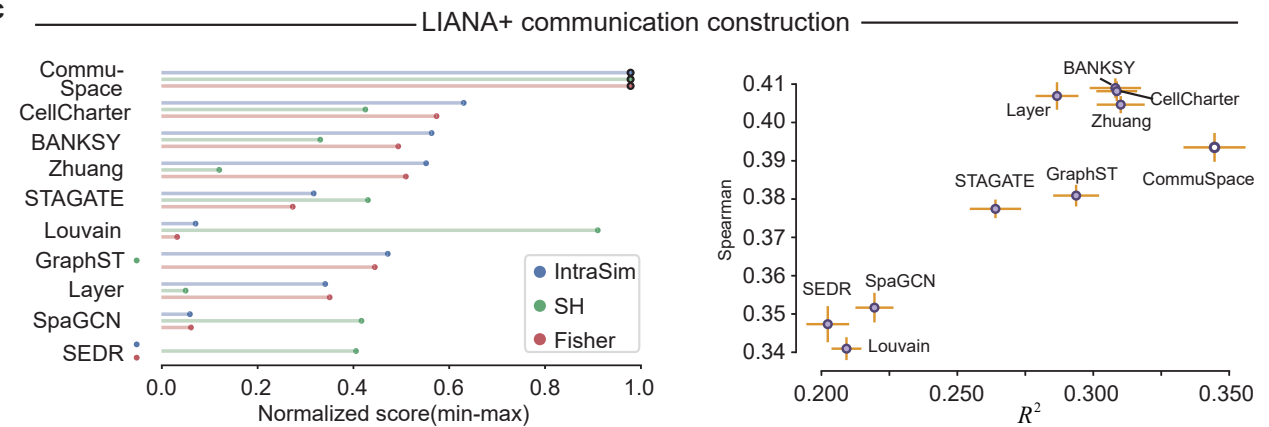


Figure S4: Evaluation of communication-organization coherence and prediction accuracy under alternative communication-feature construction strategies. (a) Schematic overview of alternative communication-feature construction and evaluation. Cell–cell communication scores are computed using CommuSpace, CellChat, or LIANA+, organized as a cell $\times$ cellular-population $\times$ LR-channel tensor, flattened across population–LR dimensions, and projected by PCA to obtain cell-level communication features. Method-derived partitions are evaluated for communication-organization coherence using IntraSim, silhouette coefficient (SH), and Fisher ratio, and for predictive consistency by predicting held-out communication profiles using Spearman correlation and R^2 across 30% held-out test cells and 10 repetitions. (b) Quantitative comparison using CellChat-derived communication features. Left, normalized IntraSim, SH, and Fisher ratio measuring communication-organization coherence across method-derived partitions. Right, prediction of held-out communication profiles evaluated by Spearman correlation and R^2 . (c) Quantitative comparison using LIANA+-derived communication features. Left, normalized IntraSim, SH, and Fisher ratio measuring communication-organization coherence across method-derived partitions. Right, prediction of held-out communication profiles evaluated by Spearman correlation and R^2 .

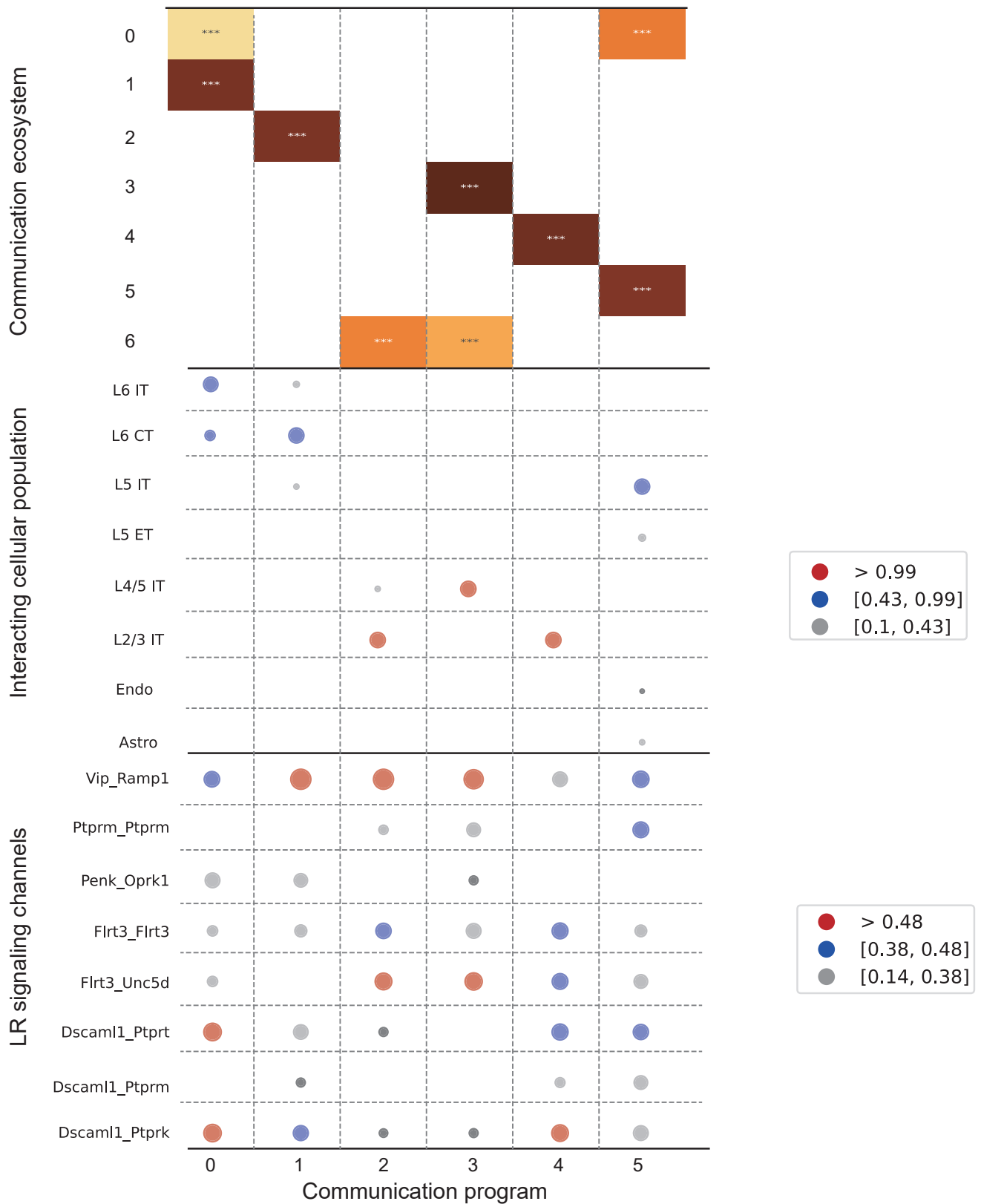


Figure S5: Communication ecosystems are linked to interpretable communication programs and signaling components in the mouse primary motor cortex. Top, heatmap showing enrichment of communication programs across communication ecosystems (CEs). Middle, program-wise loadings of interacting cellular populations associated with each communication program. Bottom, program-wise loadings of LR signaling channels associated with each communication program. Bubble size reflects loading magnitude, and color indicates normalized loading.

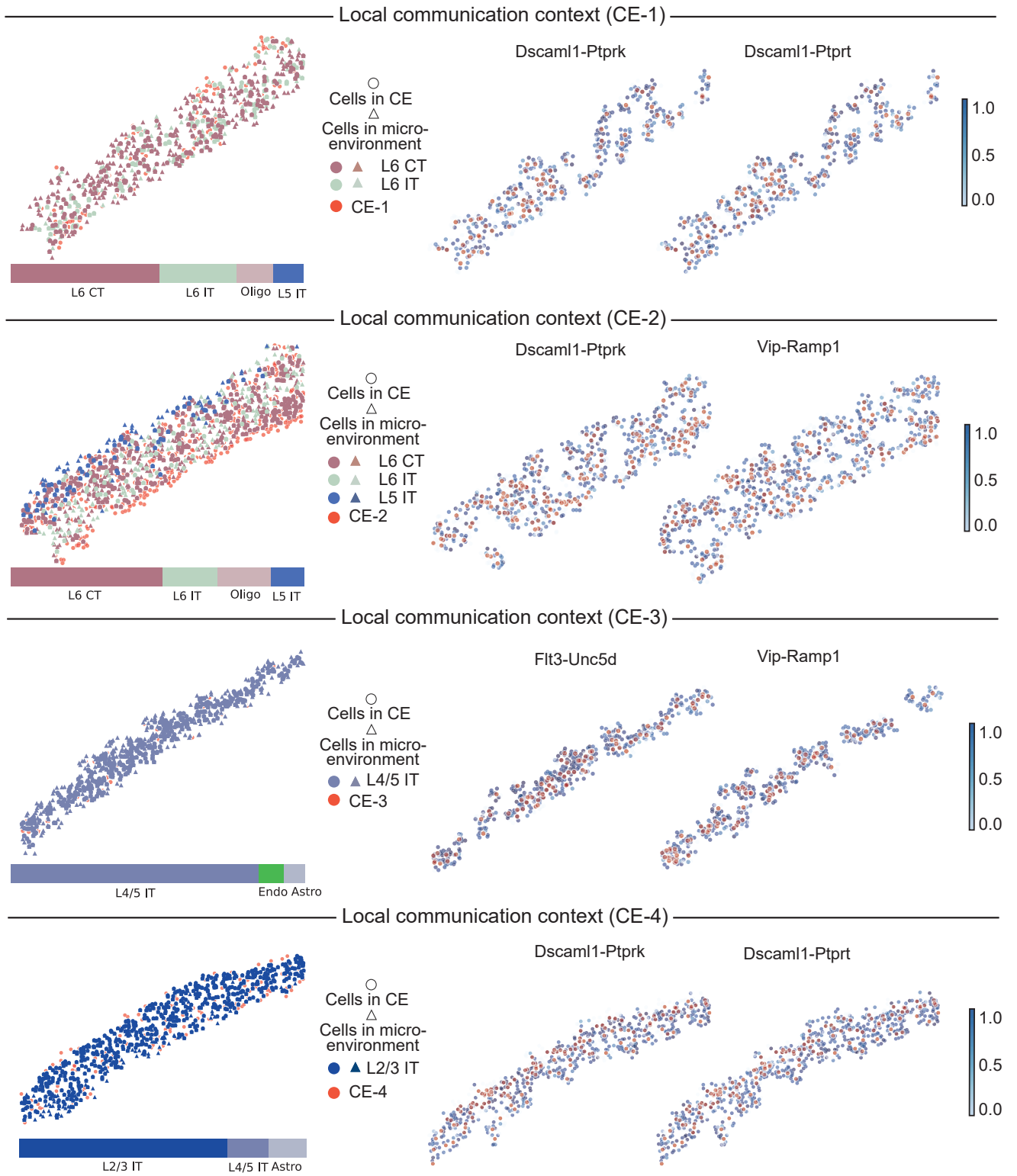


Figure S6: Local communication contexts and spatial localization of LR interactions across cortical communication ecosystems. For each communication ecosystem (CE-1–CE-4), left panels show the composition of interacting neighboring cellular populations surrounding cells assigned to the corresponding CE. Circles indicate cells in the CE, and triangles indicate interacting neighboring cells; bar plots summarize the relative composition of neighboring cellular populations in the local communication context. Right panels show spatial localization of representative LR pairs, with red points indicating CE cells with ligand expression above the 90th percentile and blue points indicating receptor-expressing neighboring cells, with darker blue denoting higher receptor expression.

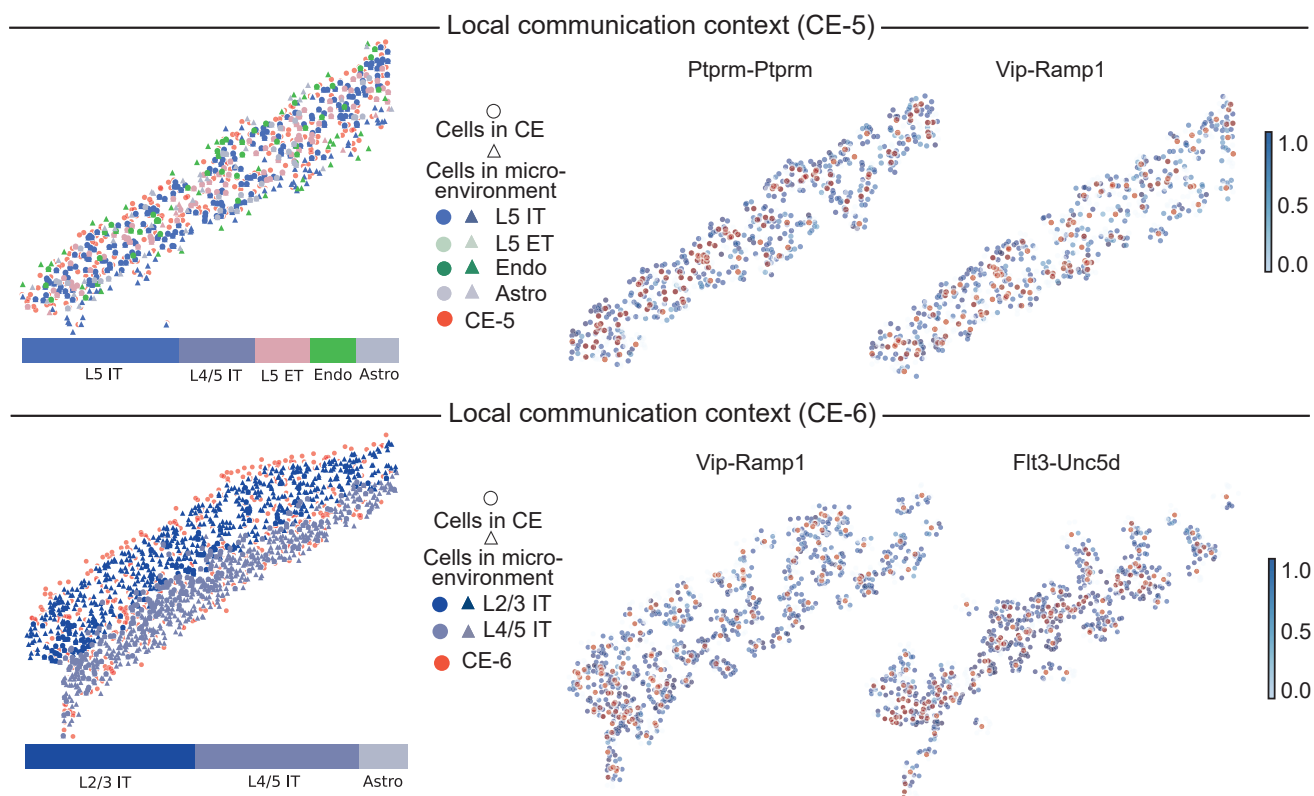


Figure S7: Local communication contexts and spatial localization of LR interactions across cortical communication ecosystems. For each communication ecosystem (CE-5 and CE-6), left panels show the composition of interacting neighboring cellular populations surrounding cells assigned to the corresponding CE. Circles indicate cells in the CE, and triangles indicate interacting neighboring cells; bar plots summarize the relative composition of neighboring cellular populations in the local communication context. Right panels show spatial localization of representative LR pairs, with red points indicating CE cells with ligand expression above the 90th percentile and blue points indicating receptor-expressing neighboring cells, with darker blue denoting higher receptor expression.

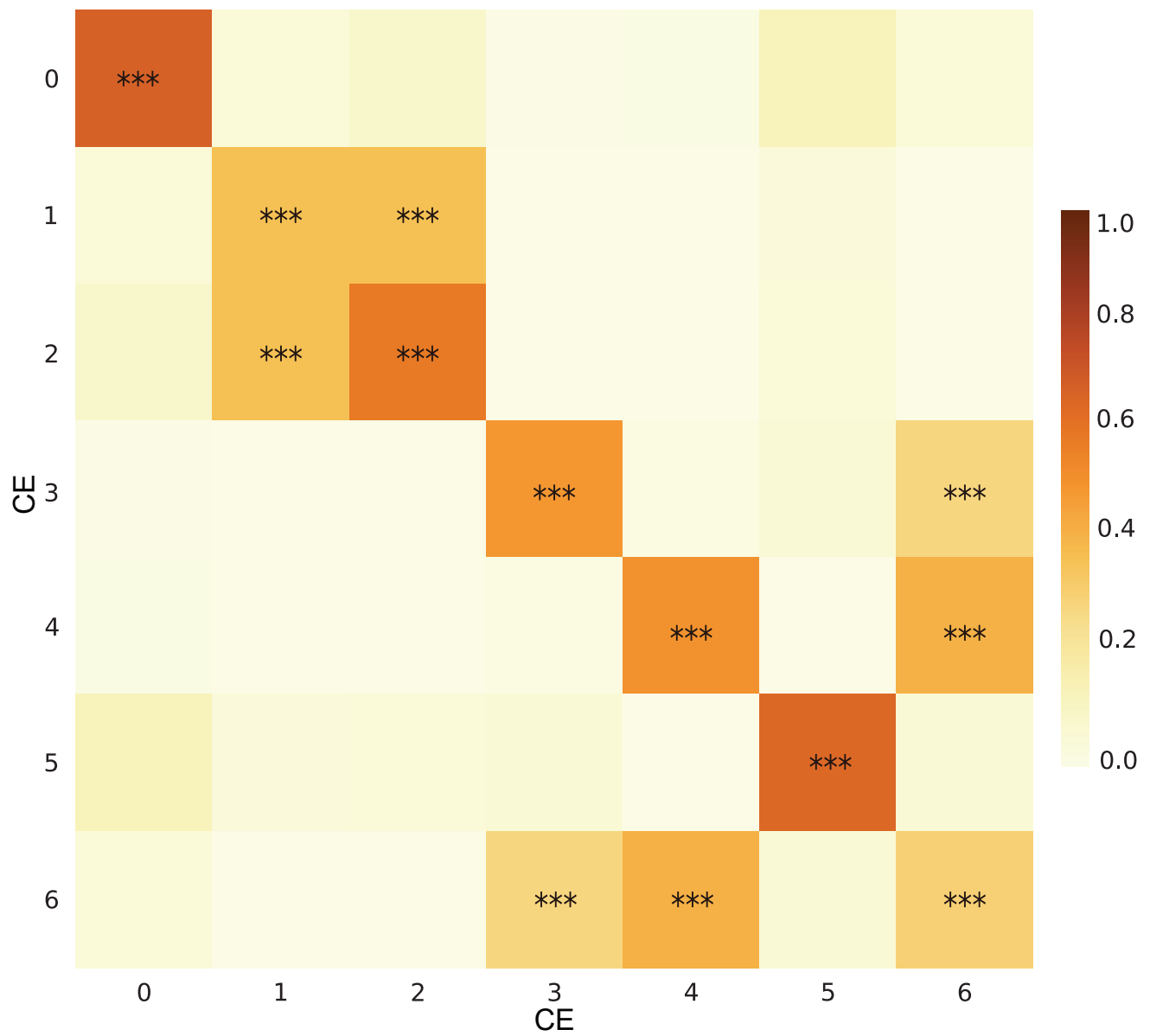


Figure S8: **Spatial co-localization patterns among cortical communication ecosystems.** Heatmap showing pairwise spatial association strength between communication ecosystems (CEs) in the mouse primary motor cortex. Warmer colors indicate stronger co-localization between CE pairs, and asterisks denote statistically significant ecosystem associations.

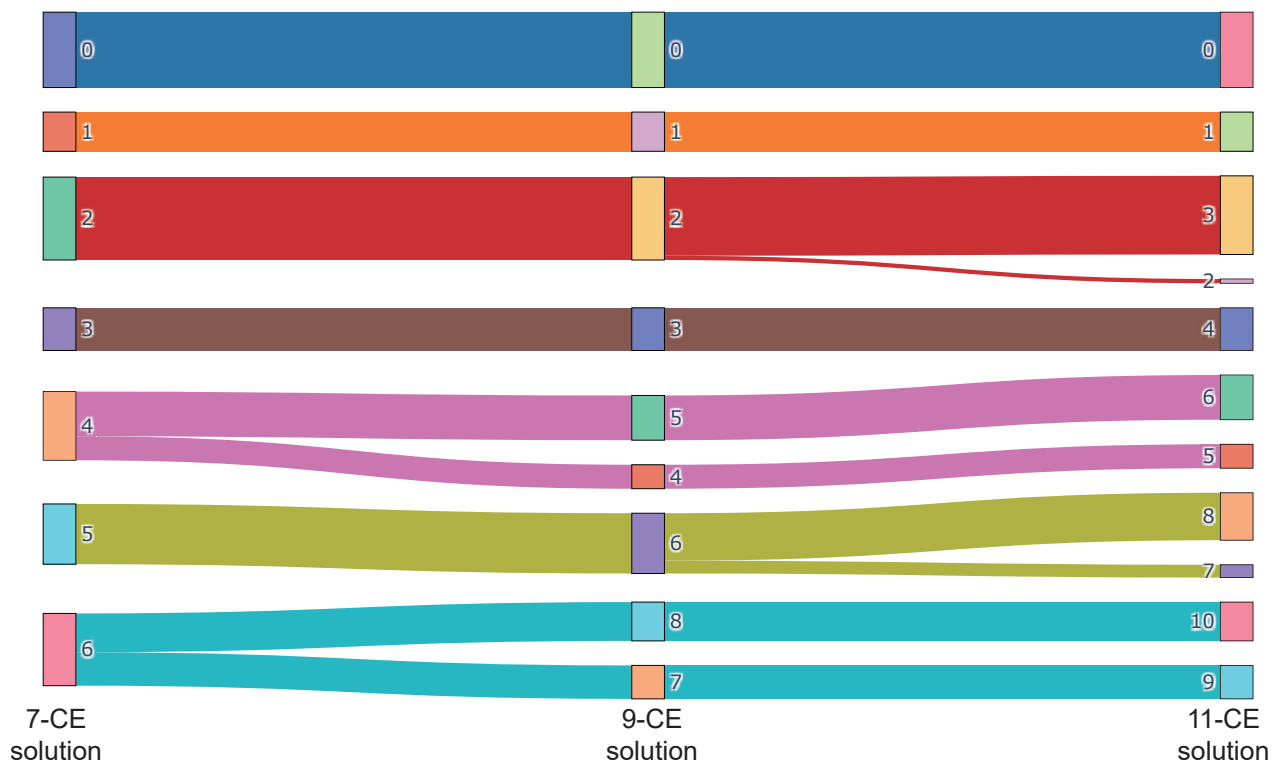


Figure S9: **Hierarchical refinement of communication ecosystems across clustering resolutions in the mouse primary motor cortex.** Sankey diagram showing the correspondence of communication ecosystem assignments as clustering resolution increases from the 7-CE solution to the 9-CE and 11-CE solutions. Each column represents ecosystem assignments at a given resolution, and flows indicate cell overlap between ecosystems across resolutions. The diagram reveals parent–descendant relationships and nested communication states within communication space.

