Improvement in productivity using capacitance as a PAT tool in bioprocesses

ABER

Introduction

In the biopharma and cell culture engineering industries, a key objective is to increase process productivity and product titer. Such improvements offer numerous advantages, including reduced costs, heightened efficiency, expanded capacity, and expedited time to market.

Capacitance technology has become a reliable, inline, real-time Process Analytical Technology (PAT) tool for measuring viable cell density in bioprocesses. Various groups have reported productivity enhancements using capacitance in multiple applications. This application note aims to summarise a few of these studies.

Increasing productivity in fed-batch applications

Over the years, multiple groups have published studies describing the use of biocapacitance in R&D, process development and manufacturing. One such group is Biogen who published a paper on the benefits of feeding using complex nutrients based on biovolume or biocapacitance[1]. The capacitance-based feeding strategy provided greater flexibility and adjusted the feed amount in real-time according to process/cell growth variations, positively impacting the process's critical quality attributes.`

In a subsequent study, the application of biocapacitance for more frequent feeding control was examined[2]. Typically, in fed batch cultures, nutrients are fed once in 24 h. The primary reason for this is because these feeds have been based on offline counts, that are usually performed once in 24 h. Since capacitance is measured in real time (performed every 4 sec), Biogen explored the possibility of feeding cells every 4 h using the capacitance based strategy instead of every 24 h.

The paper states that this 4 h strategy was more responsive to actual cell culture performance. It reduced the risk of nutrient depletion prior to the next feed. Moreover, it further reduced the risk of process failure due to underfeeding. Overall, this 4 h feed strategy based on capacitance resulted in higher cell growth and prevention of glutamate depletion.

Most importantly, this 4 h feed strategy led to an increase in product titer of 21% relative to the control process performance, where cells were fed once every 24 h based on offline counts.

A similar study was performed at the National Research Council Canada where the biocapacitance based feed strategy was compared with the standard bolus feeding process[3]. Upon comparison, the product titer obtained with the standard bolus feeding process was close to 800 mg/L. The capacitance based approach yielded close to ~1300 mg/L protein titer. In

other words, about 62.5% increase in product titer was observed with capacitance based feeds as opposed to bolus feeds.

Increasing productivity in microbial applications

Corteva works with a microbial process where reliable biomass monitoring is challenging. This is because the process requires the use of complex media, which prevents the application of classical methods for measuring cell density, such as optical density, dry cell weight etc. Furthermore, respiration exhibits poor correlation with growth due to the use of industrial fermentation media with complex raw materials, where primary metabolism is constantly changing.

In this challenging process, capacitance has emerged as the sole biomass measurement technology that functions reliably. Not only has capacitance been used to monitor the cell density in this process, but it has also been used for real time troubleshooting (to identify under-inoculation) and nutrient feed timing optimization.

Application of ABER capacitance enabled Corteva to recognize a growth deficiency that could be correlated to one of the fermentation feeds. Once the feed timing and rate were re-optimized, a 15% gain in product titer was achieved (information/data shared by Corteva via direct correspondence with ABER Instruments).

Increasing productivity in viral vector/virus based applications

Several groups have utilised capacitance measurement to monitor and improve viral vector/vaccine development and production processes. For instance, it has been reported that viral titer is closely linked to harvest time and maximum capacitance observed in the culture4. Harvest time was always ~39.6 h after peak capacitance was observed. The capacitance based method, used to identify and control harvest point, increased max virus concentration by more than 3 orders of magnitude. Using this approach, one dose/patient can be produced in 1 x 500 ml bioreactor as opposed to 20 L bioreactor. In other words, this is a 40 fold improvement in productivity.

Understanding the financial impact of increasing productivity using a PAT tool

Isolating the factors that impact productivity and in turn, impact revenue, can be challenging because of the complexity of a typical bioprocess and the number of variables involved. Nevertheless, based on the 19th annual report and survey of biopharmaceutical manufacturing capacity and production, and applying certain assumptions that can be tailored to a specific process, adequate insight can be gained into the financial impact on increasing productivity.

The following example uses some assumptions based on the report and survey mentioned above. A single 1,000 L bioreactor (fed-batch) production run can provide ≥3,000 g or 3 kg of product. With a potency of 100 mg/dose, this is over 30,000 doses/bioreactor run. At a selling price at ~1,000/dose, this provides ≥$30,000 revenue per gram of mAb or $30,000,000/bioreactor run or batch. In reality this could be lower due to an approximate 40% product loss in downstream processing.

If a PAT tool like ABER could facilitate a 1% increase in productivity, this would lead to an additional $300,000 per bioreactor run. If we were to extend this over 10 years at 20 runs per year, this would equate to an additional $60 million additional revenue with no extra bioreactor footprint. The gain in productivity due to the use of biocapacitance will depend on the process. As is evident from the studies summarised above, the productivity increases through this approach can be impressive. This should result in a significant increase in overall revenue.

References:

1) Zhang, A. et al., 2015; Advanced process monitoring and feedback control to enhance cell culture process production and robustness, Biotech and Bioeng

2) Moore, B. et al., 2019; Case study: The characterization and implementation of dielectric spectroscopy (biocapacitance) for process control in a commercial GMP CHO manufacturing process, Biotech Prog

3) Juan Reyes Davila, S. et al., 2023; CHO stable pool fed-batch process development of Sars-Cov-2 spike protein production, CCE Conference, Cancun

4) Grein, T.A., Loewe, D., Dieken, H., Salzig, D., Weidner, T. and Czermak, P., 2018. High titer oncolytic measles virus production process by integration of dielectric spectroscopy as online monitoring system. Biotechnology and bioengineering, 115(5), pp.1186-1194.

For over three decades, ABER has pioneered the development and use of dielectric instrumentation to measure cell membrane capacitance and media conductivity. Since its inception, ABER has provided the biotech industry with three generations of biomass monitors.

aberinstruments.com
sales@aberinstruments.com

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