Methods for High-Content, High-Throughput Image-Based Cell Screening

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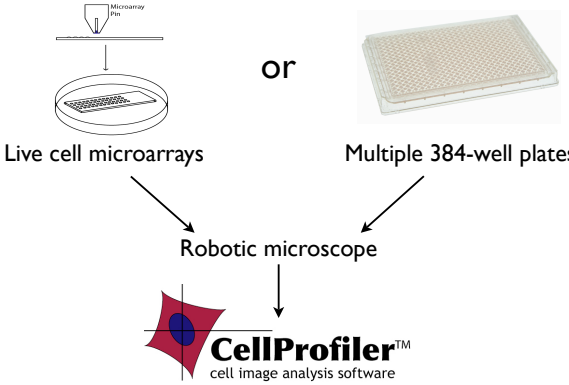
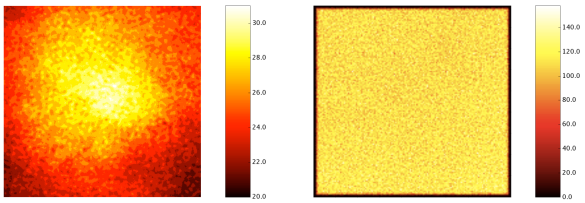
Our goal is to make meaningful biological predictions from large numbers of images of cells grown under different conditions (e.g., RNAi gene knockdowns).



Processing steps:

a) Illumination correction

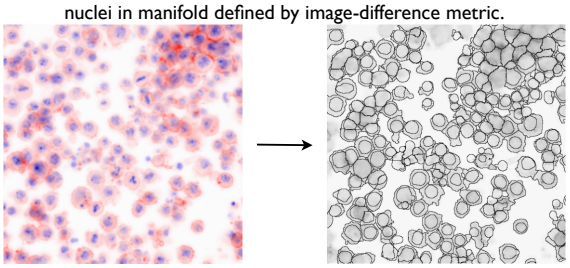
Estimate mean cell and stain distributions to find and correct illumination variation.



Mean DNA channel — Distribution of Nuclei

b) Segmentation

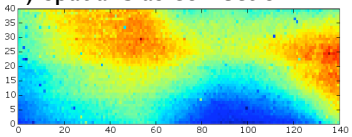
Identify nuclei, then cell boundaries as Voronoi diagram of nuclei in manifold defined by image-difference metric.



Jones et al, *Voronoi-Based Segmentation of Cells on Image Manifolds*, CVBIA, 2005

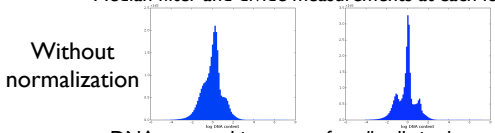
c) Measurement (cell shape, staining texture, etc.)

d) Spatial bias correction



Median per-cell DNA content, plotted by slide position

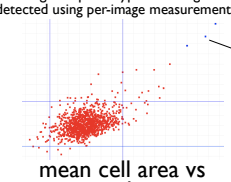
Median filter and divide measurements at each location:



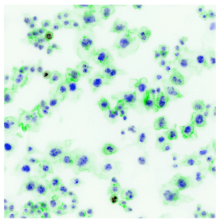
DNA content histograms for *all* cells in the screen

Analysis - Per-image

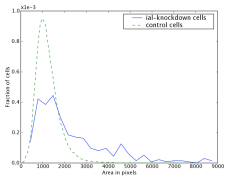
Dramatic changes in phenotype for a large number of cells can be detected using per-image measurements.



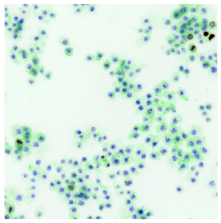
mean cell area vs mean nuclear area



ial knockdown



per-cell values

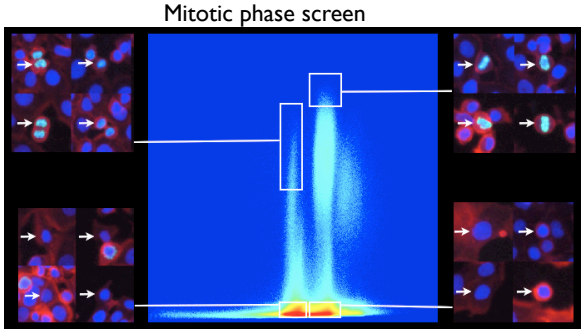


control

Analysis - Per-cell

Some phenotypes can be detected per-cell using a small set of measurements. Per-cell analysis is necessary because such phenotypes are often present in only a small fraction of cells per-image.

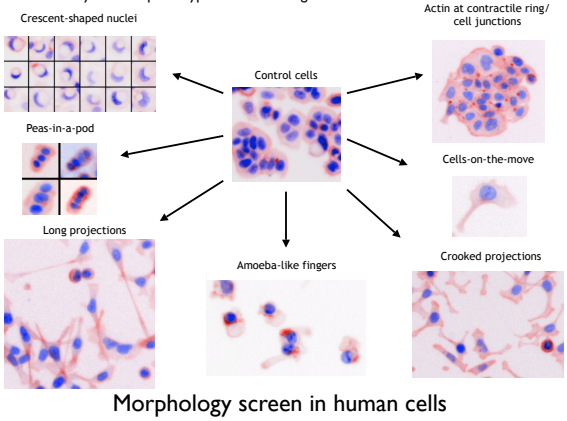
Mitotic phase screen



DNA vs phospho-histone H3 (mitosis marker)

Analysis - Automatic Classifier, per-cell

Other phenotypes require a complex combination of multiple features for identification. Machine learning, with training sets interactively created by biologists, allows automatic detection of a variety of visual phenotypes across all images in a screen.



Morphology screen in human cells

Per-cell approach gives better statistical power and more accurate predictions.

Biological verification and followup in progress.

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