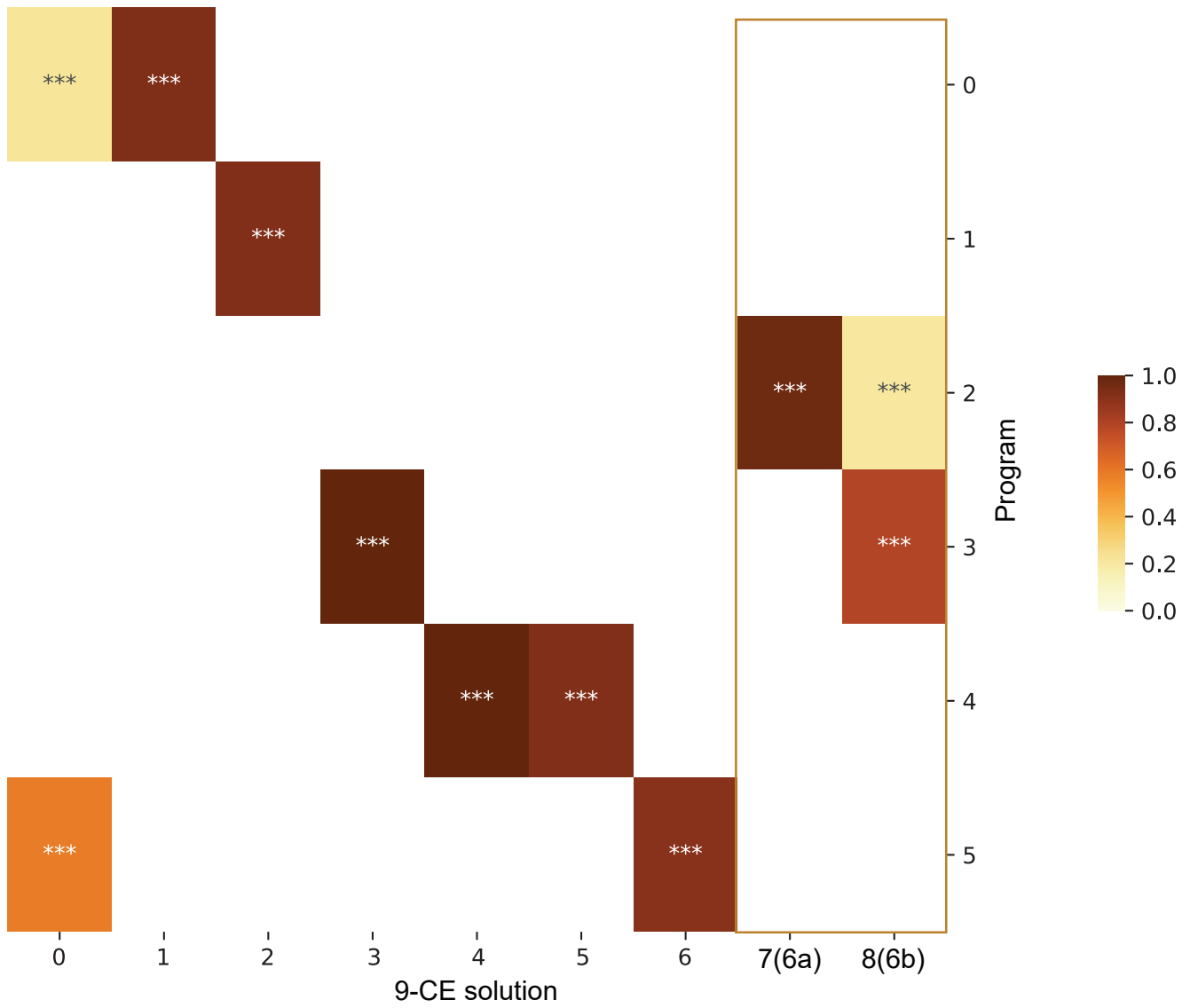


Figure S10: **Communication-program associations across the 9-CE solution in the mouse primary motor cortex.** Heatmap showing the association between latent communication programs and communication ecosystems in the 9-CE solution. Rows denote communication programs and columns denote communication ecosystems. Asterisks indicate statistically significant enrichment.

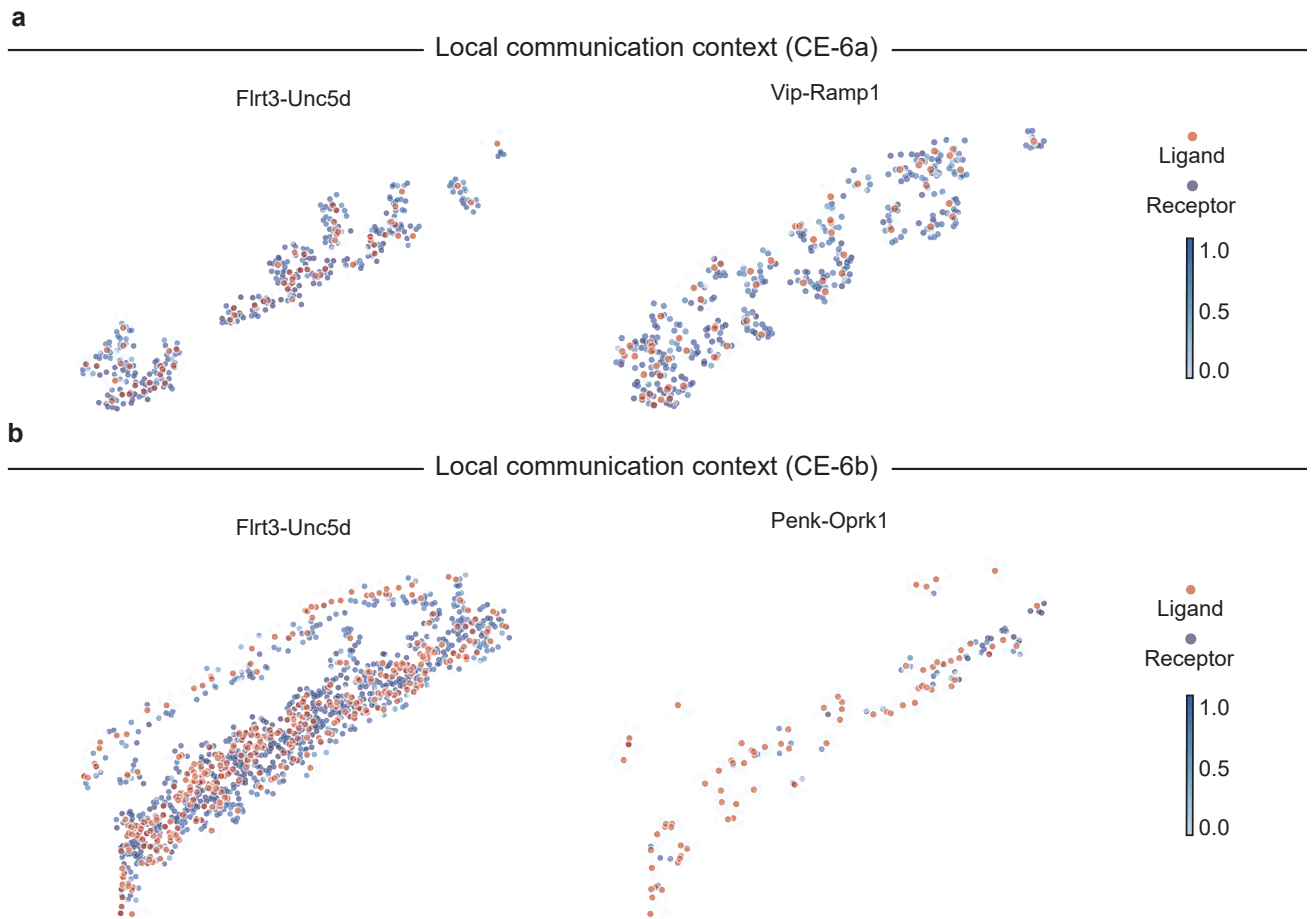


Figure S11: **Spatial localization of representative LR interactions in descendant cortical communication ecosystems CE-6a and CE-6b.** (a) Spatial localization of representative LR pairs associated with CE-6a. Red points indicate cells in CE-6a with ligand expression above the 90th percentile, and blue points indicate receptor-expressing interacting neighboring cells in the corresponding local communication context, with darker blue denoting higher receptor expression. (b) Spatial localization of representative LR pairs associated with CE-6b. Red points indicate cells in CE-6b with ligand expression above the 90th percentile, and blue points indicate receptor-expressing interacting neighboring cells in the corresponding local communication context, with darker blue denoting higher receptor expression.

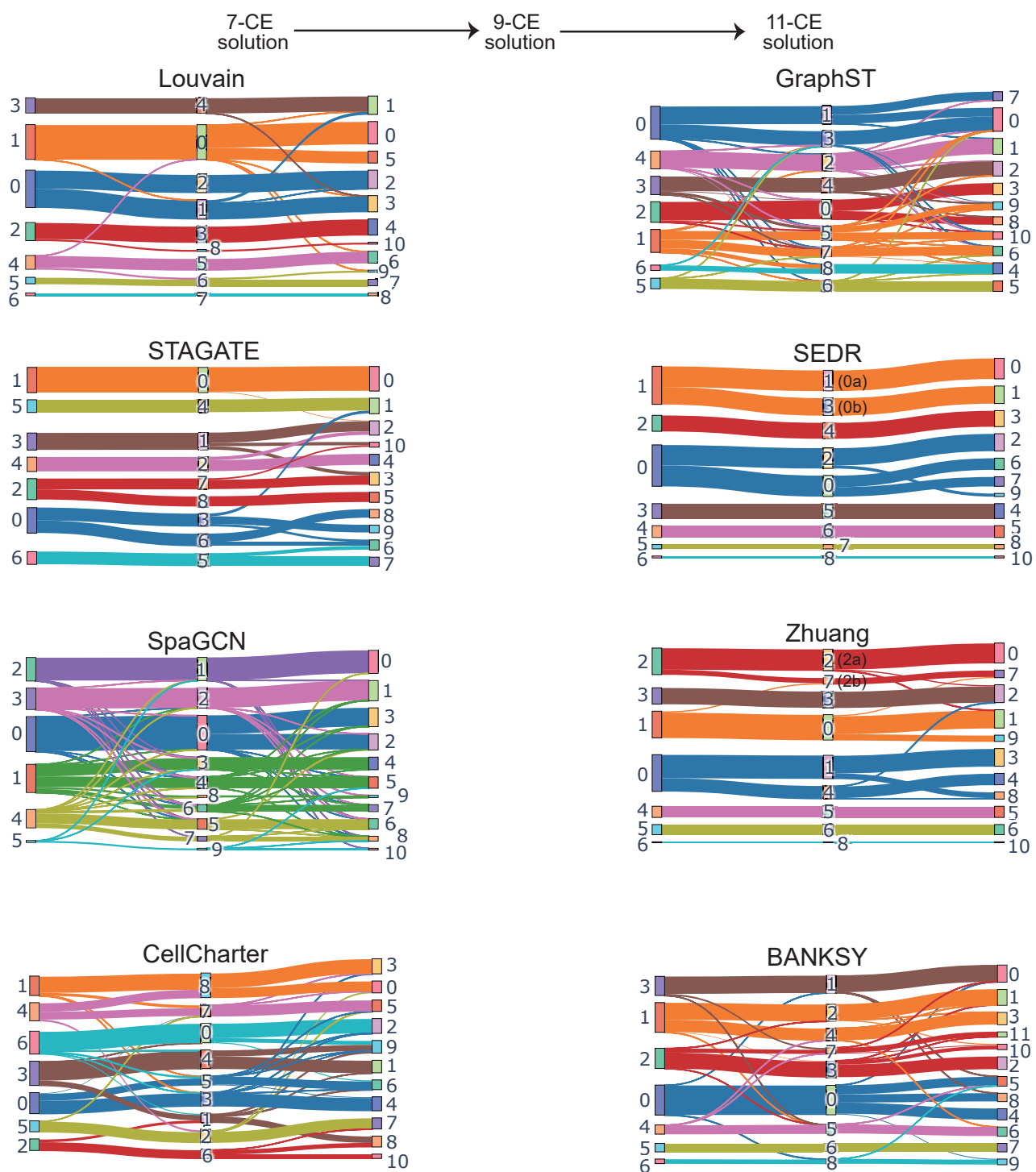


Figure S13: **Hierarchical refinement of phenotype-centered partitions across clustering resolutions in the mouse primary motor cortex.** Sankey diagrams showing the correspondence of method-derived partitions as clustering resolution increases for phenotype-centered and spatial-domain comparison methods, including Louvain, GraphST, STAGATE, SEDR, SpaGCN, Zhuang, CellCharter, and BANKSY. Each column represents partition assignments at a given resolution, and flows indicate cell overlap between partitions across resolutions. The diagrams illustrate the hierarchical refinement structure recovered by comparison methods.

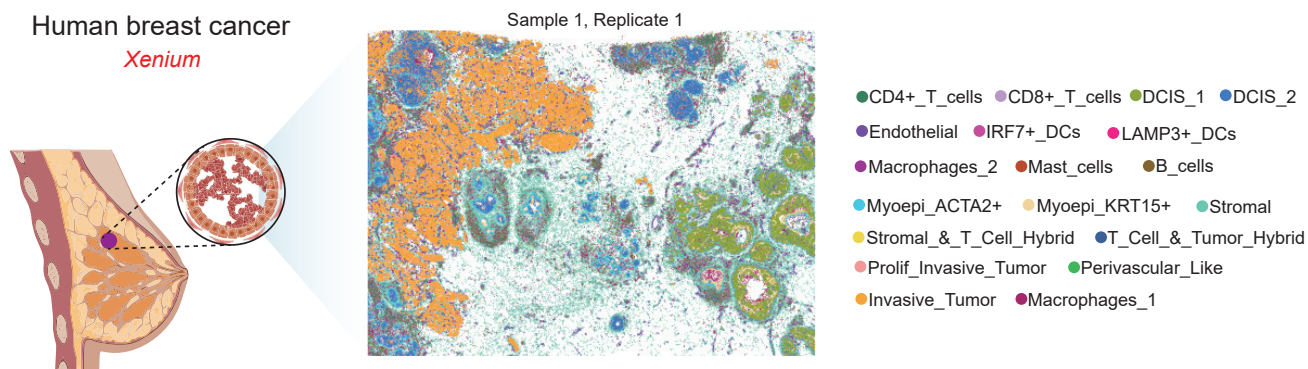


Figure S14: **Overview of the human breast cancer Xenium dataset and annotated cell types.** Left, schematic illustration of the human breast cancer tissue profiled using Xenium In Situ. Right, spatial distribution of annotated cell types in sample 1, replicate 1 with colors indicating cell-type identity.

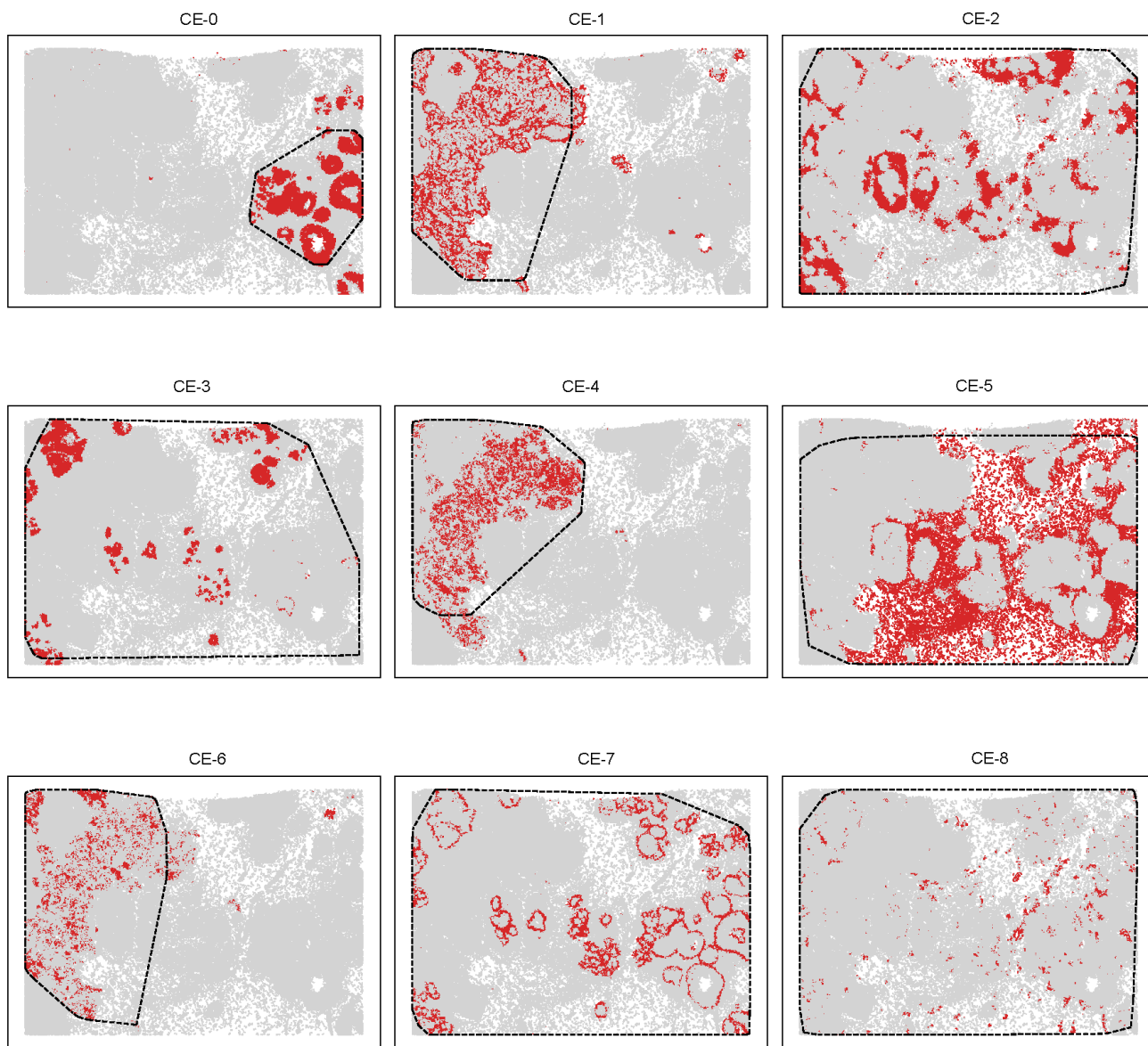


Figure S15: **Spatial distributions of communication ecosystems in the human breast cancer Xenium dataset.** Spatial localization of CE-0 to CE-8 in the human breast cancer dataset. Cells assigned to the indicated communication ecosystem are highlighted in red, while all other cells are shown in gray for spatial context. Dashed outlines indicate spatial regions enriched for each communication ecosystem.

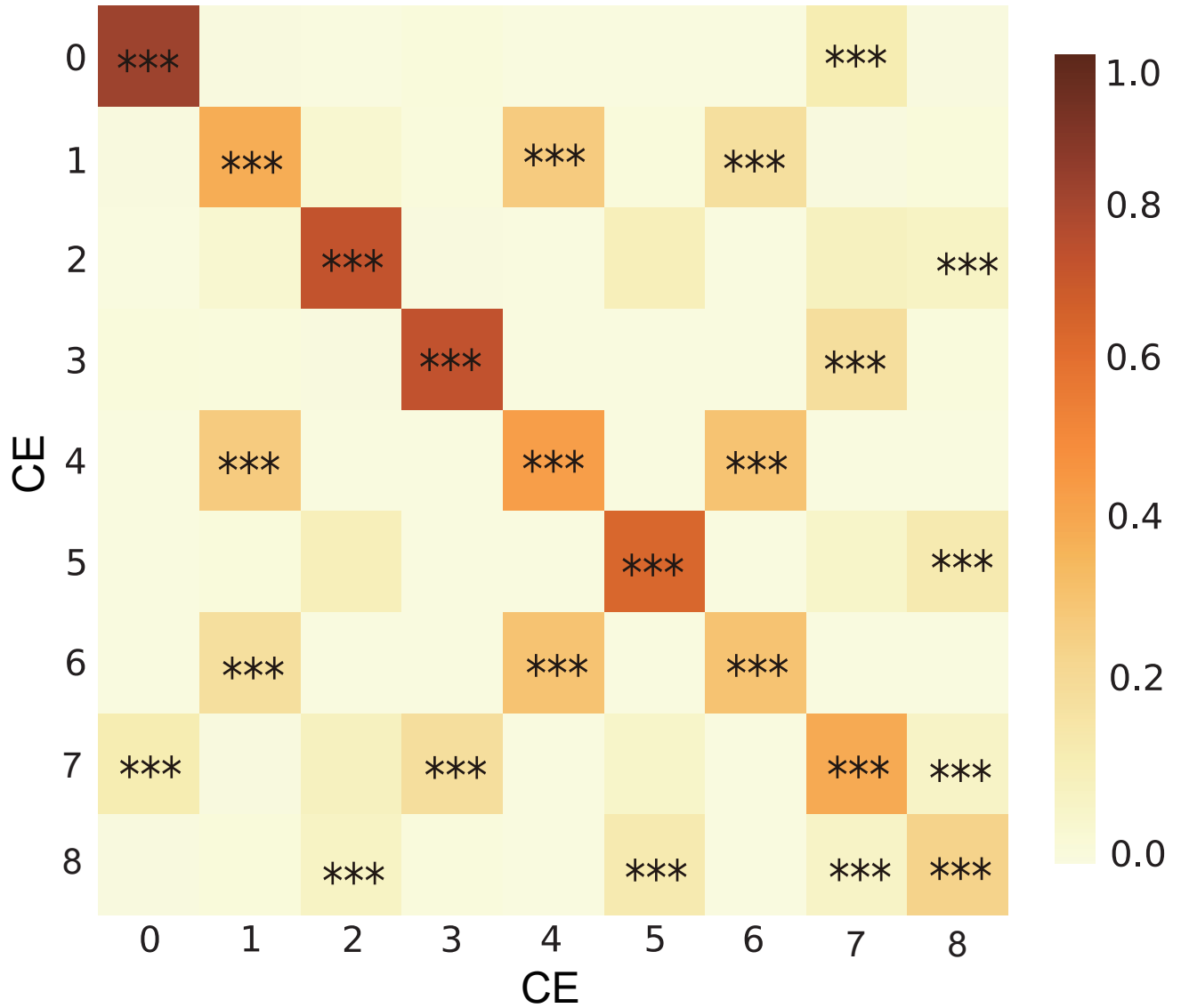


Figure S16: **Spatial co-localization patterns among communication ecosystems in human breast cancer.** Heatmap showing pairwise spatial association strength between communication ecosystems (CEs) in the human breast cancer Xenium dataset. Warmer colors indicate stronger co-localization between CE pairs, and asterisks denote statistically significant ecosystem associations.

