Metric Mirages in Cell Embeddings

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Although biological studies increasingly rely on embeddings of single cell profiles, the quality of these embeddings can be challenging to assess. Such evaluations are especially important for avoiding misleading biological interpretations, assessing the accuracy of integration methods, and establishing the zero-shot capabilities of foundational models. Here, we posit that current evaluation metrics can be highly misleading. We show this by training a three-layer perceptron, Islander , which outperforms all 11 leading embedding methods on a diverse set of cell atlases, but in fact distorts biological structures, limiting its utility for biological discovery. We then present a metric, scGraph, to flag such distortions. Our work should help learn more robust and reliable cell embeddings.

Embeddings of single cell profiles are now routinely employed as a research tool in biological investigation, to characterize cell types and states, their changes over time, and their distinction between conditions, including diseases, organs, or drug treatments (1, 2). With a dramatic growth in single cell data, including the Human Cell Atlas (3), multiple efforts have focused on universal embeddings for diverse single cell data (4–9). Given their broad utility, it is crucial to scrutinize the embeddings' quality to evaluate the performance of the underlying integration method (10) and zero-shot capabilities of the resulting foundation model (11, 12).

A critical aspect in deriving helpful cell embeddings is the correction of non-biological batch effects that stem from technical variations, such as sample handling and sequencing protocols. These variations can mask biological signals and lead to misleading interpretations. Integration methods thus aim to mitigate batch-specific discrepancies while preserving essential biological information. The effectiveness of these integrated cell embeddings is typically assessed through two lenses: how well the cells from various batches mix together; how closely cells of the same type group together.

Here, we identified an overlooked challenge in the evaluation metrics used to assess embeddings. To demonstrate the limitations of current gold standard metrics for cell profile embeddings (10), we first developed Islander (Fig. 1a), a model that scores best on established metrics, but generates biologically problematic embeddings. Islander is a three-layer perceptron, directly trained on cell type annotations with mixup augmentations (13). We tested Islander across a diverse set of 11 different human tissue cell atlases (brain (14), breast (15), eye (16), fetal gut (17), heart (18), fetal lung (19), pancreas (10), skin (20)), which cover different strengths of batch effects and diverse biological systems, overall comprising more than 3.5 million cells from 10 human organ systems. For each atlas, we trained a Islander model and then compared it with another 12 embedding baselines: three dimension reduction methods (PCA, UMAP, TSNE) (21), eight batch integration methods (Harmony (22), Scanorama (23), BBKNN (24), fastMNN (25), scVI (26), scANVI (27), scGen (28), scPoli (29)), and one foundation model (Geneformer (5)) (**Methods**). In addition, for each atlas, we compared to the performance of the original authors' integration, if available.

Across all datasets, Islander consistently outperformed all baseline strategies across all 12 metrics (10) (Fig. 1b,c, Extended Data Tables 3-13). This is largely due to the principles underlying the evaluation metrics (10), which focus on assessing the efficiency of cell embeddings in terms of the coherence of cell clustering structures with cell type labels and the blending of batches within clusters. When Islander explicitly aligns these cell embeddings with cell type annotations, it forms well-separated cell 'islands' (Fig. 1d, right), with each island comprising cells annotated as the same type. This

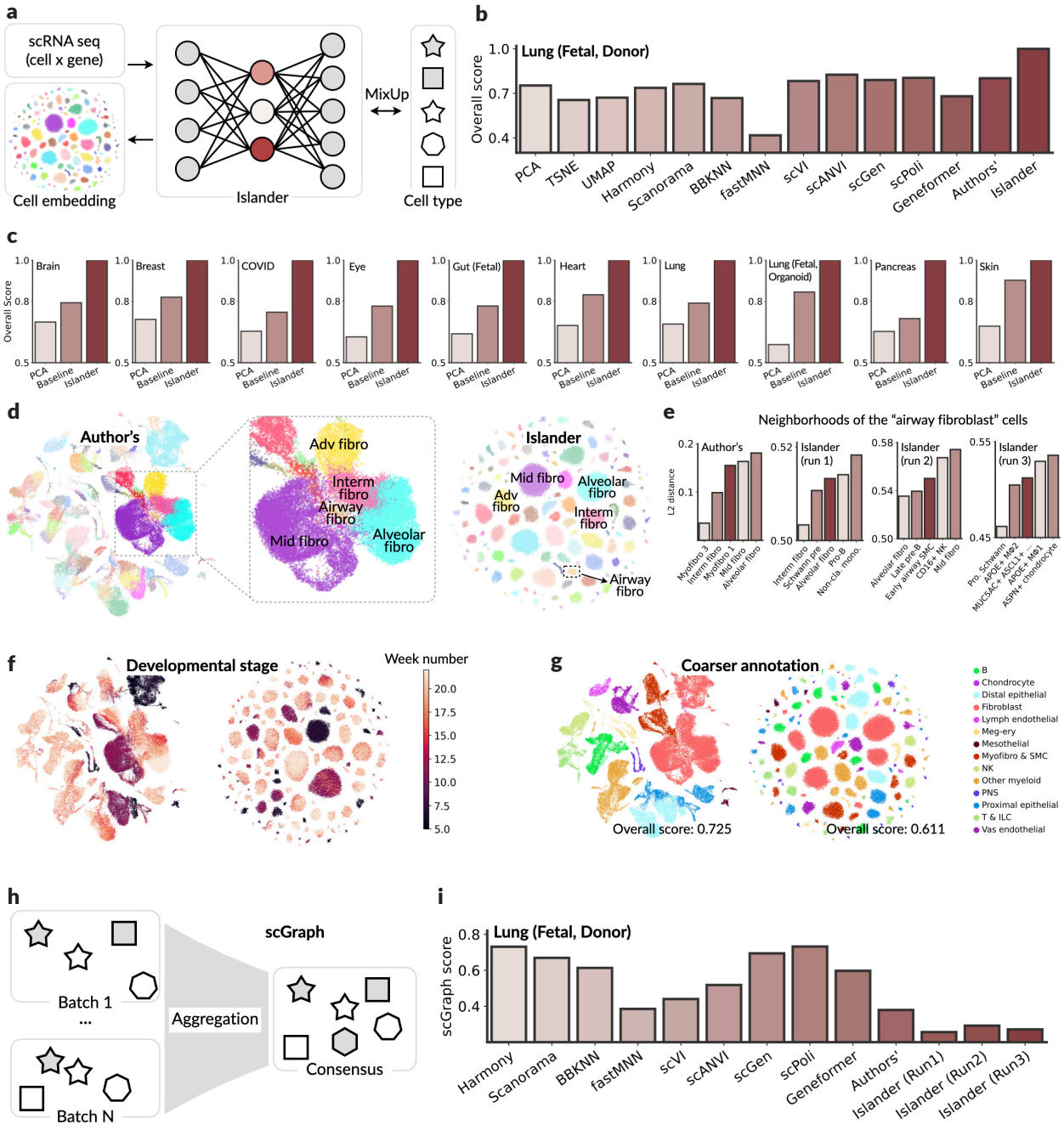

Figure 1: **Drifting Cell Islands highlight limitation of current metrics. a,** Islander overview. **b, c,** Evaluation of cell embeddings. Normalized overall score over 12 metrics (y axis, **Methods**) for each method (x axis) assessed on using the Fetal Lung Cell Atlas (b) or another 10 cell atlases (c). "Baseline": best baseline results (**Methods**). **d,** Fetal Lung Cell Atlas embedding space. Single cell profiles (dot; color-coded by cell type annotation) from the Fetal Lung Cell Atlas embedded by the author's integration method (left, inset zoom in middle) or Islander (right). Annotations: fibroblast cell subsets. **e,** "Airway fibroblast" cell neighborhood changes across Islander runs. Normalized Euclidean distance (y axis) between the centroids of airway fibroblasts and its five nearest neighbor clusters (x axis) in the 50-dimensional (of author's integration) and 16-dimensional (of Islander's) embedding space. **g,** Cell islands distort developmental stage structure and cell cell relationships. Cell embeddings as in (d), colored by developmental week (f, color bar) or coarser cell type annotations (g). **h, i.** scGraph, a metric using learned cell similarity graphs to evaluate cell embeddings. h. Method overview. i. scGraph score (y axis, higher is better) for each method (x axis) assessed using the Fetal Lung Cell Atlas.

alignment significantly boosts the biological variance conservation metrics, leading to top-tier overall performance (Extended Data Tables 3-13).

However, such structure is driven by (and complies well) with the most granular annotation level at the cost of ignoring any higher level relationships and distorting biological structures, potentially obstructing downstream analyses and future discoveries (and would thus not be an advisable for an actual integration method). In particular, when annotated cell subsets follow a continuum, as is the case for fibroblasts, Islander separates its constituent parts (Fig. 1d). In the developing human lung, the original analysis (19) identified multiple sub-types of fibroblasts, each distinguished by different marker genes and spatial locations. While the original embedding preserves a continuum between these fibroblasts (Fig. 1d, left), they are fully separated by Islander (Fig.1d, right). Similarly, the Islander embedding disrupted the developmental continuum, clearly observed in the original study (Fig. 1f, left), but obscured by Islander (Fig. 1f, right).

Moreover, the "cell islands" drifted in different ways across distinct runs, especially for smaller cell subsets. For example, in three separate runs with overall similar scores, the composition of the neighborhood of airway fibroblast cells varied substantially, involving as many as 14 distinct cell types within the five nearest neighbors (Fig. 1e, Extended Data Fig. 1, Extended Data Table 9). Thus, aside from cluster identity, the embedding may be largely arbitrary in all other relationships, and this arbitrariness would carry into downstream analysis or the biologist's interpretation.

Prompted by these limitations of the quality evaluation criteria, we reasoned that focusing solely on the most granular cell relationships in evaluation can pose a substantial limitations, whereas preserving relationships between broader cell types (coarser annotations) is an important additional criterion, and may also be more robust to noise. Indeed, when evaluating the same set of embeddings using broader cell type annotations provided by the authors, Islander now achieved an overall score of 0.523, inferior to PCA (0.557) or the top-performing scVI (26) (0.701) (Extended Data Table 14).

Because hierarchical Cell Ontology annotations are often unavailable (6), we next developed scGraph, as a new framework for quality assessment (**Methods**). For each set of cell embeddings, we define an affinity graph to elucidate the similarities between various cell types. scGraph then compares each affinity graph to a consensus graph, derived by aggregating individual graphs from different batches, based on raw reads or PCA loadings. This metrics efficiently highlights the inherent biological structures, emphasizing cell type similarities, while reducing the impact of technical variations across batches. Notably , scGraph does not require that any single batch have cells of all types (Fig. 1h), thus fitting the constraints of real datasets in the domain.

Evaluation by scGraph revealed varied performance across embeddings. Here, Islander had lower scores (Fig. 1i, Extended Data Table 15), while Harmony and scPoli excelled in capturing the complex relationships within functional cellular clusters. Indeed,Islander was the lowest scoring across seven of 11 atlases, underscoring scGraph's ability to detect the "drifting cell islands" artifact. Interestingly, scGraph favored higher-dimensional embeddings, like PCA over a PCA-derived UMAP. Note that scGraph's premise that profiles of functionally-similar cells would be proximate, may not always hold true.

