Supplementary Information: scPRINT-2: Towards the next-generation of cell foundation models and benchmarks

Table S1: detailed version of the additive benchmark

	names	GPU time per epoch	denoising	embed & batch corr.		cell type prediction		gene regulatory network prediction					
			score	lung	pancreas	lung	pancreas	OR gwps	OR omni.	AUPRC gwps	AUPRC omni.		run id
Base	ross seeds (masking; ZINB loss; + continous expr. emb.; classif. + generative task)	130	2,5 +- 1,5	50.1 +-2.1	42.3 +-2	50 +- 8	45 +- 5	3,8. +-0.7	1,4 +- 0.3	0,044 +-0.002	0,00165 +-0.00015	efwkxesx, te0uwaz1, jsls4j6n, hobjefdj, r18nhnuz	blooming-dew-714, driven-valley-750, summer-deluge-783, silent-poltergeist-843, unraveling-pumpkin-841
	medium model	180	3	50.3	42.8	65.1	60.2	4.7	1.15	0.048	0.00188	p0znio7y	solar-durian-637
	negative control	0	-24	40.2	34.2	0	0	1	0.8	0.021	0.00123		
architecture	no dropout	130	-1	49.9	45.7	47	55.1	3.9	1.5	0.044	0.00157	dipgk9u5	expert-feather-748
	large classifier	130	0	52	43	53	49	4.4	1.8	0.046	0.00148	9q261ics	chocolate-snowball-718
	MVC	130	1	51.7	44.4	54.8	45.8	3.9	1.4	0.043	0.00143	yfvvk4cb	celestial-sun-749
	no decoders / generation	90	2	52.2	44.9	53.2	47.7	4	3.5	0.044	0.00166	z3abxa21	northern-voice-777
	XPressor	160	-4	50.4	45.6	47.3	46.8	4.2	2	0.046	0.00163	dsemm200	crimson-wildflower-791
data	only Tahoe	130	0	40	33	0	0	4.8	0.5	0.0041	0.00104	mxu0p3fs	young-bush-669
	CZI + Tahoe (denoising)	130	16.1	53.9	43.1	52.6	51.1	4.5	1.9	0.046	0.00143	nmc2l1gf	lurking-cat-846
	CZI	130	1	52.3	43.1	47.8	49.1	3.8	2	0.043	0.00162	4u5c4plu	radiant-oath-793
	all databases (denoise)	140	-4	48.6	39	44.9	40.7	3.6	1.3	0.043	0.00157	ujzjjsi3	macabre-apparition-844
	200 human datasets only	130	0	49.3	43.4	40.3	50	3.5	1.8	0.044	0.00166	c60vguww	playful-frost-804
	sampling without replacement	130	0	50	45	36	34	4.5	2.4	0.045	0.0016	lg84geoq	autumn-aardvark-702
	cluster-based sampling only	130	2.7	43.3	42	49.4	40.2	3.5	1.3	0.042	0.00157	s8wwlmxr	rosy-firefly-805
	meta-cell	130	21	52.8	47.7	53.6	51.3	3.4	1.7	0.04	0.00155	gp90j8vn	unique-dawn-806
attention	softpick (larger context)	130	3.1	50	41	53.8	44.6	3.6	1.8	0.042	0.00156	s6alkcvp	eldritch-fang-834
	criss-cross (larger context)	90	5.6	51.2	42.5	42.4	43.7	x	x	x	x	u5udxv4v	uncanny-raven-835
	hyper (denoise, larger context)	160	2	50.1	43.4	42.1	40.6	3.7	0.6	0.04	0.00115	l44og0s3	silver-grass-803
loss	contrastive learning (masking + denoising)	130	21.4	49	41.5	39.5	40.4	4	1.3	0.043	0.00149	wcg8g3hr	northern-frog-797
	elastic cell similarity	130	2.5	52.7	43.1	44.8	34.9	4.3	1.6	0.046	0.00167	qn2tyayf	hopeful-monkey-796
	no embedding ind loss	130	2.2	51.6	43	50	50	4	2.3	0.043	0.00156	4v84b9nm	devoted-wave-795
	ZINB+MSE (denoising)	130	25.5	51.3	48	49.2	42.9	3.4	1.3	0.04	0.00163	bv1r4d3h	firm-silence-747
	MSE	130	-4	54	46	62	43	3.3	1.2	0.042	0.00166	mnk73zbd	generous-dawn-666
	VAE compressor	160	3	51	42	38	27	4.2	1.7	0.044	0.0016	jwkcrxb9	wild-terrain-694
pretraining task	**var. context (larger context)**	170	29.1	53	46	52.9	52.2	3.1	1.2	0.038	0.00146	44p3fv3v	apricot-snowflake-756
	TF masking	130	2.6	49.8	42.8	49.8	42.8	3.7	2.3	0.043	0.00169	8vmjnnsb	winter-meadow-772
	denoising	130	21	52.6	45.1	50.9	54.5	3.6	1.3	0.043	0.0016	bk37305v	efficient-firebrand-753
	no classification	130	3	50	40	0	0	3.9	1.2	0.043	0.00129	oxlxtzim	copper-frost-625
	adv. classifier (+larger classif)	130	1	52	42	48	43	4.1	1.6	0.044	0.0014	2tzkv7m8	sunny-morning-629
input	sum normalization (denoise)	130	12.8	45.6	46.5	21.4	22.9	2.4	1	0.029	0.00136	ldh1fw8d	snowy-galaxy-744
	no random level of denoising	130	19	54.1	45.3	50.7	45.2	3.6	2	0.041	0.00179	0ayw97iw	divine-monkey-798
	binning	130	0	51.8	45.5	58.4	52	4.2	1.3	0.047	0.00162	op7at8xm	twilight-breeze-874
	GNN expression encoder	150	44	48	42	38	35	4	1.4	0.042	0.00128	bv6d9wpl	balmy-totem-727
	using only expressed genes	130	1.2	52.2	42.9	53.2	40.1	3.8	1.3	0.043	0.00157	xz238fyr	sage-snow-873
	without gene location	130	3.4	36.2	35	4	5.9	4.8	1.5	0.048	0.0017	r2n83z4k	youthful-snowflake-792
	learn gene emb (denoising)	130	20.9	51.7	45.1	49.7	46	3.2	1.7	0.041	0.00154	npayct6q	jumping-night-755
	fine-tuned ESM3	130	21.4	51.5	42.8	55.6	44.2	3.7	1.4	0.042	0.00181	fkcgp56s	not-snowflake-755
Main	small model (V2)	1820	44	53	49	46	47	3.5	1.6	0.041	0.0015		honest-vortex-815
	medium model (V2)	5600	x	x	x	x	x	x	x	x	x		x
	medium model (V1)	520	20.9	52.6	45.6	61.8	57.6	3.4	2.2	0.041	0.0017		bewitched-poltergeist-857
	small model (V1)	160	31.7	52.4	50	44.7	44.7	3.6	1.5	0.042	0.00138		dry-smoke-852

Detailed version of the additive benchmark, listing every value.

Table S3: detailed scIB biological conservation scores on the xenium dataset

Bio Metric	Isolated labels	KMeans NMI	KMeans ARI	Silhouette label	cLISI Bio conservation	**Aggregate score**
X_pca	0.446	**0.255**	**0.036**	0.382	0.955	**0.415**
scprint_emb	0.468	**0.376**	**0.125**	0.383	0.979	**0.466**

scPRINT vs PCA on expression. ScPRINT performs better, likely by denoising the expression.

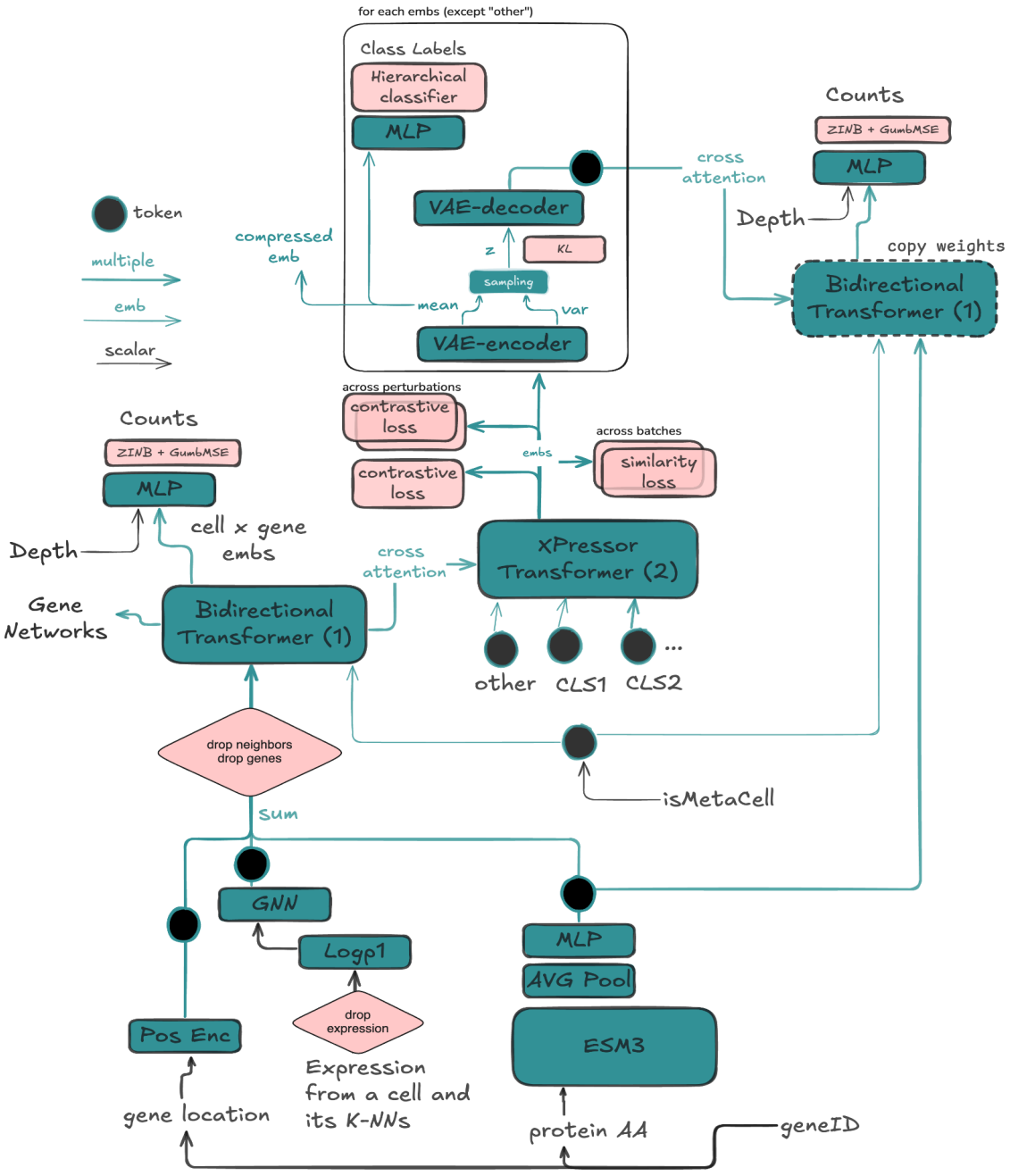
Table S4: detailed scIB scores on the unseen species integration task

