Automating Cell Profiling of Drugs with Cell Painting

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High-Throughput Phenotypic Profiling

Cell Painting [1] is a high content microscopy-based morphological profiling assay that consists of six stains imaged in five channels and revealing eight cellular components: DNA, mitochondria, endoplasmic reticulum, Golgi, cytoplasmic RNA, nucleoli, actin, and plasma membrane. Using automated image analysis for segmenting and analyzing images of the cells, over 1500 cell morphology features can be measured to interpret morphological changes directly, or in AI modeling. Recently, the use of Deep Learning in the form of Convolutional Neural Networks (CNNs) operating directly on the raw images, eliminating the need for feature extraction with image analysis, has dramatically improved the accuracy of predictions [2,3].

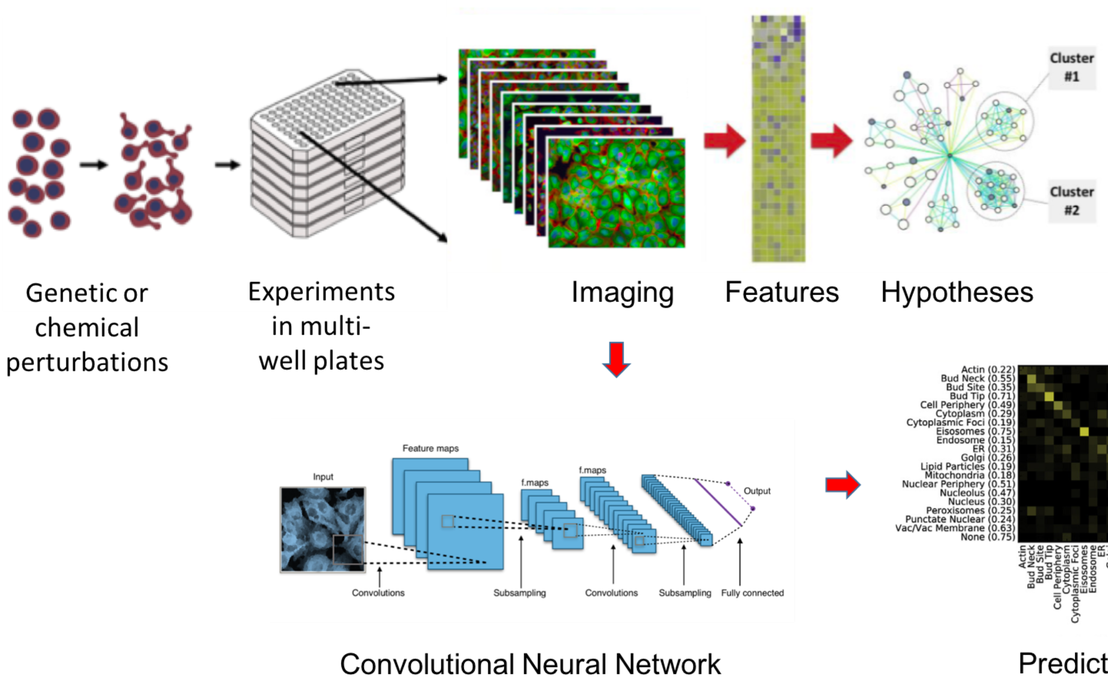

Figure 1. In Cell Painting [1], cells are seeded in multiwell plates and subjected to perturbations (e.g. treatment with compounds). After exposure time cells are fixed, stained and photographed in 5 channels with high-content microscope and the images are either subjected to an image analysis pipeline to capture phenotypic measurements (features/morphological profile), or the images can be directly used in AI/Deep Learning to predict e.g. mechanisms or pathways.

