muTish–Tools to Monitor and Handle Medium Sized Biological Entities

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A cell sorter and SmartPlate are being developed to monitor and handle medium sized biological entities, such as 3D human tissue models or cell clusters to fill gaps in high throughput screening for drug development and toxicity testing. The spheroid entities in a size range of 50 to 800 um can be characterized on-the-fly by real-time imaging, fluorescence detection and multi-frequency impedance analysis and be dispensed into multi-well plates, such as the SmartPlate where the solution in which the biological entities are dispensed is monitored for pH, glucose and lactate levels as indicator for the ongoing metabolism.

Artificial microtissues or 3D cell clusters can be used as models for replacing, reducing and refining animal testings in drug development and toxicology. However, tools for reproducible and automated handling of such biological samples are hardly available, or are very expensive. Thus, CSEM combined its expertise in fluidics, optics, sensor systems, machine learning, printed electronics, and electro chemistry, to develop new tools to monitor and handle medium sized biological samples under the umbrella of the CSEM CellFactor-technology[1]. A cell sorter is being developed which analyzes unlabeled samples using imaging or impedance analysis while tagged entities can be observed by fluorescence. Samples of interest can be individually dispensed into a multi-well plate. Furthermore, printed electrochemical sensor are being integrated into a multi-well plate creating the SmartPlate. The SmartPlate records pH, glucose and lactate levels in solution in order to monitor the metabolism of the samples over a long period of time for quality control.

Within the cell sorter, samples with a size range of 50 to 800 um are moved by a pressurized sample container. An additional sheath flow is used to center and align the samples for the detectors, where samples of interested can be dispensed into a multi-well plate by a short cross flow. Remaining samples are moved towards a second sample container.

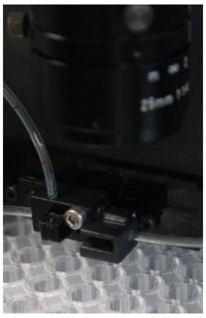

Figure 1: Detection/sorting unit of the cell sorter where fluorescence detection and imaging take place.

The built-in detectors are aligned along the sample path within the flow cell (see Figure 1) and use

- High-speed image analysis processed on a GPU (graphical processing unit)
- Fluorescence detection in combination with a lock-in amplifier (see Figure 2)
- Dual-frequency impedance analysis in combination with a lock-in amplifier

[1] S. F. Graf, *et al*., "Table-top classification and sorting system for small model organisms", in this report, page 54.

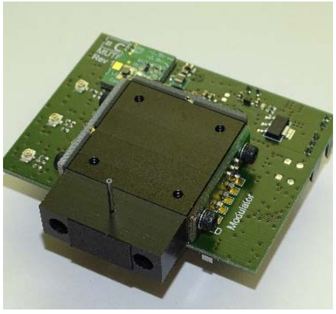

Figure 2: Fluorescence module with optical setup and electronic board with integrated digital lock-in amplifier.

The SmartPlate (see Figure 3) uses printed electrodes with conductive vias to monitor the samples in the well and read out the signals. The electrodes are biochemically modified with stable functional layers sensitive to pH, glucose and lactate.

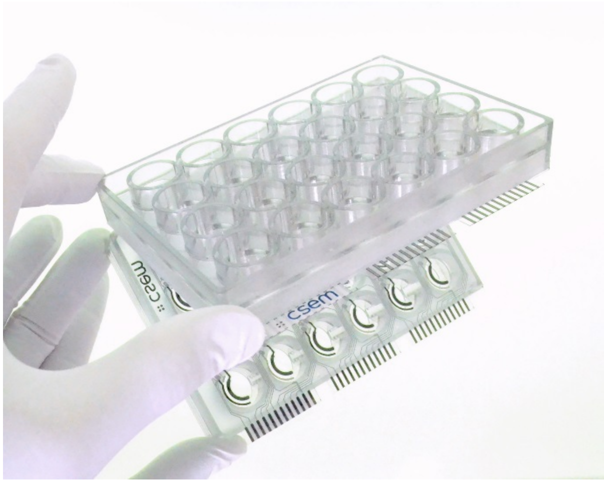

Figure 3: 24-well SmartPlate with printed and biochemically modified electrodes on the inside of the well contacted through condutive vias towards the outside to measure pH, glucose and lactate levels.

The technologies described were designed in close contact with our lead users hepia and FGen which work with neurospheres and alginate beads, respectively.

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