In conclusion, we demonstrated the limitation of current quality metrics by introducing Islander , a three-layer perceptron, an integration approach that outperforms all major methods across diverse cell atlases, but at the cost of "island-like" distortions in the biological structures in cell embedding spaces. To address the inherent limitations of current evaluation metrics, we propose a new approach, scGraph, to helps assess how well the results of an integration approach preserve cell cell relationships at multiple granularities. Our work also highlights the importance of incorporating weaker supervision, as was recently illustrated in approaches where an encoder is regularized with

an additional reconstruction loss (6), or using large-scale unsupervised pre-training (*e.g.*, Universal Cell Embedding (UCE) (7)). These advancements underline the significance of methodological choices in computational biology and offer guiding principles for future research.

Methods

Datasets and pre-processing. Raw sequencing data were downloaded from the respective data providers as of October 1, 2023; details on the datasets and their sources are provided in Extended Data Table 1. The analysis encompasses 11 cell atlases, totaling 3,510,450 cell profiles. A uniform pre-processing protocol was applied across these datasets. Specifically, cell profiles with fewer than 1,000 reads or less than 500 detected genes were filtered out, and genes present in fewer than five cells were also excluded. Normalization was performed using Scanpy (30), scaling each cell's read counts to a total of 10,000 and subsequently applying a log1p transformation.

Baselines. Eleven baseline methods were used for comparison: three dimensionality reduction baselines: PCA, t-SNE (31), and UMAP (32); eight integration methods: Harmony (22), BBKNN (24), Scanorama (23), fastMNN (25), scVI (26), scANVI (27), scGen (28), and scPoli (29); and one pre-trained foundation model: Geneformer (5), for zero-shot embedding extraction. For dimensionality reduction methods, the log1p transformed raw counts from gene-by-cell matrices were provided as input. For each integration method, default hyperparameter settings recommended by the original authors were used. For Geneformer, the largest pre-trained model weights provided by the authors (33) were used. While scANVI, scGen, and scPoli utilize cell type as parts of their computational pipelines, other integration methods do not require such information. The top 1,000 genes were identified as highly variable gene sets.

Assessment metrics. Cell embeddings was assessed using metric as described in previous study (10), and implemented in "scib-metrics" (34). The following evaluation metrics were used (abbreviations noted are used in Extended Data Tables 3-13) . 'I-label' for isolated labels, 'L-NMI' for Leiden normalized mutual information, 'L-ARI' for Leiden Averaged Rand Index, 'K-NMI'/'K-ARI' for K-means NMI/ARI, 'S-label/batch' for silhouette label/batch, 'c/i-LISI' for batch-mixing (iLISI) and cell-type separation (cLISI), 'G-Con' for graph connectivity, and 'PCR' for principal component regression. Consistent with previous studies, selection of highly variable genes enhanced the performance of data integration methods.

Islander design. Islander is as a three-layer perceptron with two hidden layers of sizes 128 and 16, respectively, and an output layer matching the total number of cell types as annotated. The first hidden layer incorporates ReLU activation and batch normalization, while cell embeddings are derived from the second hidden layer. The output layer employs a softmax normalization function. In extended experiments, a decoder module was added mirroring the original MLP structure, with output dimensions of 16, 128, and the total number of genes, respectively. Each layer in this extended setup uses ReLU activation and batch normalization, except for the final linear layer.

Training setup. The model was trained in a manner aligned with scvi-tools (35), with mini-batches of 256 randomly sampled cells from all batches, along with their cell type annotations. Islander was trained using cross-entropy loss with mixup (13) augmentations (default setting). The Adam optimizer was used with an initial learning rate of 0.001, over 10 epochs, and a cosine annealing scheduler for learning rate decay. All cells were utilized for training to maximize overfitting.

Neighborhood calculation. Neighborhoods of each cell type were identified by the Euclidean distance between the centroids of cell profiles of each type in the embedding space. To mitigate the effects of batch variation and measurement noise, a trimming strategy was applied. The outermost 20% of data, treated as outliers, were excluded before calculating the centroid coordinates. This ensures a more accurate representation of cell type proximity by focusing on the most representative data points.

scGraph. scGraph quantifies the similarity between two graphs that each represent the closeness between cell types. In these graphs, each entry (x, y) signifies the proximity of cell type x to cell type y. The first graph is derived from the provided embeddings, while the second, serving as a reference, is based on raw counts or PCA loadings from each batch. For the reference, proximity graphs are initially computed from each batch using normalized Euclidean distances between centroids of the cell type profiles. These batch-specific graphs are then amalgamated into a single consensus graph through averaging. The similarity of neighborhoods for each cell type is assessed using Pearson's rank correlation. The final score, reflecting the overall similarity and ranging from -1 to 1 (with higher values indicating greater similarity), is the average across all cell types. The goal is to align the neighborhood graphs from the embeddings with the reference graph derived from the data, indicating that cells with similar profiles are appropriately clustered in the embedding space.

Code availability. The implementation code for the Islander , as well as the tutorial notebooks sufficient to reproduce the results presented in this manuscript, can be accessed via https://github.com/Genentech/Islander. For scIB evaluation pipelines, we use the implementations by Gayso et al from https://github.com/yoseflab/scib-metrics.

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Supplementary

1. Data availability

Atlas	# Gene	# Cell	# Class	# Batch	Reference
Brain	59,357	888,263	11	4	Paper (14), Data source (36)
Breast	33,234	703,512	39	126	Paper (15), Data source (37)
COVID	33,537	559,517	31	10	Paper (38), Data source (39)
Eye	36,484	51,645	11	8	Paper (16), Data source (40)
Gut (Fetal)	26,328	62,849	21	9	Paper (17), Data source (41)
Heart	33,234	486,134	27	14	Paper (18), Data source (42)
Lung	28,024	584,444	53	166	Paper (43), Data source (44)
Lung (Fetal, Donor)	26,354	71,752	144	29	Paper (19), Data source (45)
Lung (Fetal, Organoid)	24,653	70,495	28	37	Paper (19), Data source (45)
Pancreas	19,093	16,382	14	9	Paper (10), Data source (46)
Skin	30,933	15,457	13	5	Paper (20), Data source (47)

Extended Data Table 1: Statistics of cell atlases. "# Class" represents the total number of cell types.

2. Performance

The embedding dimensions of each method is reported in Extended Data Table 2.

Method	**PCA**	**TSNE**	**UMAP**	**Harmony**	**Scanorama**	**BBKNN**	**fastMNN**
# Dim	50	2	2	50	100	2	50
Method	**scVI**	**scANVI**	**scGen**	**scPoli**	**Geneformer**	**Islander**	
# Dim	30	30	50	10	512	16	

Extended Data Table 2: Embedding dimensions of each method.

The detailed performance of each cell atlas is shown in Extended Data Tables 3-13. The best aggregated scores are highlighted in **bold**, and the term "Author's" denotes the author's integrated embeddings.

		Bio conservation							Batch correction					Aggregate score		
Method	**HVG**	I-label	L-NMI	L-ARI	K-NMI	K-ARI	S-label	cLISI	S-batch	iLISI	KBET	G-Con	PCR	Batch	Bio	Total
PCA		0.803	0.776	0.473	0.745	0.439	0.759	1.000	0.882	0.005	0.079	0.966	0.000	0.386	0.714	0.583
PCA	✓	0.817	0.841	0.653	0.746	0.442	0.769	1.000	0.921	0.094	0.119	0.899	0.000	0.407	0.752	0.614
TSNE		0.873	0.466	0.046	0.593	0.258	0.527	1.000	0.759	0.005	0.117	0.978	0.000	0.372	0.538	0.471
TSNE	✓	0.927	0.478	0.052	0.618	0.274	0.540	1.000	0.773	0.121	0.155	0.988	0.000	0.407	0.555	0.496
UMAP		0.824	0.479	0.052	0.667	0.302	0.691	1.000	0.774	0.112	0.138	0.985	0.322	0.466	0.574	0.531
UMAP	✓	0.925	0.482	0.054	0.669	0.329	0.691	1.000	0.777	0.241	0.188	0.992	0.000	0.439	0.593	0.532
Harmony		0.786	0.828	0.619	0.749	0.437	0.768	1.000	0.914	0.142	0.240	0.957	0.895	0.630	0.741	0.697
Harmony	✓	0.800	0.830	0.597	0.746	0.443	0.770	1.000	0.943	0.249	0.327	0.881	0.702	0.620	0.741	0.693
Scanorama		0.781	0.782	0.489	0.745	0.439	0.749	1.000	0.902	0.112	0.103	0.925	0.318	0.472	0.712	0.616
Scanorama	✓	0.778	0.835	0.624	0.674	0.311	0.746	1.000	0.926	0.174	0.293	0.728	0.465	0.517	0.710	0.633
BBKNN		0.868	0.480	0.053	0.687	0.349	0.754	1.000	0.787	0.308	0.205	0.987	0.764	0.610	0.599	0.603
BBKNN	✓	0.880	0.482	0.055	0.689	0.354	0.785	1.000	0.779	0.366	0.287	0.992	0.848	0.654	0.606	0.626
fastMNN	✓	0.683	0.236	0.061	0.152	0.032	0.322	0.975	0.963	0.470	0.889	0.400	0.941	**0.733**	0.352	0.504
scVI		0.772	0.814	0.590	0.677	0.326	0.638	1.000	0.884	0.099	0.116	0.983	0.154	0.447	0.688	0.592
scVI	✓	0.738	0.941	0.960	0.724	0.449	0.606	1.000	0.932	0.230	0.227	0.950	0.000	0.468	0.774	0.652
scANVI		0.785	0.790	0.555	0.709	0.374	0.692	1.000	0.865	0.123	0.127	0.985	0.367	0.493	0.701	0.618
scANVI	✓	0.888	0.827	0.608	0.791	0.597	0.801	1.000	0.887	0.345	0.272	0.983	0.464	0.590	0.787	0.709
scGen	✓	0.878	0.841	0.670	0.817	0.634	0.818	1.000	0.900	0.251	0.387	0.968	0.589	0.619	0.808	0.733
scPoli	✓	0.983	0.718	0.353	0.814	0.547	0.926	1.000	0.850	0.398	0.687	0.988	0.678	0.720	0.763	0.746
Geneformer		0.543	0.768	0.576	0.583	0.352	0.545	1.000	0.905	0.259	0.240	0.851	0.000	0.451	0.624	0.555
Islander		0.940	0.993	0.995	0.999	1.000	0.950	1.000	0.906	0.353	0.499	0.988	0.879	0.725	**0.982**	**0.879**

