

Robust morphology-based classification of cells following label-free cell-by-cell segmentation using convolutional neural networks

Gillian F. Lovell¹, Christoffer Edlund², Rickard Sjöegren², Daniel A. Porto³, Nevine Holtz³, Nicola Bevan¹, Jasmine Trigg¹, Johan Trygg², Timothy Dale¹, Timothy R. Jackson^{1*}
 1 Sartorius, Royston, SG8 5WY, UK. 2 Sartorius, Umeå. 3 Sartorius, Ann Arbor, MI
 * Corresponding author: Timothy.Jackson@sartorius.com

Introduction

- Light microscopy is a cost-effective, non-invasive, accessible modality for high-throughput live-cell imaging.
- Accurate segmentation of individual cells enables exploration of complex biological questions, particularly related to morphological change, but require sophisticated algorithms such as convolutional neural networks (CNNs).
- Many deep learning studies have limited amounts of quality training data.
- We previously reported on LIVECell, an open-source, high-quality, manually annotated and expert-validated dataset, comprising over 1.6 million annotated cells of 8 highly diverse cell types from initial seeding to full confluence, acquired on the Incucyte®.
- With minimal additional data, we fine-tune one of our publicly available LIVECell-trained models to enable quantitative analysis of complex morphological change associated with two applications, cell viability and differentiation.

Incucyte® Live-cell imaging and analysis systems

High-throughput Image Acquisition
Ideal for Deep Learning Applications
The Incucyte® generates thousands of high-quality HD phase images from a single experiment. Fluorescence imaging capabilities also facilitate data generation for validation purposes.

Integrated Software
Integrated software enables individual cells to be segmented, and analysis of single metrics (area, fluorescence within the cell).

Advanced Data Analytics
Incucyte® Advanced Label-free Classification Module enables quantification based on cell morphology; convolutional neural networks (CNNs) can be used for improved cell segmentation.

LIVECell enables morphological analysis of cells with minimal additional annotated data

Train CNN model on LIVECell
8 cell types
>1.6 million cells
>7000 images

Fine-tune model on small target dataset
700-3800 cells
15-70 images

Perform label-free cell segmentation on full experiment

Analyse morphology to classify cells

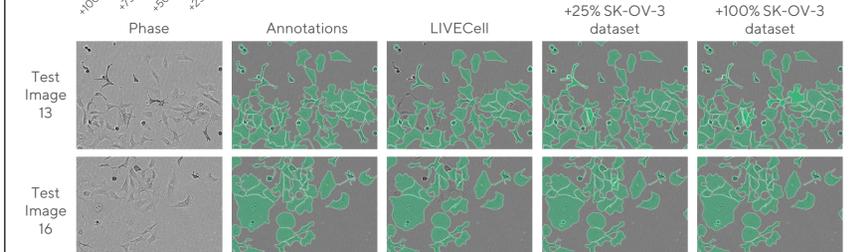
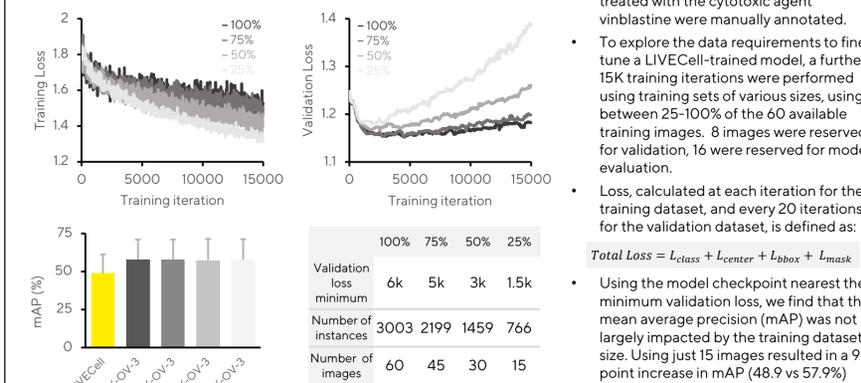
- LIVECell¹, an open-source, manually-annotated dataset, is used to generate a robust instance segmentation model trained to detect general cell features based on the CenterMask architecture².
- A small supplementary dataset is used to fine-tune LIVECell-trained models to learn cell features unique to a target application (e.g., differentiation, cell death).
- The final model is deployed to segment cells across a complete experiment.
- Using multivariate data analysis (MVDA) with common cell morphology metrics (e.g., size, intensity, texture and shape), we can measure morphological change in response to a treatment condition.

1. Edlund C¹, Jackson TR¹, Khalid N¹, Bevan N, Dale T, Ahmed S, Trygg J, Sjöegren R (in review). *Nature methods*. LIVECell: A large-scale dataset for label-free cell segmentation. *contributed equally. <https://sartorius-research.github.io/LIVECell/>
 Lee Y & Park J (2020). *Proc. IEEE/CVF Conf. Comput. Vis. Pattern Recognit. CVPR*. CenterMask: Real-Time Anchor-Free Instance Segmentation. 13906-13915.

