



HyperST: Hierarchical Hyperbolic Learning for Spatial Transcriptomics Prediction

Predicting spatial gene expression from H&E by modeling image–gene hierarchies in hyperbolic space

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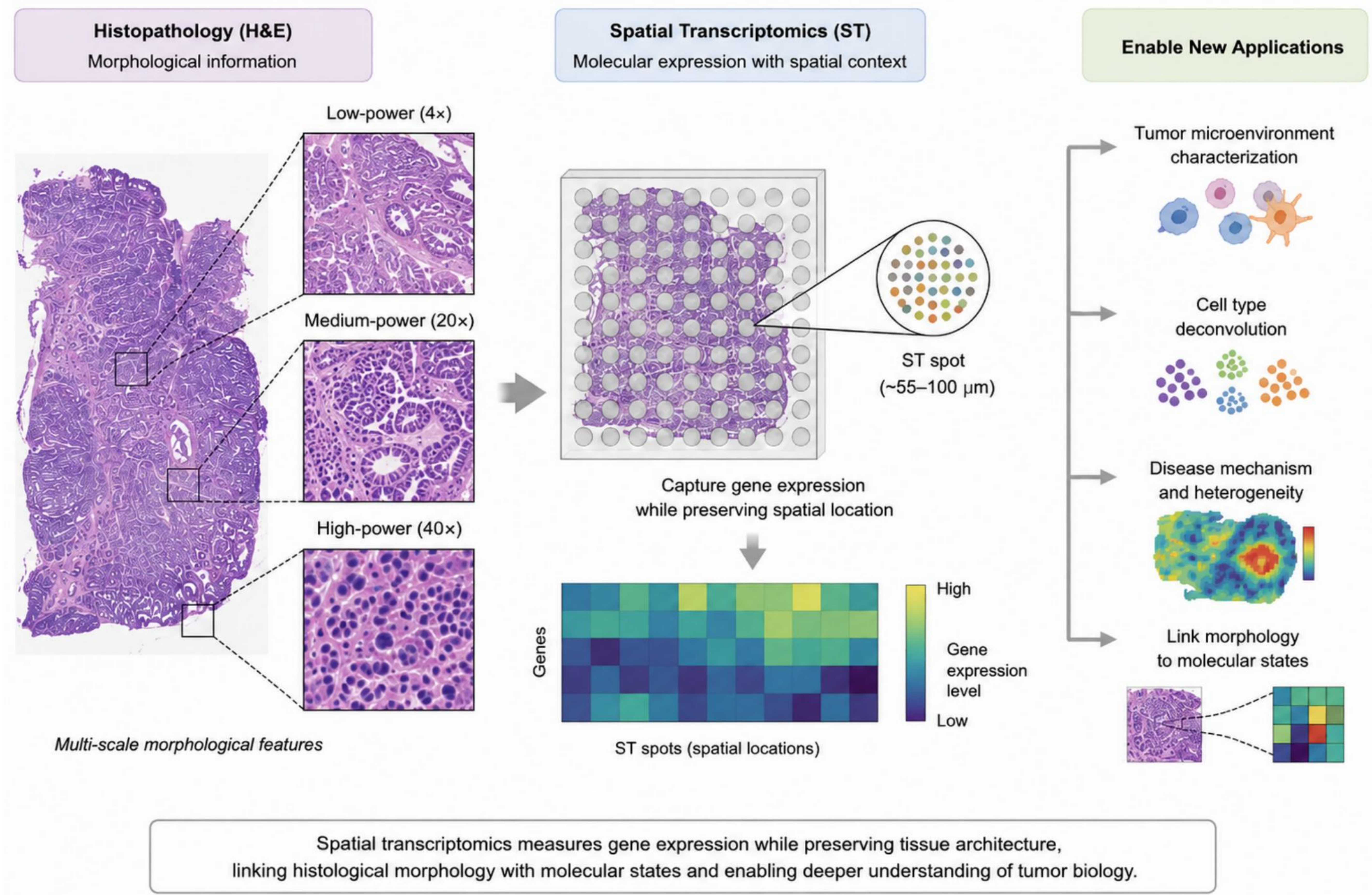
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Code: <https://github.com/liesgame/HyperST>

Background: Spatial Transcriptomics Links Morphology and Molecular States

- Combines histopathology morphology with spatially resolved gene expression
- Reveals tissue heterogeneity and cellular microenvironment
- Enables richer biological interpretation beyond morphology alone