Extended Data Table 3: Benchmarking cell embeddings, on Brain Cell Atlas

		Bio conservation							Batch correction					Aggregate score		
Method	**HVG**	I-label	L-NMI	L-ARI	K-NMI	K-ARI	S-label	cLISI	S-batch	iLISI	KBET	G-Con	PCR	Batch	Bio	Total
PCA		0.656	0.776	0.678	0.650	0.215	0.562	1.000	0.863	0.011	0.302	0.836	0.000	0.402	0.648	0.550
PCA	✓	0.568	0.797	0.701	0.691	0.261	0.582	1.000	0.879	0.021	0.377	0.759	0.000	0.407	0.657	0.557
TSNE		0.455	0.607	0.106	0.603	0.180	0.523	1.000	0.489	0.018	0.279	0.547	0.025	0.272	0.496	0.407
TSNE	✓	0.397	0.632	0.129	0.660	0.212	0.525	1.000	0.469	0.036	0.346	0.648	0.000	0.300	0.508	0.425
UMAP		0.644	0.632	0.144	0.652	0.215	0.596	1.000	0.520	0.050	0.326	0.601	0.203	0.340	0.555	0.469
UMAP	✓	0.459	0.644	0.150	0.685	0.243	0.612	1.000	0.498	0.065	0.372	0.652	0.120	0.341	0.542	0.462
Harmony		0.618	0.823	0.845	0.654	0.250	0.591	1.000	0.825	0.054	0.521	0.742	0.765	0.581	0.683	0.642
Harmony	✓	0.549	0.844	0.860	0.685	0.274	0.602	1.000	0.853	0.054	0.511	0.635	0.634	0.537	0.688	0.628
Scanorama		0.636	0.764	0.678	0.670	0.250	0.569	1.000	0.888	0.025	0.385	0.713	0.023	0.407	0.652	0.554
Scanorama	✓	0.562	0.783	0.697	0.704	0.333	0.594	1.000	0.835	0.030	0.437	0.578	0.128	0.402	0.668	0.561
BBKNN		0.399	0.639	0.141	0.683	0.234	0.651	1.000	0.489	0.072	0.381	0.616	0.412	0.394	0.536	0.479
BBKNN	✓	0.317	0.653	0.154	0.696	0.247	0.677	1.000	0.468	0.076	0.405	0.656	0.271	0.375	0.535	0.471
fastMNN	✓	0.503	0.050	0.008	0.043	0.005	0.439	0.926	0.780	0.046	0.044	0.055	0.330	0.251	0.282	0.270
scVI		0.618	0.828	0.739	0.697	0.255	0.565	1.000	0.837	0.028	0.387	0.892	0.306	0.490	0.672	0.599
scVI	✓	0.593	0.860	0.866	0.706	0.257	0.557	1.000	0.862	0.038	0.467	0.835	0.228	0.486	0.691	0.609
scANVI		0.600	0.841	0.771	0.720	0.265	0.597	1.000	0.810	0.033	0.417	0.890	0.405	0.511	0.685	0.615
scANVI	✓	0.570	0.864	0.868	0.737	0.309	0.681	1.000	0.756	0.049	0.492	0.848	0.364	0.502	0.718	0.632
scGen	✓	0.694	0.939	0.966	0.763	0.312	0.687	1.000	0.746	0.058	0.634	0.838	0.525	0.560	0.766	0.683
scPoli	✓	0.411	0.828	0.680	0.728	0.317	0.767	1.000	0.461	0.070	0.618	0.668	0.449	0.453	0.676	0.587
Author's		0.613	0.836	0.750	0.736	0.320	0.644	1.000	0.735	0.045	0.533	0.776	0.587	0.535	0.700	0.634
Geneformer		0.644	0.753	0.541	0.552	0.196	0.520	1.000	0.857	0.032	0.410	0.780	0.419	0.500	0.601	0.560
Islander		0.773	1.000	1.000	0.890	0.617	0.838	1.000	0.754	0.070	0.733	0.965	0.707	**0.646**	**0.874**	**0.783**

Extended Data Table 4: Benchmarking cell embeddings, on Breast Cell Atlas

		Bio conservation							Batch correction					Aggregate score		
Method	**HVG**	I-label	L-NMI	L-ARI	K-NMI	K-ARI	S-label	cLISI	S-batch	iLISI	KBET	G-Con	PCR	Batch	Bio	Total
PCA		0.495	0.698	0.669	0.563	0.226	0.520	0.996	0.921	0.122	0.215	0.751	0.000	0.402	0.595	0.518
PCA	✓	0.427	0.732	0.690	0.579	0.223	0.516	0.996	0.932	0.227	0.261	0.630	0.000	0.410	0.595	0.521
TSNE		0.232	0.522	0.114	0.544	0.187	0.435	0.994	0.724	0.149	0.125	0.608	0.213	0.364	0.433	0.405
TSNE	✓	0.185	0.520	0.112	0.562	0.204	0.442	0.994	0.737	0.292	0.090	0.560	0.152	0.366	0.431	0.405
UMAP		0.224	0.519	0.125	0.560	0.221	0.487	0.990	0.743	0.353	0.172	0.561	0.088	0.383	0.447	0.421
UMAP	✓	0.156	0.523	0.123	0.576	0.221	0.498	0.991	0.748	0.407	0.134	0.533	0.000	0.364	0.441	0.410
Harmony		0.485	0.697	0.674	0.563	0.218	0.522	0.996	0.936	0.319	0.411	0.711	0.609	0.597	0.593	0.595
Harmony	✓	0.420	0.725	0.668	0.578	0.220	0.517	0.995	0.938	0.320	0.457	0.590	0.514	0.564	0.589	0.579
Scanorama		0.443	0.706	0.669	0.565	0.226	0.517	0.995	0.932	0.270	0.257	0.659	0.345	0.493	0.589	0.550
Scanorama	✓	0.439	0.737	0.690	0.586	0.233	0.515	0.996	0.937	0.285	0.349	0.373	0.330	0.455	0.599	0.542
BBKNN		0.214	0.518	0.119	0.568	0.208	0.497	0.990	0.761	0.414	0.270	0.589	0.252	0.457	0.445	0.450
BBKNN	✓	0.128	0.533	0.132	0.581	0.216	0.503	0.992	0.758	0.442	0.188	0.546	0.052	0.397	0.441	0.423
fastMNN	✓	0.431	0.732	0.683	0.584	0.238	0.521	0.996	0.929	0.279	0.353	0.584	0.340	0.497	0.598	0.558
scVI		0.501	0.703	0.657	0.588	0.261	0.519	0.997	0.933	0.228	0.259	0.788	0.404	0.522	0.604	0.571
scVI	✓	0.544	0.718	0.660	0.541	0.205	0.502	0.991	0.933	0.307	0.437	0.685	0.466	0.565	0.595	0.583
scANVI		0.439	0.749	0.719	0.622	0.267	0.544	0.999	0.920	0.256	0.272	0.823	0.307	0.516	0.620	0.578
scANVI	✓	0.559	0.762	0.739	0.632	0.269	0.554	0.998	0.906	0.304	0.384	0.774	0.278	0.529	0.645	0.598
scGen	✓	0.453	0.779	0.768	0.638	0.294	0.553	0.999	0.937	0.327	0.511	0.759	0.292	0.565	0.641	0.611
scPoli		0.231	0.770	0.741	0.666	0.352	0.584	0.998	0.851	0.364	0.494	0.826	0.303	0.568	0.620	0.599
scPoli	✓	0.411	0.715	0.567	0.662	0.357	0.572	0.997	0.801	0.418	0.583	0.769	0.242	0.562	0.612	0.592
Islander		0.693	0.999	1.000	0.863	0.603	0.713	1.000	0.934	0.420	0.653	0.967	0.693	**0.733**	**0.839**	**0.797**

Extended Data Table 5: Benchmarking cell embeddings, on COVID Cell Atlas

		Bio conservation							Batch correction					Aggregate score		
Method	**HVG**	I-label	L-NMI	L-ARI	K-NMI	K-ARI	S-label	cLISI	S-batch	iLISI	kBET	G-Con	PCR	Batch	Bio	Total
PCA		0.629	0.677	0.333	0.691	0.414	0.687	1.000	0.905	0.108	0.090	0.751	0.000	0.371	0.633	0.528
PCA	✓	0.637	0.742	0.550	0.701	0.415	0.705	1.000	0.903	0.175	0.207	0.662	0.000	0.390	0.678	0.563
TSNE		0.553	0.529	0.086	0.481	0.177	0.521	1.000	0.770	0.105	0.015	0.357	0.000	0.250	0.478	0.387
TSNE	✓	0.563	0.541	0.088	0.512	0.203	0.551	1.000	0.777	0.164	0.031	0.538	0.000	0.302	0.494	0.417
UMAP		0.569	0.538	0.087	0.583	0.309	0.594	1.000	0.785	0.121	0.031	0.572	0.000	0.302	0.526	0.436
UMAP	✓	0.587	0.550	0.095	0.625	0.389	0.707	1.000	0.773	0.180	0.097	0.603	0.000	0.331	0.565	0.471
Harmony		0.644	0.769	0.649	0.701	0.393	0.721	1.000	0.900	0.360	0.227	0.802	0.855	0.629	0.697	0.670
Harmony	✓	0.641	0.855	0.967	0.773	0.546	0.718	1.000	0.900	0.389	0.273	0.643	0.626	0.566	0.786	0.698
Scanorama		0.622	0.748	0.548	0.754	0.551	0.678	1.000	0.903	0.236	0.187	0.730	0.621	0.535	0.700	0.634
Scanorama	✓	0.639	0.836	0.964	0.675	0.319	0.695	1.000	0.907	0.320	0.341	0.504	0.459	0.506	0.733	0.642
BBKNN		0.617	0.545	0.094	0.544	0.238	0.706	1.000	0.762	0.275	0.079	0.628	0.571	0.463	0.535	0.506
BBKNN	✓	0.594	0.541	0.093	0.643	0.378	0.788	1.000	0.734	0.293	0.127	0.600	0.175	0.386	0.577	0.500
fastMNN	✓	0.483	0.007	0.009	0.004	0.020	0.492	0.844	0.888	0.317	0.129	0.050	0.586	0.394	0.266	0.317
scVI		0.560	0.850	0.968	0.432	0.171	0.565	1.000	0.899	0.403	0.252	0.916	0.861	0.666	0.650	0.656
scVI	✓	0.620	0.845	0.965	0.619	0.237	0.526	1.000	0.916	0.431	0.307	0.786	0.594	0.607	0.688	0.655
scANVI		0.597	0.862	0.972	0.729	0.528	0.624	1.000	0.890	0.400	0.237	0.918	0.866	0.662	0.759	0.720
scANVI	✓	0.685	0.775	0.591	0.776	0.433	0.650	1.000	0.886	0.459	0.382	0.630	0.725	0.616	0.701	0.667
scGen	✓	0.689	0.862	0.968	0.777	0.547	0.764	1.000	0.893	0.455	0.363	0.805	0.655	0.634	0.801	0.734
scPoli		0.716	0.924	0.980	0.975	0.983	0.889	1.000	0.849	0.370	0.365	0.930	0.849	0.672	0.924	0.823
scPoli	✓	0.872	0.819	0.632	0.852	0.651	0.915	1.000	0.767	0.360	0.525	0.914	0.570	0.627	0.820	0.743
Author's		0.649	0.582	0.102	0.710	0.400	0.808	1.000	0.791	0.503	0.386	0.814	0.740	0.647	0.607	0.623
Geneformer		0.513	0.617	0.439	0.443	0.218	0.559	1.000	0.928	0.316	0.211	0.789	0.000	0.449	0.541	0.504
Islander		0.906	1.000	1.000	0.982	0.996	0.920	1.000	0.922	0.492	0.707	0.979	0.849	**0.790**	**0.972**	**0.899**

