Supplementary Notes for "Comprehensive benchmarking of RNA velocity methods across single-cell datasets"

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1 Note S1: Enrichment analysis of method rankings

To evaluate whether specific groups are significantly enriched in the top or bottom n rankings, we performed an enrichment analysis using a one-sided hypergeometric test. The P-value, defined as the probability of observing at least k methods from a specific ranking category within the selected rank cutoff, is calculated as:

$$P(X \geq k) = \sum_{i=k}^{\min(n,K)} \frac{\binom{K}{i}\binom{N-K}{n-i}}{\binom{N}{n}} \tag{1}$$

where N is the total number of evaluated methods, K is the total number of methods in the specific category, n is the cutoff size (e.g., top 10), and k is the observed number of methods from that group within the cutoff. Statistical significance is indicated by asterisks ($* : P < 0.05$, $** : P < 0.01$, $*** : P < 0.001$).

2 Note S2: Implementation of cell-specific latent time for RNA velocity methods

In this section, we describe the implementation details for obtaining cell-specific latent time (CLT) for each RNA velocity method, tailored to its temporal modeling strategy. As introduced in the manuscript, we categorized the 25 RNA velocity methods into four groups based on how they model temporal information. Specifically, Group 1 methods explicitly estimate a unified CLT, whereas Group 2 methods estimate gene-specific latent times. Group 3 methods either infer CLT indirectly through a graph-based approach or do not provide temporal outputs at all. Lastly, the Group 4 method (SDEvelo) estimates CLT using an SDE model combined with optimal transport (OT) alignment.

In this section, we describe the implementation details used to obtain cell-specific latent time (CLT) for each RNA velocity method according to its temporal modeling strategy. As introduced in the manuscript, we categorized the 25 RNA velocity methods into four groups based on how they model temporal information. Specifically, Group 1 methods explicitly estimate a unified CLT, whereas Group 2 methods estimate gene-specific latent times. Group 3 methods either infer CLT indirectly through a graph-based approach or do not provide temporal outputs at all. Lastly, the Group 4 method (SDEvelo) estimates CLT using an SDE model combined with optimal transport (OT) alignment.

We obtained CLT estimates for each group as follows:

- **Groups 1 and 4:** We directly used the CLT estimates generated simultaneously with the velocity estimates.
- **Group 2:** We followed the original implementations and applied `scvelo.tl.latent_time()` to obtain the CLT. This function heuristically aggregates gene-specific latent times by assuming that early cells tend to be early across most genes, while terminal cells tend to be late.

- **Group 3:** For methods that provide their own CLT estimation procedures, we followed their original implementations (detailed below). For the remaining Group 3 methods, which do not produce native temporal outputs, we ensured a fair comparison by applying `scvelo.tl.velocity_pseudotime()`, following the approach used in scVelo (stc). This function estimates CLT based on a graph constructed from the velocity outputs of the corresponding methods.

Method-specific implementations for Group 3:

- **cellDancer:** Uses `celldancer.pseudo_time()` following kinetic parameter estimation. This function estimates CLT by simulating RNA velocity streamlines in low-dimensional embeddings and ordering cells along dominant trajectories via graph-based time alignment.
- **Dynamo (m1):** Applies `dynamo.ext.ddhodge()` following velocity inference. This function infers a single-cell potential, which serves as a proxy for CLT, by building a velocity-informed diffusion graph and computing the scalar potential from the divergence of the graph-based vector field via Hodge decomposition.

3 Note S3: Justification for additional tasks excluded from the overall ranking

To provide a more systematic assessment, our benchmarking framework includes four additional tasks: quantification stability, simulation experiments, multimodal integration, and computational scalability. However, these were excluded from the overall rankings to ensure a fair and robust comparison focused on core performance. The specific rationale for excluding each of these tasks is detailed below.

