

Real-time Cell Density Measurement for PAT Applications

Total and Viable Cell Density In-situ Monitoring for Biopharma R&D

Industry: Biopharma R&D

Application: Perfusion and batch production of mAb using CHO cells

Hamilton products: Incyte and Dencytee

Improve Bioreactor Productivity through Real-time Measurement

The biopharmaceutical industry is constantly trying to gain a deeper understanding of their processes to improve productivity. A good example of this are initiatives such as the 2004 Process Analytical Technology (PAT) from the FDA.

During the production of monoclonal antibodies (mAb) control of the bioreactor throughout all phases of cell growth is critical to increase yield. Over time these control parameters have changed from discrete off-line measurements to continuous in-situ measurements. Continuous measurement in the bioreactor is already common for variables such as pH and dissolved oxygen. Recently more complex measurement parameters such as Total Cell Density (TCD) and Viable Cell Density (VCD) have entered the market. Studying these new parameters allows further monitoring and automation such as precise regulation of the nutrient feed based on the growth rate of cell cultures.

The Cell Culture Research Team of the University of Bielefeld (Germany) is actively studying the applications of new technologies to bioprocesses understanding. Part of their studies focuses on testing innovative in-situ sensor technologies.

In-situ Measurement of Total and Viable Cell Density

Bielefeld's Cell Culture Research Team set about to compare the accuracy of in-situ versus offline cell density measurements. They conducted both perfusion and batch experiments using CHO cell cultures for monoclonal antibody production.

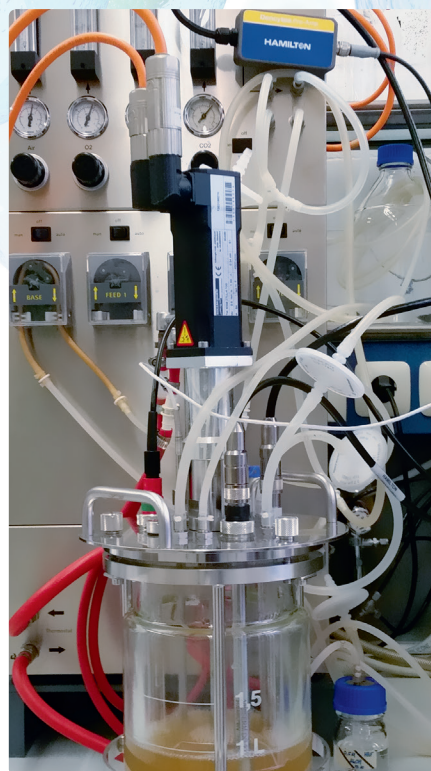


Figure 1: Set-up of the experiments and Incyte sensor's detail.

Their experiment involved a 2L bioreactor with pH and pO₂ variables kept constant throughout the runs. Cell growth was monitored inside the same bioreactor using two different cell density sensors in parallel (Fig. 1 and 2).

One Incyte sensor was used to measure viable cells based on permittivity. The total cell density was measured, as well, using a Dencytee sensor: the parameter was determined by an optical measurement of turbidity at 880 nm wavelength.

Throughout each experiment, off-line cell culture measurements were taken daily to provide comparison data.

Results

Good correlation between off-line measurements and data obtained from the Incyte and Dencytee sensor were observed in the growth phase for all experiments. The viable cell density measurement from the Incyte sensor highlighted higher accuracy in the log phase. In the perfusion cell culture

Benefits of Incyte and Dencytee Cell Density Measurement

- Continuous, accurate measurement of the cell growth enabling real-time control
- Better insight about cell health based on the parallel measurement of TCD and VCD
- Reliable and stable measurements for long-lasting continuous fermentations

correlation between in-situ and off-line measurements carried through for the death phase as well.

By measuring both TCD and VCD in parallel, it has been possible to verify that the bioprocess conditions have been ideal: the viable cell density signal being really close to the total cell density one.

The results of the three experiments are presented in the graphs (figure 3 and 4). The continuous green and blue lines represent the continuous measurement of VCD and TCD with in-situ sensors. The discrete red dots represent the daily measurement with the off-line reference method. In order to facilitate the performance comparison, the TCD raw data have been scaled to the VCD ones.

The experiments demonstrated:

- The real potential of in-situ cell density measurement. Compared to the off-line reference method, the Incyte and Dencytee allow a continuous and accurate measurement of cell density providing instant information about the status of the cell culture.



Figure 2: Dencytee sensor's detail



- The potential for rich, real-time process data by parallel measurement of the TCD and VCD signals and comparison with each other.
- The capability to deliver reliable and stable measurements independently from the process set-up. Either for shorter batch-processes as well as for long-lasting perfusion processes, the performances are the same.

The results prove that Incyte and Dencytee Cell Density Sensor are reliable tools to provide valuable measurement data for both R&D bioprocess as well as PAT tools in production.

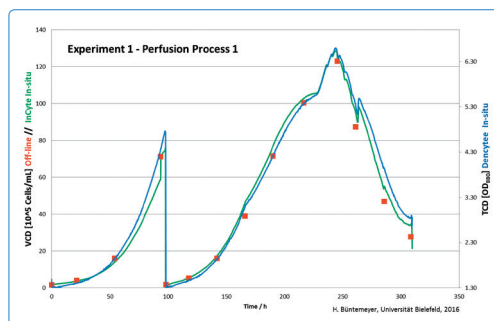


Figure 3: Performance comparison of cell density measurement for the perfusion set-up.

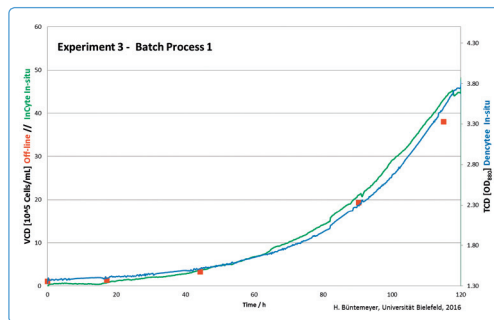


Figure 4: Performance comparison of cell density measurement for the batch set-up.

Authors

Dr. Heino Büntemeyer, Anica Schmidt

Zellkulturtechnik, Technische Fakultät, Universität Bielefeld
Universitätsstr. 25
33615 Bielefeld, Germany
www.cellculturetechnology.de

© 2017 Hamilton Bonaduz AG. All rights reserved.

[REF] 695234/00 — 11/2017

HAMILTON

Web: www.hamiltoncompany.com

USA: 800-648-5950

Europe: +41-58-610-10-10

Hamilton Americas & Pacific Rim

4970 Energy Way
Reno, Nevada 89502 USA
Tel: +1-775-858-3000
Fax: +1-775-856-7259
sales@hamiltoncompany.com

Hamilton Europe, Asia & Africa

Via Crusch 8
CH-7402 Bonaduz, Switzerland
Tel: +41-58-610-10-10
Fax: +41-58-610-00-10
contact.pa.ch@hamilton.ch

To find a representative in your area, please visit www.hamiltoncompany.com.