

# Real-Time VCD Monitoring of Moss for Therapeutic Protein Production

## In-line Measurement of Viable Cell Density in a Photobioreactor

**Industry:** Biopharma Production

**Application field:** Control of Filamentous Moss Culture

**Hamilton products:** Incyte and ArcView Controller

## Innovative Bioprocesses for Therapeutic Protein Production

Monoclonal antibodies (mAbs) and therapeutic protein are established as some of the most important biopharmaceutical products available today. Manufacturing of such products requires the establishment of robust and reproducible processes. Mammalian cell cultures routinely perform well, yet the biopharma industry still has a need for a more reproducible and facile alternative. In this context, the German Company Greenovation developed BryoTechnology, a next-generation, cGMP-compliant manufacturing technology using moss cultures for biopharmaceutical production. The technology exploits the unique advantages of the moss *Physcomitrella patens* as part of a proprietary plant system to enable production of a wide range of biopharmaceuticals. The first moss-made biopharmaceutical successfully accomplished clinical phase-I testing in November 2017.

In all production processes (traditional mammalian and more innovative moss-based), growth rate and production rate are key evaluation parameters of culture performance. Many factors, such as light and nutrition, can influence the performance of the moss culture. Therefore, a fast and reliable measurement of viable cell density is necessary for process optimization and, at a later stage, to guarantee stable and robust production. Off-line measurements are too time-consuming and do not accurately reflect the moss cell density in the bioreactor. Moss cultures grow in filaments, causing aggregation. Without distinct individual cells, an accurate correlation between the off-line measurement and in-situ signal may be difficult to accomplish. Real-time monitoring offers the option for constant control strategies, as enforced by Process Analytical Technology (PAT) from the US Food & Drug Administration (FDA).

### Benefits of Incyte

- Accurate in-line growth determination in moss cultures over longer process time
- Reliable measurement of filamentous moss cultures' growth
- Easy installation and usage

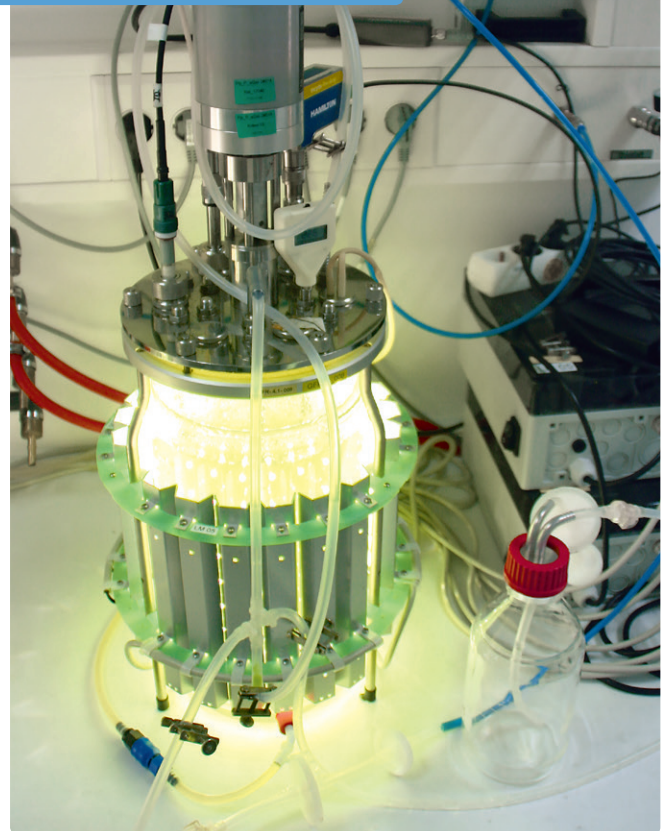


Figure 1: Small-scale photobioreactor implementing the BryoTechnology for therapeutic protein production.

The in-line cell density (permittivity) signals were compared with the off-line cell dry weight in g/L. Permittivity was also compared to other process parameters, such as concentration of important nutrients, pH, and light intensity for process optimization.

