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Comparative visual analytics for multi-modal single-cell and spatial omics data

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SUPPLEMENTARY INFORMATION

S1: Supplementary for Cytosplore Gradient Surfer (Chapter 4)

S1.1: Technical validation

We first evaluated robustness using the MERFISH spatial transcriptomics profile of a mouse visual cortex slice. To maximize the number of genes available for analysis and obtain stronger expression signals, we included only the imputed genes from the MERFISH dataset. We ran Cytosplore Gradient Surfer on the original imputed MERFISH dataset (Dataset Technical 1, DT1; 2,150 cells) as the reference. We then generated a set of derivative datasets (collectively referred to as DT2 variants) from DT1 by applying individual transformations, including rotation, reduced spatial resolution, normalization, or dimensionality reduction, and evaluated each variant relative to DT1.

S1.1.1: Robustness against dataset rotation

We rotated the spatial coordinates in DT2 by 45°, 90°, 180°, and 270° (keeping DT1 fixed) and recomputed gene–position correlations. The same top-ranking gradient genes emerged despite the geometric transformation. Layer-specific marker genes that showed a clear laminar gradient in the unrotated data remained among the highest-correlated genes after rotation, with their spatial expression patterns correspondingly rotated. This result indicates that the method identifies consistent patterns even when one dataset is rotated, as expected from its design to detect stable gradients across spatial transformations.

S1.1.2: Robustness against cell subsampling

We assessed the robustness of the method under varying spatial cell densities by randomly subsampling cells from the MERFISH dataset in DT2, removing 10–90% of the cells (rows) and repeating the analysis. The method demonstrated strong stability across all levels of data reduction. Both Spearman's and Kendall's rank correlations remained high (>0.9) even after 90% data reduction, indicating excellent concordance in gene ranking. Analysis of gene rank changes revealed that most genes exhibited no or only minor rank changes, while moderate and major shifts were infrequent. Similarly, the top 50–100 ranked genes retained over 90% stability across all reduction levels. Although rank volatility increased progressively with greater data loss, the magnitude of change remained moderate, suggesting that the method

is resilient to sampling variability. The mean absolute rank shift was approximately 10 ranks out of 314 total genes at 90% reduction, further supporting the limited impact of subsampling. Statistical analyses confirmed strong rank consistency (Spearman and Wilcoxon signed-rank test, $p < 10^{-8}$ across all levels). Extreme ranks remained stable, and gene movements showed no directional bias under subsampling.