	Bio conservation					**Batch correction**					**Aggregate score**			**Recomputed scores using the same elements**		
	Isolated labels	KMeans NMI	KMeans ARI	Silhouette label	cLISI	BRAS	iLISI	KBET	Graph connectivity	PCR comparison	Batch correction	Bio conservation	**Total**	Batch correction	Bio conservation	**Total**
scprint_2 ft (cell_type emb)	0.64	0.81	0.75	0.69	1.00	0.69	0.00	0.01	0.91	0.00	0.32	0.78	**0.60**			
scprint_2 ft	0.55	0.72	0.63	0.56	1.00	0.58	0.00	0.00	0.65	0.00	0.25	0.69	**0.51**			
scprint_zeroshot (cell_type emb)	0.57	0.41	0.31	0.53	0.98	0.65	0.00	0.77	0.00	0.28	0.56	0.45	**0.49**			
scprint_zeroshot	0.49	0.00	0.00	0.49	0.68	1.00	0.86	0.00	0.20	1.00	0.61	0.33	**0.44**			
random	0.54	0.23	0.14	0.50	0.97	0.80	0.00	0.00	0.72	0.00	0.30	0.48	**0.41**			
no integration (pca)	0.57	0.21	0.10	0.36	0.99	0.69	0.00	0.00	0.60	0.00	0.26	0.44	**0.37**			
saturn	0.81	0.97	0.49	0.13	1.00	0.79	0.13	0.05	0.91	0.92	0.62	0.92	**0.79**	0.56	0.68	**0.63**
scGen	0.60	0.77	0.49	0.23	0.99	0.88	0.23	0.16	0.91	0.92	0.85	1.00	**0.68**	0.62	0.61	**0.62**
Seurat v4 CCA	0.58	0.57	0.48	0.23	0.97	0.84	0.23	0.13	0.90	0.89	0.73	0.92	**0.50**	0.60	0.57	**0.58**
SAMap		0.62		0.01	0.98	0.91	0.01	0.22	0.74		0.60	1.00	**0.47**	0.47	0.53	**0.51**
scVI	0.51	0.55	0.50	0.23	0.95	0.83	0.23	0.09	0.91	0.98	0.80	0.93	**0.47**	0.61	0.55	**0.57**
BBKNN		0.56		0.11	0.99	0.82	0.11	0.05	0.82		0.31	0.66	**0.41**	0.45	0.55	**0.51**
Scanorama	0.56	0.54	0.49	0.27	0.96	0.76	0.27	0.09	0.84	0.93	0.59	0.79	**0.37**	0.58	0.56	**0.57**
fastMNN	0.52	0.54	0.48	0.09	0.96	0.70	0.09	0.03	0.89	0.86	0.37	0.72	**0.36**	0.51	0.52	**0.52**
Harmony	0.51	0.54	0.44	0.06	0.96	0.70	0.06	0.03	0.86	0.70	0.15	0.70	**0.16**	0.47	0.50	**0.49**

Details of the full scIB results comparing no integration, random embeddings sampled from the multivariate Gaussian, and different versions of scPRINT zero-shot or fine-tuned, using the merged embeddings or the cell type ones

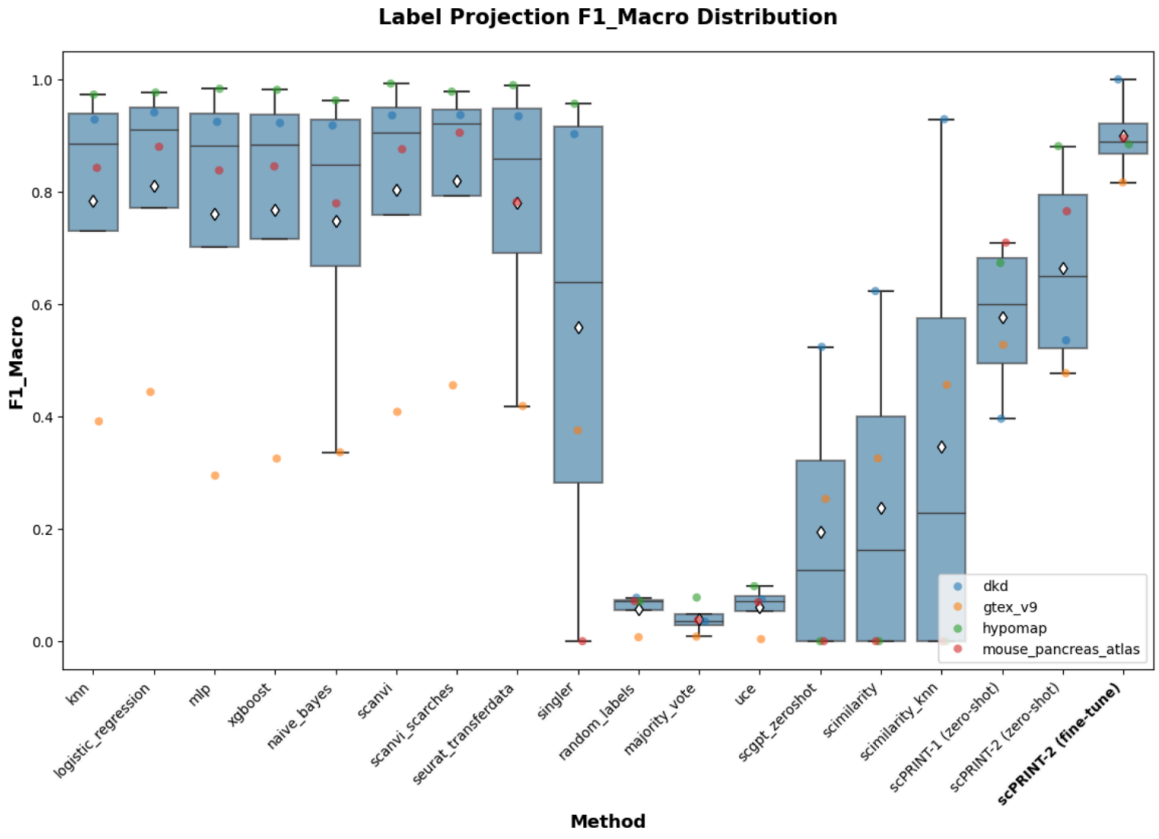
Supplementary figures

FIG S1: illustration of the full scPRINT-2's architecture, input, and output



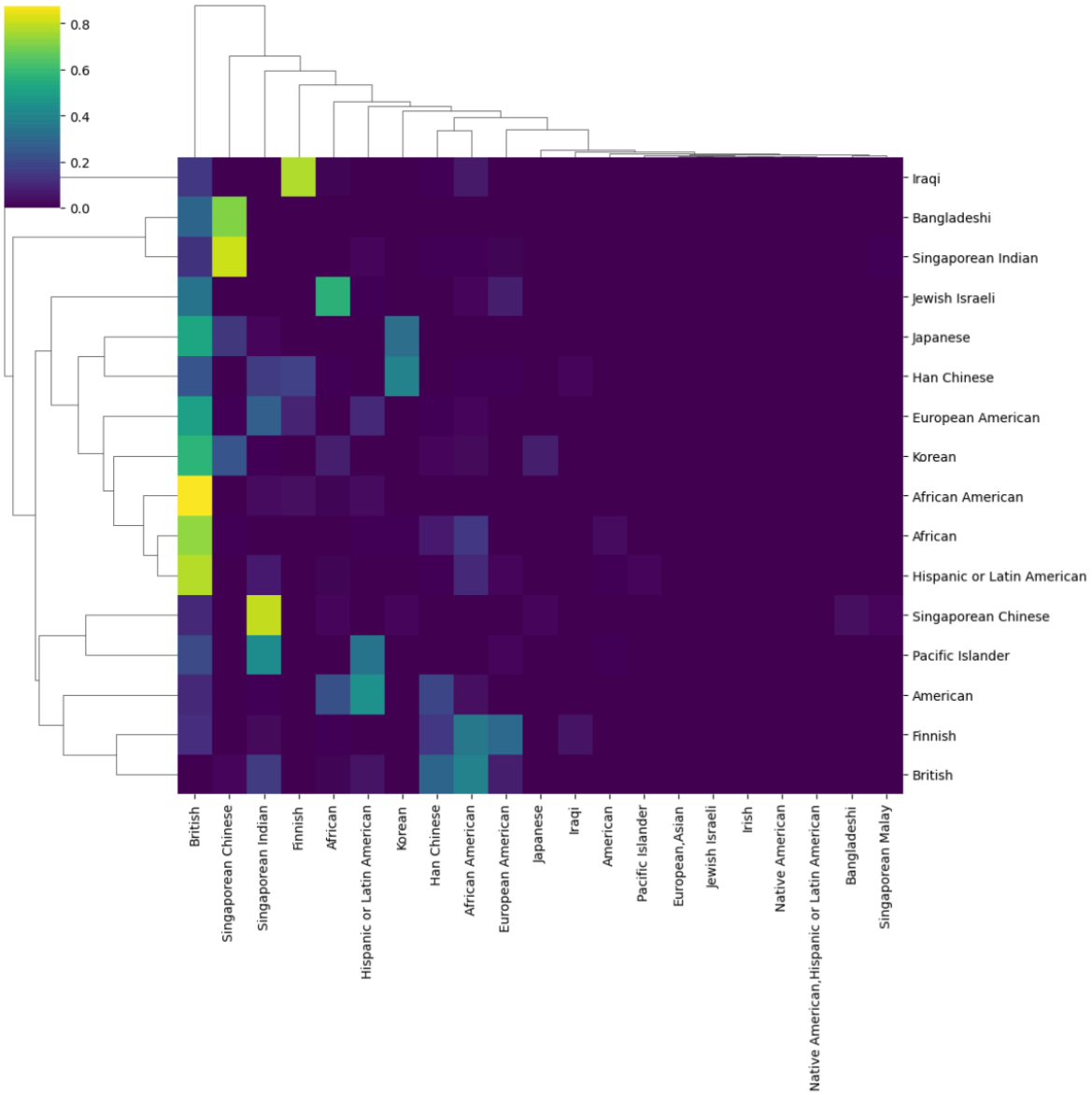
In-depth illustration of the full scPRINT-2's architecture, input, and output with all its main different components and the data flow.

FIG S2: barplot of the F1-macro scores on the label-projection task of the Open Problem benchmark



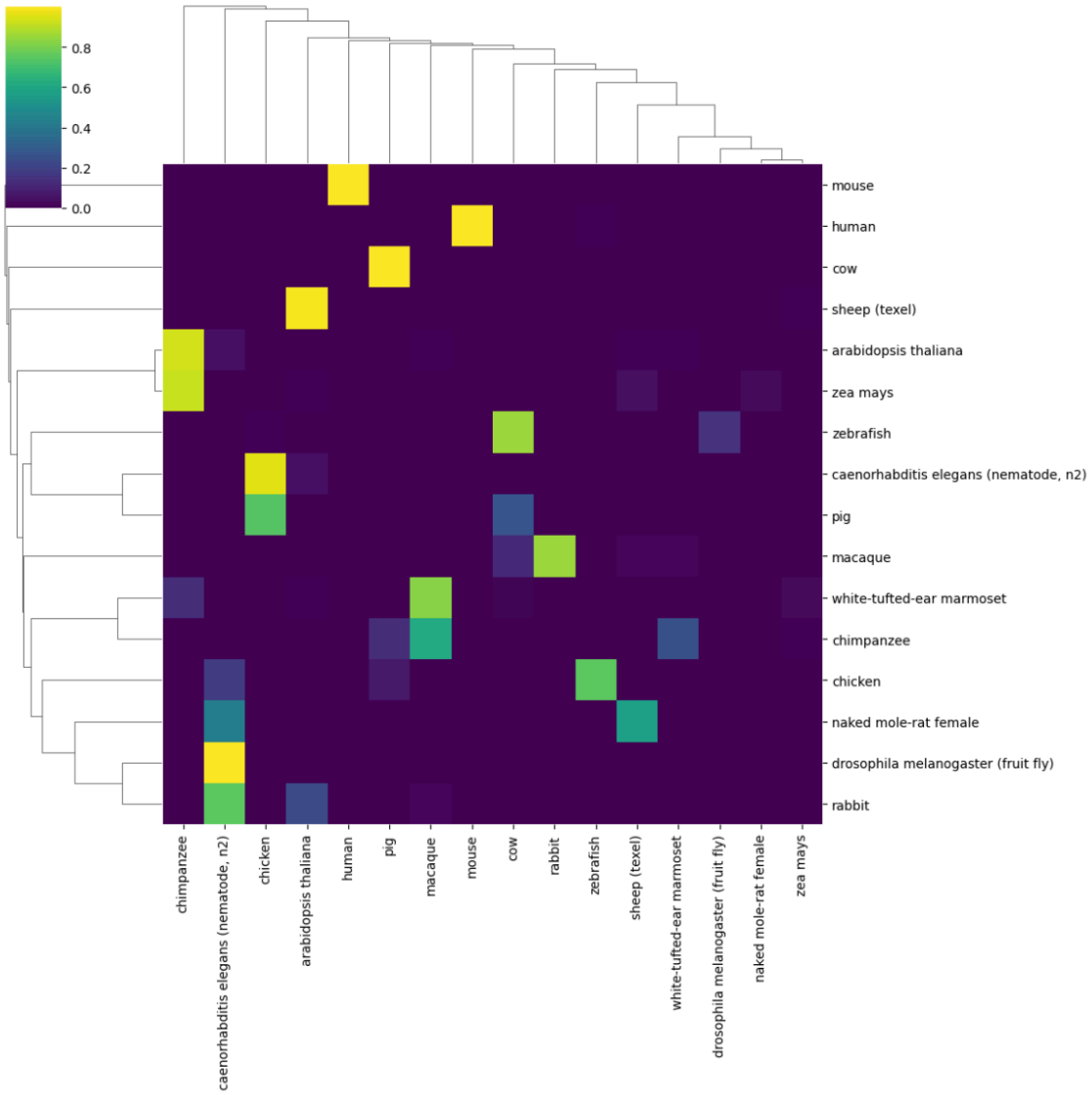
Comparison of scPRINT-1 and scPRINT-2, zero-shot and finetuned, with all other tested methods in Open Problems.

