BIOPROCESS CHARACTERIZATION AT THE MICRO-SCALE: OPTICAL SENSOR INTEGRATION IN A NOVEL CAPILLARY-WAVE MICRO-BIOREACTOR

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Due to the high demand of new biopharmaceuticals and bioproducts, the development of new cultivation platforms for high-throughput screenings, cell-based assays and bioprocess development is of high interest. Therefore, micro-bioreactors (MBRs) are a promising alternative to conventional cultivation platforms like shake flasks due to their minimal volume, sensor integration and high ability for automatization and parallelization. Especially, MBRs with a volume below 10 µL can reduce the amount of needed testing substances for cell-based assays, which is advantageous mostly for testing new biopharmaceuticals with limited availability. However, characterization of a cell culture in the lower micro-liter scale is challenging due to the limited space and the insufficient volume for sampling and offline analysis. Optical sensors are one suitable possibility to close this gap. Therefore, a novel capillary-wave micro-bioreactor (cwMBR) with a working volume of 7 µL and optical sensors for biomass, glucose, oxygen, pH and fluorescence intensity measurement was developed.

The cwMBR consists of a Foturan® glass slide with a round cavity holding a 7 µL droplet of cultivation medium, which is placed in 3D-printed mounting ensuring fixation and minimal evaporation of the droplet (Figure 1). Mixing and adequate oxygen supply of the droplet is achieved by vertical oscillation of the cwMBR, which induces capillary waves on the droplet surface (Frey et al. (2020), Meinen et al. (2019)). Process characterization within the cwMBR is enabled by optical sensors connected to read-out devices via optical fibers. An USB spectrometer enables fluorescence intensity and scattered light measurement for cell-based assays and biomass determination. Therefore, specific LEDs are connected to the cwMBR for excitation via optical fibers. Furthermore, oxygen, pH and glucose can be quantified by optical sensor spots, which are read-out by a conventional Firesting fluorimeter. The oxygen sensor contains oxygen sensitive, luminescent particles in an urethane hydrogel. Comparable to the oxygen sensor, the separated glucose sensor contains identical particles but is supplemented with glucose oxidase and a diffusion barrier for glucose. The glucose sensor measures the oxygen uptake of the glucose oxidase in presence of glucose, which is proportional to the glucose concentration up to 20 mM. Furthermore, a pH sensor containing fluorescent aza-BODIPY indicators was integrated. The setup enables full bioprocess characterization within a minimal volume by removable and easy-installable optical sensors for single or multiple application depending on the application time.

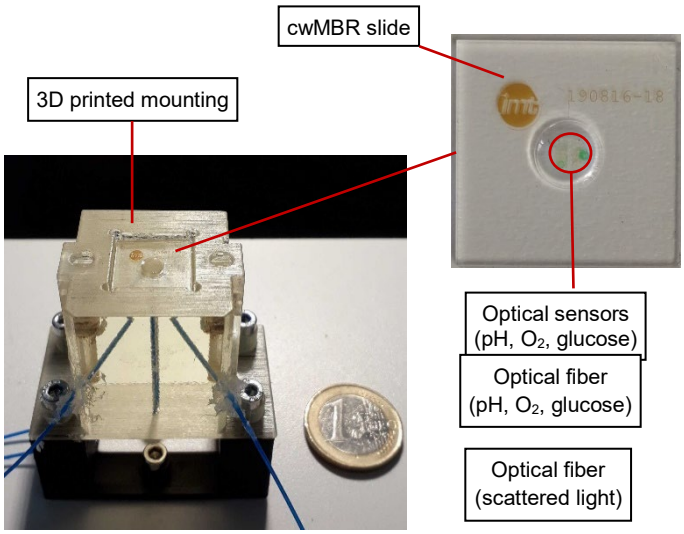

Figure 1: cwMBR platform with integrated sensors.

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