REVOLUTIONIZING BIOMEDICAL RESEARCH: INTEGRATING CUTTING-EDGE AI/ML TO UNLEASH INNOVATION IN DRUG DISCOVERY AND THERAPEUTICS DEVELOPMENT

Self-supervised Deep Learning Uncovers the Semantic Landscape of Latent Mitochondrial Phenotypes in Human Organoids to Reshape the Future of Drug Development and Diagnostics

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We aim to revolutionize pharmaceutical research by integrating organoids, advanced microscopy, and artificial intelligence into a novel drug discovery and diagnostics pipeline. Specifically, we use human lung and intestinal organoids to understand and diagnose chemical and biological threats and identify potential treatments.

Human stem cell derived lung and intestinal organoids recapitulate the epithelial lining of human lungs and intestines, creating accessible models for understanding human cell biology under specific conditions, such as exposure to pathogens or toxic substances. Typical methods for analyzing these organoids often only explore single, terminal time points and can lose spatial information. Confocal microscopy can visualize the subcellular environment, but only briefly because of its damage to the sample and rapid photobleaching effects.

We use lattice light sheet microscopy (LLSM) to capture 4D (x,y,z,time) data with low photo-toxicity and high spatio-temporal resolution. LLSM allows us to capture terabytes of 4D data in live organoids, in particular their mitochondrial morphology and dynamics. Mitochondria form an interconnected network around the cell that changes over time. This network provides 95% of the energy in the human body and regulates key cell signaling pathways, such as their response to apoptotic stressors and inflammatory mechanisms. Changes in cellular health as a result of pathogens or toxic substances can manifest as changes in the mitochondrial network.

By eye, these changes appear to be on a single axis of fragmented to fused. However, we have identified additional axes with which to classify mitochondrial phenotypes using self-supervised deep learning. This “MitoSpace” is a latent space that encodes information of how mitochondrial (and thus cellular) health is linked to mitochondrial phenotypes using unbiased image analysis. We applied 20 drugs with a variety of specific perturbations on subcellular activity to view the full range of mitochondrial phenotypes and separated them using self-supervised deep learning methods. We pair our understanding of drug mechanisms with mitochondrial phenotype and where correlated images lie in the MitoSpace to define new descriptors that are useful in biological research.

The integration of 4D organoid data from LLSM with MitoSpace allows us to accelerate drug discovery and diagnosis. Using organoid MitoSpace, we can screen drugs in relevant model systems and understand how their effects relate to each other, run human toxicity studies and predict mechanisms of action for known and unknown chemical and biological threats, and inform drug dosages using both novel and known medical countermeasures. This pipeline can be extended beyond lung and intestinal organoids to include brain, skin, and any other organ of interest. Ultimately, we believe this pipeline will reshape the drug discovery landscape by evaluating tissue-level changes at subcellular resolution in live human organoids and utilizing AI to extract the most pertinent information.