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A PLATFORM FOR HIGH-THROUGHPUT MONITORING OF SINGLE CELL AGGREGATION AND SPHEROID FORMATION

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Summary: It has been increasingly shown that monolayer cultures and whole-animal models are associated with limitations for the prediction of in vivo tissue responses. Therefore, laboratories are tending towards three-dimensional (3D) cell cultures grown in vitro, and especially spheroid cultures, as a model of native tissues. Moreover, in the field of tissue engineering, spheroids are being investigated for the in vitro fabrication of functional tissues and organs. During spheroid formation and maturation, spheroid morphology is considered an important characteristic, and is often captured using microscopy. In literature, several image analysis strategies have been proposed for the automatic extraction of morphological features of readily formed spheroids. However, these are still limited in their throughput and are not adapted to continuous monitoring of the cell aggregation kinetics present at the onset spheroid formation. Therefore, our goal is to develop an automated system for non-invasive, high-throughput monitoring of the morphological changes during this initial state of single cell aggregation to spheroids.

Agarose inserts, patterned with cylindrical, flat-bottomed micro-wells, were used for spheroid production. The morphological changes were captured using a wide field microscope equipped with a bright-field objective (4X), incubator chamber and motorized stage. A software tool was developed to automatically process the acquired images, thereby extracting morphological features (i.e. area and circularity) of each spheroid. The segmentation approach was quantitatively validated on four sets of ± 60 spheroids, including 100 and 250 cell-sized spheroids after seeding and 16 hours of aggregation. As a proof of concept, more than 1000 individual aggregation processes were monitored over time for three different types of agarose and the abovementioned spheroid sizes.

The sensitivity and precision of the automatic segmentation process, obtained by averaging over the predefined sets, were respectively 97.11 ± 2.14% and 97.28 ± 1.00%. In addition, the relative errors for the area and circularity were 1.82 ± 1.79% and 3.24 ± 2.76%, respectively. The accuracy of our method was comparable to other systems, while the achieved throughput significantly outperformed them. Therefore, the developed system has the potential to provide more insight in cell aggregation kinetics and allow for monitoring of spheroid formation during large-scale production.