Extended Data Table 6: Benchmarking cell embeddings, on Eye Cell Atlas

		Bio conservation							Batch correction					Aggregate score		
Method	**HVG**	I-label	L-NMI	L-ARI	K-NMI	K-ARI	S-label	cLISI	S-batch	iLISI	kBET	G-Con	PCR	Batch	Bio	Total
PCA		0.593	0.614	0.213	0.612	0.292	0.534	1.000	0.893	0.009	0.111	0.911	0.000	0.385	0.551	0.484
PCA	✓	0.600	0.644	0.290	0.654	0.323	0.539	1.000	0.908	0.015	0.098	0.883	0.000	0.381	0.578	0.499
TSNE		0.723	0.561	0.096	0.576	0.226	0.423	1.000	0.693	0.000	0.108	0.463	0.000	0.253	0.515	0.410
TSNE	✓	0.699	0.577	0.118	0.596	0.249	0.453	1.000	0.695	0.003	0.069	0.532	0.459	0.352	0.527	0.457
UMAP		0.727	0.584	0.163	0.564	0.223	0.394	0.999	0.686	0.007	0.153	0.661	0.000	0.301	0.522	0.434
UMAP	✓	0.690	0.606	0.180	0.570	0.238	0.443	0.999	0.681	0.020	0.086	0.683	0.000	0.294	0.532	0.437
Harmony		0.460	0.687	0.412	0.585	0.299	0.550	0.998	0.902	0.282	0.551	0.890	0.746	**0.674**	0.570	0.612
Harmony	✓	0.582	0.718	0.509	0.630	0.330	0.535	0.998	0.925	0.222	0.429	0.838	0.561	0.595	0.615	0.607
Scanorama		0.488	0.694	0.330	0.619	0.322	0.538	1.000	0.918	0.118	0.249	0.897	0.000	0.436	0.570	0.517
Scanorama	✓	0.574	0.701	0.371	0.671	0.354	0.539	1.000	0.925	0.157	0.269	0.765	0.333	0.490	0.601	0.557
BBKNN		0.411	0.662	0.255	0.650	0.305	0.504	1.000	0.720	0.281	0.441	0.795	0.292	0.506	0.541	0.527
BBKNN	✓	0.629	0.645	0.227	0.648	0.283	0.513	0.999	0.760	0.203	0.248	0.763	0.000	0.395	0.563	0.496
fastMNN	✓	0.605	0.359	0.132	0.347	0.188	0.467	0.963	0.892	0.107	0.187	0.592	0.343	0.424	0.437	0.432
scVI		0.541	0.713	0.422	0.594	0.255	0.531	0.999	0.915	0.207	0.338	0.937	0.667	0.613	0.579	0.593
scVI	✓	0.587	0.738	0.510	0.668	0.352	0.522	0.998	0.920	0.209	0.345	0.923	0.787	0.637	0.625	0.630
scANVI		0.528	0.787	0.509	0.687	0.352	0.558	1.000	0.906	0.209	0.339	0.933	0.526	0.583	0.632	0.612
scANVI	✓	0.635	0.791	0.573	0.722	0.392	0.590	1.000	0.885	0.213	0.390	0.927	0.611	0.605	0.672	0.645
scGen	✓	0.660	0.901	0.779	0.753	0.424	0.620	1.000	0.862	0.228	0.477	0.959	0.399	0.585	0.734	0.674
scPoli		0.464	0.815	0.603	0.742	0.386	0.639	1.000	0.869	0.231	0.489	0.959	0.002	0.510	0.664	0.602
scPoli	✓	0.760	0.759	0.526	0.739	0.416	0.596	1.000	0.835	0.271	0.600	0.921	0.497	0.625	0.685	0.661
Author's		0.473	0.718	0.322	0.638	0.358	0.561	1.000	0.888	0.071	0.260	0.920	0.000	0.428	0.581	0.520
Geneformer		0.518	0.534	0.280	0.334	0.128	0.477	0.986	0.881	0.133	0.349	0.719	0.362	0.489	0.465	0.475
Islander		0.859	1.000	1.000	0.966	0.946	0.833	1.000	0.922	0.313	0.565	0.959	0.303	0.612	**0.944**	**0.811**

Extended Data Table 7: Benchmarking cell embeddings, on Fetal Gut Atlas

		Bio conservation							Batch correction					Aggregate score		
Method	**HVG**	I-label	L-NMI	L-ARI	K-NMI	K-ARI	S-label	cLISI	S-batch	iLISI	KBET	G-Con	PCR	Batch	Bio	Total
PCA		0.571	0.611	0.417	0.598	0.360	0.532	0.998	0.841	0.001	0.048	0.702	0.000	0.319	0.584	0.478
PCA	✓	0.551	0.687	0.738	0.616	0.422	0.539	0.996	0.856	0.034	0.077	0.694	0.000	0.332	0.650	0.523
TSNE		0.700	0.532	0.100	0.507	0.197	0.420	0.998	0.610	0.001	0.034	0.396	0.000	0.208	0.493	0.379
TSNE	✓	0.712	0.542	0.110	0.539	0.215	0.443	0.997	0.631	0.034	0.048	0.443	0.078	0.247	0.508	0.404
UMAP		0.755	0.524	0.117	0.544	0.244	0.451	0.994	0.620	0.005	0.042	0.453	0.000	0.224	0.518	0.401
UMAP	✓	0.581	0.537	0.126	0.570	0.268	0.544	0.994	0.627	0.089	0.064	0.494	0.274	0.309	0.517	0.434
Harmony		0.584	0.797	0.782	0.729	0.764	0.647	0.996	0.891	0.255	0.333	0.817	0.000	0.459	0.757	0.638
Harmony	✓	0.458	0.725	0.763	0.617	0.412	0.566	0.995	0.904	0.143	0.189	0.691	0.464	0.478	0.648	0.580
Scanorama		0.578	0.651	0.475	0.608	0.349	0.530	0.999	0.888	0.041	0.085	0.682	0.000	0.339	0.598	0.495
Scanorama	✓	0.598	0.697	0.761	0.606	0.368	0.546	0.995	0.903	0.084	0.141	0.553	0.364	0.409	0.653	0.555
BBKNN		0.739	0.588	0.151	0.648	0.286	0.631	0.994	0.774	0.377	0.464	0.699	0.000	0.463	0.577	0.531
BBKNN	✓	0.680	0.557	0.137	0.599	0.261	0.570	0.994	0.694	0.184	0.127	0.556	0.273	0.367	0.543	0.472
fastMNN	✓	0.456	0.066	0.011	0.036	0.004	0.465	0.892	0.863	0.071	0.050	0.050	0.416	0.290	0.276	0.281
scVI		0.705	0.728	0.759	0.620	0.385	0.561	0.997	0.904	0.060	0.121	0.717	0.000	0.360	0.680	0.552
scVI	✓	0.638	0.742	0.780	0.602	0.257	0.532	0.995	0.935	0.129	0.172	0.743	0.743	0.545	0.649	0.607
scANVI		0.716	0.754	0.785	0.682	0.494	0.589	0.998	0.892	0.086	0.151	0.693	0.000	0.364	0.717	0.576
scANVI	✓	0.693	0.741	0.783	0.674	0.459	0.642	0.998	0.899	0.163	0.203	0.721	0.583	0.514	0.713	0.633
scGen	✓	0.644	0.842	0.858	0.734	0.527	0.634	1.000	0.837	0.190	0.252	0.913	0.571	0.553	0.748	0.670
scPoli		0.847	0.754	0.781	0.737	0.602	0.693	0.998	0.824	0.127	0.239	0.798	0.000	0.398	0.773	0.623
scPoli	✓	0.880	0.752	0.641	0.704	0.436	0.680	0.997	0.777	0.159	0.317	0.751	0.699	0.541	0.727	0.653
Author's		0.630	0.805	0.795	0.740	0.781	0.648	0.996	0.873	0.239	0.282	0.825	0.000	0.444	0.771	0.640
Geneformer		0.503	0.594	0.547	0.463	0.255	0.476	0.993	0.906	0.149	0.097	0.617	0.094	0.373	0.547	0.477
Islander		0.790	0.991	0.992	0.885	0.658	0.751	1.000	0.927	0.303	0.529	0.969	0.353	**0.616**	**0.867**	**0.767**

Extended Data Table 8: Benchmarking cell embeddings, on Heart Cell Atlas

		Bio conservation							Batch correction					Aggregate score		
Method	**HVG**	I-label	L-NMI	L-ARI	K-NMI	K-ARI	S-label	cLISI	S-batch	iLISI	kBET	G-Con	PCR	Batch	Bio	Total
PCA		0.516	0.653	0.288	0.643	0.313	0.537	1.000	0.867	0.002	0.317	0.852	0.000	0.407	0.564	0.502
PCA	✓	0.542	0.693	0.347	0.690	0.352	0.545	1.000	0.889	0.003	0.322	0.867	0.000	0.416	0.596	0.524
TSNE		0.569	0.627	0.146	0.584	0.214	0.399	1.000	0.526	0.002	0.271	0.448	0.000	0.249	0.505	0.403
TSNE	✓	0.575	0.648	0.173	0.611	0.225	0.443	1.000	0.519	0.004	0.275	0.556	0.000	0.271	0.525	0.423
UMAP		0.465	0.630	0.201	0.603	0.222	0.400	0.999	0.583	0.007	0.316	0.562	0.000	0.293	0.503	0.419
UMAP	✓	0.437	0.667	0.225	0.654	0.275	0.455	0.999	0.565	0.009	0.338	0.645	0.000	0.311	0.531	0.443
Harmony		0.465	0.609	0.385	0.464	0.199	0.489	0.996	0.805	0.023	0.561	0.765	0.675	0.566	0.515	0.536
Harmony	✓	0.478	0.608	0.417	0.509	0.254	0.499	0.996	0.834	0.024	0.573	0.673	0.625	0.546	0.537	0.541
Scanorama		0.599	0.663	0.271	0.634	0.336	0.527	1.000	0.900	0.006	0.392	0.524	0.000	0.364	0.576	0.491
BBKNN		0.388	0.667	0.255	0.666	0.272	0.505	0.998	0.459	0.023	0.402	0.622	0.000	0.301	0.536	0.442
BBKNN	✓	0.399	0.702	0.285	0.702	0.330	0.554	0.999	0.457	0.027	0.514	0.728	0.000	0.345	0.567	0.479
fastMNN	✓	0.502	0.001	0.000	0.001	0.000	0.490	0.877	0.593	0.062	0.192	0.003	0.999	0.370	0.267	0.308
scVI		0.602	0.799	0.644	0.680	0.339	0.561	1.000	0.835	0.008	0.415	0.931	0.383	0.514	0.661	0.602
scVI	✓	0.590	0.797	0.628	0.679	0.381	0.550	1.000	0.861	0.008	0.389	0.931	0.375	0.513	0.661	0.602
scANVI		0.547	0.843	0.742	0.769	0.516	0.595	1.000	0.813	0.012	0.443	0.937	0.371	0.515	0.716	0.636
scANVI	✓	0.530	0.845	0.770	0.763	0.487	0.620	1.000	0.778	0.017	0.508	0.913	0.301	0.503	0.716	0.631
scGen	✓	0.573	0.967	0.968	0.842	0.588	0.673	1.000	0.717	0.029	0.671	0.894	0.183	0.499	0.802	0.680
scPoli		0.628	0.835	0.760	0.796	0.609	0.662	1.000	0.597	0.025	0.658	0.909	0.184	0.475	0.756	0.643
scPoli	✓	0.655	0.830	0.709	0.799	0.633	0.662	1.000	0.597	0.025	0.658	0.909	0.150	0.468	0.755	0.640
Author's	✓	0.582	0.855	0.746	0.715	0.401	0.553	1.000	0.865	0.006	0.370	0.950	0.354	0.509	0.693	0.619
Geneformer		0.559	0.651	0.294	0.588	0.258	0.500	0.999	0.857	0.006	0.407	0.788	0.199	0.451	0.550	0.510
Islander		0.842	0.999	0.999	0.896	0.659	0.793	1.000	0.774	0.034	0.724	0.953	0.398	**0.577**	**0.884**	**0.761**