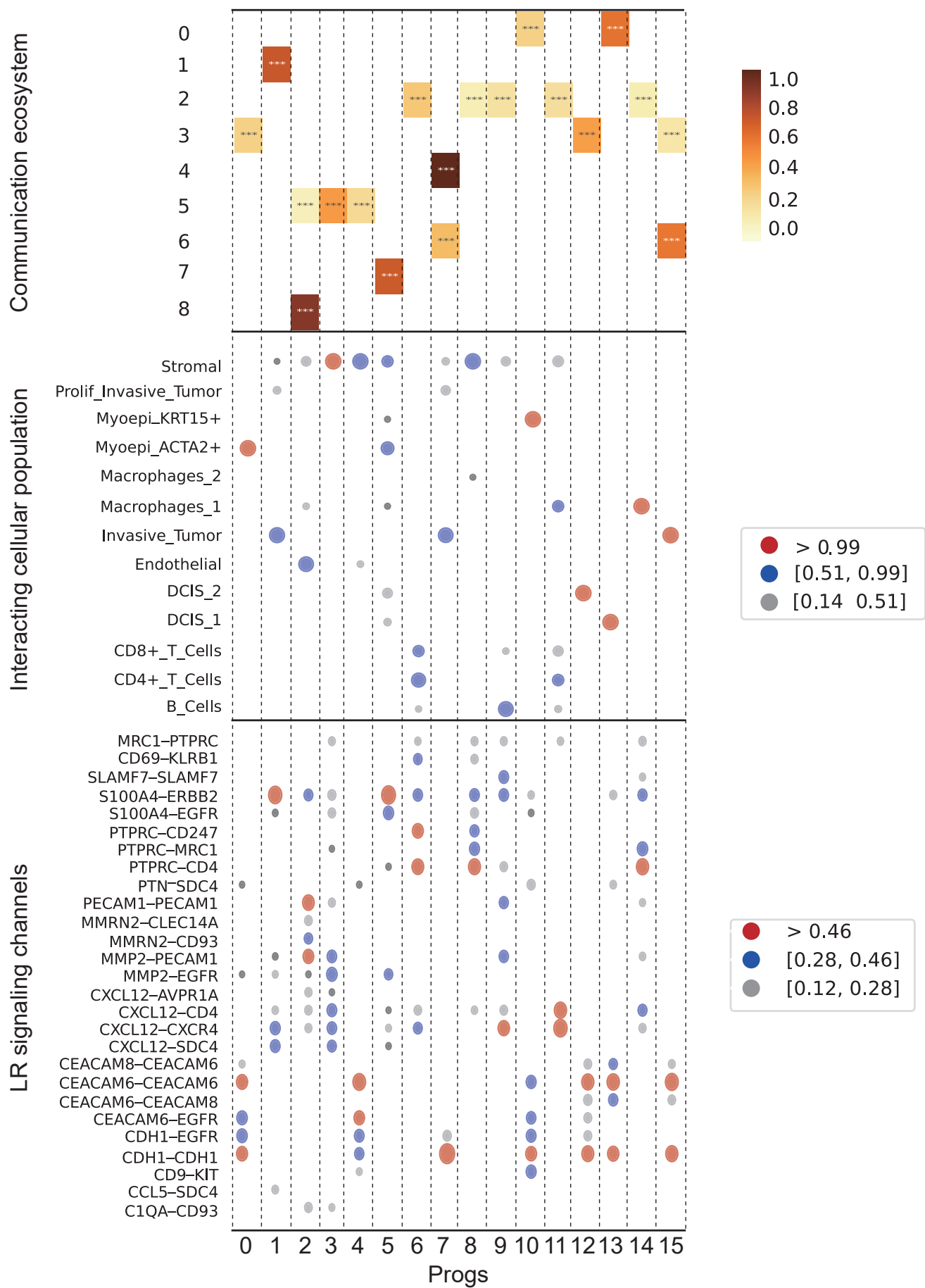


Figure S17: Communication ecosystems are linked to interpretable communication programs and signaling components in human breast cancer Xenium data. Top, heatmap showing enrichment of communication programs across communication ecosystems (CEs) in replicate 1. Middle, program-wise loadings of interacting cellular populations associated with each communication program. Bottom, program-wise loadings of LR signaling channels associated with each communication program. Bubble size reflects loading magnitude, and color indicates normalized loading.

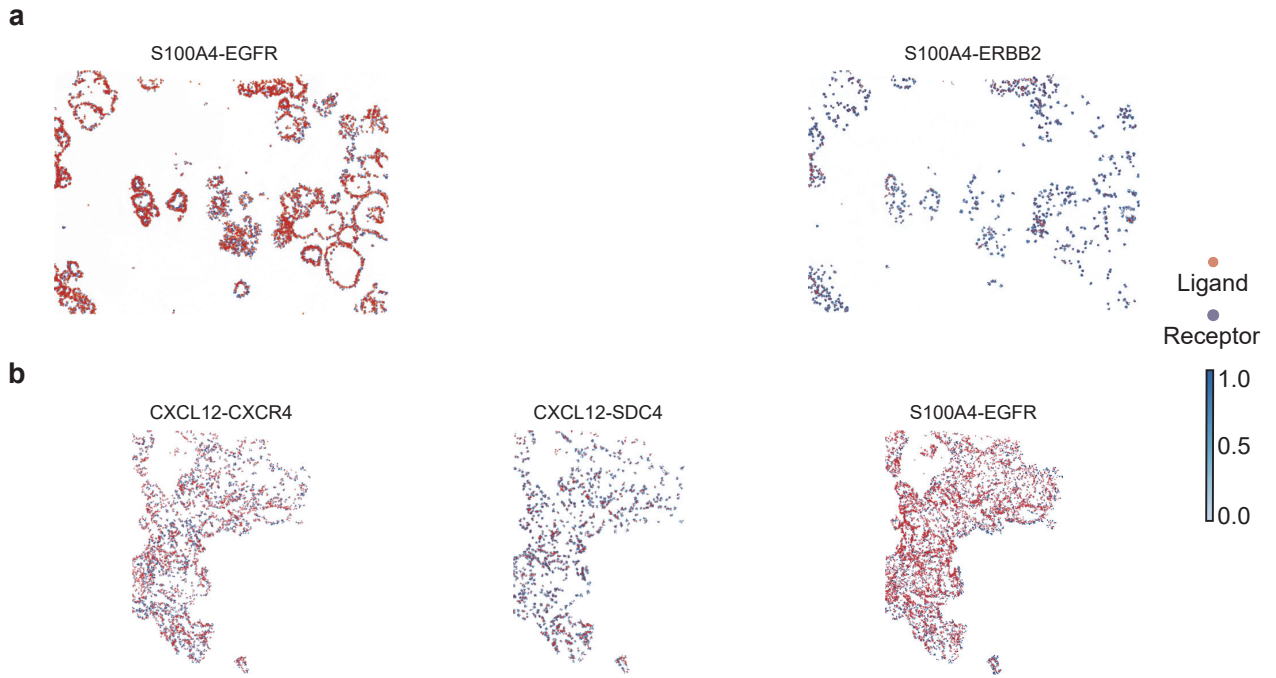


Figure S18: **Spatial localization of representative LR interactions in breast cancer boundary communication ecosystems.** (a) Spatial localization of representative LR pairs associated with CE-7, a DCIS-associated boundary ecosystem. (b) Spatial localization of representative LR pairs associated with CE-1, an invasive-tumor-associated boundary ecosystem. Red points indicate cells in the corresponding communication ecosystem with ligand expression above the 90th percentile, and blue points indicate receptor-expressing interacting neighboring cells in the corresponding local communication context, with darker blue denoting higher receptor expression.

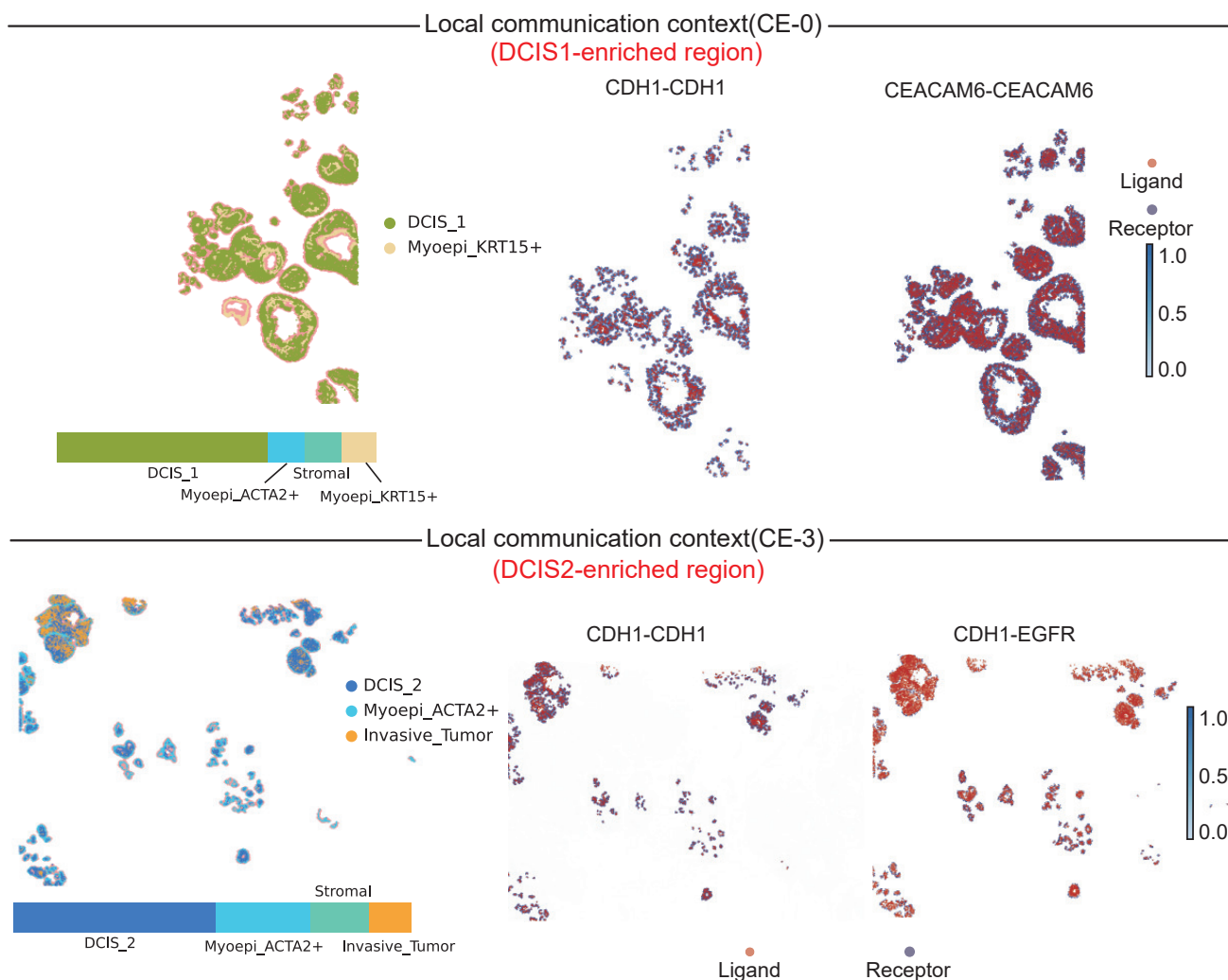


Figure S19: Local communication contexts and spatial localization of representative LR interactions in DCIS-associated breast cancer communication ecosystems. For each communication ecosystem (CE-0 and CE-3), left panels show the composition of interacting neighboring cellular populations surrounding cells assigned to the corresponding CE, and right panels show spatial localization of representative LR pairs. Red points indicate CE cells with ligand expression above the 90th percentile, and blue points indicate receptor-expressing interacting neighboring cells in the corresponding local communication context, with darker blue denoting higher receptor expression.

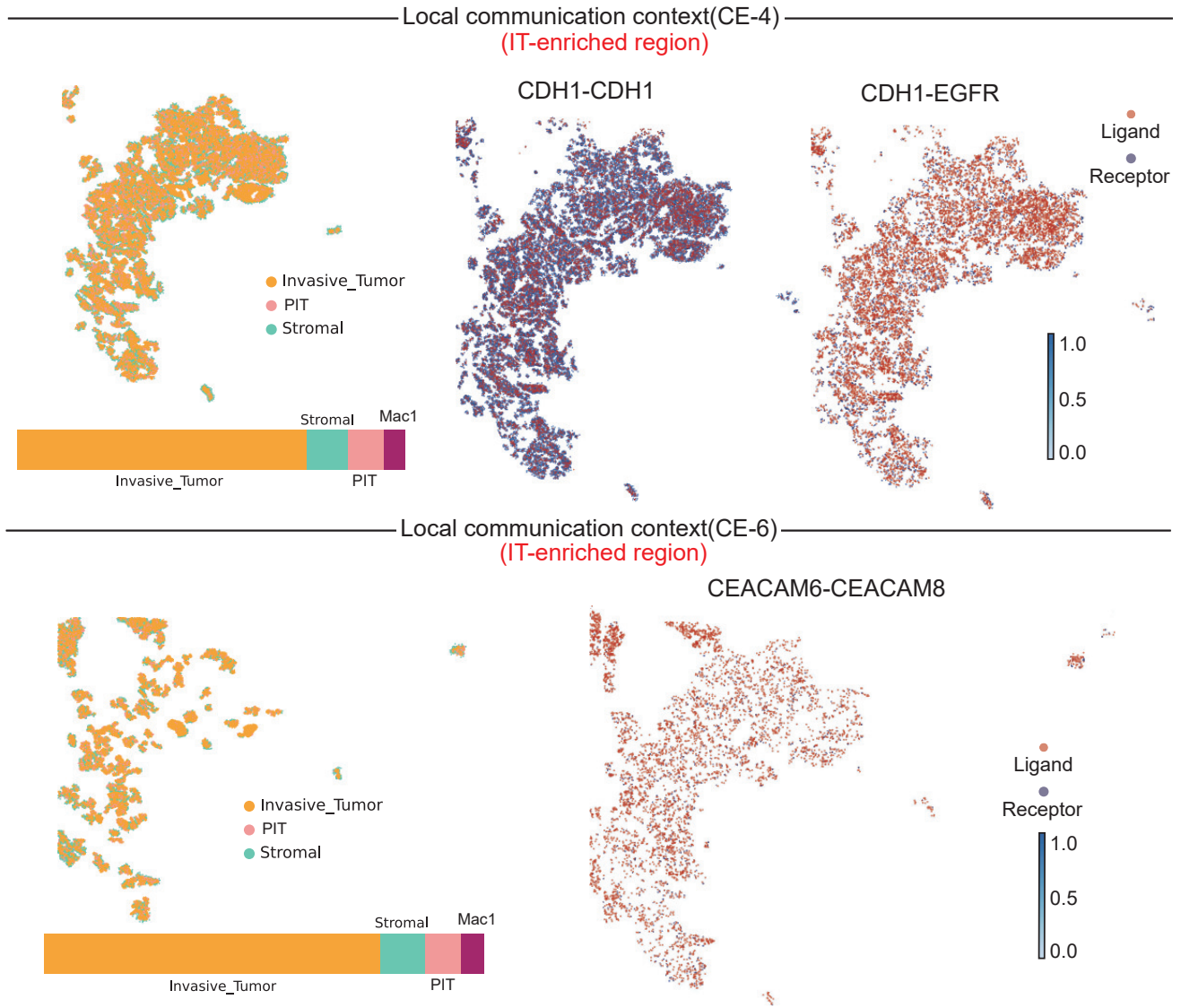
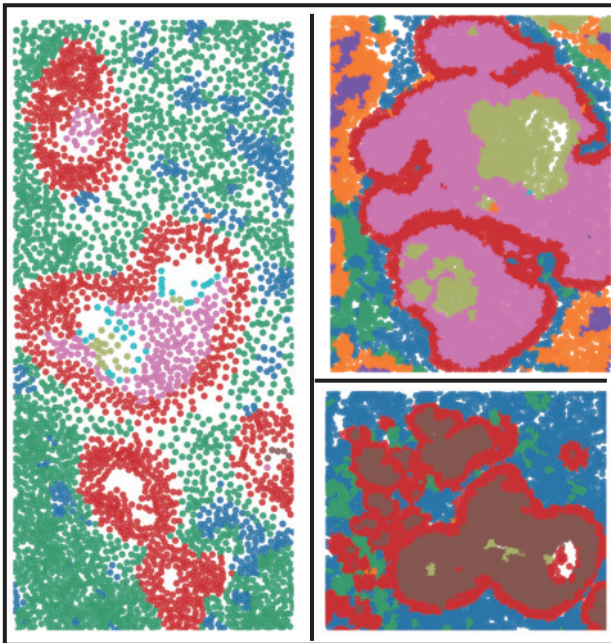
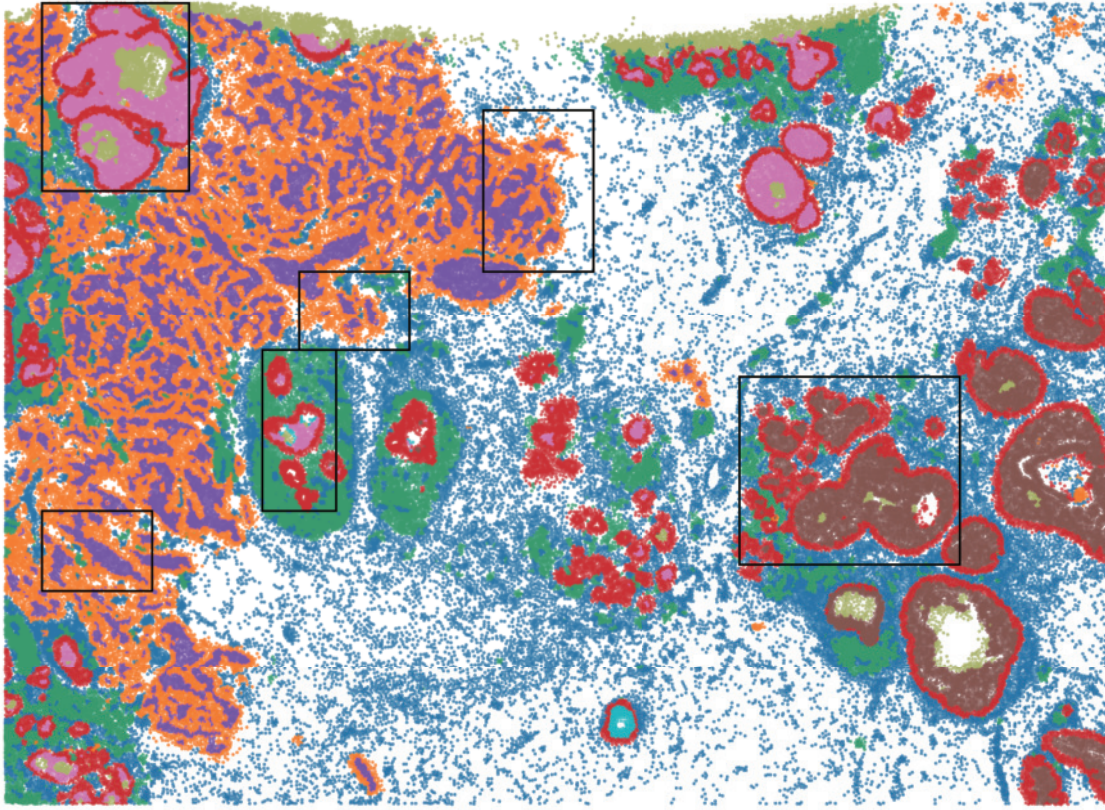
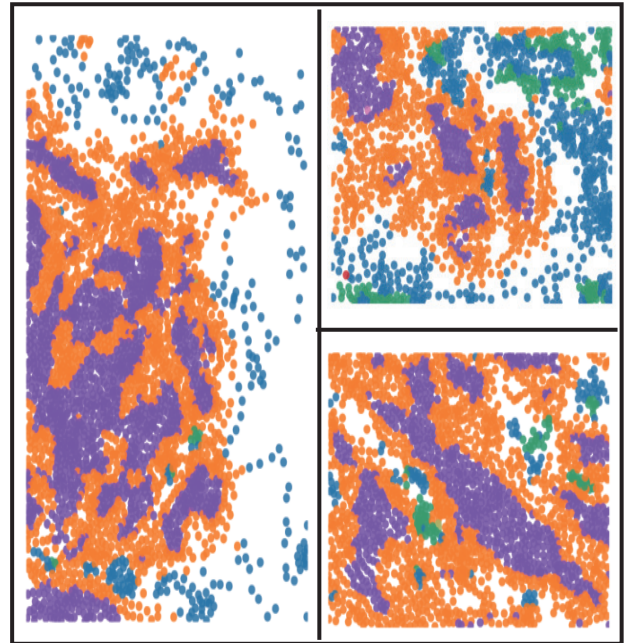


Figure S20: Local communication contexts and representative LR interactions in invasive-tumor-enriched breast cancer communication ecosystems. Local communication contexts are shown for CE-4 and CE-6, corresponding to invasive-tumor-enriched ecosystem contexts. Left panels show the composition of interacting neighboring cellular populations surrounding cells assigned to each CE, and right panels show spatial localization of representative LR pairs. Red points indicate CE cells with ligand expression above the 90th percentile, and blue points indicate receptor-expressing interacting neighboring cells in the corresponding local communication context, with darker blue denoting higher receptor expression.