Background: ST Is Powerful, but Hard to Scale



High cost
Expensive experimental profiling



Labor-intensive
Complex multi-step wet-lab workflow

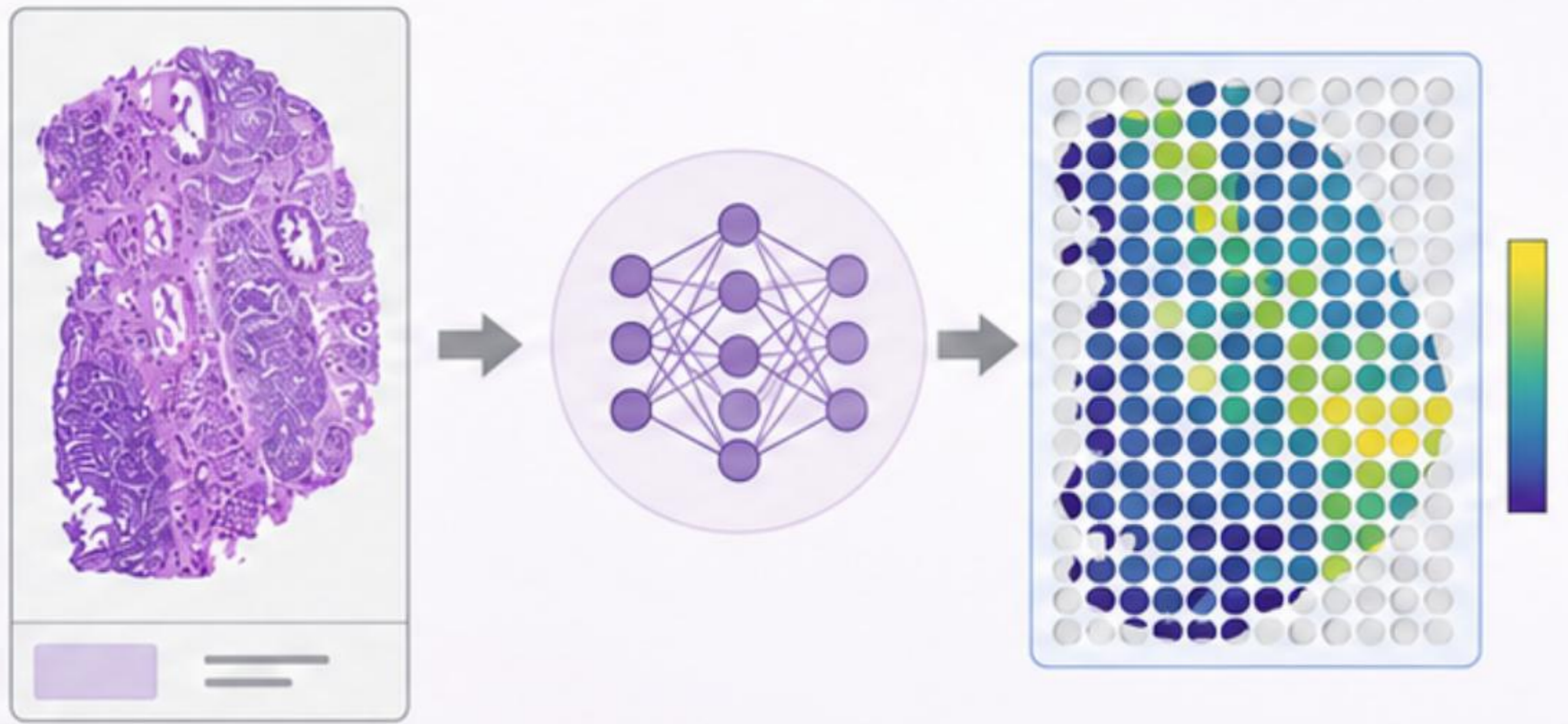


Limited accessibility
Specialized platforms are not widely available