Quantification stability was evaluated separately, as quantification is an independent upstream process whose variability could confound the direct assessment of the velocity estimation methods themselves. Therefore, this metric mainly provides practical guidance for real-world usage rather than serving as a measure of a model's intrinsic modeling capacity or biological interpretability. Simulation experiments were omitted due to the significant discrepancy between synthetic and real-world datasets. Specifically, simulations tended to bias results against deep learning (DL)-based methods while favoring those built on generative assumptions similar to the simulation. Multimodal integration was excluded because it is a specialized feature limited to a small subset of tools, making it unsuitable as a universal metric. Finally, as computational scalability reflects technical capacity rather than biological accuracy, we provide separate five-tier scalability tiers for cells and genes, respectively, to guide researchers without conflating performance with resource requirements.

4 Note S4: Additional benchmarking metrics

Distance correlation

For each simulated dataset, ground-truth RNA velocity was available in gene space. However, for methods that output only low-dimensional embedded velocities (e.g., VeloAE, scTour, and

LatentVelo (std)), direct comparison with the high-dimensional ground truth is not feasible. Distance correlation (dCor) [1, 2] was therefore used to quantify nonlinear associations between inferred and true velocity structures based on pairwise cell–cell similarities. Formally,

$$\mathrm{dCor}(\mathbf{V}^{\mathrm{true}}, \mathbf{V}^{\mathrm{inf}}) = \frac{\sum_{i,j=1}^{N} A_{ij} B_{ij}}{\sqrt{\left(\sum_{i,j=1}^{N} A_{ij}^2\right)\left(\sum_{i,j=1}^{N} B_{ij}^2\right)}}, \tag{2}$$

where A and B are double-centered pairwise Euclidean distance matrices of $\mathbf{V}^{\mathrm{true}}$ and $\mathbf{V}^{\mathrm{inf}}$, respectively:

$$A_{ij} = a_{ij} - \bar{a}_{i\cdot} - \bar{a}_{\cdot j} + \bar{a}_{\cdot\cdot}, \quad B_{ij} = b_{ij} - \bar{b}_{i\cdot} - \bar{b}_{\cdot j} + \bar{b}_{\cdot\cdot}, \tag{3}$$

with $a_{ij} = \|\mathbf{v}_i^{\mathrm{true}} - \mathbf{v}_j^{\mathrm{true}}\|_2$ and $b_{ij} = \|\mathbf{v}_i^{\mathrm{inf}} - \mathbf{v}_j^{\mathrm{inf}}\|_2$. Higher dCor values indicate stronger nonlinear concordance between inferred and true velocity structures.

Pearson's correlation

For each simulated dataset, Pearson's correlation between true and inferred CLT values was used to assess temporal accuracy. Higher correlation values indicate more accurate CLT inference.

5 Note S5: Computational environments

All analyses were performed on a Linux server running Ubuntu 22.04 LTS (Kernel 5.15), equipped with Intel Xeon Platinum 8352V CPUs (128 threads), 1 TB of RAM, and a single NVIDIA vGPU (32 GB of memory).

6 Note S6: Benchmarking datasets

Data 1

This dataset captures transcriptional dynamics in human bone marrow using single-cell RNA sequencing [3]. It profiles key bone marrow cell populations and is designed to capture major transitions in hematopoietic differentiation, including the progressive loss of cellular plasticity. For the CBDir evaluation, directional correctness was assessed across established differentiation trajectories: (Hematopoietic stem cells 1 $\rightarrow$ Hematopoietic stem cells 2), (Hematopoietic stem cells 1 $\rightarrow$ Erythroids 1), and (Erythroids 1 $\rightarrow$ Erythroids 2). Three-fold cross-validation was performed on this dataset.

