Smooth Integration

Achieving Optimal Benchtop Bioprocess Management

Improved productivity is critical to the development of highly efficient production processes for biopharmaceutical proteins. Despite the apparent value of feedback control systems in the biopharmaceutical industry there are only a few successful demonstrations.

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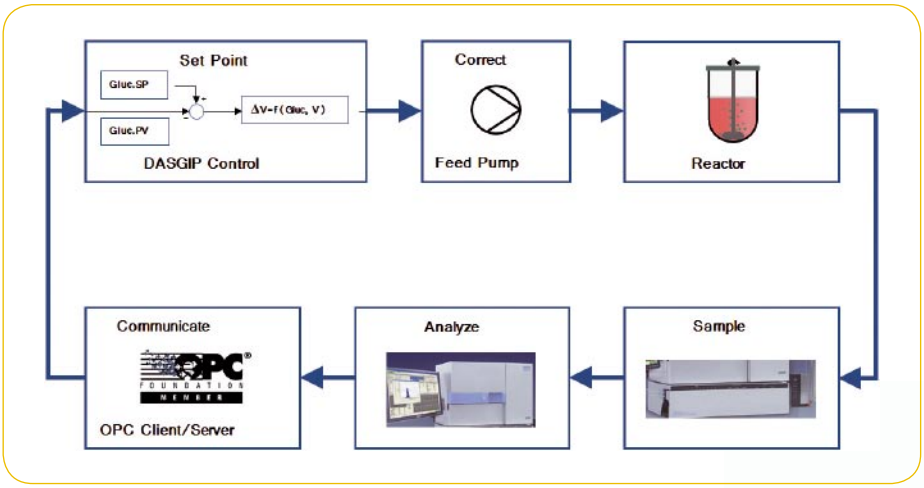

Fig.1: Closed-loop-feedback control of Glucose

Highly efficient and economic production processes are of crucial importance for the biopharmaceutical industry. A fast and reliable process development is a key factor to increase the total efficiency of drug development. In order to develop and optimize these processes a comprehensive understanding of the product quality attributes and the critical process parameters is essential.

To obtain reliable process information, a number of sophisticated devices and technologies for cultivation, production, and analysis have become mandatory for the process development. Moreover the US Food and Drug Administration (FDA) is a driving force in this matter: With the process analytical technology (PAT) initiative the FDA tries to improve process understanding [1].

In addition, the CMC-Biotech Working Group – a consortium of biotechnology companies including Abbott, Amgen, Genentech, GlaxoSmithKline, Eli Lilly, MedImmune and Pfizer – released the A-Mab Case Study in 2009 [2]. The study demonstrates the importance of identifying critical process parameters and ensuring that they meet the design space during the production process, i.e. that they stay in their acceptance ranges. Advanced control strategies can help to achieve this goal.

Although advanced bioreactors, auto sampling technologies, and analytical devices are available, a combined, integrated, and automated solution is rarely established in the process development and optimization so far. In the past, costly and non-standardized interfaces have been a major reason.

Open Communication Simplifies Lab Automation

Since Hans Baruch launched his "Robot Chemist", the first commercially available automatic discrete analyzer, 50 years ago, and Dr. Rodney Markin created the first automated laboratory management system in the early 1990s', lab automation has made great progress. Established in 1996, OPC has become a global standard for the networking of laboratory equipment. It provides an uniform and widely-supported interface for the smooth exchange of data between bioreactor controller and laboratory analyzers such as nutrient analyzers, cell counters, HPLC or mass spectrometers. Interconnectivity achieved by OPC therefore can

be considered as an enabling technology for improving process analytics and understanding.

Most commercial bioreactors are dedicated to the control of DO, pH, temperature, and agitation. Furthermore, monitoring and control of key nutrients or metabolites such as glucose, lactate, amino acids, and ammonia levels can be critical to obtain optimal and consistently high productivity in many biological systems. A bioreactor generally does not have the built-in capability to control such relevant metabolites that can affect culture conditions and, by extension, product quality.

Through the additional integration of auto samplers and analyzers, using communication protocols such as OPC, pharmaceutical laboratories observe a leap in efficiency. The combination of auto sampler, analyzer and bioreactor controller facilitates a fully automated nutrient feedback-control system – in the case of the DASGIP Parallel Bioreactor System for up to eight bioreactors and various analyzers connected to several feed pumps.

Case Study

At the University of Delaware for instance, Professor Babatunde A. Ogunnaike and his students combined a Bioprofile 100+ bioanalyzer with an autosampler (Nova Biomedical) and a Parallel Bioreactor System (DASGIP). With the OPC connection, the Bioprofile was integrated into the Bioreactor Control Software. This allows for closed-loop feedback control of glucose and glutamine concentrations in the media which are one of the key process variables (Fig. 2). All glucose and glutamine readings were stored along with the bioreactor process data in the built-in historian. The integrated bioreactor system demonstrated the successful control of glucose and glutamine media concentrations, a first step into glycosylation control [3].