BANKSY



DCIS boundary



IT boundary

Figure S21: Spatial distribution of CEs identified by BANKSY, with three representative regions of interest (ROIs) shown below for detailed comparison.

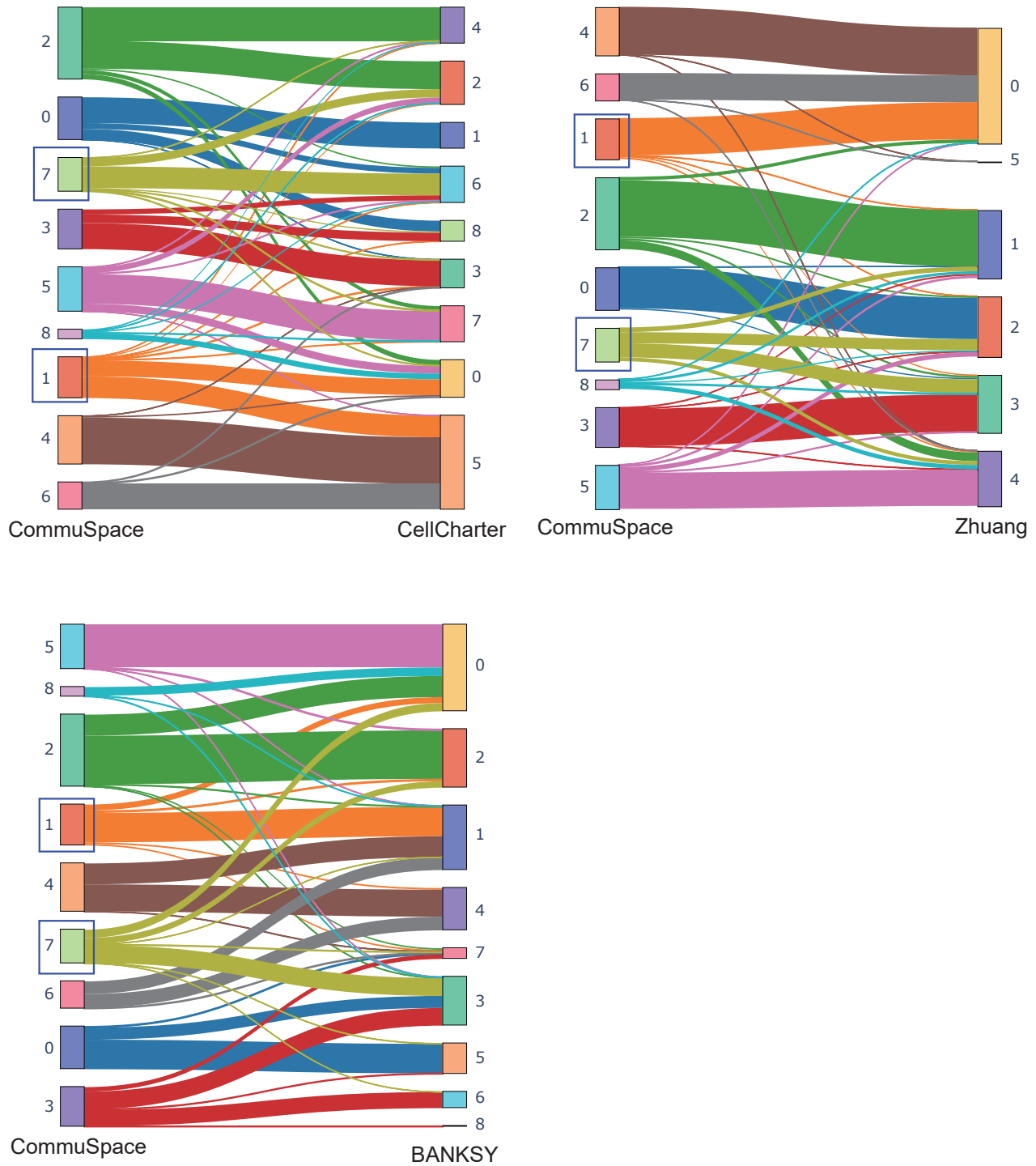


Figure S22: Sankey diagram between the communication-defined ecosystems and phenotype-defined domains with 9-CE solution for human breast cancer data.

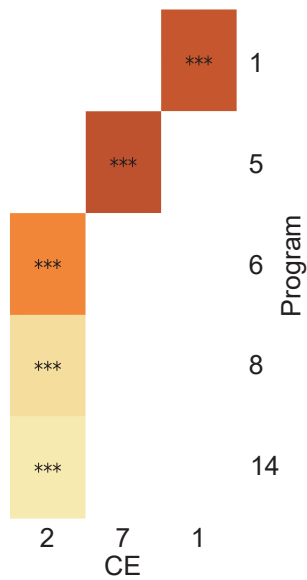


Figure S23: **Communication-program associations of ecosystem-associated CD8+ T cells.** Heatmap showing normalized associations between CD8+ T-cell communication ecosystems and latent communication programs. Columns denote CE-2, CE-7 and CE-1, and rows denote communication programs. Asterisks indicate significant ecosystem–program associations ($***p \leq 0.0001$, one-sided Mann–Whitney U test).

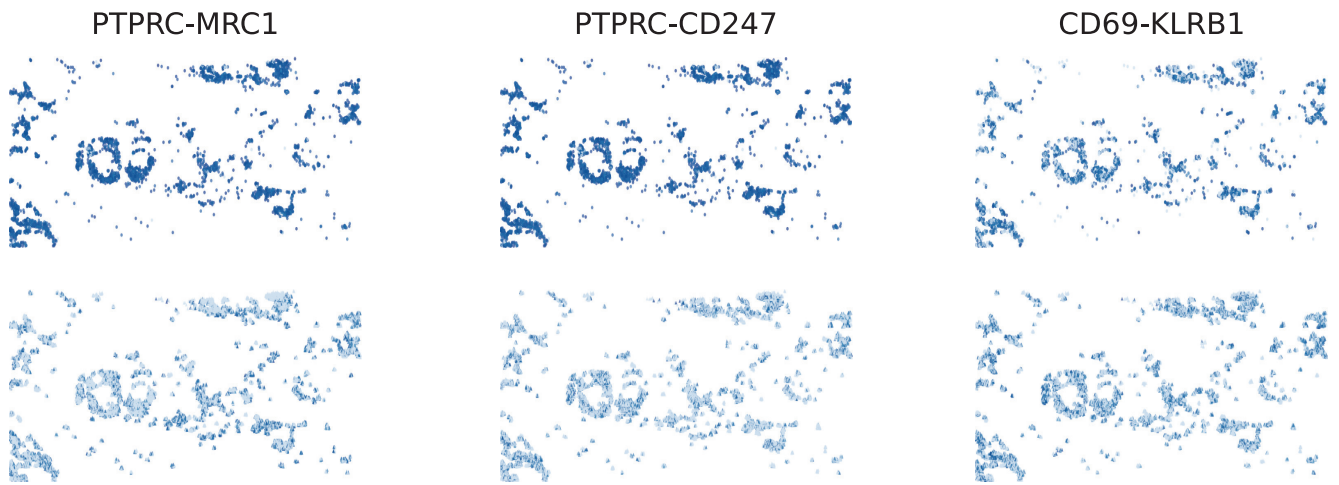


Figure S24: Local communication context and spatial localization of representative signaling interactions for CD8+ T cells in CE-2. Spatial localization of representative signaling interactions associated with CD8+ T cells in CE-2, an immune-recruitment communication ecosystem. Top panels show ligand or sender-associated expression in CD8+ T cells assigned to CE-2, and bottom panels show the corresponding receptor or receiver-associated expression in interacting neighboring cells within the local communication context. Color intensity indicates normalized expression levels.

CXCL12-CXCR4

CXCL12-SDC4

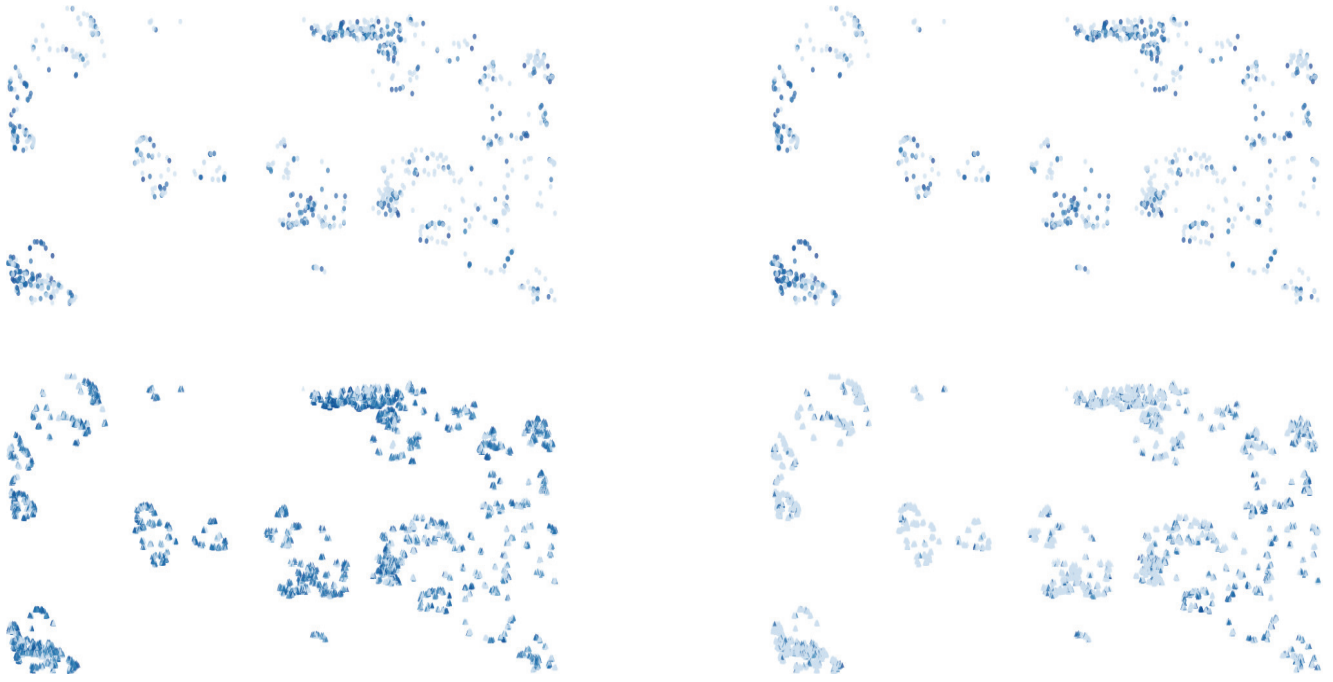


Figure S25: **Local communication context and spatial localization of representative signaling interactions for CD8+ T cells in CE-7.** Spatial localization of representative signaling interactions associated with CD8+ T cells in CE-7, a DCIS-boundary communication ecosystem. Top panels show ligand or sender-associated expression in CD8+ T cells assigned to CE-7, and bottom panels show the corresponding receptor or receiver-associated expression in interacting neighboring cells within the local communication context. Color intensity indicates normalized expression levels.

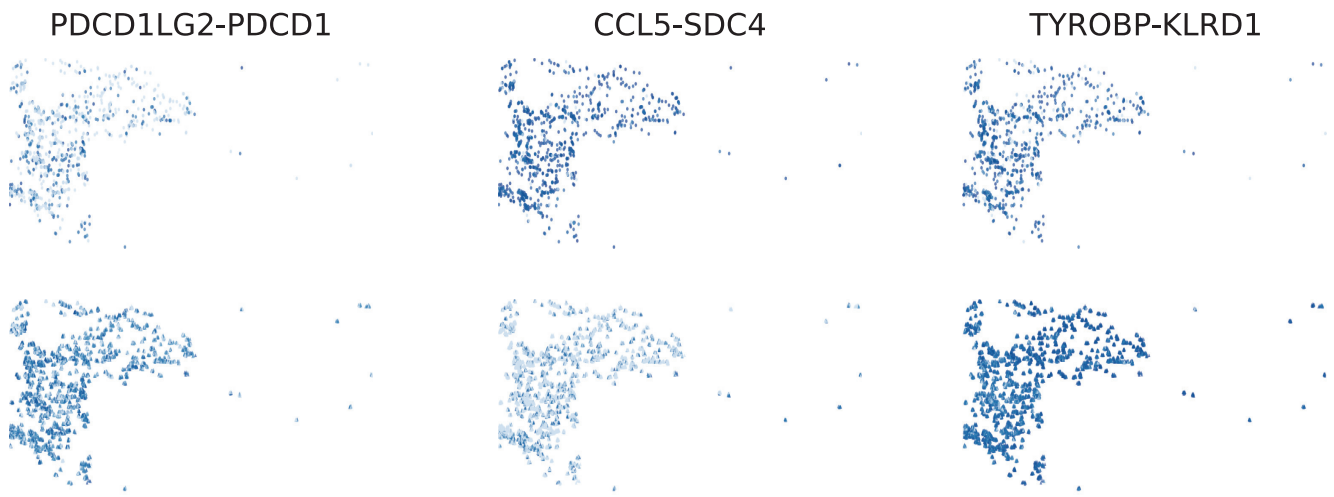


Figure S26: Local communication context and spatial localization of representative signaling interactions for CD8+ T cells in CE-1. Spatial localization of representative signaling interactions associated with CD8+ T cells in CE-1, an invasive-tumor-boundary communication ecosystem. Top panels show ligand or sender-associated expression in CD8+ T cells assigned to CE-1, and bottom panels show the corresponding receptor or receiver-associated expression in interacting neighboring cells within the local communication context. Color intensity indicates normalized expression levels.

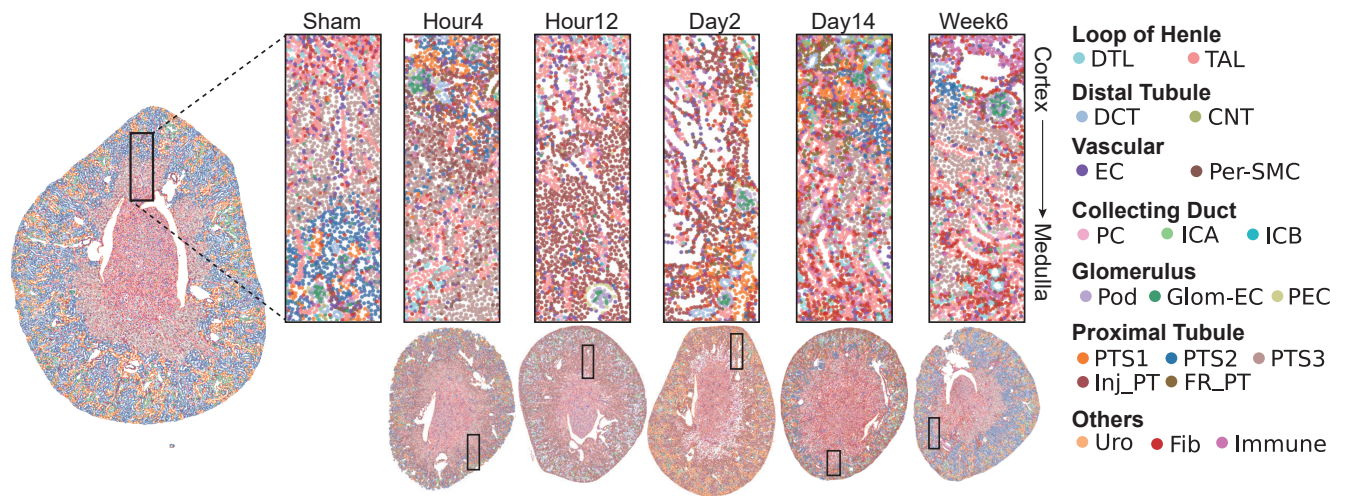


Figure S27: Spatial organization and temporal dynamics of cell types during kidney injury and repair. Left, whole-section view of the kidney tissue with cell types annotated. The boxed region indicates the area selected for detailed visualization. Middle, zoom-in views of the selected region across time points (Sham, Hour 4, Hour 12, Day 2, Day 14, and Week 6), showing the spatial distribution of cell types during injury and repair. Bottom, corresponding whole-section views for each time point, with boxed regions indicating the locations of the zoomed-in areas. Colors denote cell-type identity as indicated in the legend.

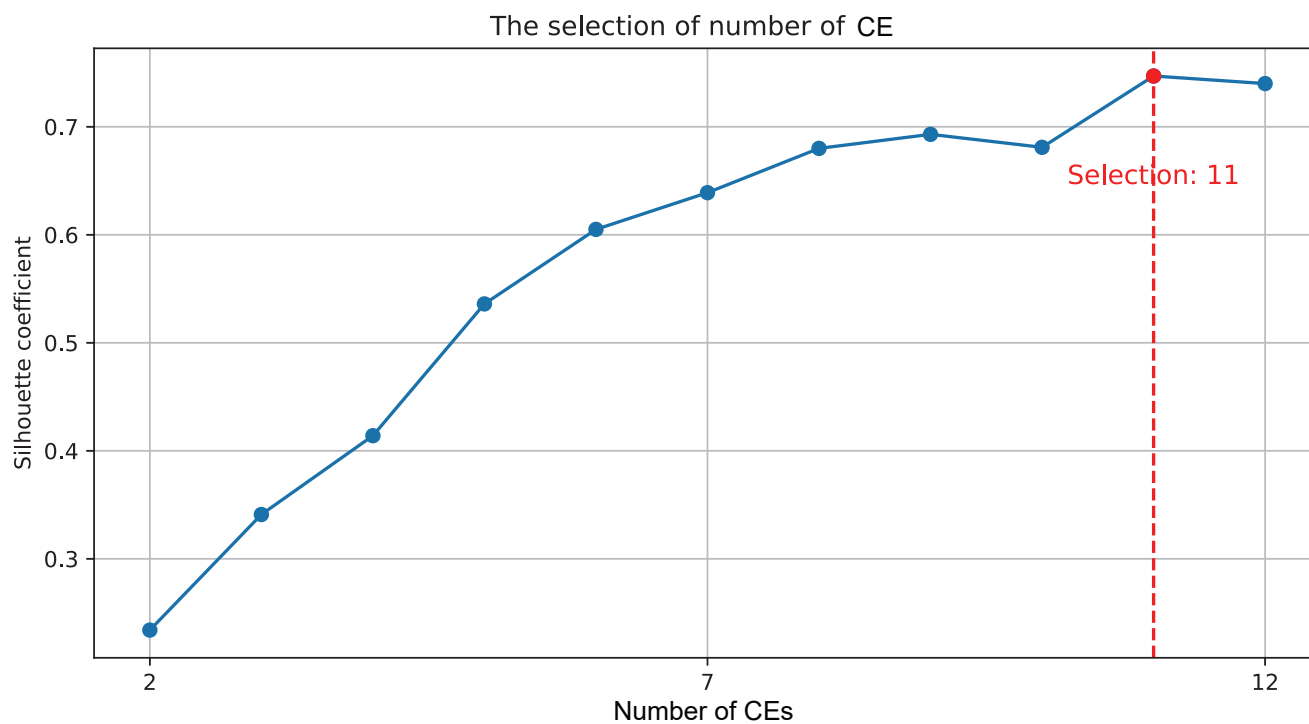


Figure S28: **Selection of the number of communication ecosystems for the kidney injury–repair dataset.** Silhouette coefficient is evaluated across candidate numbers of communication ecosystems (CEs). The selected number of CEs is 11, corresponding to the highest silhouette coefficient. The red point indicates the selected solution, and the dashed line indicates the chosen number of ecosystems.