Data 2

This dataset captures gene-regulatory dynamics in the developing human cerebral cortex using single-cell multiomic profiling [4]. It integrates single-cell RNA-seq and ATAC-seq data from primary cortical tissue collected at post-conceptional weeks 16, 20, 21, and 24, profiling major neuronal and glial populations across key stages of corticogenesis. The data span continuous differentiation trajectories from radial glia and intermediate progenitors to excitatory neurons and interneurons, with well-characterized developmental markers. For the CBDir evaluation,

directional correctness was assessed across established differentiation trajectories: (Cycling progenitor cells → Radial glia / Astrocytes), (Cycling progenitor cells → Neuronal intermediate progenitor cells / Excitatory neurons), (Neuronal intermediate progenitor cells / Excitatory neurons → Upper-layer excitatory neurons), and (Upper-layer excitatory neurons → Deep-layer excitatory neurons). Five-fold cross-validation was performed on this dataset.

Data 3

This dataset captures transcriptional dynamics in the developing dentate gyrus using droplet-based single-cell RNA sequencing (10x Genomics Chromium) [5]. Cells were profiled at two developmental time points, P12 and P35, capturing maturation of the granule cell lineage as well as other differentiated cell populations within the developing tissue. For the CBDir evaluation, directional correctness was assessed across the following differentiation trajectories: (nIPC → Neuroblast), (Neuroblast → Granule immature), (Granule immature → Granule mature), (Radial Glia-like → Astrocytes), and (OPC → OL). Two-fold cross-validation was performed on this dataset.

Data 4

This dataset captures transcriptional dynamics during mouse gastrulation using single-cell RNA sequencing and was specifically subset to the erythroid lineage [6]. It contains cells collected at nine developmental time points between embryonic day 6.5 and day 8.5, providing a focused view of erythroid differentiation within the broader gastrulation program. For the CBDir evaluation, directional correctness was assessed across known differentiation trajectories: (Blood progenitors 1 → Blood progenitors 2), (Blood progenitors 2 → Erythroid 1), (Erythroid 1 → Erythroid 2), and (Erythroid 2 → Erythroid 3). Three-fold cross-validation was performed on this dataset.

Data 5

This dataset captures transcriptional dynamics in the developing pancreas using single-cell RNA sequencing, focusing on epithelial cells and Ngn3–Venus fusion cells at embryonic day 15.5 [7]. It provides a snapshot of endocrine differentiation as progenitor cells within the pancreatic epithelium progress toward four major endocrine fates: alpha, beta, delta, and epsilon cells. For the CBDir evaluation, directional correctness was assessed across established differentiation trajectories: (Ngn3 high EP → Pre-endocrine), (Pre-endocrine → Alpha), (Pre-endocrine → Beta), (Pre-endocrine → Delta), and (Pre-endocrine → Epsilon). Three-fold cross-validation was performed on this dataset.

Data 6

This dataset captures transcriptional dynamics in mouse intestinal organoids using single-cell 5-ethynyl uridine (EU)-labeled RNA sequencing (scEU-seq), which simultaneously quantifies newly transcribed and pre-existing mRNAs [8]. For the CBDir evaluation, directional correctness was assessed across known differentiation trajectories: (Stem cells → TA cells), (TA cells →

Enterocytes), (Stem cells → Enteroendocrine progenitors), and (Enteroendocrine progenitors → Enteroendocrine cells). Three-fold cross-validation was performed on this dataset.

Data 7

This dataset profiles transcriptional dynamics in primary mouse cortical neurons using single-cell metabolically labeled new RNA tagging sequencing (scNT-seq) [9]. Neurons were stimulated with potassium chloride (KCl) and sampled at 0, 15, 30, 60, and 120 minutes. For the CBDir evaluation, directional correctness was assessed across sequential time intervals: (0 → 15), (15 → 30), (30 → 60), and (60 → 120). Three-fold cross-validation was performed on this dataset.

Data 8

This dataset characterizes gene expression in fluorescence ubiquitination cell cycle indicator (FUCCI) U2OS cells [10]. To establish discrete ground-truth temporal labels, the continuous FUCCI pseudotime was discretized into five bins following the published tutorial: `https://yoseflab.github.io/velovi_reproducibility/estimation_comparison/fucci.html`. Three-fold cross-validatio n was performed on this dataset.