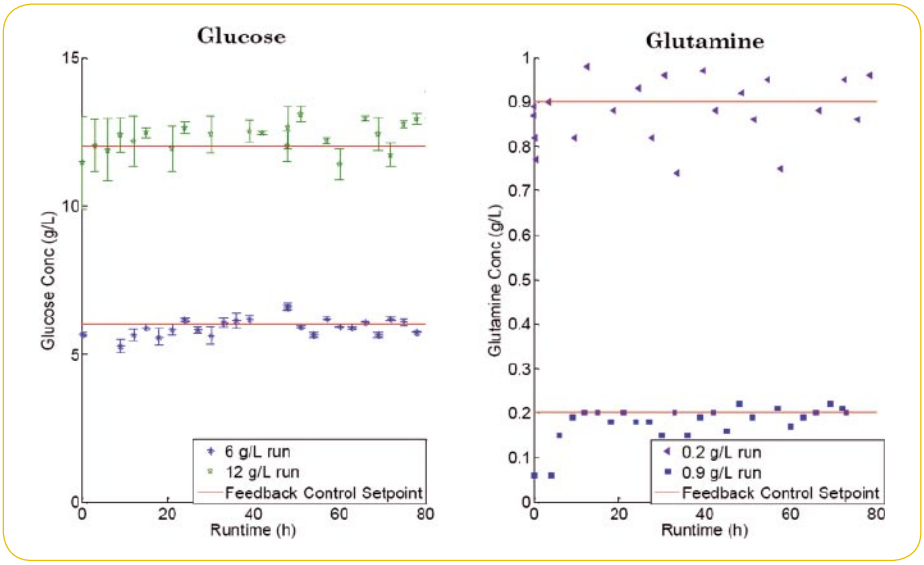

Fig.2: In order to establish a glycosylation control loop, a multi-scale model utilizing process variables to predict glycosylation patterns was developed at the University of Delaware. The controlled inputs of the model include glucose and glutamine media concentration, DO, pH, temperature and agitation rate. Specific uptake or excretion rates of glucose, glutamine, lactate, and ammonia were computed by linear regression with biomass. This model allows for model predictive control and targeted modification of process variables. At-line glucose and glutamine analysis resulted in an accurate pump flow rate and achieved a closed loop control according to the defined set-point [5].

Turning Collected Data into Valuable Information

Since such integration increases the amount of collected runtime data tremendously, a powerful data management to handle the numerous bioreactor runs in process development is a major challenge. Thus, advanced data analysis tools have become essential to turn collected data into valuable process information.

For an extended analysis or to compare individual process runs, all given information preferably should be included in a central database storage. With such a storage, a so called historian, runtime data, biological and chemical attributes like the type of organism, the composition of the culture medium, and nutrient supplements linked together for assessment. Likewise, batch information, as defined set points, control parameters and feeding strategies as well as analytical results such as product yields or viable cell densities can be used for later evaluation [4]. OPC connectivity again can serve as a standard to connect bioreactor systems to corporate historians making information accessible globally.

The DASGIP system comes with a built-in historian and provides an information management package with an easy-to-use query tool enabling a comprehensive process analysis [4]. Furthermore, it provides an OPC server for seamless integration into corporate IT infrastructure supervisory control systems or historians.

The advantages of an automated system and a closed feedback loop on the one hand and the intelligent data management on the other hand reduces development time and improve lab productivity significantly. By this means the Parallel Bioreactor Systems enable biopharmaceutical companies to establish highly efficient process development processes meeting PAT and Quality by Design (QbD) requirements with relatively little effort.

A desired goal of the PAT framework is to design and develop processes that can consistently ensure a predefined quality at the end of the manufacturing process. Such procedures would be consistent with the basic tenet of quality by design and could reduce risks to quality and regulatory concerns while improving efficiency. Gains in quality, safety and/or efficiency will vary depending on the product and are likely to come from:

- Reducing production cycle times by using on-, in-, and/or at-line measurements and controls.
- Preventing rejects, scrap, and re-processing.
- Considering the possibility of real time release.
- Increasing automation to improve operator safety and reduce human error.
- Facilitating continuous processing to improve efficiency and manage variability
- Using small-scale equipment (to eliminate certain scale-up issues) and dedicated manufacturing facilities.
- Improving energy and material use and increasing capacity.

Table1: Source: Guidance for Industry: PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance, June 2009, p. 5

References

[1] Guidance for Industry: PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance (June 2009)

[2] CMC Biotech Working Group: "A-Mab: a Case Study in Bioprocess Development"; Version 2.1, www.ispe.org/PQLI_A_Mab_Case_Study_Version_2_1.pdf

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[5] St. Amand M. *et al.:* "Chapter 3: Strategic vision for integrated PAT in biologics manufacturing and advanced control" In Undey, C.; et al. (ed): PAT Applied in Biopharmaceutical Process Development and Manufacturing: An Enabling Tool for Quality-by-Design. CRC Press (2011)

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