stDiffusion: A Diffusion Based Model For Generative Spatial Transcriptomics

Sumeer A. Khan[1], Xabier M. de Morentin[1], Vincenzo Lagani[1], Robert Lehmann[1], Narsis A. Kiani[2], David Gomez-Cabrero[1,3], Jesper Tegnér[1,2]*

[1]King Abdullah University of Science & Technology (KAUST), Saudi Arabia; [2]Karolinska Institute, Sweden; [3]Navarrabiomed, Spain; *Corresponding author

Introduction

- **Spatial Transcriptomics Challenge and Current Limitations**
  - Current spatial transcriptomics technologies provide valuable 2D organization of gene expression within tissue slices, but are limited by discrete sampling with physical gaps between slices, restricting our ability to build continuous tissue models
- **Novel Generative Modeling Approach with Diffusion Models**
  - We introduce stDiffusion, a denoising diffusion probabilistic model (DDPM) specifically tailored for spatial transcriptomics data, capable of learning generative models from tissue samples while preserving spatial relationships
- **Slice Interpolation Capabilities and 3D Potential**
  - Our model demonstrates the ability to predict unseen spatial transcriptomics data by interpolating between existing slices, setting the stage for developing continuous 3D representations of tissues from a finite number of 2D slices

Data

- **MERFISH, Starmap, and DLPFC Datasets for stDiffusion Evaluation**
  - **MERFISH Dataset**
    - Comprises 12 consecutive slices from the mouse hypothalamic preoptic region, containing 73,655 spots with 161 genes per spot. Used to evaluate stDiffusion's ability to interpolate between distinct slices
  - **Starmap Dataset**
    - Mouse visual cortex data capturing distinct cortical layers in preprocessed format with 984 spots and 1,020 genes per spot. Employed to test interpolation across different layers within a single slice
  - **DLPFC Dataset**
    - Human dorsolateral prefrontal cortex sections with manually annotated layers, containing 3,431 spots with 3,000 highly variable genes after preprocessing

Conclusion

- **Novel Framework for Spatial Transcriptomics Prediction**
  - We successfully demonstrated stDiffusion, the first denoising diffusion probabilistic model for predicting spatial transcriptomics, enabling accurate interpolation between tissue slices while preserving spatial neighborhood structures across multiple tissue types and species
- **Future Directions**
  - Building upon this foundation, future work will extend to comprehensive 3D tissue modeling, incorporate additional spatial modalities, optimize marker selection algorithms, and validate across diverse tissues to enable transformative applications in fundamental biology and precision medicine

References

- Ho, J., Jain, A. & Abbeel, P. *Denoising Diffusion Probabilistic Models.* Advances in Neural Information Processing Systems vols 2020-December (2020)
- Zeira, R., Land, M., Strzalkowski, A. & Raphael, B. J. *Alignment and integration of spatial transcriptomics data.* Nat Methods 19, 567–575 (2022)

Methods

- **Integrated Workflow for Generative Modeling of Spatial Transcriptomics**
 - stDiffusion adapts denoising diffusion probabilistic models (DDPM) principles to address the unique challenges of spatially resolved gene expression data. The network architecture incorporates cell type embedding and spatial coordinate transformation through concatenation with gene expression data
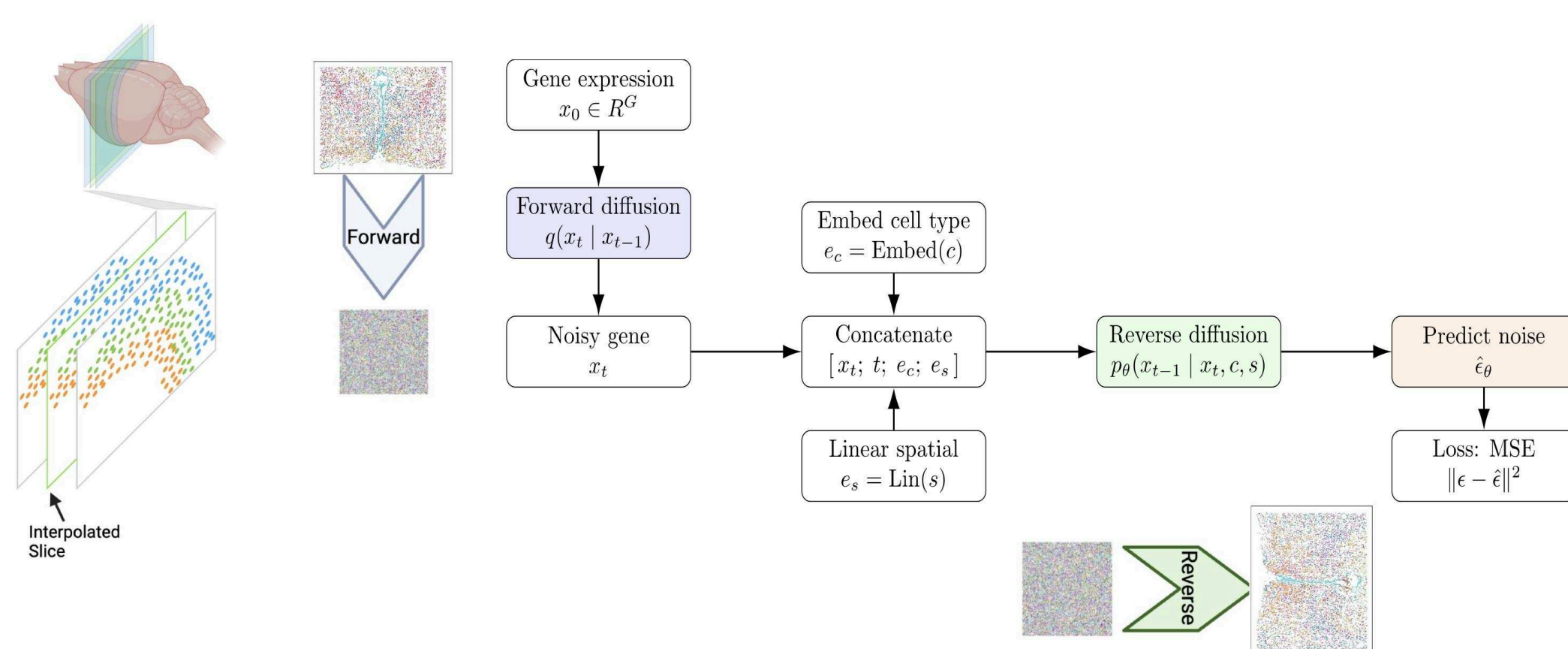
Results