Extended Data Table 9: Benchmarking cell embeddings, on Lung Cell Atlas

		Bio conservation							Batch correction					Aggregate score		
Method	**HVG**	I-label	L-NMI	L-ARI	K-NMI	K-ARI	S-label	cLISI	S-batch	iLISI	KBET	G-Con	PCR	Batch	Bio	Total
PCA		0.571	0.809	0.581	0.723	0.237	0.532	1.000	0.834	0.043	0.620	0.821	0.000	0.464	0.636	0.567
PCA	✓	0.581	0.799	0.619	0.716	0.191	0.535	0.999	0.868	0.059	0.640	0.797	0.000	0.473	0.634	0.570
TSNE		0.583	0.762	0.318	0.720	0.160	0.499	1.000	0.542	0.042	0.480	0.663	0.000	0.345	0.577	0.484
TSNE	✓	0.585	0.767	0.350	0.716	0.157	0.504	1.000	0.568	0.059	0.509	0.693	0.000	0.366	0.582	0.496
UMAP		0.580	0.765	0.387	0.713	0.162	0.489	0.999	0.576	0.068	0.572	0.708	0.000	0.385	0.585	0.505
UMAP	✓	0.548	0.771	0.404	0.713	0.162	0.524	0.999	0.586	0.085	0.560	0.707	0.000	0.388	0.589	0.508
Harmony		0.542	0.706	0.324	0.640	0.188	0.482	0.996	0.823	0.142	0.808	0.764	0.281	0.564	0.554	0.558
Harmony	✓	0.566	0.652	0.300	0.577	0.098	0.483	0.995	0.859	0.131	0.672	0.613	0.329	0.521	0.524	0.523
Scanorama		0.491	0.814	0.675	0.708	0.221	0.529	1.000	0.852	0.083	0.728	0.805	0.000	0.494	0.634	0.578
Scanorama	✓	0.565	0.778	0.657	0.719	0.195	0.528	0.999	0.896	0.070	0.697	0.646	0.000	0.462	0.635	0.565
BBKNN		0.391	0.740	0.340	0.692	0.148	0.527	0.998	0.578	0.155	0.771	0.715	0.000	0.444	0.548	0.506
BBKNN	✓	0.541	0.746	0.382	0.689	0.147	0.509	0.998	0.598	0.124	0.625	0.651	0.000	0.400	0.573	0.504
fastMNN	✓	0.397	0.181	0.036	0.180	0.015	0.375	0.968	0.781	0.157	0.095	0.048	0.557	0.328	0.307	0.316
scVI		0.549	0.706	0.351	0.629	0.125	0.513	0.996	0.826	0.133	0.835	0.843	0.399	0.607	0.553	0.574
scVI	✓	0.579	0.709	0.335	0.640	0.124	0.505	0.996	0.855	0.129	0.774	0.849	0.646	**0.650**	0.555	0.593
scANVI		0.525	0.773	0.544	0.671	0.169	0.526	0.998	0.813	0.123	0.839	0.846	0.143	0.553	0.601	0.582
scANVI	✓	0.574	0.826	0.706	0.732	0.215	0.552	1.000	0.820	0.112	0.799	0.854	0.300	0.577	0.658	0.625
scGen	✓	0.464	0.851	0.699	0.726	0.437	0.553	1.000	0.736	0.134	0.694	0.838	0.000	0.480	0.676	0.598
scPoli		0.453	0.858	0.647	0.787	0.285	0.618	1.000	0.735	0.137	0.861	0.900	0.000	0.526	0.664	0.609
scPoli	✓	0.616	0.791	0.530	0.742	0.311	0.545	0.998	0.681	0.141	0.789	0.773	0.274	0.532	0.648	0.601
Author's		0.575	0.844	0.561	0.774	0.347	0.567	1.000	0.834	0.070	0.780	0.897	0.000	0.516	0.667	0.607
Geneformer		0.492	0.640	0.304	0.520	0.107	0.475	0.996	0.829	0.114	0.672	0.624	0.410	0.530	0.505	0.515
Islander (Run1)		0.818	0.999	1.000	0.901	0.449	0.793	1.000	0.854	0.124	0.889	0.972	0.240	0.616	**0.851**	**0.757**
Islander (Run2)		0.824	0.999	1.000	0.891	0.406	0.793	1.000	0.853	0.123	0.883	0.970	0.217	0.609	0.845	0.751
Islander (Run3)		0.817	0.999	1.000	0.894	0.440	0.794	1.000	0.854	0.123	0.888	0.970	0.249	0.617	0.849	0.756

Extended Data Table 10: Benchmarking cell embeddings, on (Lung, Fetal, Donor) Cell Atlas

		Bio conservation							Batch correction					Aggregate score		
Method	**HVG**	I-label	L-NMI	L-ARI	K-NMI	K-ARI	S-label	cLISI	S-batch	iLISI	kBET	G-Con	PCR	Batch	Bio	Total
PCA		0.466	0.441	0.264	0.399	0.126	0.512	0.992	0.791	0.000	0.486	0.728	0.000	0.401	0.457	0.435
PCA	✓	0.439	0.451	0.235	0.402	0.125	0.506	0.992	0.821	0.000	0.521	0.738	0.000	0.416	0.450	0.436
TSNE		0.281	0.378	0.061	0.381	0.093	0.430	0.991	0.522	0.000	0.341	0.513	0.000	0.275	0.374	0.334
TSNE	✓	0.313	0.378	0.068	0.391	0.095	0.420	0.990	0.564	0.000	0.332	0.558	0.000	0.291	0.379	0.344
UMAP		0.294	0.396	0.105	0.396	0.102	0.429	0.985	0.546	0.000	0.402	0.587	0.000	0.307	0.387	0.355
UMAP	✓	0.382	0.393	0.097	0.398	0.111	0.468	0.986	0.578	0.000	0.491	0.647	0.000	0.343	0.405	0.380
Harmony		0.546	0.324	0.177	0.267	0.084	0.465	0.982	0.793	0.034	0.607	0.466	0.276	0.435	0.406	0.418
Harmony	✓	0.484	0.336	0.148	0.215	0.045	0.428	0.982	0.870	0.017	0.621	0.608	0.712	0.565	0.377	0.452
Scanorama		0.532	0.441	0.298	0.359	0.105	0.484	0.991	0.837	0.000	0.477	0.698	0.000	0.403	0.459	0.436
Scanorama	✓	0.442	0.430	0.249	0.386	0.119	0.488	0.991	0.824	0.000	0.548	0.595	0.081	0.410	0.444	0.430
BBKNN		0.434	0.374	0.094	0.363	0.091	0.438	0.981	0.593	0.036	0.462	0.632	0.000	0.345	0.396	0.376
BBKNN	✓	0.396	0.346	0.079	0.357	0.090	0.367	0.980	0.626	0.017	0.323	0.336	0.000	0.260	0.374	0.328
fastMNN	✓	0.440	0.254	0.111	0.161	0.035	0.444	0.955	0.846	0.006	0.106	0.131	0.463	0.310	0.343	0.330
scVI		0.485	0.344	0.251	0.164	0.032	0.457	0.977	0.870	0.024	0.581	0.706	0.821	0.600	0.387	0.473
scVI	✓	0.517	0.283	0.136	0.183	0.040	0.452	0.970	0.880	0.031	0.557	0.722	0.934	**0.625**	0.369	0.471
scANVI		0.473	0.471	0.360	0.320	0.095	0.458	0.992	0.854	0.018	0.576	0.708	0.622	0.555	0.453	0.494
scANVI	✓	0.508	0.455	0.347	0.366	0.111	0.453	0.990	0.832	0.013	0.588	0.751	0.737	0.584	0.462	0.511
scGen	✓	0.572	0.908	0.890	0.649	0.243	0.642	1.000	0.714	0.019	0.663	0.895	0.364	0.531	0.701	0.633
scPoli		0.631	0.477	0.301	0.415	0.115	0.485	0.993	0.734	0.010	0.581	0.845	0.000	0.434	0.488	0.466
scPoli	✓	0.479	0.484	0.298	0.427	0.149	0.511	0.989	0.666	0.010	0.610	0.759	0.113	0.432	0.477	0.459
Author's		0.647	0.480	0.272	0.442	0.192	0.555	0.995	0.796	0.002	0.527	0.769	0.000	0.419	0.512	0.475
Geneformer		0.436	0.337	0.208	0.242	0.074	0.477	0.980	0.828	0.012	0.466	0.457	0.598	0.472	0.394	0.425
Islander		0.785	0.955	0.890	0.736	0.313	0.752	1.000	0.844	0.027	0.687	0.978	0.000	0.507	**0.776**	**0.668**

Extended Data Table 11: Benchmarking cell embeddings, on (Lung, Fetal, Organoid) Cell Atlas