FIG S3: heatmap of ethnicity prediction relationship across samples



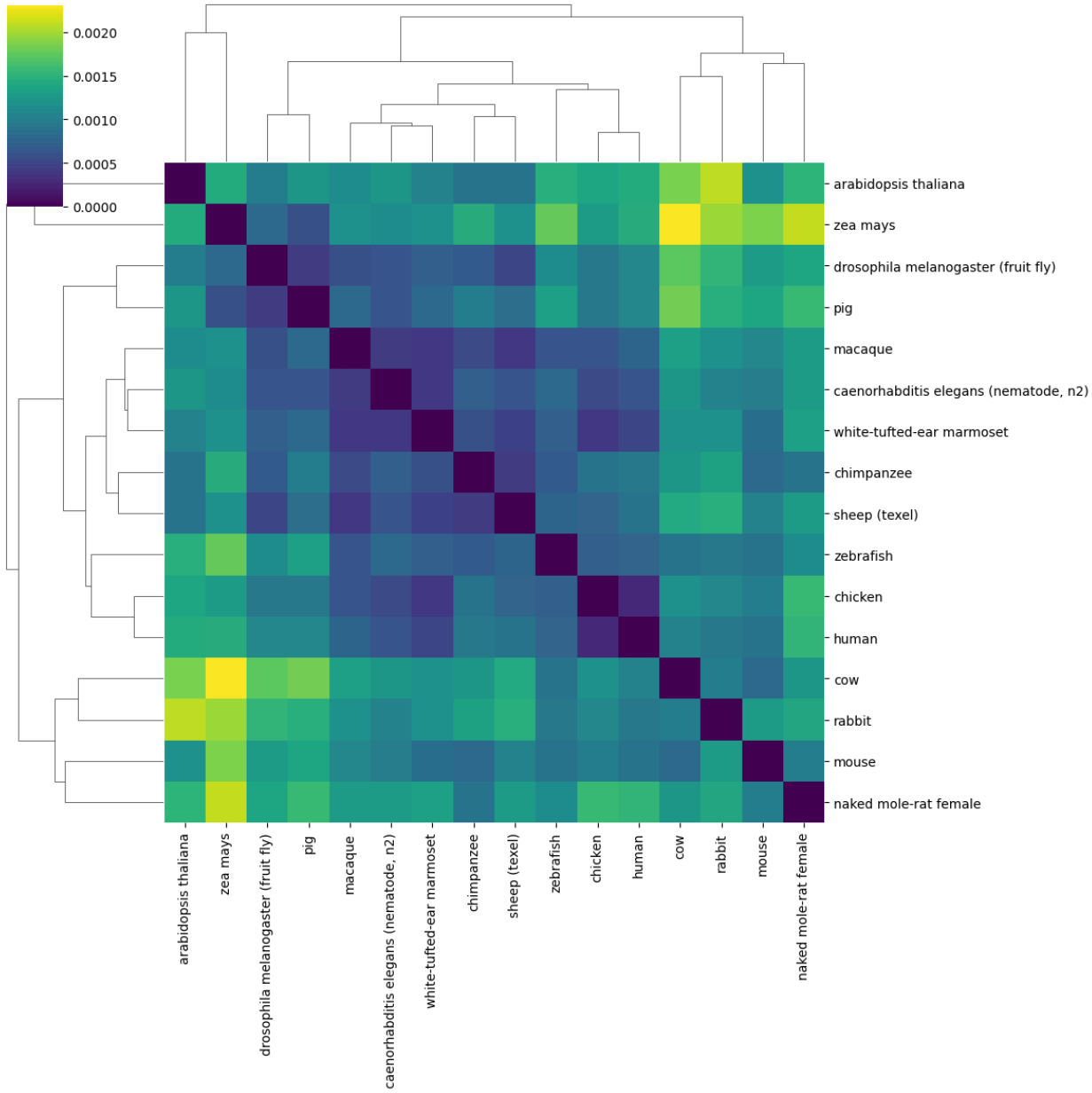
It is generated using labels predicted as top-1 (x-axis) vs second-best prediction (y-axis) across 10,000 random cells for each predicted label from the scPRINT-2 corpus.

FIG S4: heatmap of organism prediction relationship across samples



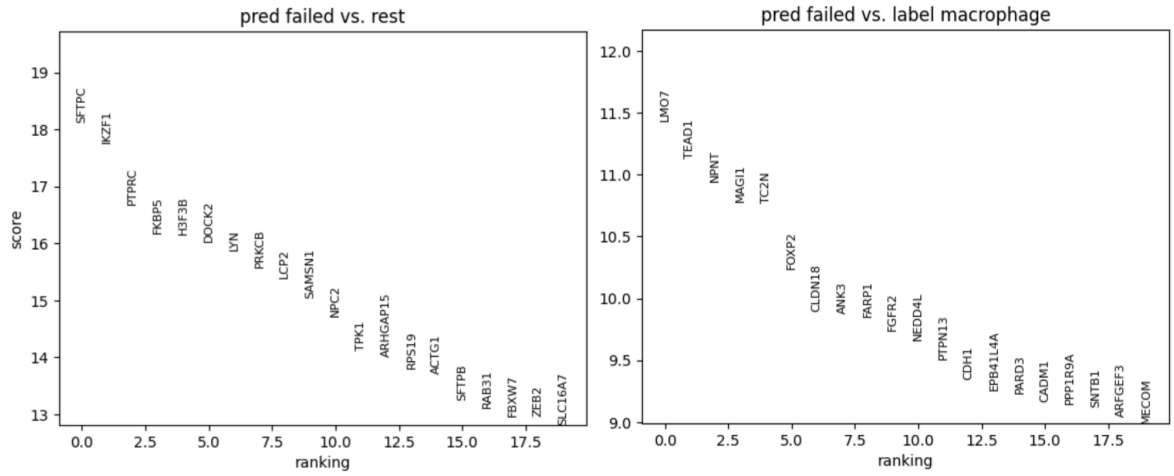
It is generated using labels predicted as top-1 (x-axis) vs second-best prediction (y-axis) across 10,000 random cells for each predicted label from the scPRINT-2 corpus.

FIG S5: heatmap of organism prediction relationship using organism embedding similarity across samples



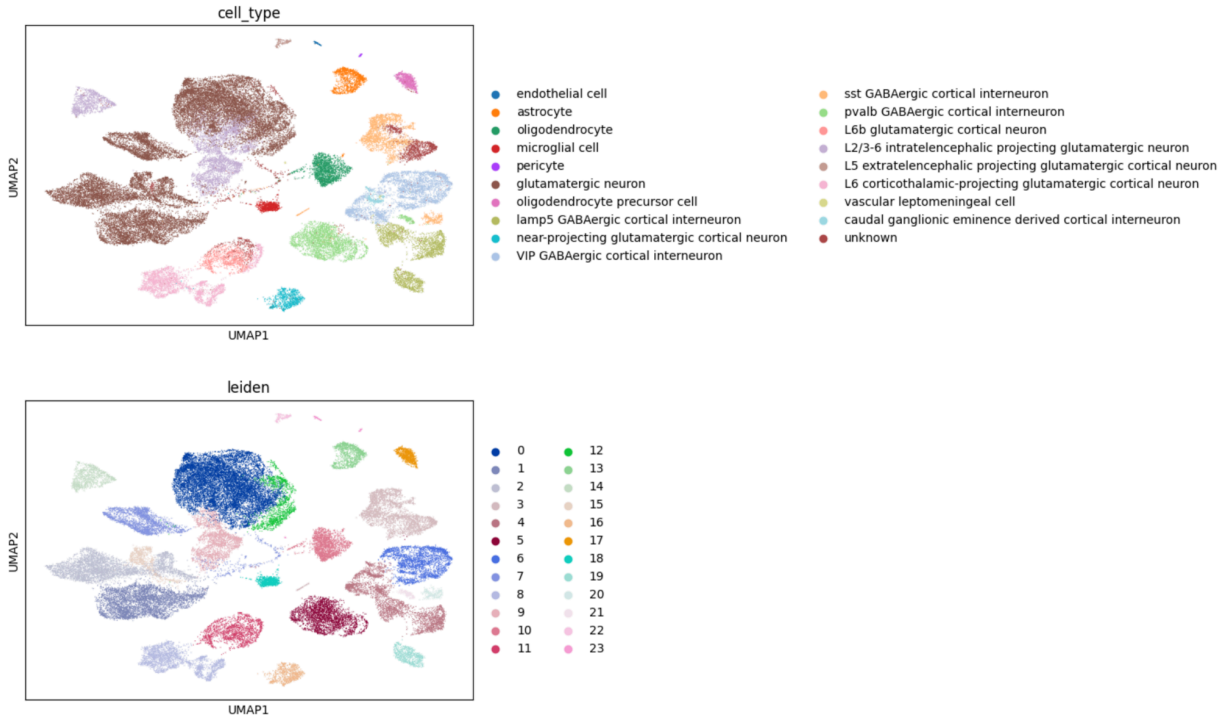
It is generated by averaging the embeddings for each predicted organism across 10,000 random cells for each predicted label in the scPRINT-2 corpus, and using the L2 distance.

FIG S6: Differential expression plots of the disagreeing cells between scPRINT-2 and ground truth



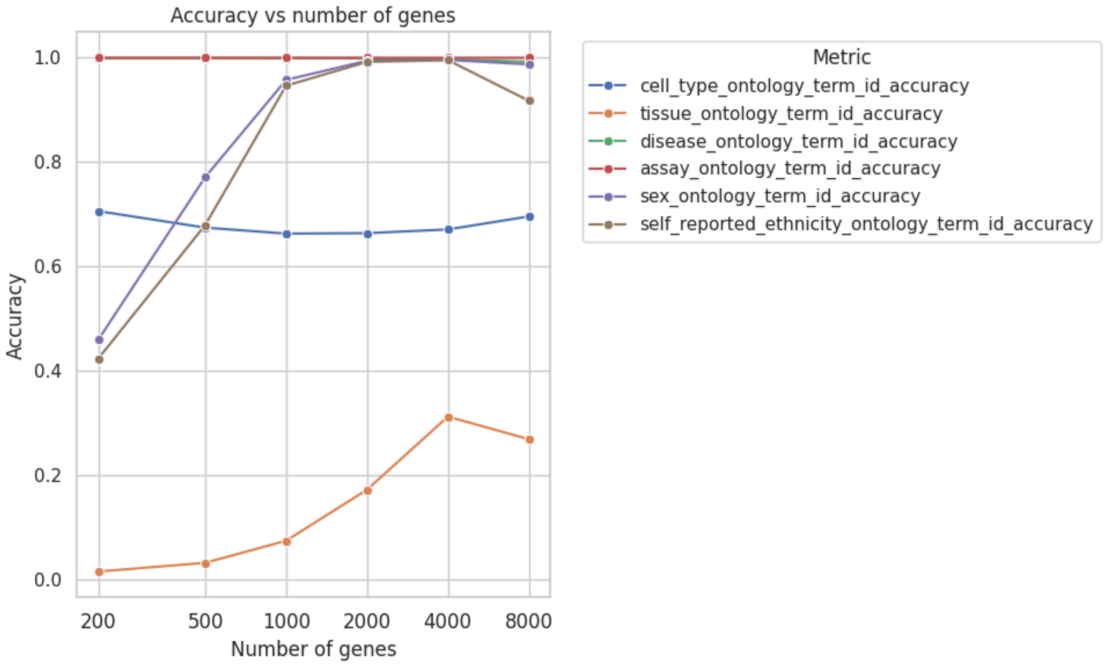
The differential expression is made on the cat/tiger cross-species dataset. “pred failed” is the macrophages labeled as type 2 pneumocytes by scPRINT-2.