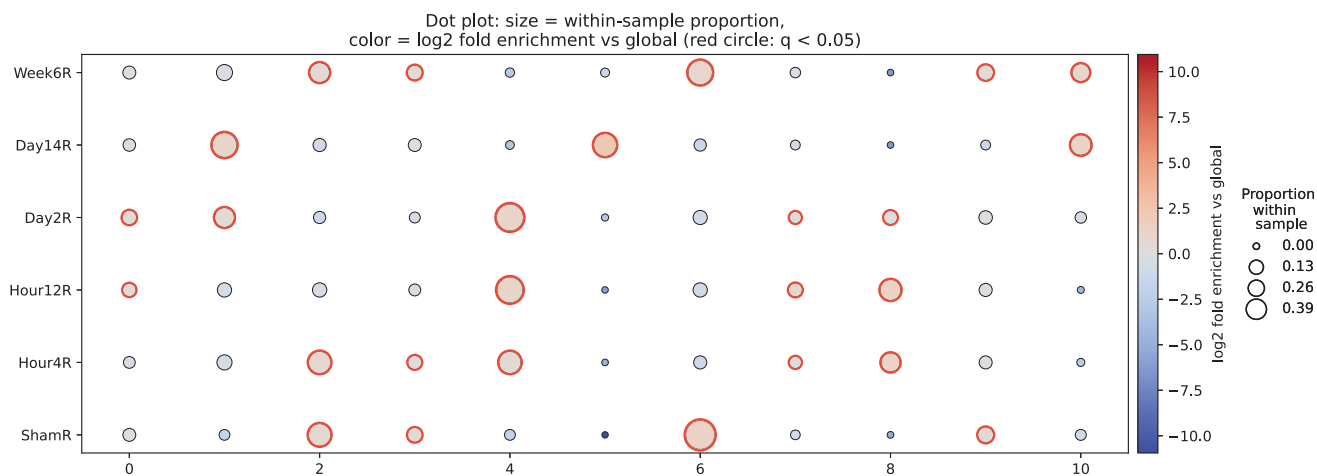


Figure S29: Temporal dynamics of communication ecosystem abundance in the kidney injury–repair dataset. Dot plot showing time point-specific abundance and enrichment of communication ecosystems (CEs) from sham to week 6 after injury. Dot size indicates the within-sample proportion of cells assigned to each CE, and color indicates log₂ fold enrichment relative to global CE abundance. Red outlines indicate statistically significant enrichment ($q < 0.05$).

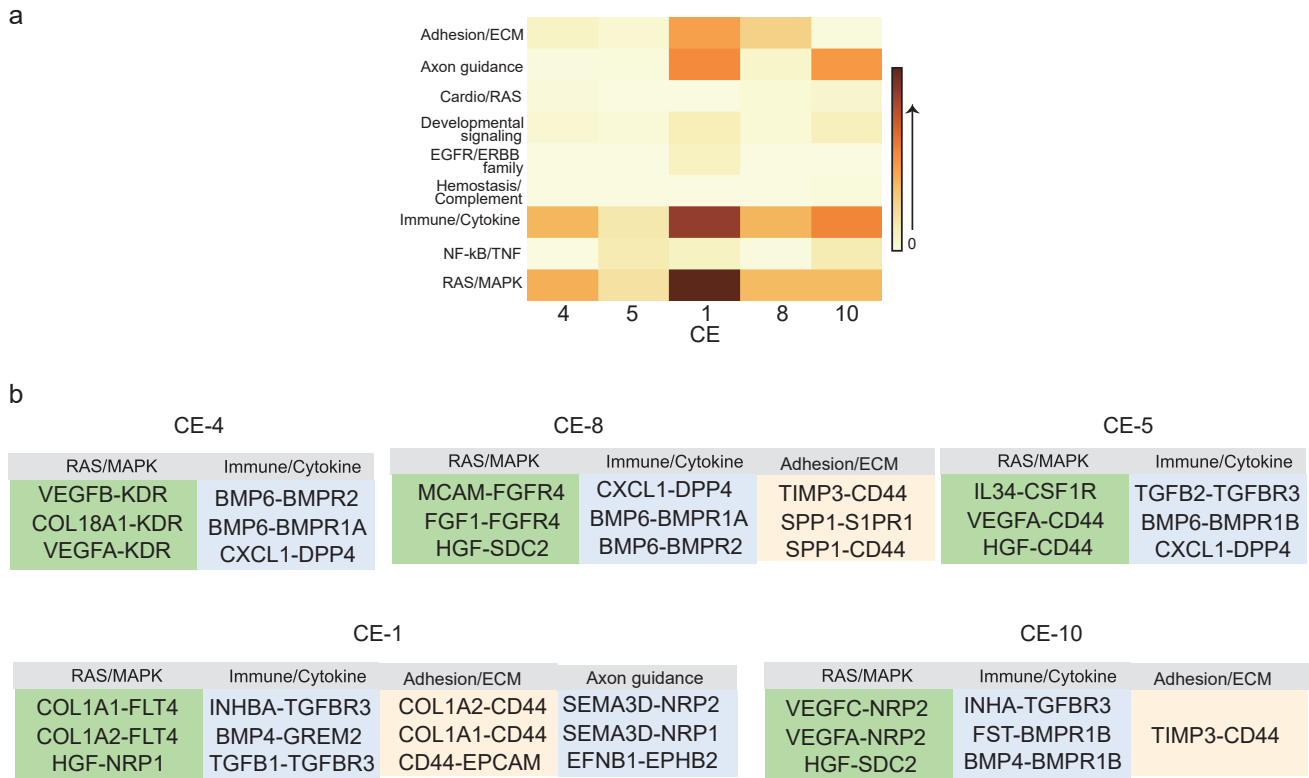


Figure S30: Pathway enrichment and representative LR signaling channels associated with kidney communication ecosystems. (a) Pathway enrichment associated with representative communication ecosystems (CEs), showing relative enrichment of signaling pathways across CE-4, CE-5, CE-1, CE-8, and CE-10. Color intensity indicates enrichment score. (b) Representative LR signaling channels contributing to selected communication ecosystems. LR pairs are grouped by associated signaling pathways, including RAS/MAPK, immune/cytokine, adhesion/ECM, and axon-guidance pathways.

2 Supplementary Text

2.1 Construction of communication tensors from local signaling relationships

CommuSpace represents each focal cell by the signaling relationships it forms with neighboring cellular populations. Let $i, j \in \{1, \dots, N\}$ index cells and $k \in \{1, \dots, K\}$ index annotated cellular populations. Let $\mathcal{L} = \{(l_p, r_p)\}_{p=1}^P$ denote a curated set of ligand–receptor (LR) gene pairs. For each cell i , $c_i \in \{1, \dots, K\}$ denotes its cellular-population annotation, and $\mathbf{s}_i \in \mathbb{R}^2$ denotes its spatial coordinate.

Spatial proximity is encoded by a directed q -nearest-neighbor graph constructed from Euclidean distances $d_{ij} = \|\mathbf{s}_i - \mathbf{s}_j\|_2$, where q denotes the number of spatial neighbors. Let $\mathcal{N}_i$ denote the set of neighboring cells of cell i , and let $\mathcal{N}_{ik} = \{j \in \mathcal{N}_i : c_j = k\}$ denote neighboring cells belonging to cellular population k .

In the default formulation used in the main Methods, the distance-dependent weight is defined as

$$w_{ij} = \begin{cases} \frac{1}{d_{ij} + \epsilon}, & j \in \mathcal{N}_i, \\ 0, & j \notin \mathcal{N}_i, \end{cases} \quad (1)$$

where $\epsilon > 0$ is a small constant introduced for numerical stability. As an optional distance transformation, a locally scaled exponential attenuation can alternatively be used, in which case

$$w_{ij} = \begin{cases} e^{-d_{ij}/\sigma_i}, & j \in \mathcal{N}_i, \\ 0, & j \notin \mathcal{N}_i, \end{cases} \quad (2)$$

where σ_i is a local scaling parameter defined as one-third of the median of the distances $\{d_{ij}\}_{j \in \mathcal{N}_i}$. Unless otherwise specified, w_{ij} denotes the inverse-distance weight in Eq. 1.

Prior to communication tensor construction, gene expression profiles can optionally be smoothed over a cell-type-restricted spatial neighborhood graph to reduce local technical noise without mixing expression across annotated cellular populations. Let $X^{(0)} \in \mathbb{R}_+^{N \times G}$ denote the original gene-expression matrix after standard preprocessing. By default, the expression matrix used for communication calculations is $X = X^{(0)}$. When optional smoothing is applied, only edges connecting cells with the same cellular-population annotation are retained from the spatial nearest-neighbor graph, yielding a same-population adjacency matrix A^{same} . Let $\hat{A}^{\text{same}}$ denote the normalized form of this adjacency matrix. The expression matrix used for communication calculations is then

$$X = (1 - \alpha)X^{(0)} + \alpha \hat{A}^{\text{same}} X^{(0)}, \quad (3)$$

where $\alpha \in [0, 1]$ controls the contribution of neighboring cells from the same cellular population. When smoothing is not used, $\alpha = 0$ and $X = X^{(0)}$. Unless otherwise specified, X denotes the expression matrix used in the corresponding analysis.

For each ligand–receptor pair $p = (l_p, r_p)$, the sender-centric communication score between focal cell i and neighboring cellular population k is defined as

$$\mathcal{T}_{ikp} = \sum_{j \in \mathcal{N}_{ik}} w_{ij} X_{i, l_p} X_{j, r_p}. \quad (4)$$

Under the default inverse-distance weighting in Eq. 1, this becomes

$$\mathcal{T}_{ikp} = \sum_{j \in \mathcal{N}_{ik}} \frac{X_{i, l_p} X_{j, r_p}}{d_{ij} + \epsilon}, \quad (5)$$

which is the sender-centric formulation used in the main Methods. If $\mathcal{N}_{ik}$ is empty, the summation is set to zero. Thus, $\mathcal{T}_{ikp}$ quantifies sender-centric signaling from focal cell i toward neighboring cellular population k through ligand–receptor signaling channel p .

The resulting sender-centric communication tensor, $\mathcal{T} \in \mathbb{R}_+^{N \times K \times P}$, organizes local signaling relationships along three axes: focal cells, neighboring cellular populations and ligand–receptor signaling channels. For each focal cell i , the tensor slice $\mathcal{T}_{i,:,:}$ summarizes its local communication architecture by encoding how the focal cell communicates with surrounding cellular populations across multiple signaling channels.

A complementary receiver-centric profile is defined as

$$\mathcal{T}_{ikp}^{\text{receiver}} = X_{i,r_p} \sum_{j \in \mathcal{N}_{ik}} w_{ij} X_{j,l_p}, \quad (6)$$

where the focal cell i acts as the receptor-expressing receiver, and neighboring cells in cellular population k act as ligand-expressing senders. The sender- and receiver-centric formulations therefore provide complementary projections of local signaling relationships around each focal cell.

To jointly represent both focal-cell roles, a combined sender–receiver tensor is constructed by concatenating the sender- and receiver-centric profiles along the LR-channel dimension:

$$\mathcal{T}_{iku}^{\text{sender-receiver}} = \begin{cases} \mathcal{T}_{iku}, & 1 \leq u \leq P, \\ \mathcal{T}_{ik,u-P}^{\text{receiver}}, & P+1 \leq u \leq 2P. \end{cases} \quad (7)$$

The corresponding LR channels are labeled as $(l_p, r_p)_{\text{sender}}$ and $(l_p, r_p)_{\text{receiver}}$ to distinguish the two focal-cell roles.

The receiver-centric formulation yields a tensor $\mathcal{T}^{\text{receiver}} \in \mathbb{R}_+^{N \times K \times P}$, whereas the combined formulation yields $\mathcal{T}^{\text{sender-receiver}} \in \mathbb{R}_+^{N \times K \times 2P}$.

Unless otherwise specified, the sender-centric tensor $\mathcal{T}$ is used as the default representation for downstream communication-program inference. The receiver-centric and combined sender–receiver tensors are used for complementary analyses of alternative focal-cell signaling roles.

2.2 Robust evaluation of communication-ecosystem assignments across alternative communication representations

To assess whether communication ecosystems (CEs) correspond to stable communication-defined organizational states rather than arbitrary partitions of cells, we evaluated CE assignments across alternative representations of local ligand–receptor (LR) activity. The underlying principle is that a biologically meaningful CE should preserve coherent signaling relationships under reasonable perturbations of the communication representation, whereas assignments that merge heterogeneous signaling states are expected to show reduced communication coherence and predictive consistency. We therefore designed a robustness-oriented evaluation framework that quantifies whether CE labels provide a compact and reproducible summary of cell–cell communication structure.

Alternative communication tensor constructions. All communication tensors were constructed using the same spatial neighborhoods and LR reference atlas, such that differences arose only from how

local LR activity was summarized. These alternative tensor constructions were used to probe the robustness of CE assignments to different formulations of local communication activity, rather than to define alternative biological labels.

In addition to the default communication tensor used in CommuSpace, we constructed an aggregated communication tensor in which communication strength is defined as the product of ligand expression in the focal cell and the weighted mean receptor expression among neighboring cells of a given type,

$$\mathcal{T}_{i,k,t}^{\text{agg}} = X_{i,l_t} \cdot \frac{\sum_{j \in \mathcal{N}_{i,k}} w_{ij} X_{j,r_t}}{\sum_{j \in \mathcal{N}_{i,k}} w_{ij} + \varepsilon}, \quad (8)$$

where w_{ij} denotes a distance-dependent weight and ε is a small constant for numerical stability. This formulation emphasizes neighborhood-level aggregation of receptor activity while preserving the focal-cell ligand contribution.

We further constructed a binary communication tensor in which ligand and receptor activities were thresholded,

$$\mathcal{T}_{i,k,t}^{\text{bin}} = \mathbb{I}(X_{i,l_t} > \tau_{l_t}) \cdot \mathbb{I}\left(\frac{1}{|\mathcal{N}_{i,k}|} \sum_{j \in \mathcal{N}_{i,k}} X_{j,r_t} > \tau_{r_t}\right), \quad (9)$$

with $\mathcal{T}_{i,k,t}^{\text{bin}} = 0$ when $\mathcal{N}_{i,k} = \emptyset$. Here, τ_{l_t} and τ_{r_t} denote gene-specific thresholds. This formulation captures the presence or absence of local signaling activity rather than its magnitude.

Communication feature representation. For each communication tensor $\mathcal{T}$, we constructed a cell-level communication feature representation by flattening the tensor along the cell-type and LR dimensions,

$$\mathbf{c}_i = \text{vec}(\mathcal{T}_{i,:,:}) \in \mathbb{R}^{KT}, \quad (10)$$

thereby preserving cell-type-resolved signaling structure for each focal cell. Principal component analysis (PCA) was then applied to obtain a low-dimensional communication feature space for downstream evaluation.

Evaluation of communication coherence. We first asked whether cells assigned to the same CE exhibited coherent communication profiles. For each communication representation, CE assignments were evaluated in the corresponding communication feature space using three complementary metrics: (i) the average pairwise cosine similarity within each CE (IntraSim), (ii) the silhouette coefficient (SH), and (iii) the Fisher ratio, defined as the ratio of between-CE variance to within-CE variance. Together, these metrics quantify within-CE communication similarity, separability between CEs and variance structure in communication space.

Evaluation of predictive consistency. To assess whether CE labels provide a compact and generalizable summary of communication structure, we performed a train–test evaluation. For each communication tensor, we constructed a cell-by-cell-type communication matrix

$$S_{i,k} = \sum_{t=1}^T \mathcal{T}_{i,k,t}, \quad (11)$$

which summarizes the communication activity of each cell across neighboring cell types.

Cells were randomly split into training and testing sets. For each CE g , we defined a CE-specific communication prototype in the training set as the mean communication profile

$$\mu_g = \frac{1}{|\mathcal{I}_g^{\text{train}}|} \sum_{i \in \mathcal{I}_g^{\text{train}}} S_i, \quad (12)$$

where $\mathcal{I}_g^{\text{train}}$ denotes the set of training cells assigned to CE g . For each test cell, its communication profile was predicted using the prototype corresponding to its CE label. Predictive performance was quantified using the coefficient of determination (R^2) and Spearman correlation between predicted and observed communication profiles.

Interpretation. Together, these analyses evaluate whether CEs represent stable organizational states in communication space. By repeating coherence and predictive-consistency analyses across alternative communication representations, we tested whether CE assignments consistently capture distinct communication modes or instead merge heterogeneous signaling patterns into the same organizational unit.

2.3 Optimization algorithm for communication-program inference

To infer interpretable and minimally redundant communication programs from the communication tensor, CommuSpace formulates communication-program inference as a constrained CANDECOMP-PARAFAC (CP) decomposition problem. Given a communication tensor $\mathcal{T}$, the goal is to learn a low-rank representation that preserves local signaling structure while yielding additive and distinguishable communication programs for downstream communication-space construction.

The optimization problem is defined as

$$\min_{\lambda, U, V, W} \quad \frac{1}{2} \|\mathcal{T} - [\lambda; U; V; W]\|_F^2 + \frac{\zeta}{2} \|U^\top U - \text{diag}(\text{diag}(U^\top U))\|_F^2 \quad (13)$$

$$\text{s.t.} \quad \|U_r\|_2^2 = 1, \|V_r\|_2^2 = 1, \|W_r\|_2^2 = 1, \quad r = 1, \dots, R, \quad (14)$$

$$U \in [0, 1]^{N \times R}, V \in [0, 1]^{K \times R}, W \in [0, 1]^{P \times R}, \lambda \in [0, +\infty)^R. \quad (15)$$

Here, $[\lambda; U; V; W] = \sum_{r=1}^R \lambda_r U_r \circ V_r \circ W_r$ denotes the rank- R CP reconstruction of $\mathcal{T}$. The factor matrices U , V and W correspond to focal cells, neighboring cell types and ligand–receptor (LR) channels, respectively. Each rank-one component defines a communication program: U_r represents the activity of program r across cells, V_r represents the neighboring cell-type context associated with the program, and W_r represents the LR channels contributing to the program.

The reconstruction term preserves the observed local communication tensor, whereas the second term imposes a weak orthogonality penalty on the cell loading matrix U . This penalty suppresses redundant communication programs by penalizing off-diagonal entries of $U^\top U$, while still allowing biologically meaningful overlap between programs. The regularization parameter $\zeta > 0$ controls the strength of this redundancy penalty. Unit-norm constraints resolve the scale ambiguity inherent to CP decomposition and make component loadings comparable across programs. Non-negativity constraints ensure that communication programs are additive, which improves interpretability of the inferred communication-space coordinates.

The optimization problem is solved using a gradient-based framework implemented in *PyTorch*, which enables automatic differentiation and GPU acceleration. Model parameters are initialized using non-negative CP decomposition, $(\lambda^0, U^0, V^0, W^0)$, computed with the `non_negative_parafac` routine

in the tensorly package. Parameters are then optimized using the Adam optimizer with an initial learning rate of 1×10^{-5} . A *ReduceLROnPlateau* scheduler adaptively decreases the learning rate when the training loss plateaus.

The regularization parameter ζ is set adaptively from the initialization as

$$\zeta = \gamma \times \frac{\|\mathcal{T} - [\lambda^0; U^0; V^0; W^0]\|_F^2}{\|(U^0)^\top U^0 - \text{diag}(\text{diag}((U^0)^\top U^0))\|_F^2 + \varepsilon}, \quad (16)$$

where γ controls the relative strength of the weak orthogonality penalty and ε is a small constant for numerical stability. Unless otherwise specified, γ is set to 0.1. The optimized cell loading matrix U provides the communication-program activity representation used to embed cells into communication space. The full optimization procedure is summarized in Algorithm 1.

2.4 Scalable optimization for large-scale communication-space construction

For large-scale spatial transcriptomics datasets, direct optimization of the regularized CP decomposition in Eqs. (13)–(15) can become computationally demanding because the cell mode of the communication tensor $\mathcal{T} \in \mathbb{R}^{N \times K \times P}$ may contain hundreds of thousands of cells. To enable scalable communication-program inference, CommuSpace uses an optimization strategy that combines subset-based initialization, block-wise alternating updates and delayed weak-orthogonality regularization. This strategy avoids loading or updating the full cell factor matrix simultaneously and yields memory usage that scales approximately linearly with the number of cells.

Subset-based initialization. We first initialize the factor matrices associated with the neighboring cell-type and LR-channel modes using a random subset of cells. Let $\mathcal{I} \subset \{1, \dots, N\}$ denote a subset of cells with $|\mathcal{I}| = N_{\text{sub}}$, and let $\mathcal{T}_{\mathcal{I}} \in \mathbb{R}^{N_{\text{sub}} \times K \times T}$ denote the corresponding sub-tensor. A non-negative CP decomposition is computed as

$$\mathcal{T}_{\mathcal{I}} \approx [\lambda^0; U_{\mathcal{I}}^0; V^0; W^0]. \quad (17)$$

The subset decomposition provides an initialization for the global communication programs. Only (λ^0, V^0, W^0) are retained for large-scale optimization, whereas the full cell loading matrix U is learned block-wise across all cells. The columns of V^0 and W^0 are normalized, and the absorbed scaling is transferred to λ^0 .

Block-wise update of the cell loading matrix. Given (λ, V, W) , updating the cell loading matrix $U \in \mathbb{R}^{N \times R}$ decomposes over rows and can therefore be performed in cell blocks. Define

$$H = (V^\top V) * (W^\top W) * (\lambda \lambda^\top) \in \mathbb{R}^{R \times R}, \quad (18)$$

where $*$ denotes the Hadamard product. The reconstruction term can be written as

$$\frac{1}{2} \|\mathcal{T} - [\lambda; U; V; W]\|_F^2 = \frac{1}{2} \text{tr}(U H U^\top) - \text{tr}(M U^\top) + \text{const}, \quad (19)$$

where $M \in \mathbb{R}^{N \times R}$ is the mode-1 MTTKRP matrix with entries $M_{ir} = \sum_{k=1}^K \sum_{t=1}^T \mathcal{T}_{ikt} V_{kr} W_{tr} \lambda_r$. The corresponding gradient with respect to U is

$$\nabla_U \frac{1}{2} \|\mathcal{T} - [\lambda; U; V; W]\|_F^2 = U H - M. \quad (20)$$

To avoid materializing all rows of U at once, the cell mode is partitioned into blocks. For a block of cells $\mathcal{B} \subset \{1, \dots, N\}$, let $U_{\mathcal{B}}$ and $\mathcal{T}_{\mathcal{B}}$ denote the corresponding cell loading submatrix and tensor block, and let $M_{\mathcal{B}}$ denote the block-specific MTTKRP. The block update is

$$U_{\mathcal{B}} \leftarrow \Pi_+(U_{\mathcal{B}} - \eta_U (U_{\mathcal{B}} H - M_{\mathcal{B}})), \quad (21)$$

where Π_+ projects onto the non-negative orthant and η_U is set according to the spectral norm of H . This update learns communication-program activities for all cells while keeping memory usage bounded by the block size.