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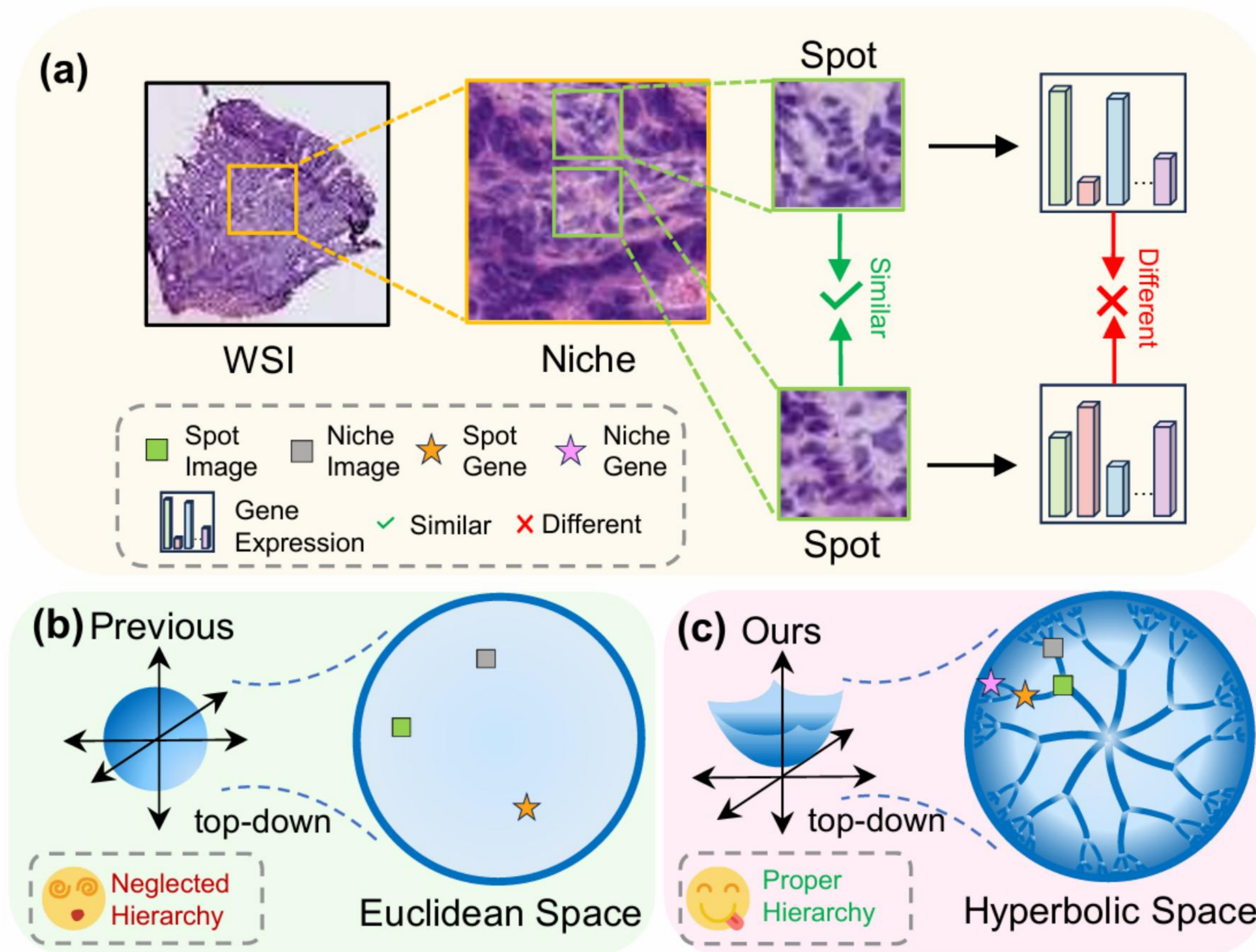
Need a scalable alternative

Predict ST from routine H&E
A scalable and cost-effective alternative to direct ST profiling