FIG S7: Umap of the smart-seq dataset used in the varying context classification task



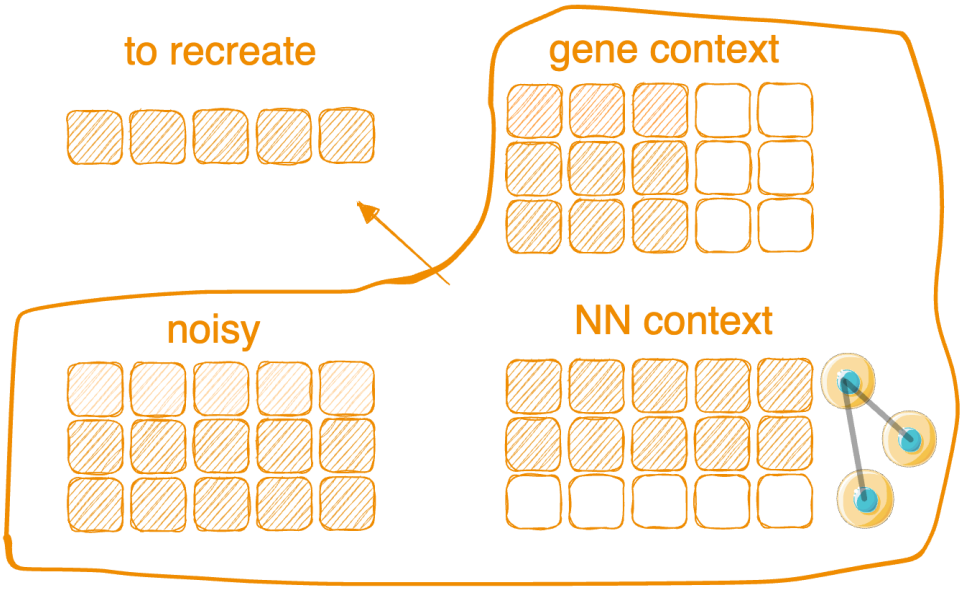
Umap of the cortical areas smart-seq v4 dataset used in the varying context classification task in results section 2, showing Leiden clusters and ground truth cell types.

FIG S8: line plot of the classification across varying context length, using the most expressed genes



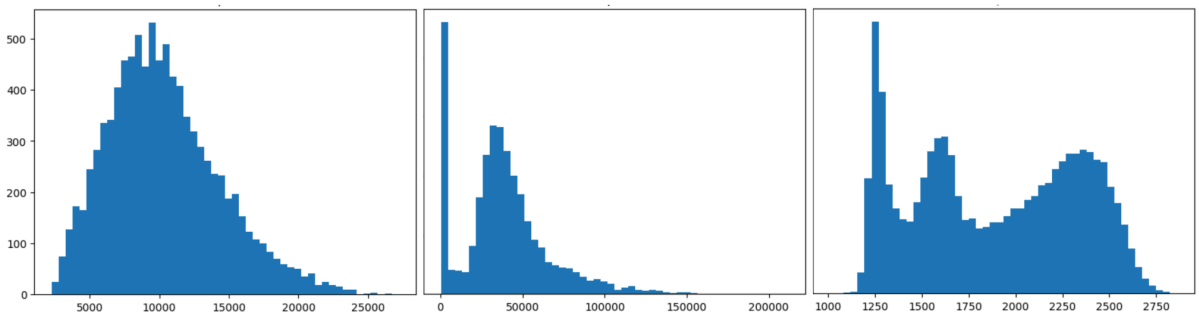
On the same dataset, but this time using the most expressed genes. Meaning each new gene in context is 200 most expressed, then 500, 1000, etc. We can see that while cell types are often defined by their most expressed genes, and thus this doesn't change classification accuracy much, other, more complex labels continue increasing in accuracy as context length increases.

FIG S9: Illustration of the multiple perturbations applied to expression data in scPRINT-2



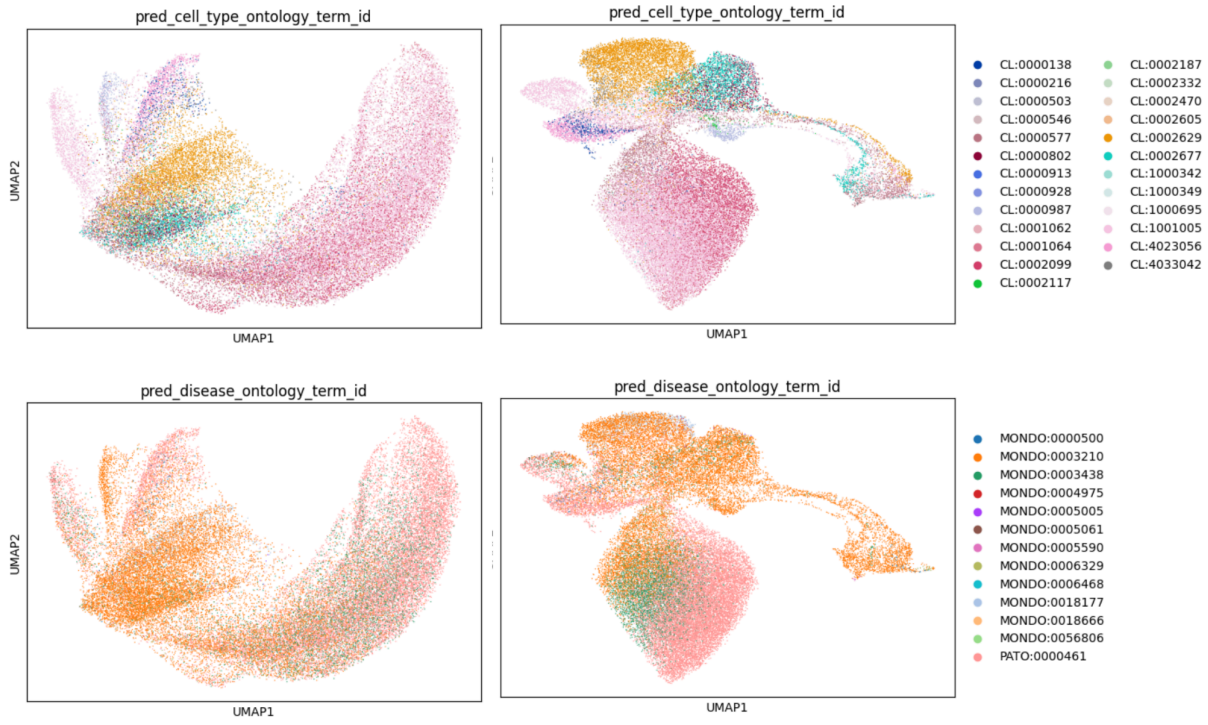
scPRINT can add noise and mask gene expression, modify the number of neighbors, and adjust context lengths.

FIG S10: distplot of the non-zero count distribution across cells from the three dataset qualities used



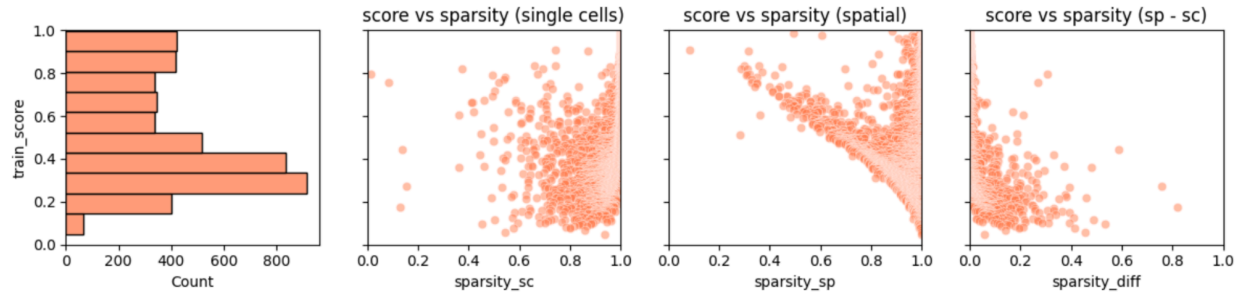
Non-zero count distributions across cells from left: good quality; center: excellent quality; right: poor quality datasets used in our denoising benchmark.

FIG S11: Umap over scPRINT-2 and PCA embeddings of the Xenium dataset



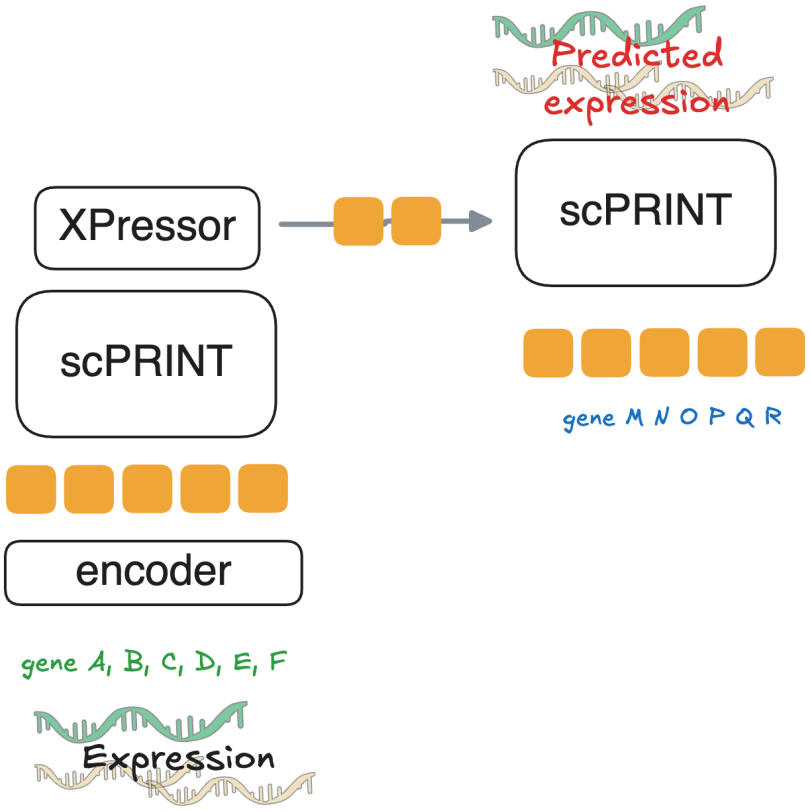
Umap of left: raw PCA expression, right: scPRINT-2 embeddings with scPRINT-2 predicted cell types and diseases.

FIG S12: Tangram mapping quality plots



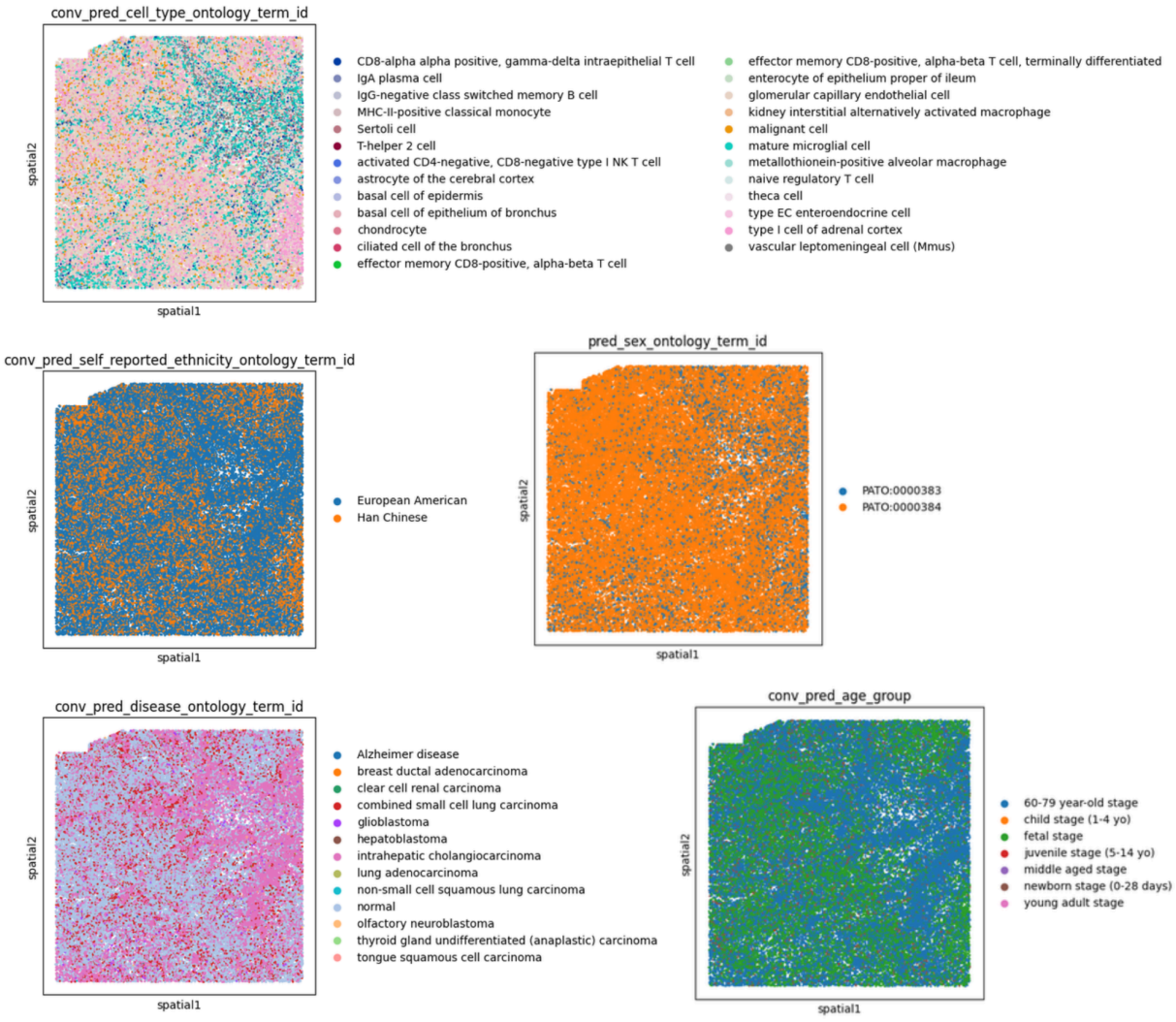
Tangram mapping quality plots on the Xenium skin melanoma datasets and 10v3 skin melanoma datasets.