		Bio conservation							Batch correction					Aggregate score		
Method	**HVG**	I-label	L-NMI	L-ARI	K-NMI	K-ARI	S-label	cLISI	S-batch	iLISI	kBET	G-Con	PCR	Batch	Bio	Total
PCA		0.496	0.594	0.214	0.459	0.313	0.499	1.000	0.770	0.000	0.057	0.553	0.000	0.276	0.511	0.417
PCA	✓	0.634	0.685	0.421	0.620	0.408	0.572	1.000	0.849	0.002	0.206	0.656	0.000	0.343	0.620	0.509
TSNE		0.363	0.573	0.161	0.438	0.203	0.417	1.000	0.482	0.000	0.030	0.424	0.000	0.187	0.451	0.345
TSNE	✓	0.954	0.634	0.236	0.589	0.340	0.451	1.000	0.546	0.000	0.060	0.550	0.000	0.231	0.601	0.453
UMAP		0.372	0.580	0.211	0.387	0.167	0.386	1.000	0.511	0.000	0.036	0.555	0.000	0.220	0.443	0.354
UMAP	✓	0.932	0.630	0.240	0.589	0.343	0.496	1.000	0.570	0.000	0.114	0.587	0.000	0.254	0.604	0.464
Harmony		0.553	0.869	0.908	0.623	0.426	0.570	1.000	0.885	0.198	0.421	0.853	0.918	0.655	0.707	0.686
Harmony	✓	0.586	0.904	0.945	0.792	0.647	0.619	1.000	0.868	0.220	0.538	0.765	0.790	0.636	0.785	0.725
Scanorama		0.555	0.754	0.564	0.614	0.392	0.556	1.000	0.905	0.037	0.278	0.863	0.674	0.551	0.633	0.601
Scanorama	✓	0.609	0.878	0.916	0.762	0.598	0.597	1.000	0.934	0.144	0.384	0.694	0.673	0.566	0.766	0.686
BBKNN		0.473	0.623	0.271	0.626	0.367	0.547	1.000	0.660	0.023	0.190	0.676	0.671	0.444	0.558	0.512
BBKNN	✓	0.923	0.681	0.319	0.723	0.461	0.695	1.000	0.669	0.062	0.217	0.850	0.628	0.485	0.686	0.606
fastMNN	✓	0.429	0.099	0.023	0.035	0.015	0.475	0.841	0.792	0.190	0.004	0.150	0.853	0.398	0.274	0.323
scVI		0.700	0.880	0.916	0.635	0.442	0.558	0.999	0.851	0.209	0.424	0.913	0.964	0.672	0.733	0.709
scVI	✓	0.664	0.920	0.953	0.743	0.451	0.573	1.000	0.881	0.277	0.527	0.910	0.856	0.690	0.757	0.731
scANVI		0.720	0.917	0.949	0.732	0.712	0.572	1.000	0.844	0.207	0.411	0.923	0.955	0.668	0.800	0.747
scANVI	✓	0.664	0.920	0.953	0.743	0.451	0.573	1.000	0.881	0.277	0.527	0.910	0.856	0.690	0.757	0.731
scGen	✓	0.813	0.960	0.981	0.833	0.638	0.700	1.000	0.777	0.286	0.637	0.938	0.754	0.678	0.847	0.779
scPoli		0.786	0.919	0.949	0.783	0.541	0.701	1.000	0.822	0.192	0.485	0.931	0.871	0.660	0.811	0.751
scPoli	✓	0.682	0.912	0.945	0.829	0.733	0.760	1.000	0.758	0.344	0.677	0.939	0.757	0.695	0.837	0.780
Islander		0.893	0.999	0.999	0.980	0.984	0.914	1.000	0.873	0.254	0.558	0.977	0.897	**0.712**	**0.967**	**0.865**

Extended Data Table 12: Benchmarking cell embeddings, on Pancreas Cell Atlas

		Bio conservation							Batch correction					Aggregate score		
Method	**HVG**	I-label	L-NMI	L-ARI	K-NMI	K-ARI	S-label	cLISI	S-batch	iLISI	kBET	G-Con	PCR	Batch	Bio	Total
PCA		0.580	0.693	0.555	0.699	0.548	0.581	0.999	0.868	0.022	0.029	0.874	0.000	0.359	0.665	0.542
PCA	✓	0.578	0.744	0.585	0.703	0.591	0.583	0.999	0.875	0.052	0.021	0.814	0.000	0.352	0.683	0.551
TSNE		0.612	0.659	0.344	0.670	0.488	0.566	1.000	0.606	0.005	0.075	0.521	0.313	0.304	0.620	0.494
TSNE	✓	0.641	0.678	0.412	0.688	0.520	0.612	1.000	0.624	0.018	0.053	0.592	0.364	0.330	0.650	0.522
UMAP		0.604	0.654	0.387	0.649	0.458	0.610	0.998	0.620	0.016	0.004	0.684	0.000	0.265	0.623	0.480
UMAP	✓	0.625	0.693	0.471	0.701	0.566	0.626	0.998	0.655	0.070	0.018	0.782	0.000	0.305	0.669	0.523
Harmony		0.554	0.895	0.873	0.809	0.708	0.646	1.000	0.928	0.437	0.721	0.891	0.000	0.595	0.784	0.708
Harmony	✓	0.579	0.825	0.776	0.784	0.726	0.588	0.999	0.923	0.334	0.545	0.766	0.753	0.664	0.754	0.718
Scanorama		0.522	0.804	0.741	0.697	0.534	0.576	0.999	0.916	0.246	0.246	0.829	0.000	0.447	0.696	0.597
Scanorama	✓	0.571	0.795	0.684	0.746	0.612	0.575	0.999	0.919	0.264	0.287	0.516	0.562	0.510	0.712	0.631
BBKNN		0.533	0.797	0.582	0.807	0.683	0.718	1.000	0.848	0.548	0.686	0.954	0.000	0.607	0.731	0.682
BBKNN	✓	0.668	0.737	0.540	0.771	0.666	0.700	0.999	0.752	0.269	0.081	0.895	0.244	0.448	0.726	0.615
fastMNN	✓	0.583	0.795	0.686	0.766	0.672	0.587	0.999	0.897	0.210	0.187	0.784	0.682	0.552	0.727	0.657
scVI		0.525	0.820	0.750	0.633	0.541	0.544	0.995	0.881	0.386	0.345	0.901	0.683	0.639	0.687	0.668
scVI	✓	0.592	0.839	0.807	0.793	0.770	0.575	0.998	0.910	0.402	0.335	0.926	0.833	0.681	0.768	0.733
scANVI		0.528	0.922	0.932	0.698	0.590	0.559	0.999	0.871	0.385	0.355	0.910	0.537	0.612	0.747	0.693
scANVI	✓	0.631	0.926	0.936	0.886	0.873	0.621	1.000	0.910	0.404	0.375	0.940	0.784	0.682	0.839	0.776
scGen	✓	0.659	0.886	0.779	0.796	0.644	0.650	1.000	0.910	0.423	0.556	0.938	0.598	**0.685**	0.773	0.738
scPoli		0.573	0.900	0.892	0.874	0.791	0.750	1.000	0.900	0.394	0.483	0.963	0.000	0.548	0.826	0.715
scPoli	✓	0.763	0.849	0.738	0.840	0.758	0.739	1.000	0.851	0.455	0.589	0.941	0.491	0.665	0.812	0.754
Author's		0.557	0.918	0.907	0.807	0.721	0.647	1.000	0.913	0.424	0.563	0.904	0.000	0.561	0.794	0.700
Geneformer		0.513	0.737	0.485	0.525	0.340	0.521	0.976	0.901	0.128	0.141	0.835	0.055	0.412	0.585	0.516
Islander		0.886	1.000	1.000	0.961	0.919	0.885	1.000	0.923	0.472	0.666	0.966	0.000	0.605	**0.950**	**0.812**

Extended Data Table 13: Benchmarking cell embeddings, on Skin Cell Atlas

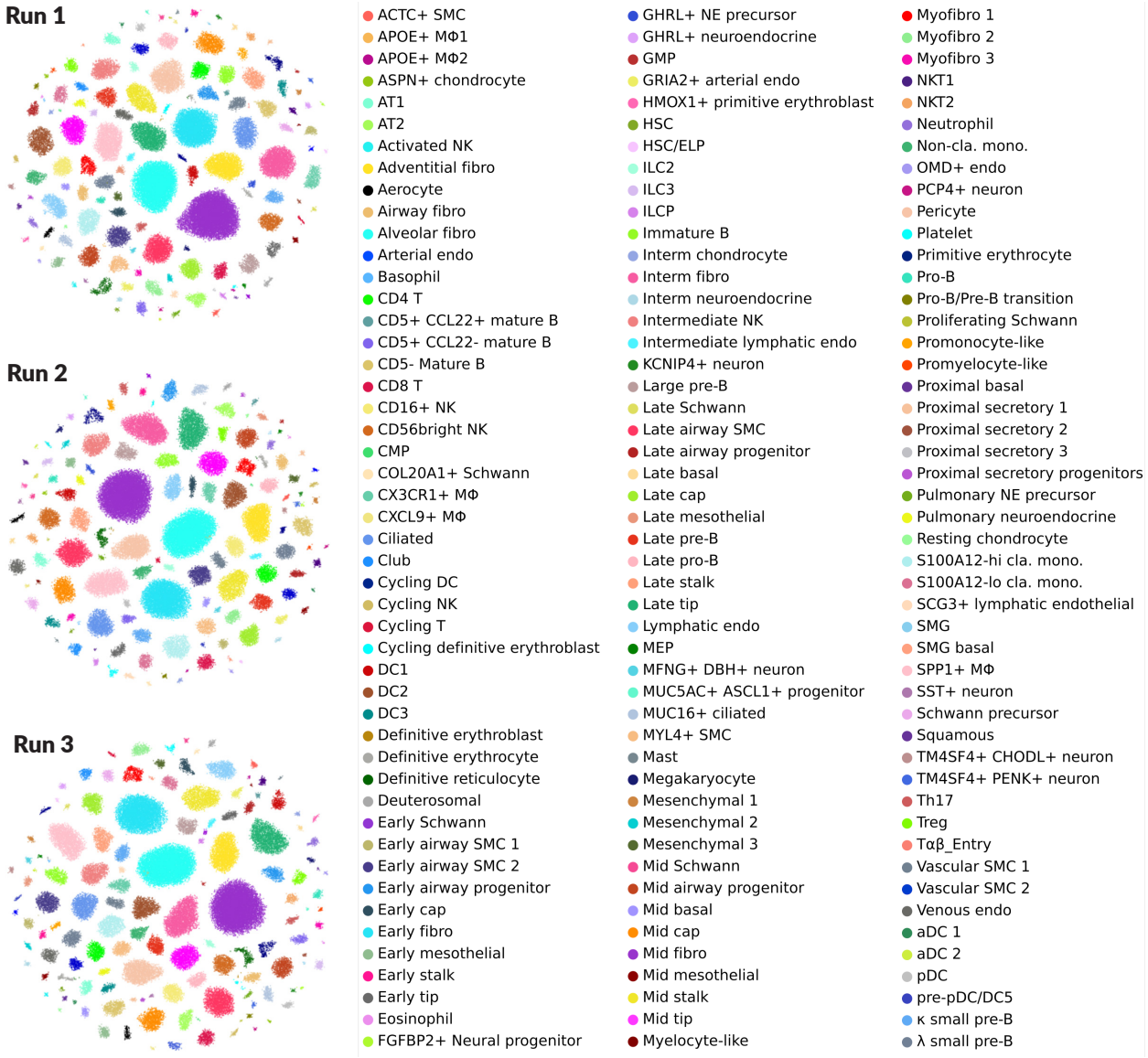
	Bio conservation							Batch correction					Aggregate score		
Method	I-label	L-NMI	L-ARI	K-NMI	K-ARI	S-label	cLISI	S-batch	iLISI	KBET	G-Con	PCR	Batch	Bio	Total
PCA	0.575	0.770	0.480	0.743	0.453	0.594	1.000	0.849	0.043	0.258	0.872	0.000	0.404	0.659	0.557
TSNE	0.291	0.594	0.099	0.636	0.270	0.510	1.000	0.625	0.042	0.205	0.633	0.000	0.301	0.486	0.412
UMAP	0.399	0.650	0.167	0.684	0.327	0.531	1.000	0.627	0.068	0.305	0.798	0.000	0.360	0.537	0.466
Harmony	0.588	0.783	0.556	0.778	0.695	0.613	1.000	0.748	0.142	0.615	0.794	0.603	0.581	0.716	0.662
Scanorama	0.569	0.790	0.477	0.732	0.464	0.589	1.000	0.869	0.083	0.396	0.942	0.132	0.484	0.660	0.590
BBKNN	0.901	0.682	0.186	0.756	0.436	0.569	1.000	0.570	0.155	0.513	0.895	0.079	0.442	0.647	0.565
scVI	0.620	0.886	0.896	0.780	0.567	0.571	1.000	0.851	0.133	0.478	0.934	0.668	**0.613**	**0.760**	**0.701**
scANVI	0.639	0.848	0.618	0.778	0.581	0.606	1.000	0.830	0.123	0.470	0.909	0.527	0.572	0.724	0.663
scPoli	0.691	0.751	0.390	0.882	0.841	0.733	1.000	0.674	0.137	0.495	0.775	0.331	0.482	0.755	0.646
Author's	0.713	0.663	0.174	0.673	0.358	0.553	1.000	0.590	0.107	0.392	0.829	0.000	0.384	0.591	0.508
Geneformer	0.506	0.759	0.550	0.547	0.319	0.527	1.000	0.848	0.113	0.403	0.834	0.405	0.521	0.601	0.569
Islander (Run1)	0.650	0.686	0.321	0.586	0.329	0.582	1.000	0.748	0.124	0.474	0.365	0.240	0.390	0.593	0.512
Islander (Run2)	0.678	0.686	0.321	0.616	0.369	0.589	1.000	0.746	0.123	0.469	0.365	0.217	0.384	0.608	0.519
Islander (Run3)	0.695	0.687	0.321	0.616	0.365	0.585	1.000	0.747	0.123	0.485	0.364	0.249	0.394	0.610	0.523
Islander (UMAP1)	0.328	0.637	0.151	0.445	0.271	0.442	1.000	0.485	0.149	0.462	0.385	0.360	0.368	0.468	0.428
Islander (UMAP2)	0.700	0.635	0.147	0.430	0.294	0.515	1.000	0.475	0.149	0.461	0.375	0.538	0.400	0.532	0.479
Islander (UMAP3)	0.354	0.634	0.147	0.405	0.259	0.495	1.000	0.494	0.152	0.473	0.375	0.312	0.361	0.471	0.427

