Machine learning and light-sheet fluorescence microscopy reveals morphometric indicators in organoids for informed anti-cancer drug discovery

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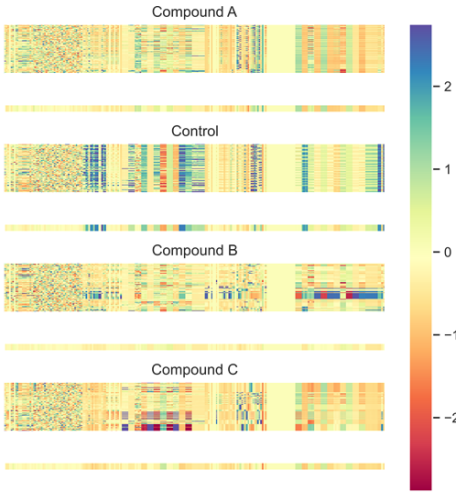

Figure 1. *After segmentation* each cell nucleus is represented by 400 shape and texture features. Each row represents a different nucleus, the colour bar shows the amplitude of each feature, each column a different feature. The single row below each compound is the median feature profile for each drug.

Recent advances in organoid culture and fast-volumetric imaging technology have facilitated previously inaccessible phenotypic characterisation of disease aetiology. Here, we present a combined methodological and analytical pipeline for detecting and quantitating the efficacy of chemotherapeutic-drug-induced morphometric differences in human-derived colorectal malignant tumour organoids[1]. Patient-derived organoids, which more closely mimic the complexity of the *in vivo* environment than traditional cell cultures, have been shown to be a good predictor of therapeutic response[2] and also offer potential for personalised medicine. By using a customised commercial airy-light-sheet microscope[3], we were able to rapidly record (~0.2Hz) the spatial fluorescence distribution of large specimen volumes (~1mm^3), enabling us to screen chemotherapeutic compounds in relatively large sample sizes (n > 200 organoids). We show how applying data-mining techniques to these rich volumetric imaging datasets can provide a series of measures of therapeutic efficacy[4] and compare our results to traditional screening assays. Furthermore, we propose a machine-learning derived titration-invariant drug similarity measure, which can be used to correlate the effects of different drug treatments with potential application in large-scale drug discovery programs.

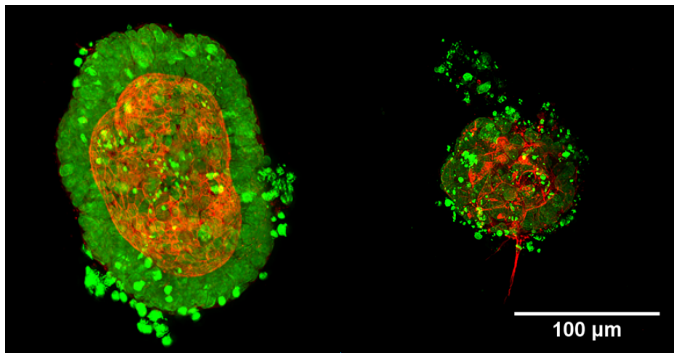

Figure 2. *Representative light sheet fluorescence microscopy images of colorectal cancer organoids, stained for DNA (DAPI, green) and F-actin (phalloidin, red). Left panel shows an untreated organoid and right image shows the same organoid type treated with an anticancer therapeutic.*

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