A059 · Agent-driven annotation and interpretation of morphological signatures in optical pooled screening

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Optical pooled screening (OPS) combines the scalability of pooled genetic perturbation with the phenotypic richness of microscopy-based imaging, using in situ sequencing to link each cell's genetic perturbation to its morphological profile at single-cell resolution. Interpreting these profiles remains a bottleneck in OPS analysis. Unlike transcriptomic readouts, which have reference gene sets, morphological features vary across screens and lack reference signatures for interpretability. We are developing scBrieflow, which departs from the convention of using perturbation-aggregated profiles to apply a variety of scverse tooling to single-cell OPS data. To scale interpretation of single-cell morphologies, we developed a companion harness, scb-explore, which provides a large language model agent structured access to the live embedding. The agent works through a constrained operation set, selecting cell populations though a variety query and feature-based rules, characterizing these cells by ranking discriminative morphological features, and rendering multi-channel image montages for inspection and hypothesis generation. Each call is recorded to yield a reproducible report. This tool allows supervised screen exploration to run autonomously. We show that scb-explore can distinguish biological signal from technical noise, curating generalizable feature profiles for cell populations of interest. It can also recover phenotypically defined populations that are not apparent from clustering alone. For example, scb-explore learns the phenotypic signature of multinucleated cells using feature-based gating and image inspection, then scores perturbations producing this phenotype. Thus, scb-explore extends OPS from population-level hit detection to automated, image-grounded discovery for powerful single cell interpretation of morphology-based functional genomics outputs.

Agent-driven annotation and interpretation of morphological signatures in optical pooled screening

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