Background: Challenge in H&E-to-ST Prediction

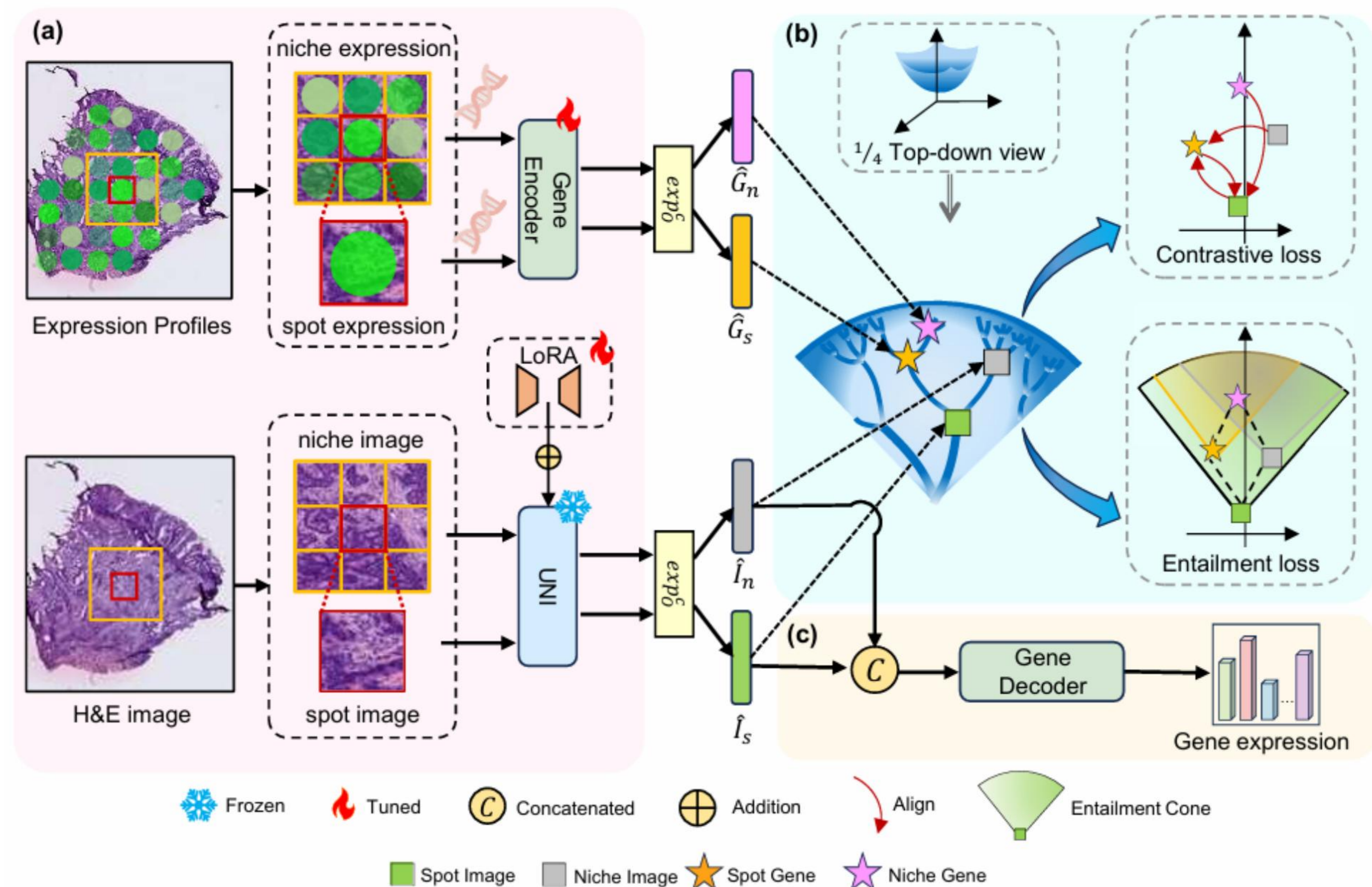
- 1. Visual–molecular mismatch:** visually similar spots may show distinct gene expression patterns.
- 2. Neglected hierarchy:** existing methods mainly align spot-level image–gene pairs and overlook niche-level context.
- 3. Flat embedding limitation:** Euclidean spaces poorly capture the hierarchical relationships among spot, niche, image, and gene representations



Method: HyperST Framework

Three labels:

- 1. Multi-level extraction:** Spot / niche features from images and gene profiles
- 2. Hyperbolic alignment:** Contrastive alignment + entailment hierarchy
- 3. Gene decoder:** Predict spot-level gene expression from H&E



Learning multi-level image–gene representations in hyperbolic space

Method: Hierarchical Hyperbolic Alignment (HHA)