Data 9

This dataset profiles the developing murine hindlimb across four embryonic time points: E11.5, E13.5, E15.5, and E18.5 [11]. Data processing was performed using `cellranger` (v8.0.0) for read alignment and `velocyto` (v0.17.17) for quantification of spliced and unspliced mRNA abundances. Three-fold cross-validation was performed on this dataset.

Data 10

This dataset captures transcriptomic diversification and maturation in the mouse primary visual cortex (V1) during postnatal development using droplet-based single-nucleus RNA sequencing. Nuclear transcriptomes were profiled at six postnatal time points (P8, P14, P17, P21, P28, and P38), spanning stages before, during, and after the critical period of ocular dominance plasticity [12]. we focused on the Gluta_NR subset, corresponding to glutamatergic neurons in the non-responsive lineage. Five-fold cross-validation was performed on this dataset.

Data 11

This dataset captures the reprogramming of mouse embryonic fibroblasts (MEFs) into induced endoderm progenitors (iEPs), with samples collected at eight time points [13]. Five-fold cross-validation was performed on this dataset.

Data 12

This dataset profiles the reprogramming of MEFs into induced pluripotent stem cells (iPSCs) under serum and 2i conditions, with samples collected at 39 time points over 18 days [14]. For

the present analysis, only the serum condition was considered. Five-fold cross-validation was performed on this dataset.

Data 13

This dataset consists of PBMCs from a 10X Genomics experiment containing 65,877 cells. It profiles major immune cell types derived from hematopoietic stem cells in the bone marrow and includes representatives of both myeloid and lymphoid lineages [15]. Five-fold cross-validation was performed on this dataset.

Data 14 & 16

These two datasets consist of PBMCs from a healthy female donor aged 25, obtained by 10x Genomics from AllCells. Data 14 [16] consists of 10,194 cells, and Data 16 [17] consists of 10,497 cells. Three-fold cross-validation was performed on both datasets.

Data 15 & 17

These two datasets consist of PBMCs from two different healthy donors. Data 15 [18] contains 8,381 cells, and Data 17 [19] contains 11,769 cells. Three-fold cross-validation was performed on both datasets.

Data 18

This dataset contains joint single-nucleus ATAC-seq and gene expression profiles from embryonic mouse brain at E18. It provides paired chromatin accessibility and transcriptional measurements that capture cellular heterogeneity across major embryonic brain regions [20]. For the CBDir evaluation, directional correctness was assessed across known differentiation trajectories: (RG, Astro, OPC $\rightarrow$ IPC), (IPC $\rightarrow$ V-SVZ), (V-SVZ $\rightarrow$ Upper layer), and (Upper layer $\rightarrow$ Deeper layer). Three-fold cross-validation was performed on this dataset.

Data 19

This dataset profiles human hematopoietic stem and progenitor cells (HSPCs) and their early erythroid and myeloid progeny [21]. The original study used Cap Analysis of Gene Expression, ChIP-seq for histone modifications, and Moloney leukemia virus integration site mapping to characterize transcriptional activity and regulatory element usage during early hematopoietic differentiation. These data capture promoter, enhancer, and super-enhancer landscapes across multipotent stem cells and lineage-committed progenitors, providing a detailed view of transcriptional states along the myeloid and erythroid lineages. For the CBDir evaluation, directional correctness was assessed across established differentiation trajectories: (HSC $\rightarrow$ MPP), (MPP $\rightarrow$ LMPP), (LMPP $\rightarrow$ GMP), (HSC $\rightarrow$ MEP), (MEP $\rightarrow$ Erythrocyte), (MEP $\rightarrow$ Prog MK), and (Prog MK $\rightarrow$ Platelet). Three-fold cross-validation was performed on this dataset.