Block-wise updates for cell-type and LR-channel factors. Given U , the neighboring cell-type factor V and the LR-channel factor W are updated using MTTKRP-based non-negative least-squares updates. Define

$$H_V = (U^\top U) * (W^\top W) * (\lambda \lambda^\top), \quad (22)$$

and

$$H_W = (U^\top U) * (V^\top V) * (\lambda \lambda^\top). \quad (23)$$

The corresponding MTTKRP matrices $M^{(V)}$ and $M^{(W)}$ are accumulated block-wise over the cell mode. The factor updates solve

$$\min_{V \geq 0} \frac{1}{2} \text{tr}(V H_V V^\top) - \text{tr}(M^{(V)} V^\top), \quad \min_{W \geq 0} \frac{1}{2} \text{tr}(W H_W W^\top) - \text{tr}(M^{(W)} W^\top), \quad (24)$$

using HALS updates. After each update, columns of V and W are normalized and the absorbed scaling is transferred to λ , maintaining a consistent CP scaling across iterations.

Delayed weak-orthogonality regularization. To improve optimization stability, CommuSpace applies the weak-orthogonality penalty after an initial reconstruction-only warm-up phase. During warm-up, the model first learns communication programs that explain the observed tensor. After warm-up, the regularization coefficient is estimated as

$$\zeta = \gamma \frac{\frac{1}{N} \|\mathcal{T} - [\lambda; U; V; W]\|_F^2}{\frac{1}{R(R-1)} \|U^\top U - \text{diag}(\text{diag}(U^\top U))\|_F^2 + \varepsilon}, \quad (25)$$

where γ controls the relative strength of the weak-orthogonality penalty and ε is a small constant for numerical stability.

The weak-orthogonality penalty is then applied periodically to reduce redundancy among cell-level communication-program activities:

$$U \leftarrow \Pi_+ (U - \eta_{\text{orth}} 2\zeta U \text{Off}(U^\top U)), \quad (26)$$

where $\text{Off}(A) = A - \text{diag}(\text{diag}(A))$. This delayed regularization encourages distinct communication programs while avoiding unstable early updates before the reconstruction structure has been learned.

Final normalization. After convergence, the columns of U are normalized to unit ℓ_2 norm and the absorbed scaling is transferred to λ . The resulting cell loading matrix U provides the communication-program activity representation used to embed cells into communication space.

This scalable optimization procedure enables CommuSpace to construct communication-space representations for datasets containing hundreds of thousands of cells while preserving the interpretability of communication programs and the numerical stability of constrained CP decomposition.

2.5 Selection of the CP rank

Selecting the CP rank determines the number of communication programs used to construct communication space. In CommuSpace, this choice balances the ability to capture recurrent local signaling structures with the interpretability and parsimony of the resulting communication-space representation. To select an appropriate rank, models are trained independently across a range of candidate ranks under identical optimization settings.

For each candidate rank R , model performance is quantified using the reconstruction fit at convergence,

$$\text{Fit}^{(R)} = 1 - \frac{\|\mathcal{T} - \widehat{\mathcal{T}}^{(R)}\|_F}{\|\mathcal{T}\|_F}, \quad (27)$$

where $\widehat{\mathcal{T}}^{(R)}$ denotes the rank- R CP reconstruction of the communication tensor $\mathcal{T}$. This score provides a normalized measure of how well the rank- R communication programs reconstruct the observed local signaling relationships.

Although increasing the rank generally improves reconstruction, the empirical fit curve can exhibit non-monotonic fluctuations due to the non-convexity of CP decomposition and stochastic optimization. To obtain a stable estimate of the gain in communication-space expressiveness, the fit curve is transformed into its monotonic envelope,

$$\widetilde{\text{Fit}}^{(R)} = \max_{R' \leq R} \text{Fit}^{(R')}. \quad (28)$$

This transformation preserves the overall improvement trend while suppressing spurious local decreases caused by optimization variability.

The final rank is selected as the knee point of the monotonic fit-rank curve using a curvature-based criterion. The knee point identifies the smallest rank beyond which additional communication programs provide diminishing improvement in tensor reconstruction. This procedure yields a parsimonious set of communication programs that captures the dominant communication structure while avoiding overparameterization of communication space.

2.6 Statistical framework for enrichment analysis

We used a unified enrichment framework to quantify associations between categorical annotations defined on the same set of cells. These annotations include communication ecosystems (CEs), dominant or discretized communication-program assignments, cell types, anatomical regions, temporal stages, disease states and other experimental or spatial conditions. This framework was used to determine whether communication-space-derived organizational states were preferentially associated with specific cellular, spatial or biological annotations.

Let $\mathcal{X} = \{x_1, \dots, x_N\}$ denote a population of N cells. Suppose two categorical annotations are defined on this population,

$$A : \mathcal{X} \rightarrow \{1, \dots, K_A\}, \quad B : \mathcal{X} \rightarrow \{1, \dots, K_B\},$$

where A and B assign each cell to one of K_A and K_B discrete categories, respectively. For example, A may denote CE assignment and B may denote cell type, time point, anatomical region or disease condition. For each category pair (a, b) , the observed overlap is defined as

$$C_{a,b} = \#\{x \in \mathcal{X} : A(x) = a \text{ and } B(x) = b\}. \quad (29)$$

Let

$$n_a = \sum_{b=1}^{K_B} C_{a,b}, \quad n_b = \sum_{a=1}^{K_A} C_{a,b}, \quad N = \sum_{a=1}^{K_A} \sum_{b=1}^{K_B} C_{a,b}$$

denote the corresponding marginal counts and total cell number.

To test whether categories a and b are associated beyond random overlap, we evaluated the null hypothesis that annotations A and B are independent given their marginal counts. Under this null model, the overlap count follows a hypergeometric distribution,

$$X \sim \text{Hypergeom}(N, n_a, n_b), \quad (30)$$

where N is the total number of cells, n_a is the number of cells in category a , and n_b is the number of cells in category b .

A one-sided enrichment p -value is computed as

$$p_{a,b} = \Pr[X \geq C_{a,b}], \quad (31)$$

which quantifies the probability of observing at least $C_{a,b}$ overlapping cells under random assignment with fixed marginal counts.

In addition to statistical significance, we quantified the strength and direction of association using conditional proportions. The proportion of category b cells assigned to category a is defined as

$$P_{a|b} = \frac{C_{a,b}}{n_b}, \quad (32)$$

whereas the proportion of category a cells annotated as category b is defined as

$$P_{b|a} = \frac{C_{a,b}}{n_a}. \quad (33)$$

These complementary quantities distinguish whether a biological annotation is concentrated within a given CE and whether that CE is predominantly composed of the annotation of interest.

Multiple hypothesis testing was controlled using the Benjamini–Hochberg procedure. Unless otherwise specified, enrichment was defined using combined thresholds on adjusted statistical significance and effect size. This enrichment framework was used to interpret communication ecosystems and communication programs in relation to cell identity, tissue location, temporal progression and disease-associated conditions.

2.7 Characterization of communication ecosystems

Communication ecosystems (CEs) are characterized along four complementary dimensions: cellular composition, communication-program activity, spatial organization and hierarchical relationships. These analyses are used to interpret CEs as communication-space-derived organizational states rather than as conventional cell-type clusters or spatial domains.

2.7.1 Cellular composition

To summarize the cellular composition of each CE, reference cell-type annotations are cross-tabulated with CE assignments to obtain a cell type-by-CE contingency table. Cell types enriched in each CE

are identified using the general enrichment framework described in Supplementary Text S2.6, with one-sided hypergeometric tests performed against the global cell-type distribution and multiple testing controlled using the Benjamini–Hochberg procedure.

Cell-type enrichment analysis distinguishes CEs dominated by a single lineage from those containing multiple cellular populations. Because CEs are defined in communication space, co-enrichment of multiple cell types within the same CE indicates convergence toward a shared communication-defined organizational state. Such co-enrichment reflects similarity in local signaling architecture, including shared communication programs, interacting cell-type contexts or ligand–receptor channels, rather than implying that all enriched cell types directly interact with one another.

2.7.2 Communication programs

To relate CEs to their underlying signaling mechanisms, CE assignments are associated with the latent communication programs inferred from tensor decomposition.

Association between CEs and communication programs. Each cell is assigned a dominant communication program according to the largest value in its cell loading vector from the cell loading matrix $U \in \mathbb{R}^{N \times R}$. CE labels and dominant communication-program labels therefore define two categorical annotations on the same set of cells. Enrichment of communication programs within CEs is assessed using the general enrichment framework described in Supplementary Text S2.6. Programs significantly enriched within a CE are interpreted as representative communication activities of that ecosystem.

Interpretation of cell-type and ligand–receptor components. Each communication program corresponds to a latent factor from tensor decomposition and is characterized by its associated loading vectors. For program r , the cell-type loading vector V_r encodes the neighboring cell-type contexts associated with the program, whereas the ligand–receptor loading vector W_r captures the LR channels contributing to the program. To identify dominant contributors, neighboring cell types and LR channels are ranked by their non-negative loadings, and the smallest set of components accounting for 90% of the cumulative loading is retained. These components define the core cellular and signaling context of each communication program.

2.7.3 Spatial relationships among communication ecosystems

Spatial relationships among CEs are assessed using neighborhood enrichment analysis implemented by the `nhood_enrichment` function in Squidpy. Cells are labeled by CE identity, and for each pair of CEs, the observed frequency of co-occurrence within spatial neighborhoods is compared against a randomized null model in which CE labels are permuted. This procedure tests whether pairs of communication-defined organizational states are spatially adjacent or spatially separated more often than expected by chance while preserving overall CE abundance. The resulting enrichment scores and significance values summarize non-random spatial relationships among CEs.

2.7.4 Hierarchical organization

Because CEs are derived from consensus hierarchical clustering of communication-space representations, their relationships can be traced across multiple resolutions. We assess hierarchical consistency

using two split-based metrics: *split purity*, which quantifies the homogeneity of fine-level CEs with respect to their parent coarse-level CEs, and *split entropy*, which measures the heterogeneity of coarse-level CEs across their fine-level subdivisions. For hierarchies with more than two levels, these metrics are computed for each consecutive pair of resolutions and then averaged to obtain overall hierarchical scores. This framework evaluates whether communication-space-derived ecosystems form coherent multiscale organizational structures.

2.8 Communication-ecosystem-dependent cell-state heterogeneity

Communication ecosystems (CEs) provide a framework for resolving heterogeneity among cells with the same lineage identity but distinct communication states. To characterize CE-dependent communication differences within the same cell type, communication-program activities are compared among cells of identical annotated cell type that occupy different CEs.

2.8.1 Within-lineage communication rewiring

For a given annotated cell type m , the cell loading matrix $U \in \mathbb{R}^{N \times R}$ is restricted to cells of that type. Let

$$\mathcal{I}_m = \{i : c(i) = m\}$$

denote the set of cells assigned to cell type m , and let

$$U^{(m)} = U_{\mathcal{I}_m, \cdot} \in \mathbb{R}^{N_m \times R}$$

denote the corresponding submatrix of communication-program activities, where $N_m = |\mathcal{I}_m|$. CE assignments are inherited from the global communication-space representation.

For each CE g , the subset of cell-type- m cells assigned to that ecosystem is defined as

$$\mathcal{I}_{m,g} = \{i : c(i) = m, z_i = g\},$$

where z_i denotes the CE label of cell i . The average communication-program activity of cell type m within CE g is summarized as

$$\bar{\mathbf{u}}_{m,g} = \frac{1}{|\mathcal{I}_{m,g}|} \sum_{i \in \mathcal{I}_{m,g}} U_i.$$

Comparing $\bar{\mathbf{u}}_{m,g}$ across CEs quantifies how cells with the same lineage identity adopt distinct communication states in different communication-defined organizational contexts.

Association between within-lineage CE subsets and communication programs. Each cell is assigned a dominant communication program according to the largest value in its cell loading vector. Within a given cell type, CE labels and dominant communication-program labels define two categorical annotations on the same subset of cells. Enrichment of communication programs within CE-specific subsets of the same cell type is assessed using the general enrichment framework described in Supplementary Text S2.6. Programs significantly enriched in a CE-specific subset are used to characterize the communication state adopted by that cell type within the corresponding ecosystem.

Interpretation of CE-dependent communication rewiring. To interpret signaling differences between CE-specific subsets of the same cell type, enriched communication programs are decomposed into their constituent cell-type and ligand–receptor components. For each program r , the cell-type loading vector V_r identifies the neighboring cellular contexts associated with the program, whereas the LR-channel loading vector W_r identifies the signaling channels contributing to the program. Neighboring cell types and LR channels are ranked by their non-negative loadings, and the smallest set of contributors accounting for 90% of the cumulative loading is retained. These components define the core communication context underlying CE-dependent rewiring within the same lineage.

2.8.2 Spatial localization and structural context

CE-assigned cells are mapped back to their spatial coordinates to determine how within-lineage communication states are organized in tissue space. For each cell type, the spatial distributions of its CE-specific subsets are quantified relative to structural regions, such as tumor core, invasive boundary, stromal compartment or other dataset-specific anatomical annotations. This analysis determines whether communication-state heterogeneity within a lineage is associated with spatial tissue architecture.

CE-dependent communication differences are summarized by comparing enriched communication programs, average program-activity profiles and dominant cell-type and LR-channel components across CEs for the same annotated cell type. This analysis separates lineage identity from communication state and identifies how the same cell type participates in distinct multicellular organizational contexts.

2.9 Dynamic remodeling trajectories in communication space

In the longitudinal kidney analysis, communication tensors from multiple time points are concatenated and decomposed jointly. This joint decomposition defines a shared set of communication programs across time, enabling cells from different temporal stages to be embedded into a common communication space. Because communication programs are inferred jointly, they are not time-specific; temporal variation is instead analyzed through changes in communication ecosystem (CE) abundance and through remodeling of CE-associated cellular microenvironments, ligand–receptor (LR) interactions and pathway-level signaling activities.

2.9.1 Time enrichment of communication ecosystems

To assess whether a CE is preferentially represented at a specific time point, associations between CE labels and time-point labels are evaluated using the general enrichment framework described in Supplementary Text 2.6. One-sided hypergeometric tests are performed under an independence null model, followed by Benjamini–Hochberg correction across time points within each CE. Time-enriched CEs are interpreted as communication-defined organizational states associated with specific phases of tissue remodeling.

2.9.2 CE-associated cellular microenvironments

CE-associated cellular microenvironments are characterized directly from the LR-resolved communication tensor described in Supplementary Text S2.1. Let $\mathcal{T}$ denote the communication tensor under the selected signaling mode. Analyses are restricted to LR channels, excluding abundance channels when

present. The LR-only tensor is defined as

$$\mathcal{O}_{i,m,t} = \mathcal{T}_{i,m,t}, \quad t \in \{1, \dots, T_{\text{LR}}\},$$

where i indexes focal cells, m indexes neighboring cell types and t indexes LR channels.

CE-level mean communication microenvironment matrices. For each CE z , let

$$\mathcal{I}_z = \{i : z_i = z\}$$

denote the set of cells assigned to CE z , with $N_z = |\mathcal{I}_z|$. The CE-associated communication microenvironment is summarized by averaging LR-resolved communication scores across cells assigned to the CE:

$$\overline{\mathcal{O}}_{m,t}^{(z)} = \frac{1}{N_z} \sum_{i \in \mathcal{I}_z} \mathcal{O}_{i,m,t}, \quad m = 1, \dots, K, \quad t = 1, \dots, T_{\text{LR}}. \quad (34)$$

This defines a matrix $\overline{\mathcal{O}}^{(z)} \in \mathbb{R}^{K \times T_{\text{LR}}}$ for each CE, capturing the neighboring cell-type contexts and LR channels associated with that communication-defined organizational state.

Selection of CE-specific microenvironment elements. To identify microenvironment features that are both strong and specific to each CE, a two-step selection procedure is applied.

First, high-value features are selected after min-max normalization within each CE:

$$\widehat{\mathcal{O}}_{m,t}^{(z)} = \frac{\overline{\mathcal{O}}_{m,t}^{(z)} - \min_{m',t'} \overline{\mathcal{O}}_{m',t'}^{(z)}}{\max_{m',t'} \overline{\mathcal{O}}_{m',t'}^{(z)} - \min_{m',t'} \overline{\mathcal{O}}_{m',t'}^{(z)} + \varepsilon}, \quad (35)$$

where $\varepsilon > 0$ is a small constant for numerical stability. Entries above the q -th quantile are retained:

$$\mathbf{1}_{\text{high}}^{(z)}(m, t) = \mathbf{1} \left\{ \widehat{\mathcal{O}}_{m,t}^{(z)} > Q_q \left(\widehat{\mathcal{O}}^{(z)} \right) \right\}, \quad (36)$$

where $q = 0.9$ unless otherwise specified.

Second, specificity is defined by fold-change relative to the mean of the remaining CEs:

$$\mu_{m,t}^{(-z)} = \frac{1}{Z-1} \sum_{z' \neq z} \widehat{\mathcal{O}}_{m,t}^{(z')}, \quad \text{FC}_{m,t}^{(z)} = \frac{\widehat{\mathcal{O}}_{m,t}^{(z)} + \varepsilon}{\mu_{m,t}^{(-z)} + \varepsilon},$$

where Z denotes the number of CEs. Entries satisfying $\text{FC}_{m,t}^{(z)} > \alpha$ are retained, with $\alpha = 1.5$ unless otherwise specified. The final CE-specific selection mask is

$$\mathbf{1}_{\text{spec}}^{(z)}(m, t) = \mathbf{1}_{\text{high}}^{(z)}(m, t) \cdot \mathbf{1} \left\{ \text{FC}_{m,t}^{(z)} > \alpha \right\}. \quad (37)$$

Dominant neighboring cell-type contexts. For each CE, selected entries are aggregated across LR channels:

$$E_m^{(z)} = \sum_{t=1}^{T_{\text{LR}}} \overline{\mathcal{O}}_{m,t}^{(z)} \mathbf{1}_{\text{spec}}^{(z)}(m, t), \quad (38)$$

and neighboring cell types are ranked by $E_m^{(z)}$. These rankings identify the cellular microenvironmental contexts most strongly associated with each CE.

2.9.3 CE-associated LR interactions and pathway-level tracing

CE-level LR contributions derived from tensor decomposition. Let W denote the communication-channel loading matrix from tensor decomposition, where $W_{t,r}$ represents the contribution of LR channel t to communication program r . For each CE z , program weights are defined as the average communication-program activity among cells assigned to that CE:

$$\pi_{r,z} = \frac{1}{N_z} \sum_{i \in \mathcal{I}_z} U_{ir}. \quad (39)$$

CE-level LR contributions are then computed as

$$H_{t,z} = \sum_{r=1}^R \pi_{r,z} W_{t,r}, \quad (40)$$

where larger values indicate stronger contributions of LR channel t to CE z .

To compare LR-channel specificity across CEs, LR contributions are optionally normalized as

$$\tilde{H}_{t,z} = \frac{H_{t,z}}{\sum_{z'=1}^Z H_{t,z'} + \varepsilon}, \quad (41)$$

so that $\sum_z \tilde{H}_{t,z} = 1$ for each LR channel t .

Mapping LR pairs to KEGG pathways. Each LR pair (L, R) is mapped to KEGG pathways based on gene-set membership. Let $\mathcal{P}$ denote the set of pathways and $\mathcal{G}(p)$ the gene set of pathway p . Pathway assignments are defined as

$$\mathcal{P}(L, R) = \begin{cases} \{p \in \mathcal{P} : L \in \mathcal{G}(p) \text{ or } R \in \mathcal{G}(p)\}, & \text{any,} \\ \{p \in \mathcal{P} : L \in \mathcal{G}(p) \text{ and } R \in \mathcal{G}(p)\}, & \text{both.} \end{cases}$$

Collapsing pathways into signaling super-classes. Pathways are optionally grouped into curated signaling super-classes. Each pathway is assigned to at most one super-class using keyword-based rules. When multiple assignments occur, a single class is selected by majority vote with fixed priority ordering.

Pathway activity and LR tracing. For each signaling super-class c and CE z , pathway-level activity is defined as

$$A_{c,z} = \sum_{t: c^*(t)=c} \tilde{H}_{t,z},$$

where $c^*(t)$ denotes the super-class assigned to LR channel t . LR pairs within each class are ranked by $\tilde{H}_{t,z}$, and top-ranked pairs are reported. This analysis links CE dynamics to interpretable pathway-level remodeling and identifies LR channels contributing to communication-defined temporal states.

2.10 Implementation of comparison methods

To evaluate communication-space-derived organization relative to existing spatial representation and domain-identification approaches, we compared CommuSpace with representative methods that integrate gene expression, spatial proximity or local neighborhood composition. These included GraphST [1], STAGATE [2], SpaGCN [3], SEDR [4], the neighborhood-composition approach of Zhang et al. [5],

BANKSY [6] and CellCharter [7]. All comparison methods were applied following their official implementations and recommended workflows, using default parameters or tutorial-recommended settings when available.

GraphST [1] is a graph-based self-supervised contrastive learning method that integrates gene expression and spatial proximity to learn cell embeddings. GraphST was applied using its default parameter settings. The learned embeddings were subsequently clustered using the Louvain algorithm, following the recommended workflow.

STAGATE [2] is a graph attention autoencoder that models gene expression and spatial relationships through a spatial neighbor graph. A spatial graph was constructed from cellular coordinates, and embeddings were learned using default model settings. Louvain clustering was applied to the learned embeddings to obtain spatial-domain assignments.

SpaGCN [3] is a graph convolutional network-based method that incorporates gene expression, spatial location and, when available, histological information. SpaGCN was implemented following the official tutorial, with parameters selected according to the recommended guidelines.

SEDR [4] combines a deep autoencoder for gene expression with a variational graph autoencoder for spatial information. Default parameters were used, and Louvain clustering was applied to the learned embeddings to obtain spatial-domain assignments.