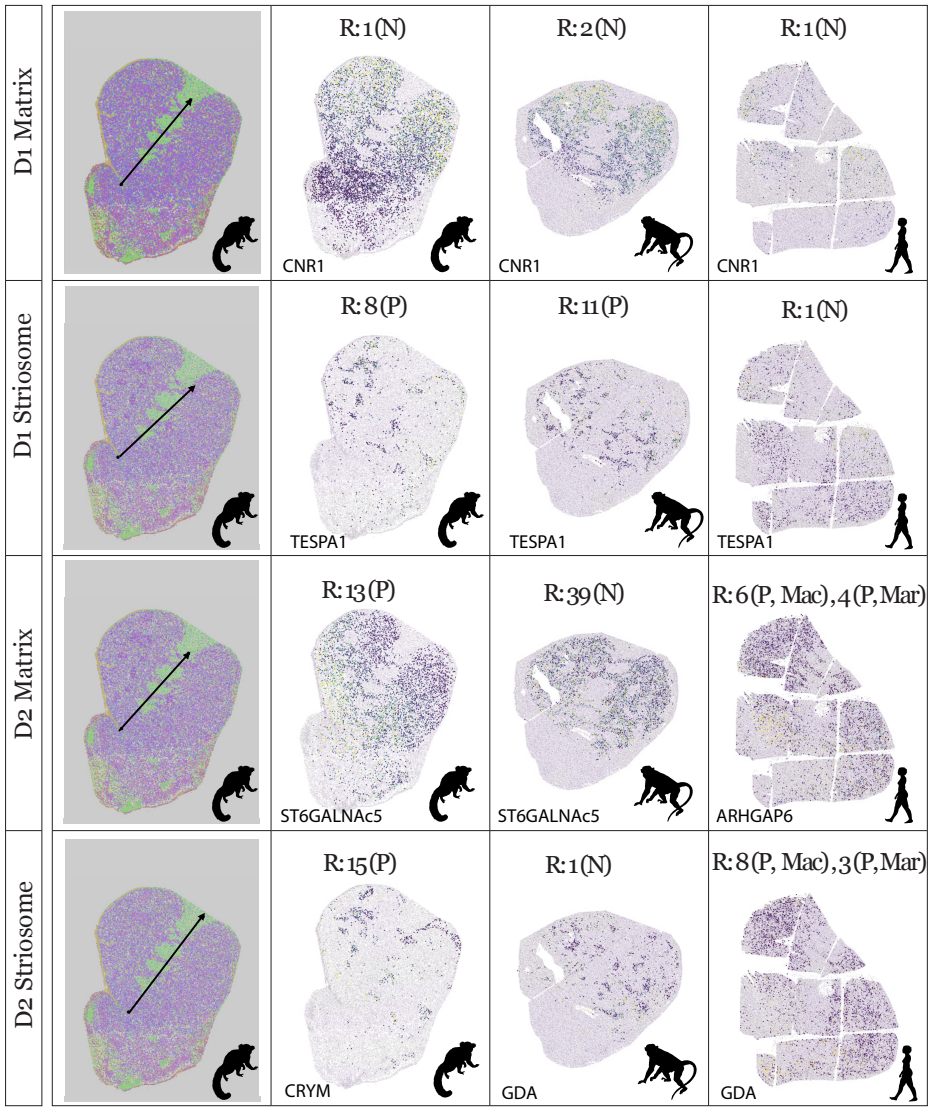
Collectively, these results indicate that the method maintains strong reproducibility and robustness under substantial spatial subsampling, ensuring that key gene rankings and biological interpretations remain consistent even with markedly reduced data density.