Extended Data Table 14: Benchmarking cell embeddings, on (Lung, Fetal, Donor) Cell Atlas, using broad cell types.

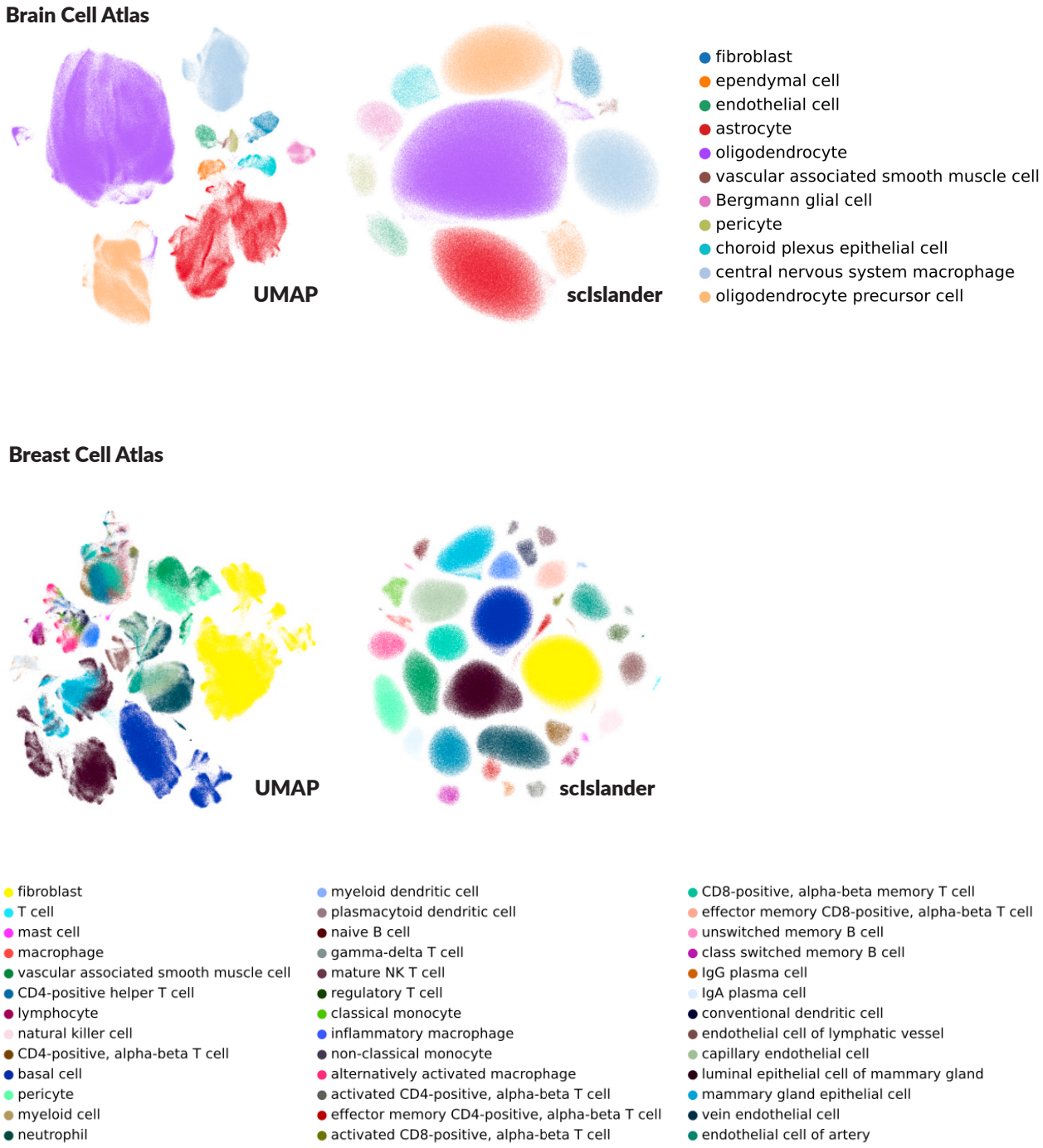
Method	**HVG**	Brain	Breast	COVID	Eye	Gut (F)	Heart	Lung (F,D)	Lung (F,O)	Lung	Pancreas	Skin
PCA		0.932	0.885	0.808	0.941	0.968	0.746	0.769	0.707	0.827	0.909	0.914
PCA	✓	0.949	0.938	0.962	0.979	0.979	0.713	0.769	0.682	0.910	0.952	0.953
TSNE		0.620	0.504	0.599	0.745	0.724	0.634	0.448	0.373	0.481	0.730	0.708
TSNE	✓	0.633	0.632	0.616	0.694	0.699	0.657	0.448	0.426	0.655	0.608	0.718
UMAP		0.580	0.592	0.649	0.695	0.652	0.532	0.563	0.462	0.635	0.621	0.637
UMAP	✓	0.684	0.617	0.726	0.762	0.634	0.618	0.563	0.354	0.652	0.624	0.703
Harmony		0.924	0.908	0.837	0.946	0.636	0.835	0.421	0.491	0.746	0.928	0.721
Harmony	✓	0.941	0.957	0.971	0.981	0.978	0.766	0.731	0.703	0.890	0.954	0.973
Scanorama		0.929	0.872	0.813	0.949	0.934	0.735	0.669	0.689	0.738	0.894	0.922
Scanorama	✓	0.915	0.916	0.930	0.924	0.946	0.727	0.669	0.718	0.774	0.913	0.936
BBKNN		0.544	0.600	0.772	0.674	0.645	0.677	0.462	0.453	0.654	0.667	0.733
BBKNN	✓	0.562	0.601	0.765	0.618	0.739	0.608	0.613	0.588	0.669	0.583	0.768
scVI		0.820	0.731	0.622	0.782	0.726	0.718	0.440	0.678	0.632	0.633	0.677
scVI	✓	0.863	0.732	0.704	0.795	0.710	0.757	0.438	0.668	0.683	0.643	0.696
scANVI		0.857	0.774	0.773	0.818	0.798	0.818	0.518	0.708	0.712	0.634	0.651
scANVI	✓	0.927	0.848	0.848	0.820	0.820	0.888	0.508	0.695	0.829	0.696	0.761
scGen	✓	0.949	0.880	0.868	0.954	0.946	0.688	0.694	0.607	0.872	0.901	0.899
scPoli		nan	nan	0.629	0.824	0.857	0.829	0.732	0.645	0.826	0.836	0.690
scPoli	✓	0.869	0.818	0.741	0.933	0.849	0.858	0.729	0.647	0.826	0.733	0.887
Author's		0.644	0.884	nan	0.593	0.676	0.829	0.379	0.337	0.634	nan	0.706
Geneformer		0.799	0.631	nan	0.693	0.821	0.693	0.597	0.625	0.668	nan	0.800
Islander		0.549	0.464	0.480	0.753	0.633	0.577	0.256	0.697	0.513	0.676	0.654

Extended Data Table 15: Benchmarking cell embeddings, using scGraph. "F", "D" and "O" represents fetal, donor and organoid, respectively. "nan" means the embeddings are not available, due to memory limitations (>500G in RAM) or unavailability of raw counts (Geneformer). We underline the worst methods among integration methods, Geneformer and Islander , for each atlas.