FIG S13: illustration of scPRINT-2's generative imputation mechanism



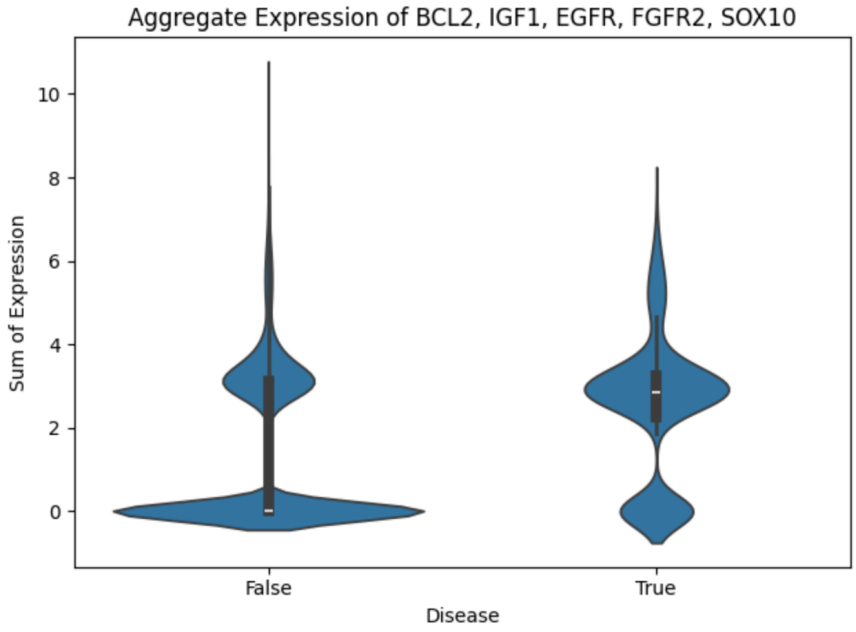
scPRINT encodes all 5000 measured genes into cell embeddings and decodes them on 5000 different unseen gene embeddings.

FIG S14: spatial plot of the Xenium melanoma dataset with scPRINT-2 predicted cell labels



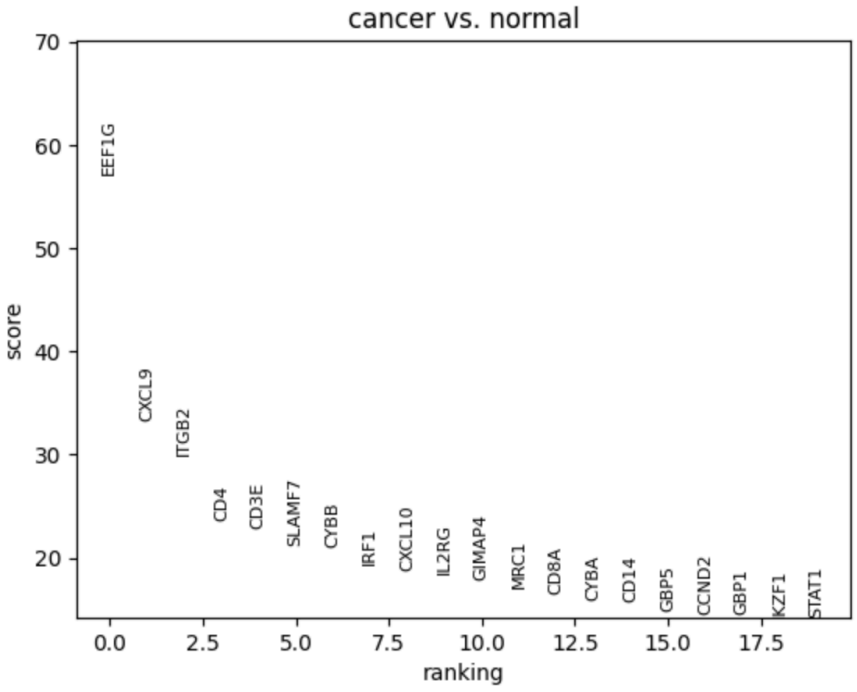
scPRINT-2 predicted cell labels for the disease, age, ethnicity, sex, and cell type labels on top of the selected Xenium skin melanoma patch.

FIG S15: violin plot comparison of the gene's expression between predicted malignant vs the rest



Violin plot showing that BCL2, IGF1, EGFR, FGFR2, SOX10, key melanoma markers are highly expressed in the malignant cell type label group vs the rest, with a p-value of 10^{-234}

FIG S16: differential expression plot of “cancer” disease labelled vs rest in the xenium dataset



Differential expression plot of cells whose disease label is “cancer” vs the rest in the Xenium skin melanoma dataset

FIG S17: Illustration of criss-cross attention

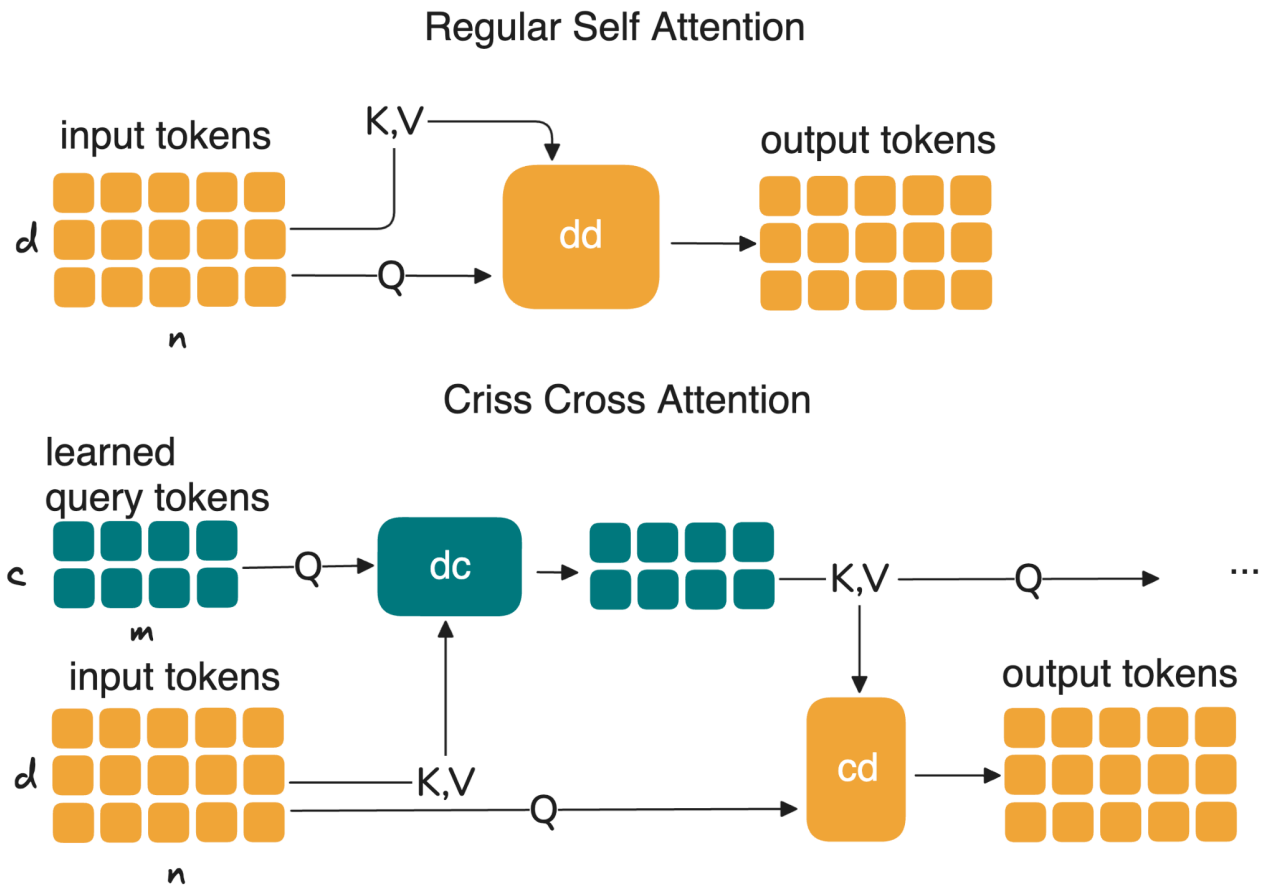
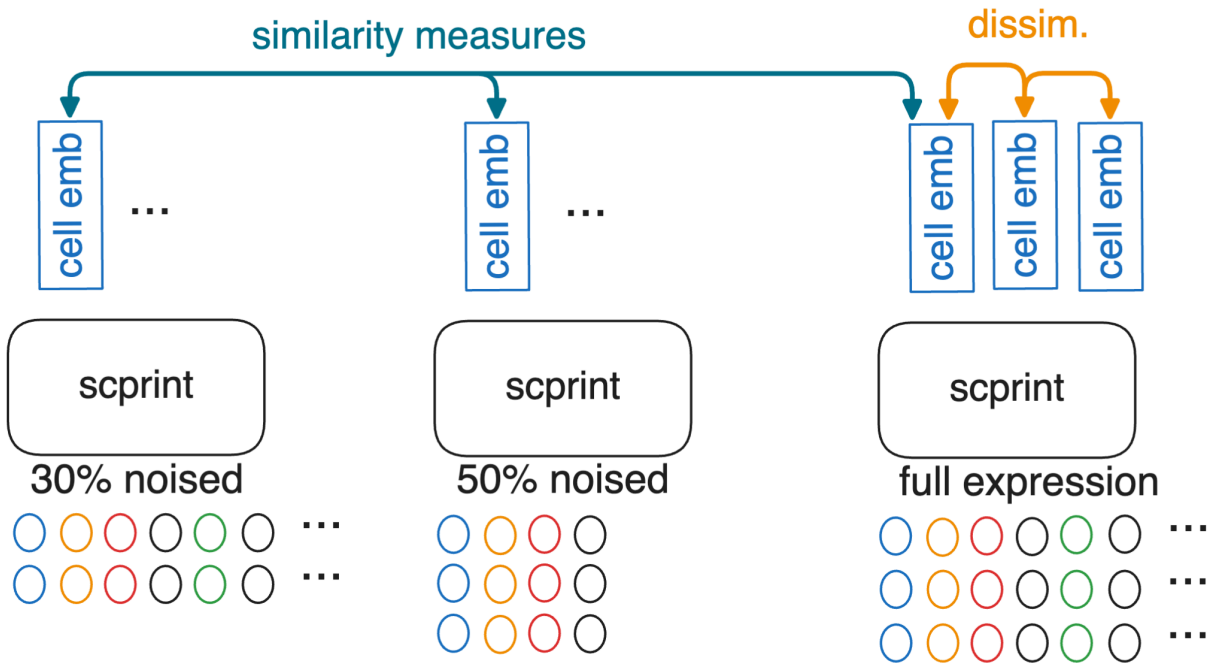