Data 20

This dataset contains joint chromatin accessibility and gene expression profiles from mouse skin generated using the SHARE-seq protocol [22]. The original study produced large-scale single-cell ATAC-seq and RNA measurements from adult skin to define cis-regulatory interactions and chromatin domains enriched for lineage-determining genes. During hair follicle differentiation, accessibility at these regulatory regions precedes gene activation, revealing chromatin priming events associated with cell fate commitment. This dataset provides high-resolution multimodal measurements that capture regulatory and transcriptional dynamics in a heterogeneous tissue. For the CBDir evaluation, directional correctness was assessed across known differentiation trajectories: (TAC-1 $\rightarrow$ TAC-2), (TAC-2 $\rightarrow$ Hair shaft cuticle/cortex), (TAC-2 $\rightarrow$ IRS), and (TAC-2 $\rightarrow$ Medulla). Three-fold cross-validation was performed on this dataset.

Data 21

This dataset utilizes scEU-seq to simultaneously quantify metabolically labeled and pre-existing unlabeled transcripts in mouse intestinal stem cells, comprising samples from both pulse and chase experiments [8]. For this study, data from the pulse experiment were selected and processed following the guidelines provided at: `https://yoseflab.github.io/velovi_reproducibility/estimation_comparison/sceu.html`. To establish discrete ground-truth temporal labels, continuous cell cycle scores were discretized into five bins. Three-fold cross-validation was performed on this dataset.

Data 22

This dataset profiles the dynamics of human hematopoiesis using scNT-seq to capture metabolic labeling information [23]. For the CBDir evaluation, directional correctness was assessed across established differentiation trajectories: (HSC $\rightarrow$ MEP-like), (HSC $\rightarrow$ GMP-like), (MEP-like $\rightarrow$ Meg), (MEP-like $\rightarrow$ Ery), (MEP-like $\rightarrow$ Bas), (GMP-like $\rightarrow$ Bas), (GMP-like $\rightarrow$ Mon), and (GMP-like $\rightarrow$ Neu). Three-fold cross-validation was performed on this dataset.

Data 23 & 24

These two datasets were generated using ODE-based dynamics with `scvelo.datasets.simulation()` in scVelo [24]. Each dataset contains 1,500 cells, with Data 23 comprising 100 genes and Data 24 comprising 500 genes. Transcription, splicing, and degradation rates were fixed at $\alpha = 5$, $\beta = 0.3$, and $\gamma = 0.5$, respectively. Three-fold cross-validation was performed on both datasets.

Data 25 & 26

These two datasets were generated using SDE-based dynamics with `sdevelo.SimData()` in SDEvelo [25]. Each dataset contains 1,600 cells, with Data 25 comprising 100 genes and Data 26 comprising 500 genes. The number of trajectories `K` was fixed at 8. Three-fold cross-validation was performed on both datasets.

Data 27 & 28

These two datasets were generated using dyngen, a multimodal simulation framework that models gene regulatory networks and transcriptional kinetics. Each dataset contains 1,500 cells with 100 target genes, 100 housekeeping genes, and a set of transcription factors determined by the specified trajectory backbone. Data 27 uses a linear backbone, whereas Data 28 uses a bifurcating backbone. Key simulation parameters were `tau` = 0.01, `census_interval` = 1, and `num_simulations` = 100. Three-fold cross-validation was performed on both datasets.

Data 29 & 30

These two datasets were generated using ODE-based dynamics with `scvelo.datasets.simulation()` in scVelo [24]. Data 29 consists of seven datasets with cell counts ranging from $n = 1,000$ to $1,000,000$, with fixed gene counts at 1,000. Data 30 consists of six datasets with gene counts ranging from $p = 1,000$ to $20,000$, with fixed cell counts at 10,000. Transcription, splicing, and degradation rates were fixed at $\alpha = 5$, $\beta = 0.3$, and $\gamma = 0.5$, respectively.

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