- **Effective Interpolation Within Slices**
  - Accurately predicted Layer 4 in DLPFC and Layer L2/L3 in Starmap data while maintaining cluster relationships, as shown by strong diagonal enrichment values
  - Demonstrated superior performance over linear interpolation in preserving spatial distribution and achieving lower normalized mean square errors across both datasets
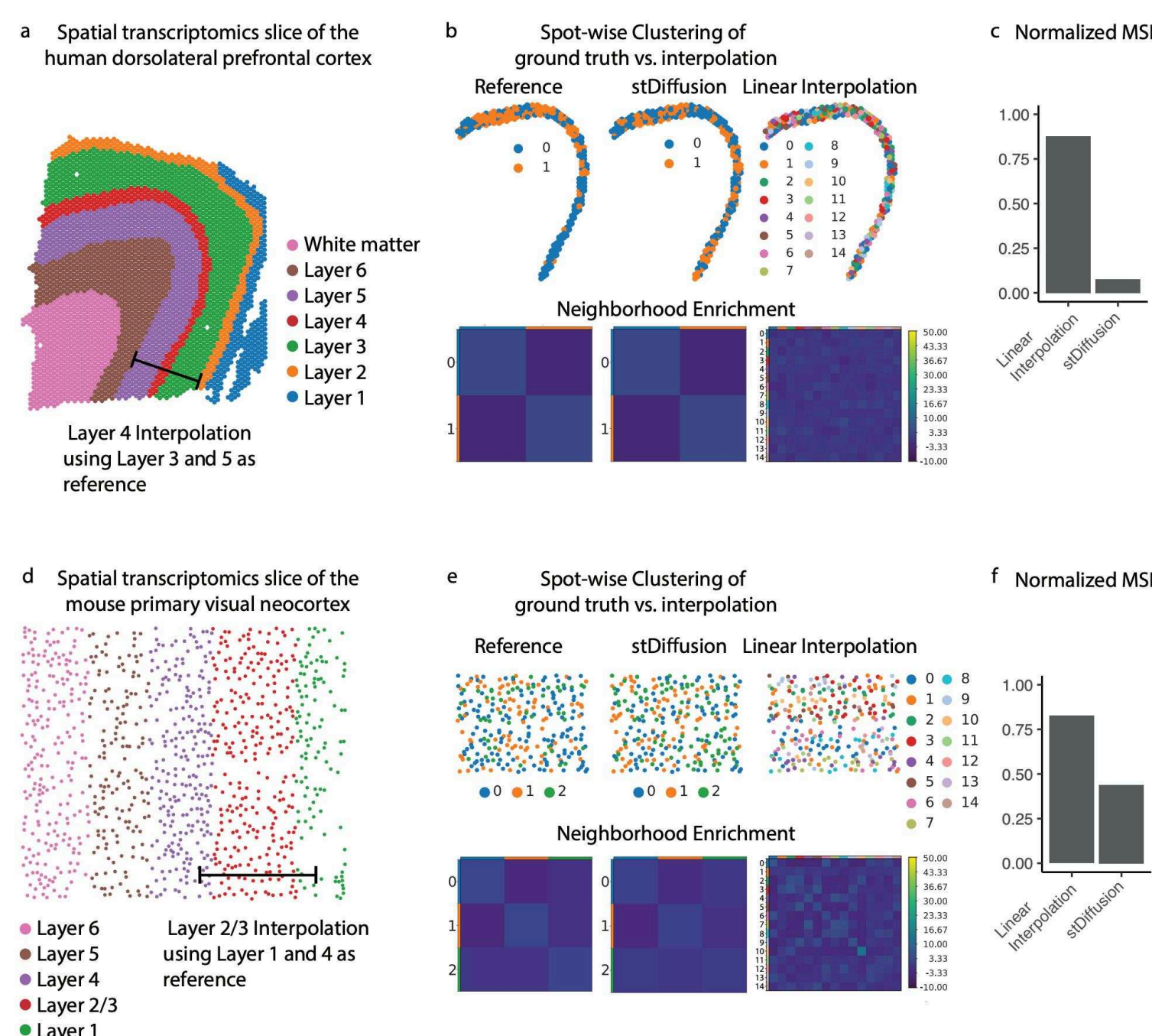
- **Effective Interpolation Across Slices**
  - stDiffusion successfully interpolated between MERFISH slices, preserving spatial structure and cluster neighborhoods while outperforming linear interpolation
  - Achieved better normalized mean square errors than linear interpolation, though showed limitations in extrapolation outside collected regions