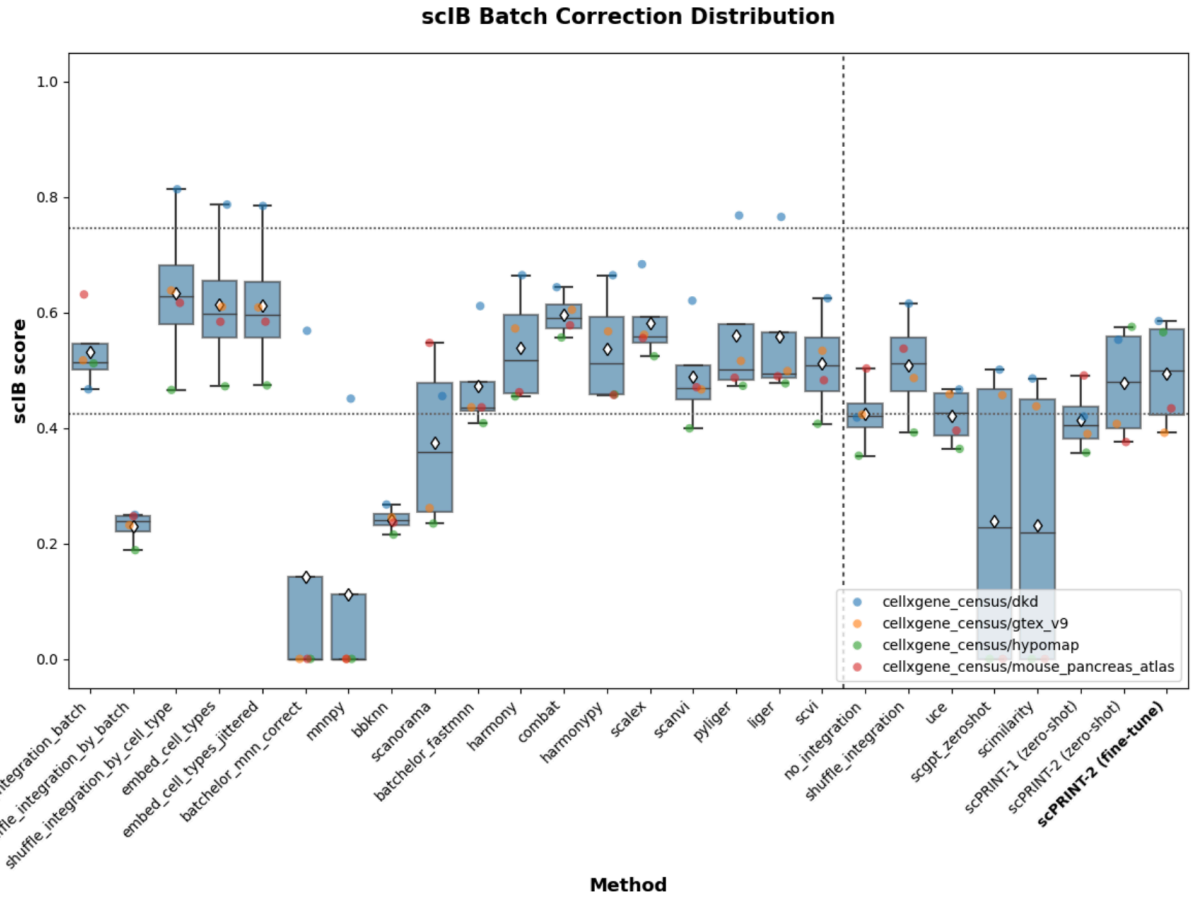
Illustration of our sub-quadratic complexity criss-cross attention mechanism

FIG S18: Illustration of the similarity and dissimilarity-based contrastive losses used in scPRINT-2



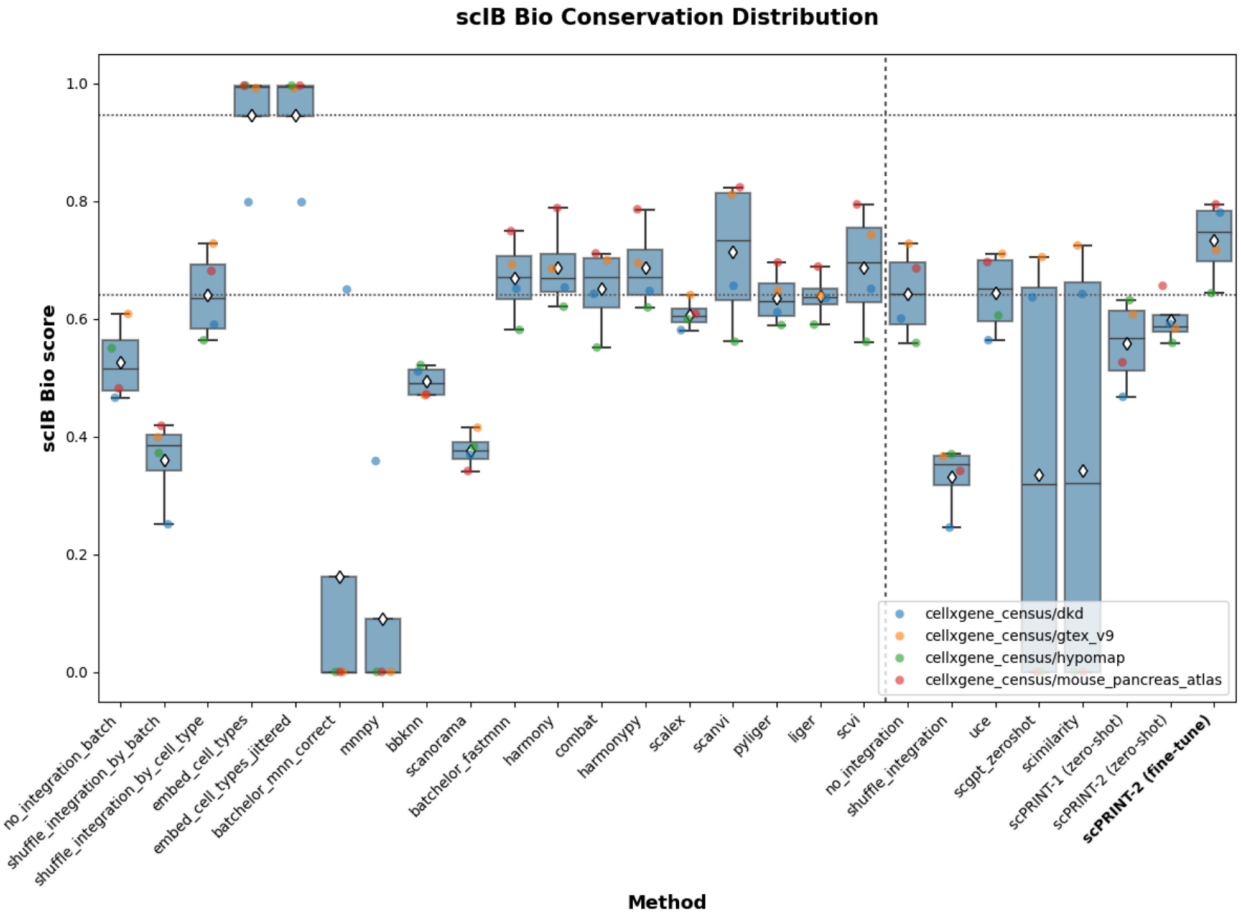
The contrastive losses push embeddings from the same cell at different noise levels to be as similar as possible.

FIG S19: whisker plot of Open Problems' batch-integration with batch-correction-only scores



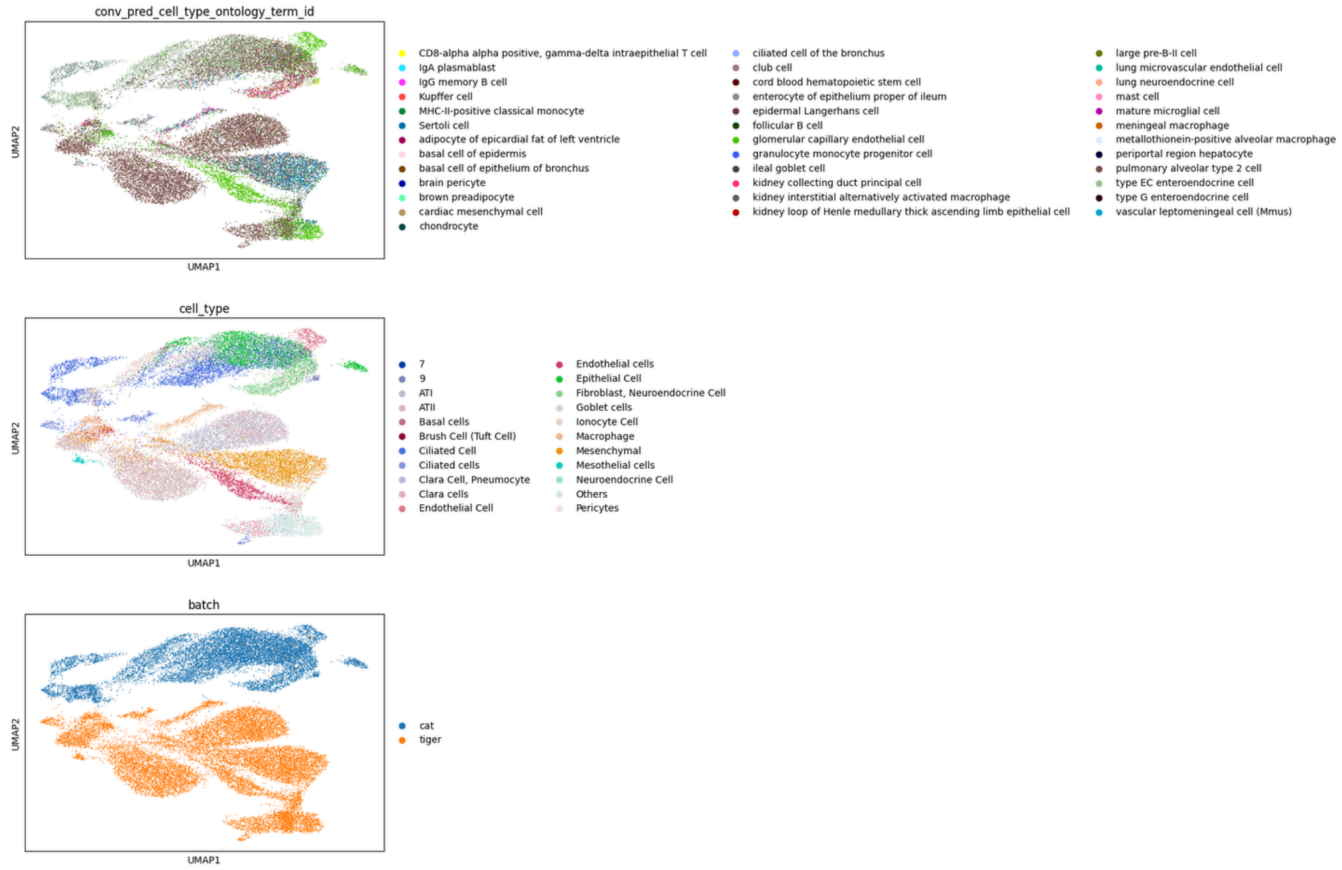
Open Problems' batch-integration with batch-correction-only scores for scPRINT-1 and scPRINT-2 zero-shot, and finetuned, and all other models assessed in open problems.

FIG S20: whisker plot Open Problems' batch-integration with Bio-conservation-only scores



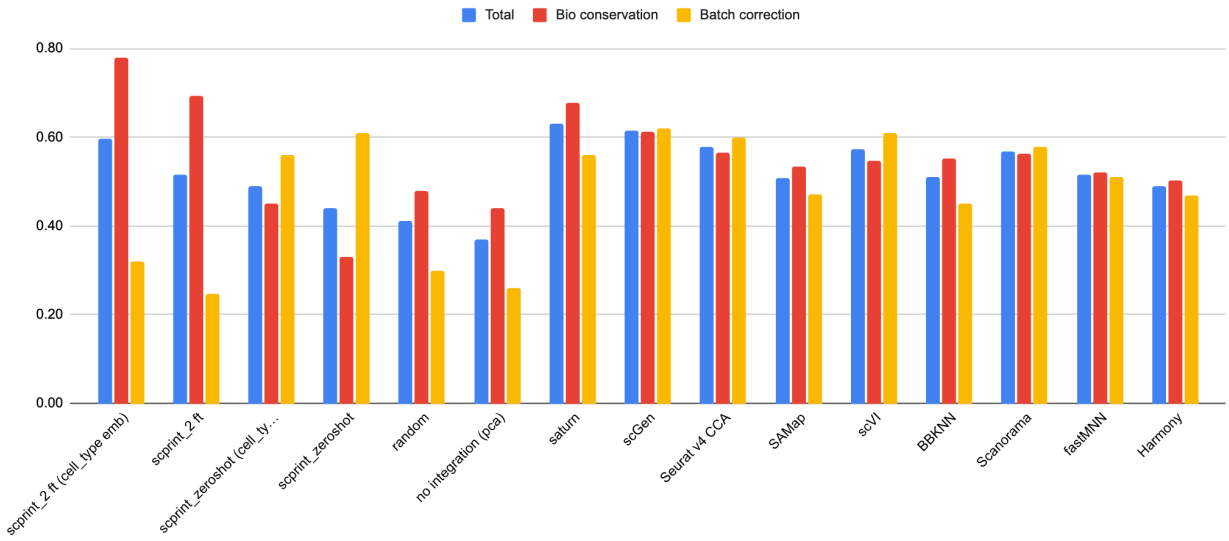
Open Problems' batch-integration with Bio-conservation-only scores for scPRINT-1 and scPRINT-2 zero-shot, and finetuned, and all other models assessed in open problems.