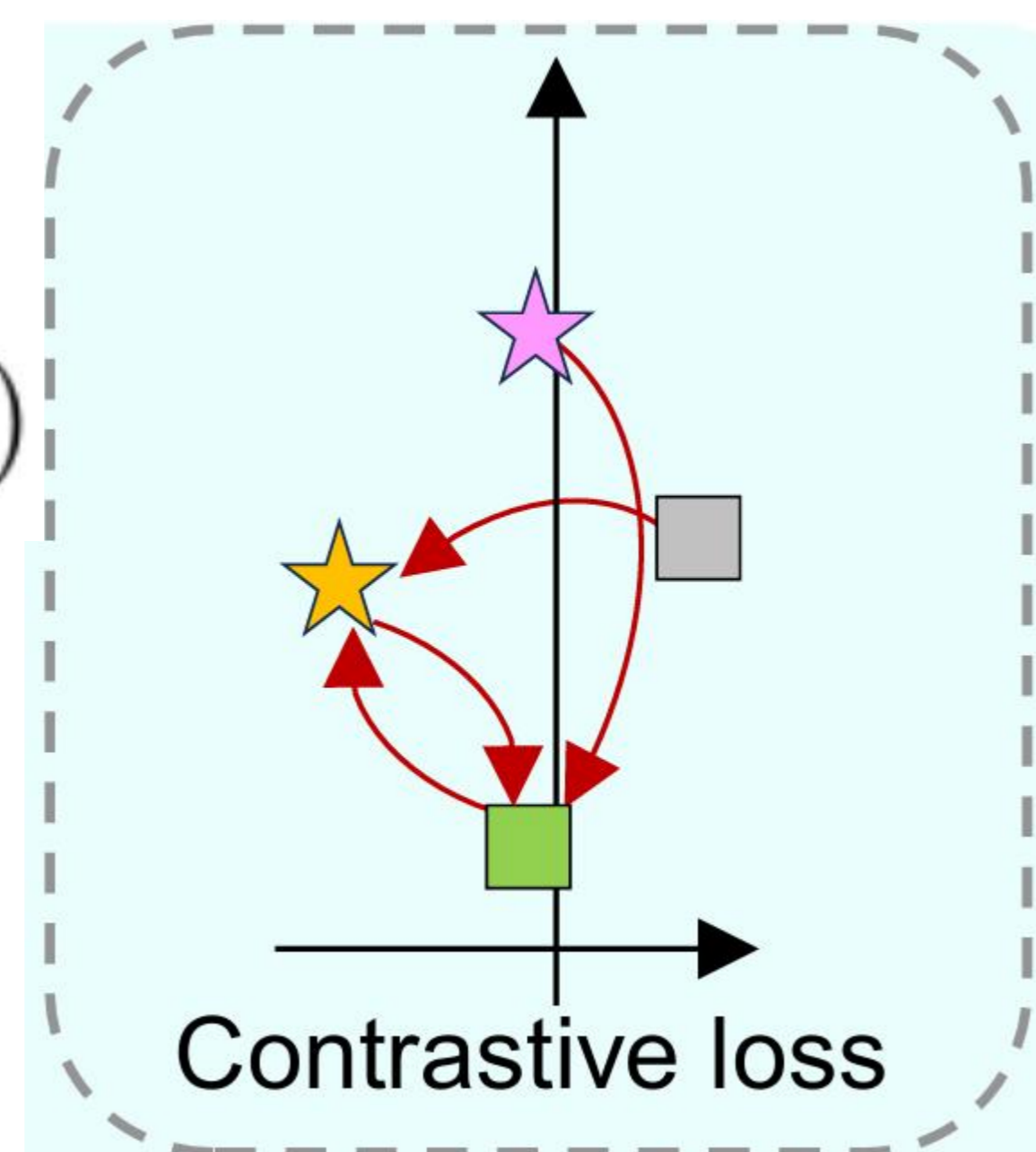
HHA consists of two complementary objectives:

Hierarchical Contrastive Alignment (HCA):

- Align image and gene representations across spot and niche levels in hyperbolic space.

$$\mathcal{L}_{align}(\hat{I}_s, \hat{G}_s) = -\frac{1}{B} \sum_{i=1}^B \log \frac{\exp(-d_{\mathbb{L}}(\hat{I}_s^i, \hat{G}_s^i)/\tau)}{\sum_{j=1}^B \exp(-d_{\mathbb{L}}(\hat{I}_s^i, \hat{G}_s^j)/\tau)}$$