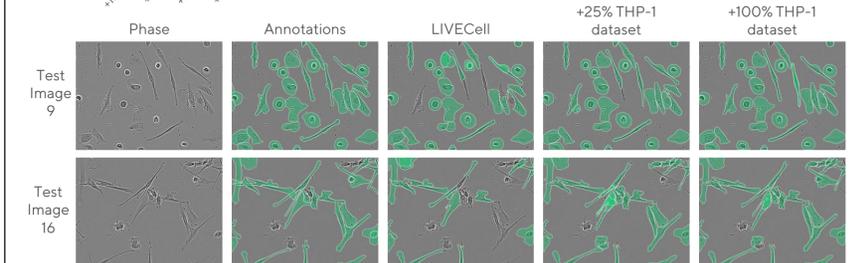
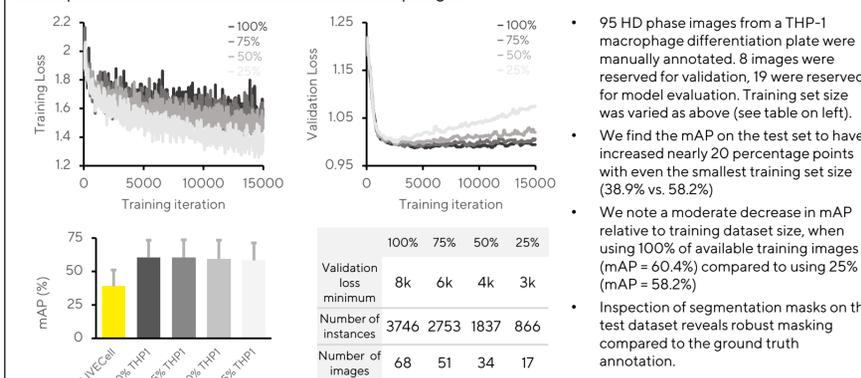
Application-specific CNN model fine-tuning

Improving the cell segmentation accuracy for specific applications requires minimal additional data to fine-tune LIVECell-trained CNN models

Example 1: Treatment-induced cell death in SK-OV-3 cells

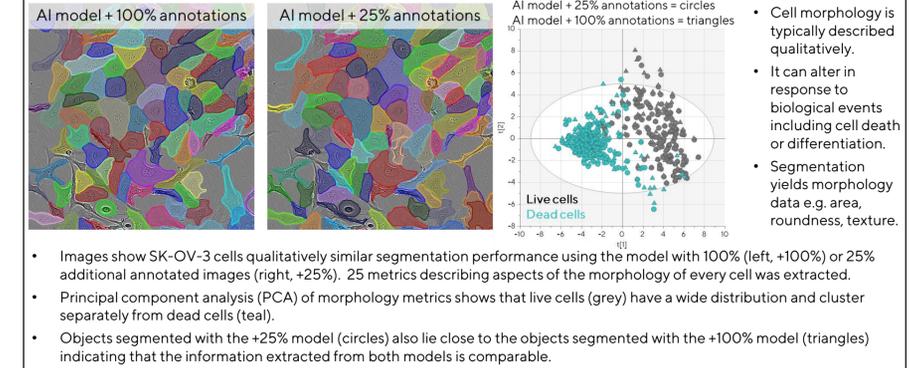


Example 2: THP-1 differentiation into macrophages

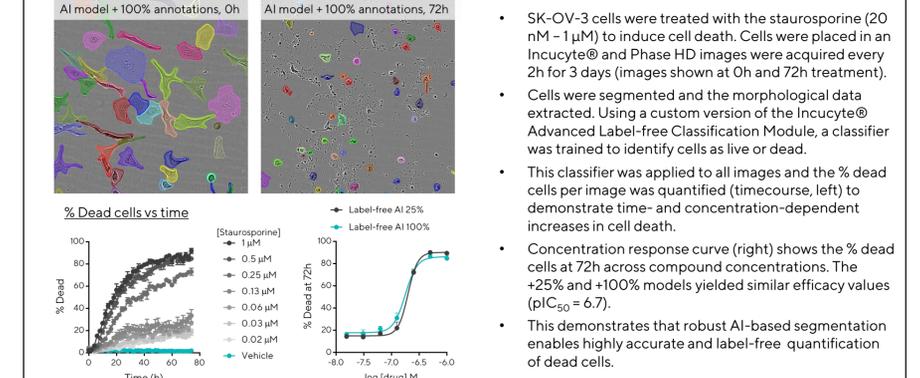


Segmentation data provides biological insight

Morphological information on cells can be derived from the cell segmentations



Cell viability can be quantified from cell morphology data using non-perturbing live cell imaging



Morphological data enables label-free quantification of monocyte differentiation