### In-line VCD Monitoring Performances

The values of in-line viable cell density and off-line total cell density obtained for the bioreactor set-up are shown in Figure 2. The in-line monitoring of Incyte shows a good comparability

to the off-line method. Deviations are assumed to be due to the total biomass determination in the off-line measurement in contrast to the viable cell determination in the in-line measurement. Further runs should be performed for a determination of the measurement methods. The signal showed high stability all along the bioprocess. Integration into the process control system is planned for automated regulation of harvesting and continuous processing. These results show that permittivity sensors can successfully be used for real-time monitoring of filamentous moss viable cell density.

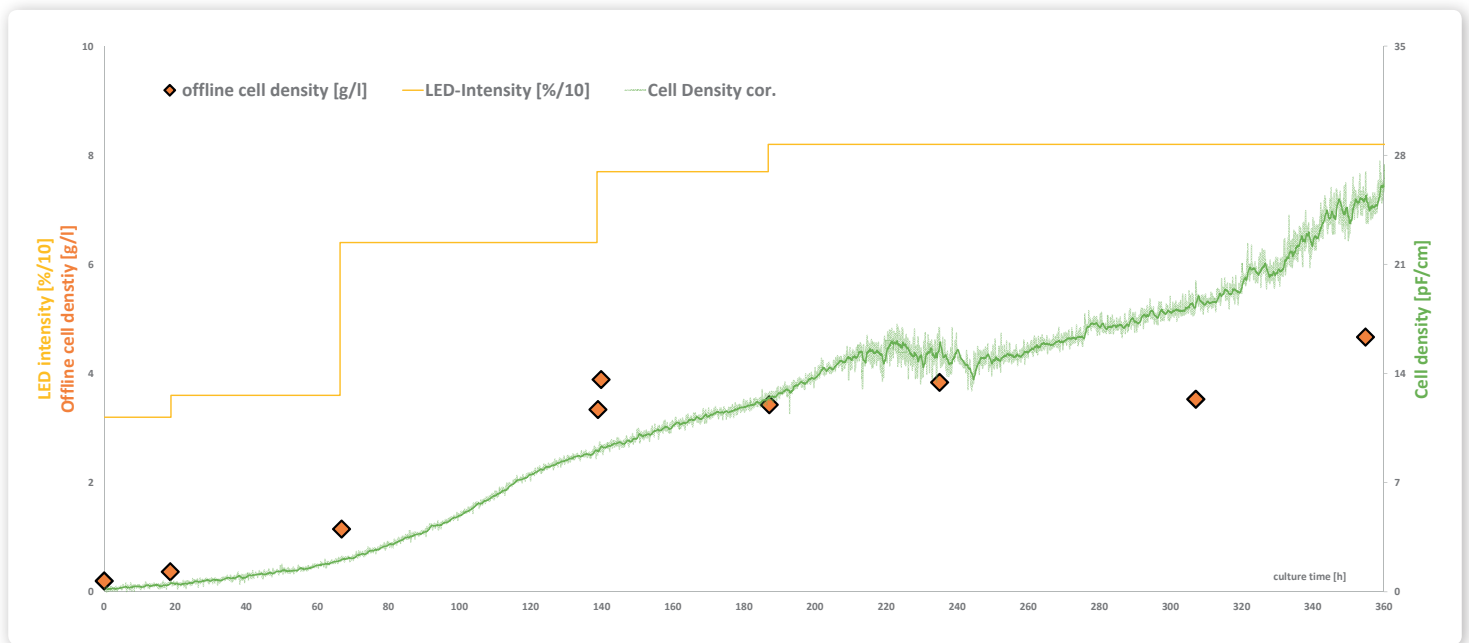


Figure 2: In-line permittivity versus off-line cell density. The green line represents the Incyte in-line measurement. The orange dots represent the total cell count with the reference off-line method.

**GREENOVATION**  
Biopharmaceuticals

#### Authors

**Jonas Koch**  
**Michael Müller**  
**Dr. Holger Niederkrüger**

#### Company

Greenovation Biotech GmbH  
Hans-Bunte-Str. 19  
79108 Freiburg  
Germany

Phone: +49 761 470 99 0  
Fax: +49 761 470 99 190  
info@greenovation.com  
www.greenovation.com

© 2018 Hamilton Bonaduz AG. All rights reserved.  
[REF] 695247/00 – [img alt="logo"] 10/2018

**HAMILTON**

Web: [www.hamiltoncompany.com](http://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](http://www.hamiltoncompany.com).