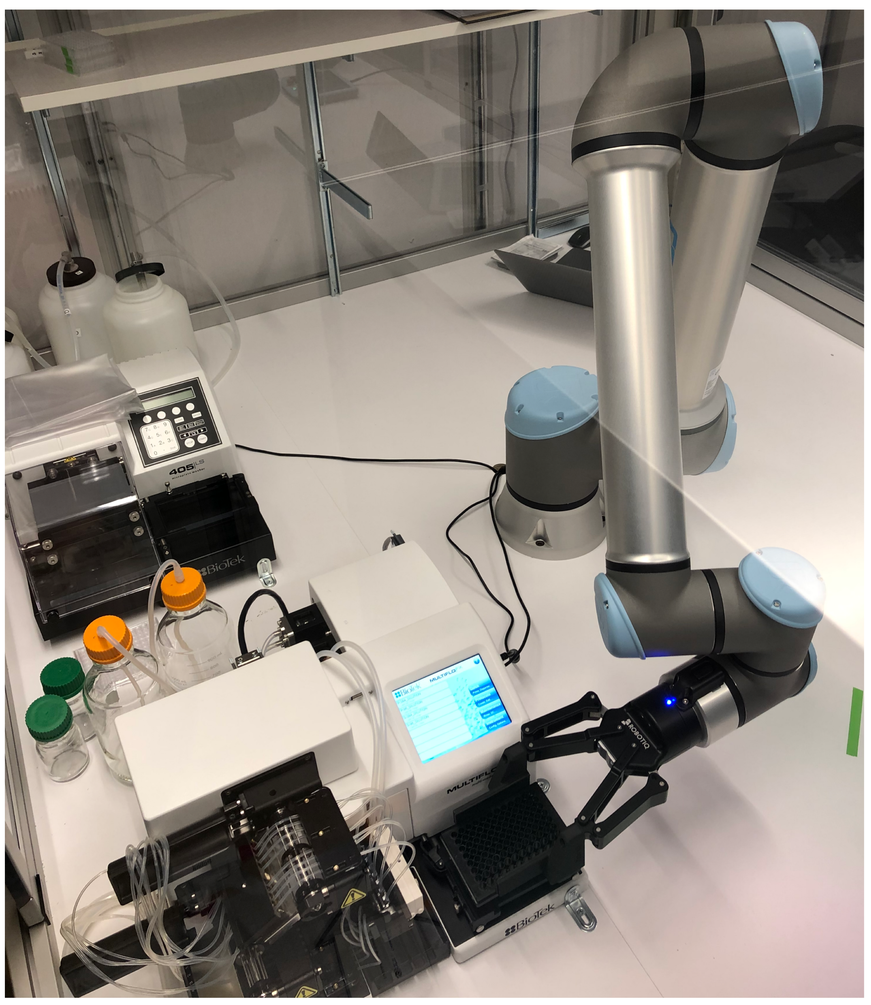

Figure 2. The lab instruments, such as washer and dispenser, are served by a plate robot (Universal Robots UR10e). A custom automation system is in development.

Equipment

We are establishing a robotized cell profiling platform with a high-content imaging microscope (ImagXpress XLS), liquid handling robot (OpenTrons OT-2), incubator, plate hotel, and a plate robot for automatic plate handling (Universal Robots UR10e), microplate washer (Biotek 405 LS) and microplate dispenser (Biotek MultiFlo FX). Computational equipment includes a local networked storage system (240 TB), two local servers (20+24 cores, 160+160 GB RAM), and a local GPU cluster (10 GPU cores, 20 CPU cores, 256 GB RAM) for demanding Deep Learning analysis.

Informatics and Modeling

We are building up an open source software stack for all components in the system. This includes drivers for all systems as well as developing automation software, data management systems and project/image visualizations (Figure 3). Services are deployed as microservices in a Kubernetes environment. For AI modeling on images we use Keras/Tensorflow via Notebooks. All source code is available on Github: https://github.com/pharmbio

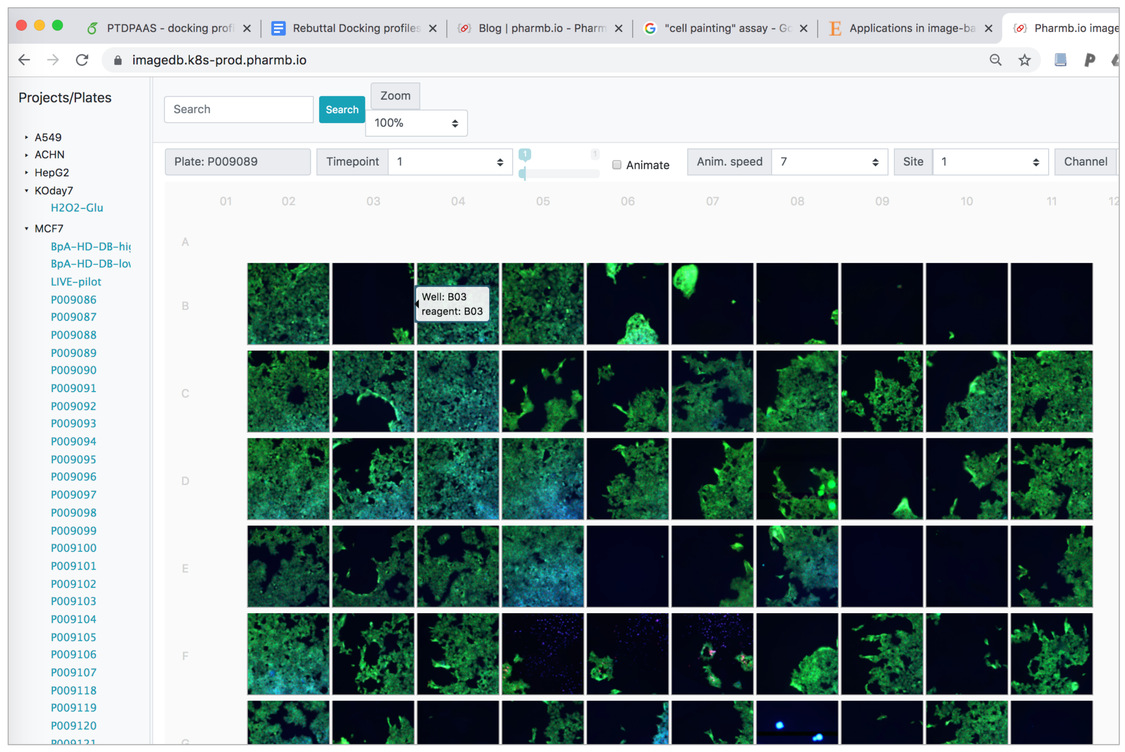

Figure 3. Screenshot from the developed project/image database, allowing for visual inspection of microplates in a web browser. Source code at: https://github.com/pharmbio

Targeted applications

We are using Cell Painting to group chemicals based on phenotypic profiles, predict mode-of-actions [3], investigate toxicity and we envision to use it in drug screening.

References

[1] Bray et al. (2016). "Cell Painting, a High-Content Image-Based Assay for Morphological Profiling Using Multiplexed Fluorescent Dyes". *Nature Protocols* 11 (9): 1757–74.

[2] Gupta A, Harrison PJ, Wieslander H, Pielawski N, Kartasalo K, Partel G, Solorzano L, Suveer A, Klemm AH, Spjuth O., Sintorn I, Wählby C. (2018) "Deep Learning in Image Cytometry: A Review". *Cytometry A*, cyto.a.23701.

[3] Kensert A, Harrison PJ, Spjuth O. (2019) "Transfer learning with deep convolutional neural network for classifying cellular morphological changes". SLAS DISCOVERY: Advancing Life Sciences R&D. 24, 4

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