scmorph: a Python package for analysing single-cell morphological profiles

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Summary

scmorph is a Python package to analyse single-cell data from morphological profiling experiments which generate large tabular data. scmorph combines domain-specific methods such as single-cell hit calling and batch correction with the versatile and scalable scverse tools to offer feature selection, dimensionality reduction and more. Overall, scmorph brings together a host of single-cell morphological profiling methods, making it applicable for a wide range of experimental designs and workflows.

Statement of need

Morphological profiling has become an essential tool in biology and drug discovery, but there is a lack of open-source software for analysing single-cell morphological data. Existing solutions are commercial, do not scale to large datasets, or do not offer single-cell specific methods (Omta et al., 2016; Serrano et al., 2025). scmorph offers a comprehensive set of methods for analysing single-cell morphological data, which do not require averaging of features across cells. By integrating with the growing scverse of single-cell tools, scmorph also opens up advanced processing capabilities including access to deep learning tools (Wolf et al., 2018).

Briefly, scmorph provides five modules to analyze morphological profiles:

- Reading and writing (IO). scmorph allows reading data from csv, sql, sqlite, and h5ad files, including from the popular CellProfiler software (Stirling et al., 2021). Once converted, scmorph works with AnnData objects stored as h5ad, which track processing steps and can easily be written to disk (Virshup et al., 2024).
- Quality control. scmorph integrates two levels of unsupervised quality control: image-level and single-cell level. Image-level correction is performed with a kNN-based outlier detection method, whereas single-cell profiles that are outliers are detected via pyod (Li et al., 2022).
- Preprocessing. Provided functions perform feature selection, compute PCA coordinates, and optionally aggregate data. For the first time in the field of morphological profiling, scmorph integrates scone as batch correction function, which retains interpretability of features (Cole et al., 2019). Additionally, the integrated feature selection methods can remove features associated with known confounders or with high correlation structures, as is common in morphological profiling experiments (Kruskal & Wallis, 1952; Lin & Han, 2021).
- Plotting. scmorph uses scanpy for easy plotting of PCA and UMAP coordinates, either in 2D or as cumulative densities, which can be useful for identifying technical artifacts

such as batch effects (Wolf et al., 2018). It also provides methods for plotting features per experimental group, such as plates.

- Downstream analysis. For experiments focused on profiling non-dynamic responses, such as a small molecule library, `scmorph` integrates functions to perform hit calling from single-cell profiles. Specifically, during hit calling `scmorph` embeds single-cell profiles into PCA space and computes the Mahalanobis distance of cells to the medoid of untreated control cells. It then compares the distances of treated cells to those of untreated cells by use of the Kolmogorov–Smirnov statistic. For dynamic systems such as differentiating cells, `scmorph` incorporates differential trajectory inference modelling via `slingshot` and `condiments` through the `rpy2` translation layer (Roux de Bézieux et al., 2024; Street et al., 2018).
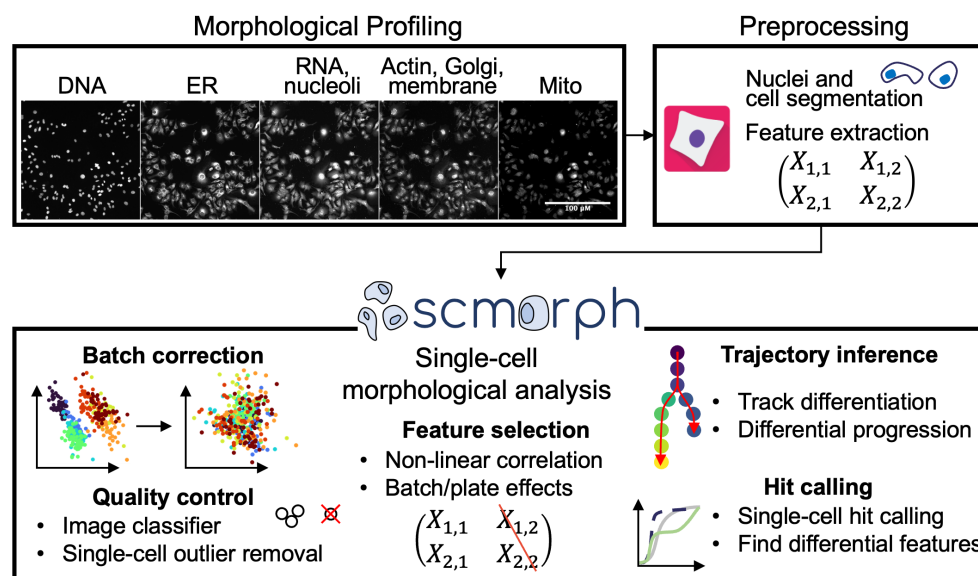
Figure 1: Overview of `scmorph` functionality. `scmorph` processes profiles generated with software such as CellProfiler to facilitate downstream analysis by performing batch correction, image- and single-cell QC, feature selection, hit calling and trajectory inference. All methods are built with single-cell analysis in mind and do not require subsampling.

In contrast to the commonly used `pycytominer` package (Serrano et al., 2025) and SPACe (Stossi et al., 2024), `scmorph` offers (i) interpretable batch correction techniques compatible with single-cell profiles, (ii) enhanced feature selection with an adapted Chatterjee correlation coefficient or Kruskal-Wallis test (Kruskal & Wallis, 1952; Lin & Han, 2021), (iii) lineage trajectory inference (Roux de Bézieux et al., 2024; Street et al., 2018), and (iv) the option to analyse multi-nucleated cells. Compared to `pycytominer`, `scmorph` also performs single-cell based hit calling. And unlike SPACe, `scmorph` is agnostic to the segmentation and feature extraction methods used upstream and therefore compatible with CellProfiler. `scmorph` also benefits from improvements of `AnnData` and `scanpy`, such as enabling out-of-core processing crucial to big data analysis (Virshup et al., 2024; Wolf et al., 2018).

Already, `scmorph` has been used to quality control morphological profiling experiments involving differentiating liver cells (Graham et al., 2025). `scmorph` is also involved in three projects involving small compound and microRNA perturbations in the domains of drug discovery and fundamental research, spanning datasets of >20M cells. Going forward, we envision that `scmorph` will enable analysis of complex and large morphological profiling experiments.

Acknowledgements

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