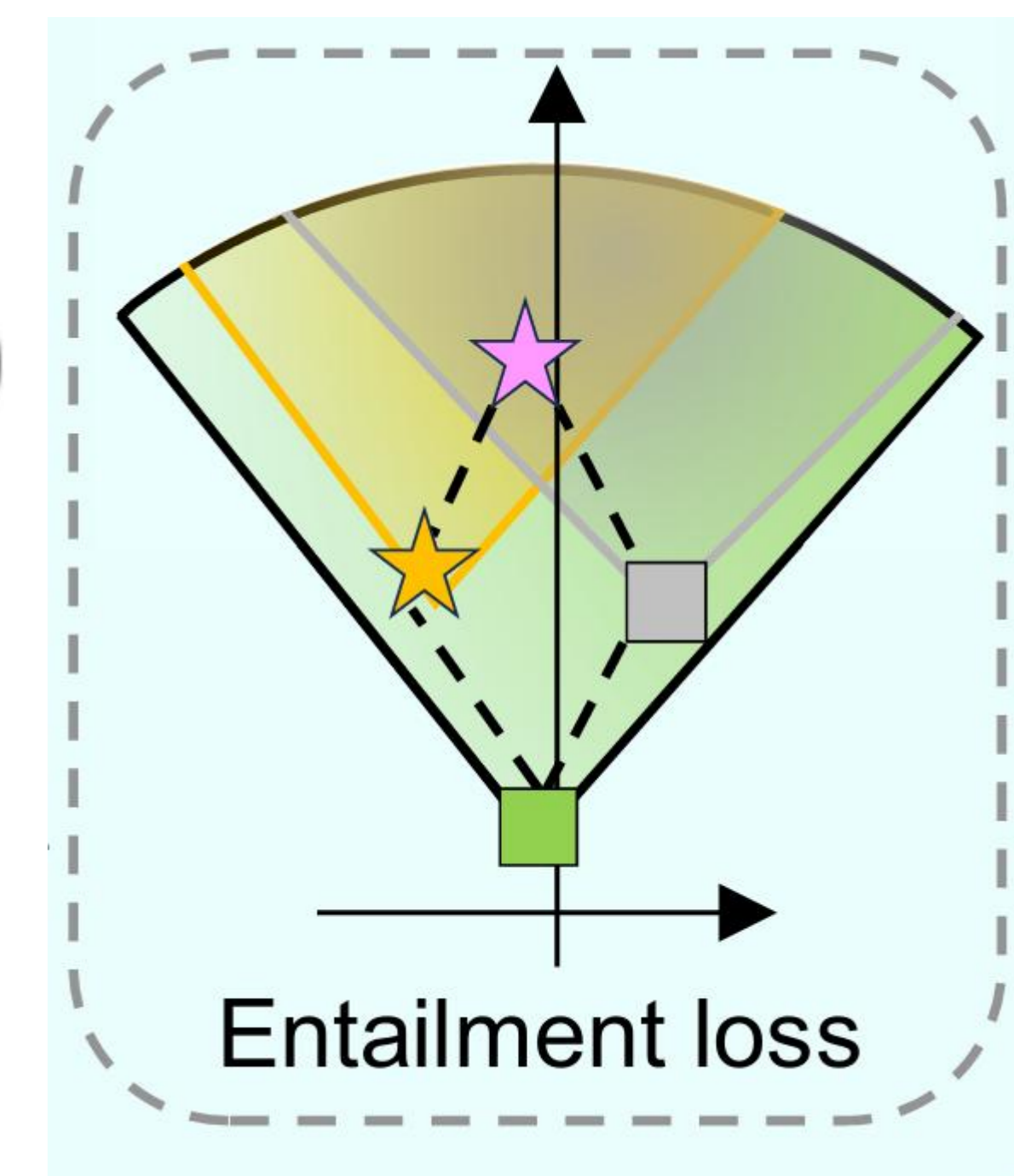
$$\mathcal{L}_{HCA} = \frac{1}{4} (\mathcal{L}_{align}(\hat{I}_s, \hat{G}_s) + \mathcal{L}_{align}(\hat{G}_s, \hat{I}_s) + \mathcal{L}_{align}(\hat{G}_n, \hat{I}_s) + \mathcal{L}_{align}(\hat{I}_n, \hat{G}_s))$$

**Hierarchical Entailment Alignment (HEA):**

- Impose information-based hierarchy: spot \rightarrow niche and image \rightarrow gene.

$$\mathcal{L}_{entail}(\mathbf{y}, \mathbf{x}) = \max(0, \text{ext}(\mathbf{y}, \mathbf{x}) - \text{aper}(\mathbf{y}))$$

$$\mathcal{L}_{HEA} = \frac{1}{4} (\mathcal{L}_{entail}(\hat{I}_s, \hat{I}_n) + \mathcal{L}_{entail}(\hat{G}_s, \hat{G}_n) + \mathcal{L}_{entail}(\hat{I}_s, \hat{G}_s) + \mathcal{L}_{entail}(\hat{I}_n, \hat{G}_n))$$