S1.1.3: Robustness against feature subsampling

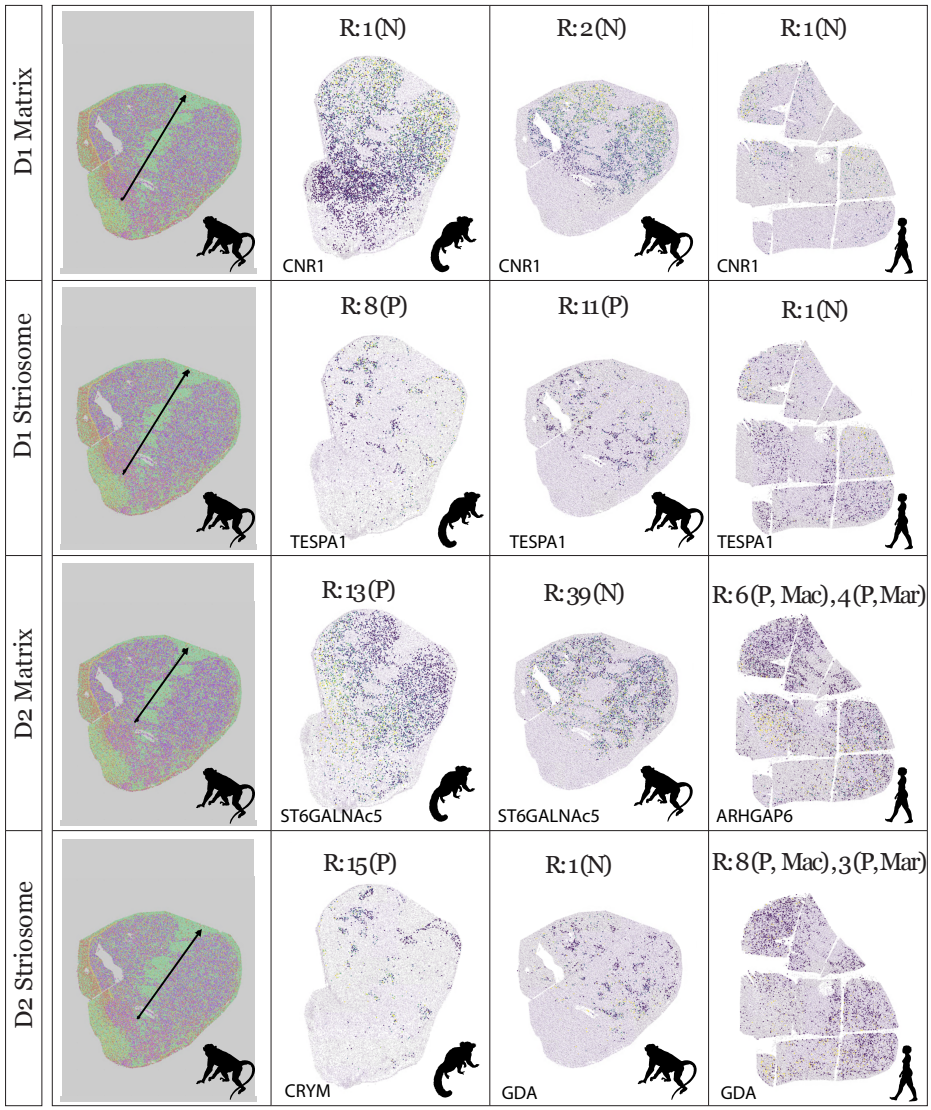
To further assess robustness under varying feature dimensionality, we simulated a realistic scenario in which datasets share only a subset of genes. We first identified the top correlated genes (correlation coefficient > 0.5; $n = 41$) showing clear expression gradients across the dataset. Among these, the top 5 genes were retained for computation across all derivative datasets, while the remaining 36 genes were divided into two groups using two strategies: (i) random reduction, where genes were randomly split, and (ii) alternating reduction, where genes were assigned based on rank order.

Using these subsets, we generated four derivative datasets by removing the corresponding gene groups from the original dataset (DT1), resulting in two random-reduction and two alternating-reduction conditions. The analysis was repeated to evaluate whether gene rankings within each dataset's top 23 correlated genes (ranked by correlation strength), consisting of 5 universally retained genes and 18 subset-specific genes, were preserved under partial gene removal. In both random and alternating reduction settings, all genes showed high preservation of their relative rank positions within the top 23, with no major rank inversions observed.

Collectively, these results demonstrate that the method remains stable even under substantial reductions in feature number. The preservation of rank structure across all reduced-dimension datasets highlights its robustness and applicability to real-world scenarios where datasets may only partially overlap in gene coverage.



Supplementary Figure 1: **Validation of conserved spatial gene expression gradients across primate species using a marmoset reference swipe.** Spatial expression maps of representative gradient-associated genes identified by interactive line-swipe analysis across human, macaque, and marmoset brain slices (P7, P9, and P13, respectively), with the line swipe performed on the marmoset slice. In the figure, R denotes rank, P denotes positive expression rank, and N denotes negative expression rank. The results illustrate that gradients identified in marmoset correspond to conserved molecular patterns observed in other primate species.



Supplementary Figure 2: **Validation of conserved spatial gene expression gradients across primate species using a macaque reference swipe.** Spatial expression maps of representative gradient-associated genes identified by interactive line-swipe analysis across human, macaque, and marmoset brain slices (P7, P9, and P13, respectively), with the line swipe performed on the macaque slice. In the figure, R denotes rank, P denotes positive expression rank, and N denotes negative expression rank. The figure further supports the robustness of the approach in identifying conserved spatial gene expression gradients across primate species.

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