FIG S21: Umap of scPRINT-2's zero-shot multi-species expression embedding using the full cell-embedding



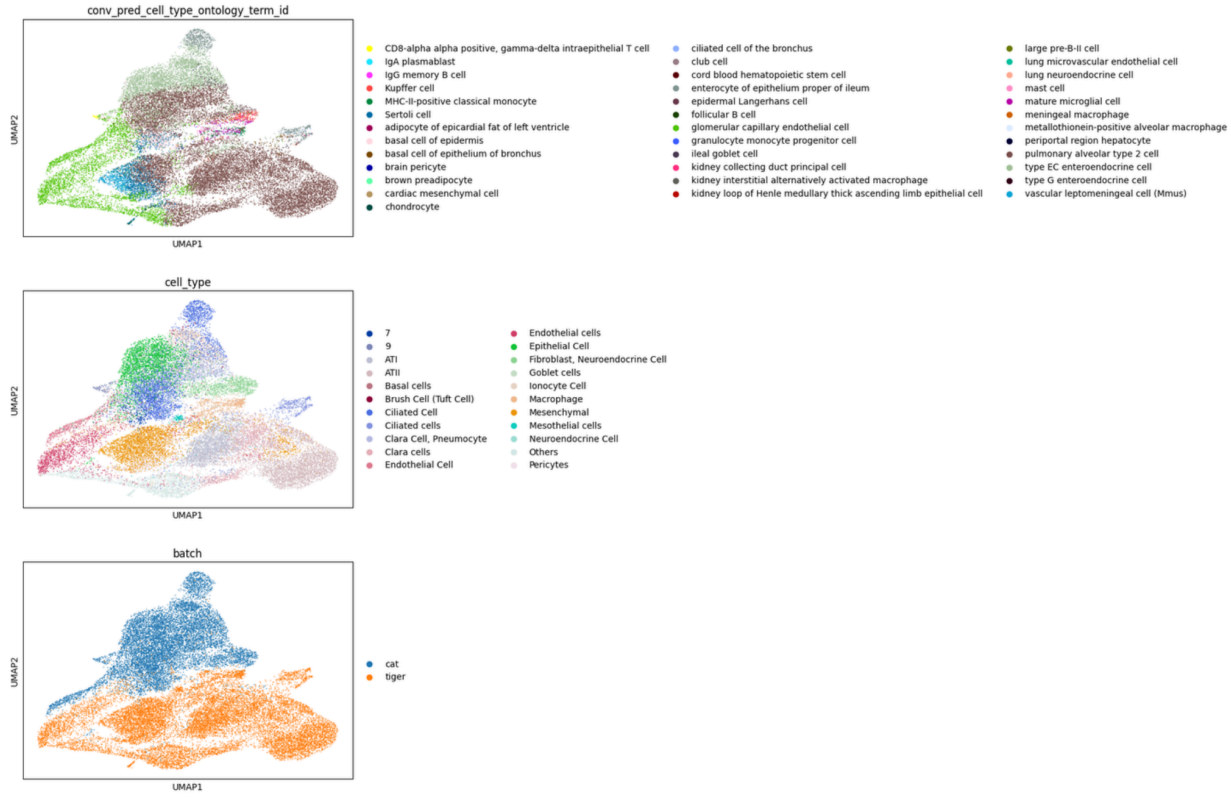
scPRINT-2's zero-shot multi-species expression embedding using the full cell-embedding from top to bottom, scPRINT-2 predicted cell type labels, ground truth cell type labels, and ground truth organism labels.

FIG S22: barplot of scIB score on scPRINT-2's multi-species integration



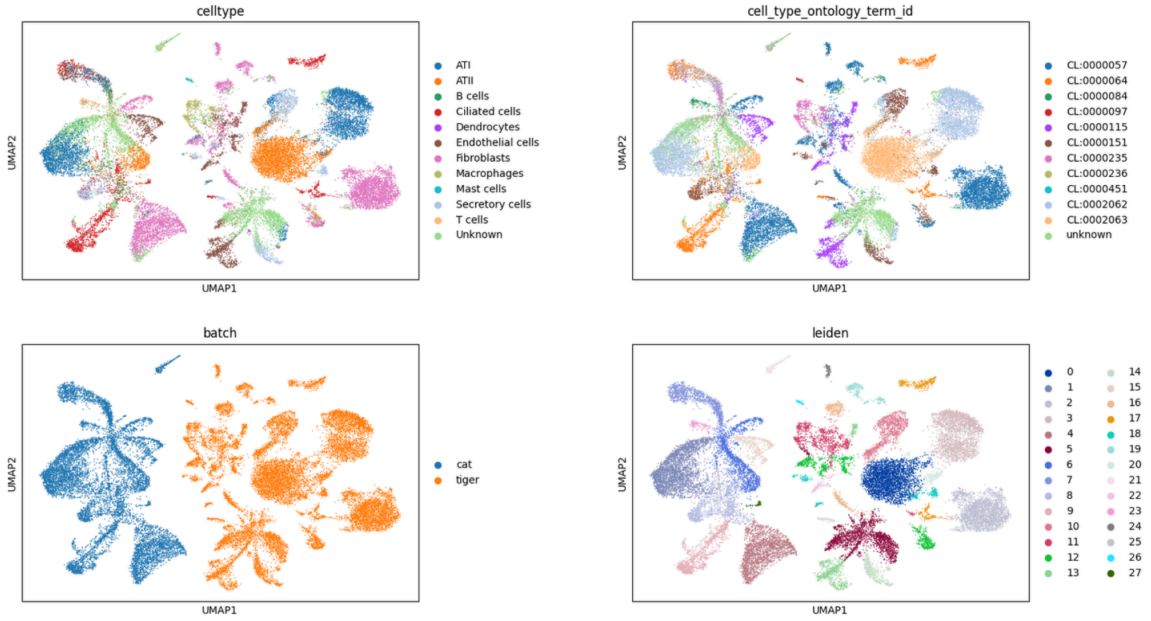
showing total, bio conservation, and batch integration across scPRINT-2 zero-shot, and fine-tuned version using both the full cell-embedding and cell-type-only cell-embedding

FIG S23: Umap of scPRINT-2's zero-shot multi-species expression embedding using the cell-type cell-embedding



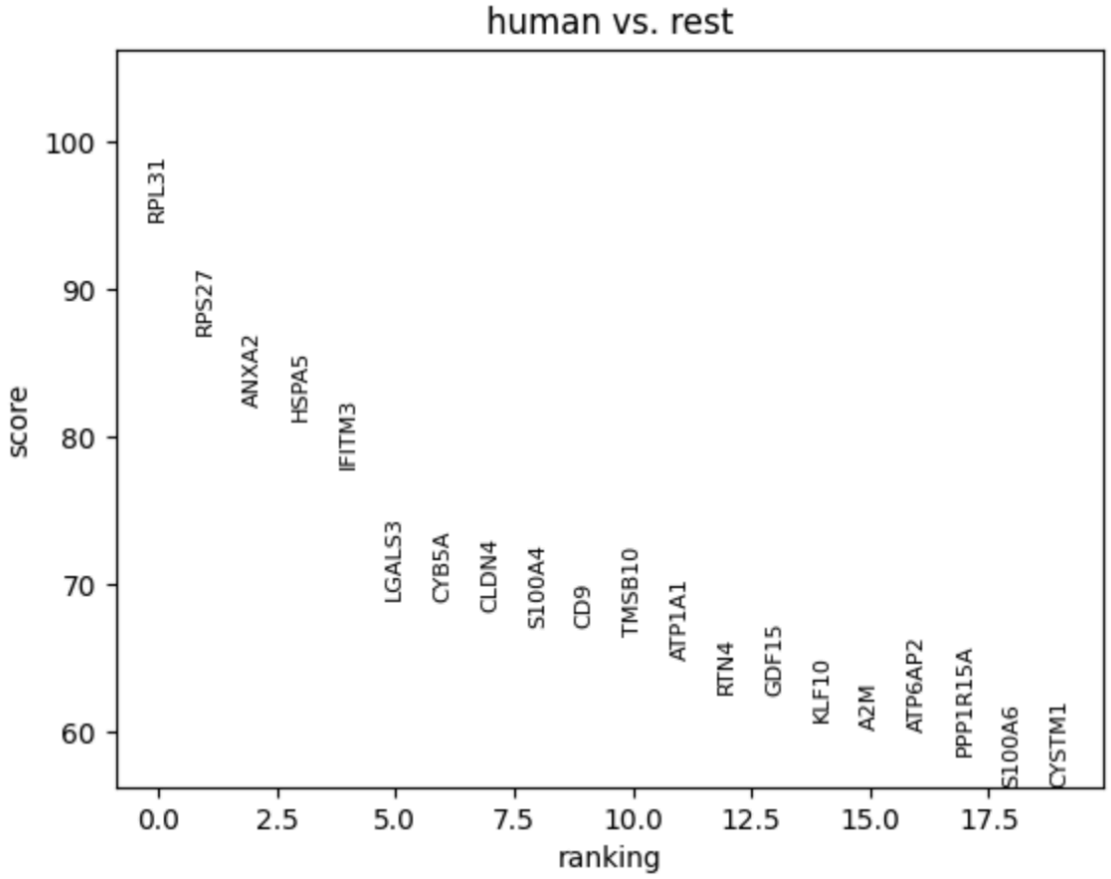
scPRINT-2's zero-shot multi-species expression embedding using the cell-type cell-embedding from top to bottom, scPRINT-2 predicted cell type labels, ground truth cell type labels, and ground truth organism labels.

FIG S24: Umap of scPRINT-2's multi-species expression embedding post-finetuning using the full cell-embedding



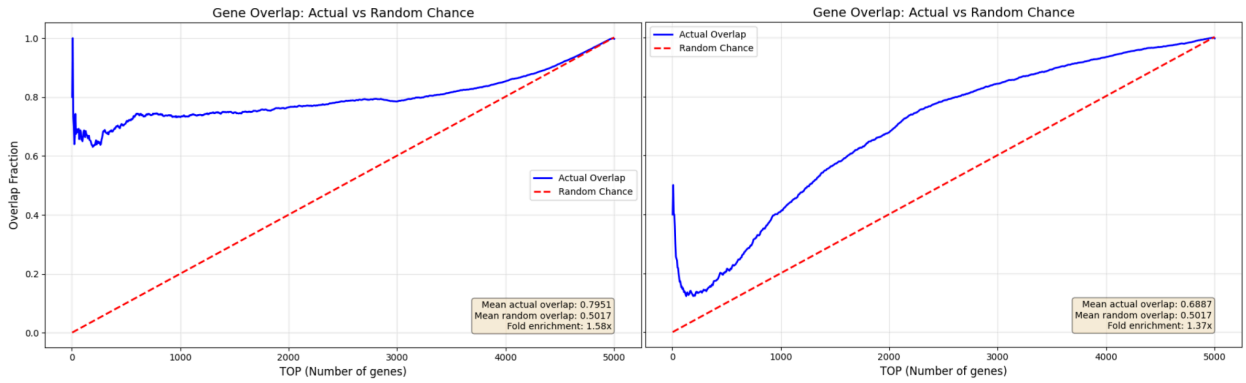
scPRINT-2's multi-species expression embedding post-finetuning using the full cell-embedding from left to right and top to bottom, ground truth cell type, scPRINT-2 predicted cell type labels, ground truth organism labels, and Leiden clusters.

FIG S25: Differential expression plot of the human vs mouse dataset from section 4



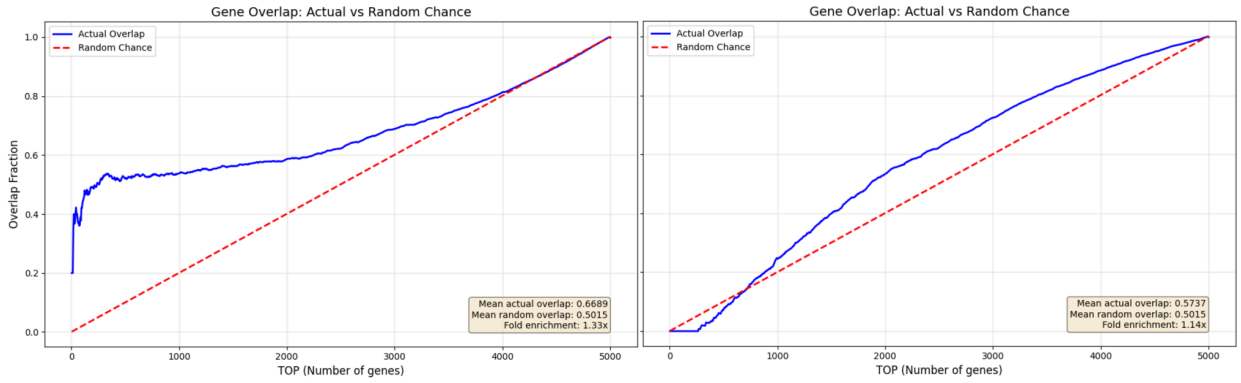
Differential expression plot of the human vs mouse dataset from section 4. Rest is mouse here.