Experimental: Overall Performance

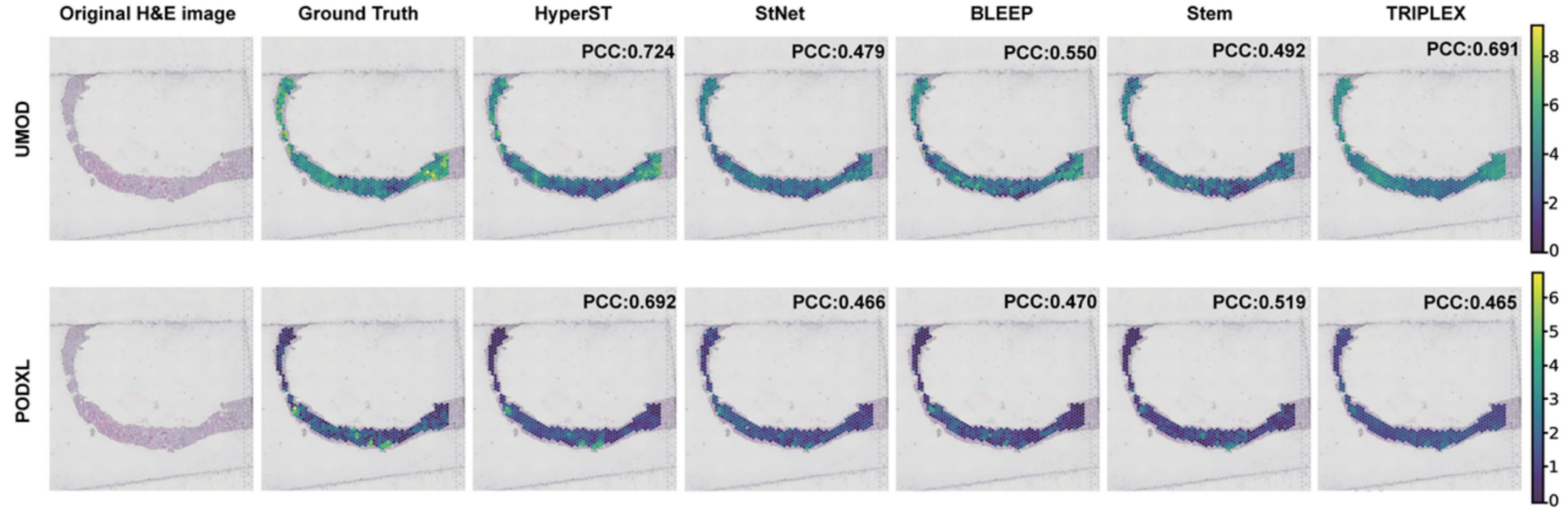
Table 1. Performance comparison on four spatial transcriptomics datasets. Higher values on PCC@10, PCC@50, PCC@200 are better. Lower values on MAE, MSE are better.

