

## Disposable Sensors for On-Line Monitoring in Disposable Bioreactors

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The pharmaceutical industry produces high-value drugs with the help of bioreactors. In view of controlling the production and insure the quality of the biomolecules, the present work goes in the direction of monitoring the bioreactor by developing disposable, single-use glucose, and pH sensors.

Synthesis of bioactive molecules in bioreactors is nowadays routinely performed using single-use bioreactors. Control of the production lines in pharmaceutical companies is, however, still being performed with the same methods used in non-disposable bioreactors: by using traditional sensors which need to be sterilized and calibrated before each batch, or by sampling of the medium.



Figure 1: The online cell culture monitoring system CITSens Bio, adapted for the use in a T-flask.

The company C-CIT AG offers ready to use, pre-calibrated, pre-sterilized plastic-based sensors which are disposable, plug and play, and do not require any preparation (Figure 1). As they are single-use, the risks due to batch-to-batch cross-contamination are avoided, as well as the time consuming preparation and re-calibration between runs. The data acquisition system is connected wirelessly to a server for data storage and on-line remote monitoring for up to 2 weeks.



Figure 2: Screen-printed dual electrode sensors for multiple parameter monitoring.

Since the market launch, users of the CITSens Bio system expressed a strong demand for a multi-parameter system. To respond to this need, combined sensors for glutamate/lactate and pH/ammonium are being developed (Figure 2).

The new generation of glucose sensors shows improved sensitivity and reproducibility in respect to the first generation sensors, with a sensitive range of 0.2-12.6 g/l, a resolution of 0.18 g/l and a sensitivity of approx. 57nA/(g/l) (Figure 3).

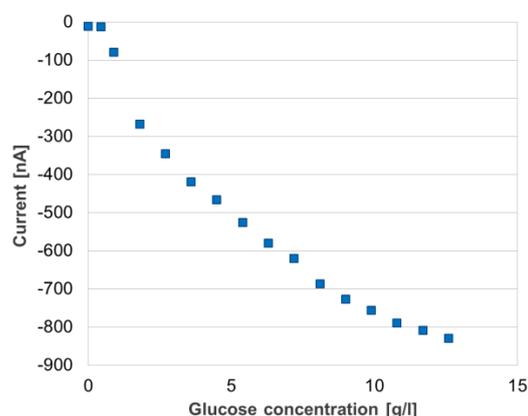


Figure 3: Calibration curve for glucose in buffer solution.

All-solid-state pH sensors are being developed and characterized in both calibration solutions and in cell culture. The sensors functional lifetime in cell culture conditions ( $T=37^{\circ}\text{C}$ , 100% humidity, 5%  $\text{CO}_2$ ) has been verified for up to 2 weeks. Sensors, gamma-sterilized before usage, are linear in the pH range from 3 to 9 for up to 16 days with a reproducible Nernstian sensitivity of 60 mV/pH unit.

Measurements in yeast cultures showed good correlation between the data provided by a traditional Mettler Toledo pH probe and the C-CIT all-solid-state disposable sensor (Figure 4).

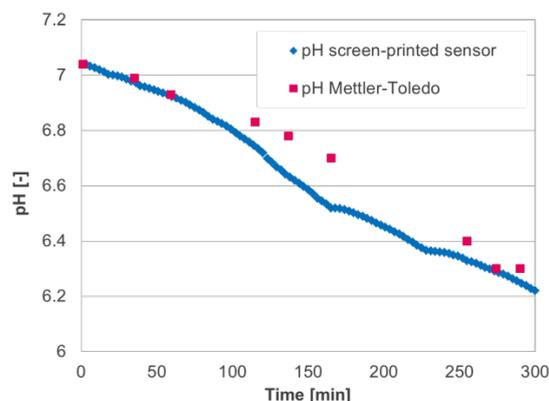


Figure 4: Correlation between the pH measurements in a yeast cell culture performed by a Mettler Toledo pH probe and the C-CIT pH screen-printed sensor.

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