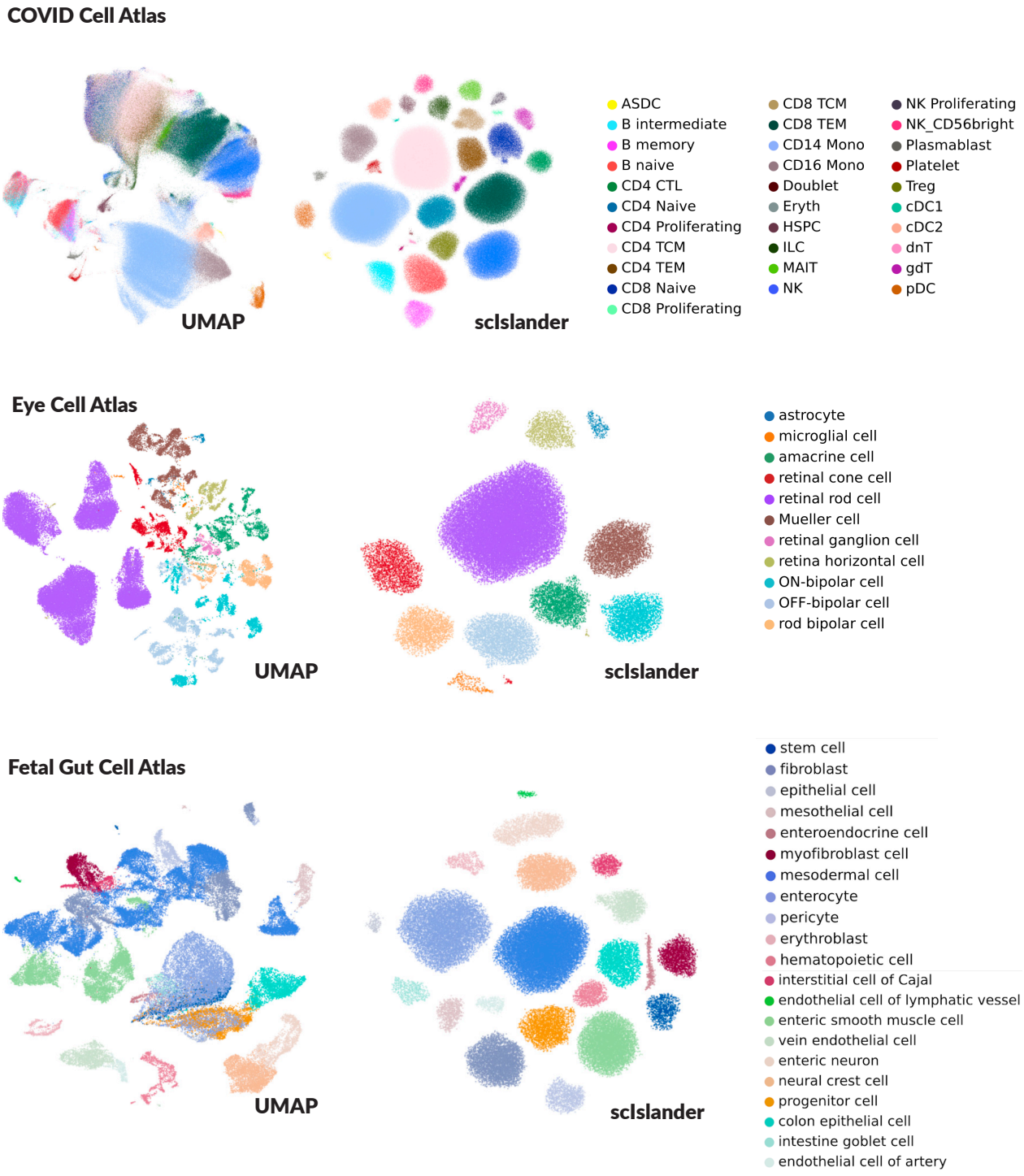
3. Visualization



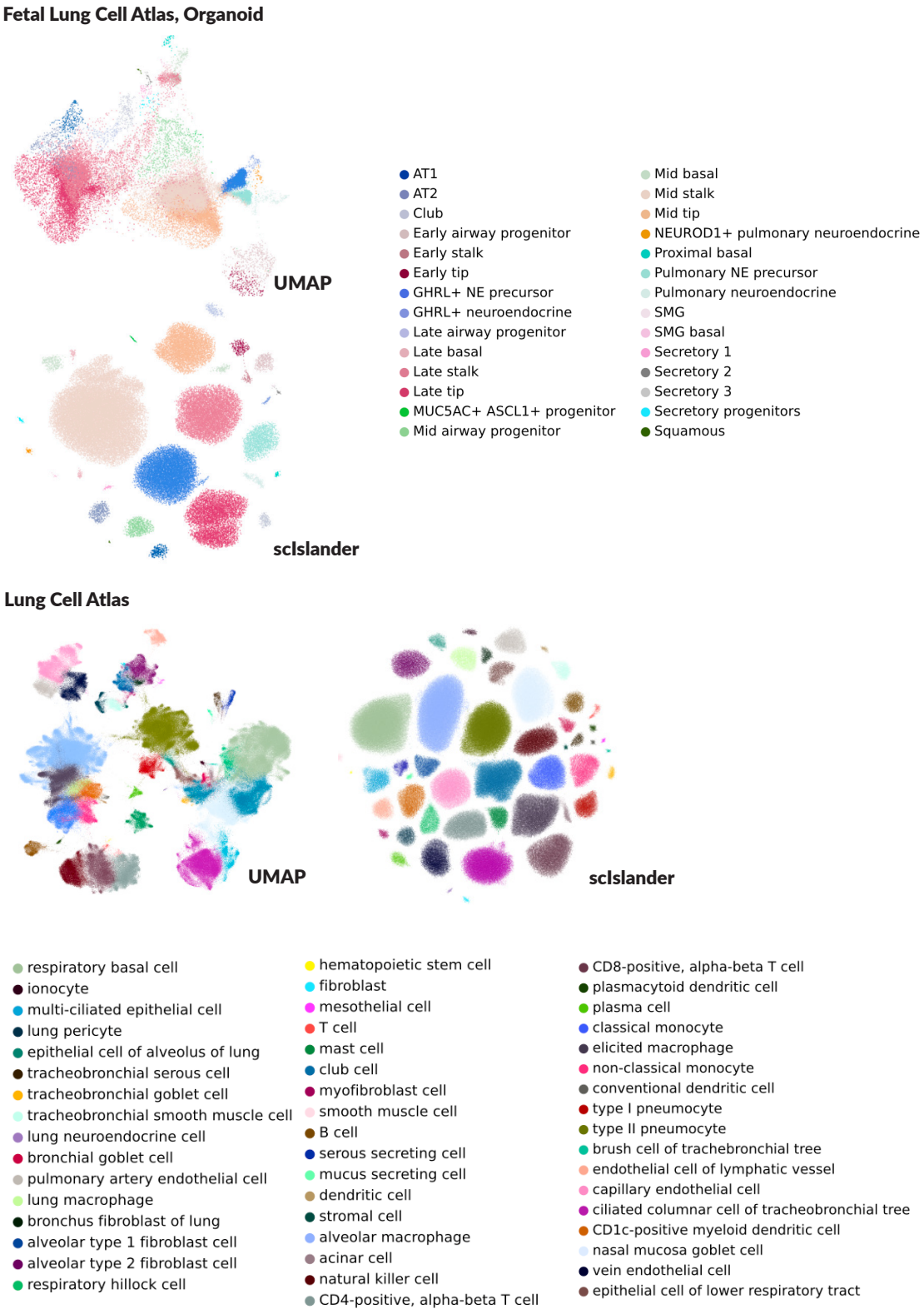
Extended Data Figure 1: **Drifting Cell Islands, different runs of Islander on fetal lung atlas.**



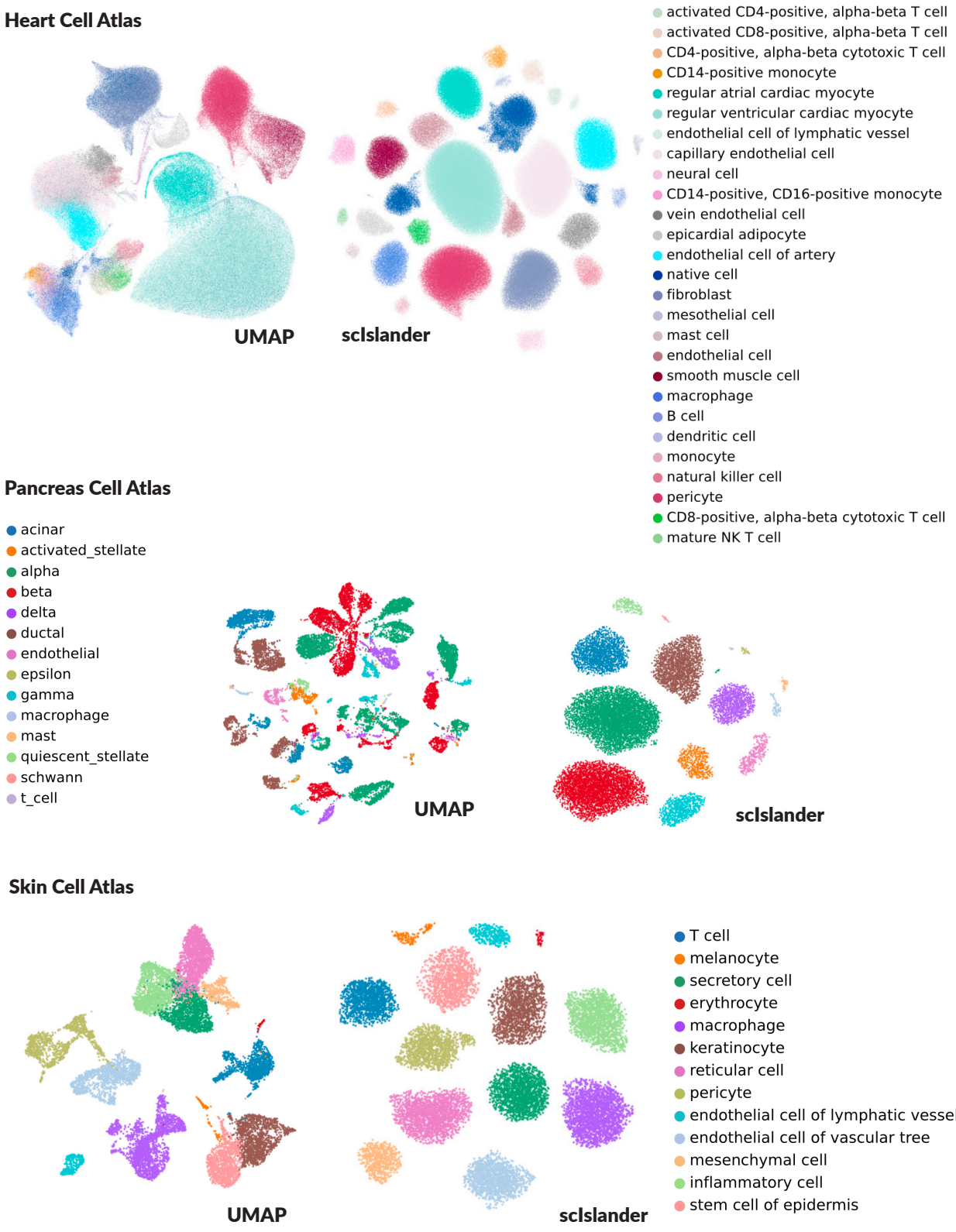
Extended Data Figure 2: **Drifting Cell Islands, Part I**



Extended Data Figure 3: **Drifting Cell Islands, Part II**



Extended Data Figure 4: **Drifting Cell Islands, Part III**



Extended Data Figure 5: **Drifting Cell Islands, Part IV**