Miniaturized Calorimeters - a Valuable Tool for Bioprocess Analysis

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Calorimetry is a powerful tool for analyzing biochemical processes e.g. enzyme catalyzed reactions and metabolic activities of microorganisms or living cells. Because heat production is not reaction specific calorimetry is applicable to a wide range of reactions and does not require any labeling or immobilization of the reactants.

The invention of miniaturized, silicon chip based calorimeters opened new opportunities. Recently, several authors have shown the possibility of detecting the metabolic heat production of micro-organisms held inside miniaturized, silicon chip based calorimeters. The activity of an ensemble of only ten mammalian cells was measured by JOHANNESSEN [1] using a micro-machined chip calorimeter cell of 720 pl volume. HIGUERA-GUISSET et al. [2] developed a special chip-calorimetric device to monitor the growth of a bacterial culture over several hours.

In the presented talk an overview of the technical features of chip calorimeters will be given including a general discussion of rules and limitations for their application in bioprocess analysis. With a newly developed flow-through chip calorimeter system [3] we demonstrated the suitability of miniaturized calorimeters for its incorporation into technical relevant bioprocesses as a monitoring device. The calorimeter is sensitive enough to detect metabolic heat production rates in microbial suspensions of only a few micro-liters. Due to the limited time constants, a fast on-line operation in connection with bioreactors is possible even for aerobic processes. The high flexibility of the calorimetric systems enables the implementation of the calorimetric chip transducers into external technical systems.

As examples for the monitoring of aerobic and anaerobic processes, the growth of *Escheria coli* DH5α and *Halomonas halodentrificans* CCM 286^T cultures, respectively, were calorimetrically determined [4]. Periodically, small quantities of bacterial suspension were taken out of a bioreactor and transferred into the calorimetric chip transducer of the system. The actual heat production rate of the bacterial culture was indicated with a time delay of less than five minutes. The time dependence of the heat production rate was sufficiently described by established thermokinetic models and agreed very well with the off-line determined carbon-distribution of the assimilated carbon-substrate.

In a second example, the high flexibility of the chip calorimeter system was demonstrated by measuring the metabolic activity of a biofilm, which was established inside the calorimetric chip transducer. In contrast to quartz micro-balances, which are possible sensors for the on-line detection of biofilm growth, calorimetric chip transducers could indicate the degree of activity of the contamination inside the tubing. As a proof of the principle, the internal surface of several calorimetric transducers was externally loaded with *Escheria coli* DH5α. Then, the metabolic activity of the bio-film was tested by injecting carbon-substrate solution into the calorimetric chip transducer, which already had been installed inside the calorimeter.

References

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