

PhyloVelo Integrates Single-cell Transcriptomics and Lineage Tracing for Cell-fate Mapping

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Single-cell RNA-sequencing (scRNA-seq) enables systematic mapping of cellular differentiation trajectories. However, accurately inferring the cell-fate transitions in the context of diseases or perturbations remains challenging due to high cellular plasticity. Here, we introduce a computational framework (PhyloVelo) to estimate the velocity of transcriptomic dynamics by leveraging monotonically expressed genes (MEGs) during cell divisions. Using simultaneous scRNA-seq and lineage information, PhyloVelo can identify MEGs and reconstruct a novel transcriptomic velocity field. PhyloVelo accurately recovered linear, bifurcated and convergent differentiations in simulation and *C. elegans* data. Application to seven lineage-resolved scRNA-seq datasets including CRISPR/Cas9 editing, lentiviral barcoding and T cell receptor repertoire showed that PhyloVelo can robustly infer complex lineage trajectories with superior performance relative to RNA velocity. We also found MEGs across tissues and organisms had similar functions in translation and ribosome biogenesis. Together, our study presents a powerful method for cell-fate analysis in diverse biological contexts. Documentation and detailed examples for using PhyloVelo are available at <https://phylovelo.readthedocs.io/>.