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Role of Interconnectivity in Enabling Improved Bioprocess Quality

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Abstract

Information technology helps to integrate Quality by Design (QbD) and Process Analytical Technology (PAT) into standard laboratory procedures and increase efficiency in process and product development. The presented case study demonstrates how novel information technologies of an advanced Eppendorf DASGIP® Parallel Bioreactor System improved process development. Seamless integration of analytical data allowed for implementation of a predictive model control and comprehensive process automation.

Introduction

An increasingly common discussion ongoing amongst bioprocess scientists and engineers alike is the idea that quality cannot be tested in to a product but must instead be deployed throughout a process.

To accomplish this objective, the US Food and Drug Administration (FDA) has teamed with the European Medicines Agency (EMA) to provide bioprocess professionals with expanded guidelines in the form of the Process Analytical Technologies Initiative and proven concepts such as Quality by Design. Both of which emphasize the need on the part of the bioprocess professional to understand that quality should be built into a product through a thorough understanding of the product and the process by which it is developed and manufactured along with a knowledge of the risks involved in manufacturing the product and how best to mitigate those risks.

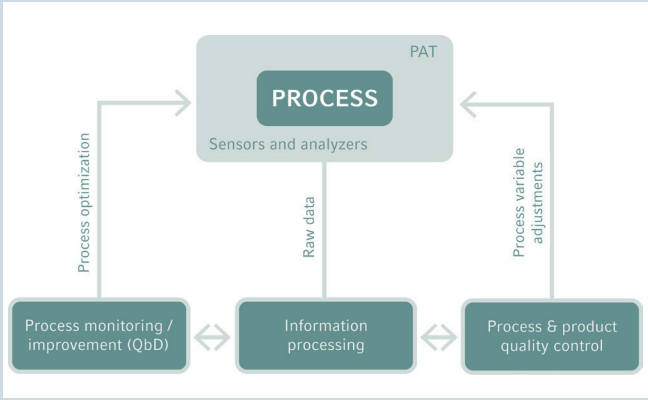

Fig. 1: Ideal configuration in bioprocessing

Materials and Methods

At the University of Delaware, Babatunde A. Ogunnaike and his team have established the foundation for effective real-time online control of glycosylation patterns on monoclonal antibodies (mAb) produced with Chinese Hamster Ovary (CHO) cells.

Fig. 2: DASGIP Parallel Bioreactors System for cell culture applications

Table 1: Effects of culture conditions on glycosylation [3].

Process variable	Effect on glycosylation
Low glucose concentration	Reduced glycan site occupancy
Low glutamine concentration	Decreased sialylation, increased hybrid and high mannose glycans
Ammonia accumulation	Reduced glycan site occupancy, drecreased terminal sialylation
pH	Variations in degree of galactosylation
Low temperature	Increased glycan site occupancy
Low dissolved oxygen	Reduced galactosylation levels
High agitation rate	Reduced glycan site occupancy

For establishing base regulatory control of key process variables known to effect glycosylation (table 1), they designed a bioreactor system with nutrient control and cellular metabolite monitoring in addition to the common bioreactor measurements. With this system pH, glucose, glutamate, glutamine, lactate, N^+, K^+, NH^+ were measured with a BioProfile® 100 Plus nutrient analyzer with autosampler (Nova Biomedical® Corporation, USA) which was integrated with the DASGIP Control* software for parallel bioreactors via OPC.

Results and Discussion

The validated bioreactor/analyzer system allowed for closed loop control of glucose and glutamine concentrations in the media.