Dataset	Model	PCC@10 \uparrow	PCC@50 \uparrow	PCC@200 \uparrow	MSE \downarrow	MAE \downarrow
Kidney	TRIPLEX	0.579 \pm 0.095	0.485 \pm 0.084	0.351 \pm 0.066	1.122 \pm 0.204	0.855 \pm 0.104
	StNet	0.523 \pm 0.105	0.435 \pm 0.095	0.305 \pm 0.064	1.167 \pm 0.217	0.847 \pm 0.078
	BLEEP	0.518 \pm 0.112	0.434 \pm 0.102	0.310 \pm 0.071	1.233 \pm 0.244	0.865 \pm 0.085
	Stem	0.535 \pm 0.111	0.414 \pm 0.084	0.271 \pm 0.059	1.380 \pm 0.347	0.911 \pm 0.115
	HyperST	0.617\pm0.094	0.526\pm0.088	0.390\pm0.070	1.077\pm0.155	0.817\pm0.058
Colorectum	TRIPLEX	0.701 \pm 0.128	0.624 \pm 0.154	0.462 \pm 0.191	1.869 \pm 0.803	1.056 \pm 0.239
	StNet	0.646 \pm 0.134	0.570 \pm 0.142	0.419 \pm 0.176	1.686 \pm 0.373	1.023 \pm 0.134
	BLEEP	0.637 \pm 0.112	0.556 \pm 0.120	0.382 \pm 0.160	2.038 \pm 0.587	1.096 \pm 0.164
	Stem	0.670 \pm 0.116	0.573 \pm 0.130	0.399 \pm 0.166	1.788 \pm 0.418	1.032 \pm 0.138
	HyperST	0.721\pm0.105	0.642\pm0.128	0.477\pm0.184	1.498\pm0.456	0.958\pm0.158
Skin	TRIPLEX	0.831 \pm 0.094	0.799 \pm 0.114	0.740 \pm 0.142	0.981 \pm 0.466	0.685 \pm 0.205
	StNet	0.804 \pm 0.105	0.779 \pm 0.117	0.726 \pm 0.140	0.993 \pm 0.469	0.689 \pm 0.198
	BLEEP	0.788 \pm 0.111	0.761 \pm 0.123	0.704 \pm 0.145	1.117 \pm 0.540	0.701 \pm 0.221
	Stem	0.782 \pm 0.094	0.748 \pm 0.113	0.687 \pm 0.138	1.276 \pm 0.703	0.730 \pm 0.261
	HyperST	0.839\pm0.086	0.812\pm0.102	0.758\pm0.129	0.932\pm0.418	0.657\pm0.182
Lung	TRIPLEX	0.567 \pm 0.247	0.499 \pm 0.272	0.393 \pm 0.272	1.537 \pm 1.307	0.849 \pm 0.446
	StNet	0.526 \pm 0.247	0.464 \pm 0.267	0.355 \pm 0.253	1.660 \pm 1.258	0.899 \pm 0.422
	BLEEP	0.488 \pm 0.212	0.412 \pm 0.235	0.311 \pm 0.230	1.803 \pm 1.507	0.891 \pm 0.465
	Stem	0.546 \pm 0.224	0.469 \pm 0.250	0.351 \pm 0.241	1.709 \pm 1.365	0.866 \pm 0.485
	HyperST	0.637\pm0.225	0.568\pm0.260	0.459\pm0.282	1.182\pm0.873	0.757\pm0.352

HyperST outperforms state-of-the-art methods by explicitly modeling multi-level image–gene hierarchy.

Experimental: Biomarker Visualization

NCBI704



Visualization maps validate prediction quality

Turner, Michael, and Natalie Staplin. "UMOD-ulating CKD risk: untangling the relationship between urinary uromodulin, blood pressure, and kidney disease." *Kidney international* 100.6 (2021): 1168-1170.
Barua, Moumita, et al. "Exome sequencing and in vitro studies identified podocalyxin as a candidate gene for focal and segmental glomerulosclerosis." *Kidney international* 85.1 (2014): 124-133.

Experimental: Alignment Ablation

Alignment	PCC@10 \uparrow	PCC@50 \uparrow	PCC@200 \uparrow	MSE \downarrow	MAE \downarrow
w/o G-I HEA	0.610 \pm 0.101	0.514 \pm 0.096	0.378 \pm 0.074	1.147 \pm 0.188	0.839 \pm 0.065
w/o HEA	0.603 \pm 0.092	0.508 \pm 0.083	0.368 \pm 0.061	1.112 \pm 0.185	0.831 \pm 0.065
w/o HEA + HCA	0.576 \pm 0.099	0.484 \pm 0.089	0.344 \pm 0.064	1.134 \pm 0.168	0.837 \pm 0.058
Spot-Niche reversed	0.602 \pm 0.101	0.507 \pm 0.097	0.368 \pm 0.071	1.136 \pm 0.158	0.838 \pm 0.059
Image-Gene reversed	0.605 \pm 0.095	0.512 \pm 0.085	0.381 \pm 0.066	1.120 \pm 0.184	0.831 \pm 0.067
Euclidean counterpart	0.599 \pm 0.091	0.505 \pm 0.091	0.369 \pm 0.074	1.156 \pm 0.177	0.843 \pm 0.063
MERU	0.586 \pm 0.099	0.494 \pm 0.090	0.355 \pm 0.062	1.148 \pm 0.205	0.842 \pm 0.071
CLIP	0.558 \pm 0.098	0.462 \pm 0.087	0.321 \pm 0.058	1.220 \pm 0.293	0.867 \pm 0.097
Ours	0.617\pm0.094	0.526\pm0.088	0.390\pm0.070	1.077\pm0.155	0.817\pm0.058

Ablations validate the hierarchy-aware design.



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