For large-scale human breast cancer and kidney datasets, GraphST, STAGATE, SpaGCN and SEDR could not be completed within a practical runtime on a server equipped with 125 GB RAM and an NVIDIA GeForce RTX 3090 GPU with 24 GB memory. These datasets were therefore excluded from large-scale comparisons involving these methods.

The neighborhood-composition approach of Zhang et al. [5] represents each cell by the composition of annotated cell types in its local spatial neighborhood. A spatial KNN graph was constructed, and cell-type annotations were encoded as a binary matrix and aggregated over neighboring cells to obtain neighborhood cell-type abundance features for each cell. The resulting matrix was row-normalized and clustered using Louvain clustering to obtain neighborhood-composition-based organizational labels.

BANKSY [6] integrates intrinsic gene expression with spatial neighborhood features to learn a neighbor-augmented representation of each cell. Neighborhood information is summarized through aggregated expression features and combined with the cell's own expression using a mixing parameter that controls the contribution of spatial context. Low-dimensional embeddings were constructed from these combined features, and clustering was performed using the Leiden algorithm. BANKSY was applied with default parameters, and the resulting clusters were used as spatial-domain assignments.

CellCharter [7] identifies spatial niches by modeling local cellular neighborhoods. A spatial graph was constructed using Delaunay triangulation to define cell-cell connectivity. A variational autoencoder was used to learn low-dimensional embeddings of gene expression profiles. For each cell, a composite feature vector was constructed by concatenating its intrinsic embedding with aggregated features from spatial neighbors. These spatially augmented representations were clustered using a Gaussian mixture model to identify tissue microenvironment labels.

For all comparison methods, the resulting cluster, domain or microenvironment labels were treated as baseline organizational assignments. These assignments were compared with communication ecosystems to assess whether communication-space representation captured organizational structure beyond transcriptional similarity, spatial proximity or neighborhood composition.

2.11 Communication-ecosystem-associated proximal tubule microenvironments during kidney injury and repair

To further dissect the spatiotemporal remodeling captured by communication space during kidney injury and repair, we extended the main-text analysis by focusing on communication ecosystem (CE)-associated proximal tubule (PT) states and their surrounding microenvironments. In the primary analysis, CE 4 was preferentially enriched during the injury phase, spanning Hour 4 to Day 2, whereas CE 5 was selectively enriched during the repair phase, spanning Day 2 to Week 6. Consistent with these temporal patterns, injured proximal tubule cells (Inj_PT) within CE 4 first emerged at Hour 4, reached peak abundance at Hour 12, declined by Day 2 and became undetectable by Day 14. In contrast, failed-repair proximal tubule cells (FR_PT) associated with CE 5 appeared later, peaked at Day 14 and declined by Week 6 without complete disappearance (Supplementary Figure S32a). These observations indicate that CE 4 captures a transient injury-associated PT communication state, whereas CE 5 defines a delayed and more persistent failed-repair PT communication state.

To delineate the microenvironmental evolution of Inj_PT cells within CE 4, we examined their spatial and communication contexts across early time points after injury. At Hour 4, CE 4-associated Inj_PT cells remained largely confined to proximal tubular segments and perivascular support cells, reflecting a localized epithelial injury state embedded within the native nephron architecture [8]. This early state was accompanied by activation of RAS/MAPK and cytokine-related signaling, consistent with acute stress responses and initial injury-associated communication. By Hour 12, this restricted configuration was rapidly remodeled, as immune and endothelial cells became prominent components of the surrounding microenvironment, indicating a transition toward an inflammatory and vascular-responsive communication state [9]. Correspondingly, adhesion- and extracellular matrix (ECM)-related pathways, including SPP1-associated signaling, were enriched, suggesting enhanced cell–cell adhesion, immune recruitment and tissue-interaction signaling. By Day 2, CE 4 underwent a further shift marked by the emergence of fibroblasts, sustained endothelial interactions and activation of ECM- and TGF- β -related signaling pathways, consistent with the onset of tissue remodeling programs [10] (Supplementary Figure S32b,c). Thus, CE 4 resolves a transient Inj_PT-associated remodeling trajectory that progresses from a proximal tubule-centered injury state to an immune–endothelial reactive environment and ultimately toward a fibroblast-associated remodeling microenvironment.

We next examined the microenvironmental evolution of FR_PT cells within CE 5 across later stages of injury and repair. At Day 2, CE 5-associated FR_PT cells were already embedded within a mixed epithelial–stromal–immune microenvironment, with prominent associations with fibroblasts, Inj_PT cells, endothelial cells and immune cells. This configuration is consistent with the early establishment of a maladaptive repair state and aligns with the recognized proinflammatory and profibrotic features of FR_PT cells after acute kidney injury [10]. By Day 14, CE 5 became more distinctly organized around fibroblasts, immune cells and endothelial populations, while developmental signaling pathways, including Notch-associated signaling, were enriched. These features indicate consolidation of a fibro-inflammatory communication state associated with persistent repair failure and progressive fibrogenic remodeling [11]. By Week 6, CE 5 remained closely linked to fibroblasts and endothelial cells, while retaining associations with injured and proximal tubular populations. This pattern suggests that failed repair does not simply terminate in a static fibrotic scar, but persists as a chronic remodeling state in which unresolved epithelial injury and stromal activation coexist (Supplementary Figure S32d,e). Thus, CE 5 captures a persistent FR_PT-associated communication state that links maladaptive epithelial repair to

sustained fibro-inflammatory remodeling.

Overall, communication ecosystems resolve distinct PT-associated remodeling trajectories during kidney injury and repair. CE 4 captures a transient injury-associated Inj_PT communication state that dynamically transitions through epithelial, immune–endothelial and fibroblast-associated microenvironments, whereas CE 5 captures a persistent failed-repair FR_PT communication state embedded within a chronically remodeled fibro-inflammatory microenvironment. These results illustrate how communication space separates proximal tubule lineage identity from context-dependent communication state and reveals temporal remodeling programs that are not fully captured by cell identity or spatial location alone.

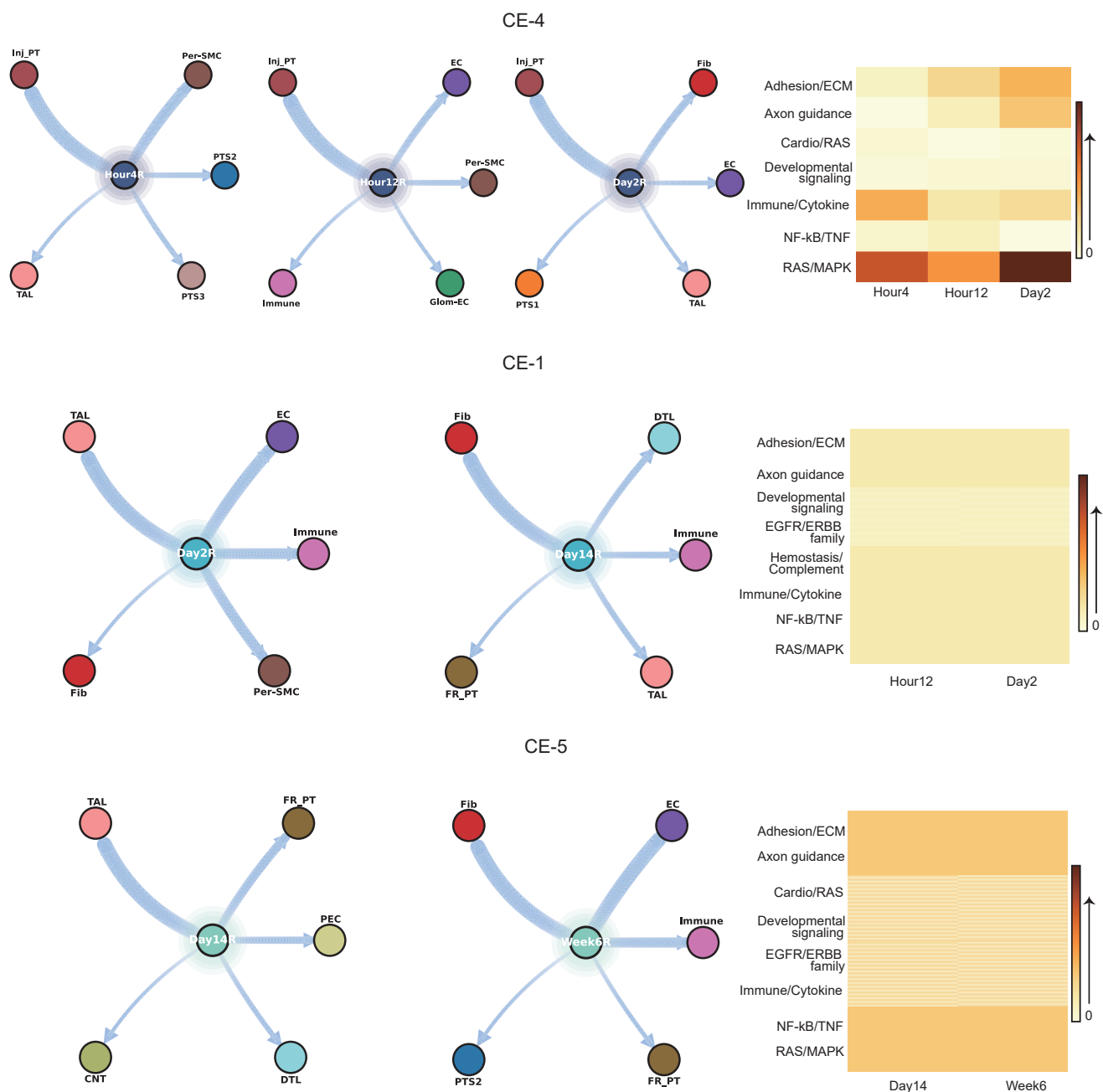


Figure S31: Temporal local communication contexts and pathway enrichment of representative kidney communication ecosystems. (a) Local communication contexts of representative communication ecosystems across injury–repair time points. Network diagrams show interacting neighboring cellular populations associated with CE-4, CE-1, and CE-5 at the indicated time points. Edge width indicates the normalized contribution of each neighboring cellular population to the local communication context of the corresponding ecosystem. (b) Pathway enrichment associated with the same communication ecosystems across time. Heatmaps show relative enrichment of signaling pathways within CE-4, CE-1, and CE-5 at the indicated time points, with color intensity indicating enrichment score.

Algorithm 1: Projected gradient training for weakly-orthogonal nonnegative CP decomposition (CommuSpace)

Input: Tensor $\mathcal{T} \in \mathbb{R}^{N \times K \times P}$; rank R ; learning rate η ; maximum epochs E ; tolerance tol ; scaling factor γ .

Output: Factors $U \in \mathbb{R}_+^{N \times R}$, $V \in \mathbb{R}_+^{K \times R}$, $W \in \mathbb{R}_+^{P \times R}$, weights $\lambda \in \mathbb{R}_+^R$; loss and fit histories.

Initialization:

Compute a nonnegative CP initialization $(\lambda^0, U^0, V^0, W^0)$ using `non_negative_parafac` (TensorLy);

Set $U \leftarrow U^0$, $V \leftarrow V^0$, $W \leftarrow W^0$ as trainable parameters;

Set $\lambda \leftarrow \lambda^0$ as a non-trainable vector;

Auto-estimation of ζ (if not provided):

Compute $\hat{\mathcal{T}}^0 \leftarrow [\lambda; U; V; W]$;

$\mathcal{L}_{\text{rec}}^0 \leftarrow \|\mathcal{T} - \hat{\mathcal{T}}^0\|_F^2$;

$G^0 \leftarrow U^\top U$;

$\mathcal{L}_{\text{orth}}^0 \leftarrow \|G^0 - \text{diag}(\text{diag}(G^0))\|_F^2$;

Set $\zeta \leftarrow \gamma \cdot \mathcal{L}_{\text{rec}}^0 / (\mathcal{L}_{\text{orth}}^0 + \epsilon)$;

Initialize Adam optimizer on (U, V, W) with step size η ;

Initialize scheduler `ReduceLROnPlateau` on the total loss;

Set $\mathcal{L}_{\text{prev}} \leftarrow +\infty$, $\text{fit}_{\text{prev}} \leftarrow +\infty$;

for $e = 1$ **to** E **do**

(1) Forward + loss computation:

Project $U \leftarrow \max(U, \epsilon)$ (element-wise);

Compute reconstruction $\hat{\mathcal{T}} \leftarrow [\lambda; U; V; W]$;

$\mathcal{L}_{\text{rec}} \leftarrow \|\mathcal{T} - \hat{\mathcal{T}}\|_F^2$;

$G \leftarrow U^\top U$;

$\mathcal{L}_{\text{orth}} \leftarrow \|G - \text{diag}(\text{diag}(G))\|_F^2$;

$\mathcal{L} \leftarrow \mathcal{L}_{\text{rec}} + \zeta \mathcal{L}_{\text{orth}}$;

(2) Gradient update:

Take one Adam step on (U, V, W) to minimize $\mathcal{L}$;

(3) Projection and CP normalization:

Project $U \leftarrow \max(U, \epsilon)$, $V \leftarrow \max(V, \epsilon)$, $W \leftarrow \max(W, \epsilon)$;

Apply CP normalization $(\lambda, U, V, W) \leftarrow \text{CPNormalize}(\lambda, U, V, W)$ such that each component column is normalized and scaling is absorbed into λ ;

(4) Scheduler and stopping criterion:

Update the learning-rate scheduler using $\mathcal{L}$;

Compute $\text{fit} \leftarrow 1 - \sqrt{\mathcal{L}_{\text{rec}}} / \|\mathcal{T}\|_F$;

if $|\mathcal{L}_{\text{prev}} - \mathcal{L}| < \text{tol}$ **then**

break;

Set $\mathcal{L}_{\text{prev}} \leftarrow \mathcal{L}$, $\text{fit}_{\text{prev}} \leftarrow \text{fit}$;

Return $U \leftarrow \max(U, 0)$, and detach (V, W, λ) ;

Algorithm 2: Extension of CommuSpace to large-scale datasets

Input: $\mathcal{T} \in \mathbb{R}^{N \times K \times P}$; rank R ; subset ratio ρ ; block size B ; epochs E ; warm-up E_{warm} ; tolerance tol ; scaling γ .

Output: U, V, W, λ .

Subset initialization:

Sample $\mathcal{I}$ and initialize (λ, V, W) via Eq. (17); initialize U ;

for $e = 1$ **to** E **do**

(1) Update U (block-wise):

 Compute H via Eq. (18);

 Update U block-wise using Eq. (20);

(2) Update V, W :

 Compute MTTKRP and H_V, H_W via Eq. (22)–(23);

 Update V, W via Eq. (24);

 Normalize V, W and absorb scaling into λ ;

(3) Adaptive orthogonality:

 Compute $\mathcal{L}_{\text{rec}}$ and $\mathcal{L}_{\text{orth}}$;

if $e = E_{\text{warm}}$ **then**

 Set ζ via Eq. (25);

(4) Periodic update:

if $e > E_{\text{warm}}$ **then**

 Update U via Eq. (26);

(5) Stopping:

 Compute $\mathcal{L} = \mathcal{L}_{\text{rec}} + \frac{\zeta}{2}\mathcal{L}_{\text{orth}}$;

if $|\mathcal{L}_{\text{prev}} - \mathcal{L}| < \text{tol}$ **then**

 break;

Final normalization:

Normalize U and absorb scaling into λ ;

Return (U, V, W, λ) ;

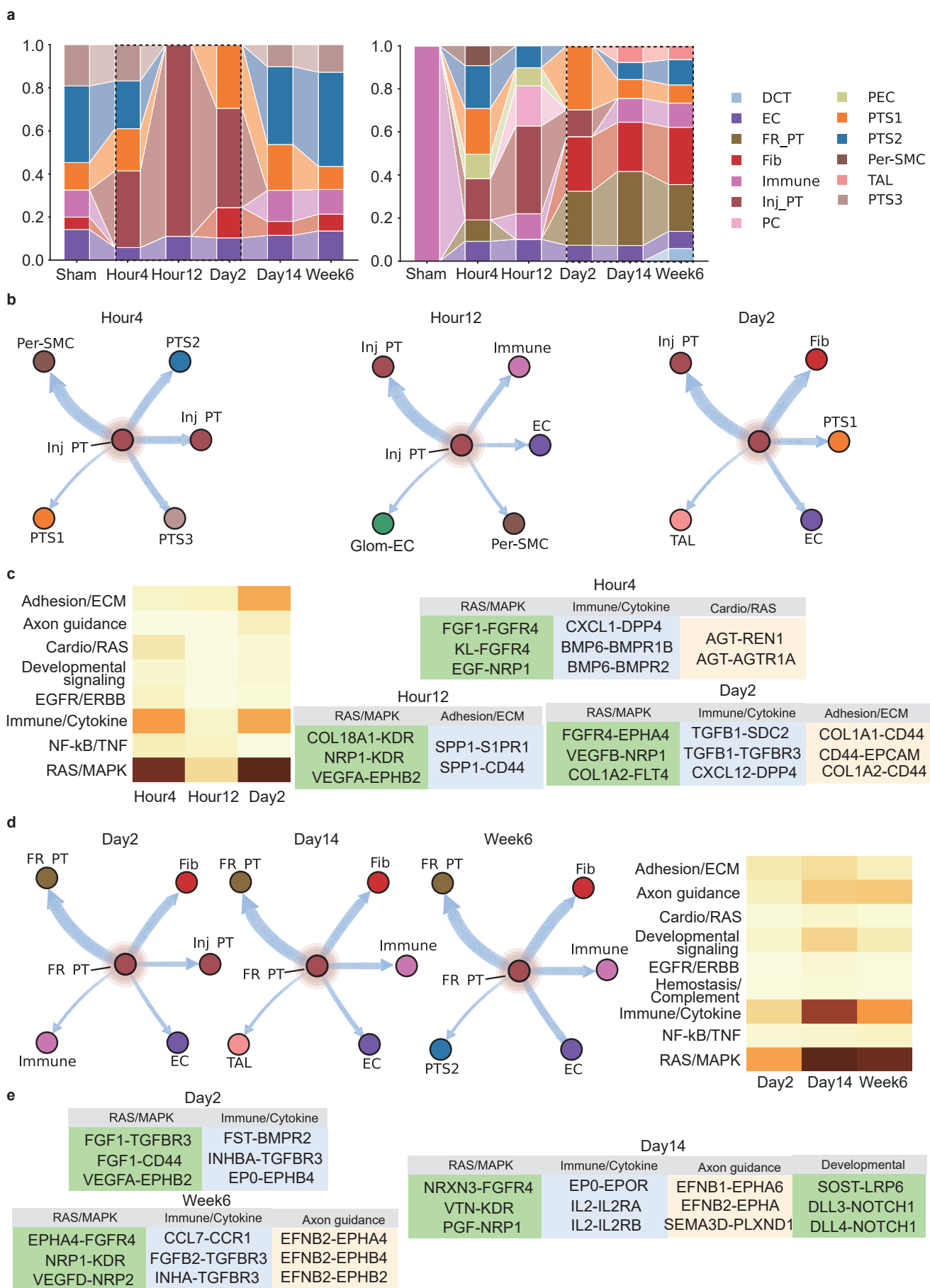


Figure S32: Ecosystem-associated proximal tubule communication contexts and time-resolved LR signaling programs during kidney injury and repair. **(a)** Temporal dynamics of cell-type composition across sham, Hour 4, Hour 12, Day 2, Day 14, and Week 6, highlighting the transient emergence of injury-associated proximal tubule (Inj_PT) cells and the delayed, persistent appearance of failed-repair proximal tubule (FR_PT) cells. **(b)** Local communication context of the Inj_PT-associated communication ecosystem at Hour 4, Hour 12, and Day 2. Edge width indicates the normalized contribution of each interacting neighboring cellular population to the local communication context. **(c)** Pathway enrichment and representative LR signaling channels associated with the Inj_PT-associated communication ecosystem across early injury time points. **(d)** Local communication context of the FR_PT-associated communication ecosystem at Day 2, Day 14, and Week 6. Edge width indicates the normalized contribution of each interacting neighboring cellular population to the local communication context. **(e)** Pathway enrichment and representative LR signaling channels associated with the FR_PT-associated communication ecosystem across later repair and remodeling time points.