A multi-scale model using process variables (glucose and glutamine media concentrations, DO, pH, temperature, and agitation rate) to predict glycosylation patterns is currently under development and will be used as the basis of a

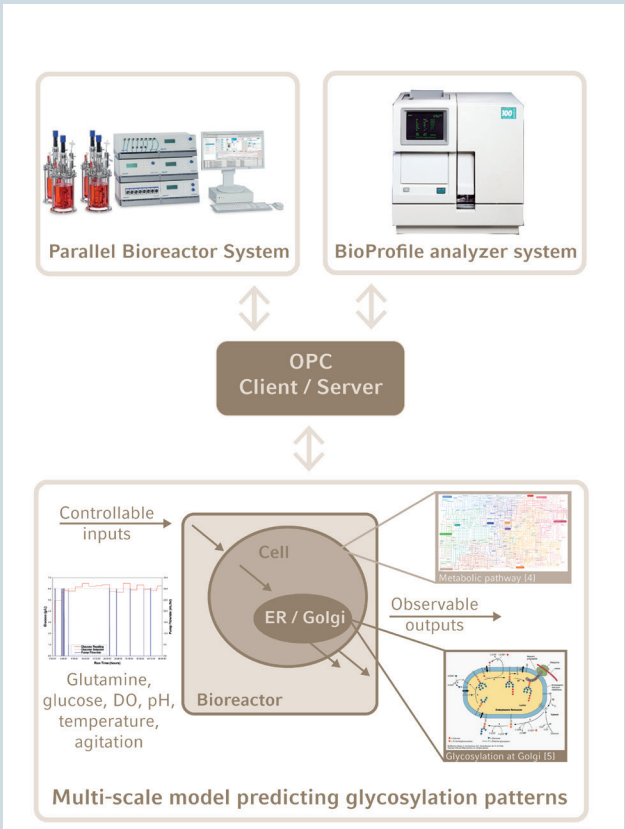

Fig. 3: Model-based online glycosylation control. Successful integration of DASGIP Parallel Bioreactors System with a Nova BioProfile 100 Plus analyzer allows for online control of critical cultivation parameters knowing to influence glycosylation (table 1). The multi-scale model utilizes the process variables to predict glycosylation patterns in between actual measurements.

* DASGIP Control is now DASware® control 5. The desribed functionality of interconnectivity with third-party lab devices is offered by our software package DASware analyze. Please refer to the ordering information on page 4.

