High-content phenotypic screening of intracellular organelles organization using generative neural networks as tool for drug screening

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Technology

Disruption in cell organization determined by the cell's organelles composition in space and proper organelle-organelle organization leads to impaired cell function in many diseases. Thus, discovery of drugs that revert the cell structure and organization to its "healthy" state is an initial step in some drug discovery pipelines. High-content image-based screening is emerging as a powerful technology to identify phenotypic differences in cell populations with several applications including drug screening, Specifically, in the "Cell Painting" assay, each image is composed of five fluorescent channels marking different cell organelles, providing a rich morphological cell descriptor suitable to identify subtle phenotypes with high sensitivity using methods from the domains of computer vision and machine learning. While current computational approaches pool image-based features from all channels, here Dr. Zaritsky developed new methodology to measure alterations in the spatial dependencies between different organelles. This enables discovery and mechanistic interpretability of the effects each treatment has on specific aspects of cell organization in terms of "breaking" existing relations between multiple cell structures, which are currently inaccessible. The novelty stems from the computational definition of quantitative measures designed to capture perturbation-induced alterations in the spatial inter-organelle organization. For a POC, they relied on high quality large-scale publicly available high-content imaging-based screening datasets. They trained generative neural networks to map different combinations of 4-to-1 fluorescent channels in control cells and quantify the alteration following a perturbation in relation to the control condition. The results indicate that this approach is feasible, and that spatial organelle dependencies are more sensitive, specific and interpretable readouts for phenotypic cell screening. Specifically, they demonstrated that (1) known phenotypes are amplified making it easier to identify subtle phenotypes, (2) new phenotypes that are missed by traditional analyses can be discovered, and (3) spatial dependencies are differentially determined based organelles composition and perturbation, implying a more specific and interpretable readout.

Application

High content phenotypic screening as additional tool for drug discovery.

Advantages

- Platform that can be used for different drugs screening
- 5-channels readout
- Features relevant functionality
- Easier to identify subtle phenotypes
- New phenotypes that are missing by traditional analyses

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