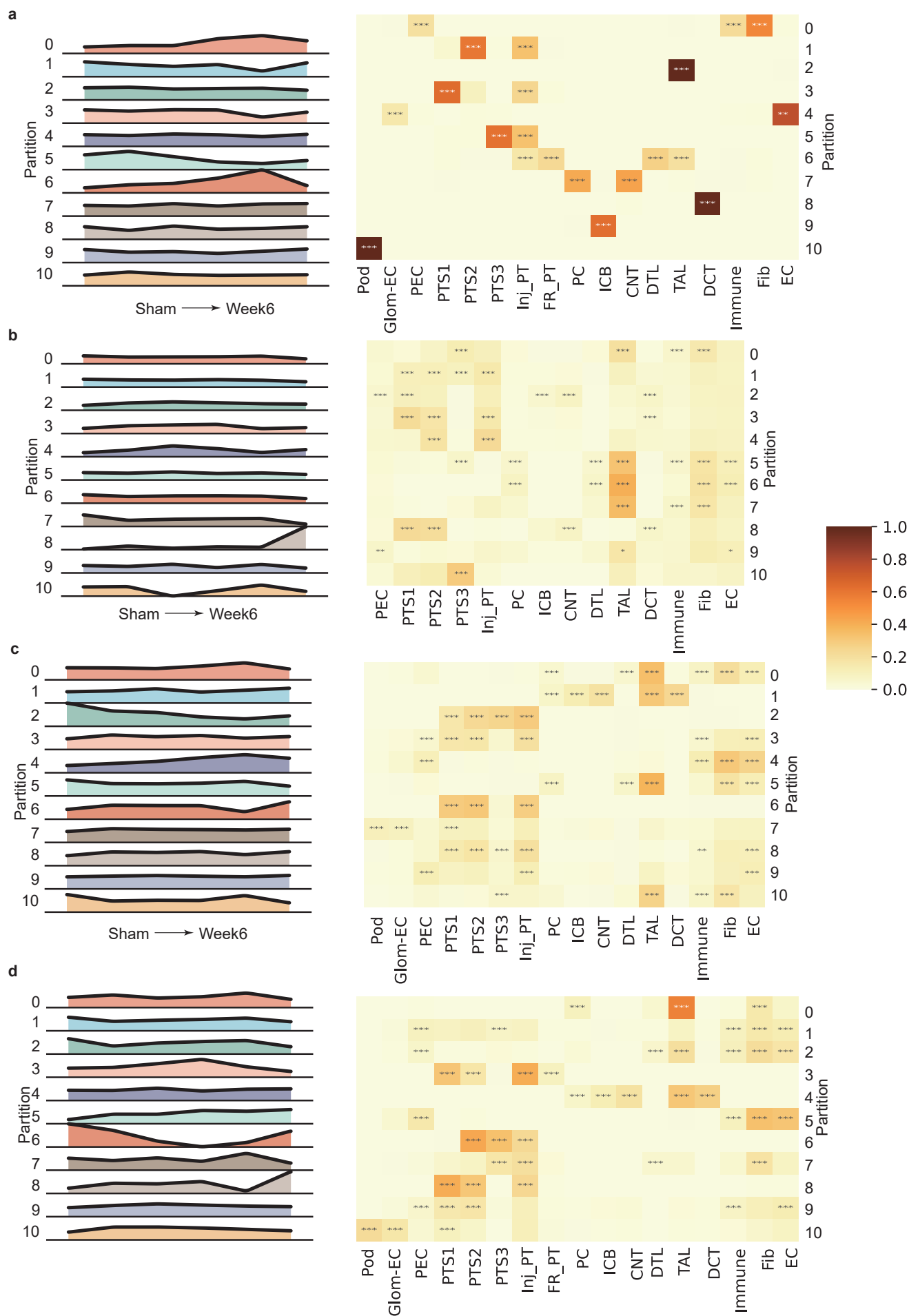


Figure S33: Temporal abundance and cell-type enrichment of method-derived partitions from comparison methods in the kidney injury–repair dataset. (a–d) Relative abundance and annotated cell-type enrichment of partitions identified by Louvain, Zhuang, BANKSY, and CellCharter, respectively. Left, temporal abundance of method-derived partitions from sham to week 6 after injury, with each curve representing the proportion of cells assigned to a partition over time. Right, heatmaps showing enrichment of annotated cell types across method-derived partitions, with asterisks indicating statistical significance.

2.12 Comparison of communication ecosystems identified under alternative focal-cell signaling modes

To assess the robustness of communication ecosystems (CEs) under alternative formulations of local signaling relationships, we applied CommuSpace to the MOp dataset using three focal-cell signaling modes: sender-centric, receiver-centric and sender–receiver-centric representations (Figure S34a). Results presented in the main text are based on the sender-centric implementation. These modes differ in how the communication tensor represents the role of each focal cell: the sender-centric mode emphasizes ligand output from the focal cell toward neighboring cellular populations, the receiver-centric mode emphasizes receptor-defined input to the focal cell from its local neighborhood, and the sender–receiver-centric mode jointly represents both focal-cell roles. Details of tensor construction for each mode are provided in Supplementary Text S2.1. Here, we compare CEs derived under these alternative representations to evaluate the stability of communication-space organization and to identify perspective-dependent refinements.

We first evaluated model fitting performance across signaling modes by examining rank-dependent fit and adjusted fit scores (Figure S34b). All three formulations exhibited similar trends, with adjusted fit scores increasing and stabilizing as rank increased, and comparable knee points identified across modes. These results indicate consistent model complexity selection under alternative focal-cell signaling assumptions. Receiver-centric and sender–receiver-centric representations showed slightly higher stabilized adjusted fit scores, consistent with improved reconstruction when receptor-defined response information was incorporated.

We next compared CE assignments across the three signaling modes and observed strong global concordance together with systematic, perspective-dependent differences in resolution (Figure S34c). Most CEs identified under the sender- and receiver-centric formulations showed near one-to-one correspondence, indicating a shared underlying communication-space structure. However, this mapping was not strictly symmetric. For example, sender-centric CE 6 was separated into CE 4 and CE 6 under the receiver-centric mode, whereas receiver-centric CE 1 was subdivided into CE 1 and CE 2 under the sender-centric mode (Figure S34d, top). These reciprocal but asymmetric refinements suggest that sender- and receiver-centric representations capture complementary aspects of multicellular communication organization, rather than redundant partitions of the same structure. This is consistent with the distinct biological roles of ligand-output programs and receptor-defined response programs in intercellular signaling [12, 13]. In contrast, CEs derived from the receiver-centric and sender–receiver-centric formulations exhibited an almost one-to-one correspondence (Figure S34d, bottom). This suggests that the joint representation largely preserves receiver-defined organization in this dataset, while ligand-driven information contributes additional context-dependent refinements [14]. Together, these results support a perspective-dependent view of communication ecosystems, in which sender- and receiver-centric modes provide complementary resolutions of the same communication-space organization.

We then examined how individual cell types were distributed across CEs under the three focal-cell signaling modes. All modes identified CEs composed of mixed neuronal and non-neuronal populations (Figure S34e), consistent with the principle that CEs are not equivalent to discrete cell-type classes. However, cell-type distributions differed across signaling perspectives. For example, L6 corticothalamic (L6 CT) neurons were distributed across CE 2 and CE 3 in the sender-centric mode but concentrated in CE 1 in the receiver-centric mode. Conversely, L2/3 neurons were largely confined to CE 4 in the sender-centric mode but distributed across multiple CEs in the receiver- and sender–receiver-centric

modes (Figure 2e and Figure S34f, left). These differences reflect the distinct grouping principles of each representation: the sender-centric mode organizes cells according to ligand-output programs, whereas the receiver-centric mode organizes cells according to receptor-defined responsiveness. Thus, neuronal populations with specialized signaling outputs but partially shared response programs can be redistributed across communication ecosystems depending on the focal-cell signaling perspective.

Non-neuronal populations showed a different pattern. These populations were more diffusely distributed under sender- and receiver-centric formulations but became enriched within a specific CE under the sender–receiver-centric mode (Figure 2e and Figure S34f). This pattern suggests that non-neuronal cells are not strongly separated by ligand output or receptor expression alone, but become more coherently organized when matched sender–receiver interactions are represented jointly.

Overall, communication ecosystems were robust across focal-cell signaling formulations, with consistent global organization in communication space. At the same time, differences in CE resolution and cell-type distribution revealed complementary sender- and receiver-defined perspectives on intercellular communication. These results indicate that mode-specific variation reflects biologically meaningful refinements of communication-space organization rather than instability of the inferred ecosystems.

Figure S34: **Comparison of communication ecosystems identified under different interaction-centric modes in the MOp dataset.** (a) Schematic overview of communication tensor construction under sender-centric, receiver-centric, and sender–receiver–centric modes. (b) Rank-dependent fit scores and adjusted fit scores for the three interaction-centric modes across candidate CP ranks are shown, with dashed lines indicating selected knee points. (c) Low-dimensional embeddings and corresponding spatial maps of communication ecosystems identified under sender-centric, receiver-centric, and sender–receiver–centric modes are shown, colored by ecosystem identity. (d) Pairwise overlap matrices show correspondence between communication ecosystem assignments obtained under different interaction-centric modes. (e) Stacked bar plots show cell-type composition of communication ecosystems identified under receiver-centric and sender–receiver–centric modes. (f) Heatmaps show cell-type enrichment patterns for communication ecosystems identified under receiver-centric and sender–receiver–centric modes.

2.13 Computational efficiency and scalability of CommuSpace

We evaluated the computational efficiency of CommuSpace by measuring runtime and peak memory usage on the human breast cancer dataset and the longitudinal kidney injury and repair dataset. All methods were run on the same server equipped with 125 GB RAM and an NVIDIA GeForce RTX 3090 GPU with 24 GB memory. CommuSpace was compared with representative spatial organization methods, including BANKSY, CellCharter, the neighborhood-composition method of Zhang, and Louvain-based clustering when applicable.

For CommuSpace, we reported two steps separately: constrained tensor decomposition and communication ecosystem (CE) identification. Tensor decomposition corresponds to construction of the communication-space representation, whereas CE identification summarizes stable regions within this space. Across both datasets, tensor decomposition required low runtime and low peak memory, indicating that the core representation-learning step of CommuSpace is computationally lightweight (Supplementary Figure S35a,b).

In the human breast cancer dataset, CE identification required additional runtime because the default procedure performs repeated clustering across seeds and resolutions to obtain robust consensus ecosystems. However, its memory usage remained moderate and substantially below the most memory-intensive baseline methods (Supplementary Figure S35a). For applications requiring only a single fixed-resolution CE assignment, this clustering step can be performed once, further reducing runtime.

In the kidney dataset, the micro-clustering strategy reduced memory usage during CE identification while adding only modest runtime (Supplementary Figure S35b). This enabled scalable analysis of a large longitudinal dataset while preserving communication-program interpretability and CE-level biological resolution.

Together, these results show that CommuSpace achieves a favorable runtime–memory trade-off by separating efficient communication-space construction from optional consensus-based CE identification. This design allows CommuSpace to scale to large spatial transcriptomics datasets without reducing tissue organization to transcriptional similarity or neighborhood composition alone.

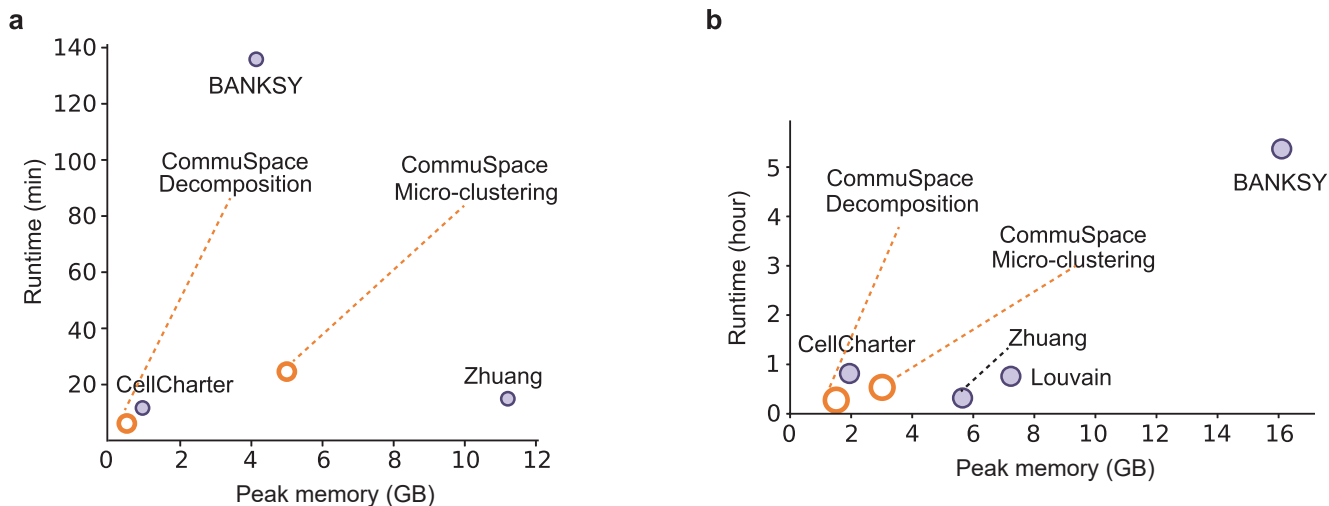


Figure S35: **Computational efficiency of CommuSpace.** **a,b**, Runtime and peak memory usage on the human breast cancer dataset (**a**) and the longitudinal kidney injury and repair dataset (**b**). All methods were run on a server with 125 GB RAM and an NVIDIA GeForce RTX 3090 GPU with 24 GB memory. CommuSpace steps are shown separately for communication-space construction by tensor decomposition and communication ecosystem identification by micro-clustering. Tensor decomposition was consistently fast and memory-efficient, whereas micro-clustering added modest runtime while preserving scalable memory usage. These results show that CommuSpace achieves favorable runtime–memory efficiency for large spatial transcriptomics datasets while retaining interpretable communication ecosystem resolution.

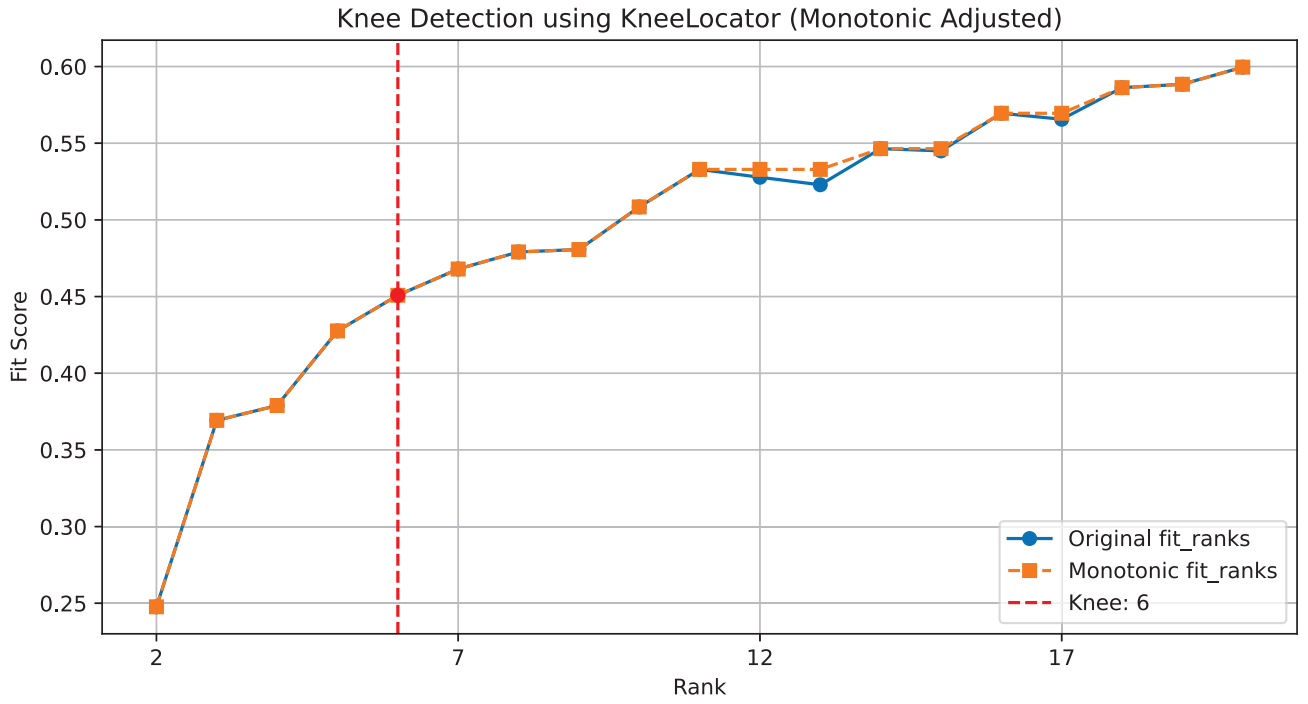


Figure S36: **Selection of the communication-program rank for the mouse primary motor cortex dataset.** CP decomposition fit scores are evaluated across candidate ranks using both original model fits and monotonic-adjusted fit curves. The knee point identified by the KneeLocator algorithm indicates the selected rank $R = 6$, which is used for communication-program inference and downstream construction of communication space.

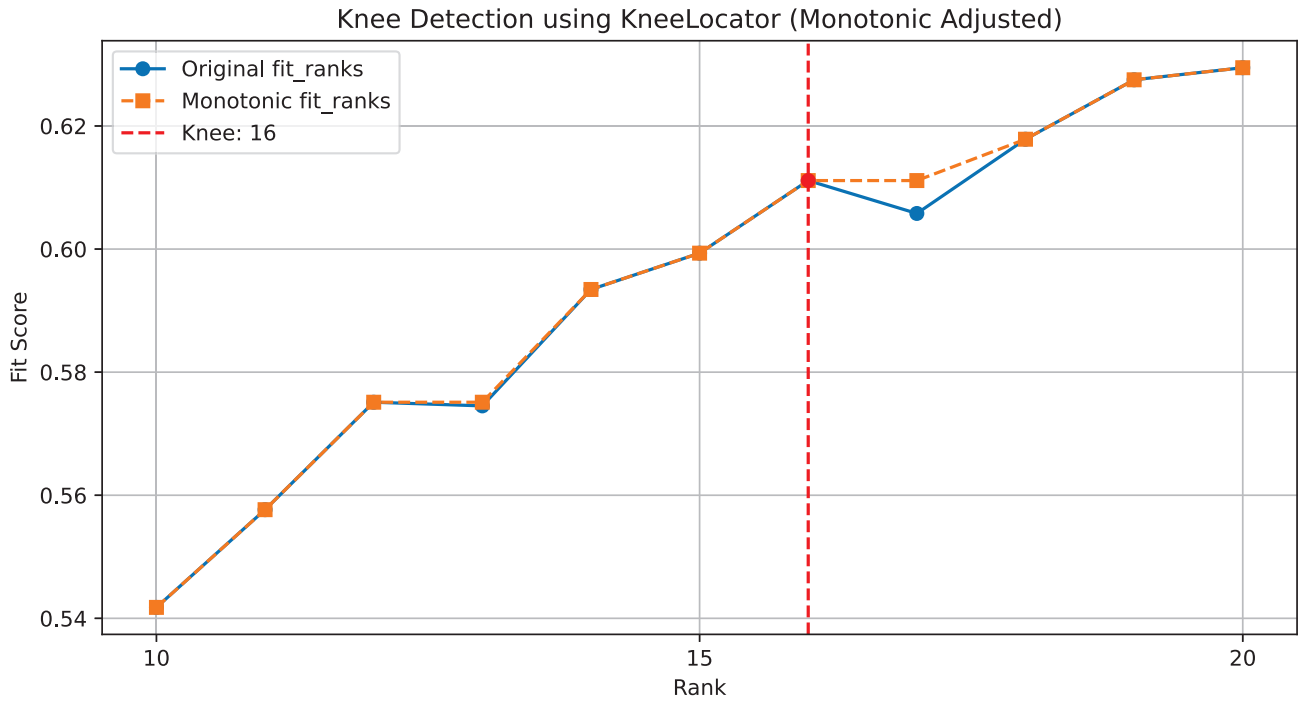


Figure S37: **Selection of the communication-program rank for the human breast cancer dataset.** CP decomposition fit scores are evaluated across candidate ranks using both original model fits and monotonic-adjusted fit curves. The knee point identified by the KneeLocator algorithm indicates the selected rank $R = 16$, which is used for communication-program inference and downstream construction of communication space.

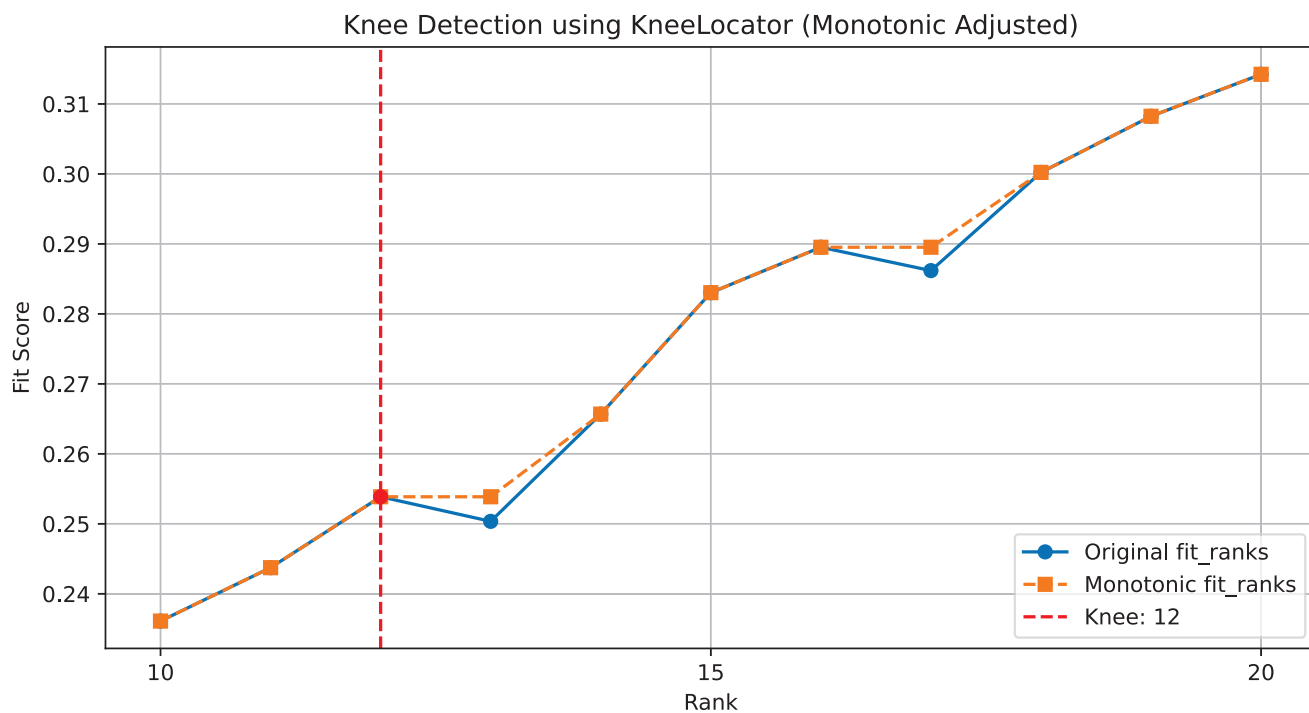


Figure S38: **Selection of the communication-program rank for the kidney datasets.** CP decomposition fit scores are evaluated across candidate ranks using both original model fits and monotonic-adjusted fit curves. The knee point identified by the KneeLocator algorithm indicates the selected rank $R = 12$, which is used for communication-program inference and downstream construction of communication space.

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