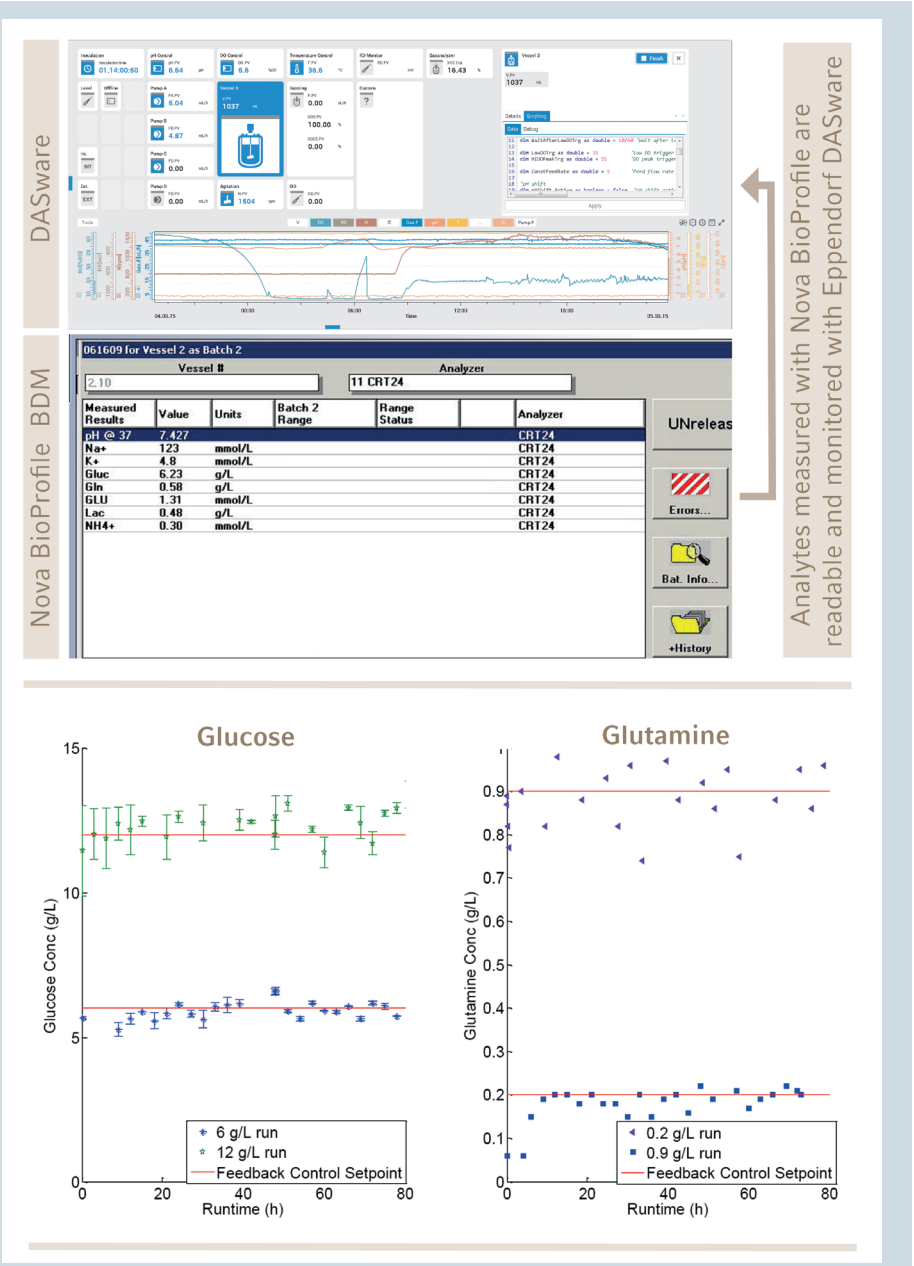

Fig. 4: Glucose and glutamine control. Nova measured analyte data was transferred to DASware control software via OPC. The At-line glucose and glutamine analysis allowed for closed loop control of the nutrients according to the defined set points.

model-predictive control strategy for glycosylation.

Further approaches will use the integration of HPLC coupled to mass spectrometry to characterize glycan micro-heterogeneity.

Conclusion

The study impressively shows how information technology can help to increase efficiency in process and product development by the integration of QbD and PAT into standard laboratory procedures.

With its DASGIP Parallel Bioreactor Systems allowing for interconnectivity with third-party analyzers, Eppendorf offers a comprehensive technology platform for advanced process development in cell culture and microbiology bioprocess applications.

References

[1] St. Amand, M. M., Millili, P., McCabe, M., and Ogunnaike, B. A. Development of Process Analytical Technology Methods for Online Control of Glycosylation during Monoclonal Antibody Production. IFPAC Meeting (2010), Baltimore

[2] Rix, K. and Grolms, M. Using Information Technology to Enhance Upstream Productivity. *BioPharm Intl.* (2010) p.22-28

[3] St. Amand, M. M., Millili, P., McCabe, M., and Ogunnaike, B. A. A Strategic vision for integrated PAT in biologics manufacturing and advanced control; in: Undey, Low, Monteiro, Koch (eds). PAT Applied in Biopharmaceutical Process Development and Manufacturing: An Enabling Tool for Quality-by-Design. CRC Press, Boca Raton, Fl. (2011)

Ordering information

Description	Order no.
DASGIP® Parallel Bioreactor System for Cell Culture, max. 50 sL/h gassing	
4-fold system with Bioblock	76DG04CCBB
8-fold system with Bioblock	76DG08CCBB
16-fold system with Bioblock	76DG16CCBB
4-fold system, benchtop	76DG04CC
8-fold system, benchtop	76DG08CC
16-fold system, benchtop	76DG16CC
DASware® control, incl. PC, OS, and licenses	
for 4-fold DASGIP® system	76DGCS4
for 8-fold DASGIP® system	76DGCS8
DASware® control professional, incl. PC, OS, and licenses	
for 4-fold DASGIP® system	76DGCSP4
for 8-fold DASGIP® system	76DGCSP8
DASware® analyze, OPC client professional incl. 1x tunneller lic. (OPC DA e.g. for ext. analyzer with autosampler)	
for 4 vessels	76DWANA4P
for 8 vessels	76DWANA8P
for 12 vessels	76DWANA12P

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