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scphylo-tools: A Python toolkit for single-cell tumor phylogenetic analysis

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Software

- Review
- Repository
- Archive

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Summary

`scphylo-tools` is a Python library designed to unify single-cell tumor phylogeny inference methods. It addresses the lack of standardization in the field by providing a cohesive interface for data processing, tree reconstruction, visualization, and benchmarking. By streamlining these tasks, `scphylo-tools` empowers researchers with limited programming expertise to easily install and utilize complex inference methods, accelerates algorithm development, and ensures reproducible benchmarking of tumor phylogeny reconstruction methods.

Statement of Need

Cancer is a dynamic evolutionary process driven by the acquisition of somatic mutations and the competitive selection of clonal populations. Single-Cell Sequencing (SCS) technologies have enabled the profiling of genomic alterations at cellular resolution, offering unprecedented insights into intratumor heterogeneity (Navin et al., 2011; Wang et al., 2014). Elucidating the phylogenetic relationships between tumor cells is essential for understanding metastasis (Leung et al., 2017; Roper et al., 2020), drug resistance (Gopalan et al., 2021; Gruen et al., 2023; Kim & Simon, 2014), and clonal dynamics (Hirsch et al., 2025; Laks et al., 2019; Liu et al., 2025).

Reconstructing the evolutionary history of a tumor from SCS data presents unique computational challenges. These datasets are plagued by high noise levels, including Allele Drop-Out (ADO), false positives, missing data, and doublet artifacts (Malikić et al., 2021; Rashidi Mehrabadi, 2022). Consequently, a diverse array of computational tools has been developed to address these challenges, including stochastic methods like SCITE (Jahn et al., 2016), infSCITE (Kuipers et al., 2017), OncoNEM (Ross & Markowetz, 2016), SiFit (Zafar et al., 2017), and SiCloneFit (Zafar et al., 2019); combinatorial approaches such as PhISCS (Malikic et al., 2019), PhISCS-BnB (Sadeqi Azer et al., 2020), SPhyR (El-Kebir, 2018), ScisTree (Wu, 2019), gpps (Ciccolella, Soto Gomez, et al., 2020), and SASC (Ciccolella, Ricketts, et al., 2020); and specialized methods including HUNTRESS (Kızılkale et al., 2022), SCIPhI (Singer et al., 2018), and Scelestial (Foroughmand-Araabi et al., 2022).

However, the software landscape remains highly fragmented. Existing methods typically function as standalone binaries or scripts with inconsistent input/output formats, rendering comparative analysis difficult. Researchers attempting to utilize these tools face a laborious process of installation, data conversion, and script wrapping. Furthermore, integrating these tools into modern Python-based environments (e.g., alongside SCANPY (F. A. Wolf et al., 2018) or Biopython (Cock et al., 2009)) often requires custom development. `scphylo-tools` addresses these challenges by wrapping diverse state-of-the-art algorithms into a single, cohesive Python API.

The target audience includes computational biologists, bioinformaticians, and cancer researchers who need to:

- Compare multiple phylogeny inference methods on the same dataset
- Benchmark new algorithms against established methods
- Integrate tumor phylogeny analysis into existing Python workflows
- Access curated single-cell cancer datasets for research

State of the Field

Several tools exist for tumor phylogeny inference, but none provide the unified framework that `scphylo-tools` offers. Individual tools like SCITE, PhISCS, and HUNTRESS each require separate installation, different input formats, and produce outputs that are not directly comparable. Workflow frameworks like Snakemake or Nextflow could orchestrate these tools, but would require significant custom development for format conversion and result standardization.

`scphylo-tools` distinguishes itself by:

1. **Unified Interface**: A consistent Python API across all wrapped methods, eliminating format conversion overhead
2. **Comprehensive Metrics**: Built-in implementation of specialized tumor tree comparison metrics (MLTD (Karpov et al., 2019), CASet/DISC (DiNardo et al., 2019), MP3 (Ciccolella, Bernardini, et al., 2020))
3. **Curated Datasets**: Direct access to published SCS datasets from landmark cancer evolution studies (Gawad et al., 2014; Hou et al., 2012; Leung et al., 2017; Morita et al., 2020; Wang et al., 2014; Y. Wolf et al., 2019)
4. **Ecosystem Integration**: Seamless integration with the Python scientific stack (NumPy, NetworkX, Matplotlib)

Software Design

`scphylo-tools` follows a modular architecture inspired by established bioinformatics packages like SCANPY. The design philosophy prioritizes:

Modular Organization: The package is organized into functional modules (`io`, `pp`, `tl`, `pl`, `ul`, `datasets`) that mirror the phylogenetic analysis workflow. This separation allows users to engage only with the components relevant to their needs.

Consistent Abstractions: All solver wrappers expose a uniform interface, handling input formatting, binary execution, and output parsing internally. Trees are represented as NetworkX `DiGraph` objects, enabling interoperability with the broader Python ecosystem.

Extensibility: New inference methods can be added by implementing a standard wrapper interface, making the package straightforward to extend as new algorithms emerge.

Reproducibility: The `datasets` module provides versioned access to published datasets, and the simulation engine enables controlled generation of synthetic data with known ground truths for algorithm validation.

Key implementation decisions include using pandas DataFrames for genotype matrices (facilitating data manipulation), NetworkX for tree structures (enabling standard graph algorithms), and Matplotlib/Graphviz for visualization (providing publication-quality outputs).

Research Impact Statement

`scphylo-tools` has been used in several published research studies:

- Analysis of melanoma subclonal evolution and immunotherapy resistance mechanisms (Gruen et al., 2023)

- Development of the Trisicell-PartF algorithm for evaluating inferred subclonal structures (Mehrabadi et al., 2025)
- Investigation of expressed mutation profiles in single cells (Mehrabadi et al., 2021)
- Metastatic migration pattern analysis using single-cell methylation sequencing (Liu et al., 2023, 2025)
- Stochastic modeling of gene expression adaptation in tumor evolution (Hirsch et al., 2025)

The package is available on PyPI. Documentation and tutorials are hosted on Read the Docs, providing comprehensive guidance for new users.

AI Usage Disclosure

No generative AI tools were used in the development of the `scphylo-tools` software, the writing of this manuscript, or the preparation of supporting documentation.

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