FIG S26: Over-representation plot of humanized mouse data vs real mouse data compared to human



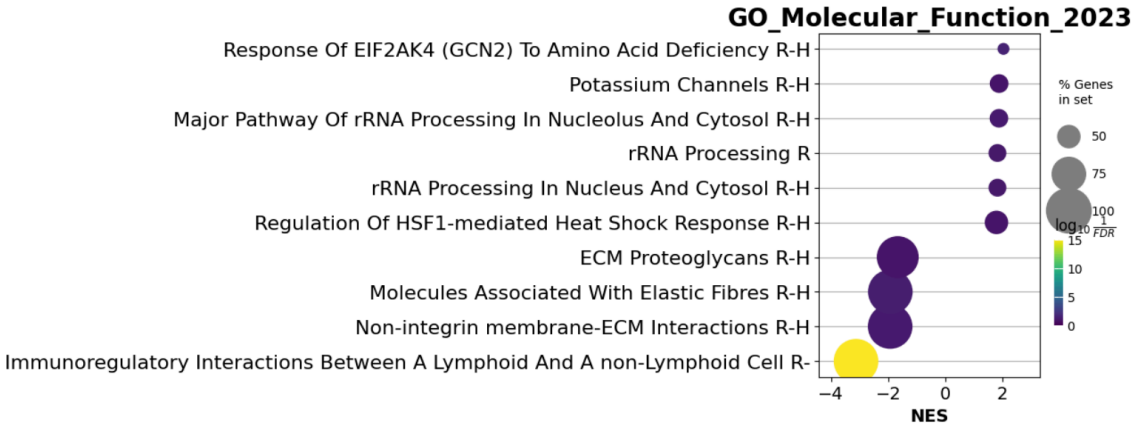
Over-representation plot of differentially expressed genes in scPRINT-2's humanized mouse data vs real mouse data compared to human.

FIG S27: Over-representation plot of female-like male data vs real female data compared to male



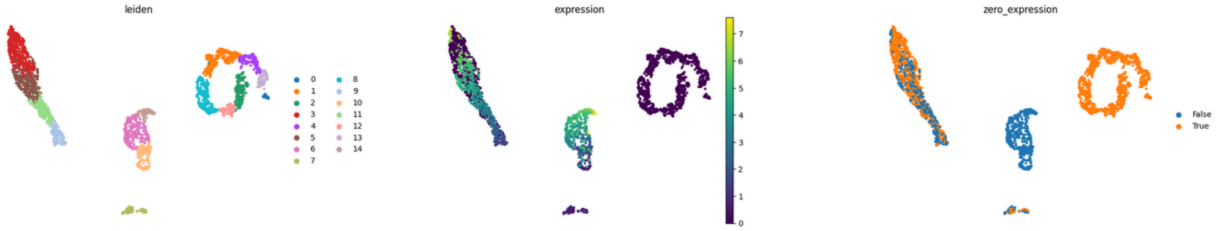
Over-representation plot of top differentially expressed genes in scPRINT-2's female-like male data vs real female data compared to male.

FIG S28: Dot Plot of Gene-set enrichment analysis over the differential expression analysis of section 4



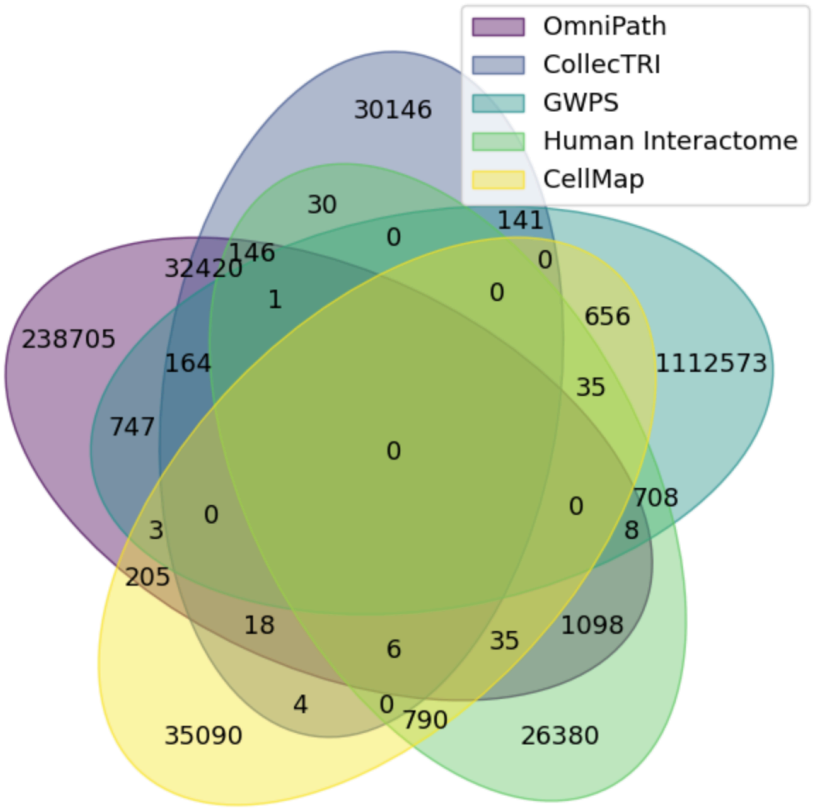
Showing the top 10 most enriched gene sets from the GO molecular function 2023 database.

FIG S29: Output gene embedding for a non-fully trained model without XPressor architecture



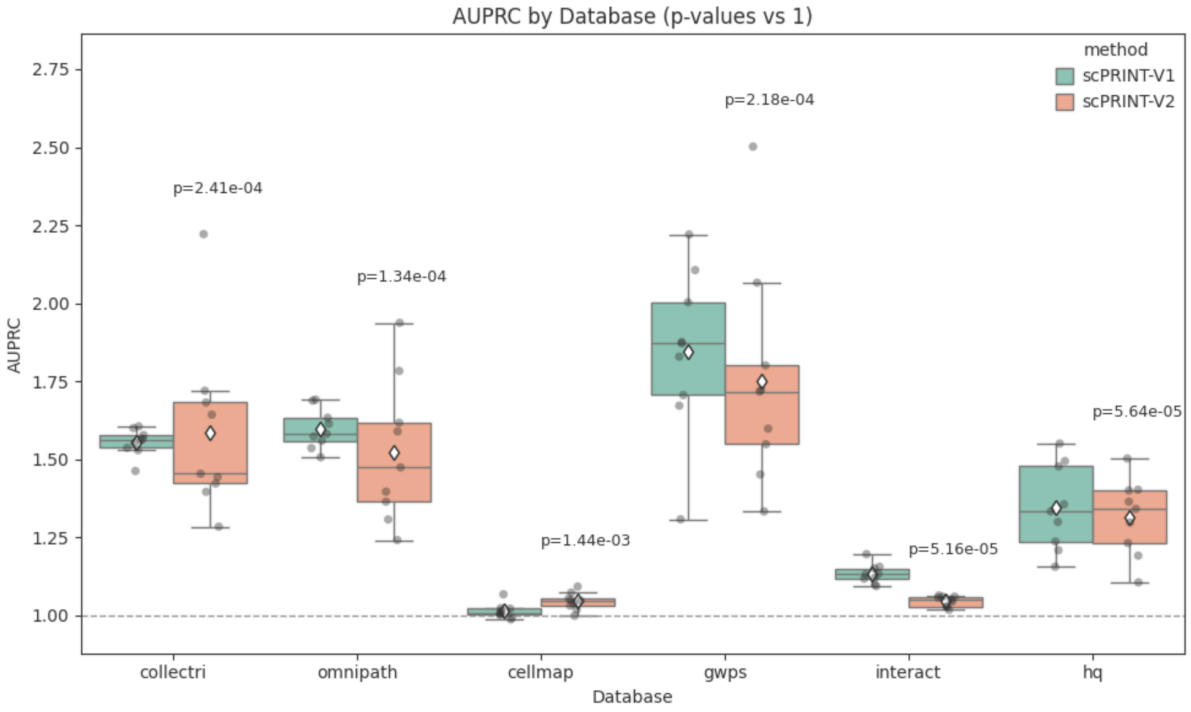
Overlaying in color, from left to right, the Leiden clusters, the expression values, and the zero vs non-zero expression. Despite displaying multiple clusters, the number of enriched pathways in each is still smaller than for a model using XPressor. (see Figure 5)

FIG S30: Venn diagram of the different ground truth gene networks



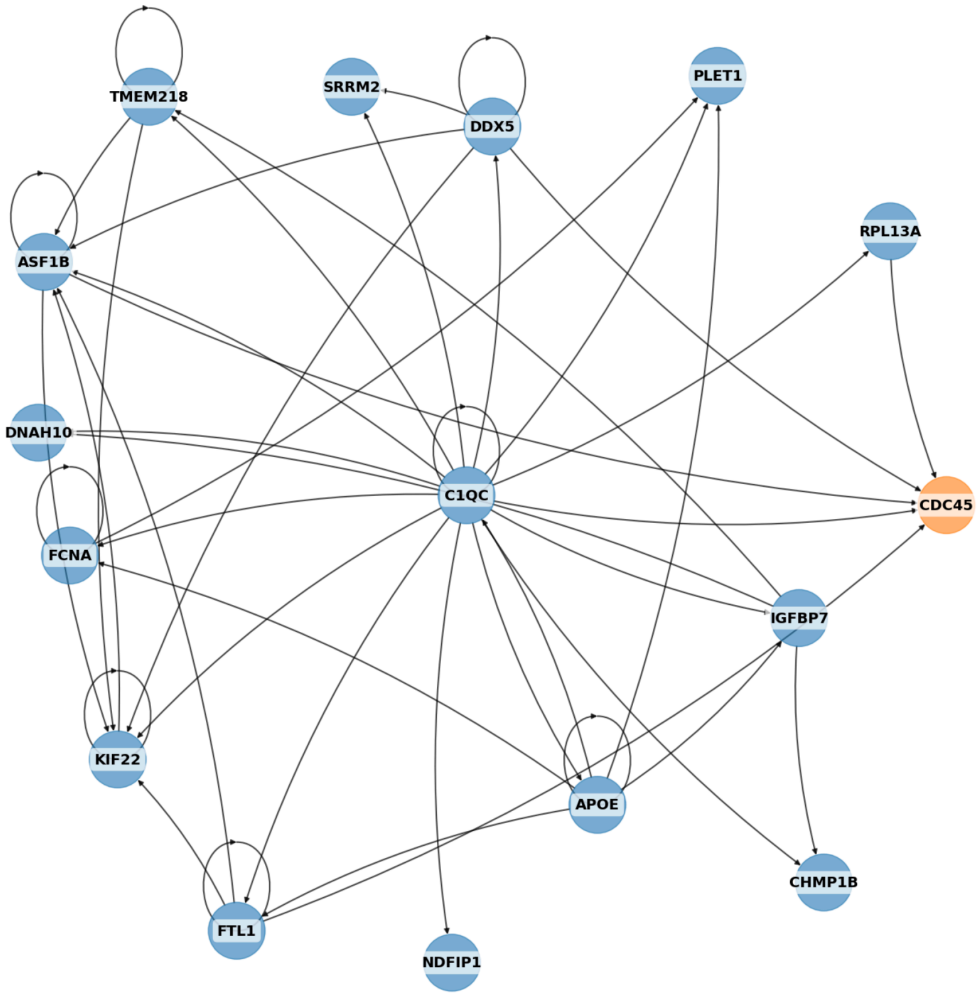
Venn diagram of the different ground truth gene networks showing overlap in the edges using gene symbols over the five ground truths used in our benchmark

FIG S31: whisker plot of AUPRC-ratio scores for scPRINT-1 and scPRINT-2



Whisker plot of AUPRC-ratio scores for the benchmark of scPRINT-1 vs scPRINT-2 using their respective GRN-extraction methods, showing that the scPRINT-2 extraction, while highlighting more relevant top connections, remains relatively similar to the scPRINT-1 version on the AUPRC-ratio scores on each of the six ground truth networks.

FIG S32: Additional scPRINT-2 generated gene network computed from CDC45



Subpart of the scPRINT-2 generated gene network using CDC45 as a seed gene and computed on 1024 mouse macrophages, showing how these networks can exhibit complex structures.